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The construction of novel perylenequinone core via efficient synthesis of versatile *ortho*-naphthoquinone as a key intermediate

Beom-Tae Kim [a,d], Ho-Seok Kim [b], Woo Sung Moon [c,d], Ki-Jun Hwang [a,b,*]

[a] *Research Center of Bioactive Materials, Chonbuk National University, Dukjindong 664-14, Chonju 561-756, Republic of Korea*
[b] *Department of Chemistry, Chonbuk National University, Dukjindong 664-14, Chonju 561-756, Republic of Korea*
[c] *Department of Pathology, Chonbuk National University Medical School, Chonbuk National University, Dukjindong 664-14, Chonju 561-756, Republic of Korea*
[d] *The Center for Healthcare Technology Development, Chonbuk National University, Dukjindong 664-14, Chonju 561-756, Republic of Korea*

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ABSTRACT

The novel perylenequinone core, 1,12-diacetonitrile-3,10-perylenequinone, was successfully prepared from the dimerization of the key intermediate, 3-acetonitrile-1,2-naphthoquinone, which was synthesized by an efficient synthetic route in relatively short reaction steps (seven steps) and satisfactory overall yield. The perylenequinone core containing the acetonitrile functionality is notable in the sense that the versatile acetonitrile group could be utilized to prepare various compounds at a later synthetic stage for the development of new and novel perylenequinone derivatives as potential photodynamic agents.

1. Introduction

4,9-Dihydroxy-3,10-perylenequinones are known to be biologically active natural pigments that contain a common extended aromatic unit in their molecules.[1] This class of compounds identified to date includes hypocrellins, cercosporin, phleichrome, and calphostines, etc. (Fig. 1). Most of these pigments are produced mainly by a wide variety of molds, and they act as photodynamic phototoxins to their hosts.[2] Due to their unique photosensitive properties, considerable attention has been paid to the promising application of these perylenequinones to the photodynamic therapy (PDT) of anticancer agents.[3] More specifically, some compounds of this class, such as cercosporin, phleichrome, and calphostins, are known to be potent and specific inhibitors of protein kinase C (PKC),[4] which is a regulatory enzyme crucial to cell division and differentiation. This inhibitory activity demonstrates that these compounds may act as promising anticancer and anti-HIV agents.[5] In addition, a recent report demonstrated that perylenequinones act as broad-spectrum fungicides by generating reactive oxygen species.[6] Therefore, because of their interesting bioactivities and potential application to the promising research areas mentioned above, considerable efforts[7] have been devoted to the development of an efficient method for the synthesis of perylenequinones, which avoids pretty lengthy reaction steps.

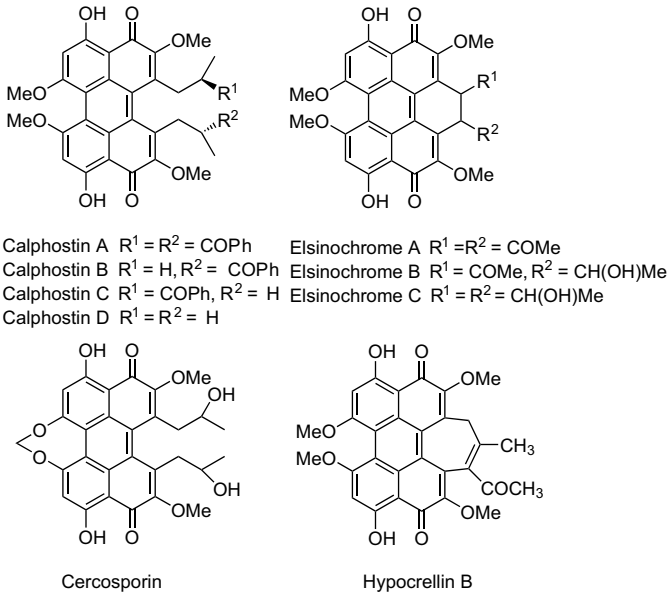

Figure 1. Molecular structures of some naturally occurring perylenequinones.

* Corresponding author. Tel.: +82 63 270 3577; fax: +82 63 270 4322.
E-mail address: kijun@chonbuk.ac.kr (K.-J. Hwang).

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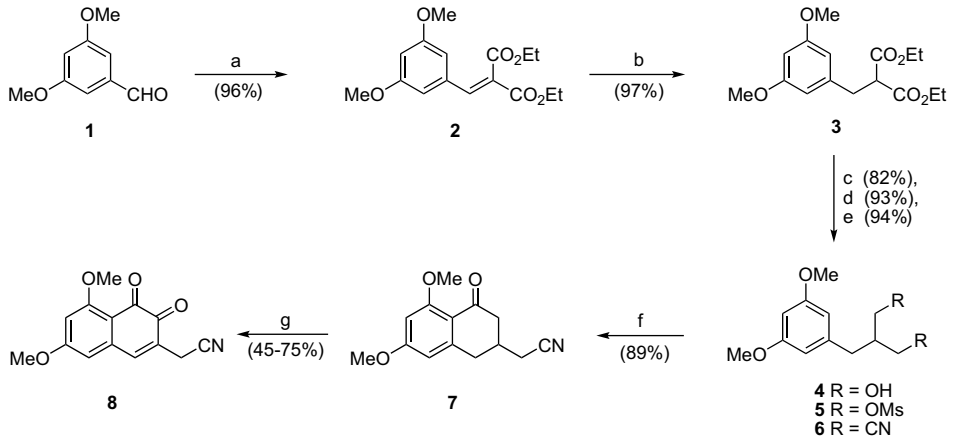


Scheme 1. The synthetic route to 1,2-naphthoquinone (**8**); (a) Ethyl malonate, piperidine, benzoic acid, rt; (b) $NaBH_4$; (c) LAH, THF, rt; (d) MsCl, pyridine, O °C; (e) NaCN, DMSO, rt; (f) (i) $ZnCl_2$, HCl, (ii) H^+, H_2O, reflux; (g) SeO_2, AcOH, 70 °C.

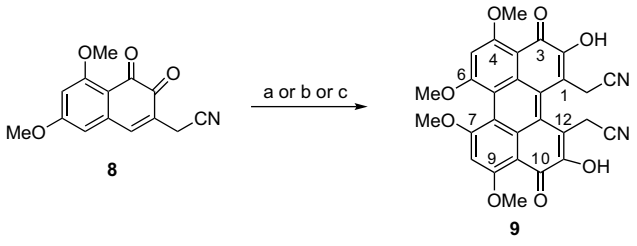
Our literature survey showed that most research has focused on the total synthesis of some natural perylenequinones,[7b,c,g,i,m] or on the investigation of the dimerization reaction conditions of 1,2-naphthoquinones,[7a,d–f] which are considered to be the key intermediates for perylenequinones. However, the synthetic routes reported previously required relatively lengthy reaction steps. In addition, there are only a few reports on the synthetic efforts to prepare the perylenequinone derivatives with diverse structural features on the perylenequinone core. The analysis of the structural features of perylenequinones reported previously also showed that the functional diversity of substitutions at the 1- and 12-position of perylenequinones is likely to play a crucial role in the dimerization step in terms of the successful formation of the perylenequinones. The diversity of these substitutions may also be responsible for large fluctuation in yields.[7]

So, the preparation of new and novel perylenequinone derivatives may be dependent on the efficient introduction of side substituents in early synthetic stages. In our synthetic program, we designed the target perylenequinone substituted with acetonitrile functionality at the 1- and 12-position of perylenequinones, which could be easily converted to other important functionalities such as ketones or amines by a common chemical process. Herein, we report the synthetic details to prepare the key intermediate, 3-acetonitrile-1,2-naphthoquinone (**8**), and its dimerized product, perylenequinones **9**.

2. Results and discussion

The construction of perylenequinoid chromophore (4,9-dihydroxy-3,10-perylenequinone) has generally been accomplished by the dimerization of an appropriately functionalized 1,2-naphthoquinone. So, our primary synthetic work was focused on the efficient construction of 3-acetonitrile-1,2-naphthoquinone (**8**) as a key intermediate for perylenequinone (Scheme 1). The synthesis began by condensing 3,5-dimethoxybenzaldehyde with ethyl malonate to produce a conjugated dicarboxylate **2**. The next compound **3** was successfully prepared by reducing compound **2** with $NaBH_4$ in 97% yield. The diester groups of dicarboxylate **3** were sequentially converted uneventfully to dinitrile **6** via diol **4** and dimesylate **5** in 72% overall yield. Several attempts were made to prepare diol **4** from dicarboxylate **2**. Thus, the direct reduction approaches to prepare diol **4** by utilizing either lithium aluminum hydride (LAH) or hydrogenation in the presence of iodine were unsuccessful. In the next step, the intramolecular Hoesch condensation method was applied to dinitrile **6** to provide bicyclic ketone **7** in 89% yield.[8] Now, the key intermediate, 3-acetonitrile-1,2-naphthoquinone (**8**), was successfully synthesized by oxidizing ketonitrile **7** with selenium dioxide in acetic acid.[9] However, the isolation yield fluctuated (45–75%) because this material showed a strong affinity for adsorbent, i.e., silica gel in separation column. Efforts to search for better separation options, such as different packing materials and solvent systems are now under progress. Our synthetic route requires relatively short reaction steps (seven steps) and the overall yield is fairly good compared with previous reports[2,7b,i,m] for other functionalized 1,2-naphthoquinones.

With this intermediate, 3-acetonitrile-1,2-naphthoquinone (**8**), in hand, we moved on to prepare the target compound, 1,12-diacetonitrile-3,10-perylenequinone (**9**). Since the substituents on the 3-position of 1,2-naphthoquinone are known to be critical in the dimerization step in terms of the large fluctuation in yields, and the successful formation of perylenequinones,[7] it was very interesting to investigate the dimerization reaction of compound **8** with the novel substituent at this position (Scheme 2). Therefore, we carefully applied several reaction conditions hitherto reported in the literature to dimerize 1,2-naphthoquinone **8**. Under an oxidative dimerization condition (10% $FeCl_3$, CH_3CN),[7d,l,m] the desired product, perylenequinone **9**, was obtained as a dark red solid, but the yield was not very satisfactory (18–34%) and inconsistent. The structure of compound **9** was elucidated by the analysis of ^1H and ^{13}C NMR, high resolution mass spectrum, UV, and IR spectra. The three broad absorption bands at 271, 490, and 562 nm from the UV spectrum and the strong absorption band at 1620 cm^{-1} from the IR spectrum are reported to be typical patterns for the quinone system.[10] In this reaction, no apparent by-products were observed except for a large amount of tar materials, suggesting the massive decomposition of putative chemical species during the reaction process. Meanwhile, Hauser et al.[7i] reported the other versatile condition in which the dimerization occurred through the acid-catalyzed process. So, by adopting Hauser's method, 1,2-naphthoquinone



Scheme 2. The dimerization of *ortho*-naphthoquinone (**8**) to perylenequinone (**9**); (a) 10% $FeCl_3$, CH_3CN, rt; (b) TFA, 0 °C; (c) TFA, 0 °C, then 6 N HCl, 2 days.

8 was treated with TFA to produce the dimerized compound **9**, which resulted in a somewhat improved and consistent yield (40%), along with a small amount of unreactive starting material (15%) and massive tar (Scheme 2). To improve the dimerization yield, several other conditions (temperature, reaction time, acid medium variation (Scheme 2, Method C), etc.) were varied with no success. So, while our results showed that the perylenequinone derivative **9** could be prepared via both oxidative and acid-catalyzed dimerization albeit in moderate yield, any apparent mechanism to operate in the dimerization process was not clear in this stage, as is evident from the results of this study.

In summary, the novel perylenequinone derivative 1,12-diacetonitrile-3,10-perylenequinone (**9**) was successfully prepared from the dimerization of the key intermediate, 3-acetonitrile-1,2-naphthoquinone (**8**), which was synthesized by an efficient synthetic route in terms of relatively short reaction steps (seven steps) and satisfactory overall yield. However, more elaborate experimental designs for the dimerization of the naphthoquinone should be considered to improve the overall yield for the perylenequinone in this multistep synthesis. The perylenequinone core **9** containing the acetonitrile functional group will be utilized very efficiently at a later stage to prepare various compounds as potential photodynamic agents. The further synthetic elaboration of compound **9** to the final bioactive 3,10-perylenequinone and the analysis of its photochemical properties are now under investigation.

3. Experimental section

3.1. General

Melting points were recorded on an Electrothermal melting point apparatus and were uncorrected. Mass spectra of compounds **2**–**6** were recorded on an HPLC 1200 series-6130 quadrupole LC/MS mass spectrometer, and HR mass spectra of compounds **7**–**9** were recorded on a Synapt HDMS (Waters). Infrared spectra were recorded on a Nicolet-Avatar-330 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol 400 MHz or 600 MHz spectrometer. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as an internal standard. UV spectra were recorded on a HP UV–Visible Chemstation spectrophotometer. All chemicals were purchased from Sigma–Aldrich Co., U.S.A., and all solvents for column chromatography were of reagent grade, and were purchased from commercial sources.

3.2. Diethyl 2-(3,5-dimethoxybenzylidene)malonate (2)

Benzoic acid (0.15 g, 1.20 mmol) was added at room temperature to a mixture of 3,5-dimethoxy benzaldehyde (**1**) (2.0 g, 12.0 mmol), diethyl malonate (1.8 mL, 12.1 mmol), and piperidine (0.18 mL, 1.80 mmol) in dry toluene (50 mL). The mixture was refluxed for 4 h, and water was removed using a Dean–Stark condenser. The mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The organic layer was washed with 5% HCl (100 mL), satd $NaHCO_3$, dried over Na_2CO_3, filtered, and evaporated in vacuo. The residue was subjected to flash column chromatography (silica gel) to afford **2** (3.55 g, 96%) as a colorless oil, which was slowly solidified upon standing at room temperature: mp: 40 °C. IR (film): 1738, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H, H-4′), 6.61 (d, 2H, J=2.0 Hz, H-2, 6), 6.49 (t, 1H, J=2.0 Hz, H-4), 4.33 (q, 2H, J=7.2 Hz, –CH_2–), 4.30 (q, 2H, J=7.2 Hz, –CH_2–), 3.77 (s, 6H, –OCH_3), 1.33 (t, 3H, J=7.2 Hz, –CH_3), 1.30 (t, 3H, J=7.2 Hz, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.52 (–CO–), 163.96 (–CO–), 160.81, 141.95, 134.60, 126.77, 107.16, 102.85, 61.63, 61.58, 55.30 (–OCH_3), 14.06, 13.86; MS $[M+H]^+$ 309.13.

3.3. Diethyl 2-(3,5-dimethoxybenzyl)malonate (3)

Sodium borohydride (0.17 g, 4.51 mmol) was added to an ice-bath cooled solution of dicarboxylate **2** (1.18 g, 4.51 mmol) in absolute ethanol (30 mL). The solution was stirred for 15 min, and then glacial acetic acid (5 mL) was added cautiously. The mixture was condensed, and the residue was resolved in ethyl acetate (150 mL). The organic layer was washed with 1 N HCl (100 mL), satd $NaHCO_3$ (100 mL×2), and brine (100 mL), dried over Na_2CO_3, filtered, and evaporated in vacuo to give a colorless oil (1.15 g, 97%). IR (film): 1731, 1597 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.35 (d, 2H, J=1.8 Hz, H-2, 6), 6.31 (t, 1H, J=1.8 Hz, H-4), 4.17 (m, 4H, –CH_2–), 3.75 (s, 6H, –OCH_3), 3.63 (t, 1H, J=7.8 Hz, H-2′), 3.16 (d, 2H, J=7.8 Hz, H-4′), 1.22 (t, 6H, J=7.8 Hz, –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.74 (–CO–), 160.74, 140.15, 106.72, 98.69, 61.38, 55.15 (–OCH_3), 53.61, 34.83, 13.94; MS $[M+H]^+$ 311.14.

3.4. 2-(3,5-Dimethoxybenzyl)propane-1,3-diol (4)

Diester **3** (17.2 g, 55.5 mmol) in dry THF (50 mL) was slowly added over 1.5 h to a suspension of lithium aluminum hydride (8.43 g, 222.2 mmol) in dry THF (50 mL). The mixture was stirred for 3 h at room temperature. The reaction was quenched by slowly adding ethyl acetate (30 mL), followed by satd NH_4Cl (30 mL). The sludge was removed by filtration and washed with ethyl acetate (100 mL×3). The combined organic layer was dried over Na_2CO_3, filtered, and evaporated in vacuo to give a colorless oil. This oily residue was further purified by the Yamazen MPLC system (flow rate: 20 mL/min, detected at 254 nm) to afford a colorless solid (10.3 g, 82%): mp: 32–34 °C. IR (film): 3450, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.34 (d, 2H, J=2.4 Hz, H-2, 6), 6.31 (t, 1H, J=2.4 Hz, H-4), 3.77 (dd, 2H, J=10.0, 4.0 Hz, H_a-1′, 3′), 3.76 (s, 6H, –OCH_3), 3.65 (dd, 2H, J=10.0, 7.2 Hz, H_b-1′, 3′), 2.77 (s, 2H, –OH), 2.54 (d, 2H, J=7.6 Hz, H-4′), 2.04 (m, 1H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.62, 142.17, 107.00, 97.90, 65.26, 55.24, 43.68, 34.59; MS $[M+H]^+$ 227.12.

3.5. 2-(3,5-Dimethoxybenzyl)propane-1,3-diol dimesylate (5)

To diol **5** (9.8 g, 43.18 mmol) in methylene chloride (100 mL) were added triethylamine (14.4 mL, 103.3 mmol) and methanesulfonyl chloride (8.02 mL, 103.3 mmol) in an ice-bath. The mixture was stirred for 3 h at ambient temperature. The mixture was poured into ice-water and extracted with methylene chloride (100 mL×2). The combined organic layer was washed with 1% HCl (100 mL×2), water (100 mL×2), dried over Na_2CO_3, filtered, and evaporated in vacuo to give a pale yellow solid (15.4 g, 93%). Compound **5** was used without further purification: mp: 65–66 °C. IR (film): 1346, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 3H, H-2, 4, 6), 4.26 (dd, 2H, J=10.0, 4.4 Hz, H_a-1′, 3′), 4.18 (dd, 2H, J=10.0, 6.0 Hz, H_b-1′, 3′), 3.77 (s, 6H, –OCH_3), 3.03 (s, 6H, –CH_3), 2.68 (d, 2H, J=7.2 Hz, H-4′), 2.46 (m, 1H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.88, 139.31, 106.89, 98.63, 67.77, 55.23, 39.81, 37.17, 33.51; MS $[M+H]^+$ 383.08.

3.6. 3-(3,5-Dimethoxybenzyl)pentanedinitrile (6)

Sodium cyanide (3.19 g, 65.1 mmol) was added to the solution of dimesylate **5** (8.30 g, 21.7 mmol) in dimethylsulfoxide (80 mL) at room temperature. The mixture was stirred for 1 h at 80 °C. The mixture was poured into ice-water and extracted with ether (200 mL×2). The combined organic layer was washed thoroughly with water (100 mL×5), dried over Na_2CO_3, filtered, and evaporated in vacuo to give an oily residue (4.97 g, 94%). IR (film): 2250, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (t, 1H, J=2.4 Hz, H-4), 6.32 (d, 2H, J=2.4 Hz, H-2, 6), 3.78 (s, 6H, –OCH_3), 2.76 (d, 2H,

J=6.8 Hz, H-4′), 2.54 (dd, 2H, J=16.4, 5.6 Hz, H_a-1′, 3′), 2.46 (dd, 2H, J=16.4, 6.0 Hz, H_b-1′, 3′), 2.41 (m, 1H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.98, 138.62, 116.84 (–CN), 106.73, 98.80, 55.20 (–OCH_3), 39.04, 34.44, 21.11; MS $[M+H]^+$ 245.12.

3.7. 2-(5,7-Dimethoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetonitrile (7)

Zinc chloride (4.71 g, 34.58 mmol) was added to a solution of dinitrile **6** (4.97 g, 20.34 mmol) in dry ether (100 mL). Hydrogen chloride gas was passed through the mixture for 2 h. The ether layer was discarded, and the resultant white solid was resolved in water and refluxed for 2 h. After cooling, the mixture was diluted with water and extracted with methylene chloride (200 mL×2). The combined organic layer was washed with satd $NaHCO_3$ (100 mL×2), brine (100 mL), and water (100 mL×2), dried over Na_2CO_3, filtered, and evaporated in vacuo to produce an off-white solid (4.45 g, 89%). Compound **7** was used without further purification: mp: 122–123 °C. IR (film): 2250, 1685, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, 1H, J=2.0 Hz, H-6), 6.35 (d, 1H, J=2.0 Hz, H-8), 3.89 (s, 3H, –OCH_3), 3.86 (s, 3H, –OCH_3), 3.09 (dd, 1H, J=15.6, 2.0 Hz, H_a-3), 2.86 (dd, 1H, J=16.8, 10.8 Hz, H_a-1), 2.77 (dd, 1H, J=16.8, 2.0 Hz, H_b-3), 2.54 (m, 1H, H-2), 2.51 (dd, 1H, J=19.2, 6.0 Hz, H_a-2′), 2.44 (dd, 1H, J=16.8, 10.8 Hz, H_b-1), 2.43 (dd, 1H, J=16.8, 6.0 Hz, H_b-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.10 (–CO–), 164.57, 162.88, 146.16, 117.63 (–CN), 115.56, 105.19, 97.79, 56.11, 55.60, 45.68, 36.43, 31.67, 23.11; HRMS (ESI): m/z 246.1030 ($[M+H]^+$, calcd for $C_{14}H_{16}NO_3$ 246.1052).

3.8. 2-(5,7-Dimethoxy-3,4-dioxo-3,4-dihydronaphthalen-2-yl)acetonitrile (8)

Selenium dioxide (0.64 g, 5.75 mmol) was added to a solution of bicyclic ketone **7** (0.47 g, 1.92 mmol) in glacial acetic acid (5 mL) with stirring and the mixture was kept for 2 h at 70 °C. The mixture was poured into ice-water and extracted with methylene chloride (50 mL×2). The organic layer was washed with satd $NaHCO_3$ and water, dried over Na_2CO_3, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford **8** (0.38 g, 77%) as a brown-red solid: mp: 198–215 °C (decomposed). IR (film): 2250, 1666, 1649 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (s, 1H, H-1), 6.90 (s, 1H, H-6), 6.71 (s, 1H, H-8), 3.92 (s, 3H, –OCH_3), 3.90 (s, 3H, –OCH_3), 3.67 (s, 2H, H-1′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.15 (–CO–), 174.16 (–CO–), 166.17, 165.04, 142.10, 137.18, 130.09, 117.53 (–CN), 112.17, 110.77, 99.83, 56.35 (–OCH_3), 56.22 (–OCH_3), 17.55; HRMS (ESI): m/z 280.0588 ($[M+Na]^+$, calcd for $C_{14}H_{11}NO_4Na$ 280.0586).

3.9. 2,2′-(2,11-Dihydroxy-4,6,7,9-tetramethoxy-3,10-dioxo-3,10-dihydroperylene-1,12-diyl)diacetonitrile (1,12-diacetonitrile-3,10-perylenequinone) (9)

Method A. A solution of 1,2-naphthoquinone **8** (170 mg, 0.66 mmol) and anhydrous ferric chloride (170 mg, 1.06 mmol) in 2 mL of anhydrous acetonitrile was stirred at room temperature for 3 h. The reaction mixture was poured into 3% aqueous HCl, and then extracted with chloroform (50 mL×3). The organic layer was washed with water, dried over Na_2CO_3, filtered, and evaporated in vacuo to afford a dark red solid. This solid was redissolved in chloroform and then mixed with a 10% aqueous ethanol solution of zinc acetate. This Zn-complex thus formed was washed with chloroform (50 mL×3), and then decomposed by 10% aqueous HCl to release perylenequinone **9**, which was again extracted with chloroform (10 mL×3). The combined extracts were evaporated in vacuo to afford a dark red solid (40 mg, 34%): mp: 212–215 °C (decomposed). IR (film) 3450, 2253, 1620 (an extended quinone system) cm^{-1}; UV λ_{max} ($CHCl_3$) 271 (lg ε=2.99), 490 (2.01), 562 (0.70); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 2H, 2, 11-OH), 6.79 (s, 2H, H-5 and H-8), 4.23 (s, 6H, –OCH_3×2), 4.15 (s, 6H, –OCH_3×2), 3.99 (d, 2H, J=16.8 Hz, H_a-2′, H_a-2″), 3.64 (d, 2H, J=16.8 Hz, H_b-2′, H_b-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.74 (–CO–), 165.82, 165.24, 151.39, 130.72, 127.66, 116.27 (–CN), 112.08, 108.43, 105.93, 94.47, 55.78, 56.42, 18.50; HRMS (ESI): m/z 513.1293 ($[M+H]^+$, calcd for $C_{28}H_{21}N_2O_8$ 513.1298). *Method B*. A neat solution of 1,2-naphthoquinone **8** (100 mg, 0.39 mmol) in trifluoroacetic acid (2 mL) was stirred at 0 °C for 4 h. The solution instantly turned green and then dark blue over 30 min. The mixture was poured into ice-cold water, and then the same purification process described in Method A was applied to afford compound **9** (40 mg, 40%). The chloroform layer after treatment with the solution of zinc acetate was concentrated in vacuo and subjected to flash column chromatography to produce the starting material **8** (elution solvent system: $CHCl_3$/MeOH=15:1 v/v, 15 mg, 15%) and an unknown material (10 mg). *Method C*. A neat solution of 1,2-naphthoquinone **8** (124 mg, 0.48 mmol) in trifluoroacetic acid (2 mL) was stirred at 0 °C for 4 h. Aqueous HCl (6 N, 5 mL) was added to the resultant blue solution and stirred for 2 days in air at the ambient temperature. The mixture was poured into ice-cold water, and then the same purification process described in Method A was applied to afford compound **9** (30 mg, 24%).

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