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A SIMPLE HIGH-YIELDING APPROACH TO PERYLENEQUINONE FROM THE NOVEL ONE-STEP DOUBLE COUPLING REACTION OF 1,2-NAPHTHOQUINONE

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Abstract: The transformation from 1,2-naphthoquinone to perylenequinone, which usually requires several steps, is stereoselectively realized *via* one step in excellent yield by a newly developed, double coupling method. The possible mechanism for this novel reaction and the properties of the resulting perylenequinone are discussed. Moreover, an improved procedure for the preparation of a 5-bromo-1,2-naphthalenediol, a reported coupling precursor to perylenequinone, is also described. These synthetic procedures open convenient ways to perylenequinone structures of significant biological potential.

Introduction

4,9-Dihydroxy-3,10-perylenequinones comprise a relatively small but growing group of chemically unique, biologically active, pigments obtainable from natural sources.[1] The natural perylenequinones of this class identified to date include hypocrellins, cercosporin, phleichrome, elsinochromes, cladochromes, erythroaphins and calphostins. Most of these natural pigments are produced by a wide variety of molds, and are the phytopathogen of their hosts. An exception is erythroaphins which occur in aphides.[1a] Weiss and Nasini have reviewed their general chemical properties,[1a] and we summarized their photosensitization reactions recently.[2] Recently considerable attention has been paid to the promising use of perylenequinonoid derivatives (especially hypocrellins) in the photodynamic therapy of human tumors.[2] In addition these versatile agents display some other important biological activities, including anti-cancer,[3a] anti-HIV[3b,d] and specific inhibition of protein kinase C,[3e,f] a key enzyme involved in cellular proliferation and differentation.[3g] These facts encouraged us to develop a convenient synthesis of functionalized perylenequinones.

Although, as early as in 1954, Calderbank *et al.* prepared 4,9-dihydroxy-3,10-perylenequinone, the parent compound of the natural perylenequinonoid pigments,[4] it was not until 1972 that Weisgraber and Weiss synthesized the first derivative of this class bearing methoxy groups, a characteristic substituent in natural perylenequinones, starting from commercial homoveratric acid.[5a] However they later modified the assigned perylenequinonoid structure to be dinaphthofuranedione.[5b,c] Only until recently, relatively few efforts have been devoted to the synthesis of perylenequinone structures. Dallacker and Leidig prepared a methoxylated perylenequinone but this compound still lacked some indispensable functionalized groups at appropriate positions.[6] Subsequently Chao and Zhang synthesized another perylenequinone bearing methoxy groups and acetic ester side chains in their correct positions by two different methods, which were then modified to provide natural perylenequinone.[7]

In the first route of Chao and Zhang, and in that of Dallacker and Leidig, a biphenyl, formed from an Ullmann coupling reaction, was elaborated into the desired pentacycle. The second route developed by Chao and Zhang utilized a double oxidative coupling reaction of a 5-bromo-1,2-naphthalenediol to generate the perylenequinonoid nucleus. However, the required 5-bromo-1,2-naphthalenediol in the second route of Chao and Zhang is difficult to prepare and readily decomposes (*vide infra*). An alternative route for the preparation of a 5-bromo-1,2-dioxygenated naphthalene was later developed by Coleman and Grant, based on a Diels-Alder [2+2] cyclo

addition but this naphthalene lacked the three carbon side chains found in natural perylenequinones.[8] Subsequently, a selective and stereospecific approach was developed for the total synthesis of phleichrome, the first successful synthesis of a natural perylenequinone. However, this approach requires at least twenty-six steps starting from commercially available reagents, and several of these steps require stringent experimental conditions.[9] Thus the procedure is inconvenient and ill-adapted for the preparation of various functionalized perylenequinones with different substituents at different positions. Therefore, we have reexamined and attempted to improve upon the double coupling method of Chao and Zhang to synthesize certain perylenequinones. During this research, we have developed a convenient and higher-yielding route to perylenequinones.

Results and Discussion

The Structures of Coupled Products of 1,2-Naphthoquinone

On the basis of the spectral data and specific chemical tests, the major coupled product of 1,2-naphthoquinone was identified to be compound **1**, which is a known compound isolated by Chao and Zhang but for which no structural data were reported.[7] The very strong 1594 cm^{-1} IR absorption band of this coupled

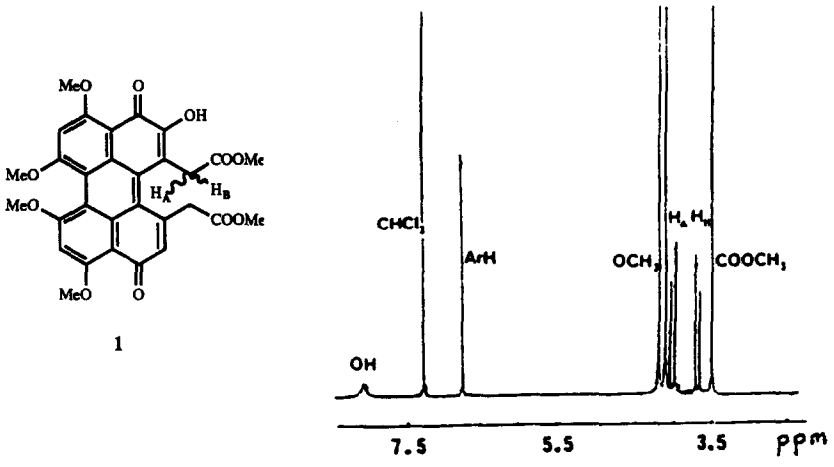

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Fig. 1. The structure and ^{1}H-NMR spectrum (in $CDCl_3$) of compound 1

product, similar to those of natural perylenequinones in position and shape, indicates this molecule contains perylenequinonoid carbonyl groups. The presence of phenolic hydroxy groups is evidenced by the broad 3260 cm^{-1} IR absorption band, the ^{1}H-NMR spectrum (Fig. 1) and D_2O exchange test and the large bathochromic shift of the UV-vis absorption band on addition of base (see Fig. 2). The positive coloration with ferric chloride (violet) and magnesium acetate (blue) together with complex formation with Zn^{2+}, Co^{2+}, Cu^{2+}, and Ni^{2+} suggest that the phenolic hydroxy of this compound is adjacent to quinonoid carbonyl group. This conclusion is supported by the low IR absorption wavelength number of the quinonoid carbonyl group and the characteristic high chemical shift of phenolic hydroxy proton (see **Fig. 1**) However, this signal (8.03 ppm), which is considerably higher in position than those of natural perylenequinones (about 16.00 ppm[10]), excludes the

presence of a *peri*-phenolic hydroxy-quinonoid carbonyl system, a very strong intramolecular hydrogen-bonding system common to natural perylenequinones. Both elemental analysis and mass spectrometric determination assign this major coupled product the molecular formula $C_{30}H_{26}O_{12}$. Thus the structure of this major product of the coupling reaction can be preliminarily ascribed to be compound **1**. This structure is finally confirmed by the ^{1}H-NMR spectrum (see **Fig. 1**) It is noteworthy that the existence of the quartet due to the methylene

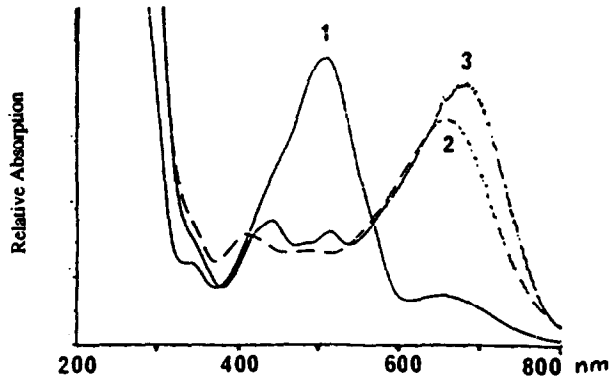


Fig. 2. The absorption spectra of compound 1 amd its magnesium ion complex in ethanol. 1. compound 1 (neutral); 2. compound 1 (basic); 3. Mg-compound 1 complex (neutral).

protons of the side chains of compound **1** are the result of the nonplanarity of the perylenequinonoid chromophore, which is characteristic of natural perylenequinones,[1a,10] and this provides further evidence for the assigned structure. On the basis of the comparison of the circular dichroism (CD) spectrum of compound **1** with those of cercosporin and hypocrellins, the twisted orientation of compound **1** was determined to be the left-hand helix shown in Fig. 3.[1,11] Only one diastereomer of **1** was isolated in 91% yield. As was found recently in a related coupling reaction involving chiral binaphthyl formation [9] no explanation can be offered for the surprisingly high diastereoselectivity exhibited by this coupling.

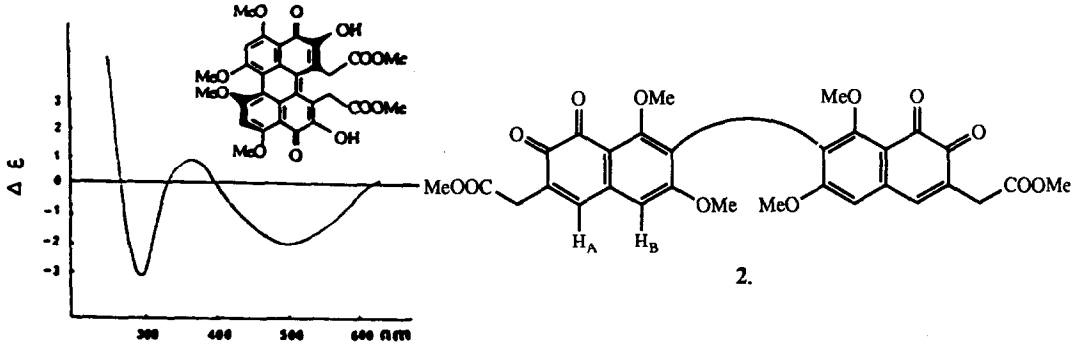


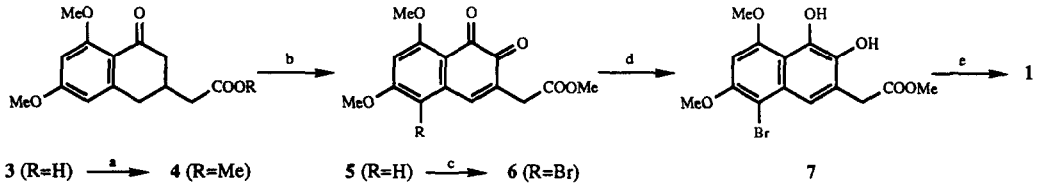
Fig. 3. The configuration and CD spectrum (in methanol) of compound 1.

In addition the structure of a minor coupled product was similarly determined to be compound **2**. Again the existence of the AB quartet arising from the *peri*-aromatic protons supports the assigned structure.[8]

Improved Double Oxidative Coupling Approach to Perylenequinones from 5-Bromo-1,2-naphthalenediol

In the course of reexamination and development of the double coupling approach of Chao and Zhang, we observed that a major limitation is the difficult separation of the desired dimethyl-3-(6-bromo-3,5-dimethoxybenzyl)glutarate from the other two undesired brominated products, *i.e.* dimethyl-3-(4-bromo-3,5-dimethoxybenzyl)glutarate and dimethyl-3-(2,6-dibromo-3,5-dimethylbenzyl)glutarate. This considerably complicates the required large-scale preparation of the desired brominated benzyl glutarate, which can be transformed into perylenequinone *via* at least eight steps.[7] Accordingly, we modified the bromination sequence to obtain the desired compound **7** by a more efficient procedure, which is summarized in Scheme 1. The improved procedure avoids the necessity for early use of chromatography for isolating the desired brominated precursors. This procedure provides compound **6** more conveniently and in fewer steps.

Scheme 1

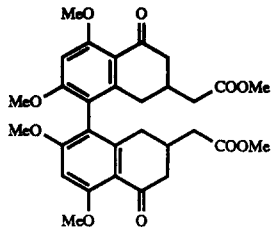


a. $MeOH/H_2SO_4$, reflux, 95%; b. SeO_2/HAc, 80-90°C, 71%; c. NBS/H_2SO_4/THF, RT, 41%; d. SO_2/MeOH-H_2O, reflux, 96%; e. $FeCl_3$/MeCN, RT, 28%.

A Novel One-Step Double Coupling Approach to Perylenequinones from 1,2-Naphthoquinone

Since natural perylenequinones are symmetrical dimers of certain naphthalenes,[1,10] the general procedure to synthesize them is first to prepare naphthalene monomers bearing the requisite substituents and to then examine the two-step coupling of these monomers to afford the target compounds.[7,9] An alternative procedure starts from biphenyl, generated from the dimerization of certain benzenoid derivatives, and then the two elaborated side chains are cyclized and the product aromatized and coupled to form the perylenequinonoid nucleus.[6-8] In all these procedures, the dimerizations are the critical steps. Generally, the overall yield of dimerization to perylenequinone from naphthalene is less than 30% even though the route from naphthalene is much more efficient than that from biphenyl.[1,6-10]

Initially we attempted to couple directly compound **4** to compound **8** without employing bromination (for Chao and Zhang's double coupling route, *vide supra*) or iodination (for Ullmann coupling reaction, *vide infra*) since it is difficult to separate the desired brominated or iodinated compounds. However, many attempted direct coupling methods for aryl-aryl bond formation[12] failed to dimerize compound **4** to compound **8**. Even thallium(III) trifluoroacetate, a powerful coupling agent,[13] only produced a trace amount of compound **8**. Furthermore, as expected, Ullmann coupling conditions generated compound **8**, starting from compound **9** in very low yield because of the electron-donating substituents on the benzenoid ring of compound **9**.[12b] While we found that ferric chloride can effect the coupling of compound **4** to generate compound **8** it simultaneously produces at least six oxidized by-products, thereby complicating this coupling reaction. Accordingly we then used ferric chloride to dimerize compound **5** to compound **10** since compound **5** can not be oxidized further by



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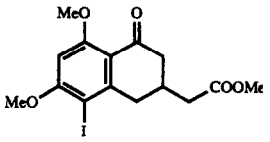

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ferric chloride. Subsequent reduction of compound **10** would give compound **11** which can be coupled to compound **1** by the method of Chao and Zhang.[7]

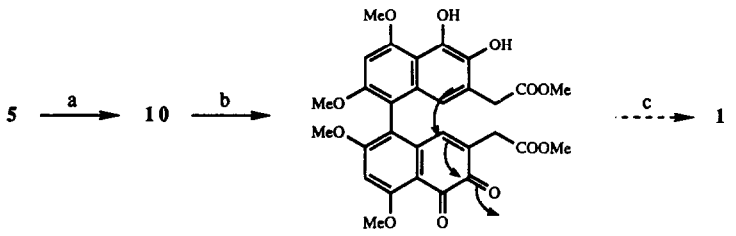
Surprisingly compound **5** can be smoothly dimerized to the target compound **1** *via* only one step in excellent yield (91%) using a solution of 10% ferric chloride in anhydrous acetonitrile, as is shown in Scheme 2. The utilization of higher proportions of a more concentrated ferric chloride solution decreases reaction time, and does not result in more by-products than dilute ferric chloride solution. This therefore represents a novel high-yielding, one-step double coupling route to perylenequinone from readily available 1,2-naphthaquinones.

Scheme 2

Compound **5** $\xrightarrow[\text{RT, 8 h, 91\%}]{\text{10\% } FeCl_3/MeCN}$ Compound **1**

By comparison with the double coupling method of Chao and Zhang, which starts from unstable compound **7**,[7] our reaction starts from stable compound **5**, saves several steps, and avoids two main problems which exist in their approach, *i.e.* the difficult isolation of the desired brominated compounds and ready decomposition of the coupling precursor. In addition, the new procedure affords much higher coupling yields than the procedure of Chao and Zhang. From the same starting material this new method can produce compound **1** in 10 times higher yield than the older procedure. In addition, we developed a simple isolation method for the purification of compound **1** which avoids troublesome chromatography because this compound is difficult to elute from a silica gel column (*vide infra*).

Scheme 3

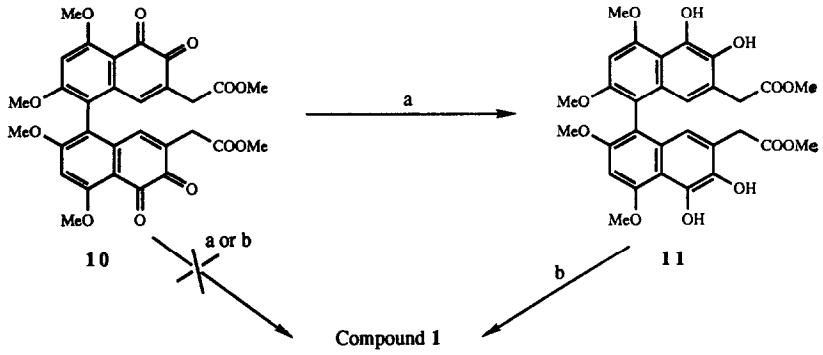


Intermediate A

a. coupling; b. reduction; c. addition-oxidation.

A possible reaction mechanism for this synthesis is shown in Scheme 3. This reaction plausibly proceeds *via* the intramolecular addition-oxidation of the phenolquinonoid system of intermediate **A**. A similar intramolecular phenolquinonoid oxidative addition reaction of 3',5'-dihydroxydibenzyl-3,4-quinone has been observed by Erdtman and Ronlan,[15a], and intermolecular addition-oxidation reactions between 1,2-naphthoquinones and naphthols have been summarized by Wanzlick.[15b] The transformation to compound **1** from compound **10** is so fast that we failed to trap the reaction intermediates. The formation of compound **2** together with compound **1** and the coupling of compound **4** to compound **8** under the same conditions suggest that ferric chloride can first couple the benzenoid ring of compound **5** to produce compound **10**, which is then quickly transformed into compound **1** *via* intramolecular reactions. In this connection, ferric chloride has been demonstrated to be an efficient coupling agent for anisoles.[12a] That compound **10** is reduced to intermediate **A** by ferrous ion (formed from the reduction of ferric ion by compound **5** which itself is oxidatively coupled into compound **10**) is supported by the fact that ferrous chloride reduces compound **10** to compound **11** (Scheme 4).

Scheme 4

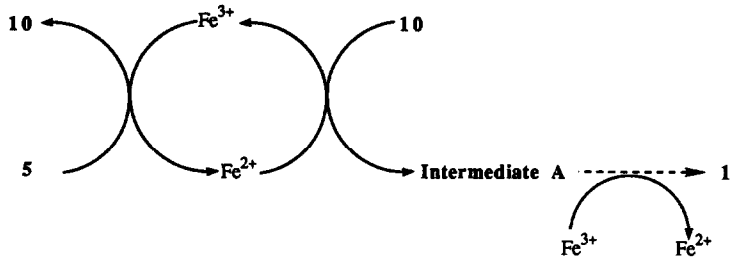


a. $FeCl_2$/MeCN, RT, 4 h; b. $FeCl_3$/MeCN, RT, 4 h.

The possible couplings of these oxidation-reduction pairs are summarized in Scheme 5. In this oxidation-reduction scheme, compound **10** and ferrous ion need to be formed in 1:1 molar proportion, ensuring that compound **10** is reduced to intermediate **A**. This characteristic might be responsible for the high yield of the coupling reaction. The fact that compound **10** cannot be coupled to compound **1** by either pure ferrous chloride or pure ferric chloride. (Scheme 4) suggests the existence of Fe^{3+}/Fe^{2+} oxidation-reduction pair is necessary for the transformation of compound **5** to compound **1**. In support of this interpretation pure ferrous chloride cannot reduce compound **10** to intermediate **A**, and pure ferric chloride cannot effect the oxidations of intramolecular adducts of intermediate **A**.

In contrast to compound **10**, compound **11** can be cyclized into compound **1** by ferric chloride together with the formation of compound **10** (Scheme 4). Ferric chloride can oxidize compound **11** to intermediate **A**, and compound **10** is, in fact, the reoxidized product of intermediate **A** by ferric chloride. Therefore, it appears that either inhibition to the formation of intermediate **A** or protection from the oxidation of its intramolecular adducts block the transformation of compound **5** to compound **1**, which supports the proposed reaction mechanism (Schemes 3 and 5).

Scheme 5



The Properties of Compound 1

As expected, compound **1** possesses the general properties of natural perylenequinones.[1a,2] Significantly it can efficiently produce singlet oxygen on visible light illumination. Interestingly its magnesium ion complex can also produce singlet oxygen on illumination and it also possesses very strong red absorption (see Fig. 1). These two characteristics might qualify the complex of **1** with magnesium ion as a promising photosensitizer for the photodynamic therapy of human tumors.[16] Investigation of this latter application, the examination of anticancer, anti-HIV and specific protein kinase C-inhibition activities of this compound are also in progress and will be reported in due course.

Experimental

All melting points were measured on an Electrohome apparatus using open-end capillary tubes and are uncorrected. Elemental analysis was conducted on a Perkin-Elmer 240B CHN analyzer. CD spectra were determined on a JASCO ORD/UV-5 in methanol. UV-vis absorption spectra were recorded on a Hewlett-Packard 8542A diode array spectrometer. IR spectra were run on a Nicolet 7199 FT spectrometer by chloroform cast. ^{1}H-NMR spectra were measured on either Bruker WH-300 or WH-400 spectrometers in deuterated chloroform with tetramethylsilane as the internal standard. Mass spectra were performed either by Associated Electrical Industries (AEI) MS-50 for electron impact (EI) ionization or AEI MS-9 for fast atom bombardment (FAB). Merck silica gel 60 was used for column chromatography and commercial Kieselgel 60 F254 plates were used for thin layer chromatography (TLC).

3,5-Dimethoxybenzylmethanol was prepared by the reduction of methyl-3,5-dimethoxybenzoate using lithium aluminum hydride in tetrahydrofuran, m.p. 48-50°C (literature[17a] m.p. 48-48.5°C).

3,5-Dimethoxybenzyl chloride was prepared according to the procedure of Adam *et al.*[17b], m.p. 47-49°C (literature m.p. 46°C).

Diethyl-3,5-dimethoxybenzylmalonate, b.p. 160-170°C/0.1 mm Hg (literature b.p. 160-165°C/0.1 mm Hg), ***2-(3,5-Dimethoxybenzyl)-1,3-propanediol***, m.p. 30-32°C (literature m.p. 32-34°C), ***2-(3,5-dimethoxybenzyl)propanediol ditosylate***, m.p. 87-89°C (literature m.p. 87-88°C) and ***3-(3,5-dimethoxybenzyl)glutaronitrile***, m.p. 52-54°C (literature m.p. 52-53°C) were synthesized by the methods of Hatch *et al.*[17c]

3-(3,5-Dimethoxybenzyl)glutaric acid, m.p. 127-129°C (literature m.p. 128-130°C) and ***1-oxo-3,4-dihydro-6,8-dimethoxy-(2H)-naphthalene-3-acetic acid*** (**3**), m.p. 215-216°C (literature m.p. 214-216°C) were obtained using the method of Kende *et al.*[17d]

All above-mentioned compounds have ^{1}H-NMR, IR and MS spectra consistent with their assigned

structures. And compounds **1-11** were synthesized as follows.

Methyl-1-oxo-3,4-dihydro-6,8-dimethoxy-(2H)-naphthalene-3-acetate (4).- Compound **3** (5 g) was dissolved in 100 mL of methanol containing 1 mL of 98% sulfuric acid and heated under reflux for 8 h under nitrogen. The resulting solution was concentrated, poured into ice water, and then extracted with ethyl acetate. The ethyl acetate phase was washed with 10% sodium bicarbonate and water, dried ($MgSO_4$) and concentrated *in vacuo* to afford a viscous oil which slowly solidified on standing. Recrystallization of the resulting solid from ethyl acetate/hexane gave 5.0 g (95% yield) of crystalline compound **4**, m.p. 82-84°C. IR: 1734 and 1670 cm^{-1}; ^{1}H-NMR: 2.00-3.00 (m, 7H), 3.67 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H) and 6.31 ppm (s, 2H); MS (EI): 278 (M).

Methyl-1,2-dioxo-6,8-dimethoxynaphthalene-3-acetate (5). - Compound **4** (4.5 g) and selenium dioxide (5 g) were dissolved in 100 mL of acetic acid containing a trace amount of water and heated at 80-90°C for 2 h with continuous stirring. The mixture was poured onto ice and extracted with chloroform. The chloroform layer was treated similarly to the procedure used in the preparation of compound **4** to afford an orange solid. This solid was chromatographed on silica gel column using 15:1 chloroform-methanol as eluent, and recrystallized from acetone to give 3.3 g (71% yield) of crystalline compound **5**, m.p. 188-189°C. IR: 1728, 1650 and 1595 cm^{-1}; ^{1}H-NMR: 3.48 (s, 2H), 3.75 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 6.48 (s, 2H) and 7.25 ppm (s, 1H); MS (EI): 292 (M+2).

Methyl-1,2-dioxo-5-bromo-6,8-dimethoxynaphthalene-3-acetate (6).- Compound **5** (1 g) and N-bromosuccinimide (0.6 g) were dissolved in 20 mL of tetrahydrofuran containing 0.5 mL of 98% sulfuric acid and stirred at room temperature for 8 h. The mixture was poured onto ice and extracted with chloroform. The chloroform layer was washed with sodium bicarbonate and water and dried ($MgSO_4$) and then evaporated *in vacuo*, and the solid residue was chromatographed on a silica gel column using 95:5 ethyl acetate-methanol as eluent. Recrystallization of the resulting solid from acetone gave 0.52 g (41% yield) of crystalline compound **6**, m.p. 200-201°C. IR: 1729, 1658 and 1590 cm^{-1}; ^{1}H-NMR: 3.49 (s, 2H), 3.73 (s, 3H), 4.02 (s, 6H), 6.48 (s, 1H), and 8.01 ppm (s, 1H); MS (EI): 370 (M+2) and 372 (M+2+2).

Methyl-1,2-dihydroxy-5-bromo-6,8-dimethoxynaphthalene-3-acetate (7).- Compound **6** (0.4 g) was dissolved in 10 mL of 4:1 methanol-water and heated under reflux while sulfur dioxide was bubbled through the reaction solution for 2 h. The resulting solution was poured into ice and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform layer gave 388 mg (96% yield) of compound **7** which is unstable and was used immediately for the next coupling reaction.

5,5-Di(methyl-1-oxo-3,4-dihydro-6,8-dimethoxynaphthalene-3-acetate) (8).- *Method A.* A sealed tube of 0.5 g of compound **9** and 2.0 g of freshly prepared copper powder was heated at 280-300°C for 1 h. The resulting mixture was extracted with chloroform, and the chromatographed on a silica gel column using 95:5 chloroform-methanol as eluent. Recrystallization of the solid thus obtained from ethyl acetate/hexane gave 130 mg (26% yield) of crystalline compound **7**, m.p. 176-178°C. IR: 1736 and 1670 cm^{-1}; ^{1}H-NMR: 2.00-3.00 (m, 14H), 3.58 (s, 6H), 3.76 (s, 3H), 3.78 (s, 3H), 3.99 (s, 6H), and 6.44 ppm (s, 2H); MS (EI): 554 (M).

Method B. Compound **4** (0.1 g) and thallium(III) trifluroacetate (0.2 g) were allowed to react according to the method of McKillop *et al.* and treated by the procedure of method A. TLC separation gave 5 mg (5% yield) of compound **8** using 8:2:1 petroleum ether-ethyl acetate-ethanol as developing agent.

Method C. Compound **4** (0.1 g) and anhydrous ferric chloride (0.1 g) were dissolved in 5 mL of anhydrous acetonitrile and stirred at room temperature overnight. The resulting solution was treated as described in method A. TLC analysis demonstrated that compound **8** was formed.

Methyl-1-oxo-3,4-dihydro-5-iodo-6,8-dimethoxy-(2H)-naphthalene-3-acetate (9).- Acetic acid solution (5 mL) containing 0.6 g of iodine monochloride was added dropwise to 10 mL of an acetic acid solution containing 1 g of compound **3** and stirred at room temperature for 4 h. The mixture was poured onto ice and extracted with chloroform. The light yellow solid obtained by evaporating the chloroform layer was allowed to react as described in the preparation of compound **4**, and then chromatographed on a silica gel column using 5:1 petroleum ether-ethyl acetate as eluent to afford 0.55 g (38% yield) of crystalline compound **9**, m.p. 179-180°C. IR: 1755 and 1660 cm^{-1}; ^{1}H-NMR: 2.00-3.00 (m, 7H), 3.69 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), and 6.36 ppm (s, 1H); MS (EI): 404 (M).

5,5'-Di(methyl-1,2-dioxo-6,8-dimethoxy-naphthalene-3-acetate) (10).- This compound was synthesized by the procedure described for compound **5**, m.p. 302-304°C. IR: 1727, 1645 and 1590 cm^{-1}; ^{1}H-NMR: 3.32 (s, 4H), 3.61 (s, 6H), 3.87 (s, 6H), 4.08 (s, 6H), 6.59 (s, 2H), and 7.00 ppm (s, 2H); MS (FAB): 579 (M+H).

5,5'-Dimethyl-1,2-dihydroxy-6,8-dimethoxynaphthalene-3-acetate (11).- This compound was synthesized by the procedure described above for compound **7**.

Dimethyl-5,8-dihydroxy-1,3,10,12-tetramethoxy-4,9-perylenequinone-6,7-diacetate (1).- *Method A (from compound 5).* A solution of compound **5** (1 g) and 0.9 g of anhydrous ferric chloride in 10 mL of anhydrous acetonitrile was stirred at room temperature for 8 h. The resulting solution was poured into 3% hydrochloric acid, and then extracted with chloroform. The chloroform layer was washed with water, dried ($MgSO_4$) and evaporated to afford a red solid. This solid was redissolved in chloroform and then mixed with a 10% aqueous ethanol solution of zinc acetate. The Zn-compound **1** complex thus formed was washed with a large amount of chloroform, and then decomposed by 10% hydrochloric acid to release compound **1**, which was again extracted with chloroform and the extract evaporated *in vacuo*. The residue was recrystallized from acetone to afford 0.9 g (91% yield) of crystalline compound **1**, m.p. 238-240°C. IR: 3260, 1738 and 1594 cm^{-1}; ^{1}H-NMR: 3.50 (s, 6H), 3.66, 3.72, 3.99, and 4.04 (q, 4H, J_{AB} = 16.5 Hz), 4.11 (s, 6H), 4.20 (s, 6H), 6.76 (s, 2H), and 8.03 (s, 2H, exch.); λ_{max}(log ε) (in ethanol): 212 (4.72), 226 (4.72), 270 (4.65), 344 (3.61), and 508 (4.46) nm; MS (FAB): 579 (M+H). Anal. calcd for $C_{30}H_{26}O_{12}$MeCOMe: C, 62.27, H, 5.07. Found: C, 62.24, H, 5.10.

The uncomplexed solid was directly chromatographed on an anhydrous magnesium sulfate column using 90:1 ethyl acetate-methanol as eluent to obtain compound **2**. IR: 1740, 1665 and 1590 cm^{-1}; ^{1}H-NMR: 3.58 (s, 4H), 3.69 (s, 6H), 3.94 (s, 6H), 3.98 (s, 6H), and 6.64, 6.65, 7.33 and 7.34 ppm (q, 4H, J_{AB} = 2.4 Hz); MS (FAB): 579 (M+H).

Method B (from compound 7). Freshly prepared compound **7** (0.1 g) was dissolved in 10 mL of anhydrous acetontrile and 0.1 g of ferric chloride in 10 mL of anhydrous acetontrile was added dropwise. The mixture was stirred at room temperature for 4 h, treated as described in method A, and chromatographed on a silica gel column using 10:1 chloroform-methanol as eluent to afford 22 mg (28% yield) of compound **1**.

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