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Synthesis of Magnaldehydes B and E and Dictyobiphenyl B by Microwave-Promoted Cross-Coupling of Boronophenols

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Magnaldehydes B and E along with their 4′-methylated derivatives are naturally occurring 2,4′-biphenols that have been isolated from the Magnoliaceae. Herein, these natural products have been synthesized from a common intermediate, which was obtained by a microwave-promoted, heterogeneously catalyzed, and protecting-group-free Suzuki–Miyaura coupling reaction in an aqueous medium. These reaction conditions were also successfully applied to a one-step synthesis of the slime mold metabolite dictyobiphenyl B.

Introduction

The isolation and structural elucidation of secondary metabolites from plants that are used in Chinese folk medicine continue to attract the interest of the scientific community. For example, *Magnolia officinalis* (Magnoliaceae) has been traditionally used for the treatment of various disorders, such as gastric distension,[1] inflammation,[2,3] and clinical depression.[4] From the bark of this plant, the neolignans magnolol and honokiol[5] have been isolated in quantities that account for 1.5% of the original mass of material, which makes them the most abundant low molecular weight constituents present in *Magnolia officinalis* (Figure 1).[1] Interestingly, some of the pharmacological activities reported for preparations that contain Magnoliaceae, which include anxiolytic activity,[4] anti-inflammatory activity,[2,3] or activity against gastrointestinal disorders,[6] can be directly correlated to the presence of magnolol and/or honokiol, Even more interesting, however, is the discovery that magnolol and honokiol demonstrate activity against different tumor cell lines,[7,8] for example, colon and liver cancer cells,[9] by inducing apoptosis[9,10] and inhibiting angiogenesis.[10] It has also been shown that magnolol can suppress metastasis by down-regulating certain matrix metalloproteinases.[11] In light of these interesting biological activities, it is not surprising that several syntheses of both magnolol[12–14] and honokiol[15–21] have been published. In addition, with a view towards the elucidation of structure–activity relationships and the discovery of derivatives with improved bioactivity, numerous non-natural analogues have been synthesized[22] and evaluated for antimicrobial activities,[7,23,24] cytotoxicity,[25–27] anti-inflammatory activity,[28] and neuroprotective or neurotrophic activity.[29–32] Although a wealth of information concerning the bioactivity and chemistry of magnolol and honokiol is available, considerably less attention has been paid to those secondary metabolites that are present in the Magnoliaceae but only in minor quantities. For example, *M. officinalis* contains several biphenols with partially oxidized one- or three-carbon side chains as well as monomethylated derivatives. The bioactivities of these compounds, named magnaldehydes,[1] have been underexplored. We are, for example, aware of only two in vitro studies of the activity of magnaldehydes B and E against selected cancer cell lines.[33,34] In addition, one study documents the inhibition of lung tumor growth in vivo by using magnaldehyde B (Figure 1).[35]

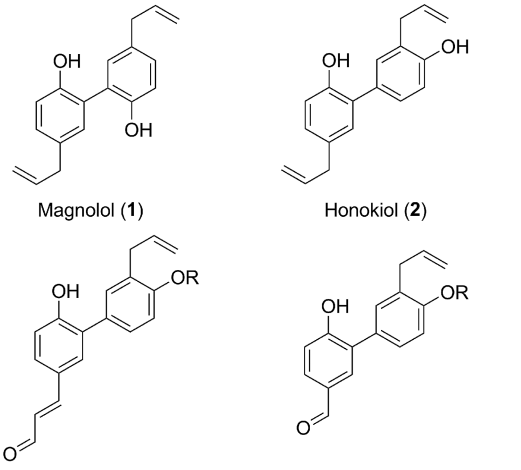

Figure 1. Structures of magnolol, honokiol, and magnaldehydes B and E along with their monomethyl ethers.

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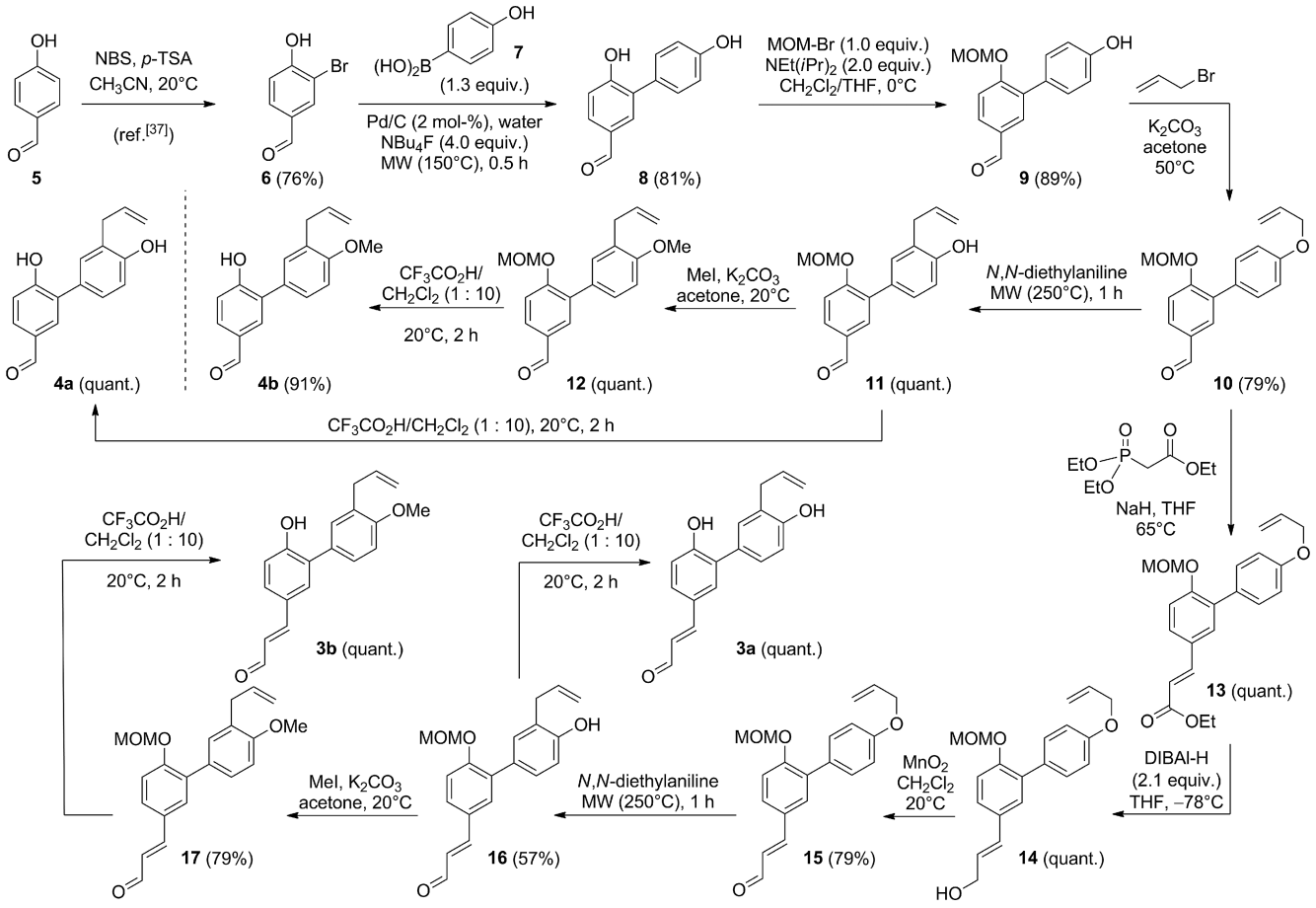
We thought that the small quantities of magnaldehydes available from natural sources as well as laborious isolation and purification procedures would impede further biological evaluation. Therefore, the chemical synthesis of the magnaldehydes would be useful to provide material for bioactivity tests and structure validation. To the best of our knowledge, only magnaldehyde B has previously been synthesized. Takeya et al. used the addition of a 4-allyloxyphenyl Grignard reagent to a spirocyclohexadienone as the key step for biphenol formation. From there, magnaldehyde B was obtained in four steps.[36]

Previously, we discovered that all of the regioisomeric biphenols can be synthesized by protecting-group-free Suzuki–Miyaura coupling reactions of boronophenols and halophenols with water as the solvent and commercial Pd/C as the precatalyst.[37,38] However, the success of the cross-coupling reactions crucially depends on the appropriate choice of additive and heating conditions to produce the desired positional isomer. On the basis of these experiences, we investigated the syntheses of magnaldehydes B (**3a**) and E (**4a**) along with their 4′-methyl ethers **3b** and **4b**, respectively, by employing a common intermediate.

Results and Discussion

By starting from commercially available *p*-hydroxybenzaldehyde (**5**), we prepared monobrominated product **6** by following our previously published procedure (Scheme 1).[37] In the next step, the *o*,*p*′-biphenol moiety was constructed by a Suzuki–Miyaura coupling reaction. These cross-coupling reactions generally require base, which is believed to accelerate the transmetalation step by enhancing the nucleophilicity of the boronic acid through the formation of the corresponding boronate (boronate mechanism) or the substitution of a Pd-bonded halide by an alkoxide or hydroxide (oxo-Pd mechanism).[39] We found that bases such as NaOH or K_2CO_3 that are typically used in Suzuki–Miyaura reactions give very low yields when combined with *p*-boronophenols such as **7**, and this might be attributed to the deprotonation of the phenol under these reaction conditions. However, we also observed significantly improved yields by combining these boronophenols with fluorides as additives.[38] Fluorides are believed to coordinate to the Pd, increase the nucleophilicity of the solvent, that is, water, through hydrogen bonding, and thereby



Scheme 1. Divergent synthesis of magnaldehydes B (**3a**) and E (**4a**) along with their 4′-monomethyl ethers **3b** and **4b**, respectively (NBS = *N*-bromosuccinimide, *p*-TSA = *para*-toluenesulfonic acid, MW = microwave, MOM = methoxymethyl, THF = tetrahydrofuran, DIBAL-H = diisobutylaluminum hydride).

facilitate the formation of the crucial Pd-hydroxy intermediates[40–42] without extensive deprotonation of the boronophenol. For these reasons, the Suzuki–Miyaura coupling of **6** and **7** was performed in the presence of NBu_4F. Upon microwave irradiation[43] in the presence of Pd/C as a catalyst and in an aqueous medium, the desired 4′,6-biphenol-3-carbaldehyde (**8**) was obtained within a short reaction time in high yield.

The 4′-hydroxy group was ultimately needed for the installation of the allyl group at the 3′-position through an *O*-allylation followed by a Claisen rearrangement. As attempts for the selective 4′-*O*-allylation failed, a protecting group detour was required. Although the hydroxy group at the 2-position is sterically more congested, we reasoned that it should be more acidic as a result of the electron-withdrawing effect of the carbonyl group at the *para* position. By using 1.0 equiv. of MOMBr in the presence of Hünig's base, we could indeed achieve the regioselective monoprotection and furnish **9** in 89% yield. Subsequent *O*-allylation under standard conditions gave **10**, which is the key intermediate and represents the branching point in our synthesis for the four natural products **3a**, **3b**, **4a**, and **4b**. The confirmation of the structure of **10** was accomplished by 2D NOE spectroscopy. Strong NOEs between the methylene protons of the allyl group and the protons at the 3′-position (NOE-1) and between the methylene protons of the MOM group and the proton at the 5-position (NOE-2) indicate that the protecting group and allyl substituent are indeed located in the correct positions (Figure 2).

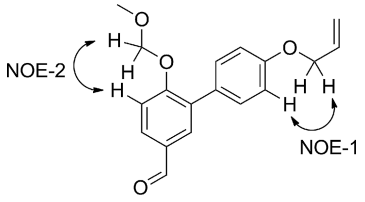
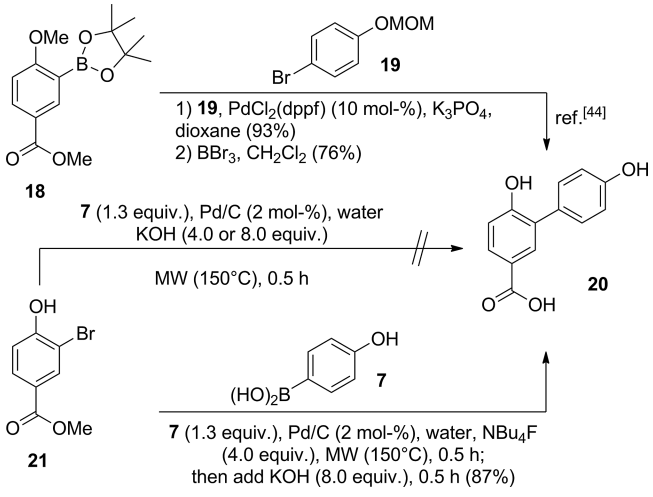


Figure 2. Structure validation of **10** through 2D NOE spectroscopy.

From allyl ether **10**, we continued towards the synthesis of magnaldehyde E (**4a**) and its 4′-methyl ether **4b** by conducting a microwave-promoted Claisen rearrangement to install the 3′-allyl chain and obtain MOM-protected magnaldehyde E (**11**) quantitatively. Cleavage of the MOM ether required some optimization. Although treatment with methanol/HCl resulted in decomposition, no conversion was observed when **11** was exposed to a 100:1 mixture of dichloromethane and CF_3CO_2H. Quantitative deprotection to give magnaldehyde E (**4a**) was eventually achieved by increasing the amount of CF_3CO_2H in the mixture to 10 vol-%. From **11**, 4′-methoxymagnaldehyde E (**4b**) was synthesized by *O*-methylation and cleavage of the MOM ether by using the conditions previously applied to **11**.

For the synthesis of magnaldehyde B (**3a**) and its methyl ether **3b**, elongation of the side chain at the 3-position was required. This was achieved by submitting aldehyde **10** to a Horner–Wadsworth–Emmons olefination followed by the reduction of resulting enoate **13** to afford allyl alcohol **14**, which was then oxidized by treatment with MnO_2 to give enal **15**. In the next step, the Claisen rearrangement was performed under the same conditions as those for the preparation of magnaldehyde E to furnish MOM-protected magnaldehyde B (**16**) in 57% yield. Compound **16** was deprotected by using a 10:1 mixture of CH_2Cl_2/CF_3CO_2H, as described above for **12**, to yield magnaldehyde B (**3a**) quantitatively. The 4′-methyl ether **3b** was synthesized from **16** through *O*-methylation followed by cleavage of the MOM ether moiety of intermediate **17**.

Although our syntheses of magnaldehydes B and E and their 4′-methyl ethers are not entirely protecting-group-free, our goal was to minimize the use of protecting group operations. Part of this objective is facilitated by the dual role of the allyl substituent, which serves as a phenol protecting group during the three step conversion of **10** into **15** and subsequently as the moiety involved in the Claisen rearrangement to install the allyl group at the 3′-position. However, more important for protecting group economy are the conditions used for the key Suzuki–Miyaura coupling reaction of the unprotected halophenol and boronophenol, that is, microwave irradiation, an aqueous medium, an immobilized Pd catalyst, and fluorides instead of hydroxides or carbonates as rate accelerating agents. To underline this point, we investigated the application of these cross-coupling conditions to the synthesis of dictyobiphenyl B (**20**), a metabolite recently isolated from the slime mold *Dictyostelium polycephalum* by Kikuchi et al.[44] These authors also synthesized dictyobiphenyl B and three other newly discovered bi- and terphenyls, because the amount of material from the biological source was insufficient for structural confirmation and biological evaluation. To this end, Kikuchi et al. used a Suzuki–Miyaura coupling reaction of fully protected pinacoloboronate **18** and MOM-protected 4-bromophenol (**19**) followed by global deprotection with BBr_3.[44] We suggest an alternative synthesis of dictyobiphenyl B, in which the roles of the nucleophilic and



Scheme 2. Kikuchi's and our synthesis of dictyobiphenyl B [**20**, dppf = 1,1′-bis(diphenylphosphino)ferrocene].

electrophilic coupling partners are reversed. By using our conditions for the protecting-group-free Suzuki–Miyaura coupling of an *o*-halo-substituted phenol and a *p*-boronophenol, methyl ester **21** underwent a coupling reaction with **7** in the presence of NBu_4F as an additive. Saponification of the methyl ester was accomplished in a one-pot fashion by adding KOH to the reaction mixture to give dictyobiphenyl B (**20**). We then checked whether the rate acceleration of the Suzuki–Miyaura coupling reaction followed by a saponification could be accomplished by using only one additive, namely KOH. To no avail, ester **21** was quantitatively hydrolyzed under these conditions, but **20** could not be detected. This observation is, however, in line with our previously reported results regarding hydroxides or hydroxide-generating additives being unsuitable promoters of Suzuki–Miyaura coupling reactions that involve *para*-boronophenols (Scheme 2).

Conclusions

In summary, we have described protecting-group-economic syntheses of four naturally occurring biphenols that are present in *M. officinalis*. By starting from the same commercially available starting materials, we prepared magnaldehyde B (19% over nine steps), 4′-methoxymagnaldehyde B (15% over ten steps), magnaldehyde E (43% over six steps), and 4′-methoxymagnaldehyde E (39% over seven steps). The structurally related natural product dictiobiphenyl B, originally isolated from the slime mold *D. polycephalum*, was obtained in a single step in 87% yield by starting from commercially available starting materials. The analytical data of the synthesized compounds are in agreement with those reported in the literature for the natural products. The key step of our synthesis is the protecting-group-free Suzuki–Miyaura coupling reaction of the appropriately substituted halophenol with *para*-boronophenol. This reaction proceeds in aqueous medium, is heterogeneously catalyzed by commercially available Pd/C, and is efficiently promoted by microwave irradiation. The use of fluorides as additives rather than hydroxides is crucial to the success of the process.

Experimental Section

General Methods: All experiments were conducted in dry reaction vessels under nitrogen. The solvents were purified by standard procedures. Deionized water was used for the cross-coupling reactions. The ^{1}H NMR spectroscopic data were recorded at 300 or 500 MHz in $CDCl_3$ with residual $CHCl_3$ (δ = 7.26 ppm) as an internal standard, in [D_4]methanol with residual CD_2HOD (δ = 3.31 ppm) as an internal standard, in [D_6]acetone with residual $CD_2HC(O)CD_3$ (δ = 2.05 ppm) as an internal standard, or in [D_6]DMSO with residual [D_5]DMSO (δ = 2.50 ppm) as an internal standard. Coupling constants (J) are reported in Hz. The ^{13}C NMR spectroscopic data were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.0 ppm) as an internal standard, in [D_4]methanol with CD_3OD (δ = 49.2 ppm) as an internal standard, in [D_6]acetone with $CD_3C(O)CD_3$ (δ = 29.9 ppm) as an internal standard, or in [D_6]DMSO with $CD_3S(O)CD_3$ (δ = 39.5 ppm) as an internal standard. IR spectra were recorded as attenuated total reflectance (ATR)-FTIR spectra. Wavenumbers ($\tilde{\nu}$) are given in cm^{-1}. The band intensities are defined as strong (s), medium (m), or weak (w). Low and high resolution mass spectra were obtained by EI/TOF. Microwave reactions were carried out in an Anton-Paar monowave 300 reactor at the reported temperature of the individual procedure (monowave, maximum power 850 W, temperature control by IR sensor, vial volume: 20 mL). *para*-Boronophenol **7** was purchased and used without further purification. 3-Bromo-4-hydroxybenzaldehyde (**6**) was synthesized according to a literature procedure.[37] The Pd/C that was used for all experiments was purchased from Sigma–Aldrich (product number 205699, 9.8–10.2% Pd on dry support, reduced, average particle size of the carbon is 15 μm, surface area of the carbon support is 750–1000 $m^2 g^{-1}$).[45]

4′,6-Dihydroxy-[1,1′-biphenyl]-3-carbaldehyde (8): Compound **6** (201 mg, 1.00 mmol), compound **7** (179 mg, 1.30 mmol, 1.30 equiv.), tetra-*n*-butylammonium fluoride trihydrate (TBAF·$3H_2O$, 1.26 g, 4.0 mmol, 4.0 equiv.), and Pd/C (10 wt.-%, 20 mg, 2 mol-%) were suspended in water (12.0 mL) in a vessel suited for microwave irradiation. The closed vessel was placed in a microwave reactor and irradiated at 150 °C for 0.5 h. After cooling the mixture to ambient temperature, it was carefully acidified by the addition of hydrochloric acid (1.0 M). The resulting mixture was extracted with methyl *tert*-butyl ether (MTBE, 3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish **8** (173 mg, 0.81 mmol, 81%). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 9.74 (s, 1 H), 8.90 (s, 1 H), 8.59 (s, 1 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.75 (dd, J = 8.3, 2.1 Hz, 1 H), 6.48 (d, J = 8.6 Hz, 2 H), 6.15 (d, J = 8.3 Hz, 1 H), 5.89 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 191.3, 160.2, 156.7, 132.5, 130.2, 129.6, 128.8, 128.5, 127.8, 116.4, 115.0 ppm. IR (ATR): $\tilde{\nu}$ = 1663 (w), 1587 (s), 1175 (s), 1123 (m), 821 (s) cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{10}O_3^+$ $[M]^+$ 214.0630; found 214.0621.

4′-Hydroxy-6-(methoxymethoxy)-[1,1′-biphenyl]-3-carbaldehyde (9): Biphenol **8** (190 mg, 0.89 mmol), $NEt(iPr)_2$ (0.31 mL, 1.78 mmol, 2.0 equiv.), and 4-(dimethylamino)pyridine (DMAP, 11 mg, 0.09 mmol, 10 mol-%) were dissolved in CH_2Cl_2/THF (2:1, 15 mL), and the resulting solution was cooled to 0 °C. A solution of MOMBr (90% technical grade, 80.5 μL, 0.89 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was slowly added to the mixture. Upon complete addition, the mixture was warmed to ambient temperature and stirred continuously for 12 h. The solution was acidified by the addition of hydrochloric acid (1.0 M), and the resulting mixture was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish **9** (204 mg, 0.79 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H), 7.85 (d, J = 2.1 Hz, 1 H), 7.81 (dd, J = 8.5, 2.2 Hz, 1 H), 7.42 (d, J = 8.7 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 2 H), 5.78 (s, 1 H), 5.41 (s, 1 H), 5.25 (s, 2 H), 3.45 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.3, 159.3, 155.5, 132.5, 132.0, 130.9, 130.9, 130.9, 129.7, 115.3, 115.0, 94.7, 56.6 ppm. IR (ATR): $\tilde{\nu}$ = 3347 (br. w), 1683 (s), 1595 (s), 1261 (s), 976 (s) cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{14}O_4^+$ $[M]^+$ 258.0887; found 258.0871.

4′-(Allyloxy)-6-(methoxymethoxy)-[1,1′-biphenyl]-3-carbaldehyde (10): Compound **9** (274 mg, 1.06 mmol), allyl bromide (183 μL, 2.12 mmol, 2.0 equiv.), and K_2CO_3 (292 mg, 2.12 mmol, 2.0 equiv.) were suspended in acetone (20 mL). The mixture was stirred at

50 °C until the starting material was completely consumed. Water was added, and the aqueous phase was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish **10** (249 mg, 0.84 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H), 7.85 (d, J = 2.1 Hz, 1 H), 7.80 (dd, J = 8.5, 2.2 Hz, 1 H), 7.47 (d, J = 8.9 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 1 H), 6.99 (d, J = 8.9 Hz, 2 H), 6.09 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H), 5.45 (ddd, J = 17.3, 3.1, 1.6 Hz, 1 H), 5.31 (ddd, J = 10.5, 2.8, 1.4 Hz, 1 H), 5.24 (s, 2 H), 4.59 (dt, J = 5.3, 1.5 Hz, 2 H), 3.45 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.2, 159.3, 158.3, 133.4, 132.5, 132.0, 131.0, 130.7, 130.7, 129.8, 117.9, 115.0, 114.6, 94.7, 69.0, 56.6 ppm. IR (ATR): $\tilde{\nu}$ = 2925 (br. w), 1693 (s), 1598 (s), 1514 (m), 982 (s) cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{18}O_4^+$ $[M]^+$ 298.1200; found 298.1193.

3′-Allyl-4′-hydroxy-6-(methoxymethoxy)-[1,1′-biphenyl]-3-carbaldehyde (11): Compound **10** (66 mg, 0.22 mmol) was dissolved in *N*,*N*-diethylaniline (3 mL) in a vessel suited for microwave irradiation. The closed vessel was placed in a microwave reactor and irradiated at 250 °C for 1.0 h. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (50 mL), and the resulting solution was washed with hydrochloric acid (1.0 M, 3×). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give compound **11** (66 mg, 0.22 mmol, quantitative yield), which was analytically pure and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H), 7.84 (d, J = 2.1 Hz, 1 H), 7.79 (dd, J = 8.5, 2.1 Hz, 1 H), 7.35–7.27 (m, 3 H), 6.89 (d, J = 8.1 Hz, 1 H), 6.06 (ddt, J = 16.6, 10.1, 6.4 Hz, 1 H), 5.45 (s, 1 H), 5.26, (s, 2 H), 5.26–5.12 (m, 2 H), 3.46 (d, J = 7.22 Hz, 2 H), 3.45 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.3, 159.3, 154.0, 136.5, 132.4, 132.1, 131.6, 130.9, 130.8, 129.8, 129.0, 125.4, 116.7, 115.7, 114.9, 94.7, 56.6, 35.2 ppm. IR (ATR): $\tilde{\nu}$ = 3331 (br. w), 1683 (m), 1594 (s), 1490 (m), 1191 (s) cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{18}O_4^+$ $[M]^+$ 298.1205; found 298.1208.

Magnaldehyde E (4a): Compound **11** (20 mg, 0.07 mmol) was dissolved in CH_2Cl_2/CF_3CO_2H (10:1, 2 mL), and the resulting solution was stirred at ambient temperature for 2 h. The mixture was diluted with ethyl acetate (50 mL), and the solution was washed with brine (3× 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give magnaldehyde E (**4a**, 17 mg, 0.07 mmol, quantitative yield) in analytically pure form. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 9.90 (s, 1 H), 7.81 (d, J = 2.1 Hz, 1 H), 7.72 (dd, J = 8.3, 2.1 Hz, 1 H), 7.37 (d, J = 2.2 Hz, 1 H), 7.33 (dd, J = 8.2, 2.3 Hz, 1 H), 7.14 (d, J = 8.3 Hz, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 6.05 (ddt, J = 16.8, 10.0, 6.7 Hz, 1 H), 5.10 (ddd, J = 17.1, 3.5, 1.6 Hz, 1 H), 5.00 (ddt, J = 10.0, 2.2, 1.2 Hz, 1 H), 3.44 (d, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 191.3, 160.8, 155.4, 138.1, 133.3, 131.8, 130.8, 130.6, 130.2, 129.6, 129.1, 127.1, 117.4, 115.7, 115.6, 35.0 ppm. IR (ATR): $\tilde{\nu}$ = 3266 (br. w), 1668 (s), 1586 (s), 1188 (s), 826 (m) cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{14}O_3^+$ $[M]^+$ 254.0943; found 254.0948.

3′-Allyl-4′-methoxy-6-(methoxymethoxy)-[1,1′-biphenyl]-3-carbaldehyde (12): Compound **11** (29 mg, 0.10 mmol) and K_2CO_3 (28 mg, 0.20 mmol, 2.0 equiv.) were dissolved in acetone (10 mL). Methyl iodide (121 μL, 1.90 mmol, 20 equiv.) was added, and the mixture was stirred at ambient temperature for 12 h. The reaction mixture was then diluted with water and the aqueous phase was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give compound **12** (30 mg, 0.10 mmol, quantitative yield), which was sufficiently pure and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H), 7.85 (d, J = 2.1 Hz, 1 H), 7.80 (dd, J = 8.5, 2.1 Hz, 1 H), 7.44–7.33 (m, 2 H), 7.31 (d, J = 8.5 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 6.03 (ddt, J = 16.8, 10.0, 6.6 Hz, 1 H), 5.24 (s, 2 H), 5.16–5.00 (m, 2 H), 3.88 (s, 3 H), 3.46 (s, 3 H), 3.43 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.1, 159.1, 156.9, 136.8, 132.3, 132.0, 130.9, 130.8, 130.5, 129.3, 128.3, 128.3, 115.6, 114.7, 110.0, 94.5, 56.5, 55.5, 34.2 ppm. IR (ATR): $\tilde{\nu}$ = 2917 (br. m), 1691 (s), 1598 (m), 1492 (s), 983 (m) cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{20}O_4^+$ $[M]^+$ 312.1362; found 312.1347.

4′-Methoxymagnaldehyde E (4b): Compound **12** (26 mg, 0.08 mmol) was dissolved in CH_2Cl_2/CF_3CO_2H (10:1, 2.0 mL), and the resulting mixture was stirred at ambient temperature for 2 h. The mixture was then diluted with ethyl acetate (50 mL), and the solution was washed with brine (3× 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give **4b** (20 mg, 0.07 mmol, 91%) as the analytically pure product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 7.82–7.73 (m, 2 H), 7.30 (dd, J = 8.3, 2.3 Hz, 1 H), 7.24 (d, J = 2.2 Hz, 1 H), 7.09 (d, J = 8.9 Hz, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 6.00 (ddt, J = 16.8, 10.1, 6.7 Hz, 1 H), 5.10 (ddd, J = 17.3, 3.2, 1.6 Hz, 1 H), 5.08 (ddd, J = 10.3, 3.2, 1.6 Hz, 1 H), 3.89 (s, 3 H), 3.44 (d, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.13, 158.40, 157.74, 136.39, 132.56, 131.24, 130.53, 130.42, 130.19, 128.91, 128.02, 127.37, 116.42, 116.22, 111.30, 55.72, 34.37 ppm. IR (ATR): $\tilde{\nu}$ = 3228 (br. m), 1668 (m), 1589 (s), 1498 (m), 1246 (s) cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{16}O_3^+$ $[M]^+$ 268.1099; found 268.1095.

Ethyl (*E*)-3-[4′-(Allyloxy)-6-(methoxymethoxy)-(1,1′-biphenyl)-3-yl-]acrylate (13): To a solution of triethyl phosphonoacetate (230 μL, 1.15 mmol, 1.5 equiv.) in dry and degassed THF (10 mL) was added NaH (60 wt.-% dispersion in mineral oil, 46 mg, 1.15 mmol, 1.5 equiv.). The mixture was stirred at 65 °C for 1 h and then cooled to 0 °C. A solution of **10** (229 mg, 0.77 mmol) in THF (5 mL) was then added. The mixture was heated to 65 °C for 5 h, cooled to ambient temperature, and partitioned between ethyl acetate (50 mL) and brine (20 mL). The aqueous phase was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish **13** (284 mg, 0.77 mmol, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1 H), 7.51–7.40 (m, 4 H), 7.20 (d, J = 8.5 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 2 H), 6.36 (d, J = 16.0 Hz, 1 H), 6.09 (ddt, J = 17.3, 10.5, 5.3 Hz, 1 H), 5.45 (dd, J = 17.3, 1.3 Hz, 1 H), 5.31 (dd, J = 10.5, 1.1 Hz, 1 H), 5.16 (s, 2 H), 4.59 (d, J = 5.2 Hz, 2 H), 4.26 (q, J = 7.1 Hz, 2 H), 3.42 (s, 3 H), 1.33 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 158.4, 156.2, 144.5, 133.7, 132.2, 130.9, 130.9, 130.7, 128.9, 128.7, 118.1, 117.0, 115.9, 114.8, 95.2, 69.3, 60.8, 56.6, 14.7 ppm. IR (ATR): $\tilde{\nu}$ = 2929 (br. m), 1709 (s), 1494 (s), 1243 (s), 833 (m) cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{24}O_5^+$ $[M]^+$ 368.1624; found 368.1625.

(*E*)-3-[4′-(Allyloxy)-6-(methoxymethoxy)-(1,1′-biphenyl)-3-yl]prop-2-en-1-ol (14): Compound **13** (350 mg, 0.95 mmol) was dissolved in THF (10 mL), and the resulting solution was cooled to –78 °C. DIBAL-H (1 M solution in CH_2Cl_2, 2.47 mL, 2.47 mmol, 2.6 equiv.) was slowly added. The mixture was hydrolyzed by the addition of brine (10 mL). The aqueous phase was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish

14 (308 mg, 0.94 mmol, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 2.2 Hz, 1 H), 7.29 (dd, J = 8.5, 2.3 Hz, 1 H), 7.15 (d, J = 8.5 Hz, 1 H), 6.94 (t, J = 17.9 Hz, 2 H), 6.59 (d, J = 15.9 Hz, 1 H), 6.29 (dt, J = 15.8, 5.8 Hz, 1 H), 6.09 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H), 5.45 (ddd, J = 17.3, 3.1, 1.5 Hz, 1 H), 5.31 (dd, J = 10.5, 1.4 Hz, 1 H), 5.11 (s, 2 H), 4.59 (dt, J = 5.3, 1.4 Hz, 2 H), 4.31 (dd, J = 5.9, 1.1 Hz, 2 H), 3.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 154.0, 133.5, 131.7, 131.0, 130.8, 130.7, 129.1, 127.3, 126.4, 117.8, 115.9, 114.5, 95.2, 69.0, 64.0, 56.3, 27.1 ppm. IR (ATR): $\tilde{\nu}$ = 3386 (br. w), 1492 (s), 1242 (s), 1079 (m), 996 (s) cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{22}O_4^+$ $[M]^+$ 326.1518; found 326.1501.

(*E*)-3-[4′-(Allyloxy)-6-(methoxymethoxy)-(1,1′-biphenyl)-3-yl]-acrylaldehyde (15): Compound **14** (133 mg, 0.41 mmol) and MnO_2 (532 mg, 6.12 mmol, 15 equiv.) were suspended in CH_2Cl_2 (20 mL). The resulting mixture was stirred at ambient temperature for 12 h, then filtered through a short pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish **15** (105 mg, 0.32 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.68 (d, J = 7.7 Hz, 1 H), 7.55–7.41 (m, 5 H), 7.29–7.23 (m, 1 H), 6.99 (d, J = 8.6 Hz, 2 H), 6.66 (dd, J = 15.8, 7.7 Hz, 1 H), 6.10 (ddt, J = 17.3, 10.6, 5.3 Hz, 1 H), 5.45 (dd, J = 17.3, 1.0 Hz, 1 H), 5.32 (dd, J = 10.4, 0.6 Hz, 1 H), 5.20 (s, 2 H), 4.60 (d, J = 5.2 Hz, 2 H), 3.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.7, 158.3, 156.9, 152.6, 133.4, 132.2, 131.3, 130.6, 130.1, 128.0, 128.2, 127.4, 117.9, 115.6, 114.6, 94.9, 69.0, 56.5 ppm. IR (ATR): $\tilde{\nu}$ = 1673 (s), 1490 (m), 1244 (s), 1125 (s), 983 (s) cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{20}O_4^+$ $[M]^+$ 324.1362; found 324.1362.

(*E*)-3-[3′-Allyl-4′-hydroxy-6-(methoxymethoxy)-(1,1′-biphenyl)-3-yl-]acrylaldehyde (16): Compound **15** (100 mg, 0.31 mmol) was dissolved in *N*,*N*-diethylaniline (3 mL) in a vessel suited for microwave irradiation. The closed vessel was placed in a microwave reactor and irradiated at 250 °C for 1.0 h. The mixture was cooled to ambient temperature and diluted with ethyl acetate (50 mL). The resulting solution was washed with hydrochloric acid (1.0 M, 3×). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield compound **16** (57 mg, 0.18 mmol, 57%), which was sufficiently pure to be used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.67 (d, J = 7.7 Hz, 1 H), 7.53–7.44 (m, 3 H), 7.32–7.22 (m, 3 H), 6.89 (d, J = 8.1 Hz, 1 H), 6.66 (dd, J = 15.8, 7.7 Hz, 1 H), 6.06 (ddt, J = 16.5, 10.1, 6.4 Hz, 1 H), 5.48 (s, 1 H), 5.27–5.13 (m, 2 H), 5.19 (s, 2 H), 3.47 (d, J = 6.4 Hz, 2 H), 3.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.0, 156.9, 153.9, 153.0, 136.4, 132.3, 131.5, 131.3, 130.2, 129.0, 129.0, 128.1, 127.3, 125.4, 116.8, 115.7, 115.6, 94.8, 56.5, 35.2 ppm. IR (ATR): $\tilde{\nu}$ = 1657 (s), 1597 (s), 1490 (m), 1270 (m), 1131 (m) cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{20}O_4^+$ $[M]^+$ 324.1362; found 324.1369.

Magnaldehyde B (3a): Compound **16** (28 mg, 0.09 mmol) was dissolved in CH_2Cl_2/CF_3CO_2H (10:1, 2 mL), and the resulting mixture was stirred at ambient temperature for 2 h and then diluted with ethyl acetate (50 mL). The mixture was washed with brine (3× 10 mL), and the organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to furnish analytically pure magnaldehyde B (**3a**, 24 mg, 0.09 mmol, quantitative yield); m.p. 152–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.60 (d, J = 7.8 Hz, 1 H), 7.53–7.42 (m, 3 H), 7.25–7.17 (m, 2 H), 7.03 (d, J = 8.2 Hz, 1 H), 6.95 (d, J = 8.8 Hz, 1 H), 6.65 (dd, J = 15.8, 7.9 Hz, 1 H), 6.04 (ddt, J = 16.6, 10.1, 6.5 Hz, 1 H), 5.69 (s, 2 H), 5.18 (ddd, J = 17.3, 3.2, 1.6 Hz, 1 H), 5.17 (ddd, J = 10.3, 2.8, 1.6 Hz, 1 H), 3.47 (d, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 156.1, 154.7, 154.3, 136.0, 131.3, 131.1, 129.8, 129.1, 128.5, 128.1, 127.2, 126.9, 126.3, 117.0, 116.8, 116.8, 35.0 ppm. IR (ATR): $\tilde{\nu}$ = 3264 (br. m), 1645 (s), 1590 (s), 1491 (m), 1280 (m) cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{16}O_3^+$ $[M]^+$ 280.1099; found 280.1093.

(*E*)-3-[3′-Allyl-4′-methoxy-6-(methoxymethoxy)-(1,1′-biphenyl)-3-yl-]acrylaldehyde (17): Compound **16** (28 mg, 0.09 mmol) and K_2CO_3 (25 mg, 0.18 mmol, 2.0 equiv.) were suspended in acetone (10 mL). Methyl iodide (107 μL, 1.72 mmol, 20 equiv.) was added, and the mixture was stirred at ambient temperature for 12 h. The mixture was diluted with water, and the aqueous phase was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give compound **17** (23 mg, 0.07 mmol, 79%) in analytically pure form. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.67 (d, J = 7.7 Hz, 1 H), 7.52 (d, J = 2.2 Hz, 1 H), 7.50–7.44 (m, 2 H), 7.36 (dd, J = 8.4, 2.3 Hz, 1 H), 7.31 (d, J = 2.2 Hz, 1 H), 7.24 (d, J = 8.5 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 6.66 (dd, J = 15.8, 7.8 Hz, 1 H), 6.03 (ddt, J = 16.7, 10.1, 6.7 Hz, 1 H), 5.12 (s, 2 H), 5.12–5.04 (m, 2 H), 3.81 (s, 3 H), 3.44 (s, 3 H), 3.43 (d, J = 6.1 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 193.9, 156.9, 156.8, 152.8, 136.9, 132.3, 131.3, 131.0, 129.7, 128.9, 128.5, 128.3, 128.1, 127.3, 115.8, 115.4, 110.1, 94.7, 56.5, 55.6, 34.3 ppm. IR (ATR): $\tilde{\nu}$ = 2927 (br. m), 1673 (s), 1489 (s), 1245 (s), 1124 (s) cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{22}O_4^+$ $[M]^+$ 338.1518; found 338.1518.

4′-Methoxymagnaldehyde B (3b): Compound **17** (20 mg, 0.06 mmol) was dissolved in CH_2Cl_2/CF_3CO_2H (10:1, 2 mL), and the resulting mixture was stirred at ambient temperature for 2 h and then diluted with ethyl acetate (50 mL). The mixture was washed with brine (3× 10 mL), and the organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to furnish **3b** (17 mg, 0.06 mmol, quantitative yield) in analytically pure form. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, J = 7.8 Hz, 1 H), 7.54–7.45 (m, 3 H), 7.32 (dd, J = 8.3, 2.1 Hz, 1 H), 7.25 (d, J = 1.9 Hz, 1 H), 7.05 (d, J = 8.2 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 6.67 (dd, J = 15.8, 7.9 Hz, 1 H), 6.03 (ddt, J = 16.8, 10.0, 6.7 Hz, 1 H), 5.57 (s, 1 H), 5.11 (ddd, J = 17.3, 3.2, 1.6 Hz, 1 H), 5.09 (ddd, J = 10.3, 2.8, 1.4 Hz, 1 H), 3.91 (s, 3 H), 3.46 (d, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.7, 157.7, 156.1, 154.1, 136.4, 131.3, 130.5, 130.3, 129.7, 129.1, 128.0, 127.7, 126.9, 126.4, 116.7, 116.2, 111.3, 55.7, 34.4 ppm. IR (ATR): $\tilde{\nu}$ = 3286 (br. w), 1657 (m), 1594 (s), 1497 (s), 1248 (m) cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{18}O_3^+$ $[M]^+$ 294.1256; found 294.1263.

Dictyobiphenyl B (20): Compound **21** (68 mg, 0.30 mmol), compound **7** (53 mg, 0.38 mmol, 1.30 equiv.), TBAF·3H_2O (372 mg, 1.18 mmol, 4.0 equiv.), and Pd/C (10 wt.-%, 5.9 mg, 2 mol-%) were suspended in water (4.0 mL) in a vessel suited for microwave irradiation. The closed vessel was placed in a microwave reactor and irradiated at 150 °C for 0.5 h. After cooling to ambient temperature, KOH (132 mg, 2.36 mmol) was added, and the mixture was irradiated again at 150 °C for 0.5 h. After cooling to ambient temperature, the mixture was carefully acidified by the addition of hydrochloric acid (1.0 M). The resulting solution was extracted with MTBE (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (pure MTBE) to furnish dictyobiphenyl B (**20**, 59 mg, 0.26 mmol, 87%) as a colorless solid, m.p. 207 °C; ref.[44] m.p. 208–210 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.96 (d, J = 2.2 Hz, 1 H), 7.84 (dd, J = 8.4, 2.2 Hz, 1 H), 7.46 (d, J = 8.7 Hz, 2 H), 7.04 (d, J = 8.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-acetone): δ = 167.6, 159.3, 157.7, 133.2, 131.3, 130.8, 129.8, 129.3,

123.1, 116.7, 115.9 ppm. IR (ATR): $\tilde{\nu}$ = 3226 (br. s), 1679 (s), 1601 (s), 1516 (m), 1231 (s) cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{10}O_4^+$ $[M]^+$ 230.0579; found 230.0584.

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