mechanically while refluxing overnight. It was filtered, and the residue was washed twice with hot ethyl acetate. The solvent was removed to yield 1.86 g of ester (90%): mp 192–194 °C (from chloroform–hexane); NMR ($CDCl_3$) δ 3.90 (3 H, s, Ar OCH_3), 3.95 (3 H, s, Ar OCH_3), 4.05 (3 H, s, Ar CO_2CH_3), 7.0–7.7 (3 H, m, Ar H_5, H_6, H_7), 8.15 (1 H, s, Ar H_2); mass spectrum *m/e* 406, 404 (M^+), 391, 389 ($M^+ - CH_3$), 376, 374 ($M^+ - 2\ CH_3$), 345 ($M^+ - CO_2CH_3$), 325 (M^+ - Br), etc.; IR (KBr) 3600–3200, 3100–2820, 1735, 1665, 1625 (sh), 1575, 1535 (sh), 1355, 1270, 1205 cm^{-1}; UV λ_{max} (EtOH) 380 nm (log ε 3.80), 353 (3.77), 275 (sh, 4.09), 260 (4.35), 228 (4.45).

Anal. Calcd for $C_{18}H_{13}O_6Br$: C, 53.35; H, 3.23. Found: C, 53.00; H, 3.00.

3-Carboxy-1,8-dimethoxy-9,10-anthraquinone (17). Acid **16** (0.15 g) was dissolved in 5 mL of dry HMPA. To this solution was added 0.05 g of sodium ethoxide. The suspension was allowed to stir at 100 °C for 4 h under an N_2 atmosphere and then poured into water, acidified, and extracted with ethyl acetate. The organic layer was washed, dried over Na_2SO_4, and evaporated to yield **17**: mp 278–279 °C (from ethyl acetate); NMR (Me_2SO-d_6) δ 3.95 (6 H, s, OCH_3), 7.6–8.25 (5 H, m, Ar H); mass spectrum *m/e* 312 (M^+), 297 ($M^+ - CH_3$), 282 ($M^+ - 2\ CH_3$), 268 ($M^+ - CO_2$); IR (KBr) 3400–2800, 1730, 1670, 1610, 1590, 1480, 1460 (sh), 1445, 1260, 1285, 1235 cm^{-1}, etc.; UV λ_{max} (EtOH) 389 nm (log ε 3.54), 259 (3.95), 227 (4.17).

1,8-Dimethoxy-4-hydroxy-9,10-anthraquinone-3-carboxylic Acid (20). To 0.5 g of acid **18** was added 2.5 g of $Ca(OH)_2$ suspended in 5 mL of water. Copper powder (0.2 g) was added, and this mixture was heated in a glass-lined stainless-steel bomb at 200 °C for 10 h. After cooling, the suspension was acidified with cold concentrated HCl to give a bright yellow product. After filtration, the product was dissolved in excess chloroform and small amounts of ethyl acetate and methanol. After filtration, the filtrate was washed with water, dried over Na_2SO_4 and evaporated to yield 0.272 g of phenol **20** (65%): mp >300 °C; mass spectrum *m/e* 328 (M^+), 313 ($M^+ - CH_3$), 298 ($M^+ - 2\ CH_3$), 284 ($M^+ - CO_2$), etc.; IR (KBr) 3650–3300, 2930, 1730, 1680, 1625, 1445, 1250; UV λ_{max} (EtOH) 461 nm (sh, log ε 2.88), 434 (3.10), 410 (sh, 3.05), 286 (2.53), 267 (3.76), 258 (3.27), 228 (3.55); NMR (Me_2SO-d_6) δ 3.90 (6 H, s, OCH_3), 7.70–8.20 (4 H, m, Ar H).

Methyl 1,4,8-Trimethoxy-9,10-anthraquinone-3-carboxylate (21). The phenol **20** (0.21 g) was suspended in 30 mL of acetone and 6 mL of dioxane. Potassium carbonate (1 g) and dimethyl sulfate (0.3 mL) were added, and the suspension was stirred while refluxing overnight. It was filtered, and the residue was washed twice with hot ethyl acetate. The combined filtrate was washed with 5% NaOH solution, and after being dried over Na_2SO_4, the solvent was removed to yield 0.19 g of ester **21** (85%): mp 156–157 °C (from chloroform–hexane); NMR ($CDCl_3$) δ 3.90, 3.96, 4.0 (12 H, 3 s, 3 × OCH_3, $COOCH_3$), 7.19 (1 H, dd, *J* = 2, 8 Hz, Ar H_7), 7.56 (1 H, t, *J* = 8 Hz, Ar H_6), 7.76 (1 H, dd, *J* = 2, 8 Hz, Ar H_5), 8.26 (1 H, s, Ar H_2); IR ($CHCl_3$) 2950, 1735, 1675, 1590, 1470, 1340, 1270 cm^{-1}, etc.; mass spectrum *m/e* 357 ($M^+ + 1$), 356 (M^+), 341 ($M^+ - CH_3$), 326 ($M^+ - 2\ CH_3$), 325 ($M^+ - OCH_3$), 311 ($M^+ - 3\ CH_3$), 296 ($M^+ - 4\ CH_3$), etc.; UV λ_{max} (EtOH) 370 nm (log ε 3.62), 260 (4.15), 227 (4.25).

Anal. Calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.52. Found: C, 64.08; H, 4.51.

Acknowledgment. We are grateful to Adria Laboratories for partial financial support of this work, to Dr. H. J. Eichel for encouragement, and to Dr. J. Short for helpful advice.

Registry No. **3**, 481-72-1; **4**, 72049-14-0; **5**, 72049-15-1; **6**, 72049-16-2; **7**, 72049-17-3; **10**, 72049-18-4; **11**, 72049-19-5; **12**, 72049-20-8; **13**, 72049-21-9; **14**, 72049-22-0; **15**, 50488-95-4; **16**, 72049-23-1; **17**, 72049-24-2; **18**, 72049-25-3; **20**, 72049-26-4; **21**, 69857-00-7; 3-methoxyphthalic acid, 14963-97-4.

Novel Ring Hydroxylation of Aloe-emodin and Further Elaboration to Anthracycline Synthons

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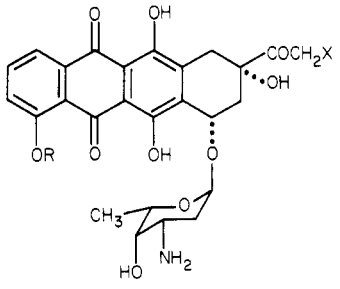
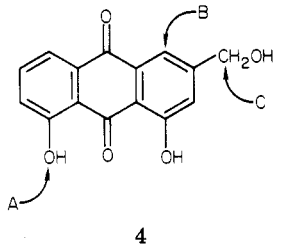
Aloe-emodin (4) has been converted in six steps to 1,4,5-trihydroxy-2-(2,3-dicarboxypropyl)-9,10-anthraquinone (17), a synthon suitable for further regiospecific elaboration into daunomycin–adriamycin analogues. A method for Friedel–Crafts acylation of anthraquinones by reduction to the anthracenone, cyclization, and reoxidation has been developed as a key feature of the synthesis.

Because of their outstanding clinical properties,[1] costliness, and side effects, interest continues unabated in the synthesis of the antitumor antibiotics adriamycin (doxorubicin) (**1**), daunomycin (**2**), and carminomycin (**3**) and novel analogues.

Part of our efforts in this area[3,4] have involved attempts to solve the regiospecificity problem through the use of aloe-emodin (**4**), a readily available natural anthraquinone. We have described previously methods for specific introduction of oxygen at C_4 (**4**, problem B).[4] In this paper we describe an alternate solution to problem B and an elaboration of functionality at the hydroxymethylene function known to be suitable for completion of the synthesis to bioactive anthracyclines (problem C).



1, R = CH_3, X = OH
2, R = CH_3, X = H
3, R = H, X = H



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Results

In our earlier work, we utilized a nucleophilic aromatic displacement reaction to introduce an oxygen function at

(1) F. Arcamone, *Lloydia*, **40**, 45 (1977).
(2) T. R. Kelly, *Annu. Rep. Med. Chem.*, **14**, 288 (1979).
(3) J. Alexander and L. A. Mitscher, *Tetrahedron Lett.*, 3403 (1978).
(4) J. Alexander, A. V. Bhatia, L. A. Mitscher, S. Omoto, and T. Suzuki, *J. Org. Chem.*, previous paper in this issue.

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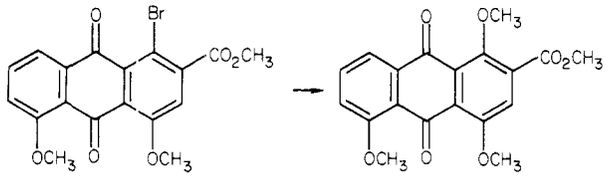
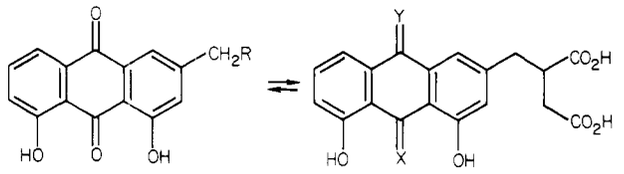
position 4 of an aloe-emodin derivative (**5** to **6**).[4] For the



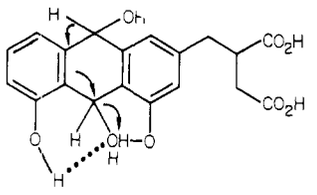
5 **6**

sake of synthetic efficiency it was felt that it would be better to introduce the missing oxygen by a sequence which involved fewer steps. Accordingly, starting with aloe-emodin ω-bromide (**7**), reaction with the anion of ethyl 2-carbethoxysuccinate produced **8** which was in turn converted in high yield to succinic acid analogue **9** by saponification–decarboxylation. This substance was further characterized as its dimethyl ester (**10**).



7, R = Br
8, R = $(EtO_2C)_2CCH_2CO_2Et$
9, R = $HO_2CCHCH_2CO_2H$
10, R = $MeO_2CCHCH_2CO_2Me$

11, Y = H_2, X = O
12, Y = O, X = H_2

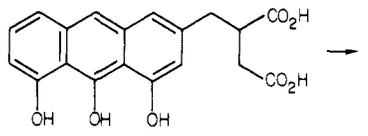


13

Because of the deactivation of the benzenoid rings by the quinone carbonyls, Friedel–Crafts-type cyclization on succinate **9** failed. We now report a solution to effecting cyclization into this type of ring based upon use of the corresponding anthracenones (**11**, **12**). This procedure should be of general utility.

Reaction with Sn–$SnCl_2$–HCl–HOAc cleanly produced a single anthracenone assigned structure **11** partly on the basis of an IR maximum at 1615 cm^{-1} for the hydrogen-bonded carbonyl. The gross structure was evident from the spectral properties of its dimethyl ester (*m/e* 384, M^+) and its ready reoxidation to the corresponding quinone (**9**). Quinone **10**, on reaction with sodium borohydride,[5] produced a different anthracenone formulated as **12** on the basis of similar considerations and the presence of an IR band at 1700 cm^{-1} for the non-hydrogen-bonded carbonyl. It was not necessary to add additional acid to effect dehydration of the intermediate dihydroanthracenediol **13**.[5] Either anthracenone proved suitable for subsequent work although **11** and its subsequent transformation products were somewhat more stable, so their use was preferred.

It was anticipated that in the strongly acidic conditions required for the Friedel–Crafts cyclization, the anthracenone would be protonated and exist predominantly in the enol form (**14**). The aromatic rings would thereby no longer be deactivated toward electrophilic substitution, and, indeed, efficient cyclization to anthracenone **15** was achieved with a variety of catalysts. Anthracenone **15** was further characterized as its dimethyl ether and methyl



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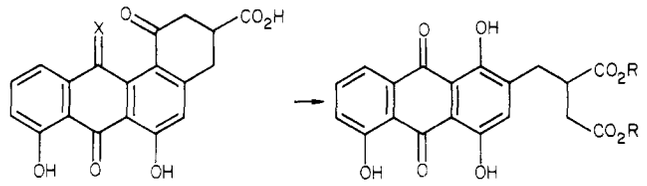
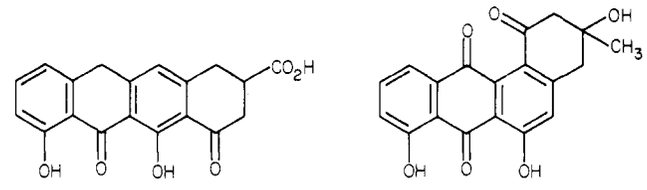


15, X = H_2
16, X = O

17, R = H
18, R = CH_3



19 **20**

ester dimethyl ether. Zinc-dust distillation produced benz[*a*]anthracene and only a trace of naphthacene, confirming that cyclization had predominantly followed the desired course rather than leading to the alternate anthracenone **19**.

Further support for the structural assignment was achieved by facile oxidation of anthracenone **15** to anthraquinone **16** and the preparation of its methyl ester and methyl ester dimethyl ether. A comparison of the quinone-associated bands in the IR spectrum of the methyl ester of **16** (ν_{max} 1705, 1695, 1670, 1630, 1600, 1590 cm^{-1}) with those reported for rabelomycin (**20**) showed a close correspondence (ν_{max} 1700, 1680, 1635, 1590, 1570 cm^{-1}).

It has been known for many years that the α position of molecules such as **14** is more reactive in Friedel–Crafts reactions than the β position[7] and that six-membered ring formation is much more facile than five-membered formation when substituted succinic acids are cyclized.[8]

The anthracenone cyclization method provides a potentially general approach to the synthesis of the small family of naturally occuring antibiotic quinones bearing this ring system (rabelomycin,[6] ochromycinone,[9] and tetrangomycin[10]).

Baeyer–Villiger oxidation of anthracenone **15** or quinone **16**, followed by hydrolytic workup, produced anthraquinone **17** in good yield. That the cyclization of anthracenone **11** had indeed led to anthracenone **15** and thence to quinone **16** received further support from the spectroscopic properties of quinones **17** and **18**. The chelated quinone carbonyl IR band occurred at 1608 cm^{-1} in **18**. This is consistent with the IR spectra of other 1,4,5-trihydroxyanthraquinones whose corresponding absorption maximum occurs at 1605 cm^{-1} and contrasts with that expected for the alternate 1,2,3-trihydroxyanthraquinones which absorb at 1661 and 1621 cm^{-1}.[11] Furthermore, the ultraviolet–visible spectrum of **17** contained maxima at 520, 503, 496, 484, 455, 285, 278, 242, and 222

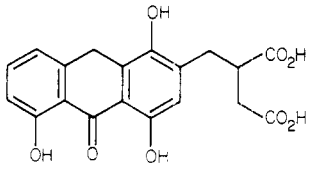
(5) T. R. Criswell and B. H. Klanderman, *J. Org. Chem.*, **39**, 770 (1974).

(6) W.-C. Liu, W. L. Parker, D. S. Slusarchyk, G. L. Greenwood, S. F. Graham, and E. Meyers, *J. Antibiot.*, **23**, 437 (1970).
(7) M. S. Newman and R. Gaertner, *J. Am. Chem. Soc.*, **72**, 264 (1950).
(8) W. S. Johnson, *Org. React.*, **2**, 116 (1944).
(9) J. H. Bowie and A. W. Johnson, *Tetrahedron Lett.*, 1449 (1967).
(10) M. P. Kunstmann and L. A. Mitscher, *J. Org. Chem.*, **31**, 2920 (1966).
(11) R. H. Thompson, "Naturally Occurring Quinones", 2nd ed., Academic Press, New York, 1971, pp 59, 67.

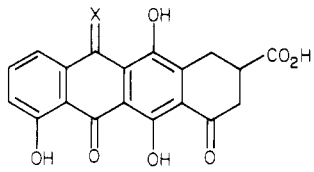
nm. 1,4,5-Trihydroxyanthraquinones are known to absorb at 523, 510 (sh), 489, 478 (sh), 459 (sh), 284, and 250 nm.[11]

This sequence of six steps provides a convenient means for the regiospecific introduction of the peri phenolic OH groups characteristic of antitumor anthracyclines **1–3** which are missing from aloe-emodin (**4**).

In principle, conclusion of this phase of the synthesis could be accomplished by repetition of the sequence anthracenone formation (**21**), cyclization, and oxidation. In



21



22, X = H_2
23, X = O

the event, however, yields were poor, and a multitude of products were formed from which the desired cyclized anthracenone (**22**) and its oxidation product (**23**) were recovered in poor yield. A contributing factor seems to be the very ready reoxidation of **21** to **17** and aromatization of the newly formed ring.

While we were in the midst of the latter studies an attractive solution to this problem appeared from two laboratories in which very closely analogous products were efficiently converted to tetracyclic anthracycline intermediates by the anion equivalent of the Friedel–Crafts reaction[12] and by intramolecular Claisen[13–15] and Marschalk reactions.[13–15]

Given the convergence of these approaches and the obvious applicability of these methods to intermediates prepared as described in our paper, we have now diverted our efforts to concluding anthracycline syntheses from aloe-emodin which do not closely parallel other routes now in print.

Experimental Section

Synthesis of 3-(Bromomethyl)-1,8-dihydroxy-9,10-anthraquinone (7). A suspension of aloe-emodin (1 g, 3.7 mmol) in 48% hydrobromic acid was refluxed for 3 h. The reaction was allowed to cool to room temperature, and the solid was filtered and washed with water before drying under vacuum. In this fashion, 1.1 g (89%) of the desired product was obtained as a yellow-brown solid, mp 214–215 °C. A second crystallization from acetic acid, using activated charcoal, raised the melting point to 218–219 °C, and the product consisted of bright yellow needles: IR (KBr) ν_{max} 3450 (OH), 1660 (C=O) cm^{-1}; UV λ_{max} (MeOH) 227 nm (ϵ 32380), 254 (16825), 259 (17140), 277 (8890), 287 (8570), 430 (9200), 455 (sh, 6350); mass spectrum (relative intensity) *m/e* 332 [M^+, 67, with an isotope peak at *m/e* 334 (65)], 288 (M^+ – 44, 21), 253 (M^+ – Br, 100), 225 (M^+ – Br – CO, 96), 197 (10), 169 (7), 168 (7), 152 (6), 151 (19), 150 (12), 141 (11), 139 (15), 127 (11), 115 (10), 105 (5), 98 (9), 89 (5), 84 (5), 77 (7), 75 (12); NMR ($CDCl_3$) δ 4.48 (2 H, s, CH_2Br), 7.09–7.80 (5 H, m, Ar H).

Anal. Calcd for $C_{15}H_9BrO_4$: C, 54.08; H, 2.72; Br, 23.99. Found: C, 53.69; H, 2.80; Br, 24.37.

1,8-Dihydroxy-3-[2,2,3-tris(ethoxycarbonyl)propyl]-9,10-anthraquinone (8). To a stirring solution of diethyl 2-carbethoxysuccinate (15 g) in DMF (30 mL) was added 64% NaH (2.6 g) in divided portions with ice–water cooling, and the mixture was stirred at room temperature for 20 min, followed by addition of a solution of 3-(bromomethyl)-1,8-dihydroxy-9,10-anthraquinone (9.6 g) and 64% NaH (2.6 g) in DMF (300 mL). The mixture was stirred for 30 min and then heated to 70 °C. Stirring was continued for an additional 3 h at 70 °C, and the mixture was stirred overnight at room temperature. The mixture was poured into water (about 1 L), acidified with concentrated HCl, and then extracted with benzene. The extract was washed with saturated NaCl solution and then evaporated to leave a dark brown syrup, which was subjected to chromatography on silica gel (200 g). Elution with benzene–$CHCl_3$ (2:1, v/v) afforded bright orange crystals (12 g), whose recrystallization from MeOH gave the desired 1,8-dihydroxy-3-[2,2,3-tris(ethoxycarbonyl)propyl]-9,10-anthraquinone as bright orange plates: mp 89–90 °C; IR ($CHCl_3$) 3600, 1735, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 8 Hz, $CO_2CH_2CH_3$), 1.3 (6 H, t, J = 8 Hz, 2 $CO_2CH_2CH_3$), 2.83 (2 H, s, CH_2CO_2Et), 3.43 (2 H, s, Ar CH_2), 4.17 (2 H, q, J = 8 Hz, $CO_2CH_2CH_3$), 4.23 (4 H, q, J = 8 Hz, 2 $CO_2CH_2CH_3$), 7.00–7.70 (5 H, m, Ar H), 13.02, 13.15 (each 1 H, s, 2 OH, exchanged with D_2O); mass spectrum *m/e* 498 (M^+), 497 (M^+ – H), 496 (M^+ – 2 H), 453 (M^+ – OC_2H_5), 452 (M^+ – HOC_2H_5), 451 (M^+ – 2 H – OC_2H_5), 425 (M^+ – CO_2CH_5), 424 (M^+ – H – $CO_2C_2H_5$), 423 (M^+ – 2 H – $CO_2C_2H_5$), 380 (M^+ – $CO_2C_2H_5$ – OC_2H_5), 379 (M^+ – H – $CO_2C_2H_5$ – OC_2H_5), 378 (M^+ – 2 H – $CO_2C_2H_5$ – OC_2H_5), etc.

Anal. Calcd for $C_{26}H_{26}O_{10}$: C, 62.65; H, 5.26. Found: C, 62.75; H, 5.25.

1,8-Dihydroxy-3-(2,3-dicarboxypropyl)-9,10-anthraquinone (9). A mixture of 1,8-dihydroxy-3-[2,2,3-tris(ethoxycarbonyl)-propyl]-9,10-anthraquinone (2 g), KOH (2 g), H_2O (15 mL), and EtOH (950 mL) was refluxed by using an oil bath. After evaporation of EtOH, H_2O was added to the residue, and this was then acidified with concentrated HCl to separate a viscous syrup which was triturated with a spatula and cooled with ice and H_2O to afford a yellow crystalline solid. The yellow solid was filtered to give 1,8-dihydroxy-3-(2,2,3-tricarboxypropyl)-9,10-anthraquinone (1.8 g). The mother liquor was extracted with AcOEt. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and then evaporated to leave a yellow crystalline solid (0.15 g). A suspension of the 1,8-dihydroxy-3-(2,2,3-tricarboxypropyl)-9,10-anthraquinone so produced (6 g) in concentrated HCl (50 mL), H_2O (50 mL), and diglyme (150 mL) was refluxed for 18 h in an oil bath. The solvent was evaporated in vacuo to leave a residue. Addition of an excess of H_2O left a crystalline powder, which was filtered (5.26 g): mp 230–231 °C; NMR ($CDCl_3$, Me_2SO-d_6) δ 3.05 (4 H, br s, Ar CH_2, CH_2CO_2H), 4.55 (1 H, br s, $CHCO_2H$), 7.12–7.80 (5 H, m, Ar H). The sparingly soluble product was further characterized as its dimethyl ester (**10**).

1,8-Dihydroxy-3-[2,3-bis(methoxycarbonyl)propyl]-9,10-anthraquinone (10). Through a stirred suspension of 1,8-dihydroxy-3-(2,3-dicarboxypropyl)-9,10-anthraquinone (100 mg) in MeOH (20 mL) was passed HCl gas for 40 min at room temperature, followed by refluxing, with stirring, overnight. The solvent was evaporated to leave a residue which was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and then evaporated to leave an orange-yellow crystalline solid (110 mg) whose recrystallization from MeOH–$CHCl_3$ afforded 1,8-dihydroxy-3-[2,3-bis(methoxycarbonyl)propyl]-9,10-anthraquinone as a brownish yellow powder: mp 151–153 °C; IR ($CHCl_3$) 3600 (OH), 1735 (C=O), 1630 (C=O) and 1610 cm^{-1}; NMR ($CDCl_3$) δ 2.62 (2 H, dd, J = 6.5, 6 Hz, CH_2CO_2Me), 3.07 (2 H, dd, J = 6, 3 Hz, Ar CH_2), 3.30 (1 H, dd, J = 6.5, 6 Hz, $CHCO_2Me$), 3.73 (3 H, s, CO_2CH_3), 3.75 (3 H, s, CO_2CH_3), 7.10–7.95 (5 H, m, Ar H), 10.88 (1 H, s, OH), 10.90 (1 H, s, OH).

Anal. Calcd for $C_{12}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.00; H, 4.47.

1,8-Dihydroxy-3-(2,3-dicarboxypropyl)-9(10*H*)-anthracenone (11). A mixture of 1,8-dihydroxy-3-(2,3-dicarboxypropyl)-9,10-anthraquinone (3.7 g), stannous chloride (4.51 g), concentrated HCl (20 mL), and AcOH (80 mL) was heated at 120 °C for 1 h with stirring by using an oil bath. After that, H_2O (60 mL) was added to the reaction mixture to afford a precipitate which was filtered and washed with water to afford a yellow-green crystalline solid (2.9 g). The mother liquor was extracted with Et_2O. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and then evaporated to leave a

(12) R. J. Boatman, B. J. Whitlock, and H. W. Whitlock, *J. Am. Chem. Soc.*, **99**, 4822 (1977).
(13) F. Suzuki, R. D. Gleim, S. Trenbeath, and C. J. Sih, *Tetrahedron Lett.*, 2303 (1977).
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yellow-green solid (700 mg). Recrystallization from $CHCl_3$–MeOH afforded the desired anthrone. For further purification, the crystalline residue was purified over a Sephadex LH-20 column (1.5 cm × 25 cm) using AcOEt as an eluent to give the pure diacid anthracenone as a pale orange crystalline mass: mp 208–210 °C dec; IR (KBr) 1705, 1615, 1600 cm^{-1}; NMR (acetone-d_6) δ 2.52 (2 H, dd, J = 5 Hz, CH_2CO_2H), 3.01 (2 H, br d, J = 5 Hz, Ar CH_2), 3.12 (1 H, br m, $CHCO_2H$), 4.35 (2 H, s, $ArCH_2Ar$), 6.80–7.70 (5 H, m, Ar H). The anthracenone was unstable to oxidation and was customarily used in the cyclization reaction immediately after preparation. When allowed to stand, after being dissolved in MeOH/KOH and aerated with oxygen for 5 min or after reaction with Jones reagent for 15 min, the anthracenone became deeply colored, and the presence of conversion to starting anthraquinone **9** was readily determined by TLC [$CHCl_3$–AcOEt–HOAc (14:3:2)]. The anthracenone was further characterized as its dimethyl ester derivative.

1,8-Dihydroxy-3-[2,3-bis(methoxycarbonyl)propyl]-9-(10*H*)-anthracenone. To methanol (20 mL), cooled with ice–water and stirred, was added dropwise acetyl chloride (1 mL), the solution was stirred for 10 min at the same temperature, and then anthracenone **11** (100 mg) was added to the above solution and stirred for 3 h at room temperature. The solvent was evaporated to leave a solid, which was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and then evaporated to leave a residue (122 mg), which was subjected to chromatography on silica gel (20 g). Elution with $CHCl_3$ afforded an orange-yellow crystalline solid (112 mg) whose recrystallization from methanol–$CHCl_3$ gave 1,8-dihydroxy-3-[2,3-bis(methoxycarbonyl)propyl]-9(10*H*)-anthracenone as a yellow powder: mp 140–142 °C; IR ($CHCl_3$) 1732 (CO), 1615 (CO), 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.56 (2 H, t, J = 5 Hz, $CH_2CO_2CH_3$), 2.97 (2 H, t, J = 5 Hz, Ar CH_2), 3.14 (1 H, d, J = 5 Hz, $CHCO_2CH_3$), 3.65 (3 H, s, CO_2CH_3), 3.68 (3 H, s, CO_2CH_3), 4.18 (2 H, s, $ArCH_2Ar$), 6.60 (2 H, s, Ar H_2, H_4), 6.77 (1 H, d, J = 8 Hz, Ar H_7), 6.90 (1 H, d, J = 8 Hz, Ar H_5), 7.33 (1 H, t, d, J = 8, 2 Hz, Ar H_6), 11.53 (2 H, s, 2 OH); mass spectrum m/e 384 (M^+), 353 ($M^+ - 31$), 352, 321, 320, 293, 292, 265, 264.

The Reaction of Diacid 10 with $NaBH_4$. Preparation of Diacid Anthracenone 12. To an ice-cooled suspension of 250 mg of diacid **10** in 20 mL of EtOH was added 300 mg of $NaBH_4$ at one time, and this was stirred for 2 h under an argon atmosphere at 5–10 °C until the reaction mixture became almost colorless (but showed strong yellow-green fluorescence). After evaporation and careful acidification with 6 N HCl, the product was extracted with AcOEt (3 × 50 mL). The AcOEt solution was worked up in the usual fashion to give 240 mg of diacid anthracenone **12**: IR (KBr) 1700 cm^{-1}; NMR (acetone-d_6) δ 2.65 (2 H, br t, J = 6 Hz, CH_2CO_2H), 3.12 (1 H, br m, $CHCO_2H$), 3.15 (2 H, br d, J = 6 Hz, Ar CH_2), 3.92 (2 H, s, $ArCH_2Ar$), 6.66–7.66 (5 H, m, Ar H); R_f 0.20, silica gel TLC with $CHCl_3$–AcOEt–HOAc (14:3:2). This anthracenone also readily reverts to anthraquinone **9** on standing, upon oxygenation in MeOH/KOH solution, and when treated with Jones reagent. The mass spectrum of its dimethyl ester, prepared as above, gave m/e 384 (M^+), 383, 353, 352, 321, 320, 293, 292, 265, 264, etc. This anthracenone was quite unstable to storage and when used in cyclization studies had to be used immediately after isolation.

6,8-Dihydroxy-1,2,3,4-tetrahydro-1-oxo-3-carboxy-7-(12*H*)-benz[*a*]anthracenone (15). Diacid anthracenone **11** (100 mg) was placed in a Parr bomb with liquid HF (10 mL) and heated at 55–60 °C for 3 h. The bomb was cooled and opened. The HF was allowed to evaporate at room temperature, and the resulting residue was triturated with water and filtered to give a red-violet mass, 94.5 mg (**15**), which was rather unstable. Customarily this material was oxidized without further treatment either to quinone **16** or to quinone **17**. A sample was purified for characterization by preparative TLC; mp 260–265 °C; IR ($CHCl_3$) 1730, 1670, 1590; mass spectrum m/e 338 (M^+), 320, 292, 264, etc. Its dimethoxy ether, mp 245–248 °C, gave a molecular ion at m/e 366, and its methyl ester dimethoxy ether (prepared in the usual way with Me_2SO_4, dry acetone, and K_2CO_3) showed the following: IR ($CHCl_3$) 1730, 1610 (sh), 1590; NMR ($CDCl_3$) δ 3.23–2.87 (5 H, br s, Ar $COCH_2$, Ar CH_2, $CHCO_2CH_3$), 3.75 (3 H, s, CO_2CH_3), 4.00 (3 H, s, OCH_3), 4.06 (5 H, s, OCH_3, $ArCH_2Ar$), 6.09–8.20 (4 H, m, Ar H); mass spectrum m/e 380 (M^+), 365, 362, 349, 321, etc.

Table I

system	R_f anthracene	R_f benz[*a*]anthracene	R_f naphthacene
(a) benzene, petroleum ether (1:1)	0.47	0.35	0.05
(b) benzene	0.82	0.79	0.38

Zinc-Dust Distillations of Anthracenone 15 and Related Molecules. Approximately 15-mg samples of aloe-emodin, succinate **10**, and anthracenone **15** were separately mixed with several volumes of fresh zinc dust and heated to a red melt in Pyrex knee tubes as previously described.[10] The tubes were cut on opposite sides of the distillate, and the contents were dissolved in benzene. The examination on silica gel using antimony pentachloride spray or UV for detection gave the results shown in Table I. Aloe-emodin produced only anthracene; succinate **10** produced a mixture of anthracene and benz[*a*]anthracene while **15** produced benz[*a*]anthracene. Only traces of naphthacene were detected with distillation of crude **15**.

Oxidation of Anthracenone 15 to 3-Carboxy-6,8-dihydroxy-1-ketobenz[*a*]anthra-7,12-quinone (16). Anthracenone **15** (390 mg) was dissolved in methanol (50 mL), and KOH (200 mg) was added. Oxygen gas was passed through the solution for 4 h, and the mixture was acidified with HCl and the MeOH removed by distillation. The residue was washed with water and filtered to give quinone **16** as a red crystalline powder: mp 229–241 °C; IR 1730, 1700, 1670, 1630, 1600, 1555 cm^{-1}; mass spectrum m/e 352 (M^+), 324, 306, 280, 167, 133, etc. Its dimethyl ether methyl ester was recrystallized from MeOH–$CHCl_3$: mp 245–248 °C; IR 1730, 1670, 1590 cm^{-1}; mass spectrum m/e 394 (M^+), 379, 364, 351, 335, 320, 308, 293, 291, 280; NMR ($CDCl_3$) δ 2.5–3.8 (1 H, m, $CHCO_2CH_3$), 3.0–3.3 (4 H, m, CH_2CO, Ar CH_2), 3.70 (3 H, s, CO_2CH_3), 4.03 (6 H, s, OCH_3), 7.18 (1 H, s, C_5 H), 7.5–7.9 (3 H, m, Ar H). Its methyl ester showed IR bands at 1730, 1705, 1695, 1670, 1630, 1600, and 1590 cm^{-1}.

1,4,5-Trihydroxy-2-(2,3-dicarboxypropyl)-9,10-anthraquinone (17) by Oxidation of Anthracenone 15. A suspension of crude cyclized anthracenone **15** (94.5 mg) in a mixture of acetic acid (2 mL), 31.5% H_2O_2 (0.5 mL), and concentrated H_2SO_4 (3 drops) was stirred for 5 days at room temperature. An excess of water was added, and a precipitate resulted. Filtration afforded a brownish crystalline solid which was dissolved as well as possible in AcOEt, and the solution was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to leave a brown crystalline solid (77.3 mg): IR 1720, 1695, 1610 cm^{-1}; UV (MeOH) 520 nm, 503, 496, 484, 455, 285, 278, 262, 222; mass spectrum m/e 386 (M^+), 369, 368 (100%), 340, 322, 294, 281, 270, 269, 242, etc. This was esterified for further characterization by dissolving it in MeOH (15 mL) and passing in HCl gas for 3 h. The solvent was removed and the residue purified by chromatography in $CHCl_3$ over a silica gel column and crystallization as brown-red plates: mp 196–198 °C (from MeOH–$CHCl_3$); IR ($CHCl_3$) 3700, 3600, 1740, 1608, 1575 cm^{-1}; NMR ($CDCl_3$) δ 2.65 (2 H, dd, J = 6.5, 6 Hz, $CH_2CO_2CH_3$), 3.03 (2 H, m, Ar CH_2), 3.30 (1 H, m, $CHCO_2CH_3$), 3.63 (3 H, s, CO_2CH_3), 3.65 (3 H, s, CO_2CH_3), 7.10 (1 H, s, Ar H_2), 7.27 (1 H, dd, J = 8, 2 Hz, Ar H_7), 7.3–7.5 (1 H, m, Ar H_6), 7.73 (1 H, dd, J = 8, 2 Hz), 10.67 (1 H, s, OH), 10.69 (1 H, s, OH), 11.33 (1 H, s, OH); mass spectrum m/e 414 (M^+), 383, 382, 355, 354, 324, 323, 296, 295, etc. Treatment of the crude Baeyer–Villiger product (200 mg), suspended in 15 mL of DMF, with silver oxide (700 mg) and methyl iodide (700 mg) by stirring in the dark for 16 h, followed by addition of fresh Ag_2O and CH_3I and 16 h of additional stirring, led to a brown syrup which was purified by preparative TLC using $CHCl_3$–EtOAc (5:1) or $CHCl_3$–MeOH (9.5:0.5) and gave the trimethoxy ether, dimethyl ester of anthraquinone **17** as a brown-yellow syrup: IR ($CHCl_3$) 1730, 1670, 1590 cm^{-1}; NMR ($CDCl_3$) 2.53–2.83 (2 H, m, $CH_2CO_2CH_3$), 2.87–3.30 (3 H, m, Ar CH_2, $CHCO_2CH_3$), 3.67 (6 H, s, 2 CO_2CH_3), 3.90 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 4.0 (3 H, s, OCH_3), 7.13–7.8 (4 H, m, Ar H); UV λ_{max} (MeOH) 242 nm, 385; mass spectrum m/e 456 (M^+), 441, 426, 425, 397, 395, 381, etc.

Saponification of the latter was accomplished by refluxing a sample (19.5 mg) in EtOH (5 mL) and H_2O (1 mL) with KOH

(0.1 g) for 3.5 h followed by evaporation, acidification, and dissolution in $CHCl_3$. Evaporation produced a yellow syrup (15 mL) of the trimethyl ether of anthraquinone **17**: IR ($CHCl_3$) 1715, 1670, 1590 cm^{-1}; NMR ($CDCl_3$) 2.47–2.83 (2 H, m, $CH_2CO_2CH_3$), 2.90–3.47 (3 H, m, Ar CH_2, $CHCO_2CH_3$), 3.88 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 7.17–8.13 (6 H, m, Ar H, CO_2H).

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Registry No. **4**, 481-72-1; **7**, 72036-12-5; **8**, 72036-13-6; **8**, free acid, 72036-14-7; **9**, 72036-15-8; **10**, 72036-16-9; **11**, 72036-17-0; **11** dimethyl ester, 72036-18-1; **12**, 72036-19-2; **15**, 72036-20-5; **15** dimethyl ether, 72036-21-6; **15** methyl ester dimethyl ether, 72036-22-7; **16**, 72036-23-8; **16** dimethyl ether methyl ester, 72036-24-9; **17**, 72036-25-0; **17** dimethyl ester, 72036-26-1; **17** trimethyl ether, 72036-27-2; **17** trimethyl ether dimethyl ester, 72036-28-3; diethyl 2-carbethoxysuccinate, 7459-46-3.

Synthesis of Alkyl 4-Hydroxy-2-alkynoates

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The lithium acetylide anion of ethyl or methyl propiolate is readily prepared by the addition of *n*-butyllithium to ethyl or methyl propiolate at low temperature. The anion rapidly adds to a variety of aldehydes or ketones to give ethyl or methyl 4-hydroxy-2-alkynoates in high yield.

We recently required a variety of alkyl 4-hydroxy-2-alkynoates and the corresponding 4-keto compounds for our studies on asymmetric reducing agents.[2] At the time of the initiation of this project there were no general procedures for preparing this class of compounds. Herein we report that the lithium anion of methyl or ethyl propiolate rapidly adds to a variety of aldehydes or ketones to give the corresponding alkyl 4-hydroxy-2-alkynoates in high yield.

Sodium or potassium salts of alkyl propiolates are reported to give low yields of addition product to ketones.[3] Grignard reagents react in a complex manner with esters of propiolic acid and do not appear to cleanly form the desired acetylenic anion.[4] It has been reported that the lithium anions of propiolic esters may be added to aldehydes although no details are given and the generality of the reaction was not demonstrated.[5]

We have found that the lithium acetylide salt of methyl or ethyl propiolate may be readily prepared at low temperature by the reaction of the propiolate ester with *n*-butyllithium.[6] The acetylenic anion rapidly adds to a variety of aldehydes and ketones to give the methyl or ethyl 4-hydroxy-2-alkynoates upon workup. The results are presented in Table I.

$$HC{\equiv}CCO_2R + n\text{-}C_4H_9Li \rightarrow LiC{\equiv}CCO_2R$$

$$LiC{\equiv}CCO_2R + R'_2CO \rightarrow R'_2C(OH)C{\equiv}CCO_2R$$

The lithium anions are relatively stable when kept at low temperature. The ethyl ester appears to be easier to handle than the methyl ester and may be prepared and used at −78 °C (dry ice/acetone bath). On the other hand to achieve good results with the methyl ester, one must maintain the reaction at <−100 °C (4:1:1 tetrahydrofuran–ether–pentane solvent; 4:1:1 low-boiling petroleum ether–acetone–isopropyl alcohol in liquid nitrogen slush bath). Either lithium compound decomposes to a black solution if warmed to 0 °C and gives very little addition product upon subsequent reaction with an aldehyde or ketone.

The addition of the anion to aldehyde or ketones appears to be rapid and quantitative. Only in the reaction with acetophenone were appreciable amounts of ketone recovered. Workup is facilitated by protonation with acetic acid or saturated ammonium chloride at low temperature. The reaction may also be quenched by the addition of trimethylsilyl chloride. The trimethylsilyl group is then removed in the acidic aqueous workup. If the reaction mixture is allowed to warm to room temperature before quenching, there is a severe loss of product.

The secondary alcohols are readily oxidized to the alkyl 4-oxo-2-alkynoates with Jones reagent. Attempts to prepare the ketones directly by the reaction of the acetylide anion with an acid chloride[7] gave poor yields of keto product.

This process provides a rapid, high-yield synthesis of a variety of alkyl 4-hydroxy-2-alkynoates. Such compounds are useful in the synthesis of lactones and other natural products.[5] The observation that the corresponding ketones

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