Supporting Information for
Reinvestigation of Mucohalic Acids, Versatile and Useful Building Blocks
for Highly Functionalized α,β -Unsaturated γ -Butyrolactones.

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General Methods

All reactions were carried out under nitrogen atmosphere unless otherwise noted. All solvents and reagents used were from commercial sources and no further purification was performed. Reactions were monitored by mass spectrometry (MS) on a Micromass Platform LC and by thin-layer chromatography on 0.25 mm E. Merck silica gel 60 plates (F₂₅₄) using UV light and aqueous potassium permanganate-sodium bicarbonate as visualizing agents. E. Merck silica gel 60 (0.040-0.063 mm and 0.063-0.200 mm particle sizes) was used for column chromatography. Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded at 400 MHz on a Varian UNITY INOVA AS400. Chemical shifts are reported as delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for deuteriochloroform. Coupling constants (*J*) are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded at 100 MHz on a Varian UNITY Plus INOVA 400. Chemical shifts are reported as delta (δ) units in parts per million (ppm) relative to the center line of the triplet at 77.3 ppm for deuteriochloroform or the center line of the septet at 40.2 ppm for DMSO-d₆. Chemical shifts are reported as delta (δ) units in parts per million (ppm) relative to deuteriochloroform. Elemental analyses were performed out-of-house by Quantitative Technologies Inc.

Experimental Details

Preparation of 3,4-dichloro-5H-furan-2-one (3). Mucochloric acid (**1**, 20.0 g, 0.118 mol) and sodium triacetoxymethylborohydride (37.6 g, 0.178 mol) were suspended in chloroform (600 mL) and cooled to 0-5°C. Acetic acid (12 mL) was added and the reaction mixture was allowed to warm to 20-25°C. Stirring at 20-25°C was continued for 3 d. The reaction mixture was diluted with water (100 mL), the phases were separated and the organic phase was washed once with water (100 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂) followed by recrystallization (CH₂Cl₂-heptane) to give **3** as a white solid: yield 8.08 g (45%).

Preparation of 3,4-dibromo-5H-furan-2-one (4). Mucobromic acid (**2**, 20.0 g, 0.0776 mol) and sodium triacetoxymethylborohydride (24.7 g, 0.116 mol) were suspended in chloroform (600 mL) and cooled to 0-5°C. Acetic acid (12 mL) was added and the reaction mixture was allowed to warm to 20-25°C. Stirring at 20-25°C was continued for 3 d. The reaction mixture was diluted with water (100 mL), the phases were separated and the organic phase was washed once with water (100 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂) followed by recrystallization (CH₂Cl₂-heptane) to give **4** as a white solid: yield 10.7 g (57%).

General procedure for bis-Suzuki coupling reactions (base screen). Compound 8a. Butenolide **4** (2.5 mmol) was combined with phenylboronic acid (2.4 equiv.), the desired base (4.0 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was refluxed for 2-3 h. The reaction mixture was partitioned between 10 mL 2N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

General procedure for bis-Suzuki coupling reactions (boronic acid screen). Compounds 8a-8f. Butenolide **3** (1.8-2.5 mmol) was combined with the desired arylboronic acid (3.0 equiv.), cesium fluoride (4.0 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was refluxed for 16-18 h. The reaction mixture was partitioned between 10 mL 1.5N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 3,4-diphenyl-5-hydroxy-5H-furan-2-one (9). Mucochloric acid (**1**, 2.5 mmol) was combined with phenylboronic acid (**7a**) (3.0 equiv.), cesium fluoride (4.0 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was refluxed for 4 h. The reaction mixture quenched with 100 mL of saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2x100 mL). The ethyl acetate extract was washed with 100 mL of saturated aqueous ammonium chloride solution and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 5-benzyloxy-3,4-dichloro-5H-furan-2-one (10). A mixture of mucochloric acid (**1**, 16.8 g, 0.100 mol), benzyl alcohol (16.2 g, 1.5 equiv.), Amberlyst® 15 (0.33 g), zinc chloride (1.4 g, 0.1 equiv.) and 300 mL of toluene was refluxed for 6h with a Dean-Stark trap in place. The reaction mixture was filtered and the toluene was removed under reduced pressure. The residue was purified by silica gel column chromatography. Yield: 13.6 g (77%).

Preparation of 5-benzyloxy-3,4-diphenyl-5H-furan-2-one (11). Butenolide **10** (2.5 mmol) was combined with phenylboronic acid (**7a**) (3.0 equiv.), cesium fluoride (4.0 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was refluxed for 4 h. The reaction mixture quenched with 100 mL of 1.5N hydrochloric acid and extracted with ethyl toluene (2x100 mL). The toluene extract was washed with water and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 3-bromo-4-(4'-methylthiophenyl)-5H-furan-2-one (13). Butenolide **4** (2.3 mmol) was combined with 4-(methylthio)phenylboronic acid (2.0 equiv.), cesium fluoride (2.67 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was stirred at 20-25°C for 3 d. The reaction mixture was partitioned between 10 mL 2N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 3-chloro-4-(4'-methylthiophenyl)-5H-furan-2-one (16). Butenolide **3** (2.3 mmol) was combined with 4-(methylthio)phenylboronic acid (2.0 equiv.), cesium fluoride (2.67 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was stirred at 20-25°C for 3 d. The reaction mixture was partitioned between 10 mL 2N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 4-(4'-methylthiophenyl)-3-phenyl-5H-furan-2-one (14). Butenolide **16** (1.0 mmol) was combined with phenylboronic acid (**7a**) (2.0 equiv.), cesium fluoride (3.0 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was stirred at 20-25°C for 2-3 d. The reaction mixture was partitioned between 10 mL 2N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 3-chloro-4-(4'-methylsulfonylphenyl)-5H-furan-2-one (17). Butenolide **13** (1.4 mmol) was combined with Oxone[®] (3.0 equiv.), 20 mL of acetone and 600 µL of water. The reaction mixture was stirred at 0-25°C for 24 h. The reaction mixture was filtered and the solids washed with more acetone. The acetone solution was concentrated under reduced pressure, and the residue was washed with water. No further purification was necessary.

Preparation of 4-(4'-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one (Vioxx[®]) (15). Butenolide **17** (0.77 mmol) was combined with phenylboronic acid (**7a**) (2.0 equiv.), cesium fluoride (2.0 equiv.), PdCl₂(PPh₃)₂ (5 mol%), BnEt₃NCl (5 mol%) and 10 mL each of degassed toluene and water. The reaction mixture was refluxed for 7 h. The reaction mixture was partitioned between 10 mL 2N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Preparation of 4-(4'-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one (Vioxx[®]) (15). Butenolide **14** (0.71 mmol) was combined with Oxone[®] (3.0 equiv.), 10 mL of acetone and 300 µL of water. The reaction mixture was stirred at 0-25°C for 24 h. The reaction mixture was filtered and the solids washed with more acetone. The acetone solution was concentrated under reduced pressure, and the residue was washed with water. No further purification was necessary.

Spectral and Analytical Data

3: White solid: mp 46-47°C. ^1H NMR (CDCl_3): δ 4.87 (s, 2H). ^{13}C NMR (CDCl_3): δ 166.1, 149.3, 121.2, 71.2. Anal. Calcd. for $\text{C}_4\text{H}_2\text{Cl}_2\text{O}_2$: C, 31.41; H, 1.32; Cl, 46.35. Found: C, 31.31; H, 1.17; Cl, 46.08.

4: White solid: mp 87-89°C. ^1H NMR (CDCl_3): δ 4.87 (s, 2H). ^{13}C NMR (CDCl_3): δ 166.9, 143.9, 114.8, 74.4. Anal. Calcd. for $\text{C}_4\text{H}_2\text{Br}_2\text{O}_2$: C, 19.86; H, 0.83; Br, 66.07. Found: C, 19.94; H, 0.79; Br, 66.15.

8a: Pale yellow solid: ^1H NMR (CDCl_3): δ 7.29-7.45 (m, 10H), 5.19 (s, 2H). ^{13}C NMR (CDCl_3): δ 173.7, 156.4, 130.9, 130.8, 130.4, 129.4, 129.2, 129.0, 128.8, 127.7, 126.2, 70.8. Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_2$: C, 81.34; H, 5.12. Found: C, 81.08; H, 4.97.

8b: Pale yellow solid: ^1H NMR (CDCl_3): δ 7.09-7.27 (m, 8H), 5.16 (s, 2H), 2.34 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (CDCl_3): δ 173.9, 156.3, 138.9, 138.6, 131.6, 131.0, 130.4, 130.0, 129.8, 129.0, 128.7, 128.1, 126.6, 126.3, 125.0, 70.9, 21.7, 21.6. Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_2$: C, 81.79; H, 6.10. Found: C, 81.75; H, 6.18.

8c: Pale yellow gum: ^1H NMR (CDCl_3): δ 7.24-7.31 (m, 2H), 6.83-7.01 (m, 6H), 5.16 (s, 2H), 3.75 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (CDCl_3): δ 173.55, 159.9, 156.4, 132.1, 131.7, 130.3, 130.0, 126.4, 121.9, 120.0, 116.8, 115.0, 114.7, 113.1, 70.8, 55.5, 55.4. Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_4$: C, 72.96; H, 5.44. Found: C, 72.71; H, 5.27.

8d: Pale yellow gum: ^1H NMR (CDCl_3): δ 7.16-7.43 (m, 8H), 5.14 (s, 2H). ^{13}C NMR (CDCl_3): δ 172.7, 155.9, 135.3, 134.8, 132.3, 131.5, 131.0, 130.7, 130.2, 129.5, 129.3, 127.6, 127.5, 126.1, 126.0, 70.7. Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{O}_2$: C, 62.98; H, 3.30; Cl, 23.24. Found: C, 62.90; H, 3.06; Cl, 23.27.

8e: Off-white solid: ^1H NMR (CDCl_3): δ 7.00-7.39 (m, 8H), 5.16 (s, 2H). ^{13}C NMR (CDCl_3): δ 172.8, 164.3, 161.8, 155.9, 132.7, 132.6, 131.9, 131.8, 131.3, 131.2, 130.7, 130.6, 126.3, 125.3, 123.6, 118.2, 118.0, 116.6, 116.5, 116.4, 116.3, 114.9, 114.6, 70.8. Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{F}_2\text{O}_2$: C, 70.59; H, 3.70; F, 13.96. Found: C, 70.37; H, 3.55; F, 14.13.

8f: Pale yellow gum: ^1H NMR (CDCl_3): δ 7.62-7.71 (m, 4H), 7.46-7.56 (m, 4H), 5.24 (s, 2H). ^{13}C NMR (CDCl_3): δ 171.6, 155.9, 132.9, 131.4, 131.0, 130.5, 130.2, 129.8, 127.9, 126.3, 124.5, 70.7. Anal. Calcd. for $\text{C}_{18}\text{H}_{10}\text{F}_6\text{O}_2$: C, 58.08; H, 2.71; F, 30.62. Found: C, 57.78; H, 2.72; F, 30.91.

9: Off-white solid: ^1H NMR (CDCl_3): δ 7.24-7.44 (m, 10H), 6.50 (d, J = 7.6 Hz, 1H), 4.82 (d, J = 8.1 Hz, 1H). ^{13}C NMR (CDCl_3): δ 171.6, 155.5, 130.8, 130.4, 129.6, 129.4, 129.1, 128.9, 128.4, 97.5. Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_3$: C, 76.18; H, 4.79. Found: C, 75.81; H, 4.76.

10: Pale yellow oil: ^1H NMR (CDCl_3): δ 7.34-7.43 (m, 5H), 5.85 (s, 1H), 4.92 (d, J = 11.5, 1H), 4.77 (d, J = 11.5, 1H). ^{13}C NMR (CDCl_3): δ 163.5, 147.9, 135.2, 129.0, 128.6, 124.5, 99.8, 71.9. Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{Cl}_2\text{O}_3$: C, 50.99; H, 3.11; Cl, 27.37. Found: C, 51.10; H, 3.05; Cl, 27.42.

11: Off-white solid: ^1H NMR (CDCl_3): δ 7.24-7.45 (m, 15H), 6.29 (s, 1H), 4.94 (d, J = 11.5, 1H), 4.84 (d, J = 11.5, 1H). ^{13}C NMR (CDCl_3): δ 170.8, 153.8, 136.0, 130.7, 130.4, 129.7, 129.6, 129.4, 129.1, 128.9, 128.85, 128.8, 128.7, 100.4, 71.5. Anal. Calcd. for $\text{C}_{23}\text{H}_{18}\text{O}_3$: C, 80.68; H, 5.30. Found: C, 80.63; H, 5.29.

13: White solid: mp 138-140°C. ^1H NMR (CDCl_3): δ 7.77-7.79 (m, 2H), 7.31-7.33 (m, 2H), 5.17 (s, 2H), 2.53 (s, 3H). ^{13}C NMR (CDCl_3): δ 170.1, 155.3, 144.9, 127.6, 125.9, 125.4, 105.5, 71.8, 15.1. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Br}_1\text{O}_2\text{S}_1$: C, 46.33; H, 3.18; Br, 28.02; S, 11.24. Found: C, 46.13; H, 3.19; Br, 28.32; S, 11.04.

14: White solid: ^1H NMR (CDCl_3): δ 7.37-7.44 (m, 5H), 7.22-7.25 (m, 2H), 7.14-7.17 (m, 2H), 5.16 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (CDCl_3): δ 173.8, 155.6, 143.0, 130.6, 129.5, 129.0, 128.0, 127.1, 126.0, 125.6, 70.6, 15.1. Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_2\text{S}_1$: C, 72.31; H, 5.00; S, 11.36. Found: C, 72.01; H, 4.87.

15: White solid: mp 197-199°C (dec.) . ^1H NMR (CDCl_3): δ 7.92 (d, $J = 8.5$, 2H), 7.51 (d, $J = 8.5$, 2H), 7.38-7.42 (m, 5H), 5.20 (s, 2H), 3.07 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 173.2, 156.7, 142.6, 136.3, 130.4, 129.8, 129.6, 129.4, 129.3, 128.1, 127.5, 124.9, 71.5, 43.8. Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_4\text{S}_1$: C, 64.95; H, 4.49. Found: C, 64.65; H, 4.40.

16: White solid: mp 156-158°C. ^1H NMR (CDCl_3): δ 7.70-7.73 (m, 2H), 7.29-7.33 (m, 2H), 5.19 (s, 2H), 2.52 (s, 3H). ^{13}C NMR (CDCl_3): δ 169.5, 151.4, 144.8, 127.6, 125.9, 124.9, 116.3, 70.2, 15.0. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Cl}_1\text{O}_2\text{S}_1$: C, 54.89; H, 3.77; Cl, 14.73; S, 13.32. Found: C, 54.93; H, 3.80; Cl, 14.48; S, 13.24.

17: White solid: ^1H NMR (CDCl_3): δ 8.10 (d, $J = 8.5$, 2H), 7.98 (d, $J = 8.5$, 2H), 5.25 (s, 2H), 3.10 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 169.1, 153.1, 143.4, 133.8, 129.2, 128.3, 118.3, 71.5, 43.9. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Cl}_1\text{O}_4\text{S}_1$: C, 48.45; H, 3.33; Cl, 13.00. Found: C, 48.42; H, 3.15; Cl, 12.66.

Chemical Structures

(-)-enterolactone: $R_1 = R_3 = \text{OH}$, $R_2 = R_4 = \text{H}$
 (-)-arctigenin: $R_1 = R_3 = R_4 = \text{OMe}$, $R_2 = \text{OH}$

Eucilat®

rubrolide C: $X = Y = \text{Br}$, $Z = \text{H}$
 rubrolide E: $X = Y = Z = \text{H}$
 rubrolide M: $X = \text{Br}$, $Y = \text{H}$, $Z = \text{Cl}$

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8a

8b

8c

8d

8e

8f

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