Preparation of Substituted Hydroquinones and Benzofurans from 1,4-Quinone Monoketals

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Abstract: An easy procedure for the preparation of 2-substituted hydroquinones, by addition of organolithium or organomagnesium compounds to 1,4-quinone monoketals followed by acid-catalyzed dienone–phenol type rearrangement, is described. Transformation of the propargylated derivatives to benzofurans is also reported.

Key words: phenols, quinones, organometallic reagents, rearrangements, heterocycles

2-Substituted hydroquinones and benzoquinones are common subunits in biologically active secondary metabolites. Incorporation of this framework during the synthesis of natural products remains a challenging problem. In our studies toward the total synthesis of frondosin A and B (Figure 1),[1] we became interested in developing efficient procedures to introduce such aromatic moieties.

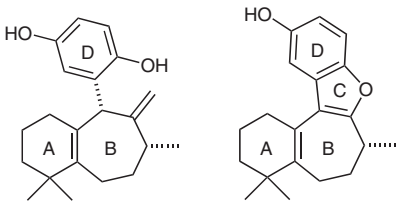

Figure 1 Two secondary metabolites with substituted hydroquinone (frondosin A) and benzofuran (frondosin B) moieties

Readily available 1,4-quinone monoketals are ideal as starting materials for the preparation of 2-substituted hydroquinones. Two approaches for this conversion are possible (Scheme 1): the 1,4-addition pathway leading, after acidic treatment, to a 4-alkoxy-3-alkylphenol (path 1) and the 1,2-addition process leading, after acid-catalyzed rearrangement of the *p*-quinol ketal intermediate, to a 4-alkoxy-2-alkylphenol (path 2).[2,3] The acid-catalyzed rearrangement of path 2 represents the ketal version of the known dienone–phenol rearrangement.[4] We report here the conversion of 1,4-quinone monoketals into 4-alkoxy-2-alkylphenols according to path 2. Furthermore, the preparation of 4-alkoxybenzofurans from quinone monoketals is also described.

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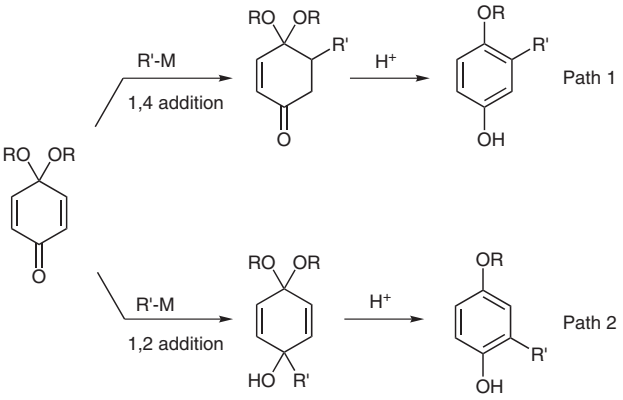


Scheme 1 Possible strategies for the transformation of 1,4-quinone monoketals into monosubstituted hydroquinones

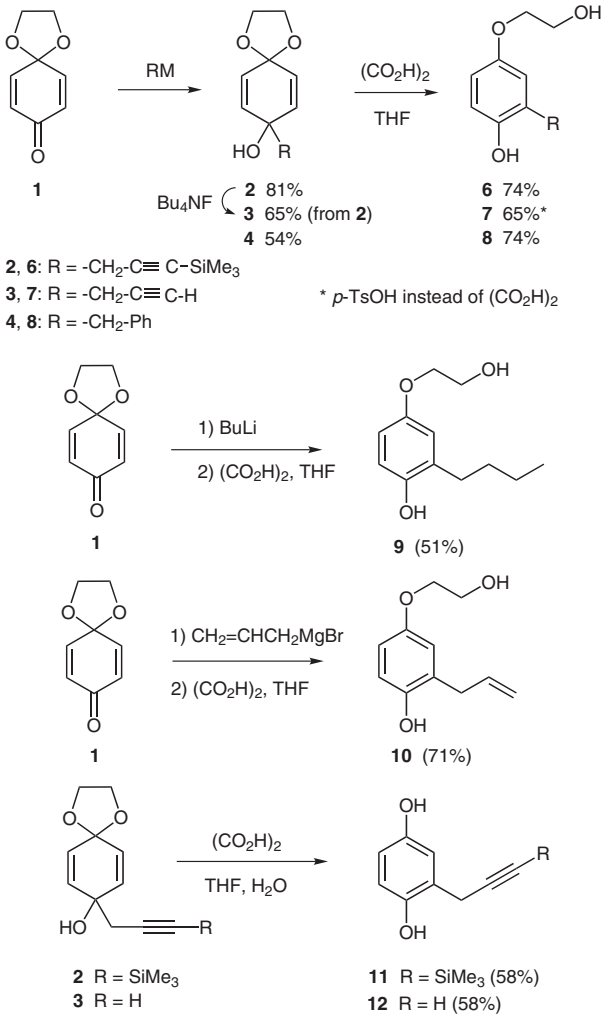
Commercially available 1,4-quinone monoketal **1** was selected for our initial study (Scheme 2).[5] 1,2-Addition of organometallics to **1** gave the corresponding *p*-quinol ketal. For instance, addition of lithiated 1-(trimethylsilyl)prop-1-yne afforded derivative **2** in 81% yield (Scheme 2). Desilylation of **2** with tetrabutylammonium fluoride gave the terminal alkyne **3** in 65% yield. On the other hand, addition of benzyllithium to **1** led to *p*-quinol ketal **4** in 54% yield. Attempts to run this reaction with commercially available benzylmagnesium chloride afforded the dienol **4** together with the 1,4-addition product.

Different acidic conditions were then tested for the *p*-quinol ketal–phenol rearrangement. The best results were obtained with protic organic acids such as oxalic acid and *p*-toluenesulfonic acid (Scheme 2). Treatment of **2** with a catalytic amount of oxalic acid (10 mol%) in refluxing tetrahydrofuran afforded the rearranged mono-O-alkylated 1,4-hydroquinone **6** in 74% yield. Terminal alkyne **3** did not react under similar conditions and required the use of *p*-toluenesulfonic acid (10 mol%) to deliver the rearranged product **7** in 65% yield. Finally, the benzylated derivative **4** afforded product **8** upon treatment with oxalic acid in 74% yield.

In several cases, better overall yields were obtained when the unstable dienol intermediates were not isolated. Thus, the crude product of the addition of butyllithium to monoprotected quinone **1** was directly treated with oxalic acid to afford the 2-butylhydroquinone **9** in 51% yield (Scheme 2). A similar result was obtained from **1** and al-

lylmagnesium bromide, leading to **10** in 71% yield over two steps (Scheme 2).

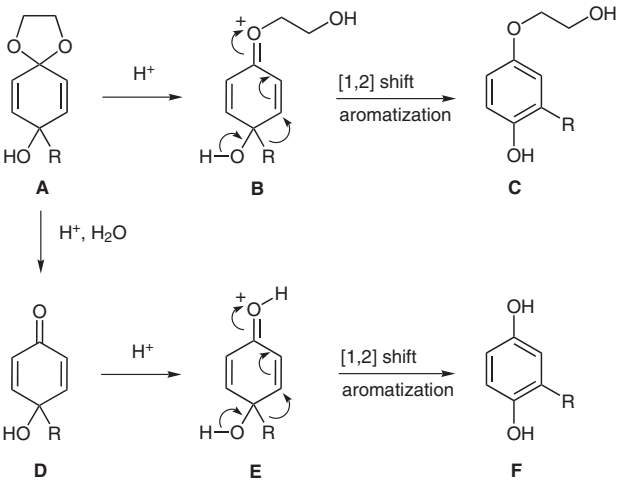
2-Hydroxyethyl ethers such as **6–10** have been reported to be converted into the free phenol via formation of the corresponding iodide followed by reduction with zinc powder.[6] However, a more direct approach to the nonprotected hydroquinones was developed. Indeed, the rearrangement of **2** and **3** catalyzed by oxalic acid in the presence of water delivered the unprotected 2-propargylhydroquinones **11** and **12** in 58% yield (Scheme 2).



Scheme 2 Preparation of monosubstituted hydroquinones from 1,4-quinone monoketals

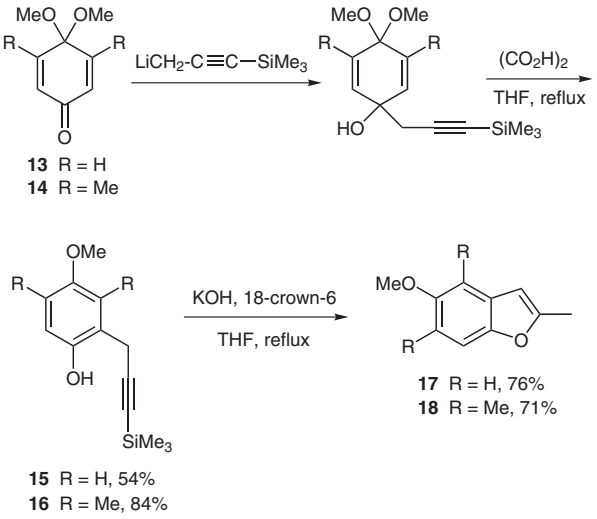
The assumed mechanism of the rearrangement is depicted in Scheme 3. Acid-catalyzed opening of the acetal function in the starting *p*-quinol monoketal **A** affords the oxonium ion **B** that gives, after 1,2-substituent shift and aromatization, the corresponding monoprotected 2-substituted-hydroquinone derivative **C**. In the presence of water, the acetal group in **A** is first hydrolyzed to *p*-quinol **D**, and under acidic conditions the protonated *p*-quinol **E** rearranges to give the 2-substituted hydroquinone **F**.

Finally, we applied this 1,2-rearrangement to the synthesis of 5-methoxybenzofurans (Scheme 4).[7] 1,2-Addition



Scheme 3 Assumed reaction mechanism for the conversion of *p*-quinol monoketals into monosubstituted hydroquinones

of lithiated 1-(trimethylsilyl)prop-1-yne to the quinone monoketals **13** and **14**[8] yielded tertiary dienols that were used without purification for the rearrangement. Treatment of the crude alcohols with oxalic acid (0.1 equiv) in refluxing tetrahydrofuran afforded **15** and **16** in 54 and 84% yield, respectively. Treatment of these two phenols with potassium hydroxide in the presence of 18-crown-6 gave benzofurans **17** and **18** in 76 and 71% yield, respectively.



Scheme 4 Preparation of 5-methoxybenzofurans from 1,4-quinone monoketals

In conclusion, we have demonstrated that addition of organolithium and organomagnesium reagents to quinone monoketals, followed by the acid-catalyzed acetal version of the dienone–phenol rearrangement represents an attractive procedure for the preparation of 2-subsituted 4-alkoxyphenol and 2-substituted hydroquinones. By using a propargylation process, straightforward access to 4-alkoxybenzofurans was developed. Application of these procedures to the preparation of frondosins is currently being investigated.

THF and CH_2Cl_2 were dried and purified over activated alumina columns prior to use. Other reagents were obtained from commercial sources and used as received. Flash chromatography was carried out over silica gel (0.063–0.200 mm); EtOAc, hexanes, MTBE, and cyclohexane were used as eluents. TLC detection was either with UV, vanillin, or $KMnO_4$ and subsequent heating. FT-IR spectra were obtained on a Mattson Unicam 5000 spectrometer. NMR spectra were obtained on Bruker AM (^{1}H, 300 MHz; ^{13}C, 75.5 MHz) and Bruker AM (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) spectrometers; the chemical shifts are expressed in ppm relative to TMS ($\delta = 0$) or $CHCl_3$ ($\delta = 7.26$) for ^{1}H and $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C NMR. MS was carried out on Vacuum Generators Micromass VG 70/70E and DS 11-250 spectrometers [CI (CH_4), EI (70 eV)]. HRMS determinations were recorded on a FTICR mass spectrometer, Bruker 4.7 BioApex II.

8-[3-(Trimethylsilyl)prop-2-ynyl]-1,4-dioxaspiro[4.5]deca-6,9-dien-8-ol (2)

A 1.4 M soln of *n*-BuLi in hexanes (4.7 mL, 6.57 mmol) was added dropwise to a soln of 1-(trimethylsilyl)prop-1-yne (0.97 mL, 6.57 mmol) in THF (200 mL) cooled to –78 °C. The mixture was stirred for 1.5 h at –78 °C, after which a soln of **1** (1.00 g, 6.57 mmol) in THF (10 mL) was added via cannula. After stirring overnight at r.t., the mixture was treated with aq sat. NH_4Cl (150 mL). The soln was extracted with MTBE (3 × 200 mL), dried ($MgSO_4$), and concentrated in vacuo; this afforded a crude yellow oil that was purified by flash chromatography (silica gel, cyclohexane–MTBE, 2:1).

Yield: 1.40 g (81%); white solid; mp 85–87 °C.

IR (KBr): 3472, 2958, 2891, 2178, 1672, 1616, 1509, 1440, 1417, 1249, 1204, 1116, 1026, 963, 843, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.11$ (d, $J = 12.5$ Hz, 2 H, CH), 5.80 (d, $J = 12.5$ Hz, 2 H, CH), 4.03 (s, 4 H, OCH_2CH_2O), 2.52 (s, 2 H, CCH_2C), 2.32 (br s, 1 H, OH), 0.15 (s, 9 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 135.2, 127.6, 101.0, 99.0, 88.7, 66.3, 65.3, 65.0, 33.1, 0.0$.

HRMS (CI): *m*/*z* calcd for $C_{14}H_{20}O_3Si$: 264.11817 [M$^+$ + 1]; found: 264.11819.

4-(2-Hydroxyethoxy)-2-[3-(trimethylsilyl)prop-2-ynyl]phenol (6)

Compound **2** (151 mg, 0.57 mmol) was stirred for 4 h at reflux in THF (5 mL) in the presence of a catalytic amount of oxalic acid (12 mg, 0.011 mmol). An aq sat. soln of $NaHCO_3$ was added until pH 7 was reached, and H_2O (10 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, cyclohexane–MTBE, 3:1).

Yield: 111 mg (74%); yellow oil.

IR (film): 3382, 2959, 2248, 2175, 1610, 1508, 1440, 1250, 1206, 1075, 1028, 910, 845, 734 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.89$ (d, $J = 2.9$ Hz, 1 H, C*H*CCH_2), 6.71 (d, $J = 8.8$ Hz, 1 H, COHC*H*CHCOHCC), 6.60 (dd, $J^1 = 8.8$ Hz, $J^2 = 2.9$ Hz, 1 H, COHCHC*H*COHCC), 6.52 (br s, 1 H, OH), 4.08–3.91 (m, 4 H, CH_2CH_2), 3.54 (s, 2 H, $CCCH_2$), 3.02 (br s, 1 H, CH_2OH), 0.19 (s, 9 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 151.2, 147.0, 122.5, 115.2, 114.5, 112.9, 102.5, 86.9, 68.6, 60.4, 20.2, –1.1$.

MS (EI, 70 eV): *m*/*z* (%) = 264 (39), 249 (31), 221 (37), 177 (42), 84 (100), 47 (25).

HRMS (CI): *m*/*z* calcd for $C_{14}H_{20}O_3Si$: 264.11817 [M$^+$ + 1]; found: 264.11819.

2-[3-(Trimethylsilyl)prop-2-ynyl]benzene-1,4-diol (11)

A soln of **2** (188 mg, 0.71mmol) in THF (5 mL) and H_2O (2 mL) was refluxed for 5 h in the presence of oxalic acid (7 mg, 0.07 mmol). The mixture was treated with aq sat. $NaHCO_3$ to reach pH 7. H_2O (10 mL) was added, the layers were separated, and the aqueous layer was extracted with MTBE (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexanes–EtOAc, 1:1).

Yield: 91 mg (58%); white solid; mp 106–107 °C.

IR (KBr): 3430, 3560, 3040, 2960, 2890, 2190, 1624, 1610, 1520, 1450, 1370, 1250, 1225, 1200, 1030, 850, 800 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.72$ (d, $J = 2.8$ Hz, 1 H, COHC*H*-CC), 6.70 (d, $J = 8.5$ Hz, 1 H, COHCHC*H*COHCC), 6.62 (dd, $J^1 = 8.5$ Hz, $J^2 = 3.0$ Hz, 1 H, COHCHC*H*COHCC), 5.41 (s, 1 H, OH), 4.82 (s, 1 H, OH), 3.56 (s, 2 H, CH_2), 0.19 (s, 9 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 149.3, 147.8, 123.4, 117.0, 116.2, 114.7, 102.8, 88.6, 21.7, –0.1$.

MS (EI, 70 eV): *m*/*z* (%) = 220 (40) [M$^+$], 205 (50), 177 (100), 131 (19), 73 (60).

HRMS (CI): *m*/*z* calcd for $C_{12}H_{16}O_2Si$: 220.09195 [M$^+$ + 1]; found: 220.09193.

8-(Prop-2-ynyl)-1,4-dioxaspiro[4.5]deca-6,9-dien-8-ol (3)

A 2.4 M soln of *n*-BuLi in hexanes (4.6 mL, 0.011 mol) was added dropwise to a stirred soln of 1-(trimethylsilyl)prop-1-yne (1.52 mL, 10.3 mmol) in THF (100 mL) cooled to –78 °C. After the addition, the mixture was stirred for 1.5 h at this temperature. A soln of **1** (1.30 g, 8.54 mmol) in THF (100 mL) was added via cannula and the reaction mixture was stirred overnight at r.t. Sat. NH_4Cl (150 mL) was added and the soln was extracted with Et_2O (3 × 200 mL) and dried ($MgSO_4$). Concentration in vacuo afforded a yellow oil.

A 1 M soln of TBAF in THF (11 mL, 11 mmol) was added dropwise to the resulting crude product in THF (20 mL). After stirring for 2.5 h at r.t., the mixture was treated with an aq sat. NH_4Cl soln (100 mL), and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic phases were washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a crude yellow oil. Purification by flash chromatography (silica gel, hexanes–EtOAc, 5:1) gave **3** as a white solid.

Yield: 1.074 g (65%); mp 81–82 °C.

IR (KBr): 3468, 3277, 3037, 2935, 2894, 2361, 2334, 2116, 1674, 1623, 1507, 1446, 1412, 1201, 1115, 1010, 948, 792, 656 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.16$–6.11 (m, 2 H, C*H*CH), 5.88–5.82 (m, 2 H, CHC*H*), 4.05 (s, 4 H, CH_2CH_2), 2.50 (d, $J = 2.6$ Hz, 2 H, $CCCH_2$), 2.26 (br s, 1 H, OH), 2.11 (t, $J = 2.6$ Hz, 1 H, CC*H*).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 135.1, 127.6, 98.8, 79.0, 71.3, 66.3, 65.1, 65.0, 31.3$.

MS (EI, 70 eV): *m*/*z* (%) = 192 (11), 153 (100), 109 (65), 81 (65), 65 (50), 39 (45).

HRMS (CI): *m*/*z* calcd for $C_{11}H_{12}O_3$: 192.07864 [M$^+$ + 1]; found: 192.07855.

4-(2-Hydroxyethoxy)-2-(prop-2-ynyl)phenol (7)

Using the procedure described for **6**, starting from **3** (172 mg, 0.89 mmol) in CH_2Cl_2 (4 mL) and a catalytic amount of *p*-TsOH (15 mg, 0.089 mmol), product **17** was obtained as a beige solid.

Yield: 111 mg (65%); mp 86–88 °C.

IR (KBr): 3364, 3289, 3094, 2969, 2932, 2874, 2116, 1619, 1602, 1514, 1448, 1306, 1255, 1230, 1075, 1058, 898, 869, 817 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.11 (br s, 1 H, OH), 7.09 (d, J = 2.8 Hz, 1 H, COC*H*CCH$_2$), 6.80 (d, J = 8.5 Hz, 1 H, COC*H*CHCOH), 6.71 (dd, J^1 = 8.5 HZ, J^2 = 2.8 Hz, 1 H, COCHC*H*COH), 4.03–4.00 (m, 2 H, OCH$_2$), 3.89–3.85 (m, 2 H, OCH$_2$), 3.57–3.56 (m, 2 H, CCH$_2$C), 3.11 (s, 1 H, CH$_2$OH), 2.62 (t, J = 2.8 Hz, 1 H, CCH).

^{13}C NMR (75.5 MHz, acetone-d_6): δ = 152.9, 148.7, 124.0, 116.0, 115.5, 113.4, 81.9, 71.4, 70.5, 61.0, 19.0.

MS (EI, 70 eV): m/z (%) = 192 (26) [M$^+$], 147 (100), 91 (32).

HRMS (ESI-MS) calcd for $C_{11}H_{13}O_3$: 193.0873; found: 193.0864.

2-(Prop-2-ynyl)benzene-1,4-diol (12)

Using the procedure described for **11**, starting from **3** (80 mg, 0.42 mmol) in THF (4 mL), H$_2$O (1 mL), and a catalytic amount of oxalic acid (4 mg, 0.042 mmol), product **12** was obtained as a pale colorless oil.

Yield: 35 mg (58%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.91 (br s, 1 H, OH), 7.78 (br s, 1 H, OH), 7.01 (d, J = 2.9 Hz, 1 H, C*H*CCH$_2$), 6.71 (d, J = 8.5 Hz, 1 H, COHC*H*CHCOHCC), 6.59 (dd, J^1 = 8.8 Hz, J^2 = 2.9 Hz, 1 H, COHCHC*H*COHCC), 3.54 (d, J = 2.6 Hz, 2 H, CH_2), 2.60 (t, J = 2.6 Hz, 1 H, HCC).

^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 152.1, 148.9, 125.1, 117.2, 116.9, 115.4, 83.4, 72.5, 20.2.

MS (EI, 70 eV): m/z (%) = 147 (100), 91 (43), 65 (29).

8-Benzyl-1,4-dioxaspiro[4,5]deca-6,9-dien-8-ol (4)

A 1.4 M soln of *n*-BuLi in hexanes (3.7 mL, 5.19 mmol) was added rapidly to a soln of TMEDA (0.78 mL, 5.19 mmol) in toluene (7 mL) under a N$_2$ atmosphere. The resulting yellow soln was heated at 80 °C with stirring for 0.5 h. A soln of **1** (0.789 g, 5.19 mmol) in toluene (7 mL) was added via cannula to the reaction mixture cooled at 0 °C, and then the mixture was stirred overnight at r.t. H$_2$O (10 mL) was added and the soln was extracted with CH$_2$Cl$_2$ (3 × 20 mL). After concentration in vacuo, the crude beige solid was washed with Et$_2$O (3 × 100 mL).

Yield: 687 mg (54%); white solid; mp 143–145 °C.

IR (KBr): 3430, 3030, 2920, 2890, 2350, 1675, 1600, 1410, 1370, 1110, 1035, 960, 700 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.39–7.22 (m, 5 H, CH arom), 6.02 (d, 2 H, CH), 7.70 (d, 2 H, CH), 4.08 (s, 4 H, CH$_2$), 2.91 (s, 2 H, CCH$_2$C), 2.22 (br s, 1 H, OH).

^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 136.4, 135.8, 130.7, 128.0, 126.7, 126.6, 99.1, 67.5, 65.1, 47.1.

MS (EI, 70 eV): m/z (%) = 244 (30) [M$^+$], 153 (100), 109 (21), 91 (47), 81 (19), 65 (21).

HRMS (CI): m/z calcd for $C_{15}H_{16}O_3$: 244.10994 [M$^+$ + 1]; found: 244.11009.

2-Benzyl-4-(2-hydroxyethoxy)phenol (8)

Using the procedure described for **6**, starting from **4** (23 mg, 0.094 mmol) in THF (1 mL) and a catalytic amount of oxalic acid (1 mg, 0.009 mmol), product **8** was obtained as a yellow oil; yield: 17 mg (74%).

Compound **8** was also obtained as follows: A 20 wt% soln of BnMgCl in THF (10.5 mL, 0.014 mol) in THF (40 mL) was cooled to –78 °C, and a soln of **1** (1.90 g, 0.012 mol) in THF (10 mL) was added via cannula. After 6 h at –78 °C, the reaction mixture was treated with sat. aq NH$_4$Cl (100 mL) and extracted with Et$_2$O (3 × 15 mL). Concentration in vacuo afforded a yellow oil that was purified by flash chromatography (silica gel, hexanes–EtOAc, 4:1) giving **8**; yield: 1.11 g (40%). During this reaction, the product of 1,4-addition, 10-benzyl-1,4-dioxaspiro[4.5]dec-6-en-8-one was also obtained as a white solid; yield: 0.93 g (30%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.34–7.20 (m, 5 H, C*H*), 6.72 (d, J = 8.5 Hz, 1 H, CHC*H*COHC), 6.70 (s, 1 H, COC*H*CHC), 6.66 (dd, J^1 = 8.5 Hz, J^2 = 3 Hz, 1 H, CH_2CH_2), 5.16 (s, 1 H, OH), 4.12–3.88 (m, 6 H, OCH$_2$CH$_2$O and PhCH$_2$), 2.38 (br s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 152.6, 148.1, 139.8, 128.7, 128.6, 128.5, 126.3, 117.4, 116.3, 113.2, 69.7, 61.5, 36.4.

MS (EI, 70 eV): m/z (%) = 244 (100) [M$^+$], 200 (85), 181 (36), 122 (100), 115 (37), 94 (52), 91 (56), 65 (34).

HRMS (CI): m/z calcd for $C_{15}H_{16}O_3$: 244.10994 [M$^+$ + 1]; found: 244.10992.

10-Benzyl-1,4-dioxaspiro[4.5]dec-6-en-8-one

Mp 64–65 °C.

IR (KBr): 3030, 2973, 2898, 1678, 1492, 1456, 1380, 1286, 1228, 1150, 1081, 1011, 948, 916, 758, 709 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31–7.12 (m, 5 H, CH arom), 6.67 (d, J = 10 Hz, 1 H, CH), 6.0 (d, J = 10 Hz, 1 H, CH), 4.21 (m, 4 H, OCH$_2$), 3.15 (dd, J^1 = 13.3 Hz, J^2 = 3.2 Hz, 1 H, CC*H*CH$_2$), 2.66–2.38 (m, 4 H, COCH_2, CHCH_2).

^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 198.6, 146.3, 138.9, 129.8, 129.1, 128.5, 126.3, 105.7, 65.7, 65.3, 44.7, 39.6, 34.4.

MS (EI, 70 eV): m/z (%) = 244 (36) [M$^+$], 216 (20), 202 (21), 126 (100), 117 (26), 104 (27), 98 (82), 91 (77), 65 (36).

HRMS (CI): m/z calcd for $C_{15}H_{16}O_3$: 244.10994 [M$^+$ + 1]; found: 244.10994.

2-Allyl-4-(2-hydroxyethoxy)phenol (10)

A 1.0 M soln of allylmagnesium bromide in Et$_2$O (3.3 mL, 3.3 mmol) in THF (30 mL) was cooled to –78 °C and a soln of **1** (0.5 g, 3.3 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred overnight (–78 °C to r.t.). The reaction was treated with aq sat. NH$_4$Cl (150 mL) and the mixture was extracted with MTBE (3 × 200 mL) and dried (MgSO$_4$). After concentration in vacuo, THF (2 mL) and oxalic acid (34 mg, 0.33 mmol) were added to the resulting yellow oil and the soln was refluxed for 4.5 h. The mixture was treated with H$_2$O (25 mL) and extracted with Et$_2$O (3 × 25 mL) to afford, after drying (MgSO$_4$) and concentration, a crude yellow oil. Purification by flash chromatography (silica gel, cyclohexane–MTBE, 4:1–2:1) furnished **10** as a yellow oil.

Yield: 453 mg (71%).

IR (film): 3360, 3080, 2930, 2870, 2370, 1640, 1610, 1510, 1440, 1210, 1070, 1050, 910, 810 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.72–6.60 (m, 3 H, C*H*), 6.04–5.83 (m, 1 H, CH), 5.74 (br s, 1 H, OH), 5.14 (m, 2 H, CCH$_2$), 4.01–3.92 (m, 4 H, CH$_2$CH$_2$), 3.34 (d, 2 H, J = 8.5 Hz, CCH$_2$), 2.80 (br s, 1 H, OH).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 152.4, 150.0, 148.3, 136.1, 127.0, 116.7, 116.2, 113.3, 69.7, 61.4, 34.8.

MS (EI, 70 eV): m/z (%) = 194 (77) [M$^+$], 150 (100), 135 (40), 107 (27), 84 (42), 77 (24).

HRMS (CI): m/z calcd for $C_{11}H_{14}O_3$: 194.09429 [M$^+$ + 1]; found: 194.09421.

2-Butyl-4-(2-hydroxyethoxy)phenol (9)

A 1.4 M soln of *n*-BuLi in hexanes (3.3 mL, 4.6 mmol) in THF (30 mL) was cooled to –78 °C and a soln of **1** (0.70 g, 4.6 mmol) in THF (10 mL) was added dropwise. The mixture was stirred overnight (–78 °C to r.t.), then treated with aq sat. NH$_4$Cl (150 mL), and extracted with MTBE (3 × 200 mL). After the soln had been dried (MgSO$_4$), the solvents were evaporated in vacuo. THF (8 mL), fol-

lowed by oxalic acid (48 mg, 0.46 mmol), was added to the resulting yellow oil, and the soln was refluxed for 4.5 h. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 55 mL). Drying ($MgSO_4$) and concentration in vacuo afforded an orange oil that was purified by flash chromatography (silica gel, cyclohexane–MTBE, 4:1).

Yield: 492 mg (51%); white solid.

IR (KBr): 3321, 2956, 2928, 2863, 1706, 1612, 1595, 1506, 1443, 1277, 1264, 1208, 1190, 1074, 980, 812, 799 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.70 (d, *J* = 3 Hz, 1 H, COCHC*H*-COHC), 6.66 (d, *J* = 8.5 Hz, 1 H, COC*H*CHCOH), 6.57 (dd, J^1 = 8.5 Hz, J^2 = 3 Hz, 1 H, COCHCC), 5.56 (s, 1 H, COH), 4.02–3.94 (m, 4 H, OCH_2CH_2O), 2.67 (br s, 1 H, OH), 2.56 (t, *J* = 7.5 Hz, 2 H, CCH_2CH_2), 1.61–1.53 (m, 2 H, $CH_2CH_2CH_2$), 1.37 (sept, *J* = 7.3 Hz, 2 H, CH_3CH_2), 0.93 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.3, 148.0, 130.2, 116.7, 115.7, 112.4, 69.8, 61.5, 31.8, 29.8, 22.5, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 210 (48) [M^+], 166 (57), 123 (100).

ESI-HRMS: *m*/*z* calcd for $C_{12}H_{19}O_3$: 211.1344; found: 211.1334.

4-Methoxy-2-[3-(trimethylsilyl)prop-2-ynyl]phenol (15)

A 2.4 M soln of *n*-BuLi in hexanes (2.8 mL, 6.8 mmol) was added dropwise at –78 °C to a soln of 1-(trimethylsilyl)prop-1-yne (0.92 mL, 6.2 mmol) in THF (80 mL). The mixture was stirred for 1 h at –78 °C and a soln of **13** (871 mg, 5.6 mmol) in THF (20 mL) was added via cannula. The reaction mixture was stirred overnight (–78 °C to r.t.) and treated with an aq sat. NH_4Cl soln (100 mL). The soln was extracted with Et_2O (3 × 200 mL) and dried ($MgSO_4$). Concentration in vacuo afforded a crude yellow oil. THF (20 mL) and oxalic acid (57 mg, 0.55 mmol) were added to this oil and the soln was refluxed for 3.5 h. The reaction mixture was treated with H_2O (10 mL) and extracted with MTBE (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 4:1) afforded **15** as a colorless oil.

Yield: 710 mg (54%).

IR (film): 3410, 2958, 2833, 2176, 1669, 1609, 1507, 1465, 1449, 1433, 1348, 1250, 1202, 1151, 1041, 935, 844, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 2.9 Hz, 1 H, COMeC*H*CCH$_2$), 6.75 (d, *J* = 8.6 Hz, 1 H, COMeCHC*H*COH), 6.69 (dd, J^1 = 8.6 Hz, J^2 = 2.9 Hz, 1 H, COMeC*H*CHCOH), 5.37 (br s, 1 H, OH), 3.77 (s, 3 H, CH_3), 3.60 (s, 2 H, CH_2), 0.19 (s, 9 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.7, 146.8, 122.2, 115.8, 113.8, 112.3, 101.9, 87.6, 54.7, 20.9, –1.1.

MS (EI, 70 eV): *m*/*z* (%) = 234 (95) [M^+], 219 (93), 191 (96), 161 (60), 145 (91), 115 (46), 73 (100).

HRMS (CI): *m*/*z* calcd for $C_{13}H_{18}O_2Si$: 234.10760 [M^+ + 1]; found: 234.10768.

5-Methoxy-2-methylbenzofuran (17)

Compound **15** (180 mg, 0.77 mmol) in THF was stirred under reflux (3 mL) with KOH (81 mg, 1.4 mmol) and 18-crown-6 (81 mg, 0.31 mmol) for 2.5 h. Sat. aq NH_4Cl (5 mL) was added to the reaction mixture and the soln was extracted with Et_2O. The combined organic phases were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude oil by flash chromatography (silica gel, hexanes–EtOAc, 60:1) gave **17** as a yellow oil.

Yield: 95 mg (76%).

IR (film): 2996, 2952, 2832, 1688, 1617, 1478, 1450, 1308, 1264, 1205, 1185, 1165, 1032, 932, 834, 791 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.8 Hz, 1 H, CHC*H*-CO), 6.97 (d, *J* = 2.4 Hz, 1 H, COMeC*H*CC), 6.83 (dd, J^1 = 8.8 Hz, J^2 = 2.4 Hz, 1 H, COMeC*H*CHCO), 6.33 (s, 1 H, CC*H*C), 3.84 (s, 3 H, OCH_3), 2.46 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.2, 154.7, 148.7, 128.7, 110.2, 109.9, 102.0, 101.7, 54.8, 13.0.

MS (EI, 70 eV): *m*/*z* (%) = 162 (100) [M^+], 147 (84), 119 (52), 91 (26).

HRMS (CI): *m*/*z* calcd for $C_{10}H_{10}O_2$: 162.06808 [M^+ + 1]; found: 162.06807.

4-Methoxy-3,5-dimethyl-2-[3-(trimethylsilyl)prop-2-ynyl]phenol (16)

A 1.4 M soln of *n*-BuLi in hexanes (1.95 mL, 2.7 mmol) was added dropwise at –78 °C to a soln of 1-(trimethylsilyl)prop-1-yne (0.41 mL, 2.7 mmol) in THF (50 mL). The mixture was stirred for 1.5 h at –78 °C and a soln of **14** (0.50 g, 2.7 mmol) in THF (10 mL) was added via cannula; stirring continued overnight (–78 °C to r.t.). The reaction mixture was treated with aq sat. NH_4Cl (100 mL) and extracted with Et_2O (3 × 200 mL). The organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil. THF (20 mL) was added to the crude oil followed by oxalic acid (57 mg, 0.55 mmol) and the soln was refluxed for 3.5 h. H_2O (10 mL) was added and the soln was extracted with MTBE (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, cyclohexane–MTBE, 4:1).

Yield: 607 mg (84%); beige solid; mp 126–127 °C.

IR ($CDCl_3$): 3600, 3446, 2960, 2250, 2170, 1615, 1476, 1450, 1410, 1250, 1230, 1170, 1015 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.54 (s, 1 H, CH), 5.56 (br s, 1 H, OH), 3.65 (s, 3 H, OCH_3), 3.57 (s, 2 H, CH_2), 2.27 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 0.15 (s, 9 H, $SiCH_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.8, 150.0, 130.3, 130.0, 119.7, 116.0, 103.3, 86.6, 60.2, 18.0, 16.0, 12.5, –0.1.

MS (EI, 70 eV): *m*/*z* (%) = 262 (70) [M^+], 247 (75), 219 (60), 189 (70), 173 (35), 116 (32), 73 (100).

HRMS (CI): *m*/*z* calcd for $C_{15}H_{22}O_2Si$: 262.13890 [M^+ + 1]; found: 262.13892.

5-Methoxy-2,4,6-trimethylbenzofuran (18)

Using the procedure described for **17**, starting from **16** (212 mg, 0.81 mmol), KOH (91 mg, 1.6 mmol), and 18-crown-6 (85 mg, 0.32 mmol) in THF (4 mL), product **18** was obtained as a yellow oil.

Yield: 129 mg (84%).

IR (film): 2921, 2827, 1610, 1588, 1449, 1406, 1292, 1222, 1196, 1163, 1102, 1054, 1006, 933, 844, 790 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.07 (s, 1 H, CH arom), 6.32 (t, *J* = 1.3 Hz, 1 H, CH), 3.75 (s, 3 H, OCH_3), 2.44 (s, 3 H, CH_3COC), 2.41 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 152.2, 150.8, 128.0, 126.4, 121.4, 109.6, 101.5, 60.2, 16.7, 14.0, 12.5.

MS (EI, 70 eV): *m*/*z* (%) = 190 (70) [M^+], 175 (100), 119 (15).

HRMS (CI): *m*/*z* calcd for $C_{12}H_{14}O_2$: 190.09938 [M^+ + 1]; found: 190.09943.

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