Enantiospecific Synthesis of β-Substituted Tryptamines

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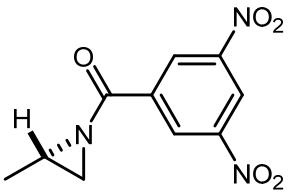
Supplemental Material

General. ^{1}H NMR spectra were recorded on a Bruker Avance (300 MHz), Bruker DRX (400 MHz), or Bruker Avance (600 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (Chloroform-*d*: 7.26 ppm or Acetone-d_6: 2.05 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker Avance 300 (75 MHz) or Bruker Avance 600 (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (Chloroform-*d*: 77.2 ppm or Acetone-d_6: 206.3 ppm).

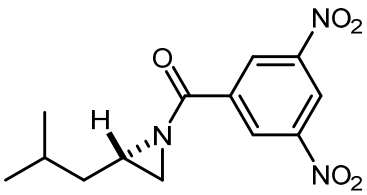
Liquid chromatography was performed using forced flow (flash chromatography) on SiliaFlash ® 60 silica gel (SiO_2, 40 to 63μm) purchased from Silacycle. Thin layer chromatography (TLC) was performed on EMD Chemicals 0.25 mm silica gel 60 plates. Visualization was achieved UV light (254 nm) or basic potassium permanganate in water followed by heating. Analytical high performance liquid chromatography (HPLC) was performed on an HP instrument equipped with an autosampler and a UV detector. A Daicel CHIRALPAK column using a mixed solvent (hexane/isopropanol) at a flow rate of 1 mL/minute with UV detection at 250 nm (unless otherwise noted) for data pertaining to calculated enantiomeric excess calculations.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of argon. All solvents were EMD Chemicals anhydrous solvents sold by VWR International. All chemicals used as purchased.



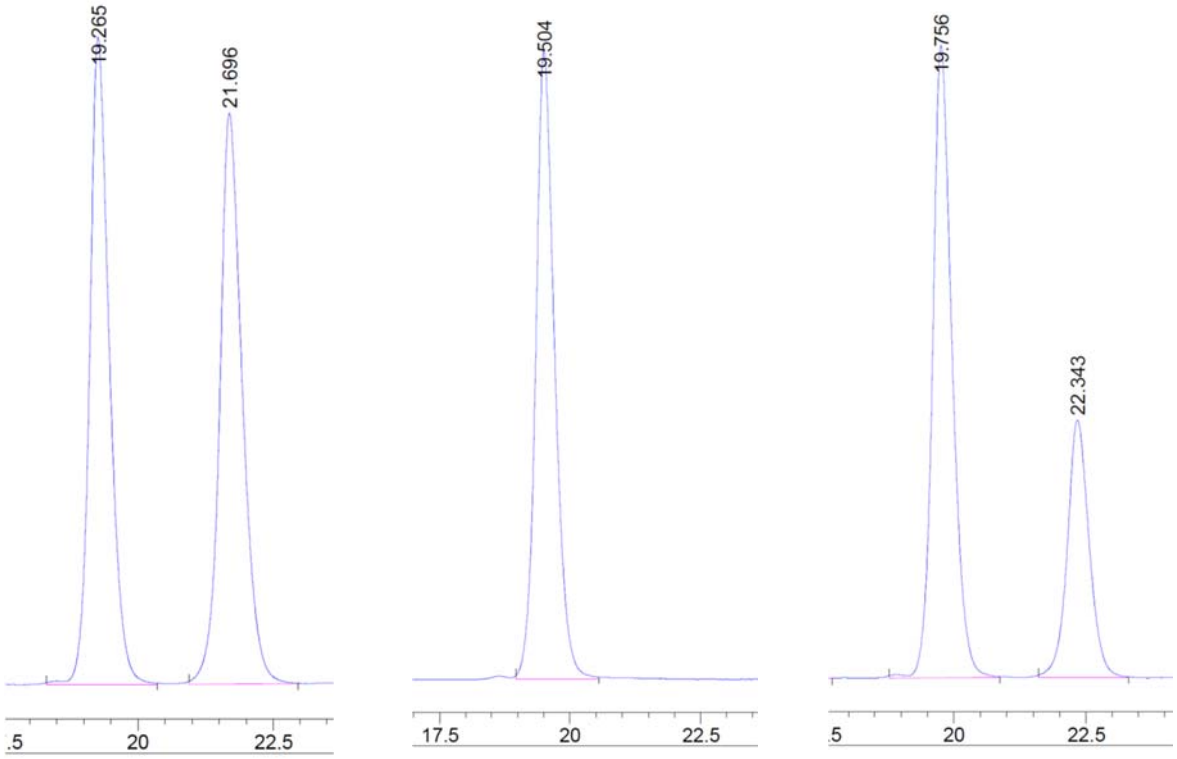
(*S*)-(3,5-dinitrophenyl)(2-methylaziridin-1-yl)methanone (*SI-1*)

Synthesized from (*S*)-alaninol as described in a previous publication.[1]

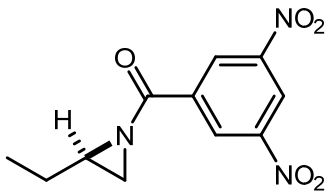


(*S*)-(3,5-dinitrophenyl)(2-isobutylaziridin-1-yl)methanone (*SI-2*) Synthesized from (*S*)-leucinol as described in a previous publication.[1] All spectral data were consistent with literature values and the enantiopurity was verified by HPLC analysis.

HPLC conditions: ChiralPakIB, 90:10 hexanes/isopropanol, 280 nm.

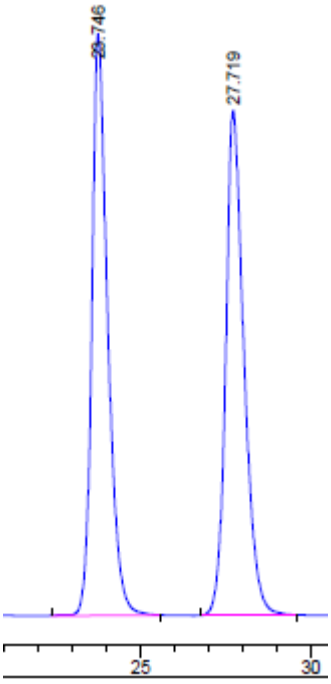


Racemic Enantiopure Spike

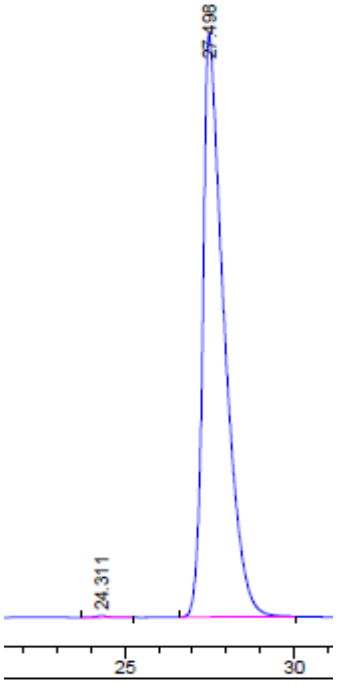


(*R*)-(3,5-dinitrophenyl)(2-ethylaziridin-1-yl)methanone (10) (*R*)-(–)-2-Amino-1-butanol (1.9 mL, 20 mmol, 1 eq) and triphenylphosphine (4.1 g, 21 mmol, 1.05 eq) were added to a flame-dried round-bottom flask charged with a Teflon®-coated stir bar. Dry acetonitrile (66 mL, 0.3 M) was added, followed by dropwise addition of diisopropylazodicarboxylate (2.1 mL 10.5 mmol, 1.05 eq). The reaction was stirred for 20 hours under argon at 80 °C. After cooling the solution to 0 °C in an ice bath, 2,5-dioxopyrrolidin-1-yl 3,5-dinitrobenzoate[1] (7.4 g, 24 mmol, 1.2 eq) was added. The reaction stirred for 1 hour and then an additional 3 hours at room temperature. The mixture was concentrated by rotary evaporation and the concentrated crude mixture was purified by silica gel chromatography (4:1 hexanes/ethyl acetate) to afford a white solid (2.78 g, 44% yield). The racemic aziridine analogue was synthesized in the same manner using racemic 2-amino-butanol as starting material. HRMS calculated for $C_{11}H_{11}N_3NaO_5^+$: 288.0591 ($M + Na^+$), found 288.0595 ($M + Na^+$). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.22 (t, *J* = 2.1 Hz, 1H), 9.16 (d, *J* = 2.1 Hz, 2H), 2.73 – 2.67 (m, 1H), 2.63 (d, *J* = 6.0 Hz, 1H), 2.38 (d, *J* = 3.8 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.68 – 1.57 (m, 1H), 1.08 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 148.7, 136.9, 128.7, 121.9, 77.3, 77.2, 77.0, 76.7, 41.0, 31.7, 25.0, 10.3. IR: (Diamond ATR) 3095, 2932, 1682, 1534 cm^{-1}.

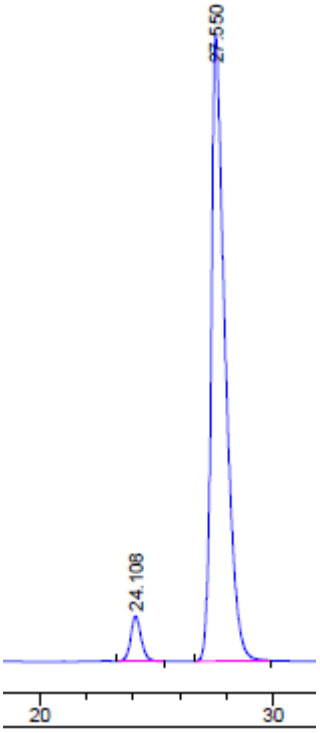
HPLC conditions: ChiralPak IB, 90:10 hexanes/isopropanol



Racemic

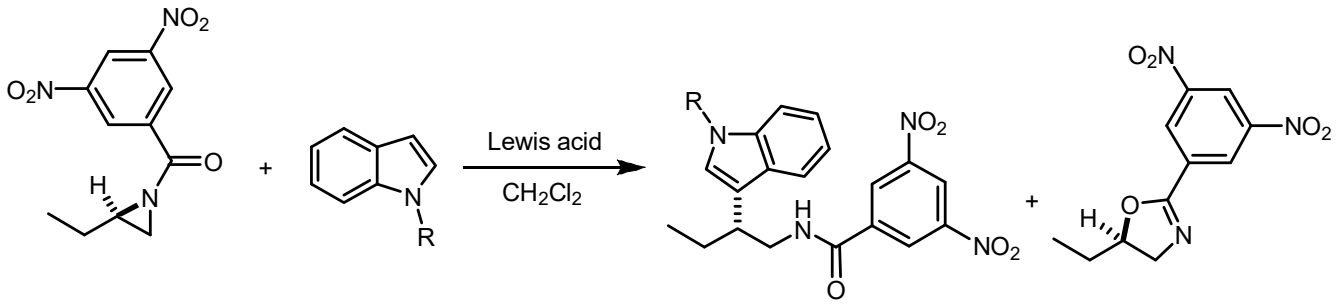


Enantiopure



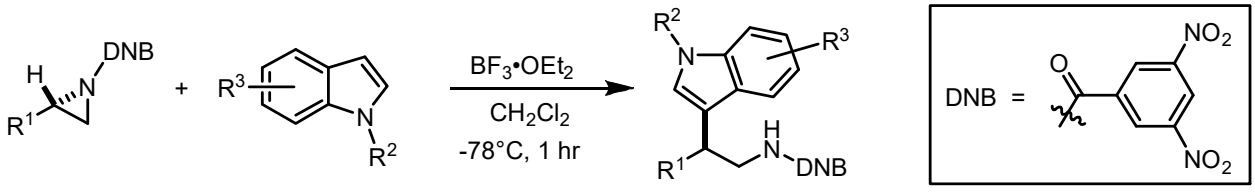
Spike

Representative procedure for Lewis acid screen (Procedure A, Table 1)



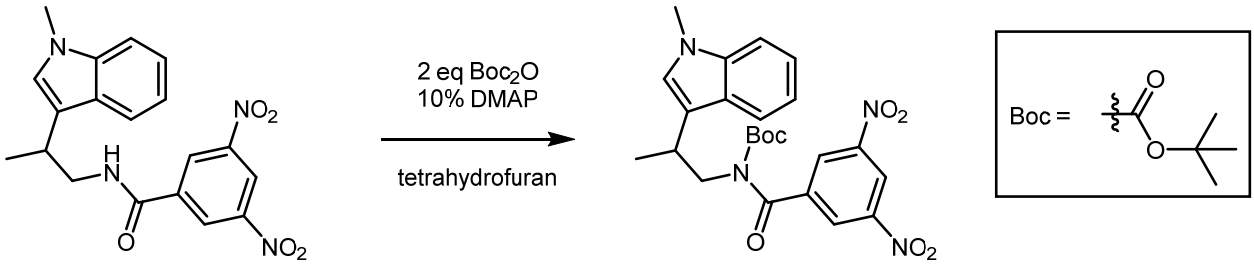
An oven dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with aziridine **10** (0.1 mmol) and the corresponding indole (0.3 mmol). Dry dichloromethane (0.2 mL, 0.2 M) was added under argon. The Lewis acid catalyst (0.01 mmol) was added, and the solution was stirred at room temperature under argon for 24 hours. After this time, the reaction mixture was concentrated in vacuo. For examples with stoichiometric Lewis acid, the solution was cooled to –78 °C in a dry ice/acetone bath, and 1M BF_3•OEt_2 in dichloromethane (0.1 mL, 0.1 mmol) was added. The reaction stirred for 1 hour under an inert atmosphere of argon at –78 °C. After this time, the reaction was quenched with 0.5 mL saturated $NaHCO_3$ and then warmed to room temperature. Organics were extracted 2 times with ethyl acetate (2 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Product yields and ratios were determined by ^{1}H NMR analysis of the unpurified mixture following the addition of 1,3,5-trimethoxybenzene as internal standard.

Representative procedure for synthesis of DNB-tryptamine products (Procedure B, Table 2)



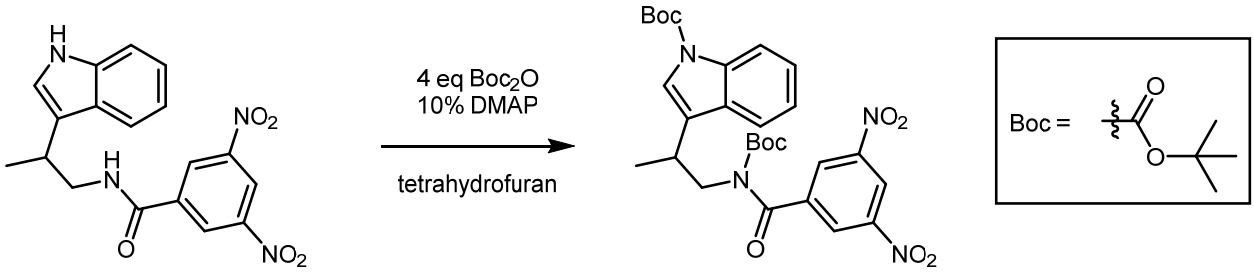
An oven dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with aziridine (0.2 mmol) and indole (0.6 mmol). Dry dichloromethane (0.8 mL, 0.25 M) was added under argon. The solution was cooled to –78 °C in a dry ice/acetone bath, and 1M BF_3•OEt_2 in dichloromethane (0.2 mL, 0.2 mmol) was added. The reaction stirred for 1 hour under an inert atmosphere of argon at –78 °C. After this time, the reaction was quenched with 0.5 mL saturated $NaHCO_3$ and then warmed to room temperature. Organics were extracted 3 times with ethyl acetate (3 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The product was purified by silica gel chromatography. All reactions were performed at least twice to determine average yields. A racemic standard for HPLC analysis was synthesized under the same conditions using the racemic analog of the starting material aziridine.

Representative procedure for *single* Boc-protection of tryptamine products (Procedure C)

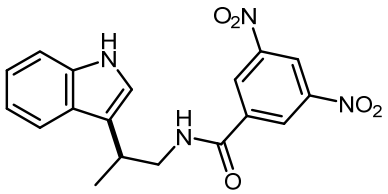


An oven-dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with tryptamine (0.025 mmol). A stock solution containing tetrahydrofuran (250 µL, 0.1 M), di-tert-butyl dicarbonate (0.05 mmol), and 4-dimethylaminopyridine (0.0012 mmol) was added to the tryptamine under inert argon atmosphere. The reaction was stirred for one hour, then was passed through a silica gel plug with 7:1 hexanes/ethyl acetate to remove excess reagent.

Representative procedure for *double* Boc-protection of tryptamine products (Procedure D)

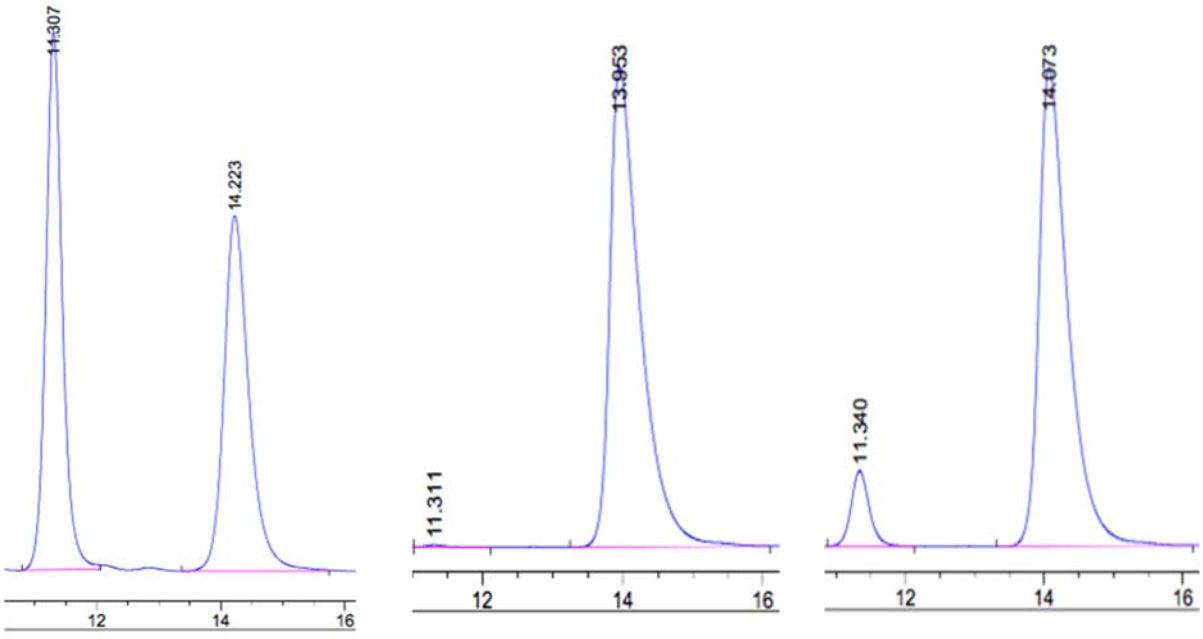


An oven-dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with tryptamine (0.025 mmol). A stock solution containing tetrahydrofuran (250 µL, 0.1 M), di-tert-butyl dicarbonate (0.10 mmol), and 4-dimethylaminopyridine (0.0012 mmol) was added to the tryptamine under inert argon atmosphere. The reaction was stirred for one hour, then was passed through a silica gel plug with 7:1 hexanes/ethyl acetate to remove excess reagent.

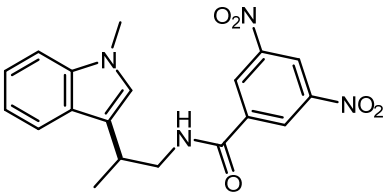


***(S)-N*-(2-(1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide (*SI-3*).** Synthesized from 1*H*-indole (70.1 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (0.5% acetone/dichloromethane) afforded an orange solid (49.4 mg, 67% yield, >99% ee). HRMS calculated for $C_{18}H_{16}N_4NaO_5^+$: 391.1013 (M + Na^+), found 391.1017 (M + Na^+). ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.06 (s, 1H), 9.03 (s, 3H), 8.59 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 3.95 – 3.81 (m, 1H), 3.69 – 3.55 (m, 1H), 3.55 – 3.42 (m, 1H), 1.44 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ, 163.6, 149.6, 139.2, 138.0, 128.3, 128.1, 122.3, 122.1, 121.5, 119.8, 119.5, 119.3, 112.4, 47.9, 32.1, 19.2. IR (NaCl plate): 3304, 3104, 1652, 1539, 1344 cm^{-1}.

HPLC conditions: ChiralPak IA, 98:2 hexanes/isopropanol, following Boc protection by procedure D.

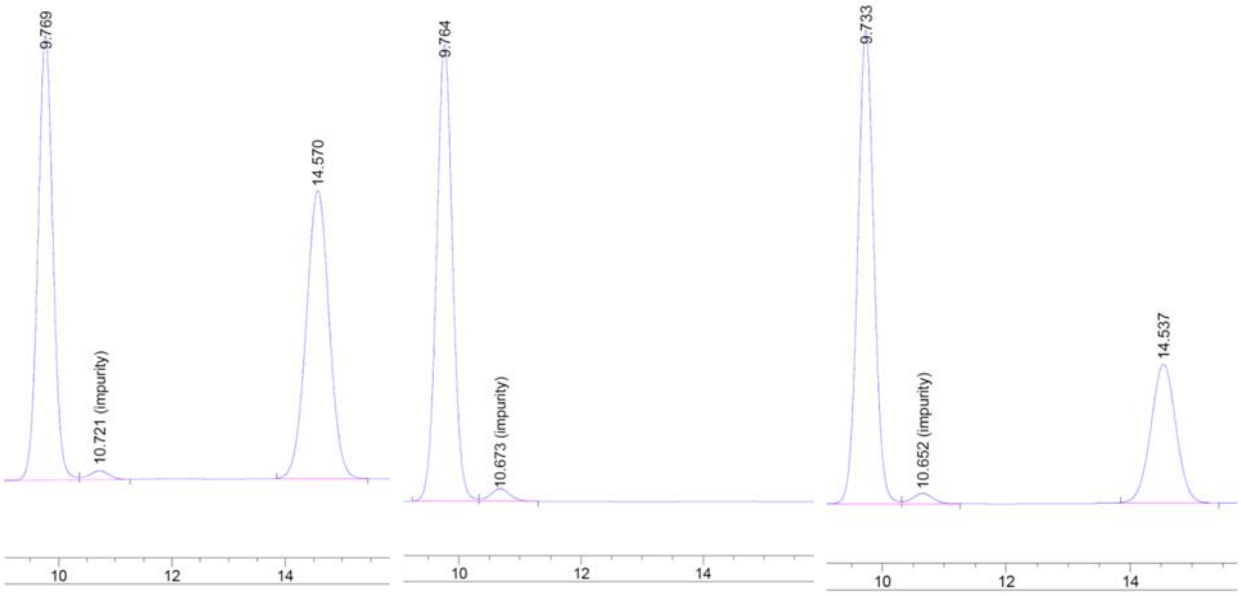


Racemic Enantiopure Spike

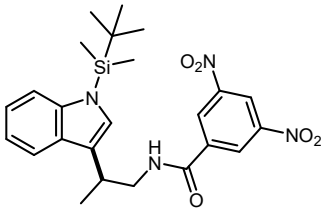


***(S)*-*N*-(2-(1-methyl-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide (*SI-4*)** Synthesized from 1-methylindole (74.9 µL, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (1% acetone/dichloromethane) afforded an orange solid (62.7 mg, 82%, >99% ee). HRMS: Calculated for $C_{19}H_{18}N_4NaO_5^+$: 405.1169 (M + Na^+), found 405.1166 (M + Na^+). ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.03 (s, 2H), 8.57 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.24 – 7.09 (m, 2H), 7.01 (t, J = 7.5 Hz, 1H), 3.92 – 3.78 (m, 1H), 3.78 (s, 3H), 3.64 – 3.53 (m, 1H), 3.53 – 3.40 (m, 1H), 1.43 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 163.6, 149.6, 139.2, 138.4, 128.5, 128.3, 126.6, 122.3, 121.5, 120.0, 119.4, 118.5, 110.4, 48.0, 32.8, 32.0, 19.2. IR (NaCl plate): 3326, 3100, 1647, 1540, 1343 cm^{-1}.

HPLC conditions: ChiralPak AD, 95:5 hexanes/isopropanol, following Boc protection by procedure C.

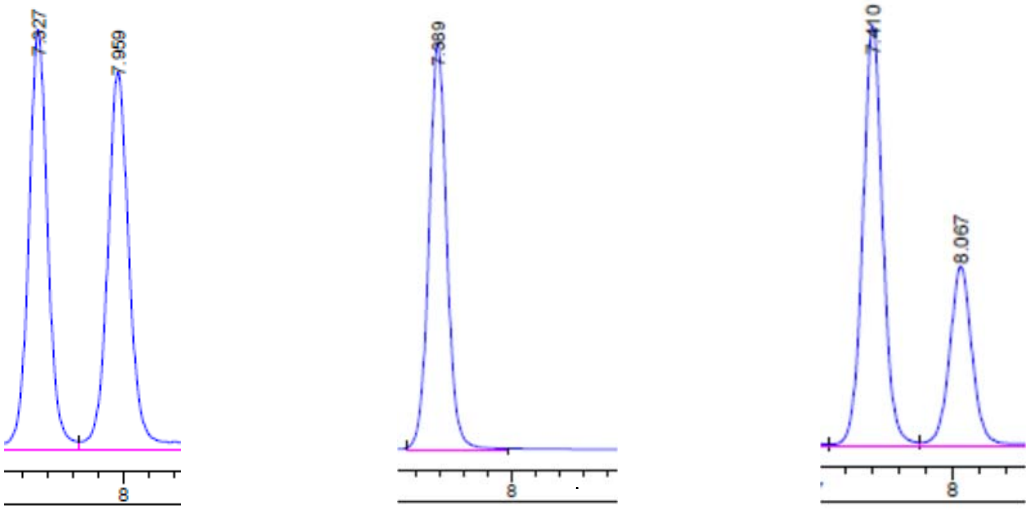


Racemic Enantiopure Spike

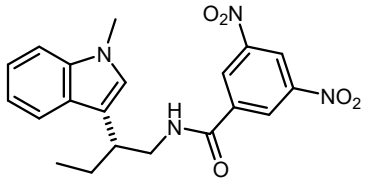


***(S)-N*-(2-(1-(*tert*-butyldimethylsilyl)-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide *(SI-5)*.** Synthesized from 1-(tert-butyldimethylsilyl)-1*H*-indole[2] (138.85 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (0.5% acetone/dichloromethane) afforded a golden solid (56.9 mg, 59% yield, >99% ee). HRMS calculated for $C_{24}H_{30}N_4NaO_5Si^+$: 505.1878 ($M + Na^+$), found 505.1877 ($M + Na^+$). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.08 (t, *J* = 2.0 Hz, 1H), 8.72 (d, *J* = 2.0 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.05 (s, 1H), 6.34 (s, 1H), 3.98 – 3.90 (m, 1H), 3.73 – 3.63 (m, 1H), 3.50 – 3.40 (m, 1H), 1.49 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.62 (s, 3H), 0.60 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.7, 148.6, 142.0, 138.2, 129.9, 127.7, 127.1, 122.2, 121.0, 120.0, 119.9, 118.8, 114.6, 46.8, 31.2, 26.4, 19.7, 18.7, -3.77, -3.78. IR (NaCl plate): 3317, 3092, 1652, 1542, 1344 cm^{-1}.

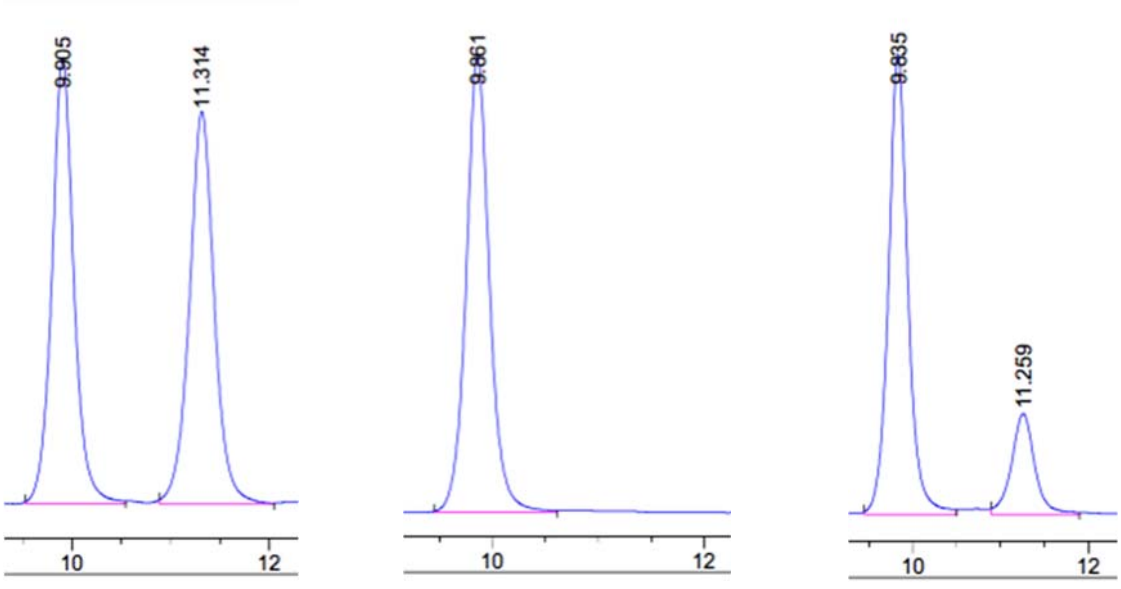
HPLC conditions: ChiralPak IB, 90:10 hexanes/isopropanol, following deprotection of the TBS group with 1M TBAF in THF and Boc protection by procedure D.



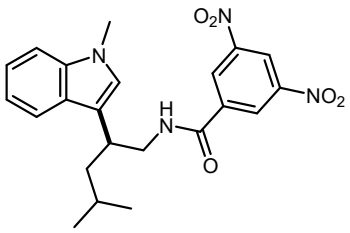
Racemic Enantiopure Spike



***(S)*-*N*-(2-(1-methyl-1*H*-indol-3-yl)butyl)-3,5-dinitrobenzamide (14).** Synthesized from 1-methylindole (74.9 µL, 0.6 mmol) and **10** (53.0 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (0.5% acetone/dichloromethane) afforded a bright orange solid (65.8 mg, 83% yield, >99% ee). HRMS calculated for $C_{20}H_{20}N_4NaO_5^+$: 419.1326 ($M + Na^+$), found 419.1322 ($M + Na^+$). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.06 (t, *J* = 2.1 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 6.23 (s, 1H), 4.11 – 4.03 (m, 1H), 3.81 (s, 3H), 3.57 – 3.49 (m, 1H), 3.21 – 3.13 (m, 1H), 1.88 (p, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.7, 148.6, 138.3, 137.6, 127.3, 127.2, 126.4, 122.4, 120.9, 119.5, 119.0, 114.9, 110.0, 45.7, 38.8, 33.0, 26.3, 12.4. IR (KBr plate): 3320, 3103, 1648, 1542, 1344 cm^{-1}. HPLC conditions: ChiralPak IB, 97:3 hexanes/isopropanol, following Boc protection by procedure C.

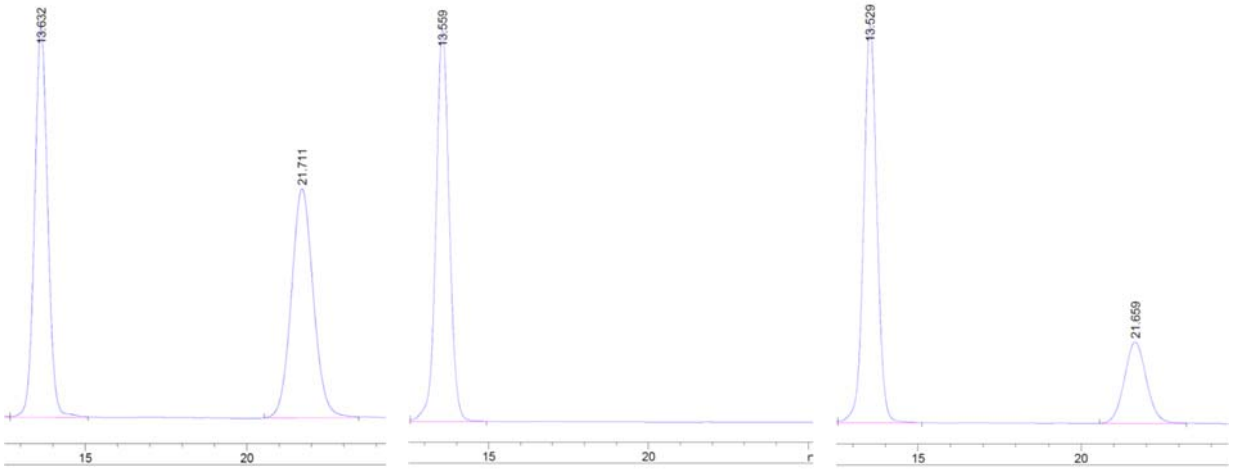


Racemic Enantiopure Spike

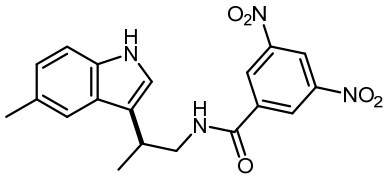


***(S)-N*-(4-methyl-2-(1-methyl-1*H*-indol-3-yl)pentyl)-3,5-dinitrobenzamide (*SI-6*).** Synthesized from 1-methylindole (74.9 μL, 0.6 mmol) and *(SI-2)* (58.7 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (2% tetrahydrofuran/dichloromethane) afforded a bright orange solid (61.1 mg, 72% yield, >99% ee). HRMS calculated for $C_{22}H_{24}N_4NaO_5^+$: 447.1639 (M + Na^+), found 447.1638 (M + Na^+). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.07 (t, *J* = 2.0 Hz,, 1H), 8.62 (d, *J* = 2.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 6.19 (s, 1H), 4.10 – 4.00 (m, 1H), 3.82 (s, 3H), 3.48 – 3.39 (m, 1H), 3.39 – 3.31 (m, 1H), 1.89 – 1.79 (m, 1H), 1.69 – 1.55 (m, 2H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.7, 148.6, 138.3, 137.6, 127.3, 127.2, 126.4, 122.4, 120.9, 119.6, 119.0, 115.1, 110.0, 46.4, 42.3, 34.8, 33.0, 25.7, 23.4, 22.3. IR (KBr plate): 3320, 3103, 1648, 1542, 1344 cm^{-1}.

HPLC conditions: ChiralPak AD, 98:2 hexanes/isopropanol, following Boc protection by procedure C.

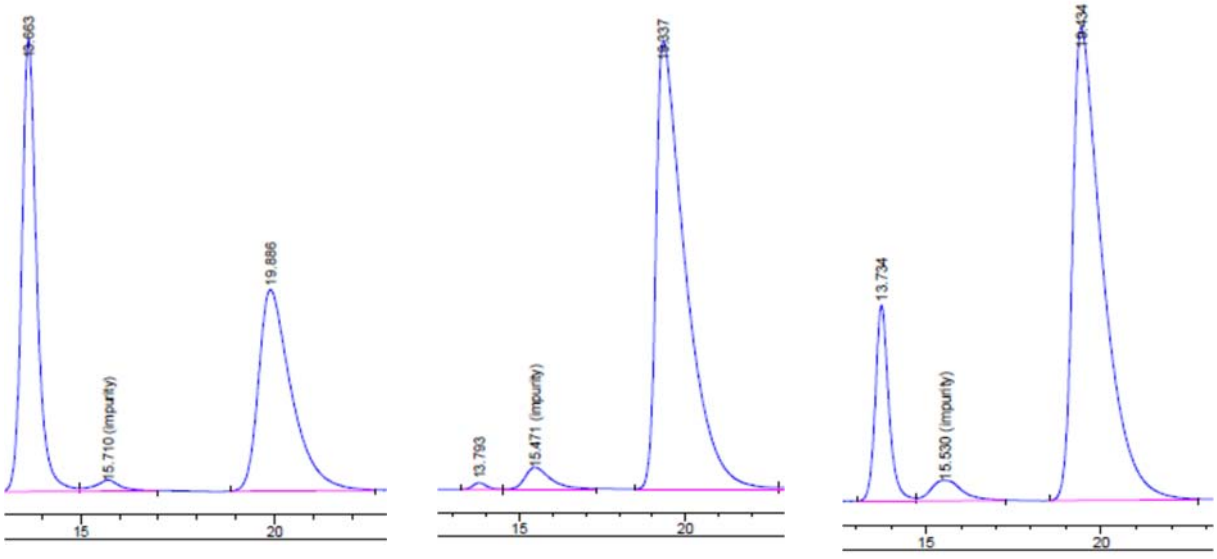


Racemic Enantiopure Spike

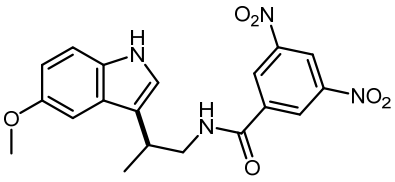


(S)-N*-(2-(5-methyl-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide *(SI-7). Synthesized from 5-methyl-1*H*-indole (78.7 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (1% acetone/ dichloromethane) afforded an orange solid (46.7 mg, 61% yield, 98.6% ee). HRMS calculated for $C_{19}H_{18}N_4NaO_5^+$ ($M + Na^+$): 405.1169 ($M + Na^+$), found 405.1165 ($M + Na^+$). ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.92 (s, 1H), 9.06 – 8.99 (m, 3H), 8.54 (s, 1H), 7.46 (s, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 3.84 – 3.77 (m, 1H), 3.68 – 3.60 (m, 1H), 3.50 – 3.41 (m, 1H), 2.34 (s, 3H), 1.42 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 163.6, 149.6, 139.2, 136.4, 128.4, 128.3, 128.3, 123.9, 122.1, 121.5, 119.5, 118.8, 112.1, 48.0, 32.0, 21.8, 19.2. IR (NaCl plate): 3308, 2926, 1653, 1653, 15401, 1344 cm^{-1}.

HPLC conditions: ChiralPak IA, 99:1 hexanes/isopropanol, following Boc protection by procedure D.

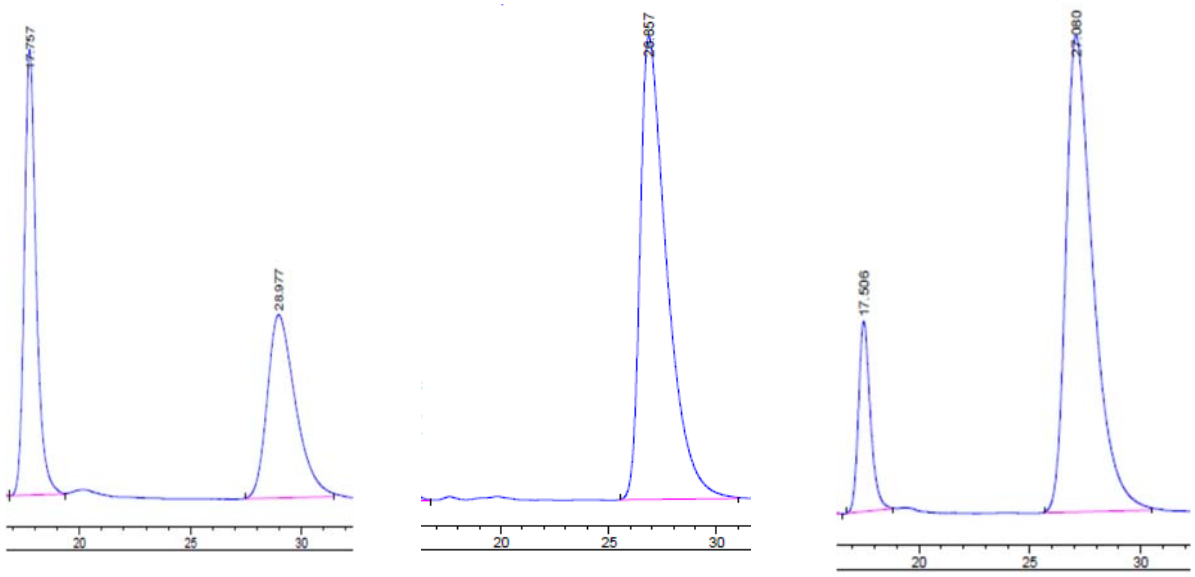


Racemic Enantiopure Spike

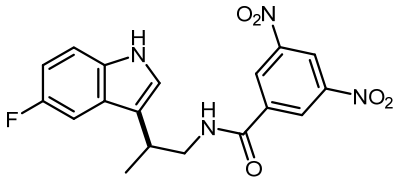


***(S)-N*-(2-(5-methoxy-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide *(SI-8)*.** Synthesized from 5-methoxy-1*H*-indole (88.3 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (0.5% acetone/ dichloromethane) afforded a red-orange solid (44.6 mg, 56% yield, >99% ee). HRMS calculated for $C_{19}H_{18}N_4NaO_6^+$: 421.1119 (M + Na^+), found: 421.1120 (M + Na^+). ^{1}H NMR (600 MHz, 90% Chloroform-*d*/10% DMSO-d_6) δ 9.46 (s, 1H), 8.95 (d, *J* = 2.1 Hz, 2H), 8.87 (t, *J* = 2.1 Hz, 1H), 8.58 (t, *J* = 5.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.86 (s, 1H), 6.59 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.60 (s, 3H), 3.59 – 3.51 (m, 1H), 3.45 – 3.35 (m, 1H), 3.28 – 3.19 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, 90% Chloroform-*d*/10% DMSO-d_6) δ 162.5, 153.1, 147.9, 138.1, 131.5, 127.7, 126.8, 121.3, 120.1, 117.8, 111.8, 111.1, 100.8, 55.5, 46.8, 30.6, 18.4. IR (NaCl plate): 3311, 2927, 1654, 1540, 1344 cm^{-1}.

HPLC conditions: ChiralPak IA, 99:1 hexanes/isopropanol, following Boc protection by procedure D.

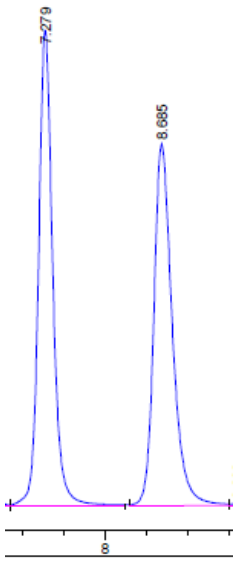


Racemic Enantiopure Spike

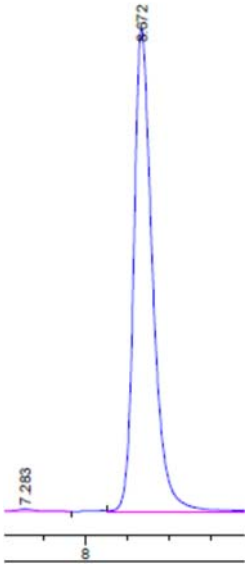


(*S*)-*N*-(2-(5-fluoro-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide *(SI-9)*. Synthesized from 5-fluoro-1*H*-indole (81.1 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (2.5% acetone/dichloromethane) afforded a golden solid (47.9 mg, 62% yield, >99% ee). HRMS calculated for $C_{18}H_{15}FN_4NaO_5^+$: 409.0919 (M + Na^+), found: 409.0919 (M + Na^+). ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.16 (s, 1H), 9.03 (s, 3H), 8.64 (s, 1H), 7.43 (dd, J = 10.0, 2.1 Hz, 1H), 7.36 (dd, J = 8.8, 4.5 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 6.87 (td, J = 9.1, 2.5 Hz, 1H), 3.94 – 3.80 (m, 1H), 3.62 – 3.49 (m, 1H), 3.49 – 3.35 (m, 1H), 1.43 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 163.5, 158.2 (d, J_{CF} = 231.7 Hz), 149.5, 139.0, 134.4, 128.3, 128.2, 124.2, 121.4, 119.4 (d, J_{CF} = 4.9 Hz), 113.1 (d, J_{CF} = 9.5 Hz), 110.2 (d, J_{CF} = 26.5 Hz), 104.4 (d, J_{CF} = 23.6 Hz), 47.7, 32.0, 18.9. IR (NaCl plate): 3302, 3100, 1650, 1540, 1344, 730 cm^{-1}.

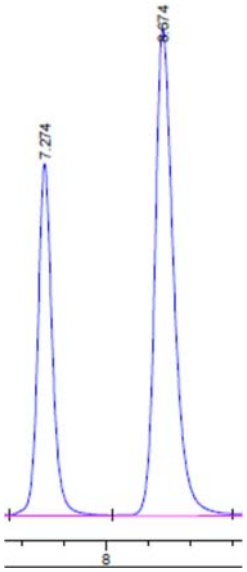
HPLC conditions: ChiralPak IA, 96:4 hexanes/isopropanol, following Boc protection by procedure D.



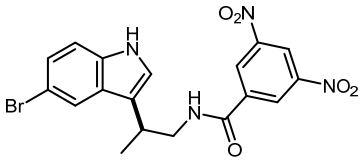
Racemic



Enantiopure

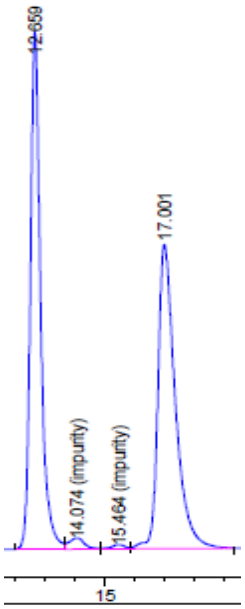


Spike

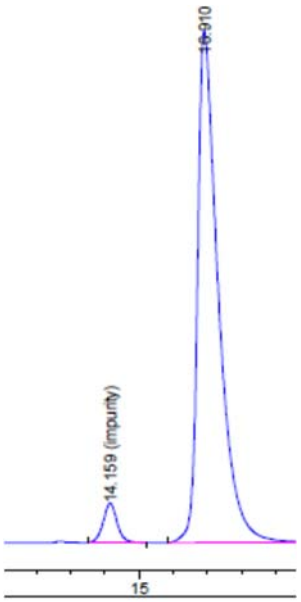


(S)-N-(2-(5-bromo-1H-indol-3-yl)propyl)-3,5-dinitrobenzamide (SI-10). Synthesized from 5-bromo-1*H*-indole (117.63 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (1.5% acetone/dichloromethane) afforded an orange solid (56.5 mg, 63% yield, >99% ee). HRMS calculated for $C_{18}H_{15}BrN_4NaO_5^+$: 469.0118 (M + Na^+), found 469.0117 (M + Na^+). ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.22 (s, 1H), 9.08 – 8.99 (m, 3H), 8.60 (s, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.00 (dd, J = 8.5, 1.9 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.67 – 3.39 (m, 2H), 1.43 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 163.6, 149.6, 139.1, 138.3, 128.3, 127.7, 126.8, 123.2, 121.5, 121.0, 120.0, 119.6, 112.2, 47.9, 32.0, 19.0. IR (NaCl plate): 3312, 2926, 1650, 1541, 1344, 730 cm^{-1}.

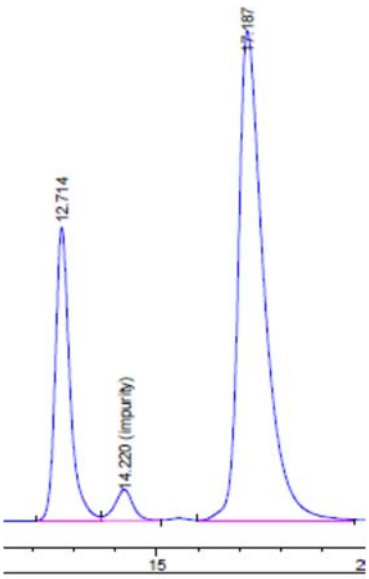
HPLC conditions: ChiralPak IA, 99:1 hexanes/isopropanol, following Boc protection by procedure D.



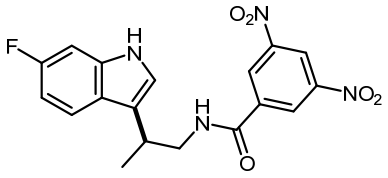
Racemic



Enantiopure

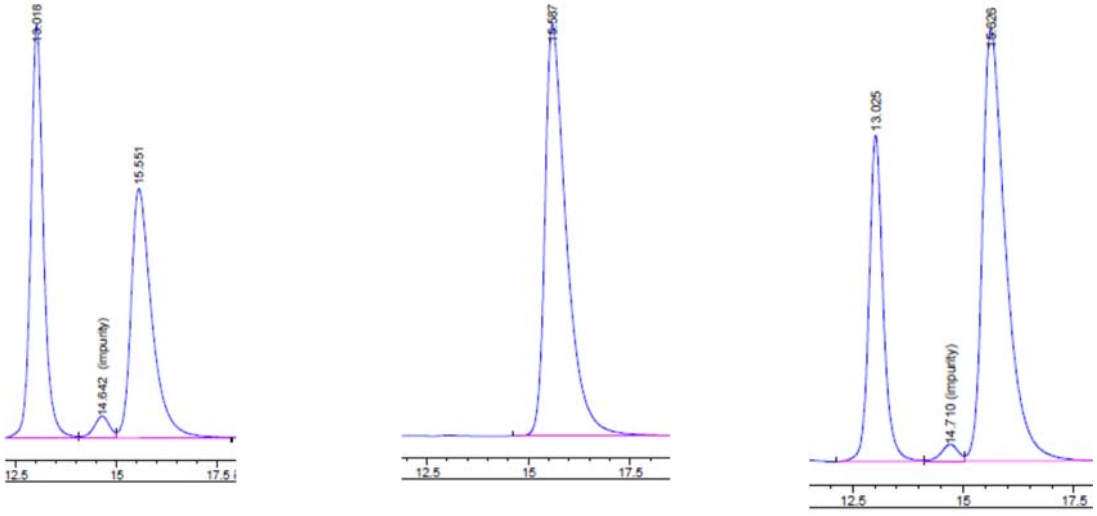


Spike

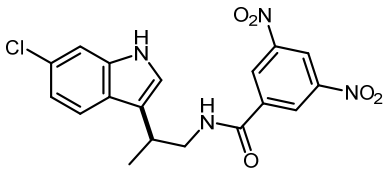


***(S)-N*-(2-(6-fluoro-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide *(SI-11)*.** Synthesized from 6-fluoro-1*H*-indole (81.1 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (0.5% acetone/dichloromethane) afforded an orange solid (55.6 mg 72% yield, >99% ee). HRMS calculated for $C_{18}H_{15}FN_4NaO_5^+$: 409.0919 (M + Na^+), found 409.0919 (M + Na^+). ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.14 (s, 1H), 9.03 (s, 3H), 8.61 (s, 1H), 7.69 (dd, J = 8.7, 5.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.10 (dd, J = 10.1, 2.4 Hz, 1H), 6.87 – 6.76 (m, 1H), 3.93 – 3.79 (m, 1H), 3.64 – 3.39 (m, 2H), 1.43 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 163.6, 160.6 (d, J_{CF}= 234.7 Hz), 149.5, 139.0, 137.8 (d, J_{CF} = 12.6 Hz), 128.2, 124.8, 122.6 (d, J_{CF} = 3.5 Hz), 121.5, 120.7 (d, J_{CF} = 10.2 Hz), 119.5, 107.9 (d, J_{CF} = 24.6 Hz), 98.2 (d, J_{CF} = 25.9 Hz), 47.9, 31.9, 19.0. IR (NaCl plate): 3306, 3098, 1657, 1542, 1344, 730 cm^{-1}.

HPLC conditions: ChiralPak IA, 98:2 hexanes/isopropanol, following Boc protection by procedure D.

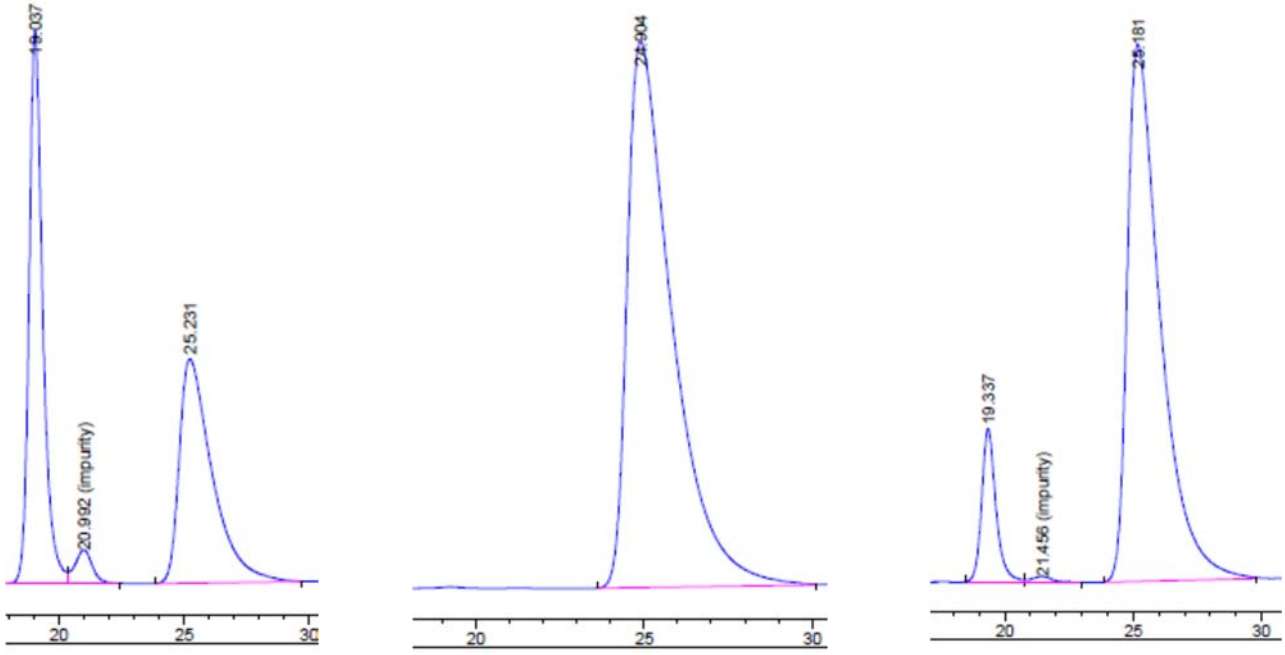


Racemic Enantiopure Spike



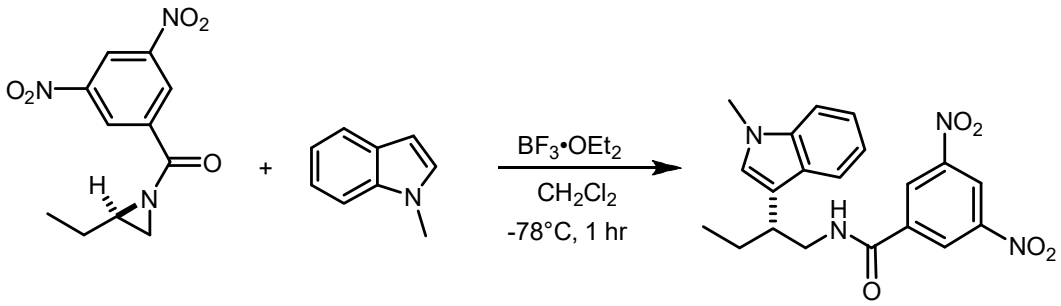
***(S)-N*-(2-(6-chloro-1*H*-indol-3-yl)propyl)-3,5-dinitrobenzamide *(SI-12)*.** Synthesized from 6-chloro-1*H*-indole (91.0 mg, 0.6 mmol) and *(SI-1)* (50.2 mg, 0.2 mmol) according to procedure B. Purification by silica gel chromatography (0.5% acetone/dichloromethane) afforded an orange solid (58.0 mg 72% yield, >99% ee). HRMS calculated for $C_{18}H_{15}ClN_4NaO_5^+$: 425.0623 ($M + Na^+$), found 425.0621 ($M + Na^+$). ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.22 (s, 1H), 9.06 – 8.97 (m, 3H), 8.61 (s, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.00 (dd, J = 8.5, 1.9 Hz, 1H), 3.91 – 3.79 (m, 1H), 3.64 – 3.40 (m, 2H), 1.43 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 163.6, 149.6, 139.1, 138.3, 128.3, 127.7, 126.9, 123.3, 121.5, 121.0, 120.0, 119.6, 112.2, 47.9, 32.0, 19.0. IR (KBr plate): 3305, 3100, 1653, 1540, 1344, 730 cm^{-1}.

HPLC conditions: ChiralPak IA, 99:1 hexanes/isopropanol, following Boc protection by procedure D.



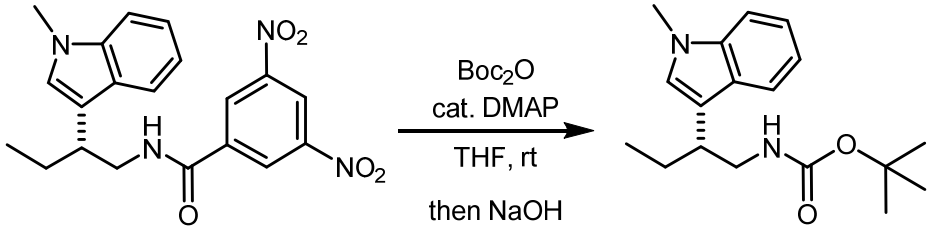
Racemic Enantiopure Spike

Gram scale DNB-tryptamine synthesis (Scheme 2)



A flame-dried 100 mL round bottom flask equipped with a magnetic Teflon®-coated stir bar was charged with aziridine **10** (1.0 g, 3.77 mmol) and 1-methylindole (1.41 mL, 11.31 mmol) under argon. Dry dichloromethane (18.85 mL, 0.2 M) was added. The solution was cooled to –78 °C in a dry ice/acetone bath, and 1M BF_3•OEt_2 in dichloromethane (3.77 mL, 3.77 mmol) was added. The reaction was stirred for 1 hour under an inert atmosphere of argon at –78 °C. After this time, the reaction was quenched with 5 mL saturated $NaHCO_3$ and then warmed to room temperature. Organics were extracted 3 times with ethyl acetate (25 mL). The combined organics were washed with 20 mL of brine. The solution was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The product was purified by silica gel chromatography (0.5% acetone/dichloromethane) to afford 1.10 g (74% yield, >99% ee) of tryptamine **14** as an orange solid.

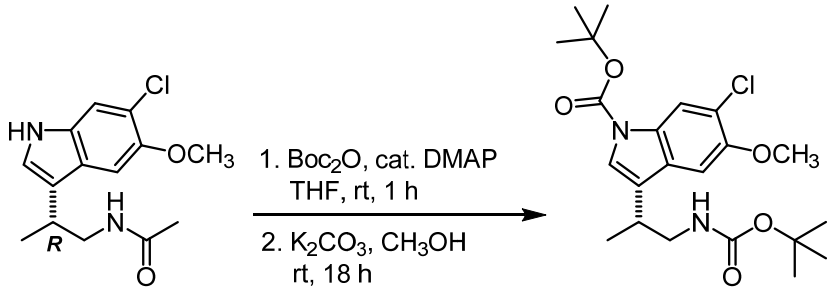
Procedure for tryptamine DNB-deprotection (Scheme 2)



An oven-dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with tryptamine **14** (119 mg, 0.3 mmol) and di-tert-butyl dicarbonate (131 mg, 0.6

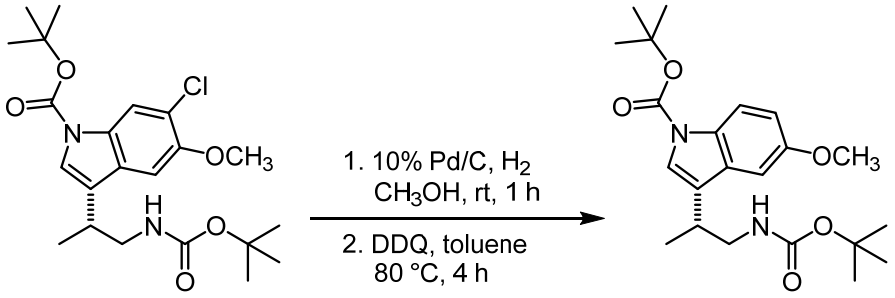
mmol). Dry tetrahydrofuran (1.5 mL, 0.2 M) was added under argon, followed by catalytic 4-dimethylaminopyridine (1.8 mg, 0.015 mmol). The reaction was stirred for 2 hours at room temperature, when all starting material was consumed. Aqueous 2 M sodium hydroxide (1.5 mL) was added and stirring at room temperature was continued. After 5 hours, the biphasic mixture was diluted with 2 mL of ethyl acetate. The organic layer was taken, and the aqueous layer was extracted with 2 x 2 mL of ethyl acetate. The combined organic layers were washed with 5 mL of 1 M sodium hydroxide and 5 mL of brine. The solution was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The product was purified by silica gel chromatography (7:1 hexanes/ethyl acetate) to afford 74 mg (82% yield) of tryptamine **15** as a clear oil. HRMS calculated for $C_{18}H_{26}N_2NaO_2^+$: 325.1886 ($M + Na^+$), found 325.1901 ($M + Na^+$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 4.47 (br s, 1H), 3.77 (s, 3H), 3.68 – 3.52 (m, 1H), 3.40 – 3.24 (m, 1H), 3.05 – 2.88 (m, 1H), 1.86 – 1.67 (m, 2H), 1.41 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 156.2, 137.5, 127.7, 126.4, 121.8, 119.6, 118.9, 115.8, 109.4, 79.1, 45.4, 39.3, 32.9, 28.6, 26.5, 12.3. IR: (Diamond ATR) 3312, 2978, 2929, 1711, 1282 cm^{-1}.

Proof of tryptamine stereochemistry (Scheme 3)



An oven-dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with (*R*)-*N*-[2-(6-Chloro-5-methoxy-1H-indol-3-yl)propyl]acetamide (**1**)[3] (28.1 mg, 0.1

mmol) and di-tert-butyl dicarbonate (87.3 mg, 0.4 mmol). Dry tetrahydrofuran (1 mL, 0.1 M) was added under argon, followed by catalytic 4-dimethylaminopyridine (1.2 mg, 0.01 mmol). The reaction was stirred for 18 hours at room temperature. The mixture was concentrated to dryness via rotary evaporation. The crude mixture was dissolved in 1 mL of dry methanol, and potassium carbonate (3 mg, 0.02 mmol) was added. The suspension was stirred at room temperature for 18 hours. The reaction was quenched with 1 mL of water. The mixture was extracted with 2 x 3 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The product was purified by silica gel chromatography (7:1 hexanes/ethyl acetate) to afford 30 mg (68% yield) of tryptamine **16** as a clear viscous oil. HRMS calculated for $C_{22}H_{31}ClN_2NaO_5^+$: 461.1814 ($M + Na^+$), found 461.1814 ($M + Na^+$). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.17 (br s, 1H), 7.34 (br s, 1H), 7.14 (br s, 1H), 4.62 (br s, 1H), 3.96 (s, 3H), 3.46 – 3.37 (m, 1H), 3.35 – 3.28 (m, 1H), 3.20 – 3.10 (m, 1H), 1.66 (s, 9H), 1.42 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.2, 151.4, 149.6 (br), 129.9 (br), 129.3 (br), 123.5 (br), 122.6 (br), 120.4 (br), 117.2, 101.9, 84.1, 79.5, 56.8, 46.6, 31.5, 28.6, 28.4, 18.1. IR: (Diamond ATR) 3418, 3003, 2979, 1732, 1705, 1275 cm^{-1}.

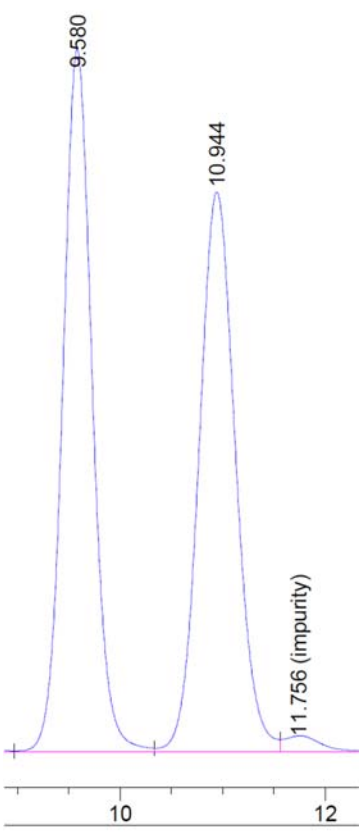


An oven-dried 1-dram vial equipped with a magnetic Teflon®-coated stir bar was charged with tryptamine **16** (7.1 mg, 0.016 mmol) and wet 10% palladium on carbon (8.4 mg, 0.0032 mmol) under argon. Dry methanol (0.5 mL, 0.03 M) was added under argon, and the

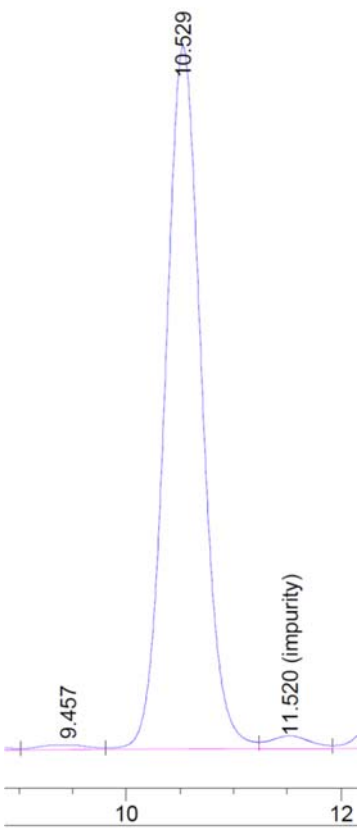
solution was purged with hydrogen gas. The reaction was stirred under a hydrogen atmosphere for 1 hour at room temperature. No starting material remained, so the mixture was filtered through a plug of Celite, and the solution was concentrated. ^{1}H-NMR indicated the product of de-chlorination with concomitant indole reduction. The crude product was re-dissolved in 0.5 mL of toluene. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (5.4 mg, 0.024 mmol) was added, and the mixture was heated to 80 °C for 4 hours under argon. The reaction was then evaporated to dryness via rotary evaporation. The product was purified by silica gel chromatography (8:1 hexanes/ethyl acetate) to afford 2.6 mg (40% yield) of tryptamine **17** as a clear film. HRMS calculated for $C_{22}H_{32}N_2NaO_5^+$: 427.2203 ($M + Na^+$), found 427.2193 ($M + Na^+$). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.99 (br s, 1H), 7.36 (br s, 1H), 7.06 (br s, 1H), 6.93 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.58 (br s, 1H), 3.87 (s, 3H), 3.40 (t, *J* = 6.3 Hz, 2H), 3.20 – 3.10 (m, 1H), 1.66 (s, 9H), 1.42 (s, 9H), 1.34 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.2, 155.9, 149.9 (br), 130.9 (br), 123.5, 122.7 (br), 116.2, 113.1, 102.5, 83.6, 79.4, 55.9, 46.3, 31.5, 29.9, 28.6, 28.4, 18.2. IR: (Diamond ATR) 3410, 3004, 2978, 1729, 1707, 1260 cm^{-1}.

Racemic and enantiopure samples generated by aziridine opening (compound *SI-8*) were converted to bis-Boc derivatives via Procedure D.

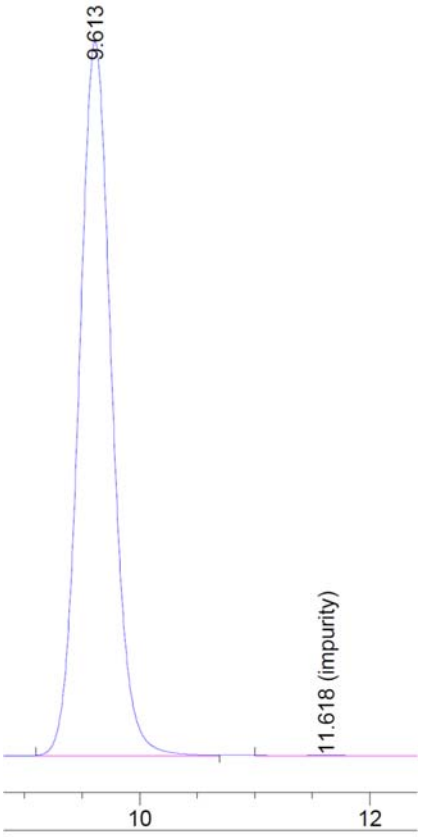
HPLC Conditions: ChiralPak IA, 97:3 hexanes/isopropanol



Racemic



Enantiopure



Authentic

[1] Rubin, H.; Cockrell, J.; Morgan, J. B. *J. Org. Chem.* **2013**, *78*, 8865–8871.
[2] Malmgren, J.; Nagendiran, A.; Tai, C. W.; Bäckvall, J. E.; Olofsson, B. *Chem. Eur. J.* **2014**, *20*, 13531–13535.
[3] Sample provided by our colleague Sridhar Varadarajan.