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SYNTHETIC STUDIES IN NOVEL HYPOCRELLIN B DERIVATIVES

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Abstract: Three novel hypocrellin B (HB) derivatives required for their potential in photodynamic therapy have been synthesized. The possible reaction mechanisms and the properties of resulting HB derivatives are discussed.

Introduction

Because of promising clinical results obtained with photodynamic therapy,[1] more and more photosensitizers continue to be isolated (from natural sources), synthesized and evaluated, the development of which is considered to be a key factor for the successful clinical application of photodynamic therapy.[2,3] Some anthraquinones, perylenequiones, cyanines, phenoxazines and phenothiazines exhibit strong light absorption in the 'phototherapeutic window'(600-1000nm), high photosensitizing efficacy and low delayed skin photosensitivity.[4] Some of the non-porphyrin photosensitizers (such as rhodamine 123, merocyanine 540 and some cyanine cationic dyes) demonstrate higher selectivity for tumor cells. They can also be explored in connection with selective carcinoma photolysis strategy based on mitochondrion-, lysosome- or DNA-directed localization mode.[4]

Interest in photodynamic therapy (PDT) of human malignancies has increased markedly since the advent and clinical application of hematoporphyrin derivatives (HPD).[3,5,6] To date PDT of cancers (in both laboratory and clinical trials) has primarily involved the use of porphyrin-based photosensitizers (in particular, photofrin-II) . This has occurred despite their their suboptimal light absorption characterisitics, source-dependent biological response and molecular composition, and difficulties associated with prolonged photosensitization of the host. [3,5] These limitations that occur with the porphyrin photosensitizers provide a strong rationale for the development of more suitable photosensitizers. We have proposed and investigated perylenequinonoid pigments (PQPs) as a new generation of PDT agents.[6]

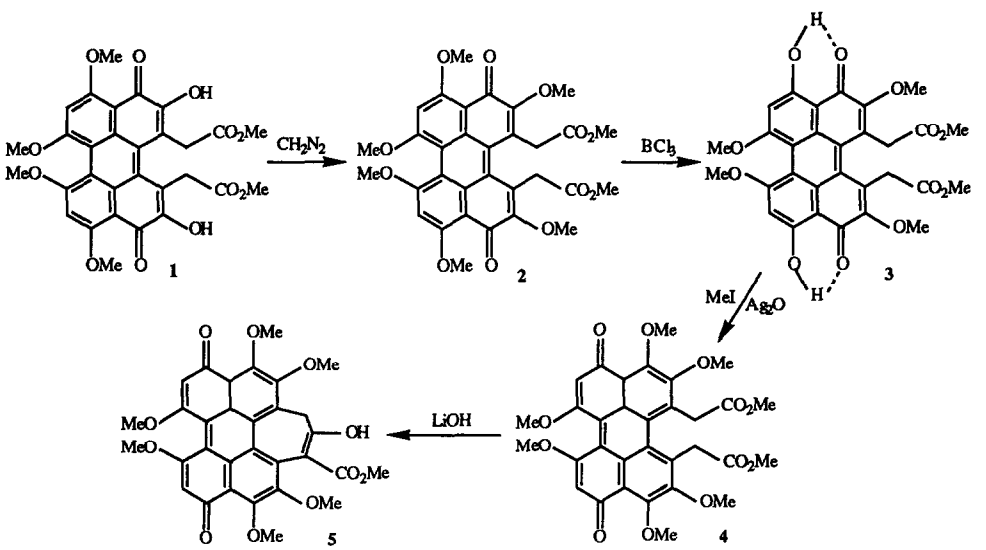
Recently we have shown that PQPs are a new class of efficient singlet oxygen ($^1O_2$) generators and demonstrate some advantages over the established $^1O_2$ sensitizers (such as porphyrins, rose bengel and methylene blue etc.). These advantages include wide UV-vis absorption, high quantum yield of $^1O_2$ generation, high stability, good solubility and small solvent and concentration effects.[4,8] More significantly PQPs have been proven to be potential sensitizers for the PDT of tumors, quite different in properties from the existing PDT agents, porphyrins and phthalocyanines.[3,5-11]

4,9-Dihydroxy-3,10-perylenequinones comprise a relatively small but growing group of natural pigments, that possess unique chemical and biological properties.[12] The natural perylenequinones of this class identified to date include hypocrellins, cercosporin, phleichrome, elsinochromes, cladochromes, erythroaphins and calphostins. Most of them are produced by a wide variety of molds and act as photodynamic phytotoxins of their hosts except for erythroaphins, which are isolated from aphids. Recently considerable attention has been paid to the promising use of perylenequinonoid derivatives (especially hypocrellins) in the photodynamic therapy of human malignancies and for their anticancer[13] and possibly anti-HIV properties.[14] The latter property was related to the potent specific inhibition of protein kinase C, a key enzyme involved in cellular proliferation and differentation.[3] These facts encouraged us to develop convenient syntheses of functionalized perylenequinones.

Until recently, relatively few efforts have been devoted to the synthesis of perylenequinone structures. Dallacker and Leidig prepared a methoxylated perylenequinone, but this compound lacked certain indispensable functional groups at key positions.[15] 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.[16] Subsequently, Diwu and Lown improved Chao and Zhang's method for the preparation of perylenequinone using the novel one-step double coupling reaction of 1,2-naphthoquinone in high yield.[7] Coleman and Grant have recently reported synthetic studies on calphostin C.[17,18] Broka synthesized phleichrome, the first successful total synthesis of a natural perylenequinone.[19] However this approach requires at least twenty-six steps starting from commercially available reagents, and several of these steps require stringent experimental conditions. We report a convenient and high yield route to synthesize key HB derivatives required in such synthetic efforts.

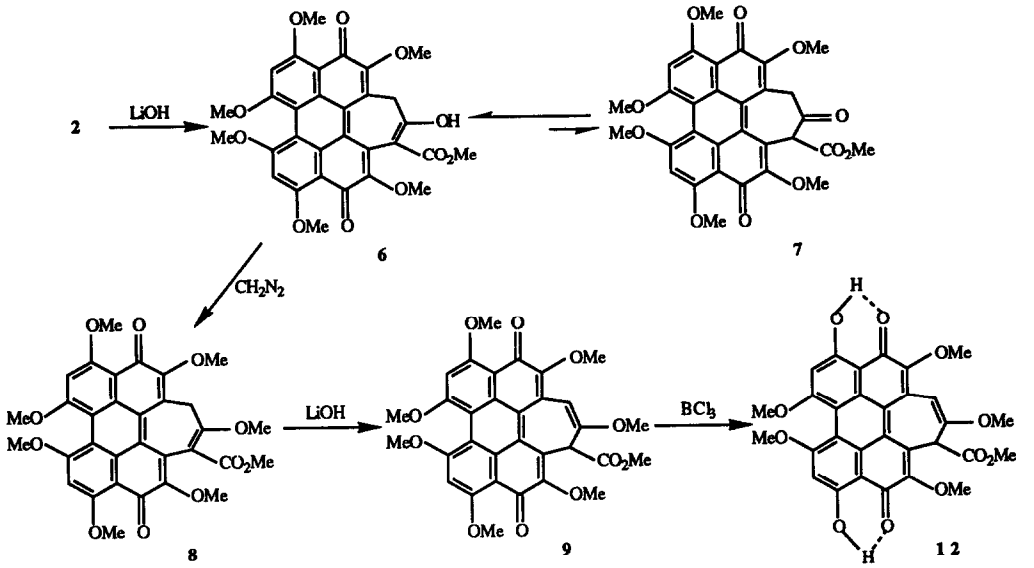
Results and Discussion

Scheme 1

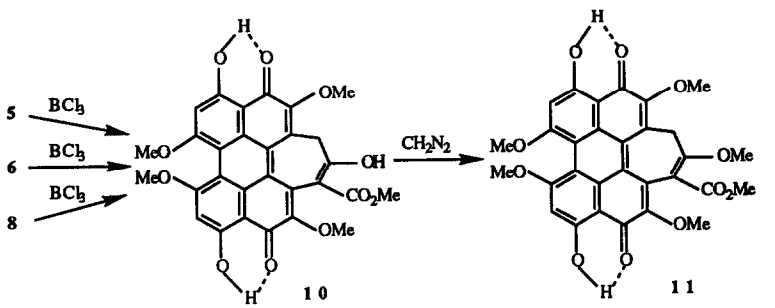


Three novel HB derivatives **10, 11, 12** were synthesized as shown in Schemes **1, 2** and **3**, respectively. Compound **1** was prepared according to the procedure described by Diwu and Lown,[7] and converted into compound **2** in high yield by treatment with diazomethane. In contrast, treatment of **1** with

Scheme 2



Scheme 3

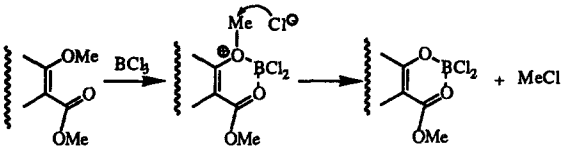


silver oxide and methyl iodide gave a complex mixture from which pure **2** could not be isolated. Compound **2** was demethylated selectively with boron trichloride to obtain perylenequinone **3** which possesses oxygen functions identical with certain natural perylenequinones except the side chains. Treatment of compound **3** with silver oxide and methyl iodide in acetone produced the yellow dimethyl ether **4** and red dimethyl ether **2**. Surprisingly, when compounds **2** and **4** were treated with weak base, lithium hydroxide solution at room

temperature, ring-closed products **5, 6** and **7** were obtained, not the anticipated dicarboxylic acid. It is evident that the allylic hydrogens in compounds **2** and **4** were removed easily by hydroxide anion, and the intramolecular Claisen ester reaction took place rapidly. NMR spectra indicated that there was only one form of **5** present in solution, but there was an equilibrium between **6** and **7** with form **6** predominating in chloroform solution. Methylation of a mixture of **6** and **7** with diazomethane in dichloromethane gave compound **8** quantitatively.

It was observed that treatment of compound **8** with 1 N lithium hydroxide solution produced the isomeric compound **9** which is more stable thermodynamically than compound **8**, and not the hydrolysis product. Demethylation of compounds **5** and **6** with boron trichloride afforded compound **10** which exists exclusively as the keto form in chloroform solution. Treatment of compound **8** with boron trichloride also provided compound **10**, because boron trichloride can demethylate all methoxy groups that are positioned ortho to a carbonyl group and can form a six-membered ring intermediate as shown in the following Scheme 4.[20]

Scheme 4



In accord with the suggested mechanism, treatment of **9**, which can not form a stable six-membered ring with boron trichloride, afforded compound **12** only. Methylation of compound **10**, which has two types of hydroxy groups, with diazomethane at room temperature yielded compound **11** in high yield. This is plausibly explained as being due to very strong intramolecular hydrogen-bonding between the phenolic-hydroxyl and quinonoid-carbonyl groups, so the phenolic hydroxyl groups have low reactivity with diazomethane.

As expected, compounds **10, 11** and **12** possess the general properties of natural perylenequinones.[12,13] Significantly, compounds **10** and **11** have similar ultraviolet-visible absorption spectra to HB, but the ultraviolet-visible absorption spectrum of compound **12** has a blue-shift relative to that of HB. These characteristics might qualify compounds **10, 11** and **12** as potential photosensitizers for the photodynamic therapy of human tumors. Such properties are under investigation and will be reported in due course.

Experimental

^{1}NMR spectra were measured on a Bruker WH-300 spectrometer in deuterated chloroform with tetramethylsilane as the internal standard. Mass spectra were performed by AEI MS-9 for fast atom bombardment (FAB). High resolution mass spectra (FAB-HRMS) were recorded on a modified MS50 mass spectrometer equipped with a VG 11-250J data system. Accurate masses were calculated interactively with the data system using a reference (such as CsI in glycerol) peak. IR spectra were run on a Nicolet 7199 FT spectrometer by chloroform cast. UV-vis absorption spectra were recorded on Hewlett-Packard 8542A diode

array spectrometer. Merck silica gel 60 was used for column chromatography and commercial Kieselgel 60 F254 plates were used for thin layer chromatography (TLC). All solvents were used as received and were reagent grade where available.

Methyl-1,2-dioxo-6,8-dimethoxynaphthalene-3-acetate was synthesized according to the method reported by Diwu and Lown.[7]

Dimethyl-5,8-dihydroxy-1,3,10,12-tetramethoxy-4,9-perylenequinone-6,7-diacetate (1): A solution of above compound (1.0 g) and 0.9 g of anhydrous ferric chloride in 10 mL of anhydrous acetonitrile was stirred at room temperature for 8hr., and the resulting solution was poured into 100 mL of 10% 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 purified by silica column chromatography using chloroform and methanol (15:1 v/v) as eluent to afford **1**, 0.93 g (93% yield) as a deep-red powder . All the spectra are identical to its assigned structure.[7]

Dimethyl-1,3,5,8,10,12-hexamethoxy-4,9-perylenequinone-6,7-diacetate (2): A solution of diazomethane in ethyl ether (5 ml) was added to a solution of **1** (100.0 mg) in 15 ml dichloromethane in an ice-water bath. The vessel was stoppered and maintained at room temperature for 2 hr. The solution was evaporated in vacuo. The residue was purified by silica gel column with chloroform and methanol (15:1 v/v) as eluent to afford **2**, 97.0 mg (92% yield) as a red solid, m.p. 155-158°C. IR: 1737.9 and 1622.6 cm^{-1}; ^{1}H-NMR: 3.47(d of AB quartet, J=16.5 Hz, 2H, 2xCH_{2a}), 3.93(d of AB quartet, J=16.5 Hz, 2H, 2xCH_{2b}), 3.54(s, 6H, 2xCO_2CH_3), 4.01(s, 6H, 2xOCH_3), 4.10(s, 6H, 2xOCH_3), 4.16(s, 6H, 2xOCH_3), 6.75(s, 2H, 2xArH); λ_{max} (in chloroform): 268 and 472 nm; MS (FAB): 608 (M+2H), calcd. for $C_{30}H_{30}O_{12}$: 606.

Dimethyl-3,10-dihydroxy-1,5,8,12-tetramethoxy-4,9-perylenequinone-6,7-diacetate (3): A solution of 0.10 ml of 1.0 M boron trichloride in dichloromethane was added dropwise to a solution of **2** (15.0 mg) in 5 ml dichloromethane in a dry ice- acetone bath. The vessel was stoppered and maintained at room temperature for 5 min. The solution was quenched with 50 ml of water and extracted with chloroform. The chloroform layer was washed with water and evaporated in vacuo to afford a red solid. The solid was purified by silica gel column chromatography using chloroform as eluent. The product **3** was obtained as a red solid (10.0 mg) in 70% yield, m.p. 226-228°C. IR: 1740.1 and 1609.3 cm:$^{-1}$; ^{1}H-NMR: 3.59(s, 6H, 2xCO_2CH_3), 3.68(d of AB quartet, J=17.0 Hz, 2H, 2xCH_{2a}), 4.18(d of AB quartet, J=17.0 Hz, 2H, 2xCH_{2b}), 4.03(s, 6H, 2xOCH_3), 4.11(s, 6H, 2xOCH_3), 6.48(s, 2H, 2xArH), 15.89(s, 2H, 2xOH); λ_{max} (in chloroform): 262, 346, 476, 552(sh) and 594(sh) nm; MS (FAB): 579 (M+H), calcd. for $C_{30}H_{26}O_{12}$: 578.

Dimethyl-1,4,5,8,9,12-hexamethoxy-3,10-perylenequinone-6,7-diacetate (4): To 10 ml of acetone containing 10.0 mg of **3**, 100 mg of silver oxide and 0.5 ml of methyl iodide were added. (The silver oxide was precipitated from a silver nitrate solution by sodium hydroxide; the precipitate was collected, thoroughly washed with water, and activated for 18 hr. at 120°C). The mixture was stirred for 10 hr. at room temperature in the dark, and then filtered and the precipitate was washed with chloroform. The filtrate was evaporated in vacuo, and the residue was chromatographed on a silica gel column using chloroform and methanol (15:1 v/v) as eluent, the first fraction was collected and evaporated in vacuo to afford 5.2 mg of **4** as a yellow solid (50% yield), m.p. 142-145°C. IR: 1738.7 and 1621.8 cm^{-1}; ^{1}H-NMR: 3.61(s, 6H, 2xCO_2CH_3), 3.67(d of AB quartet, J=16.5 Hz, 2H, 2xCH_{2a}), 4.16(d of AB quartet, J=16.5 Hz, 2H,

2xCH_{2b}), 3.93 (s, 6H, 2xOCH_3), 3.99 (s, 6H, 2xOCH_3), 4.05 (s, 6H, 2xOCH_3), 6.10 (s, 2H, 2xArH); λ_{max} (in chloroform): 250 and 442 nm; MS (FAB): 608 (M+2H), calcd. for $C_{30}H_{30}O_{12}$: 606.

2-Hydroxy-4,5,8,9,12,13-hexamethoxy-3H-cyclohepta[ghi]perylene-6,11-dione-1-methyl carboxylate (5): 1.0 ml of 1 N lithium hydroxide was added to a solution of **4** (5.0 mg) in 5 ml of methanol in an ice-water bath. The solution was stirred for 2 hr. at room temperature, and poured into 20 ml of water and neutralized with 1 N hydrochloric acid, and then extracted with chloroform. The chloroform layer was washed with water and evaporated in vacuo to afford a red solid. The solid was chromatographed on silica gel column using chloroform and methanol (15:1 v/v) as eluent. 3.1 mg of product **5** was obtained (65% yield), m.p. 115-118°C. IR: 1654.0 and 1627.2 cm^{-1}; ^{1}H-NMR: 3.20(d of AB quartet, J=12.5 Hz, 1H, 1xCH_{2a}), 4.34(d of AB quartet, J=12.5 Hz, 1H, 1xCH_{2b}), 3.57 (s, 3H, CO_2CH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 6.09 (s, 1H, ArH), 6.11 (s, 1H, ArH), 12.58 (s, 1H, OH); λ_{max} (in chloroform): 242, 302(sh), 354 and 438 nm; MS (FAB): 576 (M+2H), calcd. for $C_{31}H_{26}O_{11}$: 574.

2-Hydroxy-4,6,8,9,11,13-hexamethoxy-3H-cyclohepta[ghi]perylene-5,12-dione-1-methyl carboxylate (6) and **4,6,8,9,11,13-hexamethoxy-3H-cyclohepta[ghi]perylene-2,5,12-trione-1-methyl carboxylate (7):** An equillibrium mixture of compounds **6** and **7** were synthesized from **2** using a similar procedure as described for **5**, the yield of **6+7** together was 84% , m.p. 237-240°C. IR: 1733.0, 1654.3 and 1616.0 cm^{-1}; ^{1}H-NMR: 3.40 (s, CH), 3.47(d of AB quartet, J=13.0 Hz, H, CH_{2a}), 4.21 (d of AB quartet, J=12.5 Hz, H, CH_{2b}), 3.63(s, 3H, CO_2CH_3), 4.09(s, 3H, OCH_3), 4.11(s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 4.19 (s, 3H, OCH_3), 4.21(s, 3H, OCH_3), 6.80 (s, 1H, ArH), 6.81 (s, 1H, ArH), 12.45 (s, OH); λ_{max} (in chloroform): 272, 468 and 578(sh) nm; MS (FAB): 575 (M+H), calcd. for $C_{31}H_{26}O_{11}$: 574.

2,4,6,8,9,11,13-Heptamethoxy-3H-cyclohepta[ghi]perylene-5,12-dione-1-methyl carboxylate (8): Compound **8** was obtained in 97% yield from **6** and **7** using the same method described for **2**, m.p. 253-256°C. IR: 1719.1 and 1613.0 cm^{-1}; ^{1}H-NMR: 3.32(d of AB quartet, J=12.5 Hz, 1H, 1xCH_{2a}), 4.26(d of AB quartet, J=12.5 Hz, 1H, 1xCH_{2b}), 3.60 (s, 3H, CO_2CH_3), 4.05 (s, 6H, 2xOCH_3), 4.08 (s, 3H, OCH_3), 4.10 (s, 6H, 2xOCH_3), 4.18 (s, 6H, 2xOCH_3), 6.78 (s, 1H, ArH), 6.79 (s, 1H, ArH); λ_{max} (in chloroform): 254, 288(sh) and 472 nm; MS (FAB): 590 (M+2H), calcd. for $C_{32}H_{28}O_{11}$: 588.

2,4,6,8,9,11,13-Heptamethoxy-1H-cyclohepta[ghi]perylene-5,12-dione-1-methyl carboxylate (9): Compound **9** was synthesized from **8** using the same method described for **5**, and the yield was 61% , m.p. 201-204°C. IR: 1737.9 and 1614.0 cm^{-1}; ^{1}H-NMR: 3.41(s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.16 (s, 6H, 2xOCH_3), 5.34(d, J=2.5Hz, 1H, $\underline{CH}CO_2CH_3$), 5.86 (d, J=2.5Hz, 1H, olefenic CH), 6.76 (s, 1H, ArH), 6.77 (s, 1H, ArH); λ_{max} (in chloroform): 252, 466, 532(sh) and 582(sh) nm; MS (FAB): 590 (M+2H), calcd. for $C_{32}H_{28}O_{11}$: 588.

2,6,11-Trihydroxy-4,8,9,13-tetramethoxy-3H-cyclohepta[ghi]perylene-5,12-dione-1-methyl carboxylate (10): Compound **10** was prepared in 39%, 59% and 36% yield from **5**, **6** and **8** using the same method described for **3**, respectively, R_f(chloroform:methanol 15:1)=0.78, m.p.188-190°C. IR: 1657.4 and 1611.2 cm^{-1}; ^{1}H-NMR: 3.45(d of AB quartet, J=13.0 Hz, 1H, 1xCH_{2a}), 4.36(d of AB quartet, J=13.0 Hz, 1H, 1xCH_{2b}), 3.58 (s, 3H, CO_2CH_3), 4.01 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.12 (s, 3H,

OCH_3), 4.16 (s, 3H, OCH_3), 6.39 (s, 1H, ArH), 6.40 (s, 1H, ArH), 12.62 (s, 1H, OH), 15.90 (s, 1H, phenolic OH), 16.10 (s, 1H, phenolic OH); λ_{max} (in chloroform): 252, 342, 460, 552(sh) and 594(sh) nm; HRMS (FAB): 547.1221 (M+H), calcd. for $C_{29}H_{22}O_{11}H$: 547,1240.

6,11-Dihydroxy-2,4,8,9,13-pentamethoxy-3H-cyclohepta[ghi]perylene-5,12-dione-1-methyl carboxylate (11): Compound **11** was obtained in 71% yield from **10** using the same method described for **2**, but the mixture was only stirred for 20 min. at room temperature, R_f(chloroform:methanol 15:1)=0.48, m.p. 183-187°C. IR: 1719.3 and 1609.9 cm^{-1}; ^{1}H-NMR: 3.24(d of AB quartet, J=13.5 Hz, 1H, $1xCH_{2a}$), 4.52(d of AB quartet, J=13.5 Hz, 1H, $1xCH_{2b}$), 3.61 (s, 3H, CO_2CH_3), 4.03 (s, 6H, $2xOCH_3$), 4.12 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.40 (s, 2H, 2xArH), 15.99 (s, 1H, phenolic OH), 16.02 (s, 1H, phenolic OH); λ_{max} (in chloroform): 248, 342, 460, 552(sh) and 594(sh) nm; HRMS (FAB): 561.1401 (M+H), calcd. for $C_{30}H_{24}O_{11}H$: 561.1397

6,11-Dihydroxy-2,4,8,9,13-pentamethoxy-1H-cyclohepta[ghi]perylene-5,12-dione-1-methyl carboxylate (12): Compound **12** was isolated in 48% yield from **9** using the same method described for **3**, R_f(chloroform:methanol 15:1)=0.50, m.p. 248-250°C. IR: 1738.6 and 1613.6 cm^{-1}; ^{1}H-NMR: 3.30 (s, 3H, CO_2CH_3), 3.88 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.02(s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 5.66(d, J=2.5 Hz, 1H, $\underline{CH}CO_2CH_3$), 6.21 (d, J=2.5 Hz, 1H, olefenic CH), 6.34 (s, 1H, ArH), 6.36 (s, 1H, ArH), 15.73 (s, 1H, phenolic OH), 16.92 (s, 1H, phenolic OH); λ_{max} (in chloroform): 244, 300(sh), 346, 456, 520(sh) and 556(sh) nm; HRMS (FAB): 561.1371 (M+H), calcd. for $C_{30}H_{24}O_{11}H$: 561.1397.

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