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Nucleophilic Addition of Enolates to 1,4-Dehydrobenzene Diradicals Derived from Enediynes: Synthesis of Functionalized Aromatics

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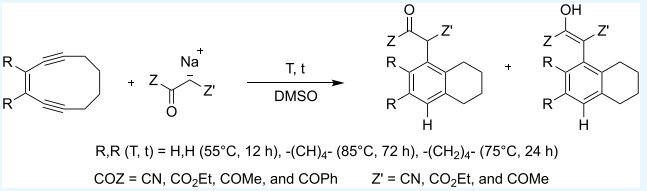
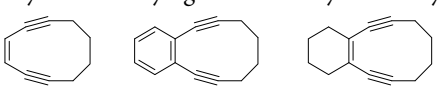
ABSTRACT: Alkylation of aromatics and formation of a new C−C bond is usually achieved by the electrophilic attack of an activated carbon species on an electron-rich aromatic ring. Herein, we report an alternative method for alkylation of aromatics via nucleophilic addition of enolates of active methylene compounds to 1,4-dehydrobenzene diradicals derived from enediynes cyclodec-1,5-diyne-3-ene, benzo[3,4]-cyclodec-1,5-diyne-3-ene, and cyclohexeno[3,4]-cyclodec-1,5-diyne-3-ene. The benzo-substituted enediyne produces slightly higher yields of alkylation products than do the other two enediynes, but the differences are not substantial. The reaction produces a new C−C bonded aromatic alkylation product, which allows the construction of complex polyfunctional structures in a few steps. Moreover, this reaction provides solely *C*-arylated products, and no *O*-arylation products were observed.



INTRODUCTION

Naturally occurring compounds containing 10-membered-ring enediynes are well-known for their remarkable antibiotic and antitumor activities.[1] The activity of these enediyne natural products stems from their enediyne core: In the presence of chemical triggers like chromosomal DNA, the enediyne moiety undergoes rearrangement to form a reactive 1,4-dehydrobenzene diradical (often called a "*p*-benzyne diradical", a designation discouraged by IUPAC, inasmuch as there is no triple bond) via a cycloaromatization known as the Bergman cyclization,[2] and the diradical then abstracts hydrogen atoms from the DNA backbone to cause oxidative DNA breakage and cell death.[3]

Therefore, it has become important to understand the formation and reactivity of 1,4-dehydrobenzene diradicals. Yet, even though enediyne **1** is the simplest model to study, its difficult synthesis, its volatility, and its reactivity even at room temperature limit its use in understanding cycloaromatization.[4] In its place, benzo-fused enediyne **2** has been extensively studied because of its easy synthetic accessibility and relative stability at room temperature.[5] Recently, we have developed cyclohexeno-fused enediyne **3** as a simple and convenient model enediyne for studying the reactivity of enediynes.[6]



1 **2** **3**

Some earlier studies involved experimental and computational evaluation of factors affecting the formation of 1,4-dehydrobenzene diradicals (or cycloaromatization), such as ring strain and geometrical effects,[4a,7] conformational and electronic effects,[5,8] and metal-ion coordination,[9] using enediynes **1** and **2** and related homologues. However, few studies explored their synthetic utility. Semmelhack et al. reported cycloaromatization of enediyne **2** in the presence of radical trapping agents such as 1,4-cyclohexadiene, CCl_4, and CBr_4 and obtained 1,4-dihydro-, 1,4-dichloro-, and 1,4-dibromo-tetrahydroanthracene adducts, respectively, in moderate yields.[5,8a,10]

In 2007 Perrin, Rodgers, and O'Connor reported nucleophilic addition of halides to the 1,4-dehydrobenzene diradical derived from enediyne **1**.[11] Subsequently, Perrin and Reyes-Rodriguez showed that the reaction also succeeds with other nucleophiles such as the pseudohalides cyanide, thiocyanate, and azide.[12]

Nucleophilic addition to 1,4-dehydrobenzenes had been a previously unexpected mode of reaction for such diradicals, which ordinarily react by radical pathways. The mechanism of halide addition is shown in Scheme 1.[11] Kinetic studies on enediyne **1** found that the reaction rate is simply first-order in enediyne and independent of the concentration of halide or even of which halide serves as a nucleophile. Therefore, the rate-limiting step is cyclization to the 1,4-dehydrobenzene diradical, which then rapidly adds halide and is protonated. Because the diradical is a singlet, with two electrons of

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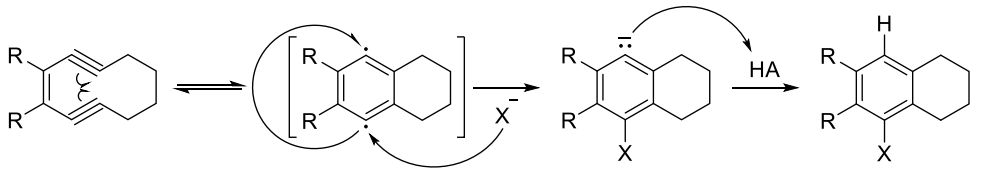
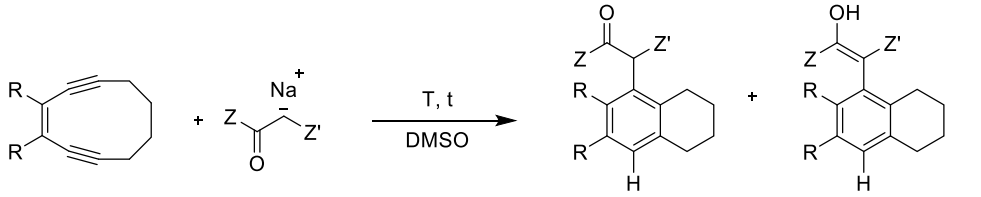
Scheme 1. Reactions of Enediynes 1 (R = H), 2 (RR = $(CH)_4$), and 3 (RR = $(CH_2)_4$) with Halides (X^-)



Scheme 2. Reaction of Enolates of Active Methylene Compounds (a–f, 50-fold Excess) with Dehydrobenzene Diradicals of Enediynes (1–3) Generated at Optimized Temperatures in DMSO



1, 2, or 3 **a-f** **4a-c, 5a-c, or 6a-c** **4d-f, 5d-f, or 6d-f**

RR	Temperature (T), time (t)
1 & **4** = HH	**1** = 55°C, 12 h
2 & **5** = -$(CH)_4$-	**2** = 85°C, 72 h
3 & **6** = -$(CH_2)_4$-	**3** = 75°C, 24 h

	COZ	Z'
a =	CN	CN
b =	CO_2Et	CN
c =	CO_2Et	CO_2Et

	Z	Z'
d =	Me	COMe
e =	Ph	CO_2Et
f =	Me	CO_2Et

opposite spin in two different atomic orbitals, those electrons can pair in one orbital while the electron pair coming from X^- is used to bond to the other orbital. Thermodynamic data showed that the halide additions are very exothermic. Moreover, the calculated energy of interaction between Cl^- and the diradical shows no activation barrier in the gas phase, and any experimentally detectable barrier arises from the energy required to desolvate the nucleophile.

Subsequently, this reaction was extended to enediynes **2**[4e] and **3**.[6] Using this strategy, Ding and Hu et al. synthesized complex products via cycloaromatization of acyclic enediynes under the action of bromide ions.[13] Also, Basak and co-workers achieved high regioselectivity in halide addition to 1,4-dehydrobenzene or 1,4-dehydropyridine diradicals derived from unsymmetrical enediynes.[14]

Beyond halide addition to 1,4-dehydrobenzene diradicals, alkylation would allow the synthesis of more complex structures. Such structures were obtained previously but by more roundabout procedures. Curran, Liu, and Taniguchi et al. carried out borylative radical cyclizations of enediyne **2** and NHC-boranes toward their further application in sp^2–sp^2 C–C bond-forming reactions such as the Suzuki–Miyaura coupling reaction.[15] Basak and co-workers reported a one-pot protocol for sp^2–sp^2 C–C bond formation in unsymmetrical aza-substituted enediynes via a regioselective halogenation of 1,4-dehydrobenzene diradicals, followed by Suzuki–Miyaura coupling with aryl boronic acids.[16] Chen and co-workers synthesized naphthalenyl triflates via regioselective annulation of benzodiynes promoted by triflic acid.[17] Using these naphthalenyl triflates, the authors then synthesized sp^2–sp^3 C–C bonded compounds by Kumada coupling, sp^2–sp^2 C–C bonded compounds by Suzuki and Stille couplings, and sp^2–sp C–C bonded compounds by Sonogashira coupling.

However, to the best of our knowledge, there are no reports of sp^2–sp^3 C–C bond formation by direct alkylation of 1,4-dehydrobenzene diradicals derived from enediynes. Generally, alkylation is achieved by the electrophilic attack by an activated carbon species, such as a carbocation, on an electron-rich aromatic ring. In contrast to this traditional methodology, we here report a new method for nucleophilic alkylation of 1,4-dehydrobenzene diradicals derived from enediynes, with the formation of a new sp^2–sp^3 C–C bond. In this study, carbanions prepared from active methylene compounds are used as carbon nucleophiles. This reaction of enolates of active methylene compounds (**a**–**f**, 50-fold excess) with dehydrobenzene diradicals of enediynes (**1**–**3**) generated at optimized temperatures is shown in Scheme 2. For conciseness, all of these carbanions are designated as enolates, even though that is a misnomer for the anion derived from malononitrile, as is the abbreviation of COZ as CN.

RESULTS

Among enediynes **1**, **2**, and **3**, enediyne **2** is the most stable toward decomposition and the easiest to handle at room temperature. Therefore, initial investigations were performed with enediyne **2** to explore its reactivity toward carbon nucleophiles. When enediyne **2** was heated at 85 °C in anhydrous DMSO with 50 equivalents of the sodium salt of malononitrile anion (**a**), the solution turned clear and after 72 h, almost all enediyne was consumed, to furnish the C–C bonded 1,4-addition product 1,2,3,4-tetrahydroanthracen-9-ylmalononitrile (**5a**) in 55% yield (Scheme 2), along with other unidentified byproducts due to competing polymerization of the enediyne or diradical. The structure of adduct **5a** was thoroughly characterized by ^1H, ^{13}C, ^1H–^1H COSY NMR, and mass spectrometry.

Similarly, nucleophilic alkylations of the diradical derived by cycloaromatization of enediyne **2** with enolates of ethyl cyanoacetate (**b**), diethyl malonate (**c**), acetylacetone (**d**), and ethyl benzoylacetate (**e**) produce the corresponding C–C bonded adducts **5b**–**e** in 35–57% yields (Scheme 2, Table 1). In these reactions, >85% of unreacted active methylene compounds could be recovered after the reaction. An exception is the reaction of ethyl acetoacetate anion (**f**) with enediyne **2**, which produces only a trace amount of **5f**, detected by mass spectrometry but not isolated. Also, after the

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Table 1. Reaction of Enolates of Active Methylene Compounds (a−e, 50-fold Excess) with Dehydrobenzene Diradicals of Enediynes (1−3) Generated at Optimized Temperatures in DMSO: Isolated Products (Yields in Parentheses)

temperature, time →	55 °C, 12 h	85 °C, 72 h	75 °C, 24 h
enolate ↓, enediyne →	**1**	**2**	**3**
a	**4a**(29)	**5a**(55)	**6a**(46)
b	**4b**(25)	**5b**(57)	**6b**(44)
c	**4c**(19)	**5c**(51)	**6c**(37)
d	**4d**(24)	**5d**(54)	**6d**(43)
e	**4e**(trace)	**5e**(35)	**6e**(22)

reaction, only ∼70% of unreacted ethyl acetoacetate was recovered.

To find the optimum conditions for the reaction of enediynes with enolates, a series of reaction conditions were explored using enediyne **2** and an excess of enolates **a**−**f** to trap the diradical as soon as it forms (Table S1). Heating enediyne **2** with 100 equiv of enolate **a** for 30 days at 75 °C in DMSO produced only a very poor 2% yield of **5a**. However, on increasing the temperature to 85 °C, the reaction yield was increased to 57% after 3 days. At 85 °C, on lowering the concentration of enolate **a** to 50 equivalents, the yield of **5a** decreases slightly to 55%. Therefore, heating enediyne **2** with a 50-fold excess of enolate at 85 °C in DMSO was considered an optimum condition for the reaction. This same approach was applied to find the optimum conditions for the reactions of enediynes **1** and **3** with enolates **a**−**f**.

Table 1 also lists results for the alkylation of the diradicals derived from enediynes **1** and **3** with enolates of active methylene compounds **a**−**f**. Enediyne **1** required only 55 °C for 12 h, and enediyne **3** required 75 °C for 24 h for the production of their diradicals. The 1,4-dehydrobenzene diradical of enediyne **1** reacts with enolates of active methylene compounds **a**−**f** and forms the corresponding 1,4-addition products **4a**−**d** in 19−29% yield, except for **4e** and **4f**, which form in only trace amounts. The dehydrobenzene diradical from enediyne **3** reacts with enolates of active methylene compounds **a**−**f** and forms the corresponding C−C bonded 1,4-addition products **6a**−**e** in 22−46% yield, except for **6f**, which forms in only trace amount. In these reactions, >85% of unreacted active methylene compounds could be recovered after the reaction, except for ethyl acetoacetate, which was recovered up to 70%.

According to ^{1}H NMR spectra, products **4a**−**c**, **5a**−**c**, and **6a**−**c** were isolated as their keto tautomer, whereas products **4d**, **5d**−**e**, and **6d**−**e** were isolated as their enol tautomer (Scheme 2, Table 1). Since **d**−**f** preferentially form enolic products **4e,f**, **5f**, and **6f** are also assigned as enols, but they were not fully characterized.

Enolates of other active methylene compounds, as listed in Scheme 3, were also tested for their reactivity toward the 1,4-dehydrobenzenes from enediynes **1**−**3**, but no corresponding 1,4-adducts were observed, perhaps because of their steric bulk (**g**−**l**) or competing decomposition (**m**−**p**). Also, some of the anions (**h**, **j**, **l**) were not completely soluble under optimized conditions.

Alkylation of enolates of active methylene compounds, especially of 1,3-dicarbonyl compounds, generally tends to afford *C*-alkylation products,[18] but *O*-alkylation products are also formed.[19] In contrast, reactions of enediyne **1**−**3** with enolates of active methylene compounds **a**−**f** selectively produce only the corresponding *C*-alkylated 1,4-addition products **4**−**6**, and no *O*-alkylated 1,4-addition products were detected.

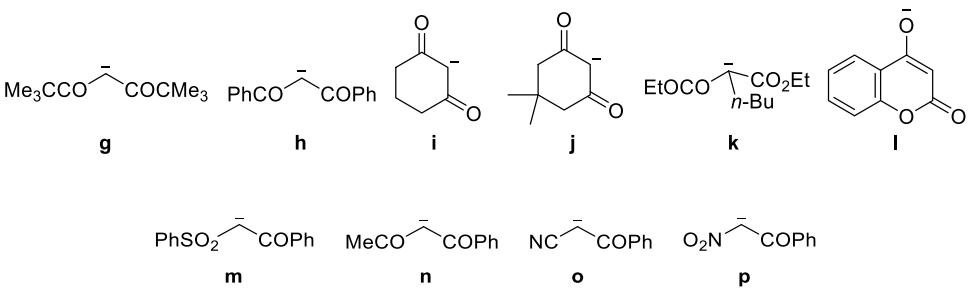
DISCUSSION

These syntheses take advantage of nucleophilic addition to 1,4-dehydrobenzenes, a previously unexpected mode of reaction for such diradicals, which ordinarily react by radical pathways. The mechanism is considered to be the same as the nucleophilic addition of halides to the 1,4-dehydrobenzene diradical derived from enediyne **1**, as in Scheme 1.[11] However, these nucleophiles provide more highly functionalized products than do the previous halides.

Although the reactions of enediynes **1**−**3** with most halides can produce a >75% yield of 1,4-adducts,[4e,6,11] and 100% with I^-, the yields of 1,4-adducts with enolates **a**−**e** are slightly lower, only 19−55%, presumably because the enolates suffer a steric hindrance that does not impede iodide addition. Besides, yields generally decrease from **5a**−**e** to **6a**−**e** to **4a**−**e** (Table 1), although the variations are not substantial. Nor are the variations easy to rationalize, although they may be a consequence of the reversibility of the cycloaromatization of **2**, or of a favorable polarizability of the additional benzene ring in the alkylation of the 1,4-dehydrobenzene from **2**.

Enolates **a**−**e** are relatively stable under the reaction conditions, and >85% of unreacted active methylene compounds were recovered after neutralizing workup. The observed low reactivity of the enolate of ethyl acetoacetate **f** toward enediynes **1**−**3** is because of the bulkiness of this enolate and also because it undergoes significant decomposition under the reaction conditions. As for the other unreactive enolates, **g**−**l** of Scheme 3 seem especially bulky, and **m**−**p** are prone to decompose under the reaction conditions. Also, enolates **h**, **j**, and **l** are not completely soluble under the reaction conditions.

Scheme 3. Enolates (as Na^+ Salts) Unreactive toward Enediynes 1−3 under Optimized Conditions



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All compounds synthesized according to Scheme 2 are new except **4a** and **4e**. Nakano et al. reported Cr and Co complexes of compound **4a**, but the compound itself was not fully characterized.[20] Liu and co-workers synthesized **4e** via ruthenium-catalyzed cycloaromatization of 1,2-diethynylcyclohexene with ethyl acetoacetate,[21] but this product was not isolated, owing to the rapid decomposition of enediyne **1** and to the bulkiness of enolate **e**. Liu and co-workers also tried to synthesize the corresponding dimethyl malonate derivative but obtained only a decarboxylated derivative.[21] In contrast, our method yields the anticipated *C*-alkylated product **4c** without any decarboxylation, although we used diethyl malonate anion instead of dimethyl malonate anion. Also, we did not need any (expensive) metal catalyst. Hashmi and co-workers synthesized several hydroarylated derivatives of 1,2-bis(iodoethynyl)-benzenes and 1,2-bis(iodoethynyl)cycloalkenes via Au-catalyzed cycloaromatization.[22] This method not only required a gold catalyst but also was restricted to terminal haloethynyl derivatives. Liu and co-workers synthesized 1-alkoxynaphthalenes via Ru-catalyzed regioselective alkoxylation of 1,2-diethynylbenzenes.[21] This reaction also worked well with 1,2-diethynylcycloalkenes. They also synthesized *N*-arylaminonaphthalenes via Ru-catalyzed aminoarylation of 1,2-diethynylbenzenes, but this method was not regioselective and also produced *C*-arylated naphthalenes.[21]

We find that only the *C*-arylated products are formed in the reactions of enolates **a**−**f** with enediynes **1**−**3**. No *O*-arylated 1,4-addition products were formed. This exclusive *C*-selectivity is probably due to the fact that the diradical is a soft electrophile (owing to the polarizability of its paired electrons), which reacts at carbon, whereas a hard electrophile (with a localized electron deficiency) would react at oxygen.[23]

It must be acknowledged that it has not been possible to capture the aryl anion in Scheme 1 with an electrophile alternative to "HA" (presumably trace water in the solvent). Unfortunately, further functionalization of the diradical does not succeed in attaching a substituent para to the incoming nucleophile. This is a consequence of the observation that the aryl anion is formed as a "naked" anion, so poorly solvated that it reacts immediately with the surrounding solvent before any alternative electrophile can capture it.[24] A further drawback is the necessity for a large excess of enolate, but this is an inexpensive reagent that can be recovered if warranted.

In summary, the products shown in Scheme 2 can be synthesized by a simple procedure, in decent yield and purity, without interference from an admixture of similar substances. According to Table 1, a total of 14 different products can be obtained. Those products carry reactive functional groups that allow further conversion into a vast and diverse array of materials.

CONCLUSIONS

We have demonstrated an alternative method for the synthesis of alkylated aromatics via nucleophilic attack of enolates of active methylene compounds **a**−**f** on the 1,4-dehydrobenzene diradicals derived from enediynes **1**−**3**. The reaction produces a series of new C−C bonded aromatic alkylation products, including tetrahydronaphthalenes, tetrahydroanthracenes, and octahydroanthracenes. These highly functionalized products can then allow the construction of more complex chemical structures via addition, cyclization, or fusion in only a few additional steps. Benzo-fused enediyne **2** reacts most efficiently as compared to cyclohexeno-fused (**3**) or unsubstituted (**1**) enediynes, but all are productive. Despite the ambident reactivity of enolates of active methylene compounds, this reaction provides solely the *C*-alkylation products, and no *O*-alkylation products were observed. The yields are not quantitative, but they are respectable for the preparation of such complex polyfunctional substances. Moreover, this methodology succeeds under relatively mild conditions.

EXPERIMENTAL SECTION

General Information. *Materials.* Common organic solvents and reagents were obtained from commercial suppliers and used as received. Sodium hydride (60% in mineral oil), diethyl malonate (99%), acetylacetone (99%), malononitrile (99%), and lithium hexamethyldisilazide (LiHMDS, 1M in THF) were obtained from Aldrich Chemical Company, Inc., and were used without further purification. Ethyl cyanoacetate (99%) and ethyl benzoylacetate (99%) were obtained from TCI Chemicals and were used without further purification. Ethyl acetoacetate (99%) was obtained from Acros Organics and was used without further purification. Chloroform-*d* ($CDCl_3$, 99.9% D), acetonitrile-d_3 (CD_3CN, 99.9% D), and dimethyl sulfoxide-d_6 (DMSO-d_6, 99.9% D) were obtained from Cambridge Isotope Laboratories, Inc., and were used without further purification.

Instrumentation. ^{1}H NMR spectra were obtained on JEOL ECA 500 MHz or Varian VX 500 MHz or Varian Mercury+ 400 MHz or Bruker AVA 300 MHz spectrometers. Tetramethylsilane (TMS, 0 ppm) or residual solvent ($CHCl_3$/$CDCl_3$, DMSO-d_5/DMSO-d_6, CHD_2CN/CH_3CN) was used as internal standard. ^{13}C NMR spectra were obtained on a Varian VX 500 MHz FT-NMR spectrometer (125.8 MHz ^{13}C), and ^{1}H−^{1}H COSY NMR spectra were obtained on a JEOL ECA 500 FT-NMR spectrometer (500.2 MHz ^{1}H). Spectra were processed either using Bruker TopSpin 4.0, Academic Edition, or MestReNova v12.0 software. GC-EI-MS (electron ionization, EI) was obtained on an Agilent 7820A gas chromatograph coupled with a 59 77B MSD detector operated in scan mode from 10 to 400 m/z. HPLC-HR-ESI/APCI-MS (electrospray ionization, ESI, or atmospheric pressure chemical ionization source, APCI) was obtained on an Agilent 6230 Accurate-Mass TOF MS system using ESI/TOF MS in a positive- or negative-ion mode.

Synthesis and Characterization. *Synthesis of Enediynes **1**−**3**.* Enediynes **1**−**3** were prepared according to their literature procedures. Their spectral data matched reported values.

*Cyclodec-1,5-diyne-3-ene (**1**).*[4d,e] It was prepared from the reaction of 1,10-dibromodeca-2,8-diyne (5.0 g, 17.1 mmol) and 1 M LiHMDS in THF (3 equiv, 51.4 mL). Pale yellow liquid (0.20 g, 9%, 0.5 M in pentane). ^{1}H NMR (500 MHz, CD_3CN), δ 5.81 (s, 2H), 2.35 (m, 4H), 1.87 (m, 4H). GC-EI-MS 130.1, calculated for $C_{10}H_{10}$ $[M]^+$: 130.1.

*Benzo[3,4]-cyclodec-1,5-diyne-3-ene (**2**).*[5] It was synthesized from 1,2-diethynylbenzene (0.5 g, 4.0 mmol) and 1,4-diiobutane (1.3 g, 4.0 mmol). White solid (0.33 g, 46%). Mp 74−75 °C (lit.[7a] 73.0−74.5 °C). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.19 (m, 2H), 2.46 (m, 4H), 1.97 (m, 4H) ppm. ^{13}C NMR (126 MHz) $CDCl_3$: δ 129.6, 128.2, 127.4, 100.1, 82.4, 28.7, and 21.6 ppm. HPLC-APCI-MS 181.1012, calculated for $C_{14}H_{13}$ $[M]^+$: 181.1012.

*Cyclohexeno[3,4]-cyclodec-1,5-diyne-3-ene (**3**).*[6] It was synthesized from 1,2-diethynylcyclohex-1-ene (0.5 g, 3.8 mmol) and 1,4-diiobutane (1.2 g, 3.9 mmol). White solid

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(0.32 g, 45%). Mp 105−106 °C (lit.[6] 105−106 °C). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.36 (m, 4H), 2.15 (m, 4H), 1.90 (m, 4H), 1.61 (m, 4H) ppm. ^{13}C NMR (126 MHz) $CDCl_3$: δ 129.6, 98.6, 85.4, 29.2, 28.1, 21.8, and 21.6 ppm. HPLC-APCI-MS 185.1327, calculated for $C_{14}H_{17}$ $[M + H]^+$: 185.1325.

*Synthesis of Active Methylene Enolates **a**−**f**.* Active methylene enolates as their sodium salts were prepared by treating them with sodium hydride according to the reported procedure.[25] Sodium hydride (fresh!) in oil (60%) was washed with several portions of dry hexanes and then mixed with an equimolar amount of CH-acids in hexane solvent under a nitrogen atmosphere. After 2 h, the precipitated salt was filtered off and washed with hexanes and then dried under vacuum at room temperature for 2 h.

Carbanions **a**−**f** were prepared according to the literature. Their spectral data matched reported values.

*Sodium Dicyanomethanide (**a**).*[26] It was synthesized from malononitrile (0.5 g, 7.6 mmol) and NaH (7.6 mmol, 1 equiv) as a white solid (0.65 g, 82%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 (s, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 130.4, −1.7 ppm.

*Sodium 1-Cyano-2-ethoxy-2-oxoethan-1-ide (**b**).*[27] It was synthesized from ethyl cyanoacetate (0.5 g, 4.6 mmol) and NaH (4.6 mmol, 1 equiv) as a white solid (0.45 g, 67%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.72 (m, 2H), 2.33 (s, 1H), 1.02 (m, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.2, 119.3, 58.8, 27.4, and 15.4 ppm.

*Sodium 1,3-Diethoxy-1,3-dioxopropan-2-ide (**c**).*[28] It was synthesized from diethyl malonate (0.5 g, 3.1 mmol) and NaH (3.1 mmol, 1 equiv) as a white solid (0.47 g, 76%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.80 (q, J = 7.0 Hz, 4H), 3.59 (s, 1H), 1.06 (t, J = 7.1 Hz, 6H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.6, 59.4, 46.8, and 14.6 ppm.

*Sodium 2,4-Dioxopentan-3-ide (**d**).*[26b,29] It was synthesized from acetylacetone (0.5 g, 5.0 mmol) and NaH (5.0 mmol, 1 equiv) as a white solid (0.54 g, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.68 (m, 1H), 1.79 (m, 6H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 185.2, 174.5, and 29.2 ppm.

*Sodium 1-Ethoxy-1,3-dioxo-3-phenylpropan-2-ide (**e**).*[26b,30] It was synthesized from ethyl benzoylacetate (0.5 g, 2.6 mmol) and NaH (2.6 mmol, 1 equiv) as a white solid (0.51 g, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74−7.60 (m, 2H), 7.35−7.15 (m, 3H), 4.92 (s, 1H), 3.87 (q, J = 7.1 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.4, 168.7, 144.8, 127.9, 127.4, 126.1, 77.7, 55.6, and 15.2 ppm.

*Sodium 1-Ethoxy-1,3-dioxobutan-2-ide (**f**).*[28] It was synthesized from ethyl acetoacetate (0.5 g, 3.8 mmol) and NaH (3.8 mmol, 1 equiv) as a white solid (0.45 g, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.25 (s, 1H), 3.81 (q, J = 7.1 Hz, 2H), 1.59 (s, 3H), 1.07 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.5, 167.9, 79.8, 55.3, 29.1, and 15.2 ppm.

*Synthesis of 1,4-Addition Products **4**−**6**.* General procedure for the reaction of enediynes **1**−**3** with active methylene enolates **a**−**f**

Enediyne (**1**, **2**, or **3**, 0.10 mmol, 5 mM) was added under N_2 to a solution of enolate (**a**−**f**, 5.0 mmol, 50 equiv, 250 mM) in anhydrous dimethyl sulfoxide (20 mL) in a 50 mL round-bottom flask and stirred at 55 °C for 12 h for **1**, 85 °C for 72 h for **2**, and 75 °C for 24 h for **3**. The mixture was then neutralized with 0.1*N* HCl, followed by extraction with diethyl ether (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the resulting crude products were purified by flash column chromatography (silica gel, 0−10% EtOAc in hexanes). About 70−90% of unreacted active methylene compounds were also recovered.

*5,6,7,8-Tetrahydronaphthalen-1-ylmalononitrile (**4a**).*[20] It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200 μL, 0.5 M in pentane) and carbanion **a** (445.3 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4a** (5.7 mg, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.8 Hz, 1H), 7.25−7.20 (m, 2H), 5.03 (s, 1H), 2.83 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.96−1.88 (m, 2H), 1.85−1.76 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 134.9, 132.0, 126.9, 125.8, 124.7, 111.9, 29.9, 27.2, 26.2, 22.9, and 22.3 ppm; GC-EI-MS 196.1, calculated for $C_{13}H_{12}N_2$ $[M]^+$: 196.1.

*Ethyl α-Cyano-5,6,7,8-tetrahydronaphthalen-1-ylacetate (**4b**).* It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200 μL, 0.5 M in pentane) and carbanion **b** (680.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4b** (6.1 mg, 25%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 7.3 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 4.89 (s, 1H), 4.30−4.21 (m, 2H), 2.86−2.76 (m, 3H), 2.66 (dt, J = 16.4, 6.3 Hz, 1H), 1.91−1.82 (m, 2H), 1.82−1.74 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 138.9, 135.2, 130.7, 129.0, 126.4, 126.2, 116.3, 63.4, 40.5, 30.1, 26.4, 23.1, 22.5, and 14.1 ppm; GC-EI-MS 243.1, calculated for $C_{15}H_{17}NO_2$ $[M]^+$: 243.1.

*Diethyl 5,6,7,8-Tetrahydronaphthalen-1-ylmalonate (**4c**).* It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200 μL, 0.5 M in pentane) and carbanion **c** (915.9 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4c** (5.5 mg, 19%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 4.88 (s, 1H), 4.28−4.16 (m, 4H), 2.79 (t, J = 6.2 Hz, 2H), 2.68 (t, J = 6.3 Hz, 2H), 1.86−1.81 (m, 2H), 1.78−1.73 (m, 2H), 1.27 (t, J = 7.1 Hz, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 138.0, 135.4, 131.8, 129.6, 126.3, 125.7, 61.9, 53.8, 30.3, 26.6, 23.4, 22.6, and 14.2 ppm; GC-EI-MS 290.2, calculated for $C_{17}H_{22}O_4$ $[M]^+$: 290.2.

*4-Hydroxy-3-(5,6,7,8-tetrahydronaphthalen-1-yl)pent-3-en-2-one (**4d**).* It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200 μL, 0.5 M in pentane) and carbanion **d** (615.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4d** (5.5 mg, 24%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.60 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.35 (t, J = 2.1 Hz, 1H), 7.12 (dd, J = 8.6, 2.5 Hz, 1H), 2.88−2.77 (m, 3H), 2.49−2.44 (m, 1H), 1.79−1.76 (m, 4H), 1.33 (s, 3H), 1.28 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 147.2, 138.2, 136.9, 128.8, 125.9, 124.1, 113.6, 31.6, 30.3, 29.6, 27.6, 23.7, and 23.1 ppm; GC-EI-MS 230.1, calculated for $C_{15}H_{18}O_2$ $[M]^+$: 230.1.

*1,2,3,4-Tetrahydroanthracen-9-ylmalononitrile (**5a**).* It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **a** (445.3 mg, 5.00 mmol) and purified by flash column chromatography (silica gel, 10% EtOAc in hexanes), to yield **5a** (13.6 mg, 55%) Mp. 189−190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 8.07 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 5.83 (s, 1H), 3.04 (dt, J = 27.7, 6.5 Hz, 4H), 1.93 (dp, J = 61.8, 6.3 Hz, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6,

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136.1, 132.7, 131.0, 128.8, 128.8, 127.4, 126.3, 122.0, 119.3, 112.0, 30.5, 28.0, 23.2, 22.3, and 21.1 ppm; HR-ESI-MS 245.1083, calculated for $C_{17}H_{13}N_2^+$ $[M - H]^+$: 245.1084.

*Ethyl α-Cyano-1,2,3,4-tetrahydroanthracen-9-ylacetate (**5b**).* It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **b** (680.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5b** (16.7 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 5.61 (s, 1H), 4.34−4.20 (m, 2H), 3.10−2.92 (m, 4H), 1.98−1.83 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 136.4, 135.9, 132.5, 129.7, 129.6, 128.4, 126.5, 125.6, 123.9, 122.6, 116.0, 63.4, 37.1, 30.7, 27.9, 23.4, 22.4, and 14.1 ppm; HR-ESI-MS 294.1486, calculated for $C_{19}H_{20}NO_2^+$ $[M + H]^+$: 294.1489.

*Diethyl 1,2,3,4-Tetrahydroanthracen-9-ylmalonate (**5c**).* It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **c** (915.9 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5c** (17.4 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.43−7.31 (m, 2H), 5.47 (s, 1H), 4.21 (q, J = 6.9 Hz, 4H), 2.98 (dt, J = 9.2, 4.5 Hz, 4H), 2.01−1.81 (m, 4H), 1.30−1.20 (m, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 136.5, 136.3, 132.6, 131.1, 128.5, 127.9, 127.3, 125.4, 124.9, 124.6, 61.9, 52.2, 30.8, 28.0, 23.5, 22.5, and 14.2 ppm; HR-ESI-MS 341.1745, calculated for $C_{21}H_{25}O_4^+$ $[M + H]^+$: 341.1747.

*4-Hydroxy-3-(1,2,3,4-tetrahydroanthracen-9-yl)pent-3-en-2-one (**5d**).* It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **d** (615.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5d** (15.1 mg, 54%) Mp. 148−149 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.82 (s, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.39 (p, J = 6.7 Hz, 2H), 3.01 (d, J = 6.0 Hz, 2H), 2.66 (q, J = 5.9, 4.5 Hz, 2H), 1.84 (p, J = 3.4 Hz, 4H), 1.67 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 136.6, 136.3, 132.4, 131.9, 131.6, 127.7, 127.6, 125.9, 125.4, 124.5, 110.2, 30.5, 28.4, 23.5, 23.5, and 23.0 ppm; HR-ESI-MS 281.1536, calculated for $C_{19}H_{21}O_2^+$ $[M + H]^+$: 281.1537.

*Ethyl β-Hydroxy-β-phenyl-α-(1,2,3,4-tetrahydroanthracen-9-yl)acrylate (**5e**).* It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **e** (1.08 g, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5e** (13.0 mg, 35%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.92 (s, 1H), 7.73 (dd, J = 17.4, 8.7 Hz, 2H), 7.52 (s, 1H), 7.33 (p, J = 6.6 Hz, 2H), 7.11 (d, J = 7.4 Hz, 3H), 6.98 (t, J = 7.6 Hz, 2H), 4.14 (q, J = 7.0 Hz, 2H), 2.90 (q, J = 6.2, 5.5 Hz, 2H), 2.55 (ddt, J = 59.8, 16.9, 6.4 Hz, 2H), 1.69 (dddd, J = 30.3, 12.0, 8.8, 4.7 Hz, 4H), 1.06 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 170.8, 136.3, 134.8, 133.0, 132.7, 132.0, 130.1, 129.9, 129.7, 128.5, 127.9, 127.7, 127.5, 127.2, 125.3, 125.2, 124.9, 99.8, 61.0, 30.4, 28.1, 23.2, 23.0, and 14.3 ppm; HR-ESI-MS 373.1798, calculated for $C_{25}H_{25}O_3^+$ $[M + H]^+$: 373.1799.

*1,2,3,4,5,6,7,8-Octahydroanthracen-9-ylmalononitrile (**6a**).* It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **a** (445.3 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6a** (11.5 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 5.69 (s, 1H), 2.89 (t, J = 5.9 Hz, 4H), 2.69 (t, J = 5.9 Hz, 4H), 1.89−1.69 (m, 8H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 135.3, 134.2, 134.2, 112.8, 29.9, 29.1, 28.1, 22.8, and 22.7 ppm; HR-ESI-MS 249.1397, calculated for $C_{17}H_{17}N_2$ $[M - H]^+$: 249.1397.

*Ethyl α-Cyano-1,2,3,4,5,6,7,8-octahydroanthracen-9-ylacetate (**6b**).* It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **b** (680.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6b** (13.1 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 5.21 (s, 1H), 4.33−4.24 (m, 2H), 2.89−2.52 (m, 8H), 1.90−1.69 (m, 8H), 1.31 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 135.7, 133.5, 131.7, 127.8, 115.8, 63.2, 37.0, 29.8, 27.1, 23.5, 22.6, and 14.2 ppm; HR-ESI-MS 298.1803, calculated for $C_{19}H_{24}NO_2$ $[M + H]^+$: 298.1802.

*Diethyl 1,2,3,4,5,6,7,8-Octahydroanthracen-9-ylmalonate (**6c**).* It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **c** (915.9 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6c** (12.8 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.04 (s, 1H), 4.23−4.17 (m, 4H), 2.63−2.54 (m, 4H), 2.42−2.34 (m, 4H), 1.93−1.80 (m, 8H), 1.21 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 136.5, 133.3, 132.1, 127.8, 61.9, 52.2, 28.1, 26.7, 24.2, 23.5, and 14.2 ppm; HR-ESI-MS 345.2061, calculated for $C_{21}H_{29}O_4$ $[M + H]^+$: 345.2061.

*4-Hydroxy-3-(1,2,3,4,5,6,7,8-octahydroanthracen-9-yl)-pent-3-en-2-one (**6d**).* It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **d** (615.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6d** (12.2 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.59 (s, 1H), 6.84 (s, 1H), 2.73 (m, 4H), 2.37 (m, 4H), 1.74 (m, 8H), 1.57 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7, 135.0, 134.9, 134.0, 129.9, 111.4, 29.9, 29.8, 27.8, 23.8, 23.3, and 23.2 ppm; HR-ESI-MS 285.1850, calculated for $C_{19}H_{25}O_2$ $[M + H]^+$: 285.1850.

*Ethyl β-Hydroxy-β-phenyl-α-(1,2,3,4,5,6,7,8-octahydroanthracen-9-yl)acrylate (**6e**).* It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **e** (1.08 g, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6e** (8.3 mg, 22%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.77 (s, 1H), 7.24−7.10 (m, 5H), 6.79 (s, 1H), 4.25 (qd, J = 7.1, 1.1 Hz, 2H), 2.68 (dt, J = 15.0, 5.0 Hz, 4H), 2.51−2.23 (m, 4H), 1.76 (qd, J = 3.9, 1.7 Hz, 8H), 1.21 (td, J = 7.1, 1.0 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 168.8, 134.9, 134.5, 134.3, 133.2, 129.9, 129.8, 128.0, 127.8, 107.7, 100.9, 60.9, 29.7, 27.5, 23.6, 23.2, and 14.6 ppm; HR-ESI-MS 377.2112, calculated for $C_{25}H_{29}O_3$ $[M + H]^+$: 377.2112.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02916.

Optimization of reaction conditions, ^{1}H and ^{13}C NMR spectra of **4**−**6**, and ^{1}H−^{1}H COSY NMR spectra of **5a** (PDF)

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Notes

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