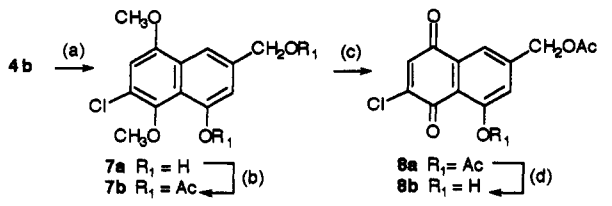
Scheme II[a]



[a] Reagents: (a) $LiAlH_4$, THF, rt, 24 h; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 3 h; (c) CAN, aq CH_3CN, rt, 1 h; (d) $AlCl_3$, CH_2Cl_2, rt, 1 h.

via demethylation[12] to the rhein ester **12b**[13] which gave rhein **12c** on room-temperature saponification.[14]

Unlike diene **11**, 1,3-dimethoxy-1,3-cyclohexadiene[15] did not give a single product upon Diels–Alder reaction with chlorojuglone **6b**. A rationale is the lability of the adduct (enol ether) to the reaction conditions (HCl produced). An alternative route to 1,3-dimethoxyanthraquinone derivatives was developed by Brassard.[16] Reaction of chlorojuglone **6b** with excess 1,1-dimethoxyethene (**14**) gave 70% of adduct **15a**. Demethylation, as above, gave selective removal of the *peri*-methoxy group to provide parietinic acid ethyl ester (**15b**), convertable to parietinic acid (**15c**)[17] *via* saponification. The second methoxy group could be demethylated using pyridinium hydrochloride[18] to furnish emodic acid (**15d**).[17]

Besides the anthraquinone-2-carboxylic acids described above, other common natural product series bear lower oxidation states such as the aldehyde or hydroxymethyl function.[1] Production of juglone synthons for the (hydroxymethyl)anthraquinones is shown in Scheme II.

Reduction[19] of diester **4b** with LAH provided diol **7a** in 78% yield. As with the carbethoxy series, it was desirable to oxidize the acetate **7b** rather than the phenol **7a**. Both acetylation[20] of diol **7a** to diacetate **7b** and CAN oxidation to juglone acetate **8a** proceeded in yields of 90%.

Juglone acetate **8a** was converted to the aloe emodin derivative **13a** using the same chemistry applied to rhein derivative **12a** above. Although the initial Diels–Alder adduct from the raction of juglone acetate **8a** with diene **11** was an oil, it could be taken directly for thermolysis to anthraquinone **13a** in 95% yield (from **8a**). Demethylation and hydrolysis were carried out as in the rhein series. Treatment of anthraquinone **13a** with aluminum chloride selectively removed the *peri*-methoxy and *peri*-acetoxy groups in 99% yield to give aloe emodin ω-acetate (**13b**)[21] which was saponified to aloe emodin (**13c**)[22] in 94% yield.

Juglone acetate **8a** was readily converted to juglone **8b** in the usual manner. The latter was converted to fallacinol (**16c**) and citreorosein (**16d**) using the same chemistry as for parietinic acid (**15c**) and emodic acid (**15d**) above. Reaction of juglone **8b** with exces alkene **14** gave the anthraquinone **16a** which was selectively demethylated to acetate **16b**[1a] and subsequently saponified to fallacinol (**16c**).[23] The latter was demethylated to citreorosein (**16d**)[1a] using the same conditions as for the production of emodic acid (**15d**).

The most exciting synthetic prospect of our functionalized juglones is that of forming additional rings at either end in a regiocontrolled manner to produce linear tetracyclics. Hydrolysis of the acetate groups in **4a** and **4b** produce naphthols which are convertible *via* salcomine-catalyzed aerial oxidation to carbethoxy naphthazarin derivatives which undergo regiospecific nucleophilic attack and in which the quinone functionality may be shifted from one ring to the other subsequently.[24] Studies are continuing on these nucleophilic reactions, as well as means for the introduction of different R_2 groups either by (a) modification of the model CH_3 group in **4c** and **4d** or (b) modification of R_2 in the succinate synthon **2** as well as alternative methods.

In summary, this work represents a flexible and reliable synthesis of functionalized juglones applicable to the synthesis of multigram quantities, which forms the basis of a number of ongoing studies.

Experimental Section

^{1}H-NMR spectra were run at 300 MHz in $CDCl_3$ unless indicated otherwise. Low-resolution mass spectra were recorded at 70 eV and are reported in mass units (m/z), and the values in parentheses are relative intensities from the base peak (as 100%). FT-IR spectra were recorded as KBr pellets. TLC was performed using Analtech silica gel plates (GF) containing fluorescent indicator. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

4-Chloro-2,5-dimethoxybenzaldehyde (1b). Trifluoroacetic acid (450 mL, 5.84 mol) was added to a mixture of 1-chloro-2,5-dimethoxybenzene (51.8 g, 300 mmol) and hexamethylenetetramine (42.0 g, 300 mmol). The solution was immediately placed in a preheated oil bath (90–95 °C) and refluxed for 12 h. The hot solution was poured onto 600 g of crushed ice and the resultant dark orange mixture rapidly stirred for 30 min. After the ice had melted, the solution was made basic with a large excess of solid $NaHCO_3$ until a yellow precipitate formed. Water (300 mL) was added and the mixture stirred until the paste solidified. The solid was filtered through a large Buchner funnel and washed with water (500 mL). The yellow mass was air dried and then recrystallized from high-boiling petroleum ether yielding **1b** (45.1 g, 75%) as a fluorescent yellow solid: mp = 106 °C; R_f = 0.45 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 10.32 (s, 1H), 7.30 (s, 1H), 6.99 (s, 1H), 3.83 (s, 6H); IR ν 2966, 2943, 2876, 2854, 2770, 1675, 1607, 1501, 1483, 1463, 1392, 1276 cm^{-1}; MS 202 (M^{2+}, 34.2), 200 (M^+, 100). Anal. Calcd for $C_9H_9O_3Cl$: C, 53.88; H, 4.52; Cl, 17.67. Found: C, 53.74; H, 4.59; Cl, 17.67.

3-Carbethoxy-4(2,5-dimethoxyphenyl)-3-butenoic Acid (3a). To a well-stirred mixture of sodium hydride (24.0 g, 1.04 mol, prepared from 40.0 g of a 60% mineral oil dispersion which had been previously washed twice with pentane and once with toluene) and toluene (500 mL) under nitrogen and at room temperature was added a catalytic amount of absolute ethanol (0.5 mL) followed by dropwise addition of a solution of diethyl succinate **2a** (209 g, 1.20 mol) and 2,5-dimethoxybenzaldehyde (**1a**) (69.7 g, 0.42 mol). The rate of addition was sufficient to maintain a steady evolution of hydrogen and a reaction temperature not exceeding 55 °C. The mixture was stirred for 1 h

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at room temperature, and then concd HCl (145 mL, 1.74 mol) followed by water (200 mL) was added. [*Note: Use of acetic acid (100 mL, 1.74 mol) and then water (200 mL) gave the product as an oil, though the yield was similar.*] The organic layer was extracted with 1 M K_2CO_3 (500 mL, 0.50 mol) and the aqueous layer acidified with concd HCl (146 mL, 1.74 mol). The yellow-orange oil which separated was extracted with with diethyl ether, dried ($MgSO_4$), and evaporated to yield **3a** (74.2 g, 60%) as an orange oil which crystallized on standing: mp = 110 °C; R_f = 0.62 (120:18:1 toluene/HOAc/MeOH); ^{1}H NMR δ 10.6 (s, 1H), 7.99 (s, 1H), 6.93–6.84 (m, 3H), 4.32 (q, 2H, J = 7.2 Hz), 3.81 (s, 3H), 3.78 (s, 3H), 3.53 (s, 2H), 1.36 (t, 3H, J = 7.2 Hz); IR ν 3050–2525, 1700, 1638, 1500, 1300, 1225 cm^{-1}; MS 294 (M^+, 50.3), 161 (100). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.59; H, 6.12.

3-Carbethoxy-4-(4-chloro-2,5-dimethoxyphenyl)-3-butenoic Acid (3b). Acid **3b** (mp = 152–153 °C) was prepared in 65% yield from the Stobbe condensation of chloroaldehyde **1b** and succinate **2a** according to the procedure described above for the preparation of acid **3a**: R_f = 0.58 (120.:18:1 toluene/HOAc/MeOH); ^{1}H NMR δ 7.95 (s, 1H), 7.01 (s, 1H), 6.97 (s, 1H), 4.33 (q, 2H, J = 7.2 Hz), 3.86 (s, 3H), 3.82 (s, 3H), 3.51 (s, 2H), 1.37 (t, 3H, J = 7.2 Hz); IR ν 3100–2520, 1700, 1500, 1388, 1287, 1225 cm^{-1}; MS 330 (M^{2+}, 15.0), 328 (M^+, 53.6), 195 (100). Anal. Calcd for $C_{15}H_{17}ClO_6$: C, 54.80; H, 5.21. Found: C, 54.92; H, 5.33.

3-Carbethoxy-4-(2,5-dimethoxyphenyl)-2-methyl-3-butenoic Acid (3c). Acid **3c** was prepared in 61% yield from the Stobbe condensation of aldehyde **1a** and succinate **2b** according to the procedure described above for the preparation of acid **3a**. The oil was used directly in the next step: R_f = 0.66 (120:18:1 toluene/HOAc/MeOH); ^{1}H NMR δ 10.4 (s (br), 1H), 8.04 (s, 1H), 7.26 (s, 1H), 6.95–6.80 (m, 2H), 4.21 (q, 2H, J = 7.2 Hz), 3.78 (s, 6H), 3.50 (q, 1H, J = 6.9 Hz), 1.20 (t, 3H, J = 7.2 Hz), 1.15 (d, 3H, J = 6.9 Hz); IR ν 3008–2922 (br), 2944, 2835, 1706, 1708, 1499, 1224 cm^{-1}. *Repeated attempts at analysis were not successful.

3-Carbethoxy-4-(4-chloro-2,5-dimethoxyphenyl)-2-methyl-3-butenoic Acid (3d). Acid **3d** (mp = 190–191 °C) was prepared in 67% yield from the Stobbe condensation of chloroaldehyde **1b** and succinate **2b** according to the procedure described above for the preparation of acid **3a**: R_f = 0.67 (120:18:1 toluene/HOAc/MeOH); ^{1}H NMR δ 12.57–12.18 (s (br), 1H), 7.59 (s, 1H), 7.16 (s, 1H), 7.04 (s, 1H), 3.77 (q, 2H, J = 7.2 Hz), 3.62 (q, 1H, J = 6.9 Hz), 1.26 (d, 3H, J = 6.9 Hz), 1.25 (t, 3H, J = 7.2 Hz); IR ν 3300– 2500 (br), 3013, 2978, 2941, 2852, 1720 (br), 1674, 1491, 1460, 1442, 1423, 1392, 1294, 1259, 1219 cm^{-1}; MS 344 (M^{2+}, 8.6) 3.42 (M^+, 24.9), 209 (100). Anal. Calcd for $C_{16}H_{19}O_6$-Cl: C, 56.06; H, 5.59. Found: C, 55.80; H, 5.76.

3-Carbethoxy-4-(2,5-dimethoxyphenyl)-4-methyl-3-butenoic Acid (3e). Acid **3e** was prepared in 61% yield from the Stobbe condensation of acetophenone derivative **1c** and succinate **2a** according to the procedure described above for the preparation of acid **3a**. The oil was used directly in the next step: R_f = 0.81 (120:18:1 toluene/HOAc/MeOH); ^{1}H NMR δ 6.84 (m, 2H), 6.65–6.57 (m, 1H), 4.28 (q, 2H, J = 7.2 Hz), 3.76 (s, 6H), 3.23 (d, 1H, J = 27.3 Hz), 3.17 (d, 1H J = 27.3 Hz), 2.39 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz); IR ν 3015–288, 2983, 2941, 2835, 1730, 1712, 1499, 1417, 1222, 1182, 1048 cm^{-1}; MS 308 (M^+, 68.4), 203 (100). *Repeated attempts at analysis were not successful.

3-Carbethoxy-4-(4-chloro-2,5-dimethoxyphenyl)-4-methyl-3-butenoic Acid (3f). Acid **3f** (mp = 149–152 °C) was prepared in 63% yield from the Stobbe condensation of chloroacetophenone derivative **1d** and succinate **2b** according to the procedure described above for the preparation of acid **3a**: R_f = 0.53 (120:18:1 toluene/HOAc/MeOH); ^{1}H NMR δ 7.00 (s, 1H), 6.70 (s, 1H), 4.28 (q, 2H, J = 7.2 Hz), 3.82 (s, 3H), 3.75 (s, 3H), 3.26 (d, 1H, J = 17.3 Hz), 3.10 (d, 1H, J = 17.3 Hz), 2.38 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz): IR ν 3021–2901 (br), 3007, 2982, 2940, 1724, 1703, 1500, 1387, 1281, 1251, 1217, 1198, 1058, 1036 cm^{-1}; MS 344 (M^{2+}, 26.8), 342 (M^+, 100). Anal. Calcd for $C_{16}H_{19}O_6Cl$: C, 56.06; H, 5.59. Found: C, 55.87; H, 5.81.

Ethyl 4-(Acetyloxy)-5,8-dimethoxy-2-naphthalenecarboxylate (4a). The crude carboxylic acid **3a** (70.1 g, 0.24 mol) was cyclized in boiling acetic anhydride (124 g, 1.21 mol) and anhydrous sodium acetate (36.1 g, 0.44 mol) under nitrogen for 3 h. The mixture was allowed to cool overnight during which time crystals of sodium acetate formed. The next day, the mixture was poured over ice (500 g) and stirred vigorously until an orange-brown spongy solid formed. The solid was washed repeatedly with fresh portions of water to remove all traces of acetic anhydride. Purification of the air-dried solid by trituration with a minimum quantity of methanol yielded **4a** (49.7 g, 65%) as an orange powder: mp = 155 °C; R_f = 0.54 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 8.92 (d, 1H, J = 1.5 Hz), 7.71 (d, 1H, 1.5 Hz), 6.89 (d, 1H, J = 8.4 Hz), 6.79 (d, 1H, J = 8.4 Hz), 4.44 (q, 2H, J = 7.2 Hz), 3.99 (s, 3H), 3.91 (s, 3H), 2.40 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 2980, 1778, 1713, 1613, 1283, 1258, 1203 cm^{-1}; MS 318 (M^+, 24), 276 (100). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.17; H, 5.57.

Ethyl 4-(Acetyloxy)-6-chloro-5,8-dimethoxy-2-naphthalenecarboxylate (4b). Bicyclic **4b** (mp = 146–147 °C) was prepared in 70% yield by cyclization of **3b** according to the procedure described above for the preparation of bicyclic **4a** except that the air-dried spongy solid was dissolved in ether, dried ($MgSO_4$), and filtered and the ether removed to yield a yellow brown solid which was taken up in a small quantity of methanol and immediately filtered: R_f = 0.84 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 8.89 (d, 1H, J = 1.8 Hz), 7.78 (d, 1H, J = 1.8 Hz), 6.87 (s, 1H), 4.45 (q, 2H, J = 7.2 Hz), 4.02 (s, 3H), 3.88 (s, 3H), 2.42 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 1760, 1700, 1595, 1490, 1435, 1340, 1275, 1200 cm^{-1}; MS 354 (M^{2+}, 10.3), 352 (M^+, 25.0), 310 (100). Anal. Calcd for $C_{17}H_{17}ClO_6$: C, 57.88; H, 4.86. Found: C, 57.86; H, 4.92.

Ethyl-4-(Acetyloxy)-5,8-dimethoxy-3-methyl-2-naphthalenecarboxylate (4c). Bicyclic **4c** (mp = 80–83 °C) was prepared in 67% yield by cyclization of **3c** according to the procedure described above for the preparation of bicyclic **4a** except that the air-dried spongy solid was extracted repeatedly with boiling high-boiling petroleum ether yielding the product as a yellow powder on cooling: R_f = 0.19 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 8.72 (s, 1H), 6.84 (d, 1H, J = 8.6 Hz), 6.71 (d, 1H, J = 8.6 Hz), 4.43 (q, 2 H, J = 7.2 Hz), 3.97 (s, 3H), 3.89 (s, 3H), 2.52 (s, 3H), 2.42 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 1760, 1718, 1597, 1275, 1202 cm^{-1}; MS 332 (M^+, 39.4), 290 (100). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.04; H, 6.13.

Ethyl 4-(Acetyloxy)-6-chloro-5,8-dimethoxy-3-methyl-2-naphthalenecarboxylate (4d). Bicyclic **4d** (mp = 148 °C) was prepared in 68% yield by cyclization of **3d** according to the procedure described above for the preparation of bicyclic **4c**: R_f = 0.30 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 8.70 (s, 1H), 6.80 (s, 1H), 4.43 (q, 2H, J = 7.2 Hz), 4.00 (s, 3H), 3.87 (s, 3H), 2.54 (s, 3H), 2.44 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 2989, 2985, 2978, 2943, 2906, 1770, 1712, 1583, 1462, 1450, 1332, 1261, 1209, 1057 cm^{-1}; MS 368 (M^{2+}, 7.7), 366 (M^+, 24.6), 324 (100). Anal. Calcd for $C_{18}H_{19}O_6Cl \cdot {}^1/_2CH_3OH$: C, 58.05; H, 5.48. Found: C, 58.35; H, 5.43.

Ethyl 4-(Acetyloxy)-5,8-dimethoxy-1-methyl-2-naphthalenecarboxylate (4e). Bicyclic **4e** (mp = 101 °C) was prepared in 68% yield by cyclization of **3e** according to the procedure described above for the preparation of bicyclic **4c**: R_f = 0.32 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 7.31 (s, 1H), 6.86 (d, 1H, J = 13.5 Hz), 6.84 (d, 1H, J = 13.5 Hz), 4.28 (q, 2H, J = 7.2 Hz), 3.89 (s, 3H), 3.88 (s, 3H), 2.95 (s, 3H), 3.27 (s, 3H), 1.42 (t, 3H, J = 7.2 Hz); IR ν 3001, 2957, 2942, 2919, 1762, 1710, 1611, 1387, 1350 , 1261, 1219, 1144, 1046 cm^{-1}; MS 332 (M^+, 43.0), 290 (100). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.35; H, 6.27.

Ethyl 4-(Acetyloxy)-6-chloro-5,8-dimethoxy-1-methyl-2-naphthalenecarboxylate (4f). Bicyclic **4f** (mp = 95–97 °C) was prepared in only 5% yield (and could not be scaled up) by cyclization of **3f** according to the procedure described above for the preparation of bicyclic **4c**: R_f = 0.22 (3:1 $CHCl_3$/pentane); ^{1}H NMR δ 7.38 (s, 1H), 6.87 (s, 1H), 4.41 (q, 2H, J = 7.2 Hz), 3.92 (s, 3H), 3.83 (s, 3H), 2.93 (s, 3H), 2.38 (s, 3H), 1.42 (t, 3H, J = 7.2 Hz); IR ν 2962, 2936, 2842, 1771, 1717, 1560, 1360, 1204, 1047 cm^{-1}; MS 368 (M^{2+}, 9.28), 366 (M^+, 29.2), 324 (100). Anal. Calcd for $C_{18}H_{19}O_6Cl$: C, 58.94; H, 5.22. Found: C, 58.79; H, 5.27.

Ethyl 4-(Acetoxy)-5,8-dihydro-5,8-dioxo-2-naphthalenecarboxylate (5a). A solution of ceric ammonium nitrate (3.58 g, 6.53 mmol) in 20 mL of water was added in portions, with rapid stirring, to a solution of the bicyclic **4a** (1.04 g, 3.27 mmol) in acetonitrile (100 mL) over a period of 5 min. A transient blue-black color was observed after each addition. The mixture was

stirred for 1 h at room temperature and then diluted with water (800 mL). The precipitated product was filtered, washed with water (100 mL) and then air dried yielding **5a** (0.754 g, 80%) as a bright yellow powder which could be further purified by recrystallization from methanol: mp = 131 °C; R_f = 0.60 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.68 (d, 1H, J = 1.5 Hz), 8.05 (d, 1H, J = 1.5 Hz), 7.03 (d, 1H, J = 10.2 Hz), 6.92 (d, 1H, J = 10.2 Hz), 4.46 (q, 2H, J = 7.2 Hz), 2.48 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 3100, 3075, 2035, 2975, 1775, 1725, 1663 (br), 1325, 1263 cm^{-1}; MS 288 (M^+, 3.2), 246 (100). Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.49; H, 4.20. Found: C, 62.58; H, 4.21.

Ethyl 4-(Acetyloxy)-6-chloro-5,8-dihydro-5,8-dioxo-2-naphthalenecarboxylate (5b). Acetoxyjuglone **5b** (mp = 148 °C) was prepared in 75% yield by oxidation of bicyclic **4b** according to the procedure described above for **5a** except that after the reaction was completed the mixture was diluted with water, extracted with ether, and dried ($MgSO_4$) and the solvent removed to yield **5b** as a yellow solid: R_f = 0.84 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.67 (d, 1H, J = 1.8 Hz), 8.07 (d, 1H, J = 1.8 Hz), 7.29 (s, 1H), 4.47 (q , 2H, J = 7.2 Hz), 2.50 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 3060, 1775, 1715, 1670, 1600, 1255, 1190 cm^{-1}; MS 324 (M^{2+}, 1.5), 322 (M^+, 3.6), 280 (100). Anal. Calcd for $C_{15}H_{11}O_6Cl$: C, 55.83; H, 3.44. Found: C, 55.58, H. 3.71.

Ethyl 4-(Acetyloxy)-5,8-dihydro-3-methyl-5,8-dioxo-2-naphthalenecarboxylate (5c). Acetoxyjuglone **5c** (mp = 144–145 °C) was prepared in 85% yield by oxidation of bicyclic **4c** according to the procedure described above for **5b**: R_f = 0.14 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.45 (s, 1H), 6.98 (d, 1H, J = 10.5 Hz), 6.88 (d, 1H, J = 10.5 Hz), 4.45 (q, 2H, J = 7.2 Hz), 2.51 (s, 3H), 2.508 (s, 3H), 1.44 (s, 3H, J = 7.2 Hz); IR ν 3073, 3056, 2983, 1768, 1724, 1688 (br), 1611, 1364, 1292, 1274, 1238, 1196, 1151, 1090 cm^{-1}; MS 302 (M^+, 1.5), 259 (100). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.64; H, 4.78.

Ethyl 4-(Acetyloxy)-6-chloro-5,8-dihydro-3-methyl-5,8-dioxo-2-naphthalenecarboxylate (5d). Acetoxyjuglone **5d** (mp = 149–150 °C) was prepared in 84% yield of oxidation of bicyclic **4d** according to the procedure described above for **5b**: R_f = 0.31 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.45 (s, 1H), 7.26 (s, 1H), 4.45 (q, 2H, J = 7.2 Hz), 2.54 (s, 3H), 2.53 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 3099, 3055, 2991, 1778, 1718, 1683, 1664, 1604, 1255, 1192, 1053 cm^{-1}; MS 338 (M^{2+}, 0.3), 336 (M^+, 0.9), 294 (100). Anal. Calcd for $C_{16}H_{13}O_6Cl$: C, 57.07; H, 3.89. Found: C, 57.26; H, 4.01.

Ethyl 4-(Acetyloxy)-5,8-dihydro-1-methyl-5,8-dioxo-2-naphthalenecarboxylate (5e). Acetoxyjuglone **5e** (mp = 101–103 °C) was prepared in 87% yield by oxidation of bicyclic **4e** according to the procedure described above for **5b**: R_f = 0.29 (3:1 $CHCl_3$/pentane); ^1H NMR δ 7.61 (s, 1H), 6.93 (d, 1H, J = 10.2 Hz), 6.82 (d, 1H, J = 10.2 Hz), 4.43 (q, 2H, J = 7.2 Hz), 2.81 (s, 3H), 2.45 (s, 3H), 1.43 (t, 3H, J = 7.2 Hz); IR ν 3078, 2988, 1765, 1726, 1661, 1299, 1243, 1216, 1243, 1216, 1203, 1105, 1043 cm^{-1}; MS 302 (M^+, 22.9), 232 (100). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.86; H, 4.82.

Ethyl 5,8-Dihydro-4-hydroxy-5,8-dioxo-2-naphthalenecarboxylate (6a). Method A. A solution of the acetoxyjuglone **5a** (0.292 g, 1.01 mmol), acetone (30 mL), and 3 M HCl (13.5 mL, 40.5 mmol) was refluxed (95 °C) for 0.5 h only! Another portion of 3 M HCl (13.5 mL, 40.5 mmol) was added and the solution refluxed for an additional 2 h only! After being cooled on ice, the mixture was extracted with ether (2 × 50 mL). The ether layer was washed with water (5 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to yield **6a** (0.187 g, 75%) as an orange oil which solidified on trituration with a small quantity of methanol. Method B. To a rapidly stirred solution of acetoxyjuglone **5a** (1.15 g, 4.0 mmol) in methylene chloride (50 mL) under nitrogen and at room temperature was added aluminum chloride (5.33 g, 40 mmol). Stirring was continued for an additional hour, and water (50 mL) followed by concd HCl (5 mL) were added cautiously at 0 °C. The mixture was extracted with methylene chloride (2 × 50 mL) and the organic layer dried ($MgSO_4$), filtered, and evaporated yielding the juglone **6a** (0.867 g, 88%) as a bright orange solid: mp – 125 °C; R_f = 0.50 (3:1 $CHCl_3$/pentane); ^1H NMR δ 11.85 (s, 1H), 8.24 (d, 1H, J = 1.5 Hz), 7.96 (d, 1H, J = 1.5 Hz), 7.040 (s, 1H), 7.035 (s, 1H), 4.45 (q, 2H, J = 7.2 Hz), 1.45 (t, 3H, J = 7.2 Hz); IR ν 3400 (br), 3100, 3000, 1738, 1 675, 1637, 1588, 1388, 1300, 1250 cm^{-1}; MS 246 (M^+, 67.3), 63 (100). Anal. Calcd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found: C, 63.51; H, 4.11.

Ethyl 6-Chloro-5,8-dihydro-4-hydroxy-5,8-dioxo-2-naphthalenecarboxylate (6b). Juglone **6b** (mp = 145–147 °C) was prepared in 75% yield (method A) and 95% yield (method B) from acetoxyjuglone **5b** according to the precedures described above for the preparation of juglone **6a**: R_f = 0.48 (3:1 $CHCl_3$/pentane); ^1H NMR δ 11.63 (s, 1H), 8.25 (d, 1H, J = 1.4 Hz), 7.97 (d, 1H, J = 1.4 Hz), 7.28 (s, 1H), 4.45 (q, 2H, J = 7.2 Hz), 1.44 (t, 3H, J = 7.2 Hz); IR ν 3408 (br), 3075, 3000, 1738, 1675, 1650, 1375, 1250 cm^{-1}; MS 282 (M^{2+}, 27.1), 2.80 (M^+, 97.3), 235 (100). Anal. Calcd for $C_{13}H_9O_5Cl$: C, 55.63; H, 3.23. Found: C, 55.61; H, 3.20.

Ethyl 5,8-Dihydro-4-hydroxy-3-methyl-5,8-dioxo-2-naphthalenecarboxylate (6c). Juglone **6c** (mp = 95 °C) was prepared in 71% yield (method A) and 86% yield (method B) from acetoxyjuglone **5c** according to the procedures described above for the preparation of juglone **6a**: R_f = 0.36 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.41 (s, 1H), 7.99 (s, 1 H), 7.00 (s, 2H), 4.43 (q, 2H, J = 7.2 Hz), 2.56 (s, 3H), 1.44 (t, 3H, J = 7.2 Hz); IR ν 3425 (br), 2995, 2960, 1726 (br), 1670, 1643, 1597, 1465, 1406, 1377, 1357, 1327, 12 90, 1261, 1155, 1099, 1082 cm^{-1}; MS 260 (M^+, 100). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.60; H, 4.59.

Ethyl 6-Chloro-5,8-dihydro-4-hydroxy-3-methyl-5,8-dioxo-2-naphthalenecarboxylate (6d). Juglone **6d** (mp = 149–150 °C) was prepared in 68% yield (method A) and 79% yield (method B) from acetoxyjuglone **5d** according to the procedures described above for the preparation of juglone **6a**. The juglone acetate **5d** (for elemental analysis) was prepared by boiling a solution of **6d** (10 mg), acetic anhydride (five drops), and concd HCl (1 drop) for 3 min. Crystals of the juglone acetate **5d** separated on cooling: R_f = 0.51 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.22 (s, 1H), 8.00 (s, 1H), 7.25 (s, 1H), 4.44 (q, 2H, J = 7.2 Hz), 2.57 (s, 1H), 1.44 (t, 3H, J = 7.2 Hz); IR ν 3415, 3086, 2990, 2978, 2941, 2930, 2850, 1722, 1659, 1640, 1595, 1405, 1373, 1262, 1249, 1228 cm^{-1}; MS 296 (M^{2+}, 29.9), 294 (M^+, 100). Anal. Calcd for the acetate $C_{16}H_{13}O_6Cl$: C, 57.14; H, 3.90. Found: C, 57.26; H, 4.01.

Ethyl 5,8-Dihydro-4-hydroxy-1-methyl-5,8-dioxo-2-naphthalenecarboxylate (6e). Juglone **6e** (mp = 102–103 °C) was prepared in 35% yield (method A) and 50% yield (method B) from acetoxyjuglone **5e** according to the procedures described above for the preparation of juglone **6a**: R_f = 0.10 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.49 (s, 1H), 7.48 (s, 1H), 6.95 (s, 2H), 4.43 (q, 2H, J = 7.2 Hz), 2.70 (s, 3H), 1.43 (t, 3H, J = 7.2 Hz); IR ν 3401 (br), 3068, 2985, 2940, 1727, 1657, 1645, 1243, 1218, 1202 cm^{-1}; MS 260 (M^+, 50.0), 232 (100). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.62; H, 4.65. Found: C, 64.22; H, 4.80.

6-Chloro-4-hydroxy-5,8-dimethoxy-2-(hydroxymethyl)-naphthalene (7a). A solution of the ester **4b** (0.261 g, 0.740 mmol) in 2 mL of THF was added over 10 min to a rapidly stirred suspension of $LiAlH_4$ (0.044 g, 1.16 mmol) in 2 mL of THF at room temperature. The mixture was stirred overnight at room temperature and then acidified at 0 °C with 20% H_2SO_4 (0.5 mL). Extraction with ether followed by evaporation yielded **7a** (0.155 g, 78%) as a light green solid: mp = 105–106 °C; R_f = 0.40 (120:18:1 toluene/HOAc/MeOH); ^1H NMR δ 9.45 (s, 1H), 7.69 (d, 1H, J = 1.5 Hz), 6.99 (d, 1H, J = 1.5 Hz), 6.72 (s, 1H), 4.79 (d, 2H, J = 5.2 Hz), 4.04 (s, 3H), 3.97 (s, 3H), 1.88 (t, 1H, J = 5.2 Hz); IR ν 3401–3132 (br), 3332 (sharp), 2952, 2847, 1603, 1507, 1376, 1346 cm^{-1}; MS 270 (M^{2+}, 5.54), 268 (M^+, 18.3), 238 (100). Anal. Calcd for the diacetate **7b** $C_{17}H_{17}O_6Cl$: C, 57.88; H, 4.86. Found: C, 57.51; H, 5.06.

4-(Acetyloxy)-6-chloro-5,8-dimethoxy-2-(acetoxymethyl)-naphthalene (7b). To a solution of the diol **7a** (0.649 g, 2.4 mmol) in 50 mL of CH_2Cl_2 was added triethylamine (3.22 mL, 2.3 mmol), *N*,*N*-dimethyl-4-aminopyridine (0.602 g, 4.93 mmol), and acetic anhydride (1.0 mL, 9.05 mmol) at room temperature. The reaction was stirred for 5 h and then washed successively with brine (6 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and water (2 × 50 mL). Evaporation of the solvent yielded **7b** (0.762 g, 90%) as a brown oil which was recrystallized from methanol: mp = 65–67 °C; R_f = 0.10 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.14 (d, 1H, J = 1.5 Hz), 7.21 (d, 1H, J = 1.5 Hz), 6.83 (s, 1H), 5.24 (s, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 2.41 (s, 3H), 2.15 (s, 3H); IR ν 2998, 2971, 2941, 1770, 1728, 1596, 1363, 1346, 1257, 1215 cm^{-1};

MS 354 (M^{2+}, 6.96), 352 (M^+, 21.8), 310 (100). Anal. Calcd for $C_{17}H_{17}O_6Cl$: C, 57.88; H, 4.86. Found: C, 57.51; H, 5.06.

4-(Acetyloxy)-2-(acetoxymethyl)-6-chloro-5,8-naphthalenedione (8a). To the diacetate **7b** (0.125 g, 0.36 mmol) in CH_3CN (50 mL) was added a solution of CAN (0.41 g, 0.75 mmol) in 5 mL of H_2O. The mixture was stirred at rt (3 h), poured into water (100 mL), and extracted with ether (3 × 100 mL). Evaporation of the solvent yielded pure juglone acetate **8a** (0.104 g, 90%) as an orange solid: mp = 118–120 °C; R_f = 0.19 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.02 (d, 1H, J = 1.5 Hz), 7.41 (d, 1H, J = 1.5 Hz), 7.28 (s, 1H), 5.23 (s, 2H), 2.49 (s, 3H), 2.19 (s, 3H); IR ν 3075, 3047, 2970, 2940, 1755, 1684, 1679, 1664, 1610, 1600, 1237, 1221, 1198 cm^{-1}; MS 324 (M^{2+}, 0.20), 322 (M^+, 0.56), 238 (100). Anal. Calcd for $C_{15}H_{11}O_6Cl$: C, 55.83; H, 3.44. Found: C, 55.69; H, 3.55.

2-(Acetoxymethyl)-6-chloro-4-hydroxy-5,8-naphthalenedione (8b). To a rapidly stirred solution of the juglone acetate **8a** (0.262 g, 0.813 mmol) and CH_2Cl_2 (50 mL) was added $AlCl_3$ (0.542 g, 4.07 mmol). The mixture was stirred at rt (1 h), and then water (50 mL) followed by concd HCl (1 mL) were added. Extraction of the mixture with ether (3 × 100 mL) and evaporation of the solvent yielded **8b** (0.192 g, 84%) as a yellow solid: mp = 143 °C; R_f = 0.28 (3:1 $CHCl_3$/pentane); ^1H NMR δ 11.69 (s, 1H), 7.61 (s, 1H, J = 1.5 Hz), 7.29 (d, 1H, J = 1.5 Hz), 7.22 (s, 1H), 5.18 (s, 2H), 2.20 (s, 3H); IR ν 3299–3132 (br), 3044, 2961, 1736, 1663, 1633, 1589, 1253, 1190 cm^{-1}; MS 282 (M^{2+}, 3.12), 280 (M^+, 10.7), 238 (100). Anal. Calcd for $C_{13}H_9O_5Cl$: C, 55.63; H, 3.23. Found: C, 55.54; H, 3.21.

Ethyl 9,10-Dihydro-4-hydroxy-9,10-dioxo-2-anthracenecarboxylate (10a). A solution of juglone acetate **5b** (0.52 g, 1.60 mmol), diene **9** (0.09 g, 8.00 mmol), and ethanol (5 mL) was refluxed for 5 h. The mixture was allowed to cool overnight, and the solid which precipitated was filtered and then recrystallized from high-boiling petroleum ether yielding **10a** (0.40 g, 85%) as a green solid: mp = 128 °C; R_f = 0.28 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.55 (s, 1H), 8.45 (d, 1H, J = 1.8 Hz), 8.37–8.34 (m, 2H), 7.97 (d, 1H, J = 1.8 Hz), 7.88–7.85 (m, 2H), 4.47 (q, 2H, J = 7.2 Hz), 1.46 (t, 3H, 7.2 Hz); IR ν 3550–3263 (br), 3095, 208 2, 2994, 2987, 1724, 1665, 1607, 1269, 1193 cm^{-1}; MS 296 (M^+, 63.8), 251 (60.8), 139 (100). *Although repeated attempts at analysis were unsuccessful, the product could be taken directly for the next step without further purification.

9,10-Dihydro-4-hydroxy-9,10-dioxo-2-anthracenecarboxylic Acid (Pachybasic Acid) (10b). A solution of the ester **10a** (0.11 g, 0.37 mmol) was stirred under N_2 and at rt with 10% NaOH (5 mL, 12.5 mmol) for 24 h. To the cooled soltuion was added 0.5 mL of concd HCl. Extraction with ether followed by evaporation of the solvent gave **10b** (0.0843 g, 85%) as a bright yellow powder: mp = 289 °C (lit.[11] mp = 286–287 °C); R_f = 0.60 (120:18:1 toluene/HOAc/MeOH); ^1H NMR: δ (DMSO-d_6) 12.24 (s, 1H), 8.22–8.15 (m, 2H), 8.09 [s (br), 1H], 7.95–7.92 (m, 2H), 7.71 [s (br), 1H]; IR ν 3222–2792 (br), 3087, 2965, 2925, 1700, 1652 (br), 1278, 1262 cm^{-1}; MS 268 (M^+, 100), 139 (40.3).

Ethyl 9,10-Dihydro-4-hydroxy-5-methoxy-9,10-dioxo-2-anthracenecarboxylate (12a). A solution of the chlorojuglone **6b** (0.100 g, 0.36 mmol), diene **11** (0.091 g, 0.54 mmol; 65% tech), and Et_3N (0.040 g, 0.39 mmol) in 25 mL of CH_2Cl_2 was stirred at rt for 24 h. The solvent was evaporated and the green oil heated at 140 °C in a preheated oil bath. After several minutes the oil solidified, yielding **12a** (0.116 g, 99%) as a dark brown solid which could be recrystallized from methanol: mp = 211–212 °C; R_f = 0.26 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.88 (s, 1H), 8.36 (d, 1H, J = 1.8 Hz), 7.99 (d, 1H, J = 7.5 Hz), 7.93 (d, 1H, J = 1.8 Hz), 7.79 (dd, 1H, J = 8.7, 7.5 Hz), 7.40 (d, 1H, J = 8.7 Hz), 4.44 (q, 2H, J = 7.2 Hz), 4.09 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 3075, 29 50, 2925, 1725, 1663, 1638, 1575, 1288, 1263, 1213 cm^{-1}; MS 326 (M^+, 100), 280 (50.3); HRMS (EI) calcd for $C_{18}H_{14}O_6$ (M^+) 326.0790, found 326.0807.

Ethyl 9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthracenecarboxylate (12b). To a rapidly stirred solution of the methyl ether **12a** (0.067 g, 0.205 mmol) in 15 mL of CH_2Cl_2 was added $AlCl_3$ (0.547 g, 4.1 mmol). The mixture was stirred at rt for 24 h, and then water (15 mL) followed by concd HCl (1 mL) were added cautiously. Extraction of the mixture with ether (3 × 50 mL) and evaporation of the solvent yielded rhein ester **12b** (0.0544 g, 85%) as a yellow powder: mp = 162–164 °C (lit.[13] = 159 °C); R_f = 0.54 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.05 (s, 1H), 12.00 (s, 1H), 8.44 (d, 1H, J = 1.5 Hz), 7.96 (d, 1H, J = 1.5 Hz), 7.90 (d, 1H, J = 7.5 Hz), 7.77–7.72 (dd, 1H, J = 8.4, 7.5 Hz), 7.35 (d, 1H, J = 8.4 Hz), 4.47 (q, 2H, J = 7.2 Hz), 1.46 (t, 3H , J = 7.2 Hz); IR ν 3122–3072 (br), 2963, 2925, 1722, 1671, 1631, 1458, 1379, 1259, 1091, 1023 cm^{-1}; MS 312 (M^+, 100), 267 (81.4).

9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthracenecarboxylic Acid (Rhein) (12c). The ester **12b** (52.2 mg, 0.167 mmol) was saponified to rhein **12c** (40.3 mg, 85%) according to the procedure described above for the preparation of **10b**: mp = 320–323 °C (lit.[14] mp = 319–321 °C); R_f = 0.60 (3:1 $CHCl_3$/pentane); ^1H NMR δ (DMSO-d_6) 13.74 (s (br), 1H), 11.87 (s, 2H), 8.10 (d, 1H, J = 1.5 Hz), 7.84–7.78 (dd, 1H, J = 7.8, 7.5 Hz), 7.73 (d, 1H, J = 1.5 Hz), 7.72–7.69 (dd, 1H, J = 7.8, 0.9 Hz), 7.40–7.37 (dd, 1H, J = 7.5, 0.9 Hz); IR ν 3233–3162 (br), 3121–2950 (br), 3065, 1698, 1630, 1610, 1454, 1268, 1192 cm^{-1}; MS 284 (M^+, 100).

1-(Acetyloxy)-3-(acetoxymethyl)-8-methoxy-9,10-anthracenedione (13a). The acetoxyjuglone **8a** (0.029 g, 0.090 mmol) and diene **11** were reacted according to the procedure described above for the preparation of **12a** yielding anthraquinone **13a** (0.032 g, 95%) as a green oil which solidified on low-temperature trituration with methanol: mp = 162–165 °C; R_f = 0.10 (3:1 $CHCl_3$/pentane); ^1H NMR δ 8.16 (d, 1H, J = 1.5 Hz), 7.92 (d, 1H, J = 7.7 Hz), 7.74–7.69 (dd, 1H, J = 8.4, 7.7 Hz), 7.39 (d, 1H, J = 1 .5 Hz), 7.35 (d, 1H, J = 8.4 Hz), 5.23 (s, 2H), 4.03 (s, 3H), 2.52 (s, 3H), 2.18 (s, 3H); IR ν 3066, 3048, 2951, 2945, 1762, 1739, 1670, 1665, 1586, 1245, 1033 cm^{-1}; MS 368 (M^+, 1.71), 326 (100). Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38. Found: C, 65.52; H, 4.43.

3-(Acetoxymethyl)-1,8-dihydroxy-9,10-anthracenedione (Aloe Emodin ω-Acetate (13b). The methyl ether **13a** (0.0205 g, 0.056 mmol) was demethylated (with concomitant deacetylation) according to the procedure described above for the preparation of **12b** yielding the naturally occurring aloe emodin derivative **13b** 0.0178 g, 99%) as a yellow-brown solid: mp = 211–213 °C (lit.[21] mp = 213–214 °C); R_f = 0.50 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.08 (s, 1H), 12.06 (s, 1H), 7.87–7.84 (dd, 1H, J = 7.2, 1.2 Hz), 7.80 (d, 1H, J = 0.9 Hz), 7.74–7.69 (dd, 1H, J = 8.4, 7.4), 7.34–7.31 (dd, 1H, J = 8.4, 1.2 Hz), 7.28 (d, 1H, J = 0.9 Hz), 5.21 (s, 2H), 2.21 (s, 3H); IR ν 3563–3344 (br), 3061, 2964, 2940, 1736, 1675, 1628, 1610, 1385, 1266 cm^{-1}; MS 312 (M^+, 26.7), 270 (100).

1,8-Dihydroxy-3-(hydroxymethyl)-9,10-anthracenedione (Aloe Emodin) (13c). The acetate **13b** (0.050 g, 0.160 mmol) was saponified according to the procedure outlined above for the preparation of **10b** yielding aloe emodin **13c** (0.041 g, 94%) as a bright yellow solid: mp = 221–225 °C (lit.[22] mp = 223–224 °C); R_f = 0.46 (120:18:1 toluene/HOAc/MeOH); ^1H NMR (DMSO-d_6) δ 11.95 (s, 1H), 11.89 (s, 1H), 7.78–7.76 (dd, 1H, J = 8.4, 7.5 Hz), 7.71–7.68 (dd, 1H, J = 7.5, 1.2 Hz), 7.66 (d, 1H, J = 1.5 Hz), 7.38 –7.35 (dd, 1H, J = 8.4, 1.2 Hz), 7.27 (d, 1H, J = 1.5 Hz), 4.61 (s, 2H); IR ν 3550–3226 (br), 2963, 2958, 2927, 1676, 1628, 1286, 1276 cm^{-1}; MS 270 (M^+, 100), 241 (66.6).

Ethyl 9,10-Dihydro-4-hydroxy-5,7-dimethoxy-9,10-dioxo-2-anthracenecarboxylate (15a). At room temperature, ketene dimethyl acetal **14** (0.704 g, 8.00 mmol) was added all at once to the solid chlorojuglone **6b** (0.484 g, 1.72 mmol) resulting in a vigorous reaction. A dry ice/acetone filled cold finger was immediately attached to the flask, the red reaction mixture was placed in a preheated oil bath, and the temperature was maintained at 100 °C for 1h. During this time the reaction mixture solidified. After evaporation of the volatile byproducts under vacuum the solid residue was triturated with diethyl ether and the precipitate filtered yielding **15a** (0.430 g, 70%) as a yellow-brown solid: mp = 216–217 °C; R_f = 0.13 (3:1 $CHCl_3$/pentane); ^1H NMR δ 13.10 (s, 1H), 8.35 (d, 1H, J = 1.5 Hz), 7.92 (d, 1H, J = 1.5 Hz), 7.49 (d, 1H, J = 2.3 Hz), 6.81 (d, 1H, J = 2.3 Hz), 4.45 (q, 2H, J = 7.2 Hz), 4.05 (s, 3H), 4.02 (s, 3H), 1.45 (t, 3H, J = 7.2 Hz); IR ν 3505–3353 (br), 3095, 3064, 2981, 2941, 2842, 1723, 1642, 1636, 1596, 1556, 1323, 1258, 1218 cm^{-1}; MS 356 (M^+, 100); HRMS (EI) calcd for $C_{19}H_{16}O_7$ (M^+) 356.0896, found 356.0892.

Ethyl 9,10-Dihydro-4,5-dihydroxy-7-methoxy-9,10-dioxo-2-anthracenecarboxylate (15b). The methyl ether **15a** (0.105 g, 0.30 mmol) was demethylated according to the procedure described above for the preparation of **12b** yielding **15b** (0.0873

g, 85%) as yellow solid: mp = 151–153 °C; R_f = 0.32 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.22 (s, 1H), 12.19 (s, 1H), 8.41 (d, 1H, J = 1.5 Hz), 7.94 (d, 1H, J = 1.5 Hz), 7.43 (d, 1H, J = 2.4 Hz), 6.73 (d, 1H, J = 2.4 Hz), 4.46 (q, 2H, J = 7.2 Hz), 3.98 (s, 3H), 1.46 (t, 3 H, J = 7.2 Hz); IR ν 3595–3306 (br), 3092, 2991, 2962, 1724, 1628, 1623, 1616, 1610, 1396, 1255, 1212 cm^{-1}; MS 342 (M^+, 100), 297 (40.7). Anal. Calcd for $C_{18}H_{14}O_7$: C, 63.14; H, 4.12. Found: C, 62.71; H, 4.22.

9,10-Dihydro-4,5-dihydroxy-7-methoxy-9,10-dioxo-2-anthracenecarboxylic Acid (Parietinic Acid) (15c). The ester **15b** (0.022 g, 0.064 mmol) was saponified to **15c** (17.1 mg, 85%) according to the procedure described above for the preparation of **10b**: mp = 312 °C (sealed tube) (lit.[17] mp = sublimes *ca.* 300 °C); R_f = 0.61 (120:18:1 toluene/HOAc/MeOH); ^1H NMR δ (DMSO-d_6) 11.94 (s, 1H), 11.86 (s, 1H), 7.92 (d, 1H, J = 1.5 Hz), 7.59 (d, 1H, J = 1.5 Hz), 7.01 (d, 1H, J = 2.4 Hz), 6.75 (d, 1H, J = 2.4 Hz), 3.87 (s, 3H); IR ν 3400 (br), 3050–2700 (br), 1700, 1629, 1600, 1400, 1260, 1210 cm^{-1}; MS 314 (M^+, 100).

9,10-Dihydro-4,5,7-trihydroxy-9,10-dioxo-2-anthracenecarboxylic Acid (Emodic Acid) (15d). In a 2-mL round-bottom flask was heated parietinic acid **15c** (0.043 g, 0.14 mmol) with pyridinium chloride (8.09 g, 70.0 mmol) at 180 °C for 6 h. Periodically, the pyridinium chloride which had sublimed was scraped from the sides of the flask into the reaction mixture. The brown mass was cooled and digested with water (50 mL). The precipitate was collected and dissolved in 5% aqueous sodium carbonate. The resulting dark purple solution was filtered, acidified with concd HCl, and extracted with ether (3 × 50 mL). Evaporation of the solvent yielded emodic acid **15d** (0.033 g, 79%) as an orange-red solid: mp = 360–365 °C (lit.[17] mp = 363–365 °C); R_f = 0.28 (120:18:1 toluene/HOAc/MeOH); ^1H NMR δ (DMSO-d_6) 12.03 (s, 1H), 11.95 (s, 1H), 11.50 (s (br), 1H), 8.03 (d, 1H, J = 1.5 Hz), 7.66 (d, 1H, J = 1.5 Hz), 7.09 (d, 1H, J = 2.4 Hz), 6.57 (d, 1H, J = 2.4 Hz); IR ν 3050 (sharp), 3150–2800 (br), 2951, 2875, 1701, 1670, 1627, 1260, 1100, 10 25 cm^{-1}; MS 300 (M^+, 100), 207 (92.8).

3-(Acetoxymethyl)-1-hydroxy-6,8-dimethoxy-9,10-anthracenedione (16a). The chlorojuglone **8b** (0.197 g, 0.703 mmol) was reacted with ketene dimethyl acetal **14** according to the procedure described above for the preparation of **15a** yielding the anthraquinone **16a** (0.188 g, 75%) as a yellow-brown solid: mp = 207 °C; R_f = 0.10 (3:1 $CHCl_3$/pentane); ^1H NMR δ 13.15 (s, 1H), 7.71 (d, 1H, J = 1.2 Hz), 7.47 (d, 1H, J = 2.3 Hz), 7.25 (d, 1H, J = 1.2 Hz), 6.80 (d, 1H, J = 2.3 Hz), 5.17 (s, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 2.19 (s, 3H); IR ν 3646–3254 (br), 3093, 2938, 2843, 1742, 1635, 1632, 1595, 1558, 1326, 1261, 1231 cm^{-1}; MS 356 (M^+, 100), 314 (54.5); HRMS (EI) calcd for $C_{19}H_{16}O_7$ (M^+) 356.0896, found 356.0890.

3-(Acetoxymethyl)-1,8-dihydroxy-6-methoxy-9,10-anthracenedione (Fallacinol ω-Acetate) (16b). The methyl ether **16a** (0.0913 g, 0.256 mmol) was demethylated according to the procedure described above for the preparation of **12b** yielding the naturally occurring anthraquinone derivative **16b** (0.0832 g, 95%) as a yellow solid: mp = 194 °C dec (lit.[1a] mp = 195–196 °C); R_f = 0.19 (3:1 $CHCl_3$/pentane); ^1H NMR δ 12.26 (s, 1H), 12.20 (s, 1H), 7.77 (d, 1H, J = 1.2 Hz), 7.40 (d, 1H, J = 2.4 Hz), 7.26 (d, 1H, J = 1.2 Hz), 6.71 (d, 1H, J = 2.4 Hz), 5.19 (s, 2H), 3.97 (s, 3H), 2.20 (s, 3H); IR ν 3595–3319 (br), 3094, 2964, 2928, 1740, 1627, 1609, 1264, 1215 cm^{-1}; MS 342 (M^+, 37.9), 300 (100).

1,8-Dihydroxy-3-(hydroxymethyl)-6-methoxy-9,10-anthracenedione (Fallacinol) (16c). The acetate **16b** (0.050 g, 0.146 mmol) was saponified according to the procedure described above for the preparation of **10b** yielding fallacinol **16c** (0.043, 98%) as a bright yellow solid: mp = 242–245 °C (lit.[28] mp = 245–247 °C); R_f = 0.43 (120:18:1 toluene/HOAc/MeOH); ^1H NMR δ 12.13 (s, 1H), 11.97 (s, 1H), 7.62 (d, 1H, J = 1.8 Hz), 7.23 (d, 1H, J = 2.1 Hz), 7.14 (d, 1H, J = 1.8 Hz), 6.83 (d, 1H, J = 2.1 Hz), 5.53 (s, 2H), 3.90 (s, 3H); IR ν 3520–3450 (br), 3092, 3082, 3048, 1670, 1630, 1617, 1566, 1481, 1385, 1371, 1324, 1297, 1267, 1217, 1170 cm^{-1}; MS 300 (M^+, 100), 271 (53.4).

1,6,8-Trihydroxy-3-(hydroxymethyl)-9,10-anthracenedione (Citreorosein) (16d). Fallacinol **16c** (0.014 g, 0.047 mmol) was demethylated according to the procedure described above for the preparation of **15d** yielding citreorosein **16d** 0.010 g (76%) as a yellow solid: mp = 286–288 °C (lit.[1a] mp = 273–275 °C); R_f = 0.16 (3:1 $CHCl_3$/pentane); ^1H NMR δ (DMSO-d_6) 12.15 (s, 1H), 11.98 (s, 1H), 11.77 (s (br), 1H), 7.79 (d, 1H, J = 0.8 Hz), 7.54 (d, 1H, J = 0.8 Hz), 7.18 (d, 1H, J = 2.4 Hz), 6.68 (d, 1H, J = 2 .4 Hz), 5.99 (s, 2H); IR ν 3500–3430 (br), 1661, 1635, 1593, 1146, 1095 cm^{-1}; MS 286 (M^+, 100).

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Supplementary Material Available: ^1H-NMR spectra of initial anthraquinone adducts **10a**, **12a**, **13a**, **15a**, and **16a** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Photolytic Ring Expansion of Cyclobutabenzofuranones. Facile Route to Benzodioxabicyclo[3.3.0]octanes

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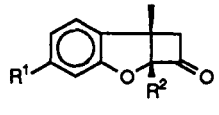
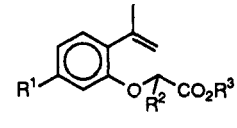
Cyclobutanones on UV irradiation suffer α-cleavage to a 1,4-diradical which undergoes three major transformations,[1] viz., (i) ring expansion, (ii) cycloelimination, and (iii) decarbonylation. The mechanistic postulates of Yates[1b] implicating an oxacarbene intermediate in the ring expansion process has been widely accepted. Trapping of the oxacarbene intermediate by an external alcohol[2] or intramolecular hydroxy group[3] to lead to γ-lactols has provided a useful synthetic application of this protocol. A crucial aspect of such ring expansions is the retention of stereochemistry when the cyclobutanone possesses an α-stereogenic center.[4] In this paper we report on the photolytic ring expansion of cyclobutabenzofuranones, representing an α-heteroatom-substituted cyclobutanone system, providing a general route to benzodioxabicyclo-[3.3.0]octanes, the bis-furan unit which is also the basic skeleton of the aflatoxin[5] family of mycotoxins.

The cyclobutabenzofuranones **1-4** were investigated. We have previously demonstrated the application of cyclobutanone **1** in a synthesis of the marine sesquiterpene



1: $R^1 = R^2 = Me$
2: $R^1 = H$, $R^2 = Me$
3: $R^1 = Me$, $R^2 = H$
4: $R^1 = Me$, $R^2 = CH_2CH{=}CH_2$

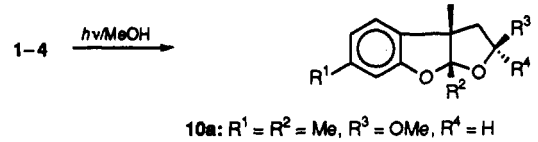


5: $R^1 = R^3 = H$, $R^2 = Me$
6: $R^1 = Me$, $R^2 = H$, $R^3 = Et$
7: $R^1 = Me$, $R^3 = Et$, $R^2 = CH_2CH{=}CH_2$
8: $R^1 = Me$, $R^2 = R^3 = H$
9: $R^1 = Me$, $R^3 = H$, $R^2 = CH_2{-}CH{=}CH_2$

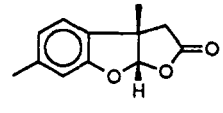
aplysin.[6] Cyclobutanones **2-4** were also synthesized similarly by way of intramolecular ketene–alkene cycloaddition of the corresponding acids **5**,[7] **8**, and **9**, respectively.

Alkylation of 2-isopropenyl-5-methylphenol with ethyl α-bromoacetate in the presence of anhydrous potassium carbonate furnished the phenoxy ester **6** in more than 80% yield. This was alkylated with allyl bromide in the presence of LDA to afford the allylated phenoxy ester **7** in a moderate yield. Basic hydrolysis of **6** and **7** provided the acids **8** and **9**, respectively. The acids **5**, **8**, and **9** on heating with *p*-toluenesulfonyl chloride and triethylamine in benzene underwent an intramolecular ketene–alkene cycloaddition[6] to furnish the cyclobutabenzofuranones **2-4**, respectively, in fair yields. In pursuance of our interest in exploring the chemistry of these cyclobutabenzofuranones in synthesis, we have investigated their photobehavior. Photolysis of **1** in methanol using a Hanovia, 450-W medium pressure lamp furnished in 56% combined yield a mixture of acetals **10a,b** as the only isolable product, in 1.5:1 proportion as revealed by ^{1}H NMR and GLC analyses (Scheme I). The structural assignment was made from ^{1}H NMR where the methoxy protons in the minor α-isomer **10b** being more shielded by the aromatic ring appeared as a singlet at δ 3.15, whereas that in the major β-isomer **10a** appeared at δ 3.42. Because of close polarity a complete separation of the isomers was not possible. Similar photolysis of the cyclobutabenzofuranones **2-4** also resulted in the formation of the corresponding acetals **11a,b–13a,b** in yields ranging between 50–58%, also in 1.5:1 proportion, with the β-methoxy isomer being the major product in each case. In one experiment involving cyclobutabenzofuranone **3**, the lactone **14** was also formed to the extent

Scheme I



10a: $R^1 = R^2 = Me$, $R^3 = OMe$, $R^4 = H$
b: $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OMe$
11a: $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = OMe$
b: $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OMe$
12a: $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = OMe$
b: $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = OMe$
13a: $R^1 = Me$, $R^2 = CH_2{-}CH{=}CH_2$, $R^3 = OMe$, $R^4 = H$
b: $R^1 = Me$, $R^2 = CH_2{-}CH{=}CH_2$, $R^3 = H$, $R^4 = OMe$



14

of 12%, with a corresponding decrease in acetal formation, which could have arisen through a reaction of the intermediate oxacarbene with oxygen.[1a] Thus the ready availability of cyclobutabenzofuranones followed by photolysis provides a convenient and general route to the benzodioxabicyclo[3.3.0]octane system, comprising the basic unit of the aflatoxins.

Photolysis of the cyclobutanone **1** in aqueous tetrahydrofuran furnished directly the hemiacetals **15a,b** in 50%

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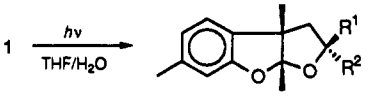
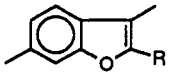
Scheme II



15a: $R^1 = OH$, $R^2 = H$
b: $R^1 = H$, $R^2 = OH$

yield in a 3:1 proportion, as determined from the ratio of integrals for the methyl protons in the ^1H NMR (Scheme II). The assignment of β-configuration to the major hemiacetal isomer in this case followed in correlation with the isomeric distribution in previous photolysis where the major β-isomer arose from nucleophilic attack on the intermediate oxacarbene more from the exo face. No attempt was made for a detailed separation of this isomeric mixture. Since there are aflatoxins also as hemiacetals and there are established procedures[8] for the conversion of such hemiacetals to the bis-furans, the present methodology can be expected to provide an expedient route to these mycotoxins from appropriately patterned starting materials.

The photolysis of **1** in the absence of a trapping agent was also investigated. Thus irradiation of **1** in petroleum ether furnished the benzofuran **16** in 37% yield as the only characterizable product, arising from a cycloelimination process. A similar photolysis of **4** was also investigated, anticipating that the terminal alkene function may act as an internal trapping source. However in this case also photolysis in cyclohexane resulted in only cycloelimination, affording the benzofuran **17** in 50% yield. The above experiments revealed that solvent markedly affects the product profile in these photolysis.[9]



16: R = Me
17: R = CH_2—CH=CH_2

Experimental Section

General. All the compounds described herein possessing asymmetric carbons are racemates. All reactions were carried out under N_2. Melting points and boiling points are uncorrected and melting points were taken in an open capillary in a sulfuric acid bath. Solvents and reagents were reagent-grade materials and were further purified by conventional methods. Petroleum ether refers to the fraction of bp 60–80 °C and Et_2O refers to diethyl ether. The purity of the products was routinely checked by TLC. Preparative TLC was performed with silica gel $^{60}HF_{254}$ (E. Merck) plates of 1-mm thickness. Na_2SO_4 was used to dry organic extracts. ot refers to oven temperature.

^1H NMR spectra of $CDCl_3$ solutions were recorded at 200 MHz or 100 MHz and that of CCl_4 solutions at 60 MHz. Peak positions are indicated in ppm downfield from internal TMS in δ units. The IR spectra are for $CHCl_3$ solutions. GLC analyses were performed with 2-m OV-17 column using N_2 as carrier gas.

Ethyl 2-(2-Isopropenyl-5-methylphenoxy)ethanoate (6). A stirred mixture of 2-isopropenyl-5-methylphenol (4.35 g, 29.4 mmol), ethyl α-bromoacetate (4.91 g, 29.4 mmol), anhydrous potassium carbonate (4.14 g, 30 mmol), and a pinch of potassium iodide in acetone (80 mL) was heated under reflux for 12 h. The reaction mixture was concentrated to one-third of the volume, diluted with water, and extracted with Et_2O. The combined organic layer was washed with cold aqueous NaOH (3 × 50 mL, 1.25 N) and water and then dried. The oily residue obtained after the removal of solvent was evaporatively distilled to afford the ester **6** as a colorless liquid (5.6 g, 82%): ot 110–120 °C (0.15 mmHg); ^1H NMR (CCl_4) δ 1.27 (t, J = 6 Hz, 3H), 2.09 (br s, 3H), 2.26 (s, 3H), 4.16 (q, J = 6 Hz, 2H), 4.45 (s, 2H), 5.00 (br s, 2H), 6.42 (br s, 1H), 6.63 (m, 1H), 6.97 (d, J = 8 Hz, 1H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.74; H, 7.46. Found: C, 71.50; H, 7.82.

2-(2-Isopropenyl-5-methylphenoxy)ethanoic Acid (8). To a magnetically stirred solution of the ester **6** (1.53 g, 6.6 mmol) in methanol (10 mL) was added cold aqueous KOH (5 mL, 5 N). Stirring was continued at rt for 24 h. Most of methanol was removed by evaporation and the reaction mixture was diluted with water, acidified with cold dilute HCl (6 N), and extracted with Et_2O. The ethereal layer was washed with saturated brine, dried, and then concentrated to furnish the acid **8** as a crystalline solid (1.1 g, 80%): crystallized from Et_2O–petroleum ether, mp 115–117 °C; ^1H NMR ($CDCl_3$) δ 2.14 (br s, 3H), 2.36 (s, 3H), 4.70 (s, 2H), 5.14 (m, 1H), 5.20 (m, 1H), 6.66 (br s, 1H), 6.68 (br d, J = 8 Hz, 1H), 7.16 (d, J = 8 Hz, 1H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.47; H, 6.99.

Ethyl 2-(2-Isopropenyl-5-methylphenoxy)pent-4-enoate (7). To a magnetically stirred solution of LDA (7.35 mmol) in dry THF (20 mL) at −78 °C was added in drops a solution of ethyl 2-(2-isopropenyl-5-methylphenoxy)ethanoate (**6**) (1.7 g, 7.3 mmol) in THF (5 mL). Stirring was continued at −78 °C for 45 min. Then allyl bromide (0.88 g, 7.3 mmol) was added and the solution was stirred at −78 °C for another 1 h, then allowed to attain rt, and left at rt for 30 min. The reaction mixture was quenched with ice and extracted with Et_2O. The ethereal layer was washed with cold dilute HCl (1 N) and then with water and dried. The oily residue obtained after removal of solvent was chromatographed through silica gel. Elution with 1% ethyl acetate in petroleum ether afforded the ester **7** as a colorless liquid (860 mg, 43%): ot 95–100 °C (0.05 mmHg); ^1H NMR (CCl_4) δ 1.18 (t, J = 6 Hz, 3H), 2.09 (br s, 3H), 2.27 (s, 3H), 2.66 (t, J = 6 Hz, 2H), 4.13 (q, J = 6 Hz, 2H), 4.63 (t, J = 6 Hz, 1H), 5.03 (m, 2H), 5.21 (m, 2H), 5.93 (m, 1H), 6.45 (br s, 1H), 6.65 (m, 1H), 7.03 (d, J = 8 Hz, 1H).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 73.71; H, 8.14.

2-(2-Isopropenyl-5-methylphenoxy)pent-4-enoic Acid (9). Hydrolysis of ester **7** (620 mg, 2.26 mmol) was carried out as for **6** to furnish the acid **9** as an oil (510 mg, 90%) [^1H NMR (CCl_4) δ 2.09 (br s, 3H), 2.33 (s, 3H), 2.72 (t, J = 6 Hz, 2H), 4.66 (t, J = 6 Hz, 1H), 5.03 (br s, 2H), 5.24 (m, 2H), 5.86 (m, 1H), 6.48 (br s, 1H), 6.69 (m, 1H), 7.03 (d, J = 8 Hz, 1H), 8.50 (br s, 1H)] and was used in the next step without further purification.

For general procedure of intramolecular ketene–olefin cycloaddition, see ref 6.

***cis*-2a,7b-Dihydro-2a,7b-dimethylcyclobuta[*b*]benzofuran-2(1*H*)-one (2):** crystalline solid, yield 550 mg (60%) from 1 g of the acid **5**; crystallized from petroleum ether, mp 82–83 °C; IR 1780 cm^{-1}; ^1H NMR (CCl_4) δ 1.43 (s, 3H), 1.56 (s, 3H), 3.10 (s, 2H), 6.92 (m, 4H).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.65; H, 6.31.

***cis*-2a,7b-Dihydro-5,7b-dimethylcyclobuta[*b*]benzofuran-2(1*H*)-one (3):** yield 350 mg (51%) from 750 mg of the acid **8**; ot 102–108 °C (0.03 mmHg); IR 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (s, 3H), 2.31 (s, 3H), 3.21 (q, A of ABX, J_{AB} = 17.75 Hz, 1H), 3.32 (q, B of ABX, J_{BA} = 17.75 Hz, 1H), 5.29 (t, X of ABX, J_{AX} = J_{BX} = 2.5 Hz, 1H), 6.70 (br s, 1H), 6.78 (m, 1H), 6.81 (d, J = 7.6 Hz, 1H).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.97; H, 6.35.

***cis*-2a,7b-Dihydro-2a-propenyl-5,7b-dimethylcyclobuta-[*b*]benzofuran-2(1*H*)-one (4):** yield 400 mg (30%) from 1.5 g of the acid **9**; ot 120–25 °C (0.3 mmHg); IR 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3H), 2.28 (s, 3H), 2.72 (m, 2H), 3.20 (m, 2H), 5.16 (br s, 1H), 5.32 (m, 1H), 5.96 (m, 1H), 6.69 (br s, 1H), 6.80 (m, 1H), 7.12 (d, J = 8 Hz, 1H).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.96; H, 7.01. Found: C, 79.20; H, 7.18.

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