DOI: 10.1002/ejoc.200700426

Synthesis of 1,1,3-Trisubstituted Naphtho[2,3-*c*]pyran-5,10-dione Derivatives as Potential Redox Switches

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Keywords: Quinones / Redox chemistry / Fluorescence / Donor–acceptor systems

Five 1,1,3-trisubstituted naphtho[2,3-*c*]pyran-5,10-dione derivatives were designed and synthesized in five steps from 2-acetyl-1,3-indandione. Prepared quinones **6a–e** instantly changed from either red or blue to yellow or orange red, when treated with sodium borohydride in methanol. The resulting reduced hydroquinones **9a–e** reverted to their original colors within a few minutes after the reducing agent was consumed or removed. Whereas no fluorescence of blue quinone **6e** was detected prior to reduction, reduced hydroquinone **9e** emitted red fluorescence with a quantum yield of 0.07.

Introduction

Naphtho[2,3-*c*]pyran-5,10-diones are an important class of naturally occurring compounds as they have favorable antimicrobial, antiparasitic, and phytotoxic activities.[1] Their broad range of biological activities have made these molecules attractive synthetic targets for organic chemists. Various synthetic strategies for the synthesis of pyranonaphthoquinones have therefore been reported in the literature.[2] The core structure of naphtho[2,3-*c*]pyran-5,10-dione contains a pyran-fused naphthoquinone moiety. Quinones are excellent electron acceptors and are known to be efficient quenchers of the singlet state donor fluorescence of various fluorophores.[3] The quenching efficiency depends on the redox potentials of the corresponding quinone–hydroquinone system. Whereas most of the prepared naphtho[2,3-*c*]pyran-5,10-dione derivatives are red because of the intrinsic pyranonaphthoquinone chromophore, the corresponding reduced hydroquinones are yellow. This information prompted us to investigate the possibility of using the naturally occurring naphtho[2,3-*c*]pyran-5,10-dione structure as a reversible redox switch. A suitable redox switch may function as a noninvasive fluorogenic probe for the real-time visualization and quantification of molecular processes in vivo.[4] Figure 1 shows the structure of the rationally designed potential donor–acceptor system with an electron-donating *N*,*N*-dimethylaminophenyl moiety as the fluorophore and an electron-withdrawing naphthoquinone as the fluorescence quencher. The quinonic moiety was directly attached to the π system of the fluorophore. The *gem*-dimethyl groups on the pyran ring at the right-hand side of the molecule were incorporated to prevent possible oxygen-promoted aromatization. In addition to serving as a fluorophore, the *N*,*N*-dimethylamino group at the *para* position of the benzene ring can further extend the UV absorption wavelength far into the visible range. The modified synthesis of the proposed 1,1,3-trisubstituted naphtho[2,3-*c*]pyran-5,10-diones is described here and their potential to function as active redox switches is evaluated.

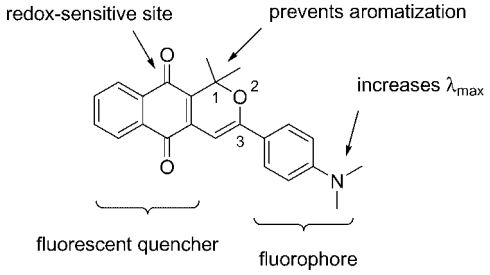

Figure 1. Design of a potential donor–acceptor system containing an *N*,*N*-dimethylaminobenzene moiety and a naphthoquinone group.

Results and Discussion

The seven-step preparation of 1,3-disubstituted naphtho[2,3-*c*]pyran-5,10-diones from naphthoquinone was previously reported.[5] The common intermediate in the synthesis was 2-acetyl-4-methoxy-1-naphthol (**1**), which was prepared from naphthoquinone in three steps. Here, a diazomethane-mediated ring expansion reaction was exploited to construct this key naphthol derivative in one pot to reduce the overall number of synthetic steps. The synthesis started with an exhaustive diazotization of commercially

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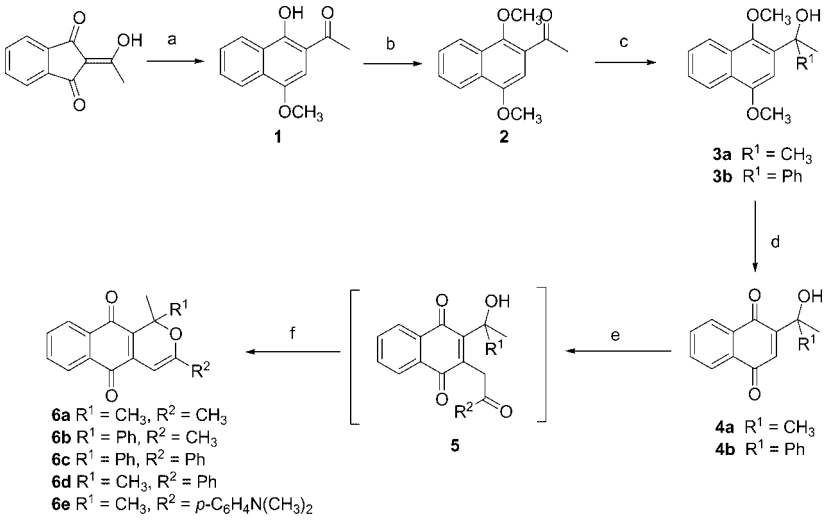
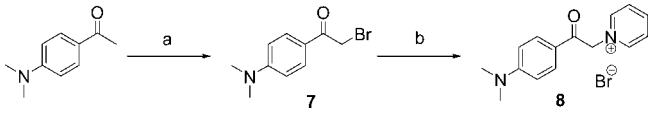


Scheme 1. Reagents and conditions: (a) CH_2N_2, CH_2Cl_2, 0 °C, 1 h; (b) K_2CO_3, CH_3I, CH_3CN, room temp., 4 d; (c) 1. R^1MgBr, THF, room temp., 1 h, 2. aqueous NH_4Cl; (d) CAN, CH_3CN/H_2O, room temp., 15 min; (e) *N*-acylmethylpyridinium salt, Et_3N, CH_3CN, 50 °C → room temp., 12 h; (f) TsOH (cat.), benzene, reflux, 10 min.

available 2-acetyl-1,3-indandione in dichloromethane to give the ring-expansion product 2-acetyl-4-methoxy-1-naphthol (**1**) (Scheme 1) in 40% yield.[6] Naphthol **1** was then treated with an excess amount of methyl iodide and potassium carbonate in dry acetone to afford the corresponding 2-acetyl-1,4-dimethoxynaphthalene (**2**) in 90% yield, which underwent reaction with either methyl or phenylmagnesium bromide in THF to form tertiary alcohols **3a** and **3b** in 80 and 35% yields, respectively. Oxidative demethylation of alcohols **3a**,**b** with 4 equiv. of cerium(IV) ammonium nitrate in aqueous acetonitrile at room temperature gave the corresponding quinones **4a**,**b** in 72–75% yields. The phenacylmethyl group was introduced into quinones **4a**,**b** by using various *N*-acylmethylpyridinium salts and triethylamine in acetonitrile under an atmosphere of nitrogen at 50 °C. The final intramolecular condensation of transient compound **5** into targets **6a**–**e** was performed in toluene, which allowed complete dehydration by treatment with 0.2 equiv. of *p*-toluenesulfonic acid over a period of 10 min in 90–97% yields.[5] Scheme 2 shows the preparation of the commercially unavailable *N*-acylmethylpyridinium bromide **8**, which was used for the synthesis of **9e** in Scheme 1. 4′-*N*,*N*-Dimethylaminoacetophenone was initially brominated in the presence of hydrobromic acid at 0 °C for 1 h to give bromomethyl ketone **7**,[7] followed by treatment with pyridine in acetone under reflux conditions to afford the corresponding pyridinium bromide **8** quantitatively. The structure of compound **6c** was confirmed by X-ray crystal crystallography, as presented in Figure 2.



Scheme 2. Reagents and conditions: (a) Br_2, HBr, 0 °C, 1 h; (b) pyridine, acetone, reflux, 6 h.

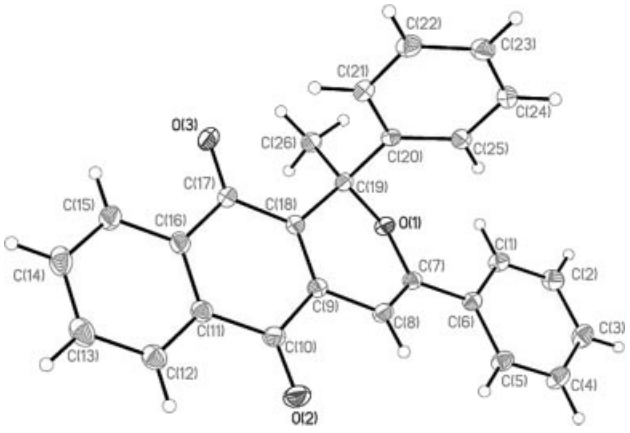


Figure 2. X-ray crystal structure of compound **6c**.

When red quinones **6a**–**d** and blue **6e** were reduced with sodium borohydride in methanol, the solutions instantly turned yellow and orange red, respectively. The resulting reduced hydroquinones **9a**–**d** returned to their original colors within a few minutes after the reducing agent was either consumed or removed (Figure 3). UV absorption measurements indicated high yields (>98%) for the chemical conversion of **6a**–**e** into **9a**–**e** as well as in the opposite direction. The structure of the air-sensitive hydroquinone was verified by trapping **9c** in situ with dimethyl sulfate under basic conditions to give the corresponding 1,4-dimethylated hydroquinone **10c**, as shown in Scheme 3.[8]

Cyclic voltammetry measurements of **6a**–**e** were performed in acetonitrile to explore the substituent effects on their redox potentials. Two one-electron reversible reduction waves were observed at a scan rate of 100 $mV\,s^{-1}$ for all synthesized compounds. Figure 4 shows the cyclic voltammogram of **6a**. The first reversible reduction wave (–0.74 V vs. Ag/AgCl) represents the addition of one electron to the quinone core to form a semiquinone anion radi-

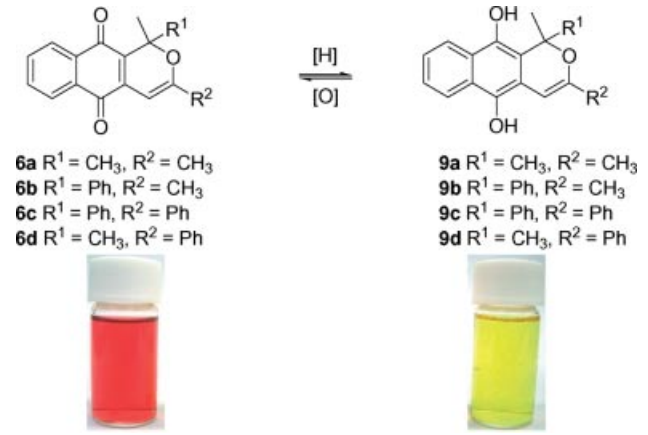
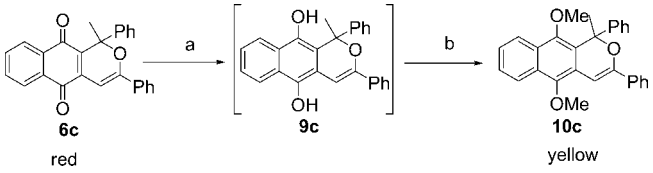


Figure 3. The redox switch between **6a**–**d** and **9a**–**d**, and the corresponding colors in the oxidized (left) and reduced forms (right).



Scheme 3. Reagents and conditions: (a) $NaBH_4$, ethanol/H_2O, 5 min; (b) 1. 10 M aqueous KOH, 5 min, 2. $SO_2(OMe)_2$, reflux, overnight.

cal. The second reversible reduction wave (–1.34 V vs. Ag/AgCl) corresponds to the subsequent addition of a second electron to the semiquinone anion radical, which produces a hydroquinone dianion. The detailed reduction potentials of naphthoquinone and the series **6a**–**e** are listed in Table 1. The results indicate that annulation of the pyran ring on naphthoquinone increases the reduction potentials. Furthermore, introduction of a benzene moiety at the C-1 or C-3 positions of **6a** decreases the reduction potentials, whereas incorporation of an electron-donating *N*,*N*-dimethylamino group at the *para* position of the benzene ring of **6d** increases the reduction potentials.

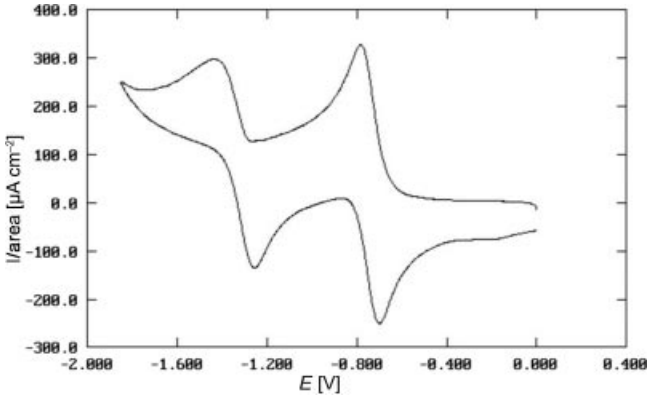


Figure 4. Cyclic voltammogram of **6a** in CH_3CN obtained by using tetra-*n*-butylammonium hexafluorophosphate (0.1 M) as the supporting electrolyte at a scan rate of 100 mV s^{-1}.

Table 1. Reduction potentials of naphthoquinone and compounds **6a**–**e** in acetonitrile with tetra-*n*-butylammonium hexafluorophosphate (0.1 M) as the supporting electrolyte.

Compound	$E^1_{1/2}$ [V][a]	$E^2_{1/2}$ [V][a]
Naphthoquinone	–0.68	–1.06
6a	–0.74	–1.34
6b	–0.71	–1.34
6c	–0.65	–1.19
6d	–0.69	–1.31
6e	–0.76	–1.34

[a] with Ag/AgCl as a reference electrode.

The absorption spectroscopic data for the series **6a**–**e** and **9a**–**e** in methanol are listed in Table 2. Figure 5 presents the UV/Vis absorption spectra of **6a** prior to and after reduction. It displays an intense band with a maximum near 280 nm and a long wavelength broad band at 485 nm before reduction. The former is attributed to π–π* transitions of the quinonic moiety; the latter is associated with the increased π delocalization of the chromophore. The reduction of quinone **6a** to hydroquinone **9a** resulted in the complete disappearance of the long-wavelength absorbance (485 nm) and the appearance of a single intense band at 389 nm, which resembles the absorption behavior of 1,4-dimethylated hydroquinone **10c**. Similar changes in the UV/Vis absorption spectrum of **6e** were also observed. This spectrum displays a long wavelength broad band at 592 nm before reduction and a shorter wavelength band at 467 nm after reduction (Figure 6). Figure 7 shows the redox switch between **6e** and **9e** and the corresponding colors in the oxidized (deep blue) and the reduced (orange red) forms. Reduction of the quinonic group of **6e** to a hydroquinone moiety converts it from an electron-withdrawing group to an

Table 2. Absorption parameters for the series **6a**–**e** and **9a**–**e** in methanol.

Compound	λ_{max} [nm]	log ε
6a	280, 485	4.07, 3.48
6b	274, 475	3.32, 3.45
6c	309, 475	3.67, 3.29
6d	311, 502	4.01, 3.62
6e	350, 592	3.19, 3.04
9a	389	3.90
9b	252, 378	3.87, 3.83
9c	405	3.63
9d	247, 413	3.87, 3.96
9e	255, 311, 467	3.01, 2.83, 3.30

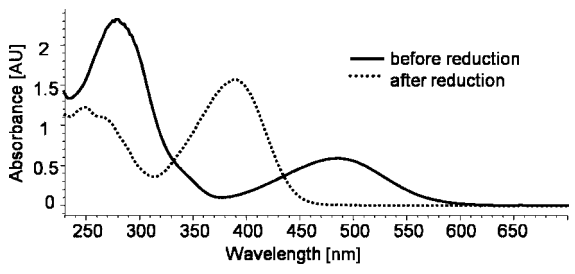


Figure 5. UV/Vis spectra of **6a** (1.97×10^{-4} M in MeOH) prior to and after reduction.

electron-donating group, which results in a profound electronic change in the system and in turn this leads to a change in the emission profile.

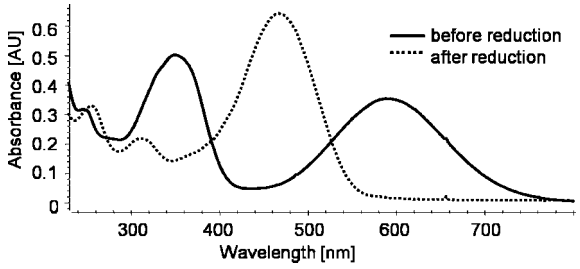


Figure 6. UV/Vis spectra of **6e** (3.26×10^{-4} M in MeOH) prior to and after reduction.

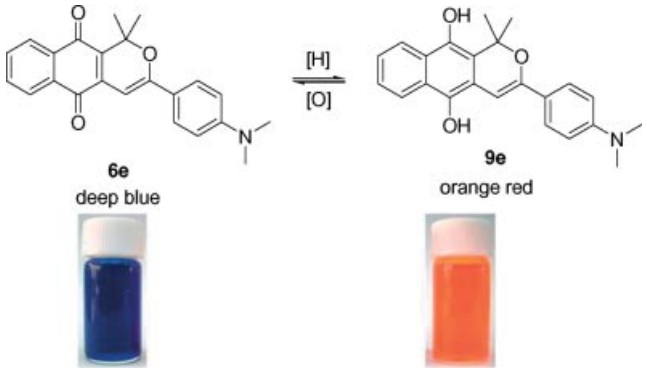


Figure 7. The redox switch between **6e** and **9e**, and the corresponding colors in the oxidized (left) and reduced forms (right).

No fluorescence emission was observed for the synthesized series **6a**–**d** in methanol, whereas their reduced products **9a**–**d** exhibit weak fluorescence emission under the same conditions. Blue quinone **6e** emitted no fluorescence in methanol at room temperature, but the corresponding reduced hydroquinone **9e** was red fluorescent with a quantum yield of 0.07. Table 3 lists the fluorescence parameters of compounds **9a**–**e** in methanol. Figure 8 shows the excitation (478 nm) and emission spectra (594 nm) of **9e** in methanol. The quenching of the intrinsic *N*,*N*-dimethylaminobenzene fluorescence in **6e** is probably caused by the efficient electronic coupling between the *N*,*N*-dimethylaminobenzene donor and the quinonic acceptor. Thus, the reversible redox process between quinone **6e** and hydroquinone **9e** can be regarded as a molecular switching system, in which the absorption and emission properties are controlled by the redox state of the quinonic moiety.

Table 3. Fluorescence parameters for the series **9a**–**e** in methanol.

Compound	λ_{ex} [nm]	λ_{em} [nm]	Stork's shift [cm^{-1}]
9a	309	512	12831
9b	301	501	13263
9c	342	451	7067
9d	344	521	9876
9e	478	594	4085

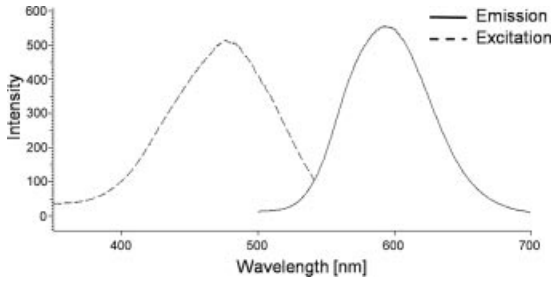


Figure 8. The excitation (478 nm) and emission (594 nm) spectra of **9e** (5.4×10^{-5} M in MeOH) at room temperature.

Conclusions

We synthesized five 1,1,3-trisubstituted naphtho[2,3-*c*]-pyran-5,10-dione derivatives in five steps with an overall yield of 10–21%. The prepared quinones can be instantly reduced by sodium borohydride in methanol with a distinct change in color. The reduced hydroquinones can be oxidized back to quinones by air. Furthermore, the absorption and emission properties of reduced hydroquinone **9e** are controlled by the redox state of the quinonic moiety.

Experimental Section

General: Melting points were determined with a Mel-Temp melting point apparatus in open capillaries and are uncorrected. MS were performed with a JOEL JMS-SX/SX 102A spectrometer. IR spectra were obtained with a 1725X FTIR spectrophotometer. Absorption spectra were acquired with an HP8453 spectrophotometer, and emission spectra were obtained with a Hitachi F-4500 fluorospectrometer. Single-crystal structures were determined with a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz with a Varian VXR300 spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in Hertz. ^1H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm). Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60 H). Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use.

Calculation of Fluorescence Quantum Yields: UV/Vis spectra were measured with an HP8453 spectrometer with a 1-cm path length quartz cell. Fluorescence spectra were measured with a Hitachi F-4500 fluorescence spectrophotometer. Coumarin 6 ($\Phi_f = 0.82$, $\lambda_{max} = 458$ nm in ethanol) was used as an external standard for the measurement of fluorescence quantum yields of **9e**. Fluorescence quantum yields were measured by comparing the integrated area under the fluorescence curve for compound **9e** and coumarin 6 at equal absorbance at the same excitation wavelength. The quantum yields were corrected for the refractive index of the solvent.

Cyclic Voltammetry Measurements: Electrochemical cyclic voltammetry experiments were performed in a three-electrode single-compartment cell by using a platinum disk working electrode, a platinum wire counter electrode and a Ag/AgCl (in a saturated KCl solution) reference electrode. The cell was driven with a PAR

Model 273A. The electrochemical reaction vessel was charged with 5 mL of an acetonitrile solution of **6a**–**e** (1×10^{-3} M) and tetra-*n*-butylammonium hexafluorophosphate (0.1 M) as the electrolyte. The solutions were deoxygenated by bubbling nitrogen through them for approximately 5 min.

2-Acetyl-4-methoxy-1-naphthol (1): To a solution of 2-acetyl-1,3-indandione (500 mg, 2.66 mmol) in dichloromethane (10 mL) was added an excess amount of diazomethane. After the mixture was stirred at 0 °C for 1 h, water (20 mL) was added to the mixture, and the product was extracted twice with dichloromethane. The extract was dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (EtOAc/hexanes, 1:9) to give **1** (230 mg, 40%) as a yellow solid. M.p. 116–117 °C (ref.[6a] 115–116 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.75 (s, 1 H), 8.45 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H), 8.19 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H), 7.69–7.55 (m, 2 H), 6.80 (s, 1 H), 3.97 (s, 3 H), 2.67 (s, 3 H) ppm.

2-Acetyl-1,4-dimethoxynaphthalene (2):[5] To a solution of **1** (500 mg, 2.31 mmol) in acetonitrile (10 mL) was added K_2CO_3 (800 mg, 5.78 mmol) and methyl iodide (1200 mg, 9.24 mmol). The mixture was stirred at room temp. for 4 d. The reaction was then quenched with water (10 mL), and the product was extracted twice with dichloromethane. The extract was dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (EtOAc/hexanes, 1:9) to give **2** (479 mg, 90%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26–8.21 (m, 1 H), 8.18–8.12 (m, 1 H), 7.60–7.55 (m, 2 H), 7.08 (s, 1 H), 3.99 (s, 3 H), 3.94 (s, 3 H), 2.80 (s, 3 H) ppm.

General Procedure for the Preparation of Compounds 3a,b: To a solution of **2** (500 mg, 2.17 mmol) in dried THF (10 mL) under a N_2 atmosphere at room temp. was added a methylmagnesium or phenylmagnesium bromide solution (8.68 mmol in THF). The mixture was stirred for 1 h and then quenched with saturated aqueous ammonium chloride. The product was extracted twice with dichloromethane. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography to give the desired product.

3-(1-Hydroxy-1,1-dimethyl)-1,4-dimethoxynaphthalene (3a):[5] Yellow liquid. Yield: 428 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24–8.21 (m, 1 H), 8.01–7.98 (m, 1 H), 7.55–7.46 (m, 2 H), 6.78 (s, 1 H), 4.92 (s, 1 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 1.72 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6, 145.9, 135.6, 128.5, 126.5, 125.8, 125.2, 122.3, 121.8, 102.1, 73.7, 63.1, 55.6, 31.7 ppm. HRMS (EI): calcd. for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256; found 246.1254.

3-(1-Hydroxy-1-methylphenyl)-1,4-dimethoxynaphthalene (3b): White solid. Yield: 234 mg (35%). M.p. 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.28 (m, 1 H), 7.39–7.89 (m, 1 H), 7.53–7.48 (m, 4 H), 7.34–7.21 (m, 3 H), 7.05 (s, 1 H), 4.08 (s, 3 H), 3.14 (s, 3 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5, 150.5, 146.6, 135.9, 128.5, 127.9, 126.6, 126.0, 125.3, 125.1, 122.4, 121.7, 102.7, 76.6, 61.4, 55.8, 30.9 ppm. IR (KBr): $\tilde{\nu}$ = 3515, 2936, 1591, 1464, 1346, 1225, 1103, 1058, 778, 704, 540 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{20}O_3$ $[M]^+$ 308.1412; found 308.1407.

General Procedure for the Preparation of Compounds 4a,b: To a solution of **3** (1 mmol) in a mixture of water (10 mL) and acetonitrile (10 mL) was added cerium(IV) ammonium nitrate (4 mmol) at room temp. The mixture was stirred for 15 min, and the product was then extracted twice with dichloromethane. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography to give the desired product.

3-(1-Hydroxy-1,1-dimethyl)-1,4-naphthoquinone (4a): Yellow solid. Yield: 156 mg (72%). M.p. 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.05 (m, 2 H), 7.80–7.73 (m, 2 H), 6.97 (s, 1 H), 3.37 (s, 1 H), 1.61 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.5, 185.4, 153.9, 134.0, 133.9, 133.0, 132.7, 131.6, 126.8, 125.9, 71.9, 29.2 ppm. IR (KBr): $\tilde{\nu}$ = 3333 (OH), 1662 (C=O), 1612 (C=O), 1592, 1337, 1307, 1260, 1182, 785, 722 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{12}O_3$ $[M]^+$ 216.0786; found 216.0787.

3-(1-Hydroxy-1-methylphenyl)-1,4-naphthoquinone (4b): Yellow solid. Yield: 209 mg (75%). M.p. 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.07 (m, 1 H), 7.99–7.96 (m, 1 H), 7.76–7.71 (m, 2 H), 7.47–7.28 (m, 5 H), 7.07 (s, 1 H), 4.42 (s, 1 H), 1.82 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.4, 185.3, 152.0, 145.5, 134.1, 133.9, 133.8, 132.3, 131.6, 128.4, 127.3, 126.8, 125.9, 124.4, 75.6, 28.8 ppm. IR (KBr): $\tilde{\nu}$ = 3506 (OH), 1656 (C=O), 1616 (C=O), 1593, 1306, 1252, 1044, 775, 720 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{14}O_3$ $[M]^+$ 278.0943; found 278.0941.

General Procedure for the Preparation of Compounds 6a–e: To a solution of **4** (1 mmol) and pyridinium salt (1 mmol) in acetonitrile (10 mL) under a N_2 atmosphere at 50 °C was added dropwise a solution of Et_3N (1 mmol) in acetonitrile (5 mL). The mixture was stirred for 2–4 h at room temp. The solvent was evaporated in vacuo, and the residue was quenched with water and extracted with dichloromethane. The extract was washed with 1 M HCl, water, and dried with $MgSO_4$. The solvent was evaporated to give the crude intermediate reaction product. To a solution of this crude product in benzene (10 mL) was added TsOH (0.2 mmol). The mixture was heated at reflux for 10 min and then poured into water and extracted with EtOAc. The extract was washed with 2 M HCl, water, and dried with $MgSO_4$. The solution was then evaporated to give the crude product, which was purified by flash chromatography on silica gel to give the desired product.

1,1,3-Trimethyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (6a): Red solid. Yield: 242 mg (95%). M.p. 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05–8.01 (m, 2 H), 7.73–7.62 (m, 2 H), 5.88 (d, $^3J_{H,H}$ = 0.6 Hz, 1 H), 1.99 (d, $^3J_{H,H}$ = 0.6 Hz, 3 H), 1.74 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.2, 182.0, 163.0, 137.2, 133.8, 133.4, 132.6, 131.2, 129.2, 125.9, 125.8, 93.0, 80.0, 26.7, 21.2 ppm. IR (KBr): $\tilde{\nu}$ = 1662 (C=O), 1622 (C=O), 1588, 1557, 1300, 721 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{14}O_3$ $[M]^+$ 254.0943; found 254.0953.

1,3-Dimethyl-1-phenyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (6b): Red solid. Yield: 297 mg (94%). M.p. 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–7.97 (m, 2 H), 7.70–7.60 (m, 2 H), 7.49–7.45 (m, 2 H), 7.36–7.24 (m, 2 H), 5.94 (s, 1 H), 2.18 (s, 3 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.0, 182.1, 163.2, 144.2, 137.7, 133.9, 133.1, 132.7, 131.2, 128.0, 127.9, 127.8, 126.1, 125.8, 125.4, 94.0, 82.4, 27.0, 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 1668 (C=O), 1616 (C=O), 1548, 1387, 1298, 767, 702 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{16}O_3$ $[M]^+$ 316.1099; found 316.1100.

1,3-Diphenyl-1-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (6c): Red solid. Yield: 367 mg (97%). M.p. 179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.04 (m, 2 H), 7.88–7.85 (m, 2 H), 7.76–7.66 (m, 2 H), 7.53–7.41 (m, 5 H), 7.34–7.26 (m, 3 H), 6.77 (s, 1 H), 2.31 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.1, 182.1, 159.6, 143.8, 138.1, 134.1, 133.4, 132.8, 131.4, 130.8, 128.9, 128.6, 128.1, 128.0, 126.3, 126.1, 126.0, 125.6, 93.0, 82.7, 77.4, 27.3 ppm. IR (KBr): $\tilde{\nu}$ = 1668 (C=O), 1608 (C=O), 1592, 1531, 1449, 1299, 715 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{18}O_3$ $[M]^+$ 378.1256; found 378.1265. CCDC-616177 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1,1-Dimethyl-3-phenyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (6d): Red solid. Yield: 300 mg (95%). M.p. 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.03 (m, 2 H), 7.83–7.80 (m, 2 H), 7.72–7.67 (m, 2 H), 7.44–7.42 (m, 3 H), 6.71 (s, 1 H), 1.84 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.1, 181.8, 159.2, 137.4, 134.0, 133.5, 133.4, 132.7, 131.3, 130.6, 128.5, 126.0, 92.3, 80.1, 26.4 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 1665 (C=O), 1642 (C=O), 1538, 1389, 1305, 709 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{16}O_3$ $[M]^+$ 316.1099; found 316.1093.

1,1-Dimethyl-3-(4-*N*,*N*-dimethylamino)-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (6e): Blue solid. Yield: 345 mg (96%). M.p. 199–200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.04 (m, 2 H), 7.75–7.61 (m, 4 H), 6.71 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 6.58 (s, 1 H), 1.82 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.8, 181.1, 160.7, 152.1, 138.3, 134.0, 133.8, 132.2, 131.5, 127.8, 125.9, 125.8, 120.7, 111.4, 89.7, 79.9, 40.1, 26.3 ppm. IR (KBr): $\tilde{\nu}$ = 1665 (C=O), 1615 (C=O), 1519, 1440, 1376, 1334, 1309, 1021 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{21}NO_3$ $[M]^+$ 359.1521; found 359.1523.

2-Bromo-4′-*N*,*N*-dimethylaminoacetophenone (7): To a solution of 4′-*N*,*N*-dimethylaminoacetophenone (500 mg, 3.06 mmol) in hydrogen bromide (10 mL) at 0 °C was added bromine (490 mg, 3.06 mmol) dropwise over 1 h. After the reaction was complete, the product was extracted twice with dichloromethane. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (EtOAc/hexanes, 1:9) to give **7** (712 mg, 96%) as a yellow solid. M.p. 88–89 °C (ref.[7] 91–92 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 6.66 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 4.36 (s, 2 H), 3.08 (s, 6 H) ppm.

1-(4′-*N*,*N*-Dimethylaminophenacyl)pyridinium Bromide (8): To a solution of **7** (500 mg, 2.07 mmol) in acetone (5 mL) was added pyridine (163 mg, 2.07 mmol). The resulting mixture was then heated at reflux for 6 h. The solution was cooled to room temp., and the precipitate was collected to give **8** (650 mg, 98%) as a yellow liquid. M.p. 250–251 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.90 (d, $^3J_{H,H}$ = 6.6 Hz, 2 H), 8.67 (t, $^3J_{H,H}$ = 6.6 Hz, 1 H), 8.16 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H), 7.94 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 6.81 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 6.32 (s, 2 H), 3.11 (s, 6 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 188.0, 156.2, 147.6, 147.3, 131.8, 128.9, 121.8, 112.1, 66.9, 40.1 ppm. IR (KBr): $\tilde{\nu}$ = 3514, 3037, 1652, 1343, 1006, 682 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{17}BrN_2O$ $[M]^+$ 320.0524; found 320.0527.

5,10-Dimethoxy-1-methyl-1,3-diphenyl-1*H*-benzo[*g*]isochromene (10c): To a solution of **6c** (50 mg, 0.13 mmol) in ethanol (5 mL) and water (5 mL) was added sodium borohydride (10 mg, 0.26 mmol) at room temp. The mixture was stirred for 5 min and then a solution of KOH (10 M, 5 mL) was added. The resulting mixture was stirred for another 5 min and then heated at reflux; dimethyl sulfate (75 mg, 0.59 mmol) was then added. The mixture was heated at reflux overnight and then cooled to room temp. The product was extracted with EtOAc and purified by column chromatography (EtOAc/hexanes, 1:9) to give **10c** (16 mg, 30%) as a yellow solid. M.p. 144–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 8.0 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H), 7.83–7.80 (m, 2 H), 7.53–7.18 (m, 4 H), 6.83 (s, 1 H), 3.98 (s, 3 H), 3.48 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2, 148.4, 145.9, 145.8, 134.7, 129.0, 128.7, 128.3, 128.1, 127.8, 127.4, 126.4, 125.1, 124.9, 123.2, 122.2, 121.7, 95.1, 82.1, 77.2, 62.3, 61.8, 27.8 ppm. IR (KBr): $\tilde{\nu}$ = 1595, 1451, 1367, 1237, 1096 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{24}O_3$ $[M]^+$ 408.1725; found 408.1720.

General Procedure for the Reduction of Compounds 6a–e: To a solution of **6a** (1.9 mg, 5 μmol) in methanol (10 mL) was added sodium borohydride (0.6 mg, 16 μmol) in one portion at room temp. The red solution turned yellow instantly with gentle swirling. After consumption of the reducing agent, the red color reappeared within 3 min under aerobic conditions. Note: If excess sodium borohydride were added, the yellow solution would turn colorless presumably due to the further reduction of the double bond adjacent to the hydroquinone moiety.

Acknowledgments

The authors would like to thank the National Science Council of Republic of China, Taiwan for financially supporting this research under contract no. NSC 95-2113-M-029-003. We also thank Drs. Cheng-Wen Whang and Wei Jyun Chien for helpful discussions.

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Received: May 14, 2007
Published Online: August 3, 2007

