

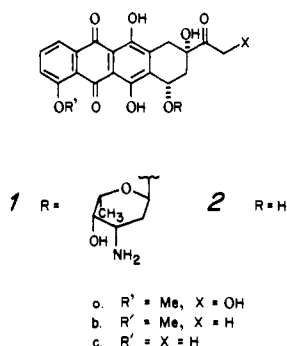
Efficient, Regiospecific Synthesis of Anthracycline Intermediates: Total Synthesis of Daunomycin

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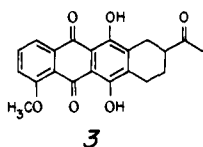
Abstract: 7,9-Dideoxydaunomycinone (**3**) was prepared from 1,5-dihydroxynaphthalene (**11**) and perillartine (**7**) by two short convergent routes, based on a new regiospecific preparation of fused quinones.

The challenge of preparing the important anticancer drugs Adriamycin (**1a**), daunomycin (**1b**), and carminomycin (**1c**) has



led an impressive number of synthetic chemists to investigate schemes directed toward these and related systems.¹ Although many elegant approaches to the aglycones (**2**) have been developed and these have led to the completion of several total syntheses, only the most recent accounts report regiospecific syntheses and, with only one or two exceptions, these do not appear promising as practical routes to the desired pharmaceuticals.

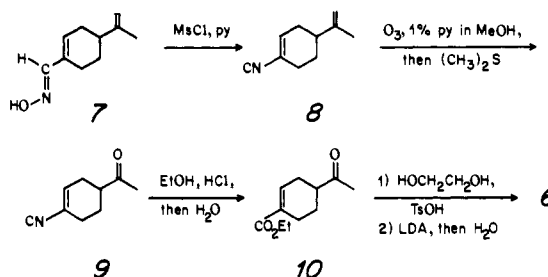
Our strategy for developing an efficient synthesis of daunomycinone (**2b**), an intermediate in the preparation of daunomycin and Adriamycin,² was to construct the carbon skeleton in a regiocontrolled sequence and to introduce the A-ring oxygen substituents by known methods.^{2b,3,4} Our goal then became the preparation of the dideoxyaglycone **3** by a short, high-yield se-



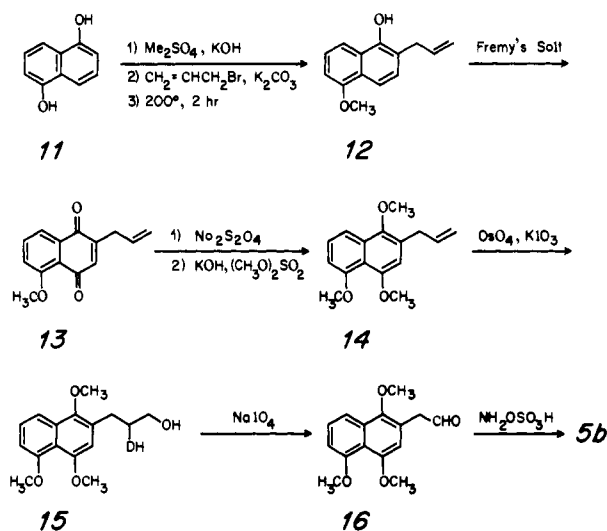
quence from inexpensive and readily available commercial products.

One retrosynthetic analysis of the target intermediate (**3**), which might serve as the basis of a novel and necessarily regiospecific synthesis, is based on a diagonal dissection of the B ring (shown for **4**). For the purpose of demonstrating the viability of this strategy, we have developed a new sequence for constructing linear quinone systems.⁵

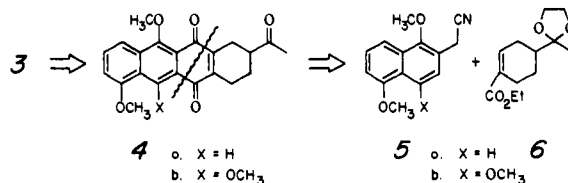
Scheme I



Scheme II



Application of this regiospecific method to the preparation of **3** suggested the use of nitrile **5a** or **5b** and ester **6** as precursors.

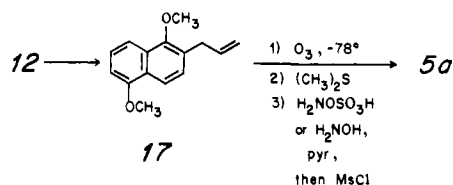


Ester **6** was prepared in five steps and 31% overall yield (Scheme I) from perillartine (**7**), a derivative of L-perillaldehyde and a commercial product used as an artificial sweetener in Japan.⁶ Perillartine was dehydrated by treatment with methanesulfonyl chloride in pyridine.⁷ Ozonolysis of the side-chain double bond

[†] Camille and Henry Dreyfus Teacher Scholar Award Recipient.
 (1) A recent and comprehensive review on "Synthetic Approaches to the Anthracycline Antibiotics" is T. R. Kelly, *Annu. Rep. Med. Chem.*, **14**, 288-298 (1979).
 (2) (a) F. Arcamone, W. Barbieri, G. Franceschi, and S. Penco, *Chem. Ind. (Milan)*, **51**, 834 (1969); F. Arcamone, G. Franceschi, and S. Penco, U.S. Patent 3 803 124 (April 9, 1974); (b) T. H. Smith, A. N. Fujiwara, D. W. Henry, and W. W. Lee, *J. Am. Chem. Soc.*, **98**, 1969 (1976).
 (3) (a) R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *Tetrahedron Lett.*, 3385 (1976); (b) F. A. J. Kerdesky and M. P. Cava, *J. Am. Chem. Soc.*, **100**, 3635 (1978); (c) C. M. Wong, D. Popien, R. Schwenk, and J. TeRaa, *Can. J. Chem.*, **49**, 2712 (1971).
 (4) A. S. Kende, Y-g. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976).

(5) (a) K. A. Parker and J. Kallmerten, *J. Org. Chem.*, **45**, 2620 (1980).
 (b) A preliminary report of this method was reported; see K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 1197 (1979).
 (6) "Merck Index", 8th ed., 1968, pp 798-9.
 (7) T. J. Bentley, J. F. McGhie, and D. H. R. Barton, *Tetrahedron Lett.*, 2497 (1965).

Scheme III



of nitrile **8** was accomplished at -78°C in methanol containing 1% pyridine;⁸ nitrile **9** was converted to the ethyl ester **10** by hydrogen chloride in ethanol.

Ketalization of keto ester **10** with ethylene glycol and toluenesulfonic acid in refluxing benzene gave ketal **6**, contaminated with a small amount of another compound; the NMR spectrum of the crude ketalization product showed absorption at 3.6 and 4.8 ppm as well as the absorptions predicted for structure **6**. Fortunately, we found that the contaminant could be removed (or isomerized to product) by treatment with 1.2 equiv of lithium diisopropylamide in tetrahydrofuran and quenching with water. Material recovered from this procedure was suitable for further transformations.

Because nitrile **5b** is more completely functionalized than **5a**, we initially considered it to be the more desirable of these two intermediates, synthons for rings C and D and C-11 of the tetracycle **3**. An obvious precursor to **5b**, the well-known 2-allyl-5-methoxynaphthoquinone (**13**), was prepared according to Schmid⁹ (Scheme II).

Reduction of quinone **13** to the hydroquinone was accomplished with sodium hydrosulfite. Treatment of this unstable intermediate with 2 equiv of sodium hydride and dimethyl sulfate afforded the trimethyl ether **14**.

Attempts to cleave the olefinic bond of **14** with ozone resulted in formation of intractable tars. Likewise, attempted oxidation of **14** using the Johnson-Lemieux conditions¹⁰ afforded tarry products. During the course of our studies, Li and Ellison reported the successful conversion of **14** to aldehyde **16** by a two-step procedure.¹¹ Two-phase oxidation of the olefin **14** using an osmium tetroxide-potassium chlorate catalyst system gives the diol **15**, which is cleaved to the aldehyde **16** with sodium periodate. Aldehyde **16** was converted to nitrile **5b** by hydroxylamine-*O*-sulfonic acid.^{12,13} In our hands, the overall yield from the known quinone **13** to **5b** is 33%.

While the above procedure does convert the inexpensive and readily available 1,5-dihydroxynaphthalene (**11**) to the desired nitrile **5b**, it suffers several drawbacks. First it has too many steps and the overall yield is too poor for it to be considered an efficient preparation. Also, at least two procedures, the Fremy's salt oxidation (**12** \rightarrow **13**) and the osmium tetroxide/periodate cleavage (**14** \rightarrow **15** \rightarrow **16**), are not amenable to large-scale synthesis. Because of these limitations of Scheme II as a convenient source of nitrile **5b**, we considered the alternative and more easily accessible synthon **5a**.

Nitrile **5a** is prepared in three steps from naphthol **12** as shown in Scheme III. Methylation gave the diether **17**.¹⁴ The ozonolysis of the allyl side chain of **17** (unlike that of **14**) proceeded satis-

(8) G. Slomp, Jr., and J. L. Johnson, *J. Am. Chem. Soc.*, **80**, 915 (1958).

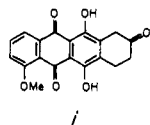
(9) W. Eisenhuth and H. Schmid, *Helv. Chim. Acta*, **41**, 2021 (1958).

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

(11) T.-t. Li and R. H. Ellison, *J. Am. Chem. Soc.*, **100**, 6263 (1978).

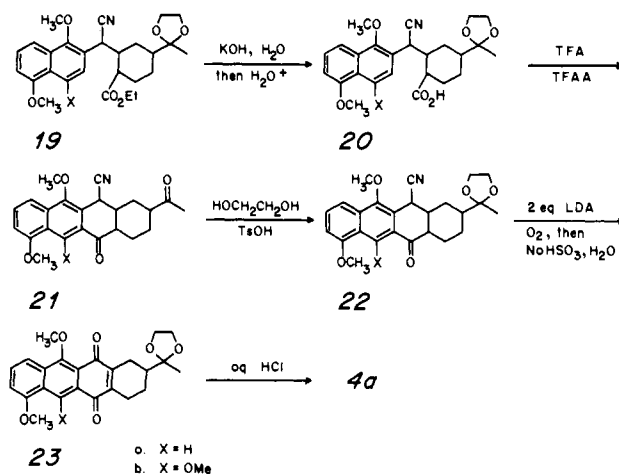
(12) (a) J. Streith, C. Fizet, and H. Fritz, *Helv. Chim. Acta*, **59**, 2786 (1976); (b) C. Fizet and J. Streith, *Tetrahedron Lett.*, 3187 (1974).

(13) The same route to nitrile **5b** was recently reported by A. S. Kende, J. Rizzi, and J. Riemer, *Tetrahedron Lett.*, 1201 (1979). These workers went on to convert nitrile **5b** to the known tetracyclic ketone **i**.

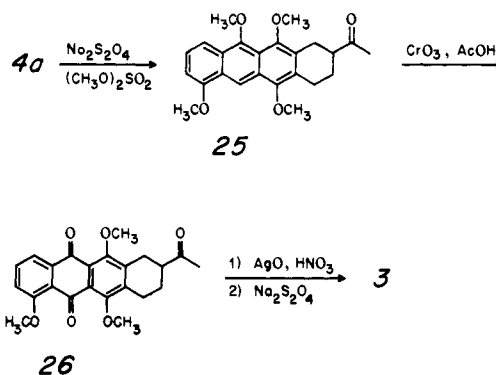


(14) P. Hill, W. F. Short, and H. Stromberg, *J. Chem. Soc.*, 937 (1937).

Scheme IV



Scheme V



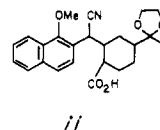
factorily, and the unstable aldehyde was converted to nitrile **5a** in 42% yield by hydroxylamine-*O*-sulfonic acid. Neither Fremy's salt nor osmium tetroxide/periodate is required in this scheme. The preparation of **5a** from 1,5-dihydroxynaphthalene was then both shorter and significantly more practical than that of **5b** (for alternative syntheses of nitriles **5** from 5-methoxy-1-naphthol (**18a**) and 4,5-dimethoxy-1-naphthol (**18b**), see below).

On the assumption that oxygen might be introduced at C-5 in some later intermediate, then, we chose to convert **5a** to tetracyclic quinone **4a** (Scheme IV) by our regioselective annelation sequence.⁵ Michael addition of the potassium enolate of nitrile **5a** to ester **6** proceeded in 60% yield (80% based on unrecovered starting nitrile).^{5b,15} Alkaline hydrolysis of the adduct **19a** afforded carboxylic acid **20a**. Acid **20a** was smoothly cyclized in refluxing trifluoroacetic acid-trifluoroacetic anhydride,¹⁶ with concomitant cleavage of the ketal, to afford the tetracyclic ketone **21a** as a mixture of diastereomers. Re-ketalization of the nonconjugated carbonyl gave the monoketal **22a**, which, on treatment with 2 equiv of lithium diisopropylamide and oxygen gas, followed by standard reductive workup, gave a single bright orange product, which was assigned structure **23a**. Hydrolysis afforded the C-9 acetyl derivative **4a**.

The completion of the synthesis of the dideoxyglycone **3** from quinone **4a** requires the introduction of an oxygen substituent at C-5. Attempts to effect the conversion of **4a** to the diacetate of quinizarin **3** by reductive acylation of the quinone moiety followed by chromium trioxide oxidation of the anthracene ring system¹⁷

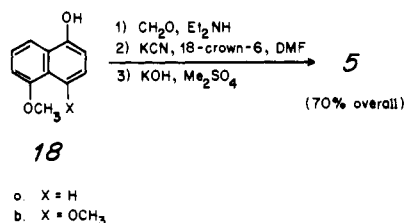
(15) K. A. Parker and J. L. Kallmerten, *J. Org. Chem.*, **45**, 2614 (1980).

(16) It is noteworthy that the 4-demethoxy analog **ii**, prepared by our now standard method, underwent no cyclization under these conditions.

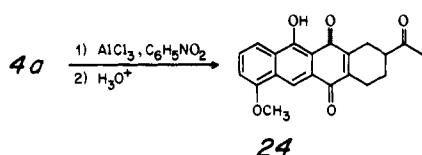


ii

Scheme VI



were unsuccessful. Direct oxidation of the 5-hydroxy-1,4-anthraquinone system^{18a} by Thiele oxidation conditions^{18b} has been reported. Therefore, quinone **24** was prepared from **4a** by selective



demethylation with aluminum chloride in nitrobenzene¹⁹ and subjected to Thiele conditions with a variety of catalysts (H_2SO_4 , HClO_4 , $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$); only total recovery or total destruction of quinone **24** was observed in these experiments.

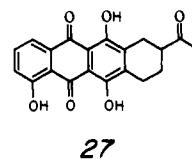
Quinone **4a** was successfully converted to 7,9-dideoxydaunomycinone (**3**) by a three-step sequence (Scheme V). Reductive methylation of **4a** using sodium hydrosulfite and dimethyl sulfate gave the tetramethoxy ketone **25** which was immediately treated with chromium trioxide in acetic acid to give the trimethoxyquinone **26**. Oxidation of the crude **26** with silver(II) oxide,²⁰ followed by reductive workup, afforded 7,9-dideoxydaunomycinone (**3**), which was identical in all respects to authentic material.²¹ The sequence was carried out without purification of the intermediates and gave a 47% yield of **3** from quinone **4a**; the overall yield for the nine-step sequence, starting from the intermediates **5a** and **6**, is 22.5%.

Recently we developed a three-step (one-pot) sequence for transforming phenols to *o*-methoxyphenyl acetonitriles.²² This procedure makes the synthesis of gram quantities of nitrile **5a** a trivial exercise; also, nitrile **5b**, the completely functionalized synthon for rings C and D, may be prepared conveniently and on a reasonable scale (Scheme VI). Therefore, we have attempted to improve the efficiency of our synthesis of the target compound **3** by applying Scheme IV to nitrile **5b** and ester **6** and simply demethylating quinone **23b**.

As expected, the potassium enolate of nitrile **5b** added smoothly to ester **6** to give the Michael adduct **19b** in 72% yield (based on unrecovered nitrile **5b**). Alkaline hydrolysis of **19b** afforded 77% of the carboxylic acid **20b** which cyclized readily in trifluoroacetic acid-trifluoroacetic anhydride to give the tetracyclic ketone **21b** in 74% yield. Reketalization of the acetyl side chain gave the ketal **22b**. Oxidation of **22b** using 2 equiv of lithium diisopropylamide and oxygen afforded the quinone **23b** in 59% yield from **21b**.

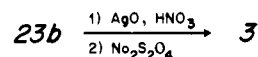
Attempts to selectively demethylate quinone **23b** with aluminum chloride in nitrobenzene gave a mixture of demethylated products. Complete demethylation of **23b** with aluminum chloride in re-

fluxing benzene gave 7,9-deoxycarminomycinone (**27**). This



material was identical with the product obtained from demethylation of authentic **3**.²¹ An attempt to effect the selective methylation of **27** by treatment with excess diazomethane in ether/methylene chloride²³ failed in our hands.

The synthesis was completed by treatment of **23b** with silver(II)



oxide-nitric acid,^{20,24} followed by aqueous sodium hydrosulfite to give the desired target compound **3** in 90% yield.²¹

This sequence provided 7,9-dideoxydaunomycinone (**3**) in six steps and 22% overall yield from nitrile **5b** and ester **6**. While the overall yield following the convergent step was not improved over that obtained from the synthesis based on nitrile **5a**, the number of manipulations required after the convergent step has been decreased. Either route must be considered efficient.

Experimental Section

Instrumentation and Materials. Infrared spectra were determined on a Perkin-Elmer 257 grating infrared spectrophotometer. Ultraviolet and visible spectra were obtained on a Perkin-Elmer 552 spectrophotometer. Nuclear magnetic resonance spectra were measured on a Varian Associates A-60A spectrometer. Fourier transform ¹H spectra were determined on a Bruker WP-60. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., and Galbraith Laboratories, Knoxville, Tenn.

Column chromatography was carried out by using (A) MN-Kieselgel, 70-270 mesh; (B) Baker Silica Gel 60, 60-200 mesh; and (C) Merck Silica Gel 60, 70-230 mesh. Individual fractions were collected by using a Gilson FC-100 microfractionator. Preparative thin-layer chromatography (TLC) was carried out by using 20 \times 20 cm plates, prepared with Merck Silica Gel PF-254.

Except where noted, reactions were carried out under nitrogen or argon atmospheres. Dry tetrahydrofuran (THF) was distilled from lithium aluminum hydride. Dry benzene and pyridine were distilled from calcium hydride. Hexamethylphosphoramide (HMPA) was distilled from sodium metal. Dry acetone was prepared by storing Baker reagent grade acetone over anhydrous CaSO_4 for 48 h.

Perillartine was purchased from Sigma Chemical Co. Hydroxylamine-*O*-sulfonic acid was obtained from Alfa.

Several new compounds were characterized by exact mass measurements rather than by combustion analyses; the problems with obtaining reliable results from combustion analyses in the anthracycline series have been noted by others.²⁵

1,5-Dimethoxynaphth-2-ylacetonitrile (5a). Dimethoxynaphthalene **17** (22.80 g, 0.1 mol) was dissolved in 400 mL of 1:1 (v/v) methanol/methylene chloride, and the solution was cooled to -78°C . A steady stream of ozonized oxygen was passed through the reaction mixture until 1.1 equiv of ozone had been delivered. The mixture was stirred an additional hour at -78°C and then 9.5 mL of dimethyl sulfide was added. The reaction mixture was slowly (ca. 12 h) warmed to ambient temperature. Concentration afforded an orange oil, which was dissolved in 100 mL of ether. This solution was washed with 100-mL portions of H_2O (3 \times) and saturated brine and dried over MgSO_4 . Concentration gave a brown oil which was chromatographed (B, eluted with 20:1 benzene:ether) to give unreacted olefin **17** (3.42 g) and an aldehyde (11.20 g) as a viscous orange oil: IR (film) 1725, 1599 cm^{-1} ; NMR (CDCl_3) δ 9.70 (t, $J = 2$ Hz, 1 H), 8.15-6.58 (m, 5 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.66 (d, $J = 2$ Hz, 2 H).

The chromatographed aldehyde (11.20 g, 0.043 mol) was dissolved in 60 mL of methanol and stirred vigorously during the addition of 8.0 g of hydroxylamine-*O*-sulfonic acid. The reaction mixture became slightly

(23) R. J. Blade and P. Hodge, *Chem. Commun.*, 85 (1979); P. Hodge, personal communication.

(24) Oxidations in similar systems have been reported; see ref 4 and 13.

(25) W. A. Remers, *Chem. Antitumor Antibiot.*, 1, 76 (1979).

(17) (a) A. S. Kende, D. P. Curran, Y. Tsay, and J. E. Mills, *Tetrahedron Lett.*, 3537 (1977); (b) J. R. Wiseman, N. I. French, R. K. Hallmark, and K. G. Chiong, *ibid.*, 3765 (1978). (c) For the oxidation of other oxygenated anthracenes, see J. E. Baldwin and K. W. Bair, *Tetrahedron Lett.*, 2559 (1978). (d) K. S. Kim, E. Vanotti, A. Suaroto, and F. Johnson, *J. Am. Chem. Soc.*, 101, 2483 (1979).

(18) (a) K. Zahn, *Chem. Ber.*, 67, 2063 (1934); (b) J. F. W. McOmie and J. M. Blatchly, *Org. React.*, 19, 199 (1972).

(19) E. Hardeger, E. Widmer, K. Steiner, and A. Pfiffner, *Helv. Chim. Acta*, 47, 2027, 2031 (1964).

(20) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 94, 227 (1972). For a similar application of the use of this reagent, see ref 13.

(21) (a) P. W. Reynolds, M. J. Manning, and J. S. Swenton, *Tetrahedron Lett.*, 2383 (1977); (b) J. S. Swenton and P. W. Reynolds, *J. Am. Chem. Soc.*, 100, 6188 (1978). We are grateful to Professor Swenton for an authentic sample of quinone **3**.

(22) K. A. Parker and T. Iqbal, *J. Org. Chem.*, 45, 1149 (1980).

warm and darkened in color. The brown solution was stirred for 0.5 h and then warmed to 60 °C for 1 h. The reaction mixture was cooled and concentrated; the residual brown oil was dissolved in ether, and the resulting solution was filtered and concentrated to give a dark oil. Chromatography (B, eluted with 20:1 benzene/ether) afforded 4.65 g of a tan solid, mp 48–51 °C (24% overall from 17, based on recovered 17): IR (CHCl₃) 2240, 1592 cm⁻¹; NMR (CDCl₃) δ 8.15–6.60 (m, 5 H), 3.82 (s, 6 H), 3.72 (s, 2 H).

Anal. Calcd for C₁₄H₁₃NO₂: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.76; H, 5.93; N, 6.02.

4-Isopropenylcyclohexene-1-carbonitrile (8). Perillartine (7, 33.0 g, 0.2 mol) was dissolved in 140 mL of dry pyridine. The mixture was cooled to 0 °C and stirred vigorously while 30.0 g (1.3 equiv) of methanesulfonyl chloride was added dropwise over a 2-h period, during which a heavy white precipitate formed. The reaction mixture was warmed to ambient temperature and stirred for 3 h. Excess pyridine and methanesulfonyl chloride were removed by distillation at aspirator pressure. The residual dark brown oil was partitioned between H₂O and ether. The ethereal solution was washed with H₂O and saturated brine and dried over MgSO₄. Concentration afforded the crude red-brown oil, which was distilled (85–86 °C at 1.6 mm) to give 27.2 g (93%) of a colorless oil: IR (film) 2220, 1640 cm⁻¹; NMR (CDCl₃) δ 6.70 (m, 1 H), 4.92–4.70 (m, 2 H), 2.51–2.06 (m, 5 H), 1.93–1.52 (m, 2 H), 1.75 (bs, 3 H).

Anal. Calcd for C₁₀H₁₃N: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.87; H, 8.82; N, 9.25.

4-Acetylcyclohexene-1-carbonitrile (9). Nitrile 8 (36.0 g, 0.25 mol) was dissolved in 500 mL of methanol and 5 mL of pyridine. The mixture was cooled to –78 °C, and then a steady stream of ozonized oxygen was passed through the solution until 1.1 equiv of ozone had been delivered. The reaction mixture was stirred an additional hour at –78 °C, and then 22 mL of dimethyl sulfide was added. The reaction mixture was allowed to warm to room temperature over 12 h. Concentration afforded a pale yellow oil, which was dissolved in 250 mL of ether. This solution was washed with three 250-mL portions of H₂O and dried over MgSO₄. Concentration gave 27.8 g of an orange oil. This material was esterified without further purification (see below). Distillation afforded analytical material as a pale oil, bp 112–117 °C at 0.9 mm: IR (film) 2220, 1710, 1640 cm⁻¹; NMR (CDCl₃) δ 6.62 (m, 1 H), 2.60–1.85 (m, 7 H), 2.16 (s, 3 H).

Anal. Calcd for C₉H₁₁NO: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.58; H, 7.36; N, 9.33.

Ethyl 4-Acetylcyclohexene-1-carboxylate (10). Hydrogen chloride gas was bubbled vigorously through 250 mL of ice-cold absolute ethanol for 10 min. Added dropwise to the solution was 27.8 g of ketonitrile 9 in 50 mL of absolute ethanol. The mixture was stirred at reflux for 12 h, during which a light precipitate formed. The reaction mixture was cooled, filtered, and concentrated. The residual brown oil was dissolved in 250 mL of ether, and this solution was washed with 200-mL portions of NaHCO₃ and H₂O, and dried over MgSO₄. Concentration afforded a yellow oil which distilled to give 20.9 g of keto ester, a colorless oil, bp 94–96 °C at 0.2 mm (44% overall from nitrile 8): IR (film) 1710, 1705, 1645 cm⁻¹; NMR (CDCl₃) δ 6.95 (m, 1 H), 4.18 (q, *J* = 7 Hz, 2 H), 2.56–1.78 (m, 7 H), 2.20 (s, 3 H), 1.28 (t, *J* = 7 Hz, 3 H).

Anal. Calcd for C₁₁H₁₆O₃: *m/e* 196.1099. Found: *m/e* 196.1094.

Ethyl 4-(2-Methyl-1,3-dioxolan-2-yl)cyclohexene-1-carboxylate (6). Keto ester 10 (4.85 g, 25 mmol) was combined with 2.0 g of ethylene glycol and 0.40 g of *p*-toluenesulfonic acid in 50 mL of dry benzene. The mixture was stirred at reflux for 24 h under a Dean–Stark trap. The mixture was cooled and poured into 80 mL of ether. This solution was washed with 10% NaHCO₃, H₂O, and saturated brine, and dried over MgSO₄. Concentration afforded a pale yellow oil which was dissolved in 20 mL of dry THF and added dropwise to a solution of lithium diisopropylamide (0.03 mol) in 70 mL of THF at –78 °C. The mixture was warmed to 0 °C and 10 mL of H₂O was added. The reaction mixture was poured into 100 mL of ether; this solution was washed with H₂O and dried over MgSO₄. Concentration afforded a pale yellow oil which was chromatographed (C, eluted with 20:1 benzene:ether) and distilled bulb-to-bulb (0.25 mm, oven temperature 125 °C) to give 4.61 g (76%) of a pale oil: IR (film) 1705, 1646 cm⁻¹; NMR (CDCl₃) δ 6.95 (m, 1 H), 4.16 (q, *J* = 7 Hz, 2 H), 3.84 (bs, 4 H), 2.85–1.50 (m, 7 H), 1.23 (s, 3 H), 1.20 (t, *J* = Hz, 3 H).

Anal. Calcd for C₁₃H₂₀O₄: *m/e* 240.1361. Found: *m/e* 240.1391.

2-[Cyano(1,5-dimethoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylic acid (20a). Cyano ester 19a¹⁴ (1.16 g, 2.5 mmol) was dissolved in 20 mL of methanol. Added was 8 mL of 0.5 N aqueous KOH, and the mixture was refluxed for 12 h. The reaction mixture was diluted with 40 mL of H₂O, washed with 40 mL of ether, and then carefully acidified with dilute HCl. The mixture was extracted with two 50-mL portions of ether. The combined ethereal solution was washed with two 50-mL portions of saturated NaHCO₃.

The combined bicarbonate solution was carefully acidified with dilute HCl and then rapidly extracted with 100 mL of ether. The organic phase was washed with H₂O and dried over MgSO₄. Concentration afforded 911 mg (84%) of a white foam, mp 105–108 °C: IR (KBr) 3300–2600, 1700, 1595 cm⁻¹; NMR (CDCl₃) δ 8.28–6.60 (m, 5 H), 4.57–4.26 (m, 1 H), 3.99 (bs, 10 H), 3.05–2.76 (m, 1 H), 2.66–1.50 (m, 8 H), 1.28 (s, 3 H).

Anal. Calcd for C₂₅H₂₉NO₆: *m/e* 439.1995. Found: *m/e* 439.1989.

8-Acetyl-6-cyano-1,5-dimethoxy-12-oxo-6,6a,7,8,9,10,10a,11-octahydronaphthacene (21a). A solution of carboxylic acid 20a (632 mg, 1.44 mol) in 5 mL of 1:1 (v/v) trifluoroacetic acid/trifluoroacetic anhydride was stirred at room temperature for 4 h and then stirred at reflux for 1 h. The mixture was cooled and carefully added to 80 mL of ice-cold saturated NaHCO₃. The resulting mixture was extracted with two 50-mL portions of methylene chloride. The combined organic solution was washed with saturated NaHCO₃ and H₂O and dried over Na₂SO₄. Concentration afforded a tan foam. Preparative TLC (eluted with 50:1 ethyl acetate/methanol) gave 496 mg (91%) of an off-white solid. Recrystallization from ethyl acetate gave tiny white crystals, mp 221–224 °C: IR (KBr) 2240, 1710, 1695, 1610 cm⁻¹; NMR (CDCl₃) δ 7.67–6.70 (m, 4 H), 4.59 (m, 1 H), 4.12 (s, 3 H), 4.05 (s, 3 H), 2.92–1.22 (m, 9 H), 2.22 (s, 3 H).

Anal. Calcd for C₂₃H₂₃NO₄: *m/e* 377.1627. Found: *m/e* 377.1609.

1,5-Dimethoxy-8-(2-methyl-1,3-dioxolan-2-yl)-7,8,9,10-tetrahydro-6,11-naphthacenedione (23a). Ketonitrile 21a (2.31 g, 6.1 mmol) was combined with 40 mg of *p*-toluenesulfonic acid and 440 mg of ethylene glycol in 40 mL of dry benzene. The mixture was stirred at reflux under a Dean Stark trap for 48 h. The reaction mixture was partitioned between methylene chloride and saturated NaHCO₃. The organic phase was washed with H₂O and dried over Na₂SO₄. Concentration gave 2.10 g (82%) of the ketal 22a as a tan foam, mp 94–98 °C: IR (KBr) 2240, 1680, 1612 cm⁻¹; NMR (CDCl₃) δ 7.70–7.48 (m, 2 H), 7.01–6.77 (m, 2 H), 4.54 (m, 1 H), 4.12 (s, 3 H), 4.03 (s, 3 H), 3.98 (s, 4 H), 2.98–1.30 (m, 9 H), 1.34 (s, 3 H).

A solution of ketal 22a (421 mg, 1 mmol) in 4 mL of 10:1 (v/v) THF/HMPA was added dropwise to a solution of lithium diisopropylamide (2.2 mmol) in 20 mL of THF at –78 °C. The resulting blue-green solution was stirred 1 h at –78 °C, and then dry oxygen gas was bubbled through the mixture for 1 h. The reaction mixture was stirred an additional 0.5 h and then warmed to 0 °C. The mixture was quenched with 2 mL of 1 N NaHSO₃ and poured into 60 mL of methylene chloride. This solution was washed with H₂O (2×) and dried over Na₂SO₄. Concentration and preparative TLC (eluted with chloroform, two developments) afforded 336 mg (82%) of the quinone 23a as a bright orange foam, mp 114–116 °C: IR (CDCl₃) 1685, 1649, 1605 cm⁻¹; NMR (CDCl₃) δ 8.18–6.97 (m, 4 H), 4.05 (s, 3 H), 4.02 (s, 3 H), 3.98 (s, 4 H), 3.04–1.28 (m, 7 H), 1.41 (s, 3 H); UV-vis (CHCl₃) nm (log ε), 247 (4.48), 266 (4.54), 374 (3.65).

Anal. Calcd for C₂₄H₂₄O₆: *m/e* 408.1573. Found: *m/e* 408.1601.

8-Acetyl-1,5-dimethoxy-7,8,9,10-tetrahydro-6,11-naphthacenedione (4a). Quinone 23a (71 mg, 0.17 mmol) was dissolved in 2.5 mL of dioxane containing 6 drops of 1 N HCl. The mixture was stirred for 24 h at ambient temperature and then poured into 40 mL of methylene chloride. This solution was washed with 40-mL portions of 10% NaHCO₃ and H₂O (2×) and dried over Na₂SO₄. Concentration afforded 61 mg (96%) of quinone 4a as a dark orange solid. Recrystallization from dioxane/H₂O gave tiny orange-red crystals, mp 202.5–204 °C: IR (CHCl₃) 1715, 1670, 1622 cm⁻¹; NMR (CDCl₃) δ 7.88–6.90 (m, 4 H), 4.04 (s, 3 H), 4.01 (s, 3 H), 3.01–1.64 (m, 7 H), 2.25 (s, 3 H); UV-vis (CHCl₃) nm (log ε), 248 (s), 265 (4.50), 387 (3.52), 442 (3.51).

Anal. Calcd for C₂₂H₂₀O₅: C, 72.51; H, 5.61. Found: C, 72.48; H, 5.25.

8-Acetyl-5-hydroxy-1-methoxy-7,8,9,10-tetrahydro-6,11-naphthacenedione (24). A solution of quinone 4a (51 mg, 0.14 mmol) in 3 mL of nitrobenzene was added to a solution of 1.2 g of aluminum chloride in 10 mL of nitrobenzene. The resulting deep blue solution was allowed to stand for 20 min and then poured into 100 g of ice and 10 mL of concentrated HCl. The deep red mixture was filtered and then heated on a steam bath for 2 h. The resulting red precipitate was collected by suction filtration and washed with H₂O. Recrystallization from chloroform-ether gave dark red prisms, mp 215–216 °C: IR (KBr) 1710, 1680 (w), 1605 cm⁻¹; NMR (CDCl₃) δ 13.89 (s, 1 H, exchanges with D₂O), 8.54 (s, 1 H), 8.00 (dd, *J* = 0.5 and 3.5 Hz, 1 H), 7.56 (t, *J* = 3.5 Hz, 1 H), 7.01 (dd, *J* = 0.5 and 3.5 Hz, 1 H), 4.02 (s, 3 H), 2.83–1.70 (m, 7 H), 2.28 (s, 3 H); UV-vis (CHCl₃) nm (log ε), 246 (4.45), 275 (s), 491 (3.69).

Anal. Calcd for C₂₁H₁₈O₅: *m/e* 350.1154. Found: *m/e* 350.1166.

7,9-Deoxydaunomycinone (3). Quinone 4a (47 mg, 0.13 mmol) was combined with potassium carbonate (400 mg) and sodium hydrosulfite (115 mg) in 12 mL of dry acetone. Then 0.4 mL of dimethyl sulfate was

added and the mixture was stirred at reflux for 18 h. The mixture was cooled and 10 mL of 1 N NaOH was added. The mixture was stirred for 2 h at ambient temperature and then partitioned between methylene chloride and H₂O. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated to give a yellow solid: NMR (CDCl₃) δ 8.17–6.67 (m, 4 H), 4.08 (s), 4.07 (s), 3.94 (s), 3.88 (s) (12 H), 3.07–1.84 (m, 7 H), 2.26 (s, 3 H).

This crude material was dissolved in 1 mL of acetic acid and added dropwise to an ice-cold solution of chromium trioxide (22 mg) in 1 mL of acetic acid. The reddish-brown mixture was allowed to warm to ambient temperature and stirred for 1 h. The reaction mixture was poured into 30 mL of methylene chloride and this solution was washed with 30-mL portions of H₂O, 10% NaHCO₃, and H₂O. The organic layer was dried over Na₂SO₄ and concentrated.

The residual brown solid was dissolved in 10 mL of acetone. To this was added 84 mg of silver(I) oxide and 1 mL of 40% nitric acid. The mixture became homogeneous after 10 min and was poured into 30 mL of methylene chloride. This solution was shaken vigorously with 30 mL of 5% sodium hydrosulfite. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated to give a dark red-brown solid. Preparative TLC of this material (eluted with chloroform, three developments) afforded 22 mg (47%) of 7,9-dideoxydaunomycinone (**3**) as a bright red solid, mp 234–239 °C (lit. 244–245 °C, ^{21b} 243–245 °C^{3a}). This material was identical with an authentic sample by ¹H NMR, IR, UV-vis, and TLC in three different solvent systems.²¹

2-Allyl-1,4,5-trimethoxynaphthalene (14). A solution of 2-allyljuglone methyl ether (**13**)⁹ (2.35 g, 10.3 mmol) in 100 mL of ether was combined in a separatory funnel with a solution of 7.2 g of sodium hydrosulfite in 100 mL of H₂O. The mixture was shaken vigorously for 20 min; then the organic phase was separated and concentrated to give the hydroquinone as a beige solid. This material was dissolved in 10 mL of THF and added dropwise to a suspension of sodium hydride (590 mg) in 40 mL of THF. The resulting deep green solution was treated with 2.9 mL of dimethyl sulfate and the mixture was stirred at reflux for 2 h. The pale yellow reaction mixture was poured into 75 mL of ether and this solution was washed with 1 N HCl, H₂O, and saturated brine and dried over Na₂SO₄. Concentration afforded 2.48 g (93%) of viscous brown oil which partially solidified on standing: IR (film) 1635 cm⁻¹; NMR (CDCl₃) δ 7.64 (dd, *J* = 8 and 1.5 Hz, 1 H), 7.30 (t, *J* = 8 Hz, 1 H), 6.73 (dd, *J* = 8 and 1.5 Hz, 1 H), 6.64 (s, 1 H), 6.29–5.68 (m, 1 H), 5.28–4.83 (m, 2 H), 3.85 (s, 9 H), 3.51 (m, 2 H).

1,4,5-Trimethoxynaphth-2-ylacetaldehyde (16). To a stirred suspension of osmium tetroxide (48 mg) and potassium chlorate (1.32 g) in 10 mL of THF was added a solution of olefin **14** (1.20 g, 4.7 mmol) in 5 mL of THF, followed by 3 mL of H₂O. The mixture was stirred at ambient temperature for 6 h and then poured into 100 mL of 10% aqueous sodium bisulfite. The mixture was extracted with two 60-mL portions of methylene chloride. The combined organic solution was washed with 60-mL portions of 10% NaHSO₃, H₂O, and saturated brine, and dried over Na₂SO₄. Concentration afforded the crude diol **15** as a brown oil: IR (film) 3450 cm⁻¹.

The crude **15** was dissolved in 4 mL of *tert*-butyl alcohol. To this solution was added 640 mg of sodium periodate followed by 3 mL of H₂O. The reaction mixture was stirred for 2 h at room temperature, during which time a light precipitate forms. The mixture was partitioned between methylene chloride and H₂O. The organic phase was washed with H₂O (2X) and dried over Na₂SO₄. Concentration afforded 570 mg (48% from olefin **14**) of the aldehyde **16** as a pale waxy solid, mp 76–84 °C (lit.¹¹ 80.5–92 °C): IR (CHCl₃) 1730 cm⁻¹; NMR (CHCl₃) δ 9.71 (t, *J* = 2 Hz, 1 H), 7.59 (dd, *J* = 8 Hz and 1.5 Hz, 1 H), 7.32 (t, *J* = 8 Hz, 1 H), 6.75 (dd, *J* = 8 Hz and 1.5 Hz, 1 H), 6.51 (s, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.73 (d, *J* = 2 Hz, 2 H).

1,4,5-Trimethoxynaphth-2-ylacetone nitrile (5b). To a stirred solution of aldehyde **16** (320 mg, 1.2 mmol) in 10 mL of methanol was added 148 mg (1.3 mmol) of hydroxylamine-*O*-sulfonic acid in 3 mL of H₂O. The mixture was stirred 1 h at ambient temperature and then warmed to 50 °C for 1 h. The reaction mixture was cooled and partitioned between methylene chloride and H₂O. The organic layer was washed with H₂O (2X) and dried over Na₂SO₄. Concentration afforded a dark oil which was subjected to chromatography (A, eluted with 50:1 benzene/ether) to give 230 mg (73%) of nitrile **5b** as a beige solid, mp 110–113 °C (lit. 110–111 °C,¹³ 113–114 °C²²): IR (CHCl₃) 2240, 1605, 1595 cm⁻¹; NMR (CDCl₃) δ 7.74–6.80 (m, 4 H), 3.94 (s, 9 H), 3.85 (s, 2 H).

Ethyl 2-[Cyano(1,4,5-trimethoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylate (19b). To a stirred suspension of potassium hydride (151 mg, 3.8 mmol) in 40 mL of dry THF was added 974 mg (3.79 mmol) of nitrile **5b** in 5 mL of THF. The resulting dark brown solution was stirred for 1 h at ambient temperature; during this time a light precipitate forms. Then 1 mL of HMPA was added and the resulting homogeneous mixture was cooled to –20 °C. A solution of

ester **6** (910 mg, 3.79 mmol) in 4 mL of THF was rapidly added. The mixture was stirred for 3 h at –20 °C, warmed to 0 °C, and stirred an additional 3 h. Finally, the mixture was warmed to ambient temperature and stirred for 12 h. The reaction was quenched by the addition of 1 mL of H₂O and the mixture was poured into 100 mL of ether. This solution was washed with two 100-mL portions of H₂O, and dried over Na₂SO₄. Concentration afforded a brown oil which was subjected to chromatography (C, eluted with 8–25% ether in benzene). Eluted first was a mixture of nitrile **5b** and ester **6**; nitrile **5b** was recovered from this mixture by crystallization from 1:1 ethyl acetate/cyclohexane (246 mg, 25%). Eluted second was the cyano ester **19b** (1.02 g, 72% based on unrecovered **5b**) as a viscous oil which solidified upon standing to give a red-brown solid, mp 73–76 °C: IR (CHCl₃) 2240, 1730, 1605 cm⁻¹; NMR (CDCl₃) δ 7.78–6.66 (m, 4 H), 4.72–3.98 (m, 3 H), 3.95 (s, 9 H), 3.90 (s, 4 H), 2.88 (m, 1 H), 2.56–1.18 (m, 1 H), 1.28 (s, 3 H).

Anal. Calcd for C₂₈H₃₅NO₇: C, 67.58; H, 7.09. Found: C, 67.83; H, 7.05.

2-[Cyano(1,4,5-trimethoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylic Acid (20b). Cyano ester **19b** (953 mg, 1.92 mmol) was dissolved in 20 mL of 1:1 (v/v) THF/ethanol. To this solution was added 2.2 mL of 1 N potassium hydroxide and the mixture was stirred at reflux for 24 h. The reaction mixture was cooled and diluted with 40 mL of H₂O. This solution was washed with 40 mL of ether and then acidified with dilute HCl and extracted with two 40-mL portions of ether. The combined ethereal solution was washed with 50 mL of saturated NaHCO₃. The aqueous layer was carefully acidified with dilute HCl and then rapidly extracted with 50 mL of ether. The organic layer was washed with H₂O and brine and dried over Na₂SO₄. Concentration afforded 697 mg (77%) of the acid **20b** as a pale foam, mp 88–93 °C: IR (CHCl₃) 3400–2650 (b), 2240, 1706, 1605, 1595 cm⁻¹; NMR (CDCl₃) δ 7.77–6.69 (m, 4 H), 4.67–4.39 (m, 1 H), 3.97 (s, 9 H), 3.90 (s, 4 H), 3.12 (m, 1 H), 2.57–1.45 (m, 8 H), 1.29 (s, 3 H).

Anal. Calcd for C₂₆H₃₁O₇N: N, 2.98. Found: N, 2.58.

8-Acetyl-6-cyano-1,5,12-trimethoxy-11-oxo-6,6a-,7,8,9,10,10a,11-octahydronaphthacene (21b). Acid **20b** (597 mg, 1.3 mmol) was dissolved in 8 mL of 1:1 (v/v) trifluoroacetic acid–trifluoroacetic anhydride, and the mixture was stirred at reflux for 3 h. The reaction mixture was cooled and quenched by careful addition to ice-cold saturated NaHCO₃. The aqueous suspension was extracted with two 40-mL portions of methylene chloride. The combined organic layers were washed with 10% NaHCO₃ and H₂O and dried over Na₂SO₄. Concentration afforded a brown foam. Preparative TLC (eluted with chloroform, two developments) and recrystallization from 5:1 ether/methylene chloride gave 384 mg (74%) of tiny tan crystals, mp 207–210 °C: IR (CHCl₃) 2240, 1710, 1685, 1605 cm⁻¹; NMR (CDCl₃) δ 7.81–6.67 (m, 3 H), 4.61 (m, 1 H), 4.02 (s, 3 H), 4.01 (s, 3 H), 3.93 (s, 3 H), 2.89–1.56 (m, 9 H), 2.21 (s, 3 H).

Anal. Calcd for C₂₄H₂₅NO₅: N, 3.44. Found: N, 3.31.

6-Cyano-8-(2-methyl-1,3-dioxolan-2-yl)-1,5,12-trimethoxy-11-oxo-6,6a-,7,8,9,10,10a,11-octahydronaphthacene (22b). Ketone **21b** (302 mg, 0.74 mmol) was combined with 100 mg of ethylene glycol, 18 mg of *p*-toluenesulfonic acid, and 260 mg of triethyl orthoformate in 8 mL of dry benzene. The mixture was stirred at ambient temperature for 48 h and then poured into 40 mL of methylene chloride. This solution was washed with 10% NaHCO₃ and H₂O and dried over Na₂SO₄. Concentration and recrystallization from 7:1 ether/methylene chloride afforded 320 mg (98%) of ketal **22b** as pale orange prisms, mp 212–214 °C: IR (CHCl₃) 2240, 1685, 1608 cm⁻¹; NMR (CDCl₃) δ 7.81–6.68 (m, 3 H), 4.57 (m, 1 H), 4.05 (s), 4.01 (s), 3.96 (s), 3.93 (s) (13 H), 2.94–1.50 (m, 9 H), 1.31 (s, 3 H). Anal. Calcd for C₂₆H₂₉NO₆: C, 69.16; H, 6.48; N, 3.10. Found: C, 68.89; H, 6.68; N, 3.38.

1,5,12-Trimethoxy-8-(2-methyl-1,3-dioxolan-2-yl)-7,8,9,10-tetrahydro-6-11-naphthacenedione (23b). A solution of ketal **22b** (118 mg, 0.27 mmol) in 3 mL of 10:1 (v/v) THF/HMPA was added dropwise to a solution of lithium diisopropylamide (0.59 mmol) in 10 mL of THF at –78 °C. The resulting dark green solution was stirred for 1 h at –78 °C, and then dry oxygen gas was bubbled through the mixture for 1 h. The reaction mixture was warmed to 0 °C over 1 h, quenched with 2 mL of H₂O, and poured into 40 mL of methylene chloride. The resulting solution was washed with 40-mL portions of 2% NaHSO₃ and H₂O and dried over Na₂SO₄. Concentration and preparative TLC (eluted with chloroform, three developments) afforded 68 mg (60%) of quinone **23b** as a bright orange solid. Recrystallization from 5:1 ether/methylene chloride gave orange prisms, mp 141–142.5 °C: IR (CHCl₃) 1670, 1620, 1580 cm⁻¹; NMR (CDCl₃) δ 8.19–6.69 (m, 3 H), 4.01 (s), 3.98 (s), 3.95 (s) (13 H), 3.05–1.48 (m, 7 H), 1.55 (s, 3 H); UV-vis (CHCl₃) nm (log ϵ), 247 (4.82), 395 (3.94), 442 (3.94).

7,9-Dideoxycarminomycinone (27). Quinone **23b** (8 mg), dissolved in 5 mL of dry benzene, was added dropwise to a stirred suspension of aluminum chloride (90 mg) in 10 mL of benzene. The deep violet

mixture was stirred at reflux for 16 h. The mixture was poured into 50 g of ice and 10 mL of concentrated HCl and heated on a steam bath for 2 h, during which time a red precipitate formed. The aqueous suspension was extracted with two 40-mL portions of methylene chloride and the combined organic solution was washed with H₂O and dried over Na₂SO₄. Concentration and preparative TLC (Kieselgel 60, eluted with chloroform, two developments) afforded 5 mg of the trihydroxyquinone **27** as a bright red solid, mp 188–192 °C dec; IR (CHCl₃) 1608 cm⁻¹; NMR (CDCl₃) δ 13.59 (s, 1 H), 12.73 (s, 1 H), 12.20 (s, 1 H), 7.98–6.71 (m, 3 H), 3.00–1.58 (m, 7 H), 2.28 (s, 3 H); UV-vis (CHCl₃) nm (log ε), 255 (4.76), 448 (4.24), 536 (4.09).

Similarly 3.5 mg of 7,9-dideoxydaunomycinone²¹ was treated with 70 mg of aluminum chloride. Following workup and chromatography, 2 mg of **27** was obtained. This material was identical in all respects with that obtained from the demethylation of **23b** described above.

7,9-Dideoxydaunomycinone (3). Quinone **23b** (28 mg) was combined with 78 mg of silver(II) oxide in 15 mL of acetone and 3 mL of 40% nitric acid was added. The mixture became homogeneous after 10 min and was poured into 40 mL of methylene chloride. This solution was

washed with 40-mL portions of 2% aqueous sodium hydrosulfite and H₂O and dried over Na₂SO₄. Concentration and preparative TLC (eluted with chloroform, four developments) gave 21 mg (90%) of 7,9-dideoxydaunomycinone (**3**) as a bright red solid, mp 236–241 °C (lit. 244–245 °C,^{21b} 243–245 °C^{3a}). This material was identical with an authentic sample²¹ by ¹H NMR, IR, UV, and TLC in three different solvent systems.

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Sesquiterpene Lactones. Total Synthesis of (±)-Eriolanin and (±)-Eriolangin

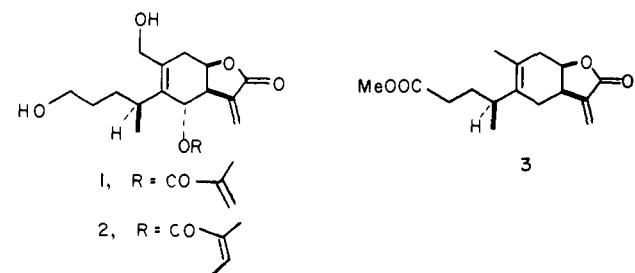
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Abstract: The total synthesis of (±)-eriolanin (**1**) and (±)-eriolangin (**2**), highly oxygenated 1,10-*seco*-eudesmanolides isolated from the chloroform extracts of *Eriophyllum lanatum* Forbes (Compositae), is described. The preparation of both **1** and **2** is accomplished in 22 steps, starting from 4α,5α-methanodecalol **8**.

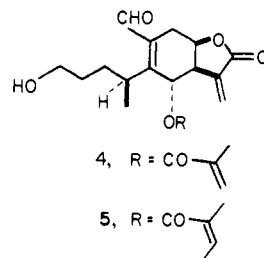
The sesquiterpene lactones (±)-eriolanin (**1**) and (±)-eriolangin (**2**) are novel antileukemic 1,10-*seco*-eudesmanolides containing three consecutive chiral centers on a cyclohexene ring in addition to a chiral center located on an acyclic side chain. Isolated from the chloroform extracts of *Eriophyllum lanatum* Forbes (Compositae) by Kupchan and co-workers,² both eriolanin and eriolangin possess significant activity in vivo against P-388 leukemia in mice and in vitro against cell cultures derived from human carcinoma of the nasopharynx (KB). The in vivo tumor-inhibitory activity associated with both **1** and **2** can be attributed to the presence within each molecule of two α,β-unsaturated carbonyl functions.³

A rare class of compounds comprised of only three members, the first 1,10-*seco*-eudesmanolide, ivangulin (**3**), was isolated by



Herz and co-workers in 1967 from *Iva angustifolia* Natl. (section Linearbractea) found in Texas and Oklahoma.⁴ The recently reported total synthesis of ivangulin⁵ confirmed the gross structural assignment put forth by Herz nearly 12 years ago and established the configuration at C(4).

Structure elucidation of the more highly oxygenated members, eriolanin and eriolangin, required, in addition to a combination of NMR, IR, and mass spectral techniques, an X-ray analysis of a mixed crystal of dehydroeriolanin (**4**) and dehydroeriolangin (**5**).^{1,6}



With no degradative studies to fall back upon, we embarked on the synthesis of eriolanin and eriolangin, realizing that success could only be claimed after we had reached the ultimate targets. Of critical importance to success was the introduction of the C(4) methyl group with the proper stereochemical relationship to the oxygenated α-methylene-γ-butyrolactone functionality. We detail below an account of the total synthesis of eriolanin and eriolangin.⁷

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