Synthesis of Cyclopentanthraquinones: Analogues of Mitomycin C

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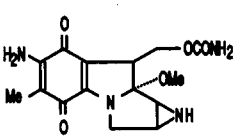
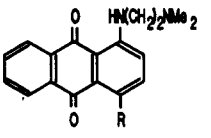
2,3-Dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (cyclopentanthraquinone) derivatives bearing a mustard side chain at C-4 and an aziridine ring at the cyclopentene moiety were synthesized. Such a compound may be viewed as an analogue of mitomycin C (MC) and may exhibit bifunctional DNA-alkylating and DNA-intercalating agent. The key intermediate, 4-hydroxy-2,3-di-O-substituted cyclopentanthraquinone, was synthesized by Deils–Alder reaction of naphthoquinone with various 4,5-dihydroxy-1-vinylcyclopent-1-ene derivatives. Introduction of a mustard side chain to the OH group at C-4 and subsequent construction of an aziridine-ring on C_2–C_3 of the cyclopentanthraquinone molecule furnished the target compound, 2,3-aziridino-4-[2-[*N*,*N*-bis(2-chloroethyl)amino]ethoxy]-2,3-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (**37**). It was found that both the aziridine function and the mustard side chain play a significant role in their cytotoxicity against leukemic L1210 and HL-60 cell growth in culture and the inhibition of topoisomerase II kDNA decatenation.

Mitomycin C (MC, 1), being used clinically for treatment of cancer, has been the subject of chemical synthesis and modification due to its potent activity and intriguing chemical structure.[1] This antibiotic is now known to act as a bifunctional alkylating agent that cross-links to DNA, after a series of biotransformations.[2] Under a variety of reductive conditions (i.e., chemical, enzymatic, catalytic, etc.), MC is activated and converted into either the corresponding semiquinone or hydroquinone mitosene intermediate, which bear two reactive sites at C-1 and C-10 and enable MC to bind covalently at the minor groove of DNA double strand.[3-10] It was reported by Tomasz et al.[3,4] that MC forms interstrand cross-links at two diagonally opposed dG residues in a CpG or GpC sequence.

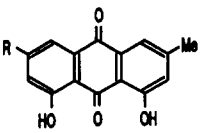
Archer et al.[11,12] reported that lucanthone (**2**) and its derivatives possess potent antischistosomal and antitumor activities. They also found that lucanthone can be biooxidized to form hycanthone (**3**), which is converted enzymically to the ester (**3**, R = CH_2OE). The ester possesses a good leaving group and is able to form a cation (**3**, R = CH_2^+) via nonenzymatic dissociation. The ion is then capable of intercalating into DNA and monoalkylating the DNA to form a covalently bound drug–DNA complex. More recently, it was shown[13] that inactive natural products, chrysophanol (**4**) and emodin (**5**), can be converted into potently active agents against certain tumor cell growth by attaching an alkylating side chain to the flat molecules (**6a** and **7a**). The 3-[[bis(2-chloroethyl)amino]methyl]-1,8-dimethoxyanthraquinones (**6b** and **7b**), which would be incapable of intercalating into DNA due to the presence of two bulky methoxy groups, did not show any significant activity.[13]



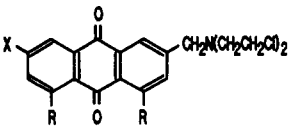
1 Mitomycin-C (MC)



2 R = Me Lucanthone
3 R = CH_2OH Hycanthone



4 R = H Chrysophanol
5 R = OH Emodin



6a X = H R = OH
6b X = H R = OMe
7a X = OMe R = OH
7b X = R = OMe

It is, therefore, of interest to design and synthesize cross-linking alkylating agents, similar to MC, with the intercalation potential. We chose the planar cyclopent[*a*]-anthracene-9,10-dione (cyclopentanthraquinone) as the chromophone, which would be anticipated to exhibit DNA intercalating and alkylating properties after introduction of an aziridine ring to C_2–C_3 and a carbamate or a mustard side-chain to C_4 of the molecule. Such compounds, unlike MC, may intercalate into DNA, and, as MC, may undergo bioreduction to the corresponding semiquinone or hydroquinones, which would be susceptible to nucleophilic attack by DNA by opening the aziridine ring. On the other hand, the activated carbamate side chain or the alkylating function (mustard side chain) on C_4 would bind

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(1) Carter, S. K.; Crooke, S. T. Mitomycin C. *Current Status and New developments*; Academic Press: New York, 1979.
(2) Moore, H. W. *Science* **1977**, *197*, 527.
(3) Tomasz, M.; Lipman, R. *Biochemistry* **1981**, *20*, 5056.
(4) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G. L., Nakanishi, K. *Science* **1987**, *235*, 1204.
(5) Horneman, U.; Keller, P. J.; Kozlowski, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 7121.
(6) Hornemann, U.; Igichi, K.; Keller, P. J.; Kozlowski, J. F.; Kohn, J. H. *J. Org. Chem.* **1983**, *48*, 5026.
(7) Andrews, P. A.; Pan S.-S.; Glover, C. J.; Bachur, N. R. *J. Am. Chem. Soc.* **1986**, *108*, 4158.
(8) Egbertson, M.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1987**, *52*, 4424.
(9) Peterson, D. M.; Fisher, J. *Biochemistry* **1986**, *25*, 4077.
(10) Hong, Y. P.; Kohn, H. *J. Am. Chem. Soc.* **1991**, *113*, 4634.
(11) Archer, S. *Ann. Rev. Pharmacol. Toxicol.* **1985**, *25*, 485.
(12) Pica-Mattoccia, L.; Cioli, D.; Archer, S. *Mol. Biochem. Parasitol.* **1988**, *31*, 87.
(13) Koyama, M.; Takahashi, K.; Chou, T-C.; Darzynkiewicz, Z.; Kapuscinski, J.; Kelly, T. R.; Watanabe, K. A. *J. Med. Chem.* **1989**, *32*, 1594.

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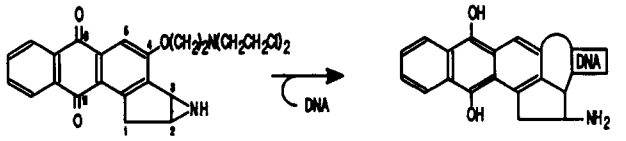
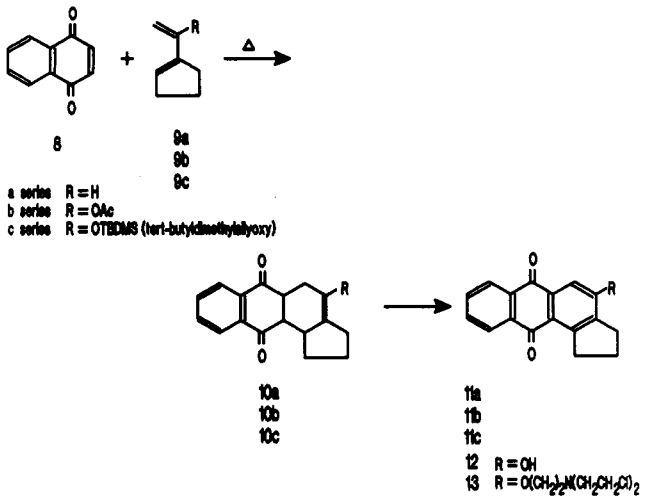
Scheme I



Scheme II

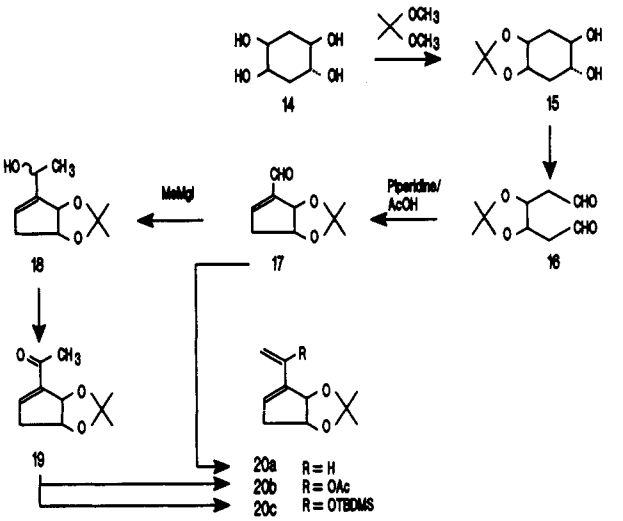


to another part of DNA resulting in the formation of a cross-linked DNA–drug complex (Scheme I). This report describes the synthesis of derivatives of cyclopent[*a*]-anthracene-9,11-dione (cyclopentanthraquinone) which bear both a mustard side chain and an aziridine ring.

Diels–Alder reaction of equimolar amounts of naphthoquinone (**8**) with the known dienes **9a**[14] and **9b**[15] afforded the tetracyclic compound 1a,2,3,5,5a,11a-hexahydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (**10a**, 82%) and its 4-acetoxy derivative (**10b**, 64%),respectively, under the conditions of Backer et al.[16] at 100 °C in toluene for several hours (Scheme II). Later, it was found that the condensation of **8** with 1-[(*tert*-butyldimethylsilyl)oxy]-1-(cyclopent-1-enyl)ethene[17] (**9c**) gave better results, as the reaction occurred at room temperature and the product **10c** was obtained in nearly quantitative yield. The Diels–Alder products **10a–c**, which were isolated in crystalline form, were then dehydrogenated to furnish cyclopentanthraquinones **11a–c** by treatment either with 10% Pd/C in refluxing xylene (**11a**, 70%; **11b**, 63%) or with DDQ in dioxane at room temperature (**11c**, 89%). Compounds **11b** (R = OAc) and **11c** (R = OTBDMS) were hydrolyzed to give the same 4-hydroxycyclopentanthraquinone (**12**), and subsequent reaction with tris(2-chloroethyl)amine afforded the cyclopentanthraquinone with a mustard side chain **16**.

In order to apply the above procedure for the synthesis of cyclopentanthraquinone bearing both the mustard side chain and the aziridine ring, we used cyclohexane-*cis*-1,2-*trans*-4,5-tetrol[18] (**14**, Scheme III) as starting material for the synthesis of the diene system. Compound **14** was allowed to react with 2,2-dimethoxypropane in DMSO in the presence of ion-exchange resin (Dowex 50w, H^+-form)

Scheme III



to give **15**, which was treated with sodium periodate to form 3,4-di-*O*-isopropylidene-3,4-dihydroxyadipinaldehyde (**16**). Intramolecular Aldol reaction of **16** was performed using a modified method of Brown et al.[19] by treatment with a mixture of piperidine/acetic acid (2:1 v/v) in toluene at 0 °C, giving rise to cyclopenyl aldehyde **17** in 53% yield.

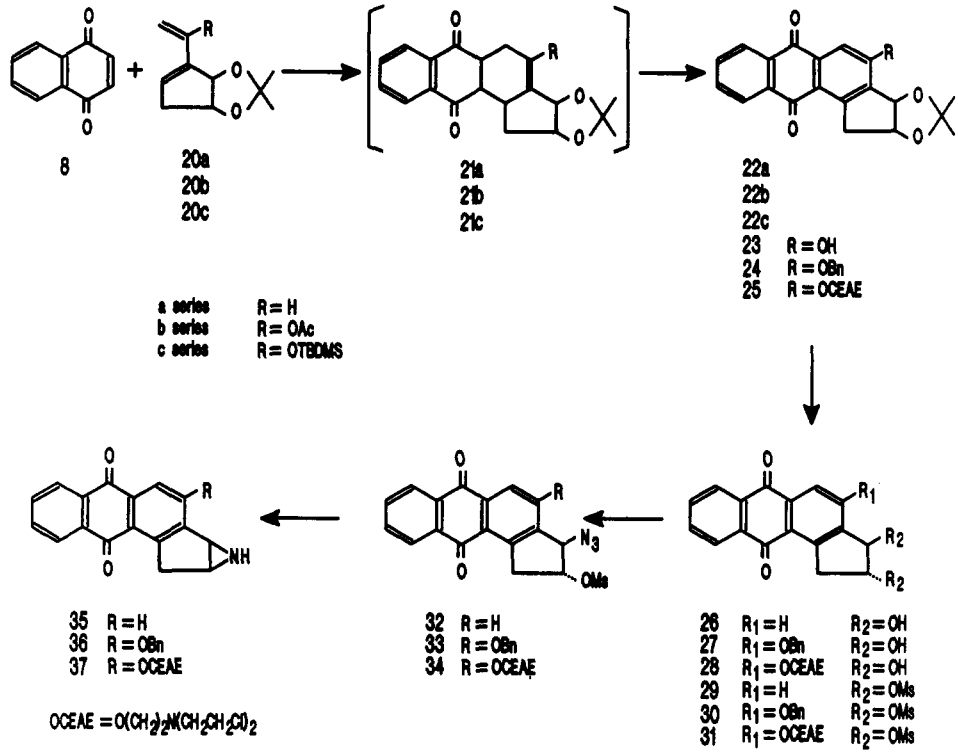
The ^1H NMR ($CDCl_3$) spectrum of **17**, which bears a cis diol, showed that the proton at C-2 is at δ 6.88 as an apparent triplet ($J_{2,3a}$ = 2.47, $J_{2,3b}$ = 2.60 Hz). The methylene protons at C-3 overlapped each other and appeared at δ 2.77–2.86 as a multiplet. The chemical shifts of the protons at C-4 and C-5 appeared at δ 4.87 and 5.50 as a multiplet and a doublet ($J_{4,5}$ = 6.04 Hz), respectively.

Compound **17** is unstable and after the reaction was completed must be neutralized immediately with aqueous $NaHCO_3$ solution and chromatographed to avoid total destruction of the aldehyde. Wittig reaction of **17** with freshly prepared triphenylphosphinemethylene gave cyclopent-1-enylethene **20a** in 54% yield. Grignard reaction of **17** with MeMgI afforded 1-[4,5-(isopropylidenedioxy)-cyclopent-1-enyl]ethanol (**18**), which was isolated as a diastereomeric mixture (2:1) in 77% yield. We also found that compound **18** can be prepared in slightly better yield (49%) directly from **15** without isolation and purification of the intermediates. Oxidation of **18** with MnO_2 gave 1-acetylcyclopent-1-ene **19**, which was then converted into dienes **20b** (R = OAc) or **20c** (R = OTBDMS) in good yields via enol lithiation by treatment with LDA followed by acylation with Ac_2O or silylation with *tert*-butyldimethylsilyl triflate (TBDMS-triflate) by a slight modification of the known procedure.[15] Although the freshly prepared dienes **20a–c** were sufficiently pure to be used in the Diels–Alder reaction with naphthoquinone (**8**), they were rather unstable at room temperature.

Diels–Alder reaction of **8** with the dienes **20a–c** (Scheme IV) afforded their respective intermediates (1a,2,3,5,5a,-11a-hexahydro-1*H*-cyclopent[*a*]anthracene-6,11-diones **21a–c**), which were not isolated, but directly oxidized to yield the corresponding 2,3-dihydrocyclopentanthraquinones by treatment with 10% Pd/C in refluxing nitroethane (**22a**, 76%) or toluene (**22b**, 30%) or with MnO_2 in dichloromethane (**22c**, 36%). It is worthy of note that

(14) Whelton, B. D.; Huitric, A. C. *J. Org. Chem.* **1971**, *36*, 1480.
(15) Caine, D.; Harrison, C. R.; Van Derveer, D. G. *Tetrahedron Lett.* **1983**, *24*, 1353.
(16) Backer, H. J.; van der Bij, J. R. *Rev. Trav. Chim.* **1943**, *62*, 561.
(17) Orban, J.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099.
(18) McCasland, G. E.; Furuta, S.; Johnson, L. F.; Schooler, J. N. *J. Org. Chem.* **1962**, *28*, 894.
(19) Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634.

Scheme IV



treatment of excess 8 (2.3 equiv) with **20b** in refluxing toluene for 6 h directly gave rise to the formation of **22b** (37%) and a small amount of 4-O-deacetylated product **23** (4%) even in the absence of 10% Pd/C. When 3 equiv of 8 was applied and heated in toluene for 20 h, compound **23** was obtained in almost quantitative yield. Apparently, the intermediate **21b** was oxidized by the excess 8 to form **22b**, which was deacetylated to yield **23**. Compound **23** can also be prepared by hydrolysis of **22b** (R = OAc) and **22c** (R = OTBDMS) with $Et_3N/MeOH/H_2O$ and tetrabutylammonium fluoride, respectively.

Treatment of **23** with benzyl bromide or with tris(2-chloroethyl)amine yielded 4-(benzyloxy)- and 4-[[[bis(2-chloroethyl)amino]ethyl]oxy]cyclopentanthraquinone (**24** and **25**), respectively. The 2,3-di-*O*-isopropylidene group of **23–25** was removed by treatment with trifluoroacetic acid at 0 °C to give the corresponding diols **26–28**. When **26** was allowed to react with methanesulfonyl chloride in pyridine, the 2,3-*cis*-bis(mesyloxy) derivative **29** was obtained in almost quantitative yield. Treatment of **29** with LiN_3 in DMF at room temperature selectively displaced the benzylic 3-(mesyloxy) group giving the 3-azido-substituted product **32** in 32% yield. Compound **32** was obtained in better yield (62%) when NaN_3 in DMSO was used instead of LiN_3/DMF at room temperature. We also found that diols **27** and **28** can be directly converted into their 3-azido derivatives **33** and **34** in 82 and 70% yield, respectively, by treatment with MsCl/pyridine followed by LiN_3/DMF without isolation of the bis(mesyloxy) intermediates. The LiN_3/DMF condition was found to give better results than NaN_3/DMSO. Upon treatment of 3-azidocyclopentanthraquinones **32–34** with triethylamine and triphenylphosphine in a mixture of THF and water, the corresponding 2,3-aziridino-2,3-*trans*-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-diones **35–37** were formed in moderate yields.

The structures of **35–37** were confirmed by ^1H NMR spectrometry. The ^1H NMR spectrum of **35** in $CDCl_3$ displayed a nonequivalent methylene function at C-1; one of the methylene protons (Ha-1) revealed at δ 3.72 as a quartet ($J_{1a,2}$ = 4.2, $J_{1a,1b}$ = 19.8 Hz), and the other proton (Hb-1) appeared at δ 3.82 as a doublet ($J_{1a,1b}$ = 19.8 Hz). The proton at C-2 and C-3 appeared at δ 3.33 and 3.44, respectively, and each displayed as a broad singlet (brs). The proton assignment was confirmed by proton–proton decoupling: irradiation of the broad singlet at δ 3.44 caused the broad singlet at δ 3.33 to form a doublet with a coupling constant of 4.2 Hz, while the signals at δ 3.72 and 3.82 were unchanged. Decoupling the broad singlet at δ 3.33 collapses the quartet at δ 3.72 (Ha-1) to a doublet with a J value of 19.8 Hz. The broad singlets at δ 3.33 and 3.44 became a doublet ($J_{2,3}$ = 4.2 Hz) and a triplet ($J_{1a,2} = J_{2,3}$ = 4.2 Hz), respectively, when the doublet at δ 3.82 (Hb-1) was irradiated. The ^1H NMR spectrum of **36** in $CDCl_3$ was also shown to have the same pattern as that of compound **35**. However, the protons, Ha-1 and H-3, shifted to δ 3.56 as a broad doublet (brd) and 3.65 (brs), respectively, due to the presence of the benzyloxy function at C-4. In **37**, the chemical shift of Ha-1 of the cyclopetene moiety partially overlapped with the mustard side chain at C-4. The Hb-1 proton displayed as a doublet at δ 3.83 with a coupling constant of 19.8 Hz.

The preliminary in vitro studies showed that the IC_{50} values for compounds **13**, **37**, and MC on inhibition of the growth of human leukemic HL-60 cell in vitro were 0.18, 0.075, and 0.004 μM, respectively, and the IC_{50} values for compounds **35**, **13**, **37**, and MC against L1210 leukemic cell were 9.09, 0.29, 0.064, and 0.005, respectively. It is apparent, therefore, that **37**, containing both the aziridine function and the mustard side chain, is more cytotoxic than **35**, lacking the mustard side chain, or **36**, the compound without the aziridine ring. It is also interesting to note that compounds **13**, **35**, and **37** were found to be more potent inhibitors than MC on topoisomerase II kDNA decatenation. Apparently, both aziridine function and mustard side chain play a significant role in the drug–

DNA interaction although the direct evidence has not been studied. Studies on detailed structure–activity relationships of the new bifunctional cyclopentanthraquinone alkylating–intercalating agents as well as the synthesis of the compounds with both aziridine ring and carbamate side chain are currently being undertaken in our laboratory.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70–230 mesh, ASTM, Merck). Thin-layer chromatography was performed on Analtech Uniplates with short-wavelength UV light for visualization. Elementary analyses were carried out by MHW Laboratories, Phoenix, AZ. ^{1}H-NMR spectra were recorded on a JEOL-FX90Q, Brucker ACF-250, or Brucker AMX-400 spectrometer with Me_4Si as the internal standard. Chemical shifts were reported in ppm (δ), and the signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), dd (double doublet), dt (double triplet), dm (double multiplet), ddt (double double triplet), ddq (double double quartet). Values reported for coupling constants are first order.

1a,2,3,5,5a,11a-Hexahydro-1*H*-cyclopent[*a*]anthracene-6,-11-dione (10a). A mixture of diene **9a**[14] (240 mg, 2.50 mmol) and 8 (370 mg, 2.30 mmol) in toluene (10 mL) was heated under reflux for 8 h. The solvent was removed in vacuo to dryness, and the residue was crystallized from ethanol to yield 479 mg (83%) of **10a**: mp 122–123 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.68–2.23 (9 H, m, 2 × H-1, H-1a, 2 × H-2, 2 × H-3, 2 × H-5), 3.32 (1 H, m, H-5a), 3.66 (1 H, t, $J_{11a,1a} = J_{5a,11a} = 4.7$ Hz, H-11a), 5.35 (1 H, br, H-4), 7.65–8.09 (4 H, m, Ar-H). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.80; H, 6.40.

By following the same procedure, the following cyclopentanthraquinones were synthesized:

4-Acetoxy-1a,2,3,5,5a,11a-hexahydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (10b) was prepared by the condensation of diene **9b**[15] (2.20 g, 14.5 mmol) and 8 (2.10 g, 13.3 mmol): yield 630 mg (64%); mp 158–160 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.60–1.91 (4 H, m, 2 × H-1, 2 × H-2), 2.09 (3 H, m, Ac), 2.17–2.55 (5 H, m, H-1a, 2 × H-3, 2 × H-5), 3.36–3.51 (1 H, m, H-5a), 3.64 (1 H, t, $J_{1a,11a} = J_{5a,11a} = 4.9$ Hz, H-11a), 7.67–8.08 (4 H, m, ArH). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.53; H, 5.99.

4-[(*tert*-Butyldimethylsilyl)oxy]-1a,2,3,5,5a,11a-hexahydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (10c) was prepared by the condensation of diene **9c**[17] (778 mg, 3.47 mmol) and 8 (300 mg, 1.90 mmol): yield 484 mg (67%); mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 0.03 and 0.06 (each 3 H, s, SiMe), 0.88 (9 H, s, *t*-Bu), 1.62–2.32 (9 H, m, 2 × H-1, 2 × H-1a, 2 × H-2, 2 × H-3, 2 × H-5), 3.25–3.48 (1 H, m, H-5a), 3.56 (1 H, t, $J_{1a,11a} = J_{5a,11a} = 4.7$ Hz, H-11a), 7.66–8.09 (4 H, m, Ar-H). Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.38; H, 7.83.

2,3-Dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (11a). A mixture of **10a** (50 mg, 0.2 mmol) and 10% Pd/C (40 mg) in xylene (8 mL) was heated under reflux for 3 h. The reaction mixture was filtered through a bed of Celite, and the filter cake was washed with $CHCl_3$. The combined filtrate and washings were evaporated in vacuo to dryness, and the residue was crystallized from Et_2O to give **11a**, 34 mg (70%): mp 125–126 °C (Et_2O) (lit.[19] mp 127 °C); ^{1}H-NMR ($CDCl_3$) δ 2.19 (2 H, dt, 2-CH_2), 3.00 (2 H, t, 3-CH_2), 3.50 (2 H, t, 1-CH_2), 7.54–8.32 (6 H, m, Ar-H). Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.35; H, 4.69.

4-Acetoxy-2,3-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (11b) was prepared in a similar manner from **10b** (1.23 g, 3.60 mmol): yield 705 mg (63%); mp 180–181 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.21 (2 H, dt, 2-CH_2), 2.37 (3 H, s, Ac), 2.88 (2 H, t, 3-CH_2), 3.56 (2 H, t, 1-CH_2), 7.89 (1 H, s, H-5), 7.71–8.31 (4 H, m, Ar-H). Anal. Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.60; H, 4.68.

4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (11c). To a solution of **10c** (190 mg, 0.50 mmol) in dioxane (5 mL) was added DDQ (260 mg, 1.1 mmol), and the mixture was stirred at room temperature for 2 h. An additional charge of DDQ (150 mg) was added to the mixture, which was stirred continuously for another 1 h. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column (2 × 20 cm) using CH_2Cl_2 as the eluent. Compound **11c** was obtained as yellow crystals, 167 mg (89%): mp 137–9 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 0.32 (6 H, s, 2 × SiMe), 1.04 (9 H, s, *t*-Bu), 2.17 (2 H, dt, H-2), 2.92 (2 H, t, H-3), 3.50 (2 H, t, H-1), 7.54 (1 H, s, H-5), 7.67–8.28 (4 H, m, Ar-H). Anal. Calcd for $C_{23}H_{26}O_3Si$: C, 72.97; H, 6.92. Found: C, 72.95; H, 6.76.

2,3-Dihydro-4-hydroxy-1*H*-cyclopent[*a*]anthracene-6,11-dione (12). A suspension of **11b** (240 mg, 0.78 mmol) in EtOH (10 mL) containing 30% aqueous NH_3 solution (3 mL) was stirred at room temperature until a clear solution was obtained. The mixture was stirred for an additional 30 min and then neutralized with AcOH. The precipitates were collected by filtration and washed successively with H_2O and Et_2O to give analytical pure **12**, 170 mg (82%) as yellow crystals: mp 307–309 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (2 H, m, CH_2-2), 2.77 (2 H, t, CH_2-3), 3.31 (2 H, t, CH_2-1), 7.42 (1 H, s, H-5), 7.71–8.12 (4 H, m, Ar-H), 10.82 (1 H, br, exchangeable, OH). Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.01; H, 4.66.

4-[2-[*N*,*N*-Bis(2-chloroethyl)amino]ethoxy]-2,3-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (13). A mixture of **12** (132 mg, 0.50 mmol), tris(2-chloroethyl)amine hydrochloride (360 mg, 1.5 mmol), and K_2CO_3 (4.0 g) in acetone (20 mL) was heated under reflux for 5 h (the deep purple color disappeared at this time). The mixture was filtered, and the filter cake was washed with $CHCl_3$. The combined filtrate and washings were evaporated in vacuo to dryness. The residue was dissolved in $CHCl_3$ (80 mL), washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column (2 × 30 cm) using toluene/EtOAc (20:1 v/v) as the eluent to give **13**, 85.0 mg (40%): mp 118–119 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 2.23 (2 H, q, $J_{1,2} = J_{2,3} = 7.41$ Hz, CH_2-2), 2.92 (2 H, t, $J_{2,3} = 7.41$ Hz, CH_2-3), 3.06 (4 H, t, $J = 7.14$ Hz, 2 × $ClCH_2CH_2N$), 3.14 (2 H, t, $J = 5.21$ Hz, CH_2N), 3.50 (2 H, t, $J_{1,2} = 7.41$ Hz, CH_2-1), 3.56 (4 H, t, $J = 7.14$ Hz, 2 × $ClCH_2$), 4.24 (2 H, t, $J = 5.21$ Hz, OCH_2), 7.60 (1 H, s, H-5), 7.69–8.30 (4 H, m, Ar-H). Anal. Calcd for $C_{23}H_{23}Cl_2NO_3$: C, 63.89; H, 5.36; N, 3.24; Cl, 16.40. Found: C, 64.00; H, 5.28; N, 3.24; Cl, 16.66.

4,5-(Isopropylidenedioxy)cyclohexane-1,2-*trans*-diol (15). A mixture of cyclohexanetetrol[18] (**14**, 10.0 g, 67.6 mmol), Dowex 50W-X8 (H^+-form, 5.0 g) in DMSO (180 mL), and 2,2-dimethoxypropane (60 mL) was stirred at room temperature for 3 days and then filtered through a bed of Celite. After removal of solvents in vacuo, the residue was chromatographed on a silica gel column (5 × 40 cm) using EtOAc as the eluent. Compound **15** was obtained as colorless crystals (Et_2O), 7.36 g (80%): mp 110–111 °C; ^{1}H NMR (D_2O) δ 1.34 and 1.50 (each 3 H, s, 2 × Me), 1.58–1.86 (2 H, m, 2 × CH), 2.02–2.43 (2 H, m, 2 × CH), 3.40 (1 H, m, H-4), 3.68 (1 H, m, H-5), 4.20–4.40 (2 H, m, H-1, H-2). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.38; H, 8.36.

3,4-(Isopropylidenedioxy)adipinaldehyde (16). Compound **15** (5.0 g, 26.6 mmol) was added portionwise to a solution of $NaIO_4$ (6.90 g) in H_2O (100 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and extracted with $CHCl_3$ (50 mL × 15). The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give 4.91 g (99%) of crude **16** as a colorless syrup, which was sufficiently pure to be used directly in the next step. A small amount of pure **16** can be obtained by chromatography on a silica gel column for analyses: ^{1}H NMR ($CDCl_3$) δ 1.36 and 1.44 (each 3 H, s, 2 × Me), 2.34–2.88 (4 H, m, 2 × CH_2), 4.60–4.83 (2 H, m, 2 × CH), 9.76 (2 H, dd, 2 × CHO). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.88; H, 7.40.

1-Formyl-4,5-(isopropylenedioxy)cyclopent-1-ene (17). A solution of the dialdehyde **16** (4.66 g, 25.0 mmol) in toluene (30 mL) was added dropwise to a solution of piperidine (1.16 mL) and AcOH (0.63 mL) in toluene (100 mL) in an ice bath. The reaction mixture was stirred at 0 °C for 4 h and then allowed to warm to room temperature for an additional 2 h. The solution was washed successively with 10% $NaHCO_3$ solution and H_2O, and the organic layer was dried (Na_2SO_4) and evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column (3 × 40 cm, toluene/EtOAc (2:1 v/v)) to yield **17**, 2.25 g

(54%), as a syrup which crystallized on storage in an ice box (mp 41–42 °C): ^{1}H NMR ($CDCl_3$) δ 1.37, 1.39 (each 3 H, s, 2 × Me), 2.77–2.81 (2 H, m CH_2-3), 4.87 (1 H, m, H-4), 5.30 (1 H, d, $J_{4,5}$ = 6.04 Hz, H-5), 6.88 (1 H, t, $J_{2,3a}$ = 2.47, $J_{2,3b}$ = 2.60 Hz, H-2), 9.82 (1 H, s, CHO). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.16.

1-[4,5-(Isopropylidenedioxy)cyclopent-1-enyl]ethanol (18). A solution of 17 (5.51 g, 32.8 mmol) in dry THF (5 mL) was added during a period of 15 min to a mixture of MeMgI [prepared rom MeI (7.10 g, 50 mmol) and Mg turnings (1.42 g, 59 mmol)] in absolute ether (30 mL), and the mixture was allowed to stand at room temperature overnight. The reaction was quenched by adding ice (50 g) and treated with 1 N HCl with vigorous stirring to dissolve the precipitate. The solution was extracted with ether (50 × 3 mL). The combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to dryness. Compound 18 (4.64 g, 77%) was obtained as a syrup (a pair of diastereomers were observed in a ratio of 2:1 from its ^{1}H NMR): ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.41 (each 3 H, s, 2 × Me), 1.38 (3 H, d, J = 5.8 Hz, *Me*CHOH), 2.50–2.58 (2 H, m, H-3), 2.80 (~$^2/_3$ H, d, $J_{CH,OH}$ = 5.8 Hz, OH), 2.95 (~$^1/_3$ H, d, $J_{CH,OH}$ = 3.6 Hz, OH), 4.40–4.58 (1 H, m, C*H*OH), 4.69–4.84 (1 H, m, H-4), 5.03–5.20 (1 H, m, H-5), 5.59–5.62 (1 H, m, H-2). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.02; H, 8.51.

Compound 18 was also prepared in 49% yield from 15 by following the above procedure, but without purifying the intermediates at each of reaction steps.

1-Acetyl-4,5-(isopropylidenedioxy)cyclopent-1-ene (19). To a vigorously stirring solution of 18 (1.30 g, 7.0 mmol) in $CHCl_3$ (20 mL) was added MnO_2 (5.0 g), and the mixture was stirred at room temperature for 1 day and then was filtered through a bed of Celite. MnO_2 (5.0 g) was added to the filtrate and then stirred for an additional 1 day. The mixture was filtered and evaporated in vacuo to dryness, and then the residue was chromatographed on a column of silica gel (3 × 30 cm) using toluene/EtOAc (2:1 v/v) as the eluent. Compound 19 was obtained as a syrup, 1.1 g (86%); ^{1}H NMR ($CDCl_3$) δ 1.36 and 1.38 (each 3 H, s, 2 × Me), 2.36 (3 H, s, Ac), 2.71–2.78 (2 H, m, 2 × H-3), 4.73–4.88 (1 H, m, H-4), 5.30 (1 H, d, $J_{4,5}$ = 5.8 Hz, H-5), 6.75 (1 H, t, $J_{2,3a}$ = $J_{2,3b}$ = 2.6 Hz, H-2). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.96; H, 7.52.

α-[4,5-(Isopropylidenedioxy)cyclopent-1-enyl]ethene (20a). A solution of the aldehyde 17 (0.50 g, 2.70 mmol) in dry THF (2 mL) was added dropwise to a solution of triphenylphosphinemethylene [(prepared from methyltriphenylphosphonium bromide (2.14 g, 6 mmol, and *n*-BuLi (6 mmol)] in dry THF (20 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature within 1 h, quenched with saturated NH_4Cl solution, and extracted with EtOAc (20 mL × 3). The combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column (*n*-pentane/Et_2O (10:1 v/v)) to give **20a**, 268 mg (54%), as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.34 (6 H, s, 2 × Me), 2.59 (2 H, brs, CH_2-3), 4.71–4.85 (1 H, m, H-4), 5.13 (1 H, d, $J_{4,5}$ = 6.21 Hz, H-5), 5.18 (1 H, dd, $J_{\beta,\beta'}$ = 0.98, $J_{\alpha,\beta}$ = 10.71 Hz, H-β), 5.47 (1 H, dd, $J_{\beta,\beta'}$ = 0.98, $J_{\alpha,\beta'}$ = 17.6 Hz, H-β′), 5.68 (1 H, t, $J_{2,3}$ = 2.74 Hz, H-2), 6.47 (1 H, dd, $J_{\alpha,\beta}$ = 10.7, $J_{\alpha,\beta'}$ = 17.6 Hz, H-α).

α-Acetoxy-α-[4,5-(isopropylidenedioxy)cyclopent-1-enyl]-ethene (20b). A solution of **36** (3.0 g, 16.5 mmol) in dry THF (16 mL) was slowly added to a solution of LDA (freshly prepared from *n*-BuLi, 25 mmol, and diisopropylamine, 25 mmol) in dry THF (50 mL) at −78 °C. After the solution was stirred for 5 min, Ac_2O (5 g, 49.5 mmol) was added to the reaction mixture and the mixture was stirred for 10 min. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with ether (100 mL × 4). The combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to dryness to give crude **20b**, 3.25 g, as syrup, which was used directly in the next step without further purification. A small amount of **20b** was purified by silica gel column chromatography (toluene/EtOAc (9:1 v/v)) for ^{1}H NMR spectrometrical measurement: ^{1}H NMR ($CDCl_3$) δ 1.37 and 1.38 (each 3 H, s, 2 × Me), 2.20(3 H, s, Ac), 2.57–2.66 (2 H, m, 2 × H-3), 4.71–4.86 (1 H, m, H-4), 4.94 (1 H, d, $J_{\beta,\beta'}$ = 1.1 Hz,H-B), 5.20 (1 H, dd, $J_{4,5}$ = 5.8, $J_{2,5}$ = 0.8 Hz, H-5), 5.30 (1 H, dd, $J_{\beta,\beta'}$ = 1.10 Hz, H-β′), 5.75 (1 H, t, $J_{2,3}$ = 2.5 Hz, H-2).

α-[(*tert*-Butyldimethylsilyl)oxy]-α-[4,5-(isopropylidenedioxy)cyclopent-1-enyl]ethene (20c). A solution of **36** (365 mg, 2.0 mmol) in dry THF (2 mL) was added to freshly prepared LDA (prepared from *n*-BuLi, 3 mmol, and diisopropylamine, 3.0 mmol) in dry THF (10 mL) at −78 °C. After the solution was stirred for 5 min, a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.80 mg, 3.0 mmol) in dry THF (3 mL) was added to the mixture. The mixture was stirred for additional 10 min. Triethylamine (3 mL) was added into the mixture and then quenched with 10% $NaHCO_3$ solution. The mixture was extracted with hexane (20 mL × 4). The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuo to dryness. The crude product **20c** (430 mg) was obtained as syrup, which was not stable and directly used in the next step without further purification: ^{1}H-NMR ($CDCl_3$) δ 0.10 and 0.18 (each 3 H, s, 2 × Si-Me), 0.96 (9 H, s, *t*-Bu), 1.38 and 1.40 (each 3 H, s, 2 × Me), 2.51–2.67 (2 H, m, 2 × H-3), 4.44 and 4.69 (each 1 H, s, H-β and H-β′), 4.74–4.90 (1 H, m, H-4), 5.13 (1 H, d, $J_{4,5}$ = 6.04 Hz, H-5), 5.94 (1 H, t, $J_{2,3}$ = 2.47 Hz, H-2).

2,3-*cis*-Dihydro-2,3-(isopropylidenedioxy)-1*H*-cyclopent-[*a*]anthracene-6,11-dione (22a). A mixture of **20a** (260 mg, 1.40 mmol) and 8 (235 mg, 1.50 mmol) in nitroethane (10 mL) was heated under reflux. The reaction was monitored by TLC (SiO_2, toluene/EtOAc (9:1 v/v)), which indicated that the starting materials were consumed and one main product (**21a**) was formed after refluxing for 4 h. To the mixture was added 10% Pd/C (430 mg), and refluxing continued for an additional 4 h. The mixture was allowed to cool to room temperature and filtered through a bed of Celite, and the filter cake was washed with nitroethane. The combined filtrate and washings were evaporated in vacuo to dryness. The residue was crystallized from EtOAc to give **22a**, 344 mg (76%), as yellow needles; mp 200–202 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 and 1.45 (each 3 H, s, 2 × Me), 3.54 (1 H, dd, $J_{1a,2}$ = 4.94 Hz, $J_{1a,1b}$ = 19.21 Hz, Ha-1), 3.88 (1 H, dd, $J_{1b,2}$ = 1.37, $J_{1a,1b}$ = 19.21 Hz, Hb-1), 5.10 (1 H, dt, $J_{1b,2}$ = 1.37, J_{1a2} = 4.94, $J_{2,3}$ = 5.76 Hz, H-2), 5.55 (1 H, d, $J_{2,3}$ = 5.76 Hz, H-3), 7.77 (1 H, d, $J_{4,5}$ = 9.06 Hz, H-4), 8.28 (1 H, d, $J_{4,5}$ = 9.05 Hz, H-5), 7.73–8.35 (6 H, m, Ar-H). Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.04. Found: C, 74.82; H, 5.11.

4-Acetoxy-2,3-*cis*-dihydro-2,3-(isopropylidenedioxy)-1*H*-cyclopent[*a*]anthracene-6,11-dione (22b). Method 1. By following the same procedure for the synthesis of **22a** but using toluene as the solvent, compound **22b** was prepared by reaction of **20b** (1.00 g, 4.50 mmol) and 8 (710 mg, 4.50 mmol): yield 516 mg (30%); mp 197–198 °C.

Method 2. A mixture of **20b** (925 mg, 4.1 mmol) and 8 (1.50 g, 9.5 mmol) in toluene (20 mL) was refluxed for 6 h and then allowed to cool to room temperature. The TLC (SiO_2, toluene/EtOAc (2:1 v/v)) showed that two products were formed (R_f = 0.69, 0.27). The mixture was filtered, and the filter cake washed with hot toluene. The combined filtrate and washings were evaporated in vacuo to dryness. The dark residue was crystallized from EtOH. Compound **22b** (R_f = 0.65), 543 mg, was collected by filtration. The mother liquor was evaporated in vacuo to dryness, and the residue was chromatographed on a silica gel column (2 × 40 cm) using toluene/EtOAc (4:1, v/v) as the eluent. Compound **22b** (30 mg, R_f = 0.69) was eluted first from the column followed by the O-deacetylated compound **23** (60 mg, 4%, R_f = 0.27). Compound **23** was identical with the one synthesized from **22b–c** by hydrolysis (see below).

Compound **22b**: yield 573 mg (37%); mp 197–199 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 and 1.41 (each 3 H, s, 2 × Me), 2.41 (3 H, s, Ac), 3.56 (1 H, dd, $J_{1a,2}$ = 5.21, $J_{1a,1b}$ = 19.48 Hz, Ha-1), 3.91 (1 dd, $J_{1b,2}$ = 1.10, $J_{1a,1b}$ = 19.84 Hz, Hb-1), 5.06 (1 H, dt, $J_{1b,2}$ = 1.10, $J_{1a,b}$ = 5.21, $J_{2,3}$ = 5.76 Hz, H-2), 5.56 (1 H, d, $J_{3,4}$ = 5.76 Hz, H-3), 7.73–8.32 (5 H, m, Ar-H). Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.83; H, 4.79. Found: C, 69.80; H, 4.80.

4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-*cis*-dihydro-2,3-(isopropylidenedioxy)-1*H*-cyclopent[*a*]anthracene-6,11-dione (22c). A mixture of crude **20c** (410 mg, ca. 1.4 mmol) and 8 (200 mg, 1.26 mmol) in toluene (10 mL) was heated under reflux for 7 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (20 mL). To this solution was added MnO_2 (1.5 g), and the mixture was stirred at room temperature for 20 min. After filtration, the filtrate was evaporated in vacuo to dryness. The residue was crystallized from MeOH to give **22c**,

244 mg (36%): mp 192–194 °C; ^{1}H-NMR ($CDCl_3$) δ 0.36 and 0.37 (each 3 H, s, 2 × SiMe), 1.18 (9 H, s, *t*-Bu), 1.27 and 1.42 (each 3 H, s, 2 × Me), 3.62 (1 H, dd, $J_{1a,2}$ = 6.0, $J_{1a,1b}$ = 19.3 Hz, Ha-1), 3.79 (1 H, dd, $J_{1b,2}$ = 1.10, $J_{1a,1b}$ = 19.48 Hz, Hb-1), 5.06 (1 H, dt, $J_{1b,2}$ = 1.10, $J_{1a,2}$ = $J_{2,3}$ = 6.0 Hz, H-2), 5.60 (1 H, d, $J_{2,3}$ = 6.0 Hz, H-3), 7.63 (1 H, s, H-5), 7.70–8.28 (4 H, m, ArH). Anal. Calcd for $C_{26}H_{30}O_5Si$: C, 69.30; H, 6.71. Found: C, 69.32; H, 6.59.

2,3-*cis*-Dihydro-2,3-(isopropylidenedioxy)-4-hydroxy-1*H*-cyclopent[*a*]anthracene-6,11-dione (23). Method 1. A mixture of **20b** (672 mg, 3 mmol) and **8** (1.42 g, 9 mmol) in toluene (12 mL) was heated under reflux for 20 h. After the mixture was cooled, the precipitated product was collected by filtration and recrystallized from ether to give **23**: 957 mg (95%).

Method 2. Synthesis of 23 from 22b. A mixture of **22b** (1.16 g, 3.07 mmol) in MeOH (20 mL) containing H_2O (6 mL) and Et_3N (3 mL) was heated at 50 °C for 1.5 h. The solvent was removed in vacuo, and the residue was coevaporated several times with MeOH. The residue was crystallized from EtOH to yield **23**, 951 mg (92%).

Synthesis of 23 from 22c. To a solution of **22c** (137 mg, 0.3 mmol) in THF/H_2O (6 mL, 4:1 v/v) was added tetrabutylammonium fluoride (100 mg). The mixture was stirred at room temperature for 15 min, diluted with $CHCl_3$ (100 mL), and then washed successively with 10% NH_4Cl solution (15 mL) and H_2O (20 mL × 3). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to dryness, and the residue was crystallized from Et_2O to afford **23** (92 mg, 90%).

The analytical data (mp, mixed mp, IR, and ^{1}H NMR) of compound **23** prepared either from method 1 or from method 2 indicated that they are identical: mp 272–274 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.20, 1.35 (each 3 H, s, 2 × Me), 3.48 (2 H, d, $J_{1,2}$ = 3.57 Hz, CH_2-1), 5.02 (1 H, m, $J_{1,2}$ = 3.57 Hz, $J_{2,3}$ = 6.31 Hz, H-2), 5.54 (1 H, d, $J_{2,3}$ = 6.31, H-3), 7.51 (1 H, s, H-5), 7.79–8.16 (4 H, m, Ar-H), 11.18 (1 H, br, exchangeable, OH). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.27; H, 4.87.

4-(Benzyloxy)-2,3-*cis*-dihydro-2,3-(isopropylidenedioxy)-1*H*-cyclopent[*a*]anthracene (24). A mixture of **23** (540 mg, 1.6 mmol), benzyl bromide (720 mg, 4.2 mmol), and K_2CO_3 (2.0 g) in acetone (15 mL) was refluxed for 1 h. The solvent was removed in vacuo, and the residue was triturated with $CHCl_3$ (200 mL), which was then washed (H_2O), dried (Na_2SO_4), and evaporated in vacuo to dryness. The residue was crystallized from $CHCl_3/Et_2O$ to give **24**, 578 mg (84%); mp 218–219 °C; ^{1}H NMR ($CDCl_3$) δ 1.32, 1.47 (each 3 H, s, 2 × Me), 3.59 (1 H, dd, $J_{1a,2}$ = 6.03, $J_{1a,1b}$ = 19.5 Hz, Ha-1), 3.84 (1 H, dd, $J_{1b,2}$ = 1.92, $J_{1a,1b}$ = 19.5 Hz, Hb-1), 5.10 (1 H, dt, $J_{1b,2}$ = 1.92, $J_{1a,2}$ = $J_{2,3}$ = 6.03 Hz, H-2), 5.43 (2 H, s, $PhCH_2$), 5.70 (1 H, d, $J_{2,3}$ = 6.03 Hz, H-3), 7.19–8.26 (10 H, m, Ar-H). Anal. Calcd for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20. Found: C, 75.87; H, 5.22.

4-[2-[*N*,*N*-Bis(2-chloroethyl)amino]ethoxy]-2,3-*cis*-dihydro-2,3-(isopropylidenedioxy)-1*H*-cyclopent[*a*]anthracene-6,11-dione (25) was prepared by following the same procedure as above by reaction of **23** (470 mg, 1.40 mmol) with tris(2-chloroethyl)amine hydrochloride (2.0 g, 8.30 mmol), 306 mg (43%): mp 156–158 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.44 (each 3 H, s, 2 × Me), 3.01–3.24 (6 H, m, 3 × NCH_2), 3.53–3.73 (6 H, m, 2 × $ClCH_2$ and CH_2-1), 4.24–4.40 (2 H, m, 2 × OCH_2–), 5.08 (1 H, dt, $J_{1a,2}$ = 2.47, $J_{1b,2}$ = 5.76, $J_{2,3}$ = 6.32 Hz, H-2), 5.61 (1 H, d, $J_{2,3}$ = 6.31 Hz, H-3), 7.67 (1 H, s, H-5), 7.70–8.29 (4 H, m, Ar-H). Anal. Calcd for $C_{26}H_{27}Cl_2NO_5$: C, 61.91; H, 5.40; Cl, 14.06; N, 2.78. Found: C, 62.03; H, 5.60; Cl, 14.11; N, 2.70.

2,3-Dihydro-2,3-*cis*-dihydroxy-1*H*-cyclopent[*a*]anthracene-6,11-dione (26). Compound **22a** (1.08 g, 3.4 mmol) was added to 80% trifluoroacetic acid (20 mL) in an ice bath. The mixture, after being stirred at room temperature for 1 h, was diluted with ice–water (200 mL). The precipitated product **26** was collected by filtration. The crude product was crystallized from EtOH (30 mL) to give **26**, 860 mg (91%): mp 206–208 °C; ^{1}H NMR (DMSO-d_6) δ 3.35–3.39 (2 H, m, 1-CH_2), 4.39–4.44 (1 H, m, H-2), 4.70 (1 H, d, *J* = 3.8 Hz, exchangeable, C-2-OH), 4.91 (1 H, dd, $J_{2,3}$ = 4.39 Hz, $J_{3,OH}$ = 7.13 Hz, H-3), 5.41 (1 H, d, $J_{3,OH}$ = 7.13 Hz, 3-OH), 7.85 (1 H, d, $J_{4,5}$ = 9.61 Hz, H-4), 8.16 (1 H, d, $J_{4,5}$ = 9.61 Hz, H-5), 7.74–8.22 (4 H, m, ArH). Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.66; H, 4.44.

4-(Benzyloxy)-2,3-dihydro-2,3-*cis*-dihydroxy-1*H*-cyclopent[*a*]anthracene-6,11-dione (27) was prepared from **24** (480 mg, 1.13 mmol) by following the same procedure as above, 356 mg (82%): mp 212–214 °C; ^{1}H NMR (DMSO-d_6) δ 3.09 (1 H, dd, $J_{1a,1b}$ = 17.56 Hz, Ha-1), 3.63 (1 H, dd, $J_{1b,2}$ = 6.72 $J_{1a,1b}$ = 17.56 Hz, Hb-1), 4.22 (1 H, m, $J_{2,3}$ = 5.22, $J_{1b,2}$ = 6.72 Hz, H-2), 4.87 (1 H, d, $J_{2,3}$ = 5.22 Hz, H-3), 5.34 (2 H, s, $PhCH_2$), 7.63 (1 H, s, H-5), 7.35–8.23 (10 H, m, Ar-H). Anal. Calcd for $C_{24}H_{18}O_5$: C, 74.60; H, 4.69. Found: C, 74.46; H, 4.67.

4-[2-[*N*,*N*-Bis(2-chloroethyl)amino]ethoxy]-2,3-dihydro-2,3-*cis*-dihydroxy-1*H*-cyclopent[*a*]anthracene-6,11-dione (28) was prepared from **25** (460 mg, 0.91 mmol) in a similar manner, 341 mg (81%): mp 130–133 °C (EtOAc/Et_2O); ^{1}H NMR ($CDCl_3$) δ 2.95–3.19 (6 H, m, 3 × NCH_2–), 3.50–3.66 (6 H, m, 2 × $ClCH_2$– and CH_2-1), 4.31 (2 H, t, *J* = 5.2 Hz, OCH_2–), 4.60 (1 H, q, $J_{1a,2}$ = $J_{1b,2}$ = $J_{2,3}$ = 5.21 Hz, H-2), 5.25 (1 H, d, $J_{2,3}$ = 5.21 Hz, H-3), 7.67 (1 H, s, H-5), 7.70–8.28 (4 H, m, Ar-H). Anal. Calcd for $C_{23}H_{23}Cl_2NO_5$: C, 59.49; H, 4.99; Cl, 15.27; N, 3.02. Found: C, 59.82; H, 5.25; Cl, 14.94; N, 3.01.

2,3-Dihydro-2,3-*cis*-bis(mesyloxy)-1*H*-cyclopent[*a*]anthracene-6,11-dione (29). A mixture of **26** (860 mg, 3.07 mmol) and mesyl chloride (1.41 g, 12.3 mmol) in pyridine (10 mL) was stirred in an ice bath for 1 h, after which the mixture was poured into ice–water (100 mL) and the precipitated product **29** was collected by filtration. The filtrate was extracted with $CHCl_3$ (50 mL × 3), washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The solid residue was combined with the solid obtained previously and recrystallized from Me_2CO to give **29**, 1.17 g (99%): mp 190–191 °C dec.; ^{1}H NMR (DMSO-d_6) δ 3.32 and 3.44 (each 3 H, s, 2 × Me), 3.81 (2 H, d, $J_{1,2}$ = 4.39 Hz, CH_2-1), 5.63 (1 H, q, $J_{1,2}$ = 4.39 Hz, $J_{2,3}$ = 4.94 Hz, H-2), 6.33 (1 H, d, $J_{2,3}$ = 4.94 Hz, H-3), 7.96 (1 H, d, $J_{4,5}$ = 7.79 Hz, H-4), 8.24 (1 H, d, $J_{4,5}$ = 7.79 Hz, H-5), 7.87–8.32 (4 H, m, Ar-H). Anal. Calcd for $C_{19}H_{16}O_9S_2$: C, 52.28; H, 3.70; S, 14.69. Found: C, 52.03; H, 3.91; S, 14.42.

3-Azido-2,3-*trans*-dihydro-2-(mesyloxy)-1*H*-cyclopent[*a*]anthracene-6,11-dione (32). A mixture of **29** (103 mg, 0.236 mmol) and LiN_3 (90.0 mg, 1.83 mmol) in DMF (6 mL) was stirred at room temperature for 1 h and then was diluted with $CHCl_3$ (50 mL). The mixture was washed with H_2O (20 mL × 5). The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated to dryness in vacuo. The solid residue was chromatographed over a silica gel column (toluene/EtOAc (2:1 v/v)) to give **32**, 30 mg (32%).

The yield of **32** was improved by treatment of **29** (873 mg, 2.0 mmol) with NaN_3 (520 mg, 8 mmol) in DMSO (20 mL). The reaction mixture was worked up by the same procedure as described above to afford **32**, 496 mg (62%): mp 209–211 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 3.37 (3 H, s, Me), 3.54 (1 H, dd, $J_{1a,2}$ = 4.73, J_{1a1b} = 18.71 Hz, Ha-1), 4.03 (1 H, dd, $J_{1b,2}$ = 6.58 Hz, J_{1a1b} = 18.71 Hz, Hb-1), 5.49 (1 H, s, H-3), 5.33–5.54 (1 H, m, H-2), 7.84–8.31 (6 H, m, ArH); IR (KBr) 2140 (N_3), 1690 cm^{-1} (C=O). Anal. Calcd for $C_{18}H_{13}N_3O_5S$: C, 56.39; H, 3.42; N, 10.96; S, 8.36. Found: C, 56.16; H, 3.62; N, 10.80; S, 8.21.

3-Azio-4-(benzyloxy)-2,3-*trans*-dihydro-2-(mesyloxy)-1*H*-cyclopent[*a*]anthracene-6,11-dione (33). To a solution of **27** (252 mg, 0.65 mmol) in pyridine (5 mL) was added mesyl chloride (300 mg, 2.6 mmol) at room temperature, and the mixture was stirred for 1 h. The TLC (SiO_2, toluene/EtOAc (4:1 v/v)) showed there was only one product with R_f = 0.75 in the mixture. The mixture was diluted with $CHCl_3$ (100 mL) and then washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to dryness to yield crude **30** (342 mg, 97%), which was used directly in the next step without further purification. A small amount of this intermediate (**30**) was recrystallized from CH_2Cl_2/Et_2O, mp 138–139 °C dec: ^{1}H NMR (DMSO-d_6) δ 3.08 and 3.34 (each 3 H, s, 2 × Me), 3.45 (1 H, dd, $J_{1a,2}$ = 6.92 Hz, $J_{1a,1b}$ = 17.81 Hz, Ha-1), 4.01 (1 H, dd, $J_{1b,2}$ = 7.41 Hz, $J_{1a,1b}$ = 17.81 Hz, Hb-1), 5.36–5.57 (1 H, m, H-2), 5.49 (2 H, s, $PhCH_2$–), 6.27 (1 H, d, $J_{2,3}$ = 5.49 Hz, H-3), 7.79 (1 H, s, H-5), 7.36–8.21 (9 H, m, Ar-H). Anal. Calcd for $C_{26}H_{22}O_9S_2$: C, 57.55; H, 4.09; S, 11.82. Found: C, 57.29; H, 4.18; S, 11.65.

The crude **30** was dissolved in DMF (5 mL), and to this solution was added LiN_3 (250 mg). After being stirred at room temperature for 1 h, the mixture was diluted with $CHCl_3$ (100 mL), washed with water, dried ($NaSO_4$), and evaporated in vacuo to dryness. The resulting dark residue was chromatographed over a silica gel column (2 × 30 cm) using $CHCl_3$ as the eluent to give **33**, 261 mg (82%): mp 178–180 °C dec ($Et_2O/CHCl_3$); ^{1}H NMR (DMSO-d_6)

δ 3.37 (3 H, s, Me), 3.61 (1 H, dd, $J_{1a,2}$ = 3.56, $J_{1a,1b}$ = 19.01 Hz, Ha-1), 3.96 (1 H, dd, $J_{1b,2}$ = 6.04, J_{1a1b} = 19.01 Hz, Hb-1), 5.41 (1 H, m, H-2) 5.42 (1 H, s, H-3), 5.50 (2 H, s, $PhCH_2$–), 7.83 (1 H, s, H-5). 7.37–8.23 (9 H, m, Ar–H); IR (KBr) 2130 (N_3), 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{19}N_3O_6S$: C, 61.34; H, 3.91; N, 8.58; S, 6.55. Found: C, 61.50; H, 4.03; N, 8.39; S, 6.31.

3-Azido-4-[2-[*N,N*-bis(2-chloroethyl)amino]ethoxy]-2,3-*trans*-dihydro-2-(mesyloxy)-1*H*-cyclopent[*a*]anthracene-6,-11-dione (34). A mixture of **28** (270 mg, 0.58 mmol) and mesyl chloride (266 mg, 2.32 mmol) in pyridine (5 mL) was stirred in an ice bath for 1 h. The mixture was poured into ice–water (50 mL), which was extracted with $CHCl_3$ (30 mL × 5). The combined $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The TLC (SiO_2, toluene/EtOAc (4:1 v/v)) showed that there was one main product, **31** (R_f = 0.42), which was obtained as a syrup: ^1H NMR ($CDCl_3$) δ 2.99–3.13 (6 H, m, 3 × NCH_2–), 3.19 and 3.23 (each 3 H, s, 2 × Me), 3.44–3.72 (4 H, 2 × CH_2Cl), 4.00–4.15 (2 H, s, OCH_2–), 4.21–4.39 (2 H, m, CH_2-1), 5.18–5.33 (1 H, m, H-2), 6.22 (1 H, d, $J_{2,3}$ = 5.48 Hz, H-3), 7.67 (1 H, s, H-5), 7.72–8.27 (4 H, m, Ar-H). Anal. Calcd for $C_{25}H_{27}Cl_2NO_9S_2$: C, 48.39; H, 4.39; Cl, 11.43; N, 2.26; S, 10.33. Found: C, 48.02; H, 4.51; Cl, 11.25; N, 2.13; S, 10.52.

To a solution of the crude **31** in DMF (5 mL) was added LiN_3 (200 mg). The mixture, after being stirred at room temperature for 1 h, was diluted with ice–water (30 mL) and extracted with $CHCl_3$ (30 mL × 4). The organic extracts were combined, washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column (2 × 30 cm) using $C_6H_5CH_3$/EtOAc (9:1 v/v) as the eluent to give **34**, 232 mg (70%) as syrup: ^1H NMR ($CDCl_3$) δ 2.98–3.25 (6 H, m, 3 × NCH_2), 3.10 (3 H, s, Me), 3.51–3.66 (4 H, t, J = 6.04 Hz, 2 × CH_2Cl), 3.86–3.94 (2 H, m, CH_2-1), 4.35 (2 H, t, J = 6.04 Hz, OCH_2–), 5.27–5.34 (1 H, m, H-2), 5.32 (1 H, s, H-3), 7.77 (1 H, s, H-5), 7.73–8.32 (4 H, m, Ar-H); IR (KBr) 2150 (N_3), 1690 (C=O) cm^{-1}; MS m/z 567. Anal. Calcd for $C_{24}H_{24}Cl_2N_4O_6S$: C, 50.80; H, 4.26; Cl, 12.50; N, 9.87; S, 5.65. Found: C, 50.32; H, 4.78; Cl, 11.35; N, 9.74; S, 5.12. Due to the instability of **34**, no satisfactory elemental analyses could be obtained.

2,3-Aziridino-2,3-*cis*-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (35). To a mixture of **32** (160 mg, 0.42 mmol) and Et_3N (0.5 mL) in THF (10 mL) containing H_2O (0.5 mL) was added triphenylphosphine (140 mg, 0.53 mmol). The mixture was stirred at room temperature for 1.5 h and then diluted with EtOAc (30 mL). The solution was washed with H_2O (15 mL × 3), dried ($NaSO_4$), and evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column (2 × 30 cm) using EtOAc as the eluent to give **35**, 53 mg (47%): mp 190–191 °C dec (EtOAc/Et_2O); ^1H NMR ($CDCl_3$) δ 1.24 (1 H, brs, NH), 3.33 (1 H, brs, H-2), 3.44 (1 H, brs, H-3), 3.72 (1 H, q, $J_{1a,1b}$ = 19.8 Hz, Ha-1), 3.82 (1 H, d, $J_{1a,1b}$ = 19.8 Hz, Hb-1), 7.79 (1 H, d, $J_{4,5}$ = 9.10 Hz, H-4), 8.27 (1 H, d, $J_{4,5}$ = 9.10 Hz, H-5), 7.77–8.30 (4 H, m, Ar-H); IR (KBr) 3400 (NH), 1700 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.91; H, 4.35; N, 5.09.

2,3-Aziridino-4-(benzyloxy)-2,3-*cis*-dihydro-1*H*-cyclopent-[*a*]anthracene-6,11-dione (36) was prepared in a similar manner as above from **33** (37 mg, 0.08 mmol), yield 19 mg (68%): mp 150–151 °C dec (Et_2O); ^1H NMR ($CDCl_3$) δ 1.48 (1 H, br, NH), 3.28 (1 H, brs, H-2), 3.56 (1 H, brd, $J_{1a,1b}$ = 19.1 Hz, Ha-1), 3.65 (1 H, brs, H-3), 3.81 (1 H, d, $J_{1a,1b}$ = 19.1 Hz, Hb-1), 5.33 (2 H, s, $-CH_2Ph$), 7.78 (1 H, s, H-5), 7.39–7.53 (5 H, m, Ph), 7.74–8.25 (4 H, m, Ar-H). Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.46; H, 4.67; N, 3.81. Found: C, 78.46; H, 4.68; N, 3.69.

2,3-Aziridino-4-[2-[*N,N*-bis(2-chloroethyl)amino]ethoxy]-2,3-*cis*-dihydro-1*H*-cyclopent[*a*]anthracene-6,11-dione (37) was prepared from **34** (120 mg, 0.21 mmol), yield 45 mg (42%): mp 105–106 °C dec (Et_2O); ^1H NMR ($CDCl_3$) δ 1.26 (1 H, brs, NH), 3.08–3.24 (6 H, m, H-2, H-3, 2 × CH_2Cl), 3.51–4.67 (7 H, m, 3 × CH_2N and Ha-1), 3.83 (1 H, d, $J_{1a,1b}$ = 19.3 Hz, Hb-1), 4.30 (2 H, t, J = 5.49 Hz, NCH_2CH_2O), 7.64 (1 H, s, H-5), 7.69–8.69 (4 H, m, Ar-H). Anal. Calcd for $C_{23}H_{22}Cl_2N_2O_3$: C, 62.03; H, 4.98; N, 6.29; Cl, 15.92. Found: C, 62.03; H, 4.91; N, 6.10; Cl, 15.71.

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