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Bis(enediyne) Macrocycles: Synthesis, Reactivity, and Structural Analysis

Heather S. Blanchette, Stephen C. Brand, Hitoshi Naruse, Timothy J. R. Weakley and Michael M. Haley*

Department of Chemistry, University of Oregon, Eugene, OR 97403-1253, USA

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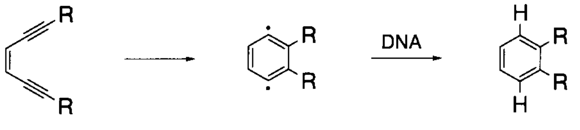
Abstract—We describe below the syntheses of five macrocycles possessing two enediyne warheads, along with the structural and thermal analyses of these bis(enediyne) compounds. The solid-state packing of compound **6** suggests the possibility for the molecule to undergo a topochemical diacetylene polymerization. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

In recent years the family of enediyne antibiotics has been the subject of intense interest. A significant body of research has elucidated much of their chemical and biological activity as anti-tumor agents.[1] It is widely recognized that the DNA-cleaving ability of these compounds is actuated by the enediyne functional domain which undergoes either a Bergman cyclization (Scheme 1) or Myers cyclization upon activation to form a diradical species to inflict DNA scissions.[2] Anti-tumor, cytotoxic properties evolve from the two radicals generated from the enediyne precursor. In order to enhance the number of cytotoxic double-stranded scissions on duplex DNA, we pursued structures capable of generating four radicals (either simultaneously or sequentially) and thus demonstrating greater anti-tumor potential.

A search of the literature revealed a variety of molecules capable of forming multiple diradicals (Fig. 1). These structures can be broken down into three fundamental motifs: (1) molecules possessing two 'independent' enediynes, e.g. **1**;[3,4]; (2) molecules based on tetraethynylethene, e.g. **2**;[5] and (3) molecules containing a dec-5-en-1,3,7,9-tetrayne moiety, e.g. **3**.[6] Although the thermal chemistry of each class has been investigated, compound **4** was the only system where products arising from Bergman chemistry were detected.[6] With this problem in mind, we embarked on the preparation of systems having two independent enediyne moieties. We report herein our work on the synthesis, structural analysis, and thermal behavior of bis(enediyne) macrocycles **5–8**, as well as work on related system **9** (Fig. 2).[7,8]



Scheme 1. Bergman cyclization of a typical enediyne moiety.

Macrocycle Synthesis

Bis(enediyne)s **5** and **6** were prepared in a straightforward

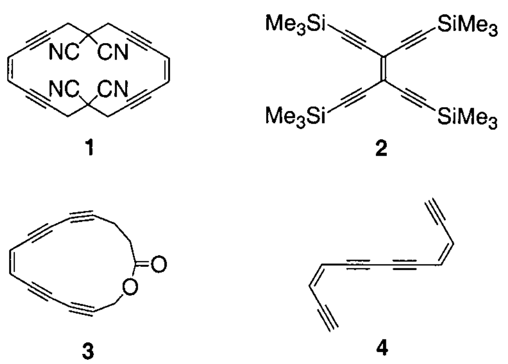


Figure 1. Examples of different bis(enediyne) motifs.

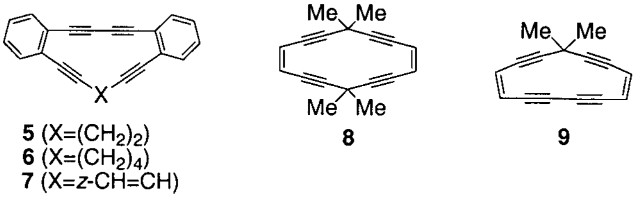


Figure 2. Target macrocycles **5–9**.

Keywords: diynes; macrocycles; polyynes; annulenes.

* Corresponding author. Tel.: +541-346-0456; fax: +541-346-0487; e-mail: haley@oregon.uoregon.edu

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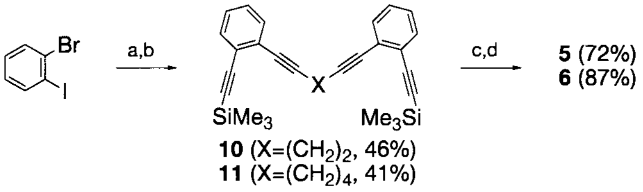
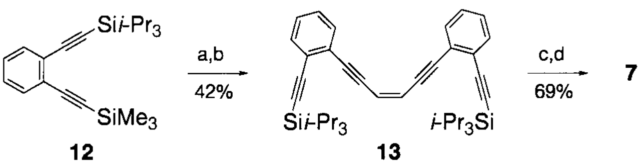


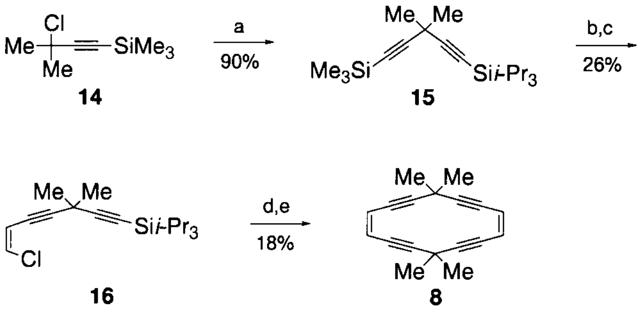
Scheme 2. Synthesis of macrocycles **5** and **6**. (a) 1,5-hexadiyne (for **10**) or 1,7-octadiyne (for **11**), $PdCl_2(PPh_3)_2$, CuI, Et_3N, piperidine, 40–45°C; (b) $Me_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, piperidine, 150°C; (c) K_2CO_3, MeOH, Et_2O; (d) CuCl, O_2, pyridine, DBU, 40–45°C.

manner (Scheme 2). Two equivalents of 1-bromo-2-iodobenzene were attached to a diyne tether via established Pd-catalyzed cross-coupling chemistry.[9] Subsequent addition of two equivalents of trimethylsilylacetylene furnished tetraynes **10** and **11**. The terminal alkynes were desilylated with K_2CO_3 in MeOH and immediately subjected to Cu-mediated oxidative coupling conditions[10] to provide the desired macrocycles **5** and **6** as off-white solids in 33 and 36% overall yield, respectively.

Owing to the reported instability of *cis*-hex-3-en-1,5-diyne,[11] compound **7** was assembled in an alternative fashion (Scheme 3). Selective desilylation of **12**[12] with K_2CO_3 in MeOH and subsequent Pd-catalyzed cross-coupling with *cis*-1,2-dichloroethene afforded monoene **13**. Desilylation with Bu_4NF and intramolecular coupling with copper salts gave macrocycle **7** as a pale yellow solid in 29% overall yield. Unlike **5** and **6**, the central ring in **7** is a fully conjugated dehydrobenzo[14]annulene derivative.[13] Upon closure, the molecule exhibited a marked downfield shift of the alkene proton resonance (δ=6.70) compared to the chemical shift of the analogous resonance in **13** (δ=6.11). The presence of the diatropic ring current in the 14-membered macrocycle is also evident in the arene proton resonances of **7**, as these are shifted downfield ca. 0.3–0.5 ppm compared to the analogous resonances in **5**.



Scheme 3. Synthesis of macrocycle **7**. (a) K_2CO_3, MeOH, Et_2O; (b) *cis*-1,2-dichloroethene, $Pd(PPh_3)_4$, CuI, THF, $BuNH_2$; (c) Bu_4NF, EtOH, THF; (d) $Cu(OAc)_2$, CuCl, pyridine.



Scheme 4. Synthesis of macrocycle **8**. (a) *i*-$Pr_3SiC{\equiv}C{-}MgBr$, CuCl, THF; (b) MeOH, THF, NaOH; (c) *cis*-1,2-dichloroethene, $Pd(PPh_3)_4$, CuI, $BuNH_2$; (d) Bu_4NF, EtOH, THF; (e) $Pd(PPh_3)_4$, CuI, $BuNH_2$

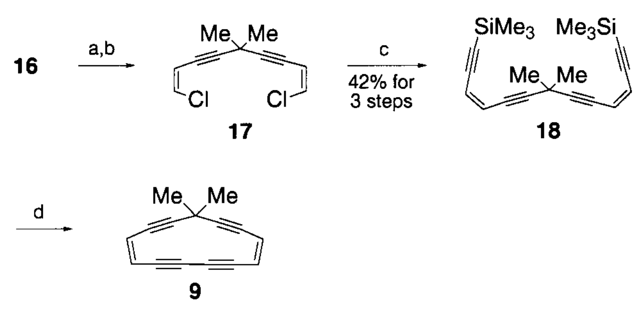
Construction of macrocycle **8** is illustrated in Scheme 4. Treatment of **14**[14] with the Grignard reagent prepared from ethylmagnesium bromide and triisopropylsilylacetylene afforded bis-protected pentadiyne **15**.[15] Selective desilylation using a catalytic amount of NaOH in 1:1 THF:MeOH followed by cross-coupling with excess *cis*-1,2-dichloroethene gave compound **16**. Removal of the triisopropylsilyl group with Bu_4NF furnished the deprotected terminal alkyne. The final cyclodimerization was accomplished by slow addition of deprotected **16** to a solution of $Pd(PPh_3)_4$, CuI, and $BuNH_2$. Macrocycle **8** was separated from oligomeric material by preparative thin layer chromatography and isolated in ca. 5% overall yield.

The preparation of macrocycle **9**, despite being a slight variation of **8**, proved to be a troublesome goal. Dichloride **17** was prepared by desilylating **16** and reacting the unprotected species with a second equivalent of *cis*-dichloroethene (Scheme 5). Addition of two equivalents of trimethylsilylacetylene provided tetrayne **18**. In situ protiodesilylation/oxidative dimerization[16] furnished a yellow solid that rapidly decomposed to dark brown film. The ^1H NMR and UV/Vis spectra of the crude material showed evidence for the formation of macrocycle **9**. Nevertheless, attempts at purification led only to recovery of polymeric materials.

Structural Analyses

Extensive studies on simple model enediynes have suggested that the distance between the distal alkynyl carbons (c···d distance) provides an approximate measure of a molecule's ability to undergo Bergman chemistry.[1,17] Experiments have shown that ideal c···d distances fall between 3.15 and 3.31 Å for cyclizations to occur at physiological temperature. Smaller values are characteristic of enediynes which are unstable at room temperature, while larger values suggest heating is needed to cyclize the molecules. Accordingly, molecular modeling of macrocycles **5**–**9** was employed to provide calculated c···d distances; results utilizing semi-empirical methods are shown in Table 1.[18]

To support the calculations, we sought to obtain X-ray



Scheme 5. Synthesis of macrocycle **9**. (a) Bu_4NF, EtOH, THF; (b) *cis*-1,2-dichloroethene, $Pd(PPh_3)_4$, CuI, Et_3N; (c) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, Et_3N; (d) $Cu(OAc)_2$, CuCl, K_2CO_3, pyridine, MeOH.

Table 1. Calculated and experimental c···d distances for bis(enediynes) **1**, **5**–**9** (Å)

Molecule	AM1	PM3	MNDO	Experimental
1	4.366	4.214	4.466	4.27[a]
5	3.792	3.826	3.878	
6	4.009	4.019	4.088	3.93
7	3.868	3.916	3.929	3.84
8	4.345	4.305	4.470	4.21
9	3.799	3.795	3.916	

[a] Ref. 2a.

structures of our macrocycles. Fortunately, three of the four stable systems provided crystals suitable for analysis. The molecular structures of **6**–**8** are illustrated in Fig. 3; selected bond lengths and bond angles are given in Table 2. As is often the case, the experimentally determined c···d distances of **6**–**8** are shorter than the values calculated at semi-empirical levels, and are well outside the range of 3.15–3.31 Å. Whereas macrocycles **6** and **8** are essentially strain-free systems, **7** displayed a moderate degree of bending in the diacetylenic linkage, with the C–C triple bonds deviating up to ca. 10° from linearity.

The molecular packing of the three macrocycles varies significantly. Annulene **7** stacks in columns where the diacetylenic linkage lies below the alkene moiety of next macrocycle. This type of staggered stacking precludes the possibility of a topochemical diacetylene polymerization, as was observed in the corresponding tribenzo[14]annulene

Table 2. Selected bond lengths (Å) and bond angles (°) for bis(enediyne)s **6**–**8**

	Macrocycle **6**		
C1–C1′	1.387(6)	C1′–C1–C2	177.5(2)
C1–C2	1.192(4)	C1–C2–C3	177.1(4)
C2–C3	1.428(4)	C2–C3–C8	119.1(3)
C3–C8	1.407(4)	C3–C8–C9	120.8(3)
C8–C9	1.429(5)	C8–C9–C10	176.4(4)
C9–C10	1.181(4)	C9–C10–C11	177.5(4)
C10–C11	1.465(5)	C10–C11–C12	114.1(3)
C11–C12	1.532(4)		
	Macrocycle **7**[a]		
C1–C22	1.374(3)	C2–C1–C22	172.3(2)
C1–C2	1.196(3)	C1–C2–C3	170.2(2)
C2–C3	1.424(3)	C2–C3–C8	118.2(2)
C3–C8	1.404(3)	C3–C8–C9	121.3(2)
C8–C9	1.433(3)	C8–C9–C10	179.0(2)
C9–C10	1.196(3)	C9–C10–C11	171.9(2)
C10–C11	1.415(3)	C10–C11–C12	128.8(2)
C11–C12	1.346(3)		
	Macrocycle **8**[b]		
C1–C1′	1.333(4)	C1′–C1–C2	123.9(1)
C1–C2	1.418(3)	C1–C2–C3	178.6(2)
C2–C3	1.188(3)	C2–C3–C4	178.3(2)
C3–C4	1.478(3)	C3–C4–C3′	109.9(2)

[a] Average values of both halves of the molecule.

[b] One of two independent yet essentially identical molecules.

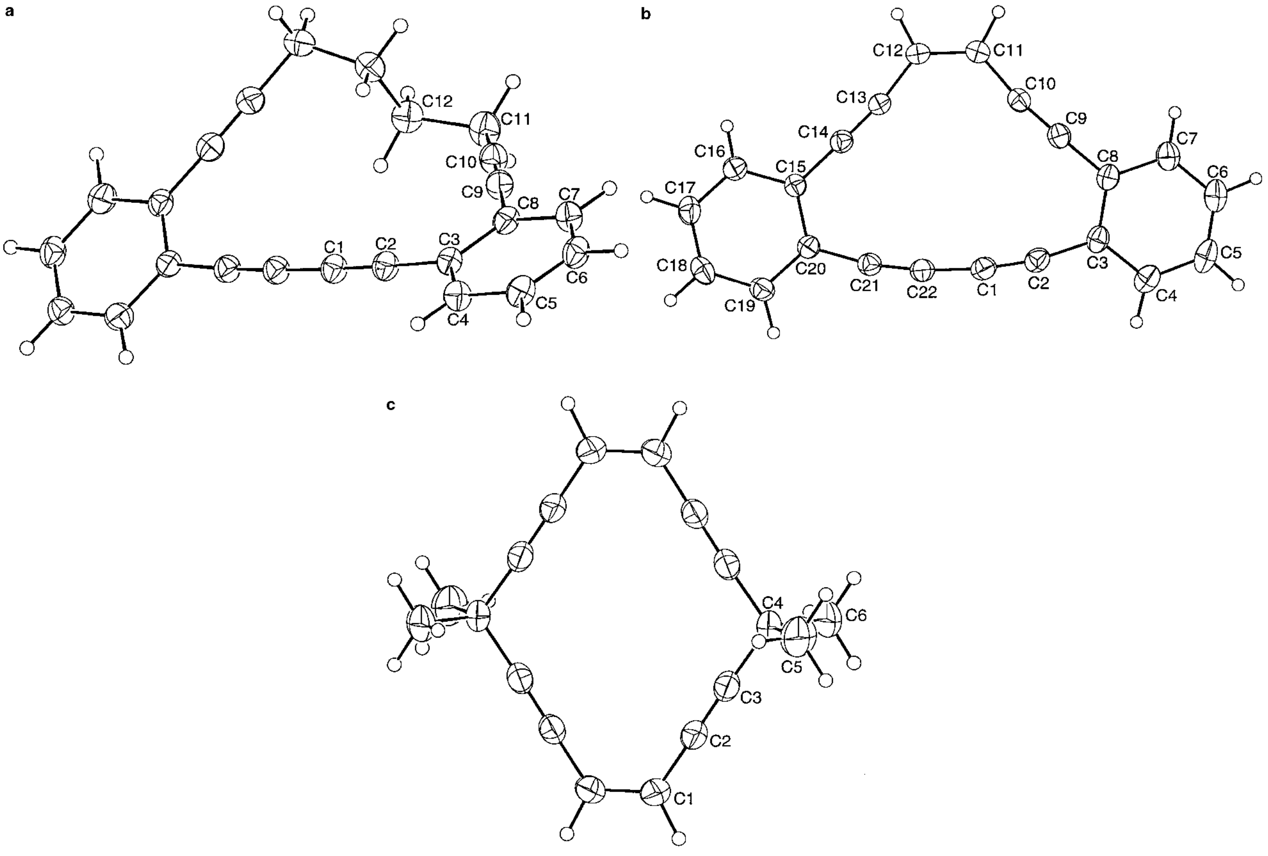


Figure 3. X-Ray crystal structures of molecules **6**–**8**. Ellipsoids are shown at the 30% probability level.

analog.[19] In contrast, the columns of **6** juxtapose the diyne units in the proper orientation required for a 1,4-polymerization. The diyne polymerization parameters for **6** are d=5.09 Å, γ=44°, and S_1=3.62 Å, which are quite close to the optimal range for such monomers (d·5 Å, γ·45°).[20] The presence of the *gem*-dimethyl groups causes compound **8** to pack loosely in the unusual C2/m space group. The only close C–C contacts are between the methyl group of one molecule and the distal alkyne carbon of another.

Thermal Studies

Given the relatively large magnitude of the c···d distances for our systems, it was expected that elevated temperatures would be required to induce Bergman chemistry; this indeed proved to be the case. Differential scanning calorimetry (DSC) showed that macrocycles **5–8** underwent irreversible exothermic reactions between 175 and 225°C, with **5** and **8** possessing secondary irreversible exothermic processes between 300 and 350°C. Only macrocycle **6** melted prior to decomposition, which unfortunately excludes the possibility of a thermally-induced diacetylene polymerization. A reasonable explanation for the broad exothermic reactions in the DSC scans is thermally-induced cyclization of the enediyne units with subsequent polymerization of the bulk material.[21] In contrast, the solution chemistry of our molecules proved to be very complex. Numerous attempts were made to isolate and characterize discreet, soluble materials. Small-scale reactions, however, suggested the formation of numerous products in approximately equal amounts. For example, reaction of **6** only occurred in 1,4-cyclohexadiene solution at a temperature greater than 225°C and produced an inseparable mixture of products. Although benzannelation to the enediyne core is known to retard cycloaromatization,[22] we were surprised by the high stability of our macrocycles. Based on these results, further cyclization experiments are not planned.

Conclusions

In our pursuit of bis(enediyne) macrocycles capable of undergoing multiple Bergman cyclization reactions, we prepared carbocycles **5–8**. Although these compounds exhibited exothermic activity indicative of Bergman cyclization followed by bulk polymerization, the higher temperatures required to initiate the cyclizations were consistent with the larger c···d distances reflected in the corresponding crystal structures. Efforts to reduce the macrocycle ring size by one carbon in the synthesis of analog **9** were unfruitful because of the instability of the resultant product. We are currently exploring the chemical transformation of **5** and **6** into dehydrobenzoannulene derivatives, as well as the polymerization behavior of the macrocycles; these results will be presented in due course.

Experimental

General

^{1}H and ^{13}C NMR spectra were acquired on a GE QE-300 instrument (^{1}H: 300.13 MHz, ^{1}C: 75.5 MHz) and a Varian Unity Inova (^{1}H: 299.95 MHz, ^{1}C: 75.43 MHz) using $CDCl_3$ as solvent unless otherwise noted. Chemical shifts are reported in ppm, with the residual protonated solvent serving as an internal standard ($CDCl_3$=7.26, CD_2Cl_2=5.32). ^{13}C NMR spectra are referenced to the central resonance of either $CDCl_3$ (77.00) or CD_2Cl_2 (54.00). Coupling constants are expressed in hertz. IR spectra were recorded using a Nicolet Magna 550 FT-IR spectrometer. UV–Vis spectra were obtained on a Cary 14 or an HP 8453 UV–Vis spectrophotometer. Melting points were measured with a MelTemp II apparatus using a digital thermometer and are uncorrected.

Commercially available reagents were used as received unless otherwise noted. THF and Et_2O were dried by distillation under N_2 from sodium and benzophenone. $BuNH_2$, Et_3N, piperidine, and pyridine were dried by distillation from calcium hydride. Solvents used in palladium mediated coupling reactions were deoxygenated prior to use by 30–45 min of Ar bubbling. Other reactions were carried out in an inert atmosphere (dry N_2 or Ar) when necessary. Flash chromatographic purification of crude products was accomplished using Whatman 230–400 mesh silica gel. Preparative chromatography was performed on a Chromatotron using 1 or 2 mm silica gel plates (EM Science 60 PF_{254} containing gypsum) or on TLC plates (Analtech Silica Gel GF, 20 cm×20 cm×1 mm).

1,6-Bis(2′-(trimethylsilylethynyl)phenyl)-1,5-hexadiyne (10). To a degassed solution of 1-bromo-2-iodobenzene (3.73 g, 13.2 mmol) and $PdCl_2(PPh_3)_2$ (0.109 g, 0.155 mmol) in Et_3N (44 mL) and piperidine (11 mL) was added CuI (0.058 g, 0.305 mmol) and 1,5-hexadiyne (0.469 g, 6.0 mmol). The reaction was stirred under Ar for 18 h at 40–45°C. After cooling, the mixture was diluted with Et_2O, filtered through Celite, and washed sequentially with 10% HCl solution, saturated aqueous $NaHCO_3$, and brine. The ethereal solution was then dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5:1 hexanes/CH_2Cl_2, R_f=0.32) afforded the desired bis(bromophenyl)diyne as a clear, colorless oil (2.05 g, 88%) which solidified upon prolonged storage at −20°C. ^{1}H NMR (CD_2Cl_2) δ 7.57 (dd, J=8.1, 1.4 Hz, 2H), 7.47 (dd, J=7.5, 1.8 Hz, 2H), 7.26 (td, J=7.7, 1.4 Hz, 2H), 7.15 (td, J=7.7, 1.8 Hz, 2H), 2.82 (s, 4H); ^{13}C NMR δ 133.42, 132.27, 128.91, 126.86, 125.66, 125.50, 93.25, 80.38, 19.86; IR (neat) ν=3069, 3054, 2226 cm^{-1}; UV–Vis (CH_2Cl_2) $\lambda_{max}(\epsilon)$ 247 (24,700), 259 (28,400), 283 (980), 292 (660) nm; HRMS calcd for $C_{18}H_{12}^{79}Br^{81}Br$: 387.9363, found: 387.9365.

To a degassed solution of bis(bromophenyl)hexadiyne (1.92 g, 5.0 mmol), $PdCl_2(PPh_3)_2$ (0.213 g, 0.30 mmol), and CuI (0.084 g, 0.44 mmol) in Et_3N (30 mL) in a glass pressure tube was added trimethylsilylacetylene (4.2 mL, 29.7 mmol) in piperidine (6 mL). The tube was sealed under Ar and stirred for 3 d at 150°C. The cooled reaction mixture was diluted with Et_2O (100 mL), filtered through Celite, and washed with chilled 10% HCl solution, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated. Repetitive chromatography (flash column, 4:1 hexanes/CH_2Cl_2, R_f=0.25; preparative

TLC, 3:1 cyclohexane/benzene) afforded **10** as a light orange oil (1.04 g, 52%). ^{1}H NMR (CD_2Cl_2) δ 7.47–7.42 (m, 4H), 7.28–7.23 (m, 4H), 2.84 (s, 4H), 0.29 (s, 18H); ^{13}C NMR (CD_2Cl_2) δ 132.60, 132.52, 128.83, 128.17, 126.87, 126.00, 104.09, 98.75, 93.25, 80.60, 20.60, 0.32; IR (neat) ν=3069, 2156 cm^{-1}; MS (EI, 70 eV) 422 (5, M$^+$), 407 (10, M$^+$−Me), 349 (49, M$^+$−SiMe$_3$), 333 (54), 319 (38), 73 (100, SiMe$_3$); HRMS calcd for $C_{28}H_{30}Si_2$: 422.1886, found: 422.1868.

1,8-Bis(2′-(trimethylsilylethynyl)phenyl)-1,7-octadiyne (11). Compound **11** was prepared in an analogous fashion to **10**. Thus, use of 1,7-octadiyne (0.637 g, 6.0 mmol) in the above procedure furnished the corresponding bis(bromophenyl)diyne as a colorless, crystalline solid (1.93 g, 77%). R_f=0.31 (5:1 hexanes/CH_2Cl_2); ^{1}H NMR (CD_2Cl_2) δ 7.57 (dd, *J*=8.1, 1.3 Hz, 2H), 7.44 (dd, *J*=7.5, 1.7 Hz, 2H), 7.25 (td, *J*=7.7, 1.3 Hz, 2H), 7.14 (td, *J*=7.8, 1.7 Hz, 2H), 2.59–2.52 (m, 4H), 1.89–1.84 (m, 4H); ^{13}C NMR δ 133.18, 132.15, 128.59, 126.77, 125.89, 125.41, 94.86, 79.74, 27.45, 19.03; IR (KBr) ν=3061, 2233 cm^{-1}; UV-Vis (CH_2Cl_2) λ_{max} (ϵ) 247 (26,400), 258 (26,900), 283 (760) nm; HRMS calcd for $C_{20}H_{16}Br_2$: 413.9619, found: 413.9626.

Bis(bromophenyl)octadiyne (2.04 g, 5.0 mmol) was treated as above. Chromatography over silica gel (hexanes/CH_2Cl_2, 20 to 35% CH_2Cl_2) gave **11** as an orange oil (1.19 g, 53%). R_f=0.44 (4:1 hexanes/CH_2Cl_2); ^{1}H NMR (CD_2Cl_2) δ 7.45–7.38 (m, 2H), 7.28–7.19 (m, 4H), 2.55 (br t, *J*=6.3 Hz, 4H), 1.85 (m, 4H), 0.26 (s, 18H); ^{13}C NMR (CD_2Cl_2) δ 132.60, 132.39, 128.75, 127.83, 127.22, 125.87, 104.20, 98.47, 94.88, 79.89, 28.55, 19.64, 0.24; IR (neat) ν=3062, 3024, 2231, 2159 cm^{-1}; UV–Vis (CH_2Cl_2) λ_{max} (ϵ) 240 (35,300), 265 (24,000), 279 (22,300), 297 (2,100), 309 (1,600) nm; MS (EI, 70 eV) 450 (69, M$^+$), 449 (70), 435 (17, M$^+$−Me), 422 (22), 407 (58), 73 (100, SiMe$_3$); HRMS calcd for $C_{30}H_{34}Si_2$: 450.2199, found: 450.2207.

1,2,7,8-Dibenzocyclotetradeca-3,5,9,13-tetrayne (5). To a solution of **10** (0.405 g, 0.96 mmol) in a mixture of MeOH (15 mL) and Et_2O (5 mL) was added K_2CO_3 (0.144 g, 1.04 mmol). After stirring for 3 h, the reaction mixture was poured into Et_2O (30 mL) and then washed with H_2O and brine. The organic layer was dried ($MgSO_4$) and concentrated to produce a brown oil which was immediately used in the next step. ^{1}H NMR δ 7.47 (d, *J*=7.5 Hz, 2H), 7.41 (d, *J*=7.6 Hz, 2H), 7.28–7.18 (m, 4H), 3.26 (s, 2H), 2.83 (s, 4H).

To a solution of deprotected **10** in pyridine (80 mL) at 40°C was added CuCl (0.101 g, 1.02 mmol), DBU (165 μL, 1.10 mmol), and additional pyridine (10 mL) to complete the transfer. O_2 was bubbled through the mixture for 90 min while maintaining the temperature of the reaction at 40–45°C. After an additional 30 min of warming, the mixture was concentrated (ca. 90%) in vacuo. To the slurry was added a solution of KCN (54 mg, 0.82 mmol) and NH_4Cl (210 mg, 3.91 mmol) in water (2 mL) and the mixture was stirred vigorously for 30 min. The ether phase was washed with 2 M HCl solution, dried ($MgSO_4$), and concentrated. Purification by preparative TLC (2:1 cyclohexane/CH_2Cl_2, R_f=0.41), then by radial chromatography (hexanes) gave **5** as a white crystalline solid (179 mg, 72%). Mp=140°C (dec); ^{1}H NMR δ 7.43 (dd, *J*=7.5, 1.2 Hz, 2H), 7.36 (dd, *J*=7.5, 1.2 Hz, 2H), 7.32–7.20 (m, 4H), 2.86 (s, 4H); ^{13}C NMR (CD_2Cl_2) δ 132.45, 130.49, 130.06, 129.61, 128.25, 124.83, 94.37, 85.45, 79.83, 79.67, 19.78; IR (KBr) ν=3057, 2208 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 252 (21,600), 266 (24,300), 313 (7,000), 324 (7,100), 335 (12,300), 360 (15,600) nm; MS (EI, 70 eV) 276 (100, M$^+$), 274 (82), 248 (14); HRMS calcd for $C_{22}H_{12}$: 276.0939, found: 276.0940.

1,2,7,8-Dibenzocyclohexadeca-3,5,9,15-tetrayne (6). Tetrayne **11** was deprotected in an analogous fashion to **10**. The resultant brown oil was used immediately in the next step. ^{1}H NMR δ 7.47 (d, *J*=7.7 Hz, 2H), 7.40 (d, *J*=7.6 Hz, 2H), 7.29–7.18 (m, 4H), 3.32 (s, 2H), 2.55 (br s, 4H), 1.88 (br s, 4H).

In a manner analogous to **10**, desilylated **11** was intramolecularly cross-coupled. Purification of the crude yellow solid obtained first by preparative TLC (2:1 cyclohexane/CH_2Cl_2, R_f=0.35), then by radial chromatography (hexanes) furnished **6** as a white crystalline solid (120 mg, 87%). Mp=141.7–142.5°C; ^{1}H NMR (CD_2Cl_2) δ 7.51 (dd, *J*=7.4, 1.4 Hz, 2H), 7.40 (dd, *J*=7.7, 1.4 Hz, 2H), 7.34–7.23 (m, 4H), 2.57–2.49 (m, 4H), 1.92–1.85 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 132.64, 131.76, 129.54, 128.70, 127.95, 125.03, 96.09, 81.94, 79.89, 77.82, 29.02, 20.30; IR (KBr) ν=3061, 2226, 2144 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 249 (12,100), 264 (12,800), 309 (7,800), 330 (12,000), 353 (14,700) nm; MS (EI, 70 eV) 304 (100, M$^+$), 303 (52), 302 (84), 300 (26), 289 (22), 276 (30); HRMS calcd for $C_{24}H_{16}$: 304.1252, found: 304.1248.

***cis*-1,6-Bis(2′-(triisopropylsilylethynyl)phenyl)hex-3-en-1,5-diyne (13).** To a solution of diyne **12**[12] (2.13 g, 6.0 mmol) in MeOH (75 mL) and Et_2O (15 mL) was added anhydrous K_2CO_3 (415 mg, 3.0 mmol). After stirring for 2 h, the mixture was diluted with Et_2O, washed with water, dried ($MgSO_4$), and concentrated. The resultant yellow oil was used immediately in the next step. ^{1}H NMR δ 7.51–7.47 (m, 4H), 7.29–7.24 (m, 4H), 3.26 (s, 1H), 1.15 (s, 21H); ^{13}C NMR δ 132.52, 132.42, 128.30, 127.89, 126.68, 124.94, 104.79, 95.28, 82.26, 81.03.

To a degassed mixture of *cis*-1,2-dichloroethene (0.237 g, 2.5 mmol), CuI (0.024 g, 0.13 mmol), $Pd(PPh_3)_4$ (0.046 g, 0.04 mmol) and $BuNH_2$ (2.0 mL) in dry THF (10 mL) was added deprotected **12**. After stirring for 18 h, the resultant dark reaction mixture was poured into hexanes and washed with 1 M HCl solution. The organic phase was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexanes) to give **13** as a pale yellow oil (0.619 g, 42%). ^{1}H NMR δ 7.55–7.48 (m, 4H), 7.28–7.24 (m, 4H), 6.11 (s, 2H), 1.16 (s, 42H); ^{13}C NMR δ 1132.40, 132.20, 128.06, 127.92, 125.98, 125.85, 119.68, 105.08, 96.44, 96.44, 90.95, 18.77, 11.30; IR (neat) ν=3061, 2156 cm^{-1}; MS (EI, 70 eV) 588 (8, M$^+$), 545 (11, M$^+$−*i*-Pr), 503 (30), 461 (30), 274 (100, M$^+$−2Si*i*-Pr$_3$); HRMS calcd for $C_{40}H_{52}Si_2$: 588.3608, found: 588.3615.

1,2,7,8-Dibenzocyclotetradeca-11-en-3,5,9,13-tetrayne

(7). To a solution of **13** (0.589 g, 1.0 mmol) in dry THF (15 mL) was added Bu_4NF (1 M, 3.0 mL, 3.0 mmol) and EtOH (2 mL). The solution was stirred for 2 h, then diluted with Et_2O. The mixture was washed with water, dried ($MgSO_4$), and concentrated. The resultant light brown oil was used immediately in the next step. ^{1}H NMR δ 7.56–7.49 (m, 4H), 7.35–7.27 (m, 4H), 6.20 (s, 2H); ^{13}C NMR δ 132.56, 128.40, 128.24, 126.07, 124.47, 119.64, 95.75, 91.01, 81.83, 81.59.

To a solution of CuCl (2.48 g, 25 mmol) and $Cu(OAc)_2$ (6.01 g, 30 mmol) in pyridine (80 mL) heated at 40°C was added deprotected **13** dissolved in pyridine (5 mL) via syringe pump (0.35 mL/h). Upon completion of addition, the reaction mixture was stirred 6 h further and then concentrated in vacuo. The dark blue-green residue was redissolved with CH_2Cl_2 and filtered through a pad of silica gel. The filtered solution was concentrated and chromatographed on silica gel (9:1 hexanes: CH_2Cl_2) to give **7** as a beige crystalline solid (189 mg, 69%). Mp=170°C (dec); ^{1}H NMR δ 7.92 (dd, J=7.5, 1.8 Hz, 2H), 7.76 (dd, J=6.9, 1.5 Hz, 2H), 7.58–7.47 (m, 4H), 6.70 (s, 2H); ^{13}C NMR δ 132.72, 129.41, 128.52, 128.45, 128.20, 123.12, 117.13, 97.42, 91.76, 85.24, 80.23; IR (KBr) ν=3061, 2206, 2148, 1572 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 258 (12,700), 297 (33,500), 313 sh (26,200), 346 (20,900), 353 (18,900), 370 (13,000) nm; MS (EI, 70 eV) 276 (25), 275 (25), 274 (100, M$^+$), 272 (29); HRMS calcd for $C_{22}H_{10}$: 274.0783, found: 274.0782.

3,3-Dimethyl-1-triisopropylsilyl-5-trimethylsilyl-1,4-pentadiyne (15). A mixture of Mg turnings (0.54 g, 22.4 mmol), dry THF (10 mL), and a catalytic amount of I_2 was treated dropwise with a solution of bromoethane (1.7 mL, 22.8 mmol) in dry THF (10 mL). After stirring an additional 15 min, a solution of triisopropylsilylactetylene (3.2 mL, 17.8 mmol) in dry THF (10 mL) was added over a 15 min period. The reaction was refluxed with stirring for 1 h, then cooled to ambient. Dry CuCl (0.20 g, 2.0 mmol) was added and the mixture was stirred for 15 min. A solution of 3-chloro-3-methyl-1-trimethylsilyl-1-butyne (**14**)[14] (3.77 g, 21.6 mmol) in dry THF (4 mL) was then added dropwise to the reaction mixture. The suspension was refluxed for 2 h. The cooled slurry was washed with a solution of NH_4Cl (1.50 g, 28.0 mmol) and KCN (0.20 g, 3.07 mmol) in water (10 mL), followed by extraction of the aqueous phase with Et_2O. The combined organic phases were washed with saturated NH_4Cl solution, then water, dried ($MgSO_4$), and concentrated. The crude product was filtered through a thin cake of silica gel (petroleum ether). Concentration in vacuo gave **15** as a clear, colorless oil (5.63 g, 90%). ^{1}H NMR δ 1.50 (s, 6H), 1.06 (br s, 21H), 0.14 (s, 9H); ^{13}C NMR δ 112.17, 110.06, 82.93, 79.26, 31.25, 27.41, 18.61, 11.27, 0.04; IR (neat) ν=2167 cm^{-1}; MS (EI, 70 eV) 320 (6, M$^+$), 305 (2, M$^+-$Me), 277 (100, M^+-i-Pr), 235 (37), 73 (75); HRMS calcd for $C_{19}H_{36}Si_2$: 320.2356, found: 320.2352.

1-Chloro-5,5-dimethyl-7-triisopropylsilylhept-1-en-3,6-diyne (16). A solution of **15** (5.63 g, 20.2 mmol) in MeOH (50 mL) and THF (50 mL) was stirred with 10% NaOH solution (1 mL) for 6 h. The reaction mixture was diluted with petroleum ether and washed with water and saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and concentrated to give a clear, colorless oil (3.56 g, 85%). ^{1}H NMR δ 2.19 (s, 1H), 1.53 (s, 6H), 1.11 (s, 21H); ^{13}C NMR δ 31.26, 26.42, 7.37, 4.39.

A mixture of *cis*-1,2-dichloroethene (0.50 g, 5.16 mmol), CuI (0.047 g, 0.25 mmol), $Pd(PPh_3)_4$ (0.046 g, 0.040 mmol) and $BuNH_2$ (0.5 mL) in dry THF (6 mL) was degassed, then treated with deprotected **15** (0.46 g, 2.23 mmol). After stirring for 9 h, the resultant dark blue reaction mixture was poured into hexanes and washed with 1 M HCl solution. The organic phase was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (hexanes) to give **16** as a clear, colorless oil (0.185 g, 30%). ^{1}H NMR δ 6.34 (d, J=7.5 Hz, 1H), 5.86 (d, J=7.5 Hz, 1H), 1.58 (s, 6H), 1.08 (s, 21H); ^{13}C NMR δ 127.85, 112.09, 111.39, 101.77, 79.60, 73.61, 31.21, 27.50, 18.59, 11.22; IR (neat) ν=2223, 2173, 1600 cm^{-1}; MS (EI, 70 eV) 310 (2, M$^+$(^{37}Cl)), 308 (2, M$^+$(^{35}Cl)), 267 (39, M$^+$(^{37}Cl)-i-Pr), 265 (100, M$^+$(^{35}Cl)-i-Pr), 237 (20), 205 (61), 199 (38); HRMS calcd for $C_{18}H_{29}ClSi$: 308.1727, found: 308.1729.

5,5,12,12-Tetramethyl-1,8-cyclotetradecadien-3,6,10,13-tetrayne (8). To a degassed solution of **16** (180 mg, 0.67 mmol) in dry THF (5 mL) was added Bu_4NF (340 mg, 1.45 mmol) and EtOH (2 mL). After stirring for 2 h, the reaction solution was diluted with petroleum ether and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated. The unstable pale yellow oil was used immediately in the next step. ^{1}H NMR δ 6.36 (d, J=7.5 Hz, 1H), 5.86 (d, J=7.5 Hz, 1H), 2.25 (s, 1H), 1.59 (s, 6H).

To a degassed solution of the deprotected enediyne in dry THF (50 mL) was CuI (100 mg, 0.53 mmol), $Pd(PPh_3)_4$ (96 mg, 0.08 mmol), and $BuNH_2$ (0.5 mL). The reaction was stirred for 17 h at ambient. The mixture was poured into saturated NH_4Cl solution and extracted twice with petroleum ether. The organic phase was filtered through a pad of silica gel and concentrated. Purification by preparative TLC (1:1 hexanes/CH_2Cl_2, R_f=0.51) gave **8** as an off-white solid (28 mg, 18%). Mp=175°C (dec); ^{1}H NMR δ 5.77 (s, 4H), 1.63 (s, 12H); ^{13}C NMR δ 119.37, 100.60, 77.13, 30.72, 27.37; IR (KBr) ν=3042, 2982, 2208, 1571 cm^{-1}; MS (EI, 70 eV) 232 (37, M$^+$), 217 (46, M$^+-$Me), 215 (55), 202 (100, M$^+-$2Me); HRMS calcd for $C_{18}H_{16}$: 232.1252, found: 232.1255.

1,9-Dichloro-5,5-dimethyl-1,8-nonadien-3,6-diyne (17). To a solution of desilylated precursor **16** (1.40 g, 9.17 mmol), generated as above, in dry THF (50 mL) was added $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), CuI (0.103 g, 0.541 mmol), $BuNH_2$ (3 mL, 30 mmol), and *cis*-dichloroethene (3.12 g, 32 mmol). The reaction was stirred at room temperature under N_2 for 5.5 h. The mixture was diluted with hexanes and washed twice with water. The organic layer was dried ($MgSO_4$) and concentrated to yield a crude brown oil. Purification on silica gel (petroleum ether) afforded **17** as a pale yellow oil (2.0 g). An analytically pure sample was prepared by radial chromatography (hexanes) to give a colorless oil. ^{1}H NMR δ 6.36 (d, J=7.5 Hz, 2H), 5.87 (d, J=7.5 Hz, 2H), 1.63 (s, 6H); ^{13}C NMR δ 128.21, 111.91, 100.92, 74.01, 30.90, 27.50; IR (neat) ν=3085, 2984, 2221, 1591 cm^{-1}; MS (EI, 70 eV) 216 (5, M$^+$(^{37}Cl)$_2$), 214 (12, M$^+$(^{35}Cl^{37}Cl)), 212 (16, M$^+$(^{35}Cl)$_2$), 201 (6, M$^+$(^{37}Cl)$_2$-Me), 199 (28, M$^+$(^{35}Cl^{37}Cl)-Me), 197 (42, M$^+$(^{35}Cl)$_2$-Me), 179 (24, M$^+$(^{35}Cl^{37}Cl)-^{35}Cl), 177 (76, M$^+$(^{35}Cl)$_2$-^{35}Cl), 162 (40), 142 (68), 141 (100); HRMS calcd for $C_{11}H_{10}Cl_2$: 212.0160, found: 212.0166.

1,13-Bis(trimethylsilyl)-7,7-dimethyl-3,10-tridecadien-1,5,8,12-tetrayne (18). A solution of dichloride **17** (generated above) in THF (50 mL) was treated with Pd(PPh$_3$)$_4$ (0.16 g, 0.14 mmol), CuI (95 mg, 0.50 mmol), BuNH$_2$ (4 mL, 40 mmol), and trimethylsilylacetylene (10 mL, 70 mmol). After stirring for 25 h, the mixture was poured diluted with petroleum ether and washed with NH$_4$Cl solution. The organic layer was dried (MgSO$_4$) and concentrated. Purification by radial chromatography (hexanes) yielded **18** as a light orange oil (1.26 g, 42% from **16**). ^{1}H NMR δ 5.84 (*AB* d, J=10.4 Hz, 2H), 5.79 (*AB* d, J=10.4 Hz, 2H), 1.64 (s, 6H), 0.21 (s, 18H); ^{13}C NMR δ 120.79, 119.36, 102.39, 101.90, 100.91, 77.43, 31.25, 27.50, −0.10; IR (neat) ν=3045, 3027, 2214, 2143, 1571 cm^{-1}; MS (EI, 70 eV) 247 (18, M$^+$+H), 233 (20, M$^+$−Me), 73 (100, SiMe$_3$); HRMS calcd for $C_{21}H_{28}Si_2$: 336.1730, found: 336.1728.

5,5-Dimethyl-1,8-cyclotridecadien-3,6,10,12-tetrayne (9). To a solution of tetrayne **18** (56 mg, 0.17 mmol) dissolved in pyridine (9 mL) and MeOH (9 mL) was added CuCl (499 mg, 5 mmol), Cu(OAc)$_2$ (915 mg, 5 mmol), and K$_2$CO$_3$ (697 mg, 5 mmol). The mixture was stirred at 40°C for 24 h. The dark blue-green solution was then diluted with CH$_2$Cl$_2$, washed successively with 10% HCl solution, saturated NaHCO$_3$ solution, and water. The organic layer was dried (MgSO$_4$), filtered, and concentrated. Chromatography on silica gel (9:1 hexanes: CH$_2$Cl$_2$) gave **9** as an unstable yellow solid that rapidly polymerized into an insoluble brown solid. ^{1}H NMR (CD$_2$Cl$_2$) δ 6.22 (d, J=10.1 Hz, 2H), 5.92 (d, J=10.1 Hz, 2H), 1.57 (s, 6H); UV (CH$_2$Cl$_2$) λ_{max} 259, 292, 316, 337, 362, 380 sh nm.

X-Ray Crystal Structures. All data were obtained on an Enraf–Nonius CAD-4 Turbo diffractometer. Structure refinement (C atoms isotropic, H atoms riding) was accomplished with teXsan (v. 1.7 for SGI workstations). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center and can be obtained from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk.

6. $C_{24}H_{16}$, M_r=304.39, colorless prism, 0.06×0.15×0.50 mm, orthorhombic, space group $P2_12_12$, a=19.947(3), b=5.065(2), c=8.365 (1) Å, V=845.2(6) Å^3, Z=2, ρ_{calc}=1.196 g cm^{-3}, Mo$_{K\alpha}$ radiation (λ=0.71073 Å), μ=0.629 cm^{-1}, F(000)=320, T=23°C, 2θ_{max}=50°, 917 independent reflections scanned, 665 reflections in refinement ($I{\cdot}\sigma(I)$), 100 parameters, R=0.040, R_w=0.038.

7. $C_{22}H_{10}$, M_r=274.32, colorless prism, 0.22×0.27×0.70 mm, orthorhombic, space group *Pbca*, a=13.592(2), b=12.540(3), c=17.043(3) Å, V=2905(2) Å^3, Z=8, ρ_{calc}=1.254 g cm^{-3}, Mo$_{K\alpha}$ radiation (λ=0.71073 Å), μ=0.66 cm^{-1}, F(000)=1136, T=22°C, 2θ_{max}=50°, 2895 independent reflections scanned, 2546 reflections in refinement ($I{\cdot}\sigma(I)$), 239 parameters, R=0.088, R_w=0.092.

8. $C_{18}H_{16}$, M_r=232.32, colorless prism, 0.07×0.15×0.32 mm, monoclinic, space group *C2/m*, a=10.3804(14), b=14.6567(11), c=9.6200(13) Å, β=93.334(11)°, V=1461.1(6) Å^3, Z=4, ρ_{calc}=1.056 g cm^{-3}, Mo$_{K\alpha}$ radiation (λ=0.71073 Å), μ=0.553 cm^{-1}, F(000)=496, T=23°C, 2θ_{max}=50°, 1345 independent reflections scanned, 897 reflections in refinement ($I{\cdot}1.5\sigma(I)$), 122 parameters, R=0.044, R_w=0.042.

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