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ANNELATIVE PHENOL SYNTHESIS

PREPARATION OF 7-METHYLJUGLONE AND 7,9,11-TRIDEOXYDAUNOMYCINONE

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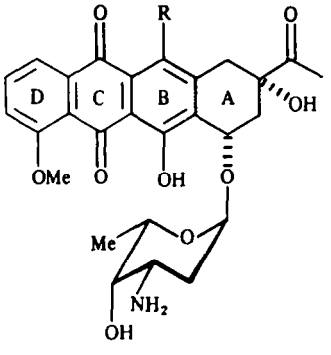
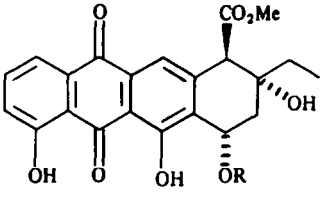
Abstract—The Michael adducts of arylacetonitrile enolates and unsaturated esters may be converted to fused phenolic systems by the following sequence: ester hydrolysis, Na/NH_3 reductive elimination of cyanide, Friedel–Crafts ring closure, and oxidation. The construction of linear polycyclic systems by this annelation procedure is illustrated by the regiospecific syntheses of 7-methyljuglone and dl-7,9,11-trideoxydaunomycinone.

The anthracycline antibiotics daunomycin (**1a**), 11-deoxy daunomycin (**1b**), and the aklavinone glycosides (**2**), have recently attracted much attention from the synthetic organic community as a result of their broad range of biological activity. This activity has been well documented,[1] and many synthetic approaches to these molecules have been reported.[2a–c]



1a R = OH Daunomycin
1b R = H 11-Deoxydaunomycin



2 R = Sugars, Aklavinone glycosides

Our retrosynthetic strategy for the synthesis of anthracycline aglycones was based on a diagonal division of the B-ring (Fig. 1); this approach allows the key C—C bond connections to be made stepwise, by inherently different chemical transformations, and therefore it necessarily affords a single regioisomer of the linear tetracycle.

This strategy was first suggested by us in 1977[3] and its subsequent application to the synthesis of dl-7,9-dideoxydaunomycinone (**7**) was reported in 1979 and 1980[4] (Scheme 1). The key step in this synthesis is the oxidative decyanation of ketone **6** which introduces the C-11 oxygen required for daunomycin.

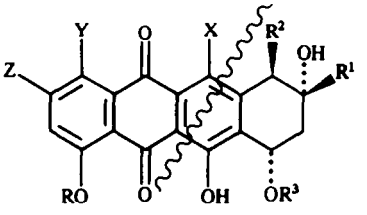


Fig. 1.

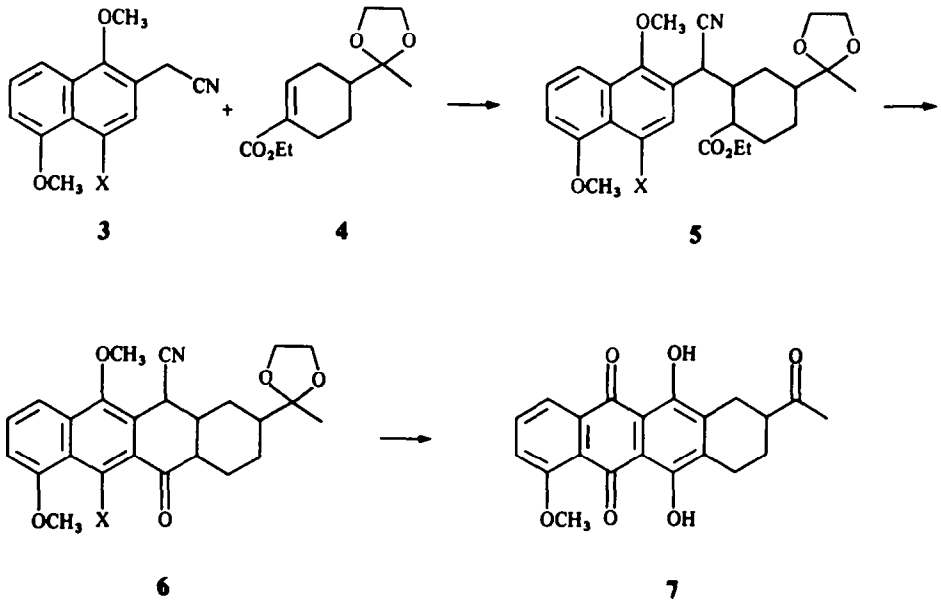
Formally, structure **6** is an HCN adduct of a B-ring phenol **8**; i.e. if we could cause the non-oxidative loss of HCN from **6** (or from **5**) we would have a functional equivalent of 7,9,11-trideoxydaunomycinone (**9**).[5]

The loss of HCN from systems not activated for elimination[6] is not well-known; therefore we elected to attempt HCN elimination by coupling a dissolving metal reductive loss of CN^- (a high-yield process for phenylacetonitrile)[7] with a subsequent oxidative step.

The compatibility of the reductive elimination of CN^- with other functionality present in **5** was first tested in the model system **10**. Although treatment of cyanoester **10a**[8] with sodium in liquid ammonia[7] afforded a complex product mixture, the same reduction conditions converted the acid **10b** to the decyanated acid **11** in 75% yield. Furthermore, treatment of acid **11** with HF effected cyclization to ketone **12** in 70% yield.

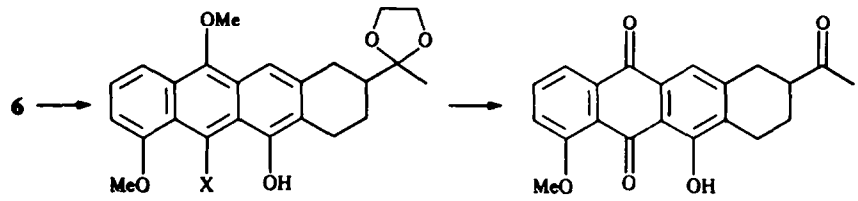
We chose to explore the potential of this approach in a model system[9] which would allow us to test not only the tetralone → naphthol conversion but to explore additional steps in the planned sequence. We chose cyanoester **13a**,[8] a potential precursor to 7-methyljuglone (**19**)[10] as a model for the more complex substrates **5**. Hydrolysis with aqueous, ethanolic KOH afforded a 87% yield of the cyanocarboxylic acid **13b**; this material was not purified but subjected immediately to Birch conditions to give the carboxylic acid **14** in 93% yield. Intramolecular Friedel–Crafts reaction led to tetralone **15**[10] in 81% yield.

Bromination of the tetralone followed by treatment with DBU converted tetralone **15** to phenol **16**[10] in 84%



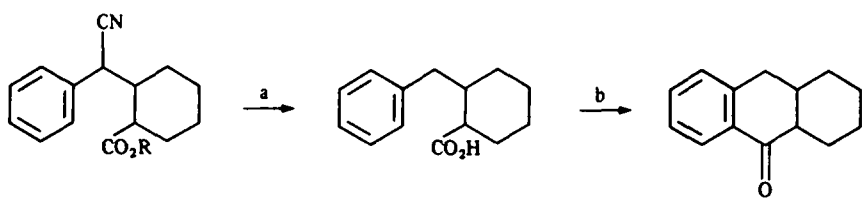
3 4 5 6 7

Scheme 1.



8 9

Scheme 2.



10a R = Et
10b R = H

11 **12**

(a) Na/NH_3; (b) HF

Scheme 3.

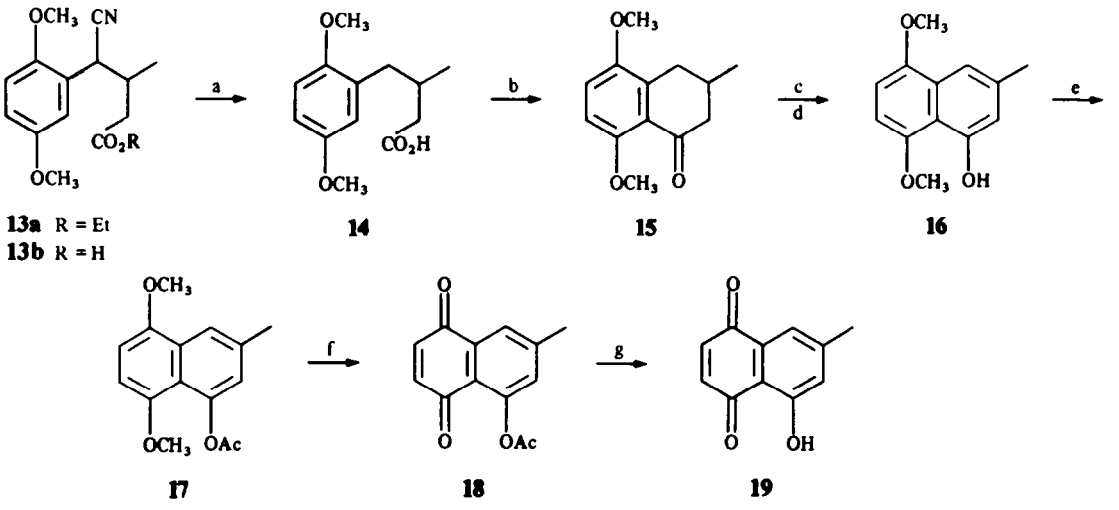
yield. The four-step procedure (**13a** → **16**) could be carried out in an overall yield of 55%.

In addition to developing the annelation procedure in the model series, we were interested in testing the feasibility of transformations which might be required for the completion of the synthesis of **9**. Therefore we attempted to elaborate the model quinone **19** from phenol **16**.

An attempt to oxidize **16** directly to 7-methyljuglone (**19**) with AgO[11] gave a mixture which contained at least four components. However, the corresponding acetate (67% from **16**) was oxidized by AgO in 83% yield to quinone **18**,[10] Deacylation in dilute H_2SO_4 afforded 7-methyljuglone in 82% yield.

Initial attempts to apply the reductive decyanation/oxidation strategy to the synthesis of 7,9,11-trideoxydaunomycinone (**9**) were frustrated by the poor behavior of cyano acid **5** (X = H, R = H) under the reductive elimination conditions. Treatment of **5** with sodium (NH_3/THF, −78° for 10 min) resulted in recovery of starting material. Longer reaction times led to mixtures which appeared to contain material which had lost OMe substituents.[12]

A possible solution to this problem was explored in an alternative, fully substituted naphthyl acetonitrile system. Exposure of **20**[13] to the reductive elimination conditions afforded a 60% yield (not optimized) of the decyanated naphthol **22**. This transformation pre-



(a) Na/NH_3, 10 min,–78°; (b) HF; (c) NBS (1 equiv), AIBN, CCl_4; (d) DBU; (e) Ac_2O, pyr.; (f) AgO, HNO_3; (g) H_2SO_4 (dil)

Scheme 4.

sumably proceeds by base induced elimination of HCN followed by reduction of the quinone methide intermediate **21**.

Application of this modified reductive decyanation procedure in the synthesis of 11-deoxyanthracyclinones then required a base stable protecting group for the phenolic OH of **20**. The benzyl group was chosen as we anticipated its removal under hydrogenation conditions.[14]

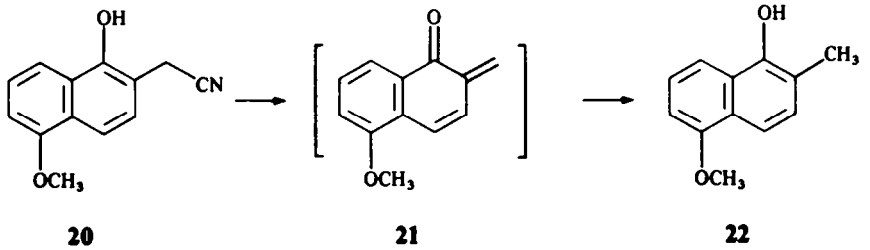
Thus, the appropriately protected naphthylacetonitrile **23** was obtained from the readily available phenol **20** in 52% yield. Michael addition of the anion derived from **23** to ester **4** at −20° afforded a 60% yield of adduct **24**. Selective hydrolysis of the ester gave acid **25**. Debenzylation was effected with H_2/Pd-C in methanol containing $BaCO_3$ to afford the naphthol **26**. Reductive decyanation proceeded to give naphthol **27**. This material proved to be somewhat unstable and was generally stored under argon in the refrigerator and used as soon as possible after preparation.

Attempts to effect Friedel–Crafts cyclization of **27** with trifluoroacetic acid/trifluoroacetic anhydride or with HF gave material which we believed to be lactone **28**. As an alternative route to further elaboration, the oxidation of the naphthol ring was effected with Fremy's salt[15] to give a quantitative yield of keto quinone **29**.

Reductive methylation of quinone **29** (aqueous hydrosulfite, then Me_2SO_4, K_2CO_3, acetone) gave a mixture of the dimethoxy and trimethoxy esters **30a** and **30b**; the mixture was subjected to hydrolysis and Friedel–Crafts cyclization (TFA, TFAA). From this reaction a mixture of tetracyclic ketones **31a** and **31b** was obtained. These were separated by chromatography and isolated in yields of 16% and 30% respectively. Each of these was subjected to oxidation by AgO (to **32**) and then by oxygen in DMF[5] to the known 7,9,11-trideoxydaunomycinone (**9**).[5] By the two-step oxidative procedure, **9** could be obtained in 45% (R = Me) yield from **31b** and in 32% yield from **31a**.

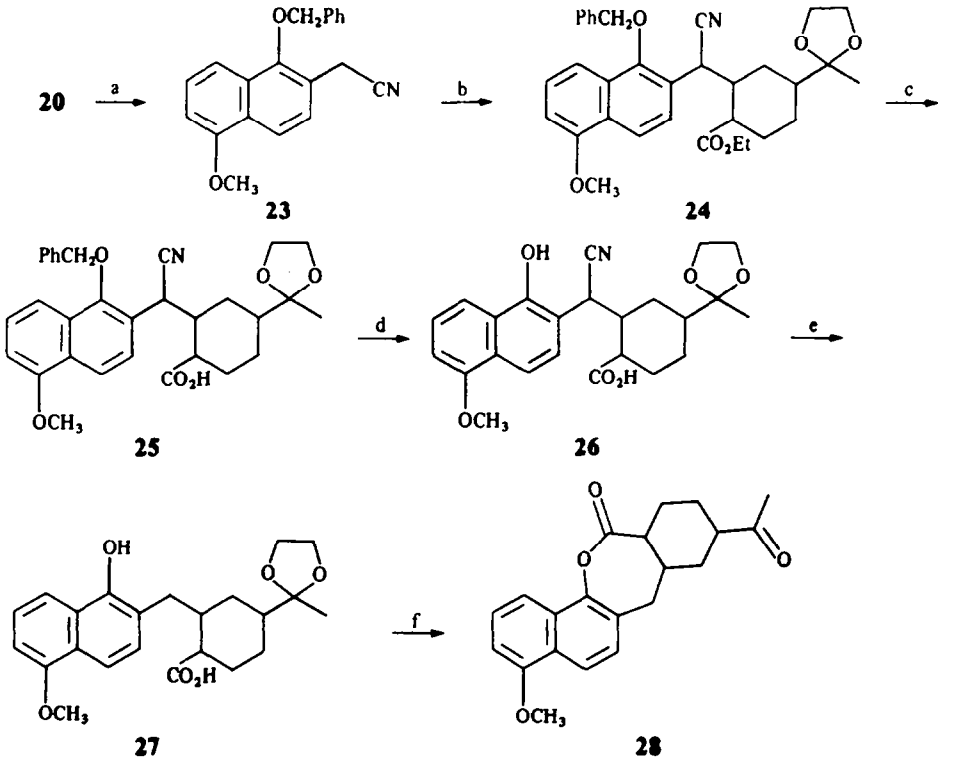
The overall yield of chromatographed, recrystallized **9** is 9% from nitrile **23**. While not as efficient as some other approaches to 11-deoxyanthracyclinones, this sequence boasts several advantages. The starting materials are inexpensive and readily available, as are all of the reagents used in the synthesis. All of the transformations in the sequence require relatively little advance preparation, and only three of the intermediates require chromatographic purification.

Furthermore, our scheme illustrates the modified reductive decyanation procedure in which the presence of an o-hydroxy substituent promotes the simple reductive elimination transformation.



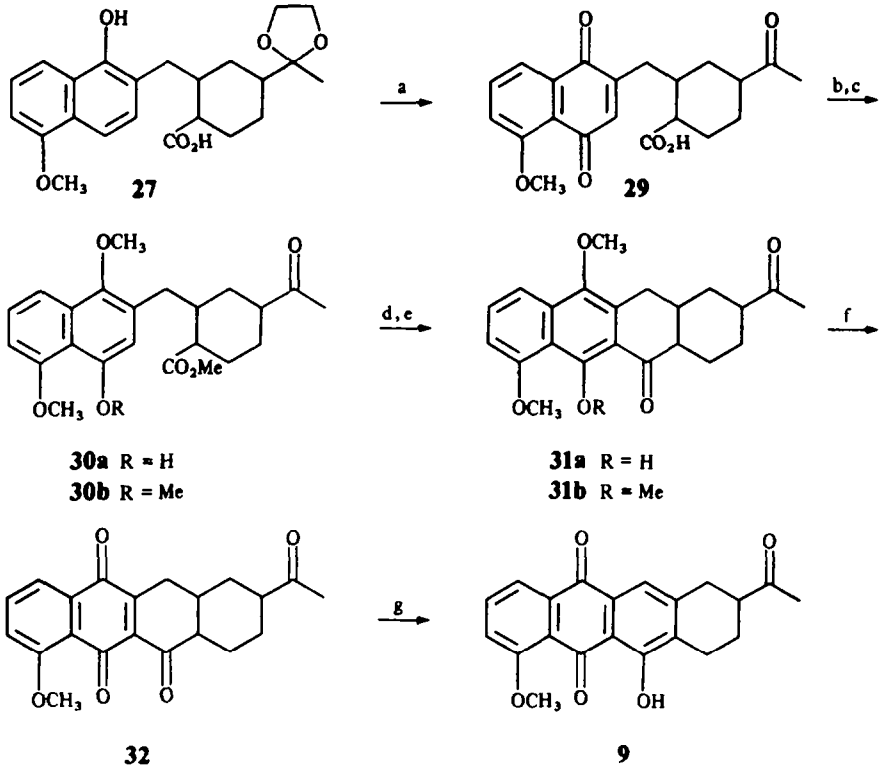
20 **21** **22**

Scheme 5.



(a) $C_6H_5CH_2Br$, K_2CO_3; (b) KH, THF, then ester **4**, 4 hr, -23°; (c) KOH, MeOH; (d) H_2, Pd/C, MeOH, $BaCO_3$; (e) Na/NH_3, 10 min, -33°; (f) HF or TFA, TFAA

Scheme 6.



(a) Fremy's salt; (b) hydrosulfite; (c) Me_2SO_4, K_2CO_3; (d) KOH, MeOH; (e) TFA, TFAA; (f) AgO, HNO_3; (g) O_2, DMF, 150°

Scheme 7.

EXPERIMENTAL

General: instrumentation and materials. M.ps were determined using a Thomas–Hoover capillary m.p. apparatus and are uncorrected. IR spectra were recorded on either a Perkin–Elmer 681 or 257 infrared spectrometer. PMR spectra were obtained at 60 MHz on either a Varian A-60, a EM-360, or a Bruker WP-60 Fourier transform spectrometer, or at 250 MHz on a Bruker WM-250 spectrometer. Multiplicity: s = singlet; d = doublet; t = triplet; q = quartet; sept = septet; m = multiplet; b = broad peak; dd = doublet of doublets. Low resolution mass spectroscopic analyses were performed at 50 eV on a Hitachi–Perkin–Elmer Model RMU-60 spectrometer, or at the Mass Spectrometry Center, University of Pennsylvania. High resolution mass spectra, either electron impact (EI) or chemical ionization (CI), were performed at the Mass Spectrometry Center.

Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from a blue soln of sodium, benzophenone ketyl. Diisopropyl amine, pyridine, diethyl amine, and dimethylformamide (DMF) were distilled from CaH_2. Ammonia was distilled from a blue soln over Na.

2-(Cyanophenyl)methyl-1-cyclohexanecarboxylic acid (**10b**)

Cyano ester **10a**[8] (5.0 g, 18 mmol) and KOH aq (37 ml, 1 N soln) were heated (24 hr, reflux) in 50 ml EtOH and 150 ml H_2O. The mixture was acidified with 10% HCl and extracted with Et_2O. The organic portion was extracted (3 ×) with $NaHCO_3$ aq. The basic wash was acidified with 10% HCl and extracted twice with Et_2O. The soln was dried ($MgSO_4$) and concentrated to give 3.37 g (75%) of a viscous oil.

An analytical sample was prepared from material of comparable purity by recrystallization from EtOH: white powder, m.p. 190–197°. IR($CHCl_3$): 2900–3100 (broad), 2230, 1705 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 7.26–7.43 (m, 6H); 4.15 (d) and 3.38 (m), (2H, mixture of *cis* and *trans*); 2.38 (d, 1H); 1.95 (m, 1H); 1.04–1.74 (m, 8H). Found: M^+ (POS CI): 243.1218; $C_{15}H_{17}O_2N$. Requires: 243.1259.

2-Phenylmethyl-1-cyclohexanecarboxylic acid (**11**)

To a stirred, blue soln of Na (147 mg, 5.5 mmol) in freshly distilled NH_3 (15 ml) at −78° was added **10b** in 10 ml dry Et_2O. After 10 min the soln was poured carefully into ether, quenched with water, and concentrated by evaporation. The residue was diluted with Et_2O and H_2O; the aqueous layer was acidified with 10% HCl (caution; possible HCN evolution) and extracted with Et_2O. The organic portion was dried (Na_2SO_4) and concentrated to give 258 mg (75%) of a beige solid.

An analytical sample was prepared from material of comparable purity by recrystallization from hexane: white powder, m.p. 89–97° (lit[16] *trans* acid: 133–134°; for *cis* acid: 86–88°). IR($CHCl_3$): 2700–3400 (broad), 1700 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 7.20–7.30 (m, 6H); 2.65 (m, 3H); 2.18 (m, 1H); 1.89 (m, 1H); 1.68 (m, 4H); 1.40 (m, 3H). Found: M^+ (EI): 218.1307; $C_{14}H_{18}O_2$. Requires: 218.1307.

Hexahydroanthrone (**12**)

Acid **11** (92 mg, 0.420 mmol) was placed in the bottom of a polyethylene cup and cooled to 0°. HF was added and the cup was covered and allowed to stand for 3 hr (more HF was added when necessary). Ice and Et_2O were then added to the mixture, and excess HF was allowed to evaporate. The residue was partitioned between H_2O and Et_2O, and the organic portion was washed with $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated to give 59 mg of a yellowish solid (70%).

An analytical sample was prepared from material of comparable purity by recrystallization from EtOH: pale powder, m.p. 97–105° (lit[16] *trans* anthrone: 109–109.5°; *cis* anthrone: 79–80°). IR($CHCl_3$): 1675, 1600 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 8.02 (m, 1H); 7.45 (m, 1H); 7.20–7.33 (m, 2H); 2.87 (m, 2H); 2.40 (m, 1H); 2.12 (m, 1H); 1.87 (m, 4H); 1.30 (m, 4H). Found: M^+ (EI): 200.1214; $C_{14}H_{16}O$. Requires: 200.1201.

3-Methyl-4,4-cyano-(2,5-dimethoxyphenyl)butyric acid (**13b**)

Procedure as for acid **10b**. A 543 mg (0.187 mmol) of ester **13a**[8] gave 433 mg (90%) of an orange oil.

An analytical sample was prepared by TLC (5% HOAc, 25% EtOAc, 70% benzene), followed by distillation (Kugelrohr, 180–185°, 1 mm), IR($CHCl_3$): 3200, 2280, 1715 cm^{-1}. NMR($CDCl_3$): δ = 9.13 (bs, 1H); 6.95 (bs, 1H); 6.85 (s, 2H); 4.31 (bd, 1H); 3.79 (s, 6H); 2.46 (m, 3H); 1.12 (d, 3H). (Found: C, 63.68; H, 6.71; N, 5.20. Calc for $C_{14}H_{17}O_4N$: C, 63.87; H, 6.51; N, 5.32%).

3-Methyl-4-(2,5-dimethoxyphenyl)-butyric acid (**14**)

A soln of **13b** (696 mg, 2.65 mmol) in 7 ml THF was added rapidly to 25 ml freshly distilled NH_3 at −78°. Na was added piecewise with stirring until the soln remained dark blue in color. The soln was stirred 10 min, then poured carefully into 100 ml anhyd. Et_2O. Solvents were evaporated, and the residue partitioned between Et_2O and $NaHCO_3$ aq. The organic portion was washed again with $NaHCO_3$ aq, and the basic, aq layers were combined and carefully acidified. This soln was extracted twice with Et_2O; the organic portions were combined and washed with H_2O (5 ×), dried ($MgSO_4$) and concentrated to yield 584 mg (92%) of a yellow oil. IR($CHCl_3$): 3200, 1720 cm^{-1} NMR($CDCl_3$): δ = 11.2 (bs, 1H); 6.68 (s, 3H); 3.68 (s, 6H); 2.50 (m, 2H); 2.15 (m, 3H); 0.95 (m, 3H).

3-Methyl-5,8-dimethoxy-1-tetralone (**15**)

Acid **14** (423 mg, 1.78 mmol) in a polyethylene cup was cooled to 0°. HF was added to cover; the cup was capped and allowed to stand for 4 hr. After evaporation of excess HF, the residue was partitioned between CH_2Cl_2 and $NaHCO_3$ aq. The organic portion was washed (3 ×) with $NaHCO_3$ aq, with water and brine, and dried ($MgSO_4$). Concentration yielded 317 mg (81%) of a pale, beige solid.

An analytical sample was prepared by sublimation: white crystals, m.p. 72–73° (lit[10] 74.5–75.5°). IR($CHCl_3$) 1690, 1624 cm^{-1}. NMR($CDCl_3$): δ = 6.95 (d, J = 5 Hz, 1H), 6.72 (d, J = 5 Hz, 1H); 3.83 (s, 3H); 3.79 (s, 3H); 3.09 (m, 1H); 2.41 (m, 3H); 1.10 (d, 3H). (Found: C, 70.66; H, 7.36. Calc for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%).

3-Methyl-5,8-dimethoxy-1-naphthol (**16**)

A mixture of **15** (73 mg, 0.332 mmol), NBS (65 mg, 0.36 mmol), and AIBN (trace) in 5 ml CCl_4 was stirred at reflux until the succinimide floated (about 45 min). The mixture was cooled, filtered, and treated with DBU (trace) at reflux for 15 min. The mixture was diluted with CH_2Cl_2, washed twice with 10% HCl, with H_2O, and with $NaHCO_3$ aq. The resulting soln was dried ($MgSO_4$) and concentrated to yield a brown solid. Flash chromatography (5% Et_2O/benzene) gave 61 mg (84%) of a yellow-green solid.

A portion recrystallized from EtOH: white crystals, m.p. 113.5–115° (lit[10] 117–118°). IR($CHCl_3$): 3380, 1640, 1617 cm^{-1}. NMR($CDCl_3$): δ = 9.34 (s, 1H); 7.48 (m, 1H); 6.75 (m, 1H); 6.57 (s, 2H); 3.98 (s, 3H); 3.94 (s, 3H); 2.46 (s, 3H).

1-Acetoxy-3-methyl-5,8-dimethoxynaphthalene (**17**)

Phenol **16** (20 mg, 0.092 mmol) and Ac_2O (0.5 ml) were stirred at reflux in 2 ml dry pyr for 2.5 hr, then stirred at room temp for an additional 2 hr. $NaHCO_3$ aq was added carefully; the soln was stirred overnight, diluted with Et_2O, and washed twice with 10% HCl, with water, $NaHCO_3$ aq and brine, and dried ($MgSO_4$). Concentration yielded 17 mg of an orange semi-solid. Prep TLC (5% Et_2O/benzene) gave 16 mg (67%) of an orange oil which solidified on standing.

An analytical sample was prepared by distillation (Kugelrohr, 160°, 0.3 mm). IR($CHCl_3$): 1745, 1610 cm^{-1}. NMR($CDCl_3$): δ = 7.95 (m, 1H); 6.96 (m, 1H); 6.70 (s, 2H); 3.96 (s, 3H); 3.89 (s, 3H); 2.53 (s, 3H), 2.37 (s, 3H). Found M^+: 260. (Found: C, 69.18; H, 5.95. Calc for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20%).

7-Methyljuglone acetate (**18**)

To a stirred soln of **17** (11 mg, 0.042 mmol) in 5 ml acetone was added 21 mg (0.17 mmol) Ag(II)O and 0.5 ml (0.254 mmol)

0.5 N HNO_3 soln. The mixture immediately became green and homogeneous. After 10 min, the soln was diluted with CH_2Cl_2 and H_2O. The organic portion was washed with 10% HCl, $NaHCO_3$ aq, and brine, and dried ($MgSO_4$). Concentration yielded 15 mg of a yellow solid, which recrystallized from EtOH to give 9 mg (92%) of yellow crystals, m.p. 148.5–150.5°. (Lit[10] 151–152°); IR($CHCl_3$): 1770, 1665, 1609 cm^{-1}; NMR($CDCl_3$): δ = 7.84 (bs, 1H); 7.18 (bs, 1H); 6.85 (s, 2H); 2.48 (s, 3H); 2.43 (s, 3H). Found M^+: 230.

7-Methyljuglone (**19**)

Acetate **18** (3 mg, 0.013 mmol) was stirred in 2 ml MeOH with 10% H_2SO_4 (few drops) for 24 hr at room temp. The mixture was partitioned between CH_2Cl_2 and H_2O, and the organic portion was washed twice with water and dried ($MgSO_4$). Concentration gave a red tar, which was chromatographed (5% Et_2O/benzene) to give 2 mg (approx 80%) of a red solid, m.p. 120.5–122° (lit[10] 123.5–124.5). IR($CHCl_3$): 1670, 1645, 1600 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 11.86 (s, 1H); 7.44 (m, 1H); 7.08 (m, 1H); 6.91 (s, 2H); 2.44 (s, 3H).

2-Methyl-5-methoxy-1-naphthol (**22**)[17]

To a stirred soln of Na (46 mg, 2.0 mmol) in 15 ml anh NH_3 at −78° under Ar was added **20** in 3 ml THF. After 10 min the blue soln was poured carefully into Et_2O and quenched with water. The mixture was allowed to warm to room temp and partitioned between Et_2O and H_2O. The organic portion was washed with 1 N NaOH aq, and the basic, aq layers were acidified carefully with 10% HCl and extracted with Et_2O (3 ×). The combined organic portions were washed (3 ×) with water, dried ($MgSO_4$), and concentrated to give 26 mg (59%) of a tan powder, m.p. 96–101°. IR($CHCl_3$): 3600 (sharp), 2880 (broad), 1600 cm^{-1}. NMR($CDCl_3$): δ = 6.70–7.85 (m, 6H); 3.99 (s, 3H); 2.38 (s, 3H).

1-Benzyloxy-5-methoxynaphth-2-yl-acetonitrile (**23**)

Two separate mixtures of 5-methoxy-1-naphthol (2.05 g, 11.8 mmol; 1.18 g, 10.4 mmol), paraformaldehyde (0.354 g, 11.8 mmol; 0.312 g, 10.4 mmol), and Et_2NH (9.8 ml, 0.094 mol; 8.6 ml, 0.083 mmol) were stirred at reflux under N_2 for 1.5 hr. The dark brown solns were then cooled and concentrated. After the addition of DMF (16 ml; 16 ml), the solns were degassed, and treated with KCN (1.5 eq) and 18-crown-6 (3.13 g, 11.8 mmol; 2.74 g, 10.4 mmol). After stirring at 80° for 3 hr, each soln was poured into 200 ml H_2O, and the resulting soln was carefully acidified with HOAc. The mixture was then extracted twice with EtOAc. The combined organic soln was washed (5 ×) with water and with brine, and dried ($MgSO_4$). Concentration yielded a brown solid. IR($CHCl_3$): 3350 (broad), 2225, 1600 cm^{-1}. NMR($CDCl_3$): δ = 6.75–7.96 (m, 6H); 3.98 (s, 3H); 3.87 (s, 2H).

The crude product, K_2CO_3 (6.1 g, 44 mmol), and benzyl bromide (3.2 ml, 26.6 mmol) were combined in 100 ml acetone and the mixture was stirred at reflux for 9 hr, then at room temp overnight. The mixture was concentrated and diluted with Et_2O and water. The aq layer was extracted with Et_2O, and the combined organic soln was washed twice with 1 N NaOH aq, with water (3 ×), and with brine, and dried ($MgSO_4$). Concentration yielded a brown tar which was chromatographed twice (flash; 1:1 hexane/Et_2O) to give a pale, yellow solid. This material was triturated with hexane/Et_2O and dried (60°, aspirator) to yield 3.5 g (52%) of a pale solid.

An analytical sample was prepared from material of comparable purity by recrystallization from EtOH: pale, pink powder (m.p. 92–94°). IR($CHCl_3$): 2222, 1598 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 6.85–8.12 (m, 10H); 5.10 (s, 2H); 4.02 (s, 3H); 3.71 (s, 2H). Found M^+ = 303. (Found: C, 79.14; H, 5.80; N, 4.61. Calc for $C_{20}H_{17}O_2N$: C, 79.19; H, 5.65; N, 4.62%).

Ethyl 2-[cyano(1-benzyloxy-5-methoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)-cyclohexane-1-carboxylate (**24**)

To a stirred suspension of KH (4.74 mmol) in 15 ml THF under Ar, was added **23** (1.43 g, 4.74 mmol) in 10 ml THF. H_2 evolved and the soln became dark brown and homogeneous. After 15 min, the soln was cooled to −20°, and **4** (1.60 g, 6.69 mmol) in 7 ml THF was added. The stirring was continued at −20° to −40° for 3.5 hr. The mixture was quenched with water and extracted twice with ether. The organic soln was washed with $NaHCO_3$ aq and with water (2 ×), and dried ($MgSO_4$). The crude product mixture was chromatographed (flash; 1:1 hexane/Et_2O) to yield 1.53 g (60%) of an organge solid.

An analytical sample was prepared from material of comparable purity by trituration (hexane/Et_2O): m.p. 158–170°. IR($CHCl_3$): 2230, 1725, 1595 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 8.13 (d, J = 9 Hz, 1H); 7.69 (d, J = 8.4 Hz, 1H); 7.46 (m, 7H); 6.88 (d, J = 7.5 Hz, 1H); 5.33 (d, J = 11.6 Hz, 1H); 4.92 (d, J = 11.5 Hz, 1H); 4.32 (d, J = 12 Hz, 1H); 4.01 (s, 3H); 3.83–4.04 (m, 6H); 2.84 (m, 1H); 2.00 (m, 4H); 1.63 (m, 4H); 1.23 (s, 3H); 1.14 (t, J = 8 Hz, 3H). Found: M^+ (EI): 543.2682; $C_{33}H_{37}O_6N$. Requires: 543.2621.

2-[Cyano(1-benzyloxy-5-methoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)-cyclohexane-1-carboxylic acid (**25**)

Ester **24** (873 mg, 1.61 mmol) was dissolved in 5 ml of benzene and treated with KOH aq (4.0 ml 1 N). Methanol was added until the mixture became homogeneous (35 ml); water was added until a ppt formed. This mixture was stirred at reflux for 36 hr with the occasional addition of more water and then concentrated and partitioned between Et_2O and 1 N NaOH. The organic soln was extracted with 1 N NaOH (2 ×), and the combined base wash was acidified and extracted with Et_2O (2 ×). This process was repeated, and the organic portions combined and washed with water (2 ×), and with brine and dried ($MgSO_4$). Concentration afforded a tan foam, 758 mg, (91%).

A portion of comparable purity was chromatographed (7:3 benzene/EtOAc): pale oil. IR($CHCl_3$): 2800–3300 (broad), 2230, 1700, 1600 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 8.13 (d, J = 8.8 Hz, 1H); 7.68 (d, J = 8.5 Hz, 1H); 7.45 (m, 8H); 6.87 (d, J = 7.7 Hz, 1H); 5.33 (d, J = 10 Hz 1H); 4.89 (d, J = 10 Hz, 1H); 4.20 (m, 1H); 4.01 (s, 3H); 3.69–3.99 (m, 4H); 2.79–2.99 (m, 2H); 1.41–2.22 (m, 7H); 0.96 (s, 3H). Found: M^+ (EI): 515.2331; $C_{31}H_{33}O_6N$. Requires: 515.2308.

2-[Cyano(1-hydroxy-5-methoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)-cyclohexane-1-carboxylic acid (**26**)

A mixture of **25** (725 mg, 1.41 mmol), $BaCO_3$ (700 mg), and 10% Pd/C catalyst (220 mg, 30%/w) was stirred in 140 ml MeOH under H_2 (1 atm) for 1.5 hr. The mixture was filtered, concentrated, and partitioned between Et_2O and water. The organic portion was washed twice with water and dried ($MgSO_4$). Concentration yielded 573 mg (96%) of a gray foam.

A portion of comparable purity was chromatographed (flash; 1:1 benzene/EtOAc): pale, viscous oil. IR($CHCl_3$): 2900–3500 (broad), 2230, 1700, 1600 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 7.86–8.00 (m, 1H); 7.37–7.68 (m, 4H); 6.85 (m, 1H); 4.64 (m, 1H); 4.00 (s, 3H); 3.61–3.89 (m, 4H); 3.14–3.28 (m, 1H); 2.79–2.90 (m, 1H); 1.68–2.50 (m, 7H); 1.14 and 1.16 (two singlets, 3H). Found: M^+ (EI): 425.1811; $C_{24}H_{27}O_6N$: 425.1838.

2-(1-Hydroxy-5-methoxynaphth-2-yl)methyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylic acid (**27**)

To a stirred soln of Na metal (0.194 g, 8.43 mmol) in about 30 ml freshly distilled NH_3 at −78° was added **25** (384 mg, 0.904 mmol) in 3 ml THF. The blue soln was warmed to −33° and stirred 10 min, then poured into wet Et_2O. The mixture was partitioned between Et_2O and water, and the aqueous layer was *carefully* (possible HCN evolution) acidified with 10% HCl and extracted twice with Et_2O. The organic portions were washed with water (5 ×), dried ($MgSO_4$), and concentrated to give 309 mg (85%) of a light brown foam.

An analytical sample was prepared by chromatography (1:1 benzene/EtOAc) and crystallization (EtOAc, hexane): white crystals, m.p. 166–168°. IR($CHCl_3$): 2900–2500 (broad), 1700, 1600 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 7.71–7.77 (m, 2H); 7.36 (t, J = 8.3 Hz, 1H); 7.19 (d, J = 8.6 Hz, 1H); 6.78 (d, J = 7.4 Hz, 1H); 3.98 (s, 3H); 3.49–3.82 (m, 4H); 2.96 (q, J = 8

Hz, 1H); 2.39–2.61 (m, 3H); 1.60–2.11 (m, 6H); 1.20–1.45 (m, 1H); 1.14 (s, 3H). Found: M^+ (EI): 400.1894; $C_{23}H_{28}O_6$. Requires: 400.1886.

Lactone **28**

(a) *TFA/TFAA conditions.* Phenol-acid **27** (59 mg, 0.15 mmol) was stirred at reflux in 1:1 TFA, TFAA (1.5 ml) for 2 hr under Ar, then stirred at room temp for 12 hr. The soln was cooled, and carefully quenched with $NaHCO_3$ aq, then extracted with EtOAc. The organic solution was washed twice with $NaHCO_3$, twice with water, wtih brine, and dried ($MgSO_4$). Concentration gave 47 mg (94%) of a brown oil. IR($CHCl_3$): 1760, 1705, 1600, 1575 cm^{-1}. Partial NMR($CDCl_3$): δ = 6.77–8.23 (m, 5H); 4.00 (s, 3H); 2.12 (s, 3H).

(b) HF *Conditions.* Phenol-acid **27** (31 mg, 0.076 mmol) was placed in a polyethylene cup, covered with liq HF, and allowed to stand at 0° for 4 hr. Excess HF was evaporated, and the residue was dissolved in EtOAc; this was washed twice with 1 N NaOH aq, once with water, and dried ($MgSO_4$). Concentration yielded 21 mg (82%) of a brown foam.

2-(Methoxynaphthoquinon-2-yl)methyl-4-acetylcyclohexane-1-carboxylic acid (**29**)

Phenol **27** (87 mg, 0.22 mmol) was stirred in 5 ml reagent acetone at room temp. A soln of Fremy's salt (200 mg, 0.87 mmol) and KH_2PO_4 (237 mg, 1.74 mmol) in 7 ml water was added cautiously. After about 20 min, when the TLC showed no starting material, the mixture was diluted with water, saturated with NaCl and KH_2PO_4, and allowed to stand overnight with occasional EtOAc extraction of the soln. After four extractions (over 18 hr), the organic solns were combined, dried ($MgSO_4$), and concentrated to give 80 mg (quantitative yield) of a yellow foam: m.p. (dec) 63–70°. IR($CHCl_3$): 2900–3500 (broad), 1705, 1655, 1585 cm^{-1} NMR($CDCl_3$): δ = 6.76–7.73 (m, 5H); 4.05 (s, 3H); 1.25–2.59 (m, 11H); 2.10 (s, 3H). Found: M^+ (EI): 370.1423; $C_{21}H_{22}O_6$. Requires: 370.1416.

Methyl-2-(1,5-dimethoxy-4-hydroxynaphth-2-yl)methyl-4-acetyl-cyclohexane-1-carboxylate (**30a**) *and methyl-2-(1,4,5-trimethoxynapth-2-yl)methyl-4-acetylcyclohexane- 1-carboxylate* (**30b**)

An EtOAc soln of **29** (65 mg, 0.176 mmol) was reduced with aq hydrosulfite in a separatory funnel over 10 min. After drying ($MgSO_4$), the soln was concentrated to a tan foam. IR($CHCl_3$): 3400 (strong), 2900–3200 (broad), 1700, 1640, 1610 cm^{-1}.

This material was stirred at reflux with (0.12 ml, 1.23 mmol) Me_2SO_4 and K_2CO_3 (239 mg, 1.76 mmol) in acetone for 18 hr. After the addition of water and 1 N NaOH aq, the mixture was stirred 1 hr and diluted with EtOAc. The organic portion was washed with water, $NaHCO_3$ (2 ×), water and brine, and dried ($MgSO_4$). Concentration yielded 61 mg of a yellow oil (**30a** + 30b). This mixture was used in the next step.

Analytical samples were prepared from material of comparable purity by chromatography (flash; 7:1 to 5:1 benzene/EtOAc). *Ester* **30a**: pale semi-solid. IR($CHCl_3$): 3400 (broad), 1725, 1705, 1610 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 9.08 (s, 1H); 7.65 (d, J = 8.4 Hz, 1H); 7.26 (t, J = 8.4 Hz, 1H); 6.78 (d, J = 8.4 Hz, 1H); 6.69 (s, 1H); 4.06 (s, 3H); 3.81 (s, 3H); 3.67 (s, 3H); 2.69 (m, 4H); 2.32 (m, 3H); 1.98 (s, 3H); 1.87 (m, 4H). Found: M^+ (EI): 400.1884; $C_{23}H_{28}O_6$. Requires: 400.1886. Ester **30b**: IR($CHCl_3$): 1725, 1705, 1595, 1580 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 7.63 (d, J = 8.4 Hz, 1H); 7.41 (t, J = 8 Hz, 1H); 6.85 (d, J = 8Hz, 1H); 6.67 (s, 1H); 3.97 (s, 3H); 3.96 (s, 3H); 3.82 (s, 3H); 3.67 (s, 3H); 3.00 (m, 1H); 2.78 (m, 3H); 2.32 (m, 2H); 1.97 (s, 3H); 1.87 (m, 5H). Found: M^+ (EI): 414.2065; $C_{24}H_{30}O_6$. Requires: 414.2040.

8-Acetyl-1,5-dimethoxy-12-hydroxy-11-oxo[6,6a,7,8,9,10,10a,11]-octahydronaphthacene (**31a**) *and 8-acetyl-11-oxo-1,5,12-trimethoxy-[6,6a,7,8,9,10,10a,11]-octahydronaphthacene* (**31b**)

A mixture of **30a** and **30b** (62 mg from the previous experiment) was stirred at reflux with KOH (0.6 ml, 1 N) in 10 ml MeOH and 6 ml water for 15 hr. Additional KOH was then added, and after refluxing 2 hr more, the mixture was concentrated and partitioned between Et_2O and water. The organic portion was washed with water, and the combined aqueous soln was acidified with 10% HCl and extracted twice with Et_2O. The organic soln was washed with water and brine and dried ($MgSC_4$). Concentration yielded 46 mg of a tan foam. IR($CHCl_3$): 2900–3500 (broad), 1700, 1600, 1580 cm^{-1}.

The acid mixture was stirred at reflux for 4 hr under argon in 1:1 TFA, TFAA. The soln was cooled, carefully added to $NaHCO_3$ aq and extracted with Et_2O (2 ×). The combined organic soln was washed with $NaHCO_3$ aq and water, and dried ($MgSO_4$). Concentration gave a dark, viscous oil, which was chromatographed (flash; 5:1–3:2 benzene/EtOAc) to yield 10 mg (0.072 mmol) of **31a**, and 20 mg (0.052 mmol) of **31b** [45% total yield from **29b**. Diketone **31a**: viscous orange oil. IR($CHCl_3$): 1700, 1680, 1615, 1570 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 8.88 (m, 1H); 7.60 (m, 2H); 4.01 (s, 3H); 3.94 (s, 3H), 3.40 (m, 1H); 3.16 (m, 1H); 1.20–2.80 (m, 1H); 2.21 (s, 3H). Found: M^+ (EI): 368.1632; $C_{22}H_{24}O_5$. Requires: 368.1624. *Diketone* **31b**: orange solid, m.p. 86–101°. IR($CHCl_3$): 1700, 1680, 1610, 1555 cm^{-1}. NMR, 250 MHz ($CDCl_3$): δ = 7.64 (d, J = 9 Hz, 1H); 7.49 (t, J = 9 Hz, 1H); 6.85 (d, J = 9 Hz, 1H); 3.99 (s, 3H); 3.91 (s, 3H); 3.85 (s, 3H); 3.40 (m, 1H); 1.28–2.66 (m, 11H); 2.20 (s, 3H). Found: M^+ (EI): 382.1781; $C_{23}H_{26}O_5$. Requires: 382.1780.

7,9,11-Deoxydaunomycinone (**9**)

From diketone **31b**. Diketone (**31b**; 12 mg, 0.031 mmol) was stirred in 5 ml acetone at room temp. Ag(II)O (16 mg, 0.13 mmol) and HNO_3 (0.25 mmol) were added, and the mixture was stirred for 15 min. When the starting material was gone (TLC), the mixture was partitioned between CH_2Cl_2 and water, and the organic portion was washed with water and dried ($MgSO_4$). Concentration gave a yellow-orange solid. IR($CHCl_3$): 1705, 1640, 1585 cm^{-1}. Partial NMR ($CDCl_3$): δ = 7.65 (m, 2H); 7.40 (m, 1H); 3.99 (s, 3H); 2.19 (s, 1H).

The crude product was stirred at 150–160° in DMF for 18 hr, while O_2 was continuously passed through the soln. The soln was cooled, diluted with water, and extracted twice with CH_2Cl_2. The combined organic soln was washed with water (5 ×), dried ($MgSO_4$), and concentrated to give 11 mg, (quantitative yield) of an orange solid.

Chromatography (flash; 4:1 benzene/EtOAc) yielded 5 mg (45%) of an orange powder, which was recrystallized from benzene, m.p. 225–228° (lit[5] 223–226°, lit[2b] 222–225°). The material was identical in all respects to authentic **9**,[18] mixed m.p. 225–228°.

From diketone **31a**. The same procedure converted 10 mg (0.027 mmol) of diketone **31a** to 9.5 mg (94%) of a red tar. Flash chromatography afforded 3 mg (32%) of an orange powder, m.p. 224–227°. IR, NMR, TLC identical with those of authentic **9**.[18]

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