(s, 3 H), 3.80 (s, 3 H), and 6.77–8.03 (m, 7 H); exact mass $C_{17}H_{16}O_5$, calcd *m/e* 300.0998, obsd *m/e* 300.1005, difference 0.0007].

Acknowledgment. We thank the National Science Foundation and The Ohio State University Small Grants Program for generous support of this work. We are indebted to Mr. Daniel Henton for a sample of dimethyl 3-methoxyphthalate.

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(20) All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements of standard samples indicated that the observed melting points were probably 1–2 °C lower than the corrected values. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrometer. ^{1}H NMR spectra were taken at 60 MHz with Varian EM-360 or A-60A instruments, with the latter observed for all critical work. ^{13}C NMR spectra were recorded on a Bruker HX-90 instrument by Dr. Charles Cottrell. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronic MS-9 double-focusing mass spectrometer. Analytical samples were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Aluminum oxide and silica gel were from E. Merck Co. Tetrahydrofuran was distilled from benzophenone ketyl directly into the reaction flask. Reactions run in an inert atmosphere made use of a three-way stopcock with $^{14}/_{20}$ joint which allowed the flask to be flame dried under vacuum and filled with purified nitrogen. Butyllithium in hexane (Ventron) was titrated in tetrahydrofuran with 1,10-phenanthroline as the indicator. The earlier anodic oxidations were performed on a cooled, magnetically stirred solution using the power supply previously described[1] and the cell in Figure 1 but without the reference electrode. More recent work was performed at constant potential relative to a platinum reference electrode using a Kepco power supply with currents between 0.5 and 2.0 A using the platinum gauze anode previously described. This potentiostat was designed by R. McCreery and built by D. Henton. Other than reducing the time of electrolysis by a factor of 2–3, the results are identical for the two systems.
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A Regiospecific Synthesis of the Anthracycline Aglycones, Daunomycinone and Adriamycinone‡

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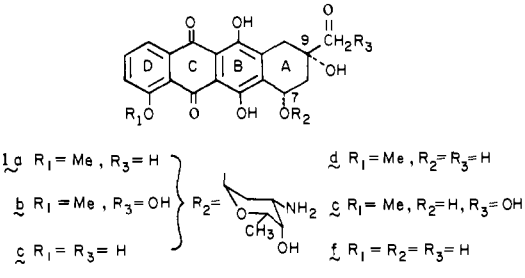
Abstract: A synthesis of (±)-7,9-deoxydaunomycinone has been accomplished in 14% overall yield from the known 3-bromo-2,5-dimethoxybenzaldehyde. This compound can be converted by known steps into daunomycin and adriamycin. The key step involves the regiospecific coupling of the eventual AB-ring system in the form of a lithiated quinone bisketal to dimethyl 3-methoxyphthalate. The utility of the analogous 2-lithio-1,4-dimethoxytetralin derivative coupling to dimethyl 3-methoxyphthalate was also studied and the reaction product converted to (±)-7,9-deoxydaunomycinone.

Introduction

The anthracyclines daunomycin (**1a**), adriamycin (**1b**), and carminomycin (**1c**) are important antibiotics of much current interest clinically, biologically, and chemically.[3] Inasmuch as the glycone, daunosamine, has been synthesized[4] and the coupling of glycone and the aglycone achieved,[5] a synthesis of the anthracycline aglycone constitutes a formal synthesis of these important compounds. Furthermore, since daunomycinone (**1d**) has been converted chemically to both adriamycinone[6] (**1e**) and carminomycinone[7] (**1f**), a synthesis of **1d** serves as a route to **1e** and **1f**. Much methodology[7-11] has been explored for the synthesis of these aglycones, and several formal syntheses of daunomycinone[8] have been report-



‡ Dedicated to Professor Melvin S. Newman on his 70th birthday.

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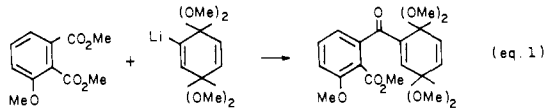
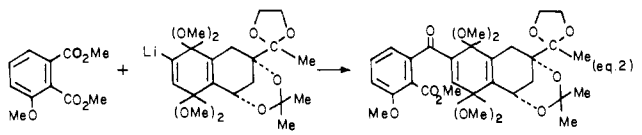
ed.[7,10b,c,11] The majority of routes to the aglycone have utilized Friedel-Crafts-type condensations[10] or Diels-Alder reactions[7,8] as key steps in building the tetracyclic ring system. These routes have generally allowed little control of the regioselectivity of the ring system or else encountered unfortunate loss of regioselectivity at some stage.[10c]

A major goal in a practical route to these anthracyclinones is a synthesis which avoids the formation and subsequent separation of regioisomers. In spite of much effort in this area only three regiospecific routes to anthracyclinones have been reported: Kende's photo-Fries rearrangement sequence,[11a] the anionic route communicated by us,[2] and an intramolecular basic catalyzed route recently reported by Sih.[11b] In addition to a regiospecific synthesis, we considered highly desirable a route which in principle would also allow the cis-1,3-diol of the A ring to be carried in protected form in the AB-ring fragment used to construct the tetracyclic ring system. Work described in the accompanying paper[12] had already established precedent for a regiospecific reaction of a lithiated quinone bisketal to dimethyl 3-methoxyphthalate (eq 1). In the idealized sequence outlined below (eq 2) we hoped to effect a similar coupling of



(eq. 1)

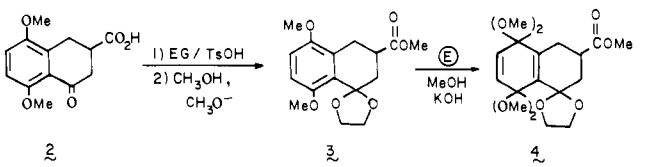


(eq. 2)

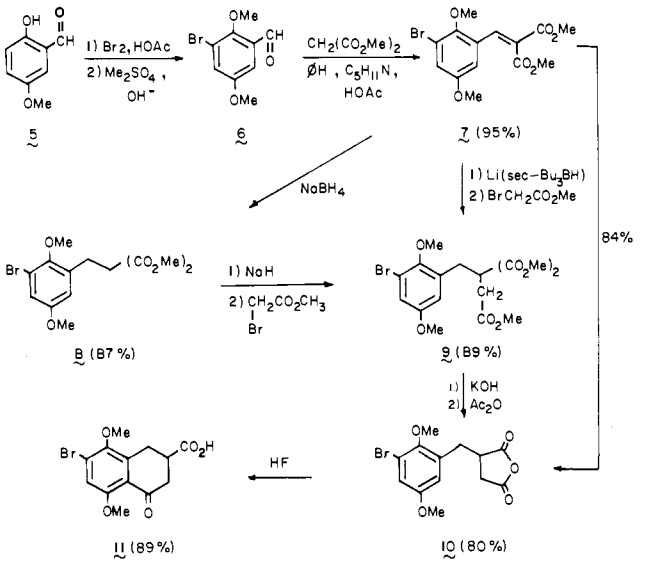
an AB-ring fragment to a D-ring component which after intramolecular ring closure would generate the intact anthracyclinone. This proposed route was especially attractive since ^{14}C-labeled diester would afford a route to ring carbon labeled systems for metabolism and tissue distribution studies. We describe here the details of the regiospecific coupling of an AB-ring component to dimethyl 3-methoxyphthalate and the efficient conversion of this material to (±)-7,9-deoxydaunomycinone. This, taken with published procedures, provides a regiospecific total synthesis of the racemic anthracyclinones daunomycinone, adriamycinone, and carminomycinone.

A Model Anodic Oxidation and Synthesis of the AB-Ring System

Since the only reported anodic oxidations of a 1,4-dimethoxy aromatic to a quinone bisketal were for 1,4-dimethoxy- and 1,2,4-trimethoxybenzene[13a,b] and since this route required that the anodic oxidation be performed on a functionalized tetralin, we first examined this electrochemical step in a model system.[14] The readily available keto acid **2** was converted to **3** by ketalization followed by ester exchange with methoxide. Anodic oxidation of **3** at platinum cleanly afforded **4.**

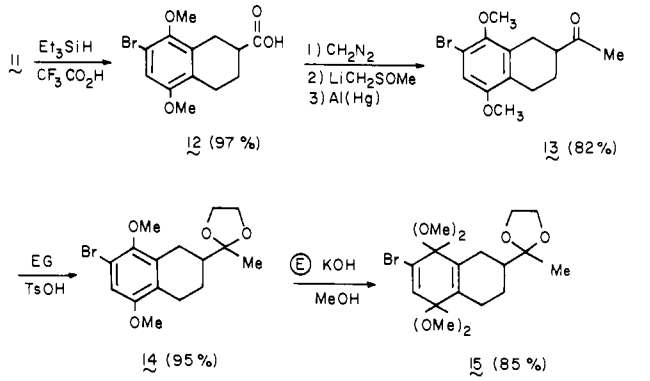


Having established that the anodic oxidation was applicable to more functionalized systems, we needed an efficient synthesis of the AB-ring portion. A route modeled after Wong's[10b] synthesis of the debrominated analogue appeared ideally suited for constructing the bicyclic ring component. Bromination of commercially available 2-hydroxy-5-methoxybenzaldehyde followed by methylation afforded **6** conveniently in 100-g lots. Reduction of the double bond of the Knoevenagel product **7**



by hydrogenation with either palladium or Raney nickel catalyst was complicated by 5–10% hydrogenolysis of the bromide. Although the use of sodium borohydride avoided this problem, an even more efficient solution took advantage of the in situ alkylation of the lithium tri-*sec*-butylborohydride reduction[15] product of **7** to afford **9** in 89% yield. The triester was then converted to **11** via standard procedures. This serves as an especially attractive route to **11** since the conversion of **7** to **10** can be conducted in 84% overall yield without purification of intermediates.

At this point two distinct paths to the tetracyclic system were considered. Since the tetralone **11** will eventually become the AB rings of daunomycinone, the presence of the ketone carbonyl is attractive since it could be converted to the 7-hydroxyl of the final product. However, surmising that the oxygen could be a potential source of trouble we elected to remove the carbonyl at this point and later introduce a hydroxyl by known methods. Reduction of **11** to **12** with triethylsilane was remarkably facile and circumvented complications encountered with more conventional methods.[16] Although not without limitations, this little-used procedure is an excellent way to reduce aryl ketones to the respective methylene compounds. Standard reactions were then employed to convert **12** to **14.**[17]

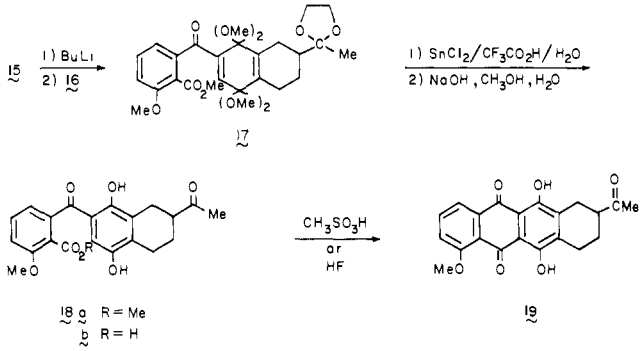


Although the anodic oxidation of **14** proceeded well, the product isolated by recrystallization was extraordinarily sensitive to traces of acid, often airborne, and had to be handled with care in base-washed apparatus to avoid decomposition.

Coupling of the AB- and D-Ring Fragments

Experience gained with model compounds enabled the metalation of **15** and its coupling to dimethyl 3-methoxyphthalate (**16**) to be performed without complication. The

lithium–bromine exchange in these systems is very rapid, being complete within 2 min at −80 °C. Yields are maximized, especially in larger runs, by a reaction temperature below −80 °C and vigorous mechanical stirring during the addition of the butyllithium. The product, **17**, is not as sensitive as **15** and may be separated fron unreacted diester and debrominated **15** by column chromatography. Material obtained in this way gave ^1H and ^{13}C NMR spectra characteristic of one isomer; no evidence for bis addition or loss of regioselectivity was observed in either the crude or the purified product. It had been previously observed that hydrolysis of quinone bisketals substituted with an aromatic ketone does not afford a quinone but a hydroquinone, even in the absence of what are commonly considered reducing agents.[19] Whatever the reason, the fortuitous behavior of **17** was welcomed since it gave a compound in the proper oxidation state for cyclization. It was subsequently established that the presence of 1 equiv of stannous chloride improved the yield of the reductive hydrolysis, and only this procedure is given. Hydrolysis of the ester was readily effected by 20% sodium hydroxide at room temperature. The ease of this reaction presumably reflects participation[20] by the adjacent carbonyl group. Final cyclization to afford **19** could be effected by either hydrogen fluoride or methanesulfonic acid. While intermediates **18a** and **18b** could be isolated, the conversion of **17** to **19** (40% yield) is best carried out without purification of intermediates. In fact, by converting crude coupling product mixture (i.e., **17**) to **19** (30%) the only chromatography in the entire synthetic sequence is eliminated. Since **19** has been converted to daunomycinone this sequence represents a regiospecific synthesis of the anthracycline aglycones.

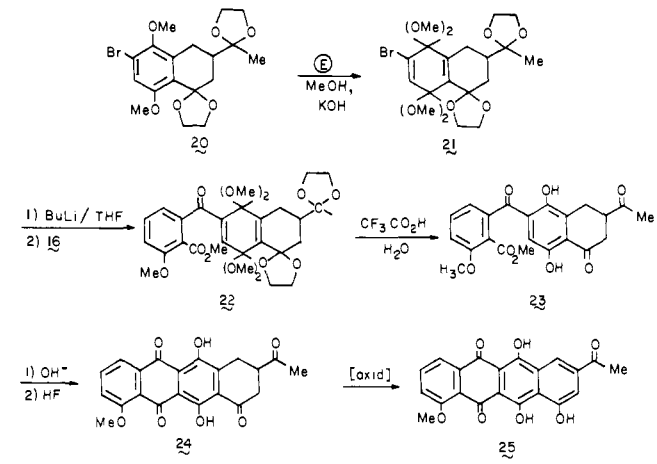


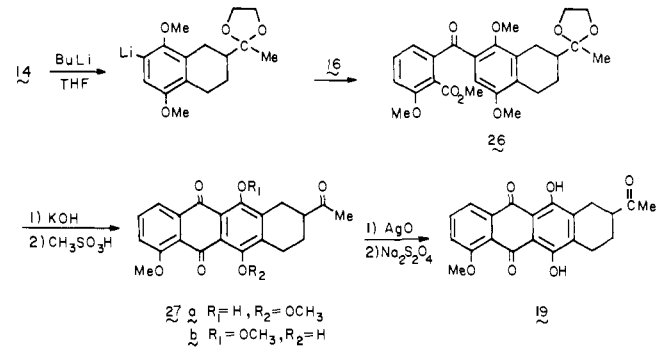
A Route to 7-Keto-9-deoxydaunomycinone

As noted earlier the reduction of the carbonyl of **11** removed an oxygen function at what would eventually be carbon 7 of the final product. Since we have subsequently found that reintroduction of the 7-hydroxy function[6b,7a,21,22] is not at all convenient for a reasonable scale reaction, it was particularly painful that the oxygen function of **11** had been removed. To determine if the keto group could be retained throughout the synthetic sequence, the reactions shown below were carried out. The ultimate product of the reaction sequence is not easy to purify or handle. Even when reasonable precautions were taken to exclude oxygen, the final reaction mixtures oxidized rapidly and it was not possible to isolate **24** free of the oxidation product, **25**.[23] An NMR spectrum of a 4:1 mixture (presumably of **24** and **25**) supported the formation of **24**. Even though the steps leading to **23** proceeded in a straightforward manner, the lability of the final reaction products precluded any utility of the sequence for our purposes and this route was abandoned.

Aryllithium Approach to (±)-7,9-Deoxydaunomycinone

Our rationale for the utilization of the lithiated quinone bisketals for the coupling of the AB- and D-ring fragments was based on considerations outlined previously.[12] However, a valid question is whether the regioselective coupling could not be effected by utilizing an aryllithium rather than the protected quinone anion. Since a model study has shown that there was at least a good deal of selectivity in the addition of 2-lithio-1,4-dimethoxybenzene to dimethyl 3-methoxyphthalate, this route was briefly examined to assess its merits vs. those of the quinone bisketal sequence. Coupling of lithiated **14** with dimethyl 3-methoxyphthalate afforded after chromatography 40% of coupling product in about 90% purity. A pure sample was separated by pressurized chromatography and showed spectroscopic properties consistent with **26**. Hydrolysis of **26** followed by cyclization afforded a dark residue which, after filtration through silica gel and precipitation, afforded 37% of a dimethoxy compound. While we favor **27a** for this material, we cannot exclude **27b**. Oxidation of **27** with silver oxide followed by reduction with sodium dithionite afforded 68% of **19**. While these yields have not been optimized, this route is not so convenient for us as the bisketal sequence. However, where the electrochemical apparatus is lacking or where the bisketal moiety interferes in the synthesis of analogues, this series of reactions may serve as a viable alternative route to anthracyclinones.





Summary

The sequence presented here allows preparation of the (±)-7,9-deoxydaunomycinone (**19**) in 13.7% overall yield from the known **6**. While a number of steps are involved many can be performed without purification of the product, and the entire sequence requires no chromatographic separations. Although the 9-hydroxy substituent is conveniently introduced into **19**,[10c] we have not been able to functionalize the 7 position on a scale needed for subsequent work. Since we anticipate needing 10–20-g quantities of (±)-daunomycinone for resolution and analogue studies, routes incorporating the 7- and 9- hydroxy substituents in the AB-ring system prior to coupling to dimethyl 3-methoxyphthalate are being explored.

Experimental Section[24]

3. A mixture of 1.0 g (3.85 mmol) of **2**, 2.0 mL of ethylene glycol, and 15 mg of *p*-toluenesulfonic acid monohydrate in 30 mL of benzene was refluxed and the water collected with a Dean-Stark trap. To the cooled solution was added 30 mL of methanolic sodium methoxide (30 mg of sodium/30 mL of methanol) and the reaction mixture stirred for 14 h. The solvent was removed in vacuo followed by dilution of the residue with 40 mL of ether. The ethereal layer was washed with water (3 × 50 mL), dried, and concentrated, and the residue recrystallized from ether/hexane to give 1.05 g (89%) of **3**: mp 136–137 °C; IR (KBr) cm^{-1} 1723 (s), 1600 (w), 1478 (m), 1262 (s), 1208 (m), 1090 (m), and 1051 (m); NMR ($CDCl_3$, 60 MHz) δ 6.75 (s, 2 H), 4.18 (m, 4 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), and 3.5–1.7 (m, 5 H).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.31; H, 6.55.

4. A solution of 0.336 g (1.09 mmol) of **3** and 0.4 g of potassium hydroxide in 60 mL of methanol was anodically oxidized at 3 °C using apparatus I. The UV maximum at 297 nm diminished smoothly and symmetrically to an optical density of 5% of its initial value. Removal of the solvent in vacuo at room temperature gave a residue which was taken up in ether (50 mL), washed with water (50 mL), and dried. Concentration afforded an oil which solidified and was recrystallized from hexane/ether to give after two recrystallizations 0.20 g (51%, yield not maximized) of **4** as white crystals: mp 69–70 °C; IR (KBr) cm^{-1} 1722 (s), 1282 (m), 1270 (m), 1258 (m), 1204 (s), 1189 (m), 1176 (m), 1083 (s, br), 1031 (m), and 968 (m); NMR ($CDCl_3$, 60 MHz) δ 6.17 (d of an AB, J = 11 Hz, 1 H), 5.92 (d of an AB, J = 11 Hz, 1 H), 4.4–3.8 (m, 4 H), 3.67 (s, 3 H), 3.22 (s, 3 H), 3.18 (s, 3 H), 3.15 (s, 6 H), and 3.1–1.8 (m, 5 H).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 58.37; H, 7.08. Found: C, 58.25; H, 6.92.

6. The method of Rubenstein[25] was used to synthesize 3-bromo-2-hydroxy-5-methoxybenzaldehyde from commercially available (Aldrich) **5** and bromine in acetic acid. The color of the product was considerably improved when the crude acetic acid solution was poured into three volumes of 5% stannous chloride dihydrate solution. Crystallization from ethanol should be carried out as rapidly as possible since the solution darkens upon standing. The dry and crystalline product, mp 109–110.5 °C (lit.[25] 107 °C), remains light yellow even on extended storage: IR (KBr) cm^{-1} 1647 (s), 1602 (s), 1455 (s), 1445 (s), 1430 (s), 1315 (s), 1236 (s), 1128 (s), and 1036 (s); NMR ($CDCl_3$, 60 MHz) δ 11.00 (s, 1 H), 9.76 (s, 1 H), 7.35 (d of an AB, J = 3 Hz, 1 H), 6.99 (d of an AB, J = 3 Hz, 1 H), and 3.78 (s, 3 H).

A 3-L flask equipped with a mechanical stirrer, nitrogen inlet, and two pressure-equalizing addition funnels was charged with 108.7 g (0.467 mmol) of 3-bromo-2-hydroxy-5-methoxybenzaldehyde, 1 L of water, and 20 g of sodium hydroxide. The mixture was heated on a steam bath and stirred under nitrogen until it became homogeneous. A total of 400 g (3.15 mol) of dimethyl sulfate and sufficient 50% sodium hydroxide to keep the medium basic were added slowly over a period of 9 h as the solution was kept hot. The yellow (presumably due to unreacted starting material) alkaline (pH 12) solution was cooled in an ice bath with stirring. The light-brown precipitate which formed was filtered, washed with 200 mL of cold water, dissolved in 600 mL of absolute ethanol, and decolorized with 1 g of charcoal. After hot vacuum filtration the volume was reduced by one-half. Addition of 600 mL of water and ice gave 100.4 g (87%) of **6** as fine, white needles: mp 62–63 °C (lit.[25] 63 °C); IR (KBr) cm^{-1} 1679 (s), 1593 (m), 1464 (s), 1413 (m), 1383 (m), 1222 (m), 1201 (m), 1101 (m), 1041 (m), and 981 (m); NMR ($CDCl_3$, 60 MHz) δ 10.29 (s, 1 H), 7.36 (d of an AB, J = 3 Hz, 1 H), 7.26 (d of an AB, J = 3 Hz, 1 H), 3.92 (s, 3 H), and 3.80 (s, 3 H). The alkaline aqueous solution was extracted with two 200-mL portions of ether to give 0.7 g of impure product.

7. A solution of 100.4 g (0.406 mol) of **6**, 59.0 g (0.447 mol) of dimethyl malonate, 1 g of piperidine, and 3 g of acetic acid was refluxed with 300 mL of benzene in an apparatus equipped for the separation of water for 6 h. The product mixture was diluted with an equal volume of ether and washed with 100-mL portions of 5% hydrochloric acid, 5% sodium bicarbonate, and brine. The aqueous washes, which were not combined, were extracted once with ether. Removal of solvent under reduced pressure followed by crystallization of the residue twice from 100-mL portions of ether with cooling to −20 °C gave 138.1 g (95%) of **7** as chunky, pale-yellow crystals, mp 57.5–59.0 °C. The mother liquors were concentrated, giving an oil which partially solidified over the period of 1 week. NMR analysis suggested that, although the greater portion of this material was **7**, significant amounts of impurities were present. The analytical sample was distilled from an 80 °C bath at 1 × 10^{-5} Torr onto the dry ice cooled cold finger of a sublimation apparatus: IR (KBr) cm^{-1} 1712 (s), 1614 (m), 1585 (m), 1463 (s), 1452 (s), 1431 (s), 1427 (m), 1403 (s), 1355 (m), 1303 (m), 1249 (s), 1230 (s), 1210 (s), 1102 (m), 1066 (s), 1040 (s), 996 (s), and 852 (m); NMR (CCl_4, 60 MHz) δ 7.78 (s, 1 H), 7.07 (d of an AB, J = 3 Hz, 1 H), 6.80 (d of an AB, J = 3 Hz, 1 H), 3.82 (s, 3 H), and 3.73 (s, 9 H); UV (CH_3OH) nm (ϵ) 330 (3800) and 280 (12 800).

Anal. Calcd for $C_{14}H_{15}O_6Br$: C, 46.81; H, 4.21; Br, 22.25. Found: C, 46.73; H, 4.26; Br, 22.44.

8. A magnetically stirred slurry of 45.4 g (0.127 mol) of **7** in 500 mL of methanol was cooled to 5 °C in an ice bath and treated over a period of 2 h with sufficient sodium borohydride to cause the UV maximum at 330 nm to decrease to less than 5% of the original value. The colorless solution was acidified with 5% hydrochloric acid, and methanol was removed under reduced pressure. The residue was diluted with 200 mL of water and extracted with four 100-mL portions of methylene chloride. The combined organic layers were washed once with 200 mL of brine, dried by passing through magnesium sulfate, and concentrated. The resultant oil was distilled in a bulb-to-bulb apparatus at 7 × 10^{-5} Torr from a 180 °C bath to give 39.83 g (87%) of **8** as a clear, colorless, very thick oil, 97% pure by GLC:IR (film) cm^{-1} 1748 (s), 1601 (m), 1570 (m), 1483 (s), 1430 (s), 1368 (m), 1290 (s), 1229 (s), 1166 (s), 1058 (s), and 1010 (m); NMR ($CDCl_3$, 60 MHz) δ 6.88 (d of an AB, J = 2.5 Hz, 1 H), 6.60 (d of an AB, J = 2.5 Hz, 1 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.63 (s, 6 H), and 3.10 (d, J = 8 Hz, 2 H); the acidic proton triplet is masked by the methoxy singlets; exact mass $C_{14}H_{17}O_6Br$ calcd *m/e* 360.020 892 8, obsd *m/e* 360.021 383 2, difference 0.0005. Various attempts to isolate analytically pure samples of this compound by column chromatography failed, as did preparative-scale GLC.

9. A 1-L flask equipped with a magnetic stirrer, nitrogen inlet, condenser, and pressure-equalizing addition funnel was charged with 40.04 g (0.111 mol) of **8** and 400 mL of dry tetrahydrofuran. Sodium hydride (5.75 g of a 56% oil dispersion, 0.134 mol) was washed free of oil with tetrahydrofuran and added in portions as a slurry in tetrahydrofuran to the solution of **8**. If evolution of hydrogen does not occur, a few drops of methanol should be added. After the solution was stirred for 20 min 18.82 g (0.123 mol) of methyl bromoacetate was added in one portion and the solution was refluxed for 1 h. The solution was cooled and filtered through Celite to remove inorganic salts. Solvent was removed and the residue was crystallized from chloroform–hexane to give 42.8 g (88%) of compact, colorless crystals melting at 104.5–106.0 °C. The analytical sample was prepared by sublimation at 2 × 10^{-5} Torr from a 90 °C bath: mp 104.5–106.0 °C; IR (KBr) cm^{-1} 1741 (m), 1720 (s), 1590 (w), 1551 (w), 1465 (m), 1431 (m), 1415 (m), 1280 (m), 1244 (m), 1232 (m), 1210 (m), 1187 (s), 1052 (m), and 996 (m); NMR (CCl_4, 100 MHz) δ 6.94 (d of an AB, J = 3 Hz, 1 H), 6.47 (d of an AB, J = 3 Hz, 1 H), 3.70 (s, 12 H), 3.66 (s, 3 H), 3.39 (s, 2 H), and 2.75 (s, 2 H).

Anal. Calcd for $C_{17}H_{21}O_6Br$: C, 47.12; H, 4.89; Br, 18.45. Found: C, 47.18; H, 4.89; Br, 18.26.

Preparation of 9 from 7. A solution of 2.00 g (5.6 mmol) of **7** in 20 mL of tetrahydrofuran in a 50-mL flask equipped with thermometer, nitrogen inlet, rubber septum, and magnetic stirrer was treated at −60 °C with 6.0 mL (6.0 mmol, 1.07 equiv) of 1 M Selectride (lithium tri-*sec*-butylborohydride in tetrahydrofuran) over 5 min. The reaction was exothermic. The solution was stirred for 10 min at −20 °C and 0.918 g (6.0 mmol) of methyl bromoacetate (neat) was added all at once via syringe. The solution was stirred for 1 h at room temperature, refluxed for 0.5 h, and stirred at room temperature for another 1.5 h before solvent was removed. The residue was neutralized with 5% hydrochloric acid, extracted with ether, and dried. Replacement of the ether with hexane gave 2.16 g (89%) of white, crystalline **9**, mp 105–106 °C.

10. A mixture of 37.4 g (86.3 mmol) of **9**, 100 mL of ethanol, 60 g of potassium hydroxide, and 250 mL of water was stirred on a steam bath for 5 h and then overnight at room temperature. The clear, almost colorless solution was extracted once with 100 mL of chloroform and poured onto 120 mL of concentrated hydrochloric acid and 150 mL of ice. The initially clear and colorless acidic solution gave crystals

of product over the period of a few hours. After 100 g of sodium chloride was dissolved into the solution it was cooled to 3 °C overnight. Filtration and washing with 200 mL of water followed by vacuum drying gave 33.74 g (100%) of a white, crystalline solid which was not purified further: mp 181 °C, with vigorous gas evolution; NMR (CF_3COOH, 60 MHz) δ 7.26 (d of an AB, J = 3 Hz, 1 H), 6.86 (d of an AB, J = 3 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.57 (s, 2 H), and 3.40 (s, 2 H).

A mixture of 32.3 g (82.6 mmol) of the above compound and 250 mL of acetic anhydride was refluxed for 20 min. The acetic anhydride was removed under reduced pressure, finally at 0.2 Torr, to give a brown solid, mp 140–143 °C, which was crystallized from 100 mL of chloroform to give 21.6 g (80%) of **10**, mp 142–144 °C. The apparently low yield is due in part to the presence of considerable sodium chloride in the synthetic sample of the acid: IR (KBr) cm^{-1} 1860 (m), 1840 (m), 1780 (s), 1760 (s), 1602 (m), 1480 (s), 1231 (m), 1222 (m), 1081 (m), 1029 (m), 944 (m), and 931 (m); NMR (Me_2SO-d_6, 60 MHz) δ 6.98 (d of an AB, J = 3 Hz, 1 H), 6.75 (d of an AB, J = 3 Hz, 1 H), 3.62 (s, 6 H), and 3.5–2.6 (m, 5 H); UV (CH_3OH) nm (ϵ) 287 (3100).

Anal. Calcd for $C_{13}H_{13}O_5Br$: C, 47.43; H, 3.98; Br, 24.28. Found: C, 47.48; H, 4.04; Br, 24.11.

Conversion of 7 to 10 without Isolation of Intermediates. Reduction of 25.0 g (69.6 mmol) of **7** in a mechanically stirred solution of 200 mL of tetrahydrofuran at −60 °C with 70 mL (70 mmol) of 1 M lithium tri-*sec*-butylborohydride in tetrahydrofuran (delivered via syringe) was allowed to proceed for 30 min. After warming to 0 °C, 10.70 g (70 mmol) of methyl bromoacetate was added, and the solution was refluxed for 3 h under nitrogen. GLC analysis of an acidified aliquot indicated the presence of **8**; 1.0 g of methyl bromoacetate was added, and an additional 2 h of reflux was sufficient to cause completion of the reaction, giving product at least 95% pure by GLC. The tetrahydrofuran was removed and the residue was converted to **10** without purification of intermediates, as described above, yielding 19.29 g (84% from **7**) after one crystallization from methylene chloride/ether.

11. Hydrogen fluoride (200 mL) was condensed into a polyethylene bottle containing 20.99 g (63.8 mmol) of **10**. After 1 h at room temperature the bottle was placed in a 40 °C water bath to evaporate most of the hydrogen fluoride. The residue, which still contained some hydrogen fluoride, was carefully quenched with ice, and 200 mL of water and ice was added. An oil separated which soon solidified (in some runs, a crystalline precipitate forms directly). Water was decanted into another polyethylene bottle and the organic residue was dissolved with stirring in 400 mL of chloroform. The organic solution was dried with magnesium sulfate after it was washed once with 200 mL of water. Reduction of the volume to 75 mL gave 19.3 g (89%) of **11**, mp 177–179 °C. The analytical sample was obtained by sublimation from a 165 °C bath at 3×10^{-5} Torr: mp 178–179 °C; IR (KBr) cm^{-1} 3500–2700 (broad), 1689 (s), 1663 (s), 1545 (m), 1460 (m), 1267 (m), 1216 (m), and 1079 (m); NMR ($CDCl_3$, 60 MHz) δ 9.56 (s, 1 H), 7.08 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), and 3.3–2.7 (m, 5 H).

Anal. Calcd for $C_{13}H_{13}O_5Br$: C, 47.43; H, 3.98; Br, 24.28. Found: C, 47.28; H, 4.12; Br, 24.09.

12. A yellow solution of 6.62 g (20.1 mmol) of **11** in 50 mL of trifluoroacetic acid was treated with 8.1 mL (5.83 g, 2.5 equiv) of triethylsilane. Initially, vigorous magnetic stirring was necessary to obtain a homogeneous mixture, and an exothermic reaction, marked by the disappearance of the yellow color, took place over a period of approximately 15 min. The trifluoroacetic acid was distilled into a dry ice-cooled vacuum pump trap at 1 Torr. The use of a warm water bath speeds this distillation, and the distilled trifluoroacetic acid may be used in the next run without further purification. The solid white residue was dissolved in excess 20% potassium hydroxide solution, washed once with ether to remove silicon-containing by-products, and acidified with concentrated hydrochloric acid. The white precipitate was filtered to give 97% yield of white, crystalline **12**, mp 180–181 °C, after vacuum drying. One crystallization from ether gave crystalline solid, mp 182–183 °C, with virtually no loss of material: IR (KBr) cm^{-1} 1701 (s), 1579 (w), 1471 (m), 1444 (m), 1429 (m), 1230 (m), and 1099 (m); NMR ($CDCl_3$, 60 MHz) δ 11.10 (s, 1 H), 6.80 (s, 1 H), 3.73 (s, 6 H), and 3.2–1.9 (m, 7 H); exact mass $C_{13}H_{15}O_4Br$, calcd m/e 314.015 415 4, obsd m/e 314.015 823 3, difference 0.0004.

Anal. Calcd for $C_{13}H_{15}O_4Br$: C, 49.54; H, 4.80. Found: C, 49.48; H, 4.72.

Alternatively, the precipitated **12** may be extracted into methylene chloride and used without analysis, as described in the next experiment. This procedure was used in this run.

13. The crude solution of **12** in methylene chloride obtained in the preceding experiment was treated with ethereal diazomethane until the yellow color persisted. Crystallization from 10 mL of methylcyclohexane gave 6.36 g (96% over two steps from **11**) of the ester: mp 85–86 °C; IR (KBr) cm^{-1} 1725 (s), 1579 (w), 1472 (m), 1437 (m), 1235 (m), 1169 (m), and 1095 (m); NMR ($CDCl_3$, 60 MHz) δ 6.80 (s, 1 H), 3.73 (s, 6 H), 3.70 (s, 3 H), and 3.2–1.5 (m, 7 H); exact mass $C_{14}H_{17}O_4Br$, calcd m/e 328.031 064 6, obsd m/e 328.031 690 4, difference 0.0006.

Anal. Calcd for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.21. Found: C, 51.14; H, 5.19.

Dimethyl sulfoxide (20 mL) and 100 mL of tetrahydrofuran were cooled under nitrogen in a 250-mL flask equipped with a mechanical stirrer and rubber septum. As the solution was vigorously stirred 20.1 mL (38.2 mmol, 2.1 equiv) of a 1.9 M solution of methyllithium in ether was added over 5 min. A white slurry of the lithium salt of dimethyl sulfoxide formed. While maintaining vigorous stirring, 6.00 g (18.2 mmol) of the ester in 10 mL of tetrahydrofuran was added as rapidly as possible. The slurry was stirred in the cold for 0.5 h and quenched with a few milliliters of methanol. Solvent was removed and the residue was poured into 50 mL of saturated ammonium chloride. The product was extracted with methylene chloride (4 × 50 mL); the organic phase was washed once with water (200 mL) and dried. Removal of solvent gave 7.5 g of a semisolid residue which was used in the next reaction without purification. In other runs the β-keto sulfoxide was isolated as a white solid after two crystallizations from ether/methylene chloride: mp 141–142 °C with softening from 137 °C (mixture of diastereomers) in 88% yield; IR (KBr) cm^{-1} 1697 (s), 1575 (m), 1469 (s), 1427 (m), 1228 (s), 1095 (s), 1050 (s), and 1037 (s); NMR ($CDCl_3$, 60 MHz) δ 6.82 (s, 1 H), 3.92 (s, 2 H) (split at 100 MHz into two peaks, the upfield signal half the height of the other), 3.75 (s, 3 H), 2.95 (m, 3 H), 2.72 (s, 3 H), and 2.5–1.5 (m, 2 H).

Anal. Calcd for $C_{15}H_{19}BrO_4S$: C, 48.00; H, 5.10. Found: C, 47.79; H, 5.09.

Aluminum amalgam, prepared from 4.9 g (10 equiv) of aluminum foil according to the method of Corey[18], was allowed to react with the crude product from the previous reaction in 360 mL of tetrahydrofuran and 40 mL of water for 45 min. Filtration followed by removal of solvent and extraction of product with methylene chloride yielded an oil which crystallized on standing. Two crystallizations from hexane gave 4.68 g (82% over two steps from **12** and **13**): mp 72.5–73.5 °C; IR (KBr) cm^{-1} 1725 (s), 1590 (w), 1580 (w), 1473 (m), 1437 (m), 1233 (m), 1166 (m), and 1094 (m); NMR ($CDCl_3$, 60 MHz) δ 6.84 (s, 1 H), 3.74 (s, 6 H), 3.2–2.0 (m, 7 H), and 2.24 (s, 3 H).

14. A solution of 4.68 g (14.9 mmol) of **13**, 3 mL of ethylene glycol, 50 mg of *p*-toluenesulfonic acid monohydrate, and 50 mL of benzene was refluxed for 6 h and the water collected in a Dean-Stark trap. The cooled solution was washed with 50 mL of 5% sodium bicarbonate solution and twice with water and dried over calcium sulfate. Removal of the solvent and recrystallization from 7 mL of hexane gave 5.07 g (95%) of **14**: mp 98–100 °C; IR (KBr) cm^{-1} 1590 (w), 1579 (w), 1464 (s), 1425 (m), 1404 (m), 1294 (m), 1232 (s), 1096 (s), and 1055 (s); NMR ($CDCl_3$, 60 MHz) δ 6.72 (s, 1 H), 3.90 (s, 4 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.3–1.0 (m, 7 H); UV (CH_3OH) nm (ϵ) 288 (2700).

Anal. Calcd for $C_{16}H_{21}BrO_4$: C, 53.79; H, 5.93. Found: C, 53.86; H, 5.89.

15. Anodic oxidation of **14** was carried out in a standard H-cell apparatus having compartments 3.0 cm in diameter separated by a medium-porosity fritted disk (see Figure 1). The anode and cathode compartments had volumes of 85 mL each. The cathode compartment contained 1.5 g of potassium hydroxide in methanol, while in the anode compartment were 1.08 g (3.03 mmol) of **15** and 1.5 g of potassium hydroxide dissolved in 10 mL of tetrahydrofuran and 50 mL of methanol. Oxidation was carried out at a constant potential of 1.3 V vs. a platinum reference electrode at 5–15 °C and with a current of 0.6 A for 2 h. The progress of the reaction was monitored by following the decrease in the UV maximum at 288 nm to about 5% of the original value. Dry ice was added to the contents of the anode compartment until the solution was only slightly basic, and the solvent was removed at or below room temperature under reduced pressure. The product was extracted with methylene chloride, and after drying with calcium sulfate, the solvent was removed to give a yellow oil. Crystallization from 5 mL of methylcyclohexane gave 1.08 g (85%)

of **15** as a white, crystalline solid melting at 80–86 °C. Further purification was not practical since the compound was extraordinarily sensitive to traces of acid. Repeated crystallizations of other runs failed to raise the melting point above the initial value, and unless rigorous precautions were taken to exclude traces of airborne acid the compound decomposed to a liquid. A combustion analysis could not be made since the product degrades slowly at room temperature. Anything which is crystalline and reasonably dry is suitable for use in the next step and exhibits spectra characteristic of a pure compound. IR (KBr) cm^{-1} 1642 (w), 1460 (m), 1433 (m), 1310 (m), 1225 (m), 1214 (m), 1184 (m), 1078 (s), 1050 (s), and 745 (m); NMR ($CDCl_3$, 60 MHz) δ 6.63 (s, 1 H), 3.90 (s, 4 H), 3.22 (s, 3 H), 3.18 (s, 3 H), 3.08 (s, 3 H), 3.05 (s, 3 H), 2.9–1.0 (m, 7 H), and 1.27 (s, 3 H); mass spectrum *m/e* 418 and 420 (parent, too weak to determine exact mass), 417 and 419 (P − 1), 403 and 405 (P − 15, $-CH_3$), 387 and 389 (P − 31, $-OCH_3$).

17. A solution of 0.623 g (1.48 mmol) of **15** in 25 mL of tetrahydrofuran in a 50-mL three-necked flask equipped with thermometer, gas inlet, mechanical stirrer, and rubber septum was cooled under argon to −90 °C with a mixed solvents/dry ice/liquid nitrogen bath. As the solution was vigorously stirred, 0.80 mL (1.76 mmol) of *n*-butyllithium was added over 15 s. The solution turned pink during the first half of the addition, then became colorless. After stirring for 3 min, 0.394 g (1.76 mmol) of dimethyl 3-methoxyphthalate in 2 mL of tetrahydrofuran was added rapidly, and after stirring for 5 min at −70 °C, 5 mL of methanol was added. After warming to room temperature, the solvent was removed and the residue was partitioned between water and methylene chloride. The organic layer was dried with calcium sulfate and solvent was removed to give 0.939 g of an off-white foam. Chromatography on 10 g of silica gel, eluting with ether (1 × 30 cm column), gave a main fraction of 0.544 g (69%) of **17** as a dry white foam or gum, homogeneous by TLC. Although well-formed crystals, mp 128–129 °C, with spectral and chromatographic properties identical with the oil, could be obtained with difficulty by slow evaporation of an ether/hexane solution of the gum, the product was not crystallized for synthetic purposes. IR (KBr) cm^{-1} 1739 (s), 1673 (s), 1580 (m), 1466 (s), 1435 (m), 1275 (s, br), and 1072 (s); ^1H NMR ($CDCl_3$, 60 MHz, of the oil) δ 7.65–6.95 (m, 3 H), 6.53 (s, 1 H), 3.97 (s, 3 H), 3.88 (s, 7 H), 3.25 (s, 3 H), 3.20 (s, 6 H), 3.17 (s, 3 H), 2.7–1.5 (m, 7 H), and 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 25 MHz, of the oil) δ 194.4, 167.8, 157.7, 141.9, 140.8, 139.6, 136.8, 136.1, 130.7, 123.4, 121.4, 114.9, 111.3, 97.3, 95.0, 64.7 (probably 2 C), 56.1, 52.2, 51.4 (probably 2 C), 50.7 (probably 2 C), 42.3, 22.9, 22.4, 22.3, and 21.1; no evidence for a mixture of regioisomers was seen.

Anal. Calcd for $C_{28}H_{36}O_{10}$: C, 63.14; H, 6.81. Found: C, 63.11; H, 7.03.

18a. The procedure for the reductive hydrolysis of **17** is given below. When **17** purified by column chromatography was used, the NMR spectrum of the light-yellow product, **18a**, indicated that the reaction was very clean. Likewise, the TLC (silica, 50% ethyl acetate/hexane) showed one yellow spot, R_f 0.4, and a faint-yellow spot at the origin which might be due to partial ester hydrolysis. Purification by plate or column chromatography was accompanied by loss in weight. A small quantity of **18a** as chunky, yellow crystals was obtained from methylene chloride: mp 210–212 °C; IR (KBr) cm^{-1} 3620 (m), 1740 (s), 1699 (m), 1619 (m), 1578 (w), 1346 (m), 1285 (m), and 780 (w); NMR ($CDCl_3$, 60 MHz) δ 7.65–6.55 (m, 3 H), 6.58 (s, 1 H), 3.88 (s, 3 H), 3.62 (s, 3 H), 3.0–1.7 (m, 7 H), and 2.23 (s, 3 H); exact mass $C_{22}H_{22}O_7$, calcd *m/e* 398.136 539 9, obsd *m/e* 398.137 160 6, difference 0.0006.

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.58. Found: C, 65.89; H, 5.59.

18b. Saponification of **18a** is described below. In one instance an attempt was made to isolate the acid. Crystallization from ether gave a very small amount of a yellow solid which melted at 223–225 °C with some crystal reorganization at about 200 °C when the sample was heated from room temperature. However, when another sample was placed in the oil bath at 205 °C the material melted instantly with the vigorous evolution of gas.

19. The procedure for cyclizing crude **18b** is described below. When hydrogen fluoride was used it was observed that a contaminant giving a yellow spot with an R_f slightly greater than that of **19** (silica, $CHCl_3$) was formed. This yellow spot was not observed in the cyclization with methanesulfonic acid.

Preparation of 19 from 17. The preparation of **17** from 1.611 g (3.84 mmol) of crystalline **15** was carried out as described above. NMR analysis indicated that the ratio of **17** to the debrominated starting material was 84:16. A solution of 0.953 g (1.1 equiv) of stannous chloride in 4 mL of water was diluted with 16 mL of trifluoroacetic acid and the slurry, cooled to room temperature, was added to the unpurified **17**. The light-yellow mixture was stirred under nitrogen for 45 min and liquids were removed under high vacuum. The residue was dissolved in 5 mL of methanol, maintained under nitrogen, and 2 mL of 20% sodium hydroxide solution was added. Stirring was continued for 30 min and the solution was acidified. The product was extracted three times by adding 10-mL portions of methylene chloride to the reaction flask, stirring, and removing the organic phase, which was not dried, with a pipet. Solvent was removed and the residue was dissolved in 10 mL of methanesulfonic acid, giving a dark red-brown solution. Heating on a steam bath for 10 min gave a deep-purple solution. Dilution with 80 mL of water, filtration, and drying afforded 1.143 g of a dark-red solid, mp 190–200 °C, with darkening and shrinking from 100 °C. Three triturations with 10-mL portions of methanol removed 0.6485 g of a brown tar containing little **19** (TLC). The remaining red solid was dissolved in 60 mL of boiling acetic acid, the volume of acetic acid reduced to 40 mL, and 10 mL of methanol added after cooling. Filtration gave 0.426 g (30%) of **19**, mp 244–245 °C (lit.[10c] 243–245 °C), with an IR spectrum identical with that of material provided by Professor C. Sih. Concentration of the mother liquors gave 26 mg of material, melting at 210–230 °C, which was discarded.

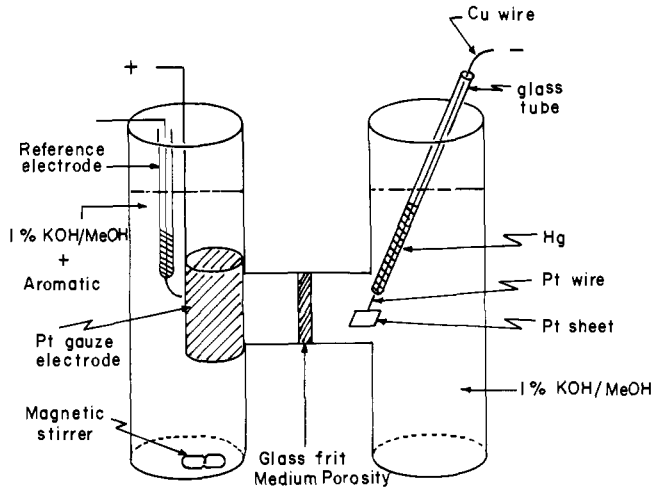


Figure 1. Divided cell apparatus.

Preparation of 20 from 11. A mixture of 14.0 g (42.6 mmol) of **11**, 100 mg of *p*-toluenesulfonic acid monohydrate, and 10 mL of ethylene glycol was vigorously refluxed with 200 mL of benzene in a flask equipped with a Dean-Stark water separator for 23 h. The acid was neutralized with bicarbonate, 100 mL of ether was added, and the organic phase was washed with water (2 × 100 mL). After drying with calcium sulfate, solvent was removed, finally under high vacuum, to give an oil. The sodium methoxide (from 50 mg of sodium and 200 mL of methanol freshly distilled from magnesium turnings) was added, and boiling without a condenser removed the last traces of benzene as the azeotrope. If this is not done the product does not precipitate from solution. Stirring at room temperature gave after a short time a precipitate. Stirring was continued for 4 h, the mixture was cooled to −20 °C, and 14.6 g (89%) of the ketal ester, mp 122–124 °C, was recovered by filtration. Although recrystallization from methanol gave material melting at 123–124.5 °C, the crude crystals were used for synthetic work. The analytical sample was sublimed at 4×10^{-5} Torr from a 110 °C bath: mp 122–124 °C; IR (KBr) cm^{-1} 1730 (m), 1611 (m), 1485 (s), 1446 (s), 1316 (m), 1269 (m), 1211 (s), 1093 (s), and 1065 (s); NMR ($CDCl_3$, 60 MHz) δ 6.97 (s, 1 H), 4.13 (m, 4 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.70 (s, 3 H), and 3.5–1.6 (m, 5 H).

Anal. Calcd for $C_{16}H_{19}BrO_6$: C, 49.62; H, 4.95; Br, 20.64. Found: C, 49.58; H, 4.93 Br, 20.14.

A solution of dimsyl anion was generated under nitrogen at 0 °C by adding 14.25 mL (2.1 equiv) of 1.9 M methyllithium in ether to 20 mL of Me_2SO (distilled from triphenylmethide and stored in

ampules) and 100 mL of tetrahydrofuran. After the solution was stirred for ca. 10 min, 4.90 g (12.66 mmol) of the ketal ester was added as a solid through the open neck of the flask as the solution was vigorously stirred with an efficient mechanical stirrer. The mixture was stirred at ice-bath temperature for 30 min. Tetrahydrofuran was removed and the residue was poured on 30 mL of saturated ammonium chloride solution and 200 mL of water. After extraction with methylene chloride (5 × 30 mL) the combined organic layers were washed twice with water (70 mL) and dried. Removal of solvent gave 6.6 g of crude product as a faintly yellow mass which gave 4.9 g (89%) of white crystals when crystallized from methylene chloride/ether: mp 153–161 °C (mixture of diastereomers); IR (KBr) cm^{-1} 1710 (m), 1572 (m), 1472 (s), 1395 (s), 1310 (m), 1237 (m), 1094 (s), 1078 (s), and 1040 (s); NMR ($CDCl_3$, 60 MHz) δ 6.85 (s, 1 H), 4.3–3.95 (m, 4 H), 3.85 (br s 2 H), 3.63 (s, 3 H), 3.62 (s, 3 H), 3.2–0.9 (m, 5 H), and 2.57 (s, 3 H).

The keto sulfoxide (4.86 g, 11.2 mmol) was reduced in the standard manner to afford 3.43 g (82%) of the ketal ketone, mp 142–144 °C, after crystallization once from 10 mL of ether and once from 30 mL of methylcyclohexane: IR (KBr) cm^{-1} 1710 (s), 1578 (m), 1475 (s), 1408 (s), 1308 (s), 1230 (m), 1172 (m), 1093 (s), and 1044 (s); NMR ($CDCl_3$, 60 MHz) δ 6.97 (s, 1 H), 4.4–4.0 (m, 4 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.4–1.6 (m, 5 H), and 2.23 (s, 3 H); mass spectrum *m/e* 370 and 372.

Anal. Calcd for $C_{16}H_{19}BrO_5$: C, 51.76; H, 5.16; Br, 21.53. Found: C, 51.86; H, 5.17; Br, 21.39.

The diketal **20** was prepared by a procedure similar to that described earlier to afford 3.64 (95%) of **20** from 3.42 g (0.2 mmol) of the ketal ketone, mp 178–180 °C, after recrystallization from methylene chloride/hexane: IR (KBr) cm^{-1} 1569 (m), 1471 (s), 1401 (s), 1300 (m), 1230 (m), 1089 (s), 1069 (s), and 1042 (s); NMR ($CDCl_3$, 60 MHz) δ 6.93 (s, 1 H), 4.1–4.3 (m, 4 H), 3.97 (s, 4 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.3–1.5 (m, 5 H), and 1.35 (s, 3 H).

Anal. Calcd for $C_{18}H_{23}BrO_6$: C, 52.06; H, 5.58. Found: C, 51.98; H, 5.56.

21. The same anodic oxidation procedure that was used to prepare **15** was used to transform 0.718 g (1.73 mmol) of **20** into 0.692 g (84%) of **21**, mp 144–145 °C. This compound apparently forms two types of crystals, since when an ether solution of **21** is cooled to 0 °C, a precipitate of very fine, white powder forms rapidly and melts at 122–124 °C. If crystals are allowed to grow slowly at room temperature with the aid of seeding, the form melting at 144–145 °C results. The two forms have identical spectral properties and may be interconverted by recrystallization. The bisketal **21** does not exhibit the extreme sensitivity to acid that **15** does and may be handled without special precautions: IR (KBr) cm^{-1} 1670 (w), 1460 (m), 1390 (w), 1335 (m), 1214 (m), 1170 (m), and 1080 (s); NMR ($CDCl_3$, 60 MHz) δ 6.57 (s, 1 H), 4.6–3.7 (m containing a prominent s at 3.93, 8 H), 3.28 (s, 6 H), 3.15 (s, 3 H), 3.12 (s, 3 H), 3.0–1.5 (m, 5 H), and 1.30 (s, 3 H).

Anal. Calcd for $C_{20}H_{29}BrO_8$: C, 50.32; H. 6.12; Br, 16.74. Found: C, 50.31; H, 5.95; Br, 16.62.

22. The metalation of **21** and coupling with dimethyl 3-methoxyphthalate was performed in the same manner as for **17**. The crude product was not so easily purified as **17** and the coupling product could be isolated pure only in low yield. Owing to complications in the latter stages of the work, no attempt was made to optimize conditions. The compound showed mp 123–126 °C; IR (KBr) cm^{-1} 1735 (s), 1673 (s), 1581 (m), 1472 (s), 1281 (s), and 1074 (s); NMR ($CDCl_3$, 60 MHz) δ 7.65–7.00 (m, 3 H), 6.40 (s, 1 H), 4.7–3.7 (m containing singlets at 3.97 and 3.90, 14 H), 3.27 (s, 6 H), 3.23 (s, 3 H), 3.22 (s, 3 H), 3.1–1.5 (m, 5 H), and 1.32 (s, 3 H); exact mass $C_{30}H_{38}O_{12}$, calcd *m/e* 590.236 304 0, obsd *m/e* 590.237 319 0, difference 0.0010.

23. Reductive hydrolysis of **22** was performed as for **18a**. As before losses in purification allowed isolation of the pure hydroquinone in low yield, mp 149–150 °C, as chunky, orange crystals: IR (KBr) cm^{-1} 1739 (m), 1715 (s), 1650 (s), 1580 (m), 1472 (s), 1431 (s), 1337 (s), 1289 (s), and 1217 (s); NMR ($CDCl_3$, 60 MHz) δ 11.45 (s, 1 H), 11.28 (s, 1 H), 7.7–6.8 (m, 4 H), 3.93 (s, 3 H), 3.68 (s, 3 H), 3.5–2.7 (m, 5 H), and 2.28 (s, 3 H); exact mass $C_{22}H_{20}O_8$, calcd *m/e* 412.115 804 8, obsd *m/e* 412.116 333 5, difference 0.0005.

Conversion of 22 to 24. The reductive hydrolysis of 0.186 g (0.31 mmol) of crude **22** and subsequent saponification was carried out as with compound **17**. The crude residue was dissolved in 5 mL of methanesulfonic acid and heated for 5 min at 90 °C. Dilution with water, filtration, and vacuum drying yielded 80 mg of a black solid which was triturated with five 1-mL portions of ether and four times with 1 mL of methanol, yielding 45 mg (38% if pure) of a black, crystalline solid, mp >220 °C. A small amount dissolved in nitrogen-flushed methanol showed visible maxima at 490 and 512 nm, as well as an inflection point at 544 nm (lit.[23] for 7-oxadaunomycinone 493, 510, and 545 nm). The product was very unstable and solutions were rapidly converted to the known **25**: visible maxima 494, 528, and 570 nm (lit.[23] 491, 525, and 567 nm); exact mass $C_{21}H_{14}O_7$, calcd *m/e* 378.073 943 1, obsd *m/e* 378.074 699 0, difference 0.0007. A Fourier transform NMR spectrum of the black solid indicated a mixture of **24** to **25** in the ratio 6:1.

26. Compound **14** (0.50 g, 1.4 mmol) was metalated with 1 equiv of *n*-butyllithium and reacted with 0.328 g (1.4 mmol) of **16** employing the same method used to prepare **17**. Workup afforded 0.777 g of a light-yellow oil which was chromatographed (10 g of silica gel, 1 × 30 cm column, 100% ether). Immediately after elution of **16** and protonated starting material, 0.36 g of a white foam was obtained which was **26** contaminated with ca. 10% of unidentified impurities. High-pressure liquid chromatography allowed isolation of a small amount of **26** pure: mp 132.5–134.5 °C; IR (KBr) cm^{-1} 1745 (s), 1672 (m), 1580 (w), 1472 (s), 1411 (m), 1350 (m), 1306 (m), and 1275 (s); NMR ($CDCl_3$, 60 MHz) δ 7.6–6.8 (m, 3 H), 6.75 (s, 1 H), 3.97, 3.88, 3.83, 3.77, and 3.52 (s, 16 H), 3.4–1.5 (m, 7 H), and 1.35 (s, 3 H).

Anal. Calcd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found: C, 66.42; H, 6.35.

27. A solution of 0.1862 g (0.396 mmol) of the ester was refluxed for 2 h with a solution of 0.5 g of potassium hydroxide, 1 mL of water, and 9 mL of methanol. The solution was then acidified with 2 mL of concentrated hydrochloric acid and stirred for an additional 30 min. Removal of the solvent followed by methylene chloride extraction yielded 161 mg of a crude acid which was not purified. This material was dissolved in 5 mL of methanesulfonic acid and heated on the steam bath for 5 min. The resulting purple-red solution was poured into 70 mL of water and extracted with methylene chloride to afford 0.139 g of dark residue. Chromatography of this material on silica gel (10 g, 1 × 30 cm column, 2% MeOH, CH_2Cl_2) gave 106 mg of a red product; considerable brown material remained at the top of the column. The product was dissolved in 0.5 mL of chloroform and precipitated with 5 mL of ether, yielding 56 mg (37%) of red crystals, mp 188–190 °C. The mother liquors consisted of a mixture (NMR, TLC) of compounds including a small amount of uncyclized starting material. The product showed IR (KBr) cm^{-1} 1701 (s), 1665 (s), 1622 (m), 1583 (s), 1370 (s), 1288 (s), 1270 (s), 1251 (s), and 1218 (s); NMR ($CDCl_3$, 60 MHz) δ 13.57 (s, 1 H), 8.0–7.2 (m, 3 H), 4.00 (s, 3 H), 3.87 (s, 3 H), 3.4–1.7 (m, 7 H), and 2.27 (s, 3 H); exact mass $C_{22}H_{20}O_6$, calcd *m/e* 380.125 97, obsd *m/e* 380.1266, difference 0.0006.

19. A mixture of 41 mg (0.108 mmol) of **27** and 100 mg (0.926 mmol) of silver(II) oxide in 20 mL of acetone was treated with 40% nitric acid until all the solids dissolved (ca. 3 min), giving an orange solution. The solution was partitioned between 70 mL of water and 30 mL of chloroform; then the orange chloroform layer was shaken with 50 mL of 2% sodium dithionite solution, resulting in a deepening of the red color. The organic layer was dried with sodium sulfate, giving 27 mg (68%, not maximized) of 7,9-deoxydaunomycinone melting at 237–240 °C (lit.[10c] 243–245 °C) after one trituration with 2 mL of methanol. One recrystallization from acetic acid raised the melting point to 242–244 °C.

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Color Dimorphism of 14-Hydroxymorphinone. X-Ray Analysis of Two Different Crystalline Modifications

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Abstract: 14-Hydroxymorphinone can be obtained in two crystalline modifications, one yellow (**1**-Y) and the other white (**1**-W), depending on the solvent used for crystallization. Infrared spectral differences suggested that there was a difference in the hydrogen bonding in the two forms. Single-crystal X-ray analyses have been carried out on both forms. The crystals of both **1**-Y and **1**-W are orthorhombic and the space group is $P2_12_12_1$; the cell dimensions of **1**-Y are a = 13.150 (3), b = 13.508 (3), and c = 7.837 (1) Å, and those of **1**-W are a = 12.918 (3), b = 14.074 (3), and c = 8.035 (2) Å. The conformations of the molecules in **1**-Y and **1**-W are very similar with possible O(14)—H- - -N intramolecular hydrogen bonding. The aromatic ring A is slightly nonplanar in these and in most other morphine derivatives. A significant difference between **1**-Y and **1**-W is in the orientation of the O–H group with respect to the C(aromatic)–O bond. In **1**-Y, the phenolic hydroxyl group forms an intermolecular hydrogen bond to a carbonyl oxygen, while in **1**-W, the phenolic hydroxyl group forms an intermolecular hydrogen bond to the aliphatic alcohol. There may be a very weak charge-transfer effect in the crystal of **1**-Y between the aromatic ring A and the ketone group in a symmetry-related molecule. This possibility, which may in part explain the color difference between the two forms, has also been examined by spectroscopic methods.

Introduction

It was observed a number of years ago that the phenolic α,β-unsaturated ketone, 14-hydroxymorphinone (**1**), can exist in two modifications, which show striking differences in color and solid-state IR spectra. They are readily interconvertible in solution: recrystallization from polar solvents, such as ethanol or acetone, yields bright yellow, transparent, square platelets (**1**-Y), while crystallization from a large volume of benzene (in which **1** is only slightly soluble) produces perfectly

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