Total Syntheses of  $(\pm)$ -Daunomycinone.<sup>1</sup> Regiospecific Preparations of  $(\pm)$ -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  $(\pm)$ -daunomycinone (2a), are described.

The important anticancer activity of the anthracycline antibiotics daunorubicin (1a),<sup>3</sup> adriamycin (1b),<sup>4</sup> and carminomycin



 $(1c)^5$  has spawned a diversity of approaches to the synthesis of their aglycones (2).<sup>6,7</sup> 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<sup>1,12</sup> and methods<sup>13,14</sup> for general regiospecific synthesis

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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<sup>15</sup> and chartreusin.<sup>16</sup> This paper describes the application of this approach to achieve two total syntheses of daunomycinone (2a). One route furnished ( $\pm$ )-7,9-dideoxydauno-mycinone (18)<sup>8-10</sup> in 38-40% overall yield from 7-methoxy-3-(phenylsulfonyl)-1(3*H*)isobenzofuranone (3).<sup>15,17</sup> The other sequence, initiated from 4-methoxy-3-(phenylsulfonyl)-1(3H)-isobenzofuranone (5),<sup>16</sup> provided 6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12-trione (7).<sup>11,18,19</sup>

### **Two Synthetic Approaches**

The general plan leading to daunomycinone (2a) derives from our strategy<sup>12</sup> and annelation methodology<sup>13</sup> 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.<sup>13</sup> Use of either 2-cyclohexen-

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2	ass anal.	(M <sup>+</sup> ) calcd found	88 C <sub>16</sub> H <sub>16</sub> O <sub>5</sub>	66 C <sub>22</sub> H <sub>22</sub> O <sub>5</sub> C, 72.16; H, 6.07 C, 72.111; H, 6.05 C, 72.16; H, 6.07	$\begin{array}{ccccc} 24 & C_{24}H_{24}O, \\ C, 67 & 91 \\ C, 67 & 91 \\ C, 67 & 91 \\ C & 68 & 03 \\ C & 61 \\ C & 68 & 03 \\ C & 61 \\ C & 6$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	18 C <sub>17</sub> H <sub>18</sub> O <sub>6</sub>	38 C <sub>25</sub> H <sub>27</sub> O <sub>7</sub> C, 68.48; H, 5.98 C, 68.50; H, 6.01	54 C <sub>25</sub> H <sub>26</sub> O <sub>8</sub> C, 66.03; H, 5.87 C, 66.07; H, 5.76 C, 66.03; H, 5.87	18 C <sub>17</sub> H <sub>18</sub> O <sub>6</sub>	32 C <sub>1</sub> ,H <sub>2</sub> ,O <sub>5</sub> C, 68.69; H, 7.30 C, 68.65; H, 7.27 C, 68.69; H, 7.30	96 C <sub>23</sub> H <sub>24</sub> O <sub>6</sub> C 60 64 H 6 20
5 6 With Conjugate Acceptors 9, 13, 14, 20, and 2-Cyclohexen-1-one		<sup>1</sup> H NMR (CDCl <sub>3</sub> ), $\delta = ml$	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 37 (s 3 H) 4 09 (s 3 H) 3 97 (a $J = 6$ Hz $2$ H) 1 36 (t $J = 6$ Hz $3$ H)	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 (t, $J = 6$ Hz, 2 H), 2.97 (t, $J = 6$ Hz, 2 H), 2.12	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)	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), 3.70-75 (m, 4 H), 7.94 (s, 3 H)	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 Hz, 1 Hz	7.96 (d) $J = 8$ , 1 Hz, 1 H), 7.46 (br t, $J = 8$ Hz, 1 H), 6.82 (d, $J = 8$ Hz, 1 H), 7.96 (d) $J = 8$ , 1 Hz, 1 H), 7.46 (br t, $J = 8$ Hz, 1 H), 3.97 (s, 3 H), 3.94 (s, 6 H), 3.83 (s, 3 H), 3.30–2.65 (m, 4 H), 7.30 (s, 3 H), 2.30 (s, 3 H), 3.94 (s, 6 H), 3.83 (s, 3 H), 3.30–2.65 (m, 4 H), 7.30 (s, 3 H), 3.94 (s, 6 H), 3.83 (s, 3 H), 3.30–2.65 (m, 4 H), 7.30 (s, 3 H), 3.94 (s, 6 H), 3.84 (s,	7.96 (45, 3.11) 7.96 (45, 1 Hz, 1 H), 7.46 (br t, J = 8 Hz, 1 H), 6.83 (4, J = 8 Hz, 1 H), 4.07 (5, 3 H), 3.98 (5, 4 H), 3.95 (5, 6 H), 3.83 (5, 3 H), 3.74 (5, 3 H), 3.40- $2.85 (m, 4 H)$	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)	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 42 (t $T = 7$ Hz, 2 H), $T = 7$ Hz, 2 Hz	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),
100 150 and 10	T him (act (act (	bp/mp, °C	117-118	205-208	138-141	108-110	129-130	173-176	179-181	98-100 110-112	100-103 (0.01 mm)	162-164
2 5 0	<i>6</i> 6 6	yield	65	68	87	70	74	70	85	49	98	88
n of Sulfor		product	10a	11a	116	11c	15a	4a	4b	19a <sup>b</sup>	21a	9
ndenestion		acceptor	6	ø	13	14	6	14	13	6	20	а
C- C-		sulfone	8	10c	10c	10c	ŝ	15c	15c	Ś	ŝ	<b>P61</b>



HO. ю 0= CH<sub>3</sub>O оснэ осн<sup>эо</sup> OCH3 OCH3 4 CH<sub>3</sub>O SO<sub>2</sub>Ar 0 ю CH<sub>3</sub>O Path B

Total Syntheses of  $(\pm)$ -Daunomycinone

20

COR

оснзоснз

SO2Ar

Path A

Scheme I

осн<sub>3</sub> осн<sub>3</sub>0

CH<sub>3</sub>O

CH₃O

<sup>a</sup> 2-Cyclohexene-1-one. <sup>b</sup> Two different crystalline forms of 19a were observed; the melting points are given.

Scheme II



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,<sup>15,17</sup> leads to daunomycinone (2a) or, alternately, to intermediate 18 which was used by Sih and co-workers<sup>8</sup> in their synthesis of 2a. The parallel path B which utilizes methoxyisobenzofuranone (5)<sup>16</sup> 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)<sup>18</sup> and certain rhodomycinones.<sup>19</sup>

### **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)<sup>20</sup> to furnish, after methylation (Me<sub>2</sub>SO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>/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<sup>21</sup> 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

Scheme III



B. I. CH2SON-C6H4CH3 2. H2O 3. CICOCOCI/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<sub>2</sub>SO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>/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.<sup>24</sup> The conversion of bicyclic lactone 12 to 5-acetyl-2-cyclohexen-1-one (14) was initiated by condensing the dianion of methanesulfinyl-p-toluidide<sup>25</sup> 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<sup>24</sup> 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 $(\pm)$ -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<sup>26</sup> to obtain a precursor to intermediate 18 which Sih

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<sup>(22)</sup> 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.

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#### Scheme IV



and co-workers<sup>8</sup> 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.<sup>27</sup>

(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<sup>27</sup> 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 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,<sup>28</sup> an analogous reaction with diol A failed.



thyllithium.<sup>29</sup> 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 Noxide<sup>30</sup> 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.<sup>31</sup> 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  $(\pm)$ -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

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Scheme V



21b.  $R = CHBrCH_2CH_3$ 21c.  $R = CH = CHCH_3$ 21d. R = CHO

synthetic sequence presented here furnished  $(\pm)$ -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,<sup>16</sup> 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 <sup>1</sup>H NMR spectrum of 21a, the nonequivalence of the protons on the methylene adjacent the aromatic ring was indicated by the presence of an ABX<sub>2</sub> 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

(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).



distillation or, preferably, by filtration through a short column of silica gel. Lemieux-Johnson<sup>33</sup> 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 ptoluenesulfonic 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<sup>34</sup> was unsuccessful.<sup>35</sup> 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.<sup>38</sup> 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<sup>39</sup> 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

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(35) Attempts to  $\alpha$ -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  $\alpha$ -bromination of 6 with phenyltrimethylammonium perbromide (PTAB)<sup>36,37</sup> 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.

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C rings through oxidative demethylation was performed in two stages. Ceric ammonium nitrate, in the presence of pyridinedicarboxylic acid *N*-oxide,<sup>30</sup> 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<sup>31</sup> followed by dithionite workup. The resulting product **25b** was deketalized to the objective naphthacenetrione 7 by treatment with trifluoroacetic acid and 10% hydrochloric acid<sup>11</sup> 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 (<sup>1</sup>H NMR) spectra were obtained on a JEOL FX-90Q spectrometer. Chemical shifts are reported as  $\delta$  values in parts per million relative to tetramethylsilane ( $\delta$  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  $5 \times 10$  cm precoated plates (Silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. Silica gel columns for chromatog-

raphy 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. Fiftygram condensations of sulfone 5 with ethyl hexenoate (20) were routinely performed.

3-Ethoxy-4,8,9-trimethoxynaphtho[2,3-c]furan-1(3H)-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  $\times$  200 mL). The ethyl acetate extracts were successively washed with water (2  $\times$  100 mL), saturated sodium bicarbonate (100 mL), and 1% sodium bisulfite (100 mL), then dried

(MgSO<sub>4</sub>), 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  $(2 \times 100 \text{ mL})$ , 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<sub>2</sub>Cl<sub>2</sub>-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 <sup>1</sup>H 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(3H)-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<sub>3</sub> (2  $\times$  100 mL) and water (2  $\times$  50 mL), then dried (MgSO<sub>4</sub>), 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<sub>2</sub>Cl<sub>2</sub>-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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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, 1 H), 4.3 H), 3.94 (s, 3 H), 3.84 (s, 3 H); mass spectrum, m/z 382 (M<sup>+</sup>·). Anal. Calcd for C<sub>21</sub>H<sub>18</sub>O<sub>5</sub>S: C, 65.95; H, 4.74. Found: C, 65.87;

H, 4.91. **3-(Thiophenyl)-4,9-dimethoxynaphtho[2,3-c]furan-1(3H)-one (10b),** mp 120-122 °C, was analogously prepared in 97% yield from **10a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>-).

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)-4,8,9trimethoxynaphtho[2,3-c]furan-1(3H)-one (15c). A vigorously stirred solution of sulfide 15b (15 g, 39.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> (2 × 150 mL), and water (100 mL), then dried (MgSO<sub>4</sub>), filtered, and evaporated. The residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-ether-hexanes to give 15.12 g (93% yield) of pure 15c: mp 147-148 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·).

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: <sup>1</sup>H NMR (acetone- $d_6$ )  $\delta$  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<sup>+</sup>·).

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<sub>2</sub>. 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<sub>4</sub>), 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>, 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  $(2 \times 300 \text{ mL})$ . The combined organic layers were dried (MgSO<sub>4</sub>) 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: <sup>1</sup>H NMR  $(CDCl_1) \delta 6.90 (dt, J = 6, 2 Hz, 1 H), 6.00 (dt, J = 6, 1 Hz, 1 H), 3.69$ (s, 3 H), 3.30-2.95 (m, 1 H), 2.70-2.54 (m, 4 H); mass spectrum, m/z154 (M<sup>+</sup>·).

5-Acetyl-2-cyclohexen-1-one (14). The dianion of methanesulfinylp-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<sub>2</sub>. 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<sub>4</sub>) 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>SO (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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·).

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<sub>4</sub> (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<sub>3</sub> solution (2 × 200 mL), then dried (MgSO<sub>4</sub>), 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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-9carboxylate (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<sub>3</sub> (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<sub>4</sub>) and filtered, and the solvent was evaporated at reduced pressure. Column chromatography (silica gel, 200 g, 1% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) of the crude product afforded, after recrystallization from hexanes, 6.87 g (89% yield) of pure 16c: mp 148-150 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.94 (dd, J = 8, 1Hz, 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<sup>+</sup>·).

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-9carboxylic 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 ( $3 \times 150$  mL). The combined ethyl acetate extracts were washed with water (100 mL), dried (MgSO<sub>4</sub>), and filtered, and the solvent was removed at reduced pressure. The initial product was recrystallized (Et<sub>2</sub>O-hexanes) to give 6.17 g (98% yield) of pure 16d: mp 165-173 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·).

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<sub>2</sub> 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<sup>29</sup> yielded the crude ketone which was further purified by chromatography (silica gel, 175 g, CH<sub>2</sub>Cl<sub>2</sub>) and then crystallized (hexanes) to give 5.70 g (94% yield) of pure 16a as light yellow needles: mp 161-162 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>), 408.

Anal. Calcd for C<sub>25</sub>H<sub>28</sub>O<sub>6</sub>: 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 azdotropically 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<sub>4</sub>), filtered and evaporated. Crystallization of the residue from hexanes afforded 5.32 g (97%) of pure ketal 16e: mp 127-131 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>-).

9-(1-Ethylenedioxyethyl)-7,8,9,10-tetrahydro-4,6,11-trimethoxy-5,12naphthacenedione (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<sub>4</sub>), 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·).

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<sub>4</sub>), 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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 = 8Hz, 1 H), 4.04 (s, 3 H), 3.95 (s, 4 H), 1.39 (s, 3 H); mass spectrum, m/z 410 (M<sup>+</sup>).

 $(\pm)$ -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 ( $3 \times 200 \text{ mL}$ ). The combined organic extracts were washed with aqueous NaHCO<sub>3</sub>, then dried (Na<sub>2</sub>-SO<sub>4</sub>), 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<sub>2</sub>Cl<sub>2</sub>-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.86 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); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub> was heated at reflux while being illuminated with an incandescent lamp. The <sup>1</sup>H 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>).

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 ( $3 \times 150$  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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>.)

Anal. Caled 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<sub>2</sub> 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 ( $2 \times 400$  mL) and brine (100 mL), then dried (MgSO<sub>4</sub>), and filtered and the solvent evaporated to give 18.2 g (95%) of aldehyde 21d as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>). 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(3H)-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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>15</sub>H<sub>14</sub>O<sub>6</sub>: C, 62.07; H, 4.86. Found: C, 62.00; H,

3-(Thiophenyl)-4,5,9-trimethoxynaphtho[2,3-c]furan-1(3H)-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  $(2 \times 150 \text{ mL})$  and brine, then dried (MgSO<sub>4</sub>), 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<sub>2</sub>Cl<sub>2</sub>-EtOAc) to give an additional 4.75 g (97% total yield) of pure sulfide 19c: mp 121-122 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·).

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(3H)-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<sub>2</sub>Cl<sub>2</sub> (3 L) and aqueous phosphate buffer (6 L).<sup>22</sup> Workup afforded 16.13 g (93% yield) of pure sulfone 19d after recrystallization from methylene chloride-hexanes: mp 138-141 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>-). Anal. Calcd for C<sub>21</sub>H<sub>18</sub>O<sub>7</sub>S: 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 etherhexanes gave 9.55 g (95% of the tetracyclic alcohol as plates): mp 106-112 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub> (2 × 200 mL) and brine (100 mL), then dried (MgSO<sub>4</sub>), and filtered and the solvent evaporated at reduced pressure. The residue was chromatographed (silica gel, 220 g, CH<sub>2</sub>Cl<sub>2</sub>) and recrystallized from ether-hexanes to give 7.39 g (86% yield) of pure 22 as clusters of red needles: mp 149–151 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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, ArCH=), 6.80 (dd, J = 7 Hz, 1 H), 6.25 (dt, J = 10, 4 Hz, ArCH=CH), 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<sup>+</sup>·).

Anal. Calcd for C<sub>23</sub>H<sub>24</sub>O<sub>5</sub>: 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<sub>4</sub>), 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; <sup>1</sup>H NMR (CDCl<sub>1</sub>)  $\delta$  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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>.) 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>-).

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<sup>17</sup> (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); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·).

Anal. Caled 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)<sup>18</sup> 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>-).

6,11-Dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,9,12trione (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 ( $4 \times 150$  mL). The combined ethyl acetate extracts were washed with water (2  $\times$  100 mL) and aqueous bicarbonate (saturated) (2  $\times$  50 mL). The organic layer was dried (MgSO<sub>4</sub>) and filtered and the solvent evaporated at reduced pressure to give crude 8c. Chromatographic purification (silica gel, 100 g, CH<sub>2</sub>Cl<sub>2</sub>-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.<sup>4,19</sup> 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 <sup>1</sup>H NMR, IR, and UV spectra were also identical: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>·), 310.

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