Synthesis F. C. Demidoff et al. Paper

Synthesis of Stilbene-Quinone Hybrids through Heck Reactions in PEG-400

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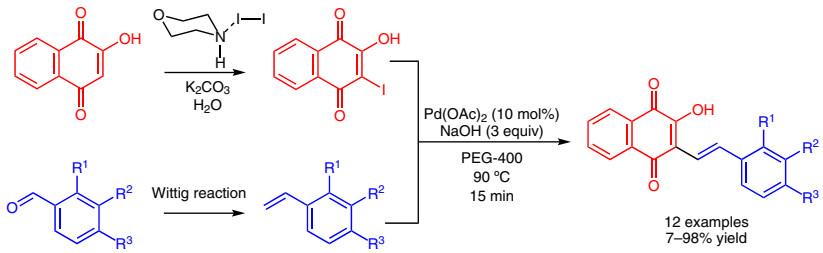
Dedicated to Professor Paulo R. R. Costa on the occasion of his 67th birthday



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Abstract Styrenes were coupled with 3-iodolawsone in PEG-400 at 90 °C, leading stereoselectively to (*E*)-stilbene-quinone hybrids through Heck reactions. The best reaction conditions were found to be the use of NaOH (3 equiv) and 10 mol% of palladium acetate at 90 °C for 15 minutes. The chemical yields of the Heck reactions using styrenes with electron-withdrawing groups (65–98%) were greater than styrenes bearing electron-donating groups (7–32%) on the aromatic ring. In particular, the chemical yields of Heck reactions involving nitrostyrenes were the best ones observed.

Key words Heck reaction, PEG-400, Wittig reaction, styrenes, naphthoquinones, stilbenes, 3-iodolawsone

Naturally occurring *p*-quinones and their synthetic analogues are important sources of antineoplastic, antimicrobial, and antiparasitic substances; and some of these compounds have been used in the clinic as chemotherapeutic agents.[1] Lapachol (**1**) (Figure 1) occurs in the wood of several species of the Bignoniaceae family and was commercialized in Brazil as an antitumor drug in the 1970s.[2] This and other xenobiotic *p*-quinones can be reduced in the mitochondria to the corresponding semiquinone radicals through the action of cytochrome P450 reductase (one electron reduction), and the resulting semiquinones can transfer one electron to molecular oxygen. The resulting superoxide anion can be transformed into hydroxyl radical, which initiates a cascade of events leading to oxidative stress.[3]

Stilbenes are currently attracting considerable attention because of their wide range of biological activities and potential therapeutic value.[4,5] A large number of stilbenes have been isolated from various plant species, for example,

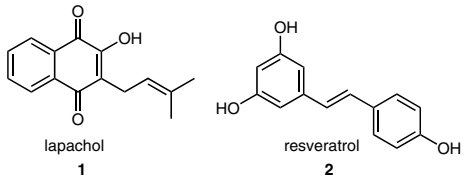


Figure 1 Structures of lapachol (**1**) and resveratrol (**2**)

resveratrol (**2**) from the skin of red grapes (Figure 1). These molecules are found mainly among members of the vegetable kingdom classified as spermatophytes, but also in bryophytes and pteridophytes.[5]

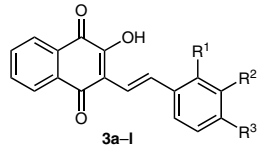
Several approaches to prepare stilbenes have been reported in the literature. Some strategies involve coupling reactions mediated by palladium salts, in particular Mizoroki–Heck, Suzuki, Stille, and Negishi reactions.[5]

The palladium-catalyzed coupling reactions of alkenes with aryl halides, known as Mizoroki–Heck (MH) reaction, are among the most important methods for carbon–carbon bond formation and have been extensively used in natural products synthesis, pharmaceutical industry, and bioorganic chemistry.[6] Among the numerous achievements on this topic, the development of 'ligand-free' catalytic systems has been one of the most challenging fields in synthetic organic chemistry, because they are the simplest and cheapest systems in comparison to the ligand-promoted ones.[7] As an environmentally benign and readily available solvent, with good solubility in organic compounds, poly(ethylene glycol) (PEG) has been widely used in the palladium-catalyzed ligand-free transformations over the last few years.[7–9] The first example of Heck reaction performed in PEG was reported in 2002 by Chandrasekhar et al., who used PEG-2000 as a solvent to carry out the Heck reaction of aryl bromides bearing electron-withdrawing or electron-donating

substituents with ethyl acrylate, styrene, and *n*-butyl vinyl ether in the presence of the catalytic system composed of PEG-2000/$Pd(OAc)_2$/Et_3N in high yields.[10]

2-Hydroxy-3-iodo-1,4-naphthoquinone (3-iodolawsone) has been used in cross coupling reactions to synthesize molecules containing the 1,4-naphthoquinone scaffold.[9,11,12] In 2007, Perez et al. described the synthesis of a series of 3-substituted 2-hydroxynaphthoquinones through Heck reactions between 3-iodolawsone and several α,β-unsaturated carbonyl derivatives in aqueous solution in moderate to good yields.[10] Recently, Louvis et al. prepared a number of 3-aryl-2-hydroxy-1,4-naphthoquinones in aqueous conditions through Suzuki–Miyaura coupling reactions between 3-iodolawsone and boronic acids. Some of these compounds showed good in vitro antifungal or trypanocidal activity.[11] In addition, de Moraes et al. reported the oxyarylation of dihydronaphthalenes with 3-iodolawsone in PEG-400 using 10 mol% of palladium acetate as catalyst and 1.1 equivalents of silver carbonate as base to prepare carbapterocarpanquinones in moderate yields.[9]

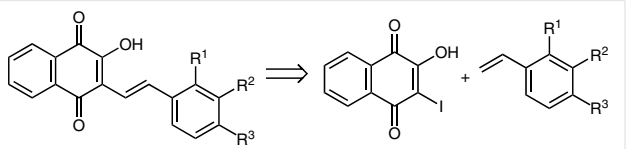
In this paper, we describe the synthesis of a series of stilbene-quinone hybrids **3a–l** (Figure 2) through Heck reactions performed in poly(ethylene glycol) 400 (PEG-400) catalyzed by palladium acetate. Stilbene-quinone **3a** was prepared in 2006 by Kazantzi et al. through Suzuki-type coupling between phenyliodonium ylide of lawsone and styrylboronic acid.[13] Recently, Malamidou-Xenikaki et al. prepared a series of stilbene-quinone hybrids, including **3b**,**i**,**k**, through metal-free cross-coupling of BF_3-activated phenyliodonium ylide of lawsone with cinnamaldehydes and aryl aldehydes.[14] We report, for the first time in this work, the synthesis of stilbene-quinones hybrids **3a–l** through Heck reactions of 3-iodolawsone with styrenes.



a) $R^1 = R^2 = R^3 = H$ — **g**) $R^1 = R^2 = OMe$; $R^3 = H$
b) $R^1 = R^2 = H$; $R^3 = OMe$ — **h**) $R^1 = R^2 = H$; $R^3 = NO_2$
c) $R^1 = R^2 = H$; $R^3 = OH$ — **i**) $R^1 = NO_2$; $R^2 = R^3 = H$
d) $R^1 = H$; $R^2 = OMe$; $R^3 = OH$ — **j**) $R^1 = H$; $R^2 = NO_2$; $R^3 = H$
e) $R^1 = H$; $R^2 = OH$; $R^3 = OMe$ — **k**) $R^1 = R^2 = H$; $R^3 = Cl$
f) $R^1 = H$; R^2–R^3 = -OCH_2O- — **l**) $R^1 = R^2 = H$; $R^3 = CF_3$

Figure 2 Stilbene-quinone hybrids prepared in this work

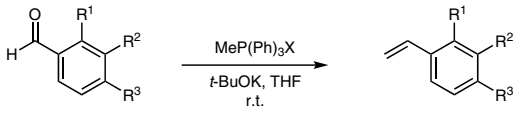
The key step in our strategy to prepare **3a–l** was the Heck reactions of 3-iodolawsone (**4**) with styrenes **5a–l** (Scheme 1). 3-Iodolawsone (**4**) was prepared from lawsone and iodomorpholine complex as described in the literature.[15]



a) $R^1 = R^2 = R^3 = H$ — **g**) $R^1 = R^2 = OMe$; $R^3 = H$
b) $R^1 = R^2 = H$; $R^3 = OMe$ — **h**) $R^1 = R^2 = H$; $R^3 = NO_2$
c) $R^1 = R^2 = H$; $R^3 = OH$ — **i**) $R^1 = NO_2$; $R^2 = R^3 = H$
d) $R^1 = H$; $R^2 = OMe$; $R^3 = OH$ — **j**) $R^1 = H$; $R^2 = NO_2$; $R^3 = H$
e) $R^1 = H$; $R^2 = OH$; $R^3 = OMe$ — **k**) $R^1 = R^2 = H$; $R^3 = Cl$
f) $R^1 = H$; R^2–R^3 = -OCH_2O- — **l**) $R^1 = R^2 = H$; $R^3 = CF_3$

Scheme 1 Synthetic strategy to prepare stilbene-quinone hybrids **3a–l**

Styrenes **5a**,**b**,**j–l** are commercially available, and styrenes **5c–i** were prepared through Wittig reactions[16] from the corresponding benzaldehydes **6c–i**, in moderate to good yields (56–98%), except for nitrostyrenes **5h**,**i**, which were obtained in only 13% and 32% yield, respectively (Scheme 2).

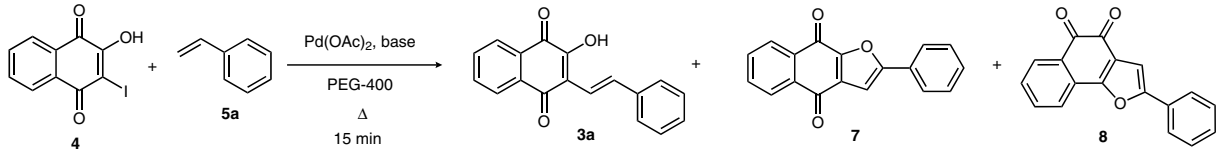


c) $R^1 = R^2 = H$; $R^3 = OH$ (98%)
d) $R^1 = H$; $R^2 = OMe$; $R^3 = OH$ (94%)
e) $R^1 = H$; $R^2 = OH$; $R^3 = OMe$ (76%)
f) $R^1 = H$; R^2–R^3 = -OCH_2O- (56%)
g) $R^1 = R^2 = OMe$; $R^3 = H$ (81%)
h) $R^1 = R^2 = H$; $R^3 = NO_2$ (13%)
i) $R^1 = NO_2$; $R^2 = R^3 = H$ (32%)

Scheme 2 Synthesis of styrenes **5c–i** through Wittig reactions from benzaldehydes **6c–i**

Our first synthetic target was the stilbene-quinone hybrid **3a**.[13,17] Initially, we carried out a study to establish the best reaction conditions. The Heck reactions between 3-iodolawsone (**4**) and styrene (**5a**) were performed on PEG-400 under heating using Ag_2CO_3, K_2CO_3, NaOH, KOH, diisopropylamine, and triethylamine as bases and mediated by catalytic amounts of palladium acetate. After 15 minutes of reaction, the formation of three compounds was observed: the stilbene-quinone hybrid **3a** and two cyclic derivatives **7** and **8**, depending on the reaction conditions (Table 1). These three compounds have already been published and all spectroscopical data are in accord with the literature.[13,17,18] We only observed the formation of olefin **3a** with *E*-configuration. This configuration was confirmed by the two doublet signals in ^1H NMR spectrum with a coupling constant value of 16.7 Hz ($J_{H,H}$ olefin).

Table 1 Optimization of the Reaction Conditions for the Heck Coupling of **4** with **5a**

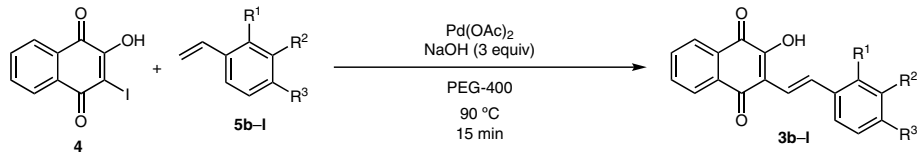


Entry[a]	Base	$Pd(OAc)_2$ (mol%)	Temp (°C)	Yield (%)[b] of **3a**	Yield (%)[b] of **7**	Yield (%)[b] of **8**
1	Ag_2CO_3 (1.1 equiv)	1	90	19	traces	–
2	Ag_2CO_3 (1.1 equiv)	5	90	14	2	–
3	Ag_2CO_3 (1.1 equiv)	10	90	46	traces	–
4	Ag_2CO_3 (1.1 equiv)	1	140	traces	6	3
5	Ag_2CO_3 (1.1 equiv)	5	140	traces	5	2
6	Ag_2CO_3 (1.1 equiv)	10	140	traces	4	2
7	K_2CO_3 (3 equiv)	10	90	46	traces	–
8	KOH (3 equiv)	10	90	64	–	–
9	NaOH (3 equiv)	10	90	81	–	–
10	*i*-Pr_2NH (3 equiv)	10	80	18	–	–
11	Et_3N (3 equiv)	10	90	29	–	–

[a] Reaction conditions: **4** (1 mmol), **5a** (1 mmol) in PEG-400 (8 g).
[b] Isolated yield.

Using Ag_2CO_3 (1.1 equiv) as base and 1 mol% of palladium acetate as catalyst, at 90 °C in PEG-400 for 15 minutes, compound **3a** was obtained in 19% yield with only traces of **7** (Table 1, entry 1). In the presence of 5 mol% of palladium acetate, **3a** was obtained in 14% yield and **7** was obtained in 2% yield (entry 2). When 10 mol% of palladium acetate was used, **3a** was obtained in 46% yield with only traces of **7** (entry 3). By increasing the temperature to 140 °C, we observed the formation of **7** and **8** in low yields with only traces of **3a** (entries 4–6). By changing the base to 1.1 or 2 equivalents of K_2CO_3, NaOH, KOH, diisopropylamine, and triethylamine, no product was formed (data not shown). Increasing the amount of these bases to 3 equivalents, in the presence of 10 mol% of palladium acetate at 90 °C over 15 minutes, 46% yield for **3a** was observed using K_2CO_3 (entry 7) and 64% yield using KOH (entry 8). The best yield for **3a** (81%) was observed when 3 equivalents of NaOH was used (entry 9). On the other hand, a decrease in the yield of **3a** was observed when diisopropylamine and triethylamine were used (entries 10 and 11). No cyclic compounds **7** and **8** were detected using NaOH, KOH, diisopropylamine, and triethylamine.

The best reaction conditions to synthesize **3a** (Table 1, entry 9), were used to prepare derivatives **3b–l** (Scheme 3). The chemical yields of Heck reactions between styrenes with electron-donating groups on the aromatic ring **5b–g** and 3-iodolawsone (**4**) were lower (7–32%) than observed for the reactions with styrenes bearing electron-withdrawing groups **5h–l** (65–98%). The chemical yield using 4-nitrostyrene (**5h**) was the best one observed (98%) for all Heck reactions. These results suggest that our Heck reactions occur through a neutral mechanism.[19] Again, we only observed the formation of olefins **3b–l** with *E*-configurations, as shown by the analysis of ^1H NMR spectra (two doublet signals with a coupling constant value about 17 Hz).



b) $R^1 = R^2 = H$; $R^3 = OMe$ (23%)
c) $R^1 = R^2 = H$; $R^3 = OH$ (20%)
d) $R^1 = H$; $R^2 = OMe$; $R^3 = OH$ (7%)
e) $R^1 = H$; $R^2 = OH$; $R^3 = OMe$ (20%)
f) $R^1 = H$; $R^2–R^3 = -OCH_2O-$ (17%)
g) $R^1 = R^2 = OMe$; $R^3 = H$ (32%)
h) $R^1 = R^2 = H$; $R^3 = NO_2$ (98%)
i) $R^1 = NO_2$; $R^2 = R^3 = H$ (87%)
j) $R^1 = R^3 = H$; $R^2 = NO_2$ (81%)
k) $R^1 = R^2 = H$; $R^3 = Cl$ (65%)
l) $R^1 = R^2 = H$; $R^3 = CF_3$ (81%)

Scheme 3 Heck reaction between 3-iodolawsone (**4**) and styrenes **5b–l**

In conclusion, all the Heck reactions were stereoselective, generating only (*E*)-stilbene-quinone hybrids. The use of Ag_2CO_3 at high temperatures in the Heck reaction led to the formation of furanonaphthoquinones **7** and **8**. NaOH was the best base for these Heck reactions, while diisopropylamine was the worst. The chemical yields of Heck reactions between styrenes with electron-donating groups on the aromatic ring **5b–g** and 3-iodolawsone (**4**) were lower than the ones observed for the reactions with styrenes bearing electron-withdrawing groups **5h–l**, suggesting that these reactions occur through a neutral mechanism.[19] The best yield for all our Heck reactions was observed using 4-nitrostyrene (**5h**).

The stilbene-quinone scaffold was previously obtained through Suzuki-type coupling between phenyliodonium ylide of lawsone and styrylboronic acid or metal-free cross-coupling of BF_3-activated phenyliodonium ylide of lawsone with cinnamaldehydes and aryl aldehydes.[13,14] Notwithstanding, here we report for the first time the synthesis of this skeleton through Heck reaction. The stilbene-quinones **3c–h,j,l** are unpublished and are being reported in this paper for the first time. Finally, these compounds are under evaluation as antiparasitic, antimicrobial, and antitumor agents.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, CD_3OD, or DMSO-d_6 at 400 MHz with a Varian MR-400 NMR spectrometer using TMS as internal standard. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV with a Shimadzu QP-5000 instrument, and HRMS (GC-EI) were recorded with a Finnigan MAT 95S instrument. Analytical TLC was performed with Schleicher & Schüll F1400/LS silica gel plates, and the spots were visualized under UV light (λ = 254 nm). For flash chromatography, Merck silica gel 60 (0.040–0.063 mm) was employed.

3-Iodolawsone (4)[15]

To a mixture of lawsone (8.7 g, 50 mmol) and K_2CO_3 (21 g, 150 mmol) in H_2O (50 mL) was added the morpholine-iodide complex (21.2 g, 62.5 mmol) in small portions every 15 min over 2 h. The reaction mixture was stirred at r.t. for an additional hour, and then filtered to remove any solids. The filtrate was cooled in an ice bath and acidified with 25% H_3PO_4 until a pH of approximately 2. The precipitate was filtered, washed with cold H_2O, and recrystallized from glacial AcOH to afford pure **4** as yellow crystals; yield: 10.85 g (72%, 36 mmol); mp 177 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, *J* = 7.3, 1.3 Hz, 1 H), 8.15 (dd, *J* = 7.3, 1.3 Hz, 1 H), 8.01 (s, 1 H), 7.77 (m, 2 H).

Wittig Reaction of Aldehydes 6; 4-Hydroxystyrene (5c);[20] Typical Procedure

A mixture of methyltriphenylphosphonium bromide (1.1 g, 3 mmol) in THF (4 mL) was treated with *t*-BuOK (562 mg, 5 mmol). After stirring for 10 min at r.t., a solution of 4-hydroxybenzaldehyde (**6c**; 244 mg, 2 mmol) in THF (2 mL) was added dropwise to the above suspension, and the resulting mixture was stirred at r.t. for 60 min, which was monitored by TLC. The resulting solution was quenched with sat. aq NH_4Cl (10 mL) and concentrated in vacuum to remove THF. The concentrated mixture was extracted with CH_2Cl_2 (40 mL). The organic layer was washed with brine (3 × 40 mL) and dried (anhyd Na_2SO_4), filtered, evaporated, and the residue was purified by chromatography over silica gel (EtOAc/*n*-hexane 5:95) to give pure **5c** as a light yellow solid; yield: 200.7 mg (98%, 1.97 mmol); mp 65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.65 (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.60 (d, *J* = 17.6 Hz, 1 H), 5.12 (d, *J* = 10.9 Hz, 1 H), 4.94 (s, 1 H).

3-Methoxy-4-hydroxystyrene (5d)[20]

Prepared from **6d** (5 mmol) using methyltriphenylphosphonium iodide (7.5 mmol); light yellow oil; yield: 705.6 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.90 (m, 2 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 6.64 (dd, *J* = 17.5, 10.9 Hz, 1 H), 5.62 (s, 1 H), 5.59 (dd, *J* = 17.5, 0.8 Hz, 1 H), 5.13 (dd, *J* = 10.9, 0.8 Hz, 1 H), 3.92 (s, 3 H).

3-Hydroxy-4-methoxystyrene (5e)[21]

Prepared from **6e** (5 mmol) using methyltriphenylphosphonium bromide (7.5 mmol); white amorphous solid; yield: 573.3 mg (76%); mp 58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 2.1 Hz, 1 H), 6.87 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 6.61 (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.60 (d, *J* = 18.3 Hz, 1 H), 5.60 (s, 1 H), 5.13 (d, *J* = 10.2 Hz, 1 H), 3.89 (s, 3 H).

5-Vinylbenzo[*d*][1,3]dioxole (5f)[22]

Prepared from **6f** (3 mmol) using methyltriphenylphosphonium iodide (4.5 mmol); colorless oil; yield: 260.7 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 1.6 Hz, 1 H), 6.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.62 (dd, *J* = 17.5, 10.8 Hz, 1 H), 5.95 (s, 2 H), 5.57 (d, *J* = 17.5 Hz, 1 H), 5.12 (d, *J* = 10.8 Hz, 1 H).

2,3-Dimethoxystyrene (5g)[23]

Prepared from **6g** (3 mmol) using methyltriphenylphosphonium iodide (4.5 mmol); light yellow oil; yield: 392.5 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.05 (dd, *J* = 17.5, 11.3 Hz, 1 H), 7.03–7.00 (m, 1 H), 6.83 (dd, *J* = 8.1, 1.4 Hz, 1 H), 5.76 (dd, *J* = 17.8, 1.4 Hz, 1 H), 5.30 (dd, *J* = 11.1, 1.4 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H).

4-Nitrostyrene (5h)[24]

Prepared from **6h** (5 mmol) using methyltriphenylphosphonium bromide (7.5 mmol) at –78 °C; clear oil; yield: 98 mg (13%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.6 Hz, 2 H), 6.79 (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.94 (d, *J* = 17.6 Hz, 1 H), 5.51 (d, *J* = 10.9 Hz, 1 H).

2-Nitrostyrene (5i)[25]

Prepared from **6i** (10 mmol) using methyltriphenylphosphonium bromide (15 mmol) at –78 °C; yellowish oil, yield: 491.3 mg (32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 1 H), 7.62 (t, *J* = 7.9 Hz, 1 H), 7.57 (d, *J* = 7.3 Hz, 1 H), 7.41 (t, *J* = 8.2 Hz, 1 H), 7.18 (dd, *J* = 17.3, 11.0 Hz, 1 H), 5.75 (d, *J* = 17.3 Hz, 1 H), 5.49 (dd, *J* = 11.0, 0.5 Hz, 1 H).

Stilbene-Quinones 3a–l; General Procedure

A mixture of 3-iodolawsone (**4**; 300 mg, 1 mmol), styrene **5** (1 mmol), NaOH (120 mg, 3 mmol), and $Pd(OAc)_2$ (23 mg, 10 mol%) in PEG-400 (8 g) was stirred for 15 min at 90 °C. The reaction was monitored by TLC. After this time, the reaction mixture was extracted with EtOAc (50 mL) and filtered over a Celite pad. Then, 25% H_3PO_4 (50 mL) was added. The organic layer was washed with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuum. The resulting oil was purified by chromatography over silica gel (EtOAc/*n*-hexane; 5:95 for **3a–g** and **3k**; 10:90 for **3l**; and 30:70 for **3h–i**) furnishing the desired pure product.

(*E*)-2-Hydroxy-3-styrylnaphthalene-1,4-dione (3a)[17]

Red amorphous solid; yield: 223.5 mg (81%); mp 160–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.7 Hz, 1 H), 7.97 (d, *J* = 7.5 Hz, 1 H), 7.92 (s, 1 H), 7.85 (d, *J* = 16.7 Hz, 1 H), 7.65 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.49 (d, *J* = 7.4 Hz, 2 H), 7.28 (d, *J* = 16.8 Hz, 1 H), 7.32–7.24 (m, 2 H), 7.19 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.12, 180.94, 151.68, 139.26, 137.75, 134.95, 133.18, 132.67, 129.52, 128.70, 128.69, 128.65, 127.17, 127.16, 127.12, 126.03, 118.66, 117.37.

LRMS: *m*/*z* = 276.

(*E*)-2-Hydroxy-3-(4-methoxystyryl)naphthalene-1,4-dione (3b)[14]

Purple amorphous solid; yield: 70.3 mg (23%); mp 125–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 7.6, 1.0 Hz, 1 H), 8.09 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.94 (d, *J* = 16.7 Hz, 1 H), 7.76 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.70 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 16.7 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.35, 180.85, 160.18, 151.16, 139.05, 134.81, 133.16, 132.71, 130.65, 129.62, 128.61, 128.60, 127.08, 125.96, 119.15, 115.25, 114.16, 114.15, 55.33.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}O_4Na$: 329.0790; found: 329.0781.

(*E*)-2-Hydroxy-3-(4-hydroxystyryl)naphthalene-1,4-dione (3c)

Purple amorphous solid; yield: 58.4 mg (20%); mp 189–190 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.17–8.02 (m, 2 H), 7.97 (d, *J* = 16.7 Hz, 1 H), 7.91–7.78 (m, 2 H), 7.50 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 16.6 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (101 MHz, acetone-d_6): δ = 184.15, 180.45, 158.10, 152.83, 137.88, 134.61, 134.49, 133.22, 133.07, 132.60, 130.29, 129.80, 128.35, 126.35, 125.47, 118.77, 115.68, 114.96.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{12}O_4Na$: 315.062780; found: 315.0624.

(*E*)-2-Hydroxy-3-(4-hydroxy-3-methoxystyryl)naphthalene-1,4-dione (3d)

Reddish-purple amorphous solid; yield: 23.7 mg (7%); mp 186–187 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.10–8.02 (m, 2 H), 7.96 (d, *J* = 16.6 Hz, 1 H), 7.89–7.80 (m, 2 H), 7.28 (d, *J* = 16.6 Hz, 1 H), 7.25 (d, *J* = 1.9 Hz, 1 H), 7.10 (dd, *J* = 8.2, 1.6 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 3.95 (s, 3 H).

^{13}C NMR (101 MHz, acetone-d_6): δ = 184.58, 181.43, 158.38, 152.84, 147.79, 147.56, 138.09, 134.73, 133.06, 132.45, 130.17, 126.35, 125.92, 125.00, 120.91, 118.65, 115.06, 110.73, 55.25.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}O_5Na$: 345.073344; found: 345.0741.

(*E*)-2-Hydroxy-3-(3-hydroxy-4-methoxystyryl)naphthalene-1,4-dione (3e)

Reddish-purple solid; yield: 65.1 mg (20%); mp 178–179 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.15–7.98 (m, 2 H), 7.85 (d, *J* = 16.7 Hz, 1 H), 7.82–7.70 (m, 2 H), 7.22 (d, *J* = 16.6 Hz, 1 H), 7.06 (d, *J* = 2.0 Hz, 1 H), 6.98 (dd, *J* = 8.3, 2.0 Hz, 1 H), 6.92 (d, *J* = 8.3 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 184.99, 181.59, 159.89, 154.45, 148.82, 147.20, 134.78, 133.52, 127.15, 126.83, 126.28, 125.76, 119.65, 111.39, 72.75, 70.18, 60.66, 56.07, 55.98.

HRMS: *m*/*z* [M – H] calcd for $C_{19}H_{13}O_5$: 321.0768; found: 321.0782.

(*E*)-2-[2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl]-3-hydroxynaphthalene-1,4-dione (3f)

Dark purple solid; yield: 53.4 mg (17%); mp 203–204 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.10 (dd, *J* = 7.5, 1.2 Hz, 1 H), 8.06 (dd, *J* = 7.6, 1.3 Hz, 1 H), 7.90 (d, *J* = 16.6 Hz, 1 H), 7.81–7.71 (m, 2 H), 7.25 (d, *J* = 16.7 Hz, 1 H), 7.12 (d, *J* = 1.6 Hz, 1 H), 6.99 (dd, *J* = 8.0, 1.7 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 5.97 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 184.47, 180.89, 155.05, 148.48, 148.01, 136.46, 134.92, 133.74, 132.74, 132.43, 130.66, 126.47, 125.92, 122.45, 118.57, 117.09, 109.01, 105.65, 101.69.

HRMS: *m*/*z* [M – H] calcd for $C_{19}H_{11}O_5$: 319.0612; found: 319.0622.

(*E*)-2-(2,3-Dimethoxystyryl)-3-hydroxynaphthalene-1,4-dione (3g)

Red solid; yield: 106.1 mg (32%); mp 151–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 16.9 Hz, 1 H), 8.18 (dd, *J* = 7.6, 0.9 Hz, 1 H), 8.11 (t, *J* = 7.9 Hz, 1 H), 8.00 (s, 1 H), 7.76 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.71 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.40 (d, *J* = 16.9 Hz, 1 H), 7.36 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 6.89 (dd, *J* = 8.1, 1.1 Hz, 1 H), 3.89 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.14, 181.03, 153.04, 151.70, 147.50, 134.94, 133.67, 133.17, 132.68, 132.03, 129.55, 127.13, 126.03, 124.13, 118.98, 118.42, 112.34, 110.66, 61.26, 55.84.

HRMS: *m*/*z* [M – H] calcd for $C_{20}H_{15}O_5$: 335.0925; found: 335.0912.

(*E*)-2-Hydroxy-3-(4-nitrostyryl)naphthalene-1,4-dione (3h)

Prepared starting from 0.52 mmol of **5h**; eluent for chromatography: EtOAc/*n*-hexane (30:70); reddish-orange solid; yield: 163.8 mg (98%); mp 153–154 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.15–8.10 (m, 3 H), 8.08 (dd, *J* = 7.4, 1.1 Hz, 2 H), 8.04 (dd, *J* = 7.3, 1.3 Hz, 2 H), 7.89–7.84 (m, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 184.18, 181.67, 162.75, 156.80, 146.89, 144.85, 134.90, 133.91, 133.65, 130.71, 130.15, 127.83, 127.18, 126.89, 126.36, 125.82, 124.57, 111.41.

HRMS: *m*/*z* [M – H] calcd for $C_{18}H_{10}NO_5$: 320.056446; found: 320.0576.

(*E*)-2-Hydroxy-3-(2-nitrostyryl)naphthalene-1,4-dione (3i)[14]

Eluent for chromatography: EtOAc/*n*-hexane (30:70); reddish-orange solid; yield: 279 mg (87%); mp 235 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 16.5 Hz, 1 H), 8.20 (d, *J* = 7.2 Hz, 1 H), 8.13 (d, *J* = 7.5 Hz, 1 H), 8.09 (s, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.86–7.78 (m, 2 H), 7.74 (t, *J* = 7.5 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 16.5 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.87, 185.79, 161.53, 153.21, 139.88, 138.70, 138.57, 137.49, 137.12, 135.44, 134.50, 134.06, 132.68, 131.32, 130.84, 129.55, 128.62, 122.02.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{11}NO_5Na$: 344.052943; found: 344.0537.

(*E*)-2-Hydroxy-3-(3-nitrostyryl)naphthalene-1,4-dione (3j)

Eluent for chromatography: EtOAc/*n*-hexane (30:70); reddish-orange solid; yield: 448.4 mg (81%); mp 222 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44–8.42 (m, 1 H), 8.21 (d, *J* = 8.2 Hz, 1 H), 8.16–8.12 (m, 2 H), 8.07 (s, 1 H), 8.00 (d, *J* = 16.6 Hz, 1 H), 7.91 (d, *J* = 7.7 Hz, 1 H), 7.84–7.78 (m, 1 H), 7.76–7.71 (m, 1 H), 7.59–7.53 (m, 1 H), 7.51 (d, *J* = 16.7 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 184.11, 180.96, 156.43, 148.72, 139.94, 135.08, 133.77, 133.55, 133.11, 132.34, 130.74, 130.61, 126.51, 126.03, 122.80, 121.64, 120.83, 117.41.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{11}NO_5Na$: 344.052943; found: 344.0534.

(*E*)-2-(4-Chlorostyryl)-3-hydroxynaphthalene-1,4-dione (3k)[14]

Eluent for chromatography: EtOAc/*n*-hexane (5:95); red solid; yield: 348.8 mg (65%); mp 190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.6 Hz, 1 H), 8.11 (d, *J* = 7.4 Hz, 1 H), 7.99 (s, 1 H), 7.92 (d, *J* = 16.7 Hz, 1 H), 7.79 (t, *J* = 7.5 Hz, 1 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 16.8 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 184.30, 180.90, 155.61, 137.05, 134.99, 134.97, 133.75, 132.96, 132.33, 130.59, 129.26, 129.24, 128.56, 128.54, 126.49, 125.97, 119.60, 117.98.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{11}ClO_3Na$: 333.028893; found: 333.0286.

(*E*)-2-Hydroxy-3-[4-(trifluoromethyl)styryl]naphthalene-1,4-dione (3l)

Eluent for chromatography: EtOAc/*n*-hexane (10:90); reddish-orange solid; yield: 278.1 mg (81%); mp 223 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.6 Hz, 1 H), 8.12 (d, *J* = 7.3 Hz, 1 H), 8.07 (s, 1 H), 7.98 (d, *J* = 16.5 Hz, 1 H), 7.85–7.72 (m, 2 H), 7.70–7.62 (m, 4 H), 7.48 (d, *J* = 16.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.08, 170.14, 137.26, 135.22, 133.35, 127.23, 127.17, 126.19, 126.18, 125.64, 125.61, 119.78, 70.58, 70.54, 69.15, 69.11, 63.57, 63.54, 29.68.

HRMS: *m*/*z* [M + H] calcd for $C_{19}H_{12}F_3O_3$: 345.073305; found: 345.1522.

2-Phenylnaphtho[2,3-*b*]furan-4,9-dione (7)[18]

This compound was obtained as a side product from the reaction between **4** and **5a**; orange solid; mp 236–237 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (dd, *J* = 7.1, 1.8 Hz, 1 H), 8.20 (dd, *J* = 7.0, 1.9 Hz, 1 H), 7.90 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.80–7.72 (m, 2 H), 7.53–7.43 (m, 3 H), 7.20 (s, 1 H).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{10}O_3Na$: 297.0522; found: 297.0528.

2-Phenylnaphtho[1,2-*b*]furan-4,5-dione (8)[18]

This compound was obtained as a side product from reaction between **4** and **5a**; reddish-purple solid; mp 193–194 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.7 Hz, 1 H), 7.78 (d, *J* = 7.7 Hz, 1 H), 7.73 (dd, *J* = 7.0, 1.1 Hz, 2 H), 7.67 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.49–7.42 (m, 3 H), 7.41–7.35 (m, 1 H), 7.01 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.32, 174.41, 159.70, 156.69, 135.40, 130.61, 130.56, 130.19, 129.21, 128.99, 128.82, 128.59, 128.38, 124.40, 124.36, 123.26, 122.24, 102.79.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{10}O_3Na$: 297.0522; found: 297.0524.

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Supporting Information

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