Kinetic and Mechanistic Studies of the Tandem Enediyne-Radical Cyclization

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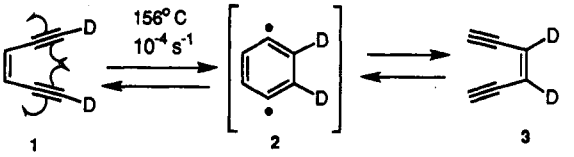
Enediynes 11 possessing a tethered olefin radical acceptor can participate in a tandem enediyne-radical cyclization to yield dihydrobenzindene derivatives 16. In the present study, the mechanism of this reaction was investigated utilizing kinetic studies to determine whether the mechanism was a radical chain, stepwise, or concerted process. Substrate concentration, 1,4-cyclohexadiene concentration, olefin geometry, and olefin electronics were varied. These experiments demonstrate that the reaction occurs under first-order kinetics over a wide variation in either substrate or 1,4-CHD concentration. The reaction rate is also independent of olefin geometry and olefin electronics. The rate constants for the reactions were similar and ranged from 3.0×10^{-4} s^{-1} to 6.0×10^{-4} s^{-1}. The data suggests that the tandem enediyne-radical cyclization proceeds through a distinct 1,4-diyl reactive intermediate such as 5 formed in the rate-determining enediyne cyclization step, followed by a radical cyclization to give 16. The tandem enediyne-radical cyclization mechanism is supported by trapping the intermediate biradical 18 in a tandem enediyne-6-*exo*-radical cyclization of 17 to give products 19a,b.

Introduction

In recent years there has been renewed interest in enediyne chemistry due to the discovery of several biologically interesting antitumor antibiotics such as neocarzinostatin,[1] calecheamicin,[2] esperamicin,[3] and dynemicin.[4,5] The biological activity of these molecules stems from a unique mechanism where their enediyne moiety undergoes a thermal cyclization to an aromatic biradical which subsequently cleaves DNA. Although the enediyne cyclization of the antibiotics was reported in 1987,[2,3] a chemical version of this reaction had been reported much earlier.[6]

Scheme I



In the early 1970's, Bergman and co-workers postulated that a parent *cis*-hex-2-ene-1,5-diyne 1 upon thermolysis will undergo a symmetrically allowed rearrangement to the thermally degenerate reactive intermediate 1,4-didehydrobenzene 2 which can collapse to starting material or the rearrangement product 3 (Scheme I).[6a] Later, it was shown that this reaction proceeded under first-order kinetics with a rate constant of $\approx 10^{-4}$ s^{-1} at 156 °C.[6b] Kinetic experiments over a 36 °C range allowed them to estimate $\Delta H^{\circ} \approx 32$ kcal/mol.[6a] Recently other enediyne cyclizations have been reported.[7]

Despite the intense interest in the biological activity of these enediynes, when we initiated our studies, there had been no reported examples where the 1,4-biradical was trapped in a subsequent radical cyclization with a pendent acceptor.[8] Since then we have developed a method of ring annulation by which an aromatic enediyne containing a

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(4) Dynemicin: Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Oki, T.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (c) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamda, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. *J. Antibiot.* **1990**, *43*, 1000.

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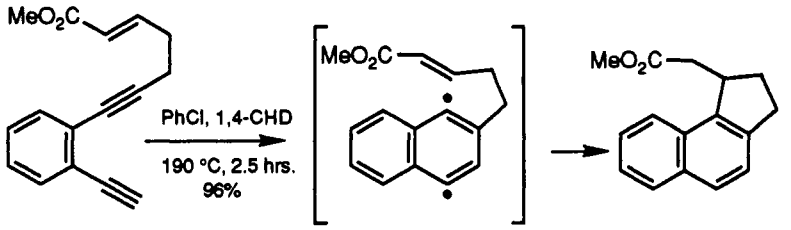
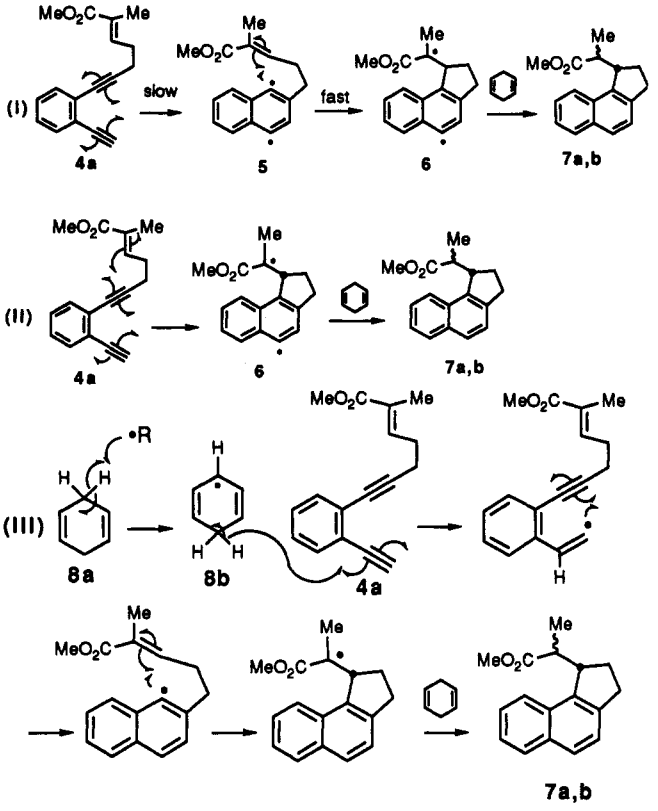
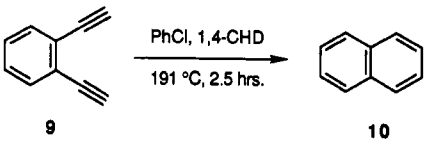
Scheme II



Scheme III



Scheme IV



radical accepting tether will undergo a thermal tandem enediyne-radical cyclization to give either a 2,3-dihydrobenz[*e*]indene or dihydrophenanthralene derivative (Scheme II).[9] We have made many advancements in this methodology since the publication of this work in early 1992.[10] The reaction times have become shorter and there has been a drastic increase in yields. Along with the development of this technique as a viable synthetic tool, we were also interested in the mechanistic pathway of the tandem enediyne-radical cyclization.

In the determination of the reaction pathway, three possible reaction mechanisms were considered (Scheme III). The first mechanism (I) considered was whether the dihydrobenzindene products were being formed through an enediyne cyclization of **4a** to yield the naphthalene diradical **5**, followed by a very fast 5-*exo* radical cyclization onto a pendent olefin to give **6** followed by hydrogen abstraction from 1,4-cyclohexadiene(1,4-CHD) to give the 2,3-dihydrobenz[*e*]indene **7a,b**. A second reaction pathway (II) that was considered involved the formation of product occurring through a concerted mechanism in which both rings of the benzindene product were being formed simultaneously to give tricycle **7a,b**. A third possible mechanism (III) for product formation could be through a radical chain reaction initiated by a hydrogen abstraction from the hydrogen donor, 1,4-cyclohexadiene **8a** by an adventitious radical source, followed by a subsequent hydrogen donation by cyclohexadiene monoradical **8b** to the enediyne substrate **4a** causing a series of radical cyclizations to the benzindene products **7a,b**.

To distinguish between these reaction pathways, kinetic studies were carried out on several aromatic enediyne substrates. Both the concentration of substrate and hydrogen atom donor were varied. The electronic nature and geometry of the pendent olefin were also varied and the kinetics of the different aromatic enediynes were determined at a reaction temperature of 191 °C. If a radical chain mechanism (III) was involved, a variation of 1,4-cyclohexadiene (1,4-CHD) concentration would be expected to affect the reaction rate. Any major variation in the rate constant with a change in olefin geometry or electronics would provide evidence for the concerted pathway (II). If there is no rate change with a variation in the electronics of the pendent olefin, this would be evidence for a stepwise process in which the formation of the five-membered ring is not involved in the rate-determining step (I). The following experimental results suggest that the tandem enediyne-radical cyclization proceeds through a distinct 1,4-diradical intermediate followed by a rapid radical cyclization with the reaction following first-order kinetics with a rate constant of $\approx 10^{-4}$ s^{-1} at 191 °C (mechanism I).

Results and Discussion

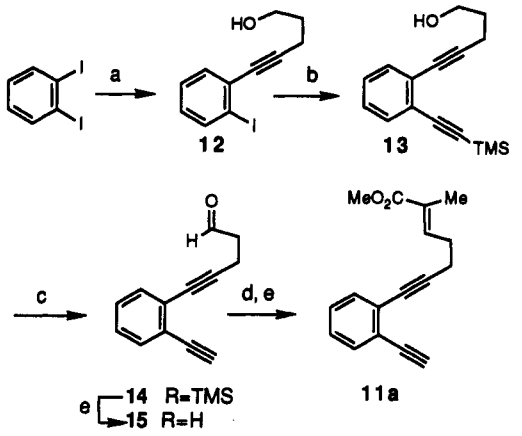
Although the rate constant for enediyne cyclizations has been shown to be $\approx 10^{-4}$ s^{-1} at 156 °C[6b] there was no rate data for the aromatic enediyne systems. To obtain a control rate constant for the tandem enediyne-radical cyclization, the parent 1,2-diethynylbenzene (**9**) was synthesized and the kinetics of the cyclization to naphthalene (**10**) were carried out with 0.001 M substrate **9** and 1 M 1,4-CHD (Scheme IV). The measured rate constant was 2.04×10^{-4} s^{-1} at 191 °C.[11]

The synthesis of enediynes **11a–g** were carried out in a straightforward manner starting with commercially available starting materials.[9,10] A representative example showing the synthesis of **11a** is shown in Scheme V.

(9) Grissom, J. W.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315.
(10) Experimental details involving the synthesis and cyclization of these systems will appear in a separate publication: Grissom, J. W.; Calkins, T. L. *J. Am. Chem. Soc.*, submitted for publication.

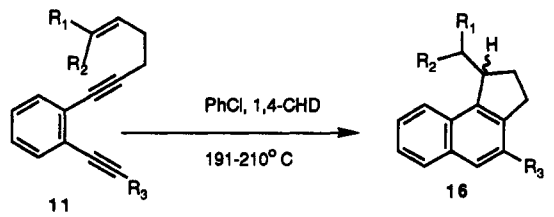
(11) We thank Professor Charles B. Grissom and Tom Evans of the University of Utah Chemistry Department for the measurement of this rate constant.

Scheme V[a]



[a] (a) 4-Pentynol, $(PPh_3)_4Pd$, CuI, NEt_3; (b) trimethylsilyl)acetylene, $(PPh_3)_4Pd$, CuI, NEt_3; (c) PCC, Celite, CH_2Cl_2; (d) trimethyl-2-methylphosphonoacetate, LiCl, DBU, CH_3CN; (e) TBAF, THF.

Scheme VI



a) R_1= CO_2Me; R_2= Me; R_3= H
b) R_1= Me; R_2= CO_2Me; R_3= H
c) R_1= CH_2OH; R_2= R_3= H
d) R_1= OAc; R_2= R_3= H
e) R_1= OMe, R_2= R_3=H
f) R_1= CO_2Me, R_2=H, R_3=CH_2OH (245 °C)
g) R_1= CO_2Me, R_2=H, R_3=$CH_2OTBDMS$ (245 °C)

a,b) 93 %, 3.5 : 1
c) 53 %
d) >99 %
e) 83 %
f) 95%
g) 70%

Starting with diiodobenzene, a palladium coupling was done with 4-pentynol to yield monocoupled alcohol **12** (74%).[12] A second palladium coupling done under the same conditions using (trimethylsilyl)acetylene as the alkyne yielded enediyne **13** (99%).[12] Oxidation with PCC gave enediyne **14** (62%) which was characterized as its free acetylene **15** upon treatment with TBAF. Enediyne **14** was submitted to a Horner–Emmons reaction followed by desilylation with TBAF to yield **11a** with an overall yield for the two steps of 92%. The thermal cyclizations of **11a–g** were carried out in chloro- or dichlorobenzene and products **16a–g** were obtained in good to excellent isolated yields (Scheme VI).[9,10]

Initial kinetic studies were performed on substrate **11a** at concentrations of 50, 10, and 1 mM at 191 °C while keeping 1,4-CHD concentration constant at 1 M (Table I, entries 1, 2, and 3). Kinetically, **11a** showed pseudo-first-order kinetics over a 50-fold concentration range with a rate constant of $\approx 3.5 \times 10^{-4}$ s^{-1} at 191 °C. To further support the idea of first-order kinetics, studies were completed in which the concentration of 1,4-CHD was varied and enediyne concentration was held constant. Two additional experiments were performed in which enediyne concentration remained constant at 0.001 M and 1,4-CHD concentration was varied from 1 M to 0.2 M and 0.02 M (Table I, entries 4 and 5). Analysis of the kinetic data from these two experiments yielded first-order rate constants of 4.7×10^{-4} s^{-1} and 6.0×10^{-4} s^{-1}, respectively. Since there was no appreciable change in the rate of the reaction, it was concluded that the rate of the tandem enediyne-radical cyclization did not depend upon the concentration of the hydrogen donor. Therefore, the radical chain mechanism (III) where 1,4-CHD enters into the rate-determining step is probably not operating. Intuitively this radical chain mechanism does not seem plausible because a hydrogen atom donation to the acetylene would be expected to occur at the least-substituted position rather than at the most-substituted end.[13]

Table I. Kinetics Study of 11a (carried out at 191 °C)

entry	substrate	concn of EDY,[a] M	concn of CHD,[b] M	k (s^{-1})	error (s^{-1})
1	**11a**	0.001	1	3.0×10^{-4}	1.2×10^{-5}
2	**11a**	0.01	1	3.4×10^{-4}	1.1×10^{-5}
3	**11a**	0.05	1	3.5×10^{-4}	1.6×10^{-5}
4	**11a**	0.001	0.2	4.7×10^{-4}	2.4×10^{-5}
5	**11a**	0.001	0.02	6.0×10^{-4}	3.3×10^{-5}

[a] EDY = enediyne. [b] CHD = 1,4-cyclohexadiene.

Table II. Kinetics Study of 11c–e (carried out at 191 °C)

entry	substrate	concn of EDY,[a] M	concn of CHD[b]	k (s^{-1})	error (s^{-1})
1	**11c**	0.006	1	4.8×10^{-4}	1.8×10^{-5}
2	**11d**	0.038[c]	1	3.6×10^{-4}	4.4×10^{-6}
3	**11e**	0.004[d]	1	4.6×10^{-4}	8.6×10^{-6}
4	**11a**	0.01	1	3.4×10^{-4}	1.1×10^{-5}
5	**11b**	0.016	1	5.0×10^{-4}	1.2×10^{-5}

[a] EDY = enediyne. [b] CHD = 1,4-cyclohexadiene. [c] Study performed on 1:1 mixture of *E*/*Z*; both isomers were consumed at the same rate. [d] Study performed on a 1:2 mixture of *E*/*Z*.

Further kinetic experiments were performed to try and distinguish between the stepwise pathway (I) and the concerted pathway (II). We assumed that if the concerted pathway was occurring, a significant rate change should be observed by changing the electronic nature of the pendent olefin. Kinetic experiments on the allylic alcohol **11c**, the enol acetate **11d**, or the methyl enol ether **11e** yielded first-order rate constants of 4.8×10^{-4} s^{-1}, 3.6×10^{-4} s^{-1}, and 4.6×10^{-4} s^{-1}, respectively, at 191 °C (Table II). These measured rate constants are in line with the 2.04×10^{-4} s^{-1} rate constant measured for the parent aromatic enediyne system. Since the rates of cyclization of enediynes **11a** and **11c–e** are slightly but not significantly different ($k = 3.0 \times 10^{-4}$ s^{-1} to 6.0×10^{-4} s^{-1}), it appears that the reaction rate does not depend on whether the olefin acceptor is electron-rich, -poor, or -neutral. Comparing the rate data for **11a** and **11b**, it does not matter greatly whether the pendent olefin radical acceptor is of the *cis* or the *trans* geometry. The first-order rate constant for the *cis* olefin **11b** was determined to be 5.0×10^{-4} s^{-1}. When compared to that of the rate of the *trans* olefin **11a** ($k = 3.4 \times 10^{-4}$ s^{-1}), no significant difference was observed. Compounds **11d** and **11e** were reacted as mixtures of 1:1 and 2:1 cis/trans (Table II). Independent GC analysis of the isomers yielded rate constants which were identical.

However, the rate of the reaction is affected by substitution on the other acetylenic position R_3. By placing a non-hydrogen substituent at R_3, a significant decrease

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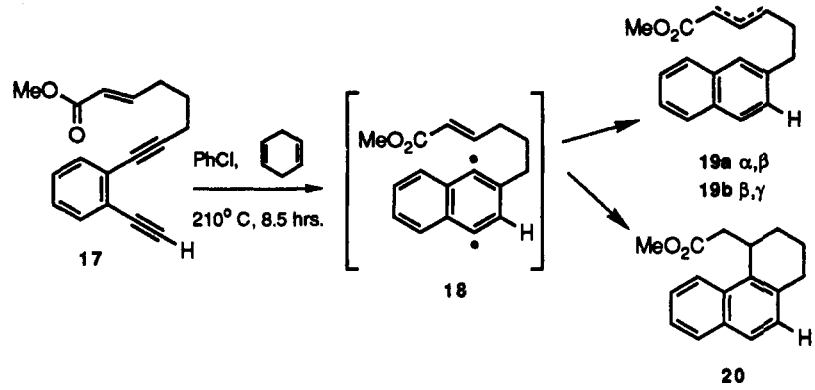
(13) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**, *109*, 2829. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (c) Ardisson, J.; Ferezou, J. P.; Julia, M.; Pancrazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001. (d) Broka, C.; Reichert, D. *Tetrahedron Lett.* **1987**, *28*, 1503.

Scheme VII



in the rate was observed in the reaction at 191 °C. When **11f** and **11g** were subjected to the same reaction conditions as **11a–e**, no reaction was observed after 90 min. Even at 245 °C, these substrates required reaction times 2–3 times longer than the reaction with the unsubstituted acetylene. The higher reaction temperatures can be explained by the increased steric factors that must be overcome to bring the disubstituted acetylenes close enough together to form the 1,4-diradical intermediate.[14]

These kinetic studies lead us to conclude that the formation of the five-membered ring does not enter into the overall rate constant of the tandem enediyne-radical cyclization; the rate-determining step appears to be the formation of the 1,4-diradical from the aromatic enediyne. The fact that the reaction rate does not depend greatly on the olefin geometry or electronics is not surprising, since it is known that the 5-*exo* aryl radical cyclization is very fast (2×10^7 at 80 °C).[15a] In addition, the rate decrease with increasing substitution on the alkyne terminus not containing the radical acceptor supports the idea that the enediyne cyclization is the rate-determining step. At this point, we feel confident that the mechanism that is operating is a very slow enediyne cyclization to form the 1,4-diradical followed by a very fast 5-*exo* radical cyclization.

The trapping of the diradical intermediate **5** before it has completed the 5-*exo* radical cyclization would lend conclusive proof to the tandem enediyne-radical cyclization mechanism I (Scheme III). One might expect intermolecular hydrogen abstraction from the solvent by the aryl radical to compete with 5-*exo* radical cyclization if the reaction was done using 1,4-CHD as solvent. When this experiment was performed, the only observed product was a tricycle arising from the tandem enediyne-radical cyclization. No products derived from intermolecular hydrogen trapping by 1,4-CHD prior to radical cyclization were observed. Presumably the radical cyclization is occurring at a faster rate than the diffusion controlled rate of hydrogen abstraction by 1,4-CHD. Although the rate of 5-*exo* aryl radical cyclization is 2×10^7 s^{-1} at 80 °C,[15a] at the higher temperatures employed in our reaction, the cyclization rate must be much faster.

Although all attempts to trap the intermediate **5** with 1,4-CHD have failed, as a comparison we have evidence for a distinct 1,4-diradical intermediate from the studies of the 6-*exo* analog **17** (Scheme VII). We have found that the thermolysis of the 6-*exo* substrate yielded three products, the tandem enediyne-radical cyclization product **20** and the simple enediyne trapped products **19a** and **19b**. The existence of aryl radical hydrogen abstraction products **19a** and **19b** indirectly proves the existence of the biradical **18**.

Table III. Variation of Concentration of 1,4-CHD in the Thermolysis of 17 (at 100% conversion)

molarity of CHD	ratio of 19a,b/20	molarity of CHD	ratio of 19a,b/20
5.0	2.53:1	2.64	1.84:1
4.75	2.34:1	2.11	1.57:1
4.23	2.27:1	1.58	1.42:1
3.7	2.07:1	1.05	1.26:1
3.17	1.95:1	0.53	1.08:1

By varying the concentration of 1,4-cyclohexadiene, we were able to shift the product distribution of the 6-*exo* analog toward the tandem enediyne-radical cyclized product **20**. The concentration was varied from 5 to 0.5 M and the best ratio that was achieved was ≈1:1 (Table III). By lowering the concentration of 1,4-CHD lower than 0.5 M, a 1:1 ratio was still obtained but polymerization began to occur. The greater the concentration of 1,4-CHD, the more likely the 1,4-diradical will be quenched before it is able to undergo a 6-*exo* cyclization into the unsaturated six carbon centers away.

The formation of β,γ-unsaturated ester **19b** suggests a competing 1,5-intramolecular hydrogen abstraction of an allylic proton by a less-stable phenyl radical to yield the allylic radical that is quenched at either the α or γ positions.[15b,f] Although the rate of the 6-*exo* alkyl radical cyclization is considerably less ($k = 4.1 \times 10^3$ s^{-1} at 80 °C) than the rate of the 5-*exo* alkyl radical cyclization ($k = 2.3 \times 10^5$ s^{-1} at 80 °C),[15a] the rate of the 6-*exo* aryl radical cyclization is probably much faster than that of the corresponding 6-*exo* alkyl radical cyclization, due to the increased reactivity of the aryl radical.[15] The 5-*exo* aryl radical cyclization (2×10^7 s^{-1}) is most certainly faster than the 6-*exo* aryl radical cyclization.[15a] Due to the facile competing 1,5-hydrogen abstraction by an aryl radical ($k \approx 10^6$ s^{-1} at 80 °C),[15b,f] researchers have been unable to obtain data for the all carbon 6-*exo* aryl radical cyclization.[15a] The competing formation of products **19a,b** and **20** suggests that the rate of 6-*exo* aryl radical cyclization is probably on about the same order of magnitude as a 1,5-hydrogen abstraction by an aryl radical ($\approx 10^6$ s^{-1} at 80 °C).[15a,b,f] It is a reasonable assumption that the tandem enediyne-6-*exo* radical cyclization operates through a similar mechanism as the 5-*exo* aryl radical

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cyclization. Therefore, it is likely that intermediates such as naphthalene diradical **5** are intermediates in the tandem enediyne-radical cyclization.

Conclusion

Kinetic studies of aromatic enediynes **11a–g** yielded some interesting results and insights as to a mechanism for the tandem enediyne radical-cyclization. Initial rate studies on **11a** show a nearly identical rate constant even at different concentrations of the enediyne or hydrogen source in the reaction. This results suggests that the reaction occurs under first-order kinetics. Since the 1,4-cyclohexadiene does not enter into the rate-determining step, the radical chain mechanism is thus ruled out. The fact that the rate of the reaction is independent of the geometry and electronic nature of the pendent olefin radical acceptor, coupled with the isolation of the enediyne-trapped product from the thermolysis of the 6-*exo* analog, shows that the tandem enediyne-radical cyclization appears to proceed through a distinct 1,4-diyl reactive intermediate formed in the rate-determining enediyne cyclization step, followed subsequently by a fast radical cyclization.

Experimental Section

All kinetic data was obtained by analytical GC on a Shimadzu GC-14A using a CR-601 integrator. The analysis was done using a 0.54 SE-54 wide-bore capillary column with helium as the carrier gas. Naphthalene was used as the internal standard in all studies. The experiments were all performed in chlorobenzene purified by passing through basic alumina. 1,4-CHD was purchased from Jannsen Chemica and used without further purification. The experiments were all conducted at 191 ± 0.1 °C. The GC data was analyzed using Enzfitter on an IBM PC.

Procedure for Kinetic Studies of 11a. Aromatic enediyne **11a** was purified by MPLC with hexanes/ethyl acetate (97:3) to give 15.3 mg of purified substrate. A master solution was made by dissolving the enediyne in 5 mL of chlorobenzene using a 5-mL volumetric flask to give a 0.0122 M master solution. To this solution was added 3.2 mg of naphthalene as an internal standard. A 0.904-mL aliquot was removed from the master solution *via* syringe and placed in a 1-mL volumetric flask followed by 0.096 μL of 1,4-cyclohexadiene to give a solution of 0.011 M in substrate and 1 M in cyclohexadiene. In each of five capillary melting point tubes was placed 0.030 mL of the 0.011 M reaction solution. The tubes were cooled to −78 °C and degassed *via* high pump vacuum and sealed at different dead volume heights. Each tube was placed in an oil bath at 200 °C. The height which upon heating that expanded completely to yield no dead volume was chosen as the proper tube size for this study. Forty-five reaction tubes were prepared by sealing under high pump vacuum with an oxygen torch. A reaction tube was placed in an oil bath at temperatures of 165, 175, 187, 191, and 195 °C to obtain a suitable half-life for our study. Analysis by analytical GC showed that 191 °C gave a half-life of approximately 40 min which was a useful value.

Fifteen reaction tubes were placed in an oil bath maintained at 191 ± 0.1 °C and removed at intervals of 1, 2, 3, 6, 10, 15, 20, 25, 30, 40, 50, 65, and 90 min. Each tube was analyzed by analytical GC at 150 °C for 2 min and then 3 °C/min for 15.5 min.

A 0.0012 M master solution was prepared by removing 0.5 mL from the 0.01216 M master solution and diluted *via* syringe to 5 mL in a volumetric flask. Then 0.096 μL of 1,4-cyclohexadiene was then placed in a 1-mL volumetric flask and diluted with chlorobenzene to 1 mL with the 0.0012 M master solution to give a 0.001 M reaction solution while 1 M in 1,4-CHD.

Fourteen reaction tubes were prepared *via* the previous method and subjected to the same thermolysis conditions and analyzed by analytical GC.

Finally, a 0.0579 M master solution was prepared by concentrating 1.0 mL of the 0.01216 M solution to 0.210 mL. Then 0.094 mL of this solution was added to 0.0096 mL of 1,4-CHD to give a concentration of 0.0523 M. In this experiment 0.010-mL reaction tubes were thermolyzed and were analyzed by the same method described above.

The percent starting material remaining was plotted versus time and the resultant exponential curve was fitted to a single exponential decay rate equation using the Enzfitter program on an IBM PC.

To a 1-mL volumetric flask was added 1.89 μL of 1,4-CHD (0.00002 mol) and 0.904 mL of the 0.0012 M master solution, and then the flask was topped off with chlorobenzene to yield a 0.001 M solution in enediyne and 0.02 M solution in 1,4-cyclohexadiene. The 0.2 M solution in 1,4-CHD was prepared in a similar manner but 18.9 μL of 1,4-CHD was added to give the required concentration. Reaction tubes were prepared and thermolyzed in a similar manner as in the previous kinetic study.

Kinetics Studies of 11b. To a 1-mL volumetric flask was added **11b** (0.0042 mg, 0.000166 mol), naphthalene (1.4 mg), 1,4-CHD (0.081 g, 1.01 mmol, 0.096 mL), and chlorobenzene (0.904 mL). The reaction solution was analyzed by analytical GC and determined to be 0.0166 M in substrate with reference to naphthalene. Reaction tubes were prepared the same as in the previous experiment and thermolyzed and analyzed in the same manner.

Kinetics Study of 11c–g. All reaction solutions for kinetic studies on **11c–g** were prepared and studied in a similar manner as **11b**.

Concentration Studies on 17. To a predried product vial was placed enediyne **16** (7.2 mg, 0.028 mmol) and then diluted with 0.280 mL of predried chlorobenzene to yield a 0.1 M master reaction solution. From that master solution, 10-μL aliquots were placed in each of 10 capillary melting point tubes. To each of these tubes was added between 1 and 10 μL (in 1-μL increments) of 1,4-CHD, respectively, and then each tube was diluted to 20 μL with the respective amount of chlorobenzene. The resulting solutions each were of the same molarity (0.5 M) with respect to enediyne and varied in concentration of 1,4-cyclohexadiene. The concentrations of 1,4-cyclohexadiene were 5, 4.75, 4.25, 3.70, 3.17, 2.64, 2.11, 1.58, 1.05, and 0.53 M respectively. All 10 tubes were then cooled to −78 °C and sealed under high vacuum with an oxygen torch. Each tube was then placed in an oil bath at 195 °C for 2 h after which the tubes were removed and allowed to cool to room temperature. The reaction mixtures containing **19a,b** and **20** were then analyzed by GC analysis on an SE-54 analytical capillary column using an isothermal program of 175 °C.

Preparation of 5-(2-Iodophenyl)-4-pentynol (12). To a predried 500-mL roundbottom flask under N_2 was added 300 mL of anhydrous NEt_3, diiodobenzene (5.0 g, 15.1 mmol, 2 mL), 0.05 equiv of tetrakis(triphenylphosphine)palladium (0.436 g, 0.76 mmol), and 0.1 equiv of CuI (0.287 g, 0.15 mmol). The reaction mixture was allowed to stir for 10 min. Then 4-pentynol (1.27 g, 15.1 mmol, 1.4 mL) was added *via* syringe. The reaction mixture was allowed to stir overnight upon which all of the alcohol had been consumed. The reaction mixture was filtered through a 60-mL coarse-fritted funnel and the precipitated ammonium salt was washed with anhydrous Et_2O. The mother liquor was concentrated *in vacuo* and purified by silica gel chromatography with hexanes/ethyl acetate (3:1) to yield 3.17 g (74%) of a brown oil: R_f 0.1, hexanes/ethyl acetate (3:1); IR (neat) 3374, 3059, 2230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, br, 1H, OH), 1.89 (p, 2H, J = 6.3 Hz), 2.59 (t, 2H, J = 6.3 Hz), 3.87 (t, 2H, J = 6.3 Hz), 6.94 (td, 1H, J = 7.5, 1.5 Hz), 7.24 (td, 1H, J = 7.5, 1.5 Hz), 7.38 (dd, 1H, J = 7.8, 1.5 Hz), 7.79 (dd, 1H, J = 7.8, 1.5 Hz); ^{13}C NMR (75 MHz) δ 16.1, 31.0, 61.7, 83.4, 93.6, 101.0, 127.7, 128.9, 130.2, 132.5, 138.6; HRMS-EI m/e calcd for $C_{11}H_{11}O$ (M^+) 285.9853, found 285.9849.

Preparation of 5-[2-[(trimethylsilyl)ethynyl]phenyl]-4-pentynol (13). This compound was prepared by a similar palladium coupling procedure as described above for **12** using 2 equiv of (trimethylsilyl)acetylene rather than 4-pentynol which was added in one portion *via* syringe. Isolation *via* silica gel chromatography hexanes/ethyl acetate (3:1) to yield a yellow oil (99%); IR (neat) 3351, 3060, 2230, 2158 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 0.30 (s, 9H), 1.74 (s, br, 1H, OH), 1.91 (p, 2H, J = 6.3 Hz), 2.63 (t, 2H, J = 6.3 Hz), 3.88 (t, 2H, J = 6.3 Hz), 7.24 (m, 2H), 7.40 (m, 2H), 7.47 (m, 1H); ^{13}C NMR δ 0.0, 16.2, 31.3, 61.8, 79.8, 93.6, 97.9, 103.8, 125.4, 126.4, 127.3, 128.2, 131.8, 132.3; HRMS-EI m/e calcd for $C_{16}H_{20}OSi$ (M^+) 256.1283, found 256.1269.

Preparation of 5-[2-[(Trimethylsilyl)ethynyl]phenyl]-4-pentynal (14) and 5-(2-ethynylphenyl)-4-pentynal (15). To a predried 25-mL roundbottom flask under N_2 was added 5-[[(2-trimethylsilyl)ethynyl]phenyl]-4-pentynol (0.265 g, 0.92 mmol), 3 equiv of PCC (0.594 g, 2.76 mmol), and 2 g of Celite. The reaction was stirred under N_2 for 1 h. The reaction mixture was plugged through Florosil with anhydrous Et_2O and concentrated *in vacuo* to yield the yellow oil aldehyde **14** (62%). The aldehyde was carried on without further purification. Removal of the TMS group was achieved by dissolving the aldehyde in 5 mL of THF, followed by the addition of an excess of TBAF. An ether/water extraction was carried out (2 × 25 mL), and the organics were dried over $MgSO_4$, filtered, and concentrated *via* rotary evaporation to yield the desilylated aldehyde **15** as a yellow oil R_f = 0.59 hexanes/ethyl acetate (3:1); IR (neat) 3283, 3063, 2236, 2106, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, 4H), 3.27 (s, 1H), 7.24 (m, 2H), 7.38 (dd, 1H, J = 6.9, 1.8 Hz), 7.47 (dd, 1H, J = 6.9, 1.8 Hz), 9.87 (s, 1H); ^{13}C NMR (75 MHz) δ 12.9, 42.5, 80.0, 80.7, 82.2, 92.2, 124.5, 126.3, 127.6, 128.5, 131.9, 132.5, 200.6; HRMS calcd for $C_{13}H_{10}O$ (M^+) 182.0732, found 182.0733.

Preparation of Methyl 5-(2-Ethynylphenyl)-2-methylhept-2-en-6-ynoate (11a). The preparation of this compound was done using 5-(2-trimethylsilyl)ethynylphenyl)-4-pentynal **14**. To a 25-mL roundbottom flask charged with 10 mL of anhydrous CH_3CN was added 1.5 equiv of trimethyl 2-methylphosphonoacetate (0.415 g, 2.1 mmol), 1.5 equiv of DBU (0.319 g, 2.1 mmol, 0.287 mL), and 2 equiv of LiCl (0.118 g, 2.8 mmol). The reaction mixture was stirred for 10 min at ambient temperature, and then 1 equiv 5-[2-[(trimethylsilyl)ethynyl]phenyl]-4-pentynal (0.394 g, 1.4 mmol) in 4 mL of CH_3CN was added dropwise to the reaction mixture *via* cannula. The reaction was finished in less than 5 min.

The reaction mixture was then plugged through SiO_2 with ethyl acetate to yield a crude mixture of olefinic isomers (10:1, trans/cis) of the trisubstituted α,β-unsaturated ester. The cis and trans isomers were separated by radical chromatography on a 2-mm plate with hexanes/ethyl acetate (93:7) and concentrated *in vacuo* to yield 0.298 g (trans) and 0.03 g (cis) as yellow oils for a combined yield of 92%. The removal of the TMS group was performed in a similar manner as described for **14** to give compound **11a** R_f = 0.6 (trans) in hexanes/ethyl acetate (3:1); R_f = 0.6 hexanes/ethyl acetate (3:1); IR (neat) 3233, 2925, 2236, 2098, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (d, 3H, J = 1.1 Hz), 2.49 (q, 2H, J = 7.3 Hz), 2.57–2.62 (m, 2H), 3.72 (s, 3H), 3.30 (s, 1H), 6.88 (tq, 1H, J = 7.3, 1.1 Hz), 7.37 (dd, 1H, J = 6.6, 1.9 Hz), 7.17–7.26 (m, 2H), 7.45 (dd, 1H, J = 6.6, 1.9 Hz); ^{13}C NMR δ 19.0, 28.0, 51.7, 79.7, 80.8, 82.2, 93.2, 124.4, 126.6, 127.3, 128.3, 128.8, 131.8, 132.4, 140.1, 163.8; HRMS-EI m/z calcd for $C_{17}H_{16}O_2$ (M^+) 252.1111, found 252.1131.

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Supplementary Material Available: Kinetics data for **11a–e** and **9**; copies of ^1H and ^{13}C NMR spectra of **12**, **13**, **15**, and **11a** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.