Total Synthesis of Anthracyclinones via Intramolecular Base-Catalyzed Cyclizations[1]

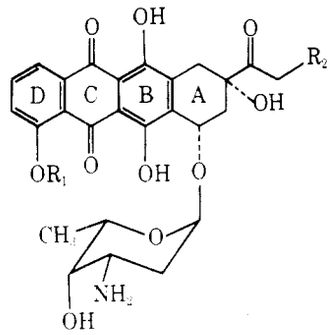
Fumio Suzuki, Steven Trenbeath, Robert D. Gleim, and Charles J. Sih*

Contribution from the School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706

Received May 1, 1978

Methods for the preparation of anthracyclinones from substituted anthraquinone derivatives are described. The construction of the alicyclic A ring was achieved via intramolecular base-catalyzed cyclizations of dihydroanthraquinones.

Daunorubicin[2] (1), doxorubicin[3] (2), and carminomycin[4] (3) are members of a large family of anthracycline antibiotics



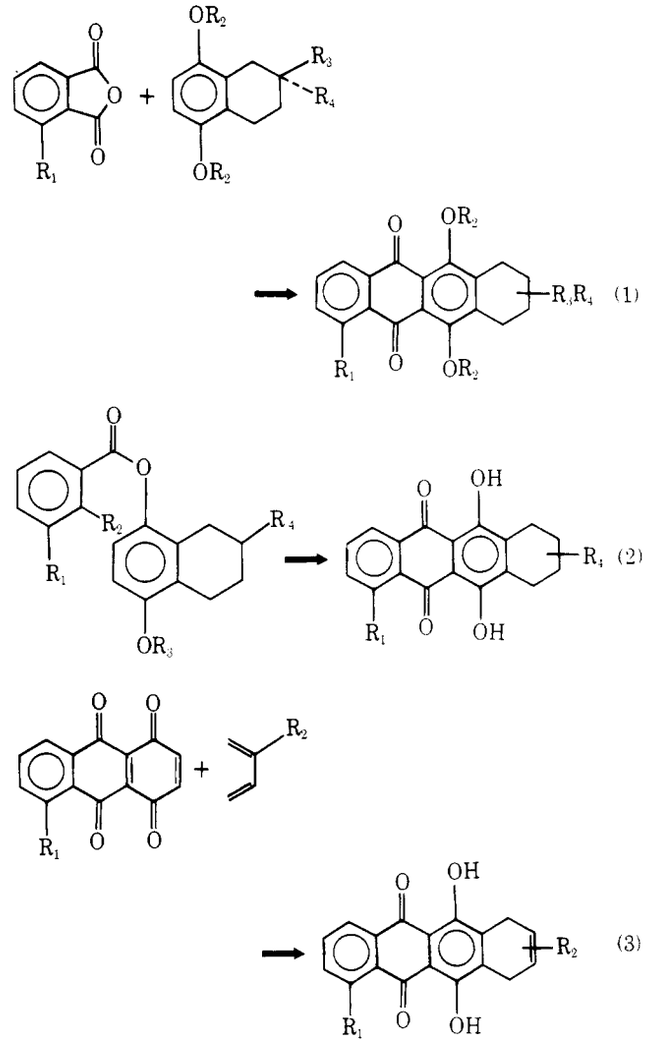
1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = CH_3$; $R_2 = OH$
3, $R_1 = H$; $R_2 = H$

produced by *Streptomyces* sp. The structures of these compounds were established by a combination of spectral analyses[5b] and chemical degradations[2a,5a] and further confirmed by X-ray analysis,[5c] which revealed these molecules to consist of a tetracyclic aglycon attached to the amino sugar daunosamine via a β-glucosidic bond. The stereochemistry of both asymmetric centers of the aglycons is of the *S* configuration, and the amino sugar is of the L configuration.

In recent years, these antibiotics have attracted considerable attention because of their remarkable effectiveness in combating a variety of human malignancies.[6] However, like many cytotoxic drugs, they also display untold side effects, the most serious being their cardiotoxicities.[7] Due to the lack of an efficient fermentation process[3b] and that a small structural difference between doxorubicin and daunorubicin can so favorably affect therapeutic characteristics,[6] there has been continual chemical interest aimed at the development of an efficient total synthesis of these antibiotics and totally synthetic analogues with improved therapeutic properties. As several suitable syntheses of daunosamine[8] and its coupling to daunomycinone[9] have already been accomplished, our research efforts have been directed to the synthesis of the aglycone moieties (anthracyclinones) of these antitumor antibiotics.

Several synthetic approaches to the tetrahydro-5,12-naphthacenedione ring system have been developed utilizing Friedel–Crafts[10] (eq 1), photo-catalyzed or Lewis acid catalyzed Fries[11] (eq 2), and Diels–Alder reactions[12] (eq 3) as illustrated in Scheme I. With a few exceptions,[11a,13] most of these synthetic schemes lack regiochemical control with respect to the orientation of ring A and D substituents. Recently, we developed a fundamentally different approach to the synthesis of anthracyclinones[1] from appropriately substituted anthraquinone derivatives. In this paper, we record the precise experimental procedures required for the successful elaboration of the alicyclic ring A since these methods are likely to find frequent use in the synthesis of anthracyclinones.

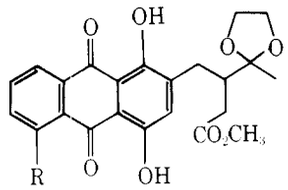
Scheme I



Anthraquinone derivatives are potential starting materials for anthracyclinone synthesis because they are readily available from microbial[14] and plant[15] sources or as intermediates of dye synthesis.[16] While one can readily envisage a regiospecific synthesis of anthracyclinones via the cyclization of appropriately substituted anthraquinone derivatives such as **4**, the success of this approach rests heavily on the development of a suitable method for the construction of ring A. To examine the feasibility of this synthetic scheme, we selected **5** as a model compound for our initial ring closure explorations, for it may be more readily prepared than **4**. Also, 4-demethoxydaunorubicin is a compound of considerable clinical importance for it possesses an improved therapeutic index[17] as compared to daunorubicin in animal studies.

Condensation of phthalic anhydride with methylhydroquinone in an $AlCl_3$–NaCl melt at 190 °C afforded 2-

0022-3263/78/1943-4159$01.00/0 © 1978 American Chemical Society

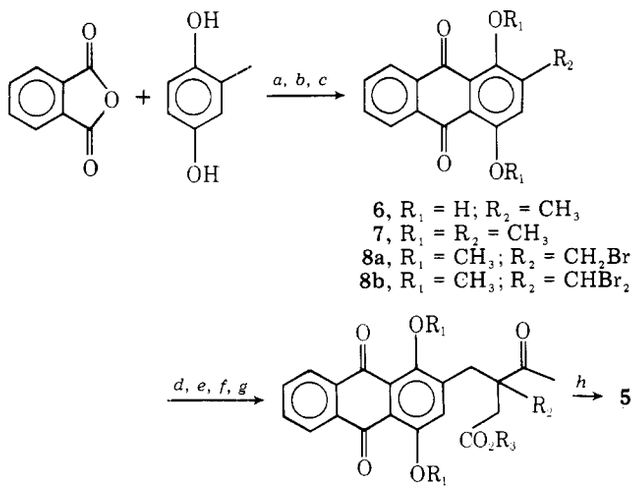


4, R = OCH_3
5, R = H

methyl-1,4-dihydroxyanthraquinone (**6**) in 79% yield. After methylation, **7** was brominated to give **8a** (55%), accompanied by residual **7** and dibromide **8b**, but **8a** was isolated by recrystallization. It is interesting to note that while bromination of **7** was comparatively rapid (2 h), bromination of 1,4-diacetoxy-2-methylanthraquinone was very slow (16 h), presumably due to the electron-withdrawing acetyl groups. Alkylation of **8a** with ethyl 3-acetyllevulinate gave **9** (88%). Simultaneous ester hydrolysis and cleavage of β-diketone were achieved by treating **9** with 8% NaOH at 60 °C. The model compound **5** was obtained by esterification of **10** with diazomethane, demethylation with BBr_3 at −78 °C, and ketalization. Operationally, the conversion of 2-methylhydroquinone to **5** may be easily executed with one chromatography in an overall yield of 23% (Scheme II).

Having the tricyclic ketal **5** in hand, we proceeded to examine experimental conditions required for cyclization using a variety of bases (NaH, LDA, NaOMe, *t*-BuOK), acids (BF_3 ethereate, PPA, HF, H_2SO_4), and solvents (DMF, HMPA, THF, MeOH, *t*-BuOK) at varying temperatures (25–160 °C), but unfortunately no cyclization of **5** was observed. We surmised that this resistance of **5** toward cyclization is attributed to the apparent strong electron-withdrawing property of the anthraquinone system. To surmount this obstacle, it appeared necessary to alter the electronic configuration of the anthraquinone system (Scheme III). This was achieved by reduction of **5** with zinc dust in acetic acid[12f] to yield a single diastereomer **13**, as evidenced by the two sharp singlets at δ 3.92 and 3.66 corresponding to the protons of the ethylene ketal and the methyl ester. When **13** was refluxed with BaO and zinc dust in acetone (condition 5, Table I), another diastereomer

Scheme II

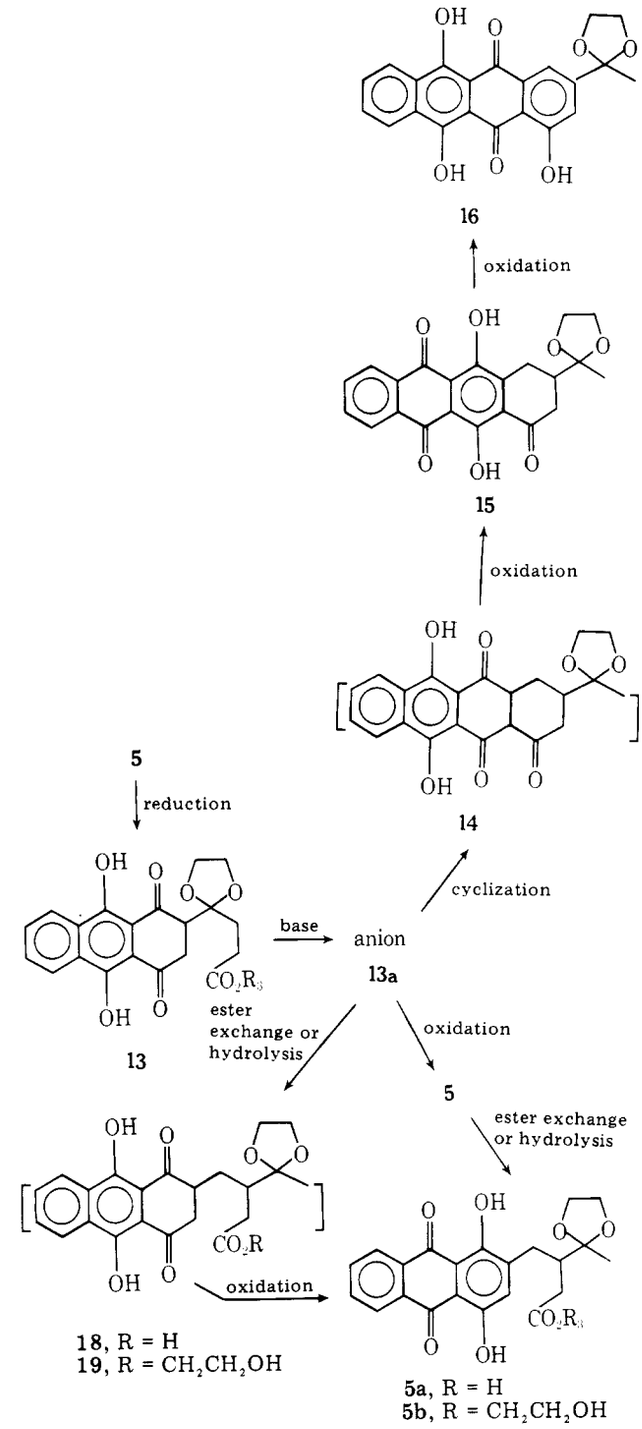


6, R_1 = H; R_2 = CH_3
7, R_1 = R_2 = CH_3
8a, R_1 = CH_3; R_2 = CH_2Br
8b, R_1 = CH_3; R_2 = $CHBr_2$

9, R_1 = CH_3; R_2 = CH_3CO; R_3 = Et
10, R_1 = CH_3; R_2 = R_3 = H
11, R_1 = CH_3; R_2 = H; R_3 = CH_3
12, R_1 = R_2 = H; R_3 = CH_3

[a] $AlCl_3$–NaCl, 190 °C. [b] $(CH_3)_2SO_4$–K_2CO_3–acetone, reflux. [c] NBS–BPO–CCl_4, reflux. [d] NaH–ethyl 3-acetyllevulinate–DMF, 25 °C. [e] 8% NaOH, 60 °C. [f] CH_2N_2. [g] BBr_3–CH_2Cl_2, −78 °C. [h] Ethylene glycol–benzene, reflux.

Scheme III



18, R = H
19, R = CH_2CH_2OH

5a, R = H
5b, R = CH_2CH_2OH

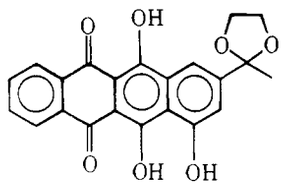
was formed as indicated by the appearance of another pair of singlets of equal intensity at δ 3.94 and 3.62. An exhaustive study of the cyclization of the leuco form **13** using a variety of conditions is tabulated in Table I. Conditions 1–4 catalyzed the oxidation of **13** back to **5**. However, the reaction path was dramatically altered when Zn dust was included in the reaction mixture (condition 6). This is evidenced by the appearance of four colored compounds on TLC plates ($CHCl_3$–acetone, 95:5): pink-red (R_f 0.52); orange and yellow (both have R_f 0.32); and brownish red (R_f 0.25). The orange and yellow compounds corresponded to **5** and residual starting material **13** respectively, by comparison with authentic samples. After preparative TLC, the brownish red band was isolated and characterized to be **15** on the basis of mass spectral and NMR data. The pink-red band was identified as an oxidation product of **15** and was assigned the structure **16**. This struc-

Table I. Reaction Conditions and Product Yield Data for the Cyclization of 5.

run	base	solvent	reducing reagents	temp, °C	time, min	major products
1	NaH or LDA	THF–HMPA			30	**5**
2	BaO	HMPA		140	18	**5**
3	NaH	DMF		140	4	**5**
4	CaO	DMF	Zn	140	35	**5**
5	BaO	acetone	Zn	reflux	180	**13**[a] + **5**
6	BaO	DMF	Zn	140	25	**15** (20%), **16** (14%), **5** & **13** (12%)[b]
7	NaH	DMF	Zn	25	3	**5**
8	NaH	DMF	$Na_2S_2O_4$	25	10	**5**
9	CaO	HMPA	Zn	140	10	**5**
10	CaO	diglyme	Zn	140	35	**15** (12%), **5** & **13** (50%)
11	CaO	*t*-BuOH	Zn	reflux	30	**5, 13**
12	CaO	ethylene glycol	Zn	140	3	**15** (49%), **5a, 5b**
13	CaO	ethylene glycol	Zn	25~80	60	**5, 5b**
14	MgO	ethylene glycol	Zn	140	9	**5, 13**
15	CaO	ethylene glycol–diglyme (3:2)	Zn	140	3	**15** (52%), **5a, 5b**

[a] Two diastereomers. [b] Values in parentheses indicate isolated yields.

tural assignment was deduced from the NMR data which showed three strongly hydrogen-bonded proton signals at δ 13.35, 12.25, and 10.37, rendering structure **17** an unlikely



17

possibility. Also, from thermodynamic considerations, one would expect that aerial oxidation of **15** would preferentially give rise to an isomer with maximum hydrogen bonding.

It is noteworthy that conditions 7 (NaH–Zn–DMF) and 8 (NaH–$Na_2S_2O_4$–DMF) afforded only **5** as a result of back oxidation of **13.** This suggests that the anion **13a** thus generated appears to be rather unstable, and neither Zn nor $Na_2S_2O_4$ suppressed the oxidation of the anion (**13a**) to the anthraquinone anion via electron transfer or some other mechanism. On the other hand, anion **13a,** generated by the use of divalent bases such as BaO or CaO, appears to be less unstable. Presumably, these divalent counterions may be involved in stabilization via complexation to allow cyclization to occur. To some extent, Zn appeared to suppress back oxidation.

Since **13** is ipso facto the diketo form of the 1,4,9,10-tetrahydroxyanthracene derivative, one may consider this cyclization to be analogous to C acylation of ambident anions of hydroquinones. It is well known that hydroxylic solvents (e.g., H_2O, CF_3CH_3OH, etc.) favor C- vs. O-alkylation of ambident anions of phenoxides or naphthoxides.[18] Conceivably, O-acylation may also occur, giving rise to the acid **18** upon workup, but this possibility appears remote in view of the involvement of seven- or eight-membered rings.

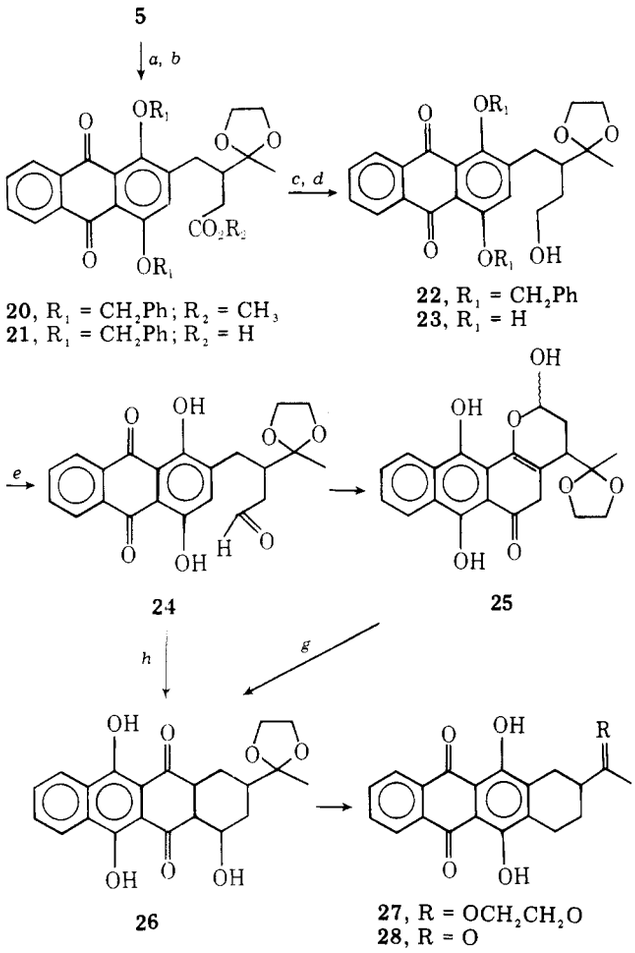
Polyhydroxylic solvents with high boiling points such as ethylene glycol were found to be the best solvent for this cyclization since in general intramolecular acylation reactions require high activation energies. For optimum results, cyclization of **13** should be carried out using the following procedure: CaO (8 equiv), Zn (2 equiv), ethylene glycol–diglyme (3:2), and heating at 140 °C for 3 min; diglyme was used for better dissolution of **13** (condition 15). It is important to emphasize that after mixing the solvents, base and **13** at −78 °C, to minimize ester exchange and back oxidation, the temperature of the reaction flask should be brought to 140 °C as quickly as possible because the glycolic ester **19** (leuco form) failed to undergo cyclization under these reaction conditions (Scheme III). This suggests that the rate of cyclization is determined by entropies of activation.

Since the intramolecular Claisen cyclization requires rather rigid experimental conditions to suppress side reactions, it may not be suitable for large-scale operations. We reasoned that if the ester grouping is transformed into an aldehyde, cyclization may be more facile due to a lowering of activation energy and may minimize competitive reactions such as back oxidation. Thus, **5** was converted into **24** via a five-step reaction sequence in 35% overall yield (Scheme IV). This included benzylation of **5** to give **20** (91%), hydrolysis of **20** (92%), reduction of **21** with diborane (68%), debenzylation of **22** (87%), and oxidation of **23** with pyridinium chlorochromate (66%). It was found that **5** was easily reduced to its corresponding anthracene derivative with either diborane or $LiAlH_4$ at 25 °C, presumably via intramolecular hydride transfer and dehydration. Thus, the hydroxyls of **5** were protected as benzyl ethers. Reduction of **24** with zinc dust in acetic acid afforded two diastereomers (**25**; 94% which were separated by preparative TLC. Both compounds gave identical mass spectra, and each diastereomer exhibited a signal at δ 13.50 or 13.58, characteristic of one hydrogen-bonded proton, but no signals corresponding to aldehydic protons were observed. These spectral data are consistent with the supposition that the expected dihydroanthraquinone derivative preferentially exists in its enol hemiacetal forms, **25.** This mixture of diastereomers (**25**) was cyclized directly without further purification using condition 15 of Table I to yield **27** as red crystals in 56% yield. Presumably, this transformation proceeds via the unstable intermediate **26,** which upon dehydration and tautomerism affords **27.** Acid deketalization of **27** afforded **28** in 92% yield.

This sequence of reduction of **24** into its leuco form, followed by base-catalyzed cyclization is mechanistically equivalent to an intramolecular Marschalk reaction. In fact, it was subsequently found that this transformation of **24** into **27** was conveniently affected in one step using $Na_2S_2O_4$ in 8% NaOH and *p*-dioxane at 90 °C in comparable yield (50%).

The successful development of methods for ring A closure in the 4-demethoxy series prompted us to focus our attention to the regiochemical synthesis of **4** from the readily available starting material 1-hydroxy-5-methoxyanthraquinone[19] (**29**) (Scheme V). Methylation of **29** at the C-2 position using dithionite and aqueous formaldehyde in 1.5 N NaOH (Marschalk reaction)[20] afforded **30** in 60% yield after silica gel chromatography. Acylation of **30** with acetic anhydride in the presence of a catalytic amount of concentrated H_2SO_4 at 25 °C gave **31** in quantitative yield. Treatment of **31** with 1.3 equiv of NBS yielded the desired bromide **32a** (60%) and di-

Scheme IV



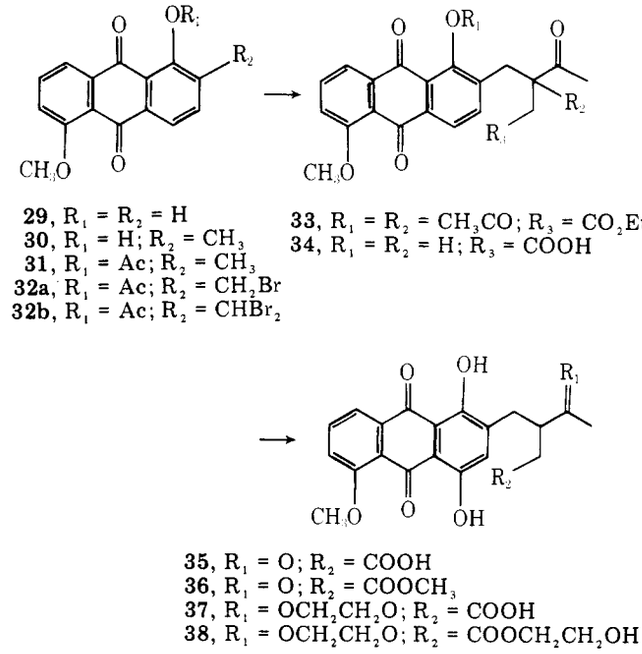
20, $R_1 = CH_2Ph$; $R_2 = CH_3$
21, $R_1 = CH_2Ph$; $R_2 = H$
22, $R_1 = CH_2Ph$
23, $R_1 = H$
24
25
26
27, R = OCH_2CH_2O
28, R = O

[a] $PhCH_2Br$, K_2CO_3–acetone, reflux. [b] 8% NaOH, *p*-dioxane, 90 °C. [c] BH_3, THF, 25 °C. [d] 5% Pd–$BaSO_4$, H_2. [e] PCC–CH_2Cl_2. [f] Zn–ACOH, 25 °C. [g] CaO, ethylene glycol–diglyme, Zn, 140 °C. [h] $Na_2S_2O_4$, 8% NaOH, *p*-dioxane, 90 °C.

bromide **32b** (27%). The monobromide **32a** was conveniently separated from the mixture by several crystallizations from $CHCl_3$–CCl_4 and silica gel chromatography. Alkylation (NaH, DMF, 25 °C) of **32a** with ethyl 3-acetyllevulinate gave **33** in 96% yield. Hydrolysis of the ester grouping and cleavage of the β-diketone (reverse Claisen) were simultaneously effected by the reaction of **33** with 5% NaOH at 65 °C (91%). The overall yield of **34** from **30** was 52%.

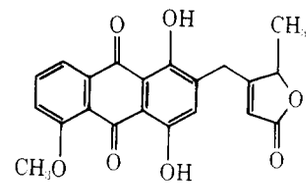
Introduction of the hydroxyl function at C-4 in **34** was accomplished using the E1bs oxidation procedure.[21] After expending a considerable amount of effort in defining the optimum reaction conditions, moderate yields of **35** (42%) were obtained along with unreacted **34** (38%), which was conveniently separated from the product without chromatography and recycled. Attempts to introduce the C-4 hydroxylation step at an earlier stage in our synthesis using **30** as substrate were unsuccessful. Apparently, this failure may be attributed to the poor solubility of **30** in the aqueous oxidative medium, and addition of DMF, Me_2SO, or THF to the reaction medium did not improve the hydroxylation process. In our experience, the presence of a carboxylic acid function is a prerequisite to obtaining reasonable yields of the hydroxylated product in the E1bs reaction since it greatly improves the solubility of the compound in the aqueous oxidative medium. The use of mixed solvents has not been fruitful, for lower yields of **35** were obtained in each instance. Attempts to oxidize **34** at C-4 using other oxidation reagents (Fremy salt, CrO_3–OAC, H_2O_2–$AlCl_3$, O_2–salcomine) did not give significant quantities of the desired product.

Scheme V



29, $R_1 = R_2 = H$
30, $R_1 = H$; $R_2 = CH_3$
31, $R_1 = Ac$; $R_2 = CH_3$
32a, $R_1 = Ac$; $R_2 = CH_2Br$
32b, $R_1 = Ac$; $R_2 = CHBr_2$
33, $R_1 = R_2 = CH_3CO$; $R_3 = CO_2Et$
34, $R_1 = R_2 = H$; $R_3 = COOH$
35, $R_1 = O$; $R_2 = COOH$
36, $R_1 = O$; $R_2 = COOCH_3$
37, $R_1 = OCH_2CH_2O$; $R_2 = COOH$
38, $R_1 = OCH_2CH_2O$; $R_2 = COOCH_2CH_2OH$

Having the desired key intermediate **35** at hand, we proceeded to examine conditions required for its cyclization using acidic reagents such as HF, concentrated H_2SO_4, PPA, and BF_3 ethereate at varying temperatures. In each instance, a complex mixture of products was formed, but no anthracyclinones were detected. When **35** was treated with HF at 100 °C,[22] with PPA at 70 °C, or with BF_3–Et_2O at 120 °C, a major product was formed which was characterized as the unsaturated lactone **39**, mp 294–297 °C.



39

Since attempts to catalyze the cyclization of **4** with conventional acidic reagents were unsuccessful, we decided to call upon the cyclization method that was used in the 4-demethoxy series. Thus, **35** was quantitatively converted into **36** with diazomethane, which was then transformed into its ethylene ketal **4** in 82% yield. However, in contrast to the 4-demethoxy series, **4** was only sluggishly and incompletely reduced into its leuco form, **40**, using zinc dust in acetic acid. It was difficult to separate **40** from **4** via preparative TLC because of the susceptibility of **40** to undergo aerial oxidation back into **4**. Attempts to accelerate this reduction process through the addition of formic or hydrochloric acid were without success. On the other hand, **4** was found to be smoothly converted into **40** in 85% yield using dithionite in 5% NaOH; a small quantity of dioxane was needed to ensure the dissolution of **4**.

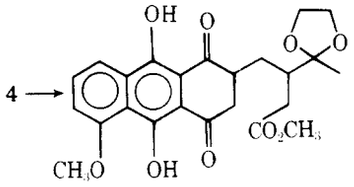
Having the dihydroanthraquinone derivative at hand, we subjected it to the same cyclization conditions (Zn, ethylene glycol–diglyme, CaO, 140 °C) successfully applied to the 4-demethoxy compounds. However, contrary to our expectations, the major products that formed were **37** and **38** and only traces of **41** (<1%) were detected. Treatment of **40** with a variety of conventional bases (NaH, LDA, *t*-BuOK, MeONa, BaO) in several solvents (DMF, THF, HMPA) with zinc dust or dithionite failed to yield detectable quantities of **41**. As

Table II. Conditions for the Cyclization of 40

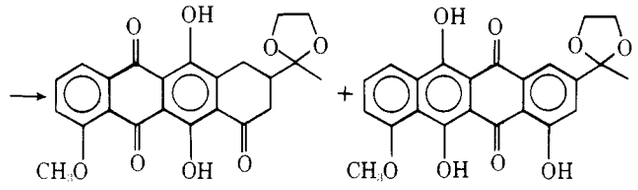
run	solvent	base	reducing reagent	reaction time, min	temp, °C	yield of 19,[a] %
1	1,2-propanediol	CaO	Zn	3	140	1–3
2	2,3-butanediol	CaO	Zn	3	140	1–3
3	2,2-dimethylpropanediol	CaO	Zn	3	140	1–3
4	glycerol	CaO	Zn	3	140	5
5	glycerol–H_2O (4:1)	CaO	Zn	3	140	8.4
6	sorbitol (10 equiv)–DMF	CaO	Zn	3	140	1
7	phenol	CaO	Zn	3	140	*b*

[a] Isolated yields. All reactions were carried out using 50 mg of **40**. Major products were different esters of **38**, depending on the solvent used. [b] The major product was **4**.

transesterification appeared to be a major side reaction and the resulting glycolic ester. **38** resisted cyclization, a series of more bulky glycols and polyhydroxylic compounds was evaluated as potential solvents for the ring closure reaction, with the hope of minimizing exchange reactions. The experimental conditions and results are summarized in Table II. It was found that by substituting glycerol–H_2O (4:1) for ethylene glycol as solvent, 8.4% of **41** was obtained, along with a trace of **42**.



40

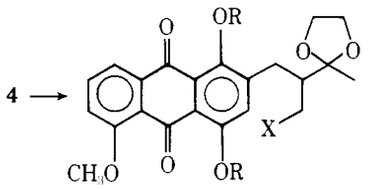


41 **42**

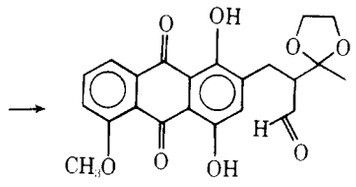
It was somewhat surprising to find that the presence of the 4-methoxyl group markedly altered the electronic properties of **40** as compared to the 4-demethoxy series. One may speculate that the substitution of a methoxyl for hydrogen on an aromatic ring raises the energy level of the LUMO as a rule,[23] thereby accelerating the oxidation of the anion, via electron transfer. However, it is also possible that the 4-methoxyl group may sterically interfere with the proper chelation of the divalent metal, thus retarding cyclization. It would be interesting to distinguish the relative importance of electronic vs. steric effects by the substitution of the methoxyl with a methyl group.[24] This unexpected turn of events forces us to utilize the intramolecular Marschalk reaction to bring our synthetic strategy into fruition. Thus, the ketal **4** was transformed into **47** via a five-step reaction sequence involving benzylation ($PhCH_2Br$, K_2CO_3–acetone; 99% yield), hydrolysis (8% NaOH, dioxane, 90 °C; 92%), reduction (BH_3, THF, 25 °C; 79%), debenzylation (H_2, Pd–$BaSO_4$, ethyl acetate; 90%), and oxidation (PCC, CH_2Cl_2, 25 °C; 65%) in 42% overall yield from **4** (Scheme VI).

Treatment of **47** with basic sodium dithionite at 90 °C followed by acidification afforded red crystalline tetracyclic compound **50**, mp 177–178.5 °C, in 55% yield. By analogy to the 4-demethoxy series, this cyclization proceeds via the intermediates **48** and **49**. We surmised that this aldol-type condensation (**48** to **49**) requires considerably less activation energy than that of the Claisen-type condensation (**40** to **41**), and thus the excess dithionite in aqueous base completely

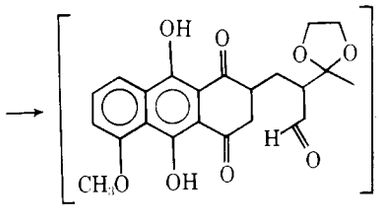
Scheme VI



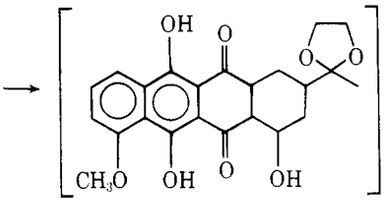
43, R = CH_2Ph; X = CO_2CH_3
44, R = CH_2Ph; X = CO_2H
45, R = CH_2Ph; X = CH_2OH
46, R = H; X = CH_2OH



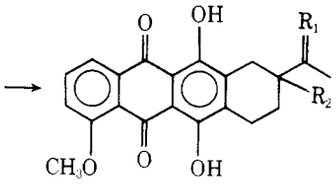
47



48



49



50, R_1 = OCH_2CH_2O; R_2 = H
51, R_1 = O; R_2 = H
52, R_1 = O; R_2 = OH

suppressed the back oxidation of **48** to **47**. Unfortunately, this aqueous basic condition readily cleaved the ester grouping in **40**, so that it is unsuitable for Claisen-type condensation. Moreover, dithionite is unstable at the high temperature required for the Claisen-type cyclization. Deketalization of **50**

with 5% H_2SO_4 in a mixture of THF–acetone afforded **51**, whose spectral properties were found to be identical with an authentic sample.[11c] Hydroxylation at C-9 in **51** was achieved via a four-step reaction sequence, which has been used for the introduction of the C-17 hydroxyl group into steroids.[25] This involved enol acetylation via continuous distillation of the reaction mixture containing **51** and a large excess of *p*-toluenesulfonic acid in acetic anhydride at 145 °C seems to favor the formation of the thermodynamically more stable $\Delta^{9,13}$ enol ether. After epoxidation with *m*-chloroperbenzoic acid, the epoxy acetate was treated successively with base and acid to ensure complete hydrolysis and rearrangement to (±)-7-deoxydaunomycinone (**52**), which was isolated by silica gel chromatography in 50% overall yield from **51**. As methods for the introduction of hydroxyl functions at C-7[12c,26] and C-14[12c,26] have already been described, this route formally constitutes a regiospecific synthesis of adriamycinone.

Equally important, these modes of base-catalyzed cyclizations will probably prove to be of general utility in other regiospecific syntheses of anthracyclinones from anthraquinone derivatives. More direct routes to the preparation of **47** from islandicin methyl ether are currently being investigated.

Experimental Section

Melting points are uncorrected. Unless otherwise stated, IR spectra were taken in $CHCl_3$ using a Perkin-Elmer Model 257 grating spectrophotometer. ^1H NMR data ($CDCl_3$) were obtained with a Varian Associates Model EM 390. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ = 0). Mass spectra were recorded using an AEI-MS-9 double focusing mass spectrometer or a Finnigan 1015 spectrometer at an ionizing voltage of 70 eV. All compounds which were submitted to mass spectrometric molecular weight determination were of high purity as determined by NMR anslysis and TLC. Carbon–hydrogen analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thin-layer chromatograms (TLC) were obtained on 250 μm silica gel G plates. Preparative layer chromatograms (PLC) were obtained on 20 × 20 × 0.25 cm silica gel 60F-254 plates (E. Merck). Column chromatography was performed with silica gel, 70–270 mesh ASTM (Macherey and Nagel). Solvent extracts of aqueous solution were dried over anhydrous $MgSO_4$. Solutions were concentrated under reduced pressure using a rotary evaporator.

2-Methyl-1,4-dihydroxyanthraquinone (6). A mixture of 184 g (1.38 mol) of $AlCl_3$ and 36 g (0.62 mol) of NaCl was added to a 2-L beaker and heated with a Bunsen burner to 180–190 °C for several minutes. To this melt was added 20 g (0.135 mol) of phthalic anhydride and 16.7 g (0.135 mol) of methylhydroquinone, and this mixture was stirred for 8 min at 180–190 °C. After cooling, the reaction was quenched with 750 mL of ice water and concentrated HCl (150 mL). After heating the mixture for 1 h on a steam bath, it was extracted with $CHCl_3$ three times. The combined $CHCl_3$ extract was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to dryness. The residue was washed with dry methanol and recrystallized from $CHCl_3$–CCl_4 to afford 27.2 g (0.107 mol, 79.3%) of pure **6**: mp 178–179 °C; IR (KBr) 1628, 1583, 1460, 1434, 1350, 1273, 1260, 1249, 1218, 726 cm^{-1}; NMR δ 13.21 (s, 1 H), 12.83 (s, 1 H), 8.25 (m, 2 H), 7.75 (m, 2 H), 7.06 (s, 1 H), 2.30 (s, 3 H); MS *m/e* (%) 254 (100, M^+), 253 (53), 239 (11), 197 (22), 152 (26), 141 (31), 140 (18), 115 (30), 105 (21), 102 (47), 77 (29).

Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.33; H, 4.13.

2-Methyl-1,4-dimethoxyanthraquinone (7). A mixture containing 27 g (0.106 mol) of **6**, 96.6 g (1.55 mol) of K_2CO_3, and 30 mL (0.316 mol) of dimethyl sulfate in 1.2 L of dry acetone was stirred under N_2 at reflux for 15 h. After filtration, the filtrate was evaporated to dryness under reduced pressure. The residue (yellow solid) was washed with methanol to remove any unreacted dimethyl sulfate and crystallized from $CHCl_3$–CCl_4 to give 27.5 g (0.097 mol, 92%) of pure **7**: mp 132.5–133.5 °C; IR (KBr) 1668, 1592, 1330, 1248, 975, 730 cm^{-1}; NMR δ 8.17 (m, 2 H), 7.69 (m, 2 H), 7.20 (s, 1 H), 4.01 (s, 3 H), 3.89 (s, 3 H), 2.42 (s, 3 H); MS *m/e* (%) 282 (100, M^+), 253 (48), 165 (62), 152 (58), 139 (59). On TLC ($CHCl_3$–acetone, 98:2), **6** and **7** possessed R_f values of 0.55 and 0.36, respectively.

Anal. Calcd for $C_{17}H_{14}O_4$: 72.33; H, 5.00. Found: C, 71.86; H, 4.93.

2-Bromomethyl-1,4-dimethoxyanthraquinone (8a). A mixture containing 25.6 g (0.0908 mol) of **7**, 17.0 g (0.0955 mol) of *N*-bromosuccinimide, and 50 mg of benzoyl peroxide in 3.1 L of carbon tetrachloride was stirred under N_2 at reflux for 2 h. During this period the reaction contents were irradiated with a sunlamp. After cooling, the succinimide (white solid) was removed by filtration, and the filtrate was evaporated under reduced pressure. Crystallization of the residue from $CHCl_3$–CCl_4 gave 19.7 g (0.0546 mol, 60%) of **8a**: mp 184–186 °C; IR (KBr) 1670, 1590, 1323, 1266, 1240, 1038, 1008, 972, 731 cm^{-1}; NMR δ 8.15 (m, 2 H), 7.70 (m, 2 H), 7.38 (s, 1 H), 4.61 (s, 2 H), 4.01 (s, 3 H), 4.00 (s, 3 H); MS *m/e* (%) 362 (98, M + 1), 360 (100), 281 (65), 252 (51), 223 (84).

Anal. Calcd for $C_{17}H_{13}O_4Br$: C, 56.53; H, 3.63. Found: C, 56.44; H, 3.71.

The mother liquor contained a mixture of **7**, **8a**, and **8b**, possessing R_f values of 0.36, 0.43, and 0.54 on TLC ($CHCl_3$–acetone, 98:2), in a ratio of 2:1:3.4, respectively. The dibromide **8b** was isolated by preparative TLC using two developments in $CHCl_3$–acetone (95:5). Crystallization of **8b** from $CHCl_3$–hexane afforded pure **8b**: mp 175–178 °C; IR ($CHCl_3$) 3018, 2940, 1672, 1593, 1462, 1394, 1318, 1266, 1237, 1037, 1002, 978 cm^{-1}; NMR δ 8.3–7.1 (m, 6 H), 4.10 (s, 3 H), 4.00 (s, 3 H); MS *m/e* (%) 442 (3), 441 (4), 440 (7) 439 (6), 438 (5), 437 (3), 361 (67), 360 (50), 359 (70), 358 (39), 280 (21), 279 (53), 273 (21), 263 (65), 262 (30), 251 (93), 243 (100), 242 (38), 237 (20).

Anal. Calcd for $C_{17}H_{12}O_4Br_2$: C, 46.39; H, 2.75. Found: C, 46.42; H, 2.78.

2-(2′-Acetyl-2′-carbethoxymethyl-3′-oxobutyl)-1,4-dimethoxyanthraquinone (9). To a suspension of 1.4 g (0.0585 mol) of NaH (prewashed with pentane) in 150 mL of dry DMF was added dropwise to 10.8 g (0.0582 mol) of ethyl 3-acetyllevulinate dissolved in 50 mL of DMF under N_2 at 25 °C. After completion of the addition, the mixture was heated at 40 °C until hydrogen evolution ceased (ca. 30 min). A solution containing 20.6 g (0.0571 mol) of **8a** in 50 mL of DMF was added dropwise to this suspension at 25 °C, and the reaction mixture was stirred for 15 h. The reaction was terminated by the addition of dilute HCl (20 mL), and the contents were extracted with ethyl acetate (150 mL × 4). The combined extract was successively washed with saturated $NaHCO_3$ and brine, dried, and evaporated to dryness. The residue was washed with dry methanol and crystallized from $CHCl_3$–ether to afford 23.5 g (0.0504 mol, 88%) of pure **9**: mp 163–163.5 °C; IR (KBr) 1724, 1700, 1670, 1281, 1262, 1242, 1157, 1042 cm^{-1}; NMR δ 8.13 (m, 2 H), 7.69 (m, 2 H), 4.07 (q, J = 7.2 Hz, 2 H), 3.93 (s, 3 H), 3.78 (s, 3 H), 3.57 (s, 2 H), 2.90 (s, 2 H), 2.20 (s, 6 H, 1.19 (t, J = 7.2 Hz, 3 H); MS *m/e* (%) 462 (8, M^+), 423 (15), 391 (51), 377 (53), 43 (100).

Anal. Calcd for $C_{26}H_{26}O_8$: C, 66.94; H, 5.62. Found: C, 66.70; H, 5.57.

2-(2′-Carboxymethyl-3′-oxobutyl)-1,4-dimethoxyanthraquinone (10). The reaction mixture contained 24.2 g (0.0519 mol) of **9** in 70 mL of 8% aqueous NaOH. After stirring the contents at 60 °C under N_2 for 3 h (a small amount of an insoluble oil was removed by Et_2O extraction), the alkaline solution was cooled and acidified with HCl. The yellow solution was separated by filtration after stirring for 30 min. The precipitate was collected by filtration, washed twice with water, dried, and evaporated to dryness. The yield of crude **10** was 18.7 g (0.0472 mol, 91%). Crystallization of **10** from $CHCl_3$–benzene gave mp 200–201.5 °C; IR (KBr) 3300–2800 (broad), 1715, 1668, 1592, 1330, 1260, 1243, 1039 cm^{-1}; NMR δ 8.73 (br, 1 H), 8.21 (m, 2 H), 7.76 (m, 2 H), 7.16 (s, 1 H), 4.03 (s, 3 H), 3.97 (s, 3 H), 2.4–3.6 (m, 5 H), 2.22 (s, 3 H); MS *m/e* (%) 396 (74), 353 (100), 265 (48), 263 (49), 165 (75), 152 (59), 151 (56), 43 (66). The relative mobilities of **9** and **10** on TLC plates were 0.55 and 0.49, respectively, when developed in ethyl acetate–acetic acid–isooctane–water (110:20:50:100 v/v).

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.67; H, 5.10.

2-(2′-Carbomethoxymethyl-3′-oxobutyl)-1,4-dimethoxyanthraquinone (11). To 18.1 g (0.0457 mol) of **10** in 300 mL of chloroform was added an excess of ethereal diazomethane at 0 °C. After stirring for 1 h, a few milliliters of acetic acid were added to destroy the unreacted diazomethane. Evaporation of the solvent and crystallization of the residue from $CHCl_3$–CCl_4 afford 17.0 g (0.0415 mol, 91%) of pure **11**: mp 129–130 °C; IR (KBr) 1726, 1703 (sh), 1669, 1329, 1314, 1260, 1242, 1039 cm^{-1}; NMR δ 8.19 (m, 2 H), 7.71 (m, 2 H), 7.13 (s, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.61 (s, 3 H), 2.4–3.6 (m, 5 H), 2.19 (s, 3 H); MS *m/e* (%) 410 (75, M^+), 379 (23), 367 (100), 165 (67), 152 (48), 43 (45).

Anal. Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found: C, 67.14; H, 5.42.

2-(2′-Carbomethoxymethyl-3′-oxobutyl)-1,4-dihydroxyanthraquinone (12). To 16.0 g (0.0390 mol) of 11 dissolved in 200 mL

of dichloromethane was added dropwise a dichloromethane (282 mL of 0.5 M solution) solution of BBr_3 (0.141 mol) under N_2 at −78 °C. After stirring for 7 h at −78 °C, aqueous $NaHCO_3$ was added and the contents were warmed up to room temperature. The organic layer was washed with brine three times, dried, and evaporated to dryness. The residue was crystallized from $CHCl_3$–CCl_4 to afford 12.7 g (0.0332 mol, 85%) of pure **12:** mp 170–180 °C; IR (KBr) 1730, 1703, 1625, 1588, 1450, 1433, 1410, 1365, 1308, 1260, 1240, 1225, 1205, 790 cm^{-1}; NMR δ 13.36 (s, 1 H), 12.81 (s, 1 H), 8.34 (m, 2 H), 7.82 (m, 2 H), 7.11 (s, 1 H), 3.62 (s, 3 H), 2.4–3.6 (m, 5 H), 2.28 (s, 3 H); MS *m/e* (%) 382 (8, M^+), 364 (42), 279 (57), 187 (100), 43 (60). The relative mobilities of **11** and **12** on TLC plates were 0.13 and 0.34, respectively, in $CHCl_3$–acetone (98:2). The monomethyl ether had an R_f value of 0.22.

Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 65.39; H, 4.96.

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-1,4-dihydroxyanthraquinone (5). A mixture consisting of 12.0 g (0.0314 mol) of **12,** 25 mL of ethylene glycol, 170 mL of benzene, and 30 mg of *p*-toluenesulfonic acid was stirred at reflux; water was collected with a Dean-Stark condenser. After 16 h, the mixture was cooled, diluted with 5% $NaHCO_3$, and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried, and evaporated to dryness. The residue (14.5 g) was chromatographed over 450 g of silica gel. Elution of the column with $CHCl_3$–EtOAC (95:5) gave 11.4 g (0.0268 mol, 85%) of pure **5:** mp 140.5–141 °C ($CHCl_3$–CCl_4); IR (KBr) 1729, 1625, 1587, 1432, 1267, 1232, 1052, 792 cm^{-1}; NMR δ 13.38 (s, 1 H), 12.86 (s, 1 H), 8.31 (m, 2 H), 7.78 (m, 2 H), 7.16 (s, 1 H), 3.96 (s, 4 H), 2.0–3.3 (m, 5 H), 1.39 (s, 3 H); MS *m/e* (%) 426 (3, M^+), 395 (3), 364 (23), 86 (52), 87 (100). The mobility of **13** on TLC plates was 0.26 when developed with $CHCl_3$–acetone (98:2).

Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.97; H, 5.21.

Zinc Reduction of 5. To 1.01 g (2.37 mmol) of **5** in 40 mL of glacial acetic acid was added 1.00 g (15.3 mmol) of zinc dust, and the reaction mixture was stirred under N_2 for 30 min at 25 °C. After dilution of the contents with 5% $NaHCO_3$, the mixture was extracted with $CHCl_3$ three times. The combined extract was washed successively with 5% $NaHCO_3$ and brine, dried, and evaporated to afford 0.92 g (2.14 mmol, 91%) of the yellow dihydroanthraquinone **13:** NMR δ 13.53 (s, 1 H), 13.50 (s, 1 H), 8.44 (m, 2 H), 7.69 (m, 2 H), 3.92 (br s, 4 H), 3.66 (s, 3 H), 1.29 (s, 3 H); MS *m/e* (%) 428 (1.8, M^+), 366 (8), 351 (5), 254 (23), 111 (18), 87 (100). On TLC plates, **13** possessed an R_f value of 0.35, whereas **5** had an R_f value of 0.32 when the plates were developed in $CHCl_3$–acetone (95:5). Compound **13** was too unstable to allow C, H analysis.

9-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-5,7,12-naphthacenetrione (15). (a) Condition 6. To 93 mg (0.21 mmol) of **18** in 3 mL of DMF was added 16 mg (0.24 mmol) of zinc dust and 300 mg (1.95 mmol) of BaO at −78 °C. After repeated flushing of the system with N_2 to remove oxygen, the mixture was heated for 25 min at 140 °C. The reaction was quenched by the addition of dilute HCl at 0 °C, and the resulting mixture was exhaustively extracted with $CHCl_3$. The combined extract was washed with brine, dried, and evaporated to dryness. The residue was subjected to preparative TLC ($CHCl_3$–acetone, 95:5). Four colored bands were noted: brownish red band (R_f 0.25); orange and yellow bands (R_f 0.32); and pink-red band (R_f 0.52). Elution of the brownish red band afforded 16 mg of **15** (20%): mp 185–187 °C ($CHCl_3$–EtOAc); IR 1690, 1669, 1630, 1586, 1405, 1235, 1210, 1048, 734 cm^{-1}; NMR δ 13.97 (s, 1 H), 13.17 (s, 1 H), 8.28 (m, 2 H), 7.80 (m, 2 H), 4.00 (s, 4 H), 2.3–3.7 (m, 5 H), 1.38 (s, 3 H); MS *m/e* (%) 394 (2, M^+), 392 (24), 377 (43), 87 (100), 43 (52).

Anal. Calcd for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 66.85; H, 4.62.

Elution of the pink-red band gave 12 mg (14%) of **16:** mp 231–233 °C ($CHCl_3$–hexane); IR 1595, 1465, 1260, 1045 cm^{-1}; NMR δ 13.35 (s, 1 H), 12.25 (s, 1 H), 10.37 (s, 1 H), 8.48 (m, 2 H), 8.10 (d, 1 H, J = 1.6 Hz), 7.80 (m, 2 H), 7.44 (d, 1 H, J = 1.6 Hz), 4.10 (m, 2 H), 3.85 (m, 2 H), 1.72 (s, 3 H); MS *m/e* (%) 392 (8, M^+), 377 (20), 87 (40), 41 (100); molecular ion at *m/e* 392.0875 (theory for $C_{22}H_{16}O_7$, 392.0894.

The orange and yellow bands consisted of a mixture of **13** and **5** as indicated by the NMR spectrum of the eluate, which totaled 10 mg.

(b) Condition 15. To 30 mg (0.07 mmol) of **18** in 0.6 mL of ethylene glycol and 0.4 mL of diglyme was added 13.7 mg (0.21 mmol) of zinc dust and 31.4 mg (0.56 mmol) of CaO at −78 °C (to minimize ester exchange). After repeated flushing of the system with N_2 to remove the last trace of oxygen, the mixture was heated for 3 min at 140°C. The reaction was quenched by the addition of dilute HCl at 0 °C, and the resulting mixture was exhaustively extracted with $CHCl_3$. The combined extract was washed with brine, dried, and evaporated to dryness. TLC analysis ($CHCl_3$–acetone, 95:5) of the residue revealed the presence of three components with relative mobilities of 0.25 (brownish red) (**15**), 0.1 (orange-red) (**5b**), and 0.00 (orange-red) (**5a**). PLC of this mixture ($CHCl_3$–acetone, 95:5) afforded 15 mg (54%) of **15.** Initially, the bottom band was composed mainly of **18** and **19,** as evidenced by a characteristic bright blue fluorescence under long wave ultraviolet light, which upon standing underwent aerial oxidation to **5a** and **5b,** respectively. As a rule, the R_f values of the leuco forms are very similar to their oxidized forms. The bottom red band (10 mg) was further purified after elution and developed in $CHCl_3$–MeOH (95:5), which gave 3 mg of **5a** [R_f 0.2; mp 198–199 °C ($CHCl_3$–acetone); IR 1720, 1624, 1589, 1430, 1266, 1204 cm^{-1}; NMR δ 13.55 (s, 1 H), 12.81 (br s, 1 H), 8.31 (m, 2 H), 7.78 (m, 2 H), 7.14 (s, 1 H), 3.94 (s, 4 H), 3.3–1.8 (m, 5 H), 1.37 (s, 3 H); MS *m/e* (%) 412 (7, M^+), 394 (22), 350 (48), 349 (23), 307 (17), 305 (16), 304 (19), 280 (20), 279 (43), 278 (17), 262 (15), 253 (35), 225 (19), 187 (13), 87 (28), 86 (21), 43 (100)] and 3 mg of **5b** [R_f 0.4; IR 3500, 2950, 1730, 1624, 1589, 1430, 1410, 1339, 1266, 1233, 1205, 1045, 951 cm^{-1}; NMR δ 13.35 (s, 1 H), 12.84 (s, 1 H), 8.28 (m, 2 H), 7.78 (m, 2 H), 7.14 (s, 1 H), 4.11 (m, 2 H), 3.98 (s, 4 H), 3.72 (m, 2 H), 3.3–1.8 (m, 5 H), 1.45 (s, 3 H); MS *m/e* (%) 456 (3, M^+), 455 (2), 395 (17), 394 (40), 393 (18), 351 (10), 350 (12), 305 (24), 304 (36), 279 (34), 253 (24), 225 (16), 87 (100), 86 (47), 43 (91)].

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-1,4-dibenzyloxyanthraquinone (20). A mixture consisting of 1.0 g (2.35 mmol) of **5,** 3.1 g (22.4 mmol) of anhydrous K_2CO_3, and 2.0 g (12 mmol) of benzyl bromide in 60 mL of acetone was refluxed under N_2 for 16 h. After filtration, the filtrate was evaporated to yield a yellow solid. After washing with methanol, crystallization from $CHCl_3$–MeOH afforded 1.29 g (2.13 mmol, 91%) of pure **20:** mp 120–122 °C; IR 1730, 1670, 1597, 1582, 1326, 1260, 1235, 1205 cm^{-1}; NMR δ 8.4–7.0 (m, 15 H), 5.30 (s, 2 H), 5.01 (s, 2 H), 3.90 (m, 4 H), 3.48 (s, 3 H), 3.2–1.5 (m, 5 H), 1.21 (s, 3 H); MS *m/e* (%) 471 (7, M − 107), 105 (3), 91 (100), 90 (51), 89 (11), 65 (4), 43 (5).

Anal. Calcd for $C_{37}H_{34}O_8$: C, 73.25; H, 5.65. Found: C, 73.41; H, 5.80.

2-(2′-Carboxymethyl-3′-ethylenedioxybutyl)-1,4-dibenzyloxyanthranthraquinone (21). A mixture containing 1.25 g (2.06 mmol) of **20** in 10 mL of 8% aqueous NaOH and 4 mL of *p*-dioxane was stirred under N_2 at 90 °C for 2 h. After cooling, dilute HCl was added and the resulting solution was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to give 1.12 g (1.89 mmol, 92%) of **21:** IR 3300–2500, 1705, 1667, 1595, 1583, 1322, 1258, 1235, 1204, 1039 cm^{-1}; NMR δ 8.18 (m, 2 H), 7.9–7.0 (m, 13 H), 5.25 (s, 2 H), 4.97 (br s, 2 H), 3.78 (m, 4 H), 3.2–1.6 (m, 5 H), 1.15 (s, 3 H); MS *m/e* (%) 575 (1.2, M − 17), 574 (0.5, M − 18), 502 (4), 486 (6), 485 (5), 440 (5), 394 (10), 279 (12), 105 (14), 91 (77), 90 (32), 87 (100).

2-[2′-(2-Hydroxyethyl)-3′-ethylenedioxybutyl]-1,4-dibenzyloxyanthraquinone (22). To 1.02 g (1.72 mmol) of **21** in 5 mL of THF was added dropwise 3.4 mL (3.4 mmol) of a THF solution of borane (1 M) at room temperature. After stirring for 1 h, 3 mL of ethanol was added and the resulting mixture was evaporated. Chromatography of the residue on 30 g of silica gel eluting the column with $CHCl_3$–MeOH (99:1) gave 671 mg (68%) of **22:** IR 3050, 2950, 2880, 1667, 1593, 1580, 1321, 1259, 1232, 1203 cm^{-1}; NMR δ 8.20 (m, 2 H), 7.9–7.1 (m, 13 H), 5.30 (br s, 2 H), 4.97 (br s, 2 H), 3.81 (m, 4 H), 3.30 (m, 2 H), 3.02 (m, 1 H), 2.7–1.3 (m, 4 H), 1.25 (s, 3 H); MS *m/e* (%) 470 (1, M^+ − 180), 469 (1), 432 (7), 431 (6), 425 (10), 424 (8), 342 (5), 335 (5), 325 (5), 173 (5), 105 (16), 92 (18), 91 (100), 90 (43), 87 (30), 86 (12).

2-[2′-(2-Hydroxyethyl)-3′-ethylenedioxybutyl]-1,4-dihydroxyanthraquinone (23). To a suspension of 427 mg of 5% Pd–$BaSO_4$ in 5 mL of ethyl acetate (presaturated with H_2) was added a solution of 427 mg (0.739 mmol) of **22** dissolved in 3 mL of ethyl acetate. The mixture was stirred under hydrogen at 25 °C for 1 h, and the contents were then filtered through Celite. The solvent was evaporated to dryness, and the residue was chromatographed over 15 g of silica gel. Elution of the column with $CHCl_3$–MeOH (99:1) afforded 258 mg (87%) of **23:** IR 3480, 2990, 2940, 2880, 1641, 1586, 1410, 1340, 1265, 1232, 1201 cm^{-1}; NMR δ 13.46 (br s, 1 H), 12.87 (br s, 1 H), 8.28 (m, 2 H), 7.78 (m, 2 H), 7.15 (s, 1 H), 3.89 (s, 4 H), 3.61 (m, 2 H), 3.09 (dd, J_1 = 12.3 Hz, J_2 = 4.2 Hz, 1 H), 2.7–1.6 (m, 4 H), 1.40 (s, 3 H); MS *m/e* (%) 398 (0.4, M^+), 336 (10), 318 (4), 304 (4), 291 (3), 254 (4), 87 (100), 86 (39), 43 (23); molecular ion at *m/e* 398.1384 (theory for $C_{22}H_{22}O_7$, 398.1363).

2-(2′-Formylmethyl-3′-ethylenedioxybutyl)-1,4-dihydroxyanthraquinone (24). To 60 mg (0.28 mmol) of pyridinium chlorochromate suspended in 3 mL of CH_2Cl_2 was added dropwise a solution

of **23** (53 mg, 0.13 mmol) in 2 mL of CH_2Cl_2 at room temperature. After stirring for 1 h, 25 mL of dry ether was added and the resulting mixture was filtered through Celite. The filtrate was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to dryness. Preparative TLC ($CHCl_3$–acetone, 95:5) afforded 34 mg (66%) of **24:** IR 2980, 1729, 1622, 1589, 1445, 1430, 1371, 1265 (sh), 1245, 1204, 1039 cm^{-1}; NMR δ 13.41 (s, 1 H), 12.88 (s, 1 H), 9.53 (m, 1 H), 8.31 (m, 2 H), 7.83 (m, 2 H), 7.14 (s, 1 H), 3.94 (s, 4 H), 1.44 (s, 3 H); MS *m/e* (%) 396 (2, M^+), 334 (3), 305 (6), 253 (2), 225 (2), 149 (11), 87 (100), 43 (55); molecular ion at *m/e* 396.1217 (theory for $C_{22}H_{20}O_7$, 396.1207).

Zinc Reduction of 24. A mixture containing 17.3 mg (0.0436 mmol) of **24,** 17 mg (0.26 mmol) of zinc dust, and 1 mL of glacial acetic acid was stirred under N_2 at 25 °C. After 30 min, 5% $NaHCO_3$ was added and the resulting solution was extracted with $CHCl_3$ three times. The combined extract was washed successively with 5% $NaHCO_3$ and brine, dried, and evaporated to give 16.4 mg (0.0412 mmol, 94%) of crude **25.** This crude material, consisting of two products, was separated by PLC ($CHCl_3$–acetone, 95:5). The more polar band was the predominant product and exhibited the following spectral properties: NMR δ 13.58 (s, 1 H), 8.46 (m, 2 H), 7.76 (m, 2 H), 3.98 (s, 4 H), 1.33 (s, 3 H); MS *m/e* (%) 398 (3, M^+), 390 (11), 365 (4), 336 (5), 318 (13), 293 (9), 275 (7), 254 (20), 87 (100), 86 (64). The less polar band showed the following: NMR δ 13.50 (s, 1 H), 8.43 (m, 2 H), 7.74 (m, 2 H), 4.01 (s, 4 H), 1.31 (s, 3 H); MS *m/e* (%) 398 (9, M^+), 380 (3), 365 (1), 336 (8), 318 (3), 293 (6), 275 (2), 254 (46), 87 (100).

8-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (27). A. To a mixture of 12.1 mg (0.0304 mmol) of **25,** 0.4 mL of ethylene glycol, and 0.3 mL of diglyme was added 5.0 mg (0.076 mmol) of zinc dust and 11.2 mg (0.2 mmol) of CaO under N_2 at 25 °C. The mixture was heated at 140 °C for 3 min. The reaction was quenched with dilute HCl at 0 °C, and the resulting mixture was extracted with $CHCl_3$ three times. The combined extracts were washed with brine, dried, and evaporated to dryness. Purification via PLC (silica gel; $CHCl_3$–acetone, 95:5) gave 6.5 mg (0.017 mmol, 56%) of **27:** mp 183–184 °C ($CHCl_3$–MeOH); IR 1635 (sh), 1625, 1592, 1450, 1400, 1380, 1280, 1266, 1242 cm^{-1}; NMR δ 13.51 (s, 1 H), 13.48 (s, 1 H), 8.35 (m, 2 H), 7.78 (m, 2 H), 4.00 (s, 4 H), 3.3–1.5 (m, 7 H), 1.40 (s, 3 H); MS *m/e* (%) 380 (21, M^+), 318 (22), 293 (16), 275 (9), 87 (100), 86 (100).

Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.17; H, 5.46.

B. To 13.1 mg (0.033 mmol) of **24** in 0.3 mL of *p*-dioxane was added 0.4 mL of 5% aqueous NaOH and 120 mg (0.689 mmol) of $Na_2S_2O_4$ under N_2 at 25 °C. After stirring for 30 min (color turned from purple to yellow after 5 min), the reaction mixture was heated at 90 °C for 1 h. Additional $Na_2S_2O_4$ (20 mg) was then added, and the heating was continued for another 30 min. The reaction was quenched with dilute HCl at 0 °C and the resulting mixture extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated. PLC purification of the residue (silica gel; $CHCl_3$–acetone, 95:5) gave 6.2 mg (0.016 mmol, 50%) of **27.**

8-Acetyl-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (28). To 2 mL of the acidic solution THF–5% H_2SO_4–acetone (1:1:1) was added 10.1 mg (0.0265 mmol) of **27.** After stirring the reaction mixture at 50 °C for 3 h, 3 mL of 5% $NaHCO_3$ was added and the contents were extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. PLC purification (silica gel; $CHCl_3$–acetone, 95:5) gave 8.2 mg (92%) of **28:** mp 180–182 °C ($CHCl_3$–MeOH); IR 1710, 1625, 1410, 1400, 1378, 1342, 1277, 1265, 1240, 1208 cm^{-1}; NMR δ 13.41 (s, 1 H), 13.36 (s, 1 H), 8.29 (m, 2 H), 7.77 (m, 2 H), 3.3–1.5 (m, 7 H), 2.27 (s, 3 H); MS *m/e* (%) 336 (18, M^+), 293 (45), 275 (30), 187 (32), 105 (21), 77 (26), 43 (100); molecular ion at *m/e* 336.1002 (theory for $C_{20}H_{16}O_5$, 336.0998).

1-Hydroxy-2-methyl-5-methoxyanthraquinone (30). To 1-hydroxy-5-methoxyanthraquinone (**29;** 26.5 g, 104 mmol) in 1.5% NaOH (2.65 L) under N_2 was added 20.5 g (117 mmol) of $Na_2S_2O_4$ at 25 °C. After stirring the mixture for 10 min at 90 °C, 8.97 g (120 mmol) of 40% CH_2O solution was added (color turned from orange-red to deep red within 10 min). After stirring at 90 °C for 60 min, the reaction mixture was cooled to 50 °C and a current of air was passed through the solution for 60 min (color changed from deep red to purple. The reaction mixture was then acidified with 10% H_2SO_4, heated at 50 °C for 1 h, and extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated. Chromatography of the residue over 700 g of silica gel (elution with $CHCl_3$) afforded 16.8 g (62.2 mmol, 60%) of **30:** mp 185–186 °C ($CHCl_3$–CCl_4); IR (KBr) 1668, 1636, 1585, 1281, 1266, 1011, 791, 781 cm^{-1}; NMR δ 12.73 (s, 1 H), 7.95 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 4.02 (s, 3 H), 2.33 (s, 3 H); MS *m/e* (%) 268 (100, M^+), 253 (88), 251 (16), 239 (17), 225 (14), 165 (16), 152 (24), 139 (17), 115 (16), 105 (10), 76 (21), 63 (16).

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.66; H, 4.65.

1-Acetoxy-2-methyl-5-methoxyanthraquinone (31). A mixture containing 15.1 g (56.3 mmol) of **30,** 1 mL of concentrated H_2SO_4, and 300 mL of acetic anhydride was stirred at 25 °C for 3.5 h. The reaction mixture was then poured into 3 L of ice water, and the resulting suspension was extraced with $CHCl_3$ three times. The combined $CHCl_3$ extract was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to yield 17.3 g (55.8 mmol, 99%) of **31:** mp 195–197 °C ($CHCl_3$–CCl_4); IR (KBr) 1750, 1672, 1588, 1263 cm^{-1}; NMR δ 8.12 (d, J = 7.8 Hz, 1 H), 7.85 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.67 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.29 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 4.02 (s, 3 H), 2.50 (s, 3 H), 2.30 (s, 3 H); MS *m/e* (%) 310 (20, M^+), 268 (100), 267 (43), 254 (37), 253 (100), 252 (34), 251 (26), 239 (26), 225 (22), 222 (15), 168 (16), 165 (24), 153 (26), 152 (44), 139 (36), 115 (13), 76 (16), 41 (81).

Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.80; H, 4.71.

1-Acetoxy-2-bromomethyl-5-methoxyanthraquinone (32a). A mixture containing 30 g (97 mmol) of **31,** 17.8 g (100 mmol) of *N*-bromosuccinimide (NBS), and 200 mg of benzoyl peroxide in 3.5 L of CCl_4 was stirred under N_2 at reflux. After 3 h, an additional 4 g (22 mmol) of NBS and 100 mg of benzoyl peroxide were added and the contents were refluxed for an additional 5 h. During reflux, the reaction mixture was irradiated with a sunlamp. After cooling, the succinimide (white solid) was removed by filtration and the filtrate was evaporated under reduced pressure. Crystallization of the residue from $CHCl_3$–CCl_4 gave 15 g (38 mmol) of **32a:** mp 213–216 °C; IR (KBr) 1762, 1672, 1587, 1267 cm^{-1}; NMR δ 8.18 (d, J = 8.0 Hz, 1 H), 7.95–7.7 (m, 2 H), 7.67 (dd, J_1 = J_2 = 7.8 Hz), 7.28 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 4.46 (s, 2 H), 4.02 (s, 3 H), 2.51 (s, 3 H); MS *m/e* (%) 390 (1, M^+ for ^{81}Br), 388 (1, M^+ for ^{79}Br), 348 (7), 346 (7), 268 (16), 267 (100), 266 (31), 239 (17), 152 (24), 76 (9), 41 (52).

Anal. Calcd for $C_{18}H_{13}O_5Br$: C, 55.54; H, 3.37. Found: C, 55.50; H, 3.47.

The mother liquor, containing residual **31, 32a,** and dibromide **32b,** was chromatographed on a silica gel column (6.25 × 90 cm). The column was eluted with $CHCl_3$, and 17-mL fractions were collected. Fractions 1–140 gave 12 g (26 mmol) of dibromide **32b:** mp 196–198 °C; IR 3015, 2940, 1781, 1674, 1589, 1578, 1265, 1167, 1005 cm^{-1}; NMR δ 8.28 (s, 2 H), 8.1–7.1 (m, 3 H), 6.90 (s, 1 H), 4.01 (s, 3 H), 2.54 (s, 3 H); MS *m/e* (%) 468 (2), 467 (2), 466 (1), 426 (6), 425 (4), 424 (4), 347 (100), 346 (55), 345 (100), 238 (40), 237 (34), 152 (47), 151 (58), 150 (40), 105 (31), 104 (19), 85 (23), 83 (27). Fractions 210–305 afforded an additional 7 g (18 mmol) of **32a.** Fractions 141–209 (5 g) consisted of a mixture of **32b** and **32a** in an approximately 1:1 ratio; fractions 306–356 (3.5 g) contained **32a** and **31** in a ratio of 2:1.

1-Acetoxy-2-(2′-acetyl-2′-carbethoxymethyl-3′-oxobutyl)-5-methoxyanthraquinone (33). To 0.865 g (36 mmol) of NaH (prewashed with dry pentane) in 50 mL of dry THF under N_2 was added dropwise a solution of 6.51 g (35 mmol) of 3-acetyllevulinic acid ethyl ester dissolved in 50 mL of dry THF at 25 °C. After completion of this addition, the mixture was heated at 40 °C until hydrogen evolution ceased (ca. 30 min). A solution of 200 mL of dry DMF containing 13.4 g (34.4 mmol) of **32a** was added dropwise at −21 °C (dry ice–CCl_4) to the reaction mixture. After warming to 25 °C, the mixture was stirred for 10 h. The reaction was quenched with dilute HCl and the resulting mixture extracted three times with ethyl acetate. The combined extract was washed with brine, dried, and evaporated to dryness. The residue was washed with dry methanol to give 16.5 g (33.5 mmol, 97%) of **33,** which was used for the subsequent reaction. Crystallization of **33** from $CHCl_3$–ether afforded an analytical sample: mp 181–182 °C; IR (KBr) 1771, 1729, 1712, 1700, 1670, 1363, 1269, 1177 cm^{-1}; NMR δ 7.85 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 7.8 (AB q, ν_A = 8.11, ν_B = 7.49, J_{AB} = 8.1 Hz, 2 H), 7.69 (dd, J_1 = J_2 = 7.8 Hz), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.04 (s, 3 H), 3.57 (s, 2 H), 2.92 (s, 2 H), 2.47 (s, 3 H), 2.22 (s, 6 H), 1.23 (t, J = 7.1 Hz, 3 H); MS *m/e* (%) 494 (0.1, M^+), 452 (1), 434 (7), 409 (12), 392 (51), 391 (100), 390 (74), 389 (20), 363 (41), 362 (23), 335 (16), 279 (14), 278 (13), 267 (14), 43 (78).

Anal. Calcd for $C_{27}H_{26}O_9$: C, 65.58; H, 5.30. Found: C, 64.98; H, 5.19.

2-(2′-Carboxymethyl-3′-oxobutyl)-1-hydroxy-5-methoxyanthraquinone (34). A mixture containing 16.5 g (33.5 mmol) of **33** in 40 mL of 5% NaOH was stirred at 65 °C under nitrogen for 5 h. After cooling, the reaction mixture was acidified and a yellow precipitate was formed after stirring for 30 min. The precipitate was collected by filtration, washed twice with water and methanol, and dried under reduced pressure to yield 11.6 g (30.4 mmol, 91%) of crude **34,** which

was used for the Elbs oxidation. Two crystallizations of **34** from $CHCl_3$–EtOAc afforded an analytical sample: mp 197–200 °C; IR (KBr) 3400–2500, 1710, 1666, 1631, 1587, 1430, 1265 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 12.85 (s, 1 H), 7.98 (dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 7.9–7.3 (m, 4 H), 6.60 (br s, 1 H), 4.06 (s, 3 H), 3.7–2.3 (m, 5 H), 2.21 (s, 3 H); MS *m/e* (%) 382 (40, M^+), 339 (16), 321 (16), 305 (33), 294 (33), 279 (32), 267 (28), 266 (21), 239 (11), 165 (20), 152 (23), 139 (18), 77 (12), 41 (100).

Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 66.07; H, 4.93.

2-(2′-Carboxymethyl-3′-oxobutyl)-1,4-dihydroxy-5-methoxyanthraquinone (35). To a solution of 8 mL of 2 M aqueous KOH containing 601 mg (1.57 mmol) of **34** was added 20 mL of aqueous $K_2S_2O_8$ (800 mg, 2.96 mmol) solution under N_2. After stirring the reaction mixture for 2 days at 25 °C, the contents were acidified with 10% HCl to pH 4.0 to precipitate the unreacted starting material (yellow solid). After extraction of the filtrate with ethyl acetate to remove traces of **34**, 575 mg (4.56 mmol) of Na_2SO_3 and 4 mL of concentrated HCl were then added. The resulting mixture was heated on a steam bath for 1 h, and the solution was exhaustively extracted with $CHCl_3$. The combined extract was washed with brine, dried, and evaporated to give 262 mg (0.658 mmol, 42%) of **35:** mp 124–125 °C ($CHCl_3$–EtOAc); IR 3300, 2500, 1705, 1613, 1575, 1440, 1275, 1217, 774 cm^{-1}; NMR δ 13.29 (s, 1 H), 13.18 (br s, 1 H), 7.99 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.76 (t, J_1 = J_2 = 7.8 Hz), 7.40 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.10 (s, 1 H), 6.87 (br s, 1 H), 4.09 (s, 3 H), 2.7–2.4 (m, 5 H), 2.24 (s, 3 H); MS *m/e* (%) 398 (20, M^+), 390 (43), 315 (17), 334 (16), 321 (16), 309 (37), 295 (16), 293 (12), 291 (12), 283 (17), 255 (22), 217 (17), 41 (100).

Anal. Calcd for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.03; H, 4.90.

The residual starting material (yellow solid) was purified by chromatography over silica gel. Elution of the column with $CHCl_3$–MeOH (5:1) afforded 227 mg of **34** (0.597 mmol, 38%).

2-(2′-Carbomethoxymethyl-3′-oxobutyl)-1,4-dihydroxy-5-methoxyanthraquinone (36). To 1.52 g (3.8 mmol) of **35** dissolved in 30 mL of $CHCl_3$ was added an excess of ethereal diazomethane at 0 °C. After stirring for 1 h, 1 drop of acetic acid was added and the solvent was evaporated under reduced pressure to yield 1.57 g (3.81 mmol, 99.7%) of **36.** Crystallization of **36** from $CHCl_3$–hexane afforded a sample: mp 147–148 °C; IR (KBr) 1733, 1715, 1620, 1580, 1281, 1262, 1222 cm^{-1}; NMR δ 13.30 (s, 1 H), 13.17 (s, 1 H), 8.02 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.75 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.38 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.08 (s, 1 H), 4.07 (s, 3 H), 3.60 (s, 3 H), 3.6–2.4 (m, 5 H), 2.26 (s, 3 H); MS *m/e* (%) 412 (49, M^+), 394 (70), 381 (19), 370 (23), 369 (21), 337 (21), 321 (25), 310 (37), 309 (81), 308 (30), 295 (27), 293 (20), 255 (34), 217 (42), 43 (100), 41 (38).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.07; H, 4.87. Found: C, 64.04; H, 5.15.

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-1,4-dihydroxy-5-methoxyanthraquinone (4). The reaction mixture, containing 1.57 g (3.81 mmol) of **36,** 3 mL of ethylene glycol, and 15 mg of *p*-toluenesulfonic acid in 50 mL of benzene, was refluxed for 14 h. The water was collected through a Dean-Stark condenser. After cooling, the contents were diluted with 5% $NaHCO_3$ and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried, and evaporated to dryness. The residue (1.74 g) was chromatographed over 46 g of silica gel. Elution of the column with $CHCl_3$–EtOAc (95:5) gave 1.42 g (82%) of **4:** mp 164–165 °C ($CHCl_3$–CCl_4); IR (KBr) 1720, 1615, 1574, 1435, 1275, 1257, 1218, 1025, 780 cm^{-1}; NMR δ 13.30 (s, 1 H), 13.19 (s, 1 H), 7.93 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.68 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.13 (s, 1 H), 4.04 (s, 3 H), 4.00 (s, 4 H), 3.52 (s, 3 H), 3.13 (dd, J_1 = 12.1 Hz, J_2 = 3.0 Hz, 1 H), 3.0–2.0 (m, 4 H), 1.41 (s, 3 H); MS *m/e* (%) 456 (5, M^+), 425 (2), 349 (20), 379 (3), 335 (3), 334 (3), 321 (5), 309 (3), 87 (100), 41 (26).

Anal. Calcd for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Found: C, 63.22; H, 5.40.

9-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-4-methoxy-5,7,12-naphthacenetrione (41). To 64 mg (0.14 mmol) of **4** in 0.4 mL of *p*-dioxane was added 200 mg (1.15 mmol) of $Na_2S_2O_4$ in 0.8 mL of 5% aqueous NaOH under N_2. After stirring at 25 °C for 30 min (color turned from dark red to yellow), 50 mg of additional $Na_2S_2O_4$ was added and the mixture was stirred for another 30 min. After quenching the reaction with dilute HCl, the resulting mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to afford 59 mg (92%) of crude **40** as a mixture of two diastereomers: IR 1730, 1630, 1609, 1585, 1395, 1265 cm^{-1}; NMR δ 14.60 (s, 1 H), 13.47 (s, 0.5 H), 13.43 (s, 0.5 H), 8.03 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.54 (t, J = 7.8 Hz, 1 H), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 4.03 (s, 3 H), 3.93 (s, 2 H), 3.91 (br s, 2 H), 3.64 (s, 1.5 H), 3.60 (s, 1.5 H), 1.5–3.4 (m, 8 H), 1.27 (s, 3 H); MS *m/e* (%) 458 (0.6, M^+), 396 (2), 284 (9), 187 (4), 155 (5), 149 (8), 111 (31), 87 (100). This mixture was used for the following cyclization reaction.

To 51 mg (0.11 mmol) of **40** suspended in 1.1 mL of glycerol and 0.28 mL of water was added 50 mg (0.87 mmol) of CaO and 20 mg (0.31 mmol) of zinc dust at −78 °C (to minimize ester exchange). After repeated flushing of the system with N_2 to remove the last traces of oxygen, the reaction mixture was heated to 140 °C for exactly 5 min. After cooling, the reaction was quenched by the addition of dilute HCl at 0 °C and the mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. TLC analysis ($CHCl_3$–acetone, 95:5) of the mixture revealed the presence of three components with relative mobilities of 0.35 (brownish red), 0.54 (red), and 0.01 (red). Purification of this mixture using PLC afforded 3.9 mg (8.4%) of **41** (R_f 0.35): mp 234–236 °C ($CHCl_3$–MeOH); IR 1625, 1593, 1285, 1205, 730 cm^{-1}; NMR δ 14.33 (s, 1 H), 13.10 (s, 1 H), 7.98 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.73 (t, J_1 = 7.8 Hz), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 4.05 (s, 4 H), 3.98 (s, 3 H), 3.6–1.5 (m, 5 H), 1.39 (s, 3 H); MS *m/e* (%) 424 (7, M^+), 423 (31), 422 (79), 407 (100), 406 (9), 363 (9), 348 (9), 335 (15), 320 (11), 87 (53); molecular ion at *m/e* 424.1159 (theory for $C_{23}H_{20}O_8$, 424.1159.

Elution of the top red band (R_f 0.54) gave 15 mg of **4,** and the bottom band (R_f 0.01) afforded 14 mg of **37 37.** [IR (KBr) 3300–2500, 1720, 1620, 1582, 1440, 1280, 1225 cm^{-1}; NMR δ 13.35 (s, 1 H), 13.22 (s, 1 H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.72 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 7.36 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.18 (s, 1 H), 6.94 (br s, 1 H), 4.06 (s, 3 H), 3.98 (s, 4 H), 3.13 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1 H), 3.0–2.0 (4H), 1.40 (s, 3 H)], which was esterified to **4** and recycled.

Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01. Found: C, 62.40; H, 5.02.

2-(2′-Carbomethoxymethyl-3′-ethylenedioxybutyl)-5-methoxy-1,4-dibenzyloxyanthraquinone (43). A mixture consisting of 550 mg (1.21 mmol) of **4,** 1 g (7.2 mmol) of anhydrous K_2CO_3, and 0.51 g (3 mmol) of benzyl bromide in 50 mL of acetone was refluxed under N_2 for 20 h. The reaction mixture was then filtered, and the filtrate was evaporated to dryness. The residue was washed with methanol to remove the unreacted benzyl bromide, and 761 mg (99%) of crude **43** was obtained. Crystallization of **43** from $CHCl_3$–MeOH gave a sample: mp 134–136 °C; IR 1759, 1670, 1588, 1205, 1015 cm^{-1}; NMR δ 7.8–7.1 (m, 14 H), 5.29 (s, 2 H), 4.99 (s, 2 H), 3.97 (s, 3 H), 3.77 (m, 4 H), 3.45 (s, 3 H), 2.97 (d, J = 9.6 Hz, 1 H), 2.65 –1.75 (m, 4 H), 1.25 (s, 3 H); MS *m/e* (%) 636 (6, M^+), 546 (5), 530 (4), 484 (4), 483 (4), 394 (6), 372 (5), 356 (4), 105 (7), 92 (20), 91 (100), 87 (93).

Anal. Calcd for $C_{38}H_{36}O_9$: C, 71.68; H, 5.70. Found: C, 71.10; H, 5.80.

2-(2′-Carboxymethyl-3′-ethylenedioxybutyl)-5-methoxy-1,4-dibenzyloxyanthraquinone (44). A mixture of 720 mg (1.13 mmol) of **43,** 8 mL of 8% aqueous NaOH, and 3 mL of *p*-dioxane was stirred under N_2 at 90 °C for 3 h. After cooling, dilute HCl was added and the resulting solution was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to yield 646 mg (92%) of crude **44.** Crystallization of **44** ($CHCl_3$–MeOH) afforded a sample: mp 173–174 °C; IR 1740, 1718, 1680, 1598, 1275, 1216 cm^{-1}; NMR δ 7.8–7.1 (m, 14 H) 6.52 (br s, 1 H), 5.24 (s, 2 H), 4.97 (s, 2 H), 3.94 (s, 3 H), 3.74 (m, 4 H), 2.93 (br d, J = 10.2 Hz, 1 H), 2.61–1.76 (m, 4H), 1.14 (s, 3 H); MS *m/e* (%) 622 (3, M^+), 532 (4), 516 (2), 514 (2), 469 (4), 442 (4), 379 (5), 372 (6), 309 (5), 283 (3), 105 (4), 92 (21), 91 (100), 87 (49).

Anal. Calcd for $C_{37}H_{34}O_9$: C, 71.37; H, 5.50. Found: C, 71.49; H, 5.60.

2-[2′-(2′-Hydroxyethyl)-3′-ethylenedioxybutyl]-5-methoxy-1,4-dibenzyloxyanthraquinone (45). To 302 mg (0.486 mmol) of **44** in 2 mL of dry THF was added dropwise 0.97 mL (0.97 mmol) of a BH_3–THF solution (1 M) at room temperature. After stirring for 1 h, 2 mL of ethanol was added and the resulting mixture was evaporated to dryness. PLC purification (silica gel; $CHCl_3$–MeOH, 95:5) of the crude material gave 235 mg (80%) of **45:** IR 1678, 1596, 1455, 1325, 1270, 1213, 1020 cm^{-1}; NMR δ 7.8–7.0 (m, 14 H), 5.31 (s, 2 H), 4.99 (s, 2 H), 4.00 (s, 3 H), 3.83 (m, 4 H), 3.32 (m, 2 H), 3.02 (dd, J_1 = 13.5 Hz, J_2 = 3.0 Hz, 1 H), 2.54–1.65 (m, 4 H), 1.25 (s, 3 H); MS *m/e* (%) 500 (4, M − 108), 91 (46), 87 (100); molecular ion at *m/e* 608.2393 (theory for $C_{37}H_{36}O_8$, 608.2410).

2-[2′-(2-Hydroxyethyl)-3′-ethylenedioxybutyl]-5-methoxy-1,4-dihydroxyanthraquinone (46). To a suspension of 5 mL of ethyl acetate and 200 mg of 5% Pd–$BaSO_4$ (presaturated with hydrogen) was added a solution of 202 mg (0.332 mmol) of **45** in 3 mL of ethyl

acetate. After stirring the mixture under H_2 for 1 h, the contents were filtered through Celite. The filtrate was evaporated, and the crude **46** was purified by PLC (elution with $CHCl_3$–MeOH, 95:5), which afforded 101 mg (71%) of pure **46:** IR 1625, 1593, 1454, 1445, 1285, 1272, 1246, 1040 cm^{-1}; NMR δ 13.35 (s, 1 H), 13.17 (s, 1 H), 7.92 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1 H), 7.68 (dd, $J_1 = J_2$ = 8.0 Hz, 1 H), 7.31 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1 H), 7.09 (s, 1 H), 4.02 (s, 3 H), 3.95 (s, 4 H), 3.61 (m, 2 H), 3.06 (dd, J_1 = 12.0 Hz, J_2 = 3.0 Hz), 2.85–1.43 (m, 4 H), 1.37 (s, 3 H); MS *m/e* (%) 428 (0.2, M^+), 366 (2), 348 (1), 335 (1), 243 (4), 165 (3), 87 (100), 86 (19); molecular ion at *m/e* 428.1471 (theory for $C_{23}H_{24}O_8$, 428.1471).

2-(2′-Formylmethyl-3′-ethylenedioxybutyl)-5-methoxy-1,4-dihydroxyanthraquinone (47). To a suspension of 60 mg (0.28 mmol) of pyridinium chlorochromate (PCC) in 3 mL of CH_2Cl_2 was added dropwise a solution of CH_2Cl_2 (2 mL) containing 60 mg (0.14 mmol) of **46** at room temperature. After stirring for 1 h, 25 mL of ether was added and the mixture was filtered through Celite. The filtrate was washed with 5% $NaHCO_3$ and brine, dried, and evaporated to dryness. PLC purification (elution with $CHCl_3$–MeOH, 95:5) of the crude **47** (48 mg) gave 39 mg (65%) of pure **47:** IR 1740, 1619, 1585, 1260, 1205 cm^{-1}; NMR δ 13.31 (s, 1 H), 13.11 (s, 1 H), 9.52 (dd, J_1 = 3.3 Hz, J_2 = 1.2 Hz), 8.02 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 1 H), 7.75 (dd, $J_1 = J_2$ = 7.8 Hz, 1 H), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.11 (s, 1 H), 4.06 (s, 3 H), 3.95 (m, 4 H), 3.17 (dd, J_1 = 12.0 Hz, J_2 = 3.1 Hz, 1 H), 3.0–2.0 (m, 4 H), 1.41 (s, 3 H); MS *m/e* (%) 426 (2, M^+), 364 (3), 335 (5), 321 (2), 255 (2), 115 (2), 87 (100); molecular ion at *m/e* 426.1291 (theory for $C_{23}H_{22}O_8$, 426.1267).

8-(1′-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (50). To a solution of 15.1 mg (0.035 mmol) of **47** in 0.3 mL of *p*-dioxane was added 0.5 mol of 5% aqueous NaOH and 130 mg of $Na_2S_2O_4$ under N_2 at room temperature. After stirring at 25 °C for 30 min, the reaction mixture was heated at 90 °C for 1 h. Additional $Na_2S_2O_4$ (20 mg) was then added, and heating was continued for another 30 min. The reaction was quenched with HCl at 0 °C, and the reaction mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. PLC purification ($CHCl_3$–acetone, 95:5) of the crude residue gave 7.9 mg (55%) of **50:** mp 177–178.5 °C ($CHCl_3$–MeOH); IR 1610, 1580, 1445, 1278, 1260 cm^{-1}; NMR δ 13.82 (s, 1 H), 13.48 (s, 1 H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 7.71 (t, $J_1 = J_2$ = 7.8 Hz, 1 H), 7.33 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H), 4.05 (s, 4 H), 4.00 (s, 3 H), 3.14 (br d, J = 18 Hz, 2 H), 2.8–1.6 (m, 5 H), 1.38 (s, 3 H); MS *m/e* (%) 410 (4, M^+), 348 (2), 323 (2), 305 (1), 87 (100), 86 (30); molecular ion at *m/e* 410.1378 (theory for $C_{23}H_{22}O_7$, 410.1365).

8-Acetyl-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (51). A solution consisting of 4.2 mg (0.01 mmol) of **50** in 2 mL of the acidic solution THF–5% H_2SO_4–acetone (1:1:1) was stirred at 50 °C. After 3, 3 mL of 5% $NaHCO_3$ was added and the resulting mixture was extracted with $CHCl_3$ three times. The combined extract was washed with brine, dried, and evaporated to dryness. PLC purification ($CHCl_3$–acetone, 95:5) afforded 3.3 mg (90%) of **51,** mp 243–245 °C, identical in all respects (NMR, IR, and mass spectra) with an authentic specimen.[5c]

(±)-7-Deoxydaunomycinone (52). To 226 mg (0.617 mmol) of **51** in 60 mL of acetic anhydride was added 705 mg (3.7 mmol) of *p*-toluenesulfonic acid (monohydrate). Continuous slow distillation of acetic anhydride and acetic acid was carried out over 6 h. An additional 135 mg of *p*-toluenesulfonic acid was then added, and the distillation was continued for another 3 h. After removing the residual acetic anhydride in vacuo, the residue was dissolved in $CHCl_3$ and chromatographed over a silica gel column (1.5 × 21 cm). The column was eluted with $CHCl_3$, and 15-mL fractions were collected. Fractions 7–11 were combined to give 254 mg (0.517 mmol) of a mixture of enol acetates as an orange-yellow solid. To this partially purified material (254 mg) in 10 mL of dry CH_2Cl_2 was added 315 mg (1.55 mmol) of *m*-chloroperbenzoic acid. After 1 h at room temperature, TLC ($CHCl_3$–acetone, 9:1) analysis showed only one major new component (epoxy acetate). To this solution was added 160 mg of Na_2SO_3, and the contents were washed with saturated $NaHCO_3$, dried, and evaporated to yield 278 mg of a yellow oil, which was treated with 8.5 mL of 0.3 N NaOH in 50% ethanol for 40 min at room temperature. After acidification and extraction with CH_2Cl_2, the residue containing partially hydrolyzed material was treated with 11 mL of an acidic solution of 150 mL of glacial acetic acid, 0.75 mL of concentrated H_2SO_4, and 5 mL of H_2O for 75 min. After dilution with water, the reaction mixture was extracted with CH_2Cl_2, washed with water, dried, and evaporated to yield 196 mg of crude red solid. Chromatography of this crude material over a small silica gel column (elution with $CHCl_3$–acetone, 99:1) afforded pure **52,** mp 229–231 °C, whose (NMR, IR, MS) spectra were indistinguishable from an authentic sample.

Acknowledgment. This work was supported by the National Institutes of Health, Grant No. CA21387.

Registry No.—**4,** 66644-11-9; **5,** 67408-45-1; **5a,** 67408-46-2; **5b,** 67408-47-3; **6,** 2589-39-1; **7,** 52541-72-7; **8a,** 63965-48-0; **8b,** 63965-49-1; **9,** 65127-10-8; **10,** 67408-48-4; **11,** 67408-49-5; **12,** 67408-50-8; **13,** 65127-15-3; **15,** 67408-51-9; **16,** 65127-17-5; **18,** 67408-52-0; **20,** 67408-53-1; **21,** 67408-54-2; **22,** 67408-55-3; **23,** 67408-56-4; **24,** 67408-57-5; **25** (isomer 1), 67408-58-6; **25** (isomer 2), 67408-59-7; **27,** 67408-60-0; **28,** 67122-26-3; **29,** 52869-21-3; **30,** 64809-72-9; **31,** 64809-77-4; **32a,** 66644-06-2; **32b,** 67408-61-1; **33,** 66644-07-3; **34,** 67408-62-2; **35,** 66644-09-5; **36,** 66644-10-8; **37,** 67408-63-3; **40** (isomer 1), 67408-64-4; **40** (isomer 2), 67408-65-5; **41,** 66644-13-1; **43,** 67408-66-6; **44,** 67408-67-7; **45,** 67408-68-8; **46,** 67408-69-9; **47,** 67408-70-2; **50,** 67408-71-3; **51,** 61857-05-4; **52,** 59367-18-9; phthalic anhydride, 85-44-9; methylhydroquinone, 95-71-6; ethyl 3-acetylevulinate, 18835-02-5.

References and Notes

(1) For preliminary reports, see F. Suzuki, R. D. Gleim, S. Trenbeath, and C. J. Sih, *Tetrahedron Lett.*, 2303 (1977), and F. Suzuki, S. Trenbeath, and C. J. Sih, *J. Am. Chem. Soc.*, **100,** 2272 (1978).

(2) (a) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbieri, and R. Mondelli, *J. Am. Chem. Soc.*, **86,** 5334 (1964); (b) J. Bernard, R. Paul, M. Boiron, C. Jacquillot, and R. Masal, Ed., "Rubidomycin", Springer-Verlag, New York, N.Y., 1969.

(3) (a) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, 1007 (1969); (b) F. Arcamone, G. Cassinelli, G. Fantini, A. Grein, P. Orezzi, C. Pol, and C. Spalla, *Biotechnol. Bioeng.*, **11,** 1109 (1969).

(4) M. G. Brazhnikova, V. B. Zbarsky, V. I. Ponomarenko, and N. P. Patapova, *J. Antibiot.*, **27,** 254 (1974).

(5) (a) F. Arcamone, G. Franceschi, P. Orezzi, S. Penco, and R. Mondelli, *Tetrahedron Lett.*, 3349, 3353 (1968); (b) R. H. Iwamoto, P. Lim, and N. S. Bhacca, *ibid.*, 3891 (1968); (c) R. Angiuli, E. Foresti, L. Riva di Sanseverino, N. W. Isaacs, O. Kennard, W. D. S. Motherwell, D. L. Wampler, and F. Arcamone, *Nature (London), New Biol.*, **234,** 78 (1971).

(6) R. H. Blum and S. K. Carter, *Ann. Intern. Med.*, **80,** 249 (1974); (b) D. W. Henry, *ACS Symp. Ser.*, **No. 30,** Chapter 2, (1976); (c) F. Arcamone, *Lloydia*, **40,** 45 (1977).

(7) (a) E. A. Lefrak, J. Pitha, S. Rosenheim, and J. A. Gottlieb, *Cancer (Philadelphia)*, **32,** 302 (1973); (b) L. Lenaz and J. A. Page, *Cancer Treat. Rev.*, **3,** 111 (1976).

(8) (a) J. P. Marsh, C. W. Mosher, E. M. Acton, and L. Goodman, *Chem. Commun.*, 973 (1967); (b) T. Yamaguchi and M. Kojima, Symposium on the Chemistry of Natural Products, Abstracts, Tokyo, 205 (1973); (c) D. Horton and W. Weckerle, *Carbohydr. Res.*, **44,** 227 (1975); (d) C. M. Wong, T. L. Ho, and W. P. Niemczma, *Can. J. Chem.*, **53,** 3144 (1975); (e) F. Arcamone, *Carbohydr. Res.*, **46,** 3 (1976).

(9) E. M. Acton, A. N. Fujiwara, and D. W. Henry, *J. Med. Chem.*, **17,** 659 (1974).

(10) (a) Z. Horii, H. Hakusui, T. Momose, and E. Yoshino, *Chem. Pharm. Bull.*, **16,** 1251 (1968); (b) J. Finkelstein and J. A. Romano, *J. Med. Chem.*, **13,** 568 (1970); (c) H. Brockmann, *Tetrahedron Lett.*, **45** (1966); (d) C. M. Wong, D. Popien, R. Schwenk, and J. Rao, *Can. J. Chem.*, **49,** 2712 (1971); (e) C. M. Wong, D. Popien, R. Schwenk and T. L. Ho, *ibid.*, **51,** 466 (1973); (f) W. Trueb and C. H. Engster, *Helv. Chim. Acta*, **55,** 969 (1972).

(11) (a) A. S. Kende, J. Belletire, T. J. Bentley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97,** 4425 (1975); (b) D. M. Miller, S. Trenbeath, and C. J. Sih, *Tetrahedron Lett.*, 1637 (1976); (c) R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *ibid.*, 3385 (1976).

(12) (a) F. Farina and J. C. Vega, *Tetrahedron Lett.*, 1655 (1972); (b) R. Winkler, *Chimia*, **20,** 122 (1966); (c) A. K. Kende, Y. G. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98,** 1967 (1976); (d) A. S. Kende, D. P. Curran, Y. S. Tsay, and J. E. Mills, *Tetrahedron Lett.*, 3537 (1977); (e) T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr., and J. M. Lyding, *J. Am. Chem. Soc.*, **99,** 5513 (1977); (f) W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, **41,** 2296 (1976).

(13) P. W. Raynolds, M. J. Manning, and J. S. Swenton, *Tetrahedron Lett.*, 2383 (1977).

(14) W. B. Turner, "Fungal Metabolites", Academic Press, New York, N.Y., 1971.

(15) R. H. Thomson, "Naturally Occurring Quinones", 2nd ed, Academic Press, New York, N.Y., 1971.

(16) J. Houben "Das Anthracen und die Anthrachinone", Georg Thieme, Leipzig, 1929.

(17) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60,** 829 (1976).

(18) (a) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81,** 2705 (1959); (b) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85,** 1148 (1963); (c) D. R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **3,** 560 (1964); (d) P. G. Duggan and W. S. Murphy, *J. Chem. Soc., Perkin Trans. 2,* 1291 (1973).

(19) K. Klemore and G. Gehrke, German Patent 1 178 441, 1964; *Chem. Abstr.* **61P,** 16027f (1964).

(20) C. Marschalk, *Bull. Soc. Chim. Fr.*, **6,** 655 (1939).

(21) S. M. Sethna, *Chem. Rev.*, **49,** 91 (1951).

(22) A considerable amount of destruction of compounds was noted at this temperature, resulting in low material balance.

(23) (a) J. Petruska, *J. Chem. Phys.*, **34,** 1120 (1961); (b) F. Suzuki and M. Oki, *Bull. Chem. Soc. Jpn.*, **49,** 596 (1975).

(24) It is interesting to note the difference in the apparent cardiac toxicities of daunorubicin vs. 4-demethoxydaunorubicin: F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. D. Marco, A. M. Cassazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976).
(25) (a) C. Marshall, T. Kritchevsky, S. Lieberman, and T. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948); (b) J. Attenburrow, L. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson, *J. Chem. Soc.*, 4547 (1961).
(26) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, **42**, 3653 (1977).

New Synthesis of (±)-Emetine from Tetrahydroprotoberberine Precursors via an α-Diketone Monothioketal Intermediate

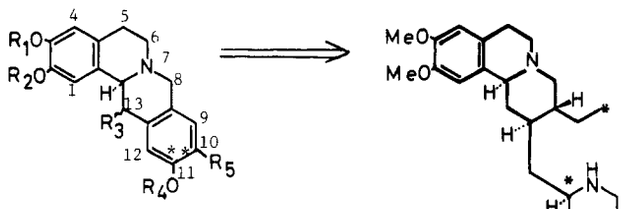
Seiichi Takano,* Makoto Sasaki, Hideyuki Kanno,
Kozo Shishido, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan 980

Received March 30, 1978

A new route to (±)-emetine (**2**) via the protoemetine derivative **29** has been developed. Protoberberine derivatives **3, 4, 5,** and **6** were converted into the α-diketone monothioketal **25,** which upon cleavage with potassium hydroxide, followed by desulfurization and esterification, yielded the protoemetine derivative **29.**

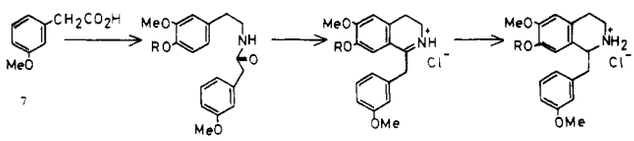
Because of the structural and biosynthetic parallelism between the ipecac and various indole alkaloids,[1] the development of efficient synthetic methods which could cover both of these classes of alkaloids has a significant practical value. We report here a new synthesis of (±)-emetine (**2**),[2] a representative ipecac alkaloid and one of the most synthesized natural products known,[3] by a completely new method which would be generally applicable to the synthesis of both the ipecac and the indole alkaloids.[4]



1 : $R_1=R_2=R_3=R_4=H$, $R_5=OH$
3 : $R_1=R_2=R_4=Me$, $R_3=R_5=H$
4 : $R_1=R_2=R_4=Me$, $R_3=CN$, $R_5=H$
5 : $R_1=R_4=Me$, $R_2=CH_2C_6H_5$, $R_3=R_5=H$
6 : $R_1=R_4=Me$, $R_2=CH_2C_6H_5$, $R_3=CN$, $R_5=H$

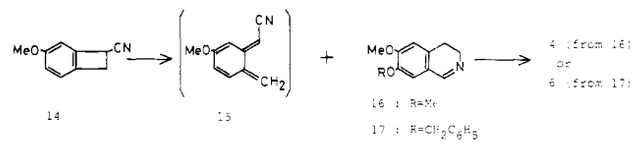
The present method proceeds through Woodward fission,[5] which had been once thought to be involved in the biogenetic pathways of the ipecac and some of the indole alkaloids. The fission between C-10 and C-11 of a tetrahydroprotoberberine precursor (e.g., **1**) was realized chemically by the cleavage reaction[6] of an α-diketone monothioketal intermediate **25** derived from tetrahydroprotoberberine precursors **3, 4, 5,** and **6.**

The starting tetrahydroprotoberberine framework was prepared by two different approaches. In the first approach, the tetrahydroprotoberberine **3** was obtained in 47% overall yield from 3-methoxybenzyl cyanide. Hydrolysis of 3-methoxybenzyl cyanide, prepared from *o*-chloroanisole and acetonitrile by a benzyne reaction[7] with methanolic potassium hydroxide, gave 3-methoxyphenylacetic acid (**7**), which on condensation with homoveratrylamine at 180 °C yielded the phenylacetamide **8** in 92% yield. The Bischler–Napieralski cyclization by phosphorus oxychloride provided the 3,4-dihydroisoquinoline **10** in 98% yield. This material was reduced with sodium borohydride followed by treating with ethereal hydrogen chloride to form the 1,2,3,4-tetrahydroisoquinoline hydrochloride **12** nearly quantitatively. Mannich condensation of the hydrochloride with 35% formalin in methyl alcohol produced the crystalline hydrochloride of 2,3,11-trimethoxytetrahydroprotoberberine (**3**) in 85% yield.



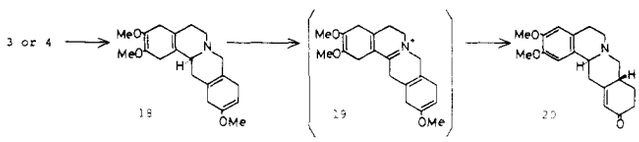
8 : R=Me
9 : $R=CH_2C_6H_5$
10 : R=Me
11 : $R=CH_2C_6H_5$
12 : R=Me
13 : $R=CH_2C_6H_5$

In the second approach, the tetrahydroprotoberberine **4,** a synthetic equivalent of **3,** was prepared by a more straightforward way using the method developed by Kametani et al.[8] Thermolysis of a 1:1 mixture of 1-cyano-5-methoxybenzocyclobutene (**14**)[9] and 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**)[10] without solvent at 140–150 °C resulted in regioselective intermolecular cycloaddition to form 13-cyano-2,3,11-trimethoxytetrahydroprotoberberine (**4**) via the *o*-quinodimethane intermediate **15** in 50% yield. The product **4** possessed a superfluous cyano group at C-13. However, this could be easily removed in a subsequent stage.



16 : R=Me
17 : $R=CH_2C_6H_5$

Dissolving metal reduction of the tetrahydroprotoberberines **3** and **4** using lithium in liquid ammonia in the presence of *tert*-butyl alcohol afforded the enol ether **18** in 76 and 74% yields, respectively. In the latter case, reductive decyanation occurred in preference to reduction of the aromatic rings, as observed in a related system.[11] Although attempts at selective reduction of ring D to give **23** under Birch conditions were unsuccessful, a selective aromatization of ring A of the enol



0022-3263/78/1943-4169$01.00/0 © 1978 American Chemical Society