Carbonyl- and Carboxyl-Substituted Enediynes: Synthesis, Computations, and Thermal Reactivity

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The influence of electron-withdrawing groups (carbonyl and carboxyl) at the alkyne termini on the reactivity of enediynes was investigated by a combination of experimental and computational techniques. While the general chemical reactivity of such enediynes, especially if non-benzannelated, is increased markedly, the thermal cyclization, giving rise to Bergman cyclization products, is changed little relative to the parent enediyne system. This is evident from kinetic measurements and from density functional theory (DFT, BLYP/6-31G* + thermal corrections) computations of the experimental systems which show that the Bergman cyclization barriers slightly (3−4 kcal/mol) increase, in contrast to earlier theoretical predictions. The effect on the endothermicities is large ($\Delta\Delta H_r = 7-12$ kcal/mol). Hence, the increased reactivity of the substituted enediynes is entirely due to nucleophiles or radicals present in solution. This was demonstrated by quantitative experiments with diethylamine and tetramethyl piperidyl oxide (TEMPO) which both give *fulvenes* through 5-*exo*-dig cyclizations.

Introduction

Enediynes are highly potent antitumor-pharmacophores with an activity exceeding that of any other anticancer drug by a factor of up to a 1000-fold.[1] While this serves well to cleave the DNA of tumor cells by Bergman-cycloaromatization of the enediyne moiety to the active species, the *p*-didehydrobenzene biradical (*p*-benzyne), many other cells are also destroyed indiscriminately. Hence, the factors controlling the formation of biradicals from enediynes need to be determined to fine-tune the activity of these highly promising drugs. The chemistry of enediynes and their thermal cyclization reactions were studied intensively over the past decade.[2] The parent reaction is now well understood both experimentally[3] and theoretically.[4]

The relationship between ring strain in the unsaturated system and its reactivity were examined in detail in a number of model studies.[4g,h,5] However, electronic substituent effects on enediyne reactivity has received considerably less attention. While Morokuma et al.[6] theoretically predicted that replacement of the acetylenic hydrogen atoms by generic electron-withdrawing substituents will lower the cyclization barriers, Schreiner and Shaik detail in their recent valence−bond study that only σ-electron-withdrawing substituents will be effective.[7] Some experimental support for these predictions comes from a study by Schmittel et al.[8] who showed an increase of thermal reactivity of 3,4-benzo-1,6-diphenylenediynes by nitro substitution; chlorosubstitution at the vinyl position (noting that chlorine is a weak σ-acceptor but a good π-donor) retards the rate of cyclization owing to π-electron donation.[9] Benzannelation at the site of the double bond, i.e., benzoenediynes, increases the endothermicity of the Bergman-cyclization significantly[10] and even changes the rate-determining step of the overall reaction.[11] Replacement of the benzene ring of aromatic

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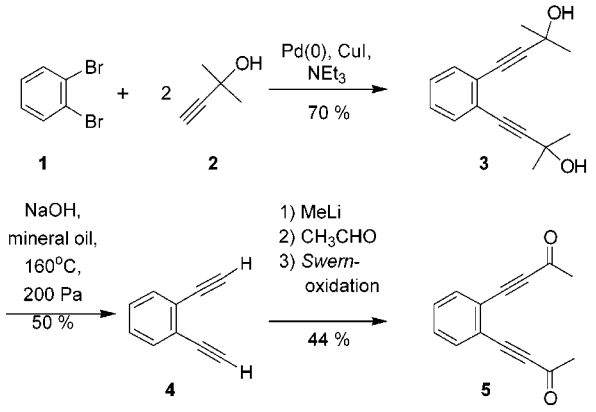
Scheme 1



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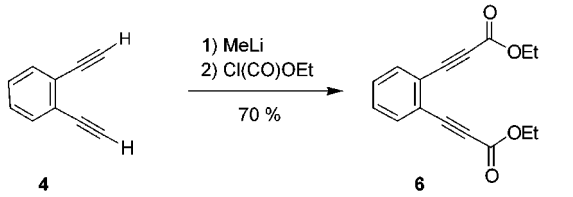

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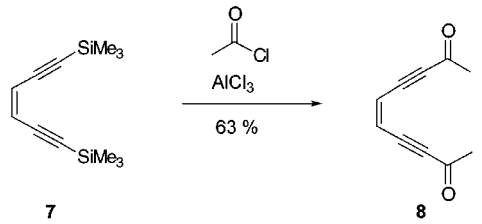
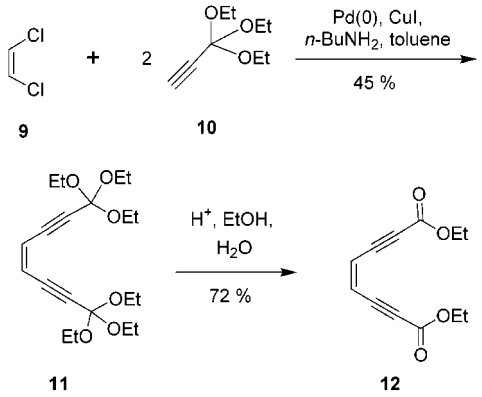


Scheme 4



diynes by quinones/dihydroquinones[12] or uracil heterocycles[13] considerably changes the rates for thermal cyclization which was explained broadly by changes of the electronic contribution to cyclization. To explore the effects of electron-withdrawing substituents, we synthesized enediynes functionalized with two of such groups: methyl carbonyl and ethyl carboxylate. In the present paper we present their synthesis, cyclization reactions, and computations addressing the effect of carbonyl substitution on the reactivity of these enediynes.

Results and Discussion

Synthesis. The title compounds **5** and **6** were synthesized (Schemes 1 and 2) by standard methods starting from 1,2-dibromobenzene (**1**)[14] which was converted into 1,2-diethynylbenzene[15] (**4**) by an improved large-scale procedure using Pd-catalyzed coupling of 1,1-dimethylhydroxy-2-propyne (2-methylbut-3-yn-2-ol, **2**) followed by base-induced retro-Favorskii rearrangement of the resulting suspension in hot mineral oil. Two-fold deprotonation of the terminal alkynes with butyllithium, reaction with ethanal followed by Swern oxidation gave diketone **5**. Reaction of bis-lithiated **4** with chloroethylformate yielded the desired bis-ester **6**.

The non-benzannelated compounds **8** and **12** are accessible in a similar fashion starting from 1,6-bis-lithio hexa-3-ene-1,5-diyne.[16] However, preparation and handling of stock solutions of the volatile hexa-3-ene-1,5-diyne can be avoided by alternative synthetic routes superior for the preparation of **8** and **12** (Schemes 3 and 4). Thus, direct conversion of 1,6-bis(trimethylsilyl)hexa-3-ene-1,5-diyne (**7**) into **8** proceeds in 63% yield by reaction with acetyl chloride in the presence of $AlCl_3$.[17] Compound **12** was obtained by palladium-catalyzed coupling of ethyl propyonate, protected as its *ortho*-ester **10**[18] and subsequent hydrolysis in ethanol. Neat solutions of **8** and **12** are not stable and polymerize within minutes; CCl_4 solutions were used to obtain spectroscopic data. To avoid major side reactions during the thermal cyclization only enediynes **5** and **6** were employed for the thermolyses.

Cyclizations Induced by Nucleophiles and Radicals. The instability of **12** prompted us to investigate its chemical reactivity more closely. Treatment of **12** with diethylamine in dichloromethane at room temperature gave spontaneously a mixture of isomeric fulvenes, as concluded from the NMR spectra of the reaction mixtures; isolation and purification was not possible due to the instability of the products. These most likely form via Michael addition of the amine followed by intramolecular 5-*exo*-dig cyclization. The nonthermally induced formation of fulvene structures from enediynes[19] has been previously reported[20] and similarly rationalized by Whitlock et al. for the addition of bromine to 1,2-bis(phenylethynyl)benzene.[21]

Much to our surprise, a fulvene is also formed when a solution of **12** was heated in the presence of the stable

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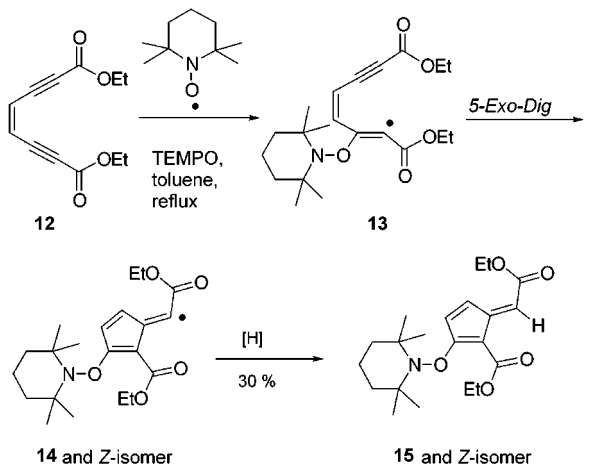
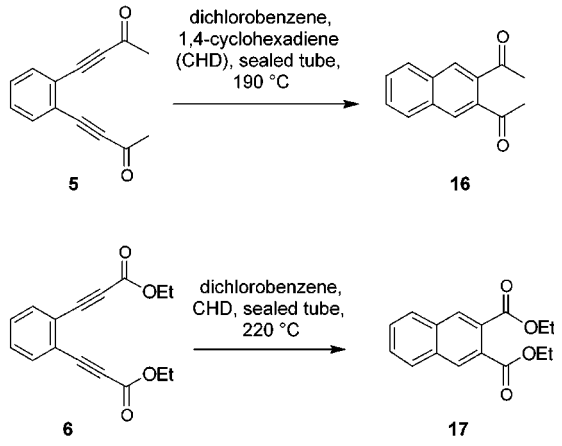
Scheme 5



Scheme 6



radical TEMPO (tetramethyl piperidyl oxide). From the reaction mixture was isolated the TEMPO-substituted fulvene **15** in 25% yield as a mixture of *syn*- and *anti*-isomers (Scheme 5). A possible rationale for the formation of **15** may be the reversible addition of TEMPO to the triple bond followed by rapid 5-*exo*-dig cyclization and trapping of the product by effective hydrogen abstraction.[22]

Thermolyses. Solutions of compound **5** and **6** in dichlorobenzene and 1,4-cyclohexadiene were heated in sealed tubes to 200 °C for several hours. Analysis of the crude reaction mixtures by GC/MS revealed the formation of the major reaction products **16** and **17** in 70 and 90% yield, respectively (Scheme 6). Preparative isolation and spectroscopic characterization showed that both enediynes underwent thermal C^1-C^6 Bergman cyclization. In the case of **5** hydrogenation of one of the triple bonds gave the partially reduced starting material as a reaction side product in ca. 20% yield. In contrast to the thermal cyclization of 1,2-diethynylbenzene (**4**), which under identical conditions gave naphthalene in more than 99% yield as shown by GC/MS, the thermal reactions of **5** and **6** are less clean giving rise to the formation of 10−15 side products, in an overall amount of 10%. Due to the very small amount of material of the individual reaction side products, it was not possible to assign their structures, but GC/MS analysis showed that some of them have the same mass as the trapped Bergman product. These results indicate that carbonyl- and carboxyl-substitution of enediynes mainly undergo Bergman cyclization but substitution opens reaction pathways other than the well-established thermal C^1-C^6 cyclization.

To investigate the thermal reaction of compound **5** and **6** more closely we followed the reaction by kinetic measurements using the previously described HPLC assay.[23] The determined half-life for compound **4** under the employed conditions (162 °C, 100 equiv of cyclohexadiene in dichlorobenzene) of $t_{1/2} = 29$ min is in good agreement with reported values.[3,23] The half-lifes for compounds **5** and **6** under identical conditions, $t_{1/2} = 481$ min and $t_{1/2} = 660$ min, respectively, are longer which shows that the terminal carbonyl- and carboxyl-substitution does not increase the thermal reactivity of the enediyne system.[24] On the contrary, the thermal reactivity is decreased (vide infra).[25]

Computations. To support and elucidate the experimental findings further, we also computed the Bergman and the five-membered ring closures for the parent as well as for the carbonyl- and carboxyl-substituted enediynes (Scheme 7). All calculations were performed with Gaussian98[26] using Becke's pure gradient-corrected exchange functional[27] and the Lee−Yang−Parr nonlocal correlation functional[28] (BLYP) with a 6-31G* basis set which has shown to give good results for the parent reaction and related biradical cyclizations.[4h,i,7,10b,29] A restricted approach was used for geometry optimizations, energy evaluations and frequency analyses of the reactants and transition structures (TS) of the Bergman product, while the biradical products as well as the TS of the five-membered ring closure were computed by an unrestricted broken spin ansatz (BS-UBLYP).[10b]

As indicated in Table 1 the cyclization barriers for the substituted enediynes are slightly higher (3−4 kcal mol^{-1}) than that of the parent system; the endothermicities are raised by ∼8 kcal mol^{-1} for the carbonyl and by ∼9 kcal mol^{-1} for the carboxyl substituent. As shown previously,[10] benzannelation merely affects the barrier heights for Bergman cyclization ($\Delta\Delta H^{\ddagger} < 1$ kcal mol^{-1}) but the biradical products become significantly more endothermic ($\Delta\Delta H_r \sim 6-10$ kcal mol^{-1}). The barriers for substituted benzannelated enediynes are virtually unchanged com-

(22) Our attempts to use other radical initiators, such as AIBN, to induce the cyclization were not successful and gave only polymeric products.

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(24) The corresponding rate constants are $k = 3.9 \times 10^{-4}$ s^{-1} (4), $k = 2.4 \times 10^{-5}$ s^{-1} (5), and $k = 1.7 \times 10^{-5}$ s^{-1} (6).

(25) Differential scanning calorimetry measurements lead to the same conclusion. König, B.; Kröner, J. Unpublished results.

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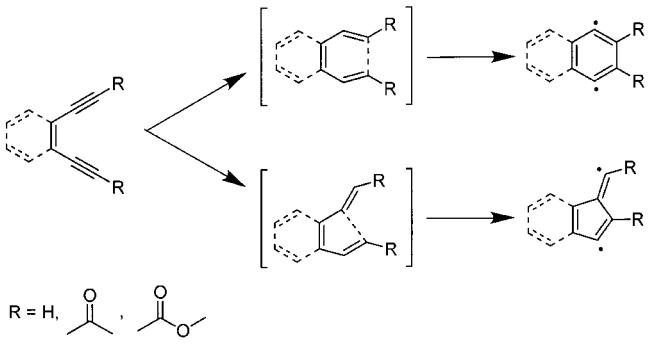
Table 1. BLYP/6-31G* Computed ΔH_{298} Values (kcal mol^{-1}) for the Cyclization of Carbonyl-Substituted Enediynes to Compared to the Parent System

R =	H	CHO	COOMe
enediynes	0.0	0.0	0.0
Bergman TS	24.3[a]	27.0	28.8
Bergman product	7.3[a]	14.8	16.0
fulvene TS	40.1[b]	—[c]	—[c]
fulvene product	40.5	30.7	37.2
benzo-enediynes	0.0	0.0	0.0
Bergman TS	23.6	27.5	28.8
Bergman product	13.2	20.2	21.7
fulvene TS	36.3[b]	—[c]	37.4
fulvene product	36.5	—[c]	34.2

[a] Experimental values[33] at this temperature: barrier = 28.2 kcal mol^{-1}, endothermicity = 8.5 kcal mol^{-1} [b] The relative energy of the TS is lower than that of the product because of the inclusion of ZPVEs, which are quite different for the two states. What this means is that the fulvene product simply would not form because there is no barrier for ring opening of the biradical product. [c] Despite extensive efforts, these structures could not be located due to the large endothermicities of the reactions.

Scheme 7



pared to their respective parent systems. A possible cyclization of enediynes to fulvenes apparently is not viable for systems with electron-withdrawing substituents examined here.[10b] Despite extensive efforts, we were unable to locate the transition structures for this type of cyclization due to an enormous energy increase along this reaction mode. This is emphasized by the vanishing barrier (including thermal and ZPVE corrections) for the parent case (R = H) for both the enediyne and the benzoenediyne (Table 1). Hence, fulvenes cannot form thermally from the substituted enediynes described in the present study.

This computational analysis also demonstrates that the increased chemical reactivity for the carbonyl- and carboxyl-substituted enediynes is not based on an increased thermal sensitivity and must instead be due to the presence of other reagents such as bases or radicals which are able to induce the observed cyclizations.

Conclusions

Enediynes with carbonyl and carboxyl substitutents at the terminal acetylenic carbon atoms were prepared by reaction of the corresponding bis-lithium acetylides with suitable electrophiles or palladium-catalyzed coupling of propynoate-*ortho*-esters with 1,2-dihalides and subsequent hydrolysis. While enediynes **8** and **12** are not stable as neat compounds due to their high tendency to polymerize, the benzannelated enediynes **5** and **6** were isolated in pure form. Thermolysis of **5** and **6** in the presence of a hydrogen donor yielded the hydrogen-trapped products of a C^1—C^6 cyclization (Bergman reaction). The thermal reactivities of **5** and **6** are similar to the parent system, but are overall even more unfavorable. Hence, in agreement with our earlier theoretical predictions, π-acceptors do not increase the thermal reactivity of enediynes. The σ-acceptor ability of the subsituents examined here apparently is outbalanced by the unfavorable π-effects. A study concerning σ-acceptors is currently underway in our laboratories. The major effect of carbonyl- and carboxyl-substitution is an increased tendency of enediynes to undergo reactions other than the Bergman cyclization.

Experimental Section

General. Melting points were taken on a hot-plate microscope apparatus and are not corrected. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in [D]-chloroform solutions unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. CC means column chromatography; PE means petrol ether with a boiling range of 60−70 °C.

1,2-Diethynylbenzene (4). A solution of **3**[30] (19.2 g, 80 mmol) in 2 mL of CH_2Cl_2 was added to 60 mL of mineral oil and 2.5 g of finely grounded KOH. The reaction mixture was heated in vacuo (200 Pa) to 160 °C, and the crude product was collected in the cooled receiver. CC (PE) gave **4** (5.00 g) in 50% yield.[15]

1,2-Bis(3-hydroxy-1-butynyl)benzene. To a solution of **4** (511 mg, 4 mmol) in 20 mL of dry THF was added at −78 °C MeLi (15 mL, 1.4 M, 21 mmol), and the mixture was stirred for 10 min. Freshly distilled ethanal (7 mL, 5.5 g, 125 mmol) was slowly added, and the reaction mixture was allowed to warm to room temperature. Aqueous NH_4Cl solution (30 mL) was added, the reaction mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were dried over Na_2SO_4. CC (PE:Et_2O = 1:1; R_f = 0.11) of the crude product gave 460 mg (54%) of 1,2-bis(3-hydroxy-1-butynyl)-benzene, as a colorless oil. ^{1}H NMR: δ 7.31−7.26 (m, 2H), 6.80−6.76 (m, 2H), 4.77−4.71 (m, 2H), 1.50−1.48 (m, 6H); ^{13}C NMR δ 24.4 (+), 24.5 (+), 58.9 (+), 58.9 (+), 83.0 (C_{quat}), 96.6 (C_{quat}), 126.3 (C_{quat}), 127.8 (+), 128.0 (+), 128.3 (+), 131.4 (+); IR (KBr): ν = 3330 cm^{-1}, 2982, 3063, 1480, 1444, 1371, 1330, 759; UV/vis (CH_3CN): λ_{max} (lg ϵ) = 192 nm (4.055), 226 (4.494), 232 (4.648), 248 (4.010), 254 (4.068), 260 (4.121), 272 (4.069), 280 (3.319), 284 (3.064); MS (70 eV): *m*/*z* (%): 127 (100), 170 (48), 214 (2) [M$^+$]. Anal. Calcd for $C_{14}H_{14}O_2$ (214.1): C 78.47; H 6.59. Found: C 78.57; H 6.61.

1,2-Bis(1-butyn-3-onyl)benzene (5). To a solution of DMSO (313 mg, 4 mmol, 0.29 mL) in CH_2Cl_2 (5 mL) was added at −78 °C oxalyl chloride (381 mg, 3 mmol, 0.26 mL), and the mixture was stirred for 15 min. 1,2-Bis(3-hydroxy-1-butynyl)-benzene (150 mg, 0.7 mmol) dissolved in CH_2Cl_2 (5 mL) was added, the reaction mixture was stirred for 15 min at −78 °C, triethylamine (810 mg, 8 mmol, 1.1 mL) was added, and the mixture was allowed to warm to room temperature. Diethyl ether (30 mL) and water (10 mL) were added, the mixture was extracted with diethyl ether (3 × 30 mL), and the combined organic phases were dried over $NaSO_4$ and evaporated in a vacuum. The crude product was purified by CC (PE:Et_2O = 2:1; R_f = 0.4) to yield 120 mg (82%) of **5**, as a yellow solid, mp 35 °C. ^{1}H NMR (200 MHz, C_6D_6) δ 2.09 (s, 6H), 6.68 (dd, ^3J = 5.7 Hz, ^4J = 3.3 Hz, 2H), 7.07 (dd, ^3J = 5.8 Hz, ^4J = 3.3 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ 32.4 (+), 86.1 (C_{quat}), 92.7 (C_{quat}), 124.5 (C_{quat}), 130.2 (+), 133.4 (+), 183.0 (C_{quat}). IR (KBr): ν = 3450 cm^{-1}, 2208, 2171, 1671, 1650, 1359, 1293. UV/vIS (CH_3CN): λ_{max} (lg ϵ) = 198 nm (4.239), 228 (4.180), 240 (4.259), 244 (4.278), 250 (4.286), 256 (4.404), 292 (4.114), 304 (4.035), 320 (3.574), 330 (3.002). MS (EI, 70 eV) *m*/*z* (%): 167 (7) [M-$COCH_3^+$], 195 (100) [M-CH_3^+], 210 (72) [M$^+$].

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HRMS: $C_{14}H_{10}O_2$: calcd 210.0680; found 210.0678. Anal. Calcd for $C_{14}H_{10}O_2$ (210.1): C 79.98; H 4.79. Found: C 79.99; H 4.78.

3-(2-(Ethoxycarbonylethynyl)phenyl)prop-2-ynoic Acid Ethyl Ester (6). To a solution of **4** (500 mg, 3.96 mmol) in 20 mL of THF was slowly added *n*-BuLi (5.3 mL, 7.9 mmol, 1.5 mol/L) at −35 °C. After stirring for 20 min, a solution of ethyl formate (1.5 mL, 15.9 mmol) in 5 mL of THF was added dropwise, and the reaction mixture was stirred for additional 30 min at this temperature, allowed to warm to room temperature, and poured into 150 mL of aqueous NH_4Cl solution. The aqueous phase was extracted four times with Et_2O (40 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in a vacuum. The crude product was purified by CC on silica (PE:Et_2O 3:1) to yield 740 mg (70%) of **6** (R_f = 0.38) as a colorless solid; mp = 46 °C. ^{1}H NMR δ 1.34 (t, 6H, CH_3, ^3J = 7.12 Hz); 4.30 (q, 4H, CH_2, ^3J = 7.12 Hz); 7.43 (2H, CH); 7.60 (2H, CH). ^{13}C NMR δ 14.0 (+), 62.2 (−), 82.7 (C_{quat}), 84.7 (C_{quat}), 123.6 (C_{quat}), 130.2 (+), 133.4 (+); 153.6 (C_{quat}). IR (KBr): ν = 2941 cm^{-1}, 2213, 1705, 1194. UV (CH_3CN): λ_{max} (lg ϵ) = 196 nm (4.311), 228 (sh, 4.391), 234 (4.473), 246 (4.462). MS (EI) (70 eV), *m*/*z* (%): 270 (22) [M$^+$], 225 (36) [M − $OCH_2CH_3^+$], 197 (24) [M − $COOCH_2CH_3^+$], 126 (100). Anal. Calcd for $C_{16}H_{14}O_4$ (270.28): C 71.10 H 5.22. Found: C 71.11 H 5.26.

Dec-4-enedi-3,6-yne-2,9-dione (8). To a solution of 1,6-bis-trimethylsilyl-3-ene-1,5-diyne (**7**) (0.22 g, 1 mmol) in 15 mL of anhydrous CH_2Cl_2 was added acetyl chloride (0.39 g, 5.00 mmol) at −20 °C. $AlCl_3$ (132 mg, 1 mmol) was added, and the reaction mixture was stirred at −20 °C for 2 h. The solvent was removed in vacuo, and the crude product was purified by CC on silica (R_f = 0.39; PE: Et_2O 1:1) to give **8** (63%, 0.10 g), as a rapidly decomposing oil; ^{1}H NMR (400 MHz, benzene-d_6) δ 2.25 (s, 6H), 6.03 (s, 2H); MS (EI) (70 eV), *m*/*z* (%) 160 (57) [M$^+$], 145 (100) [M − CH_3^+].

1,2-Bis(3,3,3-triethoxyprop-1-ynyl)ethene (11). To a solution of $Pd(PPh_3)_4$ (831 mg, 0.72 mmol), CuI (344 mg, 1.81 mmol), 3,3,3-triethoxypropyne[18] (4.66 g, 27.08 mmol), and 8 mL (81.2 mmol) of *n*-$BuNH_2$ in 80 mL of toluene at 0 °C under dinitrogen was added 1,2-dichloroethene (0.68 mL, 9 mmol) dropwisely. The ice bath was removed, and the dark reaction mixture was allowed to warm to room temperature and stirred for additional 15 h. The reaction mixture was filtered through a plug of Celite, the solvent was removed in vacuo, and the residue was purified over silica (Et_2O with 1% NEt_3). The first fraction (R_f = 0.8) gave 1.49 g (45%) of **11** as a light yellow oil. ^{1}H NMR (200 MHz, acetone-d_6) δ 1.16 (18H, CH_3, t, ^3J = 7.1 Hz), 3.67 (12H, CH_2, q, ^3J = 7.1 Hz), 5.99 (2H, CH, s). ^{13}C NMR (50 MHz, acetone-d_6) δ 15.2 (+), 59.5 (−), 80.8 (C_{quat}), 92.6 (C_{quat}), 110.0 (C_{quat}), 121.0 (+). IR (neat): ν = 2933 cm^{-1}, 2224, 1391. UV (CH_3OH): λ_{max} (lg ϵ) = 192 nm (3.764), 260 (4.051), 272 (4.000), 234 (sh, 3.870). MS (EI) (70 eV), *m*/*z* (%): 323 (20) [M − OEt^+], 249 (88) [M − $(OEt)_2$ − Et^+], 221 (44) [M − $C(OEt)_3^+$], 175 (100) [M − $C(OEt)_3$ − OEt^+], 147 (62) [$C(OEt)_3^+$].

Oct-4-ene-2,6-diynedoic Acid Diethyl Ester (12). Compound **11** (100 mg, 0.29 mmol) was dissolved in 50 mL of EtOH/H_2O (1:1), and two drops of TFA were added. The reaction mixture was stirred for 1 h at room temperature, extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was chromatographed on silica (PE:Et_2O 3:1; R_f = 0.23) to yield 46 mg (72%) of **12** as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6) δ 0.79 (t, 6H, CH_3, ^3J = 7.3 Hz), 3.79 (q, 4H, CH_2, ^3J = 7.3 Hz), 5.20 (s, 2H, CH). ^{13}C NMR (100 MHz, C_6D_6) δ 13.7 (+), 62.0 (−), 80.8 (C_{quat}), 89.5 (C_{quat}), 121.4 (+), 153.1 (C_{quat}).

***E*/*Z*-Fulvene 15.** A mixture of **12** (100 mg, 0.45 mmol) and TEMPO (702 mg, 4.5 mmol) in 80 mL of degassed toluene was refluxed under N_2 for 5 h, the solvent was removed in vacuo, and the crude product was purified by CC (PE/Et_2O 2:1) on silica to yield 52 mg (30%) of **17** (R_f = 0.35) as a red oil. ^{1}H NMR δ 1.03 (s, 6H), 1.28 (m, 12H), 1.58 (m, 6H), 4.14 (q, ^3J = 7.3 Hz, 2H); 4.23 (q, ^3J = 7.3 Hz, 2H); 5.85 (d, J^3 = 12.6 Hz, 1H); 6.25 (m, 1H); 7.81 (d, ^3J = 12.5 Hz, 1H). ^{13}C NMR δ 14.0 (+), 14.3 (+), 16.9 (−), 21.9 (+), 31.8 (+), 39.5 (−), 59.8 (−), 60.8 (C_{quat}), 61.79 (−), 84.9 (C_{quat}), 87.2 (C_{quat}), 99.8 (+), 108.9 (+), 132.8 (+); 153.8 (C_{quat}), 166.9 (C_{quat}), 167.6, (C_{quat}). IR (neat): ν = 2935 cm^{-1}, 2204, 1708. UV (CH_3OH): λ_{max} (lg ϵ) = 206 nm (3.991), 282 (4.049), 306 (4.164), 374 (2.747). MS (EI) (70 eV), *m*/*z* (%): 377 (14) [M$^+$], 362 (100) [M − CH_3], 348 (44) [M − CH_2CH_3], 332 (6) [M − OCH_2CH_3]. $C_{21}H_{31}NO_5$ (377.48): HRMS: calcd 377.2202; found 377.2194.

2,3-Diacetylnaphthalene (16). A solution of **5** (50 mg, 0.24 mmol) and 1 mL of 1,4-cyclohexadiene in 5 mL of dry toluene was heated in a sealed tube to 190 °C for 3 h. The solvent was removed in vacuo, and the crude reaction mixture was analyzed by GC/MS. The major reaction product **16**, and the partially hydrogenated starting material was obtained as inseparable 6:1 mixtures by CC (PE:Et_2O, 2:1) in 80% isolated yield. The spectroscopic data of **16** are identical to the reported values.[31] The structure of the partially hydrogenated starting material was assigned from spectroscopic data and mass spectrometry. Due to the small amount of material and the very similar polarity compared with **16**, it was not possible to obtain this reaction side product in analytically pure form.

2,3-Diethoxycarbonylnaphthalene (17). A solution of **6** (50 mg, 0.2 mmol) and 1 mL of 1,4-cyclohexadiene in 5 mL of dry toluene was heated in a sealed tube to 220 °C for 3 h. The solvent was removed in vacuo, and the crude reaction mixture was analyzed by GC/MS. The major reaction product **17** was isolated by CC (PE:Et_2O, 2:1) in 90% yield. The spectroscopic data are identical with the reported values.[32]

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Supporting Information Available: Copies of proton, carbon, and DEPT NMR spectra of compounds **6**, **8**, **11**, **12**, and **15**. All absolute energies and Cartesian coordinates for computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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