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Enediynes in 11-Membered Rings. Synthesis, Structure, and Reactivity of Highly Strained but Unusually Stable Macrocycles

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The synthesis of two new aromatic cyclic enediynes **1a** and **1b** using a double Wittig condensation, followed by bromination and di-dehydrobromination, is reported. The structures were determined using X-ray crystallography. The observed C_1-C_6 distances of the enediyne moiety in the oxygen- and sulfur-containing eleven-membered rings are quite short with 3.44 and 3.50 Å, respectively, indicating the highly strained nature of these compounds. Isodesmic calculations at the B3LYP/6-31G* level of theory indicate a strain energy of 8.2 and 5.8 kcal/mol, respectively. Despite the highly strained ring system, the compounds were found to be stable under thermal, photochemical, and electron-transfer conditions. Using BLYP/6-311+G**/BLYP/6-31G* calculations, the origin of this unusual stability was traced to the high energy of the 1,4 benzyne diradicals formed via Bergman cyclization. For the radical cation, both the C_1-C_6 and the C_1-C_5 cyclization mode previously reported for acyclic analogues of **1** were found to be energetically prohibitive.

Introduction

The chemistry of compounds containing an enediyne moiety has attracted considerable attention during the last two decades. After the discovery that the Bergman cyclization of this moiety is responsible for the biological activity of enediyne antitumor antibiotics, a large effort was devoted to the synthesis and study of the properties of these compounds.[1] More recently, the Bergman reaction and related cyclizations have been studied using a variety of experimental[2] and theoretical[3] methods. Finally, the chemistry of cyclic aromatic enediynes has sparked considerable interest due to the unusual structures and properties of these dehydroannulenes.[4]

One of the key issues in the chemistry of cyclic enediynes is the interplay of strain and structure. Nicolaou proposed that the reactivity of cyclic enediynes in the Bergman cyclization depends on the distance of the carbon atoms C_1 and C_6 of the enediyne system. If this distance is larger than ~3.31 Å, the molecule is relatively stable. If the C_1-C_6 distance is between 3.2 and 3.31 Å, the enediyne easily undergoes cyclization at room temperature, while compounds with C_1-C_6 distances of less than 3.2 Å should undergo spontaneous cyclization even at lower temperatures.[5] Snyder[6] and Magnus[7] on the other hand argued that the cyclization reaction is controlled by the difference in strain between the enediyne and the 1,4 benzyne. Additionally, stabilization of either the enediyne or the biradical by conjugation and/or substitution by heteroatoms can play a role.[8] The interplay of several of these factors was analyzed in more detail in a computational study by Schreiner.[9] The interplay of the C_1-C_6 distance with the stabilization of the enediyne unit by conjugation can then lead to significantly different reactivity.

In general, the Bergman cyclization of enediynes can be induced either thermally[10] or photochemically.[11] Although the activation of the enediyne moiety by two-electron transfer (ET) is well described,[12] the induction of the Bergman cyclization by single electron transfer (SET) is more controversial. In a number of computational studies from our group it was found that the radical cation intermediates are structurally similar, but energetically more favorable than the corresponding biradical intermediates involved in the stepwise pathway of formally pericyclic reactions.[13] On the basis of these

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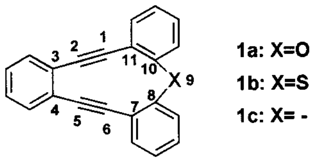

Figure 1. Cyclic aromatic enediynes **1a**−**c** studied.

findings, we hypothesized that the Bergman cyclization could be catalyzed by SET through stabilization of the intermediate. Indeed, Sankararaman reported in 1996 the C_1-C_5 cyclization of 1,2-bis(phenylethynyl)benzene under different ET conditions to form the corresponding indenes.[14] This unusual mode of cyclization was attributed to electronic state symmetry, although it is conceivable that the closer C_1-C_5 distance could also be responsible. The classification of this reaction as ET induced was disputed by Schmittel and co-workers,[15] who obtained the same products by treatment of 1,2-bis(phenylethynyl)benzene with trifluoroacetic acid. It is well-known[16] that the amminium salts used as thermal ET catalysts contain traces of acid, which has led to a misassignment of cationic, acid-catalyzed reactions as SET catalyzed.[17] The reactions induced by irradiation in the presence of triaryl pyrylium salts, where this problem does not occur, were described as direct photochemical reactions.[15a] However, it was shown subsequently that the direct photochemical reaction of 1,2-bis(phenylethynyl)benzene yields a different product.[18]

Surprisingly, the amount of accurate structural information of simple enediynes that can be used to address these questions is relatively small in comparison with the number of potentially important factors. Although there are numerous structures of cyclic enediynes reported in the Cambridge Structural Database, these fall into relatively few structural classes with the vast majority being derived from the dynemycin and calicheamicyn frameworks. In particular, there are only a few X-ray structures with an enediyne moiety in conjugation with double bonds or aromatic rings or with an enediyne moiety as part of a heterocycle available. Even though a number of these compounds have been studied by other spectroscopic methods,[4,5,8] they do not provide direct insights into the structural effects of the conjugation.

We decided therefore to synthesize compounds **1a**−**c** (Figure 1) that could be used to address these questions, elucidate their structure, and study their reactivity. Our rationale was that by modification of the linker X, the geometry of the enediyne moiety could be easily manipulated in the critical range of C_1-C_6 distances. At the same time, we hoped that even compounds with a relatively small C_1-C_6 distance would be stabilized by conjugation of the triple bond with the phenyl groups as well as by incorporation of the ene moiety in the aromatic system.[19] The effects of the structural modifications on thermal-, photochemical-, and ET-induced reactivity can then be studied for these systems.

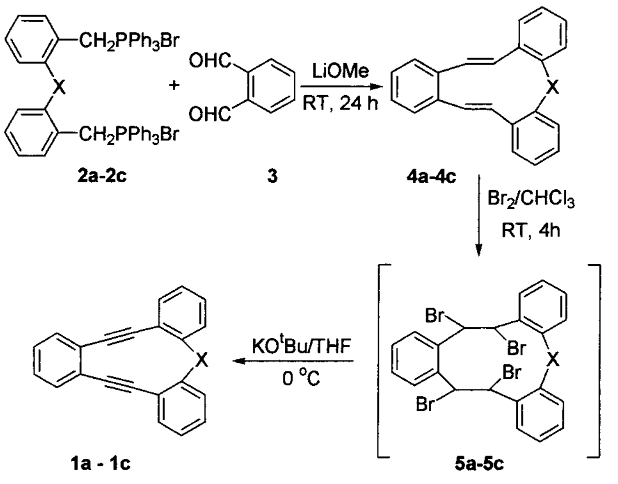

Figure 2. Synthesis of **1a** and **1b**.

Results and Discussion

Synthesis. The enediynes **1a** and **1b** were synthesized by a double-Wittig ring closing reaction using 1,2-benzenedicarboxaldehyde **3** under high dilution conditions in analogy to previously reported procedures.[20] The necessary Wittig salts **2a**−**c** can be conveniently prepared in reasonable yields by copper-catalyzed coupling of *ortho*-substituted bromo- or iodoaryls, followed by functional group manipulation on the side chain and formation of the Wittig salts using standard methods (Figure 2).[21] Bromination of the resulting dienes **4a** and **4b** gave the tetrabromides **5a** and **5b**, which were immediately subjected to elimination with potassium *tert*-butoxide to give the desired enediynes **1a** and **1b**.

Unfortunately, we were unable to obtain the corresponding 10-membered ring **1c** following this procedure. Even though the tetrabromide **5c** could be obtained by bromination of the previously described **4c**[22] at −78 °C, this relatively unstable compound could not be purified and was only characterized by mass spectrometry. Several attempted elimination reactions under low-temperature conditions were not successful and led to compound **6** as the only product (Figure 3). This is likely to be due to the very high strain in **1c**, as discussed below.

The Structure of the Enediynes. Single crystals of **1a** and **1b** suitable for an X-ray structure analysis were

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[22] **6b** is also obtained by bromination of **4c** at room temperature: Grohmann, K.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, *89*, 7119−7121. Although we cannot exclude the possibility that **6** was formed through this pathway, the mass spectroscopic evidence for **5c** and the absence of **5c** or other partial elimination products derived from it makes this possibility unlikely.

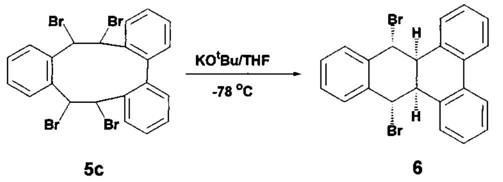

Figure 3. Formation of **6**.

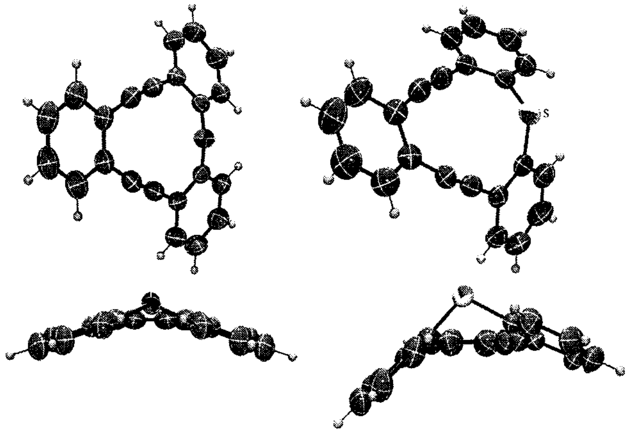

Figure 4. X-ray structures of **1a** (left) and **1b** (right).

Table 1. Selected Experimental and Calculated Geometric Parameters of 1a and 1b

	1a		1b		1c
parameter	X-ray	calcd^{a,b}	X-ray^{b}	calcd^{a,b}	calcd^{a,b}
C_1-C_2 [Å]	1.193	1.200	1.180	1.216	1.221
C_2-C_3 [Å]	1.432	1.406	1.446	1.421	1.418
C_1-C_{11} [Å]	1.426	1.404	1.439	1.422	1.420
C_1-C_6 [Å]	3.442	3.624	3.504	3.543	2.922
C_1-C_5 [Å]	3.287	3.420	3.336	3.367	3.063
θ $C_1-C_2-C_3$ [deg]	169.6	170.5	168.9	169.8	157.4
strain energy [kcal/mol]	- - -	8.2	- - -	5.8	16.7

[a] B3LYP/6-31G*. [b] Numerical average over the two nonequivalent parts of the molecule.

obtained from chloroform at 25 °C. **1b** crystallized in the monoclinic space group $P2_1/c$, and **1a** in the orthorhombic space group P_{nam}. The unit cell of **1b** shows a high degree of asymmetry, resulting from dense crystal stacking; while the unit cell the **1a** on the other hand shows the presence of a mirror plane. Figure 4 shows the crystal structure of **1a** and **1b**. Selected geometric parameters from the X-ray analyses and from B3LYP/6-31G* calculations are summarized in Table 1. It can be noted that the B3LYP/6-31G* calculations reproduce the experimentally observed geometry of **1a** and **1b** reasonably well, even though the nonbonded C_1-C_6 distance is significantly overestimated in **1a**.

The strain in the 11-membered ring leads, as expected, to a quite short C_1-C_6 distance of 3.44 and 3.50 Å in **1a** and **1b**, respectively. This distance is significantly shorter than the value of 3.66 Å observed in the analogous cyclodeca-3-ene-1,5-diyne[5] and only slightly longer than the 3.37 Å obtained for the bicyclic calicheamicyn structure.[7a] There is significant conjugation between the triple bonds and the phenyl rings on either side as indicated by the short formal single bonds of 1.43−1.45 Å. The distortion of the sp-hybridized carbons from linearity is ~10°, particularly pronounced at C_2 and C_5. The strain energies of the ring systems were calculated using the isodesmic reaction shown in Figure 5 at the B3LYP/6-31G* level of theory and gave of 8.2 and 5.8 kcal/mol for **1a** and **1b**, respectively.

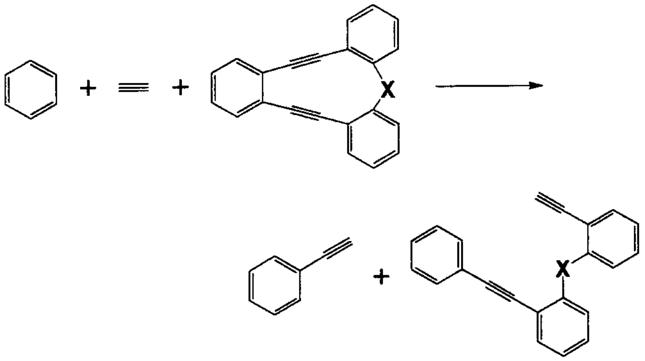

Figure 5. Isodesmic Reaction for the evaluation of the strain energy of **1a**−**c**.

These trends are even stronger in the 10-membered ring **1c**, which, with a calculated strain energy of 16.7 kcal/mol, is extremely unstable. The C_1-C_6 distance should only be 2.92 Å, well below the critical range proposed by Nicolaou.[5] It is noteworthy that in only **1c** is the C_1-C_6 distance shorter than the C_1-C_5 distance. In larger rings such as **1a** or **1b** as well as in open systems such as 1,2-bis(phenylethynyl)benzene, the C_1-C_5 distance is smaller, which could possibly be the origin of the 1−5 cyclization mode reported for the ET-induced reaction by Sanakararaman and co-workers.[14]

The distortion of the sp-hybridized carbons is also apparent in the ^{13}C spectra of **1a** and **1b**. According to Wilcox and co-workers,[20] the difference of the predicted and measured ^{13}C shifts of the acetylenic carbons or the comparison with unstrained *o*-diacetylenic substituted benzenes is a very sensitive measurement for the strain within the enediynes. The more the C_{sp} bonds bend away from the original 180° sp-hybridization angle, the more downfield shifted the resonance of the acetylenic carbons occur. In agreement with this hypothesis, and close to the values obtained for the highly strained enediyne studied by Wilcox, the chemical shift of C_1 and C_2 in **1a** and **1b** is shifted downfield (relative to as 1,2-bis(phenylethynyl)benzene) by ~5 and ~2 ppm, respectively.

Reactivity Studies. Given the strained nature of the 11-membered rings and the small C_1-C_6 distances in **1a** and **1b**, we expected that the cyclization would be easily induced by either thermal or electron-transfer methods, even though there are some reports of stable strained cyclic enediynes in the literature.[5,8a,12] We were therefore surprised to find that refluxing of **1a** or **1b** in toluene for 3 days only led to quantitative recovery of starting material. We also found **1a** and **1b** to be unreactive under ET conditions. Treatment of solutions of **1a** or **1b** with 1,4-cyclohexadiene in methylene chloride or acetonitrile with tris(4-bromophenyl)amminium hexachlorostibnate **7** in the presence of 2,6-di-*tert*-butylpyridine did not lead to a reaction.[16a] Similarly, irradiation of these solutions in the presence of 2 mol % trianisyl pyrylium tetrafluoroborate **8** did not lead to any reaction, even though the disappearance of the characteristic blue color of **7** and the weaker fluorescence of **8** after addition of **1a** and **1b** to the solutions indicated that an electron-transfer took place.[23] This nonreactivity under ET conditions despite

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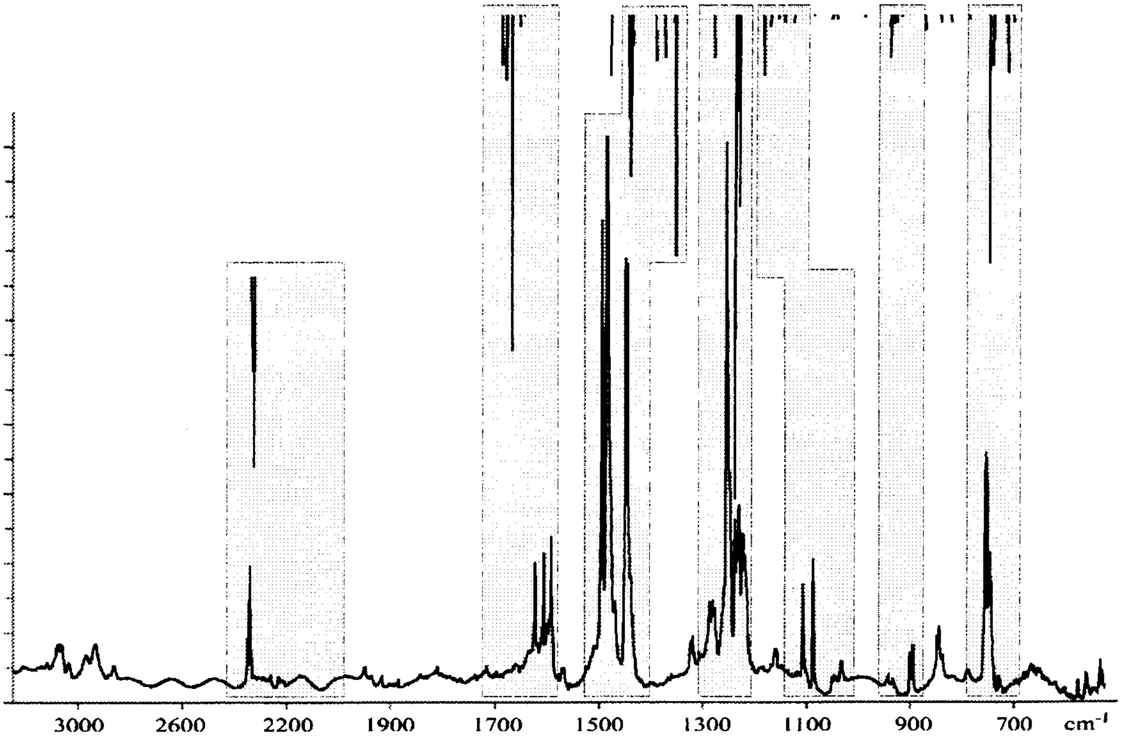

Figure 6. Experimental (bottom trace) and B3LYP/6-31G* calculated (top trace) IR spectrum of **1a**.

the higher strain and shorter C_1–C_6 and C_1–C_5 distance is in direct contrast to the results in the literature.[14]

The irradiation of **1a** in solution with a 450 W medium-pressure mercury lamp in the presence of a hydrogen atom donor also did not lead to product formation. We therefore investigated the photoreactivity of **1a** in an argon matrix at 10 K[24] in the hope that the intermediate diradical could be observed even when the final cyclization product is not obtained. The lower trace in Figure 6 shows the high-resolution IR spectrum of **1a** in an argon matrix after more than 12 h irradiation. The IR spectrum of **1a** was calculated at the B3LYP/6-31G* level of theory (Figure 6, upper trace) and compared with the spectrum. The location as well as the intensities of the IR bands were in quite good agreement and independently confirmed the correct assignment of the compound isolated in argon as the enediyne **1a**. However, this implies that **1a** is stable even under prolonged high-intensity irradiation. In addition, comparison of the spectrum with the one from authentic **1a** showed that no new absorptions were formed during irradiation. It can thus be concluded that **1a** does not undergo photochemical cyclization.

In an effort to understand this surprising nonreactivity, we investigated the thermochemistry of the cyclization. It was shown previously that for these calculations, the Hartree–Fock portion in hybrid DFT calculations introduces a significant error for the biradical species. Hybrid DFT methods are thus not suitable for the computational studies of the Bergman cyclization. Instead, pure gradient-corrected DFT methods such as the BLYP/611+G**//BLYP/6-31G* method were found to be computationally efficient tools that gave results in close agreement with the coupled cluster reference calculations. Even in these cases, the calculation of the transition structures remains difficult.[3d,9] Although the reaction rates will of course be determined by the relative energies of the corresponding transition structures, these will be even higher in energy than the intermediates. By calculating the relative energies of the intermediates, we can thus evaluate the feasibility of the reaction compared to the parent Bergman cyclization.[3,9] We therefore focused on the energy differences between the enediynes and biradicals and radical cations formed. Table 2 summarizes our results for the Bergman cyclization of **1a**–**c** and the corresponding radical cations formed by ET.

Table 2. Calculated[a] Thermochemistry of the Cyclization of 1a–c

starting material	**9**	**9**$^{\bullet+}$	**10**$^{\bullet+}$
1a	32.4	37.5	40.6
1b	34.9	33.6	32.9
1c	9.1	10.3	25.0

[a] BLYP/6-311+G**//BLYP/6-31G* in kcal/mol.

The calculated reaction energies for the formation of the biradicals **9a** and **9b** via Bergman cyclization of **1a** and **1b** are substantially higher than the reaction enthalpy of 8.5 kcal/mol obtained for the parent system.[25] The formation of the seven-membered ring in the cyclization step increases the olefinic strain[26] and destabilizes the **9a**,**b**, while **1a** and **1b** are at the same time stabilized by conjugation of the triple bond to the aromatic system.[27] The formation of an additional aromatic system in **9c** offsets this effect, decreasing the reaction energy to 9.1 kcal/mol.

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(27) For a more detailed discussion of the effects of benzannelation on the Bergman cyclization, compare refs 8 and 19.

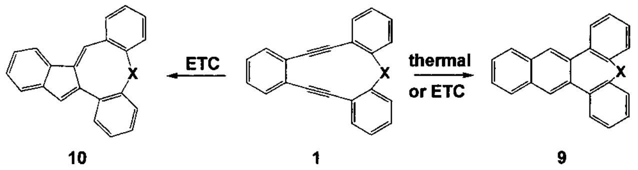

Figure 7. Possible Products of the thermal and ETC cyclization of **1a**−**c**.

Ungvc like the formally pericyclic reactions studied previously,[13] oxidation to the radical cation does not stabilize the diyl radical cation relative to the neutral, biradical version of the Bergman cyclization. Within the error than can be reasonably expected for the BLYP/611+G**//BLYP/6-31G* method, ET has little or no effect on the thermochemistry of the cyclization reactions. Therefore, the cyclization will be slow relative to competing reactions such as back ET, leading to the recovery of the starting materials. The origin of the relatively high energy of the 1,4-benzyne radical cations is likely to be the localization of the radical cation in the p-orbitals that are perpendicular to the aromatic rings, thus preventing conjugation with the aromatic system. The products **10a**$^{\bullet+}$ and **10b**$^{\bullet+}$ of C_1−C_5 cyclization of **1a**$^{\bullet+}$ and **1b**$^{\bullet+}$, which could occur in analogy to the cyclization of the enediyne radical cations reported previously,[14] are with a calculated relative energy of 40.6 and 32.7 kcal/mol, respectively, even less stable due to the unfavorable bond angles in the eight-membered ring. The cyclization of **1c**$^{\bullet+}$ to the tribenzoazulene **10c**$^{\bullet+}$ is due to the lack of aromatic stabilization, 14.7 kcal/mol less favorable than the corresponding formation of **9c**$^{\bullet+}$ through C_1−C_6 cyclization (Figure 7).

Conclusions

The hydrocarbon compounds **1a** and **1b**, which contain a enediyne as part of a 11-membered heterocycle in conjugation with multiple aromatic systems, are highly strained as evident by the distortions in their experimental and computed structures as well as their ^{13}C NMR spectra and their computed strain energies. Nevertheless, they do not undergo C_1−C_6 cyclization to form a 1,4-benzyne biradical through a Bergman cyclization under thermal, photochemical, or ET conditions. The analogous 10-membered ring **1c**, which is predicted to undergo thermal cyclization due to the formation of an aromatic system, could not be synthesized via the route used here due to the extremely strained nature of this system. The C_1−C_5 cyclization mode reported for the ET-induced cyclization of an acyclic analogue of **1**[14] was also not observed, raising additional doubts about the generality of this cyclization mode.[15a]

Experimental Section

General Remarks. All starting materials were purchased in the highest grade commercially available. NMR spectra were recorded on a Varian Unity+ 300 instrument. X-ray analysis was performed on a ENRAF Nonius CAD4 diffractometer with a fine-focus Mo-target X-ray tube (λ = 0.71073 Å). Data refinement was performed using Full-matrix least-squares on F^2 using SHELXTL.[28] The experimental setup for the matrix photolysis experiments has been described previously.[24]

Synthesis of 4a and 4b. Wittig salts (4.64 mmol) **2a** and **2b**, prepared by known procedures,[21] were dissolved in absolute methanol (500 mL) containing an excess of freshly prepared lithium methoxide and stirred under argon at room temperature 30 min. A solution of 1,2-benzenedicarboxaldehyde **3** (0.68 g, 5.1 mmol) in dry diethyl ether (120 mL) was added using a peristaltic pump within 24 h. The reaction mixture was evaporated and remaining material completely dissolved in diethyl ether. Silica gel (1.5 g) was added and the solvent evaporated until complete dryness. The dry crude reaction mixtures on silica gel were eluted through a 30 × 300 mm silica (230−400 mesh; SiliCycle) column with hexanes as eluent. The second band containing the dienes was collected to give a yield of 5.1% and 2.8% of 9-oxotribenzo[*c*,*g*,*j*]cycloundeca-1(*E*),3,5(*Z*)7,10-pentaene **4a** and 9-oxotribenzo[*c*,*g*,*j*]cycloundeca-1(*E*/*Z*),3,5(*Z*/*E*)7,10-pentaene **4b**, respectively.

4a: y = 70 mg, 5.1%; T_m = 153−155 °C; IR (KBr): $\tilde{\nu}$ = 3052.1 (w), 2995.0 (w), 2928.0 (w), 2851.7 (w), 1481.5 (s), 1440.5 (s), 1383.2 (w), 1233.1 (m), 1215.8 (s), 1187.8 (m), 1105.3 (m), 1034 (w), 992.6 (m), 896.9 (w), 841.5 (w), 792.4 (w), 758.6 (vs), 576.8 (w), 496.7 (w), 482.0 (w), 454.1 (w) cm^{-1}; ^{1}H NMR (300 MHz; CDCl$_3$): δ = 6.23 (d, 1H, ^3J = 16.8 Hz), 6.48 (dd, 1H, ^3J = 8 Hz, ^4J = 0.9 Hz), 6.60−6.72 (m, 2H), 6.88−6.96 (m, 2H), 7.12−7.44 (m, 10H); ^{13}C NMR (300 MHz; CDCl$_3$): δ = 157.25, 156.88, 136.69, 136.53, 136.20, 133.49, 131.28, 131.06, 130.99, 130.79, 130.71, 129.21, 128.35, 128.10, 127.28, 127.01, 124.69, 124.53, 123.79, 122.93, 122.67, 116.53, MS: m/z (%) = 296 (55, M$^+$), 295 (65), 281 (10), 276 (10), 265 (14), 252 (12), 239 (8), 219 (12), 205 (20), 189 (10), 178 (100), 152 (10), 138 (7), 126 (10), 113 (6). HRMS: calcd 296.1201, found 296.1143 (measured difference 5.8 mmu)

4b was obtained as an isomeric mixture (cis-cis, cis-trans, and trans-trans) which made the complete NMR analysis difficult. Yield: 40 mg; T_m = 119−121 °C; IR (KBr): $\bar{\nu}$ = 3054.9 (m), 3009.1 (m), 2961.3 (m), 2918.6 (m), 2854.8 (w), 1731.5 (m), 1586.3 (w), 1464.1 (m), 1435.9 (m), 1261.5 (m), 1198.0 (m), 1119.1 (s), 1031.2 (m), 800.6 (m), 757.4 (vs), 721.5 (s), 694.8 (m) cm^{-1}; MS: m/z (%) = 312 (52, M+), 277 (25), 263 (10), 252 (15), 234 (55), 221 (58), 197 (100), 189 (33), 178 (73), 152 (48), 134 (41), 115 (52), 102 (12); HRMS: calcd 312.0973, found 312.0978 (measured difference 0.5 mmu).

Synthesis of enediynes 1a and 1b. The diene **4a** or **4b** (0.1 mmol) was dissolved in chloroform (5 mL) and treated with 1.1 equiv of neat bromine under stirring at room temperature. After stirring for 4 h, the solvent was evaporated and the crude tetrabromide **5a** or **5b** dissolved in tetrahydrofuran (10 mL) without further purification. The solution was cooled with an ice bath, and solid KO^{t}Bu was added under argon. The reaction progress was monitored via TLC. After completion of the reaction, the mixture was chromatographed on a 30 × 300 mm silica (230−400 mesh; SiliCycle) column with hexanes. The third band was collected and evaporated under reduced pressure to give the of 9-oxotribenzo[*c*,*g*,*j*]cycloundeca-3,7,10-triene-1,5-diyne **1a** and 9-thiotribenzo[*c*,*g*,*j*]cycloundeca-3,7,-10-triene-1,5-diyne **1b** as light-yellow solids in 27% and 13.5% yield, respectively.

1a: yield: 8 mg, T_m >180 (dec); IR (KBr): $\bar{\nu}$ = 3053.9 (w), 2919.0 (m), 2851.5 (w), 2208.8 (w), 1587.3 (w), 1558.3 (w), 1477.0 (vs), 1440.7 (s), 1384.9 (m), 1249.1 (s), 1225.8 (m), 1158.4 (w), 1105.4 (m), 941.5 (w), 898.1 (w), 840.3 (w), 744.5 (vs), 459.6 (m), cm^{-1}; ^{1}H NMR (300 MHz; CDCl$_3$): δ = 7.13 (dt, 2H, ^3J = 10 Hz, ^4J = 0.9 Hz), 7.28−7.39 (m, 4H), 7.48−7.55 (m, 4H), 7.61 (dd, 2H, ^3J = 8 Hz, ^4J = 0.9 Hz); ^{13}C NMR (300 MHz; CDCl$_3$): δ = 159.35, 132.52, 129.79, 129.71, 128.38, 128.36, 124.34, 119.43, 117.39, 94.48, 93.03; MS: m/z (%) = 292 (100, M+), 263 (42), 237 (6), 131 (15), 118 (7); HRMS: calcd 292.0888, found 292.0929 (measured difference 4.1 mmu)

1b: yield: 4 mg; T_m >185 °C (dec); IR (KBr): $\nu\sim$ = 3057.0 (w), 2926.1 (m), 2855.9 (w), 2208.7 (w), 1726.5 (m), 1585.5 (w), 1478.9 (s), 1466.1 (m), 1263.9 (m), 1220.2 (w), 1121.8 (w), 1072.3 (w), 1033.7 (w), 949.5 (w), 871.6 (w), 818.5 (w), 754.1 (s) cm^{-1}; ^{1}H NMR (300 MHz; CDCl$_3$): δ = 7.3−7.4 (m, 6H), 7.58−7.64 (m, 4H), 8.0−8.6 (m, 2H); ^{13}C NMR (300 MHz; CDCl$_3$): δ = 139.85, 138.10, 132.53, 130.57, 130.53, 130.4,

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[28] SHELXTL V.5 Siemens Industrial Automation, Inc. 1994.

129.61, 129.14, 128.57, 96.08, 93.53.MS: *m*/*z* (%) = 308 (100, M+), 276 (18), 261 (12), 237 (7), 212 (10), 184 (10), 178 (8), 153 (19), 146 (15), 141 (9), 130 (6), 106 (6); HRMS: calcd 308.0660, found 308.0651 (measured difference 0.9 mmu).

Computational Studies. All computations were performed using the GAUSSIAN98 series of programs.[29] All geometries were fully optimized and subjected to harmonic frequency analysis at the level of theory indicated. Bond distances are given in angstroms, and energies are zero-point corrected and are given in kcal/mol.

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Supporting Information Available: Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 156243 (**1a**), 156245 (**1b**), and 156244 (**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk]. Crystallographic information for **1a**, **1b**, and **6**, ^{1}H and ^{13}C spectra of **1a** and **1b**, an experimental procedure for the synthesis of **6**, and BLYP/6-311+G**//BLYP/6-31G* calculated coordinates, energies, and zero-point energies of the enediynes **1a**−**c** and the cyclization products **9a**−**c** and **10a**−**c** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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