Efficient Synthesis of a Novel Perylenequinone and Its Dimethyl Ether Derivatives

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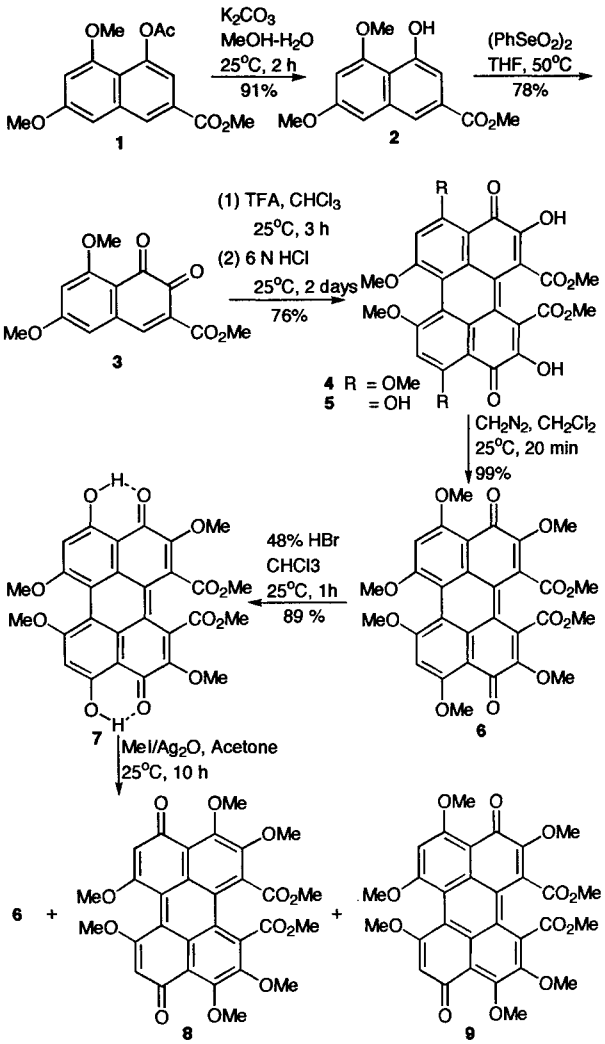
A novel perylenequinone and its dimethyl ether derivatives have been synthesized by a simple high-yield method.

Perylenequinones form a relatively small, but growing group of biologically active pigments obtained from natural sources.[1] The natural perylenequinones of this class identified to date include hypocrellins, cercosporin, phleichrome, elsinochromes, cladochromes, erythroaphins and calphostins. Most of them are isolated from fungi and act as photodynamic phytotoxins of their hosts except that erythroaphins are produced from aphids. Similar compounds have also been found recently in marine organisms.[2]

Interest in these compounds stems not only from their unique structural features, but also from their photodynamic activity. Recently considerable attention has been paid to the promising use of these agents in the photodynamic therapy of human malignancies as well as anticancer,[3] and anti-HIV-I effects.[4] They have also been shown recently to be potent and selective inhibitors of protein kinase C, a regulatory enzyme important for cellular proliferation and differentation[5] that also plays a critical role in the *trans*-activation event in HIV infected T-lymphocytes.[6] These facts encouraged us to synthesize and explore systematically the properties of new perylenequinone derivatives.

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 some indispensable functionalized groups at appropriate positions.[7] 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 perylenequinones.[8] Subsequently, Diwu and Lown improved the method of Chao and Zhang for the preparation of perylenequinone using the novel one-step double coupling reaction of 1,2-naphthoquinone in high yield.[9] Broka synthesized phleichrome, the first successful total synthesis of a natural perylenequinone.[10] However, this approach requires at least twenty-six steps starting from commercially available reagents, and several of these steps require stringent experimental conditions. Coleman and Hauser in different groups have recently reported the total synthesis of calphostins A and D by two different methods.[11] Previously, we reported a convenient route to synthesize hypocrellin derivatives in high yield.[12] Herein, we detail a synthesis of another novel perylenequinone derivative and formation of its dimethyl ethers, which are shown in the Scheme.



Scheme

The readily available naphthoate **1** was converted to compound **2** by selective hydrolysis with potassium carbonate in aqueous methanol. Oxidation of **2** with benzeneseleninic anhydride gave the *o*-napthoquinone **3** in 78% yield. Diwu has reported the use of iron(III) chloride in acetonitrile to effect oxidative dimerization of methyl 1,2-dioxo-6,8-dimethoxynaphthalene-3-acetate to the corresponding perylenequinone.[9] Under these conditions and in the present application, we obtained only trace quantities of the desired perylenequinone **4** and a modest yield (30%) of 5,5'-binaphthoquinone, a result which is similar to that obtained by Hauser et al.[11] The enantiomeric perylenequinone **4** (together with minute amounts

of demethylated perylenequinone **5**) was obtained by an adaption of Hauser's method in high yield; the difference is that oxygen was used to reoxidize the hydroquinone to the *o*-naphthoquinone in the present application. Methylation of compound **4** with diazomethane afforded compound **6** quantitatively. Compound **6** was then demethylated selectively with hydrobromic acid to afford the expected perylenequinone **7** in 89% yield.

Treatment of **7** with methyl iodide in the presence of silver oxide in acetone at 25°C afforded the red dimethyl ether **6**, yellow dimethyl ether **8** and a new orange dimethyl ether **9**. When the latter reaction was conducted at 50°C, compound **9** became the major product and was obtained in 67% yield. These three dimethyl ethers result from the phenol–quinone tautomeric equilibria of **7** among 3,10-, 4,9- and 3,9-perylenequinones. Methylation of other perylenequinones, except erythroaphin,[13] only gave red and yellow dimethyl ethers, hence the most important factors governing the tautomeric equilibria appeared to be the substitutent effects and temperature.

As expected, compound **7** possesses the general properties of natural perylenequinones. Compared with the absorption spectra of hypocrellins, the visible absorption spectrum of the compound **7** also consists of three strong, broad absorption bands, the band at $\lambda = 458$ nm is assigned to a $\pi-\pi^*$ transition, while the bands at $\lambda = 524$ and 562 nm are considered to be related to intramolecular proton transfer.[14] These latter absorption bands may prove useful for the photodynamic therapy of human tumors. Such properties are under investigation and will be reported in due course.

In conclusion, the procedure described here represents an efficient, convenient and general method for the preparation of novel type of perylenequinone **7** that can be extended to other similar perylenequinones and related natural products.

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker WH-300 spectrometer in $CDCl_3$ with TMS as the internal standard. High resolution electron impact mass spectra were recorded on Kraxtos MS 50 mass spectrometer equipped with a VG 11-250J data system. IR spectra were run on a Nicolet 7199 FT spectrometer by $CHCl_3$ cast. UV-Vis absorption spectra were recorded on a Hewlett-Packard 8542A diode array spectrometer. Merck silica gel 60 was used for column chromatography and commercial Kieselgel 60 F-254 plates were used for TLC and preparative separation. All solvents were reagent grade and used as received.

Methyl 4-acetoxy-5,7-dimethoxy-2-naphthoate **(1)** was prepared in 62% yield according to the procedure of Cameron et al.[15]

Methyl 4-Hydroxy-5,7-dimethoxy-2-naphthoate (2):
To a solution of **1** (2.7 g, 8.88 mmol) in a mixture of acetone (20 mL) and MeOH (20 mL) was added a solution of K_2CO_3 (4.0 g) in water (20 mL). After stirring for 2 h at 25°C, the reaction mixture was diluted with water (200 mL) and acidified with 1 N HCl to pH 3. The mixture was extracted with $CHCl_3$, dried (Na_2SO_4) and evaporated to afford **2** (2.1 g, 91%); mp 149–151°C.

IR (KBr): $\nu = 1715.4\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): $\delta = 9.15$ (s, 1 H, OH), 7.92 (d, 1 H, $J = 1.5$ Hz, ArH), 7.29 (d, 1 H, $J = 1.5$ Hz, ArH), 6.81 (d, 1 H, $J = 1.5$ Hz, ArH), 6.54 (d, 1 H, $J = 1.5$ Hz, ArH), 4.02 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.89 (s, 3 H, CO_2CH_3).

HRMS: *m/z* calc. for $C_{14}H_{14}O_5$ 262.08414; found 262.08444.

Methyl 6,8-Dimethoxy-1,2-dioxo-3-naphthoate (3):
A solution of **2** (586 mg, 2.24 mmol) in anhyd. THF (10 mL) was added dropwise during 15 min to a stirred suspension of 70% benzeneseleninic anhydride (1.15 g, 2.24 mmol) in THF (10 mL) at 50°C. The reaction was monitored by TLC and additional oxidant (0.23 g, 0.2 mmol) was added until no starting material remained. The cooled mixture was diluted with $CHCl_3$ (100 mL) washed with aq $NaHCO_3$ solution (10%), water and dried. Evaporation followed by column chromatography on silica gel using toluene/EtOAc (8:1) as eluent gave **3** (482 mg, 78%) as an orange solid; mp 235–237°C.

IR (KBr): $\nu = 1739.7$, 1673.6, 1660.1 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 8.70$ (s, 1 H, ArH), 6.64 (d, 1 H, $J = 2.0$ Hz, ArH), 6.58 (d, 1 H, $J = 2.0$ Hz, ArH), 4.00 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 3.90 (s, 3 H, CO_2CH_3).

HRMS: *m/z* calc. for $C_{14}H_{12}O_6$ 276.06339; found 276.06341.

Dimethyl 2,11-Dihydroxy-4,6,7,9-tetramethoxy-3,10-perylenequinone-1,12-dicarboxylate (4) and Dimethyl 2,4,9,11-Tetrahydroxy-6,7-dimethoxy-3,10-perylenequinone-1,12-dicarboxylate (5):
To a solution of **3** (268 mg, 0.97 mmol) in $CHCl_3$ (10 mL) was added CF_3CO_2H (2 mL). The mixture was stirred for 3 h at 25°C and the colour of the solution changed from orange to blue. 6 N HCl (10 mL) was added to the blue solution and stirring continued for 2 d in air at 25°C until the blue colour changed to red. The mixture was poured into water (100 mL) and extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 10% aq K_2CO_3 solution, the dark aq K_2CO_3 solution was acidified with 1 N HCl to pH 3 and extracted with $CHCl_3$. The $CHCl_3$ solution was evaporated to gave a red solid. The solid was purified by silica gel flash chromatography using $CHCl_3$/AcOH (20:1) as eluent to afford two products **4** (202 mg, 76%) and **5** (30 mg, 12%) as red solids.

4; mp 123–125°C.

IR (KBr): $\nu = 1732.2$, 1672.6 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 10.00$ (br, 2 H, 2 × OH), 6.80 (s, 2 H, 2 × ArH), 4.22 (s, 6 H, 2 × OCH_3), 4.16 (s, 6 H, 2 × OCH_3), 3.82 (s, 6 H, 2 × CO_2CH_3).

HRMS: *m/z* calc. for $C_{28}H_{22}O_{12}$ 550.11115; found 550.11159.

5:

^{1}H NMR ($CDCl_3$): $\delta = 16.04$ (s, 2 H, 2 × OH), 10.35 (s, 2 H, 2 × OH), 6.52 (s, 2 H, 2 × ArH), 4.01 (s, 6 H, 2 × OCH_3), 3.80 (s, 6 H, 2 × CO_2CH_3).

HRMS: *m/z* calc. for $C_{26}H_{18}O_{12}$ 522.07983; found 522.08197.

Dimethyl 2,4,6,7,9,11-Hexamethoxy-3,10-perylenequinone-1,12-dicarboxylate (6):
A solution of CH_2N_2 in Et_2O (30 mL) was added to a solution of **4** (200 mg, 0.17 mmol) in CH_2Cl_2 (15 mL) at 0°C. The mixture was stirred for 20 min at 25°C, and evaporated to give **6** (210 mg, 99%) as a red solid; mp 127–129°C.

IR (KBr): $\nu = 1731.0$, 1624.8 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 6.80$ (s, 2 H, 2 × ArH), 4.20 (s, 6 H, 2 × OCH_3), 4.15 (s, 6 H, 2 × OCH_3), 4.12 (s, 6 H, 2 × OCH_3), 3.82 (s, 6 H, 2 × CO_2CH_3).

HRMS: *m/z* calc. for $C_{30}H_{26}O_{12}$ 578.14246; found 578.14304.

Dimethyl 4,9-Dihydroxy-2,6,7,11-tetramethoxy-3,10-perylenequinone-1,12-dicarboxylate (7):
To a solution of **6** (100 mg, 0.17 mmol) in $CHCl_3$ (10 mL) was added 48% HBr (5 mL) with stirring for 1 h at 25°C. The mixture was poured into water (100 mL) extracted with $CHCl_3$ and dried. The residue was purified by preparative TLC using $CHCl_3$ as eluent to afford red product **7** (85 mg, 89%); mp 293–294°C.

UV-Vis ($CHCl_3$): $\lambda = 272$, 458, 524, 562 nm.

IR (KBr): $\nu = 1735.0$, 1611.8 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 16.31$ (s, 2 H, 2 × OH), 6.46 (s, 2 H, 2 × ArH), 4.22 (s, 6 H, 2 × OCH_3), 3.99 (s, 6 H, 2 × OCH_3), 3.84 (s, 6 H, 2 × CO_2CH_3).

HRMS: *m/z* calc. for $C_{28}H_{22}O_{12}$ 550.11115; found 550.11116.

Dimethyl 2,3,6,7,10,11-Hexamethoxy-4,9-perylenequinone-1,12-dicarboxylate (8) and Dimethyl 2,4,6,7,10,11-Hexamethoxy-3,9-perylenequinone-1,12-dicarboxylate (9):

To a solution of **7** (100 mg, 0.18 mmol) in acetone were added Ag_2O (200 mg) and MeI (0.5 mL). The mixture was stirred for 10 h at 25 °C in the dark, and then filtered and washed with $CHCl_3$. The filtrate was evaporated, and the residue was purified by preparative TLC using $CHCl_3$/MeOH (50:1) as eluent. Three fractions were collected and evaporated to afford yellow, orange and red solids, respectively.

Yellow dimethyl ether **8** (25 mg, 24%); mp 119–121 °C.

IR (KBr): $\nu = 1734.7, 1632.5\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 6.11$ (s, 2H, 2 × ArH), 4.07 (s, 6H, 2 × OCH_3), 4.04 (s, 6H, 2 × OCH_3), 3.90 (s, 6H, 2 × OCH_3), 3.82 (s, 6H, 2 × CO_2CH_3).

HRMS: *m/z* calc. for $C_{30}H_{26}O_{12}$ 578.14246, found 578.14121.

Orange dimethyl ether **9** (34 mg, 32%); mp 156–158 °C.

IR (KBr): $\nu = 1737.5, 1630.8\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 6.72$ (s, 1H, ArH), 6.05 (s, 1H, ArH), 4.17 (s, 6H, 2 × OCH_3), 4.05 (s, 6H, 2 × OCH_3), 3.98 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.79 (s, 6H, 2 × CO_2CH_3).

HRMS: *m/z* calc. for $C_{30}H_{26}O_{12}$ 578.14246, found 578.14269.

Red dimethyl ether **6** (25 mg, 24%) (for spectral data, see above).

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(1) Weiss, U.; Nasini, G. *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1.
Iida, T.; Kobayashi, E.; Yoshida, M.; Sano, H. *J. Antibiot.* **1989**, *XLII*, 1475.
(2) de Riccardis, F.; Iorizzi, M.; Riccio, R.; Richer de Forges, B.; Debitus, C. *J. Org. Chem.* **1991**, *56*, 6781.
(3) Diwu, Z.J.; Lown, J.W. *Photochem. Photobiol.* **1990**, *52*, 609.
Diwu, Z.; Lown, J.W. *Pharmac. Ther.* **1994**, *63*, 1.
(4) Meruelo, D.; Lavie, G. *PCT Int. appl. 1989*, WO 8909056.
Kobayashi, E.; Ando, K.; Nakano, H.; Tamaoki, T. *J. Antibiot.* **1989**, *XLII*, 153.
Nishizuka, Y. *Cancer* **1989**, *63*, 1892.
Hudson, J.B.; Zhou, J.; Chen, J.; Harris, L.; Yip, L.; Towers, G.H.N. *Photochem. Photobiol.* **1994**, *60*, 253.
(5) Kobayashi, E.; Nakano, H.; Morimoto, M.; Tamaoki, T. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 548.
Diwu, Z.; Zimmermann, J.; Meyer, T.; Lowm, J.W. *Biochem. Pharmacol.* **1994**, *47*, 373.
(6) Jakobivits, A.; Rosenthal, A.; Capon, D.J. *EMBO J.* **1990**, *9*, 1165.
Chowdhury, M.I.H.; Koyanagi, Y.; Kobayashi, S.; Hamamoto, Y.; Yoshiyama, H.; Yoshida, Y.; Yamamoto, N. *Virology* **1990**, *176*, 126.
Laurence, J.; Sikder, S.K.; Jhaveri, S.; Salmon, J.E. *Biochemm. Biophys. Res. Commun.* **1990**, *166*, 349.
(7) Dallacker, F.; Leidig, H. *Chem. Ber.* **1979**, *112*, 2672.
(8) Zhao, C.; Zhang, P. *Tetrahedron Lett.* **1988**, *29*, 225.
Zhao, C.; Zhang, X.; Zhang, P. *Liebigs Ann. Chem.* **1993**, 35.
(9) Diwu, Z.J.; Lown, J.W. *Tetrahedron* **1992**, *48*, 45.
(10) Broka, C.A. *Tetrahedron Lett.* **1991**, *32*, 859.
(11) Coleman, R.S.; Grant, E.B. *J. Am. Chem. Soc.* **1994**, *116*, 8795.
Hauser, F.M.; Sengupta, D.; Colert, S.A. *J. Org. Chem.* **1994**, *59*, 1967.
(12) Liu, J.; Diwu, Z.; Lown, J.W. *Tetrahedron* **1993**, *49*, 10785.
(13) Cameron, D.W.; Chan, H.W.S.; Thoseby, M.R. *J. Chem. Soc. (C)* **1969**, 631.
(14) Diwu, Z.; Lown, J.W. *J. Photochem. Photobiol. A: Chem.* **1992**, *64*, 273.
(15) Cameron, D.W.; Feutrill, G.I.; Pannan, L.J.H. *Aust. J. Chem.* **1980**, *33*, 2531.