Supporting Information for
**Further Utilization of Mucohalic Acids: Palladium-free, Regioselective
Etherification and Amination of α,β -Dihalo γ -Methoxycarbonyloxy and γ -
Acetoxy Butenolides**

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Table of Contents

General Methods	S2
Experimental Details	S3
Spectral and Analytical Data	S5
Chemical Structures	S8

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. 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 or the singlet at 4.81 ppm for methanol-d₆. 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 47.8 ppm for methanol-d₆. Elemental analyses were performed out-of-house by Quantitative Technologies Inc.

Experimental Details

Preparation of 5-methoxycarbonyloxy-3,4-dichloro-5H-furan-2-one (1e). Methyl chloroformate (9.92 g, 105 mmol) was added to a cold (-10 to -5°C) solution of mucochloric acid (**1c**, 16.9 g, 100 mmol) in dry dichloromethane (200 mL). Diisopropylethylamine (14.2 g, 110 mmol) was then added over 5 min and stirring at -10 to -5°C was continued for 2.5 h. The reaction mixture was quenched with water (200 mL) and diluted with dichloromethane (600 mL). The phases were separated and the red organic phase was washed with water (400 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/heptane) followed by recrystallization (ethyl acetate/heptane) to give **1e** as an off-white solid: yield 16.2 g (71%).

Preparation of 5-methoxycarbonyloxy-3,4-dibromo-5H-furan-2-one (1f). Methyl chloroformate (4.96 g, 52.5 mmol) was added to a cold (-10 to -5°C) solution of mucobromic acid (**1d**, 12.9 g, 50.0 mmol) in dry dichloromethane (200 mL). Diisopropylethylamine (7.11 g, 55.5 mmol) was then added over 10 min and stirring at -10 to -5°C was continued for 1.5 h. The reaction mixture was quenched with water (100 mL) and diluted with dichloromethane (200 mL). The phases were separated and the red organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/heptane) followed by recrystallization (ethyl acetate/heptane) to give **1f** as a beige solid: yield 7.17 g (45%).

Preparation of 5-tert-butyloxycarbonyloxy-3,4-dichloro-5H-furan-2-one (1g). Mucochloric acid (**1c**, 1.69 g, 10.0 mmol), di-tert-butyl dicarbonate (2.50 g, 11.5 mmol) and N-methylmorpholine (1.21 g, 12.0 mmol) were combined in dry dichloromethane (50 mL) and stirred at 20-25°C for 18 h. The reaction mixture was quenched with water (50 mL) and partitioned between water (20 mL) and dichloromethane (50 mL). The phases were separated and the dark organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/heptane) followed by pulping in heptane to give **1g** as a white solid: yield 0.93 g (35%).

Preparation of 5-acetoxy-3,4-dichloro-5H-furan-2-one (1h). Mucochloric acid (**1c**, 16.9 g, 100 mmol), acetic anhydride (12.3 g, 120 mmol) and Amberlyst-15 (0.7 g) were combined in dry dichloromethane (300 mL) and stirred at 20-25°C for 3 d. The reaction mixture was diluted with dichloromethane (500 mL) and washed with saturated aqueous sodium bicarbonate (3x200 mL) and brine (100 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure to give **1h** as a colorless oil: yield 20.4 g (97%).

General procedure for etherification of carbonate 1e (conditions screen). Compound 4a. Carbonate **1e** (2.0 mmol) was combined with *m*-cresol (1.1 equiv.), the desired base (0.15-0.5 equiv.) and the desired Pd catalyst (0-3 mol%) in dichloromethane (20 mL) and stirred at 20-25°C for 4-65 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) and partitioned between water (20 mL) and dichloromethane (80 mL). The organic extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/heptane).

General procedure for etherification of carbonates 1e-g and acetate 1h (phenol screen). Compounds 4a-h. Carbonate **1e**, **1f** or **1g** or acetate **1h** (2.0 mmol) was combined with the desired phenol (1.1 equiv.) and CsF (0.2 equiv.) (1.1 equiv. with **1h**) in dichloromethane (20 mL) and stirred at 20-25°C for 7-24 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) and partitioned between water (20 mL) and dichloromethane (80 mL). The organic extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/heptane).

General procedure for amination of carbonates 1e and 1f and acetate 1h. Compounds 7a-d. Carbonate **1e** or **1f** or acetate **1h** (2.0 mmol) was combined with the desired amine (1.0-2.0 equiv.) in toluene (20 mL) and stirred at 0-25°C for 2-8 h. The reaction mixture was partitioned between brine (10 mL) and toluene (20 mL). The organic phase was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/heptane).

Preparation of compound 8. Carbonate **1f** (1.0 mmol) was combined with aniline (2.0 equiv.) in N-methylpyrrolidinone (5 mL) and stirred at 20-25°C for 24 h. The reaction mixture was diluted with water (50 mL) and the resulting slurry was filtered. The solid was washed with water (10 mL) and heptane. (5 mL) and dried. No further purification was necessary.

Spectral and Analytical Data

1e: ^1H NMR (CDCl_3): δ 6.76 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (CDCl_3): δ 162.4, 153.6, 146.4, 125.3, 94.4, 56.6. Anal. Calcd. for $\text{C}_6\text{H}_4\text{Cl}_2\text{O}_5$: C, 31.75; H, 1.78; Cl, 31.24. Found: C, 31.75; H, 1.57; Cl, 31.48.

1f: ^1H NMR (CDCl_3): δ 6.76 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (CDCl_3): δ 163.3, 153.6, 141.6, 119.6, 96.6, 56.5. Anal. Calcd. for $\text{C}_6\text{H}_4\text{Br}_2\text{O}_5$: C, 22.81; H, 1.28; Br, 50.59. Found: C, 22.75; H, 1.23; Br, 50.88.

1g: ^1H NMR (CDCl_3): δ 6.73 (s, 1H), 1.54 (s, 9H). ^{13}C NMR (CDCl_3): δ 162.7, 150.8, 146.7, 93.9, 86.1, 27.8. Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{Cl}_2\text{O}_5$: C, 40.17; H, 3.75; Cl, 26.35. Found: C, 40.33; H, 3.54; Cl, 26.62.

1h: ^1H NMR (CDCl_3): δ 6.90 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (CDCl_3): δ 168.6, 162.8, 147.2, 124.7, 91.4, 20.7. Anal. Calcd. for $\text{C}_6\text{H}_4\text{Cl}_2\text{O}_4$: C, 34.15; H, 1.91; Cl, 33.60. Found: C, 34.24; H, 1.88; Cl, 33.41.

4a: ^1H NMR (CDCl_3): δ 7.21-7.25 (m, 1H), 6.92-6.98 (m, 3H), 6.21 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (CDCl_3): δ 163.0, 156.0, 147.2, 140.5, 129.9, 125.7, 124.9, 118.4, 114.7, 99.5, 21.6. 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, 51.22; H, 3.13; Cl, 27.05.

4b: ^1H NMR (CDCl_3): δ 7.07-7.11 (m, 2H), 6.85-6.89 (m, 2H), 6.14 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (CDCl_3): δ 163.0, 157.0, 149.5, 147.2, 125.0, 119.8, 115.1, 100.4, 55.9. Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{Cl}_2\text{O}_4$: C, 48.03; H, 2.93; Cl, 25.78. Found: C, 47.93; H, 2.78; Cl, 25.55.

4c: ^1H NMR (CDCl_3): δ 6.61-6.75 (m, 3H), 6.11 (s, 1H), 5.98 (s, 2H). ^{13}C NMR (CDCl_3): δ 162.9, 150.7, 148.6, 147.0, 145.1, 125.1, 110.8, 108.4, 102.0, 101.5, 100.4. Anal. Calcd. for $\text{C}_{11}\text{H}_6\text{Cl}_2\text{O}_5$: C, 45.71; H, 2.09; Cl, 24.53. Found: C, 45.78; H, 1.90; Cl, 24.76.

4d: ^1H NMR (CDCl_3): δ 7.35-7.40 (m, 2H), 7.14-7.21 (m, 3H), 6.25 (s, 1H), 3.79. ^{13}C NMR (CDCl_3): δ 163.0, 155.9, 147.0, 130.2, 125.0, 117.8, 99.4. Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{Cl}_2\text{O}_3$: C, 49.01; H, 2.47; Cl, 28.93. Found: C, 49.02; H, 2.26; Cl, 28.81.

4e: ^1H NMR (CDCl_3): δ 7.30-7.36 (m, 1H), 6.87-6.97 (m, 3H), 6.23 (s, 1H). ^{13}C NMR (CDCl_3): δ 164.7, 162.8, 162.3, 156.9, 156.8, 146.9, 131.2, 131.1, 125.2, 113.2, 113.1, 112.1, 111.9, 106.0, 105.8, 98.9. Anal. Calcd. for $\text{C}_{10}\text{H}_5\text{Cl}_2\text{F}_1\text{O}_3$: C, 45.66; H, 1.92; Cl, 26.95; F, 7.22. Found: C, 45.63; H, 1.65; Cl, 27.10; F, 7.53.

4f: ^1H NMR (CDCl_3): δ 7.13-7.25 (m, 1H), 7.07-7.08 (m, 2H), 6.21 (s, 1H). ^{13}C NMR (CDCl_3): δ 165.5, 156.6, 146.7, 136.2, 125.3, 120.6, 116.7, 98.6. Anal. Calcd. for $\text{C}_{10}\text{H}_4\text{Cl}_4\text{O}_3$: C, 38.26; H, 1.28; Cl, 45.17. Found: C, 38.64; H, 1.21; Cl, 45.35.

4g: ^1H NMR (CDCl_3): δ 7.30-7.33 (m, 2H), 7.21-7.25 (m, 1H), 7.07-7.11 (m, 1H), 6.21 (s, 1H). ^{13}C NMR (CDCl_3): δ 162.8, 156.5, 146.9, 131.4, 128.2, 125.2, 123.3, 121.2, 116.4, 99.0. Anal. Calcd. for $\text{C}_{10}\text{H}_5\text{Br}_1\text{Cl}_2\text{O}_3$: C, 37.08; H, 1.56; Br, 24.67. Found: C, 37.16; H, 1.29; Br, 25.04.

4h: ^1H NMR (CDCl_3): δ 7.22-7.25 (m, 1H), 6.95-6.99 (m, 3H), 6.22 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (CDCl_3): δ 164.0, 156.1, 142.9, 140.5, 129.9, 125.7, 119.3, 118.4, 114.6, 101.7, 21.7. Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{Br}_2\text{O}_3$: C, 37.97; H, 2.32; Br, 45.92. Found: C, 38.34; H, 2.15; Br, 46.06.

7a: ^1H NMR (CDCl_3): δ 7.28-7.36 (m, 5H), 5.11 (d, $J = 10.7$, 1H), 4.98 (d, $J = 14.9$, 1H), 4.29 (d, $J = 14.9$, 1H), 3.45 (variable) (d, $J = 10.7$, 1H). ^{13}C NMR (CDCl_3): δ 163.3, 144.4, 135.9, 129.2, 128.7, 128.3, 126.2, 81.6, 43.9. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Cl}_2\text{N}_1\text{O}_2$: C, 51.19; H, 3.51; Cl, 27.47; N, 5.43. Found: C, 51.47; H, 3.35; Cl, 27.25; N, 5.23.

7b: ^1H NMR (CDCl_3): δ 5.72-5.81 (m, 1H), 5.20-5.28 (m, 3H), 4.26-4.32 (m, 1H), 3.91 (variable) (d, $J = 9.0$, 1H), 3.79-3.85 (m, 1H). ^{13}C NMR (CDCl_3): δ 163.0, 144.1, 131.9, 126.6, 81.9, 42.8. Anal. Calcd. for $\text{C}_7\text{H}_7\text{Cl}_2\text{N}_1\text{O}_2$: C, 40.41; H, 3.39; Cl, 34.08; N, 6.73. Found: C, 40.50; H, 3.21; Cl, 33.94; N, 6.80.

7c: ^1H NMR (CDCl_3): δ 9.53 (s, 1H), 5.053.38-3.42 (m, 1H), 3.18-3.21 (m, 1H), 1.56-1.70 (m, 2H), 0.94 (t, $J = 7.3$, 1H), 0.88 (t, $J = 7.3$, 1H). ^{13}C NMR (CDCl_3): δ 181.1, 161.8, 145.5, 134.0, 50.6, 46.9, 21.8, 20.5, 11.6, 11.4. Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{Cl}_2\text{N}_1\text{O}_2$: C, 47.64; H, 6.00; Cl, 28.12; N, 5.56. Found: C, 47.30; H, 5.79; Cl, 28.31; N, 5.63.

7d: ^1H NMR (CDCl_3): δ 7.28-7.36 (m, 5H), 5.12 (d, $J = 10.7$, 1H), 4.99 (d, $J = 14.9$, 1H), 4.32 (d, $J = 14.6$, 1H), 3.46 (variable) (d, $J = 11.0$, 1H). ^{13}C NMR (CDCl_3): δ 163.6, 139.6, 136.1, 129.3, 128.9, 128.4, 122.4, 84.0, 44.5. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Br}_2\text{N}_1\text{O}_2$: C, 38.07; H, 2.61; Br, 46.05; N, 4.04. Found: C, 38.16; H, 2.53; Br, 46.28; N, 4.15.

8: ^1H NMR (CDCl_3): δ 7.37-7.42 (m, 2H), 7.27-7.31 (m, 1H), 7.15-7.18 (m, 2H), 6.92 (s, 1H), 6.74 (br s, 1H), 3.72 (s, 3H). ^{13}C NMR (CDCl_3): δ 166.2, 156.7, 153.6, 136.2, 129.9, 127.5, 124.6, 92.5, 79.5, 56.1. Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{BrN}_1\text{O}_5$: C, 43.93; H, 3.07; Br, 24.35; N, 4.27. Found: C, 43.38; H, 2.85; Br, 24.75; N, 4.30.

Chemical Structures

1c

1d

1e

1f

1g

1h

4a

4b

4c

4d

4e

4f

4g

4h

7a

7b

7c

7d

8