Total Syntheses of (±)-Daunomycinone.[1] Regiospecific Preparations of (±)-7,9-Dideoxydaunomycinone and 6,11-Dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione

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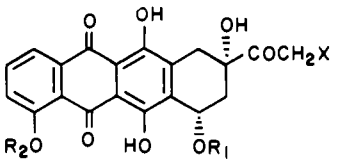
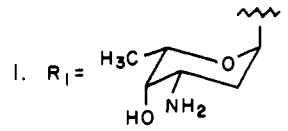
Abstract: Regiospecific total syntheses of 7,9-dideoxydaunomycinone (**18**) and 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (**7**), late stage precursors to (±)-daunomycinone (**2a**), are described.

The important anticancer activity of the anthracycline antibiotics daunorubicin (**1a**),[3] adriamycin (**1b**),[4] and carminomycin





1. R_1 = 2. R_1 = H

a. $R_2 = CH_3$, X = H
b. $R_2 = CH_3$, X = OH
c. R_2 = X = H

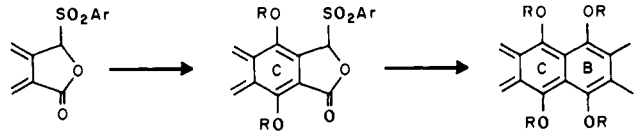
(**1c**)[5] has spawned a diversity of approaches to the synthesis of their aglycones (**2**).[6,7] In order to effect efficient preparations of these antibiotics (**1**), synthetic schemes which cope with their inherent dissymmetry are required, and recently, several such regiospecific syntheses of daunomycinone (**2a**) have been reported.[7-11]

Our own efforts in this area have resulted in the development of concepts[1,12] and methods[13,14] for general regiospecific synthesis of complex naturally occurring polycyclic aromatic systems. The diversity of structural types to which the methodology can be applied has been demonstrated by recent syntheses of the aglycones of kidamycin[15] and chartreusin.[16] This paper describes the application of this approach to achieve two total syntheses of daunomycinone (**2a**). One route furnished (±)-7,9-dideoxydaunomycinone (**18**)[8-10] in 38–40% overall yield from 7-methoxy-3-(phenylsulfonyl)-1(3*H*)isobenzofuranone (**3**).[15,17] The other sequence, initiated from 4-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**5**),[16] provided 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (**7**).[11,18,19]

Two Synthetic Approaches

The general plan leading to daunomycinone (**2a**) derives from our strategy[12] and annelation methodology[13] for regiospecific synthesis of polycyclic aromatic systems through repetitive ring annelations. As a further refinement, large latently functionalized fragments are used for ring annelations to abbreviate the overall synthesis and give a convergent aspect to the basically linear plan of the original strategy.

The oxygenated B,C ring core of rhodomycinones of the type which include **2a** are formed through tandem annelations from an initial and subsequently regenerated (phenylsulfonyl)isofuranone fragment. To accomplish this initial annelation in an



efficient manner 5-ethoxy-2-furanone is utilized as a synthon. This intermediate possesses both the capacity to transfer regiochemical integrity during ring construction and the necessary latent functionalization needed for regeneration of the phenylsulfonyl fragment.

Conceptual precedent for introduction of the terminal saturated A ring as a large fragment exists in our earlier finding that the anion of 3-(phenylsulfonyl)isobenzofuranone (**8**) smoothly condenses with 2-cyclohexen-1-one.[13] Use of either 2-cyclohexen-

(1) For the previous paper in this series, a preliminary account of the developmental studies, see: Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596.
(2) Recipient of a Career Development Award, 1978–1983, from the National Cancer Institute (Grant CA 00486).
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(13) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.
(14) For related ring annelations developed by others see: Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263. Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P.; Van Leusen, A. M. *Ibid.* **1978**, 2213.
(15) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.
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Scheme I

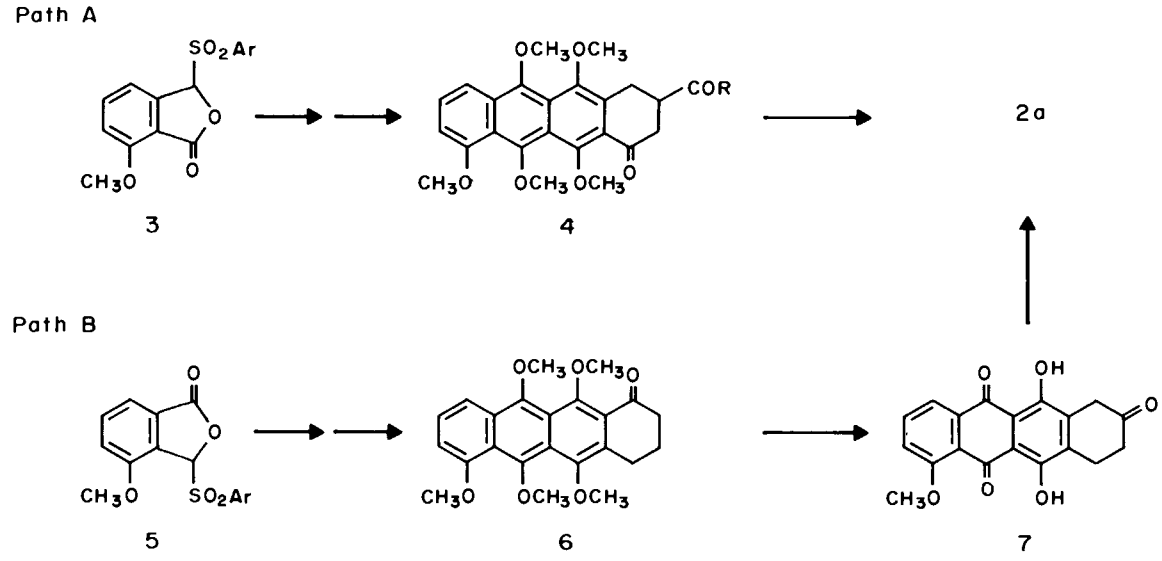
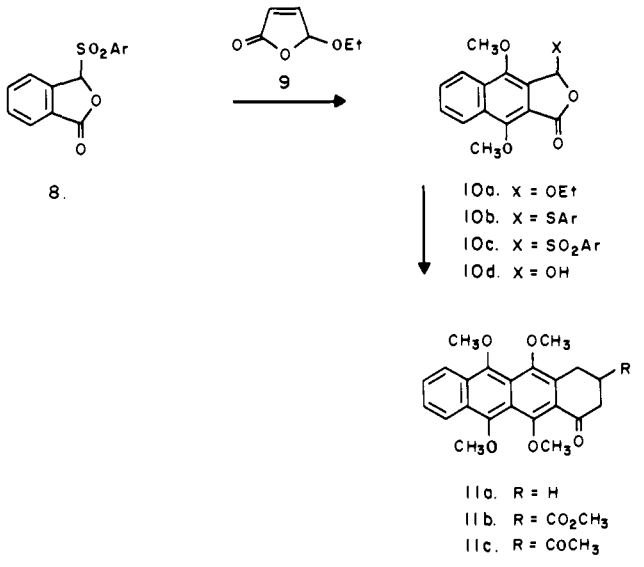


Table I. Condensation of Sulfones 3, 5, 8, 10c, 15c, and 19d with Conjugate Acceptors 9, 13, 14, 20, and 2-Cyclohexen-1-one

sulfone	acceptor	product	% yield	bp/mp, °C	^{1}H NMR ($CDCl_3$), δ	mass spectrum, *m/z* ($M^{+\cdot}$)	anal. calcd	anal. found
8	9	10a	65	117–118	8.40–8.25 (m, 1 H), 8.20–8.05 (m, 1 H), 7.70–7.45 (m, 2 H), 6.46 (s, 1 H), 4.32 (s, 3 H), 4.09 (s, 3 H), 3.92 (q, *J* = 6 Hz, 2 H), 1.36 (t, *J* = 6 Hz, 3 H)	288	$C_{16}H_{16}O_5$	
10c	*a*	11a	68	205–208	8.40–8.25 (m, 2 H), 7.70–7.40 (m, 2 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.80 (s, 3 H), 3.12 (t, *J* = 6 Hz, 2 H), 2.66 (t, *J* = 6 Hz, 2 H), 2.12 (p, *J* = 6 Hz, 2 H)	366	$C_{22}H_{22}O_5$ C, 72.11; H, 6.05	C, 72.16; H, 6.07
10c	13	11b	87	138–141	8.45–8.25 (m, 2 H), 7.70–7.40 (m, 2 H), 4.02 (s, 3 H), 3.98 (s, 6 H), 3.85 (s, 3 H), 3.72 (s, 3 H), 3.70–3.50 (m, 1 H), 3.33–2.90 (m, 4 H)	424	$C_{24}H_{24}O_7$ C, 67.91; H, 5.91	C, 68.03; H, 5.93
10c	14	11c	70	108–110	8.45–8.25 (m, 2 H), 7.60–7.40 (m, 2 H), 3.98 (s, 3 H), 3.95 (s, 6 H), 3.82 (s, 3 H), 3.75–3.50 (m, 1 H), 3.20–2.75 (m, 4 H), 2.24 (s, 3 H)	408	$C_{24}H_{24}O_6$ C, 70.57; H, 5.92	C, 70.61; H, 5.93
3	9	15a	74	129–130	7.82 (dd, *J* = 8, 1 Hz, 1 H), 7.52 (br t, *J* = 8 Hz, 1 H), 6.96 (d, *J* = 8 Hz, 1 H), 6.52 (s, 1 H), 4.12 (s, 3 H), 4.06 (s, 3 H), 4.02 (s, 3 H), 3.90 (q, *J* = 7 Hz, 2 H), 1.30 (t, *J* = 7 Hz, 3 H)	318	$C_{17}H_{18}O_6$	
15c	14	4a	70	173–176	7.96 (dd, *J* = 8, 1 Hz, 1 H), 7.46 (br t, *J* = 8 Hz, 1 H), 6.82 (d, *J* = 8 Hz, 1 H), 7.02 (s, 3 H), 3.97 (s, 3 H), 3.94 (s, 6 H), 3.83 (s, 3 H), 3.30–2.65 (m, 4 H), 2.30 (s, 3 H)	438	$C_{25}H_{27}O_7$ C, 68.48; H, 5.98	C, 68.50; H, 6.01
15c	13	4b	85	179–181	7.96 (dd, *J* = 8, 1 Hz, 1 H), 7.46 (br t, *J* = 8 Hz, 1 H), 6.83 (d, *J* = 8 Hz, 1 H), 4.07 (s, 3 H), 3.98 (s, 4 H), 3.95 (s, 6 H), 3.83 (s, 3 H), 3.74 (s, 3 H), 3.40–2.85 (m, 4 H)	454	$C_{25}H_{26}O_8$ C, 66.07; H, 5.76	C, 66.03; H, 5.87
5	9	19a[b]	49	98–100 110–112	7.96 (dd, *J* = 8, 1 Hz, 1 H), 7.45 (t, *J* = 8 Hz, 1 H), 7.02 (br d, *J* = 8 Hz, 1 H), 6.44 (s, 1 H), 422 (s, 3 H), 3.96 (s, 3 H), 3.92 (q, *J* = 7 Hz, 2 H), 3.88 (s, 3 H), H), 1.30 (t, *J* = 7 Hz, 3 H)	318	$C_{17}H_{18}O_6$	
5	20	21a	98	100–103 (0.01 mm)	7.68 (dd, *J* = 8, 1 Hz, 1 H), 7.38 (t, *J* = 8 Hz, 1 H), 6.89 (dd, *J* = 8, 1 Hz, 1 H), 4.46 (q, *J* = 7 Hz, 2 H), 3.99 (s, 3 H), 3.94 (s, 3 H), 3.80 (s, 3 H), 2.79–2.61 (m, 2 H), 1.78–1.66 (m, 2 H), 1.42 (t, *J* = 7 Hz, 3 H), 0.99 (t, *J* = 7 Hz, 3 H)	332	$C_{19}H_{24}O_5$ C, 68.65; H, 7.27	C, 68.69; H, 7.30
19d	*a*	6	88	162–164	7.93 (dd, *J* = 8, 1.1 Hz, 1 H), 7.34 (t, *J* = 8 Hz, 1 H), 6.82 (d, *J* = 8 Hz, 1 H), 4.04 (s, 3 H), 3.95 (s, 3 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 3.81 (s, 3 H), 3.12 (t, *J* = 6 Hz, 2 H), 2.71 (t, *J* = 6 Hz, 2 H), 2.18–1.90 (m, 2 H)	396	$C_{23}H_{24}O_6$ C, 69.68; H, 6.10	C, 69.64; H, 6.20

[a] 2-Cyclohexene-1-one. [b] Two different crystalline forms of 19a were observed; the melting points are given.

Scheme II



endo-18	$R_1 = COOCH_3$, $R_2 = H$	*exo*-18
exo-19,20	$R_1 = H$, $R_2 = COOCH_3$	*endo*-19,20
endo-4	$R_1 = R_2 = H$	*exo*-4

1-one or a 5-substituted 2-cyclohexen-1-one opens two avenues for elaboration of the anthracycline A ring and generates the two routes to daunomycinone (**2a**) shown in Scheme I. Final selection of the specific methoxyisobenzofuranone, **3** or **5**, to be used depends on the route selected for fabricating the terminal A ring.

The sequence in path A, initiated with methoxyisobenzofuranone **3**,[15,17] leads to daunomycinone (**2a**) or, alternately, to intermediate **18** which was used by Sih and co-workers[8] in their synthesis of **2a**. The parallel path B which utilizes methoxyisobenzofuranone (**5**)[16] for initial ring annelation and 2-cyclohexen-1-one to generate the terminal ring leads to intermediate **7** from which Kende et al. have completed elegant syntheses of both daunomycinone (**2a**)[18] and certain rhodomycinones.[19]

Developmental Studies

A model study (Scheme II) utilizing unbiased sulfone **8** was conducted to test the feasibility of these synthetic approaches. The anion of **8** was generated with LDA at −78 °C and condensed with 5-ethoxy-2-furanone (**9**)[20] to furnish, after methylation (Me_2SO_4/K_2CO_3/acetone), the ethoxyisonaphthofuranone (**10a**) in 65% yield. Heating **10a** with benzenethiol in benzene containing a catalytic amount of toluenesulfonic acid resulted in quantitative replacement of the ethoxyl substituent with a thiophenyl group furnishing **10b**.

Oxidation of **10b** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride produced sulfone **10c** in 68% yield and, unexpectedly, the naphthaldehydic acid **10d** in 30% yield. Although **10d** could be readily separated from **10c** through bicarbonate extraction and recycled to the sulfide **10b** by heating with benzenethiol, it was desirable to find conditions that precluded the formation of **10d** during the oxidation. Neither conducting the oxidation with MCPBA in the presence of added bicarbonate nor switching to other solvents such as ether, benzene, or ethyl acetate had an appreciable effect on the product composition. The use of other oxidants such as hydrogen peroxide in acetic acid or *tert*-butyl hydroperoxide catalyzed by vanadium acetylacetonate[21] proved deleterious, giving more naphthaldehydic acid **10d** than sulfone **10c**. Ultimately, almost exclusive formation of sulfone **10c** from sulfide **10b** was achieved by conducting the oxidation with MCPBA in a biphasic system of methylene chloride and phosphate buffer (pH 8).[22]

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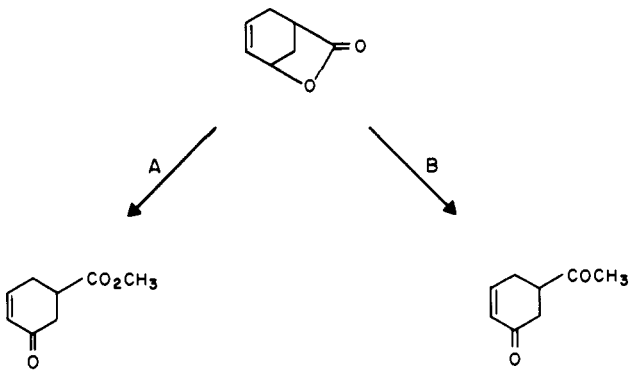
Scheme III



A. 1. CH_3OH/K_2CO_3 2. CICOCOCl/DMSO
B. 1. $\overset{\oplus}{C}H_2S\overset{\oplus}{O}N\text{-}C_6H_4CH_3$ 2. H_2O 3. CICOCOCl/DMSO

Introduction of the terminal saturated A ring as a large single entity was explored by condensing 2-cyclohexen-1-one with the anion of **10c** generated as before (LDA/THF/−78 °C). The permethylated hydronaphthacene ketone **11a** was obtained in 68% yield after methylation (Me_2SO_4/K_2CO_3/acetone) of the unstable intermediate phenolic product.

Parallel reactions with 5-(carbomethoxy)-2-cyclohexen-1-one (**13**) and 5-acetyl-2-cyclohexen-1-one (**14**) were examined as a means of introducing the terminal ring with the nine substituent in place. The well-known bicyclic unsaturated lactone **12**[23] shown in Scheme III served as a key intermediate for the preparation of both cyclohexenones. Lactone **12** was converted in 90% yield to 5-(carbomethoxy)-2-cyclohexen-1-one (**13**) by methanolysis with potassium carbonate followed by oxidation of the unsaturated alcohol intermediate with Swern's reagent.[24] The conversion of bicyclic lactone **12** to 5-acetyl-2-cyclohexen-1-one (**14**) was initiated by condensing the dianion of methanesulfinyl-*p*-toluidide[25] with the lactone. Aqueous workup cleaved off the toluylsulfinyl group from the intermediate condensation product furnishing 5-acetyl-2-cyclohexen-1-ol which was oxidized with Swern's reagent[24] to 5-acetyl-2-cyclohexen-1-one (**14**) in 61% overall yield from **12**. Individual condensations of the anion of **10c** with cyclohexenones **13** and **14** furnished, after methylation, tetracyclic products **11b** and **11c** in 87 and 70% yield, respectively.

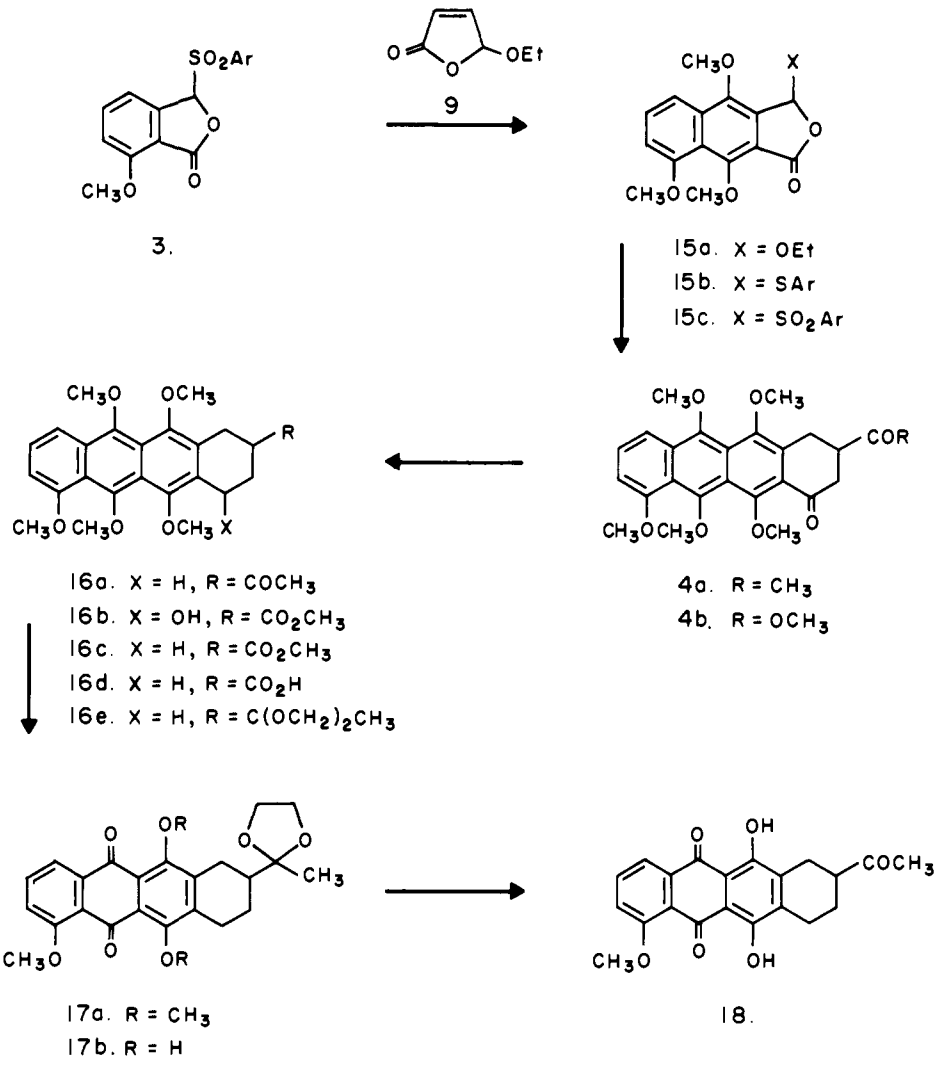
The Path A Route to Daunomycinone. Synthesis of (±)-7,9-Dideoxydaunomycinone (18)

As shown in Scheme IV, the anion of methoxyisobenzofuranone **3** was reacted with 5-ethoxy-2-furanone (**9**) to furnish ethoxyisonaphthofuranone **15a** in 74% yield, after methylation. Transformation of **15a** to thiophenyl compound **15b** and then to sulfone **15c** using the previously employed reagents and conditions was likewise routine.

Introduction of the acetyl substituted tetracyclic ring to give **4a** was accomplished in 70% yield by condensation of the anion of naphthylsulfone **15c** with 5-acetyl-2-cyclohexen-1-one (**14**) and methylation. The planned exploitation of the acetyl-substituted tetracyclic product **4a** to introduce the 9-hydroxyl group necessitated discrete manipulation of the individual ketone functionalities. However, neither selective monoketalization nor preferential reduction of either carbonyl group in **4a** was successful. Moreover, we were unable to exclusively remove the 7-oxygen functionality[26] to obtain a precursor to intermediate **18** which Sih

(22) Our decision to investigate the use of a buffered biphasic system to prepare sulfone **10c** was prompted by a recent report of the use of such a medium to prepare reactive arene epoxides. Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351.
(23) Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436. Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932.
(24) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2840.
(25) Corey, E. J.; Durst, T. *J. Am. Chem. Soc.* **1968**, *90*, 5548.

Scheme IV



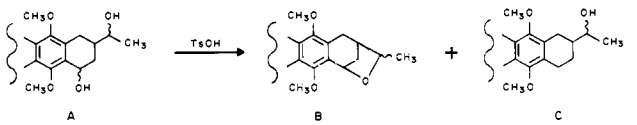
and co-workers[8] had earlier converted to daunomycinone (**2a**).

These problems led to consideration of the (carbomethoxy)-hydronaphthacene **4b** as a precursor to daunomycinone (**2a**). Condensation of the anion of naphthylsulfone **15c** with 5-(carbomethoxy)-2-cyclohexen-1-one (**13**) gave, after methylation, the regiospecifically prepared 9-(carbomethoxy)hydronaphthacene ketone **4b** in 85% yield. Reductive replacement of the 7-ketone of **4b** to obtain **16c** in 85% overall yield was achieved through sodium borohydride reduction and subsequent treatment of the alcohol intermediate **16b** with triethylsilane and trifluoroacetic acid.[27]

Of the several methods studied for converting the carbomethoxy functionality of **16c** to a methyl ketone entity, the best overall yield (92%) of **16a** was obtained by hydrolyzing **16c** to the acid **16d** and sequentially treating it with lithium hydride and methyllithium.[29]

The 9-acetyl functionality in **16a** was protected as ketal **16e** prior to cleavage of the methoxyl protective groups in the B and C rings. Selective removal of these methoxyl functionalities was accomplished in a two-step reaction sequence. Treatment of **16e** with ceric ammonium nitrate and pyridinedicarboxylic acid *N*-oxide[30] oxidatively cleaved only the 5,12-methoxyl groups of the electron-rich C ring, furnishing 5,12-quinone **17a** in 96% yield. The residual 6,11-methoxyl groups of **17a** were next cleaved by treatment with silver(II) oxide in dilute nitric acid.[31] The bisquinone intermediate formed in this oxidative demethylation reaction was reduced with bisulfite during workup and provided the tetracyclic quinone **17b** in 95% yield. The ketal functionality in **17b** was removed in 94% yield through hydrolysis with trifluoroacetic acid–hydrochloric acid and gave (±)-7,9-dideoxydaunomycinone (**18**). The physical characteristics and spectral properties of this compound were in all respects identical with an authentic sample generously furnished by Dr. John Swenton. The

(26) Our attempts to remove the 7-oxygen functionality centered on the use of the epimeric mixture of diols A prepared from **4a** through reduction



with sodium borohydride. Treatment of **19** with trifluoroacetic acid in the presence of triethylsilane[27] led to the production of a complex product mixture and not to the expected selective removal of the benzylic alcohol. The known selective dehydration and/or hydrogenolysis of benzylic alcohols over their aliphatic counterparts was also examined. Treatment of diol A with a catalytic amount of toluenesulfonic acid in benzene produced, through intramolecular capture of the benzylic carbonium ion by the hydroxyethyl group, the epimeric bicyclic ethers B as the sole product. Direct hydrogenolysis (Pd/C) of the epimeric diol mixture A in acetic acid or in ethyl acetate gave some of the saturated compound C, but again the epimeric ethers B were the major products. Although reductive replacement of the sugar residue in daunomycin can be performed by treatment with dithionite,[28] an analogous reaction with diol A failed.

(27) Adlington, M. G.; Orfanopoulous, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955.

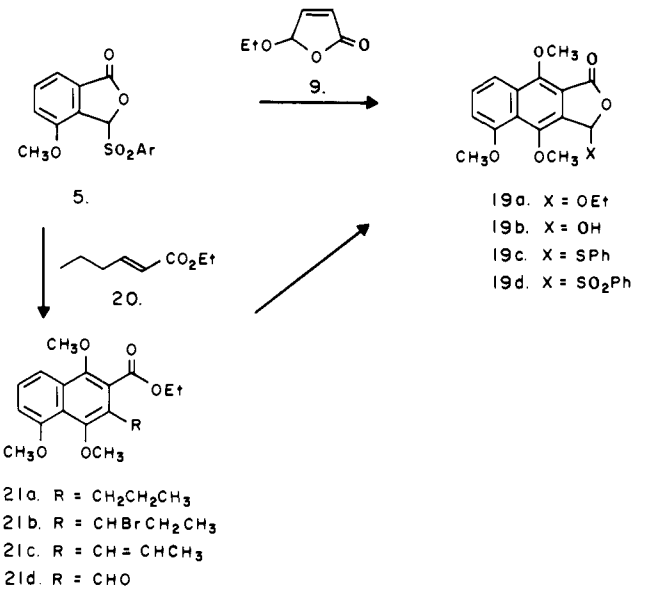
(28) Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *J. Am. Chem. Soc.* **1976**, *98*, 1969.

(29) Bare, T. M.; House, H. O. "Organic Synthesis"; Wiley: New York, 1973; Vol. 5, p 775.

(30) Syper, L.; Kloc, K.; Milochowski, J.; Szulc, Z. *Synthesis* **1979**, 521.

(31) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.

Scheme V



synthetic sequence presented here furnished (±)-7,9-dideoxydaunomycinone (**18**) in 38–40% overall yield from methoxyisobenzofuranone **3**.

The Path B Plan to Daunomycinone. Synthesis of 6,11-Dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (7)

As outlined in Scheme I, the projected preparation of naphthacenetrione **7** would employ a reaction sequence basically paralleling the previous route. Here, however, the synthesis would be initiated by using the isomeric methoxyisobenzofuranone **5**,[16] thereby resulting in a net inversion of the regiochemistry of the A ring ketone (relative to the path A plan) and providing appropriate functionalization for the subsequent ketone transposition.

Condensation of the anion of methoxyisobenzofuranone **5** with 5-ethoxy-2-furanone (**9**)[20] gave, after methylation, the expected isonaphthofuranone **19a** shown in Scheme V. However, in contrast to the very good yield obtained with the unsubstituted and isomeric methoxyisobenzofuranones **8** and **3**, the yield here was only 49%. An alternate and higher yield process for regiospecifically preparing the naphthalene intermediates **19** was developed to specifically address this problem.

Condensation of **5** with ethyl 2-hexenoate (**20**) provided the propyl-substituted naphthoate **21a** in virtually quantitative yield (98%) after methylation. Purification of naphthoate **21a** was conveniently accomplished by distillation or filtration through a short column of silica gel, thereby facilitating the preparation of large quantities of this intermediate. In the ^1H NMR spectrum of **21a**, the nonequivalence of the protons on the methylene adjacent the aromatic ring was indicated by the presence of an ABX_2 pattern which is a consequence of the restricted rotation imposed by the presence of flanking ortho functionalities.

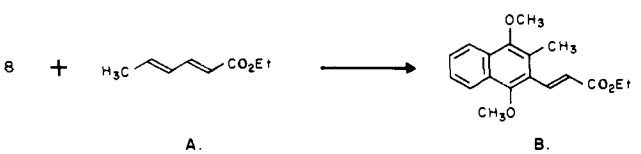
Free radical bromination of **21a** with *N*-bromosuccinimide in carbon tetrachloride afforded **21b** which was usually not purified before dehydrohalogenation with 1,8-diazabicyclo[5.4.0]undec-5-ene (DBU) in benzene to the propenyl naphthoate **21c**[32] (81% overall yield from **21a**). This product was readily purified by distillation or, preferably, by filtration through a short column of silica gel. Lemieux–Johnson[33] oxidation of the olefinic moiety of **21c** produced the aldehydonaphthoate **21d** (95% yield) as an oil which was sequentially treated with base and acid to obtain the crystalline naphthaldehydic acid **19b**. Naphthaldehydic acid **19b** was converted to thiophenyl compound **19c** through reaction with benzenethiol in benzene and a catalytic amount of *p*-toluenesulfonic acid. MCPBA oxidation of **19c** to sulfone **19d** was performed in 93% yield by using the biphasic system mentioned earlier.

The anion of **19d**, generated at −78 °C by using lithium diisopropylamide, was condensed with 2-cyclohexen-1-one to furnish, after methylation, the regiospecifically constructed tetracyclic ketone **6** in 88% overall yield (Scheme VI). Attempted transposition of the 10-ketone in **6** to the 9-position using the procedure developed by Trost and co-workers[34] was unsuccessful.[35] Conversion of **6** to the transposed ketone product was ultimately accomplished in high overall yield by using a four-step procedure recently reported by us.[38] Sodium borohydride reduction of ketone **6** followed by dehydration of the alcohol product in benzene under toluenesulfonic acid catalysis produced dihydronaphthacene **22**. Hydroxylation of the olefinic fragment in **22** with trimethylamine *N*-oxide and a catalytic amount of osmium tetroxide[39] furnished the cis-diol **23** which on momentary treatment with a catalytic amount of toluenesulfonic acid in hot benzene gave the transposed ketone product **24a**. The overall yield of **24a** from the tetracyclic starting ketone **6** was 60%.

Subsequently, it was found that any attempt to remove the protective methoxyl groups in the B and C rings of **24a** without first protecting the nine ketone functionality as the ketal resulted in an intractable mixture of products. The needed ketal **24b** was straightforwardly produced in a single step by conducting the dehydration of **23** in the presence of added ethylene glycol.

As in the previous synthesis, stepwise deprotection of the B and

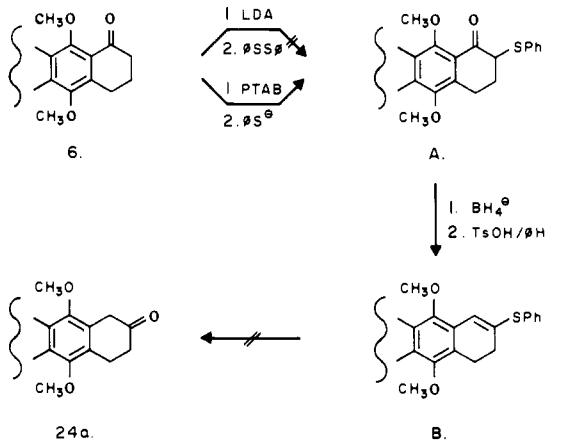
(32) In a study to determine the feasibility of generating **21c** in a single step, we explored the condensation of ethyl sorbate A with the unsubstituted sulfone **8** followed by methylation of the phenolic intermediate. The sole product of the reaction was the isomeric product B (83% yield).



(33) Pappo, R.; Allen, D. S.; Lemieux, R. V.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(34) Trost, B. M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* **1975**, *97*, 438.

(35) Attempts to α-thiophenylate **6** with LDA and diphenyldisulfide to obtain A resulted in quantitative reisolation of starting material **6**. An alternative procedure for preparing A from **6** was devised. Mono α-bromination of **6** with phenyltrimethylammonium perbromide (PTAB)[36,37] in THF, followed by displacement of the introduced bromine with sodium thiophenoxide, gave A in high overall yield. Thiophenyl ketone A proved to be unstable and, without purification, was directly reduced to the alcohol with sodium borohydride in ethanol. The alcohol product was smoothly dehydrated to the vinyl sulfide B in refluxing benzene with a catalytic amount of toluenesulfonic acid. A variety of conditions including mercuric ion catalysis, with and without added cadmium carbonate buffer, was employed to effect hydrolysis of the vinyl sulfide B to the objective ketone product **7**, but in each instance a complex product mixture resulted.



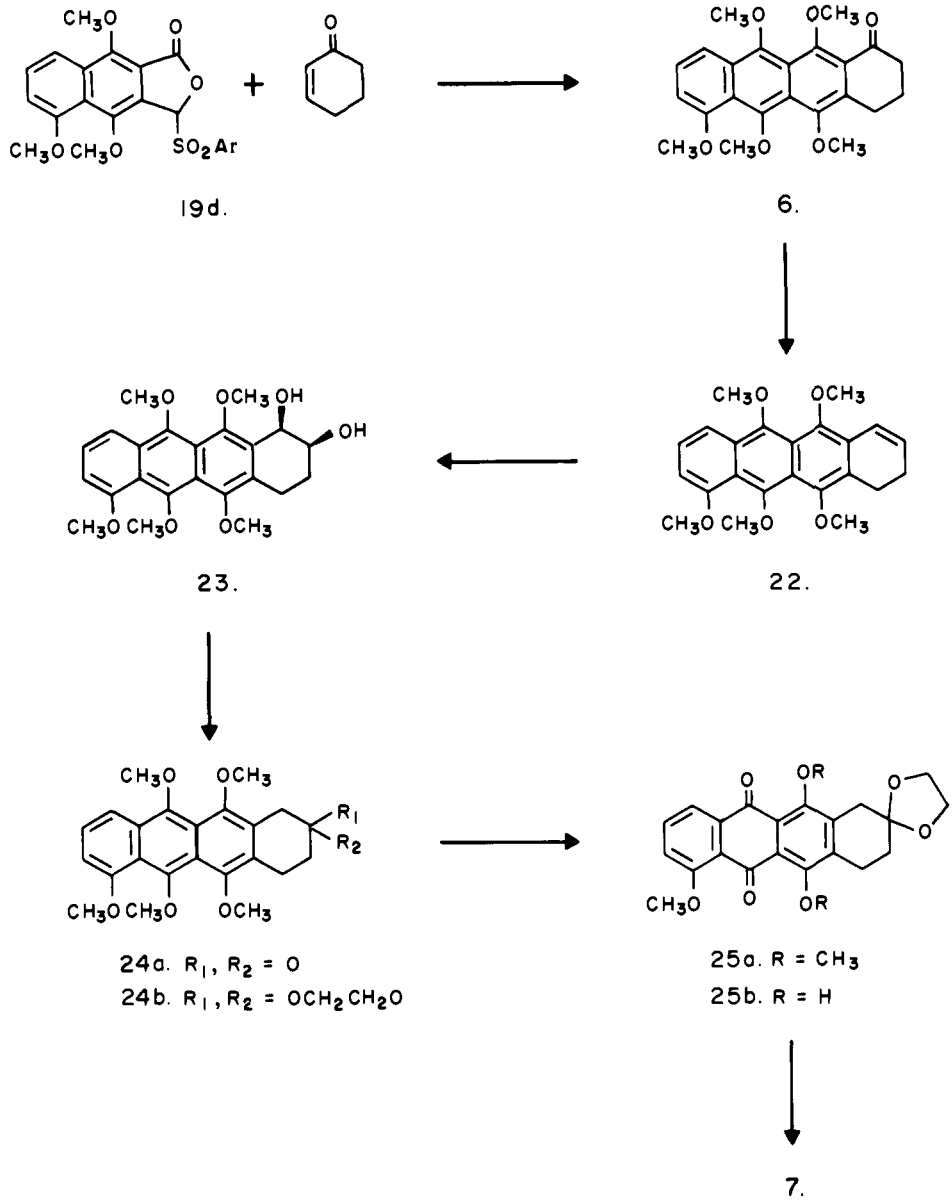
(36) Vorlander, D.; Siebert, E. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 283. Johnson, W. S.; Bass, J. D.; Williamson, K. L. *Tetrahedron* **1963**, *19*, 861.

(37) The use of other brominating agents afforded the α,α-dibromo product.

(38) Hauser, F. M.; Prasanna, S. *Synthesis* **1980**, 621.

(39) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, 449.

Scheme VI



C rings through oxidative demethylation was performed in two stages. Ceric ammonium nitrate, in the presence of pyridinedicarboxylic acid *N*-oxide,[30] selectively oxidized **24b** to quinone **25a** in excellent yield. Demethylation of the 6,11-methoxyl groups of **25a** was accomplished through silver(II) oxide oxidation in dilute nitric acid[31] followed by dithionite workup. The resulting product **25b** was deketalized to the objective naphthacenetrione **7** by treatment with trifluoroacetic acid and 10% hydrochloric acid[11] in dimethoxyethane. This final product **7** was in all respects identical with a sample generously provided by Dr. Andrew Kende.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 621 spectrophotometer and are expressed in inverse centimeters. Ultraviolet spectra were run on a Cary 15 (Varian) ultraviolet–visible spectrophotometer and are expressed in nanometers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a JEOL FX-90Q spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained with a CEC Du Pont Model 21-110B or Du Pont Model 21-491B spectrometer at an ionizing voltage of 70 eV. Carbon–hydrogen analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Analytical thin-layer chromatography (TLC) was conducted on 5 × 10 cm precoated plates (Silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. Silica gel columns for chromatography utilized E. Merck "Silica gel 60", 70–230 mesh ASTM.

Tetrahydrofuran (THF) and dimethoxyethane (DME) were dried by distillation from lithium aluminum hydride. Solvents were "reagent grade" and were not usually purified prior to use.

Sulfone Condensations. General Procedure. The following is typical of the manner in which sulfone condensations were conducted. Fifty-gram condensations of sulfone **5** with ethyl hexenoate (**20**) were routinely performed.

3-Ethoxy-4,8,9-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (15a). To a magnetically stirred solution of diisopropylamine (20.3 mL, 145 mmol) in dry THF (250 mL) under nitrogen at 0 °C was added *n*-butyllithium (60.3 mL of 2.4 M, 144 mmol). The diisopropylamide solution was maintained at 0 °C for 5 min and then cooled to −78 °C. Sulfone **3** (20 g, 65.8 mmol), as a slurry in THF (250 mL), was added to the vigorously stirred LDA solution through a large bore addition funnel. The yellow anion formed from **3** was moderately insoluble in THF and began immediately to precipitate.

5-Ethoxy-2-furanone (**9**) (20.2 g, 159 mmol) in THF (20 mL) was added to the yellow anion solution. After the solution had stirred for 5 min, the cooling bath was removed and the reaction was allowed to come to ambient temperature. During this period, the precipitated anion slowly dissolved and the solution became dark brown. The reaction was stirred at room temperature for half an hour, then heated at reflux for 30 min, cooled to 0 °C, and made acidic with dilute hydrochloric acid. The tetrahydrofuran was removed at reduced pressure and the residue taken up in ethyl acetate (3 × 200 mL). The ethyl acetate extracts were successively washed with water (2 × 100 mL), saturated sodium bicarbonate (100 mL), and 1% sodium bisulfite (100 mL), then dried

($MgSO_4$), filtered, and evaporated at reduced pressure to give the phenolic intermediate as a dark brown viscous oil. To this crude product, dissolved in acetone (500 mL), was added dimethyl sulfate (25 g, 198 mmol) and anhydrous potassium carbonate (40 g, 290 mmol), and the stirred reaction was heated at reflux under nitrogen overnight. The inorganic material was filtered off and the acetone removed at reduced pressure to give a dark brown oil which was dissolved in ethyl acetate (200 mL). For removal of the excess dimethyl sulfate, triethylamine (20 mL) was added to the ethyl acetate solution and the mixture allowed to stand for 2 h. The reaction was decanted into a separatory funnel, successively washed with dilute hydrochloric acid (10%, 100 mL) and water (2 × 100 mL), then dried, and filtered and the solvent evaporated at reduced pressure to give crude **15a**. Final purification was effected by chromatography on silica gel (300 g, CH_2Cl_2–EtOAc, 9:1) and furnished 15.1 g (74%) of pure **15a**. A sample recrystallized from CH_2Cl_2–hexanes had a melting point of 129–130 °C.

Condensations with naphthalide sulfones **10c**, **15c**, and **19d** were analogously performed. The deep purple color of anion solutions of **10c**, **15c**, and **19d** was immediately discharged on addition of the conjugate acceptor. The resultant yellow solution changed to gold, then to green, and finally to deep green. Acidification of the final green solution afforded a deep red solution of the unstable phenolic intermediate, which was immediately methylated to avoid deterioration.

In Table I are listed yields, melting points, and respective ^1H NMR spectra of the products formed from the various sulfone condensations.

Sulfide Preparations. General Procedure. 3-(Thiophenyl)-4,8,9-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (15b). A solution of **15a** (15 g, 47.1 mmol), benzenethiol (6.75 g, 61.4 mmol), and toluenesulfonic acid (0.25 g) in benzene (500 mL) was heated at reflux under a Dean–Stark head for 3 h. During the reflux period, some of the benzene (ca. 150 mL) was periodically run out to remove the ethanol formed in the reaction. The cooled reaction was successively washed with aqueous $NaHCO_3$ (2 × 100 mL) and water (2 × 50 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give a syrup. The syrup was crystallized from ether to afford pure **15b**. Column chromatographic purification of the residue from the filtrate on silica gel (300 g, CH_2Cl_2–EtOAc, 4:1) afforded an additional quantity of pure **15b**. The combined weight of pure **15b** was 17.12 g (95% yield) and had a melting point of 139–141 °C: ^1H NMR ($CDCl_3$) δ 7.72 (dd, J = 8, 1 Hz, 1 H), 7.56–6.95 (m, 6 H), 6.84 (dd, J = 8, 1 Hz, 1 H), 6.70 (s, 1 H), 4.12 (s, 3 H), 3.94 (s, 3 H), 3.84 (s, 3 H); mass spectrum, m/z 382 ($M^{+\cdot}$).

Anal. Calcd for $C_{21}H_{18}O_5S$: C, 65.95; H, 4.74. Found: C, 65.87; H, 4.91.

3-(Thiophenyl)-4,9-dimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (10b), mp 120–122 °C, was analogously prepared in 97% yield from **10a**: ^1H NMR ($CDCl_3$) δ 8.30–8.00 (m, 2 H), 7.80–7.30 (m, 5 H), 7.20–7.00 (m, 2 H), 6.82 (s, 1 H), 4.16 (s, 3 H), 4.04 (s, 3 H); mass spectrum, m/z 352 ($M^{+\cdot}$).

Anal. Calcd for $C_{20}H_{16}SO_4$: C, 68.16; H, 4.57. Found: C, 68.20; H, 4.60.

Sulfone Preparations. General Procedure. 3-(Phenylsulfonyl)-4,8,9-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (15c). A vigorously stirred solution of sulfide **15b** (15 g, 39.3 mmol) in CH_2Cl_2 (3 L) and phosphate buffer (6 L) was cooled to 15 °C before MCPBA (17.62 g, 102 mmol) was added in small portions over the course of 15 min. The reaction was stirred for 6 h at which time a TLC indicated the reaction was complete. The organic layer was successively washed with bisulfite (1%, 2 × 100 mL), aqueous $NaHCO_3$ (2 × 150 mL), and water (100 mL), then dried ($MgSO_4$), filtered, and evaporated. The residue was recrystallized from CH_2Cl_2–ether–hexanes to give 15.12 g (93% yield) of pure **15c**: mp 147–148 °C; ^1H NMR ($CDCl_3$) δ 8.05–7.40 (m, 7 H), 7.06 (d, J = 8 Hz, 1 H), 6.43 (s, 1 H), 4.27 (s, 3 H), 4.01 (s, 3 H), 3.86 (s, 3 H); mass spectrum, m/z 414 ($M^{+\cdot}$).

Anal. Calcd for $C_{21}H_{18}O_7S$: C, 60.86; H, 4.38. Found: C, 60.88; H, 4.50.

3-(Phenylsulfonyl)-4,9-dimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (10c), mp 175–176 °C, was analogously prepared in 95% yield from **10b**: ^1H NMR (acetone-d_6) δ 8.40–8.20 (m, 2 H), 8.00–7.42 (m, 7 H), 7.04 (s, 1 H), 4.36 (s, 3 H), 4.02 (s, 3 H); mass spectrum, m/z 384 ($M^{+\cdot}$).

5-(Carbomethoxy)-2-cyclohexen-1-one (13). Aqueous potassium carbonate (35%, 120 mL) was added to a solution of bicyclic lactone **12** (16.5 g, 133 mmol) in methanol (150 mL) under N_2. The mixture was stirred for 3 h and then partitioned between ether and saturated brine (400 mL each). The aqueous layer was extracted twice with ether (100 mL), the combined ether extracts were washed once with water, dried ($MgSO_4$), and concentrated, and the residue was distilled (bp 71–73 °C (0.05 mm)) to give 17.2 g (85% yield) of pure 5-(carbomethoxy)-2-cyclohexen-1-ol as an oil: ^1H NMR ($CDCl_3$) δ 5.76 (br s, 2 H), 4.40–4.20 (m, 1 H), 3.72 (s, 3 H), 2.82–2.18 (m, 3 H), 1.86–1.60 (m, 2 H).

To a magnetically stirred solution of oxalyl chloride (14.5 g, 114 mmol) in dry methylene chloride (175 mL), cooled to −78 °C under N_2, was added dropwise a solution of dry dimethyl sulfoxide (freshly distilled from calcium hydride, 15.55 g, 199 mmol) in methylene chloride (40 mL) followed by a solution of 5-(carbomethoxy)-2-cyclohexen-1-ol (14.8 g, 98 mmol) in methylene chloride (20 mL). The reaction was stirred for 30 min, triethylamine (38.5 g, 380 mmol) added, and the mixture allowed to warm to room temperature. Aqueous bicarbonate (250 mL of 5%) was added to the reaction, the organic layer separated, and the aqueous layer further extracted with methylene chloride (2 × 300 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the residue obtained after removal of the solvent was distilled (bp 61–63 °C (0.03 mm)) to give 13.1 g (90% yield) of pure ketone **13**: ^1H NMR ($CDCl_3$) δ 6.90 (dt, J = 6, 2 Hz, 1 H), 6.00 (dt, J = 6, 1 Hz, 1 H), 3.69 (s, 3 H), 3.30–2.95 (m, 1 H), 2.70–2.54 (m, 4 H); mass spectrum, m/z 154 ($M^{+\cdot}$).

5-Acetyl-2-cyclohexen-1-one (14). The dianion of methanesulfinyl-*p*-toluidide (57.3 g, 340 mmol) was prepared by adding a solution of *n*-butyllithium (283 mL of 2.4 M, 678 mmol) to a magnetically stirred solution of the toluidide in dry THF (750 mL) at −78 °C under N_2. To the dianion was added a solution of lactone **12** (21.0 g, 169 mmol) in THF (100 mL) in a thin stream. The reaction was stirred for 10 min, then siphoned into ice cold saturated brine (2 L), and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the residue obtained, after removal of the solvent, was chromatographed on silica gel (450 g, hexanes–ether, 7:3). Distillation (bp 75–77 °C (0.05 mm)) of the eluted product afforded 17.9 g (75% yield) of pure 5-acetyl-2-cyclohexen-1-ol: ^1H NMR ($CDCl_3$) δ 5.88–5.40 (m, 2 H), 4.40–4.10 (m, 1 H), 2.92–2.54 (m, 3 H), 2.18 (s, 3 H), 1.95–1.60 (m, 2 H).

The above alcohol (13.4 g, 96 mmol) was oxidized with oxalyl chloride (14.6 g, 115 mmol) and dry Me_2SO (15.68 g, 201 mmol) in the same manner as that described for **13**. The crude ketone was distilled (bp 63–64 °C (0.05 mm)) to furnish 11.90 g (90% yield) of pure 5-acetyl-2-cyclohexen-1-one (**14**) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 6.96 (dt, J = 6, 2 Hz, 1 H), 6.05 (dt, J = 6, 1 Hz, 1 H), 3.30–2.95 (m, 1 H), 2.75–2.40 (m, 4 H), 2.21 (s, 3 H); mass spectrum, m/z 138 ($M^{+\cdot}$).

Methyl 7-Hydroxy-4,5,6,11,12-pentamethoxy-7,8,9,10-tetrahydronaphthacene-9-carboxylate (16b). To a chilled (−10 °C), magnetically stirred solution of **4b** (10.0 g, 22 mmol) in THF (200 mL) and water (25 mL) was added $NaBH_4$ (0.31 g, 8 mmol). The reaction was stirred for 3 h, acidified with cold 10% HCl, and partitioned between ethyl acetate (600 mL) and saturated aqueous sodium chloride. The organic layer was washed with $NaHCO_3$ solution (2 × 200 mL), then dried ($MgSO_4$), and filtered and the solvent evaporated to give the alcohol as a pale green solid. Recrystallization from ether–hexanes gave 9.60 g (96% yield) of pure **16b** as plates: mp 115–119 °C; ^1H NMR ($CDCl_3$) δ 7.95 (dd, J = 8, 1 Hz, 1 H), 7.38 (br t, J = 8 Hz, 1 H), 6.85 (d, J = 8 Hz, 1 H), 5.50 (dt, J = 7, 1 Hz, 1 H), 4.07 (s, 3 H), 3.94 (s, 6 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 1.80–1.40 (m, 2 H).

Methyl 4,5,6,11,12-Pentamethoxy-7,8,9,10-tetrahydronaphthacene-9-carboxylate (16c). Trifluoroacetic acid (10 mL) was added in a thin stream to a vigorously stirred, chilled (−20 °C) solution of **16b** (8.0 g, 17.5 mmol) and triethylsilane (2.24 g, 19.3 mmol) in dry methylene chloride (250 mL) under nitrogen. The initial dark green color which formed on addition of the acid faded to a lighter color after 5 min. After an additional 15 min, the reaction was quenched by addition of solid $NaHCO_3$ (25 g). Water (400 mL) was added to the mixture, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL), the combined extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated at reduced pressure. Column chromatography (silica gel, 200 g, 1% EtOAc in CH_2Cl_2) of the crude product afforded, after recrystallization from hexanes, 6.87 g (89% yield) of pure **16c**: mp 148–150 °C; ^1H NMR ($CDCl_3$) δ 7.94 (dd, J = 8, 1 Hz, 1 H), 7.34 (br t, J = 8 Hz, 1 H), 6.77 (d, J = 8 Hz, 1 H), 4.05 (s, 3 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.82 (s, 6 H), 3.77 (s, 3 H), 3.60–2.75 (m, 4 H), 2.20–2.05 (m, 1 H); mass spectrum, m/z 440 ($M^{+\cdot}$).

Anal. Calcd for $C_{25}H_{28}O_7$: C, 68.17; H, 6.40. Found: C, 68.23; H, 6.51.

4,5,6,11,12-Pentamethoxy-7,8,9,10-tetrahydronaphthacene-9-carboxylic Acid (16d). To a solution of **16c** (6.50 g, 14.8 mmol) in ethanol (50 mL) was added aqueous potassium hydroxide (6.5 mL of 25%), and the mixture was heated at reflux for 30 min. Water (500 mL) was added to the reaction and the mixture acidified with hydrochloric acid and extracted with ethyl acetate (3 × 150 mL). The combined ethyl acetate extracts were washed with water (100 mL), dried ($MgSO_4$), and filtered, and the solvent was removed at reduced pressure. The initial product was recrystallized (Et_2O–hexanes) to give 6.17 g (98% yield) of pure **16d**: mp 165–173 °C; ^1H NMR ($CDCl_3$) δ 7.95 (dd, J = 8, 1 Hz, 1 H), 7.35 (br t, J = 8 Hz, 1 H), 6.78 (d, J = 8 Hz, 1 H), 4.07 (s, 3 H),

3.94 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 6 H), 3.60–2.84 (m, 4 H); mass spectrum, m/z 426 ($M^{+\cdot}$).

9-Acetyl-4,5,6,11,12-pentamethoxy-7,8,9,10-tetrahydronaphthacene (16a). A magnetically stirred solution of acid **16d** (6.0 g, 14.1 mmol) and lithium hydride (123 mg, 15.5 mmol) in dry DME (150 mL) under N_2 was heated at reflux for 2 h and then cooled to 0 °C in an ice bath. Methyllithium (13.10 mL of 1.4 M, 18.3 mmol) was added to the reaction which was then stirred at 0 °C for 10 min and at room temperature for 15 min. Workup as described[29] yielded the crude ketone which was further purified by chromatography (silica gel, 175 g, CH_2Cl_2) and then crystallized (hexanes) to give 5.70 g (94% yield) of pure **16a** as light yellow needles: mp 161–162 °C; ^1H NMR ($CDCl_3$) δ 8.01 (dd, J = 8, 1 Hz, 1 H), 7.35 (br t, J = 8 Hz, 1 H), 6.82 (d, J = 8 Hz, 1 H), 4.06 (s, 3 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 6 H), 3.40–2.90 (m, 4 H), 2.32 (s, 3 H); mass spectrum, m/z 424 ($M^{+\cdot}$), 408.

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.73; H, 6.65. Found: C, 70.75; H, 6.72.

9-(1-Ethylenedioxyethyl)-4,5,6,11,12-pentamethoxy-7,8,9,10-tetrahydronaphthacene (16e). A solution of **16a** (5.0 g, 11.8 mmol), ethylene glycol (2.0 mL), and toluenesulfonic acid (100 mg) in benzene (100 mL) was heated at reflux for 1 hour. The water generated during the reaction was azeotropically removed using a Dean-Stark apparatus. The cooled reaction was poured into aqueous bicarbonate, the benzene layer separated and washed with brine (50 mL) and water (50 mL), then dried ($MgSO_4$), filtered and evaporated. Crystallization of the residue from hexanes afforded 5.32 g (97%) of pure ketal **16e**: mp 127–131 °C. ^1H NMR ($CDCl_3$) δ 7.94 (dd, J = 9, 1 Hz, 1 H), 7.35 (br t, J = 9 Hz, 1 H), 6.76 (d, J = 7 Hz, 1 H), 4.06 (s, 3 H), 4.03 (s, 3 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 7 H), 3.20–2.32 (m, 4 H), 1.43 (s, 3 H); mass spectrum, m/z 468 ($M^{+\cdot}$).

9-(1-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-4,6,11-trimethoxy-5,12-naphthacenedione (17a). To a magnetically stirred, cold (0 °C) solution of ketal **16e** (5.20 g, 11 mmol) in a mixture of acetonitrile (150 mL) and THF (150 mL) were sequentially added powdered pyridinedicarboxylic acid *N*-oxide (5.08 g, 27 mmol) and a solution of ceric ammonium nitrate (15.22 g, 27.8 mmol) in water (35 mL). The reaction was stirred for 10 min, and then partitioned between ethyl acetate (250 mL) and brine (200 mL). The organic layer was washed with water (2 × 50 mL), dried ($MgSO_4$), and filtered and the solvent evaporated to give the crude quinone as a yellow solid. Recrystallization of the crude product from ether–hexanes gave 4.68 g (96% yield) of pure quinone **17a** as long yellow needles: mp 147–152 °C; ^1H NMR ($CDCl_3$) δ 7.69 (dd, J = 8, 1.7 Hz, 1 H), 7.54 (t, J = 8 Hz, 1 H), 7.16 (dd, J = 8, 1.6 Hz, 1 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 4 H), 3.44–2.83 (m, 4 H), 1.37 (s, 3 H); mass spectrum, m/z 438 ($M^{+\cdot}$).

Anal. Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.69; H, 6.01.

9-(1-Ethylenedioxyethyl)-6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (17b). To quinone **17a** (4.50 g, 10.3 mmol) in acetone (40 mL) was added powdered silver(II) oxide (5.10 g, 41 mmol), and the mixture was vigorously stirred for 3 min to ensure thorough mixing of the reactants. Nitric acid (8 mL of 6 N) was added to the reaction, and in 5–6 min the reaction became clear. Aqueous bisulfite (1%, 100 mL) was added and the mixture extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water (2 × 75 mL), dried ($MgSO_4$), and filtered, and the solvent was removed at reduced pressure to give 4.0 g (95% yield) of pure **17b** as a dark red solid: mp 177–179 °C; ^1H NMR ($CDCl_3$) δ 13.56 (s, 1 H), 13.20 (s, 1 H), 7.86 (dd, J = 8, 1 Hz, 1 H), 7.60 (t, J = 8 Hz, 1 H), 7.26 (d, J = 8 Hz, 1 H), 4.04 (s, 3 H), 3.95 (s, 4 H), 1.39 (s, 3 H); mass spectrum, m/z 410 ($M^{+\cdot}$).

(±)-7,9-Dideoxydaunomycinone (18). To a stirred solution of ketal **17b** (3.5 g, 8.5 mmol) in DME (30 mL) was added a mixture of trifluoroacetic acid (15 mL) and hydrochloric acid (15 mL of 10%). The reaction was stirred for 4 h and then poured into water (600 mL) and the mixture extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with aqueous $NaHCO_3$, then dried (Na_2SO_4), and filtered, and the solvent was evaporated at reduced pressure. The nearly pure product was further purified by column chromatography (silica gel, 100 g, CH_2Cl_2–EtOAc, 4:1). The collected product was recrystallized from acetic acid and gave 2.94 g (94% yield) of pure quinone **18** as deep red needles: mp 245–247 °C (lit.[8b] mp 243–245 °C, lit.[9] 244–245° C) (a mixed melting point with an authentic sample supplied by Dr. John S. Swenton was undepressed); ^1H NMR ($CDCl_3$) δ 13.60 (s, 1 H), 13.24 (s, 1 H), 7.99 (dd, J = 8, 1.3 Hz, 1 H), 7.71 (t, J = 8 Hz, 1 H), 7.33 (dd, J = 8, 1.2 Hz, 1 H), 4.04 (s, 3 H), 3.30–2.74 (m, 5 H), 2.26 (s, 3 H).

Ethyl 3-(1(*E*)-Propenyl)-1,4,5-trimethoxy-2-naphthoate (21c): A mixture of **21a** (25 g, 75.3 mmol), *N*-bromosuccinimide (14.75 g, 82.2 mmol), and benzoyl peroxide (0.10 g) in carbon tetrachloride (1.5 L) under N_2 was heated at reflux while being illuminated with an incandescent lamp. The ^1H NMR spectrum of a sample removed from the reaction after 3 h of reflux showed that the reaction was complete. The reaction was cooled to 0 °C to ensure complete precipitation of the succinimide which was then removed by filtration. The solvent was removed at reduced pressure to give crude bromo compound **21b** as an oil which was used in the next step without purification: ^1H NMR ($CDCl_3$) δ 7.67 (dd, J = 8, 1 Hz, 1 H), 7.45 (t, J = 8 Hz, 1 H), 6.91 (d, J = 8 Hz, 1 H), 5.56 (br t, J = 9 Hz, 1 H), 4.48 (q, J = 7 Hz, 2 H), 4.01 (s, 3 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 2.64–2.02 (m, 2 H), 1.45 (t, J = 7 Hz, 3 H), 0.99 (t, J = 7 Hz); mass spectrum, m/z 411 ($M^{+\cdot}$).

To bromo compound **21b** dissolved in dry benzene (1 L) was added 1,8-diazabicyclo[5.4.0]undec-5-ene (DBU) (14 g, 92 mmol), and the mixture was heated at reflux overnight. The reaction was decanted into a separatory funnel, washed with water (3 × 150 mL) and brine (200 mL), then dried, and filtered and the solvent removed at reduced pressure to afford impure **21c** as a dark oil. The impurities in the product were quite polar and filtration of the crude product through a column of silica gel (220 g, benzene) gave 20.13 g (81% yield) of essentially pure **21c** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.67 (dd, J = 8, 1 Hz, 1 H), 7.39 (t, J = 8 Hz, 1 H), 6.89 (dd, J = 8, 1 Hz, 1 H), 6.65 (dq, J = 16, 1.5 Hz, 1 H), 6.13 (dq, J = 16, 7 Hz, 1 H), 4.41 (q, J = 7 Hz, 2 H), 3.99 (s, 3 H), 3.95 (s, 3 H), 3.75 (s, 3 H), 1.89 (dd, J = 7, 1.5 Hz, 3 H), 1.39 (t, J = 7 Hz, 3 H); mass spectrum, m/z 330 ($M^{+\cdot}$).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.26; H, 6.67.

Ethyl 3-Formyl-1,4,5-trimethoxy-2-naphthoate (21d): A mixture of **21c** (20 g, 60.6 mmol), powdered sodium metaperiodate (28.5 g, 133 mmol), and osmium tetroxide (0.025 g) in THF (400 mL) and water (200 mL) was vigorously stirred overnight while N_2 was bubbled through it. The reaction was poured into ethyl acetate (400 mL), and the layers were separated. The organic layer was washed with water (2 × 400 mL) and brine (100 mL), then dried ($MgSO_4$), and filtered and the solvent evaporated to give 18.2 g (95%) of aldehyde **21d** as an oil: ^1H NMR ($CDCl_3$) δ 10.46 (s, 1 H), 7.78–7.42 (m, 2 H), 6.95 (dd, J = 8, 1 Hz, 1 H), 4.45 (q, J = 7 Hz, 2 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 1.38 (t, J = 7 Hz, 3 H); mass spectrum, m/z 318 ($M^{+\cdot}$). For purposes of purification, aldehyde **12d** was converted to the crystalline naphthaldehydic acid **19b**.

3-Hydroxy-4,5,9-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (19b). Aqueous sodium hydroxide (30 mL of 25%) was added to a solution of aldehydonaphthoate **19b** (18 g, 56.6 mmol) in ethanol (150 mL) and the mixture heated at reflux for 30 min. The reaction was cooled, diluted with water (500 mL), and then acidified with hydrochloric acid (10%). The precipitated naphthaldehydic acid was digested on the steam bath for 10 min, cooled in an ice bath, and filtered and the collected material washed with cold water. The product was dried and then recrystallized from DME-water to give 15.27 g (93% yield) of pure **19b** as needles: mp 213–215 °C; ^1H NMR ($CDCl_3$) δ 7.91 (dd, J = 8, 1 Hz, 1 H), 7.48 (t, J = 8 Hz, 1 H), 7.04 (dd, J = 8, 1 Hz, 1 H), 6.74 (d, J = 8 Hz, 1 H), 4.23 (s, 3 H), 4.18 (d, J = 8 Hz, 1 H), 4.02 (s, 3 H), 3.94 (s, 3 H).

Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 62.00; H, 4.90.

3-(Thiophenyl)-4,5,9-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (19c). A suspension of **19b** (15 g, 51.7 mmol), benzenethiol (6.85 g, 62.3 mmol), and *p*-toluenesulfonic acid (0.4 g) in benzene (600 mL) was heated at reflux for 4 h. The naphthaldehydic acid **19b** went into solution as it reacted, ultimately furnishing a clear solution. Water formed during the reaction was collected in a Dean–Stark trap.

The cooled benzene solution was washed with bicarbonate (2 × 150 mL) and brine, then dried ($MgSO_4$), and filtered. The solvent was removed at reduced pressure and the residue crystallized from ether to give 14.4 g of pure **19c** as thick needles. The filtrate was evaporated and the residue chromatographed (silica gel, 150 g, CH_2Cl_2–EtOAc) to give an additional 4.75 g (97% total yield) of pure sulfide **19c**: mp 121–122 °C; ^1H NMR ($CDCl_3$) δ 7.91 (dd, J = 8, 1 Hz, 1 H), 7.58–7.10 (m, 6 H), 7.04 (d, J = 8 Hz, 1 H), 6.81 (s, 1 H), 4.10 (s, 3 H), 4.07 (s, 3 H) and 4.05 (s, 3 H); mass spectrum, m/z 382 ($M^{+\cdot}$).

Anal. Calcd for $C_{21}H_{18}O_5S$: C, 65.95; H, 4.74. Found: C, 66.09; H, 4.74.

3-(Phenylsulfonyl)-4,5,9-trimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (19d). Oxidation of sulfide **19c** (16 g, 41.9 mmol) with MCPBA (19.06 g, 110 mmol) was accomplished in a biphasic system of CH_2Cl_2 (3 L) and aqueous phosphate buffer (6 L).[22] Workup afforded 16.13 g (93% yield) of pure sulfone **19d** after recrystallization from methylene chloride–hexanes: mp 138–141 °C; ^1H NMR ($CDCl_3$) δ 8.05–7.80 (m, 3 H), 7.65–7.38 (m, 4 H), 7.12 (dd, J = 8, 1 Hz, 1 H), 6.38 (s, 1 H), 4.17 (s, 3 H), 4.07 (s, 3 H), 4.05 (s, 3 H); mass spectrum, m/z 414 ($M^{+\cdot}$).

Anal. Calcd for $C_{21}H_{18}O_7S$: C, 60.86; H, 4.38. Found: C, 60.98; H, 4.42.

4,5,6,11,12-Pentamethoxy-7,8-dihydronaphthacene (22). Ketone **6** (10 g, 25.2 mmol) in ethanol (95%) was reduced with sodium borohydride (0.35 g, 9.2 mmol). Workup followed by recrystallization from ether–hexanes gave 9.55 g (95% of the tetracyclic alcohol as plates): mp 106–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (dd, J = 8, 1 Hz, 1 H), 7.34 (t, J = 8 Hz, 1 H), 6.77 (d, J = 8 Hz, 1 H), 5.30 (br t, J = 4 Hz, 1 H), 4.07 (s, 3 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 3.20–2.85 (m, 2 H), 2.20–1.64 (m, 4 H).

A benzene solution (550 mL) of the alcohol (9 g, 22.6 mmol) and *p*-toluenesulfonic acid (0.25 g) was heated at reflux for 15–20 min, and water formed during the dehydration was collected in a Dean–Stark trap. The dark red solution was washed with aqueous $NaHCO_3$ (2 × 200 mL) and brine (100 mL), then dried ($MgSO_4$), and filtered and the solvent evaporated at reduced pressure. The residue was chromatographed (silica gel, 220 g, CH_2Cl_2) and recrystallized from ether–hexanes to give 7.39 g (86% yield) of pure **22** as clusters of red needles: mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (dd, J = 9, 1 Hz, 1 H), 7.36 (split t, J = 8 Hz, 1 H), 7.08 (dt, J = 10, 2 Hz, ArC*H*=), 6.80 (dd, J = 7 Hz, 1 H), 6.25 (dt, J = 10, 4 Hz, ArCH=C*H*), 4.06 (s, 3 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.08 (t, J = 7 Hz, 2 H) and 2.52–2.20 (m, 2 H); mass spectrum, m/z 380 ($M^{+\cdot}$).

Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.67; H, 6.40.

***cis*-9,10-Dihydroxy-4,5,6,11,12-pentamethoxy-7,8,9,10-tetrahydronaphthacene (23).** To dihydronaphthacene **22** (7.1 g, 18.7 mmol) dissolved in acetone (160 mL) and water (40 mL) was added osmium tetroxide (0.01 g) and then trimethylamine *N*-oxide (2.8 g, 37.3 mmol). The reaction was stirred for 6 h and then partitioned between ethyl acetate (500 mL) and water (200 mL). The organic layer was separated, then washed with sodium metabisulfite solution (2 × 100 mL of 1%), dried ($MgSO_4$), and filtered and the solvent evaporated at reduced pressure. The residue was recrystallized from methylene chloride–hexanes to give 6.23 g (83% yield) of diol **23** as yellow plates: mp 125–128 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (dd, J = 8, 1 Hz, 1 H), 7.38 (t, J = 8 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H), 5.24–5.10 (m, 1 H), 4.07 (s, 3 H), 3.94 (s, 6 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 2.80–3.24 (m, 2 H), 2.21–1.85 (m, 2 H).

9-Oxo-4,5,6,11,12-pentamethoxy-7,8,9,10-tetrahydronaphthacene (24a). The procedure employed to dehydrate diol **23** to ketone **24a** was identical with the one employed to obtain **22**. From **23** (5.9 g, 14.3 mmol), there was obtained, after chromatography (silica gel, 125 g, CH_2Cl_2–EtOAc) and recrystallization from hexanes, 4.81 g (85% yield) of pure ketone **24a**: mp 171–172 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (dd, J = 8, 1 Hz, 1 H), 7.32 (br t, J = 8 Hz, 1 H), 6.75 (d, J = 7 Hz, 1 H), 4.00 (s, 3 H), 3.88 (s, 6 H), 3.80 (s, 5 H), 3.74 (s, 3 H), 3.29 (t, J = 7 Hz, 2 H), 2.52 (t, J = 7 Hz, 2 H); mass spectrum, m/z 396 ($M^{+\cdot}$).

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68 H, 6.10. Found: C, 69.70; H, 6.13.

9-Ethylenedioxy-4,5,6,11,12-pentamethoxy-7,8,9,10-tetrahydronaphthacene (24b). Two procedures are described. (A) Ketone **24a**, ethylene glycol (5 mL), and toluenesulfonic acid (0.10 g) were heated at reflux in benzene (150 mL) for 2 h. The water formed in the reaction was removed with the aid of a Dean–Stark trap. Standard workup afforded ketal **24b** in quantitative yield. (B) A more direct procedure for preparing **24b** (82% yield) was to conduct the dehydration of diol **23** in the presence of ethylene glycol (5 mL): mp 145–150 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (dd, J = 9, 1 Hz, 1 H), 7.34 (split t, J = 9 Hz, 1 H), 6.77 (dd, J = 7 Hz, 1 H), 4.09 (s, 3 H), 4.05 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 4 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.35–3.10 (m, 4 H), 2.04 (t, J = 7 Hz, 2 H); mass spectrum, m/z 440 ($M^{+\cdot}$).

Anal. Calcd for $C_{25}H_{28}O_7$: C, 68.16; H, 6.41. Found: C, 68.31; H, 6.40.

9-Ethylenedioxy-4,6,11-trimethoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (25a). The oxidation of **24b** (4.5 g, 10.2 mmol) in acetonitrile (100 mL) with pyridinedicarboxylic acid *N*-oxide (4.68 g, 25.6 mmol) and ceric ammonium nitrate[17] (14.01 g, 25.6 mmol) was performed as previously described for **17a** and gave 3.86 g (92% yield) of pure quinone **25a**: mp 147–152 °C (ether–hexanes); ^{1}H NMR ($CDCl_3$) δ 7.75 (dd, J = 8, 2 Hz, 1 H), 7.60 (t, J = 8 Hz, 1 H), 7.23 (dd, J = 8, 2 Hz, 1 H), 4.06 (s, 3 H), 3.99 (s, 3 H), 3.95 (s, 4 H), 3.89 (s, 3 H), 3.20–2.90 (m, 4 H), 1.94 (t, J = 7 Hz, 2 H); mass spectrum, m/z 410 ($M^{+\cdot}$).

Anal. Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found: C, 67.19; H, 5.51.

9-Ethylenedioxy-6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (25b). The oxidation of quinone ketal **25a** (3.52 g, 8.60 mmol) in acetone (75 mL) with argentic oxide (4.26 g, 34.4 mmol) and nitric acid (10 mL of 6 N)[18] furnished after bisulfite workup (1% solution) 3.12 g (95% yield) of quinone **25b** as deep red crystals which were used in the next step without purification: mp 226–228 °C; ^{1}H NMR ($CDCl_3$) δ 13.83 (s, 1 H), 13.43 (s, 1 H), 8.01 (dd, J = 8, 1 Hz, 1 H), 7.73 (t, J = 8 Hz, 1 H), 7.34 (dd, J = 8, 1 Hz, 1 H), 4.07 (s, 3 H), 4.06 (s, 4 H), 3.15–2.90 (m, 4 H), 1.98 (t, J = 6 Hz, 2 H); mass spectrum, m/z 382 ($M^{+\cdot}$).

6,11-Dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (7). A mixture of trifluoroacetic acid (8 mL) and hydrochloric acid (8 mL of 10%) was added to a suspension of ketal **8b** (3.15 g, 8.25 mmol) in DME (50 mL) and the solution stirred for 6 h at room temperature. The reaction was diluted with water (300 mL), and the mixture was then extracted with ethyl acetate (4 × 150 mL). The combined ethyl acetate extracts were washed with water (2 × 100 mL) and aqueous bicarbonate (saturated) (2 × 50 mL). The organic layer was dried ($MgSO_4$) and filtered and the solvent evaporated at reduced pressure to give crude **8c**. Chromatographic purification (silica gel, 100 g, CH_2Cl_2–EtOAc (4:1)), followed by recrystallization from acetic acid, gave 2.68 g (96% yield) of pure ketone **8c** with a melting point of 252–256 °C (lit.[4,19] mp 251–255 °C). A mixed melting point with an authentic sample generously supplied to Dr. Andrew Kende was undepressed. Other physical data such as the ^{1}H NMR, IR, and UV spectra were also identical: ^{1}H NMR ($CDCl_3$) δ 13.56 (s, 1 H), 13.05 (s, 1 H), 7.98 (dd, J = 8, 1 Hz, 1 H), 7.77 (t, J = 8 Hz, 1 H), 7.16 (dd, J = 8, 1 Hz, 1 H), 4.09 (s, 3 H), 3.62 (s, 2 H), 3.25 (t, J = 8 Hz, 2 H), 2.65 (t, J = 8 Hz, 2 H); mass spectrum, m/z 338 ($M^{+\cdot}$), 310.

Acknowledgment. We express our appreciation to Dr. John S. Swenton, Ohio State University, for a sample of 7,9-dideoxydaunomycinone and to Dr. Andrew S. Kende, University of Rochester, for a sample of quinone **8c**. This work was generously supported by the National Cancer Institute of the National Institutes of Health (Grant No. CA 18141).