Directed Metalation of *N,N*-Diethylbenzamides. Silylated Benzamides for the Synthesis of Naturally Occurring *peri*-Methylanthraquinones and *peri*-Methyl Polycyclic Aromatic Hydrocarbons

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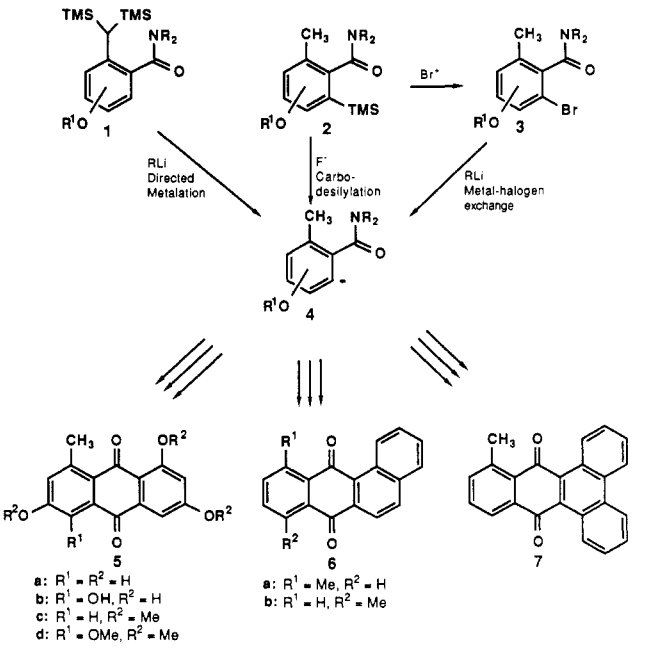
Efficient methodologies based on directed ortho metalation, fluoride-induced carbodesilylation, and metal–halogen exchange processes (Scheme I) are reported for the synthesis of *peri*-methyl-substituted anthraquinone natural products **5** and polycyclic aromatic hydrocarbons **6**, **7**. Benzamide **8** (Scheme II) is converted in a one-pot sequence into the disilylated derivative **10**, which upon metalation, condensation with 3,5-dimethoxybenzaldehyde, CsF desilylation, and TsOH cyclization leads to the key phthalide **11**. Compound **11** is transformed into deoxyerythrolaccin tris(methyl ether) **5c**, which has been previously converted into the natural product **5a**. For the synthesis of erythrolaccin tetrakis(methyl ether) **5d**, the silyl and bromo benzamides **14** and **15** (Scheme III) are condensed with 3,5-dimethoxybenzaldehyde by CsF-induced carbodesilylation and metal–halogen exchange expedients, respectively, to give the phthalide **16**, which is transformed into the target anthraquinone **5d** by methods identical with those used in **5c**. Along similar lines, the synthesis of 11-methyl-7,12-benz[*a*]anthraquinone (**6a**, Scheme IV), 8-methyl-7,12-benz[*a*]anthraquinone (**6b**), and 10-methyl-9,14-dibenz[*a,c*]anthraquinone (**7**) is described.

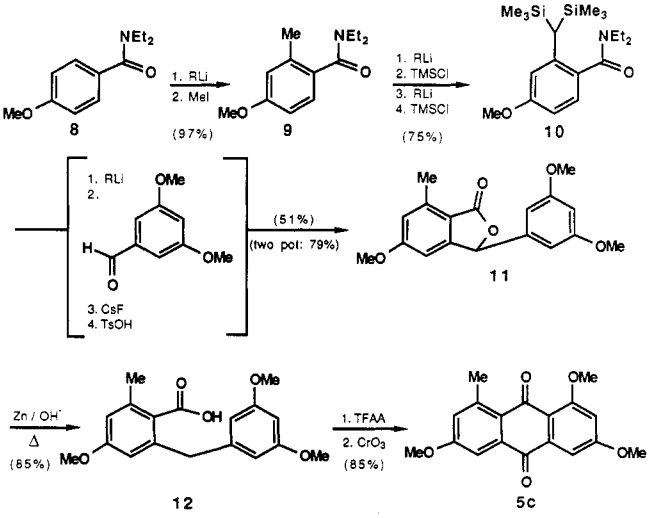
In the accompanying paper,[1] we have demonstrated that silicon protection of preferred aromatic C-H and C-methyl metalation sites is an expedient tactic for the preparation of diverse polysubstituted aromatics. These studies led to the recognition that the lithiated toluamide **4** synthon may be potentially derived from three different types of intermediates (Scheme I): metalation of α,α-disilylated *o*-toluamides **1**, fluoride-induced carbodesilylation of 2-(trimethylsilyl)-6-methylbenzamides **2**, and metal–halogen exchange of 2-bromo-6-methylbenzamides **3** which are readily obtained from **2** by ipso bromodesilylation. The very fast rate of metal–halogen exchange compared to base-catalyzed deprotonation of aromatic substrates[2] allows survival of acidic sites (e.g. Me in **3**) and other electrophilic groups under low-temperatures RLi conditions.[3] Here we detail[4] the utility of these intermediates in conjunction with regimens embodied in our original syntheses of naturally occurring anthraquinones[5] for the regiospecific construction of *peri*-methylanthraquinone natural products deoxyerythrolaccin (**5a**) and erythrolaccin (**5b**) and polycyclic aromatic hydrocarbons (PAH) **6** and **7**.

Synthesis of Naturally Occurring Anthraquinones 5a and 5b. The recent resurgence of interest in the significant class of anthraquinone natural products[6] is in large part due to the intense activity in the synthesis of the anthracyclinone antitumor antibiotics.[7] Deoxyerythrolaccin (**5a**) and erythrolaccin (**5b**), components of the stick-lac pigment of the Coccid insect, *Laccifer lacca*,[8] are

Scheme I



Scheme II



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(2) Schollkopf, U. In *Methoden der Organishe Chemie (Houben-Weyl)*; Muller, E., Ed.; George Thieme Verlag: Stuttgart, 1970; Vol. 13/1, p 148. Kobrich, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473.

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(4) Preliminary reports: Mills, R. J.; Snieckus, V. *Tetrahedron Lett.* **1984**, *479*. Mills, R. J.; Snieckus, V. *Ibid.* **1984**, 483.

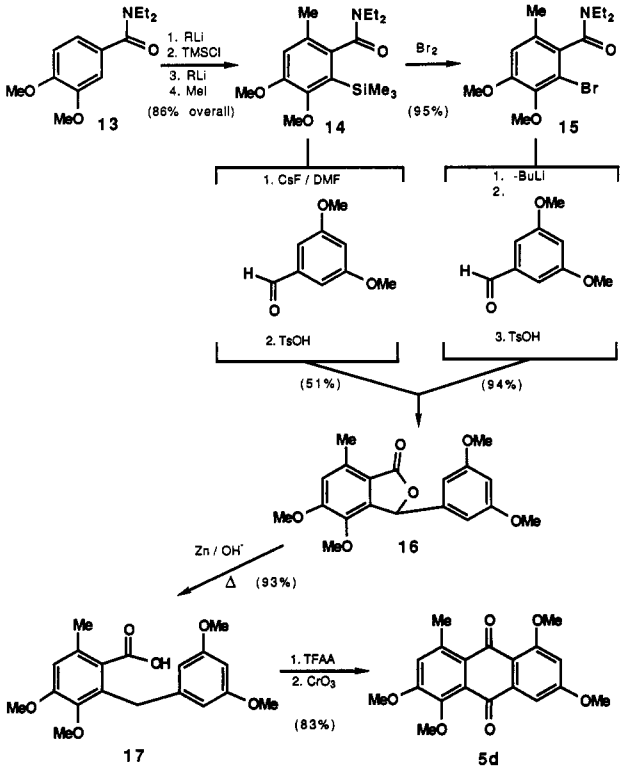
(5) deSilva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.

(6) Thomson, R. H. *Naturally Occurring Anthraquinones*, 3rd ed.; Academic Press: New York, 1987.

(7) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.

0022-3263/89/1954-4386$01.50/0

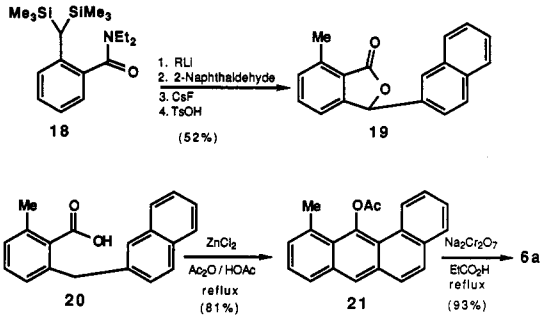
Scheme III



representative of a large number of *peri*-methyl polyoxygenated anthraquinones.[6] Compounds **5a** and **5b** have been synthesized most recently by Brassard and Roberge[9] and Brisson and Brassard[10] by routes which involve a broadly adaptive strategy of condensing haloquinones with vinylogous ketene acetal. The original synhtheses in support of structural confirmation were carried out by routes involving low-yield Friedel–Crafts methodology.[11] The corresponding tris(methyl ether) (**5c**) and tetrakis(methyl ether) (**5d**), one of which (**5c**) had been previously converted into the naturally occurring anthraquinones **5a**,[9] were chosen to test the conceptual framework implied in Scheme I.

Metalation of the readily available benzamide **8** (Scheme II) under the standard conditions (*s*-BuLi/TMEDA/THF/−78 °C) followed by MeI quench afforded the required toluamide **9**, which upon double sequential metalation and silylation led to the disilylated derivative **10** in good yield. With the *o*-methyl protection in place, compound **10** was metalated again under the standard conditions and consensed with 3,5-dimethoxybenzaldehyde. The resulting amide alcohol was not isolated but subjected to CsF-mediated double desilylation and TsOH-catalyzed cyclization to give the phthalide **11** in 53% overall yield. Abbreviation and improved efficiency for this sequence was achieved by carrying out a one-pot operation from **8** to **10** without isolation of compound **9**, which led to the isolation of phthalide **11** in 72% overall yield.[12] Hydrogenolysis

Scheme IV



using copper sulfate activated zinc[13] furnished the benzylbenzoic acid **12**, which upon sequential Friedel–Crafts cyclization[5] and CrO_3 oxidation provided deoxyerythrolaccin tris(methyl ether) **5c** whose physical and spectral properties were shown to correspond to those of authentic material (see the Experimental Section). Since compound **5c** has been converted into deoxyerythrolaccin (**5a**),[14] our route formally concludes the total synthesis of this natural product. If the two-pot conversion of **8** into **11** is taken into consideration, this constitutes the shortest and most efficient (61% overall yield) reported route for the preparation of deoxyerythrolaccin.

Although the synthesis of erythrolaccin tetrakis(methyl ether) **5d** could, in principle, be achieved by the silicon protection tactic used for the deoxyerythrolaccin derivative **5c** above, the exploration of the alternative principles of carbodesilylation and metal–halogen exchange (Scheme I) was deemed inherently desirable. To this end, the silylbenzamide **14** (Scheme III), prepared in high yield via a one-pot sequence from **13**,[1] was condensed with 3,5-dimethoxybenzaldehyde in the presence of CsF in refluxing DMF,[1] and the resulting amide alcohol was, without isolation, cyclized under acid catalysis to give the phthalide **16**. As an alternate approach to **16**, the ready availability of the *o*-bromobenzamide **15** by ipso bromodesilylation of **14** according to our model studies[1] allowed the hypothesis of competitively faster rate of metal–halogen exchange over base-catalyzed deprotonation of acidic *o*-tolyl hydrogens to be put to the experimental test. In the event, treatment of **15** with *n*-BuLi at 95 °C followed by condensation with 3,5-dimethoxybenzaldehyde and TsOH cyclization gave the same phthalide **16** in nearly quantitative yield. Zinc-mediated hydrogenolysis as before afforded the benzoic acid **17**, which, upon TFAA cyclization and CrO_3 oxidation, yielded the desired erythrolaccin tetrakis(methyl ether) **5d**, shown to be identical (mp, IR, NMR) with an authentic sample by direct comparison.[10] This route provides the most efficient synthesis (65% overall yield) of this penultimate precursor of the natural product (**5b**).

Synthesis of *peri*-Methyl PAH Quinones 6 and 7. Among the various environmentally significant PAH classes,[15] the methylbenz[*a*]anthracenes (MBA) have received considerable attention as a result of studies concerning the bay region theory of molecular carcinogenesis.[16]

(8) For a captivating discussion of the significance of the *Coccid* insects to the Indian dye and lac industries, see: Legett, W. F. *Ancient and Medieval Dyes*, Chem. Publ. Co.; Brooklyn, 1944; pp 83–91.

(9) Brassard, P.; Roberge, G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1041.

(10) Brisson, C.; Brassard, P. *J. Org. Chem.* **1981**, *46*, 1810.

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(12) The high yields in these one-pot procedures may in part be due to the known slow reactivity of TMSCl with RLi reagents at low temperature: Seyferth, D.; Weistein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.

(13) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; deSilva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955.

(14) Brassard, P.; Roberge, G., unpublished results. See: Roberge, G. Ph.D. Thesis, Universite Laval, Quebec, 1980.

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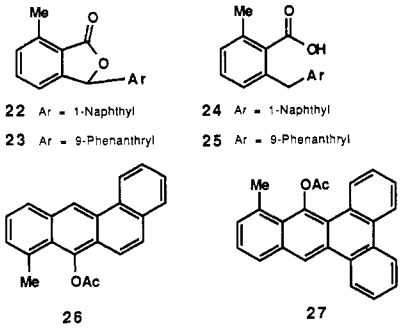
Aside from the pioneering and extensive work of Newman,[17] the availability of many MBA derivatives has been limited by the complexity of the existing synthetic methods.[18] As a logical extension of the successful synthesis of naturally occurring anthraquinones described above, we examined the utility of silicon protection of *o*-toluamide methyl hydrogens for the preparation of the *peri*-methylanthraquinones **6a**, **6b**, and **7**.

As the initial target, 11-methylbenz[*a*]anthraquinone **6a** (Scheme IV) was examined in view of its conversion into 7,11,12-trimethylbenz[*a*]anthracene, a highly carcinogenic compound of considerable value for mechanistic studies.[19] Metalation of **18**[1] followed by sequential condensation with 2-naphthaldehyde, CsF-mediated desilylation, and TsOH cyclization afforded the phthalide **19**. Application of the copper sulfate activated zinc hydrogenolysis gave the benzoic acid **20**, which, when subjected to the cyclization procedure described by Newman,[19] led to the acetoxy derivative **21**. Dichromate oxidation[19] furnished the desired 11-methylbenz[*a*]anthraquinone **6a**, which was shown to be identical with authentic material. The overall yield of this route compares favorably with that described by Newman.[19]

Starting with condensations of the same disilylated *o*-toluamide **18** with 1-naphthaldehyde and phenanthrene-9-carboxaldehyde and using identical series of reactions, the *peri*-methyl-substituted anthraquinones **6b** and **7**, respectively, were synthesized in good overall yields. The reaction sequences involve intermediates **22**, **24**, **23**, **25**, and **26**, **27**, respectively. Conversion of quinones **6a**, **6b**, and **7** into the corresponding PAH may be achieved by use of well-documented methodology.[17,20]



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Conclusions

Efficient and concise routes to naturally occurring anthraquinones **5** and polycyclic aromatic hydrocarbons **6** and **7** have been developed by taking advantage of regioselective silicon protection and activation in directed metalation (**1**), fluoride-induced carbodesilylation (**2**), and metal–halogen exchange (**3**) processes. The use of several-reaction, one-pot procedures for intermediates **11**, **16**, **19**, **22**, and **23** makes these routes particularly attractive. This new methodology has considerable advantage over classical, electrophilic-substitution regimens, which normally suffer in regioselectivity, efficacy, and harshness of conditions in order to achieve the same goal. The fluoride-mediated carbodesilylation process **14** → **16** supercedes the necessity for *o*-tolylmethyl silicon protection and, since it occurs under neutral conditions, offers a general complementary route to the directed metalation strategy for substrates with base-sensitive hydrogens and substituents. The metal–halogen exchange procedure **15** → **16**, derived via the synthetically underdeveloped ipso bromodesilylation, **14** → **15**, may serve the same purpose. Overall, the regioselectivity, efficiency, and brevity which characterize the prototype transformation to *peri*-methylanthraquinones achieved in this work should encourage the broader use of silicon protection, derived via the versatile directed ortho metalation strategy, in synthetic aromatic chemistry.

Experimental Section[21]

***N*,*N*-Diethyl-4-methoxybenzamide.** This compound was prepared by using standard procedures, mp 43–44 °C (lit.[22] mp 48 °C).

General Procedures. Lettered procedures for metalation–silylation, CsF-induced carbodesilylation, and ipso bromodesilylation refer to those detailed in the accompanying paper.[1]

***N*,*N*-Diethyl-4-methoxy-2-methylbenzamide (9).** According to procedure A, to a solution of *N*,*N*-diethyl-4-methoxybenzamide (4.559 g, 22 mmol), *s*-BuLi (17.3 mL of a 1.4 M solution, 24.2 mmol), and TMEDA (3.6 mL, 24.2 mmol) was added MeI (6.8 mL, 113 mmol). Workup in the usual manner followed by MPLC afforded 4.72 g (97%) of **9** as a colorless oil: bp 118–121 °C (0.15 mm); IR (neat ν(max) 1629 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93–1.33 (m, 6 H), 2.27 (s, 3 H), 3.01–3.71 (m, 4 H), 3.79 (s, 3 H), 6.65–6.99 (m, 2 H), 7.09 (d, J = 8.9 Hz, 1 H, C_6-H); ^{13}C NMR ($CDCl_3$) δ (rel intensity) 12.8 (33), 13.7 (31), 18.9 (65), 38.6 (30), 42.5 (28), 54.9 (86), 110.9 (100), 115.5 (100), 126.6 (92), 129.7 (40), 135.6 (51), 159.4 (42), 170.6 (28); MS *m*/*e* (rel intensity) 221 (M^+, 18), 149 (100).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.56; H, 8.86; N, 6.19.

Synthesis of Deoxyerythrolaccin Tris(methyl ether) (5c). *N*,*N*-Diethyl-2-[bis(trimethylsilyl)methyl]-4-methoxybenzamide (10). A solution of benzamide **9** (2.203 g, 9.9 mmol) in anhydrous THF (10 mL) was added dropwise to a stirred solution of *s*-BuLi (7.1 mL of a 1.4 M solution, 9.9 mmol) and TMEDA (1.5 mL, 9.9 mmol) in THF (150 mL) at −78 °C under argon. The resulting burgundy solution was stirred for 1 h at −78 °C and treated with TMSCl (1.3 mL, 9.9 mmol). The resulting clear solution was stirred for 1 h at −78 °C and subjected to the same sequence of *s*-BuLi (7.8 mL, 10.9 mmol), TMEDA (1.6 mL, 10.9 mmol), and TMSCl (3.8 mL, 29 mmol) with the same time interval. The resulting clear solution was allowed to warm to ambient temperature overnight and worked up in the usual manner to give, after HPLC, 2.836 g (75%) of **10** as a colorless oil: bp 132–134 °C (0.05 mm); IR (neat) ν(max) 1629 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 18 H), 1.14 (br, 6 H), 1.87 (s, 1 H), 3.20 (br, 4 H), 3.77 (s, 3 H), 6.51–6.96 (m, 2 H), 7.02 (d, J = 8.4 Hz, 1 H, C_6-H); ^{13}C NMR ($CDCl_3$) δ (rel intensity) 0.6 (100), 13.1 (6), 24.8 (19), 38.6 (4), 42.9 (4), 54.9 (19), 108.2 (24), 114.3 (20), 127.2 (25), 128.3 (14), 143.4 (15), 159.2 (15), 170.7 (14); MS *m*/*e* (rel intensity) 365 (M^+, 17), 364 (39), 350 (35), 279 (24), 278 (100).

Anal. Calcd for $C_{19}H_{35}NO_2Si_2$: C, 62.40; H, 9.64; N, 3.83. Found: C, 62.61; H, 9.54; N, 4.03.

***N*,*N*-Diethyl-2-[bis(trimethylsilyl)methyl]-4-methoxy-6-(trimethylsilyl)benzamide** was obtained as a minor product: 429 mg (10%), IR ($CHCl_3$) ν(max) 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 9 H), 0.13 (s, 9 H), 0.23 (s, 9 H), 0.87–1.38 (m, 6 H), 1.59 (s, 1 H), 2.70–3.27 (m, 3 H), 3.63–3.95 (m, 1 H), 3.79 (s, 3 H), 6.48 (d, J = 2.4 Hz, 1 H), 6.81 (d, J = 2.4 Hz, 1 H); MS *m*/*e* (rel intensity) 437 (M^+, 9), 422 (26), 366 (21), 265 (58), 364 (100).

5-Methoxy-7-methyl-3-(3′,5′-dimethoxyphenyl)phthalide (11). According to procedure A, benzamide **10** (1.175 g, 3.2 mmol) was treated with *s*-BuLi (2.5 mL of a 1.4 M solution, 3.5 mmol), TMEDA (0.5 mL, 3.5 mmol), and 3,5-dimethoxybenzaldehyde (560 mg, 3.4 mmol). Workup in the usual manner afforded a viscous orange oil, which was directly treated with an excess of CsF for 12 h and processed according to procedure B. The tarry

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(18) Levy, L. A.; Sashi Kumar, V. P. *Tetrahedron Lett.* **1983**, 1221 and references cited therein.
(19) Newman, M. S. *J. Org. Chem.* **1983**, *48*, 3249.
(20) Ahmed, F. U.; Ranagarajan, T.; Eisenbraun, E. J.; Keen, G. W.; Hamming, M. C. *Org. Prep. Proc. Int.* **1975**, *7*, 267.
(21) For general methods, see ref 1.
(22) Grammaticakis, P. *Bull. Soc. Chim. Fr.* **1964**, 924.

orange product was dissolved in toluene (100 mL), containing a catalytic amount of *p*-toluenesulfonic acid, and the resulting solution was refluxed for 12 h, cooled, and evaporated to dryness in vacuo. MPLC of the residue afforded 513 mg (51%) of **11** as an off white solid: mp 115–116 °C (Et_2O–CH_2Cl_2); IR ($CHCl_3$) ν(max) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (s, 3 H), 3.77–3.81 (3 s, 9 H), 6.14 (s, 1 H), 6.43 (br, 3 H), 6.58 (br, 1 H), 6.79 (br, 1 H); MS *m/e* (rel intensity) 314 (M^+, 84) 149 (100), 148 (45).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.49; H, 5.79.

Two-Pot Preparation of Phthalide 11 from *N,N*-Diethyl-4-methoxybenzamide (8). A solution of benzamide **8** (2.178 g, 9.8 mmol) in anhydrous THF (10 mL) was added dropwise to a stirred solution of *s*-BuLi (7 mL of a 1.4 M solution, 9.8 mmol) and TMEDA (1.5 mL, 10 mmol) in THF (200 mL) at −78 °C under argon. The resulting burgundy solution was stirred for 1 h at −78 °C and treated with TMSCl (1.3 mL, 10 mmol). After stirring further for 1 h at −78 °C, the now clear solution was subjected to the same sequence of treatment with *s*-BuLi (7 mL, 9.8 mmol), TMEDA (1.5 mL, 10 mmol), and TMSCl (1.3 mL, 10 mmol) with the same time interval and observation of color change. The resulting clear solution was allowed to stir at −78 °C for 1.5 h and again treated with *s*-BuLi (7 mL, 9.8 mmol) and TMEDA (1.5 mL, 10 mmol). After being stirred for 1 h at −78 °C, the yellow solution was treated with 3,5-dimethoxybenzaldehyde (1.9 g, 11.5 mmol), and the mixture was allowed to warm to ambient temperature overnight. Workup in the usual manner afforded a viscous orange oil, which was directly treated with an excess of CsF for 12 h and processed according to procedure B. The tarry orange product was dissolved in toluene (100 mL), containing a catalytic amount of *p*-toluenesulfonic acid, and the resulting mixture was refluxed for 12 h, cooled, and evaporated to dryness in vacuo. MPLC of the residue afforded 2.437 g (79%) of **11**, which was shown to be identical by direct comparison (mp, ^1H NMR, IR and MS) with the material prepared above.

4-Methoxy-6-methyl-2-(3′,5′-dimethoxybenzyl)benzoic Acid (12). A solution of phthalide **11** (223 mg, 0.7 mmol) in 10% aqueous NaOH (20 mL) containing freshly activated Zn[13] (2.5 g) was refluxed for 16 h. The solution was cooled and filtered through a sintered-glass frit, and the filtrate was acidified to pH 4 with concentrated HCl. The solution was extracted with CH_2Cl_2, and the organic extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to dryness in vacuo to furnish 190 mg (85%) of **12** as a colorless solid: mp 163–164 °C (Et_2O–hexane); IR ($CHCl_3$) ν(max) 3500, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 3.72 (s, 6 H), 3.76 (s, 3 H), 4.07 (s, 2 H), 6.32–6.61 (m, 5 H), 9.00 (br, 1 H, exchanged with D_2O); MS *m/e* (rel intensity) 317 (20), 316 (M^+, 100), 314 (47), 298 (41), 283 (29).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.67; H, 5.99.

1,3,6-Trimethoxy-8-methylanthraquinone [Deoxyerythrolaccin Tris(methyl ether), 5c]. A solution of the benzylbenzoic acid **12** (140 mg, 0.4 mmol) in anhydrous CH_2Cl_2 (5 mL) containing trifluoroacetic anhydride (0.1 mL, 0.8 mmol) was stirred at room temperature for 30 min and then evaporated to dryness in vacuo. The residue was dissolved in acetic acid (5 mL) and treated with chromium trioxide (50 mg). The mixture was stirred for 4 h at room temperature and evaporated to dryness to give a residue, which was basified with 5% Na_2CO_3 solution. The solution was extracted with CH_2Cl_2, and the organic extract was dried (Na_2SO_4), and evaporated in vacuo to give, after MPLC, 120 mg (85%) of **5c** as a yellow solid: mp 205–206 °C ($CHCl_3$) (lit.[11b] mp 205 °C), mixture mp undepressed with a synthetic sample provided by Professor P. Brassard; IR ($CHCl_3$) ν(max) 1657, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (s, 3 H), 3.94 (s, 3 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 6.80 (d, J = 2.5 Hz, 1 H, C_2-H), 7.04 (d, J = 2.7 Hz, 1 H, C_7-H), 7.39 (d, J = 2.5 Hz, 1 H, C_4-H), 7.60 (d, J = 2.7 Hz, 1 H, C_5-H).

Synthesis of Erythrolaccin Tetrakis(methyl ether) (5d). *N,N*-Diethyl-2-bromo-3,4-dimethoxy-6-methylbenzamide (15). A solution of benzamide **14**[1] (4.344 g, 13.4 mmol) in CCl_4 (50 mL) at 0 °C was treated with Br_2 (1 mL, 19.6 mmol) for 5 min and quenched with saturated $NaHSO_3$ solution (25 mL). Workup in the usual manner followed by HPLC (hexane–EtOAc, 1:1) afforded 1.275 g of starting benzamide together with 2.977 g (95% based on recovered starting material) of **15** as colorless crystals: mp 88–88.5 °C (Et_2O); IR ($CHCl_3$) ν(max) 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, 3 H), 1.20 (t, J = 7 H, 3 H), 2.19 (s, 3 H), 3.07 (q, J = 7 Hz, 2 H), 3.31–3.68 (m, 2 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 6.63 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ (rel intensity) 12.6 (78), 13.9 (87), 19.5 (63), 38.9 (87), 42.7 (95), 56.2 (84), 60.7 (77), 113.8 (100), 115.2 (35), 131.4 (76), 144.8 (21), 153.0 (38), 167.9 (36); MS *m/e* (rel intensity) 332 (3), 330 (M^+, 3), 259 (94), 257 (100), 250 (26).

Anal. Calcd for $C_{14}H_{20}BrNO_3$: C, 50.92; H, 6.11; N, 4.24. Found: C, 50.94; H, 6.42; N, 4.49.

4,5-Dimethoxy-7-methyl-3-(3′,5′-dimethoxyphenyl)phthalide (16). From *o*-Silylbenzamide 14. Under identical conditions described for the two-pot preparation of phthalide **11**, benzamide **14**[1] (324 mg, 1 mmol) was treated with CsF in the presence of 3,5-dimethoxybenzaldehyde followed by catalytic TsOH acid cyclization in toluene to afford, after MPLC, 164 mg (51%) of phthalide **16** shown to be identical (mp, IR, ^1H NMR, and MS) with material prepared as described below.

From *o*-Bromobenzamide 15. A solution of bromobenzamide **15** (1.06 g, 3.2 mmol) in THF (5 mL) was added dropwise to a mixture of *n*-BuLi (2 mL of a 1.6 M solution, 3.2 mmol) and TMEDA (0.5 mL, 3.3 mmol) in THF (50 mL) at −95 °C under argon. After the mixture was stirred for 1 h at −95 °C, a solution of 3,5-dimethoxybenzaldehyde (560 mg, 3.4 mmol) in THF (5 mL) was added, and the resulting solution was allowed to warm to room temperature overnight. Normal workup afforded a colorless oil, which was dissolved in toluene (100 mL) containing a catalytic amount of TsOH, and the solution was refluxed for 12 h, cooled, and evaporated to dryness in vacuo to afford, after MPLC, 1.029 g (94%) of **16** as colorless crystals: mp 110–111.5 °C (Et_2O–CH_2Cl_2); IR ($CHCl_3$) ν(max) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (s, 3 H), 3.41 (s, 3 H), 3.77 (s, 6 H), 3.91 (s, 3 H), 6.24 (s, 1 H), 6.45 (s, 3 H), 6.83 (s, 1 H); MS *m/e* (rel intensity) 344 (M^+, 32), 179 (20), 152 (100), 151 (51).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.08; H, 5.69.

3,4-Dimethoxy-6-methyl-2-(3′,5′-dimethoxybenzyl)benzoic Acid (17). The procedure and workup for the preparation of compound **12** was followed. From phthalide **16** (160 mg, 0.5 mmol) and freshly activated zinc (2.5 g) in 10% aqueous NaOH solution (20 mL) there was obtained 149 mg (93%) of **17** as a colorless solid: mp 119–120 °C (Et_2O–hexane); IR ($CHCl_3$) ν(max) 3499, 1691 cm^{-1}; ^1H NMR ($CHCl_3$) δ 2.39 (s, 3 H), 3.62 (s, 3 H), 3.70 (s, 6 H), 3.87 (s, 3 H), 4.11 (s, 2 H), 6.22–6.38 (m, 3 H), 6.67 (s, 1 H); MS *m/e* (rel intensity) 346 (M^+, 80), 152 (68), 151 (100).

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 66.16; H, 6.73.

1,3,5,6-Tetramethoxy-8-methylanthraquinone [Erythrolaccin Tetrakis(methyl ether), 5d]. The procedure and workup for the preparation of **5c** was followed. From benzylbenzoic acid **17** (130 mg, 0.4 mmol) and TFAA (0.1 mL, 0.8 mmol) in anhydrous CH_2Cl_2 (5 mL) there was obtained crude material, which was treated with CrO_3 (50 mg) in acetic acid (95 mL) overnight at room temperature. Standard workup followed by MPLC afforded 106 mg (83%) of **5d** as yellow crystals: mp 155–156 °C (Et_2O–CH_2Cl_2) (lit.[11a] mp 159–160 °C), mixture mp undepressed with a synthetic sample provided by Professor P. Brassard; IR ($CHCl_3$) ν(max) 1663, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (s, 3 H), 3.95 (s, 3 H), 3.97 (s, 3 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 6.74 (d, J = 2.5 Hz, 1 H, C_2-H), 6.99 (s, 1 H, C_7-H), 7.28 (d, J = 2.5 Hz, C_4-H).

Synthesis of 11-Methyl-7,12-benz[*a*]anthraquinone (6a). 7-Methyl-3-(2-naphthyl)phthalide (19). The procedure for the conversion of **10** into **11** was adopted. Benzamide **18**[1] (2.813 g, 8.4 mmol) in THF (10 mL) was metalated with a solution of *s*-BuLi (7.6 mL of a 1.3 M solution, 9.3 mmol) and TMEDA (1.4 mL, 9.3 mmol) in THF (200 mL) at −78 °C under argon, and the resulting orange mixture was treated with 2-naphthaldehyde (2.6 g, 16.8 mmol) in THF (5 mL). Following normal workup, the crude orange oil was treated with an excess of CsF for 12 h according to procedure B. Standard workup afforded an orange tar, which was cyclized using catalytic TsOH in toluene (100 mL) at reflux for 12 h. Normal workup followed by MPLC afforded 1.196 g (52%) of **19** as a colorless solid: mp 103–104 °C (Et_2O); IR ($CHCl_3$) ν(max) 1758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (s, 3 H), 6.49 (s, 1 H), 7.13 (d, J = 8 Hz, 1 H), 7.24–7.27 (m, 1 H), 7.31 (d, J = 7 Hz, 1 H), 7.47–7.53, (m, 3 H), 7.82–7.85 (m, 4 H); MS *m/e* (rel intensity)

275 (22), 274 (M^+, 100), 155 (37), 119 (36), 118 (42).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.25; H, 5.26.

6-Methyl-2-(2-naphthylmethyl)benzoic Acid (20). Following the procedure used for the preparation of **12**, phthalide **19** (512 mg, 1.9 mmol) and freshly activated Zn (5 g) in 10% NaOH solution (40 mL) was refluxed for 16 h. Normal workup afforded 480 mg (93%) of **20** as an off-white solid: mp 137–138.5 °C (Et_2O); IR ($CHCl_3$) ν(max) 3200 (br), 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 4.26 (s, 2 H), 7.02 (d, J = 7.6 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.21–7.30 (m, 2 H), 7.38–7.40 (m, 2 H), 7.59 (s, 1 H), 7.75–7.79 (m, 3 H), 9.6 (br, 1 H, exchanged with D_2O); MS m/e (rel intensity) 277 (10), 276 (M^+, 52), 259 (21), 258 (100), 215 (32), 157 (27).

Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.53; H, 5.75.

12-Acetoxy-11-methylbenz[*a*]anthracene (21). A solution of **20** (920 mg, 3.3 mmol) and $ZnCl_2$ (50 mg) in acetic acid (6 mL) and acetic anhydride (2 mL) was refluxed for 50 min. To the hot solution was carefully added water with cooling in order to maintain the temperature below 90 °C. Cooling and filtration yielded 807 mg (81%) of **21**: mp 160–161 °C (acetic acid); IR ($CHCl_3$) ν(max) 1773 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3 H), 2.98 (s, 3 H), 7.34–7.92 (m, 8 H), 8.26 (s, 1 H, C_7-H), 9.15-9.27 (m, 1 H, C_1-H); MS m/e (rel intensity) 300 (M^+, 12), 259 (21), 258 (100), 220 (28).

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.17; H, 5.51.

11-Methyl-7,12-benz[*a*]anthraquinone (6a). The procedure of Newman[19] was followed. Powdered $Na_2Cr_2O_7{\cdot}2H_2O$ (660 mg) was added all at once to a hot solution of **21** (650 mg, 2.2 mmol) in propionic acid (6 mL) with rapid swirling. After gentle reflux (5 min), spontaneous crystallization occurred, causing vigorous reflux. After a further 25 min at reflux, the mixture was diluted with acetic acid (2 mL) and cooled. The resulting crystalline material was collected, washed with HOAc, and recrystallized from propionic acid to yield 562 mg (93%) of **6a** as yellow needles: mp 192–193.5 °C (lit.[19] mp 192–194 °C); IR ($CHCl_3$) ν(max) 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (s, 3 H), 7.57–7.76 (m, 4 H, C_2-H, C_3-H, C_8-H, and C_9-H), 7.92 (d, J = 7.9 Hz, 1 H, C_6-H or C_7-H), 8.14–8.18 (m, 2 H, C_4-H and C_5-H), 8.30 (d, J = 8.7 Hz, 1 H, C_6-H or C_7-H), 9.38 (d, J = 8.7 Hz, 1 H); MS m/e (rel intensity) 273 (21), 272 (M^+, 100), 271 (28), 243 (25), 215 (56), 86 (32), 84 (48).

Synthesis of 8-Methyl-7,12-benz[*a*]anthraquinone (6b). 7-Methyl-3-(1-naphthyl)phthalide (22). Following exactly the procedure described for the preparation of **19** but substituting 1-naphthaldehyde for 2-naphthaldehyde, benzamide **18** (2.52 g, 7.5 mmol) afforded, after MPLC, 1.194 g (58%) of **22** as an off-white solid: mp 155–156 °C (CH_2Cl_2–hexane); IR ($CHCl_3$) ν(max) 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s, 3 H), 7.17 (s, 1 H), 7.21 (d, J. = 7.7 Hz, 1 H), 7.27 (d, J = 7.2 Hz, 1 H), 7.31 (d, J = 7.4 Hz, 1 H), 7.39 (t, J = 7.2 and 7.4 Hz, 1 H), 7.48 (t, J = 7.6 and 7.5 Hz, 1 H), 7.56–7.65 (m, 2 H), 7.86 (d, J = 8.3 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 8.24 (d, J = 8.4 Hz, 1 H); MS m/e (rel intensity) 275 (20), 274 (M^+, 100), 155 (25), 119 (26), 118 (48).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.24; H, 5.11.

6-Methyl-2-(1-naphthylmethyl)benzoic Acid (24). Following exactly the procedure and workup outlined for the preparation of **20**, phthalide **22** (510 mg, 1.9 mmol) afforded 502 mg (97%) of **24**: mp 128–129 °C (Et_2O); IR ($CHCl_3$) ν(max) 3400 (br), 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 4.54 (s, 2 H), 6.74 (d, J = 7.5 Hz, 1 H), 7.07–7.14 (m, 2 H), 7.2 (d, J = 6.8 Hz, 1 H), 7.37–7.43 (m, 3 H), 7.73 (d, J = 8.2 Hz, 1 H), 7.80–7.83 (m, 1 H), 7.90–7.93 (m, 1 H), 10.70 (br, 1 H, exchanged with D_2O); MS m/e (rel intensity) 276 (M^+, 53), 259 (20), 258 (100), 215 (32).

Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.66; H, 5.94.

7-Acetoxy-8-methylbenz[*a*]anthracene (26). Via the procedure used for the preparation of **21**, from benzylbenzoic acid **24** (1.831 g, 6.6 mmol) and $ZnCl_2$ (120 mg) in a mixture of HOAc (6 mL) and Ac_2O (2 mL) there was obtained 1.888 g (96%) of **26**: mp 169–170 °C (acetic acid); IR ($CHCl_3$) ν(max) 1759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3 H), 2.91 (s, 3 H), 7.22–8.06 (m, 8 H), 8.74–8.85 (m, 1 H), 9.07 (s, 1 H, C_{12}-H); MS m/e (rel intensity) 300 (M^+, 14), 259 (20), 258 (100), 99 (22).

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.87; H, 5.26.

8-Methyl-7,12-benz[*a*]anthraquinone (6b). Following exactly the procedure described for the preparation of **6a**, from anthracene **26** (1.676 g, 5.6 mmol) and $Na_2Cr_2O_7{\cdot}2H_2O$ (1.9 g) in propionic acid (15 mL) there was obtained 1.2 g (78%) of **6b** as orange prisms, mp 168–170 °C (propionic acid). Sublimation afforded a pure sample: mp 172–172.5 °C; IR ($CHCl_3$) ν(max) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1 H, C_8-H), 7.62–7.77 (m, 3 H, C_2-H, C_3-H and C_9-H), 7.92 (d, J = 8.1 Hz, 1 H, C_4-H or C_{10}-H), 8.19 (d, J = 8.6 Hz, 1 H, C_5-H), 8.22 (d, J = 7 Hz, 1 H, C_4-H or C_{10}-H), 8.34 (d, J = 8.6 Hz, 1 H, C_6-H), 9.64 (d, J = 8.8 Hz, 1 H, C_1-H); MS m/e (rel intensity) 272 (M^+, 6), 259 (45), 258 (100), 229 (30), 227 (26), 215 (60); HRMS calcd for $C_{19}H_{12}O_2$ 272.0838, found 272.0847.

Synthesis of 10-Methyl-9,14-dibenz[*a*,*c*]anthraquinone (7). 7-Methyl-3-(9-phenanthryl)phthalide (23). Following exactly the procedure outlined for the preparation of **19** but substituting 9-phenanthrenecarboxaldehyde for 2-naphthaldehyde, from benzamide **18** (2.0 g, 6.0 mmol) there was obtained, after MPLC, 1.221 g (63%) of **23**: mp 187–189 °C (CH_2Cl_2–hexane); IR ($CHCl_3$) ν(max) 1757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (s, 3 H), 7.19 (s, 1 H), 7.29 (d, J = 7.7 Hz, 1 H), 7.34 (d, J = 7.4 Hz, 1 H), 7.49–7.77 (m, 7 H), 8.30–8.33 (m, 1 H), 8.67 (d, J = 8.3 Hz, 1 H), 8.77–8.79 (m, 1 H); MS m/e (rel intensity) 325 (24), 324 (M^+, 100), 265 (23), 205 (22), 118 (68).

Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 85.40; H, 4.99.

6-Methyl-2-(9-phenanthrylmethyl)benzoic Acid (25). Following exactly the procedure outlined for the preparation of **20**, phthalide **23** (198 mg, 0.6 mmol) afforded 130 mg (65%) of **25**: mp 167–168 °C (Et_2O); IR ($CHCl_3$) ν(max) 3400 (br) 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3 H), 4.56 (s, 2 H), 6.82 (dd, J = 6.9 and 1.9 Hz, 1 H), 6.83–7.09 (m, 2 H), 7.48 (s, 1 H), 7.51–7.63 (m, 2 H), 7.79 (d, J = 8.4 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 8.64 (d, J = 8.1 Hz, 1 H), 8.69 (d, J = 8.0 Hz, 1 H), 10.03 (br, 1 H, exchanged with D_2O); MS m/e (rel intensity) 327 (24), 326 (M^+, 100), 309 (24), 308 (95), 265 (40), 148 (34).

Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.96. Found: C, 84.45; H, 5.68.

9-Acetoxy-10-methyldibenz[*a*,*c*]anthracene (27). The procedure used for the preparation of **21** was followed. From benzylbenzoic acid **25** (300 mg, 0.9 mmol) and $ZnCl_2$ (100 mg) in HOAc (6 mL) and Ac_2O (2 mL) there was obtained 310 mg (98%) of **27**: mp 187–189 °C (acetic acid); IR ($CHCl_3$) ν(max) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 2.96 (s, 3 H), 7.35–7.99 (m, 7 H), 8.44–9.15 (m, 5 H); MS m/e (rel intensity) 350 (M^+, 34), 309 (24), 308 (100), 102 (21).

Anal. Calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.21. Found: C, 85.41; H, 5.36.

10-Methyl-9,14-dibenz[*a*,*c*]anthraquinone (7). Following exactly the procedure described for the preparation of **6a**, from anthracene **27** (280 mg, 0.8 mmol) and $Na_2Cr_2O_7{\cdot}2H_2O$ (250 mg) in propionic acid (5 mL) there was obtained 231 mg (90%) of **7**: mp 209–210 °C (propionic acid); IR ($CHCl_3$) ν(max) 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (s, 3 H), 7.54 (d, J = 7.5 Hz, 1 H, C_{11}-H), 7.61 (t, J = 7.5 Hz and 7.7 Hz, 1 H, C_{12}-H), 7.73–7.83 (m, 4 H, C_2-H, C_3-H, C_6-H, and C_7-H), 8.06 (d, J = 7.4 Hz, 1 H, C_{13}-H), 8.74–8.76 (m, 2 H, C_4-H and C_5-H), 9.04 (dd, J = 8.6 Hz and 0.8 Hz, 1 H, C_1-H), 9.44 (dd, J = 8.0 Hz and 1.2 Hz, 1 H, C_8-H); MS m/e (rel intensity) 323 (25), 322 (M^+, 100), 321 (21), 294 (21), 293 (21), 265 (29).

Anal. Calcd for $C_{23}H_{14}O_2$: C, 85.70; H, 4.38. Found: C, 85.23; H, 4.45.

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