sively with 5% sodium bicarbonate solution (2 × 200 mL), brine (2 × 200 mL), and water (1 × 200 mL). The organic layer was dried (Na_2SO_4) and evaporated to an oil (317 g). The oil was crystallized from ethanol to yield yellow needles of diketone 2 (209.7 g, 64.5%). This material was dissolved in glacial acetic acid (525 mL), and concentrated sulfuric acid (24 mL) was added. The mixture was refluxed for 2.5 h, and the hot solution was poured carefully into 3–4 L of crushed ice containing 1 L of water. Vigorous stirring was continued for 45 min, and the mixture was then placed in the refrigerator overnight. The resulting solid was filtered and washed with water (4–5 L). This material was oven-dried at 60 °C to provide 3 as a light green solid (186 g, 95% yield): mp 127–128 °C, lit. mp 130 °C.[17] This product was further purified by recrystallization from 2-propanol (75% yield for the recrystallization) to afford a yellow crystalline material: mp 128–129 °C. The overall yield from 1 was 46%.

Representative Procedure for Method A: Synthesis of 7-Methoxy-3′-(trifluoromethyl)flavone (4). To a suspension of KOtBu (1.92 g, 17.1 mmol) in THF (5 mL) in an ice bath was added 2-hydroxy-4-methoxyacetophenone (1.30 g, 7.8 mmol) in THF (4 mL). The reaction was stirred for 20 min at 0 °C. After 20 min, 3-(trifluoromethyl)benzoyl chloride (1.62 g, 7.8 mmol) in THF (4 mL) was added and the reaction was stirred for 15 min at 0 °C and then 10 min at room temperature and finally refluxed for 3 h. The reaction was cooled to room temperature, acidified to pH 1 with 1 N HCl, and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with water (1 × 50 mL) and dried (Na_2SO_4). Filtration and rotary evaporation yielded the diketone which was used without purification in the next step. A solution of the diketone and 12 drops of concentrated sulfuric acid in glacial acetic acid (20 mL) was refluxed overnight. The reaction was cooled and poured into an ice/water solution. This mixture was stirred until it became an unstirrable mass, then extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with water (1 × 50 mL) and half-saturated $NaHCO_3$ (1 × 50 mL) and dried over Na_2SO_4. (In some cases with other compounds, the extraction step was unnecessary because the material was filterable from the aqueous layer). Filtration and rotary evaporation provided a dark brown solid which was purified by flash chromatography (eluting with 25% EtOAc in hexane; material loaded on column in CH_2Cl_2) yielding 4 (0.755 g, 30% overall yield): mp 142–144 °C; ^{1}H NMR (300 MHz) δ 3.93 (s, 3 H, OCH_3), 6.77 (s, 1 H), 7.01 (m, 2 H), 7.65 (m, 1 H), 7.78 (m, 1 H), 8.05 (m, 1 H), 8.13 (m, 2H); ^{13}C NMR (75 MHz) δ 55.92, 100.36, 108.35, 114.84, 117.76, 122.94, 125.48, 127.11, 127.84, 129.25, 129.66, 131.68, 132.09, 132.79, 157.95, 161.16, 164.43, 177.51; MS (CI) *m/z* 321 $[M + H]^+$. Anal. Calcd for $C_{17}H_{11}F_3O_3$: C, 63.75; H, 3.46. Found: C, 63.41; H, 3.43.

Representative Procedure for Method B: Synthesis of 3′,5′-Difluoro-5-methoxyflavone (12). To a suspension of KOtBu (1.35 g, 12.08 mmol) and THF (6 mL) at 0 °C was added 2-hydroxy-6-methoxyacetophenone (1, 1.72 g, 10.42 mmol)[16] in THF (7 mL). The reaction was stirred for 0.5 h at room temperature, cooled to 0 °C, and then treated with 3,5-difluorobenzoyl chloride (1.98 g, 11.25 mmol). The reaction mixture was then stirred at room temperature for 1 h, cooled to 0 °C, treated with KOtBu (1.35 g, 12.08 mmol), and heated at reflux overnight. The reaction mixture was adjusted to a pH of 2 using a 50/50 mixture of concentrated HCl/water. This aqueous material was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with water (2 × 50 mL), dried over Na_2SO_4, filtered, and rotary evaporated to yield the diketone which was cyclized as described above for 4 without purification. Crystallization of the crude product from 2-propanol, and further purification by a vacuum column (eluting with 100% CH_2Cl_2) afforded 12 (1.0 g, 33% overall yield): mp 206–207 °C; ^{1}H NMR (300 MHz) δ 3.98 (s, 3 H, OCH_3), 6.65 (s, 1 H), 6.82 (d, 1 H), 6.95 (m, 1 H), 7.10 (d, 1 H), 7.37 (m, 2 H), 7.58 (m, 1 H); ^{13}C NMR (75 MHz) δ 56.47, 106.19, 106.52, 106.75, 108.93, 109.05, 109.17, 109.29, 110.00, 114.47, 134.16, 134.69, 157.98, 158.28, 159.77, 161.48, 161.65, 164.79, 164.96, 177.77; MS (CI) *m/z* 289 $[M + H]^+$. Anal. Calcd for $C_{16}H_{10}F_2O_3$: C, 66.67; H, 3.50. Found: C, 66.62; H, 3.39.

Synthesis of 5-(Carboxymethoxy)flavone (18) from 2,6-Dihydroxyacetophenone. KOtBu (22.4 g, 0.2 mol) was added to dry THF (250 mL) in a 1-L, three-necked round-bottom flask equipped with an agitator, immersion thermometer, addition funnel, and nitrogen inlet. The mixture was cooled to 0–5 °C. 2,6-Dihydroxyacetophenone (30.4 g, 0.2 mol) in THF (150 mL) was added dropwise over 15 min while maintaining the temperature below 5 °C. The ice bath was removed, and the mixture was allowed to warm to room temperature and stir for an additional 50 min. The mixture was subsequently cooled to 0–5 °C and benzoyl chloride (28.1 g, 0.2 mol, 23.2 mL) was added dropwise over 15 min while maintaining the temperature below 5 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then recooled to 5 °C, and KOtBu (22.4 g, 0.2 mol) was added. This resulted in a strong exothermic reaction, and the reaction temperature rose to 20 °C. THF (100 mL) was added, and the mixture was cooled to 0–5 °C. *tert*-Butyl bromoacetate (39 g, 0.2 mol, 32.3 mL) was added dropwise while maintaining the reaction temperature below 5 °C. The ice bath was removed, and the mixture was stirred at room temperature for 2 h and recooled to 0–5 °C. KOtBu (24.3 g, 0.21 mol) was then added, resulting in an exothermic reaction. A reflux condenser was attached, and the mixture was heated overnight at reflux. The mixture was then diluted with water (100 mL) and acidified to pH 2 with 1 N HCl. The mixture was concentrated on the rotary evaporator to a syrup which was taken up in CH_2Cl_2 (300 mL) and washed successively with 5% sodium bicarbonate solution (2 × 100 mL), water (1 × 100 mL), and brine (1 × 300 mL). The organic layer was dried (Na_2SO_4) and evaporated to provide diketone 17 as an oil (70 g, 95% yield). A small portion of this material was crystallized from ethanol to afford yellow needles. This crystalline diketone 17 (2.8 g, 7 mmol) was dissolved in glacial acetic acid (15 mL), and concentrated sulfuric acid (1 mL) was added. The solution was refluxed for 30 min, and the hot solution was poured into a beaker containing crushed ice (250–300 mL). The beaker was kept in a refrigerator for 1.5 h, and the resulting solid was filtered and washed well with cold water. The product was dried overnight at 50 °C and recrystallized from glacial acetic acid, providing pure flavone 18 (1.35 g, 60% yield): mp 208–210 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 4.86 (s, 2 H, CH_2), 6.93 (m, 2 H), 7.35 (d, 1 H), 7.58 (m, 3 H), 7.69 (apparent t, 1 H), 8.05 (m, 2 H), 13.05 (br s, 1 H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 66.12, 108.56, 109.34, 111.21, 114.33, 126.41, 129.38, 131.03, 131.95, 134.45, 157.71, 157.77, 160.68, 170.09, 176.94; MS (CI) *m/z* 297 $[M + H]^+$. Anal. Calcd for $C_{17}H_{12}O_5 \cdot 0.25H_2O$: C, 67.88; H, 4.19. Found: C, 67.80; H, 4.28.

Supplementary Material Available: Physical and spectroscopic data for compounds 5–11 and 13–16, as well as the synthesis of any precursors (7 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.

(17) Donnelly, J. A.; Doran, H. J.; Murphy, J. J. *Tetrahedron* **1973**, *29*, 1037.

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

James L. Bloomer,* Kenneth W. Stagliano, and Joseph A. Gazzillo

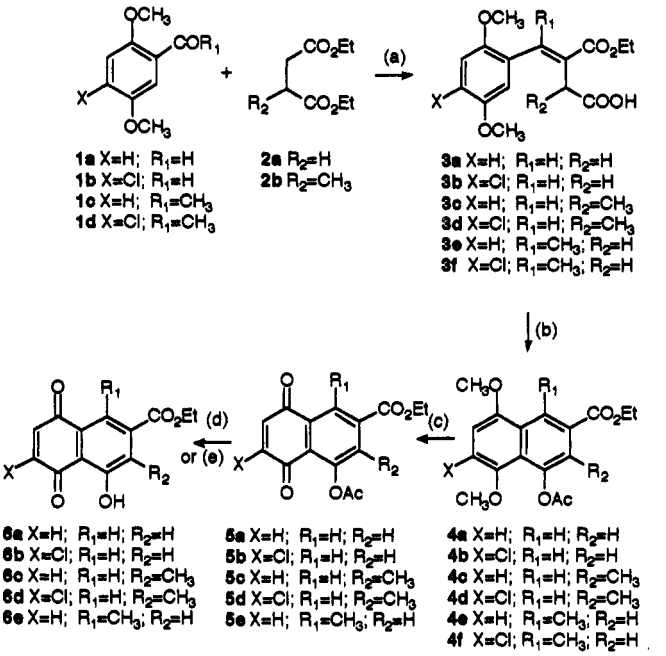
Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

Received April 13, 1993 (Revised Manuscript Received August 31, 1993)

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.

0022-3263/93/1958-7906$04.00/0

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.

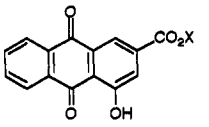
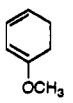
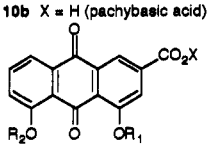
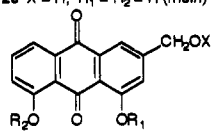
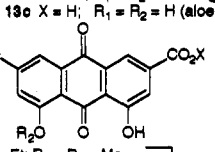
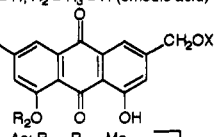
In the model system **3a**, use of less acetic anhydride for cyclization and methanol trituration rather than exhaustive ligroin extraction gave greatly improved yields as compared to the literature method noted above. In subsequent studies, however, workup methods had to be adapted to each specific 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.