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APPROACHES TO THE REGIOSPECIFIC SYNTHESIS OF ANTHRACYCLINE ANTIBIOTICS[1a]

JACK E. BALDWIN*
Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, England

and

ALGIS J. RAJECKAS[1b]
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, U.S.A.

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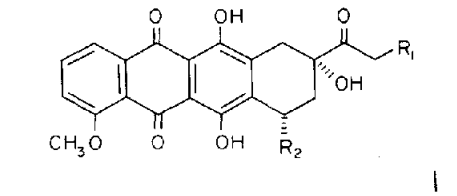
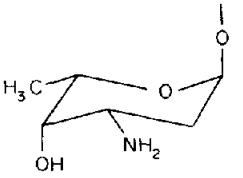
Abstract—Synthetic approaches to anthracycline antibiotics were studied through the use of Claisen rearrangements on 1-methallyloxy-5-methoxyanthraquinone (**9**) which required reducing conditions to proceed through a hydroquinone intermediate *in situ*. 1-(2'-Methylene-4'-pentenoxy)-5-methoxyanthraquinone (**13**) underwent a similar reductive rearrangement but also produced a spiro compound **16** as a result of an ene reaction between the phenol and side chain double bond. 1-Hydroxy-2-methallyl-5-methoxyanthraquinone (**11**) could not be oxidized to quinizarin **17**. 1-Hydroxy-2-methallyl-5,9,10-trimethoxyanthracene (**21**) was oxidatively coupled to the dimer at C-2. Dimer **23** reacted with diazomethane to form a 1,3-dipolar adduct **24**.

The anthracycline antibiotics daunorubicin (**1**) and especially adriamycin (**2**) are clinically useful medicinal agents for the treatment of a broad spectrum of human cancers.[2] Total syntheses of the aglycone portion of these antibiotics have been a topic of great interest in recent years due to the lack of an efficient biosynthetic process[3] as well as the search for more active analogs with reduced cardiotoxicity.[4]

Numerous partial and total syntheses of daunomycinone (**3**) and adriamycinone (**4**) have been reported using various schemes to confront the synthetic challenge.[5-22] Herein, we disclose a different approach to the synthesis of anthracyclinone precursors from 1,5-disubstituted anthraquinones.



1: R = H R_2 =
2: R = OH



3: R_1 = H, R_2 = OH
4: R_1 = OH, R_2 = OH

RESULTS AND DISCUSSION

1,5-Dichloroanthraquinone (**5**) was converted to dimethoxy derivative **6** by treatment with sodium methoxide in refluxing toluene in 85% yield.[23] 1 - Hydroxy - 5 - methoxyanthraquinone (**8**) was not readily available either by partial demethylation of quinone **6**[24] or partial methylation of 1,5-dihydroxyanthraquinone.

Quinone **6** was reduced with stannous chloride in HCl/HOAc to anthrone **7**; loss of the methyl ether at C-1 is due to hydrolysis of the vinylogous ester *in situ*.[23,25]

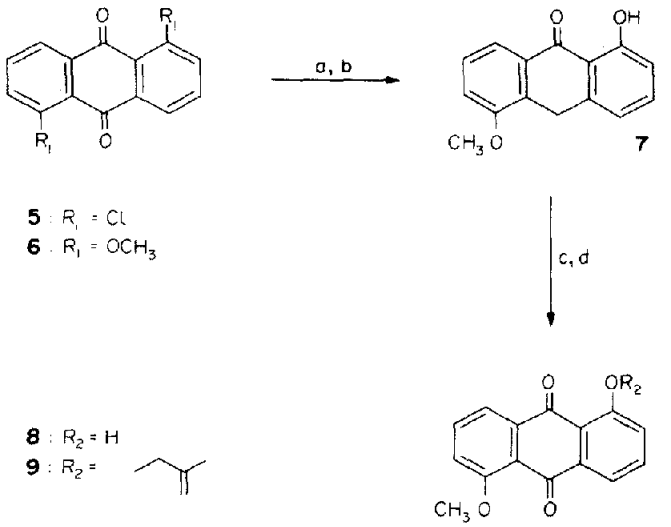
Anthrone **7** could not be successfully alkylated on the phenolic oxygen at C-1 due to the acidic nature of the methylene group at C-10. Treatment of anthrone **7** with acetic anhydride and pyridine produced 1,9 - diacetoxy - 5 - methoxyanthracene. Oxidation of anthrone **7** to quinone **8** was easily achieved with chronium trioxide in acetic acid with 10% boric acid added.[26] Alkylation of phenol **8** was carried out in refluxing acetone with methallyl chloride, potassium carbonate and potassium iodide to give ether **9** in 85% yield.

Initial attempts to rearrange methallyl ether **9** to phenol **11** were unsuccessful (170°/6 h) due to the electron withdrawing ability of the two carbonyl groups. When ether **9** was heated at 140° with Zn dust in acetic anhydride,[27] reductive acetylation of the quinone along with rearrangement of the methallyl group occurred to give triacetoxyanthracene **10** in 88% yield. Under similar conditions (Zn/HOAc/110°), ether **9** could be converted to phenol **11** in 80% yield without acetylation of the OH groups. Presumably, a hydroquinone intermediate is involved, but since no precautions were made to exclude air during work-up, autoxidation back to the quinone occurred.

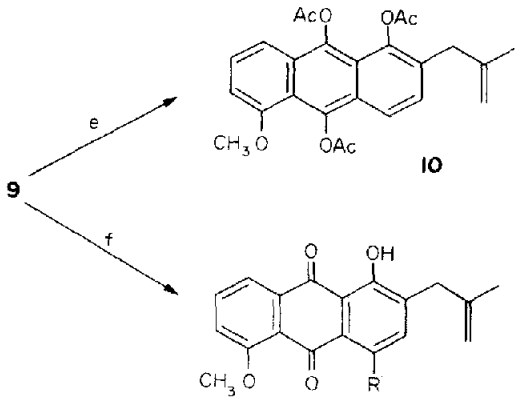
In order to check the feasibility of using a more complex side chain for the reductive Claisen rearrangement, hydroxyquinone **8** was alkylated with 2 - chloromethyl - 1,4 - pentadiene (**12**). This alkylating agent was prepared in two steps from allylzinc bromide and propargyl alcohol,[28] followed by chlorination with thionyl chloride in pyridine at 0°.[29,30] During the course of the Claisen reaction (1.5 h), the expected rearrangement product **15** was obtained, as well as an abnormal spiro compound **16** as a 1:1 mixture. Only product **15** was obtained when the heating time is of the order of 15 min.

Compound **16** can be formed as the result of an ene reaction with the terminal double bond of the side chain and the OH group in an intermediate such as phenol **14**. Spiro **16** was not convertible to normal product **15**.

Phenol **11** was not a suitable precursor to quinizarin **17**



(a) $PhCH_3$, $NaOCH_3$, reflux
(b) $SnCl_2$, HOAc, HCl, reflux
(c) CrO_3
(d) Methallyl chloride, K_2CO_3, KI, acetone, reflux



(e) Zn, Ac_2O, 140°C
(f) Zn, HOAc, $PhCH_3$, 110°C

since it was inert to a variety of oxidizing agents. Among these were chromium trioxide, lead tetraacetate, manganese dioxide, potassium nitrosodisulfonate (Fremy's salt), bromine, nitrosyl chloride, hydrogen peroxide and alkaline potassium persulfate. Diazonium salt coupling experiments were also unsuccessful. The stability of this phenol can be attributed to the deactivating effect of the quinone moiety.

To circumvent intermediate **11** because of its lack of reactivity, methallyl ether **9** was reductively acetylated to the corresponding diacetate **18** without rearrangement occurring at room temperature (Zn/HOAc/pyridine/Ac_2O). Diacetate **18** was heated at 150° but none of the expected Claisen rearrangement product was detected by NMR. However, when the crude product was subjected to an acidic oxidant such as chromium trioxide in acetic acid, acetoxyanthraquinone **19** was isolated. Quinone **19** was indistinguishable from an authentic sample. This suggests an acyl group migration to the adjacent exposed phenol, followed by hydrolysis and oxidation to quinone **11**.

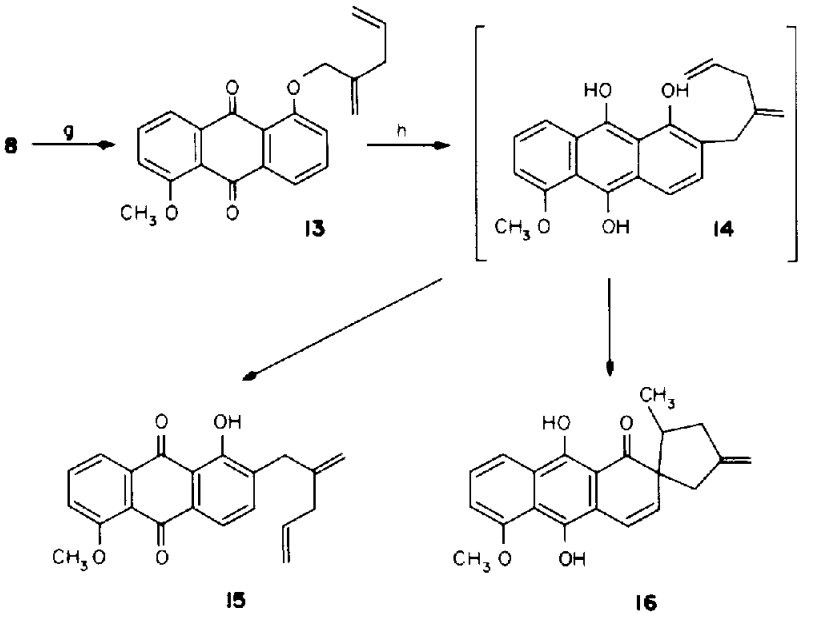
To avoid the problem of a migrating protecting group, quinone **9** was reductively methylated to trimethoxyanthracene **20** in 93% yield ($Na_2S_2O_4$/DMF/Me_2SO_4/KOH).[14] Sodium naphthalide in THF with dimethyl sulfate also reductively methylates anthraquinones; in the case of methallyl ether **9**, 1,5,9,10-tetramethoxyanthracene was obtained due to cleavage of the methallyl group and subsequent methylation.

Thermolysis of methallyl ether **20** readily formed phenol **21** in 90% yield. Unfortunately, phenol **21** could not be oxidized to a 1,4-quinone system **22** under relatively mild conditions. Vigorous reagents such as chromium trioxide or nitrous acid resulted in the demethylation of the central methyl ethers back to quinone **11**.

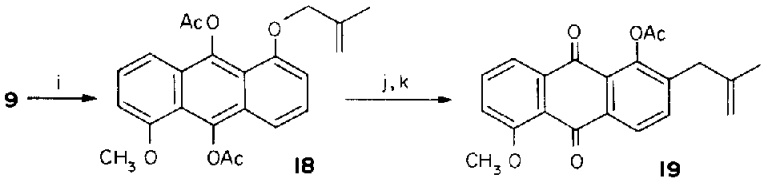
Manganese dioxide in methylene chloride at room temperature generated dimer **23**. Other reagents that were found to effect oxidative coupling, although not as efficiently, were lead dioxide, sodium periodate, Fremy's salt (aqueous THF/NaOAc) or salcomine in chloroform with $MgSO_4$.[31]

Phenol **21** did not couple with diazotized sulfanilic acid[32] or *p*-nitroaniline; a resultant azo adduct could have been reduced to the 1,4-quinone imine, a suitable precursor to quinone **22**. Dimer **23** was found to undergo a 1,3-dipolar addition with diazomethane at 5° over a period of 5 days to give adduct **24**. Pyrolysis of **24** resulted in the evolution of N_2 gas and the introduction of a new Me group in the tricyclic skeleton **25**, as well as cleavage of the dimer. The orientation of this new substituent was not determined.

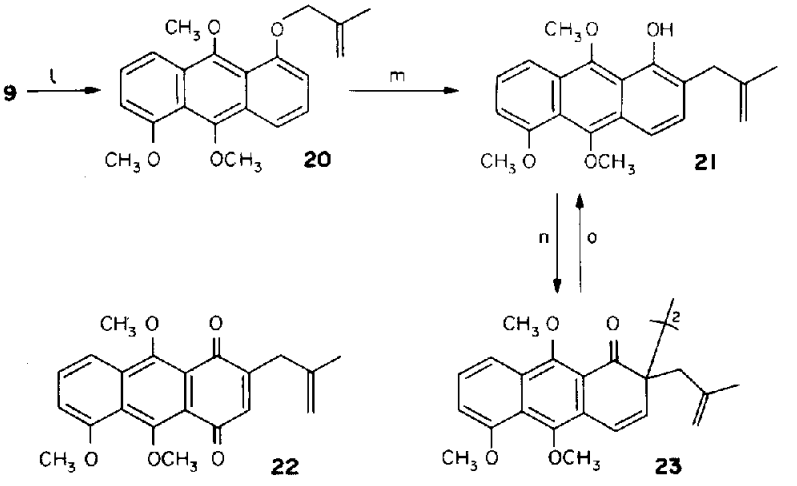
Dimer **23** could be cleaved with Zn dust in acetic acid at room temperature back to the monomeric phenol **21** quantitatively. This fact, together with the observation of



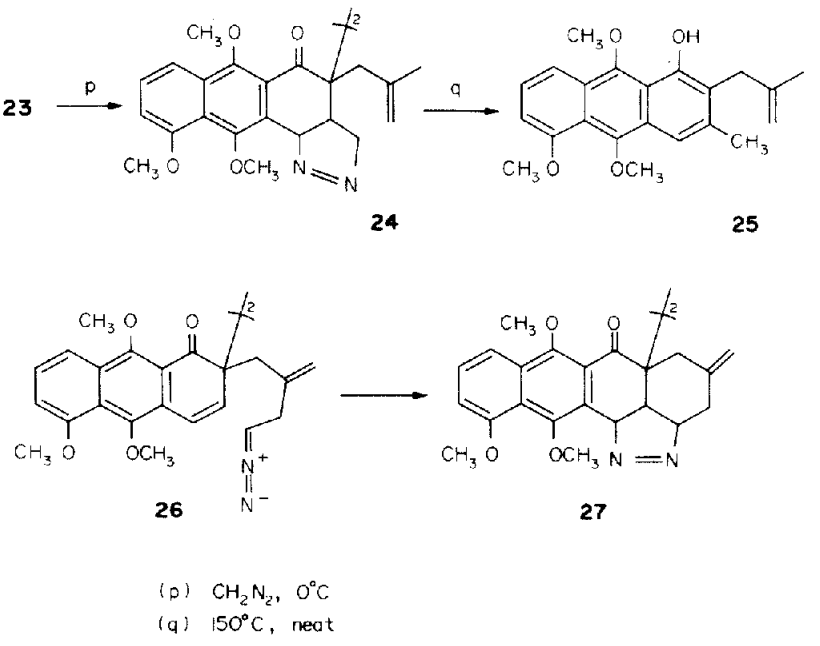
(g) Chloride **12**, K_2CO_3, acetone, reflux
(h) Zn, HOAc, toluene, 110 °C



(i) Ac_2O, pyridine, Zn, HOAc, r t
(j) $PhNMe_2$, reflux
(k) CrO_3



(l) Me_2SO_4, $Na_2S_2O_4$, KOH, DMF
(m) $PhNMe_2$, 110°C
(n) MnO_2, CH_2Cl_2, rt
(o) Zn, HOAc, rt



a 1,3-dipolar addition to the double bond in the tricyclic system, suggests that a diazo synthon in the side chain of dimer **26** could give rise to an intramolecular cyclization to tetracyclic **27**. This coupound would have the proper functionalization pattern of the aglycone nucleus.

In summary, although it appears that Claisen rearrangements of 1,5,9,10-tetraoxy substituted anthracenes are synthetically useful procedures for introducing substituents at C-2, the subsequent difficulties we encountered in introducing oxygen functionality at C-4 renders this approach to the synthesis of adriamycin type structures unsatisfactory.

EXPERIMENTAL SECTION

General procedures. M.ps were determined on a Thomas–Hoover capillary m.p. apparatus or on a Köfler hot stage microscope and are uncorrected. B.Ps are also uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

IR spectra were recorded on a Perkin–Elmer Model 700 Spectrophotometer, calibrated against polystyrene film and are expressed in cm^{-1}. UV spectra were recorded on a Coleman Hitachi 124 Double Beam Spectrophotometer with a Hitachi 164 recorder. PMR spectra at 60 MHz were obtained on Varian Associates T-60 Spectrometer, a Hitachi Perkin–Elmer R-20B Spectrometer or a Hitachi Perkin–Elmer R-24B and at 90 MHz on a Hitachi Perkin–Elmer R-22 Spectrometer.

Chemical shifts are reported in parts per million (ppm) relative to internal TMS, with the notations indicating the multiplicity of the signal, the number of protons and the coupling constant if applicable. Spin multiplicity is given by s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. The coupling constants are expressed as J values in units of Hertz. Low resolution mass spectra were determined on a Hitachi Perkin–Elmer RMU-6 Spectrometer or a Varian Associates MAT 44 Spectrometer. High resolution spectra were obtained on a CEC 110B (DuPont) Spectrometer on photo plates through the courtesy of Dr. Catherine E. Costello, NIH mass spectrometry facility at MIT.

Silica gel for column chromatography was Merck Silica Gel 60, No. 7734 or Merck Silica Gel H Type 60, No. 7736. Preparative thin layer plates were 200 × 200 × 1.25 mm using Merck Silica Gel GF 254 Type 60, No. 7730. Analytical TLC was performed on Baker-Flex Silica Gel IB-F or Merck Silica Gel 60 F-254, No. 5765.

All solvents and reagents were purified by standard procedures.[33]

1,9 - *Diacetoxy* - 5 - *methoxyanthracene.* To a soln of **7**[23] (260 mg, 1.1 mmol) in 10 ml dry pryidine was added Ac_2O (1 ml). The mixture was stirred at rt overnight. Excess Ac_2O was hydrolyzed with 5 ml water. The mixture was extracted with 75 ml ether and was washed three times with 1M HCl, once with sat NaCl aq and dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave the diacetoxyanthrancene (318 mg, 91%) as a yellow solid: m.p. 141.5–144°; NMR ($CDCl_3$) δ 2.42, 2.50 (s, 3H ea, OAc), 4.02 (s, 3H, OCH_3), 6.72–8.00 (m, 6H, aromatic), 8.80 (s, 1H, C-10); IR ($CHCl_3$) 2950, 1760, 1530, 1460, 1410 cm^{-1}.

1 - *Hydroxy* - 5 - *methoxyanthraquinone* (**8**). A soln of CrO_3 (8.3 g, 83.0 mmol) in 50 ml water and 450 ml AcOH containing boric acid (265 mg, 0.1 eq.) which was warmed to 60° was poured into a round-bottom flask containing **7**[23] (10.0 g, 41.6 mmol). The mixture was swirled and heated on a steam bath for 10 min and was poured into 1200 ml ice–water mixture. A yellow solid was collected by filtration. The crude solid was dissolved in CH_2Cl_2, washed once with water, dried (NaCl and $MgSO_4$) and solvents were evaporated *in vacuo*. Purification by passing through a plug of silica gel (100 g) gave **8** (8.0 g, 76%) as a yellow solid: m.p. 180–181.5° (lit[24] m.p. 181–183°); NMR ($CDCl_3$) δ 4.0 (s, 3H), 7.3–7.9 (m, 6H), 12.4 (s, 1H); IR ($CHCl_3$) 1670, 1640, 1590, 1460 cm^{-1}; mass spectrum *m/e* 254 (M^+).

1 - *Methallyl* - 5 - *methoxyanthraquinone* (**9**). A mixture of 1 - hydroxy - 5 - methoxyanthraquinone (5.109 g, 20.6 mmol), K_2CO_3 (3.05 g, 1.1 eq.), KI (3.35 g, 1.0 eq.) and methallyl chloride (4.00 g, 2.2 eq.) in 100 ml acetone (reagent grade, stored over K_2CO_3) was allowed to reflux for 24 h. The mixture was poured into 200 ml water and was extracted with 100 ml ether and 50 ml CH_2Cl_2. Combined organic extracts were washed with 1M NaOH until colorless, sat NaCl aq and dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave ether **9** (5.3 g, 85%) as a yellow solid: m.p. 138–140° (EtOH); NMR ($CDCl_3$) δ 1.93 (s, 3H), 4.02 (s, 3H), 4.61 (s, 2H), 5.06, 5.31 (br s, 1H ea), 7.17–7.90 (m, 6H); IR ($CHCl_3$) 1670, 1630, 1590, 1470, 1440 cm^{-1}; UV (95% EtOH) λ_{max} 212 nm (log ε 4.37), 257 (4.26); mass spectrum calc. for $C_{19}H_{16}O_4$: *m/e* 308.10486. Found: *m/e* 308.10510.

Starting material was recovered by acidifying the aqueous basic washes with conc. HCl and then was recycled for subsequent alkylations.

2 - *Methallyl* - 5 - *methoxy* - 1,9,10 - *triacetoxyanthracene* (**10**). A mixture of 677 mg (2.20 mmol) **9**, 3.9 g (59.7 mmol) Zn dust and 432 mg (5.27 mmol) NaOAc in 100 ml Ac_2O was refluxed at 140° for 1 h. After cooling, the liquid was decanted and the Zn residue

was washed with AcOH. The Ac_2O was hydrolyzed by pouring it into 250 ml water and heating on a steam bath for 20 min. Extraction with 100 ml CH_2Cl_2, followed by washing three times with water, sat $NaHCO_3$ aq, sat NaCl aq, drying over $MgSO_4$ and evaporation of solvents *in vacuo* gave 841 mg (88%) yellow solid. Recrystallization from CH_2Cl_2/hexane provided **10** (440 mg) as yellow needles: m.p. 164.5–167°; NMR ($CDCl_3$) δ 1.71 (s, 3H), 2.41, 2.48, 2.51 (s, 9H total), 3.38 (s, 2H), 3.92 (s, 3H), 4.78, 4.88 (br s, 1H each), 6.71–7.94 (m, 5H); IR ($CHCl_3$) 1760, 1615, 1560, 1540, 1470, 1370 cm^{-1}; mass spectrum calc. for $C_{25}H_{24}O_7$: *m/e* 436.15220. Found: *m/e* 436.15179.

1 - *Hydroxy* - 2 - *methallyl* - 5 - *methoxyanthraquinone* (**11**). A soln of 1.19 g (3.9 mmol) of **9** with Zn dust (1.20 g, 18.4 mmol, 4.8 eq.) in 50 ml toluene and 5 ml glacial AcOH was heated at 110° for 30 min. After cooling, the mixture was poured into 100 ml water and was extracted with 50 ml ether. After a second water wash, the extract was washed with sat NaCl aq and dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave **11** (1.18 g, 99%) as a brown solid which was recrystallized from EtOH (790 mg, 66%) as yellow plates: m.p. 129–130°; NMR ($CDCl_3$) δ 1.80 (s, 3H), 3.47 (s, 2H), 4.06 (s, 3H), 4.76, 4.90 (br s, 1H each), 7.30–8.01 (m, 5H), 12.81 (s, 1H); IR ($CHCl_3$) 1660, 1630, 1560, 2850–3100 (br m) cm^{-1}; UV (95% EtOH) λ_{max} 227 nm (log ϵ 4.30), 255 (4.12), 283 sh (3.73), 3.57 (3.62); mass spectrum calc. for $C_{19}H_{16}O_4$: *m/e* 308.10486. Found: *m/e* 308.10520.

2 - *Chloromethyl* - 1,4 - *pentadiene* (**12**).[30] To a soln of 2 - hydroxymethyl - 1,4 - pentadiene[28] (7.70 g, 78 mmol) in 200 ml ether and 4.7 ml pyridine (90 mmol) cooled to 0° was added dropwise thionyl chloride (6.27 ml, 86 mmol) in 50 ml dry ether over a 20-min period. A white ppt formed immediately; the mixture was allowed to stand at rt overnight. The mixture was poured into 100 ml ice water, washed three times with cold water and three times with sat NaCl aq. After drying with $MgSO_4$, the mixture was concentrated on a steam bath to leave 6.74 g (74%) crude brown liquid. Distillation at atmospheric pressure gave **12** as a clear white liquid (4.04 g, 45%): b.p. 123–126°; NMR ($CDCl_3$) δ 2.91 (d, 2H, J = 6 Hz), 4.03 (s, 2H), 4.94 (br s, 2H), 5.10 (br s, 2H), 5.40–6.15 (m, 1H); IR (film) 3075, 2980, 1630, 1435, 1260, 1000 cm^{-1}; mass spectrum *m/e* 116 (M^+).

1 - (2' - *Methylene* - 4' - *pentenoxy*) - 5 - *methoxyanthraquinone* (**13**). To a soln of **8** (1.5 g, 5.90 mmol) in 100 ml reagent grade acetone was added K_2CO_3 (1.63 g, 11.8 mmol), **12** (1.375 g, 11.8 mmol) and KI (1.99 g, 11.8 mmol). The mixture was allowed to reflux under a N_2 overnight (20 h). After allowing the mixture to cool, the mixture was poured into 150 ml water and was extracted with 100 ml ether. The ether extract was washed twice with 1M NaOH to remove unreacted starting material, once with $Na_2S_2O_3$, sat NaCl aq and was dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave **13** (1.75 g, 89%) as a yellow solid which was recrystallized from EtOH: m.p. 105–106°; NMR ($CDCl_3$) δ 2.99, 3.07 (br s, 1H each, allylic CH_2), 4.04 (s, 3H, OMe), 4.68 (s, 2H, OCH_2), 5.07–5.47 (m, 4H, vinyl H), 5.72–6.17 (m, 1H, vinyl H), 7.20–7.98 (m, 6H, aromatic); IR ($CHCl_3$) 1660, 1640, 1580 cm^{-1}; mass spectrum calc for $C_{21}H_{18}O_4$: *m/e* 334.12051. Found: *m/e* 334.12321.

1 - *Hydroxy* - 2 - (2' - *methylene* - 4' - *pentenyl*) - 5 - *methoxyanthraquinone* (**15**). To a soln of **13** (38 mg, 0.12 mmol) in 10 ml toluene and 1 ml glacial AcOH which was purged with N_2 for 5 min and heated to 100° was added Zn dust (50 mg, 0.77 mmol) with stirring. After 20 min the mixture was poured into water and was extracted with 25 ml ether. The ether extract was washed twice with water, sat NaCl aq and was dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave **15** (37 mg) as yellow crystals: m.p. 76–78°; NMR ($CDCl_3$) δ 2.82, (d, 2H, J = 5 Hz, allylic CH_2), 3.48 (s, 2H, $ArCH_2$), 4.06 (s, 3H, OMe), 4.76, 4.91, 5.18 (3 br s, 4H, vinyl H), 5.61–6.14 (m, 1H, vinyl H), 7.31–8.01 (m, 5H, aromatic), 12.84 (s, 1H, OH); IR ($CHCl_3$) 1660, 1630, 1590 cm^{-1}; mass spectrum calc. for $C_{21}H_{18}O_4$: *m/e* 334.12051. Found: *m/e* 334.12414.

Spiro tetracycle **16**. To a soln of **13** (587 mg, 1.76 mmol) in 25 ml toluene was added 1.50 g Zn dust (22.9 mmol) and 1 ml AcOH which was heated at reflux for 1.5 h. After cooling the mixture was diluted with ether, washed with water, sat $NaHCO_3$ aq, sat NaCl aq and dried over $MgSO_4$. Evaporation of solvents *in vacuo* left 580 mg brown oil. Chromatography on 35 g Silica Gel H (Type 60) with a positive pressure and hexane/EtOAc gradient (80/20–50/50) provided two major components: R_f 0.33–0.53 (spiro **16**) and R_f 0.14–0.18 (diene **15**) as measured on a TLC plate. Spiro **16** was an orange solid (202 mg, 34%): m.p. 110–112.5°; NMR ($CDCl_3$) δ 0.78, 0.86 (d, 3H, J = 7 Hz), 2.10–3.04 (m, 5H, aliphatic), 4.08 (s, 3H, OCH_3), 4.98 (br s, 2H, $=CH_2$), 5.74, 5.86 (s, 1H, ea), 6.94–7.44 (m, 3H), 8.02, 8.11 (s, 1H ea), 9.09 (s, 1H, ArOH), 13.89 (s, 1H, H-bound OH); IR ($CHCl_3$) 1610, 1570, 1460, 1390 cm^{-1}; mass spectrum calc. for $C_{21}H_{20}O_4$: *m/e* 336.13616. Found: *m/e* 336.13160. Normal product **15** was a yellow solid (216 mg, 37%).

1 - *Methallyloxy* - 5 - *methoxy* - 9,10 - *diacetoxyanthracene* (**18**). To a soln of **9** (279 mg, 0.91 mmol) in 10 ml dry pyridine with 260 μl glacial AcOH (4.52 mmol) and 430 μl Ac_2O (4.54 mmol) which was purged with N_2 for 5 min was added activated Zn dust[34] (308 mg, 4.71 mmol). The mixture was stirred at rt under N_2 for 20 h. Excess Ac_2O was hydrolyzed by adding 1 ml water and stirring the mixture for 20 min. The mixture was poured into 100 ml water and was extracted with 75 ml ether. The ether extract was washed three times with 1M HCl, once with sat NaCl aq and was dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave **18** (338 mg, 98%) as a yellow solid which was recrystallized from EtOH as yellow microneedles: m.p. 168.5–170°; NMR ($CDCl_3$) δ 1.92 (s, 3H, vinyl CH_3), 2.47, 2.51 (s, 6H total, OAc), 3.94 (s, 3H, OMe), 4.60 (s, 2H, OCH_2), 5.10, 5.20 (br s, 1H each), 6.76–7.71 (m, 6H, aromatic); IR ($CHCl_3$) 1760, 1655, 1615, 1540 cm^{-1}; UV λ_{max} (95% EtOH) 260 nm (log ϵ 5.11); mass spectrum calc. for $C_{23}H_{22}O_6$: *m/e* 394.14164. Found: *m/e* 394.14119.

1 - *Acetoxy* - 2 - *methallyl* - 5 - *methoxyanthraquinone* (**19**). To a soln of **11** (1.028 g, 3.33 mmol) in 20 ml dry pyridine was added 5 ml Ac_2O (52.6 mmol, excess) which was allowed to stir at rt overnight. Water (10 ml) was added to hydrolyze excess Ac_2O by stirring for 20 min. The mixture was diluted with 100 ml ether and was washed three times with 1M HCl, once with sat $NaHCO_3$ aq, once with sat NaCl aq and dried over $MgSO_4$. Evaporation of solvents *in vacuo* gave **19** (1.1065 g, 95%) as a yellow solid which could be recrystallized from 95% EtOH as yellow needles: m.p. 155–156°; NMR ($CDCl_3$) δ 1.70 (s, 3H vinyl CH_3), 2.45 (s, 3H, OAc), 3.40 (s, 2H, $ArCH_2$), 4.05 (s, 3H, OMe), 4.70, 4.95 (s ea, 2H, $=CH_2$), 7.20–8.25 (m, 5H, aromatic); IR ($CHCl_3$) 1760, 1670, 1650 (sh), 1585, 1450 cm^{-1}; mass spectrum calc. for $C_{21}H_{18}O_5$: *m/e* 350.11841. Found: *m/e* 350.11542.

1,1 - *Methallyloxy* - 5,9,10 - *anthracene* (**20**). To a soln of **9** (2.00 g, 6.49 mmol) in 75 ml DMF was added sodium dithionite (2.5 g, 14.36 mmol) and Me_2SO_4 (1.4 ml, 14.8 mmol). 1M KOH was added dropwise (100 ml) over a period of 1 h. The mixture was poured into 250 ml water and was extracted with 150 ml ether and 50 ml CH_2Cl_2. Combined organic extracts were washed twice with water, three times with 1M HCl, once with sat NaCl aq, dried over $MgSO_4$ and evaporated *in vacuo* to give **20** (2.04 g, 93%) which was purified by chromatography on Silica Gel H (70% hexane/30% EtOAc): m.p. 113–114.5° (yellow plates, 95% EtOH); NMR ($CDCl_3$) δ 2.0 (s, 3H, vinyl CH_3), 3.95 (s, 6H, OCH_3), 4.05 (s, 3H, OCH_3), 4.65 (s, 2H, $ArOCH_2$), 5.05, 5.3 (br s, 1H ea, $=CH_2$), 6.75 (br d, 2H, J = 8 Hz), 7.4 (m, 2H), 8.0 (br d, 2H, J = 8 Hz); IR ($CHCl_3$) 2925, 2840, 1620, 1530, 1450 cm^{-1}; UV (95% EtOH) λ_{max} 260 nm; mass spectrum calc. for $C_{21}H_{22}O_4$: *m/e* 338.15181. Found: *m/e* 338.15159. (Found: C, 74.79; H, 6.70. Calc. for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55%).

1 - *Hydroxy* - 2 - *methallyl* - 5,9,10 - *trimethoxyanthracene* (**21**). A Soln of **20** (5.1 g, 15.1 mmol) in 50 ml $PhNMe_2$ was heated at 170° for 45 min. The mixture was diluted with 100 ml ether and was washed three times with 1M HCl, once with sat NaCl aq, dried over $MgSO_4$ and evaporated *in vacuo* to give **21** (4.89 g, 96%) as a yellow oil: NMR ($CDCl_3$) δ 1.8 (s, 3H, vinyl CH_3), 3.5 (s, 2H, $ArCH_2$), 3.95, 4.0 (2 s, 9H total, OCH_3), 4.75 (br s, 2H, $=CH_2$), 6.6–7.85 (m, 5H, aromatic), 9.9 (s, 1H, OH); IR ($CHCl_3$) 3350, 2950, 1620, 1560, 1530, 1460 cm^{-1}; mass spectrum *m/e* 338 (M^+). When chromatographed on silica gel (98% CH_2Cl_2/2% ether) the yellow oil crystallized after standing several days, m.p. 78–80.5°.

Oxidative coupling of phenol **21** (*dimer* **23**). To a soln of **21** (4.89 g, 14.5 mmol) in 100 ml CH_2Cl_2 was added 3.5 g MnO_2

(40.3 mmol, 2.8 eq.) which was stirred at rt for 1.5 h. The mixture was filtered through Celite and the solvent was evaporated *in vacuo* to leave 4.7 g brown solid (96%). Chromatography on silica gel with 55% CH_2Cl_2/45% ether gave dimer **23** as a yellow solid: m.p. 170–172° (hexane/EtOAc); NMR ($CDCl_3$) δ 1.5 (s, 6H, vinyl CH_3), 2.6 and 3.2 (ABq, J = 16 Hz, 4H, $ArCH_2$), 3.95, 4.05, 4.1 (3s, 6H ea, OCH_3), 4.5 (s, 4H, =ch$_2$), 5.3, 5.85 (br s, 2H ea, vinyl H), 6.9–8.0 (m, 6H, aromatic); IR ($CHCl_3$) 2925, 2850, 1645, 1605, 1565, 1460 cm^{-1}; UV (95% EtOH) λ_{max} 232, 267 (broad) nm; mass spectrum calc. for $C_{21}H_{22}O_4$: *m/e* 338.15181. Found: *m/e* 338.15134. (Found: C, 74.63; H, 6.24. Calc. for $(C_{21}H_{21}O_4)_2$: C, 74.76; H, 6.27%).

Cleavage of dimer **23** *to phenol* **21**. A soln of dimer **23** (1.97 g, 2.9 mmol) in 25 ml glacial AcOH to which 2.5 g Zn dust was added was stirred at rt for 1 h. The mixture was decanted into a separatory funnel with 75 ml CH_2Cl_2 and was washed once with water, twice with sat $NaHCO_3$ aq, once with sat NaCl aq, dried over $MgSO_4$ and was evaporated *in vacuo* to give **21** (1.79 g, 91%).

Spectral properties were indistinguishable from those previously reported.

Dipolar addition of diazomethane to dimer **23** (*adduct* **24**). To a soln of **23** (70 mg) in 5 ml CH_2Cl_2 was added 15 ml diazomethane soln (freshly distilled).[35] The mixture was swirled, stoppered and was allowed to stand at 0–5° in the refrigerator. After 114 h, the solvents were removed *in vacuo* to give **24** (89.5 mg) as a yellow solid: m.p. 169–171°, with the evolution of N_2; NMR ($CDCl_3$) δ 1.7 (s, 6H, vinyl CH_3), 3.0 and 3.4 (ABq, J = 14 Hz, 4H, vinyl CH_2), 3.35, 3.4, 3.95 (3s, 6H ea, OCH_3), 4.45 (d, J = 6 Hz, 4H), 4.85, 5.0 (br s, 4H, $=CH_2$), 6.6–7.8 (m, 6H, aromatic); IR ($CHCl_3$) 2925, 2850, 1690, 1575, 1460 cm^{-1}; UV (95% EtOH) λ_{max} 222, 264 nm; mass spectrum calc. for $(C_{22}H_{33}O_4)_2$: *m/e* 702.31927. Found: *m/e* 702.31841 ($M^+ - 2N_2$). Mass spectrum calc. for $C_{22}H_{23}O_4$ (monomer): *m/e* 352.16746. Found: *m/e* 352.16820.

Pyrolysis of diazo adduct **24** (*anthracene* **25**). Diazo adduct **24** (80 mg) was heated neat under N_2 at 185° for 40 min. Gas evolution was observed. The brown oil which was obtained after cooling was chromatographed on a preparative silica gel plate with a 98% CH_2Cl_2/2% ether solvent system to give **25** (20 mg, R_f 0.44–0.66): NMR ($CDCl_3$) δ 1.87 (s, 3H, vinyl CH_3), 2.45 (s, 3H, aromatic CH_3), 3.53 (s, 2H, $ArCH_2R$), 3.57, 4.03 (s, 3H, 6H, OCH_3), 4.43, 4.75 (br s, 1H ea, $=CH_2$), 6.6–7.7 (m, 4H, aromatic), 9.93 (s, 1H, ArOH); IR ($CHCl_3$) 3325, 2950, 1640, 1560, 1530, 1450 cm^{-1}; mass spectrum *m/e* 352 (M^+), 337 ($M - CH_3$), 307 ($M - (CH_3)_3$).

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