A New Approach to the Synthesis of Benzo[*b*]naphtho[2,3-*b*]furan-6,11-diones and 2-Benzyl-3-hydroxynaphthalene-1,4-diones

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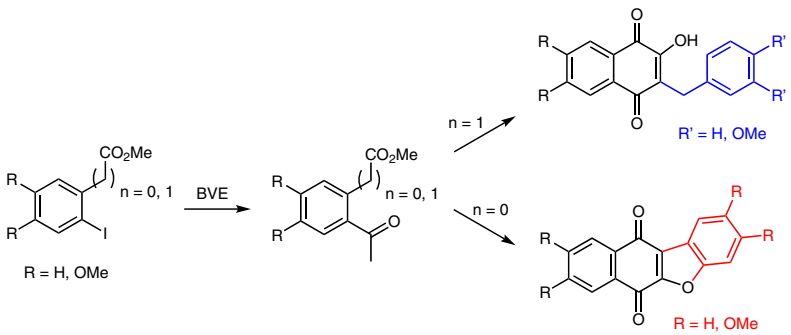

Received: 11.09.2017
Accepted after revision: 02.11.2017
Published online: 27.11.2017
DOI: 10.1055/s-0036-1591729; Art ID: so-2017-d0040-op
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Abstract Here we describe modified syntheses of *o*-acetylbenzoic acids and *o*-acetylphenylacetic acids by Heck palladium-catalysed arylation of *n*-butyl vinyl ether with *o*-iodobenzoic acids or with *o*-iodophenylacetic acids, respectively. General syntheses of benzo[*b*]naphtho[2,3-*b*]furan-6,11-diones from *o*-acetylbenzoic acids and 2-benzyl-3-hydroxynaphthalene-1,4-diones from *o*-acetylphenylacetic acids are also reported.

Key words fused-ring systems, Heck reaction, quinones, palladium, heterocycles, halides, furans

The synthesis of naphthoquinones is of great significance because of the widespread occurrence of the 1,4-naphthoquinone nucleus in numerous natural and synthetic compounds of biological and industrial interest.[1–8] Specifically, considerable attention has been devoted to 2-hydroxy-1,4-naphthoquinones (**I**) and 2-hydroxy-3-phenyl-1,4-naphthoquinones (**II**) (Figure 1), on account of their biological properties, their industrial applications, and their potential as intermediates in the synthesis of oxygenated and nitrogenated heterocyclic quinones, including 5*H*-benzo[*b*]carbazole-6,11-diones (benzocarbazolequinones)[9,10] benzo[*b*]naphtho[2,3-*b*]furan-6,11-diones (benzofuronaphthoquinones)[11,12] and 5*H*-dibenzo[*c*,*g*]chromene-5,7,12-triones (benzopyronaphtho-quinones).[13,14] Benzocarbazolequinones (**III**, Figure 1) became important synthetic targets once their antineoplastic activity was established.[15–18] On the other hand, a representative example of benzofuronaphthoquinones is compound **IV** (Figure 1) and a representative example of benzopyronaphthoquinones **V** (Figure 1) is the quinonoid anticoccidial antibiotic WS-5995-A.[19–21] The antineoplastic activity displayed by compounds **III**, **IV** and **V** has been related to the well-known antitumor properties of ellipticine (Figure 1).[15–18] The antineoplastic activity of these compounds has been attributed to their ring systems, which contain an embedded 2-phenylnaphthalene-like structure in a planar conformation, which facilitates its intercalation between adjacent pairs of DNA bases, thereby interfering with DNA replication and transcription.[22] In addition, the quinone moiety present in the ring skeleton explains the cytotoxic properties of these compounds and enhances the strength of intercalative binding to DNA through the formation of charge-transfer interactions with the electron-rich DNA bases.[23–25]

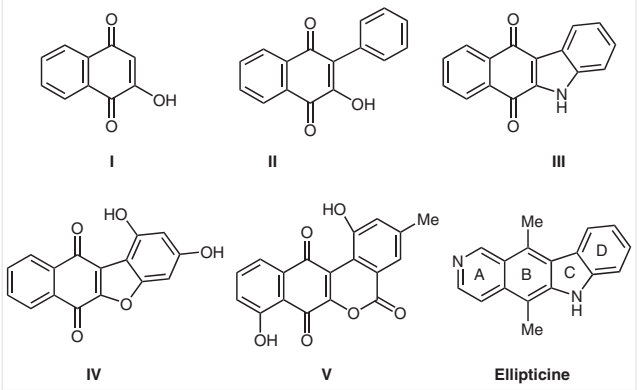
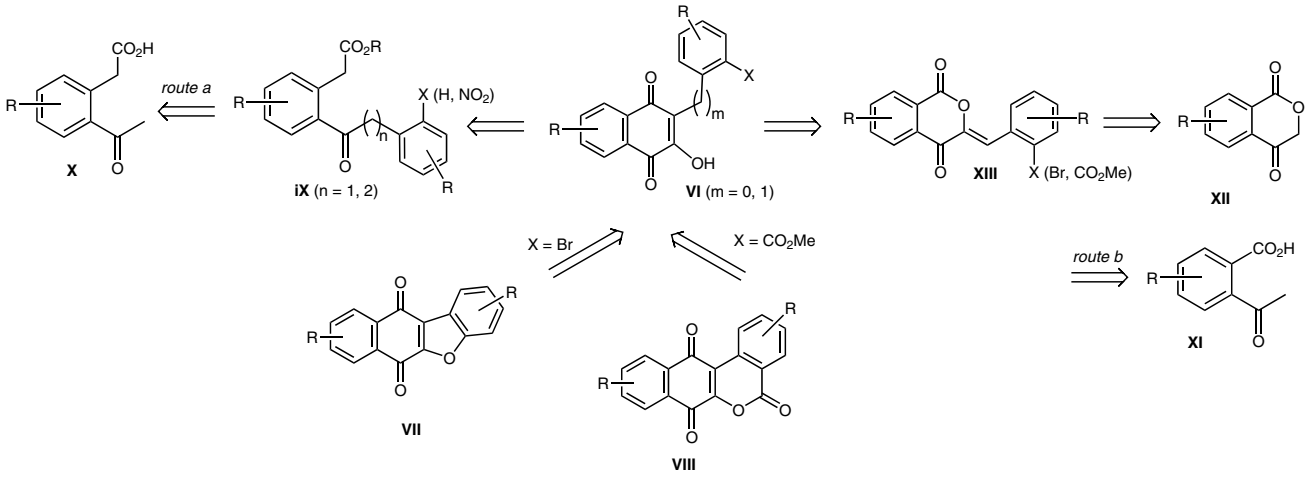


Figure 1 Representative 2-hydroxy-1,4-naphthoquinones and tetracyclic naphthoquinones related to ellipticine

From a chemical point of view, particular interest has been devoted to 2-hydroxy-3-phenyl-1,4-naphthoquinones (**VI**, *m* = 0, Scheme 1), because they proved to be convenient

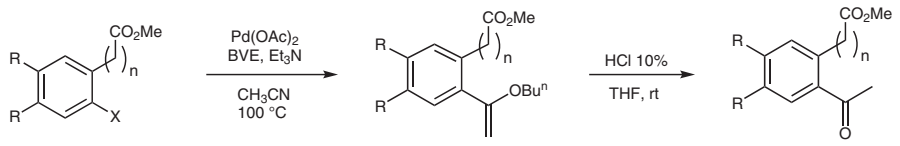


Scheme 1 Retrosynthetic plan towards benzofuronaphthoquinones **VII**, benzopyronaphthoquinones **VIII** and 2-hydroxy-3-benzyl-1,4-naphthoquinones **VI** (*m* = 1)

precursors for the synthesis of naphthoquinone derivatives **VII**, **VIII** and **IX**, and related compounds.[15–18] Accordingly, a range of methods for the preparation of these powerful scaffolds have been developed, including our previously reported general syntheses from *o*-acetylphenylacetic acids **XI** (*route a*)[26] and from *o*-acetylbenzoic acids **XII** (*route b*).[27] *Route a* was found to be of limited scope because it only allowed benzocarbazolequinones **III** to be prepared. These tetracyclic naphthoquinones were alternatively obtained through *route b*, by a sequence involving the condensation of isochroman-1,4-diones **XII** with *p*-nitrobenzaldehydes, followed by rearrangement of the resulting 3-benzylideneisochroman-1,4-diones **XIII** (X = NO_2) to the corresponding naphthoquinones (*m* = 0) and subsequent generation of the nitrogen ring.[28,29] These two general approaches to benzocarbazolequinones allowed the limitations of previous syntheses of these targets to be overcome.[10,11,30–32] As a continuation of this work, herein we report studies on the synthesis of benzofuronaphthoquinones **VII** and benzopyronaphthoquinones **VIII** from *o*-acetylbenzoic acids **XI**, via 3-hydroxy-2-phenylnaphthoquinones **VI** (Scheme 1). The synthesis of 2-benzyl-3-hydroxynaphthalene-1,4-diones (**VI**, *m* = 1) and *o*-acetylphenylacetic acids **X** is also described.

Our previous, general and straightforward synthesis *o*-acetylbenzoic acids involved a Heck coupling reaction between electron-rich *n*-butyl vinyl ether (BVE) and 2-bromobenzoates **1a–b**, using the conditions described by Cabri et al.[33] (Scheme 2).[27] Firstly, a Heck reaction between BVE and methyl *o*-bromobenzoate (**1a**) provided the expected α-arylation product **2a** only. This regiochemical outcome was attributed to the presence of TlOAc and a chelating phosphine in the reaction medium. The aryl vinyl ether **2a** was immediately reacted with 10% aqueous HCl for 1 hour at room temperature, to afford ketoester **3a** in 90% yield. On the other hand, the coupling reaction between the electron-rich methyl 2-bromo-4,5-dimethoxybenzoate dimethoxy derivative **1b** and BVE, under the same conditions, gave ketoester **3b** in lower yield, via aryl vinyl ether **2b**.

Surprisingly, the same regioselectivity was observed when the coupling reaction of **1a** and **1b** with BVE was performed under classical Heck conditions, which required longer reaction times, but avoided the use of toxic thallium salts and expensive phosphines. The uncommonly high α-regioselectivity achieved under these classical conditions may be the result of an interaction between the *o*-carbomethoxy group of aryl halides **1** and the palladium complex involved in the Heck coupling.



1a: R = H, X = Br (n = 0), **1b**: R = OMe, X = Br (n = 0)
1c: R = H, X = I (n = 0), **1d**: R = OMe, X = I (n = 0)
1e: R = H, X = Br (n = 1), **1f**: R = OMe, X = Br (n = 1)
1g: R = H, X = I (n = 1), **1h**: R = OMe, X = I (n = 1)

2a: R = H (n = 0)
2b: R = OMe (n = 0)
2c: R = H (n = 1)
2d: R = OMe (n = 1)

3a: R = H (n = 0)
3b: R = OMe (n = 0)
3c: R = H (n = 1)
3d: R = OMe (n = 1)

Scheme 2 Heck coupling of methyl *o*-iodobenzoates **1c**,**d** and methyl *o*-iodophenylacetates **1g**,**h** and with BVE: synthesis of methyl *o*-acetylbenzoates **3a**,**b** and methyl *o*-acetylphenylacetates **3c**,**d**

Table 1 Formation of **3a**,**b** and **3c**,**d**

Entry	Substrate	Catalyst[a]	Solvent	Time	Product	Yield (%)
1	**1c**	$Pd(OAc)_2/Ph_3P$ (7.5 mol%)	CH_3CN	4 h	**3a**	90
2	**1d**	$Pd(OAc)_2/Ph_3P$ (10 mol%)	CH_3CN	16 h	**3b**	84
3	**1g**	$Pd(OAc)_2/Ph_3P$ (2.5 mol%)	CH_3CN	16 h	**3c**	68
4	**1h**	$Pd(OAc)_2/Ph_3P$ (2.5 mol%)	CH_3CN	1 week	**3d**	60

[a] All the experiments were carried out at 100 °C.
[b] See ref.[23]
[c] See ref.[22]

On the other hand, similar regioselectivities and yields were previously achieved for the coupling of *o*-bromophenylacetates **1e** and **1f** with BVE, both under the Cabri and classical conditions. *o*-Acetylphenylacetates **3c** and **3d** were obtained respectively, via the corresponding enol ethers **2c** and **2d**.

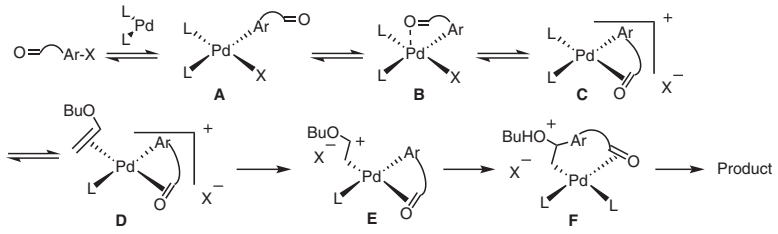
The similar reaction of BVE with methyl iodobenzoates **1c–d**, and with methyl iodophenylacetates **1g–h** was then studied under these classical conditions, in order to assess the influence of the halogen on this Heck coupling reaction. A selective α-arylation was again observed, similar reaction times were required, and similar yields were achieved (Table 1, entries 1,2 and 3,4).

A tentative explanation for the role played by the carbomethoxy group of both types of substrates (**1a–d** or **1e–h**) in the Heck reaction is depicted in Scheme 3. The insertion of Pd(0) into the carbon–halogen bond of the starting aryl halide would lead to complex B, via complex A. Dissociation of the halogen atom should give a cationic complex C, with internal association of the methoxycarbonyl group. Removal of a ligand L provided a free position that can be used to link a BVE unit. Next, the *o*-carbomethoxy group could assist the insertion of Pd(0) through chelation (complex D).[34] It has been proposed that chelation between the carbonyl group and the palladium atom could play an important role in promoting high regioselectivities.[33] This may be supported by the fact that the regioselectivity in Heck reactions is dependent on the ionic versus neutral mechanisms proposed for this reaction, and that branched alkenes are mainly obtained from electron-rich alkenes, such as BVE, under ionic mechanism conditions.[35–38] The predominance of electronic over steric effects is responsible for the regioselectivity observed in this reaction.

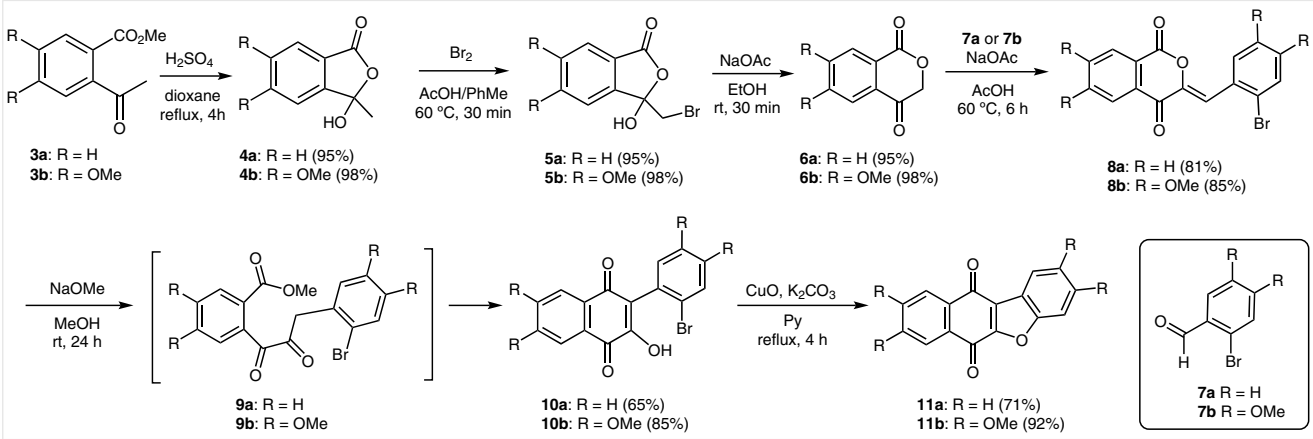
According to our synthetic plan, methyl *o*-acetylbenzoate **3a** was hydrolysed, by refluxing a solution of this ketoester and 20% aqueous H_2SO_4 under reflux for 2 h.[39] This afforded the corresponding benzoic acid lactol **4a** in 95% yield (Scheme 4), which readily provided bromomethyl lactol **5a** in 96% yield, upon treatment with bromine in acetic acid/toluene. Finally, treatment of **5a** with NaOAc in ethanol gave isochroman-1,4-dione **6a** in 98% yield.[27,39] Ketoester **3b** was similarly and efficiently converted into isochroman-1,4-dione **6b** via compounds **4b** and **5b**.

Reaction of isochroman-1,4-dione **6a** with *o*-bromobenzaldehyde (**7a**) in ammonium acetate/acetic acid provided the new benzylideneisochroman-1,4-dione **8a** in 81% yield. Treatment of **8a** with sodium methoxide in methanol gave the known 3-bromophenyl-2-hydroxy-1,4-naphthoquinone **10a** in 65% yield, through rearrangement of intermediate **9a**.[11] A similar condensation of isochroman-1,4-dione **6b** with 2-bromo-4,5-dimethoxybenzaldehyde (**7b**), resulted in the formation of benzylideneisochroman-1,4-dione **8b**, which rearranged readily to the expected 3-bromophenyl-2-hydroxy-1,4-naphthoquinone **10b**. As quinones **10a** and **10b** were previously converted into benzofuronaphthoquinones **11a** and **11b**, respectively,[30,31,40] the present approach constitutes a novel, general synthesis of these tetracyclic quinones, that overcomes limitations of our previous routes.

In an attempt to apply this synthetic strategy to the preparation of 5*H*-dibenzo[*c*,*g*]chromene-5,7,12-triones, when isochroman-1,4-dione **6a** was reacted with *o*-methoxycarbonylbenzaldehyde, under the same conditions as for **8a**, the expected benzylideneisochroman-1,4-dione **11** was obtained in 75% yield (Scheme 5). However, when this compound was reacted with sodium methoxide in methanol, the resulting compound was not the desired 3-methoxycarbonyl-2-hydroxynaphthoquinone **15** that should result from intermediate **12**. Compound **14** was obtained in 70% yield. Probably, the favoured process is now the lactonisation of enol **13** of intermediate **12**.



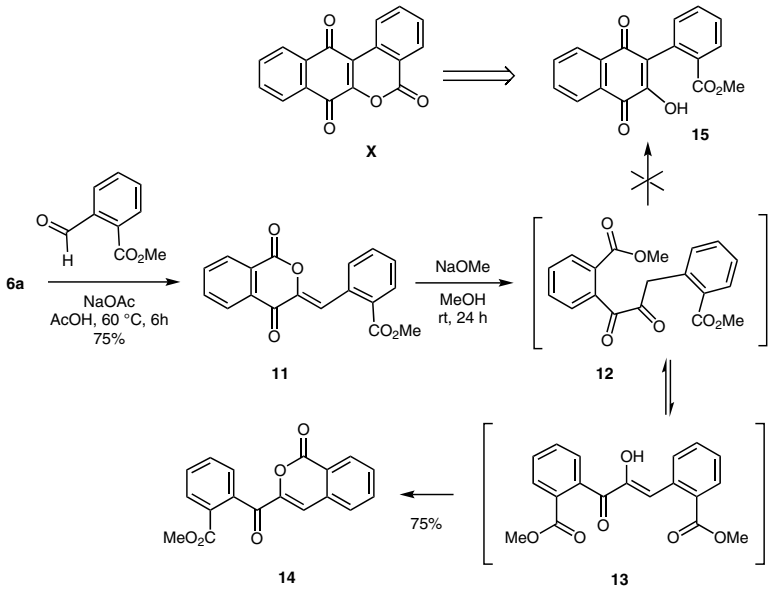
Scheme 3 Mechanistic explanation for the regiochemistry observed in the Heck coupling reaction of methyl *o*-halophenylacetates and methyl *o*-halobenzoates with BVE



Scheme 4 Synthesis of benzo[*b*]naphtho[2,3-*b*]furanquinones **11a**,**b** from methyl 2-acetylbenzoates via isochroman-1,4-diones **6a**,**b**

On the other hand, it is interesting to note that 3-alkyl-2-hydroxy-1,4-naphthoquinones have received considerably less attention than the corresponding 3-phenyl 2-hydroxy-1,4-naphthoquinones. Its most significant component is lapachol, a natural occurring phenolic compound isolated from the bark of the lapacho tree, which possess antitumor and antiparasitic properties.[41–44] A family of compounds structurally related to lapachol are 3-benzyl-2-hydroxy-1,4-naphthoquinones, which were previously prepared by alkylation of 2-hydroxy-1,4-naphthoquinones with alkyl halides or by condensation with aldehydes. Thus, alkylation of lawsone with benzyl chlorides, under basic conditions, provided the 3-benzyl-2-hydroxy-1,4-naphthoquinones with a range of 38–43% yield.[42,45] Thus 3-benzyl-2-hydroxy-1,4-naphthoquinones were alternatively obtained by condensation of lawsone with benzaldehydes, in a range of 75–85% yield.[46,47]

As an additional contribution to this field, we report here the synthesis of 3-benzyl-2-hydroxy-1,4-naphthoquinones **20a–d** from *o*-acetylphenylacetic acids **16a**,**b**, which were obtained by hydrolysis of the respective methyl *o*-acetylphenylacetates **3c**,**d** (Scheme 6). Thus, condensation of *o*-acetylphenylacetic acid (**16a**) with benzaldehyde (**7c**) provided the corresponding α,β-unsaturated derivative **17a** (50%), which, upon catalytic hydrogenation, gave *o*-phenylpropylphenylacetic acid **18a** in high yield (93%). Subsequent treatment of this ketoacid with *t*-BuOK in *t*-BuOH, resulted in the unreported benzylnaphthoquinone **20a** in 57% yield. Reaction of **17a** with 3,4-dimethoxybenzaldehyde (**7d**) provided the unknown benzylnaphthoquinone **20b** in 72%



Scheme 5 Unsuccessful approach to the synthesis of 5*H*-dibenzo[*c*,*g*]chromene-5,7,12-triones **X**

yield, via compounds **17b** and **18b**. Reaction of *o*-acetylphenylacetic acid **16b** with benzaldehyde gave the known 3-benzylnaphthoquinone **20c**, via compounds **17c** and **18c**. Finally, when **16b** reacted with 3,4-dimethoxibenzaldehyde, the known benzylnaphthoquinone **20d** was obtained in 39% yield, via compounds **17d** and **18d**. This new synthesis of 3-benzyl-2-hydroxy-1,4-naphthoquinones proved to be more efficient than previously reported approaches.[42,45]

As a whole, we have revisited our general and efficient method for the preparation of methyl *o*-acetylbenzoates and methyl *o*-acetylphenylacetates. A slight modification consisting of the replacement of the starting *o*-bromobenzoic acid esters and the *o*-bromophenylacetic acid esters by the corresponding aryl iodides, allow these ketoacids to be obtained in similar yields and stereoselectivities.

In addition, a new synthetic application of the *o*-acetylbenzoic acid derived isochroman-1,4-diones, involving transformation into benzo[*b*]naphtho[2,3-*b*]furan-6,11-diones was developed. This new, general synthesis of these targets allows easy and efficient access to a variety of antitumor quinones, for chemical and biological studies.

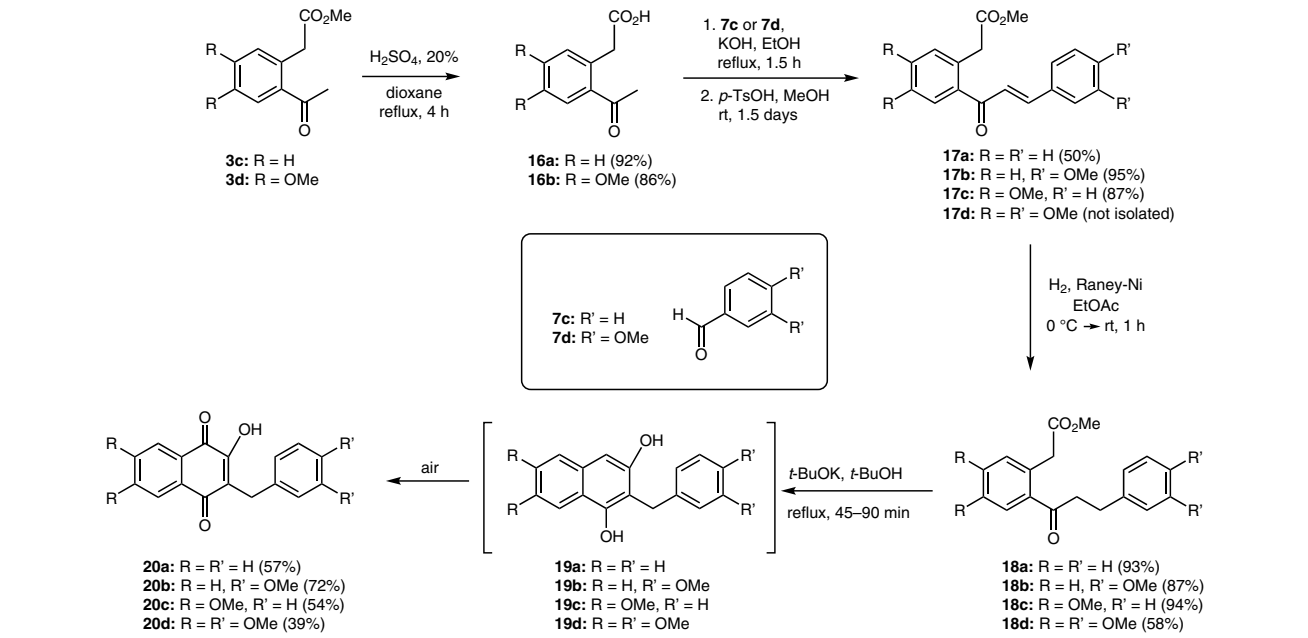
The practically unexplored *o*-phenylpropionylphenylacetic acids are promising scaffolds for the development of a range of further synthetic applications. Interestingly, the 2-benzyl-1,4-naphthoquinone nucleus is embedded in the tetracyclic structures of benzo[*b*]acridine-6,11,12(5*H*)-triones[48] and 11*H*-benzo[*b*]naphtho[2,3-*e*]pyran-6,11,12-triones.[49] This structural relationship opens an opportunity for a new synthetic approach to these targets, and provides access to libraries of both practically unexplored kind of compounds, for chemical and biological studies.

Work is in progress aimed at the exploration of these promising chemical goals.

Melting points were determined with a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded with a JASCO FT/IR-400 spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, with a Bruker WM-250 apparatus using $CDCl_3$ solutions containing tetramethylsilane (TMS) as internal standard. ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or quintuplet (p). All first-order splitting patterns were assigned based on the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained with a HP 5988A mass spectrometer. Elemental analyses were performed with an EA 1108 CHNS Fisons instrument. Thin-layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and dichloromethane/methanol or EtOAc/hexane mixtures as eluents; the TLC spots were visualised with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solutions of extracts in organic solvents were dried with anhydrous sodium sulphate.

Methyl 2-Acetylbenzoates and Methyl 2-(2-Acetylphenyl)acetates 3; General Procedure

In a sealed tube fitted with Teflon screw cap, solutions of **1c**, **1d**, **1g** and **1h** (1.2 mmol), BVE (0.09 mmol), Pd $(OAc)_2$ (7.5%), PPh_3 (0.18 mmol) and Et_3N (0.90 mL) in anhydrous and deoxygenated CH_3CN (2.5 mL), were heated to 100 °C for 4 h. The respective reaction mixture was filtered through Celite, washed with CH_2Cl_2, and the filtrates



Scheme 6 Synthesis of 3-benzyl-2-hydroxy-1,4-naphthoquinones **20a–d** from *o*-acetylphenylacetic acids **16a,b**

were washed with distilled water (25 mL). The organic phases were dried with anhydrous Na_2SO_4 and concentrated to dryness. The residues were dissolved in a mixture of 10% THF/HCl (40 mL, 1:1) and the solution were stirred for 2 h at r.t., the solvent was evaporated and the residues were extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with 10% aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and the solvent evaporated off. The residues were purified by column chromatography (EtOAc/hexane, 2:3), to give **3a–d**.

Methyl 2-Acetylbenzoate (3a)[50]

Yield: 182 mg (90%); colourless oil.

IR: 1710 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 7.32–7.67 (m, 3 H, 3 × Ar-H), 7.77–7.92 (m, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 29.7 (CH_3), 52.4 (OCH_3), 126.4 (CH), 128.8 (C), 129.6 (CH), 130.0 (CH), 132.0 (CH), 142.6 (C), 167.4 (C=O), 202.8 (C=O).

MS: *m*/*z* (%) = 178 (100) [M^+].

Methyl 2-Acetyl-4,5-dimethoxybenzoate (3b)

Yield: 186 mg (84%); white solid; mp 118–120 °C (EtOAc).

Methyl 2-(2-Acetylphenyl)acetate (3c)

Yield: 164 mg (68%); colourless oil.

Methyl 2-(2-Acetyl-4,5-dimethoxyphenyl)acetate (3d)

Yield: 128 mg (60%); white solid; mp 64–67 °C (Et_2O).

IR (NaCl): 1703 (C=O), 1600 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 3.89 (s, 2 H, CH_2); 3.93 (s, 6 H, 2 × CH_3), 6.72 (s, 1 H, Ar-H), 7.33 (s, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.5 (CH_3), 40.2 (CH_3), 51.8 (OCH_3), 56.0 (OCH_3), 56.2 (OCH_3), 113.9 (CH), 115.5 (CH), 129.2 (C), 129.4 (C), 147.5 (Ar-OCH_3), 152.0 (Ar-OCH_3), 172.2 (C=O), 199.1 (C=O).

MS: *m*/*z* (%) = 239 (21) [M^+], 223 (100).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.08; H, 6.19.

3-Hydroxy-3-methyl-3*H*-isobenzofuran-1-ones 4; General Procedure

20% Aqueous H_2SO_4 (10 mL) was added to solutions of **3a** and **3b** (5.62 mmol) in dioxane (18 mL) and the reaction mixtures were heated at reflux for 2 h. The mixtures were allowed to cool to r.t., poured into water (20 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), dried with anhydrous Na_2SO_4 and concentrated to dryness, to give **4a** and **4b**, respectively.

3-Hydroxy-3-methyl-3*H*-isobenzofuran-1-ones (4a)

Yield: 0.88 g (95%); white solid; mp 116–118 °C ($CHCl_3$).

IR (NaCl): 3267 (OH), 1726 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.95 (s, 3 H, CH_3), 5.71 (br s, 1 H, OH), 7.47–7.60 (m, 2 H, 2 × Ar-H), 7.63–7.82 (m, 2 H, 2 × Ar-H).

^{13}C NMR (CD_3OD): δ = 26.4 (CH_3), 108.1 (C), 123.5 (CH), 125.9 (CH), 127.6 (C), 131.4 (CH), 135.8 (CH), 151.9 (C), 170.4 (C=O).

MS: *m*/*z* (%) = 165 (67) [M + H^+], 147 (100).

Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.98; H, 4.66.

3-Hydroxy-5,6-dimethoxy-3-methyl-3*H*-isobenzofuran-1-one (4b)

Yield: 1.04 g (98%); white solid; mp 143–145 °C (EtOAc).

IR (NaCl): 3378 (OH), 1719 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.90 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.44 (br s, 1 H, OH), 6.96 (s,1 H, Ar-H), 7.15 (s, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 26.3 (CH_3), 56.2 (OCH_3), 56.3 (OCH_3), 103.8 (CH, C), 106.2 (CH), 117.9 (C), 143.8 (C), 150.8 (C), 154.7 (C), 169.0 (C=O).

MS: *m*/*z* (%) = 224 (29) [M^+], 209 (100).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.16; H, 5.26.

3-Bromomethyl-3-hydroxy-3*H*-isobenzofuran-1-ones 5; General Procedure

Bromine (1.2 mL, 23.4 mmol) was added dropwise, under stirring, to solutions of lactols **4** and **4b** (23.4 mmol) in a mixture of AcOH/toluene (1:2, 90 mL) heated at 60 °C. The reaction mixtures were stirred for 30 minutes, evaporated to dryness, and the residues were crystallised from $CHCl_3$ to afford **5a** and **5b**, respectively.

3-Bromomethyl-3-hydroxy-3*H*-isobenzofuran-1-one (5a)

Yield: 5.46 g (96%); white solid; mp 115–117 °C ($CHCl_3$).

IR (NaCl): 3260 (OH), 1752 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.85 (d, *J* = 4.4 Hz, 2 H, CH_2), 5.34 (br s, 1 H, OH), 7.55–7.84 (m, 4 H, 4 × Ar-H).

^{13}C NMR ($CDCl_3$, CD_3OD): δ = 35.1 (CH_2), 104.4 (C), 122.7 (CH), 125.2 (CH), 126.9 (C), 130.9 (CH), 134.6 (CH), 146.9 (C), 168.4 (C=O).

MS: *m*/*z* (%) = 245 (77) [M + H]$^+$, 243 (80) [M + H]$^+$, 227 (98), 225 (100).

Anal. Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.90; Br, 32.87. Found: C, 44.15; H, 3.21.

3-Bromomethyl-3-hydroxy-5,6-dimethoxy-3*H*-isobenzofuran-1-one (5b)

Yield: 1.60 g (90%); white solid; mp 132–134 °C ($CHCl_3$).

IR (NaCl): 3219 (OH), 1740 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.84 (s, 2 H, CH_2), 3.93 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 7.07 (s, 1 H, Ar-H), 7.20 (s, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 36.2 (CH_2), 56.4 (OCH_3), 56.5 (OCH_3), 103.1 (C-OH), 104.3 (CH), 106.1 (CH), 119.0 (C), 140.6 (C), 151.7 (C), 155.0 (C), 168.2 (C=O).

MS: *m*/*z* (%) = 304 (19) [M + H]$^+$, 302 (20) [M + H]$^+$, 223 (100).

Anal. Calcd for $C_{11}H_{11}BrO_5$: C, 43.59; H, 3.66; Br, 26.36. Found: C, 43.86; H, 3.81.

Isochroman-1,4-diones 6; General Procedure

NaOAc (21.40 mmol) was added in portions to solution of **5a** and **5b** (21.40 mmol) in EtOH (11 mL). The reaction mixtures were stirred at r.t. for 30 min and then were concentrated to dryness, under vacuum. The solids were washed with water and dried under vacuum to give compounds **6a** and **6b**, respectively

Isochroman-1,4-dione (6a)[36]

Yield: 3.40 g (98%); white solid; mp 147–148 °C ($CHCl_3$).

IR (NaCl): 1725 (C=O), 1695 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.14 (s, 2 H, CH_2), 7.82–7.95 (m, 2 H, 2 × Ar-H), 8.06–8.10 (m, 1 H, Ar-H), 8.25–8.29 (m, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 73.3 (CH_2), 125.5 (CH), 127.8 (C), 130.7 (CH), 131.7 (C), 134.6 (CH), 135.8 (CH), 161.4 (C=O), 189.4 (C=O).

Anal. Calcd for $C_9H_9O_3$: C, 66.67; H, 3.73. Found: C, 61.03; H, 3.59.

6,7-Dimethoxyisochroman-1,4-dione (6b)

Yield: 1.18 g (95%); white solid; mp 253–255 °C ($CHCl_3$).

IR (NaCl): 1714 (C=O), 1683 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.04 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 5.11 (s, 2 H, CH_2), 7.47 (s, 1 H, Ar-H), 7.66 (s, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 56.6 (OCH_3), 56.8 (OCH_3), 73.4 (CH_2), 106.1 (CH), 111.4 (CH), 122.6 (C), 126.5 (C), 154.2 (C), 155.2 (C), 161.6 (C=O), 188.6 (C=O).

MS: *m*/*z* (%) = 222 (34) [M$^+$], 164 (100).

Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.67; H, 4.23.

3-Benzylidene-isochromane-1,4-diones 8; General Procedure

NH_4OAc (209 mg, 2.71 mmol) was added to a solution of **6a** and **6b** (1.23 mmol) and the respective aldehyde (1.23 mmol) in AcOH (5 mL), and the resulting solutions were heated at 60 °C for 6 h. The reaction mixtures were allowed to cool to r.t., water (10 mL) was then added and the precipitated solids were washed with water and dried, to give **8a**, **8b** or **12**.

3-(2-Bromobenzylidene)isochroman-1,4-dione (8a)

Yield: 988 mg (81%); yellow solid; mp 130–132 °C (MeOH).

IR (NaCl): 1746 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.19–7.29 (m, 1 H, Ar-H), 7.38–7.46 (m, 1 H, Ar-H), 7.58–7.69 (m, 2 H, =CH, Ar-H), 7.86–7.93 (m, 2 H, 2 × Ar-H), 8.24–8.36 (m, 3 H, 3 × Ar-H).

^{13}C NMR ($CDCl_3$): δ = 118.1 (CH), 126.6 (C), 126.7 (C), 126.9 (CH), 127.7 (CH), 130.6 (CH), 131.2 (CH), 131.5 (C), 132.5 (CH), 133.1 (C), 133.2 (CH), 135.2 (2 × CH), 145.4 (C), 157.8 (C=O), 176.6 (C=O).

MS: *m*/*z* (%) = 328 (44) [M$^+$], 330 (39) [M$^+$], 249 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{10}BrO_3$: 328.9808; found: 328.9813.

3-(2-Bromo-4,5-dimethoxybenzylidene)-6,7-dimethoxyiso-chroman-1,4-dione (8b)

Yield: 342 mg (85%); yellow solid; mp 289–290 °C (MeOH).

IR (NaCl): 1734 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.94 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.07 (s, 6 H, 2 × OCH_3), 7.12, 7.27, 7.58, 7.65, 8.08 (5s, 5 H, 4 × Ar-H, =CH).

MS: *m*/*z* (%) = 450 (10) [M$^+$], 448 (10) [M$^+$], 369 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}BrO_7$: 449.0230; found: 449.0219.

3-(2-Carbomethoxybenzylidene)isochromane-1,4-dione (11)

Yield: 284 g (75%); yellow solid; mp 227–229 °C (MeOH).

IR (NaCl): 1763 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.90 (s, 3 H, CH_3), 7.42 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.59 (t, *J* = 7.5 Hz, 1 H, H-Ar), 7.81–7.91 (m, 3 H, H-C= and 2 × H-Ar), 7.96 (d, *J* = 7.7 Hz, 1 H, Ar-H), 8.07 (d, *J* = 7.7 Hz, 1 H, Ar-H), 8.19–8.31 (m, 2 H, 2 × Ar-H).

^{13}C NMR ($CDCl_3$): δ = 52.3 (CH_3), 118.9 (CH=C), 126.7 (CH-Ar), 126.8 (C-Ar), 129.2 (CH-Ar), 130.4 (CH-Ar), 130.6 (CH-Ar), 131.7 (CH-Ar), 131.8 (C-Ar), 132.1 (CH-Ar), 132.2 (C-Ar), 133.1 (C-Ar), 135.0 (2 × CH), 144.7 (C=CH), 157.9 (CO), 167.1 (CO), 176.7 (CO).

MS: *m*/*z* (%) = 309.3 (53) [M + H]$^+$, 174.2 (100) [M-$C_8H_7O_2$].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}O_5$: 309.3702; found 309.3706.

2-Phenyl-3-hydroxynaphthalene-1,4-diones 10; General Procedure

A solution of NaOMe (56.7 mg, 1.05 mmol) in MeOH (15 mL) was added dropwise to stirred solutions of benzylideneisochromane-1,4-dione **8a** and **8b** (0.5 mmol) in MeOH (20 mL) cooled at 0 °C. The resulting solutions were stirred for 24 h at r.t., poured into water (15 mL) and acidified with aqueous 1 M HCl. The mixtures were extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The residues were purified by recrystallisation from MeOH, to yield **10a**, **10b** or **15**.

2-(2-Bromophenyl)-3-hydroxy-1,4-naphthoquinone (10a)

Yield: 325 mg (65%); red solid; mp 172–174 °C (MeOH).

IR (NaCl): 3425 (OH), 1675 (C=O), 1641 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.24–7.31 (m, 2 H, 2 × Ar-H), 7.37–7.45 (m, 1 H, Ar-H), 7.66–7.85 (m, 3 H, 3 × Ar-H), 8.15–8.21 (m, 2 H, 2 × Ar-H).

^{13}C NMR ($CDCl_3$): δ = 122.6 (C), 123.9 (C), 126.3 (CH), 127.1 (CH), 127.3 (CH), 129.3 (C), 130.1 (CH), 131.4 (CH), 131.8 (C), 132.7 (C, CH), 133.2 (CH), 135.4 (CH), 152.7 (C), 181.6 (C=O), 182.7 (C=O).

MS: *m*/*z* (%) = 331 (95) [M + H]$^+$, 329 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{10}BrO_3$: 328.9808; found: 328.9795.

2-(2-Bromo-4,5-dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-1,4-naphthoquinone (10b)

Yield: 170 mg (85%); red solid; mp 222–224 °C (MeOH).

3-(2-Carbomethoxybenzoyl)-1*H*-isochromen-1-one (14)

Yield: 690 mg (70%); red solid; mp 139–141 °C (MeOH/CH_2Cl_2).

IR (NaCl): 1765 (CO) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.79 (s, 3 H, CH_3), 7.33 (s, 1 H, Ar-H), 7.41–7.49 (m, 1 H, H-Ar); 7.55–7.72 (m, 4 H, H-C= and 3 × Ar-H), 7.77 (t, *J* = 7.5 Hz, 1 H, Ar-H), 8.07 (d, *J* = 7.7 Hz, 1 H, Ar-H), 8.31 (d, *J* = 7.7 Hz, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 52.6 (CH_3), 110.5 (CH=C), 122.7 (C-Ar), 127.9 (CH-Ar), 128.1 (CH-Ar), 129.4 (C-Ar), 130.0 (C-Ar), 130.5 (CH-Ar), 131.8 (CH-Ar), 130.7 (CH-Ar), 132.2 (CH-Ar), 132.8 (CH-Ar), 135.1 (C-Ar), 139.4 (CH-Ar), 149.6 (C = CH), 160.4 (CO), 166.3 (CO), 189.3 (CO).

MS: *m*/*z* (%) = 309 (65) [M + H]$^+$, 174 (100) [M-$C_8H_7O_2$].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}O_5$: 309.3523; found: 309.3525.

***o*-Acetylphenylacetic Acids 17; General Procedure**

20% Aqueous sulphuric acid (3.5 mL) was added, under nitrogen, to a solution of compounds **3c** and **3d** (1.56 mmol) in dioxane (9.0 mL) and the mixtures were heated at reflux for 4 h. The reaction mixtures were added over 10% aqueous NaOH (2 × 15 mL) and extracted with Et_2O (10 mL). The aqueous extracts were cooled at 0 °C and 20% H_2SO_4

was added until pH 3.0. The suspensions were extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were washed with water (15 mL), dried with anhydrous Na_2SO_4 and concentrated to dryness under vacuum, to give residues that were purified by recrystallisation, to afford compounds **17a** or **17b**.

2-(2-Acetylphenyl)acetic Acid (16a)

Yield: 255 mg (92%); mp 135 °C (MeOH).

IR (NaCl): 3440 (COOH), 1707 (C=O), 1671 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, CD_3OD): δ = 2.50 (s, 3 H, CH_3), 3.81 (s, 2 H, CH_2), 4.23 (s, 1 H, COOH), 7.17 (d, *J* = 7.3 Hz, 1 H, Ar-H), 7.29–7.41 (m, 2 H, 2 × Ar-H), 7.73 (d, *J* = 7.5 Hz, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.3 (CH_3), 39.9 (CH_3), 127.8 (CH), 132.0 (CH), 132.5 (CH), 134.3 (C), 136.93 (C), 173.8 (C=O), 202.4 (C=O).

MS: *m*/*z* (%) = 178 (13) [M^+], 160 (28), 135 (85), 132 (100).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.26; H, 5.78.

2-(2-Acetyl-4,5-dimethoxyphenyl)acetic Acid (16b)

Yield: 461 mg (86%); mp 172–173 °C (MeOH).

IR (NaCl): 3020 (COOH), 1730 (C=O), 1638 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, CD_3OD): δ = 2.60 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 3.97 (s, 6 H, 2 × OCH_3), 6.78 (s, 1 H, Ar-H), 7.35 (s, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$, CD_3OD): δ = 28.2 (CH_3), 40.2 (CH_3), 55.7 (OCH_3), 55.9 (OCH_3), 113.5 (CH), 115.1 (CH), 128.6 (C), 129.5 (C), 147.0 (Ar-OCH_3), 151.8 (Ar-OCH_3), 173.7 (C=O), 200.3 (C=O).

MS: *m*/*z* (%) = 238 (13) [M^+], 185 (39), 179 (100).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.23; H, 6.12.

Methyl 2-(2-Cinnamoylphenyl)acetates 17; General Procedure

15% Aqueous KOH (2 mL) was added to stirred solutions of **16a** and **16b** (0.90 mmol) and the appropriate aldehyde (1.10 mmol) in EtOH (5 mL). The mixtures were heated at reflux for 45 min, cooled and acidified with 10% aqueous HCl (10 mL). The suspensions were extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with water (3 × 15 mL), dried with anhydrous Na_2SO_4 and concentrated to dryness under vacuum, to give a yellow oil, that were dissolved in MeOH (20 mL). A catalytic amount of *p*-toluensulphonic acid was added and the mixtures were stirred at r.t. for 1.5 days. The reaction mixtures were concentrated under vacuum and the remaining oils were purified by flash column chromatography, using CH_2Cl_2 as eluent, to provide **17a–d**.

Methyl 2-(2-Cinnamoylphenyl)acetate (17a)

Yield: 127 mg (50%); colourless oil.

IR (NaCl): 1735 (C=O), 1723 (C=O), 1662 (C=O), 1636 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.63 (s, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 7.20–7.50 (m, 7 H, Ar-H), 7.53–7.70 (m, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 38.9 (CH_3), 51.8 (OCH_3), 125.3 (CH), 126.96 (CH), 128.3 (2 × CH), 128.8 (2 × CH), 128.9 (CH), 130.5 (Ar-H), 131.0 (CH), 132 (CH), 133.7 (C), 134.4 (C), 138.44 (C), 145.7 (CH), 171.7 (C=O), 194.7 (C=O).

MS: *m*/*z* (%) = 280 (6) [M^+], 220 (100).

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.10; H, 5.83.

Methyl (*E*)-2-(2-(3-(3,4-dimethoxyphenyl)acryloyl)phenyl)acetate (17b)

Yield: 363 mg (95%); colourless oil.

IR (NaCl): 1734 (C=O); 1656 (C=O), 1632 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, CD_3OD): δ = 3.63 (s, 2.7 H, OCH_3), 3.65 (s, 2.7 H, OCH_3), 3.87–3.92 (m, 9.5 H, 2 × CH_2 +4 × OCH_3), 6.70–6.90 (m, 2.3 H, Ar-H), 7.00–7.19 (m, 3.5 H, Ar-H), 7.19–7.51 (m, 4.8 H, Ar-H), 7.53–7.69 (m, 1.9 H, Ar-H).

^{13}C NMR ($CDCl_3$, CD_3OD): δ = 38.8 (CH_3), 51.8 (OCH_3), 55.69 (OCH_3), 55.7 (OCH_3), 55.8 (OCH_3), 55.8 (OCH_3), 108.9 (CH), 109.7 (Ar-H), 110.9 (Ar-H), 111.0 (CH), 121.4 (CH), 123.2 (CH), 123.5 (CH), 124.7 (CH), 126.9 (CH), 127.4 (C), 127.8 (CH), 128.6 (CH), 128.9 (CH), 130.8 (CH), 131.9 (CH), 133.4 (C), 133.5 (C), 138.7 (C), 138.8 (C), 141.9 (CH), 146.0 (CH), 146.3 (CH), 149.0 (C), 149.1 (C), 150.2 (C), 151.3 (C), 171.7 (C=O), 194.8 (C=O), 194.9 (C=O).

MS: *m*/*z* (%) = 340 (22) [M^+], 281 (26), 164 (24), 151 (100).

Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.23; H, 6.17.

Methyl 2-(2-Cinnamoyl-4,5-dimethoxyphenyl)acetate (17c)

Yield: 184 mg (87%); colourless oil.

IR (NaCl): 1734 (C=O), 1655 (C=O).

^1H NMR ($CDCl_3$, CD_3OD): δ = 3.68 (s, 3 H, CH_3), 3.86 (s, 2 H, CH_2), 3.92 (s, 3 H, OCH_3); 3.95 (s, 3 H, OCH_3), 6.82 (s, 1 H, Ar-H), 7.21–7.31 (m, 2 H, Ar-H), 7.39–7.43 (m, 3 H, Ar-H), 7.57–7.67 (m, 3 H, Ar-H).

^{13}C NMR ($CDCl_3$, CD_3OD): δ = 39.1 (CH_3), 51.9 (OCH_3), 56.0 (OCH_3), 56.2 (OCH_3), 112.5 (CH), 114.8 (CH), 125.2 (CH), 128.4 (2 × CH), 128.9 (2 × Ar-H), 130.5 (Ar-H), 130.8 (C), 134.7 (C), 145.1 (Ar-H), 147.4 (Ar-OCH_3), 151.2 (Ar-OCH_3), 173.1 (C=O), 193.1 (C=O).

MS: *m*/*z* (%) = 340 (13) [M^+], 281 (100).

Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.72; H, 5.61.

Methyl (*E*)-2-(2-(3-(3,4-Dimethoxyphenyl)acryloyl)-4,5-dimethoxyphenyl)acetate (17d)

This product was not isolated; it was directly used in the next step.

Methyl 2-(2-(3-Phenylpropanoyl)phenyl)acetates 18; General Procedure

A Raney-nickel H_2O suspension (ca. 50% w/w) was added over degassed solutions of **17a**, **17b**, **17c** and **17d** (0.45 mmol) in EtOAc (20 mL) and the resulting suspensions were purged with hydrogen and stirred at 0 °C under hydrogen (1 atm) for 30 min, then at r.t. for a further 30 min. Hydrogen was then removed by purging with nitrogen and the metallic catalyst was filtered off over a Celite pad that was washed with EtOAc. The solvents were removed under vacuum, to afford the respective products **18a–d**, as chromatographically pure oils.

Methyl 2-(2-(3-Phenylpropanoyl)phenyl)acetate (18a)

Yield: 121 mg (93%); colourless oil.

IR (NaCl): 1735 (C=O), 1682 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.97–3.06 (m, 2 H, CH_2), 3.23–3.31 (m, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 3.92 (s, 2 H, CH_2), 7.15–7.38 (m, 7 H, Ar-H), 7.44 (dt, *J* = 1.15, 7.4 Hz, 1 H, Ar-H), 7.74 (dd, *J* = 1.4, 7.6 Hz, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 30.1 (CH_2), 39.9 (CH_2), 42.4 (CH_2), 51.8 (OCH_3), 126.0 (CH), 127.3 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 129.0 (CH), 131.7 (CH), 132.6 (CH), 134.1 (C), 137.2 (C), 141.1 (C), 171.9 (C=O), 202.5 (C=O).

MS: *m*/*z* (%) = 282 (100) [M^+].

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.71; H, 6.64.

Methyl 2-(2-(3-(3,4-Dimethoxyphenyl)propanoyl)phenyl)acetate (18b)

Yield: 328, mg (87%); colourless oil.

IR (NaCl): 1734 (C=O), 1684 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.97 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.25 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.48 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, CH_3), 3.91 (s, 2 H, CH_2), 6.78 (s, 3 H, Ar-H), 7.25 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.30–7.49 (m, 2 H, Ar-H), 7.75 (d, *J* = 7.5 Hz, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 29.6 (CH_2), 39.7 (CH_2), 42.5 (CH_2), 51.7 (OCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 111.7 (CH), 111.6 (CH), 120.0 (CH), 127.2 (CH), 128.9 (Ar-H), 131.6 (CH), 132.5 (CH), 133.7 (C), 134.0 (C), 147.2 (Ar-OCH_3), 148.7 (Ar-OCH_3), 171.8 (C=O), 202.5 (C=O).

MS: *m*/*z* (%) = 342 (26) [M^+], 151 (100).

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.35; H, 6.63.

Methyl 2-(4,5-Dimethoxy-2-(3-phenylpropanoyl)phenyl)acetate (18c)

Yield: 225 mg (94%); colourless oil.

IR (NaCl): 1733 (C=O), 1672 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.98–3.07 (m, 2 H, CH_2), 3.19–3.27 (m, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.89 (s, 2 H, CH_2), 3.92 (s, 3 H, OCH_3), 6.72 (s, 1 H, Ar-H), 7.16–7.38 (m, 6 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 39.4 (CH_2), 40.1 (CH_2), 42.2 (CH_2), 51.8 (OCH_3), 55.9 (OCH_3), 56.1 (OCH_3), 112.6 (CH), 115.3 (CH), 126.1 (CH), 128.4 (2 × CH), 128.5 (2 × Ar-H), 128.9 (C), 129.1 (C), 141.3 (C), 147.3 (CH), 151.6 (Ar-OCH_3), 172.2 (C=O), 200.3 (C=O).

MS: *m*/*z* (%) = 342 (8) [M^+], 209 (100).

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.45; H, 6.41.

Methyl 2-(2-(3-(3,4-Dimethoxyphenyl)propanoyl)-4,5-dimethoxyphenyl)acetate (18d)

Yield: 89 mg (58%); colourless oil.

IR (NaCl): 1735 (C=O), 1671 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.97 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.22 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 3.80–3.97 (m, 14 H, 4 × OCH_3+CH_2), 6.70–6.90 (m, 4 H, Ar-H), 7.18–7.31 (m, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 30.0 (CH_3), 40.0 (CH_2), 42.4 (CH_2), 51.7 (OCH_3), 55.7 (OCH_3), 55.7 (OCH_3), 55.8 (OCH_3), 56.0 (OCH_3), 111.1 (CH), 111.7 (CH), 112.6 (CH), 115.2 (CH), 120.0 (CH), 128.9 (C), 129.0 (C), 133.8 (C), 147.2 (2 × Ar-OCH_3), 148.7 (Ar-OCH_3), 151.5 (Ar-OCH_3), 172.0 (C=O), 200.3 (C=O).

MS: *m*/*z* (%) = 402 (63) [M^+], 209 (73), 151 (100).

Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.65; H, 6.66.

2-Benzyl-3-hydroxy-1,4-naphthalene-1,4-diones 20; General Procedure

t-BuOK (257 mg, 2.10 mmol) was added to stirred solutions of **18a**, **18b**, **18c** and **18d** (0.42 mmol) in anhydrous *t*-BuOH (5 mL) at 0 °C. The resulting mixtures were heated at reflux for 1.5 h, then cooled and poured into 10% aqueous HCl (10 mL). The new mixtures were extracted with $CHCl_3$ (3 × 15 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, and concentrated to dryness under vacuum. The residues were purified by column chromatography (1:3, EtOAc/hexane), to afford compounds **20a**, **20b**, **20c** and **20d**, respectively.

2-Benzyl-3-hydroxynaphthalene-1,4-dione (20a)

Yield: 65, mg (57%); orange solid; mp 148–150 °C (MeOH/Et_2O).

IR (NaCl): 3334 (OH), 1655 (C=O), 1640 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.94 (s, 2 H, CH_2), 7.13–7.28 (m, 3 H, Ar-H), 7.37–7.41 (m, 2 H, Ar-H), 7.46 (s, 1 H, OH), 7.61–7.16 (m, 2 H, Ar-H), 8.03–8.12 (m, 2 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 29.1 (CH_2), 123.0 (C), 126.1 (CH), 126.3 (CH), 126.9 (CH), 128.4 (2 × Ar-H), 129.2 (2 × CH), 129.3 (C), 132.7 (C), 132.9 (CH), 134.9 (Ar-H), 138.9 (C), 153.0 (CH), 181.6 (C=O), 184.3 (C=O).

MS: *m*/*z* (%) = 264 (100) [M^+].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}O_3$: 265.0859; found: 265.0843.

2-(3,4-Dimethoxybenzyl)-3-hydroxynaphthalene-1,4-dione (20b)

Yield: 56 mg (72%); red solid; mp 160–162 °C (MeOH).

IR (NaCl): 3355 (OH), 1659 (C=O), 1638 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.88 (s, 2 H, CH_2), 6.75 (d, *J* = 8 Hz, 1 H, Ar-H), 6.92–6.96 (m, 2 H, Ar-H), 7.47 (s, 1 H, Ar-H), 7.63–7.77 (m, 2 H, Ar-H), 8.04–8.13 (m, 2 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.6 (CH_2), 55.8 (2 × OCH_3), 111.8 (CH), 112.6 (CH), 121.1 (CH), 123.2 (C), 126.1 (CH), 126.9 (CH), 129.3 (C), 131.3 (C), 132.7 (C), 132.9 (CH), 134.9 (CH), 147.5 (C), 148.7 (C), 152.8 (C), 181.7 (C=O), 184.5 (C=O).

MS: *m*/*z* (%) = 324 (94) [M^+], 293 (100), 138 (53).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}O_5$: 325.1071; found: 325.1089.

2-Benzyl-3-hydroxy-6,7-dimethoxynaphthalene-1,4-dione (20c)

Yield: 63 mg (54%); red solid; mp 148 °C (decomp).

IR (NaCl): 3341 (OH), 1638 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.90 (s, 2 H, CH_2), 3.98 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH3), 7.12–7.31 (m, 4 H, 4 × Ar-H), 7.35–7.41 (m, 2 H, Ar-H+OH), 7.45 (s, 1 H, Ar-H), 7.54 (s, 1 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 29.0 (CH_2), 55.5 (OCH_3), 56.5 (OCH_3), 107.6 (CH), 108.7 (CH), 121.7 (C), 123.4 (C), 126.2 (CH), 128.0 (C), 128.4 (2 × CH), 129.1 (2 × CH), 139.1 (C), 152.5 (C), 152.8 (C), 154.4 (C), 180.9 (C=O), 184.2 (C=O).

MS: *m*/*z* (%) = 324 (100) [M^+].

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}O_5$: 325.1071; found: 325.1058.

2-(3,4-Dimethoxybenzyl)-3-hydroxy-6,7-dimethoxynaphthalene-1,4-dione (20d)

Yield: 43 mg (39%); red solid; mp 180 °C (MeOH).

IR (NaCl): 3312 (OH), 1652 (C=O), 1646 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 3.84 (s, 2 H, CH_2), 3.86 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 6.76 (d, *J* = 8.1 Hz, 1 H, Ar-H), 6.90–6.98 (m, 2 H, Ar-H), 6.46 (s, 1 H, Ar-H), 7.55 (m, 2 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.5 (CH_2), 55.8 (2 × OCH_3), 56.4 (OCH_3), 56.5 (OCH_3), 107.5 (CH), 108.7 (CH), 111.0 (CH), 112.5 (CH), 121.0 (CH), 121.9 (C), 123.4 (C), 127.9 (C), 132.6 (C), 147.4 (C), 148.7 (C), 152.5 (C), 152.6 (C), 154.4 (C), 180.1 (C=O), 184.2 (C=O).

MS: *m*/*z* (%) = 384 (55) [M^+], 353 (46), 138 (100).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{21}O_7$: 385.1282; found: 385.1276.

Funding Information

This work has received financial support from the Xunta de Galicia (Centro singular de investigación de Galicia accreditation 2016–2019, ED431G/09; and Project GRC2014/040), the European Union (European Regional Development Fund-ERDF), FONDECYT (Research Grants 1161816 and 1141264) and Galchimia S.A.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591729.

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