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Efficient Syntheses of Rugulosin Analogues

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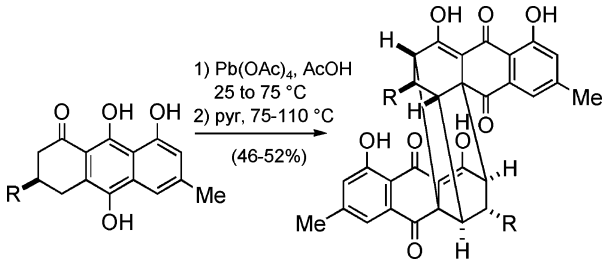
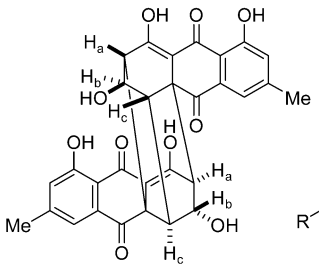


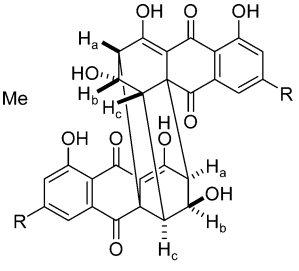
Oxidation of **3b** or **14c,d** with $Pb(OAc)_4$ in AcOH for 20 min at 25 °C and 1 h at 75 °C gave flavoskyrin-type dimers **6b** and **15c,d** in 53−86% yield. Heating a solution of **6b** or **15c,d** in pyridine under air for 1 h at 75−80 °C and then for 1−2 h at 110 °C afforded rugulosin-type dimers **10b** and **17c,d** in 61−88% yield. This two-step sequence provides a practical route to this unusual natural product skeleton.

Introduction

Rugulosin (**1**) is a member of an important family of fungal toxins whose structures were finally determined by Shibata and co-workers in the 1970s.[1,2] Graciliformin (**2a**) differs from rugulosin in the stereochemistry of the secondary alcohols, which are endo in **2a** and exo in **1**.[3] Clardy recently isolated cytoskyrin A (**2b**) with potent activity (12.5 ng/mL) in the biochemical induction assay from an endophytic fungus.[4] The structural novelty and potent biological activity of these compounds[5] make them significant synthetic targets.



1 (rugulosin)



2a, R = Me (graciliformin)
2b, R = OMe (cytoskyrin A)

Shibata proposed a biosynthetic scheme for these compounds and established that it is chemically viable in model systems.[1e] Oxidation of **3** with $Pb(OAc)_4$ in AcOH afforded quinone **4** (see Scheme 1). Treatment of **4** with a drop of pyridine in chloroform overnight resulted in enolization to give **5**, which underwent a Diels−Alder-type dimerization with the enone acting as both diene and dienophile to give **6**, with the flavoskyrin skeleton. A solution of **6** was then kept in pyridine for 3 weeks with occasional heating. This resulted in retro-conjugate addition to give **7** and Michael addition of the enolate to the quinone to generate **8**, with the rubroskyrin skeleton. Air oxidation of the hydroquinone to the quinone generated **9**, which underwent a second Michael addition of the enolate to give **10**, with the rugulosin/graciliformin/cytoskyrin A skeleton. Although this work elegantly supported the proposed biogenetic scheme, it did not provide a practical route to analogues. Yields are unspecified and appear to be low. The conversion of **6c** to **10c** proceeded in 1% yield.

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(1) (a) Ogihara, Y.; Kobayashi, N.; Shibata, S. *Tetrahedron Lett.* **1968**, 1881−1886. (b) Shibata, S. *Pure Appl. Chem.* **1973**, *33*, 109−128. (c) Takeda, N.; Seo, S.; Ogihara, Y.; Sankawa, U.; Iitaka, I.; Kitagawa, I.; Shibata, S. *Tetrahedron* **1973**, *29*, 3703−3719. (d) Seo, S.; Sankawa, U.; Ogihara, Y.; Iitaka, Y.; Shibata, S. *Tetrahedron* **1973**, *29*, 3721−3726. (e) Yang, D.-M.; Sankawa, U.; Ebizuka, Y.; Shibata, S. *Tetrahedron* **1976**, *32*, 333−335.

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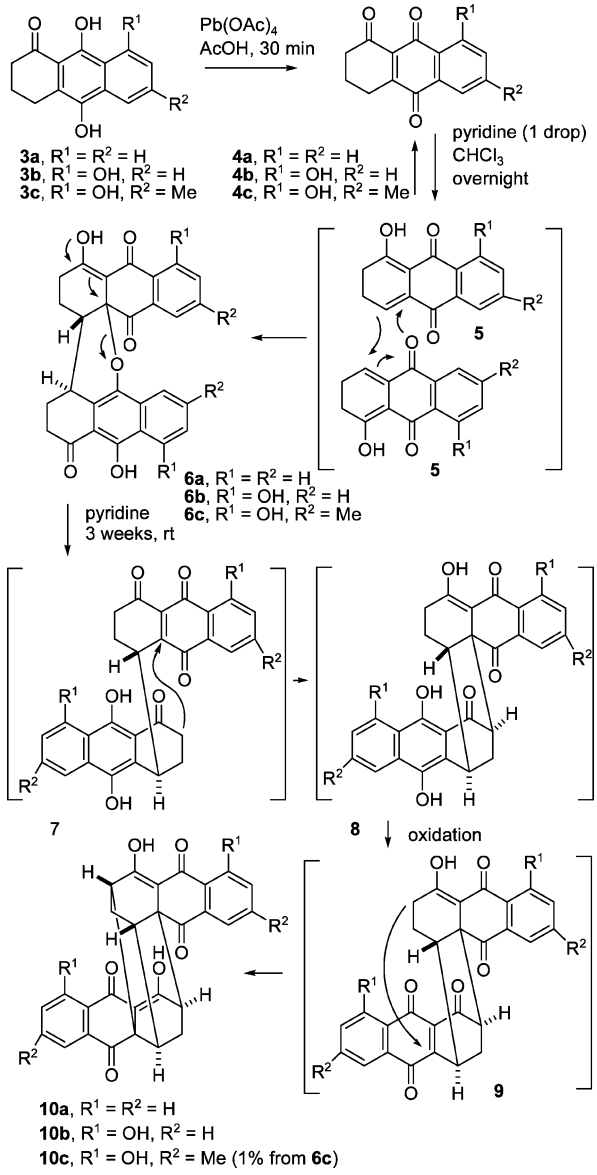
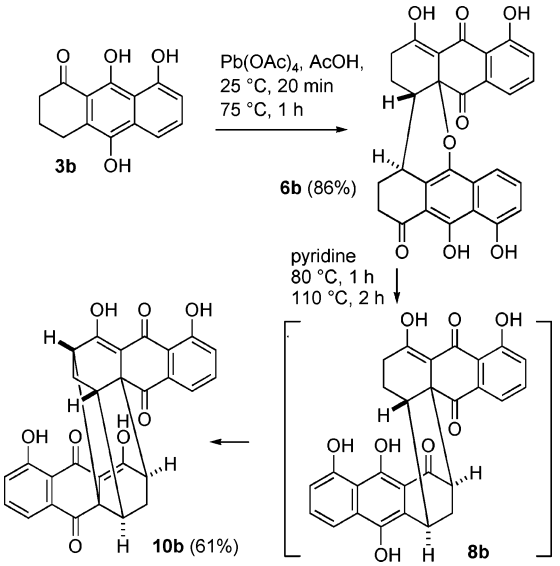
SCHEME 1. Shibata's Synthesis of Rugulosin Model 10



Results and Discussion

We started by optimizing this route to rugulosin analogues. Oxidation of **3b**[6] with $Pb(OAc)_4$ in AcOH for 20 min at 25 °C generated orange quinone **4b**. Solid **4b** cleanly formed yellow **6b** on standing for 1−2 months. More efficiently, simply reacting **3b** with $Pb(OAc)_4$ in AcOH for 20 min at 25 °C to form **4b** and then heating for 1 h at 75 °C effected enolization to give **5b** and Diels−Alder dimerization of **5b** to give a very satisfying 86% yield of flavoskyrin-type dimer **6b** from **3b** (see Scheme 2). All of the dimers in this series decompose and streak on silica gel. Chromatography has traditionally been carried out on silica gel impregnated with oxalic acid.[1a] Dimer **6b** precipitates out of hot AcOH as it is formed and can be isolated in pure form simply by filtration and washing with AcOH.

SCHEME 2. Improved Route to Rugulosin Model 10b



Heating a solution of **6b** in pyridine under air for 1 h at 80 °C provided mainly **8b**. The temperature was increased to 110 °C and heating was continued for 2 h, resulting in oxidation to the quinone and the second Michael addition. Concentration under reduced pressure and chromatography on silica gel impregnated with 10% oxalic acid provided rugulosin analogue **10b** in 61% yield with spectral data that corresponded well with those reported for the natural products.[1−3,7] This sequence provides a practical route to **10b** in 52% overall yield.

The remaining problem was the preparation of **14** with an R group that could be converted to a hydroxy group after dimerization. Nature apparently carries out the dimerization sequence with a hydroxy group present, possibly by reduction of emodin.[8] However, under laboratory conditions, **14**, R = OH, would simply dehydrate and tautomerize to the phenol. We initially considered that a $SiMe_2Ph$ group would be a suitable latent hydroxy group since it can be converted to an alcohol by a Fleming−Tamao oxidation. Condensation[9,10] of racemic 5-dimethyphenylsilyl-2-cyclohexenone (**11a**)[11] with cyanophthalide **12**[10c] using *t*-BuOK in DMSO afforded **13a** in a highly variable 10−60% yield (see Scheme 3). Unfortunately, oxidation of **13a** with $Pb(OAc)_4$ to the quinone also oxidatively cleaved the silyl group generating a phenol. As expected, the base-catalyzed formation of **13b** from **12** and racemic 5-benzyloxy-2-cyclohexenone

(6) Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Gordon, P. N.; Pilgrim, F. J.; Brunings, K. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 5455−5475.

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(9) For a review of annulations of phthalides with cyclohexenones leading to the anthracenes, see: Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1995**, *51*, 5207−5236.

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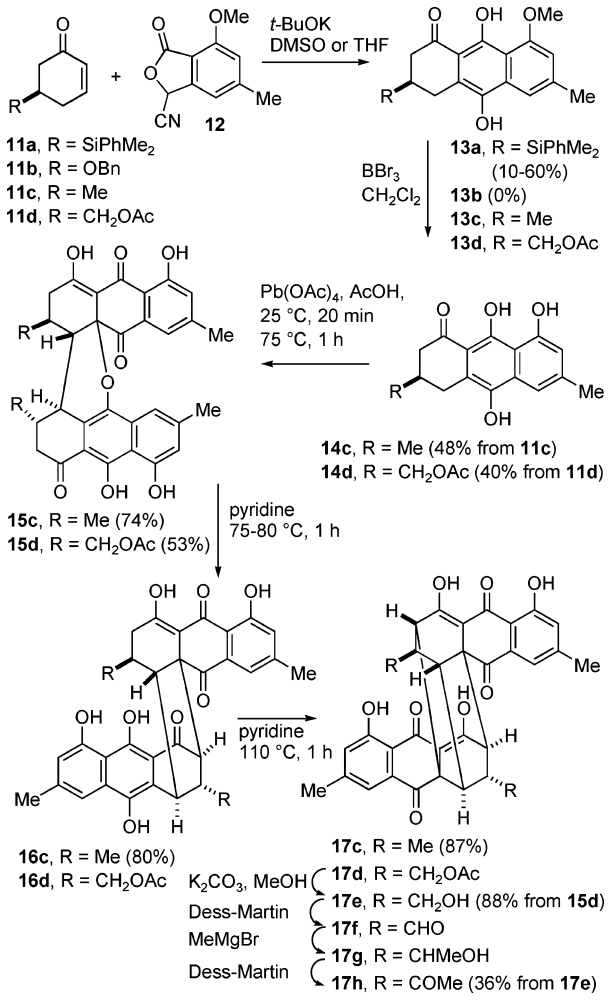
(11) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811−814.

SCHEME 3. Preparation of Rugulosin Model 17



(**11b**)[12] was unsuccessful; elimination of benzyl alcohol occurred leading to the formation of phenol.

We then decided to confirm the validity of this approach by using racemic 5-methyl-2-cyclohexenone (**11c**), which would establish the effect of a substituent on the saturated ring on the dimerization. Condensation of **11c**[13] with cyanophthalide **12**[10c] using *t*-BuOK in DMSO provided crude **13c**, which was demethylated with BBr_3 in CH_2Cl_2 at −78 to 25 °C for 3 h to afford a 48% overall yield of **14c**. Oxidation of **14c** with $Pb(OAc)_4$ in AcOH at 25 °C for 20 min and 1 h at 75 °C afforded 74% of the desired flavoskyrin-type dimer **15c** as a single diastereomer that precipitated from AcOH. The stereochemistry could not be assigned at this point because of the complexity of the spectrum of the unsymmetrical dimer. No precipitate formed on oxidation of the less polar methyl ether **13c**, making purification and analysis difficult.

A suspension of **15c** in pyridine was stirred for 1 h at 75 °C and concentrated. Chromatography on silica gel impregnated with 10% oxalic acid provided 80% of a single rubroskyrin-type dimer **16c**, whose stereochemistry could also not be easily determined. Finally, heating **16c** in pyridine under air at 85−110 °C for 1 h resulted in oxidation and Michael addition to give a quantitative yield of symmetrical dimer **17c** that was recrystallized (87%) from acetone. The stereochemistry of **17c** and, by inference, **15c** and **16c** was established by analysis of the coupling constants. In rugulosin the coupling constant between H_a and H_b is 5.5 Hz, whereas that between H_b and H_c is 0 Hz.[1] In graciliformin (**2a**) and cytoskyrin A (**2b**) both coupling constants are 0 Hz.[3,4] In dimer **17c**, the coupling constant between H_a and H_b is 4.9 Hz, whereas that between H_b and H_c is 0 Hz, indicating that **17c** has the rugulosin stereochemistry with exo methyl groups.

The Diels−Alder reaction occurred preferentially as expected on the faces opposite the methyl substituent to give **15c**. It is noteworthy that only one of four possible stereoisomers was formed from racemic **14c**. Like enantiomers can dimerize to give **15c** or the diastereomer with the opposite stereochemistry at both methyl groups. Unlike enantiomers can dimerize to give diastereomers with opposite stereochemistry at one methyl group. Apparently, the steric effect of the methyl substituent is sufficient that only like enantiomers dimerize to give **15c**.

We then examined a similar sequence starting with racemic 5-acetoxymethyl-2-cyclohexenone (**11d**)[14] with the hope that a Baeyer−Villiger oxidation would introduce the desired hydroxy group. Analogous condensation of **11d** and **12** afforded **13d**, which was deprotected to provide a 40% overall yield of **14d**. Oxidation of **14d** with $Pb(OAc)_4$ gave 53% of flavoskyrin-type dimer **15d**. Heating **15d** in pyridine at 80 to 110 °C afforded symmetrical dimer **17d**, which was hydrolyzed with K_2CO_3 in MeOH to afford diol **17e** in 88% overall yield from **15d**. Oxidation of **17e** with Dess−Martin periodinane afforded the unstable bis aldehyde **17f**. Addition of **17f** to MeMgBr in THF afforded bis secondary alcohol **17g**, which was oxidized to the bis methyl ketone **17h** in 36% overall yield from diol **17e**.

Unfortunately, all attempts to effect a Baeyer−Villiger oxidation of **17f** or **17h** with *m*-CPBA were unsuccessful. Complex mixtures were obtained; analysis of the NMR spectra suggested that oxidation had occurred at the *β*-hydroxyenone moiety rather than the desired formyl or acetyl groups. This was confirmed by oxidizing the simpler and more readily available model **10b** with *m*-CPBA and $NaHCO_3$ in $CHCl_3$ for 1 h to give 33% of monohydroxylated dimer **18** after careful chromatography on oxalic acid impregnated silica gel (see Scheme 4). The spectral data for **18** are analogous to those of the natural products cytoskyrin B (**20**)[4] and hydroxyrugulosin (**19**),[1c] which has been prepared by oxidation of rugulosin (**1**) with CF_3CO_3H.[1c]

Oxidation of **10b** with Oxone and HCl in DMF inadvertently generated chlorine in situ,[15] which added to both *β*-hydroxyenones to give 71% of the bis α-chlorodione **21** (see Scheme 5). Heating **21** with activated charcoal in $CHCl_3$ at reflux for 30 min apparently effected reduction to give **22**, which underwent an intramolecular substitution to give **23**, in which the original anthracenes

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(13) Chong, B.-D.; Ji, Y.-I.; Oh, S.-S.; Yang, J.-D.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323−9325.
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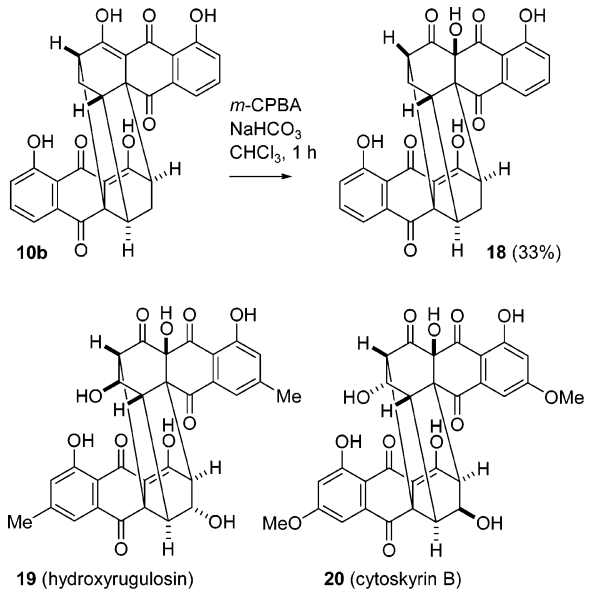
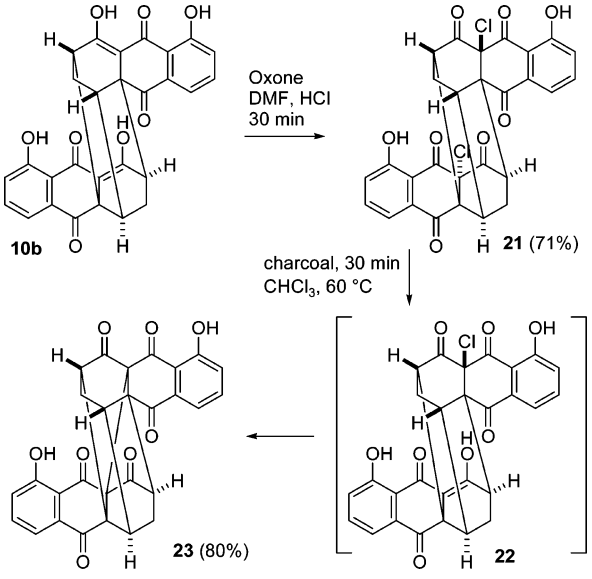
(15) Dieter, R. K.; Nice, L. E.; Velu, S. E. *Tetrahedron Lett.* **1996**, *37*, 2377−2380.

SCHEME 4. Hydroxylation of 10b



are now linked by four carbon−carbon bonds. No reaction occurs in the absence of activated charcoal, indicating that it is necessary for the reduction.[16] Oxidation of rugulosin (**1**) with MnO_2 gave dehydrorugulosin with the same ring system as **23** in unspecified yield.[1c] No reaction occurred on treatment of **10b** with MnO_2. Dehydrorugulosin and **23** are easily characterized by the shift of a carbonyl absorption to higher frequency at 1760 cm^{-1} since formation of the fourth carbon−carbon link results in the formation of a cyclopentanone. The structure of rugulin, a natural product reported to have this ring system[17] that does not have an IR absorption above 1720 cm^{-1}, may have been misassigned.

SCHEME 5. Formation of Quadruple Linked Dimer 23



In conclusion, we have developed a practical two-step sequence to rugulosin analogues. Oxidation of **3b** or **14c,d** with $Pb(OAc)_4$ in AcOH for 20 min at 25 °C and 1 h at 75 °C gave flavoskyrin-type dimers **6b** and **15c,d** in 53−86% yield. Heating a solution of **6b** or **15c,d** in pyridine under air for 1 h at 75−80 °C and 1−2 h at 110 °C afforded rugulosin-type dimers **10b** and **17c,d** in 61−88% yield.

Experimental Section

General Procedures. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ, coupling constants in Hz, and IR spectra in cm^{-1}. 10% Oxalic acid impregnated silica gel was prepared by adding 100 g of silica gel to a solution of 10 g of oxalic acid in 200 mL of MeOH and concentrating the resulting suspension to dryness under reduced pressure.

8,9,10-Trihydroxy-1,2,3,4-tetrahydroanthracene-1-one (3b).[6] A solution of 1,8-dihydroxyanthraquinone (3 g, 12.49 mmol) in 50 mL of 4% aqueous NaOH solution was hydrogenated over 0.5 g of Pd/C catalyst in a Parr shaker at 50 psi for 2.5 h. The resulting mixture was filtered rapidly into 2 M aqueous HCl solution (30 mL) and the crystalline product was recrystallized from the aqueous acetone (charcoal) to yield 1.63 g (54%) of **3b** as brown needles: ^{1}H NMR 15.89 (s, 1, OH), 9.87 (s, 1, OH), 7.55 (dd, 1, J = 8.0, 7.9), 7.47 (d, 1, J = 7.9), 6.90 (d, 1, J = 8.0), 4.62 (s, 1, OH), 2.94 (t, 2, J = 6.1), 2.76 (t, 2, J = 6.1), 2.17 (tt, 2, J = 6.1, 6.1).

3a,3b,4,5-Tetrahydro-1,7,8,17-tetrahydroxy-2*H*-dibenzo[*c*,*mn*]naphtho[2,3-*g*]xanthene-6,13,18(3*H*)-trione (6b). To a stirred suspension of **3b** (300 mg, 1.23 mmol) in 7 mL of acetic acid was added $Pb(OAc)_4$ (545 mg, 1.23 mmol) in one portion at 25 °C. The yellow suspension became a clear orange solution. The reaction mixture was stirred at 25 °C for 20 min, warmed to 75 °C, and stirred for another 20 min. A yellow precipitate formed from the hot AcOH solution. After stirring at 75 °C for another 40 min, the yellow precipitate was filtered and washed with AcOH to give 257 mg (86%) of flavoskyrin-type dimer **6b** as a mustard-colored fine solid: mp 193 °C (dec); ^{1}H NMR 15.87 (s, 1, OH), 14.58 (s, 1, OH), 11.52 (s, 1, OH), 9.76 (s, 1, OH), 7.18 (dd, 1, J = 8.0, 8.0), 7.133 (d, 1, J = 8.0), 7.129 (dd, 1, J = 8.0, 8.0), 6.73 (d, 1, J = 8.0), 6.63 (d, 1, J = 8.0), 6.47 (d, 1, J = 8.0), 2.56−2.91 (m, 7), 2.12−2.29 (m, 3); ^{13}C NMR 203.5, 195.8, 193.1, 183.4, 161.9, 160.6, 158.0, 138.9, 136.3, 135.6, 132.4, 132.0, 123.1, 122.1, 118.1, 115.9, 112.3, 111.6, 111.4, 107.8, 105.8, 81.5, 39.0, 38.1, 37.9, 29.8, 29.2, 25.3; IR (KBr) 3387, 2937, 1714, 1617, 1584.

1,7,9,15-Tetrahydroxy-5*H*,6*H*-6,13a,5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,16(14*H*)-tetrone (10b). A suspension of **6b** (160 mg, 0.33 mmol) in dry pyridine (10 mL) was stirred at 80 °C for 1 h under air and the reaction mixture became a homogeneous light brown solution. The ^{1}H NMR spectra showed the formation of a mixture a rubroskyrin-type dimer **8b** and symmetrical dimer **10b**. The resulting mixture was stirred at 110 °C for another 2 h. Removal of the pyridine under reduced pressure gave crude **10b** (185 mg, 116%) as a brown solid. Flash chromatography on 10% oxalic acid impregnated silica gel (20:1 hexanes/EtOAc) gave a mixture of **10b** and oxalic acid, which was diluted with CH_2Cl_2, washed with H_2O, brine, dried (Na_2SO_4) and concentrated to give 97 mg (61%) of **10b** as a yellow solid: mp 260 °C; ^{1}H NMR 14.82 (s, 2, OH), 11.72 (s, 2, OH), 7.62−7.68 (m, 4), 7.27 (dd, 2, J = 7.5, 1.8), 3.67 (br s, 2), 2.95 (d, 2, J = 4.9), 2.17 (ddd, 2, J = 12.8, 4.9, 1.2), 1.61 (d, 2, J = 12.8); ^{13}C NMR 194.4 (2 C), 188.0 (2 C), 186.5 (2 C), 161.6 (2 C), 136.2 (2 C), 132.2 (2 C), 124.5 (2 C), 119.7 (2 C), 116.6 (2 C), 105.3 (2 C), 58.6 (2 C), 54.9 (2 C), 48.0 (2 C), 29.9 (2 C); IR (KBr) 1686, 1613, 1577, 1458.

3,4-Dihydro-9,10-dihydroxy-8-methoxy-3,6-dimethyl-1(2*H*)-anthracenone (13c). A solution of 5-methyl-2-cyclohexenone (**11c**)[13] (120 mg, 1.09 mmol) and **12**[10c] (221 mg, 1.09 mmol) in dry DMSO (5 mL) was cooled to 0 °C and treated with *t*-BuOK (1.0 M in THF, 3.27 mL, 3.27 mmol). The

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resulting mixture was allowed to warm to at 25 °C, stirred for 50 min and acidified with 3 M aqueous HCl solution. The solution was diluted with ether (180 mL), washed with H_2O and brine, dried (Na_2SO_4) and concentrated to give 420 mg (135%) of crude **13c** as a yellow solid, which was used in the next step without further purification. Pure **13c** can be obtained by washing with CH_2Cl_2 (5 × 3 mL) and drying the remaining bright yellow fine solid under vacuum: mp 189−191 °C; ^{1}H NMR 14.92 (s, 2, OH), 7.42 (s, 1), 6.70 (s, 1), 4.01 (s, 3), 3.11 (br dd, 1, J = 15.8, 2.4), 2.74 (ddd, 1, J = 15.8, 3.7, 1.8), 2.50 (s, 3), 2.43 (dd, 1, J = 15.8, 10.4), 2.41 (dd, 1, J = 15.8, 9.8), 2.24−2.34 (m, 1), 1.15 (d, 3, J = 6.7); ^{13}C NMR 204.0, 160.8, 159.8, 141.8, 137.7, 132.6, 119.4, 113.3, 112.9, 109.6, 108.2, 56.1, 46.3, 31.4, 28.9, 22.6, 21.4; IR (KBr) 3509, 1618, 1584.

3,4-Dihydro-8,9,10-trihydroxy-3,6-dimethyl-1(2*H*)-anthracenone (14c). To a stirred solution of crude **13c** (420 mg) in dry CH_2Cl_2 (150 mL) at −78 °C was added a solution of BBr_3 (1.0 M in CH_2Cl_2, 5.45 mL, 5.45 mmol). The reaction mixture was stirred at −78 to 25 °C for 3 h, cooled to 0 °C, and treated with saturated aqueous $NaHCO_3$ solution. The resulting mixture was stirred at 0 °C for 30 min and acidified with 3 M aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a brownish yellow solid (400 mg). The crude product was washed with CH_2Cl_2 (5 × 3 mL), and the remaining orange solid was dried under vacuum to give 98 mg of pure **14c**. The CH_2Cl_2 wash was combined and concentrated to give a brown residue that was purified by flash chromatography on methanol-deactivated silica gel (10:1 hexanes/EtOAc) to give another 44 mg (48% combined yield for two steps) of **14c** as an orange solid: mp 196−198 °C; ^{1}H NMR 15.87 (s, 2, OH), 9.88 (s, 1, OH), 7.25 (s, 1), 6.75 (s, 1), 3.12 (br dd, 1, J = 15.8, 2.4), 2.76 (br dd, 1, J = 15.8, 1.8), 2.47 (s, 3), 2.40−2.45 (m, 2), 2.24−2.37 (m, 1), 1.20 (d, 3, J = 6.7); ^{13}C NMR 204.1, 160.7, 158.2, 143.7, 138.5, 131.7, 117.6, 113.1, 111.6, 110.9, 108.4, 45.5, 31.0, 29.1, 22.4, 21.4; IR (KBr) 3458, 2955, 1643, 1618, 1518, 1404.

3a,3b,4,5-Tetrahydro-1,7,8,17-tetrahydroxy-3,4,10,15-tetramethyl-2*H*-dibenzo[*c*,*mn*]naphtho[2,3-*g*]xanthene-6,13,18(3*H*)-trione (15c). To a stirred suspension of methyl ketone **14c** (115 mg, 0.42 mmol) in AcOH (1.5 mL) at 25 °C was added a suspension of $Pb(OAc)_4$ (187 mg, 0.42 mmol) in 2.5 mL of AcOH. The yellow suspension became a clear orange solution. After stirring at 25 °C for 20 min, the reaction mixture was warmed to 75 °C and stirred for another 20 min with the formation of a yellow precipitate. The solution was stirred at 75 °C for another 40 min and the yellow precipitate was filtered and washed with AcOH to give 84 mg (74%) of flavoskyrin-type dimer **15c** as a yellow fine solid: mp 201 °C; ^{1}H NMR 16.18 (s, 1, OH), 14.55 (s, 1, OH), 11.31 (s, 1, OH), 9.75 (s, 1, OH), 6.91 (s, 1), 6.60 (s, 1), 6.45 (s, 1), 6.15 (s, 1), 2.11−2.86 (m, 8), 2.15 (s, 3), 2.00 (s, 3), 1.31 (d, 3, J = 5.5), 1.30 (d, 3, J = 5.5); IR (KBr) 3356, 1715, 1619, 1585; ^{13}C NMR data are not available because **15c** is not stable in solution.

7,8,8a,9-Tetrahydro-4,6,10,14,15-pentahydroxy-2,8,12,19-tetramethyl-9,17-methanonaphtho[2′,3′:5,6]cyclohept-[1,2-*d*]anthracene-5,16,18(17*H*)-trione (16c). A suspension of dimer **15c** (60 mg, 0.11 mmol) in dry pyridine (10 mL) was stirred at 75 °C for 1 h under air and concentrated to give a light brown solid. Flash chromatography on 10% oxalic acid impregnated silica gel (10:1 to 6:1 hexanes/EtOAc) gave a mixture of dimer **16c** and oxalic acid, which was diluted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4) and concentrated to give 48 mg (80%) of **16c** as a rust-colored solid: mp 197−199 °C; ^{1}H NMR 14.85 (s, 1, OH), 14.23 (s, 1, OH), 12.00 (s, 1, OH), 9.63 (s, 1, OH), 7.38 (s, 1), 7.22 (s, 1), 7.08 (s, 1), 6.82 (s, 1), 4.74 (s, 1, OH), 3.89 (dd, 1, J = 6.1, 4.3), 3.87 (d, 1, J = 6.1), 2.92 (d, 1, J = 3.7), 2.54 (ddq, 1, J = 3.7, 4.3, 6.7), 2.50 (s, 3), 2.45 (s, 3), 2.33 (1, dq, J = 6.7, 6.7), 1.58 (d, 1, J = 18.9), 1.17 (dd, 1, J = 18.9, 6.7), 0.90 (d, 3, J = 6.7), 0.83 (d, 3, J = 6.7); ^{13}C NMR 202.5, 195.6, 190.7, 178.2, 162.2, 159.6, 158.5, 148.1, 144.3, 140.3, 133.0, 131.5, 124.0, 120.4, 118.9, 114.6, 113.9, 111.6, 111.0, 107.7, 103.9, 63.4, 57.8, 45.0, 44.9, 39.4, 33.6, 27.2, 22.6, 22.5, 22.1, 11.8; IR (KBr) 3427, 2955, 2929, 1699, 1620, 1572; HRMS (FAB) calcd for $C_{32}H_{28}O_8$ (M^+) 540.1784, found 540.1809.

(5a*R,6*S*,13a*R*,14*S*,17*S*,18*S*,19*S*,20*S*)-1,7,9,15-Tetrahydroxy-3,11,17,20-tetramethyl-5*H*,6*H*-6,13a,5a,14-[1,2,3,4]-butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,16(14*H*)-tetrone (17c).** A solution of **16c** (30 mg, 0.06 mmol) in 4 mL of pyridine was stirred at 85−110 °C under air for 1 h and concentrated to give 40 mg (134%) of **17c** containing some pyridine residue as a light brown solid. Recrystallization from acetone gave 26 mg (87%) of pure **17c** as a peach-colored solid: mp 260 °C (dec); ^{1}H NMR 14.79 (s, 2, OH), 11.72 (s, 2, OH), 7.49 (s, 2), 7.09 (s, 2), 3.41 (s, 2), 2.78 (d, 2, J = 4.9), 2.60 (dq, 2, J = 4.9, 6.7), 2.45 (s, 6), 0.85 (d, 6, J = 6.7); ^{13}C NMR 194.6 (2 C), 185.7 (2 C), 183.3 (2 C), 161.8 (2 C), 148.0 (2 C), 132.2 (2 C), 124.3 (2 C), 120.8 (2 C), 114.7 (2 C), 105.8 (2 C), 59.2 (2 C), 58.3 (2 C), 52.5 (2 C), 34.6 (2 C), 22.1 (2 C), 13.6 (2 C); IR (KBr) 1687, 1610, 1577; HRMS (FAB) calcd for $C_{32}H_{27}O_8$ (MH^+) 539.1706, found 539.1706.

3-Acetoxymethyl-3,4-dihydro-9,10-dihydroxy-8-methoxy-6-methyl-1(2*H*)-anthracenone (13d). To a stirred solution of *t*-BuOK (1.0 M in THF, 7.8 mL, 7.8 mmol) in 8 mL of dry THF at −78 °C was added a solution of cyanophthalide **12**[10c] (530 mg, 2.61 mmol) in 5 mL of dry THF over 15 min. The resulting mixture was stirred at −78 °C for 30 min and a solution of 5-acetoxymethyl-2-cyclohexenone (**11d**)[14] (500 mg, 2.98 mmol) in dry THF (3 mL) was added. The reaction mixture was stirred at −78 °C for 1 h, warmed to 0 °C and stirred for another 1 h. Aqueous HCl solution (3 M) was added to quench the reaction. The reaction mixture was diluted with EtOAc (120 mL), washed with H_2O and brine, dried (Na_2SO_4) and concentrated to give 1.19 g (133%) of crude **13d** as a yellow solid, which was used in the next step without further purification. Pure **13d** can be obtained by washing with CH_2Cl_2 (5 × 5 mL) to give a bright yellow fine solid that was dried under vacuum: mp 202−204 °C; ^{1}H NMR (DMSO-d_6) 14.62 (s, 1, OH), 8.47 (s, 1, OH), 7.51 (s, 1), 6.81 (s, 1), 4.07 (d, 2, J = 6.1), 3.88 (s, 3), 3.23 (br d, 1, J = 15.8), 2.50−2.73 (m, 3), 2.46 (s, 3), 2.35−2.47 (m, 1), 2.06 (s, 3); ^{13}C NMR (DMSO-d_6) 203.6, 170.4, 159.5, 159.4, 141.1, 138.7, 133.9, 120.1, 113.6, 112.5, 109.7, 108.1, 66.8, 55.8, 40.6, 33.0, 26.2, 22.1, 20.7; IR (KBr) 3315, 2954, 1738, 1590; HRMS (DEI) calcd for $C_{19}H_{20}O_6$ (M^+) 344.1260, found 344.1257.

3-Acetoxymethyl-3,4-dihydro-8,9,10-trihydroxy-6-methyl-1(2*H*)-anthracenone (14d). To a stirred solution of crude acetoxymethyl ketone **13d** (1.9 g) in dry CH_2Cl_2 (400 mL) at −78 °C was added a solution of BBr_3 (1.0 M in CH_2Cl_2, 13.5 mL, 13.5 mmol). The reaction mixture was stirred at −78 °C for 1 h and at 0 °C for 16 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, stirred at 0 °C for 30 min, and acidified by 3 M aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a brownish yellow solid. The crude product was washed with acetone (5 × 5 mL) and the remaining orange solid was dried under vacuum to give 212 mg of pure **14d**. The CH_2Cl_2 wash was combined and concentrated to give a brown residue that was purified by flash chromatography on methanol-deactivated silica gel (4:1 to 2:1 hexanes/EtOAc) to give another 132 mg of **14d** (40% combined yield for two steps) as an orange solid: mp 209−211 °C; ^{1}H NMR (DMSO-d_6) 15.59 (s, 1, OH), 9.78 (s, 1, OH), 8.63 (s, 1, OH), 7.41 (s, 1), 6.69 (s, 1), 4.08 (d, 2, J = 6.1), 3.23 (dd, 1, J = 15.8, 3.0), 2.54−2.76 (m, 3), 2.41−2.47 (m, 1), 2.41 (s, 3), 2.06 (s, 3); ^{13}C NMR (DMSO-d_6) 204.0, 170.4, 158.9, 157.2, 142.3, 139.6, 133.2, 118.7, 112.9, 112.4, 110.4, 108.8, 66.7, 39.9, 33.1, 25.9, 21.9, 20.7; IR (KBr) 3421, 2969, 1723, 1636, 1616; HRMS (DEI) calcd for $C_{18}H_{18}O_6$ (M^+) 330.1103, found 330.1113.

3,4-Bisacetoxymethyl-3a,3b,4,5-tetrahydro-1,7,8,17-tetrahydroxy-10,15-dimethyl-2*H*-dibenzo[*c*,*mn*]naphtho-[2,3-*g*]xanthene-6,13,18(3*H*)-trione (15d). To a stirred suspension of **14d** (673 mg, 2.04 mmol) in AcOH (5 mL) at 25 °C was added $Pb(OAc)_4$ (904 mg, 2.04 mmol) in one portion. The yellow suspension became a clear orange solution. After stirring at 25 °C for 20 min, the reaction mixture was warmed to 75 °C and stirred for another 20 min, and a yellow precipitate started to form. After stirring at 75 °C for another 40 min, the yellow precipitate was filtered and washed with AcOH to give 355 mg (53%) of flavoskyrin-type dimer **15d** as a bright yellow fine solid: mp 178−180 °C; ^{1}H NMR 16.20 (s, 1, OH), 14.60 (s, 1, OH), 11.29 (s, 1, OH), 9.73 (s, 1, OH), 6.92 (s, 1), 6.62 (s, 1), 6.49 (s, 1), 6.18 (s, 1), 4.58 (dd, 2, J = 11.6, 3.1), 4.18 (dd, J = 11.6, 5.5), 4.11 (dd, J = 11.6, 5.5), 3.00−3.10 (m, 1), 2.89−2.96 (m, 3), 2.62−2.78 (m, 3), 2.46−2.56 (m, 1), 2.16 (s, 9), 2.02 (s, 3); IR (KBr) 3387, 1746, 1711, 1621, 1588; HRMS (FAB) calcd for $C_{36}H_{33}O_{12}$ (MH^+) 657.1972, found 657.1964; ^{13}C NMR data are not available because **16d** is not stable in solution.

(5a*R,6*S*,13a*R*,14*S*,17*S*,18*S*,19*S*,20*S*)-17,20-Bisacetoxymethyl-1,7,9,15-tetrahydroxy-3,11-dimethyl-5*H*,6*H*-6,13a,-5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,16(14*H*)-tetrone (17d).** A suspension of **15d** (145 mg, 0.22 mmol) in dry pyridine (10 mL) was stirred at 80 °C for 1 h under air giving a homogeneous light brown solution. ^{1}H NMR spectra showed the formation of a mixture a rubroskyrin-type dimer **16d** and symmetrical dimer **17d**. The reaction mixture was stirred at 110 °C for another 1 h. Removal of pyridine gave **17d** and some pyridine residue (156 mg, 108%) as a brown solid, which was used in the next step without further purification. Pure **17d** can be obtained by recrystallization from acetone giving orange crystals: mp 260 °C (dec); ^{1}H NMR 14.56 (s, 2, OH), 11.71 (s, 2, OH), 7.52 (s, 2), 7.12 (s, 2), 3.99 (dd, 2, J = 11.6, 7.3), 3.80 (dd, 2, J = 11.6, 7.9), 3.57 (br s, 2), 2.95 (dd, 2, J = 5.5, 1.2), 2.79−2.84 (m, 2), 2.46 (s, 6), 1.95 (s, 6); ^{13}C NMR 193.5 (2 C), 186.6 (2 C), 181.1 (2 C), 170.6 (2 C), 162.1 (2 C), 148.6 (2 C), 131.8 (2 C), 124.6 (2 C), 121.2 (2 C), 114.4 (2 C), 105.5 (2 C), 62.4 (2 C), 58.0 (2 C), 55.9 (2 C), 48.7 (2 C), 39.6 (2 C), 22.2 (2 C), 20.6 (2 C); IR (KBr) 1743, 1686, 1614, 1572; HRMS (FAB) calcd for $C_{36}H_{31}O_{12}$ (MH^+) 655.1856, found 655.1845.

(5a*R,6*S*,13a*R*,14*S*,17*S*,18*S*,19*S*,20*S*)-1,7,9,15-Tetrahydroxy-17,20-dihydroxymethyl-3,11-dimethyl-5*H*,6*H*-6,-13a,5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,16(14*H*)-tetrone (17e).** To a stirred solution of crude **17d** (156 mg) in MeOH (6 mL) was added K_2CO_3 (304 mg, 2.2 mmol). The reaction mixture turned brown. The resulting mixture was stirred at 25 °C for 2 h and quenched with 3 M aqueous HCl solution. The yellow solid that precipitated from the reaction mixture was filtered, washed with H_2O, and dried under vacuum to give 110 mg (88% from **15d**) of diol **17e** as a yellow solid: mp 231−232 °C; ^{1}H NMR 14.63 (s, 2, OH), 11.71 (s, 2, OH), 7.48 (s, 2), 7.10 (s, 2), 3.580 (dd, 2, J = 11.0, 6.7), 3.575 (s, 2), 3.41 (dd, 2, J = 11.0, 8.6), 3.04 (d, 2, J = 5.5), 2.75 (ddd, 2, J = 8.6, 6.7, 5.5), 2.45 (s, 6); ^{13}C NMR 193.9 (2 C), 186.4 (2 C), 181.9 (2 C), 161.9 (2 C), 148.4 (2 C), 132.1 (2 C), 124.4 (2 C), 121.1 (2 C), 114.5 (2 C), 105.7 (2 C), 61.4 (2 C), 58.1 (2 C), 55.7 (2 C), 48.3 (2 C), 42.9 (2 C), 22.2 (2 C); IR (KBr) 3453, 2959, 1686, 1610, 1571; HRMS (FAB) calcd for $C_{32}H_{27}O_{10}$ (MH^+) 571.1604, found 571.1584.

(5a*R,6*S*,13a*R*,14*S*,17*S*,18*S*,19*S*,20*S*)-17,20-Diformyl-1,7,9,15-tetrahydroxy-3,11-dimethyl-5*H*,6*H*-6,13a,5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,16(14*H*)-tetrone (17f).** To a stirred solution of diol **17e** (27 mg, 0.047 mmol) was added Dess−Martin periodinane (40 mg, 0.095 mmol) in one portion. The reaction mixture was stirred at 25 °C for 1 h and concentrated to give a yellow solid (67 mg). The ^{1}H NMR spectra showed a quantitative conversion to bis aldehyde **17f** and byproduct from the Dess−Martin periodinane. The crude material was used in the next step without further purification. Pure **17f** can be obtained by recrystallization from $CHCl_3$: mp 230−231 °C; ^{1}H NMR 14.39 (s, 2, OH), 11.65 (s, 2, OH), 9.56 (s, 2), 7.58 (s, 2), 7.13 (s, 2), 4.00 (br s, 2), 3.43 (br d, 2, J = 5.5), 3.32 (d, 2, J = 5.5), 2.48 (s, 6); ^{13}C NMR 197.6 (2 C), 192.9 (2 C), 187.1 (2 C), 180.4 (2 C), 162.3 (2 C), 149.0 (2 C), 131.2 (2 C), 124.9 (2 C), 121.6 (2 C), 114.3 (2 C), 105.9 (2 C), 62.0 (2 C), 58.2 (2 C), 53.7 (2 C), 48.0 (2 C), 22.2 (2 C); IR (KBr) 3418, 1711, 1682, 1616, 1570; HRMS (FAB) calcd for $C_{32}H_{23}O_{10}$ (MH^+) 567.1291, found 567.1316.

(5a*R,6*S*,13a*R*,14*S*,17*S*,18*S*,19*S*,20*S*)-17,20-Diacetyl-1,7,9,15-tetrahydroxy-3,11-dimethyl-5*H*,6*H*-6,13a,5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,16(14*H*)-tetrone (17h).** To a stirred solution of MeMgBr (3.0 M in ether, 200 μL, 0.6 mmol) in dry THF (1 mL) at 0 °C was added a solution of crude **17f** (67 mg) in dry THF (2 mL) over 5 min. The resulting mixture was stirred at 0 °C for 30 min and quenched with 2 M aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvent gave crude **17g** as a brown residue that was dissolved in $CHCl_3$ (2 mL). Dess−Martin periodinane (40 mg, 0.095 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred at 25 °C for 2 h and concentrated to give brown residue, which was purified by flash chromatography on 10% oxalic acid impregnated silica gel (1:1 pentane/ether) to give a mixture of bis ketone **17h** and oxalic acid, which was diluted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4) and concentrated to give 10 mg (36% for 3 steps) of bis ketone **17h** as a yellow solid: ^{1}H NMR 14.39 (s, 2, OH), 11.68 (s, 2, OH), 7.61 (s, 2), 7.12 (s, 2), 3.84 (br s, 2), 3.43 (br d, 2, J = 5.5), 3.31 (d, 2, J = 5.5), 2.48 (s, 6), 2.00 (s, 6).

1,7,9,15a-Tetrahydroxy-5*H*,6*H*-6,13a,5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,8,13,-15,16(14*H*)-pentone (18). To a stirred solution of **10b** (35 mg, 0.073 mmol) in $CHCl_3$ (1 mL) was added solid $NaHCO_3$ (31 mg, 0.363 mmol) and *m*-CPBA (90%, 70 mg, 0.403 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h and concentrated to give an orange solid. Flash chromatography on 10% oxalic acid impregnated silica gel (8:1 to 4:1 hexanes/EtOAc) gave a mixture of **18** and oxalic acid, which was diluted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4) and concentrated to give 12 mg (33%) of **18** as a yellow solid: mp 241 °C; ^{1}H NMR 14.06 (s, 1, OH), 11.85 (s, 1, OH), 11.24 (s, 1, OH), 7.64−7.69 (m, 4), 7.28−7.32 (m, 2), 3.951 (br s, 1), 3.947 (s, 1, OH), 3.73 (br s, 1), 3.09 (d, 1, J = 4.9), 2.83 (d, 1, J = 4.9), 2.49 (d, J = 12.2), 2.17−2.23 (m, 2), 1.57 (d, 1, J = 12.2); ^{1}H NMR (DMSO-d_6) 14.15 (s, 1, OH), 11.84 (s, 1, OH), 11.12 (s, 1, OH), 7.79 (dd, 1, J = 8.0, 8.5), 7.76 (dd, 1, J = 8.0, 8.5), 7.59 (d, 1, J = 8.0), 7.56 (d, 1, J = 8.0), 7.38 (d, 1, J = 8.5), 7.35 (d, 1, J = 8.5), 3.74 (br s, 1), 3.52 (br s, 1), 2.86 (d, 1, J = 4.9), 2.74 (d, 1, J = 4.9), 2.35 (d, J = 12.2), 1.92−2.01 (m, 2), 1.64 (d, 1, J = 12.2); ^{13}C NMR 199.9, 194.1, 193.4, 193.1, 186.0, 183.1, 160.9, 160.7, 136.9, 136.5, 133.8, 132.7, 124.1, 123.8, 119.2, 118.6, 116.7, 115.7, 106.1, 75.2, 63.8, 59.9, 56.4, 51.3, 47.7, 44.6, 34.0, 26.0; IR (KBr) 3409, 2948, 1730, 1660, 1615, 1575, 1436; HRMS (FAB) calcd for $C_{28}H_{19}O_9$ (MH^+) 499.1029, found 499.1007.

7a,15a-Dichloro-1,9-dihydroxy-5*H*,6*H*-6,13a,5a,14-[1,2,3,4]butanetetraylcycloocta[1,2-*b*:5,6-*b*′]dinaphthalene-5,7,8,13,15,16(14*H*)-hexone (21). To a stirred solution of **10b** (31 mg, 0.064 mmol) in DMF (3 mL) was added Oxone (197 mg, 0.32 mmol) and 3 mL of 3 M aqueous HCl solution. The resulting reaction mixture was stirred at 25 °C for 30 min. The yellow solid that precipitated from the solution was filtered, washed with H_2O and dried under vacuum to give 25 mg (71%) of **21** as a pale yellow solid: mp 207 °C (dec); ^{1}H NMR 11.24 (s, 2, OH), 7.67−7.74 (m, 4), 7.38 (dd, 2, J = 7.9, 1.2), 4.12 (s, 2), 3.32 (d, 2, J = 4.3), 2.79 (d, 2, J = 13.4), 2.16 (dd, 2, J = 13.4, 4.3); ^{13}C NMR 195.4 (2 C), 189.5 (2 C), 187.7 (2 C), 163.3 (2 C), 137.3 (2 C), 131.7 (2 C), 125.8 (2 C), 120.1

(2 C), 113.7 (2 C), 62.5 (2 C), 61.7 (2 C), 57.7 (2 C), 44.9 (2 C), 29.7 (2 C); IR (KBr) 3397, 3174, 1741, 1705, 1665, 1603, 1578, 1454; MS (APCI) for $C_{28}H_{17}Cl_2O_8$ (MH^+) 551.

4,12-Dihydroxy-7,15a,7a,15-[1,2,3,4]butanetetrayl-7a*H*,-15a*H*-pentaleno[1,6*a*-*b*:3a,4-*b*′]dinaphthalene-5,6,8,13,14,-16(7*H*,15*H*)-hexone (23). To a stirred solution of **21** (20 mg, 0.036 mmol) in $CHCl_3$ (3 mL) was added activated charcoal and the reaction mixture was heated to 60 °C for 30 min. The solution was filtered through Celite and concentrated to give 14 mg (80%) of **23** as a pale yellow solid: mp 268 °C (dec); ^{1}H NMR 11.84 (s, 2, OH), 7.69 (dd, 2, J = 8.5, 7.3), 7.54 (dd, 2, J = 7.3, 1.2), 7.34 (dd, 2, J = 8.5, 1.2), 3.73 (s, 2), 3.12 (d, 2, J = 7.9), 2.82 (dd, 2, J = 14.0, 7.9), 2.31 (d, 2, J = 14.0); ^{13}C NMR 199.9 (2 C), 192.0 (2 C), 190.6 (2 C), 162.3 (2 C), 137.5 (2 C), 134.3 (2 C), 125.0 (2 C), 118.8 (2 C), 118.4 (2 C), 75.0 (2 C), 65.3 (2 C), 57.4 (2 C), 50.1(2 C), 38.5 (2 C); IR (KBr) 3401, 1762, 1687, 1634, 1454; HRMS (FAB) calcd for $C_{28}H_{17}O_8$ (MH^+) 481.0923, found 481.0935.

The coupling constant between H_a and H_b increases from 4.9 Hz in **10b** to 7.9 Hz in **23**. The same coupling constant increases from 5.5 Hz in **1** (rugulosin) to 7.5 Hz in dehydrorugulosin.[1c]

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Supporting Information Available: Experimental details for the preparation of **12**, a table of ^{13}C NMR spectra, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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