Reaction of 4 with Hexaethylene Glycol. Via the general procedure using hexaethylene glycol (334 mg, 1.2 mmol), five fractions were isolated by chromatography (ThLC, Al_2O_3), eluting with C_6H_{12}/EtOAc (1:1).

Fraction A afforded **8,11,14,17,20,23,26-heptaoxa-32,33-diazatricyclo[26.3.1.1^{2,6}]tritriaconta-1(32),2,4,6(33),28,30-hexaene (6d)** as a colorless oil: 107 mg (19%); R_f = 0.49; ^{1}H NMR δ 3.41 (m, η-δ-CH_2, 16 H), 3.65 (m, γ-CH_2, 4 H), 3.71 (m, β-CH_2, 4 H), 4.74 (s, α-CH_2, 4 H), 7.44 (d, 5-py*H*, J = 7.9 Hz, 2 H), 7.81 (t, 4-py*H*, J = 7.9 Hz, 2 H), 8.31 (d, 3-py*H*, J = 7.9 Hz, 2 H); IR (neat) 1560, 1425, 1095 (COC), 780 cm^{-1}; MS (*m/e*) 462 (M$^+$, 33), 287 (30), 227 (24), 213 (43), 199 (100), 184 (91); UV (95% EtOH) see Figure 2. Anal. Calcd for $C_{24}H_{34}N_2O_7$: C, 62.30; H, 7.41; N, 6.06. Found: C, 62.38; H, 7.52; N, 5.91.

Fraction B afforded **8,11,14,17,20,23,26,39,42,45,48,51,54,57-tetradecaoxa-62,63,64,65-tetraazapentacyclo[57.3.1.1^{2,6}.1^{28,32}.1^{33,37}]hexahexaconta-1(62),2,4,6(63),28,30,32(64),33,35,37(65),59,60-dodecaene (7d)** as a pale yellow oil: 17 mg (3%); R_f = 0.16; ^{1}H NMR δ 3.69 (m, η-β-CH_2, 48 H), 4.75 (s, α-CH_2, 8 H), 7.47 (d, 5-py*H*, J = 7.9 Hz, 4 H), 7.78 (t, 4-py*H*, J = 7.9 Hz, 4 H), 8.26 (d, 3-py*H*, J = 7.9 Hz, 4 H); IR (neat) 1545, 1415, 1086 (COC), 765 cm^{-1}. Anal. Calcd for $(C_{24}H_{34}N_2O_7)_2$: C, 62.30; H, 7.41; N, 6.06. Found: C, 62.40; H, 7.42; N, 5.86.

Fractions C, D, and E afforded 3:3-(**8d**) [yellow oil; 9.7%; R_f = 0.14], 4:4-(**9d**) [yellow oil; 3%, R_f = 0.08], and 5:5-(**10d**) [yellow oil; 13.4%; R_f = 0.03] macrocycles, respectively. Elemental analyses were within acceptable limits (±0.03), and all spectral data were identical with that of **7d**.

Complex Preparation. To a MeOH solution (10 mL) of the ligand (0.5 mmol) was added an equimolar amount (1 equiv/dipyridine) of the metal salt in MeOH (2 mL) with stirring. The solution was refluxed for 1 h, EtOAc was added dropwise, and the solution was allowed to stand for 4–20 h at 20 °C. The resulting crystals were collected; physical and spectral data are given in Table III.

X-ray Experimental. Intensity data for **5** and **7a** were collected on an Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator and either Mo Kα or Cu Kα radiation. Variable scan rates were employed in the $\omega - 2\theta$ scans designed to achieve approximately equal relative precision for all significant data, subject to a maximum of 120 s for any one scan. One quadrant of data within the angular limits given in Table III was collected for each crystal. Data reduction included corrections for background, Lorentz, and polarization effects. Equivalent data were averaged, and data considered observed by the criteria furnished in the supplementary material were used in the refinements. Structures were solved using MULTAN[18] and refined by full-matrix least-squares methods based on F with weights $w = \sigma^{-2}(F_o)$. Both crystals scattered rather weakly, and in the case of **5**, insufficient data were available to allow full anisotropic refinement. Only oxygen atoms and carbon atoms C12 through C15 were treated anisotropically; all other heavy atoms were refined isotropically. For **7a**, all non-hydrogen atoms were refined anisotropically. In both structures, hydrogen atoms were discernible from difference maps, but were placed in calculated positions as fixed contributions. Final R factors and residual electron densities are given in the supplementary material.

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Supplementary Material Available: Crystal data, tables of (average) bond distances, (average) bond angles, coordinates for all atoms, and anisotropic thermal parameters for $C_{28}H_{28}N_4O_4$ (**5**) and $C_{32}H_{36}N_4O_6$ (**7a**) (10 pages). Ordering information is given on any current masthead page.

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1(4*H*)-Naphthalenones in Anthracyclinone Synthesis: A New Route for the Total Synthesis of (±)-Aklavinone

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A brief route for total synthesis of (±)-aklavinone (**1a**), the aglycon of the anticancer antibiotic aclacinomycin (**1b**), is described. Key features of the synthesis are the development of a brief, efficient route to the 1(4*H*)-naphthalenone **11**, which was used as a synthon for the A and B rings, and homologation of keto aldehyde **17** to the keto anthraquinone acetic ester **16** via the intermediacy of the ketene thioacetal **19**.

The discovery that aclacinomycin-A1 (**1b**), shown in Figure 1, had significant anticancer activity[1-4] prompted strong interest in the synthesis of the aromatic fragment in this antibiotic. To date, some ten[5-13] syntheses of the aglycon **1a** and two[11,14] of the structurally similar auramycin aglycon **1c** have been published.

We have previously shown that regiospecific, convergent syntheses of tetracyclic intermediates to anthracycliones can be accomplished through condensation of 1(4*H*)-naphthalenones with phenylsulfonyl isobenzofuranones[15]

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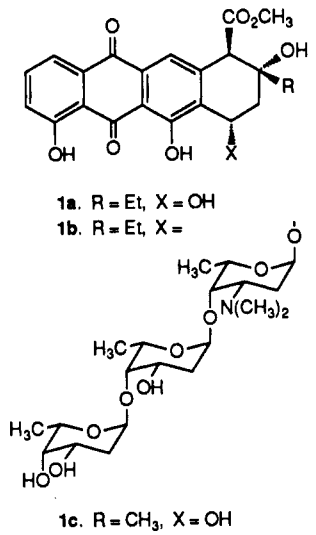
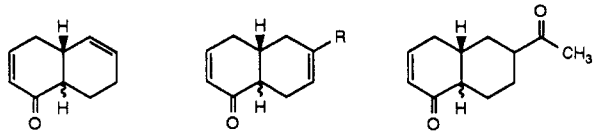
0022-3263/89/1954-5110$01.50/0



1a. R = Et, X = OH
1b. R = Et, X =
1c. R = CH_3, X = OH

Figure 1.



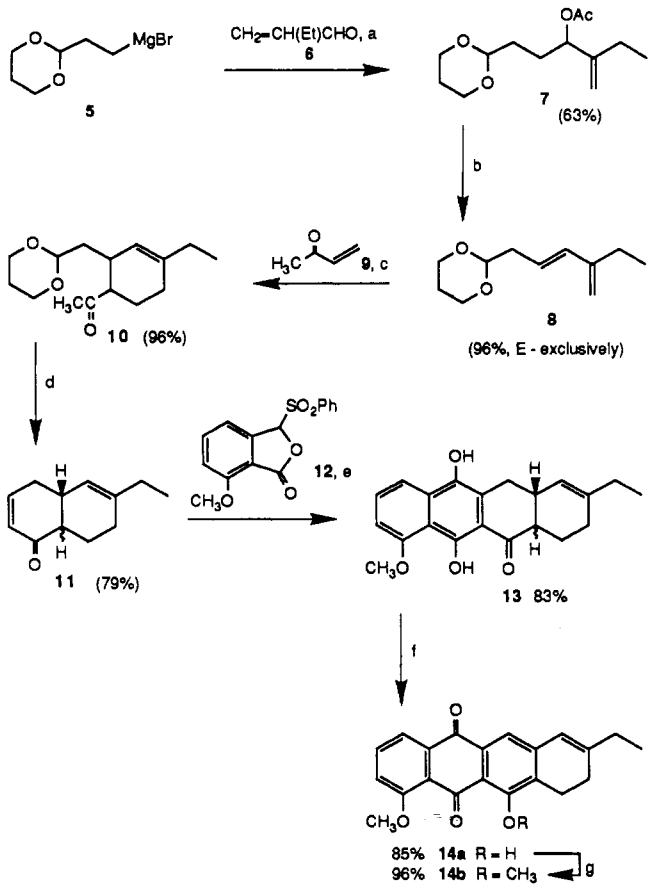
2 3a. R = CH_3 3b. R = Et 4

Figure 2.

and, in conjunction with those studies, reported syntheses of the 1(4*H*)-naphthalenones **2**,[16] **3**,[17] and **4**,[18,19] shown in Figure 2. We have now developed a brief and efficient route for preparation of multigram quantities of the 1-(4*H*)-naphthalenone **11** and have employed it to accomplish a new synthesis of (±)-aklavinone (**1a**).

Preparation of the naphthalenone **11**, which ultimately becomes the A and B rings of aklavinone (**1a**), was performed as indicated in Scheme I. Reaction of the Grignard reagent **5** derived from 2-(2-bromoethyl)-1,3-dioxane with 2-ethylacrolein (**6**) gave, following acetylation of the alcohol intermediate, the allylic acetate **7** in 63% yield. Treatment of **7** with a catalytic amount of palladium acetate and triphenylphosphine in refluxing dioxane[20] led to exclusive formation of the *E*-diene **8** in 96% yield.[21] Diels–Alder cycloaddition of **8** with methyl vinyl ketone (**9**) (neat, sealed tube, 150 °C) furnished regiospecifically the cyclohexene **10** (96%) as a mixture of cis and trans isomers. On a small scale, the individual isomers of **10** were separated by HPLC and their structures established through 2D NMR. Since there would undoubtedly be additional epimerization in the ring closure of **10** to **11**, the mixture was directly used in the next step. In earlier work,[16,18,19] we reported a three-step sequence for construction of the enone fragment in 1(4*H*)-naphthalenones through intramolecular cyclization of acetal and ketone functionalities. In conjunction with the present study, we have established conditions to accomplish this transformation in one step and in better overall yield. Thus, treatment of **10** with dilute perchloric acid in THF resulted in hydrolysis of the trimethylene acetal with concomitant

Scheme I[a]



[a] (a) Ac_2O, Py; (b) $Pd(OAc)_2$ (catalytic), Ph_3P, $CaCO_3$, dioxane, 110 °C; (c) sealed tube, 150 °C; (d) $HClO_4$, H_2O; (e) LiOtBu, THF; (f) O_2, DMF, 100 °C. (g) K_2CO_3, $DMSO_4$, acetone; 96%.

intramolecular aldol cyclization and dehydration to the unsaturated hydronaphthacenone **11** (79%). While small-scale separation of the individual isomers of **11** was performed in order to fully characterize them, the isomeric mixture was used in subsequent steps, since the bridging carbons at C-4a and C-8a ultimately would be converted from tetrahedral sp^3 to planar sp^2 centers during fabrication of the naphthacenone ring system.

Condensation of the anion of the phthalidesulfone **12**, generated with lithium *tert*-butoxide in THF, with the naphthalenone **11** furnished the hexahydronaphthacenone **13** as a mixture of cis and trans isomers in 83% yield. Aromatization of the B ring and oxidation of the C ring to a quinone was accomplished by heating **13** in DMF under an oxygen atmosphere. The resultant naphthacenone **14a**, obtained in 85% yield, was identical in all respects (melting point, TLC, ^1H NMR) with an alternatively prepared sample. Methylation of **14a** (K_2CO_3, $DMSO_4$, acetone; 96%) furnished the methyl ether derivative **14b**.

A modified version of the sequence originally described by Boeckmann and Sum[9] was investigated for conversion of **14b** to anthraquinone acetic ester **16**. Oxidative cleavage of the 9,10-olefinic moiety in **14b** to give the anthraquinone keto acid **15a** was accomplished in 78% yield using periodate and catalytic permanganate.[22] The use of thionyl chloride to convert **15a** to the acid chloride **15b** gave substantial amounts of the 1,3-diketone from intramolecular acylation. Gesson et al.,[14] noting similar results,

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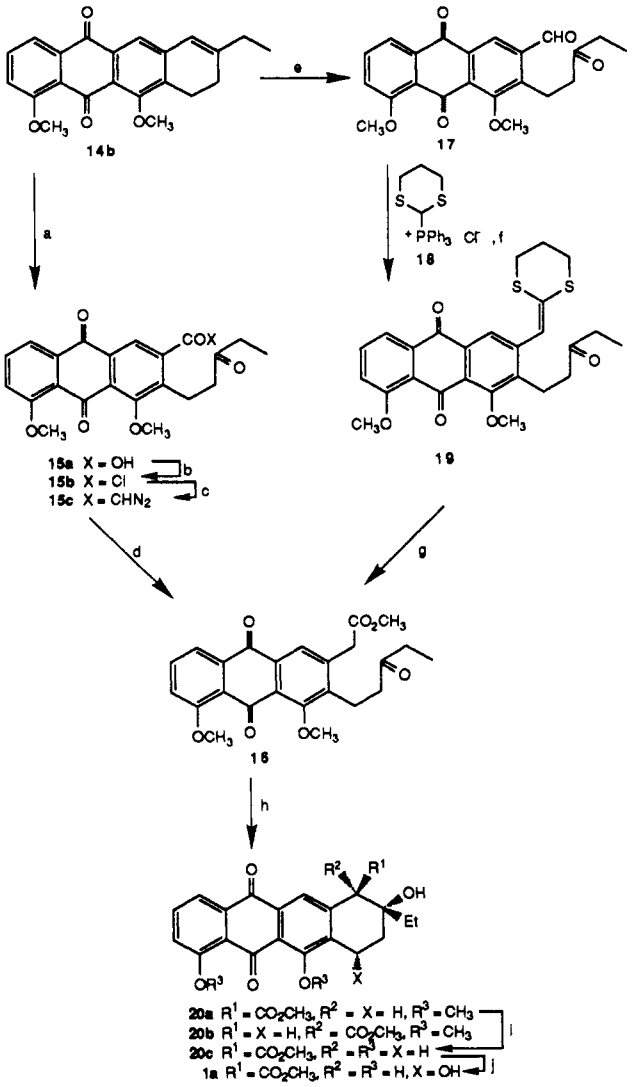
Scheme II[a]



[a] (a) $NaIO_4$, K_2CO_3, cat. $KMnO_4$, *t*-BuOH–H_2O; 78%; (b) ClCOCOCl/PhH; (c) CH_2N_2, Et_2O–THF; 96% from **15a**; (d) Ag_2O, CH_3OH; 89%; (e) O_3, MeOH–CH_2Cl_2; 96%; (f) BuLi, THF; 89%; (g) $HgCl_2$, CH_3OH; 81%; (h) $Mg(OCH_3)_2$, CH_3OH; 90%; (i) $AlCl_3$, CH_2Cl_2; 97%; (j) NBS, H_2O, CCl_4; 89%.

reported the use of oxalyl chloride. With oxalyl chloride, the acid **15a** was smoothly converted to the acid chloride **15b**. Reaction of the acid chloride **15b** with diazomethane furnished the diazo ketone **15c** (96%), which on Wolff rearrangement in methanol gave the homologated ester **16** (89%).

Although the preceding sequence was effective, we decided to investigate an alternative method for converting **14b** to **16**, which would avoid the use of diazomethane, and this is shown in Scheme II. Initial attempts to prepare the keto aldehyde **17** through ozonolysis of **14b** in either dichloromethane or methanol, followed by reductive workup with dimethyl sulfide, gave moderate and variable yields (35–65%) of product. In marked contrast, the use of a 4:1 dichloromethane–methanol mixture as a medium for the ozonolysis gave the keto aldehyde **17** in 96% yield. Although **17** would appear to be especially unstable with respect to intramolecular aldol cyclization, this proved not to be a problem, and condensation of **17** with the ylide derived from **18**[23] proceeded smoothly to furnish the ketene thioacetal **19** in 89% yield. Mercuric chloride catalyzed methanolysis[24] of **19** then gave the homologated ester **16** (80%). The overall yield of **16** from **14b** is comparable to that obtained from the diazoketone route. Advantages are that fewer steps are required and the sequence is amenable to scaleup.

Intramolecular aldol cyclization of the keto ester **16** using magnesium methoxide[13] afforded a 4:1 ratio of diastereoisomeric hydroxy esters **20a** and **20b**, respectively, which were separated by chromatography (90%). The protocol originally reported by Kende and Rizzi[5] was employed to convert **20a** to aklavinone (**1a**). Demethylation of **20a** to **20c** was accomplished in 96% yield with aluminum chloride in dichloromethane. Introduction of the 7-hydroxyl group was accomplished with greater than 25:1 diastereoselectivity through homolytic bromination of **20c** with subsequent solvolysis. The physical and spectral (melting point, mixed melting point, ^1H NMR) properties of the synthetic product were identical in all respects with those of an authentic sample of (±)-aklavinone (**1a**).

In summary, the 12-step sequence reported here provides (±)-aklavinone (**1a**) in 17% overall yield. The preparation is practical since the steps leading to the naphthalenone **11** can be performed on a large scale and all of the products can be purified by distillation. Homologation of the aldehyde **17** to the anthraquinone acetic ester **16** via the ketene dithioacetal is likewise advantageous. The naphthacenone intermediate **14** should also be useful for synthesis of other A ring substitution patterns in related compounds and this is under investigation.

Experimental Section

Melting points were taken on a hot-stage microscope and are uncorrected. Proton NMR spectra were recorded at 300 MHz. Analytical thin-layer chromatography plates (silica gel 60 F-254, layer thickness 0.25 mm) were manufactured by E. Merck and Co. Column chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

2-(3-Acetoxy-4-methylenehexyl)-1,3-dioxane (7). Dibromoethane (0.5 mL) was added to a magnetically stirred suspension of Mg (3.9 g, 0.16 mol) in dry THF (35 mL) under N_2 and allowed to react for 15 min. A solution of 2-(2-bromoethyl)-1,3-dioxane (21 g, 0.11 mol) in THF (50 mL) was added dropwise over a period of 0.5 h. During the first 5–10 min of the addition, the exothermic reaction was cooled in an ice–water bath. When the addition was complete, the reaction was heated at reflux for 10 min. The Grignard solution was allowed to cool to room temperature, stirred for 0.5 h, and then chilled in an ice–water bath while a solution of 2-ethylacrolein (**6**) (11.8 g, 0.14 mol) in THF (15 mL) was added dropwise. The resulting mixture was stirred at 0–5 °C for 2 h, allowed to warm to room temperature, and then stirred for an additional 2 h. The reaction was cooled in an ice–water bath and quenched with saturated NH_4Cl solution (20 mL). Ether (100 mL) was added, and the phases were separated. The aqueous layer was extracted with an additional 50-mL portion of ether, and the combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue (20.8 g) was kept under vacuum (0.05–0.1 Torr) for 2–3 h and then used in the next step without purification.

A mixture of the allylic alcohol (20.8 g), pyridine (40 mL), and acetic anhydride (23 mL) was stirred at room temperature for 36 h. Excess pyridine and acetic anhydride were evaporated at 0.05 Torr. The residue was dissolved in ether (50 mL) and stirred with 10% $NaHCO_3$ solution (30 mL) for 0.5 h. The layers were separated, and the aqueous phase was extracted with an additional 30-mL portion of ether. The combined ether extracts were washed successively with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. Vacuum distillation of the residue gave 16.5 g (63%) of pure acetate **7**:

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(24) Schubert, U. *Synthesis* **1978**, 364.

bp 95 °C/0.04 Torr; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7.3 Hz), 1.34 (m, 1 H), 1.57 (m, 3 H), 1.74 (q, 2 H, J = 7.3 Hz), 2.05 (s, 3 H), 2.06 (m, 2 H), 3.75 (ddd, 2 H, J = 10.5, 9.8 and 2.4 Hz), 4.09 (dd, 2 H, J = 9.8 and 3 Hz), 4.53 (t, 1 H, J = 5 Hz), 4.88 (s, 1 H), 4.99 (s, 1 H), 5.18 (t, 1 H, J = 6.3 Hz); MS m/z 241 (M − 1).

(*E*)-2-(4-Methylene-2-hexenyl)-1,3-dioxane (8). A mixture of the allylic acetate **7** (16 g, 66.03 mmol), PPh_3 (3.46 g, 13.2 mmol), $Pd(OAc)_2$ (0.30 g, 1.32 mmol), and anhydrous $CaCO_3$ (6.6 g, 66 mmol) in freshly distilled dioxane (40 mL) was heated at reflux for 6 h, at which time, analysis of a TLC indicated the absence of starting material. The suspension was filtered, and the filter cake was washed with ether. The filtrate was concentrated and the residue was distilled to give 11.6 g (96%) pure *E*-diene **8** with bp 80–81 °C/0.25 Torr. The product was homogeneous by capillary GLC analysis (SiO_2): ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3 H, J = 7 Hz), 2.05 (m, 2 H), 2.20 (q, 2 H, J = 7 Hz), 2.41 (dd, 2 H, J = 5.9 Hz and J = 6.4 Hz), 3.76 (m, 2 H), 4.1 (m, 2 H), 4.56 (t, 1 H, J = 5.5 Hz), 4.91 (s, 2 H), 5.70 (dt, 1 H, J = 16 and 6.5 Hz), 6.16 (d, 1 H, J = 16 Hz); MS m/z 182 (M^+). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.51; H, 10.00.

1-Acetyl-2-[(1,3-dioxa-2-cyclohexyl)methyl]-4-ethylcyclohex-3-ene (10). The diene **8** (11 g, 0.060 mol), methyl vinyl ketone (**9**) (7.5 mL, 0.090 mol), and hydroquinone (100 mg) were heated in a sealed tube at 145–150 °C for 24 h. The sealed tube was chilled in a dry ice acetone bath and then opened, and the contents were transferred to a flask. Excess **9** was evaporated, and the residual oil was distilled in vacuo to furnish 14.6 g (96%) of pure Diels–Alder adduct **10** with bp 115–116 °C/0.05 Torr; MS m/z 252 (M^+). A sample of distilled material was separated into individual isomers by HPLC (Dynamax-60R silica gel column): ^{1}H NMR less polar isomer ($CDCl_3$) δ 0.98 (t, 3 H, J = 7.65 Hz), 1.20–2.15 (m, 10 H), 2.16 (s, 3 H), 2.40 (m, 1 H), 2.72 (m, 1 H), 3.73 (m, 2 H), 4.05 (m, 2 H), 4.52 (dd, 1 H, J = 5.9 and 4.4 Hz), 5.27 (dtt, 1 H, J = 3.42, 1.95, and 1.47 Hz); ^{1}H NMR more polar isomer ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.16 Hz), 1.20–2.20 (m, 10 H), 2.16 (s, 3 H), 2.68 (m, 1 H), 2.8 (m, 1 H), 3.75 (m, 2 H), 4.09 (m, 2 H), 4.56 (dd, 1 H, J = 6.35 and 3.91 Hz), 5.49 (dtt, 1 H, J = 5.86, 2.44, and 1.46 Hz).

6-Ethyl-4a,7,8,8a-tetrahydro-1(4*H*)-naphthalenone (11). A magnetically stirred mixture of the keto acetal **10** (14 g, 0.055 mol), THF (150 mL), H_2O (80 mL), and 3 N $HClO_4$ (80 mL) was heated at reflux under N_2 for 3.5 h. The THF was removed under aspirator vacuum at room temperature, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined ether extracts were washed successively with saturated $NaHCO_3$ solution (50 mL), H_2O (2 × 100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated. Distillation of the residue furnished 7.72 g (79%) of pure enone **11** with bp 93–94 °C/0.6 Torr; MS m/z 176 (M^+). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.71; H, 9.05.

A sample of the distilled material was separated into individual isomers by HPLC (Dynamax-60R silica gel column): ^{1}H NMR less polar isomer ($CDCl_3$) δ 1.02 (t, 3 H, J = 7 Hz), 1.36 (m, 1 H), 1.95 (q, 2 H, J = 7 Hz), 2.0–2.2 (m, 4 H), 2.30–2.55 (m, 3 H), 5.22 (dtt, 1 H, J = 3.42, 1.95, and 1.47 Hz), 6.05 (ddd, 1 H, J = 10.2, 2.44, and 1.95 Hz), 6.98 (ddd, 1 H, J = 10.2, 5.5, and 2.4 Hz); IR (film) 1681 cm^{-1}; ^{1}H NMR more polar isomer ($CDCl_3$) δ 0.97 (t, 3 H, J = 7 Hz), 1.68 (m, 1 H), 1.95 (q, 2 H, J = 7 Hz), 2.0–2.10 (m, 3 H), 2.15–2.25 (m, 1 H), 2.45–2.63 (m, 2 H), 2.8 (m, 1 H), 5.30 (dtt, 1 H, J = 5.86, 2.44, and 1.46 Hz), 5.99 (dt, 1 H, J = 10.2 and 1.95 Hz), 6.86 (dt, 1 H, J = 10.2 and 4.40 Hz); IR (film) 1668 cm^{-1}.

4-Methoxy-5,12-dihydroxy-9-ethyl-7,8,10a,11-tetrahydro-6(6a*H*)-naphthacenone (13). To a cold (−78 °C) magnetically stirred solution of lithium *tert*-butoxide, prepared from *tert*-butyl alcohol (2.8 mL, 30 mmol) and *n*-BuLi (18.75 mL of 1.6 M solution, 30 mmol) in dry THF (40 mL) under N_2 was added the sulfone **12** (3.34 g, 11 mmol) as a slurry in THF (30 mL). Upon complete addition of the sulfone, the orange-yellow mixture of partially precipitated anion was stirred for 15 min at −78 °C. A solution of the naphthalenone **11** (1.76 g, 10 mmol) in THF (30 mL) was added by syringe, and the mixture was stirred at −78 °C for 1 h. The cooling bath was removed, and the reaction was allowed to warm to room temperature and then heated at reflux for 30 min, during which time an orange-red precipitate formed. The reaction mixture was cooled to 0 °C and acidified with 2 N HCl (40 mL). The THF was evaporated under reduced pressure, and the aqueous mixture was extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed successively with H_2O (2 × 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. Trituration of the syrupy residue with Et_2O gave 2.31 g (68.3%) of **13** as orange-red crystals, which were filtered, washed thoroughly with Et_2O, and dried. Evaporation of the Et_2O filtrate and washings followed by chromatography of the residue (silica gel; CH_2Cl_2–EtOAc, 95:5) gave an additional 0.48 g of **13** (overall yield 82.5%). A sample recrystallized from CH_2Cl_2–hexanes had mp 182–185 °C: ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7.3 Hz), 1.53 (m, 1 H), 2.04 (q, 2 H, J = 7.2 Hz), 2.15 (m, 2 H), 2.65–2.25 (m, 4 H), 3.20 (dd, 1 H, J = 14.6 and 3.1 Hz), 4.03 (s, 3 H), 5.37 (m, 1 H), 6.88 (dd, 1 H, J = 8 and 1 Hz), 7.55 (t, 1 H, J = 8 Hz), 7.65 (dd, 1 H, J = 8 and 1 Hz), 14.76 (s, 1 H); MS m/z 338 (M^+).

4-Methoxy-6-hydroxy-9-ethyl-7,8-dihydronaphthacene-5,12-dione (14a). Oxygen was bubbled through a heated (100 °C) solution of **13** (2.31 g, 6.83 mmol) in DMF (50 mL) for 6 h. The oxygen flow was terminated, and the solution was cooled in an ice–water bath. Addition of H_2O (50 mL) to the solution precipitated **14a** as orange crystals, which were collected by filtration, washed with H_2O, and dried to give 1.89 g (83%) of pure **14a** with mp 156–158 °C: ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7.6 Hz), 2.27 (q, 2 H, J = 7.6 Hz), 2.34 (t, 2 H, J = 8.8 Hz), 2.94 (t, 2 H, J = 8.8 Hz), 4.07 (s, 3 H), 6.29 (s, 1 H), 7.34 (dd, 1 H, J = 8 and 1 Hz), 7.44 (s, 1 H), 7.71 (t, 1 H, J = 8 Hz), 7.95 (dd, 1 H, J = 8 and 1 Hz), 13.28 (s, 1 H); MS m/z 334 (M^+).

4,6-Dimethoxy-9-ethyl-7,8-dihydronaphthacene-5,12-dione (14b). A mixture of **14a** (1.67 g, 5 mmol), dimethyl sulfate (0.95 mL, 10 mmol), and powdered K_2CO_3 (3.45 g, 25 mmol) in dry acetone (80 mL) was heated at reflux for 5 h, cooled, and filtered. Triethylamine (2 mL) was added to the filtrate, and the mixture was allowed to react at room temperature for 0.5 h. Acetone and excess triethylamine were evaporated at reduced pressure. The oily residue was suspended in H_2O and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The yellow residue was recrystallized (EtOAc–hexanes) to give 1.67 g (96%) of pure methyl ether **14b** with mp 133–135 °C: ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7.54 Hz), 2.3 (m, 4 H), 2.98 (t, 2 H, J = 8.26 Hz), 3.94 (s, 3 H), 4.02 (s, 3 H), 6.34 (s, 1 H), 7.30 (dd, 1 H, J = 8.38 and 1.18 Hz), 7.63 (dd, 1 H, J = 8.38 and 7.69 Hz), 7.66 (s, 1 H), 7.84 (dd, 1 H, J = 7.69 and 1.18 Hz); MS m/z 348 (M^+). Anal. Calcd for $C_{22}H_{20}O_4$: C, 72.49; H, 9.95. Found: C, 72.51; H, 10.00.

3-(3-Oxopentyl)-4,5-dimethoxy-9,10-dioxoanthracene-2-carboxylic Acid (15a). To a magnetically stirred suspension of **14b** (2.5 g, 7.3 mmol) and anhydrous K_2CO_3 (1.5 g, 11 mmol) in *tert*-butyl alcohol (30 mL) were simultaneously added solutions of $NaIO_4$ (11.0 g, 51.4 mmol) in H_2O (100 mL) and $KMnO_4$ (186 mg, 1.2 mmol) in H_2O (40 mL). The $NaIO_4$ solution was added over 1 h, and the $KMnO_4$ solution was added over 2 h. The progress of the reaction was monitored by TLC, and after 6 h at room temperature the reaction was complete. In order to reduce excess oxidizing agents, $NaHSO_3$ (1.68 g, 16.2 mmol) was added, and the mixture was stirred in an ice bath for 3 h. The precipitated salts were removed by filtration, and the filtrate was acidified to pH 2 with 10% H_2SO_4. The mixture was extracted with EtOAc (4 × 100 mL), and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue (3.19 g) was recrystallized (EtOAc–hexanes) to furnish 2.27 g (78%) of pure acid **15a** as yellow crystals with mp 199–201 °C: ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7.32 Hz), 2.47 (q, 2 H, J = 7.32 Hz), 2.92 (t, 2 H, J = 7.32 Hz), 3.27 (t, 2 H, J = 7.32 Hz), 3.98 (s, 3 H), 4.03 (s, 3 H), 4.2–2.9 (br s, 1 H, CO_2H), 7.34 (dd, 1 H, J = 8.05 and 1.1 Hz), 7.69 (t, 1 H, J = 8.05 Hz), 7.87 (dd, 1 H, J = 8.05 and 1.05 Hz), 8.48 (s, 1 H); IR (KBr, cm^{-1}) 3422 (br d), 2940, 1701, 1678, 1586; MS m/z 396 (M^+).

2-Formyl-3-(3-oxopent-1-yl)-4,5-dimethoxy-9,10-anthracenedione (17). A magnetically stirred solution of **14b** (348 mg, 1 mmol) in anhydrous CH_2Cl_2–MeOH (4:1, 30 mL) was ozonized (flow rate 0.5 mL/min, power 50 W) for 15–20 min at −78 °C, at which point the solution turned greenish blue and analysis of a TLC indicated the absence of starting material. Excess ozone was purged from the reaction by bubbling oxygen

through the solution for 15–20 min. The solution became yellow during this period. Excess dimethyl sulfide (1 mL) and pyridine (20 μL) were added at −78 °C, and the reaction was allowed to warm to room temperature and stand overnight. Excess dimethyl sulfide and CH_2Cl_2 were removed at reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed successively with 0.5 N HCl (20 mL), 5% $NaHCO_3$ (20 mL), H_2O, and brine, dried ($MgSO_4$), filtered, and evaporated at reduced pressure to furnish 365 mg (96%) of essentially pure keto aldehyde **17**. A sample recrystallized from CH_2Cl_2–hexanes gave yellow needles with mp 158–160 °C: ^1H NMR ($CDCl_3$) δ 1.07 (t, 3 H, J = 7.33 Hz), 2.45 (q, 2 H, J = 7.33 Hz), 2.73 (t, 2 H, J = 7.40 Hz), 3.41 (t, 2 H, J = 7.40 Hz), 3.99 (s, 3 H), 4.04 (s, 3 H), 7.36 (dd, 1 H, J = 8.19 and 1.95 Hz), 7.71 (dd, 1 H, J = 8.19 and 7.62 Hz), 7.88 (dd, 1 H, J = 7.62 and 1.95 Hz), 8.46 (s, 1 H), 10.36 (s, 1 H); MS m/z 380 (M^+), 351, 323, 309, 295. Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.50; H, 5.41.

2-[(1,3-Dithia-2-cyclohexylidene)methyl]-3-(3-oxopent-1-yl)-4,5-dimethoxy-9,10-anthracenedione (19). To a magnetically stirred, cold (−20 °C) suspension of the phosphonium salt **18** (164 mg, 0.39 mmol) in dry THF (10 mL) under N_2 was added n-BuLi (0.21 mL, 1.6 M, 0.34 mmol) dropwise. The bright yellow solution of the phosphonium ylid was stirred at −20 °C for 30 min, and then a solution of the keto aldehyde **17** (100 mg, 0.26 mmol) in dry THF (10 mL) was added dropwise. The resultant mixture was allowed to warm to room temperature and stirred for 3.5 h, at which time the solution had become bright orange and analysis of a TLC indicated the absence of the keto aldehyde **17**. Ether (50 mL) and brine (30 mL) were added, and the phases were separated. The aqueous layer was again extracted with Et_2O (25 mL), and the combined organic extracts were washed with H_2O (50 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was chromatographed on silica gel (30 g, 2:2:1 CH_2Cl_2–EtOAc–hexanes) to give 113 mg (89%) of **19**. A sample recrystallized from CH_2Cl_2–hexanes gave yellow crystals with mp 130–132 °C: ^1H NMR ($CDCl_3$) δ 1.08 (t, 3 H, J = 7.3 Hz), 2.21 (quintet, 2 H, J = 5.86 Hz), 2.43 (q, 2 H, J = 7.3 Hz), 2.65 (t, 2 H, J = 7.3 Hz), 2.97 (t, 4 H, J = 5.86 Hz), 3.04 (t, 2 H, J = 7.3 Hz), 3.95 (s, 3 H), 4.02 (s, 3 H), 6.83 (s, 1 H), 7.30 (dd, 1 H, J = 8.0 and 1.9 Hz), 7.65 (t, 1 H, J = 8.0 Hz), 7.85 (dd, 1 H, J = 8.0 and 1.9 Hz), 8.15 (s, 1 H); MS m/z 482 (M^+), 425, 351.

Methyl [4,5-Dimethoxy-3-(3-oxopent-1-yl)anthraquinon-2-yl]acetate (16). A mixture of the ketene dithioacetal **19** (120 mg, 0.248 mmol) and mercuric chloride (236 mg, 0.87 mmol) in 9:1 methanol–H_2O (25 mL) was heated at reflux under N_2 for 4 h. The reaction mixture was cooled, CH_2Cl_2 (30 mL) was added, and the insoluble salts were removed by filtration. Water (20 mL) was added to the filtrate, and the layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (20 mL), and the combined organic extracts were washed with saturated NH_4Cl (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed on silica gel (20 g, 1:1:1 EtOAc–CH_2Cl_2–hexanes) to furnish 85 mg (81%) of pure keto ester **16** with mp 141–143 °C (lit.[13] mp 142–145 °C): ^1H NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7.35 Hz), 2.42 (q, 2 H, J = 7.35 Hz), 2.75 (t, 2 H, J = 7.51 Hz), 2.99 (t, 2 H, J = 7.51 Hz), 3.71 (s, 3 H), 3.86 (s, 2 H), 3.96 (s, 3 H), 4.02 (s, 3 H), 7.32 (dd, 1 H, J = 7.81 and 1.95 Hz), 7.66 (dd, 1 H, J = 7.81 and 7.46 Hz), 7.84 (dd, 1 H, J = 7.46 and 1.95 Hz), 7.87 (s, 1 H); MS m/z 424 (M^+).

Methyl 4,6-Dimethoxy-9(*R*,*S*)-ethyl-9(*R*,*S*)-hydroxy-5,12-dioxo-7,8,9,10-tetrahydronaphthacene-10(*R*,*S*)-carboxylate (20a) and Methyl 4,6-Dimethoxy-9(*S*,*R*)-ethyl-9(*S*,*R*)-hydroxy-5,12-dioxo-7,8,9,10-tetrahydronaphthacene-10(*R*,*S*)-carboxylate (20b). To a magnetically stirred solution of $Mg(OCH_3)_2$ (0.6 g, 7 mmol), prepared from Mg (170 mg, 7 mmol) in dry methanol (50 mL), was added in one portion keto ester **16** (297 mg, 0.7 mmol). The resultant mixture was stirred under N_2 for 5 h at room temperature and then cooled in an ice–water bath and carefully neutralized with 2 N HCl. The mixture was partitioned between brine (50 mL) and CH_2Cl_2 (100 mL), and the phases were separated. The aqueous layer was extracted once more with CH_2Cl_2 (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Flash chromatography of the residue on silica gel (50 g, CH_2Cl_2–Et_2O–hexanes, 2:1:1) gave 210 mg of **20a** and 60 mg of **20b** (combined yield, 90%). Data for **20a**: mp 194–197 °C (lit.[13] mp 193–197 °C); ^1H NMR ($CDCl_3$) δ 1.07 (t, 3 H, J = 7.6 Hz), 1.52–1.72 (m, 3 H), 1.9 (dt, 1 H, J = 14 and 7 Hz), 2.28 (ddd, 1 H, J = 14.0, 10.5 and 7.3 Hz), 2.93 (ddd, 1 H, J = 18.0, 10.5 and 7.3 Hz), 3.12 (ddd, 1 H, J = 18.0, 7.3 and 6.7 Hz), 3.71 (s, 3 H), 3.96 (s, 1 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 7.30 (d, 1 H, J = 8.30 Hz), 7.64 (t, 1 H, J = 8.30 Hz), 7.82 (d, 1 H, J = 8.30 Hz), 7.83 (s, 1 H); MS m/z 424 (M^+). Data for **20b**: mp 131–135 °C (lit.[19] mp 138–140 °C); ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.21 Hz), 1.53–1.63 (m, 2 H), 1.77 (dt, 1 H, J = 14.0 and 7.0 Hz), 2.26 (dt, 1 H, J = 14.0 and 7 Hz), 2.90 (dt, 1 H, J = 18.0 and 7 Hz), 3.07 (s, 1 H), 3.15 (dt, 1 H, J = 18.0 and 7 Hz), 3.85 (s, 3 H), 3.92 (s, 1 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 7.32 (dd, 1 H, J = 8.28 and 1.93 Hz), 7.66 (dd, 1 H, J = 8.28 and 7.85 Hz), 7.77 (s, 1 H), 7.84 (dd, 1 H, J = 7.85 and 1.93 Hz); MS m/z 424 (M^+).

Methyl 9(*R*,*S*)-Ethyl-4,6,9(*R*,*S*)-trihydroxy-5,12-dioxo-7,8,9,10-tetrahydronaphthacene-10(*R*,*S*)-carboxylate (20c). To a magnetically stirred suspension of anhydrous $AlCl_3$ (390 mg, 2.9 mmol) in dry CH_2Cl_2 (15 mL) under N_2 was added a solution of the hydroxy ester **20a** (62 mg, 0.146 mmol) in dry CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 40 h, poured into cold 1:1 5% HCl–brine (20 mL), and stirred until the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. Chromatography of the residue on silica gel (10 g, 2:1:1 CH_2Cl_2–ether–hexane) furnished 56 mg (97%) of pure **20c** with mp 219–222 °C (lit.[13] mp 220–222 °C). The spectral characteristics of this product were in full agreement with those reported for an authentic sample, and a mixed melting point was undepressed: ^1H NMR ($CDCl_3$) δ 1.09 (t, 3 H, J = 7.2 Hz), 1.55–1.65 (m, 1 H), 1.65–1.75 (m, 1 H), 1.88–1.98 (m, 1 H), 2.23–2.37 (m, 1 H), 2.76–2.92 (m, 1 H), 3.0–3.13 (m, 1 H), 3.73 (s, 3 H), 3.94 (s, 1 H), 7.28 (dd, 1 H, J = 8.3 and 1.7 Hz), 7.64 (s, 1 H), 7.66 (dd, 1 H, J = 7.9 and 8.3 Hz), 7.80 (dd, 1 H, J = 7.9 and 1.7 Hz), 12.09 (s, 1 H), 12.48 (s, 1 H); MS m/z 396 (M^+).

Methyl 9(*R*,*S*)-Ethyl-4,6,7(*S*,*R*),9(*R*,*S*)-tetrahydroxy-5,12-dioxo-7,8,9,10-tetrahydronaphthacene-10(*R*,*S*)-carboxylate (1a). To a stirred hot solution of **20c** (57 mg, 0.14 mmol) in dry CCl_4 (50 mL) containing AIBN (3 mg) was added dropwise a solution of Br_2 (46 mg, 15 μL, 0.28 mmol) in CCl_4 (25 mL) under N_2. The mixture was heated at reflux for 1 h; at that time analysis of a TLC indicated the absence of starting material. The reaction was cooled, transferred to a separatory funnel, and washed with 10% $NaHSO_3$ solution (25 mL). The organic phase was evaporated to dryness under reduced pressure at room temperature, and the residue was taken up in 1:1 THF–H_2O (20 mL) and stirred for 2 h at room temperature. The THF was removed at reduced pressure at room temperature, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were successively washed with $NaHCO_3$ solution (20 mL), H_2O (20 mL), and brine (20 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Trituration of the residue with hexanes and then filtration provided 52.5 mg (88.5%) of **1a** as an orange solid with mp 211–213 °C (lit.[9,19] mp 211–213 °C, lit.[5] mp 210–214 °C). A mixed melting point with an authentic sample[9] was undepressed: ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7.26 Hz), 1.50–1.65 (m, 1 H), 1.65–1.80 (m, 1 H), 2.27 (d, 1 H, J = 14.65 Hz), 2.55 (dd, 1 H, J = 14.65 and 4.76 Hz), 3.39 (br s, 1 H), 3.71 (s, 3 H), 3.87 (br s, 1 H), 4.09 (s, 1 H), 5.39 (d, 1 H, J = 4.76 Hz), 7.31 (dd, 1 H, J = 8.4 and 1.7 Hz), 7.70 (t, 1 H, J = 8.4 Hz), 7.71 (s, 1 H), 7.83 (dd, 1 H, J = 8.4 and 1.7 Hz), 11.96 (s, 1 H), 12.73 (s, 1 H); MS m/z 412 (M^+).

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