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A STEREOSPECIFIC TOTAL SYNTHESIS OF AKLAVINONE

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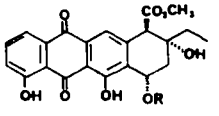
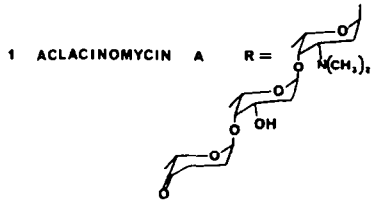
Abstract—A stereospecific synthesis of aklavinone (**2**) in 16 steps from 5-methoxy-1-tetralone with an overall yield of 6.5% is described. Regiospecific control in forming the BCD-ring chromophore was accomplished by coupling of a preformed bicyclic AB-ring aldehyde (**29**) with a nucleophilic D-ring carboxamide (**3**), with stepwise bond formation as illustrated in equation 2. The coupled product was subsequently transformed into (±)-aklavinone. An enantioselective synthesis of aklavinone was achieved in 53%. e.e. using the procedure of Sharpless for the asymmetric epoxidation of allylic alcohol **24**.[13]

Aclacinomycin A (**1**), a second generation anthracycline, is a clinically important antitumor antibiotic isolated from *Streptomyces galilaeus* in 1975.[1] It exhibits strong antineoplastic activity similar to that of adriamycin with 10 to 15 times less cardiotoxicity.[2] Certain side effects associated with the first generation anthracyclines daunomycin and adriamycin are observed to a much lesser extent with aclacinomycin A. Included in these side effects are alopecia, bone marrow hypoplasia, and renal lesions.[3] The interesting activity of aclacinomycin A, together with recent advances in the enzymatic glycosidation of aklavinone (**2**),[4] has prompted a flurry of activity aimed at the total synthesis of aklavinone.[5]

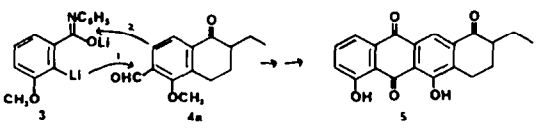




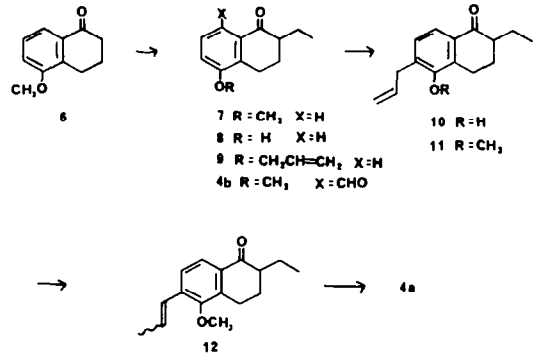
1 ACLACINOMYCIN A R =

2 AKLAVINONE R = H

In order to achieve a total synthesis of aklavionone two strategic considerations must be confronted. First is the regiospecific construction of the BCD-ring chromophore, and second, the timely elaboration of the A-ring functionality. The first of these considerations, in particular the lack of a hydroxyl group at the C-11 position, precludes various B-ring quinone strategies employed for the syntheses of first generation anthracyclinones such as daunomycinone.[6] However, regiospecific control in the construction of the BCD-ring chromophore could be achieved using a nucleophilic carboxamide and an appropriately substituted AB-ring aldehyde as illustrated in Eq. 1.[7] Aldehyde **4a** was initially chosen as the AB-ring synthon. It was hoped that a carbonyl group at the C-10 position would allow construction of the A-ring functionality of aklavinone at a later stage.



The preparation of aldehyde **4a** (Scheme 1) starts with the readily available 6-methoxytetralone (**6**). Monoalkylation of tetralone **6** was not as simple as expected, and under most conditions mixtures of mono-, di-, and non-alkylated products were observed. The monoalkylated product could be prepared exclusively if the lithium enolate of **6** was added inversely to a large excess of ethyl iodide. However, this was not practical for large scale reactions, and an alternative procedure was needed. The major difficulty in these alkylations involves separation of the monoalkylated product from the dialkylated product. The procedure that was ultimately used involved generation of a boron enolate followed by alkylation with ethyl iodide.[8] By using the boron enolate none of the dialkylated product was observed and purification of the monoalkylated product was trivial. The required generation of the boron enolate was accomplished by reacting the lithium enolate of **6** with triethanolamine borate in DMSO. Subsequent addition of ethyl iodide yielded 80% of the desired tetralone **7** with 14% of unreacted starting material, which was easily separated by silica gel chromatography.



6 → 7 R = CH₃ X = H; 8 R = H X = H; 9 R = CH₂CH=CH₂ X = H; 4b R = CH₃ X = CHO → 10 R = H; 11 R = CH₃ → 12 → 4a

Scheme 1.

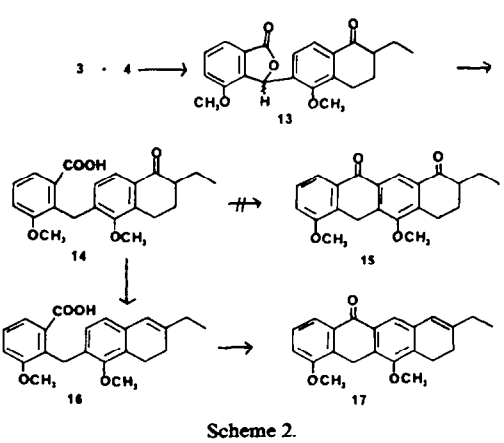
Direct formylation of tetralone **7** using Lewis acid catalysis yielded a single crystalline aldehyde. It was impossible to determine by NMR if this was the desired C-7 aldehyde **4a**, or the undesired C-9 aldehyde **4b** involving substitution para to the methoxy group. In order to ascertain which aldehyde was produced, the compound was demethylated to its corresponding phenol. If the desired ortho aldehyde were formed, then the carbonyl stretching frequency in the IR should show a shift to lower energy due to internal H-bonding of the phenol hydrogen to the aldehyde. However, there was no significant change in the IR, strongly suggesting

that the undesired aldehyde was produced. Further proof was obtained by Baeyer-Villiger oxidation of the aldehyde moiety to the corresponding phenol.[9] This time there was a considerable shift in the carbonyl region of the IR from 1675 cm^{-1} to 1640 cm^{-1}, as a result of hydrogen bonding to the tetralone carbonyl. This unequivocally proved that the undesired C-9 aldehyde **4b** was produced, since only a phenol at the C-9 position is capable of internally hydrogen bonding to the tetralone carbonyl.

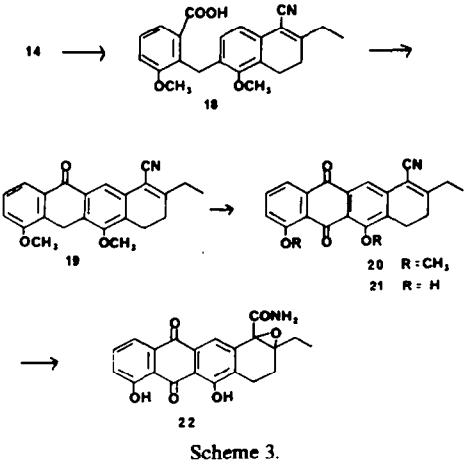
In order to alter this regioselectivity, tetralone **7** was demethylated in 96% yield to phenol **8** by using NaSEt in refluxing DMF for 2 hr.[10] The phenol was then alkylated with allyl bromide and potassium carbonate in refluxing acetone followed by heating in dimethylaniline at 200° for 24 hr to achieve a Claisen rearrangement. This gave C-allyl tetralone **10** in 87% yield from phenol **8**. Remethylation of **10** with methyl iodide and potassium carbonate in refluxing acetone gave a quantitative yield of protected phenol **11**. Isomerization of the allylic double bond with potassium t-butoxide in refluxing t-butanol gave a 93% yield of compound **12** as a mixture of *cis* and *trans* isomers (observed by NMR). Ozonolysis of the mixture in dichloromethane at −78°C gave the desired bicyclic aldehyde **4a** in 80% yield.

With aldehyde **4a** in hand, attention was focused on coupling the AB-ring synthon with the D-ring carboxamide (Scheme 2). Thus, nucleophilic carboxamide **3** was prepared by treating 3-methoxybenzanilide with 2 equivalents of n-BuLi-TMEDA at −78°, then warming to −20°.[7a] Once the dianion was formed, aldehyde **4a** was added at −78° and the reaction was warmed to room temp over 16 hr. After an acidic workup, phthalide **13** was obtained in 80% yield. Reduction of **13** with zinc dust in aqueous NaOH and pyridine gave ketoacid **14** in 95% yield.[11] Attempts to form the C-ring of aklavinone by cyclodehydration of **14** to compound **15** were unsuccessful under a variety of conditions. It was concluded that the C-10 ketone was sufficient to deactivate the B-ring towards electrophilic attack. To verify this, ketoacid **14** was reduced with sodium borohydride followed by dehydration to unsaturated compound **16**. Ring closure of **16**, under relatively mild conditions using trifluoroacetic acid-trifluoroacetic anhydride in dichloromethane at room temperature, gave the cyclized product **17** in good yield. Anthrone **17** was a useful intermediate in the synthesis of decarbomethoxyaklavinone.[12]

Having established that the ketone was preventing C-ring formation, attempts were made to functionalize the C-10 positon at an earlier stage (Scheme 3). Thus, treatment of ketoacid **14** with excess trimethylsilyl cyanide gave the expected cyanohydrin which was promptly dehydrated using p-toluenesulfonic acid in refluxing benzene to yield 84% of unsaturated nitrile **18**. Reaction of acid **18** with sulfuric acid at 0° for 2 hr was found to be the optimum condition for the formation of the C-ring. This gave anthrone **19** in 94% yield. Oxidation of **19** with Jones reagent in 1:1 aqueous acetone gave quinone **20** in 76% yield after chromatography on silica gel. Deprotection of the methoxy groups was accomplished in 94% yield by treatment of **20** with aluminum chloride in dichloromethane. The deprotected compound **21** was then reacted with basic hydrogen peroxide in methanol to give epoxy amide **22** in 72% yield. Epoxy amide **22** converges with the Confalone synthesis of aklavinone and thus constitutes a formal total synthesis of aklavinone.[5a] However, the conversion of the amide functionality into the desired carbomethoxy moiety was not as facile as expected. The first step, preparation of an imino ether, proceeded smoothly and in reasonable yields by treating amide **22** with trimethyloxonium fluoroborate. However, hydrolysis of the iminoether gave as the major product epoxy amide **22**, and only 10 to 25% of the expected methyl ester. It has been postulated by Confalone that the problem stems from severe steric crowding about the C-10 position. In order to get the desired methyl ester, a tetrahedral intermediate must form. However, because of the C-11 peri interaction and the C-9 ethyl group, such an intermediate is unfavorable due to steric crowding. On the other hand, hydrolysis of the iminoether back to epoxy amide **22** avoids the formation of a tetrahedral intermediate and becomes the favored pathway. Attempts to hydrolyze amide **22** into the corresponding carboxylic acid using a variety of acid or base reagents failed to produce any of the desired product. Only unreacted amide or decomposition products were observed. This is consistent with the postulate that the C-10 position is sterically hindered, and that a tetrahedral intermediate is not favored. At this point it was concluded that an alternative AB-ring synthon that avoids the ultimate use of a C-10 amide intermediate would have considerable advantages.

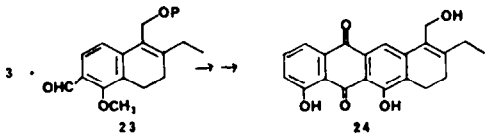


Scheme 2.



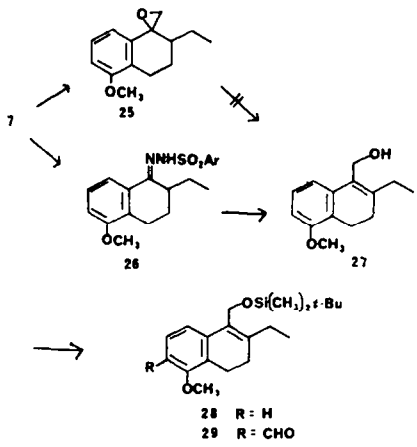
Scheme 3.

Reconsideration of the strategy used for constructing the BCD-ring chromophore led to the new approach illustrated in Eq. 2. The advantages of this approach are twofold. First is the use of an AB-ring synthon such as compound **23**, where "P" represents a suitable protecting group. This would ultimately lead to compound **24** which contains a hydroxymethyl group at the C-10 position. Oxidation of the C-10 alcohol followed by esterification of the resulting acid would then give the desired C-10 carbomethoxy group and thus avoid the undesirable amide. Secondly, **24** is an achiral allylic alcohol, and in principle could be enantioselectively epoxidized using the procedure of Sharpless.[13]



Introduction of a hydroxymethyl group into the AB-ring synthon is shown in Scheme 4. Initial attempts to introduce the desired functionality involved epoxide **25**, which was prepared in 80% yield by reacting tetralone **7** with the ylide of trimethylsulfonium iodide in DMSO.[14] Treatment of the epoxide under acidic conditions or with trimethylsilyl triflate yielded the isomeric aldehyde and none of the desired allylic alcohol.[15] Other attempts to convert the epoxide into allylic alcohol **27** using bases such as lithium diethylamide gave either no reaction or decomposition products. Eventually, the successful preparation of alcohol **27** was accomplished using the Bond modification of the Shapiro reaction.[16] Treatment of ketone **7** with 2,4,6-triisopropylbenzenesulfonyl-hydrazone in acidic methanol for 24 hr gave hydrazone **26** in 85% yield. Reaction of **26** with two equivalents of n-BuLi in THF at −78° then warming to room temp gave a vinyl anion which was trapped with dimethylformamide. Chromatography on silica gel gave an aldehyde which was subsequently reduced with sodium borohydride to give alcohol **27** in 54% yield. Alternatively, the vinyl anion could be trapped with paraformaldehyde to give alcohol **27** directly, but the yield was better using the two step approach. Alcohol **27** was then protected as its tert-butyldimethylsilyl (TBDMS) ether **28**, using TBDMS chloride and imidazole in dichloromethane.[17] The choice of a sterically encumbered protecting group was necessary to avoid competitive lithiation at the positon para to the methoxy moiety in the subsequent step. Thus, treatment of **28** with one equivalent of t-BuLi-TMEDA complex in hexanes at 0° for 4 hr, followed by inverse quench with DMF in THF gave as a single compound the desired aldehyde **29** in 80% yield from alcohol **27**.

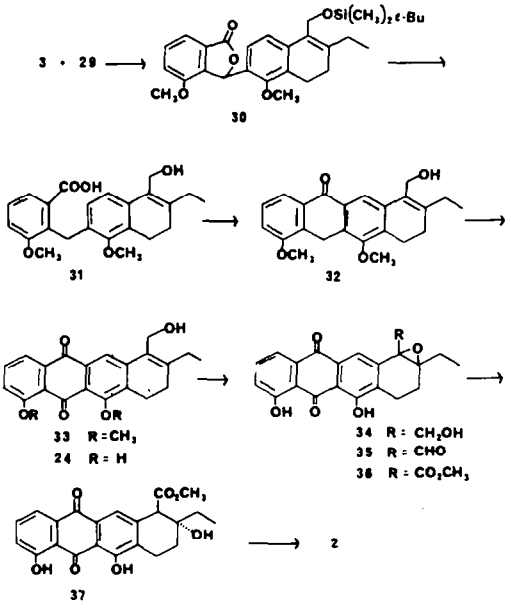
Aldehyde **29** was then coupled with the nucleophilic carboxamide **3** as previously described (Scheme 5). This resulted in an 80% yield of phtalide **30** after a mild acid workup. Reduction of **30** with Zn dust in refluxing sodium hydroxide gave the deprotected hydroxy acid **31** in 95% yield.[11] Cyclodehydration of acid **31** proceeded smoothly using trifluoroacetic anhydride in dichloromethane at 0° for 4 hr. This resulted in anthrone **32** which was immediately oxidized to anthraquinone **33** by passing oxygen gas through a solution of **32** in methanol and Triton B. Interestingly,



Scheme 4.

the allylic alcohol was stable to the ring forming conditions, and the overall yield of **33** from hydroxy acid **31** was 60%. At this point, major difficulties were encountered in deprotecting the B and D-ring hydroxyl groups. The allylic hydroxyl group appeared to be unstable to Lewis acid reagents such as aluminum chloride or boron tribromide, and nucleophilic reagents including LiSMe, NaCN, or $PhNMe^-$ gave as a major product a compound in which the A-ring had been aromatized. Ultimately, demethylation was achieved by treatment of **33** with LiI and benzoic acid in a 1 : 1 mixture of pyridine : collidine at 145° for 90 min.[18] Under these conditions quinone **33** was converted into triol **24** in 92% yield contaminated with approximately 3% of the unwanted aromatic A-ring derivative. Due to difficulties in separating this unwanted compound from the triol, it was carried through for a few steps until purification was easier.

Epoxidation of allylic alcohol **24** with m-chloroperbenzoic acid in dichloromethane and aqueous sodium bicarbonate buffer gave epoxide **34** in 90% yield. Oxidation of alcohol **34** with PCC in



Scheme 5.

dichloromethane gave epoxy aldehyde **35**. At this stage the undesired aromatic A-ring compound could be separated by preparative TLC, resulting in a 79% yield of **35**. Sodium chlorite oxidation of **35** in aqueous dioxane, employing sulfamic acid as a chlorine scavenger,[19] followed by treatment with diazomethane gave the epoxy ester **36** in 95% yield. Stereospecific hydrogenolysis of epoxide **36** with $Pd/BaSO_4$ in a 1:1 mixture of ethanol: triethanolamine gave carbinol **37** in 76% yield.[20] As determined by high field NMR only one stereoisomer was present. The stereochemical outcome of the reduction was established by comparing the observed NMR of **37**, itself a natural product known as galirubinone D, with that of a synthetic sample prepared by Dr. P. Confalone. The high degree of stereospecificity observed in this reaction is not typical of Pd-catalyzed reductions involving cyclohexene epoxides.[21] Therefore, it is regarded as unlikely that this reduction is the result of a direct C—O bond hydrogenolysis. We suggest that the mechanism shown in Fig. 1 may account for the observed stereospecificity. Initially, the C-ring quinone is reduced to the corresponding hydroquinone. Triethanolamine, then acting as a base, opens the epoxide yielding a quinone methide-like intermediate. This can then be either reduced from the alpha face followed by air oxidation on workup, or more likely, a proton involved in an acid base type reaction could be delivered to the C-10 position from the alpha face with possible assistance from the neighboring OH group. Independent support for this type of mechanism is the observation by the Confalone group that the reduction does not proceed in the absence of triethanolamine.

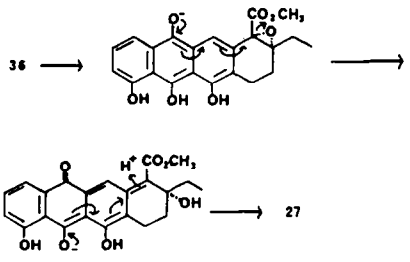


Fig. 1.

Finally, homolytic bromination of carbinol **37** with bromine in carbon tetrachloride followed by solvolysis of the crude bromide with 1:1 aqueous THF gave 88% of aklavinone **2**. Interestingly, the observed stereospecificity for the introduction of the C-7 OH group was greater than 10 to 1 favoring the natural *cis* isomer. This is in contrast to reported observations in the daunomycinone-like molecules where there is an acyl group at the C-9 position. However, it is consistent with results involving molecules where there is a simple alkyl group such as ethyl at the C-9 position.[22] It is postulated that in the daunomycinone case the C-13 carbonyl can assist in directing the incoming molecule of water resulting in the predominance of the *trans* diol. In aklavinone there is no C-13 carbonyl, thus the C-9 alcohol can help direct the water molecule resulting in the natural *cis* diol.

One of the advantages of this approach was that allylic alcohol **24** could be enantioselectively epoxidized using the procedure of Sharpless.[13] Treatment of **24** with titanium (IV) isopropoxide, (−)-diethyl d-tartrate, and t-BuOOH in dichloromethane for 3 days gave optically active epoxide **34** in 85% yield. An enantiomeric excess of 53 ± 2% was determined by ^{1}H-NMR analysis of the corresponding MTPA ester of **34**.[23] This was also confirmed by converting the optically active epoxide into aklavionone and comparing the observed rotation ($[\alpha]_D = +112$ in dioxane) with that reported for natural aklavionone ($[\alpha]_D = +213$ in dioxane).[24]

EXPERIMENTAL

General. All m.ps were taken in glass capillary tubes on a Fieser Mel-Temp apparatus and are reported uncorrected in degrees Centigrade. M.ps are reported for crude compounds unless recrystallization solvents are indicated.

PMR spectra were recorded on a JEOL model JNM-MH-100 MHz spectrometer, a JEOL model FT-100 MHz spectrometer (100 FT), or a Bruker WH 400 MHz-FT spectrometer (400 FT). Chemical shifts are expressed in δ values (ppm) with TMS as an internal standard unless otherwise stated. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, and m = multiplet.

IR spectra were recorded on a Perkin-Elmer model 137 spectrometer and are calibrated with the 1601 cm^{-1} peak of polystyrene. All absorption frequencies are reported in cm^{-1}.

Low resolution mass spectra (MS) were recorded on a Dupont 21-490B mass spectrometer at 75 eV unless otherwise noted.

Chemical analyses were performed by Galbraith Laboratories, Inc. in Knoxville, Tennessee.

2-Ethyl-5-methoxy-1-tetralone (7)

Diisopropylamine (6.2 g, 0.044 mol) in 15 ml of dry THF was cooled to −20° and purged with N_2. To this was added *n*-BuLi in hexanes (0.044 mol) dropwise, and the soln was stirred 30 min before warming to 0°. Then 5-methoxy-1-tetralone (7.0 g, 0.040 mol) in 25 ml of dry THF was added dropwise, and the mixture was warmed to rt over 1 hr. Triethanolamine borate (7.0 g, 0.044 mol) and 100 ml of dry DMSO were added all at once, and this was stirred vigorously at rt. After 2 hr, 20 ml of EtI (0.20 mol) was added and the reaction was stirred at rt overnight. The mixture was poured into water and extracted with ether. The organic phase was washed with 10% HCl, H_2O, and brine; then dried over $MgSO_4$ and the solvent removed at reduced pressure. Chromatography on SiO_2 (50:1 support, 3% acetone in hexanes) resulted in 6.5 g (80%) of **7** as a clear oil (Tosyl hyd. m.p. 177–178° from MeOH) and 1.0 g (14%) of starting tetralone. NMR($CDCl_3$): δ 7.71 (1H, d, J = 8); 7.30 (1H, t, J = 8); 7.03 (1H, d, J = 8); 3.87 (3H, s); 3.23–1.23 (7H, m); 0.99 (3H, t, J = 8). MS: 204 (M^+), 189, 176 (100%), 161. IR($CHCl_3$): 2932, 1680, 1585, 1460, 1440, 1350, 1310.

2-Ethyl-5-hydroxy-1-tetralone (8)

NaH, 50% in oil, (10.0 g, 0.20 mol) was washed with hexanes before 100 ml of dry DMF was added. This was then purged with N_2 and ethanethiol (19.0 ml, 0.26 mol) in 100 ml of dry DMF was added dropwise at 0° while stirring vigorously. When the addition was complete, the mixture was warmed to rt for 0.5 hr. To this was added **7** (10.8 g, 0.05 mol) in 50 ml of dry DMF, and the soln was refluxed for 1.5 hr. The cooled reaction was poured into 500 ml of 10% HCl and extracted well with ether. The organic phase was washed with H_2O and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. This gave 9.8 g (98%) of **8** as a white solid (m.p. 127–129° from ether–pentane). NMR($CDCl_3$): δ 8.80 (1H, s); 7.65 (1H, d of d, J = 6, 3); 7.32–7.16 (2H, m); 3.28–1.40 (7H, m); 1.00 (3H, t, J = 8). MS: 190(M^+), 175, 162 (100%). IR($CHCl_3$): 3600, 3340 (br), 1680, 1602, 1590, 1470, 1280. (Found: C, 75.39; H, 7.45. Calc for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%).

6-Allyl-2-ethyl-5-hydroxy-1-tetralone (**10**)

Hydroxytetralone **8** (9.0 g, 0.047 mol) was dissolved in 200 ml of acetone. Powdered anhyd. K_2CO_3 (13.0 g, 0.094 mol) and allyl bromide (10.0 ml, 0.110 mol) were added and the stirred mixture was refluxed for 5 hr under an atmosphere of N_2. The cooled mixture was filtered, and the remaining salts were washed with fresh acetone. The filtrate was evaporated at reduced pressure and gave allyl ether **9** as an orange oil. NMR($CDCl_3$): δ 7.76 (1H, d, J = 8); 7.32 (1H, t, J = 8); 7.08 (1H, d, J = 8); 6.36–5.98 (1H, m); 5.60–5.28 (2H, m); 4.65–4.58 (2H, m); 3.32–1.26 (7H, m); 1.00 (3H, t, J = 8). Crude ether **9** was taken up in 12 ml of N,N-dimethylaniline and heated to 200° for 24 hr under an atmosphere of N_2. The cooled soln was poured into ether and washed well with 10% HCl. The organic phase was washed with H_2O and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. Recrystallization of the crude compound from ether–pentane gave 9.5 g (87%) of allyl tetralone **10** as a white solid (m.p. 76–78° from ether–pentane). NMR($CDCl_3$): δ 7.65 (1H, d, J = 8); 7.11 (1H, d, J = 8); 6.27–5.83 (1H, m); 5.55 (1H, s); 5.31–5.11 (2H, m); 3.50 (2H, d, J = 6); 3.22–1.40 (7H, m); 1.01 (3H, t, J = 8). MS: 230 (M^+), 215, 202 (100%). IR($CHCl_3$): 3500 (br), 1680, 1610, 1578, 1454, 1430. (Found: C, 78.40; H, 7.93. Calc for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%).

6-Allyl-2-ethyl-5-methoxy-1-tetralone (**11**)

Hydroxytetralone **10** (7.1 g, 0.03 mol) was dissolved in 160 ml of acetone. Powdered anhyd. K_2CO_3 (8.4 g, 0.06 mol) and MeI (15.0 ml, 0.24 mol) were added, and the stirred mixture was refluxed under N_2 for 7 hr. The cooled soln was filtered, and the remaining salts were washed with fresh acetone. Evaporation of the filtrate under reduced pressure gave 7.3 g (100%) of **11** as a white solid (m.p. 49–51° from ether–pentane). NMR($CDCl_3$): δ 7.78 (1H, d, J = 8); 7.14 (1H, d, J = 8); 6.18–5.76 (1H, m); 5.16–4.96 (2H, m); 3.76 (3H, s); 3.45 (2H, d, J = 6); 3.32–1.32 (7H, m); 0.98 (3H, t, J = 6). MS: 244 (M^+), 229, 216 (100%), 201. IR($CHCl_3$): 2940, 1680, 1600, 1562, 1454, 1417.

2-Ethyl-5-methoxy-6-(1-propenyl)-1-tetralone (**12**)

A stirred soln of **11** (7.3 g, 0.030 mol) and t-BuOK (5.0 g, 0.045 mol) in 100 ml of t-BuOH was refluxed under an atmosphere of N_2 for 6 hr. The cooled soln was poured into 10% HCl and extracted with ether. The ether layer was washed with H_2O and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. The crude compound was recrystallized from ether–pentane and gave 7.0 g (93%) of **12** as a white solid (m.p. 69–70° from ether–pentane). NMR($CDCl_3$): δ 7.79 (1H, d, J = 8); 7.40 (1H, d, J = 8); 6.80–6.20 (2H, m); 3.76 (3H, s); 3.28–1.32 (7H, m); 2.93 (3H, d, J = 6); 0.98 (3H, d, J = 6). MS: 244 (M^+), 229, 216 (100%), 201. IR($CHCl_3$): 2940, 1680, 1595, 1565, 1452, 1414. (Found: C, 78.71; H, 8.40. Calc for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25%).

2-Ethyl-6-formyl-5-methoxy-1-tetralone (**4a**)

Ozone was passed through a solution of **12** (5.0 g, 0.02 mol) in 100 ml of CH_2Cl_2 at −78° until the solvent turned light blue. N_2 gas was then passed through to remove excess O_3, and 6 ml of Me_2S was added. The mixture was warmed to rt and an additional 6 ml of Me_2S were added. After 6 hr, the solvent was evaporated at reduced pressure, and the oily solid was collected and washed with ether–pentane. Digestion of the solid in ether gave 3.8 g (80%) of **4a** as a white solid (m.p. 99–100°). NMR($CDCl_3$): δ 10.56 (1H, s); 8.00 (1H, d, J = 8); 7.84 (1H, d, J = 8); 4.00 (3H, s); 3.42–1.39 (7H, m); 1.02 (3H, t, J = 8). MS: 232 (M^+), 217, 204 (100%). IR($CHCl_3$): 2960, 1690, 1574, 1418, 1406, 1387. (Found: C, 72.15; H, 6.92. Calc for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%).

2-Ethyl-5-methoxy-6-[1-(7-methoxy-2-oxa-3-oxo)indanyl]-1-tetralone (**13**)

A soln of 3-methoxybenzanilide (0.98 g, 4.3 mmol) and TMEDA (1.4 ml, 8.6 mmol) in 30 ml of dry THF was cooled to −78° and purged with N_2. To the stirred soln, n-BuLi (8.6 mmol) in hexanes was added dropwise. The reaction was stirred 0.5 hr before warming to −20° for 5 hr. The mixture was then recooled to −78° and **4a** (1.0 g, 4.3 mmol) in 30 ml of dry THF was added. The mixture was maintained at −78° for 6 hr then warmed to rt and stirred overnight. This was then poured into 10% HCl and extracted with ether. The ether phase was washed well with 10% HCl, H_2O, and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. The white solid was collected and washed with ether to give 1.1 g (70%) of **13** (m.p. 160–166° from ether). NMR($CDCl_3$): δ 7.92–6.85 (5H, m); 6.88 (1H, s); 3.98 and 3.91 (3H, two s); 3.80 (3H, s); 3.46–1.40 (7H, m); 1.02 (3H, t, J = 8). MS: 366 (M^+), 351, 338 (100%), 331, 323. IR($CDCl_3$): 1770, 1685, 1615, 1495, 1275. (Found: C, 71.96; H, 6.06. Calc for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05%).

6-(2-Carboxy-6-methoxyphenyl)methyl-2-ethyl-5-methoxy-1-tetralone (**14**)

A mixture of **13** (2.0 g, 5.46 mmol), Zn dust (25.0 g, excess), $CuSO_4$ (0.1 g, cat.), 9 ml of pyridine, and 100 ml of 1 N NaOH were refluxed under an atmosphere of N_2 for 24 hr with vigorous stirring. The cooled soln was filtered through celite and the Zn was washed with fresh 1 N NaOH. The filtrate was washed with ether then acidified with conc HCl. This was then extracted well with $CHCl_3$. The organic phase was washed with 10% HCl, H_2O, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. This gave 1.9 g (95%) of **14** as a white solid (m.p. 168–170° from EtOH). NMR($CDCl_3$): δ 8.75 (1H, bs); 7.80–7.68 (2H, m); 7.44 (1H, t, J = 8); 7.20 (1H, d, J = 8); 6.72 (1H, d, J = 8); 4.56 (2H, s); 3.84 (3H, s); 3.78 (3H, s); 3.60–1.40 (7H, m); 0.98 (3H, t, J = 8). MS: 368 (M^+, 100%), 340, 322. IR($CHCl_3$): 1770, 1685, 1615, 1496. (Found: C, 71.52; H, 6.68. Calc for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57%).

6-(2-Carboxy-6-methoxyphenyl)methyl-1-cyano-2-ethyl-3,4-dihydronaphthalene (**18**)

A mixture of **14** (0.83 g, 2.25 mmol), trimethylsilylcyanide (0.86 ml, 6.75 mmol), and 2 mg of zinc iodide in 5 ml of CH_2Cl_2 was stirred at rt for 48 hr. The solvent was evaporated at reduced pressure, and the residue was dissolved in 15 ml of THF. To this was added 15 ml of 10% HCl and the mixture was stirred for 2hr. This was then poured into $CHCl_3$, and the organic phase was washed with H_2O, sat. $NaHSO_3$, and brine; then evaporated at reduced pressure. The crude cyanohydrin was then taken up in 40 ml of benzene and PTSA (~ 10 mg) was added. This was refluxed for 3 hr with azeotropic removal of H_2O. The cooled soln was evaporated at reduced pressure, and the resulting brown solid was collected and washed with 95% EtOH. This gave 0.74 g (84%) of **18** as a white solid (m.p. 221–223° from $CHCl_3$). NMR (100 FT, $CDCl_3$): δ 7.62 (1H, d, J = 8); 7.34 (1H, t, J = 8); 7.13–7.01 (2H, m); 6.59 (1H, d, J = 8); 4.43 (2H, s); 3.76 (3H, s), 3.71 (3H, s); 2.88 (2H, t, J = 8); 2.72–2.32 (4H, m); 1.17 (3H, t, J = 8). MS: 377 (M^+, 100%), 359. (Found: C, 73.10; H, 6.29; N, 3.65. Calc for $C_{23}H_{23}N_1O_4$: C, 73.20; H, 6.14; N, 3.71%).

1-Cyano-5,7-dimethoxy-2-ethyl-3,4,6-trihydronaphthacene-11-one (**19**)

A soln of **18** (0.5 g, 1.28 mmol) in 15 ml of conc H_2SO_4 was stirred at 0° for 2 hr. This was then poured over ice and extracted with $CHCl_3$. The organic phase was washed with H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. This gave 0.46 g (96%) of **19** as a yellow solid (m.p. 240–242° from ether–$CHCl_3$). NMR ($CDCl_3$): δ 7.88 (1H, s), 7.68 (1H, d, J = 8); 7.16 (1H, t, J = 8), 6.83 (d, J = 8); 3.88 (2H, s); 3.76 (3H, s); 3.72 (3H, s); 2.82 (2H, t) J = 8); 2.50–2.24 (4H, m); 1.10 (3H, t, J = 8). MS: 359 (M^+, 100%), 344, 328, 315. IR($CHCl_3$): 2216, 1660, 1592, 1460, 1420, 1330, 1315. (Found: C, 76.58; H, 5.93; N, 3.77. Calc for $C_{23}H_{21}N_1O_3$: C, 76.87; H, 5.88; N, 3.90%).

1-Cyano-5,7-dimethoxy-2-ethyl-3,4-dihydroxynaphthacene-6,11-dione (**20**)

Anthrone **19** (0.46 g, 1.28 mmol) was dissolved in 30 ml of 1:1 acetone–CH_2Cl_2. To this was added 5.4 ml of Jones

reagent over a 2 hr period. This was stirred an additional 4 hr then poured into H_2O. This was extracted with $CHCl_3$, and the organic phase was washed with H_2O and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. Chromatography on SiO_2 with 1% MeOH in CH_2Cl_2 as eluant gave 0.35 g (74%) of **20** as a yellow solid (m.p. 211–212° from CH_2Cl_2). NMR ($CDCl_3$): δ 8.02 (1H, s); 7.81 (1H, d, J = 8); 7.62 (1H, t, J = 8); 7.27 (1H, d, J = 8); 4.01 (3H, s); 3.94 (3H, s); 3.02 (2H, t, J = 8); 2.70–2.44 (4H, m); 1.22 (3H, t, J = 8). MS: 373 (M^+), 358 (100%), 344, 326. IR($CHCl_3$): 2219, 1680, 1677, 1590, 1330, 1288. (Found: C, 73.80, H, 5.12; N, 3.74. Calc for $C_{23}H_{19}N_1O_4$: C, 73.98; H, 5.12; N, 3.75%).

1-Cyano-5,7-dihydroxy-2-ethyl-3,4-dihydroxynaphthacene-6,11-dione (**21**)

To a soln of **20** (0.24 g, 0,64 mmol) in 40 ml of CH_2Cl_2 at 0°, was added anhyd. $AlCl_3$ (0.68 g, 5.12 mmol). This was then warmed to rt and stirred for 8 hr. The mixture was then poured into sat. oxalic acid soln, and enough ether was added to extract the CH_2Cl_2. This was stirred vigorously for 2 hr replacing the oxalic acid soln twice. The organic phase was then washed with H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The orange solid was collected and washed with ether to give 0.21 g (95%) of **21** (m.p. 234–236° from CH_2Cl_2). NMR (400 FT, $CDCl_3$): 12.38 (1H, s); 12.04 (1H, s); 7.92 (1H, s); 7.84 (1H, d, J = 8); 7.70 (1H, t, J = 8); 7.30 (1H, d, J = 8); 2.98 (2H, t, J = 8); 2.70 (2H, q, J = 8); 2.58 (2H, d, J = 8); 1.26 (3H, t, J = 8). IR(KBr): 2200, 1670, 1600(br), 1450, 1410. (Found: C, 73.20; H, 4.66; N, 3.88. Calc for $C_{21}H_{15}N_1O_4$: C, 73.04; H, 4.37; N, 4.05%).

1-Carboxamide-5,7-dihydroxy-1,2-epoxy-2-ethyl-3,4-dihydronaphthacene-6,11-dione (**22**)

To a soln of **21** (0.29 g, 0.84 mmol) in 15 ml of MeOH was added 1 ml of H_2O_2 and 3.4 ml of 1 N NaOH. After stirring for 4 hr at rt, this was poured into 10% HCl and extracted with $CHCl_3$. The organic phase was washed with H_2O and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The orange solid was collected and washed with ether to give 0.23 g (72%) of **22** (m.p. 251–252° from $CHCl_3$). NMR (400 FT, $CDCl_3$): δ 12.43 (1H, s); 12.05 (1H, s); 8.07 (1H, s); 7.84 (1H, d, J = 8); 7.69 (1H, t, J = 8); 7.29 (1H, d, J = 8); 6.55 (1H, bs); 5.84 (1H, bs); 3.29–3.24 (1H, m); 2.44–2.40 (2H, m); 2.00–1.80 (3H, m); 1.15 (3H, t, J = 8). MS: 379 (M^+), 361, 351 (100%), 335, 307. IR(KBr): 1660, 1630, 1450, 1270. (Found: C, 66.25; H, 4.58; N, 3.51. Calc for $C_{21}H_{17}N_1O_6$: C, 66.49; H, 4.51; N, 3.69%).

Triisopropylbenzenesulfonyl hydrazone of 2-ethyl-5-methoxy-1-tetralone (**26**)

To a soln of methoxy tetralone **7** (15.9 g, 0.078 mol) in 70 ml of anhyd. MeOH was added powdered 2,4,6, - triisopropylbenzenesulfonylhydrazide (23.3 g, 0.078 mol), followed by 8 ml of conc HCl. The hydrazide quickly went into soln, and soon after a fine ppt began to appear. The reaction was then placed in a refrigerator overnight, and the resulting white solid was collected and washed with cold MeOH to give 32 g (85%) of **26** (m.p. 161–163° from MeOH). NMR (400 FT, $CDCl_3$): δ 7.88 (1H, bs); 7.59 (1H, d, J = 8); 7.17 (2H, s); 7.08 (1H, t, J = 8); 6.76 (1H, d, J = 8); 4.31 (2H, septet, J = 8); 3.79 (3H, s); 2.89 (1H, septet, J = 8); 2.85–2.76 (2H, m); 2.58–2.49 (m, 1H); 2.09–2.03 (1H, m); 1.75 (1H, t of t, J = 12, 4); 1.51–1.43 (2H, m); 1.31 (12H, d, J = 8); 1.24 (6H, d, J = 8); 0.98 (3H, t, J = 8). IR($CHCl_3$): 2960, 1600, 1550, 1462, 1257, 1150. (Found: C, 69.46; H, 8.14; N, 5.90; S, 6.42. Calc for $C_{28}H_{40}N_2O_3S$: C, 69.39; H, 8.32; N, 5.78; S, 6.20%).

2-Ethyl-1-hydroxymethyl-5-methoxy-3,4-dihydronaphthalene (**27**)

A soln of **26** (10.0 g, 0.021 mol) in 50 ml of dry THF was cooled to −78° and purged with N_2. Addition of n-BuLi (0.044 mol) in hexane over 15 min resulted in a deep orange colored dianion. This was stirred 3 hr at −78° and then warmed to rt to expel N_2 and generate the vinyl anion. After 30 min at rt the mixture was cooled in an ice bath and paraformaldehyde (1.32 g, 0.042 mol) was added. The reaction was stirred an additional 3hr, then poured into water and extracted with ether. The organic phase was washed with 1 N NaOH, H_2O, and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. Chromatography on SiO_2 with 3% acetone in hexanes yielded 2.0 g (45%) of **27** (m.p. 87–89° from ether).

DMF-$NaBH_4$ method. A soln of **26** (36.0 g, 0.074 mol) in 200 ml of dry THF was treated with n-BuLi (0.164 mol) in hexanes and the vinyl anion was generated as described above. The mixture was cooled in an ice bath and dry DMF (17.0 ml, 0.22 mol) was added. The reaction was stirred at rt overnight, then poured into water and extracted with ether. The organic phase was washed well with H_2O and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. Chromatography on SiO_2 with 3% acetone in hexanes gave an α,β-unsaturated aldehyde which was treated directly with $NaBH_4$ (1.7 g, 0.045 mol) in 70 ml of EtOH at rt for 1 hr. This was then poured into water, and extracted with ether. The ether phase was washed with H_2O and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. This gave 8.71 g (54%) of **27** which was identical to the alcohol obtained above. NMR ($CDCl_3$): δ 7.36–7.23 (2H, m); 6.92–6.78 (1H, m); 4.65 (2H, s); 3.90 (3H, s); 2.79 (2H, t, J = 8); 2.49–2.17 (4H, m); 1.52 (1H, bs); 1.20 (3H, t, J = 8). MS: 218 (M^+), 200 (100%), 187, 185, 171, 159. IR($CHCl_3$): 3450 (br), 1600, 1580, 1470, 1444, 1390. (Found: C, 77.27; H, 8.42. Calc for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%).

1(t-butyldimethylsiloxy)methyl-2-ethyl-5-methoxy-3,4-dihydronaphthalene (**28**)

To a soln of alcohol **27** (6.9 g, 0.032 mol) and imidazole (4.7 g, 0.069 mol) in 70 ml of dry DMF was added t-butyldimethylsilyl chloride (5.2 g, 0.035 mol). This was stirred under an atmosphere of N_2 at rt for 2 hr, then poured into water. The aqueous layer was extracted with 3:1 ether-pentane, and then the organic phase was washed with 10% HCl, H_2O, and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. This left 10.5 g (100%) of ether **28** as a clear oil which was used without further purification. NMR (CH_2Cl_2 = 5.25 as standard, $CDCl_3$): δ 7.20–7.16 (2H, m); 6.80–6.65 (1H, m); 4.60 (2H, s); 3.84 (3H, s); 2.82–2.69 (2H, m); 2.27–2.15 (4H, m); 1.11 (3H, t, J = 8); 0.96 (9H, s); 0.16 (6H, s). MS: 332 (M^+), 291, 275 (100%), 258. IR ($CHCl_3$): 1600, 1575, 1470, 1440, 1260, 1220.

1-(t-butyldimethylsiloxy)methyl-2-ethyl-6-formyl-5-methoxy-3,4-dihydronaphthalene (**29**)

A soln of ether **28** (5.8 g, 0.017 mol) and TMEDA (3.1 ml, 0.020 mol) in 40 ml of hexanes was cooled to −10° and purged with N_2. A pentane soln of t-BuLi (0.017 mol) was added over 10 min, and this was stirred 4 hr at 0°. The deep red soln was then inversely added dropwise, via a two headed needle, to a soln of dry DMF (2.6 ml, 0.034 mol) in 20 ml of dry THF at 0°. This was then stirred overnight at rt before being poured into dilute NH_4Cl and extracted with ether. The organic phase was washed with 10% HCl, H_2O, and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. Chromatography on SiO_2 with 3% acetone in hexanes gave 5.0 g (80%) of **29** (m.p. 50–51° from pentane). NMR(CH_2Cl_2 = 5.25 as standard, $CDCl_3$): δ 10.29 (1H, s); 7.62 (1H, d, J = 8); 7.29 (1H, d, J = 8); 4.53 (2H, s); 3.80 (3H, s); 2.79–2.63 (2H, m); 2.40–2.11 (4H, m); 1.06 (3H, t, J = 8); 0.85 (9H, s); 0.07 (6H, s). MS: 360 (M^+), 346, 303 (100%), 273. IR($CHCl_3$): 1680, 1595, 1560, 1455, 1420, 1386, 1335. (Found: C, 70.12; H, 9.17; Si, 7.59. Calc for $C_{21}H_{32}O_3Si$: C, 69.96; H, 8.94; Si, 7.79%).

1-(t-Butyldimethlysiloxy)methyl-2-ethyl-5-methoxy-6-[1-(7-methoxy-2-oxa-3-oxo)indanyl]-3,4-dihydronaphthalene (**30**)

A soln of 3-methoxybenzanilide (3.44 g, 0.015 mol) and TMEDA (4.8 ml, 0.031 mol) in 100 ml of dry THF was cooled to −78° and purged with N_2. A hexane soln of n-BuLi (0.030 mol) was added dropwise and this was stirred an additional 30 min at −78°. The mixture was warmed to −20° for 4 hr and then recooled to −78° before aldehyde **29** (5.4 g, 0.015 mol) in

80 ml of dry THF was added dropwise. The reaction was warmed to rt overnight, then poured into H_2O and extracted with ether. The ether phase was stirred vigorously with an equal volume of sat. oxalic acid soln for 2 hr. The layers were separated and the organic phase was washed with 10% HCl, H_2O, sat. $NaHCO_3$, and brine; then dried over $MgSO_4$ and evaporated at reduced pressure. Trituration of the resulting oil with ether—petroleum ether gave 5.9 g (80%) of phthalide **30** (m.p. 111–113° from ether). NMR (400 FT, $CDCl_3$): δ 7.57–7.51 (2H, m); 7.16 (1H, d, J = 8); 7.09 (1H, d, J = 8); 6.76 (1H, s); 6.65 (1H, d, J = 8); 4.42 (1H, d, J = 11); 4.37 (1H, d, J = 11); 3.77 (3H, s); 3.71 (3H, s); 2.87–2.68 (2H, m); 2.34 (2H, q, J = 7); 2.14 (2H, t, J = 8); 1.10 (3H, t, J = 8); 0.89 (9H, s); 0.08 (6H, s). MS: 494 (M^+), 441 (100%), 366, 234, 197. IR($CHCl_3$): 1770, 1615, 1500, 1300, 1280, 1260. (Found: C, 70.66; H, 7.97; Si, 5.88. Calc for $C_{28}H_{38}O_5Si$: C, 70.41; H, 7.74; Si, 5.68%).

6-(2-Carboxy-6-methoxyphenyl)methyl-2-ethyl-1-hydroxymethyl-5-methoxy-3,4-dihydronaphthalene (**31**)

A 500 ml Morton flask was charged with **30** (4.5 g, 9.1 mmol), Zn dust (50 g, excess), $CuSO_4$ (0.3 g, catalytic), 200 ml of 1 N NaOH, and 15 ml of pyridine. The mixture was stirred vigorously at reflux with an overhead stirrer for 48 hr. The cooled soln was filtered through filter aid, and washed with ether. The aqueous layer was acidified with conc. HCl then extracted well with $CHCl_3$. The organic phase was washed with 10% HCl, H_2O, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The white solid was collected and washed with pentane to give 3.3 g (95%) of **31** (m.p. 148–149° from ether–petroleum ether). NMR (400 FT, $CDCl_3$): δ 7.58 (1H, d, J = 8); 7.31 (1H, t, J = 8); 7.06 (1H, d, J = 8); 7.02 (1H, d, J = 8); 6.56 (1H, d, J = 8); 4.53 (2H, s); 4.41 (2H, s); 3.74 (3H, s); 3.67 (3H, s); 2.77 (2H, t, J = 8); 2.33 (2H, q, J = 8); 2.23 (2H, t, J = 8); 1.08 (3H, t, J = 8). MS: 382 (M^+), 365 (100%), 346, 331. IR(KBr): 3500 (br), 1700, 1460, 1270, 1200. (Found: C, 72.13; H, 6.90. Calc for $C_{23}H_{26}O_5$: C, 72.24; H, 6.85%).

5,7-Dimethoxy-2-ethyl-1-hydroxymethyl-3,4-dihydronaphthacene-6,11-dione (**33**)

To a soln of **31** (1.5 g, 3.9 mmol) in 30 ml of CH_2Cl_2 at 0° was added 1.5 ml of trifluoroacetic anhydride. This was stirred at 0° for 3 hr before 20 ml of water was added. After 10 min the layers were separated and the organic phase was washed with H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated under reduced pressure. The crude **32** [NMR (400 FT, $CDCl_3$): δ 8.07 (1H, s); 7.97 (1H, d, J = 8); 7.43 (1H, t, J = 8); 7.11 (1H, d, J = 8); 5.42 (2H, s); 4.13 (2H, s); 3.97 (3H, s); 3.86 (3H, s); 2.93 (2H, t, J = 8); 2.42 (2H, q, J = 8); 2.37 (2H, t, J = 8); 1.14 (3H, t, J = 8)] was taken up in 30 ml of CH_2Cl_2 and added dropwise over 3 hr to a mixture of 40% Triton B in MeOH (16.3 g, 39.0 mmol) in an additional 30 ml of MeOH while O_2 was passed through. Upon completion of addition O_2 was passed through the soln for an extra 3 hr before it was poured into 10% HCl. This was extracted with CH_2Cl_2, and the organic phase was washed to give 0.37 g (92%) of **24** (m.p. 199–201 from $CHCl_3$-hexanes) which was contaminated with *ca* 3% of the aromatic A-ring compound. This was used without further purification. NMR (400 FT, $CDCl_3$): δ 12.35 (1H, s); 12.19 (1H, s); 7.99 (1H, s); 7.83 (1H, d, J = 8); 7.66 (1H, t, J = 8); 7.28 (1H, t, J = 8); 4.69 (2H, s); 2.89 (2H, t, J = 8); 2.45 (2H, q, J = 8); 2.38 (2H, t, J = 8); 1.55 (1H, bs); 1.17 (3H, t, J = 8). MS: 350 (M^+), 333 (100%), 320, 305, 293. IR(KBr): 3500 (br), 1670, 1610, 1590, 1455, 1375, 1270. (Found: C, 71.70; H, 5.20. Calc for $C_{21}H_{18}O_5$: C, 71.99; H, 5.17%).

5,7-Dihydroxy-1,2-epoxy-2-ethyl-1-hydroxymethyl-3,4-dihydronaphthacene-6,11-dione (**34**)

To a soln of alcohol **24** (370 mg, 1.06 mmol) in 100 ml of CH_2Cl_2 was added 80% MCPBA (370 mg, 2.12 mmol) and 50 ml of 0.5 N $NaHCO_3$. This was stirred vigorously for 24 hr before the two layers were separated. The organic phase was washed with sat. $NaHSO_3$, H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The orange solid was collected and washed with 2:1 petroleum ether–ether to give 348 mg (90%) of **34** (m.p. 185–187° from $CHCl_3$-hexanes) which was used without further purification. With 10% HCl, H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The yellow solid was collected and washed with 1:1 MeOH-pentane to give 0.89 g (60%) of **33** (m.p. 233–234° from CH_2Cl_2-hexanes). NMR (400 FT, $CDCl_3$): δ 8.12 (1H, s); 7.85 (1H, d, J = 8); 7.64 (1H, t, J = 8); 7.31 (1H, d, J = 8); 4.72 (2H, s); 4.03 (3H, s); 3.93 (3H, s); 2.92 (2H, t, J = 8); 2.43 (2H, q, J = 8); 2.33 (2H, t, J = 8); 1.70 (1H, bs); 1.15 (3H, t, J = 8). MS: 378 (M^+), 363, 360, 348, 344, 330 (100%). IR(KBr): 3500 (br), 1670, 1660, 1580, 1470, 1445, 1360. (Found: C, 72.87; H, 5.97. Calc for $C_{23}H_{22}O_5$: C, 73.00; H, 5.85%).

5,7-Dihydroxy-2-ethyl-1-hydroxymethyl-3,4-dihydronaphthacene-6,11-dione (**24**)

To a soln of **33** (0.435 g, 1.15 mmol) in 40 ml of 1:1 pyridine–collidine was added benzoic acid (0.70 g, 5.75 mmol) and LiI (1.54 g, 11.50 mmol). This was purged with H_2, then heated to 145° for 2 hr. The cooled mixture was poured into 10% HCl and extracted well with $CHCl_3$. The organic phase was washed with 10% HCl until all the pyridine and collidine had been removed. This was then washed with H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The orange solid was collected and washed with 2:1 petroleum ether–MeOH.

Sharpless method: To a soln of (−)-diethyl-d-tartrate (0.50 ml, 2.9 mmol) and titanium (IV) isopropoxide (0.86 ml, 2.9 mmol) in 80 ml of dry CH_2Cl_2 was added alcohol **24** (0.20 g, 0.5 mmol) and 20 ml of dry CH_2Cl_2. After stirring for 5 min, t-butylhydrogenperoxide (1 M in CH_2Cl_2, 5.7 ml, 5.7 mmol) was added and the mixture was placed in a refrigerator at −10° for 48 hr. To this was then added 30 ml of 20% aqueous tartaric acid, and the mixture was stirred for 1 hr at rt. The organic phase was washed with 10% HCl, H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The crude oil was triturated with hexanes and filtered. This gave 180 mg (86%) of epoxide **34** which was identical to the one above. NMR (400 FT, $CDCl_3$): δ 12.34 (1H, s); 12.07 (1H, s); 8.23 (1H, s); 7.84 (1H, d, J = 8); 7.67 (1H, t, J = 8); 7.29 (1H, d, J = 8); 4.42 (1H, d, J = 12); 4.27 (1H, d, J = 12); 3.17 (1H, d of d, J = 12, 4); 2.54–2.45 (1H, m); 2.35–2.31 (1H, m); 2.10–2.01 (1H, m); 1.94–1.84 (2H, m); 1.59 (1H, bs); 1.13 (3H, t, J = 8). MS: 366 (M^+), 347, 345, 331, 317, 304, 290 (100%). IR($CHCl_3$): 3600, 1670, 1620, 1600, 1470, 1450, 1270. (Found: C, 68.46: H, 4.56. Calc for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95%).

5,7-Dihydroxy-1,2-epoxy-2-ethyl-1-formyl-3,4-dihydronaphthacene-6,11-dione (**35**)

To a soln of **34** (340 mg, 0.93 mmol) in 40 ml of CH_2Cl_2 was added PCC (600 mg, 2.79 mmol). This was stirred at rt for 24 hr then filtered through filter aid. The resulting soln was then chromatographed on SiO_2 preparative TLC plates (1000 μ) with 3% MeOH in CH_2Cl_2 as eluant. This gave 264 mg (78%) of yellow **35** (m.p. 210–212° from CH_2Cl_2-hexanes). NMR (400 FT, $CDCl_3$): δ 12.40 (1H, s); 12.01 (1H, s); 10.00 (1H, s); 8.05 (1H, s); 7.84 (1H, d, J = 8); 7.70 (1H, t, J = 8); 7.31 (1H, d, J = 8); 3.41 (1H, d of d, J = 17, 4); 2.55–2.46 (1H, m); 2.43–2.37 (1H, m); 2.03–1.92 (2H, m); 1.83–1.74 (1H, m); 1.10 (3H, t, J = 8). MS: 364 (M^+), 347, 345, 335, 317 (100%), 306. IR($CHCl_3$): 3600, 1730, 1670, 1620, 1605, 1470, 1450, 1270. (Found: C, 69.01; H, 4.53. Calc for $C_{21}H_{16}O_6$: C, 69.23; H, 4.42%).

1-Carbomethoxy-5,7-dihydroxy-1,2-epoxy-2-ethyl-3,4-dihydronaphthacene-6,11-dione (**36**)

To a soln of **35** (210 mg, 0.58 mmol) in 40 ml of 10% aqueous dioxane at 0° was added sulfamic acid (112 mg, 1.16 mmol) and powdered $NaClO_2$ (104 mg, 1.16 mmol). This was stirred for 15

min before being poured into $CHCl_3$ and washed with H_2O and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The crude solid was taken up in 30 ml of CH_2Cl_2 and cooled in an ice bath. A diazomethane soln in ether (prepared by treatment N-nitrosomethylurea with 10% KOH and ether) was added dropwise while monitoring the reaction by TLC. When reaction was complete, solvent was evaporated at reduced pressure and the yellow solid was collected and washed with pentane to give 215 mg (95%) of epoxyester **36** (m.p. 221–224° from CH_2Cl_2-hexanes). NMR (400 FT, $CDCl_3$): δ 12.41 (1H, s); 12.03 (1H, s); 7.83 (1H, d, J = 8); 7.76 (1H, s); 7.70 (1H, t, J = 8); 7.31 (1H, d, J = 8); 4.00 (3H, s); 3.26 (1H, d of d, J = 12, 4); 2.53–2.38 (2H, m); 1.97–1.89 (1H, m); 1.88–1.78 (1H, m); 1.76–1.66 (1H, m); 1.13 (3H, t, J = 8). MS: 394 (M^+), 379, 377, 367 (100%), 352, 335. IR($CHCl_3$): 3600, 1750, 1670, 1625, 1605, 1480, 1425, 1210. (Found: C, 66.62; H, 4.76. Calc for $C_{22}H_{18}O_7$: C, 66.99; H, 4.60%).

7-Deoxyaklavinone (**37**)

To a soln of epoxy ester **36** (300 mg, 0.76 mmol) in 40 ml of EtOH and 30 ml of triethanoamine was added 150 mg of 5% Pd–$BaSO_4$ which was stirred under 1 atm. of H_2 for 2.5 hr. The soln was then filtered through filter aid, and O_2 was bubbled through the soln for 15 min. This was then acidified with sat. oxalic acid and poured into $CHCl_3$. The organic phase was washed with 10% HCl, H_2O, sat. $NaHCO_3$, and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The yellow solid was collected and washed with 2:1 petroleum ether–ether to give 230 mg (76%) of **37** (m.p. 220–222° from MeOH–CH_2Cl_2, Lit. m.p. 224–225°). NMR (400 FT, $CDCl_3$): δ 12.51 (1H, s); 12.10 (1H, s); 7.82 (1H, d, J = 8); 7.67 (1H, t, J = 8); 7.66 (1H, s); 7.29 (1H, d, J = 8); 3.94 (1H, s); 3.73 (3H, s); 3.10–3.03 (1H, m); 2.90–2.80 (1H, m); 2.37–2.27 (1H, m); 1.96–1.90 (1H, m); 1.77–1.67 (1H, m); 1.65–1.58 (1H, m); 1.51 (1H, bs); 1.09 (3H, t, J = 8). MS: 396 (M^+), 378, 364, 340, 319 (100%), 307, 279. IR: 3600 (br), 1730, 1670, 1620, 1450, 1290.

Aklavinone (**2**)

N_2 was passed through a suspension of **37** (190 mg, 0.48 mmol) in 300 ml of CCl_4 for 15 min, which was then heated to 70° to dissolve the compound. When all the carbinol went into soln, AIBN (3 mg, catalytic) and 0.5 N Br_2 in CCl_4 (1.4 ml, 0.72 mmol) were added and 70° was maintained for 1hr. The reaction was monitored by TLC and additional Br_2 soln was added (in 0.1 ml portions) if necessary. When complete the reaction was cooled and washed with 10% $NaHSO_3$. The solvent was evaporated at reduced pressure to *ca* 10 ml and then stirred vigorously with 100 ml of 1:1 aqueous THF for 1 hr. This was then extracted with $CHCl_3$. The organic phase was washed with H_2O and brine; then dried over Na_2SO_4 and evaporated at reduced pressure. The resulting oil was triturated with hexanes and filtered. This gave 174 mg (88%) of (**2**) as an orange solid (m.p. 210–214° from benzene, Lit. m.p. 171–174°).[25] NMR (400 FT, $CDCl_3$): δ 12.73 (1H, s); 11.96 (1H, s); 7.83 (1H, d, J = 8); 7.71 (1H, s); 7.70 (1H, t, J = 8); 7.31 (1H, d, J = 8); 5.38 (1H, bs, $\nu_{\frac{1}{2}}$ = 10 Hz); 4.09 (1H, s); 3.85 (1H, bs); 3.70 (3H, s); 3.39 (1H, bs); 2.54 (1H, d of d, J = 12, 4); 2.27 (1H, d, J = 12); 1.77–1.68 (1H, m); 1.61–1.53 (1H, m); 1.10 (3H, t, J = 8). MS: 412 (M^+), 394, 377, 376 (100%), 361, 344, 335. IR($CHCl_3$): 3500 (br), 1730, 1675, 1630, 1450, 1290.

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[25] The (±)-**2** herein prepared is identical with natural aklavinone supplied by Dr. T. Oki (Sanraku Ocean Ltd.) and Dr. P. Confalone (Roche). Its identity was independently confirmed by Professor Y. Kishi through comparison with a sample of (±)-**2** synthesized in his laboratories.[5]