JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

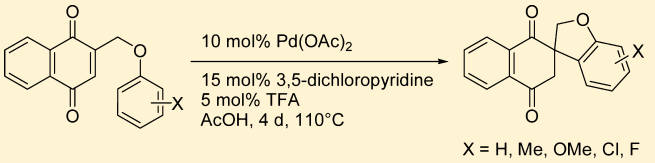
# Palladium(II)-Catalyzed Synthesis of 2*H*,3′*H*-Spiro[benzofuran-3,2′-naphthoquinones]

Pieter Claes, Jan Jacobs, Bart Kesteleyn, Tuyen Nguyen Van,[†] and Norbert De Kimpe*

Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

Supporting Information

**ABSTRACT:** 2*H*,3′*H*-Spiro[benzofuran-3,2′-naphthoquinones], constituting a new spiroheterocyclic skeleton, were synthesized starting from 2-aryloxymethyl-1,4-naphthoquinones by means of a palladium(II)-catalyzed reaction, which is a new spirocyclic transformation. Under optimal conditions, i.e. 10 mol % of palladium(II) acetate, 15 mol % of 3,5-dichloropyridine, and 5 mol % of trifluoroacetic acid in acetic acid at 110 °C, various 2*H*,3′*H*-spiro[benzofuran-3,2′-naphthoquinones] were synthesized in yields strongly dependent on the substitution pattern of the aryloxy group. Unsubstituted or *ortho*-substituted 2-aryloxymethyl-1,4-quinones were found to rearrange toward the corresponding 2-(4-hydroxyaryl)-1,4-quinones upon treatment with trifluoroacetic acid.

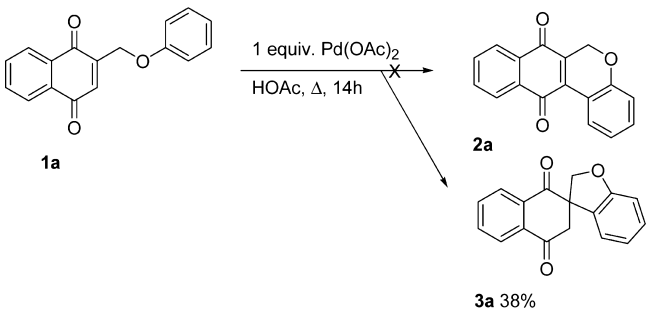



## INTRODUCTION

Our research group has been involved substantially in the synthesis of bioactive heterocyclic quinones and related natural products.[1] During our study of the tetracyclic benzopyranonaphthoquinone derivative **2a**, its synthesis was envisaged by means of a palladium(II)-catalyzed intramolecular oxidative coupling.[2] Thus, 2-phenoxymethyl-1,4-naphthoquinone **1a** was reacted with 1 equiv of palladium(II) acetate in boiling acetic acid for 14 h, yielding a single compound. Surprisingly, the obtained compound contained two aliphatic $CH_2$'s and had the same mass as 2-phenoxymethyl-1,4-naphthoquinone (**1a**). Moreover, a quaternary carbon was present at 58 ppm ($^{13}C$ NMR, $CDCl_3$), indicative of an aliphatic quaternary center next to an electron-withdrawing group or atom. Thus, the molecular skeleton of the spirocyclization product 2*H*,3′*H*-spiro[benzofuran-3,2′-naphthalene]-1′,4′-dione (**3a**) was proposed, which was isolated in 38% yield (Scheme 1).

In the present study, this surprising reaction was thoroughly investigated. To the best of our knowledge, the 2*H*,3′*H*-spiro[benzofuran-3,2′-naphthoquinone] structural motif has never been prepared before. Even though several methods to synthesize structurally similar spiroheterocyclic compounds exist in the literature,[3] the oxygen atom is always directly connected to the spirocyclic carbon.

**Scheme 1. Formation of 2*H*,3′*H*-Spiro[benzofuran-3,2′-naphthalene]-1′,4′-dione (3a)**




## RESULTS AND DISCUSSION

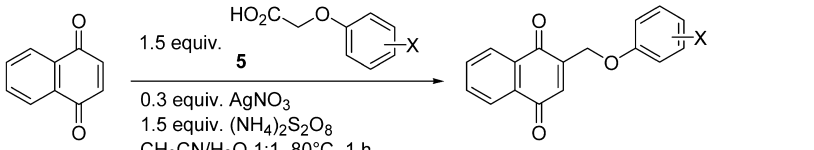
The starting 2-aryloxymethyl-1,4-quinones **1** were synthesized by means of a radical aryloxymethylation of naphthoquinone **4** using phenoxyacetic acids **5** in water with ammonium persulfate as a radical initiator and a catalytic amount of $AgNO_3$ as a radical transfer agent.[4] In order to ensure full solubility of the starting phenoxyacetic acids **5**, acetonitrile had to be added as a cosolvent. Thus, 2-aryloxymethyl-1,4-naphthoquinones **1a–j** were synthesized in 46–89% yield (Scheme 2).

Initially, it was investigated whether or not the spirocyclization could be a Friedel–Crafts type reaction by reacting a myriad of hard and soft metal salts with 2-phenoxymethyl-1,4-naphthoquinone (**1a**) in glacial acetic acid. None of the tested metal salts, i.e. LiCl, $MgBr_2$, $TiCl_4$, $(NH_4)_2Ce(NO_3)_6$, $FeCl_3$, AgOAc, $AlCl_3$, $NiCl_3$, $Co_2(SO_4)_3$, $SnCl_4$, and $Cu(OTf)_2$, yielded the desired spiroquinone **3a**. Strong acids, such as $CF_3COOH$, *p*TsOH, $H_2SO_4$, and TfOH, also did not effect the desired conversion. As quinones oxidize Pd(0) to Pd(II), palladium-catalyzed reactions in quinone chemistry are limited to Pd(II) catalysis.[5] Therefore, we attempted to optimize the conversion following the reaction conditions reported by Stolz et al.,[6] i.e. 40 mol % of ethyl nicotinate and 10 mol % of $Pd(OAc)_2$ in 4/1 *tert*-amyl alcohol/AcOH. Disappointingly, no conversion of **1a** was observed. It appeared that, no matter which ligand was used, the palladium complex only remained

**Received:** May 3, 2013

   dx.doi.org/10.1021/jo400852z | *J. Org. Chem.* XXXX, XXX, XXX–XXX

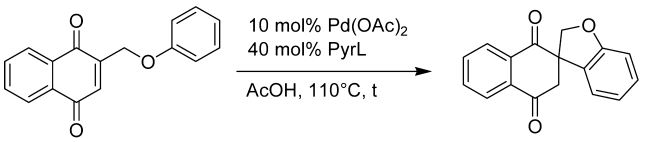
**Scheme 2. Synthesis of 2-Aryloxymethyl-1,4-naphthoquinones 1**




**1a** X = H 62% **1f** X = 3-OMe 57%
**1b** X = 2-Me 73% **1g** X = 4-OMe 46%
**1c** X = 3-Me 89% **1h** X = 4-*t*-Bu 66%
**1d** X = 4-Me 62% **1i** X = 4-F 59%
**1e** X = 2-OMe 50% **1j** X = 4-Cl 56%

stable in pure acetic acid and decomposed in all other solvents or combinations thereof (4/1 *tert*-amyl alcohol/AcOH, DMF, DMA, or pinacolone). Together with the fact that addition of 1 equiv of NaOAc leads to a complex mixture (Table 1, entry 2), it can be concluded that a protic acid should play a crucial role in the reaction mechanism. From Table 1 it is clear that the more electron poor the ligand, the faster the reaction. However, most reactions end prematurely due to decomposition of the palladium complex (entries 5−8). Only 3,5-dichloropyridine (entry 4) led to full conversion, but the reaction was very sluggish and took 12 days to attain completion. When ligands were introduced bearing two coordinating nitrogen atoms such as 2,2′-bipyridines and phenanthrolines, little (entry 9) or no conversion (entries 10−13) toward spiroquinone **3a** was observed. In addition, the conditions recently reported by Li et al.,[7] in which 20 mol % of *N*-acetylglycine was used as the ligand and hexafluoroisopropyl alcohol as the solvent, were tested but no significant conversion was observed even when the solvent was changed to acetic acid.

**Table 1. Ligand Screening for the Spirocyclization Reaction using 40 mol % Pyridine Ligand in Acetic Acid**




**1a** **3a**

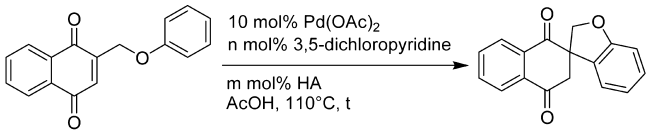
| entry | PyrL | *t* | result[a] |
|---|---|---|---|
| 1 | ethyl nicotinate | 20 h | no conversn to **3a** |
| 2 | ethyl nicotinate + 1 equiv NaOAc | 20 h | complex reaction mixture |
| 3 | pyridine-3-carbonitrile | 23 h | no conversn to **3a** |
| 4 | 3,5-dichloropyridine | 12 d | **3a** (53%) |
| 5 | 5-bromo-2-chloropyridine | 20 h | 29% conversn to **3a** |
| 6 | 2,5-dichloropyridine | 7 h | 26% conversn to **3a** |
| 7 | 2,6-dibromopyridine | 18 h | 15% conversn to **3a** |
| 8 | 2-chloro-3-nitropyridine | 23 h | <10% conversn to **3a** |
| 9 | 2,2′-bipyridinyl | 15 h | <10% conversn to **3a** |
| 10 | 4,4′-dibromo-2,2′-bipyridine | 15 h | no conversn to **3a** |
| 11 | 2,2′-bipyridine-3,3′-dicarboxylic acid | 15 h | no conversn to **3a** |
| 12 | 1,10-phenanthroline-5,6-dione | 15 h | no conversn to **3a** |
| 13 | 5-chloro-1,10-phenanthroline | 15 h | no conversn to **3a** |

[a]All reactions were monitored by LC-MS and stopped when no further conversion was observed.

When the amount of ligand was varied between 10 and 40 mol %, the reaction time could be reduced to 7 days using 15 or 30 mol % of ligand (Table 2, entries 2 and 5) without lowering the yield. For further experiments, it was decided to work with 15 mol % of ligand. When 5−15 mol % of trifluoroacetic acid (TFA) was added, the reaction time could be reduced to 4 days. When 5 mol % of TFA was used, compound **3a** was obtained in 62% yield (entry 7), while more TFA led to lower yields (entries 8 and 9). The addition of stronger acids (*p*-toluenesulfonic acid, methanesulfonic acid, and trifluoromethanesulfonic acid) led to significant decomposition of the palladium complex, and no full conversion was observed after 4 days. Replacement of TFA by the higher boiling heptafluorobutyric acid (HFBA) did not result in an increased yield (entry 10).

The yield of the spirocyclization reaction was strongly dependent on the substitution pattern of the aryloxy group of the starting 2-(aryloxymethyl)-1,4-naphthoquinones **1** (Scheme 3). While *meta*- and *para*-substituted aryloxy groups gave spiroquinones **3** in good yields, little (**1b**) or no (**1e**) conversion was observed in the case of *meta*-substituted aryloxy

**Table 2. Fine Tuning of the Catalytic Cycle for the Spirocyclization Reaction toward Spironaphthoquinone 3a[a]**



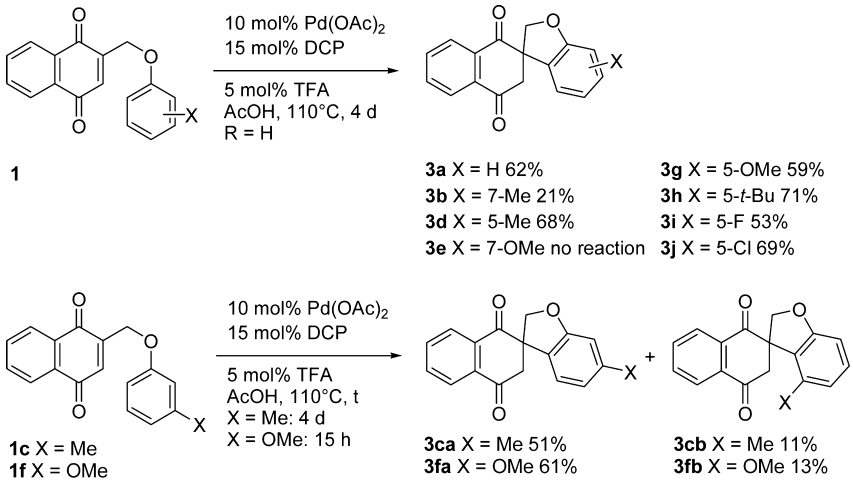

**1a** **3a**

| entry | *n* | *m* | HA | *t* (days) | yield (%) | entry | *n* | *m* | HA | *t* (days) | yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 10 | – | – | 7 | 38 | 6 | 40 | – | – | 12 | 53 |
| 2 | 15 | – | – | 7 | 53 | **7** | **15** | **5** | **TFA** | **4** | **62** |
| 3 | 20 | – | – | 9 | 30 | 8 | 15 | 10 | TFA | 4 | 42 |
| 4 | 25 | – | – | 8 | 38 | 9 | 15 | 15 | TFA | 4 | 35 |
| 5 | 30 | – | – | 7 | 52 | 10 | 15 | 5 | HFBA | 4 | 49 |

[a]HFBA = $CF_3(CF_2)_2COOH$.

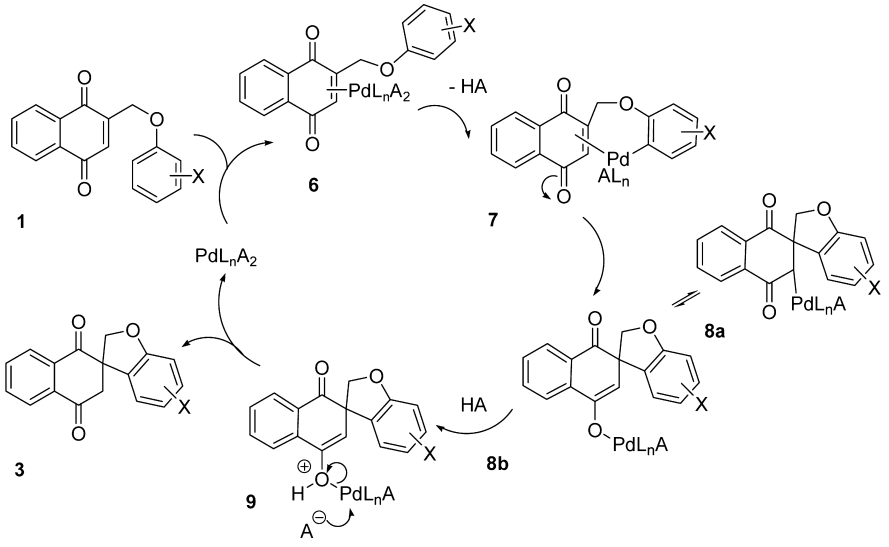

dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

**Scheme 3. Synthesis of 2*H*,3′*H*-Spiro[benzofuran-3,2′-naphthalene]-1′,4′-diones 3[a]**




[a]DCP = 3,5-dichloropyridine.

**Scheme 4. Proposed Catalytic Cycle of the Spirocyclization Reaction of 2-Aryloxymethyl-1,4-naphthoquinones 1 toward Spironaphthoquinones 3[a]**




[a]HA = HOAc, TFA.

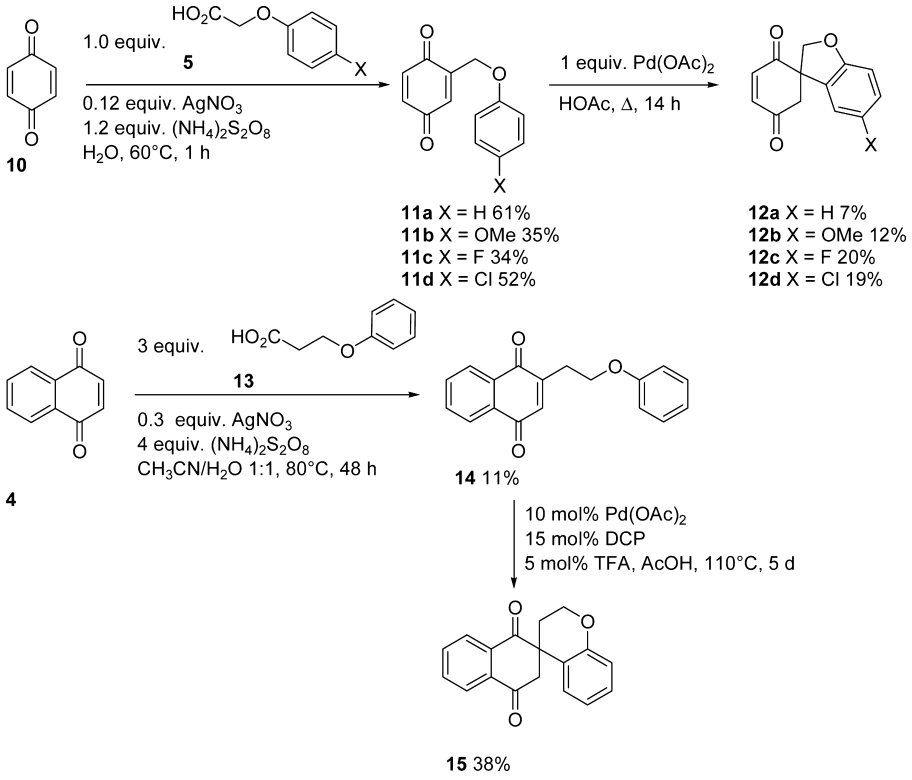
groups. Replacement of acetic acid by hexafluoroisopropyl alcohol also did not give any reaction. Apart from the fact that only one reactive position is available for cyclization, there is no satisfying explanation so far for this observation. In the case of *meta*-substituted compounds, regioisomers were formed in a ratio of about 5/1. Interestingly, in the case of naphthoquinone **1f**, the reaction was complete after only 15 h. This is attributed to the electron-donating properties combined with the sterically favored position of the methoxy group. Other apparent differences in yield based on the electronic nature of the substituents were not observed.

On the basis of the aforementioned observations, a reaction mechanism is proposed. Initial coordination of the palladium catalyst with the naphthoquinone moiety, which behaves as a $\pi$-acid ligand, increases the electron deficiency of the palladium center.[8] Arene palladation of the naphthoquinone−Pd(II) complex **6** leads to the organopalladium intermediate **7** (Scheme 4). This intermediate **7** will undergo an intramolecular Michael addition leading to palladium enolate **8a**.[4c,9,10] Acid-mediated regeneration of the palladium complex followed by tautomerization finally leads to spiroquinone **3**. It is believed that the addition of TFA accelerates the hydrolysis of palladium enolate **8b**, thus giving rise to shorter reaction times. It should be noted that the reaction is a cycloisomerization and does not need a cooxidant as do most other palladium(II)-catalyzed reactions.[4,11]

Application of the optimized spirocyclization conditions to aryloxymethylbenzoquinones **11** led only to complex reaction mixtures. 2*H*,3′*H*-Spiro[benzofuran-3,2′-benzoquinones] **12** could only be synthesized in low yields using a full 1 equiv of palladium(II) acetate in boiling acetic acid. This is attributed to the high reactivity of the benzoquinone moiety, which also explains the lower yields of the radical alkylation reaction in comparison to 2-aryloxymethyl-1,4-naphthoquinones **1**. Next, the synthesis of the six-membered-ring spiroquinone **15** was envisaged starting from 2-(2-phenoxyethyl)-1,4-naphthoquinone **14**, which was prepared starting from 1,4-naphthoquinone **4** and 3-phenoxypropionic acid **13** under the aforementioned


dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

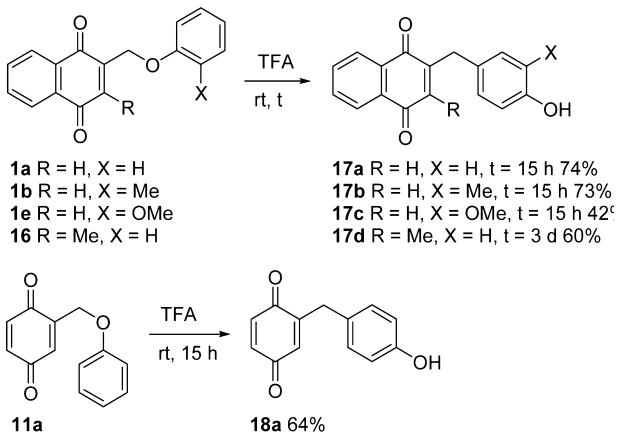
**Scheme 5. Synthesis of 2*H*,3′*H*-Spiro[benzofuran-3,2′-benzoquinones] 12 and 3′*H*-Spiro[chroman-3,2′-naphthalene]-1′,4′-dione (15)**




radical reaction conditions. However, as the intermediate radical is not stabilized, 2-(2-phenoxyethyl)-1,4-naphthoquinone **14** could only be obtained in 11% yield. The spirocyclization reaction of **14** was found to be significantly slower than that of phenoxymethyl-1,4-naphthoquinone **1a** and was stopped after 5 days. From this reaction, 3′*H*-spiro-[chroman-3,2′-naphthalene]-1′,4′-dione (**15**) was isolated in 38% yield, together with 22% of starting material **14** (Scheme 5). No reaction was observed when substrates structurally related to phenoxymethyl-1,4-naphthoquinone **1a** such as 3-methyl-2-phenoxymethyl-1,4-naphthoquinone (**16**), *N*-mesyl-, *N*-acyl-, or *N*-benzoyl-2-phenylaminomethyl-1,4-naphthoquinones, and 2-phenoxymethylchromen-4-one were subjected to the optimized spirocyclization conditions or to reaction with a full 1 equiv of palladium(II) acetate.

During the reaction optimization it was found that when 2-phenoxymethyl-1,4-naphthoquinone (**1a**) was stirred overnight at room temperature in pure TFA, 2-(4-hydroxybenzyl)-1,4-naphthoquinone **17a** was formed in 74% yield as the sole reaction product (Scheme 6). All attempts to execute this Claisen rearrangement on aryloxymethylnaphthoquinones **1** bearing a *meta*- and *para*-substituted aryloxy group gave complex mixtures. Aryloxymethylnaphthoquinones **1b,e** bearing an *ortho*-substituted aryloxy group did react via this Claisen rearrangement pathway to provide the corresponding phenols **17b,c**, but in the case of 2-(2-methoxyphenoxymethyl)-1,4-naphthoquinone (**1e**) the yield was low due to the formation of several side products. For 3-methyl-2-phenoxymethyl-1,4-naphthoquinone (**16**), the Claisen rearrangement did occur, but only after 3 days, and resulted in the formation of 2-(4-hydroxybenzyl)-3-methyl-1,4-naphthoquinone (**17d**) in 60% yield. Claisen rearrangement of 2-phenoxymethyl-1,4-benzoquinone **11a** yielded 2-(4-hydroxybenzyl)-1,4-benzoquinone

**Scheme 6. Synthesis of 2-(4-Hydroxybenzyl)-1,4-quinones 17 and 18a**




**18a** in 64% yield. No reaction was observed upon treatment of *N*-mesyl-, *N*-acyl-, or *N*-benzoyl-2-phenylaminomethyl-1,4-naphthoquinones or 2-phenoxymethylchromen-4-one with TFA.

In conclusion, a new spiroheterocyclic molecular skeleton was synthesized starting from 2-aryloxymethyl-1,4-naphthoquinones **1** and 2-(2-phenoxyethyl)-1,4-naphthoquinone (**13**) using palladium(II) catalysis. Under optimal conditions, 10 mol % of palladium(II) acetate, 15 mol % of 3,5-dichloropyridine, and 5 mol % of trifluoroacetic acid in acetic acid at 110 °C were used. Good yields were obtained for *meta*- and *para*-substituted aryloxymethyl-1,4-naphthoquinones **1**. Unfortunately, the reaction seems to be limited to naphthoquinone substrates. Unsubstituted or *ortho*-substituted 2-aryloxymethyl-1,4-quinones **1**, **16**, and **11a** were found to


dx.doi.org/10.1021/jo400852z | *J. Org. Chem.* XXXX, XXX, XXX–XXX

rearrange toward the corresponding 2-(4-hydroxyaryl)-1,4-quinones **17** and **18** upon treatment with trifluoroacetic acid.

## EXPERIMENTAL SECTION

**General Experimental Methods.** $^{1}$H NMR spectra were recorded at 300 MHz using TMS as internal standard, $^{13}$C NMR spectra were recorded at 75 MHz, and $^{19}$F NMR spectra were recorded at 282 MHz using $CFCl_3$ as internal standard. Peak assignments were performed with the aid of APT and HSQC spectra. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). The reported melting points are not corrected. Flash chromatography was carried out using a glass column with silica gel (particle size 0.035−0.07 mm, pore diameter ca. 6 nm) or by means of an automated flash chromatography system. Solvent systems were determined via initial TLC analysis (silica gel). Preparative TLC was performed on plates ($F_{254}$) measuring 20 cm × 20 cm × 2 mm. HRMS spectra were recorded using a tandem TOF spectrometer. The reaction progress was monitored by means of LC analysis. All solvents and chemicals were used without further purification.

**Synthesis of 2-Aryloxymethyl-1,4-naphthoquinones 1 and 16.** To a solution of 37.5 mmol of phenoxyacetic acid **5** in 80 mL of distilled water and 80 mL of acetonitrile were successively added 3.95 g (25 mmol, 1.5 equiv) of 1,4-naphthoquinone (**4**) and 1.27 g (7.5 mmol) of $AgNO_3$. The mixture was heated to 80 °C until dissolution was complete. The resulting solution was stirred vigorously while a solution of 8.56 g (37.5 mmol) of ammonium peroxydisulfate in 80 mL of distilled water was added dropwise. Throughout the addition, the reaction mixture was maintained at 80 °C. After the addition was complete, the mixture was stirred for 5 min at 80 °C and was then cooled to 5−10 °C in an ice bath. The precipitated solid was collected by suction filtration, washed with 50 mL of cold water, and pressed to remove most of the liquid. Inorganic contaminants, usually present in small amounts, were removed by dissolving the solid in 350 mL of boiling acetone and filtering the hot solution. Concentration of the filtrate in vacuo gave a dark red crude product, which was recrystallized from ethanol. In the case of 3-methyl-2-phenoxymethyl-1,4-naphthoquinone (**16**), 2-methyl-1,4-naphthoquinone was used.

*2-Phenoxymethyl-1,4-naphthoquinone (**1a**):* 4.10 g, 62%; yellow needles; mp 163 °C (lit.[12] mp 163−164 °C). $^{1}$H NMR ($CDCl_3$): δ 5.05 (2H, d, *J* = 2.0 Hz, $CH_2O$), 6.98−7.02 (3H, m, 3 × $CH_{Ar}$), 7.17 (1H, t, *J* = 2.0 Hz, CH-3), 7.29−7.34 (2H, m, 2 × $CH_{Ar}$), 7.72−7.78 (2H, m, CH-6 and CH-7), 8.07−8.13 (2H, m, CH-5 and CH-8). $^{13}$C NMR ($CDCl_3$): δ 63.5 ($CH_2O$), 114.8 (2 × $CH_{Ar}$), 121.8 ($CH_{Ar}$), 126.4 and 126.5 (CH-5 and CH-8), 129.8 (2 × $CH_{Ar}$), 132.1 ($C_{quat}$), 133.9 and 134.0 (CH-6 and CH-7), 134.2 (CH-3), 146.3 ($C_{quat}$), 157.9 ($C_{quat}$), 184.7 (C═O), 184.8 (C═O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): ν 1659 (C═O), 1586, 1299, 1240 (C−O). MS ($ES^+$; *m*/*z* (%)): 265 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{17}H_{11}O_3]^-$ 263.0708, found 263.0716.

*2-(2-Methylphenoxymethyl)-1,4-naphthoquinone (**1b**):* 5.08 g, 73%; yellow crystals; mp 160.0 °C. $^{1}$H NMR ($CDCl_3$): δ 2.34 (3H, s, $CH_3$), 5.09 (2H, d, *J* = 2.2 Hz, $CH_2O$), 6.89−6.95 (2H, m, 2 × $CH_{Ar}$), 7.16−7.22 (3H, m, 2 × $CH_{Ar}$ and CH-3), 7.74−7.81 (2H, m, 2 × $CH_{Ar}$), 8.09−8.16 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 16.5 ($CH_3$), 63.5 ($CH_2O$), 111.1 ($CH_{Ar}$), 121.4 ($CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 127.0 ($C_{quat}$), 127.1 ($CH_{Ar}$), 131.1 ($CH_{Ar}$), 132.00 ($C_{quat}$), 132.03 ($C_{quat}$), 133.8 (CH-3), 133.9 ($CH_{Ar}$), 134.2 ($CH_{Ar}$), 146.6 ($C_{quat}$), 155.9 ($C_{quat}$), 184.7 (C═O), 184.8 (C═O). IR ($cm^{-1}$): ν 1657 (C═O), 1588, 1296, 1245 (C−O), 748. MS ($ES^+$; *m*/*z* (%)): 279 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1008.

*2-(3-Methylphenoxymethyl)-1,4-naphthoquinone (**1c**):* 6.19 g, 89%, yellow solid; mp 166.5 °C. $^{1}$H NMR ($CDCl_3$): δ 2.35 (3H, s, $CH_3$), 5.07 (2H, d, *J* = 2.2 Hz, $CH_2O$), 6.78−6.84 (3H, m, 3 × $CH_{Ar}$), 7.17−7.23 (2H, m, $CH_{Ar}$ and CH-3), 7.74−7.80 (2H, m, 2 × $CH_{Ar}$), 8.08−8.15 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 21.6 ($CH_3$), 63.5 ($CH_2O$), 111.6 ($CH_{Ar}$), 115.6 ($CH_{Ar}$), 122.6 ($CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 129.5 ($CH_{Ar}$), 132.02 ($C_{quat}$), 132.03 ($C_{quat}$), 133.9 ($CH_{Ar}$), 134.0 ($CH_{Ar}$), 134.2 ($CH_{Ar}$), 139.9 ($C_{quat}$), 146.4 ($C_{quat}$), 157.9 ($C_{quat}$), 184.7 (C═O), 184.8 (C═O). IR ($cm^{-1}$): ν 1660 (C═O), 1583, 1296 (C−O), 1250 (C−O). MS ($ES^+$; *m*/*z* (%)): 279 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1025.

*2-(4-Methylphenoxymethyl)-1,4-naphthoquinone (**1d**):* 4.31 g, 62%; yellow needles; mp 145.5 °C. $^{1}$H NMR ($CDCl_3$): δ 2.30 (3H, s, $CH_3$), 5.05 (2H, d, *J* = 2.2 Hz, $CH_2O$), 6.89 (2H, d, *J* = 8.3 Hz, 2 × $CH_{Ar}$), 7.11 (2H, d, *J* = 8.3 Hz, 2 × $CH_{Ar}$), 7.18 (1H, t, *J* = 2.2 Hz, CH-3), 7.73−7.80 (2H, m, 2 × $CH_{Ar}$), 8.07−8.15 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 20.6 ($CH_3$), 63.7 ($CH_2O$), 114.6 (2 × $CH_{Ar}$), 126.4 (2 × $CH_{Ar}$), 130.2 (2 × $CH_{Ar}$), 131.0 ($C_{quat}$), 132.1 ($C_{quat}$), 133.9 (2 × $CH_{Ar}$), 134.2 ($C_{quat}$), 146.4 ($C_{quat}$), 155.8 ($C_{quat}$), 184.6 (C═O), 184.7 (C═O). IR ($cm^{-1}$): ν 1659 (C═O), 1628, 1509, 1296, 1244 (C−O), 1232 (C−O). MS ($ES^+$; *m*/*z* (%)): 279 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1015.

*2-(2-Methoxyphenoxymethyl)-1,4-naphthoquinone (**1e**):* 3.68 g, 50%; yellow solid; mp 193 °C. $^{1}$H NMR ($CDCl_3$): δ 3.91 (3H, s, $CH_3O$), 5.16 (2H, d, *J* = 1.8 Hz, $CH_2O$), 6.87−7.02 (4H, m, 4 × $CH_{Ar}$), 7.23 (1 H, t, *J* = 1.8 Hz, CH-3), 7.74−7.80 (2H, m, 2 × $CH_{Ar}$), 8.08−8.15 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 56.0 ($CH_3O$), 65.0 ($CH_2O$), 112.2 ($CH_{Ar}$), 114.2 ($CH_{Ar}$), 121.0 ($CH_{Ar}$), 122.5 ($CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 132.04 ($C_{quat}$), 132.07 ($C_{quat}$), 133.9 (CH-3), 134.0 (2 × $CH_{Ar}$), 146.4 ($C_{quat}$), 147.3 ($C_{quat}$), 149.8 ($C_{quat}$), 184.8 (2 × C═O). IR ($cm^{-1}$): ν 1659 (C═O), 1589, 1505, 1253, 1230 (C−O), 739. MS ($ES^+$; *m*/*z* (%)): 295 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_4]^+$ 295.0970, found 295.0964.

*2-(3-Methoxyphenoxymethyl)-1,4-naphthoquinone (**1f**):* 4.19 g, 57%; yellow solid; mp 130.0 °C. $^{1}$H NMR ($CDCl_3$): δ 3.81 (3H, s, $CH_3O$), 5.07 (2H, d, *J* = 2.2 Hz, $CH_2O$), 6.55−6.61 (3H, m, 3 × $CH_{Ar}$), 7.17−7.24 (2H, m, CH-3 and $CH_{Ar}$), 7.74−7.80 (2H, m, 2 × $CH_{Ar}$), 8.07−8.15 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 55.4 ($CH_3O$), 63.6 ($CH_2O$), 101.3 ($CH_{Ar}$), 106.8 ($CH_{Ar}$), 107.3 ($CH_{Ar}$), 126.4 (2 × $CH_{Ar}$), 130.2 ($CH_{Ar}$), 132.1 ($C_{quat}$), 133.9 ($CH_{Ar}$), 134.0 ($CH_{Ar}$), 134.2 ($CH_{Ar}$), 138.7 ($C_{quat}$), 146.2 ($C_{quat}$), 159.1 ($C_{quat}$), 161.0 ($C_{quat}$), 184.6 (C═O), 184.7 (C═O). IR ($cm^{-1}$): ν 1657 (C═O), 1588, 1298, 1249 (C−O). MS ($ES^+$; *m*/*z* (%)): 295 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_4]^+$ 295.0970, found 295.0969.

*2-(4-Methoxyphenoxymethyl)-1,4-naphthoquinone (**1g**):* 3.38 g, 46%; yellow crystals; mp 136.1−137.1 °C. $^{1}$H NMR ($CDCl_3$): δ 3.77 (3H, s, $CH_3O$), 5.02 (2H, d, *J* = 2.2 Hz, $CH_2O$), 6.82−6.96 (4H, m, 4 × $CH_{Ar}$), 7.18 (1 H, t, *J* = 2.2 Hz, CH-3), 7.19−7.80 (2H, m, 2 × $CH_{Ar}$), 8.07−8.14 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 55.8 ($CH_3O$), 64.3 ($CH_2O$), 114.9 (2 × $CH_{Ar}$), 115.7 (2 × $CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 132.1 ($C_{quat}$), 133.9 (CH-3), 134.0 ($CH_{Ar}$), 134.2 ($CH_{Ar}$), 146.5 ($C_{quat}$), 152.0 ($C_{quat}$), 154.5 ($C_{quat}$), 184.7 (C═O), 184.8 (C═O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): ν 1659, 1508, 1234. MS ($ES^+$; *m*/*z* (%)): 295 (M + $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{18}H_{13}O_4]^-$ 293.0814, found 293.0822.

*2-(4-tert-Butylphenoxymethyl)-1,4-naphthoquinone (**1h**):* 5.29 g, 66%; yellow solid; mp 139.0 °C. $^{1}$H NMR ($CDCl_3$): δ 1.31 (9H, s, $(CH_3)_3C$), 5.07 (2H, d, *J* = 2.2 Hz, $CH_2O$), 6.93 (2H, d, *J* = 9.1 Hz, 2 × $CH_{Ar}$), 7.19 (1 H, t, *J* = 2.2 Hz, CH-3), 7.34 (2H, d, *J* = 9.1 Hz, 2 × $CH_{Ar}$), 7.74−7.80 (2H, m, 2 × $CH_{Ar}$), 8.07−8.16 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 31.6 (($CH_3)_3C$), 34.2 (($CH_3)_3C$), 63.7 ($CH_2O$), 114.3 (2 × $CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 126.6 (2 × $CH_{Ar}$), 132.1 ($C_{quat}$), 133.9 ($CH_{Ar}$), 134.0 ($CH_{Ar}$), 134.2 ($CH_{Ar}$), 144.5 ($C_{quat}$), 146.5 ($C_{quat}$), 155.6 ($C_{quat}$), 184.7 (C═O), 184.8 (C═O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): ν 1661 (C═O), 1591, 1512, 1297, 1245 (C−O). MS ($ES^+$; *m*/*z* (%)): 321 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{21}H_{21}O_3]^+$ 321.1491, found 321.1479.

*2-(4-Fluorophenoxymethyl)-1,4-naphthoquinone (**1i**):* 4.16 g, 59%; yellow crystals; mp 158.6−159.0 °C. $^{1}$H NMR ($CDCl_3$): δ 5.04 (2H, d, *J* = 2.0 Hz, $CH_2O$), 6.91−7.05 (4H, m, 4 × $CH_{Ar}$), 7.17 (1H, s, CH-3), 7.75−7.81 (2H, m, 2 × $CH_{Ar}$), 8.09−8.13 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): δ 64.3 ($CH_2O$), 115.8 ($J_{CF}$ = 6.9 Hz, 2 × $CH_{Ar}$), 116.2 ($J_{CF}$ = 23.2 Hz, 2 × $CH_{Ar}$), 126.5 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 132.1 ($C_{quat}$), 134.0 ($CH_{Ar}$), 134.1 ($CH_{Ar}$), 134.3 (CH-3), 146.0 ($C_{quat}$), 154.0 ($C_{quat}$) 157.8 ($J_{CF}$ = 238.8 Hz, $C_{quat}$), 184.6 (C═O),


dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

184.7 (C=O), one trisubstituted olefinic carbon is not observed. $^{19}$F NMR ($CDCl_3$): $\delta$ −125.03 - −122.60 (1F, m). IR ($cm^{-1}$): $\nu$ 1655, 1506, 1206. MS ($ES^+$; $m/z$ (%)): 281 ($M - H^+$, 70). HRMS ($ES^-$): calcd for $[C_{17}H_{10}FO_3]^-$ 281.0614, found 281.0628.

*2-(4-Chlorophenoxymethyl)-1,4-naphthoquinone (**1j**):* 1.49 g, 20%; yellow needles; mp 165.9−166.0 °C (lit.[13] mp 167−169.5 °C). $^1$H NMR ($CDCl_3$): $\delta$ 5.21 (2H, s, $CH_2O$), 6.84 (2H, d, $J$ = 8.5 Hz, 2 × $CH_{Ar}$), 7.21 (1H, s, CH-3), 7.24 (2H, d, $J$ = 8.5 Hz, 2 × $CH_{Ar}$), 7.78−7.81 (2H, m, 2 × $CH_{Ar}$), 8.14−8.19 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 63.9 ($CH_2O$), 116.1 (2 × $CH_{Ar}$), 126.5 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 126.7 ($C_{quat}$), 129.7 (2 × $CH_{Ar}$), 132.0 ($C_{quat}$), 132.0 ($C_{quat}$), 134.0 ($CH_{Ar}$), 134.1 ($CH_{Ar}$), 134.3 (CH-3), 145.8 ($C_{quat}$), 156.5 ($C_{quat}$), 184.6 (C=O), 184.7 (C=O). IR ($cm^{-1}$): $\nu$ 1655, 1596, 1221. MS ($ES^+$; $m/z$ (%)): 299 ($M + H^+$, 93). HRMS ($ES^-$): calcd for $[C_{17}H_{10}ClO_3]^-$ 297.0319, found 297.0314.

*3-Methyl-2-phenoxymethyl-1,4-naphthoquinone (**16**):* 4.87 g, 70%; yellow crystals; mp 110.4 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.33 (3H, s, $CH_3$), 5.13 (2H, s, $CH_2O$), 6.96−7.00 (3H, m, 3 × $CH_{Ar}$), 7.23−7.34 (2H, m, 2 × $CH_{Ar}$), 7.67−7.77 (2H, m, 2 × $CH_{Ar}$), 8.09−8.17 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.3 ($CH_3$), 60.7 ($OCH_2$), 114.8 (2 × $CH_{Ar}$), 121.5 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 126.7 ($CH_{Ar}$), 129.7 (2 × $CH_{Ar}$), 131.9 ($C_{quat}$), 132.2 ($C_{quat}$), 133.8 ($CH_{Ar}$), 133.9 ($CH_{Ar}$), 140.1 ($C_{quat}$), 148.4 ($C_{quat}$), 158.5 ($C_{quat}$), 183.7 (C=O), 185.3 (C=O). IR ($cm^{-1}$): $\nu$ 1664, 1589, 1294. MS ($ES^+$; $m/z$ (%)): 279 ($M + H^+$, 25). HRMS ($ES^-$): calcd for $[C_{18}H_{13}O_3]^-$ 277.0865, found 277.0873.

**Synthesis of 2′*H*,3*H*-Spiro[benzofuran-3,2′-naphthoquinones] 3.** In a 10 mL vial were added 3,5-dichloropyridine (0.15 mmol, 22 mg), trifluoroacetic acid (0.05 mmol, 6 mg), palladium(II) acetate (0.10 mmol, 22 mg), 2-aryloxymethyl-1,4-naphthoquinones **1** (1 mmol), and 4 mL of acetic acid. The flask was sealed, and the contents were stirred at 110 °C for 4 days. The reaction mixture was then diluted with chloroform, filtered over a pad of Celite, washed once with water and twice with aqueous sodium hydrogen carbonate, and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1/9) yielded 2′*H*,3*H*-spiro[benzofuran-3,2′-naphthoquinones] **3**. Upon (LC−)MS analysis most spiroquinones were found to give very poor mass spectrometric ionizations. The regioisomeric spironaphthoquinones **3c,f** were further separated by means of preparative HPLC.

*2*′*H*,3′*H*-Spiro[benzofuran-3,2′-naphthalene]-1′,4′-dione (**3a**):* 164 mg, 62%; yellow crystals; mp 88.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.30 (1H, d, $J_{ab}$ = 16.8 Hz, C$H_a$H$_b$C=O), 3.32 (1H, d, $J_{ab}$ = 16.8 Hz, CH$_a$H$_b$C=O), 4.31 (1H, d, $J_{ab}$ = 8.8 Hz, C$H_a$H$_b$O), 5.43 (1H, d, $J_{ab}$ = 8.8 Hz, CH$_a$H$_b$O), 6.64−6.73 (2H, m, 2 × $CH_{Ar}$), 6.86 (1H, d, $J$ = 8.3 Hz, $CH_{Ar}$), 7.17 (1H, dxt, $J$ = 1.6 and 7.2 Hz, $CH_{Ar}$), 7.78−7.87 (2H, m, 2 × $CH_{Ar}$), 8.12−8.22 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 48.8 ($CH_2$C=O), 58.4 ($C_{spiro}$), 77.6 ($CH_2O$), 110.9 ($CH_{Ar}$), 121.0 ($CH_{Ar}$), 123.8 ($CH_{Ar}$), 126.8 ($CH_{Ar}$), 127.5 ($C_{quat}$), 128.5 ($CH_{Ar}$), 130.3 ($CH_{Ar}$), 134.6 ($C_{quat}$), 134.9 ($CH_{Ar}$), 134.9 ($CH_{Ar}$), 135.6 ($C_{quat}$), 159.9 ($C_{quat}$), 193.9 (C=O), 194.0 (C=O). IR ($cm^{-1}$): $\nu$ 1694, 1590. MS ($ES^-$; $m/z$ (%)): 263 ($M - H^+$, 100). HRMS ($ES^+$): calcd for $[C_{17}H_{13}O_3]^+$ 265.0865, found 265.0856.

*2*′*H*,3′*H*-Spiro[7-methylbenzofuran-3,2′-naphthalene]-1′,4′-dione (**3b**):* 58 mg, 21%; yellow solid; mp 160.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.21 (3H, s, $CH_3$), 3.28 (1H, d, $J_{ab}$ = 16.2 Hz, C$H_a$H$_b$C=O), 3.30 (1H, d, $J_{ab}$ = 16.2 Hz, CH$_a$H$_b$C=O), 4.29 (1H, d, $J_{ab}$ = 9.1 Hz, C$H_a$H$_b$O), 5.42 (1H, d, $J_{ab}$ = 9.1 Hz, CH$_a$H$_b$O), 6.46 (1H, d, $J$ = 7.7 Hz, CH-6), 6.59 (1H, t, $J$ = 7.7 Hz, CH-5), 6.97 (1H, d, $J$ = 7.7 Hz, CH-4), 7.76−7.85 (2H, m, 2 × $CH_{Ar}$), 8.09−8.19 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 15.25 ($CH_3$), 48.79 ($CH_2$C=O), 58.70 ($C_{spiro}$), 76.73 ($CH_2O$), 120.86 (CH-5), 121.16 (CH-6), 121.24 ($C_{quat}$), 126.73 ($CH_{Ar}$), 128.43 ($CH_{Ar}$), 131.41 (CH-4), 134.66 ($C_{quat}$), 134.80 ($CH_{Ar}$), 134.87 ($CH_{Ar}$), 135.62 ($C_{quat}$), 158.32 ($C_{quat}$), 193.95 (C=O), 194.14 (C=O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): $\nu$ 1689 (C=O), 1592, 1247 (C−O), 753. MS ($ES^+$; $m/z$ (%)): 279 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1005.

*2*′*H*,3′*H*-Spiro[6-methylbenzofuran-3,2′-naphthalene]-1′,4′-dione (**3ca**):* 142 mg, 51%; yellow solid; mp 108.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.25 (3H, s, $CH_3$), 3.29 (2H, s, $CH_2$C=O), 4.29 (1H, d, $J_{ab}$ = 9.3 Hz, C$H_a$H$_b$O), 5.42 (1H, d, $J_{ab}$ = 9.3 Hz, CH$_a$H$_b$O), 6.50 (2H, s, 2 × $CH_{Ar}$), 6.68 (1H, s, $CH_{Ar}$), 7.76−7.89 (2H, m, 2 × $CH_{Ar}$), 8.10−8.20 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 21.6 ($CH_3$), 48.8 ($CH_2$C=O), 58.2 ($C_{spiro}$), 77.8 ($CH_2O$), 111.5 ($CH_{Ar}$), 121.7 ($CH_{Ar}$), 123.4 ($CH_{Ar}$), 124.7 ($C_{quat}$), 126.8 ($CH_{Ar}$), 128.4 ($CH_{Ar}$), 134.7 ($C_{quat}$), 134.8 ($CH_{Ar}$), 134.9 ($CH_{Ar}$), 135.6 ($C_{quat}$), 140.8 ($C_{quat}$), 160.2 ($C_{quat}$), 194.0 (C=O), 194.1 (C=O). IR ($cm^{-1}$): $\nu$ 1687 (C=O), 1591, 1253 (C−O), 1245 (C−O), 759. MS ($ES^+$; $m/z$ (%)): 279 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1012.

*2*′*H*,3′*H*-Spiro[4-methylbenzofuran-3,2′-naphthalene]-1′,4′-dione (**3cb**):* 31 mg, 11%; white solid. mp 179.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.20 (3H, s, $CH_3$), 3.23 (1H, d, $J_{ab}$ = 16.2 Hz, CH$_a$H$_b$C=O), 3.53 (1H, d, $J_{ab}$ = 16.2 Hz, CH$_a$H$_b$C=O), 4.43 (1H, d, $J_{ab}$ = 8.8 Hz, C$H_a$H$_b$O), 4.48 (1H, d, $J_{ab}$ = 8.8 Hz, C$H_a$H$_b$O), 6.74 (1H, d, $J$ = 8.3 Hz, $CH_{Ar}$), 6.78 (1H, d, $J$ = 7.7 Hz, $CH_{Ar}$), 7.17 (1H, t, $J$ = 7.7 Hz, $CH_{Ar}$), 7.80−7.85 (2H, m, 2 × $CH_{Ar}$), 8.09−8.14 (1H, m, $CH_{Ar}$), 8.18−8.22 (1H, m, $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 19.5 ($CH_3$), 47.5 ($CH_2$−C=O), 60.0 ($C_{spiro}$), 79.7 ($CH_2O$), 108.1 ($CH_{Ar}$), 123.7 ($CH_{Ar}$), 126.4 ($C_{quat}$), 127.0 ($CH_{Ar}$), 128.2 ($CH_{Ar}$), 130.1 ($CH_{Ar}$), 134.8 ($CH_{Ar}$), 135.0 ($CH_{Ar}$), 135.3 ($C_{quat}$), 135.5 ($C_{quat}$), 160.3 ($C_{quat}$), 194.4 (C=O), 195.4 (C=O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): $\nu$ 1691 (C=O), 1682 (C=O), 1591, 1463, 1288 (C−O), 985. MS ($ES^+$; $m/z$ (%)): 279 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1011.

*2*′*H*,3′*H*-Spiro[5-methylbenzofuran-3,2′-naphthalene]-1′,4′-dione (**3d**):* 189 mg, 68%; bright orange solid; mp 108.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.09 (3H, s, $CH_3$), 3.28 (1H, d, $J_{ab}$ = 16.2 Hz, C$H_a$H$_b$C=O), 3.31 (1H, d, $J_{ab}$ = 16.2 Hz, CH$_a$H$_b$C=O), 4.28 (1H, d, $J_{ab}$ = 9.3 Hz, C$H_a$H$_b$O), 5.36 (1H, d, $J_{ab}$ = 9.3 Hz, CH$_a$H$_b$O), 6.44 (1H, d, $J$ = 1.7 Hz, CH-4), 6.75 (1H, d, $J$ = 8.5 Hz, CH-7), 6.95 (1H, dd, $J$ = 8.5 and 1.7 Hz, CH-6), 7.78−7.88 (2H, m, 2 × $CH_{Ar}$), 8.12−8.20 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 20.8 ($CH_3$), 48.7 ($CH_2$−C=O), 58.4 ($C_{spiro}$), 77.9 ($CH_2O$), 110.5 ($CH_{Ar}$), 124.1 ($CH_{Ar}$), 126.8 ($CH_{Ar}$), 127.6 ($C_{quat}$), 128.4 ($CH_{Ar}$), 130.4 ($C_{quat}$), 130.8 ($CH_{Ar}$), 134.6 ($C_{quat}$), 134.8 ($CH_{Ar}$), 134.9 ($CH_{Ar}$), 135.6 ($C_{quat}$), 157.9 ($C_{quat}$), 194.0 (C=O), 194.2 (C=O). IR ($cm^{-1}$): $\nu$ 1692 (C=O), 1591, 1490, 1246 (C−O), 759. MS ($ES^+$; $m/z$ (%)): 279 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1016.

*2*′*H*,3′*H*-Spiro[6-methoxybenzofuran-3,2′-naphthalene]-1′,4′-dione (**3fa**):* 180 mg, 61%; yellow solid; mp 129 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.29 (2H, s, $CH_2$C=O), 3.71 (3H, s, $OCH_3$), 4.30 (1H, d, $J_{ab}$ = 8.8 Hz, C$H_a$H$_b$O), 5.44 (1H, d, $J_{ab}$ = 8.8 Hz, CH$_a$H$_b$O), 6.23 (1H, dd, $J$ = 8.4 and 2.2 Hz, CH-5), 6.42 (1H, d, $J$ = 2.2 Hz, CH-7), 6.50 (1H, d, $J$ = 8.4 Hz, CH-4), 7.77−7.87 (2H, m, 2 × $CH_{Ar}$), 8.11−8.20 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 48.8 ($CH_2$C=O), 55.6 ($OCH_3$), 57.8 ($C_{spiro}$), 78.3 ($CH_2O$), 97.1 ($CH_{Ar}$), 106.9 ($CH_{Ar}$), 119.6 ($C_{quat}$), 124.0 ($CH_{Ar}$), 126.8 ($CH_{Ar}$), 128.4 ($CH_{Ar}$), 134.6 ($C_{quat}$), 134.8 ($CH_{Ar}$), 134.9 ($CH_{Ar}$), 135.6 ($C_{quat}$), 161.4 ($C_{quat}$), 161.9 ($C_{quat}$), 194 (C=O), 194.0 (C=O). IR ($cm^{-1}$): $\nu$ 1687 (C=O), 1595, 1498, 1281 (C−O), 1147 (C−O). MS ($ES^+$; $m/z$ (%)): 295 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_4]^+$ 295.0970, found 295.0969.

*2*′*H*,3′*H*-Spiro[4-methoxybenzofuran-3,2′-naphthalene]-1′,4′-dione (**3fb**):* 38 mg, 13%; pale white solid; mp 156.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.17 (1H, d, $J_{ab}$ = 16.5 Hz, C$H_a$H$_b$C=O), 3.49 (3H, s, $OCH_3$), 3.58 (1H, d, $J_{ab}$ = 16.5 Hz, CH$_a$H$_b$C=O), 4.35 (1H, d, $J_{ab}$ = 9.1 Hz, C$H_a$H$_b$O), 5.00 (1H, d, $J_{ab}$ = 9.1 Hz, CH$_a$H$_b$O), 6.36 (1H, d, $J$ = 8.3 Hz, $CH_{Ar}$), 6.52 (1H, d, $J$ = 8.3 Hz, $CH_{Ar}$), 7.16 (1H, t, $J$ = 8.3 Hz, $CH_{Ar}$), 7.72−7.82 (2H, m, 2 × $CH_{Ar}$), 8.10−8.15 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 47.3 ($CH_2$C=O), 58.8 ($OCH_3$), 58.1 ($C_{spiro}$), 80.0 ($CH_2O$), 103.8 ($CH_{Ar}$), 115.5 ($C_{quat}$), 126.1 ($CH_{Ar}$), 128.1 ($CH_{Ar}$), 131.4 ($CH_{Ar}$), 134.1 ($CH_{Ar}$), 134.38 (2 × $CH_{Ar}$), 134.44 ($C_{quat}$), 136.3 ($C_{quat}$), 156.5 ($C_{quat}$), 161.6 ($C_{quat}$), 194.1 (C=O), 195.2 (C=O). IR ($cm^{-1}$): $\nu$ 1687 (C=O), 1594, 1464, 1248 (C−O), 1093 (C−O), 753. MS ($ES^+$; $m/z$ (%)): 295 ($M + H^+$, 100). HRMS ($ES^+$) calcd for $[C_{18}H_{15}O_4]^+$: 295.0970, found 295.0964.

*2*′*H*,3′*H*-Spiro[5-methoxybenzofuran-3,2′-naphthalene]-1′,4′-dione (**3g**):* 174 mg, 59%; orange crystals; mp 133.4 °C. $^1$H NMR


dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

($CDCl_3$): $\delta$ 3.28 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC{=}O$), 3.32 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC{=}O$), 3.57 (3H, s, $OCH_3$), 4.29 (1H, d, $J_{ab}$ = 9.1 Hz, $CH_aH_bO$), 5.34 (1H, d, $J_{ab}$ = 9.1 Hz, $CH_aH_bO$), 6.23 (1H, d, $J$ = 2.8 Hz, CH-4), 6.69 (1H, dd, $J$ = 2.8 and 8.8 Hz, CH-6), 6.77 (1H, d, $J$ = 8.8 Hz, CH-7), 7.77−7.86 (2H, m, 2 × $CH_{Ar}$), 8.08−8.20 (2H, m, 2 × $CH_{Ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 48.6 ($CH_2C{=}O$), 56.0 ($OCH_3$), 58.8 ($C_{spiro}$), 78.0 ($CH_2O$), 110.6 (CH-4), 110.8 (CH-7), 114.7 (CH-6), 126.8 ($CH_{Ar}$), 128.4 ($CH_{Ar}$), 134.6 ($C_{quat}$), 134.82 ($CH_{Ar}$), 134.86 ($CH_{Ar}$), 135.5 ($C_{quat}$), 154.1 ($C_{quat}$), 154.2 ($C_{quat}$), 193.7 (C=O), 194.0 (C=O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): $\nu$ 1686, 1483. MS ($ES^+$; $m/z$ (%)): 293 (M − $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_4]^+$ 295.0970, found 295.0964.

*2H,3′H-Spiro[5-tert-butylbenzofuran-3,2′-naphthalene]-1′,4′-dione (**3h**):* 227 mg, 71%; orange solid; mp 145.0 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 1.06 (9H, s, $(CH_3)_3C$), 3.29 (1H, d, $J_{ab}$ = 16.2 Hz, $CH_aH_bC{=}O$), 3.33 (1H, d, $J_{ab}$ = 16.2 Hz, $CH_aH_bC{=}O$), 4.30 (1H, d, $J_{ab}$ = 9.3 Hz, $CH_aH_bO$), 5.38 (1H, d, $J_{ab}$ = 9.3 Hz, $CH_aH_bO$), 6.64 (1H, d, $J$ = 2.2 Hz, CH-4), 6.77 (1H, d, $J$ = 8.5 Hz, CH-7), 7.18 (1H, dd, $J$ = 2.2 8.5 Hz, CH-6), 7.77−7.88 (2H, m, 2 × $CH_{Ar}$), 8.09−8.14 (1H, m, $CH_{Ar}$), 8.19−8.22 (1H, m, $CH_{Ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 31.5 ($(CH_3)_3C$), 34.3 ($(CH_3)_3C$), 48.6 ($CH_2C{=}O$), 58.7 ($C_{spiro}$), 77.7 ($CH_2O$), 110.1 ($CH_{Ar}$), 120.6 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 127.0 ($C_{quat}$), 127.2 ($CH_{Ar}$), 128.4 ($CH_{Ar}$), 134.8 (2 × $CH_{Ar}$), 135.7 ($C_{quat}$), 144.0 ($C_{quat}$), 157.7 ($C_{quat}$), 194.0 (C=O), 194.2 (C=O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): $\nu$ 1690 (C=O), 1497 (C−O), 1263 (C−O), 1342, 820. MS ($ES^+$; $m/z$ (%)): 338 (M + $NH_4^+$, 100). HRMS ($ES^+$): calcd for $[C_{21}H_{24}NO_3]^+$ 338.1756, found 338.1749.

*2H,3′H-Spiro[5-fluorobenzofuran-3,2′-naphthalene]-1′,4′-dione (**3i**):* 150 mg, 53%; yellow crystals; mp 154.6−155.1 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 3.29 (1H, d, $J_{ab}$ = 16.2 Hz, $CH_aH_bC{=}O$), 3.32 (1H, d, $J_{ab}$ = 16.2 Hz, $CH_aH_bC{=}O$), 4.34 (1H, d, $J$ = 8.8 Hz, $CH_aH_bO$), 5.38 (1H, d, $J$ = 8.8 Hz, $CH_aH_bO$), 6.37 (1H, dd, $J_{HF}$ = 2.8 Hz, $J_{HF}$ = 8.3 Hz, CH-4), 6.77 (1H, dd, $J_{HH}$ = 8.8 Hz, $J_{HF}$ = 4.4 Hz, CH-7), 6.86 (1H, ddd, $J_{HH}$ = 2.8 and 8.8 Hz, $J_{HF}$ = 8.3 Hz, CH-6), 7.79−7.89 (2H, m, 2 × $CH_{Ar}$), 8.09−8.22 (2H, m, 2 × $CH_{Ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 48.6 ($CH_2C{=}O$), 58.7 ($C_{spiro}$), 78.8 ($CH_2O$), 110.0 ($J_{CF}$ = 19.6 Hz, CH-4), 111.3 ($J_{CF}$ = 3.5 Hz, CH-7), 116.7 ($J_{CF}$ = 24.2 Hz, CH-6), 127.0 ($CH_{Ar}$), 128.5 ($CH_{Ar}$), 128.6 ($C_{quat}$), 134.4 ($C_{quat}$), 135.1 (2 × $CH_{Ar}$), 135.4 ($C_{quat}$), 156.0 ($C_{quat}$), 157.2 ($J_{CF}$ = 238.8 Hz, $C_{quat}$), 193.4 (C=O), 195.6 (C=O). $^{19}F$ NMR ($CDCl_3$): −122.20- −122.58 (1F, m). IR ($cm^{-1}$): $\nu$ 1686, 1482. MS ($ES^-$; $m/z$ (%)): 281 (M − $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{17}H_{10}FO_3]^-$ 281.0614, found 281.0612.

*2H,3′H-Spiro[5-chlorobenzofuran-3,2′-naphthalene]-1′,4′-dione (**3j**):* 206 mg, 69%; brown oil. $^1H$ NMR ($CDCl_3$): $\delta$ 3.29 (1H, d, $J_{ab}$ = 16.2 Hz, $CH_aH_bC{=}O$), 3.31 (1H, d, $J_{ab}$ = 16.2 Hz, $CH_aH_bC{=}O$), 4.33 (1H, d, $J$ = 9.1 Hz, $CH_aH_bO$), 5.36 (1H, d, $J$ = 9.1 Hz, $CH_aH_bO$), 6.61 (1H, d, $J$ = 2.2 Hz, $CH_{Ar}$), 6.74−6.81 (1H, m, $CH_{Ar}$), 7.07−7.18 (1H, m, $CH_{Ar}$), 7.78−7.89 (2H, m, 2 × $CH_{Ar}$), 8.11−8.19 (2H, m, 2 × $CH_{Ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 48.5 ($CH_2C{=}O$), 58.5 ($C_{spiro}$), 78.4 ($CH_2O$), 111.9 ($CH_{Ar}$), 116.8 ($C_{quat}$), 123.9 ($CH_{Ar}$), 125.7 ($C_{quat}$), 127.0 ($CH_{Ar}$), 128.5 ($CH_{Ar}$), 129.5 ($C_{quat}$), 130.3 ($CH_{Ar}$), 135.2 (2 × $CH_{Ar}$), 135.4 ($C_{quat}$), 158.7 ($C_{quat}$), 193.5 (C=O), 193.6 (C=O). IR ($cm^{-1}$): $\nu$ 1693, 1474. MS ($ES^-$; $m/z$ (%)): 297 (M − $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{17}H_{10}ClO_3]^-$ 297.0319, found 297.0314.

**Synthesis of 2-Aryloxymethyl-1,4-benzoquinones 11.** To 125 mL of distilled water, the appropriate phenoxyacetic acid **5** (50 mmol), 5.40 g (50 mmol) of 1,4-benzoquinone **10**, and 1 g (6 mmol) of $AgNO_3$ were added successively. The mixture was then heated to 60−65 °C until dissolution was complete. The resulting solution was stirred vigorously while a solution of 13.7 g (60 mmol) of ammonium peroxydisulfate in 25 mL of water was added at a rate of 0.5 mL/min for the first 40 min and then at a rate of 0.25 mL/min for the last 20 min. Throughout the addition, the reaction mixture was maintained at 60−65 °C. After the addition was complete, the mixture was stirred for 5 min at 65 °C and was then cooled to 5−10 °C using an ice bath. The precipitated solid was collected by suction filtration, washed with 50 mL of cold water, and pressed to remove most of the liquid. Inorganic contaminants, usually present in small amounts, were removed by dissolving the solid in 350 mL of boiling acetone and filtering the hot solution. Concentration of the filtrate in vacuo gave a dark red crude product, which was recrystallized from ethanol. For the aryloxymethyl-1,4-benzoquinone derivatives **11b−d** full dissolution of the starting materials did not occur at 65 °C and small amounts of acetonitrile were added until full dissolution occurred.

*2-Phenoxymethyl-1,4-benzoquinone (**11a**):* 6.53 g, 61%; mp 138 °C (Lit.[3] 137−138 °C), $^1H$ NMR ($CDCl_3$): $\delta$ 4.92 (2H, d, $OCH_2$, $J$ = 1.7 Hz), 6.74−6.85 (2H, m, 2 × =CH), 6.94−7.03 (4H, m, 4 × =CH), 7.28−7.36 (2H, m, 2 × =CH). $^{13}C$ NMR ($CDCl_3$): $\delta$ 63.1 ($OCH_2$), 114.7 (2 × =CH), 121.9 (=CH), 129.8 (2 × =CH), 131.9 (=CH), 136.5 (=CH), 136.8 (=CH), 144.2 ($C_{quat}$), 157.8 ($C_{quat}$), 186.9 (C=O), 187.3 (C=O). IR ($cm^{-1}$): $\nu$ 1651 (C=O), 1600, 1496, 1247 (C−O). MS ($ES^-$; $m/z$ (%)): 213 (M − H, 35). HRMS ($ES^-$): calcd for $[C_{13}H_9O_3]^-$ 213.0552, found 213.0561.

*2-(4-Methoxyphenoxymethyl)-1,4-benzoquinone (**11b**):* 4.27 g, 35%; red powder; mp 146.0 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 3.78 (3H, s, $OCH_3$), 4.87 (2H, d, $CH_2O$, $J$ = 1.7 Hz), 6.78−6.98 (7H, m, CH-3,5,6 and 4 × $CH_{Ar}$), $^{13}C$ NMR ($CDCl_3$): $\delta$ 55.8 ($OCH_3$), 63.9 ($OCH_2$), 114.9 (2 × $CH_{Ar}$), 115.7 (2 × $CH_{Ar}$), 131.8 (=CH), 136.5 (=CH), 136.8 (=CH), 144.4 ($C_{quat}$), 151.9 ($C_{quat}$), 154.6 ($C_{quat}$), 186.9 (C=O), 187.3 (C=O). IR ($cm^{-1}$): $\nu$ 1646, 1231. MS ($ES^-$; $m/z$ (%)): 244 ($M^-$, 100). HRMS ($ES^-$): calcd for $[C_{14}H_{11}O_4]^-$ 243.0657, found 243.0664.

*2-(4-Fluorophenoxymethyl)-1,4-benzoquinone (**11c**):* 3.95 g, 34%; brown needles; mp 158.9 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 4.91 (2H, d, $CH_2O$, $J$ = 1.7 Hz), 6.74−7.23 (7H, m, CH-3,5,6 and 4 × $CH_{Ar}$), $^{13}C$ NMR ($CDCl_3$): $\delta$ 63.9 ($OCH_2$), 115.8 (2 × $CH_{Ar}$, $J_{C-F}$ = 8.1 Hz), 116.2 (2 × $CH_{Ar}$, $J_{C-F}$ = 23.1 Hz), 131.9 (=CH), 136.5 (=CH), 136.8 (=CH), 144.0 ($C_{quat}$), 153.9 ($C_{quat}$), 157.9 ($C_{quat}$, $J_{C-F}$ = 240.0 Hz), 186.8 (C=O), 187.2 (C=O). $^{19}F$ NMR ($CDCl_3$): $\delta$ −122.37 to −122.46 (1F, m). IR ($cm^{-1}$): $\nu$ 1649, 1506, 1219. MS ($ES^-$; $m/z$ (%)): 231 (M − $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{13}H_8FO_3]^-$ 231.0458, found 231.0467.

*2-(4-Chlorophenoxymethyl)-1,4-benzoquinone (**11d**):* 6.47 g, 52%; yellow needles; mp 155.8 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 4.89 (2H, dd, $CH_2O$, $J$ = 1.1 and 2.5 Hz), 6.77−6.95 and 7.25−7.30 (7H, m, CH-3,5,6 and 4 × $CH_{Ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 63.5 ($OCH_2$), 116.0 (2 × $CH_{Ar}$), 126.8 ($C_{quat}$), 129.7 (2 × $CH_{Ar}$), 131.9 (=CH), 136.5 (=CH), 136.8 (=CH), 143.7 ($C_{quat}$), 156.4 ($C_{quat}$), 186.7 (C=O), 187.1 (C=O). IR ($cm^{-1}$): $\nu$ 1648, 1626, 1491, 1249. MS ($ES^-$; $m/z$ (%)): 247 and 249 (M − $H^+$, 100 and 32). HRMS ($ES^-$): calcd for $[C_{13}H_8ClO_3]^-$ 247.0162, found 247.0172.

**Synthesis of 2′*H*,3*H*-Spiro[benzofuran-3,2′-benzoquinones] 12.** A solution of 2-aryloxymethyl-1,4-benzoquinones **11** (1.5 mmol) and palladium(II) acetate (1.5 mmol, 0.37 g) in acetic acid (30 mL) was heated under reflux for 14 h. The reaction mixture was poured into water and extracted with dichloromethane. The combined organic extracts were washed with water and with a saturated solution of sodium hydrogen carbonate and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Flash chromatography on silica gel or preparative TLC with ethyl acetate/hexane (1/4) yielded 2′*H*,3*H*-spiro-[benzofuran-3,2′-benzoquinones] **12**. Upon (LC−)MS analysis most spiroquinones were found to give very poor mass spectrometric ionizations.

*2H,3′H-Spiro[benzofuran-3,2′-benzene]-1′,4′-dione (**12a**):* 22 mg, 7%; pale white crystals; mp 114.5 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 3.09 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC{=}O$), 3.14 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC{=}O$), 4.21 (1H, d, $J$ = 9.9 Hz, $CH_aH_bO$), 5.24 (1H, d, $J$ = 9.9 Hz, $CH_aH_bO$), 6.81 (2H, m, 2 × $CH_{Ar}$), 6.94 (2H, s, 2 × =CH), 7.00−7.05 (1H, m, $CH_{Ar}$), 7.18−7.88 (1H, m $CH_{Ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 48.2 ($CH_2C{=}O$), 58.0 ($C_{spiro}$), 77.5 ($CH_2O$), 111.1 ($CH_{Ar}$), 121.1 ($CH_{Ar}$), 123.5 ($CH_{Ar}$), 127.0 ($C_{quat}$), 130.6 ($CH_{Ar}$), 141.2 (=CH), 141.7 (=CH), 159.8 ($C_{quat}$), 194.9 (C=O), 195.6 (C=O). IR ($cm^{-1}$): $\nu$ 1682, 1478. MS ($ES^-$; $m/z$ (%)): 213 (M − $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{13}H_{11}O_3]^+$ 215.0708, found 215.0704.

*2H,3′H-Spiro[5-methoxybenzofuran-3,2′-benzene]-1′,4′-dione (**12b**):* 44 mg, 12%; yellow crystals; mp 129.7 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 3.08 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC{=}O$), 3.15 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC{=}O$), 3.71 (3H, s, $OCH_3$), 4.20 (1H, d, $J$ = 9.1 Hz,


dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

$CH_aH_bO$), 5.19 (1H, d, $J$ = 9.1 Hz, $CH_aH_bO$), 6.57−6.63 (1H, m, $CH_{Ar}$), 6.73−6.80 (2H, m, 2 × $CH_{Ar}$), 6.95 (2H, br. s, 2 × =CH). $^{13}$C NMR ($CDCl_3$): $\delta$ 48.1 ($CH_2C$=O), 56.2 ($OCH_3$), 58.4 ($C_{spiro}$), 77.9 ($CH_2O$), 110.1 ($CH_{Ar}$), 111.1 ($CH_{Ar}$), 115.2 ($CH_{Ar}$), 127.9 ($C_{quat}$), 141.2 (=CH), 141.7 (=CH), 153.9 ($C_{quat}$), 154.3 ($C_{quat}$), 195.0 (C=O), 195.4 (C=O). IR ($cm^{-1}$): $\nu$ 1678, 1482, 1470. MS ($ES^-$; $m/z$ (%)): 243 (M − $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{14}H_{12}O_4]^-$ 244.0741, found 244.0717.

*2H,3′H-Spiro[5-fluorobenzofuran-3,2′-benzene]-1′,4′-dione* ***(12c):*** 70 mg, 20%; yellow viscous oil. $^1$H NMR ($CDCl_3$): $\delta$ 3.10 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC$=O), 3.15 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC$=O), 4.26 (1H, d, $J$ = 9.4 Hz, $CH_aH_bO$), 5.22 (1H, d, $J$ = 9.4 Hz, $CH_aH_bO$), 6.71−6.95 (3H, m, 3 × $CH_{Ar}$), 6.96 (2H, s, 2 × =CH). $^{13}$C NMR ($CDCl_3$): $\delta$ 48.1 ($CH_2C$=O), 58.3 ($C_{spiro}$), 78.2 ($CH_2O$), 110.8 ($J_{CF}$ = 25.4 Hz, $CH_{Ar}$), 111.5 ($J_{CF}$ = 8.1 Hz, $CH_{Ar}$), 117.0 ($J_{CF}$ = 24.2 Hz, $CH_{Ar}$), 128.0 ($J_{CF}$ = 8.1 Hz, $C_{quat}$), 141.1 (=CH), 141.9 (=CH), 150.9 ($C_{quat}$), 157.3 ($J_{CF}$ = 238.8 Hz, $C_{quat}$), 194.6 (C=O), 195.0 (C=O). $^{19}$F NMR ($CDCl_3$): −122.82 to −122.89 (1F, m). IR ($cm^{-1}$): $\nu$ 1684, 1482. MS ($ES^-$; $m/z$ (%)): 231 (M − $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{13}H_{10}FO_3]^+$ 233.0609, found 233.0614.

*2H,3′H-Spiro[5-chlorobenzofuran-3,2′-benzene]-1′,4′-dione* ***(12d):*** 71 mg, 19%; yellow crystals; mp 129.7 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.09 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_b$-C=O), 3.15 (1H, d, $J_{ab}$ = 16.5 Hz, $CH_aH_bC$=O), 4.23 (1H, d, $J$ = 9.9 Hz, $CH_aH_bO$), 5.23 (1H, d, $J$ = 9.9 Hz, $CH_aH_bO$), 6.79 (1H, d, $J$ = 8.3 Hz, $CH_{Ar}$), 6.96 (3H, br s, 2 × =CH and $CH_{Ar}$), 7.17 (1H, dd, $J$ = 2.2 and 8.3 Hz, $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 48.0 ($CH_2$−C=O), 58.0 ($C_{spiro}$), 78.2 ($CH_2O$), 112.1 ($CH_{Ar}$), 123.7 ($CH_{Ar}$), 128.8 ($C_{quat}$), 125.8 ($C_{quat}$), 130.6 ($CH_{Ar}$), 141.0 (=CH), 141.9 (=CH), 158.5 ($C_{quat}$), 194.4 (C=O), 194.9 (C=O). IR ($cm^{-1}$): $\nu$ 1686, 1474. MS ($ES^-$; $m/z$ (%)): 247 and 249 (M − $H^+$, 100 and 35). HRMS ($ES^-$): calcd for $[C_{13}H_8ClO_3]^-$ 247.0168, found 247.0161.

**Synthesis of 2-(2-Phenoxyethyl)-1,4-naphthoquinone (14).** A mixture of 1,4-naphthoquinone (**4**; 30 mmol, 4.74 g), silver nitrate (9 mmol, 1.5 g), and 3-phenoxypropionic acid (**13**; 45 mmol, 7.47 g) in acetonitrile was heated to 85 °C, and to the stirred reaction mixture was added a solution of ammonium persulfate (60 mmol, 13.68 g) in demineralized water (30 mL) dropwise over 30 min, after which the reaction mixture was kept at the same temperature for 24 h. A second portion of 3-phenoxypropionic acid (45 mmol, 7.47 g) was added in one portion, followed by the addition of a second portion of a solution of ammonium persulfate (60 mmol, 13.68 g) in demineralized water (30 mL). The resulting reaction mixture was stirred for 24 h at 85 °C. Water (1 L) was added, and the aqueous solution was extracted with ethyl acetate. The combined organic extracts were washed with a saturated solution of sodium hydrogen carbonate and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude reaction mixture, which contained still about 80% of 1,4-naphthoquinone **4**, was chromatographed over a short column of silica gel using 1/9 ethyl acetate/petroleum ether. Recrystallization from ethyl acetate afforded pure 2-(2-phenoxyethyl)-1,4-naphthoquinone (**14**): 918 mg, 11%; mp 141.4−142 °C, yellow crystals. $^1$H NMR ($CDCl_3$): $\delta$ 3.06 (2H, td, $J$ = 6.1 and 1.3 Hz, $CH_2CH_2O$), 4.24 (2H, t, $J$ = 6.1 Hz, $CH_2CH_2O$), 6.88−6.98 (4H, m, 3 × $CH_{Ar}$ and CH-3), 7.25−7.30 (2H, m, 2 × $CH_{Ar}$), 7.71−7.77 (2H, m, 2 × $CH_{Ar}$), 8.06−8.13 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 29.9 ($CH_2CH_2O$), 65.1 ($CH_2O$), 114.5 (2 × $CH_{Ar}$), 121.1 ($CH_{Ar}$), 126.1 ($CH_{Ar}$), 126.6 ($CH_{Ar}$), 129.5 (2 × $CH_{Ar}$), 132.1 (2 × $C_{quat}$), 133.7 ($CH_{Ar}$), 133.8 ($CH_{Ar}$), 136.7 (CH-3), 147.7 ($C_{quat}$), 158.4 ($C_{quat}$), 184.9 (C=O), 185.9 (C=O). IR ($cm^{-1}$): $\nu$ 1655 (C=O), 1620, 1602, 1593 ($CH_{Ar}$), 1307, 1257, 768. MS ($ES^+$; $m/z$ (%)): 278 (M + $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{18}H_{13}O_3]^-$ 277.0865, found 277.0874.

**Synthesis of 3′*H*-Spiro[chroman-3,2′-naphthalene]-1′,4′-dione (15).** In a 10 mL vial were added 3,5-dichloropyridine (0.15 mmol, 22 mg), trifluoroacetic acid (0.05 mmol, 6 mg), palladium(II) acetate (0.10 mmol, 22 mg), 2-(2-phenoxyethyl)-1,4-naphthoquinone (**14**; 1.0 mmol), and 4 mL of acetic acid. The vial was sealed with a septum, and the contents were stirred at 110 °C for 4 days. The reaction mixture was then diluted with chloroform, washed once with water and twice with sodium hydrogen carbonate, and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Flash chromatography on silica gel with 1/9 ethyl acetate/hexane yielded 3′*H*-spiro[chroman-3,2′-naphthalene]-1′,4′-dione (**15**); 106 mg, 36%; white needles; mp 94.2−94.8 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.12 (1H, ddd, $J$ = 14.2, 7.6, and 5.0 Hz, $CH_aCH_bCH_2O$), 2.30 (1H, ddd, $J$ = 14.2, 5.3, and 3.3 Hz, $CH_aCH_bCH_2O$), 3.13 (1H, d, $J$ = 16.2 Hz, $CH_aH_bC$=O), 3.64 (1H, d, $J$ = 16.2 Hz, $CH_aH_bC$=O), 4.11−4.25 (2H, m, $CH_2O$), 6.88−6.94 (2H, m, 2 × $CH_{Ar}$), 7.04−7.08 (1H, m, $CH_{Ar}$), 7.17−7.26 (1H, m, $CH_{Ar}$), 7.78−7.81 (2H, m, 2 × $CH_{Ar}$), 8.05−8.15 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 33.1 ($CH_2CH_2O$), 49.3 ($C_{spiro}$), 51.3 ($CH_2$−C=O), 61.8 ($CH_2O$), 117.8 ($CH_{Ar}$), 120.9 ($CH_{Ar}$), 122.3 ($C_{quat}$), 126.3 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 129.0 ($CH_{Ar}$), 133.3 ($C_{quat}$), 134.4 ($CH_{Ar}$), 134.8 ($CH_{Ar}$), 154.9 ($C_{quat}$), 195.2 (C=O), 198.3 (C=O), one trisubstituted olefinic carbon is not observed. IR ($cm^{-1}$): $\nu$ 1691 (C=O), 1595 ($CH_{Ar}$), 1492, 1292, 1226, 755. MS ($ES^+$; $m/z$ (%)): 278 (M + $H^+$, 3), 86 (39), 84 (64), 49 (100). HRMS ($ES^+$): calcd for $[C_{18}H_{15}O_3]^+$ 279.1021, found 279.1014.

**Synthesis of 2-(4-Hydroxybenzyl)-1,4-quinones 17 and 18a.** A solution of 2-phenoxymethyl-1,4-quinones (1.5 mmol) in 6 mL of trifluoroacetic acid was stirred for 15 h (for 2-phenoxymethyl-1,4-quinones **1a,b,e** and **11a**) or 3 days (for 3-methyl-2-phenoxymethyl-1,4-naphthoquinone (**10**)) at room temperature. Subsequently, trifluoroacetic acid was evaporated in vacuo, and the residue was dissolved in 20 mL of chloroform. This solution was washed with water, saturated aqueous $NaHCO_3$, and brine (3 × 10 mL). Drying over $MgSO_4$ and evaporation of the solvent in vacuo gave the crude product, which was purified further by means of column chromatography on silica gel (solvent system petroleum ether/ethyl acetate). 2-(4-Hydroxybenzyl)-1,4-benzoquinone (**18a**) quickly polymerizes after purification; therefore, no HRMS or elementary analysis could be recorded. Attempts to derivatize this compound **18a** by acetylation resulted in a complex mixture.

*2-(4-Hydroxybenzyl)-1,4-naphthoquinone* ***(17a):*** 293 mg, 74%; brown crystals; mp 159.6−160.2 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.83 (2H, s, $CH_2Ar$), 5.08 (1H, br s, ArOH), 6.61 (1H, s, CH-3), 6.80 (2H, d, $J$ = 8.3 Hz, 2 × $CH_{Ar}$), 7.11 (2H, d, $J$ = 8.3 Hz, 2 × $CH_{Ar}$), 7.70−7.76 (2H, m, 2 × $CH_{Ar}$), 8.02−8.13 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 35.0 ($CH_2Ar$), 115.8 (2 × $CH_{Ar}$), 126.2 ($CH_{Ar}$), 126.8 ($CH_{Ar}$), 128.8 ($C_{quat}$), 130.8 (2 × $CH_{Ar}$), 132.2 ($C_{quat}$), 132.3 ($C_{quat}$), 133.8 ($CH_{Ar}$), 133.9 ($CH_{Ar}$), 135.6 (CH-3), 151.3 ($C_{quat}$), 154.6 ($C_{quat}$), 185.2 (C=O), 185.4 (C=O). IR ($cm^{-1}$): $\nu$ 3395 (OH), 1650 (C=O), 1593, 1509, 1265, 1220. MS ($ES^+$; $m/z$ (%)): 265 (M + $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{17}H_{11}O_3]^-$ 263.0708, found 263.0704.

*2-(4-Hydroxy-3-methylbenzyl)-1,4-naphthoquinone* ***(17b):*** 305 mg, 73%; green solid; mp 151.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.23 (3H, s, $CH_3$), 3.79 (2H, s, $CH_2Ar$), 5.10 (1H, br. s, ArOH), 6.61 (1H, s, CH-3), 6.73 (1H, d, $J$ = 7.9 Hz, CH-5′ or CH-6′), 6.94 (1H, d, $J$ = 7.9 Hz, CH-5′ or CH-6′), 6.98 (1H, s, CH-2′), 7.71−7.74 (2H, m, CH-6 and CH-7), 8.02−8.11 (2H, m, CH-5 and CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 15.9 ($CH_3$), 35.0 ($CH_2Ar$), 115.3 (CH-5′ or CH-6′), 124.4 ($C_{quat}$), 126.2 and 126.8 (CH-5 and CH-8), 128.1 (CH-5′ or CH-6′), 128.6 ($C_{quat}$), 132.1 (CH-2′), 132.2 ($C_{quat}$), 132.3 ($C_{quat}$) 133.9 and 133.9 (CH-6 and CH-7), 135.6 (CH-3), 151.5 ($C_{quat}$), 153.0 ($C_{quat}$), 185.3 (C=O), 185.6 (C=O). IR ($cm^{-1}$): $\nu$ 3380 (OH), 1652 (C=O), 1595, 1336, 1267. MS ($ES^+$; $m/z$ (%)): 279 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{13}O_3]^-$ 277.0865, found 277.0862.

*2-(4-Hydroxy-3-methoxybenzyl)-1,4-naphthoquinone* ***(17c):*** 185 mg, 42%; yellow crystals; mp 169.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.83 (2H, s, $CH_2Ar$), 3.88 (3H, s, $OCH_3$), 5.55 (1H, br. s, ArOH), 6.61 (1H, s, CH-3), 6.74−6.75 (2H, m, 2 × $CH_{Ar}$), 6.88 (1H, d, $J$ = 8.8 Hz, CH-5′ or CH-6′), 7.72−7.75 (2H, m, CH-6 and CH-7), 8.03−8.13 (2H, m, CH-5 and CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 35.5 ($CH_2Ar$), 56.0 ($OCH_3$), 111.9 ($CH_{Ar}$), 114.8 ($CH_{Ar}$), 122.4 ($CH_{Ar}$), 126.2 and 126.8 (CH-5 and CH-8), 128.4 ($C_{quat}$), 132.2 ($C_{quat}$), 132.3 ($C_{quat}$) 133.8 and 133.9 (CH-6 and CH-7), 135.6 (CH-3), 144.7 ($C_{quat}$), 146.8 ($C_{quat}$), 151.3 ($C_{quat}$), 185.3 (C=O), 185.4 (C=O). IR ($cm^{-1}$): $\nu$ 3355 (OH), 1652 (C=O), 1590, 1517, 1274, 1234. MS ($ES^+$; $m/z$ (%)): 295 (M + $H^+$, 100). HRMS ($ES^-$): calcd for $[C_{18}H_{13}O_4]^-$ 293.0814, found 293.0809.


dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

*2-(4-Hydroxybenzyl)-3-methyl-1,4-naphthoquinone (**17d**):* 250 mg, 60%; orange crystals; mp 50.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.25 (3H, s, $CH_3$), 3.94 (2H, s, $CH_2Ar$), 5.43 (1H, br s, ArOH), 6.73 (2H, d, $J$ = 8.3 Hz, 2 × $CH_{Ar}$), 7.09 (2H, d, $J$ = 8.3 Hz, 2 × $CH_{Ar}$), 7.66−7.72 (2H, m, 2 × $CH_{Ar}$), 8.04−8.10 (2H, m, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.3 ($CH_3$), 31.7 ($CH_2Ar$), 115.6 (2 × $CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.6 ($CH_{Ar}$), 129.9 (2 × $CH_{Ar}$), 130.0 ($C_{quat}$), 132.1 ($C_{quat}$), 132.2 ($C_{quat}$), 133.6 ($CH_{Ar}$), 133.6 ($CH_{Ar}$), 144.3 ($C_{quat}$), 145.7 ($C_{quat}$), 154.4 ($C_{quat}$), 185.0 (C═O), 185.7 (C═O). IR ($cm^{-1}$): $\nu$ ($cm^{-1}$) 3481 (OH), 1653 (C═O), 1514. MS ($ES^+$; $m/z$ (%)): 279 (M + $H^+$, 65). HRMS ($ES^-$): calcd for $[C_{18}H_{13}O_3]^-$ 277.0870, found 277.0825.

*2-(4-Hydroxybenzyl)-1,4-benzoquinone (**18a**):* 206 mg, 64%; red viscous oil. $^1$H NMR ($CDCl_3$): $\delta$ 3.66 (2H, d, $J$ = 1.4 Hz, $CH_2Ar$), 6.06 (1H, br s, ArOH), 6.37 (1H, dd, $J$ = 1.6 and 3.9 Hz, CH-3), 6.72−6.79 (2H, m, CH-5 and CH-6), 6.80 (2H, d, $J$ = 8.3 Hz, 2 × $CH_{Ar}$), 7.04 (2H, d, $J$ = 8.3 Hz, 2 × $CH_{Ar}$). $^{13}$C NMR ($CDCl_3$): $\delta$ 34.5 ($CH_2Ar$), 115.9 (2 × $CH_{Ar}$), 128.2 ($C_{quat}$), 130.7 (2 × $CH_{Ar}$), 133.2 (═CH), 136.5 (═CH), 136.9 (═CH), 149.3 ($C_{quat}$), 154.9 ($C_{quat}$), 187.6 (C═O), 188.2 (C═O). IR ($cm^{-1}$): $\nu$ 3372 (OH), 1651 (C═O), 1513. MS ($ES^-$; $m/z$ (%)): 213 (M − $H^+$, 100). Due to the instability of this compound, no HRMS or elementary analysis could be performed.

**Synthesis of N-protected 2-Phenylaminomethyl-1,4-naphthoquinones.** 2-Formyl-1,4-dimethoxynapthalene (1 g, 4.62 mmol) and aniline (426 mg, 4.62 mmol, 1 equiv) were dissolved in 10 mL of dry methanol and stirred at room temperature for 1 h in a dry flask fitted with a $CaCl_2$ tube. Next, the reaction mixture was cooled to 0 °C and $NaBH_4$ (175 mg, 4.62 mmol, 1 equiv) was added portionwise and the reaction mixture was warmed to room temperature. After 30 min, the solvent was evaporated in vacuo and the residue dissolved in EtOAc (10 mL) which was washed with brine (2 × 10 mL). Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded 1.26 g (94%) of pure 2-phenylaminomethyl-1,4-dimethoxynaphthalene as a yellow oil which solidified upon standing.

*2-Phenylaminomethyl-1,4-dimethoxynaphthalene:* 1.26 g, 94%; orange solid; mp 96.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.94 (6H, s, 2x$OCH_3$), 4.51 (2H, s, $CH_2O$), 6.71−6.76 (3H, m, 3 × $CH_{Ar}$), 6.82 (1H, s, CH-3), 7.20 (2H, td, $J$ = 2.2 and 6.9 Hz, 2 × $CH_{Ar}$), 7.45−7.58 (2H, m, CH-6 and 7), 8.07 (1H, dd, $J$ = 1.1 and 8.3 Hz, CH-5 or CH-8), 8.23 (1H, dd, $J$ = 1.1 and 8.3 Hz, CH-5 or CH-8), NH not observed. $^{13}$C NMR ($CDCl_3$): $\delta$ 43.5 ($CH_2N$), 55.8 ($OCH_3$), 62.6 ($OCH_3$), 104.4 (CH-3), 113.2 (2 × $CH_{Ar}$), 117.9 ($CH_{Ar}$), 122.0 ($CH_{Ar}$), 122.6 ($CH_{Ar}$), 125.6 ($CH_{Ar}$), 126.3 ($C_{quat}$), 126.9 ($CH_{Ar}$), 127.4 ($C_{quat}$), 128.8 ($C_{quat}$), 129.5 (2 × $CH_{Ar}$), 147.4 ($C_{quat}$), 148.7 ($C_{quat}$), 152.4 ($C_{quat}$). IR ($cm^{-1}$): $\nu$ 3377 (NH), 1600 ($CH_{Ar}$), 1505, 1374, 1091 (C−N), 752. MS ($ES^+$; $m/z$ (%)): 294 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{19}H_{20}NO_2]^+$ 294.1494, found 294.1484.

2-Phenylaminomethyl-1,4-dimethoxynaphthalene was dissolved in 10 mL of pyridine and , cooled to 0 °C, and mesyl chloride (0.35 mL, 5.67 mmol, 1.3 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. Next, the reaction mixture was poured into 20 mL of ice water and extracted with EtOAc (3 × 10 mL). The combined organic fractions where washed with HCl (2 M, 3 × 10 mL) and brine (10 mL). Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded 1.36 g (84%) of pure *N*-mesyl-2-phenylaminomethyl-1,4-dimethoxynapthalene.

*N-Mesyl-2-phenylaminomethyl-1,4-dimethoxynaphthalene:* 1.36 g, 84%; pale white solid; mp 131.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.04 (3H, $CH_3SO_2$), 3.67 (3H, s, $OCH_3$), 3.93 (3H, s, $OCH_3$), 5.10 (2H, s, $CH_2O$), 6.85 (1H, s, CH-3), 7.18−7.34 (3H, m, 3 × $CH_{Ar}$), 7.42−7.52 (2H, m, 5 × $CH_{Ar}$),7.42−7.52 (2H, m, CH-6 and CH-7), 7.92−7.95 (1H, m, CH-5 or CH-8), 8.16−8.20 (1H, m, CH-5 or CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 37.8 ($CH_3SO_2$), 49.0 ($CH_2N$), 55.8 ($OCH_3$), 62.7 ($OCH_3$), 104.4 (CH-3), 122.1 ($CH_{Ar}$), 122.6 ($CH_{Ar}$), 124.1 ($C_{quat}$), 125.8 ($CH_{Ar}$), 126.5 ($C_{quat}$), 126.8 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 128.3 ($C_{quat}$), 128.9 (2 × $CH_{Ar}$), 129.5 (2 × $CH_{Ar}$), 139.3 ($C_{quat}$), 147.8 ($C_{quat}$), 152.1 ($C_{quat}$). IR ($cm^{-1}$): 1597 ($CH_{Ar}$), 1338 (S═O), 1154 (S═O), 771. MS ($ES^+$; $m/z$ (%)): 201 (M − PhNMs$^-$, 100). HRMS ($ES^+$): calcd for $[C_{13}H_{13}O_2]^+$ 201.0916, found 201.0915.

2-Phenylaminomethyl-1,4-dimethoxynaphthalene (635 mg, 2.16 mmol) and $Et_3N$ (0.33 mL, 1.1 equiv.) were dissolved in 4 mL of dry dichloromethane. The mixture was cooled to 0 °C, and acetyl chloride or benzoyl chloride (1.1 equiv) was added dropwise. The mixture was warmed to room temperature and stirred overnight. Next, $Et_3NHCl$ was filtered off and the filtrate was extracted once with brine (5 mL). Purification by column chromatography on silica gel (PE/EA) gave the corresponding N-protected 2-phenylaminomethyl-1,4-dimethoxynaphthalenes.

*N-Acetyl-2-phenylaminomethyl-1,4-dimethoxynaphthalene:* 449 mg, 62%; yellow crystals; mp 80 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.94 (3H, $CH_3C$═O), 3.44 (3H, s, $OCH_3$), 3.97 (3H, s, $OCH_3$), 5.18 (2H, s, $CH_2O$), 6.84 (1H, s, CH-3), 7.0.1−7.06 (2H, m, 2 × $CH_{Ar}$), 7.20−7.33 (3H, m, 3 × $CH_{Ar}$), 7.43−7.52 (2H, m, CH-6 and CH-7), 7.88−7.93 (1H, m, CH-5 or CH-8), 8.19−8.23 (1H, m, CH-5 or CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.9 ($CH_3CO$), 46.7 ($CH_2N$), 55.8 ($OCH_3$), 62.2 ($OCH_3$), 104.6 (CH-3), 122.1 ($CH_{Ar}$), 122.5 ($CH_{Ar}$), 125.5 ($CH_{Ar}$), 125.6 ($C_{quat}$), 126.4 ($C_{quat}$), 126.4 ($C_{quat}$), 126.6 ($CH_{Ar}$), 128.1 ($CH_{Ar}$), 128.4 (2 × $CH_{Ar}$), 129.7 (2 × $CH_{Ar}$), 142.9 ($C_{quat}$), 147.8 ($C_{quat}$), 152.1 ($C_{quat}$), 171.0 (C═O). IR ($cm^{-1}$): $\nu$ 1645 (C═O), 1631, 1594 ($CH_{Ar}$), 1494, 1369, 1228 (C−N), 670. MS ($ES^+$; $m/z$ (%)): 336 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{21}H_{22}NO_3]^+$ 336.1600, found 336.1593.

*N-Benzoyl-2-phenylaminomethyl-1,4-dimethoxynaphthalene:* 418 mg, 51%; white solid; mp 143.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.62 (3H, s, $OCH_3$), 3.92 (3H, s, $OCH_3$), 5.43 (2H, s, $CH_2O$), 6.91−7.06 (5H, m, 5 × $CH_{Ar}$), 7.12−7.22 (4H, m, 4 × $CH_{Ar}$), 7.36−7.50 (4H, m, 4 × $CH_{Ar}$), 7.96 (1H, d, $J$ = 7.7 Hz, CH-5 or CH-8), 8.22 (1H, d, $J$ = 7.7 Hz, CH-5 or CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 47.9 ($CH_2N$), 55.8 ($OCH_3$), 62.4 ($OCH_3$), 104.0 (CH-3), 122.1 ($CH_{Ar}$), 122.5 ($CH_{Ar}$), 125.6 ($CH_{Ar}$), 125.9 ($C_{quat}$), 126.4 ($C_{quat}$), 126.8 ($CH_{Ar}$), 127.0 ($CH_{Ar}$), 127.9 (2 × $CH_{Ar}$), 128.0 (2 × $CH_{Ar}$), 128.5 ($C_{quat}$), 128.7 (2 × $CH_{Ar}$), 129.1 (2 × $CH_{Ar}$), 129.8 ($CH_{Ar}$), 136.3 ($C_{quat}$), 143.5 ($C_{quat}$), 147.6 ($C_{quat}$), 152.3 ($C_{quat}$), 171.3 (C═O). IR ($cm^{-1}$): $\nu$ 1637 (C═O), 1594, 1366, 1090 (C−O). MS ($ES^+$; $m/z$ (%)): 398 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{26}H_{24}NO_3]^+$ 398.1756, found 398.1757.

To a stirred solution of an N-protected 2-phenylaminomethyl-1,4-dimethoxynapthalene (2 mmol) in $CH_3CN$ (8 mL) was added a solution of cerium ammonium nitrate (2.74 g, 5 mmol, 2.5 equiv) in water (8 mL). The reaction mixture was stirred for 10 min at room temperature. Next, the reaction mixture was poured into 20 mL of $CH_2Cl_2$ and washed two times with brine. Drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded pure N-protected 2-phenylaminomethyl-1,4-naphthoquinones.

*N-Mesyl-2-phenylaminomethyl-1,4-naphthoquinone:* 490 mg, 66%; yellow solid; mp 220.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 3.00 (3H, $CH_3SO_2$), 4.92 (2H, d, $J$ = 1.7 Hz, $CH_2O$), 7.14 (1H, t, $J$ = 1.7 Hz, CH-3), 7.30−7.35 (1H, m, $CH_{Ar}$), 7.38−7.47 (4H, m, 4 × $CH_{Ar}$), 7.69−7.77 (2H, m, CH-6 and CH-7), 8.01−8.08 (2H, m, CH-5 and CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 37.3 ($CH_3SO_2$), 49.4 ($CH_2N$), 126.5 ($CH_{Ar}$), 128.0 (2 × $CH_{Ar}$), 128.5 ($CH_{Ar}$), 129.9 (2 × $CH_{Ar}$), 132.0 ($C_{quat}$), 132.1 ($C_{quat}$), 133.9 ($CH_{Ar}$), 134.3 ($CH_{Ar}$), 135.5 ($CH_{Ar}$), 139.4 ($C_{quat}$), 145.6 ($C_{quat}$), 184.5 (C═O), 184.9 (C═O). IR ($cm^{-1}$): $\nu$ 1659 (C═O), 1595 ($CH_{Ar}$), 1338 (S═O), 1306, 1160 (S═O), 1093 (C−N), 774. MS ($ES^+$; $m/z$ (%)): 342 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{18}H_{16}NO_4S]^+$ 342.0800, found 342.0802.

*N-Acetyl-2-phenylaminomethyl-1,4-naphthoquinone:* 604 mg, 90%; amber solid; mp 164.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.00 (3H, s, $CH_3CO$), 4.89 (2H, d, $J$ = 1.7 Hz, $CH_2O$), 6.92 (1H, t, $J$ = 1.7 Hz, CH-3), 7.24−7.51 (5H, m, 5 × $CH_{Ar}$), 7.70−7.77 (2H, m, CH-6 and CH-7), 8.03−8.10 (2H, m, CH-5 and CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.6 ($CH_3C$═O), 48.6 ($CH_2N$), 126.2 ($CH_{Ar}$), 126.4 ($CH_{Ar}$), 127.6 (2 × $CH_{Ar}$), 128.4 ($CH_{Ar}$), 130.0 (2 × $CH_{Ar}$), 132.0 ($C_{quat}$), 132.1 ($C_{quat}$), 133.88 ($CH_{Ar}$), 133.93 ($CH_{Ar}$), 134.0 ($CH_{Ar}$), 143.1 ($C_{quat}$), 145.8 ($C_{quat}$), 171.1 (NC═O), 184.7 (2 × C═O). IR ($cm^{-1}$): $\nu$ 1658 (C═O), 1299, 782. MS ($ES^+$; $m/z$ (%)): 306 (M + $H^+$, 100). HRMS ($ES^+$): calcd for $[C_{19}H_{16}NO_3]^+$ 306.1130, found 306.1123.

*N-Benzoyl-2-phenylaminomethyl-1,4-naphthoquinone:* 795 mg, quantitative; yellow solid; mp 180.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 5.04


dx.doi.org/10.1021/jo400852z | J. Org. Chem. XXXX, XXX, XXX−XXX

(2H, d, $J$ = 1.7 Hz, $CH_2O$), 6.90 (1H, t, $J$ = 1.7 Hz, CH-3), 6.99−7.22 (8H, m, 8 × $CH_{Ar}$), 7.27−7.30 (2H, m, 2 × $CH_{Ar}$), 7.59−7.65 (2H, m, CH-6 and CH-7), 7.92−8.01 (2H, m, CH-5 and CH-8). $^{13}$C NMR ($CDCl_3$): $\delta$ 49.4 ($CH_2N$), 126.3 ($CH_{Ar}$), 126.5 ($CH_{Ar}$), 127.1 (2 × $CH_{Ar}$), 128.0 (2 × $CH_{Ar}$), 129.1 (2 × $CH_{Ar}$), 129.5 (2 × $CH_{Ar}$), 130.4 ($CH_{Ar}$), 132.06 ($C_{quat}$), 132.14 ($C_{quat}$), 133.91 ($CH_{Ar}$), 133.96 ($CH_{Ar}$), 134.1 ($CH_{Ar}$), 135.0 ($C_{quat}$), 143.6 ($C_{quat}$), 145.9 ($C_{quat}$), 170.7 (NC═O), 184.8 (C═O), 184.9 (C═O). IR ($cm^{-1}$): $\nu$ 1644 (C═O), 1632 (C═O), 1365, 1299, 700. MS ($ES^+$; $m/z$ (%)): 368 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{24}H_{18}NO_3]^+$ 368.1287, found 368.1289.

**Synthesis of 2-Phenoxymethylchromen-4-one.** 2-Phenoxymethylchromen-4-one was synthesized following a literature procedure describing the synthesis of 2-(4-chlorophenoxy)methylchromen-4-one:[14] 1.50 g, 56%; white crystals; mp 96.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ 4.98 (2H, d, $J$ = 1.2 Hz, $CH_2O$), 6.54 (1H, s, CH-3), 6.96−7.05 (3H, m, 3 × $CH_{Ar}$), 7.29−7.36 (2H, m, 2 × $CH_{Ar}$), 7.41 (1H, dt, $J$ = 8.1, 1.1 Hz, CH-8), 7.46 (1H, d, $J$ = 8.1 Hz, CH-8), 7.65−7.68 (1H, ddd, $J$ = 8.1, 7.4, 1.7 Hz, CH-6), 8.19 (1H, dd, $J$ = 1.4 and 8.0 Hz, CH-5). $^{13}$C NMR ($CDCl_3$): $\delta$ 65.7 ($CH_2O$), 109.6 (CH-3), 114.8 (2 × $CH_{Ar}$), 118.0 ($CH_{Ar}$), 122.0 ($CH_{Ar}$), 124.0 ($C_{quat}$), 125.3 ($CH_{Ar}$), 125.6 ($CH_{Ar}$), 129.7 (2 × $CH_{Ar}$), 133.9 ($CH_{Ar}$), 156.1 ($C_{quat}$), 157.6 ($C_{quat}$), 163.9 ($C_{quat}$), 177.7 (C═O). IR ($cm^{-1}$): $\nu$ 1647 (C═O), 1466, 1355, 1243 (C−O), 1220 (C−O), 751. MS ($ES^+$; $m/z$ (%)): 253 ($M + H^+$, 100). HRMS ($ES^+$): calcd for $[C_{16}H_{13}O_3]^+$ 253.0865, found 253.0859.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Figures giving $^1$H and $^{13}$C NMR spectra of all compounds discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail for N.D.K.: norbert.dekimpe@UGent.be.

### Present Address

†Institute of Chemistry, Vietnam Academy of Science & Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi, Viet Nam.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are indebted to the "Research Foundation Flanders (FWO-Vlaanderen)" for financial support of this research.

## ■ REFERENCES


(1) (a) Kesteleyn, B.; Nguyen Van, T.; De Kimpe, N. *Tetrahedron* **1999**, *59*, 2091−2102. (b) Kesteleyn, B.; Van Puyvelde, L.; De Kimpe, N. *J. Org. Chem.* **1999**, *64*, 438−440. (c) Kesteleyn, B.; Van Puyvelde, L.; De Kimpe, N. *J. Org. Chem.* **1999**, *64*, 1173−1179. (d) Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 635−639. (e) Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 640−644. (f) Nguyen Van, T.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 5941−5946. (g) Claessens, S.; Jacobs, J.; Van Aeken, S.; Abbaspour Tehrani, K.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 7555−7559.

(2) (a) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5546−5550. (b) Yogo, M.; Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 328−334. (c) Singh, P. K.; Rohtagi, B. K.; Khanna, R. N. *Synth. Commun.* **1992**, *22*, 987−993.

(3) (a) Huang, C.; Liu, B. *Chem. Commun.* **2010**, *46*, 5280−5282. (b) Takenaga, N.; Uchiyama, T.; Kato, D.; Fujioka, H.; Dohi, T.; Kita, Y. *Heterocycles* **2011**, *82*, 1327−1336.

(4) Jacobsen, N.; De Franco, R. J.; Benson, R. E. *Org. Synth.* **1977**, *56*, 68−71.

(5) (a) Knölker, H.-J.; Reddy, K. R. *Heterocycles* **2003**, *60*, 1049−1052. (b) Molina, M. T.; Navarro, C.; Moreno, A.; Csákÿ, A. G. *Org. Lett.* **2009**, *11*, 4938−4941. (c) Zhao, Y.; Zhang, Y.; Wang, J.; Li, H.; Wu, L.; Liu, Z. *Synlett* **2010**, *15*, 2352−2356. (d) Moon, Y.; Hong, S. *Chem. Commun.* **2012**, *48*, 7191−7193. (e) Rao, M. L. N.; Giri, S. *RSC Adv.* **2012**, *2*, 12739−12750.

(6) (a) Ferreira, E. M.; Stolz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9578. (b) Zhang, H.; Ferreira, E. M.; Stolz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144−6148.

(7) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245−1247.

(8) (a) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619−4631. (b) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem. Eur. J.* **2001**, *7*, 2481−2489. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904−11905. (d) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978−11987.

(9) (a) Albéniz, C. A.; Catalina, M. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571. (b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817.

(10) Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 4455−4464.

(11) (a) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, *2*, 218−219. (b) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870−7871. (c) Zheng, C.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2012**, *134*, 16496−16499. (d) Jana, R.; Pathak, T. P.; Jensen, K. H.; Sigman, M. S. *Org. Lett.* **2012**, *14*, 4074−4077. (e) Izawa, Y.; Zheng, Z.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3672−3675.

(12) Jacobsen, N.; Torssell, K. *Liebigs Ann. Chem.* **1972**, *763*, 135−147.

(13) Aldersly, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. F.; Ennis, D. S. *J. Chem. Soc., Perkin Trans. I* **1990**, *8*, 2163−2174.

(14) Guryar, M. K.; Bagavant, G. *Curr. Sci. India* **1978**, *47*, 683−4.