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AN EFFICIENT, REGIOSPECIFIC SYNTHESIS OF (±)-DAUNOMYCINONE

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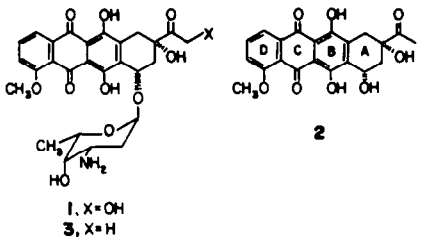
Abstract—The development of a general strategy for the control of regiochemistry in the Diels–Alder reactions of substituted naphthazarins is described. Application of this strategy to the synthesis of (±)-daunomycinone (2) employs two successive regiochemically controlled Diels–Alder reactions and leads to a ten-step, regiospecific synthesis of (±)-2 in 36% overall yield (Scheme 4).

The efficacy of Adriamycin (1) and other anthracyclines in the treatment of human cancers[1] has stimulated vigorous synthetic activity for the past decade.[2] In 1980 we reported in a brief communication[3] a short, efficient synthesis of racemic daunomycinone (2), the aglycone of daunomycin (3), which was a culmination of several

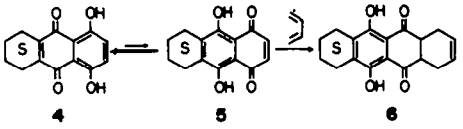


1, X = OH
3, X = H

2

years of effort in anthracyclinone synthesis. The objective of this paper is to provide an overview of the stages involved in the conceptual development of that synthesis and to record the experimental details of its realization.

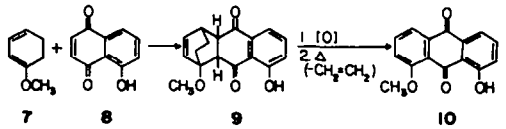
Our approach to the construction of the tetracyclic nucleus of daunomycinone (2), initially undertaken without regard to regiochemistry, was suggested by two previous reports in the literature. The first (Eq. 1),[4] due



4 5 6

(Eq. 1)

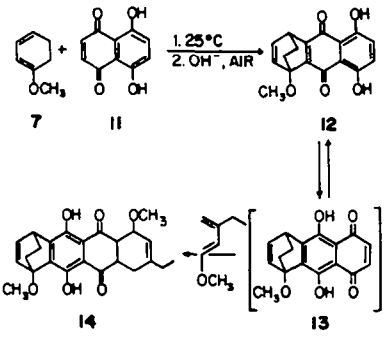
to Fariña and Vega, indicated that substituted naphthazarins, e.g., 4, exist primarily in the tautomeric form exemplified in 4. But while 4 is the favoured isomer, it nonetheless exists in a facile equilibrium with the minor tautomer 5 and if one adds a diene to this tautomeric equilibrium the minor tautomer (5) can be selectively trapped out in a Diels–Alder reaction to give the linearly annelated adduct 6 (Eq. 1). The second report, due to Birch and Powell,[5] provided a method (Eq. 2) for annelating an aromatic ring onto a quinone.



7 8 9 10

(Eq. 2)

Amalgamation of these two concepts using a model diene as the A-ring synthon afforded an expeditious route to the desired tetracyclic system (Scheme 1).[6]

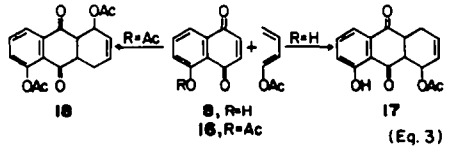


7 11 12 14 13

Scheme 1.

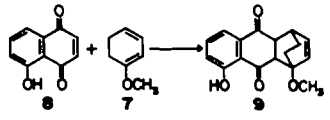
Scrutiny, as detailed elsewhere,[6] of the regiochemical outcome of this sequence indicated, however, that the principal regioisomer produced possessed the undesired regiochemistry indicated in 14. We had thus developed a regioantiselective approach to daunomycinone (2); there remained some room for improvement.

Additional data in the literature suggested a possible solution to our predicament. Specifically, in conjunction with work ultimately culminating in the synthesis of terramycin, Inhoffen, Muxfeldt *et al.* observed (Eq. 3)[7] that while the Diels–Alder reaction of juglone (8) with 1-acetoxybutadiene gives a product wherein 17 is the principal (but not exclusive) regioisomer produced, use of juglone acetate (16), leads to a reversal in regiochemistry, affording 18 as the principal (but again not exclusive) adduct. Some years later Birch and



18 8, R=H 16, R=Ac 17

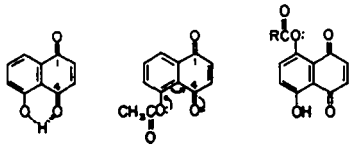
(Eq. 3)



8 7 9

(Eq. 4)

Powell had reported[5] that reaction of juglone (**8**) with 1-methoxycyclohexa-1,3-diene (**7**) affords (Eq. 4) adduct **9** regiospecifically. While Inhoffen, Muxfeldt *et al.*[7] did not provide any rationale to account for the regiochemical dichotomy embodied in Eq. 3, Birch and Powell[5] suggested that the regiospecificity of the reaction in Eq. 4 could be rationalized by taking into account the H-bonding interaction between the *peri*-OH group and the C-4 carbonyl (see **19**). In effect, they

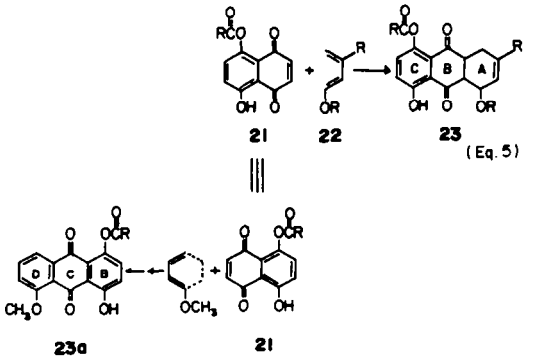


19 **20** **21**

proposed that the H-bonding interaction would drain electron density away from the C-4 CO group, thereby rendering it the most electron deficient (and hence regiochemically determining) substituent on the C_2—C_3 double bond.

If that hypothesis were correct, it seemed to us that the opposite directing effect of the *peri*-acetoxy group (Eq. 3) could be similarly rationalized, since delocalization of the lone pair electrons on the oxygen (see arrows in **20**) into the C-4 CO would render the C-4 CO the more electron rich of the two CO groups and the C-1 CO would, by default, determine the regiochemical outcome.[8,9]

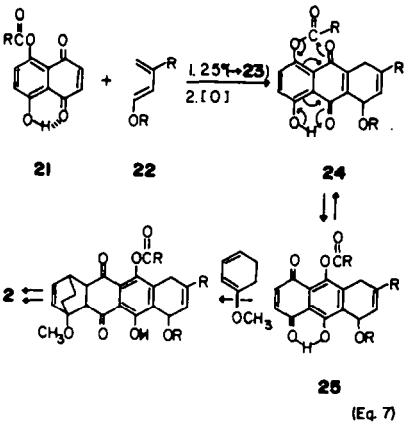
Furthermore, it seemed to us that if the two foregoing hypotheses were valid, incorporation of both an OH group and an acyloxy group into a single molecule (e.g., **21**) so that their opposing directing effects could operate in a complementary fashion might allow for a high degree of orientational control. Thus, if **21** were to serve as a BC-ring synthon and undergo cycloaddition with a diene such as **22**, expeditious incorporation of the A-ring would result (Eq. 5). Alternatively, were **21** to function as a CB (as opposed to a BC) synthon, Diels–Alder reaction as indicated in Eq. 6 would permit the rapid deployment of the D-ring (*cf* Eq. 2).



21 **22** **23** (Eq. 5)

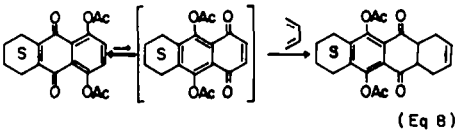
23a **21** (Eq 6)

Of singular interest to us was the possibility that two successive Diels–Alder reactions patterned after Eqs 5 and 6 might be employed to quickly assemble the tetracyclic framework of the anthracyclinone nucleus with full regiochemical control. The basic concept is outlined in Eq. 7. Crucial to the success of the plan was the putative equilibrium between **24** and **25**. The existence of this equilibrium would, *inter alia*, provide a



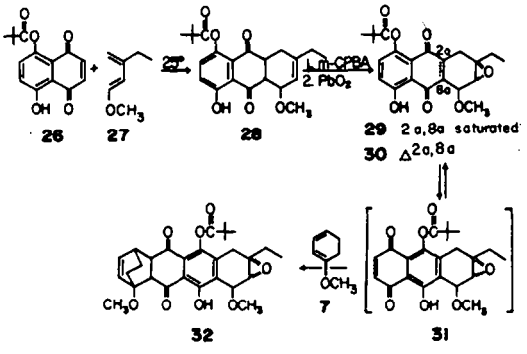
21 **22** **24** **25** (Eq. 7)

vehicle for the intramolecular transfer[10] of the directing groups, thereby bringing the same regiochemical control to the second Diels–Alder as operated in the first. The possibility that such a **24** ⇄ **25** equilibrium might indeed obtain was suggested by the observations of Fariña and Vega[4] summarized in Eqs 1 and 8.



(Eq 8)

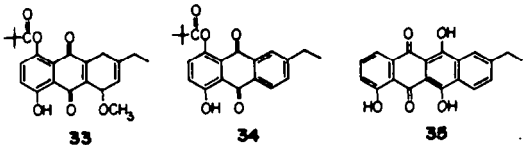
Our hopes were borne out by model studies (Scheme 2). Thus, as previously reported,[11] Diels–Alder reaction between **26** and **27** proceeded regiospecifically to provide **28**. Attempts to oxidize **28** to **33** were derailed by formation of **34**; but **29**, wherein the epoxide moiety both suppresses tendencies towards aromatization and serves as a latent C-9 OH group, could be oxidized to the requisite quinone **30**. That an equilibrium between **30** and **31** did indeed exist and that intramolecular



26 **27** **28** **29** 2a,8a saturated **30** Δ2a,8a **32** **7** **31**

Scheme 2.

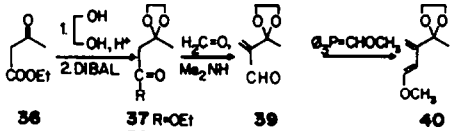
transfer of the two directing groups occurred was shown by formation of **32** upon exposure of **30** to 1-methoxycyclohexa-1,3-diene (**7**). While **32** was obtained as a mixture of stereoisomers (which was of little ultimate consequence), degradation of **32** to **35** established that **32** was regiochemically homogeneous



33 **34** **35**

and that the two Diels–Alder reactions had each occurred with complete regiospecificity.[11]

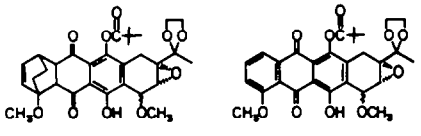
With the results of Scheme 2 in hand, suspension of model studies in favor of pursuit of the ultimate target seemed called for. To that end the fully functionalized A-ring precursor, diene **40**, was prepared using the sequence outlined in Eq. 9, which makes **40** available in



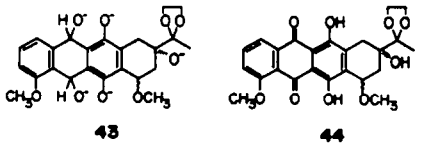
36 **37** R=OEt **38** R=H **39** **40**

(Eq. 9)

multigram quantities.[12,13] Replacement of **27** by **40** in Scheme 2 allowed the preparation of compounds such as **41** and **42**, albeit not without some difficulty. Unfortunately, myriad attempts to elaborate the desired A-ring functionality from **41**, **42** or several related compounds were unremittingly fruitless. We had envisioned, for example, that reduction of **42** with



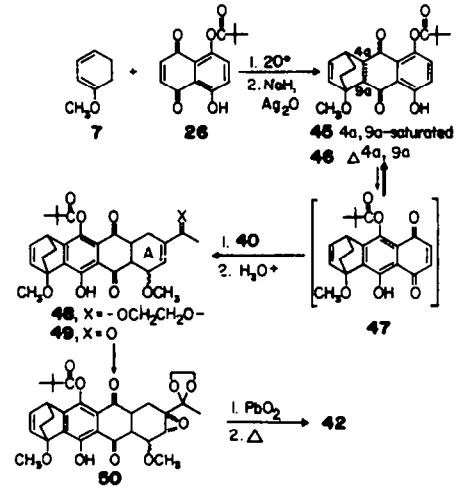
41 **42**



43 **44**

excess lithium aluminum hydride would afford intermediates such as **43** which could be converted to compounds such as **44** upon oxidative workup. In practice, however, exposure of **42** to lithium aluminum hydride and to numerous other reducing agents led to irretrievable devastation of the anthraquinone nucleus.

Reversal of the order of the two Diels–Alder reactions provided ready access to compounds such as **48–50** (Scheme 3), but again innumerable attempts to

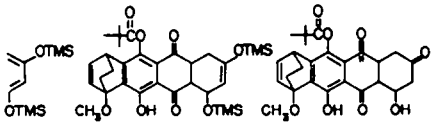


7 **26** **45** 4a, 9a-saturated **46** Δ4a, 9a **47** **50**

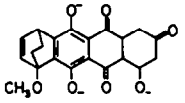
Scheme 3.

elaborate the A-ring functionality (e.g. 1,4-hydrosilylation/oxidation of **49**) were uniformly unsuccessful. Thus, despite the investment of a very substantial amount of effort to use **40** as the A-ring precursor, we were forced to abandon it.

Fortunately, at about that time Krohn *et al.*[14] in a synthesis of 4-demethoxydaunomycinone—a molecule which poses no regiochemical problem—had demonstrated the merits of **51**[15] as an A-ring precursor. Substitution of **51** for **40** in Scheme 3 provided ready access to **52** and thence **53**, but reaction of **53** with ethynyl magnesium bromide failed, apparently because of competing attack of the Grignard reagent on the C-11 carbonyl. Speculating that such attack would be suppressed if the substrate were the corresponding phenoxide **54** (or the magnesium chelate thereof), we



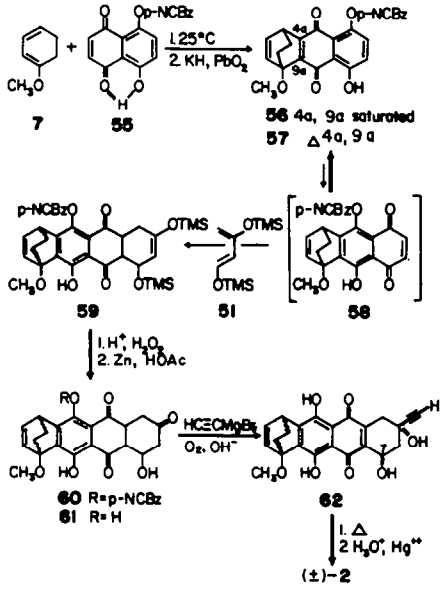
51 **52** **53**



54

sought to cleave the pivalate group prior to the Grignard reaction. Unfortunately, the extreme propensity of **53** to suffer A-ring aromatization made it impossible to remove the pivalate group without wreaking havoc with the A-ring.

Several other protecting/directing groups were, accordingly, examined.[16] The *para*-nitrobenzyloxycarbonyl (*p*-NCBz) moiety proved to be the group of choice and allowed us to bring the synthesis to a successful conclusion (Scheme 4).



7 **55** **56** 4a, 9a saturated **57** Δ4a, 9a **59** **51** **58** **60** R=p-NCBz **61** R=H **62** (±)-2

Scheme 4.

With careful experimental execution this synthesis provides (±)-daunomycinone in ten steps and 36% overall yield from commercially available naph-

thazarin. Because of their lability, the sequence from **55** to **61** is best effected without purification of intermediates, and affords **61** in 89% overall yield. Elaboration of **62** provides (49%) a separable 83:17 mixture of (±)-**2** and its C-7 epimer. The (±)-**2** so obtained exhibits spectral and solubility properties identical with those previously reported[14b] for (±)-**2**; TLC and HPLC comparison of (±)-**2** with authentic, naturally derived (+)-**2** confirms the identity. In no instance was the regioisomer of **2** detected.[17]

EXPERIMENTAL

M.ps were determined in Pyrex capillaries and are uncorrected. NMR spectra were recorded on either an Hitachi Perkin-Elmer Model R-24 or a Varian FT-80A spectrometer; chemical shifts are reported in ppm downfield from internal Me_4Si. Routine mass spectra were obtained using an Hitachi Perkin-Elmer RMS-4 spectrometer; high resolution mass spectra were obtained at the NIH-supported Regional Mass Spectrometry Facility at the Massachusetts Institute of Technology thanks to the cooperation of Dr. C. E. Costello. IR and UV-vis spectra were recorded on Perkin-Elmer spectrometer Models 421 and 575, respectively. E.M. Reagents Silica Gel 60 F-254 plates (0.2 mm) were used for analytical TLC. **In addition to visual examination and examination under short and long wavelength UV light, developed plates were routinely exposed to vapors from conc NH_4OH, which promotes very diagnostic color changes.** For preparative TLC, Analtech Silica Gel G or GF plates were employed. Dry-column chromatography[18] was carried out using Silica Gel Woelm for Dry-Column Chromatography obtained from ICN. Flash column chromatography was conducted according to the method of Still *et al.*[19] using Silica Gel 60 (particle size 0.040–0.063 mm, E.M. Reagents). High-pressure liquid chromatographic (HPLC) separations were effected using a Varian Model 5000 chromatograph equipped with a Varian Varichrome UV-vis detector.

Reactions sensitive to air or moisture were conducted in oven- or flame-dried glassware under an atmosphere of dry N_2. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl; CH_2Cl_2 from CaH_2. Pet. ether refers to the fraction boiling from 30–50°. Elemental analyses were performed by Galbraith Laboratories, Inc.

5,8-Dihydro-4-hydroxy-5,8-dioxo-1-naphthalenyl 2,2-dimethylpropanoate (naphthazarin monopivalate, **26**)

To a well-stirred soln of 10.0 g (52.5 mmol) of naphthazarin (Fluka) in 600 ml of benzene at *ca* 70° was added 27.2 ml (134 mmol) of pivalic anhydride. One ml of conc H_2SO_4 was then added dropwise and the mixture maintained at *ca* 70° with stirring and monitored by TLC (benzene). After approximately 3 hr the mixture was cooled, washed with water (4 × 250 ml) and brine and dried (Na_2SO_4). Volatiles were removed first at aspirator vacuum and then at < 1 torr (bath temp 80–90°). The residue was dissolved in 200 ml CH_2Cl_2, 40 g of dry-column silica gel was added and the CH_2Cl_2 was removed on a rotary evaporator (aspirator). The product/silica gel mixture was placed on top of a 10 cm × 50 cm column of dry-column silica gel. Elution with 1:1 benzene/pet. ether gave **26** in 60–70% yield. An analytical sample, m.p. 140.5–141°, was obtained as fine orange needles by recrystallization from pet. ether; NMR ($CDCl_3$) δ 1.43 (9H, s), 6.84 (1H, s), 6.85 (1H, s), 7.25 (2H, s), 12.39 (1H, s).

Anal. calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.95; H, 5.19.

Ethyl 2-(2-methyl-2-dioxolanyl)acetate (**37**)[20]

A mixture of 130 g (1 mol) of freshly distilled ethyl acetoacetate, 124 g (2 mol) of ethylene glycol and 2 g of *p*-toluenesulfonic acid in 400 ml of benzene was heated under reflux in an oil bath for 8 hr. A Dean-Stark trap was used to remove water generated during the reaction. When the reaction was complete the mixture was washed once with 400 ml of 5% $NaHCO_3$ aq and dried over Na_2SO_4. The liquid residue after removal of solvent was distilled, b.p. 110°/20 torr (lit.[20] b.p.: 99.5–101°/17–18 torr) to give **37** (150 g, 0.86 mol) in 86% yield; NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7 Hz), 1.45 (3H, s), 2.62 (2H, s), 3.95 (4H, s), 4.15 (2H, q, J = 7 Hz).

2-(2-Methyl-2-dioxolanyl)ethanal (**38**)

To a rapidly mechanically stirred soln of 100 g (0.57 mol) of **37** in 600 ml of CH_2Cl_2 (reagent grade stored over 3A molecular sieves) at −78° was added diisobutylaluminum hydride (100 g, 0.70 mol, 1.2 equiv., 20% soln in hexane) *via* a dropping funnel over a period of 15 min under N_2. After the addition of hydride was complete, the mixture was stirred for another hr at −78° and then poured into a 4-l flask containing 1 l of distilled water. The mixture was stirred mechanically for 15 min, and a total of 400 ml of 4 N HCl was then added at 5 min intervals in four equal portions. The mixture was vigorously stirred mechanically after each addition. The organic layer was separated and dried over Na_2SO_4. The liquid obtained after removal of solvent was distilled (b.p. 70–72°/16 torr; lit.[13] b.p.: 68–69.5°/11 torr) to give 64 g (85%) of **38**; NMR ($CDCl_3$) δ 1.40 (3H, s), 2.67 (2H, d, J = 3 Hz), 4.00 (4H, s), 9.75 (1H, t, J = 3 Hz).

Anal. calcd for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.15; H, 7.78.

2-(2-Methyl-2-dioxolanyl)-2-propenal (**39**)

To a stirred mixture of 75 ml (0.42 mol) of 25% aqueous dimethylamine and 33 ml (0.42 mol) of an aqueous 37% soln of formaldehyde was slowly added glacial AcOH (25 ml, 0.42 mol) while cooling in an ice bath. The resulting mixture was stirred for another 10 min in an ice bath and 50 g (0.38 mol) of **38** was then added in one portion. This mixture was stirred at 25°. Reaction progress was monitored by NMR (an aliquot of the mixture was extracted with an equal volume of $CDCl_3$ in an NMR tube). When NMR analysis indicated the absence of starting material (*ca* 1 hr), the mixture was shaken with an equal volume of $CHCl_3$ and 50 g of solid $NaHCO_3$. After separation from the organic layer, the aqueous phase was extracted once with 200 ml of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The liquid obtained after removal of solvent was distilled to give 17 g (33%) of **39**, b.p. 90°/15 torr; NMR ($CDCl_3$) δ1.56 (3H, s), 3.70–4.21 (4H, m), 6.12 (1H, d, J = 1 Hz), 6.51 (1H, d, J = 1 Hz), 9.65 (1H, s).

Anal. calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.04. Found: C, 58.99; H, 6.95.

trans 1-Methoxy-3-(2-methyl-2-dioxolanyl)-1,3-butadiene (**40**)

To a stirred suspension of 30 g (0.09 mol) of (methoxymethyl)triphenylphosphonium chloride (Aldrich, dried at 100°/0.02 torr for 8 hr) in 1 l of dry THF at 0° under N_2 was added t-BuLi[21] (43 ml of a 2.1 M soln in n-pentane), over 15 min. The red ylide soln was stirred at this temp for another hr and added into a soln of 12.8 g (0.090 mol) of **39** in 500 ml of dry THF over 20 min at 0° under N_2. The resulting mixture was stirred for 1 hr then quenched with 300 ml of water. This soln was extracted with ether (3 × 300 ml). The ether extracts were combined, the solvents evaporated *in vacuo*, and the residue treated with 300 ml of n-pentane. The solid which precipitated from the pentane soln was removed by filtration and the filtrate was dried over Na_2SO_4. The liquid obtained after removal of solvent was purified by vacuum distillation (b.p. 55°/0.3 torr) to give 7 g (46%) of an approximately 9:1 mixture of **40** and its *cis* isomer. This mixture was generally used without further purification although in some instances[12] removal of trace impurities by medium pressure liquid chromatography[22] on silica gel [5 g of silica gel 60 (particle size 0.040–0.063 mm, E. Merck) per gram of diene; CH_2Cl_2 elution] was advantageous. A sample of pure *trans* **40** was obtained by preparative VPC (6′ × 1/4″ column of 20% SE-30 on Chromosorb, 200°); NMR ($CDCl_3$): δ 1.50 (3H, s),

3.60 (3H, s) 3.95 (4H, m), 5.03 (1H, m), 5.09 (1H, d, J = 2 Hz), 5.42 (1H, d, J = 12 Hz), 6.94 (1H, d, J = 12 Hz).

Anal. Calcd for $C_9H_{14}O_3$ (mixture of stereoisomers): C, 63.53; H, 8.24. Found: C, 63.70; H, 8.37.

Diels–Alder reaction of naphthazarin monopivalate (**26**) *and* 1-*methoxycyclohexa*-1,3-*diene* (**7**): 1,4,4a,9,9a,10-*hexahydro*-8-*hydroxy*-1-*methoxy*-9,10-*dioxo*-1,4-*ethanoanthracen*-5-*yl* 2,2-*dimethylpropanoate* (**45**)[23]

To a soln of 10.00 g (36.5 mmol) of **26** in 40 ml of CH_2Cl_2 maintained at 20° in a water bath (reaction is mildly exothermic) was added 17 ml of **7**, (Aldrich technical grade:[24] contains *ca* 30% of 1-methoxycyclohexa-1,4-diene). After 1 hr the initial dark color of the reaction had almost completely faded and the reaction was judged complete by TLC (9:1 C_6H_6/Et_2O). Removal of volatiles *in vacuo* gave 24 g of a beige solid smelling of the diene. Recrystallization from 300 ml of abs EtOH gave a first crop of 11.44 g of **45**; evaporation of the filtrate and crystallization of the residue from 70 ml abs EtOH gave an additional 1.31 g of **45** for a total yield of 93.4%. Recrystallization from abs EtOH gave analytically pure **45** as short, pale-yellow needles, mp 149–52°; NMR ($CDCl_3$) δ 1.36 (9H, s), 1.4–2.0 (4H, m), 2.8–3.4 (3H, m), 3.43 (3H, s), 5.8–6.3 (2H, m), 7.07 (2H, s), 11.84 (1H, s).

Anal. calcd for $C_{22}H_{24}O_3$: C, 68.74; H, 6.29. Found: C, 68.52; H, 6.49.

1,4,9,10-*Tetrahydro*-8-*hydroxy*-1-*methoxy*-9,10-*dioxo*-1,4-*ethanoanthracen*-5-*yl* 2,2-*dimethylpropanoate* (**46**)[23]

In an oven-dried 1-l 3-necked round-bottomed flask under N_2 was placed 1.32 g (27.5 mmol) of a 50% dispersion of NaH in mineral oil. The NaH was rinsed with 10 ml of hexane to remove most of the mineral oil; then 600 ml of dry THF followed by 12.75 g (33.2 mmol) of recrystallized **45** was added. The resulting mixture was stirred at room temp for 1.25 hr (at which point it had become dark green) and then 108 g of Ag_2O (Fisher purified grade) was added in one portion. Stirring was continued and the progress of the reaction monitored by TLC (9:1 C_6H_6/Et_2O). When the reaction was judged complete (*ca* 16 hr) it was filtered under vacuum through celite (CAUTION: residual NaH); the celite was then washed with THF until the washes were nearly colorless. The combined filtrate and washes were diluted with 2 l of 10% aq (+)-tartaric acid solution and extracted twice with CH_2Cl_2 (1000 ml; 600 ml). The combined CH_2Cl_2 extracts were dried by gravity filtration and concentrated *in vacuo* to give 14.0 g of an orange foam which was crystallized from 80 ml of ether to give a first crop of 6.45 g of **46** as an orange solid (filtered under positive nitrogen pressure). Evaporation of the filtrate and recrystallization of the residue from ether at −15° gave an additional 4.46 g (TLC showed substantial amounts of **46** also remained in the mother liquor). The first and second crops were combined, dissolved in *ca* 350 ml of hot ether and the soln concentrated to a volume of 60 ml on a steam bath (CAUTION: foaming). The soln was allowed to cool slowly to room temp and subsequently stored at −15° overnight. A first crop of 7.01 g (55%) of **46** as orange needles m.p. 109.5–110.5° (dec with gas evolution) was obtained (additional **46** can be obtained by dry-column chromatography of the mother liquors, eluting with 9:1 CH_2Cl_2/Et_2O); NMR ($CDCl_3$) δ 1.41 (9H, s), 1.3–1.9 (4H, m). 3.67 (3H, s), 4.3–4.5 (1H, m), 6.2–6.8 (2H, m), 7.15 (2H, br s), 12.8 (1H, s); the presence of the minor tautomer (**47**) to an extent of approximately 20% was revealed by singlets at δ1.46, 3.73 and 13.1.

Anal. calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.33; H, 5.80.

Diels–Alder reaction of **40** *and* **46**: 1,4,6,6a,7,10,10a,11-*octahydro*-12-*hydroxy*-1,10-*dimethoxy*-8-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-6,11-*dioxo*-1,4-*ethanonaphthacen*-5-*yl* 2,2-*dimethylpropanoate* (**48**)[23]

To a soln of 1.07 g (2.8 mmol) of quinone **46** in 2.5 ml of CH_2Cl_2 was added 1.17 g (6.9 mmol) of diene **40** and the reaction was stirred under N_2 for 24 hr at 20° at which time no **46** could be detected by TLC (9:1 CH_2Cl_2/Et_2O; the adduct appears as a low-R_f, colorless, diffuse spot which is green fluorescent under long wavelength UV). Petroleum ether was added dropwise to induce precipitation of 437 mg (28.2%) of an amorphous, pale-yellow solid which was collected and which was judged to be a single isomer (stereochemistry was not established)[25] by NMR and TLC [^{1}H NMR of the filtrate after evaporation revealed the presence of additional **48** and different amounts of four other products (as judged by singlets in the δ 12–14 region), three of which are presumably[26] stereoisomers—*exo*[26] and *endo* adducts *syn* or *anti* to the D-ring bridge]. Recrystallization from EtOH gave analytically pure material as pale yellow, fine needles m.p. 206° (dec); NMR ($CDCl_3$) δ 1.40 (9H, s), 1.55 (3H, s) 1.3–2.1 and 2.9–3.6 (9H, m's), 3.00 (3H, s), 3.73 (3H, s), 3.8–4.2 (5H, m), 6.0–6.9 (3H, m), 13.1 (1H, s).

Anal. calcd for $C_{31}H_{36}O_9$: C, 67.38; H, 6.57. Found: C, 67.45; H 6.56.

Hydrolysis of **48** *to* **49**: 8-*acetyl*-1,4,6,6a,7,10,10a,11-*octahydro*-12-*hydroxy*-1,10-*dimethoxy*-6,11-*dioxo*-1,4-*ethanonaphthacen*-5-*yl* 2,2-*dimethylpropanoate*[23]

To 40 ml of ice cold 50% aq trifluoroacetic acid was added 140 mg of ketal **48**. The reaction was stirred at 0° for 0.5 hr, diluted with CH_2Cl_2, and washed thrice with cold water and once each with pH 7 buffer and brine. The organic layer was dried over Na_2SO_4 for several hours in the refrigerator and concentrated to give 132 mg of a pale-yellow solid. Recrystallization from 35 ml of abs EtOH gave 93 mg (72%) of pale-yellow needles, m.p. 195° (dec); NMR ($CDCl_3$, only distinctive peaks given) δ 1.38 (9H, s), 2.36 (3H, s), 3.12 (3H, s), 3.72 (3H, s), 6.2–7.0 (3H, m), 13.03 (1H, s).

Epoxidation of **48**: 1a,2,2a,3,5,8,10,10a,11,11a-*decahydro*-9-*hydroxy*-8,11-*dimethoxy*-1a-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-3,10-*dioxo*-5,8-*ethanonaphthaceno*[2,3-*b*]*oxiren*-4-*yl* 2,2-*dimethylpropanoate* (**50**)

To a soln of 130 mg (0.24 mmol) of the adduct **48** (the stereoisomer described above) in 3 ml of $CDCl_3$ cooled in an ice bath was added 48 mg (0.28 mmol) of *m*-chloroperbenzoic acid (previously purified by washing with pH 7.5 phosphate buffer and drying *in vacuo*). The mixture was stirred until all of the peracid had dissolved and then stored at 5°C for 6 days at which time a starch-iodide test was negative. NMR analysis indicated regiospecific A-ring epoxidation. The reaction was diluted with 50 ml of CH_2Cl_2 and washed successively with Na_2SO_3 aq, pH 7 buffer and brine. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to yield 134 mg (100%) of a yellow powder. Recrystallization from 20 ml of abs EtOH gave 98.5 mg (73%) of **50** as a pale-yellow powder, m.p. 192° (dec); NMR ($CDCl_3$, only distinctive peaks are given) δ 1.45 (9H, s), 1.62 (3H, s), 3.08 (3H, s), 3.75 (3H, s), 4.0 (5H, broad s), 6.2–6.6 (1H, dd, J = 6, 9 Hz), 6.75 (1H, d, J = 9 Hz), 13.1 (1H, s).

Anal. calcd for $C_{31}H_{36}O_{10}$: C, 65.48; H, 6.38. Found: C, 65.21; H, 6.40.

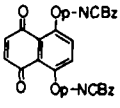
1a,2,4,9,11,11a-*Hexahydro*-10-*hydroxy*-8-11-*dimethoxy*-1a-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4,9-*dioxonaphthaceno*[2,3-*b*]*oxiren*-3-*yl* 2,2-*dimethylpropanoate* (**42**)

To a soln of 32 mg (0.056 mmol) of epoxide **50** in 50 ml of CH_2Cl_2 was added 3.55 g of freshly prepared[28] lead dioxide and the slurry was stirred at room temp until no starting material was present (*ca* 2 hr) as judged by TLC analysis (99:1 CH_2Cl_2/MeOH). The soln was suction filtered through celite and the solid washed thoroughly with CH_2Cl_2 and ether. The filtrate and washes were combined and concentrated *in vacuo*. After preparative TLC (99:1 CH_2Cl_2/MeOH) and recrystallization from EtOH 22 mg (71%) of 2a,10a-dehydro-**50** was obtained as an orange solid, m.p. 160° (dec); NMR ($CDCl_3$, only distinctive peaks given) δ 1.50 (3H, s), 1.53 (9H, s), 3.51 (3H, s), 3.75 (3H, s), 4.02 (4H, s), 5.04 (1H, br s), 6.2–6.9 (2H, m), 13.03 (1H, s). This material was then heated at reflux for 2 hr

in xylene (to effect the retro Diels–Alder reaction), the xylene removed *in vacuo* and the residue purified by preparative TLC (3:1 ether/pet. ether) to give 20 mg (66%) of **42** as a yellow solid which melted at 217–221° after recrystallization from ethanol; NMR ($CDCl_3$); δ 1.52 (3H, s), 1.57 (9H, s), 2.7–3.4 (2H, broadened ABq, J = 18 Hz), 3.51 (3H, s), 3.70 (1H, broadened d, J = 3 Hz), 4.06 and 4.09 (7H, two s), 5.43 (1H, broadened d, J = 3 Hz), 7.2–8.0 (3H, m), 13.88 (1H, s); mass spectrum *m/e* 538 (M^+ for $C_{29}H_{30}O_{10}$).

5, 8-Dihydro-4-hydroxy-5,8-dioxo-1-naphthalenyl (4-nitrophenyl)-methyl carbonate (**55**, p-*nitrocarbobenzoxynaphthazarin*)

To a magnetically stirred soln of 4.42 g (23.3 mmol) of **11** in 200 ml of dry THF in a 500-ml round-bottomed flask under N_2 was added at ambient temp a soln of 10.0 g (46.4 mmol) of *p*-nitrobenzyl chloroformate (Fluka) in 25 ml of THF followed by 973 mg of calcium hydride powder (40 mesh). Progress of the reaction was monitored by NMR and TLC (7:3 pentane/EtOAc). When the reaction was about 80% complete (*ca* 45 hr) it was quenched by addition of 600 ml of 5% NaH_2PO_4 aq. The mixture was extracted with 600 ml of CH_2Cl_2 and the CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Removal of solvent *in vacuo* gave a solid which was stirred with 1.5 l of pet. ether for 24 hr (to remove *p*-nitrobenzyl alcohol). The insoluble solid (9 g) was collected by filtration and the filtrate (A), which contained some naphthazarin, retained (see below). The solid was dissolved in 600 ml of CH_2Cl_2 and titrated with 0.1M NaOH until all the naphthazarin had been extracted into the aqueous phase as revealed by TLC of the organic layer. The aqueous layer was separated and saved (B, see below); the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give 7.91 g of solid which was subjected to flash column chromatography[29] on a 100 mm diameter column (the chromatography is simplified by filtering the CH_2Cl_2 soln of crude **55** prior to its application to the column to partially remove the diprotected naphthazarin (**63**) which is poorly soluble in CH_2Cl_2). Elution with CH_2Cl_2 gave 5.32 g of pure **55**. Further elution with ethyl acetate afforded 2.1 g of **63**, m.p. 227–230°.



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Filtrate A (above), which contained some naphthazarin, was evaporated and the residue partitioned between CH_2Cl_2 and 0.1N NaOH as above. The aqueous layer was separated and combined with B (from above). The resulting deep purple soln was stirred with CH_2Cl_2 and saturated aq NaH_2PO_4 until all of the naphthazarin had been extracted into the CH_2Cl_2 phase. The dark red CH_2Cl_2 layer was separated, washed with brine, dried and evaporated to give 1.13 g of naphthazarin.

The biscarbonate **63** (2.1 g, see above)) was stirred with glacial AcOH (60 ml), THF (30 ml) and Zn dust (3 g) for 2 hr at which time all of **63** had been converted to **11**. The mixture was diluted with CH_2Cl_2, washed first with brine and then with 0.1N NaOH (until the aqueous layer remained only weakly acidic). After additional washes with brine (2 × 300 ml) the CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to give 585 mg of **11**.

Based on unrecovered **11** the yield of **55** is quantitative.

An analytical sample of **55**, reddish crystals m.p. 185–6°, was obtained by recrystallization from EtOH; NMR ($CDCl_3$ δ 5.43 (2H, s), 6.89 and 6.92 (two s, total 2H), 7.36 (2H, s), 7.68 (2H, d, J = 8 Hz), 8.28 (2H, d, J = 8 Hz), 12.32 (1H, s).

Anal. calcd for $C_{18}H_{11}NO_8$: C, 58.54; H, 3.00; N, 3.79. Found: C, 58.79; H, 3.18; N, 3.79.

Conversion of **55** *to* **61** *without purification of intermediates*

(a) *Diels–Alder reaction of* **55** *and* **7**. To a soln of 1.40 g (3.8 mmol) of **55** in 100 ml of dry CH_2Cl_2 under N_2 was added 2.5 ml of 1-methoxycyclohexa-1,3-diene (Aldrich technical grade). The soln was stirred at room temp for 8 hr, the solvent removed *in vacuo* and the residue stirred with 50 ml of petroleum ether for 3 h. The solid **56** was collected by filtration, rinsed with petroleum ether, and used directly in the next reaction.

(b) *Oxidation of* **56** *to* **57**. The crude **56** was dissolved in 200 ml of dry (*twice* distilled from sodium benzophenone ketyl) THF under N_2 and cooled to −78°. A suspension of *ca* 1 equiv. (0.15 g)[30] of oil-free KH [obtained by rinsing a suspension of KH in mineral oil (Alfa-Ventron) several times with THF] in THF was then added. The mixture was allowed to warm to 0° over 0.5 hr and 1.4 g of PbO_2 (J. T. Baker, reagent grade, dried at 80°/0.1 torr for 2hr) was added. After stirring overnight at 4°, 200 ml each of cold 20% aq tartaric acid and ether were added. The organic layer was separated and the aqueous layer extracted with ether. The ether layers were combined, washed with brine, dried and concentrated to give crude **57** which was used directly in the next reaction.

(c) *Diels–Alder reaction of* **57** (⇄ **58**) *with* **51**. To a soln of the crude quinone in 150 ml of dry CH_2Cl_2 was added 2 ml of **51**[15] at ambient temp and the reaction was stirred under N_2. After 4 hr an additional 1 ml of **51** was added and stirring continued until (*ca* 48 h) no **57** was detectable by TLC (4:1 pentane/EtOAc). Volatiles were then removed under high vacuum and the residue hydrolysed directly.

(d) *Hydrolysis of* **59** *to* **60**. The crude adduct **59** was dissolved in 20 ml of THF, cooled to 0° and 4 ml of 3N aq HCl and 4 ml of 30% H_2O_2 were added.[31] After 30 min, when TLC (3:2 pentane/EtOAc) showed the reaction to be complete, the mixture was extracted with 200 ml of CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated to give crude **60** which was used directly in the next reaction.

(e) *Conversion of* **60** *to* **61**: *removal of the* p-*nitrobenzyl carbonate group*. Crude **60** was dissolved in 10 ml of THF, cooled to 0°, and stirred while 5 ml of glacial AcOH and 1.4 g of Zn dust were added. After 30 min TLC (3:2 pentane/EtOAc) revealed reaction was complete. The mixture was diluted with 250 ml of CH_2Cl_2, neutralized (to pH 6) with satd $NaHCO_3$ aq and the layers separated. The aqueous layer was extracted with CH_2Cl_2; the CH_2Cl_2 layers were combined and washed with brine, dried and evaporated to give a solid residue. This was stirred 15 min with dry ether and the solid filtered off to give 1.11 g of pure **61**. Petroleum ether was added to the ethereal filtrate which precipitated more pure **61**; this process was repeated once more to give a total of 1.29 g (89%) of **61** of > 95% purity as judged by TLC and NMR.

Characterization of intermediates in the conversion of **55** *to* **61**

(*a*) 1,4,4a,9,9a,10 - *Hexahydro*- 8 - *hydroxy* - 1 - *methoxy* - 9,10 - *dioxo* - 1,4 - *ethanoanthracen* - 5 - *yl*(4 - *nitrophenyl*) *methyl carbonate* (**56**). Analytically pure material was obtained as pale-yellow crystals, m.p. 148–9°, by recrystallization from EtOAc; NMR ($CDCl_3$) δ 1.57–1.84 (4H, m), 2.9–3.4 (3H, m), 3.47 (3H, s), 5.39 (2H, s), 5.83–6.15 (2H, m), 7.21 and 7.25 (two s, total 2H), 7.66 (2H, d, J = 8 Hz), 8.27 (2H, d, J = 8 Hz), 11.90 (1H, s).

Anal. calcd for $C_{25}H_{21}NO_9$: C, 62.62; H, 4.41; N, 2.92. Found: C, 62.80; H, 4.58; N, 3.12.

(b) (4-*Nitrophenyl*)*methyl* 1,4,9,10-*tetrahydro*-8-*hydroxy*-1 - *methoxy* - 9,10 - *dioxo* - 1,4 - *ethanoanthracen* - 5 - *yl carbonate* (**57**). Yellow crystals, m.p. 115–116°, were obtained upon recrystallization from EtOAc/Et_2O; NMR ($CDCl_3$) δ 1.27–1.83 (4H, m), 3.68 (3H, s), 4.39 (1H, br d, J = 6 Hz), 5.45 (2H, s), 6.37 (1H, dd, J = 7 and 6 Hz), 6.62 (1H, d, J = 7 Hz), 7.29 (2H, s), 7.70 (2H, d, J = 8 Hz), 8.28 (2H, d, J = 8 Hz), 12.75 (1H, s).

Anal. calcd for $C_{25}H_{19}NO_9$: C, 62.89; H, 4.01; N, 2.93. Found: C, 62.92; H, 3.81; N, 2.95.

(c)(4-*Nitrophenyl*)*methyl* 1,4,6,6a,7,10,10a,11-*octahydro*-12-*hydroxy*-1-*methoxy*-6,11-*dioxo*-8,10-*bis*(*trimethylsilyloxy*)-1,4-*ethanonaphthacen*-5-*yl carbonate* (**59**).[23] This material, a mixture of two stereoisomers, could be separated (with substantial losses) into its components by flash column chromatography using 9:1 pet. ether/EtOAc. The compounds are extremely sensitive white solids and no attempt was made to obtain combustion analyses. The less mobile of the two isomers (**59a**) gave the NMR ($CDCl_3$) δ −0.28 (9H, s), 0.25 (9H, s), 1.50–1.87 (4H, m), 2.10–2.29 (2H, m), 2.89–3.49 (2H, m), 3.75 (3H, s), 4.20 (1H, d, J = 5 Hz), 4.56 (1H, dd, J = 3 and 6 Hz), 4.95 (1H, d, J = 6 Hz), 5.43 (2H, s), 6.38 (1H, dd, J = 6 and 8 Hz), 6.75 (1H, d, J = 8 Hz), 7.71 (2H, d, J = 8.6 Hz), 8.27 (2H, d, J = 8.6 Hz), 13.24 (1H, s); the more mobile isomer (**59b**) gave the NMR ($CDCl_3$) δ −0.25 (9H, s), 0.25 (9H, s), 1.50–1.87 (4H, m), 2.1–2.3 (2H, m), 2.9–3.5 (2H, m), 3.75 (3H, s), 4.20 (1H, d, J = 5 Hz), 4.56 (1H, dd, J = 3 and 6 Hz), 4.95 (1 H, d, J = 6 Hz), 5.43 (2H, s), 6.38 (1H, dd, J = 6 and 8 Hz), 6.75 (1H, d, J = 8 Hz), 7.71 (2H, d, J = 8 Hz), 8.27 (2H, d, J = 8 Hz), 13.22 (1H, s).

(d) 1,4,6a,9,10,10a-*Hexahydro*-10,12-*dihydroxy*-1-*methoxy*-6,8,11(7H)-*trioxo*-1,4-*ethanonaphthacen*-5-*yl* (4-*nitrophenyl*)*methyl carbonate* (**60**).[23] Anal. calcd for $C_{29}H_{25}NO_{11}$: C, 61.81; H, 4.44; N, 2.48. Found (for a mixture of the two stereoisomers): C, 61.81; H, 4.72; N, 2.42.

The individual stereoisomers could be obtained as amorphous solids by separate hydrolyses (*vide supra*) of **59a** and **59b**. The more mobile (3:2 pentane/EtOAc) isomer gave the NMR [$(CD_3)_2CO$] δ 1.62 (4H, m), 2.4–3.0 (m, 4H after D_2O exch), 3.67 (3H, s), 3.83 (2H, m), 4.25 (1H, br d), 4.77 (1H, br s), 5.48 (2H, s), 6.43 (1H, dd, J = 8 and 6 Hz), 6.77 (1H, d, J = 8 Hz), 7.81 (2H, d, J = 9 Hz), 8.31 (2H, d, J = 9 Hz), 13.29 (1H, s); the less mobile isomer gave the NMR [$(CD_3)_2CO$] δ 1.68 (4H, m), 2.4–3.0 (m, 4H after D_2O exch), 3.67 (3H, s), 3.78–3.96 (2H, m), 4.29 (1H, br d), 4.75 (1H br s), 5.47 (2H, s), 6.41 (1H, dd, J = 6 and 8 Hz), 6.76 (1H, d, J = 8 Hz), 7.80 (2H, d, J = 9 Hz), 8.30 (2H, d, J = 9 Hz), 13.29 (1H, s).

(e) 1,4,6a,9,10,10a-*Hexahydro*-5,10,12-*trihydroxy*-1-*methoxy*-1,4-*ethanonaphthacene*-6,8,11(7H)-*trione* (**61**).[23] The two stereoisomers were obtained by separate hydrolyses of the stereoisomers of **60**. The isomer more mobile on TLC (1:1 EtOAc/pentane) was obtained as an off-white solid which turns red at 170–71° and melts at 185–7°; NMR [$(CD_3)_2CO$] δ 1.6 (4H, m), 2.4–3.4 (m, 4H after D_2O exch), 3.66 (3H, s), 3.71–3.90 (2H, m), 4.48 (1H, br d), 4.69 (1H, br d), 6.47 (1H, dd, J = 6 and 8 Hz), 6.74 (1H, d, J = 8 Hz), 11.88 (1H, s), 13.05 (1H, s). Recrystallization of the less mobile isomer gave an off-white solid m.p. 164–165°; NMR [$(CD_3)_2CO$] δ 1.6 (4H, m), 2.4–3.4 (m, 4H after D_2O exch), 3.66 (3H, s); 3.70 (1H, m), 3.9 (1H, m), 4.6 (2H, m), 6.47 (1H, dd, J = 6 and 8 Hz), 6.71 (1H, d, J = 7 Hz), 11.93 (1H, s), 13.04 (1H, s).

8-*Ethynyl*-1,4,7,8,9,10-*hexahydro*-5,8,10,12-*tetrahydroxy*-1-*methoxy*-1,4-*ethanonaphthacene*-6,11-*dione* (**62**)[23,32]

To an ice-cold soln of 30 equiv. of ethynyl magnesium bromide (freshly prepared from CH_3CH_2MgBr and acetylene) in 50 ml of dry THF under N_2 was added dropwise over 10 min a soln of 110 mg (0.29 mmol) of **61** (as a mixture of the two stereoisomers) in 25 ml of dry THF. The reaction was stirred at 0° for 2.25 hr and then stirred with 30 ml of a saturated aq solution of (+)-tartaric acid and 100 ml of ether. The organic layer was separated, washed with brine, dried and evaporated. The residue was oxidized by dissolution in 10 ml of THF, addition of 20 ml of 5% $NaHCO_3$ aq and stirring at 0° while open to the air. After 1 hr 50 ml of 5% aq (+)-tartaric acid and 200 ml of ether were added and the layers separated. The organic layer was washed with brine and the solvents evaporated to give a residue which was purified by flash chromatography (pet. ether/EtOAc) to give 86 mg (74%) of **62** as a mixture of three stereoisomers which was ordinarily used directly in the next reaction.

For purposes of characterization the three isomers were separated by careful preparative TLC (7:2 CH_2Cl_2/Et_2O). The most mobile stereoisomer, m.p. 139–141° (dec, gas evolution) after recrystallization from EtOAc/pet. ether, exhibited the following spectral properties (only distinctive peaks given): IR ($CHCl_3$), 3300 cm^{-1} (≡C—H); NMR ($CDCl_3$) δ 1.6 (4H, br m), 2.55 (1H, s), 3.72 (3H, s), 4.55 (1H br d), 5.15 (1H, br s), 6.45 (1H, s), 12.89 (1H, s), 13.54 (1H, s); MS: *m/e* (% base peak) 380 ($M^+ - CH_2{=}CH_2$) (12%), 362 ($M^+ - CH_2{=}CH_2, -H_2O$) (20%), 344 ($M^+ - CH_2{=}CH_2, -2H_2O$) (100%). The stereoisomer of intermediate mobility, m.p. 151–53° (dec) displayed the following spectral properties (only distinctive peaks given): IR ($CHCl_3$), 3380 cm^{-1} (≡C—H); NMR ($CDCl_3$) δ 1.6 (4H, br m), 2.55 (1H, s), 3.72 (3H, s), 4.59 (1H, br d, J = 4 Hz), 5.17 (1H, br s), 6.45 (1H, dd, J = 6 and 8 Hz), 6.70 (1H, d, J = 8 Hz), 12.90 (1H, s), 13.53 (1H, s); MS: *m/e* (% of base peak) 380 ($M^+ - CH_2{=}CH_2$) (12.5%), 362 ($M^+ - CH_2{=}CH_2, -H_2O$) (20%), 344 ($M^+ - CH_2{=}CH_2, -2H_2O$) (100%). The lest mobile stereoisomer, m.p. 245° (dec), gave rise to the following spectra (only distinctive peaks given): IR ($CHCl_3$) 3300 cm^{-1} (≡C—H); NMR ($CDCl_3$) δ 1.7 (4H, br m), 2.59 (1H, s), 3.73 (3H, s), 3.98 (1H, m), 4.55 (1H, br d), 5.20 (1H, m), 6.45 (1H, dd, J = 8 and 6 Hz), 6.70 (1H, d, J = 8 Hz) 12.92 (1H, s), 13.57 (1H, s); MS: *m/e* (% of base peak) 408 (M^+) (5%), 380 ($M^+ - CH_2{=}CH_2$) (87%), 362 ($M^+ - CH_2{=}CH_2, -H_2O$) (100%), 344 ($M^+ - CH_2{=}CH_2, -2H_2O$) (34%).

cis *and* trans 8-*Ethynyl*-7,8,9,10-*tetrahydro*-6,8,10,11-*tetrahydroxy*-1-*methoxynaphthacene*-5,12-*dione* (**64**)[23]

A soln of 200 mg (0.49 mmol) of the stereoisomeric mixture of oxidized Grignard products (**62**) in 5 ml of *o*-xylene was heated in an oil bath at 145° for 30 min. After cooling to room temp, 30 ml of pentane was added; after stirring the precipitated solid was collected by filtration and washed with ether to give 165 mg (89%) of a mixture [pure by TLC (24:1 CH_2Cl_2/MeOH)] of the two stereoisomers of **64** which was ordinarily subjected directly to hydration.

The two isomers can be separated by using either silica plates (24:1 CH_2Cl_2/MeOH) or, preferably, C_{18}-reverse phase chromatography (e.g. Whatman $KC_{18}F$ plates, eluting with *ca* 20:1 MeOH/H_2O).

Anal. calcd for $C_{21}H_{16}O_7$: C, 66.31; H, 4.24. Found (for mixture of isomers): C, 66.12; H, 4.49.

The major, more mobile (on silica gel) isomer, which possesses the natural stereochemistry, melts sharply with decomposition at 270–71° after recrystallization from $CHCl_3$. High resolution ms: 380.0867 (M^+); calc for $C_{21}H_{16}O_7$: 380.0896. The ^{1}H-NMR spectrum in $CDCl_3/CF_3COOH$ exhibited peaks *inter alia* at δ 2.66 (1H, s), 4.07 (3H, s) and 7.4–8.0 (3H, m). The less mobile (silica gel) "7-epi" isomer, for which we were unable to record a satisfactory ^{1}H-NMR spectrum, exhibited a molecular ion at 380.0897 (calc for $C_{21}H_{16}O_7$: 380.0896).

(±)-*Daunomycinone* (**2**) *and* (±)-7-*epi-daunomycinone*

The mixture of stereoisomers of **64** from above (165 mg) was taken up in 30 ml of THF and 300 mg of $HgSO_4$ and 5 ml of 40% H_2SO_4 were added. The mixture was stirred overnight at room temp and extracted twice with 200 ml of CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated to give 129 mg (75%) of an 83:17 mixture (as determined by HPLC[33]) of (±)-**2** and (±)-epi-2. The (±)-**2** so obtained, m.p. 240° (dec) [lit.[14b] m.p.: 280° (dec)] after recrystallization from $CHCl_3$ exhibits spectral and solubility properties identical with those previously reported for (±)-**2**; HPLC[33] and TLC comparison in a variety of solvent systems with authentic, naturally derived (+)-**2** confirmed the identity.

Samples of (±)-7-epi-**2** upon recrystallization from $CHCl_3$ or THF/Et_2O melted with decomposition at 248° and 253-4°, respectively [lit.[14b] m.p.: 269° (dec)]. The ^{1}H-NMR spectrum of (±)-7-epi-2 is in agreement with that reported.[14b]

Because of the limited solubility of (±)-2, separation from (±)-7-epi-2 by chromatography is best achieved before hydration of the acetylene.

Treatment of (±)-7-epi-2 with CF_3COOH converts it largely (TLC) to (±)-2, as previously reported.[34]

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REFERENCES AND NOTES

[1] For a recent leading reference see F. Arcamone, *Chronicles of Drug Discovery* (Edited by J. S. Bindra and D. Lednicer) Vol. 2, p. 171. Wiley-Interscience: New York (1983).

[2] For recent surveys see [a]V. Snieckus and N. Altintas, *The Total Synthesis of Natural Products* (Edited by J. ApSimon) Vol. 8; Wiley-Interscience: New York, in press; [b]K. Krohn, *Angew. Chem.* in press.

[3] T. R. Kelly, J. Vaya and L. Ananthasubramanian, *J. Am. Chem. Soc.* **102**, 5983 (1980); *Idem.*, U.S. Patents 4,415,498 (1983) and 4,472,312 (1984).

[4] F. Fariña and J. C. Vega, *Tetrahedron Lett.* 1655 (1972).

[5] V. H. Powell, *Tetrahedron Lett.* 3463 (1970); A. J. Birch and V. H. Powell, *Ibid.* 3467 (1970).

[6] T. R. Kelly, J. W. Gillard and R. N. Goerner, Jr., *Tetrahedron Lett.* 3873 (1976).

[7] H. H. Inhoffen, H. Muxfeldt, H. Schaefer and H. Kramer, *Croat. Chem. Acta* **29**, 329 (1957); H. Muxfeldt, *Angew. Chem.* **74**, 825 (1962). For full paper see H. Muxfeldt, G. Haas, G. Hardtmann, F. Kathawala, J. B. Mooberry and E. Vedejs, *J. Am. Chem. Soc.* **101**, 689 (1979).

[8] Such an explanation would predict that alkoxy groups would exert influences on regiochemistry analogous to those of acyloxy groups: they do. For a leading reference see T. R. Kelly, N. D. Parekh and E. N. Trachtenberg, *J. Org. Chem.* **47**, 5009 (1982).

[9] For an alternate explanation see K. N. Houk, I. M. Tegmo-Larrson and M. D. Roseboom, *J. Org. Chem.* **46**, 2338 (1981).

[10] For details of the analogous "*acylwanderung*" [H. Brockmann, H. Greve and A. Zeeck, *Tetrahedron Lett.* 1929 (1971)] in the case of naphthazarin monoacetate see I. C. Calder, D. W. Cameron and M. D. Sidell, *J. Chem. Soc.* D 360 (1971). See also S. Alvarado, F. Fariña and J. L. Martin, *Tetrahedron Lett.* 3377 (1970).

[11] T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr. and J. M. Lyding, *J. Am. Chem. Soc.* **99**, 5513 (1977).

[12] For a preliminary report on the synthesis of **40** and its use in other ventures see T. R. Kelly and W.-G. Tsang, *Tetrahedron Lett.* 4457 (1978).

[13] For an alternative synthesis of **38** see T. Oishi, M. Nagai and Y. Ban, *Tetrahedron Lett.* 491 (1968).

[14] [a]K. Krohn and K. Tolkiehn, *Tetrahedron Lett.* 4023 (1978); [b]*Chem. Ber.* **112**, 2640 (1979), [c]For related studies see F. Fariña and P. Prados, *Tetrahedron Lett.* 477 (1979).

[15] For the preparation of **51** see T. Ibuka, Y. Mori and Y. Inubushi, *Tetrahedron Lett.* 3169 (1976).

[16] Due to the *pronounced* tendency of compounds akin to **60** and **61** to suffer A-ring aromatization, severe constraints are imposed on the reaction conditions employable for deprotection. "Directing" groups other than pivaloyl and *p*-nitrocarbobenzyloxy which were examined and found wanting, for one or more reasons, include acetyl, CBz, t-BOC, t-butyldimethylsilyl, chloroacetyl and *o*-nitrobenzoyl.

[17] Daunomycinone (**2**) and its regioisomer are easily distinguishable by the chemical shifts of the ^{1}H-NMR resonances of the phenolic hydroxyl protons;[14b] ^{1}H-NMR spectra of crude reaction mixtures contained no resonances attributable to the regiomer.

[18] B. Loev and M. M. Goodman, *Chem. & Ind.* 2026 (1967).

[19] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).

[20] For a different procedure see E. J. Salmi, *Chem. Ber.* **71**, 1083 (1938).

[21] We thank Prof. B. Trost for suggesting the use of this base; use of n-BuLi gave **40** contaminated with the diene resulting from addition of n-BuLi to **39** followed by dehydration.

[22] An apparatus modeled after that devised by Meyers *et al.* (A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson and C. D. Liang, *J. Org. Chem.* **44**, 2247 (1979)), was employed. We thank Prof. Meyers for a preprint of this paper.

[23] For indexing purposes the ring system is numbered in the Experimental Section of this paper in accordance with the numbering system of *Chemical Abstracts*, which is at variance with the numbering system introduced by Brockmann [H. Brockmann, *Prog. Chem. Org. Nat. Prods.* **21**, 121 (1963)] that is used by most workers in the anthracycline field.

[24] Prior to **7** becoming commercially available it was prepared by isomerization of 1-methoxy-1,4-cyclohexadiene (*i*) with tristriphenylphosphinerhodium chloride in ethanol-free chloroform (A. J. Birch and G. S. R. Subba Rao, *Tetrahedron Lett.* 3797 (1968)). Failure to remove the EtOH from the $CHCl_3$ apparently results in the formation of some of the ethoxy analog of **7** as ultimately evidenced by the contamination of **46** with a small amount of its ethoxy analog. We thank Dr. Max Brinkman of Heico for a generous gift of *i*.

[25] Although not rigorously established, the regiochemistry of **48** is assigned by analogy to Schemes 2 and 4.

[26] Although intermolecular Diels–Alder reactions generally proceed via an *endo* transition state,[27] we believe that in the present instance an *exo* transition state competes effectively because steric interactions between **47** and the bulky ketal grouping in **40** destabilize the *endo* transition state. In this context we note that the Diels–Alder reaction of **40** with naphthazarin diacetate affords two adducts in a 1 : 1.8 ratio; these must be *exo* and *endo* isomers since regioisomerism is not possible.

[27] For pertinent examples see, *inter alia* [a]footnote 12 in F. Fariña and P. Prados, *Tetrahedron Lett.* 477 (1979); [b]B. M. Trost, D. O'Krongly and J. L. Belletire, *J. Am. Chem. Soc.* **102**, 7595 (1980); [c]the paper of R. C. Gupta, P. A. Harland and R. J. Stoodley in this Symposium in Print; and [d]ref. 7.

[28] L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. 1; p. 534. Wiley: New York, (1967).

[29] It is possible to separate **55** and **63** without employing chromatography by adding an aqueous soln of $Cu(OAc)_2$ (*ca* 1 equiv. based on **55**) to a dilute THF soln of **55/63**, collecting the precipitated copper complex of **55** and regenerating **55** by vigorously stirring (Morton flask) the crude complex with CH_2Cl_2/aq NaH_2PO_4. The yield for this process is somewhat lower than when chromatography is employed, in part because complex formation does not proceed to completion.

[30] This procedure was first developed in 1979 and has been repeated numerous times over the intervening period by various individuals. During the past two years it has been necessary to change the amount of KH used to 0.05 equiv. in order for the oxidation to proceed as well as it did initially. It is unclear why this modification became necessary although it is possible that the nature (e.g. particle size) of commerical KH has changed during the past five years. With 0.05 equiv. of KH the reaction is much slower but cleavage of the *p*-NCBz, which became a major side reaction, is suppressed.

[31] Use of conventional methods (e.g. KF/MeOH or H_3O^+) for cleaving the TMS groups led to extensive A-ring aromatization.[16] The potential utility of H_2O_2 in this

context was first noted in the course of an unsuccessful attempt to deacetylate the corresponding acetate (**59**, Ac instead of *p*-NCBz) by using aqueous hydrogen peroxide [see W. P. Jencks, *J. Am. Chem. Soc.* **80**, 4585 (1950)] in which case desilylation (but not deacetylation) occurred.

[32] Based on the procedure of A. S. Kende, Y.-G. Tsay and J. E. Mills, *J. Am. Chem. Soc.* **98**, 1967 (1976). For experimental details, see A. S. Kende, J. E. Mills and Y.-G. Tsay, U.S. Patents 4021457, (1977) and 4070382, (1978).

[33] This ratio was determined on a Varian 5000 chromatograph equipped with a 30 cm × 4 mm CH-10 Micro Pak column and a UV detector (λ_{max} and ε values of (±)-**2** and (±)-epi-**2** are identical) by using a 40:60 acetonitrile/water solvent mixture [flow rate, 1 ml/min; retention times for (±)-**2** and (±)-epi-**2**, 12 and 6 min, respectively]. We thank Dr. W. Pegg for suggesting the solvent system.

[34] *Cf* C. M. Wong, R. Schwenk, D. Popien and T.-L. Ho *Can. J. Chem.* **51**, 466 (1973) and ref. 32.