

with FBDS gives a mixture of major products.²⁸ Thus, the tri-functional nature of TTDS adds specificity beyond that of a related bifunctional material with the same leaving group.

The reactions of trimesoyl tris(methyl phosphate) (TTMP) with hemoglobin under the same reaction conditions have also been studied.²¹ In those cases, the principal reaction products result from cross-linking the terminal amino group of the β subunits, Val-1, to the ϵ -amino group of Lys-82, with the principal product being the triply cross-linked species ($\alpha\alpha\beta(82\text{Lys},1\text{-Val})$ -trimesoyl- $\beta(82\text{Lys})$). TTMP reacts with carbonmonoxyhemoglobin to produce a small amount (15%) of the $\alpha\alpha\beta(82\text{Lys})$ -trimesoyl-Lys82 β . Since the acyl core is the same in TTMP and TTDS, the nature of the leaving group must determine the cross-linking site.

Examination by structural modeling of TTDS clearly shows that the reaction site is well-shielded by the aryl groups. The

3,5-dibromosalicylate moiety is an unusually bulky leaving group, and this partially controls the regioselectivity of its derivatives as cross-linking reagents for hemoglobin. Analysis of the structure of deoxyhemoglobin¹² shows that the 82 β Lys amino groups are accessible, even to a bulky reagent. Thus, electrostatic forces direct TTDS to the DPG binding site, and the bulkiness of the reagent causes its opportunities for reaction to be limited once it is within the site.

Conclusions

The reaction of TTDS with hemoglobin demonstrates that high-yield production of cross-linked proteins can be achieved using a reagent which combines aspects of chemical selectivity. Applications of the reagent to stabilization of other proteins will depend on the specific structural features of those proteins.

Acknowledgment. We thank Leuming Feng for preliminary studies on the synthesis of TTDS.

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Redox-Controlled Bergman Cycloaromatizations. Designed Enediynes with DNA-Cleaving Properties and Antitumor Activity

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Abstract: Enediynes **7** and **9** were designed for their potential to act as radical-generating species upon oxidation to the corresponding quinone. Their synthesis entailed a chromium–nickel-mediated ring closure of iodo aldehyde **6**. Investigations with these molecules and their derivatives **8** and **10** demonstrated the anticipated acceleration of the Bergman cycloaromatization of the oxidized species as compared to the reduced compounds and potent DNA-cleaving and antitumor properties.

Introduction

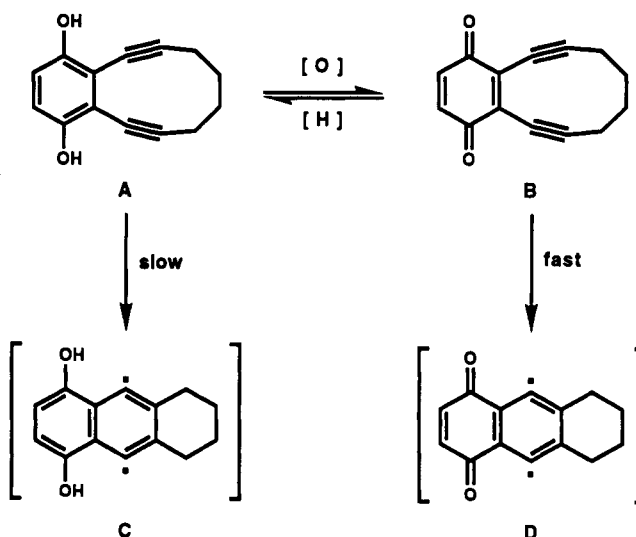
Naturally occurring enediyne anticancer antibiotics^{1,2} are triggered to exert their biological actions by bioreductive processes which initiate Bergman cycloaromatization³ leading to DNA cleavage. Several designed enediynes^{1,4} have been shown to undergo the Bergman reaction upon activation with acid, base, or UV irradiation. In this paper, we report the design, synthesis, and evaluation of a series of cyclic enediynes in which the Bergman cycloaromatization is controlled by the redox process hydroquinone \rightleftharpoons quinone (Scheme I). Given the ease by which the processes are driven in either direction both in vitro and in vivo, the synthesis and evaluation of such systems was deemed important and may have considerable potential.

On the basis of previous observations with arene-substituted enediynes,⁵⁻⁷ we postulated that hydroquinone systems of type A (Scheme I) should be quite stable toward cycloaromatization to form benzenoid diradical C, whereas oxidation to the quinone (B) should result in lowering of the activation energy for this process and, therefore, faster cyclization to diradical D. This hypothesis was tested by synthesizing compounds **7–10** as shown in Scheme II.

Results and Discussion

The readily available diiodide **1**⁸ was sequentially coupled with $\text{Me}_3\text{SiC}\equiv\text{CH}$ and $\text{tBuMe}_2\text{SiO}(\text{CH}_2)_4\text{C}\equiv\text{CH}$ under the catalytic influence of $\text{Pd}(\text{O})\text{--Cu}(\text{I})$ to afford the diacetylenic compound

Scheme I. Redox-Controlled Bergman Cycloaromatization



3 via **2**. Formation of the dipivaloyl ester of **3** followed by desilylation furnished compound **4** in 71% overall yield. Iodination

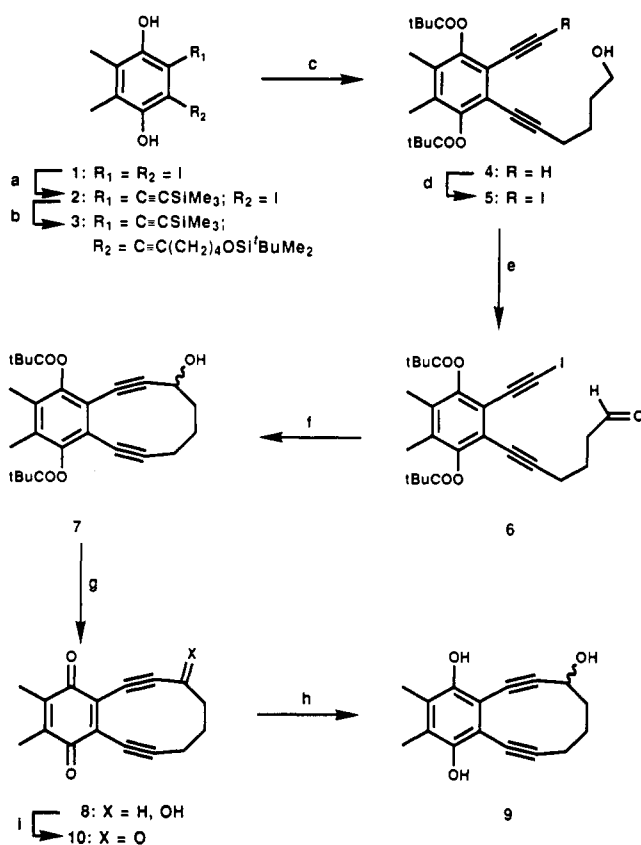
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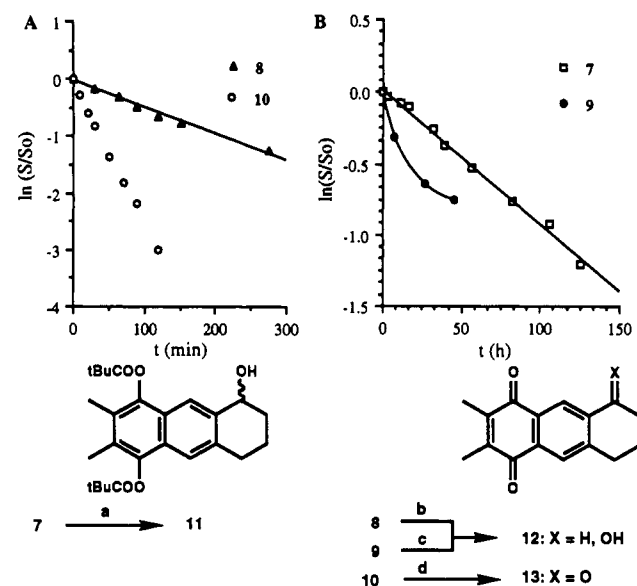
Table I. Cytotoxicities of Enediynes 7–10

cell type	cell line	7 ^a	8 ^a	9 ^a	10 ^a
Normal Cell Line					
Chinese hamster ovary	CHO	$\sim 10^{-4}$	3.1×10^{-5}	1.3×10^{-5}	$< 10^{-4}$
human mammary epithelial	HMEC	$< 10^{-4}$	3.1×10^{-5}	2.5×10^{-5}	$< 10^{-4}$
normal human dermal fibroblast	NHDF	$\sim 10^{-4}$	3.1×10^{-5}	2.5×10^{-5}	$< 10^{-4}$
normal human epidermal keratinocytes	NHEK	2.5×10^{-5}	3.1×10^{-5}	1.3×10^{-5}	$< 10^{-4}$
Cancer Cell Line					
pancreatic carcinoma	Capan 1	1.3×10^{-5}	3.1×10^{-5}	1.3×10^{-5}	$\sim 10^{-4}$
colon carcinoma	HT-29	1.3×10^{-5}	6.3×10^{-5}	2.5×10^{-4}	5.0×10^{-5}
melanoma	SK-Mel-28	$\sim 10^{-4}$	6.3×10^{-5}	2.5×10^{-5}	$\sim 10^{-4}$
lung carcinoma	H-322	$\sim 10^{-4}$	1.3×10^{-4}	2.5×10^{-4}	$\sim 10^{-4}$
lung carcinoma	UCLA-P3	1.3×10^{-5}	6.3×10^{-5}	2.5×10^{-5}	5.0×10^{-5}
breast carcinoma	MCF-7	5.0×10^{-5}	6.3×10^{-5}	2.5×10^{-5}	1.3×10^{-5}
ovarian carcinoma	Ovar-3	1.3×10^{-5}	6.3×10^{-5}	2.5×10^{-5}	2.5×10^{-5}
promyelocytic leukemia	HL-60	$\sim 10^{-4}$	7.8×10^{-6}	1.6×10^{-6}	2.5×10^{-5}
T-cell leukemia	Molt-4	$\sim 10^{-4}$	5.0×10^{-7}	$\sim 10^{-5}$	$\sim 10^{-6}$
mouse leukemia	P388	1.3×10^{-5}	2.0×10^{-6}	3.1×10^{-6}	

^a IC₅₀ values (M).**Scheme II.** Synthesis of Enediynes 7–10^a

^a (a) 3.1 equiv of $HC \equiv CSiMe_3$, 0.06 equiv of $(Ph_3P)_2PdCl_2$, 0.17 equiv of CuI , 2.0 equiv of Pr_2NH , PhH , 25 °C, 8 h, 58%. (b) 6 equiv of $HC \equiv C(CH_2)_4OSi^tBuMe_2$, 0.1 equiv of $(Ph_3P)_4Pd$, 0.16 equiv of CuI , 6.5 equiv of Pr_2NH , PhH , 25 °C, 13 h, 88%. (c) (1) 10 equiv of $tBuCOCl$, pyridine, 60–65 °C, 1 h, 100%; (2) excess $BF_3 \cdot OEt_2$, $CHCl_3$, 35 °C, 4.5 h; (3) 1.0 equiv of TBAF, THF, 25 °C, 5 min, 71% for two steps. (d) 5.0 equiv of I_2 , excess morpholine, PhH , 45 °C, 40 min, 89%. (e) 2.5 equiv of PCC, CH_2Cl_2 , 25 °C, 1.5 h, 86%. (f) 9.0 equiv of $CrCl_2$, 0.64 equiv of $NiCl_2$, 25 °C, 4.5 h, 75%. (g) excess $LiAlH_4$, THF, $-78 \rightarrow 0$ °C, 10 min, 96%. (h) saturated aqueous $Na_2S_2O_4$ wash, 91%. (i) 4.0 equiv of PCC, 4 Å molecular sieves, CH_2Cl_2 , 25 °C, 0.5 h, 49%.

of the terminal acetylene of 4 with iodine–morpholine led to iodide 5 (89%), which served as a precursor to iodo aldehyde 6 (PCC,

Scheme III. Cycloaromatization Studies with Enediynes 7–10^a

^a (a) 1,4-cyclohexadiene, toluene, 100–110 °C, 54.5 h, 25%, $t_{1/2} = 74$ h (110 °C, toluene- d_8 , graph B). 8: (b) 1,4-cyclohexadiene, benzene, 60 °C, 6 h, 42%, $t_{1/2} = 2.6$ h (55 °C, THF- d_8 , graph A). 9: (c) 1,4-cyclohexadiene, $PhH-THF$, 85 °C, 7 h, 20%; kinetic studies (O_2 extrusion, toluene- d_8 , THF- d_8 , 110 °C) show that it is not a first-order reaction and only ca. 30% of 9 reacted after 45.5 h (graph B). 10: (d) THF- d_8 , 55 °C, 2 h, 30%, $t_{1/2} = 32$ min (graph A).

86%). The crucial ring closure of 6 was carried out with a $CrCl_2-NiCl_2$ system,⁹ leading to the targeted enediyne 7 in 75% yield. Compound 7 proved to be quite stable at ambient temperature and was smoothly deprotected by exposure to excess $LiAlH_4$ to afford, after workup, the quinone system 8 (96%), presumably through the intermediacy of the air-sensitive hydroquinone 9. Reduction of the thermally labile 8 to the hydroquinone system 9, relatively stable under neutral conditions, was smoothly effected by treatment with $Na_2S_2O_4$ (91% yield). Finally, PCC oxidation of 8 afforded the tricyclic compound 10, which proved to be the most reactive member of the series 7–10.

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(8) Diiodide 1 was readily prepared from 2,3-dimethylhydroquinone in 82% overall yield by bromination followed by iodine exchange. We thank E. Schweiger and D. Johnson for these procedures and early synthetic work.

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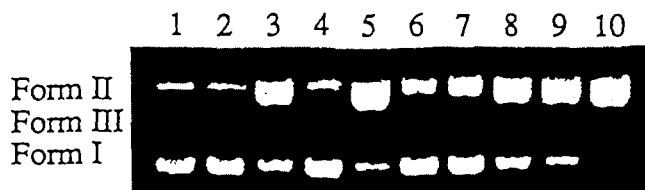


Figure 1. Supercoiled DNA interaction with selected compounds. Φ X174 DNA (100 μ M base pairs) was incubated for 15 h at 37 $^{\circ}$ C with compounds 7–10 and 12 in buffer (50 μ M Tris-HCl, pH 7.4) and analyzed by electrophoresis (1% agarose gel, ethidium bromide stain). Lane 1: DNA control. Lane 2: 12 (100 μ M). Lane 3: 10 (100 μ M). Lane 4: 7 (100 μ M). Lane 5: 8 (100 μ M). Lanes 6–10: 9 (50, 100, 500, 1000, and 5000 μ M). Key: I, form I DNA; II, form II DNA; III, form III DNA.

Cycloaromatization experiments with compounds 7–10 (Scheme III) revealed the following half-lives: 7 ($t_{1/2}$ = 74 h at 110 $^{\circ}$ C); 8 ($t_{1/2}$ = 2.6 h at 55 $^{\circ}$ C); 9 (110 $^{\circ}$ C, has complicated kinetics due to ease of conversion to 8 even under oxygen extrusion conditions, but seems quite stable prior to oxidation); 10 ($t_{1/2}$ = 32 min at 55 $^{\circ}$ C). These observations confirmed our expectation for these compounds and prompted DNA-cleaving experiments and cytotoxicity studies.

The interaction of compounds 7–10 with supercoiled DNA (Φ X174) at pH 7.4 and 37 $^{\circ}$ C is shown in Figure 1. As anticipated, the stable pivalate derivative 7 exhibited no DNA-cleaving activity, whereas compounds 8–10 showed significant DNA-damaging properties. It is presumed that the damage on DNA caused by these agents is at least partly due to their abilities to produce diradical species such as those exhibited in Scheme I (structures C and D). Tested against a variety of cell lines,¹⁰ these compounds exhibited varying degrees of antitumor activity (Table I) with the most impressive results obtained with compounds 8 and 10 (e.g. Molt 4 leukemia cells: IC_{50} for 8, 5.0×10^{-7} M; IC_{50} for 10, 1×10^{-6} M).

The described chemistry adds significantly to the repertoire of designed enediynes with DNA-cleaving properties and antitumor activities and provides yet another useful activation mechanism for these systems. The central role of redox chemistry in chemical and biological systems may provide impetus for further studies with these molecules both in vitro and in vivo.

Experimental Section

General Techniques. NMR spectra were recorded on a Bruker AMX-500. 1 H NMR multiplicities were reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad. IR spectra were recorded on a Perkin-Elmer Model 553 UV-vis spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a VC ZAB E mass spectrometer under FAB conditions. Melting points were obtained with a Thomas-Hoover Unimelt apparatus.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) by using UV light and either 7% ethanolic phosphomolybdic acid-heat or 5% anisaldehyde and 5% sulfuric acid in ethanol-heat as a developing reagent. Preparative thin-layer chromatography was performed on 0.5 mm \times 20 cm \times 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically (1 H NMR) homogeneous materials, unless otherwise stated. Reaction temperatures were measured externally.

DNA Cleavage Studies. Supercoiled Φ X174 DNA was purchased from New England Biolabs. The cleavage reactions were carried out by combining 9 μ L of DNA (100 μ M in base pairs) in pH 7.4 Tris-acetate buffer and 1 μ L of the tested compounds in ethanol. The mixtures were incubated at 37 $^{\circ}$ C for 15 h. The results were analyzed using 1% agarose gel electrophoresis and detected with ethidium bromide fluorescence.

Kinetic Studies of Bergman Cyclization. A freshly prepared sample in an NMR tube was heated at the indicated temperature. The reaction course was followed by 1 H NMR spectroscopy (Bruker, AMX-500) with

benzene as the internal standard. The data were analyzed using the Cricket Graph program.

3-Iodo-5,6-dimethyl-2-(2-(trimethylsilyl)ethynyl)hydroquinone (2). To a degassed solution of 1⁸ (3.60 g, 9.23 mmol), Pd(PPh₃)₂Cl₂ (0.36 g, 0.46 mmol), and CuI (0.30 g, 1.58 mmol) in dry benzene (110 mL) was added (trimethylsilyl)acetylene (4.0 mL, 28.6 mmol) and diisopropylamine (2.5 mL, 18.5 mmol). The resulting mixture was stirred at room temperature for 8 h and then concentrated in vacuo. The residue was purified by flash chromatography (7% ethyl acetate in petroleum ether) to give 2 (1.5 g, 58% based on 80% conversion) as a yellow solid. 2: mp 77–78.5 $^{\circ}$ C; IR (CCl₄) ν_{max} 3505, 2959, 2146 cm^{-1} ; 1 H NMR (500 MHz, CDCl₃) δ 5.62, 5.01 (2 s, 2 H, phenolic OH), 2.25, 2.16 (2 s, 6 H, 2 aromatic CH₃), 0.31 (s, 9 H, Si(CH₃)₃); 13 C NMR (125 MHz, CDCl₃) δ 150, 147, 127, 124, 112, 106, 102, 86, 14, 12, 0; HRMS (FAB) calcd for C₁₃H₁₇O₂Si 360.0043, found 360.0043.

5,6-Dimethyl-3-[6-(dimethyl-*tert*-butylsiloxy-1-hexynyl)-2-(2-(trimethylsilyl)ethynyl)hydroquinone (3). To a degassed solution of 2 (3.50 g, 7.88 mmol), Pd(PPh₃)₄ (1.20 g, 1.04 mmol), and CuI (0.27 g, 1.4 mmol) in dry benzene (120 mL) was added 6-dimethyl-*tert*-butylsiloxy-1-hexyne (12.60 g, 47.3 mmol) and diisopropylamine (8.9 mL, 66 mmol). The resulting mixture was stirred at room temperature for 19 h and then concentrated in vacuo. The residue was purified by flash chromatography (7% ethyl acetate in petroleum ether) to give 3 (3.8 g, 88%) as a yellow solid. 3: R_f 0.37 (7% ethyl acetate in petroleum ether); mp 69–70 $^{\circ}$ C; IR (CCl₄) ν_{max} 3512, 2954, 2857, 2143 cm^{-1} ; 1 H NMR (500 MHz, CDCl₃) δ 5.61, 5.59 (2 s, 2 H, phenolic OH), 3.67 (t, J = 6.6 Hz, 2 H, CH₂O), 2.56 (t, J = 6.6 Hz, 2 H, C \equiv CH₂), 2.18, 2.17 (2 s, 6 H, 2 aromatic CH₃), 1.73–1.71 (m, 4 H, CH₂CH₂), 0.90 (s, 9 H, C(CH₃)₃), 0.28 (s, 9 H, Si(CH₃)₃), 0.06 (s, 6 H, Si^{*tert*}Bu(CH₃)₂); 13 C NMR (125 MHz, CDCl₃) δ 149, 148, 126, 124, 108, 107, 104, 100, 99, 74, 63, 32, 26, 25, 20, 13, 12, 0, –5; HRMS (FAB) calcd for C₂₅H₄₄O₃Si₂ 444.2516, found 444.2525.

5,6-Dimethyl-3-(6-hydroxy-1-hexynyl)-2-ethynylhydroquinone 1,4-Dipivaloyl Ester (4). To a solution of 3 (3.3 g, 7.43 mmol) in pyridine (25 mL) was added pivaloyl chloride (9.5 mL, 74.3 mmol) at 0 $^{\circ}$ C. The ice bath was removed, and the solution was heated at 60 $^{\circ}$ C for 2 h. The mixture was allowed to cool to room temperature, partitioned between ether and water, and neutralized with 2 N aqueous HCl. The separated organic phase was washed with water, dried over MgSO₄, and concentrated in vacuo. The resulting yellow oil (4.4 g) was used without further purification.

The crude product obtained above was dissolved in CH₂Cl₂ (50 mL) and was treated at room temperature with BF₃·Et₂O (6.1 mL, 50 mmol). The resulting solution was stirred at room temperature for 4.5 h. The mixture was diluted with CH₂Cl₂, thoroughly washed with saturated aqueous NaHCO₃ solution, and then concentrated in vacuo. The residue was dissolved in THF (50 mL) and was treated with TBAF (7.2 mL, 7.2 mmol) at ambient temperature. After being stirred for 5 min, the solution was diluted with ether. The organic phase was washed twice with water, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography (33% ethyl acetate in petroleum ether) to give 4 (1.8 g, 59%) as a white solid. 4: R_f 0.20 (33% ethyl acetate in petroleum ether); mp 119–120 $^{\circ}$ C (from ethyl acetate-petroleum ether); IR (CCl₄) ν_{max} 3543, 2972, 2871, 1754 cm^{-1} ; 1 H NMR (500 MHz, CDCl₃) δ 3.66 (t, J = 6.5 Hz, 2 H, CH₂OH), 3.34 (s, 1 H, C \equiv CH), 2.45 (t, J = 6.5 Hz, 2 H, C \equiv CH₂), 2.05 (2 s, 6 H, 2 aromatic CH₃), 1.77–1.62 (m, 4 H, CH₂CH₂), 1.40 (s, 18 H, 2 \times C(CH₃)₃); 13 C NMR (125 MHz, CDCl₃) δ 176, 149, 147, 132, 130, 120, 118, 98, 88, 75, 72, 63, 39, 32, 27, 25, 19, 13; HRMS (FAB) calcd for C₂₆H₃₄O₅Cs (M + Cs) 559.1461, found 559.1491. Anal. Calcd for C₂₆H₃₄O₅: C, 73.21; H, 8.03. Found: C, 73.11; H, 8.09.

5,6-Dimethyl-3-(6-hydroxy-1-hexynyl)-2-(2-iodoethynyl)hydroquinone 1,4-Dipivaloyl Ester (5). To a solution of 4 (1.74 g, 4.08 mmol) in dry benzene (60 mL) was added morpholine (5.2 mL, 59.4 mmol) and iodine (5.22 g, 20.6 mmol). The resulting solution was heated at 45 $^{\circ}$ C for 40 min and was then concentrated in vacuo. The residue was purified by flash chromatography (33% ethyl acetate in petroleum ether) to give 5 (2.01 g, 89%) as a white solid. 5: R_f 0.17 (33% ethyl acetate in petroleum ether); IR (CCl₄) ν_{max} 3543, 2972, 2871, 1754 cm^{-1} ; 1 H NMR (500 MHz, CDCl₃) δ 3.72 (t, J = 6.0 Hz, 2 H, CH₂OH), 2.47 (t, J = 7.0 Hz, 2 H, C \equiv CH₂), 2.05, 2.04 (2 s, 6 H, 2 aromatic CH₃), 1.82–1.64 (m, 4 H, –CH₂CH₂–), 1.41, 1.40 (2 s, 18 H, 2 \times C(CH₃)₃); 13 C NMR (125 MHz, CDCl₃) δ 176, 149, 147, 132, 130, 120, 118, 98, 88, 75, 72, 63, 39, 32, 27, 25, 19, 13; HRMS (FAB) calcd for C₂₆H₃₄IO₅ (M + H) 553.1451, found 553.1451.

5,6-Dimethyl-3-(6-oxo-1-hexynyl)-2-(2-iodoethynyl)-hydroquinone Dipivaloyl Ester (6). To a solution of 5 (2.01 g, 3.64 mmol) in CH₂Cl₂ (50 mL) was added PCC (1.18 g, 5.46 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with ether and filtered through celite. The organic phase was washed with statu-

(10) We thank Dr. W. Wrasidlo of The Scripps Research Institute for these assays.

rated aqueous NaHCO_3 solution and water and then dried over MgSO_4 . The solution was concentrated in vacuo, and the residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) to give 6 (1.72 g, 86%) as a yellow solid. 6: R_f 0.18 (20% ethyl acetate in petroleum ether); mp 126–127 °C (from ethyl acetate–petroleum ether); IR (CCl_4) ν_{max} 2959, 2872, 1757, 1729 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.87 (s, 1 H, CHO), 2.75 (t, J = 6.5 Hz, 2 H, CH_2CHO), 2.50 (t, J = 6.5 Hz, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.05, 2.04 (2 s, 6 H, 2 aromatic CH_3), 1.90 (dddd, J = 6.5 Hz, 2 H, $-\text{CH}_2-$), 1.40, 1.39 (2 s, 18 H, 2 \times $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 202, 176, 149, 147, 132, 131, 120, 119, 97, 89, 85, 76, 43, 39, 27, 21, 19, 13; HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{31}\text{IO}_3\text{Cs}$ ($M + \text{Cs}$) 683.0271, found 683.0271.

2,3-(3-Hydroxyocta-1,7-diyne-1,8-diyl)-5,6-dimethylhydroquinone 1,4-Dipivaloyl Ester (7). A suspension of 6 (0.45 g, 0.82 mmol), CrCl_2 (900 mg, 7.36 mmol), and NiCl_2 (68 mg, 0.52 mmol) in dry THF (70 mL) was stirred at room temperature for 40 min. The mixture was diluted with ether, washed twice with water, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) to give 7 (0.26 g, 75%) as a white solid. 7: R_f 0.19 (20% ethyl acetate in petroleum ether); mp 185 °C dec (from ethyl acetate–petroleum ether); UV (CHCl_3) λ_{max} (relative intensity) 242 (1.59), 269 (0.78), 314 (0.18) nm; IR (CCl_4) ν_{max} 3400, 2973, 2872, 1755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.55 (dd, J = 8.9, 4.2 Hz, 1 H, CHOH), 2.44–2.42 (m, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.17–2.10 (m, 2 H, CH_2CHOH), 2.10 (br s, 6 H, 2 aromatic CH_3), 1.42, 1.41 (2 s, 18 H, 2 \times $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 176, 146, 145, 131, 130, 122, 121, 104, 102, 81, 78, 63, 39, 38, 27, 24, 21, 13; HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{33}\text{O}_5\text{Cs}$ ($M + \text{Cs}$) 557.1304, found 557.1315. Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{O}_5$: C, 73.56; H, 7.60. Found: C, 73.55; H, 7.58.

2,3-(3-Hydroxyocta-1,7-diyne-1,8-diyl)-5,6-dimethylquinone (8). To a solution of 7 (45 mg, 0.11 mmol) in THF (3 mL) was added LiAlH_4 (1.1 mL, 1.1 mmol) at -78 °C. The mixture was stirred for 1 min at -78 °C and then was allowed to warm to room temperature, stirred for 10 min, and then recooled to -78 °C before quenching with methanol. The mixture was partitioned between water and ether, and the aqueous layer was reextracted with ether. The organic phases were combined, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by flash chromatography (50% ethyl acetate in petroleum ether) to give 8 (26 mg, 96%) as a white solid. 8: R_f 0.40 (50% ethyl acetate in petroleum ether); mp 80 °C dec (from ethyl acetate–petroleum ether); UV (CHCl_3) λ_{max} (relative intensity) 238 (0.61), 260 (0.64), 298 (1.18), 423 (0.12) nm; IR (CCl_4) ν_{max} 3290, 2935, 2197, 1654 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.69 (dd, J = 8.5 and 3.0 Hz, 1 H, CHOH), 2.50 (ABqdd, $\Delta\nu$ = 31.3 Hz, J = 15.0, 8.5, and 2.5 Hz, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.27–2.08 (m, 3 H, CH_2CHOH and $-\text{CH}_2-$), 2.04 (s, 6 H, 2 aromatic CH_3), 1.88–1.79 (m, 1 H, $-\text{CH}_2-$); ^{13}C NMR (125 MHz, CDCl_3) δ 182, 141, 138, 137, 129, 116, 111, 81, 79, 63, 37, 23, 22, 13; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3\text{Cs}$ ($M + \text{Cs}$) 386.9997, found 287.0005.

2,3-(3-Hydroxyocta-1,7-diyne-1,8-diyl)-5,6-dimethylhydroquinone (9). To a solution of 7 (45 mg, 0.11 mmol) in THF (3 mL) was added LiAlH_4 (1.1 mL, 1.1 mmol) at -78 °C. The mixture was stirred for 1 min at -78 °C and then was allowed to warm to room temperature, stirred for 10 min, and recooled to -78 °C. The reaction mixture was quenched with methanol, diluted with ether, washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_4$ solution, dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by flash chromatography (50% ethyl acetate in petroleum ether) to give 9 (26 mg, 96%) as a white solid. 9: R_f 0.25 (50% ethyl acetate

in petroleum ether); mp 185 °C dec (from ethyl acetate–petroleum ether); UV (CHCl_3) λ_{max} (relative intensity) 241 (0.83), 285 (0.32), 347 (0.45) nm; IR (CCl_4) ν_{max} 3042, 2978, 2876 cm^{-1} ; ^1H NMR (500 MHz, acetone- d_6) δ 7.43, 7.21 (2 s, 2 H, phenolic OH), 4.53 (ddd, J = 8.5, 6.0, and 3.0 Hz, 1 H, CHOH), 4.29 (d, J = 6.0 Hz, 1 H, OH), 2.43–2.40 (m, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.13 (s, 6 H, 2 aromatic CH_3), 2.13–2.05 (m, 3 H, CH_2CHOH and $-\text{CH}_2-$), 1.75–1.67 (m, 1 H, $-\text{CH}_2-$); ^{13}C NMR (125 MHz, THF- d_4) δ 149, 148, 126, 125, 114, 113, 104, 103, 82, 80, 64, 40, 25, 22, 13; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$ (M^+) 256.1099, found 256.1099.

2,3-(3-Oxooceta-1,7-diyne-1,8-diyl)-5,6-dimethylquinone (10). A suspension of 8 (27.2 mg, 0.11 mmol), PCC (92.3 mg, 0.43 mmol), and 4 Å molecular sieves (110 mg) in CH_2Cl_2 (4 mL) was stirred at room temperature for 0.5 h. The mixture was passed through a short column of silica gel with 33% ethyl acetate and petroleum ether as eluent to give 10 (13.2 mg, 49%) as an orange solid. 10: R_f 0.32 (33% ethyl acetate in petroleum ether); IR (CCl_4) ν_{max} 2927, 2343, 1680, 1660 cm^{-1} ; ^1H NMR (500 MHz, THF- d_4) δ 2.85–2.82 (m, 2 H, COCH_2), 2.74–2.70 (m, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.20–2.10 (m, 2 H, $-\text{CH}_2-$), 2.01 (s, 6 H, 2 aromatic CH_3); MS (EI, 70 eV) 254 [($M + 2$) $^+$, presumably cycloaromatized product].

Cycloaromatizations of 7–10. Compounds were heated in NMR tubes at the indicated temperatures (Scheme III) until the starting material was consumed (for 7 and 9, the reactions were stopped after heating for 45 and 125 h, respectively). The solvent was removed under vacuo, and the product was purified by flash chromatography. Purified compounds 11–13 exhibited the following physical data.

1,4-Bis((*tert*-butylcarbonyl)oxy)-8-hydroxy-2,3-dimethyl-5,6,7,8-tetrahydroanthracene (11). 25% yield; R_f 0.20 (20% ethyl acetate in petroleum ether); IR (CCl_4) ν_{max} 3518, 2959, 2871, 1750 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.80, 7.75 (2 s, 1 H, H-9), 7.29 (s, 1 H, H-10), 5.35 (br s, 1 H, OH), 4.66 (br s, 1 H, CHOH), 2.91–2.80 (m, 2 H, H-4), 2.14 (s, 6 H, 2 aromatic CH_3), 2.00–1.88 (m, 2 H, H-2), 1.72–1.63 (m, 2 H, H-3), 1.53, 1.52 (2 s, 18 H, 2 \times $\text{C}(\text{CH}_3)_3$); HRMS (FAB) calcd for $\text{C}_{26}\text{H}_{34}\text{O}_5\text{Cs}$ ($M + \text{Cs}$) 559.1461, found 559.1472.

8-Hydroxy-2,3-dimethyl-5,6,7,8-tetrahydro-1,4-anthracenedione (12). 40% yield; R_f 0.25 (33% ethyl acetate in petroleum ether); UV (CHCl_3) λ_{max} (relative intensity) 226 (0.51), 262 (0.84), 343 (0.11) nm; IR (CCl_4) ν_{max} 3610, 2931, 2874, 1720, 1660 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.16, 7.79 (2 s, 2 H, H-9, H-10), 4.86 (t, J = 5.0 Hz, 1 H, H-1), 2.95–2.80 (m, 2 H, H-3), 2.12–1.96 (m, 2 H, H-4), 1.95–1.78 (m, 2 H, H-3); MS (EI, 70 eV) 256 (M^+); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$ 256.1099, found 256.1100.

2,3-Dimethyl-5,6,7,8-tetrahydro-1,4,8-anthracenetriene (13). 30% yield; R_f 0.19 (20% ethyl acetate in petroleum ether); IR (CCl_4) ν_{max} 1698, 1663, 1552 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.70, 7.95 (2 s, 2 H, H-9, H-10), 3.11 (t, J = 6.5 Hz, 2 H, H-2), 2.74 (t, J = 7.0 Hz, 2 H, H-4), 2.21–2.15 (m, 8 H, H-3 and aromatic CH_3); MS (EI, 70 eV) 254 (M^+), 228, 200, 172, 117; HRMS (EI, 70 eV) calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3$ 254.0943, found 254.0948.

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