Determination of Absolute Configuration of Trimeric Indole Alkaloid, Psychotrimine, by First Asymmetric Total Synthesis

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Supporting Information

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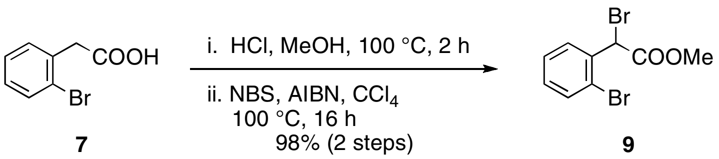
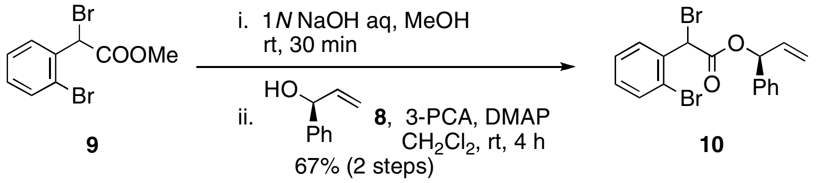
General. UV: recorded in MeOH on a JASCO V-560 instrument. IR: recorded on a JASCO FT/IR-230 spectrophotometer. ^{1}H and ^{13}C NMR spectra: recorded on a JEOL JNM A-400, or JNM ECP-400 or JNM ECP-600 spectrometers, *J* values are given in Hz. EI-MS: direct probe insertion at 70 eV recorded on a JEOL JMS GC-mate spectrometer. ESI-MS: recorded on a Thermo Fisher Scientific Exactive spectrometer. Optical rotation: measured with a JASCO P-1020 polarimeter. Melting point: measured with a Yanaco Micro Melting Point Apparatus MP-500P. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick), or precoated amino-silica gel plates (Fuji Silysia Chemical). Column chromatography: Silica Gel 60N [KANTO, 40-50 μm (for flash column chromatography)], or Chromatorex NH [Fuji Silysia Chemical, 100-200 mesh (for amino-silica gel column chromatography)]. High performance liquid chromatography (HPLC): CHIRALPAK IB (Daicel Chemical Industries).

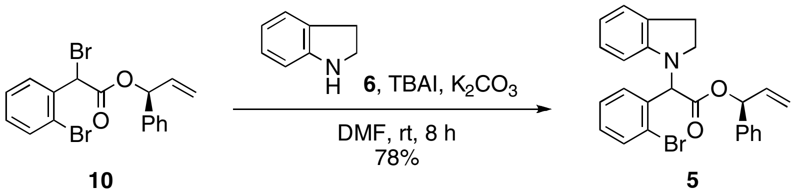


Dibromo compound 9: To a stirred solution of 2-bromophenyl acetic acid (**7**, 11.8 g, 54.87 mmol) in MeOH (13.0 mL) was added concd HCl aq (10 drops) at room temperature and the mixture was stirred for 2 h at 100 °C under Ar atmosphere. The reaction mixture was cooled down to room temperature and diluted with Et_2O. The whole was washed with sat. $NaHCO_3$ aq, washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without purification. To a stirred solution of the above crude product in CCl_4 (110.0 mL) were added NBS (10.8 g, 60.68 mmol) and AIBN (456 mg, 2.77 mmol) at room temperature and the mixture was stirred at 100 °C for 16 h under Ar atmosphere. The reaction mixture was cooled down to room temperature. After adding Et_2O, the mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 16.5 g (98%, 2 steps) of **9** as a colorless oil. UV (MeOH) λ_{max} nm: 205. IR (ATR) ν_{max} cm^{-1}: 2952, 1739 (CO), 1470, 1434, 1217, 1145, 1026, 999, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.77 (1H, dd, J = 8.0, 1.7), 7.56 (1H, dd, J = 8.1, 0.9), 7.36 (1H, br-ddd, J = 7.7, 7.7, 1.3), 7.20 (1H, ddd, J = 8.1, 7.3, 1.6), 5.91 (1H, s, CHBr), 3.81 (3H, s, CO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.3 (CO), 135.4, 133.0, 130.9, 130.5, 128.2, 123.5, 53.6, 45.6; EI-MS *m/z* (%): 310 (2, $[M+4]^+$), 308 (3, $[M+2]^+$), 306 (2, $[M^+]$), 251 (9), 249 (18), 247 (9), 229 (45), 227 (46), 149 (64), 148 (85), 83 (100); HR-EI-MS calcd for $C_9H_8O_2{}^{79}Br_2$ $[M^+]$: 305.8890, found: 305.8898.

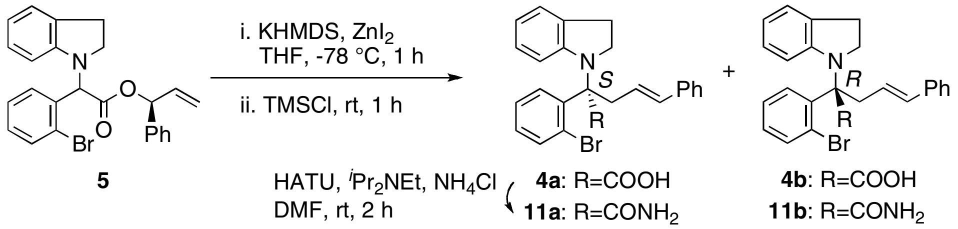


Ester 10: To a stirred solution of **9** (7.50 g, 24.35 mmol) in MeOH (100 mL) was added 1*N* NaOH aq (50.0 μL, 73.05 mmol) at 0 °C under Ar atmosphere and the mixture was stirred at room temperature. After stirring for 30 min, 1*N* HCl aq was added to the reaction mixture until pH 2-3 and the whole was extracted two times with $CHCl_3$, and extracted once with MeOH/$CHCl_3$ = 20:80. The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude product that was subjected to the next reaction without purification. To a stirred solution of the above crude product in dry CH_2Cl_2 (20.0 mL) were added pyridine-3-carboxylic anhydride (3-PCA, 5.26 g, 24.35 mmol), and DMAP (144 mg, 1.21 mmol) at room temperature under Ar atmosphere. After stirring for 10 min at the same temperature, a solution of chiral allyl alcohol **8** (3.07 g, 24.35 mmol) in dry CH_2Cl_2 (40.0 mL) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched by adding sat. $NaHCO_3$ aq and the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 15:85) to afford 6.72 g (67%, 2 steps) of **10** (a mixture of diastereomers) as a yellow oil. $[\alpha]_D^{23}$ –40.0 (*c* 0.68, $CHCl_3$); UV (MeOH) λ_{max} nm: 207; IR (ATR) ν_{max} cm^{-1}: 3065, 1742 (CO), 1469, 1265, 1211, 1178, 1139, 978, 929, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.74 (1H, dd, J = 8.0, 1.7), 7.63

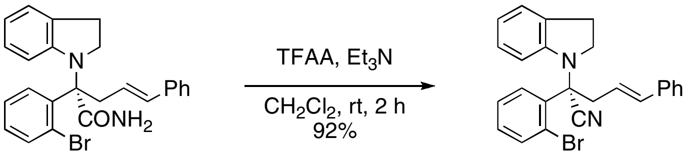
(1H, dd, *J* = 7.9, 1.6), 7.56 (1H, br-ddd, *J* = 8.2, 7.0, 1.3), 7.39-7.14 (16H, overlapped), 6.32-6.28 (2H, overlapped), 6.05-5.88 (4H, overlapped), 5.38-5.21 (4H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 166.61, 166.57, 137.8, 135.4, 135.19, 135.15, 133.0, 132.9, 131.1, 131.0, 130.52, 130.46, 128.6, 128.5, 128.3, 128.1, 128.0, 127.1, 127.0, 123.6, 117.9, 117.6, 78.5, 78.4, 46.1, 46.0; EI-MS *m*/*z* (%): 412 (1, $[M+4]^+$), 410 (3, $[M+2]^+$), 408 (1, $[M]^+$), 331 (22), 329 (24), 251 (10), 249 (19), 247 (11), 198 (16), 196 (27), 117 (100), 115 (100); HR-EI-MS calcd for $C_{17}H_{14}O_2{}^{79}Br_2$ $[M^+]$: 407.9360, found: 407.9355.



Ester 5: To a stirred solution of indoline (**6**, 906 mg, 7.62 mmol), K_2CO_3 (1.05 g, 7.62 mmol) and TBAI (511 mg, 1.39 mmol) in dry DMF (30.0 mL) was added a solution of **10** (2.84 g, 6.93 mmol) in dry DMF (10.0 mL) via canula at 0 °C under Ar atmosphere. The mixture was stirred for 8 h at room temperature and then diluted with Et_2O and H_2O. After stirring for 10 min, the whole was extracted three times with Et_2O. The combined organic layers were washed with H_2O, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 8:92) to afford 2.25 g (73%) of **5** (a mixture of diastereomers) as a yellow oil. $[\alpha]_D^{20}$ –43.3 (*c* 0.72, $CHCl_3$); UV (MeOH) λ_{max} nm: 303, 252, 206; IR (ATR) ν_{max} cm^{-1}: 3031, 1736 (CO), 1605, 1487, 1258, 1155, 742, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.65-7.61 (2H, m), 7.40-6.95 (20H, overlapped), 6.70-6.64 (2H, m), 6.46 and 6.37 (each 1H, d, *J* = 7.7), 6.35-6.31 (2H, m), 5.97 (1H, ddd, *J* = 17.1, 10.4, 6.1), 5.87 (1H, ddd, *J* = 16.8, 10.9, 6.0), 5.69 (1H, s), 5.66 (1H, s), 5.28-5.13 (4H, overlapped), 3.62 (1H, ddd, *J* = 9.2, 9.2, 9.2), 3.54 (1H, ddd, *J* = 9.2, 9.2, 9.2), 3.18-3.12 (2H, m), 2.99-2.88 (4H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.6, 169.5, 169.4, 150.5, 138.6, 138.3, 138.1, 136.0, 135.7, 135.3, 135.1, 134.9, 134.1, 133.3, 133.2, 132.7, 131.5, 129.9, 129.84, 129.76, 129.7, 128.9, 128.49, 128.45, 128.32, 128.26, 128.11, 128.07, 127.5, 127.34, 127.27, 127.22, 127.16, 127.12, 127.06, 125.4, 125.3, 125.0, 124.53, 124.46, 118.14, 118.11, 117.6, 117.3, 117.0, 106.7, 106.6, 77.0, 76.7, 63.4, 63.1, 49.8, 49.6, 28.2; EI-MS *m*/*z* (%): 449 (10, $[M+2]^+$), 447 (10, $[M]^+$), 288 (100), 286 (100), 206 (31), 117 (79); HR-ESI-MS calcd for $C_{25}H_{22}O_2NBrNa$ $[M+Na]^+$: 470.0726, found: 470.0708.



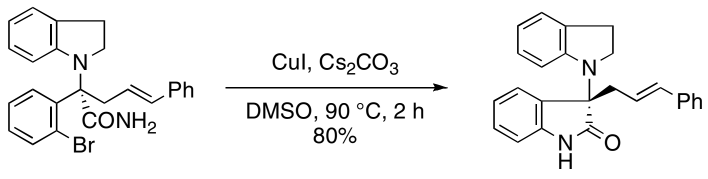
Amide 11a: To a stirred solution of **5** (1.0 g, 2.2 mmol) in dry THF (25.0 mL) were added dropwise KHMDS (27.0 mL, 13.5 mmol, 0.5M in toluene) and a solution of ZnI_2 (4.5 g, 13.2 mmol) in dry THF (25.0 mL) at –78 °C under Ar atmosphere. After 1 h, TMSCl (52.8 mL, 22.0 mmol) was added to the above mixture at –78 °C and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by adding 10% NH_4Cl aq and the whole mixture was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without purification. To a stirred solution of the above crude product in dry DMF (30.0 mL) were added HATU (1.8 g, 2.6 mmol), *i*-Pr_2NEt (3.3 mL, 13.2 mmol), and NH_4Cl (0.5 g, 8.8 mmol) at room temperature under Ar atmosphere. After stirring for 2 h, the reaction mixture was quenched by adding H_2O and the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 40:60) to afford 786 mg (79%, 74% ee) of **11a** as a pale yellow amorphous, which was recrystallized from ethyl acetate to give a racemic **11a** (85 mg, mp 173-179 °C) and a filtrate (700 mg) consisting of optically active **11a** (96% ee): $[\alpha]_D^{24}$ +26.4 (*c* 1.46, $CHCl_3$); UV (MeOH) λ_{max} nm: 256, 204; IR (ATR) ν_{max} cm^{-1}: 3455, 3161, 1682, 1603, 1485, 1253, 961, 738; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.66 (1H, dd, *J* = 8.1, 1.6), 7.61 (1H, dd, *J* = 8.0, 1.4), 7.30-7.13 (7H, overlapped), 7.08 (1H, d, *J* = 6.2), 6.74 (1H, dd, *J* = 7.6, 7.6), 6.63 (1H, br-dd, *J* = 7.3, 7.3), 6.24 (1H, d, *J* = 15.9, CH=C$\underline{H}$Ph), 6.10 (1H, ddd, *J* = 15.8, 7.0, 7.0, C$\underline{H}$=CHPh), 5.93 (1H, br-s, CON$\underline{H_2}$), 5.77 (1H, d, *J* = 8.1), 5.48 (1H, br-s, CON$\underline{H_2}$), 3.97 (1H, br-ddd, *J* = 9.4, 9.4, 3.0), 3.60 (1H, br-ddd, *J* =10.0, 10.0, 10.0), 3.50 (1H, br-dd, *J* = 14.7, 7.4), 3.29 (1H, br-dd, *J* = 14.8, 6.7), 3.14-2.97 (2H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.5 (CO), 148.7, 137.6, 137.0, 135.5, 133.0, 132.0, 131.3, 129.3, 128.3, 127.0, 126.9, 126.4, 126.0, 125.8, 124.9, 122.0, 118.3, 110.9, 72.4 ($\underline{C}$CO), 49.5, 39.0, 27.9; HR-ESI-MS calcd for $C_{25}H_{23}ON_2BrNa$ $[M+Na]^+$: 469.0886, found: 469.0868; HPLC (column: CHIRALPAK IB, eluent: *n*-hexane/EtOH = 80:20, flow late: 0.5 mL/min, temperature: 30 °C, retention time: t_R (**11a**) = 18.49 min, t_R (**11b**) = 20.2 min).



11a **13**

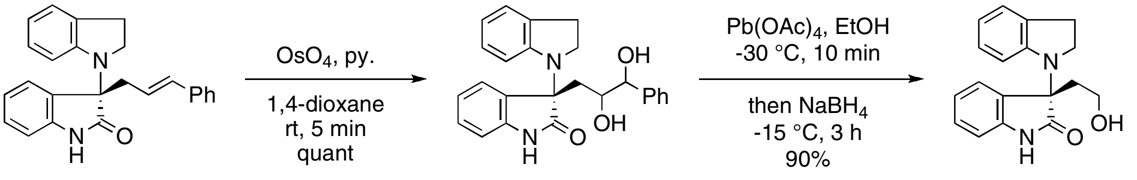
Nitrile 13: To a stirred solution of **11a** (50.0 mg, 0.11 mmol) in dry CH_2Cl_2 (1.1 mL) were added NEt_3 (0.1 mL, 0.73 mmol) and TFAA (60.0 μL, 0.44 mmol) at 0 °C under Ar atmosphere and then the mixture was stirred for 2 h at room temperature. The reaction was quenched by adding sat. $NaHCO_3$ aq and the whole mixture was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 44.0 mg (92%) of **13** as a pale yellow amorphous. Enantiomeric excess of **13** was increased to 99.9% ee by recrystallization from ethyl acetate. mp 155-157 °C (ethyl acetate); $[\alpha]_D^{20}$ +150.3 (*c* 0.63, $CHCl_3$); UV (MeOH) λ_{max} nm: 293, 284, 255, 203; IR (ATR) ν_{max} cm^{-1}: 2920, 2849, 2364 (CN), 1603, 1482, 1258, 976, 742; ^1H NMR (400MHz, $CDCl_3$) δppm: 7.77 (1H, dd, *J* = 8.0, 1.5), 7.67 (1H, d, *J* = 7.8), 7.33 (1H, dd, *J* = 7.6, 7.6), 7.27-7.17 (6H, overlapped), 7.12 (1H, d, *J* = 7.3), 6.82 (1H, dd, *J* = 7.8, 7.8), 6.73 (1H, dd, *J* = 7.3, 7.3), 6.38 (1H, d, *J* = 15.6), 5.92 (1H, d, *J* = 8.1), 5.82 (1H, ddd, *J* = 15.4, 7.6, 7.6), 3.94 (1H, br-ddd, *J* = 8.4, 8.4, 1.8), 3.62-3.53 (2H, overlapped), 3.28 (1H, dd, *J* = 14.0, 7.4), 3.18-3.01 (2H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 148.0, 136.6, 136.1, 135.6, 134.4, 131.1, 131.0, 130.2, 128.5, 127.7, 127.5, 126.8, 126.3, 124.5, 121.5, 120.3, 120.1, 117.5 (CN), 111.4, 67.3, 50.1, 40.7, 28.1; EI-MS *m/z* (%): 430 (1, $[M+2]^+$), 428 (1, $[M]^+$), 403 (62), 401 (63), 118 (100); HR-EI-MS calcd for $C_{25}H_{21}N_2{}^{79}Br$ $[M^+]$: 428.0888, found: 428.0888; HPLC (column; CHIRALPAK IB, eluent; *n*-hexane/EtOH= 98:2, flow late; 0.5 mL/min, temperature; 30 °C, retention time; 20.39 min).

Fig. 1 X-ray crystallographic analysis (ORTEP) of nitrile **13**.



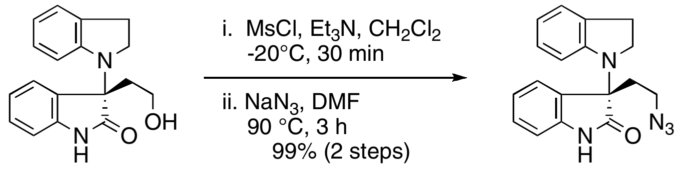
11a **3**

Oxindole 3: A round-bottomed flask was charged with amide **11a** (719.1 mg, 1.6 mmol), copper (I) iodide (305.8 mg, 1.6 mmol), and Cs_2CO_3 (790.0 mg, 2.4 mmol). The flask was fitted with a rubber septum, evacuated and then backfilled with Ar. Freshly degassed dry DMSO (2.5 mL) was added to the flask and the resulting suspension was stirred for 2 h at 90 °C. The reaction mixture was cooled to room temperature and quenched with 5% NH_4OH aq and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 30:70) to afford 469.3 mg (80%) of **3** as a pale yellow amorphous. $[\alpha]_D^{24}$ –99.2 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max} nm: 293, 284, 254, 206; IR (ATR) ν_{max} cm^{-1}: 3060, 1692 (CONH), 1604, 1469, 1251, 742; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.01 (1H, br-s, N_1-H), 7.33 (1H, d, *J* = 7.3), 7.28-7.23 (3H, overlapped), 7.21-7.18 (3H, overlapped), 7.03 (2H, overlapped), 6.85 (1H, d, *J* = 7.9), 6.68 (1H, dd, *J* = 7.7, 7.7), 6.59 (1H, dd, *J* = 7.3, 7.3), 6.38 (1H, d, *J* = 15.7, CH=C$\underline{\text{H}}$Ph), 5.93 (1H, ddd, *J* = 15.2, 8.4, 6.8, C$\underline{\text{H}}$=CHPh), 5.65 (1H, d, *J* = 7.9), 4.20 (1H, ddd, *J* =9.2, 9.2, 9.2), 3.95 (1H, ddd, *J* = 7.9, 7.9, 5.2), 3.16 (1H, dd, *J* = 13.4, 6.2), 3.06-2.93 (3H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.2, 149.9, 139.7, 137.0, 134.9, 130.9, 130.4, 129.0, 128.4, 127.4, 127.1, 126.2, 124.7, 124.5, 123.0, 122.1, 118.8, 110.1, 108.7, 67.0, 50.2, 41.5, 28.1; HR-ESI-MS calcd for $C_{25}H_{22}ON_2Na$ $[M+Na]^+$: 389.1624, found: 389.1613.



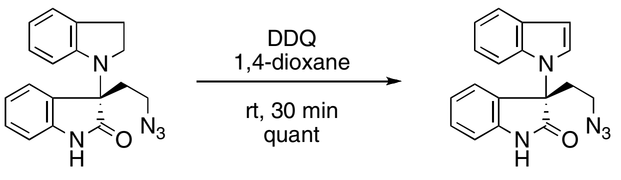
3 **S1** **14**

Primary alcohol 14: To a stirred solution of **3** (1.5 g, 4.1 mmol) in dry 1,4-dioxane (50.0 mL) was added a solution of OsO_4 (1.35 g, 4.7 mmol) in dry pyridine (13.5 mL) at room temperature under Ar atmosphere. After 5 min, $NaHSO_3$ (0.86 g), H_2O (144.0 mL) and pyridine (96.0 mL) were added to the reaction mixture. After stirring for 1 h, the whole mixture was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 80:20) to afford 1.59 g (quant) of **S1** as a pale yellow amorphous. To a stirred solution of **S1** (1.15 g, 2.9 mmol) in dry EtOH (180.0 mL) was added $Pb(OAc)_4$ (1.45 g, 3.2 mmol) at –30 °C under Ar atmosphere. After 10 min, $NaBH_4$ (630.0 mg, 14.5 mmol) was added to the mixture and warmed up to –15 °C. After stirring for 3 h at –15 °C, the reaction was quenched with H_2O, and then the whole mixture was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 90:10) to afford 766.6 mg (90%) of **14** as a yellow amorphous: $[\alpha]_D^{24}$ –43.1 (*c* 0.91, $CHCl_3$); UV (MeOH) λ_{max} nm: 291, 252, 206; IR (ATR) ν_{max} cm^{-1}: 3203, 2923, 2851, 1707 (CONH), 1618, 1604, 1469, 1469, 1250, 1028, 742; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.76 (1H, br-d, *J* = 6.0), 7.27-7.21 (2H, overlapped), 7.04-6.98 (2H, overlapped), 6.85 (1H, d, *J* = 7.9), 6.70 (1H, dd, *J* = 7.5, 7.5), 6.60 (1H, dd, *J* = 7.0, 7.0), 5.77 (1H, d, *J* = 8.1), 4.02 (1H, ddd, *J* = 9.0, 9.0, 9.0), 3.85 (1H, ddd, *J* = 8.2, 8.2, 5.8), 3.69 (1H, br-ddd, *J* = 11.8, 5.9, 5.9), 3.57 (1H, br-ddd, *J* = 12.0, 6.0, 6.0), 2.98-2.94 (2H, overlapped), 2.56 (1H, ddd, *J* = 13.6, 6.8, 6.8), 2.43 (1H, ddd, *J* = 13.0, 6.5, 6.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 180.1 (CO), 149.5, 140.2, 131.1, 130.2, 129.2, 127.1, 124.5, 124.3, 123.2, 119.0, 110.6, 109.0, 65.7, 58.2, 50.3, 40.4, 28.0; HR-ESI-MS calcd for $C_{18}H_{18}O_2N_2Na$ $[M+Na]^+$: 317.1260, found: 317.1251.



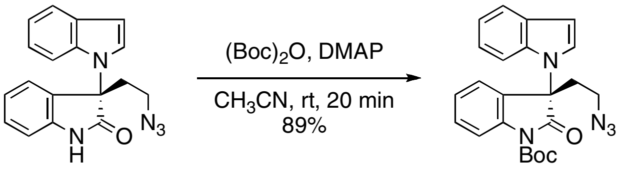
14 **15**

Azide 15: To a stirred solution of **14** (600.0 mg, 2.0 mmol) and Et_3N (330 μL, 2.4 mmol) in dry CH_2Cl_2 (36.0 mL) was added MsCl (183 μL, 2.2 mmol) at –20 °C under Ar atmosphere. After stirring for 30 min, the reaction was quenched with H_2O, and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without purification. To a stirred solution of the above crude product in dry DMF (11.0 mL) was added NaN_3 (658.5 mg, 10.0 mmol) and the mixture was stirred at 90 °C for 3 h. The reaction mixture was cooled down to room temperature and H_2O was added to the mixture, and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 50:50) to afford 641.8 mg (99%, 2 steps) of **15** as a colorless amorphous: $[\alpha]_D^{24}$ –58.8 (*c* 0.82, $CHCl_3$); UV (MeOH) λ_{max} nm: 290, 252, 206; IR (ATR) ν_{max} cm^{-1}: 3211, 2956, 2094 (N_3), 1712 (CONH), 1617, 1469, 1248, 743; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.57 (1H, br-s), 7.32 (1H, br-dd, *J* = 7.7, 7.7), 7.30 (1H, d, *J* = 7.0), 7.09-7.03 (2H, overlapped), 6.95 (1H, d, *J* = 7.5), 6.71 (1H, dd, *J* = 7.1, 7.1), 6.61 (1H, dd, *J* = 6.9, 6.9), 5.67 (1H, d, *J* = 8.2), 4.06 (1H, br-ddd, *J* = 9.5, 9.5, 9.5), 3.82 (1H, ddd, *J* = 8.2, 8.2, 5.0), 3.30 (2H, m), 2.98 (2H, overlapped), 2.49 (2H, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.3 (CO), 149.4, 140.0, 131.0, 129.53, 129.48, 127.2, 124.6, 124.4, 123.4, 119.1, 110.7, 108.9, 65.4, 50.2, 46.4, 36.7, 28.0; HR-ESI-MS calcd for $C_{18}H_{17}ON_5Na$ $[M+Na]^+$: 342.1325, Found: 342.1317.



15 **16**

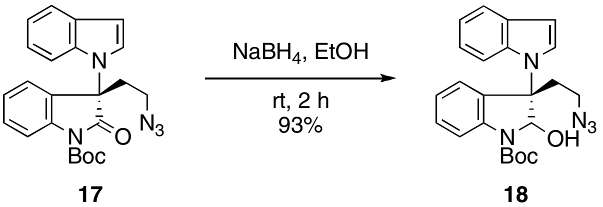
Indole 16: To a stirred solution of **15** (863.1 mg, 2.7 mmol) in dry 1,4-dioxane (42.0 mL) was added DDQ (635.0 mg, 4.0 mmol) at 0 °C under Ar atmosphere. After stirring for 30 min at room temperature, the reaction mixture was evaporated and purified by amino-silica gel open column chromatography (ethyl acetate/*n*-hexane = 90:10) to afford 887.1 mg (quant) of 16 as a colorless amorphous. $[\alpha]_D^{24}$ –39.4 (*c* 1.00, $CHCl_3$); UV (MeOH) λ_{max} nm: 290, 259, 210; IR (ATR) ν_{max} cm^{-1}: 3218, 2920, 2096 (N_3), 1719 (CONH), 1618, 1470, 1455, 1208, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.04 (1H, br-s, NH), 7.59 (1H, d, *J* = 7.9), 7.51 (1H, d, *J* = 3.5), 7.35 (1H, br-ddd, *J* = 7.6, 7.6, 1.6), 7.10-7.02 (3H, overlapped), 6.94 (1H, d, *J* = 7.9), 6.90 (1H, ddd, *J* = 8.4, 7.1, 1.2), 6.65 (1H, dd, *J* = 3.5, 0.7), 6.60 (1H, dd, *J* = 8.5, 0.8), 3.40-3.27 (2H, overlapped), 2.98 (1H, ddd, *J* = 12.0, 8.9, 6.8), 2.77 (1H, ddd, *J* = 13.0, 8.8, 5.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 176.6 (CO), 140.0, 135.5, 130.4, 129.8, 128.2, 125.0, 124.3, 123.8, 122.2, 121.2, 120.2, 111.1, 111.0, 103.1, 65.4, 46.1, 36.1; HR-ESI-MS calcd for $C_{18}H_{15}ON_5Na$ $[M+Na]^+$: 340.1169, found: 340.1158.



16 **17**

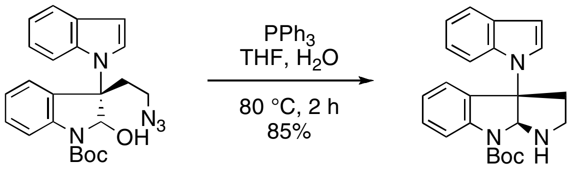
Oxindole 17: To a stirred solution of **16** (490.8 mg, 1.55 mmol) in dry CH_3CN (15.0 mL) were added DMAP (196.1 mg, 1.7 mmol) and $(Boc)_2O$ (353.0 mg, 1.7 mmol) at 0 °C. After stirring for 20 min at room temperature, the reaction mixture was evaporated and purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 40:60) to afford 572.5 mg (89%) of **17** as a colorless amorphous. $[\alpha]_D^{24}$ –34.6 (*c* 1.20, $CHCl_3$); UV (MeOH) λ_{max} nm: 290, 268, 217; IR (ATR) ν_{max} cm^{-1}: 2959, 2918, 2094 (N_3), 1772, 1734, 1286, 1250, 1147, 772, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.09 (1H, d, *J* = 8.2), 7.57 (1H, br-ddd, *J* = 7.8, 0.9, 0.9), 7.49 (1H, ddd, *J* = 8.3, 7.9, 1.4), 7.44 (1H, d, *J* = 3.5), 7.20 (1H, ddd, *J* = 7.5, 7.5, 0.9), 7.14 (1H, br-dd, *J* = 7.6, 1.5), 7.03 (1H, ddd, *J* = 7.9, 7.1, 0.9), 6.91 (1H, ddd, *J* = 8.5, 7.1, 1.2), 6.61 (1H, dd, *J* = 3.5, 0.9), 6.45 (1H, br-dd, *J*

= 8.4, 0.7), 3.34 (1H, ddd, *J* = 12.6, 8.1, 4.7), 3.19 (1H, ddd, *J* = 12.6, 7.8, 7.8), 3.01 (1H, ddd, *J* = 13.2, 8.0, 8.0), 2.72 (1H, ddd, *J* = 13.1, 8.0, 5.0), 1.62 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.5, 148.9 (CO), 139.6, 135.5, 130.7, 129.9, 126.5, 125.5, 125.1, 124.1, 122.2, 121.2, 120.3, 116.0, 111.2, 103.3, 85.2 ($\underline{C}(CH_3)_3$), 65.3, 46.1, 37.0, 28.0; HR-ESI-MS calcd for $C_{23}H_{23}O_3N_5Na$ $[M+Na]^+$: 440.1693, found: 440.1678.



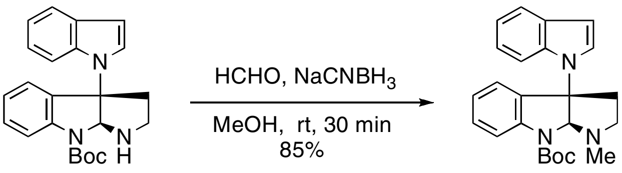
17 **18**

Hemiaminal 18: To a stirred solution of **17** (569.1 mg, 1.36 mmol) in dry EtOH (31.9 mL) was added $NaBH_4$ (150.0 mg, 4.1 mmol) at 0 °C. After stirring for 2 h at room temperature, H_2O was added at 0 °C and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 20:80) to afford 531.1 mg (93%) of **18** as a colorless amorphous. $[\alpha]_D^{24}$ –84.2 (*c* 2.01, $CHCl_3$); UV (MeOH) λ_{max} nm: 291, 281, 240, 222, 205; IR (ATR) ν_{max} cm^{-1}: 3441 (OH), 2977, 2935, 2094 (N_3), 1678, 1604, 1484, 1454, 1368, 1289, 1254, 1225, 1158, 739; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.63 (1H, m), 7.44 (1H, dd, *J* = 7.8, 7.8), 7.39-7.29 (2H, overlapped), 7.18-7.11 (3H, overlapped), 7.00 (1H, d, *J* = 3.3), 6.43 (1H, d, *J* = 3.5), 6.12 (1H, br-s), 3.62 (1H, ddd, *J* = 11.5, 11.5, 5.1), 3.24 (1H, ddd, *J* = 13.7, 10.4, 5.1), 2.89 (1H, ddd, *J* = 12.0, 10.5, 5.0), 2.58 (1H, ddd, *J* = 13.7, 10.9, 5.0), 1.58 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 141.0, 134.6, 130.8, 130.5, 127.9, 126.0, 125.8, 123.3, 121.8, 121.5, 120.0, 115.3, 112.2, 101.5, 90.2, 83.5, 68.6, 47.4, 34.1, 28.4; HR-ESI-MS calcd for $C_{23}H_{25}O_3N_5Na$ $[M+Na]^+$: 442.1850, found: 442.1829.



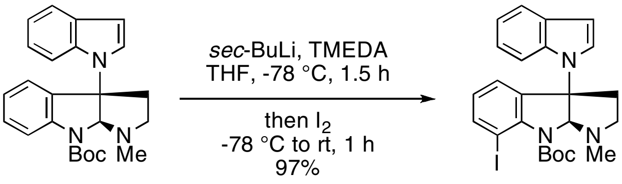
18 **19**

Pyrrolidinoindoline 19: To a stirred solution of **18** (188.1 mg, 0.45 mmol) in THF (3.8 mL) and H_2O (0.6 mL) was added PPh_3 (150.0 mg, 0.56 mmol) and the mixture was stirred for 2 h at 80 °C. The reaction mixture was evaporated and purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 20:80) to afford 143.0 mg (85%) of **19** as a colorless oil. $[\alpha]_D^{24}$ –11.2 (*c* 0.26, $CHCl_3$); UV (MeOH) λ_{max} nm: 291, 281, 240, 220, 204; IR (ATR) ν_{max} cm^{-1}: 3372, 2976, 1694, 1482, 1456, 1367, 1316, 1249, 1157, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.94 (1H, br-s), 7.61 (1H, m), 7.36-7.29 (3H, overlapped), 7.19 (1H, br-d, *J* = 7.3), 7.09 (2H, overlapped), 7.01 (1H, dd, *J* = 7.6, 7.6), 6.48 (1H, d, *J* = 3.2), 5.87 (1H, br-s), 3.32-3.20 (2H, overlapped), 2.94 (1H, m), 2.43 (1H, dd, *J* = 11.5, 4.6), 1.56 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 143.3 (CO), 135.2, 130.3, 130.1, 126.1, 124.9, 123.2, 121.7, 121.2, 119.8, 114.6, 111.8, 101.3, 82.9, 81.8, 73.7, 44.2, 39.9, 28.5; HR-ESI-MS calcd for $C_{23}H_{25}O_2N_3Na$ $[M+Na]^+$: 398.1839, Found: 398.1823.



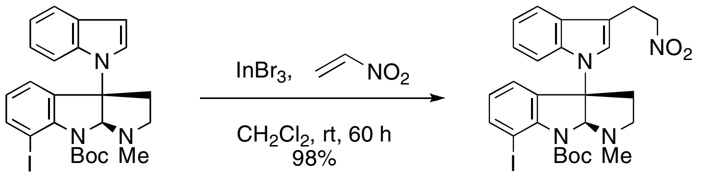
19 **2**

Pyrrolidinoindoline 2: To a stirred solution of **19** (271.4 mg, 0.72 mmol) in MeOH (12.0 mL) were added HCHO (105 μL, 0.94 mmol) and $NaBH_3CN$ (130.5 mg, 1.4 mmol) at 0 °C and the mixture was stirred for 30 min at room temperature. The reaction mixture was evaporated and purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 20:80) to afford 239.3 mg (85%) of **2** as a white solid. Enantiomeric excess was increased to 99% ee by recrystallization from MeOH. mp 119-123 °C (MeOH); $[\alpha]_D^{24}$ –48.6 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max} nm: 291, 281, 243 (sh), 221, 203; IR (ATR) ν_{max} cm^{-1}: 2972, 1701, 1483, 1457, 1388, 1308, 1222, 1164, 739, 716; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.84 (1H, br-s), 7.60 (1H, m), 7.37 (1H, m), 7.33 (1H, br-dd, *J* = 8.4, 8.4), 7.25 (1H, overlapped), 7.19 (1H, br-d, *J* = 3.3), 7.13-7.04 (3H, overlapped), 6.44 (1H, d, *J* = 3.3), 5.82 (1H, s, N-CH-N), 3.25 (1H, ddd *J* = 11.7, 10.2, 6.8), 3.05 (1H, ddd, *J* = 9.1, 7.0, 1.9), 2.64 (3H, s), 2.59 (1H, overlapped), 2.39 (1H, ddd, *J* = 11.8, 4.9, 1.9), 1.54 (9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.0 (CO), 143.6, 135.2, 131.3, 130.2, 130.0, 126.2, 124.9, 123.4, 121.7, 121.1, 119.8, 116.5, 111.8, 101.1, 85.7, 81.9 ($\underline{C}(CH_3)_3$), 74.2, 52.6, 37.7, 36.7 (*N*-CH_3), 28.3 ($C(\underline{C}H_3)_3$); HR-ESI-MS calcd for $C_{24}H_{27}O_2N_3Na$ $[M+Na]^+$: 412.1995. found: 412.1980; HPLC (column; CHIRALPAK IB, eluent; *n*-hexane/EtOH= 85:15, flow late; 0.5 mL/min, temperature; 30 °C, retention time; 17.53 min).



2 **20**

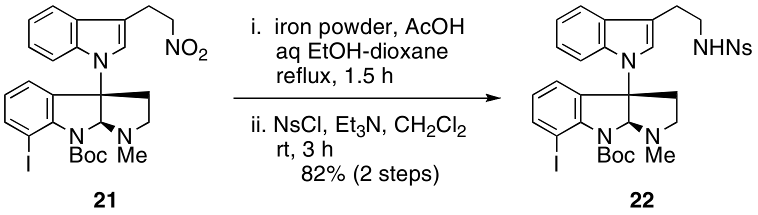
Iodide 20: To a stirred solution of **2** (136.7 mg, 0.35 mmol) and TMEDA (0.32 mL, 2.1 mmol) in dry THF (4.0 mL) was added dropwise *sec*-BuLi (1.40 mL, 1.40 mmol, 1.0M solution in cyclohexane) at –78 °C. After 1.5 h, a solution of I_2 (0.33 g, 1.43 mmol) in dry THF (4.0 mL) was added to the above mixture. The reaction mixture was stirred for 15 min at –78 °C and stirred for 1 h at room temperature. The reaction was quenched by adding a mixture of sat. $Na_2S_2O_3$ aq and sat. $NaHCO_3$ aq (1:1). The whole mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 30:70) to afford 174.9 mg (97%) of **20** as a pale yellow amorphous. $[\alpha]_D^{24}$ +170.7 (*c* 0.36, $CHCl_3$); UV (MeOH) λ_{max} nm: 292, 284, 220; IR (ATR) ν_{max} cm^{-1}: 2975, 2801, 1706 (CO), 1151, 737; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.81 (1H, dd, J = 8.0, 0.8), 7.60 (1H, m), 7.26-7.22 (2H, overlapped), 7.17 (1H, m), 7.11-7.06 (2H, overlapped), 6.87 (1H, dd, J = 7.7, 7.7), 6.48 (1H, br-d, J = 3.4), 5.52 (1H, s), 3.24 (1H, ddd, J = 12.1, 8.6, 6.8), 3.02 (1H, ddd, J = 9.4, 6.6, 3.0), 2.62 (3H, s, N_1-CH_3), 2.54 (1H, ddd, J = 8.9, 8.9, 5.4), 2.34 (1H, ddd, J = 12.1, 5.3, 3.2), 1.45 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.6 (CO), 146.2, 140.7, 136.7, 135.4, 130.2, 126.6, 126.1, 124.5, 121.9, 121.1, 119.9, 111.6, 101.7, 89.0, 85.5, 82.4 ($\underline{C}(CH_3)_3$), 74.4, 51.9, 37.5, 36.7 (N-CH_3), 28.1 ($C(\underline{C}H_3)_3$); HR-ESI-MS calcd for $C_{24}H_{26}O_2N_3INa$ $[M+Na]^+$: 538.0962, found: 538.0951.



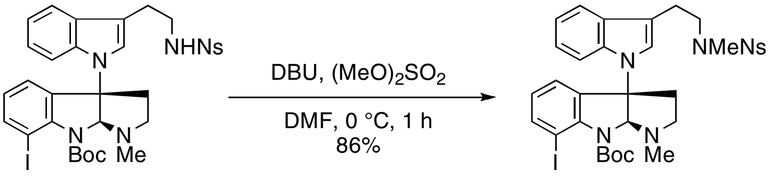
20 **21**

Michael adduct 21: To a stirred solution of **20** (165.0 mg, 0.28 mmol) and $InBr_3$ (45.5 mg, 0.11 mmol) in dry CH_2Cl_2 (8.3 mL) was added dropwise nitroethylene (0.63 mL, 0.63 mmol, 1M solution in benzene) at 0 °C and the mixture was stirred for 60 h at room temperature under Ar atmosphere. The reaction was quenched by adding sat. $NaHCO_3$ aq, and the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 30:70) to afford 184.9 mg (98%) of **21** as a pale yellow amorphous. $[\alpha]_D^{24}$ +140.9 (*c* 0.49, $CHCl_3$); UV (MeOH) λ_{max} nm: 294, 286, 222; IR (ATR) ν_{max} cm^{-1}: 2973, 1701 (CO), 1542 (NO_2), 1454, 1354, 1248, 1161, 735; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.82 (1H, dd, J = 7.9, 1.1), 7.53 (1H, m), 7.19 (1H, dd, J = 7.6, 1.2), 7.16-7.10 (4H, overlapped), 6.88 (1H, dd, J = 7.8, 7.8), 5.48 (1H, s), 4.62 (2H, dd, J = 7.3, 7.3, $CH_2C\underline{H_2}NO_2$), 3.43 (2H, dd, J = 7.2, 7.2, $C\underline{H_2}CH_2NO_2$), 3.18 (1H, ddd, J = 12.1, 8.5, 6.7), 3.00 (1H, ddd, J = 9.3, 6.5, 2.9), 2.61 (3H, s, N_1-CH_3), 2.51 (1H, ddd, J = 9.0, 9.0, 5.3), 2.31 (1H, br-ddd, J = 12.1, 5.2, 3.0), 1.45 (9H, s, $C(CH_3)_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.3 (CO), 146.1, 140.8, 136.4, 135.7, 128.9, 126.7, 124.5, 124.4, 122.5, 120.1, 118.5, 112.0, 108.9, 88.9, 85.5, 82.5 ($\underline{C}(CH_3)_3$), 75.6, 74.3, 51.8, 37.6, 36.5 (N_1-CH_3), 28.1

(C(C̲H$_3$)$_3$), 23.5 (C̲H$_2$CH$_2$NO$_2$); HR-ESI-MS calcd for $C_{26}H_{29}O_4N_4INa$ [M+Na]$^+$: 611.1126, found: 611.1118.

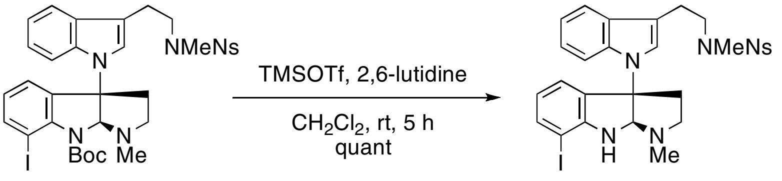


Nosyl amide 22: To a stirred solution of **21** (174.0 mg, 0.29 mmol) in 70% EtOH aq (8.6 mL) and 1,4-dioxane (5.6 mL) were successively added AcOH (0.3 mL, 4.06 mmol) and iron powder (138.0 mg, 2.03 mmol) at 0 °C, and the mixture was refluxed for 1.5 h under Ar atmosphere. The reaction mixture was cooled to room temperature and basified with concentrated NH_4OH. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20% MeOH/$CHCl_3$ and the aqueous layer was extracted three times with 20% MeOH/$CHCl_3$. The combined organic layers were dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without purification. To a stirred solution of the above crude product in dry CH_2Cl_2 (3.5 mL) were added Et_3N (72.3 μL, 0.43 mmol) and *o*-NsCl (92.0 mg, 0.35 mmol) at room temperature and the reaction mixture was stirred for 3 h at room temperature under Ar atmosphere. The reaction was quenched by adding sat. Na_2CO_3 aq and the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 50:50) to afford 180.8 mg (82%, 2 steps) of **22** as a pale yellow amorphous. $[\alpha]_D^{24}$ +102.4 (*c* 0.79, $CHCl_3$); UV (MeOH) λ_{max} nm: 291, 284, 220; IR (ATR) ν_{max} cm^{-1}: 2978, 1709 (CO), 1537 (NO_2), 1455, 1336 (SO_2), 1245, 1154 (SO_2), 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.06 (1H, br-d, 7.4), 7.82 (1H, dd, 7.9, 1.1), 7.66-7.56 (3H, overlapped), 7.29 (1H, dd, *J* = 7.5, 1.1), 7.26 (1H, d, *J* = 8.2), 7.08 (2H, overlapped), 7.02 (1H, ddd, *J* = 7.7, 7.7, 1.2), 6.90 (2H, overlapped), 5.45 (1H, s), 5.36 (1H, br-dd, *J* = 5.3, 5.3), 3.40 (2H, br-ddd, *J* = 6.2, 6.2, 6.2), 3.15 (1H, ddd, *J* = 12.0, 8.7, 6.7), 3.02-2.88 (3H, overlapped), 2.61 (3H, s), 2.49 (1H, ddd, *J* = 9.1, 9.1, 5.2), 2.31 (1H, br-ddd, *J* = 12.0, 5.1, 2.8), 1.44 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.6 (CO), 147.4, 146.1, 140.8, 136.4, 135.9, 133.3, 132.6, 130.9, 128.8, 126.7, 125.4, 124.8, 124.7, 122.1, 119.6, 118.5, 111.9, 109.9, 88.9, 85.3, 82.4 (C̲(CH$_3$)$_3$), 74.3, 51.8, 43.4, 37.5, 36.5 (N_1-CH$_3$), 28.1 (C(C̲H$_3$)$_3$), 25.3 (C̲H$_2$CH$_2$NHNs); HR-ESI-MS calcd for $C_{32}H_{34}O_6N_5INaS$ [M+Na]$^+$: 766.1167, found: 766.1157.



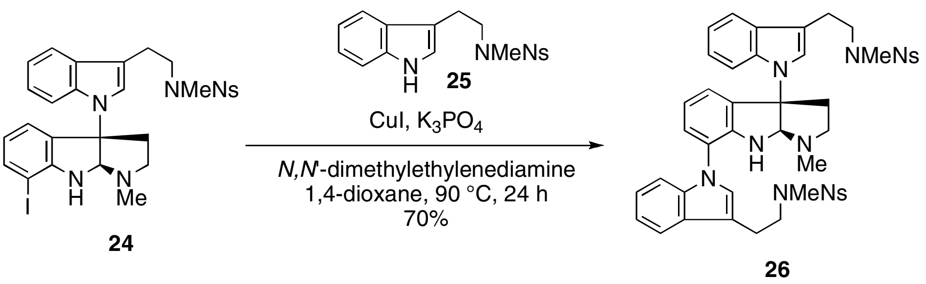
22 **23**

Nosyl amide 23: To a stirred solution of **22** (94.4 mg, 0.13 mmol) in dry DMF (1.2 mL) were successively added DBU (61.2 ʃL, 0.39 mmol) and dimethylsulfate (37.6 ʃL, 0.39 mmol) at 0 °C, and the mixture was stirred for 1 h at the same temperature under Ar atmosphere. The reaction was quenched by adding 5% $NaHCO_3$ aq and the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 45:55) to afford 82.7 mg (86%) of **23** as a pale yellow amorphous. $[\alpha]_D^{24}$ +43.4 (*c* 0.63, $CHCl_3$); UV (MeOH) λ_{max} nm: 295 (sh), 286, 222; IR (ATR) ν_{max} cm^{-1}: 2926, 1701 (CO), 1542 (NO_2), 1339 (SO_2), 1155, 738; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.93 (1H, m), 7.81 (1H, dd, *J* = 7.9, 0.9), 7.65-7.52 (4H, overlapped), 7.21 (1H, dd, *J* = 7.5, 0.9), 7.13 (1H, s), 7.11-7.08 (3H, overlapped), 6.87 (1H, dd, *J* = 7.7, 7.7), 5.47 (1H, s), 3.51 (2H, m), 3.18 (1H, m), 3.04-2.96 (3H, overlapped), 2.96 (3H, s), 2.61 (3H, s), 2.51 (1H, ddd, *J* = 8.9, 8.9, 5.2), 2.31 (1H, *J* = 12.0, 5.1, 3.1), 1.46 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.6 (CO), 148.0, 146.0, 140.7, 136.6, 135.7, 133.3, 132.6, 131.5, 130.7, 129.4, 126.7, 124.5, 124.3, 124.0, 122.2, 119.7, 118.8, 111.7, 110.9, 88.9, 85.4, 82.4 ($\underline{C}(CH_3)_3$), 74.3, 51.8, 50.5, 37.7, 36.6 (N_1-CH_3), 34.7 ($N(Ns)\underline{C}H_3$), 28.1 ($C(\underline{C}H_3)_3$), 24.2 ($\underline{C}H_2CH_2NMeNs$); HR-ESI-MS calcd for $C_{33}H_{36}O_6N_5INaS$ $[M+Na]^+$: 780.1323, found: 780.1320.

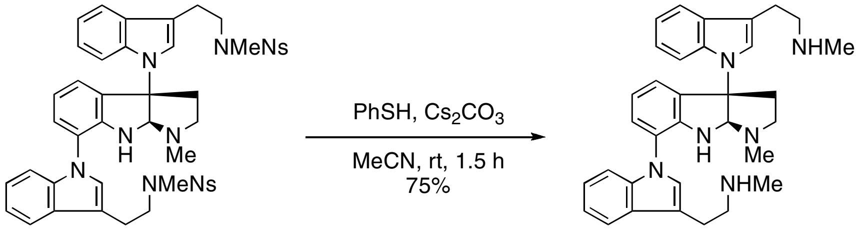


23 **24**

Nosyl amide 24: To a stirred solution of **23** (82.7 mg, 0.11 mmol) in dry CH_2Cl_2 (1.8 mL) were successively added 2,6-lutidine (0.31 mL, 2.66 mmol) and trimethylsilyl trifluoromethanesulfonate (0.26 mL, 1.46 mmol) at 0 °C and the reaction mixture was stirred for 5 h at room temperature under Ar atmosphere. The reaction was quenched by adding sat. Na_2CO_3 aq and the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 50:50) to afford 71.8 mg (quant) of **24** as a pale yellow amorphous. $[\alpha]_D^{24}$ +10.1 (*c* 0.55, $CHCl_3$); UV (MeOH) λ_{max} nm: 296, 289, 218; IR (ATR) ν_{max} cm^{-1}: 3377 (NH), 2924, 2850, 1541 (NO_2), 1340 (SO_2), 1159 (SO_2), 734; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.92 (1H, d, *J* = 7.9), 7.64-7.51 (4H, overlapped), 7.47 (1H, d, *J* = 7.9), 7.28 (1H, m), 7.22 (1H, s), 7.07 (2H, m), 6.98 (1H, d, *J* = 7.5), 6.46 (1H, dd, *J* = 7.5, 7.5), 5.26 (1H, d, *J* = 2.2), 4.58 (1H, br-s), 3.52 (2H, m), 3.18 (1H, m), 3.03 (3H, m), 2.97 (3H, s), 2.68 (1H, br-ddd, *J* = 9.6, 9.6, 5.1), 2.52 (3H, s), 2.39 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.7, 148.0, 138.0, 135.7, 133.2, 132.6, 131.4, 130.7, 129.6, 129.3, 124.4, 124.2, 124.0, 121.8, 120.6, 119.5, 118.8, 112.0, 110.5, 84.8, 78.0, 75.0, 51.4, 50.6, 39.2, 36.0 (N_1-CH_3), 34.7 (N(Ns)$\underline{C}H_3$), 24.2 ($\underline{C}H_2CH_2$NMeNs); HR-ESI-MS calcd for $C_{28}H_{29}O_4N_5IS$ $[M+H]^+$:658.0979, found: 658.0972.



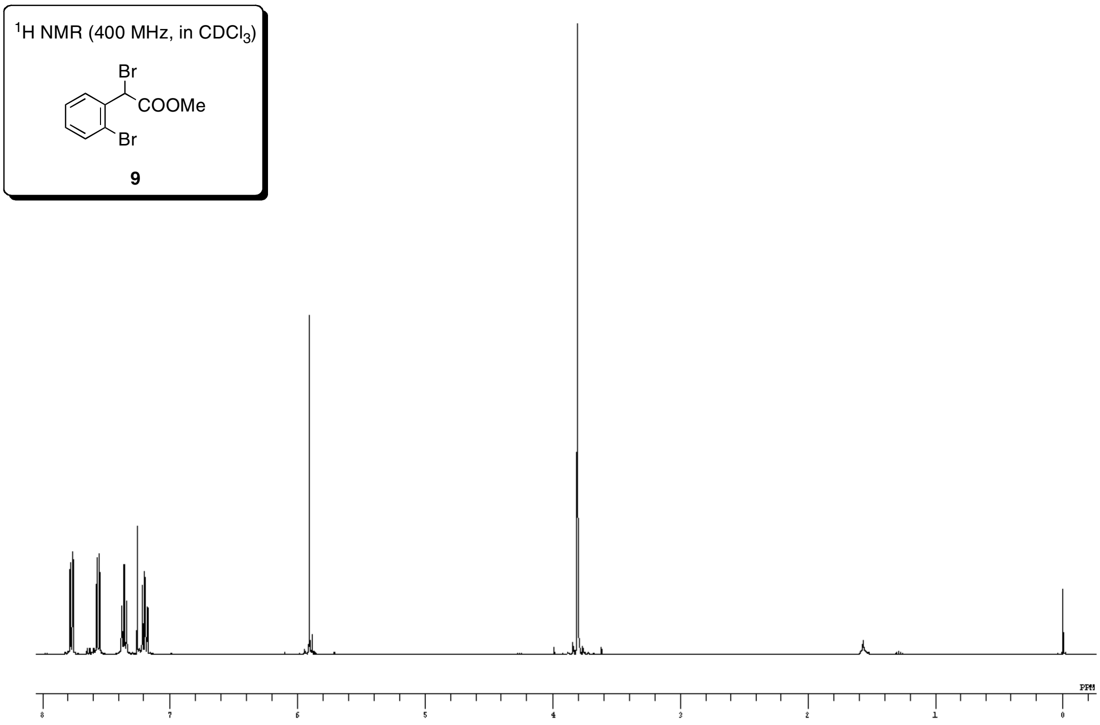
Trimer 26: A 10 mL test tube was charged with nosyl amide **24** (52.6 mg, 0.080 mmol), tryptamine derivative **25** (29.2 mg, 0.081 mmol), copper (I) iodide (13.2 mg, 0.069 mmol), and K_3PO_4 (29.5 mg, 0.138 mmol). The test tube was fitted with a rubber septum, evacuated and then backfilled with Ar. *N,N'*-Dimethylethylenediamine (15.0 μL, 0.138 mmol) and degassed dry 1,4-dioxane (0.5 mL) was added to the test tube and the resulting pale blue suspension was warmed to 90 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through a short pad of silica gel (eluent: ethyl acetate). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 70:30) to afford 49.8 mg (70%) of **26** as a pale yellow oil. $[\alpha]_D^{24}$ +109.9 (*c* 0.19, $CHCl_3$); UV (MeOH) λ_{max} nm: 289, 221; IR (ATR) ν_{max} cm^{-1}: 3394 (NH), 2918, 1541, 1457, 1339 (SO_2), 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.94 (1H, dd, *J* = 7.3, 1.8), 7.91 (1H, dd, *J* = 7.9, 1.3), 7.68-7.52 (9H, m), 7.39 (1H, m), 7.28-7.19 (4H, m), 7.17 (1H, dd, *J* = 7.8, 1.0), 7.12-7.05 (3H, m), 6.79 (1H, dd, *J* = 7.7, 7.7), 5.24 (1H, d, *J* = 2.4), 4.50 (1H, br-d, *J* = 2.2), 3.72-3.59 (2H, m), 3.55 (1H, br-ddd, *J* = 7.6, 7.6, 3.6), 3.23 (1H, br-ddd, *J* = 11.0, 11.0, 6.8), 3.17 (2H, dd, *J* = 7.4, 7.4), 3.06 (2H, dd, *J* = 7.5, 7.5), 3.06 (1H, overlapped), 2.99 (3H, s), 2.98 (3H, s), 2.78 (1H, br-ddd, *J* = 9.6, 9.6, 5.2), 2.53 (1H, br-ddd, *J* = 11.7, 4.8, 1.6), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.1, 145.9, 136.0, 135.8, 133.4, 133.2, 132.6, 132.5, 131.6, 131.5, 131.4, 130.8, 130.7, 129.3, 128.1, 127.1, 126.1, 124.4, 124.1, 124.0, 123.7, 122.4, 121.7, 121.0, 120.0, 119.4, 119.1, 118.84, 118.75, 112.7, 112.1, 111.1, 110.4, 85.8, 51.6, 50.6, 39.1, 36.1, 34.7, 34.5, 24.3, 24.0; HR-ESI-MS calcd for $C_{45}H_{45}O_8N_8S_2$ $[M+H]^+$:889.2796, found: 889.2789.



26

psychotrimine (**1**)

Psychotrimine 1: To a stirred solution of **26** (13.9 mg, 0.016 mmol) in dry acetonitrile (0.8 mL) were added Cs_2CO_3 (15.2 mg, 0.048 mmol) and thiophenol (3.6 μL, 0.035 mmol) at 0 °C and the reaction mixture was stirred for 1.5 h at room temperature under Ar atmosphere. The reaction mixture was diluted with $CHCl_3$, filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by amino-silica gel open column chromatography (methanol/ethyl acetate = 20:80) to afford 6.1 mg (75%) of psychotrimine (**1**) as a pale yellow oil. $[\alpha]_D^{24}$ +221.0 (*c* 0.31, $CHCl_3$); UV (MeOH) λ_{max} nm: 295, 222, 205; IR (ATR) ν_{max} cm^{-1}: 3359 (NH), 2926, 2792, 1732, 1603, 1455, 735; ^1H NMR (600 MHz, $CDCl_3$) δ ppm: 7.72 (1H, d, *J* = 8.0), 7.62 (1H, m), 7.38 (1H, m), 7.27 (3H, m), 7.21 (1H, m), 7.20 (1H, s), 7.19 (1H, dd, *J* = 7.7, 0.8), 7.10 (3H, m), 6.81 (1H, dd, *J* = 7.7, 7.7), 5.26 (1H, s), 4.40 (1H, br-s), 3.29 (1H, ddd, *J* = 11.7, 10.0, 6.9), 3.10 (1H, m), 3.08 (2H, m), 3.00 (2H, m), 2.97 (2H, m), 2.93 (2H, m), 2.82 (1H, ddd, *J* = 9.6, 9.6, 5.2), 2.55 (1H, br-ddd, *J* = 12.0, 5.4, 2.2), 2.50 (3H, s), 2.45 (3H, s), 2.43 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 145.8, 136.0, 131.8, 129.6, 128.4, 127.2, 125.9, 124.2, 123.6, 122.3, 121.6, 121.3, 119.8, 119.3, 119.24, 119.20, 114.8, 112.4, 112.0, 111.1, 85.9, 76.6, 51.9, 51.6, 39.0, 36.3, 36.2, 25.6, 25.5; HR-ESI-MS calcd for $C_{33}H_{39}N_6$ $[M+H]^+$: 519.3231, found: 519.3224.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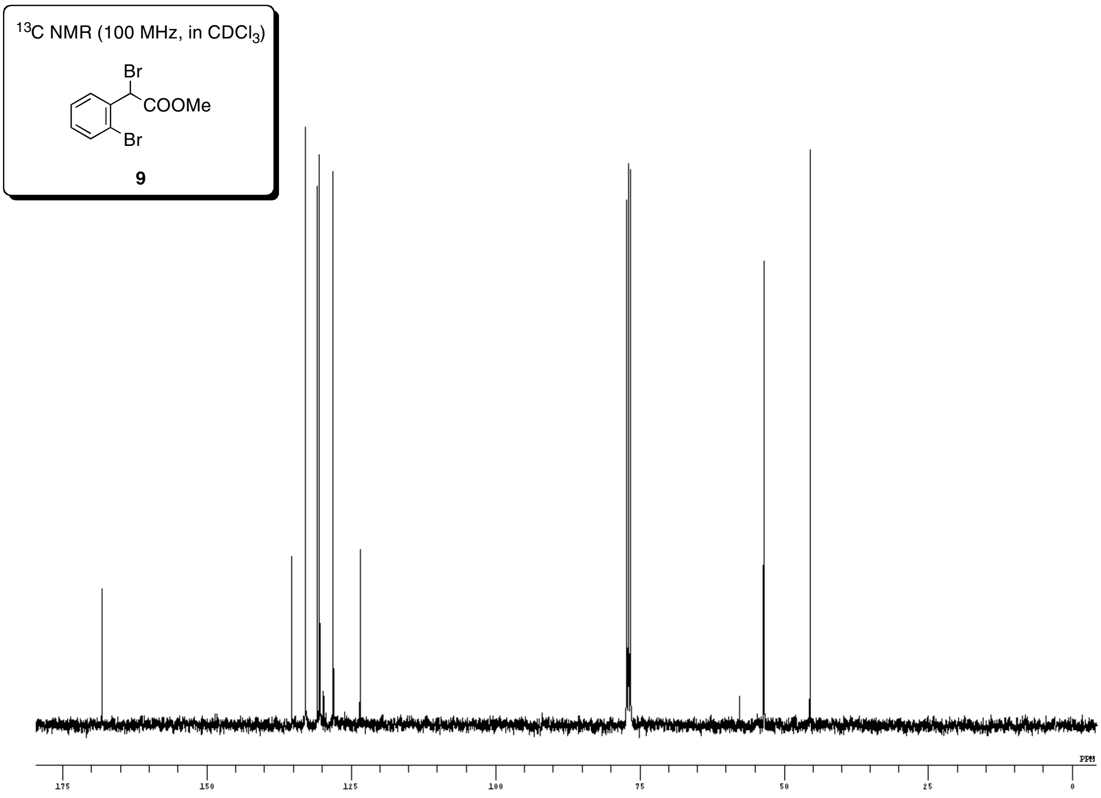
Br
COOMe
Br
9
8
7
6
5
4
3
2
1
0
PPM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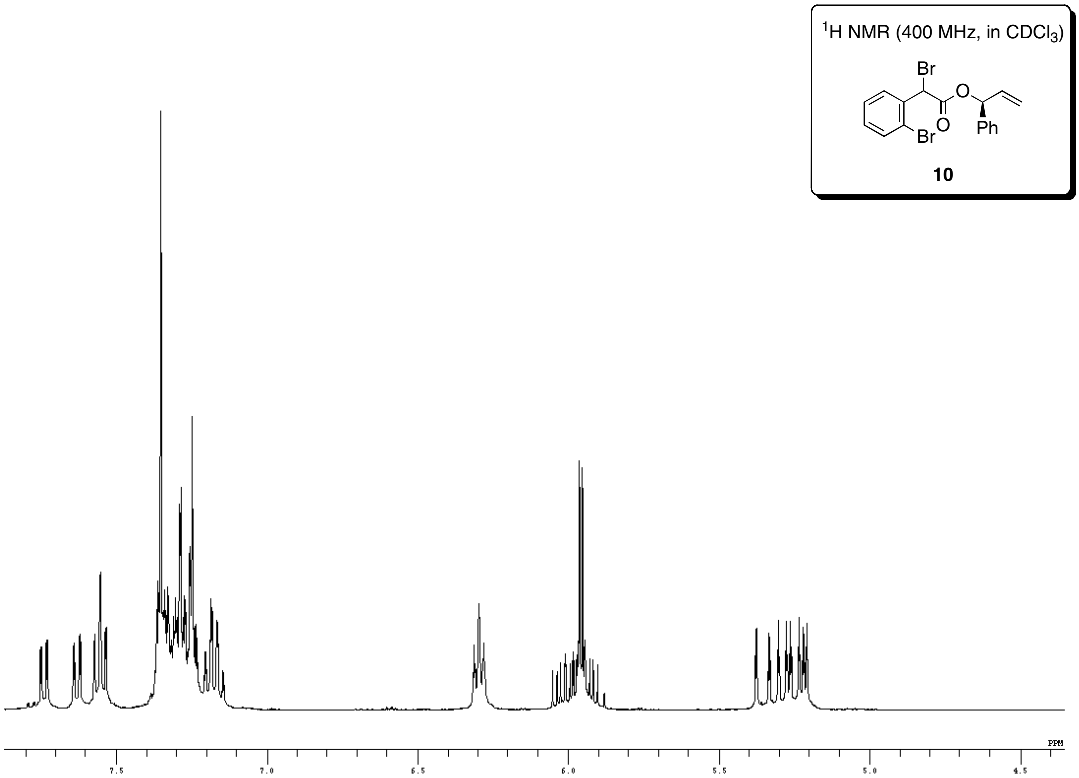
Br
COOMe
Br
9
175
150
125
100
75
50
25
0
PPM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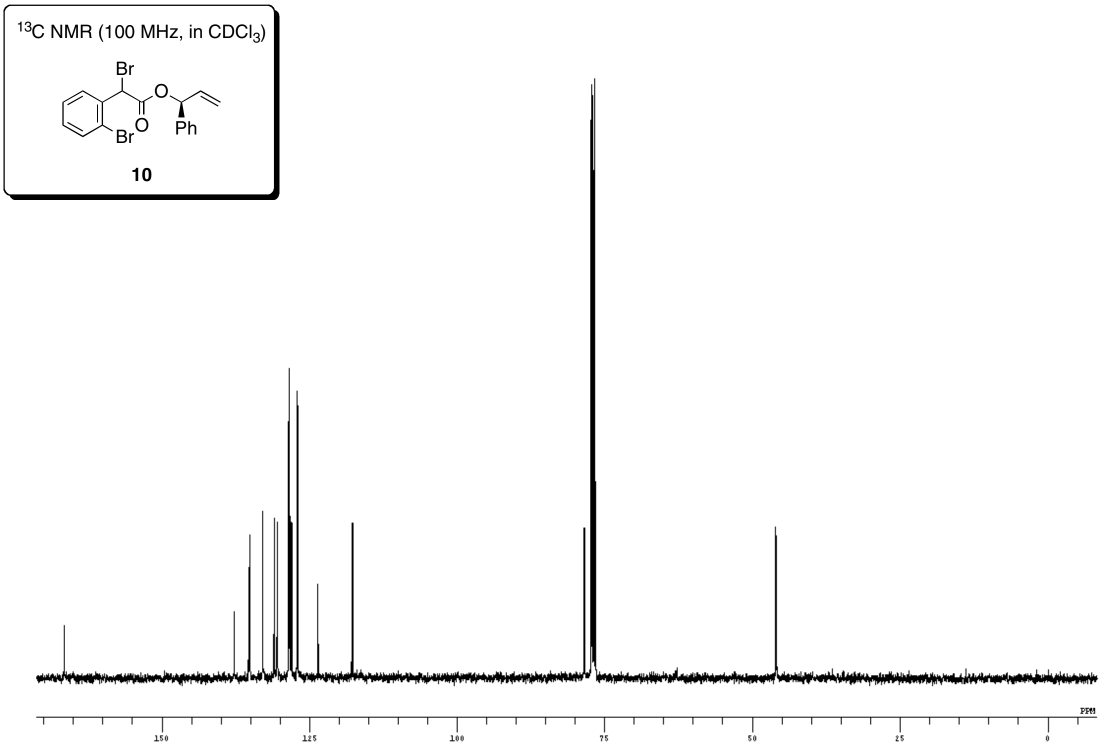
Br
O
O
Br
Ph
10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM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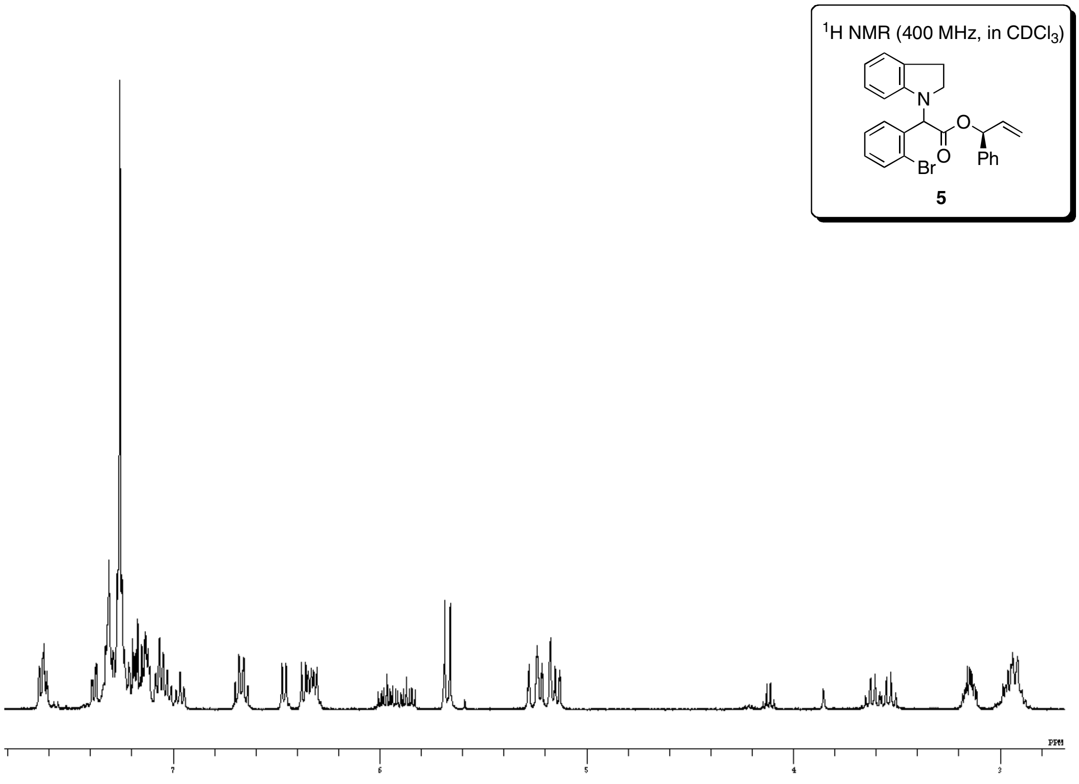
Br
O
O
Br
Ph
10
150
125
100
75
50
25
0
PPM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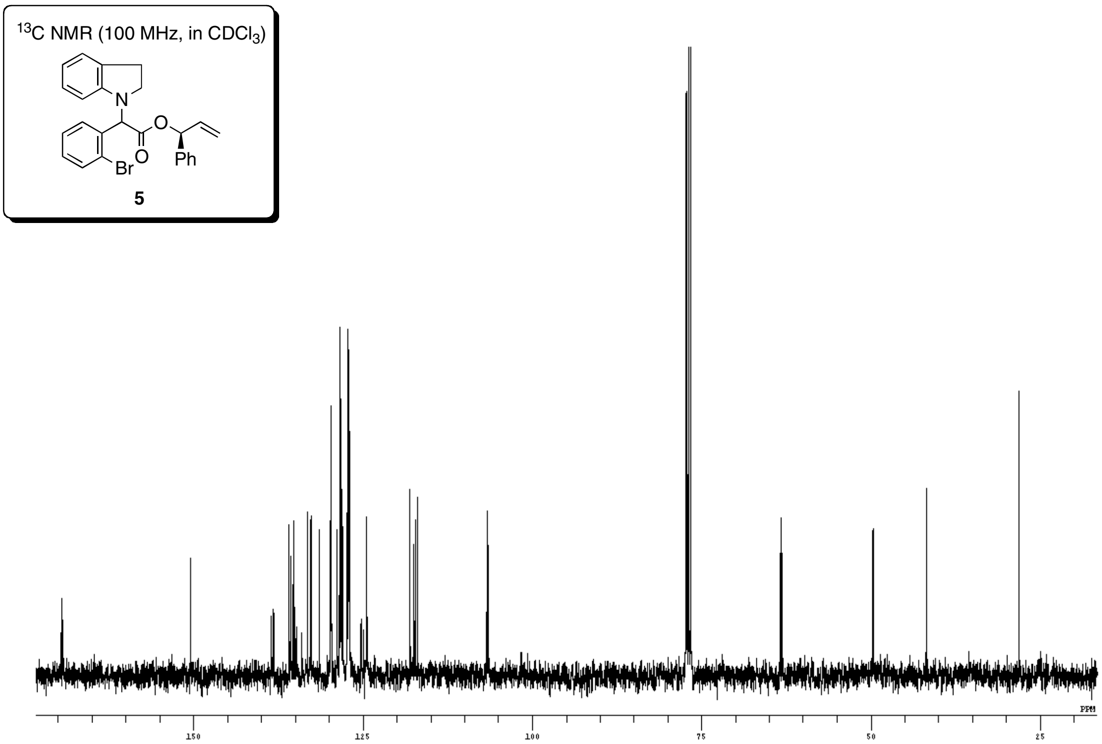
N
O
O
Br
Ph
5
7
6
5
4
3
PPM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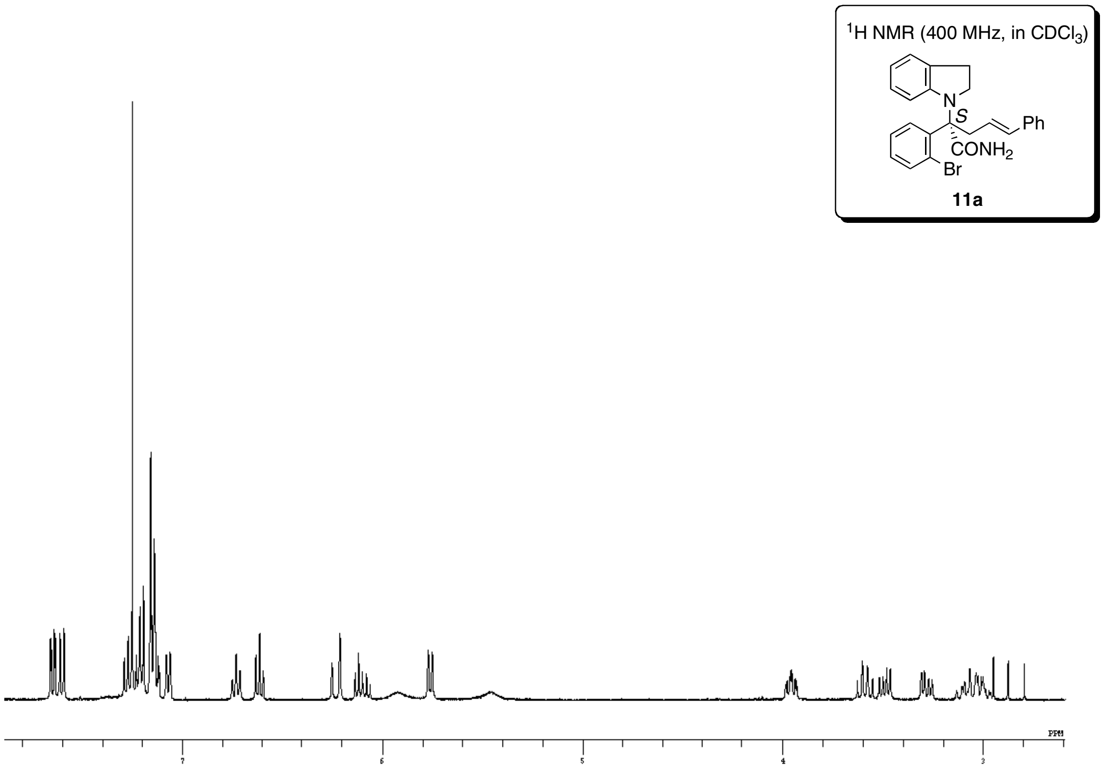
O
O
Br
Ph
5
150
125
100
75
50
25
PPM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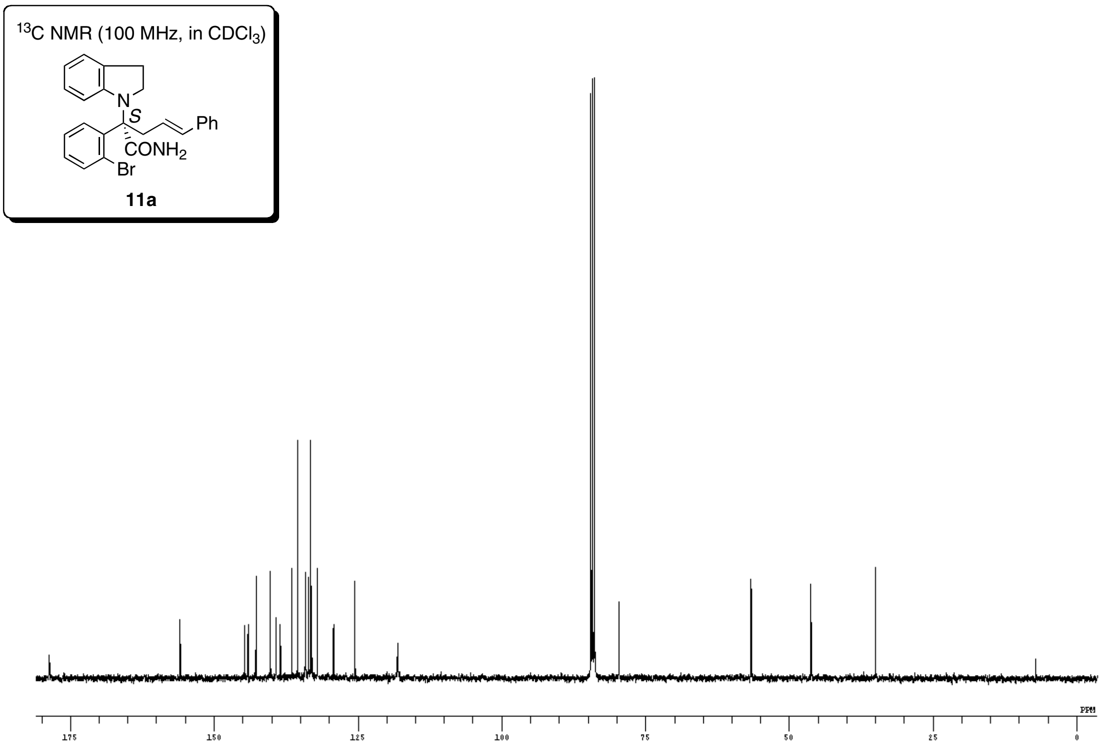
N
S
Ph
CONH$_2$
Br
11a
PPM
7
6
5
4
3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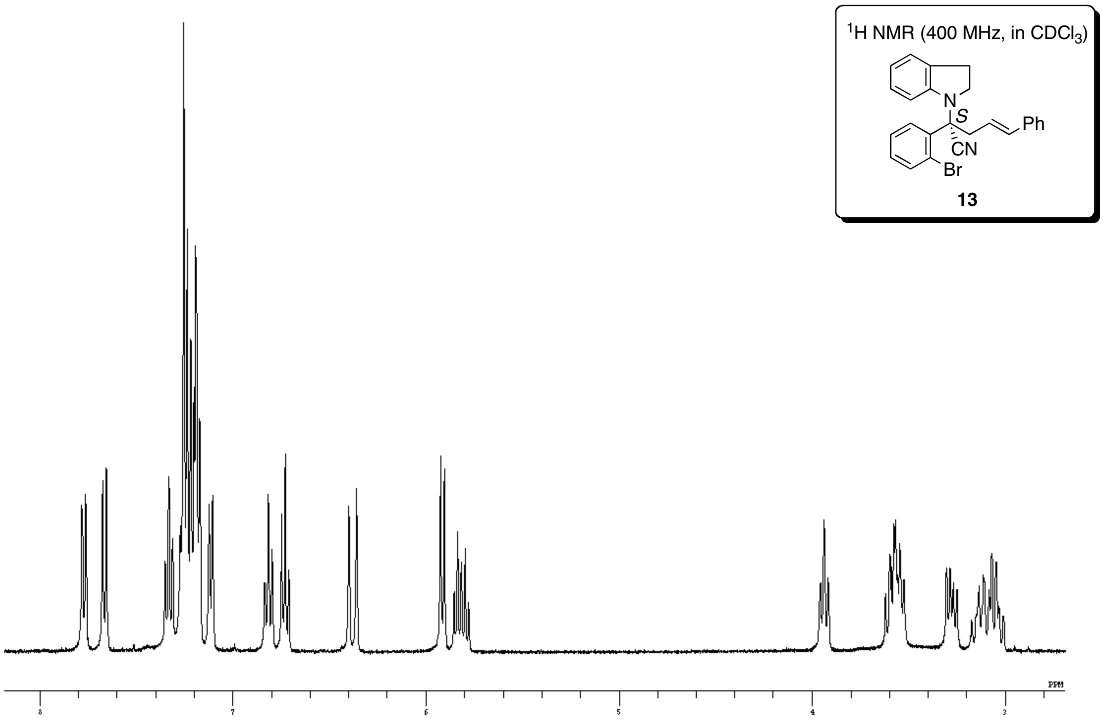
N
S
Ph
CONH$_2$
Br
11a
PPM
175
150
125
100
75
50
25
0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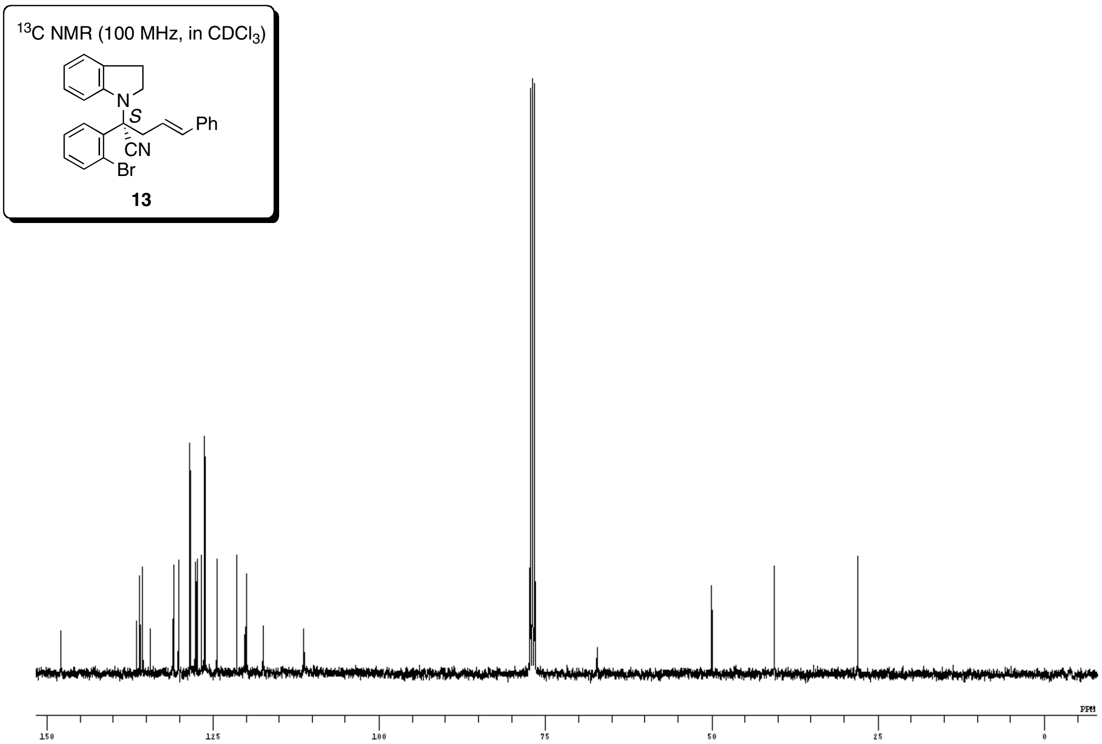
N
S
Ph
CN
Br
13
8
7
6
5
4
2
PPM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S
Ph
CN
Br
13
150
125
100
75
50
25
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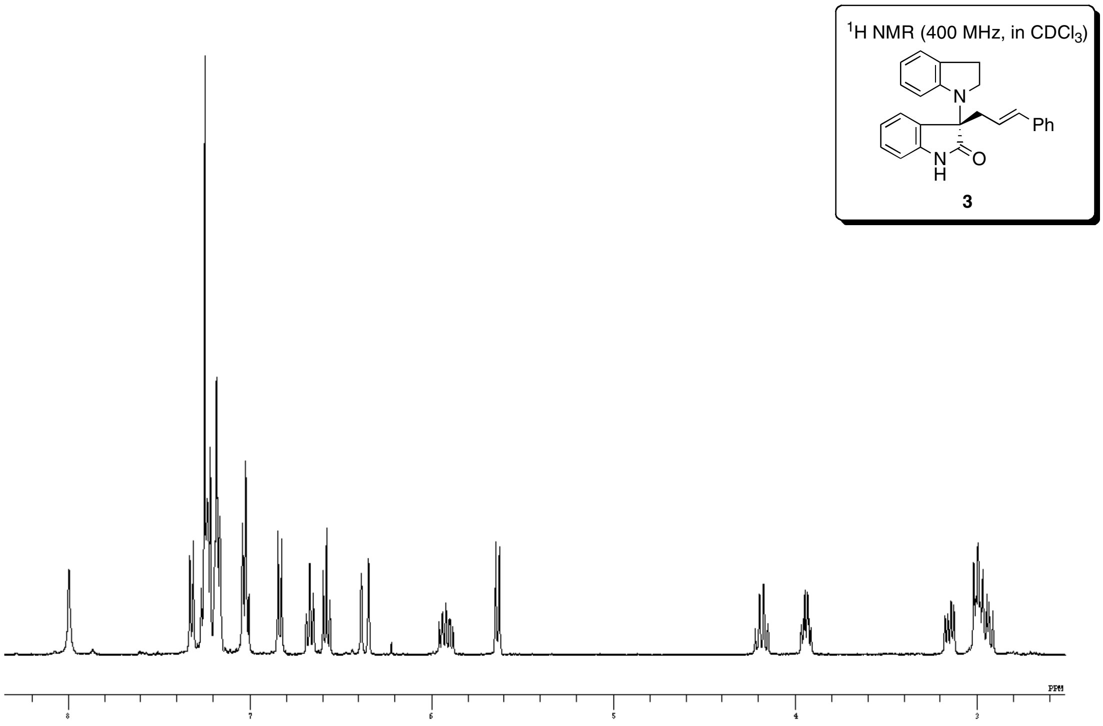
PPM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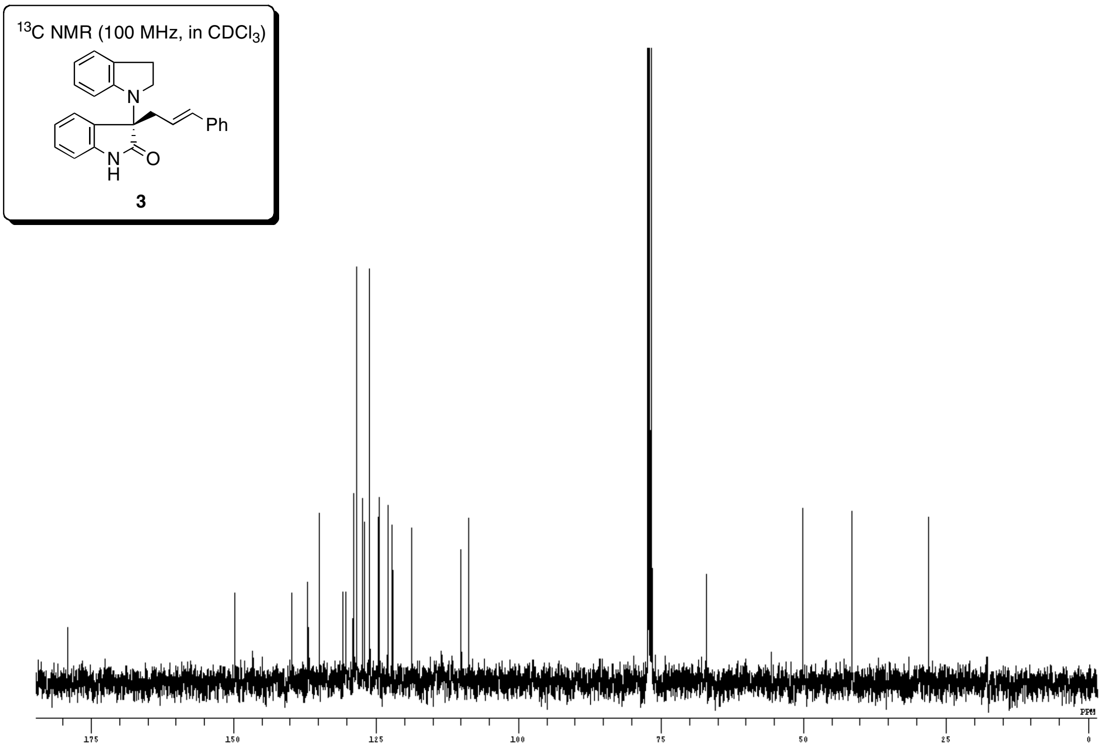
Ph
N
H
O
3
PPM
8
7
6
5
4
3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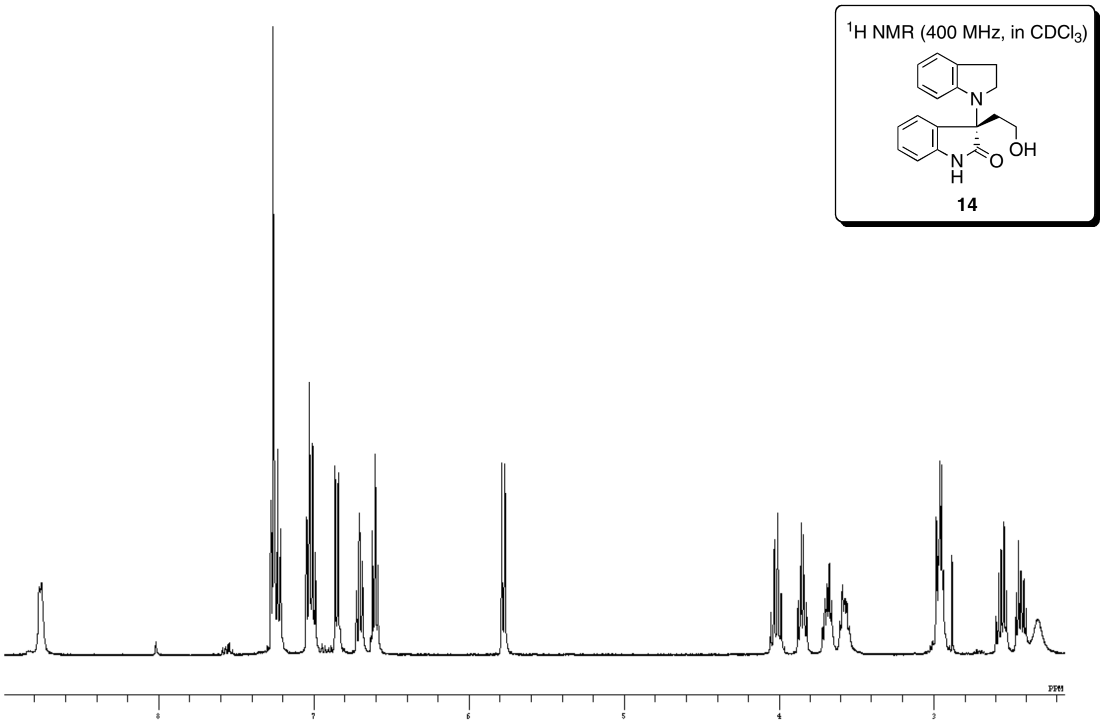
N
Ph
N
H
O
3
PPM
175
150
125
100
75
50
25
0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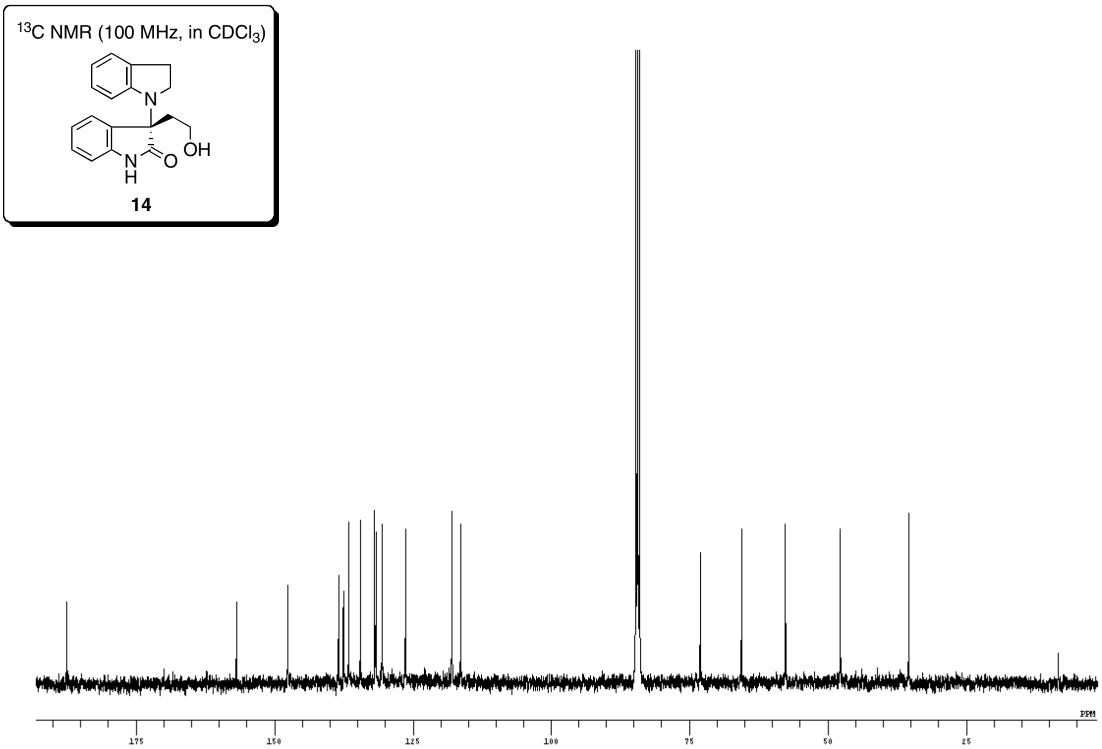
N
N
H
O
OH
14
PPM
8
7
6
5
4
3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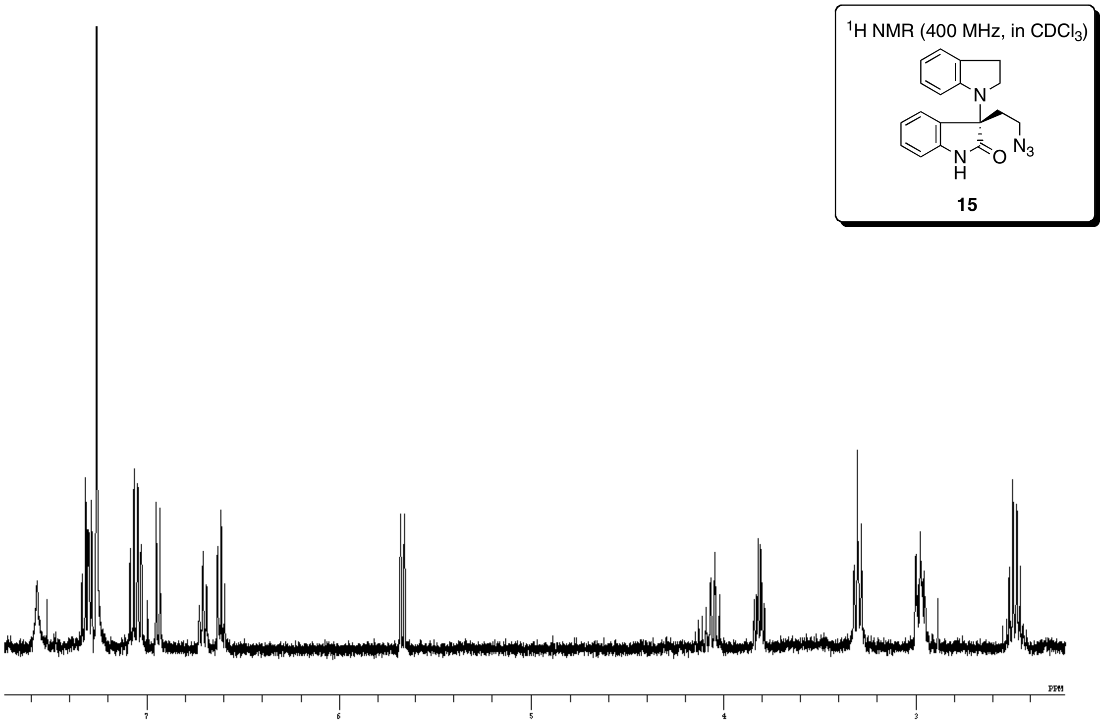
N
H
O
OH
14
PPM
175
150
125
100
75
50
25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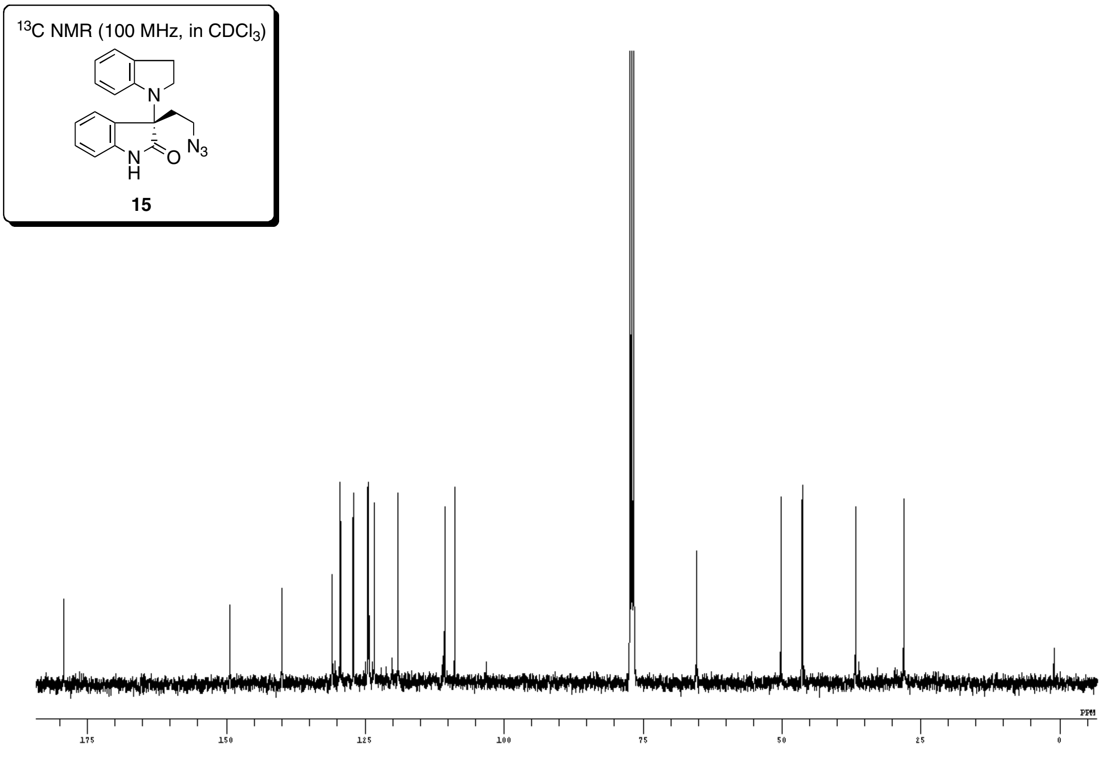
N
N$_3$
N
H
O
15
7
6
5
4
3
PPM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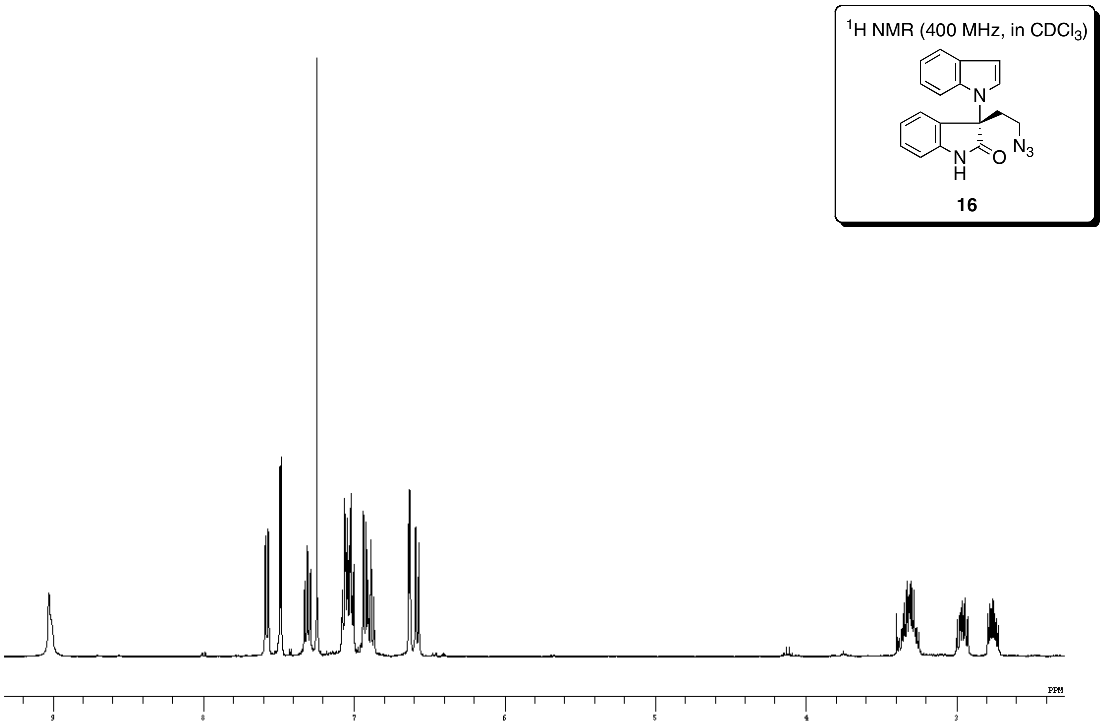
N
N$_3$
N
H
O
15
175
150
125
100
75
50
25
0
PPM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N
H
O
N$_3$
16
PPM
9
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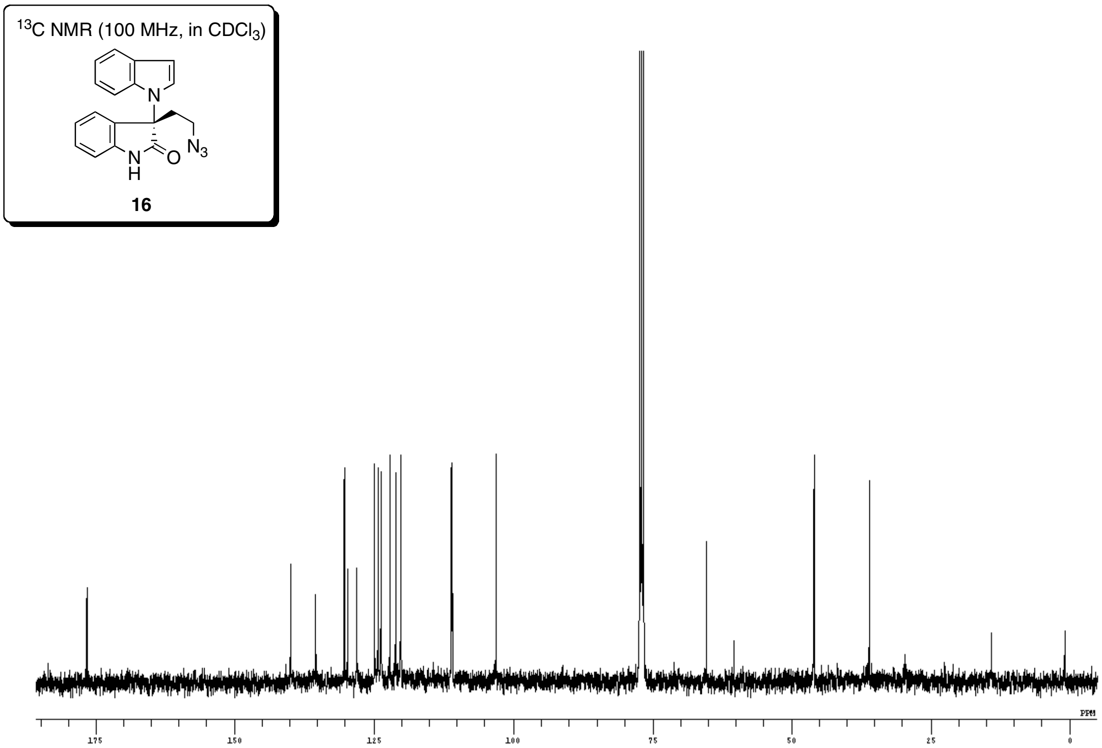
7
6
5
4
3


^{13}C NMR (100 MHz, in CDCl$_3$)
N
N
H
O
N$_3$
16
PPM
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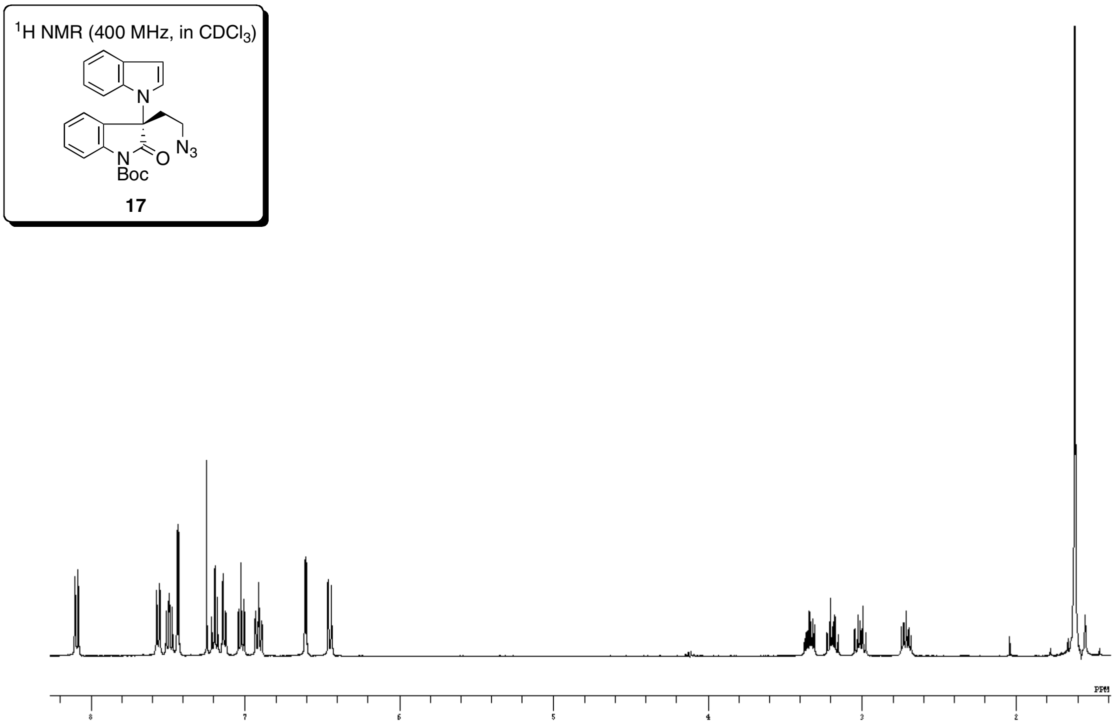
100
75
50
25
0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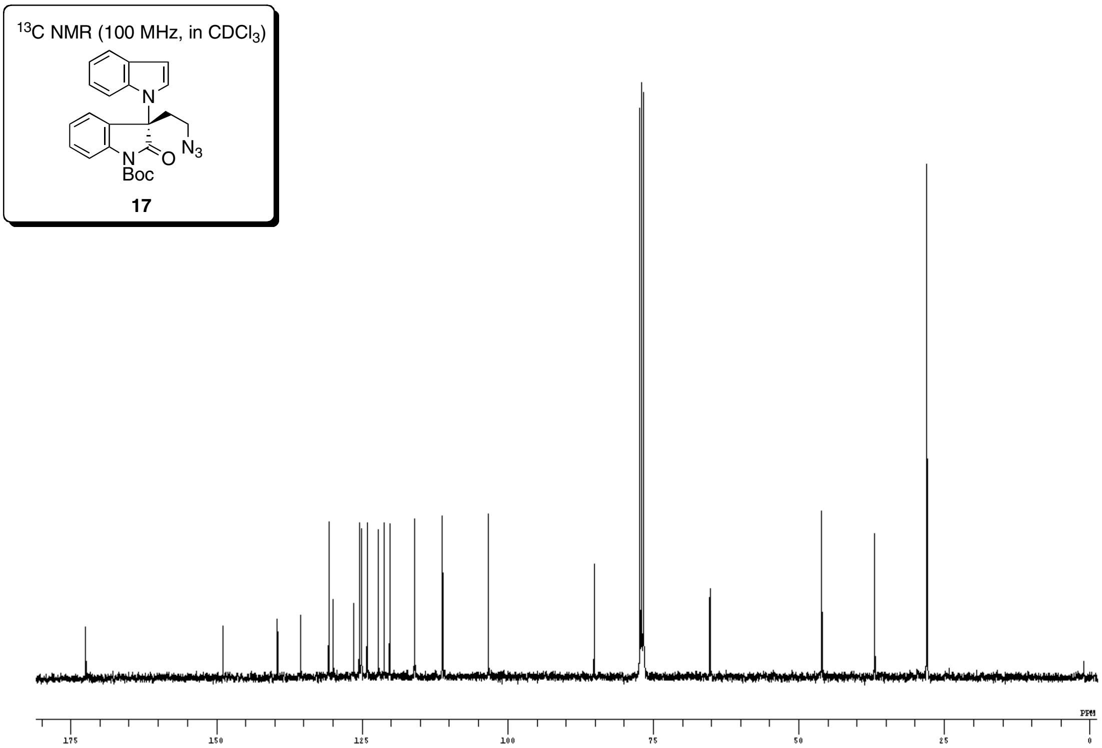
N
N
O
N_3
Boc
17
PPM
8
7
6
5
4
3
2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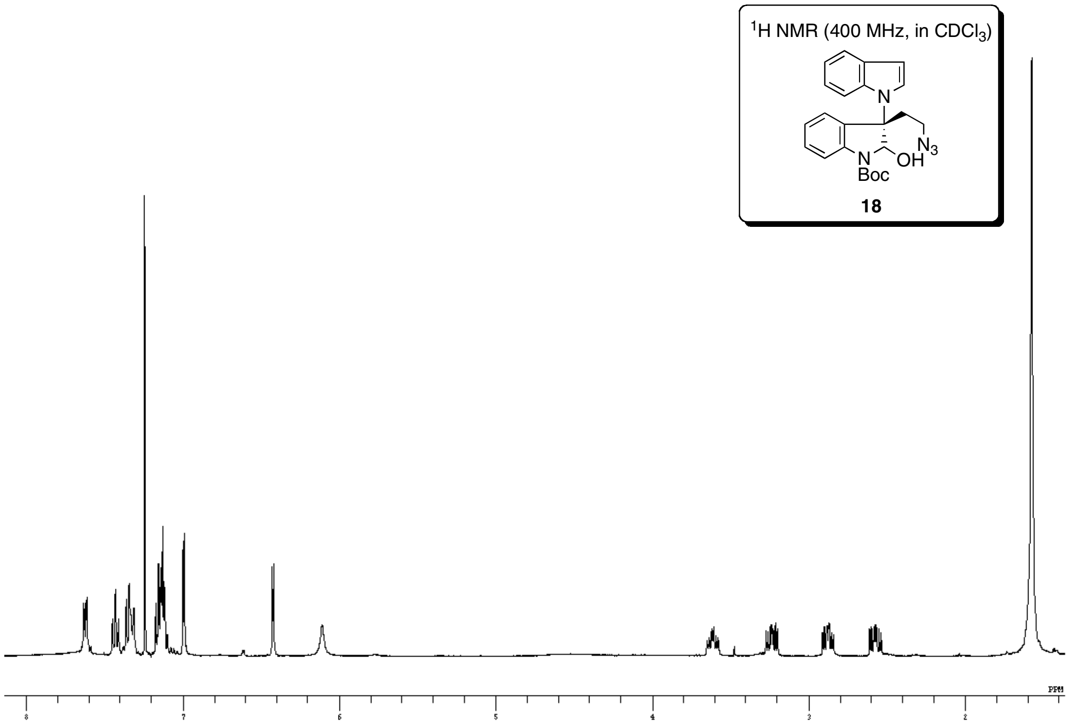
N
N
O
N_3
Boc
17
PPM
175
150
125
100
75
50
25
0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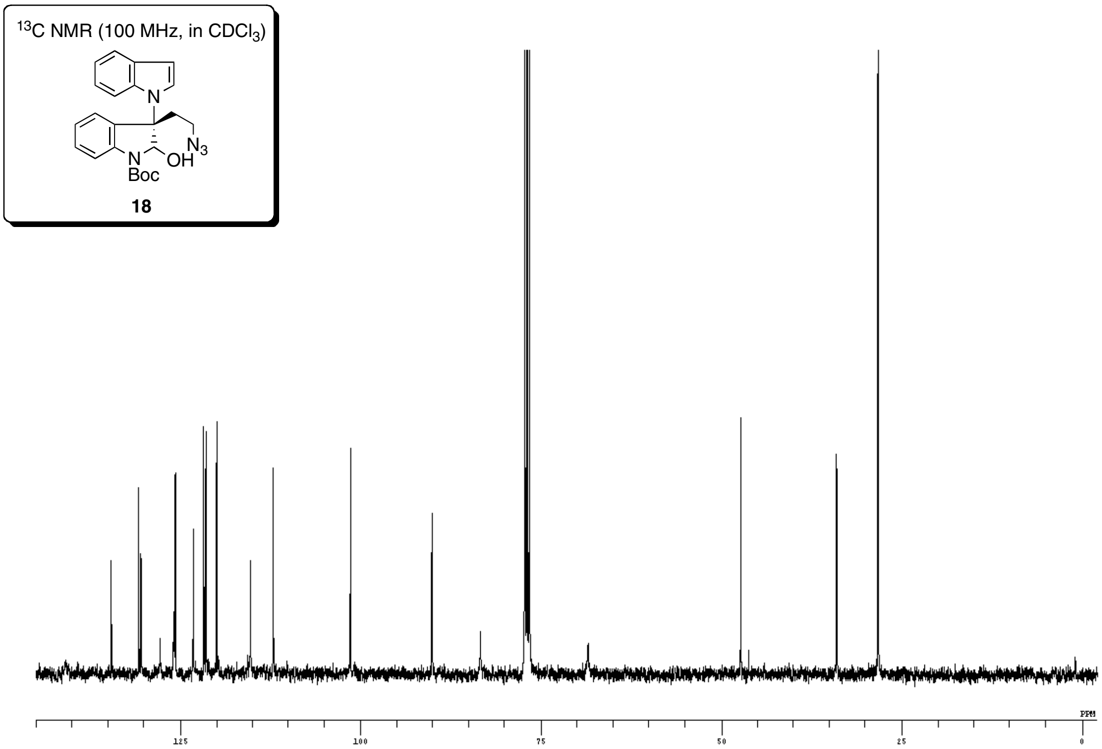
N
N$_3$
N
OH
Boc
18
8
7
6
5
4
3
2
PPM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N$_3$
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OH
Boc
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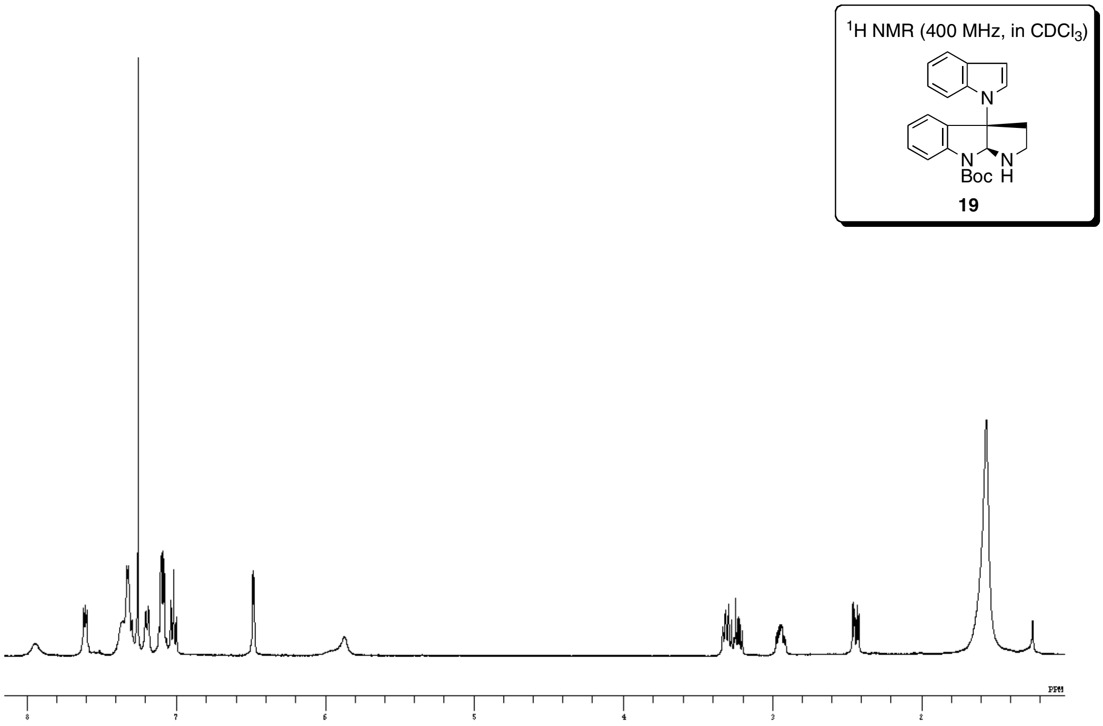
125
100
75
50
25
0
PPM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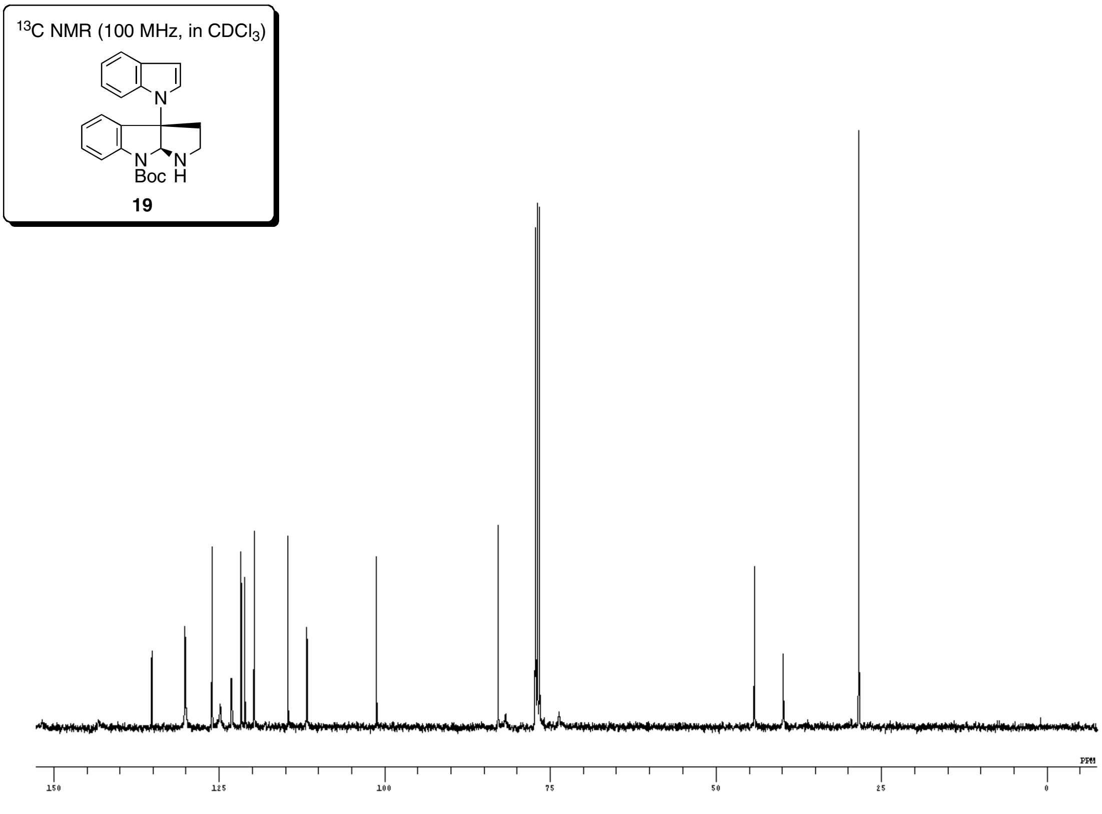
N
N
N
Boc H
19
PPM
8
7
6
5
4
3
2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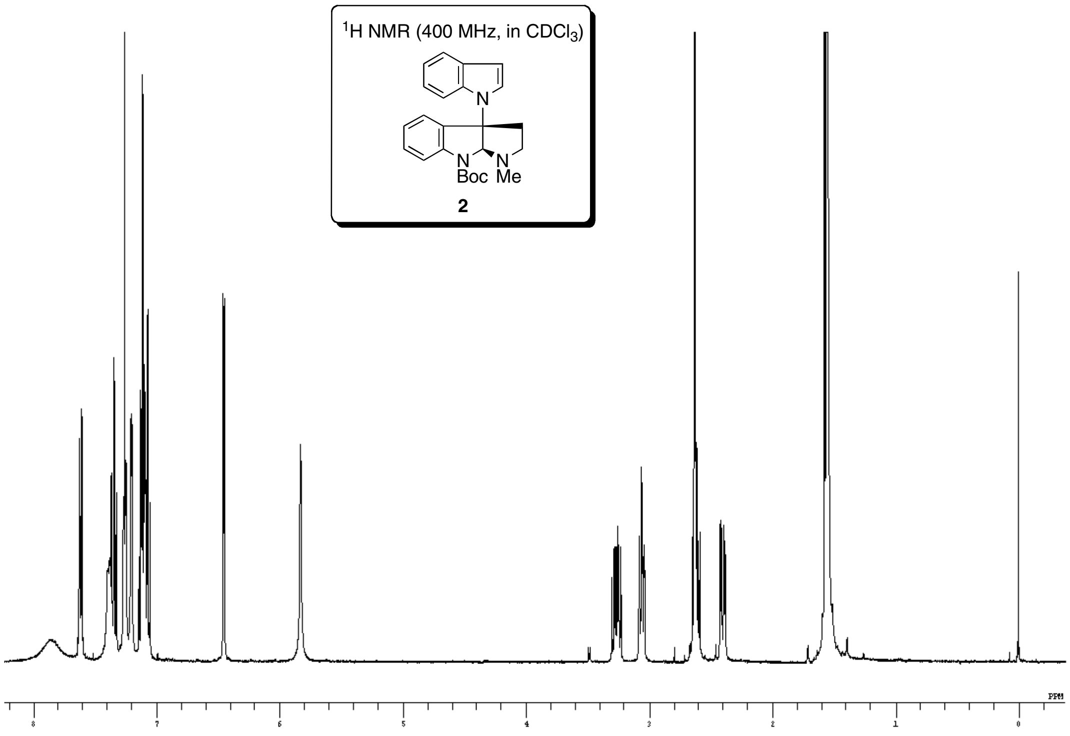
N
N
N
Boc H
19
PPM
150
125
100
75
50
25
0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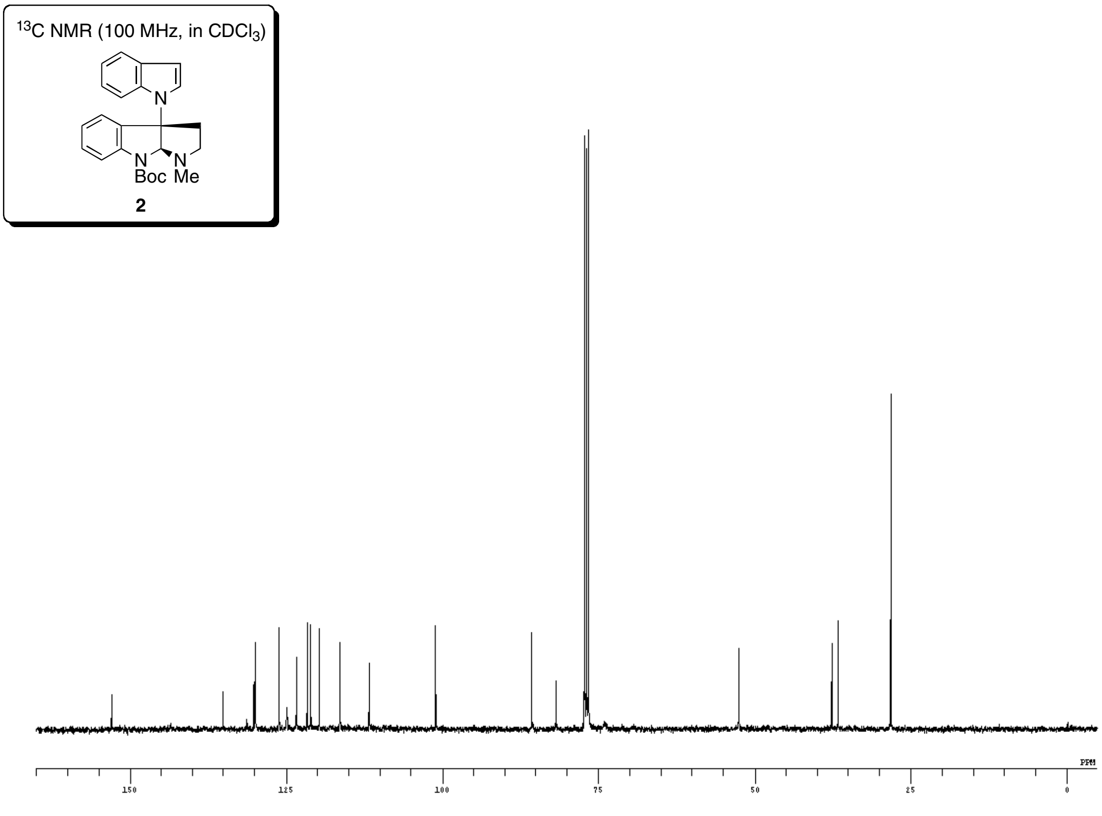
N
N
N
Boc
Me
2
8
7
6
5
4
3
2
1
0
PPM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N
N
N
Boc
Me
2
150
125
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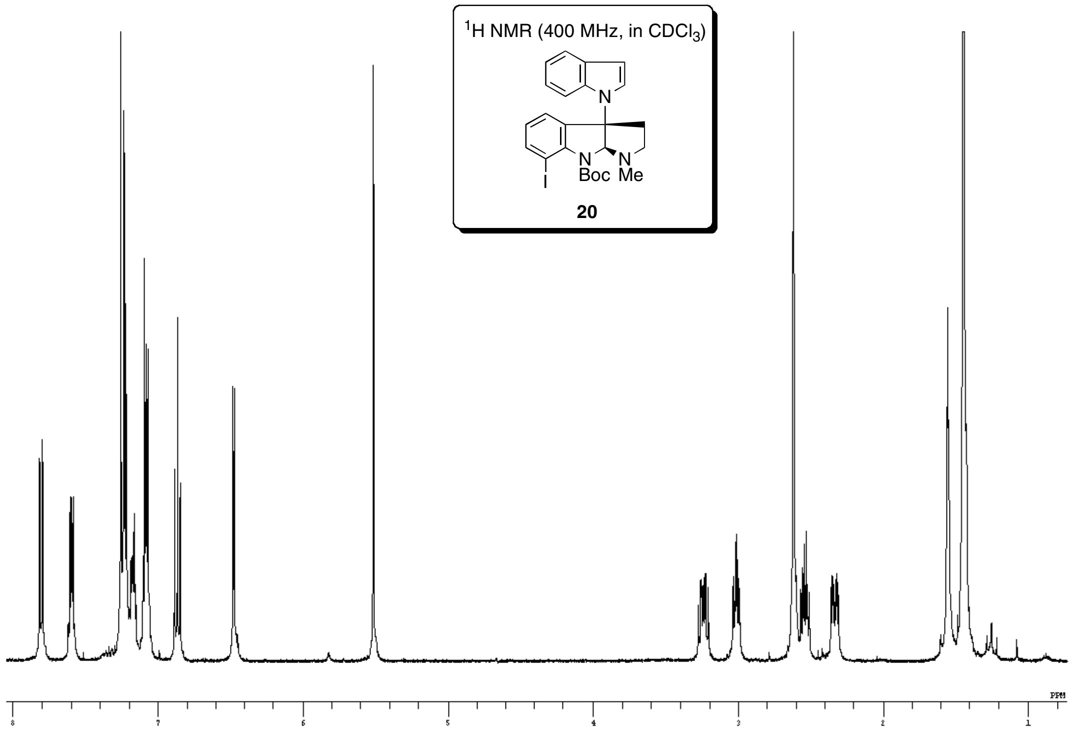
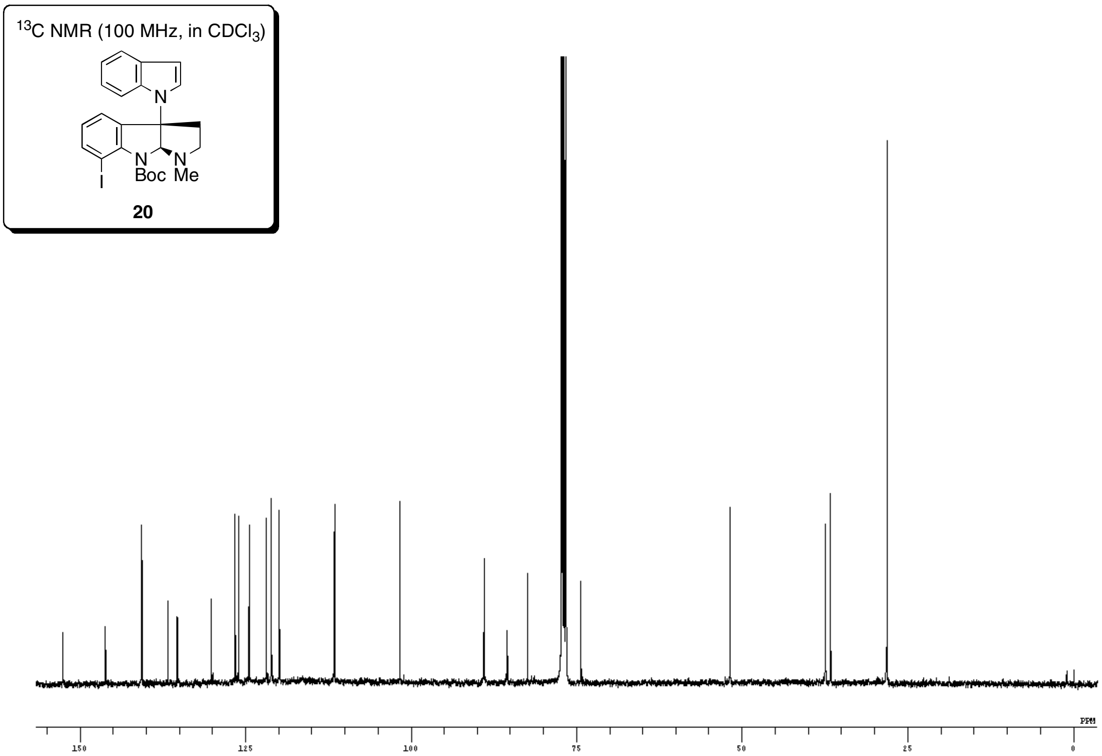
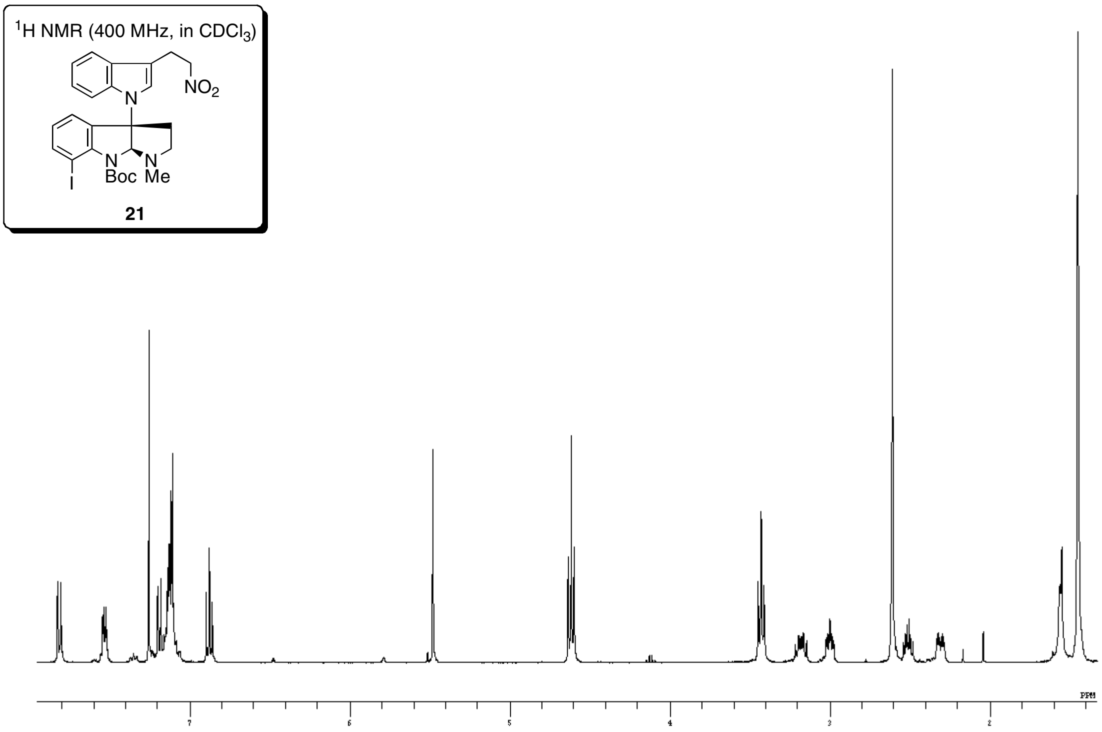
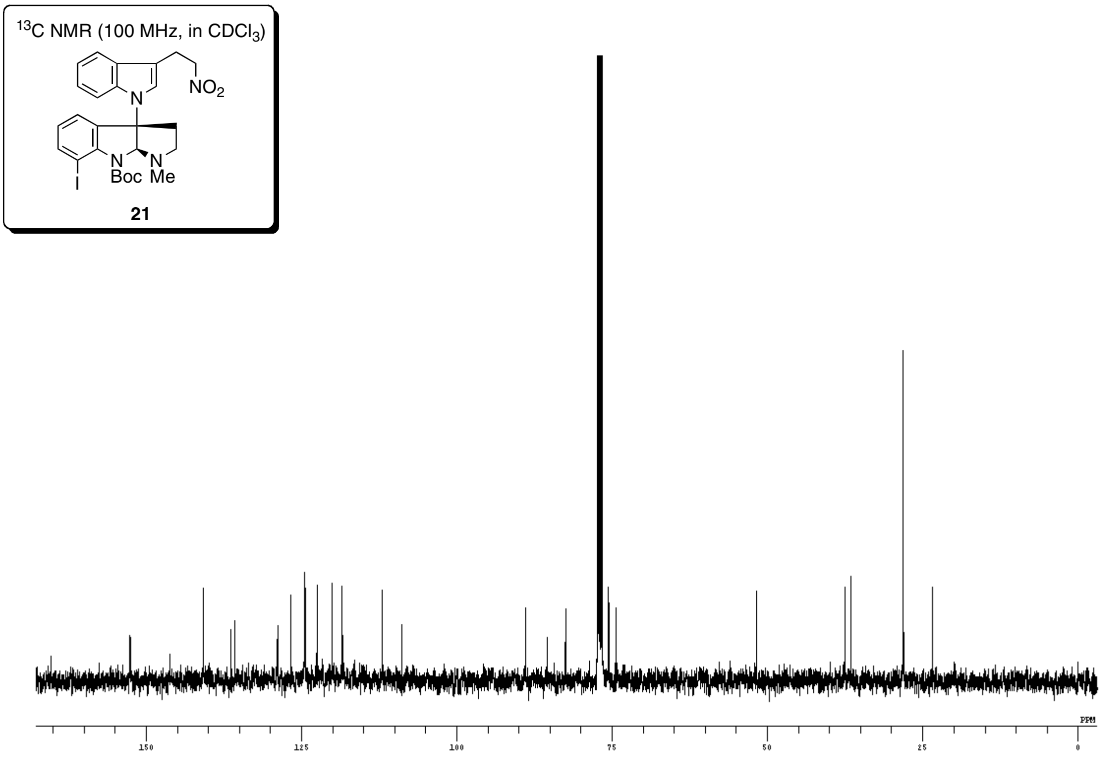
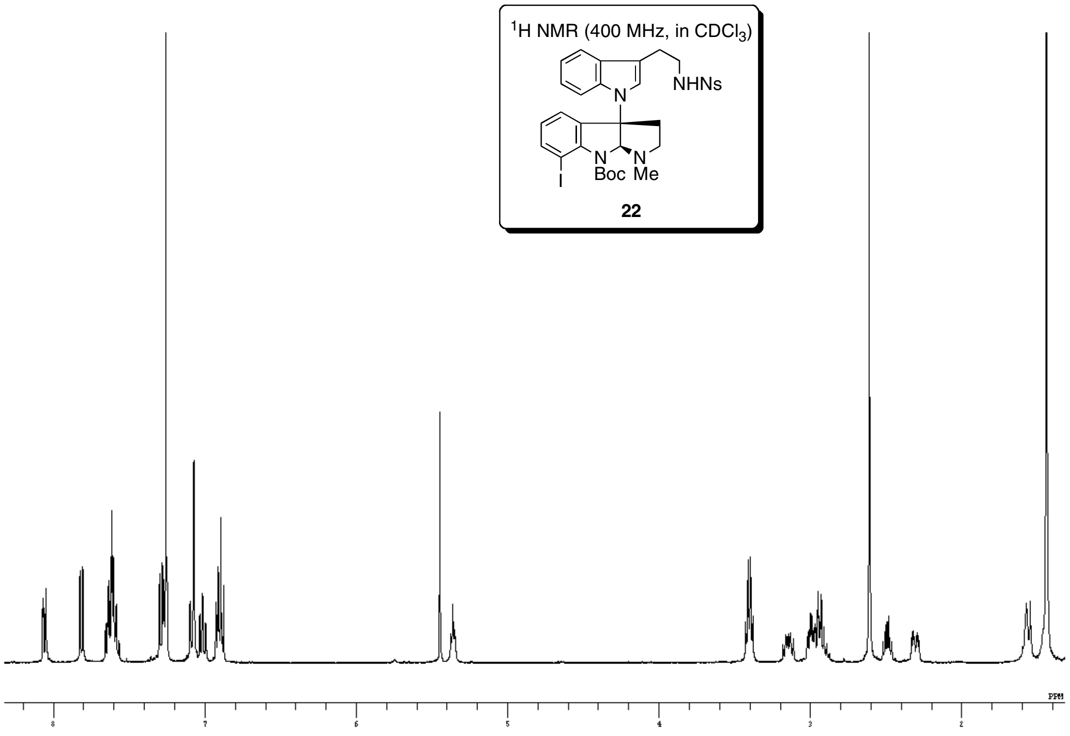
75
50
25
0
PPM

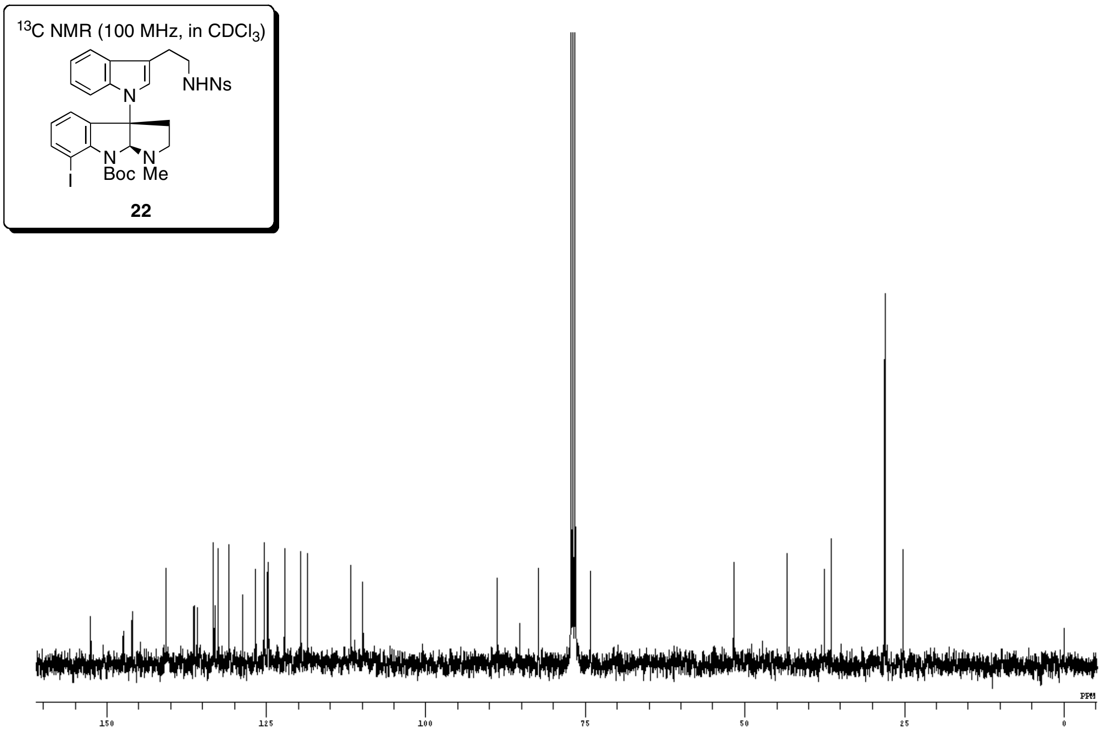

^{1}H NMR (400 MHz, in CDCl$_3$)
N
N
N
Boc
Me
I
20
PPM
8
7
6
5
4
3
2
1

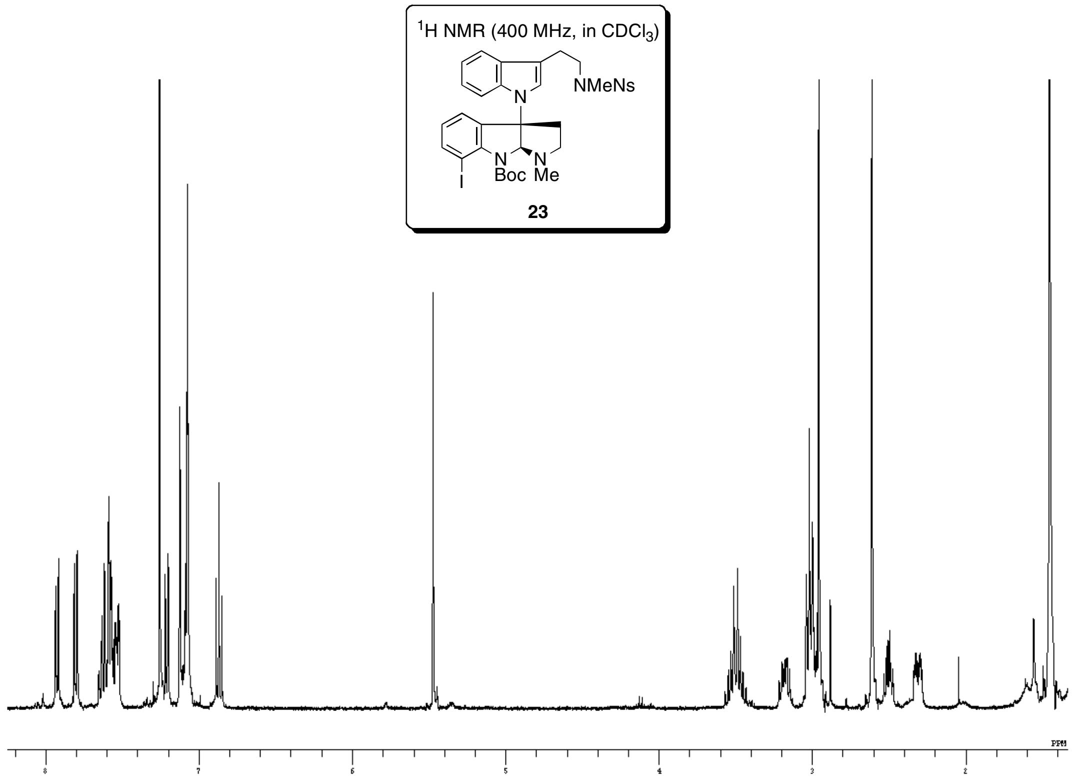

^{13}C NMR (100 MHz, in CDCl$_3$)
N
N
N
Boc
Me
I
20
PPM
150
125
100
75
50
25
0

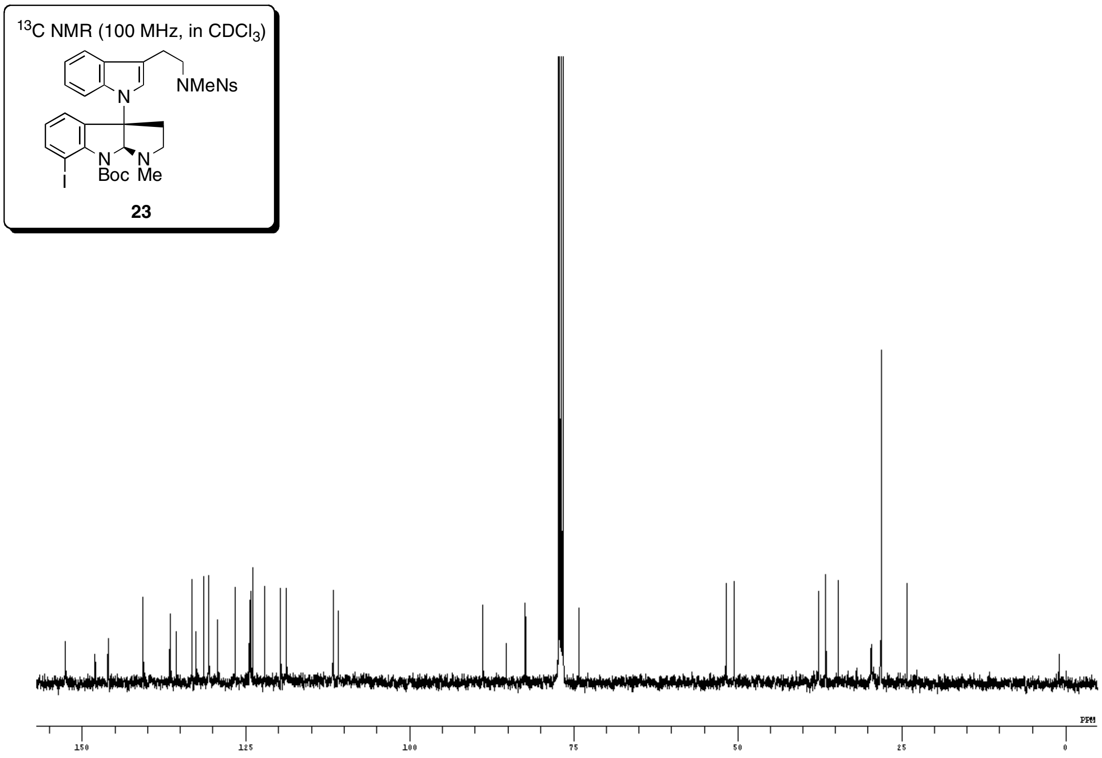

^{1}H NMR (400 MHz, in CDCl$_3$)
NO$_2$
N
N
N
I
Boc
Me
21
PPM
7
6
5
4
3
2

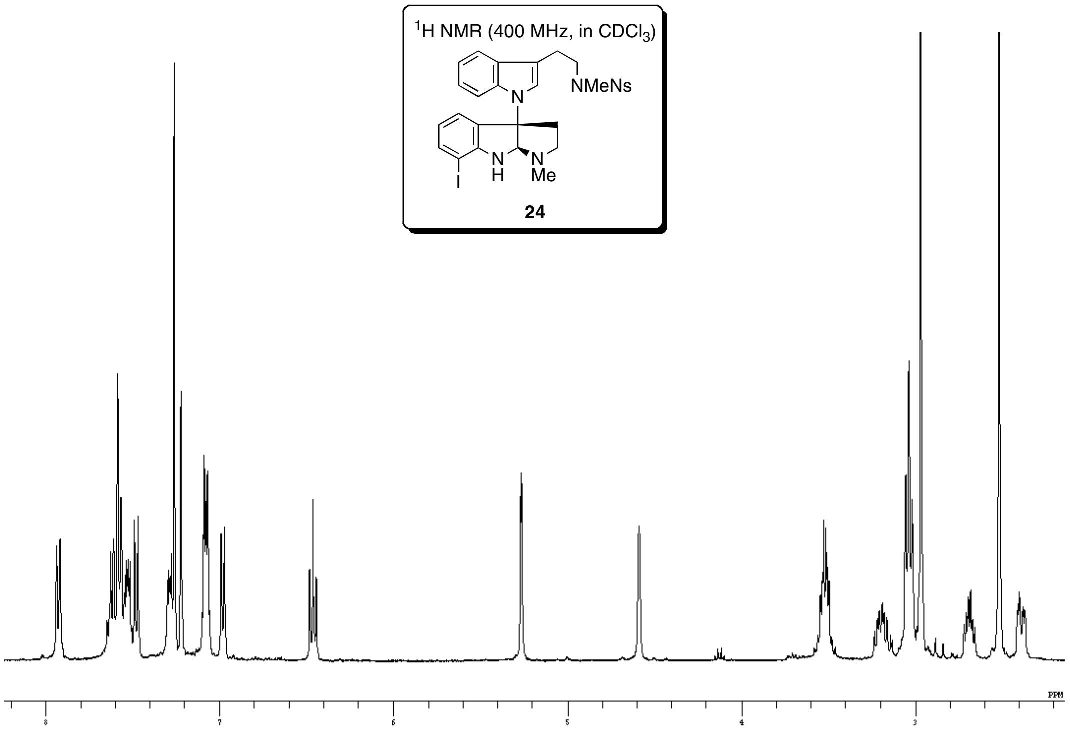

^{13}C NMR (100 MHz, in CDCl$_3$)
NO$_2$
N
N
N
I
Boc
Me
21
PPM
150
125
100
75
50
25
0

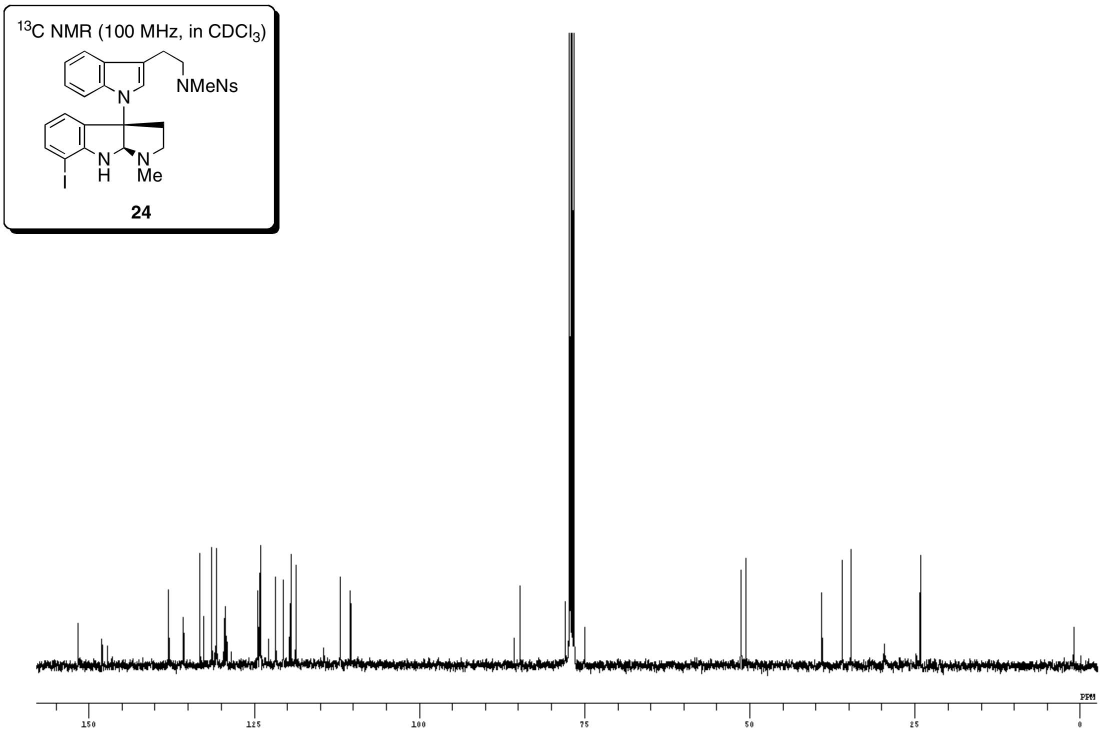

^{1}H NMR (400 MHz, in CDCl$_3$)
N
NHNs
N
N
Boc
Me
I
22
PPM
8
7
6
5
4
3
2

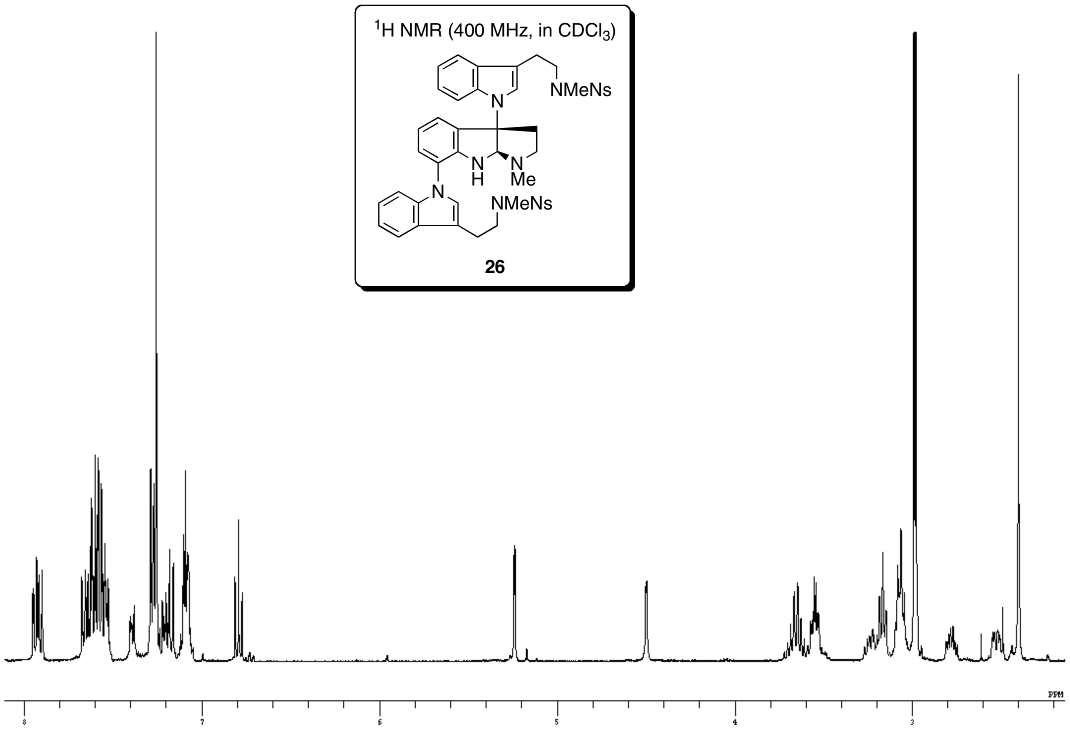

^{13}C NMR (100 MHz, in CDCl$_3$)
N
NHNs
N
N
Boc
Me
I
22
PPM
150
125
100
75
50
25
0

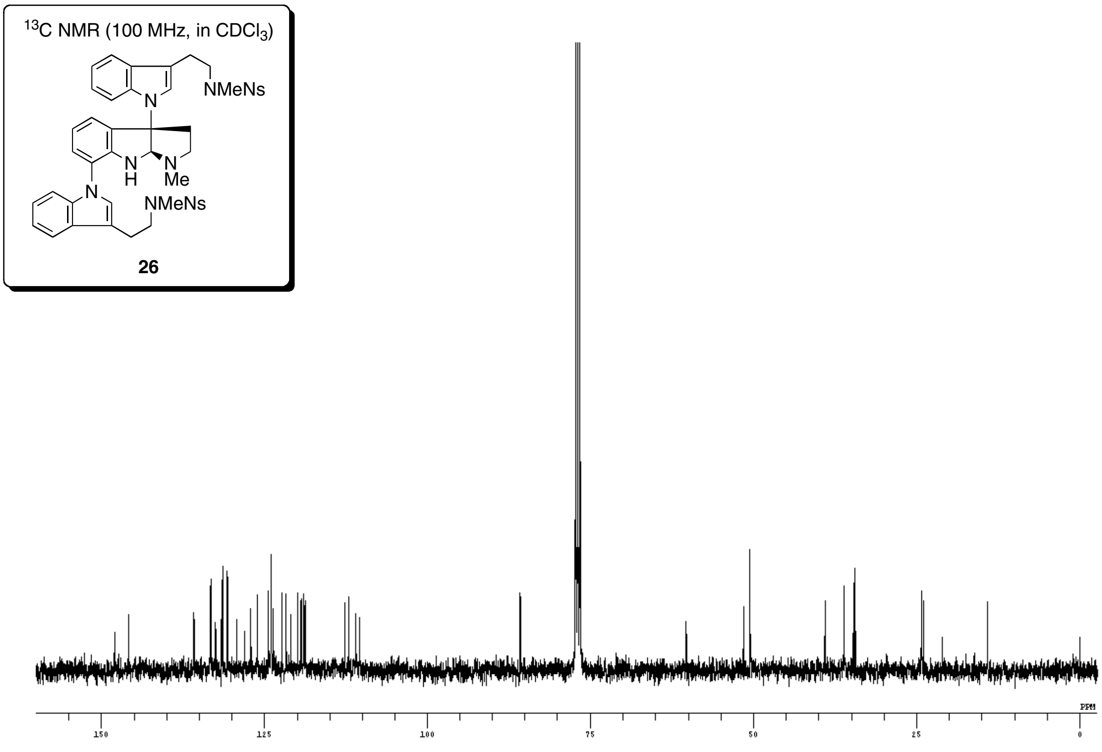

^{1}H NMR (400 MHz, in CDCl$_3$)
NMeNs
N
N
N
Boc
Me
I
23
8
7
6
5
4
3
2
PPM

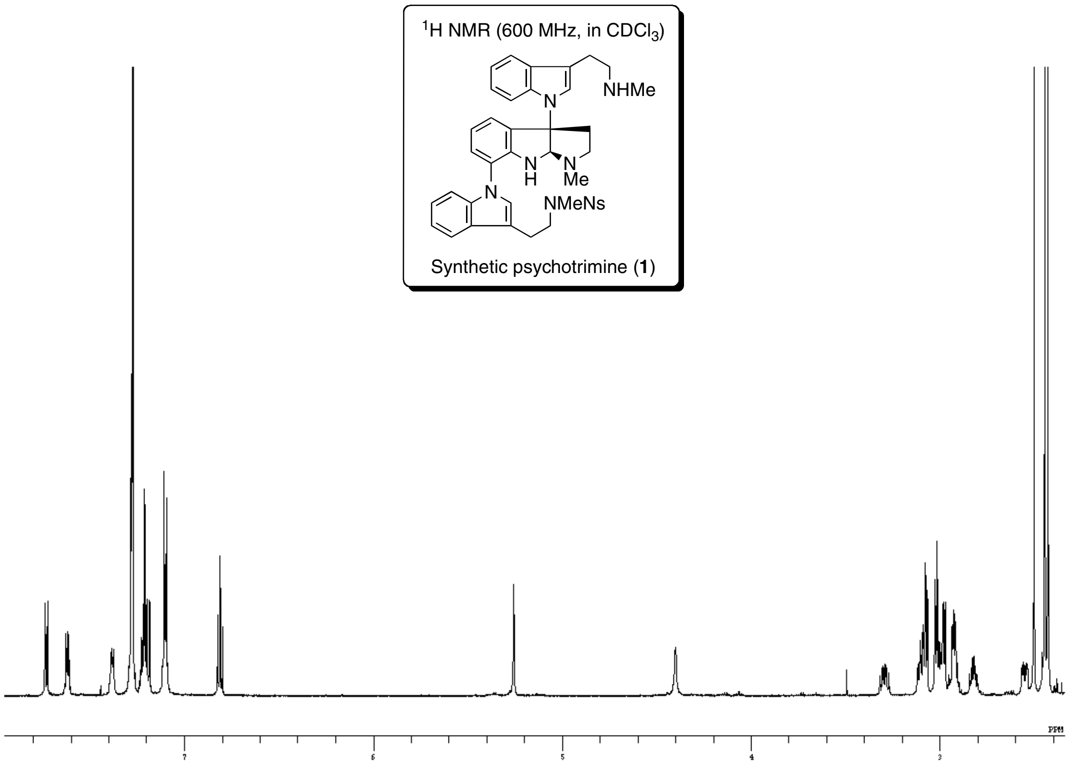

^{13}C NMR (100 MHz, in CDCl$_3$)
NMeNs
N
N
N
Boc
Me
I
23
150
125
100
75
50
25
0
PPM

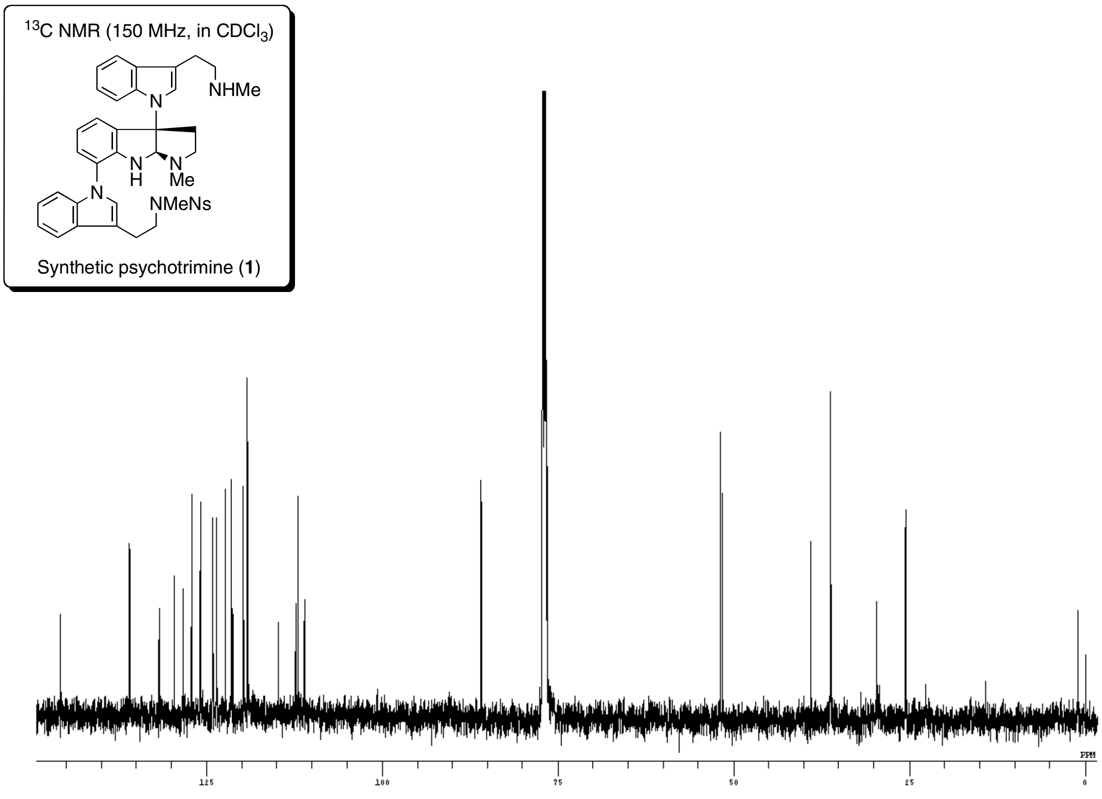

^{1}H NMR (400 MHz, in CDCl$_3$)
NMeNs
N
N
H
N
Me
I
24
8
7
6
5
4
3
PPM


^{13}C NMR (100 MHz, in CDCl$_3$)
NMeNs
N
N
H
N
Me
I
24
150
125
100
75
50
25
0
PPM


^{1}H NMR (400 MHz, in CDCl$_3$)
NMeNs
N
N
H
N
Me
N
NMeNs
26
8
7
6
5
4
3
PPM


^{13}C NMR (100 MHz, in CDCl$_3$)
NMeNs
N
N
H
N
Me
N
NMeNs
26
150
125
100
75
50
25
0
PPM


^{1}H NMR (600 MHz, in CDCl$_3$)
NHMe
N
N
H
N
Me
N
NMeNs
Synthetic psychotrimine (1)
PPM
7
6
5
4
3


^{13}C NMR (150 MHz, in CDCl$_3$)
NHMe
N
N
H
N
Me
N
NMeNs
Synthetic psychotrimine (1)
PPM
125
100
75
50
25
0