Supporting information for

Biological studies and target-engagement of the 2-*C*-methyl-D-erythritol 4-phosphate cytidylyltransferase (IspD)-targeting antimalarial agent (1*R*,3*S*)-MMV008138 and analogs

Maryam Ghavami,[†] Emilio F. Merino,[‡,§] Zhong-Ke Yao,[†] Rubayet Elahi,[‡] Morgan E. Simpson,[‡] Maria L. Fernández-Murga,[‡] Joshua H. Butler,[§] Michael A. Casasanta, [‡] Priscilla M. Krai,[‡] Maxim M. Totrov,[¶] Daniel J. Slade,[‡] Paul R. Carlier,*[,†] and Maria Belen Cassera*[,‡,§]

[†]Department of Chemistry and Virginia Tech Center for Drug Discovery, Hahn Hall South, 800 West Campus Drive, Virginia Tech, Blacksburg, Virginia 24061, United States
[‡]Department of Biochemistry and Virginia Tech Center for Drug Discovery, Engel Hall, 340 West Campus Drive, Virginia Tech, Blacksburg, Virginia 24061, United States
[§]Department of Biochemistry and Molecular Biology, and Center for Tropical and Emerging Global Diseases (CTEGD), 120 Green St., University of Georgia, Athens, Georgia 30602, United States
[¶]Molsoft LLC, 11199 Sorrento Valley Road, San Diego, California 92121, United States

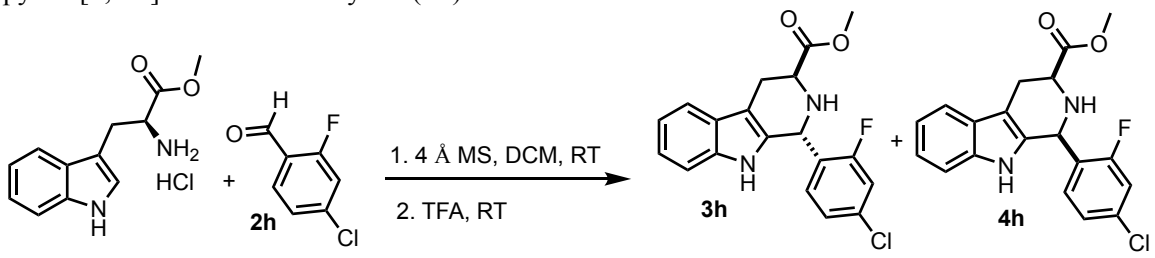
Table of Contents

A. Synthetic procedures & analytical data for new compounds described in the manuscript:

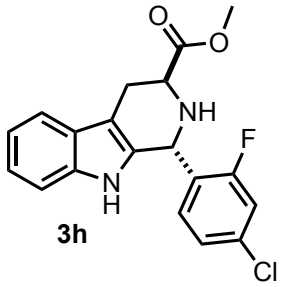
General:
Compounds were purchased from Sigma-Aldrich, Enamine, Astatech, Arkpharm and were used without purification, unless otherwise noted. ^{1}H NMR spectra were recorded at 400 or 500 MHz; the corresponding ^{13}C NMR resonant frequencies were 101 and 126 MHz respectively; the corresponding ^{19}F NMR resonant frequencies were 376 and 470 MHz. Preparative HPLC was performed using a Waters HPLC system (Waters 2545 Binary Gradient Module, Waters 2767 Sample Manager, Waters Systems Fluidics Organizer, Waters SQ Detector 2, Waters 515 HPLC Pump, Waters 2489 UV/Vis Spectrometer) equipped with a Phenomenex Kinetex C18 column (5 µm particle size, 100 x 21.2 mm, AXIA Packed) operating at 15 mL/min. Compounds **1a**, *ent*-**1a**, **1b-g**, **1t-v**, **1x**, **3a**, **6a**, **7a**, **7e**, **5a**, *ent*-**5a, 11a** were prepared as previously described.[1] Fosmidomycin (FOS) was purchased from Sigma-Aldrich as the sodium salt hydrate form.
Note that for simplicity, new amino acids **1h-s**, **w**, **y-af** are drawn below and named according to their uncharged form, rather than as the zwitterions depicted in the manuscript. As stated in the manuscript, *trans*- and *cis*-isomers of the Pictet-Spengler adducts were separated by column chromatography on silica gel, and distinguished using the literature ^{13}C NMR empirical rule.[2] In every case the cis-isomer eluted before the trans-isomer.

1. Synthesis of 1h

a. methyl (1*R*,3*S*)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3h**) and methyl (1*S*,3*S*)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4h**)

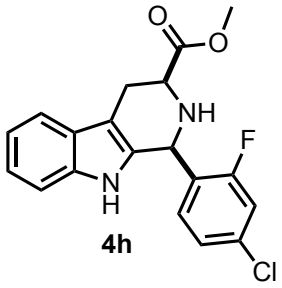


To a mixture of L-tryptophan methyl ester hydrochloride, (0.942 g, 3.7 mmol), 4 Å molecular sieves (1.0 g, powder form) and 4-chloro-2-fluorobenzaldehyde (**2h**) (0.59 g, 3.7 mmol), DCM (10 mL) were added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.57 mL, 7.4 mmol) was then added dropwise, and the reaction mixture was stirred at room temperature for an additional 24 hours. An aqueous solution of $NaHCO_3$ (1.5 g, 18.0 mmol, in 30 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **3h** (0.47 g, 36% yield) as a white solid and **4i** (0.66 g, 49% yield) as a white solid.



methyl (1*R*,3*S*)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3h**)

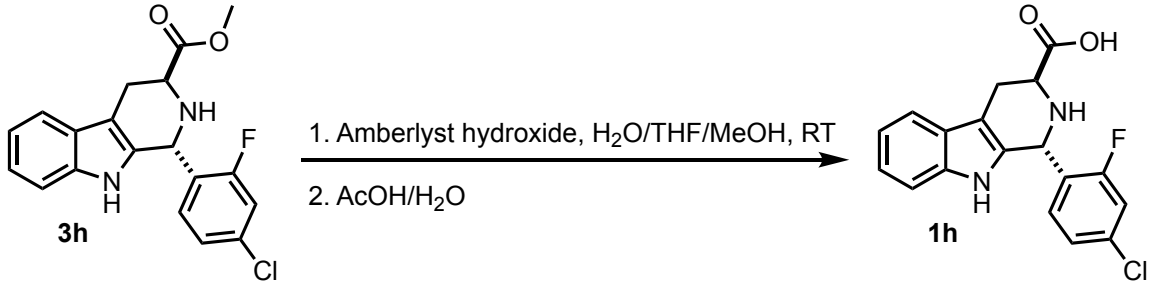
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.55 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.21 – 7.11 (m, 3H), 7.05 – 6.96 (m, 2H), 5.77 (s, 1H), 3.90 (dd, *J* = 7.7, 5.1 Hz, 1H), 3.74 (s, 3H), 3.24 (ddd, *J* = 15.3, 5.1, 1.1 Hz, 1H), 3.08 (ddd, *J* = 15.4, 7.7, 1.4 Hz, 1H), 2.62 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.82 (dd, *J* = 10.0, 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 160.5 (d, ^1J = 249.8 Hz), 136.2, 134.5 (d, ^3J = 10.5 Hz), 131.3, 130.5 (d, ^3J = 4.9 Hz), 127.8 (d, ^2J = 13.4 Hz), 126.8, 124.5 (d, ^4J = 3.6 Hz), 122.3, 119.7, 118.3, 116.5 (d, ^2J = 25.4 Hz), 110.9, 109.4, 52.4, 52.2, 47.7 (d, ^3J = 3.2 Hz), 24.8.



methyl (1*S*,3*S*)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4h**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.34 (t, *J* = 8.1 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.21 – 7.09 (m, 4H), 5.65 (t, *J* = 2.2 Hz, 1H), 3.98 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.83 (s, 3H), 3.23 (ddd, *J* = 15.1, 4.2, 1.9 Hz, 1H), 3.00 (ddd, *J* = 15.1, 11.1, 2.5 Hz, 1H), 2.51 (s, 1H), 1.59 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.74 (t, *J* = 8.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 160.6 (d, ^1J = 249.9 Hz), 136.1, 134.9, 134.8, 132.9, 130.9 (d, ^3J = 4.8 Hz), 126.9, 126.6 (d, ^2J = 13.2 Hz), 125.3 (d, ^3J = 3.5 Hz), 122.2, 119.8, 118.2, 116.4 (d, ^2J = 25.5 Hz), 110.9, 109.4, 56.6, 52.3, 50.4 (d, ^3J = 3.4 Hz), 25.5.

b. (1*R*,3*S*)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1h**)

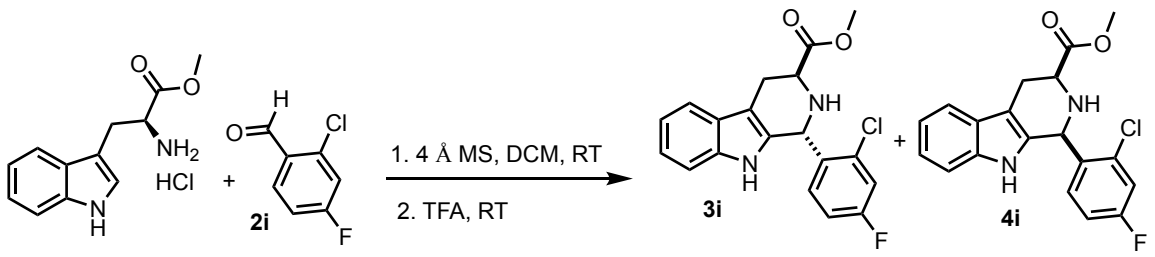


To a solution of **3h** (72.0 mg, 0.2 mmol) in THF / MeOH / H_2O (2 mL / 2 mL / 2 mL) was added Amberlyst hydroxide resin (1.0 g, 4.2 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. The residue was suspended in a minimum amount of MeOH, and the desired product was precipitated by the addition of Et_2O and hexane. The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1h** (66 mg, 96% yield) as a yellow powder.

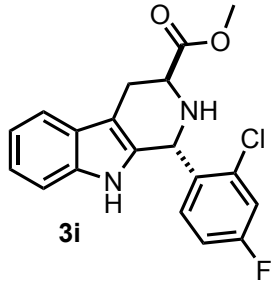
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.49 (dd, *J* = 10.0, 2.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.05 (td, *J* = 8.0, 1.2 Hz, 1H), 6.99 (td, *J* = 8.0, 0.8 Hz, 1H), 6.89 (t, *J* = 8.0 Hz, 1H), 5.68 (s, 1H), 3.65 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.08 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.87 (ddd, *J* = 15.2, 8.0, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4 (s), 160.3 (d, J = 248 Hz), 136.2 (s), 132.8 (d, J = 10 Hz), 132.2 (s), 131.4 (d, J = 5 Hz), 128.7 (d, J = 14 Hz), 126.4 (s), 124.3 (d, J = 3 Hz), 121.1 (s), 118.5 (s), 117.8 (s), 116.0 (d, J = 26 Hz), 111.1 (s), 107.9 (s), 51.8 (s), 46.9 (d, J = 3 Hz), 24.6 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -116.2 (t, J = 9.0 Hz). HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}ClFN_2O_2$: 345.0801. Found: 345.0722.

2. Synthesis of 1i

a. methyl (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3i**) and methyl (1*S*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4i**)

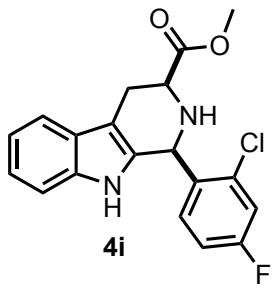


To a mixture of L-tryptophan methyl ester hydrochloride, (1.27 g, 5 mmol), 4 Å molecular sieves (2.5 g, powder form) and 2-chloro-4-fluorobenzaldehyde (**2i**) (0.79 g, 5 mmol), DCM (18 mL) were added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10.0 mmol) was then added dropwise, and the reaction mixture was stirred at room temperature for an additional 4 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **3i** (0.7 g, 40% yield) as an off white solid and **4i** (1.0 g, 56% yield) as a white solid.



methyl (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(3i)**

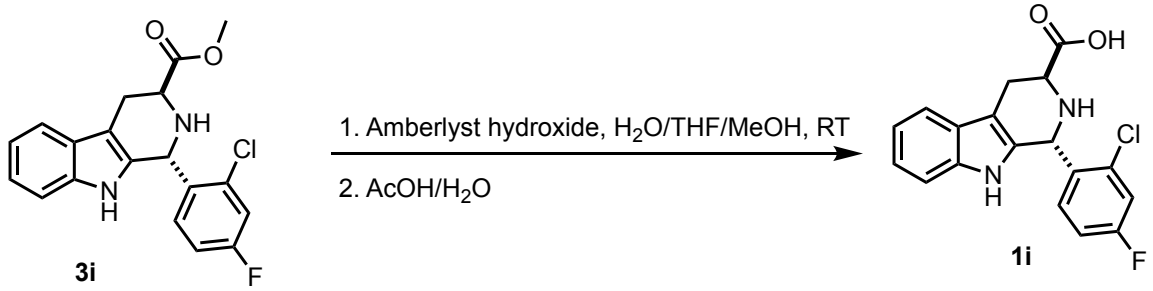
^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 6.89 – 6.75 (m, 2H), 5.80 (s, 1H), 4.22 (s, 3H), 3.75 (dd, *J* = 14.2, 4.2 Hz, 1H), 3.75 (s, 3H), 3.27 (dd, *J* = 15.4, 4.7 Hz, 1H), 3.03 (ddd, *J* = 15.4, 9.4, 1.5 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -112.15 (q, *J* = 7.9 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.4, 161.9 (d, ^1J = 250.6 Hz), 136.5, 134.6 (d, ^4J = 3.6 Hz), 134.2 (d, ^3J = 10.4 Hz), 131.2 (d, ^3J = 8.8 Hz), 128.8, 126.3, 121.8, 119.0, 117.9, 117.1 (d, ^2J = 24.9 Hz), 113.6 (d, ^2J = 20.9 Hz), 111.0, 108.8, 52.1, 51.3, 51.2, 24.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}ClFN_2O_2$: 359.0957. Found: 359.0954.



methyl (1*S*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(4i)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.55 (d, J = 6.4 Hz, 1H), 7.40 (dd, J = 8.7, 6.2 Hz, 1H), 7.25 – 7.10 (m, 4H), 6.95 (td, J = 8.3, 2.6 Hz, 1H), 5.79 (s, 1H), 3.99 (dd, J = 11.0, 4.1 Hz, 1H), 3.83 (s, 3H), 3.25 (ddd, J = 15.1, 4.1, 1.8 Hz, 1H), 3.02 (ddd, J = 15.0, 11.0, 2.5 Hz, 1H), 2.60 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.23 (q, J = 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 162.1 (d, ^1J = 251.0 Hz), 136.3, 134.8, 134.2 (d, ^3J = 10.4 Hz), 133.5, 131.8 (br s), 126.9, 122.2, 119.8, 118.3, 117.0 (d, ^2J = 25.3 Hz), 115.1 (d, ^2J = 21.0 Hz), 111.0, 109.4, 56.7, 53.8, 52.4, 25.5. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}ClFN_2O_2$: 360.0989. Found: 360.0989.

b. (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**1i**)

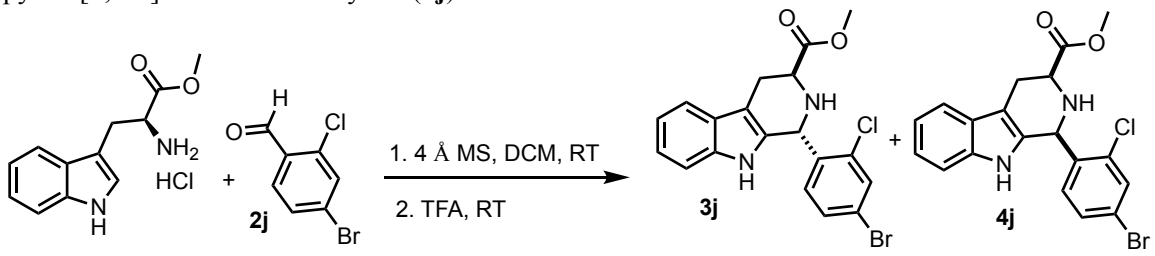


To a solution of **3i** (108.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.26 g, 5.3 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 36 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 6 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 6 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.5 mL), and the product was precipitated by the addition of DCM (2 mL), Et_2O (5 mL) and hexane (10 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1i** (97 mg, 94% yield) as a yellow powder.

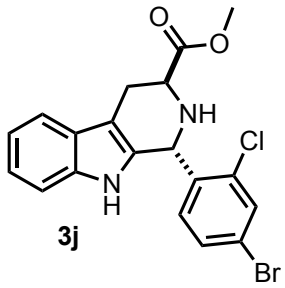
^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 8.5, 2.2 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.44 (s, 1H), 3.99 (dd, J = 8.4, 5.4 Hz, 1H), 3.50 (dd, J = 16.8, 5.7 Hz, 1H), 3.26 (ddd, J = 16.3, 8.5, 1.4 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -110.50 (q, J = 7.4 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 172.0, 163.2 (d, ^1J = 252.3 Hz), 137.3, 136.1 (d, ^3J = 10.8 Hz), 132.7 (d, ^3J = 9.5 Hz), 129.0 (d, ^4J = 3.8 Hz), 126.2, 125.8, 122.4, 119.2, 117.9, 117.2 (d, ^2J = 25.6 Hz), 114.6 (d, ^2J = 21.8 Hz), 110.9, 108.1, 53.6, 51.0, 22.4. HRMS (MALDI) $[M+H]^+$ calculated for $C_{18}H_{15}ClFN_2O_2$: 345.0801. Found: 345.0798.

3. Synthesis of 1j

a. methyl (1*R*,3*S*)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3j**) and methyl (1*S*,3*S*)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4j**)



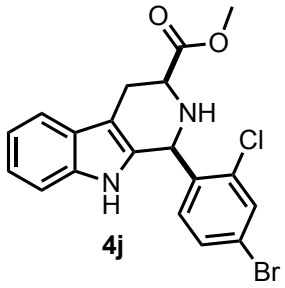
To a mixture of L-tryptophan methyl ester hydrochloride, (0.76 g, 3 mmol), 4 Å molecular sieves (1.0 g, powder form) and 4-bromo-2-chlorobenzaldehyde (**2j**) (0.66 g, 3 mmol), DCM (10 mL) were added under nitrogen. After 5 minutes 0.05 mL of TFA was added and the resulting mixture was stirred for 24 hours at room temperature. TFA (0.6 mL, 8.0 mmol) was then added dropwise, and the reaction mixture was stirred at room temperature for an additional 24 hours. An aqueous solution of $NaHCO_3$ (1.1 g, 13.0 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **3j** (0.47 g, 37% yield) as a white solid and **4j** (0.65 g, 52% yield) as a white solid.



3j

methyl (1*R*,3*S*)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3j**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.29 – 7.24 (m, 2H), 7.22 – 7.11 (m, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.85 (s, 1H), 3.84 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.73 (s, 3H), 3.26 (ddd, *J* = 15.4, 5.0, 1.2 Hz, 1H), 3.10 (ddd, *J* = 15.4, 7.7, 1.6 Hz, 1H), 2.78 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 138.3, 136.2, 134.5, 132.5, 131.4, 131.2, 130.1, 126.7, 122.3, 122.1, 119.7, 118.3, 111.0, 109.6, 52.2, 52.2, 51.2, 24.8.

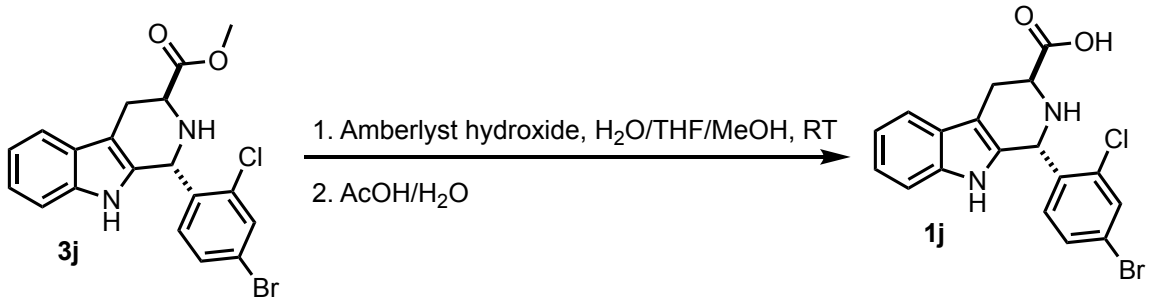


4j

methyl (1*S*,3*S*)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4j**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.37 – 7.29 (m, 2H), 7.25 – 7.21 (m, 1H), 7.19 – 7.09 (m, 2H), 5.78 (br s, 1H), 3.99 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.83 (s, 3H), 3.24 (ddd, *J* = 15.1, 4.1, 1.9 Hz, 1H), 3.01 (ddd, *J* = 15.1, 11.0, 2.5 Hz, 1H), 2.63 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 137.8, 136.2, 134.3, 133.1, 132.2, 131.7, 130.9, 126.8, 122.4, 122.2, 119.8, 118.3, 111.0, 109.4, 56.6, 53.9, 52.4, 25.4.

b. (1*R*,3*S*)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1j**)

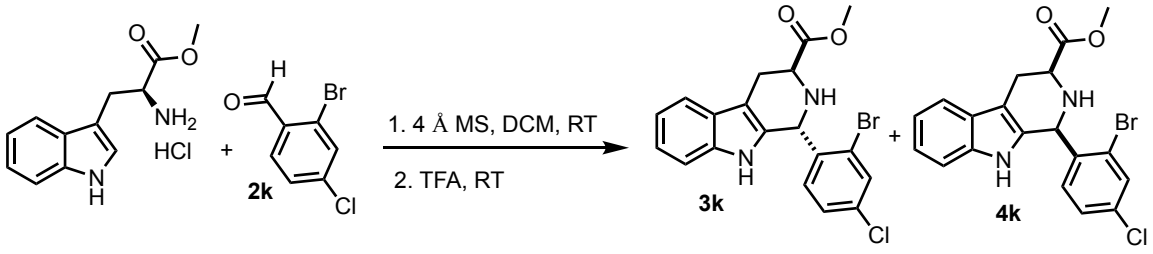


To a solution of **3j** 84.0 mg, 0.2 mmol) in THF / MeOH / H_2O (2 mL / 2 mL / 2 mL) was added Amberlyst hydroxide resin (0.8 g, 3.4 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. The residue was suspended in a minimum amount of MeOH, and the desired product was precipitated by the addition of Et_2O and hexane. The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1j** (80 mg, 99% yield) as a yellow powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (td, *J* = 7.2, 1.2 Hz, 1H), 6.99 (td, *J* = 8.0, 1.2 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.70 (s, 1H), 3.58 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.08 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.84 (ddd, *J* = 15.2, 8.0, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.8, 139.6, 136.6, 134.7, 132.7, 132.2, 132.1, 130.4, 126.8, 121.6, 121.4, 118.9, 118.2, 111.6, 108.7, 51.8, 51.1, 25.2. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}BrClN_2O_2$: 405.0000. Found: 404.9964.

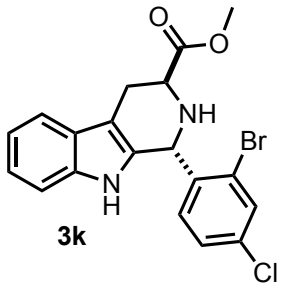
4. Synthesis of 1k

a. methyl (1*R*,3*S*)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3k**) and methyl (1*S*,3*S*)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4k**)



To a mixture of L-tryptophan methyl ester hydrochloride, (0.76 g, 3 mmol), 4 Å molecular sieves (1.0 g, powder form) and 2-bromo-4-chlorobenzaldehyde (**2k**) (0.66 g, 3 mmol), DCM (10 mL) were added under nitrogen. After 2 minutes 0.06 mL of TFA was added and the resulting mixture was stirred for 24 hours at room temperature. TFA (0.5 mL, 6.5 mmol) was then added dropwise, and the reaction mixture was stirred at room temperature for an additional 24 hours. An aqueous solution of $NaHCO_3$ (0.92 g, 11.0 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash

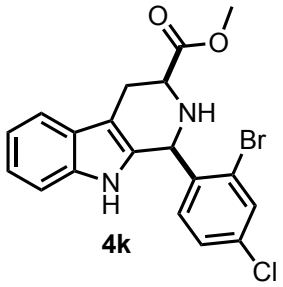
chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **3k** (0.53 g, 42% yield) as an white solid and **4k** (0.64 g, 51% yield) as a white solid.



3k

methyl (1*R*,3*S*)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3k**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.26 – 7.22 (m, 1H), 7.20 – 7.10 (m, 3H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.81 (d, *J* = 1.3 Hz, 1H), 3.83 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.72 (s, 3H), 3.24 (ddd, *J* = 15.3, 5.1, 1.2 Hz, 1H), 3.09 (ddd, *J* = 15.3, 7.6, 1.5 Hz, 1H), 2.80 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 139.3, 136.2, 134.5, 132.8, 131.6, 131.0, 127.7, 126.7, 124.3, 122.3, 119.7, 118.3, 111.0, 109.6, 53.5, 52.2, 52.2, 24.8.

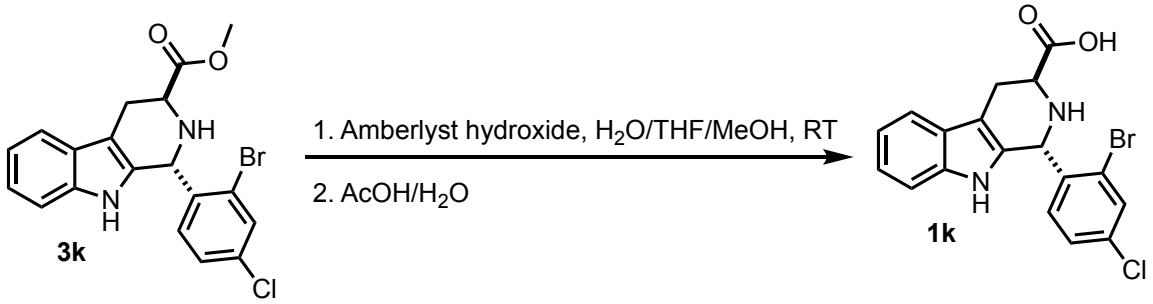


4k

methyl (1*S*,3*S*)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4k**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.24 – 7.21 (m, 2H), 7.13 (dd, *J* = 7.5, 1.8 Hz, 2H), 5.76 (s, 1H), 3.98 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.81 (s, 3H), 3.22 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.00 (ddd, *J* = 15.1, 11.0, 2.5 Hz, 1H), 2.66 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 139.0, 136.2, 134.8, 132.4, 131.6, 128.6, 126.8, 123.9, 122.2, 119.8, 118.2, 110.9, 109.3, 56.5, 56.4, 52.3, 25.4.

b. (1*R*,3*S*)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1k**)



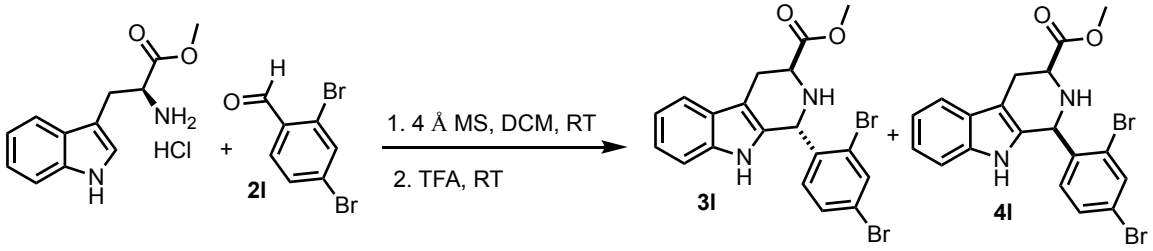
3k **1k**

To a solution of **3k** (84.0 mg, 0.2 mmol) in THF / MeOH / H_2O (2 mL / 2 mL / 2 mL) was added Amberlyst hydroxide resin (0.8 g, 3.4 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. The residue was suspended in a minimum amount of MeOH, and the desired product was precipitated by the addition of Et_2O and hexane. The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1k** (78 mg, 96% yield) as an off white solid.

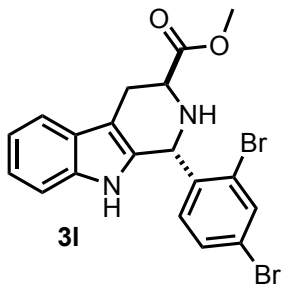
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.06 (td, *J* = 8.0, 1.2 Hz, 1H), 6.99 (td, *J* = 7.2, 1.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.67 (s, 1H), 3.57 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.09 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.85 (dd, *J* = 15.2, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 140.2, 136.2, 132.9, 123.4, 132.0, 131.5, 127.5, 126.3, 124.5, 121.2, 118.5, 117.8, 111.2, 108.3, 53.1, 51.3, 24.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}BrClN_2O_2$: 405.0000. Found: 404.9904.

5. Synthesis of 1l

a. methyl (1*R*,3*S*)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3l**) and methyl (1*S*,3*S*)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4l**)

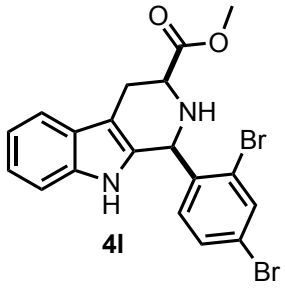


To a mixture of L-tryptophan methyl ester hydrochloride, (0.38 g, 1.44 mmol), 4 Å molecular sieves (0.8 g, powder form) and 2,4-dibromobenzaldehyde (**2l**) (0.38 g, 1.44 mmol), DCM (16 mL) were added under nitrogen. After 2 minutes 0.01 mL of TFA was added and the resulting mixture was stirred for 24 hours at room temperature. TFA (0.15 mL, 2.0 mmol) was then added dropwise, and the reaction mixture was stirred at room temperature for an additional 24 hours. An aqueous solution of $NaHCO_3$ (0.6 g, 7.0 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **3l** (0.25 g, 38% yield) as an orange-yellow solid and **4l** (0.4 g, 60% yield) as a white-yellow solid.



methyl (1*R*,3*S*)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3l**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.26 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.19 – 7.10 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 5.74 (d, *J* = 1.2 Hz, 1H), 3.80 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.71 (s, 3H), 3.24 (ddd, *J* = 15.4, 5.0, 1.1 Hz, 1H), 3.06 (ddd, *J* = 15.3, 8.0, 1.5 Hz, 1H), 2.81 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 139.8, 136.3, 135.5, 131.5, 131.3, 130.6, 126.7, 124.7, 122.4, 122.3, 119.7, 118.3, 111.0, 109.6, 53.6, 52.2, 52.1, 24.8.

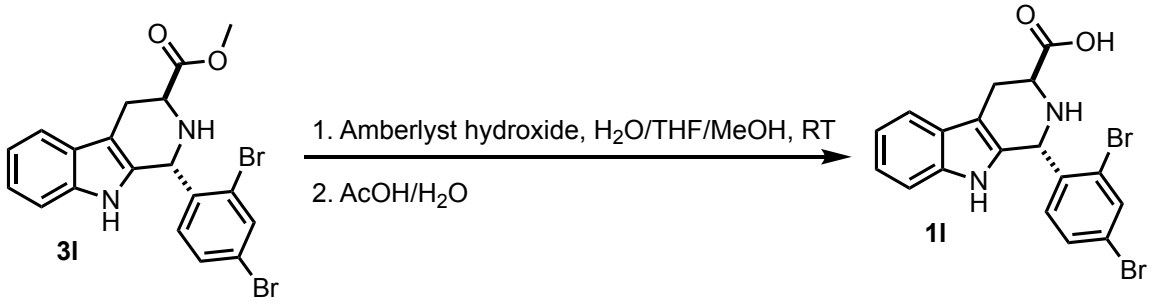


4l

methyl (1*S*,3*S*)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4l**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.0 Hz, 1H), 7.68 (s, 1H), 7.55 – 7.51 (m, 1H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.08 (m, 3H), 5.74 (s, 1H), 3.97 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.81 (s, 3H), 3.23 (ddd, *J* = 15.1, 4.1, 1.9 Hz, 1H), 3.01 (ddd, *J* = 15.1, 11.0, 2.5 Hz, 1H), 2.65 (br s, 1H). ^{13}C NMR (101 MHz $CDCl_3$) δ 173.0, 139.6, 136.2, 135.1, 133.1, 132.0, 131.4, 126.8, 124.3, 122.6, 122.2, 119.7, 118.3, 111.0, 110.0, 109.3, 56.5, 52.4, 25.4.

b. (1*R*,3*S*)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1l**)



3l **1l**

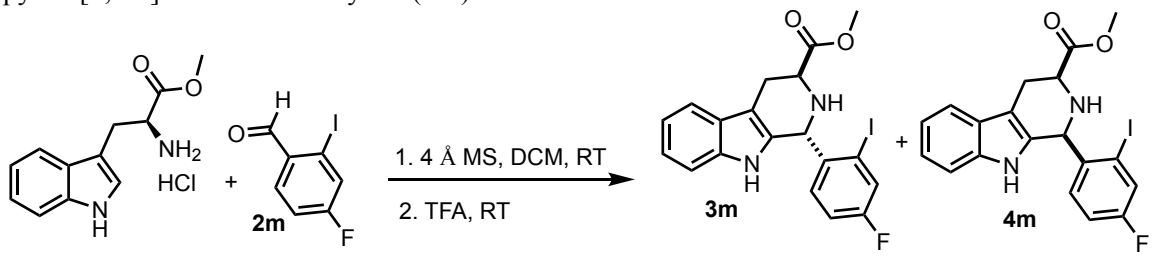
To a solution of 3k (93.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.0 g, 4.2 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH : H_2O : MeOH (1:1:1; 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH : H_2O : MeOH (1:1:1; 4 mL). The combined filtrates were concentrated in vacuo. To the residue was added The residue was suspended in a minimum amount of MeOH, and the desired product was precipitated by the addition of Et_2O and hexane. The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1l** (46 mg, 50% yield) as a yellow solid.

^{1}H NMR (100 MHz, CD_3OD) δ 8.00 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.0, 1H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.15 (td, *J* = 7.2, 1.2 Hz, 1H), 7.07 (td, *J* = 7.2, 1.2 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.37 (s, 1H), 3.96 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.47 (dd, *J* = 16.0, 5.6 Hz,

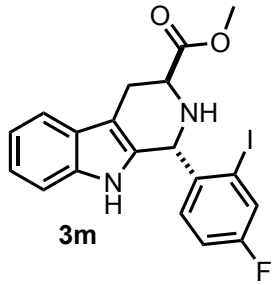
1H), 3.22 (dd, J = 16.0, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.6, 138.7, 136.9, 135.5, 133.9, 132.6, 127.8, 127.4, 127.2, 125.6, 123.8, 120.6, 119.3, 112.4, 109.7, 55.2, 54.9, 24.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}Br_2N_2O_2$: 450.9475. Found: 450.9378.

6. Synthesis of 1m

a. methyl (1*R*,3*S*)-1-(4-fluoro-2-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3m**) and methyl (1*S*,3*S*)-1-(4-fluoro-2-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4m**)

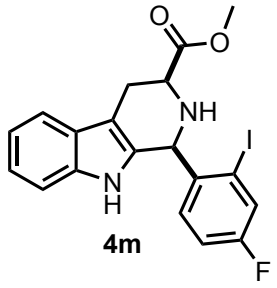


To a mixture of L-tryptophan methyl ester hydrochloride, (0.64 g, 2.5 mmol), 4 Å molecular sieves (1.25 g, powder form) and 4-fluoro-2-iodobenzaldehyde (**2m**) (0.66 g, 2.5 mmol, 95%), DCM (7.5 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.4 mL, 5.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 5 days. An aqueous solution of $NaHCO_3$ (0.6 g, 7.2 mmol, in 5 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane/ DCM / EtOAc) to give **3m** (0.41 g, 36% yield) as an off white solid and **4m** (0.72 g, 64% yield) as a yellow solid.



methyl (1*R*,3*S*)-1-(4-fluoro-2-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3m**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (ddd, J = 8.0, 2.5, 0.4 Hz, 1H), 7.61 (br s, 1H), 7.58 – 7.55 (m, 1H), 7.28 – 7.25 (m, 1H), 7.21 – 7.12 (m, 2H), 6.97 – 6.87 (m, 2H), 5.71 (s, 1H), 3.88 (dd, J = 7.1, 5.1 Hz, 1H), 3.74 (s, 3H), 3.26 (ddd, J = 15.4, 5.2, 1.3 Hz, 1H), 3.12 (ddd, J = 15.4, 7.1, 1.6 Hz, 1H), 2.80 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.23 to -112.31 (m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, δ 161.8 (d, ^1J = 252.9 Hz), 139.8 (d, ^4J = 3.3 Hz), 136.4, 132.4, 130.7 (d, ^3J = 8.1 Hz), 126.9, 126.9 (d, ^2J = 22.9 Hz), 122.4, 119.9, 118.5, 115.5 (d, ^2J = 20.7 Hz), 111.1, 109.5, 99.4 (d, ^3J = 8.3 Hz), 58.0, 52.5, 52.4, 24.9. HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{16}FIN_2NaO_2$: 473.0133. Found: 473.0143.

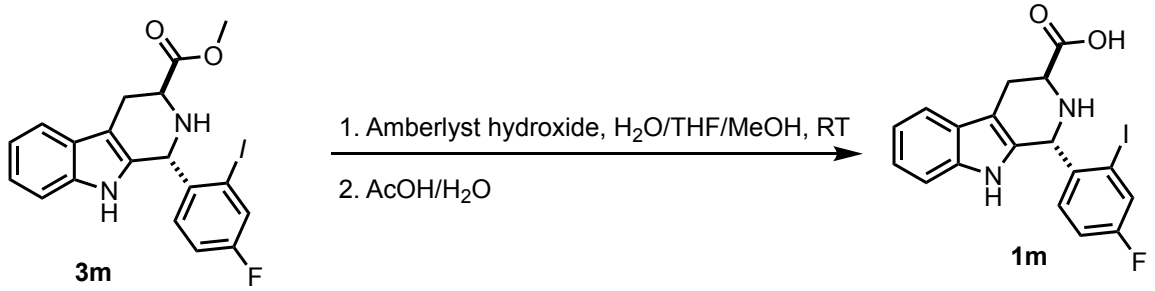


4m

methyl (1*S*,3*S*)-1-(4-fluoro-2-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4m**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.0, 2.6 Hz, 1H), 7.54 (ddd, *J* = 7.3, 1.8, 0.8 Hz, 1H), 7.47 (br s, 1H), 7.32 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.19 – 7.10 (m, 2H), 7.03 (dd, *J* = 7.9, 2.4 Hz, 1H), 5.63 (s, 1H), 4.01 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.83 (s, 3H), 3.24 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.02 (ddd, *J* = 15.1, 11.1, 2.5 Hz, 1H), 2.68 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.54 (q, *J* = 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 162.0 (d, ^1J = 253.1 Hz), 139.5, 136.3, 133.9, 131.3 (d, ^3J = 8.2 Hz), 127.0, 126.1 (d, ^2J = 23.3 Hz), 122.3, 119.9, 118.4, 116.5 (d, ^2J = 20.7 Hz), 111.1, 109.4, 99.1, 61.6, 56.7, 52.5, 25.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}FIN_2O_2$: 451.0313. Found: 451.0318.

b. (1*R*,3*S*)-1-(4-fluoro-2-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1m**)



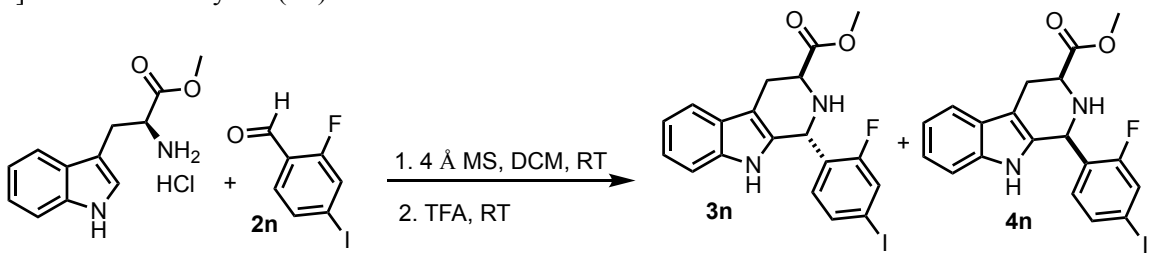
3m **1m**

To a solution of **3m** (113.0 mg, 0.25 mmol) in THF / MeOH / H_2O (2.5 mL / 2.5 mL / 2.5 mL) was added Amberlyst hydroxide resin (0.89 g, 3.75 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2.5 mL). An aqueous solution of AcOH (50%, 5 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 6 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.3 mL), and the product was precipitated by the addition of Et_2O (3 mL) and hexane (9 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1m** (90 mg, 82% yield) as an off white-bright yellow solid.

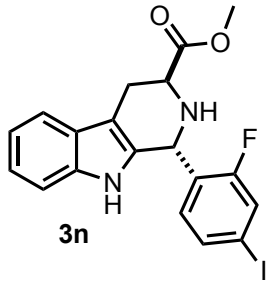
^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.55 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.26 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.10 – 7.04 (m, 1H), 6.98 (dd, *J* = 8.7, 5.8 Hz, 1H), 6.26 (s, 1H), 3.93 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.47 (ddd, *J* = 16.2, 5.4, 0.9 Hz, 1H), 3.20 (ddd, *J* = 16.3, 8.9, 1.5 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -111.86. ^{13}C NMR (101 MHz, CD_3OD) δ 173.5, 163.6 (d, ^1J = 254.3 Hz), 138.5, 135.5 (d, ^4J = 3.6 Hz), 133.0 (d, ^3J = 8.7 Hz), 128.3, 128.1 (d, ^2J = 24.3 Hz), 126.9, 123.6, 120.4, 119.2, 116.7 (d, ^2J = 21.5 Hz), 112.2, 109.4, 102.3 (d, ^3J = 8.9 Hz), 59.6, 54.4, 23.9. HRMS (ESI) $[2M+Na]^+$ calculated for $C_{36}H_{28}F_2I_2N_4NaO_4$: 895.0060. Found: 895.0052.

7. Synthesis of 1n

a. methyl (1*R*,3*S*)-1-(2-fluoro-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3n**) and methyl (1*S*,3*S*)-1-(2-fluoro-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4n**)

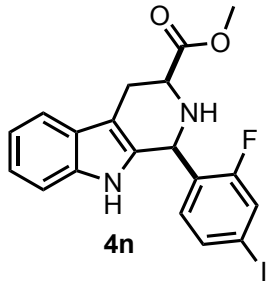


To a mixture of L-tryptophan methyl ester hydrochloride, (0.64 g, 2.5 mmol), 4 Å molecular sieves (1.25 g, powder form) and 2-fluoro-4-iodobenzaldehyde (**2n**) (0.66 g, 2.5 mmol, 95%), DCM (7.5 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.4 mL, 5.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 5 days. An aqueous solution of $NaHCO_3$ (0.6 g, 7.2 mmol, in 5 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane/ DCM / EtOAc) to give **3n** (0.39 g, 35% yield) as a yellow solid and **4n** (0.73 g, 56% yield) as a yellow solid.



methyl (1*R*,3*S*)-1-(2-fluoro-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3n**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 1H), 7.58 – 7.53 (m, 1H), 7.50 (dd, J = 9.4, 1.7 Hz, 1H), 7.37 (dd, J = 8.0, 1.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.21 – 7.10 (m, 2H), 6.84 – 6.70 (m, 1H), 5.76 (s, 1H), 3.89 (dd, J = 7.7, 5.0 Hz, 1H), 3.74 (s, 3H), 3.24 (ddd, J = 15.4, 5.1, 1.1 Hz, 1H), 3.07 (ddd, J = 15.3, 7.8, 1.6 Hz, 1H), 2.61 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.76 – -117.00 (m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 160.4 (d, ^1J = 251.9 Hz), 136.3, 133.6 (d, ^3J = 3.6 Hz), 131.4, 131.3 (d, ^3J = 4.3 Hz), 129.2 (d, ^2J = 13.6 Hz), 126.9, 125.2 (d, ^2J = 24.3 Hz), 122.5, 119.9, 118.4, 111.1, 109.6, 92.9 (d, ^3J = 8.3 Hz), 52.5, 52.4, 47.9, 24.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}FIN_2O_2$: 451.0313. Found: 451.0313.



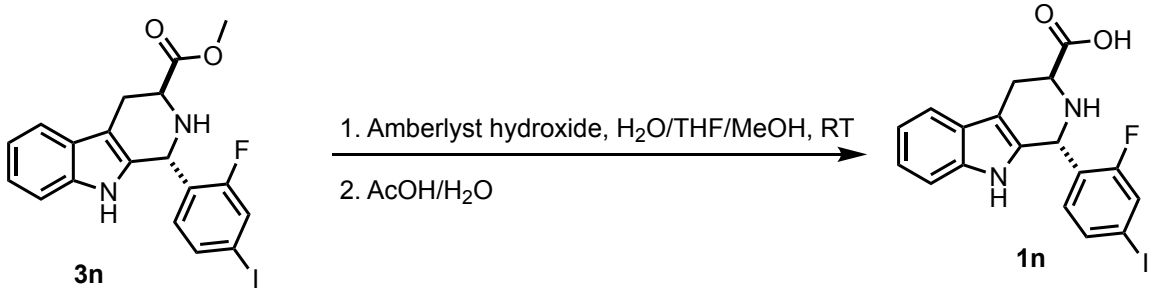
4n

methyl (1*S*,*3S*)-1-(2-fluoro-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4n**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 3H), 7.48 – 7.42 (m, 1H), 7.26 – 7.21 (m, 1H), 7.19 – 7.09 (m, 3H), 5.63 (t, *J* = 2.2 Hz, 1H), 3.97 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.82 (s, 3H), 3.23 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 2.99 (ddd, *J* = 15.1, 11.1, 2.5 Hz, 1H), 2.51 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.81 (t, *J* = 8.5 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 160.5 (d, ^1J = 251.9 Hz), 136.3, 134.3 (d, ^3J = 3.6 Hz), 133.0, 131.6 (d, ^3J = 4.2 Hz), 128.0 (d, ^2J = 13.0 Hz), 127.0, 125.1 (d, ^2J = 24.5 Hz), 122.3, 119.9, 118.4, 111.1, 109.6, 93.4 (d, ^3J = 8.3 Hz), 56.8, 52.5, 50.7, 25.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}FIN_2O_2$: 452.0345. Found: 452.0338.

b. (*1R*,3*S*)-1-(2-fluoro-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1n**)



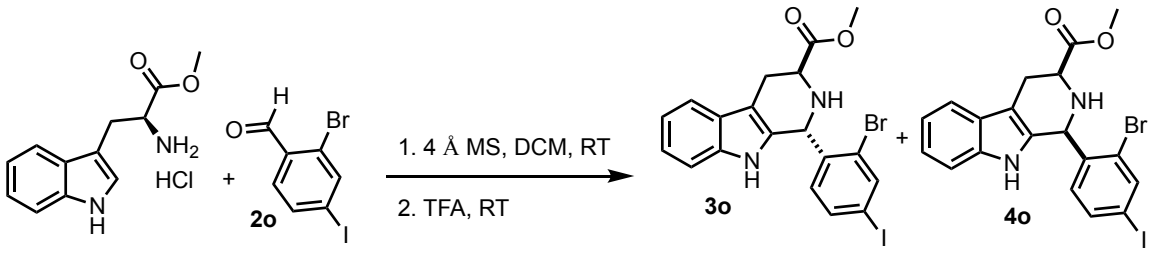
3n **1n**

To a solution of **3n** (113.0 mg, 0.25 mmol) in THF / MeOH / H_2O (2.5 mL / 2.5 mL / 2.5 mL) was added Amberlyst hydroxide resin (0.89 g, 3.75 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2.5 mL). An aqueous solution of AcOH (50%, 5 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 5 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.3 mL), and the product was precipitated by the addition of Et_2O (3 mL) and hexane (9 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1n** (81 mg, 74% yield, 90% purity) as a yellow solid.

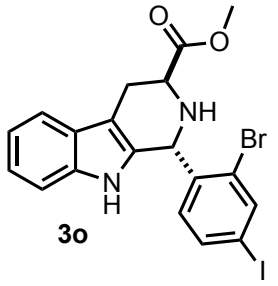
^{1}H NMR (400 MHz, CD_3OD/ $CDCl_3$) δ 7.72 (dd, *J* = 9.4, 1.5 Hz, 1H), 7.56 (dd, *J* = 13.0, 6.6 Hz, 2H), 7.27 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.14 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.79 (t, *J* = 7.9 Hz, 1H), 6.23 (s, 1H), 3.99 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.47 (dd, *J* = 16.3, 5.5 Hz, 1H), 3.24 (ddd, *J* = 16.7, 8.5, 1.3 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD/ $CDCl_3$) δ -116.07 (t, *J* = 8.7 Hz). ^{13}C NMR (101 MHz, CD_3OD/ $CDCl_3$) δ 172.1, 160.6 (d, ^1J = 254.7 Hz), 137.3, 134.1 (d, ^3J = 3.6 Hz), 132.2 (d, ^3J = 2.9 Hz), 125.8, 125.7, 125.1 (d, ^2J = 24.2 Hz), 122.5 (d, ^2J = 13.5 Hz), 122.3, 119.2, 117.8, 110.9, 108.2, 95.4 (d, ^3J = 8.3 Hz), 53.7, 48.4, 22.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}FIN_2O_2$: 437.0157. Found: 437.0166.

8. Synthesis of 1o

a. methyl (1*R*,3*S*)-1-(2-bromo-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3o**) and methyl (*1S*,*3S*)-1-(2-bromo-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4o**)

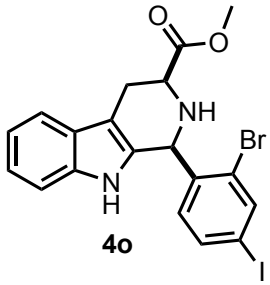


To a mixture of L-tryptophan methyl ester hydrochloride, (0.51 g, 2.0 mmol), 4 Å molecular sieves (1.0 g, powder form) and 2-bromo-4-iodobenzaldehyde (**2o**) (0.63 g, 2.5 mmol, 98%), DCM (7.5 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.31 mL, 4.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 6 days. An aqueous solution of $NaHCO_3$ (0.5 g, 6 mmol, in 4.5 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane/ DCM / EtOAc) to give **3o** (0.36 g, 35% yield) as a white solid and **4o** (0.68 g, 65% yield) as a yellow solid.



methyl (*1R*,3*S*)-1-(2-bromo-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3o**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.7 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.58 – 7.55 (m, 1H), 7.49 (ddd, *J* = 8.2, 1.8, 0.5 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.23 – 7.11 (m, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 5.81 (s, 1H), 3.85 (dd, *J* = 7.6, 5.0 Hz, 1H), 3.74 (s, 3H), 3.25 (ddd, *J* = 15.3, 5.1, 1.2 Hz, 1H), 3.10 (ddd, *J* = 15.3, 7.6, 1.5 Hz, 1H), 2.83 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 141.1, 140.5, 136.6, 136.2, 131.6, 131.5, 126.7, 124.8, 122.3, 119.7, 118.3, 110.9, 109.6, 93.8, 53.7, 52.2, 52.2, 24.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_3$: 510.9513. Found: 510.9521.

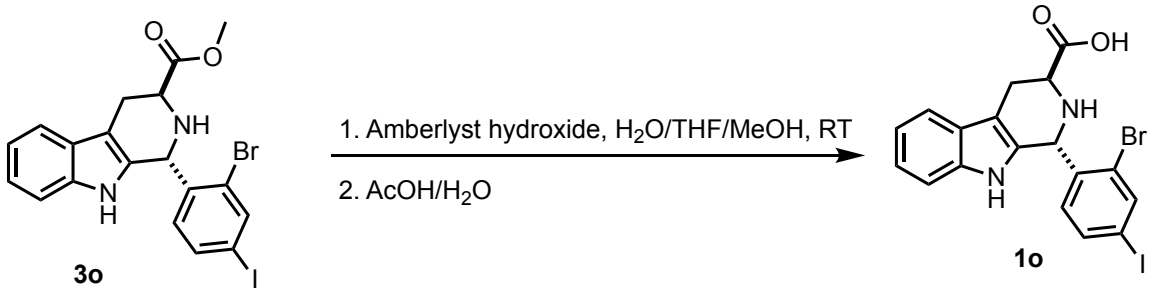


4o

methyl (1*S*,3*S*)-1-(2-bromo-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4o**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.7 Hz, 1H), 7.62 – 7.49 (m, 3H), 7.26 – 7.22 (m, 1H), 7.19 – 7.09 (m, 3H), 5.75 (s, 1H), 3.99 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.83 (s, 3H), 3.24 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.01 (ddd, *J* = 15.1, 11.0, 2.5 Hz, 1H), 2.68 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 140.8, 140.2, 137.3, 136.2, 133.1, 132.1, 126.8, 124.4, 122.2, 119.8, 118.2, 110.9, 109.3, 94.1, 56.6, 56.5, 52.3, 25.3. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}BrIN_2O_2$: 510.9513. Found: 510.9502.

b. (1*R*,*3S*)-1-(2-bromo-4-iodophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1o**)



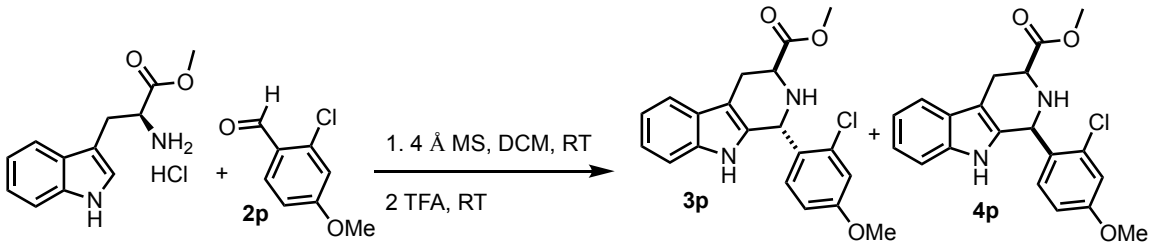
3o **1o**

To a solution of **3o** (128.0 mg, 0.25 mmol) in THF / MeOH / H_2O (2.5 mL / 2.5 mL / 2.5 mL) was added Amberlyst hydroxide resin (0.89 g, 3.75 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2.5 mL). An aqueous solution of AcOH (50%, 5 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 5 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.3 mL), and the product was precipitated by the addition of Et_2O (3 mL) and hexane (9 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1o** (94 mg, 76% yield) as a pale yellow solid.

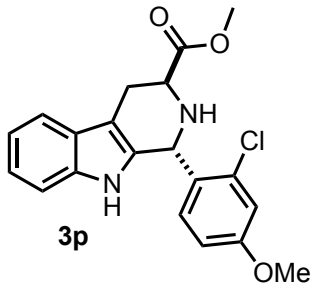
^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, *J* = 1.7 Hz, 1H), 7.71 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 6.4 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.33 (s, 1H), 3.93 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.50 – 3.42 (m, 1H), 3.21 (ddd, *J* = 16.2, 8.7, 1.5 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.7, 142.7, 138.7, 138.6, 136.1, 133.9, 127.8, 127.3, 127.2, 123.8, 120.6, 119.3, 112.3, 109.7, 97.2, 55.4, 54.9, 24.1. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}BrIN_2O_2$: 496.9356. Found: 496.9370.

9. Synthesis of 1p

a. methyl (*1R*,3*S*)-1-(2-chloro-4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3p**) and methyl (1*S*,3*S*)-1-(2-chloro-4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4p**)

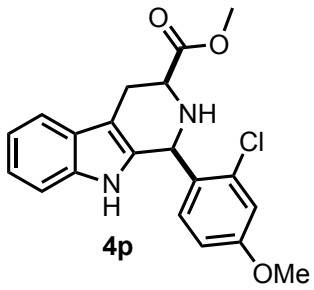


To a mixture of L-tryptophan methyl ester hydrochloride, (1.27 g, 5.0 mmol), 4 Å molecular sieves (2.5 g, powder form) and 2-chloro-4-methoxybenzaldehyde (**2p**) (0.89 g, 5.0 mmol, 95%), DCM (15 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 6 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (60 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×60 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1.5 hexane/ DCM / EtOAc) to give **3p** (0.94 g, 51% yield) as a white solid and **4p** (0.72 g, 39% yield) as a yellow solid.



methyl (1*R*,3*S*)-1-(2-chloro-4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3p**)

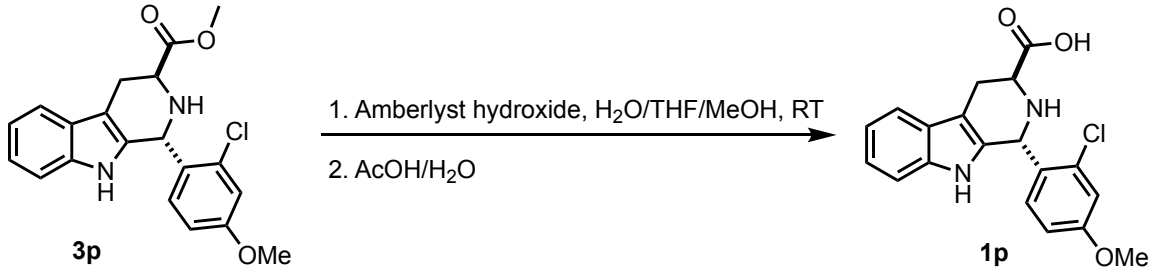
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 4.0 Hz, 1H), 7.63 – 7.50 (m, 1H), 7.30 – 7.23 (m, 1H), 7.22 – 7.08 (m, 2H), 7.00 (d, *J* = 2.6 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.6 Hz, 1H), 5.82 (d, *J* = 1.7 Hz, 1H), 3.86 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.78 (d, *J* = 1.0 Hz, 3H), 3.73 (s, 3H), 3.25 (ddd, *J* = 15.3, 5.0, 1.1 Hz, 1H), 3.08 (ddd, *J* = 15.4, 8.0, 1.5 Hz, 1H), 2.76 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 159.8, 136.3, 134.4, 132.5, 131.2, 130.8, 127.0, 122.2, 119.7, 118.4, 115.5, 112.8, 111.1, 109.6, 55.7, 52.3, 52.3, 51.3, 25.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_3$: 375.1189. Found: 375.122.



methyl (1*S*,3*S*)-1-(2-chloro-4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4p**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.09 (m, 2H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.76 (s, 1H), 4.00 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.23 (ddd, *J* = 15.1, 4.2, 1.9 Hz, 1H), 3.01 (ddd, *J* = 15.1, 11.0, 2.6 Hz, 1H), 2.59 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 160.0, 136.2, 134.3, 134.3, 131.1, 130.5, 127.2, 122.1, 119.8, 118.3, 114.9, 114.0, 111.0, 109.2, 56.9, 55.8, 53.9, 52.4, 25.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_3$:371.1157. Found: 371.1176.

b. (1*R*,3*S*)-1-(2-chloro-4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1p**)

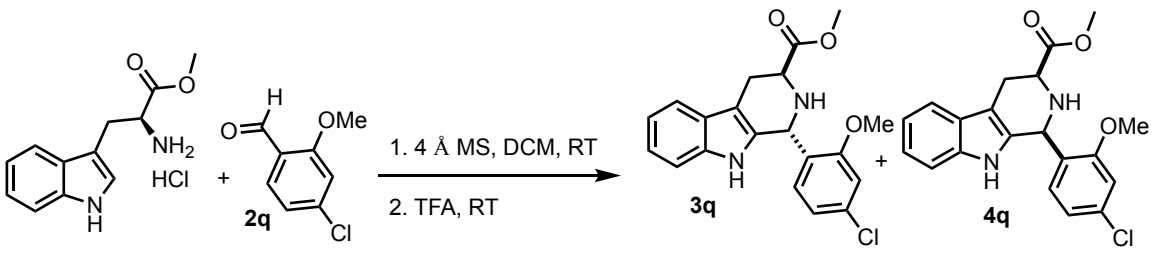


To a solution of **3p** (167.0 mg, 0.45 mmol) in THF / MeOH / H_2O (4.5 mL / 4.5 mL / 4.5 mL) was added Amberlyst hydroxide resin (1.61 g, 6.75 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 5 mL). An aqueous solution of AcOH (50%, 10 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 10 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.6 mL), and the product was precipitated by the addition of Et_2O (6 mL) and hexane (18 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1p** (160 mg, 99% yield) as a pale yellow solid.

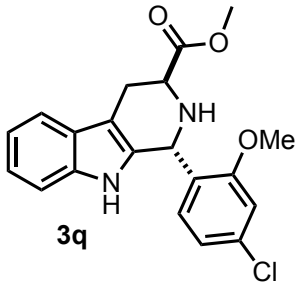
^{1}H NMR (400 MHz, CD_3OD/ $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.02 (m, 3H), 6.93 (d, *J* = 8.7 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.37 (s, 1H), 3.94 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.81 (s, 3H), 3.48 (dd, *J* = 16.3, 5.5 Hz, 1H), 3.23 (dd, *J* = 16.3, 8.9 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD/ $CDCl_3$) δ 173.4, 162.7, 138.5, 136.8, 133.2, 127.7, 126.9, 125.4, 123.6, 120.4, 119.1, 116.6, 114.2, 112.2, 109.3, 56.2, 54.7, 52.7, 23.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2O_3$: 357.1000. Found: 357.1028

10. Synthesis of 1q

a. methyl (1*R*,3*S*)-1-(4-chloro-2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3q**) and methyl (1*S*,3*S*)-1-(4-chloro-2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4q**)



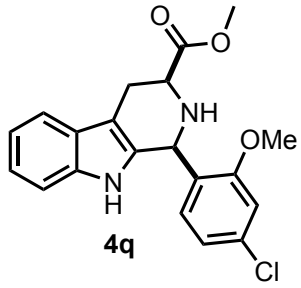
To a mixture of L-tryptophan methyl ester hydrochloride, (0.637 g, 2.5 mmol), 4 Å molecular sieves (1.25 g, powder form) and 4-chloro-2-methoxybenzaldehyde (**2q**) (0.45 g, 2.5 mmol, 95%), DCM (7.5 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.38 mL, 5.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 5 days. An aqueous solution of $NaHCO_3$ (0.6 g, 7.5 mmol, in 5 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 2 hexane/ DCM / EtOAc) to give **3q** (0.47 g, 50% yield) as a white solid and **4q** (0.40 g, 43% yield) as a yellow solid.



3q

methyl (1*R*,3*S*)-1-(4-chloro-2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3q**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.58 – 7.51 (m, 1H), 7.31 – 7.23 (m, 2H), 7.19 – 7.10 (m, 2H), 6.94 (d, *J* = 1.2 Hz, 1H), 6.81 – 6.79 (m, 1H), 5.76 (s, 1H), 3.95 (s, 3H), 3.82 (dd, *J* = 8.7, 4.7 Hz, 1H), 3.74 (s, 3H), 3.22 (ddd, *J* = 15.2, 4.8, 0.9 Hz, 1H), 3.03 (ddd, *J* = 15.2, 8.7, 1.5 Hz, 1H), 2.77 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 157.6, 136.3, 134.5, 132.6, 129.9, 128.8, 127.0, 122.1, 120.5, 119.7, 118.3, 111.6, 111.0, 109. 5, 56.1, 52.3, 52.3, 48.8, 25.2. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_3$: 371.1157. Found: 371.1163.

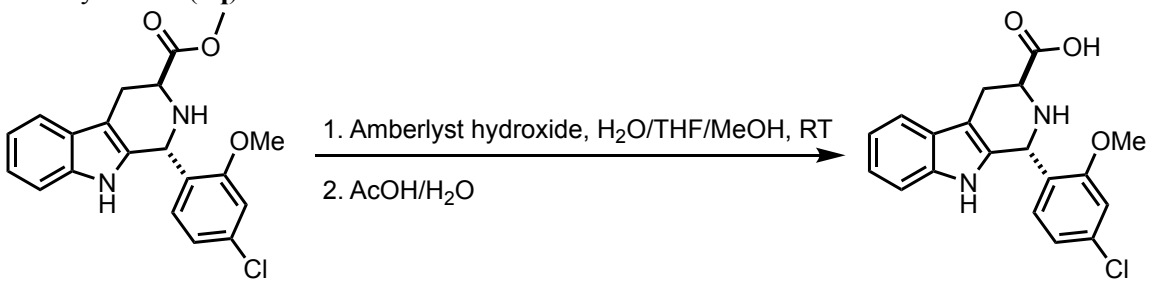


4q

methyl (1*S*,3*S*)-1-(4-chloro-2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4q**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 7.55 – 7.48 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.17 – 7.06 (m, 2H), 6.97 (d, *J* = 1.9 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.67 (t, *J* = 2.1 Hz, 1H), 3.97 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.21 (ddd, *J* = 15.0, 4.2, 1.9 Hz, 1H), 2.98 (ddd, *J* = 15.1, 11.0, 2.6 Hz, 1H), 2.56 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 157.9, 136.1, 134.7, 134.5, 130.3, 127.9, 127.2, 121.9, 121.5, 119.7, 118.2, 111.8, 110.9, 108.9, 56.9, 56.2, 52.4, 51.3, 25.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_3$: 371.1157. Found: 371.1166.

b. (1*R*,3*S*)-1-(4-chloro-2-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1q**)



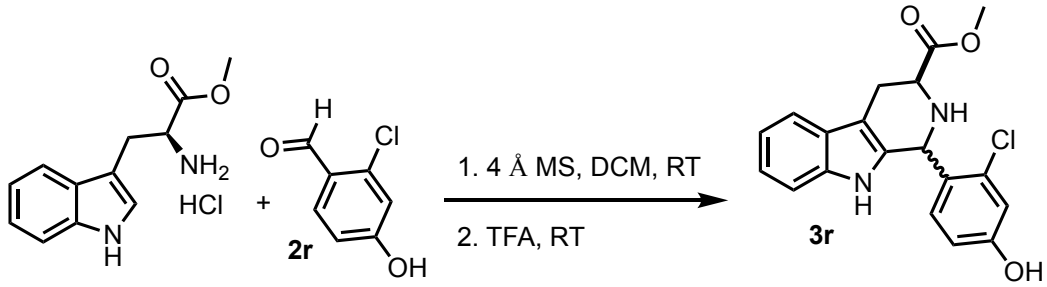
3q **1q**

To a solution of **3q** (103.0 mg, 0.28 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.0 g, 4.2 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 5 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 5 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.35 mL), and the product was precipitated by the addition of Et_2O (4 mL) and hexane (10 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1q** (96 mg, 97% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.29 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.97 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.26 (s, 1H), 4.01 (s, 3H), 3.88 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.47 (ddd, *J* = 16.4, 5.5, 0.9 Hz, 1H), 3.20 (ddd, *J* = 16.4, 9.4, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.5, 159.8, 138.7, 138.4, 132.8, 127.5, 127.3, 123.7, 122.7, 121.9, 120.6, 119.2, 113.1, 112.3, 109.5, 56.9, 55.1, 50.7, 23.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2O_3$: 357.1000. Found: 357.1027.

11. Synthesis of 1r

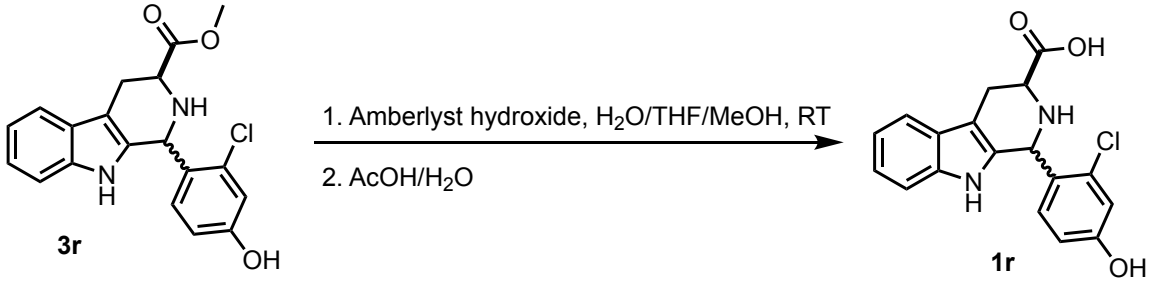
a. methyl (*S*)-1-(2-chloro-4-hydroxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3r**)



To a mixture of L-tryptophan methyl ester hydrochloride, (1.27 g, 5.0 mmol), 4 Å molecular sieves (2.5 g, powder form) and 2-chloro-4-hydroxybenzaldehyde (**2r**) (0.82 g, 5.0 mmol, 95%), DCM (15 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 3 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc:MeOH (60:5 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc:MeOH (3×60:5 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography

(5 : 5 : 2 hexane/ DCM / EtOAc) to give **3r** (1.1 g, 60% yield) as a mixture of diastereomers (2:1 by ^{1}H NMR) as an off white solid.
^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (ddd, *J* = 7.7, 1.3, 0.8 Hz, 0.66H), 7.44 (ddd, *J* = 7.5, 1.4, 0.7 Hz, 0.33H), 7.28 – 7.19 (m, 1H), 7.11 – 6.97 (m, 2.0 + 0.33H), 6.94 – 6.90 (m, 1H), 6.71 (dd, *J* = 8.5, 2.5 Hz, 0.33H), 6.59 (d, J = 0.9 Hz, 0.66H), 6.59 (s, 0.66H), 5.78 – 5.74 (m, 0.66H), 5.70 (s, 0.33H), 3.97 (dd, *J* = 10.9, 4.4 Hz, 0.33H), 3.80 (dd, *J* = 9.4, 4.7 Hz, 0.66H), 3.78 (s, 0.33H×3), 3.74 (s, 0.66H×3), 3.26 – 3.14 (m, 1H), 3.03 – 2.90 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.7, 174.5, 159.5, 159.5, 138.2, 138.2, 135.2, 134.7, 133.0, 132.2, 130.4, 128.1, 127.9, 122.6, 122.4, 119.9, 119.9, 118.7, 118.5, 117.6, 115.8, 114.9, 112.1, 112.0, 109.6, 61.5, 57.8, 52.8, 52.7, 52.7, 52.6, 26.3, 25.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}ClN_2O_3$: 357.1000. Found: 357.1016.

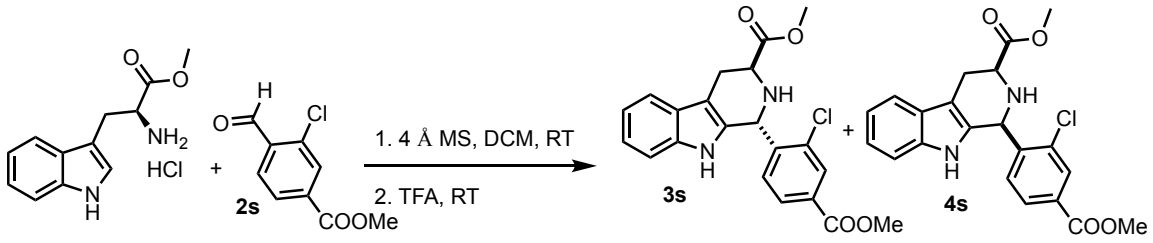
b. (*S*)-1-(2-chloro-4-hydroxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1r**)



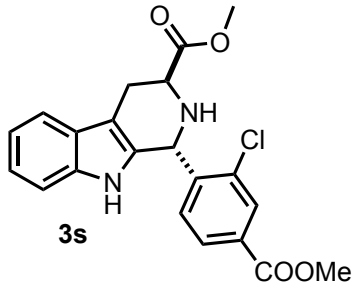
To a solution of **3r** (160.0 mg, 0.45 mmol) in THF / MeOH / H_2O (4.5 mL / 4.5 mL / 4.5 mL) was added Amberlyst hydroxide resin (1.61 g, 6.75 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 5 mL). An aqueous solution of AcOH (50%, 10 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 10 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.6 mL), and the product was precipitated by the addition of Et_2O (6 mL) and hexane (18 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1r** (146 mg, 95% yield) as a pale yellow solid.
^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (s, 0.33H), 7.53 (t, *J* = 8.8 Hz, 1H), 7.27 (t, *J* = 6.6 Hz, 1H), 7.11 (dt, *J* = 27.4, 7.2 Hz, 2H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.5 Hz, 0.66H), 6.32 (s, 0.66H), 6.19 (s, 0.33H), 4.14 (dd, *J* = 12.2, 4.9 Hz, 0.33H), 3.93 (dd, *J* = 9.3, 5.5 Hz, 0.65H), 3.56 – 3.45 (m, 1H), 3.21 (dd, *J* = 16.3, 9.3 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 183.4, 182.9, 167.3, 167.3, 145.8, 145.7, 143.7, 143.1, 142.9, 142.1, 140.5, 138.5, 137.9, 136.0, 135.9, 130.5, 130.3, 127.9, 127.2, 127.1, 125.6, 124.4, 123.4, 120.8, 120.6, 117.6, 66.1, 60.9, 60.3, 58.1, 40.2, 34.6, 34.1, 30.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{16}ClN_2O_3$: 343.0844. Found: 343.0857.

12. Synthesis of 1s

a. methyl (1*R*,3*S*)-1-(2-chloro-4-(methoxycarbonyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3s**) and methyl (1*S*,3*S*)-1-(2-chloro-4-(methoxycarbonyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4s**)

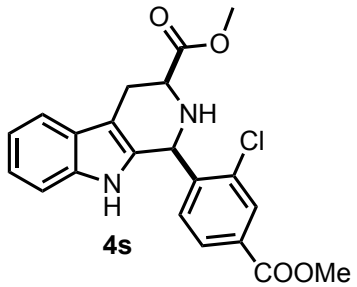


To a mixture of L-tryptophan methyl ester hydrochloride, (0.764 g, 3.0 mmol), 4 Å molecular sieves (1.5 g, powder form) and methyl 3-chloro-4-formylbenzoate (**2s**) (0.63 g, 3.0 mmol, 95%), DCM (9.0 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.46 mL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 5 days. An aqueous solution of $NaHCO_3$ (0.72 g, 8.5 mmol, in 6 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (3 : 3 : 1 hexane/ DCM / EtOAc) to give **3s** (0.37 g, 31% yield) as an off white solid and **4q** (0.90 g, 74% yield) as a yellow solid.



methyl (1*R*,3*S*)-1-(2-chloro-4-(methoxycarbonyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3s**)

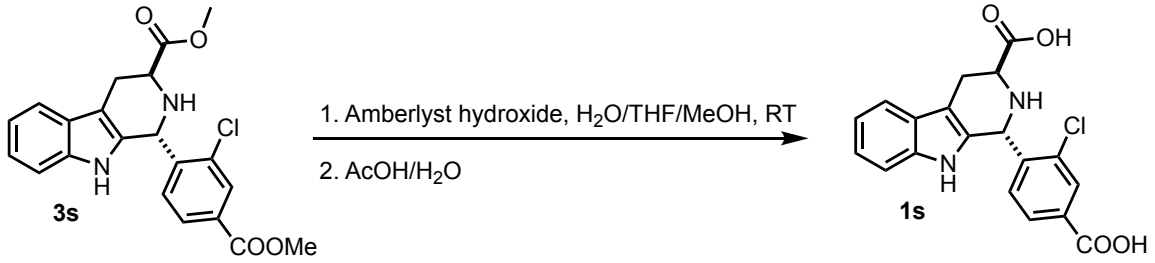
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.7 Hz, 1H), 7.84 (s, 1H), 7.74 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.61 – 7.53 (m, 1H), 7.31 – 7.24 (m, 1H), 7.22 – 7.10 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 1H), 3.91 (s, 3H), 3.85 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.73 (s, 3H), 3.27 (ddd, *J* = 15.4, 5.0, 1.2 Hz, 1H), 3.10 (ddd, *J* = 15.4, 7.8, 1.5 Hz, 1H), 2.82 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 165.7, 144.1, 136.4, 133.9, 131.4, 131.2, 131.1, 130.1, 128.0, 126.9, 122.5, 119.9, 118.5, 111.2, 109.7, 52.6, 52.4, 51.6, 24.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{21}H_{20}ClN_2O_4$: 400.1138. Found: 400.1147.



methyl (1*S*,3*S*)-1-(2-chloro-4-(methoxycarbonyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4s**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.6 Hz, 1H), 7.82 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.70 (d, *J* = 3.3 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.27 – 7.22 (m, 1H), 7.19 – 7.08 (m, 2H), 5.91 – 5.84 (m, 1H), 4.01 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.25 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.03 (ddd, *J* = 15.1, 11.0, 2.5 Hz, 1H), 2.67 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 165.7, 143.7, 136.3, 133.8, 133.0, 131.4, 130.9, 130.6, 128.7, 126.9, 122.4, 119.9, 118.4, 111.1, 109.5, 56.7, 54.2, 52.7, 52.5, 25.5. HRMS (ESI) $[M+H]^+$ calculated for $C_{21}H_{20}ClN_2O_4$: 399.1106. Found: 399.1123.

b. (1*R*,3*S*)-1-(4-carboxy-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1s**)

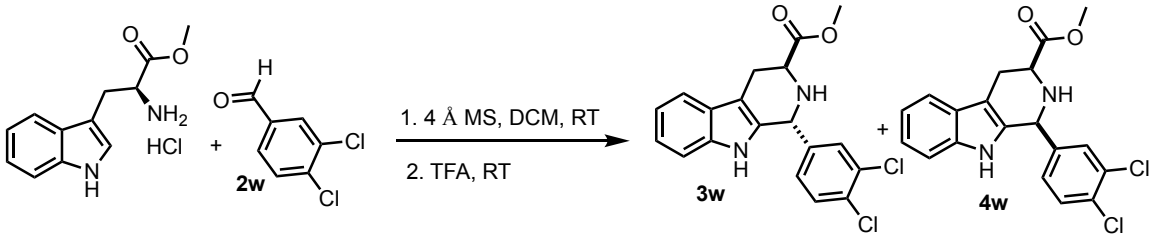


To a solution of **3s** (120.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (2.1 g, 9.0 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 10 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 10 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.4 mL), and the product was precipitated by the addition of Et_2O (4 mL) and hexane (12 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1s** (90 mg, 80% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.91 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.27 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.08 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.48 (s, 1H), 4.03 (dd, *J* = 8.3, 5.4 Hz, 1H), 3.50 (ddd, *J* = 16.5, 5.6, 0.9 Hz, 1H), 3.29 – 3.23 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.9, 166.6, 137.3, 136.9, 135.1, 134.5, 131.1, 130.7, 128.2, 126.1, 125.8, 122.4, 119.2, 117.9, 110.9, 108.1, 53.6, 51.4, 22.5. HRMS (MALDI) $[M+H]^+$ calculated for $C_{19}H_{16}ClN_2O_4$: 371.0793. Found: 371.0798.

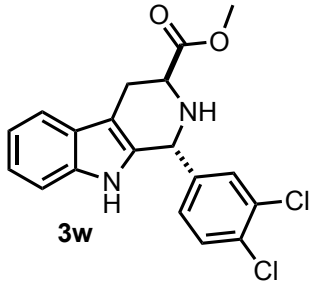
13. Synthesis of 1w

a. methyl (1*R*,3*S*)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3w**) and methyl (1*S*,3*S*)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4w**)



To a mixture of L-tryptophan methyl ester hydrochloride, (0.8 g, 3.14 mmol), 4 Å molecular sieves (2 g, powder form) and 3,4-dichlorobenzaldehyde (**2w**) (0.55 g, 3.14 mmol), DCM (20.0 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room

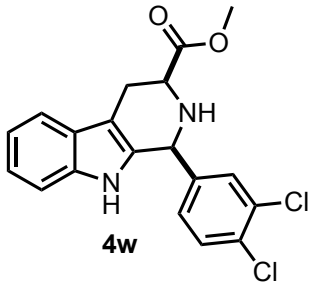
temperature. TFA (0.5 mL, 6.5 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 24 hours. An aqueous solution of $NaHCO_3$ (1.7 g, 20 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (7 : 3 : 1 DCM/ hexane / EtOAc) to give **3w** (0.27 g, 23% yield) as a white solid and **4w** (0.95 g, 70% yield) as a white solid.



3w

methyl (1*R*,3*S*)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3w**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.61 – 7.51 (m, 1H), 7.36 (d, *J* = 10.2 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.16 (dd, *J* = 7.3, 1.1 Hz, 2H), 7.08 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.27 (d, *J* = 1.4 Hz, 1H), 3.90 (dd, *J* = 7.0, 5.4 Hz, 1H), 3.70 (s, 3H), 3.25 (ddd, *J* = 15.5, 5.4, 1.3 Hz, 1H), 3.09 (ddd, *J* = 15.5, 7.0, 1.5 Hz, 1H), 2.51 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 142.4, 136.3, 132.8, 132.1, 130.6, 130.3, 127.7, 126.8, 122.3, 119.7, 118.4, 111.1, 108.7, 53.9, 52.4, 52.2, 24.7.

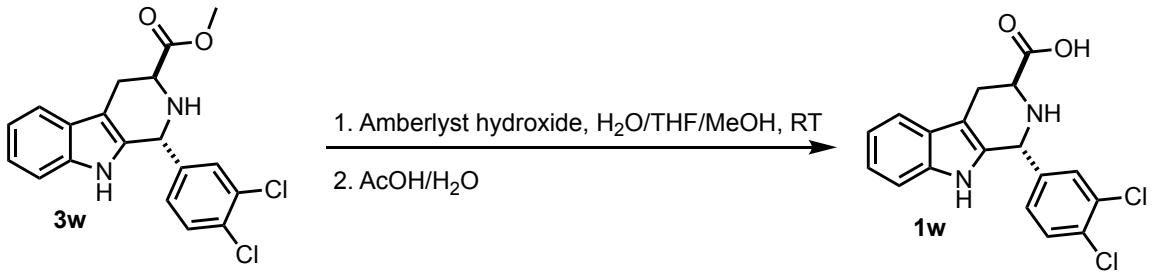


4w

methyl (1*S*,3*S*)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4w**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.49 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.43 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.41 (s, 1H), 7.25 – 7.20 (m, 2H), 7.18 – 7.09 (m, 2H), 5.20 (s, 1H), 3.93 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.81 (d, *J* = 0.9 Hz, 3H), 3.22 (dddd, *J* = 15.1, 4.2, 1.9, 1.0 Hz, 1H), 2.99 (dddd, *J* = 14.9, 11.1, 2.5, 0.9 Hz, 1H), 2.51 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 141.1, 136.2, 133.4, 133.1, 132.7, 130.9, 130.5, 127.9, 126.9, 122.3, 119.8, 118.3, 111.0, 109.3, 57.7, 56.6, 52.4, 25.5.

b. (1*R*,3*S*)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1w**)

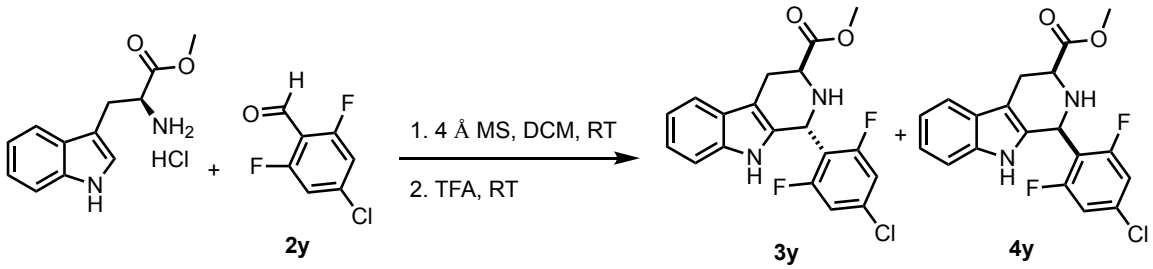


To a solution of **3w** (105.0 mg, 0.28 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.0 g, 4.2 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 6 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 6 mL). The combined filtrates were concentrated in vacuo. The residue was suspended in a minimum amount of MeOH, and the desired product was precipitated by the addition of Et_2O and hexane. The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1w** (78 mg, 77% yield) as an off white-yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7. 53 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.05 (td, *J* = 8.0, 1.2 Hz, 1H), 6.98 (td, *J* = 8.0, 1.2 Hz, 1H), 5.40 (s, 1H), 3.68 (dd, *J* = 6.8, 4.8 Hz, 1H), 3.07 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.90 (dd, *J* = 15.2, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 143.9, 136.2, 133.0, 130.8, 130.3, 130.2,129.8, 128.7, 126.4, 121.1, 118.5, 117.8, 111.1, 107.2, 53.0, 51.9, 24.4. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}Cl_2N_2O_2$: 361.0505. Found: 361.0483.

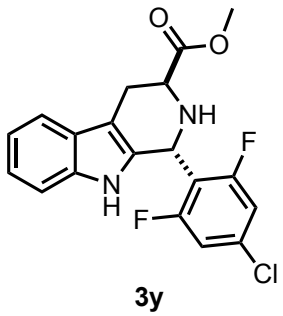
14. Synthesis of 1y

a. methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3y**) and methyl (1*S*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4y**)



To a mixture of L-tryptophan methyl ester hydrochloride, (1.27 g, 5 mmol), 4 Å molecular sieves (2.5 g, powder form) and 4-chloro-2,6-difluorobenzaldehyde (**2y**) (0.88 g, 5 mmol), DCM (18 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 4 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 3 : 1 : 1 hexane /

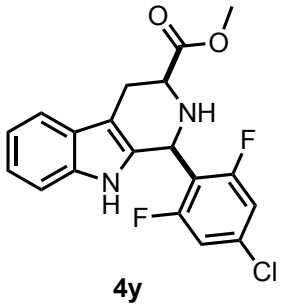
DCM / $CHCl_3$ / Et_2O) to give **3y** (0.59 g, 31% yield) as a white solid and **4y** (1.20 g, 64% yield) as a white solid.



3y

methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3y**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.06 (dtd, *J* = 17.0, 7.1, 1.3 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 5.84 (s, 1H), 4.17 (s, 1H), 4.05 (t, *J* = 5.8 Hz, 1H), 3.70 (s, 3H), 3.23 (ddd, *J* = 15.4, 5.3, 1.5 Hz, 1H), 3.10 (ddd, *J* = 15.4, 6.5, 1.7 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -111.72 (d, *J* = 8.4 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.9, 161.3 (dd, ^1J = 253.1, ^3J = 9.2 Hz), 136.2, 134.8 (t, ^3J = 13.7 Hz), 131.1, 126.6, 121.4, 118.8, 117.7, 116.4 (t, ^2J = 16.3 Hz), 112.8 (dd, ^2J = 27.9, ^4J = 2.8 Hz), 110.8, 106.7, 53.4, 52.0, 44.3 (t, ^3J = 2.8 Hz), 24.4. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{16}ClF_2N_2O_2$: 377.0863. Found: 377.0859.

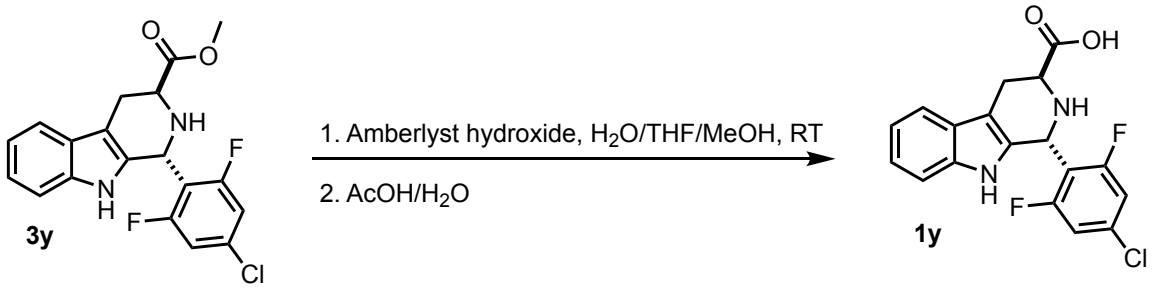


4y

methyl (1*S*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4y**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 7.56 – 7.50 (m, 1H), 7.25 – 7.10 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 2H), 5.69 (s, 1H), 3.96 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.82 (s, 3H), 3.23 (ddd, *J* = 15.3, 4.4, 1.9 Hz, 1H), 2.97 (ddd, *J* = 15.2, 11.2, 2.6 Hz, 1H), 2.49 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.40 (d, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 161.6 (dd, ^1J = 253.9, ^3J = 8.9 Hz), 136.0, 135.7 (t, ^2J = 13.6 Hz), 132.5, 127.1, 122.2, 119.9, 118.3, 114.9 (t, ^2J = 18.3 Hz), 113.77 – 113.16 (m), 111.0, 108.6, 57.3, 52.4, 47.9 (t, ^3J = 3.3 Hz), 25.8. HRMS (ESI) $[2M+Na]^+$ calculated for $C_{38}H_{30}Cl_2F_4N_4NaO_4$: 775.1472. Found: 775.1460.

b. (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**1y**)

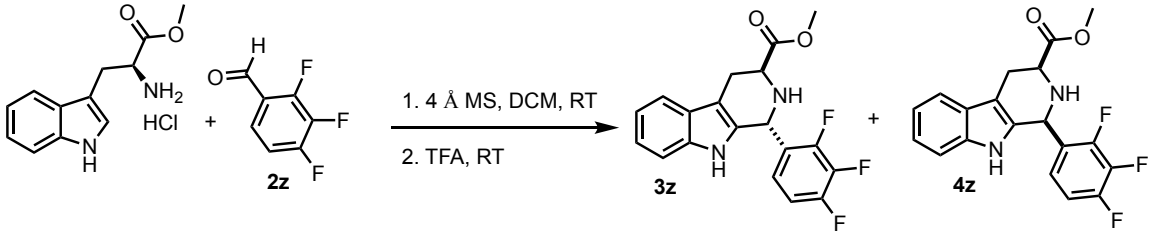


To a solution of **3y** (113.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.26 g, 5.3 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 6 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 6 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (1 mL), and the product was precipitated by the addition of DCM (5 mL), Et_2O (10 mL) and hexane (40 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1y** (106 mg, 97% yield) as a yellow powder.

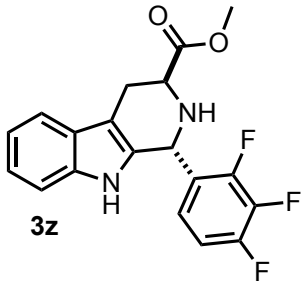
^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, J = 7.9 Hz, 1H), 7.28 – 6.97 (m, 5H), 6.23 (s, 1H), 4.07 (t, J = 6.0 Hz, 1H), 3.41 – 3.23 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ -110.99. (br s). ^{13}C NMR (101 MHz, CD_3OD) δ 175.8, 162.8 (dd, ^1J = 254.3, ^3J = 8.3 Hz), 138.1, 137.8 (t, ^3J = 13.8 Hz), 128.7, 127.4, 122.9, 120.1, 118.9, 114.2 (dd, ^2J = 26.8, ^4J = 2.9 Hz), 113.6 (t, ^3J = 17.7 Hz), 112.0, 107.8, 56.4, 45.6, 24.1. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{14}ClF_2N_2O_2$: 363.0706. Found: 363.0699.

15. Synthesis of 1z

a. methyl (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3z**) and methyl (1*S*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4z**)

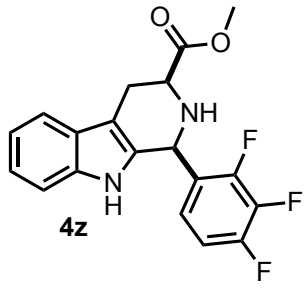


To a mixture of L-tryptophan methyl ester hydrochloride, (1.27 g, 5 mmol), 4 Å molecular sieves (2.5 g, powder form) and 2,3,4-trifluorobenzaldehyde (**2z**) (0.8 g, 5 mmol), DCM (18 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 4 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 1 hexane / DCM / Et_2O) to give **3z** (0.60 g, 34% yield) as white solid and **4z** (1.02 g, 56% yield) as a white solid.



methyl (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3z**)

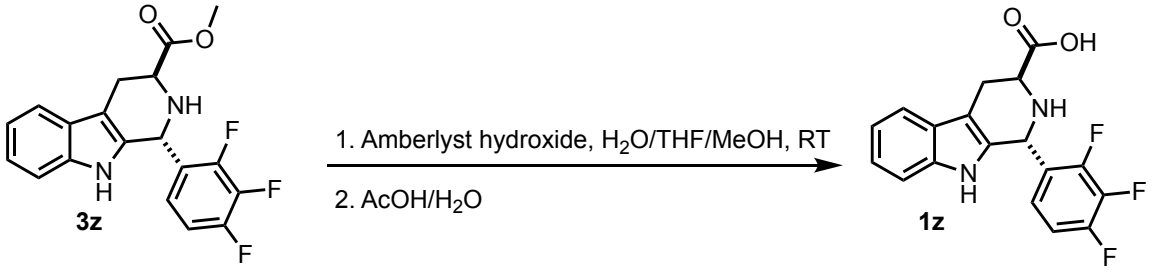
^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.21 – 7.09 (m, 2H), 6.87 – 6.77 (m, 1H), 6.72 – 6.64 (m, 1H), 5.70 (s, 1H), 3.85 (dd, *J* = 8.2, 5.0 Hz, 1H), 3.73 (s, 3H), 3.22 (dd, *J* = 15.4, 5.0 Hz, 1H), 3.02 (dd, *J* = 15.3, 8.1 Hz, 1H), 2.52 (s, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -134.32 (dq, *J* = 22.1, 7.0 Hz), -139.72 (dt, *J* = 19.9, 6.9 Hz), -159.72 (tdd, *J* = 20.3, 7.6, 1.7 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.7, 151.5 (ddd, ^{1}J = 250.7, ^{2}J = 10.5, ^{3}J = 4.6 Hz), 148.9 (ddd, ^{1}J = 250.2, ^{2}J = 10.1, ^{3}J = 3.4 Hz), 139.9 (dt, ^{1}J = 252.4, ^{2}J = 15.3 Hz), 136.2, 130.8, 126.7, 126.7 (ddd, ^{2}J = 11.4, ^{3}J = 3.3, ^{4}J = 1.7 Hz), 123.1 (dt, ^{3}J = 8.3, ^{4}J = 4.2 Hz), 122.4, 119.7, 118.3, 111.8 (dd, ^{2}J = 17.1, ^{3}J = 3.7 Hz), 111.0, 109.6, 52.2, 52.1, 47.8, 24.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{16}F_3N_2O_2$: 361.1158. Found: 361.1152.



methyl (1*S*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4z**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.53 (dd, *J* = 8.1, 2.8 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.18 – 7.05 (m, 3H), 6.91 (tdd, *J* = 9.1, 6.9, 2.1 Hz, 1H), 5.62 (s, 1H), 3.95 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.82 (s, 3H), 3.22 (ddd, *J* = 15.1, 4.1, 1.9 Hz, 1H), 2.98 (ddd, *J* = 15.2, 11.1, 2.5 Hz, 1H), 2.48 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.86 – -134.01 (m), -140.58 (dt, *J* = 19.5, 6.6 Hz), -159.70 (tdd, *J* = 20.4, 6.9, 2.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 151.7 (ddd, ^{1}J = 252.2, ^{2}J = 9.6, ^{3}J = 3.0 Hz), 149.3 (ddd, ^{1}J = 250.3, ^{2}J = 8.7, ^{3}J = 2.8 Hz), 139.8 (dt, ^{1}J = 252.5, ^{2}J = 15.5 Hz), 136.3, 132.6, 126.9, 125.6 (dd, ^{3}J = 9.4, ^{4}J = 3.5 Hz), 123.7 (dd, ^{3}J = 8.1, ^{4}J = 4.2 Hz), 122.4, 119.9, 118.4, 112.9 (dd, ^{2}J = 17.4, ^{3}J = 3.7 Hz), 111.1, 109.7, 56.7, 52.5, 50.5, 25.5. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{16}F_3N_2O_2$: 361.1158. Found: 361.1151.

b. (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**1z**)



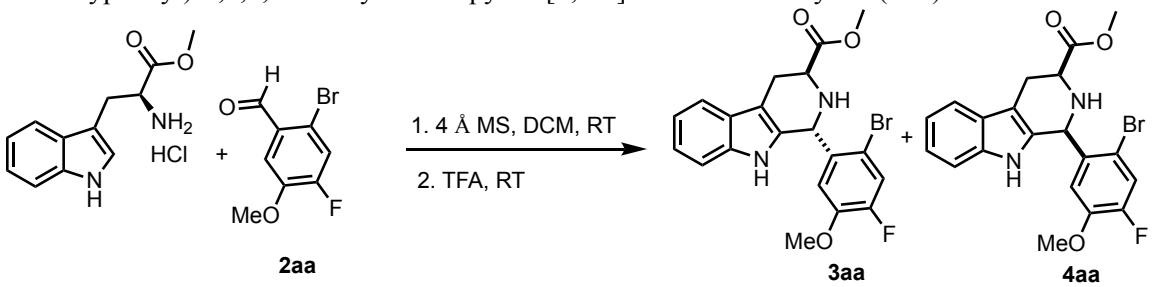
To a solution of **3z** (108.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.26 g, 5.3 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 6 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 6 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (2 mL), and the product was precipitated by the addition of Et_2O (20 mL) and hexane (60 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1z** (74 mg, 76% yield) as a yellow powder.

^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.08 (t, J = 7.6, 6.9 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.25 (s, 1H), 4.00 (dd, J = 8.6, 5.4 Hz, 1H), 3.48 (dd, J = 16.3, 5.5 Hz, 1H), 3.35 (s, 1H), 3.24 (dd, J = 16.3, 8.6 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -133.83 – -134.04 (m), -138.38 (dt, J = 18.3, 8.3 Hz), -162.48 (td, J = 19.5, 7.1 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.5, 154.5 (ddd, ^1J = 249.8, ^2J = 8.5, ^3J = 2.8 Hz), 151.2 (ddd, ^1J = 251.7, ^2J = 9.2, ^3J = 2.6 Hz), 141.3 (dt, ^1J = 249.0, ^2J = 17.8 Hz), 138.7, 127.2, 126.9, 126.7 – 126.3 (m), 123.9, 122.1 (dd, ^3J = 12.5, ^4J = 1.6 Hz), 120.6, 119.3, 113.9 (d, ^2J = 21.6 Hz), 112.3, 109.8, 54.9, 54.8, 24.0.

HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{13}F_3N_2NaO_2$: 370.0853. Found: 370.0852.

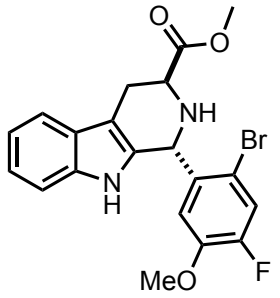
16. Synthesis of 1aa

a. methyl (1*R*,3*S*)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3aa**) and methyl (1*S*,3*S*)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4aa**)



To a mixture of L-tryptophan methyl ester hydrochloride, (0.76 g, 3 mmol), 4 Å molecular sieves (1.0 g, powder form) and 2-bromo-4-fluoro-5-methoxybenzaldehyde (**2aa**) (0.7 g, 3 mmol), DCM (10 mL) was added under nitrogen. After 5 minutes 0.05 mL of TFA was added and the resulting mixture was stirred for 24 hours at room temperature. TFA (0.5 mL, 6.5 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 24 hours. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified

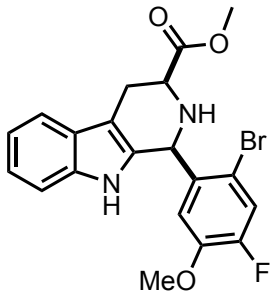
by flash chromatography (5 : 5 : 1 hexane / DCM / Et_2O) to give **3aa** (0.639 g, 30% yield) as white crystals and **4aa** (0.72 g, 56% yield) as a white solid.



3aa

methyl (1*R*,3*S*)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3aa**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.60 – 7.52 (m, 1H), 7.35 (d, J = 10.4 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.22 – 7.08 (m, 2H), 6.76 (d, J = 8.9 Hz, 1H), 5.86 (d, J = 1.6 Hz, 1H), 3.99 (t, J = 5.6 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.29 (ddd, J = 15.4, 5.5, 1.6 Hz, 1H), 3.20 (ddd, J = 15.4, 5.7, 1.6 Hz, 1H), 2.79 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.74 (t, J = 9.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 151.7 (d, ^1J = 251.8 Hz), 147.3 (d, ^2J = 10.4 Hz), 137.1 (d, ^3J = 3.8 Hz), 136.1, 132.1, 126.8, 122.2, 120.5 (d, ^2J = 21.4 Hz), 119.6, 118.3, 114.7 (d, ^4J = 2.3 Hz), 113.0 (d, ^3J = 8.3 Hz), 111.0, 108.7, 56.5, 53.5, 53.1, 52.2, 24.3.

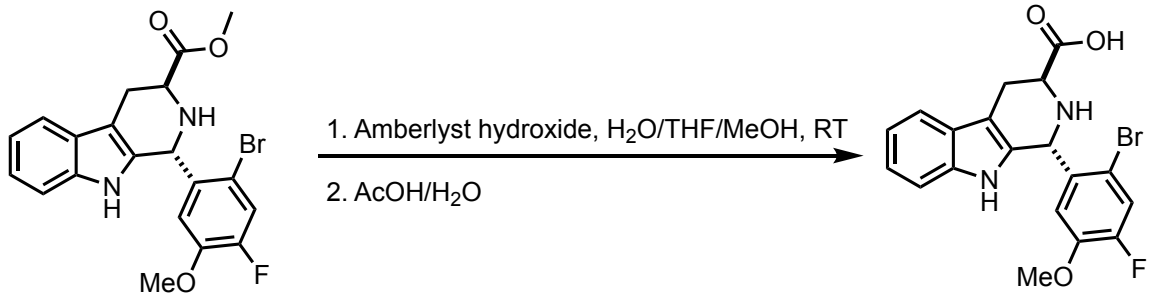


4aa

methyl (1*S*,3*S*)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4aa**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.57 – 7.52 (m, 1H), 7.36 (d, J = 10.4 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.19 – 7.08 (m, 3H), 5.74 (br s, 1H), 4.00 (dd, J = 11.0, 4.1 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.24 (ddd, J = 15.0, 4.1, 1.8 Hz, 1H), 3.03 (ddd, J = 15.0, 11.1, 2.5 Hz, 1H), 2.74 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.26 (d, J = 9.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 151.8 (d, ^1J = 252.2 Hz), 147.8 (d, ^3J = 10.4 Hz), 136.4, 136.1, 133.5, 126.9, 122.1, 120.0 (d, ^2J = 21.6 Hz), 119.7, 118.2, 114.5, 112.4 (d, ^3J = 8.2 Hz), 111.0, 108.9, 56.9, 56.7, 56.4, 52.4, 25.3.

b. (1*R*,3*S*)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1aa**)

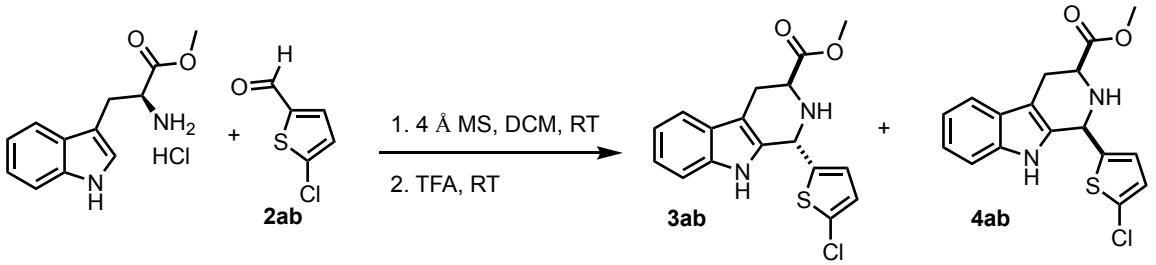


To a solution of **3aa** (87.0 mg, 0.2 mmol) in THF / MeOH / H_2O (2 mL / 2 mL / 2 mL) was added Amberlyst hydroxide resin (1.0 g, 4.2 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The residue was suspended in a minimum amount of MeOH, and the desired product was precipitated by the addition of Et_2O and hexane. The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1aa** (84 mg, 100% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.05 (td, *J* = 6.8, 1.2 Hz, 1H), 6.98 (td, *J* = 8.0, 1.2 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 5.70 (s, 1H), 3.77 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.55 (s, 3H), 3.12 (ddd, *J* = 15.2, 5.2, 0.8 Hz, 1H), 2.91 (ddd, *J* = 15.2, 7.2, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6 (s), 150.7 (d, J = 247 Hz), 146.2 (d, *J* = 10 Hz), 137.8 (d, *J* = 3 Hz), 136.3 (s), 132.7 (s), 126.3 (s), 121.1 (s), 120.1 (d, *J* = 21 Hz), 118.4 (s), 117.8 (s), 115.0 (s), 13.1 (d, *J* = 9 Hz), 111.2 (s), 107.9 (s), 56.1 (s), 53.3 (s), 51.8 (s), 24.4 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -134.0 (t, *J* = 10.0 Hz). HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}BrFN_2O_3$: 419.0401. Found: 419.0392.

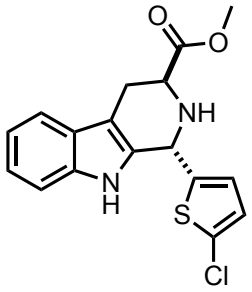
17. Synthesis of 1ab

a. methyl (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3ab**) and methyl (1*R*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4ab**)



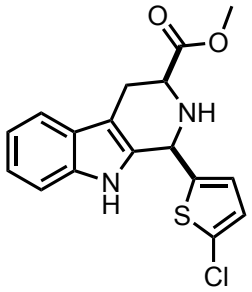
To a mixture of L-tryptophan methyl ester hydrochloride, (1.25 g, 5 mmol), 4 Å molecular sieves (2.5 g, powder form) in DCM (15 mL), 5-chlorothiophene-2-carbaldehyde (**2ac**) (0.53 mL, 5 mmol) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 6 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 0.6; hexane / DCM / EtOAc) to give **3ab** (1.04 g, 60% yield) as a yellow solid and **4ab** (0.134 g, 8% yield) as a

yellow/orange solid and a mixture of **3ab** and **4ab** (0.52 g, 30%) that was not further separated.



3ab

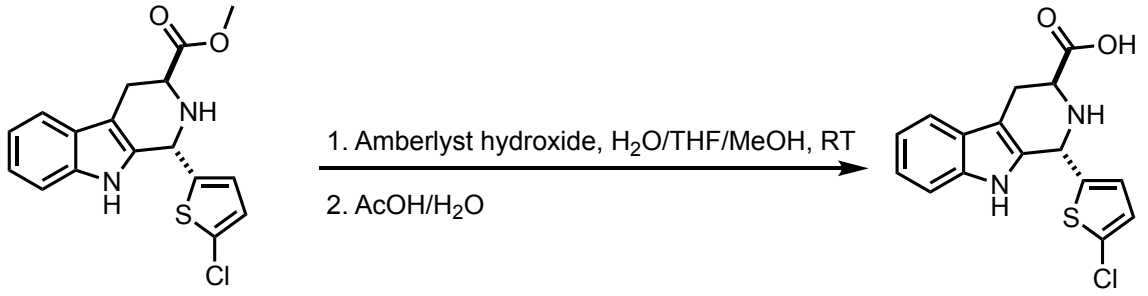
methyl (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3ab**): note that in this case the *trans*-isomer is (1*S*,3*S*)-configured, due to the higher Cahn-Ingold-Prelog priority of S in the thiophene than the N in the indole.
^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.9, 7.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.75 (dd, *J* = 15.4, 5.0 Hz, 2H), 5.55 (s, 1H), 4.01 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.78 (dd, *J* = 15.1, 9.1 Hz, 3H), 3.23 (dd, *J* = 15.4, 5.0 Hz, 1H), 2.99 (dd, *J* = 15.6, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CD_3OD/CDCl_3$) δ 173.7, 144.6, 136.3, 131.8, 129.7, 126.3, 125.4, 125.2, 121.7, 118.9, 117.8, 111.0, 109.9, 107.2, 51.9, 51.7, 50.6, 24.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{17}H_{16}ClN_2O_2S$: 347.0616. Found: 347.0606.



4ab

methyl (1*R*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4ab**): note that in this case the *cis*-isomer is (1*R*,3*S*)-configured, due to the higher Cahn-Ingold-Prelog priority of S in the thiophene than the N in the indole.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.20 – 7.10 (m, 2H), 6.95 (d, *J* = 3.7 Hz, 1H), 6.82 (d, *J* = 3.8 Hz, 1H), 5.46 (d, *J* = 2.2 Hz, 1H), 3.92 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.83 (s, 3H), 3.20 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 2.98 (ddd, *J* = 15.1, 11.2, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.7, 144.6, 136.3, 131.8, 129.7, 126.3, 125.5, 125.2, 121.7, 118.9, 117.8, 111.0, 109.9, 107.2, 51.9, 51.7, 50.6, 24.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{17}H_{16}ClN_2O_2S$: 345.0459. Found: 345.044.

b. (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**1ab**): note that in this case the *trans*-isomer is (1*S*,3*S*)-configured, due to the higher Cahn-Ingold-Prelog priority of S in the thiophene than the N in the indole.



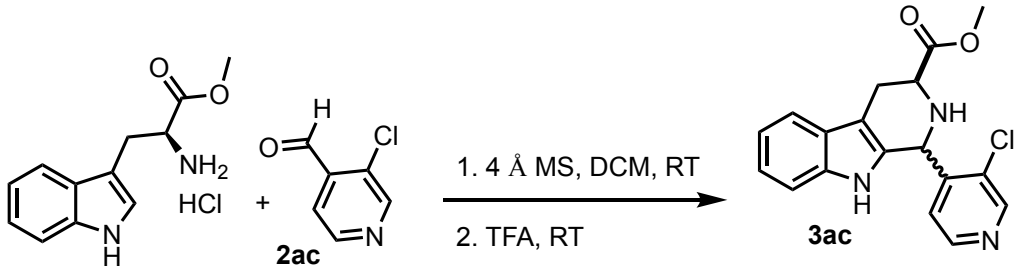
3ab **1ab**

To a solution of **3ab** (39.0 mg, 0.2 mmol) in THF / MeOH / H_2O (2 mL / 2 mL / 2 mL) was added Amberlyst hydroxide resin (0.90 g, 3.78 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 3 days, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.5 mL), and the product was precipitated by the addition of DCM (2 mL), Et_2O (5 mL) and hexane (10 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1ab** (58 mg, 88% yield) as a yellow powder.

^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.91 – 6.82 (m, 2H), 5.90 (s, 1H), 3.97 (dd, *J* = 8.0, 2.7 Hz, 1H), 3.31 (dd, *J* = 16.0, 2.7 Hz, 1H), 3.06 (dd, *J* = 15.5, 10.8 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 177.4, 141.5, 138.4, 132.5, 130.4, 129.6, 127.6, 127.4, 123.5, 120.4, 119.3, 112.3, 109.1, 54.8, 51.9, 24.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{16}H_{14}ClN_2O_2S$: 333.0459. Found: 333.0448.

18. Synthesis of 1ac

a. methyl (*S*)-1-(3-chloropyridin-4-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3ac**)

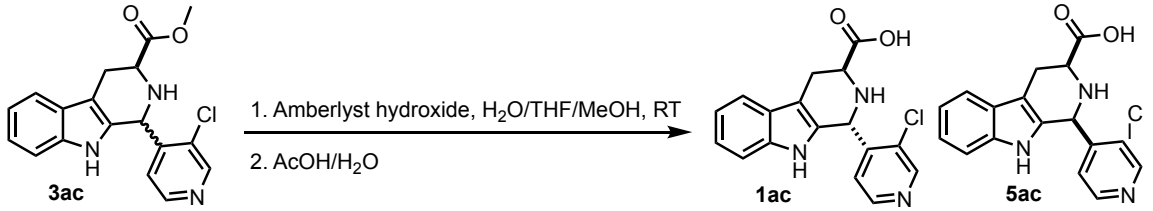


2ac **3ac**

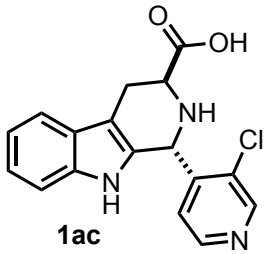
To a mixture of L-tryptophan methyl ester hydrochloride, (0.76 g, 3.0 mmol), 4 Å molecular sieves (1.5 g, powder form) and 3-chloroisonicotinaldehyde (**2ac**) (0.43 g, 3.0 mmol, 98%), DCM (9.0 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.46 mL, 6.0 mmol) was then added dropwise followed by addition of 5 mL of dry THF. The reaction mixture was stirred at room temperature for an additional 5 days. An aqueous solution of $NaHCO_3$ (0.72 g, 8.5 mmol, in 6 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified

by flash chromatography (1 : 1 : 2.5 hexane / DCM / EtOAc) to give **3ac** (0.93 g, 91% yield) as a bright yellow solid as a mixture of diastereomers (60:40 by ^{1}H NMR).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 – 8.43 (m, 2H), 8.28 (t, *J* = 5.2 Hz, 1H), 7.61 – 7.51 (m, 1H), 7.35 (d, *J* = 5.2 Hz, 0.6H), 7.31 – 7.25 (m, 1H), 7.23 – 7.09 (m, 2H), 6.94 (d, *J* = 5.0 Hz, 0.4H), 5.85 (br s, 0.4H), 5.80 (br s, 0.6H), 3.99 (dd, *J* = 11.0, 4.1 Hz, 0.6H), 3.86 (dd, *J* = 7.3, 5.1 Hz, 0.4H), 3.83 (s, 0.6H×3), 3.73 (s, 0.4H×3), 3.32 – 3.22 (m, 2H), 3.14 (dd, *J* = 7.4, 1.6 Hz, 0.6H), 3.11 (dd, *J* = 7.3, 1.6 Hz, 0.4H), 3.03 (ddd, *J* = 15.1, 11.0, 2.5 Hz, 1H), 2.73 (br s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 172.9, 149.6, 149.4, 148.2, 148.1, 147.9, 136.6, 136.6, 132.1, 131.5, 131.4, 130.5, 126.7, 126.7, 124.8, 124.4, 122.5, 122.4, 119.9, 119.8, 118.5, 118.4, 111.2, 109.6, 109.6, 56.5, 53.7, 52.5, 52.5, 52.4, 50.9, 25.4, 24.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{17}ClN_3O_2$: 342.1004. Found: 342.0990.

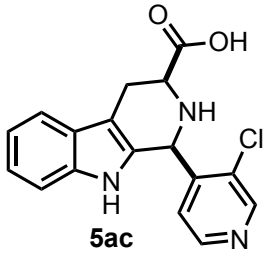
b. (1*R*,3*S*)-1-(3-chloropyridin-4-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1ac**) and (1*S*,3*S*)-1-(3-chloropyridin-4-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5ac**)



To a solution of **3ac** (170.0 mg, 0.5 mmol) in THF / MeOH / H_2O (5 mL / 5 mL / 5 mL) was added Amberlyst hydroxide resin (1.78 g, 7.5 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 5 mL). An aqueous solution of AcOH (50%, 8 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 8 mL). The combined filtrates were concentrated in vacuo to give 170 mg of crude product. 100 mg of the crude product was purified by preparative reverse phase HPLC. HPLC solvent A is 0.1% formic acid in filtered 17 MΩ H_2O and solvent B is 0.1% formic acid in HPLC grade acetonitrile. A non-linear gradient of 5-95%B over 30 minutes was used. Collected samples were frozen over dry ice and lyophilized to afford **1ac** (23 mg, 23% yield) as an off white-bright yellow solid and **5ac** (30 mg, 30%) as 85:15 (cis: trans) mixture of an off white-bright yellow solid.



(1*R*,3*S*)-1-(3-chloropyridin-4-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1ac**)
^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (s, 1H), 8.44 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.56 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.28 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.11 (dddd, *J* = 28.2, 8.1, 7.1, 1.2 Hz, 2H), 7.01 (d, *J* = 5.0 Hz, 1H), 6.23 (s, 1H), 3.92 (dd, *J* = 8.5, 5.2 Hz, 1H), 3.42 (ddd, *J* = 16.0, 5.3, 0.9 Hz, 1H), 3.19 (ddd, *J* = 16.0, 8.5, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.3, 150.8, 149.3, 145.6, 138.6, 133.9, 128.1, 127.4, 126.5, 123.7, 120.6, 119.3, 112.3, 110.2, 54.5, 52.1, 24.6.
HRMS (ESI) $[M+H]^+$ calculated for $C_{17}H_{15}ClN_3O_2$: 328.0847. Found: 328.0855.



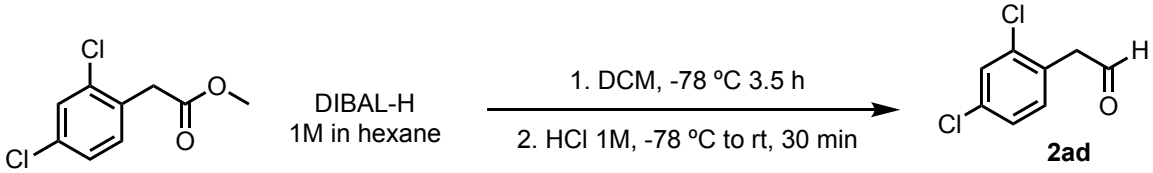
5ac

(1*S*,3*S*)-1-(3-chloropyridin-4-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5ac**) 85:15 (cis: trans)

^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (s, 0.85H), 8.74 (s, 0.15H), 8.52 (d, *J* = 5.1 Hz, 0.85H), 8.44 (d, *J* = 5.2 Hz, 0.15H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.15 – 7.02 (m, 2H), 6.21 (d, *J* = 6.8 Hz, 1H), 4.21 (dd, *J* = 11.7, 4.8 Hz, 0.85H), 3.91 (dd, *J* = 8.4, 5.2 Hz, 0.15H), 3.52 – 3.38 (m, 1H), 3.24 – 3.10 (m, 1H).^{13}C NMR (101 MHz, CD_3OD) δ 173.9, 151.0, 149.3, 144.9, 138.8, 134.0, 129.5, 127.5, 125.9, 123.5, 120.6, 119.2, 112.4, 110.2, 59.8, 55.2, 25.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{17}H_{15}ClN_3O_2$: 328.0847. Found: 328.0850.

19. Synthesis of 1ad

a. 2-(2,4-dichlorophenyl)acetaldehyde **(2ad)**

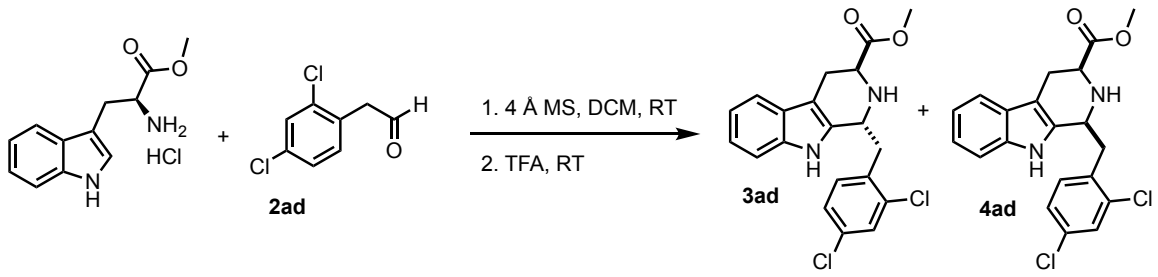


2ad

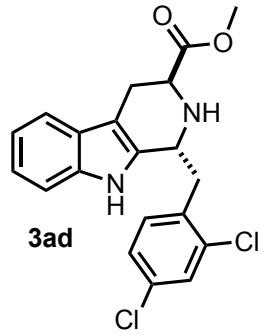
A solution of methyl 2-(2,4-dichlorophenyl)acetate (1.04 g, 4.50 mmol) in dry CH_2Cl_2 (25 mL) under nitrogen, was cooled to -78 °C and diisobutylaluminium hydride 1 M in hexanes (4.7 mL) was added drop wise. The reaction was stirred for 3.5 hours followed by slow addition of 1 M aqueous HCl solution (22 mL) at -78 °C. The mixture was warmed up to room temperature and stirred for 30 minutes. The resulting solution was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, concentrated in vacuo and purified by flash chromatography (4:1; hexane / EtOAc) to give **2ad** (0. 56 g, 66% yield, 95% pure) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.25 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 3.83 (d, *J* = 1.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 135.2, 134.2, 132.4, 129.5, 129.3, 127.5, 47.6.

b. methyl (1*R*,3*S*)-1-(2,4-dichlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3ad**) and methyl (*1S*,3*S*)-1-(2,4-dichlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4ad**)

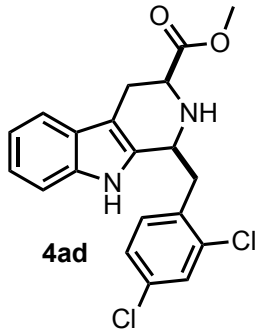


To a mixture of L-tryptophan methyl ester hydrochloride, (0.937 g, 3.45 mmol), 4 Å molecular sieves (1.5 g, powder form) in DCM (12 mL), 2-(2,4-dichlorophenyl)acetaldehyde (**2ad**) (0.6 m, 3 mmol) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.46 mL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 7 days. An aqueous solution of $NaHCO_3$ (0.84 g, 10.0 mmol, in 7 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (30 mL). After vigorous stirring for 15 min, the phases were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (5 : 5 : 0.5; hexane / DCM / EtOAc) to give **3ad** (0.65 g, 56% yield) as a yellow solid and **4ad** (0.18 g, 15% yield) as a dark yellow.



methyl (1*R*,3*S*)-1-(2,4-dichlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3ad**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.52 – 7.48 (m, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.25 – 7.09 (m, 4H), 4.54 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.04 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.76 (s, 3H), 3.25 (dd, *J* = 13.7, 5.1 Hz, 1H), 3.15 (ddd, *J* = 15.3, 5.0, 1.0 Hz, 1H), 3.04 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.95 (ddd, *J* = 15.3, 8.5, 1.4 Hz, 1H), 1.75 (s, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 136.1, 135.1, 134.7, 134.5, 133.6, 132.8, 129.7, 127.4, 127.0, 122.2, 119.8, 118.3, 110.9, 107.92, 52.4, 52.4, 50.5, 39.4, 25.4. HRMS (ESI) $[M+Na]^+$ calculated for $C_{20}H_{18}Cl_2N_2NaO_2$: 412.0669. Found: 412.0654.

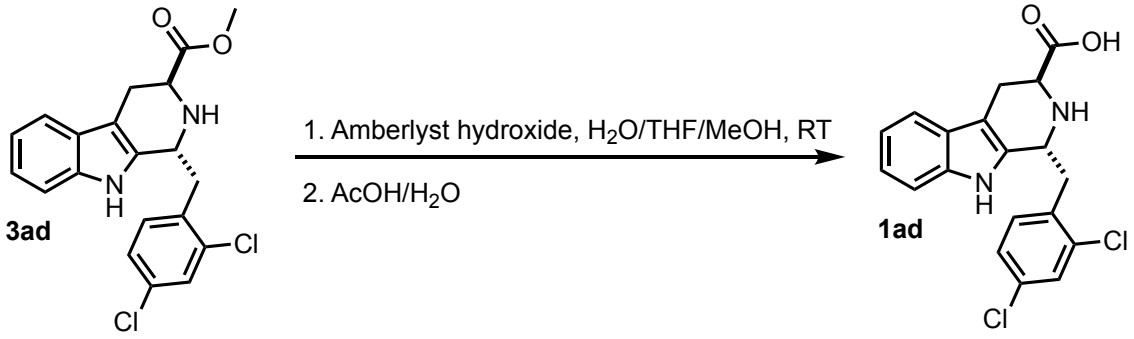


4ad

methyl (1*S*,*3S*)-1-(2,4-dichlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4ad**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.21 – 7.08 (m, 2H), 4.54 (ddt, *J* = 8.8, 4.7, 2.2 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.42 (dd, *J* = 13.7, 4.8 Hz, 1H), 3.15 (ddd, *J* = 15.1, 4.1, 1.9 Hz, 1H), 2.97 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.86 (ddd, *J* = 15.1, 11.1, 2.5 Hz, 1H), 2.01 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 136.1, 135.1, 134.5, 134.0, 133.8, 132.7, 129.9, 127.6, 127.1, 122.2, 119. 9, 118.3, 111.0, 108.9, 56.4, 52.4, 52.1, 39.3, 25.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{19}Cl_2N_2O_2$: 389.0818. Found: 389.0802.

c. (1*R*,3*S*)-1-(2,4-dichlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1ad**)



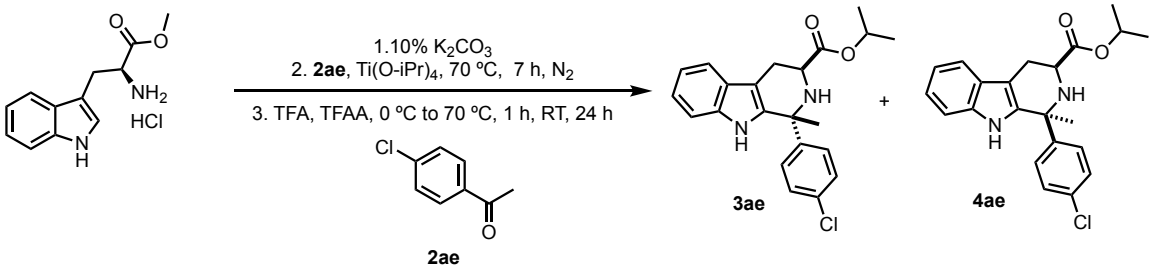
3ad **1ad**

To a solution of **3ad** (97.0 mg, 0.25 mmol) in THF / MeOH / H_2O (2.5 mL / 2.5 mL / 2.5 mL) was added Amberlyst hydroxide resin (0.90 g, 3.75 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.35 mL), and the product was precipitated by the addition of Et_2O (3.5 mL) and hexane (10.5 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1ad** (58 mg, 62% yield) as a yellow solid.

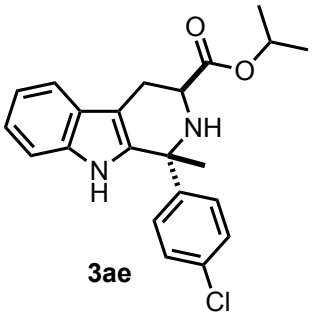
^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (d, *J* = 2.1 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.21 (m, 3H), 7.15 – 7.09 (m, 1H), 7.07 – 7.01 (m, 1H), 5.15 (t, *J* = 7.2 Hz, 1H), 4.24 (dd, *J* = 8.5, 5.9 Hz, 1H), 3.67 – 3.52 (m, 1H), 3.51 – 3.37 (m, 2H), 3.18 (ddd, *J* = 16.5, 8.6, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.4, 138.5, 136.6, 135.5, 134.3, 133.1, 130.8, 129.3, 128.8, 127.4, 123.5, 120.5, 119.2, 112.3, 107.7, 55.2, 52.6, 37.1, 23.8. HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{16}Cl_2N_2NaO_2$: 397.0481. Found: 397.0466.

20. Synthesis of 1ae

a. isopropyl (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3ae**) and isopropyl (1*S*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4ae**)

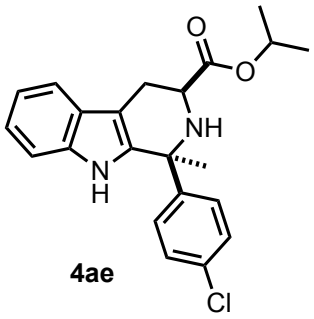


L-tryptophan methyl ester hydrochloride (1.5 g, 6.0 mmol) was basified with (70 mL) of 10% aqueous K_2CO_3 solution and stirred for 30 min. The solution was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was mixed with 1-(4-chlorophenyl)ethan-1-one (0.58 mL, 5.0 mmol), Ti(O-^{i}Pr)$_4$ (2.3 mL ,7.5 mmol), and was heated at 70 °C for 7 hours under nitrogen. To this mixture was then added TFA (3.8 mL, 50.0 mmol) and TFAA (0.7 mL, 5.0 mmol) at 0 °C followed by heating at 70 °C for 1 hour. Subsequently, the reaction was cooled to room temperature and stirred for 24 hours. The reaction mixture was diluted with MeOH (75 ml), passed through a short celite column and washed thoroughly with MeOH. The eluent was concentrated in vacuo (ca. 40 ml) and the residue was neutralized with 10% NaOH solution and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (2.5 : 2.5 : 0.5; hexane / DCM / EtOAc) to give **2ae** (430 mg, 62%), **3ae** (300 mg, 16% yield) as a crystalline white solid and **4ae** (140 mg, 7%) as a bright yellow solid.



isopropyl (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3ae**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.56 (ddt, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.38 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.28 – 7.11 (m, 6H), 5.07 (p, *J* = 6.3 Hz, 1H), 3.46 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.09 (dd, *J* = 15.4, 4.8 Hz, 1H), 2.81 (dd, *J* = 15.4, 11.3 Hz, 1H), 2.27 (br s, 1H), 1.83 (s, 3H), 1.27 (dd, *J* = 12.4, 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 144.6, 137.0, 136.1, 133.2, 128.4, 128.2, 127.1, 122.4, 119.9, 118.6, 111.1, 109.0, 68.7, 56.7, 52.4, 29.4, 26.1, 22.0, 21.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{22}H_{24}ClN_2O_2$: 383.1521. Found: 383.1491.

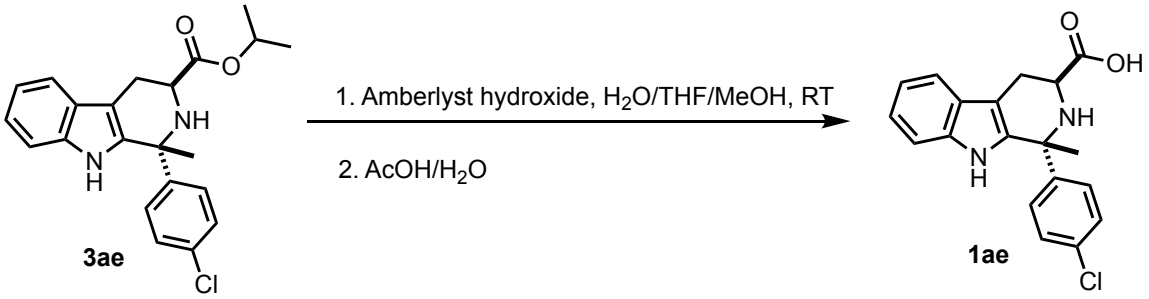


4ae

isopropyl (1*S*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4ae**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 1H), 7.46 – 7.36 (m, 3H), 7.32 – 7.21 (m, 3H), 7.20 – 7.09 (m, 2H), 5.12 (p, *J* = 6.3 Hz, 1H), 4.00 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.20 (dd, *J* = 15.1, 4.2 Hz, 1H), 2.87 (dd, *J* = 15.1, 11.1 Hz, 1H), 2.25 – 2.00 (br s, 1H), 1.91 (s, 3H), 1.32 (t, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 144.1, 138.6, 136.2, 133.8, 129.9, 129.0, 128.8, 128.7, 127.0, 122.3, 119.8, 118.5, 111.1, 108.4, 68.9, 56.9, 53.4, 26.4, 25.8, 22.0, 22.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{22}H_{24}ClN_2O_2$: 383.1521. Found: 383.1497.

b. (1*R*,3*S*)-1-(4-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1ae**)



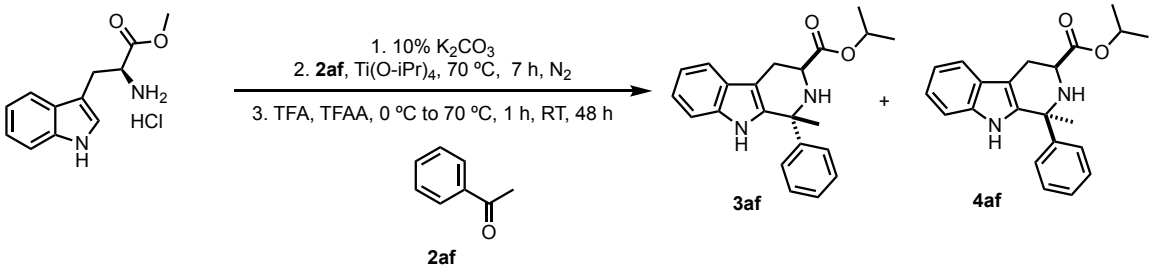
3ae **1ae**

To a solution of **3ae** (114.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3.0 mL / 3.0 mL / 3.0 mL) was added Amberlyst hydroxide resin (1.1 g, 4.5 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.4 mL), and the product was precipitated by the addition of Et_2O (4.0 mL) and hexane (12.0 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1ae** (60 mg, 60% yield) as a pale orange solid.

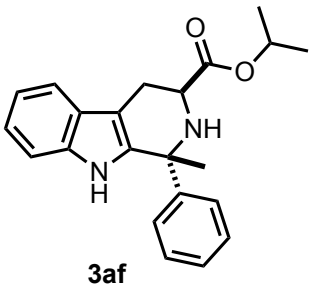
^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.39 (ddt, *J* = 16.8, 8.2, 0.9 Hz, 3H), 7.31 – 7.24 (m, 2H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.64 – 3.55 (m, 1H), 3.44 (dd, *J* = 16.5, 5.3 Hz, 1H), 3.12 (dd, *J* = 16.5, 12.0 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.4, 139.1, 138.7, 136.6, 132.6, 130.5, 130.2, 127.2, 123.9, 120.8, 119.6, 112.5, 109.2, 62.3, 55.8, 25.3, 24.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2O_2$: 341.1051. Found: 341.1033.

21. Synthesis of 1af

a. isopropyl (1*R*,3*S*)-1-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3af**) and isopropyl (1*S*,3*S*)-1-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4af**)



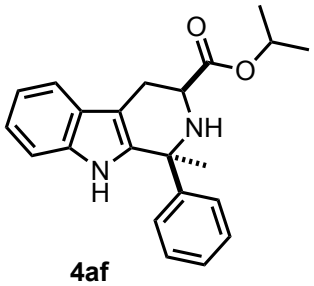
L-tryptophan methyl ester hydrochloride (1.1 g, 4.0 mmol) was basified with (50 mL) of 10% aqueous K_2CO_3 solution and stirred for 30 min. The solution was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was mixed with acetophenone (0.24 g, 2.0 mmol), Ti(O-^{i}Pr)$_4$ (1.0 mL, 3.0 mmol), and was heated at 70 °C for 7 hours under nitrogen. To this mixture was then added TFA (1.53 mL, 20.0 mmol) and TFAA (0.28 mL, 2.0 mmol) at 0 °C followed by heating at 70 °C for 1 hour. Subsequently, the reaction was cooled to room temperature and stirred for 48 hours. The reaction mixture was diluted with MeOH (50 ml), passed through a short celite column and washed thoroughly with MeOH. The eluent was concentrated in vacuo (ca. 20 ml) and the residue was neutralized with 10% NaOH solution and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (3 : 1.5 : 0.3; hexane / DCM / THF) to give (**3af**) (400 mg, 57% yield) as a white solid and (**4af**) (120 mg, 17%) a white solid.



3af

isopropyl (1*R*,3*S*)-1-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3af**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.59 – 7.54 (m, 1H), 7.39 – 7.35 (m, 1H), 7.28 – 7.13 (m, 8H), 5.07 (p, *J* = 6.3 Hz, 1H), 3.50 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.10 (dd, *J* = 15.4, 4.8 Hz, 1H), 2.82 (dd, *J* = 15.4, 11.3 Hz, 1H), 1.87 (s, 3H), 1.26 (dd, *J* = 14.2, 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 146.0, 137.5, 136.1, 128.8, 128.4, 127.4, 127.2, 126.6, 122.2, 119.8, 118.6, 111.1, 109.0, 68.6, 57.1, 52.4, 29.5, 26.1, 22.0, 21.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{22}H_{25}N_2O_2$: 349.1911. Found: 349.1923.

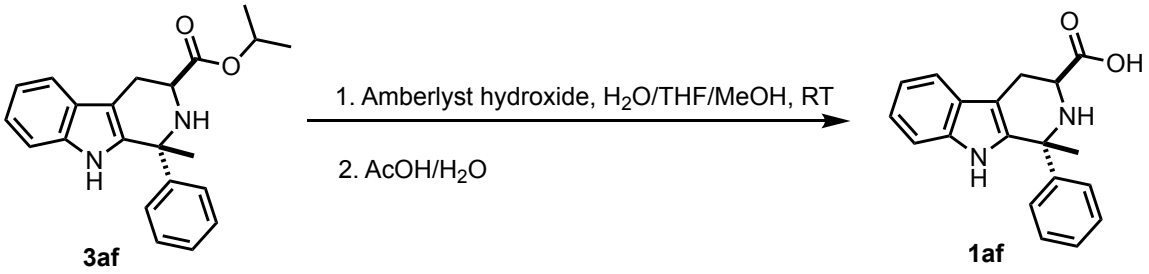


4af

isopropyl (1*S*,3*S*)-1-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4af**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 1H), 7.48 – 7.43 (m, 2H), 7.42 (s, 1H), 7.36 – 7.21 (m, 5H), 7.18 – 7.09 (m, 2H), 5.12 (p, *J* = 6.3 Hz, 1H), 4.02 (dd, *J* = 11.0, 4.2 Hz, 1H), 3.20 (dd, *J* = 15.1, 4.2 Hz, 1H), 2.87 (dd, *J* = 15.1, 11.1 Hz, 1H), 1.93 (s, 3H), 1.31 (t, *J* = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 173.1, 145.5, 139.3, 136.2, 128.8, 127.9, 127.2, 127.1, 122.1, 119.7, 118.5, 111.0, 108.3, 68.8, 57.2, 53.5, 26.5, 25.9, 22.0, 22.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{22}H_{25}N_2O_2$: 349.1911. Found: 349.1924.

b. (1*R*,3*S*)-1-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**1af**)



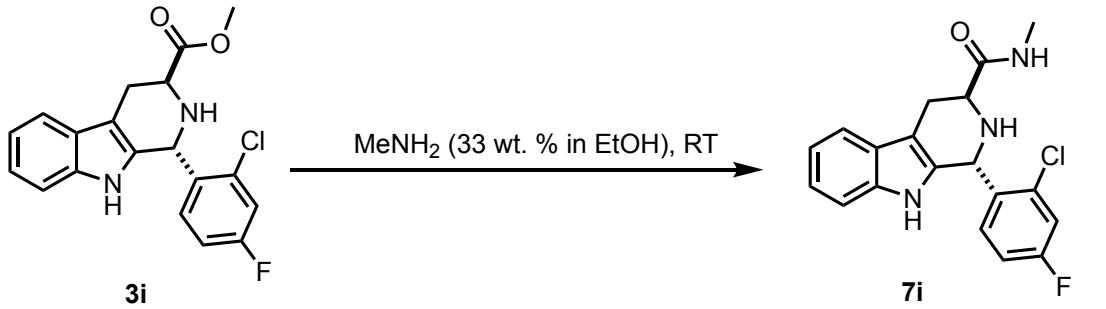
3af **1af**

To a solution of **3af** (114.0 mg, 0.33 mmol) in THF / MeOH / H_2O (3.0 mL / 3.0 mL / 3.0 mL) was added Amberlyst hydroxide resin (1.2 g, 5.0 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 24 hours, after which the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%, 4 mL) was added to release the product from the resin, and the solution containing the product was collected by filtration. The resin beads were rinsed another 4 times with aq. AcOH (50%, 4 mL). The combined filtrates were concentrated in vacuo. To the residue was added MeOH (0.4 mL), and the product was precipitated by the addition of Et_2O (4.0 mL) and hexane (12.0 mL). The suspension was stirred for 30 min and filtered. The solid was washed with hexane to afford **1af** (81 mg, 80% yield) as an off-white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.59 – 7.05 (m, 9H), 3.61 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.44 (dd, *J* = 16.4, 5.3 Hz, 1H), 3.13 (dd, *J* = 16.4, 12.0 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.7, 138.4, 136.7, 131.0, 128.6, 128.2, 126.7, 125.3, 121.9, 118.9, 117.7, 110.7, 107.1, 61.0, 53.9, 23.8, 22.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{19}N_2O_2$: 307.144. Found: 307.1447.

22. Synthesis of 7i

(1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (**7i**)

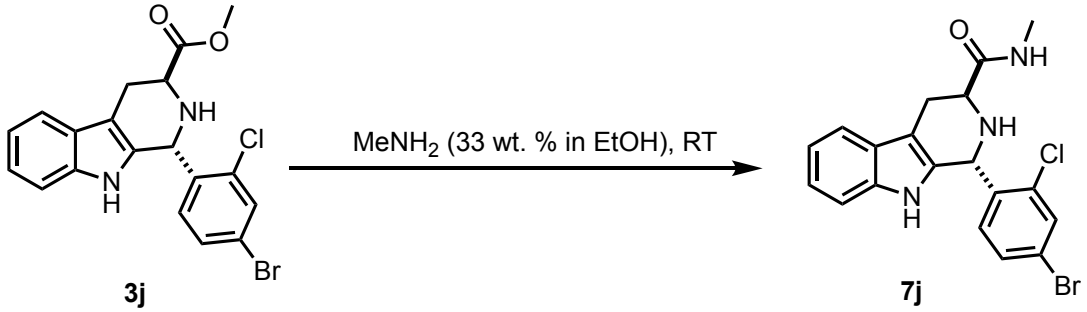


3i **7i**

To a round bottom flask was added **3i** (72.0 mg, 0.2 mmol) and methylamine solution (4.2 mL, 33 wt. % in absolute ethanol, 33.4 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 2 days. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 0.1 DCM / MeOH) to give **7i** (65 mg, 90% yield).
^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, *J* = 7.9 Hz, 1H), 7.31 (dt, *J* = 8.5, 1.9 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 7.5, 7.1 Hz, 1H), 6.73 (t, *J* = 6.6, 5.6 Hz, 1H), 5.70 (s, 1H), 3.52 (dd, *J* = 10.0, 3.9 Hz, 1H), 3.17 (d, *J* = 15.5 Hz, 1H), 2.82 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.73 (s, 3H).^{19}F NMR (376 MHz, CD_3OD) δ -114.34 (q, *J* = 8.0 Hz).^{13}C NMR (101 MHz, CD_3OD) δ 175.8, 163.4 (d, ^{1}J = 248.9 Hz), 138.2, 136.4 (d, ^{4}J = 3.1 Hz), 136.2 (d, ^{3}J = 10.4 Hz), 133.0, 132.7 (d, ^{3}J = 8.9 Hz), 127.9, 122.8, 119.9, 118.8, 118.2 (d, ^{2}J = 25.2 Hz), 114.5 (d, ^{2}J = 21.1 Hz), 112.1, 110.5, 53.1, 52.7, 26.3, 26.2. HRMS (MALDI) $[M+H]^+$ calculated for $C_{19}H_{18}ClFN_3O$: 358.1117. Found: 358.1109.

23. Synthesis of 7j

(1*R*,3*S*)-1-(4-bromo-2-chlorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**7j**)

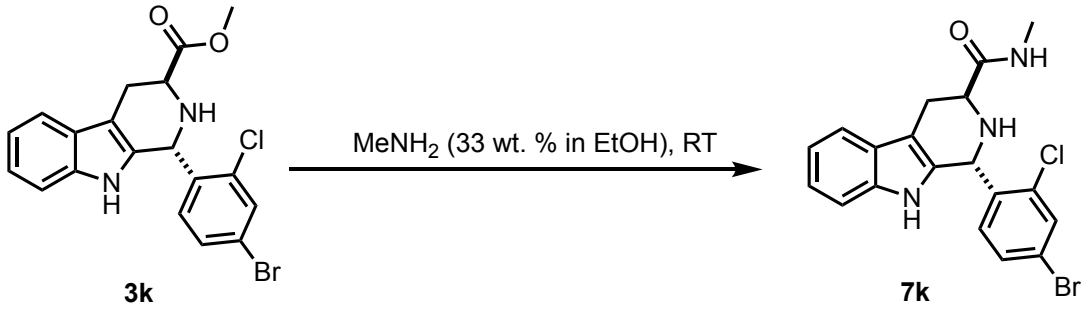


3j **7j**

To a round bottom flask was added **3j** (84.0 mg, 0.2 mmol) and methylamine solution (1.5 mL, 33 wt. % in absolute ethanol, 12.0 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 24 hours. The reaction was concentrated under vacuo and then purified by recrystallization from DCM/Et_2O/Hex to give **7i** (80 mg, 95% yield) as a white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.72 (q, *J* = 4.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 8.4, 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 7.6, 0.8 Hz, 1H), 6.99 (td, *J* = 7.6, 0.8 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.55 (d, *J* = 4.8 Hz, 1H), 3.35 (m, 1H), 3.10 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.99 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.68 (dd, *J* = 15.2, 9.6 Hz, 1H), 2.59 (d, *J* = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 139.2, 136.1, 134.7, 132.6, 131.7, 131.6, 129.7, 126.5, 121.1, 120.1, 118.4, 117.7, 111.1, 109.2, 51.4, 50.8, 25.4, 25.2. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}BrClN_3O$: 418.0316. Found: 418.0239.

24. Synthesis of 7k

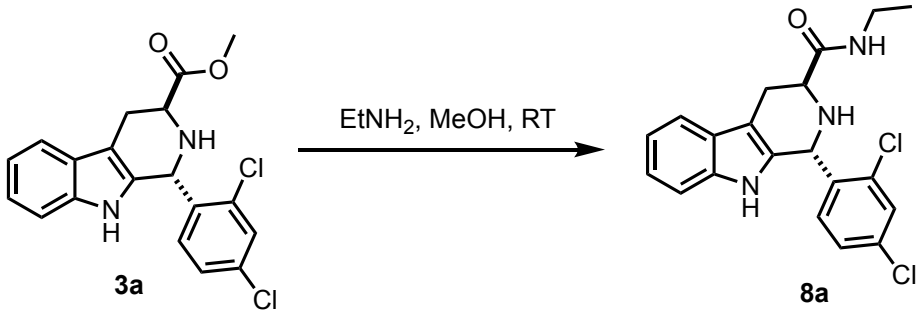
(1*R*,3*S*)-1-(2-bromo-4-chlorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**7k**)



To a round bottom flask was added **3k** (84.0 mg, 0.2 mmol) and methylamine solution (1.5 mL, 33 wt. % in absolute ethanol, 12.0 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 24 hours. The reaction was concentrated under vacuo and then purified by recrystallization from DCM/Et_2O/Hex to give **7k** (79 mg, 94% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.72 (q, *J* = 4.8 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (td, *J* = 8.0, 1.2 Hz, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 4.4 Hz, 1H), 3.35 (m, 1H), 3.31 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.99 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.69 (ddd, *J* = 15.2, 9.2, 0.8 Hz, 1H), 2.60 (d, *J* = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 140.3, 136.1, 132.7, 132.6, 132.1, 131.2, 127.2, 126.5, 124.9, 121.1, 118.5, 117.7, 111.1, 109.1, 53.1, 51.3, 25.4, 25.1. HRMS (ESI) [M+H]+ calculated for $C_{19}H_{18}BrClN_3O$: 418.0316. Found: 418.0256.

25. Synthesis of 8a

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-*N*-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide **(8a)**

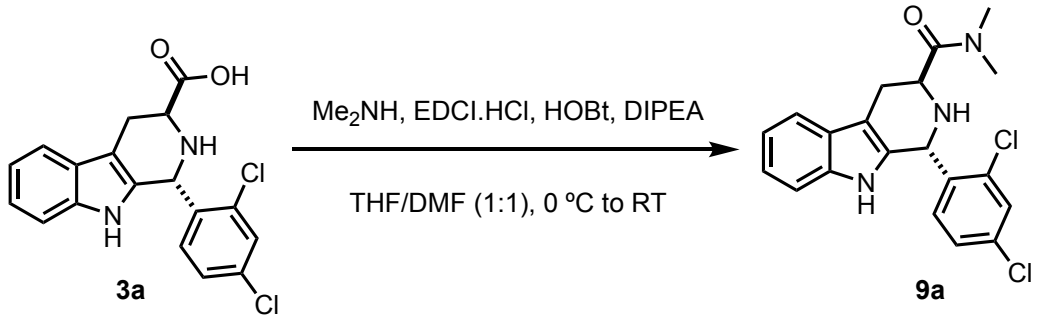


To a one-dram vial was added **3a** (62.0 mg, 0.17 mmol) and ethylamine (2.0 mL, 2 M in methanol, 4.0 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 30 hours. The reaction was concentrated under vacuo and then purified by flash chromatography (10 : 1; DCM / EtOAc) to give **9a** (58.0 mg, 90% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.79 (t, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.56 (d, *J* = 4.8 Hz, 1H), 3.37 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.10 (m, 3H), 2.99 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.70 (dd, *J* = 15.2, 9.2 Hz, 1H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 138.9, 136.1, 134.4, 132.6, 132.5, 131.2, 129.0, 126.8, 126.5, 121.1, 118.5, 117.7, 111.1, 109.1, 51.4, 50.6, 33.3, 25.2, 14.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}Cl_2N_3O$: 388.0978. Found: 388.0830.

26. Synthesis of 9a

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-*N*,*N*-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide **(9a)**

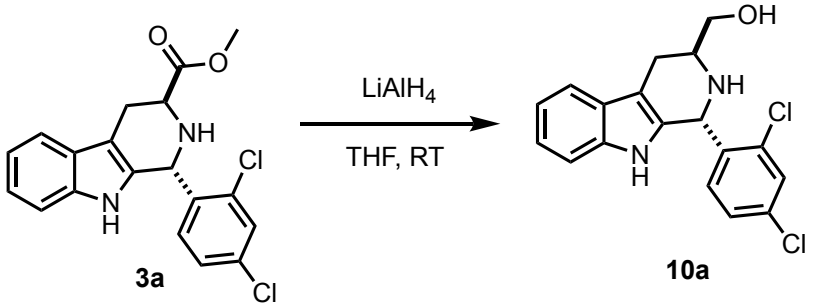


To a solution of **3a** (100 mg, 0.28 mmol) in THF/DMF (1 : 1, 5 mL) was added EDCI hydrochloride (69 mg, 0.36 mmol) at 0°C, the resulting mixture was stirred for 15 minutes at the same temperature. A solution of dimethylamine (277μL, 2 M in methanol, 0.55 mmol) and DIPEA (96 μL, 0.55 mmol) in THF (1 mL) was added dropwise at 0°C. After being stirred for 2 hours at 0°C, the reaction mixture was warmed slowly to room temperature, and was stirred for additional 21 hours. The solvents was removed under vacuum, the residue was purified by flash chromatography (10 : 1; DCM / EtOAc , then 100 : 7 : 1; DCM / EtOAc / MeOH =) to afford **9a** (66 mg, 62% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.28 (dd, J = 8.4, 2.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.06 (td, J = 7.2, 1.2 Hz, 1H), 6.99 (td, J = 8.0, 1.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.53 (d, J = 4.4 Hz, 1H), 3.66 (td, J = 11.2, 5.2 Hz, 1H), 3.11 (dd, *J* = 11.2, 4.0 Hz, 1H), 2.81 (m, 4H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 138.7, 136.1, 134.7, 132.5, 132.4, 131.3, 129.0, 126.7, 126.6, 121.1, 118.4, 117.8, 111.1, 109.5, 50.8, 47.8, 35.8, 35.1, 24.1. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}Cl_2N_3O$: 388.0978. Found: 388.0847.

27. Synthesis of 10a

((1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)methanol **(10a)**



To a suspension of $LiAlH_4$ (5.7 mg, 0.15 mmol) in dry THF (1 mL) was added a solution of **3a** (25 mg, 0.066 mmol) in dry THF (1 mL) at room temperature. The resulting reaction mixture was stirred for 80 minutes at room temperature. The reaction was quenched with H_2O/THF (0.2 mL H_2O and 1 mL THF). The mixture was condensed to dry and purified by flash chromatography (10 : 1; DCM / MeOH) to afford **10a** (17 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15 (m, 2H), 7.05 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.59 (s, 1H), 3.71 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.52 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.07 (hep, *J* = 2.0 Hz, 1H), 2.82 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.52 (dd, *J* = 15.2, 10.4 Hz, 1H), 2.43 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.3, 134.6, 134.3, 131.7, 130.9, 129.8,

126.9, 126.7, 122.3, 119.7, 118.3, 111.0, 110.8, 65.4, 51.5, 50.0, 24.2. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{17}Cl_2N_2O$: 347.0713. Found: 347.0540.

B. Purification of *Pf*IspD and kinetic parameters determination.

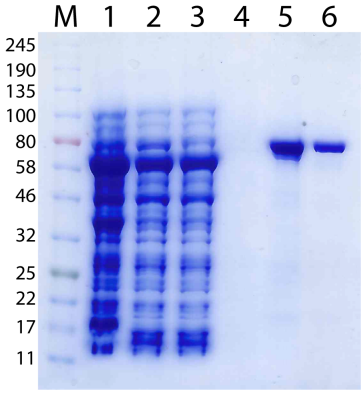


Figure S1. *Pf*IspD was purified from ArcticExpress (DE3) RIL *E. coli* using Ni-NTA affinity and size-exclusion chromatography. Purifications yield ~2 mg/L of culture. SDS-PAGE analysis was performed on a 4-20% gradient gel (CBS Scientific). Lanes on the gel: M: Marker (Color Prestained Protein Standard, Broad Range (11–245 kDa)), 1: Total cell lysate, 2: Soluble lysate, 3: Ni-NTA column flowthrough, 4: 40 mM imidazole wash of Ni-NTA column, 5: Ni-NTA elution in 250 mM imidazole, 6: size-exclusion purified *Pf*IspD.

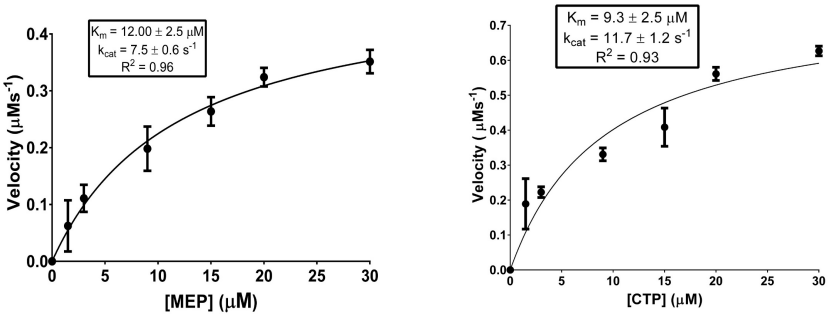


Figure S2. Kinetic parameters determined using PhosphoWorks™ Fluorimetric Pyrophosphate Assay Kit (AAT Bioquest®, Inc.). The data represents the mean and S.E.M from at least three independent experimental replicates.

C. References:

(1) Yao, Z.-K.; Krai, P. M.; Merino, E. F.; Simpson, M. E.; Slebodnick, C.; Cassera, M. B.; Carlier, P. R. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1515-1519.

(2) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976-6984.