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A GENERAL ROUTE FOR TOTAL SYNTHESIS OF 9-ALKYL-9-HYDROXY AKLAVINONES AND PYRROMYCINONES

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Abstract—A general route for convergent, regiospecific synthesis of 9-alkyl-9-hydroxy anthracyclinones with the aklavin and pyrromycin oxygenation patterns is described.

Anthracyclinones with the A-ring substitution patterns **a** through **d** of Fig. 1 are not known to occur naturally when the chromophore has the aklavin **1** or pyrromycin **2** oxygenation pattern.[2,3] While preparation of these compounds was initially achieved through partial degradation of existing 10-carbomethoxy substituted anthracyclines,[6] more recently procedures for total synthesis of the aklavin group have been reported. Using the anthraquinone chrysophanol as a starting material, Krohn *et al.*[7] described a linear route for preparation of the Me and Et substituted series **1a–d**. Kishi and McNamara[8] devised an elegant chiral preparation of **1b** (R = Et) in conjunction with their work on aklavinone.

The annelation methodology[9,10] developed by us for the total synthesis of complex polycyclic aromatic systems of varying structural type and with a variety of oxygenation patterns has been established as a general solution to the problem of effecting brief and efficient regiospecific construction of anthracycline type compounds.[11] While these procedures were initially employed in linear routes,[11a–f] our recent development of methods for regiospecific synthesis of highly functionalized 1(4H)-naphthalenones[11g,h] and cyclohexenones[11i] has expanded their use to convergent schemes which permit preparation of multigram quantities of anthracyclinones.

In this paper we describe the development of routes to the 9-Me and 9-Et substituted 1(4H)-naphthalenones **7a** and **7b** and their use in the total synthesis of **1a**, **1c** and **1d** (R = Et) with the aklavin oxygenation pattern and to accomplish the first total synthesis of the 9-Me substituted pyrromycins **2a**, **2b** and **11c**. The compound **11c** is the aglycon fragment of the semi-synthetic anticancer antiobiotic 7-con-O-methylnogarol.[6c–e] These syntheses further demonstrate the diversity of anthracyclinones which can be readily obtained through condensation of phthalide-sulfones[9,11] with latently functionalized 1(4H)-naphthalenones and cyclohexenones.

The Me and Et substituted 1(4H)-naphthalenones **7a** and **7b** which served as synthons for the A- and B-rings were prepared as shown in Scheme 1. Synthesis of the alkyl substituted hydronaphthalone precursors **5a** and **6a** was devised in part from the initial report of Wenkert *et al.*[12] that contrary to the usual poor results obtained

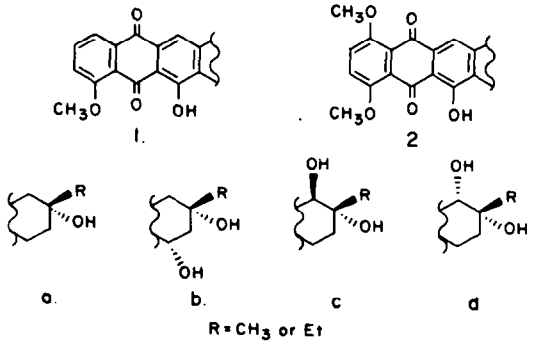
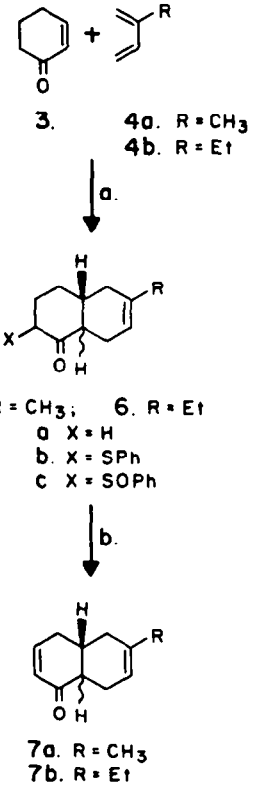


Fig. 1.



a. 1. BF_3, Et_2O (R = CH_3, 80%; R = Et, 75%) 2 LiCIPA, $PhSSO_2Ph$ (87-91%) 3. $NaIO_4$, MeOH (91-94%)
b. 1. Δ, CCl_4, $CaCO_3$ (68-71%)

Scheme 1.

from the Diels–Alder reaction of cycloalkenones with dienes, high yields of adducts can be obtained by initially complexing the cycloalkenone with aluminum chloride. Moreover, since Lewis acids are known to favor the formation of a single regioisomer during cycloaddition,[13] the reaction of cyclohexenone (3) with 2-substituted butadienes was expected to occur in a highly selective manner.

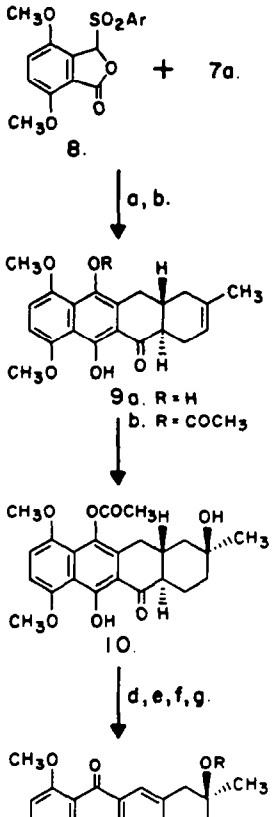
In contrast to the high yield reported for cycloaddition of 3 with butadiene, only a modest yield (12%) of the adduct **5a** was obtained when isoprene (**4a**) was reacted with 3 under aluminum chloride catalysis. Nearly all the cyclohexenone (3) was reclaimed during workup and a large amount of polymeric residue was obtained, therefore, it was concluded that extensive polymerization of the isoprene had occurred. A qualitative examination of different Lewis acids revealed that boron trifluoride etherate was the optimal catalyst for Diels–Alder reaction of cyclohexenone (3) with isoprene (**4a**) (RT, 48h, 85% conversion) and the naphthalone **5a** was obtained as a mixture of isomers in 80% yield.[14,15]

The stereo- and regiochemistry of the naphthalone **5a** was experimentally established. Shortly after initiation of the Diels–Alder reaction, *tlc* analysis showed a single product was present, however, as the reaction proceeded, a second product formed and ultimately became the major component. The *cis, trans* geometric relationship implied by these observations was confirmed by chromatographically separating and then equilibrating (NaOH—EtOH) the individual isomers to identical mixtures. The regioselectivity of the boron trifluoride catalyzed reaction was shown to be >95% through capillary GC-MS analysis of the naphthalenone using molecular weight as a criteria.

Cycloaddition of 2-ethyl-1,3-butadiene (**4b**) and cyclohexenone 3 was carried out under identical conditions and gave the 6-Et substituted naphthalone **6a**. While the rate of reaction was much slower (48 hr, 65% conversion) the yield of **6a** was respectable (75%). The observed difference in the relative rates of reaction of isoprene (**4a**) and 2-ethyl-1,3-butadiene (**4b**) with cyclohexenone 3 can be straightforwardly explained from the transition state geometry presented in Fig. 2. The steric interaction between the 2-substituent on the diene and the axially oriented 5-proton on the cyclohexenone and the larger volume of the ethyl group retard the rate of reaction of **4b** with 3.

The 2,3-unsaturation in the naphthalenones **7a** and **7b** was introduced using the reaction sequence developed by Trost and Massiot.[16] Kinetic deprotonation (lithium cyclohexylisopropyl amide, THF, −78°) of the individual ketones **5a** and **6a** followed by reaction of the anions with phenylbenzenethiosulfate produced isomeric mixtures of the thiophenylated **5b** and **6b** in 87 and 91% yield, respectively. Oxidation ($NaIO_4$, MeOH) of the sulfide moiety in **5b** and **6b** gave the corresponding sulfoxides **5c** and **6c** (91–94%) which were pyrolyzed (CCl_4, $CaCO_3$) to the 1(4H)-naphthalenones **7a** and **7b** in 68 and 71% yield, respectively. Although the individual naphthalenones **7a** and **7b** were mixtures of *cis* and *trans* isomers, separation of the components was not necessary at this point since the bridging carbons would later be converted from tetrahedral sp^3 to planar sp^2 centers.

The use of the Me substituted naphthalenone **7a** as a precursor to **2a**, **2b** and **11c** is shown in Scheme 2. The chemistry employed in this sequence was designed to be compatible with ultimately performing a total synthesis of 7-con-0-methylnogarol. The anion of the phthalide-sulfone **8**,[11a] generated at −78° with lithium *t*-butoxide in THF, was condensed with **7a** to give the regiospecifically constructed, latently functionalized, tetrahydronaphthacenone **9a** in 86% yield. Selective acetylation of **9a** to the monoacetate **9b** (Ac_2O, Py, RT; 92%) was necessary to protect the hydroquinone system against oxidation during subsequent introduction of the 9-OH group. Reaction of **9b** with mercuric



a. LiOtBu, THF (86%) b. Ac_2O, Py (92%) c. $Hg(NO_3)_2$, NaOH, $NaBH_4$, (81%) d. NaOH, O_2 (83%) e. Ac_2O, Et_3N, DMAP (82%) 2. KOH, DME-H_2O (93%) f. NBS, CCl_4, $CHCl_3$, H_2O (67%) g KOH, DME-H_2O (88%) h. CF_3CO_2H, NaOMe (92%)

Scheme 2.

Fig. 2.

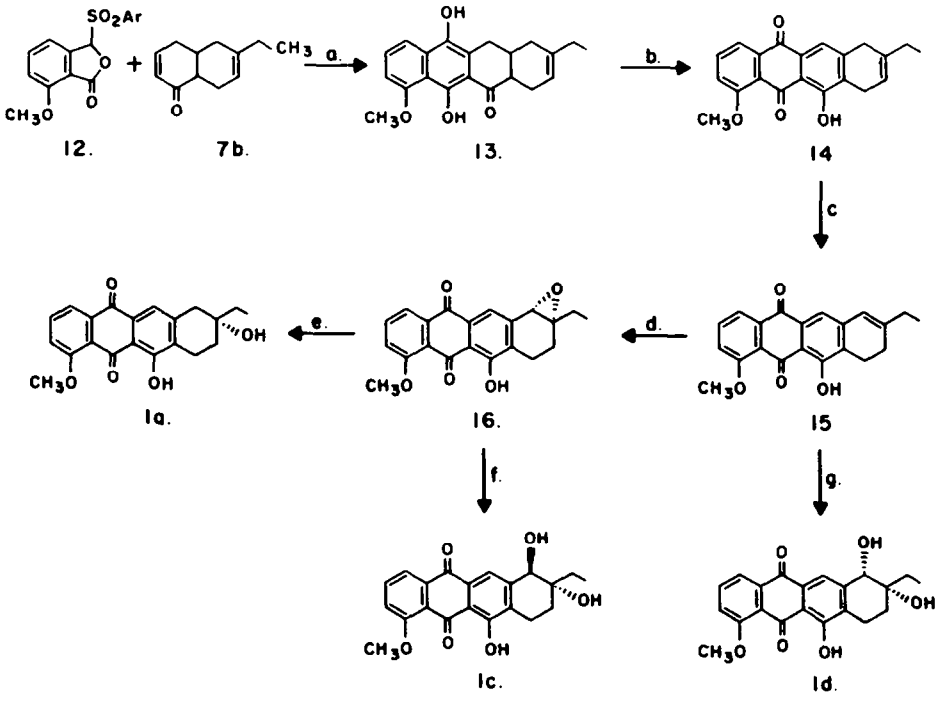
nitrate[17] (1.2 equiv, THF—H_2O) followed by sequential treatment of the organomercury intermediate with sodium hydroxide and sodium borohydride selectively reduced the carbon-mercury bond without reducing the 6-CO group and gave **10** in 81% yield. Deacetylation, aromatization of the B-ring, and oxidation of the C-ring to a quinone furnishing **2a** were accomplished in a single step in 83% yield by bubbling oxygen through an ethanolic potassium hydroxide solution of **10** at 65°.

An indepth study of derivatives of **2a** was carried out in order to determine the optimum pattern of functionalization for high yield stereospecific introduction of the 7-OH group. Ultimately, it was found that a phenolic group at the six position and protection of the 9-OH functionality as its acetate derivative were required to prevent aromatization of the A-ring. The monoacetate **11a** was prepared by initially converting **2a** to the diacetate (Ac_2O, Et_3N, DMAP[18]; 82%) and then selectively cleaving (1 equiv. KOH, DME, H_2O, RT; 93%) the phenolic acetate moiety. Hydroxylation of **11a** at the seven position by homolytic bromination and solvolysis[19] (Br_2, AIBN, CCL_4, H_2O; 67%) gave **11b** as a 9:1 mixture of epimeric alcohols in 67% yield. The major isomer was separated and assigned the *cis* stereochemistry based on results obtained from similar hydroxylations. Hydrolysis of the acetoxyl moiety in **11b** (KOH, DME, H_2O, 65°, N_2; 88%) gave the *cis*-diol product **2b**. Stereospecific introduction of the seven OMe group was accomplished using a procedure originally developed by Wiley *et al.*[6c] in conjunction with their work on 7-con-0-methylnogarol. Sequential treatment of **2b** with trifluoroacetic acid and sodium methoxide furnished **11c** in 91% yield.

The different synthetic route shown in Scheme 3 employed the Et substituted 1(4H)-naphthalenone **7b** to regiospecifically construct the hydroxylated products **1a**, **1c** and **1d** with the aklavin oxygenation pattern. Condensation of the anion of the methoxyphthalidesulfone **12**[20] (LiOtBu, THF, −78°) with **7b** gave the regiospecifically constructed hydronaphthacenone **13** in 91% yield. Heating the hydronaphthacene **13** in DMF under an oxygen atmosphere effected direct aromatization and oxidation to the naphthacenedione **14** (68% yield).

Isomerization of the olefinic entity in **14** from the 8,9- to the 9,10-position would give **15**,[21] the intermediate employed by Krohn *et al.*[7a] to prepare **1a** and **1b** (R = Et). Protonation of the olefin in **14** was expected to generate a tertiary carbonium ion at the 9-position which would then undergo selective elimination to give the thermodynamically more stable 9,10-olefinic product **15**. While treatment of **14** with toluenesulfonic acid in aprotic media gave some **15**, the slow rate of conversion led us to examine other catalysts for this process. Rapid and quantiative conversion to **15** was effected by treating **14** with zinc bromide in methylene chloride for 24 hr at room temperature.

Manipulation of the olefinic entity in **15** to selectively furnish the *cis*- and *trans*-diols **1c** and **1d** and the 9-hydroxylated product **1a** was straightforwardly realized. Treatment of **15** with MCPBA furnished the epoxide **16** (98%) which was hydrogenolyzed (Pd/C, triethanolamine, EtOH) to the 9-hydroxy product **1a** in 91% yield. This compound was identical with a sample prepared and generously provided by Dr. Krohn. Sulfuric acid catalyzed opening of the epoxide in **16** gave the *trans*-diol product **1c** in 81% yield. The *cis*-diol **1d** was prepared directly from **15** in 96% yield through *cis*-hydroxylation[22] (cat. OsO_4, TMNO) of the olefinic



a. LiOtBu (91%) b. DMF, O_2, 50°C (78%) c TsOH, $ZnCl_2$, CH_2Cl_2 (98%) d. MCPBA, CH_2Cl_2 (94%) e. H_2, Pd/C, triethanolamine (91%) f. H_2SO_4-H_2O, acetone (81%) g. Cat. OsO_4, TMNO (96%)

Scheme 3.

entity. Since introduction of the 7-OH group in **1a** has been reported previously,[7] the developed route provides a convenient route to **1b** as well.

In summary, the accomplished investigation provides a flexible and general route for efficient regiospecific total synthesis of 9-alkyl substituted anthracyclinones with a wide variety of chromophore oxygenation patterns. A number of the intermediates obtained in this study are potentially useful precursors to other anthracyclinones and this is being explored.

EXPERIMENTAL

M.ps were taken on a Kofler hot-stage microscope and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL FX90Q spectrophotometer. Chemical shifts are reported as δ values in ppm and spectra were obtained in $CDCl_3$ unless otherwise noted. Mass spectra were obtained with a CEC DuPont Model 21-110B or DuPont Model 21-491B spectrometer at an ionizing voltage of 70 eV. Capillary GLC-mass spectrometry was performed on a model 40-21 Finnigan spectrometer. Carbon-hydrogen analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Analytical TLC was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck & Co. Radial preparative thick layer chromatography was performed on a Chromatotron (Harrison Research) using rotors coated to 4 mm thickness (silica gel 60 PF-254 manufactured by E. Merck & Co.). Silica gel column chromatography utilized E. Merck silica gel 60, 70-230 mesh ASTM.

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH). Solvents were reagent grade and were not usually purified prior to use.

3,4,4a,5,8,8a-*Hexahydro-6-methyl-1(2H)-naphthalenone* (**5a**). Freshly distilled boron trifluoride etherate (71 ml; 0.58 mol) was added to a cold (0°) magnetically stirred soln of **3** (50 g, 0.52 mol) in dry ether (1.2 l) under N_2. The mixture was allowed to react for 2 hr; isoprene (200 ml, 2.0 mol) was added and the soln was left at room temp for 48 hr.

A satd $NaHCO_3$ soln was added to the cold (0°) reaction to decompose the BF_3. The ether layer was separated and the aqueous phase was further extracted with ether (2 × 200 ml). The combined ether soln were washed with $NaHCO_3$ aq (2 × 50 ml) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Fractional distillation of the residue gave 7.6 g of **3** and 57.2 g (67% yield based on reclaimed **3**) of **5a** as a mixture of isomers (~70:30) with bp 64° (0.2 mm). ^{1}H-NMR δ 5.42–5.20 (m, 1H), 2.80–1.76 (m, 12H), 1.63 (s, 3H); mass spectrum, *m/z* 164 ($M^{+\cdot}$). (Found: C, 80.45; H, 9.80. Calc for $C_{11}H_{16}O$: C, 80.43; H, 9.81%).

Radial chromatography of a small sample gave the individual *trans* and *cis* isomers which on treatment with ethanolic NaOH gave identical mixtures (92:8). Capillary GC-MS analysis of **5a** showed < 5% of other material with a molecular weight of 164.

6-*Ethyl*-3,4,4*a*,5,8,8*a*-*hexahydro*-1(2*H*)-*naphthalenone* (**6a**). The preparation of **6a** was accomplished in a manner analogous to **5a**. From **3** (14.5 g, 0.15 mol), BF_3 (20.4 ml, 0.15 mol) and **4b** (18.45 g, 0.225 mol) in dry ether (300 ml) there was obtained 13.1 g of **6a** (75.5% yield based on reclaimed cyclohexenone) with bp 83° (0.15 mm). ^{1}H-NMR δ 5.38 (br m, 1H), 2.40–1.42 (m, 14H), 0.98 (t, J = 7.40 Hz, 3H); mass spectrum, *m/z* 178 ($M^{+\cdot}$). (Found: C, 80.91; H, 10.20. Calc for $C_{12}H_{18}O$: C, 80.84; H, 10.17%).

3,4,4a,5,8,8a - *Hexahydro- 6-methyl- 2-phenylthio-* 1(2*H*)-*naphthalenone* (**5b**). A soln of **5a** (26.5 g, 0.16 mol) in dry THF (150 ml) was added dropwise to a magnetically stirred soln of lithium cyclohexylisopropyl amide (0.178 mol) in THF (300 ml) at −78° under N_2. After complete addition, the reaction was kept at −78° for 10 min, then warmed to 0° for 5 min and finally cooled back to −78°. The anion soln was transferred by means of a cannula to a magnetically stirred cold (−78°) soln of benzenethiosulfonate in THF (200 ml) which produced a white ppt. The mixture was warmed to 10°, then transferred to a separatory funnel. Ether (900 ml) was added and organic layer washed with dil HCl (1N; 2 × 300 ml). The combined aqueous washes were extracted with ether (200 ml). The combined organic soln were dried ($MgSO_4$), filtered, and the solvent evaporated at reduced pressure to give 38.2 g (87%) of the α-keto sulfide **5b** as a syrupy residue which was used in the next step without purification. A sample of **5b** recrystallized from MeOH gave clusters of needles with m.p. 115–116°. ^{1}H-NMR δ 7.62–7.20 (m, 5H), 5.34 (br m, 1H), 4.18–3.86 (m, 1H), 3.02–1.61 (m, 10H), 1.56 (s, 3H); mass spectrum, *m/z* 272 ($M^{+\cdot}$).

6-*Ethyl*-3,4,4*a*-5,8,8*a*-*hexahydro*-2-*phenylthio*-1(2*H*)-*naphthalone* (**6b**). Compound **6b** was prepared using a procedure identical to that employed for preparation of **5b**. From naphthalone **6a** (12.5 g, 70 mmol) there was obtained 17.9 g (89%) of **6b**. A sample recrystallized from MeOH had m.p. 120–121° ^{1}H-NMR δ 7.60–7.15 (m, 5H), 5.36 (br m, 1H), 4.10–3.80 (m, 1H), 2.90–1.44 (m, 12H), 0.95 (t, J = 7.25 Hz, 3H); mass spectrum, *m/z*, 286 ($M^{+\cdot}$).

3,4,4*a*,5,8,8*a*-*Hexahydro- 6-methyl- 2-phenylsulfinyl-* 1(2*H*)-*naphthalone* (**5c**). A magnetically stirred soln of **5b** (36.0 g, 0.13 mol) in MeOH (650 ml) was added to a suspension of powdered sodium metaperiodate (34.0 g, 0.16 mol) in water (250 ml). The mixture was vigorously stirred overnight, then diluted with EtOAc and water (600 ml each). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 200 ml). The combined organic solns were washed with brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure to give 35.8 g (94%) of **5c** as a buff-coloured solid. ^{1}H-NMR δ 7.92–7.40 (m, 5H), 5.30 (br m, 1H), 4.00–3.52 (m, 1H), 3.06–1.66 (m, 10H), 1.48 (s, 3H).

6-*Ethyl*-3,4,4*a*,5,8,8*a*- *hexahydro- 2-phenylsulfinyl-* 1(2*H*)-*naphthalone* (**6c**). Oxidation of **6b** to **6c** was accomplished using the procedure employed to prepare **5c**. From sulfide **6b** (16.5 g, 58 mmol) and sodium metaperiodate (13.7 g, 64 mmol) there was obtained 15.8 g (91%) of **6c**. Recrystallization of a sample from MeOH gave pure material, homogeneous by TLC with m.p. 127–129° (dec). ^{1}H-NMR δ 7.85–7.55 (m, 5H), 5.38 (br m, 1H), 3.62–3.28 (m, 1H), 2.90–1.70 (m, 12H), 0.97 (t, J = 7.25 Hz, 3H).

6-*Methyl*-4*a*,5,8,8*a*-*tetrahydro*-1(4*H*)-*naphthalenone* (**7a**). A vigorously stirred mixture of **5c** (32.5 g, 0.1 mol), $CaCO_3$ (110 g) and CCl_4 (450 ml) was heated at reflux for 4 hr. The reaction was cooled and then filtered to remove inorganic material. The filtrate was washed once with brine (50 ml), then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Fractional distillation of the residue gave 12.4 g (68%) of **7a** with b.p. 60–61° (0.075 mm). ^{1}H-NMR δ 6.86 (dt, J = 10.0 and 4.18 Hz, 1H), 5.90 (dt, J = 10 and 1.98 Hz, 1H), 5.52–5.36 (m, 1H), 2.72–1.76 (m, 8H), 1.60 (s, 3H). (Found: C, 81.42; H, 8.75. Calc for $C_{11}H_{14}O$: C, 81.44; H, 8.70%).

6-*Ethyl*-4a,5,8,8a-*tetrahydro*-1(4H)-*naphthalenone* (**7b**). Pyrolysis of **6c** to give **7b** was performed in a manner identical to that employed to prepare **7a**. From **6c** (15.2 g, 50 mmol) there was obtained 6.30 g (71%) of **7b** with b.p. 67–71° (0.07 mm) as a mixture of isomers. ^{1}H-NMR δ 6.87 (dt, J = 9.98 and 3.96 Hz, 1H), 5.94 (dt, J = 9.98 and 2.20 Hz, 1H), 5.45 (br m, 1H), 2.70–1.55 (m, 10H), 0.97 (t, J = 7.35 Hz, 3H).

5,12 - *Dihydroxy* - 1,4 - *dimethoxy* - 9 - *methyl* - 7,10,10a,11 - *tetrahydro* - 6(6aH) - *naphthacenone* (**9a**). A slurry of **8** (8.4 g, 108 mmol) in dry THF (80 ml) was added through a large bore dropping funnel to a magnetically stirred soln of lithium t-butoxide (108 mmol) in THF (200 ml) under N_2 at −78°. The yellow mixture was allowed to react for 10 min, at which point a soln of **7a** (6.98 g, 43 mmol) in THF (80 ml) was added in a thin stream. The cooling bath was immediately removed and the soln was allowed to warm to room temp. Several color changes occurred and ultimately a deep red soln was present. The reaction was heated at reflux for 30 min, then cooled (0°) and acidified with dil HCl (2N) to pH 1. The THF was removed at reduced pressure and the residue was taken up in EtOAc (325 ml). The phases were separated and the organic layer was successively washed with water (50 ml), $NaHSO_3$ (3%, 200 ml),

water (50 ml) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure to give a brown syrupy residue. Trituration with ether furnished 8.15 g of slightly impure **9a** which was recrystallized (CH_2Cl_2—Et_2O). The ether filtrate from the trituration and the recrystallization were combined and evaporated. Column chromatography of this material on silica gel (210 g; CH_2Cl_2—EtOAc; 9 : 1) gave an additional 2.76 g (86% total yield) of **9a**. A sample recrystallized from CH_2Cl_2 had m.p. 235–237°. ^{1}H-NMR δ 14.61 (s, 1H), 9.50 (s, 1H), 6.94 (d, J = 8.35 Hz, 1H), 6.70 (d, J = 8.35 Hz, 1H), 5.60–5.40 (m, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 1.80–1.00 (m, 5H), 1.54 (s, 3H); mass spectrum, *m/z* 396 ($M^{+\cdot}$).

11 - *Acetoxy* - 1,4 - *dimethoxy* - 5 - *hydroxy* - 7,10,10a,11 - *tetrahydro* - 6(6aH) - *naphthalenone* (**9b**). Ac_2O (8.7 ml, 84 mmol) was added to a magnetically stirred cooled (5°) soln of **9a** (6.62 g, 18.7 mmol) in pyridine (60 ml). The cooling bath was removed and the reaction was stirred at room temp overnight. The mixture was poured slowly into an ice-water mixture (400 ml) and vigorously stirred for 2 hr in order to decompose excess Ac_2O. The mixture was extracted with EtOAc (3 × 200 ml) and the combined organic solns were washed with water (2 × 50 ml), dil HCl (1N, 50 ml) and with brine. The EtOAc soln was dried ($MgSO_4$), filtered and evaporated at reduced pressure. Recrystallization of the residue from CH_2Cl_2-hexanes gave 4.42 g of **9b** as needles with m.p. 235–236°. An additional 2.35 g of **9b** (92% total yield) was obtained from chromatography of the filtrate on silica gel. ^{1}H-NMR δ 15.22 (s, 1H), 6.99 (d, J = 8.80 Hz, 1H), 5.49 (br m, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.30–2.08 (m, 8H), 2.37 (s, 3H), 1.69 (s, 3H); mass spectrum, *m/z* 396 ($M^{+\cdot}$). (Found: C, 69.77; H, 6.02. Calc for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10%).

11 - *Acetoxy* - 5,9 - *dihydroxy* - 1,4 - *dimethoxy* - 6a,7,8,10,10a,11 - *hexahydro* - 9 - *methyl* - 6 - *naphthalenone* (**10**). Mercuric nitrate (4.51 g, 13.2 mmol) was added to a soln of the acetate **9b** in THF—H_2O (250 ml, 2 : 1) and the mixture stirred at room temp for 2 hr. A soln of NaOH (4.2 g) in water (25 ml) was then added to the reaction and after 5 min the mixture was cooled to 10° and a soln of $NaBH_4$ (0.82 g) in NaOH aq (25 ml of 0.5 N) was added. The dark green reaction was poured into EtOAc and water (200 ml each) and the phases were separated. The aqueous layer was back extracted with EtOAc (2 × 100 ml) and the combined organic solns were washed with brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Column chromatography of the residue (silica gel, 210 g; CH_2Cl_2—EtOAc, 9 : 1) gave 0.41 g of unreacted **9b**. Further elution (CH_2Cl_2—EtOAc, 3 : 2) gave 3.68 g (81%) of **10** which after recrystallization (CH_2Cl_2—hexanes) had m.p. 256–259°. ^{1}H-NMR δ 15.08 (s, 1H), 6.98 (d, J = 8.80 Hz, 1H), 6.78 (d, J = 8.80 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 2.35 (s, 3H), 1.29 (s, 3H); mass spectrum, *m/z* 414 ($M^{+\cdot}$).

(±) - 6,9 - *Dihydroxy* - 1,4 - *dimethoxy* - 9 - *methyl* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**2a**). KOH (1.75 g, 31.2 mmol) in water (10 ml) was added to a magnetically stirred soln of **10** (3.15 g, 7.61 mmol) in THF-EtOH-water (70 ml each) heated at 40°. O_2 was bubbled through the mixture for 0.5 hr, at which time analysis of a TLC showed complete conversion of **10** to **2a**. The reaction was diluted with cold (0°) water, neutralized with dil HCl and extracted with EtOAc (4 × 125 ml). The combined organic phases were washed with brine (50 ml), then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Chromatography of the residue on silica gel (180 g; CH_2Cl_2—EtOAc, 3 : 2) furnished 2.32 g (83%) of **2a** with m.p. 263–264°. ^{1}H-NMR δ 13.13 (s, 1H), 7.42 (s, 1H), 7.36 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 2.92 (s, 2H), 2.90 (m, 2H), 2.02–1.84 (m, 2H), 1.38 (s, 3H); mass spectrum, *m/z* 368 ($M^{+\cdot}$). (Found: C, 68.51; H, 5.45. Calc for $C_{21}H_{20}O_6$: C, 68.46; H, 5.47%).

(±) - 9 - *Acetoxy* - 1,4 - *dimethoxy* - 6 - *hydroxy* - 9 - *methyl* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**11a**). A mixture of **2a** (2.25 g, 6.11 mmol), Ac_2O (25 ml), Et_3N (2.0 ml, 14.8 mmol) and dimethylamino pyridine (0.02 g) was stirred overnight at room temp. The reaction was poured over an ice-water mixture and vigorously stirred for 2 hr to hydrolyze the excess Ac_2O, then extracted with EtOAc (3 × 150 ml). The combined organic solns were dried ($MgSO_4$), filtered and evaporated at reduced pressure to give 2.26 g (82%) of the 6,9-diacetate with m.p. 192–193° after recrystallization from CH_2Cl_2-hexanes. ^{1}H-NMR δ 7.78 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.48 (s, 3H), 1.89 (s, 3H), 1.64 (s, 3H); mass spectrum, *m/z* 452 ($M^{+\cdot}$).

A soln of KOH (0.3 g, 5.3 mmol) in water (10 ml) was added to a magnetically stirred soln of the diacetate (2.20 g, 4.87 mmol) in dimethoxyethane-water (70 ml, 1 : 1) under N_2. The progress of the reaction was carefully monitored by TLC and after 2 hr, the dark red mixture was diluted with cold (0°) water (150 ml) and neutralized to pH 3 with 3 N HCl. The mixture was extracted with EtOAc (3 × 100 ml) and the combined organic solns were washed with brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Chromatography of the residue on silica gel (150 g; CH_2Cl_2—EtOAc, 4 : 1) gave 1.86 g (93%) of the monoacetate **11a** with m.p. 206–208°. ^{1}H-NMR δ 13.10 (s, 1H), 7.40 (s, 1H), 7.35 (s, 2H), 4.01 (s, 3H), 3.93 (s, 3H), 3.39 (d, J = 18.5 Hz, 1H), 2.97 (d, J = 18.5 Hz, 1H), 2.83 (m, 2H), 2.42 (m, 2H), 1.92 (s, 3H), 1.64 (s, 3H); mass spectrum, *m/z* 410 ($M^{+\cdot}$). (Found: C, 67.29; H, 5.43. Calc for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40%).

cis - (±) - *Acetoxy* - 6,7 - *dihydroxy* - 1,4 - *dimethyoxy* - 9 - *methyl* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**11b**). Azobisisobutyronitrile (0.84 g, 5.15 mmol) and Br_2 (1.56 ml of a 3M soln in CCl_4; 5.15 mmol) were added in rapid succession to a magnetically stirred refluxing mixture of the monacetate **11a** in $CHCl_3$ (55 ml), CCl_4 (25 ml) and water (35 ml). After 20 min, more azobisisobutyronitrile (0.40 g) and Br_2 (0.9 ml of the above soln) were added. The reaction was continued for a further 15 min, then diluted with CH_2Cl_2 and 3% thiosulfate soln (250 ml each). The phases were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 100 ml). The combined organic solns were dried ($MgSO_4$), filtered and evaporated at reduced pressure. Column chromatography of the residue on silica gel (160 g; CH_2Cl_2—EtOAc, 3 : 2) gave 1.22 g (67%) of **11b** with m.p. 200–203°. ^{1}H:NMR δ 13.44 (s, 1H), 7.46 (s, 1H), 7.38 (s, 2H), 5.18 (t, J = 1.5 Hz, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.40 (d, J = 18.4 Hz, 1H), 2.80 (d, J = 18.4 Hz, 1H), 2.04 (m, 2H), 1.90 (s, 3H), 1.65 (s, 3H); mass spectrum, *m/z* 426 ($M^{+\cdot}$).

cis - (±) - 1,4 - *Dimethoxy* - 9 - *methyl* - 6,7,9 - *trihydroxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**2b**). KOH (0.35 g) in water (30 ml) was added to a magnetically stirred soln of **11b** in dimethoxyethane-water (110 ml, 2 : 1) under N_2. The soln was heated at 65° for 1 hr, then neutralized with 2N HCl and extracted with CH_2Cl_2 (3 × 150 ml). The combined organic solns were dried ($MgSO_4$), filtered and evaporated to give 920 mg (88%) of **2b** with m.p. 262–264°. ^{1}H-NMR δ 13.39 (s, 1H), 7.47 (s, 1H), 7.37 (s, 2H), 5.27 (m, 1H), 3.99 (s, 6H), 3.46 (d, J = 18.2 Hz, 1H), 2.84 (d, J = 18.2 Hz, 1H), 2.26 (m, 2H), 1.43 (s, 3H); mass spectrum, *m/z* 384 ($M^{+\cdot}$).

cis - (±) - 6,9 - *Dihydroxy* - 9 - *methyl* - 7,8,9,10 - *tetrahydro* - 1,4,7 - *trimethoxynaphthacene* - 5,12 - *dione* (**11c**). Cold trifluoroacetic anhydride (10 ml) was added to **2b** and the soln was magnetically stirred under N_2 for 10 min, then evaporated at reduced pressure maintaining the water bath at 20–25°. To the residue was added a freshly prepared soln of NaOMe (0.86 g) in MeOH (10 ml). The mixture was stirred at room temp for 30 min, then diluted with water (150 ml), neutralized (3N HCl) and extracted with EtOAc (3 × 150 ml). The combined organic phases were dried (MgSO4), filtered and evaporated at reduced pressure. Chromatography of the residue over silica gel (130 g; CH_2Cl_2—EtOAc, 4:1) gave 810 mg (92%) of **11c** with m.p. 224–226° after recrystallization from CH_2Cl_2–ether. ^{1}H-NMR δ 13.31 (s. 1H), 7.45 (s, 1H), 7.36 (s, 2H), 4.89 (dd, J = 3.95 and 1.54 Hz, 1H), 4.67 (s, OH), 4.01 (s, 3H), 3.99 (s, 3H), 3.59 (s, 3H), 3.12 (d, J = 16.26 Hz, 1H), 2.78 (d, J = 16.26 Hz, 1H), 2.23 (dt, J = 16.20 and 1.54 Hz, 1H), 1.71 (m, 1H), 1.40 (s, 3H); mass spectrum *m/z* 384 ($M^{+\cdot}$). (Found: C, 65.69; H, 5.25. Calc for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24%).

(±) - 5,12 - *Dihydroxy* - 9 - *ethyl* - 4 - *methoxy* - 7,10,10a,11 - *tetrahydro* - 6(6aH) - *naphthacenone* (**13**). Preparation of **13** was conducted in a manner analogous to that employed to prepare

9a. From the phthalidesulfone **12** (8.76 g, 28.9 mmol), 1(4H)-naphthalenone **7b** (6.1 g, 34.7 mmol) and lithium t-butoxide (87.0 mmol) in THF (230 ml) there was obtained 8.87 g (91%) of **13** with m.p. 202°. ^{1}H-NMR δ 15.07 (s, 1H), 7.64–7.40 (m, 2H), 6.86 (dd, J = 6.82 and 2.30 Hz, 1H), 5.53 (m, 1H), 4.02 (s, 3H), 3.21–1.82 (m, 10H), 1.04 (t, J = 7.30 Hz, 3H); mass spectrum, *m/z* 338 ($M^{+\cdot}$).

7,10 - *Dihydro* - 9 - *ethyl* - 6 - *hydroxy* - 4 - *methoxynaphthacene* - 5,12 - *dione* (**14**). O_2 was gently bubbled through a soln of **13** (1.40 g) in DMF (70 ml) heated at 50° for 24 hr. Water (500 ml) was added and the ppt was collected and air dried. Column chromatography of the product on silica gel (100 g; CH_2Cl_2—EtOAc, 97:3) and recrystallization of the collected material from CH_2Cl_2—hexanes gave 1.08 g (78%) of **14** with m.p. 221–222°. ^{1}H-NMR δ 13.37 (s, 1H), 7.96 (dd, J = 8.22 and 1.32 Hz, 1H), 7.71 (t, J = 8.22 Hz, 1H), 7.55 (s, 1H), 7.35 (d, J = 8.2 Hz, 1 H), 5.64 (s, 1H), 4.07 (s, 3H), 3.40 (s, 4H), 2.13 (q, J = 6.15 Hz, 2H), 1.10 (t, J = 6.15 Hz, 3H); mass spectrum, *m/z* 334 ($M^{+\cdot}$). (Found: C, 75.46; H, 5.46. Calc for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43%).

7,8 - *Dihydro* - 9 - *ethyl* - 6 - *hydroxy* - 4 - *methoxynaphthacene* - 5,12 - *dione* (**15**). Toluenesulfonic acid (50 mg) and $SnCl_4$ (8.8 ml of a 10% soln in CH_2Cl_2, 3.38 mmol) were added to a magnetically stirred soln of **14** in dry CH_2Cl_2 (300 ml). The dark purple soln, protected from moisture, was stirred at room temp overnight, then diluted with $NaHCO_3$ soln (240 ml of 5%). The phases were separated and the aqueous layer was back extracted with CH_2Cl_2 (3 × 100 ml). The combined organic solns were dried ($MgSO_4$), filtered and evaporated at reduced pressure. Column chromatography of the residue on silica gel (125 g; CH_2Cl_2—EtOAc, 98:2) and recrystallization (CH_2Cl_2—hexanes) of the collected material gave 0.99 g (98%) of **15** with m.p. 169–171°. ^{1}H-NMR δ 13.23 (s, 1H), 7.88 (dd, J = 7.50 and 0.88 Hz, 1H), 7.67 (t, J = 7.51 Hz, 1H), 7.40 (s, 1H), 7.31 (d, J = 7.50 Hz, 1H), 6.26 (s, 1H), 4.05 (s, 3H), 2.93 (t, J = 8.35 Hz, 2H), 2.44–2.02 (m, 4H), 1.14 (t, J = 7.48 Hz, 3H); mass spectrum, *m/z* 334 ($M^{+\cdot}$).

9,10 - *Epoxy* - 9 - *ethyl* - 6 - *hydroxy* - 4 - *methoxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**16**). A soln of MCPBA (0.61 g, 3.53 mmol) in CH_2Cl_2 (50 ml) was added to the magnetically stirred soln of **15** (0.85 g, 2.54 mmol) in CH_2Cl_2 (200 ml) under N_2. The mixture was allowed to react overnight, then transferred to a separatory funnel. The CH_2Cl_2 soln was successivly washed with $NaHSO_3$ (1%), $NaHCO_3$ aq (5%, 2 × 200 ml) and water, then dried ($MgSO_4$) and filtered. Addition of hexane to the partially evaporated CH_2Cl_2 soln gave 380 mg of pure **16** with m.p. 208–211°. Evaporation of the filtrate and column chromatography of the residue on silica gel (90 g; CH_2Cl_2—EtOAc, 95:5) gave an additional 460 mg (94% total yield) of pure **16**. ^{1}H-NMR δ 13.25 (s, 1H), 7.96 (dd, J = 7.70 and 0.91 Hz, 1H), 7.80 (s, 1H), 7.73 (t, J = 7.72 Hz, 1H), 7.34 (d, J = 7.78 Hz, 1H), 4.07 (s, 3H), 3.73 (s, 1H), 3.08 (m, 2H), 2.48 (m, 2H), 1.88 (q, J = 7.92 Hz, 2H), 1.06 (t, J = 7.92 Hz); mass spectrum, *m/z* 350 ($M^{+\cdot}$).

6,9 - *Dihydroxy* - 9 - *ethyl* - 4 - *methoxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**1a**). A mixture of **16** (0.82 g, 2.34 mmol), triethanolamine (55 ml) and Pd—C (10%, 35 mg) in EtOH—EtOAc (200 ml, 1:1) was hydrogenated on a Parr apparatus under 22 psi of hydrogen for 3 hr. The reaction was filtered through a celite pad and the filtrate was diluted with EtOAc (300 ml) and water (100 ml) and the phases separated. The organic layer was repeatedly washed with small quantities (50 ml) of 3N HCl until the aqueous phase was acidic. The EtOAc soln was next washed with water (100 ml), $NaHCO_3$ aq (5%, 100 ml) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Column chromatography of the residue on silica gel (100 g; CH_2Cl_2—EtOAc, 9:1) gave 750 mg (91%) of **1a** with m.p. 189–190°; lit. m.p. 185–186°. The TLC behavior and ^{1}H-NMR spectrum of this product was identical with a sample generously provided by Dr. Krohn and a mixed m.p. was undepressed. ^{1}H-NMR δ 13.35 (s, 1H), 7.94 (dd, J = 7.42 and 0.88 Hz, 1H), 7.70 (t, J = 7.42 Hz, 1H), 7.47 (s, 1H), 7.14 (d, J = 7.38 Hz, 1H), 4.06 (s, 3H), 2.88 (m, 4H), 2.02–1.28 (m, 4H), 1.03 (t, J = 7.47 Hz, 3H); mass spectrum, *m/z* 352 ($M^{+\cdot}$).

trans-(±) - 9 - *Ethyl* - 4 - *methoxy* - 7,9,10 - *trihydroxy* - 7,8,9,10-*tetrahydronaphthacene*-5,12-*dione* (**1c**). H_2SO_4 (6N, 0.75 ml was added to a magnetically stirred soln of **16** (160 mg, 0.46 mmol) in acetone (200 ml). The reaction was heated at 45° for 0.5 hr, then poured into $NaHCO_3$ aq (5%, 100 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic phases were washed with brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Recrystallization of the residue from CH_2Cl_2 furnished 140 mg (81%) of **1c** as large plates which melted sharply at 200–202° after initially softening at 125–130°, then resolidifying. ^{1}H-NMR δ 13.24 (s, 1H), 7.93 (d, J = 7.65 Hz, 1H), 7.85 (s, 1H), 7.70 (t, J = 7.64 Hz, 1H), 7.29 (dd, J = 7.62 and 0.89 Hz, 1H), 4.59 (d, J = 5.28 Hz, 1H), 4.06 (s, 3H), 2.84 (m, 2H), 2.63 (d, J = 5.28 Hz, 1H), 2.30–1.28 (m, 4H), 1.03 (t, J = 7.48 Hz, 3H); mass spectrum, *m/z* 368 ($M^{+\cdot}$).

(±) - 9 - *Ethyl* - 4 - *methoxy* - 7,cis - 9,10 - *trihydroxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**1d**). A solution of **15** (150 mg, 0.45 mmol), trimethylamine N-oxide (110 mg, 0.94 mmol) and OsO_4 (1 ml of a 2% soln in t-BuOH) in acetone (100 ml) and water (25 ml) was magnetically stirred under N_2 at room temp for 6 hr, then diluted with bisulfite soln to destroy the excess osmium tetroxide. The mixture was extracted with EtOAc (3 × 100 ml) and the combined organic solns were washed with water and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was recrystallized from CH_2Cl_2–ether to give 160 mg (96%) of pure **1d** with m.p. 262–264°. ^{1}H-NMR δ 13.32 (s, 1H), 7.94 (d, J = 7.41 Hz, 1H), 7.92 (s, 1H), 7.73 (t, J = 7.42 Hz, 1H), 7.31 (d, J = 7.40 Hz, 1H), 4.52 (d, J = 5.72 Hz, 1H), 4.07 (s, 3H), 2.85 (dd, J = 13.10 and 6.10 Hz, 1H), 2.61 (d, J = 5.72 Hz, OH), 2.20–1.35 (m, 4H), 1.02 (t, J = 7.04 Hz, 3H); mass spectrum, *m/z* 368 ($M^{+\cdot}$).

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