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REGIOSPECIFIC TOTAL SYNTHESIS OF (±)-DAUNOMYCINONE FROM AN 11-DEOXYDAUNOMYCINONE PRECURSOR

FRANK M. HAUSER* and VACELI M. BAGHDANOV
Department of Chemical, Biological and Environmental Sciences, Oregon Graduate Center, Beaverton, Oregon 97006 U.S.A.

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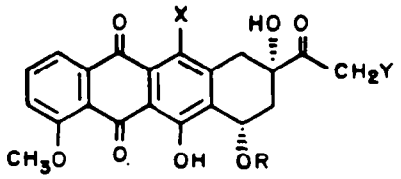
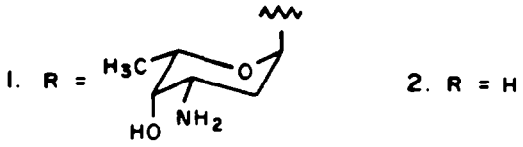
Abstract—A new route for large scale preparation of the 1(4H)-naphthalenone **4** from perillaldehyde **10** was developed. Condensation of **4** with the methoxyphthalidesulfone **3** gave the 11-deoxydaunomycinone precursor **5a** which was used as an intermediate to daunomycinone (**2a**).

The established therapeutic use of daunorubicin (**1a**)[1] and adriamycin (**1b**)[2] as anticancer agents[3] and the report that 11-deoxydaunorubicin (**1c**) and 11-deoxyadriamycin (**1d**) are less cardiotoxic[4] has generated strong interest in the total synthesis of these important compounds.[5-7]





a X = OH, Y = H
b X = Y = OH
c X = Y = H
d X = H, Y = OH

Background: Recently, we reported the use of the reaction sequence shown in Scheme 1 as a procedure for efficient regiospecific preparation of the acetyl substituted naphthacenone **6**,[7] an established intermediate to 11-deoxydaunomycinone (**2c**).[6e,f] At that time, it was recognized that introduction of an oxygen functionality at the 11-position in **5a** would provide a potentially expedient route to **9** which can be converted to daunomycinone (**2a**). In effect, **5a** could serve as a common intermediate to two important classes of anthracyclinones.

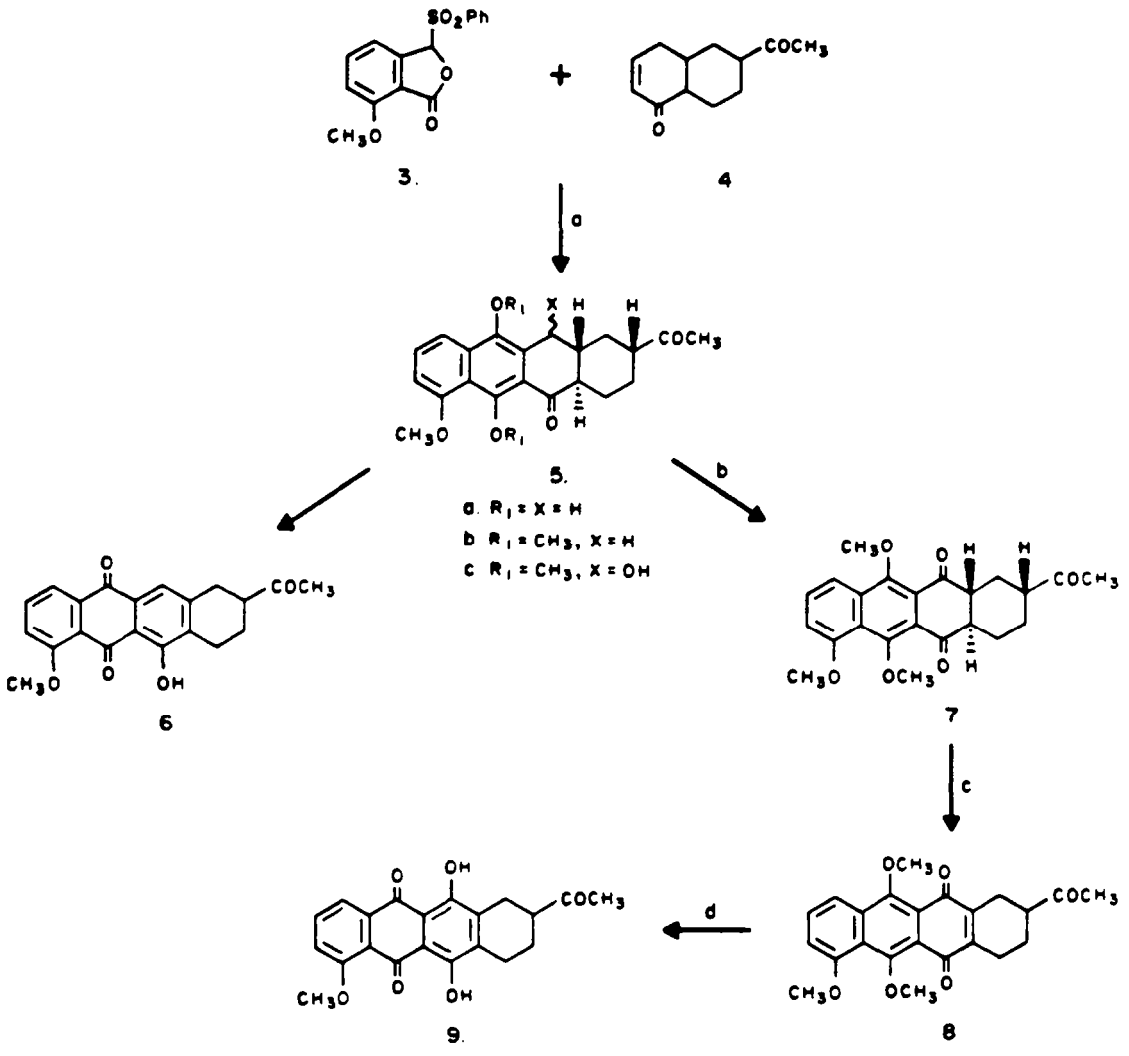
In the previously reported synthesis, several grams of **5a** were prepared through condensation of the phthalidesulfone **3**[7-9] with the naphthalenone **4**. The limitations imposed on the product quantity originate with the method of preparation of **4**. Large scale synthesis of this key intermediate was stymied by the required use of methyl copper at low temperature (−30°) under dilute reaction conditions to effect transformation of a diacid chloride intermediate to a dimethylketone.

In this paper, we describe the development of a new and practical route for large scale synthesis of the 1(4H)-naphthalenone **4**. Also presented is the development of a reaction sequence to transform the hydronaphthacenone **5a** to the established[5f,n] daunomycinone precursor **9**.

1(4H)-*Naphthalenone* (**4**): Because it has both a masked methyl ketone and the correct regiochemical pattern of functionalization, commercially available perillaldehyde (**10**) was selected as a starting material for the preparation of the 1(4H)-naphthalenone **4**. Another factor influencing this selection was that the unsaturated moiety in **10** was ideal for elaboration of the B-ring with an unsaturated enone fragment.

The conversion of perillaldehyde (**10**) to **4** was accomplished as shown in Scheme 2. Grignard addition of allylmagnesium bromide to **10** gave the homoallyl alcohol **11** (98%) which on oxy-Cope rearrangement (KH, DME, Δ)[10] furnished the aldehyde **12** in 73% yield as a mixture of geometric isomers. Reaction of **12** with methyllithium followed by Swern oxidation (ClCOCOCl, DMSO, Et_3N)[11] gave the methyl ketone **13** in 77 to 83% overall yield. Simultaneous oxidative cleavage of the allyl and isopropylidene functionalities in **13** was accomplished in a single step through ozonolysis (O_3, MeOH, −65°) with reductive workup (DMS, 12 hr). The initially received product (95% yield) was determined to be the keto dimethylacetal **14a** from the methoxyl absorptions at 3.29 ppm in its ^{1}H-NMR spectrum and from its quantitative hydrolysis to the aldehyde **14b** on brief treatment with dilute aqueous acid.

Two procedures were developed to transform the keto dimethylacetal **14a** to the 1(4H)-naphthalenone **4**. Simply refluxing a solution of **14a** in THF with aqueous hydrochloric acid for several hours gave, after chromatography, the naphthalenone **4** in approximately 52% yield. The yield proved to be somewhat erratic and a more reliable, although more involved, procedure was developed to convert **14a** to **4**. Brief exposure of **14a** to dilute hydrochloric acid in THF quantitatively furnished the aldehyde **14b**. Intramolecular aldol cyclization and dehydration to **4** and its hydrogen chloride addition product was accomplished by reacting **14b** with an ether solution of dry hydrogen chloride. Subsequent treatment of the mixture with triethylamine in benzene at reflux



Scheme 1.

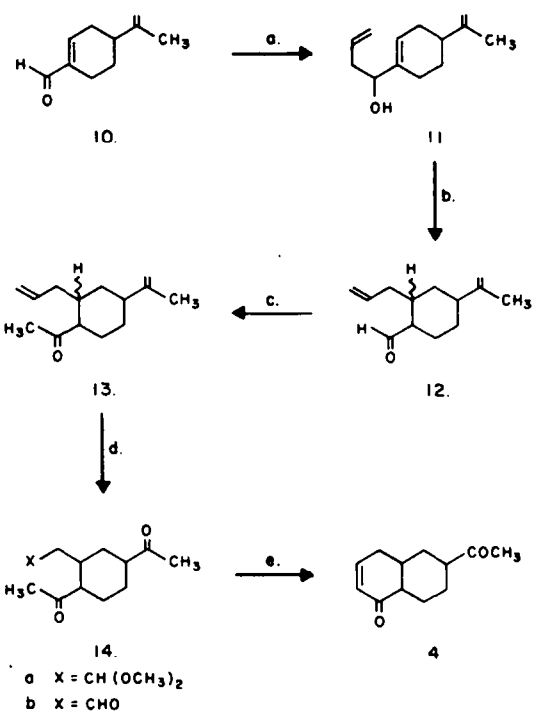
dehydrohalogenated the chlorine containing adduct to the 1(4H)-napthalenone **4**. Although **4** was crystalline, purification through fractional recrystallization was tedious, and ultimately distillation proved more expedient.

The developed sequence, which has been used to prepare 50 gram quantities of **4** from perillaldehyde (**10**), is quite practical since the reactions can be conducted on a large scale, and all the intermediates and the final product are readily purified by distillation.

7,9-Dideoxydaunomycinone (**9**): Standard condensation of the 1(4H)-naphthalenone **4** with the lithium t-butoxide generated anion of the phthalidesulfone **3** was used to produce the hydronaphthacenone **5a**.[7–9] As in earlier work, the occurrence of **5a** as a mixture of geometric isomers was evident only after methylation (K_2CO_3, Me_2SO_4, butanone, 2 days, Δ; 79%) to the dimethylether **5b**.[12] Equilibration of the initially received **5b** with sodium hydroxide in ethanol gave a single isomer with the all *trans* stereochemistry.

Homolytic bromination and solvolysis were envisioned as a means for the regiospecific introduction of an oxygen functionality at C-11 in the hydronaphthacene intermediate **5a**. MacKay *et al.*[13] have reported that benzylic bromination of the similarly substituted hydroanthracenone **15** is difficult but prior conversion to the borate derivative **15c** results in regiospecific introduction of a bromine atom. Because of the implied difficulties that might be encountered, a similar study, shown in Scheme 3, was conducted on derivatives of the anthracenone **15a** prior to undertaking the bromination of **5b**.

The hydroanthracenone **15a** was conveniently prepared through phthalidesulfone condensation with 2-cyclohexen-1-one,[9e] then methylated (Me_2SO_4, K_2CO_3) to furnish the dimethylether derivative **15b**. In contrast to the report of MacKay *et al.*, **15b** was found to smoothly undergo direct homolytic bromination (NBS, CCl_4, hν). Subsequent solvolysis (THF, H_2O) of the bromo intermediate afforded the hydroxy compound **15d** (65% overall yield) which on Collins oxidation[14] (CrO_3—2Py, CH_2Cl_2; 67%) gave the *leuco* quinone **16**. The existence of **16** solely in the keto form was shown by its ^{1}H-NMR spectrum; the methylene

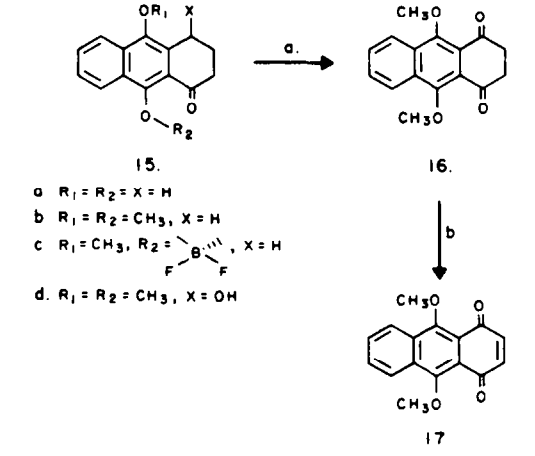


a allylmagnesium bromide (98%) b. KH/DME (73%)
c. 1 MeLi, Et2O 2 ClCOCOCl, DMSO, Et3N (83%) d 1 O3, MeOH 2 DMS (95%) e 1 HCl, Et2O 2 Et3N, PhH (52%)

Scheme 2.

protons occurred as a singlet at 3.05 ppm and there were no phenolic protons. The ability of selenium dioxide to effect dehydrogenation of 1,4-dione systems[15] was employed to chemically verify the structural assignment. Treatment of **16** with selenium dioxide gave the anthracenedione **17** in 90% yield.

The same reaction sequence was employed to transform the hydronaphthacene **5b** to **7**. Homolytic bromination (NBS, CCl_4, hv) of **5b** gave the 11-bromo intermediate which was solvolyzed in aqueous THF. The product, an isomeric mixture of 11-hydroxy compounds **5c** (60–70% overall yield), was readily



a 1 NBS, CCl_4 – H_2O (65%) 2 $CrO_3 \cdot 2Py$ (67%)
b SeO_2, CH_2Cl_2 (90%)

Scheme 3.

separated from other by-products by filtration through florisil. Jones (CrO_3, acetone) or Collins[14] (CrO_3—2Py, CH_2Cl_2) oxidation of **5c** gave the *leuco* quinone **7** (58–63% yield) as evidenced by the absence of phenolic absorptions in the ^{1}H-NMR spectrum.

In initially planning this approach to **9**, it was recognized that selective demethylation of the 5,12-methoxyl groups would be crucial to the overall success of this route, and might well require a number of manipulative steps.[5f] A straightforward solution to this potentially troublesome transformation was devised based on the well known capacity of boron halides to selectively demethylate methoxyl functionalities *ortho* to carbonyl groups.[16] First, it was necessary to alter the electronic properties of the carbonyl group in **7** so that only complexation, and not enol borate formation,[17] would occur. Dehydrogenating **7** to the tetrahydronaphthacenone **8** (84% yield) with selenium dioxide (CH_2Cl_2, cat. CF_3CO_2H) readily accomplished the desired change and generated the correct oxidation state of the final product. Treatment of **8** with boron trichloride at −60° proceeded in the expected regiospecific manner to furnish **9** (79% yield) which was identical with a sample prepared earlier by us using a different route.[5f]

EXPERIMENTAL

M.ps are uncorrected and were taken on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin–Elmer 621 spectrophotometer and expressed in wavenumbers. Proton and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer. Chemical shifts were reported as δ values in ppm relative to TMS. Mass spectra were obtained with a DuPont 21-491B spectrometer at an ionizing voltage of 70 eV. 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 and Co. Silica gel for column chromatography was from E. Merck (60, 70–230 mesh ASTM). Florosil for column chromatography was from Fisher Scientific (100–200 mesh).

Tetrahydrofuran (THF) was distilled from lithium aluminum hydride ($LiAlH_4$). CH_2Cl_2, CCl_4, and dimethylsulfoxide (DMSO) were distilled from CaH_2. Dimethoxyethane (DME), hexane, and t-BuOH were distilled from Na. Methylethylketone (MEK) was dried over $MgSO_4$ and filtered. Pyridine was distilled from BaO. Hexane, CH_2Cl_2, and EtOAc for extraction or chromatography purposes were simple distilled. Chromium trioxide was dried at 100° under vacuum. Allyl bromide and triethylamine were distilled prior to use. All other reagents were used without purification.

1 - (1 - *Hydroxy* - 3 - *butenyl*) - 4 - (1 - *methylethenyl*) - *cyclohexane* (**11**). Allyl magnesium bromide was prepared by dropwise addition of a soln of allyl bromide (22.8 ml, 0.264 mol) and 1,2-dibromoethane (13.6 ml, 0.160 mol) in ether (50 ml) to a chilled (0°) magnetically stirred mixture of Mg turnings (15.3 g, 0.640 mol) in anhyd ether (200 ml) under N_2. To insure that the Grignard reagent had completely formed, the reaction was stirred a further 2 hr. *o*-Perillaldehyde **10** (25 g, 0.150 mol) in ether (50 ml) was added dropwise over 1 hr to the still chilled Grignard reagent, then stirred overnight. The excess Mg was filtered off using a Buchner funnel with no filter paper and the resulting soln was quenched by addition of excess NH_4Cl aq (400 ml). The layers were separated and the aqueous phase further extracted with ether (2 × 200 ml). The combined organic layers were washed successively with NH_4Cl aq (200 ml), $NaHCO_3$ aq (200 ml), water (200 ml) and brine. Evaporation of the ether at reduced pressure and distillation of the residue gave 30 g (93%) of **11** as a light yellow oil with b.p. 102–105° (1.5 mm) which was homogeneous by TLC. ^{1}H-NMR δ 6.0–5.5 (m, 2H), 5.30–5.00 (m, 2H), 4.71 (brd s,

2H), 4.03 (t, 1H, J = 8 Hz), 1.73 (s, 3H), 2.4–1.0 (m, 8H); mass spectrum, *m/z* 192 ($M^{+\cdot}$); IR(film) cm^{-1} 3400, 3080, 1640, 990, 910, 880.

2 - (2 - *Propenyl*) - 4 - (1 - *methylethenyl*) - *cyclohexane carboxaldehyde* (**12**). KH in oil (227 g, 35%, 79.5 g KH, 1.70 mol) was washed successively with dry hexane (3 × 200 ml) and once with dry DME (200 ml) to remove the oil, then suspended in dry DME (1–1.5 l) with magnetic stirring under N_2. The alcohol **11** (95.6 g, 0.498 mol) in DME (100 ml) was slowly added dropwise to the hydride suspension so as to maintain a moderate rate of H_2 evolution. Once addition was completed, the mixture was stirred for 0.5 hr at room temp to ensure anion formation. The orange–red soln was heated at reflux for 48 hr and during this period it turned dark red. The reaction was cooled to room temp and the excess KH was decomposed by dropwise addition of isopropyl alcohol (160 ml). Addition of glacial AcOH (120 ml) to neutralize the reaction produced a ppt which dissolved on addition of water (200 ml). The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 200 ml). The combined organic solutions were evaporated at reduced pressure and the resultant oil was taken up in ether (800 ml) and washed successively with $NaHCO_3$ aq (2 × 200 ml) and brine (200 ml), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Distillation of the residue gave 70 g (73%) of **12** as a light yellow oil with b.p. 90–95° (3 mm). The ^{1}H-NMR spectrum and a TLC showed the product to be a 1:1 mixture of isomeric aldehydes. ^{1}H-NMR δ 9.71, 9.67 (s, 1H-combined), 6.0–5.3 (m, 1H), 5.20–4.80 (m, 2H), 4.69 (brd s, 2H), 1.71, 1.67 (s, 3H-combined), 2.6–1.0 (m, 11H). IR(film) cm^{-1} 3080, 2700, 1730, 1645, 995, 910, 885. (Found: C, 81.31; H, 10.32. Calc for $C_{13}H_{20}O$: C, 81.20; H, 10.48%).

1 - *Acetyl* - 4 - (1 - *methylethenyl*) - 2 - (2 - *propenyl*) - *cyclohexane* (**13**). A soln of **12** (70 g, 0.365 mol) in ether (200 ml) was added dropwise over a 1 hr period to a chilled (−10–0°), magnetically stirred solution of MeLi (316 ml, 1.5 M, 0.474 mol) in anhyd ether (200 ml) under N_2. The reaction was heated at reflux for 10 min and then quenched by the slow addition of water (200 ml) followed by glacial AcOH (30 ml). The layers were separated and the organic phase was washed with water (2 × 200 ml), $NaHCO_3$ aq (100 ml) and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 74.3 g (98%) of **12** which was used in the next step without purification. A TLC of the product showed two spots. ^{1}H-NMR δ 5.9–5.3 (m, 1H), 5.15–4.90 (m, 2H), 4.68 (brd s, 2H), 4.3–3.3 (m, 1H), 1.69 (s, 3H), 1.25 (s, 3H), 2.4–1.8 (m, 13H), IR(film) cm^{-1} 3380, 3080, 1645, 990, 905, 890.

To a chilled (−60°) magnetically stirred soln of oxalyl chloride (25.3 ml, 0.288 mol) in dry CH_2Cl_2 (500 ml) under N_2 was slowly added a soln of DMSO (40.8 ml, 0.577 mol) in CH_2Cl_2 (100 ml) over a 20 min period. Then a soln of the above alcohol (30.0 g, 0.144 mol) in CH_2Cl_2 (200 ml) was added slowly over a 25 min period. The reaction was stirred for an additional 25 min. Then Et_3N (120 ml) was added in a thin stream which produced a ppt. After an additional 15 min, the reaction was warmed to room temp and the ppt dissolved. Water (150 ml) was added and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 200 ml) and the combined organic layers were washed with Na_2CO_3 aq (100 ml) and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Distillation of the residue at reduced pressure gave 24.6 g (82%) of **13** as a light yellow oil with b.p. 90–100° (2 mm). The ^{1}H-NMR spectrum and a TLC analysis showed the product was a mixture of isomeric ketones. ^{1}H-NMR δ 5.9–5.4 (m, 1H), 5.26–4.84 (m, 2H), 4.68 (m, 2H), 2.14, 2.10 (s, 3H-combined), 1.70, 1.60 (s, 3H-combined), 2.4–1.0 (m, 9H). IR (film) cm^{-1} 3080, 1715, 1645, 990, 912, 890; mass spectrum, *m/z* 206 ($M^{+\cdot}$).

1,4 - *Diacetyl* - 2 - (2,2 - *dimethoxyethyl*) - *cyclohexane* (**14a**). O_3 was bubbled through a cold (−70°) soln of **13** (29.1 g, 0.141 mol) in MeOH (300 ml) until the blue color of O_3 persisted (~ 3.5 hr). The ozonolysis apparatus was turned off and O_2 followed by N_2 was flushed through the reaction until the blue color of excess O_3 disappeared. To the still cold reaction was added dimethyl sulfide (100 ml) and the mixture allowed to warm to room temp and stir overnight. When a starch–iodide test was negative, nitrogen was flushed through the soln to remove excess dimethyl sulfide. The soln was concentrated at reduced pressure at room temp to one-fourth the original volume, then diluted with EtOAc (200 ml) and brine (100 ml). The EtOAc layer was separated, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to yield 33.7 g (94%) of the dimethyl acetal **14a** which was homogeneous by TLC but an iosmeric mixture by NMR and was used in the next step without further purification. ^{1}H-NMR δ 4.6–4.2 (m, 1H), 3.48, 3.31, 3.21 (s, 6H-combined), 2.15, 2.11 (s, 6H-combined), 2.6–1.2 (m, 9H). IR(film) cm^{-1} 1700; mass spectrum, *m/z* 226 ($M - OCH_3)^{+\cdot}$.

6 - *Acetyl* - 4*a*,5,6,7,8,8a - *hexahydro* - 1(4*H*) - *naphthalenone* (**4**). Two procedures were employed to transform **14a** to **4**. *Method A*: The dimethylacetal **14a** (14.1 g, 55 mmol) was dissolved in THF (180 ml) containing HCl (6 N, 80 ml) and magnetically stirred at room temp (0.5 hr). The mixture which turned green was warmed on a steam bath for 20 min and NaCl (excess) and ether (80 ml) were added. The mixture was stirred with heating for 30 min and then at room temp for 40 min. The layers were separated and the aqueous phase was further extracted with ether (500 ml). The combined ether solns were washed with $NaHCO_3$ aq (200 ml) and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (100 g, benzene) gave 5.6 g (53%) of **4** as a mixture of isomers which solidified on standing. This material exhibited identical TLC behavior and had a ^{1}H-NMR spectrum corresponding to an alternatively prepared sample of **4**. *Method B*: The dimethyl acetal **14a** (28.7 g, 112.0 mmole) dissolved in a mixture of THF (50 ml) and HCl (1N, 60 ml) was stirred at room temp for 2 hr. Solid $NaHCO_3$ (excess) was added and the mixture extracted with EtOAc (2 × 100 ml). The organic phases were combined and successively washed with water (100 ml), $NaHCO_3$ aq (100 ml), and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 25.2 g of **14b**. ^{1}H-NMR δ 9.71 (s), 2.7–1.0 (m).

An anhyd ether soln of HCl (0.97 N, 110 ml) was added to a magnetically stirred soln of the above aldehyde in anhyd ether (325 ml) under N_2. The mixture was stirred at room temp for 20 hr, then excess sat $NaHCO_3$ aq was added and the layers separated. The ether soln was washed with water (200 ml), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 23.8 g of a dark oil. A ^{1}H-NMR spectrum of this material showed the presence of the enone **4**. A septet at ~ 4.05 ppm indicated some HCl addition product of the enone **4** was present. In order to convert this secondary material back to the naphthalenone **4**, the oil was taken up in benzene (200 ml) and Et_3N (15 ml) was added. The mixture was heated at reflux for 2.5 hr, then cooled. The benzene soln was washed with water (200 ml), HCl (2N, 200 ml), water (200 ml), and KOH (1 N, 100 ml), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Filtration of the residue through silica gel (10 g, EtOAc) yielded 23.0 g of a viscous oil which was extracted with hot hexane (liquid–liquid extractor). Evaporation of hexane under vacuum gave 18.5 g (64% from the acetal) of **4** which crystallized upon cooling. After two recrystallizations from hexane the material had m.p. 94–99°. A more expedient procedure for purification of **4** was to distill (b.p. 120°, 0.8 mm) the product from the initial chromatography. ^{1}H-NMR δ 7.08–6.80 (m, 1H), 6.10–5.80 (m, 1H), 2.16 (s, 3H), 2.60–1.10 (m, 11H). ^{13}C-NMR δ 210.6, 199.9, 148.4, 129.3, 50.0, 39.9, 34.5, 33.2, 27.8, 27.6, 24.6; mass spectrum, *m/z* 192 ($M^{+\cdot}$). The TLC behavior, IR, ^{1}H- and ^{13}C-NMR spectra were identical with that of an alternatively prepared sample.[7]

9 - *Acetyl* - 5,12 - *dihydroxy* - 4 - *methoxy* - 7,8,9,10,10a,11 - *hexahydro* - 6(6aH) - *naphthacenone* (**5a**). The phthalide sulfone **3** (10.0 g, 32.9 mmol) was added in powder form to a magnetically stirred cold (−70°C) soln of lithium t-butoxide (98.7 mmol) prepared from n-BuLi (2.1 M, 47.0 ml, 98.7 mmol) and t-BuOH (9.6 ml, 102 mmol) in dry THF (100 ml). The resulting yellow soln was stirred for 15 min, then **4** (6.63 g, 34.5 mmol) was added in powder form. The reaction was stirred for 15 min during which time the soln turned red. The ice bath was

removed and the reaction, while stirring, was allowed to come to room temp and react for 2 hr. HCl was added (4 M, 25 ml, 100 mmol) giving a yellow soln which was concentrated under reduced pressure to one-half volume. The precipitated product was filtered off and transferred into boiling acetone (250 ml). The soln, upon cooling, was filtered to yield 9.0 g (77%) of **5a** as a yellow powder with m.p. 223–227°. ^{1}H-NMR (1.5% CF_3CO_2H—$CDCl_3$) δ 7.8–7.4 (m, 3H), 6.94 (dd, 1H, J = 8 Hz, J = 2 Hz), 4.03 (s, 3H), 2.31 (s, 3H), 3.5–1.2 (m, 11H); mass spectrum, *m/z* 354 ($M^{+\cdot}$).

9 - *Acetyl* - 4,5,12 - *trimethoxy* - 7,8,9,10,10a,11 - *hexahydro* - 6(6aH) - *naphthacenone* (**5b**). Anhyd K_2CO_3 (87 g, 630 mmol) and dimethylsulfate (48 ml, 50.8 mmol) were added to **5a** (9.0 g, 25.4 mmol) dissolved in dry methyl ethyl ketone (1 l). The mechanically stirred mixture was heated at reflux for two days. The reaction was cooled and the carbonate was filtered off and washed with hot methyl ethyl ketone (700 ml). Et_3N (100 ml) was added to the filtrate and stirred for several hours to destroy excess dimethyl sulfate. The solvent was evaporated at reduced pressure and the residue was taken up in EtOAc (900 ml) and washed with water (3 × 500 ml); then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Repeated recrystallization of the yellow residue from EtOAc-hexanes gave 6.14 g (63%) of pure **5b** with m.p. 178–180°. Chromatography of the combined recrystallization filtrates on silica gel (100 g, 10–20% EtOAc-hexanes) furnished 2.25 g (23%; 88% overall) of **5b** as a mixture of geometric isomers. Brief treatment of this mixture with alcoholic NaOH gave a single product with TLC, behavior, ^{1}H-NMR spectrum and m.p. identical with the major isomer. ^{1}H-NMR δ 7.7–7.4 (m, 2H), 6.86 (d, 1H, J = 8 Hz), 3.99 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 2.20 (s, 3H), 3.6–1.3 (m, 11H); mass spectrum, *m/z* 382 (M^+).

9 - *Acetyl* - 11 - *hydroxy* - 5,6,12 - *trimethoxy* - 7,8,9,10,10a,11 - *hexahydro* - 6(6aH) - *naphthacenone* (**5c**). To **5b** (4.0 g, 10.5 mmol) dissolved in hot dry CCl_4 (1.3 l) was added N-bromosuccinimide (2.3 g, 12.6 mmol). The mixture was magnetically stirred and heated at reflux under illumination (275 W sunlamp) for exactly 20 min, then immediately chilled in an ice bath. The precipitated succinimide was filtered off and the CCl_4 evaporated at reduced pressure (bath < 40°). The residue was taken up in THF (300 ml), water (300 ml) was added and the mixture stirred at room temp for 2.5 hr. The reaction solution was concentrated under vacuum to 2/3 volume and sat $NaHCO_3$ aq (50 ml) was added. The mixture was extracted with EtOAc (3 × 150 ml) and the organic phase was washed with water (100 ml) and brine, then dried (Na_2SO_4), filtered, and evaporated at reduced pressure. Chromatography of the residue on florosil (100 g, 10% EtOAc-CH_2Cl_2 followed by MeOH) yielded 2.68 g (64%) of nearly pure **5c** which after recrystallization (CH_2Cl_2—CCl_4) had m.p. 123–125°. ^{1}H-NMR ($CDCl_3$) δ 7.7–7.3 (m, 2H), 6.84 (d, 1H, J = 9 Hz), 5.14 (brd s, 1H), 3.97, 3.86, 3.84 (s, 9H-combined), 2.17, 2.05 (s, 3H-combined), 3.3–1.5 (m, 10H); mass spectrum, *m/z* 398 ($M^{+\cdot}$).

9 - *Acetyl* - 4,5,12 - *trimethoxy* - 6a,7,8,9,10,10a - *hexahydro* - *naphthacene* - 6,11 - *dione* (**7**). The alcohol **5c** (5.15 g, 12.9 mmol) dissolved in CH_2Cl_2 (50 ml) was added in one portion to a magnetically stirred soln of Collins reagent prepared from pyridine (42 ml, 0.52 mol) and CrO_3 (15.5 g, 0.155 mol) in CH_2Cl (400 ml). The reaction was stirred at room temp for 1 hr, then decanted, and the CH_2Cl_2 soln evaporated. Both the residue from the reaction and the evaporation were extracted with hot EtOAc (3 × 200 ml) which was then filtered. The combined EtOAc extracts were washed with Na_2CO_3 aq (2 × 100 ml), water (200 ml) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure to give 2.75 g (54%) of **7** as a 1 : 1 mixture of isomers which was used in the next step without further purification. ^{1}H-NMR δ 7.96 (d, 1H, J = 9 Hz), 7.59 (t, 1H, J = 9 Hz), 7.06 (d, 1H, J = 9 Hz), 4.02, 3.99, 3.97, 3.95 (s, 9H-combined), 2.21, 2.14 (s, 3H-combined), 2.3–1.4 (m, 9H); mass spectrum, *m/z* 396 ($M^{+\cdot}$).

9 - *Acetyl* - 4,5,12 - *trimethoxy* - 7,8,9,10 - *tetrahydro* - *naphthacene* - 6,11 - *dione* (**8**). A mixture of **7** (2.65 g, 6.7 mmol), seleniun dioxide (1.49 g, 13.4 mmol), trifluoroacetic acid (4 ml) and water (2 ml) in CH_2Cl_2 (250 ml) was stirred at room temp for 3 hr. The reaction was decanted and the residue was washed with CH_2Cl_2. Addition of CaO-solution (200 ml) to the combined organic layer precipitated colloidal selenium and gave an emulsion. The selenium was removed by filtration through a celite pad and the organic layer was separated, washed with water (200 ml) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Chromatography of the residue on silica gel (100 g, 0–15% EtOAc—CH_2Cl_2) gave 1.98 g (75%) of **8** as orange crystals with m.p. 183–185° after recrystallization (CH_2Cl_2—CCl_4). ^{1}H-NMR δ 7.94 (d, 1H, J = 9 Hz), 7.60 (t, 1H, J = 9 Hz), 7.06 (d, 1H, J = 9 Hz), 4.01 (s, 6H), 3.96 (s, 3H), 2.27 (s, 3H), 2.6–2.2 (m, 5H); mass spectrum, *m/z* 394 ($M^{+\cdot}$). (Found : C, 69.90; H, 5.60. Calc for $C_{23}H_{22}O_6$: C, 70.03; H, 5.62%).

9 - *Acetyl* - 6,11 - *dihydroxy* - 4 - *methoxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* (**9**). Boron trichloride (60 ml, 1 M soln in CH_2Cl_2, 60 mmol) was added to a soln of **8** (1.83 g, 4.6 mmol) in dry CH_2Cl_2 (250 ml) at −60° under N_2 and the mixture magnetically stirred for 3 hr. MeOH (20 ml) was added to destroy the excess boron trichloride and the dark mixture was allowed to warm to room temp. NaOH aq (2 N, 130 ml) was added and the resulting blue soln was stirred for 1 hr. Acidification with HCl (12 M, 10–20 ml) gave a deep red-colored CH_2Cl_2 soln and a red ppt which was neither soluble in CH_2Cl_2 nor water and was presumed to be the boron complex of **9**. In order to hydrolyze the complex, the CH_2Cl_2 soln and the ppt were combined and the solvent evaporated at reduced pressure. The residue was taken up in MeOH (200 ml) containing NaOH (10 ml, 6 N) and stirred for 2 hr and then acidified with HCl (12 M). The resulting mixture was neutralized with $NaHCO_3$ aq and concentrated, and the residue repeatedly extracted with EtOAc (100 ml). The combined EtOAc extracts were evaporated and the dark red residue was taken up in CH_2Cl_2 (200 ml) and filtered through silica gel (20 g). The eluted material was recrystallized from CH_2Cl_2-hexane to give 1.35 g (79%) of **9** as red crystals with m.p. 244–247°. The TLC behavior and the ^{1}H-NMR spectrum of **9** were identical with an alternatively prepared sample [5f] and a mixed m.p. was undepressed. ^{1}H-NMR δ 8.04 (d, 1H, J = 8 Hz), 7.74 (t, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz), 4.08 (s, 3H), 3.2–2.4 (m, 5H), 2.29 (s, 3H); mass spectrum, *m/z* 366 ($M^{+\cdot}$).

1 - *Hydroxy* - 9,10 - *dimethoxy* - 2,3 - *dihydro* - 1(4H) - *anthracenone* (**15d**). To the dimethyl ether **15b** (2.4 g, 9.4 mmol) dissolved in dry boiling CCl_4 (1 l) under N_2 was added N-bromosuccinimide (2.0 g, 11.3 mmol) and the mixture heated at reflux was illuminated with a sunlamp for exactly 20 min. The reaction was then immediately chilled in an ice bath and the precipitated succinimide filtered off. The solvent was evaporated under vacuum (bath < 40°) and the dark residue redissolved in THF (100 ml) containing water (100 ml) and stirred at room temp for 1 hr. Solid $NaHCO_3$ (4 g) was added to the soln which was then extracted with EtOAc (4 × 50 ml). The combined organic phases were washed with water (100 ml) and brine (50 ml), then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography of the residue on florosil (50 g) with hexanes-CH_2Cl_2 (1 : 1) yielded 1.7 g (65%) of essentially pure **15d** with m.p. 124–126° (CH_2Cl_2-hexane). ^{1}H-NMR δ 8.3–8.1 (m, 1H), 8.1–7.9 (m, 1H), 7.7–7.4 (m, 2H), 5.47 (brd s, 1H), 3.97, 3.95 (s, 6H-combined), 3.34 (brd s, 1H), 3.2–2.0 (m, 4H).

9,10 - *Dimethoxy* - 2,3 - *dihydroanthracene* - 1,4 - *dione* (**16**). To a soln of Collins reagent prepared from pyridine (9.5 ml, 118 mmol) and CrO_3 (5.9 g, 59 mmol) in dry CH_2Cl_2 (130 ml) was added a soln of **10d** (1.54 g, 5.7 mmol) in CH_2Cl_2 (23 ml) in one portion. After stirring for ½ hr at room temp under N_2, ether (50 ml) was added and the mixture filtered through celite. The filtrate was washed with water (75 ml) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was recrystallized (ether–hexane) to give 1.02 g (67%) of orange–yellow needles with m.p. 137–140°. ^{1}H-NMR δ 8.5–8.3 (m, 2H), 7.8–7.6 (m, 2H), 4.06 (s, 6H), 3.06 (s, 4H); mass spectrum, *m/z* 270 ($M^{+\cdot}$).

9,10 - *Dimethoxy* - 1,4 - *anthracenedione* (**17**). To the anthraquinone **16** (300 mg, 1.1 mmol) dissolved in a soln of CH_2Cl_2 (10 ml) and *p*-dioxane (10 ml) was added selenium

dioxide (246 mg, 2.2 mmol) and heated to reflux for 2 hr. Then dilute HCl (30 ml, 4 N) and ether (60 ml) were added and the mixture filtered and the layers separated. The aqueous layer was further extracted with ether (2 × 50 ml), then washed with water (50 ml), brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was recrystallized (MeOH) to yield 270 mg (90%) of **17** as orange crystals with m.p. 192–195°. ^{1}H-NMR δ 8.5–8.3 (m, 2H), 7.9–7.7 (m, 2H), 6.89 (s, 2H), 4.06 (s, 6H). (Found: C, 71.60; H, 4.55. Calc for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%).

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[17] Attempted demethylation of **7** using boron trichloride gave complex product mixtures. This observation led us to postulate that the failure to achieve complete reaction was a consequence of the formation of enol borate derivatives which are likely to be less reactive toward demethylation.