Supporting Information for
First Direct Reductive Amination of Mucochloric Acid, a Simple and Efficient Method to Prepare Highly Functionalized α,β -Unsaturated γ -Butyrolactams

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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 or the singlet at 2.52 ppm for DMSO-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 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

General procedure for reductive amination reactions (solvent screen). Compound 7. Sodium triacetoxyborohydride (1.5 equiv., 2.53 g, 15.0 mmol) was slowly added to a mixture of mucochloric acid (**1**, 1.68 g, 10.0 mmol) and benzylamine (1.1 equiv., 1.18 g, 11.0 mmol) in desired solvent (50 mL). The reaction mixture was stirred at 20-25°C for 24h. The reaction mixture was partitioned between water (200 mL) chloroform (200 mL), the phases were separated and the organic phase was washed once with water (200 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by recrystallization.

General procedure for reductive amination reactions (aniline screen). Compound 8. Sodium triacetoxyborohydride (1.5 equiv.) was slowly added to a mixture of mucochloric acid (**1**, 1.68 g, 10.0 mmol) and desired aniline (1.1 equiv.) in chloroform (50 mL) and acetic acid (0.5 mL). The reaction mixture was stirred at 20-25°C for 24h. The reaction mixture was partitioned between water (200 mL) chloroform (200 mL), the phases were separated and the organic phase was washed once with water (200 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by recrystallization.

General procedure for reductive amination reactions (aniline screen). Compounds 9-15. Sodium triacetoxyborohydride (3.0 equiv.) was slowly added to a mixture of mucochloric acid (**1**, 1.68 g, 10.0 mmol) and desired aniline (1.0 equiv.) in dichloromethane (50 mL) and acetic acid (30 mL). The reaction mixture was stirred at 20-25°C for 24h. The reaction mixture was partitioned between water (200 mL) chloroform (200 mL), the phases were separated and the organic phase was washed once with water (200 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by recrystallization.

General procedure for reductive amination reactions (amine screen). Compounds 16-20. Sodium triacetoxyborohydride (1.5 equiv.) was slowly added to a mixture of mucochloric acid (**1**, 1.68 g, 10.0 mmol) and desired 'aniline' (1.1 equiv.) in chloroform (50 mL) and acetic acid (0.5 mL). (For reactions that included molecular sieves, 2 g of powdered 4A molecular sieves were added.) The reaction mixture was stirred at 20-25°C for 24h. The reaction mixture was partitioned between water (200 mL) chloroform (200 mL), the phases were separated and the organic phase was washed once with water (200 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by recrystallization.

Spectral and Analytical Data

7: Orange-yellow solid: ^1H NMR (CDCl_3): δ 7.22-7.37 (m, 5H), 4.65 (s, 2H), 3.89 (s, 2H). ^{13}C NMR (CDCl_3): δ 164.4, 140.1, 136.0, 129.2, 128.4, 128.3, 125.7, 53.0, 47.1. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Cl}_2\text{N}_1\text{O}_1$: C, 54.57; H, 3.75; N, 5.79; Cl, 29.29. Found: C, 54.62; H, 3.40; N, 5.64; Cl, 29.21.

8: Off-white solid: ^1H NMR (CDCl_3): δ 7.87 (d, J = 2.2, 2H), 6.29 (t, J = 2.2, 1H), 4.44 (s, 2H), 3.80 (s, 6H). Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{N}_1\text{O}_3$: C, 50.02; H, 3.85; N, 4.86; Cl, 24.61. Found: C, 49.78; H, 3.63; N, 4.78; Cl, 24.84.

9: Yellow solid: ^1H NMR (CDCl_3): δ 7.68 (t, J = 1.9, 1H), 7.56-7.59 (m, 1H), 7.32 (t, J = 8.3, 1H), 7.14-7.17 (m, 1H), 4.48 (s, 2H). ^{13}C NMR (CDCl_3): δ 162.9, 140.2, 139.4, 135.4, 130.7, 126.6, 125.3, 118.9, 116.7, 53.7. Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{Cl}_3\text{N}_1\text{O}_1$: C, 45.75; H, 2.30; N, 5.34. Found: C, 45.83; H, 2.26; N, 5.13.

10: Pale yellow solid: ^1H NMR (CDCl_3): δ 8.35 (t, J = 2.2, 1H), 8.25-8.27 (m, 1H), 8.02-8.05 (m, 1H), 7.59 (t, J = 8.3, 1H), 4.58 (s, 2H). ^{13}C NMR (CDCl_3): δ 163.2, 149.0, 140.8, 139.4, 130.7, 126.6, 124.6, 119.8, 112.9, 53.7. Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{Cl}_2\text{N}_2\text{O}_3$: C, 43.98; H, 2.21; N, 10.26. Found: C, 44.08; H, 2.23; N, 10.10.

11: Yellow-brown solid: ^1H NMR ($\text{DMSO}-d_6$): δ 9.66 (s, 1H), 7.29 (t, J = 2.2, 1H), 7.20 (t, J = 8.0, 1H), 7.04-7.07 (m, 1H), 6.59-6.62 (m, 1H), 4.82 (s, 2H). ^{13}C NMR ($\text{DMSO}-d_6$): δ 162.5, 158.5, 141.9, 139.9, 130.4, 124.5, 112.4, 109.9, 106.8, 54.2. Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{Cl}_2\text{N}_1\text{O}_2$: C, 49.21; H, 2.89; N, 5.74. Found: C, 49.23; H, 2.84; N, 5.53.

12: Off-white solid: ^1H NMR (CDCl_3): δ 7.41 (t, J = 2.2, 1H), 7.29 (t, J = 8.0, 1H), 7.07-7.10 (m, 1H), 6.72-6.75 (m, 1H), 4.47 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (CDCl_3): δ 162.8, 160.5, 139.9, 139.5, 130.2, 126.4, 110.8, 110.6, 105.0, 55.6, 53.8. Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{Cl}_2\text{N}_1\text{O}_2$: C, 51.19; H, 3.51; N, 5.43. Found: C, 51.53; H, 3.30; N, 5.35.

13: Orange-yellow solid: ^1H NMR (CDCl_3): δ 7.99-8.02 (m, 2H), 7.77-7.80 (m, 2H), 4.54 (s, 2H), 2.59 (s, 3H). ^{13}C NMR ($\text{DMSO}-d_6$): δ 197.1, 163.0, 143.0, 142.8, 133.2, 130.1, 124.5, 118.3, 54.1, 27.2. Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{Cl}_2\text{N}_1\text{O}_2$: C, 53.36; H, 3.36; N, 5.19. Found: C, 53.61; H, 3.35; N, 5.12.

14: Yellow solid: ^1H NMR ($\text{DMSO}-d_6$): δ 8.11-8.17 (m, 2H), 7.66-7.67 (m, 2H), 4.92 (s, 2H). ^{13}C NMR ($\text{DMSO}-d_6$): δ 163.1, 143.0, 139.6, 131.2, 128.6, 124.3, 123.9, 122.3, 119.1, 112.6, 54.1. Anal. Calcd. for $\text{C}_{11}\text{H}_6\text{Cl}_2\text{N}_2\text{O}_1$: C, 52.20; H, 2.39; N, 11.07. Found: C, 52.19; H, 2.19; N, 10.93.

15: Pale yellow solid: ^1H NMR (DMSO- d_6): δ 12.88 (br s, 1H), 7.99-8.01 (m, 2H), 7.87-7.89 (m, 2H), 4.92 (s, 2H). ^{13}C NMR (DMSO- d_6): δ 167.4, 163.1, 143.0, 142.6, 131.2, 126.9, 124.4, 118.5, 54.1. Anal. Calcd. for $\text{C}_{11}\text{H}_7\text{Cl}_2\text{N}_1\text{O}_3$: C, 48.56; H, 2.59; N, 5.15. Found: C, 48.42; H, 2.38; N, 5.02.

16: Off-white solid: ^1H NMR (CDCl_3): δ 4.02 (s, 2H), 3.54 (q, $J = 7.3$, 2H), 1.20 (t, $J = 7.3$, 3H). Anal. Calcd. for $\text{C}_6\text{H}_7\text{Cl}_2\text{N}_1\text{O}_1$: C, 40.03; H, 3.92; N, 7.78; Cl, 39.39. Found: C, 40.06; H, 3.76; N, 7.74; Cl, 39.09.

17: White solid: ^1H NMR (CDCl_3): δ 7.25-7.36 (m, 5H), 5.59 (q, $J = 7.1$, 1H), 3.94 (d, $J = 18.8$, 1H), 3.62 (d, $J = 18.5$, 1H), 1.60 (d, $J = 7.1$, 3H). ^{13}C NMR (CDCl_3): δ 164.1, 140.1, 139.7, 129.1, 128.3, 127.3, 125.5, 50.5, 49.7, 17.5. Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{N}_1\text{O}_1$: C, 56.27; H, 4.33; N, 5.47; Cl, 27.68. Found: C, 56.17; H, 4.20; N, 5.27; Cl, 27.34. $[\alpha]_D^{20} +113.1$ ($c=7.0$, CHCl_3).

18: White solid: ^1H NMR (CDCl_3): δ 7.25-7.40 (m, 5H), 5.17 (dd, $J = 8.3$, $J = 4.4$, 1H), 4.06-4.27 (m, 2H), 4.10 (d, $J = 18.8$, 1H), 3.85 (d, $J = 18.8$, 1H), 3.15 (t, $J = 6.1$, 1H). ^{13}C NMR (DMSO- d_6): δ 164.2, 141.9, 138.4, 131.7, 129.3, 128.3, 128.0, 124.2, 61.6, 58.5, 51.7. Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{N}_1\text{O}_2$: C, 52.96; H, 4.07; N, 5.15; Cl, 26.06. Found: C, 53.09; H, 3.92; N, 4.98; Cl, 25.73. $[\alpha]_D^{20} +40.0$ ($c=5.3$, CHCl_3).

19: White solid: ^1H NMR (CDCl_3): δ 7.25-7.40 (m, 5H), 5.17 (dd, $J = 8.3$, $J = 4.4$, 1H), 4.08-4.26 (m, 2H), 4.09 (d, $J = 18.8$, 1H), 3.85 (d, $J = 19.0$, 1H), 3.11 (br s, 1H). Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{N}_1\text{O}_2$: C, 52.96; H, 4.07; N, 5.15. Found: C, 53.09; H, 3.94; N, 5.06. $[\alpha]_D^{20} -38.6$ ($c=5.6$, CHCl_3).

20: White solid: ^1H NMR (CDCl_3): δ 7.17-7.33 (m, 4H), 5.67 (d, $J = 6.6$, 1H), 4.87-4.92 (m, 1H), 4.20 (d, $J = 19.3$, 1H), 3.78 (d, $J = 19.0$, 1H), 3.67 (br s, 1H), 3.30 (dd, $J = 16.9$, $J = 7.3$, 1H), 2.97 (dd, $J = 16.9$, $J = 5.4$, 1H). ^{13}C NMR (CDCl_3): δ 165.9, 141.6, 141.3, 137.6, 129.4, 127.7, 125.8, 125.7, 124.8, 73.0, 59.7, 53.1, 40.0. Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{Cl}_2\text{N}_1\text{O}_2$: C, 54.95; H, 3.90; N, 4.93; Cl, 24.95. Found: C, 54.77; H, 3.54; N, 4.84; Cl, 24.72. $[\alpha]_D^{20} -7.4$ ($c=5.4$, CHCl_3).

Chemical Structures