Syntheses and Bioactivities of Substituted 9,10-Dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrones. Unusual Reactivities with Amines

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A number of substituted 9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrones have been synthesized and their anticancer and antimalarial activities evaluated. A one-pot synthesis of 2,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4-dione (**4**) was achieved by heating a mixture of 1,4-dimethoxyanthracene, methoxyhydroquinone, silver oxide, and zinc iodide in toluene. Regioselective bromination of **4** and 2-methoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (**7**) with *N*-bromosuccinimide provided 2-bromo-3,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]-benzenoanthracene-1,4-dione and 2-bromo-3-methoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (**1**), respectively. The reactions of **1** with aliphatic primary amines and secondary amines, respectively, produced different products, a result most likely attributed to the different basicities (or nucleophilicities) and steric effects of the two kinds of amines. The structure of the displacement product, 2-bromo-3-[2-(*tert*-butoxycarbonyl)ethylamino]-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone, from the reaction of **1** with *tert*-butyl 3-aminopropanoate was unequivocally determined by a single-crystal X-ray analysis. IC_{50} values of triptycene bisquinones for the inhibition of L1210 leukemia cell viability are in the 0.11−0.27 μM range and for the inhibition of Plasmodium falciparum 3D7 are in the 4.7−8.0 μM range.

I. Introduction

The unique shape and spectral properties of triptycenes and triptycene quinones have attracted a number of studies on their synthesis and application in new devices,[1] but only limited reports on biological activities.[2] In our studies of beltenes[3] and their nanotubes and biological activity, triptycene bisquinones were required. Fortuitously, a number of triptycene bisquinones, particularly substituted analogues,[4] show potent anticancer[5] and antimalarial activities. Herein are reported the synthesis of 2-bromo-3-methoxy-9,10-dihydro-9,10-[1,2]-benzenoanthracene-1,4,5,8-tetrone (**1**) (a substituted triptycene bisquinone), its unusual addition reactions with aliphatic primary and secondary amines, and a summary of its biological activities.

II. Results and Discussion

In the reported synthesis of 5,8-disubstituted triptycene monoquinones,[1] a sequence of three reactions was carried out: Diels−Alder reaction of 1,4-dimethoxyanthracene (**2**)[6] and *p*-benzoquinone followed by isomerization[1c] of the adducts (stereoisomers) with potassium hydroxide and then oxidation with silver oxide. We have successfully combined these three reactions into one simple operation, viz. heating a mixture of anthracene **2** (derived from the reduction of 1,4-anthracenedione[5] with sodium hydrosulfite followed by sodium hydride and iodomethane), 1.4 equiv of methoxyhydroquinone (**3**), 2.7

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(2) Driscoll, J. S.; Hazard, G. F. Jr.; Wood, H. B., Jr.; Goldin, A. *Cancer Chemother. Rep.* **1974**, P2, *4*(2), 1.

(3) Reviews: (a) Schroder, A.; Mekelburger, H.-B.; Vogtle, F. *Top. Curr. Chem.* **1994**, *172*, 179. (b) Kohnke, F. H.; Mathias, J. P.; Stoddart, J. F. *Top. Curr. Chem.* **1993**, *165*, 1. (c) Stoddart, J. F. *J. Inclusion Phenom. Mol. Recog. Chem.* **1989**, *7*, 227. (d) Kohnke, F. H.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 892. Calculation of beltenes and cyclacenes: (e) Alder, R. W.; Sessions, R. B. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1849. (f) Angus, R. O., Jr.; Johnson, R. P. *J. Org. Chem.* **1988**, *53*, 314. (g) Choi, H. S.; Kim, K. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2256 and references therein. For other synthetic studies: (h) Kintzel, O.; Luger, P.; Weber, M.; Schluter, A.-D. *Eur. J. Org. Chem.* **1998**, 99. (i) Cory, R. M.; McPhail, C. L. *Tetrahedron Lett.* **1996**, *37*, 1987. (j) Graham, R. J.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 5770. (k) Alder, R. W.; Allen, P. R.; Edwards, L. S.; Fray, G. I.; Fuller, K. E.; Gore, P. M.; Hext, N. M.; Perry, M. H.; Thomas, A. R.; Turner, K. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3071.

(4) A preliminary report was presented at the 35th Midwest Regional Meeting of the American Chemical Society, St. Louis, MO; Oct 2000, Abstract No. 166.

(5) Our previously reported anti-cancer studies: Perchellet, E. M.; Magill, M. J.; Huang, X.; Brantis, C. E.; Hua, D. H.; Perchellet, J. P. *Anti-cancer Drugs*, **1999**, *10*, 749.

(6) Criswell, T. R.; Klanderman, B. H. *J. Org. Chem.* **1974**, *39*, 770.

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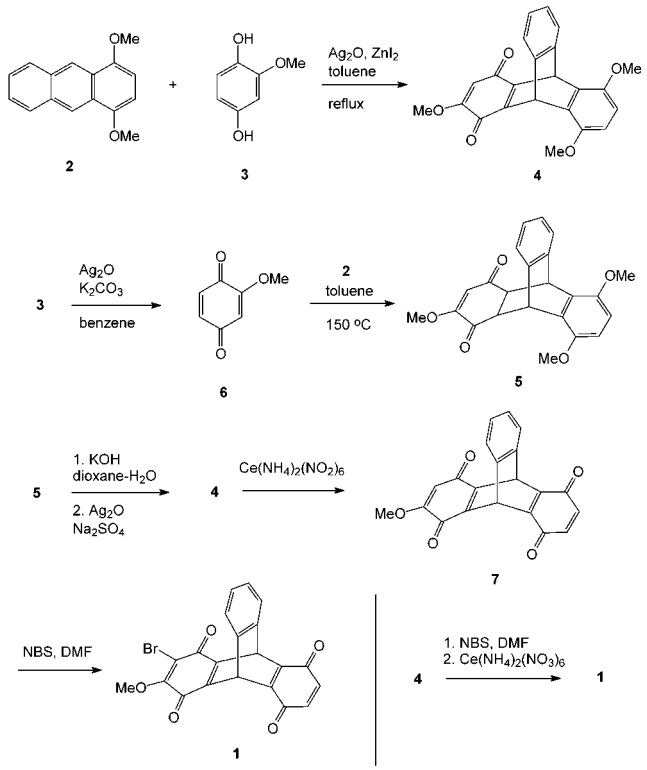
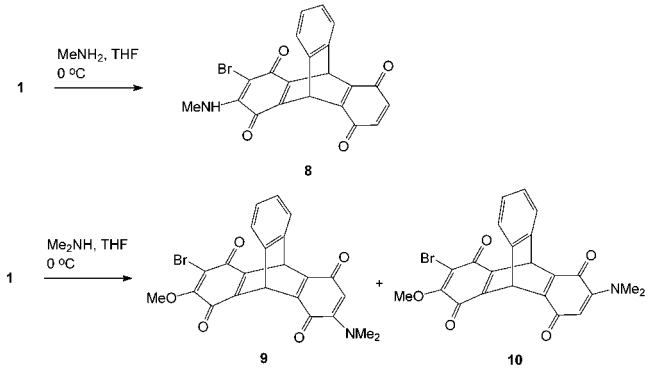
Scheme 1



equiv of silver oxide, and 0.2 equiv of zinc iodide in toluene under reflux for 4 days gave a 70% yield of triptycene monoquinone **4** (Scheme 1). Presumably, silver oxide oxidizes methoxyhydroquinone to methoxy-*p*-benzoquinone, which undergoes a Diels−Alder reaction with anthracene **2** to give adducts **5** (two stereoisomers). Compound **5** then undergoes oxidation with silver oxide to give quinone **4**. A catalytic amount of zinc iodide was added to facilitate the Diels−Alder reaction. No other regioisomers (such as isomers with the methoxy substituent attached at C4a) were detected. To verify the reaction sequence, methoxyquinone **6**, obtained from the oxidation of **3** with silver oxide and potassium carbonate in benzene (98% yield), was treated with anthracene **2** in toluene at 150 °C in a sealed tube to give adducts **5** (48% yield). Isomerization of ketones **5** with KOH in *p*-dioxane and water[1c] followed by oxidation with silver oxide gave monoquinone **4** (95% overall yield). Oxidation of monoquinone **4** with ceric ammonium nitrate[1c] afforded a 94% yield of triptycene bisquinone **7**. Regioselective bromination of **7** was achieved by the treatment with *N*-bromosuccinimide (NBS) in DMF at 25 °C for 10 h to give bromoquinone **1** (45% yield). Alternatively, compound **1** was also obtained from the bromination of monoquinone **4** with NBS in DMF at 40 °C followed by oxidation with ceric ammonium nitrate (59% overall yield). Apparently, the reactivity of the methoxyquinone moiety toward NBS is greater than that of quinone and 1,4-dimethoxyphenyl moieties.[7] It is likely that the methoxy substituent of **7** or **4** (at C2) enhances the

Scheme 2



nucleophilicity of the adjacent double-bonded carbon resulting in the bromination.

To permit an examination of the reactivities of triptycene bromoquinone **1** and the synthesis of new analogues, **1** was treated with primary and secondary amines (Scheme 2).[8] Surprisingly, compound **1** reacts with primary amines such as methylamine and secondary amines such as dimethylamine to give different regioisomeric products. Hence, treatment of bromide **1** with methylamine in THF at 0 °C for 20 min gave a 66% yield of displacement product **8** and a 21% recovery of **1**. On the other hand, when **1** was treated with dimethylamine in THF at 0 °C, regioisomers **9** and **10** (1:1 ratio) were isolated in 96% yield and separated by silica gel column chromatography. The regiochemistry of **9** and **10** has not been determined.[9] The presence of a bromine atom in the products was indicated by their mass spectra in which the M + 2 peaks (^{81}Br isotope) were almost equal in intensity to those of the molecular (EI) or quasimolecular (CI) ions. No other byproducts were identifiable in these reactions. These unusual addition reactions are unprecedented. It has been reported that *p*-benzoquinone undergoes addition reactions[10] with aliphatic primary amines to give a mixture of products including mono- and diadducts from the 1,4-addition reactions, while tetrachloro-1,4-benzoquinone and 2,3-dichloro-1,4-naphthoquinone react with secondary amines to give displacement products[11] (addition to the double bond followed by elimination of chlorine). Contrary to these literature results, bromide **1** reacts with primary amines to undergo displacement of the methoxy group instead of bromine[11c] and with secondary amines exclusively undergoes simple 1,4-addition on the unsubstituted quinone ring followed by oxidation. Presumably, a less basic primary amine, like methylamine,[12] undergoes 1,4-addition reaction on the more electron-deficient bromoquinone ring. Since the C2-bromine of **1** is an electron-withdrawing group, the resulting anion from the addition of an amine on C3

(7) It should be noted that 2-methyl-9,10-dimethoxyanthracene reacts with NBS to give 2-methyl-9,10-anthraquinone: (a) Jiang, H.; Xu, H.; Ye, J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 925. Under our reaction conditions, no oxidation of the 1,4-dimethoxyphenyl ring moiety of **4** with NBS was observed. Bromination of juglone (5-hydroxy-1,4-naphthoquinone) with NBS has been reported: (b) Wurm, G.; Geres, U. *Arch. Pharm*. **1989**, *322*, 155.

(8) Nucleophilic reactions of quinones have been reviewed: Kutyrev, A. *Tetrahedron* **1991**, *47*, 8043. Nucleophilic reactions of triptycene quinones have not been reported.

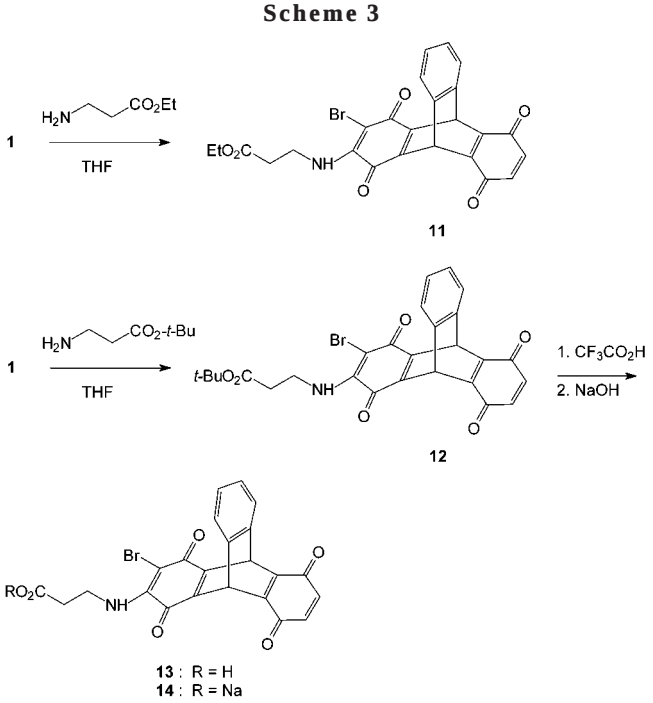
(9) Recrystallization of compounds **9** or **10** from different organic solvents such as ethyl acetate, diethyl ether, diisopropyl ether, ethanol, etc. failed to provide single crystals suitable for X-ray analysis.

(10) Ott, R.; Pinter, E.; Kajtna, P. *Monatsh. Chem*. **1980**, *111*, 813.

(11) (a) Gauss, W. Heitzer, H.; Petersen, S. *Liebigs Ann. Chem*. **1972**, *764*, 131. Displacement of 2-methoxy-1,4-naphthoquinone[11a] and 6-methoxy-5,8-quinolinequinone has also been reported: (b) Pratt, Y. T.; Drake, N. L. *J. Am. Chem. Soc*. **1955**, *77*, 37. Displacement of 7-bromo-6-methoxy-5,8-quinolinedione with ammonia: (c) Liao, T. K.; Nyberg, W. H.; Cheng, C. C. *Angew. Chem., Int. Ed. Engl*. **1967**, *6*, 82.

(12) The pK_b values of methylamine and dimethylamine are 3.38 and 3.23, respectively: Hand C. W.; Blewitt, H. L. *Acid−Base Chemistry*; Macmillan: New York, 1986; pp 253, 254.

Scheme 3



would be more stabilized than that from the addition on C2. On the other hand, a more basic secondary amine, like dimethylamine (a more reactive amine than methylamine),[12] is less affected by the electronic effect of the quinone ring and is more affected by steric effects, and consequently prefers to add on the unsubstituted (less hindered) quinone moiety to provide compounds **9** and **10**.

Due to the potent anticancer activity of amine **8** (vide infra) and the need for water-soluble analogues, aliphatic primary amines containing an ester function were used to synthesize various triptycene quinones, and their biological activities were studied (Scheme 3).

Treatment of bromide **1** with ethyl 2-aminopropanoate in THF at −40 °C for 6 h afforded a 46% yield of displacement product **11** along with 30% recovered starting material **1**. No other regioisomers were detected. Similarly, reaction of **1** with *tert*-butyl 2-aminopropanoate at −40 °C for 8 h gave a 62% yield of **12**. Recrystallization of **12** in hexane/ethyl acetate (5:1) afforded single crystals whose structure was unequivocally shown by X-ray analysis (Figure 1).[13] Interestingly, in the stacking of crystals, the three different bridges (rings) of triptycene **12** stack with the same groups of three other molecules with an average distance of ∼3.7 Å. That is, the phenyl ring of a molecule stacks with the phenyl ring of another molecule, unsubstituted quinone ring stacks with an unsubstituted quinone ring, and the substituted quinone ring stacks with a substituted quinone ring (C2 of one molecule is on top of C4 of another molecule). A hydrogen bond was present between the NH and the C4-oxygen (a distance of 2.186 Å). Deprotection of the *tert*-butyl ester of **12** by treatment with trifluoroacetic acid in dichloromethane gave a quantitative yield of acid **13**. The water-soluble sodium salt **14** was obtained by the treatment of **13** with 1 equiv of sodium hydroxide.

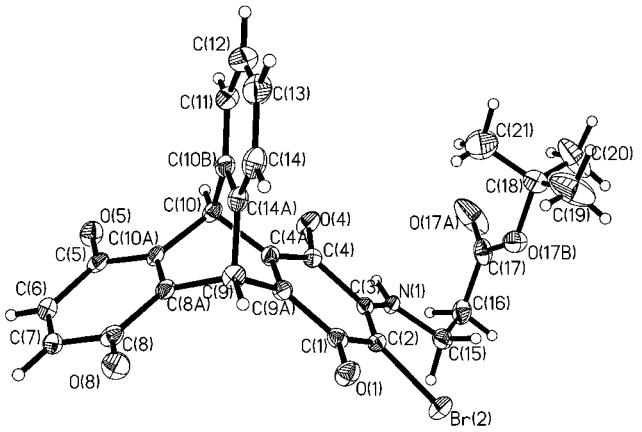


Figure 1. ORTEP drawing of X-ray structure of **12**.

Table 1. Cytotoxicities of Triptycene Bisquinone Analogs in the L1210 Leukemic Cell System in Vitro

compd	IC_{50} (μM)	compd	IC_{50} (μM)
1	0.135 ± 0.009	**11**	0.110 ± 0.008
7	0.125 ± 0.012	**12**	0.176 ± 0.014
8	0.270 ± 0.015	**13**	0.694 ± 0.042
9	0.116 ± 0.010	**14**	2.151 ± 0.093

Anticancer and antimalarial activities of triptycene bisquinones have been evaluated. Table 1 summarizes IC_{50} values (the concentrations of drugs required to inhibit by 50% the viability of L1210 leukemic cells at day 4) of various triptycene bisquinones. In general, the IC_{50} values are in the 0.11−0.27 μM range with the exception of carboxylic acid **13** and its sodium salt **14**. Possibly, the ability of sodium salt **14** to pass through the cell membrane may decrease as the water solubility increases. This would, in turn, decrease the ability of this compound to destroy cancer cells. The IC_{50} value of daunomycin, a known anticancer drug, under similar treatment conditions is 0.030 μM.[5] Triptycene bisquinones induce DNA cleavage and inhibit nucleoside transport. In contrast, daunomycin is a DNA topoisomerase II inhibitor that does not block nucleoside transport. Moreover, triptycene bisquinones **7**−**9** and ritonavir[14] inhibit *Plasmodium falciparum* 3D7 (a malaria strain)[15a] with IC_{50} values of 8.0, 4.7, 5.6, and 9.7 μM, respectively. Malaria protease plasmepsin II[15b−d] was also inhibited by compounds **8**, **9**, and ritonavir,[14] and IC_{50} values of these compounds are 9.7, 23.6, and 0.10 μM, respectively. Presumably, these reactive triptycene bisquinones, such as **8** and **9**, undergo addition reactions with lysine,[16] tryptophan, histidine, and cysteine[17] residues of proteins to produce cross-linked proteins.

(13) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre as no. CCDC 175022. The coordinates can be obtained on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. *R* factor of the X-ray analysis is 0.0379 and the crystals have a space group of *C*2/*c*. It should be noted that only one single-crystal X-ray structure of triptycene monoquinone has been reported: Wiehe, A.; Senge, M. O.; Kurreck, H. *Liebigs Ann. Chem*. **1997**, 1951.

(14) Ritonavir, a protease inhibitor, was used for comparison. Danner, S. A.; Carr, A.; Leonard, J. M.; Lehman, L. M.; Gudiol, F.; Gonzales, J.; Raventos, A.; Rubio, R.; Bouza, E.; Pintado, V.; Aguado, A. G.; Garcia de Lomas, J.; Delgado, R.; Borleffs, J. C. C.; Hsu, A.; Valdes, J. M.; Boucher, C. A. B.; Cooper, D. A. *N. Engl. J. Med*. **1995**, *333*, 1528.

(15) The protocol for bioassay for *P. falciparum* 3D7: (a) Opsenica, D.; Pocsfalvi, G.; Juranic, Z.; Tinant, B.; Declercq, J.-P.; Kyle, D. E.; Milhous, W. K.; Solaja, B. A. *J. Med. Chem*. **2000**, *43*, 3274. Bioassay for plasmepsin inhibition: (b) Jiang, S.; Prigge, S. T.; Wei, L.; Gao, Y.; Hudson, T. H.; Gerena, L.; Dame, J. B.; Kyle, D. E. *Antimicrobial Agents Chemother*. **2001**, *45*, 2577. (c) Carroll, C. D.; Orlowski, M. *Adv. Exp. Med. Biol*. **1998**, *436*, 375. (d) Carroll, C. D., T. O. Johnson, S. Tao, G. Lauri, M. Orlowski, I. Y. Gluzman, D. E. Goldberg, and R. E. Dolle. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3203.

III. Conclusions

A one-pot synthesis of 2,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4-dione (**4**) was accomplished in high yield by heating a mixture of 1,4-dimethoxyanthracene (**2**), methoxyhydroquinone (**3**), silver oxide, and zinc iodide in toluene. A regioselective bromination of triptycene bisquinone **7** with NBS was found to provide 2-bromo-3-methoxy-9,10-dihydro-9,10-[1,2]-benzenoanthracene-1,4,5,8-tetrone (**1**). Under similar reaction conditions, monoquinone **4** was also brominated with NBS to provide the C2-bromo derivative. Unusual displacement and addition reactions of **1** with aliphatic primary and secondary amines, respectively, provided a number of potent anticancer agents. Other nucleophilic reagents such as thiols and aminocarbohydrates may be suitable for the above reactions. The potent anticancer and antimalarial activities provide lead compounds for further investigation in new drug discovery. The aforementioned reactions and biological studies are being undertaken.

IV. Experimental Section

General Methods. NMR spectra were obtained at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$, unless otherwise indicated. IR spectra are reported in wavenumbers (cm^{-1}). FAB spectra were taken by using Xe beam (8 KV) and *m*-nitrobenzyl alcohol as matrix. High-resolution mass spectra were obtained using the MALDI technique and $CHCl_3$/MeOH (1:1) as a matrix. Davisil silica gel, grade 643 (200−425 mesh), was used for the flash column chromatographic separation.

1,4-Dimethoxyanthracene (2). To a cold (0 °C) methanol (20 mL) solution of 1.00 g (0.0042 mol) of quinizarin under argon was added 0.638 g (0.0168 mol) of sodium borohydride. The resulting mixture was stirred at 0 °C for 1 h. To it, was added 11 mL of 6 N HCl dropwise at 0 °C over a period of 10 min. The precipitated orange solids were collected, washed several times with distilled water, dried under vacuum, and recrystallized from acetone−ether to give 0.83 g (95% yield) of anthracene-1,4-dione[18] as yellow crystals: mp 204−206 °C; ^{1}H NMR δ 8.60 (s, 2 H, C9,10 H), 8.10 (dd, J = 6.4, 3.2 Hz, 2 H, C5,8 H), 7.70 (dd, J = 6.4, 3.2 Hz, 2 H, C6,7 H), 7.10 (s, 2 H, C2,3 H); ^{13}C NMR δ 184.7 (s, C=O), 140.1 (d), 134.8 (s), 130.2 (d), 129.6 (d), 128.9 (d), 128.4 (s).

To 2.00 g (1.00 mmol) of 1,4-anthracenedione was added a solution of 6.68 g (38.0 mmol) of sodium hydrosulfite in 50 mL of water and 50 mL of 1,4-dioxane. The resulting mixture was stirred at 25 °C for 3 h and added to 100 mL of water. The mixture was cooled over an ice−water bath, and the precipitated dark green solid was collected by filtration, washed twice with water, and dried under vacuum to give 1.75 g (87% yield) of 1,4-dihydroxyanthracene: mp 167−169 °C; ^{1}H NMR δ 8.70 (s, 2 H, C9,10 H), 8.05 (m, 2 H, C5,8 H), 7.50 (s, 2 H, C6,7 H), 6.60 (s, 2 H, C2,3 H); ^{13}C NMR δ 145.4, 130.5, 128.4, 125.3, 125.2, 120.6, 105.6.

To a 0.275 g (11.0 mmol) of oil-free sodium hydride under argon were added 1.00 g (4.80 mmol) of 1,4-dihydroxyanthracene, 0.75 mL (12.0 mmol) of iodomethane, and 10 mL of dry DMF. The solution was stirred at 25 °C for 1.5 h, diluted with 20 mL of water, and acidified with 6 N HCl (pH ∼2). The mixture was extracted three times with ethyl acetate, and the combined extract was washed twice with water and brine, dried ($MgSO_4$), and concentrated to give 1.07 g (94% yield) of compound **2**. Crystallization from ether/hexane (1:1) gave 0.89 g (78% yield) of yellow solids: mp 132−133 °C (lit.[6] 134−136 °C); MS (FAB) *m*/*z* 239 (M + 1), 238 (M^+); ^{1}H NMR δ 8.70 (s, 2 H, C9,10 H), 7.97 (dd, J = 6.1, 3.6 Hz, 2 H, C5,8 H), 7.40 (dd, J = 6.6, 3.2 Hz, 2 H, C6,7 H), 6.55 (s, 2 H, C2,3 H), 3.97 (s, 6 H, OCH_3); ^{13}C NMR δ 149.5 (s, C8a,10a), 131.5 (s, C4a,9a), 128.5 (d, C9,10), 125.5 (d, C5,8), 120.7 (d, C6,7), 100.9 (d, C2,3), 55.6 (s, OCH_3).

2,5,8-Trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4-dione (4). A mixture of 2.00 g (8.40 mmol) of 1,4-dimethoxyanthracene (**2**), 1.411 g (10.1 mmol) of methoxyhydroquinone (**3**), 3.90 g (16.8 mmol) of silver oxide, and 0.536 g (1.68 mmol) of zinc iodide in 30 mL of toluene under argon was refluxed for 3 d. To the mixture were added 0.25 g (1.79 mmol) of **3** and 1.30 g (5.60 mmol) of silver oxide, and the reaction mixture was refluxed for another day. The reaction mixture was cooled, diluted with 200 mL of dichloromethane, and filtered through Celite, and the filtrate was washed with aqueous NH_4Cl and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as solvent to give 2.21 g (70% yield) of **4**: mp 108−110 °C; ^{1}H NMR δ 7.43 (dd, J = 5.5, 3 Hz, 2 H), 7.00 (dd, J = 5.5, 3 Hz, 2 H), 6.52 (s, 2 H, C6,7 H), 6.25 (s, 1 H), 6.23 (s, 1 H), 5.71 (s, 1 H, C3 H), 3.79 (s, 6 H, OCH_3), 3.72 (s, 3 H, OCH_3); ^{13}C NMR δ 183.5 (C=O), 178.2 (C=O), 158.4, 153.8, 150.9, 150.5, 149.6, 149.5, 144.3, 144.1, 133.6, 133.5, 125.2 (2 C), 124.5, 124.4, 109.5, 105.6, 56.4, 56.38, 56.3, 41.5, 41.2. Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 73.51; H, 5.07.

2,5,8-Trimethoxy-4a,9,9a,10-tetrahydro-9,10-[1,2]benzenoanthracene-1,4-dione (5). A mixture of 1.00 g (7.10 mmol) of methoxyhydroquinone (**3**), 2.50 g (10.7 mmol) of silver oxide, and 1.20 g (8.50 mmol) of K_2CO_3 in 50 mL of benzene was stirred under argon at 25 °C for 3 h, and the mixture was filtered through Celite and washed with 5 mL of dichloromethane. The filtrate was concentrated to give 0.970 g (99% yield) of methoxybenzoquinone (**6**):[19] ^{1}H NMR δ 6.72 (s, 2 H), 5.95 (s, 1 H), 3.84 (s, 3 H); ^{13}C NMR δ 187.4, 181.6, 137.1, 134.4, 111.5, 107.6, 56.2. This material was used in the next step without purification.

A solution of 0.70 g (2.90 mmol) of **2** and 1.00 g (7.20 mmol) of **6** in 10 mL of toluene in a sealed tube was heated at 150 °C for 1 d, cooled to 25 °C, concentrated to dryness, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as solvent to give 0.52 g (48% yield) of compounds **5** as a mixture of stereoisomers (1:1) along with 0.62 g of **6**. The stereoisomers were partially separated by silica gel column chromatography; the stereochemistry has not been assigned. Compound **5**, less polar isomer: MS *m*/*z* 376 (M^+), 375; ^{1}H NMR δ 7.24−7.18 (m, 2 H), 7.08−7.04 (m, 2 H), 6.65 (s, 2 H, C6,7 H), 5.61 (s, 1 H), 5.33 (bs, 2 H), 3.82 (s, 6 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.12 (d, J = 9 Hz, 1 H), 3.06 (d, J = 9 Hz, 1 H); ^{13}C NMR δ 197.4 (C=O), 193.5 (C=O), 162.0, 148.7, 141.9, 140.4, 139.8, 131.6, 131.4, 129.3, 126.6, 125.3, 125.0, 113.7, 109.5, 109.3, 56.7, 56.4, 49.3, 48.6, 42.7, 42.6, 42.4. More polar isomer: mp 175−176 °C; MS *m*/*z* 376 (M^+), 375; ^{1}H NMR δ 7.40 (m, 2 H), 7.16 (m, 2 H), 6.60 (d, J = 8.8 Hz, 1 H), 6.56 (d, J = 8.8 Hz, 1 H), 5.65 (s, 1 H, =CH), 5.33 (bs, 2 H, C9,10 H), 3.76 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.13 (d, J = 9 Hz, 1 H), 3.08 (d, J = 9 Hz, 1 H); ^{13}C NMR δ 197.0 (C=O), 193.2 (C=O), 162.0, 149.7, 149.3, 142.1, 141.9, 130.1, 129.3, 126.7, 126.6, 124.2, 124.17, 113.4, 110.2, 109.8, 56.7, 56.6, 56.2, 49.6, 48.7, 42.7, 42.5. Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.11; H, 5.68.

1,4-Dihydroxy-2,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]-benzenoanthracene. To a solution of 0.77 g (2.0 mmol) of **5** (a mixture of stereoisomers) in 30 mL of 1,4-dioxane and 30 mL of water was added 1.12 g (20 mmol) of KOH. The solution was stirred at 25 °C for 1 h, acidified with 1 N HCl, and extracted three times with dichloromethane. The combined extract was washed with brine, dried ($MgSO_4$), and concen-

(16) Compound **1** reacted with L-lysine to give the expected C-3 displacement product. These data along with a full account of biological studies will be reported in due course.

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trated to give 0.77 g (100% yield) of 1,4-dihydroxy-2,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene: mp 257−259 °C; MS *m*/*z* 376 (M^+); ^{1}H NMR δ 7.43 (dd, J = 5.5, 3 Hz, 1 H), 7.38 (dd, J = 5.5, 3 Hz, 1 H), 6.96 (dd, J = 5.5, 3 Hz, 2 H), 6.51 (s, 2 H, C6,7 H), 6.29 (s, 1 H, C3 H), 6.09 (s, 1 H), 5.98 (s, 1 H), 5.3 (s, 1 H, OH), 4.96 (bs, 1 H, OH), 3.81 (s, 3 H, OCH_3), 3.805 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3); ^{13}C NMR (DMSO-d_6) δ 148.5, 148.3, 146.4, 146.0, 145.7, 144.1, 135.5, 135.0, 134.6, 132.6, 124.6, 124.4, 123.5, 123.3, 123.1, 109.0, 108.8, 97.4, 56.1 (2 C), 56.0, 40.4, 39.8. Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.45; H, 5.11.

Oxidation of 1,4-Dihydroxy-2,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene to 4. To a mixture of 0.77 g (2.0 mmol) of 1,4-dihydroxy-2,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene and 0.60 g (4.2 mmol) of sodium sulfate (anhydrous) in 15 mL of dried acetone under argon at 25 °C was added 0.56 g (4.0 mmol) of silver oxide. The mixture was heated under reflux for 6 h, cooled to 25 °C, diluted with dichloromethane, and filtered through Celite. The filtrate was concentrated to give 0.77 g of the crude product. Column chromatography on silica gel using a gradient mixture of hexane and ethyl acetate as solvent gave 0.73 g (95% yield) of **4**.

2-Methoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (7). To a solution of 0.77 g (2.0 mmol) of **4** in 16 mL of acetonitrile, 26 mL of 1,4-dioxane, and 10 mL of water was added 2.0 g (3.6 mmol) of ceric ammonium nitrate at 25 °C. The solution was stirred for 12 h, diluted with dichloromethane, and washed with water. The organic layer was dried ($MgSO_4$) and concentrated to give the crude product. Crystallization from ether gave 0.65 g (95% yield) of **7**: MS (CI) *m*/*z* 345 (M + 1), 317 (−CO); ^{1}H NMR δ 7.48 (dd, J = 5.5, 3 Hz, 2 H), 7.07 (dd, J = 5.5, 3 Hz, 2 H), 6.65 (s, 2 H, C6,7 H), 6.2 (s, 1 H), 6.18 (s, 1 H), 5.78 (s, 1 H, C3 H), 3.78 (s, 3 H, OCH_3); ^{13}C NMR δ 182.2, 182.17, 182.0, 176.9, 158.5, 152.5, 151.6, 151.5, 149.6, 142.2, 142.0, 135.4, 135.3, 125.8 (2 C), 125.4, 125.3, 105.7, 56.6 (OCH_3), 42.2, 41.9. Anal. Calcd for $C_{21}H_{12}O_5$: C, 73.25; H, 3.51. Found: C, 73.01; H, 3.80.

2-Bromo-3-methoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (1). To a solution of 0.30 g (0.87 mmol) of **7** in 20 mL of DMF under argon at 25 °C was added 0.16 g (0.87 mmol) of *N*-bromosuccinimide. After the solution was stirred for 10 h, it was diluted with water and extracted twice with ethyl acetate. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as solvent to give 0.29 g (45% yield) of **1**: mp 207−210 °C; MS EI *m*/*z* 424 and 422 (1:1, M^+), 344 (M − Br), 300, 287, 232, 152, 126; ^{1}H NMR δ 7.48 (dd, J = 5.5, 3 Hz, 2 H), 7.09 (dd, J = 5.5, 3 Hz, 2 H), 6.66 (s, 2 H, C6,7 H), 6.23 (s, 1 H), 6.16 (s, 1 H), 4.17 (s, 3 H, OCH_3); ^{13}C NMR δ 182.2 (s, CO), 182.0 (s, CO), 176.2 (s, CO), 175.5 (s, CO), 156.2, 151.6, 151.4, 150.2, 141.8, 135.5, 135.4, 126.2, 126.1, 126.07, 126.0, 125.6, 125.4, 117.2, 61.7 (OCH_3), 43.0, 42.1. Anal. Calcd for $C_{21}H_{11}BrO_5$: C, 59.60; H, 2.62. Found: C, 59.33; H, 2.87.

Synthesis of 1 from Bromination of 4 Followed by Oxidation. To a solution of 90 mg (0.24 mmol) of **4** in 5 mL of DMF under argon at 25 °C was added 52 mg (0.30 mmol) of *N*-bromosuccinimide (NBS). The solution was stirred at 40 °C for 12 h, diluted with diethyl ether, washed twice with water and once with brine, dried ($MgSO_4$), and concentrated to give 109 mg (quantitative yield) of 2-bromo-3,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4-dione: MS (EI) *m*/*z* 454, 452 (1:1, M^+); ^{1}H NMR δ 7.44 (dd, J = 5.5, 3 Hz, 2 H), 7.01 (dd, J = 5.5, 3 Hz, 2 H), 6.54 (s, 2 H, C6,7 H), 6.29 (s, 1 H), 6.22 (s, 1 H), 4.14 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3); ^{13}C NMR δ 177.7, 177.0, 156.4, 153.2, 151.6, 149.8, 149.7, 144.14, 144.1, 133.4, 125.7, 125.6 (2 C), 124.8, 124.7, 117.6, 109.9, 109.8, 61.8, 60.6, 56.6, 42.5, 41.6. This material was used in the next step without purification.

To a solution of 0.109 g (0.240 mmol) of 2-bromo-3,5,8-trimethoxy-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4-dione in 5 mL of acetonitrile, 6 mL of 1,4-dioxane, and 2 mL of water was added 0.660 g (1.20 mmol) of ceric ammonium nitrate. The solution was stirred at 25 °C for 6 h, diluted with ether, washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ether as eluant to give 60 mg (59% yield) of **1**.

2-Bromo-3-(methylamino)-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (8). A solution of 0.200 g (0.473 mmol) of **1** and 0.47 mL (0.946 mmol) of methylamine (2.0 M in THF) in 1 mL of THF was stirred under argon at 0 °C for 1 h. The solution was concentrated to dryness and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as solvent to give 0.132 g (66% yield) of **8** and 41 mg (21% recovery) of **1**. Compound **8**: mp >350 °C (polymerized); MS (CI) *m*/*z* 424, 422 (∼1:1; M + 1); ^{1}H NMR δ 7.48 (dd, J = 5, 3 Hz, 1 H), 7.45 (dd, J = 5, 3 Hz, 1 H), 7.07 (dd, J = 5, 3 Hz, 2 H), 6.64 (s, 2 H, C6,7 H), 6.28 (s, 1 H), 6.10 (s, 1 H), 5.88 (bs, 1 H, NH), 3.33 (d, J = 5.6 Hz, 3 H, CH_3N); ^{13}C NMR (acetone-d_6) δ 183.33, 183.3, 178.2, 170.9, 154.4, 152.3, 152.0, 148.0, 147.0, 143.7, 143.5, 136.4, 136.3, 126.5 (2 C), 126.0, 125.7, 125.0, 44.3, 42.9, 33.2. Anal. Calcd for $C_{21}H_{12}BrNO_4$: C, 59.74; H, 2.86. Found: C, 59.74; H, 2.76.

2-Bromo-3-methoxy-6-(dimethylamino)-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (9) and 2-Bromo-3-methoxy-7-(dimethylamino)-9,10-dihydro-9,10-[1,2]-benzenoanthracene-1,4,5,8-tetrone (10). To a solution of 0.200 g (0.473 mmol) of **1** in 2 mL of THF under argon at 0 °C was added 0.24 mL (0.473 mmol) of dimethylamine (2.0 M in THF). After being stirred at 0 °C for 2 h, the reaction solution was concentrated to dryness and column chromatographed on silica gel using a mixture of benzene and ethyl acetate (10:1) as solvent to give 0.099 g (48% yield) of **9** (less polar isomer; the regiochemistry has not been determined) and 0.098 g (48% yield) of **10** (more polar).

Less polar isomer: MS (CI) *m*/*z* 468, 466 (∼1:1; M + 1); ^{1}H NMR δ 7.47−7.43 (m, 2 H, Ar−H), 7.05−7.02 (m, 2 H, Ar−H), 6.22 (s, 1 H), 6.14 (s, 1 H), 5.38 (s, 1 H, C7 H), 3.80 (s, 3 H, OCH_3), 3.11 [s, 6 H, $(CH_3)_2N$]; ^{13}C NMR δ 181.4 (2 C), 181.2 (2 C), 153.7, 150.4, 149.3, 144.1, 143.9, 142.2, 141.8, 139.1, 127.1, 125.5, 125.3, 124.7, 124.2, 102.5, 61.1, 42.8, 42.7, 42.0, 41.4; HRMS *m*/*z* 466.0285 (466.0290, calcd for $C_{23}H_{17}BrNO_5$, M−H^+).

More polar isomer: MS (CI) *m*/*z* 468, 466 (∼1:1; M + 1); ^{1}H NMR δ 7.48−7.42 (m, 2 H, Ar−H), 7.04−7.01 (m, 2 H, Ar−H), 6.24 (s, 1 H), 6.16 (s, 1 H), 5.39 (s, 1 H, C7 H), 3.79 (s, 3 H, OCH_3), 3.10 [s, 6 H, $(CH_3)_2N$]; ^{13}C NMR δ 181.6 (2 C), 181.4 (2 C), 154.0, 150.7, 149.6, 144.9, 144.0, 142.6, 141.5, 139.8, 127.2, 125.6 (2 C), 125.0, 124.3, 102.4, 61.2, 43.0 (2 C), 42.0, 41.9; HRMS *m*/*z* 466.0285 (466.0290, calcd for $C_{23}H_{17}BrNO_5$, M − H^+).

2-Bromo-3-[2-(ethoxycarbonyl)ethylamino]-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (11). To a mixture of 5.70 mg (0.236 mmol) of oil-free NaH in 2 mL of DMF under argon at 0 °C was added 36.3 mg (0.236 mmol) of β-alanine ethyl ester hydrochloride (ethyl 3-aminopropanoate hydrochloride). The solution was stirred at 0 °C for 30 min and cooled to −46 °C, and a solution of 100 mg (0.236 mmol) of **1** in 1 mL of DMF was added via cannula. The solution was stirred at −46 °C for 6 h, diluted with a mixture of ethyl acetate and benzene (1:1), washed twice with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as solvent to give 55 mg (46% yield) of **11** and 30 mg (30% recovery) of **1**. Compound **11**: mp 119−121 °C; MS *m*/*z* 510, 508 (∼1:1; M + 1), 422, 420 (1:1); ^{1}H NMR δ 7.45−7.42 (m, 2 H, Ar-H), 7.08−7.04 (m, 2 H, Ar-H), 6.65 (s, 2 H, C6,7 H), 6.3 (bs, 1 H, NH), 6.27 (s, 1 H), 6.10 (s, 1 H), 4.16 (q, J = 7 Hz, 2 H, OCH_2), 4.03 (q, J = 6 Hz, 2 H, CH_2N), 2.64 (t, J = 6 Hz, 2 H, CH_2CO), 1.26 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR δ 184.0, 183.6, 182.6, 182.3, 177.3, 171.7, 154.5, 151.8, 151.7, 147.4, 144.3, 142.4, 142.2, 135.8, 135.5, 126.2, 126.1, 125.9, 125.3, 61.3, 43.7, 42.2, 40.5, 35.4, 14.4. Anal. Calcd for $C_{25}H_{18}BrNO_6$: C, 59.07; H, 3.57. Found: C, 58.69; H, 3.72.

2-Bromo-3-[2-(*tert*-butoxycarbonyl)ethylamino]-9,10-dihydro-9,10-[1,2]benzenoanthracene-1,4,5,8-tetrone (12). To a mixture of 12.0 mg (0.496 mmol) of oil-free NaH in 2 mL of DMF under argon at 0 °C was added 90.0 mg (0.496 mmol) of β-alanine *tert*-butyl ester hydrochloride. The solution was

stirred at 0 °C for 30 min and cooled to −46 °C, and a solution of 201 mg (0.496 mmol) of **1** in 1 mL of DMF was added via cannula. The solution was stirred at −46 °C for 8 h, diluted with a mixture of ethyl acetate and benzene (1:1), washed twice with water and brine, dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane and ethyl acetate (10:1) as solvent to give 165 mg (62% yield) of **12**: mp 171−173 °C; MS *m*/*z* 538, 536 (~1:1; M + 1), 482, 480 (1:1); ^{1}H NMR δ 7.45−7.42 (m, 2 H, Ar-H), 7.08−7.04 (m, 2 H, Ar-H), 6.64 (s, 2 H, C6,7 H), 6.27 (s, 1 H), 6.22 (bs, 1 H, NH), 6.10 (s, 1 H), 4.00 (q, J = 6.7 Hz, 2 H, CH_2N), 2.55 (t, J = 6.7 Hz, 2 H, CH_2CO), 1.44 (s, 9 H, CH_3); ^{13}C NMR δ 182.3, 182.0, 177.0, 173.5, 170.6, 154.1, 151.4, 151.37, 147.0, 144.2, 142.1, 141.9, 135.4, 135.2, 128.8, 125.8, 125.76, 125.5, 125.0, 81.5, 43.5, 41.9, 40.5, 36.2, 28.0 (3 C). Anal. Calcd for $C_{27}H_{22}BrNO_6$: C, 60.46; H, 4.13. Found: C, 60.75; H, 4.39.

***N*-(2-Bromo-9,10-dihydro-1,4,5,8-tetraoxo-9,10-[1,2]benzenoanthracene-3-yl)-3-aminopropanoic Acid (13).** A solution of 0.100 g (0.187 mmol) of **12** and 0.2 mL (2.60 mmol) of trifluoroacetic acid in 5 mL of dichloromethane was stirred at 0 °C for 1 h and then at 25 °C for 2 h. The solution was concentrated to dryness and crystallized from benzene to give 0.090 g (100% yield) of purple solid: mp 149−151 °C; MS *m*/*z* 482, 480 (~1:1; M + 1), 422, 420 (1:1); ^{1}H NMR δ 7.49−7.46 (m, 2 H), 7.08−7.06 (m, 2 H), 6.64 (s, 2 H), 6.27 (s, 1 H), 6.22 (bs, 1 H, NH), 6.10 (s, 1 H), 4.04 (q, J = 6 Hz, 2 H, CH_2N), 3.40 (bs, 1 H, OH), 2.73 (t, J = 6 Hz, 2 H, CH_2); ^{13}C NMR (CD_3OD) δ 182.8, 182.77, 177.2, 174.2, 174.1, 151.6, 151.4, 147.6, 145.6, 142.9, 142.6, 137.9, 135.4, 129.0, 128.9, 128.2, 128.18, 126.1, 125.2, 43.8, 42.4, 42.3, 34.8; HRMS *m*/*z* 483.0304 (483.0317, calcd for $C_{23}H_{18}BrNO_6$, M − H^+; bisquinone rings were reduced under the mass spectrum measuring conditions). Anal. Calcd for $C_{23}H_{14}BrNO_6$: C, 57.52; H, 2.94. Found: C, 56.72; H, 2.88.

Cell Viability Assay.[5] L1210 lymphocytic leukemia cells were seeded in triplicate at an initial density of 9375 cells/mL of RPMI 1640 medium supplemented with 8.25% fortified bovine calf serum and penicillin (100 IU/mL)−streptomycin (100 μg/mL) and incubated at 37 °C in 48 well Costar cell culture plates for 4 d in the presence or absence (control) of increasing concentrations of the triptycene bisquinones. Daunomycin was tested under similar conditions for comparison. The viability of drug-treated cells was assessed from their ability to bioreduce the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) reagent in the presence of phenazine methosulfate (PMS) into a water-soluble formazan product which absorbs at 490 nm.[20] After 4 d in culture, cell samples (about 10^6/0.5 mL/well for controls) were further incubated at 37 °C for 3 h in the dark in the presence of 0.1 mL of MTS/PMS (2:0.1) reagent, and their relative cell viability was estimated by recording the absorbance at 490 nm, using an automatic microplate reader.[5] Cell viability results (means ± SD, n = 3) were expressed as the percentage of the net absorbance of MTS/formazan after bioreduction by vehicle-treated control tumor cells at day 4 (A_{490nm} = 1.837 ± 0.125, 100 ± 7%). Blank values (A_{490nm} = 0.325 at day 4) for cell-free culture medium supplemented with MTS/PMS reagent were subtracted from the results. IC_{50} values were calculated from linear regression of the slopes of the log-transformed concentration−survival curves.

Antimalarial Activity Assay. The reported protocol[15a] was followed.

Plasmepsin Assay. The substrate used for the plasmepsin assay (BACHEM) is a synthetic peptide (Dabcyl-Glu-Arg-Nle-Phe-Leu-Ser-Phe-Pro-Edans) designed to mimic the cleavage site present in hemoglobin. The kinetic constants for the substrate are K_m = 0.78 s^{-1} and $K_{cat.}$ = 0.10 μM for *P. falciparum* plasmepsin and K_m = 0.69 s^{-1} and $K_{cat.}$ = 0.16 μM for *P. vivax* plasmepsin. The substrate is conjugated with the fluorescent donor EDANS and the quencher DABCYL.[21] Fluorescence is only detectable when the EDANS group is separated from the DABCYL group by cleavage of the substrate.[22] Compounds were manually added to 96-well plates followed by the addition of assay buffer (15 mM NaCl, 100 mM formate, pH 4.4) using an automated dilutor. After thorough mixing and dilution, the contents of the plates were transferred to test plates, and plasmepsin enzyme solution was added with the dilutor. After a 10-min incubation at 37 °C, background fluorescence was measured with a fluorescence plate reader. Finally, the substrate was added (final concentration of 10 μM), and the reaction mixture was incubated for 30 min at 37 °C followed by fluorescence detection. Each compound in this prescreen was tested in triplicate at the concentration of 10 μg/mL. Compounds that reduced the activity of plasmepsin by 50% or more at this concentration were selected for a second screen to determine IC_{50} values.

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Supporting Information Available: X-ray details for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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