Supporting Information
for DOI: 10.1055/s-0034-1379986
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The Synthesis of 5,5-Disubstituted Piperidinones via a Reductive Amination–Lactamization Sequence: The Formal Synthesis of (±)-Quebrachamine

Supporting Information

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Experimental

General Considerations

Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 ppm for ¹³C). ¹⁹F spectra were externally referenced to neat trifluorotoluene (referenced to -63.9 ppm). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Optical rotations were recorded in cells of 10 cm path length using a Perkin-Elmer 241 digital polarimeter.

All reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F₂₅₄) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

dimethyl 3-ethyl-3-formylpimelate 2 was prepared using the following procedure: Pyrrolidine (50.0 ml, 609 mmol) and K₂CO₃ (21.0 g, 150 mmol) were stirred at 0 °C. Butyraldehyde (36.4 ml, 406 mmol) was added dropwise to the solution. The solution was mixed for 20 hours then filtered through celite, and the volatiles were removed. The cured 1-(but-1-enyl)pyrrolidine was dissolved in Methanol (391 ml). methyl acrylate (118.0 ml, 1302 mmol) was added and the solution was heated to reflux for 21 hours. The reaction mixture was then cooled and acetic acid (24.0 ml) and H₂O (156.0 ml) was added abd the mixture was heated to reflux for an additional 7 hours. The volatiles were then removed and H₂O (820.0 ml) was added, and the solution was extracted four times with DCM. The organics were then washed with aqueous sodium bicarbonate and brine sequentially. The organic layer was dried and the solvent removed. The crude product was purified by fractional distillation (140-142 °C at 1 mmhg) to yield pure 2 as a yellow oil, 54% (54 g, 221 mmol). ¹H-NMR (600 MHz, CDCl₃): δ = 9.37 (s, 1H), 3.62 (s, 6H), 2.17 (ddd, J = 7.6, 7.6, 3.5 Hz, 4H), 1.81 (ddd, J = 8.22, 7.1, 1.8 Hz, 4H), 1.51 (q, J = 7.6 Hz, 2H), 0.79 (t, J = 7.0, Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 205.0, 173.4, 51.9, 51.0, 28.2, 26.0, 24.3, 7.6; IR (thin film): 2954, 2708, 1732, 1438, 1377, 13.77, 1120, 991, 886, 784; HRMS (M+1) calc’d for C₁₂H₂₀O₅ = 245.1384, found = 245.1397.

S2
General Experimental Procedure for the Synthesis of Piperidinones 3a-i: dimethyl 3-ethyl-3-formylpimelate (1 equivalent) and primary amine (1 equivalent) were dissolved in methanol. Sc(OTf)_3 (0.025 equivalent) was then added and the mixture was stirred for 1-2 hours, followed by the addition of NaBH₄ (1.25 equivalent). Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with ethyl acetate. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinones 3a-i.

Piperidinone 3a was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), 2-(1H-indol-3-yl)ethanamine (144 mg, 0.90 mmol), Sc(OTf)_3 (20 mg, 0.041 mmol), NaBH₄ (37 mg, 0.98 mmol), and Methanol (2 ml). Yielded piperidinone 3a as a light yellow oil, 96% (280 mg, 0.79 mmol). Rᵣ = 0.33, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 8.22 (brs, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 2.35 Hz, 1H), 3.70-3.59 (m, 5H), 3.03 (dd, J = 12.3, 7.4 Hz, 2H), 2.92 (AB system, 2H), 2.37 (dd, J = 7.04, 7.04 Hz, 2H), 2.19-2.07 (m, 2H), 1.66-1.60 (m, 1H), 1.59-1.51 (m, 3H), 1.34-1.27 (m 1H), 1.27-1.20 (m, 1H), 0.74 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.9, 169.5, 136.3, 127.5, 122.1, 122.0, 119.3, 118.7, 113.0, 111.2, 57.2, 51.7, 48.5, 34.3, 29.7, 28.9, 28.5, 28.2, 26.8, 23.1, 7.3; IR (thin film): 3258, 3055, 2929, 2876, 1736, 1624, 1498, 1458, 1435, 1366, 1230, 1170, 743; HRMS calc'd for C₂₁H₂₉N₂O₃ = 356.2100, found = 356.2091.

Piperidinone 3b was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), tert-butyl 3-(2-aminoethyl)-1H-indole-1-carboxylate (234 mg, 0.90 mmol), Sc(OTf)_3 (20 mg, 0.041 mmol), NaBH₄ (37 mg, 0.98 mmol), and Methanol (2 ml). Yielded piperidinone 3b as a light yellow oil, 76% (285 mg, 0.62 mmol). Rᵣ = 0.43, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 8.12 (brs, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.41 (brs, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.26-7.23 (m, 1H), 3.70-3.63 (m, 4H), 3.59-3.53 (m, 1H), 3.02-2.91 (m, 4H), 2.38 (dd, J = 7.0, 7.0 Hz, 2H), 2.23-2.13 (m, 2H), 1.70-1.51 (m, 1H), 1.40-1.32 (m, 1H), 1.31-1.23 (m, 1H), 0.79 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.6, 169.4, 149.5, 135.4, 130.3, 124.3, 123.0, 122.4, 118.9, 117.6, 115.1, 82.3, 57.2, 51.6, 47.9, 34.3, 29.5, 29.1, 28.4, 28.12, 28.08, 26.5, 22.8, 7.2; IR (thin
Piperidinone 3c was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (300 mg, 1.23 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (237 mg, 1.35 mmol), Sc(OTf)₃ (30 mg, 0.061 mmol), NaBH₄ (56 mg, 1.48 mmol), and Methanol (3 ml). Yielded piperidinone 3c as a yellow oil, 76% (346 mg, 0.93 mmol). Rf =0.27, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 3.76 (dd, J = 5.9, 5.9 Hz, 2H), 3.67 (s, 3H), 3.49-3.40 (m, 2H), 3.18 (AB system, 2H), 2.35 (dd, J = 7.0, 7.0 Hz, 2H), 2.25-2.22 (m, 2H), 1.75-1.66 (m, 2H), 1.63-1.55 (m, 2H), 1.44-1.38 (m, 1H), 1.36-1.30 (m, 1H), 0.89 (s, 9H), 0.84 (t, J = 7.3 Hz, 3H), 0.05 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.8, 169.6, 61.6, 58.9, 51.7, 50.5, 34.5, 29.7, 28.9, 28.5, 28.3, 26.9, 25.8, 18.1, 7.4, -5.5; IR (thin film): 2930, 2858, 1740, 1646, 1493, 1470, 1436, 1363, 1256, 1105, 1054, 1006, 921, 837, 778; HRMS (M+1) calc’d for C₁₉H₂₇NO₃Si = 372.2565, found = 372.2565.

Piperidinone 3d was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (726 mg, 2.97 mmol), 2-(phenylthio)ethanamine (500 mg, 3.26 mmol), Sc(OTf)₃ (36 mg, 0.073 mmol), NaBH₄ (135 mg, 3.57 mmol), and Methanol (7 ml). Yielded piperidinone 3d as a red oil, 64% (660 mg, 1.89 mmol). Rf = 0.23, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.38 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.0 Hz, 1H), 3.67 (s, 3H), 3.57-3.49 (m, 2H), 3.14 (dd, J = 7.0, 7.0 Hz, 2H), 3.05 (AB system, 2H), 2.33 (dd, J = 7.0, 7.0 Hz, 2H), 2.24-2.21 (m, 2H), 1.70-1.66 (m, 2H), 1.58-1.50 (m, 2H), 1.41-1.30 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.7, 169.8, 129.0, 128.8, 126.0, 58.1, 51.8, 48.1, 34.6, 30.5, 29.7 29.1, 28.4, 28.3, 26.7, 7.4 (missing 1 carbon presumably due to overlap); IR (thin film): 2932, 2876, 1736, 1642, 1492, 1438, 1363, 1295, 1229, 1168, 1025, 741, 693; HRMS calc’d for C₁₉H₁₇NO₃S = 349.1712, found = 349.1719.

Piperidinone 3e was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), phenylmethanamine (88 mg, 0.82 mmol), Sc(OTf)₃ (10 mg, 0.020 mmol), NaBH₄ (39 mg, 1.031 mmol), and Methanol (2 ml). Yielded piperidinone 3e as an orange oil, 81% (202...
mg, 0.67 mmol). $R_t = 0.28$, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta = 7.32$-$7.30$ (m, 2H), 7.27-$7.24$ (m, 3H), 4.57 (AB system, 2H), 3.65 (s, 3H), 2.91 (AB system, 2H), 2.46 (dd, $J = 7.0$, 1.2 Hz, 2H), 2.18-$2.12$ (m, 1H), 2.04-$1.98$ (m, 1H), 1.63-$1.59$ (m, 4H), 1.33-$1.22$ (m, 2H), 0.71 (t, $J = 7.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 173.7$, 169.5, 137.1, 128.6, 128.3, 127.5, 55.4, 51.7, 50.3, 34.3, 30.0, 28.9, 28.5, 28.2, 26.5, 7.2; IR (thin film): 3454, 3056, 3062, 3029, 2948, 1736, 1647, 1494, 1454, 1363, 1229, 1069, 1002, 854, 703; HRMS calc’d for C$_{18}$H$_{25}$NO$_3$ = 303.1834, found = 303.1825.

Piperidinone 3f was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), butan-1-amine (60 mg, 0.82 mmol), Sc(OTf)$_3$ (10 mg, 0.020 mmol), NaBH$_4$ (39 mg, 1.031 mmol), and Methanol (2 ml). Yielded piperidinone 3f as a yellow oil, 86% (190 mg, 0.71 mmol). $R_t = 0.38$, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta = 3.67$ (s, 3), 3.36-$3.26$ (m, 2H), 2.99 (AB system, 2H), 2.33 (dd, $J = 7.0$, 7.0 Hz, 2H), 2.27-$2.19$ (m, 2H), 1.73-$1.64$ (m, 2H), 1.63-$1.54$ (m, 2H), 1.50-$1.45$ (m, 2H), 1.42-$1.27$ (m, 4H), 0.91 (t, $J = 7.0$ Hz, 3H), 0.84 (t, $J = 7.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 173.8$, 169.2, 56.5, 51.8, 47.1, 34.4, 29.9, 29.2, 29.1, 28.5, 28.3, 26.7, 20.1, 13.9, 7.4; IR (thin film): 2957, 2872, 1739, 1644, 1494, 1466, 1435, 1366, 1317, 1229, 1167, 1000; HRMS calc’d for C$_{15}$H$_{27}$NO$_3$ = 269.1991, found = 269.1986.

Piperidinone 3g was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), 4-methoxyaniline (101 mg, 0.82 mmol), Sc(OTf)$_3$ (10 mg, 0.020 mmol), NaBH$_4$ (39 mg, 1.031 mmol), and Methanol (2 ml). Yielded piperidinone 3g as a brown oil, 31% (82 mg, 0.26 mmol). $R_t = 0.32$, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta = 7.12$ (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.34 (AB system, 2H), 2.59 (dd, $J = 7.0$, 7.0 Hz, 2H), 2.31-$2.21$ (m, 2H), 1.84-$1.76$ (m, 2H), 1.75-$1.71$ (m, 2H), 1.53-$1.41$ (m, 2H), 0.87 (t, $J = 7.6$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 173.7$, 170.0, 158.1, 136.2, 127.2, 114.5, 60.4, 55.4, 51.7, 34.9, 30.0, 29.0, 28.9, 28.3, 28.8, 7.4; IR (thin film): 2929, 1736, 1656, 1512, 1464, 1295, 1245, 1178, 1033, 832; HRMS calc’d for C$_{18}$H$_{25}$NO$_4$ = 319.1784, found = 319.1778.

Piperidinone 3h was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), prop-2-en-1-
Piperidinone 3h was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (200 mg, 0.82 mmol), cyclohexanamine (81 mg, 0.82 mmol), Sc(OTf)₃ (10 mg, 0.020 mmol), NaBH₄ (39 mg, 1.031 mmol), and Methanol (2 ml). Yielded piperidinone 3h as a yellow oil, 83% (171 mg, 0.68 mmol). Rᵣ =0.30, 100% EtOAc in hexanes; 

¹H-NMR (600 MHz, CDCl₃): δ = 5.76-5.69 (m, 1H), 5.17 (ddd, J = 10.0, 7.0, 1.2 Hz, 2H), 4.08-3.92 (m, 2H), 3.67 (s, 3H), 2.96 (AB system, 2H), 2.38 (dd, J = 7.0, 7.0 Hz, 2H), 2.27-2.18 (m, 2H), 1.69 (ddd, J = 10.6, 7.0, 3.5 Hz, 2H), 1.64-1.57 (m, 2H), 1.40-1.32 (m, 2H), 0.84 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.8, 169.3, 132.9, 117.9, 55.7, 51.8, 49.6, 34.4, 29.9, 29.1, 28.4, 28.3, 26.7, 7.4; IR (thin film): 3079, 2949, 2878, 1740, 1636, 1493, 1436, 1364, 1314, 1270, 1228, 1195, 996, 926, 853, 726; HRMS calc’d for C₁₄H₂₃NO₃ = 253.1678, found = 253.1678.

General Experimental Procedure 1 for the Synthesis of 5-(3-hydroxypropyl)piperidin-2-one 4a-c:
Piperidinone (1 equivalent) was dissolved in methanol, followed by the addition of NaBH₄ (5 equivalents). The mixture was heated to reflux for 10 mins, and then cooled to room temperature. Then additional NaBH₄ (5 equivalents) was added followed by a 10 min reflux period, this process was continued until a total of 40 equivalents NaBH₄ was added. Upon complete addition of NaBH₄, water was slowly added to the reaction mixture and extracted 3 times with ethyl acetate. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAC/Hexanes) to yield the desired piperidinones 4a-c.

General Experimental Procedure 2 for the Synthesis of 5-(3-hydroxypropyl)piperidin-2-one 4a-c: dimethyl 3-ethyl-3-formylpimelate (1 equivalent) and primary amine (1 equivalent) were dissolved in methanol. Sc(OTf)₃ (0.025 equivalent) was then added and the mixture was stirred for 1-2 hours,
followed by the addition of NaBH₄ (5 equivalents). The mixture was heated to reflux for 10 mins, and then cooled to room temperature. Then additional NaBH₄ (5 equivalents) was added followed by a 10 min reflux period, this process was continued until a total of 40 equivalents NaBH₄ was added. Upon complete addition of NaBH₄, water was slowly added to the reaction mixture and extracted 3 times with ethyl acetate. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinones 4a-c.

5-(3-hydroxypropyl)piperidin-2-one 4a was prepared using general experimental procedure 1. Reagents employed: piperidinone 3c (677 mg, 1.82 mmol), NaBH₄ (2750 mg, 72.88 mmol), and Methanol (30 ml). Yielded 4a as a thick yellow oil, 99% (630 mg, 1.81 mmol). Rₜ = 0.14, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 3.71 (dd, J = 5.3, 5.3 Hz, 2H), 3.56 (dd, J = 5.9, 5.9 Hz, 2H), 3.46-3.42 (m, 1H), 3.37-3.33 (m, 1H), 3.14 (AB system, 2H), 2.47 (brs, 1H), 2.29 (dd, J = 7.0, 7.0 Hz, 2H), 1.55 (dd, J = 7.0, 7.0 Hz, 2H), 1.46-1.34 (m, 4), 1.33-1.26 (m, 2H), 0.84 (s, 9H), 0.79 (t, J = 7.6 Hz, 3H), 0.00 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ = 170.1, 62.9, 61.4, 59.3, 50.5, 34.5, 30.0, 29.8, 28.5, 27.1, 26.2, 25.8, 18.1, 7.4, -5.5; IR (thin film): 2930, 2858, 1626, 1497, 1464, 1418, 1362, 1255, 1101, 1058, 837, 778; HRMS (M+1) calc’d for C₁₈H₃₇NO₃Si = 344.2622, found = 344.2615.

5-(3-hydroxypropyl)piperidin-2-one 4b was prepared using general experimental procedure 1. Reagents employed: piperidinone 3e (540 mg, 1.55 mmol), NaBH₄ (2340 mg, 61.80 mmol), and Methanol (30 ml). Yielded 4b as an orange oil, 100% (498 mg, 1.55 mmol). Rₜ = 0.22, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.39 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 3.63 (dd, J = 6.5 Hz, 2H), 3.53 (dd, J = 8.2, 6.5, 2H), 3.31 (dd, J = 7.0, 7.0 Hz, 2H), 3.06 (AB system, 2H), 2.33 (dd, J = 7.0, 7.0 Hz, 2H), 1.55 (dd, J = 7.0, 7.0 Hz, 2H), 1.51-1.43 (m, 4H), 1.42-1.33 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 170.1, 129.0, 128.7, 128.0, 126.0, 63.2, 62.5, 58.4, 48.0, 34.6, 30.4, 30.0, 29.9, 28.6, 27.1, 26.3, 7.5 (missing 1 carbon presumably due to overlap); IR (thin film): 2938, 2866, 1623, 1496, 1438, 1418, 1363, 1297, 1229, 1066, 741, 692; HRMS calc’d for C₁₈H₂₃NO₂S = 321.1762, found = 321.1769.
5-(3-hydroxypropyl)piperidin-2-one 4c was prepared using general experimental procedure 1. Reagents employed: piperidinone 3e (1600 mg, 5.30 mmol), NaBH₄ (10 x 10³ mg, 264.00 mmol), and Methanol (79 ml). Yielded 4c as a dark yellow oil, 100% (1459 mg, 5.30 mmol). Rᵣ = 0.14, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.32-7.30 (m, 2H), 7.27-7.24 (m, 3H), 4.55 (AB system, 2H), 3.51 (dd, J = 5.9, 5.9 Hz, 2H), 2.92 (AB system, 2H), 2.43 (dd, J = 7.0, 7.0 Hz, 2H), 1.62 (m, 3H), 1.43-1.35 (m, 1H), 1.34-1.16 (m, 5H), 0.71 (t, J = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 169.8, 137.3, 128.5, 128.3, 127.4, 63.1, 55.7, 50.3, 34.3, 30.2, 29.9, 28.5, 26.9, 26.2, 7.3; IR (thin film): 3395, 2939, 2866, 1620, 1496, 1454, 1419, 1363, 1308, 1229, 1067, 1028, 703; HRMS calc’d for C₁₃H₂₅NO₂ = 275.1885, found = 275.1880.

5-(3-hydroxypropyl)piperidin-2-one 4a was prepared using general experimental procedure 2. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (633 mg, 2.59 mmol), 2-(tert-butyl(dimethylsilyloxy)ethanamine (500 mg, 2.85 mmol), Sc(OTf)₃ (32 mg, 0.65 mmol), NaBH₄ (3920 mg, 103.62 mmol), and Methanol (65 ml). Yielded 4a as a thick yellow oil, 72% (640 mg, 1.86 mmol).

5-(3-hydroxypropyl)piperidin-2-one 4b was prepared using general experimental procedure 1. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (1880 mg, 7.70 mmol), 2-(phenylthio)ethanamine (1300 mg, 8.48 mmol), Sc(OTf)₃ (94 mg, 0.19 mmol), NaBH₄ (11650 mg, 308.00 mmol), and Methanol (98 ml). Yielded 4b as an orange oil, 60% (1485 mg, 4.62 mmol).

5-(3-hydroxypropyl)piperidin-2-one 4c was prepared using general experimental procedure 1. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 2 (4560 mg, 18.67 mmol), phenylmethanamine (2000 mg, 18.67 mmol), Sc(OTf)₃ (231 mg, 0.47 mmol), NaBH₄ (35300 mg, 933.12 mmol), and Methanol (250 ml). Yielded 4c as a dark yellow oil, 81% (4160 mg, 15.11 mmol).
Piperidine 5a was prepared using the following procedure: Piperidinone 3c (250 mg, 0.67 mmol) was dissolved in THF (25 ml) followed by the addition of Red-Al® (65% by weight) (0.82 ml, 2.69 mmol). Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with EtOAc. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired product 5a as an orange oil, 72% (160 mg, 0.49 mmol). Rf = 0.11, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 3.71 (dd, J = 6.5, 6.5 Hz, 2H), 3.61 (ddd, J = 6.5, 6.5, 2.3 Hz, 2H), 2.51-2.39 (m, 3H), 2.31-2.19 (m, 2H), 2.08-2.04 (m, 1H), 1.61-1.50 (m, 2H), 1.49-1.37 (m, 3H), 1.36-1.25 (m, 4H), 1.20-1.16 (m, 1H), 0.88 (s, 9H), 0.77 (t, J = 7.0 Hz, 3H), 0.05 (s, 6H); 13C NMR (150 MHz, CDCl3) δ = 63.8, 63.6, 61.3, 61.2, 55.4, 35.3, 33.6, 28.3, 25.9, 21.9, 18.3, 7.3, 5.3 (missing 2 carbon presumably due to overlap); IR (thin film): 2933, 2857, 1463, 1255, 1103, 1068, 836, 776; HRMS calc’d for C18H39NO2Si = 329.2750, found = 329.2754.

Piperidine 5b was prepared using the following procedure: Piperidinone 3e (131 mg, 0.43 mmol) was dissolved in THF (10 ml) followed by the addition of Red-Al® (65% by weight) (0.53 ml, 1.74 mmol). Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with EtOAc. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired product 5b as brown oil, 98% (110 mg, 0.42 mmol). Rf = 0.23, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 7.34-7.28 (m, 4H), 7.24-7.22 (m, 1H), 3.60 (dd, J = 5.9, 5.9 Hz, 2H), 3.46-3.38 (m, 2H), 2.45-2.36 (m, 1H), 2.31-2.22 (m, 1H), 2.17-2.10 (m, 1H), 2.03-1.94 (m, 1H), 1.65-1.51 (m, 2H), 1.47-1.14 (m, 2H), 1.38-1.23 (m, 6H), 0.73 (t, J = 7.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ = 128.9, 128.0, 126.8, 63.8, 63.5, 62.5, 54.8, 35.4, 33.8, 26.2, 21.8, 18.4, 7.2 (missing 2 carbon presumably due to overlap); IR (thin film): 2936, 2858, 2793, 2754, 1453, 1350, 1059, 739, 698; HRMS calc’d for C17H23NO = 261.2093, found = 261.2097.

**General Experimental Procedure for Alcohol 4c Oxidation to Aldehyde 7:** Alcohol 4c (1 equivalent) was dissolved in EtOAc, followed by the addition of IBX (3 equivalents). The mixture was heated to reflux with rapid stirring until consumption of starting material as determined by TLC analysis. The reaction mixture was filter through Celite® with EtOAc and the solvent was removed to yield the desired aldehyde 7.
Aldehyde 7 was prepared using general experimental procedure. Reagents employed: piperidinone 4c (580 mg, 2.11 mmol), IBX (1770 mg, 6.32 mmol), and EtOAc (40 ml). Yielded 7 as a dark yellow oil, 82% (475 mg, 1.74 mmol). Rf =0.31, 100% EtOAc in hexanes; \(^1\text{H-NMR (600 MHz, CDCl}_3\):} \(\delta = 9.65\) (s, 1H), 7.33-7.30 (m, 2H), 7.28-7.24 (m, 3H), 4.55 (AB system, 2H), 2.92 (AB system, 2H), 2.46 (dd, \(J = 7.0, 7.0\) Hz, 2H), 2.27-2.21 (m, 1H), 2.07-2.01 (m, 1H), 1.67-1.59 (m, 2H), 1.58-1.52 (m, 2H), 1.30-1.22 (m, 2H), 0.70 (t, \(J = 7.6\) Hz, 3H); \(^{13}\text{C NMR (150 MHz, CDCl}_3\):} \(\delta = 201.2, 169.5, 137.1, 128.6, 128.3, 127.5, 55.1, 50.1, 37.8, 34.1, 30.1, 28.4, 26.7, 25.5, 7.2\); IR (thin film): 2936, 1722, 1603, 1496, 1454, 1420, 1364, 1309, 1265, 1232, 703; HRMS calc’d for \(\text{C}_{17}\text{H}_{23}\text{NO}_2\) = 273.1729, found = 273.1728.

**General Experimental Procedure for the Synthesis of Alkyne 8:** Aldehyde 7 (1 equivalent) was dissolved in MeOH, followed by the addition of \(\text{K}_2\text{CO}_3\) (4.7 equivalents). Dimethyl 1-diazo-2-oxopropylphosphonate (2.5 equivalents) as added drop wise in MeOH and the mixture was stirred rapidly until consumption of starting material as determined by TLC analysis. Brine was added to the reaction mixture and extracted 3 times with ethyl acetate. The combined organic layer was washed thoroughly 2 times with water, and once with brine. The organic layer was dried and the solvent was removed to yield alkyne 8.

Alkyne 8 was prepared using general experimental procedure. Reagents employed: piperidinone 7 (430 mg, 1.57 mmol), \(\text{K}_2\text{CO}_3\) (1020 mg, 7.38 mmol), dimethyl 1-diazo-2-oxopropylphosphonate (755 mg, 3.93 mmol), and MeOH (16 ml). Yielded 8 as a pale yellow foam, 97% (410 mg, 1.52 mmol). Rf = 0.52, 100% EtOAc in hexanes; \(^1\text{H-NMR (600 MHz, CDCl}_3\):} \(\delta = 7.33-7.30\) (m, 2H), 7.27-7.23 (m, 3H), 4.56 (AB system, 2H), 2.93 (AB system, 2H), 2.50-2.40 (m, 2H), 2.06-2.00 (m, 1H), 1.94-1.88 (m, 2H), 1.62 (dd, \(J = 7.6, 7.6\) Hz, 2H), 1.58-1.52 (m, 2H), 1.35-1.23 (m, 2H), 0.72 (t, \(J = 7.0\) Hz, 3H); \(^{13}\text{C NMR (150 MHz, CDCl}_3\):} \(\delta = 169.5, 137.1, 128.6, 128.2, 127.4, 84.0, 68.5, 55.4, 50.2, 34.6, 32.6, 29.9, 28.4, 26.5, 12.7, 7.3\); IR (thin film): 3290, 3230, 2940, 2877, 1641, 1494, 1454, 1420, 1363, 1309, 1264, 1230, 1029, 703, 629; HRMS calc’d for \(\text{C}_{18}\text{H}_{23}\text{NO} = 269.1780\), found = 269.1781.

**General Experimental Procedure for the Synthesis of Piperidone 9:** Aniline (1.2 equivalents) was dissolved in THF and the flask was purged with argon. Alkyne 8 (1 equivalent) was then added drop wise
in THF and the flask was purged with argon. Cul (0.05 equivalent) and PdCl2(PPh3)2 (0.025 equivalent) were then added to the reaction mixture and the flask was purged with argon. Diisopropylamine was then added to the reaction mixture and the solution was stirred in the absence of light for 12 hours. The reaction mixture was then diluted with DCM and water. The aqueous was extracted 2 times with DCM. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinone 9.

Piperidinone 9 was prepared using general experimental procedure. Reagents employed: alkyne 8 (330 mg, 1.23 mmol), aniline (322 mg, 1.47 mmol), PdCl2(PPh3)2 (22 mg, 0.031 mmol), Cul (12 mg, 0.063 mmol), Diisopropylamine (1.1 ml), and THF (3 ml). Yielded 9 as a dark yellow oil, 93% (413 mg, 1.15 mmol). Rf = 0.33, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 7.33-7.30 (m, 2H), 7.27-7.24 (m, 3H), 7.20 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 7.0 Hz, 1H), 6.68-6.65 (m, 2H), 4.58 (AB system, 2H), 4.11 (brs, 2H), 2.99 (AB system, 2H), 2.62-2.45 (m, 2H), 2.36-2.30 (m, 1H), 2.24-2.18 (m, 1H), 1.70-1.60 (m, 4H), 1.41-1.30 (m, 2H), 0.76 (t, J = 7.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ = 169.5, 147.6, 137.1, 132.0, 129.0, 128.6, 128.2, 127.4, 117.9, 114.2, 108.5, 94.8, 77.3, 55.6, 50.3, 34.8, 33.5, 30.1, 28.5, 26.5, 13.9, 7.4; IR (thin film): 3458, 3335, 3029, 2936, 1632, 1493, 1454, 1311, 1263, 1157, 1029, 748, 702; HRMS calc’d for C24H38N2O = 360.2202, found = 360.2218.

General Experimental Procedure for the Synthesis of Indoles 10: Piperidinone 9 (1 equivalent) was dissolved in toluene. ZnBr2 (1.2 equivalent) was then added to the reaction mixture and the solution was heated to reflux for 12 hours. Water was added and the reaction mixture was extracted 3 times with EtOAc. The combined organic layer was washed 2 times with water. The organic layer was dried and the solvent was removed to yield the desired indoles 10.

Indole 10 was prepared using general experimental procedure. Reagents employed: piperidinone 9 (375 mg, 1.04 mmol), ZnBr2 (281 mg, 1.25 mmol), and Toluene (8.6 ml). Yielded 10 as a yellow foam, 100% (375 mg, 1.04 mmol). Rf = 0.39, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 7.69 (brs, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.34-7.27 (m, 6H), 7.12 (t, J = 7.0 Hz, 1H), 7.06 (t, J = 7.0, 1H), 6.16 (s, 1H), 4.56 (AB system, 2H), 3.01 (AB system, 2H), 2.62-2.57 (m, 1H), 2.48 (dd, J = 7.0 Hz, 2H), 2.39-2.34 (m, 1H), 1.71-1.85 (m, 4H), 1.42-1.37 (m, 2H), 0.80 (t, J = 7.6, 3H); 13C NMR (150 MHz, CDCl3) δ = 169.7,
Piperidine 11 was prepared using the following procedure: Piperidinone 10 (99 mg, 0.27 mmol) was dissolved in THF (12 ml) and cooled to 0 °C. Red-Al® (65% by weight) (0.52 ml, 1.71 mmol) was added drop wise and the solution was mixed for 3.5 hours at 0 °C. Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with ether. The organic layers were combined and washed 2 times with water. The organic was dried and the solvent was removed to yield desired product 11 as an orange oil, 97% (91 mg, 0.26 mmol). Rf = 0.60, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 8.04 (brs, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.36-7.31 (m, 4H), 7.28-7.25 (m, 2H), 7.11 (t, J = 7.0 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.23 (s, 1H), 3.46 (AB system, 2H), 2.62-2.56 (m, 1H), 2.52-2.46 (m, 1H), 2.31-2.21 (m, 2H), 2.02-1.87 (m, 2H), 1.71-1.65 (m, 2H), 1.63-1.56 (m, 1H), 1.46-1.40 (m, 2H), 1.37-1.31 (m, 1H), 1.28-1.24 (m, 2H), 0.81 (t, J = 7.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ = 140.7, 135.9, 128.92, 128.85, 128.1, 126.9, 120.8, 119.6, 119.5, 110.2, 99.0, 63.4, 62.1, 55.0, 35.8, 33.9, 29.7, 22.0, 21.9, 7.3 (missing 2 carbon presumably due to overlap); IR (thin film): 3408, 2931, 2856, 1457, 12.88, 779, 745, 699; HRMS calc’d for C24H30N2O = 346.2409, found = 346.2408.

12 was prepared using the following procedure: Piperidine 11 (290 mg, 0.84 mmol) was dissolved in Methanol (9.5 ml) followed by the addition of Pd/C (10% Pd on C) (290 mg). To the slurry was then added ammonium formate (264 mg, 4.19 mmol) and the reaction was heated to reflux for 3 hours. Upon completion by TLC analysis the reaction mixture was filtered through celite washing with chloroform. The volatiles were removed to yield the desired product 12 as an orange oil, 97% (208 mg, 0.81 mmol). Rf = 0.12, 10% MeOH in EtOAc; (Note that based washed CDCl3 was used to suppress in situ solvent protonation) 1H-NMR (600 MHz, CDCl3): δ = 9.31 (brs, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.11-7.05 (m, 2H), 6.23 (s, 1H), 4.76 (brs, 1H), 2.97-2.95 (m, 1H), 2.78 (d, J = 12.9 Hz, 1H), 2.69-2.63 (m, 3H), 2.47 (d, J = 12.32 Hz, 1H), 2.02 (ddd, J = 14.7, 8.2, 8.2 Hz, 1H), 1.70-1.61 (m, 2H), 1.54-1.49 (m, 2H), 1.46-1.39 (m, 1H), 1.34-1.25 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ = 140.11, 136.1, 128.6, 120.6, 119.47, 119.2, 110.5, 98.9, 53.3, 46.1, 34.5, 33.6, 32.8, 28.4, 21.9, 21.0, 7.0; IR (thin film):
3400, 3275, 2930, 2856, 1458, 1419, 1287, 781, 740; HRMS calc’d for C_{17}H_{24}N = 256.1939, found = 256.1936.
MeO₂C

CO₂Me

CHO

2
PhS
MeO₂C
3d