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ANTHRAQUINONE DYE INTERMEDIATES AS PRECURSORS OF AKLAVINONE-TYPE ANTHRACYCLINONES

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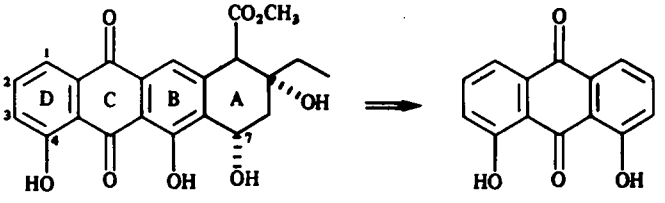
Abstract—The commercially available dye intermediates 1-hydroxyanthraquinone, 1-amino-2-methylanthraquinone and 1,8-dihydroxyanthraquinone (chrysazin) have been elaborated in a regiospecific manner into tetracyclic ketonitriles. The latter are potential precursors of the anthracycline aglycone aklavinone and its 4-deoxy analog.[1]

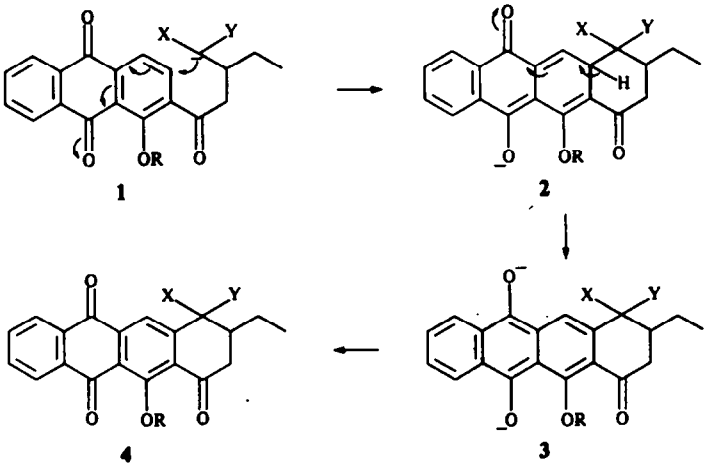
Examination of the anthracycline aklavinone (and its 4-deoxy analog) reveals that the aromatic nucleus of the complex structure is that of a simple hydroxyanthraquinone. We decided to explore the practicality of employing simple hydroxyanthraquinones as starting materials in the synthesis of important anthracycline aglycones such as aklavinone. Our basic idea was to graft a suitably functionalized A-ring onto a cheap, available anthraquinone, using as a key step an anionic aromatic substitution reaction onto the electron deficient anthraquinone system.[2] Our paper describes approaches to the model system 4-deoxyaklavinone, as well as the naturally derived aglycone aklavinone.[3] We begin by discussing our 4-deoxyaklavinone strategy.



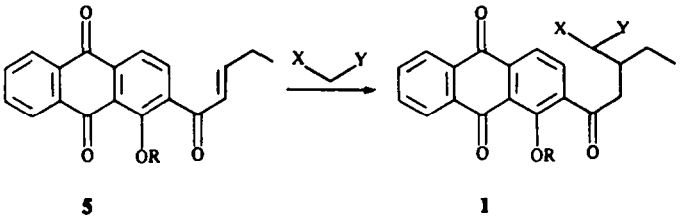
aklavinone chrysazin

Our basic idea was to incorporate a suitably functionalized side-chain onto an anthraquinone which could generate an anion capable of attacking the electron deficient anthraquinone nucleus to give, after tautomerization (or proton abstraction) the intermediate hydroquinone (3) which we felt could be easily oxidized to the aklavinone-related structure (4).

We chose as our key intermediate, the enone (5). We felt that a carbonyl at C_7 would not only provide the latent C_7 OH group, but also increase the susceptibility of the anthraquinone nucleus to nucleophilic attack. Furthermore, the desired intermediate (1) should be available *via* Michael addition of an activated methylene compound to the enone (5). We chose 1-hydroxy-anthraquinone as our first starting material because of its ease of manipulation, ready availability and the prospect of synthesizing a 4-deoxyanthra-



Scheme 1.



5 1

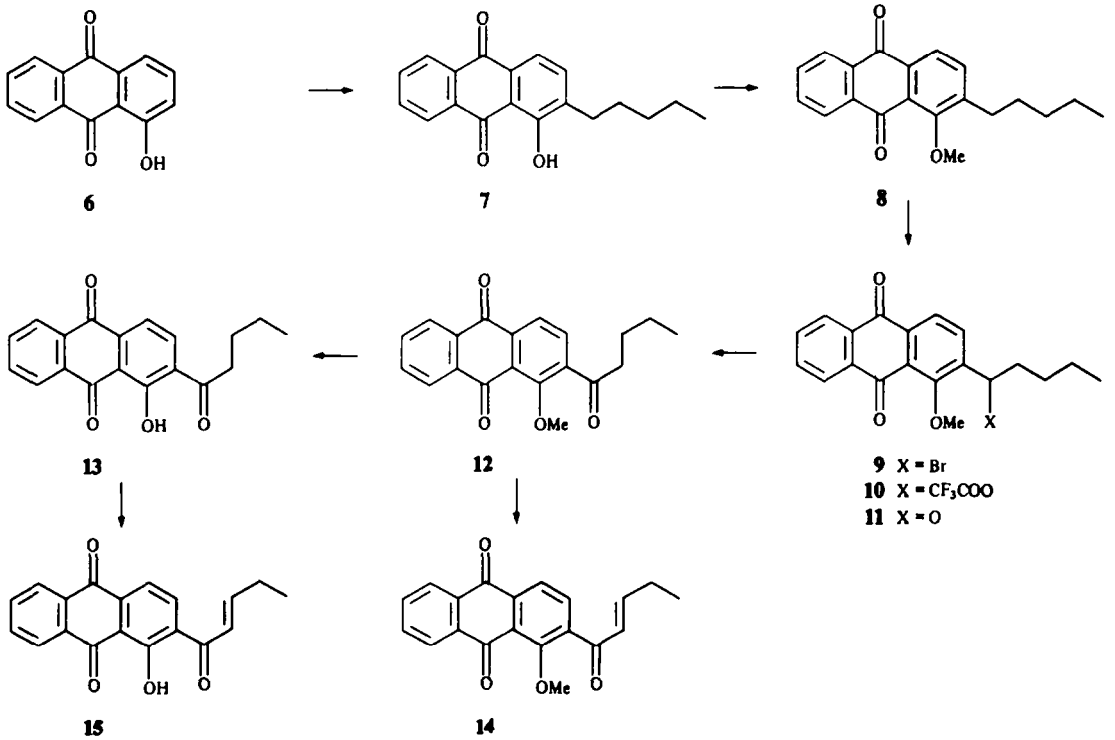
Scheme 2.

cycline. 1-Hydroxyanthraquinone (6) was subjected to a Marshalk alkylation using n-valeraldehyde to give, in 38% yield, 1-hydroxy-2-pentylanthraquinone (7).[4] Following protection of the OH group as a methyl ether (8), benzylic bromination was achieved with N,N-dibromo-5,5-dimethylhydantoin (DBH).[5] Treatment of the bromide (9) with AgO_2CCF_3 followed by basic hydrolysis of the ester (10) and oxydation of the alcohol (11) with PCC gave the ketone (12) in 25% overall yield from 6. Phenylselenation of the methoxyketone (12) and the derived hydroxyketone (13) gave, after formation of the selenides (12a and 13a) and elimination, the enones (14 and 15) respectively.[6]

Recently, we have developed an alternate and improved procedure for the synthesis of ketone 12. Diazotization of the commercially available amino anthraquinone (16) with nitrosyl sulfuric acid and decomposition of the resulting diazonium salt gave the hydroxyanthraquinone (17). Methylation with dimethyl sulfate in acetone gave the methyl ether (18), which afforded the pure monobromide (19) on treatment with DBH in 84% overall yield from 16.[5] The bromide (19) was converted quantitatively into the phosphonium bromide with triphenylphosphine in n-butyl acetate; conversion to the phosphonium fluoroborate (20) was achieved by precipitation from a methanolic solution with HBF_4. The ylid, which formed with dimsyl sodium, reacted with butyraldehyde to provide the *trans* olefin (21) in 80% yield.[7] The desired ketone (12) was obtained by regiospecific hydroboration of the olefin (directed by the OMe group) and direct chromic acid oxidation.[8]

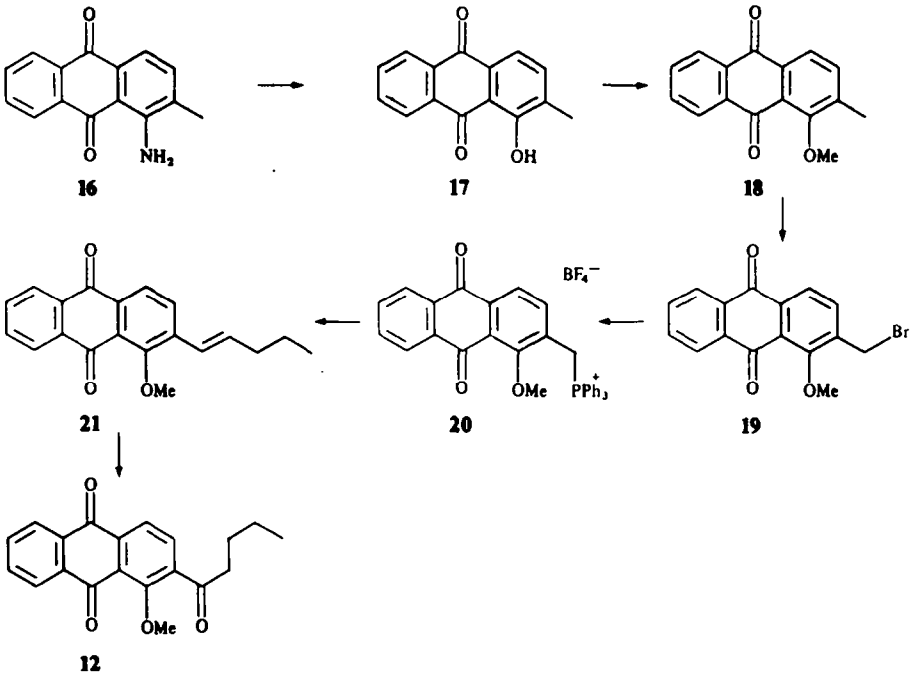
Michael addition of t-butyl cyanoacetate to the methoxyenone (14) led directly to a single isomer of the 1,2-benzanthraquinone (22) in 73% yield. Formation of 22 can be explained by addition of the anion of the Michael adduct (23) to an α-position of the anthraquinone system, followed by expulsion of a methoxide ion.

A similar Michael addition of t-butyl cyanoacetate to the hydroxy enone (15) which bears an extremely poor leaving group on the α-position, afforded only the expected Michael adduct (24) after 1 hr. However, after 6 hr, the desired β-cyclization product (25) was

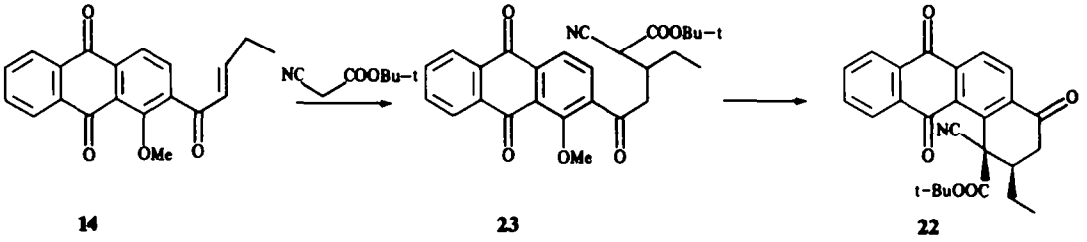


9 X = Br
10 X = CF_3COO
11 X = O

Scheme 3.



Scheme 4.



Scheme 5.

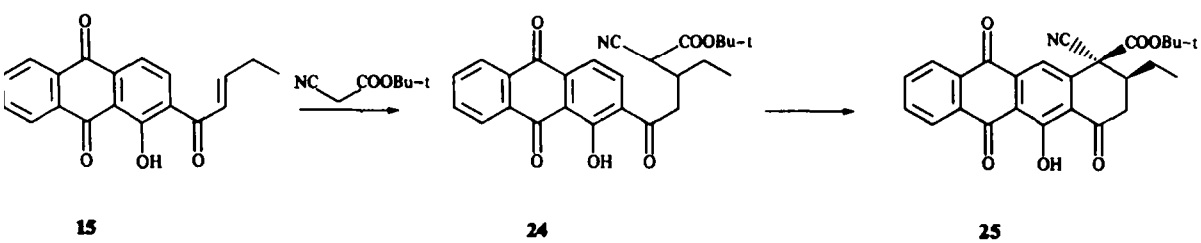
obtained as a single isomer in 75% yield. The use of methyl cyanoacetate provided an analogous cyclization product (**26**) in poor yield.

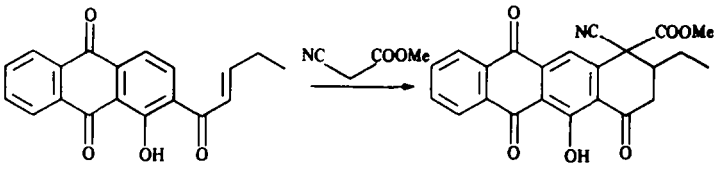
Acid catalyzed hydrolysis of the ester (**25**) led directly to the cyanoketone (**27**) by decarboxylation of the acid. Reduction of this ketone (**27**) with $NaBH_3CN$ provided the alcohol (**28**). Alternatively, a protected form of **27** could be obtained by treatment of the cyclization product (**25**) with propanedithiol, trimethylsilyl triflate and trimethylsilyl chloride to give the dithioketal (**29**).

To our knowledge, the formation of **22** from **14** involves the first case of *ipso* substitution on an anthraquinone by a nucleophilic carbon other than cyanide. Of more significance, the formation of the cyclization product (**25**) illustrates a new methodology for the annulation of anthraquinones. Studies are underway in our laboratory to use this methodology for the synthesis of 4-deoxyaklavinone.

1,8-Dihydroxyanthraquinone (chrysazin, **30**) was a convenient starting material for our anthraquinone-based approach to aklavinone. We envisioned the enone (**31**) and the tetracyclic nitrile (**32**) as key intermediates in our strategy. Conversion of 1,8-dihydroxyanthraquinone to the enone (**31**) was carried out as follows.

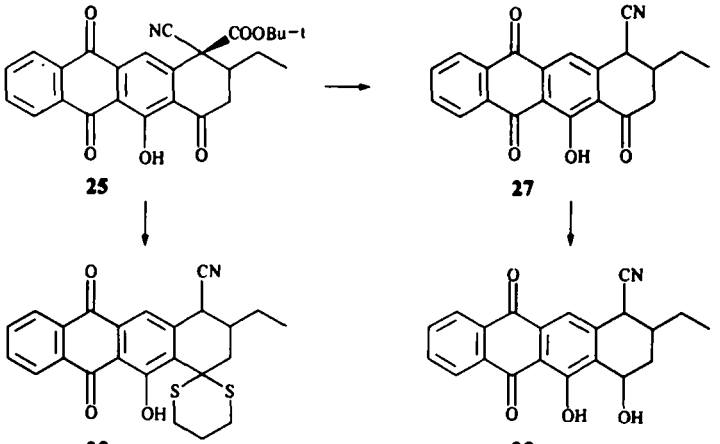
The selective protection of one of the hydroxyls of





15 26

Scheme 6.



25 27 29 28

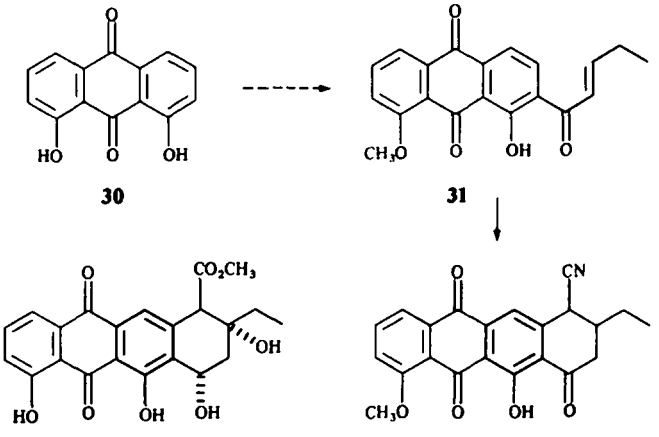
Scheme 7.

chrysazin was accomplished by a procedure employed by Mitscher in the aloe-emodin series.[10] The 1,8-dihydroxyanthraquinone was heated in Ac_2O with dissolved $B(OH)_3$, and thereby selectively acetylated through the intermediacy of a boroacetate protecting group.

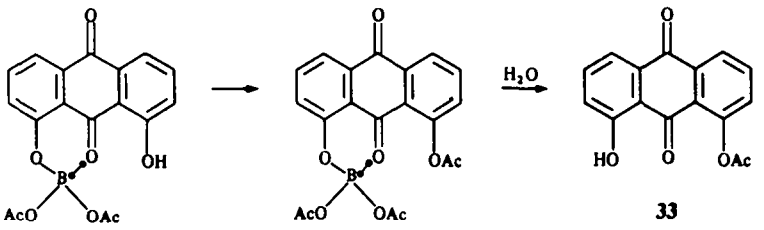
The monoacetate (33) was methylated using dimethyl sulfate and K_2CO_3 in refluxing acetone. Workup by heating in aqueous base hydrolyzes the acetate to give 1-hydroxy-8-methoxyanthraquinone (34) in 90% overall yield.

The formation of a pure substituted allylic ether such as 35 proved to be a problem in earlier anthraquinone syntheses.[11] Alkylations using bromides more complicated than allyl bromide gave low yields due to substitution at both α and β positions. The Mitsunobu-type alkylation reaction totally eliminated this problem, as ether (35) was obtained pure in 87% yield using 1-penten-3-ol.[12]

The reaction was carried out using diethyl azodicarboxylate and triphenylphosphine in THF (0° to RT). Claisen rearrangement of ether (35) could be accomplished by two different methods. The rearrangement was initially carried out in 85% yield by heating in



30 31 aklavinone 32



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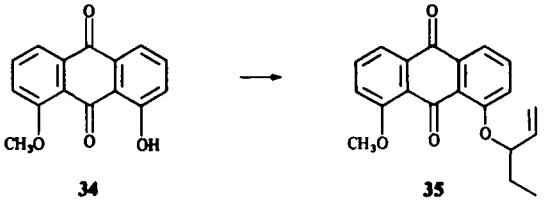


34 35

N,N-dimethylaniline at 170° for 1 hr. The superior methodology involved the reductive conditions of Roberts and Rutledge ($Na_2S_2O_4$, DMF–H_2O 1:1) which allowed the rearrangement to proceed smoothly and cleanly at 50–70° for 1–2 hr in 87–90% yield.[13]

Attempts to convert the Claisen rearrangement product (**36**) to the corresponding enone (**31**) directly by oxidation or by bromination/hydrolysis/oxidation sequence proved futile.

Isomerization of the double bond in the Claisen product side-chain from the 2-position to the conjugated 1-position was accomplished best using transition metal catalysis. The catalyst $PdCl_2(PhCN)_2$ (30 g/1 g cat] in refluxing benzene moved the double bond in ~81% yield.[14] A better catalyst proved to be $RhCl_3 \cdot 3H_2O$ in refluxing ethanol [100 g/1 g cat] which caused isomerization in >90% yield giving pure product (**37**).[15] Various bases were employed to isomerize the olefin but yields were poor and product mixtures resulted.

Various additions were carried out regioselectively across the conjugated alkene (**37**) in approaches to the enone (**31**). The addition of the elements [O, S], [O, Se] and [O, Br] were accomplished regioselectively as follows.[16,17]

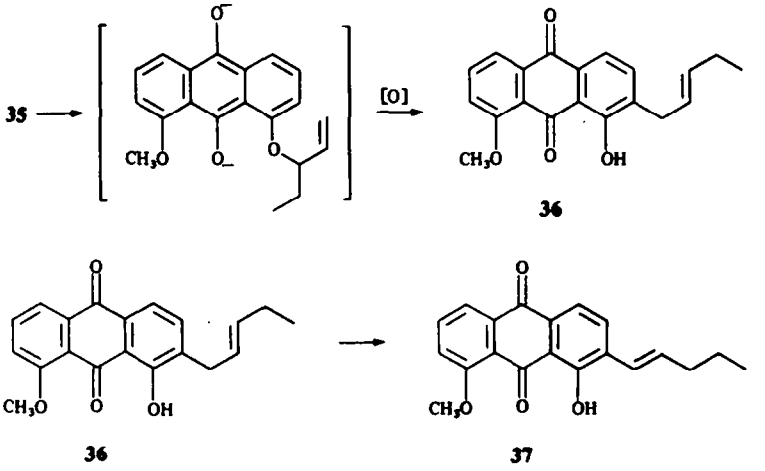
We found the bromohydrin easiest to elaborate to the required enone. Hydroxyalkene (**37**) was first protected as its methyl ether derivative (**38**), then treated with NBS in H_2O/acetone (1:1) to yield the bromohydrin (**39**) in 79% yield. The bromohydrin (**39**) was oxidized in near quantitative yield to the bromoketone with the Jones Reagent. The methoxy *ortho* to the alkyl side chain was selectively deprotected with $AlCl_3$ in CH_2Cl_2 in ~89% yield. The hydroxy bromoketone (**40**) was then converted to the enone (**31**) via two similar methodologies.

The bromide could be displaced from **40** using NaSePh in EtOH/THF mixture in high yield to give the α-selenoketone which could be converted to the enone in one step with MCPBA through the intermediacy of a selenoxide which eliminates pyrolytically at room temperature. The enone was obtained from the bromide in 83% yield for the two steps.

The sulfur analog of this procedure involved displacing the bromide from **40** with NaSPh using phase-transfer conditions (PhSH, NaOH, benzene-H_2O, catalyst) in ~90% yield. The corresponding sulfide (**41**) was oxidized to a sulfoxide using $NaIO_4$ in HOAc/H_2O mixture in good yield.[18]

The sulfoxide was pyrolysed to enone (**31**) in high yield by heating in CCl_4 at 70° for 3 hr.[19]

The key step in our approach was a tandem Michael-vicarious aromatic substitution ring closure. Vicarious aromatic substitutions have been studied in simple aromatic systems, but appear to have been no use in natural product synthesis.[20] This was carried out most auspiciously using $PhSCH_2CN$ as Michael donor and dimsyl sodium-DMSO as base-solvent system. The hydroxyenone (**31**) was added dropwise as a DMSO solution to the preformed anion (3.5 eq. $NaCH_2SOCH_3$—DMSO) and the solution allowed to



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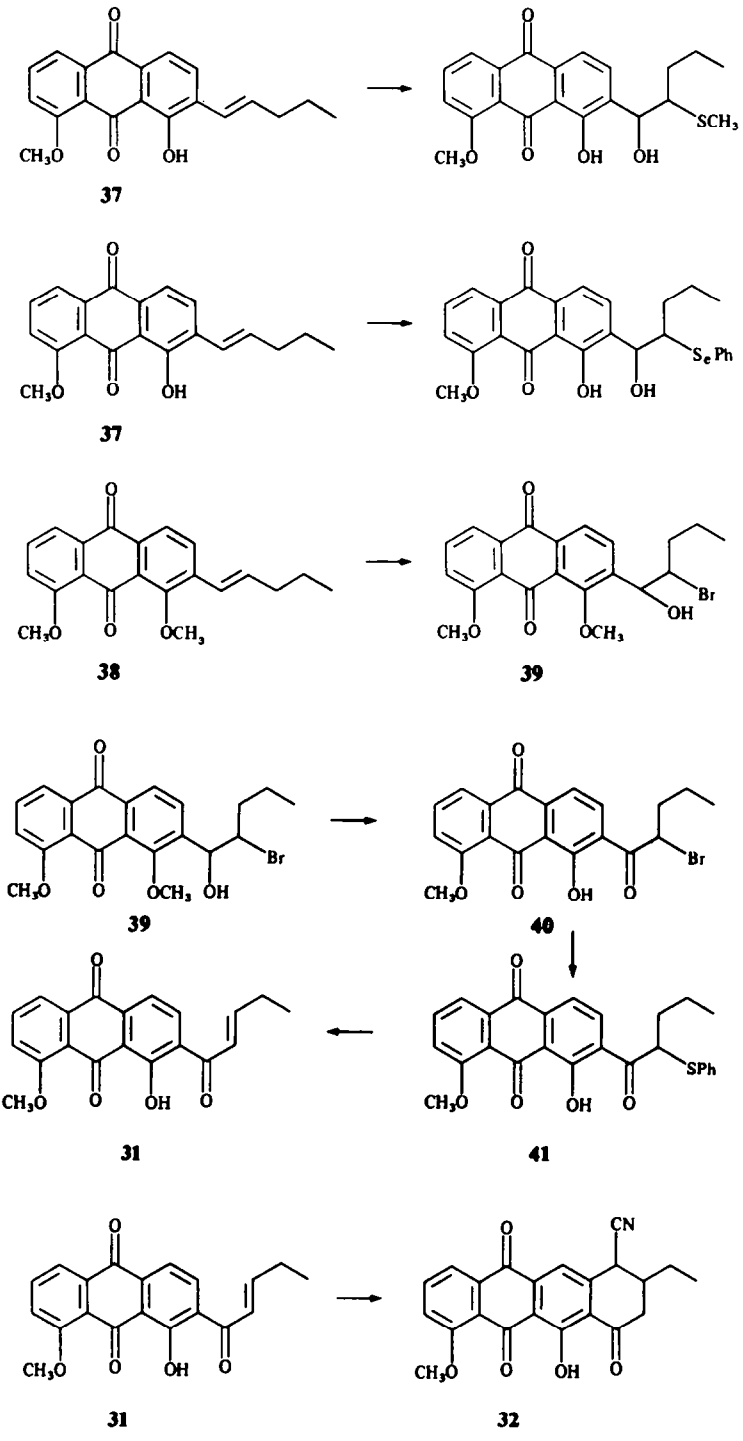

stir at room temperature for approx 2 hr. The mixture was neutralized with HOAc, diluted with CH_2Cl_2, washed with H_2O, and column chromatographed on silica gel to yield crystalline (**32**; m.p. 138–140°) in 83% yield. This tetracyclic ketone-nitrile, obtained in 22% overall yield from chrysazin, contains much useful functionalization in the A-ring. Studies on the conversion of this intermediate to aklavinone are presently underway in our laboratories.

EXPERIMENTAL

M.ps were determined on a Thomas–Hoover apparatus and are uncorrected. Mass and IR (KBr) spectra were determined by using Perkin–Elmer 270B and 137 spectrometers, respectively. NMR spectra were recorded on a Bruker 250 FT machine with $CDCl_3$ solns containing Me_4Si as an internal standard and are reported in δ units (J values are in hertz). Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed and dried over

anhydrous Na_2SO_4 prior to filtration and evaporation. All solvents were dried prior to use.

1-Hydroxy-2-pentylanthraquinone (**7**)

To a soln of **6** (5.0 g, 22 mmol) dissolved in 1.5% NaOH (300 ml) under N_2 at 60° was added sodium hydrosulfite (10.0 g, 57 mmol) and the temp raised to 75°. After 15 min a soln of n-valeraldehyde (8.1 g, 94 mmol) in EtOH (10 ml) was added dropwise and the temp increased to 90°. After 1 hr the mixture was cooled, air bubbled through it for 30 min and then acidified with 10% HCl. The soln was heated for 20 min on a steam bath and the green product filtered off, washed neutral, dried, and chromatographed (silica gel, CH_2Cl_2). Recrystallization from EtOH afforded orange needles of **7** (2.6 g, 38%): m.p. 102–104°; ^{1}H-NMR ($CDCl_3$) 0.89–0.94 (t, 3H, J = 7 Hz), 1.34–1.42 (m, 2H), 1.60–1.71 (m, 2H), 2.73–2.79 (t, 2H, J = 7 Hz), 7.52–7.83 (m, 4H), 8.27–8.34 (m, 2H), 13.00 (s, 1H). (Found: C, 77.74; H, 5.95. Calc for $C_{19}H_{18}O_3$: C, 77.55; H, 6.12%).

1-Methoxy-2-pentylanthraquinone (**8**)

A suspension of **7** (1 g, 3.4 mmol), K_2CO_3 (8 g, 5.8 mmol) and methyl-*p*-toluenesulfonate (10 g, 54.0 mmol) in DMF (25 ml) and 2-butanone (25 ml) was refluxed for 2.5 hr. The cooled mixture was then poured into water, the ppt filtered off, washed and dried. The product was chromatographed (neutral alumina, CH_2Cl_2) to afford **8** (0.8 g, 76%) as a pale yellow solid after recrystallization from EtOH: m.p. 88–91°; ^{1}H-NMR ($CDCl_3$) 0.90–0.94 (t, 3H, J = 7 Hz), 1.35–1.44 (m, 2H), 1.62–1.72 (m, 2H), 2.74–2.81 (t, 2H, J = 7 Hz), 3.94 (s, 3H), 7.60–7.63 and 8.07–8.10 (AB q, 2H, J = 8.25 Hz), 7.72–7.82 (m, 2H), 8.23–8.30 (m, 2H). (Found: C, 77.71; H, 6.66. Calc for $C_{20}H_{20}O_3$: C, 77.92; H, 6.49%).

2-(1'-Bromopentyl)-1-methoxyanthraquinone (**9**)

A suspension of **8** (160 mg, 0.52 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (130 mg, 0.45 mmol) in CCl_4 (10 ml) was refluxed for 3 hr. The reaction was then cooled, the solvent evaporated and the residue chromatographed (silica gel, CH_2Cl_2) to give **9** (115 mg, 57%) as yellow needles after recrystallization from EtOH: m.p. 93–96°; ^{1}H-NMR ($CDCl_3$) 0.88–0.93 (t, 3H, J = 7 Hz), 1.24–1.61 (m, 4H), 2.09–2.18 (m, 1H), 2.20–2.36 (m, 1H), 4.04 (s, 3H), 5.58–5.64 (t, 1H, J = 7 Hz), 7.74–7.85 (m, 2H), 7.95–7.98 and 8.17–8.20 (AB q, 2H, J = 8.25 Hz), 2.84–8.31 (m, 2H). (Found: C, 62.21; H, 5.01; Br, 20.90. Calc for $C_{20}H_{19}BrO_3$: C, 62.02; H, 4.91; Br, 20.67%).

1-Methoxy-2-(1'-oxopentyl)anthraquinone (**12**)

(a) *From the bromide* (**9**). To a soln of **9** (2.8 g, 7.4 mmol) in trifluoroacetic acid (15 ml) was added silver trifluoroacetate (2.2 g, 9.9 mmol). After 30 min the solvent was evaporated, $CHCl_3$ added and the insoluble salts filtered off. Following evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 ml) and stirred for 1.5 hr with PCC (2.0 g, 9.3 mmol). Ether (50 ml) was then added and the soln filtered through florisil. Evaporation of the solvent followed by chromatography of the residue (silica gel, CH_2Cl_2) afforded **12** (1.4 g, 58%) as fine yellow needles after recrystallization from EtOH: m.p. 80–82°; ^{1}H-NMR ($CDCl_3$) 0.90–0.96 (t, 3H, J = 7 Hz), 3.96 (s, 3H), 7.76–7.86 (m, 3H), 8.16–8.31 (m, 3H). (Found: C, 74.39; H, 5.70. Calc for $C_{20}H_{18}O_4$: C, 74.53; H, 5.59%).

(b) *From the olefin* (**21**). To a soln of BH_3 · THF (42 ml, 0.97 M) under N_2 at 0° was added a soln of **21** (5 g, 16.3 mmol) in THF over 10 min. The soln was allowed to warm to room temp and stirring continued for 2.5 hr. Excess hybrid was decomposed at 0° by careful addition of H_2O. A soln of sodium dichromate (21 g) in H_2SO_4 (17 ml) and H_2O (209 ml) was then added and the mixture refluxed for 2 hr. Upon cooling the reaction mixture was poured into a large volume of water and the yellow product filtered off, washed and dried. Recrystallization from EtOH afforded **12** (3.8 g, 73%) as a yellow solid solid identical in all respects to the ketone prepared from **9**.

1-Methoxy-2-(1'-oxo-2'-selenophenylpentyl)anthraquinone (**12a**)

To a soln of **12** (0.71 g, 2.2 mmol) in EtOAc (20 ml) under N_2 was added phenylselenenyl chloride (0.51 g, 2.6 mmol) and HCl (conc 3 drops). After 24 hr the soln was washed neutral with water and dried over Na_2SO_4. The solvent was evaporated and the residue chromatographed (silica gel, CH_2Cl_2) to give **12a** as yellow needles (0.60 g, 82%) after recrystallization from EtOH: m.p. 100–103°; ^{1}H-NMR ($CDCl_3$) 1.04–1.10 (t, 3H, J = 7 Hz), 1.58–1.72 (m, 2H), 1.84–1.93 (m, 1H), 2.04–2.13 (m, 1H), 3.94 (s, 3H), 4.64–4.70 (t, 1H, J = 7 Hz), 7.18–7.41 (m, 5H), 7.76–7.87 (m, 2H), 7.90–7.93 and 8.14–8.17 (AB q, 2H, J = 8.25 Hz), 8.18–8.29 (m, 2H). (Found: C, 65.50; H, 4.70; Se, 17.00. Calc for $C_{26}H_{22}O_4Se$: C, 65.27; H, 4.60; Se, 17.73%).

1-Hydroxy-2-(1'-oxo-2'-selenophenylpentyl)anthraquinone (**13a**)

Using the same procedure as for **12a**, **13a** was obtained in quantitative yield from **13**: m.p. 98–98.5°; ^{1}H-NMR ($CDCl_3$) 0.97–1.03 (t, 3H, J = 7.15 Hz), 1.51–1.58 (m, 2H), 1.63–1.76 (m, 1H), 1.79–2.02 (m, 1H), 4.99–5.05 (t, 1H, J = 7.15 Hz), 7.15–7.37 (m, 5H), 7.83–7.88 (m, 3H), 8.12–8.16 (m, 1H), 8.29–8.34 (m, 2H), 13.6 (s, 1H). (Found: C, 64.98; H, 4.34; Se, 16.93. Calc for $C_{25}H_{20}O_4Se$: C, 64.80; H, 4.32; Se, 17.05%).

1-Hydroxy-2-(1'-oxopentyl)anthraquinone (**13**)

To a well stirred soln of **12** (0.35 g, 1.1 mmol) in CH_2Cl_2 was added anhyd $AlCl_3$ (0.50 g, 3.7 mmol). After stirring for 24 hr the solvent was removed, and THF (0.5 ml) and 10% HCl (10 ml) added. After stirring for 3 hr the product was filtered off, washed and dried to afford **13** (0.25 g, 83%) as yellow needles after recrystallization from EtOH: m.p. 125–126°; ^{1}H-NMR ($CDCl_3$) 0.92–0.98 (t, 3H, J = 7.0 Hz), 1.34–1.46 (m, 2H), 1.69–1.77 (m, 2H), 3.10–3.16 (m, 2H), 8.27–8.34 (m, 2H), 13.59 (s, 1H). (Found: C, 73.93; H, 5.23. Calc for $C_{19}H_{16}O_4$: C, 74.03; H, 5.19%).

1-Hydroxy-2-methylanthraquinone (**17**)

To a well stirred soln of **16** (26 g, 0.11 mmol) in H_2SO_4 (120 ml) at 5° was added a soln of nitrosylsulfuric acid (24 ml, 5.0419 M in 87% H_2SO_4) over 30 min. The mixture was stirred at room temp for 3 hr and then slowly heated to 100°. After nitrogen evolution ceased (2 hr) the cooled soln was poured onto ice and the yellow crystals filtered off, washed neutral with water and dried. Recrystallization from DMF afforded **17** as yellow needles (22 g, 85%): m.p. 181–182° (lit. 4 182–183°).

1-Methoxy-2-methylanthraquinone (**18**)

To a soln of **17** (14 g, 59 mmol) and finely ground anhyd K_2CO_3 (7 g, 85 mmol) in refluxing acetone (265 ml) and 2-butanone (265 ml) was added Me_2SO_4 (14 ml, 147 mmol) dropwise over 1 hr. After approximately one half of the Me_2SO_4 was added, an additional portion of K_2CO_3 (7 g, 85 mmol) was added. After 3 hr the mixture was cooled, poured into 10% NaOH and the orange ppt filtered off, washed neutral with water and dried. Recrystallization from DMF gave **18** (14 g, 95%) as golden needles: m.p. 162–164° (lit. 5*a* 164–165°); ^{1}H-NMR ($CDCl_3$) 2.417 (s, 3H), 3.921 (s, 3H). 7.57–7.60 and 8.01–8.04 (AB q, 2H, J = 8 Hz), 7.72–7.77 (m, 2H), 8.23–8.27 (m, 2H).

2-Bromomethyl-1-methoxyanthraquinone (**19**)

To a well stirred refluxing soln of **18** (14 g, 56 mmol) in dry CCl_4 (170 ml) was added 1,3-dibromo-5,5-dimethylhydantoin (DBH) (4.4 g, 15 mmol) and dibenzoylperoxide (0.10 g). After 0.5 hr an additional portion of DBH (4.4 g, 15 mmol) was added followed by dibenzoylperoxide (0.10 g). After 3.5 hr the reaction was cooled to room temp, the solvent evaporated and the crystalline mass triturated with water. Filtration of the product and recrystallization from AcOH afforded **19** as yellow needles (17 g, 93%): m.p. 188–189° (lit. 15*a* 194–195.5°); ^{1}H-NMR ($CDCl_3$) 4.00 (s, 3H), 4.60 (s, 2H), 7.72–7.90 (m, 3H), 8.00–8.30 (m, 3H).

[2-(1-Methoxyanthraquinonyl)methyl]triphenylphosphonium fluoborate (**20**)

To a stirred soln of **19** (12.9 g, 39 mmol) in n-butylacetate (130 ml) at 100° was slowly added triphenylphosphine (17.6 g, 67 mmol). After 5 min the reaction was cooled to room temp and the yellow crystals filtered off and subsequently dissolved in MeOH (90 ml). Addition of fluoboric acid (20 ml) precipitated the phosphonium salt (**20**) as yellow needles (27.3 g, 97%) which were filtered, washed with ether and dried. (Found: C, 69.56; H, 4.37. Calc for $C_{33}H_{24}BF_4O_3P$: C, 69.51; H, 4.21%).

1-Methoxy-2-(pent-1'-enyl)anthraquinone (**21**)

To a soln of dimsyl sodium (prepared from NaH (50%, 0.42 g, 8.8 mmol) in DMSO (10 ml) under N_2), was added a soln of the phosphonium salt (**20**) (5 g, 8.3 mmol) in DMSO (10 ml). After 10 min, n-butylaldehyde (0.81 ml, 9.2 mmol) was added and the reaction heated at 60° for 45 min. The cooled mixture was extracted with CH_2Cl_2, washed with brine and then water. The solvent was evaporated and residue chromatographed (silica gel, CH_2Cl_2) to afford **21** (2.55 g, 80%) as yellow crystals from EtOH: m.p. 114–116°; ^{1}H-NMR ($CDCl_3$) 0.95–1.10 (t, 3H, J = 7.7 Hz), 1.51–1.59 (m, 2H), 2.25–2.34 (q, 2H, J = 7 Hz), 3.92 (s, 3H), 6.42–6.48 (m, 1H), 6.81–6.81 (d, 1H, J = 15.9 Hz), 7.74–7.78 (m, 2H), 7.85–7.88 and 8.07–8.01 (AB q, 2H, J = 8.25 Hz), 8.22–8.38 (m, 2H). (Found: C, 78.29; H, 5.94. Calc for $C_{20}H_{18}O_3$: C, 78.43; H, 5.88%).

1-Methoxy-2-(1'-oxopent-2'-enyl)anthraquinone (**14**)

To a well stirred soln of **12a** (0.50 g, 1.1 mmol) in CH_2Cl_2 (15 ml) and sat Na_2HPO_4 (30 ml) was added 70% *m*-chloroperbenzoic acid (0.53 g, 2.2 mmol) over 30 min in small portions. After 1.5 hr the phases separated and the organic layer washed successively with 10% Na_2SO_3, sat $NaHCO_3$ aq and then water. Evaporation of the solvent and recrystallization from EtOH gave **14** (0.24 g, 70%) as shiny yellow plates: m.p. 105–109°; ^{1}H-NMR ($CDCl_3$) 1.07–1.13 (t, 3H, J = 7 Hz), 2.29–2.35 (m, 2H), 3.93 (s, 3H), 6.58–6.65 (m, 1H). 6.83–6.92 (m, 1H), 7.74–7.86 (m, 3H), 8.18–8.3 (m, 3H). (Found: C, 74.98; H, 5.09. Calc for $C_{20}H_{16}O_4$: C, 75.00; H, 5.00%).

1-Hydroxy-2-(1'-oxopent-2'-enyl)anthraquinone (**15**)

The enone **15** was prepared from **13a** in 89% yield using the same procedure as for the conversion of **12a** to **14**: m.p. 116–120°; ^{1}H-NMR ($CDCl_3$) 1.12–1.18 (t, 3H, J = 7.70 Hz), 2.34–2.39 (m, 2H), 6.84–6.91 (m, 1H), 7.05–7.44 (m, 1H), 7.81–7.96 (m, 3H), 8.25–8.30 (m, 3H), 13.34 (s, 1H). (Found: C, 74.39; H, 4.56. Calc for $C_{19}H_{14}O_4$: C, 74.50; H, 4.58%).

1-t-Butoxycarbonyl-1-cyano-2,3-dihydro-2-ethyl-4-ketobenz[a]anthra-7,12-quinone (**22**)

To a suspension of NaH (50%, 30 mg, 0.63 mmol) in DMF (1 ml) under N_2 was added t-butyl cyanoacetate (0.80 g, 8.85 mmol). After 15 min a soln of **14** (0.10 g, 0.31 mmol) in DMF (2 ml) was added. After 14 hr the mixture was exposed to air and then quenched with dilute HOAc. The product was extracted with CH_2Cl_2, washed, dried and chromatographed (silica gel, CH_2Cl_2) to give after recrystallization from EtOH **22** as a yellow green solid (90 mg, 73%); m.p. 202–204°; ^{1}H-NMR ($CDCl_3$) 1.03–1.09 (t, 3H, J = 7 Hz), 1.56 (s, 9H), 1.62–1.64 (m, 1H), 2.20–2.2 (m, 1H), 2.55–2.57 (m, 1H), 2.84–3.09 (m, 2H), 7.83–7.86 (m, 2H), 8.27–8.32 (m, 2H), 8.52–8.59 (AB q, 2H, J = 8.25 Hz). (Found: C, 72.52; H, 5.39; N, 3.29. Calc for $C_{26}H_{23}NO_3$: C, 72.72; H, 5.36; N, 3.26%).

2-(3'-t-Butoxycarbonylmethyl-3'-cyanomethyl-1'-oxopentyl)-1-hydroxyanthraquinone (**24**)

To a suspension of NaH (50%, 32 mg, 0.67 mmol) in DMF (1 ml) under N_2 was added t-butyl cyanoacetate (0.5 g, 3.5 mmol). After 15 min a soln of **15** (70 mg, 0.23 mmol) was added and after 1 hr the reaction was quenched by pouring onto ice and HOAc. The soln was extracted with CH_2Cl_2 and washed neutral with water. The solvent was evaporated and the residue chromatographed (silica gel, hexane/EtOAc (3:1)) to afford the Michael adduct **24** (55 mg, 53%) as a mixture of isomers. Recrystallization from MeOH afforded golden yellow needles: m.p. 127–131°; ^{1}H-NMR ($CDCl_3$) 0.99–1.05 (two t, 3H, J = 7.15), 1.50 and 1.53 (s, 9H), 2.80–2.85 (m, 1H), 3.23–3.50 (m, 2H), 3.74–3.75 and 3.95–3.97 (d, 1H, J = 3.85 Hz, 4.40 Hz), 7.85–7.89 (m, 3H), 8.13–8.38 (m, 3H), 13.71 and 13.78 (two s, 1H); high resolution mass spectrum *m/e* 447.1650 (calc for $C_{26}H_{25}NO_6$: 447.1674).

1-t-Butoxycarbonyl-10-cyano-8,9-dihydro-9-ethyl-6-hydroxy-7-oxo-5,12-naphthacenedione (**25**)

To a soln of dimsyl sodium (prepared from NaH (50%, 0.15 g, 3.3 mmol) and DMSO (20 ml) under N_2) was added t-butyl cyanoacetate (0.23 ml, 1.6 mmol). After 15 min the solid **15** was added and the purple mixture stirred for 2.5 hr. The mixture was then exposed to air for 5 min and poured onto ice and HOAc. Extraction with CH_2Cl_2 and brine followed by washing, drying and removal of the solvent gave a red oil which was chromatographed (silica gel, CH_2Cl_2/EtOAc (4:1)) to afford the desired product **25** (0.49 g, 67%) after recrystallization from MeOH: m.p. 157–159° (dec); ^{1}H-NMR ($CDCl_3$) 1.05–1.11 (t, 3H, J = 7.7 Hz), 1.63 (s, 9H), 1.73–1.81 (m, 2H), 2.75–2.84 (m, 2H), 2.96–3.05 (m, 1H), 7.83–7.88 (m, 2H), 7.91 (s, 1H), 8.26–8.36 (m, 2H), 14.02 (s, 1H). (Found: C, 69.93; H, 5.29; N, 3.02. Calc for $C_{26}H_{23}NO_6$: C, 70.11; H, 5.17; N, 3.15%).

1-Carbomethoxy-10-cyano-8,9-dihydro-9-ethyl-6-hydroxy-7-oxo-5,12-naphthacenedione (**26**)

Using the same experimental conditions for the anionic cyclization converting **15** to **25**, the reaction of methyl cyanoacetate with **15** provided **26** in 11% yield: m.p. 195–196°; ^{1}H-NMR ($CDCl_3$) 1.03–1.09 (t, 3H, J = 7.5 Hz), 1.53–1.66 (m, 2H), 2.77–2.83 (m, 2H), 2.99–3.05 (m, 2H), 4.01 (s, 3H), 7.80 (s, 1H), 7.84–7.88 (m, 2H), 8.27–8.36 (m, 2H), 14.02 (s, 1H); high resolution mass spectrum *m/e* 403.1042 (calc for $C_{23}H_{17}NO_6$: 403.1056).

Synthesis of ketonitrile (**27**)

A soln of **25** (0.50 g, 1.1 mmol) in HOAc (350 ml) containing H_2SO_4 (3 drops) was refluxed under N_2 for 0.5 hr. The soln was cooled to room temp and pyridine (10 drops) was added. The mixture was then concentrated, extracted with CH_2Cl_2 and washed with brine and then water. Evaporation of the solvent followed by rapid filtration of the residue (silica gel, CH_2Cl_2) afforded after recrystallization from benzene **27** (0.33 g, 83%) as a yellow solid: m.p. 205–206°; ^{1}H-NMR ($CDCl_3$) 1.04–1.10 (t, 3H, J = 7.4 Hz), 1.55–1.77 (m, 2H), 2.30–2.45 (m, 1H), 2.80–3.01 (m, 2H), 4.25 (d, 1H, J = 3.9 Hz), 7.80–7.85 (m, 3H), 8.25–8.34 (m, 2H), 13.97 (s, 1H). (Found: C, 72.63; H, 4.40. Calc for $C_{21}H_{15}NO_4$: C, 73.04; H, 4.38%).

Synthesis of cyano alcohol (**28**)

To a soln of **27** (0.19 g, 0.55 mmol) in CH_2Cl_2 (24 ml) and MeOH (24 ml) was added HOAc to give a soln of pH 5. $NaBH_3CN$ (0.17 g, 2.8 mmol) was added and the soln stirred for 2 hr under N_2. The mixture was then extracted with CH_2Cl_2 and washed with H_2O to give after evaporation of the solvent and recrystallization from benzene **28** (0.18 g, 93%) as a mixture of isomers: m.p. 190–191.5°; ^{1}H-NMR ($CDCl_3$) 1.06–1.23 (two t, 3H), 1.65–1.85 (m, 1H), 1.85–2.10 (m, 1H), 2.30–2.63 and 2.86–3.10 (m, 1H), 3.75–3.90 (two d, 1H, J = 10 Hz), 5.13–5.33 (q, 1H, J = 10 Hz), 7.73–7.93 (m, 2H), 8.00 (s, 1H), 8.26–8.41 (m, 2H), 13.53 (s, 1H), 13.58 (s, 1H); high resolution mass spectrum *m/e* 347.1161 (calc for $C_{21}H_{17}NO_4$: 347.1158).

Synthesis of dithioketal (**29**)

To a soln of **25** (50 mg, 0.11 mmol) in $CHCl_3$ (12 ml) under N_2 was added propane dithiol (12 mg, 0.11 mmol), TMSCl (18.3 mg, 0.17 mmol) and a catalytic amount of TMSOTS. The reaction was stirred 16 hr and then quenched with H_2O, extracted with CH_2Cl_2 and washed with 10% NaOH aq and water. The solvent was evaporated and the residue chromatographed (silica gel, CH_2Cl_2/EtOAc (3:1)) to afford

29 an orange solid, as a mixture of isomers (37 mg, 75%); m.p. 234–235°; ^{1}H-NMR ($CDCl_3$) 1.09–1.16 (m, 3H), 2.14–2.19 (m, 2H), 2.66–2.90 (m, 2H), 3.04–3.30 (m, 6H), 3.85 (d, 0.64H, J = 9.1 Hz), and 4.13 (d, 0.37H, J = 2.3 Hz), 7.74 (s, 0.64H), 7.81–7.85 (m, 2H), 8.00 (s, 0.37H), 8.26–8.35 (m, 2H), 14.22 (s, 0.35H), 14.25 (s, 0.65H). (Found: C, 65.72; H, 4.85. Calc for $C_{24}H_{21}NO_3S_2$: C, 66.18; H, 4.86%).

1-*Hydroxy*-8-*acetoxyanthraquinone* (**33**)

To a homogeneous stirred soln of boric acid (50 g, 0.21 mol) in Ac_2O (500 ml) was added 1,8-dihydroxyanthraquinone (50 g, 0.21 mol) at 90°. The mixture was stirred at this temp for 10 hr then cooled to room temp. The orange mixture was poured into cold water (3 l) and stirred for 1 hr. The resulting yellow solid was filtered off, washed with a large volume of water and dried. 56 g (95%) of monoacetate **33** was obtained: m.p. 184–185° (lit. m.p.) ^{1}H-NMR ($CDCl_3$) 2.49 (s, 3H), 7.31 (d, 1H, J = 7.7 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.66 (t, 1H, J = 7.7 Hz), 7.82 (m, 2H), 8.30 (d, 1H, 7.7 Hz), 12.58 (s, 1H).

1-*Hydroxy*-8-*methoxyanthraquinone* (**34**)

To a stirred soln of **33** (50 g, 0.18 mol) in acetone (600 ml) was added powdered anhyd K_2CO_3 (40 g, 0.29 mol) and Me_2SO_4 (40 ml, 53.3 g, 0.42 mol) and heated to 70° for 8 hr. The mixture was cooled to room temp, the green precipitated 1-methoxy-8-acetoxy-anthraquinone was not isolated but poured into 10% HCl aq. The resulting yellow solid was filtered off, washed with an excess of water and dried. 43.5 g (95%) of the monomethoxy **34** was obtained: m.p. 185–186°; ^{1}H-NMR ($CDCl_3$) 4.09 (s, 3H), 7.29 (d, 1H, J = 8.6 Hz), 7.37 (d, 1H, J = 8.6 Hz), 7.62 (t, 1H, J = 8.2 Hz), 7.76 (m, 2H), 7.97 (s, 1H, J = 8.2 Hz).

1-*Methoxy*-8-O-(1-*penten*-3-*yl*)*anthraquinone* (**35**)

To a stirred soln of **34** (20 g, 78.7 mmol), triphenylphosphine (26 g, 95.9 mmol), and 1-penten-3-ol (12 ml, 10.1 g, 0.117 mol) in dry THF (300 ml) at 0°, was added dropwise from an addition funnel diethyl-azodicarboxylate (20 ml, 20.12 g, 0.127 mol) dissolved in dry THF (50 ml). After addition, the mixture was stirred at room temp for 1 hr. THF was removed under reduced pressure to give a dark red syrup which was filtered through neutral alumina with CH_2Cl_2 and then chromatographed (silica gel, hexane–ethyl acetate (3:1)). 22.1 g (87%) of the yellow ether was obtained. m.p. 97–98.5°; ^{1}H-NMR ($CDCl_3$) 1.10 (t, 3H, J = 7.4 Hz), 1.98 (m, 2H), 4.01 (s, 3H), 4.68 (m, 1H), 7.28 (m, 2H), 7.59 (m, 2H), 7.81 (m, 2H). High resolution mass spectrum: Calc for $C_{20}H_{18}O_4$: 322.1204. Found: 322.1201.

1-*Hydroxy*-2-(2-*pentenyl*)-8-*methoxyanthraquinone* (**36**)

To a stirred soln of **35** (5 g, 15.5 mmol) in DMF (100 ml) and water (100 ml) under N_2, was added sodium dithionite (3.1 g, 21.8 mmol). The reaction was heated to 70° for 1 hr then cooled to room temp, air was bubbled in for 1 hr, and the mixture was diluted with CH_2Cl_2 (300 ml). The organic phase was separated and washed repeatedly with water. The product was concentrated *in vacuo* and chromatographed (silica gel, CH_2Cl_2). Recrystallization from EtOH yields 4.35 g (87%) of orange **36**: m.p. 127–128°; ^{1}H-NMR ($CDCl_3$) 0.99 (t, 3H, J = 7.5 Hz), 2.06 (m, 2H), 3.45 (m, 2H), 4.08 (s, 3H), 5.61 (m, 2H), 7.35 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.73 (m, 2H), 7.95 (d, 1H, J = 7 Hz), 13.33 (s, 1H). High resolution mass spectrum: Calc for $C_{20}H_{18}O_4$: 322.1204. Found: 322.1201.

1-*Hydroxy*-2-(1-*pentenyl*)-8-*methoxyanthraquinone* (**37**)

To a stirred soln of **36** (10 g, 31.0 mmol) in abs EtOH (200 ml) was added $RhCl_3$ (100 mg, 1 mol%). The mixture was gently refluxed under N_2 for 10 hr. The EtOH was removed *in vacuo* and the dark red product was chromatographed (silica gel, hexane–EtOAc (3:1)) to give the isomerized alkene in a near quantitative yield. M.p. 109–110°; ^{1}H-NMR ($CDCl_3$) 1.05 (t, 3H, J = 7 Hz), 1.65 (m, 2H), 2.37 (m, 2H), 4.13 (s, 3H), 6.64 (m, 1H), 6.91 (d, 1H, J = 16 Hz), 7.40 (d, 2H, J = 8 Hz), 7.79 (m, 3H), 7.98 (d, 1H, J = 7.5 Hz), 13.58 (s, 1H). (Found: C, 74.35; H, 5.68. Calc for $C_{20}H_{18}O_4$: C, 74.55; H, 5.63%).

1,8-*Dimethoxy*-2-(1′-*penetenyl*)*anthraquinone* (**38**)

To a stirred soln of **37** (10 g, 31.0 mmol) in acetone (300 ml) under N_2 was added powdered anhyd K_2CO_3 (8 g, 57.8 mmol) and Me_2SO_4 (5 ml, 6.66 g, 52.8 mmol). The mixture was refluxed for 10 hr, cooled and poured into water (1 l). The yellow solid was filtered off, dried and chromatographed (silica gel, hexane–EtOAc (3:1)) to give 9.7 g (93%) of **38**. M.p. 88–89.5°; ^{1}H-NMR ($CDCl_3$) 0.98 (t, 3H, J = 7.3 Hz), 1.54 (m, 2H), 2.28 (m, 2H), 3.96 (s, 3H), 4.02 (s, 3H), 6.45 (m, 1H), 6.80 (d, 1H, J = 16 Hz), 7.29 (d, 1H, J = 8.4 Hz), 7.64 (t, 1H, J = 8.2 Hz), 7.82 (m, 2H), 7.95 (d, 1H, J = 8.2 Hz). High resolution mass spectrum: Calc for $C_{21}H_{20}O_4$: 336.1361. Found: 336.1350.

1,8-*methoxy*-2-(2′-*bromo*-1′-*hydroxypentyl*)*anthraquinone* (**39**)

To a stirred soln of **38** (10 g, 29.7 mmol) in aqueous acetone (water 50 ml, acetone 200 ml) at 0° was added N-bromosuccinimide (7.25 g, 40.7 mmol). Upon completion, the acetone was removed under reduced pressure and the aqueous layer extracted with CH_2Cl_2 (3 × 50 ml). The CH_2Cl_2 extracts were dried, concentrated and chromatographed (silica gel, hexane–EtOAc (2:1)) to give 10.2 g (79%) of **39**: m.p. 138–139°; ^{1}H-NMR ($CDCl_3$) 0.82 (t, 3H, J = 7.3 Hz), 1.1–1.9 (m, 4H), 3.95 (s, 3H), 4.07 (s, 3H), 4.61 (m, 1H), 5.41 (d, 1H, J = 7.3 Hz), 7.32 (s, 1H, J = 8.4 Hz), 7.84 (t, 1H, J = 8 Hz), 7.9 (m, 2H), 8.04 (d, 1H, J = 8.1 Hz). (Found: C, 58.20; H, 4.88. Calc for $C_{21}H_{21}BrO_5$: C, 58.21; H, 4.88%).

1,8-*Dimethoxy*-2-(2′-*bromo*-1′-*oxopentyl*)*anthraquinone* (**39a**)

Bromohydrin **39** (5 g, 11.5 mmol) was dissolved in acetone (150 ml). A 2.1N Jones reagent soln was added dropwise with cooling on ice during additions and warming to room temp between additions until the reaction was complete. The mixture was extracted with ether (3 × 100 ml) and the ether extracts were washed with $NaHCO_3$ aq and water. The organic layer was dried, concentrated and chromatographed (silica gel, hexane–EtOAc (3:1)) to give 4.7 g (94%) of **39a**: m.p. 107–108°; ^{1}H-NMR ($CDCl_3$) 1.05 (t, 3H, J = 7.5 Hz), 1.58 (m, 2H), 2.12 (m, 2H), 4.01 (s, 3H), 4.09 (s, 3H), 5.24 (m, 1H), 7.36 (d, 1H, J = 6.9 Hz), 7.73 (t, 1H, J = 7 Hz), 7.84 (m, 2H), 8.10 (d, 1H, J = 7.1 Hz). (Found: C, 58.12; H, 4.66. Calc for $C_{21}H_{19}BrO$: C, 58.48; H, 4.44%).

1-*Hydroxy*-8-*methoxy*-2-(2′-*bromo*-1′-*oxopentyl*)*anthraquinone* (**40**)

To a stirred soln of the dimethoxyketobromide (5 g, 11.6 mmol) in CH_2Cl_2 (150 ml) under N_2 was added $AlCl_3$ (1.8 g, 13.5 mmol). The mixture was stirred overnight at room temp before concentration under reduced pressure to give a dark red tar. The tar is dissolved in 10% HCl aq (200 ml) and THF (50 ml) and stirred overnight. The reaction is diluted with water and the product is filtered off, dried, and chromatographed (silica gel, hexane–EtOAc (3:1)) to give 4.3 g (89%) of **40** as an orange solid. M.p. 144–145°; ^{1}H-NMR ($CDCl_3$) 1.03 (t, 3H, J = 7.1 Hz), 1.59 (m, 2H), 2.15 (m, 2H), 4.10 (s, 3H), 5.65 (m, 1H), 7.41 (d, 1H, J = 9.1 Hz), 7.83 (m, 2H), 7.97 (d, 1H, J = 7.1 Hz), 8.07 (d, 1H, J = 8 Hz), 14.08 (s, 1H). High resolution mass spectrum: Calc for $C_{20}H_{17}O_5Br$; 416.0258. Found: 416.0210.

1-*Hydroxy*-8-*methoxy*-2-(1′-*oxo*-2′-*phenylthiopentyl*)*anthraquinone* (**41**)

NaOH (1.1 g, 27.5 mmol), thiophenol (2.7 ml, 2.9 g, 26.4 mmol), benzene (50 ml), water (3 ml) and cetyltrimethyl-ammonium bromide (100 mg, 2 mole%) was stirred vigorously for 10 min and **40** (5g, 12.0 mmol) was added dropwise. After 2 hr the reaction was neutralized with 10% HCl aq, the phases were separated, and the aqueous layer was extracted with benzene (50 ml). The combined organic portions were dried, concentrated, and chromatographed (silica gel, hexane–EtOAc (3:1)) to give 4.8 g (90%) of **41**. M.p. 91–92.5°; ^{1}H-NMR ($CDCl_3$) 0.99 (t, 3H, J = 7.2 Hz), 1.9 (m, 4H), 4.09 (s, 3H), 4.96 (t, 1H, J = 7.2 Hz), 7.25 (m, 5H), 7.39 (d, 1H, J = 8.3 Hz), 7.78 (m, 2H), 7.97 (m, 2H), 13.92 (s, 1H). High resolution mass spectrum: Calc for $C_{26}H_{22}O_5S$: 446.1188. Found: 446.1210.

1-Hydroxy-8-methoxy-2-(1-oxo-2-sulfoxophenylpentyl)anthraquinone (**41a**)

To a stirred soln of **41a** (3.1 g, 6.7 mmol), in AcOH (75 ml) at 10° was added sodium metaperiodate (1.6 g, 7.5 mmol) dissolved in a minimum amount of water. The reaction is stirred overnight at room temp, diluted with water and neutralized with $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 × 50 ml), dried, concentrated, and chromatographed (silica gel, hexane–EtOAc (1:1) to give 2.6 g (85%) of the orange **41a**. M.p. 139–140°; ^{1}H-NMR ($CDCl_3$) 0.88 (t, 3H, J = 7.32), 1.51 (m, 2H), 2.13 (m, 2H), 4.11 (s, 3H), 5.17 (m, 1H), 7.39 (m, 4H), 7.79 (m, 5H), 7.96 (d, 1H, 8.1 Hz), 14.29 (s, 1H).

1-Hydroxy-8-methoxy-2-(1'-oxo-2'-pentenyl)anthraquinone (**31**)

The sulfoxide (3 g, 6.5 mmol) was heated in CCl_4 (75 ml) under N_2 at 70° for several hr. When elimination is complete, the CCl_4 is removed under reduced pressure, and the product is chromatographed (silica gel, hexane–EtOAc (2:1)). Recrystallization from EtOH gives the enone (**31**) in a near quantitative yield: m.p. 119–121°; ^{1}H-NMR ($CDCl_3$) 1.15 (t, 3 Hz, J = 7.5 Hz), 1.73 (m, 2H), 2.32 (m, 2H), 4.04 (s, 3H), 6.92 (d, 1H, J = 15.6 Hz), 7.06 (m, 1H), 7.39 (d, 1H, J = 7.9 Hz), 7.78 (m, 1H), 7.87 (d, 1H, J = 8.01 Hz), 7.97 (d, 1H, J = 8.0 Hz), 13.67 (s, 1H). (Found: C, 71.40; H, 4.70. Calc for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79%).

Ketonitrile (**32**)

NaH (60 mg, 2.6 mmol) was placed in a flame-dried, N_2-flushed, three-neck flask and was washed with dry hexane. The NaH was suspended in dry DMSO, heated at 75° until the suspension cleared and allowed to cool to room temp. The cyanosulfide (382 mg, 2.6 mmol) in 2 ml of DMSO was added and stirred for 1.5 hr before **31** (250 mg, 0.74 mmole) dissolved in a minimum amount of DMSO was added. Michael addition was complete within 10 min (TLC) and the cyclization was over in 1 hr. The reaction was quenched with AcOH, and the mixture diluted with CH_2Cl_2 (100 ml). The organic product was washed repeatedly with water, concentrated, and chromatographed (silica gel, EtOAc–hexane (2:1)) to give 231 mg (83%) of **32**: m.p. 138–140°; ^{1}H-NMR ($CDCl_3$) 4.20 (s, 1H), 7.90 (s, 1H), 7.84 (m, 2H), 7.39 (d, 1H), 4.15 (d, 1H), 4.07 (s, 3H), 2.88 (m, 2H), 2.49 (m, 1H), 1.73 (m, 2H), 1.05 (t, 3H); high resolution mass spectrum, Calc for $C_{22}H_{17}O_5N$ *m/e* 375.1107, observed *m/e* 375.1114.

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