Intramolecular [4+2] Cycloadditions of Conjugated Enynes:

Scope and Mechanism

by

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For my mother, father, and sister.

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by
Alexandra E. Gould

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Degree of Doctor of Philosophy in Chemistry

ABSTRACT

An exploration of the intramolecular cycloadditions of conjugated enynes with alkenes and alkynes has revealed a fairly general method for the preparation of substituted aromatic and dihydroaromatic compounds. The cycloaddition proceeds when the substrates are heated and when they are treated with Lewis or protic acids. A variety of substrates were examined to explore the scope of the cycloaddition. Substrates with different enyne substitution patterns, different tether lengths, and different activating substitutents on the alkene or alkyne enynophile were studied.

The mechanism of the enyne cycloaddition was also invesitgated. Under different conditions, it appears that different mechanisms may be operating. Under thermal conditions, a cyclic allene may be involved as an intermediate; while under protic or Lewis acid conditions, a dienyl cation may be an intermediate. Under acidic conditions, the reaction proceeds suprafacially with respect to the "enynophile" component.

Thesis Supervisor: Rick L. Danheiser
Title: Professor of Chemistry

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Part I

Introduction and Background

Chapter 1

Introduction and Background

Cycloaromatization Reactions

Cycloaromatization reactions have recently attracted much attention due to their role in the mechanism of action of several biologically active compounds, such as the calicheamicins, esperamicins, dynemicins, and neocarzinostatins.[1] Three general types of cycloaromatization processes are known, the Bergman cyclization, the neocarzinostatin and closely related Myers cyclizations, and the Moore cyclization, and all are characterized by the formation of an intermediate biradical from a highly unsaturated conjugated system.[2] The Bergman cyclization involves an enediyne, the neocarzinostatin and Myers cyclizations involve a cumulene enyne, and the Moore cyclization involves a enynyl ketene.

Bergman and Jones described the mechanism of the Bergman cyclization in 1972.[3a] Upon heating to 200 °C,[3] a deuterium labeled enediyne will undergo scrambling (Scheme 1). This transformation is proposed to proceed through the aromatic biradical shown, and has recently been demonstrated to occur upon irradiation.[4] The DNA-cleaving ability of enediyne antibiotics, such as the calicheamicins, esperamicins, and dynemicins,[1b] results from formation of a biradical species via a Bergman cyclization. As shown in Scheme 2,

---

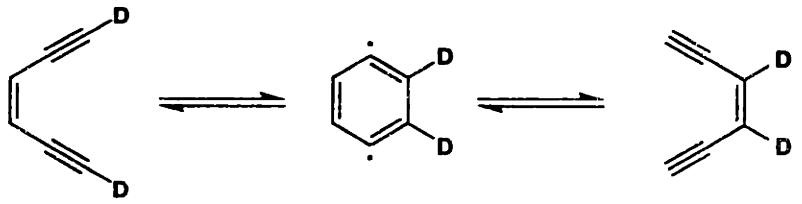
[1]For recent reviews of endiyne antibiotics see: (a) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Eng.* **1991**, *30*, 1387. (c) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry* Stang, P. J.; Diederich, F. Eds.; VCH: Wienheim, 1995; pp 203-253. For a review of the calicheamicins, see: (d) Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235.

[2]For a recent review see: Gleiter, R.; Kratz, D. *Angew. Chem. Int. Ed. Eng.* **1993**, *32*, 842.

[3](a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. Masamune described a similar transformation prior to Bergman's mechanistic study, see: (c) Darby, N.; Kim, C. U.; Salaün, J. A.; Takada, S. S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1516. See also: (d) Mayer, J.; Sondheimer, F. *J. Am. Chem. Soc.* **1966**, *88*, 602. (e) Pilling, G. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1971**, *93*, 1970.

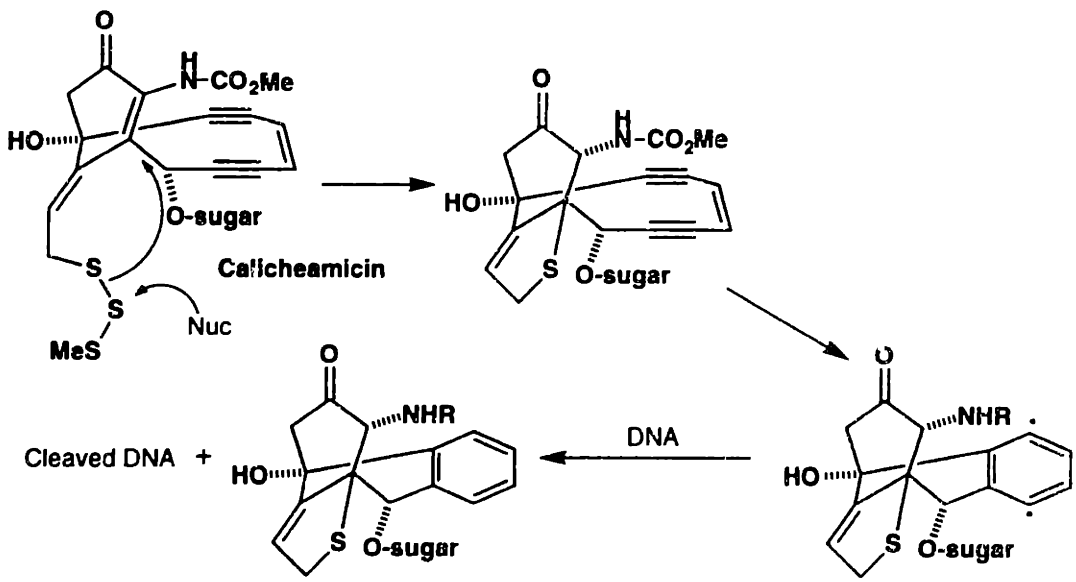
[4]Turro, N. J.; Evenzahav, A.; Nicolaou, K. C. *Tetrahedron Lett.* **1994**, *35*, 8089.

Scheme 1



calicheamicin is first activated by trisulfide cleavage, followed by an internal Michael addition which brings the enediyne moiety into a reactive orientation. Bergman cyclization occurs, and the resulting biradical abstracts hydrogen atoms from DNA causing DNA cleavage.

Scheme 2



The discovery of the second type of cycloaromatization involving cumulene enynes is closely linked to natural products chemistry. The isolation of neocarzinostatin (NCS)[5] in 1965 as a two component antibiotic[6] did not generate great interest until 1985, when Edo

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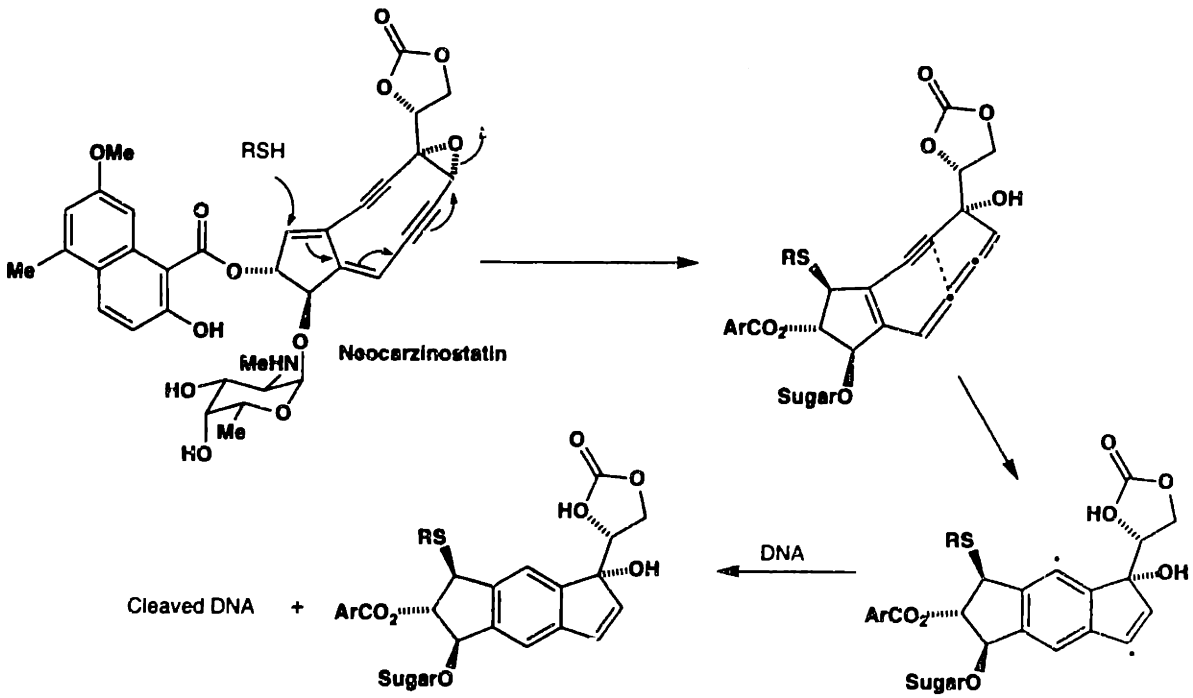
[5]For a recent review, see: Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191.
[6]Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68.

and co-workers proposed a structure for the NCS chromophore.[7] Two years later, Andrew G. Myers proposed a mechanism to account for the biological activity of NCS that involves the cycloaromatization of a cumulene enyne to give an aromatic biradical species (Scheme 3). [8] This species is responsible for DNA cleavage. The cycloaromatization of these

Scheme 3



cumulene enynes has been studied extensively by Myers and others.[9,10] Myers examined the related cyclization of a less complicated enyne allene which generates the toluene diradical **2** (Scheme 4). He found that compound **1** cyclized upon thermolysis in 1,4-cyclohexadiene (a hydrogen atom donor) to give toluene in 60% yield along with insertion products **3** and **4** (1:1 ratio) in 40% yield.[9c]

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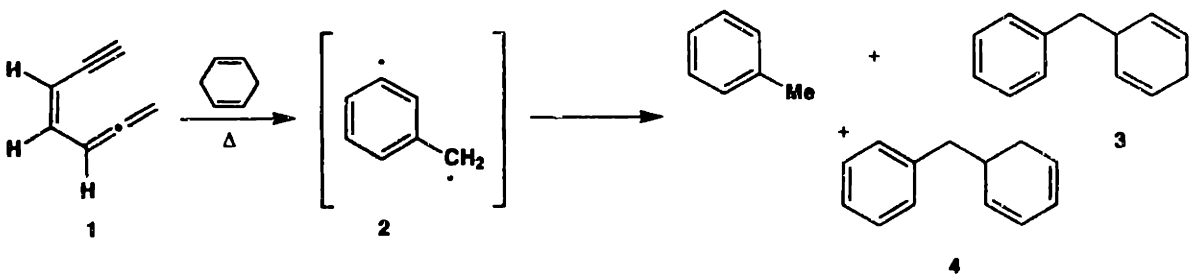
[7]Edo, K.; Mizugaki, M.; Koide, H.; Seto, H ; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.

[8]Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493.

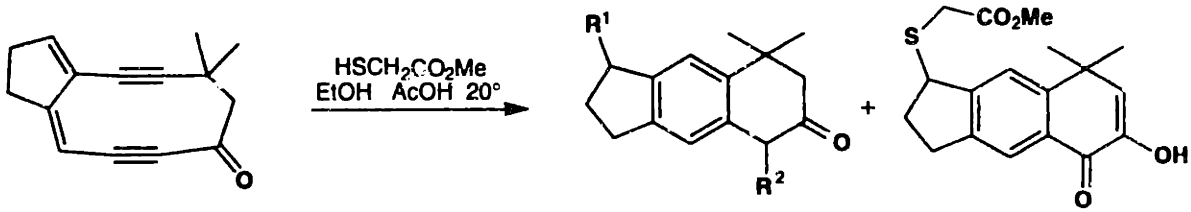
[9](a) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (b) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146. (c) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (d) Hensens, O. D.; Goldberg, I. H. *Biochemistry* **1989**, *28*, 1019.

Scheme 4



Hirama and co-workers[10] have studied several systems more directly related to the NCS chromophore. The ten-membered ring analog **5** cyclizes under aerobic and anaerobic conditions when treated with methyl thioglycolate and ethanolic acetic acid to give a mixture of products (Scheme 5). Compounds **6a**, **6b**, and **7** are produced under aerobic conditions; compounds **6a** and **6c** are produced under anaerobic conditions. The cyclization proceeds more quickly under aerobic conditions, leading these workers to propose a radical-initiated, as well as a nucleophile-initiated mechanism for cyclization.[10a,b]

Scheme 5



5

6a R^1=SCH_2CO_2Me R^2=H
6b R^1=R^2=SCH_2CO_2Me
6c R^1=OEt R^2=H

7

The Moore cyclization (Scheme 6) is a third important type of cycloaromatization. While this reaction has not been linked to the biological activity of any natural products, its mechanism is related to that of other cycloaromatizations. Moore found that alkynylcyclobutenones such as **8** undergo ring opening to give ketene enynes **9** which

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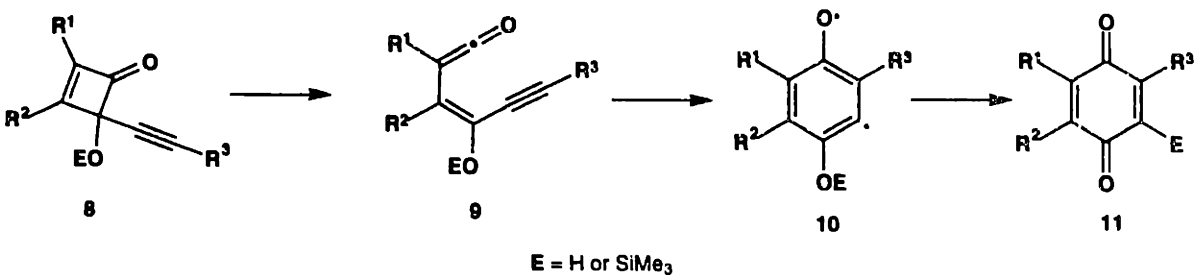
[10](a) Hirama, M.; Fufiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. (b) Fujiwara, K.; Kurisake, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329. (c) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688.

cyclize upon heating.[11] The resulting phenolic diradical **10** is then trapped to provide 1,4-benzoquinones **11** in moderate to good yields. They propose biradical **10** as an intermediate based on intramolecular trapping experiments.

Scheme 6



Cycloaromatization reactions with their biradical intermediates are appealing candidates for use in the development of synthetic methods. The creation of two new radical species which can be trapped intra- or intermolecularly offers an expedient way to build up polycyclic systems from linear ones. Moore has studied applications of his reaction to the synthesis of polycyclic compounds by building internal traps for the intermediate radicals. In one example,[12] thermolysis of alkynylcyclobutenone **12** in *para*-xylene provided the methylenebenzofuran **17** in 73% yield. Moore proposes that the alkynylcyclobutenone undergoes ring opening to give the ketene enyne **13**, which then rearranges to the phenolic biradical **14** via cycloaromatization. A sequence of intramolecular radical addition and substitution reactions leads to the benzofuran product.

Several other groups have also examined the possibility of using cycloaromatization reactions to initiate radical cyclizations in this way.[13,14] In 1994, Grissom reported the use

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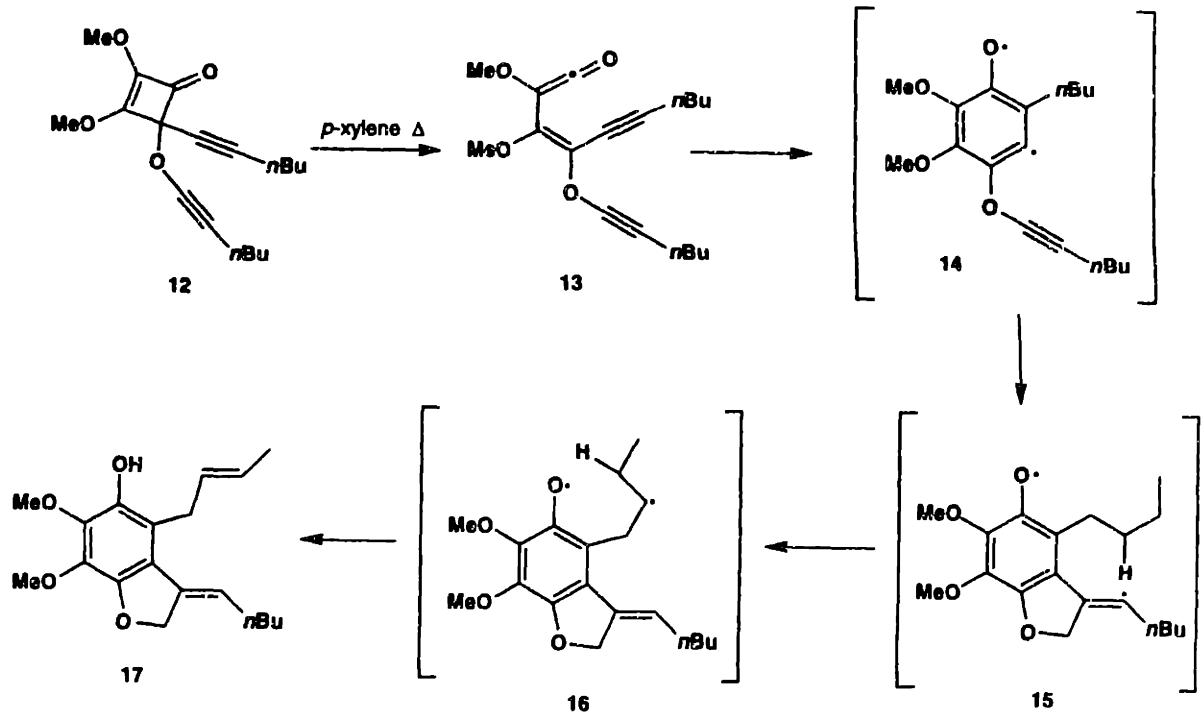
[11]Karlsson, J. O.; Nguyen, N. V.; Foland, L., D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392. Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

[12]Xu, S. L.; Tiang, M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6104. For more examples of this type, see references cited therein.

[13]For a recent review, see: Wang, K. K. *Chem. Rev.* **1996**, *96*, 207.

[14] For examples see: (a) Andemichael, Y. W.; Gu, Y. G.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 794. (b) Andemichael, Y. W.; Huang, Y.; Wang, K. K. *J. Org. Chem.* **1993**, *58*, 1651. (c) Grissom, J. W.; Calkins, T. L.; McMillen, H. A. *J. Org. Chem.* **1993**, *58*, 6556. (d) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559. (e) Grissom, J. W.; Calkins, T. L.; Egan, M. *J. Am. Chem. Soc.* **1993**,

Scheme 7

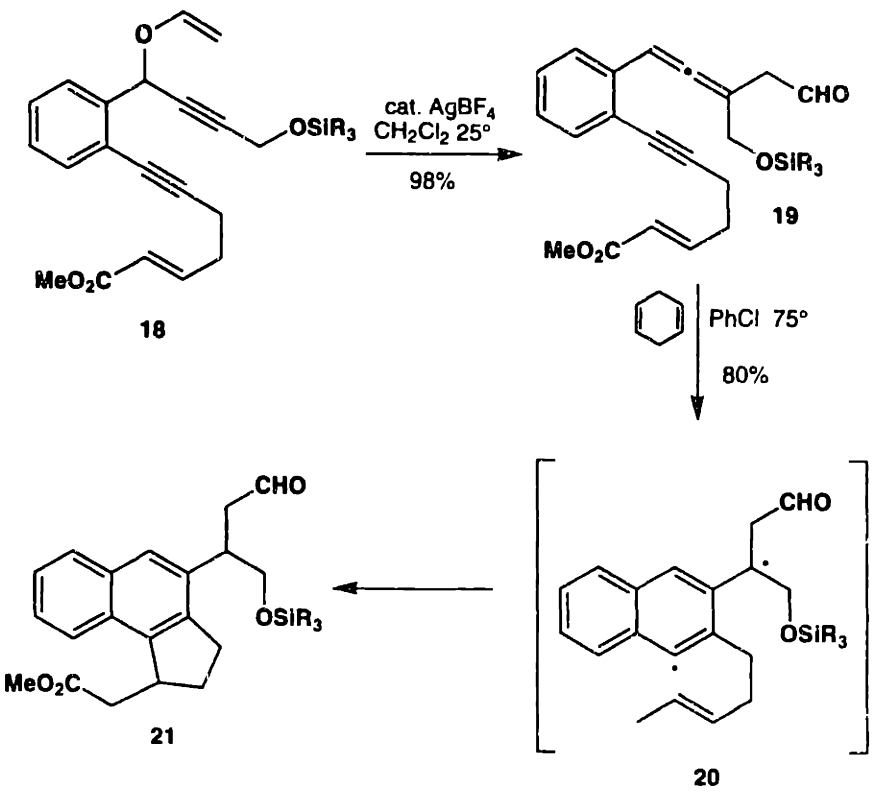


of an allene enyne cycloaromatization to form tricyclic naphthalene derivatives (Scheme 8).[13g] As shown below, vinyl propargyl ether **18** was treated with silver tetrafluoroborate to give the allene arenyne **19** in high yield. Thermolysis of **19** at 75 °C in the presence of 1,4-cyclohexadiene provided the tricyclic product **21** in 80% yield.

While the reactions discussed above involve interesting and novel chemistry, for several reasons we consider the potential synthetic utility of the cycloaromatization reaction to be rather limited. First, these reactions use fairly complicated reactants to produce only moderately complicated products. In addition, while yields in some cases are high, the scope of these reactions is not wide. Most importantly, cycloaromatization reactions are cyclizations, forming only one bond, and thus are not intrinsically convergent processes.

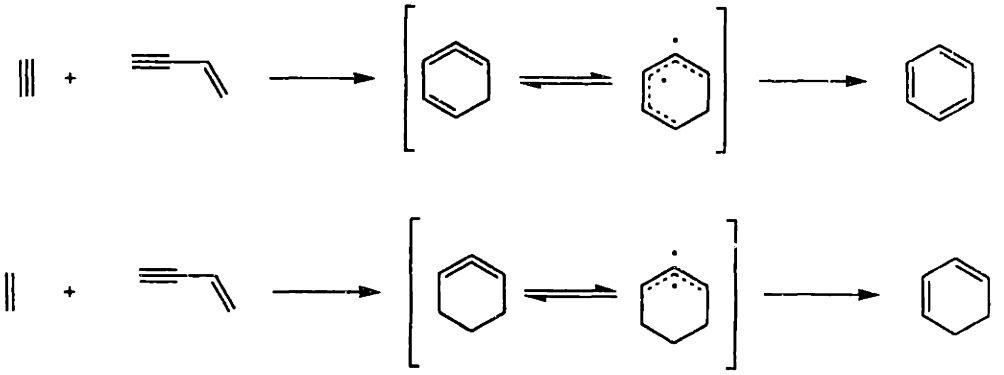
115, 11744. (f) Grissom, J. W.; Slattery, B. J. *Tetrahedron Lett.* **1994**, *35*, 5137. (g) Grissom, J. W.; Calkins, T. L.; Huang, D.; McMillen, H. *Tetrahedron* **1994**, *50*, 4635. (h) Magriotis, P. A.; Kim, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2972. (i) Wang, Y.; Finn, M. G. *J. Am. Chem. Soc.* **1995**, *117*, 8045.

Scheme 8



We are interested in using highly unsaturated, conjugated molecules as components in new organic reactions and have found cycloaromatization reactions to be an intriguing starting point for the design of new transformations. Specifically, we decided to explore the possibility of developing new ring-forming strategies based on *cycloadditions* of highly

Scheme 9



unsaturated, conjugated compounds. For example, as shown in Scheme 9, the [4+2]

cycloaddition of an enyne with an alkene or alkyne would provide a high energy intermediate, shown in brackets. This intermediate can then isomerize to give an aromatic or dihydroaromatic product. The advantages of this ring-forming strategy include ease of synthesis of the reactants and increased convergent character relative to cyclization reactions. My goals in this work were to explore the feasibility, scope, and mechanism of an intramolecular variant of the cycloaddition reactions.

Enyne Cycloadditions: Introduction

Cycloadditions are one of the premier tools for carbon-carbon bond formation in organic synthesis. The Diels-Alder reaction and other cycloadditions are characterized as extremely convergent, regio- and stereoselective reactions. Their utility is proven by the widespread use of these reactions in the synthesis of natural products and commercially important organic compounds.

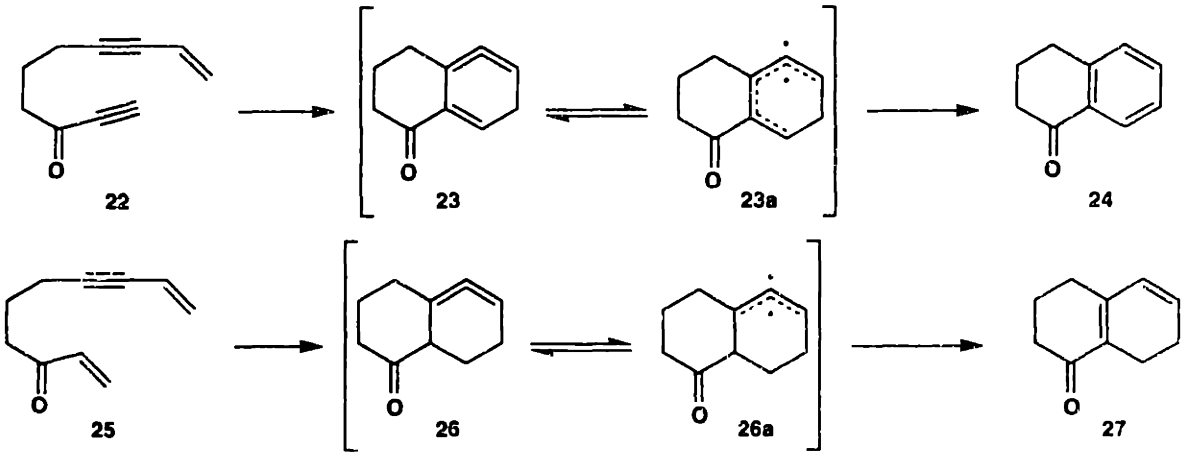
The cycloaddition of a conjugated enyne (Scheme 9) offers the advantages mentioned above along with some other more specific advantages. The Diels-Alder cycloaddition involves the reaction of a diene with a dienophile. Unfortunately, in some cases, the synthesis of the 1,3-diene moiety is difficult, while the conjugated enyne moiety can be more easily constructed. The acidity of the acetylenic proton and the ability of acetylenes to undergo several different transition-metal catalyzed coupling reactions provide many different methods to form conjugated enynes.

The products of the proposed enyne cycloaddition are aromatic and dihydroaromatic compounds, systems that are also available through variants of the Diels-Alder reaction. However, versions of the Diels-Alder reaction that lead to such unsaturated products require the use of relatively complex reactants such as α-pyrones. In short, we believed the enyne cycloaddition has the potential to be a useful tool in organic synthesis, complementary to the familiar Diels-Alder reaction.

We decided to begin our work by examining the *intramolecular* reaction of enynes with alkene or alkyne enynophiles. Intramolecular reactions have an entropic advantage over intermolecular reactions, and we expected these reactions to proceed with greater facility. In addition, intramolecular cycloadditions have the advantage of forming two rings in one synthetic step.

If enyne **22** undergoes a [4+2] cycloaddition, the direct product will be a 1,2,4-cyclohexatriene **23** (Scheme 10), which (vide infra) may exist as the planar diradical **23a**, and can isomerize to give the tetralone **24**. Enyne **25** can undergo a similar reaction to give dihydroaromatic product **27** via intermediates **26**. These strained cyclic allenes and

Scheme 10



biradicals are very high energy intermediates, and whether such cycloadditions are feasible is a reasonable question. In addition, the enyne and alkyne moieties do not appear, upon examination of molecular models, to be able to achieve significant orbital overlap. The chemistry of cyclic allenes and the reactivity of alkynes in pericyclic reactions, along with thermodynamic considerations of the reaction, will be discussed in the next sections.

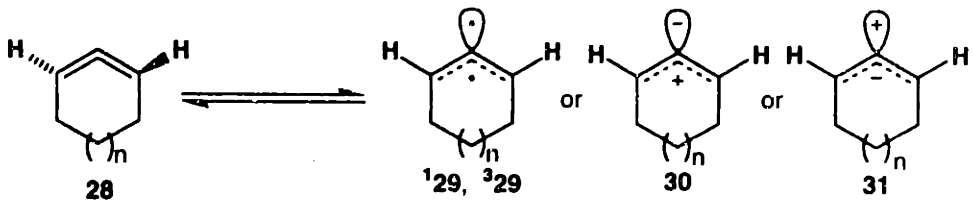
Cyclic Allenes

As discussed above, a possible intermediate in our proposed cycloaddition is a cyclic allene or "isoaromatic" species. These systems are known and have been studied for

many years.[15] An allene consists of three carbon atoms bound to each other with two orthogonal double bonds and two σ bonds. This usually linear array can be accommodated without distortion by rings of ten carbons or more; as the rings become smaller, however, the allene must distort. This distortion occurs in two coupled physical movements of the carbon atoms of the allene, bending and twisting. The distortion of the allene also leads to a loss of the degeneracy of the π* orbitals. All of this results in a potential for high reactivity and helps to explain the chemistry of cyclic allenes.

A cyclic allene is chiral, but as the ring size decreases the allene moiety must bend more and more to accommodate the smaller ring. Eventually, the energy required for maintaining the two π bonds of the allene is overcome by the energy of ring strain, and the allene bends and twists enough to break one of the two π bonds. The result is a planar achiral molecule with three parallel p orbitals and an sp^2 orbital at the central carbon of the

Scheme 11



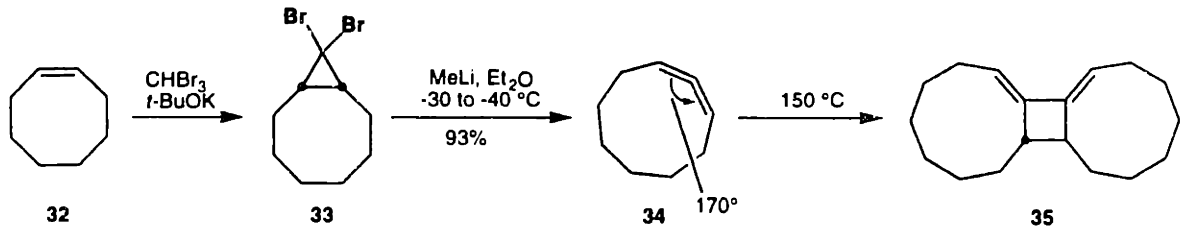
allene. This planar isomer has four possible electronic configurations. a singlet and triplet diradical, ^{1}**29** and ^{3}**29**, and two zwitterions, **30** and **31**. In other words, as n in Scheme 11 decreases, the energy of the planar isomers **29-31** approaches that of the chiral allene **28**. These planar isomers of cyclic allenes become important as the ring size shrinks to seven and below (n<2), making the isolation and study of small cyclic allenes difficult.

---

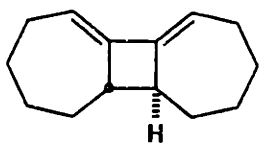
[15]For reviews on cyclic allenes, see: (a)Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111. (b) Johnson, R. P. In *Molecular Structure and Energetics*; Liebman, J. F.; Greenberg, A., Eds.; VHC: Deerfield Beach, Florida, 1986; Vol. 3, Chapter 3.

The smallest, isolable, unsubstituted, cyclic allene, 1,2-cyclononadiene (**34**) was first synthesized by Blomquist in 1951.[16] This compound is available in large quantities via a cyclopropane ring expansion of bicyclo[6.1.0]nonane **33** (Scheme 12).[17] This allene is bent 10° from linearity and undergoes a [2+2] cycloaddition upon heating to give the dimer **35**. Other cyclic allenes have been synthesized and are stable at room temperature. One example is 1-*tert*-butyl-1,2-cyclooctadiene, which was stable to GLC purification and is characterized by a 1942 cm^{-1} stretch in the IR and ^{13}C NMR resonances at 202, 118, and 94 ppm.[18]

Scheme 12



The dimer of 1,2-cycloheptadiene, **36**, has been isolated, but to date the allene itself has not been isolated or characterized. MNDO calculations on the allene predict it to be bent 27° from linearity with the two hydrogens twisted out of plane by 28°.[15a] Optically active cycloadducts of this allene have been isolated as evidence for the chirality of the intermediate allene.[19]



36

The cyclic allene 1,2-cyclohexadiene, with the high constraints of the six membered

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[16]Blomquist, A.; Burger, R. E., Jr.; Liu L. H.; Bohrer, J. C.; Sucsy, A. C.; Kleis, J. *J. Am. Chem. Soc.* **1951**, *73*, 5510.

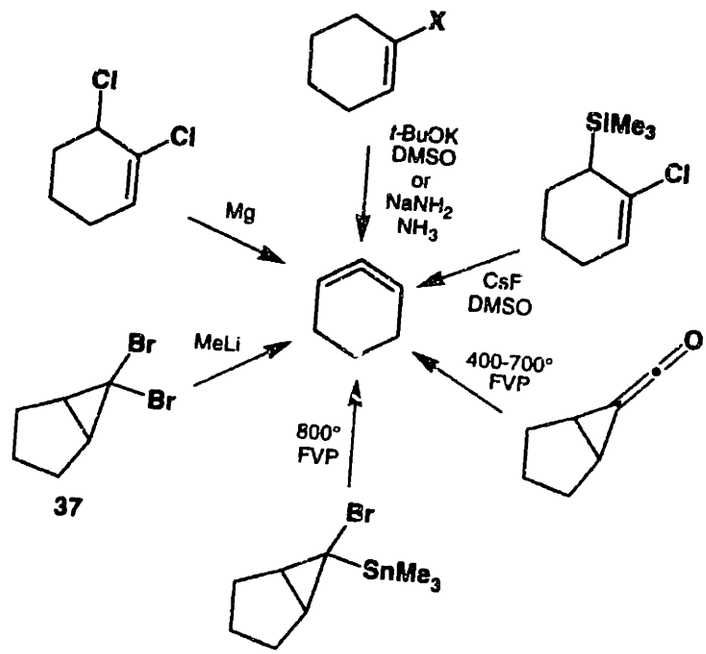
[17](a) Skatteböl, L . *Tetrahedron Lett.* **1961**, 167. (b) Skatteböl, L.; Solomon, S. *Org. Synth.* **1969**, *49*, 35.

[18]Price, J. P.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679.

[19]Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7608.

ring, has been synthesized, trapped, and modeled in several ways. The syntheses[17a,20] and subsequent trapping of this allene resemble those of the larger ring cyclic allenes. As

Scheme 13



shown in Scheme 13, synthetic routes to this allene include standard preparations as well as flash vacuum pyrolysis of the cyclopropyl ketene[21] or the bromostannylcyclopropane,[22] treatment of the dichloride with magnesium, and fluoride-induced β-elimination of an allylsilane.[23] The best route to this allene, however, involves the ring expansion of the dibromocyclopropane **37** developed by Moore and Moser.[27a,17] The chemistry of this allene involves mainly [2+2] but also [4+2] cycloadditions with acyclic and cyclic dienes, as well as tetramer formation and nucleophilic attack at the central carbon.[24,25,26,27]

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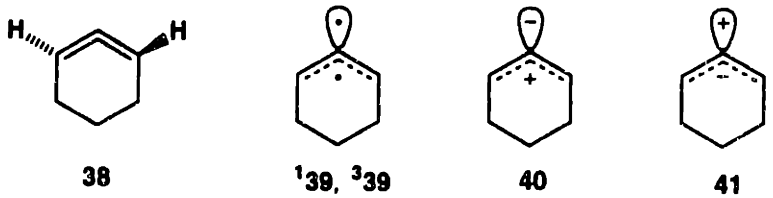
[20](a)Wittig, G.; Fritze, P. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 684. (b) Wittig, G.; Fritze, P. *Justus Liebigs Ann. Chem.* **1968**, *711*, 82.
[21]Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *27*, 542.
[22]Runge, A.; Sander, W. *Tetrahedron Lett.* **1986**, *27*, 5835.
[23]Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578.
[24]Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997.

In 1970, Moore and Moser proposed either the planar, polar structure **40**, with a nucleophilic central carbon atom, or the triplet diradical ^{3}**39** as the ground state for this

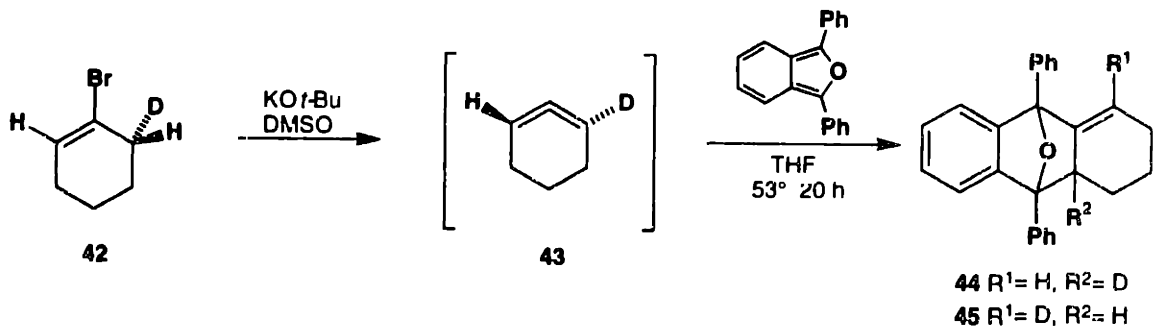
Scheme 14



38 ^{1}**39**, ^{3}**39** **40** **41**

allene.[27a] Later, Underwood and Dillon performed INDO calculations that supported both of these structures as minima in the ground state. Unfortunately, these calculations were based on the assumption that the ground state was planar. Balci and Jones, however, performed an elegant experiment to prove that the ground state of this allene was indeed chiral.[19] Relying on the different rates of elimination of HBr and DBr, these researchers treated the optically active deuterated vinyl bromide **42** with potassium *tert*-butoxide in dimethylsulfoxide. The intermediate allene **43** was trapped with 1,3-diphenylbenzo[*c*]furan

Scheme 15



42 **43**

44 R^1= H, R^2= D
45 R^1= D, R^2= H

to give a mixture of optically active [4+2] cycloadducts. As optically active products were

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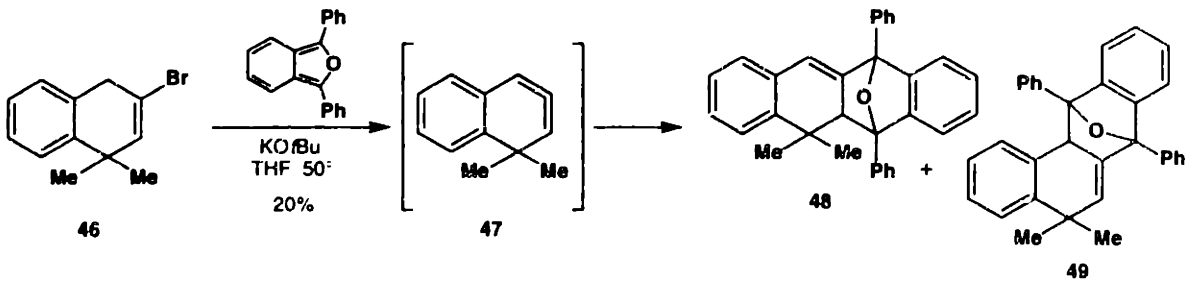
[25]Christl, M.; Schreck M. *Chem. Ber.* **1987**, *120*, 915. Christl, M.; Schreck, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 449.
[26]Harnos, S.; Tivakornpannarai, S.; Waali, E. E. *Tetrahedron* **1986**, *27*, 3701.
[27](a) Moore, W. R.; Moser, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 5469. (b) Moore, W. R.; Moser, W. R. *J. Org. Chem.* **1970**, *35*, 908.

isolated, an optically active intermediate must be involved. If an optically inactive intermediate was involved, then the products would be racemic. Loss of optical activity in the products was observed when the reaction was carried out at 80 °C, indicating a fairly low barrier for isomerization for **43**. Johnson and co-workers[28] have performed ab initio SCF, MSCSCF and Mölier-Plesset calculations that support the chiral allene structure. According to these calculations, the barrier to inversion, which occurs through the singlet diradical, is approximately 15 kcal/mole; the allene is bent 25° out of planarity, and the hydrogen atoms are twisted 30.4° out of the plane. Recently, Janoschek calculated the barrier to inversion in the cyclic allene to be 8.7 kcal/mole.[31]

In our proposed cycloaddition of an enyne with an alkyne (Scheme 9), an isoaromatic species would be formed. Compounds of this type are not isolable but have been studied, both experimentally and theoretically. Miller and Shi reported the trapping of the isonaphthalene **47** in 1987 as shown in Scheme 16.[29] Treatment of a solution of vinyl bromide **46** and 1,3-diphenylisobenzo[*c*]furan in THF with potassium *tert*-butoxide at 50 °C gave a 3:2 ratio of cycloadducts **48** and **49** in 20% yield. Compound **46** was also reported to react with potassium *tert*-butoxide in the absence of 1,3-diphenylisobenzo[*c*]furan at 50 °C; nucleophilic addition to the central atom of the cyclic allene provided an enol ether.

Scheme 16



In 1992, Christl and co-workers announced the trapping of two isoaromatic

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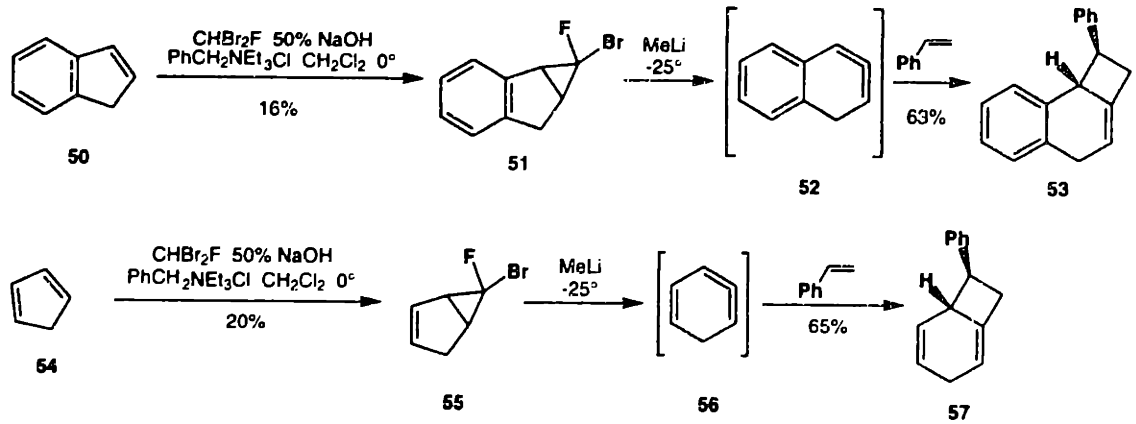
[28]Angus, R. O., Jr.; Schmidt, M. W.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 532.
[29]Miller, B.; Shi, X. *J. Am. Chem. Soc.* **1987**, *109*, 578.

compounds, isonaphthalene (**52**) and isobenzene (**56**).[30] These compounds were prepared in a similar fashion, as shown in Scheme 17, by treatment of indene and cyclopentadiene with bromofluorocarbene to give compounds **51** and **55**. A solution of **51** or **55** and

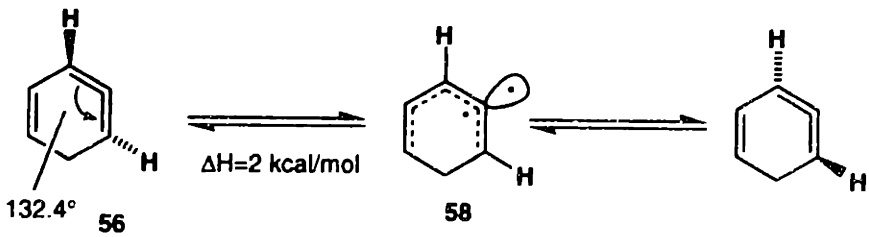
Scheme 17



styrene was then treated with methyllithium at -25 °C. Compounds **53** and **57** were isolated in 63 and 65% yield, respectively. These products are not the thermodynamic ones; the allenes react to give the non-conjugated products indicating that the reaction is under kinetic control. These allenes were also prepared via the corresponding dibromocyclopropanes, as described above for 1,2-cyclononadiene;[17] however, the yields of the cycloadducts were lower via this route.

Janoschek has performed several calculations on isobenzene (**56**).[31] Using the

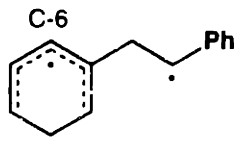
Scheme 18



[30]Christl, M.; Braun, M.; Müller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473.
[31]Janoschek, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476.

semiempirical AM1 method, he found the heat of formation of compound **56** to be 93.7 kcal/mole. The compound is predicted to be chiral (at low temperatures), with the allene bent almost 48° from linearity. The energy of racemization for this molecule is very low, only 2 kcal/mole, and racemization is predicted to occur through the singlet biradical **58**.

Janoschek also performed calculations on the intermediate biradical proposed to be involved in the reaction of styrene with compound **56** in order to explain the regioselectivity of the ring closure. The pentadienyl radical **59** has maximum spin density



59

at the C-6 carbon, and the dihedral angles in the intermediate favor ring closure at the observed position. Recently, Roth, Hopf, and Horn reported the heat of formation for diradical **58** to be 105.1 +/- 1.0 kcal/mole.[32] This value was determined by establishing the NO and O_2 dependence on the trapping of diradical **58** generated by thermolysis of (Z)-1,3-hexadien-5-yne.

Alkynes in Pericyclic Reactions

Due to the required linear ground state geometry of an alkyne, molecules containing a carbon-carbon triple bond might be considered unreactive in reactions like pericyclic processes which require a cyclic transition state. In fact, acetylenes are ready partners in pericyclic reactions, and in some cases, are more reactive than the corresponding alkenes.[33] For example, in 1962, Huntsman and Hall found that acetylene **60** undergoes intramolecular ene reaction at a lower temperature than the corresponding alkene **62**.[34] In a review of the intramolecular ene reaction, Oppolzer and Snieckus report that, in general,

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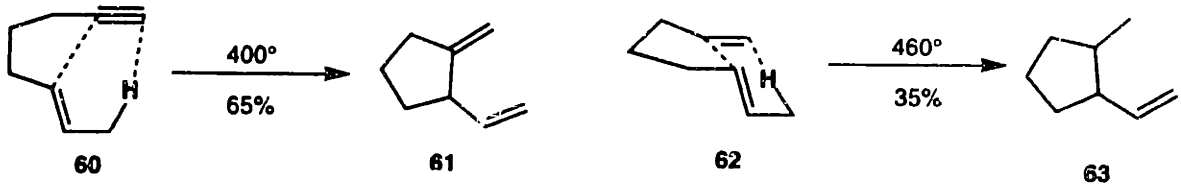
[32]Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765.

[33]For a review of acetylenes in pericyclic reactions, see: Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765.

acetylenes react under more mild conditions than the analogous alkenes.[35]

Scheme 19



60 **61** **62** **63**

The reactivity of alkynes in pericyclic reactions can be explained by examining what is occuring during the reaction. To obtain the appropriate orbital overlap required for a six membered ring transition state, an alkyne must bend. However, the cylindrical π cloud of a carbon-carbon triple bond allows this bending to occur without a large loss in orbital overlap and without requiring a large amount of energy. In addition, the acetylenic π bond is relatively weak when compared to a carbon-carbon σ bond or an alkenyl π bond. Alkynes react well in pericyclic reactions in part because they are easily bent, and the energy required to break a π bond of a triple bond (ca. 54 kcal/mol) is rather small compared to the energy gained from the formation of a new carbon-carbon σ bond (ca. 82 kcal/mol).

Huntsman and Wristers[36] found that the enthalpy and entropy of activation for the Cope rearrangement of the diyne **64** are similar to that for diene **65**.[37] Other workers have explored the reactivity of acetylenes and alkenes in pericyclic reactions by designing competition experiments. In one example, either an alkyne or an alkene can undergo Claisen reaction.[38] The products actually isolated are only those resulting from the Claisen reaction of the alkene moiety, indicating that the alkyne is less reactive in this pericyclic reaction. Some questions have been raised, however, about the design of the substrate and

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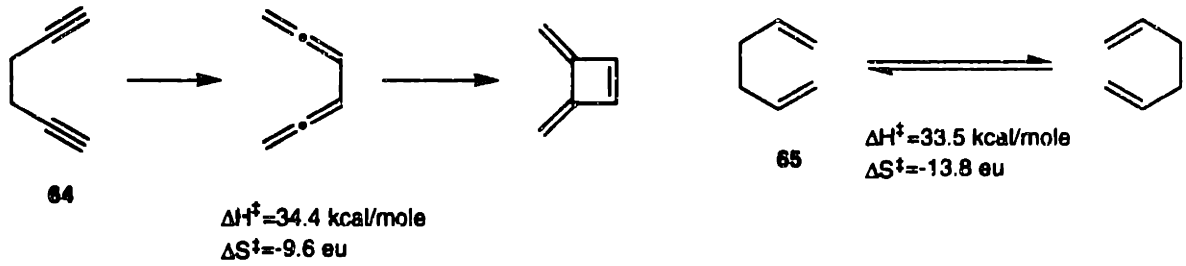
[34]Huntsman, W. D.; Hall, R. P *J. Org. Chem.* **1962**, *27*, 1988.
[35]Oppolzer, W.; Sneickus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.
[36]Huntsman, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 342.
[37]Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299.

the identity of the products,[23] and further study of this reaction is needed. In general, alkynes can and do react as well or better than alkenes in pericyclic reactions.

Scheme 20



Thermodynamic Considerations

The cyclic allene we propose as an intermediate in the cycloaddition of enynes is a species with known properties including the heat of formation. Benson found that accurate heats of formation could be calculated by adding together the heats of formation for various groups within molecules. [39] A group is an atom other than hydrogen and the atoms attached to it; for example, ethanol has three groups: a carbon bound to three hydrogens and a carbon (C-(C)$(H)_3$), a carbon bound to two hydrogens, a carbon, and an oxygen (C-(C)(O)$(H)_2$, and an oxygen bound to a carbon and a hydrogen (O-(C)(H)). The values for the heats of formation for several groups are listed in tables.[39] For our proposed reaction, once the heats of formation for the reactants are calculated, then the enthalpy of the reaction can be calculated by subtracting the value for the heat of formation of the cyclic allene intermediate calculated by Janoschek. Using this information and Benson group additivities, the proposed intermolecular cycloaddition, shown in Scheme 9, was found to be exothermic with an enthalpy of reaction of -29.7 kcal/mol.

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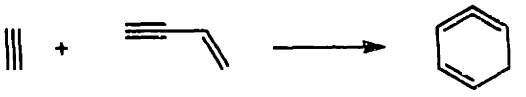
[38](a) Bancel, S.; Cresson, P. *C. R. Acad. Sci. Paris, Sec. C* **1969**, *268*, 1808. (b) Bancel, S.; Cresson, P. *C. R. Acad. Sci. Paris. Sec. C* **1970**, *270*, 2161. (c) Huche, M. *Tetrahedron Lett.* **1976**, 2607.

[39]For Benson group additivity values see: Benson, S. W. *Thermochemical Kinetics*; Wiley: New York, 1976. For a recent review on Benson additivities, see: Cohen, N.; Benson, S. W. *Chem. Rev.* **1993**, *93*, 2419.

As shown in Scheme 21, the heats of formation for acetylene[40] and the cyclic allene **56** are known, and only the heat of formation for 1-buten-3-yne needs to be calculated. Using Benson additivites, each of the four carbons is considered to be a group with a corresponding energy. The sum of these four energies is the calculated value for the heat of formation for the enyne. Inserting these values into equation 1 in Scheme 21 gives the enthalpy of reaction, which is -29.7 kcal/mol. This result is supported by an examination

Scheme 21



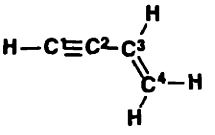
56

$\Delta\Delta H_f = \Delta H_f(\mathbf{56}) - \Delta H_f(\text{acetylene}) - \Delta H_f(\text{enyne})$ (1)

$\Delta H_f(\mathbf{56}) = 93.7$ kcal/mol

$\Delta H_f(\text{acetylene}) = 54.194$ kcal/mol

$\Delta H_f(\text{enyne})$



$C^1 = C_t\text{-}H$	26.93 kcal/mol
$C^2 = C_t\text{-}C_d$	29.20 kcal/mol
$C^3 = C_d\text{-}(H)(C_t)$	6.78 kcal/mol
$C^4 = C_d\text{-}(H)_2$	6.26 kcal/mol
$\Delta H_f(\text{enyne}) =$	69.17 kcal/mol

$\Delta\Delta H_f = \Delta H_f(\mathbf{56}) - \Delta H_f(\text{acetylene}) - \Delta H_f(\text{enyne})$
$= (93.7 - 54.194 - 69.17)$ kcal/mol
$= -29.7$ kcal/mol

of the bond energies involved; two weak acetylenic π bonds are being broken (51 kcal/mol each), and two strong carbon-carbon σ bonds are being formed (84 kcal/mole each).[41] In addition, Johnson has recently reported calculations at the MP4/6-31G*//MP2/6-31G* level

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[40] Rossini, F. D.; Pitzer, K. S.; Arnett, R. L.; Braun, R. M.; Pimentel, G. C. *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*; Carnegie: Pittsburg, 1953.
[41] Mean bond energy values at 25 °C. March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985, p 23.

that predict a heat of formation for the cycloaddition to be -25.4 kcal/mol.[42] For comparison, the enthalpies of reaction for the Bergman and Myers cyclizations are +14 kcal/mole[3] and -15 kcal/mole[9c] respectively.

Summary

We are interested in developing synthetically useful cycloaddition strategies based on processes mechanistically related to cycloaromatization reactions. Although the proposed enyne cycloadditions appear to require the formation of highly strained cyclic allene intermediates, calculations indicate that the desired reaction may in fact be exothermic. Additional support for the feasibility of this cycloaddition was found in the literature, where scattered examples of the cycloaddition of conjugated enynes and related reactions exist. The next chapter summarizes these literature findings and offers a brief discussion of the mechanism of the reaction.

---

[42] Johnson, R. P. Presented at the 1995 International Chemistry Congress of the Pacific Basin Societies, Honolulu, Hawaii, December 1995.

Chapter 2

Previous Studies on the [4+2] Cycloadditions of Conjugated Enynes and Related Reactions

Several examples of the reaction of conjugated enynes with alkenes and alkynes can be found in the literature.[43] The earliest examples of reactions of this general type involve not enynes, but rather arenynes. Intramolecular reactions of arenynes were discovered around the turn of the century, while the first examples of cycloadditions of enynes were not reported until the 1930's. Since then, various researchers have explored both the inter- and intramolecular reactions of enynes. This chapter reviews three classes of cycloadditions: intramolecular reactions of arenynes, and the inter- and intramolecular reactions of enynes. In addition, a brief overview of possible mechanism for these cycloadditions is provided to set the stage for a discussion of our experimental results which follows in the next chapter.

Arenynes in Cycloadditions

The ability of arenynes to undergo cycloaddition reactions was first discovered around the turn of the century. This process has proven useful in the synthesis of natural products, has been the subject of some interesting mechanistic discussion, and continues to be explored today. Although the cycloadditions of both arenynes and enynes give similar products and occur under similar conditions, the mechanisms of the two classes of reactions may differ. However, the cycloadditions of enynes have their roots in this

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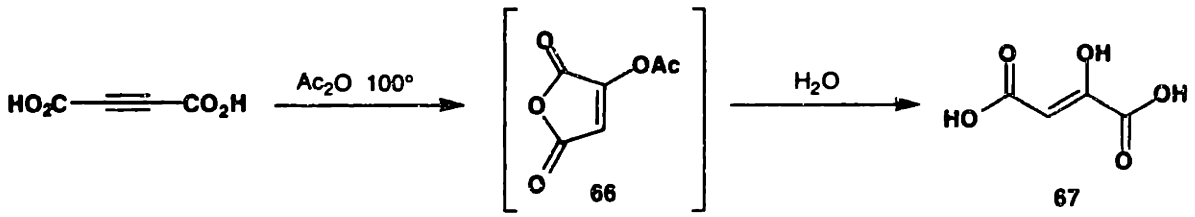
[43]See: Onishchenko, A. S. *Diene Synthesis*; Israel Program for Scientific Translations: Jerusalem, 1964; pp 249-254, 635-637. Vartanyan, S. A. *Russ. Chem. Rev.* **1962**, *31*, 529. Viehe, H. G. *Chemistry of Acetylenes*; Marcel Dekker: New York, 1969; pp 494-496. Johnson, A. W. *The Chemistry of the Acetylenic Compounds*; Langmans, Green, and Co.: New York, 1950; pp 6-9.

arenyne reaction, and this is where our overview begins.

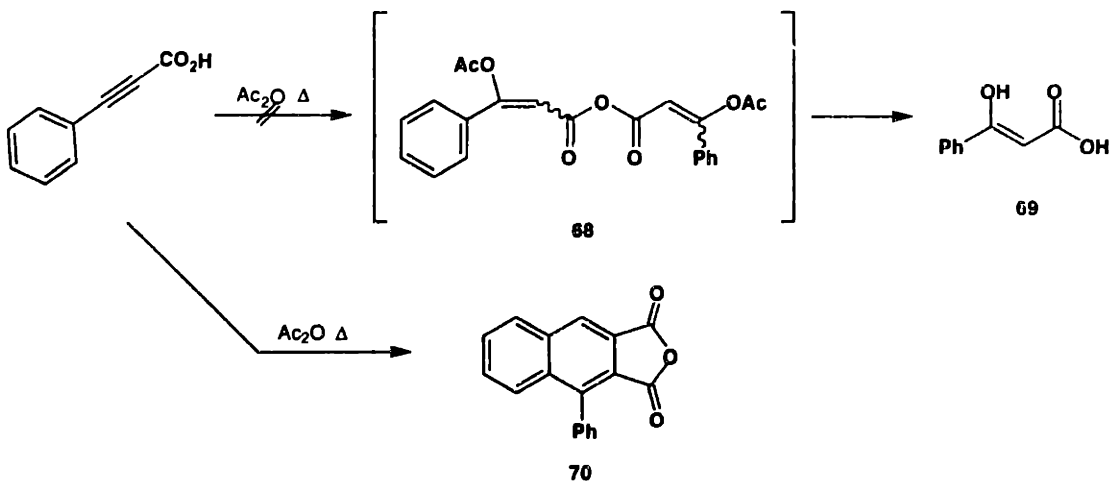
In 1895, Arthur Michael and John Bucher reported the synthesis of oxalacetic acid (**67**) from acetylene dicarboxylic acid and acetic anhydride.[44] Upon heating to 100 °C, the diacid and acetic anhydride combine to form acetoxymaleic acid (**66**) which is hydrolyzed

Scheme 22



with water to give the desired product **67** (Scheme 22). In 1898, while expanding the scope of this chemistry, Michael and Bucher reported the reaction of phenylpropiolic acid with acetic anhydride.[45] This reaction, however, did not give the desired β-

Scheme 23



hydroxycinnamic acid **69**, but instead provided a naphthalene derivative that they correctly identified as 1-phenyl-2,3-naphthalene dicarboxylic anhydride (**70**). We believe this

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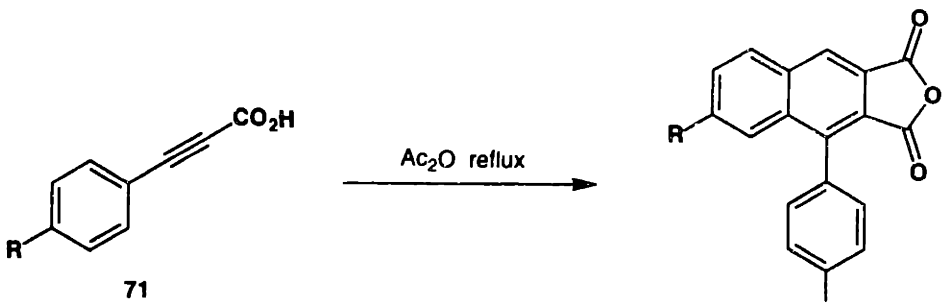
[44]Michael, A.; Bucher, J. E. *Chem. Ber.* **1895**, *28*, 2511.
[45]Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, *20*, 89.

reaction is the first example of an arenyne reacting with an alkyne to form an aromatic product in which two new carbon-carbon bonds have formed and an isomerization has occurred. Michael and Bucher continued to explore this reaction and found that ester and acid chloride derivatives of phenylpropiolic acid and substituted phenylpropiolic acids react in similar ways.[46] They proposed two possible mechanisms to account for these transformations, which will be discussed in Part III, Chapter 1.

Baddar and co-workers expanded on the chemistry of Michael and Bucher some 50 years later. In a series of papers,[47-51] these researchers examined the conditions and regiochemical course of the reaction using substituted phenylpropiolic acids. Very mild conditions promoted the reaction of phenylpropiolyl chloride with silver phenylpropiolate. The reaction could be effected by heating on a water bath, by exposing the reaction mixture to sunlight, or even by simply allowing the mixture to stand at room temperature. This led Baddar to propose the formation of the symmetric phenylpropiolic anhydride followed by cyclization.[48] In order to examine the regiochemical course of the reaction, Baddar and co-workers next studied the reactions of some unsymmetrical anhydrides. First, they

Scheme 24

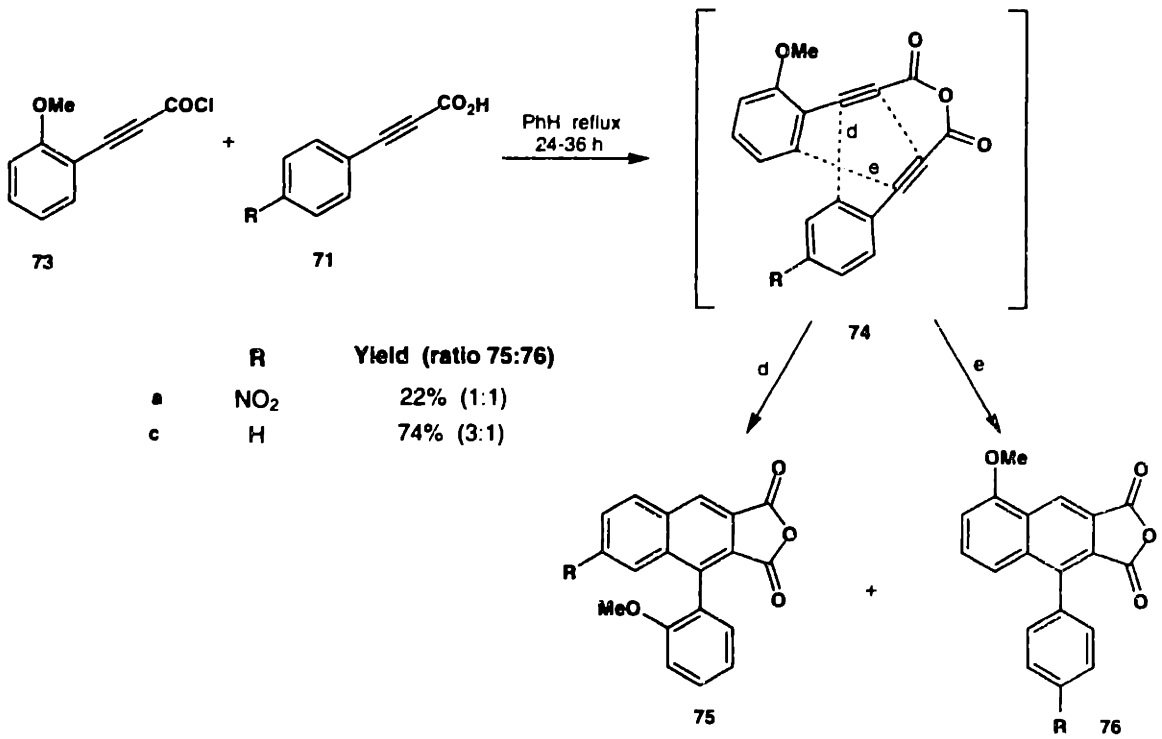


	R	time	yield
a	NO_2	2 h	65%
b	OMe	4 h	82%

[46]Bucher, J. E. *J. Am. Chem. Soc.* **1910**, *32*, 212.
[47]Baddar, F. G. *J. Chem. Soc.* **1947**, 224.
[48]Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1948**, 1267.

established the viability of *p*-nitro and *p*-methoxyphenylpropiolic acids in the dimerization (Scheme 24).[48] When heated to reflux in acetic anhydride for 2 hours, *p*-nitrophenylpropiolic acid (**71a**) gives compound **72a** in 65% yield. The *p*-methoxy substrate **71b** reacts more slowly, requiring 4 hours at reflux, to afford compound **72b** in 82% yield. Next, Baddar and co-workers formed unsymmetrical anhydrides **74** from acid chlorides **73** and acids **71**. These compounds can react to give different regiochemical products (Scheme 25). It was found that, in the case of anhydride **74c**, the acetylene attached to the more electron rich ring acts predominantly as the arenynophile (path d), attacking the unsubstituted arenyne to give mainly compound **75c**.[49] However, the nitro-

Scheme 25



	R	Yield (ratio 75:76)
a	NO_2	22% (1:1)
c	H	74% (3:1)

substituted anhydride **74a** reacts without selectivity and in poor yield. Baddar's explanation of this result refers to the electron withdrawing character of the nitro group, which he believes retards the cyclization by decreasing the electron density in the aromatic

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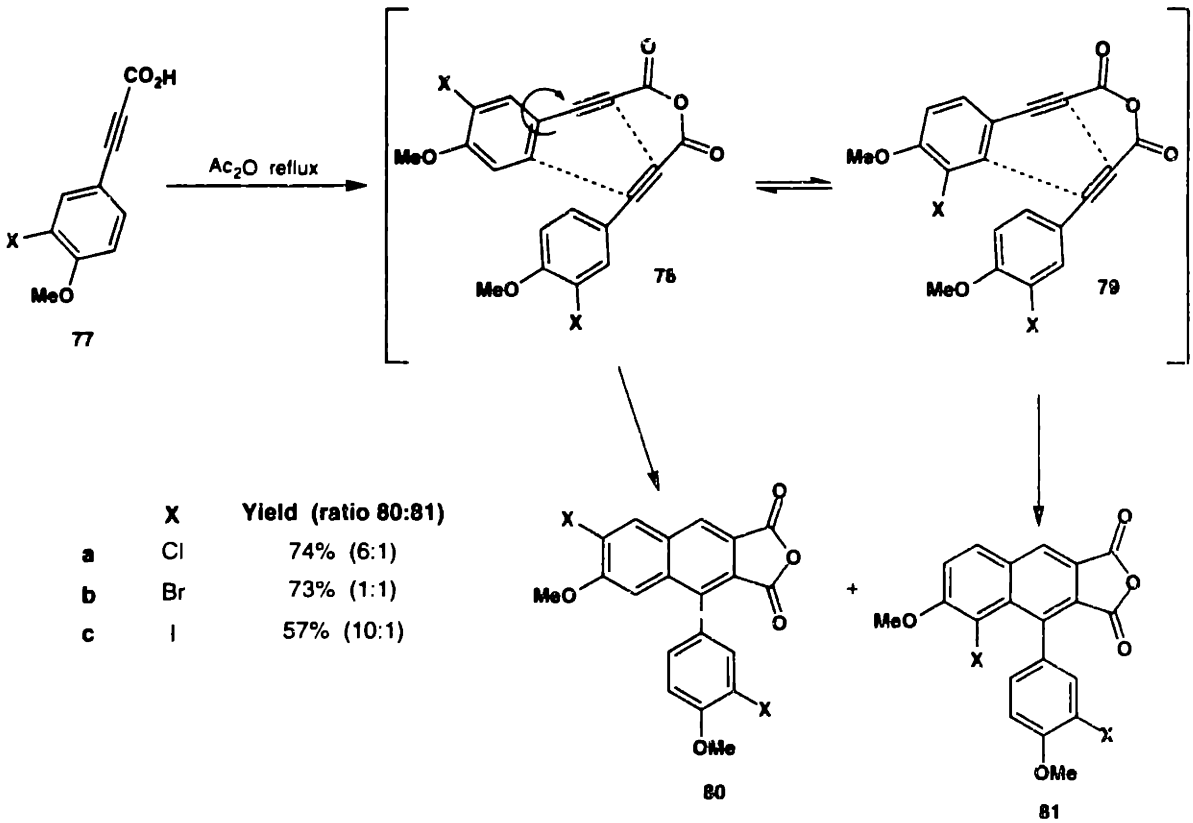
[49]Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1951**, 1844.

ring and the acetylene.

Baddar and co-workers also examined the role of steric and electronic effects on the regiochemical course of the reaction with *m,p*-disubstituted phenylpropiolic acid anhydrides and found that in most cases there is no regioselectivity.[50] However, some selectivity was observed with a series of 3-halo-4-methoxyphenylpropiolic acids, as shown in Scheme 26.[51] Thus, heating the 3-halo-4-methoxyphenylpropiolic acids **77** in acetic

Scheme 26



anhydride formed two different naphthalene products **80** and **81**. The most selective reaction involved the iodinated compound **77c** which gave a 10:1 ratio of the regioisomers; the yield, however, was only 57%. The chlorinated substrate **77a** reacted with fair selectivity with a 6:1 ratio and an improved yield of 74%. The brominated compound **77b**

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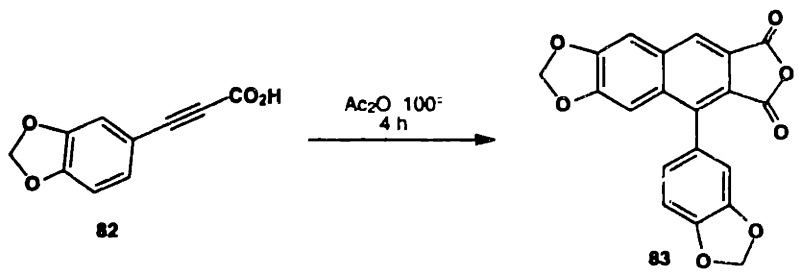
[50]Baddar, F. G.; Fahim, H. A.; Galaby, M. A. *J. Chem. Soc.* **1955**, 465.

reacted in good yield, but with no selectivity. The large size of the iodine substituent and the electron withdrawing power of the chlorine substituent both favor product **80**, which is less hindered than product **81** and results from attack via **78**, para to the electron withdrawing substituent.

Although the studies of Baddar and his co-workers did not reveal any clear trends in the dimerization of arylpropiolic acids, this work did expand the scope of the reaction. As we shall see, their work allowed others to explore the use of this dimerization in natural product synthesis.

Haworth and Kelly reported the synthesis of some compounds related to cubebinolide, a natural phenolic resin, in 1936.[52] Thermolysis of disubstituted phenylpropiolic acid **82** in acetic anhydride for 4 hours provided the anhydride **83** as yellow prisms after recrystallization from glacial acetic acid. No yield was reported, but this chemistry laid the groundwork for further use of this reaction in synthesis.

Scheme 27



Until 1963, only arylpropiolic anhydrides were explored as players in the arenyne cycloaddition. At this time, Campbell and Grimmett described the reaction of phenylpropiolic acid with propiolic acid in acetic anhydride to give 2,3-naphthalene dicarboxylic anhydride.[53] No yield was reported, and dimerization of the phenylpropiolic acid was problematic.

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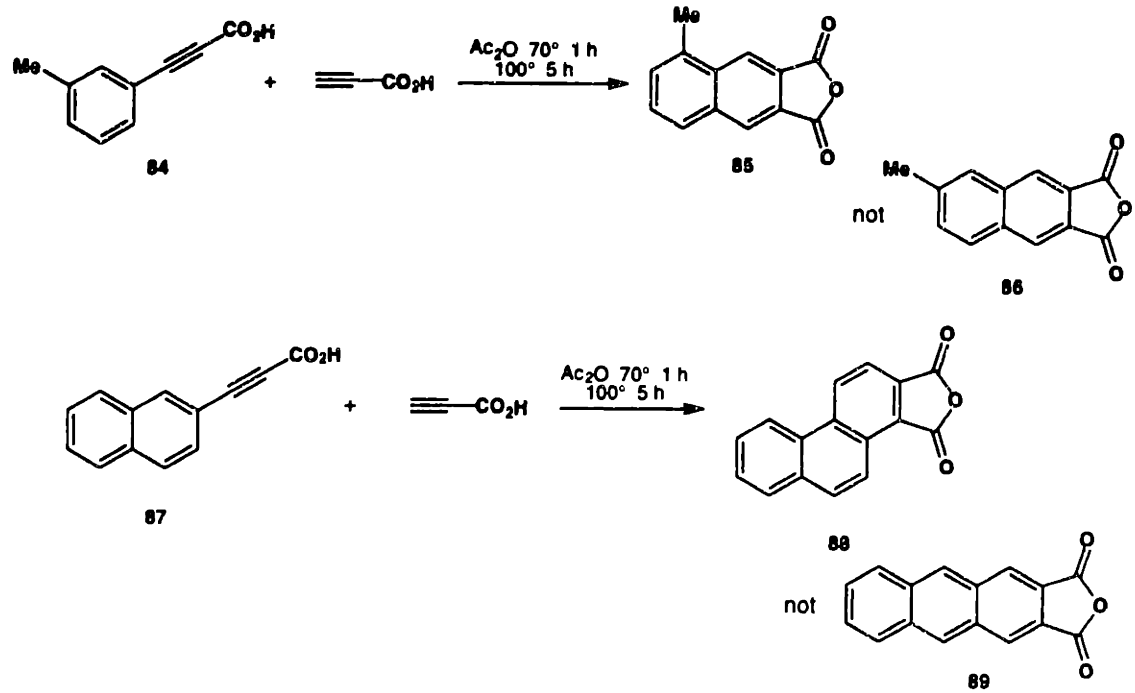
[51]Baddar, F. G.; Moussa, G. E. M.; Omar, M. T. *J. Chem. Soc. (C)* **1968**, 110.
[52]Haworth, R. D.; Kelly, W. *J. Chem. Soc.* **1936**, 745.
[53]Campbell, A. D.; Grimmett, M. R. *Aust. J. Chem.* **1963**, *16*, 854.

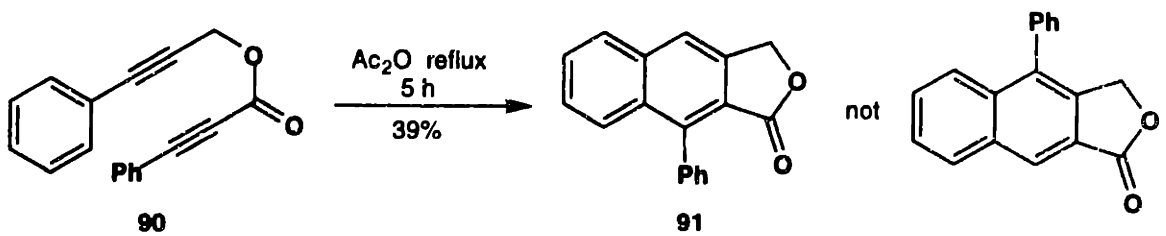
These researchers also examined the reaction of *m*-tolylpropiolic acid **84** and 2-naphthalenepropiolic acid **87** (Scheme 28), which gave products in which the new carbon-carbon bond is formed exclusively at the more hindered site. Campbell's report laid the groundwork for further exploration of this reaction.

Scheme 28



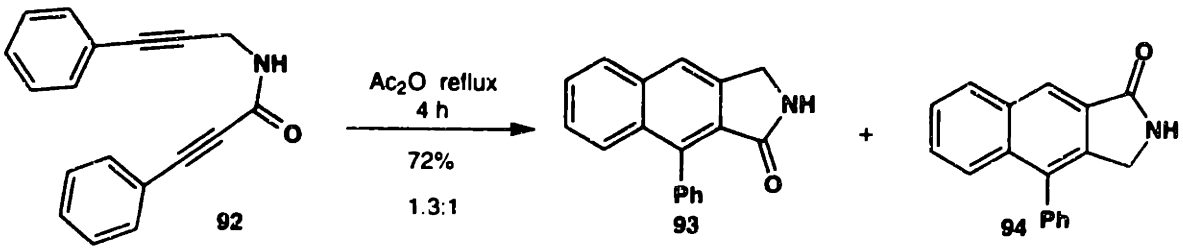
The cycloaddition chemistry of arenynes was limited to the use of anhydrides derived from acids or acid derivatives, until 1966. At that time, Klemm and co-workers

Scheme 29



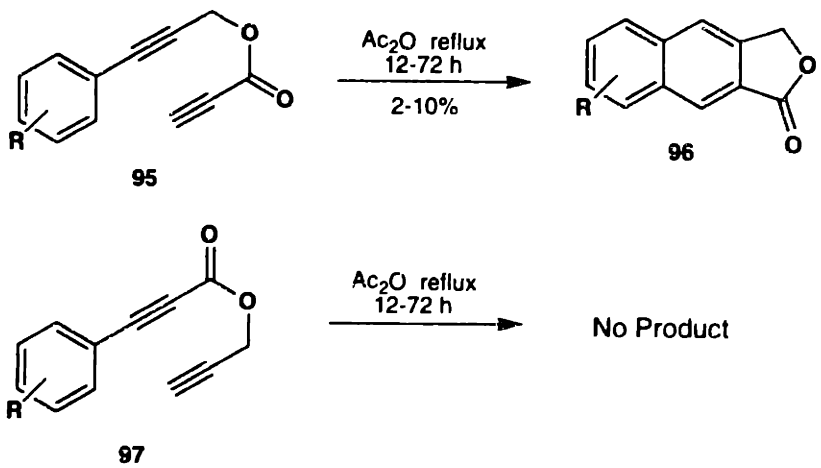
found that ester **90** gave the lactone **91** in 39% yield when heated in acetic anhydride.[54] With the unsubstituted phenylpropiolic case, only **91** was formed; however substituted phenylpropiolic esters gave regioisomeric mixtures of cycloadducts.[55] These mixtures were also observed when propargyl amides were used as substrates (Scheme 30).[55] The Klemm laboratory went on to apply this reaction to the synthesis of several lignan lactones.[56]

Scheme 30



In 1971, Klemm and co-workers published a paper outlining some of the limitations of this variation of the cycloaddition of arenynes (Scheme 31).[57] Ester **95**, with

Scheme 31



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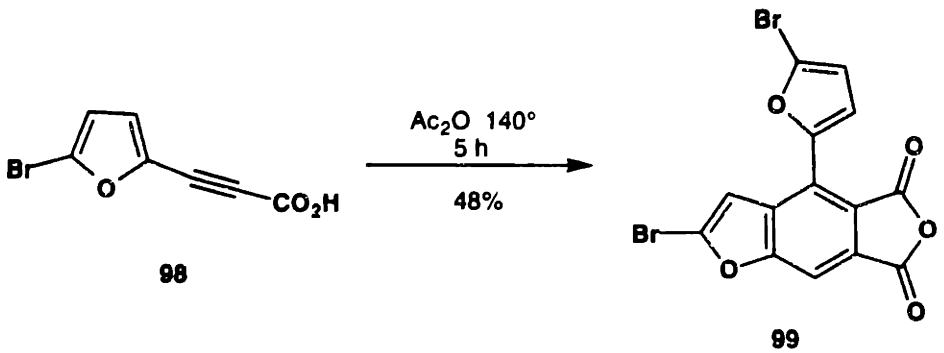
[54]Klemm, L. H.; Hsu Lee, D.; Gopinath, K. W.; Klopfenstein, C. E. *J. Org. Chem.* **1966**, *31*, 2376.
[55](a) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 2571. (b) Klemm, L. H.; McGuire, T. M. *J. Heterocyclic Chem.* **1972**, *9*, 1215.
[56](a) Klemm, L.H.; Gopinath, K. W.; Hsu Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T. M. *Tetrahedron* **1966**, *22*, 1797. (b) Klemm, L. H.; Tran, V. T.; Olson, D. R. *J. Heterocyclic Chem.* **1976**, *13*, 741.
[57] Klemm, L. H.; Klemm, R. A.; Santhanam, P. A.; White, D. V. *J. Org. Chem.* **1971**, *36*, 2169.

an unsubstituted arenynophile, provided naphthalene **96** in very poor yield. Ester **97**, with an electron deficient arenyne and an unactivated alkyne, did not undergo the cycloaddition at all. The reactions of these ester substrates have a more limited scope when compared to the anhydride arenynes, and these results may have implications for the mechanism of the reaction.

In an interesting variation on the arenyne cycloaddition, Vereshchagin and co-workers found that furylpropiolic acid **98** will also undergo a cycloaddition when heated in acetic anhydride (Scheme 32).[58]

Scheme 32



98 **99**

Results published by Stevenson in 1965 [59,60] and by Ward in 1973 [61] provided an improved procedure for the dimerization of arylpropiolic acids. Using dicyclohexyl-carbodiimide as a coupling agent, Stevenson reported the dimerization of a substituted aryl propiolic acid **100** in dimethoxyethane at -12 °C, to afford a 1:1 ratio of **101** and **102** in 40% yield (Scheme 33). The reaction required 24 hours. Stevenson did not comment on the formation of this monobrominated cycloadduct **102** until a later paper where he mentions the formation of a second dibrominated cycloadduct with the bromine at C-5 rather than at C-4.[60] Stevenson states that the bromine lost in monobromonaphthalene **102** could be implicated in the formation of the C-5 brominated cycloadduct, but he does not

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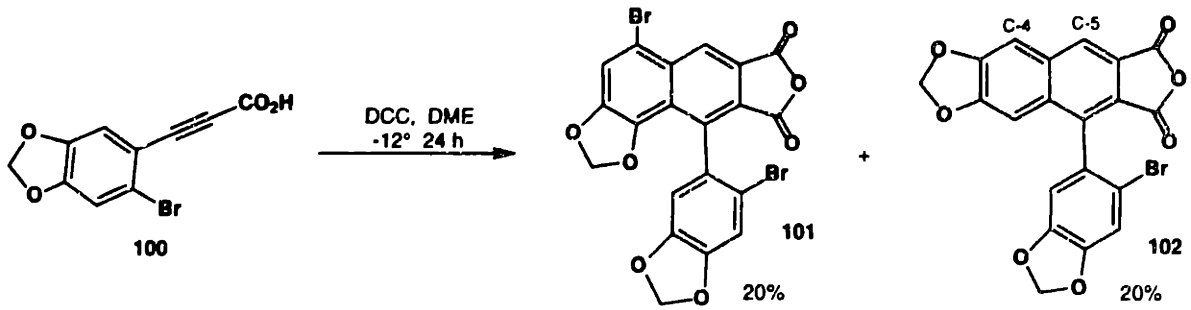
[58]Vereshchagin, L. I.; Korshunov, S. P.; Aleksandrova, S. L.; Bol'shedvorshaya, R. L. *J. Org. Chem. USSR (Engl. Transl.)* **1965**, *1*, 967; *Zh. Org. Khim.* **1965**, *1*, 960.
[59]Brown, D.; Stevenson, R. *J. Org. Chem.* **1965**, *30*, 1759.
[60]Holmes, T. L.; Stevenson, R. *J. Chem. Soc. (C)* **1971**, 2091.

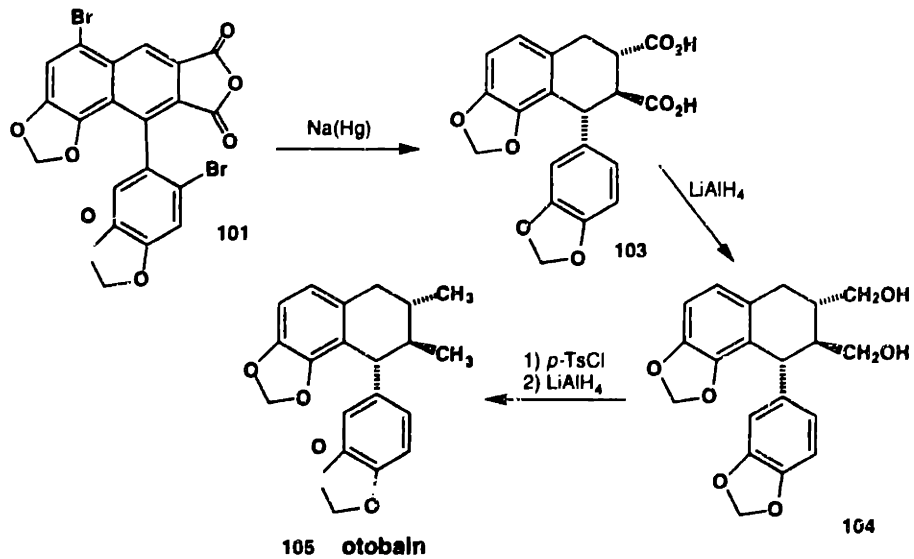
offer a mecnanism or any data on the amount of each compound produced in the reaction. Ward's more extensive account reported the dimerization of several arylpropiolic acids in ethyl acetate or methylene chloride at 0 °C or room temperature. Yields for these reactions, which took several hours, were mainly in the eighties and nineties, a large improvement over those previously reported.

Scheme 33



Stevenson used his mild coupling procedure in the synthesis of several natural

Scheme 34



products, including otobain[62] and helioxanthin.[60] Both of these compounds are members of the lignan family, a group of 1-arylnaphthalene lactone natural products with a wide

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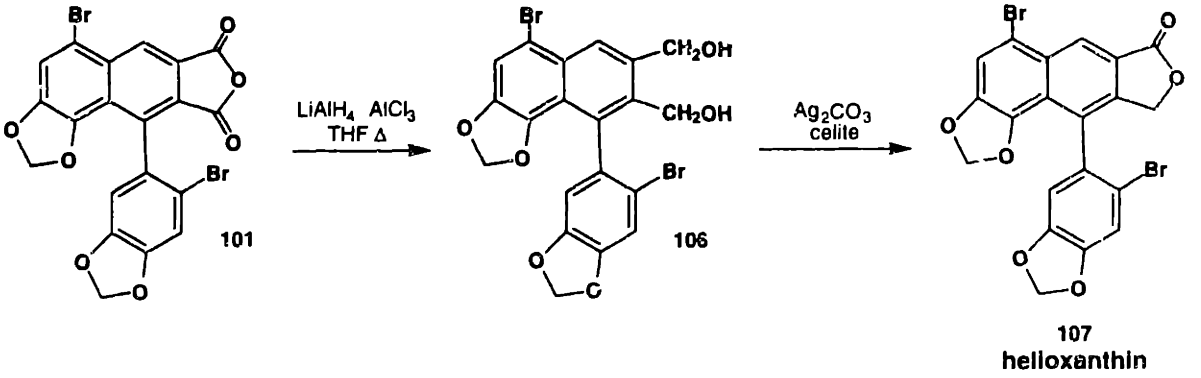
[61]Cadby, P. A.; Hearn, M. T.W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557.

[62](a) Brown, D.; Stevenson, R. *Tetrahedron Lett.* **1964**, 3213. (b) Maclean, I.; Stevenson, R. *Chem. Ind.* **1965**, 1379. (c) Maclean, I.; Stevenson, R. *J. Chem. Soc. (C)* **1966**, 1717.

range of biological activity.[63] Dibromonaphthalene **101** is a common intermediate in both syntheses. In the synthesis of otobain (Scheme 34), debromination and reduction of the B ring of **101** with sodium amalgam gave the dicarboxylic acid **103**. Reduction of the diacid with lithium aluminum hydride, conversion of the diol **104** to the bis-*p*-toluenesulfonate, and further reduction gave otobain (**105**). Heiloxanthin was synthesized in two steps from dibromonaphthalene **101** (Scheme 35). Reduction of the anhydride to the diol **106**, and selective oxidation with Fétizon's reagent gave the desired lignan **107**.

Scheme 35



Stevenson also reported highly efficient dimerizations of arylpropiolic acids in the presence of an acid scavenger.[64] Phenylpropiolic acids **72c** and **82** gave 1-phenyl-2,3-naphthalene dicarboxylic anhydrides **70** and **83** in 88% and 87% yields, respectively, when treated at room temperature with 0.5 equivalent of thionyl chloride in the presence of the acid scavenger P4-VP, a co-polymer of 4-vinylpyridine. In the second example, note the formation of the less hindered product, a result that differs from the ester arenyne case.[57]

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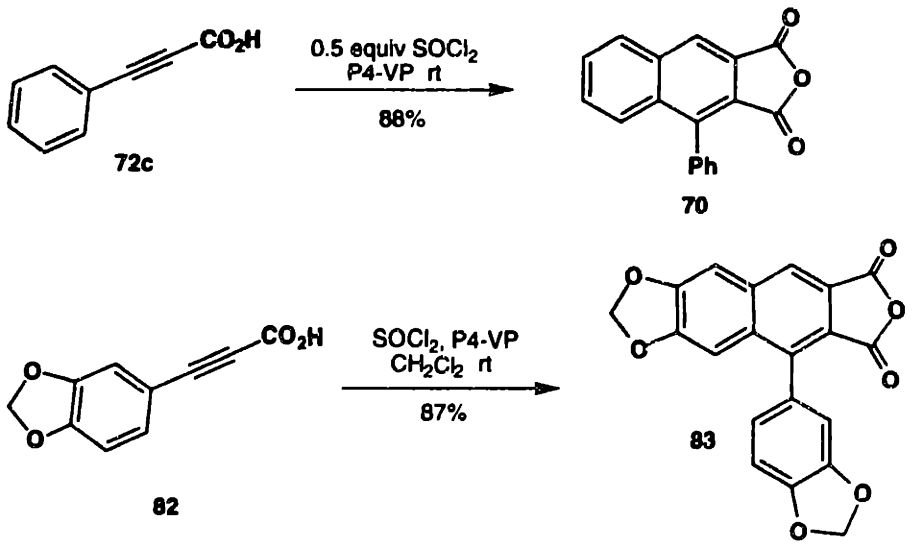
[63]For a review, see: MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207.
[64]Stevenson, R.; Weber, J. V. *J. Natural Products* **1989**, *52*, 367.

Scheme 36



By 1990, the dimerization of arenynes had become well advanced, providing a viable entryway into the construction of naphthalene and other aromatic derivatives. As we have seen, these reactions can be carried out under mild conditions and proceed in good yields. In some cases, the reactions occur with good regioselectivity. Proof of the utility of this reaction is its use in several total syntheses, as described by Klemm[56] and Stevenson.[60,62] In the next section, the inter- and intramolecular reactions of enynes with alkynes and alkenes will be discussed.

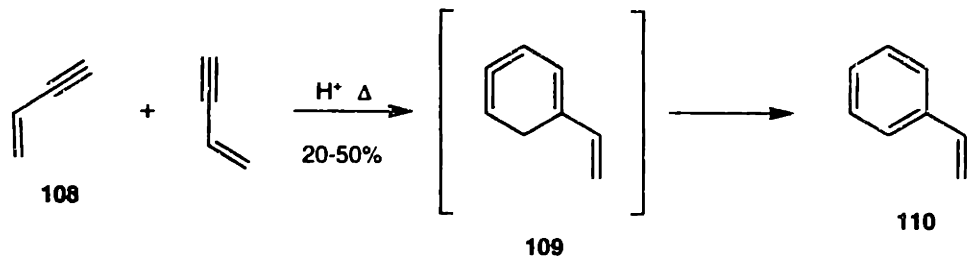
Intermolecular Cycloadditions of Conjugated Enynes

The exploration of the cycloadditions of conjugated enynes began shortly after Michael and Bucher's report on the dimerization of phenylpropiolic acids. Interest in enynes was not based solely upon Michael and Bucher's work, however. The polymerization of alkenes and a curiosity about the behavior of conjugated systems prompted many researchers to investigate the reactivity of conjugated enynes.

Vinylacetylene, as the simplest conjugated enyne, was studied by H. B. Dykstra

who was interested in its reactivity in polymerization reactions.[65] In 1934, he found that when vinylacetylene was heated in the presence of 1 to 10 mole percent of various acids or anhydrides, styrene was formed in 20 to 50% yield based on recovered starting material (Scheme 37). Heating the enyne **108** in the presence of Cu_2Cl_2 led to a highly conjugated polymer and heating the compound without any additive gave a polymer containing cyclobutane rings. For the protic acid catalyzed reaction, Dykstra proposed a cyclic allene intermediate **109** resulting from a "Diels-Alder diene" reaction; he comments that the proposed intermediate **109** appears to be "stereochemically impossible" and suggests a concomitant cycloaddition and isomerization to give the product directly.

Scheme 37



H+= AcOH, HCl, phthalic anhydride, etc.

In 1937 and 1938, German researchers reported the reactions of an electron rich enyne (**111**) with two enynophiles.[66] Maleic anhydride was found to react with the enyne to give the tetrahydrophenanthrene product **112** in 43 to 61% yield. This product can continue to react with maleic anhydride in a typical Diels-Alder reaction to give the expected bicyclic system **113** (Scheme 38). These workers also report the reaction of this enyne with a less activated enynophile, methyl propiolate. This reaction requires heating, but the yield is quite good, providing the dihydrophenanthrene products **114** and **115** in 60% overall yield (Scheme 39). Compound **115** is the major product of this reaction.

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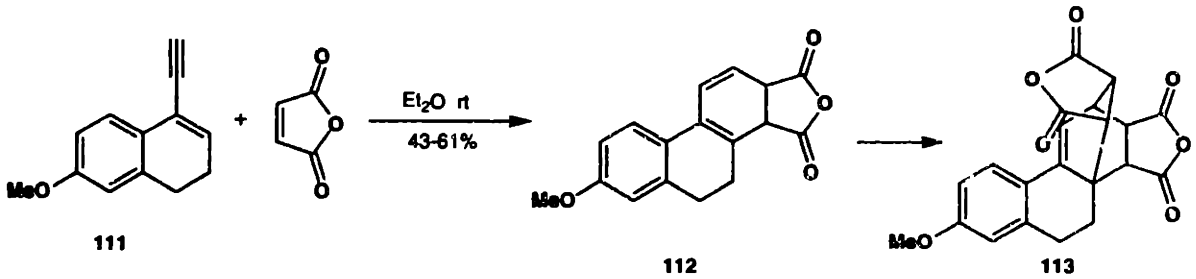
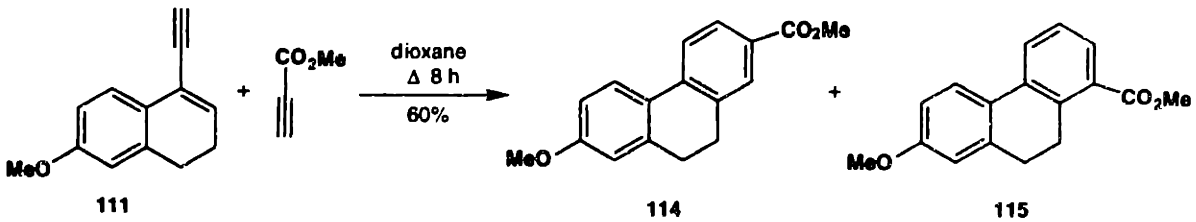
[65]Dykstra, H. B. *J. Am. Chem. Soc.* **1934**, *56*, 1625.

Scheme 38



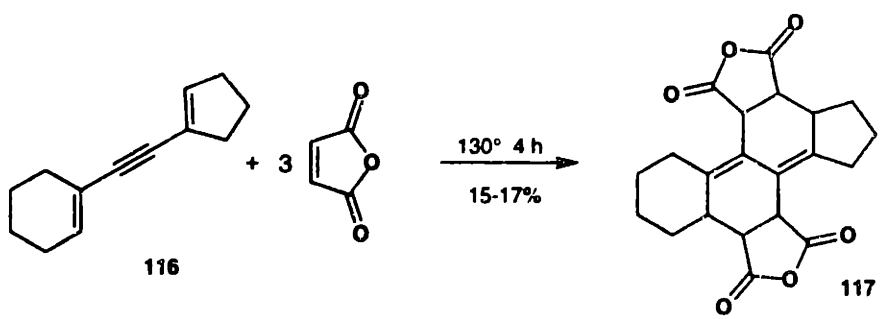
Recently, this work has been revisited by Miller and Ionescu who report that the reaction does not proceed unless an acid such as HCl is present.[67] They present a mechanism for this reaction which will be discussed in full in a later chapter.

Scheme 39



In the 1940's, Lewis J. Butz and co-workers reported the synthesis of various steriodal compounds using a dienyne in a double cycloaddition. For example, they found that the dienyne **116** would add two equivalents of maleic anhydride to give compound

Scheme 40



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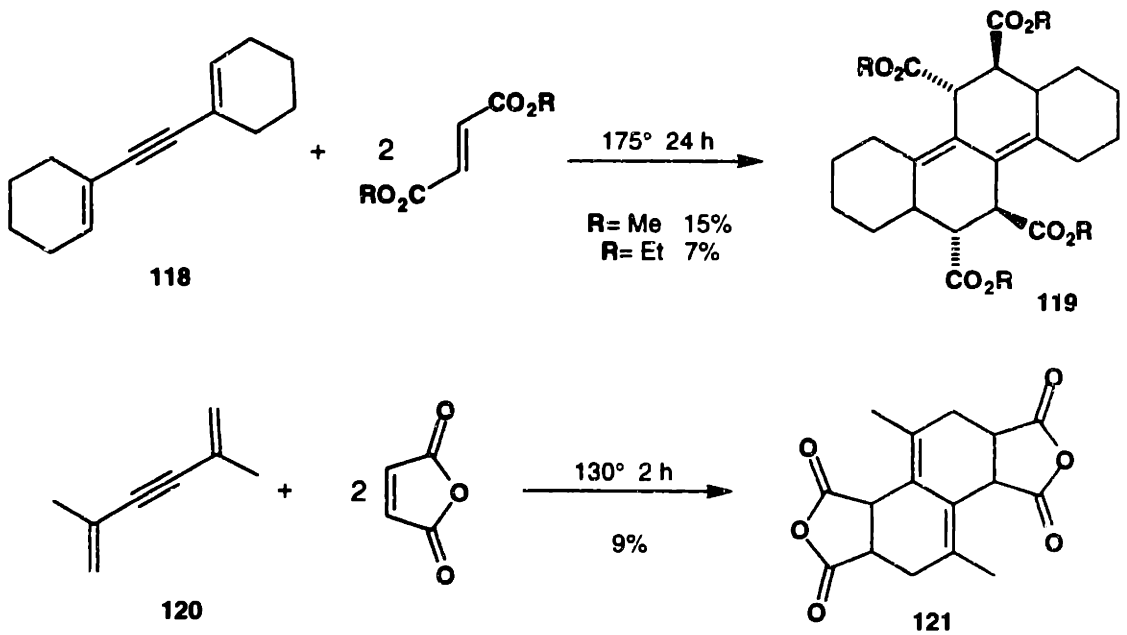
[66]Dane, E.; Höss, O.; Bindseil, A. W.; Schmitt, J. *Ann. Chem.* **1937**, *523*, 39. Dane, E.; Höss, O.; Schmitt, J.; Schön, O. *Ann. Chem.* **1938**, *536*, 183.
[67]Miller, B.; Ionescu, D. *Tetrahedron Lett.* **1994**, *35*, 6615.

117 with the steroid backbone in one step (Scheme 40), albeit in very low yield.[68] Best results were obtained with the use of three equivalents of maleic anhydride. Butz explored these double addition reactions with several dienynes and enynophiles and found that most of these reactions proceeded in low to moderate yields.[69] Two further examples are shown in Scheme 41. The trans relationship of the esters in compound **119** was established by comparison with the tetraester obtained by hydrolysis and esterification of dianhydride

Scheme 41



117.[69a] Butz also proposed several interesting mechanisms for this reaction,[70] which will be discussed later. Miller and co-workers have recently confirmed the stereochemistry depicted in Scheme 41 for the products.[71]

In 1952, Ray and co-workers reported the use of maleimide in reactions similar to

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[68]Butz, L. B.; Gaddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Am. Chem. Soc.* **1940**, *62*, 995. Butz. L. W.; Joshel, L. M. *J. Am. Chem. Soc.* **1941**, *63*, 3344.

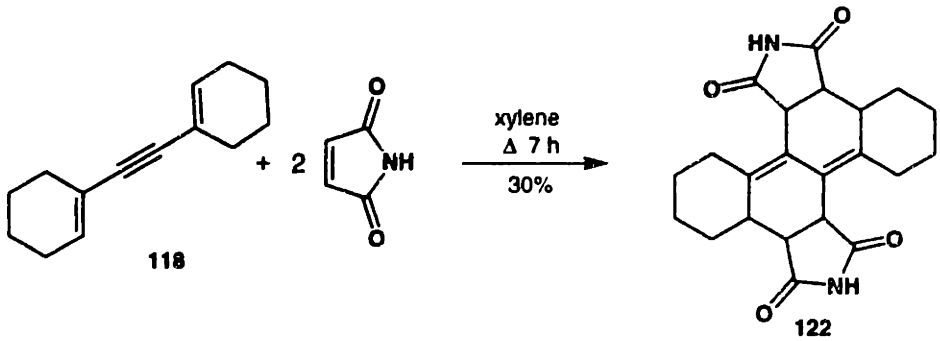
[69](a) Butz. L. W.; Joshel, L. M. *J. Am. Chem. Soc.* **1942**, *64*, 1311. (b) Nudenberg, W.; Butz, L.W. *J. Am. Chem. Soc.* **1943**, *65*, 2059. (c) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J. *J. Am. Chem. Soc.* **1947**, *69*, 924.

[70]Butz, L. B.; Gaddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940**, *5*, 379.

[71] Ionescu, D.; Silverton, J. V.; Dickinson, L. C.; Miller, B. *Tetrahedron Lett.* **1996**, *37*, 1559.

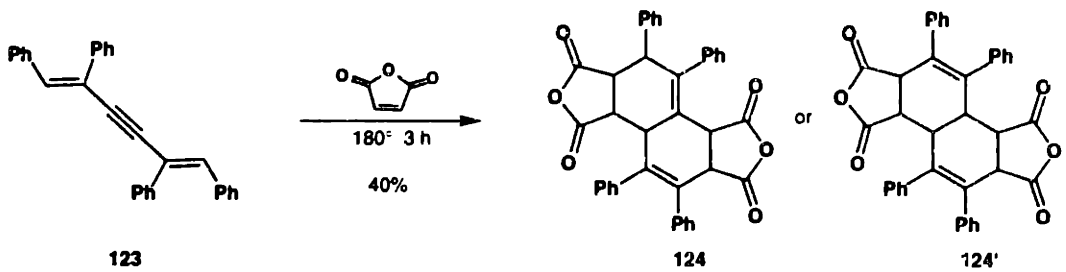
those of Butz.[72] Maleimide added twice to 1,1'-dicyclohexenylacetylene (**118**) to give the hexacyclic product **122** in 30% yield (Scheme 42). These authors claim that this reaction affords one stereoisomer, but no evidence for this claim was presented. Ray found that other less activated alkenes such as acrolein, acrylonitrile and crotonic acid did not react with the dienynes.

Scheme 42



Other workers have reported similar double condensation reactions with activated alkenes. Israelashvili and Edlitz-Pfeffermann reported the reaction of tetraphenyl dienyne **123** with two equivalents of maleic anhydride at 180 °C. This reaction provided one of the dianhydrides **124** or **124'** in 40% yield.[73]

Scheme 43



A. W. Johnson discovered that acetylenes do not react in this double addition reaction as readily as alkenes do. He found that acetylene dicarboxylic acid did not react with 2,5-dimethyl-1,5-hexadien-3-yne **120** when heated in a sealed tube.[74] This, along

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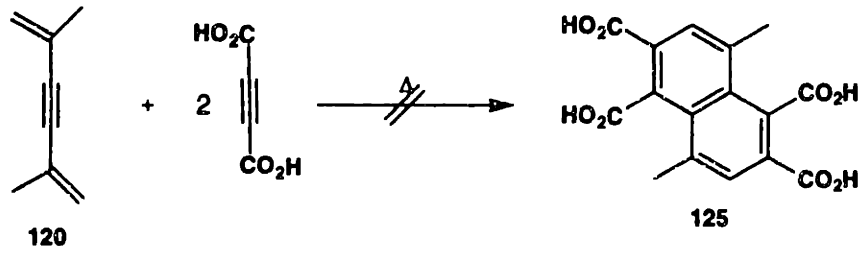
[72]Ray, F. E.; Sawicki, E.; Borum O. H. *J. Am. Chem. Soc.* **1952**, *74*, 1247.
[73]Israelashvili, S.; Edlitz-Pfeffermann, J. *J. Am. Chem. Soc.* **1952**, *74*, 5780.
[74]Johnson, A. W. *J. Chem. Soc.* **1945**, 715.

with some other results that are discussed later, led him to believe that the intermolecular reaction of enynes with enynophiles is more difficult than the intramolecular one.

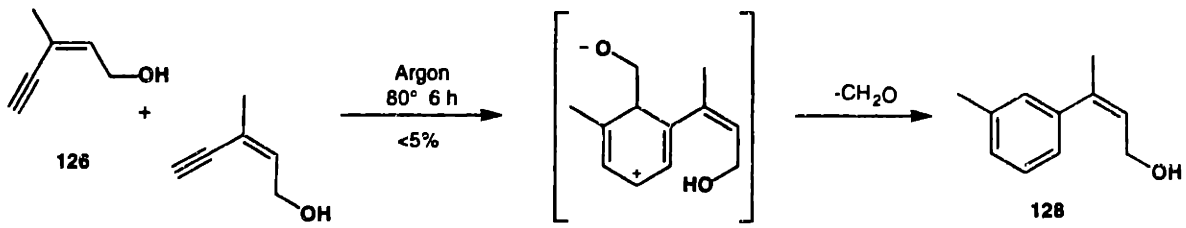
Scheme 44



120 125

More recently, Nekipelova and Fentsov found that allylic alcohol **126** dimerized (and polymerized) upon heating at 80 °C for 6 hours.[75] The styrene product **128**, which

Scheme 45



126 127 128

they observed to form in less than five percent yield, has lost a molecule of formaldehyde. The authors propose that fragmentation occurs from a zwitterionic intermediate like **127**.

The intermolecular reaction of enynes with alkenes and alkynes do proceed, although problems with efficiency and selectivity exist. Several workers have examined the corresponding intramolecular reactions of conjugated enynes. Taking advantage of the entropic differences in this reaction has led to increased yields in some cases.

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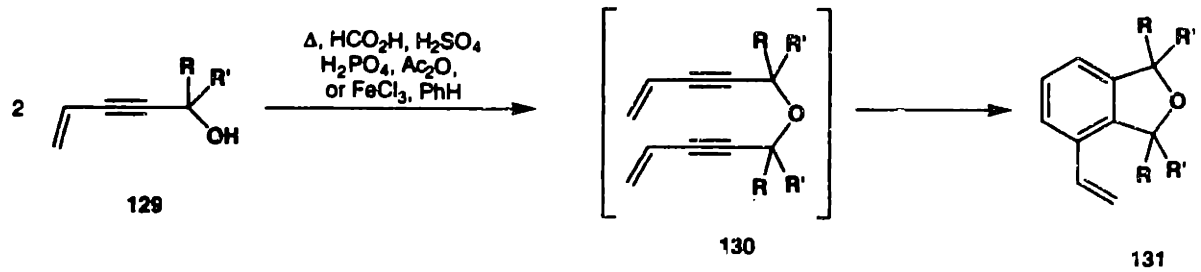
[75]Nekipelova, T. D.; Fentsov, D. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1989**, *38*, 1885; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 2052.

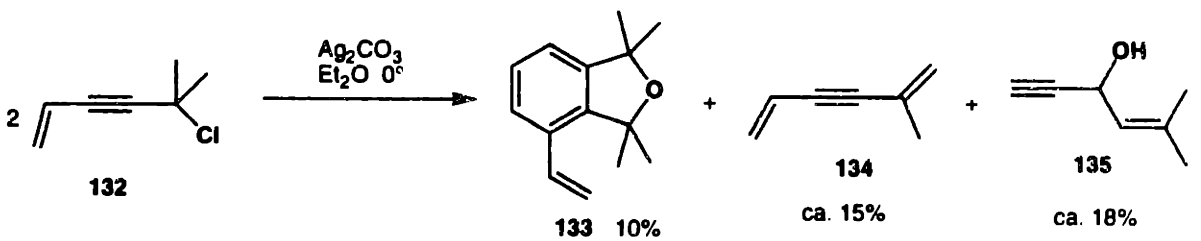
Nazarov and co-workers have investigated the dimerization of various propargylic alcohols under thermal and acidic conditions (Scheme 46).[76] These workers found that

Scheme 46



the ethers derived from tertiary propargylic alcohols (e.g. R=R'=Me) cyclize in moderate yields (40-60%), that secondary ethers (R=Me, R'=H) cyclize in low yields (20-25%), and that primary ethers do not cyclize at all. In order to determine whether ether formation precedes ring formation, Nazarov et al. attempted to isolate the symmetric ether **130** (R=R'=Me) by forming it under mild conditions. Thus as shown in Scheme 47, chloride

Scheme 47



132 was treated with silver carbonate in ether at 0 °C. Surprisingly, no acyclic ether was isolated, but the vinylisocoumarin **133** was isolated in 10% yield, along with vinylacetylene **134** and dimethylvinylethynyl carbinol **135**. Further attempts to isolate the

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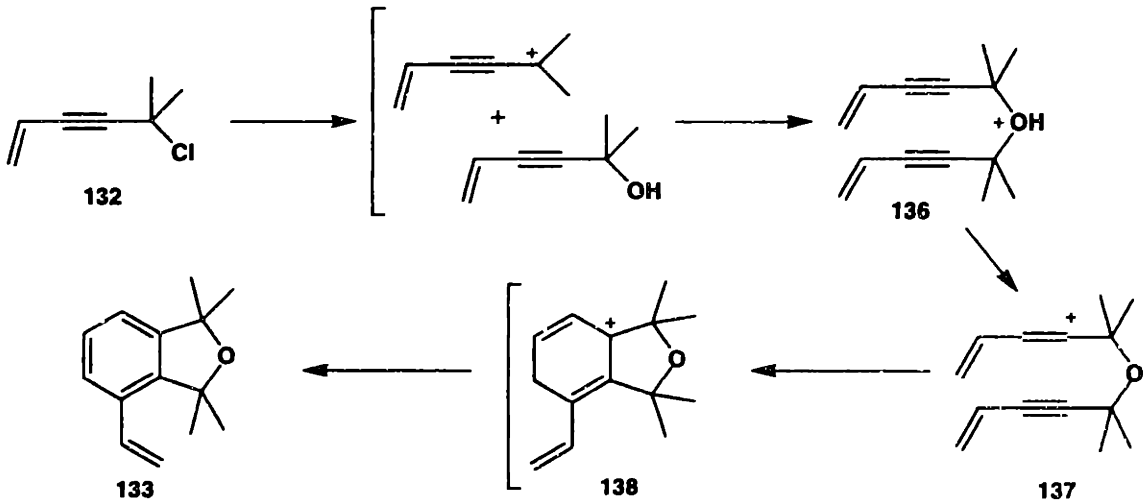
[76] Nazarov, I. N.; Verkholetova, G. P., Torgov, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, *29*, 3277.

proposed ether intermediate **130** were unsuccessful.

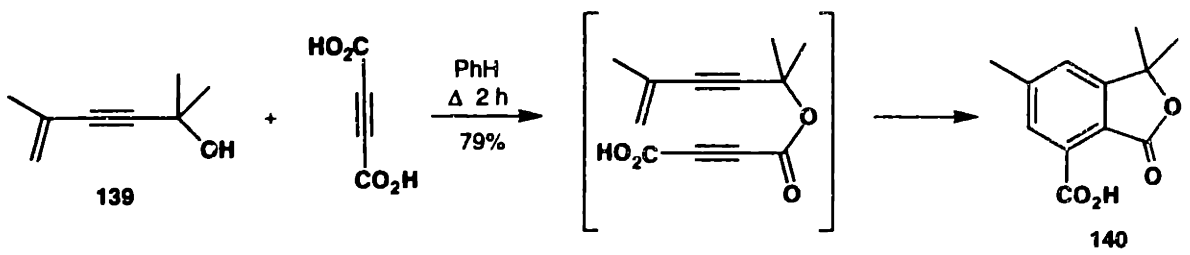
Nazarov also discussed the mechanism of these cycloadditions, and to the best of our knowledge, was the first to propose the involvement of a vinyl cation in the reaction. Specifically, as outlined in Scheme 48, Nazarov proposed that S_N1 displacement generates the protonated ether **136**, and proton transfer to the acetylene of one enyne gives the dienyl cation **137**. [4+2] Cycloaddition of the vinyl cation species provides the cyclohexadienyl cation **138**, which then undergoes elimination to produce the aromatic product **133**. Further discussion of this mechanism follows at the end of this chapter and in Part III.

Scheme 48



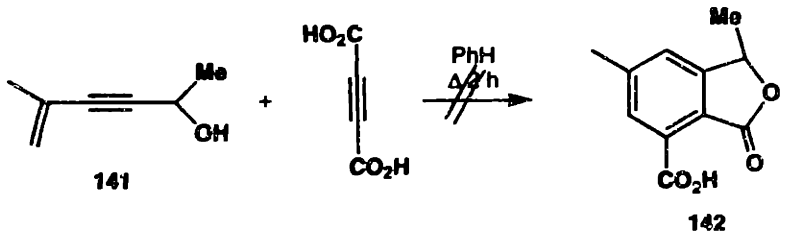
In 1945, A. W. Johnson reported the reaction of an enyne alcohol (**139**) with

Scheme 49



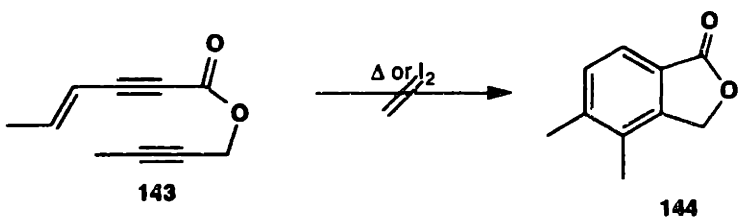
acetylene dicarboxylate in benzene or ethyl acetate to give the cycloaddition product **140** in 79% yield.[74] Esterification is suggested to occur first, as shown in Scheme 49, followed by cycloaddition. Johnson found that the secondary alcohol hex-3-en-5-yn-2-ol (**141**) did

Scheme 50



not provide the desired cycloadduct after thermolysis in benzene in the presence of acetylene dicarboxylic acid. Once again, as Stevenson found with arenynes,[64] esters are less reactive than other systems in the cycloaddition. Interestingly, ester **143**, which is an inverse electron demand substrate, did not react when heated or treated with iodine (Scheme 51).

Scheme 51



In 1974, Armenian researchers reported the intramolecular cycloadditions of several unsaturated ethers (Scheme 52).[77] The enyne ether **145** is transformed to aromatic ether **146** when heated in refluxing benzene for 10 hours. The yield of this reaction is very high; the unactivated acetylene **147**, however, requires higher temperatures and longer reaction times to give the aromatic product **148** in only 19% yield.

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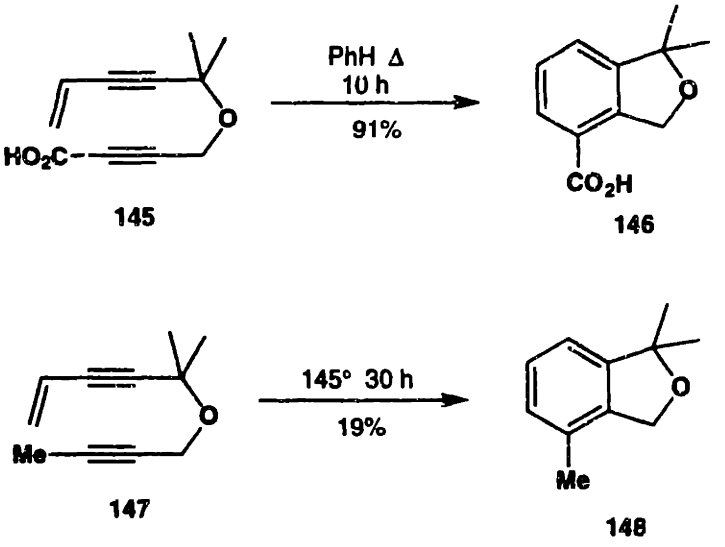
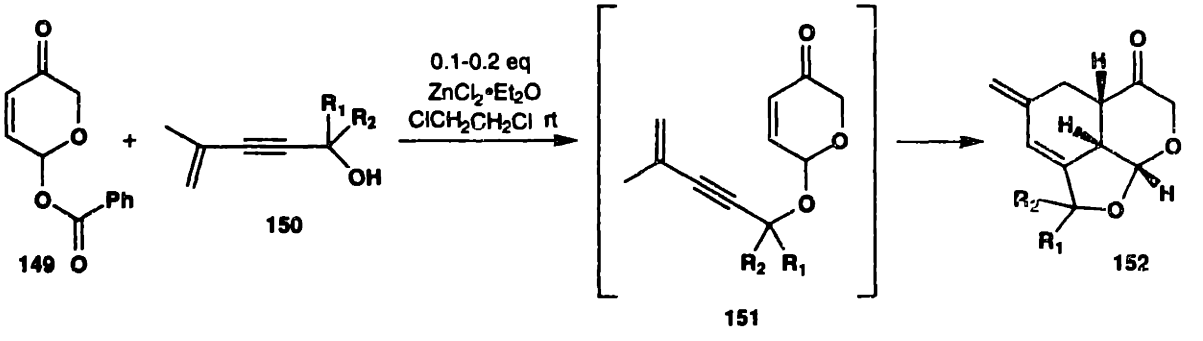
[77]Hakopian, L. A.; Gesalian, G. I.; Grigorian, S. G.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 764. Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 768. Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1975**, *28*, 72.

Scheme 52



While we were exploring the scope and mechanism of the intramolecular cycloaddition of conjugated enynes, Hoffmann and co-workers reported a detailed investigation of various intramolecular enyne cycloadditions of the type illustrated in

Scheme 53



Scheme 53.[78] Treatment of the acetal **149** and enyne alcohol **150** with a Lewis acid provides acetal **151**. This new acetal then undergoes a cycloaddition to give the tricyclic product **152**. The yields for this reaction vary depending on substitution, but can be as high as 42%. When acetal **151** was prepared by a two step procedure, isolated, and then

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[78]Hoffman, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999.

subjected to the reaction conditions, the yields did not improve. Hoffmann's discussion of the mechanism of this reaction will be presented in Part III.

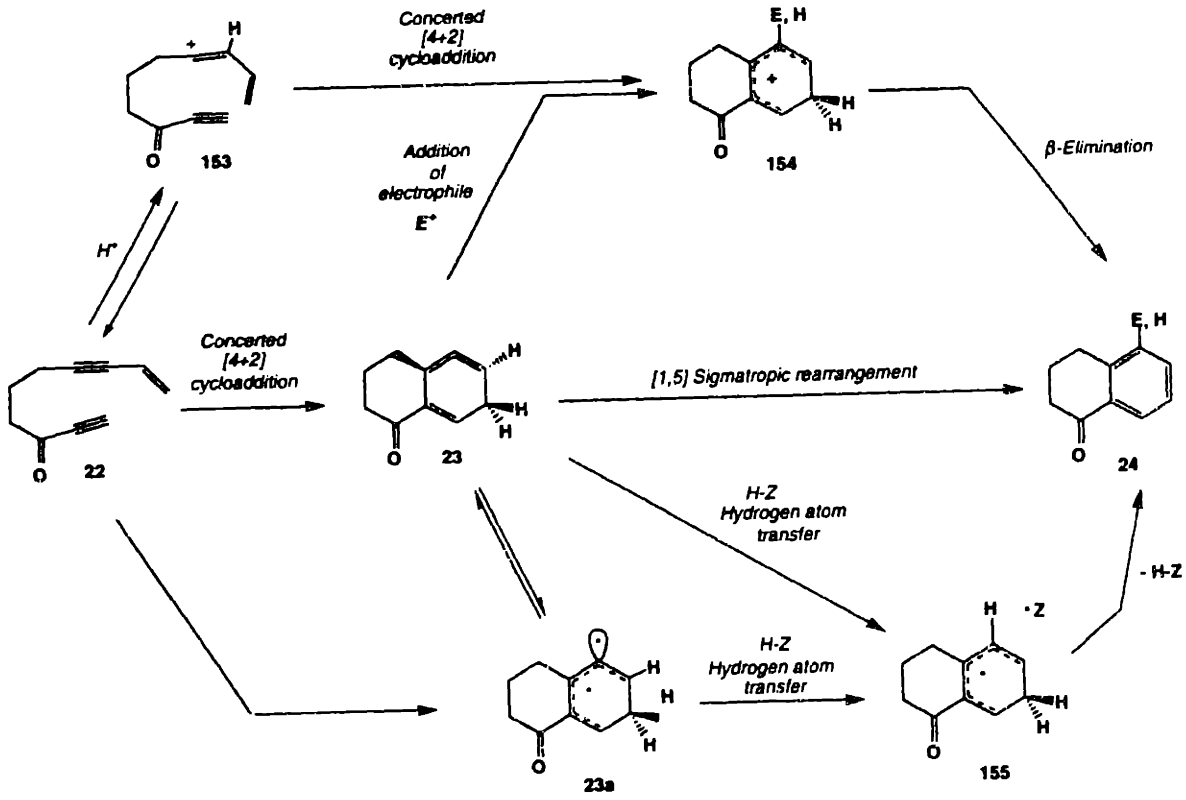
In summary, the literature has many examples of inter- and intramolecular cycloadditions of enynes and arenynes. All of these reactions have oxygen or nitrogen in the connecting chain and are used to form heterocycles. In general, these reactions involve carboxylic acids and their derivatives, alcohols, and/or amines, which are coupled to form anhydrides, esters, ethers, and amides. These coupled substrates then cyclize with heating in the presence of an acid or anhydride. Recently, more mild conditions have been found to promote the cycloaddition, and these reactions proceed at or below room temperature in good yields. In some cases, silver salts, which are known to have an affinity for acetylenic bonds, have been shown to promote the reaction; however, the exact role of these salts is not clear. They may simply be facilitating formation of the anhydride or ether formation, or they may actually be promoting the cycloaddition by complexation to the acetylene of the enyne. Some work has been done in promoting the reaction with Lewis acids.

A Brief Introduction to the Mechanism of Enyne Cycloadditions

Many different mechanisms can be and have been proposed for this reaction. This section presents several of the different possibilities. A thorough discussion of the mechanism is the subject of Part III.

As shown in Scheme 54 for the intramolecular version of the reaction, the transformation of the enynesubstrate into an aromatic or dihydroaromatic species can be separated into two distinct stages. The first involves the formation of the two new carbon-carbon bonds, the transformation of enyne **22** to an intermediate (**154**, **23**, or **23a**); the second involves the isomerization of the newly formed cyclic system to the aromatic product. In the first stage, we propose that the cycloaddition proceeds via a concerted, or a very fast stepwise, reaction. Others have proposed stepwise bond formation, however this type of mechanism does not avoid the need for an isomerization step.

Scheme 54



The stepwise or concerted cycloaddition proceeds through a cyclic allene (**23**), cationic (**154**), or biradical intermediate (**23a**). A [4+2] cycloaddition of the enyne with the enynophile could give a highly strained cyclic allene **23** that may exist in equilibrium with the planar diradical species **23a**, as discussed in Chapter 1 and first suggested by Dykstra[65] and Butz.[70] Alternatively, radical cyclization of the enyne would give the diradical species **23a** directly. Finally, electrophilic attack on the enyne could give the vinyl cation **153** as originally suggested by Nazarov.[76] This vinyl cation could then undergo a Diels-Alder reaction to give the cyclohexadienyl cation **154**.

Once the two new carbon-carbon bonds have been formed, the intermediates will react to give the aromatic, or in the case of an alkene enynophile the dihydroaromatic, product. Cyclic allene **23** can be quenched by addition of an electrophile to the central carbon of the allene. This electrophilic addition to the allene would provide the cyclohexadienyl cation **154**, which can eliminate a proton and generate the aromatic

product **24**. Addition of a hydrogen or other atom to the cyclic allene would give a planar cyclohexadienyl radical **155**. Radical **155** could also be formed by reaction of the highly reactive sp^2 radical in the biradical species **23a** with an atom source. The cyclohexadienyl radical **155** would then lose a hydrogen atom to form aromatic product **24**. Finally, in a completely intramolecular mechanism, the cyclic allene **23** could undergo a [1,5]-sigmatropic shift to give the aromatic product **24** directly.

Scattered reports of cycloadditions of enynes and arenynes have appeared throughout most of this century. Examples are known to proceed when substrates are heated, irradiated, or treated with Lewis or protic acids. A variety of interesting mechanisms have been proposed for these reactions. However, at the outset of our studies, relatively little was known about the scope of the reaction and its potential utility in organic synthesis. In addition, almost nothing was known about the stereochemical course of the reaction involving olefinic enynophiles, and no examples had been reported leading to completely carbocyclic products.

The goal of my thesis research has been to systematically investigate the scope and synthetic utility of the intramolecular [4+2] cycloaddition of conjugated enynes as applied to the construction of carbocyclic compounds. This work is the subject of Part II of this thesis. We have also carried out studies on the mechanism and stereochemistry of the reaction, and this work is the subject of Part III.

Part II

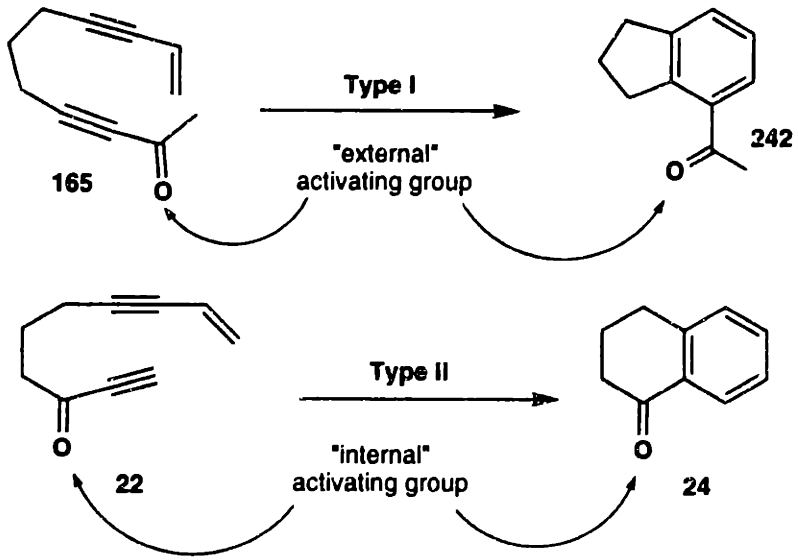
Intramolecular Cycloadditions of Conjugated Enynes: Scope

Chapter 1

Synthesis of Cycloaddition Substrates

For the purpose of discussion, the enyne substrates prepared for our investigation of the scope of the intramolecular cycloaddition are classified as type I and type II. Type I substrates are enynes like compound **165** (Scheme 55) in which the enynophile is activated by a withdrawing group that is exocyclic to the newly formed rings. Type II substrates are

Scheme 55



enynes like compound **22**, in which the enynophile is activated by a group incorporated in the connecting chain that links the enyne to the enynophile moiety. In this section, most of the enynophiles are acetylenic derivatives, although as we shall see later, alkene enynophiles also undergo this reaction, and the preparation of some of these substrates is also discussed.

This chapter is organized into a discussion of the synthesis of type I substrates, followed by a section on type II substrates. In exploring the scope of the reaction of type I substrates, three issues were examined. Substrates with different enyne substitution

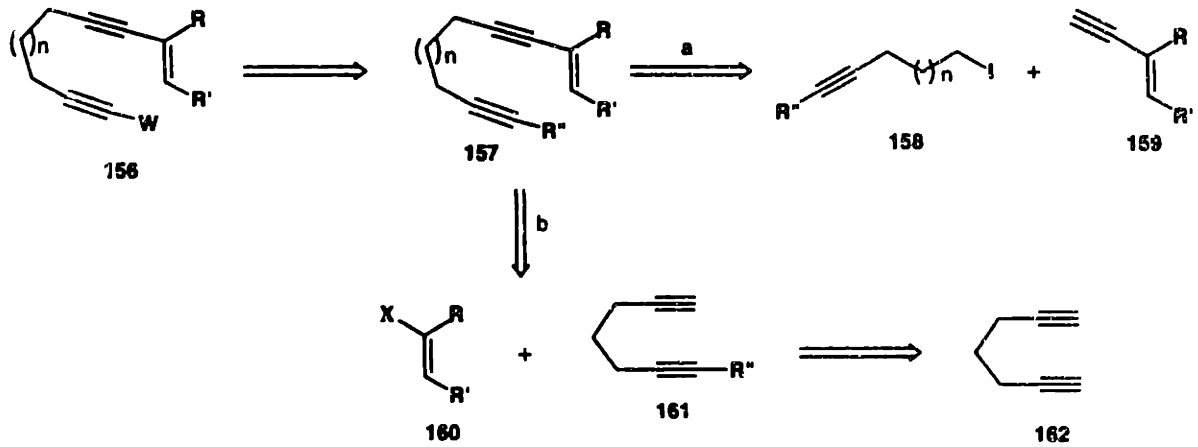
patterns, different numbers of carbons connecting the enyne and enynophile (different tether lengths), and different enynophile activating groups were synthesized and subjected to different cycloaddition reaction conditions. Work on the scope of the type II cycloaddition was started by a visiting scientist in our laboratory, Roberto Fernández de la Pradilla, who studied the effects of changing the tether length and of substituting the enyne and enynophile with different withdrawing groups. Work on these substrates continued with the examination of the effect of enyne substitution on the reaction.

This chapter discusses the synthesis of the cycloaddition substrates, and Chapter 2 focuses on our study of the cycloaddition reactions of these compounds. The final chapter in this section includes a discussion of some other results obtained during the exploration of the scope of this reaction in the Danheiser laboratory, along with a summary of our work in this area.

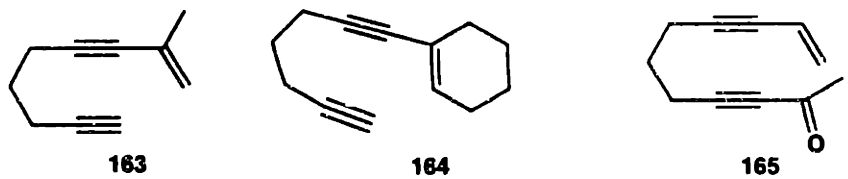
Synthesis of Type I Cycloaddition Substrates

One of the attractive features of the enyne cycloaddition strategy relative to the Diels-Alder reaction is that the enyne substrates are ofter easily prepared by taking advantage of the wide range of carbon-carbon bond forming reactions based on alkynes. As shown in Scheme 56, our retrosynthetic analysis of type I substrate **156** involves both alkylation and coupling reactions of terminal alkynes. Different withdrawing groups can be introduced to the parent enyne **157** by reaction of the acetylide anion (e.g. R" = Li) with an electrophile or by modification of an existing functionality (R"= alkyl). The enyne intermediate of type **157** can be prepared in two different ways, either by alkylation of commercially available enyne **159** with a suitable alkyl iodide **158** (path a), or by transition-metal mediated coupling of mono-substituted diacetylene **161** with vinyl halide or triflate **160** (path b). Overall, our enyne substrates **156** can be prepared in as few as three steps.

Scheme 56



Alkylation and coupling procedures were used to prepare substrates with three different enyne substitutions: the isopropenylacetylene **163**, the cyclohexenylacetylene **164**, and the vinyl acetylene **165**.



Substrates **163** and **164** were both prepared by alkylation of the acetylide derivatives of commercially available enynes with an appropriate alkylating agent.[79] Optimum conditions for the preparation of enyne **163** involved deprotonation of enyne **166** with *n*-BuLi at -50 °C in tetrahydrofuran,[80] followed by addition of 10 equivalents of a polar aprotic solvent, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or hexamethylphosphoramide (HMPA),[81,82] and 1-iodo-4-pentyne (which is readily prepared

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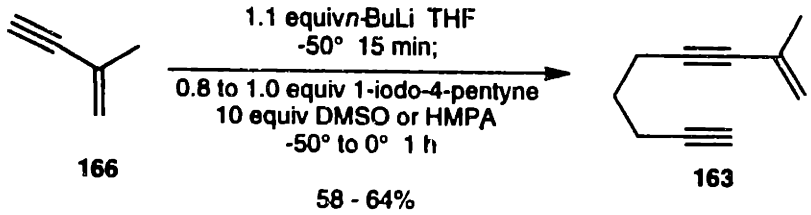
[79] For a review on the alkylation of acetylenes, see: (a) Jacobs, T. L. *Organic Reactions* **1949**, *5*, 1. (b) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988. (c) Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Flemming, I., Eds.; Pergamon: Oxford, 1991, Vol.3, pp 271-292.

[80] Escher, S.; Niclass, Y. *Helv. Chem. Acta* **1991**, *74*, 179. Ramamurthy, V.; Liu, R. S. H. *J. Org. Chem.* **1975**, *40*, 3460.

[81] For the use of polar aprotic additives in the alkylation of acetylenes, see: (a) Schill, G.; Merkel, C. *Chem. Ber.* **1978**, *111*, 1446. (b) Beckmann, W.; Doerjer, G.; Logemann, E.; Merkel, C.; Schill, G.; Zürcher, C. *Synthesis* **1975**, 423. (c) Brattesani, D. N.; Heathcock, C. H. *Syn. Commun.* **1973**, *3*, 245. (d) Schwartz, M.; Waters, R. M. *Synthesis* **1972**, 567. (e) Chong, J. M.; Wong, S. *Tetrahedron Lett.* **1986**, *27*, 5445.

from the 1-chloro-4-pentyne).[83] Acetylide alkylations of this general type have been reported to proceed with greater efficiency in the literature,[79,81,84] and several attempts to improve the yield of the alkylation of **166** were made. The reaction was found to proceed in the presence of dimethylsulfoxide (DMSO)[81c] instead of DMPU or HMPA, although the

Scheme 57



yield did not improve. No product formation was observed when 1-chloro-4-pentyne was used at low temperatures, but if the reaction mixture was warmed to reflux after the addition of the chloride at -50 °C, the desired product was obtained in 50% yield. Unfortunately, similar treatment of the iodide gave **163** in poor yield. Neither increasing the reaction time nor decreasing the reaction temperature provided improvement. In fact, in one attempt, the reaction gave a 54% yield after just fifteen minutes at -20 °C.

One reason for the modest yield obtained in the preparation of enyne **163** may be the volatility of the compound and the fact that it forms an azeotrope with some solvents. Enyne **163** codistilled at reduced pressure on the rotary evaporator with diethyl ether and methylene chloride, and it also codistilled with ether at atmospheric pressure.

Cyclohexenylacetylene (**167**) is also a commercially available compound and is less volatile than isopropenylacetylene. Cyclohexenylacetylene was alkylated with iodopentyne

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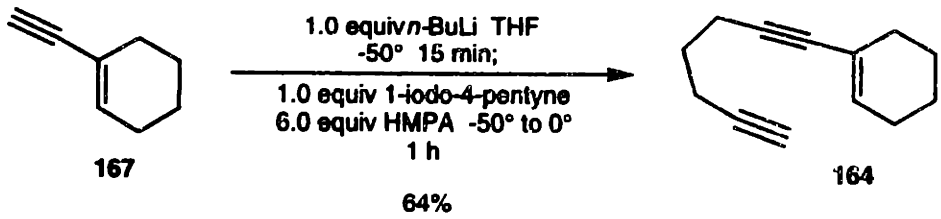
[82] For a review on the use of HMPA, see: Normant, H. *Angew. Chem.; Int. Ed. Engl.* **1967**, *6*, 1046.
[83] Jackson, P. M.; Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2909. Olah, G. A.; Bollinger, J. M.; Brinich, J. *J. Am. Chem. Soc.* **1968**, *90*, pp. Eglington, E. G.; Whiting, M. C. *J. Chem. Soc.* **1950**, 3650.
[84] For the use of lithium amide in liquid ammonia for the alkylation of acetylenes,see: (a) Rao, A. V. R.; Reddy, S. P.; Reddy, E. R. *J. Org. Chem.* **1986**, *51*, 4158.)b) Flahaut, F.; Miginiac, P. *Helv. Chem. Acta* **1978**, *61*, 2275. (c) Smith, W. N.; Kuehn, E. D. *J. Org. Chem.* **1973**, *38*, 3588. For the use of

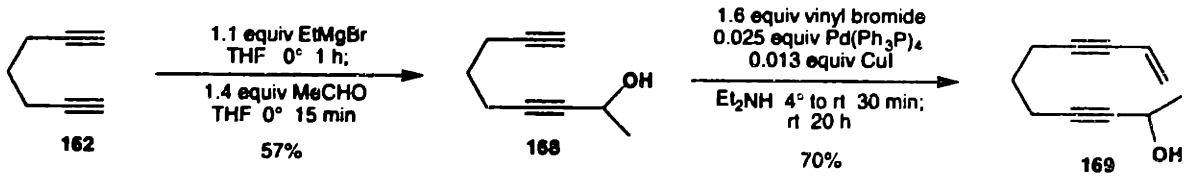
under the same conditions as those described above. Successful alkylation was confirmed by four peaks in the acetylenic region of the ^{13}C NMR spectrum at 68.6 (terminal acetylenic carbon), 82.9, 83.4, and 85.7 ppm.

Scheme 58



The synthesis of the vinyl acetylene substrate **165** began with 1,6-heptadiyne (**162**). Due to the catalytic nature of the transition-metal mediated coupling reaction used to create the enyne moiety, selective mono-coupling of the vinyl bromide to **162** could not be guaranteed. Consequently, the diyne **162** was first converted to monopropargyl alcohol

Scheme 59



168 following Trost's procedure.[85] Treatment of diyne **162** with one equivalent of ethylmagnesium bromide at 0 °C followed by the addition of excess acetaldehyde provided **168** in 57% yield. Use of the Grignard reagent was key, as reaction of the lithium acetylide gave the desired product in no higher than 25% yield. The main byproduct, the bispropargyl alcohol, was formed in about 40% yield.

Palladium(0) and copper(I) catalyzed coupling of alkyne **168** with vinyl bromide

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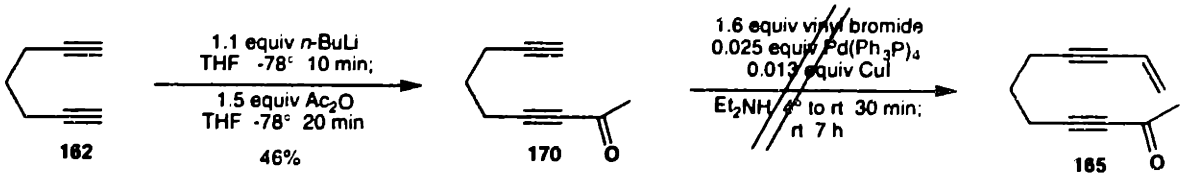
lithium acetylide alone, see: (d) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J.Chem. Soc., Perkin Trans 1* **1986**, 1339.

[85] Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268.

was achieved using the Sonogashira modification of the Castro-Stephens coupling.[86] The structure of enyne **169** was confirmed in part by the presence of three new vinylic proton peaks in the ^{1}H NMR spectrum at 5.77, 5.55, and 5.38 ppm each integrating as one hydrogen.

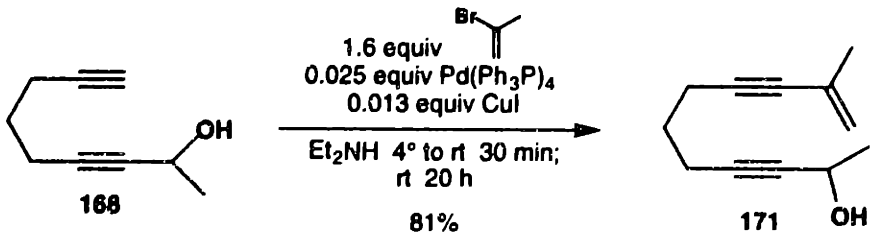
A more direct route to the enyne **165** was also pursued. As shown in Scheme 60, diyne **162** was treated with *n*-butyllithium and then with acetic anhydride to give alkynyl ketone **170** in 46% yield. The use of ethylmagnesium bromide was not explored here, but might lead to better results. Coupling of alkynyl ketone **170** with vinyl bromide was then attempted using the coupling conditions employed above. Not unexpectedly, none of the desired product was isolated, and the starting material decomposed during the reaction.

Scheme 60



A similar cross-coupling strategy was also used to prepare isopropenylacetylene substrates. As shown in Scheme 61, propargyl alcohol **168** was coupled to isopropenyl

Scheme 61



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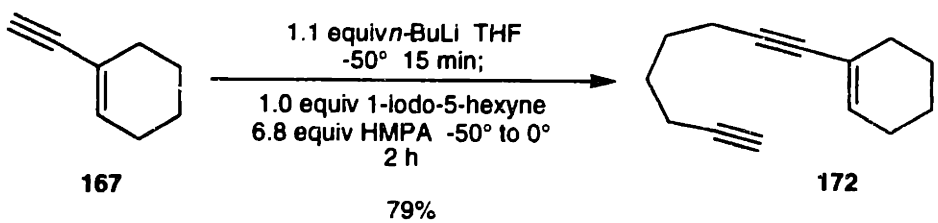
[86] For recent reviews, see: Rossi, R.; Carpita, A.; Bellina, F. *Organic Prep. and Proc. Int.* **1995**, *27*, 127. Campbell, I. B. In *Organocopper Reagents- A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University: Oxford, 1994; pp. xxx. Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Flemming, I., Eds.; Pergamon: Oxford, 1991, Vol 3, pp 521-549. See also: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

bromide in 81% yield. Although this route to the methyl ketone derivative **173** involves one more step, as compared to the alternative alkylation route, none of the intermediates in this pathway are as volatile or as difficult to work with as enyne **163**.

With the ability to make substrates with variously substituted enyne moieties in hand, we next examined the synthesis of substrates with different tether lengths. As will be discussed in the next chapter, the effect of tether length has been found to be important in the efficiency of intramolecular Diels-Alder reactions,[87] and we were interested in the effect it might have on the intramolecular cycloaddition of conjugated enynes.

Two compounds were prepared to explore this aspect of the scope of the reaction. Enyne **164** with a three-carbon tether was prepared as previously described, and a homologous compound, enyne **172**, was prepared in an analogous manner using 1-iodo-5-hexyne instead of 1-iodo-4-pentyne. The iodohexyne was prepared in 76% yield from 5-hexyn-1-ol by treatment with triphenylphosphine, iodine, and imidazole.[88] The alkylation proceeds in good yield, providing enyne **172** in 79% yield.

Scheme 62



With three synthetic intermediates with differently substituted enyne moieties in hand, the next step was functionalization. Taking advantage of the acidity of the acetylenic proton and nucleophilicity of the acetylide anion yet again, different substituents were introduced to activate the enynophile triple bond. The strategy employed here involved

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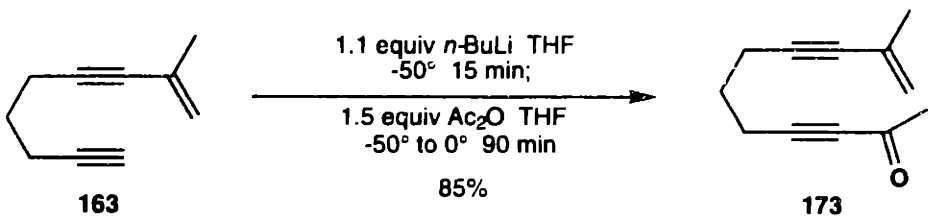
[87] For reviews, see: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Flemming, I., Eds.; Pergamon: Oxford, 1991, Vol. 5, pp 513-550. Roush, W. R. In *Advances in Cycloadditions*; Curran, D. P., Ed.; JAI: somewhere, 1990, Vol. 2, pp 91-146. Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

treatment of the acetylide derivative with an electrophile to obtain a variety of substituted enynes.

Synthesis of the methyl ketone involved deprotonation of enyne **163** with *n*-BuLi in tetrahydrofuran at -50 °C, followed by dropwise addition of this solution to a cooled solution of acetic anhydride and tetrahydrofuran.[89] The inverse addition limits acetylide anion attack on the newiy formed alkynyl ketone, as well as the quenching of the acetylide anion by proton transfer from the methyl ketone product. Reaction of the zinc acetylide, prepared from the lithium acetylide and zinc chloride, with acetyl chloride[90] gave the desired ketone in only 30% yield. Quenching the lithium acetylide with N,N-dimethylacetamide[91] provided the ketone in less than 30% yield, although once again the reaction did not go to completion.

Scheme 63



163 **173**

The cyclohexenyl derivatives **174** and **175** were prepared in analogous manners with similar success (Scheme 64).

Oxidation of propargyl alcohols **169** and **171** was accomplished with buffered pyridinium chlorochromate[92] to give the desired ketones **165** and **173** in 78 and 83% yield

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[88]Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883. Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am .Chem. Soc.* **1987**, *109*, 6187. Berlage, U.; Schmidt, J.; Milkova, Z.; Welzel, P. *Tetrahedron Lett.* **1987**, *28*, 3095.

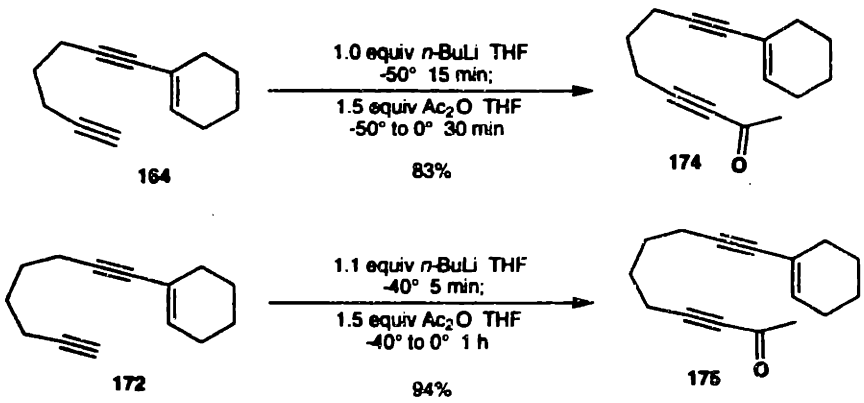
[89] Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 104.

[90] Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 105.

[91] Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 103.

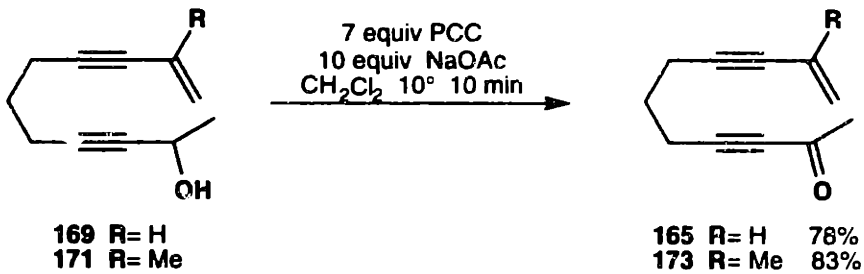
[92] For a review of PCC, see: Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245. See also Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

Scheme 64



respectively, as shown in Scheme 65. Other oxidants which we have used to effect the oxidation of related propargylic alcohols will be discussed later.

Scheme 65



Esters are common activating groups for Diels-Alder dienophiles, and enyne cycloaddition substrates incorporating ester groups were prepared next. During the course of work on the synthesis of the methyl ester, several attempts were made to avoid the isolation of the enyne **163**, due to its volatility. One such attempt involved alkylating isopropenylacetylide with iodopentyne and then generating and acylating the acetylide derivative of the product in the same flask. Enyne **163** was prepared as above using 10 equivalents of DMPU or HMPA. Two hours after the addition of the iodide, the reaction mixture was cooled to -50 °C, and *n*-BuLi was added to form the acetylide. Finally, excess methyl chloroformate[93] was added to form the methyl ester. Warming the reaction mixture to room temperature over one hour provided the desired product **176** in 30% yield.

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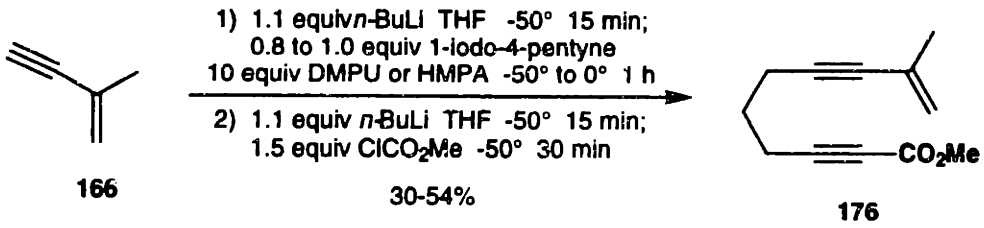
[93] Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 101.

Scheme 66

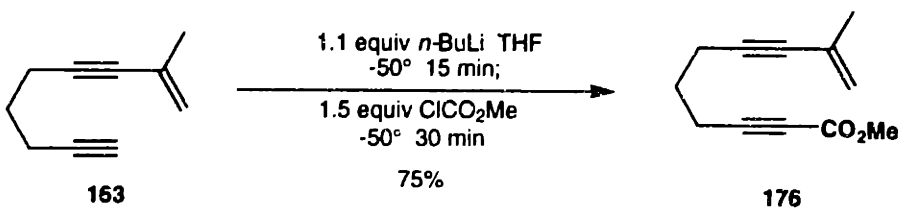


166 176

Unfortunately, neither reaction in this sequence went to completion. The results were not improved by the use of dimethylsulfoxide, which gave only a trace of the desired product **176**. Due to the disappointing yield and the difficulty of purification, this one pot procedure was abandoned.

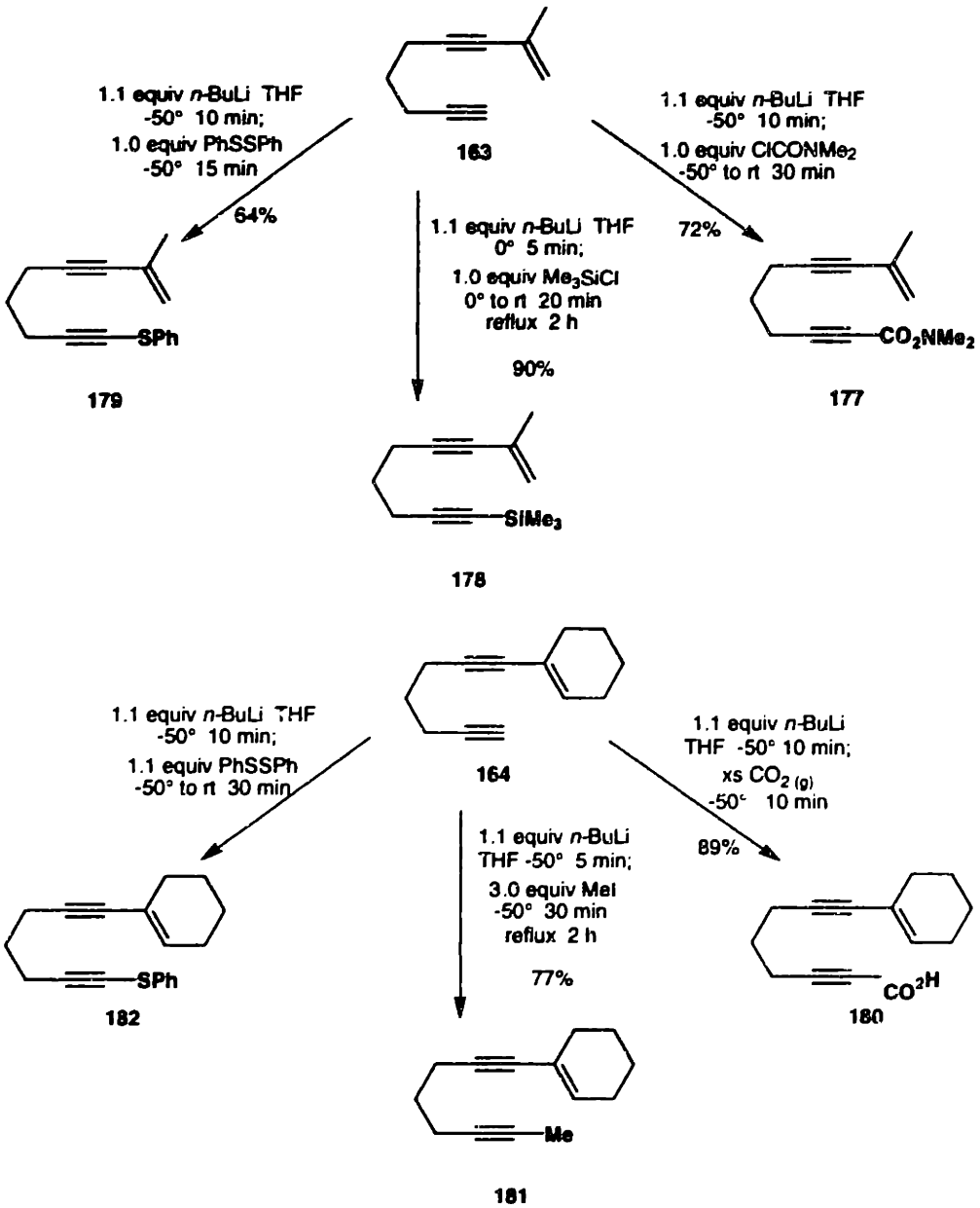
The next logical step was to try the reaction in two steps without purification of the troublesome enyne **163**. Alkylation of an excess of the lithio(isopropenyl)acetylene with iodopentyne in the presence of dimethylsulfoxide[81e] gave enyne **163** which was isolated, but not purified, and redissolved in tetrahydrofuran. Deprotonation of **163** and treatment of the resulting solution with methyl chloroformate at -30 °C gave the desired product **176** in an improved overall yield of 54%. Carrying out the deprotonation of enyne **163** at 0 °C led to lower yields. For comparison purposes, the enyne **163**, previously purified, was deprotonated at -50 °C and then treated with methyl chloroformate. This provided the desired ester **176** in 75% yield, or 44% yield for the two steps. The two pot, "no purification" procedure thus gives superior yields.

Scheme 67



163 176

Scheme 68



Other derivatives of the enyne were synthesized in analgous ways as shown in Scheme 68.[94,95,96,97,98]

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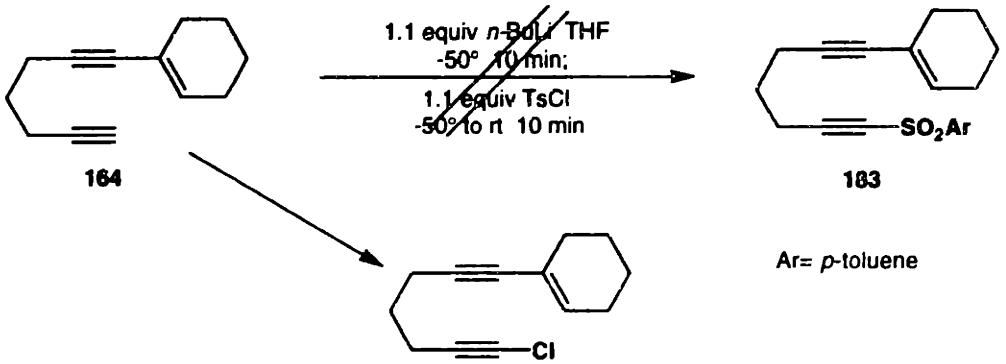
[94]For the preparation of *N,N*-dimethylamides, see: Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 107.

[95] For the preparation of trimethylsilyl acetylenes, see: Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 120.

[96] For the preparation of phenyl and alkylsulfide acetylenes, see: Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 238.

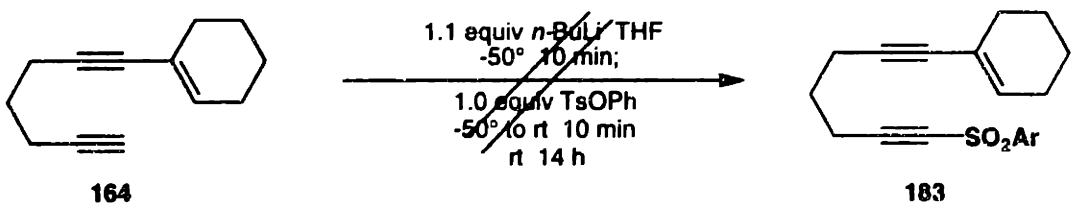
The synthesis of a sulfone derivative was a particular challenge. The first attempts to form the sulfone involved direct sulfonylation of **164**. Enyne **164** was deprotonated and treated with *p*-toluenesulfonyl chloride (TsCl). No change was noted by TLC analysis, but the ^{1}H NMR spectrum showed the absence of an acetylenic proton. It is

Scheme 69



known that chloroacetylenes can be formed in this way.[99] In another attempt, the acetylide anion was treated with phenyl *p*-tolylsulfonate (TsOPh).[100] No reaction was observed in this case, and starting material was recovered.

Scheme 70



Next, oxidation of the phenyl sulfide **182** was attempted. Treatment of phenyl sulfide **182** with oxone (potassium hydrogen persulfate, $KHSO_5$)[101] in methanol or

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[97] For the preparation of acetylene carboxylic acids, see: Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 100.

[98] For the preparation of methyl acetylenes, see: Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 52.

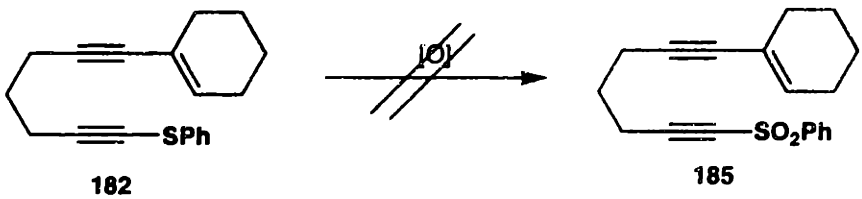
[99] Viehe, H.-G. Ed., *Chemistry of Acetylenes*; Dekker: New York, 1969, pp 673, 683.

[100] Baarschers, W. H. *Can. J. Chem.* **1976**, *54*, 3056.

[101] Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

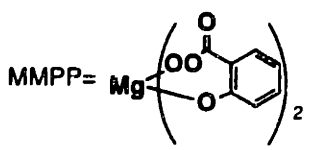
ethanol and water provided the desired sulfone in yields under 40%. These reactions never proceeded to completion and were not clean. Treatment of the sulfide with *m*-chloroperbenzoic acid (*m*-CPBA),[102] tetra-*n*-butylammonium oxone (*n*-$BuNHSO_5$),[103] sodium perborate ($NaBO_3 \cdot 4H_2O$),[104] the magnesium salt of monoperoxyphthalic acid (MMPP),[105] or osmium tetraoxide with *N*-morpholine oxide as the co-oxidant[106] provided the sulfone in poor or nonreproducible yields (Scheme 71).

Scheme 71



182 **185**

Condtions	Results
3 equiv oxone, MeOH, H_2O, 0° to rt, 5 h	4% **185** and **182**
3 equiv oxone, EtOH, H_2O, 0° to rt, 3 to 8 h	14 to 31% **185**, **182**, and decomposition
2.5 equiv *m*-CPBA, CH_2Cl_2	10 to 21% **185**
n-Bu_4NHSO_5, CH_2Cl_2, rt, 4 d	**182** remained
$NaBO_3 \cdot 4H_2O$, AcOH, 50°, 2 h	decomposition
xs MMPP, EtOH 0 to 10°, 4 to 20 h	some **185** and sulfoxide
cat. OsO_4, NMO, Me_2CO, H2O, rt, 12 h	no reaction



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[102] Riera, A.; Marti, M.; Moyano, A.; Periças, M. A.; Santamaria, J. *Tetrahedron Lett.* **1990**, *31*, 2173. Shen, M.; Schultz, A. G. *Tetrahedron Lett.* **1981**, *22*, 3347.

[103] Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532.

[104] McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987**, *43*, 1753. Page, G. O. *Syn. Commun.* **1993**, *23*, 765.

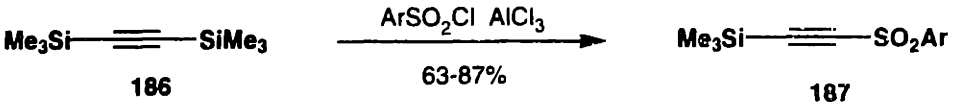
[105] Chich, D.; Ritchie, T. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 945. Cho, I.; Choi, S. Y. *Makromol. Chem., Rapid Commun.* **1991**, *12*, 399. Görlitzere, K.; Bömeke, M. *Arch. Pharm.* **1992**, *325*, 9. Siemens, L. M.; Rotlnek, F. W.; Trzupek, L. S. *J. Org. Chem.* **1990**, *33*, 3507.

[106] Kaldor, S. W.; Hammond, M. *Tetrahedron Lett.* **1991**, *32*, 5043.

Some thought was given to why this oxidation is so difficult. The sulfur atom in the phenyl alkynyl sulfide **182** is fairly electron deficient. It is bonded to an sp^2 hybridized carbon and an sp hybridized carbon, both of which are more electron deficient than an sp^3 carbon due to the increased s character in each bond. This electron deficiency would account for the lack of reactivity to oxidation, which involves the nucleophilic attack of the sulfur atom on the oxygen of the oxidizing agent. In addition, many of the oxidizing agents employed can also be used to oxidize double or triple bonds. Unfortunately, this particular sulfur atom's lack of nucleophilicity combined with the rest of the molecule's delicate nature results in a very difficult oxidation.

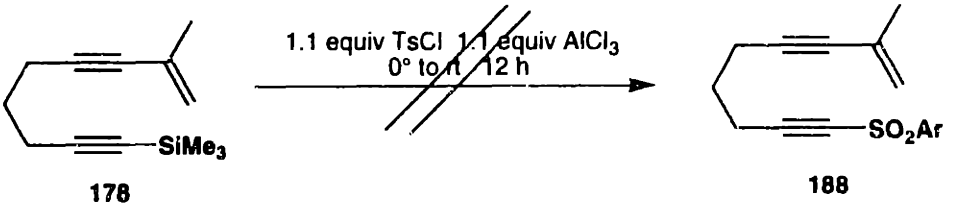
Battacharya and co-workers have used aluminum chloride and *p*-toluenesulfonyl chloride to prepare alkynyl sulfone **187** from bis-trimethylsilyl acetylene (**186**).[107]

Scheme 72



Unfortunately, when silyl acetylene **178** was subjected to these conditions, only decomposition was observed. When the product sulfone **188**, obtained in small amounts form the oxidation reactions described above, was subjected to the reaction conditions, it decomposed also.

Scheme 73



A very different approach to the synthesis of **188** was based on the synthesis of

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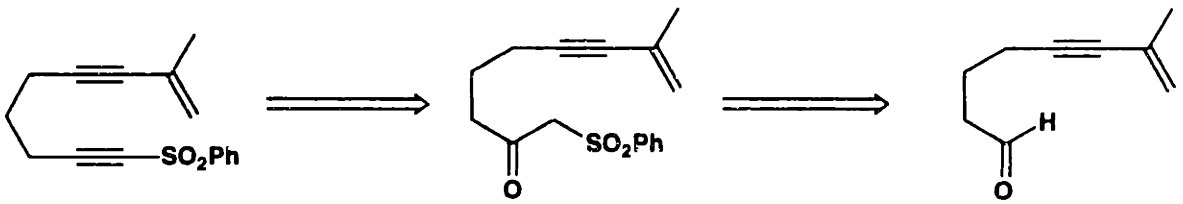
[107] Battacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organometal. Chem. Syn.* **1970/71**, *1*, 145.

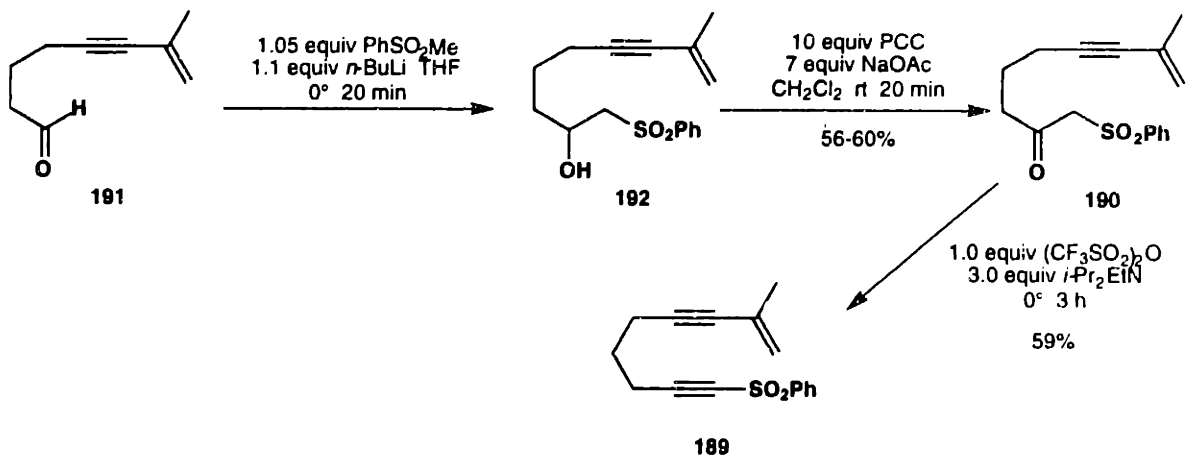
alkynyl sulfones from β-keto sulfones reported by Clasby and Craig in 1992.[108] One method for the preparation of the requisite β-keto sulfones involves alkylation of an aldehyde with lithio(phenylsulfonyl)methane and oxidation. Although this approach requires more steps and than the routes we explored earlier, it requires no sulfide oxidation, and it ultimately succeeded in providing the desired sulfone.

Scheme 74



Use of this route required the synthesis of β-keto sulfone **190** (Scheme 74) which can be derived from aldehyde **191**. Aldehyde **191**, which has been prepared in two ways and will be discussed in a later section of this chapter, was treated with the lithium

Scheme 75



derivative of methyl phenyl sulfone to give β-keto sulfone **192** in about 71% yield as estimated by NMR. The desired product was contaminated with unreacted methyl phenyl

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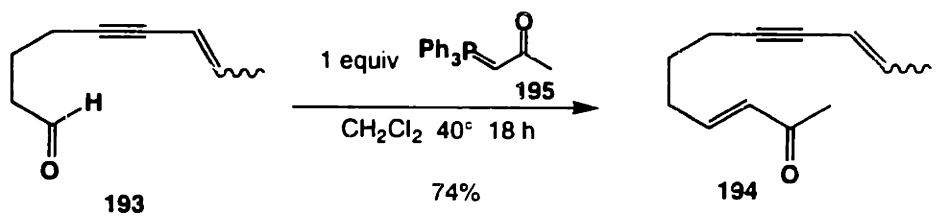
[108] Clasby, M. C.; Craig, D. *Synlett* **1992**, 825.

sulfone. The resulting impure alcohol **192** was oxidized with buffered PCC (pyridinium chlorochromate and sodium acetate)[86] to give the desired β-keto sulfone **190** in 56 to 60% yield for the two steps. Alkynyl sulfone **189** was finally obtained in 59% yield by treatment of the keto sulfone with trifluoromethanesulfonic anhydride in the presence of Hünig's base at 0 °C. The strong characteristic stretching bands at 1325 and 1155 cm^{-1} in the IR spectrum of the product provided evidence for the formation of the sulfone.[109]

Another aldehyde, **193**, was a starting point for the synthesis of the only type I substrate with an olefinic enynophile that was prepared. As shown in Scheme 76, aldehyde **193** was heated to reflux in the presence of ylide **195**.[110] Enyne **194** was produced in 74% yield, as a mixture of enyne stereoisomers. The ^1H NMR spectrum of **194** indicated that the enone double bond was exclusively formed as the trans isomer.

Scheme 76



In summary, type I substrates with three different enyne substitutions, two different tether lengths, and seven different enynophiles were prepared. Type II substrates were also prepared, and as mentioned above, this work was begun by Roberto Fernández de la Pradilla. A discussion of the preparation of these compounds follows in the next section.

Synthesis of Type II Cycloaddition Substrates

Several type II substrates were synthesized to examine the scope of this varient of the enyne cycloaddition. As with the type I substrates, compounds with different

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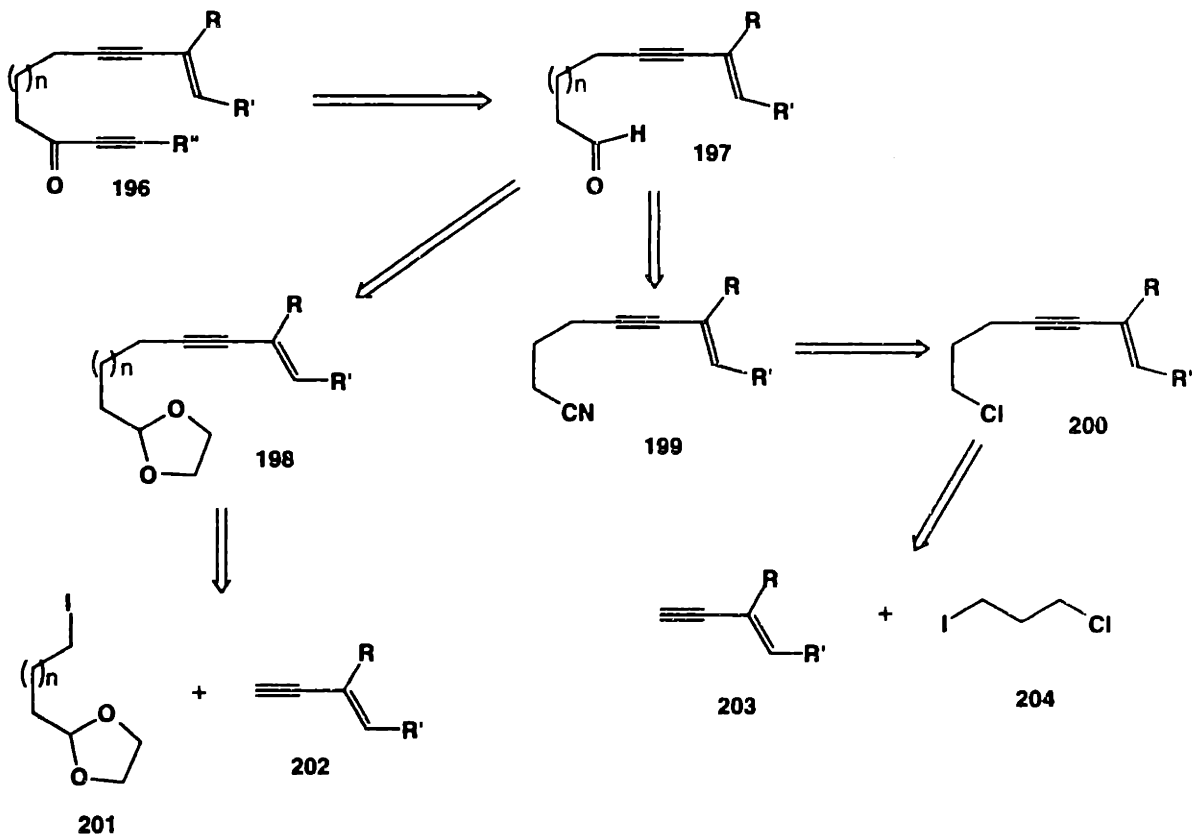
[109] Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981, p 133.

substituents on the enynophile, with different tether lengths, and with different enyne substitution patterns were prepared. Roberto Fernández de la Pradilla began the work on the type II substrates by making compounds with different tether lengths and different enynophile substitutions.

As shown in Scheme 77, type II substrates of the general form **196** are a bit more complicated to prepare than the type I compounds. The alkynyl ketone portion of **196** is best prepared via aldehyde **197**. Aldehydes of type **197** were prepared in two different ways: from acetal **198** or nitrile **199**. Acetal **198** is derived from the alkylation of enyne **202**. Nitrile **199** is derived from chloride **200**, which is prepared by the alkylation of enyne **203** with chloroiodopropane.

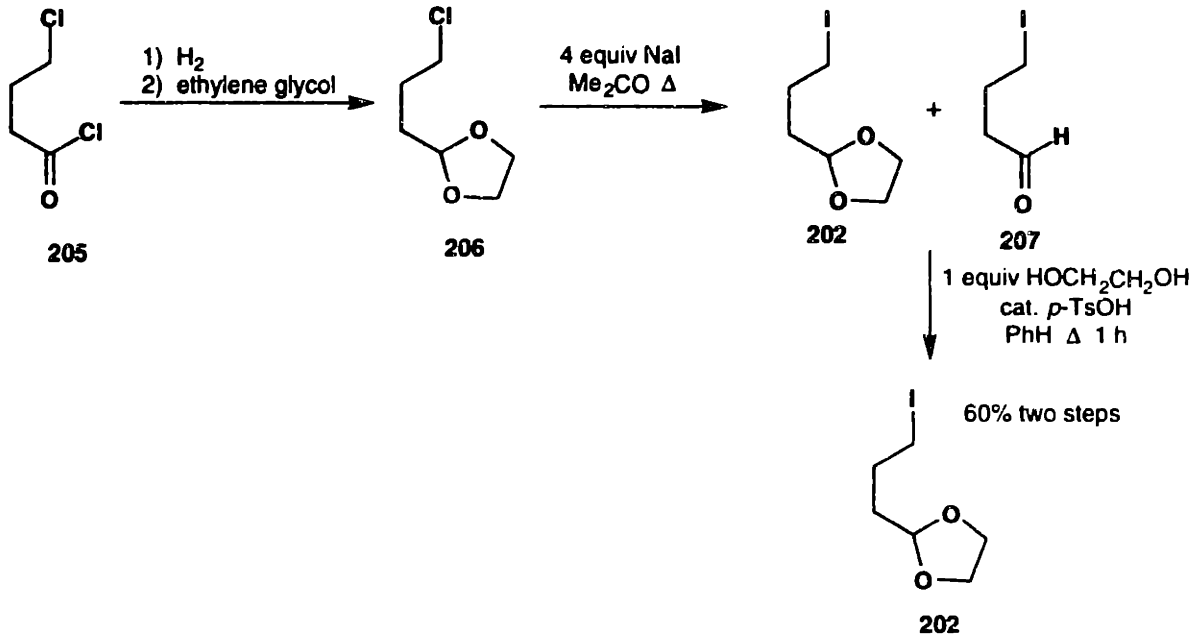
Scheme 77



[110] Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2486. Ramirez, F.; Dershowitz, S.; *J. Org. Chem.* **1957**, *22*, 41. Chamberlin, K. S.; Le Goff, E. *Synth. Commun.* **1978**, *8*, 579.

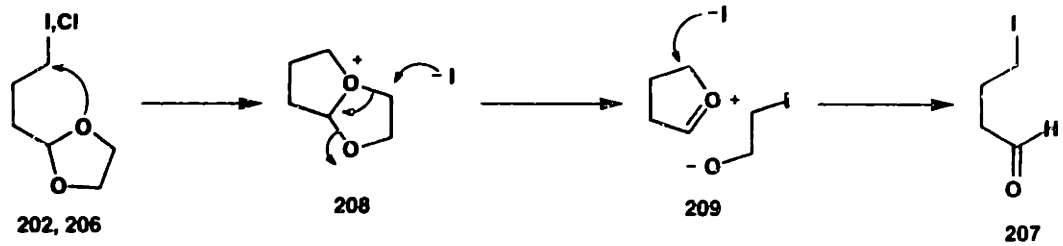
In order to investigate the effect of tether length on the cycloaddition, two substrates were prepared with three and four carbon tethers (n=1 and 2, Scheme 77). Fernández began his work by preparing the four carbon tether substrate. As shown in Scheme 78, the

Scheme 78



iodo acetal intermediate **202** could be prepared in three steps from chloro acid chloride **205**. Reduction and acetal formation provided chloro acetal **206**.[111] When **206** was subjected to Finkelstein conditions,[111] two iodides were produced. One was the desired

Scheme 79

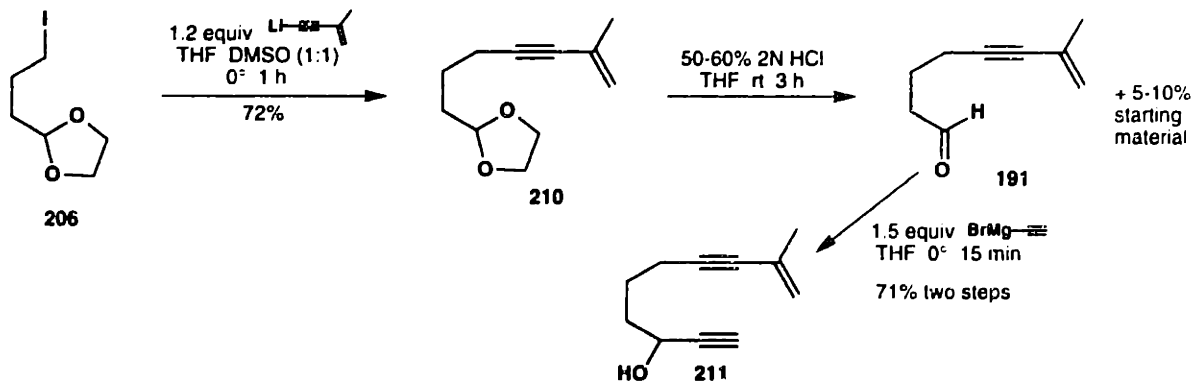


[111] Pleshakov, M. G.; Vasilev, A. E.; Sarycheva, I. K.; Preobrazhenskii, N. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1961**, *31*, 1433; *Zh. Obshch. Khim.* **1961**, *31*, 1545.

iodo acetal **202**, and the other was the iodo aldehyde **207**, which is the result of an internal displacement of the halide by one of the acetal oxygens to form oxonium ion **208**. Sequential attacks by iodide give the iodo aldehyde **207**. The mixture of **202** and **207** was converted to acetal **202** under standard conditions. The yield for this sequence from chloride **206** to pure acetal **202** was 60%.

Iodo acetal **202** was then alkylated with lithio(isopropenyl)acetylene in the presence of DMSO;[81e] this alkylation is similar to the alkylation used in the synthesis of type I substrates and proceeded in 72% yield. Hydrolysis of the acetal proved to be troublesome, but was finally accomplished using 2*N* aqueous hydrochloric acid in tetrahydrofuran.[112] This reaction did not go to completion, but due to its instability, aldehyde **191** was not purified. The mixture was treated with ethynylmagnesium bromide, and the propargyl alcohol **211** was isolated in 71% yield for the two steps. Oxidation of the alcohol to the desired ketone **212** proved to be difficult. Many oxidants were tried, including chromium

Scheme 80



trioxide,[113] manganese dioxide, and the Swern reagent. Pyridinium chlorochromate (PCC)[92] buffered with sodium acetate proved to give the best results for this oxidation,

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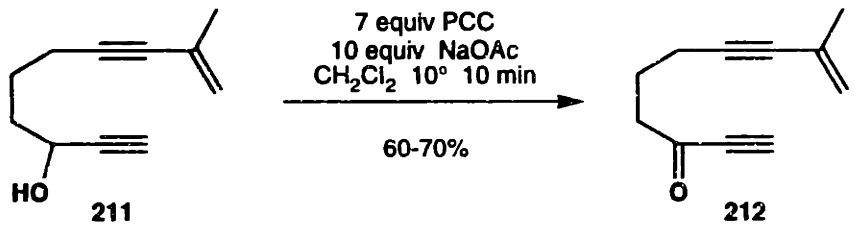
[112] Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.

[113] Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. Poos, G. I.; Arth, G. E.; Beyler, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 422. Djerassi, C.; Hart, P. A.; Warawa, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 78.

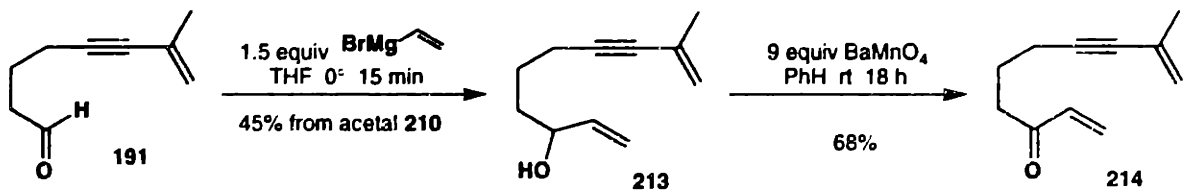
although the reaction had to be run at low temperature with a large excess of oxidant. Long reaction times or reaction at ambient temperatures led to product decomposition, and the reaction did not scale up well. As we shall see, the use of the Dess-Martin periodinane, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one,[114] solved the problem of scale up and provided better yields than PCC.

Scheme 81



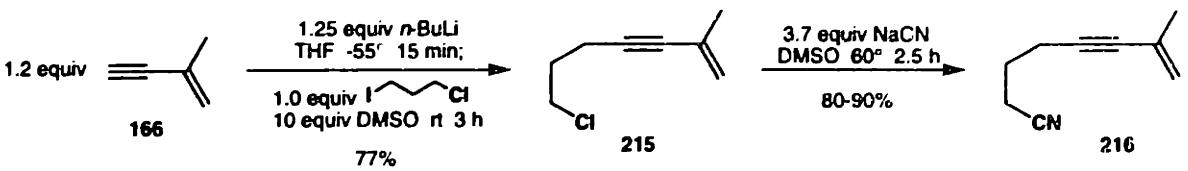
In a similar sequence of reactions, the vinyl ketone enyne substrate **214** was prepared. Treatment of aldehyde **191** with vinylmagnesium bromide provided the allylic alcohol **213** in 45% yield from the acetal **210**. Pyridinium chlorochromate oxidation of this alcohol was capricious, but barium manganate ($BaMnO_4$) in benzene provided the desired enone **214** in 69% yield.

Scheme 82



Enyne **212** was also prepared from nitrile **216**. Alkylation of enyne **166** with

Scheme 83



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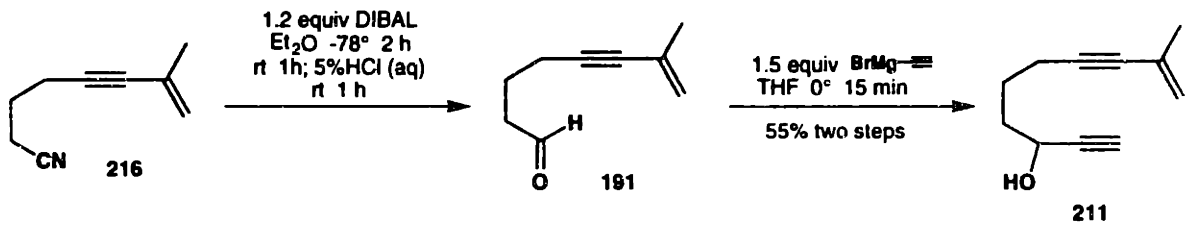
[114] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. For an improved method of preparation, see: Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

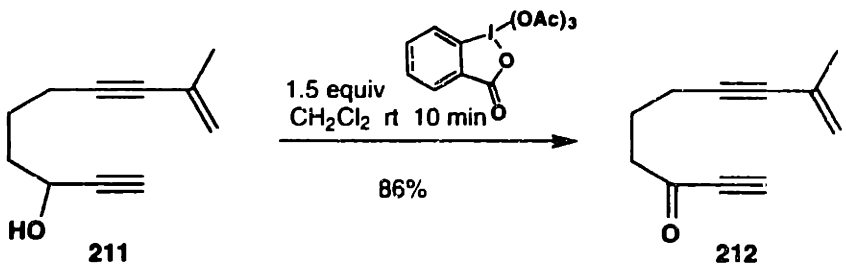
chloroiodopropane took place under our now standard conditions to give chloride **215** in 77% yield. Chloride **215** was warmed in DMSO and sodium cyanide to give the desired nitrile **216** in good yield.[115] Reduction to the imine with diisobutylaluminum hydride and

Scheme 84



hydrolysis with hydrochloric acid[116] provided aldehyde **191**, which was not purified, but instead treated directly with ethynylmagnesium bromide to give the propargyl alcohol **211** in 55% yield. Oxidation of the alcohol was then accomplished with the Dess-Martin periodinane[114] to give the enyne **212** in 86% yield. Enyne **212** was characterized by a carbon-carbon triple bond stretching band at 2100 cm^{-1} and a carbonyl stretching band at 1680 cm^{-1}. This sequence is shorter than the original sequence by one step and uses less precious starting materials.

Scheme 85



Preparation of the three carbon tether substrate **222** began with acrolein. Following Larson's procedure, treatment of acrolein with trimethylsilyl chloride, sodium

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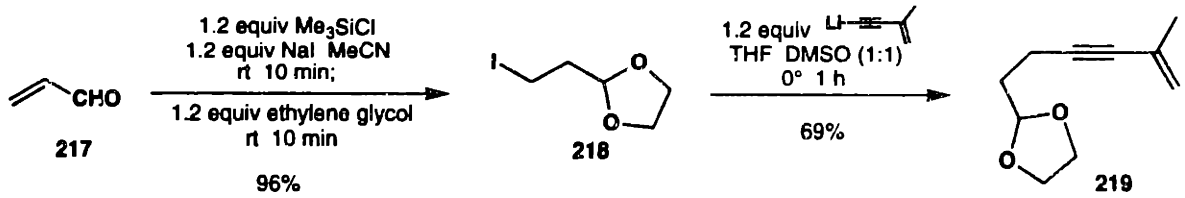
[115] *J. Org. Chem.* **1960**, *25*, 257. *J. Org. Chem.* **1960**, *25*, 877.

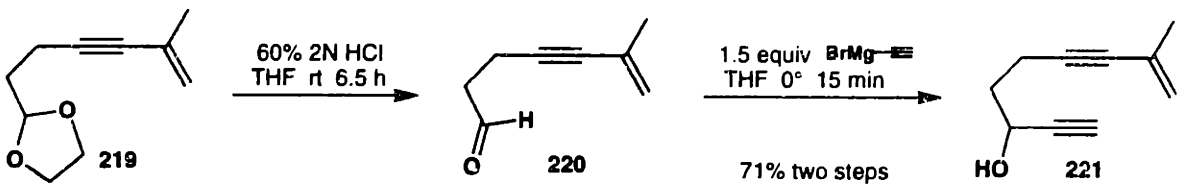
[116] Bradsher, C. K.; Edgar, K. J. *J. Org. Chem.* **1981**, *46*, 4600. Proudfoot, J. R.; Li, X.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 2026. Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. Reitz, A. B.; Nortey, S. O.; Maryanoff, B. V.; Liotta, D.; Monahan, R., III *J. Org. Chem.* **1987**, *52*, 4191.

Scheme 86



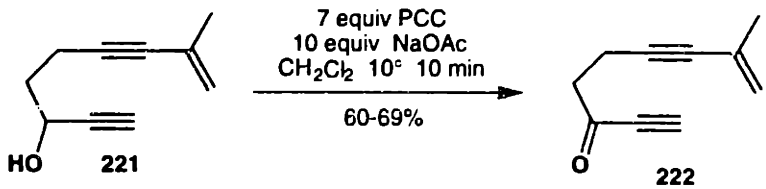
iodide, and ethylene glycol in acetonitrile[117] provided iodo acetal **218** in 96% yield. Alkylation of this iodo acetal with the lithium derivative of isopropenylacetylene provided the enyne acetal **219** in 69% yield.[81c] Hydrolysis[112] of acetal **219** gave aldehyde **220** which was treated immediately with ethynylmagnesium bromide to give the propargyl alcohol **221** in 71% yield for the two steps. A concentrated solution of aldehyde **220**

Scheme 87



decomposed when allowed to stand at room temperature in air for several hours, so best results were obtained when it was converted to **221** without purification. Oxidation of the alcohol to the ketone **222** was accomplished with pyridinium chlorochromate buffered

Scheme 88



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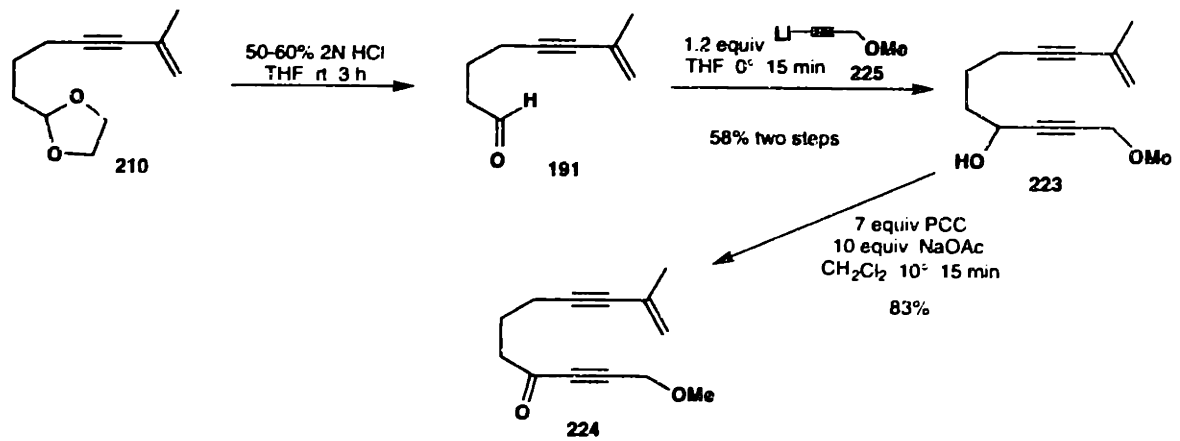
[117] Larson, G. L.; Klesse, R. *J. Org. Chem.* **1985**, *50*, 3627. Stowell, J. C.; King, B. T.; Hauck, H. F. Jr. *J. Org. Chem.* **1983**, *48*, 5381.

with sodium acetate.[92] This reaction also required slightly lower than ambient temperatures in order to prevent decomposition of the product.

Fernández also prepared two enynes with substituted enynophiles, in order to explore the effect of both steric and electronic factors on the reaction. Enyne **224** was

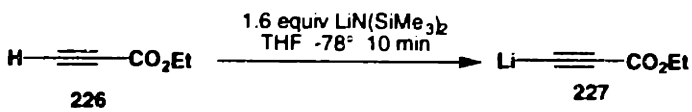
Scheme 89



prepared in a manner analogous to that of enyne **212**. Acetal **210** was hydrolyzed and alkylated with the lithium derivative of propargyl methyl ether **225**. These reactions gave the propargyl alcohol **223** in 58% yield. The alcohol was then oxidized to the ketone **224** with PCC/NaOAc[92] in 83% yield.

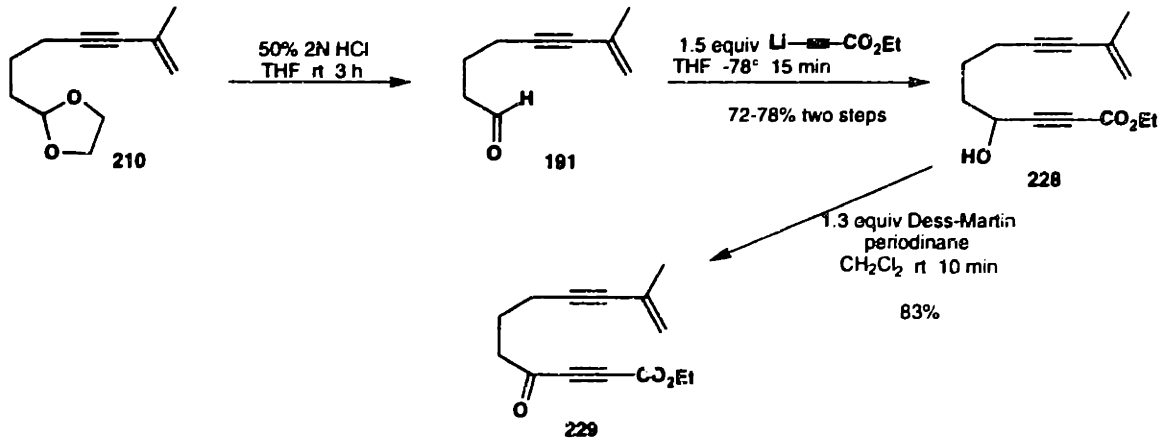
The electron deficient enyne **229** was prepared as shown in Scheme 91. Roberto Fernández and Suzi Allemann prepared this enyne, which proved to be a bit tricky to make. The lithium derivative of ethyl propiolate **227** could not be prepared in good yield with butyllithium or a Grignard reagent; however, treatment of the alkyne **226** with lithium

Scheme 90



hexamethyldisilylamide[118] followed by dropwise addition to a solution of the freshly prepared aldehyde **191** provided the alcohol **228** in good yield. Dess-Martin oxidation[114] provided the desired ketone **229** in 83% yield.

Scheme 91



The effect of substituents on the enyne moiety proved to be an interesting area of study in the type II series, and so four substrates with different enyne substitution patterns were prepared. The isopropenylacetylene substitution pattern has been the focus of our previous studies. Three other substrates that were prepared include a vinyl acetylene substrate, an *n*-propenylacetylene substrate, and a 1-methyl-1-propenylacetylene substrate. The synthesis of these substrates required us to re-evaluate our retrosynthetic analysis of the generic substrate **196**, because the required starting enyne moieties were not commercially available. Thus, we decided to construct the enyne moiety in a manner similar to that used in the synthesis of some of our type I substrates. As shown in Scheme 92, the enyne alcohol **230** can be derived from either a Castro-Stephens type coupling of acetylene **233** with a bromoalkene **160**, or via a transition-metal mediated coupling involving a bromoacetylene **231** and an organometallic compound **232**.

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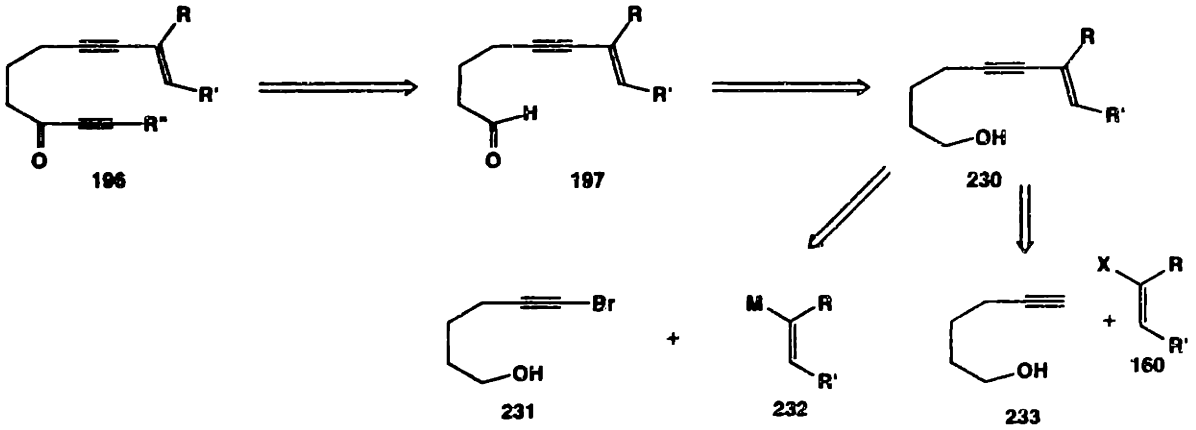
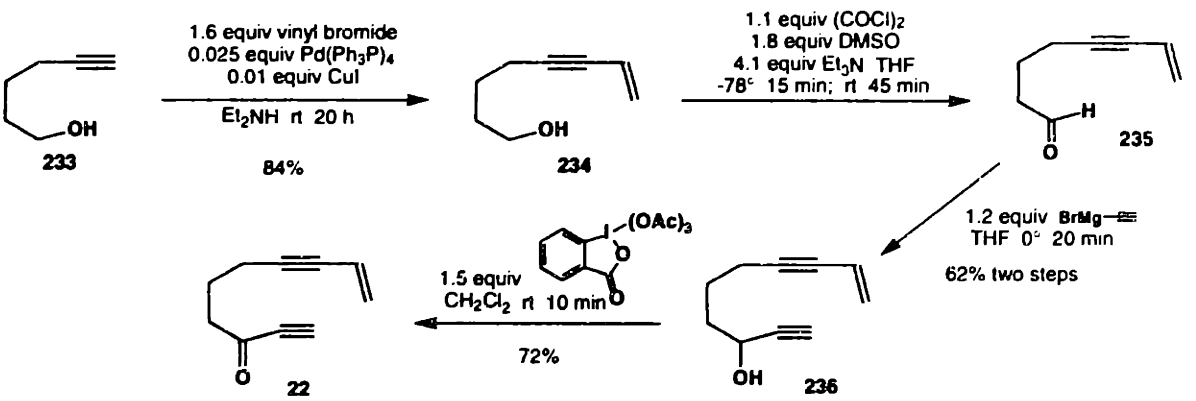
[118] Crimmins, M. T.; Bantermet, P. G.; Tropper, B. W.; Vallin, I. M.; Watson, P. S.; MeKerlie, L. A.; Reinhold, T. L.; Cheung, A. W.-H.; Stetson, K. A.; Dedopoulou, D.; Gray, J. L. *J. Org. Chem.* **1983**, *58*, 1038.

Scheme 92



The vinyl acetylene substrate **22** was prepared using the Sonagashira modification of the Castro-Stephens reaction.[86] As shown in Scheme 93, 6-hexyn-1-ol (**233**) was coupled to vinyl bromide in the presence of palladium tetrakistriphenylphosphine and copper (I) iodide to give enyne alcohol **234** in 84% yield. This alcohol was converted to the desired enyne **22** in 37% overall yield for three steps according to the sequence previously described for the preparation of **212**.

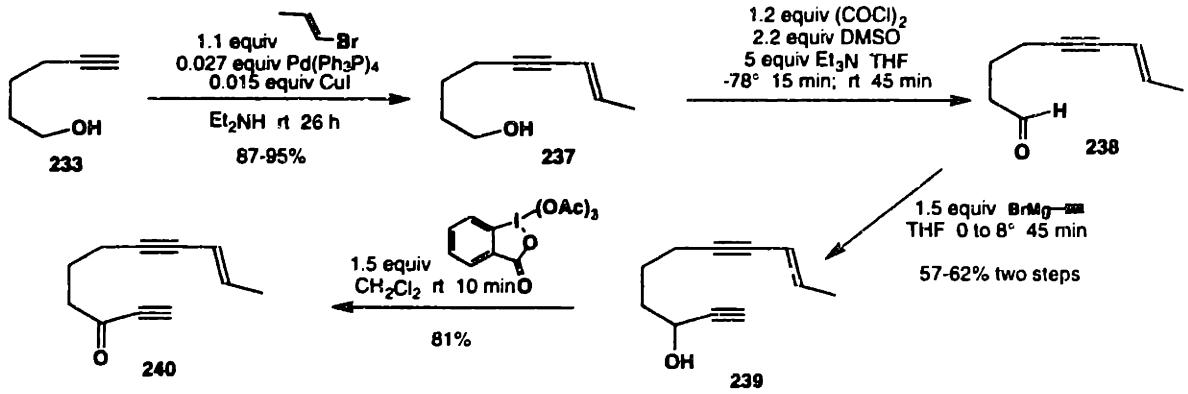
Scheme 93



The propenylacetylene derivative **240** was prepared via an analogous strategy in 40-48% overall yield (Scheme 94). This time, coupling with *E*-1-bromo-1-propene, instead of vinyl bromide, provided enyne alcohol **237** in excellent yield. The large coupling constant (J=16 Hz) between the two vinyl protons in the ^{1}H NMR confirms the trans geometry of the alkene. The coupling reaction was found to proceed more rapidly with the E isomer of 1-bromopropene. A 75:25 Z:E mixture of bromopropenes underwent

coupling to give a 12:88 Z:E mixture of enynes. Unfortunately, this mixture was not separable by any of the methods tried, so the coupling was best performed with pure trans bromide.

Scheme 94



Synthesis of the final enyne substrate **241** required a different route. 2-Bromo-2-butene is commercially available only as a 75:25 mixture of Z and E isomers. Use of the commercially available material would give a mixture of enynes, and the two isomers would be difficult to separate. We desired an isomerically pure substrate. Hydroboration of 2-butyne would provide a vinyl boron intermediate with the required alkene geometry,[119] and Suzuki coupling of this vinyl boron reagent to bromoacetylene **231**[120] would provide enyne alcohol **237**. In the event, vinyl borane **238** was prepared from an excess of 2-butyne and 9-BBN in THF at 0 °C; this solution was then allowed to sit in the freezer (-5 °C) for 24 to 36 hours to ensure complete hydroboration. The bromoacetylene **231** was prepared from alkyne **233** using N-bromosuccinimide (NBS) and catalytic silver nitrate.[121] This preparation of compound **231** proved better than the reaction of the dilithium derivative with NBS. The bromoacetylene **231** and borane reagent **238** were then heated to reflux in THF in the presence of palladium tetrakistriphenylphosphine, sodium methoxide, and methanol to give the enyne alcohol **237** in approximately 75% yield.

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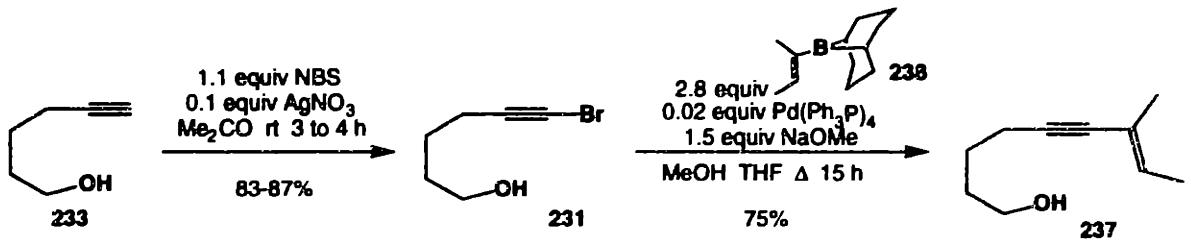
[119] Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96.
[120] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.
[121] Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem.; Int. Ed. Engl.* **1984**, *23*, 727.

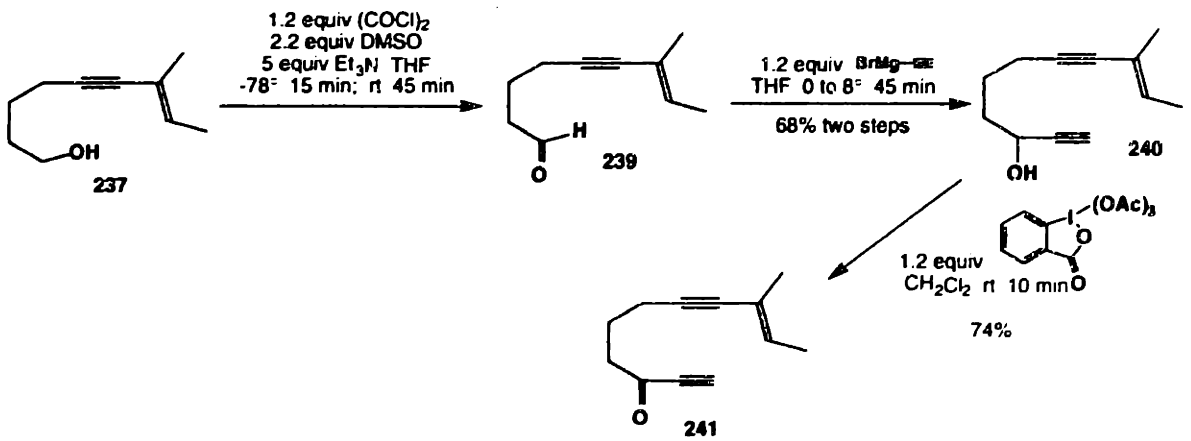
Purification of this alcohol was complicated by the presence of cyclooctanediol, which is the oxidation product of 9-BBN derivatives. The diol was present in varying amounts, and could not be removed by column chromatography. Pure **237** was finally obtained by

Scheme 95



fractional Kugelrohr distillation of the mixture. The alcohol **237** was then oxidized, reacted with ethynylmagnesium bromide, and oxidized again, as described above, to give the desired ynone substrate **241** which was characterized by a quartet in the ^{1}H NMR spectrum at 5.53 ppm and an acetylenic proton at 2.95 ppm.

Scheme 96



The synthesis of the substrates for our study of the enyne cycloaddition exploited the acidity of acetylenic protons as well as the ability of acetylenes to undergo various coupling reactions. A wide variety of substrates were prepared and they were subjected to several cycloaddition conditions, which will be described in the next chapter.

Chapter 2

Intramolecular Cycloadditions of Conjugated Enynes

As described in the previous chapter, the versatility of acetylene chemistry allowed us to prepare a wide variety of enyne cycloaddition substrates. These substrates were prepared for the systematic exploration of the scope of the proposed reaction. This chapter begins with a discussion of our work to establish the feasibility of the intramolecular enyne cycloaddition under several different reaction conditions. In this phase of our investigation, we were guided by the results of previous work on conditions for the well-studied Diels-Alder reaction.[122] Next, the intramolecular cycloadditions of type I and II substrates are described and where appropriate, compared to simular Diels-Alder reactions. In the final chapter of this section, a summary of this work will be presented along with a discussion of some of the other substrates and cycloadditions that have been explored in our group.

Feasibility and Optimization of the Cycloaddition

The feasibility of the reaction was initially explored using two substrates, the ketone **173** and the corresponding ester **176**. We began by exploring the uncatalyzed reaction. Intramolecular Diels-Alder reactions proceed at temperatures ranging from room temperature to over 250 °C. In our initial experiment, we dissolved enyne **173** in toluene, thoroughly degassed the solution, and then heated it from 50 to 160 °C for two days; the desired cycloadduct **243** was obtained in 22% yield along with 52% of the starting

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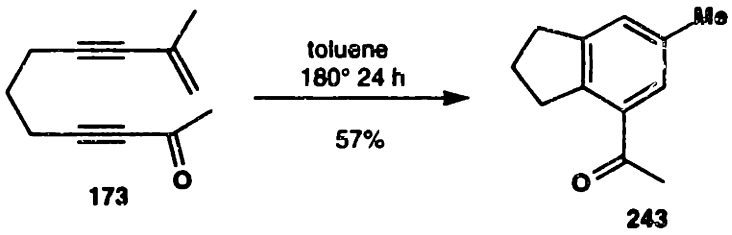
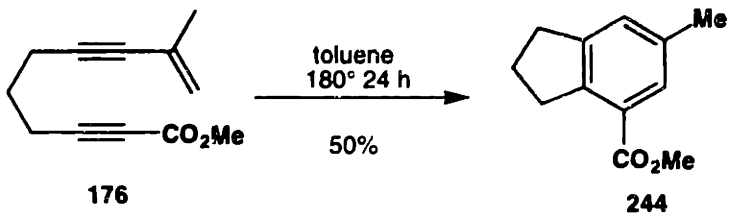
[122] For reviews, see: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 513-550. Roush, W. R. In *Advances in Cycloadditions*; Curran, D. P., Ed.; Jai: Greenwich, CT, 1990; Vol. 2, pp 91-146. Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. Ciganek, E. *Organic Reactions* **1984**, *32*, 1.

Scheme 97



enyne. Heating the substrate to 180 °C for 24 hours drove the cycloaddition to completion and provided the desired hydrindane in 57% yield (Scheme 97). In a similar fashion, ester **176** gave cycloadduct **244** in 50% yield at 180 °C (Scheme 98).

Scheme 98

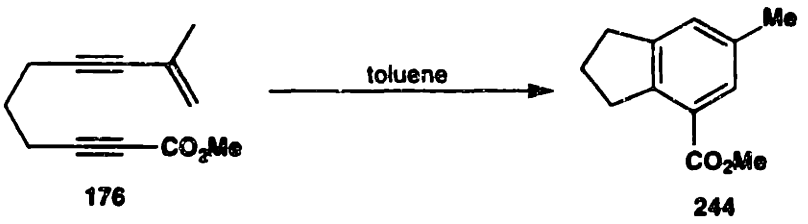


With these results in hand, the next step was to optimize the conditions for these cycloadditions by varying temperature, concentration, and reaction time. The effect of varying solvent choice will be discussed later in the section on cycloadditions of type I substrates.

The first area of interest was the temperature required for the reaction. Ideally, we wanted the reaction to proceed in a reasonable amount of time at a temperature that was easily obtained by an oil bath and that would not cause too much decomposition of the enyne starting material. Several reactions were run at different temperatures, and a ^{1}H NMR spectrum of each of the crude reaction mixtures was analyzed for the relative amounts of starting material and product. As shown in Scheme 99, a temperature of 180 °C is required for the reaction to go to completion in a reasonable amount of time.

Intramolecular cycloadditions are usually run at very low concentrations to avoid undesirable intermolecular reactions. Our reactions are more complicated, as they involve

Scheme 99

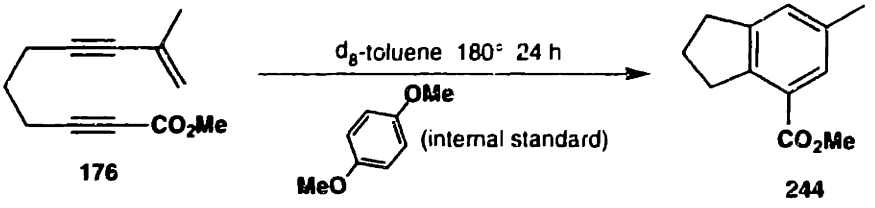


176 244

Temperature	Time	Prod : SM (NMR ratio)
130°	72 h	0:100
150°	48 h	25:75
165°	27 h	60:40
180°	6 h	100:0

both an intramolecular reaction and an isomerization. This isomerization could be either an inter- or intramolecular process (see Scheme 54, Part I, Chapter 2). In order to examine the effect of concentration on the reaction, several cycloadditions were run using enyne **176** at different concentrations. The reactions run at high (1 M) and low (0.01 M) concentrations had more side products than the reactions run at intermediate concentrations (0.1 - 0.25 M), as determined by TLC and NMR analysis of the crude reaction mixtures. These results were supported by the following NMR experiment. The enyne **176** and a known amount of 1,4-dimethoxybenzene (an internal standard) were dissolved in d_8-

Scheme 100



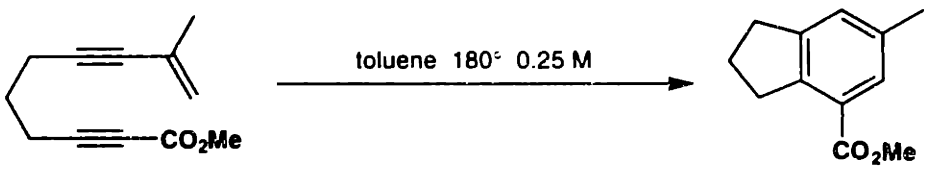
176 244

Concentration	Amount of Product (NMR)
0.05 M	8%
0.2 M	29%
1.0 M	19%

toluene, degassed, and sealed. The tubes were then heated to 180 °C for 24 hours, cooled to room temperature, and examined by ^{1}H NMR. As shown in Scheme 100, the reaction run at the intermediate concentration gave the highest yield of product. Further experiments demonstrated that the optimal concentration for this cycloaddition is 0.1 molar. The implications of these concentration experiments on the reaction mechanism will be discussed in a later chapter.

The next area of interest was the reaction time. As shown in Scheme 101, at 0.25 M the reaction was complete in 6 hours, most reactions were run, however, for 7 to 9 hours. Longer reaction times were also required for cycloadditions run at more dilute concentrations, because less starting material is lost to polymerization and other side reactions under these conditions. The cycloadditions were run at lower concentrations when additives were introduced, as will be discussed later.

Scheme 101



176

Time	Prod : SM (NMR ratio in crude reaction mixture)
2 h	~0:100
4.5 h	40:60
6 h	100:0

244

Larger scale cycloadditions were then attempted under these optimized conditions. Unfortunately, on a scale of over 100 mg, the reaction did not give reproducible results. Enyne **176** gave the cycloadduct **244** in only 25 to 35% yield after 7 hours at 180 °C. The yield had dropped by at least 15%, and yet we believed that the reactions were being run in exactly the same way. Temperature regulation and loss of starting material to polymerization were identified as potential problems. In order to achieve better temperature control, the reaction was carried out in a high boiling solvent at reflux. A cycloaddition run in *p*-cymene (bp 178-179 °C) at reflux for 9 hours provided only 27% of the desired

product. This cycloaddition was not as clean as judged by TLC analysis as the sealed tube reactions, and it pointed out the usefulness of employing sealed tubes, which allow the reaction mixture to be thoroughly degassed before heating. Although reactions run in refluxing solutions are also degassed before heating, these solutions can still pick up traces of oxygen and other gases through leaks over extended reaction times.

Concerns about the presence of oxygen in the reaction mixture led to more intrest in the stability of the highly unsaturated starting material at elevated temperatures. Several additives have been used in intramolecular cycloadditions and related reactions to prevent polymerization of organic compounds at high temperatures. For this reason, radical inhibitors like phenols, thiophenols, and dihydroaromatic compounds were considered.[123] Phenols and thiophenols are commonly used as radical inhibitors and are attractive for use in our reaction for an additional reason. A high energy intermediate which isomerizes to an aromatic species is proposed for the cycloaddition in Part I, Chapter 2 (Scheme 54). We believed that a stabilizer that could both donate and accept a proton or hydrogen atom might facilitate the isomerization step and lead to a cleaner reaction.

In the event, the best results were obtained with phenolic additives, which when included in the reaction mixture led to the reproducible formation of the desired cycloadduct in 44 to 50% yield, on a 100 mg scale. Unfortunately, thiophenols proved to be too nucleophilic. When the ester enyne **176** was heated in the presence of 2,4,6-trimethylthiophenol, no cycloadduct and only more polar spots were observed by TLC. Although no pure compounds were isolated from this reaction, we believe the alkynyl ketone was attacked by the thiophenol in a Michael type addition, and further decomposition then occurred. When the dihydroaromatic compound γ-terpinene (**245**) was used as an additive in the cycloaddition, the cycloadduct was obtained in only 31%

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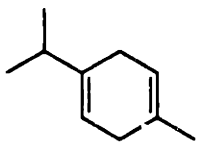
[123] For reviews of antioxidants, see: Scott, G. In *Atmospheric Oxidation and Antioxidants*; Scott, G., Ed.; Elsevier: New York, 1993, Vol. 1, pp 121-160. Stevens, M. P. J. Chem. Ed. **1993**, *70*, 535. Pitteloud, R.; Dubs, P *Chimia* **1994**, *48*, 417.

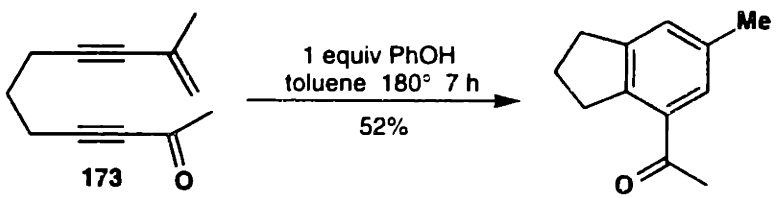
yield. Other phenols were also explored; BHT (4-methyl-2,6-di-*tert*-butylphenol) and *p*-methoxyphenol were found to be effective radical scavengers and possible proton or hydrogen atom shuttles, and all three phenols can be used, sometimes interchangeably, in the cycloadditions. In general, BHT and phenol were used for the cycloadditions of type II and type I substrates respectively. In the case of the less polar substrates which give nonpolar cycloadducts, the more polar *p*-methoxyphenol was used to simplify purification.



245

Under the optimized conditions, enyne **173** was heated to 180 °C in toluene in the presence of one equivalent of phenol, and the desired cycloadduct **243** was obtained in 52% yield. The desired product is characterized by singlets at 7.63 and 7.21 ppm in the ^{1}H

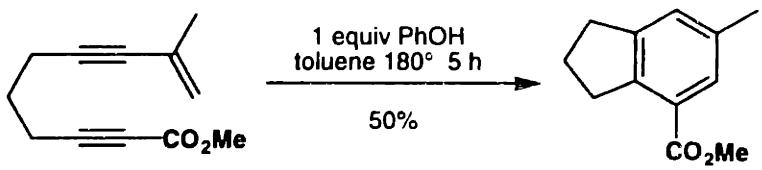
Scheme 102



173 **243**

NMR spectrum. The methyl ester enyne **176** provided the cycloadduct **244** when heated to 180 °C for 5 hours; the reaction does not proceed to completion, with 16% of the starting

Scheme 103

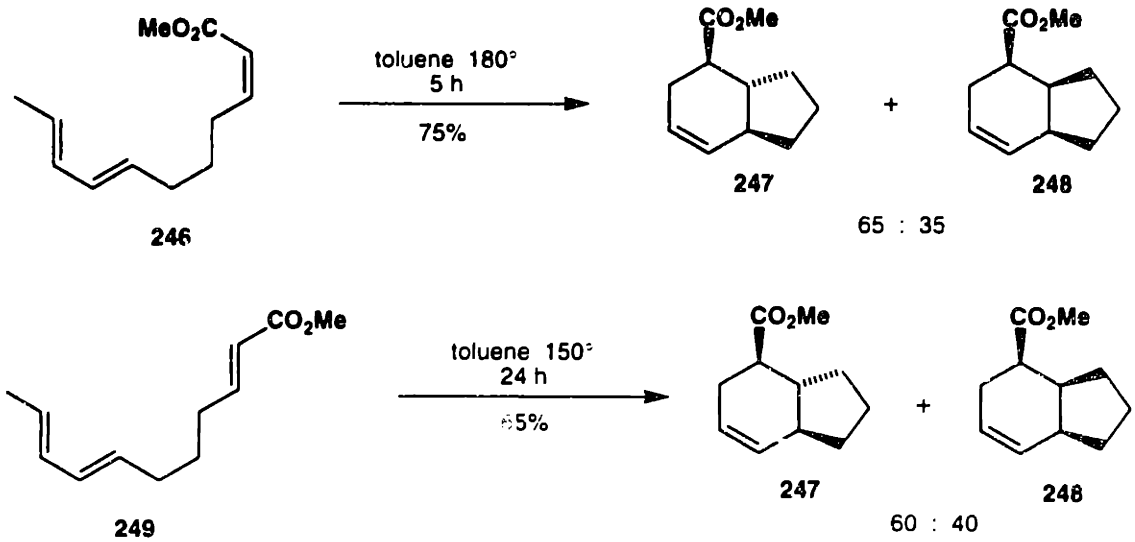


176 **244**

material being recovered. The yield for this reaction was 50%, or 61% based on recovered starting material.

For comparison purposes, the intramolecular Diels-Alder reactions of dienes **246** and **249**[124] are shown in Scheme 104. Although these dienes differ from our substrates quite dramatically, the similarities of the two types of transformations in terms of conditions encouraged us to explore some of the different methods that have been used to promote intramolecular Diels-Alder cycloadditions.

Scheme 104



Lewis acids are known to catalyze or promote intramolecular [4+2] cycloadditions such as Diels-Alder and ene reactions,[122,125,126] and we wondered if the enyne cycloaddition could also be promoted in this way. Roberto Fernández de la Pradilla, who was working on the cycloadditions of some type II substrates while I was working on the type I substrates, explored the use of Lewis acids to promote the cycloaddition. He focused on alkynyl ketone **212** and found that aluminum chloride, titanium tetrachloride,

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[124] Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061.

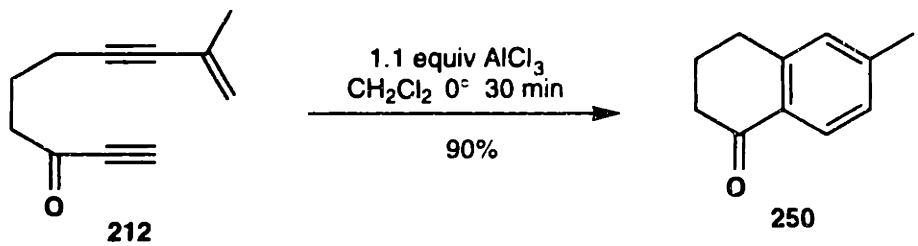
[125] Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC: Boca Raton, 1996; pp 21-90, 267-328. See also: Kobayashi, S. *Synlett* **1994**, 689.

[126] For a general review of the acceleration of Diels-Alder reactions, see: Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

dimethylaluminum chloride, and zinc(II) halides caused the cycloaddition to occur at or below room temperature.

Aluminum chloride[127] proved to be the best Lewis acid for this substrate giving the desired tetralone **250** in 90% yield after only 30 minutes at 0 °C. This tetralone was characterized by a singlet at 7.03 ppm and two doublets at 7.91 and 7.09 ppm (J= 8.0 Hz) in the ^1H NMR spectrum. As shown in Scheme 105, 1.1 equivalent of the Lewis acid are needed for this reaction to take place at 0 °C. Only 0.3 equivalent of $AlCl_3$ are needed when the reaction is run at room temperature, although the yield falls due to the formation of side products. If 3 equivalents of acid are used, the reaction will also occur at -78 °C. Titanium tetrachloride also promotes the reaction at -78 °C; 2 equivalents of $TiCl_4$ are required, and the reaction is not as clean as the aluminum chloride-promoted reaction.

Scheme 105



212 **250**

The more mild Lewis acid, dimethylaluminum chloride,[128,129] provides the desired tetralone in only 49% yield, and the reaction in this case is much slower. This result is significant as this Lewis acid is also a proton scavenger,[128] indicating that the cycloaddition occurs even with no HCl present.

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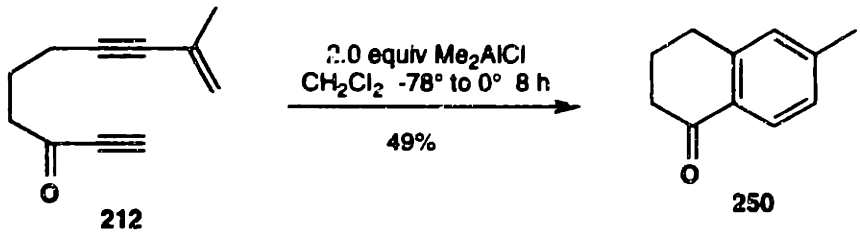
[127] For examples of $AlCl_3$ as a catalyst in intramolecular Diels-Alder reactions, see: (a) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4267. (b)Wenkert, E.; Naemura, K. *Syn. Commun.* **1973**, *3*, 45.

[128] For an overview on the use of alkylaluminum halides in pericyclic reactions, see: Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668. Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk. T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

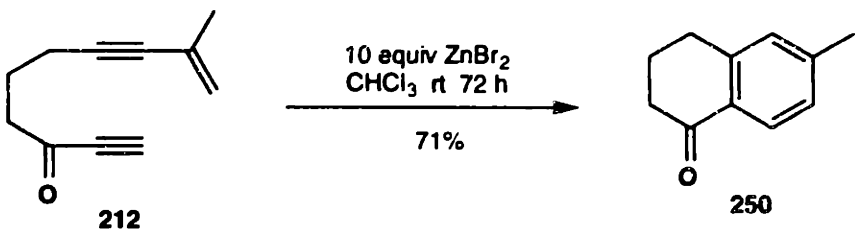
[129] For the use of Me_2AlCl in intramolecular Diels-Alder reactions, see: (a) Marshall, J. A.; Audia, J. E.; Grotte, J.; Shearer, B. G. *Tetrahedron*, **1986**, *42*, 2893. (b) Marshall, J. A.; Grote, J.; Shearer, B. *J. Org. Chem.* **1986**, *51*, 1635. (c)Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236. (d)Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 4877. (e) Sakan, K.; Smith, D. A. *Tetrahedron Lett.* **1984**, *25*, 2081.

Scheme 106



Fernández found that three zinc halide Lewis acids promote the cycloaddition: zinc chloride, zinc bromide, and zinc iodide; the effectiveness of these acids was related to the solvent used. The reaction was very slow in methylene chloride, due to the low solubility of the acid in this solvent. The reaction proceeded more quickly in chloroform, which dissolves the zinc halides more readily. Optimal results were obtained with commercial

Scheme 107

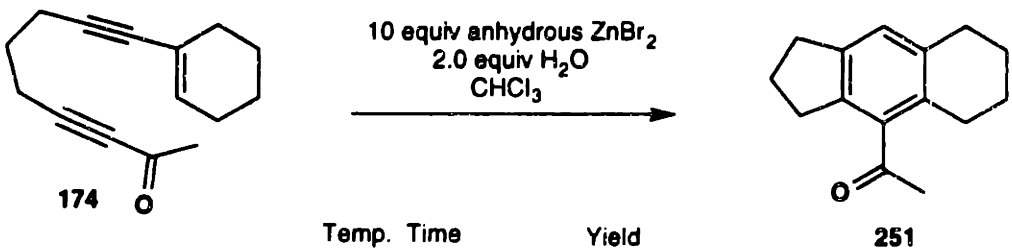


(unpurified) chloroform and 10 equivalents of zinc bromide. Commercial chloroform contains traces of ethanol and water, and these contaminants can react with zinc bromide to form HBr. The catalytic species here could indeed be HBr, not zinc bromide

In order to further investigate the role of HBr in the cycloaddition, some experiments were performed with zinc bromide in the presence of known amounts of water. Zinc bromide was first dried by heating under vacuum overnight, and the chloroform was distilled. Fernández had already shown that the cycloaddition did not proceed quickly under completely anhydrous conditions with type II enyne **212**. The type I cyclohexenylacetylene substrate **174** was treated with 10 equivalents of dry zinc bromide and chloroform. Known amounts of water (1, 2, and 5 equivalents) were then added to different reaction mixtures. With a single equivalent of water, some cycloadduct was

observed, but even with 2 or 5 equivalents the reaction was not complete after a day at room temperature. As shown in Scheme 108, heating the reaction mixture to reflux with 2 equivalents of water gave a 49% yield of cycloadduct **251** after 13 hours, confirming the need for HBr in the reaction mixture.

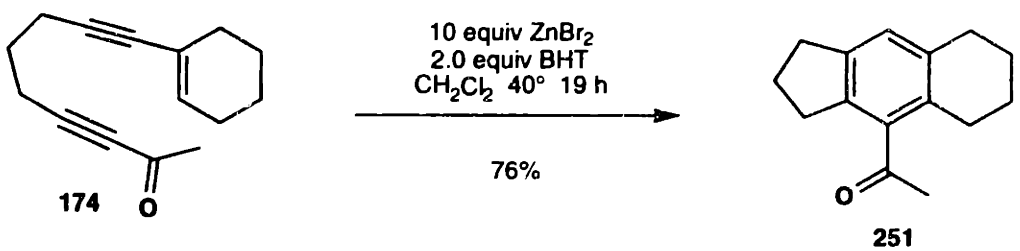
Scheme 108



Temp.	Time	Yield
rt	24 h	<50% complete
80°	13 h	49%
80°	20 h	51%

While water was an obvious choice as an additive, our previous experience with BHT, which also has a free hydroxyl group, led us to try it as an additive. Enyne **174** was dissolved in methylene chloride and treated with 10 equivalents of zinc bromide and 2 equivalents of BHT. After 13 hours at room temperature, the reaction was proceeding slowly, and clean conversion to product could be observed by TLC. Warming the reaction to reflux provided the desired cycloadduct **251** in 76% yield. The cycloadduct **251** is characterized by a singlet at 6.98 ppm in the ^1H NMR spectrum, and by a strong IR

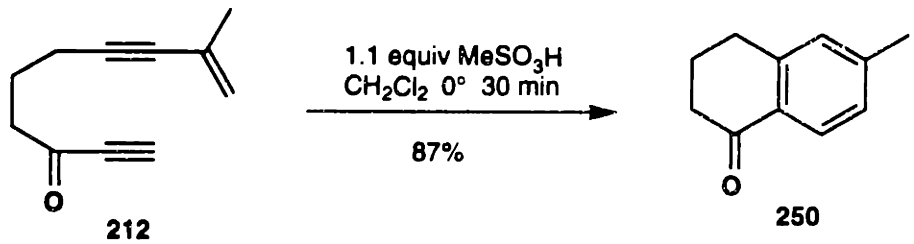
Scheme 109



stretching band at 1690 cm^{-1}, indicative of a ketone conjugated to an aromatic ring.[130] The actual structure of the reagent promoting this reaction is unclear. It is conceivable that zinc phenoxide and HBr are formed.

Given our zinc bromide results, Fernández tried several protic acids including trifluoroacetic, *p*-toluenesulfonic, methanesulfonic, camphorsulfonic, and trifluoromethanesulfonic acids. He found that methanesulfonic acid provided the best results. As shown below, when treated with 1.1 equivalent of methanesulfonic acid at 0 °C, enyne **212** provides the desired tetralone **250** in 87% yield.

Scheme 110



212 **250**

With several different conditions established as viable in promoting the cycloaddition, the next step was to examine the scope of the reaction using a variety of substrates. Most of the cycloadditions discussed below were attempted using the standard conditions discussed above and were not optimized.

Cycloadditions of Type I Substrates

As in the discussion of the synthesis of cycloaddition substrates, the review of the cycloadditions of type I substrates will begin with the results of varying the enyne substitution pattern. A discussion of the different tether lengths and different activating groups will follow.

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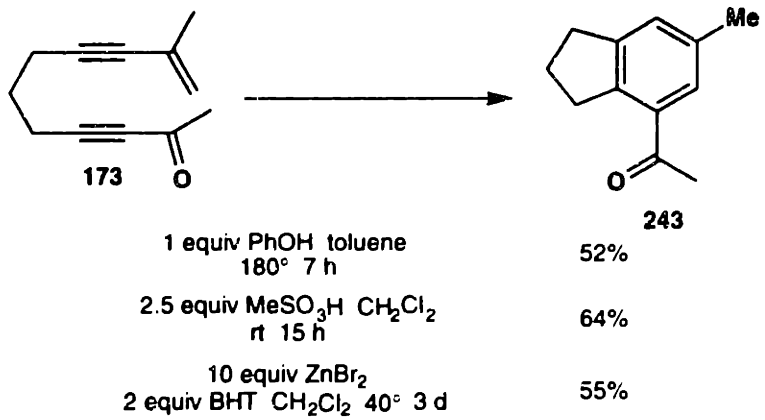
[130] Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981, p 117.

Different Enyne Substitution Patterns

Three substrates with different enyne substitutions were prepared and found to undergo the cycloaddition under several different conditions. As mentioned in the feasibility discussion above, enyne **173** is transformed into cycloadduct **243** in 52% yield after heating at 180 °C in toluene with 1 equivalent of phenol for 7 hours (Scheme 103). The reaction also proceeds under Lewis and protic acid conditions as shown in Scheme 111.

Scheme 111



The cyclohexenylacetylene **174** had provided a good yield of the cycloadduct **251** under the zinc bromide conditions, as shown above in Scheme 108. The cycloaddition of this substrate using a variety of other Lewis acids was also examined. When enyne **174** is treated with aluminum chloride, the cycloadduct is formed in 24% yield. Decomposition of the enyne substrate was also observed. Use of the less reactive Lewis acid, dimethylaluminum chloride, gives a slightly improved yield; the addition of BHT to the reaction mixture did not improve the yield significantly. Note that when BHT is added to an alkylaluminum species, it reacts to give a dialkoxyaluminum species.[131] As shown in

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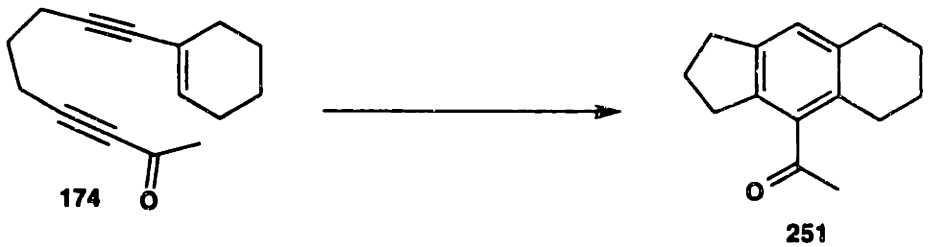
[131] Yamamoto and co-workers have found that phenols and alcohols react with trimethylaluminum to give aryloxyaluminum species, see: Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074. Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 9011. Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588. Roush has reported the use of menthoxyaluminum dichloride in intramolecular Diels-Alder reactions.[127a] This Lewis acid was prepared by treating a solution of ethylaluminum dichloride with menthol.

Scheme 112, several other conditions were explored with this substrate, but none provided improved yields. Zinc bromide is clearly the reagent of choice for this substrate.

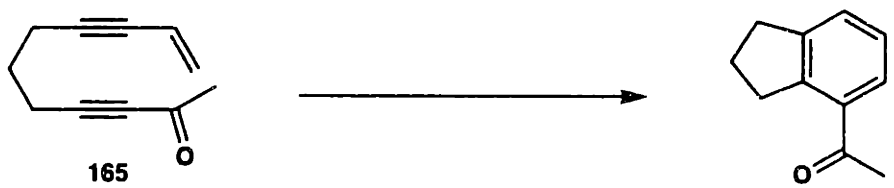
Scheme 112



1.0 equiv PhOH toluene 180° 7 h	~21%
2.0 equiv $TiCl_4$ CH_2Cl_2 -78° 5 min	Unidentified product
1.0 equiv $MeSO_3H$ CH_2Cl_2 rt 2 d	NR
1.0 equiv $MeSO_3H$ $C_2H_2Cl_2$ 80° 24 h	NR

The vinyl acetylene substrate **165** also underwent the cycloaddition (Scheme 113).

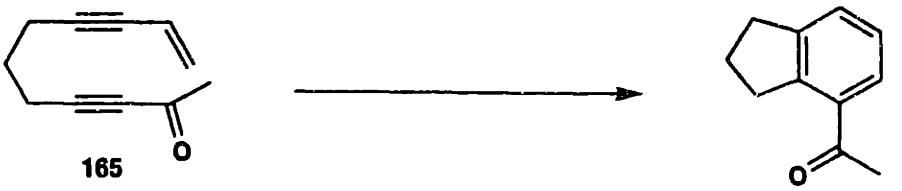
Scheme 113



1equiv PhOH toluene 180° 9.5 h	43%
2.5 equiv $MeSO_3H$ CH_2Cl_2 rt 108 h	54%

This enyne provided cycloadduct **252** in 43% yield after 9.5 hours in toluene at 180 °C. The reaction with methanesulfonic acid was sluggish, but it provided the desired indane **252** in 54% yield after almost 5 days. Poor yields of cycloadduct were obtained when the substrate was treated with either zinc bromide or aluminum chloride, as shown in Scheme 114.

Scheme 114



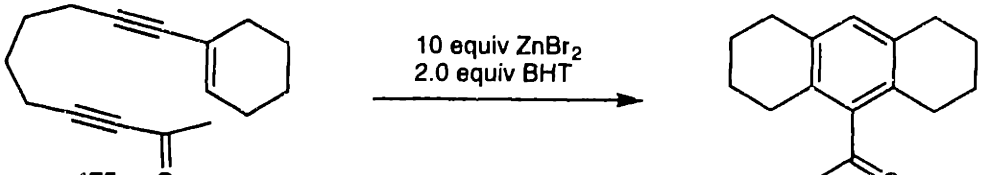
10 equiv $ZnBr_2$ 2 equiv BHT CH_2Cl_2 rt 45 h	NR
10 equiv $ZnBr_2$ 2 equiv BHT 0.2 equiv H_2O CH_2Cl_2 40° 14 h	~24%
10 equiv $ZnBr_2$ Et_2O rt 8h; 0.05 equiv BHT rt 12 h	NR
0.5 equiv $AlCl_3$ CH_2Cl_2 0°-rt 2h rt 22 h	19%

Of the three different substrates, the best yield overall for a cycloaddition was obtained with the cyclohexenyl compound **174**. The most versatile substrate was enyne **173**, which gave moderate yields under several conditions. With the survey of enyne substitution complete, the effect of the tether length was explored.

Different Tether Lengths

The only substrate prepared with a four instead of three carbon tether was cyclohexenyne **175**. As shown below, this enyne gives the tricyclic cycloadduct **253** in good yield when heated in the presence of zinc bromide and BHT; however, the rate of this reaction is much slower than the corresponding rate of the three carbon tether substrate. Reaction at 180 °C without Lewis acid gave **253** in only 6% yield; no starting material was recovered from this reaction.

Scheme 115



CH_2Cl_2 40° 6.5 d	71%
$ClCH_2CH_2Cl$ 80° 18 h	60%

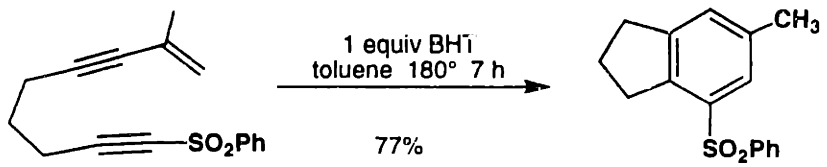
The longer tether length slows the rate of the reaction, and yields for the longer

tether length substrate are lower. The slower reaction rate agrees with the increased entropy component required to bring the longer tether into a reactive conformation. Having explored the cycloaddition of substrates with different enynes and tether lengths, we next focused on the cycloadditions of substrates with different enynophile activating groups.

Different Enynophile Activating Groups

This survey began with the best substrate for the thermal cycloaddition, enyne sulfone **189**, which provided cycloadduct **254** in 77% yield after 7 hours at 180 °C.

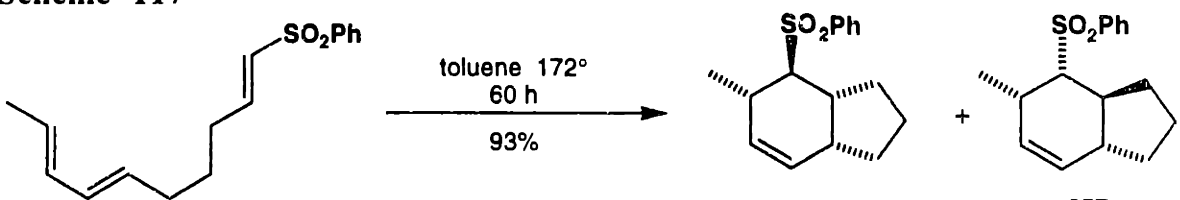
Scheme 116



189 **254**

Diels-Alder reactions of sulfones are well known.[132,133,134] Craig and co-workers[133] have found that the α,β-unsaturated sulfone **255** undergoes Diels-Alder cycloaddition at 172 °C. This reaction requires 60 hours to give the desired products in excellent yields.

Scheme 117



255 **256** **257**

1 : 1

Alkynyl sulfone **189** cyclized only under thermal conditions; this substrate either decomposed or did not react under Lewis or protic acid conditions. This lack of reactivity with Lewis acids was a bit surprising, since the literature contains examples of both inter- and intramolecular cycloadditions of sulfones that are catalyzed by Lewis acids.[132,134]

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[132]For a review of sulfur functionalities in cycloadditions, see: De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755.

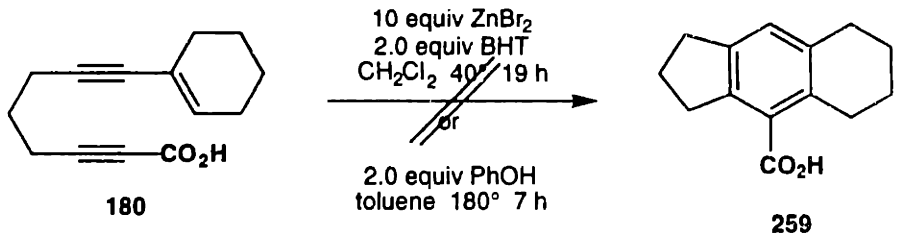
[133]Craig, D.; Fischer, D. A.; Kemal, Ö.; Plessner, T. *Tetrahedron Lett.* **1988**, *29*, 6369.

[134] For an example of an intermolecular reaction, see: Snider, B. B.; Kirk, T. C.; Roush, D M.; Gonazlez, D. *J. Org. Chem.* **1980**, *45*, 5015.

As discussed in the feasibility section of this chapter, methyl ester **176** provides the cycloadduct under thermal conditions in 52% yield (Scheme 103). No other conditions were explored with this substrate.

Carboxylic acid enyne **180** was subjected to the standard thermal conditions, involving heating in toluene with 2 equivalents of phenol at 180 °C for 7 hours. Neither the desired cycloadduct **259** nor the starting material was isolated. Instead, the phenyl ester of the starting material was found as identified by ^{1}H NMR. This substrate did not cyclize under zinc bromide conditions either. The starting material was consumed, and no new products were isolated.

Scheme 118



Several researchers have explored the use of water as a solvent in cycloadditions.[126,135,136] Although our reaction is intramolecular, we were interested in the effect water would have on the cycloaddition. The sodium salt of enyne **180** was prepared by treatment with 0.95 equivalent of sodium bicarbonate in water.[136b-e] BHT was added to the reaction mixture, and the solution was heated to 100 °C for one day. No reaction was observed and most of the starting material was recovered unchanged.

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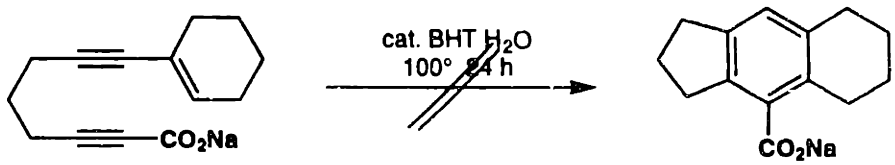
[135] For reviews on water as a solvent for organic reactions, see: Li, C.-H. *Chem. Rev.* **1993**, *93*, 2023. Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. Grieco, P. A. *Aldrichchemica Acta* **1991**, *24*, 59. Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. Symons, M. C. R. *Acc. Chem. Res.* **1981**, *14*, 179.

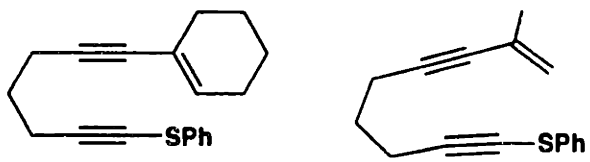
[136](a) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1988**, *42*, 2847. (b)Yoshida, K.; Grieco, P. A. *Chem. Lett.* **1985**, 155. (c) Yishica, K.; Grieco, P. A. *J. Org. Chem.* **1984**, *49*, 5257. (d) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. (e) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3139. (f) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613. Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239. (g) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7812. (h) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241.

Scheme 119



260 261

Having examined several cycloadditions with electron-deficient substrates, we next investigated reactions involving substrates lacking electron-withdrawing substituents. The alkynyl sulfide **182** did not provide the desired cycloadduct when treated with zinc



182 179

bromide or aluminum chloride. No reaction was observed when the substrate was treated with dimethylaluminum chloride, and partial decomposition of the starting material occurred when the reaction was heated to 180 °C in toluene.

In order to determine if a higher temperature was required, the sulfide **179** was dissolved in cyclohexane and heated to 250 °C in the presence of 1 equivalent of *p*-methoxyphenol. This, unfortunately, gave a black tar. In short, phenyl sulfide derivatives fail to give the cycloadduct under a variety of conditions.

Diels-Alder reactions of sulfides are known,[132] including some intramolecular examples, as shown in Scheme 120. The uncatalyzed reactions usually involve inverse electron demand substrates like the diene ester **264**.[137] Many cycloadditions of simple sulfide substrates are catalyzed by cation radical salts.[138] For example, sulfide **266** undergoes a cycloaddition at 0 °C to give the cycloadduct **267** in 38% yield when treated

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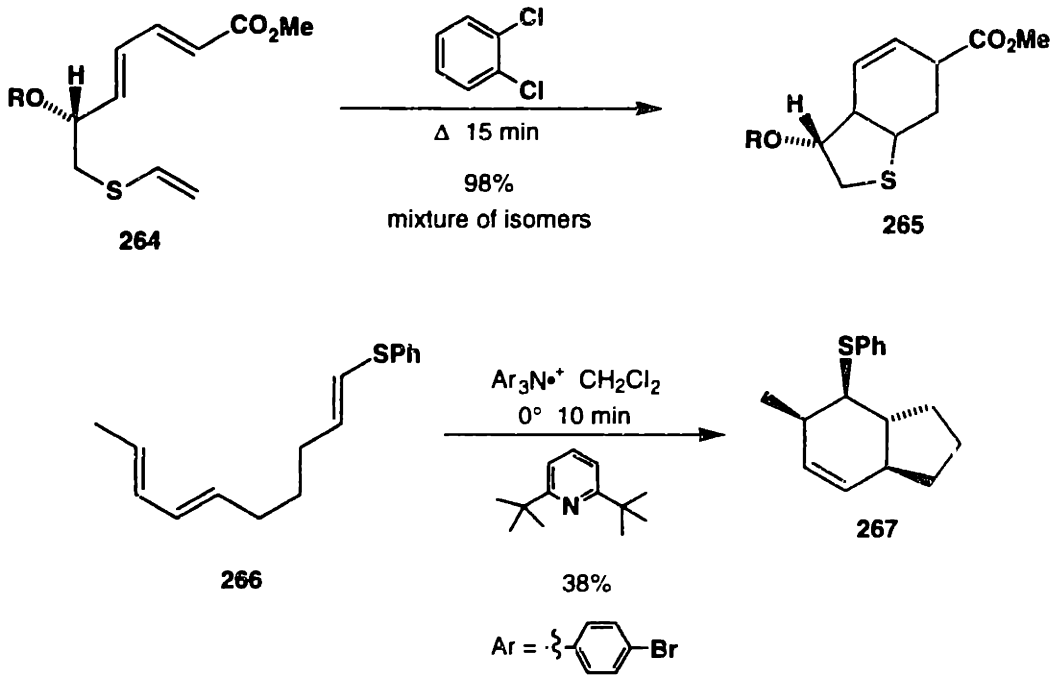
[137] Williams, D. R.; Gaston, R. D. *Tetrahedron Lett.* **1986**, *27*, 1485.

[138] For a review of cation radical salts and their role in Diels-Alder catalysis, see: Bauld, N. L. *Tetrahedron* **1989**, *45*, 5307.

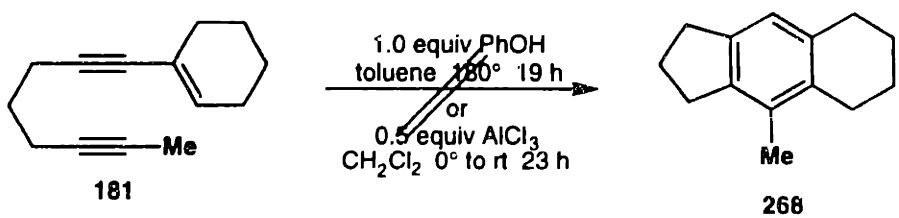
with the triarylaminium salt, tris(4-bromophenyl)aminium hexachloroantimonate.[139] These salts oxidize the vinyl sulfide to form a cation radical which then undergoes the cycloaddition. Although these conditions were not explored with our enyne substrates, it would be interesting to see what happens with this type of catalyst.

Scheme 120



The dialkyl-substituted acetylene enynophile **181** did not provide any cycloadduct under thermal and aluminum chloride conditions. In the first case, starting material was recovered, indicating that the substrate may be too hindered to react. In the presence of aluminum chloride, only decomposition was observed.

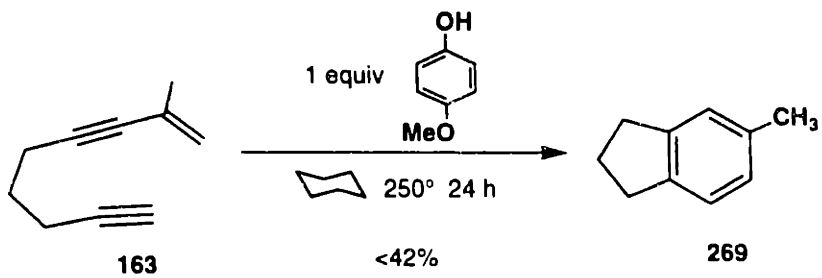
Scheme 121



[139] Harirchian, B.; Bauld, N. L. *Tetrahedron Lett.* **1987**, *28*, 927.

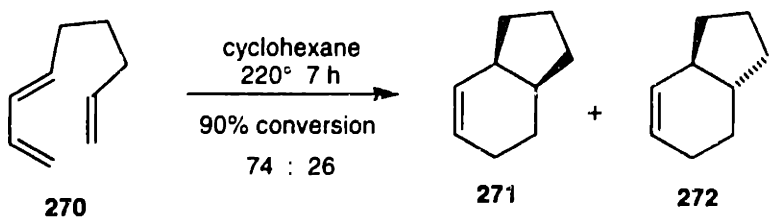
Better results were obtained with unactivated enynophiles using the isopropenyl-acetylene substrates. Enyne **163** was heated to 260 to 300 °C on a small scale to obtain a 50% yield of the desired cycloaddition product **269**.[140] Unfortunately, when the reaction was attempted on a larger scale, the yield was lower and was not reproducible. Ultimately, the desired compound was obtained in 32 to 42% yield with a purity of between 75 and 80% as determined by ^{1}H NMR (estimated yield: 26%). The disappointing yield for this reaction may be due in part to the volatility of the cycloadduct **269**.

Scheme 122



Lin and Houk have reported the Diels-Alder cycloaddition of unactivated diene **270**, which cyclized at 220 °C in cyclohexane to give a mixture of cis and trans cycloadducts.[141] The reaction proceeds to 90% conversion, but no yield is reported. It is interesting to note that this Diels-Alder reaction and the enyne cycloaddition described above proceed under similar thermal conditions.

Scheme 123



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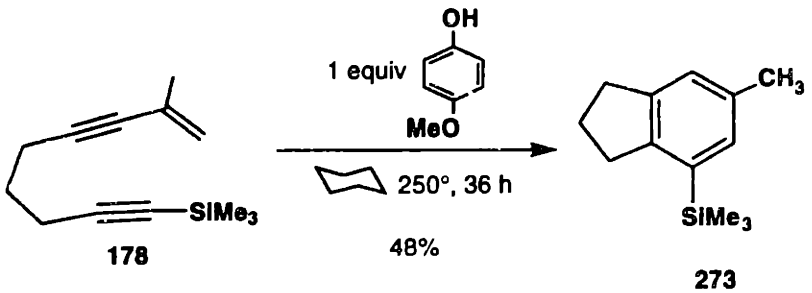
[140]Spectral data agree with published results, see: Collins, M. J.; Gready, J. E.; Sternhill, S.; Tansey, C. W. *Aust. J. Chem.* **1990**, *43*, 1547. Adamczyk, M.; Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, *49*, 4226.

[141] Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269. For further calculations on this unactivated Diels-Alder reaction, see: Brown, F. K.; Singh, U. C.; Kollman, P. A.; Raimondi, L.; Houk, K. N.; Bock, C. W. *J. Org. Chem.* **1992**,*57*, 4862.

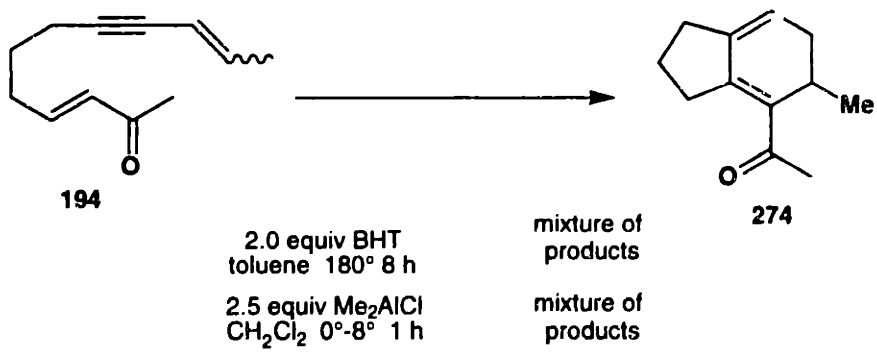
The trimethylsilyl acetylene **178** gave cycloadduct **273** in 48% yield when heated to 250 °C for 36 hours. BHT was not used in this reaction; instead, the more polar *p*-methoxyphenol was used, because it was easily separated from the cycloadduct.

Scheme 124



Finally, one type of alkene enynophile was prepared in the type I series of substrates. This compound gave a mixture of products when treated with methanesulfonic acid. When heated to 180 °C in toluene, a mixture of several compounds was obtained as determined by ^{1}H NMR. The cycloadditions of this substrate seemed bound to give many products and were not explored any further.

Scheme 125



While many of these cycloadditions were unfruitful, some valuable things were learned about this reaction. Several different electron deficient substrates were found to undergo the cycloaddition in moderate to good yields. Even a substrate with an unactivated enynophile (**163**) undergoes the reaction, albeit in low yield, and the silyl enyne **178** also participates in the cycloaddition. In general, the isopropenyl enynes react most smoothly; although with zinc bromide, the cyclohexenyl ketones are very good substrates. When

compared to a Diels-Alder reaction, the enyne cycloaddition is not as facile in general, but does proceed under similar conditions.

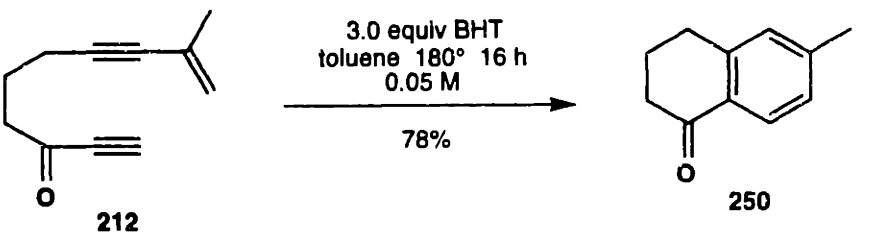
Cycloadditions of Type II Substrates

The discussion of the cycloadditions of type II substrates will be divided into three sections dealing with substrates with different enynophile substitution, substrates with different tether lengths, and finally substrates with different enyne substitution patterns. Roberto Fernández did all of the work on the substrates in the first two areas. Further studies on the effect of solvent on the cycloaddition and enyne substitution were addressed after Fernández had left our group.

Different Enynophile Activating Groups

As described in the section on optimization, enyne **212** is a good substrate for the cycloaddition, providing the cycloadduct **250** in good yields under protic and Lewis acid conditions. Fernández also found that enyne **212** is a good substrate under thermal conditions, providing the desired product in 78% yield. The initial conditions for this reaction involved 3 equivalents BHT in toluene at 180 °C for 16 hours; Fernández ran the reaction at 0.05 M, one half the concentration generally used in the type I cycloadditions.

Scheme 126

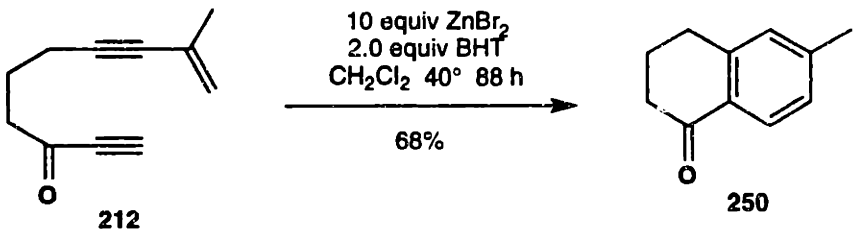


212 **250**

In order to make a direct comparison of this substrate with the type I substrates, the enyne was also treated with zinc bromide as shown in Scheme 127. Refluxing methylene chloride was required, and after 88 hours enyne **212** provided the desired product in 68% yield. Due to solubility problems, the reaction is much slower when methylene chloride

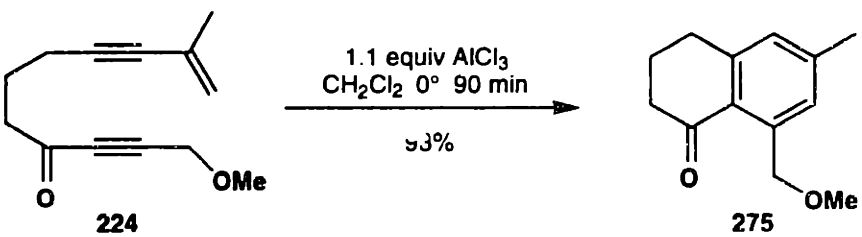
rather than chloroform is used, but the yields are similar.

Scheme 127



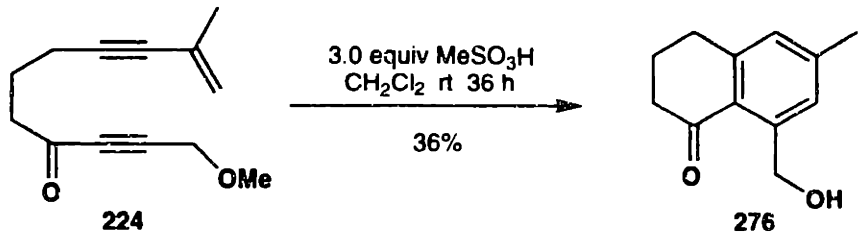
Two substrates with disubstituted enynophiles were prepared, compounds **224** and **229**, to explore the effect of substitution on the cycloaddition. The methoxymethylene substrate **224** was found to cyclize in excellent yield when treated with aluminum chloride, as shown in Scheme 128. The disubstituted enynophile substrates react more slowly than the monosubstituted enynophile substrates, as enyne **212** requires only 30 minutes at 0 ℃ to give the desired tetralone. This may be due to an increase in steric bulk around the enynophile. We have found this decrease in rate to be a general trend in the cycloaddition,

Scheme 128



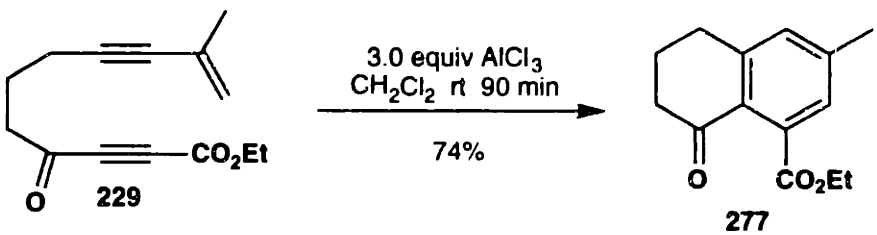
as will be seen in the next chapter. When treated with methanesulfonic acid, enyne **224** did not give the desired tetralone **275**, but rather tetralone **276**, in which the methyl ether had been cleaved, in 36% yield. Several other compounds observed in the reaction mixture were the result of attack on the enyne moiety by the acid. As will be discussed in a later chapter, enynes can be hydrolyzed under protic acid conditions to form α,β-unsaturated enones. This type of product has been observed when the cycloaddition reaction is sluggish. Clearly, the different modes of activation involved with protic and Lewis acids are affected by the substitution on the enyne.

Scheme 129



The other substrate with a substituted enynophile that was investigated is **229** with a doubly activated enynophile. This enynophile, with two electron withdrawing groups, was expected to be very reactive in the cycloaddition. While the substrate did not live up to expectations, it did provide some interesting results. Treatment of enyne **229** with aluminum chloride provided the desired tetralone **277** in 74% yield after 90 minutes at

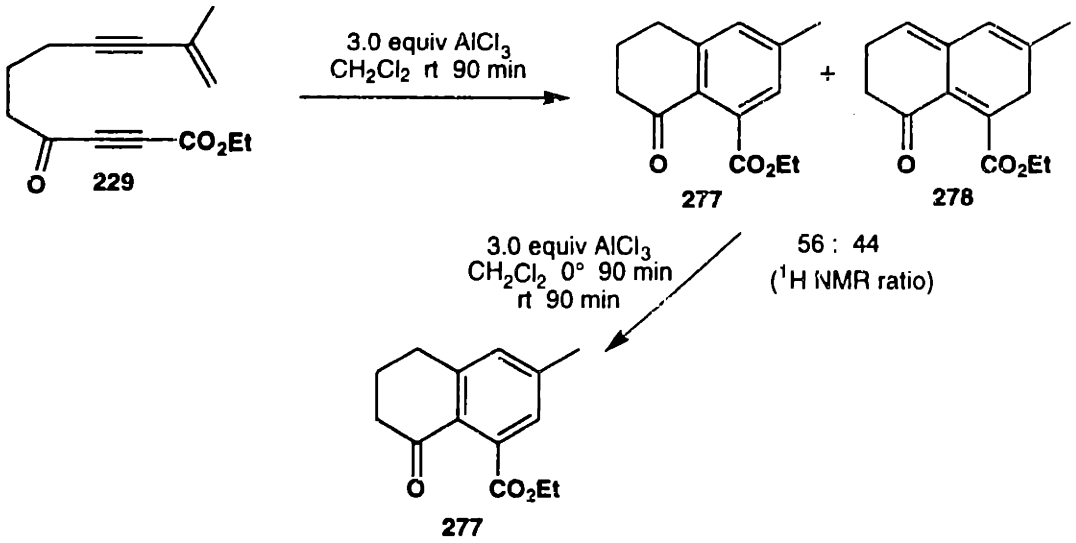
Scheme 130



room temperature. While monitoring the reaction, Fernández observed an intermediate by TLC. The reaction was then run at 0 °C and quenched after 20 minutes. A ^1H NMR spectrum of the crude reaction mixture showed a 56:44 mixture of two compounds, the desired tetralone **277** and another compound, **278**. This mixture was resubjected to the reaction conditions, and after 90 minutes at 0 °C, no change was observed by TLC. The reaction mixture was then warmed to room temperature, and conversion of the mixture to the desired product was complete after 90 minutes. The formation of this side product and its implications on the mechanism will be addressed in Chapter 1 of Part III.

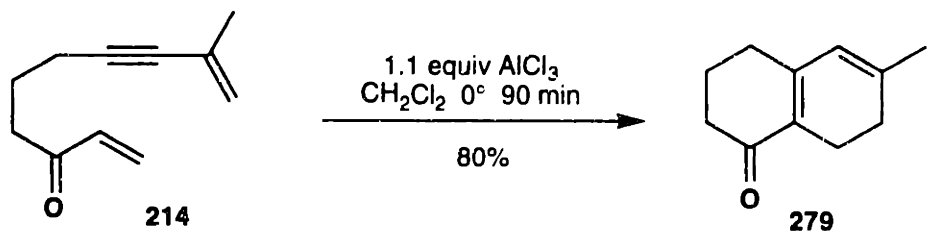
Compound **229** gave tetralone **277** in 69% yield when heated in toluene in the presence of 3 equivalents of BHT at 130 °C for 16 hours.

Scheme 131



The enyne substrate **214**, with an olefinic enynophile, was found to give the dihydroaromatic cycloadduct **279** in good yield after 90 minutes at 0 °C when treated with aluminum chloride. In this case, only one isomer of the dihydroaromatic product. the

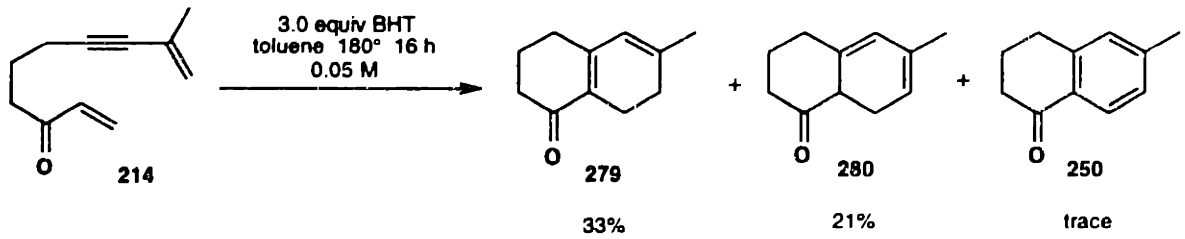
Scheme 132



thermodynamically more stable conjugated one, was isolated. However, when the enyne was heated in toluene, a mixture of products was isolated (Scheme 133). The two dihydroaromatic products **279** and **280** result from the loss of different hydrogen atoms or protons from the intermediate. The aromatic product, which was not isolated but was observed by NMR, is not unexpected under the reaction conditions. The presence of multiple products under thermal conditions meant that these conditions would not be useful for further cycloaddition studies with the alkene enynophiles. As we shall see in later

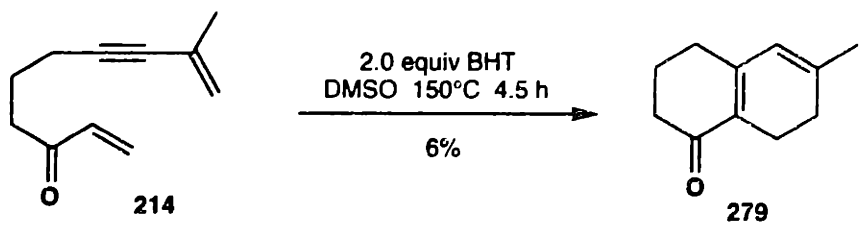
chapters, Lewis and protic acid conditions are best employed with these type of substrates.

Scheme 133



Although water did not promote the reaction as desired with cyclohexenylacetylene substrate **251**, we were interested in other solvents that have properties similar to water[126] and might facilitate the cycloaddition. Inspired by the work of Jung[142] and Liotta[143] in the area of intramolecular Diels-Alder reactions, we explored the use of ethylene glycol and DMSO as solvents. In order to examine these solvents, two type II substrates, enyne **212** and **214**, were used. Heating enyne **214** in ethylene glycol at 150 °C for 2 hours gave a 37% yield of the cycloadducts **279** and **280**. This yield was not as high as the reaction in toluene, but the low temperature and short reaction time were encouraging. Unfortunately, other conditions only led to extensive decomposition of the enyne and low yields of the products. Heating the enyne in DMSO at 180 °C for 4.5 hours gave a 6% yield of the cycloadduct **279**.

Scheme 134



In the hope that the alkene substrate was just too delicate for these polar conditions, another substrate, enyne **212**, was subjected to the ethylene glycol conditions. When the enyne was added to ethylene glycol that had been dried over 4Å sieves, decomposition

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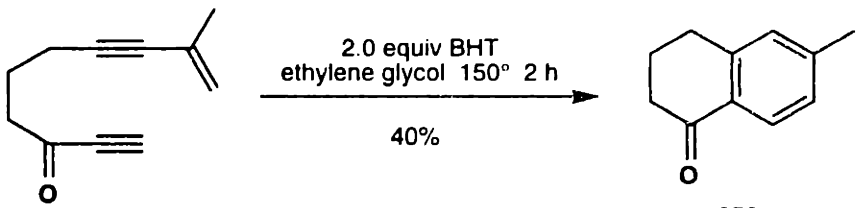
[142] Jung, M. E. *Synlett* **1990**, 186.
[143] Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3745.

began immediately. Apparently, the drying procedure acidified the solvent. Undried ethylene glycol was then used, and a 40% yield of the tetralone **250** was obtained after 2 hours at 150 °C in the presence of 2 equivalents of BHT. Further attempts to optimize this reaction did not give improved yields, and the exploration of these solvents was abandoned. Other work has been done with different solvent systems using different substrates. Brenda Palucki has explored the use of 5.0 M lithium perchlorate in ether as a solvent for this reaction. Further discussion of this work will be addressed in Part III, Chapter 2.

Scheme 135



212 **250**

Different Tether Lengths

Unlike the type I substrates, most of the type II substrates had four carbon tethers connecting the enyne to the enynophile. This was based on work done by Jung and Halweg[144] who found that compound **281** was more reactive in intramolecular Diels-Alder

Scheme 136

281 **282**

reactions than the homologous compound **282**. The shorter chain length of compound **282** prevents effective overlap of the carbonyl and alkene orbitals in the transition state, and the Diels-Alder reaction requires high temperatures similar to those required by a

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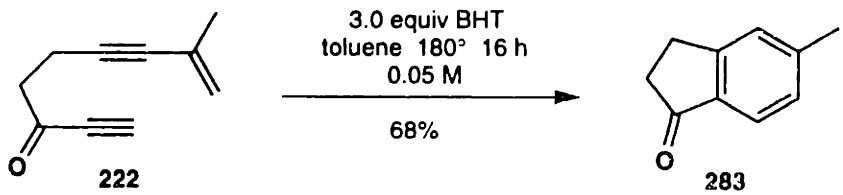
[144] Jung, M., E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929 and references cited therin.

simple unactivated triene.

Fernández prepared enyne substrate **222** to evaluate this reactivity hypothesis in the enyne cycloaddition. As shown below, enyne **222** does undergo a cycloaddition when heated in toluene at 180 °C to give cycloadduct **283** in 68% yield after 16 hours. Recall that the cycloaddition of the homologous enyne **212** proceeds under similar conditions. The alkynyl ketone, with its cylinder of electron density around two carbons of the triple bond, can remain closer to full conjugation in the transition state than an alkenyl ketone can. This maintenance of conjugation allows the reaction of **222** to proceed at a rate similar to the reaction of **212**. It is worth noting that the thermal cycloaddition of **281** proceeds at 0 °C, while the enyne **212** requires 180 °C, so clearly there are other differences in the cycloadditions of substrates **212** and **281**. Under a variety of Lewis or protic acid conditions, enyne **222** does not react to give the desired product.

Scheme 137



222 **283**

In summary, the different enynophiles examined all undergo the cycloaddition in moderate to good yield. Substitution slows the reaction. Further evidence of the slower rate of reactions with alkyne substitution will be seen in the next chapter.

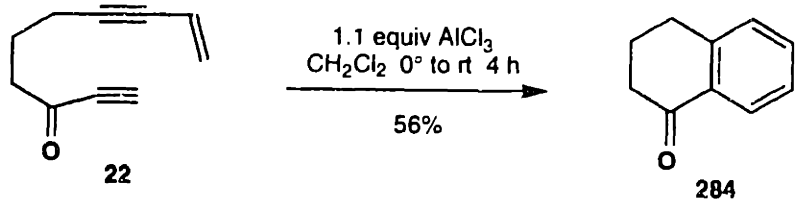
Different Enyne Substitution Patterns

The final area of interest in our study of the scope of the cycloaddition was the effect of enyne substitution on the reaction. Interest in this area resulted from work exploring the use of other alkenes as enynophiles. A total of four differently substituted enynes were prepared as described previously. The reactivity of these substrates is suprisingly varied; some substrates give excellent yields, while others only a trace of cycloadduct.

The first type II enyne studied was the isopropenylacetylene substrate **212**. The cycloaddition of this compound can be effected by both protic and Lewis acids as well as by simple heating to 180 °C, as seen in Scheme 139, Scheme 105, Scheme 127, and Scheme 126. The yields for these reactions range from 68 to 90%, with the exception of the reaction with dimethylaluminum chloride which only gives a 49% yield.

The vinyl acetylene substrate **22** gave the desired cycloadduct under many conditions, although in general, reactions of this enyne were not as facile as those of isopropenylacetylene **212**. Treatment with aluminum chloride at 0 °C, followed by slow warming to room temperature over 4 hours provided tetralone **284**[145] in 56% yield. This reaction was slower and not as efficient as the aluminum chloride reaction of enyne **212**.

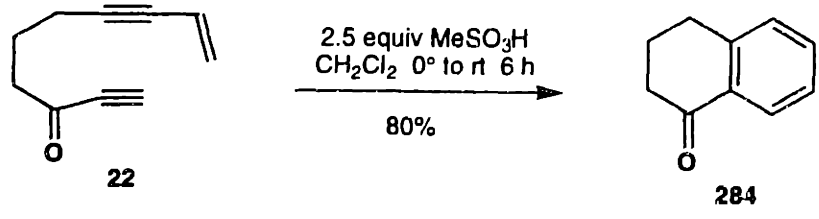
Scheme 138



22 284

Methanesulfonic acid promoted the cycloaddition as well (Scheme 139). After 6 hours between 0 and 23 °C, the cycloadduct was isolated in 80% yield. Purification of this

Scheme 139



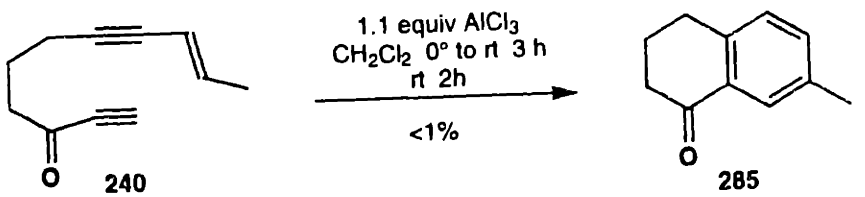
22 284

[145] ^1H and ^{13}C NMR data agree with published reports, see: (a) Patra, A.; Misra, S. K. *Mag. Res. Chem.* **1991**, *29*, 749. (b) Boykin, D. W.; Dewprashad, B.; Eisenbraun, E. J. *J. Org. Chem.* **1990**, *55*, 425. (c) Buchanan, G. W.; Wightman, R. H.; Dawson, B. A. *Mag. Res. Chem.* **1989**, *27*, 606. (d) Adamczyk, M. Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, *49*, 4226. (e) Morin, F. G.; Horton, W. J.; Grant, D. M.; Dalling, D. K.; Pugmire, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 3992.

compound was complicated by the presence of an impurity that was difficult to separate by column chromatography. Thermolysis of the enyne in toluene at 180 °C for 8 hours provided only a 37% yield of the desired product, which was less than 95% pure by ^{1}H NMR.

The *n*-propenylacetylene substrate **240** was a poor type II substrate for the cycloaddition. This compound decomposed under the standard conditions and did not react under more mild ones. Treatment with 1.1 equivalent of aluminum chloride at 0 °C produced no reaction, and upon stirring at room temperature for 1 day, the enyne decomposed to baseline material by TLC. A trace of product **285** was observed when the reaction was monitored by TLC. As shown in Scheme 94, after 2 hours at room temperature, less than 1% of the product was isolated. When methanesulfonic acid and zinc bromide were used, similar results were obtained. At low temperatures no reaction or slow decomposition was observed, and at higher temperatures decomposition was the only

Scheme 140

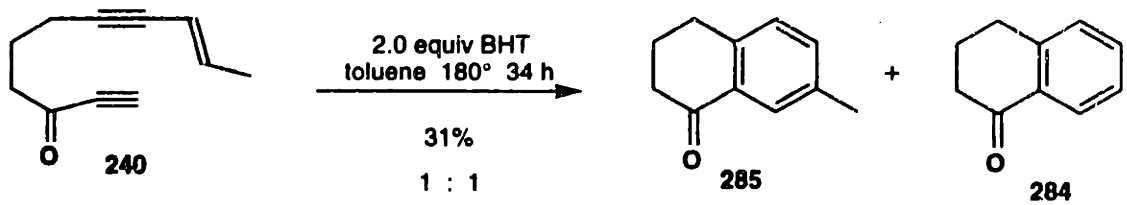


240 **285**

observed reaction. The thermal reaction provided some interesting results, however. Thermolysis of the enyne at 180 °C in toluene for 34 hours gave one main product as observed by TLC analysis. The material isolated was a 1:1 mixture of products by ^{1}H NMR. One of the compounds was the desired product, tetralone **285**,[145b] and the other compound was tetralone **284**. As both of these compounds are known[145b] and the unsubstituted tetralone **284** had been recently prepared, confirmation of their identities was possible by comparing ^{1}H NMR spectra. Further confirmation was provided by GC/MS which showed two peaks in the GC trace, one peak had a mass of 146 m/z (corresponding to unsubstituted tetralone **284**) and one peak had a mass of 160 m/z (corresponding to

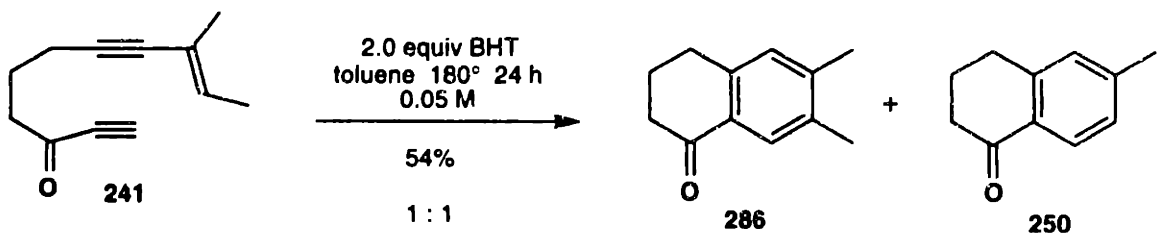
methyl tetralone **285**). The compounds were formed in an overall yield of 31%, as determined by ^{1}H NMR.

Scheme 141



The strange loss of a methyl group was observed again with the 1-methyl-1-propenylacetylene substrate **241**. Thermolysis of this enyne at 180 °C for 24 hours provided a mixture of products. As shown in Scheme 142, the desired tetralone **286**[145b] was isolated as an inseparable 1:1 mixture with tetralone **250**. Confirmation of the identities of the two components of the mixture was possible by comparing the ^{1}H NMR spectra of the pure products (pure dimethyl tetralone **286** was obtained as described below)

Scheme 142

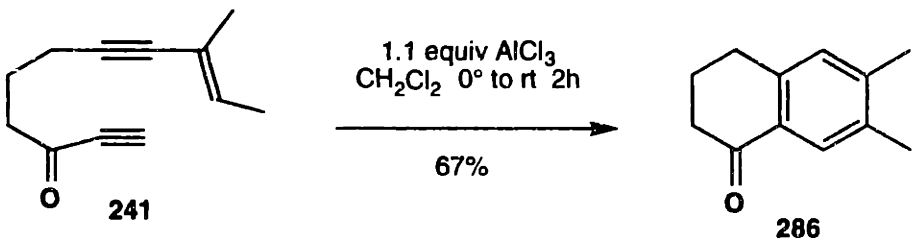


with that of the mixture. Further confirmation was obtained from GC/MS. Two peaks were evident on the GC trace; the first one gave a mass of 160 m/z, which corresponded to the methyl tetralone **250**. The second peak gave a mass of 174 m/z, which corresponded to the dimethyl tetralone **286**. The yield for this reaction was 54% overall, as determined by ^{1}H NMR. Further discussions of these results will be addressed in Part III Chapter 2. Clearly, the terminal methyl substituent on the enyne is a problem in the thermal reaction.

Under other reaction conditions, the 1-methyl-1-propenylacetylene substrate **241** was much better behaved. Treatment of this enyne with aluminum chloride provided the desired cycloadduct, with no sign of demethylated compound, in 67% yield. The reaction,

which required 2 hours, is slower than the corresponding reaction with isopropenylacetylene substrate **212**. Cycloadduct **286** was characterized by two singlets in the ^{1}H NMR spectrum at 7.78 and 7.00 ppm. The enyne did not react cleanly when treated with methanesulfonic acid.

Scheme 143



The isopropenyl substitution pattern gives the best results for the type II substrates. As with the type I compounds, the vinyl acetylene substrates also react well. The disubstituted enyne provides a moderate yield under Lewis acid conditions, but under thermal ones, the interesting loss of a methyl group complicates the reaction.

Overall, the type I and II substrates provide cycloadducts in a range of yields. Type II substrates tend to be more reactive than type I compounds, and their reactions proceed in better yields. In the next chapter, a review of some of the other types of substrates and cycloadditions examined in our group will be presented along with a summary of the scope of this reaction and some conclusions that we have drawn.

Chapter 3

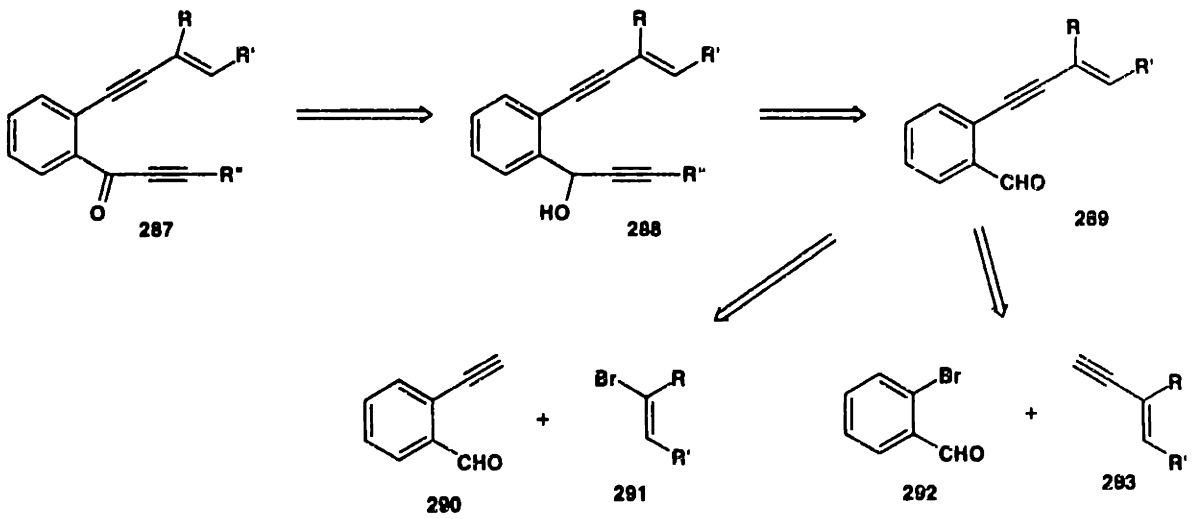
The Scope of the Enyne Cycloadditions: Summary and Conclusions

Other workers in the Danheiser laboratory have explored the scope of the [4+2] cycloaddition of conjugated enynes. This chapter will review some of their work and present a summary of our conclusions about the scope of this cycloaddition.

Synthesis of Fluorenones

Anna Helgason examined the use of the enyne cycloaddition in the synthesis of fluorenones. These studies were designed to determine whether further conformational constraints might facilitate the reaction. The substrates used in this investigation were disubstituted benzenes such as **287** (Scheme 144), which were prepared in four steps via two pathways that proceed via aldehyde **289**. Aldehyde **289** was prepared in turn in

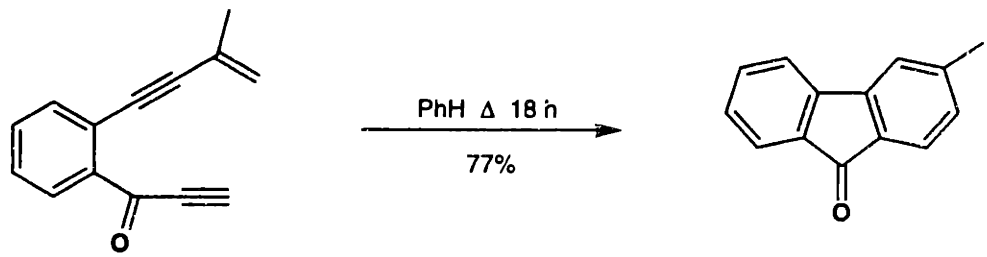
Scheme 144



two ways via modified Castro-Stevens[86] coupling reactions. Either alkyne **290** was coupled with vinyl halide **291**, or bromobenzaldehyde **292** was coupled to enyne **293**. The aldehyde **289** was then treated with ethynylmagnesium bromide to give propargyl alcohol **288** which was oxidized with the Dess-Martin reagent to give the desired cycloaddition substrate **287**.[146]

Helgason's first substrate, the isopropenylacetylene **294**,[147] was found to cyclize in 77% yield when heated to reflux in benzene for 18 hours (Scheme 145). Since Helgason found that several ketones of type **287** were unstable to isolation and concentration, oxidation with Dess-Martin periodinane and cycloaddition were performed as two sequential steps without isolation of the unstable ketones.[148]

Scheme 145



294 **295**

The cyclohexenylacetylene **296** was found to oxidize cleanly to the ketone and undergo cycloaddition rather quickly, requiring only 3 hours at 80 °C to give the desired fluorenone **297** in 88% yield.[149] This substrate also cyclized in the presence of the Lewis acids aluminum chloride and dimethylaluminum chloride in 38% and 19% yields respectively.[150] Each of these Lewis-acid promoted reactions was improved by the addition of BHT to the reaction mixture; the desired fluorenone was formed in 53% and 40% yield under these conditions. BHT can react with either Lewis acid to give an alkoxyaluminum

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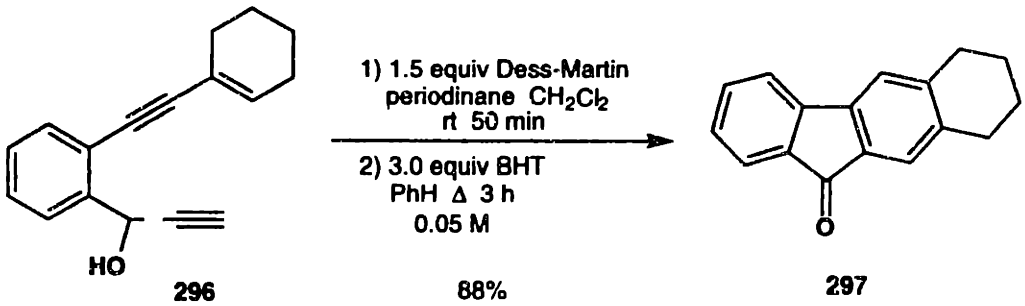
[146] For a full account of the synthesis of these compounds, see: Helgason, A. L. Ph. D. Thesis, Massachusetts Institute of Technology, May 1994, pp 144-167.
[147] *Ibid.* pp 148-149.
[148] *Ibid.* pp 151-154.
[149] *Ibid.* pp 153-154.

species that could then catalyze the reaction.[131] Although, hydrochloric acid is produced in the reaction of BHT with aluminum chloride, the use of protic acids was not explored in promoting this reaction.

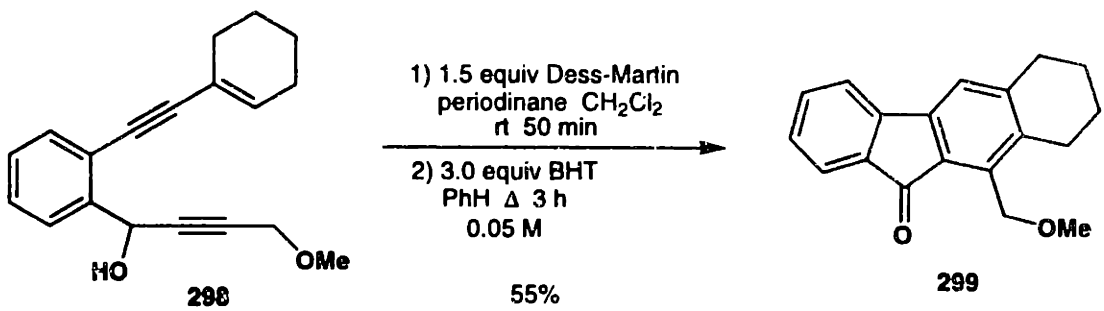
Scheme 146



296 88% **297**

The substituted acetylenic ketone derived from **298** was found undergo the cycloaddition much more slowly than the unsubstituted acetylenic ketone derived from **296**.[151] This substituted substrate required heating to reflux in toluene (instead of benzene) for 3 hours to give the desired fluorenone **299** in 53% yield. Fluorenone **299** could also be obtained by treating the enyne with either aluminum trichloride or dimethylaluminum chloride in the presence of BHT; the yields for these reactions were 46% and 37% respectively.

Scheme 147



298 55% **299**

The final set of substrates examined by Helgason involved the ester-substituted

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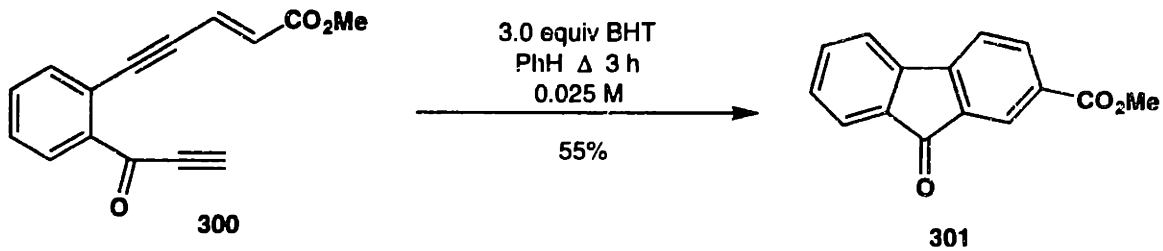
[150] *Ibid.* pp 154-156.
[151] *Ibid.* pp 156-158.

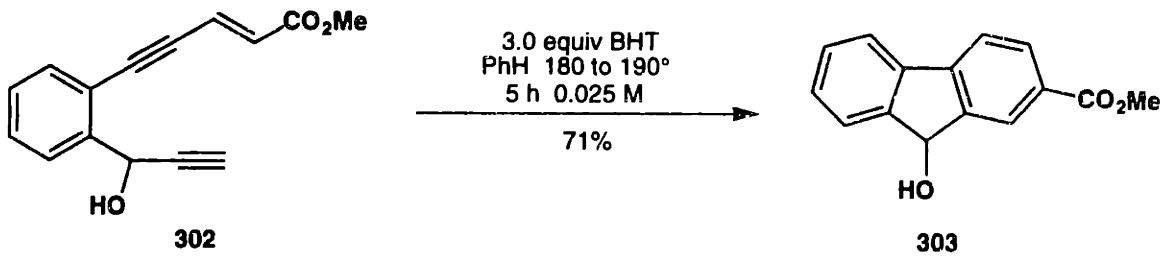
enynes such as **300**.[152] The doubly electron deficient substrate **300**, which was stable at 5 °C and could be stored for several weeks, provided the desired cycloadduct **301** in 55% yield when the reaction was run at 0.025 M. Lower yields were obtained at higher concentrations, and no desired product was obtained when ketone **300** was treated with Lewis acids.

Scheme 148



The cycloaddition of inverse electron demand substrate **302** was also explored.[153] As shown in Scheme 149, this propargylic alcohol was found to cyclize at a higher temperature (180 to 190 °C) than the ketone **300**, but the yield was much improved. Compound **303** was produced in 71% yield after 5 hours.

Scheme 149



Helgason found that fluorenones could be produced in fair to excellent yield under thermal conditions. The temperatures required for the cycloaddition are much lower than those required for the other substrates that have been examined. In general, Lewis acids did not provide improved yields, although the low temperatures required for the thermal cycloaddition make this point less important. Some of the trends observed with other

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[152] *Ibid.* pp 159-162.
[153] *Ibid.* p 162.

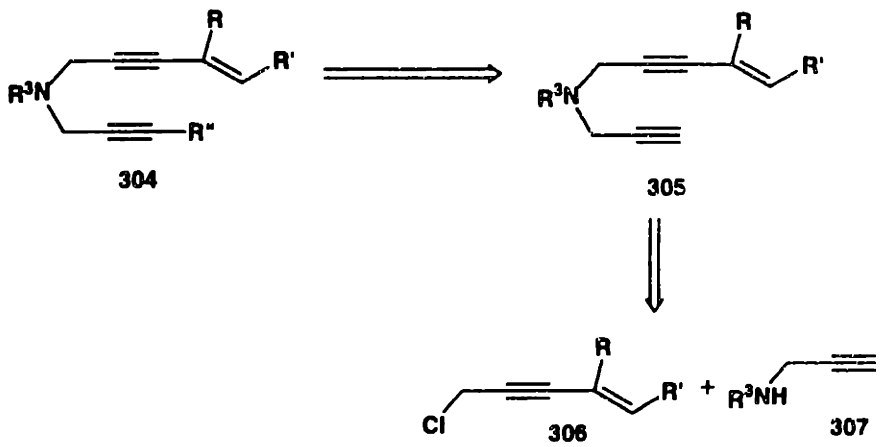
substrates were also observed here, including the decrease in rate that occurs with substitution on the enynophile.

Synthesis of Heterocycles

Using our current technology, several different carbocyclic frameworks can be prepared. We were interested in expanding the scope of the enyne cycloaddition to include substrates in which the enyne and enynophile were linked with heteroatom-containing tethers. These reactions could provide useful synthetic routes to a number of heterocyclic systems. In addition, we felt that certain stereochemical and mechanistic questions might be more easily addressed using these types of substrates. Some examples of heterocycle formation using the enyne cycloaddition can be found in the literature;[55] however, we intended to focus on unexplored areas. Toward this goal, Brenda Palucki has been exploring the scope of enyne cycloadditions of substrates with nitrogen and oxygen-substituted tethers. A summary of these reactions is included here because the mechanistic discussion of Part III is based in part on these results.

Palucki has explored reactions of both type I and type II systems, as well as a new

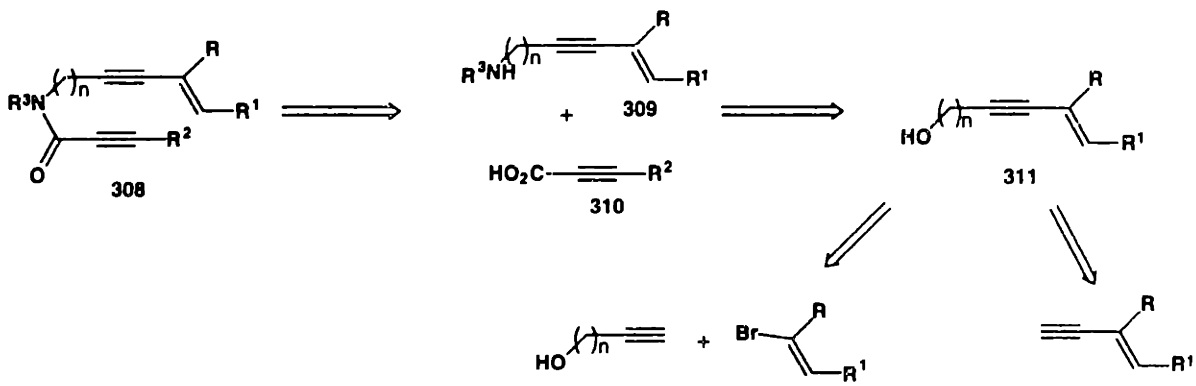
Scheme 150



variant of the cycloaddition to prepare carbazoles. As shown below, the type I nitrogen-based substrates were prepared via alkylation of a protected, commercially available

propargyl amine **307** with chloride **306** to give enyne **305**. Further elaboration of the unsubstituted alkyne of **305** provided the desired substrate **304**. The type II substrates **308** were prepared via the coupling of an acid **309** with an amine **309**. The amine was derived from the corresponding enyne alcohol **311** via an alkylation or coupling reaction. The ester substrates, all type II, were prepared in a similar manner using propargyl alcohols **311**. The ease of synthesis of these compounds makes them appealing targets for the further study of the cycloaddition. As in previous chapters, the discussion of these substrates is divided into separate sections on type I and type II substrates.

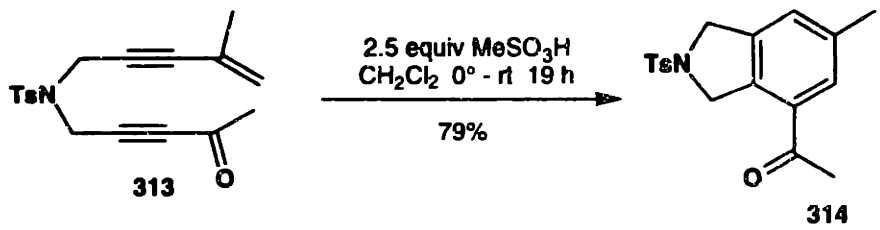
Scheme 151



Type I Substrates and Cycloadditions

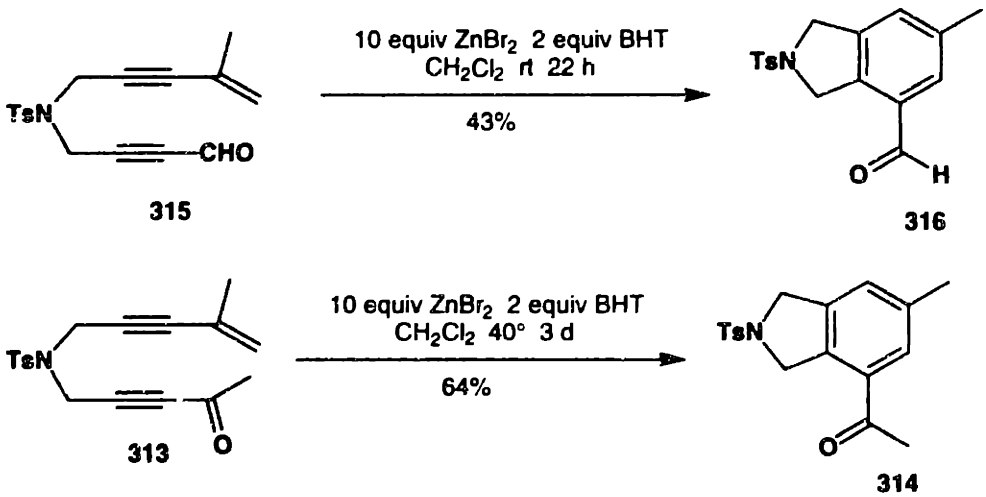
Palucki prepared two type I substrates with different electron withdrawing groups. As shown in Scheme 152, enyne **313** provided cycloadduct **314** in 79% yield when treated with methanesulfonic acid. Reaction with zinc bromide provided the cycloadduct in 64% yield (Scheme 153), while heating the enyne at 122 °C for 3 hours provided only 36% of the desired product. When compared to the enyne **173** which contains a methylene in place of a tosylamine moiety, amine **313** provides similar results with zinc bromide and reacts more quickly under thermal and protic acid conditions. The yield in the thermal reaction is lower, however.

Scheme 152



When it was determined that the enyne **313** cyclized fairly well under Lewis and protic acid conditions, enyne aldehyde **315** was prepared. Marshall has found that aldehydes will undergo certain cycloadditions at a faster rate and with higher selectivity than the corresponding ketones.[154] The enhancement may be due to the increased electron withdrawing ability of the aldehyde group compared to an ester or keto group. Rate and selectivity enhancement are especially prounounced when the reactions are run with Lewis

Scheme 153



acids, which will coordinate to the basic aldehyde moiety further enhancing the electon deficiency of the dienophile. Palucki found that enyne **315** provided compound **316** in 43% yield when treated with zinc bromide at room temperature for slightly less than a day

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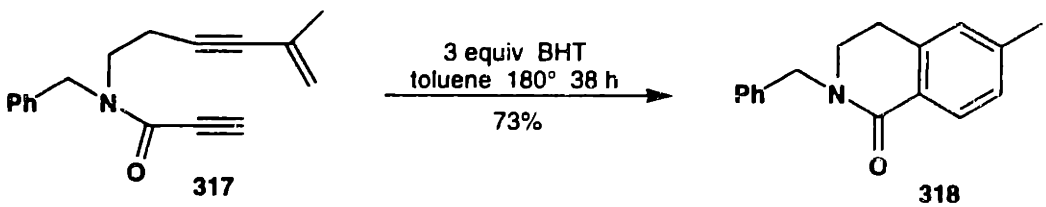
[154]Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5279. Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236. Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G.

(Scheme 153). The rate of this reaction is indeed faster than the corresponding ketone substrate **313** which required reaction at 40 °C for 3 days to go to completion. The lower yield of aldehyde **316** compared to ketone **314** may be attributed to its lack of stability under the reaction conditions. Given the similarity of reactivity between the nitrogen containing and all carbon substrates, no further work was done to explore the scope of the type I substrates.

Type II Substrates and Cycloadditions

The type II substrates that were examined can be divided into three groups, substrates with different tether lengths, substrates with different enynophile substitutions, and substrates with different enyne substitutions. Beginning with the substrates with different tether length, Palucki found that amide enyne **317**, prepared from a homopropargyl amine and propiolic acid, underwent the cycloaddition only under thermal conditions. Heating **317** to 180 °C in toluene for 38 hours produced compound **318** in 73% yield (Scheme 154). Other conditions were explored but did not provide any of the desired product.

Scheme 154



317 **318**

The amide enyne **319**, with one less carbon in the connecting chain, is one of the best substrates for the cycloaddition. This enyne afforded the desired cycloadduct **320** in 94% yield when heated to 120 °C for 6 hours in toluene (Scheme 155). The cycloaddition of this enyne also proceeds in the presence of methanesulfonic acid (56% yield) and zinc

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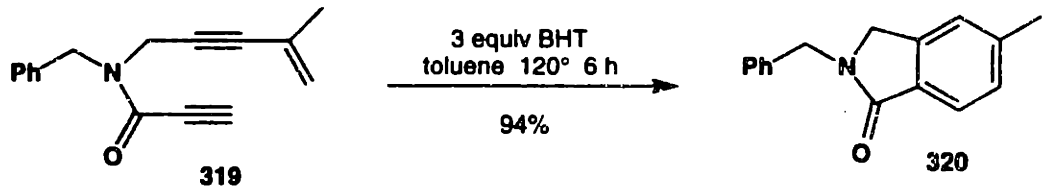
Tetrahedron **1986**, *42*, 2893. Marshall, J. A.; Crote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186.

bromide (less than 30% yield).

Scheme 155



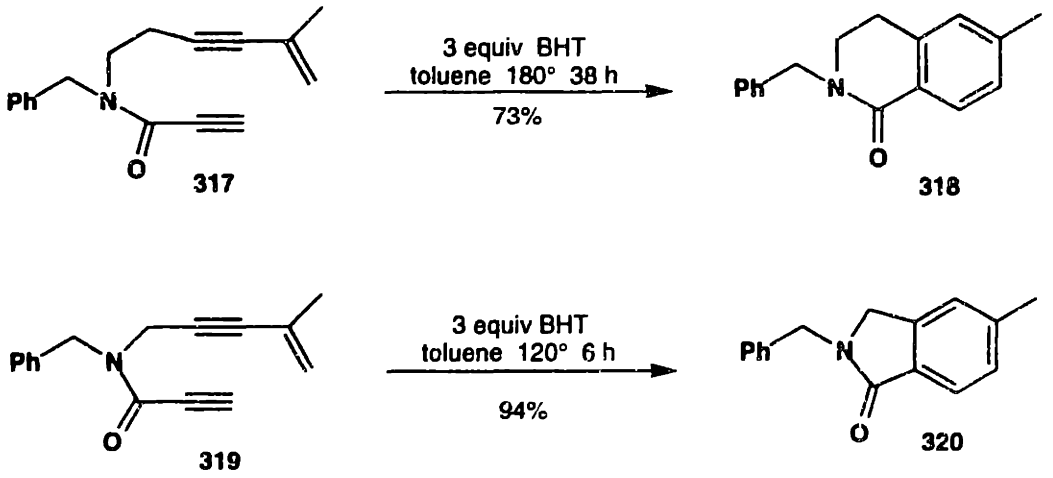
The amide enyne substrates are characterized by the presence of rotamers, which are visible as separate compounds in the ^{1}H NMR spectrum. The slow rotation of these amides means that these substrates exist in part in a conformation that is unable to undergo the cycloaddition (see **321r**, Scheme 156). The use of a bulkier substituent on the amine might shorten the reaction time by forcing the molecule to exist predominantly in the reactive conformation (**321**). To address this issue, Palucki prepared several substrates

Scheme 156

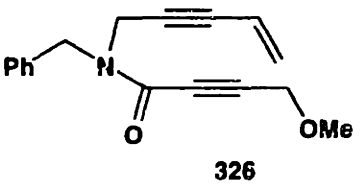
such as **321** with a methylbenzyl substituent on the amine. She found that the bulkier amide **321** cyclized at a faster rate under when heated in benzene, showing that the bulkier amide does affect the cycloaddition rate.

Substitution on the enynophile of these type II substrates slowed the reaction rate dramatically. As shown in Scheme 157, the enynes **322** and **324** underwent cycloaddition in significantly lower yield than the unsubstituted acetylenic substrate **314** (see Scheme 154). Substrates with methyl or *n*-propyl substitution on the enynophile provided cycloadducts in only modest yield under a variety of conditions.

Scheme 157



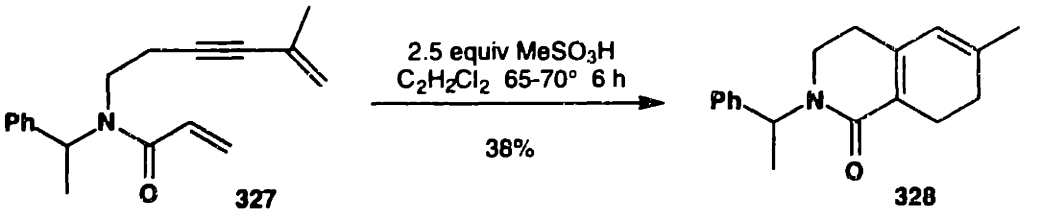
To study the effect of enyne substitution on the cycloaddition, Palucki subjected enyne **326** to various reaction conditions. She found that this enyne provided only poor yields of the cycloadduct in all cases. The cycloadditions in general are not clean, and purification of the cycloadduct was difficult.



326

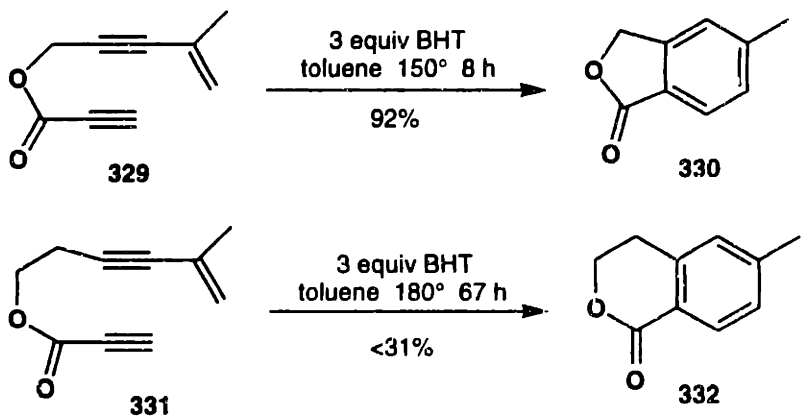
Several alkene enyne substraies were prepared and subjected to a variety of reaction conditions. The best yields were obtained with enyne **327** which gave only a 38% yield of compound **328** when treated with methanesulfonic acid in refluxing dichloroethane for 6 hours. Due to the disappointing reactivity of these substrates, no further enynes of this type were explored.

Scheme 158



Another area of interest was the scope of type II cycloadditions involving acetylenic esters as enynophiles. Palucki prepared two ester substrates, **329** and **331**, by coupling propiolic acid with a propargyl alcohol and a homopropargyl alcohol, respectively. These substrates cyclized only under thermal conditions; Lewis and protic acids gave either no reaction or decomposition products. This result was not unexpected, as coordination of a Lewis or protic acid to the ester moiety increases the energy of the desired conformation for the cycloaddition by increasing the dipole of the carbonyl. To the best of our knowledge, intramolecular Diels-Alder reactions of esters are not catalyzed by Lewis or protic acids.[155] The two substrates did cyclize under thermal conditions, however. Enyne **329** generated the desired compound **330** in 92% yield after 8 hours in toluene at 150 °C. Enyne **331** formed the desired compound **332** in a disappointing 31% yield after extended heating at 180 °C. This reaction was not clean, and purification of the product was difficult.

Scheme 159



These results are in line with those found in the literature. Johnson[74] and Stevenson[59,60] both found that ester enyne and arenyne substrates were not as reactive as anhydrides. Johnson also found that unsubstituted and monosubstituted esters, such as the one created in Scheme 160 from alcohol **141**, do not react upon heating in benzene. Palucki found that the unsubstituted esters, prepared from primary alcohols, did react,

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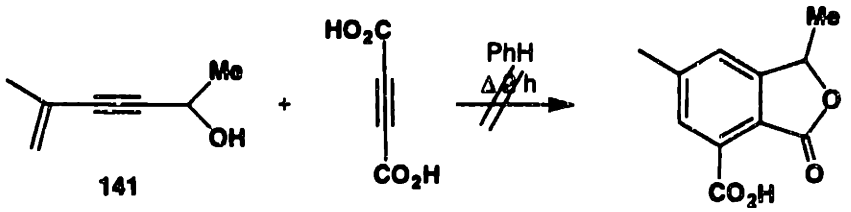
[155] For a discussion of intramolecular Diels-Alder reactions of esters and amides, see: Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5172. See also: Boeckman , R.

although at higher temperatures.

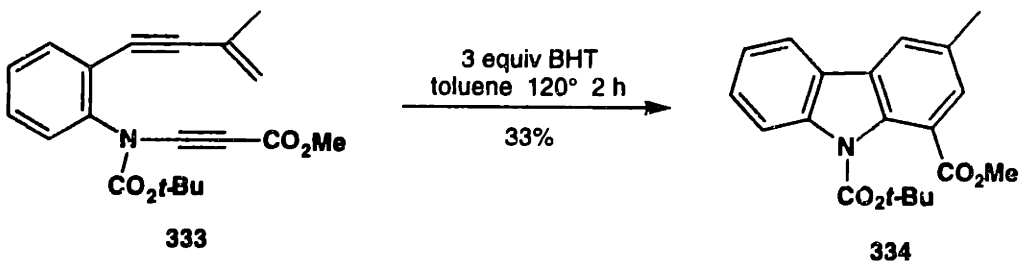
Scheme 160



Carbazole Synthesis

The efficient synthesis of carbazoles was the next goal that Palucki addressed. She first prepared substrate **333** via a novel conjugate addition of an arylamide to the methyl ester of bromopropiolate. The ynamine **333** was found to undergo the reaction only under thermal conditions, as shown in Scheme 161, to give the desired carbazole **334** in 33% yield. Treatment of **333** with Lewis or protic acids led to decomposition of the starting material. Other substrates were prepared with different nitrogen protecting groups, but the cycloadditions of these compounds were no better.

Scheme 161



Summary and Conclusions

This chapter and the previous one have discussed the scope of the [4+2] cycloadditions of conjugated enynes. Aromatic, heteroaromatic, polyaromatic, and dihydroaromatic products can be obtained using this chemistry. What follows next is a

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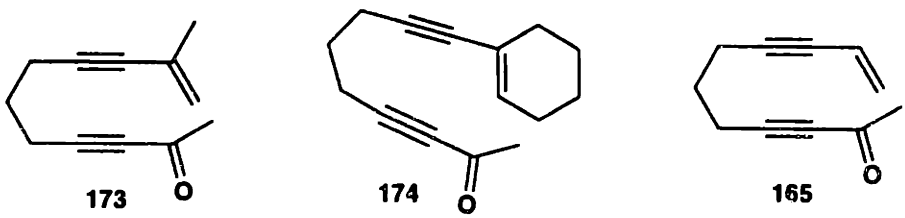
K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1792, and references cites therein.

brief summary of the scope of the enyne cycloaddition based on results from this laboratory. Further discussions of the implication of these results on the mechanism will be addressed in Part III of this thesis.

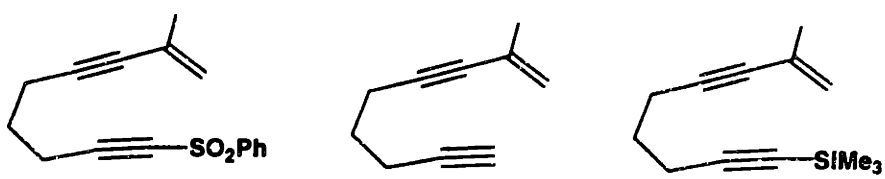
Various type I substrates were prepared to examine the effect of enyne substitution, of tether length, and of different enynophile substituents on the reaction. The effect of enyne substitution on the cycloaddition varies depending on reaction conditions. Under Lewis acid conditions, the cyclohexenylacetylene **174** provides the best results. Under protic acid conditions, both the isopropenyl and vinyl acetylenes **165** and **173** react in moderate yields, while the cyclohexenylacetylene substrate did not react at all. Under thermal conditions, the isopropenyl substrate gave the best results; however, the vinyl acetylene also reacts well. A determination of the best type I substrate clearly depends on the conditions used.



173 174 165

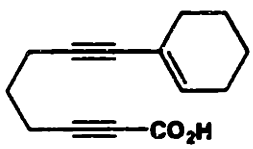
In the brief exploration of the effect of tether length on the reaction, the type I substrates with a four carbon tether required longer reaction times than the substrates with a three carbon tether.

A thorough investigation of the effect of different enynophiles was made. The best results were obtained with the phenyl sulfone **189** under thermal conditions. Other electron withdrawing substituents provided the desired products in moderate yields when

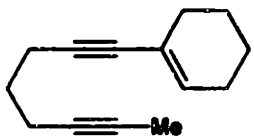


189 163 178

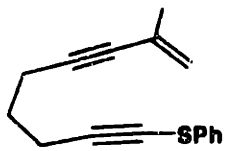
heated to 180 °C. Higher temperatures and longer reaction times were required for the unsubstituted enyne **163** and the trimethylsilyl enyne **178**. Although a more thorough study is required, acid **180**, methyl acetylene **181**, and the phenyl sulfides **179** and **182** did not cyclize under any conditions. Under Lewis acid conditions, Palucki found that



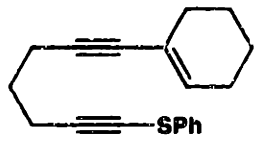
180



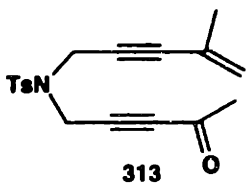
181



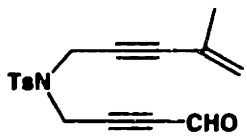
179



182



313



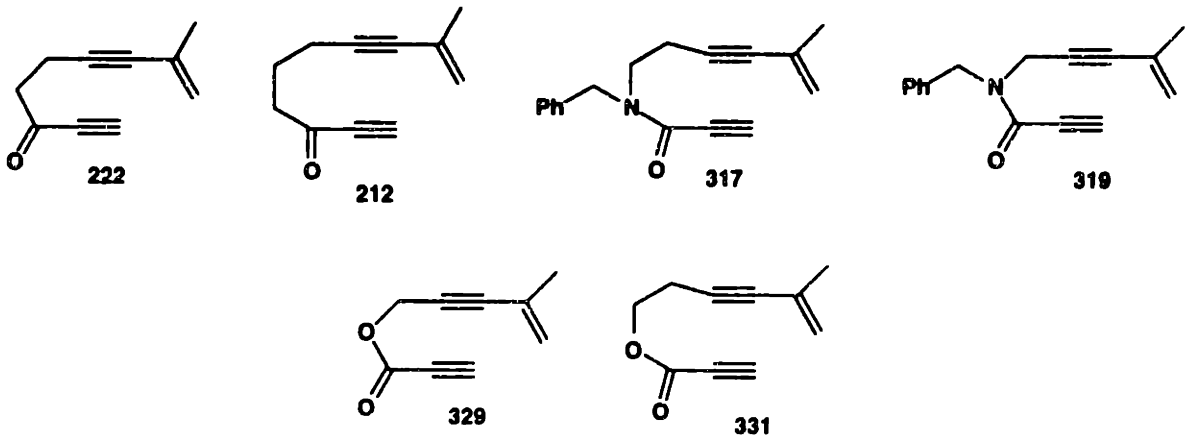
315

aldehyde **315** was more reactive than methyl ketone **313**. Only one alkene enynophile was explored here, and no desired product was obtained under a variety of conditions.

Several type II substrates were prepared, and they were varied in enynophile substitution, tether length, and enyne substitution. In both the all-carbon and nitrogen-tether substrates, substitution on the enynophile was detrimental to the rate of the reaction or to the yield. With the nitrogen-tethered enynes, enynophile substitution lead to lower yields, although the rate for consumption of starting material was similar that of the unsubstituted enynophile substrates. The all-carbon enynes with enynophile substituents provided the desired products in generally similar yields, but at slower rates under protic and Lewis acid conditions. Thermal conditions were not thoroughly explored with these all-carbon substrates.

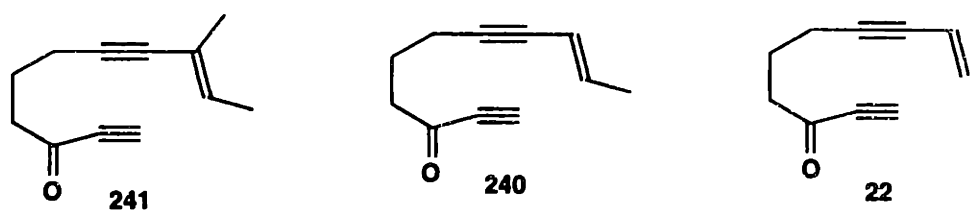
Type II substrates with alkenes as enynophiles undergo the cycloaddition with similar efficiency to the alkyne enynophile substrates in the all carbon cases. The nitrogen-tether enynes with alkene enynophiles did not cyclize in above 40% yield.

In the type II series, the effect of changing the tether length differed depending on the substrate. With the all-carbon enynes, the thermal reaction of the three-carbon tether enyne **222** is slower than the reaction of the four-carbon tether enyne **212**. No cycloaddition occurred at all with three-carbon tether substrate **222** under Lewis or protic



acid conditions. With the heteroatom-tethered enynes, the shorter tether substrates **319** and **329** cyclized faster and in much better yields than **317** or **331**, under thermal conditions. Under protic and Lewis acid conditions, the oxygen substituted enynes are unreactive, while the nitrogen substituted enynes give poor to moderate yields.

Enyne substitution plays a large role in the success of type II cycloadditions. By far the most consistent substrate is the isopropenyl substrate **212**. The more substituted enyne **241** gave good results only with methanesulfonic acid, while the vinyl acetylene **22** underwent the cycloaddition in good yield in the presence of aluminum trichloride. The worst substrate by far for this reaction is the terminally substituted enyne **240** which did not cyclize in above 10% yield under any of the conditions explored.



In most cases, the cycloaddition of a conjugated enyne with an enynophile can be accomplished under one of several conditions. We have found that in general, the type II enynes are better substrates for this reaction than the type I compounds, providing the desired products in cleaner reactions. These reactions can be used to prepare many different cyclic systems and may prove useful in a total synthesis. This section has provided a detailed discussion of the scope of this reaction. The next section will outline the progress we have made in exploring the mechanisms of this reaction.

Part III

Intramolecular Cycloadditions of Conjugated Enynes : Mechanism

Chapter 1

Introduction and Background

In Parts I and II, we discussed the history and scope of the [4+2] cycloadditions of conjugated enynes. In this part, the mechanism of this reaction will be addressed. We will begin with a survey of the mechanisms that have been proposed in the literature, including a brief overview of the reactivity of enynes. Next, a discussion of the experimental data we have collected will be presented. The final chapter will focus on our studies of cycloadditions of several substrates with alkene enynophiles. Using these substrates, we have further examined the mechanistic details of the cycloaddition, including whether the enynophile reacts in a suprafacial or antarafacial manner, and whether the reaction displays endo or exo selectivity.

The study of the mechanism of this reaction is complicated by the multiple pathways that are possible; in addition, different mechanisms may be followed depending on the conditions under which the transformation is carried out. This section does not definitively identify a single mechanism for the reaction, but we have tried to address and rule out certain pathways.

The reaction of conjugated enynes and arenynes with alkynes has been known for almost a century. During this time, the mechanisms of these reactions have been considered by several researchers. This chapter presents an overview of the proposed mechanisms for these reactions, including discussions of stepwise and concerted bond formation. In order to more clearly address the mechanism of these cycloadditions, some aspects of the chemistry of enynes are also reviewed.

A brief summary of the possible mechanisms for the reaction was presented at the end of Part I, Chapter 2. Now, in a more detailed overview, the mechanistic options for this reaction will be readdressed. In this chapter, we will examine general and specific

mechanisms for both intermolecular and intramolecular cycloadditions, although we have been mainly interested in the intramolecular reaction. Although intermolecular enyne reactions and arenyne reactions may occur through different pathways, all proposed mechanisms are presented and considered as options for the intramolecular reaction.

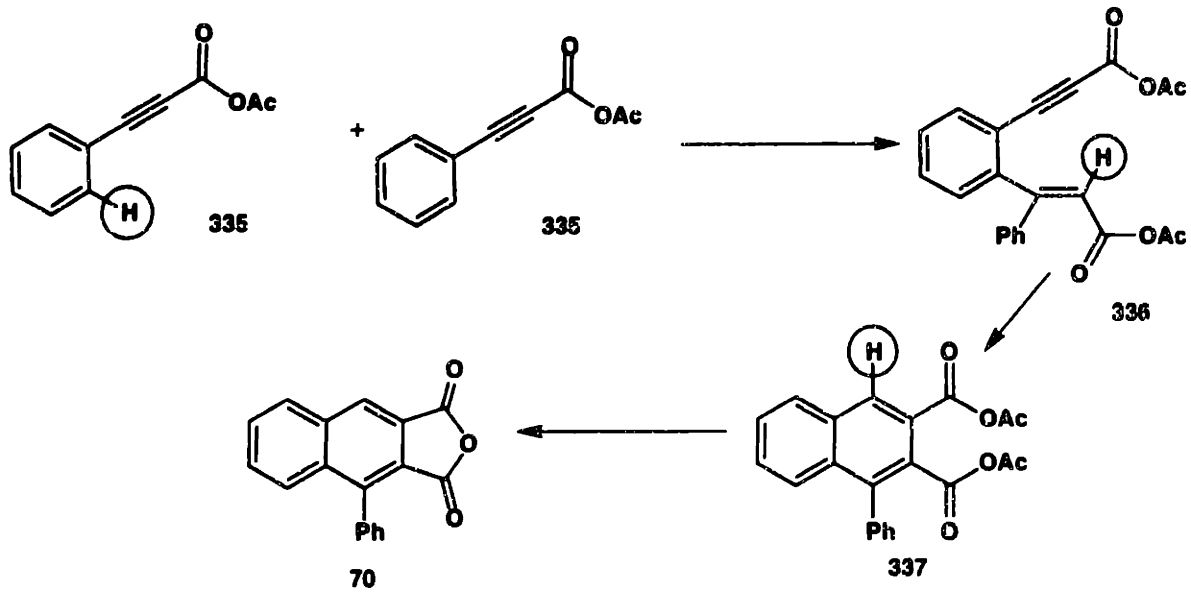
The mechanism of the carbon-carbon bond formation stage of the overall reaction, which involves either a stepwise or concerted process, will be discussed first. Initial proposals for the mechanism of this stage of the reaction invoked a stepwise formation of the carbon-carbon bonds with the development of zwitterionic intermediates and hydride migration. Other researchers have proposed a concerted reaction mechanism with isomerization occurring either before or after the carbon-carbon bond forming process. As we will see, inspiration for the concerted mechanisms comes from the Diels-Alder reaction. Several options for the concerted reaction will be examined. These options include the formation of a cyclic allene or biradical through direct cycloaddition and the cycloaddition of a dienyl cation. All of these mechanistic possibilities have been proposed in the literature to date, and we will begin with the earliest proposed mechanism.

Stepwise Mechanisms for the Enyne Cycloaddition

When Michael and Bucher published their account of the dimerization of phenylpropiolic acid in 1898,[45] they suggested two possible mechanisms to account for the reaction. These routes were devised before the nature of bonding was well understood, but they are of historical interest and have served as a basis for other mechanistic proposals. Both of these pathways involve the stepwise formation of the new ring. Scheme 162 depicts an intermolecular transfer of hydrogen from one molecule of propiolic anhydride **335** to another with simultaneous carbon-carbon bond formation to give intermediate **336**. This intermediate then undergoes a molecular rearrangement, in which the circled hydrogen is transferred to the β-carbon of the acetylene, and the two activated carbons in the resulting

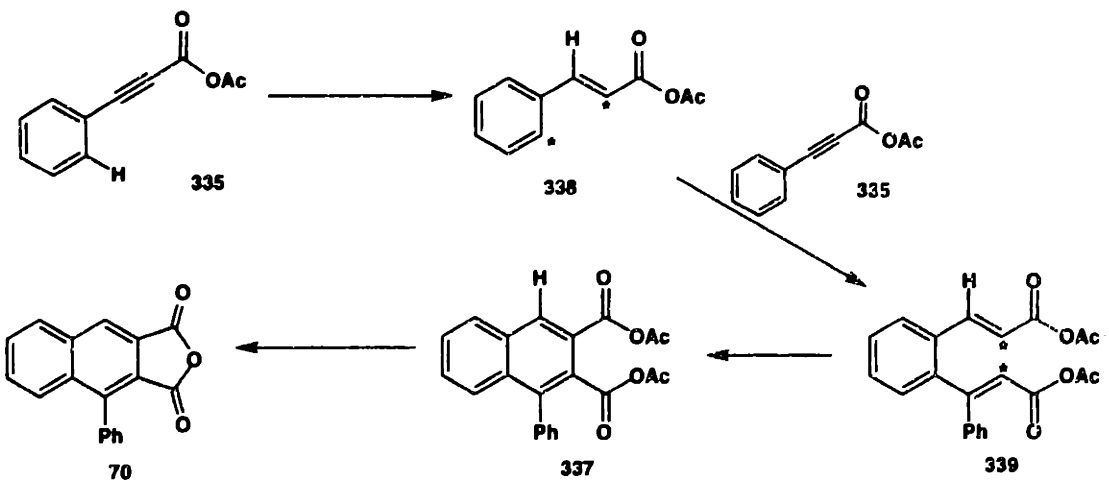
intermediate form a new bond providing **337**. The final step in this pathway is the formation of the cyclic anhydride to give the isolated product **70**.

Scheme 162



The second route suggested by Michael and Bucher involves the intramolecular transfer of a hydrogen from the ortho position on the aromatic ring to the β-carbon of the acetylene to give intermediate **338** as shown in Scheme 163 (the lack of an electron octet

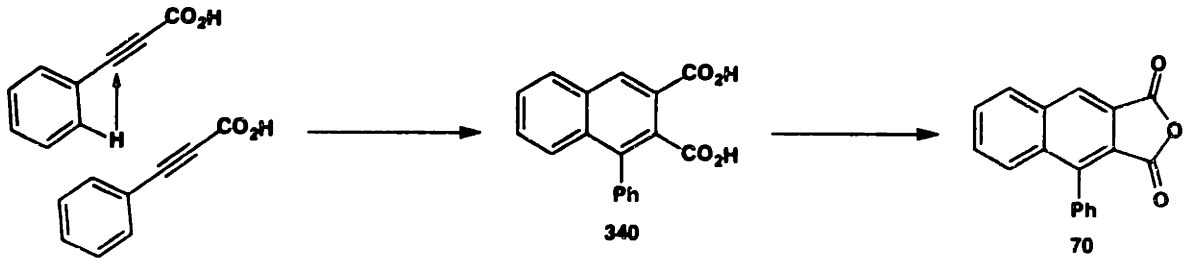
Scheme 163



around a carbon is symbolized as a star). Intermediate **338** then "polymerizes" with a second molecule of **335** to give diene **339**, and then naphthalene **337**. The final step, once again, involves anhydride formation to provide **70**.

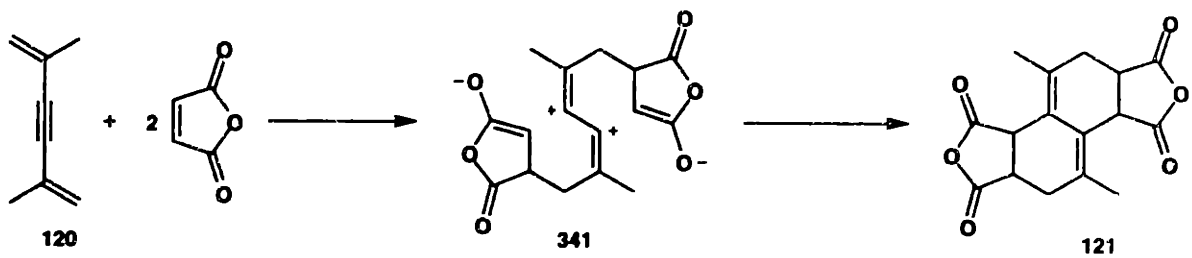
After further work, Bucher characterized phenylpropiolic acids "as having a strong tendency to polymerize, with the wandering of an ortho hydrogen, to phenylnaphthalene derivatives", as shown in Scheme 164.[46] Baddar later employed a mechanism similar to the one outlined in Scheme 163 to explain the regioselectivity he observed in his reactions.[48-51]

Scheme 164



Butz and co-workers have proposed a stepwise pathway involving ionic intermediates for the intermolecular reaction of enynes with alkenes[70] (Scheme 165). Butz studied the reaction of dienyne **120** and several related compounds with various electron

Scheme 165

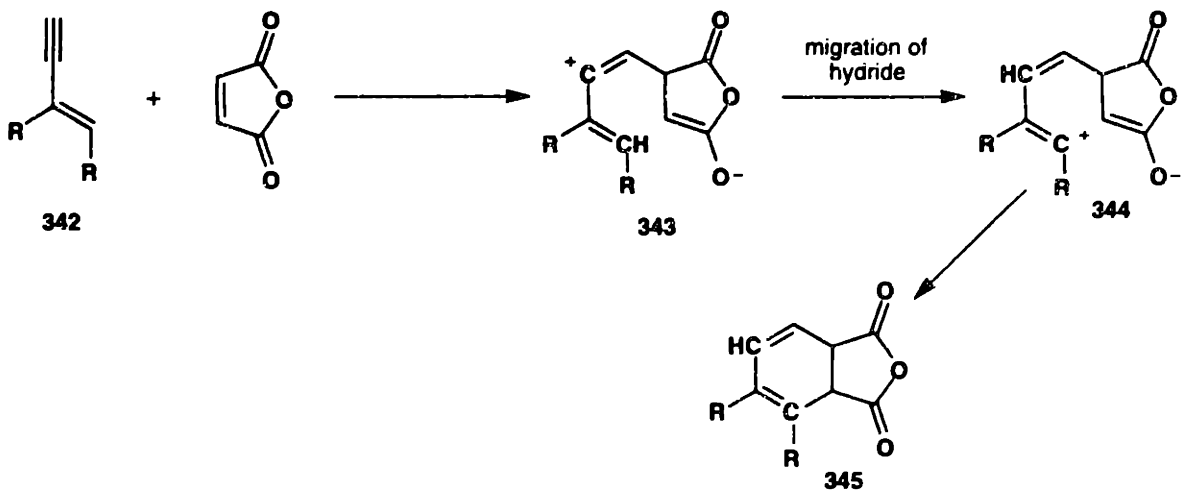


deficient alkenes. Here, two molecules of maleic anhydride react with the dienyne **120** to give the zwitterionic species **341**. This species then cyclizes to give **121**. Butz emphasizes the symmetry of the dienyne as key in the simultaneous addition of the two

molecules of maleic anhydride. He compares this mechanism to the reaction of HCl with divinyl acetylene which gives a dichloro diene via two successive 1,4 additions.[156] He also suggested a concerted mechanism for this particular reaction which will be discussed later.

Butz proposed two other mechanisms for a reaction studied by Dane[66] which involves an electron rich enyne reacting with maleic anhydride. These mechanisms address

Scheme 166



both the bond formation, which is proposed to be stepwise, and the isomerization steps of the reaction. The first mechanism involves nucleophilic attack by the acetylene of enyne **342** on the anhydride. The dienyl cation **343** then undergoes a [1,3]-hydride migration to give the dienyl cation **344**, which then cyclizes producing the bicycle **345**. The second mechanism involves nucleophilic attack by the alkene of the enyne on the anhydride to give propargyl cation **346** (Scheme 167). Migration of a hydride gives either dienyl cation **347** directly or allenyl cation **348** which can isomerize further to dienyl cation **347**. Cation **347** can then cyclize to give bicycle **345**. Other scientists[67] have proposed a concerted mechanism for this particular electron rich substrate, and this mechanism will be discussed later.

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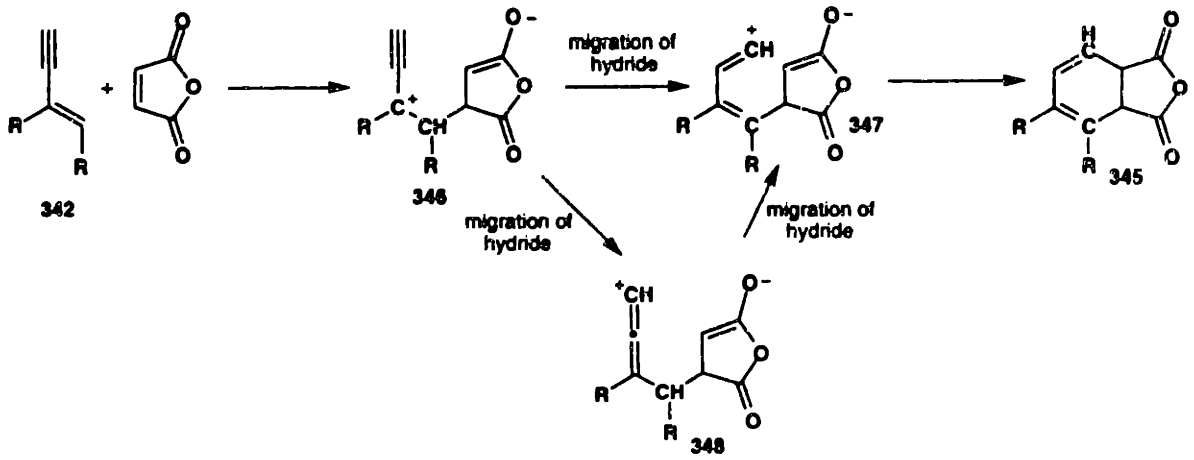
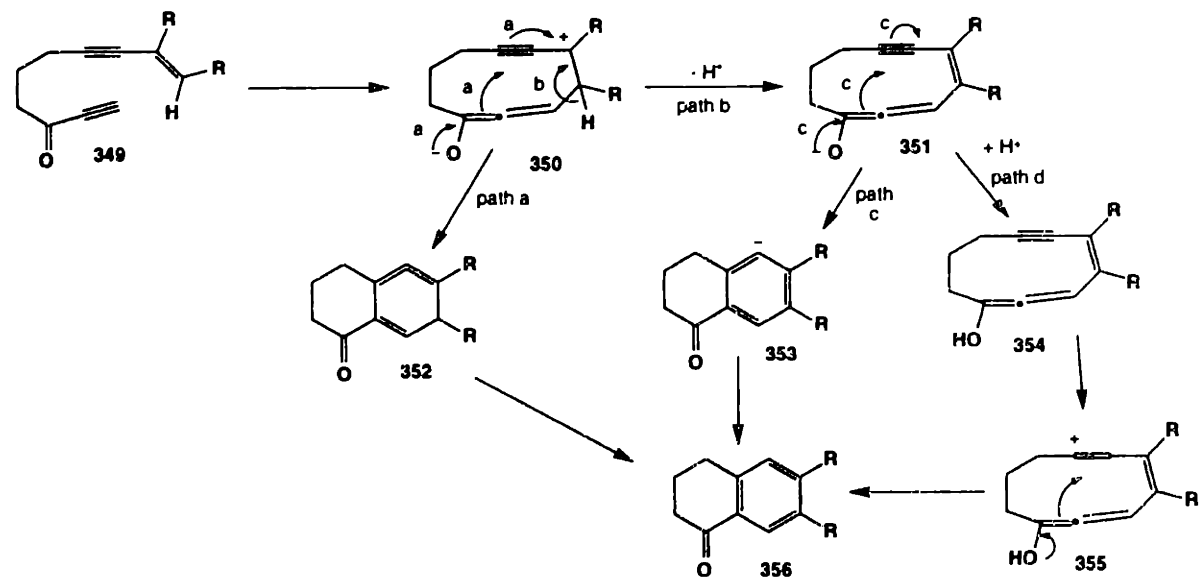
[156] Coffman, D. D.; Nieuwland, J. A.; Carothers, W. H. *J. Am. Chem. Soc.* **1933**, *55*, 2045.

Scheme 167



In a general sense, similar stepwise mechanisms can be proposed for the intramolecular reaction of enyne with an alkyne. For type II substrates as shown in

Scheme 168



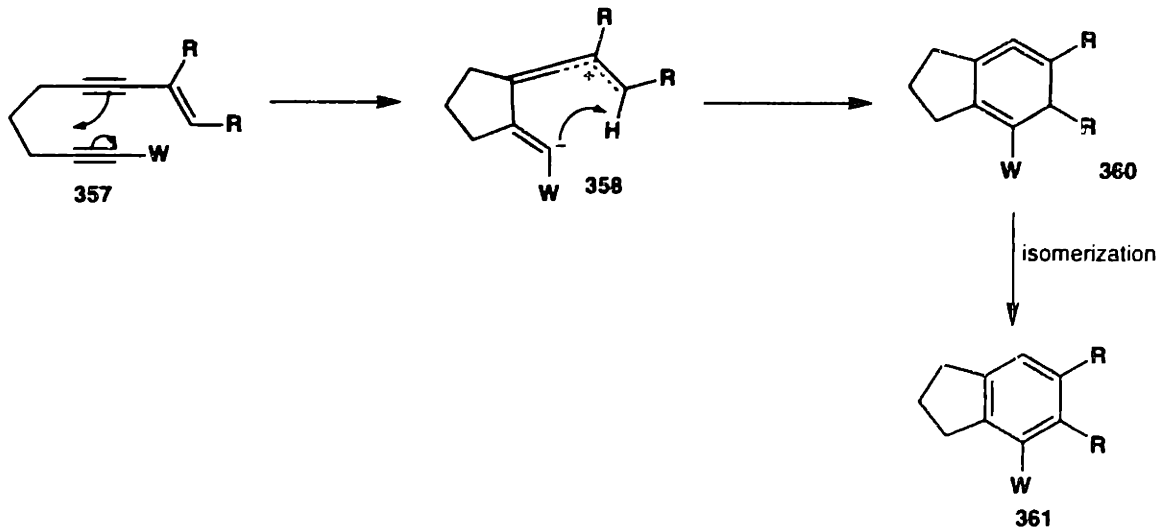
Scheme 168, a Michael type addition to the alkynyl ketone would form one carbon-carbon bond and create the zwitterionic intermediate **350**. This zwitterion can then react with the propargyl/allenyl cation to give cyclic allene **352** (path a), or undergo an elimination to give the enyne **351**. Enyne **351** can either cyclize to give **353** and be protonated (path c),

or be protonated to give enol **354** (path d) which then can undergo protonation and cyclization.

Several problems exist with this mechanism. The formation of 10-membered ring intermediate **350** is unlikely because it is extremely strained. The stepwise addition does not necessarily avoid the formation of a cyclic allene or similar high energy species.

A similar mechanism can be proposed for type I substrates. As shown in Scheme 169, a Michael type addition to the electron deficient alkyne would form one carbon-carbon

Scheme 169



bond creating zwitterionic intermediate **358**. One possible pathway to product involves the anionic moiety of the zwitterion **358** reacting with the dienyl cation moiety to give cyclic allene **360**, which then isomerizes to the aromatic product. Other stepwise mechanisms can be proposed for both types of substrates, but all are characterized by one of several problems: large ring closure, zwitterion formation, and cyclic allene or other strained ring formation.

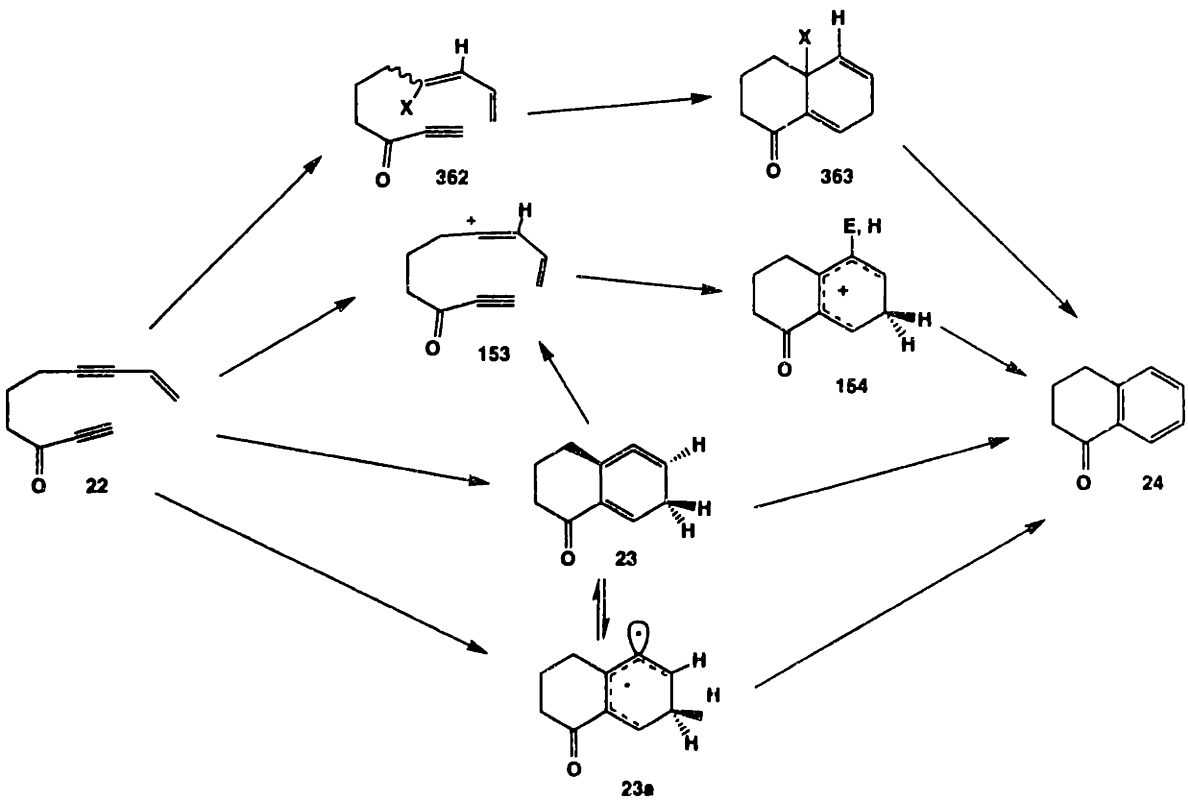
While the reaction may indeed proceed in a stepwise fashion, differentiation of a stepwise and a concerted reaction may be difficult if the stepwise reaction is fast. As we

shall see, when substituted alkene enynophiles were used in the reaction, the stereochemistry about the double bond was maintained suggesting that the reaction is, at the very least, a fast stepwise reaction.

Concerted Mechanisms for the Enyne Cycloaddition

Several workers have proposed concerted reaction mechanisms for enyne cycloaddition with high energy intermediates that subsequently isomerize to aromatic species. Scheme 170 presents a summary of the options for concerted cycloaddition mechanisms. Addition of HX across the triple bond of enyne **22** could give substituted diene **362,** which reacts in a [4+2] cycloaddition providing diene **363**. The resulting

Scheme 170

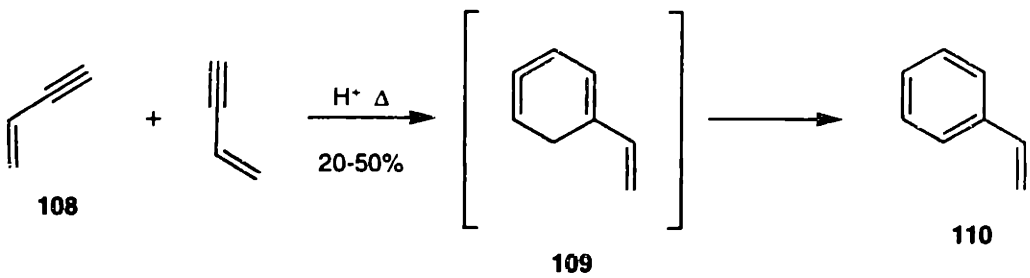


diene **363** could then lose HX to give the aromatic product **24**. Alternatively, protonation of enyne **22** could afford dienyl cation **153**. This cation could then undergo a Diels-Alder

reaction to give the cyclohexadienyl cation **154** which would lose a proton to form tetralone **24**. In a third option, enyne **22** could undergo a cycloaddition directly to give cyclic allene **23** which could then isomerize to aromatic product **24**. In a final alternative, enyne **22** could undergo direct cyclization to generate biradical **23a** which could isomerize to **24**. The first three mechanistic pathways have been proposed in the literature previously, and our group has recently added the fourth possibility.[157] We will begin this discussion with the mechanism proceeding via a cyclic allene intermediate.

Dykstra,[65] while studying vinyl acetylene and its polymerization, was the first to connect the enyne cycloaddition and the Diels-Alder reaction; this relationship was more straightforward perhaps than the relationship between the Diels-Alder reaction and the

Scheme 171



H+= AcOH, HCl, phthalic anhydride, etc.

Michael-Bucher type reaction. Dykstra suggested cyclic allene **109** as an intermediate in the dimerization of vinyl acetylene in the presence of protic acids to give styrene (Scheme 171). He noted that the formation of allene **109** was "practically impossible stereochemically." Dykstra provided no experimental evidence for this mechanism and did not explain the need for acid to promote the dimerization.

Butz and co-workers have also proposed a cyclic allene intermediate in the enyne

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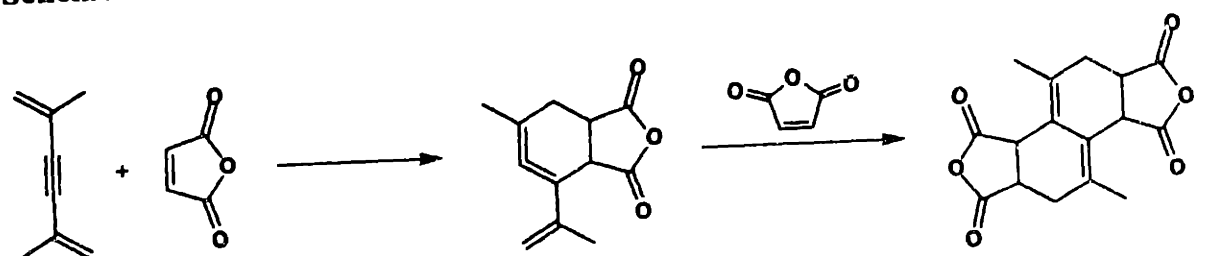
[157]Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.

cycloaddition, in addition to three other possible mechanisms for the reaction.[70] They noted that the reaction of enynes with electron-deficient alkenes must be different from the reaction of dienes and proposed the concerted cycloaddition mechanism shown below involving allene **364** which "may exist long enough to add another molecule of maleic anhydride". Support for this mechanism was based on Favorskii's isolation of 1,2-cycloheptadiene.[158]

Scheme 172



120 **364** **121**

We have proposed a cyclic allene intermediate for the intramolecular enyne cycloadditions. A cyclic allene intermediate in an intramolecular cycloaddition will be more strained due to the constraints of the second ring. As discussed in Part I, Chapter 2, cyclic allenes similar to **23** have been trapped and characterized to some degree, and a recent report gave more information.

During the course of our work, Johnson reported the studies on the vapor phase pyrolysis of enyne substrates **365** and **163** at 600 °C.[42] Alkene **365** provided the cyclopentenyl acetylene **367**, which may be derived from the cyclic allene intermediate **366** via a retro-[4+2] cycloaddition with loss of ethylene. Thermolysis of the alkyne **163** furnished three products, the indane **269** observed in our solution phase reaction of the same substrate, an isomeric indane **369**, and a cyclopentene derivative **370**. Johnson proposes that formation of the two indanes may result from a 1,2-hydrogen shift in the cyclic allene to give carbene intermediate **371**, followed by hydrogen or methyl shifts

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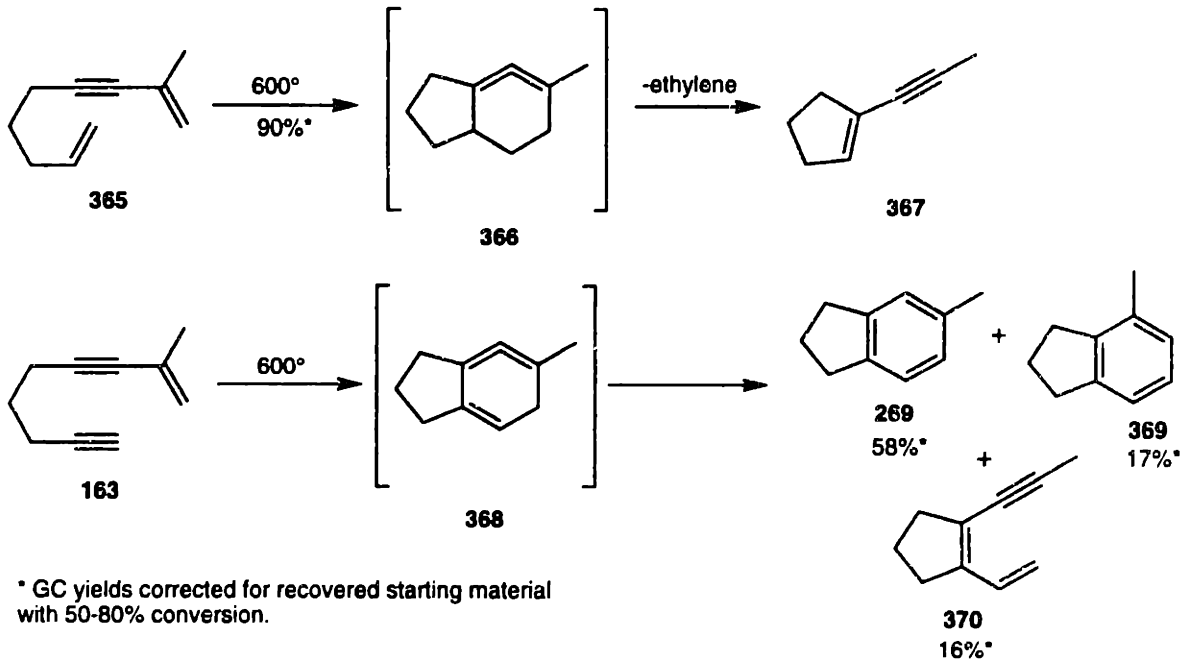
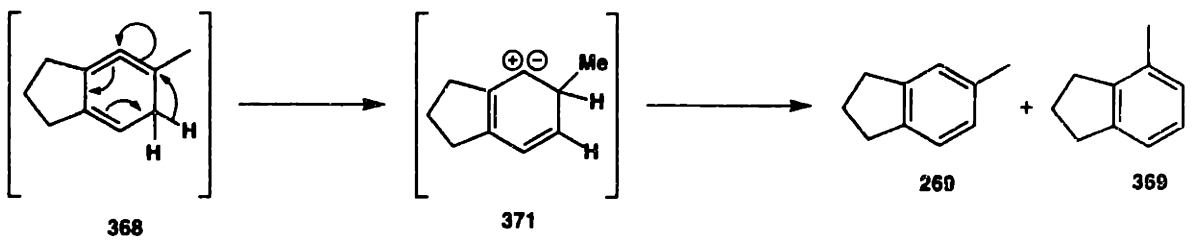
[158] Favorskii, A. E. *Bull. Soc. Chim.* **1936**, *3*, 1727.

Scheme 173



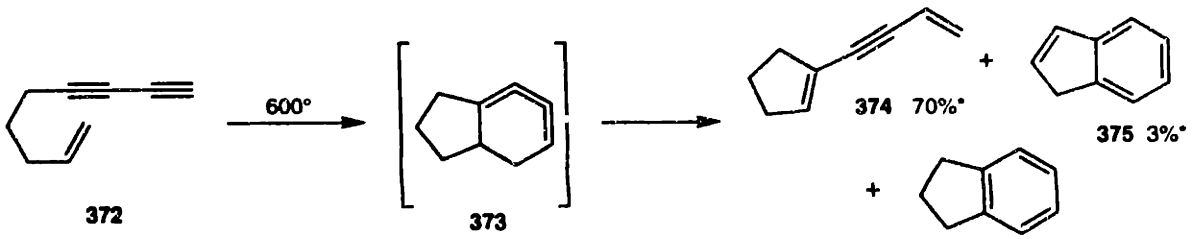
(Scheme 174). The cyclopentene derivative may arise through a 6-electron electrocyclic ring opening of the cyclic allene **368**. The observed products, particularly the

Scheme 174



cyclopentene derivatives, are evidence for a cyclic allene intermediate. Johnson also described the intramolecular cycloaddition of a diyne with an alkene, as shown in Scheme 175; a mixture of products is obtained which lends support to a cyclic cumulene intermediate.

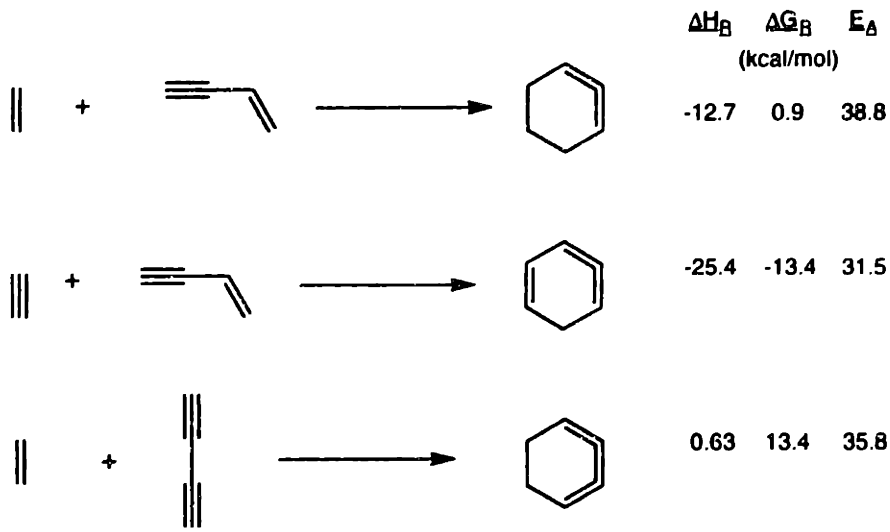
Scheme 175



* GC yields corrected for recovered starting material with 50-80% conversion.

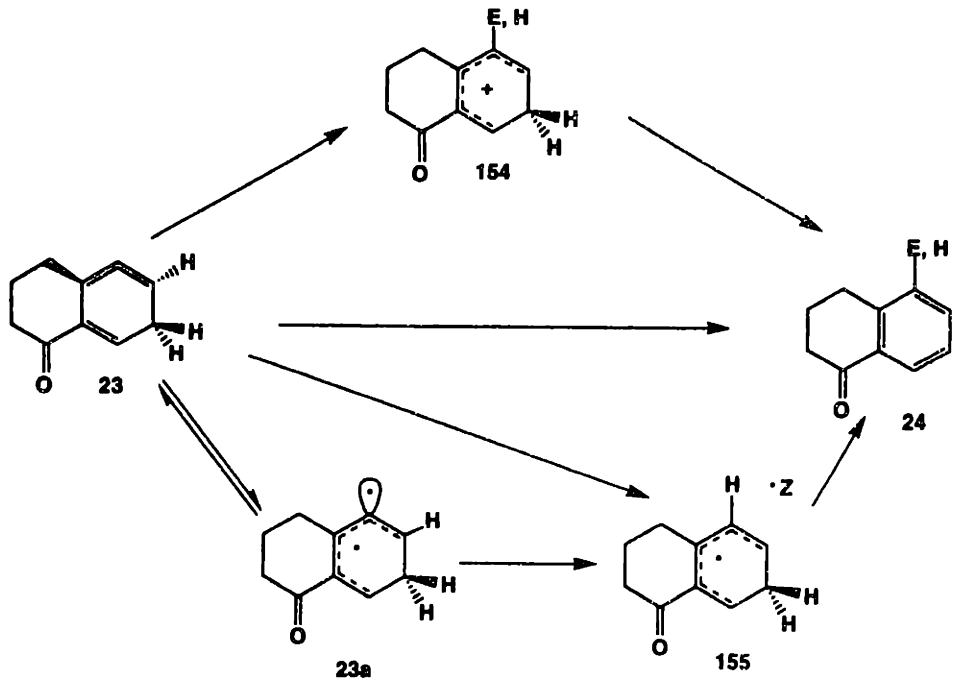
Finally, Johnson has performed higher level calculations on these types of reactions, finding that the intermolecular reaction of an alkene with an enyne is slightly endothermic while the corresponding reaction of an alkyne is exothermic. The reaction of an alkene with a diyne is also endothermic (Scheme 176). As discussed in Part I, our calculations using Benson addivities predicted a heat of reaction of -29.7 kcal/mol for the cycloaddition of acetylene with vinyl acetylene.

Scheme 176



We proposed that cyclic allene intermediates are involved in the enyne cycloaddition when the reaction is carried out under some conditions. Depending on reaction conditions, this intermediate could have several fates (Scheme 177). Cyclic allene **23** can be protonated to give cyclohexadienyl cation **154**. Loss of a proton from **154** will give the

Scheme 177

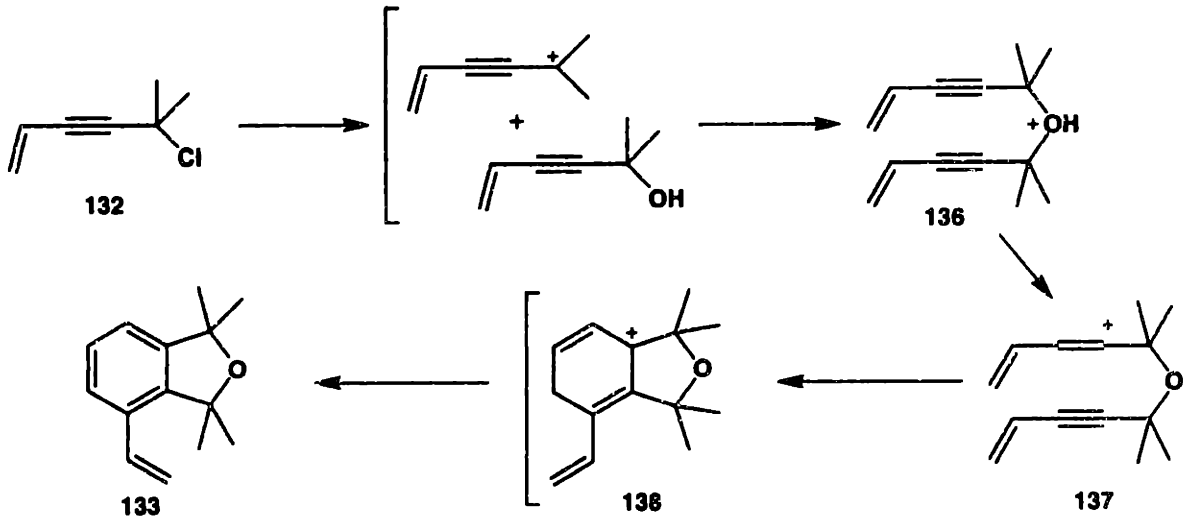


tetralone **24**. Thus, only a catalytic amount of acid is required to effect the isomerization. An intramolecular [1,5] sigmatropic shift will give **24** directly, although geometric constraints may prohibit this reaction. Compounds similar to cyclic allene **23** and biradical intermediate **23a** are predicted to be close in energy and may exist in equilibrium.[31] Both cyclic allene **23** and biradical **23a** can abstract a hydrogen atom from a suitable donor to give cyclohexadienyl radical **155**. Radical **155** can then lose a hydrogen atom to give the aromatic product **24**. As we shall see in the next chapter, some evidence exists for the intermediacy of a cyclic allene or biradical intermediate when the reaction is carried out at elevated temperatures.

Concerted mechanisms with ionic intermediates avoid the highly strained cyclic allene intermediate, but they introduce an interesting intermediate of their own. The "dienyl cation" pathway, first proposed by Nazarov, has since been considered by several groups. As shown in Scheme 178, Nazarov proposed that the protonated ether **136** can undergo

proton transfer to afford the dienyl cation **137**.[76] Note that protonation occurs to give a

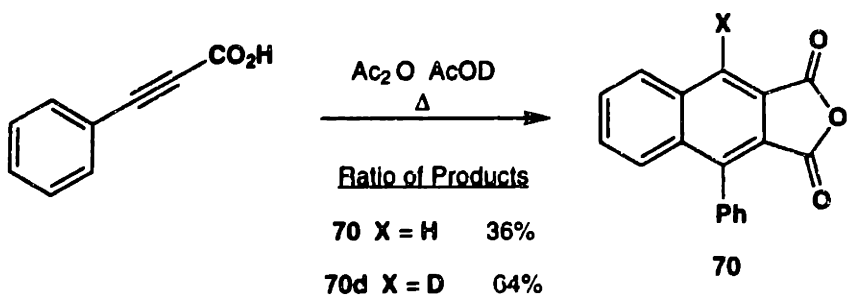
Scheme 178



vinyl cation that is not stabilized by resonance. As discussed later in this chapter, this protonation does not give the thermodynamically favored cation. Nazarov proposes that this cation then undergoes a cycloaddition and elimination to give cycloadduct **133**.

Whitlock and co-workers[159] proposed a similar mechanism for the dimerization of phenylpropiolic acid. They found that when phenylpropiolic acid was heated in the

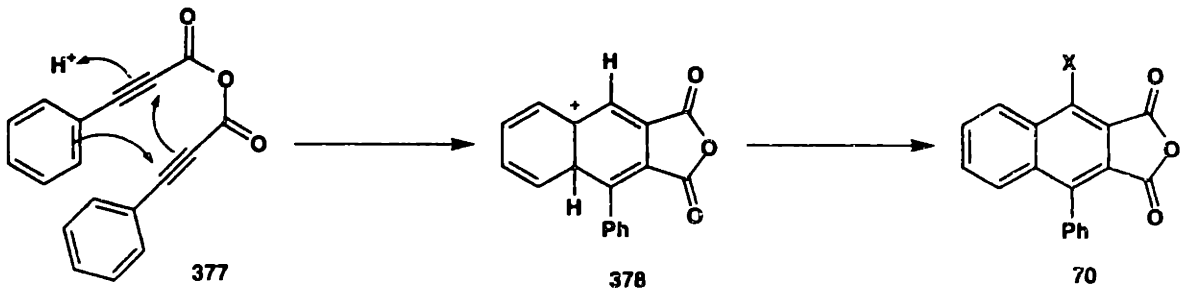
Scheme 179



[159] Whitlock, H. W., Jr.; Wu, E.-M.; Whitlock, B. J. *J. Org. Chem.* **1969**, *34*, 1857.

presence of acetic anhydride and deuterated acetic acid, substantial deuterium incorporation occurred, as shown in Scheme 179. This experiment led Whitlock to propose the mechanism illustrated in Scheme 180. The symmetrical anhydride of phenylpropiolic acid (**377**) undergoes simultaneous protonation and ring formation to give cyclohexadienyl cation **378**. This cation then loses a proton to give the observed phenylnaphthalene **70**.

Scheme 180

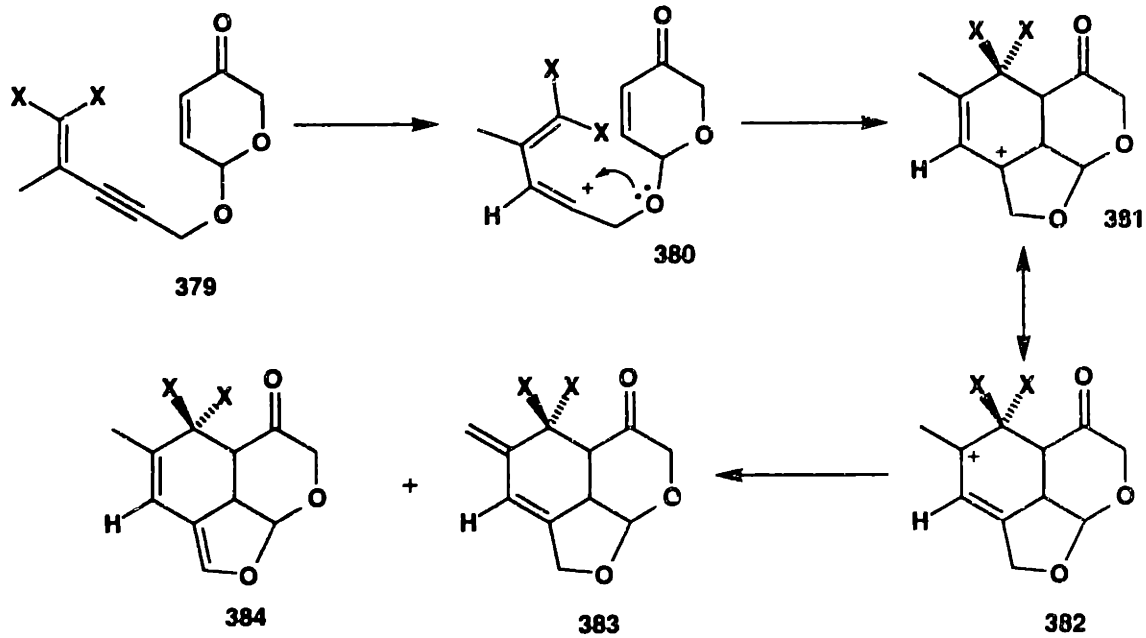


Whitlock's experiment and mechanism raise some questions. He proposed protonation of the alkyne at the benzylic position to give a positive charge, or at least a developing positive charge, α to a carbonyl group, in a manner similar to Nazarov's protonation of a different system. Thermodynamically favored protonation would occur in exactly the opposite manner to give the benzylic cation. Protonation of the acetylene could be reversible, and the cycloaddition of the dienyl cation may be facile, thus driving the equilibrium. However, Whitlock's results do not rule out other mechanisms, including those proceeding via the protonation of a cyclic allene intermediate. In addition, Stevenson[59,60,64] and Ward[61] have both found that the dimerization of arylpropiolic acids can occur under very mild conditions, in the absence of acid, and even in the presence of an acid scavenger. Although protonation of the alkyne may be involved in the mechanism of arenyne cycloadditions, Whitlock's results are not conclusive.

During the course of our investigations, Hoffmann and co-workers[78] proposed a mechanism involving a dienyl cation as outlined in Scheme 181. In the presence of zinc

chloride etherate or Amberlyst 15 H^+, enyne acetal **379** (X = H) was found to undergo a cycloaddition to give tricycles **383** and **384**. Protonation of the alkyne to give dienyl cation **380** was proposed to occur in the illustrated fashion due to the neighboring oxygen whose lone pairs were suggested to stabilize the positive charge. The dienyl cation then undergoes cycloaddition to give the allylic cation **381**, which can eliminate a proton in two ways to generate the observed products.

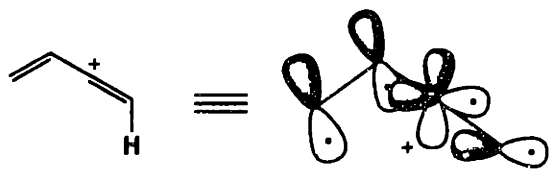
Scheme 181



Hoffmann performed numerous experiments to explore this mechanism. He found that the reaction did not proceed when the tether length was increased by one carbon; the acetal derived from a homopropargylic alcohol did not react. The increased separation might decrease the ability of the oxygen to stabilize the dienyl cation. He also found that the deuterium labeled substrate **379** (X = D) did not undergo scrambling upon cyclization, indicating that protonation at the olefinic terminus of the enyne and generation of the propargylic cation intermediate were not occurring. In addition to applying this mechanism to his own work, Hoffmann suggests that the other enyne and arenyne cycloadditions may proceed through this mechanism.

At this point, a discussion of the reactivity of enynes with protic and Lewis acids is needed. Enynes are known to react with hydrogen halides and other electrophiles in a 1,2 or 1,4 manner.[160] Protonation occurs exclusively on the acetylene, and the products obtained are dienyl halides (from 1,2 addition) or allenyl halides from (1,4 addition). The

Scheme 182



385

intermediate cationic species is not the cation proposed by Nazarov, Whitlock, and Hoffmann, but rather dienyl cation **385**. Dienyl cation **385**, shown in Scheme 182, has two π bonds orthogonal to each other, and the vinyl cation is stabilized by allylic resonance.[161] This type of cation has been shown to be more stable than simple vinyl cations by solvolysis experiments.[161]

An example of the formation of this type of dienyl cation is found in the Rupe rearrangement.[162] This rearrangement, as shown in Scheme 183, involves dehydration of a propargyl alcohol followed by hydration of the triple bond. For example, in the presence of protic acids, alcohol **386** ionizes to give the propargylic cation **387**, which loses a proton to give enyne **167**. Protonation of the acetylene moiety of enyne **167** gives the dienyl cation **388**. This cation is trapped with water, and the methyl ketone **390** is formed.

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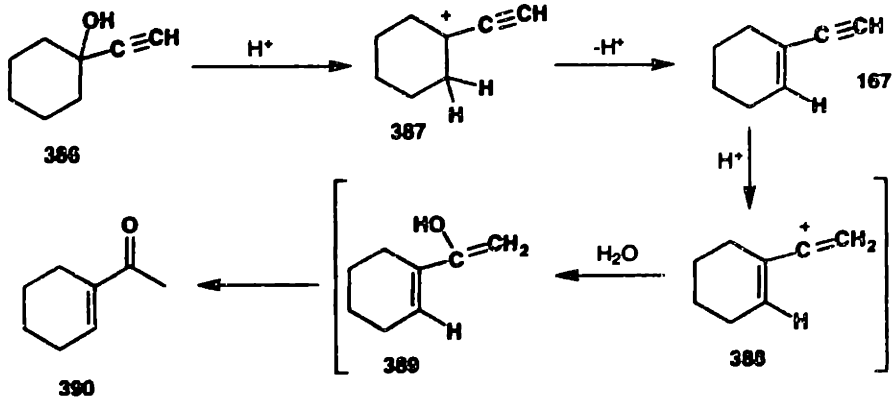
[160] Petrov, A. A. *Russ. Chem. Rev.* **1960**, *29*, 489.

[161] Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*, Academic: New York, 1979, pp 216-222.

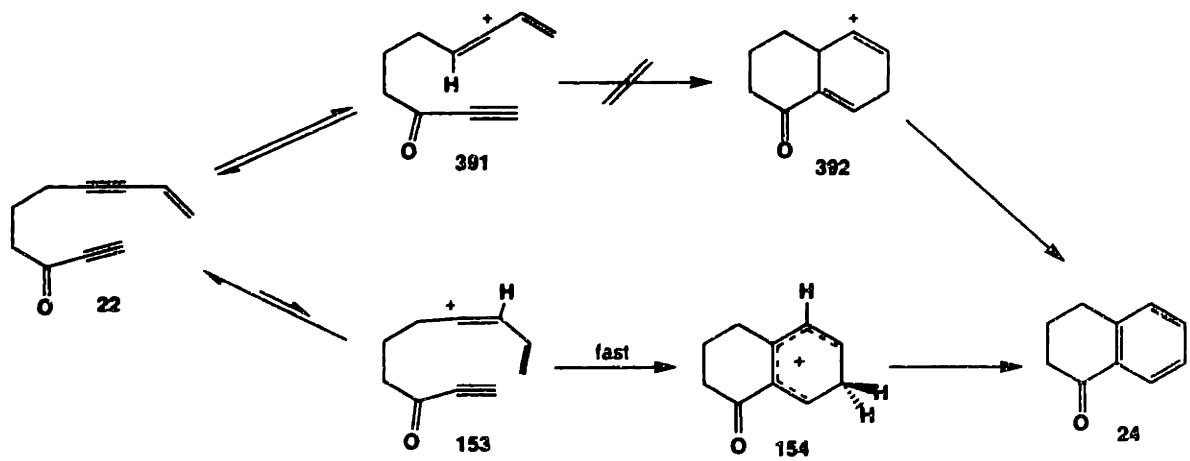
[162] For a review of the Rupe and Meyer-Schuster reactions, see: Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

Scheme 183



Given the observed behavior of enynes with protic acids, the proposed cationic mechanisms do not seem viable. However, if protonation is reversible, the mechanism may be valid. As shown in Scheme 184, the favored protonation of an enyne gives cation **391**, which could undergo an unfavorable cycloaddition to the high energy adduct **392**. Formation of dienyl cation **153** may be disfavored in the equilibrium, but cycloaddition of this dienyl cation may be fast and very favorable. In this process, a high energy vinyl cation is transformed into a relatively stable pentadienyl cation, and the transition state for

Scheme 184

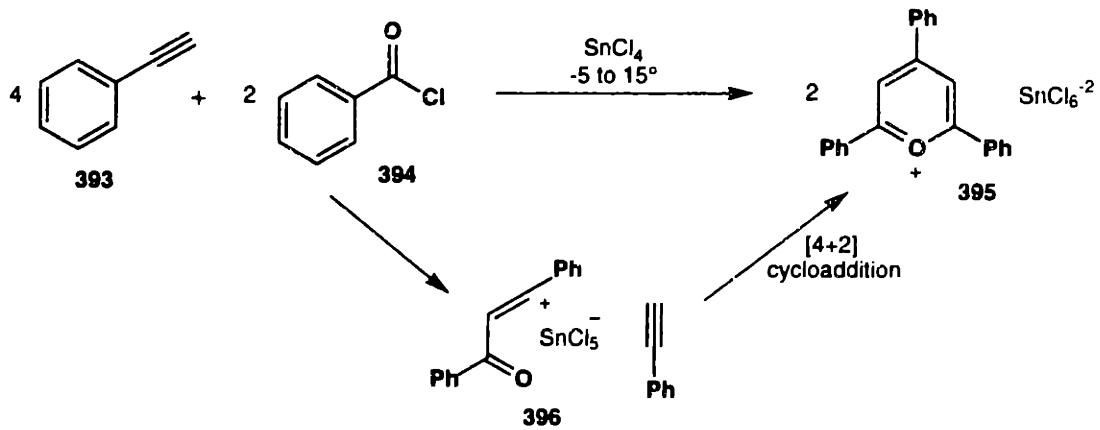


this reaction should benefit from the increase in delocalization of a positive charge. This charge acceleration effect in a cycloaddition is reminiscent of the charge accelerating effects

on sigmatropic rearrangements previously demonstrated in our laboratories and others.[163] Thus, under equilibrium conditions, the enyne can be protonated to give both dienyl cations **153** and **391**, but only cation **153** can react quickly, generating the cyclohexadienyl cation **154** and then the aromatic product **24**.

The cycloadditions of dienyl cations are not well known. Polar cycloadditions, as this type of reaction has been named, are known to occur with certain heterodienes, [164] but this type of cycloaddition has not been established for all-carbon substrates. For example, Schmidt has found that treatment of a mixture of phenylacetylene and benzoyl chloride **394** with tin tetrachloride gave the pyrylium salt **395**.[165] Electrophilic attack on the acetylene by an acylium ion is proposed to provide the cationic species **396**. This heterodiene then

Scheme 185



reacts with another molecule of phenylacetylene in a [4+2] cycloaddition (or stepwise process) to give the pyrylium ion. These reactions occur at or below room temperature in the presence of a Lewis acid catalyst. Schmidt has found that β-chloro enones **397** and even β-chloro ketones **398** will react with aryl acetylenes to give pyrylium ion products.

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[163] For a review, see: Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Eds.; Pergamon: Oxford, 1991; Vol. 5, p 999.

[164] For a review of polar cycloadditions, see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212.

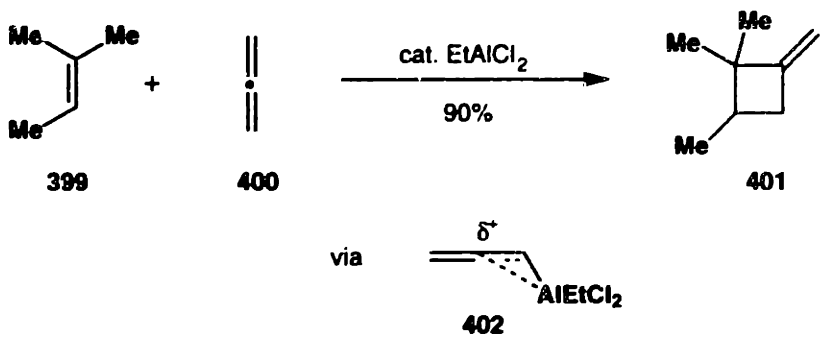
[165] Schmidt, R. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 387. Schmidt, R. R. *Chem. Ber.* **1965**, *98*, 334.

In addition, nitriles, cyanates, and cyanamides can be used to produce other heterocycles. Although the dienyl cation mechanism discussed above for enyne cycloadditions is quite different, the mild conditions required for these heterocycloadditions add support for a facile Diels-Alder reaction after protonation.

397 398

Polar [2+2] cycloadditions of alkenes, alkynes, and allenes are also known. Lukas, Baardman, and Kouwenhoven found that Lewis acids can be used to promote [2+2] cycloadditions.[166] As shown in Scheme 186, alkene **399** and allene **400** react in the presence of ethylaluminum dichloride to give the cyclobutane **401**.[166a] The reaction is proposed to proceed through a Lewis acid complex **402**. The reaction proceeds best with

Scheme 186



hindered and electron rich alkenes, and can be promoted by several different Lewis acids. As shown in Scheme 187, these workers also found that alkynes will undergo a similar reaction in the presence of a Lewis acid, presumably through a similar cationic

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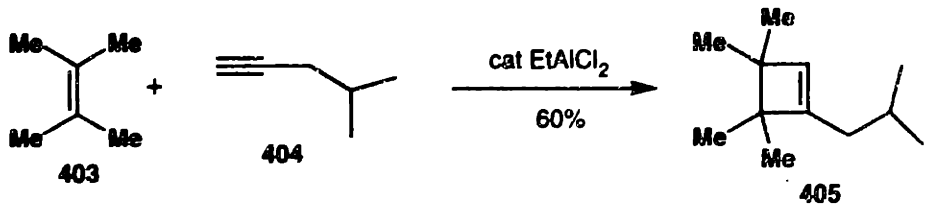
[166] a) Lukas, J. H.; Kouwenhoven, A. P.; Baardman, F. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 709. b) Lukas, J. H.; Baardman, F.; Kouwenhoven, A. P *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 369.

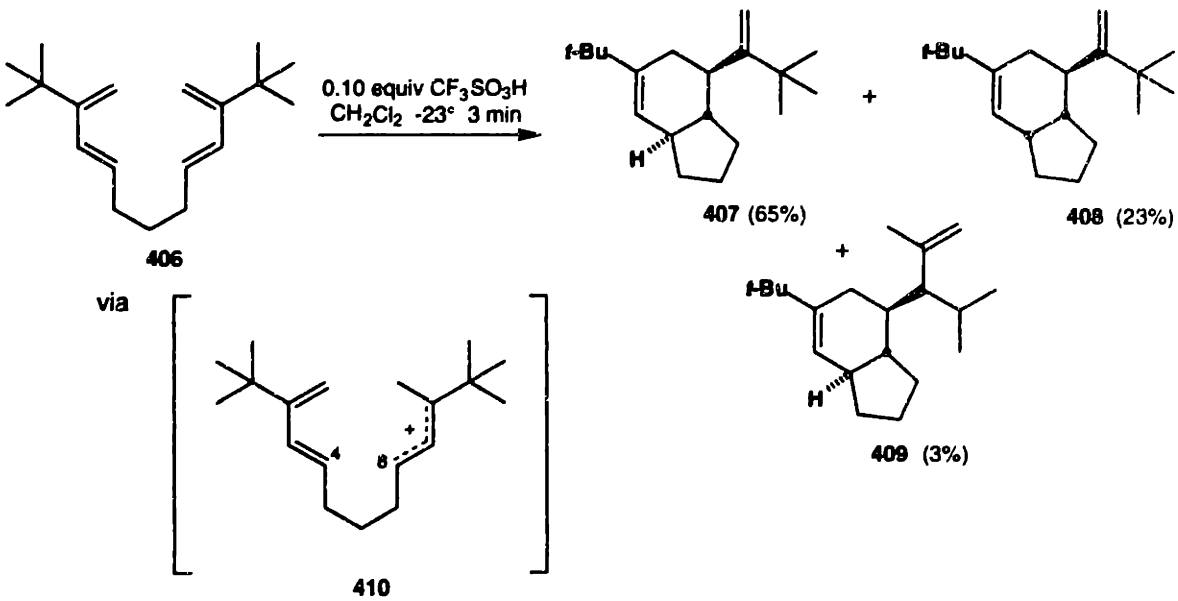
Scheme 187



mechanism.[166b] The ability of ethylaluminum dichloride to catalyze the reaction in good yield indicates that the reaction is not being promoted by a protic acid, as alkylaluminum chlorides are proton scavengers.[126] It also indicates that Lewis acids can complex multiple bonds to form electron deficient species that react in cycloadditions. In other words, Lewis acids could be promoting the enyne cycloaddition by activating the enyne.

Although dienyl cation cycloadditions are not well known, other carbon-based cationic species are known to be involved in [4+2] cycloaddition reactions. Gassman and

Scheme 188

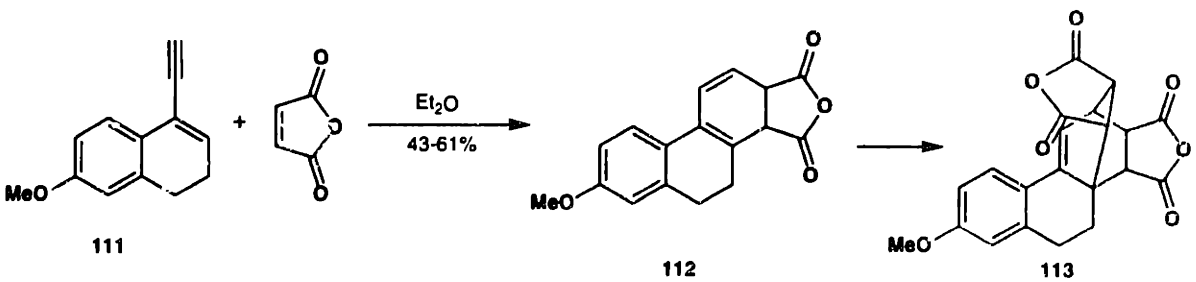


co-workers found that allyl cations will act as dienophiles in Diels-Alder reactions.[167] Allyl cations generated from the protonation of a diene or the ionization of an allyl alcohol or ether can react in either an inter or intramolecular fashion with dienes. As shown in Scheme 188, when tetraene **406** is treated with a protic acid at -23 °C, three cycloaddition products are generated. The major product, trans-fused hydrindan **407**, isomerizes to the cis-fused hydrindan **408** under the reaction conditions. The third product, hydrindan **409**, results from a Wagner-Meerwein shift of a methyl group after the cycloaddition followed by elimination. This reaction was shown to proceed in a stepwise fashion in which the bond between carbons 4 and 8 is formed first.[167a,c,d]

Ionic mechanisms for cycloadditions have been postulated for many reactions. In our case, an ionic concerted cycloaddition involves a disfavored protonation or Lewis acid complexation and a previously unknown polar cycloaddition to give a cationic carbocycle. This pathway does avoid the cyclic allene or biradical intermediate and may be occurring under either protic or Lewis acid conditions.

Other mechanisms have been proposed to account for the enyne cycloaddition. These mechanisms are more substrate specific and involve rearrangements of the enyne. In the 1930's, Dane and co-workers found that the electron rich enyne **111** reacted with

Scheme 189



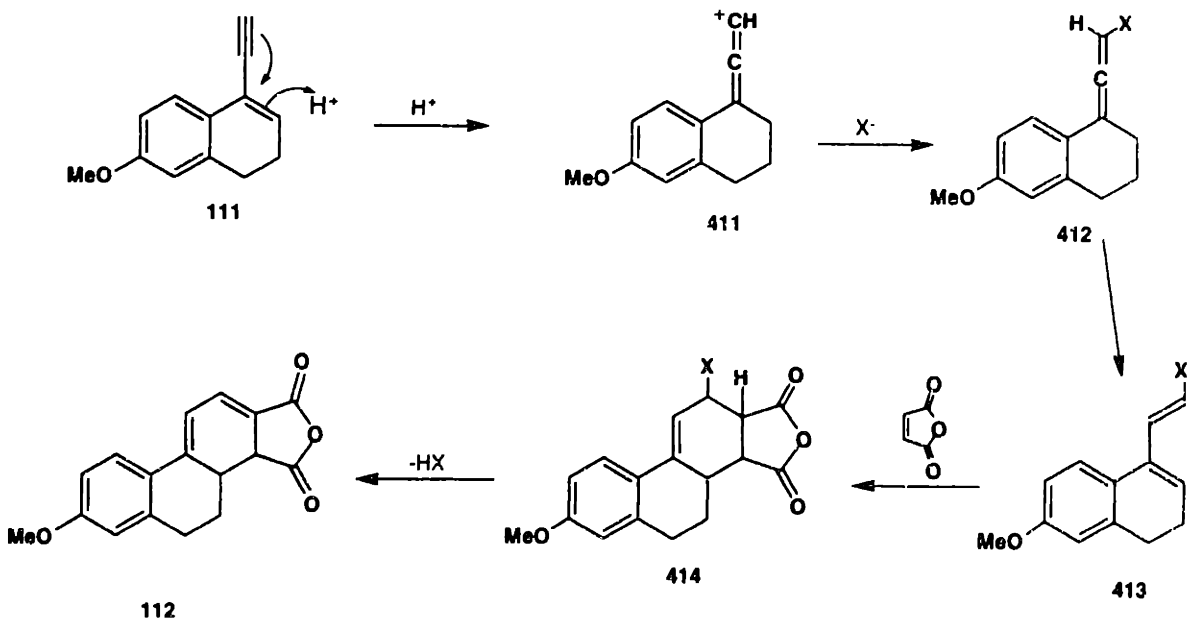
111 112 113

[167] (a) Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 6085. (b) Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 7993. (c) Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986**, *51*, 3075. (d) Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8623, 8624. (e) Gassman, P. G.; Singleton, D. A.; Kagechika, H. *J. Am. Chem. Soc.* **1991**, *113*, 6271.

maleic anhydride in ether overnight to give cycloadduct **112**.[66] As we have seen, the mechanism of this particular reaction has been speculated on by Butz.

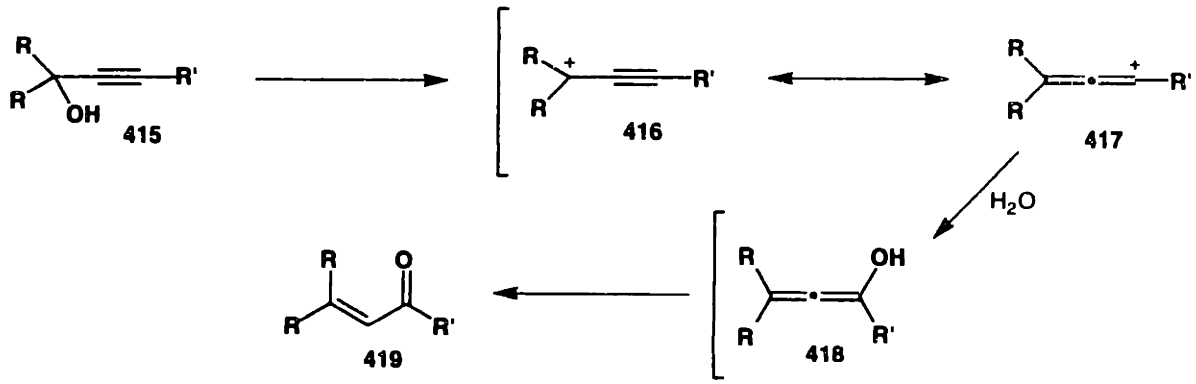
Recently, this reaction has been revisited by Miller and Ionescu[67] who found that the reaction did not proceed unless a sub-stoichiometric amount of either HCl or HBr gas was added to the reaction mixture. The need for acid led these workers to suggest that the reaction is indeed acid catalyzed, although not in a manner previously proposed. This enyne is more electron rich due to its conjugation to a methoxybenzene ring than an unsubstituted enyne, and Miller and Ionescu propose a mechanism that involves the formation of a halodiene that then reacts with maleic anhydride. As shown in Scheme 178, the halodiene is formed by protonation of the enyne to give the benzylic cation in resonance with the allenyl cation **411**. The allenyl cation is quenched to give the allenyl halide **412**. Protonation at the central carbon of the allene to give a benzylic cation followed by elimination gives the halo diene **413**, which then undergoes a Diels-Alder cycloaddition. Elimination of HX regenerates the catalyst and affords the observed product **112**.

Scheme 190



This mechanism is closely related to the Meyer-Schuster rearrangement, which involves acid-promoted ionization of a propargyl alcohol **415** to give a propargyl cation **416**,[162] as shown in Scheme 191. This propargyl cation has no α protons (R= Ar or *t*-Bu) and cannot undergo elimination as in the Rupe rearrangement (Scheme 183). Allenyl cation **417**, is then trapped by water to give the allenyl alcohol **418** which then tautomerizes to give the enone or enal product **419**.

Scheme 191



This mechanism was considered as a new possibility in our exploration of the enyne cycloaddition. The cycloaddition proceeds in the presence of protic acids, and we were interested in the reactivity of enynes in the presence of acids. Although Miller's mechanism might be quite specific for electron rich enynes, we included it in our list of mechanistic options.

A final option for the reaction involves the acid catalyzed isomerization of the enyne to a vinyl allene **420** that then undergoes cycloaddition and isomerization (Scheme 192). Intramolecular cycloadditions of vinyl allenes are known[168] and have been used to construct

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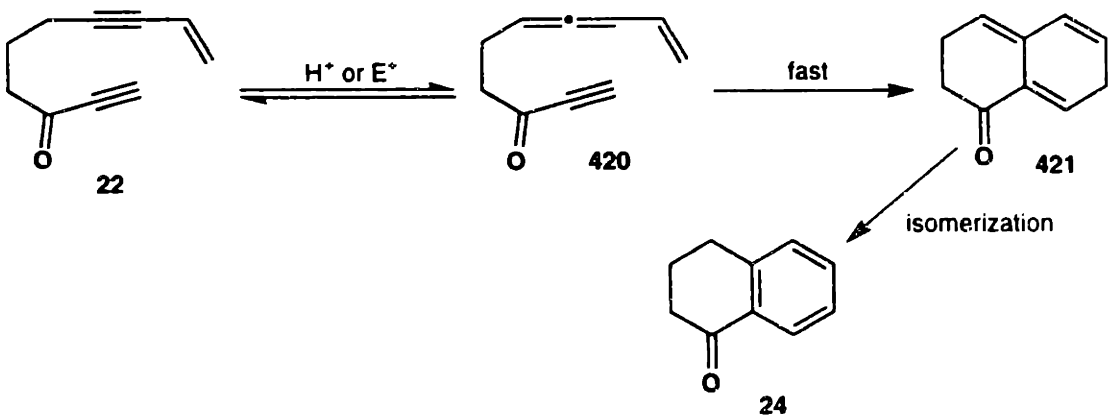
[168] For some examples, see: Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. Snider, B. B.; Burbaum. B. W. *J. Org. Chem.* **1983**, *48*, 4370.

similar systems to those produced in the enyne cycloaddition.[169] The vinyl allenes in these reactions were derived from a base catalyzed isomerization of the enyne. In our case, however, no base is present, and if an allene is involved, an acid catalyzed isomerization must be involved. The isomerization of an alkyne to an allene under protic acid conditions has been studied.[160] Carr and co-workers found that allenes react quickly under acidic conditions to give alkynes while the reverse reaction is much slower.[170] However, as with the enyne protonation mechanism, an equilibrium may draw the enyne through the vinyl

Scheme 192



allene to the cycloadduct. Helgason's successful work on the preparation of fluorenones involved substrates that were incapable of isomerization to a vinyl allene, and several other researchers including Nazarov and Hoffmann have prepared substrates with gem dimethyl substituents α to the alkyne of the enyne that also underwent the cycloaddition. Thus, we have not considered this mechanistic alternative further.

The reaction of enynes with alkenes and alkynes can occur through many possible mechanisms. This chapter has discussed a variety of options. The reaction may be

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[169] Iwai, I.; Hiraoka, T. *Chem. Pharm. Bull.* **1963**, *11*, 1564. Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1964**, *12*, 1094.

[170] Barry, B. J.; Beale, W. J.; Carr, M. D.; Hei, S.-K.; Reid, I. *J. Chem. Soc., Chem. Comm.* **1973**, 177.

stepwise or concerted, and the concerted reaction can occur through a variety of paths. Protonation or isomerization of the enyne and then cycloaddition will give the desired product. Direct cycloaddition can also occur to give a cyclic allene or biradical species. Our attempts to determine which options are viable will be discussed in the next chapter and will focus mainly on the different types of concerted reactions.

Chapter 2

Experimental Results

The last chapter presented several mechanistic alternatives for the cycloaddition of conjugated enynes with alkenes or alkynes. We are interested in elucidating the mechanism of the intramolecular version of this reaction, and this chapter focuses on the experimental data that we have collected in an attempt to evaluate various mechanistic pathways.

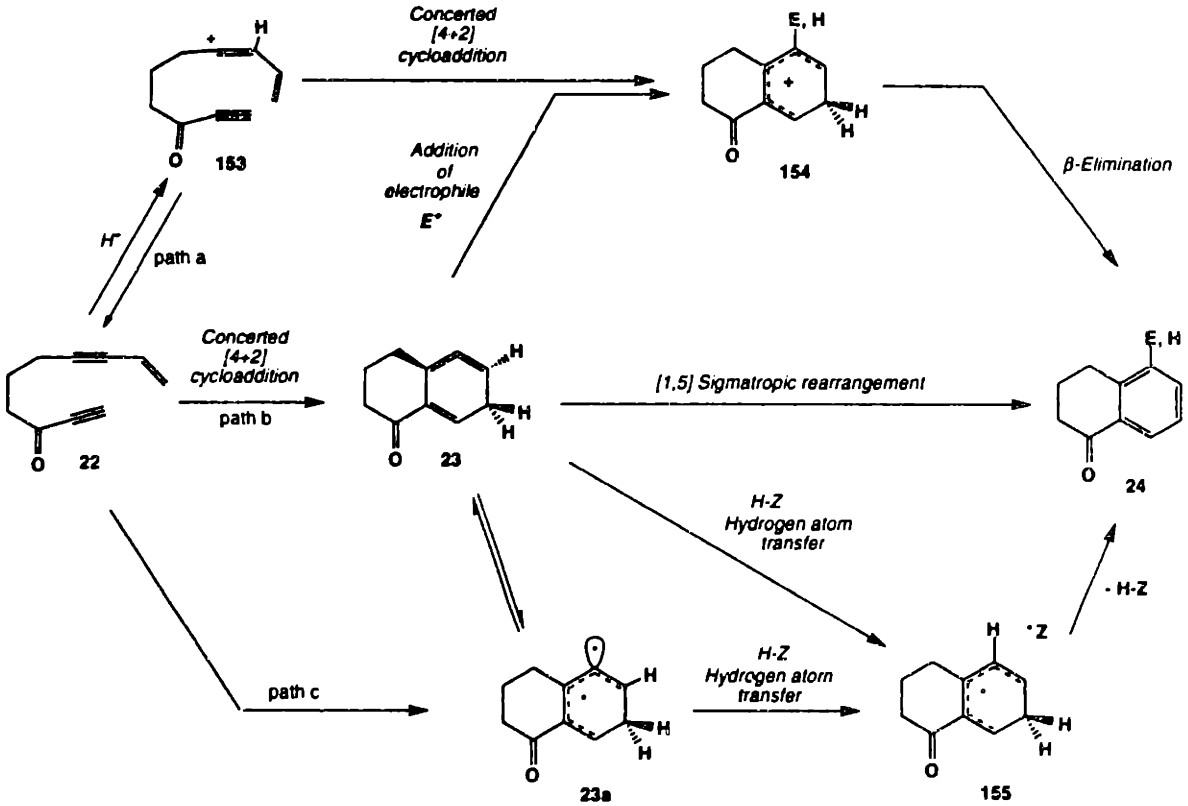
As described in Part II, the intramolecular cycloaddition of conjugated enynes occurs under a variety of conditions and with a variety of substrates. Many mechanisms have been proposed for this reaction, and under different conditions, different mechanisms may be operating. To simplify the presentation of the data and its interpretation, different reaction conditions will be considered separately in this chapter, and separate mechanistic options will be proposed for the reaction under different conditions. The initial work on the mechanism of this reaction focused on the transformation under thermal conditions, and this chapter begins with a discussion of the these experiments, including the preparation and cycloaddition of a substrate designed to trap a cyclic allene or biradical intermediate. The next area of interest is the mechanism of the reaction under Lewis or protic acid conditions.

The Enyne Cycloaddition under Thermal Conditions

Under thermal conditions, we consider the mechanistic options to include a dienyl cation cycloaddition (path a in Scheme 193) as well as a concerted cycloaddition to give a cyclic allene or biradical species (paths b and c). In all of these mechanisms, the isomerization of an intermediate to the observed aromatic product is required. This isomerization can occur through the elimination of a proton from cyclohexadienyl cation

154, which is the result of a dienyl cation cycloaddition, or via an electrophilic addition to cyclic allene **23**. Isomerization can also occur via a [1,5] sigmatropic hydrogen shift in allene **23**, through atom abstraction by the cyclic allene to give cyclohexadienyl radical **155**, or through the biradical **23a**, which could undergo hydrogen atom transfer to give radical **155**. Cyclohexadienyl radical **155** could then lose a hydrogen atom to afford the

Scheme 193



tetralone **24**. The stepwise mechanisms for six-membered ring formation were not considered, because as discussed in the last chapter, we do not consider them to be likely pathways. Further work has been done under other conditions to address this stepwise versus concerted mechanism issue, and this work will be discussed in the next chapter.

In examining the mechanism of the reaction under thermal conditions, we have looked at the kinetics of the reaction, evaluated the formation of side products, explored the possibility of trapping intermediates both inter- and intramolecularly, and studied the

reactions of some specially designed substrates. Some of the early results were obtained during the optimization of the reaction, and these results will be discussed first. Kinetics experiments showed that the reaction is unimolecular in enyne, but may be catalyzed by BHT. The trapping experiments and the side products observed indicated that any intermediates involved in the cycloaddition are highly reactive and difficult to trap. Finally, specially designed substrates were prepared and subjected to the reaction conditions to evaluate the possibility of a dienyl cation mechanism.

During the initial optimization of the thermal reaction, studies on the effect of concentration showed that optimal results were obtained with an intermediate concentration. This result gave the first clues to the mechanism of the reaction. The yield of an intramolecular reaction should increase somewhat with decreasing concentrations, because any bimolecular side reactions will be slowed at lower concentrations. One of the potential mechanisms for this reaction involves two intramolecular steps, a cycloaddition to give a cyclic allene, followed by a [1,5] sigmatropic rearrangement to give the aromatic product. Experimentation showed that both high and low concentrations afforded poorer yields than an intermediate concentration. If the reaction was purely intramolecular, then low concentrations would give the highest yields. As this was not the case, the sigmatropic rearrangement was considered less likely as a possible component in the reaction mechanism.

These results indicated that both an intramolecular process and an intermolecular process might be involved. At high concentrations, intermolecular side reactions interfered with the intramolecular cycloaddition, and at low concentrations the necessary intermolecular step is slowed, and the yield falls.

During the course of our studies on the scope of this reaction, different solvents were examined. If the reaction proceeds through a polar transition state or intermediate, then solvents capable of stabilizing charged species might facilitate the reaction by lowering the energy of the transition state. The reaction was studied in DMSO and ethylene glycol as

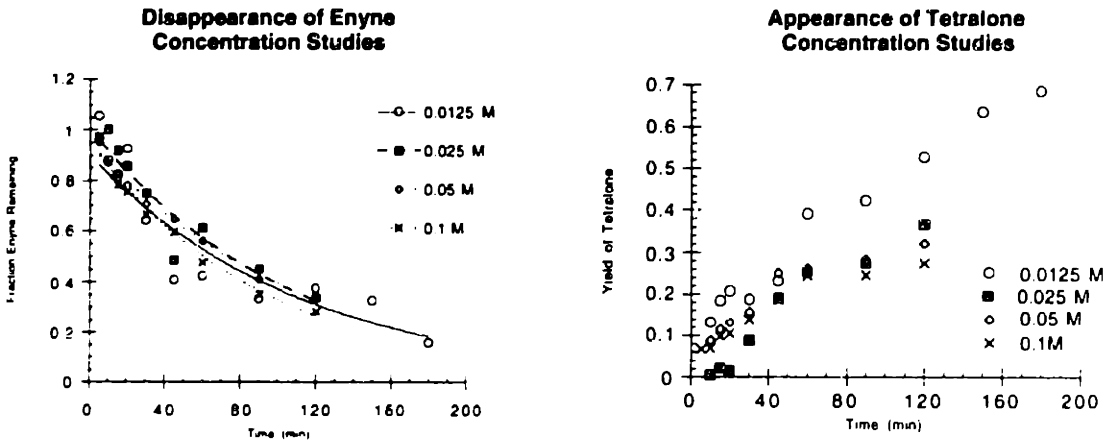
described in Part II, Chapter 2, and disappointing results were obtained. The reaction does proceed at lower temperatures in these solvents, but the yields for these reactions are universally low. *n*-Butanol was also investigated as a solvent; it did not provide useful results either. Aromatic solvents have been found to give the best results for this reaction. Cyclohexane has also been used in cases with volatile products, and yields are generally lower with this solvent. Unfortunately, due to the low yields of these reactions in solvents other than benzene and toluene, no firm conclusions can be drawn.

Once optimization of the reaction under thermal conditions was complete, we decided to explore the kinetics of the reaction. We felt that learning more about the kinetics would allow us to discount some reaction mechanisms. If the steps after the cycloaddition are fast, then in theory, the two types of cycloadditions (path a versus path b and c, Scheme 193) could be differentiated. Cyclic allene and biradical formation (paths b and c) are unimolecular processes, and if the reaction is proceeding through these mechanisms, then the rate of the reaction will be directly proportional to the concentration of starting material. On the other hand, the dienyl cation mechanism (path a) involves protonation of the enyne by another species followed by cycloaddition. This pathway will also be affected by concentration, but the rate should be dependent on the concentration of both the enyne and the proton source. BHT or adventitious acid could be responsible for the protonation of the enyne in this mechanism.

An experiment was carried out to investigate the order of the reaction with respect to the enyne. In the first phase of the experiment, the initial concentration of the enyne was varied, while the concentration of BHT was kept constant. NMR tubes were prepared containing enyne **212** in deuterated toluene, a known amount of 1,4-dimethoxybenzene as an internal standard, and BHT (0.05 M for each solution); the enyne was present in concentrations of 0.1 M, 0.05 M, 0.025 M, and 0.0125 M respectively in each tube. In order to ensure that each reaction mixture was exposed to the same exact conditions, all the reactions except the one at 0.0125 M enyne concentration were run simultaneously in the

same heating bath. The reaction with 0.0125 M enyne concentration was performed separately after the first three experiments had been completed, and some differences in oil bath temperature may have occurred. All of the tubes were degassed, sealed, and heated in an oil bath at 176 to 180 °C. At given intervals, the tubes were removed from the oil bath, and the reaction mixtures were analyzed by ^{1}H NMR spectroscopy. The integrals of the starting material and product in the NMR spectra were measured. As shown in Scheme 194, the rates of disappearance of enyne and appearance of product are similar for all of the reactions monitored.

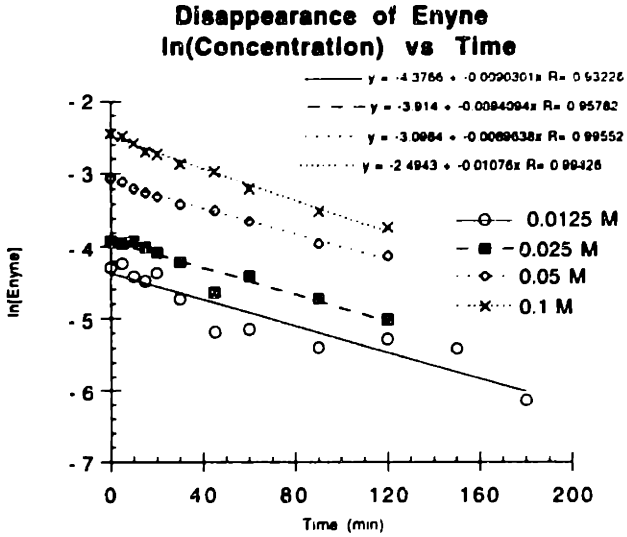
Scheme 194



The next step in evaluating the kinetic data was to graph the natural logarithm of the concentration of the enyne versus time (Scheme 195). If linear plots are observed, then the reaction is first order in enyne according to the first order rate law equation. All four concentrations provide straight lines with slopes that agree to within 10% indicating that the reaction is first order with respect to the enyne.

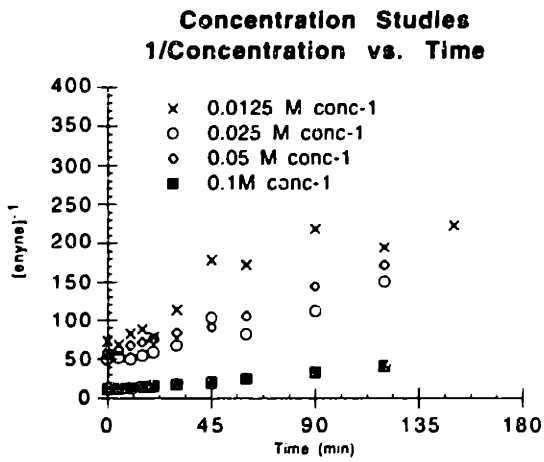
Many second order reactions also give linear plots when the natural logarithm of concentration versus time is plotted. However, a reaction that is second order will also give a straight line when the inverse of concentration versus time is plotted. As shown in

Scheme 195



Scheme 196, when plotted in this way, the data for the concentration experiments does not

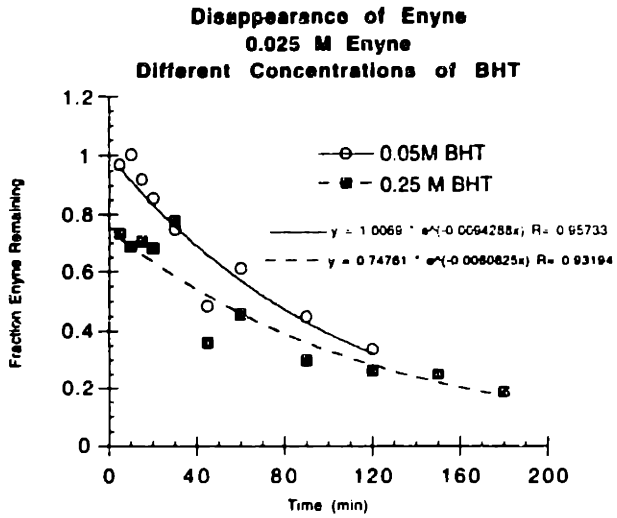
Scheme 196



fit a straight line for all of the concentrations. These results indicated that the reaction was first order with respect to enyne **212**, but they did not rule out the possibility that BHT could be acting as a catalyst. The next step was to evaluate the role of BHT in the mechanism by monitoring the reaction at different concentrations of BHT.

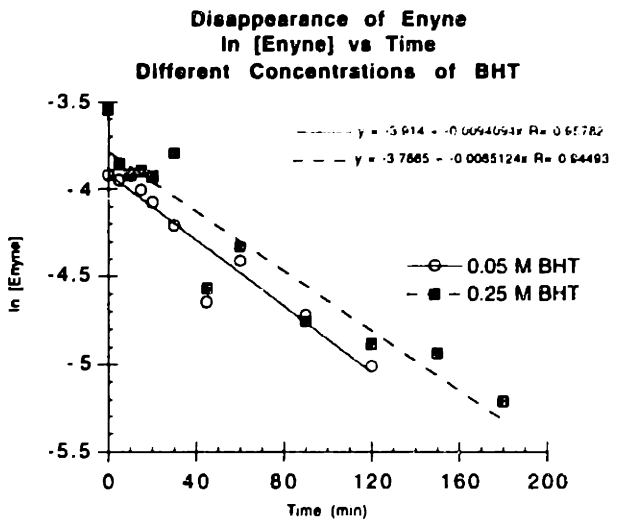
A second experiment was designed to vary the concentration of BHT and to monitor the disappearance of enyne. An NMR tube was prepared with a solution that was 0.025 M in enyne and 0.25 M in BHT; the solution also contained a known amount of the

Scheme 197



internal standard 1,4-dimethoxybenzene. The experiment proceeded as described above, and was compared to a previously run reaction at 0.025 M in enyne **212** and 0.5 M in BHT. The data derived from ^{1}H NMR spectra are compared in Scheme 197. The rate of

Scheme 198



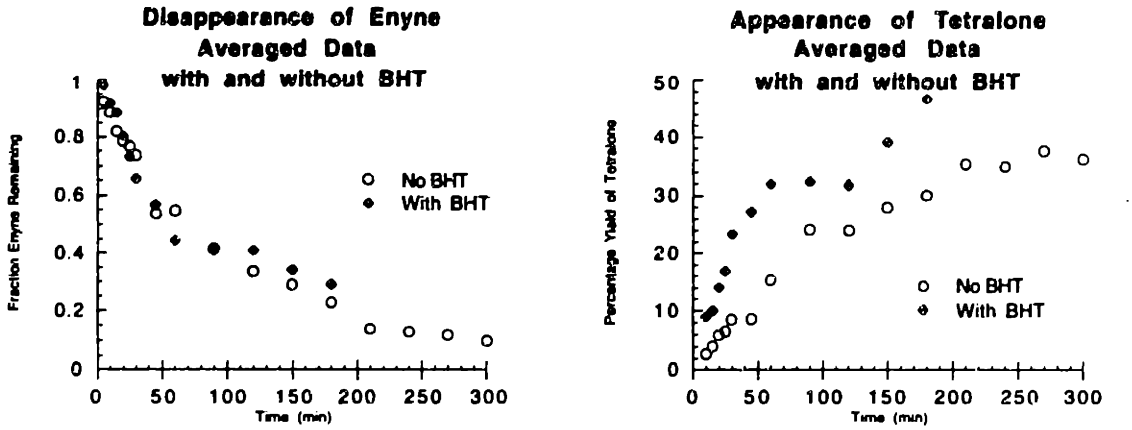
disappearance of enyne with 0.25 M BHT is different from the rate with 0.05 M BHT. This difference in rates, which is not terribly large, is also seen in a graph of the natural logarithm of concentration of enyne versus time (Scheme 198). One reason for the

difference in rates may be that the data were collected in different runs, and slight differences in conditions, especially temperature, will affect the rate of the reaction. If the differences rate are real, then BHT may be involved as a catalyst of the cycloaddition.

Further experiments were needed to explore the involvement of BHT in the reaction. However, the accuracy of the integrals in the NMR decreased as the concentration of BHT increased and the relative concentration of enyne fell, and we were not comfortable with the results we were obtaining.

A clue to the role of BHT in catalysis of the reaction existed in some data I had already collected, however. The rate of the cycloaddition had been monitored on three different occasions in the absence of BHT and on four occasions in the presence of BHT, during the course of the studies to be discussed below. This data was averaged, and graphed to give the plots shown in Scheme 199. If the reaction is catalyzed by BHT, then the rate of the reaction with BHT will be different from the rate of the reaction without BHT. As shown below, product formation is more efficient in the presence of BHT, but the rate of disappearance of starting enyne is similar under the two reaction conditions. The difference in yields in the two reactions over the time observed can be explained by the following scenarios: first, BHT may be involved in a more efficient conversion of the intermediates formed after the cycloaddition to the product, and second, BHT may inhibit polymerization of the starting material, allowing more enyne to be converted to product. The second rationale requires polymerization of the starting material and cycloaddition to occur with similar rates or else a difference in the rate of enyne disappearance would be noted. The difference in rates of product formation also indicates that BHT catalysis may be a possibility, but the lack of difference in rate of disappearance of enyne may indicate that BHT is not a great catalyst. Other methods can be used to explore the rate of this reaction, but as yet we have not continued this investigation. We did, however, begin considering different methods for evaluating the role of BHT in the reaction

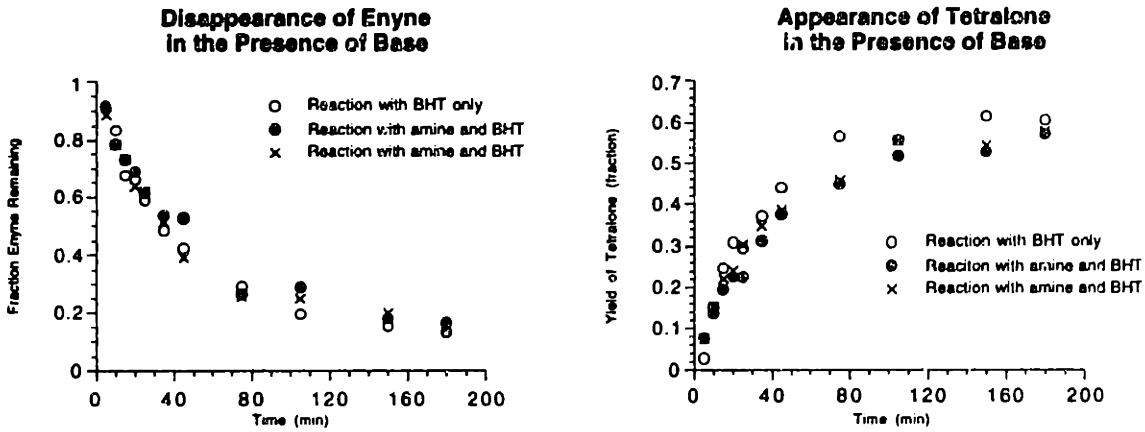
Scheme 199



If the reaction is proceeding through a dienyl cation mechanism, then introducing a proton scavenger into the reaction mixture should slow the reaction by inhibiting protonation of the enyne. The proton scavenger does not completely remove acid from the reaction mixture, but rather it reacts with the acids present to generate a weaker proton source. Thus, an acid catalyzed reaction should be slowed. A set of experiments was designed to investigate this hypothesis by monitoring the reaction by NMR as described above. The first experiment involved the standard thermal conditions and 2,6-di-*tert*-butylpyridine (**423**). Three NMR tubes were charged with enyne **212**, d_8-toluene, 1.0 equivalent of BHT, and an internal standard. To two of the tubes, 2,6-di-*tert*-butylpyridine (**423**) (1.1 equivalent) was added. The tubes were degassed, sealed, and heated in an oil bath at 190 °C. As in the concentration experiment, the tubes were removed at given times, and the amount of starting enyne and product tetralone were measured by ^{1}H NMR. The rates of disappearance of starting material and of appearance of tetralone (Scheme 200) do not change in the presence of the amine base, indicating that the reaction mechanism is probably not dependent on proton catalysis. However, the results may not be quite so clearcut. BHT is a phenol with a pK_a of approximately 11[171] and the conjugate

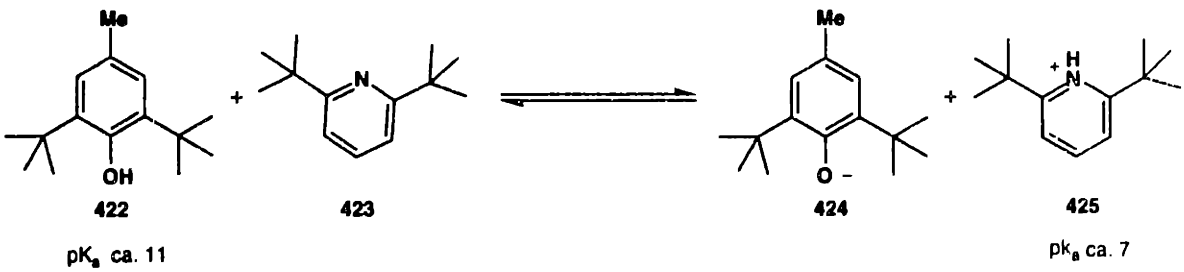
[171] 2,4,6-trimethylphenol has a pKa of 10.89 in water at 25 °C. *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Interscience: London, 1971; pp 274-275.

Scheme 200



acid of 2,6-di-*tert*-butylpyridine has a pK_a of approximately 7.[172] At room temperature, these two compounds will exist mainly as **422** and **423**, and this acid scavenger will have no effect on the reaction if the mechanism involves protonation of the enyne by BHT. This base was added to react with any more acidic species present in the reaction mixture, as reactions have been catalyzed by trace acids found on the walls of the glass reaction vessel. If adventitious acid is present, then the base should react with it, however the phenol will remain protonated and able to catalyze the reaction.

Scheme 201



Since the results with base and BHT were not as clean cut as desired, BHT was eliminated from the reactions in the next experiment. In each experiment, two NMR tubes

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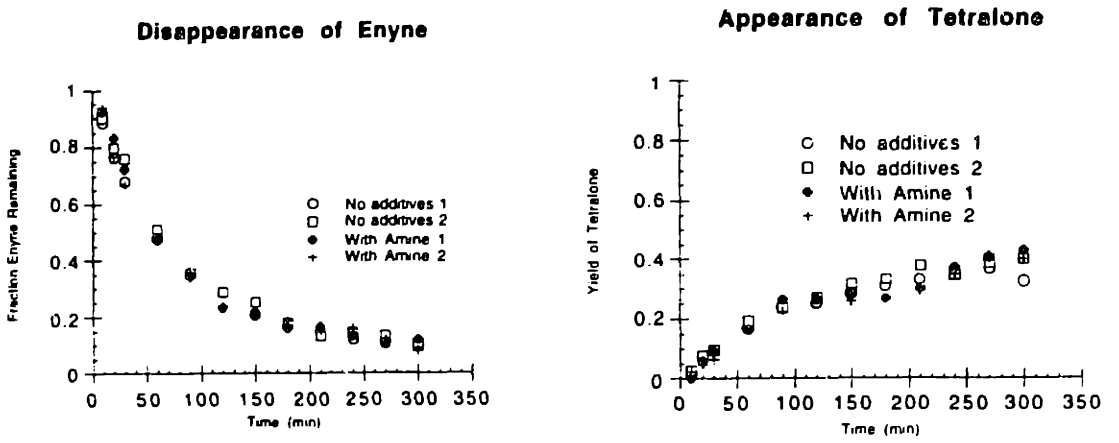
[172] 2,6-dimethylpyridine has a pKa of 6.69 in water at 25 °C. *Rodd's Chemistry of Carbon Compounds*; Coffey S., Ed.; Elsevier: New York, 1976; Vol. 4f, p 158.

were prepared with a solution of the enyne in d_8-toluene and an internal standard. One of the tubes was also treated with 0.9 to 1.0 equivalents of the amine **396**. The tubes were degassed, sealed, and heated at approximately 180 °C in an oil bath. As shown in Scheme 202, the rate of disappearance of starting material and of appearance of product are similar for both reaction mixtures. These results confirm those obtained when the reaction was run with BHT, and could indicate that a proton catalyzed reaction is not occurring. Once again,

Scheme 202



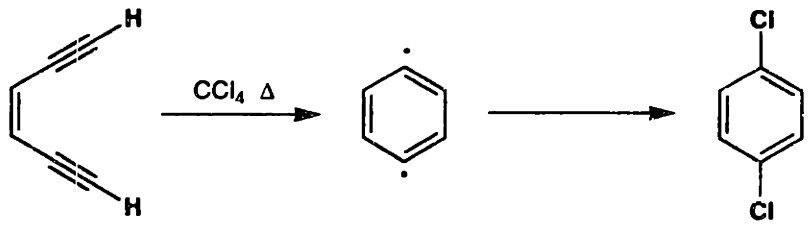
some questions about the strength of the proton scavenger used and its effectiveness at 180 °C can be raised. The pyridine **423** is not a particularly strong base, but it should be able to deprotonate a dienyl cation, thus slowing the rate of reaction through a dienyl cation mechanism. As no change in rate has been observed, we feel that the reaction may not be acid promoted.

Our NMR experiments did not provide conclusive results, and further investigation was needed. So we shifted our focus from the kinetics of the reaction to the trapping of intermediates in the reaction pathway. Specifically, we were interested in running the reaction under conditions or with substrates that would allow for the trapping a cyclic allene or biradical intermediate.

As discussed earlier, the design of the enyne cycloaddition is based in part on the cycloaromatization reactions of enediynes and allenynes. These reactions proceed via

biradical intermediates whose presence has been demonstrated on the basis of various trapping experiments. One of the most common trapping methods involves the use of carbon tetrachloride as a solvent. Bergman[3a,b] and Myers[9c] have both used this as proof for the presence of a biradical intermediate in the cycloaromatization reactions they have studied. As shown in Scheme 203, when endiyne **426** is heated in the presence of CCl_4, cyclization occurs, and the intermediate biradical abstracts two chlorine atoms from the solvent to form 1,4-dichlorobenzene (**428**).

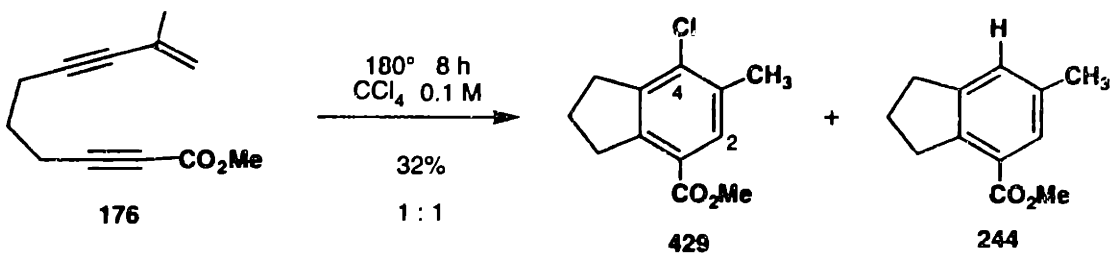
Scheme 203



426 **427** **428**

Heating enyne **176** in the presence of carbon tetrachloride provided a mixture of products. The ^1H NMR spectrum of these products showed that the indane **244** was present with an equal amount of with a similar compound characterized by a single aromatic proton. GC/MS showed this mixture to consist of indane **244** and a compound with a molecular ion at 224 and an ion of one third intensity at 226. This corresponds to a

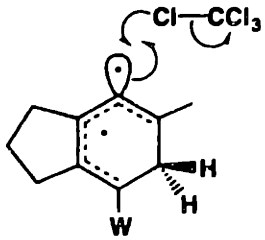
Scheme 204



176 **429** **244**

molecular formula consistant with chlorine incorporation[173] as in chloroindane **429**. High resolution mass spectroscopy confirmed the molecular formula, and ^{1}H NMR spectroscopy showed the only aromatic proton in **429** is at C-2, indicating chlorine was incorporated at C-4, as shown in Scheme 204. The presence of chlorinated indane is consistant with a biradical intermediate; chlorine incorporation may occur via the mechanism shown in Scheme 205. No chlorine incorporation was observed when cycloadduct **244** was heated at 180 °C in the presence of carbon tetrachloride for 8 hours.

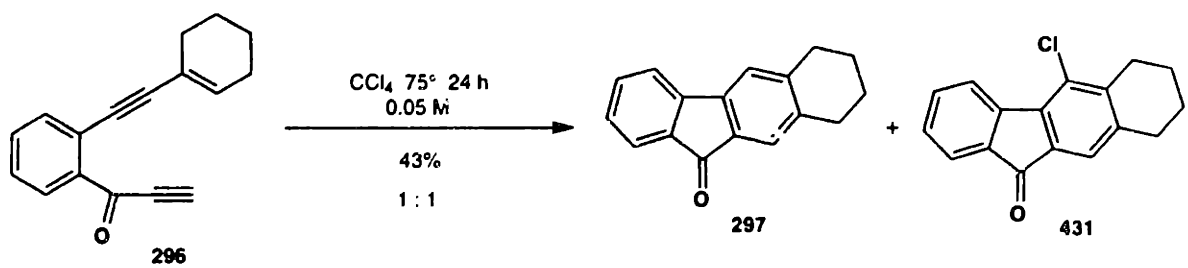
Scheme 205



430

Two other substrates were also subjected to these reaction conditions. Enyne **296**, studied by Anna Helgason, was heated in carbon tetrachloride at reflux. This reaction required 24 hours, much longer than the time required for reaction in benzene at reflux (3 hours), and provided a 1:1 mixture of the chlorinated and non-chlorinated fluorenones **431** and **297** in 43% overall yield. The yield of the reaction in refluxing benzene was 88%. GC/MS also confirmed the presence of chlorine in this reaction mixture.

Scheme 206



296 **297** **431**

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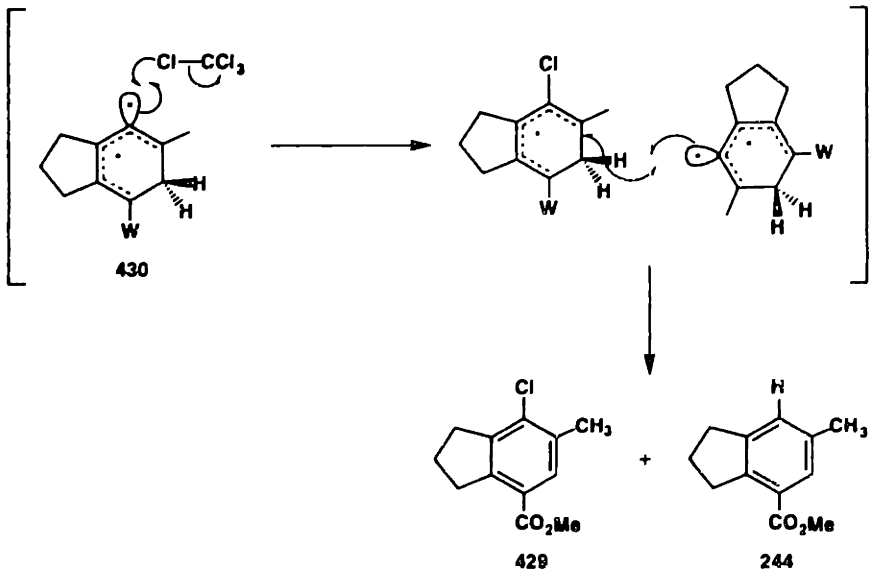
[173] Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981; pp 35-37.

The 1:1 mixtures obtained in these two experiments may be significant. The formation of the products may be coupled, where an intermediate biradical reacts with carbon tetrachloride to form a chlorocyclohexadienyl radical (Scheme 207), which then serves as an extremely reactive hydrogen atom source for another biradical intermediate. The validity of this mechanism could be tested by running the reaction at different concentrations of enyne in carbon tetrachloride.

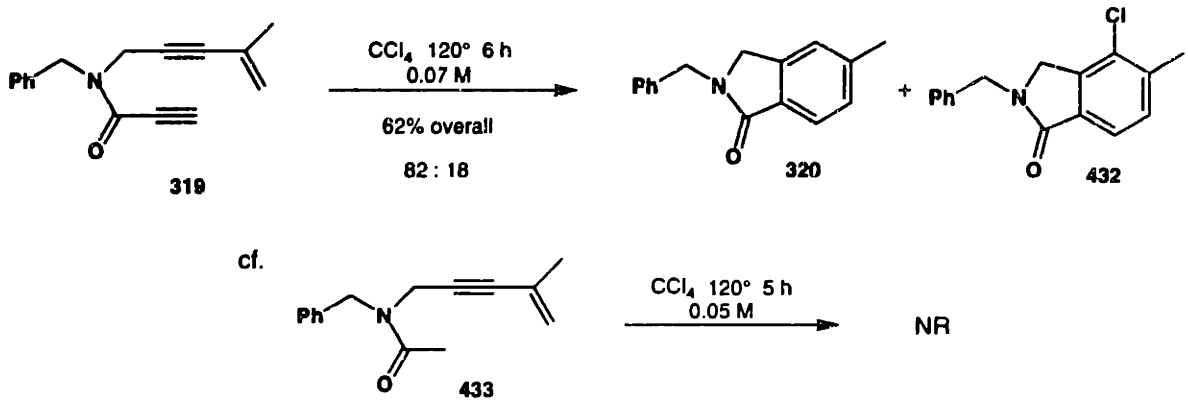
Scheme 207



Brenda Palucki found that the amide enynes did not undergo chlorination as readily as the two other substrates. Enyne **319** provided mainly nonchlorinated cycloadduct **320** when heated in carbon tetrachloride at 120 °C for 6 hours, as shown in Scheme 208. Once again, the reaction provided a mixture of products; ^{1}H NMR indicated that an 82:18 mixture of nonchlorinated to chlorinated cycloadduct was obtained. An important control experiment showed that enyne **433** does not undergo chlorination when heated to 120 °C for 5 hours, indicating that the enyne moiety is not affected by the reaction conditions. The decrease of chlorination products in the cycloaddition of enyne **319** may indicate that this substrate does not proceed through the radical pathway as readily and may be proceeding through a dienyl cation intermediate. The amide functionality may also encourage a polar isomerization of a cyclic allene involving a cyclohexandienyl cation intermediate, rather

than a radical based isomerization. If this type of polar isomerization is occurring, then chlorine incorporation may not be as facile. The decrease in chlorine incorporation may also indicate that the starting material and products compete more effectively with carbon tetrachloride as atom donors.

Scheme 208



The decreased yield observed in all cases with carbon tetrachloride may be attributed to polymerization of the starting material. Recall that the optimal conditions for the thermal cycloadditions involved the use of a reactive hydrogen atom donor such as BHT. Carbon tetrachloride produces radicals upon heating, and free radical polymerization of the starting material is possible. In addition, the decreased yield may be related to the lack of complete chlorine incorporation. If the carbon tetrachloride is not a reactive enough source of atoms to aid in the isomerization of an intermediate to the aromatic cycloadduct, then the intermediate may be attacking either starting material or product to obtain hydrogen atoms. In addition, the low yield may be explained in terms of a reaction mechanism involving a cyclohexadienyl cation intermediate that is not favored in the nonpolar reaction medium of carbon tetrachloride. Semmelhack has also observed incomplete chlorine incorporation in his studies of Bergman type cyclizations of dialkynylarenes.[174] He does not offer an explanation, but proposes that the mechanism may be more complicated than

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[174] Semmelhack, M. F.; Neu, T.; Foubelo, F. *Tetrahedron Lett.* **1992**, *33*, 3277. Semmelhack, M. F.; Neu, T.; Foubelo, F. *J. Org. Chem.* **1994**, *59*, 5038.

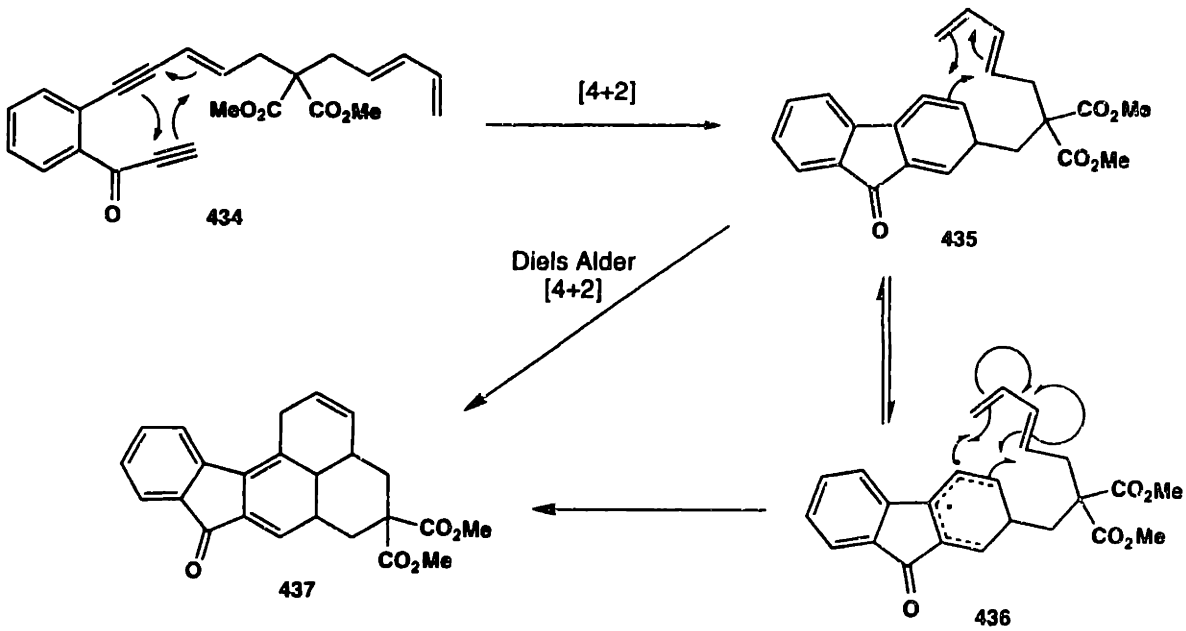
the simple cycloaromatization mechanism originally proposed by Bergman.

The lack of complete chlorine incorporation may just be a sign of the poor atom donating ability of carbon tetrachloride, especially in comparison with a cyclohexadienyl radical intermediate. The enyne cycloaddition differs from the cycloaromatization reaction in a key way. In the cycloaromatization reaction, two atoms are needed to quench the aromatic biradical. In the enyne cycloaddition, atom transfer is required. To get from the biradical intermediate **430** (Scheme 205) to the aromatic cycloadduct, a hydrogen atom must be gained at C-4 and lost at C-2. This means that an excellent atom donor exists within the reaction mixture itself that can compete with carbon tetrachloride. In an attempt to increase heteroatom incorporation, other more potent atom donors such as bromotrichloromethane were investigated. Unfortunately, when the enyne was dissolved in CCl_3Br and heated to 180 °C, a black tar was formed. Other solvents with good atom-donating ability such as THF were considered and investigated with other substrates, however, as mentioned above, the presence of an excellent atom donor, even at low concentration, in the reaction mixture gives a bias to the incorporation of hydrogen over other atoms.

The carbon tetrachloride trapping experiments led us to consider the development of a substrate with the ability to trap an intermediate species intramolecularly. Wang and Grissom have prepared several substrates that are designed to undergo tandem cyclizations after an initial cycloaromatization.[13,14] The design of a substrate that would undergo an enyne cycloaddition to give a cyclic allene or biradical that then reacted further with a suitable trap built into the substrate might expand the scope of the reaction and could shed light on the mechanism.

As shown in Scheme 209, a substrate with an appended diene **434** could undergo the [4+2] enyne cycloaddition to give the cyclic allene **435**. This allene would then be intramolecularly trapped in a Diels-Alder cycloaddition to give the pentacyclic product **437**.

Scheme 209

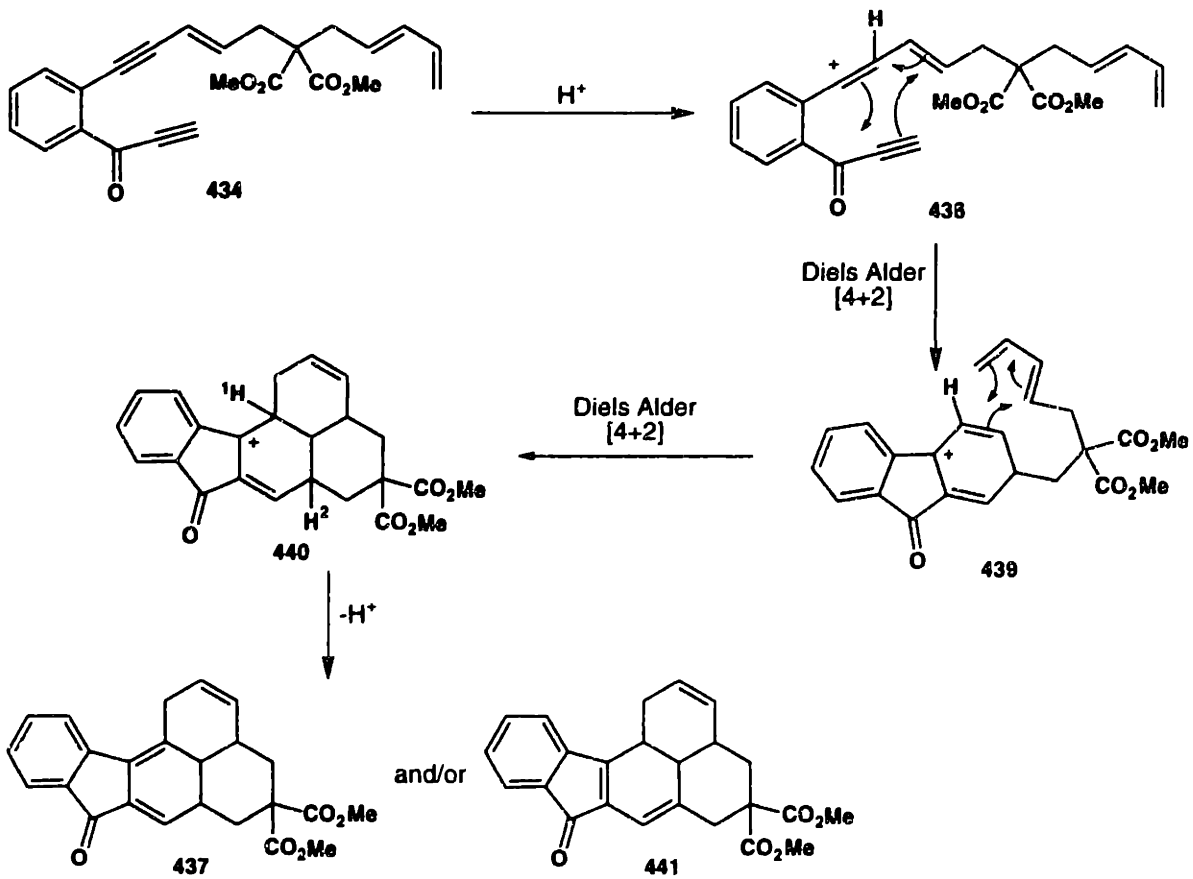


Other mechanistic pathways could also provide pentacyclic product **437**. As discussed earlier, at elevated temperatures cyclic allene **435** may exist in equilibrium with the biradical **436**. This biradical could be trapped in a similar fashion to give the same pentacyclic product.

The isolation of pentacyclic product **437** would not rule out a dienyl cation mechanism, however. As shown in Scheme 210, protonation and cycloaddition would give the cyclohexadienyl cation **439** which could also be trapped by the tethered diene to give cationic intermediate **440**. Elimination of a proton, either H^1 or H^2, would then provide **437** or **441**, or a mixture of the two cycloadducts. Isolation of a mixture of pentacyclic products would indicate a dienyl cation mechanism was involved, however, it would not be conclusive. If trapping occurred, then further substrates with more selective reactivities could be designed.

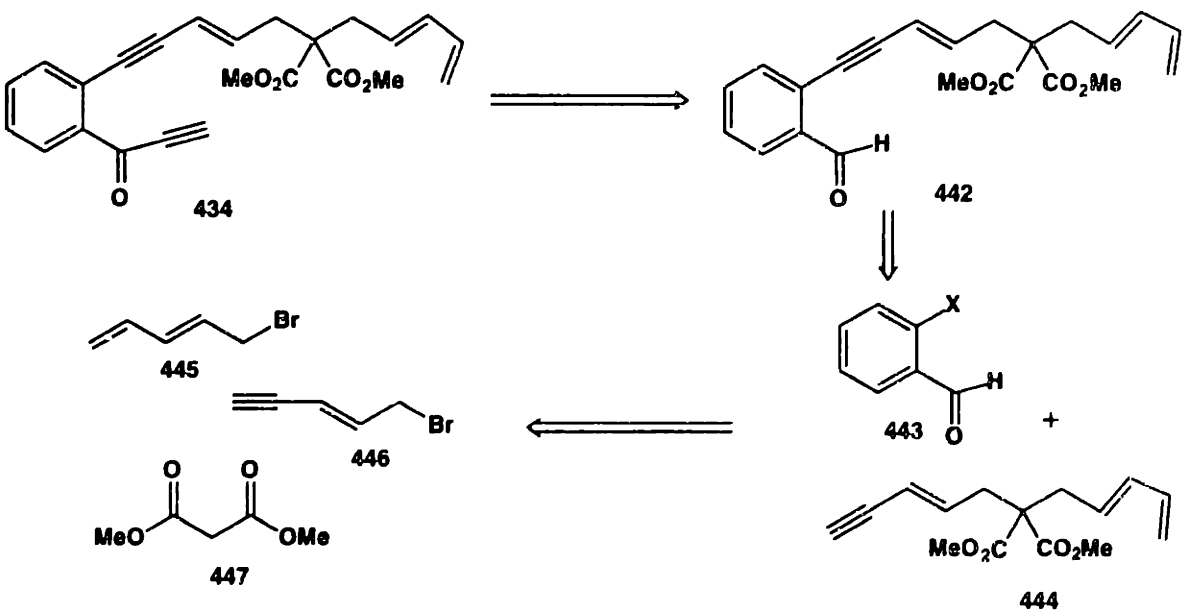
We focused specifically on the substrates originally studied by Anna Helgason because they cyclized in good yield at moderate temperatures and were easily assembled.

Scheme 210



As shown in Scheme 211, this substrate was prepared according to the previously

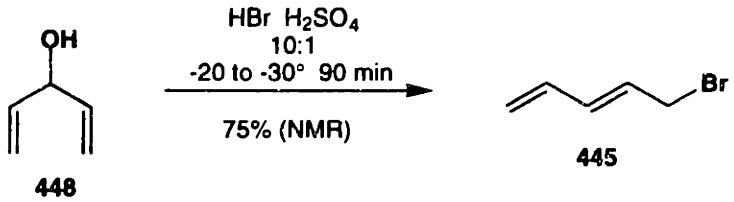
Scheme 211



developed strategy. The enyne ketone **434** was prepared from aldehyde **442** by addition of acetylide and oxidation. The aldehyde **442** was derived from a coupling of aryl halide **443** and enyne diester **444**.[86] The diester **444** is prepared by successive alkylations of dimethyl malonate.

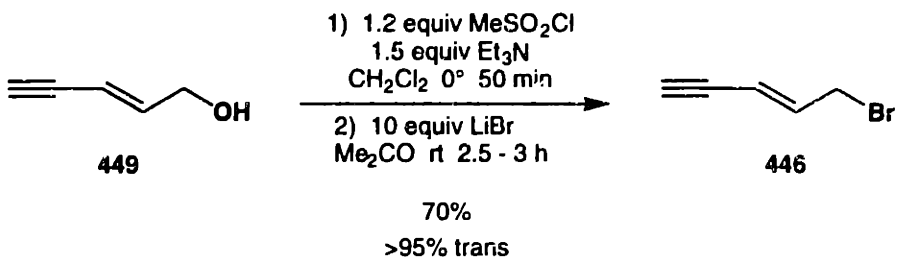
Preparation of enyne **434** began with the preparation of allylic bromides **445** and **446**. Bromo diene **445** is a known compound prepared by treating 1,4-pentadien-3-ol with a mixture of HBr and H_2SO_4 at low temperature according to the procedure of Harvey

Scheme 212



and Lund.[175] The bromide **445** was obtained in 75% yield as determined by ^{1}H NMR. This bromide is volatile and therefore was often isolated as a mixture with ether. Bromo enyne **446** was prepared from the commercially available enyne alcohol **449** following the general procedure for converting alcohols to halides developed by Ziegler and co-workers.[176] This reaction provided **446** in 70% yield contaminated with less than 5% of

Scheme 213



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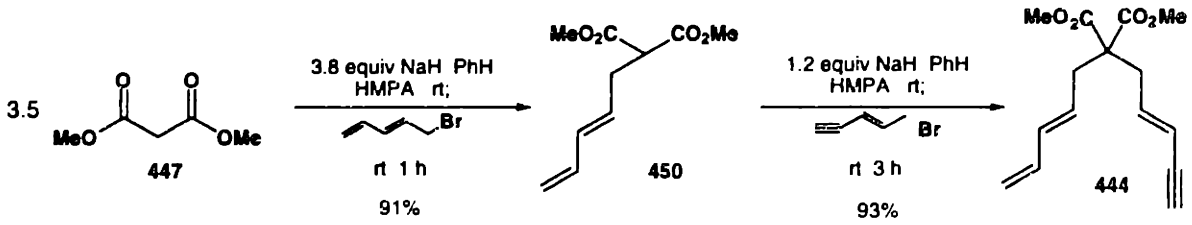
[175] Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066. Harvey and Lund report an 82% yield for the formation of bromide **445**, and a 74% yield for the formation of malonate **450**.
[176] Ziegler, F. E.; Klein S. I.; Pata, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

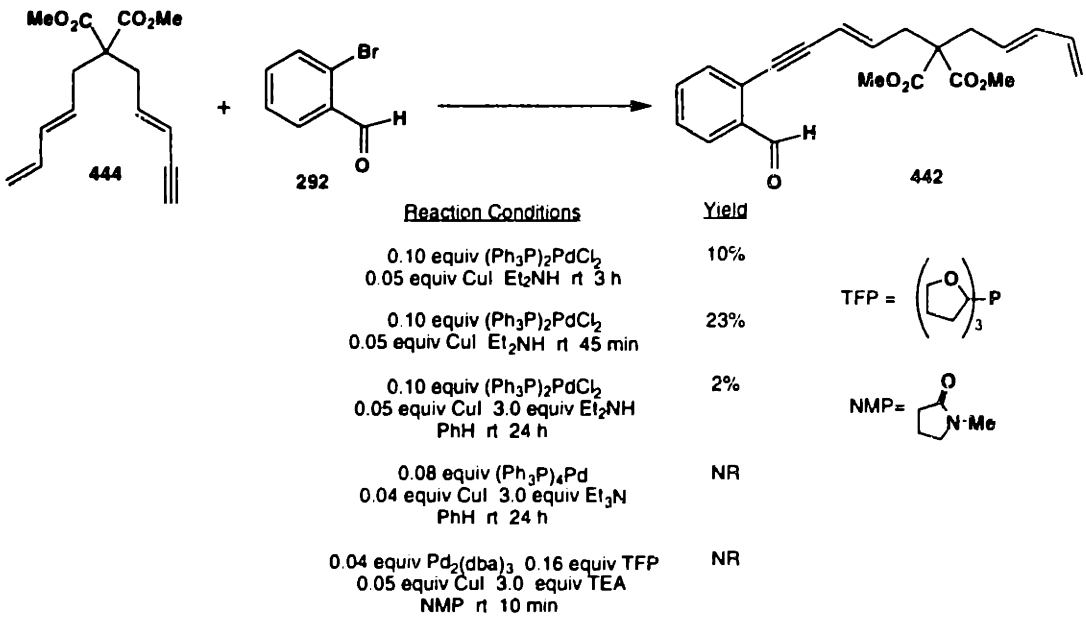
the cis isomer as determined by ^{1}H NMR analysis. The procedures employed for the alkylations of dimethylacetoacetate also followed the work of Harvey and Lund, who had previously prepared diene diester **450**.[175] Alkylation of **447** with bromo diene **445** was performed first. Treatment of malonate **447** with sodium hydride in benzene at room temperature followed by addition of the bromide **445** and HMPA gave the desired alkylated diester **450** in excellent yield. The second alkylation required a slightly longer reaction time but provided the desired enyne diene **444** in 93% yield.

Scheme 214



With the enyne **444** in hand, the next step was a transition-metal mediated coupling with an aryl halide to give aryl enyne **442**. As shown in Scheme 215, initial attempts to

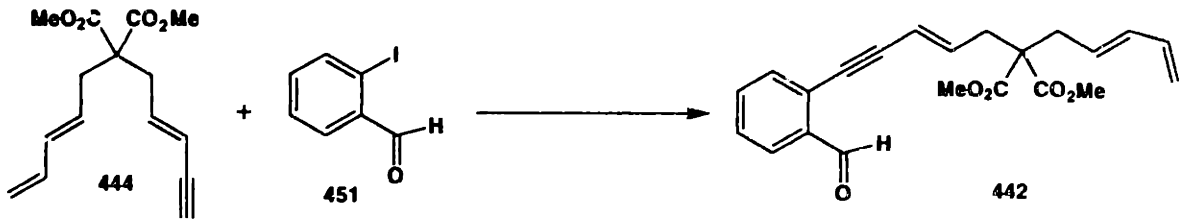
Scheme 215



couple enyne **444** with 2-bromobenzaldehyde (**292**) were disappointing.[86] Prolonged

reaction times led to decomposition of the product as observed by TLC, and the coupling was slow even under conditions designed to speed the reaction.[177] The use of iodobenzaldehyde **451**[178] was then condsidered as aryl iodides are known to undergo oxidative addition more quickly than aryl bromides. The use of aryl iodide **451** provided substantial improvement, giving aryl enyne **442** in 51% yield (Scheme 216). Further improvement resulted from increasing the amount of CuI used and switching to the very reactive catalyst system of $Pd_2(dba)_3$ and trifurylphosphine. These reaction conditions gave the desired product **442** in 60% yield.

Scheme 216



Reaction Conditions	Yield
0.10 equiv $(Ph_3P)_2PdCl_2$ 0.05 equiv CuI 3.0 equiv Et_2NH NMP rt 15 min	51%
0.08 equiv $(Ph_3P)_4Pd$ 0.4 equiv CuI 3.0 equiv Et_3N PhH rt 4.5 h	52%
0.04 equiv $Pd_2(dba)_3$ 0.16 equiv TFP 0.11 equiv CuI 3.0 equiv TEA NMP rt 18 min	36%
0.04 equiv $Pd_2(dba)_3$ 0.16 equiv TFP 0.25 equiv CuI 3.0 equiv TEA NMP rt 20 min	44%
0.04 equiv $Pd_2(dba)_3$ 0.16 equiv TFP 0.52 equiv CuI 3.0 equiv TEA NMP rt 10 min	60%

The next step in the synthesis was the elaboration of the formyl group to the alkynyl ketone. This was accomplished in two steps following the work of Anna Helgason.[148] Reaction of the aldehyde with ethynylmagnesium bromide provided the desired propargyl alcohol **452** in 88% yield. The alcohol **452** was then oxidized using the Dess-Martin

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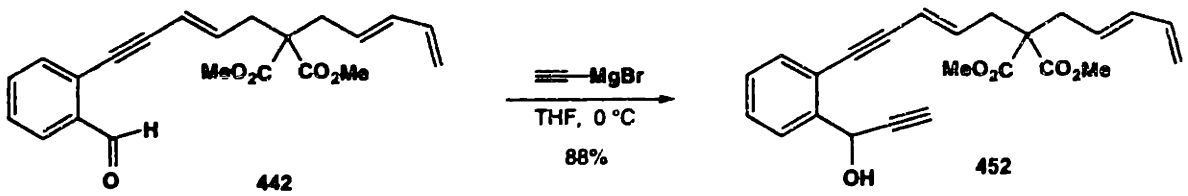
[177] Schriber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631.

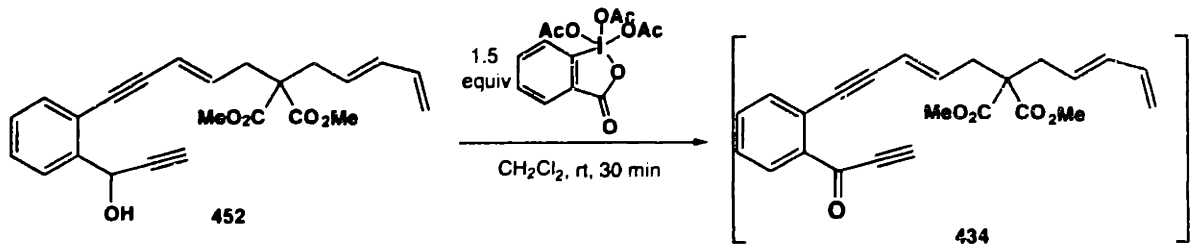
[178] 2-iodobenzaldehyde was prepared by PCC oxidation of 2-iodobenzylalcohol.

Scheme 217



periodinane[114] to give alkynyl ketone **434**, which like many of Helgason's substrates, was unstable to concentration. Following the established procedure,[148] the alcohol was oxidized and after an aqueous workup, filtered through a pad of silica gel to remove any periodinane byproducts. The ketone, now in a solution of methylene chloride, was then concentrated to a volume of about 3 mL, and a known amount of benzene or toluene was

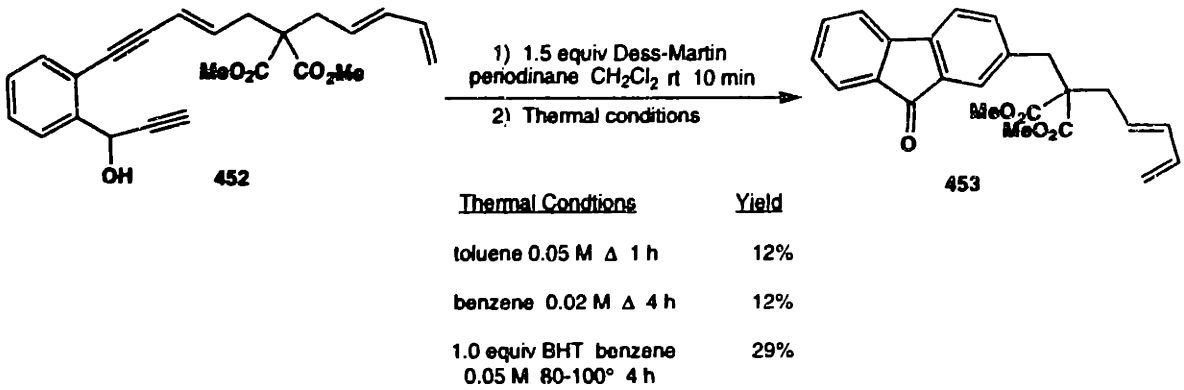
Scheme 218



unstable oil

added. Further concentration removed any residual methylene chloride, and the reaction mixture was prepared for the cycloaddition. As shown in Scheme 219, heating the substrate in either toluene or benzene gave fluorenone **453**. Initial experiments gave low yields for the reaction, and no intramolecular trapping product was observed. An improved yield of 29% of fluorenone **453** was obtained by running the reaction in a sealed tube at 80 to 100 °C for four hours in the presence of 1 equivalent of BHT. Oxidation of **452** and treatment of the resulting ketone with 3 equivalents of dimethylaluminum chloride provided impure cycloadduct **453** in low yield as well.

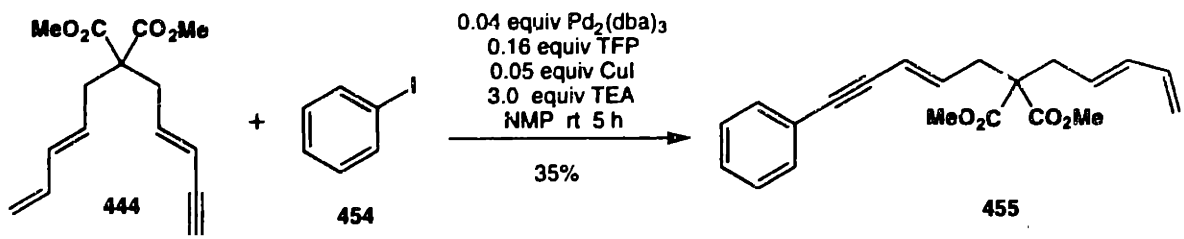
Scheme 219



Thermal Condtions	Yield
toluene 0.05 M Δ 1 h	12%
benzene 0.02 M Δ 4 h	12%
1.0 equiv BHT benzene 0.05 M 80-100° 4 h	29%

The lack of intramolecular trapping was disappointing. The diene moiety may not be reactive enough to trap an intermediate before other reactions occurred. The reactions were not clean, and we wondered about the stability of the enyne diene moiety under the reaction conditions. To investigate this question, substrate **455** was prepared by coupling iodobenzene with the enyne **444** as shown in Scheme 220. When arylenyne **455** was heated in benzene for 3 hours with and without BHT, three spots appeared by TLC. These spots were similar to those observed in the thermal reactions of enyne **434**, leading us to question the stability of the enyne diene moiety under the reaction condtions. If polymerization of the diene was occurring, this might account for the low yields. Anna Helgason also investigated some intramolecular trapping substrates and obtained similar results. No more work was done in this area given our lack of success with these substrates.

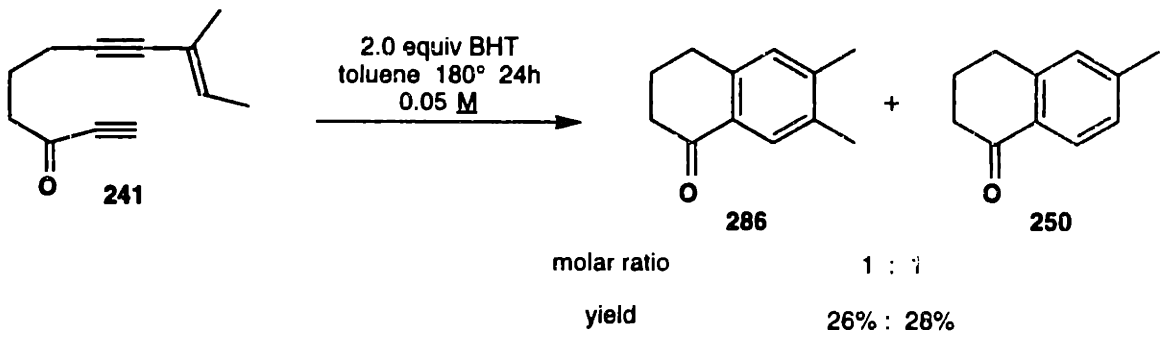
Scheme 220



As mentioned in Part II, Chapter 2, the methylpropenylacetylene substrate **241** gave a mixture of products when heated to 180 °C in toluene (Scheme 221). The desired

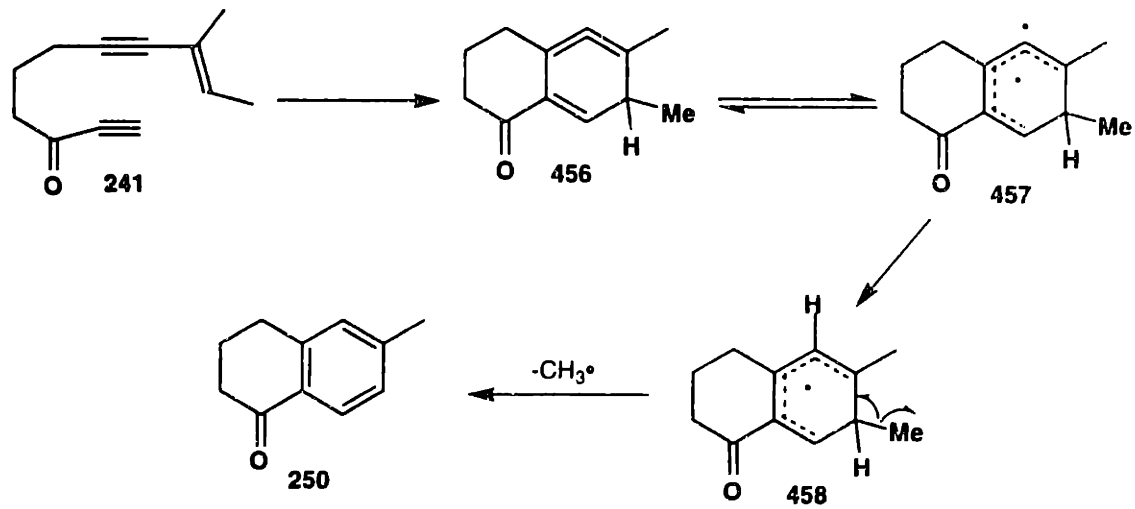
product **286** was isolated in impure form, and an NMR spectrum of this product showed a 1:1 molar ratio of two compounds, the desired dimethyletralone **286** and methyltetralone **250**. The presence of the two tetralones in the mixture was confirmed by GC/MS, which showed two peaks with masses corresponding to the two compounds.

Scheme 221



Loss of a methyl group was surprising. Aromatization of an intermediate in this reaction requires loss of a proton or hydrogen atom at the position of demethylation, and a

Scheme 222

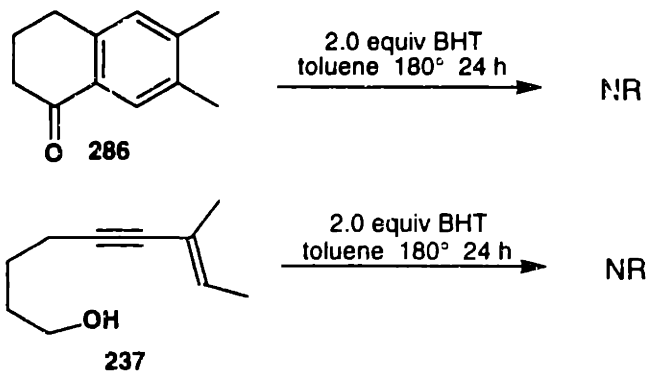


proton is much more likely to be lost than a methyl cation. However, in the case of radical fragmentation, the high heat of formation of a hydrogen atom makes loss of a methyl

radical a favorable process in comparison.[179,180] A possible mechanism for methyl loss is shown below; the methyl radical can then react with solvent, BHT, starting material, or product. A similar mechanism involving stepwise transfer of an electron and then a proton from BHT to the allene **456** could also provide the biradical intermediate **457**.[181]

Several experiments were run to determine what factors affected the ratio of products. Initially, the reactivity of the product and enyne moiety of the substrate under the reaction conditions were investigated (Scheme 223). No reaction is observed when the product dimethyltetralone **286** is heated under the reaction conditions for 24 hours. Under these conditions, enyne alcohol **237** does not react either. These results confirmed that the loss of methyl was occurring as the substrate was undergoing the reaction and not before the reaction began or after the product had been formed.

Scheme 223



[179] For reviews on organic free radicals, see: Cadogan, J. I. G.; Hickson, C. L.; McNab, H. *Tetrahedron*, **1986**, *42*, 2135. Kochi, J. K. *Free Radicals*; John Wiley and Sons: New York, 1973. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley and Sons: Chichester, 1995.

[180] For examples of methyl fragmentation, see: Hart, H.; DeVrieze, J. D. *Tetrahedron Lett.* **1968**, 4257. Franz, J. A.; Camaioni, D. M. *J. Org. Chem.* **1980**, *45*, 5247. For the reaction of methyl radicals with phenols, see: Mulcahy, M. F. R.; Tucker, B. G.; Williams, D. J.; Wilmshurst, J. R. *Aust. J. Chem.* **1967**, *20*, 1155 and references cited therein.

[181] For a discussion of the involvement of phenols in single electron transfer catalysis of a sigmatropic rearrangement, see: Jacobi, P. A.; Armacost, L. M.; Brielmann, H. L.; Cann, R. O.; Kravitz, J. I.; Martinelli, M. J. *J. Org. Chem.* **1994**, *59*, 5292. Jacobi, P. A.; Brielmann, H. L.; Cann, R. O. *J. Org. Chem.* **1994**, *59*, 5305.

Having established that the methyl group was lost during the reaction, further experiments were designed to explore the effect of reaction conditions on the product ratio. BHT is an electron rich system, and could be susceptible to alkylation by a methyl cation[182] or radical.[179,180] As shown in Scheme 224, running the reaction in the absence of BHT increased the amount of the normal cycloadduct **286**, and the overall yield of the cycloadduct did not change signifcantly (Reaction 2). However, in the absence of BHT demethylation was still occurring, indicating that while BHT might be responsible for some demethylation, the solvent was also involved. To investigate the involvement of toluene in the demethylation, the reaction was run at one half the previous concentration of enyne, at 0.025 M (Reaction 6). This provided a 1.66 : 1 ratio of tetralones **286** and **250**. More demethylation (38%) was occurring at this concentration then at 0.05 M (29%), indicating that the solvent might also be involved in the demethylation process.

Next, solvents that were less likely to undergo electrophilic substitution were examined. Using cyclohexane, which should be completely inert to electrophilic substitution, at 0.05 M with BHT provided a 2.4 : 1 ratio of dimethyltetralone **286** to tetralone **250**; a similar ratio was obtained with toluene at 0.05 M without BHT. The amount of demethylation with cyclohexane and BHT was much less than when the reaction was carried out in toluene with BHT. Cyclohexane had an effect on the reaction, but the yield for this reaction was 20%. The low yield indicated that enyne or tetralone may be attacked and degraded in this reaction. Chlorobenzene was also employed as a solvent, and gave a 1.1 : 1 ratio of **286** : **250** in the presence of BHT. The cycloaddition was also run in chlorobenzene alone, and a 3.4 : 1 ratio of **286** : **250** was obtained in slightly lower yield. The similarity between the run in chlorobenzene with BHT and the run in toluene with BHT may indicate that BHT is the sole actor in accepting the methyl radical or cation

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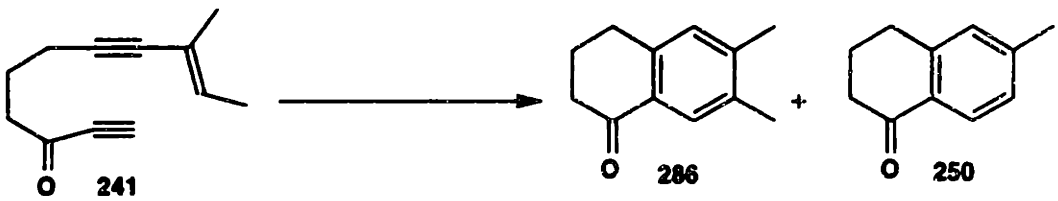
[182] Alkylphenolates are known to react with alkylating agents like ethyl iodide to give either aryl ethers or alkylated phenols, depending on steric hinderance. For examples, see: (a) Curtin, D. Y.; Crawford, R. J. *J. Am. Chem. Soc.* **1957**, *79*, 3156. (b) Curtin, D. Y.; Wilhelm, M. *J. Org. Chem.* **1958**, *23*, 9. (c)

in these reactions. However, some demethylation is seen in when the reaction is run in chlorobenzene alone. As chlorobenzene is electron deficient, and therefore should be resistant to electrophilic aromatic substitution, the presence of the demethylated product **250** may indicate a radical mechanism.

Scheme 224



Reaction	Conditions	Molar Ratio (286 : 250)	Percent Demethylation	Yields	Total Yield
1	2 equiv BHT toluene 0.05 M 180° 24 h	1 : 1	50%	26% **286** 28% **250**	54%
2	toluene 0.05 M 180° 17 h	2.4 : 1	29%	35% **286** 15% **250**	50%
3	10 equiv THF toluene 0.05 M 180° 17 h	6 : 1	14%	22% **286** 5% **250**	27%
4	2.0 equiv 4-MeOPhOH toluene 0.05 M 180° 24 h	1 : 1.7	63%	16% **286** 26% **250**	42%
5	2.0 equiv BHT cyclohexane 0.05 M 180° 8 h	2.4 : 1	29%	14% **286** 6% **250**	20%
6	toluene 0.025 M 180° 33 h	1.66 : 1	38%	32% **286** 20% **250**	52%
7	2.0 equiv BHT PhCl 0.05 M 180° 15 h	1.1 : 1	48%	27% **286** 23% **250**	50%
8	PhCl 0.05 M 180° 15.5 h	3.4 : 1	23%	24% **286** 15% **250**	39%

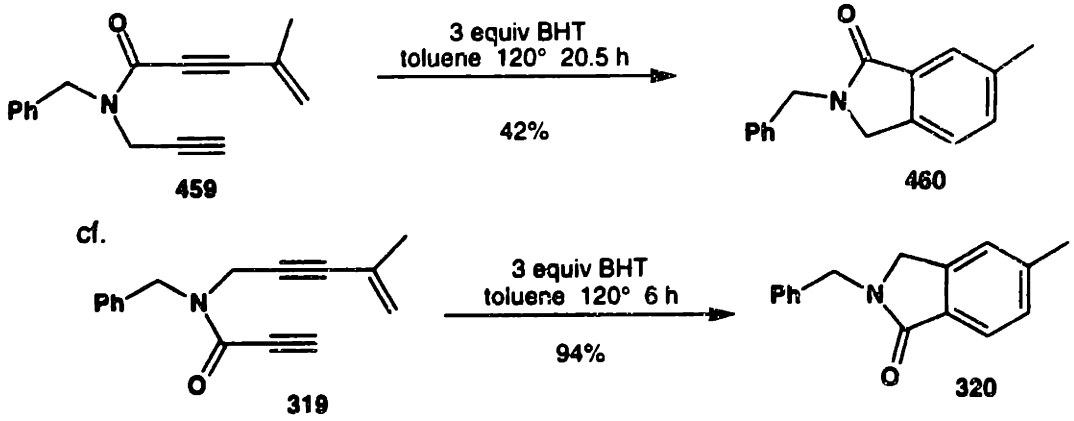
Curtin, D. Y.; Dybvig, D. H. *J. Am. Chem. Soc.* **1962**, *84*, 255. (d)Kornblum, N.; Seltzer, R. *J. Am. Chem. Soc.* **1961**, *83*, 3668.

The amount of demethylated tetralone **250** is increased by using more electron rich phenols like *p*-methoxyphenol as an atom donor. Interestingly, no methylated phenol was isolated or seen in the crude ^{1}H NMR spectrum of the reaction run with methoxyphenol. In the reactions with BHT, most, but not all, of the BHT was recovered unchanged from the reaction mixture. In the case of BHT, the transfer of a methyl group from an intermediate to the electron rich BHT could give a substituted cyclohexadiene that could polymerize or otherwise react and not be isolated.

None of these experiments explains the fate of the methyl group. Given the yields of this reaction, the methyl group could be transferred to BHT, starting material, or product, all of which could then decompose. Although no firm conclusions can be drawn about the mechanism of methyl loss, a radical mechanism is consistent with the results, as the loss of a methyl cation seems unlikely.

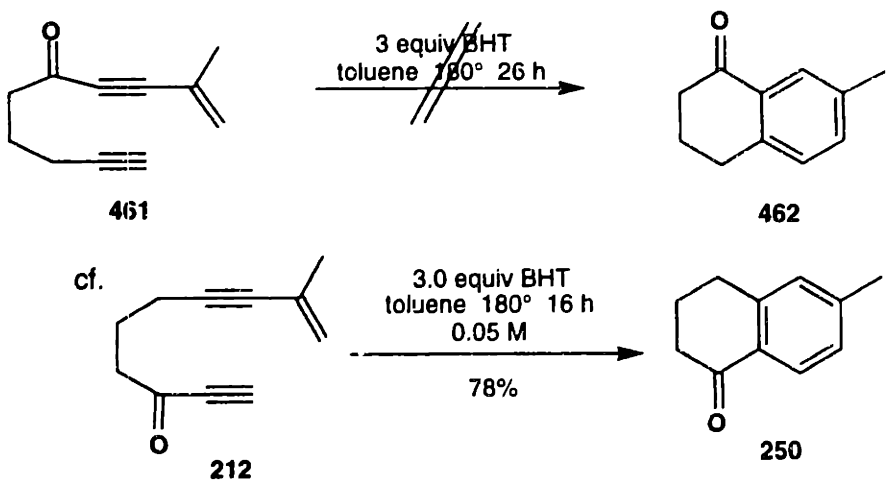
The results of our trapping experiments combined with the formation of demethylated side products led us to believe that the intermediate involved in these reactions was highly reactive. We moved on to exploring the design of substrates that would shed light on the mechanism of the reaction due to their reactivity. Brenda Palucki prepared two substrates with the two-fold purpose of further exploring the scope of the cycloaddition and investigating the role of a dienyl cation in the mechanism. The dienyl cation mechanism begins with protonation of the alkyne of the enyne. In theory, substrates with electron deficient enynes should react slowly or not at all. Palucki prepared two electron deficient enyne substrates, amide **459** and enyne ketone **461** (Scheme 226). Amide **459** provided lactam **460** in 43% yield when heated to 120 °C in toluene for 20.5 hours. This reaction was slower than the thermal reaction of enyne amide **319**, Scheme 225, which gave cycloadduct **320** in 94% yield after just 6 hours at 120 °C. As shown in Scheme 226, the second substrate, enyne **461**, did not cyclize at all after heating at 180 °C for 26 hours, while the cycloaddition of enyne **212** proceeded in good yield at 180 °C. These results indicate that the thermal reaction may be proceeding via a dienyl cation mechanism.

Scheme 225



Protonation of the electron deficient enynes of substrates **459** and **461** should be much less favorable than protonation of the enynes of substrates **319** and **212**, and thus the rate of cycloaddition may be expected to be slower. The difference in reactivity between the two electron deficient enyne substrates can be explained be the difference in electron withdrawing ability of the amide and ketone. The amide will be less electron withdrawing than the ketone, and thus protonation of the enyne moiety may be more favorable in the amide case. However, the difference in reactivity between the electron deficient enyne

Scheme 226



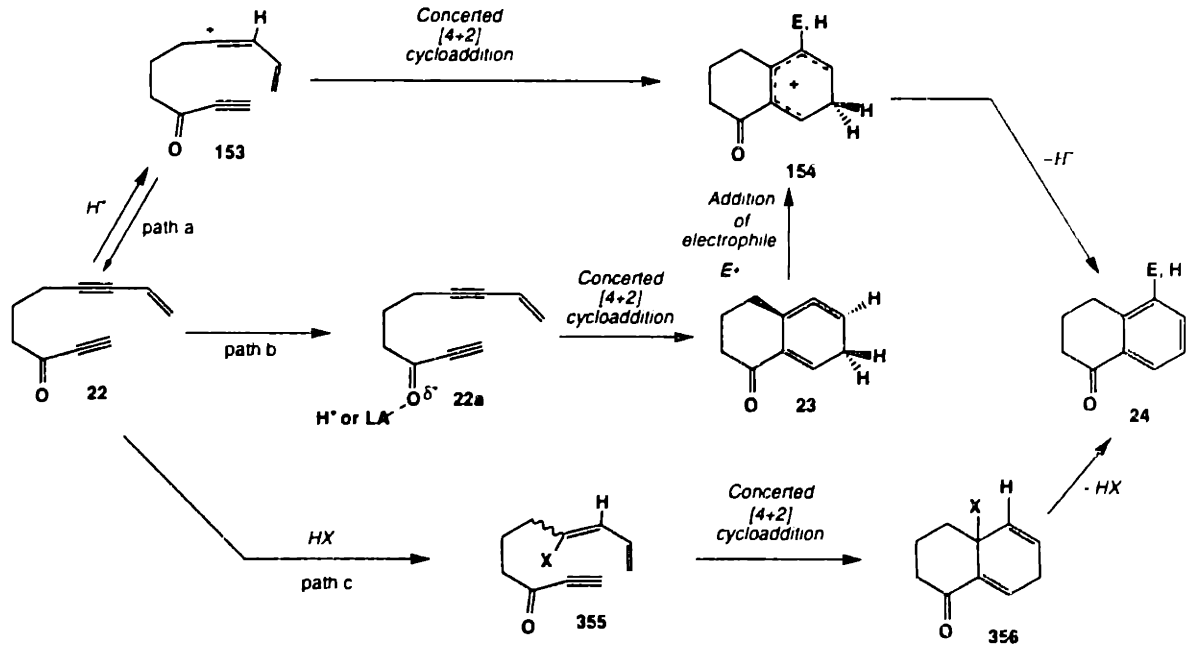
substrates **459** and **461** and the enyne substrates **319** and **212** may also be attributed to a decrease in reactivity. The enynophiles of enyne substrates **459** and **461** are not activated, and the interaction of their frontier orbitals may not be as favorable as the interaction in the enyne substrates **319** and **212**.

Although no firm conclusions can be drawn about the mechanism of the enyne cycloaddition under thermal conditions, based on the work discussed, some hypotheses can be put forward. Much of the data discussed here disfavors the involvement of a dienyl cation in the cycloaddition. The NMR experiments examining the order of the reaction indicate that the reaction is first order in enyne, and catalysis by an acid other than BHT is unlikely. The presence of an acid scavenger does not inhibit or even slow the reaction, whether or not BHT is present. The consumption of enyne occurs at the same rate with and without BHT, but the appearance of product is faster when BHT is included. The incorporation of chlorine into the products when the reaction is run in carbon tetrachloride suggests the involvement of a radical intermediate. The incomplete chlorination of the products, the lack of trapping by our internal trapping substrate **434**, and the demethylation of enyne **241** support a highly reactive intermediate that undergoes aromatization readily with an early transition state. The electron deficient enyne substrates, **459** and **461**, did not cyclize as well as substrates without electron deficient enynes. This lack of reactivity could support a dienyl cation mechanism, but the electron deficient substrates just may not be reactive enough to undergo the cycloaddition at a rate competitive with the enynes **319** and **212**. Overall, under thermal conditions we feel that a concerted cycloaddition to give a cyclic allene or biradical may be consistent with the data accumulated for this reaction, although the dienyl cation cycloaddition has not been ruled out in all systems.

The Enyne Cycloaddition under Protic and Lewis Acid Conditions

For cycloadditions promoted by Lewis and protic acids, we have considered three mechanistic paths as most likely, two of which are the same as the paths considered for the thermal version of this reaction. As shown in Scheme 227, path a involves protonation of enyne **22** to give dienyl cation **153**, which then undergoes a Diels-Alder cycloaddition to give cyclohexadienyl cation **154**. This type of mechanism was first suggested by Nazarov.[76] Following path b, enyne **22** undergoes direct cycloaddition to give the cyclic allene **23**, first suggested by Dykstra and Butz,[65,70] which is then attacked by an electrophile to give cyclohexadienyl cation **154**. Loss of a proton from this common intermediate then provides cycloadduct **24**. The third mechanism we have considered is based on a proposal by Miller[67] (path c). Under protic acid conditions, the enyne is isomerized through a multistep mechanism to halodiene **355**, which then undergoes a Diels-Alder cycloaddition and loss of HX to give the cycloadduct **24**.

Scheme 227



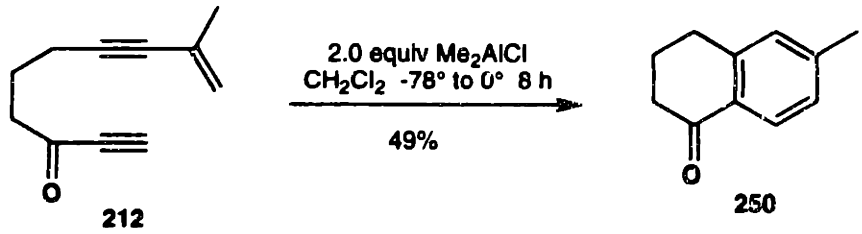
Under Lewis or protic acid conditions, the main difference between these mechanisms is the method of activation of the substrate. Paths a and c assume interaction

of an electrophile with the enyne moiety of the substrate, while path b assumes a more standard interaction in which activation of the enynophile carbonyl by protonation or coordination lowers the activation energy for the reaction. In the following discussion, mechanisms are proposed for the reaction under both Lewis and protic acid conditions; it should be noted, however, that in some cases (e. g. reactions involving zinc bromide or aluminum chloride) the identity of the species promoting the cycloaddition is unclear. Our work in studying the reaction under these conditions is not complete, and Brenda Palucki is working on this area currently.

In exploring the scope of this reaction, we observed that the reaction proceeds at low temperatures when substrates are treated with a variety of Lewis and protic acids. The best results were obtained with methanesulfonic acid, zinc bromide, aluminum chloride, and dimethylaluminum chloride. Neither zinc nor aluminum halides are known to coordinate to alkynes, but both are notoriously hard to dry. The fact that two of the best Lewis acids for promoting this reaction can be contaminated with protic acids (either HCl or HBr) leads to confusion as to the role of these acids in the reaction. Protic acids are known to catalyze rearrangements of enynes by attacking the alkyne moiety.[160-162] The issue of contamination is underlined by the fact that the zinc bromide reactions did not proceed at all when run under very dry conditions. However, the cycloadditions do proceed in the presence of dimethylaluminum chloride, a Lewis acid that is also a proton scavenger,[128] although the yields for these reactions are usually lower than the yields for reactions promoted by other Lewis acids.

Cycloadditions promoted by dimethylaluminum chloride have provided interesting side products. As shown in Scheme 228, treatment of enyne **212** with 2 equivalents of dimethylaluminum chloride at -78 to 0 °C provides the desired tetralone in 49% yield. However, Roberto Fernandez found that enyne **212** provided a mixture of products when treated with dimethylaluminum chloride under slightly different conditions. Specifically,

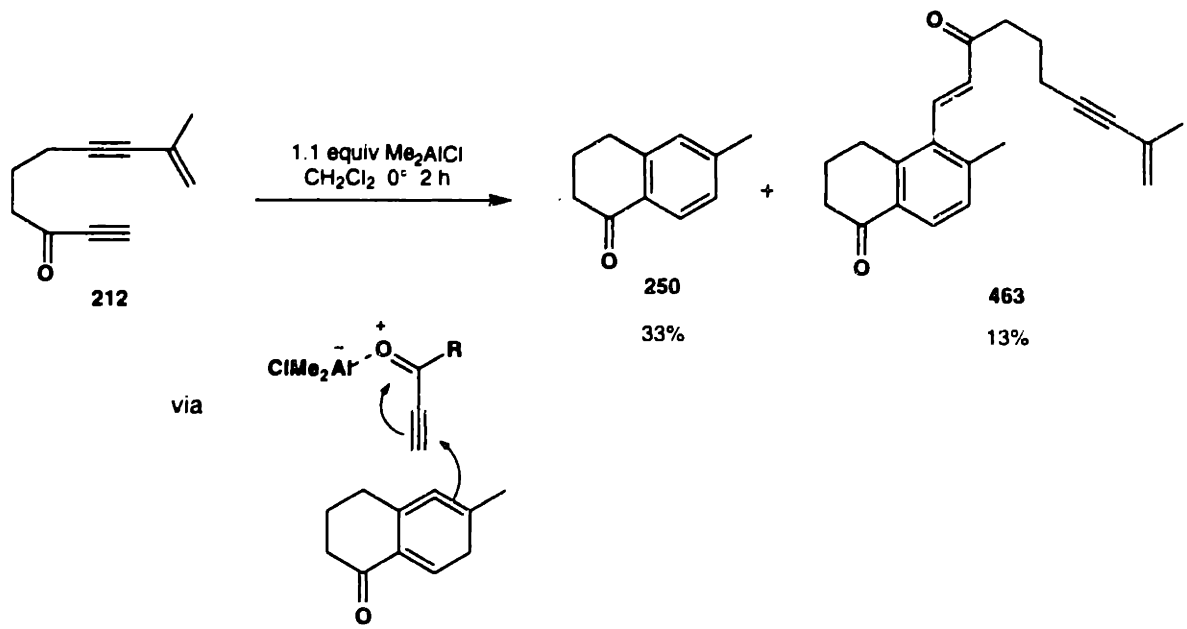
Scheme 228



212 250

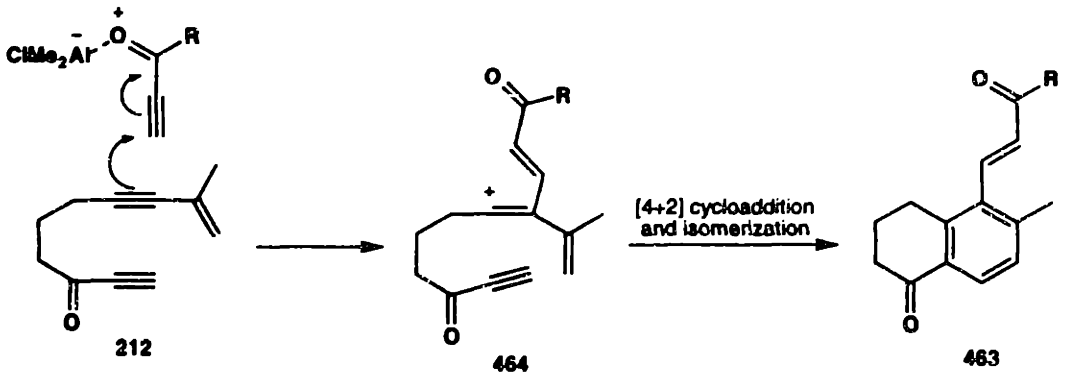
when the enyne is treated with only 1.1 equivalent of dimethylaluminum chloride at 0 °C, a mixture of the desired tetralone **250** and a substituted tetralone **463** was obtained. In the absence of a proton source, the cyclic allene which is nucleophilic due to strain, could react

Scheme 229



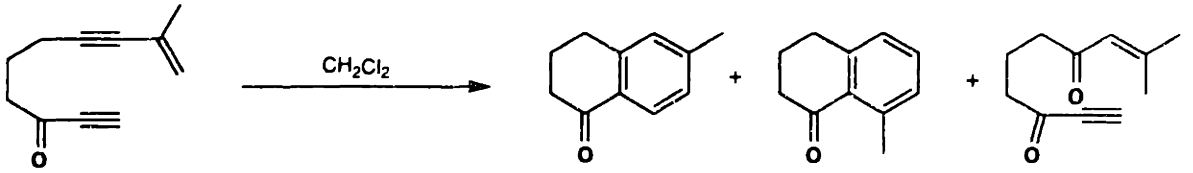
with the alkynyl ketone of an activated substrate, as shown, to give the substituted tetralone. The isolation of this byproduct does not rule out the two mechanisms involving electrophilic attack on enyne, however, as a Michael type addition of the enyne moiety to the alkynyl ketone can occur to give dienyl cation **464** followed by cycloaddition. Substitution does not occur after product formation as the tetralone **250** does not undergo substitution when treated with an alkynyl ketone in the presence of dimethylaluminum chloride.

Scheme 230



Both Fernandez and Palucki have observed side products that provide evidence for the involvement of electrophilic attack on the enyne moiety under protic acid conditions. In optimizing the protic-acid promoted cycloaddition of enyne **212** (Scheme 231), Fernandez found that when 1 equivalent or less of methanesulfonic acid was used, a new tetralone (**465**) and diketone **466** were formed in trace amounts. Recall that optimal conditions for the formation of desired tetralone **250** with protic acid involve 2.5 equivalents of

Scheme 231

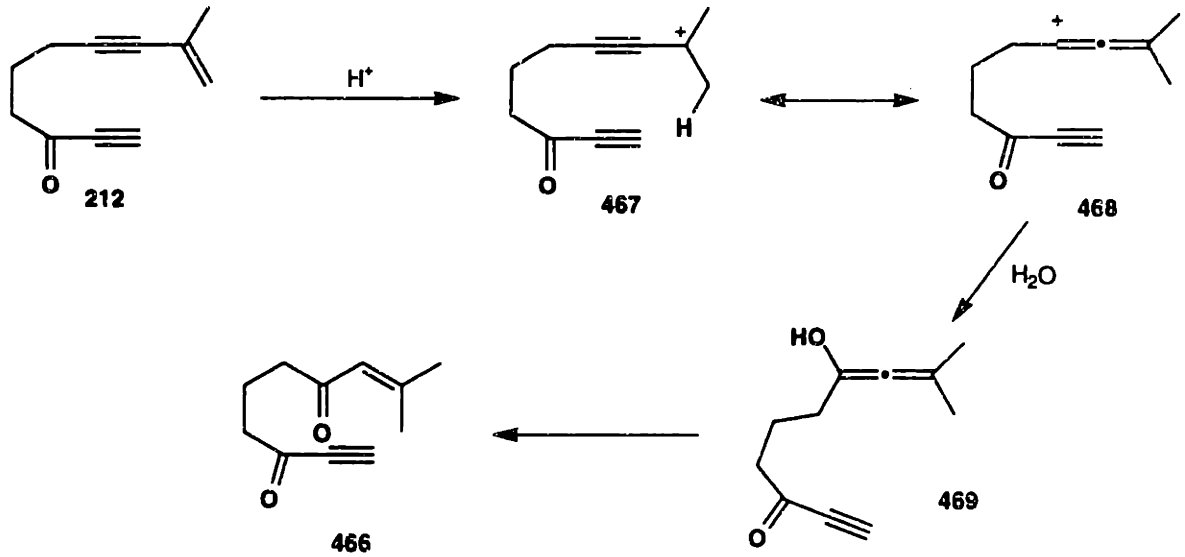


Conditions	250	465	466
0.5 equiv $MeSO_3H$ 0° to rt 19 h	72	5	9
0.5 equiv $MeSO_3H$ 0° to rt 28 h	83	6	6
1.0 equiv $MeSO_3H$ rt 19 h	85	4	11

methanesulfonic acid at 0 °C for 30 minutes in methylene chloride. As shown below, the diketone byproduct **466** may be formed through a mechanism similar to the Meyer-Schuster rearrangement.[162] Protonation of the alkene moiety of the enyne provides the propargyl cation **467**, which is in resonance with allenyl cation **468** and is trapped with

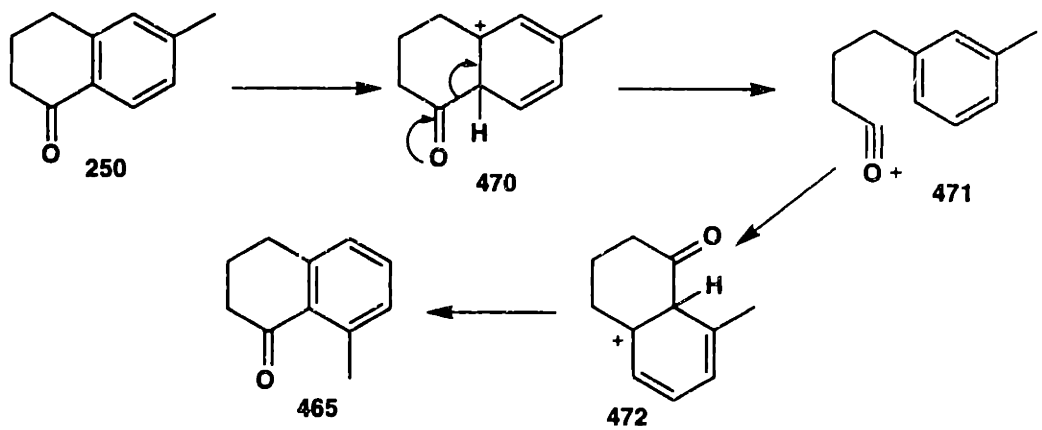
water to give **469**. Tautomerization then provides the α,β-unsaturated ketone **466**.

Scheme 232



The other tetralone (**465**) may be formed from the rearrangement of desired tetralone **250** through a retro-Friedel-Crafts acylation and normal Friedel-Crafts acylation (Scheme 233). This side product has not been noted in other reactions, although only small amounts were observed by Fernandez.

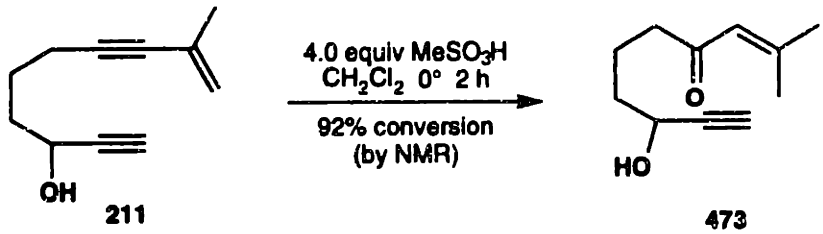
Scheme 233



A Meyer-Schuster rearrangement product **473** was also formed when the enyne alcohol **211** was treated with an excess of methanesulfonic acid at 0 °C (Scheme 234), and Palucki has observed the formation of a Meyer-Schuster type product when enyne **322** is

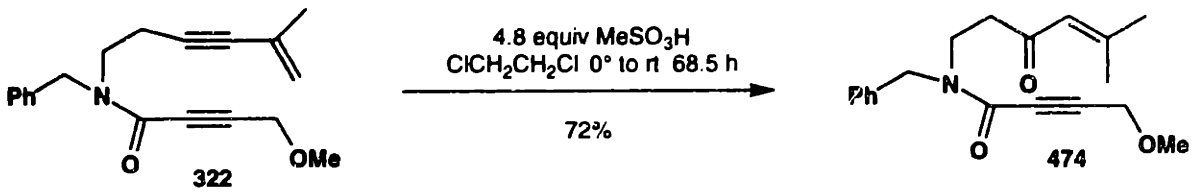
treated with a large excess of methanesulfonic acid at 0 °C (Scheme 235). Neither of these

Scheme 234



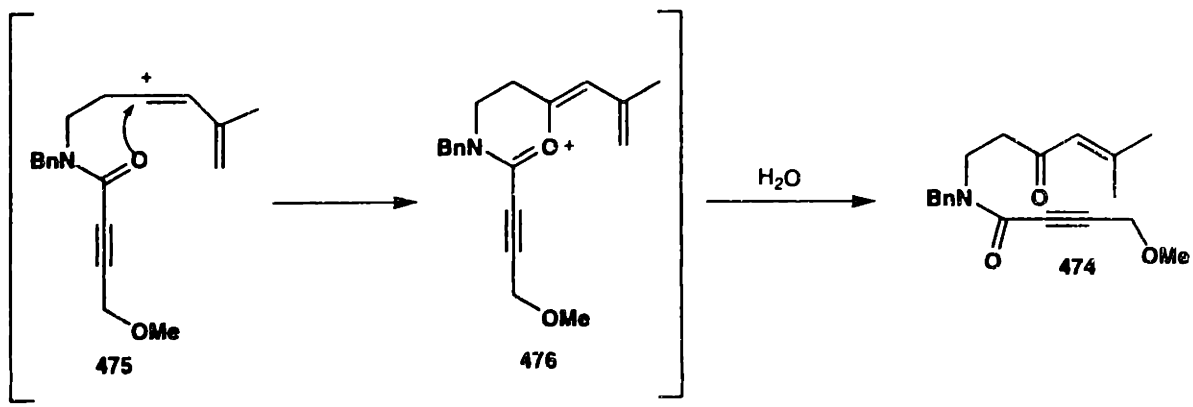
enynes (**221** or **322**) undergo cycloaddition readily under any of the conditions we usually employ, leading us to propose that the appearance of the diketone occurs when the enyne

Scheme 235



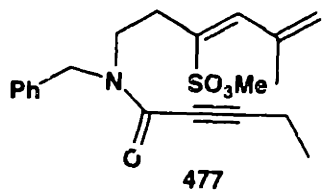
cycloaddition is slow or does not occur at all. The implication is that reversible enyne protonation is occurring under protic acid conditions, and that when the cycloaddition is slow, side products are formed. The rearrangement products would most easily form if

Scheme 236



water or another nucleophile is present to trap the cationic intermediates. Carmen Garcia, a visiting scientist in our laboratory, examined this issue and found that even under strictly anhydrous conditions, the formation of these side products occurred slowly. Garcia's results are consistant with an intramolecular trapping of the dienyl cation. As shown below, the dienyl cation **475** may be trapped by the carbonyl oxygen of the amide moiety to give the cationic species **476**, which may hydrolyze upon aqueous workup to give the observed diketone.

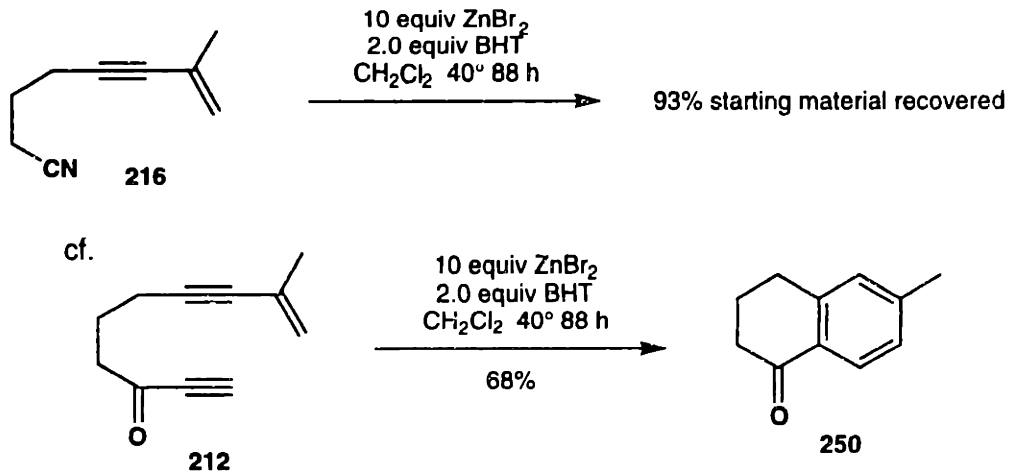
The Meyer-Schuster derived side products may actually be intermediates in the reaction pathway that have been quenched. If a mechanism like the one proposed by Miller is occurring, then in the case of methanesulfonic acid, the dienyl sulfonate **477** would be formed which undergoes [4+2] cycloaddition and elimination of $MeSO_3H$ to give the tetralone. Unfortunately, we have been unable to isolate any dienyl sulfonate intermediate or to detect it by NMR.



477

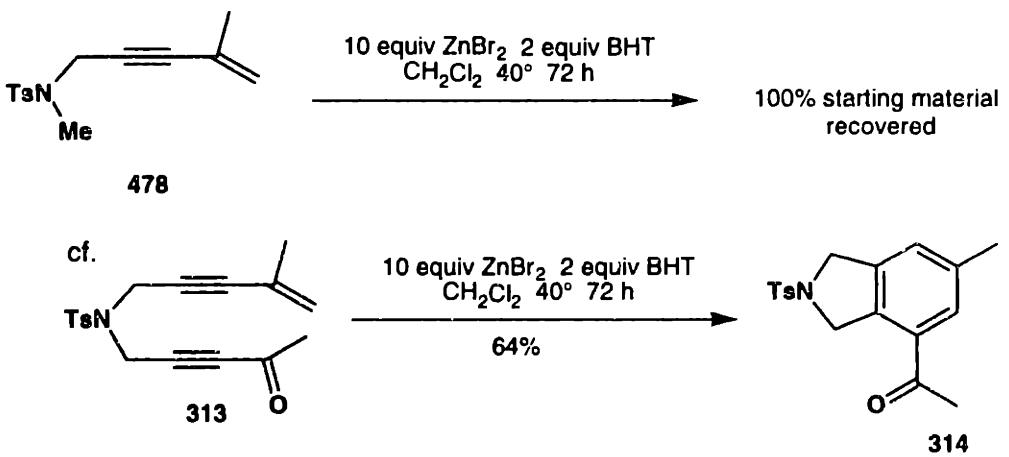
We have also addressed the viability of Miller's mechanism with respect to zinc bromide promoted reactions. Zinc bromide promotes the enyne cycloaddition; however, best results are obtained when the Lewis acid is not rigorously dried. Under these conditions, some HBr is present and may be capable of promoting the reaction, through any of the three mechanisms proposed. Carmen Garcia undertook an investigation of these conditions, hoping to isolate a dienyl bromide or some sort of enyne isomerization product. To investigate the reactivity of the enyne under the reaction conditions, Garcia prepared two model enynes, **216** and **478**, which are incapable of cycloaddition, and subjected them to the zinc bromide cycloaddition conditions. As shown in Scheme 237, the enyne nitrile **216** did not react when treated with zinc bromide in refluxing methylene chloride for 3

Scheme 237



days. For comparison, the related enyne **212** provides a 68% yield of cycloadduct when exposed to similar conditions. Similar results were obtained with the sulfonamide enyne **478** (Scheme 238). These results may discount the dienyl bromide mechanism proposed

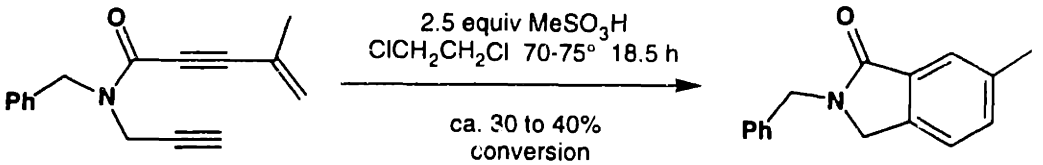
Scheme 238



by Miller. Neither a dienyl bromide nor rearranged products are isolated in either case, lending credence to the proposal that protonation of the enyne may be reversible, and the concentration of the reactive dienyl cation is low. When protonation occurs to give this cation, the cycloaddition must be facile, thus driving the equilibrium.

Palucki exposed the electron deficient enyne substrates **459** and **461** (Scheme 226) to both Lewis and protic acid conditions. Amide enyne **459** reacted slowly under forcing methanesulfonic acid conditions (Scheme 239) and not at all upon exposure to zinc bromide. No cycloadduct was produced when enyne **461** was treated with either aluminum chloride or methanesulfonic acid; only starting material and other products were obtained. The lack of reactivity of these substrates with electron deficient enyne moieties supports the dienyl cation mechanism.

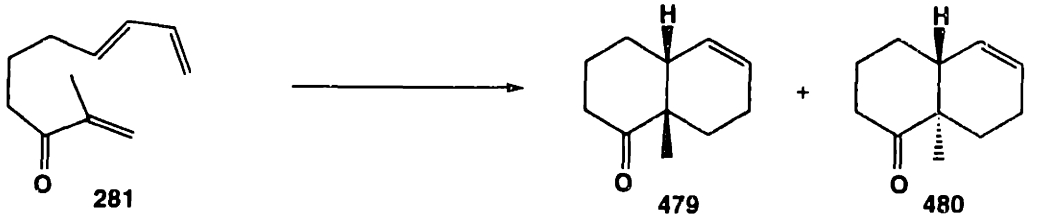
Scheme 239



459 **460**

Concentrated lithium perchlorate in ether is known to accelerate intermolecular Diels-Alder reactions,[183] and has recently been shown to accelerate intramolecular ones as well.[184] Grieco and co-workers found that diene **281** underwent Diels-Alder cycloaddition

Scheme 240



281 **479** **480**

Benzene 120° 18 h	72% 1.6 : 1
5.0 M $LiClO_4$-Et_2O rt 24 h	65% 3.0 : 1

[183] Dailey, W. P.; Forman, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 2761. Grieco, P. A.; Beck, J. P. *Tetrahedron Lett.* **1993**, *34*, 7367. Greico, P. A. *Aldrichchemica Acta* **1991**, *24*, 59. Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1306. Desimoni, G.; Gaita, G.; Righetti, P. P. *Tetrahedron Lett.* **1995**, *36*, 2855 and references cited therein. Braun, R.; Sauer, J *Chem. Ber.* **1986**, *119*, 1269. Reetz, M. T.; Gansauer, A. *Tetrahedron* **1993**, *49*, 6025.

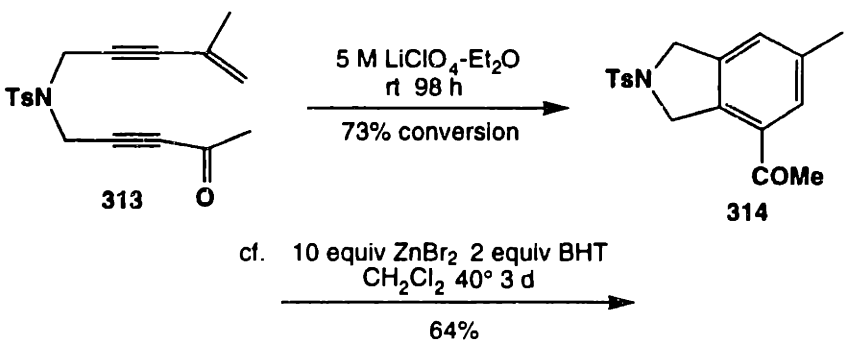
[184] Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663.

at room temperature when treated with 5.0 M lithium perchlorate in ether.[184] The reaction proceeded in good yield and with better endo-exo selectivity than the corresponding reaction in benzene at 120 °C. The effect of lithium perchlorate on the Diels-Alder reaction has been attributed to the ability of a "naked" lithium cation to behave as a Lewis acid and activate the carbonyl.

Brenda Palucki has studied the effect of 5.0 M lithium perchlorate in ether on the [4+2] enyne cycloaddition. We were particularly interested in lithium perchlorate because the "naked" lithium cation[183] is a hard acid and as such will have a high affinity for hard bases like carbonyl groups, but should have little affinity for soft bases such as alkynes. We felt that these conditions would help us distinguish between the dienyl cation mechanism and cyclic allene mechanism. If the enyne cycloaddition was accelerated by lithium perchlorate solution, then we felt we could dismiss the dienyl cation mechanism since it is unlikely that a lithium cation would react with an enyne to generate such a cation.

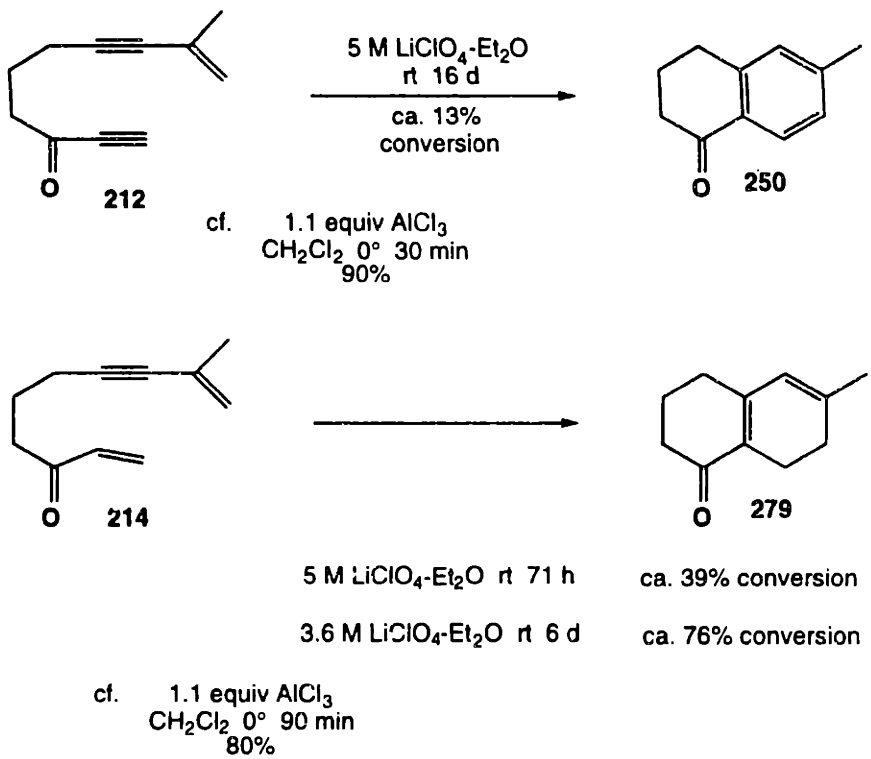
Palucki found that the lithium perchlorate conditions promoted the reaction at a very slow rate. As shown in Scheme 241, enyne **313** provides a 73: 27 mixture of cycloadduct **314** and starting material after more than 4 days in 5 M lithium perchlorate solution.

Scheme 241



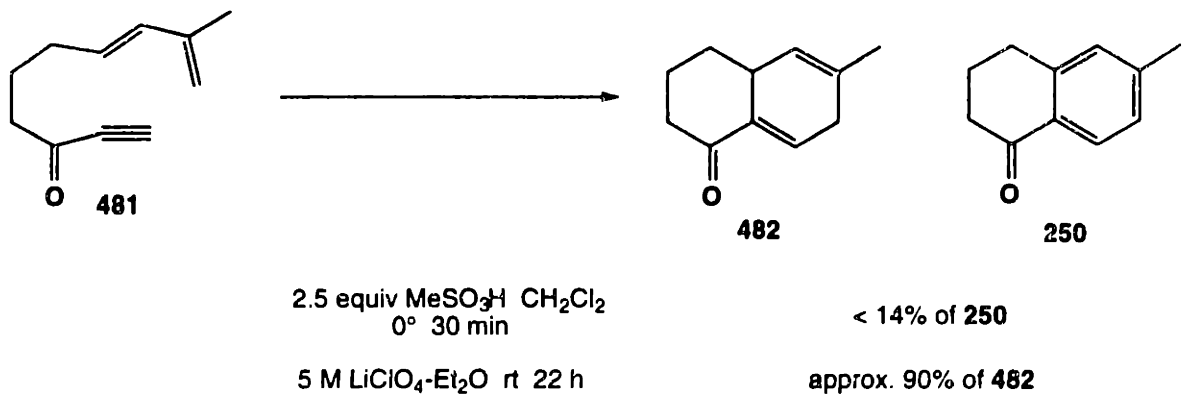
Enynes **212** and **214** also undergo cycloaddition in the presence of lithium perchlorate, although these enyne cycloadditions are again very slow.

Scheme 242



Grieco had not investigated any alkynyl ketones as dienophiles in his studies. Due to the differences in our results, we felt the need to prepare an alkynyl ketone Diels-Alder substrate and explore its reactivity before we could continue our comparisons. Palucki

Scheme 243



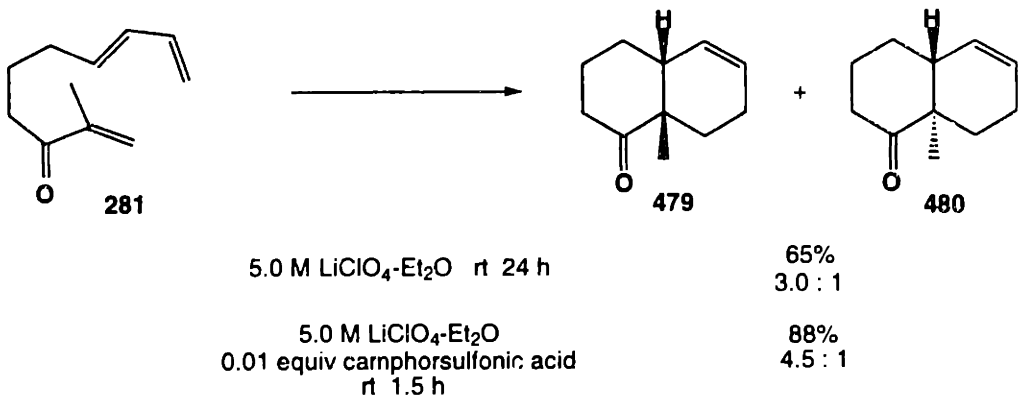
prepared diene **481** (Scheme 243) and found that when treated with lithium perchlorate on a small scale, the desired cycloadduct **482** was obtained in good yield. The alkynyl ketone

dienophile reacted at a similar rate to the enone dienophile. Interestingly, methanesulfonic acid provided a very poor yield of the tetralone **250**; formation and decomposition of the desired cycloadduct **482** could not be ruled out under these highly acidic conditions.

Enyne **212** reacted very slowly under lithium perchlorate conditions, especially when compared to the corresponding diene **481**. The difference in reactivity indicated that an interaction with the enyne moiety might be involved in promoting the reaction. However, formation of the cycloadducts did occur, indicating that dienyl cation formation was not mandatory for cycloaddition to take place.

Grieco reports that the addition of a protic acid to the lithium perchlorate solution enhances the rate, selectivity, and yield of the Diels-Alder reaction, as shown in Scheme 244. Protic acid alone, however, does not promote the reaction.[185] Palucki treated enyne

Scheme 244



212 with 5.0 M lithium perchlorate in ether and 0.01 equivalent of methanesulfonic acid. The rate of this reaction was much faster than the rate of the reaction with lithium perchlorate alone. Although lithium cation coordination to the alkynyl ketone did promote the reaction slowly, the addition of a protic acid, with the potential ability to attack the alkyne of the enyne, enhanced the rate substantially. Given these results, we feel that

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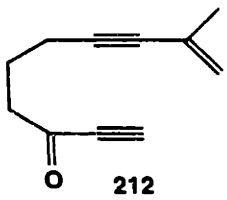
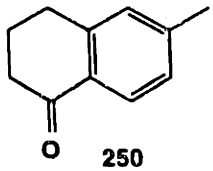
[185] Grieco, P. A., Indiana University, personal communication, 1995.

under protic acid conditions, the dienyl cation mechanism may be operating.

Scheme 245



212



250

5 M $LiClO_4$-Et_2O rt 16 d	ca. 13% conversion
5 M $LiClO_4$-Et_2O 0.01 equiv $MeSO_3H$ rt 5 d	ca. 50% conversion
0.01 equiv $MeSO_3H$ Et_2O rt 43 h	No reaction
0.01 equiv $MeSO_3H$ CH_2Cl_2 rt 4 d	No reaction

The cycloaddition of conjugated enynes under Lewis and protic acid conditions may be proceeding via several mechanisms. The work we have done so far indicates that the cycloaddition may proceed via a dienyl cation under protic acid conditions. However, our work has also shown that a concerted cycloaddition possibly involving a cyclic allene as an intermediate is possible when protic acid is not present. Further mechanistic studies in this area are continuing in our laboratories.

Chapter 3

Stereochemical Aspects

In the previous chapters, the scope and mechanism of the enyne cycloaddition have been discussed, focusing mainly on those substrates with alkynyl enynophiles. This chapter discusses the work we have done on substrates with alkenyl enynophiles. Using alkene enynophiles, we can analyze some aspects of the cycloaddition that are not addressable with alkyne enynophiles, namely areas relating to the stereochemical course of the reaction.

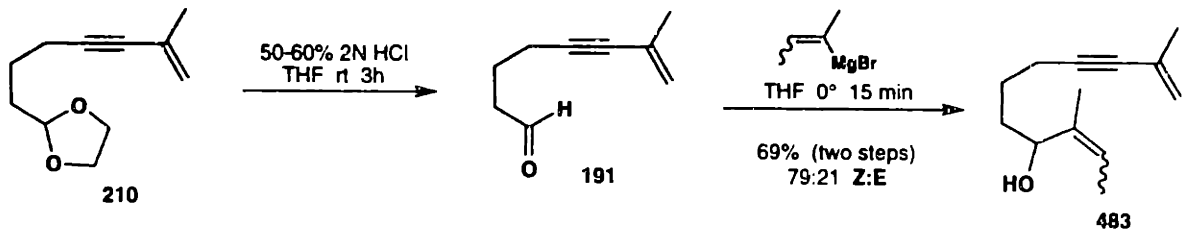
Diels-Alder cycloadditions are highly regio- and stereoselective reactions that are known to proceed in a concerted suprafacial manner with respect to the dienophile in most cases. In other words, the double bond geometry in an alkenyl dienophile is translated into ring stereochemistry in the product. In addition, Diels-Alder reactions tend to give endo products, due to the increased stabilization obtained from secondary orbital interactions in the transition state. Exceptions to this selectivity exist, and reaction conditions can change product compositions. We were interested in determining if the enyne cycloaddition proceeds in a supra or antarafacial manner, and if the reaction proceeds to give endo or exo products. This chapter discusses the syntheses and cycloadditions of substrates designed to answer these questions.

Stereochemical Course of the Enyne Cycloaddition with Respect to the Enynophile

Roberto Fernández de la Pradilla prepared small amounts of two alkene enynophile substrates to determine if the cycloaddition proceeds suprafacially with respect to the enynophile component. Two trisubstituted enone substrates were prepared as a mixture

and separated by chromatography. As shown in Scheme 246, acetal **210** (prepared as described on page 73) was hydrolyzed with HCl to give aldehyde **191**. Treatment of this aldehyde with the Grignard reagent prepared from 2-bromo-2-butene, which is commercially available as a 75:25 mixture of Z and E isomers, gave allylic alcohol **483** as a

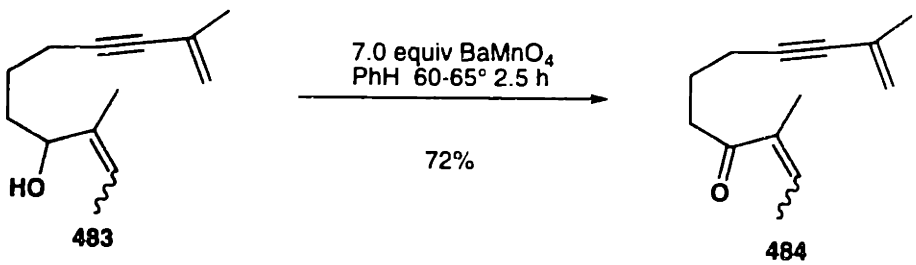
Scheme 246



210 191 483

mixture of olefin stereoisomers. Oxidation of the alcohol with barium manganate provided enone **484**, also as a mixture of isomers, in moderate yield. These enone isomers could then be separated by column chromatography, and Fernández obtained a reasonable amount of the major Z isomer along with smaller quantities of the E isomer.

Scheme 247

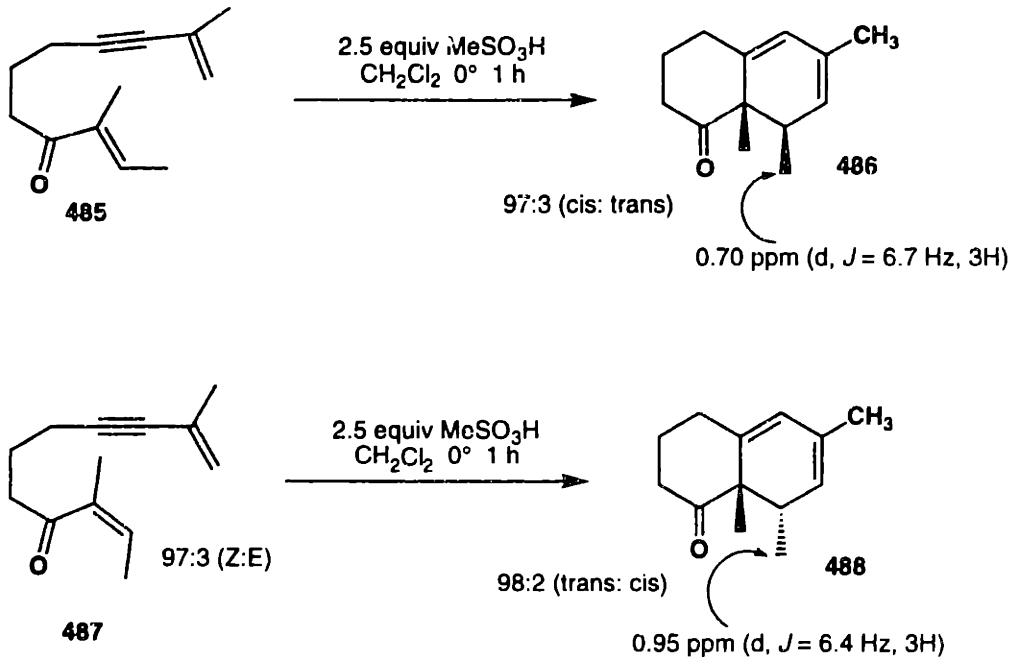


483 484

These enynes cyclized well under protic acid conditions, as shown in Scheme 248. Both isomers gave the desired cycloadducts in good yield, and each enone gave only one product in the cycloaddition. *E*-Enone **485** provided cycloadduct **486** which was characterized by a doublet at 0.70 ppm (J=6.7 Hz, 3H) corresponding to the protons of the methyl group attached to C-8 (Scheme 248). *Z*-Enone **487** provided cycloadduct **488** which was characterized by a slightly downfield-shifted doublet at 0.95 ppm (J=6.4 Hz, 3H) also corresponding to the protons of the methyl group attached to C-8 (Scheme 248).

In each cycloaddition, traces of the other isomer of the cycloadduct were visible in the ^1H NMR spectrum. The stereospecificity of the reaction suggested that the cycloaddition is a concerted process that proceeds in a suprafacial fashion with respect to the enynophile.

Scheme 248



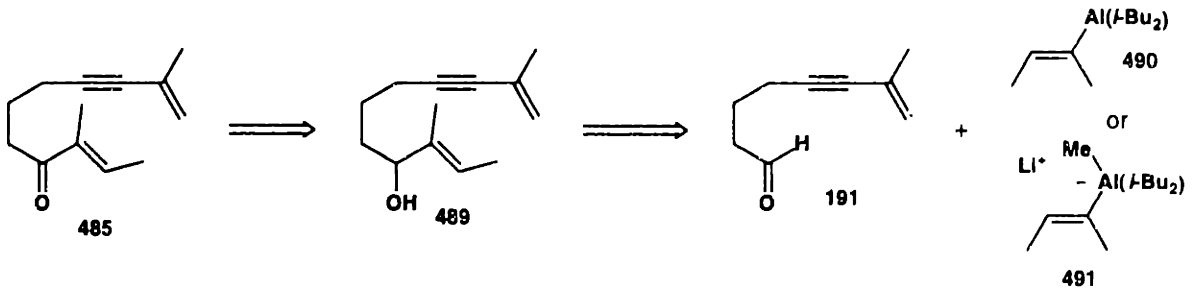
In this preliminary study, Fernández was only able to prepare small quantities of each substrate, and was thus unable to determine yields for these reactions. In addition, the route to these enynes used by Fernández provided the two enones as a mixture of olefin isomers In order to avoid the tedious chromatographic separation of these isomers on a larger scale, we were interested in a different approach that would provide each substrate as a pure compound.

Attention was first focused on the preparation of the E isomer, enyne **485**, which was prepared in very small amounts in Fernández's route. The first approach to *E*-enone **485** was based on work by Zweifel and Steele who found that vinylalanates generated from vinylalanes and methyllithium react with simple aldehydes, carbon dioxide, iodine,

and water to give the expected substituted alkenes. [186] Newman later found that the addition of methyllithium was not necessary, and that vinylalanes themselves will react with aldehydes and ketones at room temperature.[187]

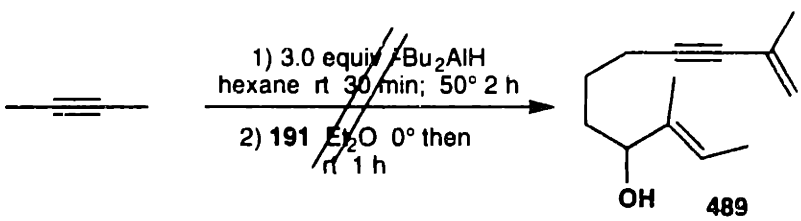
Our plan, then, was to hydroaluminate 2-butyne with diisobutylaluminum hydride and react the resulting vinylalane **490** (or vinylalanate **491**) with aldehyde **191** to give

Scheme 249



allylic alcohol **489**. Before we attempted this set of reactions, however, two model studies were done. These studies, involving 2-butyne and simple aldehydes, gave disappointing results, and not surprisingly, when 2-butyne was treated with three equivalents of diisobutylaluminum hydride and then with aldehyde **191**, none of the desired enone was

Scheme 250



obtained (Scheme 250). Hydroalumination of 2-butyne may be the step causing the poor yields, as the boiling point of 2-butyne is 27 °C, and heating is required to affect

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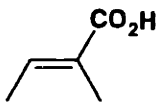
[186] Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2754, 5085. Zweifel, G.; Miller, J. A. *Organic Reactions* **1984**, 375.

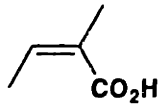
[187] Newman, H. *Tetrahedron Lett.* **1971**, 4571.

hydroalumination.

Both tiglic and angelic acids are known compounds.[188] But while tiglic acid (**492**) and many of its derivatives are commercially available at reasonable prices, angelic acid (**493**) is very expensive. Several esters of angelic acid are reasonably priced. The commercial availability of tiglic acid and tiglic aldehyde led us to explore their use in the preparation of *E*-enone substrate **485**. Our first attempts involved the coupling reactions of tigloyl chloride with organometallic reagents.



tiglic acid
492



angelic acid
493

Although organozinc reagents are known to react with acid chlorides to give ketones, this transformation proceeds in higher yields and with better selectivities in the presence of palladium(0) catalysts.[189] Negishi[190] and others[191] have reported methods for the preparation of organozinc reagents and their reaction with acid chlorides. Due to its versatility, we first examined Yoshida's methodology for the preparation of organozinc reagents from alkyl iodides and zinc-copper couple[192]. As shown in Scheme 251, an organozinc reagent was prepared by treating iodide **494**, prepared from the corresponding chloride, with zinc-copper couple in benzene and DMF at room temperature for 1 hour and then at 50 °C for 3 hours. The resulting organozinc reagent was then treated with tigloyl

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[188] For a review of the chemistry of these compounds, see: Buckles, R. E.; Mock, G. V.; Locatell, L., Jr. *Journal* **1955**, *vol.*, 659.

[189] For recent reviews, see: Erdik, E. *Tetrahedron* **1992**, *48*, 9577. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

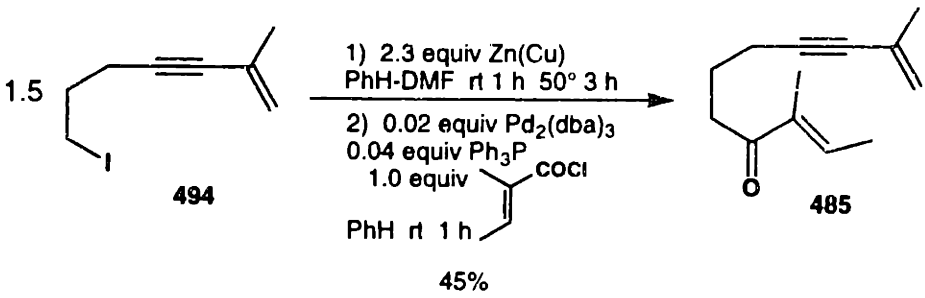
[190] Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T. *Tetrahedron Lett.* **1983**, *24*, 5181 and references cited therein.

[191] Gray, R. A. *J. Org. Chem.* **1984**, *49*, 2288. Sato, T.; Naruse, K.; Enokiya, M.; Fijisawa, T. *Chem Lett.* **1981**, 1135.

[192] (a) Tamaru, Y.; Ochiai, H.; Sanda, F.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5529. (b) Tamaru, Y.; Ockiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5559. (c) Tamaru, Y.; Ockiai, H.; Nakamura, T.; Yoshida, Z.-i. *Organic Synthesis* **1988**, *67*, 98.

chloride (prepared from tiglic acid and oxalyl chloride), $Pd_2(dba)_3$, and triphenylphosphine

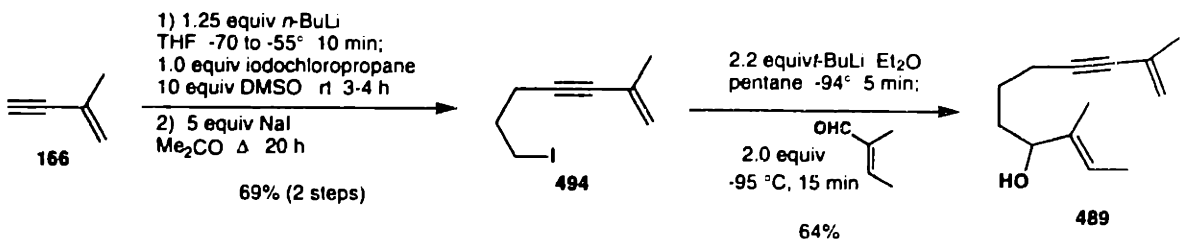
Scheme 251



in benzene. After one hour at room temperature, the desired enone **485** was isolated in 45% yield. Multiple compounds were produced in this reaction, and to minimize the formation of side products the reaction was carried out using different catalyst systems (trifurylphosphine, $Pd_2(dba)_3$), different additives (dimethylacetamide was added),[192b] and different methods of organozinc formation.[190,191] Unfortunately, none of these changes provided enone **485** in a higher yield, and this route was abandoned.

Isomerically pure *E*-enone **485** was successfully prepared in good yield from iodide **494** and tiglic aldehyde. As shown in Scheme 252, the iodide was prepared in two

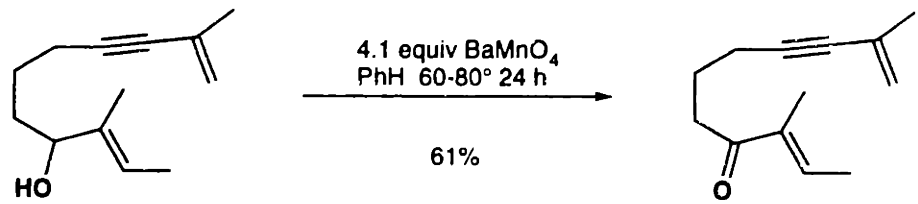
Scheme 252



steps from isopropenylacetylene (**166**) in moderate yield. Iodide **494** was then treated

with *t*-butyllithium in an ether-pentane solution at -94 °C,[193,194] and the resulting alkyl lithium species was treated with tiglic aldehyde. This procedure provided allylic alcohol **489** as a single isomer in moderate yield. Oxidation of the alcohol **489** with barium manganate, following Fernández's procedure, provided *E*-enone **485** in 61% yield. Confirmation of the E configuration was obtained by comparison with Fernández's compounds. The vinyl proton of the enone in the E isomer is shifted downfield in the ^1H NMR spectrum compared to the corresponding proton in the Z isomer.

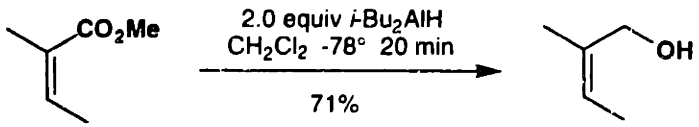
Scheme 253



489 **485**

Given our success with tiglic aldehyde, we hoped to use angelic aldehyde in a similar fashion. Unfortunately, angelic aldehyde, to the best of our knowledge, is not a known compound. In spite of this, we hoped to be able to prepare and react this aldehyde

Scheme 254



495 **496**

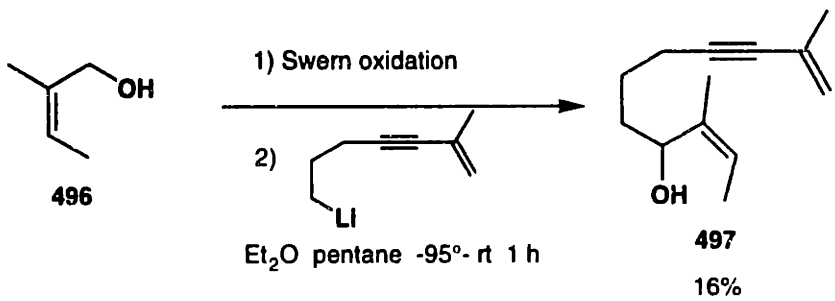
with the organolithium species derived from iodide **494**. Reduction of the methyl ester of angelic acid with diisobutylaluminum hydride provided the allylic alcohol **496** as one isomer in 71% yield. Allylic alcohol **496** was then oxidized to the aldehyde under Swern

---

[193]For the preparation of primary alkyllithiums from alkyl iodides, see: Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. Negishi, E.-i.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406. Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080.

conditions and then immediately treated with the alkyllithium species derived from iodide **494** (Scheme 255).[195] The desired product, secondary allylic alcohol **497**, was obtained in a disappointing 16% yield. Further attempts to increase the yield of this reaction were unsuccessful.

Scheme 255



Weinreb amides can also be used to prepare substituted ketones from acid derivatives,[196,197] and this method was investigated next. Conversion of the methyl ester of angelic acid (**495**) to the Weinreb amide followed by treatment with an organolithium or Grignard reagent would efficiently provide the desired enone. In the event, treatment of methyl ester **495** with either dimethylaluminum or dichloroaluminum *N*-methoxy-*N*-methyl amide provided the α,β-unsaturated amide **498** in which the double bond had isomerized to the E geometry. Isomerization of the double bond could be occurring via a Michael addition-elimination sequence in which the less hindered E isomer is formed. The aluminum amides were prepared from either trimethylaluminum[196b] or dimethylaluminum chloride and the hydrochloride salt of *N*-methoxy-*N*-methyl amine. Confirmation of the

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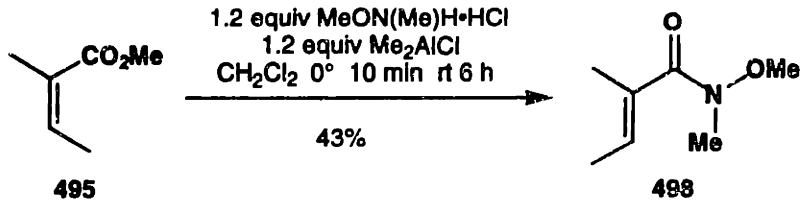
[194] For a recent review of lithium-halogen exchange reactions, see: Bailey W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.

[195] Ireland and Norbeck have reported the direct addition of nucleophilic reagents to crude Swern reaction mixtures, see: Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

[196] For the preparation of amides from esters, see: (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M *Synth. Commun.* **1982**, *12*, 989. (c) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Synthesis* **1980**, *59*, 49. (d) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105.

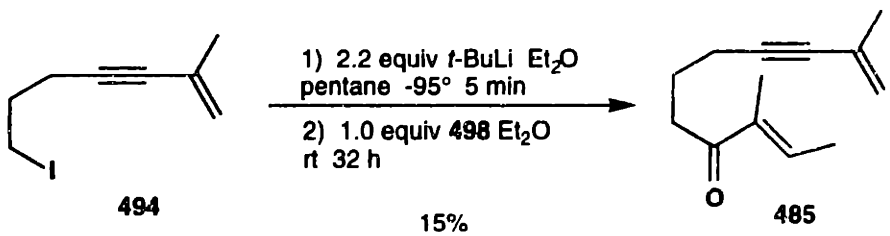
[197] For a review on the use of the Weinreb amide in synthesis, see: Sibi, M. P. *Organic Prep. and Proc. Int.* **1993**, *25*, 17. See also: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme 256



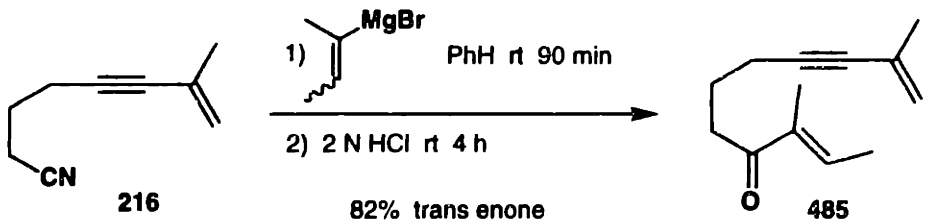
presence of the E double bond geometry was obtained when amide **498** was treated with the lithium derivative of iodide **494**. *E*-Enone **485** was isolated as the only product, in poor yield.

Scheme 257



Another attempt to prepare *Z*-enone **487** involved the addition of the Grignard reagent derived from 2-bromo-2-butene (75:25 Z:E mixture) to a nitrile.[198] As shown in

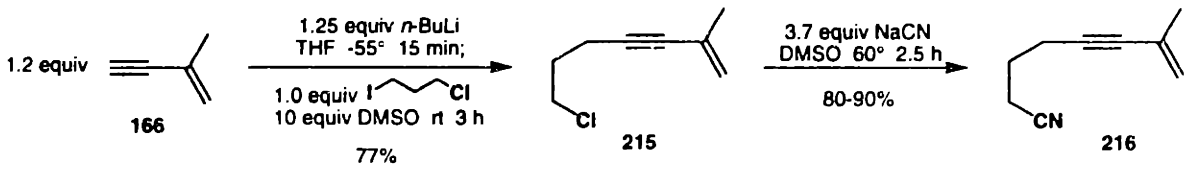
Scheme 258



[198] Hauser, C. R.; Jumphlett, W. J.; Weiss, M. J. *J. Am. Chem. Soc.* **1948**, *70*, 426. Pickard, P. L.; Vaughan, D. J. *J. Am. Chem. Soc.* **1950**, *72*, 876. Canonne, P.; Foscolos, G. B.; Lemay, G. *Tetrahedron Lett.* **1980**, *21*, 155. Matsuda, I.; Murata, S.; Izumi, Y. *J. Org. Chem.* **1980**, *45*, 237. Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1986**, *51*, 5338.

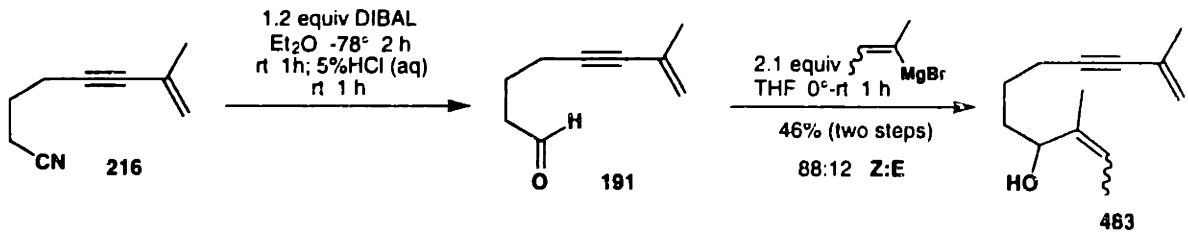
Scheme 258, the addition of the vinyl Grignard reagent to nitrile **216** proceeds in excellent yield, but provides only the E enone. In this case, isomerization of the double bond may be occurring during the hydrolysis of the imine. Z-Enone **487** was finally prepared in large quantities as a mixture with the *E*-enone **485**, following a procedure similar to the one pioneered by Fernández. Nitrile **216** was prepared from isopropenylacetylene (**166**)

Scheme 259



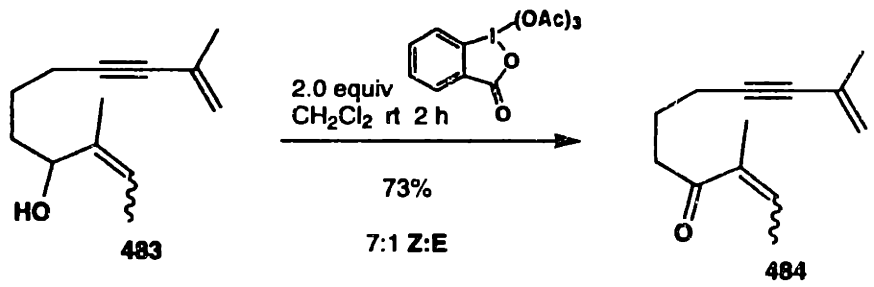
in two steps, as shown in Scheme 259 and described previously (see page 74). Nitrile **216** was then reduced to the imine with diisobutylaluminum hydride and hydrolyzed with aqueous hydrochloric acid to produce aldehyde **191**. Treatment of this aldehyde with the Grignard reagent derived from 2-bromo-2-butene (an 80:20 mixture of Z and E isomers)

Scheme 260



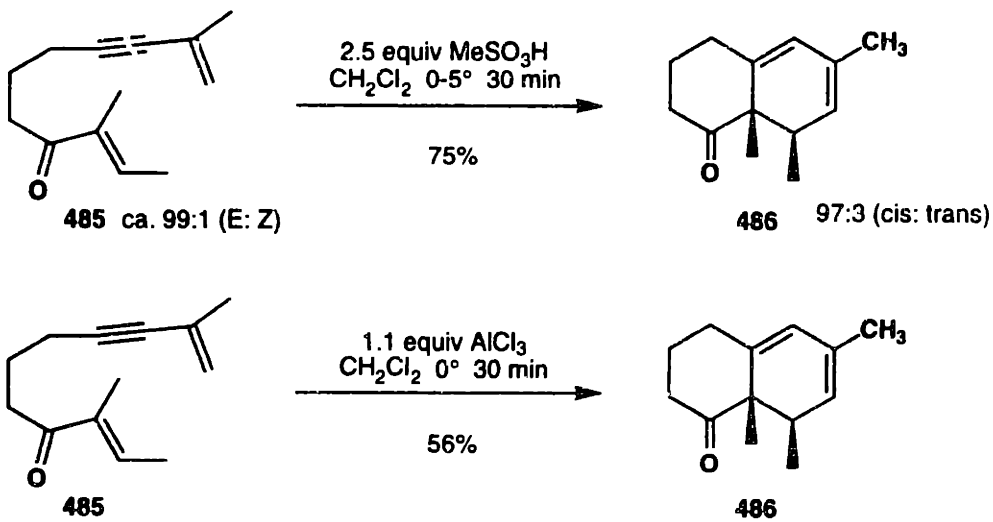
provided the allylic alcohol **483** as an 88:12 mixture of Z and E isomers as determined by ^{1}H NMR. Oxidation of the alcohols with the Dess-Martin periodinane[114] provided a 7:1 mixture of enones **484** which could be separated by column chromatography to give the *Z*-enone **487** with less than 3% contamination by the E isomer.

Scheme 261



With the desired substrates in hand, the next step was to scale up the cycloadditions first performed by Fernández. These cycloadditions proceeded in excellent yield with near complete stereospecificity. As shown below, *E*-enone substrate **485** provided cycloadduct **486** in good yield when treated with methanesulfonic acid at 0 °C. This cycloaddition also

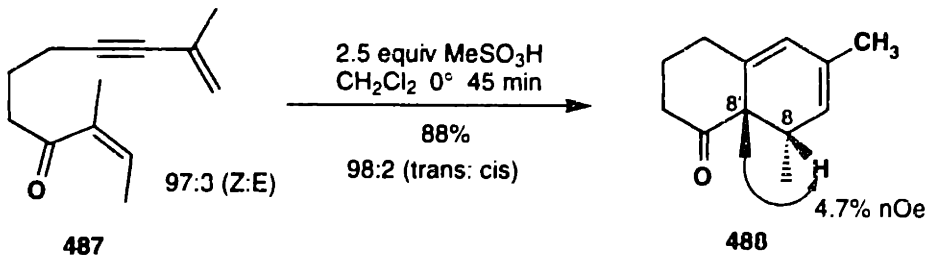
Scheme 262



proceeded in the presence of $AlCl_3$ at 0 °C (Scheme 262), but cyclization in the absence of acid did not occur even after prolonged heating at 180 °C. The *Z*-enone substrate **487** also cyclized in good yield in the presence of methanesulfonic acid to give cycloadduct **488** as a single isomer (Scheme 263). As discussed above, these results indicate that the cycloaddition is proceeding in a suprafacial manner with respect to the enone moiety and that a concerted or very fast stepwise reaction must be occurring. In an attempt to prove the

structure of each of the cycloadducts, Fernandez performed an nOe experiment on each cycloadduct. He observed a 4.7% enhancement of the resonance corresponding to proton at C-8 when the resonance corresponding to the methyl at C-8' was irradiated in cycloadduct **488**. No nOe was observed between the methyl at C-8' and the proton at C-8 in the other isomer, cycloadduct **486**. Given that the each isomeric substrate provided only one product, further confirmation of the exact structures of these cycloadducts was not pursued.

Scheme 263

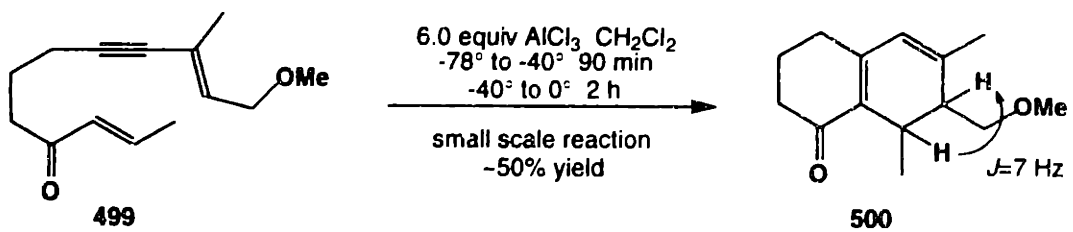


487 **488**

Endo-Exo Selectivity in the Enyne Cycloaddition

With the enyne cycloaddition now confirmed to be a suprafacial reaction, the next area of interest was the exploration of the endo-exo selectivity of the process. Fernández had also prepared a small amount of the enyne substrate **499** which cyclized in moderate yield to give one isomer of cycloadduct **500**, which was characterized by a coupling constant of 7 Hz between the two methine protons (Scheme 264). The relative

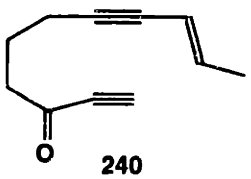
Scheme 264



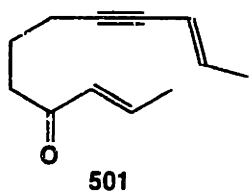
499 **500**

stereochemistry of the cycloadduct was not determined. We were interested exploring this area further, and felt that given the moderate yield obtained in the cycloaddition of **499**, other substrates should be considered.

The most simple substrate, in terms of substitution, for the exploration of the endo-exo selectivity of the reaction is enone **501**. Work on this enone substrate began before the corresponding alkyne substrate **240** (see below) had been prepared. The preparation of the enone substrate **501** is very similar to that previously described for the preparation of the ynone substrate **240**, although this route was not the first to be explored.



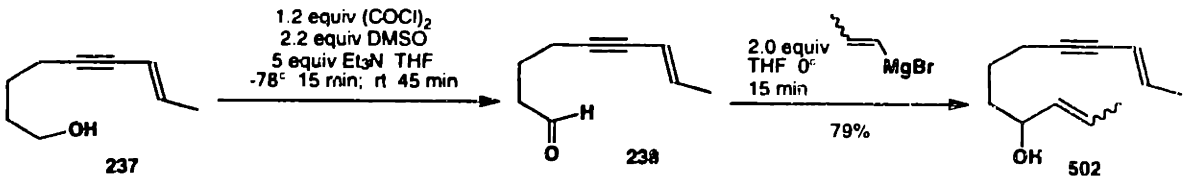
240



501

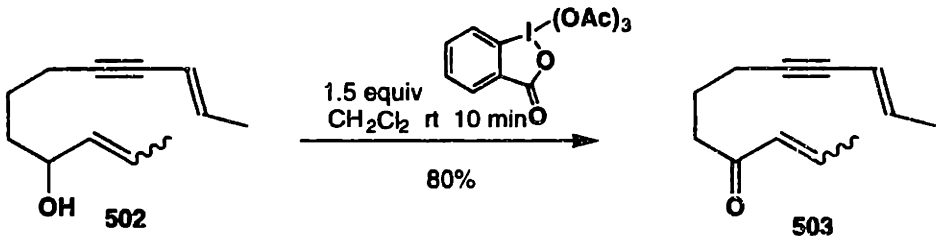
The enyne moiety of the substrate was constructed with a palladium catalyzed coupling[86] of *E*-1-bromopropene with 5-hexyn-1-ol as described in Part II, Chapter 1. The resulting enyne alcohol **237** was then oxidized and treated with the Grignard reagent derived from a 77:23 mixture of *cis*- and *trans*-1-bromopropene to give the allylic alcohol **502**, as a mixture of isomers. While the addition of the vinyl Grignard reagent to the

Scheme 265



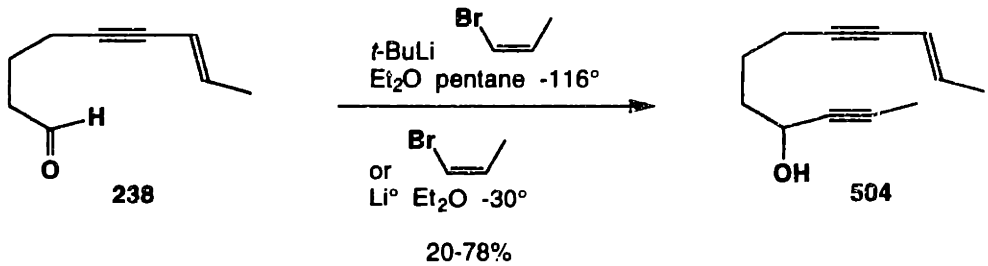
aldehyde proceeded in good yield, the allylic alcohol product was always contaminated with a propargylic alcohol. The source of this contaminant will be discussed later. The allylic alcohol **502** was then oxidized to give the desired enone **503** in good yield as a mixture of isomers that were easily separated by column chromatography.

Scheme 266



Unfortunately, all attempts to prepare allylic alcohol **502** as a single isomer failed. Although several accounts in the literature report the successful generation of the lithium derivative of *cis*-1-bromopropene,[199] formation of this species led to elimination of HBr to give propyne. This elimination was confirmed by the conversion, often in good yield, of aldehyde **238** to the propargyl alcohol **504**.

Scheme 267



Other routes for the stereoselective preparation of enone **501** were also examined. The Wittig reaction is known to proceed with good selectivity to give trans enones under certain conditions, and we felt that the preparation of the enone moiety via a Wittig reaction would provide the desired substrate efficiently. Keck[200] has used 1-triphenyl-phosphoranylidene-2-propanone[201] (**195**) to prepare substituted α,β-unsaturated ketones. As shown in Scheme 268, application of this strategy to the synthesis of enone **501**

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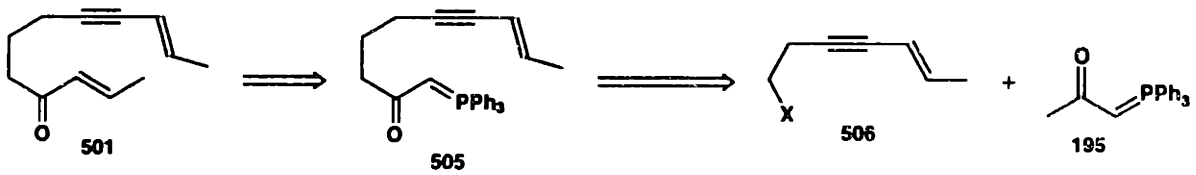
[199] Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839. Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785. Björkling, F.; Norin, T.; Unelius, R. *Synth. Commun.* **1985**, *15*, 463.

[200] Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487.

[201] The preparation and chemistry of 1-triphenylphosphoranylidene-2-propanone is the subject of work by Wolfe and Cooke, see: Taylor, J. D.; Wolf, J. F. *J. Chem. Soc.; Chem. Commun.* **1972**, 876. Cooke, M. P., Jr. *J. Org. Chem.* **1973**, *38*, 4082. Sancaktar, E. A.; Taylor, J. D.; Hay, J. V.; Wolfe, J. F. *J. Org. Chem.* **1976**, *41*, 509. Cooke, M. P., Jr.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955.

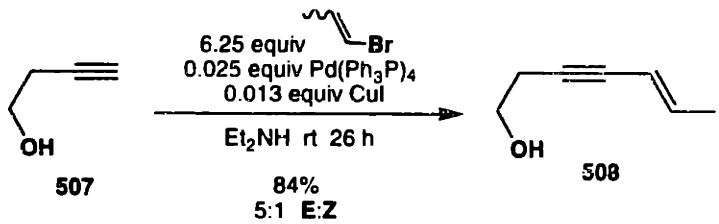
required the preparation of phosphorus ylide **505**. This ylide could be obtained via the alkylation of the enolate of phosphoranylidene ketone **195** with a homopropargyl halide, tosylate, or mesylate. These homopropargyl compounds could be derived from the corresponding homopropargylic alcohol.

Scheme 268



Using coupling strategies already developed for the preparation of homologous substrates, enyne alcohol **508** was prepared from 1-bromopropene and 3-butyn-1-ol in

Scheme 269



good yield. As shown in Scheme 270, the alcohol was then converted to the tosylate, iodide, bromide,[202] and mesylate.[203] Each of these compounds was then treated with either the lithium or magnesium enolate of phosphorane **195**. Unfortunately, none of these substrates provided the desired ylide **505**. As shown in Scheme 271, the tosylate derivative did not react, while the other three substrates provided product other than the desired one. Elimination can be a problem in substitution reactions with homopropargylic compounds; the electron withdrawing alkyne moiety causes acidification of the propargyl

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[202] Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637.
[203] Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

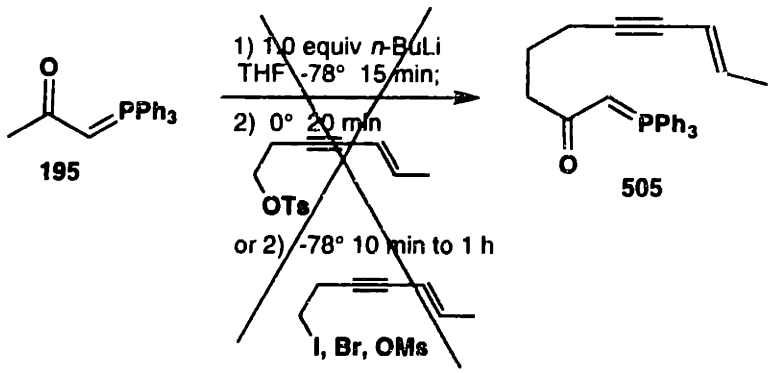
Scheme 270

508 506

X	Conditions	Yield
OTs	1.1 equiv *n*-BuLi THF -78° 15 min; 1.0 equiv TsCl THF 0° - rt 2 h	72%
I	1.5 equiv I_2 1.0 equiv Ph_3P 1.5 equiv imidazole THF 0° - rt 3 h	77%
Br	2.8 equiv Ph_3P 3.0 equiv NBS 1.2 equiv pyridine CH_2Cl_2 rt 10 min	72%
OMs	1.5 equiv Et_3N CH_2Cl_2 0° 15 min; 1.2 equiv $MeSO_2Cl$ 0° 45 min	89%

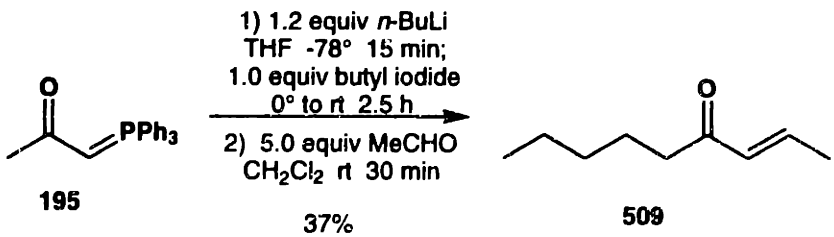
proton and facilitates deprotonation and elimination. The alkylating agent appeared to be

Scheme 271



the culprit in this reaction, since in a model reaction, alkylation of the phosphoranylidene

Scheme 272

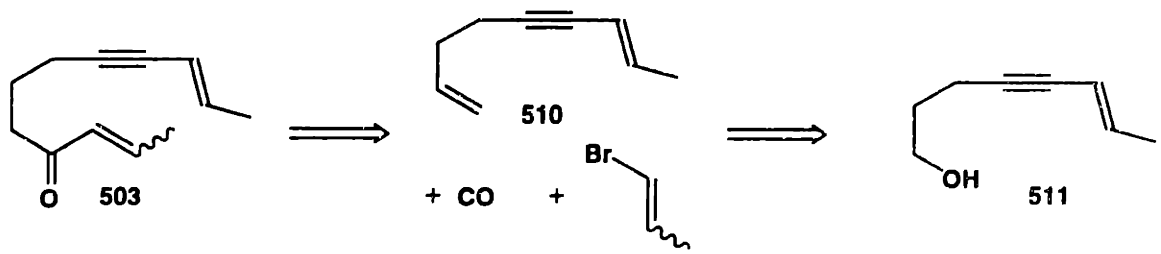


195 with *n*-butyl iodide followed by the addition of acetaldehyde provided the expected

disubstituted enone **509** in 37% yield.

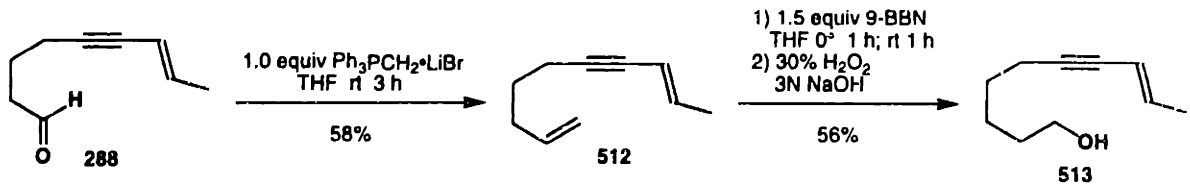
Another approach to the enone substrate that we investigated involved a carbonylative Suzuki coupling reaction to form the enone moiety. As shown in the retrosynthetic scheme below, this approach requires the preparation of enyne alkene **510**, which can be obtained from alcohol **511** via oxidation and Wittig homologation. Before

Scheme 273



preparing the required compounds, however, we needed to confirm that the hydroboration of **510** would be possible at the terminal alkene. In a model study, aldehyde **288** was treated with methylenetriphenylphosphine[204] in THF at room temperature to give alkene **512** in moderate yield. This olefin was then treated with 9-BBN in THF at 0 °C; after two hours, the reaction mixture was treated with basic hydrogen peroxide to give the desired alcohol **513**. The selectivity of the reaction was confirmed by the ^{1}H NMR spectrum which revealed the presence of the two distinct vinyl protons of the enyne moiety at 6.04 ppm (dquartet, J= 15.5, 6.9 Hz, 1H) and 5.46 ppm (dt, J= 15.5, 2.0 Hz, 1H).

Scheme 274



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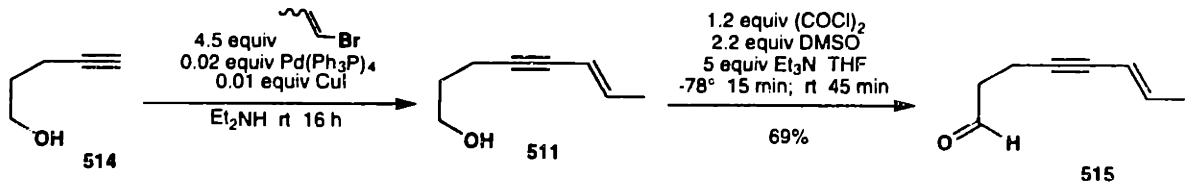
[204] Methylenetriphenylphosphane was prepared from Ph_3PMe and *n*-BuLi as described in the following paper: Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82.

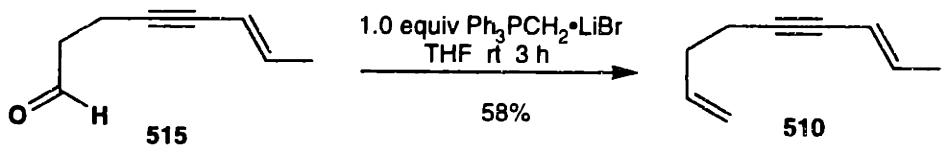
With the selectivity of the hydroboration established, the preparation of coupling components began. Alcohol **511** was prepared via the now familiar palladium-catalyzed coupling of a vinyl bromide with an acetylene.[86] The coupling of these substrates, however, did not proceed as well as usual, and the reaction did not go to completion. However, enough of the desired enyne **511** was isolated to allow further

Scheme 275



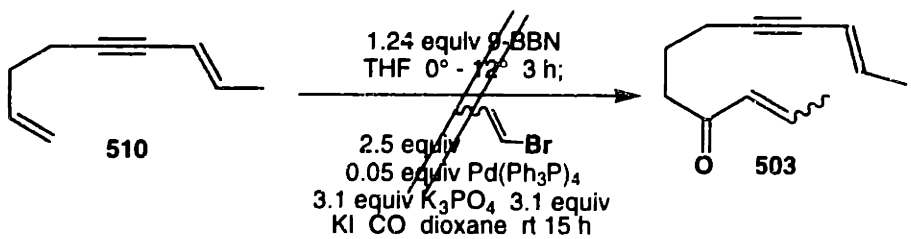
reactions to be explored. Alcohol **511** was oxidized under Swern conditions, and the

Scheme 276



resulting aldehyde **515** was treated with methylenetriphenylphosphine to give the desired alkene **510**. Unfortunately, the carbonylative coupling reaction,[205] did not proceed well, providing none of the desired product under the conditions described by Suzuki (Scheme 277). No starting material was recovered from this reaction which gave a mixture of products. Other conditions were explored, but none provided any of the desired product.

Scheme 277



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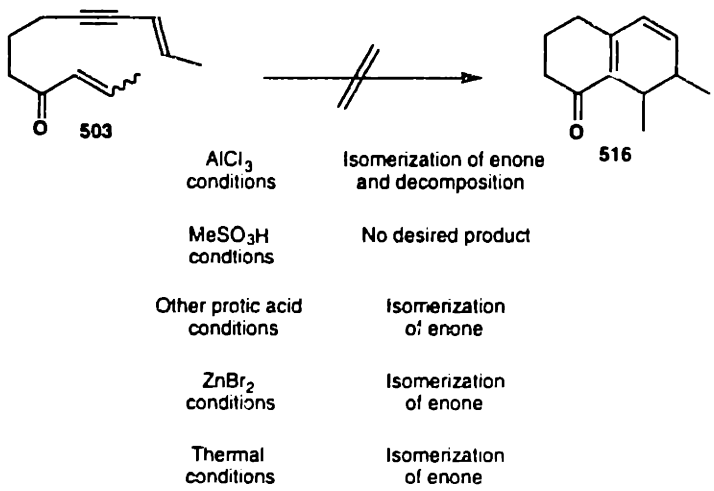
[205] Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1999.

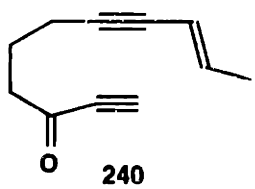
It was at this point that the desired enone substrate was prepared as described in Scheme 265 and 266. This procedure gave the substrate as a mixture of enone stereoisomers, which could be separated by column chromatography These stereoisomers were not separated in the initial exploration of the cycloaddition.

With the desired substrate in hand, the cycloaddition was now examined.

Scheme 278

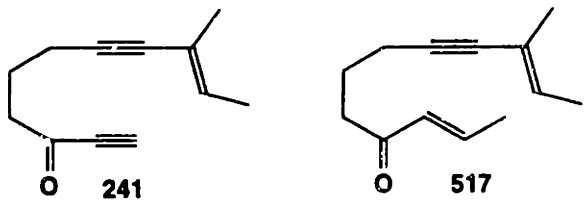


Unfortunately, as shown in Scheme 278, no cycloadduct was isolated under a variety of conditions. This result was disappointing, and at the time this substrate was prepared, the alkyne enynophile substrate **240**, shown below, was also synthesized. As described in Part II, Chapter 2, this alkynyl substrate also did not cyclize in good yield under any conditions. The combination of these results led us to consider other substrates for the study of the endo/exo selectivity of this reaction.



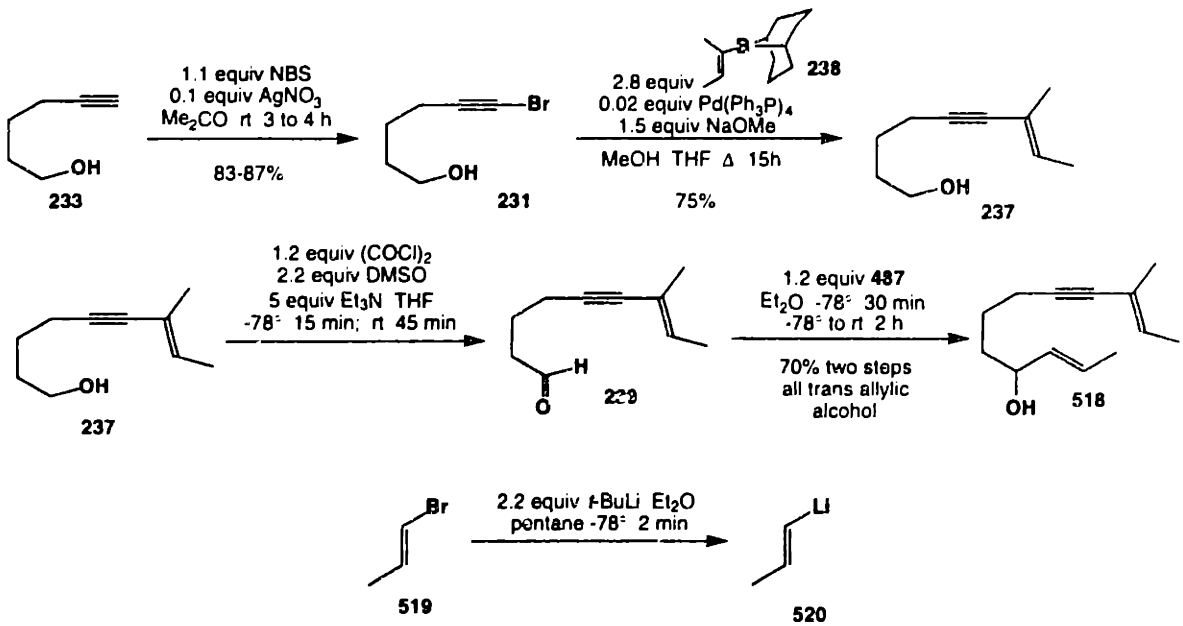
As the ynone substrate **241** underwent cycloaddition in reasonable yields under Lewis and protic acid conditions, we felt that a substrate of this type with an alkene

enynophile **517** could be prepared to study the endo/exo selectivity of the reaction. Enone



substrate **517** was prepared in a manner similar to that described for the synthesis of alkyne **241** (Scheme 279). Alkyne **233** was brominated to give bromoalkyne **231**. Suzuki coupling of this bromide with the 9-BBN derivative of 2-butyne provided the desired enyne **237** in 75% yield. Enyne alcohol **237** was then oxidized and treated with the vinyllithium reagent **520**, prepared from 1-bromopropene and *tert*-butyllithium. The solvent system was crucial for the preparation of the isomerically pure vinyllithium reagent

Scheme 279



520.[206] Elimination of HBr to give propyne had been problem in the formation of these

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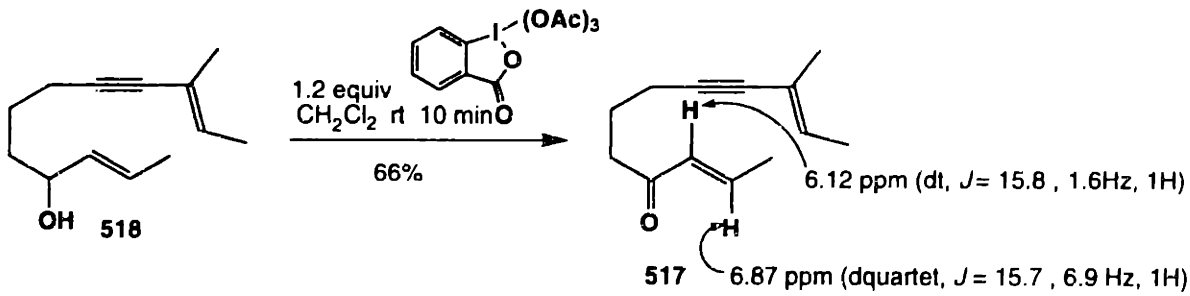
[206] Bailey, W. F.; Jiang, X. L.; McLeod. C. E. *J. Org. Chem.* **1995**, *60*, 7791.

lithium reagents; however, under the conditions described by Bailey,[206] no elimination product was observed, and a good yield of the isomerically pure allylic alcohol **518** was obtained. Oxidation of the allylic alcohol **518** with the Dess-Martin periodinane provided the desired substrate **517**, in 66% yield. For unknown reasons, the yield for this oxidation was consistently lower than that for other related substrates. Confirmation of the formation of a single enone isomer was provided by the ^{1}H NMR spectrum, which showed three vinyl protons: a quartet at 5.81 ppm (J=7.0 Hz) corresponding to the vinyl proton on the enyne moiety, a doublet of triplets at 6.12 ppm (J = 15.8, 1.6 Hz), and a doublet of quartets at 6.87 ppm (J = 15.7, 6.9 Hz) corresponding to the two vinyl protons of the enone moiety. The large coupling constant (J = 15.7 Hz) is indicative of trans orientation about a double bond.[207]

Scheme 280



The Suzuki coupling approach provided the desired enone substrate, but it was not the first approach we considered. The enyne moiety of substrates **241** and **517** is not commercially available, and therefore had to be constructed. Our usual method of enyne preparation, the Sonagashira modification of the Castro-Stevens coupling,[86] was not an option, because 2-bromo-2-butene is only available commercially as a mixture of isomers. We then considered other methods for the synthesis of enynes. Several methods are

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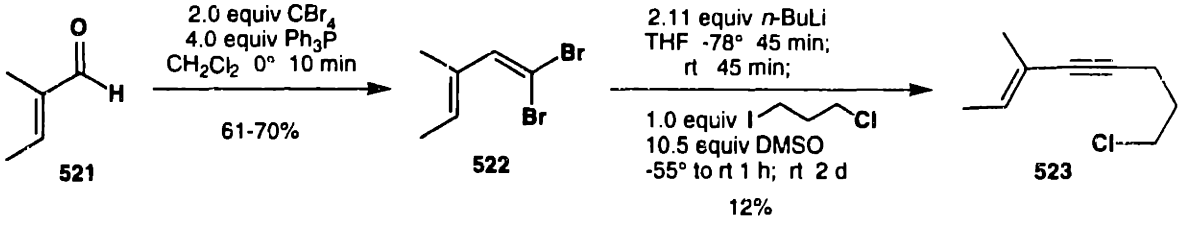
[207] Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981; p 235.

known for the conversion of an aldehyde to an acetylene,[208] which would be a particularly convenient route given the commercial availability of tiglic aldehyde. We chose to investigate the Corey-Fuchs acetylene synthesis[208a] first. This method allowed direct functionalization of the enyne without isolation, and 3-methyl-3-penten-1-yne is a volatile liquid that might prove difficult to isolate from a reaction mixture.

Treatment of tiglic aldehyde (**521**) with carbon tetrabromide in the presence of triphenylphosphine provided the 1,1-dibromoalkene **522** in 61 -70% yield. The addition of zinc to the reaction mixture led to lower yields of the desired product. The 1,1-dibromoalkene **522** was then treated with 2 equivalents of *n*-butyllithium at -78 °C to effect dehydrohalogenation and halogen-metal exchange; this treatment provided the lithium derivative of 3-methyl-2-propenyl acetylene which was treated with chloroiodopropane and dimethylsulfoxide. Unfortunately, this sequence did not provide the desired alkylated enyne **523** in good yield. Further attempts to optimize the reaction, including the use of different solvent systems and the use of one equivalent each of *n*-butyllithium and methyllithium, did not improve the yield. As the alkylation was not proceeding well, this route was abandoned.

Scheme 281



Another route we devised to the 3-methyl-2-propenylacetylene substrate was based on Negishi's work on the coupling of vinylboranes with acetylides in the presence of

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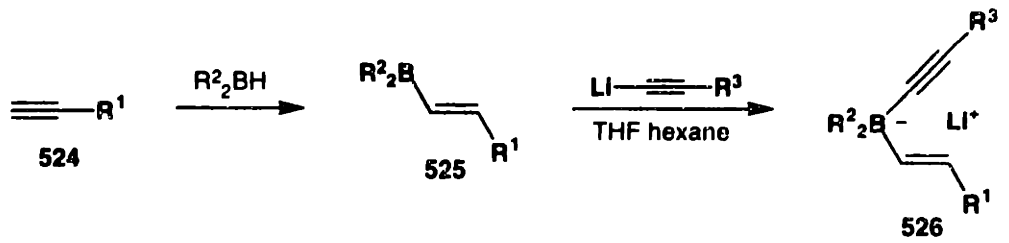
[208] Most of these acetylene syntheses are based on the Wittig reaction, for examples, see: (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (c) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (d) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1975**, 458. (e) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021. (f) Bartlett, P. A.; Green, F. R., Jr.; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852.

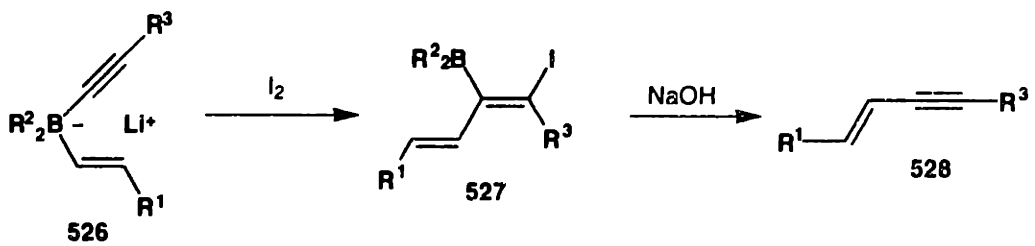
iodine.[209] Negishi reported that *trans*-enynes can be prepared in a manner similar to the method reported by Zweifel.[186] Negishi's method, however, uses boranes instead of alanes. According to Negishi's report, hydroboration of a terminal alkyne provides a vinyl borane (**525**, Scheme 282). Addition of a lithium acetylide to the vinylborane gives the borate species **526**. Treatment of the borate complex with iodine at low temperature

Scheme 282



furnishes the vinyl iodoborate species **527** (Scheme 283). This iodo species reacts with the added sodium hydroxide to produce the enyne (**528**).

Scheme 283



Although few examples were provided, a plan based on this chemistry was implemented for the preparation of the 3-methyl-2-propenylacetylene substrate which required the coupling of the vinylborane derived from 2-butyne and an alkyne. 5-Hexyn-1-ol, protected as the methoxymethylene ether,[210] would serve as the nucleophilic acetylide species in this reaction. The vinylborane species was prepared by combining 2-butyne with either 9-BBN or disiamylborane at 0 °C in THF for 1 hour. We later found that

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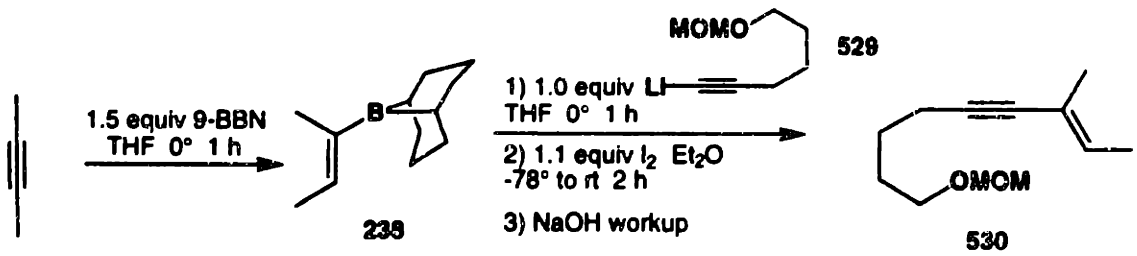
[209] Negishi, E.-i.; Lew, G.; Yoshida, T. *J. Chem. Soc.* **1973**, 874.

formation of these vinylborane species required several hours at 0 °C. As shown in Scheme 284, the vinylborane derived from 9-BBN (**238**) was treated with lithium acetylide

Scheme 284



529 at 0 °C, and then with iodine at -78 °C. Unfortunately, none of the desired enyne **530** was isolated from this reaction. Similar results were obtained with disiamylborane. The poor results could be due to the short reaction time allowed for the formation of the vinylborane species.

In summary, the best route developed for the preparation of enone substrate **517** involved a Suzuki coupling to give the enyne moiety as shown in Scheme 279 and 280. The cycloaddition was the final step in the exploration of the endo/exo selectivity this reaction. Enone substrate **517** was exposed to several types of reaction conditions, and only small amounts of the desired product were produced. Some of the conditions explored are outlined in Scheme 285. Less than 30% yield of the cycloadduct was obtained when the reaction was run in the presence of methanesulfonic acid or aluminum chloride at concentrations of 0.10 or 0.05 M. As the poor yield could be attributed to decomposition of the cycloadduct during the reaction, the reaction was run a higher dilution. The rate of the reaction slowed dramatically, but an improved 40% yield was obtained when the reaction was run at 0.025 M on a small scale. Unfortunately, when the reaction was scaled up, the cycloaddition required more time, providing the cycloadduct **531** in 29% yield; no other identifiable products were isolated from the reaction mixture.

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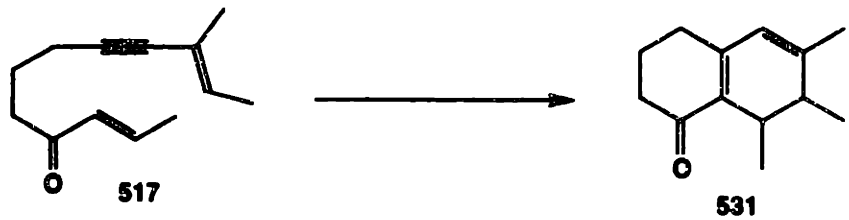
[210] Stork, G.; Takahaski, T. *J. Am Chem. Soc.* **1977**, *99*, 1275. and RLD org syn.

Scheme 285

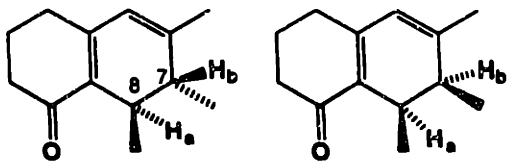


517 531

Conditions	Yield
2.0 equiv BHT toluene 180° 59 h	traces
2.5 equiv $MeSO_3H$ CH_2Cl_2 0° 30 min	~21% (small scale)
0.5 equiv $AlCl_3$ CH_2Cl_2 0.09 M 0° 4 h; rt 19 h	26% (small scale)
0.75 equiv $AlCl_3$ CH_2Cl_2 0.025 M rt 5 d	40% (small scale)
0.8 equiv $AlCl_3$ CH_2Cl_2 0.025 M rt 25 d	29%

The cycloadditions of enone substrate **517** provided the cycloadduct in low yield, but as a single isomer (a trace of the other isomer was visible in the ^1H NMR spectrum). Determination of the relative stereochemistry of the cycloadduct has not been completed. The ^1H NMR spectrum of the cycloadduct indicates that the 2 methine protons (H_a and H_b, shown below) are not coupled to each other. Although the coupling may be too small to be seen, this lack of coupling indicates that the dihedral angle between the two protons is between about 60 and 100°.[211] Although, these angles rule out a diaxial relation between the two protons, they do not rule out the trans isomer **531 endo**. In a normal tetralone ring system, the lowest energy conformation for a methyl group would be in the equatorial position, due to 1,3 diaxial interactions. However, cycloadduct **531** is not a normal tetralone ring system, and the absence of axial substituents lowers the energy of an axial

[211] Assuming a coupling of 1 Hz or larger would be observed, the Karplus correlation for vicinal protons indicates these angles. See: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981; p 210.

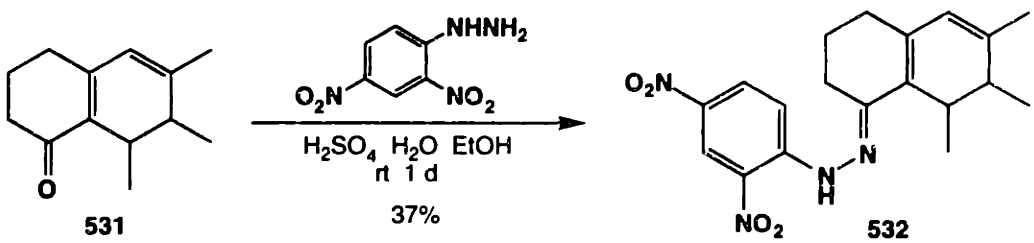


531 endo **531 exo**

methyl conformation. In addition, a methyl group in the equatorial position will experience 1,3 allylic strain with the vinyl methyl at C-6. Therefore, it is possible that for either isomer, the lowest energy conformation involves either one or both of the methyls at C-7 and C-8 to be axial.

Due to the crowded nature of the cycloadduct's NMR spectrum, further experiments involving NMR were not pursued. We decided that the best method to determine the relative stereochemistry of the cycloadduct **531** would be to obtain a crystal structure. To this end, the 2,4-dinitrophenylhydrazone **532** was prepared from cycloadduct **531**.[212] No isomerization was observed in the formation of the hydrazone. X-Ray diffraction quality crystals of this red solid are currently being prepared.

Scheme 286



531 **532**

Although our work is not complete in the realm of stereochemistry, we have determined that the enyne cycloaddition is a suprafacial reaction under protic and Lewis acid conditions. The cycloaddition also proceeds with high selectivity for a yet to be determined endo or exo product.

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[212] Shriner, R. L.; Fuson, R. C.; Curtin, D. Y.; Morrill, T. C. *The Systematic Identification of Organic Compounds*; John Wiley and Sons: New York, 1985. Behforouz, M.; Bolan, J. L.; Flynt, M. S. *J. Org. Chem.* **1985**, *50*, 1186.

Summary

The intramolecular cycloaddition of conjugated enynes is fairly general reaction, capable of producing substituted indenes and tetralones, as well as heterocycles and dihydroaromatic products. The cycloaddition proceeds when the reaction mixture is heated or treated with Lewis or protic acids.

The mechanism of this reaction is not completely clear. Under different conditions, different mechanisms may be operating. Under thermal conditions, a cyclic allene may be involved as an intermediate, while under protic or Lewis acid conditions, a dienyl cation may be an intermediate. The enyne cycloaddition can be described as a [4+2] cycloaddition that occurs in a suprafacial manner with respect to the enynophile, at least under acidic conditions. Work is continuing to further explore the scope and mechanism of the cycloaddition.

Part IV

Experimental Section

General Procedures

All reactions were performed in glassware that was flame dried under vacuum and then purged with nitrogen or argon. Reaction mixtures were stirred magnetically unless otherwise indicated, except for thermal cycloaddition reactions in sealed tubes which were not stirred. Thermal cycloaddition reactions were placed in a deep oil bath that was maintained at a constant temperature with a thermocouple. Air and/or moisture sensitive reagents and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated with the use of a Büchi rotary evaporator at approximately 20 mmHg unless otherwise indicated.

Materials

Commercial grade reagents were used without further purification except as indicated below.

Distilled under nitrogen, argon, or vacuum from calcium hydride: dichloromethane, dimethylsulfoxide, hexamethylphosphoramide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, *N*,*N*-diisopropylethylamine, diethylamine, triethylamine, toluene, benzene, *N*-methylpyrrolidinone, cyclohexane, chlorobenzene, pentane, and hexane.

Distilled under nitrogen, argon, or vacuum from sodium benzophenone ketyl or dianion: benzene, toluene, diethyl ether, and tetrahydrofuran.

Distilled under nitrogen or argon from phosphorus pentoxide: carbon tetrachloride.

Distilled under nitrogen or argon: 2-methyl-2-buten-3-yne, 2,3-dimethyl-2-propenal, acetic anhydride, methyl chloroformate, trimethylsilyl chloride,

diphenyldisulfide, trifluoromethanesulfonic anhydride, methyl iodide (also passed through Al_2O_3), and oxalyl chloride.

Purification of other reagents was accomplished in the following manner: zinc bromide, and aluminum chloride were dried under vacuum at room temperature (0.1 mmHg) for 2 to 14 hours, *N*-bromosuccinimide was recrystallized from water, sodium cyanide and sodium iodide were dried at 100 °C (0.1 mm Hg) for 12 to 16 hours, methyl iodide, chloroiodopropane, 1-iodo-4-pentyne, and 1-iodo-5-hexyne were passed through a pad of Al_2O_3 immediately before use.

Alkyllithium reagents were titrated in benzene or hexane with menthol using 1,10-phenanthroline as an indicator.

Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated, glass-backed silica gel 60 F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) ultraviolet irradiation, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 °C, (d) immersion of the plate in an ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, and (e) immersion of the plate in an ethanolic solution of 3% *p*-vanillin containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C.

Column chromatography was performed by using 230-400 mesh Merck or Baker silica gel.

Instrumentation

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected.

Infrared spectra (IR) were recorded using a Perkin-Elmer 1320 grating spectrophotometer.

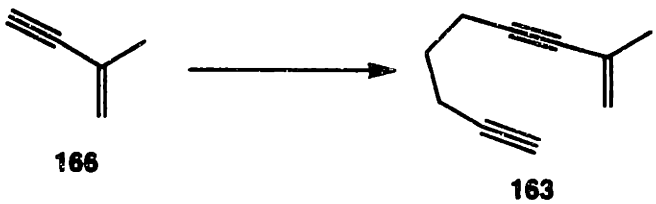
^{1}H NMR spectra were recorded with a Varian XL-300 (300 MHz) and a Varian Unity 300 (300 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ), relative to tetramethylsilane (with the single peak of chloroform at 7.26 ppm used as a standard).

^{13}C NMR spectra were determined on a Varian XL-300 (75 MHz) and a Varian Unity 300 (75 MHz) spectrophotometer. Chemical shifts are reported in parts per million (δ), relative to tetramethylsilane (with the central peak of $CDCl_3$ at 77.0 ppm used as a standard).

High resolution mass spectra (HRMS) were measured on a Finnegan MATT-8200 spectrometer.

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, New Jersey.

Experimental Procedures and Spectra



166 163

I:

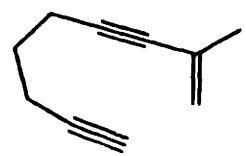
A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 2-methyl-1-buten-3-yne **166** (2.14 g, 3.13 mL, 32.4 mmol) and 65 mL of THF and cooled at -50 °C. *n*-BuLi (2.71 M solution in hexane, 13.6 mL, 35.7 mmol) was added dropwise over ca. 5 min. After 5 min, 1-iodo-4-pentyne (6.90 g, 35.7 mmol) and HMPA (63.9 g, 62.0 mL, 357 mmol) were added sequentially via syringe in one portion. The reaction mixture was allowed to warm to room temperature over 2 h, and then treated with 25 mL of saturated NH_4Cl solution and 50 mL of pentane. The aqueous phase was separated and extracted with 25 mL of pentane, and the combined organic phases were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and carefully concentrated (60-100 mmHg) to give 5.6 g of a pale yellow oil. The residual THF was removed by distillation at atmospheric pressure. Purification by two successive Kugelrohr distillations (0.2 mm Hg, bath temperature 100 °C) afforded 2.48 g (58%) of **163** as a colorless oil.

II:

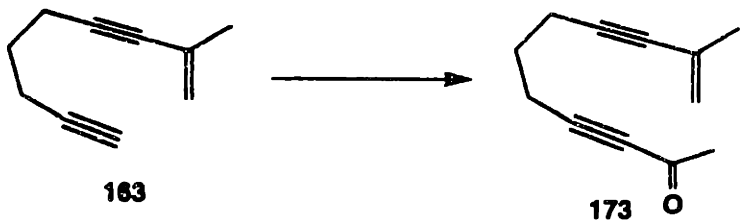
A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 2-methyl-1-buten-3-yne **166** (0.295 g, 0.43 mL, 4.47 mmol) and 9 mL of Et_2O and then cooled at -50 °C. *n*-BuLi (2.62 M solution in hexane, 1.90 mL, 35.7 mmol) was added dropwise via syringe over 1 min. After 5 min, 1-iodo-4-pentyne (0.955 g, 4.92 mmol) and DMPU (6.4 g, 6.0 mL, 49.2 mmol) were added sequentially via syringe in one portion. The reaction mixture was allowed to warm to room temperature over 2 h and was then treated with 25 mL of H_2O. The resulting two

phase mixture was diluted with 50 mL of Et_2O; the aqueous phase was separated and extracted with two 25 mL portions of Et_2O. The combined organic phases were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and carefully concentrated (60-100 mm Hg). The resulting oil was diluted with 20 mL of hexane, and this solution was washed with 15 mL of H_2O, 15 mL of brine, dried over $MgSO_4$, and filtered. Removal of the hexane by distillation at atmospheric pressure provided 0.560 g of a yellow oil. Column chromatography on 56 g of silica gel (elution with petroleum ether) provided 0.377 g (64%) of **163** as a colorless oil.

IR (film):	3300, 3090, 2950, 2860, 2580, 2220, 2110, 1625, 1445, 1385, 1360, 1345, 1325, 1310, 1200, 1020, and 910 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.21 (d, J = 1.1 Hz, 1 H), 5.14-5.15 (m, 1 H), 2.43 (t, J = 7.0 Hz, 2 H), 2.32 (td, J = 2.2, 7.0 Hz, 2 H), 1.97 (t, J = 2.9 Hz, 1 H), 1.87 (t, J = 1.1 Hz, 3 H), and 1.76 (app quintet, J = 7.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	127.1, 120.6, 87.9, 83.6, 82.5, 68.7, 27.6, 23.7, 18.3, and 17.5 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{10}H_{11}$ 131.0861 Found 131.0861.

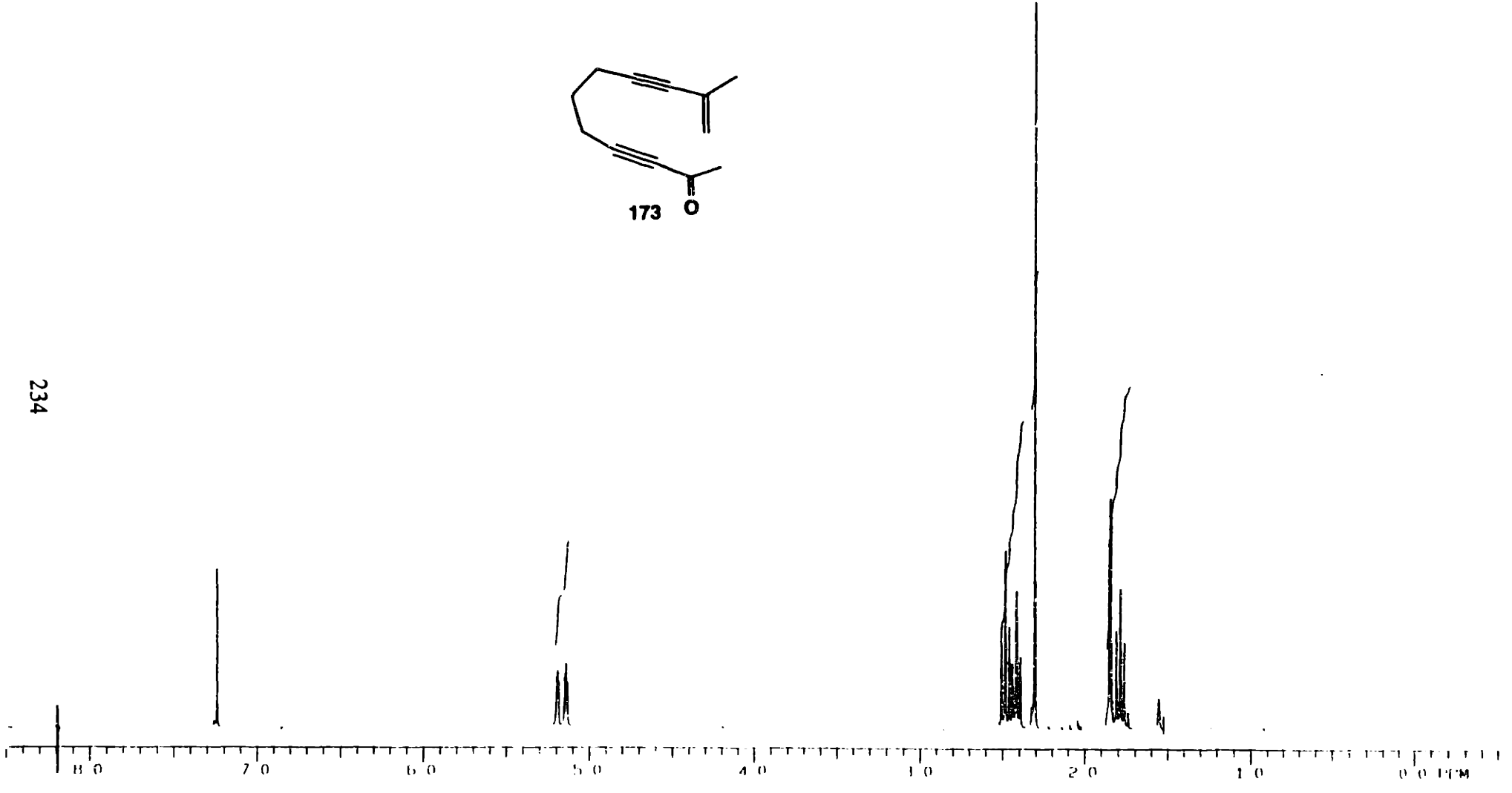


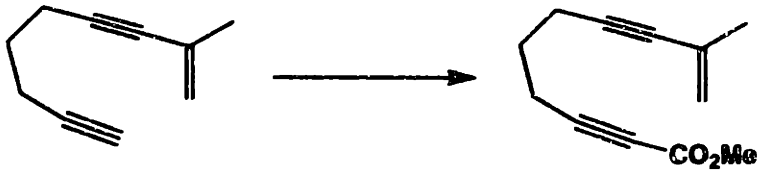
163



A 100-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and glass stopper was charged with 2-methyl-1-nonen-3,8-diyne **163** (0.400 g, 3.03 mmol) and 30 mL of THF, and then cooled at -50 °C. *n*-BuLi (2.47 M solution in hexane, 1.35 mL, 3.33 mmol) was added dropwise over ca. 1 min, and the resulting mixture was stirred for 15 min. Another 100-mL, three-necked, round-bottomed flask equipped as above was charged with Ac_2O (0.46 g, 0.47 mL, 4.54 mmol) and 1.2 mL of THF and cooled to -50 °C. The lithium acetylide solution was transferred into the Ac_2O solution via cannula over 4 min. The resulting mixture was stirred at -50 °C for 30 min and then treated with 10 mL of saturated NH_4Cl solution and 1 mL of concentrated NH_4OH. The resulting two-phase mixture was allowed to warm to room temperature and diluted with 15 mL of Et_2O. The aqueous layer was separated and extracted with 15 mL of Et_2O, and the combined organic layers were washed with 15 mL of saturated NH_4Cl solution, 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.49 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.45 g (85%) of **173** as a pale yellow oil.

IR (film):	3300, 3060, 2920, 2190, 1675, 1595, 1410, 1345, 1270, 1215, 1000, 950, and 880 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.19-5.20 (m, 1 H), 5.13-5.15 (m, 1 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.41 (t, J = 6.8 Hz, 2 H), 2.30 (s, 3 H), 1.85 (t, J = 1.5 Hz, 3 H), and 1.79 (app quintet, J = 7.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	184.6, 126.9, 120.8, 82.6, 81.6, 32.6, 26.7, 23.6, 18.4, and 17.9 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{12}H_{13}O$ 173.0967 Found 173.0966.

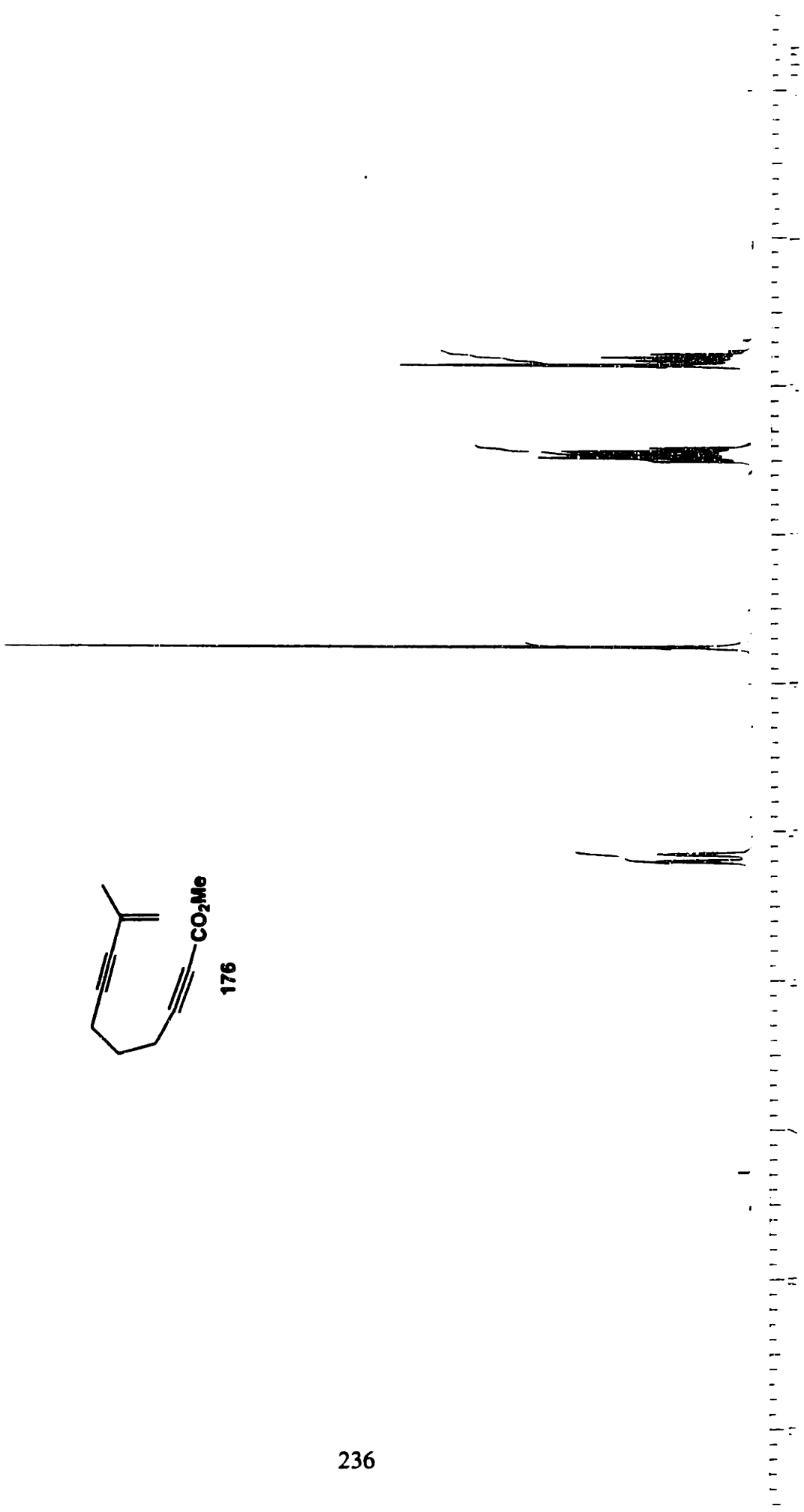

173
O
8.0
7.0
6.0
5.0
4.0
1.0
2.0
1.0
0.0 PPM



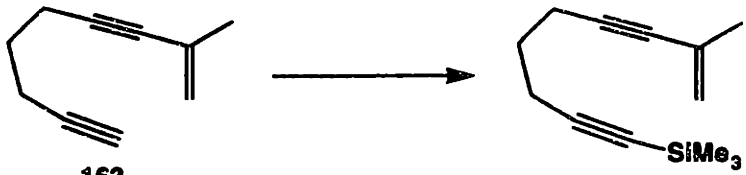
163 **176**

A 100-mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter and rubber septum was charged with 2-methyl-1-nonen-3,8-diyne **163** (0.500 g, 3.78 mmol) and 15 mL of THF and cooled at -50 °C. *n*-BuLi (2.47 M solution in hexane, 1.68 mL, 4.16 mmol) was added dropwise over 1 min. After 15 min, methyl chloroformate (0.535 g, 0.430 mL, 5.67 mmol) was added via syringe in one portion; the reaction mixture was allowed to warm to room temperature over 15 min. Water (10 mL) and 20 mL of Et_2O were added, and the organic phase was separated and washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.947 g of a yellow oil. Purification by column chromatography on 50 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.543 g (75%) of **176** as a colorless oil.

IR (film):	3400, 3090, 2950, 2240, 1715, 1610, 1435, 1370, 1330, 1310, 1250, 1080, 895, 810, and 750 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.20 (s, 1 H), 5.16 (s, 1 H), 3.76 (s, 3 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.44 (t, J = 6.7 Hz, 2 H), 1.86 (s, 3 H), and 1.81 (app quintet, J = 7.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	153.9, 126.8, 120.7, 89.6, 87.1, 82.9, 73.2, 52.5, 26.7, 23.7, 18.5, and 17.8 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{12}H_{13}O_2$ 189.0916 Found 189.0916.



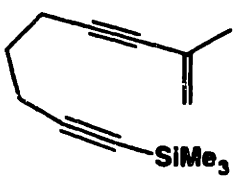
176



163 178

A 50-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, glass stopper, and rubber septum was charged with 2-methyl-1-nonen-3,8-diyne **163** (1.00 g, 7.56 mmol) and 15 mL of THF. The solution was cooled to 0 °C, and *n*-BuLi (2.71 M solution in hexane, 2.80 mL, 7.56 mmol) was added dropwise via syringe over 2 min. After 5 min, chlorotrimethylsilane (0.82 g, 0.96 mL, 7.56 mmol) was added via syringe in one portion, and the reaction mixture was allowed to warm to room temperature and then heated at reflux for 2 h. The solution was cooled to room temperature, poured into 10 mL of H_2O, and extracted with 15-mL and 10-mL portions of Et_2O. The combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.35 g of a colorless oil. Purification by column chromatography on 20 g of silica gel (elution with pentane) provided 1.38 g (90%) of **178** as a colorless oil.

IR (film):	3300, 3100, 2965, 2220, 2175, 1610, 1425, 1370, 1325, 1310, 1285, 1040, 1020, 940, 890, 840 (b), 755, and 690 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.20 (s, 1 H), 5.14 (s, 1 H), 2.40 (t, J = 7.2 Hz, 2 H), 2.34 (t, J = 7.1 Hz, 2 H), 1.86 (d, J = 2.5 Hz, 3 H), 1.74 (app quintet, J = 7.1 Hz, 2 H), and 0.14 (s, 9 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	127.1, 120.5, 106.3, 88.1, 85.0, 82.4, 28.0, 23.9, 19.2, 18.5, and 0.3 ppm.
HRMS	Calcd for $C_{13}H_{20}Si$ 204.1335 Found 204.1333.



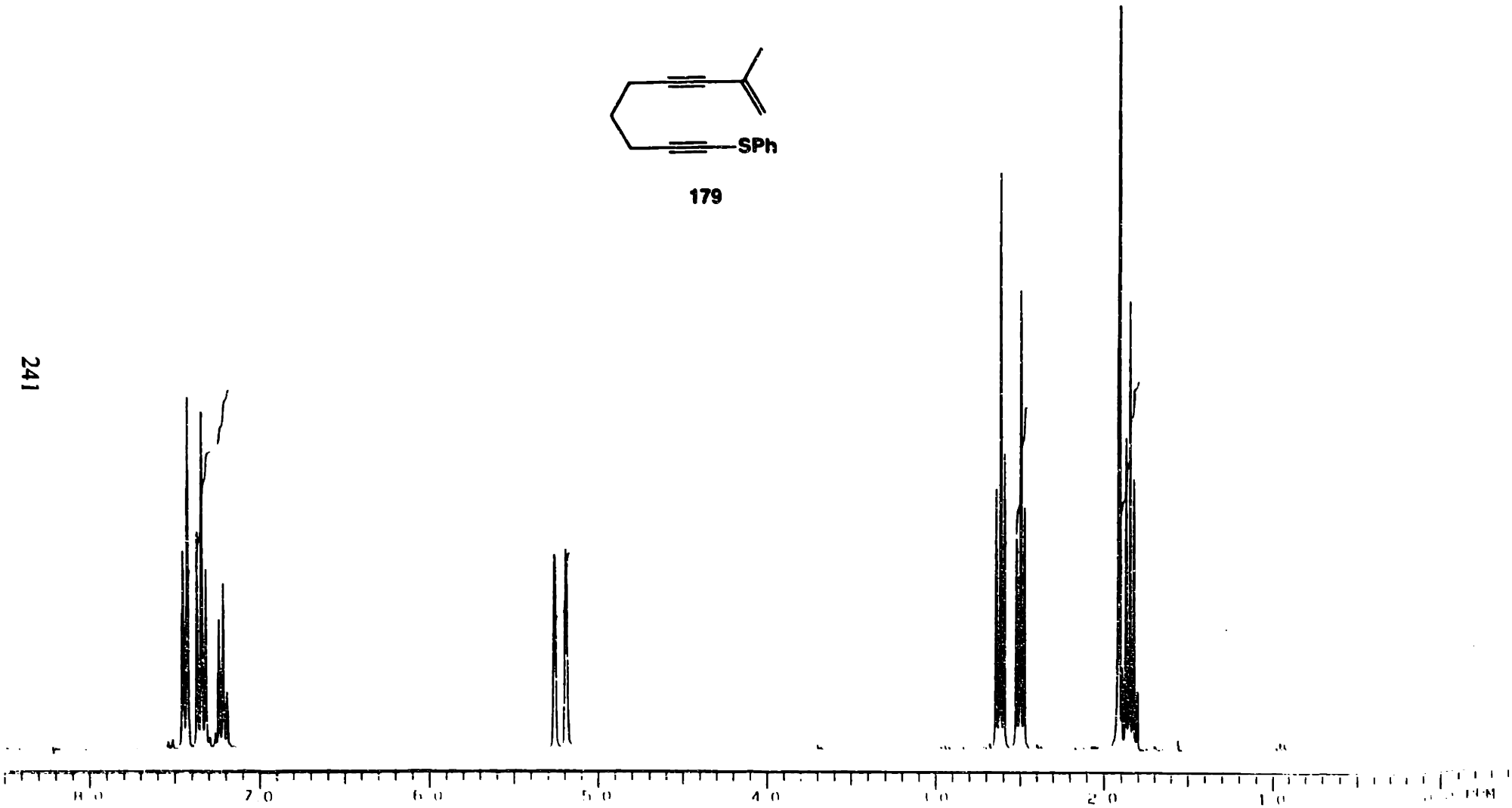
178

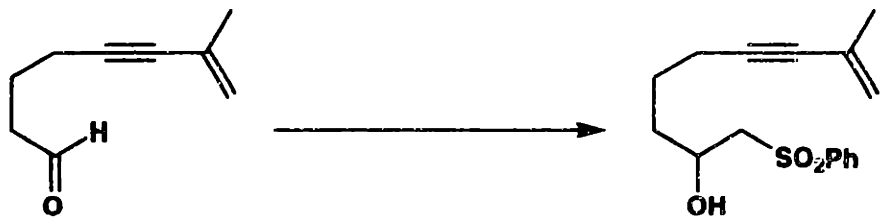
163 **179**

A 100-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, addition funnel, glass stopper, and rubber septum was charged with 2-methyl-1-nonen-3,8-diyne **163** (0.500 g, 3.78 mmol) and 45 mL of THF. The solution was cooled to -50 °C, and *n*-BuLi (2.71 M solution in hexane, 1.50 mL, 4.16 mmol) was added dropwise via syringe over 2 min. After 5 min, a solution of diphenyldisulfide (0.825 g, 3.78 mmol) in 10 mL of THF was added to the cooled reaction mixture dropwise via the addition funnel over 5 min, and the resulting mixture was stirred at -50 °C for 15 min. The cooling bath was removed, and 15 mL of a solution of saturated NH_4Cl and 20 mL of Et_2O were added to the reaction mixture. The organic phase was separated and washed with three 10-ml portions of saturated K_2CO_3 solution and once with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.3 g of a colorless oil. TLC showed some thiophenol remained in the crude reaction mixture, so the oil was redissolved in 20 mL of Et_2O and extracted with two 5-mL portions of saturated K_2CO_3 solution, once with 5 mL of 3% NaOH solution, and once with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. The oil was filtered through 40 g of Al_2O_3 using 3% ethyl acetate in hexane. Purification by column chromatography on 40 g of silica gel (elution 3% ethyl acetate in hexane) provided 0.581 g (64%) of **179** as a colorless oil.

IR (film):	3050, 2940, 2855, 2820, 2210, 1610, 1580, 1475, 1435, 1365, 1340, 1325, 1310, 1290, 1080, 1020, 890, and 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.44 (dd, *J* = 7.1, 1.6 Hz, 2 H), 7.34 (td, *J* = 7.9, 2.2 Hz, 2 H), 7.20 (dd, *J* = 7.0, 2.2 Hz, 1 H), 5.26 (d, *J* = 1.2 Hz, 1 H), 5.18-5.20 (m, 1 H), 2.62 (t, *J*

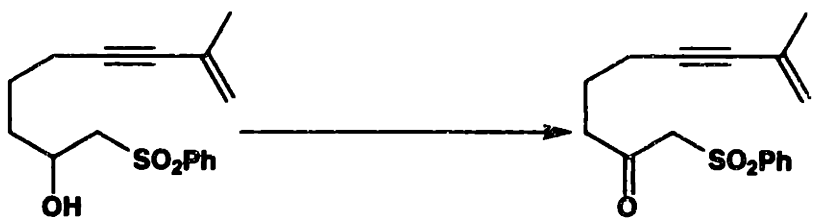
	= 7.0 Hz, 2 H), 2.49 (t, J = 7.0 Hz, 2 H), 1.91 (t, J = 1.5 Hz, 3 H), and 1.85 (t, J = 7.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	133.5, 129.0, 127.0, 126.1, 125.8, 120.6, 98.7, 87.8, 82.6, 65.6, 27.7, 23.7, 19.4, 18.4, and 12.4 ppm.


SPh
179
241
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM



191 192

A 50-mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter and rubber septum was charged with methyl phenyl sulfone (0.544 g, 3.48 mmol) and 6.6 mL of THF. This solution was cooled to 0 °C, and *n*-BuLi (1.38 mL, 3.49 mmol, 2.52 M solution in hexane) was added via syringe over 1 min. The resulting mixture was stirred for 5 min. A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum was charged with 7-methyl-7-octen-5-ynal **191** (0.226 g, 1.66 mmol) and 3 mL of THF. This solution was transferred via cannula to the sulfone solution over 1 min, and the resulting mixture was stirred for 20 min at 0 °C. Saturated NH_4Cl solution (5 mL) and 10 mL of Et_2O were then added. The aqueous phase was separated and extracted with 10 mL of Et_2O. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.64 g of a yellow oil. Purification by column chromatography on 120 g of silica gel (elution with 20% ethyl acetate in hexane) provided 0.711 g of a 51:49 mixture of **192** and methyl phenyl sulfone which was used directly in the next step.



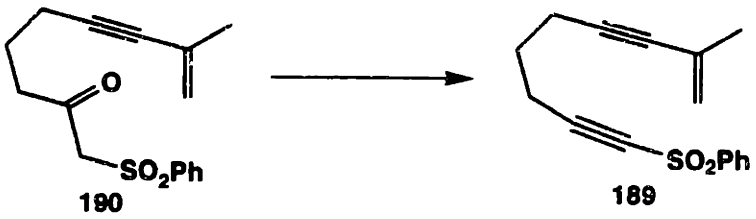
192 190

A 25-mL, one-necked, round-bottomed flask equipped with a nitrogen inlet adapter was charged with a 51:49 mixture of alcohol **192** and methyl phenyl sulfone prepared as described above (0.385 g) and 8.5 mL of CH_2Cl_2. This solution was cooled to ca. 8 °C,

and NaOAc (0.680 g, 8.30 mmol) was added in one portion. The solution was stirred for 5 min, and then pyridinium chlorochromate (1.25 g, 5.80 mmol) was added in one portion. After 30 min, the brown slurry was then applied to 10 g of silica gel and eluted with CH_2Cl_2 to give 0.323 g of a yellow oil. Purification by column chromatography on 30 g of silica gel (elution with 20% ethyl acetate in hexane) provided 0.146 g (60%) of **190** as a colorless oil.[213]

^{1}H NMR (300 MHz, $CDCl_3$)	7.88-7.91 (m, 2 H), 7.66-7.69 (m, 1 H), 7.56-7.61 (m, 2 H), 5.16-5.21 (m, 1 H), 5.15-5.16 (m, 1 H), 4.18 (s, 2 H), 2.86 (app t, J = 7.2 Hz, 2 H), 2.32 (app t, J = 6.8 Hz, 2 H), 1.87 (s, 3 H), and 1.79 (app quintet, J = 6.9 Hz, 2 H) ppm.

[213] Other yields for this reaction ranged from 56 to 60%.

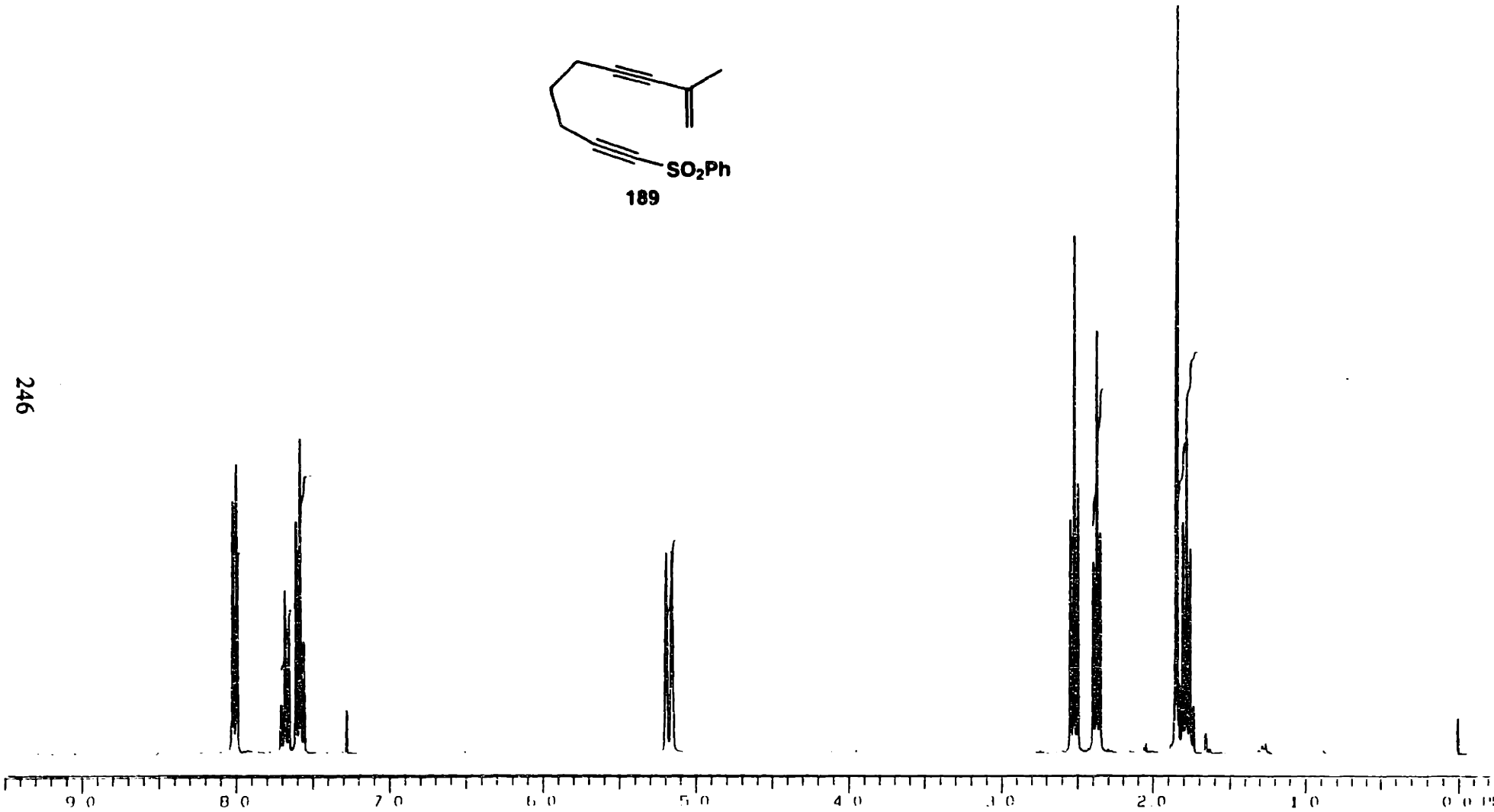


A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 9-methyl-1-phenylsulfonyl-9-nonen-7-yn-3-one **190** (0.130 g, 0.447 mmol) and 2.2 mL of CH_2Cl_2. The solution was cooled to 0 °C, and N,N-diisopropylethylamine (0.171 g, 0.230 mL, 1.34 mmol) was added dropwise via syringe over 1 min. After 2 min, trifluoromethanesulfonic anhydride (0.126 g, 0.075 mL, 0.447 mmol) was added via syringe in one portion. The reaction mixture was stirred at 0 °C for 3 h and then treated with 1 mL of saturated NH_4Cl solution and 5 mL of CH_2Cl_2. The aqueous phase was separated and extracted with three 2-mL portions of CH_2Cl_2, and the combined organic layers were then washed with two 5-mL portions of saturated NH_4Cl solution, two 5-mL portions of H_2O, and 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.121 g of a pale yellow oil. Column chromatography on 10 g of silica gel (elution with 20% ethyl acetate in hexane) provided 0.094 g (72%) of **189** as a colorless oil.[214]

IR (film):	3085, 3060, 2940, 2200, 1730, 1610, 1580, 1445, 1370, 1325 (b), 1290, 1240, 1155, 1085, 1040, 995, 950, 895, 835, 755, 725, and 680 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.00 (dd, J = 7.3, 2.0 Hz, 2 H), 7.66-7.71 (m, 1 H), 7.58 (td, J = 7.4, 1.3 Hz, 2 H), 5.19-5.20 (m, 1 H), 5.15-5.17 (m, 1 H), 2.52 (t, J = 7.3 Hz, 2 H), 2.37 (t, J = 6.6 Hz, 2 H), 1.84 (s, 3 H), and 1.78 (app quintet, J = 7.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	141.8, 134.0, 129.3, 127.2, 126.8, 121.0, 96.6, 86.6, 83.2, 78.5, 26.1, 23.6, 18.4, and 17.9 ppm.

[214] Other yields for this reaction ranged from 53 to 74%.

HRMS	Calcd for $C_{16}H_{16}SO_2$	272.0872
	Found	272.0869.

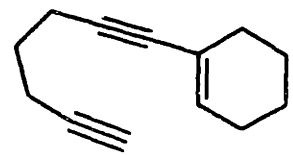

SO2Ph
189
246
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

167 **164**

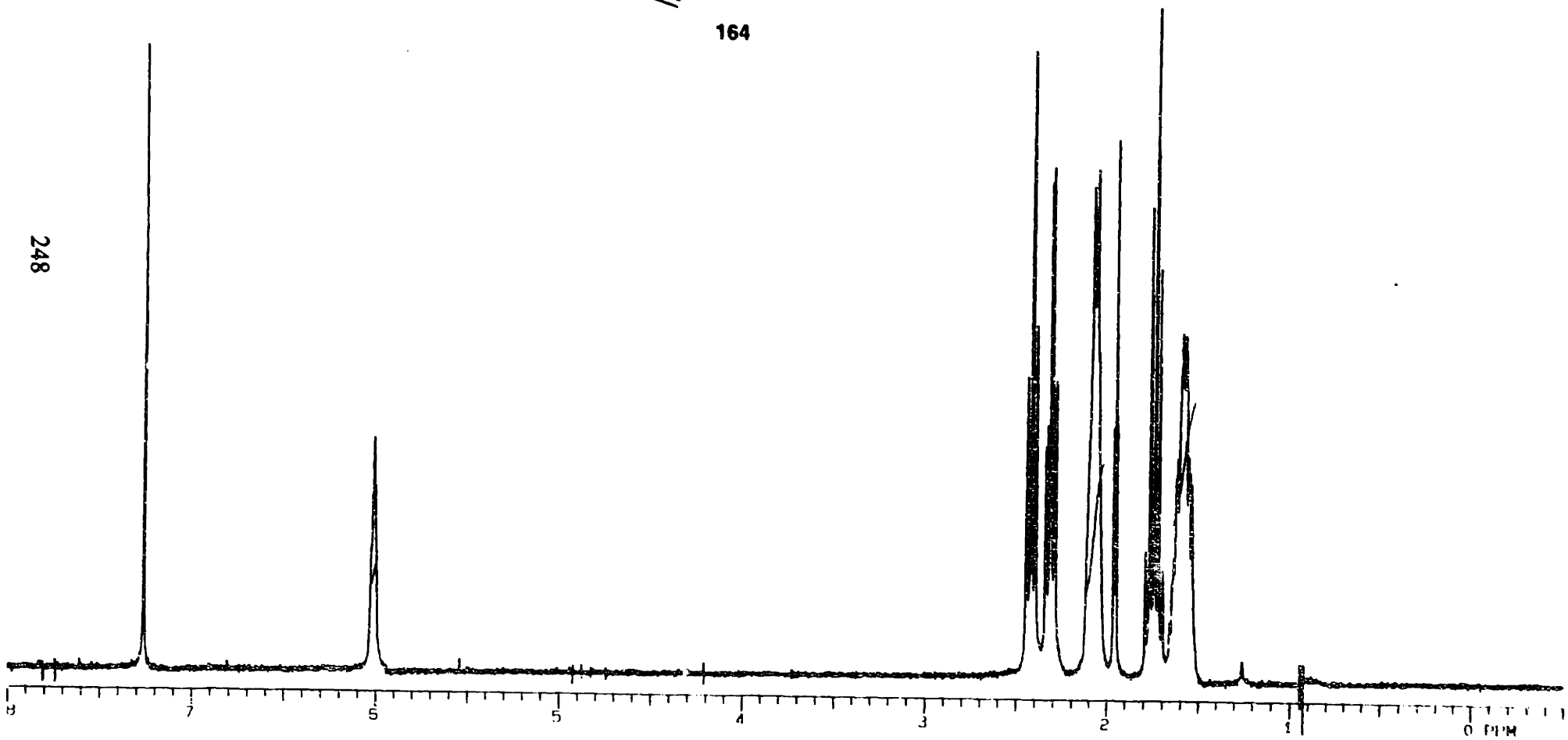
A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and nitrogen inlet adapter was charged with 1-ethnylcyclohexene **167** (2.55 mL, 2.30 g, 21.7 mmol) and 72 mL of THF. This flask was cooled to -50°C, and *n*-BuLi (8.6 mL of a 2.52 M solution in hexane, 21.7 mmol) was added dropwise via syringe. After 5 min, 1-iodo-4-pentyne (4.20 g, 21.7 mmol) and HMPA (22.3 g, 23.0 mL, 130 mmol) were added. This reaction mixture was allowed to warm to room temperature over 2 h, and 35 mL of saturated NH_4Cl solution and 50 mL of Et_2O were added. The aqueous layer was extracted with 25 mL of Et_2O . The combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 4.3 g of a slightly yellow oil. Purification by column chromatography on 100 g of silica gel (elution with hexane) provided 2.39 g (64%) of **164** as a pale yellow oil.[215]

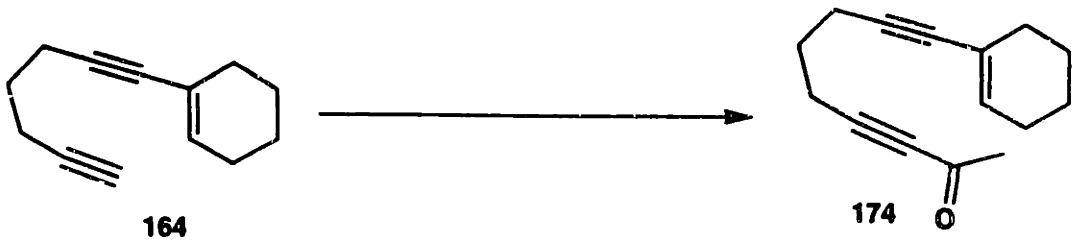
IR (film):	3290, 3020, 2920, 2860, 2110, 1430, 1340, 1265, 1235, 1205, 1130, 1070, 1030, 915, and 840 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.00-6.02 (m, 1 H), 2.42 (t, J = 7.0 Hz, 2 H), 2.32 (td, J = 7.1, 2.7 Hz, 2 H), 2.06-2.09 (m, 4 H), 1.96 (t, J = 2.7 Hz, 1 H), 1.76 (app quintet, J = 7.0 Hz, 2 H), and 1.53-1.70 (m, 4 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	133.1, 120.7, 85.7, 83.4, 82.9, 68.6, 29.5, 27.8, 25.5, 22.4, 21.6, 18.3, and 17.5 ppm.
HRMS	Calcd for $C_{13}H_{16}$ 172.1253 Found 172.1231.

[215] Other yields for this reaction ranged from 46 to 68%.



164



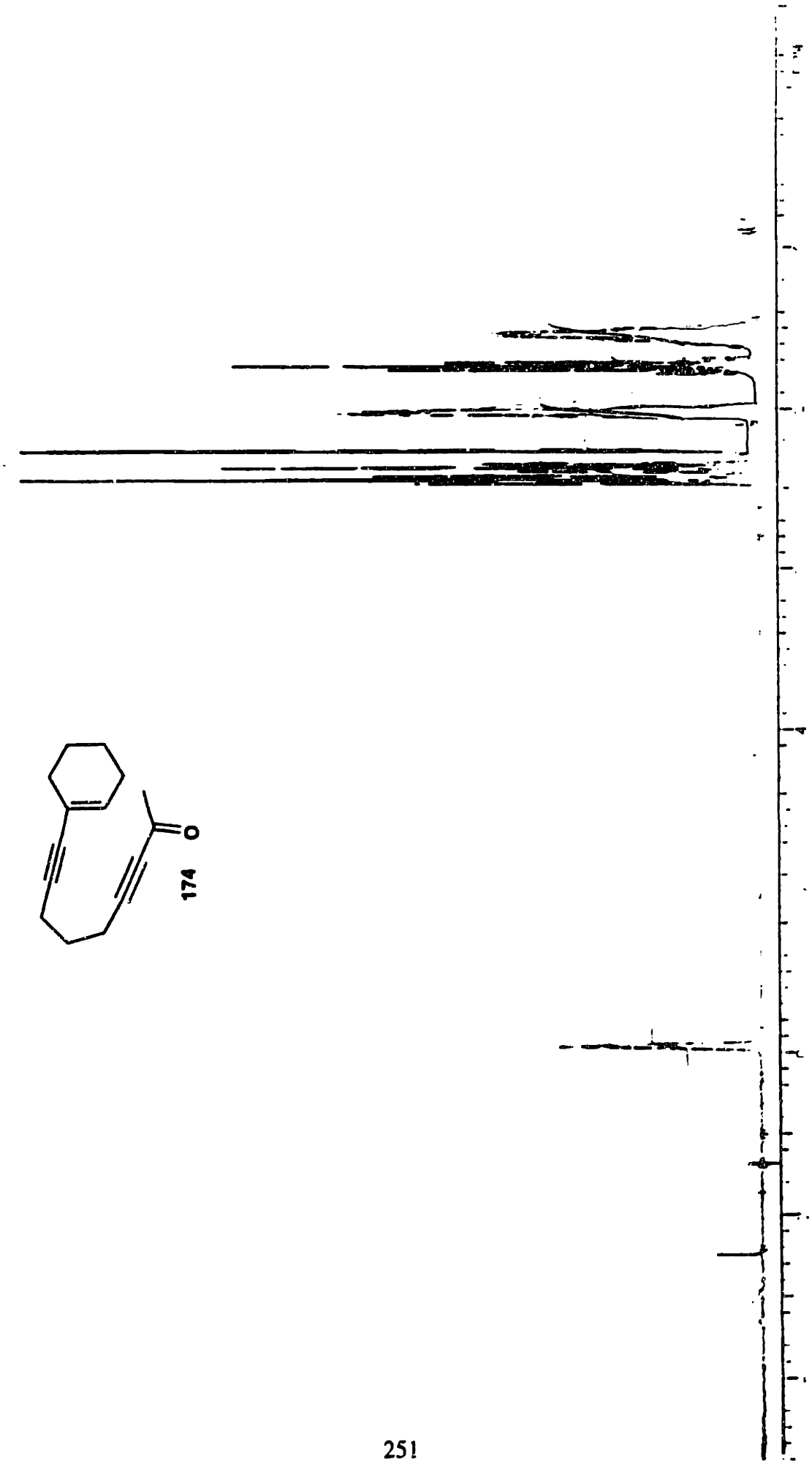


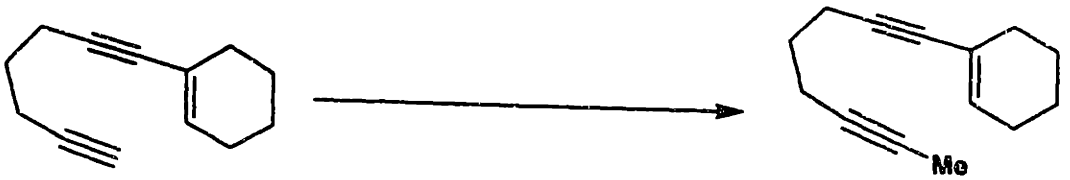
164 174

A 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and glass stopper was charged with 1-(1,6-heptadiynyl)cyclohexene **164** (1.27 g, 7.35 mmol) and 70 mL of THF. The solution was cooled to -50 °C, and *n*-BuLi (3.30 mL, 2.45 M solution in hexane, 8.08 mmol) was added dropwise over 2 min and then stirred at -50 °C for 15 min. Another three-necked, round-bottomed flask equipped as above was charged with acetic anhydride (1.13 g, 1.15 mL, 11.0 mmol) and 10 mL of THF and cooled to -50 °C. The lithium acetylide solution was then added to the acetic anhydride solution via cannula over 2 min with stirring. After 30 min, 40 mL of saturated NH_4Cl solution and 4 mL of concentrated NH_4OH were added to the reaction mixture, which was then warmed to room temperature. The reaction mixture was extracted with 70-mL and 40-mL portions of Et_2O, and the combined organic phases were washed with 25 mL of saturated NH_4Cl solution, 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 2.1 g of a yellow oil. Purification by column chromatography on 100 g of silica gel (elution with 3% ethyl acetate in hexane) provided 1.31 g (85%) of **174** as a yellow oil.

IR (film):	3330, 3020, 2930, 2870, 2860, 2660, 2220, 1770, 1740, 1680, 1455, 1435, 1360, 1330, 1415, 1295, 1235, 1140, 1080, 1050, 1020, 970, 920, 845, and 800 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.96 (t, J = 1.8 Hz, 1 H), 2.44 (t, J = 7.1 Hz, 2 H), 2.37 (t, J = 6.9 Hz, 2 H), 2.26 (s, 3 H), 1.95-2.02 (m, 4 H), 1.73 (app quintet, J = 7.0 Hz, 2 H), and 1.48-1.58 (m, 4 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$)	184.6, 133.6, 120.6, 92.8, 85.1, 83.4, 81.5, 32.6, 29.4, 26.9, 25.4, 22.2, 21.4, 18.4, and 17.9 ppm.

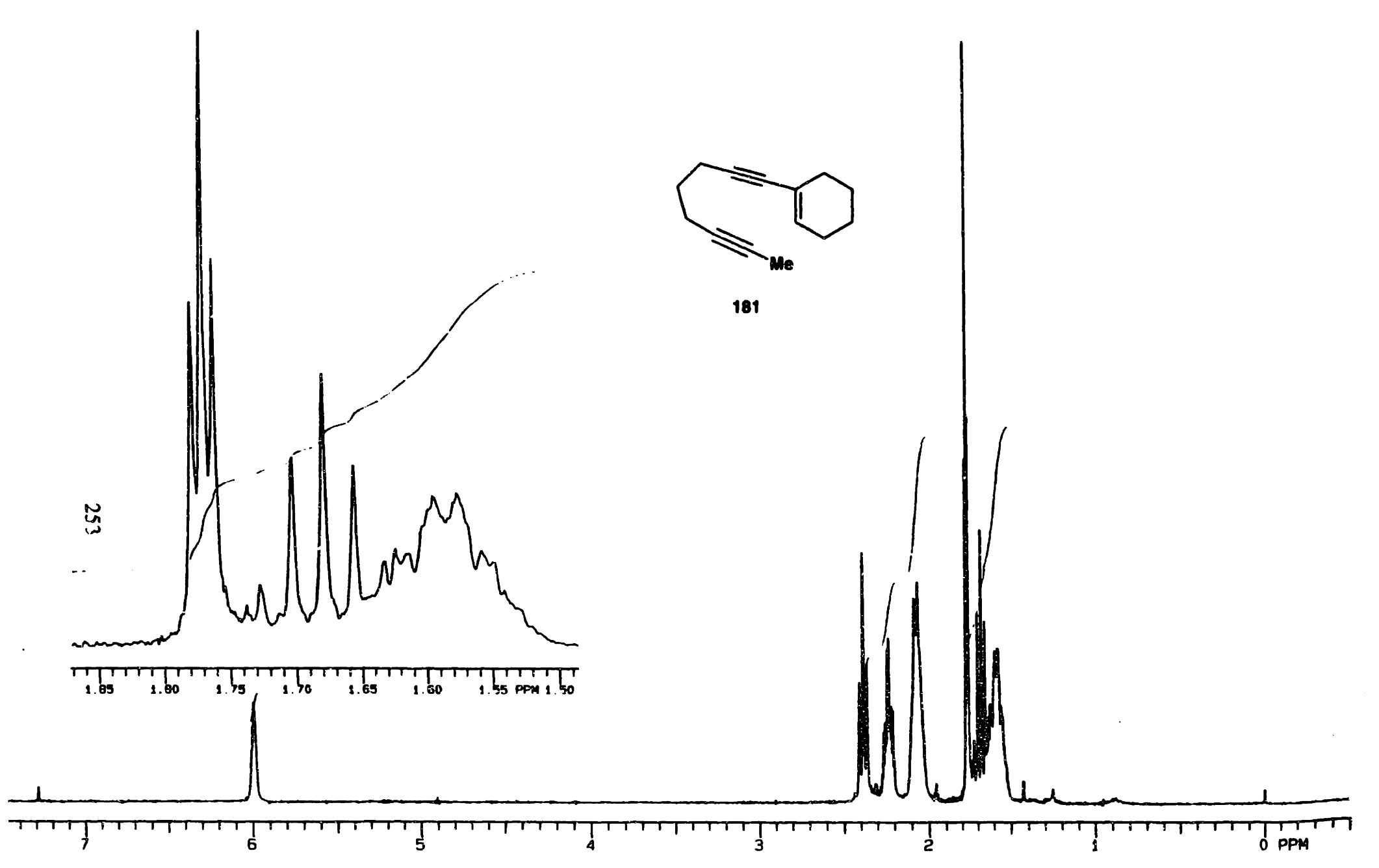

O
174

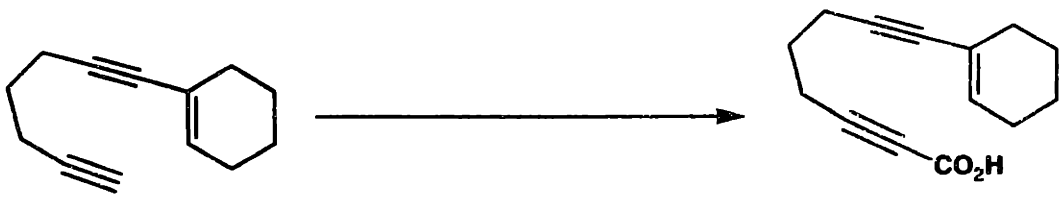


164 **181**

A 25-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and glass stopper was charged with 1-(1,8-nondiynyl)cyclohexene **164** (0.268 g, 1.56 mmol) and 5.2 mL of THF. The solution was cooled to -50°C, and *n*-BuLi (0.71 mL of a 2.52 M solution in hexane, 1.79 mmol) was added dropwise over 1 min. The reaction mixture was stirred for 15 min, and then methyl iodide (0.290 mL, 0.664 g, 4.68 mmol) was added dropwise via syringe over 1 min. The reaction mixture was allowed to warm to room temperature over 30 min and then was quenched with 2 mL of saturated NH_4Cl and 5 mL of Et_2O. The organic phase was separated and extracted with 2 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.245 g of a colorless oil. Purification by column chromatography on 12 g of silica gel (elution with hexane) gave 0.225 g (77%) of **181** as a colorless oil.

IR (film):	3025, 2925, 2860, 2835, 1430, 1355, 1310, 1290, 1270, 1240, 1210, 1130, 1070, and 1050 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.99 (app d, J = 1.8 Hz, 1 H), 2.39 (t, J = 7.0 Hz, 2 H), 2.23 (tquartet, J= 7.0, 2.4 Hz, 2 H), 2.06-2.08 (m, 4 H), 1.77 (t, J = 2.7 Hz, 3 H), 1.68 (app quintet, J = 7 Hz, 2 H), and 1.54-1.62 (m, 4 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	133.1, 120.8, 86.2, 82.7, 78.2, 75.9, 29.6, 28.5, 25.6, 22.4, 21.6, 18.5, 18.0, and 3.5 ppm.

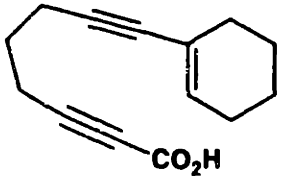

Me
181
253
1.85
1.80
1.75
1.70
1.65
1.60
1.55 PPM 1.50
7
6
5
4
3
2
1
0 PPM



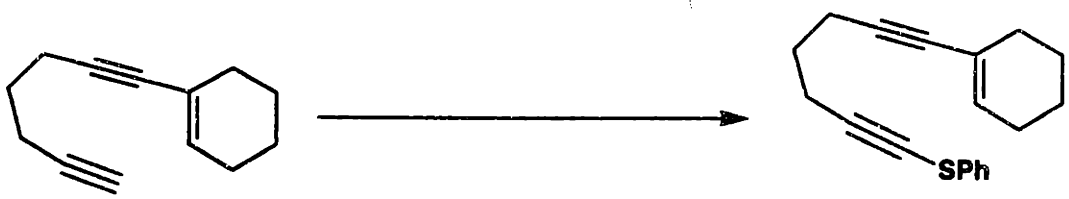
164 **180**

A 100-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and glass stopper was charged with 1-(1,8-nondiynyl)cyclohexene **164** (0.500 g, 2.90 mmol) and 29 mL of THF. The solution was cooled to -50 °C, and *n*-BuLi (1.30 mL of a 2.45 M solution in hexane, 3.19 mmol) was added dropwise over 2 min. The reaction mixture was stirred for 15 min, and the rubber septum was replaced with a gas inlet adapter attached through an empty drying tube to a CO_2 (gas) tank. A steady stream of CO_2 was bubbled through the reaction mixture for 20 min. The reaction mixture was warmed to room temperature, and 10 mL of saturated NH_4Cl solution and 20 mL of Et_2O were added. The aqueous phase was washed with 20 mL of Et_2O, and the combined organic phases were extracted with two 15-mL portions of 3% NaOH solution. The combined basic aqueous phases were then treated with 10% HCl solution until the solution reached pH 3. The resulting cloudy solution was extracted twice with 20 mL of Et_2O, and the combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.626 g of a yellow oil. Purification by column chromatography on 12 g of silica gel (elution with 20% ethyl acetate in hexane) provided 0.560 g (89%) of **180** as a yellow solid.

IR (film):	3000 (broad), 2640, 2520, 2230, 1700, 1400, 1330, 1260, 1130, 1045, 915, and 840 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	11.5 (s, 1 H), 5.97 (s, 1 H), 2.47 (d, J = 7.0 Hz, 2 H), 2.39 (t, J = 6.8 Hz, 2 H), 2.03-2.08 (m, 4 H), 1.76 (app quintet, J = 6.9 Hz, 2 H), and 1.52-1.58 (m, 4 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	158.3, 133.7, 120.6, 91.5, 85.0, 83.6, 72.9, 29.5, 26.8, 25.6, 22.4, 21.6, 18.6, and 17.9 ppm.



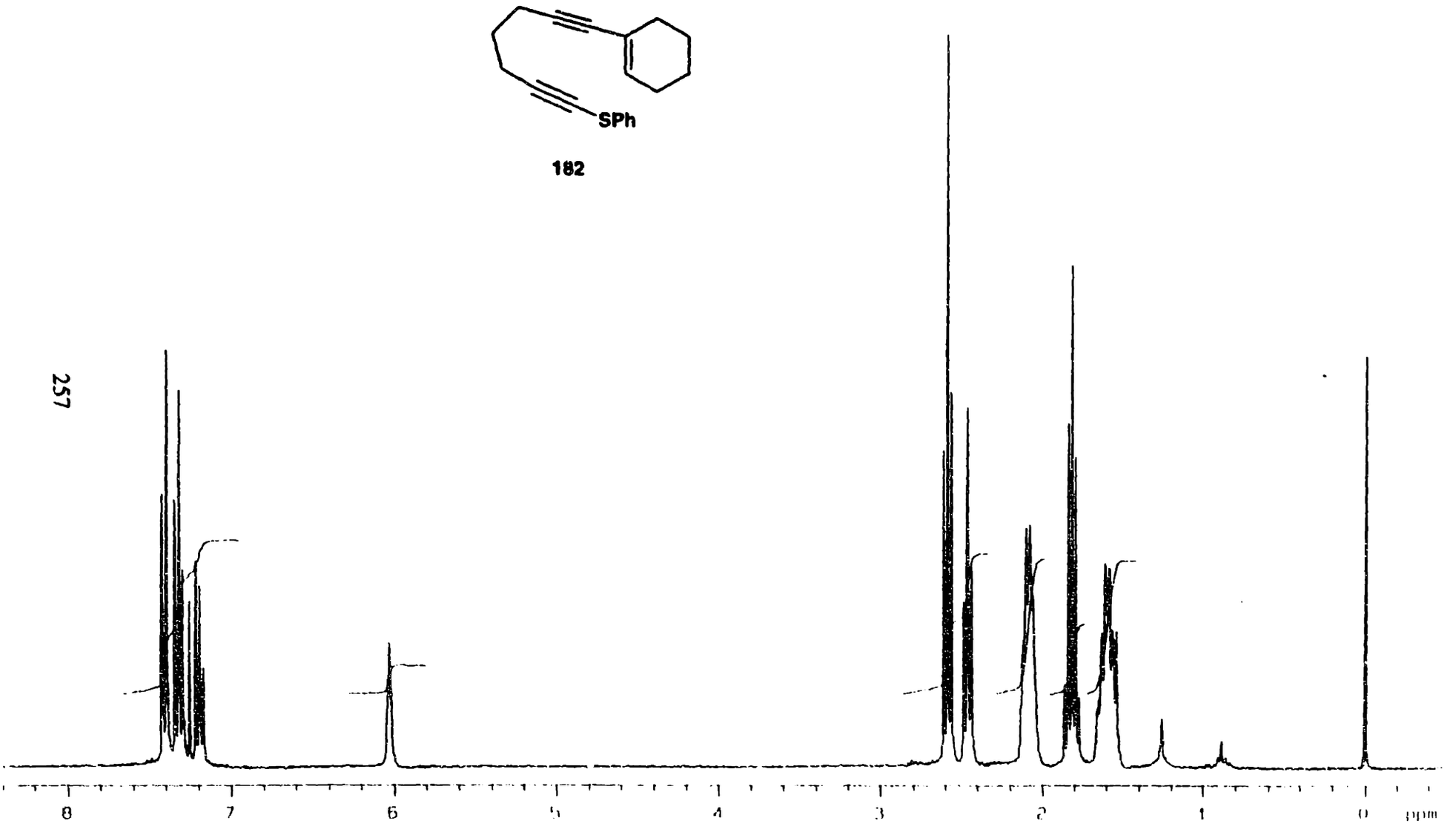
180



164 182

A 50-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, addition funnel, glass stopper, and rubber septum was charged with 1(1,8-nondiynyl)cyclohexene **164** (0.200 g, 1.16 mmol) and 12 mL of THF. The solution was cooled to -50 °C, and *n*-BuLi (2.71 M solution in hexane, 1.50 mL, 4.16 mmol) was added dropwise via syringe over 2 min. After 5 min, a solutiont of diphenyldisulfide (0.304 g, 1.40 mmol) in 1.5 mL of THF was added to the cooled reaction mixture dropwise over 5 min via the addition funnel, and the reaction mixture was stirred at -50 °C for 30 min. The cooling bath was removed, and 5 mL of a solution of saturated NH_4Cl and 5 mL of Et_2O were added to the reaction mixture. The aqueous phase was extracted with 5 mL Et_2O, and the combined organic phases were washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.429 g of a colorless oil. Purification by column chromatography on 12 g of silica gel (elution 5% ethyl acetate in hexane) provided 0.504 g (>100%) of **181** as a colorless oil. This material was contaminated with thiophenol, which was removed by extraction with saturated K_2CO_3 solution.

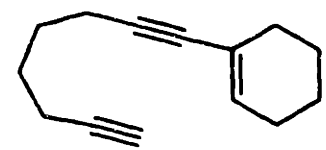
IR (film):	3050, 3020, 2930, 2850, 2825, 2320, 1580, 1475, 1440, 1340, 1325, 1305, 1265, 1235, 1205, 1170, 1130, 1080, 1045, and 1020 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.39-7.43 (m, 2 H),7.29-7.35 (m, 2 H), 7.17-7.22 (m, 1 H), 6.02-6.05 (m, 1 H), 2.59 (t, J = 6.9 Hz, 2 H), 2.46 (t, J = 6.9 Hz, 2 H), 2.05-2.13 (m, 4 H), 1.82 (app quintet, J = 6.9 Hz, 2 H), and 1.54-1.66 (m, 4 H) ppm.


SPh
182
257
8
7
6
5
4
3
2
1
0
ppm

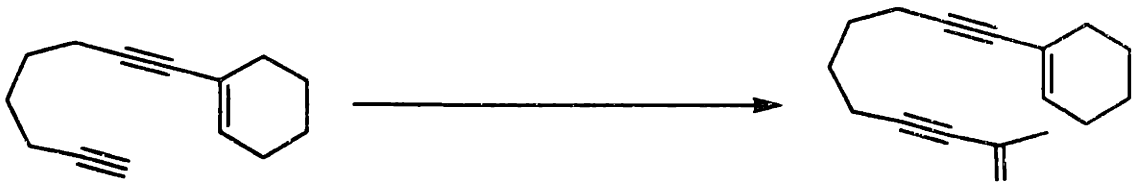
167 172

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and nitrogen inlet adapter was charged with 1-ethynylcyclohexene **167** (2.0 mL, 1.81 g, 17.0 mmol) and 57 mL of THF. This flask was cooled to -50 °C, and *n*-BuLi (7.60 mL, 2.45 M solution in hexane, 18.7 mmol) was added dropwise via syringe over 5 min. After 10 min, 1-iodo-5-hexyne (3.54 g, 17.0 mmol) and HMPA (20.6 g, 20.0 mL, 115 mmol) were added. The resulting mixture was allowed to warm to 0 °C over 2 h, and then 25 mL of saturated NH_4Cl solution were added. The aqueous phase was separated and extracted twice with 25 mL of Et_2O. The combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 6.3 g of a yellow oil. Purification by column chromatography on 300 g of silica gel (elution with pentane) provided 2.52 g (79%) of **172** as a yellow oil.

IR (film):	3300, 3020, 2920, 2850, 2240, 2110, 1430, 1325, 1265, 1130, 910, 840, 795, and 735 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.97-6.00 (m, 1 H), 2.28-2.32 (m, 2 H), 2.17-2.23 (m, 2 H), 2.01-2.09 (m, 4 H), 1.92 (t, J = 2.5 Hz, 1 H), and 1.52-1.64 (m, 8 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	133.2, 120.8, 86.6, 84.2, 82.7, 68.4, 29.6, 27.9, 27.6, 25.6, 22.5, 21.7, 18.9, and 18.1 ppm.
HRMS	Calcd for $C_{14}H_{18}$ 186.1409 Found 186.1411.



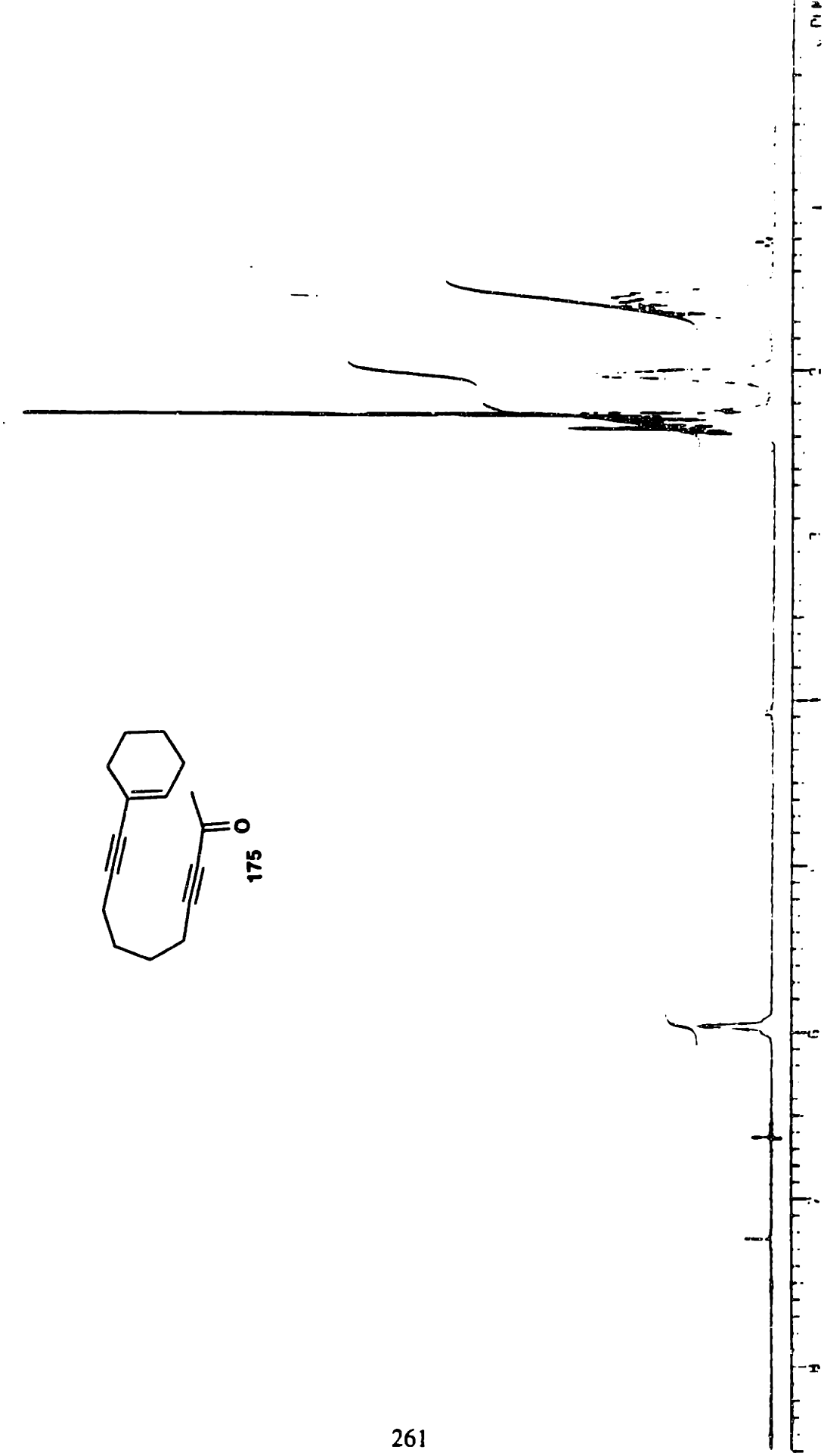
172



172 175

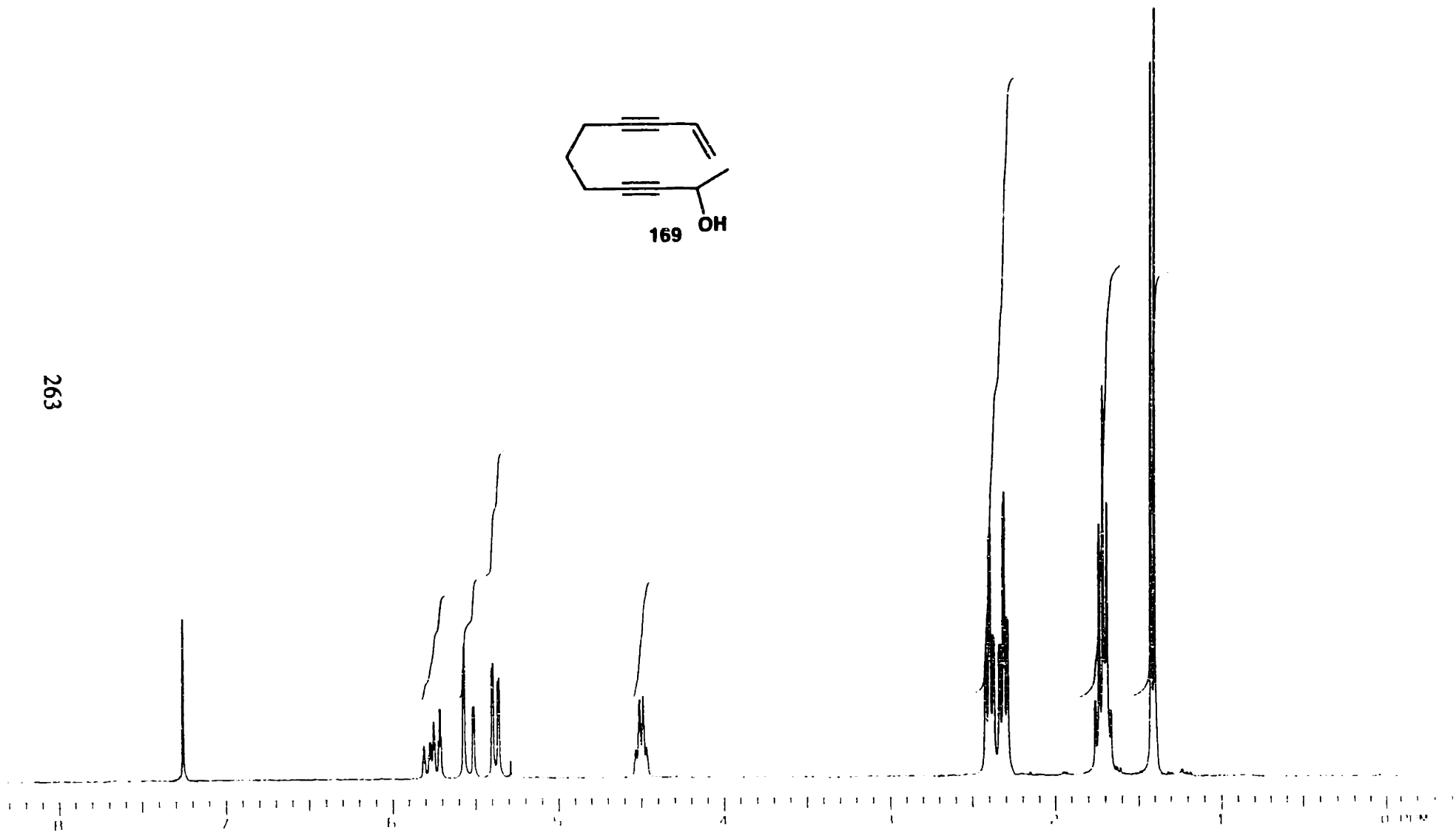
A 100-mL, one-necked, round-bottomed flask equipped with a nitrogen inlet needle and rubber septum was charged with 1-(1,7-octadiynyl)cyclohexene **172** (0.949 g, 5.09 mmol) and 50 mL of THF. The solution was cooled to -50 °C, and *n*-BuLi (2.28 mL, 2.45 M solution in hexane, 5.60 mmol) was added dropwise over 3 min. After 15 min, another three-necked, round-bottomed flask equipped as above was charged with acetic anhydride (0.775 g, 0.790 mL, 7.59 mmol) and 20 mL of THF and cooled to -50 °C. The lithium acetylide solution was then added to the acetic anhydride solution via cannula with stirring over 8 min. After 30 min, 25 mL of saturated NH_4Cl solution and 2 mL of concentrated NH_4OH were added to the reaction mixture, which was allowed to warm to room temperature. The aqueous phase was separated and extracted with 30-mL and 20-mL portions of Et_2O. The combined organic phases were washed with 25 mL of saturated NH_4Cl solution, 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.5 g of a yellow oil. Purification by column chromatography on 150 g of silica gel (gradient elution with hexane to 3% ethyl acetate in hexane) provided 0.911 g (94%) of **175** as a yellow oil.

IR (film):	3330, 3020, 2930, 2860, 2835, 2205, 1675, 1430, 1360, 1325, 1225, 1130, 1070, 1040, 1015, 965, 915, 840, and 800 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.96 (s, 1 H), 2.25-2.38 (m, 7 H), 2.00-2.04 (m, 4 H), and 1.51-1.68 (m, 8 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	184.5, 133.3, 120.7, 93.4, 86.2, 82.9, 81.5, 32.8, 29.6, 27.9, 26.8, 25.6, 22.4, 21.6, 18.8, and 18.6 ppm.


O
175

A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with 3,8-nonadiyn-2-ol **168** (0.296 g, 2.17 mmol), 11 mL of diethylamine, and a solution of vinyl bromide (1.74 mL, 3.48 mmol, 2 M solution in diethyl ether). This solution was cooled to about 4 °C in an ice water bath, and $Pd(Ph_3P)_4$ (63 mg, 0.054 mmol) and copper(I) iodide (5 mg, 0.026 mmol) were added to the reaction mixture, which was then allowed to warm to room temperature and stirred for 21 hours. The mixture was then filtered, and the precipitate was rinsed with 10 mL of Et_2O. The filtrate was extracted with 5 mL of saturated NH_4Cl solution, and the organic phase was washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Purification by column chromatography on 15 g of silica gel (gradient elution with 10-20% ethyl acetate in hexane) gave 0.291 g of a yellow/orange oil. This oil was dried to constant weight to give 0.246 g of **169** (70%).

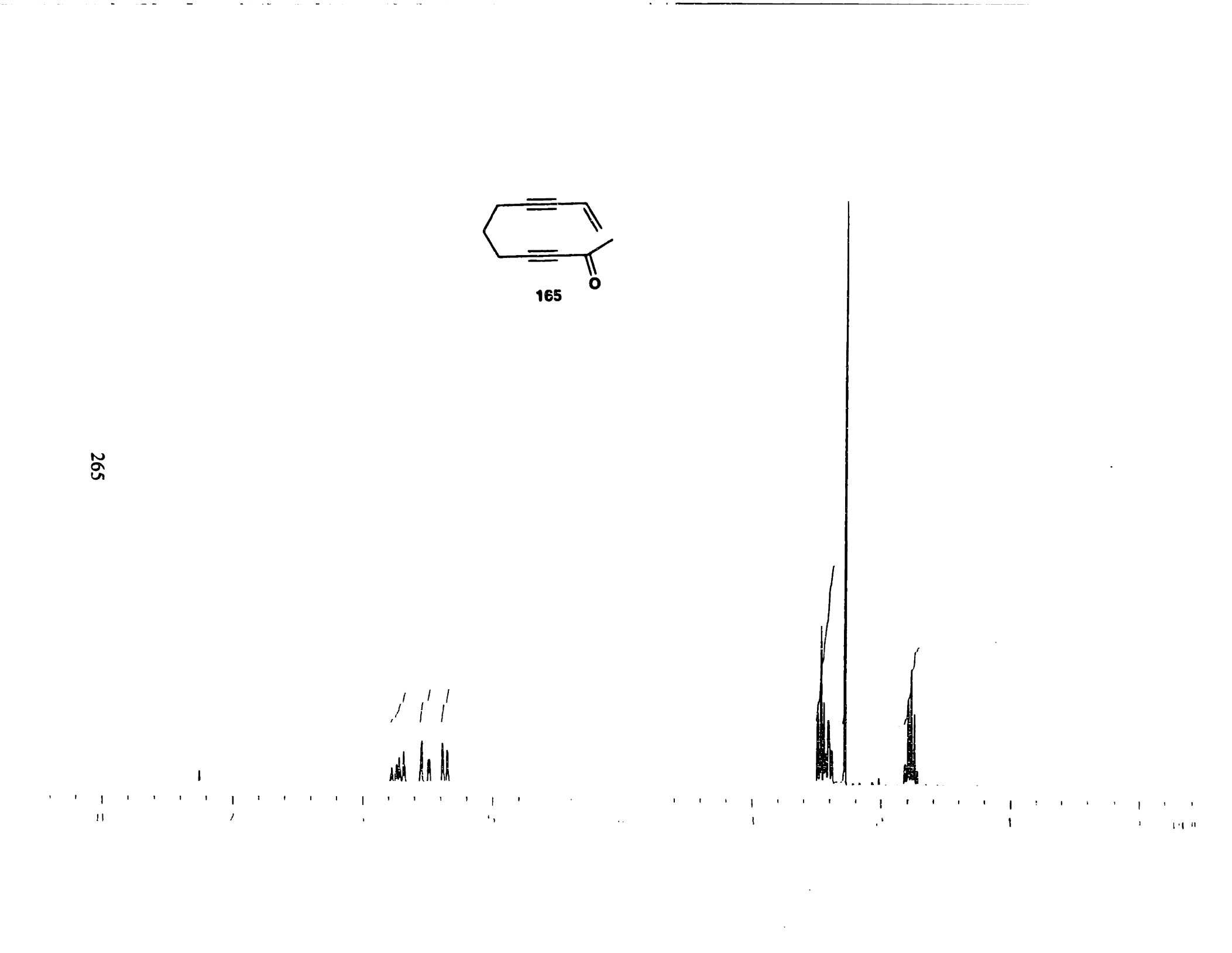
IR (film):	3340, 3195, 2975, 2930, 2900, 2835, 2300, 2220, 1840, 1607, 1450, 1435, 1415, 1375, 1330, 1290, 1155, 1075, 1010, 920, and 890 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.77 (ddt, J = 17.6, 11.0, 2.0 Hz, 1 H), 5.55 (dd, J = 17.5, 2.2 Hz, 1 H), 5.38 (dd, J = 10.9, 2.2 Hz, 1 H), 2.41 (td, J = 6.9, 1.9 Hz, 2 H), 2.33 (td, J = 6.9, 1.8 Hz, 2 H), 1.73 (app quintet, J = 7 Hz, 2 H), and 1.43 (d, J = 6.5 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	125.8, 117.4, 89.8, 83.5, 82.9, 79.9, 58.6, 27.7, 24.7, 18.5, and 17.8 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{11}H_{13}O$ 161.0966 Found 161.09670.

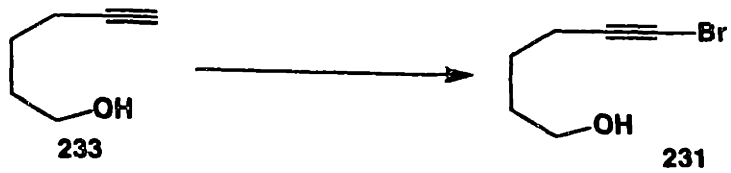

OH
169
263

169 165

A 25-mL, one-necked, round-bottomed flask equipped with an argon inlet adapter was charged with the 10-undecen-3,8-diyn-2-ol **169** (0.150 g, 0.915 mmol), NaOAc (0.375 g, 4.57 mmol), and 10 mL of CH_2Cl_2. This solution was cooled to about 8 °C and stirred for 5 min. Pyridinium chlorochromate (0.69 g, 3.2 mmol) was added, and after 20 min at 8 °C, more pyridinium chlorochromate (0.200 g, 0.928 mmol) was added, as the reaction was not complete. After 10 min, this slurry was applied to the top of 2 g of silica gel and eluted with CH_2Cl_2 to give 0.250 g of a yellow oil. Purification of this oil by column chromatography on 5 g of silica gel (gradient elution with 10-20% Et_2O in pentane) gave 0.115 g of **165** as a colorless oil (78%).

IR (film):	3040, 3000, 2930, 2200, 1675, 1415, 1355, 1260, 1225, 1010, 970, 915, and 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.73 (ddt, J = 17.7, 11.0, 2.1 Hz, 1 H), 5.52 (dd, J = 17.7, 2.4 Hz, 1 H), 5.37 (dd, J = 11.1, 2.4 Hz, 1 H), 2.49 (t, J = 7.0 Hz, 2 H), 2.43 (td, J = 6.9, 2.1 Hz, 2 H), 2.31 (s, 3 H), and 1.73 (app quintet, J = 7.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	184.7, 126.1, 117.3, 92.6, 89.0, 81.7, 80.4, 32.7, 26.7, 18.5, and 18.0 ppm.
HRMS	Calcd for $C_{11}H_{12}O$ 160.08882 Found 160.08847.

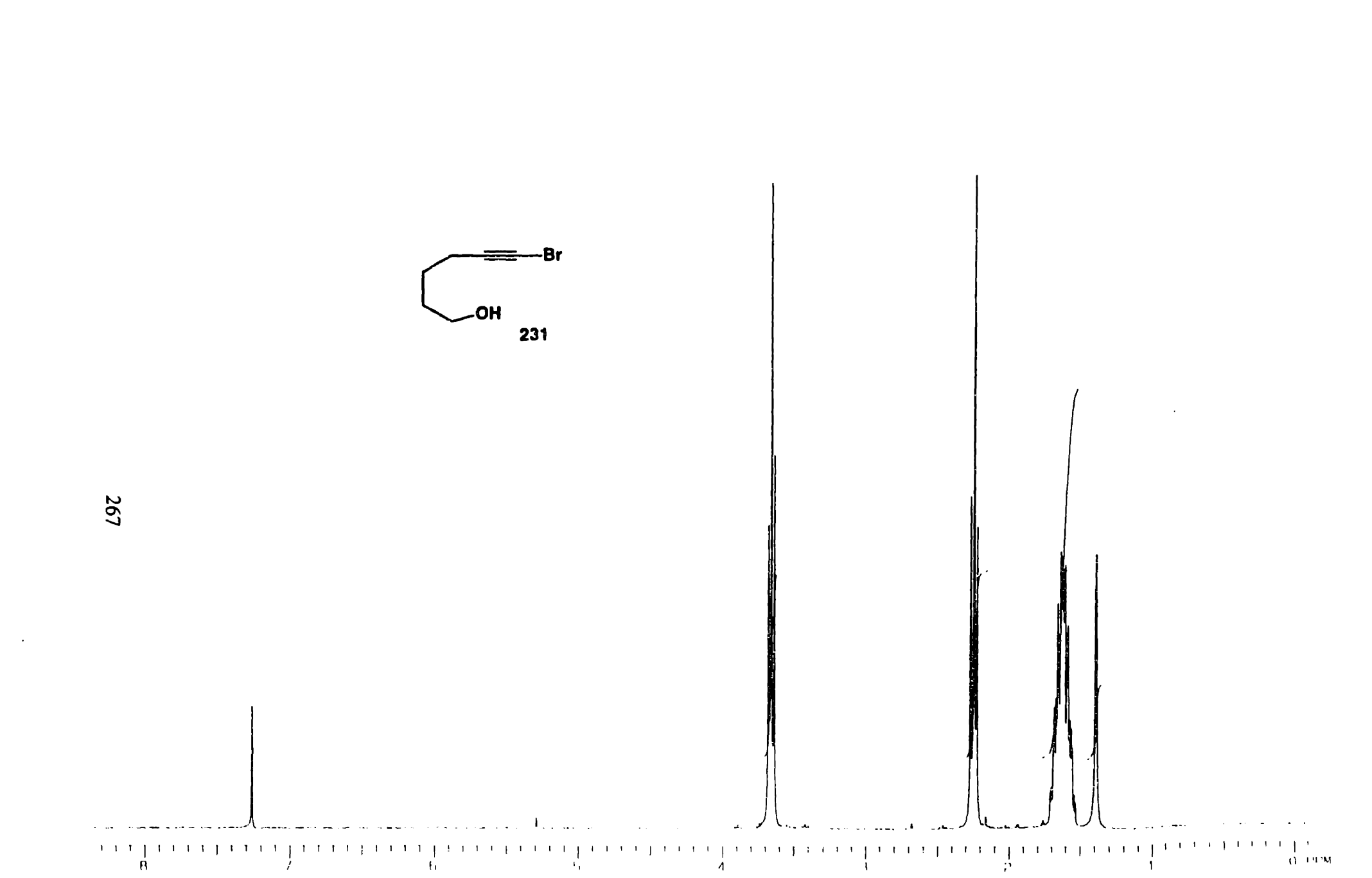

O
165
265



233 231

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 5-hexyn-1-ol **233** (1.68 mL, 1.50 g, 15.28 mmol), 100 mL of acetone, *N*-bromosuccinimide (3.00 g, 16.81 mmol), and silver nitrate (0.260 g, 1.53 mmol). After 4 hours at room temperature, the reaction mixture was concentrated to about 50 mL. Water (15 mL) and 30 mL of Et_2O were added. The aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 3.42 g of a colorless oil. Purification by column chromatography on 100 g of silica gel (gradient elution with 20 to 50% Et_2O in pentane) provided 2.25 g (83%) of **231** as a colorless oil.

IR (film):	3350, 2940, 2870, 2250, 2220, 1450, 1430, 1370, 1330, 1260, 1160, 860, and 850 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	3.67 (t, J = 6.1 Hz, 2 H), 2.26 (t, J = 6.7 Hz, 2 H), 1.72-1.57 (m, 4 H), and 1.41 (s, 1 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	80.0, 62.3, 38.0, 31.7, 24.6, and 19.4 ppm.
HRMS	Calcd for C_6H_8BrO: 175.983676 Found: 175.98362.


Br
OH
231
267
8
7
6
5
4
3
2
1
0 PPM

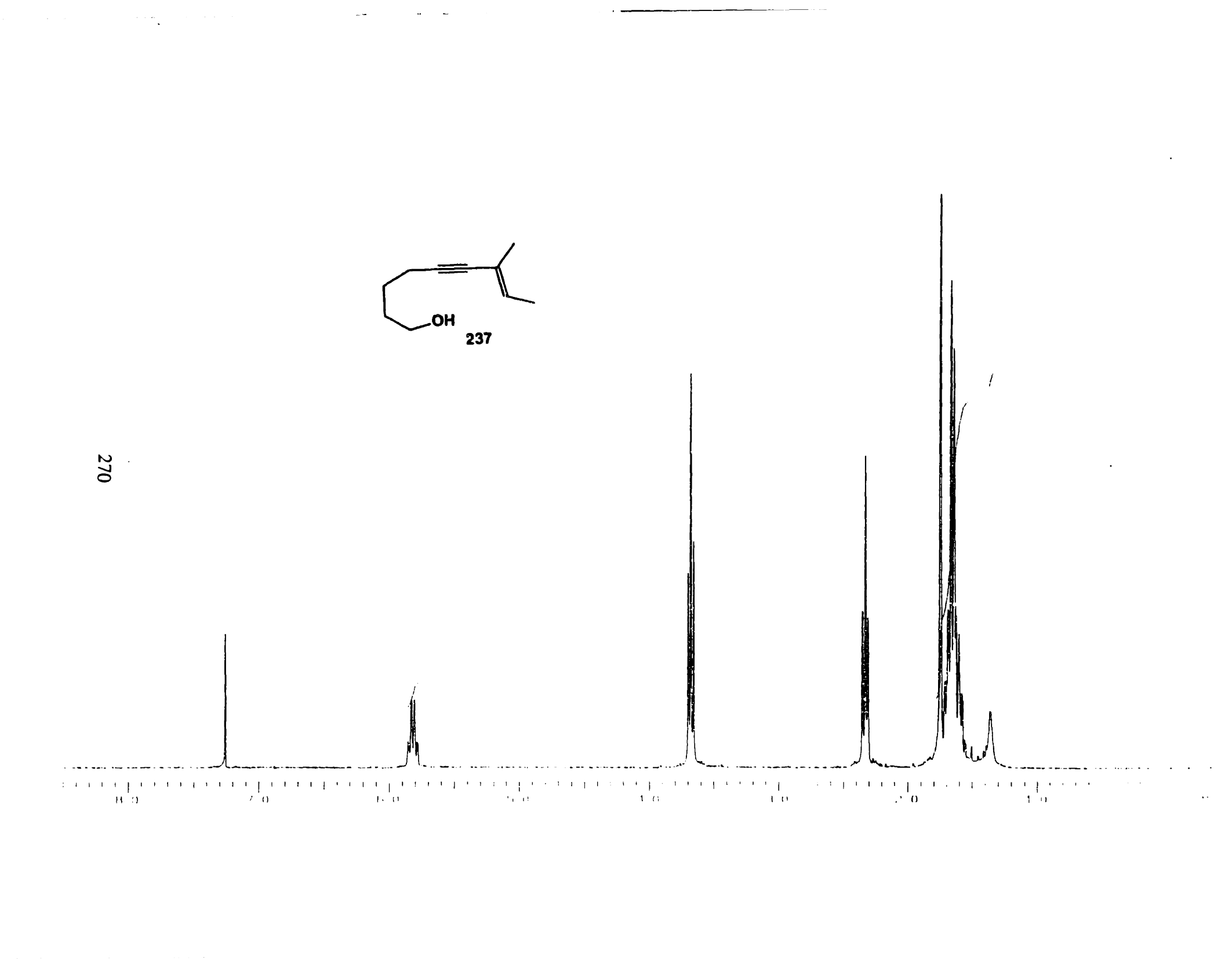
Borane synthesis:

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and nitrogen inlet adapter was charged with a solution of 9-BBN (62.3 mL, 0.5 M solution in THF, 31.6 mmol) and cooled to 0 °C. After 10 min, 2-butyne (4.16 mL, 2.9 g, 53.11 mmol) was added. After 2 h at 0 °C, the reaction mixture was sealed and placed in the freezer (-8 °C) for 24 h.

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, nitrogen inlet adapter, reflux condenser, and rubber septum was charged with the 6-bromo-7-hexyn-1-ol **231** (2.0 g, 11.3 mmol), 56 mL of THF, and $Pd(Ph_3P)_4$ (0.261 g, 0.226 mmol). After 15 min, the borane solution and NaOMe (34 mL, 16.95 mmol, 0.5 M solution in methanol) were each added via cannula over about 5 min, and the reaction mixture was heated to reflux for 26 h. The reaction mixture was then cooled to 0 °C, and 15 mL 30% H_2O_2 and 15 mL of 3 N NaOH solution were added. After 1 h, the reaction mixture was extracted with three 15-mL portions of water and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Purification by column chromatography on 100 g of silica gel (gradient elution with hexane to 5% ethyl acetate in hexane) gave a pale yellow oil. Further purification by Kugelrohr distillation (bath temperature 80-180 °C, 0.4 mmHg, 1 bulb at room temperature and 1 bulb at 0 °C) gave 1.3 g (75%) of **237** as a colorless oil.

IR (film): 3340, 3020, 2940, 2870, 2220, 1860, 1680, 1635, 1440, 1385, 1340, 1250, 1165, 1065, 990, 940, and 830 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$)	5.81-5.83 (m, 1 H), 3.68 (t, J = 6.0 Hz, 2 H), 2.33 (t, J = 6.6 Hz, 2 H), 1.75 (s, 3 H), 1.57-1.73 (m, 4 H), 1.65 (d, J = 6.3 Hz, 3 H), and 1.36 (bs, 1 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	131.0, 118.7, 85.7, 84.0, 77.4, 62.5, 31.9, 25.1, 19.0, 17.1, and 13.9 ppm.
HRMS	Calcd for $C_{10}H_{16}O$: 152.120115 Found: 152.12006.


OH
237
270

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with oxalyl chloride (0.415 mL, 0.600 g, 4.73 mmol) and 20 mL of THF. This solution was cooled to -78 °C, and DMSO (0.615 mL, 0.677 g, 8.67 mmol) was added dropwise over 2 min. After 5 min at -78 °C, a solution of 7-methyl-7-nonen-5-yn-1-ol **237** (0.600 g, 3.94 mmol) in 10 mL of THF was added via cannula over 3 min (10 mL of THF was used to rinse the flask). After 15 min, triethylamine (2.6 mL, 2.0 g, 19.7 mmol) was added via syringe over 2 min, and the resulting mixture was stirred at -78 °C for 15 min and at room temperature for 45 min. Then 10 mL of saturated NH_4Cl solution and 20 mL of Et_2O were added, and the aqueous phase was extracted with 15 mL of Et_2O. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated (carefully) to give 0.658 g of **239** as a yellow oil. This oil was used without further purification in the next reaction.

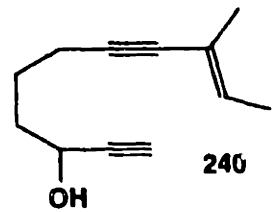
A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 7-methyl-7-nonen-5-yn-1-al **239** (0.658 g crude material, assumed 3.94 mmol) and 40 mL of THF. This solution was cooled to 0°, and ethynylmagnesium chloride solution (9.5 mL, 4.73 mmol, 0.5 M solution in THF) was added via syringe over 5 min. After 10 min, 10 mL of saturated NH_4Cl solution and 20 mL of Et_2O were added. The aqueous phase was separated and extracted with 15-mL portions of Et_2O. The combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.738 g of a brown oil. Purification by column chromatography on 60 g of silica gel (gradient elution with 10-20% ethyl acetate in hexane) gave 0.470 g of **240** as a yellow oil (68% from the alcohol).

IR (film): 3360, 3300, 3040, 2960, 2870, 2220, 2120, 1850, 1635, 1440, 1385, 1340, 1250, 1215, 1175, 1160, 1075, 1030, 895, and 830 cm^{-1}.

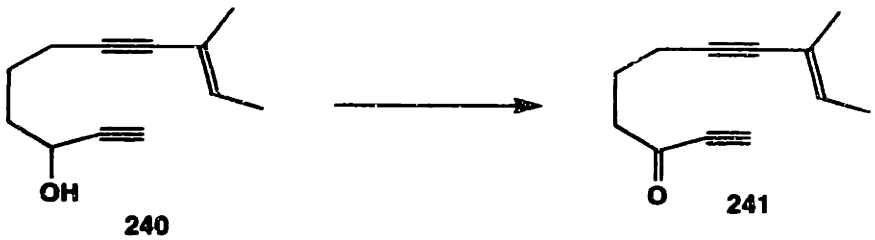
^1H NMR (300 MHz, $CDCl_3$) 5.82 (qd, J = 6.6 =, 1.6 Hz, 1 H), 4.42 (d, J = 1.7 Hz, 1 H), 2.47 (d, J = 1.8 Hz, 1 H), 4.38-2.35 (t, J = 6.8 Hz, 2 H), 1.85-1.93 (m, 3 H), 1.75 (s, 3 H), 1.68-1.73 (m, 2 H), and 1.65 (d, J = 6.8 Hz, 3 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) 131.0, 118.6, 85.3, 84.7, 84.2, 73.0, 61.9, 36.7, 24.4, 18.9, 17.1, and 13.9 ppm.

HRMS Calcd for $[M-H]^+$ $C_{12}H_{15}O$: 175.1122
Found: 175.11181.



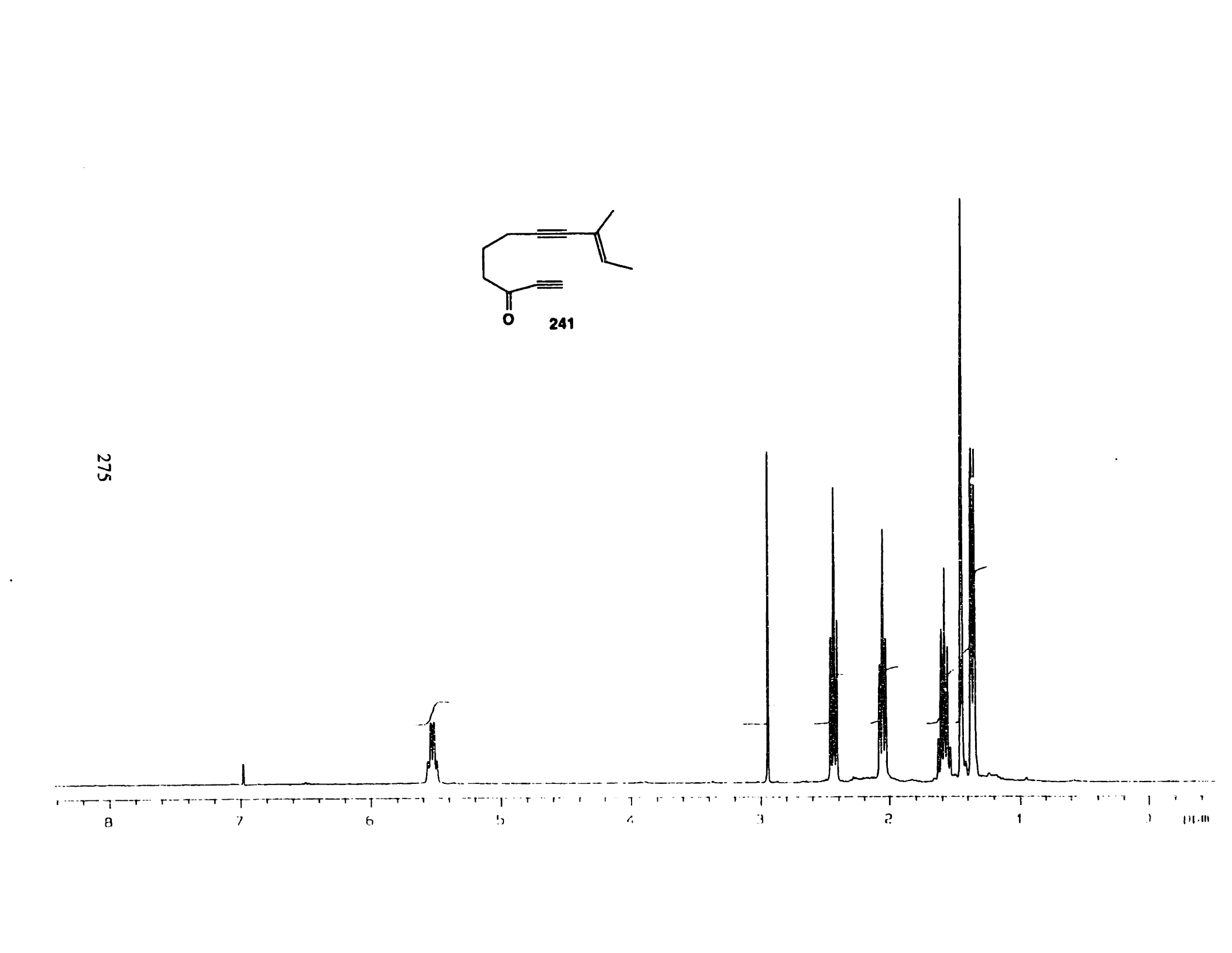
240

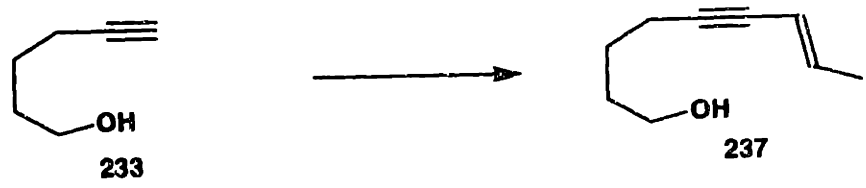


240 241

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 9-methyl-9-undecen-1,7-diyn-3-ol **240** (0.211 g, 1.20 mmol), 12 mL of CH_2Cl_2, and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1-oxide (0.609 g, 1.44 mmol). This solution was stirred at room temperature for 45 min and then concentrated to about 5 mL. The resulting slurry was treated with 5 mL of Et_2O, and extracted with 5 mL of saturated $NaHCO_3$ solution. The aqueous phase was extracted with two 5-mL portions of Et_2O. The combined organic phases were extracted with 5 mL of half saturated $NaHCO_3$, 5 mL of H_2O, and 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. Purification by column chromatography on 10 g of silica gel (elution with 3% ethyl acetate in hexane) gave 0.532 g of **241** as a colorless oil (74%).

IR (film):	3260, 3020, 2930, 2850, 2220, 2095, 1785, 1450, 1375, 1340, 1310, 1245, 1220, 1110, 1040, and 835 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.53 (quartet, J = 6.9 Hz, 1 H), 2.95 (s, 1 H), 2.44 (td, J = 7.2, 1.8 Hz, 2 H), 2.06 (t, J = 7.0 Hz, 2 H), 1.63-1.54 (m, 2 H), 1.45 (s, 3 H), and 1.36 (d, J = 6.9 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	186.6, 131.2, 188.5, 84.7, 84.4, 81.3, 78.5, 44.2, 22.7, 18.4, 17.0, and 13.8 ppm.
HRMS	Calcd for $C_{12}H_{14}O$: 174.104465 Found: 174.10430.

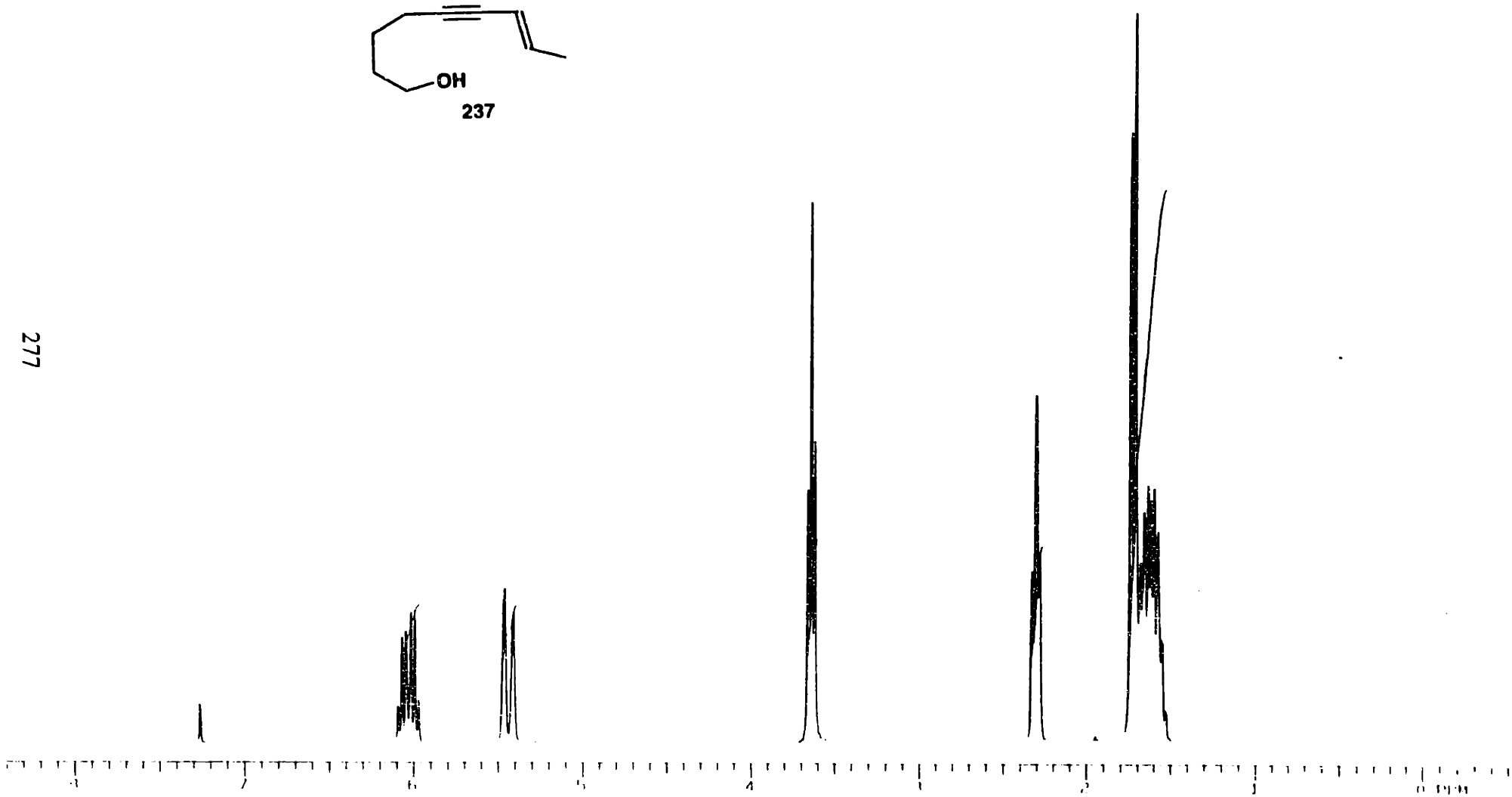

O
241
275
8
7
6
5
4
3
2
1
0
ppm

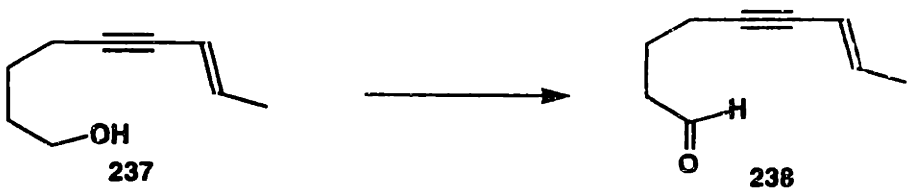


A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 5-hexyn-1-ol **233** (0.77 mL, 0.69 g, 7.0 mmol), 35 mL of diethylamine, *trans*-1-bromo-1-propene (0.66 mL, 0.93 g, 7.7 mmol), $Pd(Ph_3P)_4$ (0.220 g, 0.190 mmol), and copper(I) iodide (20 mg, 0.105 mmol). This solution was protected from the light and stirred at room temperature for 26 h. The reaction mixture was then filtered through celite; Et_2O was used to rinse the precipitate well. Saturated NH_4Cl solution (15 mL) was added to the filtrate, and the aqueous phase was separated andextracted with four 10-mL portions of Et_2O. The combined organic phases were extracted with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give an opaque yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 10% ethyl acetate in hexane) gave 0.916 g of **237** as a yellow oil (95%).[216]

IR (film):	3350, 3030, 3000, 2950, 2920, 2875, 2220, 1735, 1450, 1435, 1380, 1330, 1300, 1205, 1165, 1065, 1040, 980, and 960 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.03 (dq, J = 15.7, 6.7 Hz, 1 H), 5.44 (dd, J = 15.7, 1.9 Hz, 1 H), 3.64 (t, J = 6.1 Hz, 2 H), 2.31 (t, J = 5.75 Hz, 2 H), 1.73 (d, J = 6.8 3 H), and 1.52-1.68 (m, 5 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	138.1, 110.9, 87.9, 79.5, 62.3, 31.8, 25.0, 19.0, and 18.3 ppm.
HRMS	Calcd for $C_9H_{14}O$: 138.104465 Found: 138.10450.

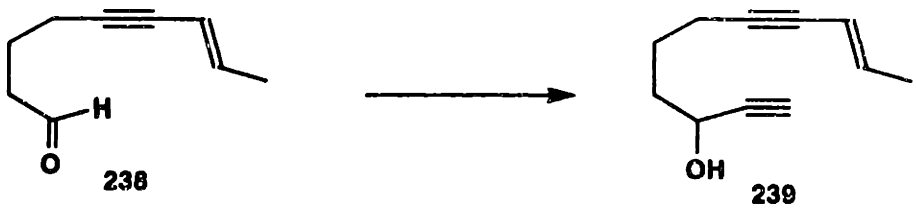
[216] Other yields for this reaction ranged from 65 to 91%.


OH
237
277



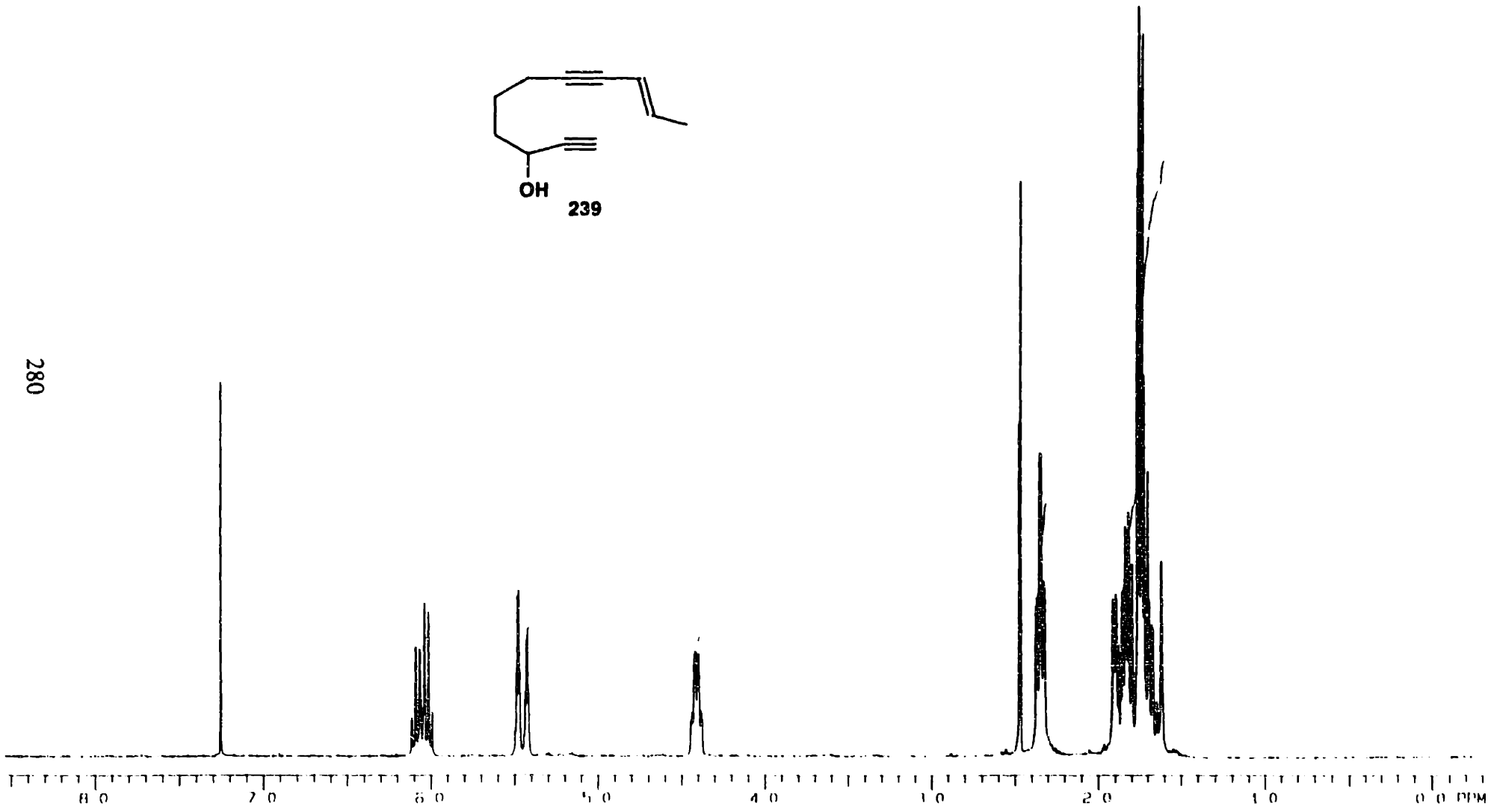
237 238

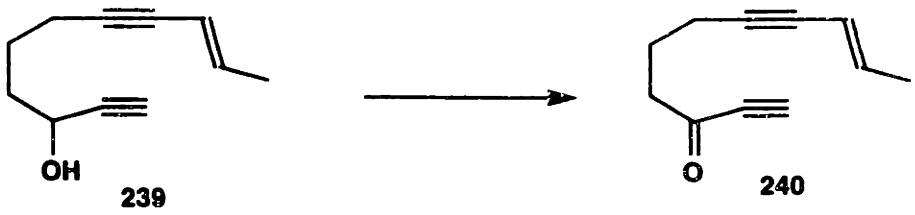
A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with oxalyl chloride (0.350 mL, 0.505 g, 3.98 mmol) and 25 mL of CH_2Cl_2. This solution was cooled to -78 °C, and DMSO (0.565 mL, 0.622 g, 7.96 mmol) was added dropwise over 4 min. After stirring the reaction at -78 °C for 5 min, a solution of 7-nonen-5-yn-1-ol **237** (0.500 g, 3.62 mmol) in 10 mL of CH_2Cl_2 was added via cannula over 3 min (10 mL CH_2Cl_2 was used to rinse the flask). After 15 min, triethylamine (2.52 mL, 1.83 g, 18.1 mmol) was added via syringe over 3 min. This mixture was stirred at -78 °C for 15 min and at room temperature for 45 min, and then 10 mL of water and 20 mL of Et_2O were added. The aqueous phase was separated and extracted with 15 mL of Et_2O. The combined organic phases were washed with 10 mL of 10% HCl solution and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated (carefully) to give 0.658 g of a yellow oil. Purification by column chromatography on 5 g of silica gel (elution with 20% CH_2Cl_2 in pentane) gave 0.435 g of a yellow oil, impure aldehyde **238** that was used in the next reaction.



A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 7-nonen-5-yn-1-al **238** (0.493 g crude material, assumed 3.62 mmol) and 30 mL of THF. This solution was cooled to 0 °C, and ethynylmagnesium bromide solution (10.9 mL, 5.43 mmol, 0.5 M solution in THF) was added via syringe over 5 min. After 10 min, 10 mL of saturated NH_4Cl solution and 20 mL of Et_2O were added. The aqueous phase was separated and extracted with two 10-mL portions of Et_2O. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.757 g of an orange oil. Purification by column chromatography on 21 g of silica gel (gradient elution with 5-10% ethyl acetate in hexane) gave 0.366 g of **239** as a yellow oil (62% from the alcohol).

IR (film):	3380, 3330, 3030, 2940, 2920, 2870, 2250, 2220, 2110, 1440, 1380, 1330, 1300, 1165, 1070, 1025, 955, 910, and 735 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.06 (dq, J = 15.6, 6.8 Hz, 1 H), 5.46 (dq, J = 15.5, 2 Hz, 1 H), 4.38-4.45 (m, 1 H), 2.47 (d, J = 3.6 Hz, 1 H), and 1.62-1.91 (m, 5 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	138.2, 110.8, 87.5, 84.6, 79.7, 73.0, 61.8, 36.6, 24.4, 18.9, and 18.4 ppm.

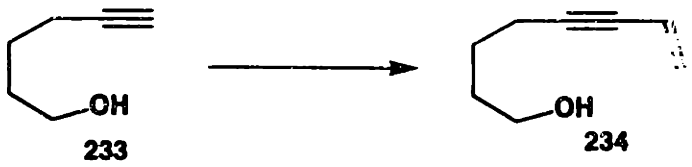

OH
239
280
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM



A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 9-undecen-1,7-diyn-3-ol **239** (0.500 g, 1.20 mmol), 30 mL of CH_2Cl_2, and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1-oxide (1.57 g, 3.70 mmol). This solution was stirred at room temperature for 45 min. The resulting slurry was concentrated on the rotary evaporator to about 5 mL, treated with 5 mL of Et_2O, and extracted with 10 mL of saturated $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 10-mL portions of Et_2O. The combined organic phases were extracted with 10 mL of half saturated $NaHCO_3$, 10 mL of H_2O, and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. Purification by column chromatography on 25 g of silica gel (elution with 3% ethyl acetate in hexane) gave 0.400 g of **240** as a pale yellow oil (81%).

IR (film):	3250, 3005, 2930, 2905, 2200, 2085, 1675, 1435, 1400, 1365, 1330, 1300, 1210, 1105, 1035, and 950 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.06 (dq, J = 15.6, 6.9 Hz, 1 H), 5.44 (dq, J = 16.4, 2.2 Hz, 1 H), 3.22 (s, 1 H), 2.73(t, J = 7.3 Hz, 2 H), 2.35 (t, J = 6.6 Hz, 2 H), 1.87 (app quintet, J = 6.8 Hz, 2 H), and 1.75 (d, J = 6.8 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	186.6, 138.5, 110.8, 86.6, 81.4, 80.3, 78.3, 78.5, 44.2, 22.7, 18.5, and 18.4 ppm.
HRMS	Calcd for $C_{11}H_{12}O$: 160.088815 Found: 160.08878.

240

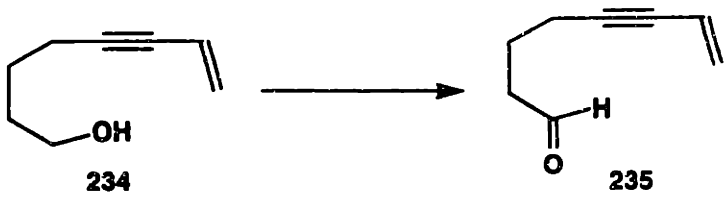


233 234

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and nitrogen inlet adapter was charged with 5-hexyn-1-ol **233** (2.2 mL, 1.96 g, 19.97 mmol) and 70 mL of diethylamine. The solution was cooled to 0 °C, and vinyl bromide (2.3 mL, 3.5 g, 32.6 mmol), $Pd(Ph_3P)_4$ (0.558 g, 0.509 mmol), and copper(I) iodide (39 mg,0.204 mmol) were added. The reaction mixture was protected from the light and stirred at room temperature. After 23 hours, the solution was filtered through celite; the precipitate was washed thoroughly with Et_2O. The filtrate was then extracted with 25 mL of saturated NH_4Cl solution. The aqueous phase was separated and extracted with two 10-mL portions of Et_2O. The combined organic phases were extracted with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Purification by column chromatography on 50 g of silica gel (elution with 10% ethyl acetate in hexane) gave 2.12 g (87%) of **234** as a yellow oil.

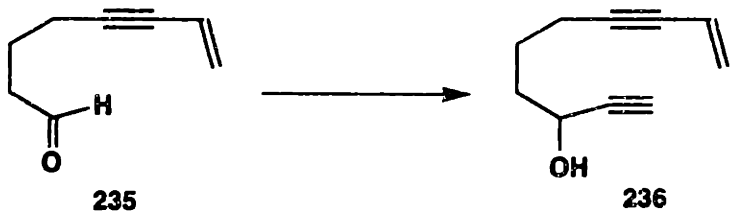
IR (film):	3340, 3095, 3005, 2940, 2860, 2220, 2000, 1835, 1720, 1605, 1450, 1430, 1410, 1370, 1330, 1245, 1160, 1060, 975, and 915 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.76 (ddt, J= 17.7, 11.1, 2.1 Hz, 1 H), 5.53 (dd, J = 17.7, 2.4 Hz, 1 H), 5.37 (dd, J= 11.1, 2.4 Hz, 1 H), 3.66 (t, J = 6.3 Hz, 2 H), 2.34 (t, J = 6.7 Hz, 2 H),and 1.55-1.73 (m, 5 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	125.6, 117.5, 90.6, 79.7, 62.4, 31.8, 24.9, and 19.1 ppm.

OH
234



234 235

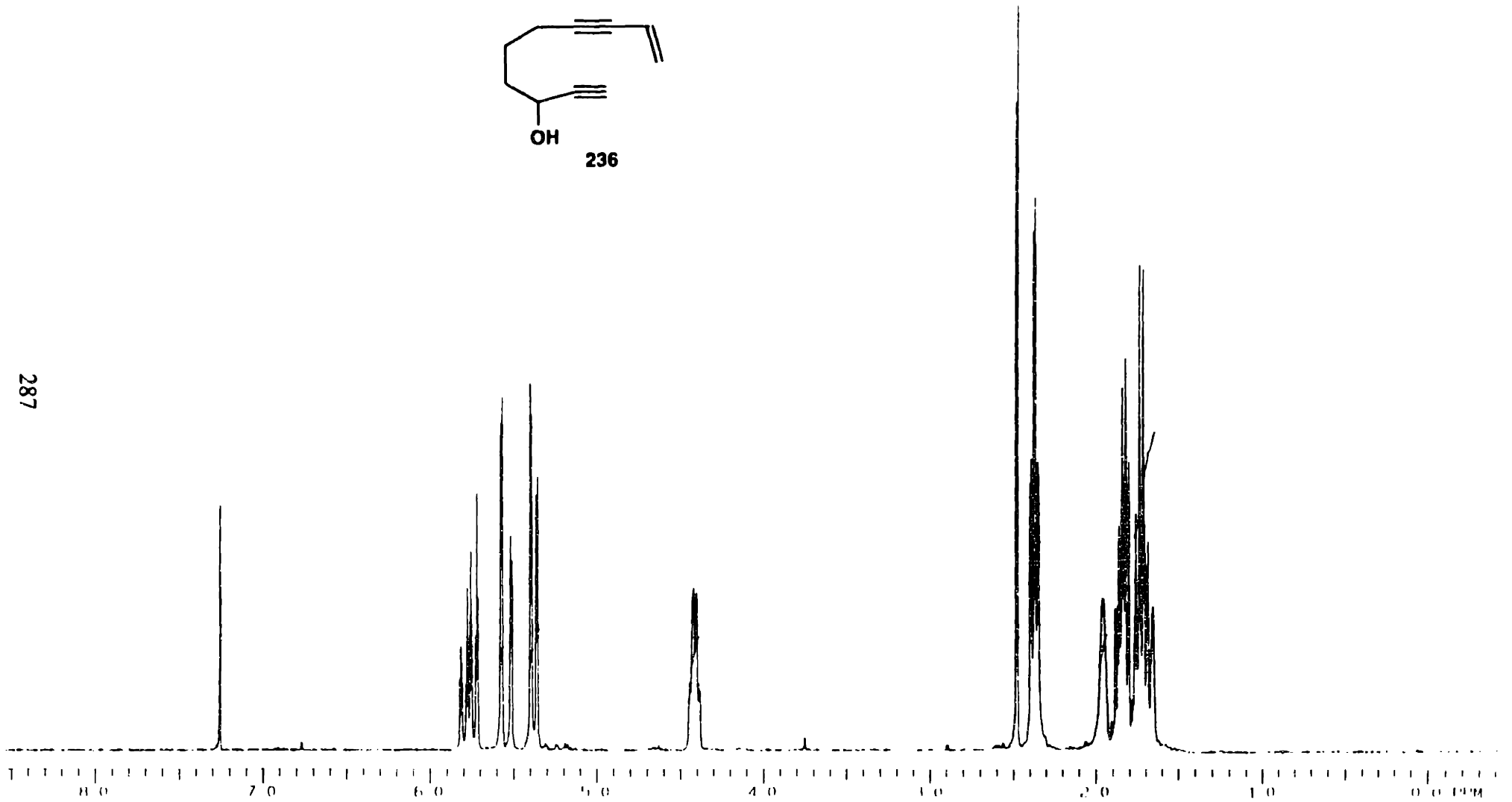
A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with oxalyl chloride (0.150 mL, 0.217 g, 1.71 mmol) and 3.2 mL of THF. This solution was cooled to -78 °C, and DMSO (0.20 mL, 0.220 g, 2.82 mmol) was added dropwise over 90 sec. After 5 min at -78 °C, a solution of the 7-octen-5-yn-1-ol **234** (0.200 g, 1.61 mmol) in 7 mL of THF was added via cannula over 3 min (3 mL THF was used to rinse the flask). After 15 min, triethylamine (0.91 mL, 0.66 g, 6.5 mmol) was added via syringe over 1 min. This mixture was stirred at -78 °C for 15 min and at room temperature for 45 min, and then 5 mL of water and 5 mL of Et_2O were added. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O. The combined organic phases were washed with 5 mL of brine, dried over K_2CO_3, filtered, and concentrated (carefully) to give 0.225 g of **235** as a yellow oil. This oil was used without further purification in the next reaction.

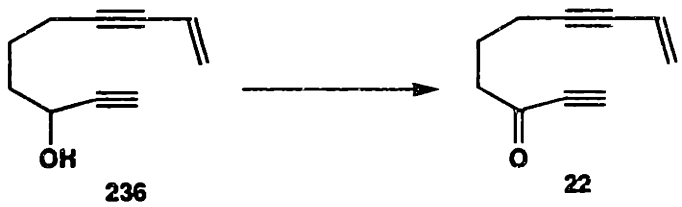


235 236

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 7-octen-5-yn-1-al **235** (0.225 g crude material, assumed 1.61 mmol) and 10 mL of THF. This solution was cooled to 0 °C, and ethynylmagnesium bromide (3.9 mL, 1.95 mmol, 0.5 M solution in THF) was added via syringe over 3 min. After 20 min, 4 mL of saturated NH_4Cl solution and 5 mL of Et_2O were added. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O. The combined organic phases were washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.216 g of a brown oil. Purification by column chromatography on 20 g of silica gel (elution with 10% ethyl acetate in hexane) gave 0.147 g of **236** as a yellow oil (62% from the alcohol).

IR (film):	3360, 3300, 3100, 3010, 2950, 2860, 2220, 2115, 1840, 1610, 1455, 1430, 1410, 1335, 1290, 1210, 1160, 1070, 1020, 980, and 920 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.76 (ddt, J = 17.6, 10.6, 2.4 Hz, 1 H), 5.54 (dd, J = 17.6, 2.5 Hz, 1 H), 5.38 (dd, J = 10.6, 2.5 Hz, 1 H), 4.38-4.45 (m, 1 H), 2.37 (td, J = 6.8, 2 Hz, 2 H), 1.95-1.96 (m, 1 H), 1.80-1.88 (m, 2 H), and 1.65-1.78 (m, 1 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	125.7, 117.5, 90.2, 84.6, 79.9, 73.1, 61.9, 36.6, 24.1, and 19.0 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{10}H_{11}O$: 147.0809 Found: 147.08102.


OH
236
287
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

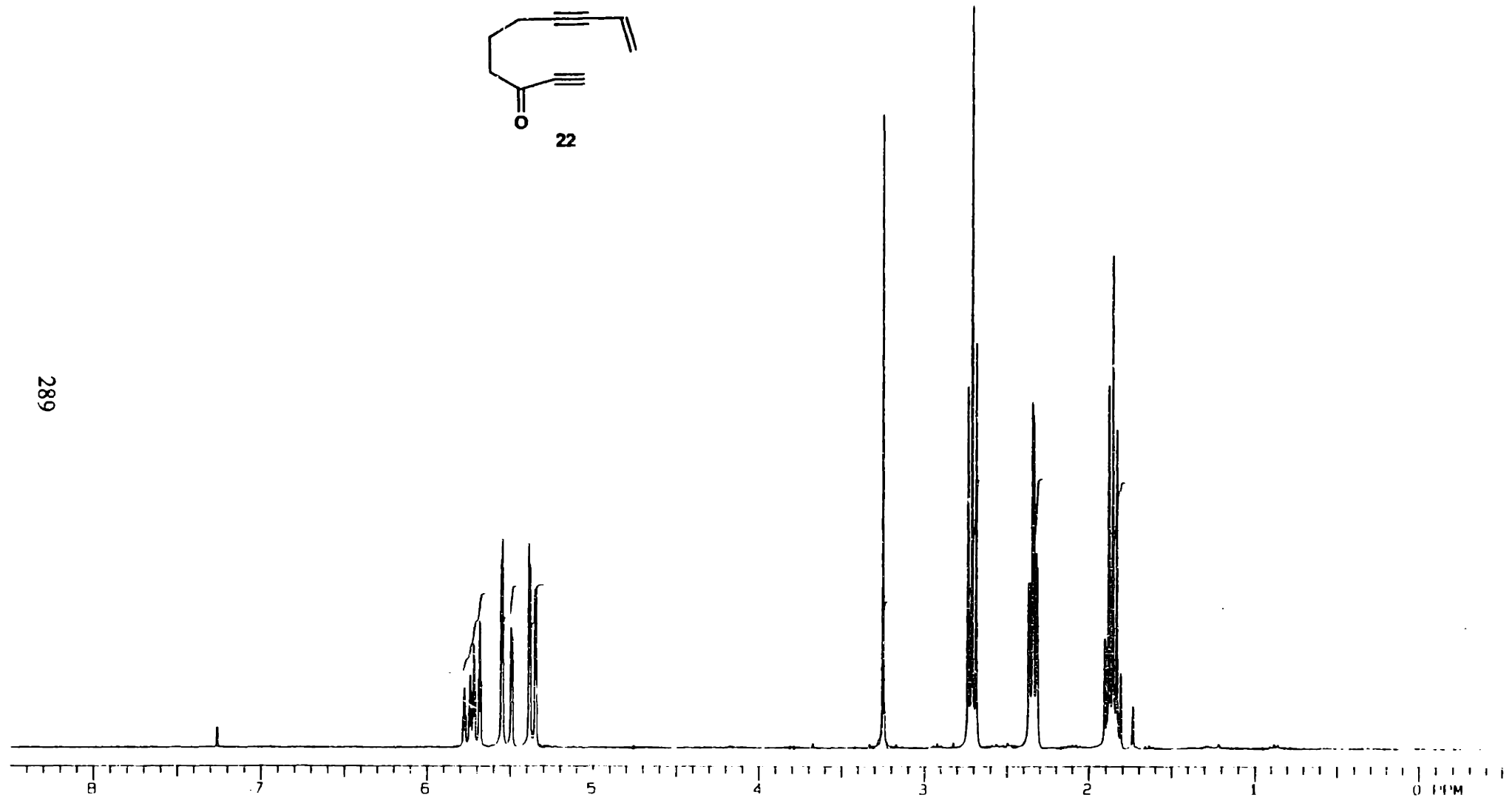


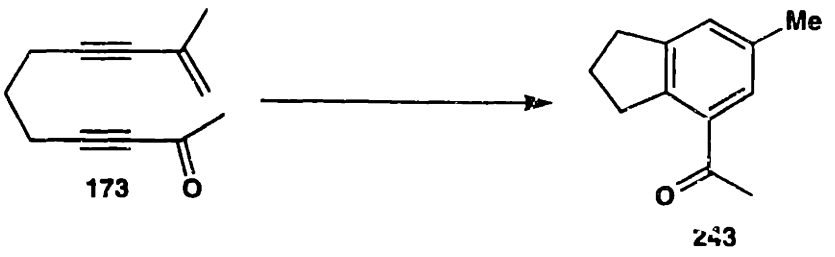
236 22

A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 9-decen-1,7-diyn-3-ol **236** (0.752 g, 5.07 mmol), 50 mL of CH_2Cl_2, and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1-oxide (3.23 g, 7.61 mmol) and stirred at room temperature for 45 min. The slurry was concentrated on a rotary evaporator to about 5 mL, treated with 15 mL of Et_2O, and extracted with 10 mL of saturated $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 10-mL portions of Et_2O. The combined organic phases were extracted with 10 mL of half saturated $NaHCO_3$, 10 mL of H_2O, and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.079 g of an orange slurry. Purification by column chromatography on 20 g of silica gel (gradient elution with hexane to 5% ethyl acetate in hexane) gave 0.532 g of **22** as a pale yellow oil (72%).[217]

IR (film):	3270, 3100, 3010, 2960, 2940, 2900, 2840, 2230, 2100, 1850, 1690, 1455, 1435, 1410, 1370, 1335, 1310, 1295, 1220, 1165, 1110, 1050, 1035, 980, 925, 870, and 835 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.73 (ddt, J = 17.5, 10.8, 2 Hz, 1 H), 5.52 (dd, J = 18, 2.3 Hz, 1 H), 5.37 (dd, J = 11, 2.3 Hz, 1 H), 3.24 (d, J = 2.1 Hz, 1 H), 2.71 (t, J = 7.3 Hz, 2 H), 2.34 (td, J = 6.9, 2 Hz, 2 H), and 1.86 (app quintet, J = 7 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	186.4, 125.9, 117.3, 89.3, 81.3, 80.4, 78.6, 44.1, 22.5, and 18.5 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{10}H_{11}O$: 147.0809 Found: 147.08102.

[217] Other yields for this reaction ranged form 60 to 72%.


O
22
8
7
6
5
4
3
2
1
0 PPM



173 243

I Thermal Procedure:

A threaded Pyrex tube (ca. 50 mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with 10-methyl-10-undecen-3,8-diyn-2-one **173** (0.215 g, 1.21 mmol), 12.1 mL of toluene, and phenol (0.114 g, 1.21 mmol). The solution was degassed by three freeze-pump-thaw cycles, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was immersed in a 180 °C oil bath for 7 h and then allowed to cool to room temperature. Concentration of the liquid gave 0.311 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 3% ethyl acetate-hexane) provided 0.111 g (52%) of **243** as a yellow solid. A second purification on 10 g of silica gel (elution with 3% ethyl acetate-hexane) gave a white solid (mp 28-29 °C).

II Lewis Acid Procedure:

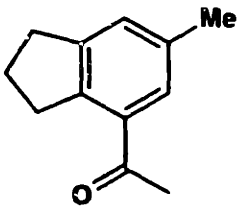
A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with 10-methyl-10-undecen-3,8-diyn-2-one **173** (0.200 g, 1.15 mmol) and 23 mL of CH_2Cl_2. $ZnBr_2$ (3.13 g, 13.90 mmol) and 4-methyl-2,6-di-*tert*-butylphenol (0.507 g, 2.03 mmol) were then added to the solution. The reaction mixture was heated at reflux for 3 days and then allowed to cool to room temperature. A saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture, and the milky white solution was filtered. The aqueous layer was separated and extracted with 10 mL of CH_2Cl_2, and the combined organic layers were washed with 15 mL of H_2O, 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.731 g of a brown oil. Column chromatography on 60 g of silica gel (elution with hexane to 10% ethyl acetate-hexane) and

on 15 g of silica gel (elution with hexane to 3% ethyl acetate-hexane) provided 0.111 g (55%) of **243** as a white solid (mp 28-29 °C).

III Protic Acid Procedure

A 50-mL, three-necked, round bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 10-methyl-10-undecen-3,8-diyn-2-one **173** (0.193 g, 1.11 mmol) and 38 mL of CH_2Cl_2. Methanesulfonic acid (0.190 mL, 0.276 g, 2.87 mmol) was added dropwise via syringe, and the resulting solution was stirred for 15 hours at room temperature. $NaHCO_3$ (approximately 0.5 g) and 10 mL of H_2O were added to the reaction mixture. The aqueous phase was separated and extracted with two 10-mL portions of CH_2Cl_2, and the combined organic phases were extracted with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.316 g of a black oil. Purification by column chromatography on 20 g of silica gel (elution with 3% ethyl acetate in hexane) 0.123 g of **243** as a yellow solid.

IR (film)	2930, 2220, 1725, 1660, 1595, 1560, 1435, 1415, 1340, 1310, 1265, 1225, 1185, 1085, 1030, 970, 900, 830, and 715 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.45 (s,1 H), 7.21 (s, 1 H), 3.18 (t, J = 7.4 Hz, 2 H), 2.85 (t, J = 7.6 Hz, 2 H), 2.55 (s, 3 H), 2.36 (s, 3 H), and 2.04 (app quintet, J = 7.7 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	199.9, 146.4, 142.3, 135.7, 133.8, 129.3, 128.0, 33.7, 32.2, 28.3, 25.2, and 21.0 ppm.
Elemental Analysis:	Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.63; H, 8.31.



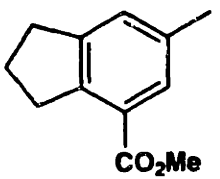
243

292

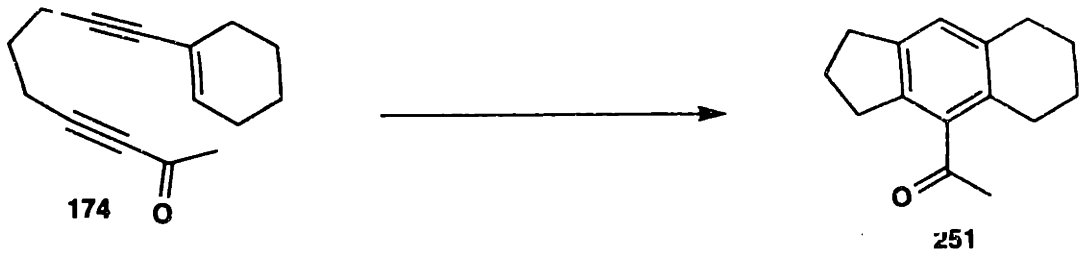
176 244

A threaded Pyrex tube (ca. 50 mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with methyl 9-methyl-9-decen-2,7-diynoate **176** (0.200 g, 1.05 mmol), 10.4 mL toluene, and phenol (0.099 g, 1.05 mmol). The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was immersed in a 180 °C oil bath for 7 h and then allowed to cool to room temperature. Concentration of the liquid gave 0.315 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 3% ethyl acetate-hexane) provided 0.100 g (52%) of **244** as a yellow oil and 0.038 g of unreacted enyne **176**.

IR (film)	2950, 2840, 1715, 1610, 1580, 1460, 1435, 1380, 1335, 1280, 1240, 1210, 1165, 1110, 1020, 995, 965, and 880 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.63 (s,1 H), 7.21 (s, 1 H), 3.88 (s, 3 H), 3.22 (t, J = 7.4 Hz, 2 H), 2.88 (t, J = 7.4 Hz, 2 H), 2.34 (s, 3 H), and 2.06 (app quintet, J = 7.6 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	167.5, 145.7, 143.5, 135.6, 129.3, 128.3, 125.9, 51.6, 33.5, 32.5, 25.1, and 21.0 ppm.
HRMS	Calcd for $C_{12}H_{14}O_2$: 190.0994 Found: 190.0993.

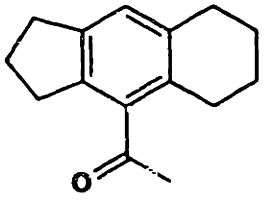


244



A 50 mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with 1-cyclohexenyl-1,6-nonadiyn-8-one **174** (0.200 g, 0.933 mmol) and 18.7 mL of CH_2Cl_2. $ZnBr_2$ (2.10 g, 9.33 mmol) and 4-methyl-2,6-di-*tert*-butylphenol (0.411 g, 1.87 mmol) were then added to the solution, and the reaction mixture was heated at reflux for 19 hours. Saturated $NaHCO_3$ solution (7 mL) was added to the cooled reaction mixture, and the milky white solution was filtered. The aqueous phase of the filtrate was separated and extracted with 10 mL of CH_2Cl_2, and the combined organic phases were then washed with 10 mL of H_2O, 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.612 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with hexane to 3% ethyl acetate-hexane) gave 0.153 g (76%) of **251** as a pale yellow solid.

IR (film)	3360, 2930, 2840, 1690, 1600, 1570, 1445, 1430, 1350, 1270, 1255, 1215, 1175, 1140, 1065, 1000, 940, 910, and 865 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.97 (s, 1 H), 2.84 (t, J = 7.9 Hz, 2 H), 2.81 (t, J = 7.9 Hz, 2 H), 2.75 (bs, 2 H), 2.66 (bs, 2 H), 2.46 (s, 3 H), 2.04 (app quintet, J = 7.4 Hz, 2 H) and 1.78-1.74 (m, 4 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	207.3, 142.1, 138.7, 136.8, 135.8, 129.9, 126.0, 32.2, 31.6, 31.5, 29.9, 26.8, 25.6, 23.1, and 22.8 ppm.
HRMS	Calcd for $C_{15}H_{18}O$: 214.1358 Found: 214.1356.



251

165 252

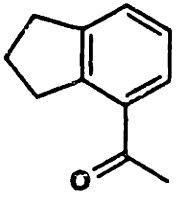
I Thermal Procedure

A threaded Pyrex tube (ca. 20 mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with 10-undecen-3,8-diyn-2-one **165** (0.133 g, 0.830 mmol), 8.3 mL of toluene, and phenol (0.078 g, 0.830 mmol). The solution was degassed by three freeze-pump-thaw cycles, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 9.5 h and then allowed to cool to room temperature. Concentration gave a brown oil. Purification by column chromatography on 15 g of silica gel (elution with 3% ethyl acetate-hexane) provided 0.057 g (43%) of **252** as a yellow oil.

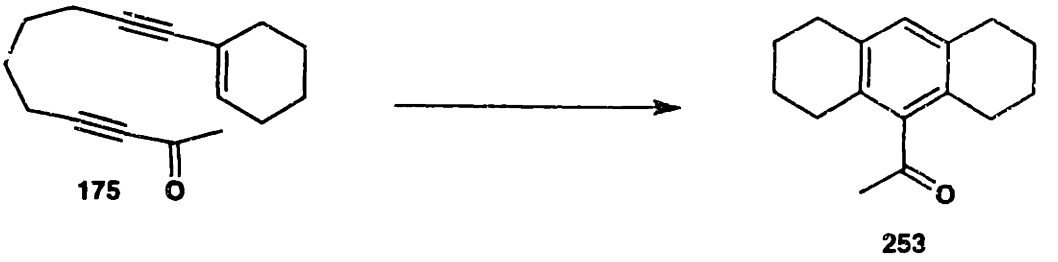
II Protic Acid Procedure

A 100-mL, one-necked, round-bottomed flask equipped with a nitrogen inlet needle and rubber septum was charged with 10-undecen-3,8-diyn-2-one **165** (0.207 g, 1.29 mmol) and 47 mL of CH_2Cl_2. Methanesulfonic acid (0.210 mL, 0.310 g, 3.23 mmol) was added via syringe over 90 sec, and the resulting mixture was stirred at room temperature for 108 h. $NaHCO_3$ (approximately 0.5 g) and 15 mL of H_2O were added. The aqueous phase was separated and extracted with 10 mL of CH_2Cl_2, and the combined organic phases were washed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to give 0.229 g of a brown oil. Purification by column chromatography on 10 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.112 g (54%) of **252** as a white solid (mp 39-40.5 °C).

IR (film)	2960, 1660, 1585, 1440, 1360, 1245, 1220, and 1110 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.66 (d, J = 7.7 Hz, 1 H), 7.41 (d, J = 6.8 Hz, 1 H), 7.24 (app t, J = 7.4 Hz, 1 H), 3.26 (t, J = 7.5 Hz, 2 H), 2.92 (t, J = 7.6 Hz, 2 H), 2.59 (s, 3 H), and 2.07 (app quintet, J = 7.6 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	146.2, 145.3, 133.9, 128.5, 127.4, 126.1, 34.0, 32.3, 28.3, 25.0, and 12.5 ppm.
Elemental Analysis	Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55 Found: C, 82.16; H, 7.32.



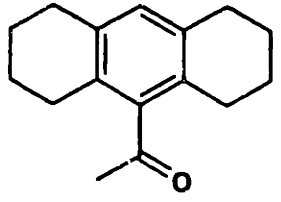
252



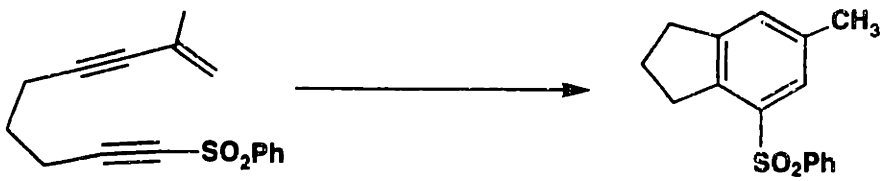
253

A 50 mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with 1-cyclohexenyl-1,7-decadiyn-9-one **175** (0.200 g, 0.876 mmol) and 17.5 mL of 1,2-dichloroethane. $ZnBr_2$ (1.97 g, 8.76 mmol) and 4-methyl-2,6-di-*tert*-butylphenol (0.386 g, 1.75 mmol) were then added to the solution, and the reaction mixture was heated at reflux for 18 h. Saturated $NaHCO_3$ solution (7 mL) was added to the reaction mixture, and the milky white solution was filtered. The aqueous phase of the filtrate was separated and extracted with 10 mL of Et_2O. The combined organic phases were washed with 10 mL of H_2O, 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.675 g of a brown oil. Purification by column chromatography on 50 g of silica gel (gradient elution with hexane to 3% ethyl acetate-hexane) gave 0.120 g (60%) of **253** as a yellow solid; further purification by column chromatography as above provided **253** as a white solid (mp = 65-66 °C).

IR (film)	2930, 2850, 1695, 1430, 1345, 1280, and 1150 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.81 (s, 1 H), 2.71 (bs, 4 H), 2.56 (bs, 4 H), 2.44 (s, 3 H), and 1.78-1.73 (m, 8 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	209.2, 142.3, 134.5, 129.9, 128.2, 32.0, 39.3, 26.2, 23.1, and 22.9 ppm.
HRMS	Calcd for $C_{16}H_{20}O$: 228.1514 Found: 228.1513.



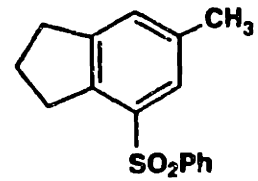
253



189 254

A threaded Pyrex tube (ca. 50 mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with 8-methyl-1-phenylsulfonyl-8-nonen-1,6-diyne **189** (0.188 g, 0.690 mmol), 6.9 mL of toluene, and 4-methyl-2,6-di-*tert*-butylphenol (0.152 g, 0.690 mmol). The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 180-200 °C oil bath for 7 h and then allowed to cool to room temperature. Concentration of the reaction mixture gave 0.145 g of a brown solid. Purification by column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexane) provided 0.145 g (77%) of **254** as a brown solid. An analytical sample was obtained by recrystallization from hexane- CH_2Cl_2 as a white solid, mp 131.0-132.5 °C.

IR (CCl_4)	2960, 1450, 1435, 1315, 1260, 1240, 1145, 1090, 1070, 875, 855, 710, and 685 cm^{-1}.	
^1H NMR (300 MHz, $CDCl_3$)	7.89-7.92 (m, 2 H), 7.72 (s, 1 H), 7.46-7.58 (m, 3 H), 7.24 (s, 1 H), 3.02 (app t, J = 7.5 Hz, 2 H), 2.86 (app t, J = 7.5 Hz, 2 H), 2.39 (s, 3 H), and 2.02 (quintet, J = 7.4 Hz, 2 H) ppm.	
^{13}C NMR (75 MHz, $CDCl_3$)	147.4, 141.6, 140.4, 137.0, 136.3, 130.4, 128.9, 127.5, 127.1, 126.5, 32.3, 31.9, 24.9, and 21.0 ppm.	
Elemental Analysis	Calcd for $C_{16}H_{16}O_2S$:	C, 70.56; H, 5.92
	Found:	C, 70.29; H, 5.74.



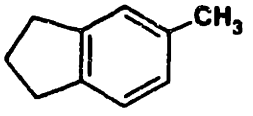
254

303

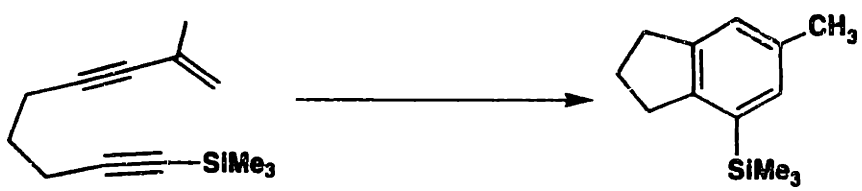
163 269

A stainless steel Parr reaction vessel (ca. 100 mL capacity) was charged with 2-methyl-1-nonen-3,8-diyne **163** (0.220 g, 1.66 mmol), 17 mL of cyclohexane, and 4-methoxyphenol (0.206 g, 1.66 mmol). The solution was degassed by placing a one-holed rubber stopper over the top of the vessel and bubbling nitrogen gas through the solution for 5 min and then sealed with the steel top equipped with a pressure gauge. The reaction mixture was heated to ca. 250 °C (top of the vessel 250 °C, bottom of the vessel 270 °C) for 24 h and then allowed to cool to room temperature. The brown reaction mixture was loaded directly onto a column of 20 g of silica gel and eluted with pentane to give 0.117 g (53%) of a pale yellow oil. Repurification by Kugelrohr distillation (ca. 25 mm Hg, 150 °C bath temp) gave **10** as a colorless oil. ^{1}H and ^{13}C NMR data were consistent with published data.[140]

IR (film)	2975, 2895, 2805, 1595, 1495, 1445, 1380, 1320, 1270, 1140, 1040, and 810 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	7.14 (d, J = 7.6 Hz, 1 H), 7.08 (s, 1 H), 6.97 (d, J = 7.2 Hz, 1 H), 2.89 (app t, J = 7.3 Hz, 4 H), 2.35 (s, 3 H), and 2.08 (app quintet, J = 7.4 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	144.2, 141.0, 135.4, 126.6, 125.0, 124.0, 32.9, 32.5, 25.7, and 21.3 ppm.
HRMS	Calcd for $C_{10}H_{12}$: 132.0939 Found: 132.0939.



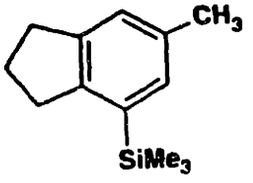
269



178 273

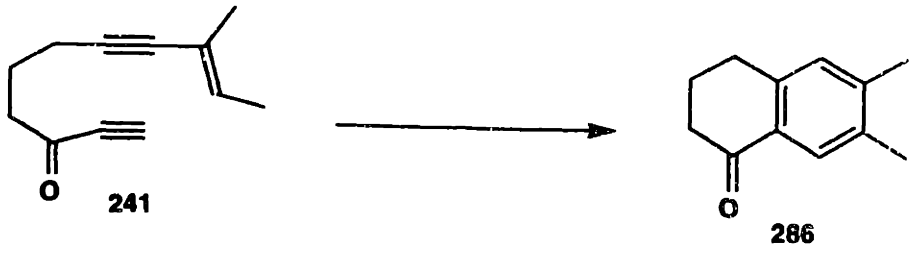
A stainless steel Parr reaction vessel (ca. 100 mL capacity) was charged with 2-methyl-9-trimethylsilyl-1-nonen-3,8-diyne **178** (0.200 g, 0.978 mmol), 9.8 mL of cyclohexane, and 4-methoxyphenol (0.121 g, 0.978 mmol). The solution was degassed by placing a one-holed rubber stopper over the top of the vessel and bubbling nitrogen gas through the solution for 5 min. The vessel was then sealed with a steel top equipped with a pressure gauge. The reaction mixture was heated to ca. 250 °C (top of the vessel 230 °C, bottom of the vessel 270 °C) for 36 h and then allowed to cool to room temperature. The brown reaction mixture was loaded directly onto a column of 20 g of silica gel and eluted with pentane to provide 0.096 g (48%) of **273** as a pale yellow oil. Column chromatography on silica gel and (elution with pentane) furnished an analytical sample of **273** as a colorless oil.

IR (film)	3000, 2950, 2835, 1440, 1385, 1305, 1245, 1180, 1150, 1100, 1030, 890, 830, 750, and 680 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.16 (s, 1 H), 7.13 (s, 1 H), 2.98 (app t, J = 7.3 Hz, 2 H), 2.90 (app t, J = 7.3 Hz, 2 H), 2.37 (s, 3 H), 2.10 (app quintet, J = 7.4 Hz, 2 H), and 0.34 (s, 9 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	146.3, 143.4, 134.8, 134.7, 132.2, 126.0, 33.6, 32.5, 25.6, 21.4, and -0.5 ppm.
HRMS	Calcd for $C_{13}H_{20}Si$: 204.1334 Found: 204.1335.



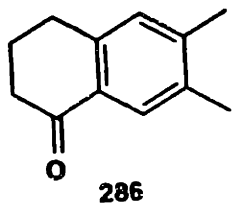
273

307



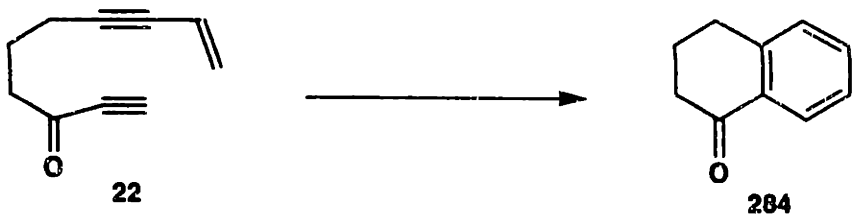
A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 9-methyl-9-undecen-1,7-diyn-3-one **241** (0.150 g, 0.861 mmol) and 15 mL of CH_2Cl_2. The solution was cooled to 0 °C, and aluminum chloride (0.131 g, 0.961 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 2 h. Saturated $NaHCO_3$ solution (5 mL) was added, and the aqueous phase was separated and extracted with three 10-mL portions of Et_2O. The combined organic phases were extracted with 10 mL each of H_2O and brine, dried with $MgSO_4$, filtered, and concentrated to give 0.212 g of a yellow oil. Purification by column chromatography on 15 g of silica gel (gradient elution with hexane to 3% ethyl acetate in hexane) provided 0.103 g (67%) of **286** as a yellow solid. Repurification by Kugelrohr distillation (ca. 0.1 mm Hg, bath temp 150 °C) gave a white solid (mp 38.5-40 °C). ^1H and ^{13}C NMR data are consistent with reported values.[144]

IR (film)	3000, 2940, 2875, 1670, 1475, 1450, 1410, 1355, 1345, 1270, 1220, 1180, and 1125 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.79 (s, 1 H), 7.01 (s, 1 H), 2.87 (t, J = 6.0 Hz, 2 H), 2.60 (t, J = 6.5 Hz, 2 H), 2.27 (s, 3 H), 2.26 (s, 3 H), and 2.09 (app quintet, J = 6.3 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	198.3, 134.0, 142.1, 135.0, 130.4, 129.7, 127.7, 39.1, 29.1, 23.4, 19.9, and 19.2 ppm.
Elemental Analysis	Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10 Found: C, 82.74; H, 7.89.



286

309



22 284

I Lewis Acid Procedure:

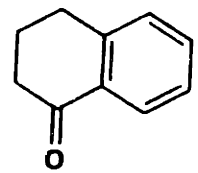
A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 9-decen-1,7-diyn-3-one **22** (0.200 g, 1.37 mmol) and 27 mL of CH_2Cl_2. The solution was cooled to 0 °C, and aluminum chloride (0.205 g, 1.51 mmol) was added in one portion. The reaction mixture was allowed to warm from 0 °C to room temperature over 2 h and was stirred at room temperature for 2 h. Triethylamine (a few drops) and saturated $NaHCO_3$ solution (7 mL) were added, and the aqueous phase was separated and extracted with two 10-mL portions of Et_2O. The combined organic phases were extracted with 10 mL each of H_2O and brine, dried with $MgSO_4$, filtered, and concentrated to give 0.275 g of a yellow oil. Purification by column chromatography on 10 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.128 g of impure **284** as an orange oil. Repurification by Kugelrohr distillation (ca. 0.1 mm Hg, bath temp 100 °C) gave 0.112 g (56%)of **284** as a colorless oil.

II Protic Acid Procedure

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 9-decen-1,7-diyn-3-one **22** (0.200 g, 1.37 mmol) and 27 mL of CH_2Cl_2. The solution was cooled to 0 °C, and methanesulfonic acid (0.220 mL, 0.329 g, 3.42 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm from 0 °C to room temperature over 6 h. Saturated $NaHCO_3$ solution (7mL) and triethylamine (a few drops) were added to the reaction mixture. The aqueous phase was extracted with two 7-mL portions of CH_2Cl_2,

and the combined organic phases were extracted with 7 mL each of H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to give 0.450 g of a brown oil. Purification by column chromatography on 20 g of silica gel (elution with 3% ethyl acetate in hexane) 0.165 g of impure **243** as an orange oil. Repurification by Kugelrohr distillation (ca. 0.1 mm Hg, bath temp 100 °C) gave 0.161 g of impure **243**. All spectroscopic data agrees with published accounts.[144]

IR (film)	3070, 3030, 2940, 2870, 1740, 1690, 1605, 1485, 1460, 1450, 1420, 1350, 1330, 1300, 1260, 1230, 1185, 1140, 1120, 1100, 1050, 1030, 910, 905, and 805 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.03 (d, J = 7.8 Hz, 1 H), 7.46 (t, J = 7.4 Hz, 1 H), 7.30 (d, J = 7.3 Hz, 1 H), 7.24 (d, J = 7.7 Hz, 1 H), 2.96 (t, J = 6.0 Hz, 2 H), 2.65 (t, J = 6.4 Hz, 2 H), and 2.13 (app quintet, J = 6.0 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	198.2, 144.4, 133.3, 132.6, 128.7, 127.1, 126.6, 39.1, 29.7, and 23.2 ppm.



284

^{1}H NMR Experiments: Different Concentrations of Enyne

212 **250**

A 1.0 M solution (2 mL) of enyne **212** in d_6-benzene and a solution of 20 mg of 1,4-dimethyoxybenzene in 1 mL of d_6-benzene were prepared. Four NMR tubes equipped with a rubber septum and nitrogen inlet adapter were charged with the enyne, 4-methyl-2,6-di-*tert*-butylphenol (BHT), d_6-benzene, and 1,4-dimethoxybenzene in the amounts shown below (Tubes 1-4). These solutions were then degassed by three cycles of freeze, pump, thaw, and the tubes were sealed. A ^{1}H NMR spectrum of each solution was taken, and the integrals for the methoxy group of the 1,4-dimethoxybenzene and the vinyl protons of the enyne were measured. The tubes were then immersed in a 176-180 °C oil bath and removed after 5 min of reaction time. A ^{1}H NMR spectrum was taken of each mixture, and the integrals were again measured. This process of immersion and removal to take NMR spectra was repeated at 10, 15, 20, 30, 45, 60, 90, and 120 min.

A 1.0 M solution (2 mL) of enyne **212** in d_6-benzene and a solution of 1,4-dimethyoxybenzene in d_6-benzene (20 mg in 1mL) were prepared. An NMR tube equipped with a rubber septum and nitrogen inlet adapter was charged with the enyne, 4-methyl-2,6-di-*tert*-butylphenol (BHT), d_6-benzene, and 1,4-dimethoxybenzene in the amounts shown below (Tube 4). These solutions were then degassed by three cycles of freeze, pump, thaw, and the tubes were sealed. A ^{1}H NMR spectrum of the solution was taken, and the integrals for the methoxy group of the 1,4-dimethoxybenzene and the vinyl protons of the enyne were measured. The tube was then immersed in a 177-182 °C oil bath and removed after 5 min of reaction time. A ^{1}H NMR spectrum was taken of each mixture, and the

integrals were again measured. This process of immersion and removal to take an NMR spectrum was repeated at 10, 15, 20, 30, 45, 60, 90, 120, 150, and 180 min.

Tube 1: 0.10 M solution of enyne in C_6D_6.

Reagent	Amount
enyne 212	0.06 mL of a 1 M solution (9.6 mg, 0.06 mmol)
BHT	6.6 mg (0.03 mmol)
d_6-benzene	0.49 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Tube 2: 0.05 M solution of enyne in C_6D_6.

Reagent	Amount
enyne 212	0.03 mL of a 1 M solution (4.8 mg, 0.03 mmol)
BHT	6.6 mg (0.03 mmol)
d_6-benzene	0.52 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Tube 3: 0.025 M solution of enyne in C_6D_6.

Reagent	Amount
enyne 212	0.015 mL of a 1 M solution (2.4 mg, 0.015 mmol)
BHT	6.6 mg (0.03 mmol)
d_6-benzene	0.535 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

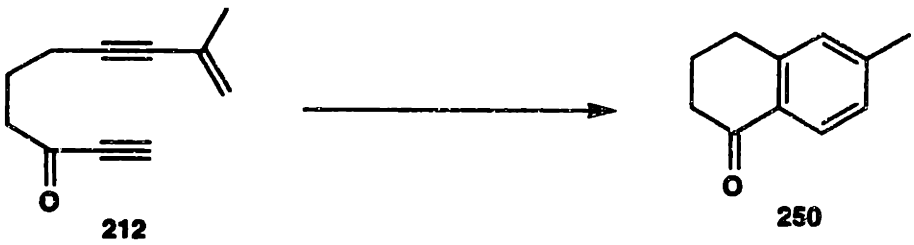
Tube 4: 0.0125 M solution of enyne in C_6D_6.

Reagent	Amount
enyne 212	0.006 mL of a 1 M solution (1.0 mg, 0.006 mmol)
BHT	5.5 mg (0.025 mmol)
d_6-benzene	0.444 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Data Derived from NMR Spectra: Different Enyne Concentrations

Time (min)	Integral 1,4-dimethoxy-benzene	Error on integral	Integral enyne 212	Error on integral	Mmol enyne 212	Error on mmol	Fraction enyne 212 remaining	Error on fraction	Integral tetralone 250	Error on integral	Mmol tetralone	Error on mmol	Fraction Yield	Error on yield
0.1 M Run 1/31/94														
0	6.8	0.2	16.17	0.2	5.16E-02	2.16E-03								
5	18.13	0.2	41.77	0.2	1.33E-01	4.56E-03	2.583	0.196	1.46	0.2	9.33E-03	1.55E-03	0.181	0.038
10	12.7	0.2	26.45	0.2	3.17E-02	5.89E-04	0.614	0.037	1.05	0.2	2.52E-03	5.07E-04	0.049	0.012
15	21.8	0.2	40.52	0.2	6.93E-02	1.43E-03	1.342	0.084	2.53	0.2	8.65E-03	8.26E-04	0.168	0.023
20	13.34	0.2	23.95	0.2	2.39E-02	4.18E-04	0.462	0.027	1.67	0.2	3.33E-03	4.29E-04	0.064	0.011
30	20.8	0.2	32.86	0.2	5.35E-02	1.13E-03	1.036	0.065	3.41	0.2	1.11E-02	8.18E-04	0.215	0.025
45	15.79	0.2	22.45	0.2	2.34E-02	4.34E-04	0.454	0.027	3.53	0.2	7.37E-03	4.89E-04	0.143	0.015
60	17.83	0.2	20.24	0.2	2.78E-02	6.28E-04	0.539	0.035	5.19	0.2	1.43E-02	7.31E-04	0.276	0.026
90	21.9	0.2	18.28	0.2	2.23E-02	4.93E-04	0.431	0.028	6.42	0.2	1.56E-02	6.63E-04	0.303	0.025
120	14.43	0.2	9.66	0.2	9.58E-03	2.86E-04	0.185	0.013	4.7	0.2	9.32E-03	4.82E-04	0.181	0.017
0.05 M Run 1/31/94														
0	9.34	0.2	12.13	0.2	2.82E-02	1.07E-03								
5	19.68	0.2	24.36	0.2	2.69E-02	4.94E-04	0.953	0.054	0	0.2				
10	17.4	0.2	19.71	0.2	2.46E-02	5.32E-04	0.872	0.052	1	0.2	2.30E-03	5.28E-04	0.089	0.022
15	17	0.2	18.23	0.2	2.33E-02	5.30E-04	0.826	0.050	1.27	0.2	3.25E-03	5.49E-04	0.115	0.024
20	22.11	0.2	22.43	0.2	2.20E-02	3.96E-04	0.781	0.044	1.89	0.2	3.71E-03	4.27E-04	0.132	0.020
30	21.67	0.2	19.83	0.2	1.99E-02	3.84E-04	0.705	0.040	2.21	0.2	4.43E-03	4.42E-04	0.157	0.022
45	23.04	0.2	19.38	0.2	1.83E-02	3.47E-04	0.648	0.037	3.75	0.2	7.07E-03	4.38E-04	0.251	0.025
60	23.43	0.2	17.05	0.2	1.58E-02	3.20E-04	0.560	0.033	3.98	0.2	7.38E-03	4.34E-04	0.262	0.025
90	21.82	0.2	11.58	0.2	1.15E-02	3.05E-04	0.409	0.026	4.02	0.2	8.00E-03	4.72E-04	0.284	0.027
120	22.62	0.2	10.08	0.2	9.68E-03	2.78E-04	0.343	0.023	4.7	0.2	9.03E-03	4.64E-04	0.320	0.029
0.025 M Run 1/31/94														
0	14.88	0.2	8.16	0.2	1.19E-02	4.52E-04								
5	15.74	0.2	8.37	0.2	1.15E-02	4.23E-04	0.970	0.072	0	0.2				
10	20.97	0.2	11.52	0.2	1.19E-02	3.21E-04	1.002	0.065	0.03	0.2	6.21E-05	4.15E-04	0.005	0.035
15	21.74	0.2	10.96	0.2	1.09E-02	3.01E-04	0.919	0.060	0.13	0.2	2.60E-04	4.02E-04	0.022	0.035
20	16.11	0.2	7.57	0.2	1.02E-02	3.96E-04	0.857	0.066	0.06	0.2	1.62E-04	5.41E-04	0.014	0.046
30	16.31	0.2	6.69	0.2	8.91E-03	3.76E-04	0.748	0.060	0.4	0.2	1.07E-03	5.46E-04	0.089	0.049
45	16.97	0.2	6.77	0.2	5.78E-03	2.35E-04	0.485	0.038	0.89	0.2	2.28E-03	5.39E-04	0.191	0.052
60	16.53	0.2	5.55	0.2	7.29E-03	3.51E-04	0.612	0.053	1.15	0.2	3.02E-03	5.62E-04	0.254	0.057
90	18.41	0.2	4.54	0.2	5.36E-03	2.94E-04	0.450	0.042	1.38	0.2	3.26E-03	5.07E-04	0.273	0.053
120	42.28	0.2	7.79	0.2	4.00E-03	1.22E-04	0.336	0.023	4.25	0.2	4.37E-03	2.26E-04	0.367	0.033
0.0125 M 2/10/94														
0	134.56		42.53		6.86E-03									
5	131.03		43.71		7.05E-03		1.028		0					
10	104.8		29.15		4.83E-03		0.704		2.18		7.23E-04		0.105	
15	133.98		34.77		7.21E-03		1.050		3.89		1.61E-03		0.235	
20	118		34.5		5.59E-03		0.815		3.86		1.25E-03		0.182	
30	125		25.3		4.66E-03		0.679		3.59		1.36E-03		0.198	
45	120		23.18		4.03E-03		0.587		4.37		1.52E-03		0.221	
60	120.42		16.08		2.91E-03		0.424		7.45		2.70E-03		0.393	
90	157.02		16.5		2.98E-03		0.434		10.5		3.79E-03		0.552	
120	131.21		15.48		2.14E-03		0.312		10.94		3.03E-03		0.441	
150	130.18		13.41		2.22E-03		0.324		13.05		4.32E-03		0.630	
180	140.25		7		1.17E-03		0.170		15.17		5.06E-03		0.738	

^{1}H NMR Experiments: Different Concentrations of BHT



212 250

A 1.0 M solution (2 mL) of enyne **212** in d_6-benzene and a solution of 20 mg of 1,4-dimethyoxybenzene in 1 mL of d_6-benzene were prepared. An NMR tube equipped with a rubber septum and nitrogen inlet adapter was charged with the enyne, 4-methyl-2,6-di-*tert*-butylphenol (BHT), d_6-benzene, and 1,4-dimethoxybenzene in the amounts shown below. The solution was then degassed by three cycles of freeze, pump, thaw and the tube was sealed. A ^{1}H NMR spectrum of the reaction mixture was taken, and the integrals for the methoxy group of the 1,4-dimethoxybenzene and the vinyl protons of the enyne were measured. The tube was then immersed in a 177-182 °C oil bath and removed after 5 min of reaction time. A ^{1}H NMR spectrum was taken of each reaction mixture, and the integrals were again measured. This process of immersion and removal to take an NMR spectrum was repeated at 10, 15, 20, 30, 45, 60, 90, 120, 150, and 180 min. The data collected here was then compared to the data collected in the enyne concentration experiment above for tube 3 (0.025 M enyne and 0.05 M BHT)

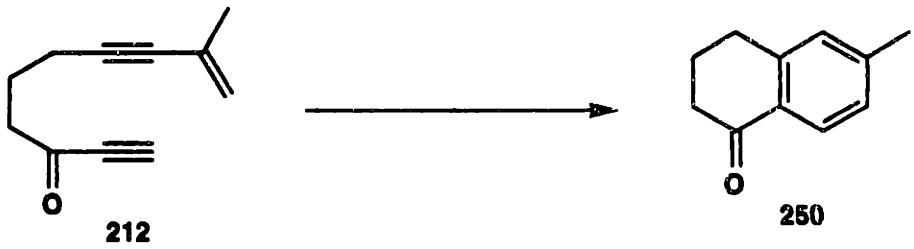
Tube 5: 0.25 M BHT reaction mixture.

Reagent	Amount
enyne **212**	0.012 mL of a 1 M solution (2.0 mg, 0.012 mmol)
BHT	27.5 mg (0.125 mmol)
d_6-benzene	0.39 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Data Derived from NMR Spectra: Different BHT Concentrations

Time (min)	Integral 1,4-dimethoxy-benzene	Error on integral	Integral enyne 212	Error on integral	Mmol enyne 212	Error on mmol	Fraction enyne 212 remaining	Error on fraction	Integral tetralone 250	Error on integral	Mmol tetralone	Error on mmol	Fraction Yield	Error on yield
0.05 M BHT (0.025 M Enyne) Run 1/31/94														
0	14.88	0.2	8.16	0.2	1.19E-02	5 E-04								
5	15.74	0.2	8.37	0.2	1.15E-02	4 E-04	0.970	0.072	0	0.2				
10	20.97	0.2	11.52	0.2	1.19E-02	3 E-04	1.002	0.065	0.03	0.2	6.21E-05	4 E-04	0.005	0.035
15	21.74	0.2	10.96	0.2	1.09E-02	3 E-04	0.919	0.060	0.13	0.2	2.60E-04	4 E-04	0.022	0.035
20	16.11	0.2	7.57	0.2	1.02E-02	4 E-04	0.857	0.066	0.06	0.2	1.62E-04	5 E-04	0.014	0.046
30	16.31	0.2	6.69	0.2	8.91E-03	4 E-04	0.748	0.060	0.4	0.2	1.07E-03	5 E-04	0.089	0.049
45	16.97	0.2	6.77	0.2	5.78E-03	2 E-04	0.485	0.038	0.89	0.2	2.28E-03	5 E-04	0.191	0.052
60	16.53	0.2	5.55	0.2	7.29E-03	4 E-04	0.612	0.053	1.15	0.2	3.02E-03	6 E-04	0.254	0.057
90	18.41	0.2	4.54	0.2	5.36E-03	3 E-04	0.450	0.042	1.38	0.2	3.26E-03	5 E-04	0.273	0.053
120	42.28	0.2	7.79	0.2	4.00E-03	1 E-04	0.336	0.023	4.25	0.2	4.37E-03	2 E-04	0.367	0.033
0.25 M BHT(0.025 M Enyne) 2/10/94														
0	22.74	0.2	15.7	0.2	1.44E-02	3 E-04								
5	20.55	0.2	10	0.2	1.06E-02	3 E-04	0.733	0.038	0	0.2				
10	26.66	0.2	12.2	0.2	9.94E-03	2 E-04	0.689	0.032	1.14	0.2	1.86E-03	3 E-04	0.129	0.026
15	27.73	0.2	13	0.2	1.02E-02	2 E-04	0.706	0.032	1.83	0.2	2.87E-03	3 E-04	0.199	0.028
20	18.57	0.2	8.43	0.2	9.86E-03	3 E-04	0.684	0.039	0.57	0.2	1.33E-03	5 E-04	0.092	0.035
30	21.11	0.2	10.92	0.2	1.12E-02	3 E-04	0.779	0.039	1.52	0.2	3.13E-03	4 E-04	0.217	0.035
45	40.51	0.2	14.54	0.2	5.20E-03	1 E-04	0.360	0.015	3.44	0.2	3.69E-03	2 E-04	0.256	0.022
60	39.5	0.2	12	0.2	6.60E-03	1 E-04	0.458	0.020	6.76	0.2	7.43E-03	3 E-04	0.515	0.029
90	42.8	0.2	8.5	0.2	4.31E-03	1 E-04	0.299	0.015	8.06	0.2	8.18E-03	2 E-04	0.567	0.029
120	40.64	0.2	7.1	0.2	3.79E-03	1 E-04	0.263	0.015	8.42	0.2	9.00E-03	3 E-04	0.624	0.032
150	19.53	0.2	3.24	0.2	3.60E-03	3 E-04	0.250	0.023	4.35	0.2	9.68E-03	5 E-04	0.671	0.052
180	41.92	0.2	5.26	0.2	2.73E-03	1 E-04	0.189	0.012	8.13	0.2	8.42E-03	2 E-04	0.584	0.030

^{1}H NMR Experiments: Reactions in the Presence of an Acid Scavenger, (with BHT)



212 250

A 0.1 M solution (2 mL) of enyne **212** and 4-methyl-2,6-di-*tert*-butylphenol in d_8-toluene and a solution of 20 mg of 1,4-dimethyoxybenzene in 1 mL of d_8-toluene were prepared. Three NMR tubes equipped with a rubber septum and nitrogen inlet adapter were charged with the enyne, 4-methyl-2,6-di-*tert*-butylphenol (BHT), d_8-toluene, and 1,4-dimethoxybenzene in the amounts shown below. Tubes 2 and 3 were also charged with 2,6-di-*tert*-butylpyridine (DTP). These solutions were then degassed by three cycles of freeze, pump, thaw and the tubes were sealed. A ^{1}H NMR spectrum of each solution was taken, and the integrals for the methoxy group of the 1,4-dimethoxybenzene and the vinyl protons of the enyne were measured. The tubes were then immersed in a 176-180 ℃ oil bath and removed after 5 min of reaction time. A ^{1}H NMR spectrum was taken of each mixture, and the integrals were again measured. This process of immersion and removal to take an NMR spectrum was repeated at 10, 15, 20, 25, 30, 35, 45, 75, 105, 150, and 180 min.

Tube 1: Enyne with BHT.

Reagent	Amount
enyne 212	4.8 mg, 0.030 mmol (0.300 mL of a 0.1 M solution)
BHT	6.6 mg, 0.030 mmol
d_8-toluene	0.3 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Tube 2: Enyne with BHT and Base.

Reagent	Amount
enyne 212	4.0 mg, 0.025 mmol (0.250 mL of a 0.1 M solution)
BHT	5.5 mg (0.025 mmol)
2,6-di*t*-butyl-pyridine	5.3 mg (0.028 mmol)
d_8-toluene	0.250 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

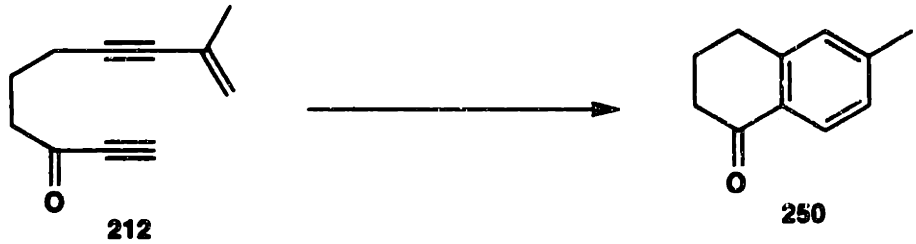
Tube 3: Enyne with BHT and Base

Reagent	Amount
enyne 212	4.0 mg, 0.025 mmol (0.250 mL of a 0.1 M solution)
BHT	5.5 mg (0.025 mmol)
2,6-dit-butyl-pyridine	5.3 mg (0.028 mmol)
d_8-toluene	0.250 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Data Derived from NMR Spectra: Reactions with Base and BHT

Time (min)	Integral 1,4-dimethoxy-benzene	Error on integral	Integral enyne 212	Error on integral	Mmol enyne 212	Error on mmol	Fraction enyne 212 remaining	Error on fraction	Integral tetralone 250	Error on integral	Mmol tetralone	Error on mmol	Fraction Yield	Error on yield
No Base Run 12/15/93														
0	17.7	0.1	8.7	0.1	1.07E-02	2 E-04								
5	63	0.1	28.34	0.1	9.77E-03	5 E-05	0.915	0.020	0.44	0.1	3.03E-04	7 E-05	0.028	0.007
10	64.4	0.1	26.4	0.1	8.90E-03	5 E-05	0.834	0.019	2.4	0.1	1.62E-03	7 E-05	0.152	0.009
15	66.21	0.1	21.97	0.1	7.21E-03	4 E-05	0.675	0.016	4.01	0.1	2.63E-03	7 E-05	0.246	0.011
20	65.07	0.1	21.1	0.1	7.04E-03	4 E-05	0.660	0.015	4.94	0.1	3.30E-03	7 E-05	0.309	0.012
25	67.2	0.1	19.4	0.1	6.27E-03	4 E-05	0.587	0.014	4.85	0.1	3.14E-03	7 E-05	0.294	0.012
35	66.2	0.1	15.8	0.1	5.18E-03	4 E-05	0.486	0.012	6.04	0.1	3.96E-03	7 E-05	0.371	0.013
45	65.8	0.1	13.7	0.1	4.52E-03	4 E-05	0.424	0.011	7.12	0.05	4.70E-03	4 E-05	0.440	0.011
75	75.3	0.1	5.4	0.2	3.12E-03	1 E-04	0.292	0.016	10.49	0.05	6.05E-03	4 E-05	0.567	0.013
105	81.2	0.1	3.9	0.2	2.09E-03	1 E-04	0.195	0.014	11.1	0.05	5.94E-03	3 E-05	0.556	0.013
150	80.1	0.1	3	0.1	1.63E-03	6 E-05	0.152	0.008	12.1	0.1	6.56E-03	6 E-05	0.615	0.016
180	80	0.5	2.6	0.2	1.41E-03	1 E-04	0.132	0.013	11.9	0.1	6.46E-03	9 E-05	0.605	0.019
With Base 1 Run 12/15/93														
0	12.2	0.1	5.3	0.1	9.44E-03	3 E-04								
5	36.2	0.1	14.4	0.1	8.64E-03	8 E-05	0.916	0.034	0.6	0.1	7.20E-04	1 E-04	0.076	0.015
10	37.19	0.05	12.67	0.05	7.40E-03	4 E-05	0.784	0.025	1.1	0.1	1.28E-03	1 E-04	0.136	0.016
15	37.5	0.1	11.9	0.1	6.89E-03	8 E-05	0.730	0.028	1.59	0.1	1.84E-03	1 E-04	0.195	0.018
20	38.5	0.1	11.5	0.1	6.49E-03	7 E-05	0.688	0.026	1.9	0.1	2.14E-03	1 E-04	0.227	0.019
25	36.8	0.1	9.8	0.1	5.78E-03	7 E-05	0.613	0.025	1.8	0.1	2.12E-03	1 E-04	0.225	0.019
35	38.2	0.1	8.9	0.1	5.06E-03	7 E-05	0.536	0.022	2.6	0.1	2.96E-03	1 E-04	0.313	0.021
45	38	0.1	8.7	0.1	4.97E-03	7 E-05	0.527	0.022	3.1	0.1	3.54E-03	1 E-04	0.376	0.023
75	43.2	0.1	5	0.1	2.51E-03	6 E-05	0.266	0.013	4.21	0.05	4.23E-03	6 E-05	0.449	0.019
105	43.7	0.1	5.5	0.1	2.73E-03	6 E-05	0.290	0.014	4.92	0.05	4.89E-03	6 E-05	0.518	0.020
150	45.67	0.05	1.8	0.1	1.71E-03	1 E-04	0.181	0.015	5.23	0.05	4.97E-03	5 E-05	0.527	0.020
180	43.1	0.05	1.55	0.05	1.56E-03	5 E-05	0.166	0.010	5.34	0.05	5.38E-03	6 E-05	0.570	0.021
With Base 2 Run 12/15/93														
0	12	0.1	5	0.1	9.05E-03	3 E-04								
5	38.4	0.1	14.2	0.1	8.03E-03	8 E-05	0.888	0.034	0.6	0.1	6.79E-04	1 E-04	0.075	0.015
10	37.8	0.1	12.35	0.05	7.10E-03	5 E-05	0.784	0.027	1.2	0.1	1.38E-03	1 E-04	0.152	0.017
15	39	0.1	11.9	0.1	6.63E-03	7 E-05	0.732	0.029	1.8	0.1	2.00E-03	1 E-04	0.222	0.019
20	39.9	0.1	10.6	0.1	5.77E-03	7 E-05	0.638	0.026	2	0.1	2.18E-03	1 E-04	0.241	0.019
25	39.5	0.1	10.2	0.1	5.61E-03	7 E-05	0.620	0.025	2.5	0.1	2.75E-03	1 E-04	0.304	0.022
35	37.3	0.1	8	0.1	4.66E-03	7 E-05	0.515	0.022	2.7	0.1	3.14E-03	1 E-04	0.347	0.024
45	38.4	0.1	6.27	0.1	3.55E-03	7 E-05	0.392	0.018	3.08	0.1	3.48E-03	1 E-04	0.385	0.024
75	42.9	0.1	4.6	0.1	2.33E-03	6 E-05	0.257	0.013	4.08	0.05	4.13E-03	6 E-05	0.457	0.020
105	45.17	0.05	4.7	0.1	2.26E-03	5 E-05	0.250	0.013	5.21	0.05	5.01E-03	5 E-05	0.554	0.022
150	45.7	0.1	1.9	0.1	1.81E-03	1 E-04	0.200	0.017	5.17	0.05	4.91E-03	6 E-05	0.543	0.022
180	46.2	0.1	1.4	0.2	1.32E-03	2 E-04	0.145	0.025	5.55	0.05	5.22E-03	6 E-05	0.577	0.023

^{1}H NMR Experiments: Reactions in the Presence of an Acid Scavenger (no BHT)



212 250

A 1.0 M solution (2 mL) of enyne **212** in d_6-benzene and a solution of 1,4-dimethyoxybenzene in d_6-benzene (20 mg in 1mL) were prepared. Four NMR tubes equipped with a rubber septum and nitrogen inlet adapter were charged with the enyne, d_8-toluene, and 1,4-dimethoxybenzene in the amounts shown below. Tubes 3 and 4 were also charged with 2,6-di-*tert*-butylpyridine (DTP). These solutions were then degassed by three cycles of freeze, pump, thaw and the tubes were sealed. A ^{1}H NMR spectrum of each solution was taken, and the integrals for the methoxy group of the 1,4-dimethoxybenzene and the vinyl protons of the enyne were measured. The tubes were then immersed in a 176-180 °C oil bath and removed after 10 min of reaction time. A ^{1}H NMR spectrum was taken of each mixture, and the integrals were again measured. This process of immersion and removal to take an NMR spectrum was repeated at 20, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 min.

Tube 1: Enyne Alone.

Reagent	Amount
enyne 212	3.2 mg, 0.02 mmol (0.02 mL of a 1 M solution)
d_8-toluene	0.3 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Tube 2: Enyne Alone.

Reagent	Amount
enyne 212	3.2 mg, 0.02 mmol (0.02 mL of a 1 M solution)
d_8-toluene	0.3 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Tube 3: Enyne with Base.

Reagent	Amount
enyne 212	3.2 mg, 0.020 mmol (0.02 mL of a 1 M solution)
2,6-di*t*-butyl-pyridine	3.5 mg (0.018 mmol)
d_8-toluene	0.33 mL
1,4-dimethoxy-	0.05 mL of a 20 mg/mL

benzene	solution (1 mg)

Tube 4: Enyne with Base.

Reagent	Amount
enyne 212	3.2 mg, 0.020 mmol (0.02 mL of a 1 M solution)
2,6-di*t*-butyl-pyridine	3.5 mg (0.018 mmol)
d_8-toluene	0.33 mL
1,4-dimethoxy-benzene	0.05 mL of a 20 mg/mL solution (1 mg)

Data Derived from NMR Spectra: Reactions with and without Base

Time (min)	Integral 1,4-dimethoxy-benzene	Integral enyne 212	Mmol enyne 212	Fraction enyne 212 remaining	Error on fraction	Integral tetralone 250	Mmol tetralone	Fraction Yield	Error on yield
No Base Run 1 3/2/94									
0	49.66	40.94	0.0179						
10	26.63	19.76	0.0161	0.90	0.14	0.29	0.0005	0.03	0.00
20	54.52	35.74	0.0142	0.80	0.16	1.72	0.0014	0.08	0.02
30	52.80	33.08	0.0136	0.76	0.15	2.07	0.0017	0.10	0.02
60	109.00	46.00	0.0092	0.51	0.10	8.66	0.0035	0.19	0.04
90	110.00	32.00	0.0063	0.35	0.07	10.75	0.0042	0.24	0.05
120	110.00	26.00	0.0051	0.29	0.23	12.24	0.0048	0.27	0.22
150	106.50	22.08	0.0045	0.25	0.25	13.91	0.0057	0.32	0.32
180	92.03	13.57	0.0032	0.18	0.07	12.67	0.0060	0.33	0.13
210	42.00	4.60	0.0024	0.13	0.03	6.54	0.0068	0.38	0.08
240	105.00	12.00	0.0025	0.14	0.03	15.00	0.0062	0.35	0.07
270	101.00	11.00	0.0024	0.13	0.03	15.00	0.0069	0.38	0.08
300	105.00	9.00	0.0019	0.10	0.02	17.28	0.0071	0.40	0.08
No Base Run 2 3/2/94									
0	44.30	39.26	0.0192						
10	71.85	56.32	0.0170	0.88	0.13	0.48	0.0003	0.02	0.00
20	37.07	25.06	0.0147	0.76	0.15	1.20	0.0014	0.07	0.01
30	38.39	23.14	0.0131	0.68	0.14	1.63	0.0018	0.10	0.02
60	94.70	40.14	0.0092	0.48	0.10	7.06	0.0032	0.17	0.03
90	96.45	30.32	0.0068	0.35	0.07	10.17	0.0046	0.24	0.05
120	97.06	24.58	0.0055	0.29	0.23	10.85	0.0049	0.25	0.20
150	93.59	17.38	0.0040	0.21	0.21	11.80	0.0055	0.28	0.28
180	92.03	13.57	0.0032	0.17	0.07	12.67	0.0060	0.31	0.12
210	55.00	7.00	0.0028	0.14	0.03	8.03	0.0063	0.33	0.07
240	94.00	10.00	0.0023	0.12	0.02	14.60	0.0067	0.35	0.07
270	86.00	8.00	0.0020	0.10	0.02	14.02	0.0071	0.37	0.07
300	47.00	4.00	0.0018	0.10	0.02	6.75	0.0062	0.32	0.06

Time (min)	Integral 1,4-dimethoxy-benzene	Integral enyne 212	Mmol enyne 212	Fraction enyne 212 remaining	Error on fraction	Integral tetralone 250	Mmol tetralone	Fraction Yield	Error on yield
With Base Run 1 3/2/94									
0	19.40	16.82	0.0188						
10	9.81	7.86	0.0174	0.92	0.14	0.00	0.0000	0.00	0.00
20	16.08	11.60	0.0157	0.83	0.17	0.41	0.0011	0.06	0.01
30	41.25	25.90	0.0136	0.72	0.14	1.63	0.0017	0.09	0.02
60	43.52	17.80	0.0089	0.47	0.09	3.10	0.0031	0.16	0.03
90	40.00	12.00	0.0065	0.35	0.07	4.56	0.0050	0.26	0.05
120	70.00	14.00	0.0043	0.23	0.18	8.00	0.0050	0.26	0.21
150	80.00	14.00	0.0038	0.20	0.20	10.00	0.0054	0.29	0.29
180	180.00	25.00	0.0030	0.16	0.06	21.00	0.0051	0.27	0.11
210	42.00	6.00	0.0031	0.16	0.03	5.50	0.0057	0.30	0.06
240	34.96	4.00	0.0025	0.13	0.03	5.63	0.0070	0.37	0.07
270	40.90	4.00	0.0021	0.11	0.02	7.17	0.0076	0.40	0.08
300	38.59	4.00	0.0023	0.12	0.02	7.18	0.0081	0.43	0.09
With Base Run 2 3/2/94									
0	16.23	14.29	0.0191						
10	10.65	8.79	0.0179	0.94	0.14	0.10	0.0004	0.02	0.00
20	22.83	15.40	0.0147	0.77	0.15	0.48	0.0009	0.05	0.01
30	28.80	16.92	0.0128	0.67	0.13	0.81	0.0012	0.06	0.01
60	36.54	15.60	0.0093	0.48	0.10	2.76	0.0033	0.17	0.03
90	94.33	28.00	0.0064	0.34	0.07	9.26	0.0043	0.22	0.04
120	95.43	20.00	0.0046	0.24	0.19	11.15	0.0051	0.27	0.21
150	112.00	20.30	0.0039	0.21	0.21	12.75	0.0049	0.26	0.26
180	110.00	18.00	0.0036	0.19	0.07	13.00	0.0051	0.27	0.11
210	44.97	6.00	0.0029	0.15	0.03	5.86	0.0057	0.30	0.06
240	45.17	6.40	0.0031	0.16	0.03	6.93	0.0067	0.35	0.07
270	29.00	3.00	0.0022	0.12	0.02	5.30	0.0079	0.42	0.08
300	28.00	2.00	0.0016	0.08	0.02	4.93	0.0076	0.40	0.08

Data Derived from NMR Spectra: Reactions without BHT or Base Averages

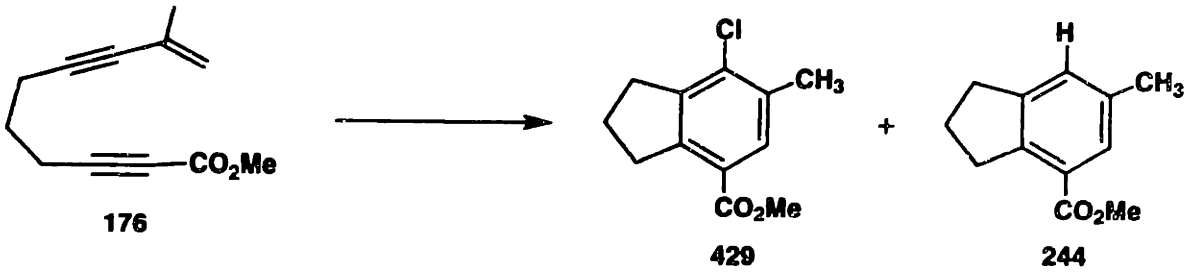
Time (min)	Integral 1,4-dimethoxy-benzene	Integral enyne 212	Mmol enyne 212	Fraction enyne 212 remaining	Integral tetralone 250	Mmol tetralone	Fraction Yield	Time (min)	Average Fraction Enyne Remaining	Std. Dev. on Average Fration Enyne Rem.	Average Yield (Fraction)	Std. Dev. on Average Yield
Reactions with no base or BHT												
Run 1/24/94								0				
0	28	28	0.0217					5	0.92	0.01		
5	36	33.1	0.0200	0.92	0			10	0.89	0.02	0.03	0.03
10	89	76.7	0.0187	0.86	3	0.0015	0.07	15	0.82	0.08	0.04	0.03
15	67	52.1	0.0169	0.78	2	0.0013	0.06	20	0.78	0.03	0.06	0.02
20	68.7	52.5	0.0166	0.76	1.8	0.0011	0.05	25	0.77		0.06	
25	89.3	68.4	0.0166	0.77	2.9	0.0014	0.06	30	0.73	0.04	0.09	0.01
30	88.5	67.3	0.0165	0.76	3.9	0.0019	0.09	45	0.54	0.25	0.09	0.02
45	102.8	73	0.0154	0.71	5	0.0021	0.10	60	0.55	0.07	0.15	0.03
60	103	66.2	0.0140	0.64	6.2	0.0026	0.12	90	0.41	0.09	0.24	0.03
90	85	45.7	0.0117	0.54	12	0.0061	0.28	120	0.33	0.08	0.24	0.03
120	85	38.2	0.0098	0.45	8.2	0.0042	0.19	150	0.29	0.10	0.28	0.04
150	83	33.8	0.0088	0.41	9.8	0.0051	0.24	180	0.23	0.10	0.30	0.04
180	83	28	0.0073	0.34	10.7	0.0056	0.26	210	0.14	0.01	0.35	0.03
								240	0.13	0.01	0.35	0.00
Run 2/4/94								270	0.37	0.44	0.26	0.21
0	14.42	16.77	0.0337					300	0.36	0.48	0.36	0.05
5	24.1	34.76	0.0313	0.93	0							
10	18.82	26.36	0.0304	0.90	0	0.0000	0.00					
15	19.25	25.58	0.0289	0.86	0.29	0.0007	0.02					
20	23.8	30.09	0.0275	0.82	0.62	0.0011	0.03					
25												
30	25.42	29.12	0.0249	0.74	1.26	0.0022	0.06					
45	46.34	26.02	0.0122	0.36	2.7	0.0025	0.08					
60	48.32	41.62	0.0187	0.56	4.96	0.0045	0.13					
90	54.05	34.56	0.0139	0.41	8.67	0.0070	0.21					
120	59.08	28.96	0.0106	0.32	11.21	0.0082	0.24					
Run 3/2/94 a												
0	44.30	39.26	0.0192									
5												
10	71.85	56.32	0.0170	0.88	0.48	0.0003	0.02					
15												
20	37.07	25.06	0.0147	0.76	1.20	0.0014	0.07					
25												
30	38.39	23.14	0.0131	0.68	1.63	0.0018	0.10					
45												
60	94.70	40.14	0.0092	0.48	7.06	0.0032	0.17					
90	96.45	30.32	0.0068	0.35	10.17	0.0046	0.24					
120	97.06	24.58	0.0055	0.29	10.85	0.0049	0.25					
150	93.59	17.38	0.0040	0.21	11.80	0.0055	0.28					
180	92.03	13.57	0.0032	0.17	12.67	0.0060	0.31					
210	55.00	7.00	0.0028	0.14	8.03	0.0063	0.33					

Time (min)	Integral 1,4-dimethoxy-benzene	Integral enyne 212	Mmol enyne 212	Fraction enyne 212 remaining	Integral tetralone 250	Mmol tetralone	Fraction Yield		Time (min)	Average Fraction Enyne Remaining	Std. Dev. on Average Fration Enyne Rem.	Average Yield (Fraction)	Std. Dev. on Average Yield
240	94.00	10.00	0.0023	0.12	14.60	0.0067	0.35						
270	86.00	8.00	0.0020	0.10	14.02	0.0071	0.37						
300	47.00	4.00	0.0018	0.10	6.75	0.0062	0.32						
Run 3/2/94 b													
0	49.66	40.94	0.0179										
5													
10	26.63	19.76	0.0161	0.90	0.29	0.0005	0.03						
15													
20	54.52	35.74	0.0142	0.80	1.72	0.0014	0.08						
25													
30	52.80	33.08	0.0136	0.76	2.07	0.0017	0.10						
45													
60	109.00	46.00	0.0092	0.51	8.66	0.0035	0.19						
90	110.00	32.00	0.0063	0.35	10.75	0.0042	0.24						
120	110.00	26.00	0.0051	0.29	12.24	0.0048	0.27						
150	106.50	22.08	0.0045	0.25	13.91	0.0057	0.32						
180	92.03	13.57	0.0032	0.18	12.67	0.0060	0.33						
210	42.00	4.60	0.0024	0.13	6.54	0.0068	0.38						
240	105.00	12.00	0.0025	0.14	15.00	0.0062	0.35						
270	101.00	11.00	0.0024	0.13	16.00	0.0069	0.38						
300	105.00	9.00	0.0019	0.10	17.28	0.0071	0.40						

Data Derived from NMR Spectra: Reactions with BHT Averages

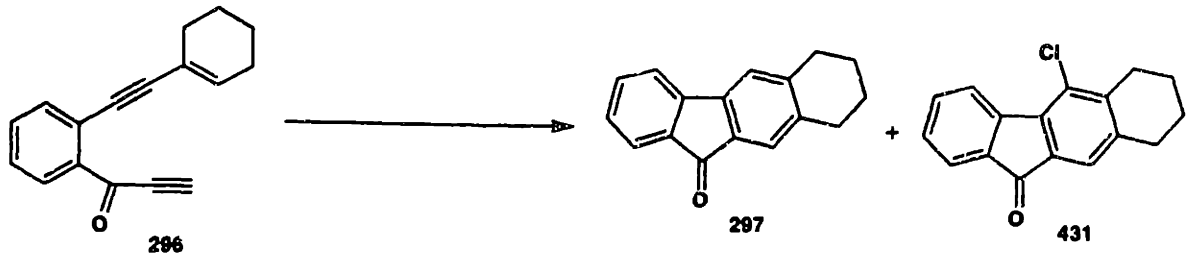
Time (min)	Integral 1,4-dimethoxy-benzene	Integral enyne 212	Mmol enyne 212	Fraction enyne 212 remaining	Integral tetralone 250	Mmol tetralone	Fraction Yield	Time (min)	Average Fraction Enyne Remaining	Std. Dev. on Average Fration Enyne Rem.	Average Yield (Fraction)	Std. Dev. on Average Yield
Reactions with no base or BHT												
Run 1/31/94								0				
0	9.34	12.13	0.0282					5	0.98	0.04		
5	19.58	24.36	0.0269	0.95	0			10	0.92	0.05	0.09	0.00
10	17.4	19.71	0.0246	0.87	1	0.0025	0.09	15	0.89	0.05	0.10	0.05
15	17	18.23	0.0233	0.83	1.27	0.0032	0.12	20	0.80	0.03	0.14	0.08
20	22.11	22.43	0.0220	0.78	1.89	0.0037	0.13	25	0.73		0.17	0.10
30	21.67	19.83	0.0199	0.70	2.21	0.0044	0.16	30	0.66	0.12	0.23	0.12
45	23.04	19.38	0.0183	0.65	3.75	0.0071	0.25	45	0.57	0.12	0.27	0.16
60	23.43	17.05	0.0158	0.56	3.98	0.0074	0.26	60	0.44	0.14	0.32	0.18
90	21.82	11.58	0.0115	0.41	4.02	0.0080	0.28	90	0.35	0.13	0.28	0.16
120	22.62	10.08	0.0097	0.34	4.7	0.0090	0.32	120	0.29	0.16	0.24	0.16
								150	0.24	0.15	0.28	0.20
Run 1/24/94								180	0.20	0.13	0.33	0.24
0	20.8	32.7	0.0341					210	0.53	0.62	0.20	0.14
5	11	16.8	0.0332	0.97	0			240	0.49	0.59	0.15	0.11
10	28	40.2	0.0312	0.91	1.9	0.0029	0.09	270	0.49	0.60	0.16	0.11
15	26.2	37.8	0.0313	0.92	2.1	0.0035	0.10	300	0.64	0.51	0.15	0.10
20	27	35.6	0.0286	0.84	2.1	0.0034	0.10					
25	42	54	0.0279	0.82	3.5	0.0036	0.11					
30	25.1	30.6	0.0265	0.78	3.8	0.0066	0.19					
45	20.5	22.1	0.0234	0.69	3	0.0064	0.19					
60	30.1	28.2	0.0203	0.60	5.9	0.0085	0.25					
90	35	26.3	0.0163	0.48	9	0.0112	0.33					
120	26	16.7	0.0140	0.41	6.5	0.0109	0.32					
150	26	14	0.0117	0.34	8	0.0134	0.39					
180	24.2	11.1	0.0100	0.29	8.9	0.0160	0.47					
Run 2/4/94												
0	13.45	19.42	0.0314									
5	10.13	15.06	0.0323	1.03	0							
10	10.66	15.02	0.0306	0.98	0.73	0.0030	0.09					
15	13.3	17.55	0.0287	0.91	0.81	0.0026	0.08					
30	11.07	12.59	0.0247	0.79	1.54	0.0060	0.19					
45	22.56	21.78	0.0210	0.67	3.96	0.0076	0.24					
60	22.28	17.44	0.0170	0.54	4.15	0.0081	0.26					
90	23.21	15.11	0.0141	0.45	6.2	0.0116	0.37					
120	21.55	10.16	0.0102	0.33	6.61	0.0133	0.42					
90	96.45	30.32	0.0068	0.22	10.17	0.0046	0.15					
120	97.06	24.58	0.0055	0.18	10.85	0.0049	0.15					
150	93.59	17.38	0.0040	0.13	11.80	0.0055	0.17					
180	92.03	13.57	0.0032	0.10	12.67	0.0060	0.19					
210	55.00	7.00	0.0028	0.09	8.03	0.0063	0.20					
240	94.00	10.00	0.0023	0.07	14.60	0.0067	0.22					
270	86.00	8.00	0.0020	0.06	14.02	0.0071	0.23					
300	47.00	4.00	0.0018	0.06	6.75	0.0062	0.20					

Chlorine Incorporation Experiments

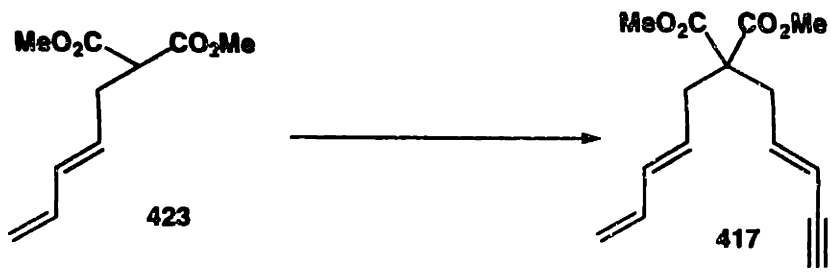


176 429 244

A threaded Pyrex tube (ca. 30 mL capacity) equipped with rubber septum and a nitrogen inlet needle was charged with methyl 9-methyl-9-decen-2,7-diynoate **176** (0.150g, 0.788 mmol) and 7.9 mL of carbon tetrachloride. The solution was degassed by three freeze-pump-thaw cycles, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was immersed in a 180 °C oil bath for 8 h and then allowed to cool to room temperature. Concentration of the liquid gave 0.261 g of a brown oil. Column chromatography on 20 g of silica gel (elution with 3% ethyl acetate-hexane) provided 0.053 g of a mixture of **402** and **244** as a yellow oil.

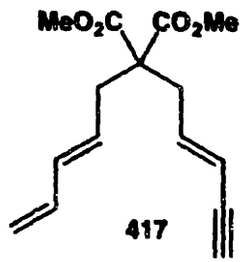


A 25-mL, round-bottomed flask equipped with an argon inlet adapter and reflux condenser was charged with 2-(2-cyclohexenylethynyl)phenyl-2-propyn-1-one **296** (0.102 g, 0.435 mmol) and 8.7 mL of carbon tetrachloride. The solution was heated at reflux for 24 h, and then allowed to cool and concentrated to give a brown oil. Purification by column chromatography on 1 g of silica gel (elution with hexane) gave 39 mg of a mixture of two compounds. Repurification by column chromatography on 1 g of silica gel (elution with hexane) provided two compounds, 25 mg of mainly **404** as a yellow solid and 21 mg of mainly **297** as a yellow solid.

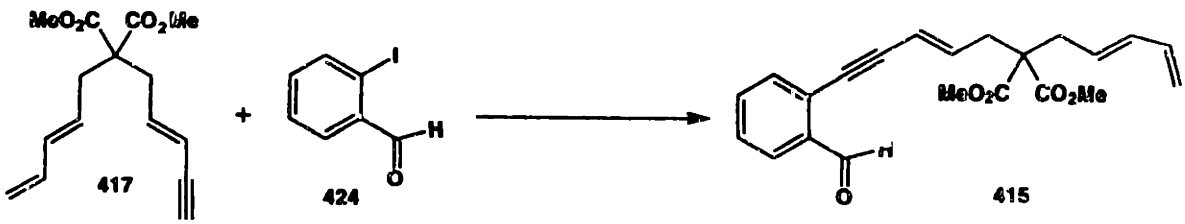


A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and nitrogen inlet adapter was charged with 70 mL of benzene, hexamethylphosphoramide (1.63 g, 1.59 mL, 9.12 mmol), and sodium hydride (0.230 g, 5.76 mmol, 60% dispersion in mineral oil). Diester **423** (1.00 g, 5.04 mmol) was added to the reaction mixture via syringe over 30 sec. This solution was stirred for 20 min at room temperature, and 1-bromo-2-penten-4-yne (0.700 g, 4.80 mmol) was added in one portion via syringe. The reaction mixture was stirred at room temperature for 2.25 h. Saturated $NaHCO_3$ solution (10 mL) was added, and the resulting solution was separated and extracted with two 30-mL portions of Et_2O. The combined organic phases were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.87 g of a yellow oil. Purification by column chromatography on 50 g of silica gel (elution with benzene) gave 1.17 g of **417** as an oil (93%).

IR (film)	3280, 3000, 2950, 2100, 1725, 1600, 1435, 1200, 1095, 1080, 1005, 960, and 905 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.26 (ddd, J = 16.8, 10.3, 10.3 Hz, 1 H), 6.01-6.20 (m, 2 H), 5.41-5.54 (m, 2H), 5.13 (d, J = 16.7 Hz, 1 H), 5.02 (d, J = 10.1 Hz, 1 H), 3.72 (s, 6H), 2.82 (d, J = 2.4 Hz, 1 H), and 2.64-2.68 (m, 4 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	170.5, 139.4, 136.2, 135.2, 127.1, 116.7, 112.7, 81.6, 57.6, 52.6, 36.6, and 36.1 ppm.



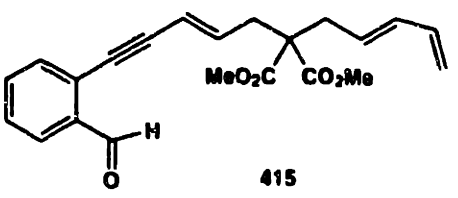
417



A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with the alkyne **417** (0.095 g, 0.362 mmol), 3.6 mL of *N*-methylpyrrolidinone, 2-iodobenzaldehyde (0.088 g, 0.381 mmol), and triethylamine (0.159 mL, 0.116 g, 1.143 mmol). To this mixture were added trifurylphosphine (0.014 g, 0.060 mmol), $Pd_2(dba)_3$ (0.014 g, 0.015 mmol), and copper (I) iodide (0.036 g, 0.190 mmol), and this solution was stirred at room temperature for 10 min. Saturated NH_4Cl solution (1 mL) and Et_2O (5 mL) were added. The aqueous phase was separated and extracted with two 2-mL portions of Et_2O, and the combined organic phases were washed with 3 mL of brine, dried over $MgSO_4$, filtered and concentrated to give 0.173 g of a yellow oil. Purification by column chromatography on 7 g of silica gel (elution with 10% ethyl acetate in hexane) provided 80 mg of **415** as a pale yellow oil (60%).[218]

IR (film)	3000, 2955, 2840, 2740, 2150, 2095, 1725, 1690, 1600, 1475, 1435, 1390, 1250, 1200, 1095, 1000, 955, 820, 760, and 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	10.47 (s, 1 H), 7.87 (d, J = 7.9 Hz, 1 H), 7.51-7.55 (m, 2 H), 7.36-7.42 (m, 1 H), 6.26 (ddd, J = 17.0, 10.2, 10.1 Hz, 1 H), 6.06-6.19 (m, 2 H), 5.78 (d, J = 15.7 Hz, 1 H), 5.48 (dt, J = 15, 7.5 Hz, 1 H), 5.13 (d, J = 16.6 Hz, 1 H), 5.01 (d, J = 9.7 Hz, 1 H), 3.73 (s, 6 H), 2.73 (dd, J = 2.4, 1.0 Hz, 1 H), and 2.68 (d, J = 7.6 Hz, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	191.3, 170.5, 139.4, 136.2, 135.6, 135.3, 133.5, 133.0, 128.4, 127.1, 127.0, 126.7, 116.8, 113.1, 94.3, 84.6, 57.7, 52.6, 36.7, and 36.3 ppm.

[218] Other yields for this reaction ranged from 36 to 44% (0.11 - 0.25 equivalents of CuI were used in these reactions).

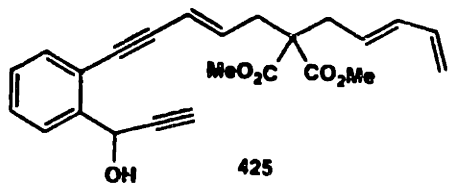


415

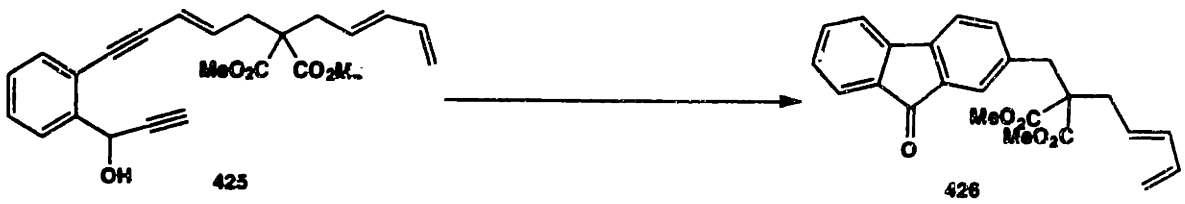
A 100-mL, one-necked, round bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with aldehyde **415** (0.184 g, 0.502 mmol) and 50 mL of THF. This solution was cooled to 0 °C, and ethynylmagnesium bromide (1.00 mL, 0.500 mmol, 0.5 M solution in THF) was added dropwise via syringe. The reaction mixture was stirred for 5 min; the reaction was not complete by TLC, so more ethynylmagnesium bromide (0.5 mL, 0.25 mmol, 0.5 M solution in THF) was added. After another 5 min, saturated NH_4Cl solution (20 mL) and 20 mL of Et_2O were added to the reaction mixture. The aqueous phase was separated and extracted with 20 mL of Et_2O, and the combined organic phases were washed with 15 mL of brine, dried with $MgSO_4$, filtered and concentrated to give a yellow oil. Purification by column chromatography on 2 g of silica gel (10 to 30% ethyl acetate in hexane) gave 0.163 g of a **425** as a yellow oil (83%).[219]

IR (film)	3420, 3250, 2985, 2920, 2205, 1985, 1700, 1580, 1455, 1415, 1200, 980, 930, and 880 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.79 (dd, J = 7.6, 1.1 Hz, 1 H), 7.44 (dd, J = 7.2, 2.0 Hz, 1 H), 7.28-7.36 (m, 2 H), 6.26 (ddd, J = 17.0, 10.2, 10.1 Hz, 1 H), 6.05-6.16 (m, 2 H), 5.82-5.84 (m, 1 H), 5.78 (d, J = 15.4 Hz, 1 H), 5.50 (dt, J = 15, 7.5 Hz, 1 H), 5.15 (dd, J = 16.5, 1.4 Hz, 1 H), 5.04 (dd, J = 10.4, 1.7 Hz, 1 H), 3.74 (s, 6 H), 2.66-2.75 (m, 5 H), and 2.64 (d, J = 2 Hz, 1 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	170.8, 141.5, 138.5, 136.4, 135.4, 132.4, 128.8, 127.3, 126.5, 121.4, 116.8, 113.5, 93.0, 86.1, 83.0, 74.6, 61.8, 57.8, 52.6, 36.6, and 36.2 ppm.

[219] Other yields for this reaction ranged from 88-91%.

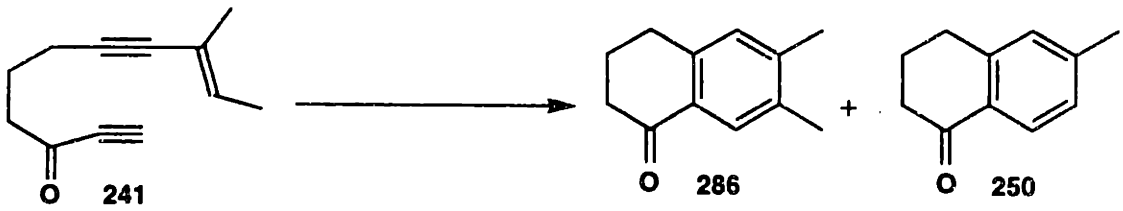


425



A 25-mL, one-necked, round bottomed flask equipped with a rubber septum and argon inlet needle was charged with alcohol **425** and 3.8 mL of CH_2Cl_2. 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1-oxide (0.243 g, 0.573 mmol) was added to the reaction mixture, and this solution was stirred at room temperature for 10 min. Saturated $NaHCO_3$ solution (1 mL) and Et_2O (5 mL) were added, and the reaction mixture was extracted with 5 mL of Et_2O. The aqueous phase was separated and extracted with 5 mL of Et_2O, and the combined organic phases were washed with 3 mL of half saturated $NaHCO_3$ and 3 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. This oil was quickly dissolved in 20% ethyl acetate in hexane and filtered through 5 g of silica gel (elution with 20% ethyl acetate in hexane). The filtrate was then concentrated, immediately dissolved in 7.4 mL of benzene, and transferred to a resealable tube with a side arm equipped with a nitrogen inlet adapter and rubber septum. 4-Methyl-2,6-di-*tert*-butylphenol (0.084 g, 0.382 mmol) was added, and the reaction mixture was degassed (three cycles of freeze, pump, thaw). The tube was then sealed and heated in a 80-100 °C oil bath for 4 h. The reaction mixture was then allowed to cool to room temperature and concentrated to give 0.260 g of a red/ orange oil. Purification by column chromatography on 4 g of silica gel (elution with 20% ethyl acetate in hexane) gave 43 mg of **426** as a yellow oil (29%).

Thermal Reactions with Loss of Methyl Group



A threaded Pyrex tube (ca. 30 mL capacity) equipped with rubber septum and a nitrogen inlet needle was charged with 9-methyl-9-undecen-1,7-diyn-3-one **241** (0.045 g, 0.258 mmol), 5.7 mL of toluene, and 4-methyl-2,6-di-*tert*-butylphenol (0.126 g, 0.574 mmol). The solution was degassed by bubbling nitrogen gas through it for 10 min, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was immersed in a 180 °C oil bath for 25 h and then allowed to cool to room temperature. Concentration of the reaction mixture gave 0.170 g of a brown oil. Purification by column chromatography on 5 g of silica gel (elution with 3% ethyl acetate-hexane) provided 0.026 g of a mixture of **286** and **250** as a yellow oil.

The other thermal reactions shown in Scheme 226 were carried out in the same way using the reagents listed below.

Toluene, 0.05 M

Reagent	Amount
enyne 241	0.060 g (0.344 mmol)
toluene	5.7 mL
tetralones 286	29 mg (2.4:1 ratio)
and 250	49% yield

Toluene, THF, 0.05 M

Reagent	Amount
enyne 241	0.045 g (0.258 mmol)
toluene	5.7 mL
THF	0.207 g, 0.23 mL (2.87 mmol)
tetralones 286	12 mg (6:1 ratio)
and 250	26% yield

Toluene, 1,4-dimethoxybenzene, 0.05 M

Reagent	Amount
enyne 241	0.050 g (0.287mmol)
toluene	5.7 mL
1,4-dimethoxy-benzene	0.071 g (0.574 mmol)
tetralones 286	20 mg (1:1.7 ratio)
and 250	42% yield

Cyclohexane, BHT, 0.05 M

Reagent	Amount
enyne 241	0.020 g (0.115 mmol)
cyclohexane	2.3 mL
BHT	0.050 g (0.229 mmol)
tetralones 286	4 mg (2.4:1 ratio)
and 250	20% yield

Toluene, 0.025 M

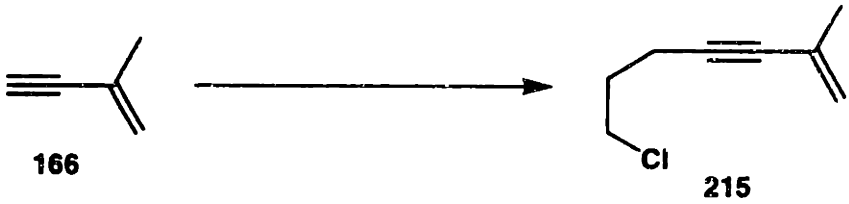
Reagent	Amount
enyne 241	0.030 g (0.172 mmol)
toluene	7 mL
tetralones 286	15 mg (1.6:1 ratio)
and 250	52% yield

Chlorobenzene, BHT, 0.05 M

Reagent	Amount
enyne 241	0.020 g (0.115 mmol)
chlorobenzene	2.3 mL
BHT	0.050 g (0.229 mmol)
tetralones 286	10.3 mg (1.1:1 ratio)
and 250	50% yield

Chlorobenzene, 0.05 M

Reagent	Amount
enyne 241	0.021 g (0.120 mmol)
chlorobenzene	2.3 mL
tetralones 286	6 mg (3.4:1 ratio)
and 250	39% yield



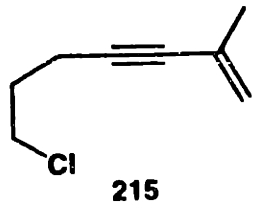
166 215

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with 2-methyl-1-buten-3-yne **166** (2.90 mL, 1.98 g, 30.0 mmol) and 60 mL THF. The solution was cooled to -55 °C, and *n*-BuLi (12.6 mL, 31.25 mmol, 2.48 M solution in hexane) was added dropwise over 3 min. After 5 min, 1-iodo-3-chloropropane (2.70 mL, 5.11g, 25 mmol) and DMSO (17.7 mL, 19.5 g, 250 mmol) were added over 2 and 4 min respectively, and the reaction mixture was allowed to warm to room temperature. After 2 h at room temperature, 15 mL saturated NH_4Cl solution and 25 mL of Et_2O were added. The aqueous phase was separated and extracted with 20 mL of Et_2O, and the combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 3.02 g of a colorless oil. Purification by column chromatography on 30 g of silica gel (elution with pentane) provided 2.77 g (77%) of **215** as a colorless oil.[220]

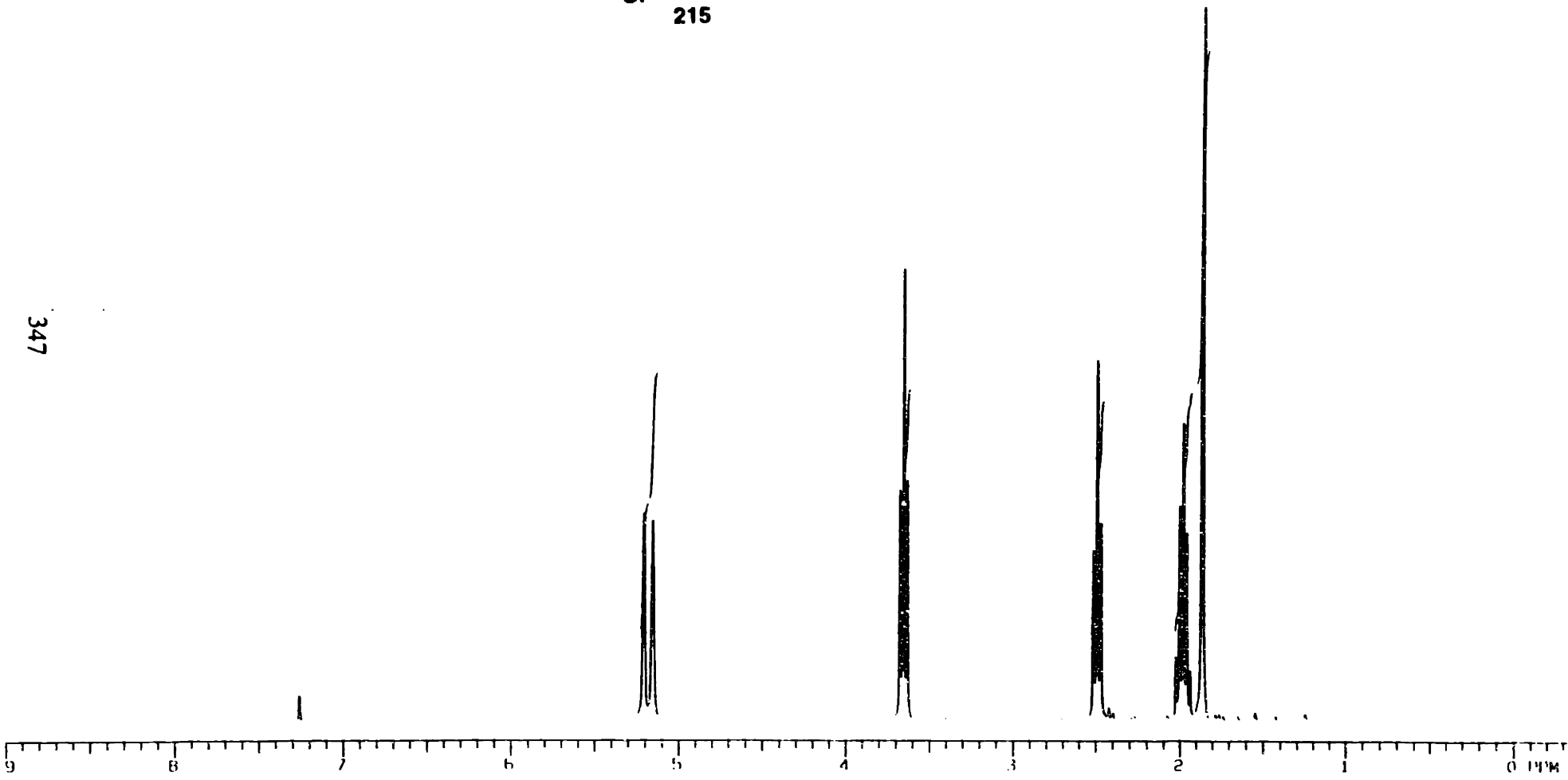
IR (film):	3095, 2960, 2925, 2875, 2840, 2220, 1800, 1620, 1445, 1375, 1355, 1330, 1300, 1010, 990, 970, 910, 860, 785, 770, and 740 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.21 (s, 1 H), 5.16 (s 1 H), 3.66 (t, J = 6.4 Hz, 2 H), 2.49 (t, J = 6.9 Hz, 2 H), 1.98 (app quintet, J = 6.6 Hz, 2 H), and 1.86 (s, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	127.0, 120.9, 87.1, 82.7, 43.7, 31.4, 23.7, and 16.7 ppm.
HRMS	Calcd for $C_8H_{11}Cl$: 142.054928

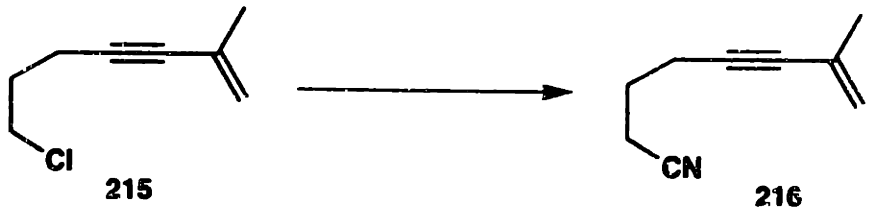
[220] Yields for this reaction ranged from 72 to 95%, and the product was not always purified before use in subsequent reactions.

Found: 142.05496.



215





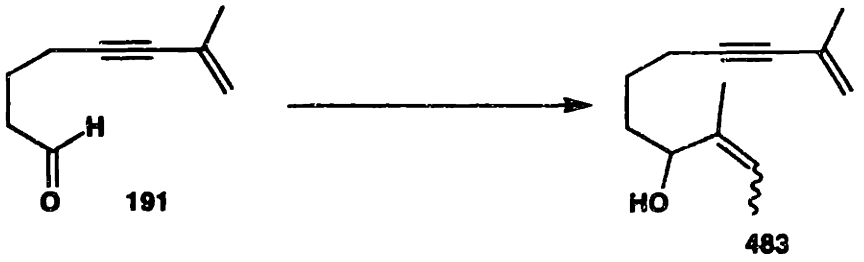
215 216

A two-necked, 10-mL, round-bottomed flask equipped with a glass stopper, reflux condenser, and nitrogen inlet adapter was charged with 7-chloro-2-methyl-1hepten-3-yne **215** (0.500 g, 3.50 mmol) and 4.7 mL distilled DMSO. Freshly dried NaCN (0.630 g, 12.8 mmol) was added in one portion, and the reaction mixture was heated to 60 °C for 2.5 h. The reaction mixture was then cooled to room temperature, and 2 mL each of Et_2O, CH_2Cl_2, and H_2O were added to dissolve the brown reaction mixture. The aqueous phase was separated and extracted with 5 mL of Et_2O, and the combined organic phases were the extracted with 5 mL of brine, dried with $MgSO_4$, filtered, and concentrated to give 0.409 g of a yellow oil. Purification by column chromatography on 5 g of silica gel (gradient elution with hexane to 5% ethyl acetate in hexane) gave 0.378 g (80%) of **216** as a pale yellow oil.

IR (film):	3090, 2945, 2915, 2245, 2215, 1800, 1605, 1455, 1430, 1375, 1345, 1335, 1310, 1300, 1285, 1005, and 900 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.21 (s, 1 H), 5.16 (d, J = 1.5 Hz, 1 H), 2.51-2.45 (m, 4 H), 1.89 (app dt, J = 7.0 Hz, 1.3 Hz, 2 H), and 1.85 (s, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	126.65, 121.23, 119.13, 85.88, 83.56, 24.54, 23.56, 18.30, and16.06 ppm.
HRMS	Calcd for $C_9H_{11}N$: 133.08915 Found: 133.08908 +/- .00026.

216

A 50-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and nitrogen inlet adapter was charged with nitrile **216** (0.200 g, 1.50 mmol) and 15 mL of Et_2O. This solution was cooled to -78 °C, and diisobutylaluminum hydride (3.0 mL, 3.0 mmol, 1 M solution in hexane) was added via syringe over 1 min. After 2.5 h at -78 to -50 °C, 10 mL of 5% HCl solution were added. This mixture was stirred at room temperature for 12 h. The aqueous phase was separated and extracted with 10 mL of Et_2O, and the combined organic phases were extracted with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.219 g of **191** as a yellow oil. This oil was used without further purification in the next reaction.



A two-necked, 25-mL, round-bottomed flask equipped with a reflux condenser, nitrogen inlet adapter, and rubber septum was charged with Mg (0.189 g, 7.78 mmol) and 1 mL of THF. A few crystals of I_2 were added, and about 5 drops of 2-bromo-2-propene in a syringe were added. The mixture was heated to reflux with a heat gun. After a few drops of 1,2-dibromoethane were added, the reaction mixture was heated to reflux again with the heat gun, the reaction began (gas evolution). More THF was added (5 mL) and the rest of 2-bromo-2-propene (0.75 mL total, 1.0 g, 7.40 mmol, approximately 70:30 Z:E) was added slowly over about 5 min. The reaction mixture was heated to reflux for 3 h and then cooled to room temperature.

A two-necked, 50-mL, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 7-methyl-7-octen-5-yn-1-al **191** (0.200 g crude material, assumed 1.5 mmol) and 10 mL of Et_2O. This solution was cooled to 0 °C, and the Grignard solution described above (0.8 mL, 0.8 mmol) was added. The reaction was not complete by TLC, and so more Grignard solution (1.3 mL, 1.3 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 h. Saturated NH_4Cl solution (3 mL) was added, and the aqueous phase was separated and extracted with 5 mL of Et_2O. The combined organic phases were extracted with 3 mL of brine, dried with K_2SO_4, filtered, and concentrated to give 0.273 g of a yellow oil. Purification by column chromatography on 10 g of silica gel (5% ethyl acetate in hexane) provided 0.133 g of **483** (7:1 mixture E:Z) as a pale yellow oil (46% from nitrile).[221]

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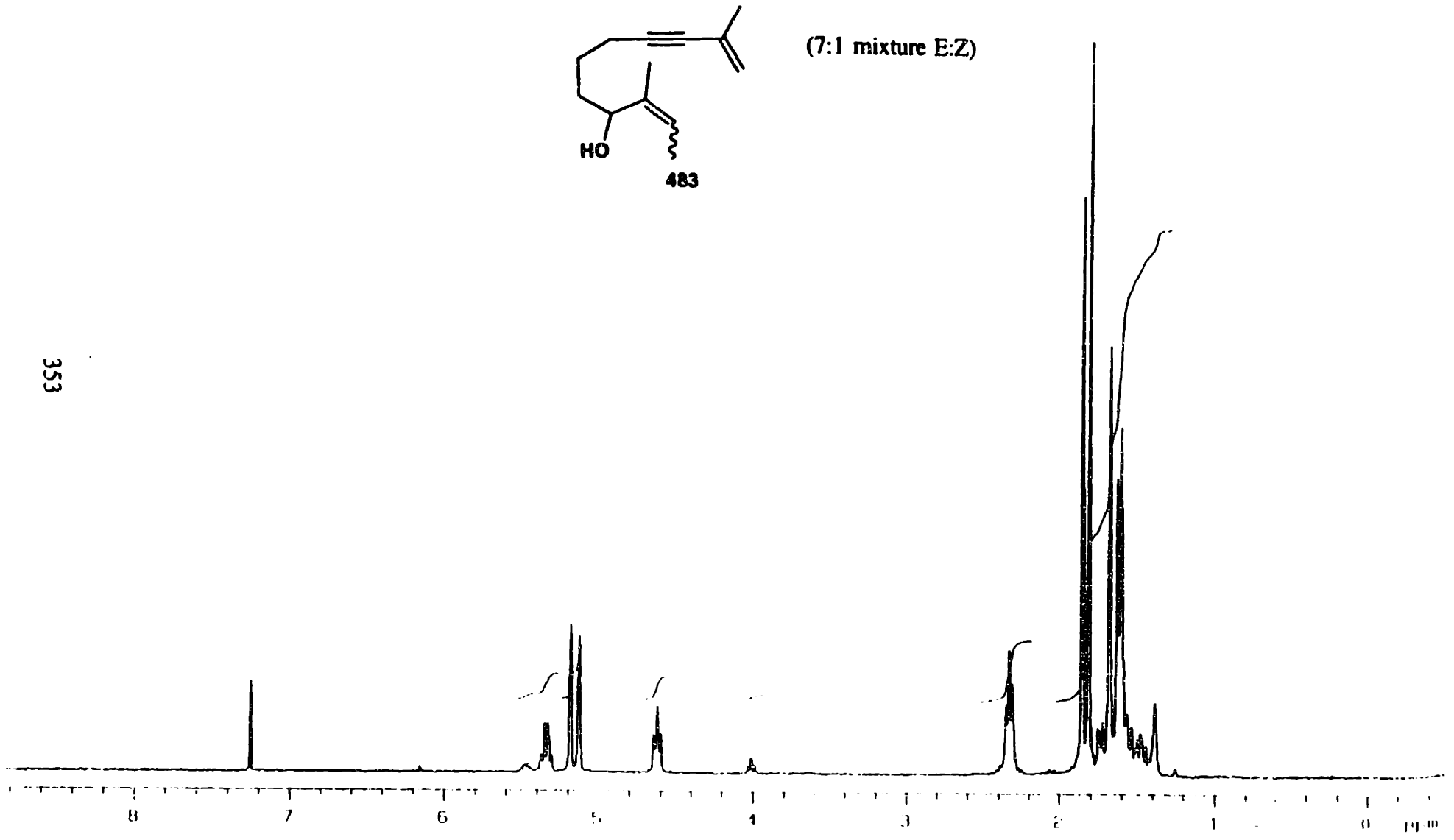
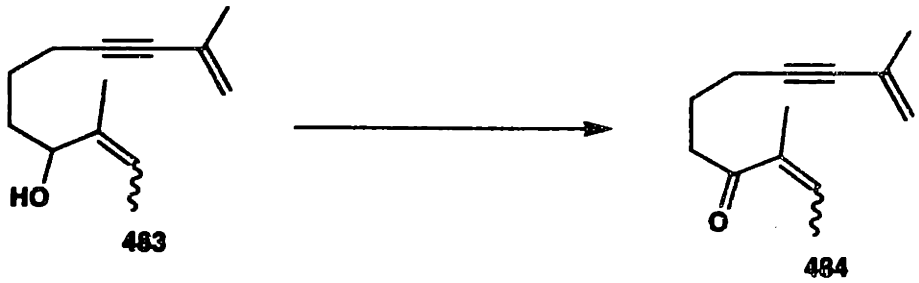
[221] Yields for these reactions ranged from 39 to 53%.

IR (film):	3355 (b), 3085, 2935, 2855, 2215, 1785, 1700, 1615, 1450, 1435, 1370, 1330, 1285, 1060, 1030, 1005, 895, and 820 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	5.34 (quartet, J = 6.7 Hz, 1 H), 5.19 (s, 1 H), 5.13 (s, 1 H), 4.63 (app t, J = 6.3 Hz, 1 H), 2.32-2.36 (m, 2 H), 1.86 (s, 3 H), 1.82 (s, 3 H), 1.40-1.76 (m, 3 H), 1.68 (s, 3 H), and 1.60-1.63 (m, 2 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	137.1, 127.2, 121.8, 120.4, 88.9, 82.1, 68.7, 33.8, 24.8, 23.8, 19.1, 17.1, and 12.8 ppm.
HRMS	Calcd for $C_{13}H_{20}O$: 192.151415 Found: 192.15168 +/- 0.00036.


HO
483
(7:1 mixture E:Z)
8
7
6
5
4
3
2
1
0
ppm



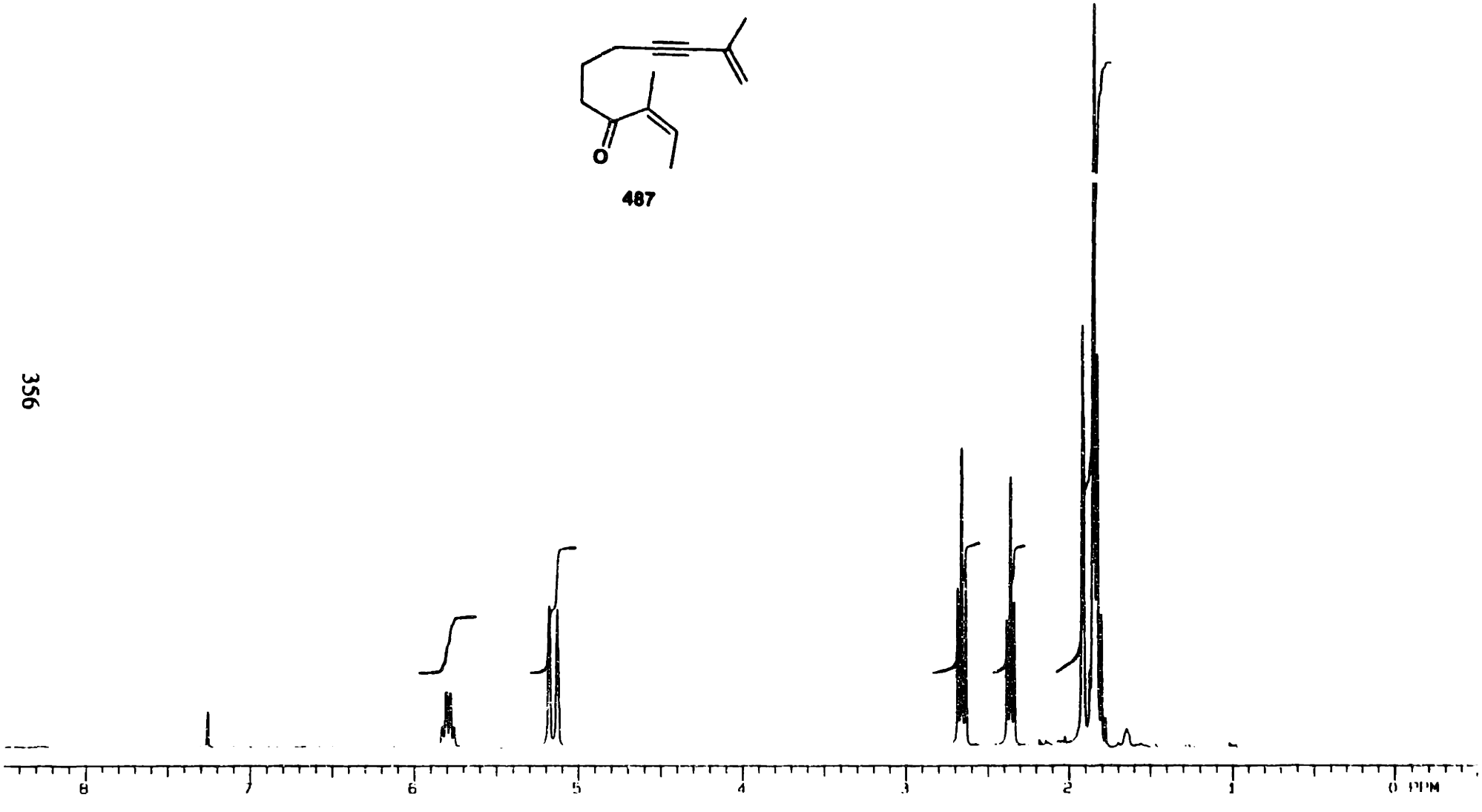
483 484

A three-necked, 25-mL, round-bottomed flask equipped with a rubber septum, glass stopper, and nitrogen inlet adapter was charged with 3,10-dimethyl-2,10-undecadien-8-yn-4-ol **483** (0.244 g, 1.27 mmol) and 13 mL of CH_2Cl_2. This solution was protected from the light, and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1-oxide (1.00 g, 2.55 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ solution (5 mL) was then added, and the aqueous phase was separated and extracted with 5 mL of CH_2Cl_2. The combined organic phases were extracted with 5 mL each of half saturated $NaHCO_3$, H_2O, and brine, dried with K_2CO_3, filtered, and concentrated to give a yellow solid. Purification by column chromatography on 20 g of silica gel (gradient elution with 10 to 20% ethyl acetate in hexane) gave 0.177 g of **484** as a 7:1 Z:E mixture of the isomeric enones (73%). The two isomers could be separated by further column chromatography (17 g of silica gel, elution with 25% CH_2Cl_2 in petroleum ether).[222]

IR (film):	2930, 2220, 1680, 1610, 1435, 1370, 1285, 1230, 1095, 1000, and 890 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.79 (dq, J = 7.2, 1.4 Hz, 1 H), 5.18 (s, 1 H), 5.13 (s, 1 H), 2.66 (t, J = 7.2 Hz, 2 H), 2.36 (t, J = 6.8 Hz, 2 H), 1.91 (d, J = 1.4 Hz, 3 H), and 1.80-1.87 (m, 8 H) ppm.

[222] Yields for this reaction ranged from 71 to79%.

^{13}C NMR (75 MHz, $CDCl_3$)	205.03, 136.21, 132.71, 127.13, 120.53, 88.34, 82.60, 40.51, 20.75, 22.59, 20.69, 18.64, and 15.60 ppm.
HRMS	Calcd for $C_{13}H_{18}O$: 190.13765 Found: 190.13601 +/- 0.0036.

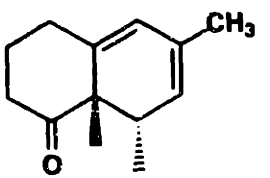


487

487 488

A 50-mL, one-necked, round bottomed flask equipped with a rubber septum and nitrogen inlet needle was charged with 3,10-dimethyl-2,10-undecadien-8-yn-4-one **487** (0.166 g, 0.875 mmol) and 34 mL of CH_2Cl_2. The solution was cooled to 0 °C, and methanesulfonic acid (0.142 mL, 0.210 g, 2.19 mmol) was added dropwise via syringe over about 1 min. This solution was stirred at 0 °C for 45 min, and then about 1 g of solid $NaHCO_3$ was added. The reaction mixture was extracted with 10 mL of H_2O. The aqueous phase was separated and extracted with 10 mL of CH_2Cl_2, and the combined organic phases were washed with 10 mL each of H_2O (containing two drops of 10% aqueous HCl) and brine, dried with K_2CO_3, filtered, and concentrated to give 0.157 g of a yellow solid. Purification by column chromatography on 10 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.146 g of **454** as a yellow solid (88%) (mp 64.5-65.5 °C).

IR (film):	2965, 2930, 2920, 2840, 1700, 1445, 1375, 1355, 1335, 1180, and 1060 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.80 (bs, 1 H), 5.73 (app t, J = 4.3 Hz, 1 H), 2.65 (dt, J = 15.4, 4.9 Hz, 1 H), 2.40-2.64 (m, 3 H), 2.21-2.29 (m, 1 H), 2.17-2.21 (m, 1 H), 1.73 (s, 3 H), 1.66 (bs, 1 H), 1.11 (s, 3 H), and 0.70 (d, J = 6.7 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	216.3, 138.5, 132.4, 122.1, 121.8, 49.3, 38.8, 35.1, 33.4, 23.8, 23.6, 27.8, and 16.8 ppm.
HRMS	Calcd for $C_{13}H_{18}O$: 190.13765 Found: 190.13583 +/- 0.0036.



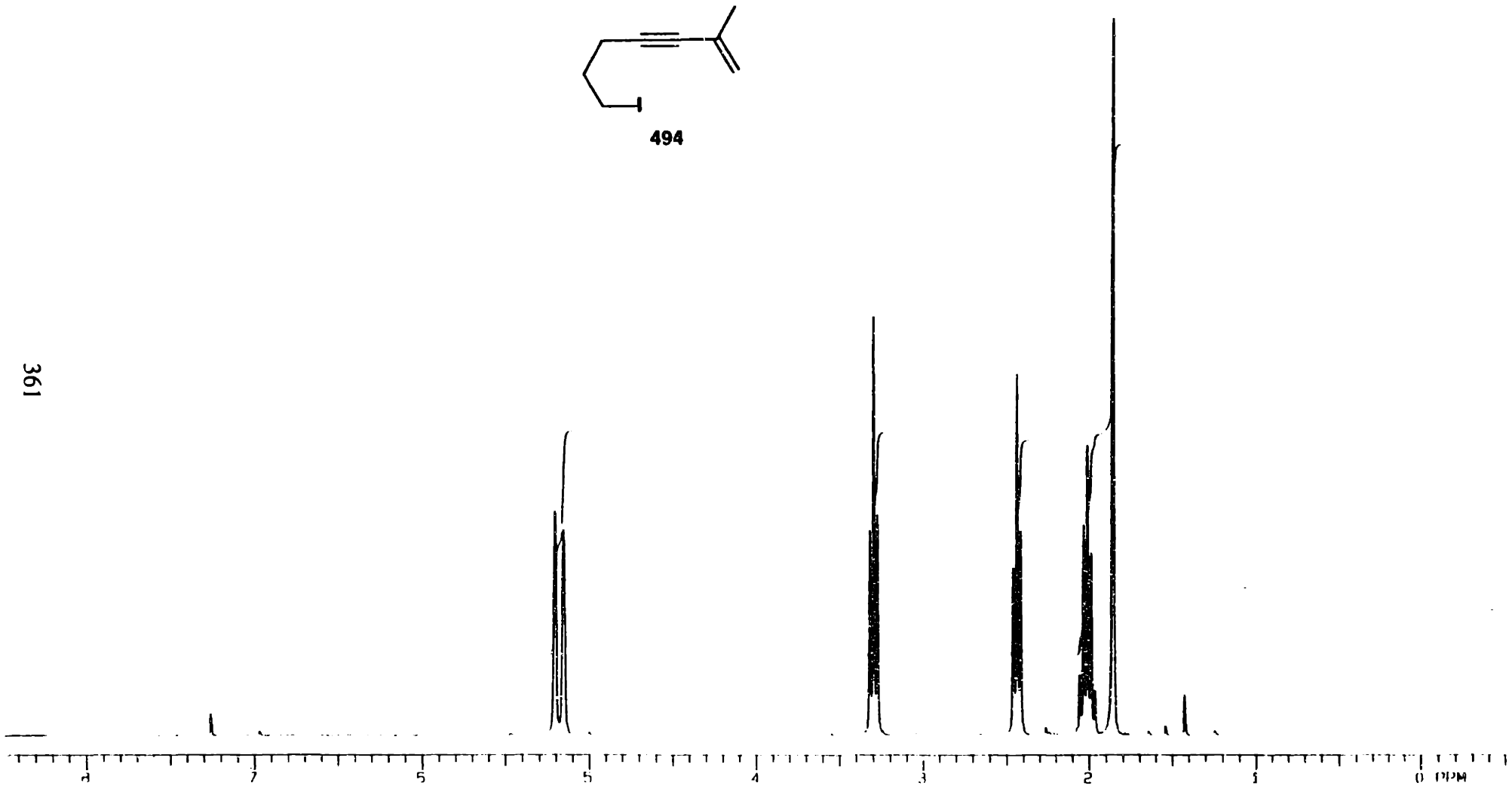
488

215 **494**

A one-necked, 50-mL, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with 7-chloro-2-methyl-1-hepten-3-yne **215** (2.0 g, 14.02 mmol), 14 mL of acetone, and NaI (10.50 g, 70 mmol). This solution was heated to reflux for 1 h, and to about 50 °C for 20 h. The reaction mixture was then cooled to room temperature and concentrated to a yellow/orange solid. Et_2O (15 mL) and H_2O (10 mL) were added, and the aqueous phase was separated and extracted with 10 mL of Et_2O. The combined organic phases were washed with 5 mL each of saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated to give 2.67 g of a pale yellow oil. Purification by column chromatography on 10 g of silica gel (elution with pentane) gave 2.38 g of **494** as a pale yellow oil (73%).[223]

IR (film):	3640, 3100, 2960, 2925, 227525, 1795, 1608, 1430, 1375, 1350, 1290, 1265, 1225, 1170, 1160, 1120, 1010, 895. 845, and 750 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.21 (s, 1 H), 5.16 (d, J = 1.5 Hz, 1 H), 3.30 (t, J = 6.7, 2 H), 2.44 (t, J = 6.7, 2 H), 2.01 (app quintet J = 6.7, 2 H), and 1.86 (s, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	127.01, 120.92, 86.81, 82.97 32.22, 23.74, 20.36, and 5.30 ppm.
HRMS	Calcd for $C_8H_{11}I$: 233.990552 Found: 233.99098 +/- 0.00044.

[223] Other yields for this reaction ranged from 73 to 75%.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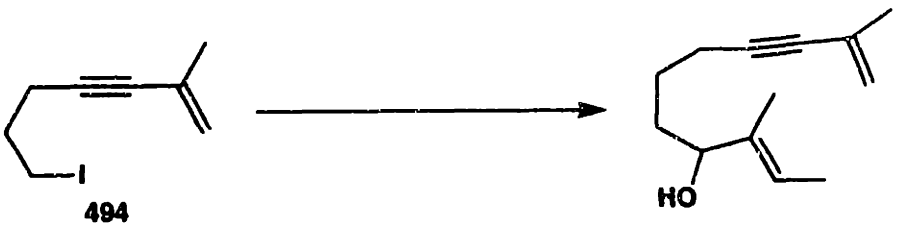


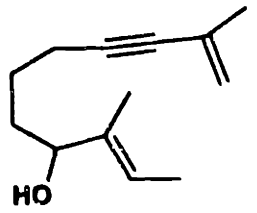
494 489

A three-necked, 250-mL, round-bottomed flask equipped with a glass stopper, rubber septum, and nitrogen inlet adapter was charged with 7-iodo-2-methyl-1-hepten-3-yne **494** (0.500 g, 2.14 mmol, passed through Al_2O_3), 18 mL of pentane, and 25 mL of Et_2O. This solution was cooled to -94 °C (hexane, liquid nitrogen bath) and stirred for 10 min. *t*-BuLi (2.9 mL, 4.70 mmol, 1.62 M solution in pentane) was added via syringe over 3 min to the cooled reaction mixture. The resulting solution was stirred for 5 min at -94 °C, and then *E*-2,3-dimethyl-2-propenal (0.42 mL, 0.365 g, 4.35 mmol) was added in one portion via syringe. The reaction mixture was stirred at -94 °C for 10 min, and then allowed to warm to room temperature over 20 min. Saturated NH_4Cl solution (5 mL) and 10 mL of Et_2O were added to the reaction mixture. The aqueous phase was separated and extracted with 10 mL of Et_2O. Combined organic phases were washed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to give a colorless oil. Purification by column chromatography on 50 g of silica gel (gradient elution with 10-20% ethyl acetate in hexane) gave 0.277 g of **489** as a colorless oil (67%).[224]

IR (film):	3350 (b), 3080, 2930, 2860, 2215, 1615, 1435, 1375, 1330, 1285, 1060, 995, 890, and 825 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.45-5.48 (m, 1 H), 5.18 (dt, *J* = 1.0, 0.5 Hz, 1 H), 5.11-5.14 (m, 1 H), 3.98-4.03 (m, 1 H), 2.31 (t, *J* = 6.7 Hz, 2 H), 1.86 (s, 3 H) 1.40-1.68 (m, 10 H), and 1.47 (bs, 1 H) ppm.

[224] Yields for this reaction ranged from 64 to 67%.

^{13}C NMR (75 MHz, $CDCl_3$)	137.74, 127.24, 120.97, 120.37, 89.01, 82.13, 76.59, 33.86, 25.02, 23.81, 19.14, 13.02, and 10.80 ppm.
HRMS	Calcd for $(M-H)^+ C_{13}H_{19}O$: 191.14359 Found: 191.14321+/-0.00054



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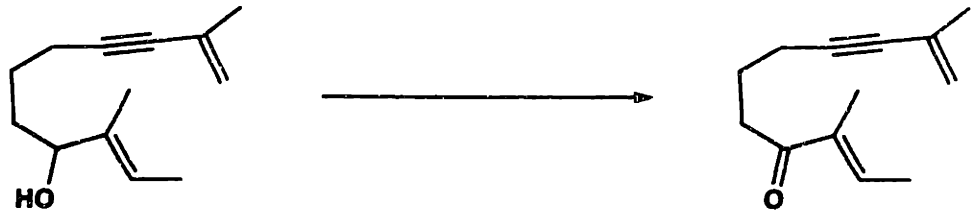
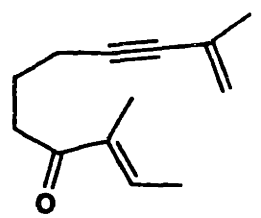


489 **485**

A one-necked, 50-mL, round-bottomed flask equipped with a reflux condenser and nitrogen inlet adapter was charged with 3,10-dimethyl-2-10-undecaien-8-yn-4-ol **489** (0.680 g, 3.55 mmol), 37 mL of benzene, and $BaMnO_4$ (4.12 g, 14.47 mmol, 90% of powder is active oxidant). The reaction mixture was heated to 60 to 80 °C for 24 h, cooled to room temperature, and filtered through celite. The precipitate was washed well with Et_2O. The filtrate was then concentrated to give 0.649 g of a pale yellow oil. Purification by column chromatography on 35 g of silica gel (elution with 3% ethyl acetate in hexane) gave 0.412 g of **485** as a colorless oil (61%).[225]

IR (film):	3310, 3100, 2440, 2230, 1665, 1615, 1440, 1395, 1375, 1330, 1290, 1240, 1080, 1045, 1010, 985, and 895 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.77 (dq, J = 6.8, 2.5 Hz, 1 H), 5.18 (s, 1 H), 5.12-5.14 (m, 1 H), 2.78 (t, J = 7.3 Hz, 2 H), 2.34 (t, J = 6.8 Hz, 2 H), 1.80-1.87 (m, 8 H), and 1.77 (t, J = 1.8 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	201.13, 138.28, 137.15, 127.18, 120.49, 88.54, 82.49, 35.78, 23.78, 23.70, 18.81, 14.73, and 10.98 ppm.
HRMS	Calcd for $C_{13}H_{18}O$: 190.135765 Found: 190.13583 +/- 0.00036.

[225] Yields for this reaction ranged from 58 to61%.



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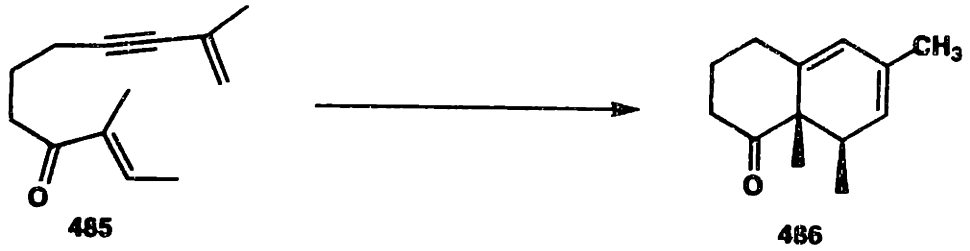


485 486

I Protic Acid Procedure

A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet needle was charged with *E*-3,10-dimethyl-2,10-undecadien-8-yn-4-one **485** (0.200 g, 1.05 mmol) and 41 mL of CH_2Cl_2. The solution was cooled to 0 °C, and methanesulfonic acid (0.170 mL, 0.252 g, 2.63 mmol) was added dropwise via syringe over about 1 min. This solution was stirred at 0 to 5°C for 30 min, and then about 1 g of $NaHCO_3$ was added. The reaction mixture was extracted with 10 mL of H_2O. The aqueous phase was separated and extracted with 10 mL of CH_2Cl_2, and the combined organic phases were washed with 10 mL each of H_2O and brine, dried with $MgSO_4$, filtered, and concentrated to give 0.289 g of a yellow solid. Purification by column chromatography on 20 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.151 g of **486** as a yellow oil (75%).[226]

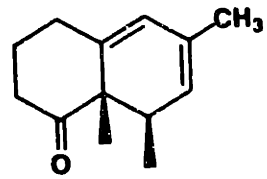
II Lewis Acid Procedure

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with aluminum chloride (0.109 g, 0.821 mmol) and 10 mL of CH_2Cl_2. The solution was cooled to 0 °C, and *E*-3,10-dimethyl-2,10-undecadien-8-yn-4-one **485** (0.142 g, 0.746 mmol) and 5 mL of CH_2Cl_2 were added in dropwise via cannula over 2 min. The reaction mixture was stirred at 0 °C for 30 min. Triethylamine (2 mL) and 10% aqueous HCl (5 mL) were added, and the

[226] Other yields for this reaction ranged from 61-91%.

aqueous phase was separated and extracted with 10 mL of CH_2Cl_2. The combined organic phases were extracted with 10 mL each of H_2O and brine, dried with $MgSO_4$, filtered, and concentrated to give 0.166 g of a yellow oil. Purification by column chromatography on 14 g of silica gel (elution with 3% ethyl acetate in hexane) provided 0.080 g (56%) of **452** as an orange oil.

IR (film):	2960, 2890, 1700, 1445, 1375, 1340, 1285, 1260, 1195, 1130, 1085, 1060, 1040, 905, 880, and 860 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.80 (s, 1 H), 5.50 (app t, J = 4.3 Hz, 1 H), 2.59-2.67 (m, 1 H), 2.37-2.54 (m, 3 H), 1.88-2.07 (m, 3 H), 1.72 (s, 3 H), 1.10 (s, 3 H), and 0.95 (d, J = 6.4 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	214.9, 143.5, 134.8, 120.1, 48.9, 37.0, 37.0, 33.0, 25.3, 22.8, 16.5, and 12.5 ppm
HRMS	Calcd for $C_{13}H_{18}O$: 190.135765 Found: 190.13583 +/- 0.00036.



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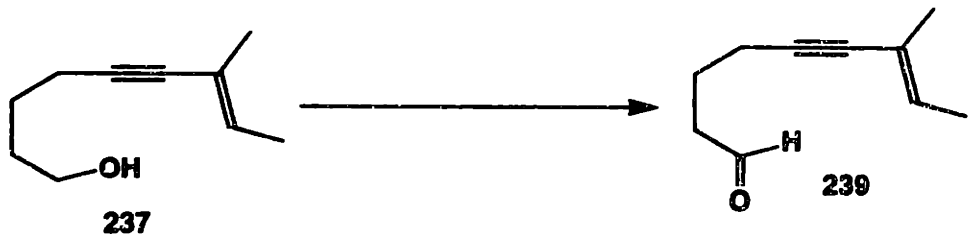
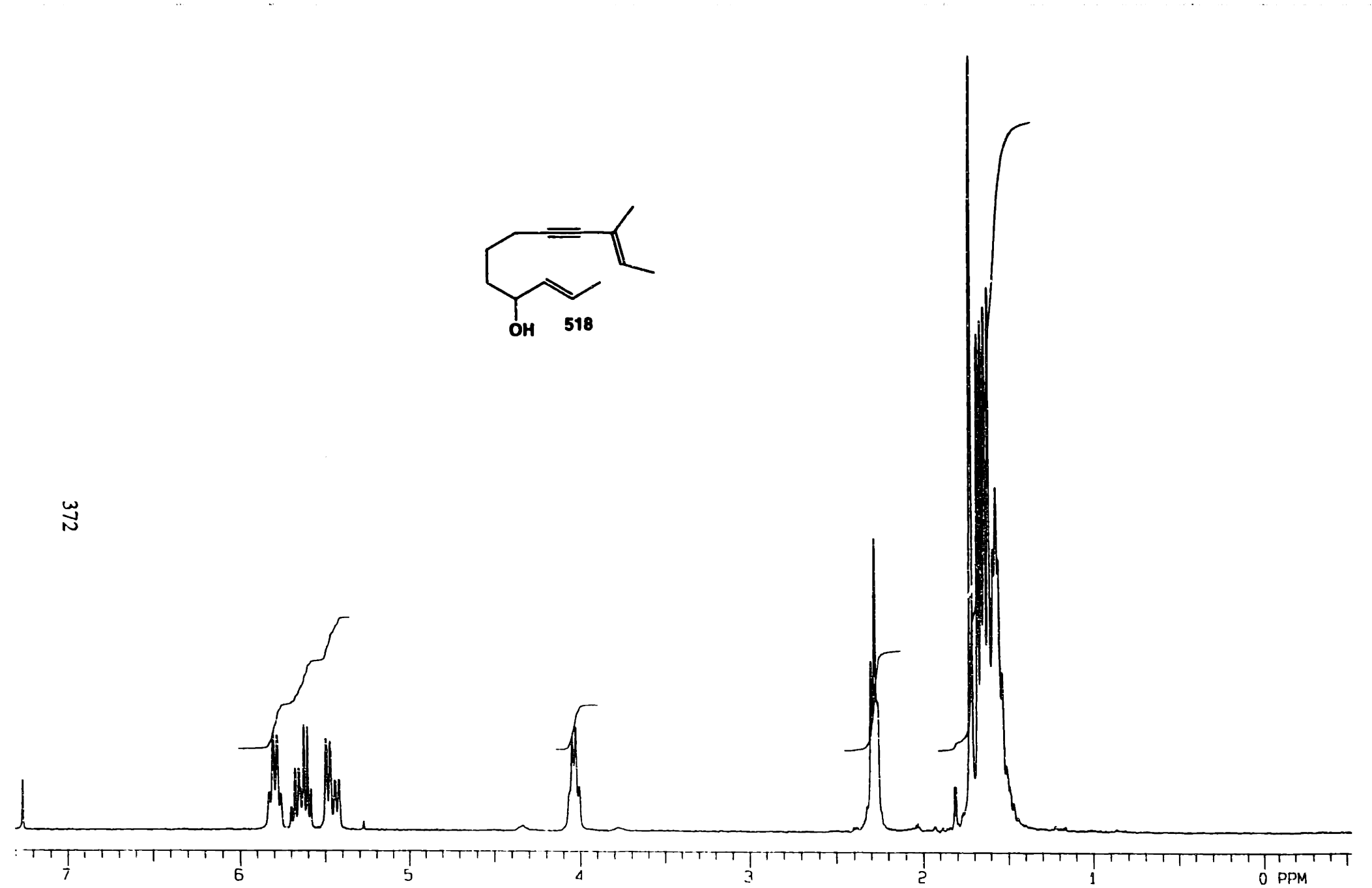


A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with oxalyl chloride (0.14 mL, 0.200 g, 1.58 mmol) and 10 mL of CH_2Cl_2. This solution was cooled to -78 °C, and DMSO (0.20 mL, 0.255 g, 2.88 mmol) was added dropwise over 1 min. After stirring the reaction at -78 °C for 5 min, a solution of the alcohol **237** (0.200 g, 1.31 mmol) in 5 mL of THF was added via cannula over 2 min (2 mL THF was used to rinse the flask). After 15 min, triethylamine (0.87 mL, 0.663 g, 6.55 mmol) was added via syringe. This mixture was stirred at -78 °C for 15 min and at room temperature for 45 min, and then 5 mL of saturated NH_4Cl solution and 10 mL of Et_2O were added. The aqueous phase was extracted with 10 mL of Et_2O. The combined organic phases were washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated (carefully) to give 0.253 g of **239** as a yellow oil. This oil was used without further purification in the next reaction.

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and nitrogen inlet adapter was charged with 1-bromo-1-propene (0.13 mL, 0.190 g, 1.57 mmol), 6 mL of Et_2O, and 9 mL of pentane. This solution was cooled to -78 °C and *tert*-butyllithium (2.2 mL, 3.41 mmol, 1.55 M solution in pentane) was added via syringe over 4 min. After 2 min, this solution was added to a solution of aldehyde **239** (0.253 g crude material, assumed 1.31 mmol) in 5 mL of Et_2O at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and allowed to warm to room temperature over 2 h. Saturated NH_4Cl solution (5 mL) and 10 mL of Et_2O were added. The aqueous phase was separated and extracted with two 10-mL portions of Et_2O. The combined organic phases were washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 10% ethyl acetate in hexane) gave 0.176 g of **518** as a colorless oil (70% from the alcohol).

IR (film):	3360, 3040, 2940, 2885, 2230, 1680, 1450, 1385, 1340, 1250, 1120, 1070, 1000, 970, 930, and 835 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.80 (d, J = 7.0 Hz, 1 H), 5.64 (dq, J = 15.2, 6.4 Hz, 1 H), 5.46 (ddd, J = 15.2, 7.0, 1.3 Hz 1 H), 4.04 (bquartet, J = 6.4 Hz, 1 H), 2.27-2.31 (m, 2 H), 1.73 (s, 3 H), 1.68 (d, J = 6.4 Hz, 3 H), 1.64 (d, J = 7.0 Hz, 3 H), and 1.51-1.60 (m, 5 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	134.1, 130.9, 130.8, 126.9, 118.7, 85.8, 83.9, 72.6, 36.3, 24.9, 19.1, 17.6, 17.1, and 13.8 ppm.
HRMS	Calcd for $[M-H]^+$ $C_{13}H_{18}O$: 191.143590 Found: 191.14358.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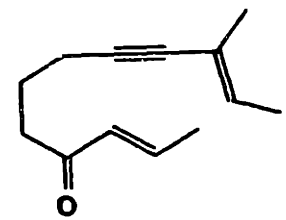
A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with 10-methyl-2,8-dodecadien-8-yn-4-ol **518** (0.170 g, 0.884 mmol), 9 mL of CH_2Cl_2, and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one 1-oxide (0.450 g, 1.06 mmol). This solution was stirred at room temperature for 45 min and was then concentrated down to about 5 mL, treated with 5 mL of Et_2O, and extracted with 5 mL of saturated $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O. The combined organic phases were extracted with 5 mL of half saturated $NaHCO_3$, 5 mL of H_2O, and 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. Purification by column chromatography on 10 g of silica gel (elution with 3% ethyl acetate in hexane) gave 0.122 g of **517** as a pale yellow oil (66%).

IR (film):	3040, 2945, 2920, 2880, 2225, 1700, 1680, 1635, 1460, 1415, 1380, 1340, 1325, 1290, 1250, 1220, 1185, 1130, 1095, 1045, 975, and 835 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.87 (d quartet, J = 15.7, 6.9 Hz, 1 H), 6.12 (dt, J = 15.8, 1.6 Hz, 1 H), 5.81 (quartet, J = 7.0 Hz, 1 H), 2.66 (t, J = 7.3 Hz, 2 H), 2.33 (t, J = 6.9 Hz, 2 H), 1.89 (dd, J = 6.9, 1.6 Hz, 3 H), 1.82 (quintet, J = 7.1 Hz, 2 H), 1.74 (s, 3 H), and 1.65 (d, J = 7.0 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	199.9, 142.5, 132.0, 131.0, 118.6, 85.2, 84.3, 38.6, 23.2, 18.7, 18.2, 17.1, and 13.9 ppm.
HRMS	Calcd for $C_{13}H_{18}O$: 190.135765 Found: 190.13601.



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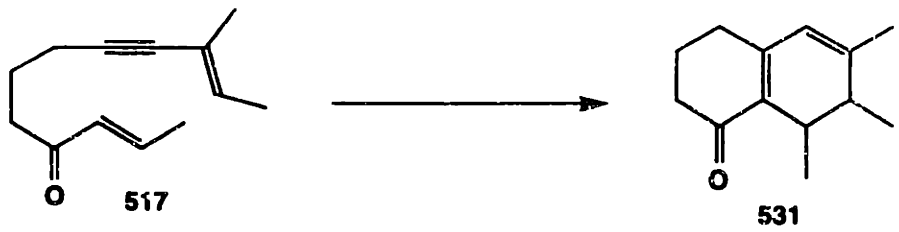
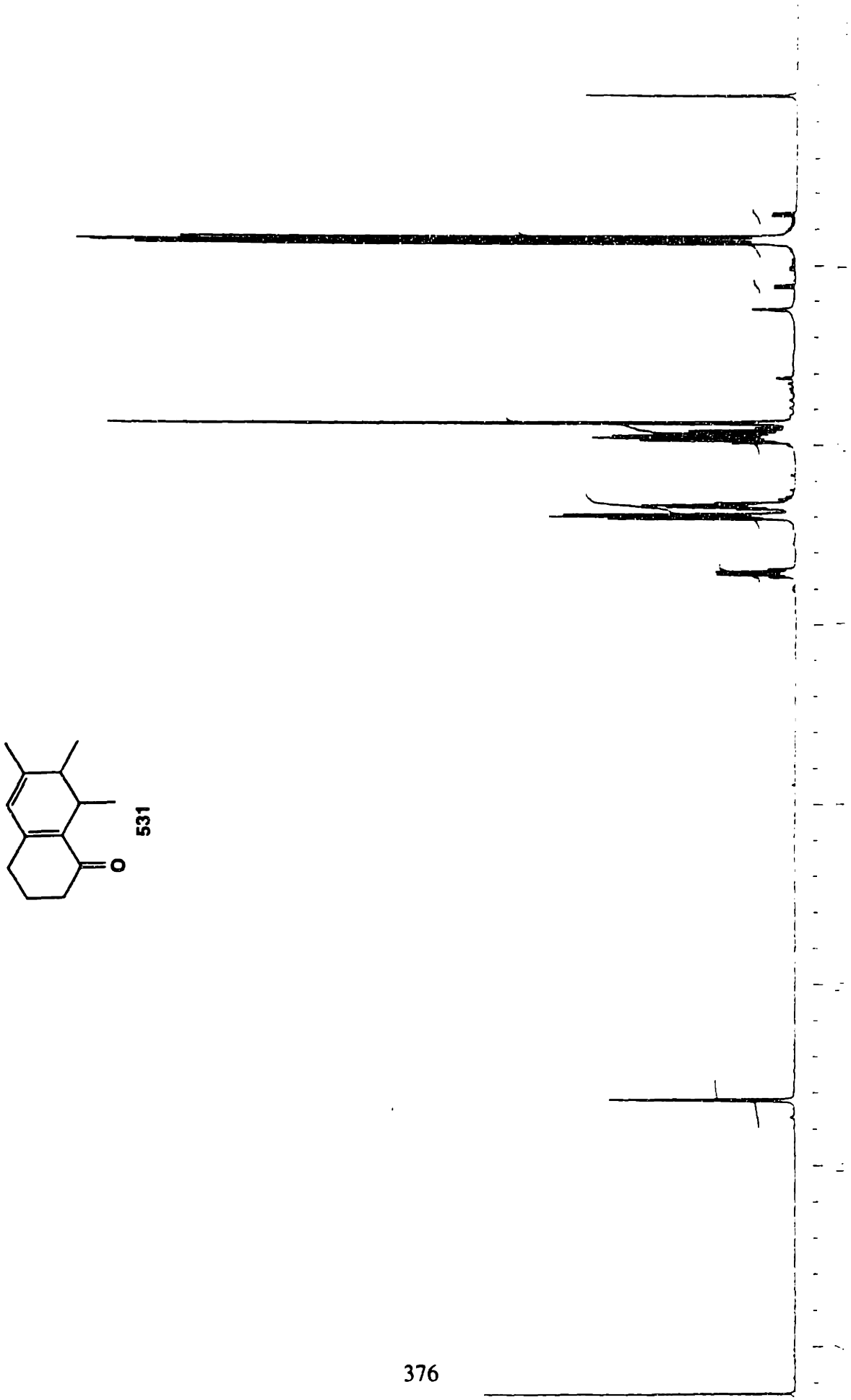


A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, nitrogen inlet adapter, and glass stopper was charged with 10-methyl-2,10-dodecadien-8-yn-4-one **517** (0.129 g, 0.677 mmol) and 27 mL of CH_2Cl_2. This solution was cooled to 0 °C, and aluminum chloride (0.043 g, 0.315 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 3 h, and stirred at room temperature for 13 d. After 13 d, another 5 mL of CH_2Cl_2 and aluminum chloride (0.010 g, 0.073 mmol) were added. After 20 d, more aluminum chloride (0.023 g, 0.169 mmol) was added. Saturated $NaHCO_3$ solution (5 mL) and Et_2O (15 mL) were added. The aqueous phase was separated and extracted with 5 mL of Et_2O, and the combined organic phases were washed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to give an orange oil. Purification by column chromatography on 5 g of silica gel (gradient elution with hexane to 3% ethyl acetate in hexane) provided 38 mg of **531** as a yellow oil (29%).

IR (film):	2955, 2924, 2868, 1698, 1656, 1643, 1577, 1454, 1387, 1357, 1288, 1264, 1193, 1175, 1131, 959, 887, 835, 805, and 672 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.64 (d, J = 1.5 Hz, 1 H), 2.72 (quartet, J = 7.0 Hz, 1 H), 2.38-2.41 (m, 2 H), 2.32-2.36 (m, 2 H), 1.95-1.99 (m, 2 H), 1.93 (quartet, J = 7.0 Hz, 1 H), 1.88 (d, J = 1.5 Hz, 3 H), 0.87 (d, J = 7.0 Hz, 3 H), and 0.85 (d, J = 7.0 Hz, 3 H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	198.8, 150.7, 149.0, 130.1, 120.9, 53.4, 41.3, 38.0, 31.2, 29.7, 22.8, 18.3, and 17.7 ppm.



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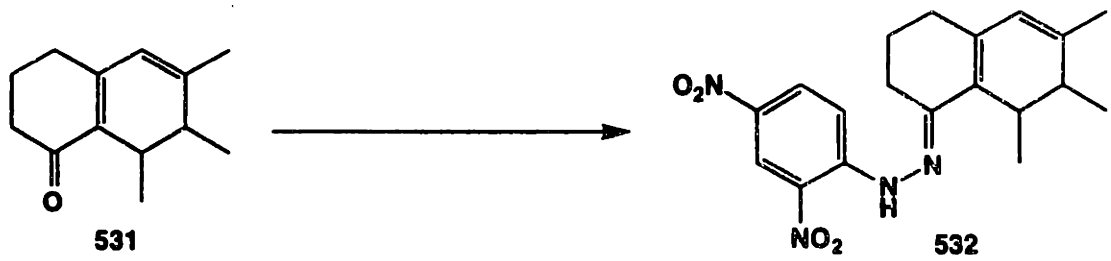

An Erlenmeyer flask was charged with 2,4-dinitrophenylhydrazine (0.500 g, 2.52 mmol) and 2.5 mL of concentrated H_2SO_4. A solution of 3.5 mL of water and 12.5 mL of 95% EtOH was added to the acidic solution. This solution was used in the preparation of the hydrazone **532**.

A 25-mL, one-necked, round-bottomed flask equipped with a nitrogen inlet adapter was charged with the ketone **531** (52 mg, 0.273 mmol) and 3 mL of 95% EtOH. The 2,4-dinitrophenylhydrazine solution (2.4 mL, 64 mg, 0.328 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the red precipitate was rinsed well with 10 mL of EtOH, 5 mL of $NaHCO_3$, and 5 mL of water. The precipitate was then dissolved in CH_2Cl_2 and concentrated to give a red powder. More of the hydrazone obtained by extracting the filtrate with two 5-mL portions of CH_2Cl_2. The organic phase was then extracted with 5 mL of brine, dried over Mg_2SO_4, filtered, and concentrated to give 0.225 g of a red powder. The combined red solids were then recrystallized in MeOH/CH_2Cl_2 to give 37 mg (37%) of **532** as red needles (mp 228-229 °C).