

Synthesis of Dihydrobenzofurans via Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodophenyl Acetates

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General. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz respectively. All melting points are uncorrected. Thin layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates, and visualization was performed with UV light (254 nm) and an acidic KMnO_4 solution. Low resolution mass spectra were recorded on a triple quadripole mass spectrometer. High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. Iodine, acetic anhydride, pyridine, 1,3-cyclohexadiene, and 2,3-dimethyl-1,3-butadiene, *o*-iodophenol, methyl *p*-hydroxybenzoate, *p*-hydroxyacetophenone, *p*-hydroxybenzaldehyde, *p*-nitrophenol, *o*-methoxyphenol, *m*-methoxyphenol, *p*-methoxyphenol, resorcinol, β -naphthol, *trans,trans*-2,4-Hexadiene (95% pure) were purchased from commercial sources. 2-Iodophenol acetate (**1**),¹ 4-acetyl-2-iodophenol acetate (**10**),² 4-formyl-2-iodophenol acetate (**12**),³ 4-iodoresorcinol diacetate (**21**),⁴ 1-iodo-2-naphthol acetate,⁵ 4-methoxy-2-iodophenol,⁶ 3-methoxy-2-iodophenol,⁷ *E*-1-phenyl-1,3-butadiene⁸ and 1,5,5-trimethyl-3-methylenecyclohexene⁹ were prepared according to literature procedures.

General iodination/acylation procedure. Compounds **16**, **21** and **23** were prepared by direct acylation of the corresponding phenols. Compounds **5** and **7** were prepared by acylation of the corresponding *o*-iodophenols, which in turn were prepared by iodination of the corresponding phenols according to the procedure for the iodination of hydroxycoumarins⁷ indicated below.

Iodine (5.0 mmol) dissolved in 50 mL of satd aq KI solution was slowly added to a solution of the corresponding phenol (5.0 mmol) in the minimal amount of aq ammonia solution at 0-5 °C. The resulting reaction mixture was stirred for 2 h, left overnight in the refrigerator, and then acidified by 20 % aq HCl to pH = 4-5. The precipitated *o*-iodophenol was extracted with ether, and the organic layer was washed with water. After evaporation of the ether, the resulting solid was dissolved in 20 mL of acetic anhydride (a minimal amount of DMF can be used as a co-solvent) in the presence of 1 mL of pyridine and stirred for 24 h at 100 °C. Then the reaction mixture was quenched with chilled water

(caution, heat evolution!) and after 2 h extracted by CH₂Cl₂. The organic extract was washed with water and aq NH₄Cl solution, and dried over anhydrous MgSO₄ for 4 h. After evaporation of the CH₂Cl₂, the resulting white solid was purified by column chromatography using silica gel as a stationary phase and 5:1 hexanes-ethyl acetate as the eluent. The following compounds were prepared using this procedure.

Methyl 4-acetoxy-3-iodobenzoate (11). Obtained in a 96 % yield: white solid, mp 69-72 °C; ¹H NMR (CDCl₃) δ 2.38 (s, 3H), 3.92 (s, 3H), 7.17 (d, *J* = 8.0 Hz, 1H), 8.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.5, 52.8, 90.6, 123.1, 129.6, 131.1, 141.1, 155.0, 165.2, 168.3; IR (neat) 1788, 1766 cm⁻¹; HRMS *m/z* 291.9601 (calcd for C₁₀H₉IO₄, 291.9596).

2-Iodo-4-nitrophenol (20). Obtained in a 98 % yield as a yellow solid; the ¹H and ¹³C NMR spectra matched data reported in the literature.⁸

2-Iodo-4-methoxyphenyl acetate (22). Obtained in a 65 % yield as a colorless solid, mp 89-91 °C; ¹H NMR (CDCl₃) δ 2.36 (s, 3H), 3.77 (s, 3H), 6.60 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.5, 55.9, 79.1, 109.5, 114.4, 139.4, 152.1, 161.1, 168.8; IR (neat) 1766, 1588 cm⁻¹; HRMS *m/z* 319.9551 (calcd for C₉H₉IO₃, 319.9546).

2-Iodo-3-methoxyphenyl acetate (25). Obtained in a 63 % yield: yellow solid, mp 92-94 °C; ¹H NMR (CDCl₃) δ 2.37 (s, 3H), 3.90 (s, 3H), 6.65-6.77 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.6, 56.0, 83.7, 108.6, 115.7, 130.0, 152.8, 159.9, 168.8; IR (neat) 1771, 1583 cm⁻¹; HRMS *m/z* 291.9601 (calcd for C₉H₉IO₃, 291.9596).

General procedure for the synthesis of dihydrobenzofurans. The *o*-iodophenyl acetate (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (0.5 mmol) and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, filtered and the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes/ethyl acetate

as the eluent to afford after solvent removal the final product. The following new compounds were prepared using this procedure.

1',4,5,5'-Tetrahydrodibenzofuran (8). Obtained in a 72 % yield as a colorless oil; the ^1H and ^{13}C NMR spectra matched the data reported in the literature.¹⁰

2-Methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran (9). Obtained in a 92 % yield as a colorless oil; the ^1H and ^{13}C NMR spectra matched the data reported in the literature.⁹

3-Methyl-2-(*E*-1-propenyl)-2,3-dihydrobenzofuran (10). Obtained in a 75 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.16 (d, $J = 7.2$ Hz, 3H), 1.77 (d, $J = 8.0$ Hz, 3H), 3.40-3.50 (m, 1H), 5.09 (t, $J = 8.4$ Hz, 1H), 5.60-5.70 (m, 1H), 5.83-5.90 (m, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 7.86 (t, $J = 8.0$ Hz, 1H), 7.08-7.15 (m, 2H); IR (neat) 3029, 1593 cm^{-1} ; HRMS m/z 174.1048 (calcd for $\text{C}_{12}\text{H}_{14}\text{O}$, 174.1045). This compound was insufficiently stable to get clean ^{13}C spectra.

Methyl 2-methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran-5-carboxylate (12). Obtained in a 100 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.55 (s, 3H), 1.80 (dd, $J = 1.2, 0.8$ Hz, 3H), 3.02 (d, $J = 16.0$ Hz, 1H), 3.24 (d, $J = 16.0$ Hz, 1H), 3.85 (s, 3H), 4.84 (q, $J = 1.2$ Hz, 1H), 5.06 (q, $J = 0.8$ Hz, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 0.8$ Hz, 1H), 7.86 (dd, $J = 8.4, 0.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 40.9, 52.1, 91.8, 109.4, 110.6, 122.6, 127.1, 127.2, 131.4, 147.3, 163.2, 167.3; IR (neat) 1714, 1612 cm^{-1} ; m/z 232.1102 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 232.1099).

Methyl 2-(*E*-2-phenylethenyl)-2,3-dihydrobenzofuran-5-carboxylate (13). Obtained in a 96 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 3.11 (dd, $J = 15.6, 7.6$ Hz, 1H), 3.48 (dd, $J = 15.6, 9.2$ Hz, 1H), 3.88 (s, 3H), 5.42-5.70 (m, 1H), 6.35 (dd, $J = 16.0, 7.6$ Hz, 1H), 6.71 (d, $J = 16.0$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 7.24-7.45 (m, 3H), 7.85-7.95 (m, 2H); ^{13}C NMR (CDCl_3) δ 35.9, 52.1, 85.0, 109.4, 123.0, 127.0, 127.3, 127.8, 128.5, 128.9, 129.2, 131.5, 133.1, 136.2, 163.7, 167.2; IR (neat) 1713, 1615 cm^{-1} ; HRMS m/z 280.1103 (calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3$, 280.1099).

Methyl *trans*-3-methyl-2-(*E*-1-propenyl)-2,3-dihydrobenzofuran-5-carboxylate (14). Obtained in a 77 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.18 (d, $J = 7.2$ Hz, 3H), 1.78 (d, $J = 6.6$ Hz, 3H), 3.45-3.55 (m, 1H), 3.87 (s, 3H), 5.19 (t, $J = 8.8$ Hz, 1H), 5.62 (dd, $J = 16.0, 8.0$ Hz, 1H), 5.88 (dq, $J =$

16.0, 6.6 Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 7.80 (d, $J = 0.8$ Hz, 1H), 7.82 (dd, $J = 7.6, 0.8$ Hz); ^{13}C NMR (CDCl_3) δ 16.14, 18.16, 39.49, 52.07, 89.02, 109.4, 115.6, 122.9, 126.1, 126.2, 131.3, 131.9, 133.6, 163.0, 167.2; IR (neat) 1714, 1612 cm^{-1} ; HRMS m/z 232.1102 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 232.1099).

Dihydrobenzofuran 15. Obtained in a 60 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 0.99 (s, 3H), 1.07 (s, 3H), 1.71 (s, 3H), 1.45-2.05 (m, 4H), 3.09 (s, 2H), 3.85 (s, 3H), 5.49 (s, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H), 7.84 (dd, $J = 8.0, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 24.1, 29.0, 29.7, 31.0, 43.1, 44.4, 48.2, 52.0, 77.0, 77.3, 77.6, 89.4, 109.3, 122.2, 122.9, 126.9, 127.6, 131.3, 138.0, 163.0, 167.3; IR (neat) 1712, 1611 cm^{-1} ; HRMS m/z 286.1572 (calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$, 286.1569).

5-Acetyl-2-methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran (17). Obtained in an 88 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.57 (s, 3H), 1.82 (dd, $J = 1.6, 0.8$ Hz, 3H), 2.54 (s, 3H), 3.04 (d, $J = 15.6$ Hz, 1H), 3.27 (d, $J = 15.6$ Hz, 1H), 4.87 (q, $J = 1.2$ Hz, 1H), 5.08 (q, $J = 0.8$ Hz, 1H), 6.81 (d, $J = 9.2$ Hz, 1H), 7.78-7.85 (m, 2H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 26.7, 40.9, 92.0, 109.3, 110.6, 125.9, 127.6, 130.7, 130.8, 147.2, 163.4, 196.9; IR (neat) 1674, 1606 cm^{-1} ; HRMS m/z 216.1153 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2$, 216.1150).

2-Methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran-5-carboxaldehyde (19). Obtained in a 98 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.59 (s, 3H), 1.82 (dd, $J = 1.2, 0.8$ Hz, 3H), 3.07 (d, $J = 15.6$ Hz, 1H), 3.29 (d, $J = 15.6$ Hz, 1H), 4.88 (q, $J = 1.2$ Hz, 1H), 5.08 (q, $J = 0.8$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 7.67-7.73 (m, 2H), 9.82 (s, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 40.7, 92.4, 110.0, 110.8, 126.3, 128.4, 130.5, 133.4, 147.0, 164.6, 190.9; IR (neat) 2747, 1688, 1606 cm^{-1} ; HRMS m/z 202.0997 (calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$, 202.0994).

2-Methyl-5-nitro-2-(1-methylethenyl)-2,3-dihydrobenzofuran (21). Obtained in a 72 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.82 (dd, $J = 1.2, 0.8$ Hz, 3H), 1.83 (s, 3H), 3.09 (d, $J = 15.6$ Hz, 1H), 3.32 (d, $J = 15.6$ Hz, 1H), 4.90 (q, $J = 1.2$ Hz, 1H), 5.08 (q, $J = 0.8$ Hz, 1H), 6.82 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.05 (d, $J = 2.0$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.9, 26.3, 40.7, 93.3,

109.5, 111.1, 121.7, 126.1, 128.3, 141.9, 146.6, 164.5; IR (neat) 1598, 1516 cm^{-1} ; HRMS m/z 219.0898 (calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3$, 219.0895).

5-Methoxy-2-methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran (23). Obtained in a 58 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.56 (s, 3H), 1.81 (dd, $J = 1.2, 0.8$ Hz, 3H), 2.94 (d, $J = 14.8$ Hz, 1H), 3.18 (d, $J = 14.8$ Hz, 1H), 3.77 (s, 3H), 4.83 (q, $J = 1.2$ Hz, 1H), 5.07 (d, $J = 0.8$ Hz, 1H), 6.36-6.43 (m, 2H), 7.00 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.2, 26.3, 41.0, 55.7, 91.1, 96.4, 105.9, 110.1, 118.7, 125.2, 148.0, 160.3, 160.6; IR (neat) 1616, 1497 cm^{-1} ; HRMS m/z 204.1153 (calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$, 204.1150).

4-Methoxy-2-(*E,E*-4-phenyl-1,3-butadienyl)phenyl acetate (24). Obtained in a 64 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 2.37 (s, 3H), 3.84 (s, 3H), 6.64 (d, $J = 14.0$ Hz, 1H), 6.67 (d, $J = 14.4$ Hz, 1H), 6.81 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.90-7.10 (m, 3H), 7.12 (d, $J = 2.8$ Hz, 1H), 7.26 (dd, $J = 8.8, 7.2$ Hz, 1H), 7.35 (t, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 21.2, 55.9, 110.7, 114.4, 123.7, 125.8, 126.8, 128.1, 128.9, 129.3, 130.8, 131.7, 134.2, 137.3, 142.0, 157.6, 170.0; IR (neat) 1755, 1589 cm^{-1} ; HRMS m/z 294.1261 (calcd for $\text{C}_{19}\text{H}_{18}\text{O}_3$, 294.1256).

4-Methoxy-2-methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran (26). Obtained in a 67 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.55 (s, 3H), 1.81 (dd, $J = 1.6, 0.8$ Hz, 3H), 2.96 (d, $J = 15.6$ Hz, 1H), 3.18 (d, $J = 15.6$ Hz, 1H), 3.82 (s, 3H), 4.83 (q, $J = 0.8$ Hz, 1H), 5.09 (d, $J = 1.2$ Hz, 1H), 6.40 (d, $J = 8.0$ Hz, 1H), 6.47 (d, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 26.4, 39.1, 55.6, 90.7, 102.8, 103.1, 110.0, 113.6, 129.3, 147.9, 156.8, 160.4; IR (neat) 1609, 1493 cm^{-1} ; HRMS m/z 204.1153 (calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$, 204.1150).

6-Acetoxy-2-methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran (28). Obtained in a 40 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.55 (s, 3H), 1.81 (t, $J = 0.8$ Hz, 3H), 2.28 (s, 3H), 2.98 (d, $J = 15.6$ Hz, 1H), 3.22 (d, $J = 15.6$ Hz, 1H), 4.84 (q, $J = 0.8$ Hz, 1H), 5.07 (d, $J = 0.8$ Hz, 1H), 6.50-6.58 (m, 2H), 7.09 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 21.4, 26.3, 41.1, 91.5, 103.9, 110.3, 113.3,

124.4, 125.1, 147.6, 151.0, 159.9, 169.8; IR (neat) 1762, 1607 cm^{-1} ; HRMS m/z 232.1102 (calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, 232.1099).

2-Methyl-2-(1-methylethenyl)-2,3-dihydrofuro[3,2-*b*]naphthalene (30). Obtained in a 48 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.63 (s, 3H), 1.86 (s, 3H), 3.29 (d, J = 16.0 Hz, 1H), 3.51 (d, J = 16.0 Hz, 1H), 4.88 (s, 1H), 5.15 (s, 1H), 7.13 (d, J = 11.6 Hz, 1H), 7.23-7.34 (m, 1H), 7.40-7.50 (m, 1H), 7.55 (d, J = 11.6 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.0, 26.6, 40.6, 91.0, 110.2, 112.5, 118.0, 122.8, 122.9, 126.8, 129.0, 129.2, 129.3, 131.2, 148.1, 156.6; IR (neat) 1631, 1465 cm^{-1} ; HRMS m/z 224.1205 (calcd for $\text{C}_{16}\text{H}_{16}\text{O}$, 224.1201).

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