Preparation of Functionalized Juglone Acetates and Juglones *via* 1,4-Dimethoxynaphthalene Derivatives: Synthesis of Anthraquinones Related to Rhein and Aloe Emodin

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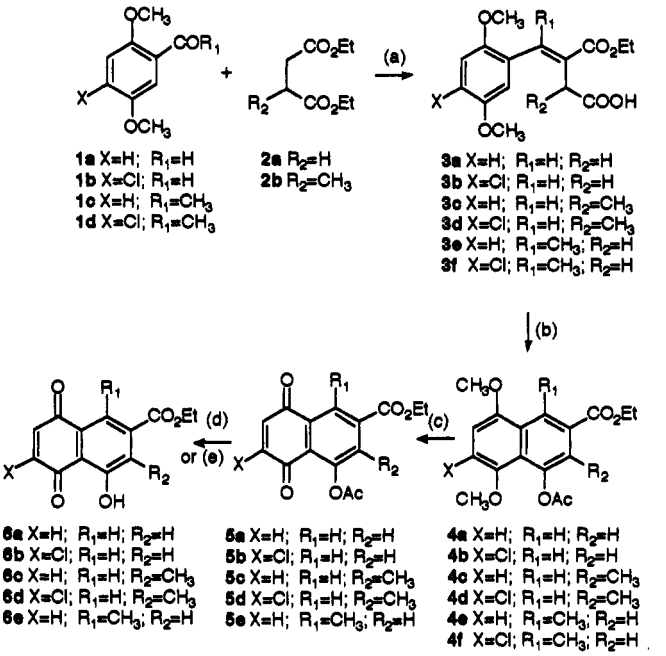
Since juglones have established themselves as important anthracycline and polyketide synthons, we became interested in efficient methods for their synthesis. In particular, we noted that the 3-halojuglones were of special importance since these had excellent regiochemistry in Diels–Alder reactions.[1] At the inception of our studies one of the most generally useful preparative procedures involved reaction of silylated dienes[2] with halogenated benzoquinones. Since preparation of the former may require rigorous experimental conditions, development of an alternative procedure appeared to be desirable. This paper describes an alternative approach to juglones which is based on condensative and intramolecular acylation methods, which provides a sound synthetic basis for the elaboration of both linear and bent polycyclic arrays in a regiocontrolled manner.

Retrosynthetically, the requisite quinone moiety could be derived *via* demethylation/oxidation of 1,4-dimethoxynaphthalene derivatives. To synthesize this type of derivative we investigated as a model the Stobbe reaction of 2,5-dimethoxybenzaldehyde (**1a**) with diethyl succinate (**2a**) followed by an intramolecular acylation. As a starting point, we tried the Stobbe conditions and cyclization used by Whalley in the synthesis of eleutherolic acid.[3] Using a modified workup we were able to obtain the Stobbe acid product **3a** as a crystalline solid rather than an oil, though the yield was not substantially improved. A 3-fold excess of succinate ester was required for best results to minimize formation of double condensation products (fulgic acids) which formed highly colored bisaryl lactones (fulgides[4]) if carried through the cyclization. In the cyclization of the model system we were able to double the yield obtained

Scheme I[a]



[a] Reagents: (1) NaH, cat. EtOH, toluene, 40 °C, 1 h then concd HCl, 25 °C, 1 h; (b) Ac_2O, NaOAc, 140 °C, 3 h; (c) CAN, aq CH_3CN, 25 °C, 1 h; (d) 3 M HCl, acetone, 95 °C, 2.5 h; (e) $AlCl_3$, CH_2Cl_2, 25 °C, 1 h.

via the literature method noted above by modification of reaction and workup conditions.

Production of juglones from our bicyclic precursors **4a–4e** required hydrolysis of the acetate, demethylation, and oxidation, so several synthetic sequences were possible. We initially studied hydrolysis of the acetate prior to the other steps. While this could be achieved easily using acidic ethanol (which allowed the ethyl ester to be retained), the resultant phenol was sensitive to subsequent reactions. We found that oxidation and demethylation could be achieved in a single step by the use of cerium(IV) ammonium nitrate (CAN). Initially, we used 90% acetic acid as the solvent but found that upon scaling the reaction up to 10 g, when the solvent was removed at 70 °C on the rotary evaporator, exposure of the residue to air gave a potentially dangerous spontaneous ignition. Since CAN oxidation/demethylation of 1,4-dimethoxynaphthalene had been reported in acetonitrile[5] we applied these conditions to our dimethoxy acetate **4a**. The reported workup by extraction and sublimation was not feasible in our case; however, juglone acetate **5a** could be isolated easily in pure form by simple dilution with a large excess of water.

The hydrolysis of juglone acetates with ethanolic sulfuric acid had been reported;[6] however, our juglone acetate **5a** proved too sensitive to these conditions. Our optimized hydrolytic conditions used HCl in acetone but required strict adherence to a 2.5-h reaction time. A much more mild and higher yielding method proved to be aluminum chloride in dichloromethane at ambient temperature.

Having developed the necessary methods for the efficient preparation of juglones, our objectives were (a) introduc-

(1) For reviews on the use of juglones as polyketide and anthracycline synthons see: (a) Thomson, R. H. *Naturally Occurring Quinones III—Recent Advances*, 3rd ed.; Chapman and Hall: London, 1987; pp 125–607. (b) Thomson, R. H. In *The Total Synthesis of Natural Products*; Apsimon, J. W., Ed.; John Wiley & Sons: New York, 1992; Vol. 8, pp 311–533. (c) Kelly, T. R. *Tetrahedron* **1984**, *40*(22), 4537–4789.

(2) For syntheses and synthetic utility of silylated dienes see: (a) Brisson, C.; Brassard, P. *J. Org. Chem.* **1981**, *46*, 1810–1814. In this study, the dienes were prepared and reacted in tetrahydrofuran which appeard difficult to scale up. (b) We thank the reviewer for pointing out that silylated dienes may in fact be carried out on a substantial scale. See: Benfaremo, N.; Cava, M. P. *J. Org. Chem.* **1985**, *50*, 139–141.

(3) Handford, B. O.; Whalley, W. B.; Loder, J. W. *J. Chem. Soc.* **1963**, 3896–3897. In the previous studies, the Stobbe reaction used acetic acid in the workup and gave the acid as an oil. Substitution of HCl in the acidification step gave a crystalline product, though in similar yield. The cyclization step used much more acetic anhydride than our procedure and involved a laborious exhaustive ligroin extraction. By using less acetic anhydride and a methanol trituration of the crude product we were able to approximately double the yield to 65%. Subsequent to our studies we noted that the acid **3a** had been prepared as an oil and cyclized to **4a**. See: Harper, S. H.; Kemp, A. D.; Tannock, *J. Chem. Soc.* **1970**, 626–636.

(4) Stobbe, H. *Liebigs Ann. Chem.* **1911**, *A380*, 1–41.

(5) Jacob, P.; Callery, P. S.; Shulgin, A. T. Castagnoli, N. *J. Org. Chem.* **1976**, *41*(22), 3627–3629.

(6) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91–95.

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tion of the desired chloro substituent to enhance regiocontrol in the quinone ring toward Diels–Alder reactivity and (b) introduction of additional groups on the nonquinone ring at R_1 and R_2 to allow synthesis of linear or bent polycyclic arrays. Extension to the chloro series X = Cl required 4-chloro-1,5-dimethoxybenzaldehyde (**1b**). We had initially prepared that compound by a four-step sequence from 2,5-dimethoxytoluene and carried it out on to a ring D analog anthracycline synthon *via* the juglone acetate **5b**.[7] We have since found that a modified Duff reaction[8] could produce the desired aldehyde from 2-chloro-1,4-dimethoxybenzene in a single step. Other starting materials for our syntheses were either commercially available such as acetophenone derivative **1c** or else easily prepared by literature methods such as chloroacetophenone derivative **1d** *via* acylation of the corresponding chlorodimethoxybenzene[9] or diethyl methylsuccinate, available from Fischer esterification of the corresponding acid.[10]

Using the modified workup described above, yields of Stobbe products were all in the range 60–67%, with the chloro derivatives (**3b**, **3d**, and **3f**) tending to be slightly higher in yield and crystalline. Only the methyl series $R_2 = CH_3$ (**3c**) and $R_1 = CH_3$ (**3e**) were oils. While satisfactory elemental analyses of the latter were never achieved, they could be taken directly for subsequent cyclization without sacrificing purity or yield of the bicyclic product. Yields of the methyl series where R_1 or $R_2 = CH_3$ were comparable to the model $R_1 = R_2 = H$ in spite of the fact that fulgic acid formation should not be a problem. This was true whether X = H or X = Cl.

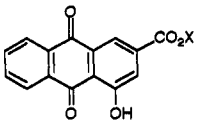
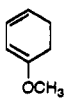
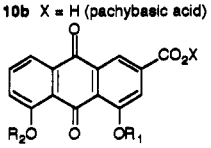
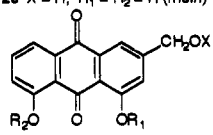
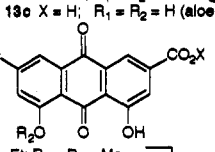
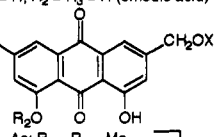
In the model system **3a**, use of less acetic anhydride for cyclization and methanol trituration rather than exhaustive ligroin extraction gave greatly improved yields as compared to the literature method noted above. In subsequent studies, however, workup methods had to be adapted to each specific case. With one notable exception all our cyclization yields were in the range 65–70%. Chlorobicyclic **4b** formed similarly to the model **4a** but required a rapid methanol trituration and immediate filtration for purification. Three of the methyl series (**4c–4e**) required ligroin extraction. Only in the case of bicyclic **4f** was a poor yield obtained, so subsequent reactions were not pursued. Isolation of bicyclic product **4f** required crystalline acid precursor.

The CAN oxidations were also consistent in yield (75–87%), though products **5b–5e** did not precipitate spontaneously on dilution with water. The latter could be obtained easily by ether extraction subsequent to dilution, which often yielded pure crystalline material upon evaporation.

The free juglones were best prepared by using a 10-fold molar excess of aluminum chloride in dichloromethane which gave yields in the range 79–90% with the exception of **6e** (50%). The HCl/acetone method was more experimentally demanding due to the higher temperatures and time sensitivity noted above. The yields were somewhat lower (68–75%), with 35% for **6e**.

The juglone acetates and juglones prepared above may be converted to a number of natural products using commercially available cosynthons and straightforward synthetic procedures. Yields for most of the synthetic steps were in the range 85–99%.

Table I. Synthesis of (Hydroxymethyl)anthraquinones and Anthraquinone-2-carboxylic Acids *via* Cycloaddition Reactions of Juglones Followed by Demethylation and Saponification[a]

entry	diene	juglone	product(s)
1	 **9**	**5b** 	(a) → **10a** X = Et; **10b** X = H (pachybasic acid)
2	 **11**	**6b** 	(a) → **12a** X = Et; R_1 = H; R_2 = Me; **12b** X = Et; $R_1 = R_2$ = H; (b); **12c** X = H; $R_1 = R_2$ = H (rhein)
3	**11**	**8a** 	(a) → **13a** X = Ac; R_1 = Ac; R_2 = Me; **13b** X = Ac; $R_1 = R_2$ = H; (b); **13c** X = H; $R_1 = R_2$ = H (aloe-emodin)
4	 **14**	**6b** 	**15a** X = Et; $R_2 = R_3$ = Me; (b); **15b** X = Et; R_2 = H; R_3 = Me; (a) → **15c** X = H; R_2 = H; R_3 = Me (parietinic acid); **15d** X = H; $R_2 = R_3$ = H (emodic acid); (c)
5	**14**	**8b** 	**16a** X = Ac; $R_2 = R_3$ = Me; (b); **16b** X = Ac; R_2 = H; R_3 = Me; (a) → **16c** X = H; R_2 = H; R_3 = Me (fallacinol); **16d** X = H; $R_2 = R_3$ = H (citreorosein); (c)

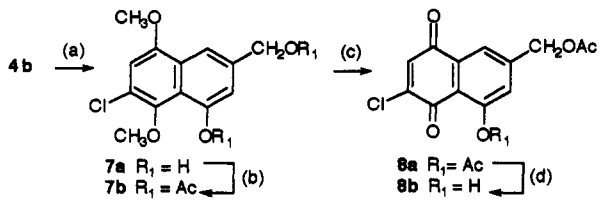
[a] Reagents: conditions for formation of the initial anthraquinone adducts **10a**, **12a**, **13a**, **15a**, and **16a** are given in the experimental section; (a) 10% NaOH (aq), rt, 24 h; (b) $AlCl_3$, CH_2Cl_2, rt, 24 h; (c) pyr·HCl, 160 °C, 6 h.

The most obvious application of our carboethoxyjuglone synthons was to natural anthraquinone-2-carboxylic acids represented by entries 1, 2, and 4 of Table I. Reaction of juglone acetate **5b** with 1-acetoxy-1,3-butadiene (**9**) in refluxing ethanol gave the ethyl ester of pachybasic acid (**10a**) in 85% yield in a single step involving no less than four discrete processes: Diels–Alder cycloaddition, loss of HCl, loss of acetic acid, and ethanolysis of the phenolic acetate. The ester **10a** was readily saponified at ambient temperature to yield pachybasic acid (**10b**).[11]

The chlorojuglone synthons were designed with a view toward regiospecific reaction with electron-rich dienes. In the synthesis of rhein (**12c**), reaction of chlorojuglone **6b** with 1-methoxy-1,3-cyclohexadiene (**11**) gave an adduct which was suitable for direct thermolysis to the methoxy ester **12a** (99% for 2 steps). The latter was convertible

(7) Bloomer, J. L.; Gazzillo, J. A. *Tetrahedron Lett.* **1989**, *30*(10), 1201–1204.
(8) Smith, W. E. *J. Org. Chem.* **1972**, *37*(24), 3972–3973.
(9) Bartram, C. A.; Battye, D. A.; Worthing, C. R. *J. Chem. Soc.* **1963**, 4691–4693.
(10) Vogel, A. I. *J. Chem. Soc.* **1948**, 624–644.
(11) Bellaart, A. C.; Koningsberger, C. *Rec. Trav. Chim.* **1961**, *80*, 409–414.

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

(12) Gleim, R. D.; Trenbeath, S.; Suzuki, F.; Sih, C. J. *J. Chem. Soc., Chem. Commun.* **1978**, 242–244.
(13) Robinson, R.; Simonsen, J. L. *J. Chem. Soc.* **1909**, 1085–1096.
(14) For an alternative approach to rhein see: Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1982**, *47*(2), 383–384.
(15) Birch, A. J.; Rao, G. S. In *Advances in Organic Chemistry: Methods and Results*; Taylor, E. C., Ed.; Wiley Interscience: New York, 1972; pp 1–67.
(16) Banville, J.; Grandmaison, J.-L.; Lang, G.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 80–87.
(17) Eder, R.; Hauser, F. *Helv. Chim. Acta* **1925**, *8*, 126–139.
(18) Hassall, C. H.; Morgan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2853–2861.
(19) Tietze, L. F.; Eicher, T. *Reactions and Synthesis in the Organic Chemistry Laboratory*; University Science Books: California, 1989; p 53.
(20) Bindra, J. S.; Grodski, A. *J. Org. Chem.* **1977**, *42*(5), 910–911.
(21) Sharma, M.; Rangaswami, S. *Ind. J. Chem. Sect. B* **1977**, *15B*(10), 884–885.
(22) For an alternative Diels–Alder-based approach to aloe emodin and related anthraquinones see: Benfaremo, N.; Cava, M. P. *J. Org. Chem.* **1985**, *50*, 139–141.
(23) Seshadri, T. R.; Subramanian, S. S. *Proc. Indian Acad. Sci.* **1949**, *30A*, 67–73.
(24) Bloomer, J. L.; Stagliano, K. W. *Tetrahedron Lett.* **1993**, *34*(5), 757–760.

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.