Synthetic Studies of the Tandem Enediyne–Mono- and Bis-Radical Cyclizations

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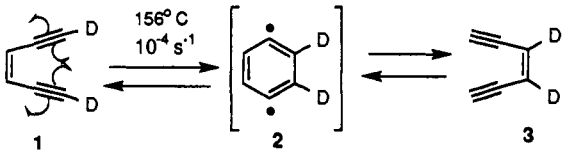
Abstract: The readily synthesized enediynes **12a–j** possessing a tethered olefin radical acceptor can participate in a tandem enediyne–radical cyclization to yield dihydrobenzindene derivatives **14a–j**. In the present study, the scope of this reaction was expanded to include a wide variety of olefin acceptors. Substitution at both ends of olefin leads to the formation of two diastereomers **14b** and **14c** in a 3.5:1 ratio when R_3 is Me and R_2 is CO_2Me. The structures of the dihydrobenzindene products **14b** and **14c** were confirmed by generating a radical from **25** by a tributyltin hydride reaction which undergoes radical cyclization; this radical is similar to the enediyne-generated radical, which also cyclizes. It was shown that, in **14i** and **14j**, a substituent at R_1 slowed the reaction but still resulted in a good to excellent yield of product. A tandem enediyne–6-*exo*-radical cyclization of **16** was also carried out but did not work as well as its 5-*exo* counterpart **12a**. Finally, an enediyne **33** containing two olefinic tethers was cyclized in a process to form tetracycle **34** where three rings were formed in one synthetic operation.

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]

In the early 1970s Bergman and co-workers postulated that a parent dideuterio-*cis*-hex-3-ene-1,5-diyne **1** upon thermolysis will undergo a symmetrically allowed rearrangement to the degenerate reactive intermediate 1,4-didehydrobenzene **2**, which can collapse to starting material or to the rearrangement product **3** (Scheme I).[6] Recently, other enediyne cyclizations have also been reported.[7]

Scheme I



Despite the intense interest in the biological activity of these enediynes, prior to our initial report[10] there have been no reported examples where the 1,4-biradical has been trapped in a subsequent radical cyclization with a pendent acceptor. Aryl radicals are known to be very reactive in 5-*exo* radical cyclizations with olefins, occurring with a rate constant of about 10^8 s^{-1} at 80 °C.[8] Aryl radicals that participate in radical cyclization reactions have often been generated from the treatment of aryl halides with tributyltin hydride in the presence of a radical initiator.[8b,c,9] We envisioned using the Bergman cyclization to generate two radicals which could each participate in further radical cyclizations for the construction of multicyclic systems (Scheme II). Thus, a construction of three rings from an acyclic precursor **4** would be possible.

Utilizing this strategy, we have developed a method of ring annulation by which an aromatic enediyne containing a radical-

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(3) Esperamicins: (a) Konishi, M.; Ohkuma, H.; Saitoh, K.; Kaweguchi, H.; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T. W. *J. Antibiot.* **1985**, *38*, 1605. (b) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (c) Golik, J.; Dubay, G.; Groenewold, G.; Kaweguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461.

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(5) For a general overview on the enediyne antibiotics, see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497.

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

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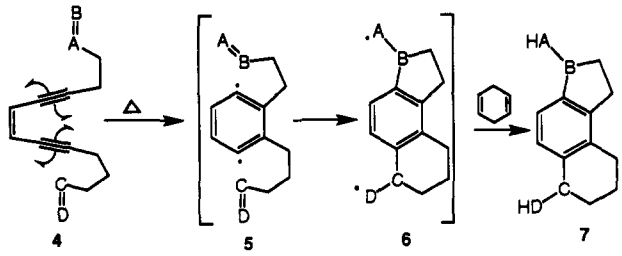
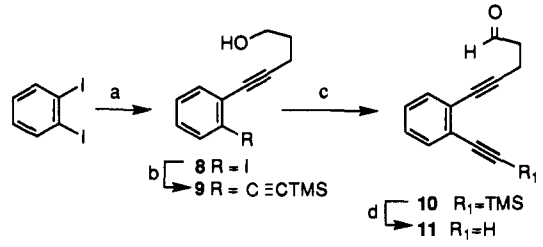
Scheme II



Scheme III[a]



[a](a) 4-Pentynol (1.5 equiv), $(PPh_3)_4Pd$ (0.05 equiv), CuI (0.1 equiv), NEt_3 (74%); (b) (trimethylsilyl)acetylene (2 equiv), $(PPh_3)_4Pd$ (0.05 equiv), CuI (0.1 equiv), NEt_3 (99%); (c) PCC (3 equiv), Celite, CH_2Cl_2 (62%); (d) TBAF, THF (100%).

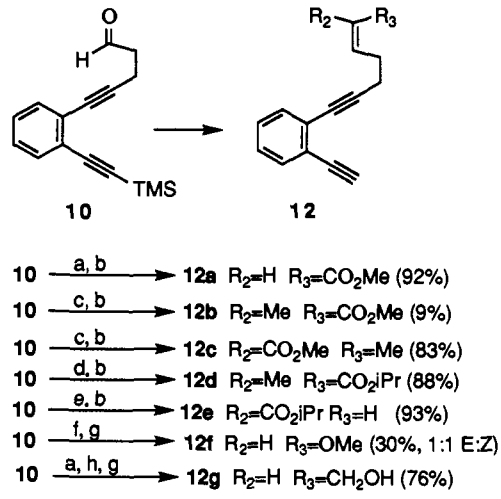
accepting tether will undergo a thermal tandem enediyne–radical cyclization to give either a 2,3-dihydrobenz[*e*]indene or dihydrophenanthralene derivative.[10] Since then, there have been reports by Wang, Padwa, and Moore utilizing the aromatic radical generated from eneyne allenes or eneyne ketenes in radical cyclizations.[11]

Extensive advancements have been made in the tandem enediyne–radical cyclization reaction since the communication of this work in early 1992.[10,12] We have investigated the use of various hydrogen donors, electronically diverse and configurationally different olefins, and the construction of various ring sizes. The observed reaction times have become shorter, and there has been a drastic increase in yields. The full details of our study of the tandem enediyne–radical cyclization are contained within this paper.

Synthesis of Aromatic Enediynes

The success of the tandem enediyne–radical cyclization is enhanced by the ease in which the test substrates are synthesized. Starting from commercially available materials, enediynes **12a–g** were synthesized from a common precursor **10** in two or three additional steps.[13] 5-(2-((Trimethylsilyl)ethynyl)phenyl)-4-pentynal (**10**) was constructed from diiodobenzene *via* palladium(0) coupling with 4-pentynol to yield the mono-coupled alcohol **8** (74%) followed by a second Pd(0) coupling with (trimethylsilyl)-acetylene (TMS acetylene) to yield the aromatic enediyne **9** (99%) (Scheme III). Subsequent PCC oxidation of **9** to aldehyde **10** (62%), followed by desilylation with tetrabutylammonium fluoride (TBAF) in THF, afforded 5-(2-ethynylphenyl)-4-pentynal **11** (62% over two steps). The pentynal was characterized as the free acetylene **11**, but all further elaborations were performed on the silylated **10** and desilylation was achieved in the final step of the substrate synthesis.

Scheme IV[a]



[a](a) Trimethyl phosphonoacetate (1.5 equiv), LiCl (2 equiv), DBU (1.5 equiv), CH_3CN; (b)TBAF, THF; (c) trimethyl 2-methylphosphonoacetate (1.5 equiv), LiCl (2 equiv), DBU (1.5 equiv), CH_3CN; (d) isopropyl dimethyl 2-methylphosphonoacetate (1.5 equiv), LiCl (2 equiv), DBU (1.5 equiv), CH_3CN; (e) isopropyl dimethyl phosphonoacetate (1.5 equiv), LiCl (2 equiv), DBU (1.5 equiv), CH_3CN; (f) (methoxymethyl)-triphenylphosphonium bromide (5.1 equiv), KO-*t*-Bu (5 equiv), THF; (g) (ca.) K_2CO_3, MeOH; (h) DIBAL (2.1 equiv), CH_2Cl_2.

Compound **12a** was synthesized by a Roush–Masamune variation on the Horner–Emmons reaction on **10** with trimethyl phosphonoacetate and DBU/LiCl, followed by desilylation with TBAF in THF, to yield **12a** (92%) (Scheme IV).[15] The cis/trans isomers **12b** and **12c** were synthesized in a similar manner as **12a** in 92% combined yield using trimethyl 2-methylphosphonoacetate in a Horner–Emmons reaction followed by desilylation with TBAF to yield the cis/trans mixture of **12b** and **12c**, which was separable with hexanes/ethyl acetate (97:3) *via* silica gel radial chromatography. Trimethyl 2-methylphosphonoacetate was easily prepared in an Arbuzov reaction between trimethyl phosphite and commercially available methyl 2-bromopropiolate.[16] **12d** was prepared in a similar manner as **12a** *via* a Horner–Emmons reaction with isopropyl dimethyl 2-methylphosphonoacetate followed by desilylation with TBAF (88% over two steps). **12e** was similarly prepared by using isopropyl dimethyl phosphonoacetate in the Horner–Emmons reaction followed by desilylation with TBAF (93% over two steps).

The methyl enol ether **12f** was prepared in a 2:1 cis/trans ratio from **10** by a Wittig reaction with (methoxymethyl)triphenylphosphonium bromide and potassium *tert*-butoxide. Desilylation was achieved by stirring in MeOH over a catalytic amount of K_2CO_3 (30% over two steps). **12g** was prepared by DIBAL reduction of **12a** at −78 °C followed by desilylation with K_2CO_3/MeOH to yield the allylic alcohol (76% over two steps).

The enol acetate **12h** and methyl octenynoate **16** were also prepared from a common precursor aldehyde **15** (Scheme V). To prepare this aldehyde, 5-hexynol was coupled with diiodobenzene in a modified Castro–Stevens coupling to give alcohol **13a** (46%).[13,14] Another palladium coupling with TMS acetylene yielded enediyne **13b** (81%). A subsequent PCC oxidation provided aldehyde **15** (88%). Refluxing of **15** in acetic anhydride with catalytic NaOAc and K_2CO_3 followed by desilylation with TBAF in THF yielded **12h**, as a 1:1 cis/trans mixture in quantitative yield based on recovered, desilylated **15**.[17] The methyl octenynoate **16** was synthesized in the same manner as **12a** by

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(14) Spectroscopic data for **9** and **13b** are contained in ref 7a.

(15) (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. P.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

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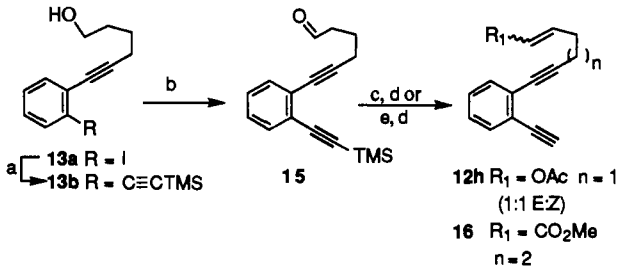
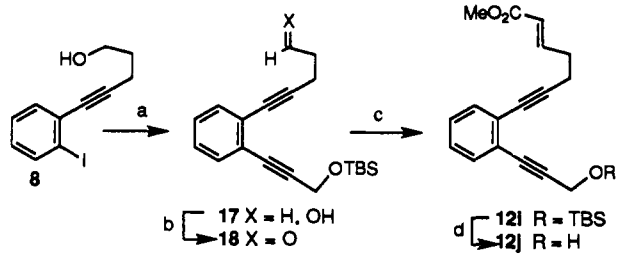
Scheme V[a]



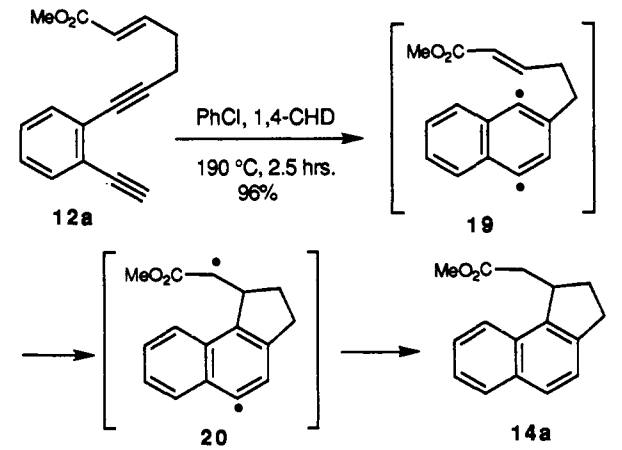
[a](a) (Trimethylsilyl)acetylene (2 equiv), $(PPh_3)_4Pd$ (0.05 equiv), CuI (0.1 equiv), NEt_3 (81%); (b) PCC (3 equiv), Celite, CH_2Cl_2 (88%); (c) (ca.) NaOAc, (ca.) K_2CO_3, Ac_2O (quantitative on recovered starting material); (d) TBAF, THF; (e) trimethyl phosphonoacetate (1.5 equiv), LiCl (2 equiv), DBU (1.5 equiv), CH_3CN (91%).

Scheme VI[a]



[a](a) (*tert*-Butyldimethylsiloxy)propyne (2 equiv), $(PPh_3)_4Pd$ (0.05 equiv), CuI (0.1 equiv), NEt_3 (99%); (b) PCC (3 equiv), Celite, CH_2Cl_2 (80%); (c) trimethyl phosphonoacetate (1.5 equiv), LiCl (2 eq), DBU (1.5 eq), CH_3CN (90%); (d) TBAF, THF (98%).

Scheme VII



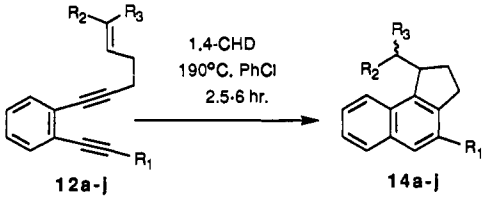
carrying out a Horner–Emmons reaction of aldehyde **15** followed by desilylation with TBAF (91% over two steps).

Compounds **12i** and **12j** were synthesized in a similar reaction sequence as **12a** starting with alcohol **8** (Scheme VI). (*tert*-Butyldimethylsiloxy)propyne was employed in the second palladium coupling to yield the aromatic enediyne **17** (99%). Oxidation with PCC gave aldehyde **18** (80%) followed by Horner–Emmons with trimethyl phosphonoacetate to give **12i** (90%). Desilylation with TBAF in THF subsequently provided **12j** (98%).

Thermal Cyclization of Aromatic Enediynes

When compound **12a** was heated to 191 °C in chlorobenzene in a sealed vial with a significant amount of head space in the tube in the presence of 1,4-cyclohexadiene (1,4-CHD: hydrogen atom donor), the 2,3-dihydrobenz[*e*]indene **14a** was isolated in 72% yield.[10] (Scheme VII). The reaction proceeds through an enediyne cyclization to give biradical **19** followed by radical cyclization to give biradical **20**. Hydrogen trapping with 1,4-CHD yields tricycle **14a**. Some polymerization product was noted. Critical to the success of this reaction is that the sealed tube containing the reaction mixture only has enough empty space to allow for the expansion of the liquid. Otherwise, much of the 1,4-CHD goes into the gas phase, and polymerization and reduced yields are observed.

Table I. Tandem Enediyne–Radical Cyclizations



substrate	R_1	R_2	R_3	product	yield (%)
12a	H	CO_2Me	H	**14a**	96
12b	H	CO_2Me	Me	**14b,c**[a]	73
12c	H	Me	CO_2Me	**14b,c**[a]	73
12d[b]	H	CO_2iPr	Me	**14d,d'**[c]	95
12e[d]	H	CO_2iPr	H	**14e**	93
12f[d]	H	OMe	H	**14f**	83
12g	H	CH_2OH	H	**14g**	73
12h[e]	H	OAc	H	**14h**	>99
12i[f]	CH_2OTBS	CO_2Me	H	**14i**	70
12j[f]	CH_2OH	CO_2Me	H	**14j**	95

[a] Formed as a 3.5:1 ratio of diastereomers. [b] Reacted as a 1.6:1 mixture of *E*:*Z* olefins. [c] Formed as a 2.8:1 ratio of diastereomers. [d] Reacted as a 2:1 mixture of *Z*:*E* olefins. [e] Reacted as a 1:1 mixture of *Z*:*E* olefins. [f] These reactions were carried out at 245 °C or greater.

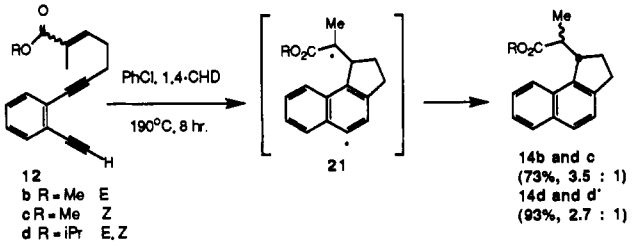
To compensate for the problem of polymerization, we began performing our reactions in reusable reaction vials which were constructed by sealing off one end of a # 11 screw-top glass joint. The reaction was then sealed with a nylon screw cap and heated on a bench top oil bath. When substrate **12a** was thermolyzed under the revised conditions, the yield increased to 96% (Scheme VII, Table I).

The high mass recovery is somewhat remarkable given that the yields for the standard Bergman cyclizations tend to be much lower.[6] The increased yields may be explained by a more stable radical intermediate. Since the 5-*exo*-radical cyclization is a very efficient process, the lifetime of the less stable 1,4-diyl should be very short. There was no evidence for products arising from hydrogen abstraction of **19** to trap the biradical before radical cyclization, even when the reaction was carried out in neat 1,4-CHD, therefore, the radical cyclization must be occurring at a rate that exceeds the diffusion-controlled rate of 1,4-CHD.[12a] Radical cyclization would then result in an α-carbomethoxy-stabilized benzindene biradical **20**, which is then readily quenched by 1,4-CHD to yield tricycle **14a**. As a cheaper, higher boiling alternative to 1,4-cyclohexadiene as a hydrogen donor, commercially available γ-terpinene can be used instead without any decrease in yields.

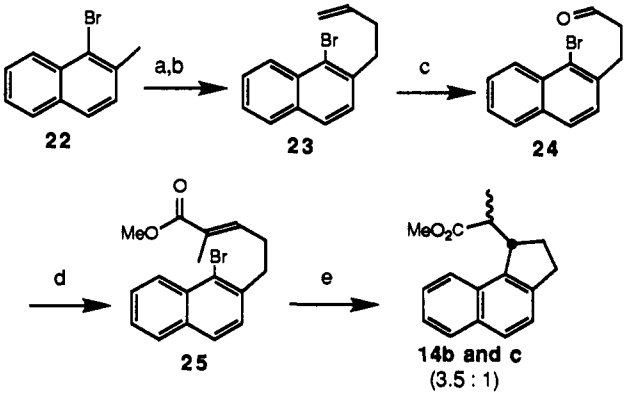
Substrates **12b** and **12c** were investigated to determine what effect olefin geometry has on the reaction. The thermolysis of either the *E*-olefin **12b** or the *Z*-olefin **12c** led to a 3.5:1 mixture of diastereomers **14b** and **14c** (Scheme VIII, Table I). The olefin geometry did not have an effect on the reaction yield or diastereoselectivity. This result shows that the benzindene biradical intermediate **21** is the same in both the *E*- and *Z*-olefin cyclization no matter what the olefin geometry is and that the radical quenching of **21** occurs through an identical transition state in both cases.

To study what effect the ester substituent had on the diastereoselectivity of the reaction, the isopropyl ester **12d** (as a mixture of *E*- and *Z*-isomers) was also studied (Scheme VIII, Table I). This attempt to improve the diastereoselectivity of the tandem enediyne–radical cyclization by increasing the bulk of

Scheme VIII



Scheme IX[a]



[a](a) NBS, benzoyl peroxide, CCl_4 (60%); (b) allylmagnesium chloride, Et_2O (89%); (c) O_3, 5% MeOH in CH_2Cl_2 (73%); (d) trimethyl 2-methylphosphonoacetate (1.5 equiv), DBU (1.5 equiv), LiCl (2 equiv), CH_3CN (70%); (e) *n*-Bu_3SnH, AIBN, toluene reflux (95%).

the ester resulted in a reduced 2.7:1 diastereomeric ratio of products **14d** and **14d'**; however, the yield was improved to 93%.

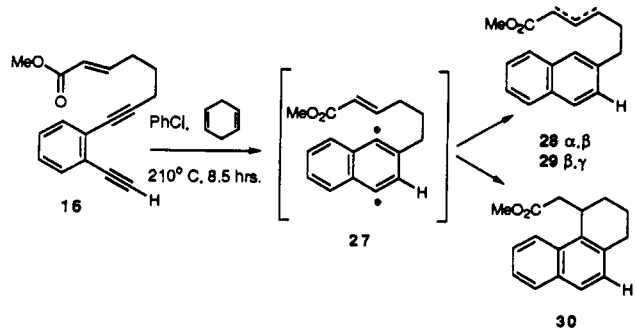
In an attempt to bias the diastereoselectivity, **12b** and **12c** were thermolyzed in the presence of the larger molecule γ-terpinene, resulting in a similar 3.5:1 diastereomeric ratio. Apparently, the ester substituent is too far from the radical-quenching position to participate in the transition state of the radical-quenching reaction. Thinking a chiral hydrogen donor could vary the diastereoselectivity and perhaps provide some enantioselectivity to the reaction, we employed β-pinene as the hydrogen donor in the thermolysis. This permutation only resulted in complex reaction mixtures, presumably because β-pinene is not an efficient hydrogen donor due to its inability to aromatize following hydrogen abstraction.

The identities of **14b** and **14c** were proven by synthesizing the compounds using an independent route (Scheme IX). 1-Bromo-2-methylnaphthalene **22** was brominated under free radical conditions (60%), and the resultant bromide was coupled with allylmagnesium bromide to yield bromo olefin **23** (89%).[18] Ozonolysis (73%) yielded **24** followed by a Horner–Emmons reaction to yield the bromo ester **25** in 70% yield. Subsequent free radical cyclization using tributyltin hydride and AIBN yielded **14b** and **14c** in 95% yield, identical to the structures generated by the tandem enediyne–radical cyclization.[18] The same 3.5:1 mixture of diastereomers **14b** and **14c** was obtained from the simple radical cyclization. This result suggests that the radical intermediates in the tandem enediyne–radical cyclization and the tributyltin hydride radical cyclization are identical.

In order for the tandem enediyne–radical cyclization to be successful for natural product synthesis, the reaction needs to work with a wide variety of olefin acceptors. When compounds **12e–h** were heated to 191 °C in chlorobenzene in the presence of 1,4-CHD, the 2,3-dihydrobenz[*e*]indenes **14e–h** were isolated in good to excellent yields (Table I), proving that the tandemene-

(18) Abeywickrema, A. A.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.

Scheme X



diyne–radical cyclization is successful with a wide variety of olefin acceptors, including olefins that are electron rich, deficient, or neutral.

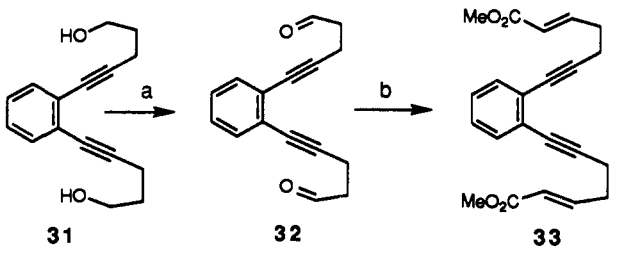
The thermal cyclization of the 6-*exo* analog **16** was not as straightforward as its 5-*exo* counterparts **12a–j**. The presence of a methylene group five carbon centers away from the aryl radical causes a competing reaction between 1,5-hydrogen abstraction and 6-*exo* cyclization. The thermolysis of **16** with a 1,4-CHD concentration of 5 M yielded three products: the tandem enediyne–radical cyclized product **30** and the simple enediyne trapped products **28** and **29** (Scheme X). The ratio of **28** and **29** to **30** was 2.53:1. The α,β- and β,γ-unsaturated esters **28** and **29** probably arise both from 1,4-CHD trapping of biradical **27** and from a 1,5-hydrogen abstraction to yield an allylic radical which could be quenched by 1,4-CHD in either the α or γ positions.

In an attempt to preclude 1,5-hydrogen abstraction and shift the product distribution toward the 6-*exo* radical cyclized product **30**, the concentration of 1,4-cyclohexadiene was varied over the range 5–0.2 M. The best ratio that was achieved was ≈1:1 at 0.5 M 1,4-CHD. The greater the concentration of 1,4-CHD, the more likely the 1,4-diyl will be quenched before it is able to undergo a 6-*exo* cyclization into the unsaturation six carbon centers away. A 1:1 ratio of **28** and **29** to **30** at 0.5 M CHD was the best ratio that was obtained. When the concentration of 1,4-CHD is lowered below 0.5 M, a 1:1 ratio of **28** and **29** to **30** was still obtained but polymerization began to occur. These results demonstrate that a 1,5-hydrogen abstraction is occurring since reducing the concentration of 1,4-CHD still leads to hydrogen abstraction products **28** and **29**. Clearly, due to the competing hydrogen abstraction process, the tandem enediyne–6-*exo*-radical cyclization is not as efficient as the corresponding 5-*exo* cyclizations. This result is not surprising given the fact that 5-*exo*-radical cyclizations tend to be faster than their 6-*exo* counterparts.[19]

An important question that needed to be answered was whether both radicals of the enediyne-generated diyl intermediate could undergo radical cyclization in a process that would construct three rings in one synthetic step. Substrates **12i** and **12j** were thermolyzed to test whether a non-hydrogen substituent at the acetylenic position not containing an olefinic tether would hinder the tandem enediyne–radical cyclization. (Table I). These substrates did not react in chlorobenzene at 190–200 °C. Temperatures greater than 245 °C were required to facilitate the enediyne cyclization. The higher temperatures can be explained by the increased steric requirements that must be overcome in the formation of the 1,4-aromatic biradical. Thermolysis of **12i** and **12j** at 245 °C in dichlorobenzene yielded the 2,3-dihydrobenzindene products **14i** and **14j** in 70 and 95% yields, respectively (Table I). Clearly, the additional substituent on the other acetylenic carbon is slowing the rate of the reaction, since the temperature required to effect the tandem enediyne–radical cyclization is higher.

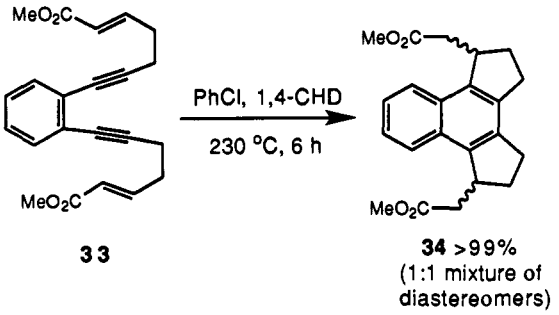
(19) (a) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974** 472. (b) Chatgilialogu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

Scheme XI[a]



[a](a) ClCOCOCl, DMSO, NEt_3 (95%); (b) trimethyl 2-methylphosphonoacetate, LiCl, DBU, CH_3CN (76%).

Scheme XII



At these higher temperatures, it was necessary to modify the method in which the reaction was conducted since the sealed vessel tended to burst open. The solvent was changed to *o*-dichlorobenzene to lower the vapor pressure, but at these high temperatures, the reaction vessel integrity was still unpredictable. Therefore, reactions requiring temperatures of >210 °C were carried out in a thick-walled glass tube which had been sealed and then placed in a stainless steel reaction vessel. The steel vessel was then filled with dichlorobenzene, so that the internal pressure of the reaction tube would be offset by the internal pressure of the steel vessel, thus preventing explosion of the reaction tube.

Given the success of substrates **12i** and **12j** in the tandem enediyne–radical cyclization, enediyne **33** was synthesized to test whether a tandem enediyne–biradical cyclization would be successful (Scheme XI). Diiodobenzene was coupled with 4-pentynol (2 equiv) using palladium as a catalyst to give the bis alcohol **31** (91%). A subsequent Swern oxidation to give **32** (95%) and bis Horner–Emmons reaction (76%) yielded the enediyne **33**.

Upon thermolysis, two diastereomers are formed in a 1:1 mixture in a greater than 99% isolated yield, offering a rapid entry into tricyclic systems in a convergent manner (Scheme XII). Once again, the formation of an α-carbomethoxy biradical stabilizes the biradical intermediate, presumably explaining the high yields in this reaction.

Additional investigations have been done on other enediyne substrates containing olefins in both tethers with electron-donating groups such as CH_2OH and OMe on the olefin; however, at the high temperatures required to effect these cyclizations (>240 °C), substrate decomposition occurs. Therefore, we are currently working on several low-temperature alternatives that are showing promise and that should allow us to eventually overcome these temperature limitations.

Conclusion

Enediynes possessing a tethered olefin radical acceptor can participate in a tandem enediyne–radical cyclization to yield dihydrobenzindene derivatives. In the present study, the scope of this reaction was expanded to include a wide variety of olefin acceptors. It was shown that substituents on the acetylene not undergoing the radical cyclization slowed the reaction but a good to excellent yield of product still resulted. Finally an enediyne containing two olefinic tethers was cyclized in a process where three rings were formed in one synthetic operation.

We expect that the tandem enediyne–radical cyclization will prove to be a useful method for the preparation of various biologically active carbocycles and heterocycles. The reactions are clean and high yielding, and the high temperatures needed for the tandem enediyne–mono-radical cyclization do not appear to be generally deleterious to the substrates. The results for the tandem enediyne–bis-radical cyclization are more complex. In addition, after the tandem enediyne–radical cyclization, a radical remains that could undergo further radical reactions. Further efforts involving lowering the reaction temperatures and applying this methodology to natural product synthesis are in progress.

Experimental Section

General. Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or by cannula. Thermolysis at temperatures of less than 210 °C were carried out in a #11 Ace Screw-top joint which had been sealed by a glass blower. Reactions requiring temperatures of >210 °C were carried out in a thick-walled glass tube which had been sealed under high vacuum and then placed in a stainless steel reaction vessel which had been machined by our in-house machine shop. Reaction mixtures were deoxygenated with slow bubbling of dry N_2 for 20–30 min.

All solvents were distilled before use: dichloromethane from calcium hydride; diethyl ether and tetrahydrofuran from sodium benzophenone ketyl; triethylamine from calcium hydride. Chloro- and dichlorobenzene were purified by passing them through basic alumina. Reagents purchased from Aldrich Chemical Co., Pfaltz and Bauer, Lancaster, and Jannsen Chemica were used without further purification. Flash columns were packed with 230–400-mesh silica gel (EM Science).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-300 or Varian Unity-300 (300 MHz) instrument. The chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane or upfield from $CHCl_3$. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz on a Varian XL-300 or Varian Unity-300 instrument and are reported (ppm) relative to the center line of a triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were measured with a Perkin-Elmer 298 infrared spectrophotometer. Mass spectra were determined on a Finnigan MAT 95 high-resolution gas chromatograph/mass spectrometer with a Finnigan MAT ICIS II operating system.

GC analysis was performed on a Shimadzu GC-14A with a CR-601 integrator containing a 0.54-mm-wide bore capillary column using helium as the carrier gas and a FID detector.

Preparation of 5-(2-Iodophenyl)-4-pentynol (8). To a predicted 500-mL round-bottomed flask under N_2 were added 300 mL of anhydrous NEt_3, diiodobenzene (5.0 g, 15.1 mmol, 2 mL), 0.05 equiv of tetrakis-(triphenylphosphine)palladium(0) (0.436 g, 0.76 mmol), and 0.1 equiv of CuI (0.287 g, 0.15 mmol), and the reaction 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 course-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}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (bs, 1H), 1.89 (p, 2H, J = 6.5 Hz), 2.59 (t, 2H, J = 6.7 Hz), 3.87 (t, 2H, J = 6.3 Hz), 6.94 (td, 1H, J = 8.0, 1.1 Hz), 7.24 (td, 1H, J = 8.0, 1.1 Hz), 7.38 (dd, 1H, J = 7.8, 1.5 Hz), 7.79 (dd, 1H, J = 8.0, 1.1 Hz); ^{13}C NMR (75 MHz) δ 16.1, 31.0, 61.7, 83.4, 93.6, 101.0, 127.7, 128.8, 130.1, 132.4, 138.5; HRMS-EI m/z calcd for $C_{11}H_{11}O$ (M^+) 285.9853, found 285.9849.

Preparation of 5-(2-((Trimethylsilyl)ethynyl)phenyl)-4-pentynol (9).[7a] **9** was prepared from **8** (0.487 g, 1.68 mmol) in a similar coupling procedure as that described for **8** using 2 equiv of (trimethylsilyl)acetylene (0.330 g, 3.4 mmol, 0.475 mL) added in one portion *via* syringe. Purification by SiO_2 chromatography with hexanes/ethyl acetate (3:1) yielded 0.430 g (>99%) as a yellow oil: IR (neat) 3351, 3060, 2230, 2158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 9H), 1.74 (bs, 1H, OH), 1.91 (pentet, 2H, J = 6.3 Hz), 2.63 (t, 2H, J = 6.3 Hz), 3.88 (q, 2H, J = 6.3 Hz),

7.24 (m, 2H), 7.40 (m, 1H), 7.47 (m, 1H); ^{13}C NMR (75 MHz) 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/z calcd for $C_{16}H_{20}OSi$ (M^+) 256.1283, found 256.1269.

Preparation of 5-(2-Ethynylphenyl)-4-pentynal (11). To a predried 25-mL round-bottomed flask under N_2 were added **9** (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 approximately 1 h. The reaction mixture was plugged through Florisil with anhydrous Et_2O and concentrated *in vacuo* to yield 0.164 g (62%) as a yellow oil **10**. 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. After ether/water extraction (2 × 25 mL), the organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the desilylated aldehyde as a yellow oil: R_f 0.59 hexanes/ethyl acetate (3:1); IR (neat) 3283, 3063, 2236, 2106, 1728 cm^{-1}; ^{1}H 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-EI m/z calcd for $C_{13}H_{10}O$ (M^+) 182.0732, found 182.0733.

Preparation of Methyl 7-(2-Ethynylphenyl)hept-2-en-6-ynoate (12a). To a 25-mL round-bottomed flask charged with 10 mL of anhydrous CH_3CN were added 1.5 equiv of trimethyl phosphonoacetate (0.149 g, 0.82 mmol, 0.132 mL), 1.5 equiv of DBU (0.124 g, 0.82 mmol, 0.111 mL), and 2 equiv of LiCl (0.47 g, 1.1 mmol). The reaction mixture was stirred for 10 min at room temperature, and then 1 equiv of 5-(2-((trimethylsilyl)ethynyl)phenyl)-4-pentynal (0.140 g, 1.4 mmol) in 4 mL of CH_3CN was added dropwise to the reaction mixture *via* cannulae/N_2. The reaction was over instantaneously. The reaction was extracted with ether/water, and the organics were dried over $MgSO_4$ and concentrated *in vacuo*. The cis and trans isomers were separated by radial chromatography on a 2-mm plate with hexanes/ethyl acetate (93:3) and concentrated *in vacuo*. Removal of the TMS group was achieved by dissolving the yellow oil in THF and treating with excess TBAF, followed by ether/water extraction. Drying of the organic layer over anhydrous $MgSO_4$, filtering, and then concentration *in vacuo* yielded 0.097 g of **12a** as a yellow oil (88% over 2 steps): R_f 0.51 in hexanes/ethyl acetate (3:1); IR (neat) 3281, 2232, 2107, 1719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48–2.55 (m, 2H), 2.6–2.65 (m, 2H), 3.35 (s, 1H), 3.72 (s, 3H), 5.94 (dt, 1H, J = 15.7, 1.4 Hz), 7.11 (dt, 1H, J = 15.7, 7.0 Hz), 7.23 (m, 2H), 7.39 (m, 1H), 7.46 (m, 1H); ^{13}C NMR (75 MHz) δ 18.7, 31.3, 51.5, 80.2, 80.9, 82.3, 92.7, 122.1, 124.6, 126.6, 127.5, 128.4, 131.9, 132.4, 147.1, 166.9; HRMS-EI m/z calcd for $C_{16}H_{14}O_2$ (M^+) 238.0994, found 238.0990.

Preparation of Methyl 7-(2-Ethynylphenyl)-2-methylhept-2-en-6-ynoate (12b,c). Compound **10** (0.359 g, 1.4 mmol) was subjected to similar Horner–Emmons conditions as those in the formation of **12a** using 1.5 equiv of trimethyl 2-methylphosphonoacetate (0.415 g, 2.1 mmol) and worked up in a similar manner to yield (**12b** (0.030 g) and **12c** (0.298 g) as yellow oils (92% combined): R_f 0.6 in hexanes/ethyl acetate (3:1); IR (neat) 3233, 2236, 2098, 1697 cm^{-1}; ^{1}H 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), 3.30 (s, 1H), 3.72 (s, 3H), 6.88 (tq, 1H, J = 7.3, 1.1 Hz), 7.17–7.26, (m, 2H), 7.37 (dd, 1H, J = 6.6, 1.9 Hz), 7.45 (dd, 1H, J = 6.6, 1.9 Hz); ^{13}C NMR (75 MHz) δ 12.7, 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, 168.3; HRMS-EI m/z calcd for $C_{17}H_{16}O_2$ (M^+) 252.1111, found 252.1131.

Preparation of Isopropyl 7-(2-Ethynylphenyl)-2-methylhept-2-en-6-ynoate (12d). Compound **10** (0.107 g, 0.38 mmol) was subjected to similar Horner–Emmons conditions as those in the formation of **12a** using 1.5 equiv of isopropyl dimethyl 2-methylphosphonoacetate (0.127 g, 0.57 mmol) and worked up in a similar manner to yield 0.059 g (88%, 10.5:1 trans/cis) as a yellow oil. Trans: R_f 0.58 in hexanes/ethyl acetate (9:1); IR (neat) 3285, 3061, 2230, 2109, 1708, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, 6H, J = 6.3 Hz), 1.84 (d, 3H, J = 1.4 Hz), 2.44–2.53 (m, 2H), 2.55–2.61 (m, 2H), 3.30 (s, 1H), 5.03 (septet, 1H, J = 6.3 Hz), 6.84 (tq, 1H, J = 6.8, 1.4 Hz), 7.17–7.26 (m, 2H), 7.36–7.38 (m, 1H), 7.43–7.46 (m, 1H); ^{13}C NMR (75 MHz) δ 12.6, 19.0, 21.9, 28.0, 67.7, 79.7, 80.8, 82.2, 93.4, 124.5, 126.7, 127.4, 128.4, 129.5, 131.9, 132.4, 139.5, 167.6; HRMS-EI m/z calcd for $C_{19}H_{20}O_2$ (M^+) 280.1446, found 280.1455. Cis: R_f 0.58 in hexanes/ethyl acetate (9:1); IR (neat) 3285, 3061, 2981, 2230, 2109, 1708, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 6H, J = 6.3 Hz), 1.89 (d, 3H, J = 1.4 Hz), 2.56–2.61 (m, 2H), 2.74 (q, 2H, J = 7.1 Hz), 3.24 (s, 1H), 5.03 (septet, 1H, J = 6.3 Hz), 6.11 (tq, 1H, J = 6.8, 1.4 Hz), 7.17–7.26 (m, 2H), 7.36–7.38 (m, 1H), 7.43–7.46 (m, 1H); ^{13}C NMR (75 MHz) δ 19.6, 20.6, 21.9, 28.6, 67.6, 79.6, 80.5, 82.4, 93.9, 124.4, 126.8, 127.3, 128.8, 129.5, 131.8, 132.5, 140.0, 167.5; HRMS-EI m/z calcd for $C_{19}H_{20}O_2$ (M^+) 280.1446, found 280.1450.

Preparation of Isopropyl 7-(2-Ethynylphenyl)-hept-2-en-6-ynoate (12e). Compound **10** (0.064 g, 0.23 mmol) was subjected to similar Horner–Emmons conditions as those in the formation of **12a** using isopropyl dimethyl phosphonoacetate (0.072 g, 0.34 mmol) and worked up in a similar manner to yield (0.057 g, 8.5:1 trans/cis, 93%) as a yellow oil. **12e** was used as a mixture of isomers. Trans: R_f 0.67 in hexanes/ethyl acetate (9:1); IR (neat) 3276, 2234, 2107, 1717, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 6H, J = 6.2 Hz), 2.52 (qt, 2H, J = 6.6, 1.5 Hz), 2.60–2.66 (m, 2H), 3.38 (s, 1H), 5.06 (septet, 1H, J = 6.2 Hz), 5.93 (dt, 1H, J = 15.6, 1.6 Hz), 7.09 (dt, 1H, J = 15.6, 6.6 Hz), 7.19–7.29 (m, 2H), 7.38–7.41 (m, 1H), 7.46–7.49 (m, 1H); ^{13}C NMR (75 MHz) δ 18.6, 21.8, 31.2, 67.5, 80.0, 81.0, 82.3, 92.8, 123.0, 124.5, 126.6, 127.4, 128.4, 131.9, 132.4, 146.4, 166.0; HRMS-EI m/z calcd for $C_{15}H_{11}O$ ($M^+ - C_3H_7O$) 207.0773, found 207.0791.

Preparation of 6-(2-Ethynylphenyl)-1-methoxyhex-1-en-6-yne (12f). To a predried 25-mL round-bottomed flask was added 15 mL of anhydrous THF and subsequently cooled to −78 °C, and then 5.2 equiv of (methoxymethyl)triphenylphosphonium chloride (1.05 g, 3.07 mmol) and 5 equiv of potassium *tert*-butoxide (0.333 g, 2.97 mmol) were added, allowed to stir for 1 h under N_2, and then warmed to room temperature for 10 min. The reaction mixture was then cooled to −78 °C, and 5-(2-((trimethylsilyl)ethynyl)phenyl)-4-pentynal (0.167 g, 0.54 mmol) in 5 mL of THF was added dropwise *via* cannulae/N_2. The reaction was complete within 20 min, after which it was quenched with saturated NH_4Cl and allowed to warm to room temperature. Ether/water extraction (2 × 25 mL) followed by drying of the organic layers over $MgSO_4$, filtration, and concentration *in vacuo* yielded an oil. Purification was carried out *via* SiO_2 column chromatography with hexanes/ethyl acetate (95:5). The silylated product was dissolved in 5 mL of MeOH and stirred over (cat.) K_2CO_3. The reaction mixture was concentrated *in vacuo* and purified *via* SiO_2 column chromatography with hexanes/ethyl acetate (98:2) to yield 0.039 g (30% over two steps) of a yellow oil. GC analysis revealed a 2:1 mixture of cis/trans isomers. (Note: The analytical data for **12f** was gathered on the mixture of cis/trans isomers.) R_f 0.66 in hexanes/ethyl acetate (3:1); IR (neat) 3284, 3060, 2929, 2234 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ trans) δ 2.38 (qt, 2H, J = 6.3, 1.3 Hz), 2.46–2.51 (m, 2H), 3.58 (s, 3H), 3.26 (s, 1H), 5.55 (q, 1H, J = 7.2 Hz), 5.92 (dt, 1H, J = 6.3, 1.3 Hz), 7.16–7.28 (m, 2H), 7.36–7.41 (m, 1H), 7.43–7.48 (m, 1H); HRMS-EI m/z calcd for (trans) $C_{15}H_{14}O$ (M^+) 210.1032, found 210.1041; ^{1}H NMR (300 MHz, $CDCl_3$ cis) δ 2.25 (q, 2H, J = 7.3 Hz), 2.46–2.51 (m, 2H), 3.27 (s, 1H), 3.51 (s, 3H), 4.87 (dt, 1H, J = 12.6, 7.3 Hz), 6.40 (d, 1H, J = 12.6 Hz), 7.16–7.28 (m, 2H), 7.36–7.41 (m, 1H), 7.43–7.48 (m, 1H); ^{13}C NMR (75 MHz) δ 21.5, 27.3, 55.9, 79.5, 80.5, 82.4, 94.3, 101.2, 124.3, 126.9, 127.2, 128.4, 131.9, 132.4, 148.0; HRMS-EI m/z calcd for $C_{15}H_{14}O$ (M^+) 210.1032, found 210.1038.

Preparation of 7-(2-Ethynylphenyl)-hept-2-en-6-yn-1-ol (12g). To a predried 50-mL flask were added 10 mL of anhydrous CH_2Cl_2 and 1 equiv of **12a** (0.126 g, 0.41 mmol), and then the reaction mixture was purged with N_2, followed by cooling of the reaction mixture to −78 °C. DIBAL (1.5 M) in toluene (0.90 mmol, 0.596 mL) was added slowly *via* syringe. The reaction was complete within 1 h. The reaction was quenched with MeOH at −78 °C and allowed to warm to room temperature, upon which Rochelle's salts were added and the reaction was stirred for an additional 6 h. CH_2Cl_2/water extraction (2 × 25 mL) was followed by drying of the organic layers over $MgSO_4$, concentration of crude product *in vacuo*, and purification by radial chromatography on a 2-mm plate with hexanes/ethyl acetate (3:1). The silylated product was then dissolved in 5 mL of MeOH and stirred over (cat.) K_2CO_3. Upon complete desilylation, the reaction mixture was extracted with ether/water (2 × 25 mL) and the organic layer was dried over $MgSO_4$. Concentration following filtration yielded 0.065 g (76%) of a clear oil: R_f 0.2 in hexanes/ethyl acetate (3:1); IR (neat) 3372, 3294, 2231, 2105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (bs, 1H), 2.37 (dq, 2H, J = 7.0, 0.7 Hz), 2.55 (t, 2H, J = 7.0 Hz), 3.33 (s, 1H), 4.10 (bs, 2H), 5.70–5.90 (m, 2H), 7.19–7.29 (m, 2H), 7.40 (dd, 1H, J = 6.6, 1.6 Hz), 7.48 (dd, 1H, J = 6.6, 1.6 Hz); ^{13}C NMR (75 MHz) δ 19.6, 31.3, 63.6, 79.6, 80.6, 82.4, 93.9, 124.3, 126.9, 127.3, 128.5, 130.4, 131.0, 131.9, 132.5; HRMS-EI m/z calcd for $C_{15}H_{14}O$ (M^+) 210.0999, found 210.1022.

Preparation of 6-(2-Ethynylphenyl)-1-acetoxyhex-1-en-5-yne (12h). To a 10-mL round-bottomed flask fitted with a reflux condensor were added 5 mL of acetic anhydride, (cat.) K_2CO_3, (cat.) NaOAc, and **15** (0.130 g, 0.46 mmol). The reaction was stirred under reflux for 3 days,

upon which there existed a mixture of silylated and desilylated enol acetates and starting materials. The reaction mixture was extracted with ether/water (2 × 25 mL), followed by subsequent drying of the organic layers over $MgSO_4$, and concentration *in vacuo* following filtration yielded a mixture of silylated and desilylated products and starting material. The mixture was dissolved in 5 mL of THF, cooled to −78 °C, and treated with an excess of TBAF in THF. Ether/water extraction, drying of the organic layer over $MgSO_4$, followed by concentration *in vacuo*, and purification by radial chromatography on a 2-mm plate with hexanes/ethyl acetate (9:1) yielded 0.050 g (>99% based on recovered starting material) of a yellow oil. GC analysis revealed a 1:1 mixture of olefinic isomers. (Note: The NMR data for the isomers of **12h** are indistinguishable. Therefore we listed the data for both compounds in the same experimental data). R_f 0.68 hexanes/ethyl acetate (3:1); IR (neat) 3285, 2232, 2108, 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, an inseparable 1:1 mixture of cis and trans isomers) δ 2.10 (s, 3H), 2.13 (s, 3H), 2.32 (qd, 2H, J = 6.9, 1.5 Hz), 2.45–2.57 (m, 6H), 3.26 (s, 1H), 3.28 (s, 1H), 5.08 (dt, 1H, J = 6.9, 6.4 Hz), 5.61 (dt, 1H, J = 12.4, 7.5 Hz), 7.08 (dt, 1H, J = 6.4, 1.5 Hz), 7.20–7.28 (m, 5H), 7.36–7.40 (m, 2H), 7.42–7.48 (m, 2H); ^{13}C NMR (75 MHz, as a mixture of cis and trans) δ 19.6, 20.3, 20.8, 23.9, 26.8, 46.2, 79.5, 79.9, 80.5, 80.6, 82.3, 93.4, 93.7, 112.0, 113.1, 124.3, 126.7, 127.3, 128.4, 131.8, 131.9, 132.4, 132.5, 134.7, 136.3, 167.9, 168.1; HRMS-EI m/z calcd for $C_{16}H_{14}O_2$ (M^+) 238.0992, found 238.0973.

Preparation of Methyl 7-(2-(3-(*tert*-Butyldimethylsiloxy)propynyl)-phenyl)-1-hept-2-en-6-ynoate (12i). Compound **18** (0.139 g, 0.42 mmol) was subjected to similar Horner–Emmons conditions as **12a** and worked up in a similar manner to yield 0.118 g (90%) as a clear oil. GC analysis revealed a 37:1 trans/cis ratio. R_f 0.52 in hexanes/ethyl acetate (3:1); IR (neat) 3062, 2929, 2232, 1722, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.92 (s, 9H), 2.45–2.62 (m, 4H), 3.72 (s, 3H), 4.57 (s, 2H), 5.92 (dt, 1H, J = 15.6, 1.4 Hz), 7.04 (dt, 1H, J = 15.6, 6.6 Hz), 7.19 (m, 2H), 7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −5.0, 16.5, 18.7, 25.9, 29.7, 31.5, 52.3, 63.2, 80.3, 83.5, 91.4, 92.2, 122.0, 125.2, 125.8, 127.4, 127.8, 131.9, 132.1, 146.9, 166.7; HRMS-EI m/z calcd for $C_{23}H_{30}O_3Si$ (M^+) 382.1964, found 382.1955.

Preparation of Methyl 7-(2-(3Hydroxypropynyl)phenyl)hept-2-en-6-ynoate (12j). To a 10-mL round-bottomed flask were added **12i** (0.024 g, 0.07 mmol) and 5 mL of THF, and then excess TBAF (1 M in THF) was added to the stirring mixture *via* pipet. The reaction mixture was stirred until all of the starting material was consumed by thin layer chromatography. The reaction was quenched with H_2O and extracted with Et_2O. The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield **12j** (0.017 g) as a yellow oil (98%): R_f 0.21 in hexanes/ethyl acetate (3:1); IR (neat) 3429, 2221, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (qt, 2H, J = 6.9, 1.2 Hz), 2.65–2.69 (m, 2H), 2.94 (t, 1H, J = 6.7 Hz), 3.72 (s, 3H), 4.52 (d, 2H, J = 6.7 Hz), 5.98 (dt, 1H, J = 15.7, 1.6 Hz), 7.18–7.26 (m, 3H), 7.33–7.43 (m, 2H); ^{13}C NMR (75 MHz) δ 18.6, 31.1, 51.4, 51.7, 80.6, 83.8, 91.4, 92.2, 121.9, 125.2, 125.9, 127.5, 128.0, 132.0, 132.2, 147.7, 167.6; LRMS-CI m/z calcd $C_{17}H_{16}O_3$ ($M^+ - H_2O$) 251; HRMS-EI m/z calcd for $C_{17}H_{14}O_2$ (M^+ − OH) 250.0945, found 250.0969.

Preparation of 6-(2-Iodophenyl)hex-5-en-1-ol (13a). To a predried 50-mL round-bottomed flask under N_2 were added 30 mL of anhydrous NEt_3, diiodobenzene (1.0 g, 3 mmol, 0.396 mL), 0.05 equiv of tetrakis(triphenylphosphine) (0.105 g, 0.15 mmol), and 0.1 equiv of CuI (0.055 g, 0.3 mmol), and the reaction was allowed to stir for 10 min. Then 5-hexynol (0.441 g, 4.5 mmol, 0.496 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 course-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 0.411 g (48%) of a brown oil: R_f 0.25 in hexanes/ethyl acetate (3:1); IR (neat) 3376, 3059, 2232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, br, 1H, OH), 1.75 (m, 4H), 2.50 (t, 2H, J = 6.9 Hz), 3.71 (q, 2H, J = 5.7 Hz), 6.93 (td, 1H, J = 7.8, 1.5 Hz), 7.24 (td, 1H, J = 7.8, 1.2 Hz), 7.37 (dd, 1H, J = 7.8, 1.5 Hz), 7.79 (dd, 1H, J = 7.8, 1.2 Hz); ^{13}C NMR (75 MHz) δ 19.3, 24.7, 31.9, 62.5, 83.2, 94.2, 101.0, 127.7, 128.8, 130.3, 132.5, 138.6; HRMS-EI m/z calcd for $C_{12}H_{13}IO$ (M^+) 300.0010, found 300.0016.

Preparation of 6-(2-((Trimethylsilyl)ethynyl)phenyl)-5-hexynol (13b).[7a] Compound **13** (0.505 g, 1.75 mmol) was subjected to a similar coupling procedure as compound **9** using tetrakis(triphenylphosphine)palladium (0.061 g, 0.09 mmol), CuI (0.033 g, 0.175 mmol), and TMS-acetylene (0.342 g, 3.49 mmol, 0.493 mL) and was worked up in a similar way to yield 0.401 g (81%) as a brown oil: R_f 0.12 in hexanes/ethyl acetate (3:1); IR (neat) 3354 (br), 3061, 2232, 2158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 9H), 1.41 (bs, 1H), 1.78 (m, 4H), 2.55 (t, 2H, J = 6.6 Hz), 3.75 (t, 2H, J = 6.0 Hz), 7.25 (m, 2H), 7.41 (m, 1H), 7.47 (m, 1H); ^{13}C NMR (75 MHz) δ 0.0, 19.3, 25.0, 31.9, 62.4, 79.6, 94.2, 97.8, 103.8, 125.4, 126.7, 127.2, 128.1, 131.8, 132.2; HRMS-EI m/z calcd for $C_{17}H_{22}OSi$ (M^+) 270.1440, found 270.1424.

Preparation of 6-(2-Ethynylphenyl)-5-hexynal. Compound **15** was characterized as the desilylated derivative. Compound **14** (0.401 g, 1.42 mmol) was oxidized in a similar manner as **11** using 3 equiv of PCC (1.60 g, 4.26 mmol) and worked up and desilylated in a similar way to yield 0.301 g (75%) of a yellow oil: R_f 0.38 in hexanes/ethyl acetate (3:1); IR (neat) 3283, 3063, 2232, 2106, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.94 (p, 2H, J = 6.9 Hz), 2.55 (t, 2H, J = 6.9 Hz), 2.72 (td, 2H, J = 6.9, 1.2 Hz), 3.27 (s, 1H), 7.24 (m, 2H), 7.39 (dd, 1H, J = 6.9, 2.4 Hz), 7.47 (dd, 1H, J = 6.9, 2.4 Hz), 9.83 (t, 1H, J = 1.2 Hz); ^{13}C NMR (75 MHz) δ 18.9, 21.0, 42.7, 80.2, 80.5, 82.5, 93.2, 124.4, 126.6, 127.5, 128.5, 131.8, 132.5, 202.0; HRMS-EI m/z calcd for $C_{13}H_{10}O$ (M^+) 196.0888, found 196.0880.

Preparation of Methyl 8-(2-Ethynylphenyl)-oct-2-ene-7-ynoate (16). Compound **15** (0.069 g) was subjected to similar Horner–Emmons conditions as **12a** using 1.5 equiv of trimethyl phosphonoacetate (0.067 g, 0.37 mmol, 0.060 mL), 1.5 equiv of DBU (0.056 g, 0.37 mmol, 0.051 mL), and 2 equiv of LiCl (0.021 g, 0.5 mmol) and worked up and desilylated in a similar way to yield 0.058 g (91% over two steps) as a yellow oil: R_f 0.54 in hexanes/ethyl acetate; IR (neat) 3282, 2924, 2231, 2107, 1718, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (p, 2H, J = 7.0 Hz), 2.41–2.53 (m, 4H), 3.27 (s, 1H), 3.72 (s, 3H), 5.90 (dt, 1H, J = 15.6, 1.5 Hz), 6.99 (dt, 1H, J = 15.6, 7.1 Hz), 7.24–7.40 (m, 2H), 7.42 (dd, 1H, J = 7.7, 1.1 Hz), 7.47 (dd, 1H, J = 7.7, 1.1 Hz); ^{13}C NMR (75 MHz) δ 19.0, 26.9, 31.0, 51.4, 79.9, 80.5, 82.5, 93.6, 121.6, 124.4, 126.7, 127.3, 128.4, 131.8, 132.5, 148.4, 166.9; HRMS-CI m/z calcd for $C_{17}H_{17}O_2$ (M^+) 253.1228, found 253.1225.

Preparation of 5-(2-(3-*tert*-Butyldimethylsiloxy)propynyl)phenyl)-4-pentynol (17). To a predried 25-mL round-bottomed flask under N_2 were added 1 equiv of **8** (0.241 g, 0.81 mmol), 8 mL of anhydrous NEt_3, 0.05 equiv of tetrakis(triphenylphosphine)palladium (0.047 g, 0.045 mmol), and 0.1 equiv of CuI (0.015 g, 0.081 mmol), and the reaction was allowed to stir for 10 min. Then 2 equiv of (*tert*-butyldimethylsiloxy)-pentyne (0.275 g, 1.62 mmol) was added *via* syringe in one portion. The reaction mixture was allowed to stir until all of the starting material had been consumed by thin layer chromatography and then worked up in a similar manner as **12a** to yield 0.287 g (>99%) as a brown oil: IR (neat) 3389, 2237, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.93 (s, 9H), 1.85 (p, 2H, J = 6.4 Hz), 2.16 (bs, 1H), 2.57 (t, 2H, J = 6.6 Hz), 3.88 (t, 2H, J = 6.4 Hz), 4.59 (s, 2H), 7.19–7.22 (m, 2H), 7.34–7.39 (m, 2H); ^{13}C NMR (75 MHz) δ −5.0, 16.2, 18.4, 25.9, 31.1, 52.4, 61.3, 80.0, 83.8, 91.0, 93.6, 125.2, 126.3, 127.2, 127.9, 131.6, 132.0; HRMR-EI m/z calcd for $C_{16}H_{19}O_2Si$ ($M^+ - C_4H_9$) 271.1161, found 271.1158.

Preparation of 5-(2-(3-*tert*-Butyldimethylsiloxy)propynyl)phenyl)-4-pentynal (18). Compound **17** (0.260 g, 0.80 mmol) was oxidized in a similar manner as **11** using 3 equiv of PCC (0.515 g, 2.39 mmol) and worked up in a similar manner as **11** to yield 0.209 g (80%) of a yellow oil: R_f 0.65 in hexanes/ethyl acetate (3:1); IR (neat) 3063, 2225, 1737, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.92 (s, 9H), 2.77 (s, 4H), 4.57 (s, 2H), 7.18–7.21 (m, 2H), 7.44–7.47 (m, 2H), 9.86 (s, 1H); ^{13}C NMR (75 MHz) δ −5.1, 12.9, 18.3, 25.8, 42.5, 52.3, 80.2, 83.4, 91.4, 91.7, 125.3, 125.7, 127.5, 127.9, 131.9, 132.1, 200.5; HRMS-EI m/z calcd for $C_{16}H_{17}O_2Si$ ($M^+ - C_4H_9$) 269.0992, found 269.0995.

Preparation of 2,3-Dihydro-1-((methoxycarbonyl)methyl)benz[*e*]indene (14a) *via* Tandem Enediyne–Radical Cyclization. To a predried reaction vial were added methyl 7-(2-(ethynylphenyl)hept-2-en-6-ynoate **12a** (0.101 g, 0.44 mmol) and 8 mL of anhydrous chlorobenzene. The reaction mixture was deoxygenated by bubbling N_2 through the solution for 20 min, and then 20 equiv of 1,4-cyclohexadiene (0.708 g, 0.836 mL) was added *via* syringe. The reaction was sealed under a stream of N_2 with a nylon screw cap and heated to 195 °C for 4.5 h. A small portion of starting material remained by TLC. Workup was achieved by plugging the reaction mixture through a plug of SiO_2 with hexanes to wash away the reaction solvent, followed by ethyl acetate to collect the crude product. Purification was achieved by radial chromatography on a 2-mm plate with hexanes/ethyl acetate (95:5) to yield 0.096 g (96%): R_f 0.68 in hexanes/ethyl acetate (3:1); IR (neat) 3053, 1734, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (dddd, 1H, J = 13.3, 7.7, 1.1, 1.1 Hz), 2.33–2.43 (m, 2H), 2.80 (dd, 1H, J = 15.3, 3.3 Hz), 2.99 (ddd, 1H, J = 15.3, 8.8, 1.1 Hz), 3.18 (dd, 1H, J = 15.3, 8.8 Hz), 3.72 (s, 3H), 4.12–4.17

(m, 1H), 7.36–7.52 (m, 3H), 7.69 (d, 1H, J = 8.3 Hz), 7.85 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 31.0, 31.5, 38.6, 40.4, 51.7, 123.3, 123.5, 124.7, 126.2, 128.7, 129.5, 132.8, 140.6, 140.7, 173.3; HRMS-EI m/z calcd for $C_{16}H_{16}O_2$ (M^+) 240.1150, found 240.1153.

Preparation of 2,3-Dihydro-1-((methoxycarbonyl)methyl)benz[*e*]indene (14b,c) *via* Tandem Enediyne–Radical Cyclization. Compound **14b,c** (0.056 g, 3.5:1 diastereomeric ratio) was prepared in a similar manner as **14a** from **12b,c**. Separation of the diastereomers was achieved by preparatory HPLC on a SiO_2 column with hexanes at 5 mL/min for 12.5 min, then 99:1 hexanes/ethyl acetate at 5 mL/min for 17.5 min, and then 98:2 hexanes/ethyl acetate, followed by concentration *in vacuo* to yield each diastereomer as a clear oil (73% combined yield) Major: R_f 0.8 in hexanes/ethyl acetate (3:1); IR (neat) 3053, 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 3H, J = 7.0 Hz), 2.08–2.32 (m, 2H), 2.78–2.90 (m, 2H), 3.01–3.12 (m, 1H), 3.41 (s, 3H), 3.85 (t, 1H, J = 7.3 Hz), 7.22 (d, 1H, J = 8.2 Hz), 7.30 (ddd, 1H, J = 8.2, 6.7, 1.0 Hz), 7.42 (ddd, 1H, J = 8.2, 6.7, 1.0 Hz), 7.62 (d, 1H, J = 8.2 Hz), 7.71 (d, 1H, J = 8.2 Hz), 7.78 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz) δ 16.7, 31.9, 43.3, 47.1, 51.4, 123.3, 124.4, 124.5, 125.8, 127.8, 128.6, 130.7, 132.7, 140.2, 141.6, 176.4; HRMS-EI m/z calcd for $C_{17}H_{18}O_2$ (M^+) 254.3320, found 254.1317. Minor: R_f 0.8 in hexanes/ethyl acetate (3:1); IR (neat) 3051, 1734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, 3H, J = 7.0 Hz), 2.30 (m, 2H), 2.98 (ddd, 1H, J = 14.1, 2.1, 1.8 Hz), 3.08–3.24 (m, 2H), 3.72 (s, 3H), 4.27 (dt, 1H, J = 9.1, 1.8 Hz), 7.35 (d, 1H, J = 8.3 Hz), 7.41 (ddd, 1H, J = 8.3, 6.7, 1.3 Hz), 7.49 (ddd, 1H, J = 8.3, 6.7, 1.3 Hz), 7.70 (d, 1H, J = 8.3 Hz), 7.86 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 10.3, 26.7, 42.8, 45.7, 51.7, 123.3, 123.7, 124.7, 126.1, 127.9, 128.8, 129.8, 133.0, 139.1, 141.9, 176.3; HRMS-EI m/z calcd for $C_{17}H_{18}O_2$ (M^+) 254.3320, found 254.1308.

Preparation of 2,3-Dihydro-1-((Isopropoxycarbonyl)methyl)benz[*e*]indene (14d,d') *via* Tandem Enediyne–Radical Cyclization. Compound **14d,d'** (0.040 g) was prepared in a similar manner as **14a** from **12d** and isolated as a mixture of diastereomeric clear oils (95%). Analytical GC analysis revealed a 2.7:1 diastereomeric ratio. The mixture of diastereomers were trans-esterified to the methyl ester, and the characterization data were compared to compounds **14b,c**. By examination of the data, confirmation of the benz[*e*]indene adduct was established.

Preparation of 2,3-Dihydro-1-((Isopropoxycarbonyl)methyl)benz[*e*]indene (14e) *via* Tandem Enediyne–Radical Cyclization. Compound **14e** (0.048 g) was prepared in a similar manner as **14a** from **12e** and isolated as a clear oil (93%): R_f 0.78 in hexanes/ethyl acetate (3:1); IR (neat) 3054, 1728, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 3H, J = 6.2 Hz), 1.25 (d, 3H, J = 6.2 Hz), 2.11 (dddd, 1H, J = 13.0, 7.8, 1.7, 1.4 Hz), 2.30–2.46 (m, 2H), 2.76 (m, 1H), 2.98 (ddd, 1H, J = 16.0, 9.2, 1.4 Hz), 3.20 (ddd, 1H, J = 16.0, 9.2, 7.8 Hz), 4.09–4.16 (m, 1H), 5.06 (septet, 1H, J = 6.3 Hz), 7.37 (d, 1H, J = 8.3 Hz), 7.41 (ddd, 1H, J = 8.3, 6.7, 1.5 Hz), 7.49 (ddd, 1H, J = 8.3, 6.7, 1.5 Hz), 7.69 (d, 1H, J = 8.3 Hz), 7.85 (d, 1H, J = 8.3 Hz), 7.86 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 21.8, 21.9, 30.8, 31.5, 39.2, 40.5, 67.7, 123.4, 123.7, 124.7, 126.2, 127.6, 128.7, 129.6, 132.9, 140.7, 140.9, 172.5; HRMS-EI m/z calcd for $C_{18}H_{20}O_2$ (M^+) 268.1475, found 268.1469.

Preparation of 2,3-Dihydro-1-(methoxymethyl)benz[*e*]indene (14f) *via* Tandem Enediyne–Radical Cyclization. Compound **14f** (0.019 g) was prepared in a similar manner as **14a** from **12f** and isolated as a yellow oil (83%): R_f 0.8 in hexanes/ethyl acetate (3:1); IR (neat) 3051, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27–2.37 (m, 3H), 2.91–3.02 (m, 1H), 3.13–3.26 (m, 1H), 3.37 (s, 3H), 3.71 (ddd, 1H, J = 9.2, 4.3, 3.7 Hz), 3.89–3.97 (m, 1H), 7.38 (d, 1H, J = 8.2 Hz), 7.40 (ddd, 1H, J = 8.2, 6.8, 1.4 Hz), 7.48 (ddd, 1H, J = 8.2, 6.8, 1.4 Hz), 7.69, (d, 1H, J = 8.2 Hz), 7.84 (d, 1H, J = 8.2 Hz), 7.90 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz) δ 28.8, 31.7, 44.4, 58.9, 74.8, 123.4, 124.1, 124.6, 126.0, 127.6, 128.6, 130.3, 132.8, 138.9, 141.7; HRMS-EI m/z calcd for $C_{15}H_{16}O$ (M^+) 212.1173, found 212.1187.

Preparation of 2,3-Dihydro-1-(2-hydroxyethyl)benz[*e*]indene (14g) *via* Tandem Enediyne–Radical Cyclization. Compound **14g** (0.074 g) was prepared in a similar manner as **14a** from **12g** and isolated as a clear oil (73%): R_f 0.23 in hexanes/ethyl acetate (3:1); IR (neat) 3326, 3052, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (bs, 1H), 1.75 (dddd, 1H, J = 15.6, 11.7, 8.8, 1.4 Hz), 2.20–2.13 (m, 2H), 2.26–2.42 (m, 2H), 2.98 (ddd, 1H, J = 16.1, 8.8, 1.1 Hz), 3.18 (ddd, 1H, J = 16.1, 8.8, 2.2 Hz), 3.75–3.86 (m, 2H), 7.37 (d, 1H, J = 8.3 Hz), 7.41 (td, 1H, J = 8.3, 1.8 Hz), 7.48 (td, 1H, J = 8.3, 1.8 Hz), 7.68 (d, 1H, J = 8.3 Hz), 7.85 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 30.6, 31.8, 37.1, 40.0, 61.8, 123.3, 124.0, 124.6, 125.9, 127.2, 128.6, 129.8, 132.8, 140.3, 142.4; HRMS-EI m/z calcd for $C_{15}H_{16}O$ (M^+) 212.1185, found 212.1193.

Preparation of 2,3-Dihydro-1-(acetoxymethyl)benz[*e*]indene (14h) *via* Tandem Enediyne–Radical Cyclization. Compound **14h** (0.014 g) was prepared in a similar manner as **14a** from **12h** and isolated as a yellow oil (>99%): R_f 0.74 in hexanes/ethyl acetate (3:1); IR (neat) 3055, 1739, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.22 (dddd, 1H, J = 13.0, 8.0, 1.2, 1.2 Hz), 2.27–2.37 (m, 1H), 2.99 (ddd, 1H, J = 16.2, 8.9, 1.8 Hz), 3.20 (ddd, 1H, J = 16.2, 9.8, 7.0 Hz), 3.92–4.03 (m, 2H), 4.43–4.51 (m, 1H), 7.40 (d, 1H, J = 8.2 Hz), 7.43 (td, 1H, J = 8.2, 1.4 Hz), 7.52 (td, 1H, J = 8.2, 1.4 Hz), 7.73 (d, 1H, J = 8.2 Hz), 7.86 (d, 1H, J = 8.2 Hz), 7.98 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz) δ 21.1, 28.8, 31.7, 43.3, 66.2, 123.4, 124.1, 124.8, 126.3, 128.1, 128.6, 130.4, 132.8, 138.0, 141.7, 171.3; HRMS-EI m/z calcd for $C_{16}H_{16}O_2$ (M^+) 240.1168, found 240.1159.

Preparation of 2,3-Dihydro-1-(methoxycarbonyl)methyl-5-((*tert*-butyldimethylsiloxyl)methyl)benz[*e*]indene (14i). Compound **14i** (0.084 g) was prepared in a similar manner as **14a** from **12i**. The reaction was run in anhydrous dichlorobenzene and required temperatures of 250 °C for the reaction to occur. The reaction was performed in a sealed tube which was placed in a stainless steel bomb filled with dichlorobenzene. Purification was performed as in the previous examples to yield a yellow oil (70%): R_f 0.55 in hexanes/ethyl acetate (3:1). IR (neat) 3062, 2952, 1740, 1079 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.96 (s, 9H), 2.06–2.16 (m, 2H), 2.48 (ddd, 2H, J = 15.4, 11.1, 3.0 Hz), 2.93–3.09 (m, 2H), 3.72 (s, 3H), 4.81 (s, 2H), 4.14 (m, 1H), 7.37–7.48 (m, 2H), 7.71 (s, 1H), 7.79–7.86 (m, 2H); ^{13}C NMR (75 MHz) δ –5.2, 18.5, 26.0, 29.3, 30.9, 38.6, 40.2, 51.7, 63.7, 123.5, 124.4, 124.9, 125.8, 128.7, 128.8, 133.2, 135.7, 138.7, 141.1, 173.4; HRMS-EI m/z calcd for $C_{23}H_{32}O_3Si$ (M^+) 384.2121, found 384.2107.

Preparation of 2,3-Dihydro-1-(methoxycarbonyl)methyl-5-(hydroxymethyl)benz[*e*]indene (14j). Compound **14j** (0.075 g) was prepared in a similar manner as **14i** from **12j** and isolated as a yellow oil (95%): R_f 0.75 in hexanes/ethyl acetate (1:1); IR (neat) 3424, 3055, 1737, 1011 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (bs, 1H), 2.13 (dddd, 1H, J = 13.2, 7.2, 1.2, 1.2 Hz), 2.37 (m, 2H), 2.78 (dd, 1H, J = 15.3, 3.2 Hz), 2.98–3.15 (m, 2H), 3.17 (s, 3H), 4.13 (ddd, 1H, J = 11.0, 7.2, 3.2 Hz), 4.81 (bs, 2H), 7.42 (td, 1H, J = 8.2, 1.3 Hz), 7.49 (td, 1H, J = 8.2, 1.3 Hz), 7.71, (s, 1H), 7.82 (d, 1H, J = 8.2 Hz), 7.85 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz) δ 29.2, 30.8, 38.6, 40.2, 51.7, 63.8, 123.5, 125.1, 125.2, 126.2, 128.7, 129.0, 133.2, 135.2, 139.1, 141.5, 173.3; HRMS-EI m/z calcd for $C_{17}H_{18}O_3$ (M^+) 270.1264, found 270.1260.

Preparation of 1-Bromo-2-(3-oxopropyl)naphthalene (24). To a predried 100-mL round-bottomed flask under N_2 were added 75 mL of 5% MeOH in CH_2Cl_2 and 1-bromo-2-(3-butenyl)naphthalene (1.5 g, 5.74 mmol) **23**,[18] and then the reaction mixture was cooled to –78 °C. Ozone was passed through the solution for 1 min at 75 mV, and then the reaction mixture was checked by TLC for the presence of starting material. This procedure was repeated three times until all of **23** was consumed. Then dimethyl sulfide (2 mL) was added, and the reaction mixture was allowed to stir overnight to decompose the ozonide. The reaction mixture was ether/water extracted (2 × 50 mL), and the organic layer was dried over $MgSO_4$. The volatile solvents were removed *in vacuo*. The crude product was purified by silica gel chromatography with hexanes/ethyl acetate (95:5) to yield 1.11 g (73%) of a clear oil: R_f 0.36 hexanes/ethyl acetate (3:1); IR (neat) 3054, 1724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (td, 2H, J = 7.4, 1.2 Hz), 3.29 (t, 2H, J = 7.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.48 (ddd, 1H, J = 7.8, 7.4, 1.3 Hz), 7.57 (ddd, 1H, J = 7.8, 7.4, 1.3 Hz), 7.72 (d, 1H, J = 8.4 Hz), 7.78 (dt, 1H, J = 8.4, 0.6 Hz), 8.29 (dt, 1H, J = 8.4, 0.6 Hz), 9.84 (t, 1H, J = 1.2 Hz); ^{13}C NMR (75 MHz) δ 29.9, 43.9, 123.7, 126.1, 127.0, 127.4, 127.8, 127.9, 128.0, 132.4, 133.2, 137.8, 200.9; HRMS-EI m/z calcd for $C_{13}H_{11}O$ (M^+) 261.9993, found 261.9989.

Preparation of 1-Bromo-2-(1-methoxy-1-oxo-2-penten-5-yl)naphthalene (25). To a predried 50-mL round-bottomed flask were added 25 mL of anhydrous CH_3CN, 1.5 equiv of DBU (0.816 g, 5.36 mmol, 0.80 mL), 1.5 equiv of trimethyl 2-methylphosphonoacetate (1.05 g, 5.36 mmol), and 2 equiv of LiCl (0.303 g, 7.14 mmol), and the reaction mixture was allowed to stir for 10 min. Then 1 equiv of **24** (0.94 g, 1 mmol) was added in 5 mL of CH_3CN. The reaction was complete within 5 min. The reaction mixture was extracted with ether/water, and the organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification with silica gel radial chromatography (hexanes/ethyl acetate, 95:5) yielded 0.828 g (70%) as a yellow oil: R_f 0.51 in hexanes/ethyl acetate (3:1); IR (neat) 3051, 1717, 1116 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, 3H, J = 1.5 Hz), 2.59 (q, 2H, J = 7.6 Hz), 3.11 (t, 2H, J = 7.6 Hz), 3.77 (s,

3H), 6.92 (tq, 1H, J = 7.6, 1.5 Hz), 7.32 (d, 1H, J = 8.3 Hz), 7.49 (m, 1H), 7.58 (m, 1H), 7.73 (d, 1H, J = 8.3 Hz), 7.79 (dd, 1H, J = 8.3, 0.6 Hz), 8.33 (dd, 1H, J = 8.3, 0.6 Hz); ^{13}C NMR (75 MHz) δ 12.3, 29.0, 36.2, 51.7, 123.6, 125.8, 127.1, 127.2, 127.6, 127.7, 127.9, 128.4, 132.4, 133.1, 138.4, 140.5, 168.3; HRMS-EI m/z calcd for $C_{20}H_{17}BrO_2$ (M^+) 332.0410, found 332.0411.

Radial Cyclization of 25. To a predried three-necked 50-mL flask fitted with a reflux condensor and an addition funnel under N_2 were added 20 mL of toluene, 1 equiv of **25** (0.403 g, 1.2 mmol), and (cat.) AIBN. The reaction was heated to reflux, and 1.64 equiv of tributyltin hydride (0.576 g, 1.98 mmol, 0.53 mL) in 5 mL of toluene was added dropwise over 1 h. The reaction mixture was refluxed until complete by TLC (approximately 2.5 h) and concentrated *in vacuo*. Then 25 mL of anhydrous ether and 25 mL of saturated KF were added and stirred for 15 min. The reaction was extracted with ether/water (2 × 50 mL), and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification was achieved by SiO_2 column chromatography with hexanes/ethyl acetate (95:5) to yield 0.298 g (98%) of **14b,c** (3.5:1 diastereomeric ratio) as a yellow oil.

Tandem Enediyne–Radical Cyclization of 16 (28–30). Compounds **28**, **29**, and **30** were prepared in a similar manner as **14a** and isolated as clear oils. Compounds **28** and **29** were isolated as an inseparable mixture to yield 0.012 g (45%). Compound **30** was isolated to yield 0.012 g (45%) as a clear oil: R_f 0.5 in hexanes/ethyl acetate (3:1); IR (neat) 3050, 2931, 1734, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89–2.00 (m, 4H), 2.60 (m, 2H), 2.92 (m, 2H), 3.76 (s, 3H), 4.05 (m, 1H), 7.16 (d, 1H, J = 8.3 Hz), 7.40 (ddd, 1H, J = 7.8, 6.9, 1.3 Hz), 7.51 (ddd, 1H, J = 7.8, 6.9, 1.3 Hz), 7.61 (d, 1H, J = 8.3 Hz), 7.78 (dd, 1H, J = 8.3, 1.3 Hz), 8.39 (dd, 1H, J = 8.3, 1.3 Hz); ^{13}C NMR (75 MHz) δ 17.6, 26.7, 30.0, 30.6, 39.7, 51.7, 122.6, 124.7, 126.2, 126.3, 128.1, 128.8, 131.4, 132.5, 133.6, 134.1, 173.3; HRMS-EI m/z calcd $C_{17}H_{18}O_2$ (M^+) 254.1307, found 254.1295. **28** and **29** were isolated as a mixture of olefinic isomers. The mixture of isomers was treated with DBU in THF for 3 days to isomerize the double bond into conjugation with the carbonyl and then was characterized as **28**: R_f 0.48 in hexanes/ethyl acetate (3:1); IR (neat) 3050, 2918, 1718, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (p, 2H, J = 7.4 Hz), 2.26 (q, 2H, J = 7.4 Hz), 2.79 (t, 2H, J = 7.5 Hz), 3.72 (s, 3H), 5.83 (d, 1H, J = 15.6 Hz), 6.99 (dt, 1H, 15.6, 6.9 Hz), 7.30 (m, 1H), 7.42 (m, 2H), 7.59 (s, 1H), 7.77 (m, 2H); ^{13}C NMR (75 MHz) δ 29.6, 31.6, 35.4, 51.5, 121.3, 122.3, 125.1, 125.2, 125.8, 125.9, 126.5, 127.1, 127.4, 127.6, 127.9, 149.0, the carbonyl carbon was not detected; HRMS-EI m/z calcd for $C_{17}H_{18}O_2$ (M^+) 254.1307, found 254.1296.

Preparation of 1,2-Bis(1-hydroxy-4-pentyn-5-yl)benzene (31). Compound **30** (4.0 g, 12.1 mmol, 1.58 mL) was subjected to the same coupling procedure as in the preparation of **8** using 2 equiv of 4-pentynol (2.375 g, 24.2 mmol, 2.65 mL), 0.5 equiv of tetrakis(triphenylphosphine)-palladium(0) (0.699 g, 0.6 mmol), and 0.1 equiv of CuI (0.203 g, 1.21 mmol) and worked up in a similar manner followed by purification *via* silica gel column chromatography with hexanes/ethyl acetate (1:1) and concentration *in vacuo* to yield 2.56 g (91%) of a brown oil: R_f 0.25 in hexanes/ethyl acetate (1:1); IR (neat) 3318, 2225, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (p, 4H, J = 6.4 Hz), 2.56 (t, 4H, J = 6.7 Hz), 3.58 (bs, 2H), 3.80 (m, 4H), 7.13–7.16 (m, 2H), 7.31–7.34 (m, 2H); ^{13}C NMR (75 MHz) δ 16.1, 31.2, 61.2, 80.1, 93.2, 125.9, 127.3, 131.7; HRMS-EI m/z calcd for $C_{16}H_{18}O_2$ (M^+) 242.1275, found 242.1291.

Preparation of 1,2-Bis(1-oxo-4-pentyn-5-yl)benzene (32). To a predried 50-mL round-bottomed flask under N_2 was added 10 mL of CH_2Cl_2, cooled to –60 °C (CO_2/$CHCl_3$), and then 2.2 equiv of oxalyl chloride (0.363 g, 2.85 mmol, 0.249 mL) and 4.4 equiv of DMSO (0.433 g, 5.67 mmol, 0.402 mL) were added *via* syringe. The reaction mixture was allowed to stir for 5 min, and then 1 equiv of 1,2-bis(5-hydroxy-1-pentynyl)-benzene (**31**) (0.302 g, 1.29 mmol) was introduced *via* cannulae/N_2 dropwise in 2.5 mL of CH_2Cl_2. The reaction mixture was stirred for 15 min, and then 10 equiv of NEt_3 (1.305 g, 12.9 mmol, 2.09 mL) was added *via* syringe. The reaction mixture was stirred for an additional 10 min at –60 °C and then warmed to room temperature (total reaction time 1 h). Extraction with H_2O (2 × 25 mL) and CH_2Cl_2 (2 × 25 mL), followed by drying of the organic layer over $MgSO_4$, filtration, and concentration *in vacuo*, yielded 0.280 g (95%) of a yellow oil. **31** was then used without further purification: R_f 0.68 in hexanes/ethyl acetate (1:1); IR (neat) 3060, 2225, 1719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (s, 8H), 7.19–7.27 (m, 2H), 7.35–7.38 (m, 2H), 9.81 (s, 2H); ^{13}C NMR (75 MHz) δ 12.8, 42.4, 80.2, 91.6, 125.6, 127.6, 131.8, 200.6; HRMS-EI m/z calcd for $C_{16}H_{14}O_2$ (M^+) 238.1000, found 238.0997.

Preparation of 1,2-Bis(1-methoxy-1-oxohept-2-en-6-yn-7-yl)benzene (33). Compound **32** (0.087 g, 0.38 mmol) was subjected to a similar Horner–Emmons reaction as **12a** using 2.5 equiv of trimethyl phosphonoacetate (0.173 g, 0.95 mmol, 0.154 mL), 2.5 equiv of DBU (0.144 g, 0.95 mmol, 0.130 mL), and 4 equiv of LiCl (0.64 g, 1.52 mmol) and worked up in a similar way to yield 0.109 g (76%) of a yellow oil: R_f 0.87 in hexanes/ethyl acetate (3:1); IR (neat) 2949, 2228, 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50–2.57 (m, 4H), 2.62–2.66 (m, 4H), 3.73 (s, 6H), 5.95 (dt, 2H, J = 15.7, 1.5 Hz), 7.08 (dt, 2H, J = 15.7, 6.7 Hz), 7.20–7.26 (m, 2H), 7.37–7.43 (m, 2H); ^{13}C NMR (75 MHz) δ 15.9, 31.1, 61.4, 80.0, 93.1, 125.9, 127.3, 127.4, 131.9, 147.0, 166.8; HRMS-EI m/z calcd for $C_{22}H_{22}O_4$ (M^+) 350.1510, found 350.1513.

Tandem Enediyne–Radical Cyclization of 21 To Yield the Bis-Tandem Enediyne Radical Cyclized product (34). To a predried reaction vial were added **33** (0.067 g, 0.2 mmol) and ≈8 mL anhydrous dichlorobenzene. The reaction mixture was degassed with N_2 for 20 min, and 20 equiv of 1,4-cyclohexadiene (0.285 g, 4 mmol, 0.336 mL) was added *via* syringe. The reaction vial was heated to 245 °C for 3 h, upon which all of the starting material had been consumed by thin layer chromatography. Workup was performed in the usual manner to yield 0.067 g (>99%) as a clear oil. All analytical data was gathered on an inseparable (1:1) mixture of diastereomers. Some of the NMR shifts in the ^{13}C are indistinguishable between the two diastereomers: R_f 0.6 in hexanes/ethyl acetate (3:1); IR (neat) 3061, 1718, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (m, 2H), 2.29–2.45 (m, 4H), 2.75 (dd, 1H, J = 9.6, 3.2 Hz), 2.80 (dd, 1H, J = 9.6, 3.2 Hz), 2.86–2.90 (m, 2H), 2.99–3.17 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 4.10–4.14 (m, 2H), 7.44–7.48 (m, 4H), 7.85–7.89 (m, 4H); ^{13}C NMR (75 MHz) δ 30.0, 31.0, 31.1, 38.7, 38.8, 40.5, 51.7, 124.6, 125.1, 125.2, 129.0, 129.0, 137.7, 137.8, 140.5, 173.4; HRMS-EI m/z calcd for $C_{22}H_{24}O_4$ (M^+) 352.1668, found 352.1671.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **8–10, 12–18, 24, 25,** and **30–34** and ^{1}H NMR spectra for **8, 12d,f,h, 14a, 28,** and **29** (41 pages). This material is contained in many 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.