THF at −78 °C for 5 min. Acetylene was then passed over the solution to maintain an acetylene atmosphere. A solution of **26** (50.7 mg, 0.31 mmol) in 1 mL of THF was added. The solution was warmed to −20 °C and stirred for 2.5 h. The reaction was quenched with 2 mL of saturated aqueous sodium bicarbonate solution. Normal workup gave 66.7 mg of crude product. Examination of the NMR spectrum indicated that 3:1:1 mixture of **32**, **33**, and **34** was present: ^{1}H NMR (**32**) δ 4.83 (d, 1, J = 1.8), 4.69 (d, 1, J = 1.8); (**34**) δ 6.07 (s, 1), 5.63 (ddd, 1, J = 12, 3.5, 3.5), 5.32 (ddd, 1, J = 12, 2.5, 2.5).

Evaporative distillation (100 °C, 0.2 Torr) of the crude product gave 41.2 mg of a 1:3 mixture of propargylic alcohol **32** and dienone **33** indicating that the oxy-Cope rearrangement of **32** occurred on heating. Alcohol **34** remained in the pot under these distillation conditions. A solution of the distillate in THF was heated at reflux for 2 h and concentrated in vacuo. Flash chromatography of the residue on silica gel (20:1 hexane–EtOAc) gave 19.4 mg (33%) of pure **33**: ^{1}H NMR δ 6.08 (ddd, 1, J = 12.0, 4.5, 2.9), 5.84 (br s, 1, $W_{1/2}$ = 2.4 Hz), 5.46 (dddd, 1, J = 12.0, 2.8, 2.3, 1.9), 3.09 (ddd, 1, J = 18.9, 2.8, 2.8), 2.76 (ddd, 1, J = 18.9, 4.5, 2.3), 2.65 (br s, 1), 2.41 (br s, 1), 1.20–1.75 (m, 6), 1.32 (s, 3); ^{13}C NMR δ 206.9 (CO), 144.4 (=C), 141.4 (=CH), 136.9 (=CH), 130.8 (=CH), 63.3, 43.1 (C), 38.2, 36.3, 29.0, 27.8, 27.1, 23.4; IR ($CDCl_3$) 3010, 2941, 2870, 1650, 1603 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$ 188.1202, found 188.1207.

1-Methyltricyclo[6.4.0.0^{3,10}]dodeca-2,4-dien-7-one (36) and 10-Methylbicyclo[6.4.0]dodeca-5,7,9-trien-4-one (38). A solution of **26** (80.6 mg, 0.50 mmol) in 1 mL of THF was added to a suspension of sodium acetylide (24.6 mg, 0.51 mmol) in THF at 25 °C. The solution was heated at reflux for 2 h, cooled to room temperature, and quenched with 5 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was extracted with five portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 90 mg of crude product. Flash chromatography on silica gel (20:1 hexane–EtOAc) gave 23.2 mg (25%) of **36** followed by 15.3 mg (17%) of **38**.

Spectral data for **36**: ^{1}H NMR δ 6.36 (br d, 1, J = 9.4), 5.71 (s, 1), 5.34 (ddd, 1, J = 9.4, 4.1, 4.1), 2.96 (br s, 2), 2.73 (br s, 1), 2.36 (d, 1, J = 6.6), 1.23–1.85 (m, 6), 1.32 (s, 3); ^{13}C NMR δ 211.6 (CO), 147.4 (=C), 136.8 (=CH), 130.6 (=CH), 129.1 (=CH), 63.9, 47.0, 46.7 (C), 37.6, 28.4, 27.3, 24.3, 23.7; IR ($CDCl_3$) 3020, 2950, 2870, 1677, 1630, 1605 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$ 188.1202, found 188.1199.

Spectral data for **38**: ^{1}H NMR δ 6.56 (dd, 1, J = 12.3, 6.3), 6.00 (br s, 1), 5.96 (d, 1, J = 6.3), 5.88 (dd, 1, J = 12.3, 1.7), 2.65–2.85 (m, 2), 1.45–2.25 (m, 7), 1.85 (s, 3); ^{13}C NMR δ 206.3, 148.5, 142.5, 138.7, 129.6, 125.3, 122.4, 38.4, 35.9, 32.8, 26.4, 26.4, 24.1; IR ($CDCl_3$) 3015, 2930, 2865, 2835, 1650, 1633, 1570, 1450, 1435, 1410, 1130, 819 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$ 188.1202, found 188.1207.

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Regio- and Stereospecific Syntheses of 4-Deoxyadriamycinone and 4,6-Dideoxyadriamycinone from a Common Intermediate

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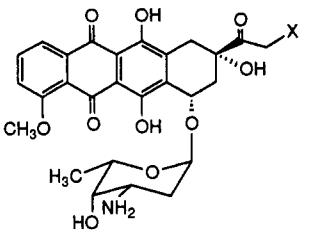
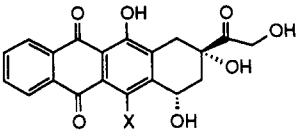
Regio- and stereospecific total syntheses of (±)-4-deoxyadriamycinone (**2a**) and (±)-4,6-dideoxyadriamycinone (**2b**) from commercially available quinizarin (**3**) are described. A key feature of these preparations was the delineation of conditions for Claisen rearrangement of **4c** to furnish specifically either **5a** or **6a**.

Adriamycin (**1a**) has the widest spectrum of activity of any anticancer agent in clinical use and is less toxic than the structurally similar daunorubicin (**1b**).[1] Recently, we reported the first methodology for regio- and stereospecific synthesis of the A-ring fragment present in adriamycinone and, in conjunction with that work, described the total synthesis of (±)-6-deoxyadriamycinone.[2] Unlike previous preparations of the A-ring substitution pattern present in **1a**,[3] our synthesis was not predicated upon the intermediacy of a methyl ketone intermediate.

In order to establish the potential of this methodology for synthesis of adriamycinone and also to explore its potential for providing a practical route to 4-deoxyadriamycinone (**2a**), we undertook the reaction sequence shown in part in Scheme I. Conversion of commercially available quinizarin (**3**) to the substituted anthraquinone **4c**, via the intermediacy of **4a** and **4b**, was accomplished through sequential monoetherification with 2-chloromethyl-1-butene[4] (K_2CO_3, DMF; 50%), hydroxymethylation[5] (CH_2=O, $Na_2S_2O_4$, NaOH, H_2O–CH_3OH; 67–78%), and methylation ($DMSO_4$, K_2CO_3, acetone; 95%).



1a. X = OH Adriamycin
1b. X = H Daunorubicin



2a. X = OH, 4-Deoxyadriamycinone
2b. X = H, 4,6-Dideoxyadriamycinone

Claisen rearrangement of **4c** in DMF–water in the presence of sodium dithionite[6] did not give the desired product **6a**, but instead solely furnished **5a** from regios-

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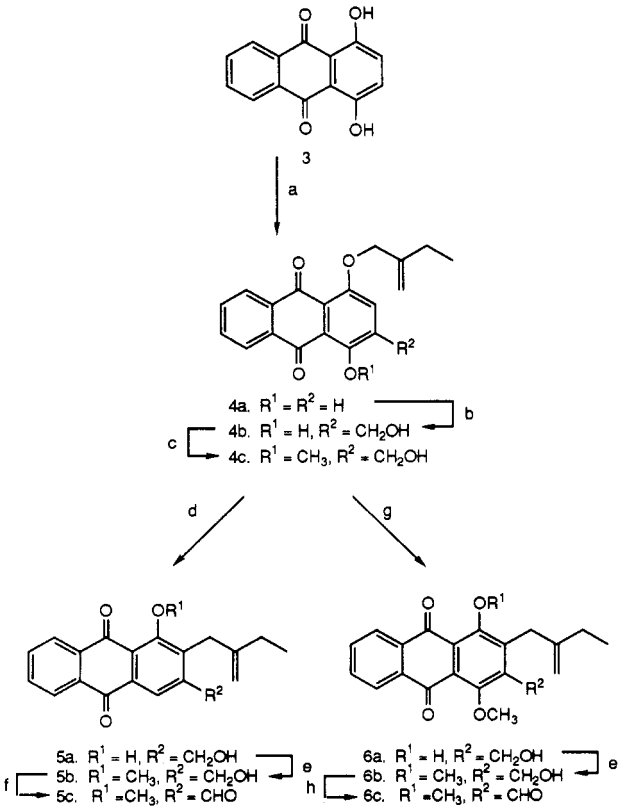
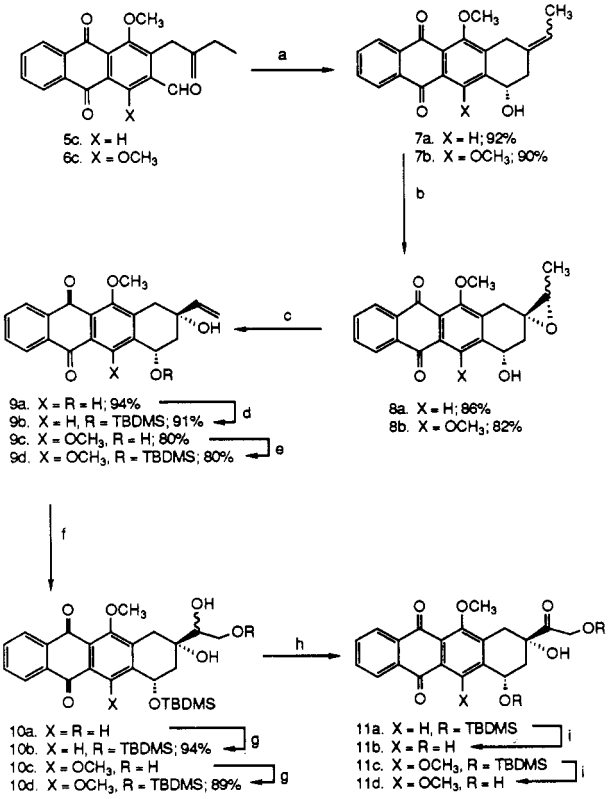
Scheme I[a]



[a] (a) K_2CO_3, $ClCH_2C(=CH_2)CH_2CH_3$, DMF, 50%; (b) $CH_2=O$, $Na_2S_2O_4$, NaOH, CH_3OH–H_2O; 67–78%; (c) $DMSO_4$, K_2CO_3, acetone, 95%; (d) $Na_2S_2O_4$, DMF–H_2O, 100 °C, 86%; (e) $DMSO_4$, K_2CO_3, acetone, 98%; (f) $BaMnO_4$, CH_2Cl_2, 90%; (g) $Na_2S_2O_4$, DMSO–H_2O, 100 °C, 86%; (h) PCC, CH_2Cl_2, 74%.

Scheme II[a]



[a] (a) $SnCl_4·5H_2O$, CH_2Cl_2; (b) *t*-BuOOH, $VO(AcAc)_2$, CH_2Cl_2; (c) PhSeNa, EtOH–DME, 30% H_2O_2; (d) TBDMSCl, imidazole, DMF; (e) TBDMSTf, 2,6-lutidine, CH_2Cl_2; (f) OsO_4, TMNO, acetone–water, 96%; (g) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, 89–94%; (h) pyridine–SO_3, DMSO, Et_3N, 91%; (i) aqueous HF, CH_3CN, 98%.

pecific C-4 demethoxylation. This material was identical with an alternatively prepared sample.[7] Although not widely recognized as such, regiospecific deoxygenation is a general reaction of hydroxy- and methoxyanthraquinones.[8]

The problem that we faced was how to stop the demethoxylation. Initially, we attempted to alter the course of the reaction by varying the amount of added base and dithionite. While we were able to somewhat mitigate the loss of the methoxyl group, mixtures of the methoxylated and demethoxylated products **5a** and **6a** were invariably obtained, and at high concentrations of base, other side reactions, such as reductive conversion of the hydroxymethyl to a methyl group, were observed.

The first indication that the methoxyl group could be retained was the observation of only modest (~5%) demethoxylation when the Claisen reaction was conducted in methanol. A similar result was obtained when the reaction was conducted in ethanol. In both cases, however, large amounts of solvent were required to obtain homogeneous reaction conditions. Ultimately, DMSO proved to be the solvent of choice. In this medium, a preparatively useful concentration was obtained with retention of the methoxyl group to specifically furnish **6a** from **4c**. It is noteworthy that the final conditions for selective preparation of either the methoxylated product **6a** or the demethoxylated compound **5a**, through reductive Claisen rearrangement of **4c**, does not require any added base; only a change of solvents is needed.

The sequence developed earlier for synthesis of 6-deoxyadriamycinone[2] was used, as shown in Schemes I and II, to convert **5a** and **6a** to (±)-4,6-dideoxyadriamycinone (**2b**) and (±)-4-deoxyadriamycinone (**2a**), respectively. For preparation of 4,6-dideoxyadriamycinone (**2b**), the anthraquinone **5a** was methylated ($DMSO_4$, K_2CO_3, acetone; 98%) to **5b** and then oxidized with $BaMnO_4$[10] to the aldehyde **5c**. Intramolecular ene reaction of **5c** catalyzed by stannic chloride furnished exclusively the tetracyclic olefinic product **7a**,[9] which was converted stereospecifically to the epoxide **8a** through Sharpless epoxidation [$VO(AcAc)_2$, *t*-BuOOH].[11] Opening of the epoxide in **8a** with phenylselenide anion, followed by oxidative elimination of selenoxide,[12] produced the *cis*-7,9-dihydroxy olefinic alcohol **9a**. The 7-hydroxyl group in **9a** was protected as the TBDMS ether (TBDMSCl, imidazole)[13] and the 13,14-olefinic moiety was hydroxylated (catalytic OsO_4, TMNO)[14] to furnish **10a**. Chemospecific protection of the

(7) An authentic sample of **5a** was available from a model study related to the total synthesis of γ-citromycinone.[9] This material was prepared through condensation of 3-(phenylsulfonyl)isobenzofuranone with 5-(hydroxymethyl)-2-cyclohexen-1-one. Aromatization of the hydronaphthacenone intermediate, conversion to the butenyl ether and Claisen rearrangement furnished **5a**.

(8) For examples, see: Perkin, A. G.; Story, R. C. *J. Chem. Soc.* **1928**, 229. Barnett, E. de B. *Ibid.* **1922**, 1376. Perkin, A. G.; Story, C. W. H. *Ibid.* **1929**, 1399. Broadbent, A. D.; Meschwitz, W.; Steward, J. *Can. J. Chem.* **1986**, *64*, 2338. Harwood, L. M.; Hodgkinson, L. C.; Sutherland, J. K.; Taowers, P. *Can. J. Chem.* **1984**, *62*, 1922.

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primary alcohol in **10a** as the TBDMS ether **10b** (TBDMSCl, Et_3N, catalytic DMAP, CH_2Cl_2),[15] followed by oxidation of the 13-hydroxyl group with pyridine–SO_3 complex,[16] produced the ketone **11a**. Removal of the TBDMS groups in **11a**, with aqueous HF in acetonitrile[17] gave **11b**, which on demethylation with boron trichloride furnished (±)-4,6-dideoxyadriamycinone (**2b**).

With two exceptions, the synthesis of 4-deoxyadriamycinone **2a** from the quinone **6a** was accomplished in an analogous manner. The hydroxymethyl group in **6b** could not be oxidized to the aldehyde **6c** with barium manganate. For this transformation, pyridinium chlorochromate[18] proved to be an effective oxidant furnishing the aldehyde **6c** in 74% yield. The second exception was protection of the C-7 hydroxyl in **9c**. Here, it was necessary to use TBDMS–triflate[19] to convert **9c** to the TBDMS ether **9d**.

In summary, the accomplished sequences permit regio- and stereospecific syntheses of two adriamycinone analogues from a common intermediate, the anthraquinone **4c**. Although the origins of the reaction dichotomy are unclear, it is noteworthy that a simple change of solvent used for reductive Claisen rearrangement of the quinazarin allyl ether **4c** permits either retention or regiospecific loss of the 6-oxygen functionality. It should be noted that these preparations possess many practical aspects; the starting material is inexpensive, and our experience with the sequence indicates that the individual steps can be run on a moderate scale. With the exception of allyl ether compound **4a**, virtually all of the intermediates can be purified through crystallization.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 621B infrared spectrophotometer and are expressed in wave numbers. Proton NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported as δ values in ppm relative to TMS. EI (70 eV) and FAB mass spectra were obtained with a Hewlett-Packard spectrometer. Analytical thin-layer chromatography plates (silica gel 60 F-254, layer thickness 0.25 mm) were manufactured by E. Merck and Co. Silica gel for column chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

1-*O*-(2-Methylenebut-1-yl)-4-hydroxyanthracene-9,10-dione (4a). Powdered anhydrous potassium carbonate (5.5 g, 40 mmol) was added in small portions to a magnetically stirred solution of quinizarin (9.6 g, 40 mmol) in dry DMF (200 mL) under nitrogen. The thick slurry of potassium salt that formed over 15–30 min was thinned with additional DMF (200 mL). The mixture was heated to 55–60 °C for 0.5 h, and then ethallyl chloride[4] (21 g, 0.20 mol) was added. The mixture was heated at 65–70 °C for 40 h and then cooled (5 °C) and acidified with HCl (1 N, 80 mL). Water (300 mL) and CH_2Cl_2 (300 mL) were added, and the mixture was stirred thoroughly. The phases were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed successively with water (400 mL) and brine (400 mL) and then dried ($MgSO_4$), filtered, and evaporated to give 11 g of crude material. The residue was divided into three equal portions, which on chromatography (200 g silica gel; 3:1 CH_2Cl_2-hexanes) provided 6.17 g (50%) of the monoallylic ether **4a** as red-orange crystals: mp 134–135 °C; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7.3 Hz), 2.25 (q, 2 H, J = 7.3 Hz), 4.67 (s, 2 H), 5.08 (s, 1 H), 5.35 (s, 1 H), 7.29 (d, 1 H, J = 9.23 Hz), 7.38 (d, 1 H, J = 9.23 Hz), 7.79 (m, 2 H), 8.29 (m, 2 H), 13.04 (s, 1 H); MS, m/z 308 (M^+).

1-*O*-(2-Methylenebut-1-yl)-3-(hydroxymethyl)-4-hydroxyanthracene-9,10-dione (4b). Oxygen-free nitrogen[20] was bubbled through a suspension of the allylic ether **4a** (4.93 g, 16 mmol) in methanol (300 mL), while NaOH (1 N, 64 mL, 64 mmol) was added dropwise. During addition of the sodium hydroxide solution, the suspension gradually dissolved to form a reddish purple colored solution. The reaction was cooled to 0 °C, and a solution of sodium dithionite (5.57 g, 32 mmol) in water (20 mL) was added. After 5–10 min, an aqueous solution of formaldehyde (37%, 4 mL) was added, and the mixture was stirred at 0 °C for 3–4 h. Water (300 mL) was added, and the reaction mixture was exposed to air for 30 min and then acidified with HCl (1 N, 64 mL). The red-orange precipitate was collected, washed with water, and then vacuum dried. The filtrate and washings were combined and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed successively with water (150 mL) and brine (150 mL) and then dried ($MgSO_4$), filtered, and evaporated. Recrystallization (CH_2Cl_2) of the combined residue from the extraction and the material that was collected by filtration gave 2.61 g of red crystals with mp 146–148 °C. The filtrate from the crystallization was concentrated and then chromatographed (100 g of silica gel; 6:1 CH_2Cl_2–Et_2O) to give an additional 1.01 g of pure **4b** (67% overall yield): ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7.2 Hz), 2.25 (q, 2 H, J = 7.2 Hz), 2.44 (br t, 1 H, J = 4.0 Hz) 4.67 (s, 2 H), 4.85 (d, 2 H, J = 4.0 Hz), 5.09 (s, 1 H), 5.39 (s, 1 H), 7.50 (s, 1 H), 7.78 (m, 2 H), 8.28 (m, 2 H), 13.42 (s, 1 H); MS, m/z 338 (M^+).

1-*O*-(2-Methylenebut-1-yl)-3-(hydroxymethyl)-4-methoxyanthracene-9,10-dione (4c). A magnetically stirred suspension of **4b** (676 mg, 2 mmol), powdered anhydrous K_2CO_3 (1.38 g, 10 mmol), and dimethyl sulfate (0.38 mL, 4.0 mmol) in dry acetone (50 mL) was heated at reflux under nitrogen for 3 h. The mixture was cooled to room temperature, and the salts were removed by filtration. Triethylamine (1 mL) was added to the filtrate and stirred for 0.5 h. The filtrate was evaporated to dryness at reduced pressure, and the residue was suspended in water and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed successively with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was chromatographed (50 g of silica gel; 3:1 CH_2Cl_2–Et_2O) to give 667 mg (95%) of pure **4c** with mp 117–119 °C: ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H, J = 7.2 Hz), 2.2 (br m, 1 H), 2.25 (q, 2 H, J = 7.2 Hz), 3.92 (s, 3 H), 4.69 (s, 2 H), 4.89 (d, 2 H, J = 5.1 Hz), 5.10 (s, 1 H), 5.40 (s, 1 H), 7.49 (s, 1 H), 7.73 (m, 2 H), 8.20 (m, 2 H); MS, m/z 352 (M^+).

1-Hydroxy-2-(2-methylenebut-1-yl)-3-(hydroxymethyl)-4-methoxyanthracene-9,10-dione (6a). A solution of sodium dithionite (1.58 g, 9.0 mmol) in water (5 mL) was added to a magnetically stirred solution of **4c** (1.6 g, 4.55 mmol) in DMSO (100 mL) and water (50 mL) under nitrogen. The mixture was heated on a steam bath for 1 h, and then oxygen was bubbled through the hot solution for 15–20 min. Cold water (50 mL) was added, and the solution was chilled in an ice bath. The product was collected by filtration, and the filtrate was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. Chromatography (50 g of silica gel, 6:1 CH_2Cl_2–ether) of the combined residue from the extraction and the filtration gave 1.38 g (86%) of pure **6a** with mp 113–115 °C: ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7.2 Hz), 2.21 (q, 2 H, J = 7.2 Hz), 2.46 (t, 1 H, J = 7.20 Hz), 3.65 (s, 2 H), 3.99 (s, 3 H), 4.37 (s, 1 H), 4.73 (d, 2 H, J = 7.2 Hz), 4.83 (s, 1 H), 7.80 (m, 2 H), 8.30 (m, 2 H), 13.69 (s, 1 H); MS, m/z 352 (M^+).

1,4-Dimethoxy-2-(2-methylenebut-1-yl)-3-(hydroxymethyl)anthracene-9,10-dione (6b). A magnetically stirred suspension of **6a** (1.51 g, 4.4 mmol), powdered anhydrous K_2CO_3 (3 g, 21 mmol), and dimethyl sulfate (0.81 mL, 8.6 mmol) in dry acetone (50 mL) was heated at reflux under nitrogen for 3 h. The mixture was cooled to room temperature, and the inorganic salts were removed by filtration. Triethylamine (2 mL) was added to the filtrate, and the mixture was stirred for 0.5 h. The acetone

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and excess triethylamine were evaporated at reduced pressure. The residue was suspended in water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic phases were successively washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. Chromatography of the residue (50 g of silica gel, 40% EtOAc–hexanes) gave 1.54 g (98%) of pure **6b** as a yellow semisolid: ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H, J = 7.3 Hz), 2.23 (q, 2 H, J = 7.3 Hz), 2.61 (br t, 1 H, J = 6 Hz, OH), 3.64 (s, 2 H), 3.87 (s, 3 H), 4.01 (s, 3 H), 4.24 (s, 1 H), 4.71 (d, 2 H, J = 6 Hz), 4.85 (s, 1 H), 7.74 (m, 2 H), 8.18 (m, 2 H); MS, m/z 366 (M^+). Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.23; H, 5.88.

1,4-Dimethoxy-2-(2-methylenebut-1-yl)-3-formylanthracene-9,10-dione (6c). To a stirred suspension of pyridinium chlorochromate (1 g, 4.64 mmol) and Celite (1 g) in dry CH_2Cl_2 (15 mL) was added a solution of **6b** (0.75 g, 2.05 mmol) in CH_2Cl_2 (15 mL) under nitrogen. The resultant mixture was stirred at room temperature for 2 h. Anhydrous ether (25 mL) was added, and the mixture was stirred thoroughly. The suspension was filtered through a small pad of Celite and the residue was washed with ether. The filtrate was evaporated at reduced pressure, and the oily residue was chromatographed (50 g silica gel, 15:1 CH_2Cl_2–Et_2O) to provide 550 mg (74%) of pure aldehyde **6c** with mp 90–92 °C: ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7.60 Hz), 2.19 (q, 2 H, J = 7.60 Hz), 3.79 (s, 2 H), 3.89 (s, 3 H), 4.02 (s, 3 H), 4.14 (s, 1 H), 4.76 (s, 1 H), 7.80 (m, 2 H), 8.20 (m, 2 H), 10.49 (s, 1 H); MS, m/z 364 (M^+).

(±)-(*E*,*Z*)-6,11-Dimethoxy-7-hydroxy-9-ethylidene-7,8,9,10-tetrahydronaphthacene-5,12-dione (7b). Stannic chloride pentahydrate (140 mg, 0.4 mmol) was added to a magnetically stirred solution of the aldehyde **6c** (520 mg, 1.43 mmol) in CH_2Cl_2 (70 mL) at room temperature, and the mixture was allowed to react for 1 h. The reaction was chilled in an ice bath and then quenched with 5% sodium bicarbonate solution (40 mL). The organic phase was separated and washed successively with 50-mL portions of water and brine and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Recrystallization of the residue from CH_2Cl_2–hexanes gave 470 mg (90%) of **7b** as yellow crystals with mp 88–90 °C dec: ^1H NMR ($CDCl_3$) δ 1.77 (d, 3 H, J = 6.8 Hz), 2.6 (m, 2 H), 2.73–2.97 (m, 1 H), 3.37–3.60 (m, 1 H), 3.93 (s, 3 H, OCH_3 of one isomer), 3.96 (s, 3 H, OCH_3 of other isomer), 4.03 (s, 3 H, OCH_3 of one isomer), 4.04 (s, 3 H, OCH_3 of other isomer), 5.22–5.32 (m, 1 H), 5.6 (q, 1 H, J = 6.8 Hz, vinylic H of one isomer), 5.74 (q, 1 H, J = 6.8 Hz, vinylic H of other isomer), 7.75 (m, 2 H), 8.23 (m, 2 H); MS, m/z 364 (M^+).

(±)-*cis*-3,4-Dihydro-5,12-dimethoxy-4-hydroxyspiro[naphthacene-2(1*H*),2′(*E*,*Z*)-methyloxirane]-6,11-dione (8b). To a cold (0 °C) magnetically stirred solution of the homoallylic alcohol **7b** (441 mg, 1.21 mmol) and vanadyl acetylacetonate (40 mg, 0.15 mmol) in dry CH_2Cl_2 (75 mL) under nitrogen was added *tert*-butyl hydroperoxide (1.0 mL, 3 mmol, 3 M in toluene). The mixture was stirred for 4 h at 0–5 °C and then quenched with 5% sodium sulfite solution (20 mL). The organic layer was separated and washed successively with water (30 mL) and brine (30 mL) and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue (50 g of silica gel; 2:1 ether–CH_2Cl_2) furnished 378 mg (82%) of pure *syn*-epoxide **8b** as a mixture of isomers: mp 155–157 °C dec: ^1H NMR ($CDCl_3$) δ 1.44 (d, 3 H, J = 6.0 Hz, CH_3 of one isomer), 1.46 (d, 3 H, J = 6.0 Hz, CH_3 of the other isomer), 1.95 (dd, 1 H, J = 14.0 and 5.3 Hz), 2.27 (dd, 1 H, J = 14.0 and 4.3 Hz), 2.8–2.97 (m, 1 H), 3.12 (q, 1 H, J = 6.0 Hz), 3.2 (m, 1 H), 3.42–3.52 (m, 1 H), 3.90 (s, 3 H, OCH_3 of one isomer), 3.92 (s, 3 H, OCH_3 of other isomer), 4.07 (s, 3 H, OCH_3 of both isomers), 5.37 (m, 1 H), 7.76 (m, 2 H), 8.22 (m, 2 H); MS (CI), m/z 381 (M + 1).

(±)-*cis*-(7,9-Dihydroxy)-6,11-dimethoxy-9-ethenyl-7,8,9,10-tetrahydronaphthacene-5,12-dione (9c). Sodium borohydride (176 mg, 4.6 mmol) was added in small portions to a magnetically stirred solution of diphenyl diselenide (736 mg, 2.3 mmol) in absolute ethanol (80 mL) under nitrogen. A slurry of the epoxide **8b** (400 mg, 1.05 mmol) in dry DME (80 mL) was added, and the reaction was stirred overnight. The solution was cooled in an ice bath, and hydrogen peroxide (23 mL, 30%) was added dropwise. The reaction was allowed to warm to room temperature and stand overnight. Water (160 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed successively with 100-mL portions of water and brine and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue (40 g of silica gel; 60% EtOAc in hexanes) gave 320 mg (80%) of pure olefinic diol **9c** with mp 175–176 °C dec: ^1H NMR ($CDCl_3$) δ 2.00 (dd, 1 H, J = 15.0 and 5.3 Hz), 2.05 (s, 1 H), 2.35 (ddd, 1 H, J = 15.0, 2.3 and 2.3 Hz), 2.76 (d, 1 H, J = 18.2 Hz), 3.28 (dd, 1 H, J = 18.2 and 2.2 Hz), 3.4 (br s, 1 H), 3.90 (s, 3 H), 4.05 (s, 3 H), 5.23 (dd, 1 H, J = 10.8 and 1.7 Hz), 5.26 (m, 1 H), 5.47 (dd, 1 H, J = 17.0 and 1.7 Hz), 6.09 (dd, 1 H, J = 17.0 and 10.8 Hz), 7.76 (m, 2 H), 8.19 (m, 2 H); MS (CI), m/z 381 (M + 1). Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.47; H, 5.29. Found: C, 69.60; H, 5.52.

(±)-*cis*-7-[(*tert*-Butyldimethylsilyl)oxy]-9-hydroxy-6,11-dimethoxy-9-ethenyl-7,8,9,10-tetrahydronaphthacene-5,12-dione (9d). To a cold (0–5 °C) magnetically stirred solution of the vinyl diol **9c** (380 mg, 1 mmol) and 2,6-lutidine (0.6 mL, 5 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen was added dropwise (*tert*-butyldimethylsilyl)trifluoromethane sulfonate (0.46 mL, 2 mmol), and the resultant mixture was warmed to room temperature and stirred for 24 h. Excess silylating agent was destroyed by addition of methanol (2 mL, 0.5 h). Water (20 mL) was added, and the mixture was stirred thoroughly. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed successively with 25-mL portions of 0.5 N hydrochloric acid solution, saturated sodium bicarbonate solution, water, and brine and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The oily residue was chromatographed (40 g of silica gel; 1:1 EtOAc–hexanes) to provide 395 mg (80%) of pure siloxy ether **9d** with mp 127–129 °C: ^1H NMR ($CDCl_3$) δ 0.15 (s, 3 H), 0.27 (s, 3 H), 0.85 (s, 9 H), 1.88 (dd, 1 H, J = 14.0 and 4.0 Hz), 2.24 (ddd, 1 H, J = 14.0, 2.5 and 2.0 Hz), 2.76 (d, 1 H, J = 18.5 Hz), 3.32 (dd, 1 H, J = 18.5 and 2.1 Hz), 3.89 (s, 3 H), 3.91 (s, 3 H), 5.16 (dd, 1 H, J = 10.7 and 2.0 Hz), 5.16 (s, 1 H, OH), 5.32 (dd, 1 H, J = 4.0 and 2.5 Hz), 5.45 (dd, 1 H, J = 17.1 and 2.0 Hz), 6.01 (dd, 1 H, J = 17.1 and 10.7 Hz), 7.73 (m, 2 H), 8.18 (m, 2 H); MS (CI), m/z 495 (M + 1).

(±)-*cis*-7-[(*tert*-Butyldimethylsilyl)oxy]-9-hydroxy-6,11-dimethoxy-9-[1-oxo-2-[(*tert*-butyldimethylsilyl)oxy]-ethyl]-7,8,9,10-tetrahydronaphthacene-5,12-dione (11c). A solution of the vinylic alcohol **9d** (240 mg, 0.486 mmol), trimethylamine *N*-oxide dihydrate (0.108 g, 0.971 mmol), and osmium tetraoxide stock solution (0.6 mL, 0.02 M in 3:1 *t*-BuOH–CCl_4, 0.024 mmol) in acetone (14 mL) and water (6 mL) was stirred at room temperature for 16 h. The reaction was quenched with 5% sodium sulfite solution (10 mL), and the acetone was evaporated at reduced pressure. The residue was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic solution was successively washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography (30 g of silica gel; ether) of the oily residue gave 246 mg (96%) of pure triol **10c**.

A solution of the triol **10c** (230 mg, 0.435 mmol), (dimethylamino)pyridine (6 mg, 0.04 mmol), triethylamine (0.28 mL, 2 mmol), and *tert*-butyldimethylsilyl chloride (85 mg, 0.56 mmol) in dry CH_2Cl_2 (4 mL) was stirred at ambient temperature for 3 days. The excess silylating agent was destroyed with methanol (1 mL). Water (10 mL) and CH_2Cl_2 (20 mL) were added, and the layers were separated. The organic solution was washed successively with water (10 mL) and brine (10 mL) and then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was chromatographed (30 g of silica gel; 3:7 EtOAc–hexanes) to give 249 mg (89%) of pure disilyoxy ether **10d**.

To a stirred solution of the diol **10d** (157 mg, 0.244 mmol) and triethylamine (1 mL, 7.3 mmol) in dry DMSO (2 mL) under nitrogen was added sulfur trioxide–pyridine complex (0.39 g, 2.44 mmol), and the mixture was stirred at room temperature for 24 h. The reaction was quenched with water (20 mL, 15 min), and the product was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed successively with water (20 mL) and brine (20 mL) and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography (30 g of silica gel; 1:4 EtOAc–hexanes) of the residue furnished 142 mg (91%) of pure hydroxy ketone **11c** as yellow crystals with mp 157–159 °C dec: ^1H NMR ($CDCl_3$) δ 0.11 (s, 3 H) 0.12 (s, 3 H), 0.13 (s, 3 H), 0.27 (s, 3 H), 0.84 (s, 9 H), 0.94 (s, 9 H) 2.03 (dd, 1 H, J = 14.0 and 3.4 Hz), 2.26 (ddd, 1 H, J = 14.0, 2.5, and 2.0 Hz), 3.13

(d, 1 H, J = 18.6 Hz), 3.28 (dd, 1 H, J = 18.6 and 1.3 Hz), 3.88 (s, 3 H), 3.92 (s, 3 H), 4.85 (d, 1 H, J = 19.9 Hz), 4.96 (d, 1 H, J = 19.9 Hz), 5.33 (dd, 1 H, J = 3.4 and 2.5 Hz), 5.38 (s, 1 H), 7.73 (m, 2 H), 8.18 (m, 2 H); MS (CI), m/z 641 (M + 1).

(±)-*cis*-7,9-Dihydroxy-6,11-dimethoxy-9-(1-oxo-2-hydroxyethyl)-7,8,9,10-tetrahydronaphthacene-5,12-dione (11d). Aqueous hydrofluoric acid (10 mL of a 5% solution in acetonitrile) was added dropwise to a stirred solution of the silyloxy ether **11c** (98 mg, 0.15 mmol) in acetonitrile (4 mL) under nitrogen, and the mixture was stirred at room temperature for 1 h. The acetonitrile was evaporated at room temperature under reduced pressure, and the aqueous suspension was extracted with EtOAc (3 × 25 mL). The combined organic extracts were successively washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography (15 g of silica gel; EtOAc) of the residue furnished 62 mg (98%) of pure **11d** as yellow crystals with mp 166–168 °C: ^{1}H NMR ($CDCl_3$) δ 2.14 (dd, 1 H, J = 14.5 and 5.0 Hz), 2.38 (ddd, 1 H, J = 14.5, 2.9 and 1.8 Hz), 2.98 (br s, 1 H, OH), 3.04 (d, 1 H, J = 18.8 Hz), 3.29 (dd, 1 H, J = 18.8 and 2.1 Hz), 3.44 (br s, 1 H, OH), 3.88 (s, 3 H), 4.03 (s, 3 H), 4.68 (d, 1 H, J = 2.1 Hz, C9-OH), 4.77 (t, 2 H, J = 4.2 Hz), 5.29 (m, 1 H), 7.75 (m, 2 H), 8.18 (m, 2 H); MS (CI), m/z 413 (M + 1); IR ($CHCl_3$) cm^{-1} 3600–3450, 3150, 2925, 2243, 1794, 1720, 1670. Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 64.18; H, 4.62.

1-Hydroxy-2-(2-methylenebut-1-yl)-3-(hydroxymethyl)-anthracene-9,10-dione (5a). To a stirred solution of **4c** (634 mg, 1.8 mmol) in DMF (30 mL) and water (15 mL) under nitrogen was added sodium dithionite (627 mg, 3.6 mmol). The resultant mixture was heated on a steam bath for 1.5 h. Oxygen was bubbled through the hot solution for 15 min and then cold water (40 mL) was added. The precipitated product was extracted with CH_2Cl_2 (3 × 50 mL), and the combined extracts were washed successively with water (50 mL) and brine (50 mL) and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 545 mg (86%) of essentially pure **5a**. A sample recrystallized from CH_2Cl_2–hexanes had mp 133–135 °C. The melting point and ^{1}H NMR spectrum were identical with those of an alternatively prepared sample:[7] ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7.3 Hz) 1.97 (br s, 1 H, OH), 2.16 (q, 2 H, J = 7.3 Hz), 3.54 (s, 2 H), 4.37 (s, 1 H), 4.77 (s, 3 H, CH_2OH and vinylic H), 7.79 (m, 2 H), 8.01 (s, 1 H), 8.31 (m, 2 H), 13.03 (s, 1 H, phenolic OH); MS, m/z 322 (M^+).

1-Methoxy-2-(2-methylenebut-1-yl)-3-(hydroxymethyl)-anthracene-9,10-dione (5b). Methyl ether **5b** was prepared in 98% yield in a manner identical with that employed for the preparation of **6b**. A sample recrystallized from CH_2Cl_2–hexanes had mp 72–74 °C: ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7.3 Hz), 1.97 (br s, 1 H, OH), 2.19 (q, 2 H, J = 7.3 Hz), 3.56 (s, 2 H), 3.89 (s, 3 H), 4.24 (s, 1 H), 4.78 (s, 1 H), 4.79 (d, 2 H, J = 5.9 Hz), 7.78 (m, 2 H), 8.27 (m, 2 H), 8.31 (s, 1 H); MS, m/z 336 (M^+).

1-Methoxy-2-(2-methylenebut-1-yl)-3-formylanthracene-9,10-dione (5c). Barium manganate (4.0 g, 15.6 mmol) was added in portions to a magnetically stirred solution of **5b** (1.05 g, 3.125 mmol) in dry CH_2Cl_2 (200 mL) under nitrogen. The suspension was stirred at room temperature for 4 h and then filtered, and the filtrate was evaporated under reduced pressure to give 0.94 g (90%) of pure aldehyde. A sample recrystallized from CH_2Cl_2–hexanes had mp 92–93 °C: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 7.3 Hz), 2.25 (q, 2 H, J = 7.3 Hz), 3.92 (s, 2 H), 3.93 (s, 3 H), 4.18 (s, 1 H), 4.86 (s, 1 H), 7.82 (m, 2 H), 8.31 (m, 2 H), 8.66 (s, 1 H), 10.26 (s, 1 H); MS, m/z 334 (M^+).

(±)-(*E*,*Z*)-7-Hydroxy-9-ethylidene-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (7a). Ene cyclization of the olefinic aldehyde **5c** (670 mg, 2 mmol) was carried out in a manner similar to that described for **6c**, except that the reaction time was only 15 min. After the usual workup, the initial product was recrystallized from CH_2Cl_2–hexanes to furnish 615 mg (92%) of **7a** as yellow crystals with mp 173–175 °C dec: ^{1}H NMR ($CDCl_3$) δ 1.71 (d, 3 H, J = 6.8 Hz, CH_3 of minor isomer), 1.74 (d, 3 H, J = 6.8 Hz CH_3 of major isomer), 2.1 (br s, 1 H, OH) 2.53 (m, 1 H), 2.70 (m, 1 H), 3.40–3.80 (m, 2 H), 3.92 (s, 3 H, OCH_3 of minor isomer), 3.96 (s, 3 H, OCH_3 of major isomer), 4.85 (t, 1 H, J = 5.4 Hz, C7-H of major isomer), 4.90 (t, 1 H, J = 5.4 Hz, C7-H of minor isomer), 5.57 (q, 1 H, J = 6.8 Hz, C=C*H* of major isomer), 5.68 (q, 1 H, J = 6.8 Hz, C=C*H* of minor isomer), 7.76 (m, 2 H), 8.22 (s, 1 H), 8.25 (m, 2 H); MS, m/z (FAB) 335 (M + 1).

(±)-*cis*-3,4-Dihydro-4-hydroxy-12-methoxyspiro[naphthacene-2(1*H*),2′(*E*,*Z*)-methoxyoxirane]-6,11-dione (8a). Sharpless epoxidation of **7a** (334 mg, 1 mmol) was carraied out in a manner identical with that employed for the preparation of **8b**. After the usual workup, the residue was chromatographed to furnish 301 mg (86%) of pure *syn*-epoxide **8a** as a mixture of isomers with mp 164–167 °C dec: ^{1}H NMR (DMSO-d_6) δ 1.30 (d, 3 H, J = 5.2 Hz), 1.88 (m, 1 H), 2.16 (m, 1 H), 2.77 (m, 1 H), 3.05 (m, 2 H), 3.81 (s, 3 H, OCH_3 of major isomer), 3.84 (s, 3 H, OCH_3 of minor isomer), 4.79 (m, 1 H), 5.95 (m, 1 H), 7.90 (m, 2 H), 8.18 (m, 2 H), 8.27 (s, 1 H); MS, m/z (FAB) 351 (M + 1).

(±)-*cis*-7,9-Dihydroxy-9-ethenyl-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (9a). The procedure employed for the preparation of **9c** was used. From the epoxide **8a** (175 mg, 0.5 mmol) was obtained 164 mg (94%) of pure olefinic diol **9a** with mp 186–188 °C: ^{1}H NMR ($CDCl_3$) δ 2.06 (dd, 1 H, J = 14.5 and 5.3 Hz), 2.35 (ddd, 1 H, J = 14.5, 2.6 and 2.6 Hz), 2.79 (s, 1 H), 2.81 (d, 1 H, J = 18.7 Hz), 3.25 (dd, 1 H, J = 18.7 and 1.8 Hz), 3.88 (s, 3 H), 3.98 (d, 1 H, J = 9.3 Hz), 4.90 (m, 1 H), 5.25 (d, 1 H, J = 10.7 Hz), 5.45 (d, 1 H, J = 17.1 Hz), 6.11 (dd, 1 H, J = 17.1 and 10.7 Hz), 7.77 (m, 2 H), 8.22 (s, 1 H), 8.23 (m, 2 H); MS, m/z (FAB) 351 (M + 1).

(±)-*cis*-7-[(*tert*-Butyldimethylsilyl)oxy]-9-hydroxy-9-ethenyl-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (9b). A solution of vinylic diol **9a** (151 mg, 0.43 mmol), imidazole (147 mg, 2.16 mmol), and *tert*-butyldimethylsilyl chloride (163 mg, 1.08 mmol) in dry DMF (6 mL) was stirred under nitrogen for 24 h. The excess silylating agent was destroyed with methanol (1 mL, 0.5 h). Water was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed successively with 25-mL portions of water and brine and then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue (silica gel, 30% EtOAc–hexanes) furnished 182 mg (91%) of pure silyloxy ether **9b** with mp 143–145 °C: ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 6 H), 0.90 (s, 9 H), 2.07 (dd, 1 H, J = 14.1 and 4.3 Hz), 2.16 (ddd, 1 H, J = 14.1, 4.3 and 2.3 Hz), 2.87 (d, 1 H, J = 18.0 Hz), 3.23 (dd, 1 H, J = 18.0 and 2.2 Hz), 3.93 (s, 3 H), 4.2 (br s, 1 H, OH), 5.03 (t, 1 H, J = 4.3 Hz), 5.16 (dd, 1 H, J = 10.8 and 1.6 Hz), 5.39 (dd, 1 H, J = 17.5 and 1.6 Hz), 6.01 (dd, 1 H, J = 17.5 and 10.8 Hz), 7.76 (m, 2 H), 8.13 (s, 1 H), 8.25 (m, 2 H); MS, m/z (FAB) 465 (M + 1).

(±)-*cis*-7-[(*tert*-Butyldimethylsilyl)oxy]-9-hydroxy-9-[1-oxo-2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (11a). The diastereoisomeric mixture of triols **10a** were prepared in 96% yield in a manner identical with that employed for the preparation of **10c**. The diastereoisomeric mixture of triols **10a** were converted to an isomeric mixture of disilyloxy ethers **10b** in 94% yield by using the procedure described for the preparation of **10d**. Then, following the procedure described in the preparation of **11c**, the isomeric mixture of alcohols **10b** (123 mg, 0.20 mmol) was oxidized to give 111 mg (91%) of pure ketone **11a** with mp 134–136 °C: ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.24 (s, 3 H), 0.27 (s, 3 H), 0.88 (s, 9 H), 0.94, (s, 9 H), 2.12–2.26 (m, 2 H), 3.09 (d, 1 H, J = 18.0 Hz), 3.29 (d, 1 H, J = 18.0 Hz) 3.91 (s, 3 H), 4.82 (d, 1 H, J = 19.7 Hz), 4.93 (d, 1 H, J = 19.7 Hz), 4.99 (s, 1 H, OH), 5.08 (t, 1 H, J = 3.4 Hz), 7.77 (m, 2 H), 8.07 (s, 1 H), 8.25 (m, 2 H); MS, m/z (FAB) 611 (M + 1).

(±)-*cis*-7,9-Dihydroxy-9-(1-oxo-2-hydroxyethyl)-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (11b). The silyloxy ether **11a** was desilylated in 98% yield by using the procedure employed for **11d**. A sample recrystallized from EtOAc–hexanes had mp 139–141 °C: ^{1}H NMR ($CDCl_3$) δ 2.15 (dd, 1 H, J = 14.2 and 3.4 Hz), 2.37 (d, 1 H, J = 14.2 Hz), 3.02 (d, 1 H, J = 18.7 Hz), 3.24 (dd, 1 H, J = 18.7 and 1.8 Hz), 3.80 (s, 3 H), 4.74 (d, 1 H, J = 20.5 Hz), 4.83 (d, 1 H, J = 20.5 Hz), 4.86 (m, 1 H), 5.02 (br s, 1 H), 7.75 (m, 2 H), 8.05 (s, 1 H), 8.10 (m, 1 H), 8.18 (m, 1 H); MS, m/z (FAB) 383 (M + 1); IR (film, cm^{-1}) 3550–3300, 1730, 1670. Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.97; H, 4.75. Found: C, 66.22; H, 4.52.

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