Supporting Information

Synthesis and Pharmacological Evaluation of DHβE analogs as Neuronal Nicotinic Acetylcholine Receptor Antagonists

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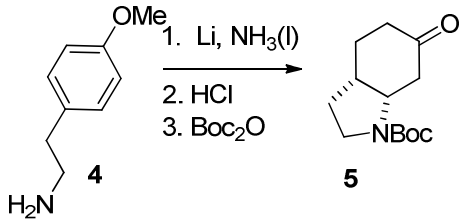
1.1. Material and methods

All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry THF, DMF, and CH_2Cl_2 were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and either ninhydrine or potassium permanganate stain as an indicator. SiliCycle silica gel (60 Å, academic grade, particle size 40–63 μm) was used for flash column chromatography and SiliCycle silica gel (60 Å, academic grade, particle size 15–40 μm) was used for dry column vacuum chromatography.[1] NMR spectra were recorded on Bruker 400 and 600 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. Melting points (mp) were measured using a MPA100 Optimelt melting point apparatus and are uncorrected. Low-resolution mass spectra (LRMS) were obtained by either GCMS (Shimadzu GC-17A) or LCMS (Agilent 1100, Xbridge column, ESI mass detector). High-resolution mass spectra (HRMS) were obtained using a Micromass Q-TOF 2 instrument. **Abbreviations.** THF: tetrahydrofuran; DMF: *N,N*-dimethyl formamide; MeOH: methanol; EtOAc: ethyl acetate; AcOH: acetic acid, LAH: lithium aluminum hydride.

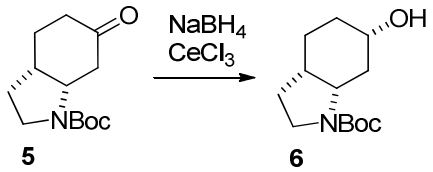
1.2. Experimental



5: tert-butyl 6-oxooctahydro-1H-indole-1-carboxylate
4-methoxy phenethylamine (**4**, 6.1 g, 40.5 mmol) was dissolved in absolute ethanol (50 ml) under N_2 atm. and cooled to -50°C. Liquid ammonia (60 ml) was lead through KOH-pellets and added to the system and lithium suspension in mineral oil (25%) was added carefully over 1h until a blue color persisted for more than 15 minutes. Then the cooling bath was removed and ammonia was evaporated overnight. The remaining mixture was concentrated *in vacuo* and water (100 ml) was added. The mixture was extracted with Ether (5x150 ml) and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo* to obtain a crude oil. The oil was dissolved in 5M hydrochloric acid (100 ml) and stirred at 80 °C for 3 hours. The mixture was pH-adjusted with solid sodium hydroxide until a pH-value of 10 was reached. Then THF (75 ml) and Boc_2O (8.84g, 40.5 mmol) was added and the mixture was stirred at rt overnight. THF was evaporated and the mixture was extracted with ethyl acetate (4x100 ml). The combined organic layers were washed with brine (40 ml), dried with Na_2SO_4, filtered, evaporated onto celite and purified by dry column vacuum chromatography (Heptane->EtOAc, 10%) to obtain **5** as a yellow oil (6.0 g, 25.1 mmol, 62% yield over 3 steps).
R_f = 0.58 (silica gel, MeOH/EtOAc/heptanes, 10:45:45); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.97 - 4.21 (m, 1 H), 3.34 - 3.56 (m, 2 H), 2.70 - 2.90 (m, 1 H), 2.47 - 2.59 (m, 1 H), 2.30 - 2.45 (m, 2 H), 2.15 - 2.26 (m, 1 H), 1.98 - 2.12 (m, 2 H), 1.76 - 1.93 (m, 2 H), 1.38 - 1.54 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm

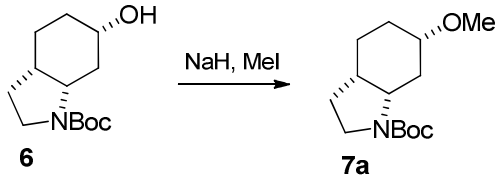
[1] Dry column vacuum chromatography: Pedersen, D.S.; Rosenbohm, C. *Synthesis* **2001**, 2431

210.7, 154.2, 79.7, 56.2, 53.4, 45.4, 40.7, 37.0, 32.5, 28.5 , 24.8; LRMS (GCMS) calcd for $C_{13}H_{21}NO_3$+ [M+] 239.1521 found 239.



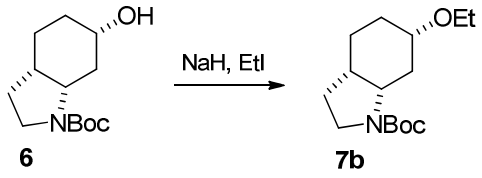
5 **6**

6: tert-butyl 6-hydroxyoctahydro-1H-indole-1-carboxylate
5 (6.0 g, 25.1 mmol, 1 eq) was dissolved in MeOH (100 ml) under N_2 atm. and $CeCl_3$ (0.927 g, 3.76 mmol, 0.15 eq) was added to the solution. Then the mixture was cooled to -30°C and $NaBH_4$ (2.847 g, 75.21 mmol, 3 eq) was added slowly over 15 minutes and the mixture was stirred for additional 2h at -30°C. MeOH was evaporated, brine (100 ml) was added, and the mixture was extracted with EtOAc (4x125ml). The combined organic layers were washed with water (50 ml), dried with Na_2SO_4, filtered, evaporated onto celite and purified by dry column vacuum chromatography (Heptane->EtOAc, 10%) to obtain **6** as a white solid (5.4 g, 22.3 mmol, 89 %).
R_f = 0.19 (silica gel, heptanes/EtOAc, 1:1); Mp = 97.1 - 98.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.71 - 3.91 (m, 1 H), 3.50 - 3.62 (m, 1 H), 3.40 - 3.49 (m, 1 H), 3.25 - 3.37 (m, 1 H), 2.13 - 2.38 (m, 2 H), 1.85 - 1.99 (m, 1 H), 1.62 - 1.84 (m, 5 H), 1.41 - 1.49 (m, 9 H), 1.27 - 1.41 (m, 1 H), 1.09 - 1.24 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.1, 79.0, 68.7, 56.0, 45.0, 37.1, 36.3, 29.8, 28.5 , 26.1, 23.4; LRMS (GCMS) calcd for $C_{13}H_{23}NO_3$+ [M+] 241.1658 found 241.



6 **7a**

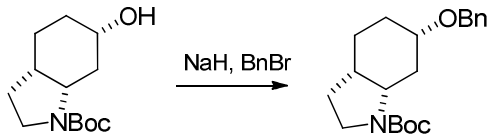
7a: tert-butyl 6-methoxyoctahydro-1H-indole-1-carboxylate
6 (1.87 g, 7.75mmol, 1 eq) was dissolved in dry DMF (30 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (0.787 g, 19.38 mmol, 2.5 eq) was added slowly. The mixture was stirred at 0 °C for 30 min. The ice-bath was removed and methyl iodide (2.0 ml, 32.13 mmol, 4.1 eq) was added. The mixture was stirred at rt for 12 hours. TLC showed full conversion of starting material. Brine (50 ml) was added and the mixture was extracted with ethyl acetate (3x100 ml). The combined organic layers were dried with Na_2SO_4, washed with water (70 ml), filtered, evaporated *in vacuo* on celite and purified by column chromatography (EtOAc:Heptane 1:1) to obtain **7a** as a colorless oil (1.80 g, 7.05 mmol, 91%).
R_f = 0.54 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.64 - 3.93 (m, 1 H), 3.37 - 3.51 (m, 1 H), 3.21 - 3.37 (m, 4 H), 2.99 - 3.11 (m, 1 H), 2.11 - 2.55 (m, 2 H), 1.76 - 1.99 (m, 3 H), 1.57 - 1.75 (m, 2 H), 1.45 (s, 9 H), 1.21 - 1.36 (m, 1 H), 0.95 - 1.13 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.1, 78.9, 77.4, 55.6, 44.9, 36.8, 33.8, 32.8, 28.5 , 26.9, 26.1, 23.4; LRMS (GCMS) calcd for $C_{14}H_{25}NO_3$+ [M+] 255.1834 found 255.



6 **7b**

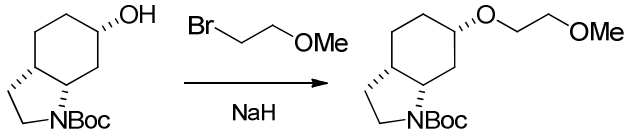
7b: tert-butyl 6-ethoxyoctahydro-1H-indole-1-carboxylate
6 (201.1 mg, 0.833 mmol, 1 eq) was dissolved in dry DMF (5 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (73.5 mg, 1.838 mmol, 2.2 eq) was added slowly. The mixture was stirred

at 0 °C for 30 min. The ice-bath was removed and ethyl iodide (0.36 ml, 2.49 mmol, 3 eq) was added. The mixture was stirred at rt overnight. TLC showed almost full conversion of starting material. Brine was added (20 ml) and the mixture was extracted with ethyl acetate (4x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by column chromatography (Heptane→EtOAc, 5 % grad) to obtain **7b** a as colorless oil (138 mg, 0.510 mmol, 61 %).
R_f = 0.69 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.67 - 3.90 (m, 1 H), 3.09 - 3.21 (m, 1 H) 3.21 - 3.61 (m, 4 H), 2.26 - 2.52 (m, 1 H), 2.10 - 2.26 (m, 1 H), 1.75 - 2.01 (m, 3 H), 1.57 - 1.74 (m, 2 H), 1.45 (s, 9 H), 1.26 - 1.38 (m, 1 H), 1.13 - 1.23 (m, 3 H), 1.00 - 1.12 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.1, 78.9, 75.8, 63.2, 56.2, 44.8, 36.8, 34.3, 28.5 , 26.9, 25.9, 23.5, 15.6; LRMS (GCMS) calcd for $C_{15}H_{27}NO_3$+ [M+] 269.1991 found 269.



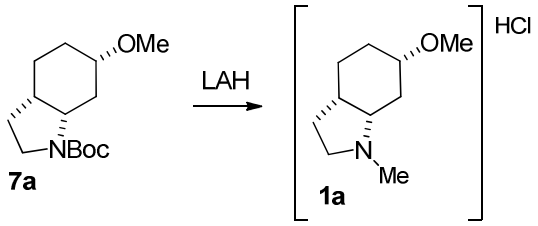
6 **7c**

7c: tert-butyl 6-(benzyloxy)octahydro-1H-indole-1-carboxylate
6 (200 mg, 0.829 mmol, 1 eq) was dissolved in dry DMF (9 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (83 mg, 2.07 mmol, 2.5 eq) was added slowly. The mixture was stirred at 0 °C for 30 min. The ice-bath was removed and benzyl bromide (425 mg, 2.49 mmol, 3.0 eq) was added. The mixture was stirred at rt overnight. TLC showed full conversion of starting material. Brine (20 ml) was added and the mixture was extracted with ethyl acetate (4x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by column chromatography (EtOAc:Heptane 1:1) to obtain **7c** as a colorless oil (252 mg, 0.760 mmol, 92 %).
R_f = 0.70 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.22 - 7.42 (m, 5 H), 4.45 - 4.67 (m, 2 H), 3.68 - 3.94 (m, 1 H), 3.39 - 3.54 (m, 1 H), 3.22 - 3.38 (m, 2 H), 2.30 - 2.63 (m, 1 H), 2.12 - 2.28 (m, 1 H), 1.77 - 2.06 (m, 3 H), 1.57 - 1.77 (m, 2 H), 1.33 - 1.54 (m, 10 H), 1.10 - 1.30 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.1, 138.8, 128.3, 127.5, 126.9, 78.9, 75.6, 69.9, 56.1, 44.8, 36.8, 34.1, 28.5 , 26.9, 25.9, 23.4; LRMS (GCMS) calcd for $C_{20}H_{29}NO_3$+ [M+] 331.2147 found 331.



6 **7d**

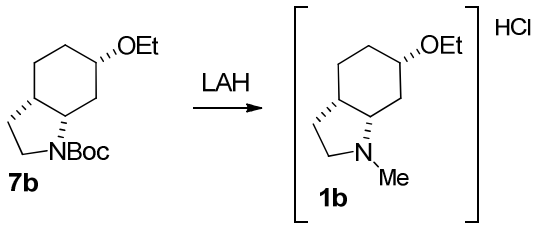
7d: tert-butyl 6-(2-methoxyethoxy)octahydro-1H-indole-1-carboxylate
6 (498 mg, 2.07 mmol, 1 eq) was dissolved in dry DMF (9 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (210 mg, 5.26 mmol, 2.5 eq) was added slowly. The mixture was stirred at 0 °C for 30 min. The ice-bath was removed and methoxy ethylbromide (0.60 ml, 6.39 mmol, 3.1 eq) was added. The mixture was stirred at rt overnight. Brine was added (20 ml) and the mixture was extracted with ethyl acetate (4x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by column chromatography (EtOAc:Heptane 1:1) to obtain **7d** as a colorless oil (254 mg, 0.850 mmol, 41 %).
R_f = 0.34 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.69 - 3.90 (m, 1 H), 3.41 - 3.69 (m, 5 H), 3.38 (m, 3 H), 3.25 - 3.35 (m, 1 H), 3.20 (m, 1 H), 2.29 - 2.55 (m, 1 H), 2.11 - 2.27 (m, 1 H), 1.75 - 2.01 (m, 3 H), 1.57 - 1.75 (m, 2 H), 1.45 (s, 9 H), 1.23 - 1.41 (m, 1 H), 1.12 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.0, 79.0, 76.6, 72.3, 67.2, 59.1, 56.1, 44.8, 36.8, 34.1, 28.6 , 26.5, 25.9, 23.4; LRMS (GCMS) calcd for $C_{16}H_{29}NO_4$+ [M+] 299.2097 found 299.



1a: 6-methoxy-1-methyloctahydro-1H-indole, HCl

7a (500 mg, 1.96 mmol, 1 eq) was dissolved in dry THF (10 ml) and added $LiAlH_4$ (223 mg, 5.88 mmol, 3 eq). Then refluxed for 3 h for full conversion of starting material and quenched by adding ether (10 ml), and dropwise addition of water (225 µl), 15 % NaOH solution (225 µl) and H_2O (450 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (5 ml) dropwise whereby a precipitate was formed at the bottom of the flask. The supernatant was removed and the remains were evaporated to dryness to provide the title compound as a white solid (371mg, 1.80 mmol, 92%). (Note that the diastereomerically pure compound appears as a mixture of diastereoisomers in the NMR spectra due to the two possible orientations of the protonated amine).

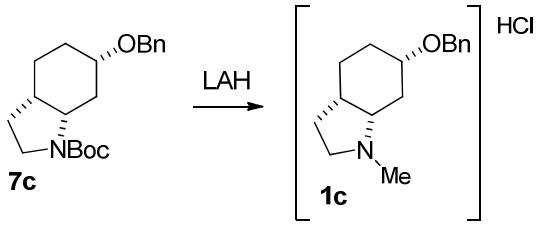
R_f (free amine) = 0.45 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (br s, 1 H), 9.57 (br s, 1 H), 3.85- 4.02 (m, 2H), 3.75 (m, 1H), 3.54 (m, 1H), 3.49 – 3.38 (m, 2H), 3.32 (m, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 3.19 – 3.07 (m, 2H), 2.99 (m, 1H), 2.79 (d, J = 5.1 Hz, 2H), 2.60 (d, J = 5.1 Hz, 2H), 2.46 (m, 1H), 2.14 – 1.49 (m, 15 H), 1.31 – 1.16 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 76.9, 74.6, 66.4, 62.1, 55.9, 55.7, 54.6, 51.0, 35.8, 35.2, 35.1, 28.5, 27.2, 26.3, 25.8, 25.6, 24.7, 22.4, 22.1; HRMS calcd for $C_{10}H_{20}NO$+ [M+] 170.1545 found 170.1533.



1b: 6-ethoxy-1-methyloctahydro-1H-indol, HCl

7b (52 mg, 0.19 mmol, 1 eq) was dissolved in dry THF (5 ml) under N_2 atm. LAH (22 mg, 0.58 mmol, 3 eq) was added and the mixture was refluxed for 3 h. TLC showed full conversion of starting material. The reaction was quenched by adding ether (5 ml), and dropwise addition of water (22 µl), 15 % NaOH solution (22 µl) and H_2O (44 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1 ml) dropwise whereby a colorless oil was formed at the bottom of the flask. The supernatant was removed and the remaining viscous oil evaporated to dryness. **1b** was isolated as a yellow oil (41 mg, 0.19 mmol, 96 %). (Note that the diastereomerically pure compound appears as a mixture of diastereoisomers in the NMR spectra due to the two possible orientations of the protonated amine).

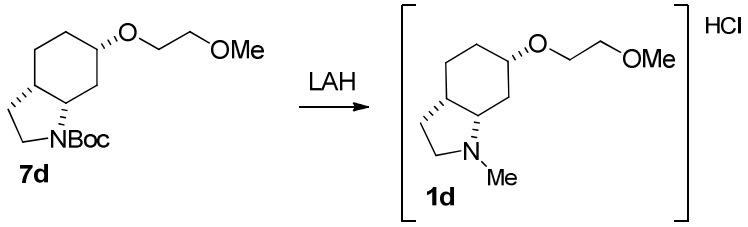
R_f (free amine) = 0.53 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.44 (br s, 1 H), 9.61 (br s, 1 H), 3.66 - 3.82 (m, 2 H), 3.18 - 3.60 (m, 8 H), 2.92 - 3.17 (m, 2 H), 2.56 - 2.82 (m, 6 H), 2.40 - 2.49 (m, 2 H), 1.88 - 2.16 (m, 4 H), 1.45 - 1.88 (m, 10 H), 1.17 - 1.33 (m, 2 H), 1.03 - 1.16 (m, 6 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 74.7, 72.6, 66.1, 62.8, 62.5, 61.7, 54.1, 50.6, 40.5, 35.3, 34.6, 34.4, 28.8, 26.4, 26.3, 26.0, 25.6, 24.2, 22.0, 21.8, 15.5, 15.3; HRMS calcd for $C_{11}H_{22}NO$+ [M+] 184.1701 found 184.1716.



1c: 6-(benzyloxy)-1-methyloctahydro-1H-indol, HCl

7c (130 mg, 0.392 mmol, 1 eq) was dissolved in dry THF (8 ml) under N_2 atm. LAH (45 mg, 1.18 mmol, 3 eq) was added and the mixture was refluxed for 3 h. TLC showed full conversion of starting material. The reaction was quenched by adding ether (5 ml), and dropwise addition of water (45 µl), 15 % NaOH solution (45 µl) and H_2O (90 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1 ml) dropwise where by a colorless oil was formed at the bottom of the flask. The supernatant was removed and the remaining viscous oil evaporated to dryness. The title compound was isolated as a yellow oil (108 mg, 0.38 mmol, 98 %). (Note that the diastereomerically pure compound appears as a mixture of diastereoisomers in the NMR spectra due to the two possible orientations of the protonated amine).

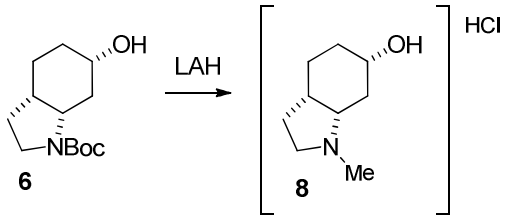
R_f (free amine) = 0.57 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.56 (br s, 1 H), 9.87 (br s, 1 H), 7.21 - 7.48 (m, 10 H), 4.39 - 4.64 (m, 4 H), 3.30 - 3.77 (m, 8 H), 2.92 - 3.23 (m, 2 H), 2.82 (s, 3 H), 2.65 (s, 3 H), 2.43 - 2.50 (m, 2 H), 2.11 - 2.26 (m, 2 H), 1.49 - 2.09 (m, 10 H), 1.23 - 1.44 (m, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 138.8, 138.6, 128.2, 128.2, 127.3, 127.3, 74.8, 72.5, 69.1, 69.0, 66.0, 61.7, 54.1, 50.6, 40.6, 35.3, 34.6, 34.4, 28.8, 26.4, 26.3, 25.9, 25.5, 24.2, 22.0, 21.8; HRMS calcd for $C_{16}H_{24}NO^+$ [M+] 246.1858 found 246.1869.



1d: 6-(2-methoxyethoxy)-1-methyloctahydro-1H-indol, HCl

7d (105 mg, 0.351 mmol, 1 eq) was dissolved in dry THF (8 ml) under N_2 atm. LAH (40 mg, 1.05 mmol, 3 eq) was added and the mixture was refluxed for 1.5 h. TLC showed full conversion of starting material. The reaction was quenched by adding ether (5 ml), and dropwise addition of water (40 µl), 15 % NaOH solution (40 µl) and H_2O (80 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1 ml) dropwise where by a colorless oil was formed at the bottom of the flask. The supernatant was removed and the remaining viscous oil evaporated to dryness. The title compound was isolated as a yellow oil (78 mg, 0.31mmol, 89 %). (Note that the diastereomerically pure compound appears as a mixture of diastereoisomers in the NMR spectra due to the two possible orientations of the protonated amine).

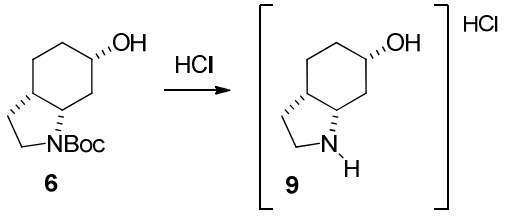
R_f (free amine) = 0.45 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.53 (br s, 1 H), 9.78 (br s, 1 H),, 3.36 - 3.64 (m, 12 H), 3.19 - 3.30 (m, 8 H), 2.90 - 3.18 (m, 2 H), 2.80 (s, 3 H), 2.61 (s, 3 H), 2.40 - 2.49 (m, 2 H), 1.87 - 2.16 (m, 4 H), 1.46 - 1.87 (m, 10 H), 1.15 - 1.32 (m, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 75.2, 73.2, 71.5, 71.3, 66.7, 66.6, 66.2, 61.7, 58.2, 58.1, 54.0, 50.6, 40.6, 35.3, 34.6, 34.5, 28.5, 26.6, 26.3, 26.0, 25.5, 24.2, 22.0, 21.6; HRMS calcd for $C_{12}H_{24}NO_2^+$ [M+] 214.1807 found 214.1803.



8: 1-methyloctahydro-1H-indol-6-ol, HCl

6 (500 mg, 2.07 mmol, 1 eq) was dissolved in dry THF (10 ml) and added $LiAlH_4$ (236 mg, 6.22 mmol, 3 eq). Then refluxed for 3 h for full conversion of starting material and quenched by adding ether (10 ml), and dropwise addition of water (240 µl), 15 % NaOH solution (240 µl) and H_2O (480 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (5 ml) dropwise whereby a precipitate was formed at the bottom of the flask. The supernatant was removed and the remains were evaporated to dryness in order to provide the title compound as a white solid (360 mg, 1.88 mmol, 91%). (Note that the diastereomerically pure compound appears as a mixture of diastereoisomers in the NMR spectra due to the two possible orientations of the protonated amine).

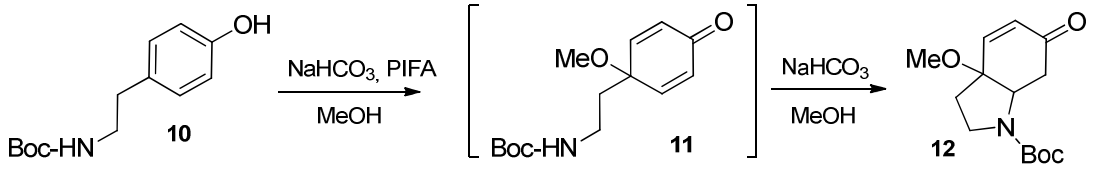
R_f (free amine) = 0.39 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (br s, 1H), 9.54 (br s, 1H), 4.78 (br s, 1H), 3.82 – 3.72 (m, 1H), 3.72 – 3.65 (m, 1H), 3.52 (dtd, J = 11.7, 5.4, 3.3 Hz, 1H), 3.49 – 3.35 (m, 3H), 3.12 (tdd, J = 11.8, 7.7, 4.9 Hz, 1H), 2.99 (m, 1H), 2.80 (s, 3H), 2.59 (s, 3H), 2.44 (m, 2H), 2.05 (m,1H), 1.99 – 1.75 (m, 5H), 1.65 (m, 5H), 1.52 (dtd, J = 11.2, 6.8, 3.6 Hz, 4 H), 1.36 – 1.17 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 66.6, 66.3, 64.2, 61.7, 53.9, 50.5, 35.1, 34.7, 34.5, 30.3, 29.4, 29.2, 28.8, 26.7, 24.2, 22.1, 21.6; HRMS calcd for $C_9H_{18}NO$+ [M+] 156.1388 found 156.1400.



9: octahydro-1H-indol-6-ol, HCl

6 (47 mg, 0.20 mmol, 1 eq) was dissolved in ether (1 ml) and 2M HCl in ether (0.97 ml, 1.95 mmol, 10 eq) was added dropwise to the solution. The mixture was stirred at rt for 2 h to furnish the desired product as the HCl salt. The supernatant was removed and the remaining viscous oil evaporated to dryness to provide the title compounds as a yellow viscous oil (29 mg, 0.16 mmol, 84%). (Note that the diastereomerically pure compound appears as a mixture of diastereoisomers in the NMR spectra due to the two possible orientations of the protonated amine).

R_f (free amine) = 0.34 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 2H), 8.35 (s, 2H), 3.57 (m, 4H), 3.46 – 3.30 (m, 2H), 3.22 – 3.04 (m, 2H), 2.31 – 2.13 (m, 2H), 1.96 – 1.76 (m, 6H), 1.72 – 1.31 (m, 10H); ^{13}C NMR (101 MHz, DMSO) δ 65.2, 56.8, 42.2, 35.4, 32.2, 29.1, 26.2, 21.1; HRMS calcd for $C_8H_{16}NO$+ [M+] 142.1232 found 142.1254



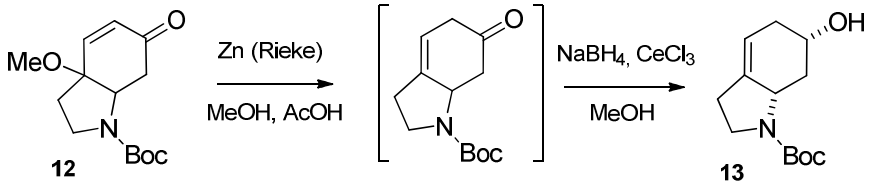
12: tert-butyl 3a-methoxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate

N-Boc-tyramine (**10**, 2.0 g, 8.43 mmol, 1.0 eq) was dissolved in MeOH (50 ml) under N_2 atm. $NaHCO_3$ (2.83 g, 33.7 mmol, 4.0 eq) was added. The mixture was stirred for 10 min and then cooled to 0°C. PIFA (4.35 g, 10.1 mmol, 1.2 eq) was added in small portions over 30 min. and then stirred for additionally 30 min. The

reaction was filtered, concentrated *in vacuo* onto celite, and purified by dry column vacuum chromatography (Heptane -> EtOAc, 10% grad.) to obtain **11** as a colorless oil (1.46 g, 5.48 mmol, 65 %). Then redissolved in a solution of $NaHCO_3$ (2.30 g, 27.4 mmol, 5.0 Eq) in MeOH (50 ml) and stirred at rt for 15 h. The solvent was removed *in vacuo* and brine (50 ml) was added to the mixture. The mixture was extracted with ethyl acetate (4x40 ml), and the combined organic layers were washed with brine (30 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* onto celite and purified by dry column vacuum chromatography (Heptane -> EtOAc, 10% grad.) to obtain **12** as a yellow oil (1.38 g, 5.16 mmol, 94 %).

11: R_f = 0.68 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 10.3 Hz, 2H), 6.30 (d, *J* = 10.3 Hz, 2H), 4.73 (s, 1H), 3.14 (m, 5H), 1.85 (t, *J* = 7.2 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 155.7, 150.1, 131.6, 79.4, 74.7, 53.0, 39.8, 36.1, 28.4; LRMS (LCMS) calcd for $C_{14}H_{22}NO_4$+ [M+] 268.1549 found 268.

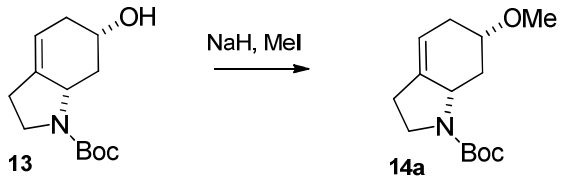
12: R_f = 0.70 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.70 - 6.87 (m, 1 H), 6.14 (m, 1 H), 4.26 - 4.54 (m, 1 H), 3.42 - 3.70 (m, 2 H), 3.28 (s, 3 H), 2.95 - 3.19 (m, 1 H), 2.40 (m, 1 H), 2.16 - 2.27 (m, 1 H), 2.06 - 2.16 (m, 1 H), 1.39 - 1.52 (m, 9 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 196.9, 154.1, 148.2, 131.5, 82.0, 80.2, 58.0, 51.5, 44.8, 43.0, 34.5, 28.5; LRMS (LCMS) calcd for $C_{14}H_{22}NO_4$+ [M+] 268.1549 found 268.



13: tert-butyl 6-hydroxy-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxylate

12 (1.20 g, 4.489 mmol, 1 eq) was dissolved in MeOH (60 ml). Zn (Rieke) (30 ml suspension, 1.50 g, 22.94 mmol, 5.1 eq) and AcOH (480 µl, 1.9 eq) were added. The mixture was stirred at rt for 25 min, TLC showed full conversion of starting material. The mixture was filtered through celite and the filter was washed with MeOH. $CeCl_3$ (150 mg, 0.609 mmol, 0.14 eq) was added. The mixture was cooled to -30°C and $NaBH_4$ (500 mg, 12.86 mmol, 2.9 eq) was added over 15 min. The mixture was stirred for additional 2 hours at -30°C. TLC showed full conversion of the ketone-intermediate. The mixture was evaporated *in vacuo* on celite and purified by dry column vacuum chromatography (Heptane -> EtOAc-> MeOH, 10% Grad.) to obtain **13** as a yellow oil (876 mg, 3.66 mmol, 82 %).

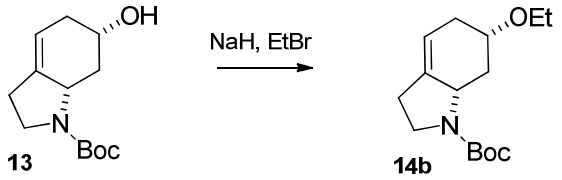
R_f = 0.38 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.44 - 5.54 (m, 1 H), 3.93 - 4.07 (m, 2 H), 3.62 - 3.77 (m, 1 H), 3.15 (m, 1 H), 2.64 - 2.86 (m, 1 H), 2.35 - 2.55 (m, 2 H), 2.25 - 2.35 (m, 1 H), 1.94 - 2.04 (m, 1 H), 1.82 - 1.93 (m, 1 H), 1.48 (s, 9 H), 1.23 - 1.33 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.9, 138.8, 118.2, 79.5, 66.5, 56.0, 46.2, 38.5, 34.7, 30.2, 28.5; ; LRMS (GCMS) calcd for $C_{13}H_{21}NO_3$+ [M+] 239.1521 found 239.



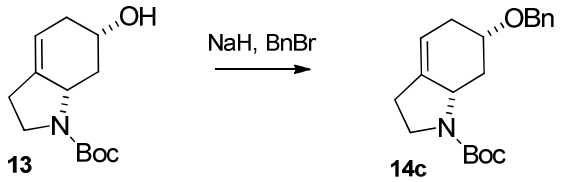
14a: tert-butyl 6-methoxy-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxylate

13 (300 mg, 1.25 mmol, 1 eq) was dissolved in dry DMF (15 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (125 mg, 3.12 mmol, 2.5 eq) was added slowly. The mixture was stirred at 0 °C for 30 min. The ice-bath was removed and methyl iodide (315 µl, 5.06 mmol, 4.0 eq) was added. The mixture was stirred at rt overnight. TLC showed almost full conversion of starting material. Brine was added (20 ml) and the mixture was extracted with ethyl acetate (3x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by

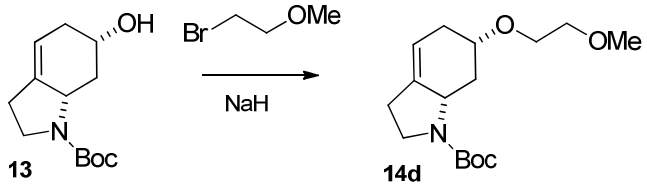
column chromatography (Heptane→EtOAc, 5 % grad) to obtain the title compound as a colorless oil (282 mg, 1.11 mmol, 89 %).
R_f = 0.72 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.44 - 5.58 (m, 1 H), 3.89 - 4.05 (m, 1 H), 3.65 - 3.79 (m, 1 H), 3.47 - 3.59 (m, 1 H), 3.39 (s, 3 H), 3.09 - 3.23 (m, 1 H), 2.81 - 3.01 (m, 1 H), 2.37 - 2.57 (m, 2 H), 2.26 - 2.36 (m, 1 H), 1.92 - 2.04 (m, 1 H), 1.44 - 1.54 (s, 9 H), 1.02 - 1.20 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.9, 139.1, 118.1, 79.4, 75.3, 56.1, 56.0, 46.2, 34.1, 32.0, 30.2, 28.6 ; ; LRMS (GCMS) calcd for $C_{14}H_{23}NO_3$+ [M+] 253.1678 found 253.



14b: tert-butyl 6-ethoxy-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxylate
13 (180 mg, 0.752 mmol, 1 eq) was dissolved in dry DMF (10 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (125 mg, 3.134 mmol, 4.2 eq) was added slowly. The mixture was stirred at 0 °C for 20 min. The ice-bath was removed and ethyl bromide (141 µl, 1.888 mmol, 2.5 eq) was added. The mixture was stirred at rt overnight. TLC showed full conversion of starting material. Brine was added (20 ml) and the mixture was extracted with ethyl acetate (3x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by column chromatography (Heptane→EtOAc, 5 % grad) to obtain the title compound as a colorless oil (82 mg, 0.308 mmol, 41 %).
R_f = 0.75 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.41 - 5.60 (m, 1 H), 3.88 - 4.06 (m, 1 H), 3.66 - 3.77 (m, 1 H), 3.56 - 3.66 (m, 2 H), 3.47 - 3.57 (m, 1 H), 3.08 - 3.22 (m, 1 H), 2.76 - 2.97 (m, 1 H), 2.36 - 2.55 (m, 2 H), 2.25 - 2.35 (m, 1 H), 1.92 - 2.08 (m, 1 H), 1.49 (s, 9 H), 1.22 (m, 3 H), 1.07 - 1.17 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.8, 139.0, 118.3, 79.3, 73.5, 63.7, 56.1, 46.2, 34.9, 32.4, 30.2, 28.5 , 15.6; ; LRMS (GCMS) calcd for $C_{15}H_{25}NO_3$+ [M+] 267.1834 found 267.

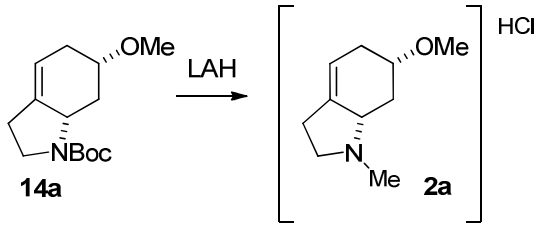


14c: tert-butyl 6-(benzyloxy)-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxylate
13 (274 mg, 1.15 mmol, 1 eq) was dissolved in dry DMF (10 ml) under N_2 atm. The mixture was cooled to 0 °C and NaH in a 60% suspension (150 mg, 3.750 mmol, 3.3 eq) was added slowly. The mixture was stirred at 0 °C for 20 min. The ice-bath was removed and benzyl bromide (600 µl, 5.05 mmol, 4.4 eq) was added. The mixture was stirred at rt overnight. TLC showed full conversion of starting material. Brine was added (20 ml) and the mixture was extracted with ethyl acetate (3x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by column chromatography (EtOAc:Heptane 1:2) to obtain **14c** as bright yellow solid (246 mg, 0.747 mmol, 65 %).
R_f = 0.86 (silica gel, heptanes/EtOAc, 1:1); Mp: (108.2 – 109.1 °C); R_f = 0.57 (silica gel, heptanes/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 - 7.41 (m, 5 H), 5.43 - 5.61 (m, 1 H), 4.45 - 4.77 (m, 2 H), 3.87 - 4.07 (m, 1 H), 3.61 - 3.80 (m, 2 H), 3.09 - 3.23 (m, 1 H), 2.87 - 3.07 (m, 1 H), 2.47 - 2.58 (m, 1 H), 2.36 - 2.46 (m, 1 H), 2.27 - 2.36 (m, 1 H), 2.02 - 2.17 (m, 1 H), 1.50 (s, 9 H), 1.13 - 1.34 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.9, 138.7, 128.4, 127.8, 127.6, 127.5, 118.2, 79.4, 73.2, 70.3, 56.1, 46.2, 34.6, 32.4, 30.2, 28.54; LRMS (GCMS) calcd for $C_{20}H_{27}NO_3$+ [M+] 329.1991 found 329.



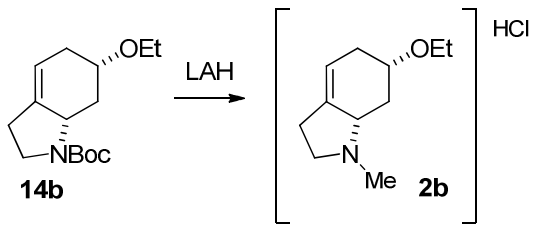
14d: tert-butyl 6-(2-methoxyethoxy)-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxylate

13 (198 mg, 0.827 mmol, 1 eq) was dissolved in dry DMF (10 ml) under N_2 atm. The mixture was cooled to 0 ^oC and NaH in a 60% suspension (100 mg, 2.500 mmol, 3.0 eq) was added slowly. The mixture was stirred at 0 ^oC for 15 min. The ice-bath was removed and 2-methoxy ethylbromide (200 µl, 2.128 mmol, 2.6 eq) was added. The mixture was stirred at rt overnight. TLC showed almost full conversion of starting material. Brine was added (20 ml) and the mixture was extracted with ethyl acetate (3x20 ml). The combined organic layers were washed with water (40 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* on celite and purified by column chromatography (EtOAc:Heptane 1:1) to obtain **14d** as a yellowish oil (90 mg, 0.302 mmol, 37 %).
R_f = 0.55 (silica gel, heptanes/EtOAc, 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.40 - 5.56 (m, 1 H), 3.89 - 4.01 (m, 1 H), 3.58 - 3.75 (m, 4 H), 3.54 (m, 2 H), 3.38 (s, 3 H), 3.14 (m, 1 H), 2.78 - 3.01 (m, 1 H), 2.36 - 2.55 (m, 2 H), 2.23 - 2.35 (m, 1 H), 1.96 - 2.11 (m, 1 H), 1.48 (s, 9 H), 1.07 - 1.29 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 154.8, 139.0, 118.2, 79.3, 74.4, 72.2, 67.7, 59.1, 56.0, 46.2, 34.5, 32.2, 30.2, 28.5; LRMS (GCMS) calcd for $C_{16}H_{27}NO_4$+ [M+] 297.1940 found 297.



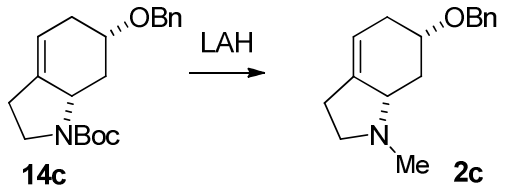
14a: 6-methoxy-1-methyl-2,3,5,6,7,7a-hexahydro-1H-indol, HCl

2a (90 mg, 0.355 mmol, 1 eq) was dissolved in dry THF (5 ml) under N_2 atm. LAH (45 mg, 1.186 mmol, 3.3 eq) was added and the mixture was refluxed for 1 h, quenched by adding ether (5 ml), and dropwise addition of water (45 µl), 15 % NaOH solution (45 µl) and H_2O (90 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1 ml) dropwise whereby a precipitate was formed at the bottom of the flask. The supernatant was removed and the remains were evaporated to dryness in order to provide the title compound as an off-white solid (61 mg, 0.297 mmol, 84 %).
R_f (free amine) = 0.40 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^1H NMR (400 MHz, D_2O) δ ppm 5.71 - 5.83 (m, 1 H), 3.65 - 3.90 (m, 3 H), 3.42 (s, 3 H), 3.20 - 3.33 (m, 1 H), 2.95 (s, 3 H), 2.75 - 2.86 (m, 1 H), 2.67 - 2.74 (m, 1 H), 2.55 - 2.67 (m, 2 H), 1.91 - 2.09 (m, 1 H), 1.42 (q, *J* = 11.29 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ ppm 133.5, 120.7, 73.9, 65.0, 55.5, 53.7, 37.2, 31.1, 28.6, 25.9; HRMS calcd for $C_{10}H_{18}NO$+ [M+] 168.1388 found 168.1380

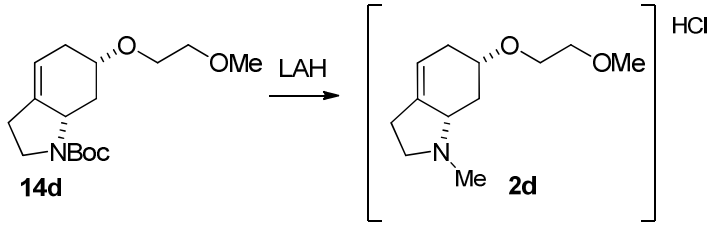


2b: 6-ethoxy-1-methyl-2,3,5,6,7,7a-hexahydro-1H-indol, HCl

14b (80 mg, 0.2994 mmol, 1 eq) was dissolved in dry THF (5 ml) under N_2 atm. LAH (40 mg, 1.054 mmol, 3.5 eq) was added and the mixture was refluxed for 1 h, quenched by adding ether (5 ml), and dropwise addition of water (40 µl), 15 % NaOH solution (40 µl) and H_2O (80 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1 ml) dropwise whereby a viscous oil was formed at the bottom of the flask. The supernatant was removed and the remains were evaporated to dryness in order to provide the title compound as a yellow oil (63 mg, 0.290 mmol, 97 %).
R_f (free amine) = 0.45 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, D_2O) δ ppm 5.71 - 5.82 (m, 1 H), 3.75 - 3.89 (m, 3 H), 3.58 - 3.73 (m, 2 H), 3.19 - 3.32 (m, 1 H), 2.95 (s, 3 H), 2.73 - 2.86 (m, 1 H), 2.54 - 2.71 (m, 3 H), 1.94 - 2.05 (m, 1 H), 1.44 (q, *J*=11.17 Hz, 1 H), 1.13 - 1.23 (m, 3 H); ^{13}C NMR (101 MHz, D_2O) δ ppm 132.0, 122.2, 72.9, 66.1, 64.4, 55.0, 37.6, 31.0, 29.4, 25.6, 14.5; HRMS calcd for $C_{11}H_{20}NO^+$ [M+] 182.1545 found 182.1547.

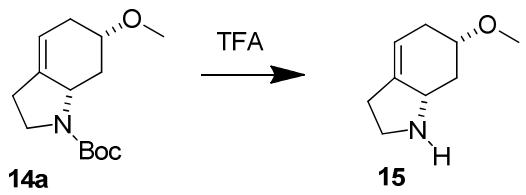


12c: 6-(benzyloxy)-1-methyl-2,3,5,6,7,7a-hexahydro-1H-indole
11c (240 mg, 0.729 mmol, 1 eq) was dissolved in dry THF (10 ml) under N_2 atm. LAH (82 mg, 2.161 mmol, 3.0 eq) was added and the mixture was refluxed for 1 h. TLC showed almost full conversion of starting material. Excess of LAH was quenched by adding Ether (5 ml), H_2O (82 µl), 15 % NaOH solution (82 µl) and H_2O (164 µl). The mixture was filtered, concentrated *in vacuo* on celite and purified by dry column vacuum chromatography (Hep→EtOAc (10 % TEA), 5 % grad) to obtain the title compound as a yellow oil (67 mg, 0.275 mmol, 38 %).
R_f (free amine) = 0.47 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 - 7.41 (m, 5 H), 5.30 - 5.45 (m, 1 H), 4.64 (s, 2 H), 3.64 - 3.81 (m, 1 H), 3.15 (m, 1 H), 2.48 - 2.58 (m, 1 H), 2.33 - 2.47 (m, 7 H), 2.22 (q, *J*=9.03 Hz, 1 H), 2.04 - 2.16 (m, 1 H), 1.22 - 1.41 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 140.5, 138.7, 128.3, 127.6, 127.5, 116.0, 73.9, 70.3, 65.9, 55.9, 40.3, 34.0, 32.3, 27.6; HRMS calcd for $C_{16}H_{22}NO^+$ [M+] 244.1701 found 244.1709.



2d: 6-(2-methoxyethoxy)-1-methyl-2,3,5,6,7,7a-hexahydro-1H-indol, HCl
14d (90 mg, 0.303 mmol, 1 eq) was dissolved in dry THF (6 ml) under N_2 atm. LAH (38 mg, 1.001 mmol, 3.3 eq) was added and the mixture was refluxed for 1 h. TLC showed full conversion of starting material. Excess of LAH was quenched by adding Ether (5 ml), H_2O (38 µl), 15 % NaOH solution (38 µl) and H_2O (76 µl). The mixture was filtered and the filter was washed with ether. The mixture was evaporated until almost all solvent was removed. Ether (5 ml) and 2 M HCl in Ether (0.5 ml) was added. A yellowish oil was formed at the bottom of the flask. The supernatant was removed and the remaining solvent was evaporated *in vacuo*. **2d** was isolated as yellow oil (72 mg, 0.291 mmol, 96 %).
R_f (free amine) = 0.31 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, D_2O) δ ppm 5.68 - 5.80 (m, 1 H), 3.69 - 3.90 (m, 5 H), 3.62 (t, *J*=4.27 Hz, 2 H), 3.37 (s, 3 H), 3.27 (q, *J*=10.30 Hz, 1 H), 2.95 (s, 3 H), 2.74 - 2.86 (m, 1 H), 2.54 - 2.72 (m, 3 H), 1.96 - 2.09 (m, 1 H), 1.46 (q, *J*=11.42 Hz, 1 H); ^{13}C NMR

(101 MHz, D_2O) δ ppm 132.0, 122.1, 73.4, 71.2, 67.2, 66.1, 58.1, 55.0, 37.7, 30.8, 29.3, 25.6; HRMS calcd for $C_{12}H_{22}NO_2$+ [M+] 212.1651 found 212.1656.

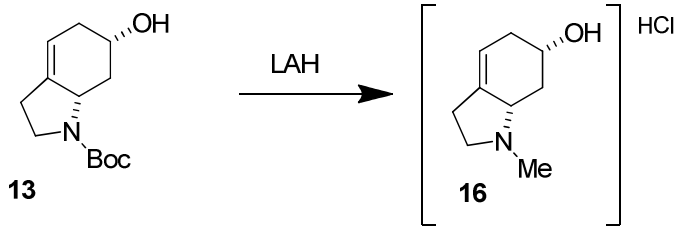


14a **15**

15: 6-methoxy-2,3,5,6,7,7a-hexahydro-1H-indole

A solution of **14a** (33 mg, 0.13 mmol, 1.0 Eq) in dry DCM (2 ml) was cooled to 0°C and added TFA (0.50 mL, 50 Eq) and stirred for 1 h. Then evaporated crude onto Celite and purified by dry column vacuum chromatography (EtOAc -> MeOH (10% NH_3), 10% Grad.) to obtain **15** as a colorless oil (17 mg, 0.11 mmol, 85%).

R_f (free amine) = 0.55 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, MeOD) δ 5.55 (dq, *J* = 4.4, 2.2 Hz, 1H), 3.56 (m, 2H), 3.39 (s, 3H), 3.21 (ddd, *J* = 11.3, 8.5, 4.5 Hz, 1H), 3.07 (ddd, *J* = 11.3, 9.2, 7.6 Hz, 1H), 2.60 – 2.44 (m, 4H), 2.02 – 1.89 (m, 1H), 1.30 (q, *J* = 11.2 Hz, 1H); ^{13}C NMR (101 MHz, MeOD) δ 139.6, 118.9, 76.8, 59.0, 56.4, 45.8, 34.2, 33.0, 29.5; HRMS calcd for $C_9H_{16}NO$+ [M+] 154.1232 found 154.1228.

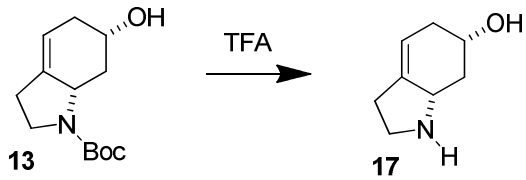


13 **16**

16: 1-methyl-2,3,5,6,7,7a-hexahydro-1H-indol-6-ol, HCl

13 (100 mg, 0,418 mmol, 1.0 Eq) was dissolved in dry THF (5 ml), cooled to 0 °C, and slowly added LAH (48 mg, 1,25 mmol, 3.0 Eq). Then refluxed for 3 h for full conversion of starting material and quenched by adding ether (5 ml), and dropwise addition of water (50 µl), 15 % NaOH solution (50 µl) and H_2O (100 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1.5 ml) dropwise whereby a precipitate was formed at the bottom of the flask. The supernatant was removed and the remains were evaporated to dryness to provide the title compound as white hydroscopic solid (69 mg, 0.364 mmol, 87 %).

R_f (free amine) = 0.46 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, MeOD) δ 5.76 (dt, *J* = 4.7, 2.4 Hz, 1H), 3.95 (dddd, *J* = 11.8, 9.4, 6.0, 3.5 Hz, 1H), 3.79 (ddd, *J* = 12.0, 9.0, 3.3 Hz, 2H), 3.29 – 3.21 (m, 1H), 2.95 (s, 3H), 2.87 – 2.74 (m, 1H), 2.64 (m, 1H), 2.56 – 2.44 (m, 2H), 2.03 (m, 1H), 1.53 (q, *J* = 11.2 Hz, 1H); ^{13}C NMR (101 MHz, MeOD) δ 133.7, 124.0, 67.6, 66.2, 56.1, 38.4, 35.1, 34.1, 27.0; HRMS calcd for $C_9H_{16}NO$+ [M+] 154.1232 found 154.1247.

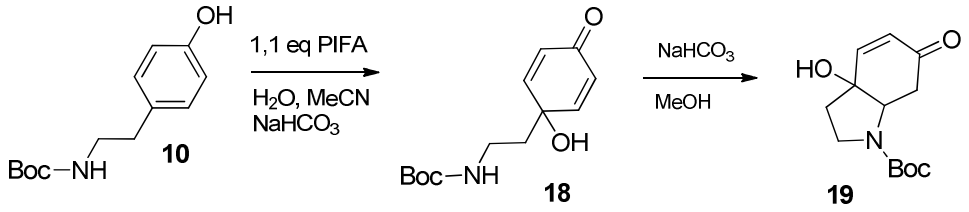


13 **17**

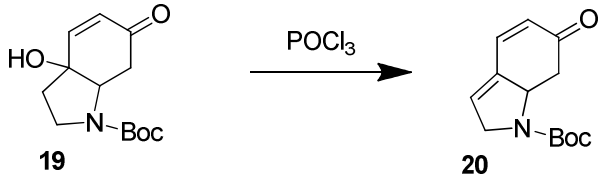
17: 2,3,5,6,7,7a-hexahydro-1H-indol-6-ol

A solution of **13** (33 mg, 0.13 mmol, 1.0 Eq) in dry DCM (4 ml) was cooled to 0°C and added TFA (1.0 mL, 50 Eq) and stirred for 1 h. Then evaporated crude onto Celite and purified by dry column vacuum

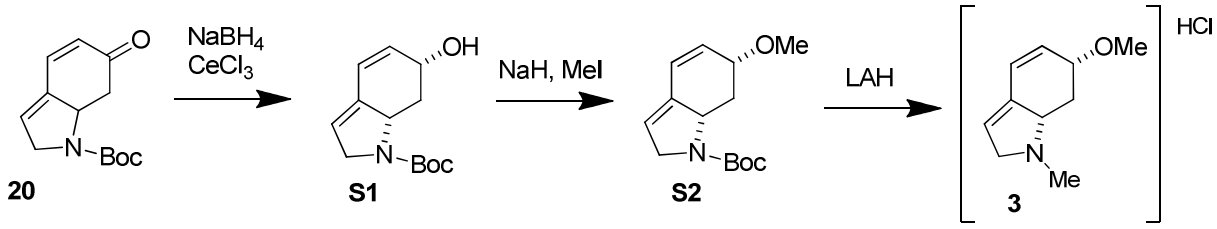
chromatography (EtOAc -> MeOH (10% NH_3), 10% Grad.) to obtain **17** as a colorless oil (32 mg, 0.23 mmol, 89 %).
R_f (free amine) = 0.38 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, MeOD) δ 5.63 (dt, *J* = 4.6, 2.3 Hz, 1H), 3.94 (m, 1H), 3.81 – 3.67 (m, 1H), 3.34 – 3.27 (m, 1H), 3.21 (ddd, *J* = 11.6, 9.6, 7.3 Hz, 1H), 2.68 – 2.41 (m, 3H), 2.41 – 2.32 (m, 1H), 2.00 (m, 1H), 1.49 (q, *J* = 11.2 Hz, 1H); ^{13}C NMR (101 MHz, MeOD) δ 137.2, 120.9, 66.8, 59.1, 45.5, 36.7, 35.5, 28.8; LRMS (LCMS) calcd for $C_8H_{14}NO$+ [M+] 140.1075 found 140.1082.



19: tert-butyl 3a-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate
N-Boc-tyramine (1.2 g, 5.06 mmol, 1.0 eq) was dissolved in MeCN (40 ml) and water (10 ml) under N_2 atm. and $NaHCO_3$ (1.70 g, 20.2 mmol, 4.0 eq) was added. The mixture was cooled to 0°C and then PIFA (2.61 g, 6.07 mmol, 1.2 eq) was added in small portions over 30 min. and then stirred for additionally 30 min. The reaction was filtered, concentrated *in vacuo* onto celite, and purified by dry column vacuum chromatography (Heptane -> EtOAc -> MeOH, 10% grad.) to obtain **18** as a colorless oil (0.88 g, 3.47 mmol, 69 %). Then redissolved in a solution of $NaHCO_3$ (1.46 g, 17.4 mmol, 5.0 Eq) in MeOH (20 ml) and stirred at rt for 15 h. The solvent was removed *in vacuo* and brine (30 ml) was added to the mixture. The mixture was extracted with ethyl acetate (3x30 ml), and the combined organic layers were washed with brine (20 ml), dried with Na_2SO_4, filtered, evaporated *in vacuo* onto celite and purified by dry column vacuum chromatography (Heptane -> EtOAc -> MeOH, 10% grad.) to obtain **19** as a yellow oil (0.81 g, 3.20 mmol, 92 %).
18: R_f = 0.62 (silica gel, heptanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.88 – 6.76 (m, 2H), 6.19 – 6.04 (m, 2H), 4.77 (s, 1H), 3.19 (m, *J* = 6.9 Hz, 2H), 2.97 (s, 1H), 1.87 (t, *J* = 7.0 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2, 156.2, 150.5, 128.1, 79.9, 68.9, 40.4, 36.1, 28.4; LRMS (LCMS) calcd for $C_{13}H_{20}NO_4$+ [M+] 254.1392 found 254.
19: R_f = 0.61 (silica gel, heptanes/EtOAc, 1:1); LRMS (LCMS) calcd for $C_{13}H_{20}NO_4$+ [M+] 254.1392 found 254.



20: tert-butyl 6-oxo-2,6,7,7a-tetrahydro-1H-indole-1-carboxylate
19 (550 mg, 2.17 mmol, 1.0 Eq) was dissolved in pyridine (10 ml) and $POCl_3$ (0.506 ml, 5.43 mmol, 2.5 Eq) was added dropwise at rt and stirred for 15 h. Then the mixture was cooled on ice and a saturated aqueous solution of sodium bicarbonate (50 ml) was added and after stirring for 10 minutes, the mixture was extracted with dichloromethane (3×30 mL). The combined organic phases were washed with brine (30 mL), dried with magnesium sulfate and concentrated *in vacuo* to provide the title compound as a colorless oil (439 mg, 1.87 mmol, 86 % yield). The product was moved on crude in the next step.
R_f = 0.68 (silica gel, Heptane/EtOAc, 1:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 (t, *J* = 8.5 Hz, 1H), 6.01 – 5.69 (m, 2H), 4.82 – 4.64 (m, 1H), 4.29 (d, *J* = 17.9 Hz, 2H), 3.29 – 3.14 (m, 1H), 2.37 (ddd, *J* = 20.0, 13.8, 7.7 Hz, 1H), 1.42 (d, *J* = 5.7 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 154.4, 138.5, 135.6, 129.6, 125.3, 80.6, 61.4, 55.5, 46.1, 28.5; LRMS (LCMS) calcd for $C_{13}H_{18}NO_3$+ [M+] 236.1287 found 236.



3: 6-methoxy-1-methyl-2,6,7,7a-tetrahydro-1H-indole, HCl

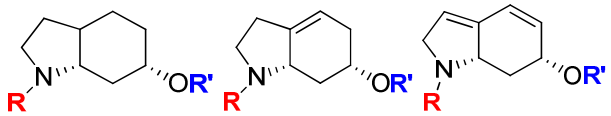
20 (103 mg, 0.438 mmol) and $CeCl_3$ (11 mg, 0.044 mmol, 0.10 Eq) was dissolved in MeOH (5 ml) and cooled to 0 ^oC. Then sodium borohydride (16.6 mg, 0.438 mmol, 1.0 Eq) was added and stirred for 30 min for full conversion of starting material. The mixture was evaporated directly onto celite and purified by dry column vacuum chromatography (Heptane->EA->MeOH, 10% grad.) to furnish diene-ol (**S1**) as a colorless oil as a mixture of rotamers (93 mg, 0.392 mmol, 90%). R_f = 0.75 (silica gel, Heptane/EtOAc, 1:2); LRMS (LCMS) calcd for $C_{13}H_{20}NO_3$+ [M+] 238.1443 found 238.

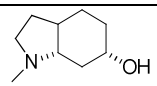
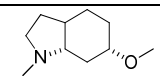
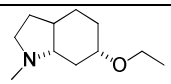
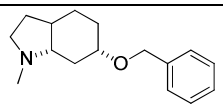
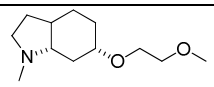
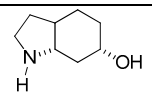
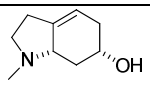
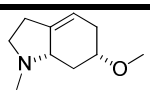
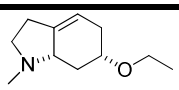
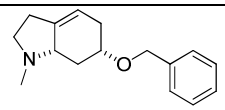
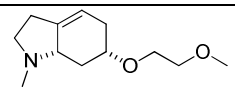
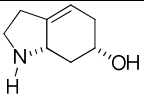
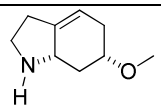
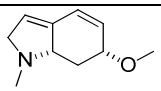
The diene-ol (**S1**, 93 mg, 0.392 mmol, 1.0 eq) was dissolved in dry DMF (3 ml) and cooled to 0 degreees, addition of sodium hydride (24 mg, 0.600 mmol, 1.5 eq) and stirred for 30 min. Then methyl iodide (0.123 ml, 1.96 mmol, 5.0 eq) was added and the mixture was stirred at rt for 15 h. Brine was added to the mixture (30 ml) and extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (2x10 mL), dried with magnesium sulfate, filtered, concentrated *in vacuo* onto cellite, and purified by dry column vacuum chromatography (Heptane->EtOAc, 5% grad). To furnish the methylether (**S2**) as a colorless oil as a mixture of rotamers (85 mg, 0.338 mmol, 86%). R_f = 0.70 (silica gel, Heptane/EtOAc, 1:2); LRMS (LCMS) calcd for $C_{14}H_{22}NO_3$+ [M+] 252.1600 found 252.

The methylether (**S2**, 85 mg, 0.338 mmol, 1.0 Eq) was dissolved in dry THF (3 ml) and added LAH (39 mg, 1.01 mmol, 3.0 Eq) slowly at rt. Then refluxed for 3 h for full conversion. and quenched by adding ether (5 ml), and dropwise addition of water (40 µl), 15 % NaOH solution (40 µl) and H_2O (80 µl) under vigorous stirring for 30 min and dried with magnesium sulfate. The mixture was filtered and added 2M HCl in Ether (1.5 ml) dropwise whereby a viscous oil was formed at the bottom of the flask. The supernatant was removed and the remains were evaporated to dryness to provide the title compound **3** as a yellow oil (61 mg, 0.302 mmol, 89 % yield).

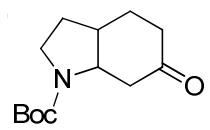
R_f (free amine) = 0.43 (silica gel, EtOAc/MeOH/TEA, 45:45:10); ^{1}H NMR (400 MHz, MeOD) δ 6.34 (dd, *J* = 10.1, 2.2 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 5.73 (d, *J* = 2.2 Hz 1H), 4.46 – 4.32 (m, 1H), 4.31 – 4.22 (m, 1H), 4.11 (m, 1H), 3.61 – 3.53 (m, 1H), 3.44 (s, 3H), 3.08 (s, 3H), 1.79 – 1.64 (m, 1H), 1.64 – 1.54 (m, 1H); ^{13}C NMR (101 MHz, MeOD) δ 138.0, 136.5, 121.8, 117.6, 76.7, 69.8, 62.8, 57.0, 38.7, 32.0, 30.2; HRMS calcd for $C_{10}H_{16}NO$+ [M+] 166.1232 found 166.1225

1.3. Pharmacological data



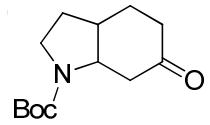
			Binding K_i (μM)			Functional IC_{50} (μM)	
Compound	R	R'	α4β2	α4β4	α3β4	α4β2	α3β4
DHβE	-	-	0.82 [6.09 ± 0.07]	~100	~100	1.2 [5.92 ± 0.06]	~100
8 	Me	H	□300	□300	□300	□300	□300
1a 	Me	Me	~300	□300	□300	□300	□300
1b 	Me	Et	~300	□300	~300	□300	□300
1c 	Me	Bn	~100	~300	~100	□300	□300
1d 	Me	$(CH_2)_2OMe$	~300	□300	~300	□300	□300
9 	H	H	□300	□300	□300	□300	□300
16 	Me	H	~300	□300	□300	□300	□300
2a 	Me	Me	**3.4** [5.46 ± 0.07]	~100	~300	**~30**	□300
2b 	Me	Et	~300	□300	□300	□300	□300
2c 	Me	Bn	~300	~300	~300	□300	□300
2d 	Me	$(CH_2)_2OMe$	□300	□300	□300	□300	□300
17 	H	H	□300	□300	□300	□300	□300
15 	H	Me	~300	□300	□300	~100	□300
3 	Me	Me	~30	□300	□300	~100	□300

1.4. NMR spectra



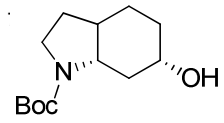
5

$CDCl_3$, 400 MHz



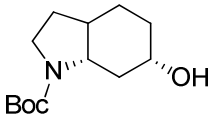
5

$CDCl_3$, 101 MHz



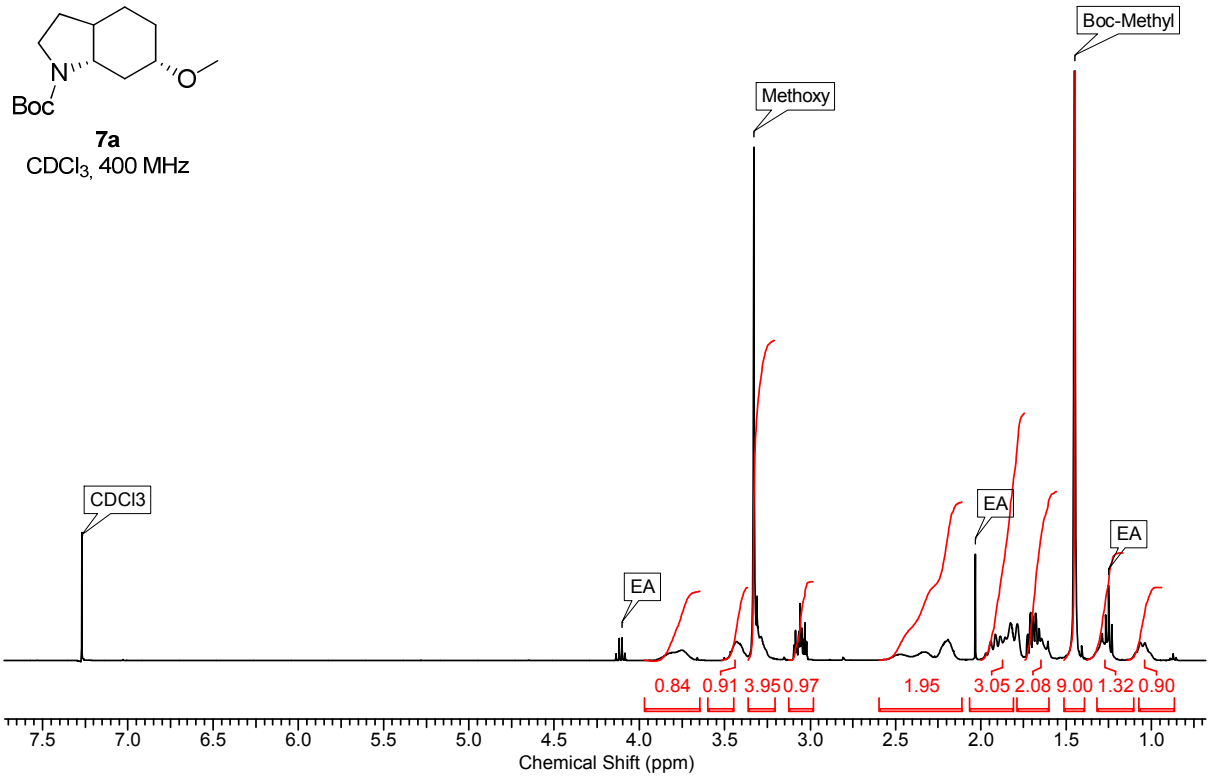
6

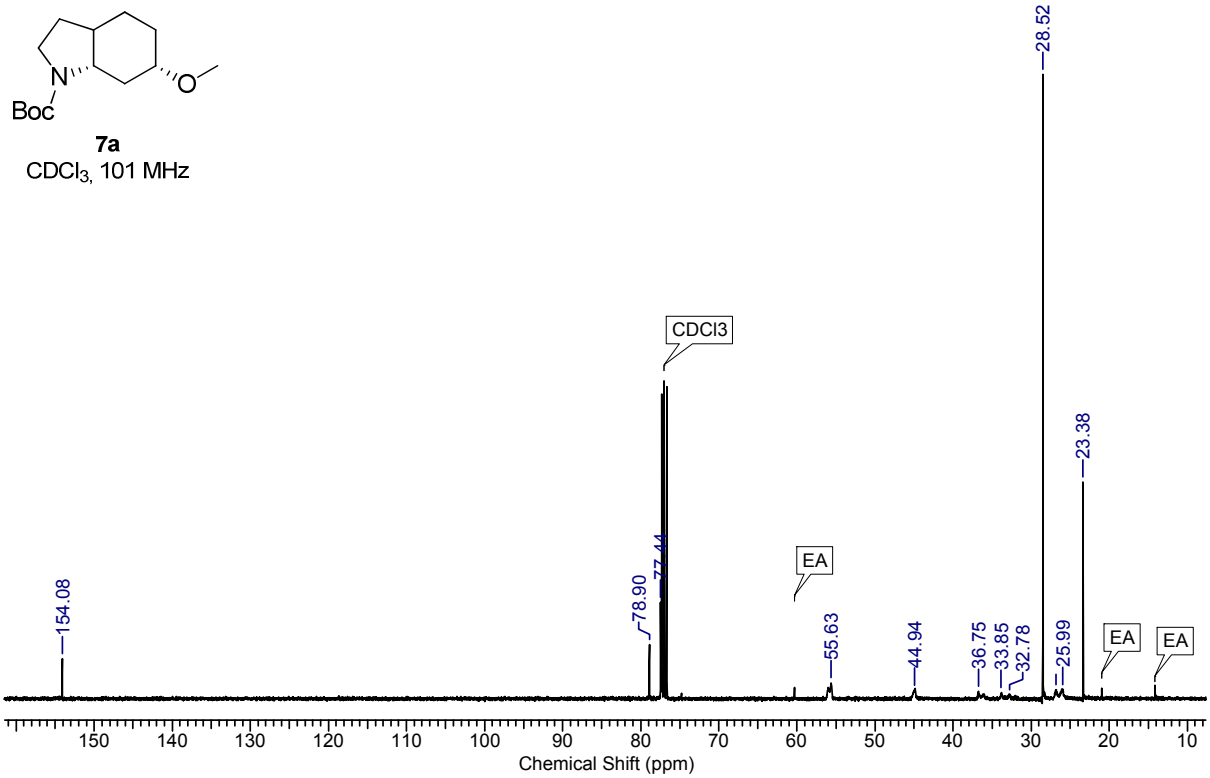
$CDCl_3$, 400 MHz

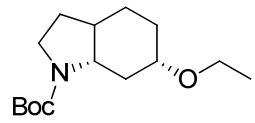


6

$CDCl_3$, 101 MHz

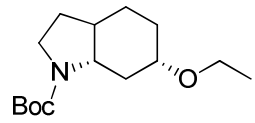

Boc
7a
CDCl3, 400 MHz
Boc-Methyl
Methoxy
CDCl3
EA
EA
EA
0.84 0.91 3.95 0.97 1.95 3.05 2.08 9.00 1.32 0.90
Chemical Shift (ppm)


Boc
7a
CDCl3, 101 MHz
28.52
CDCl3
23.38
154.08
78.90
77.44
EA
55.63
44.94
36.75
33.85
32.78
25.99
EA
EA
Chemical Shift (ppm)



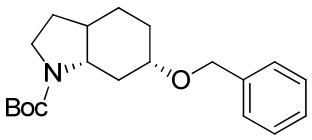
7b

$CDCl_3$, 400 MHz



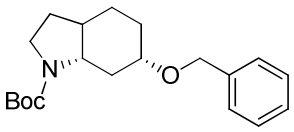
7b

$CDCl_3$, 101 MHz



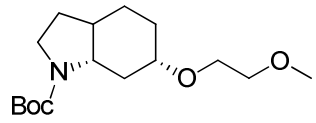
7c

$CDCl_3$, 400 MHz



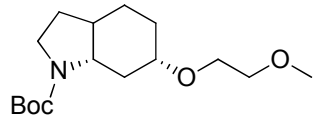
7c

$CDCl_3$, 101 MHz



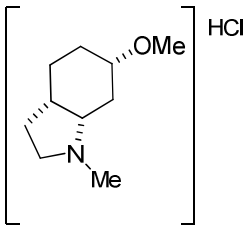
7d

$CDCl_3$, 400 MHz

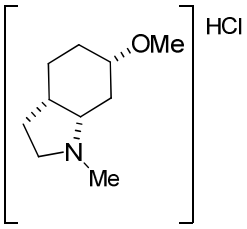


7d

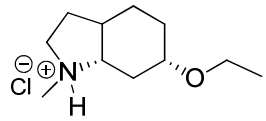
$CDCl_3$, 101 MHz



1a
DMSO-d_6, 400 MHz

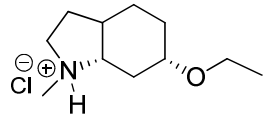


1a
DMSO-d_6, 101 MHz



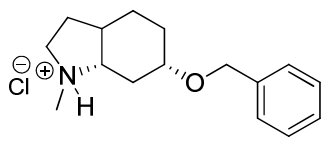
1b

DMSO-d_6, 400 MHz



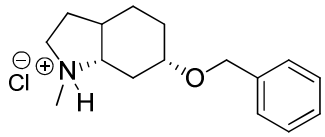
1b

DMSO-d_6, 101 MHz



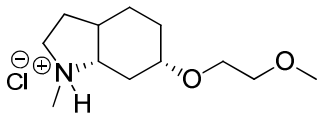
1c

DMSO-d_6, 400 MHz



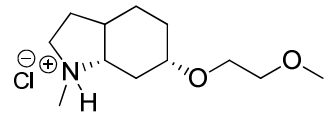
1c

DMSO-d_6, 101 MHz



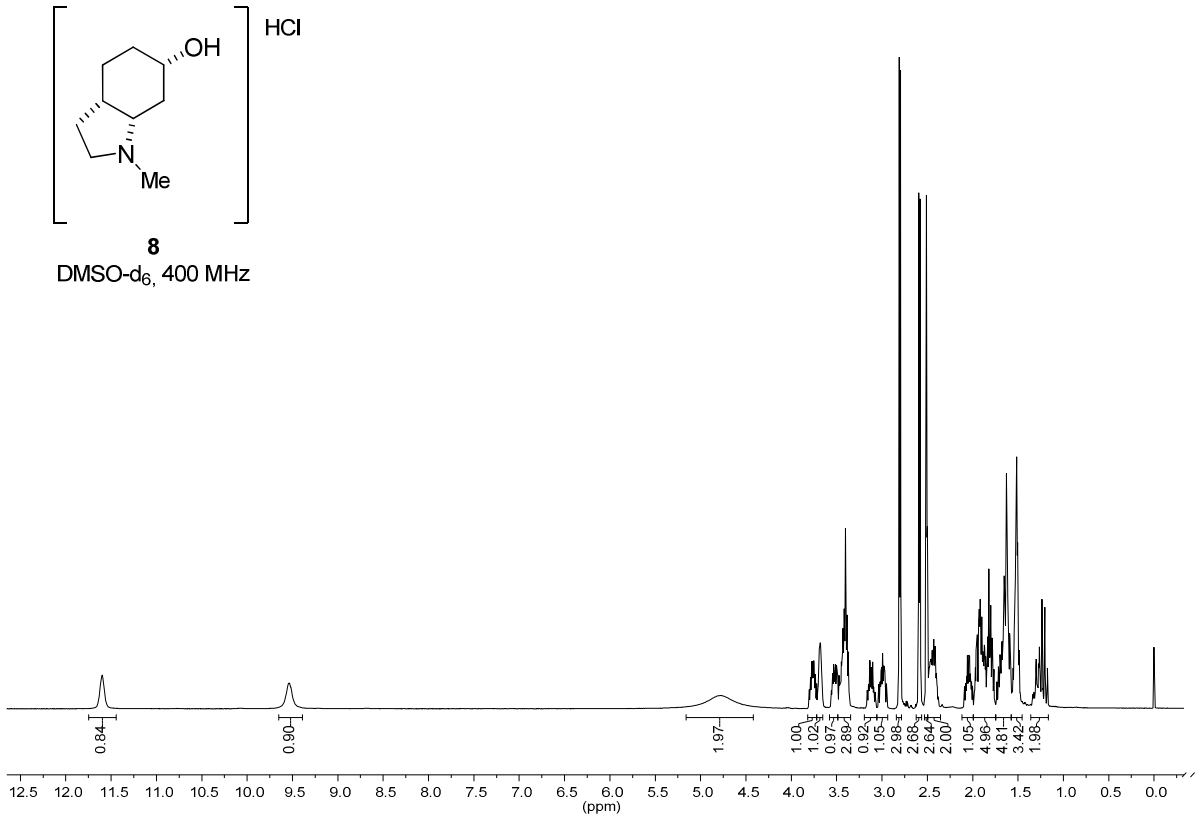
1d

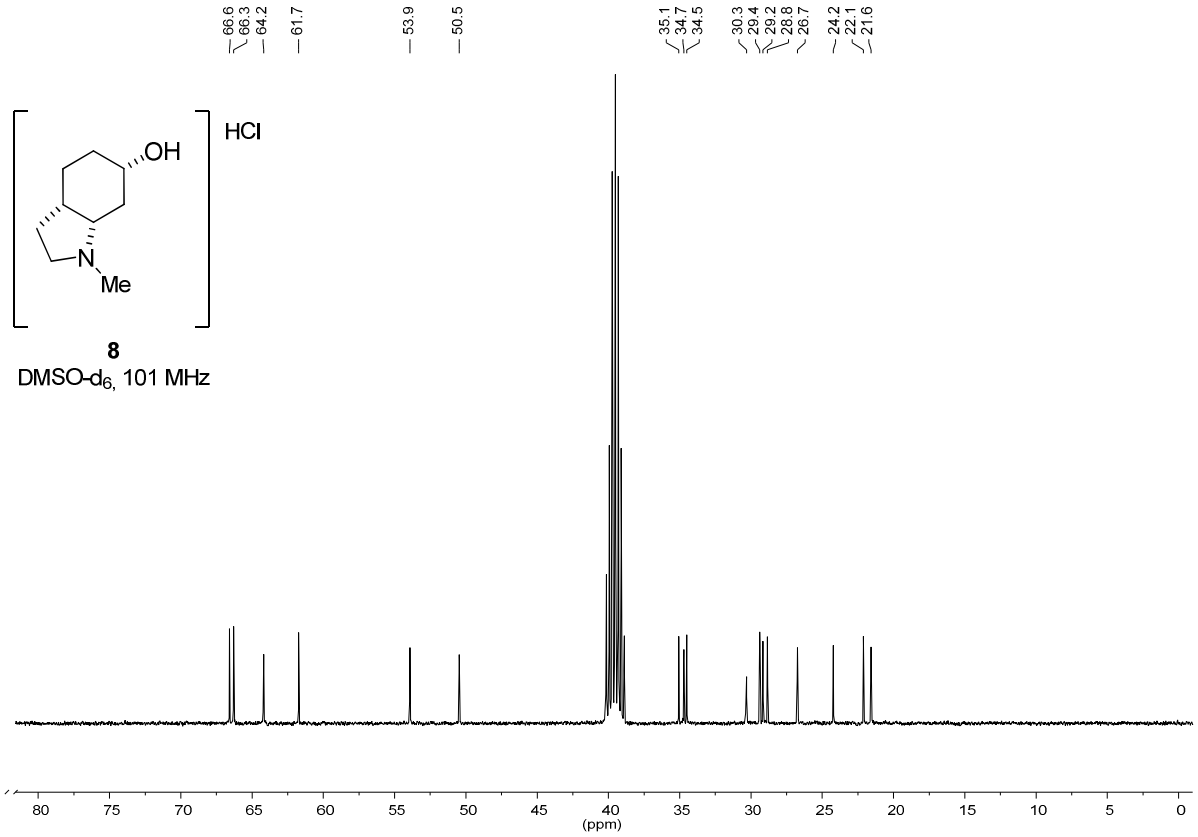
DMSO-d_6, 400 MHz



1d

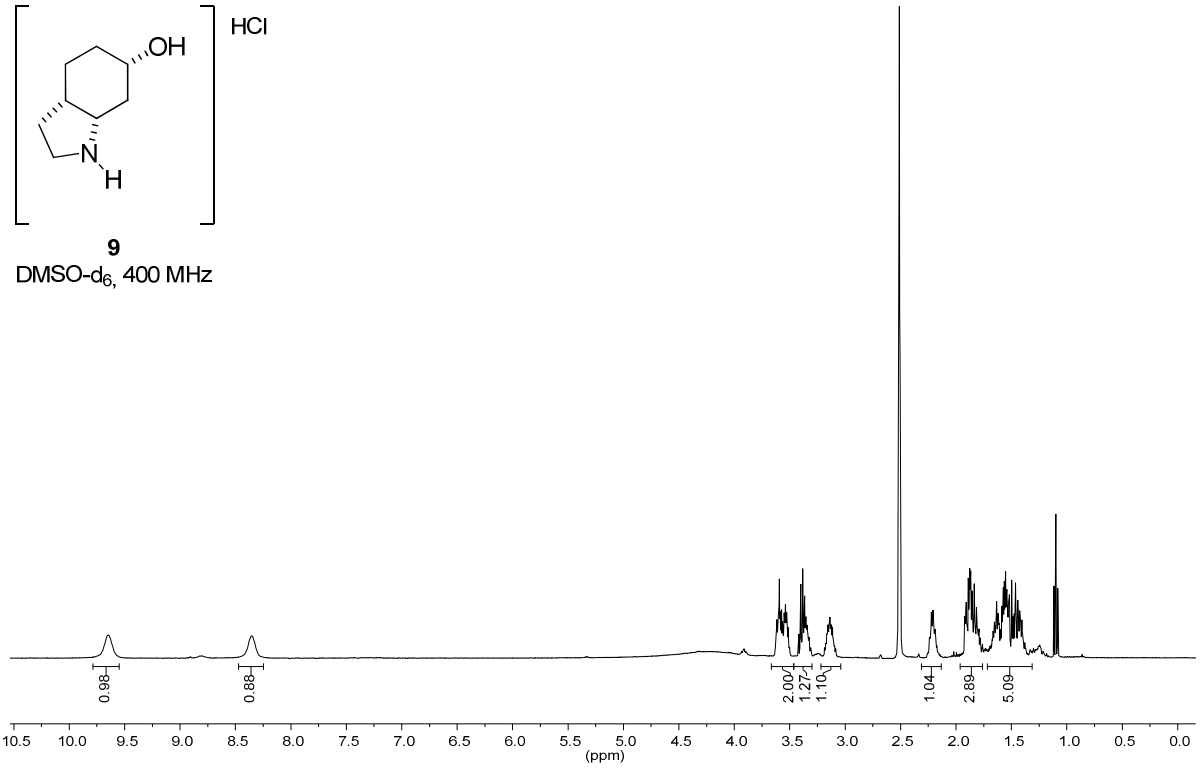
DMSO-d_6, 101 MHz

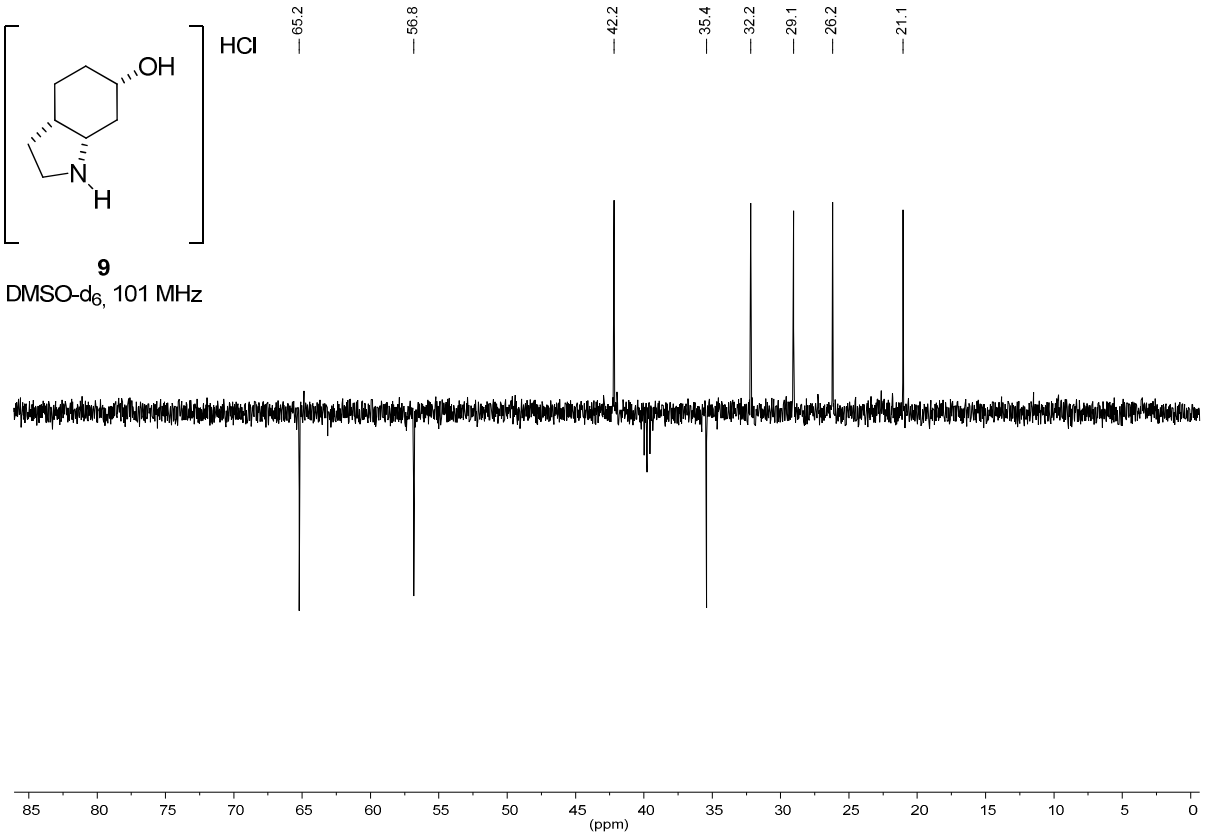

OH
HCl
N
Me
8
DMSO-d6, 400 MHz
0.84
0.90
1.97
1.00
1.02
0.97
2.89
0.92
1.05
2.98
2.68
2.64
2.00
1.05
4.96
4.81
3.42
1.98
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)



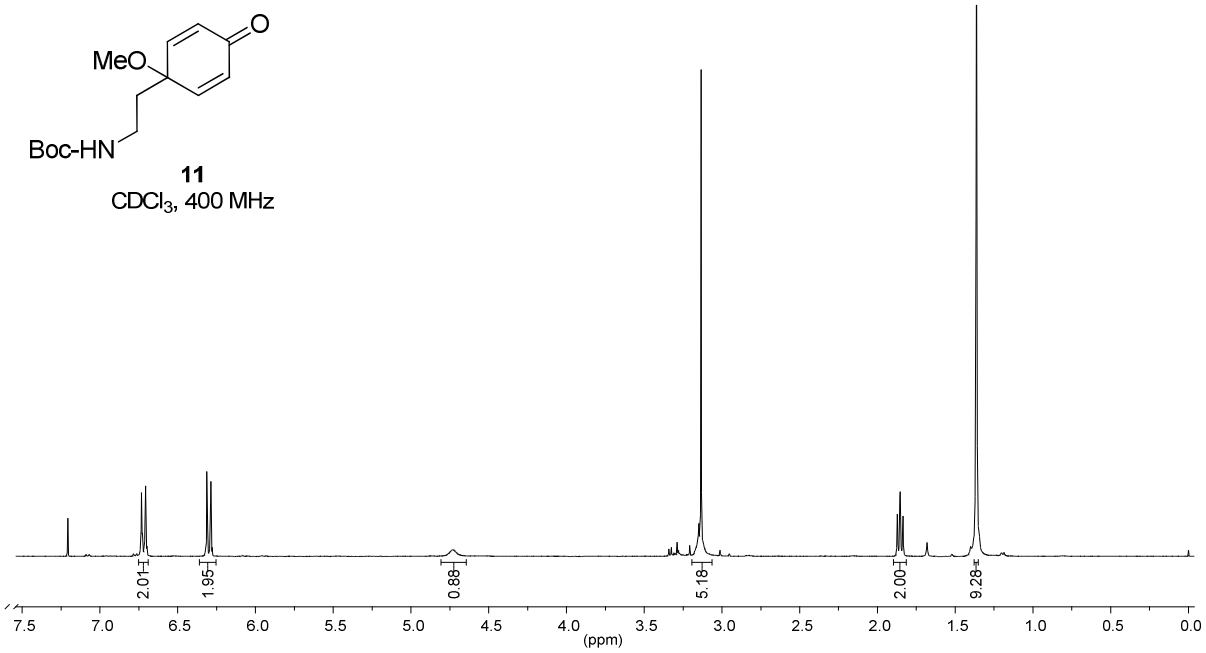
8

DMSO-d_6, 101 MHz

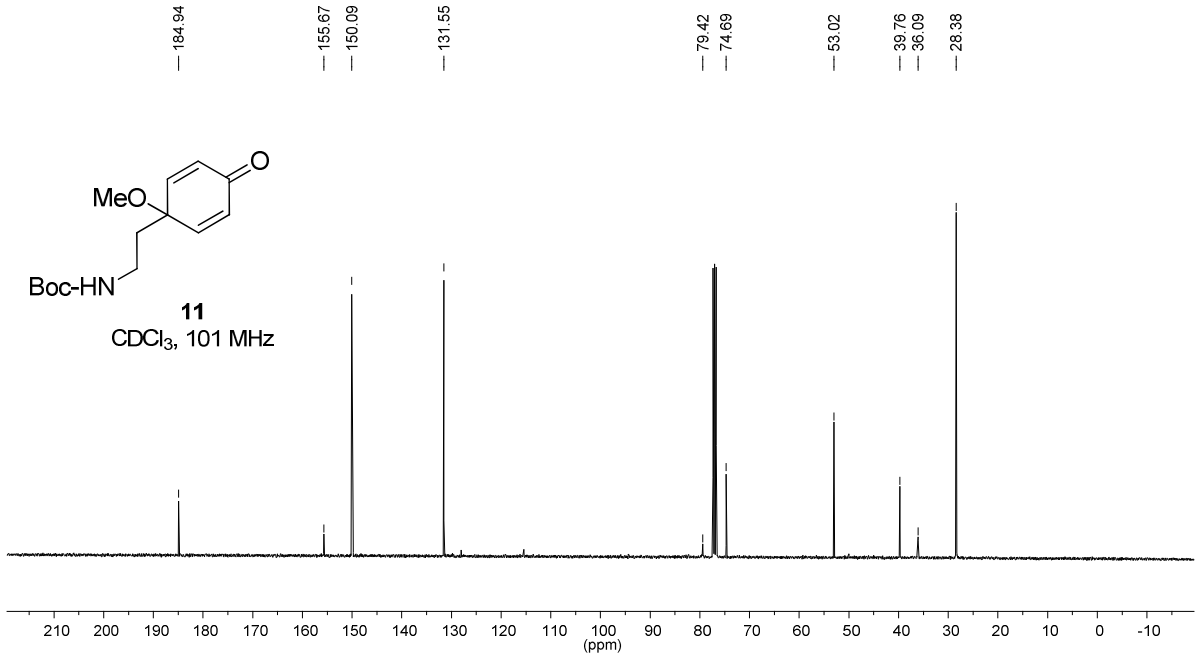

OH
HCl
N
H
9
DMSO-d6, 400 MHz
0.98
0.88
2.00
1.27
1.10
1.04
2.89
5.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

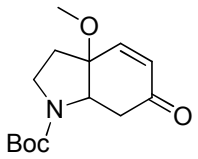


9
DMSO-d_6, 101 MHz



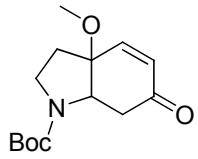
11
$CDCl_3$, 400 MHz


184.94
155.67
150.09
131.55
79.42
74.69
53.02
39.76
36.09
28.38
MeO
O
Boc-HN
11
CDCl3, 101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)



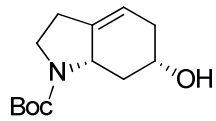
12

$CDCl_3$, 400 MHz



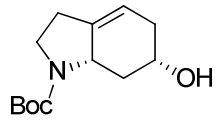
12

$CDCl_3$, 101 MHz



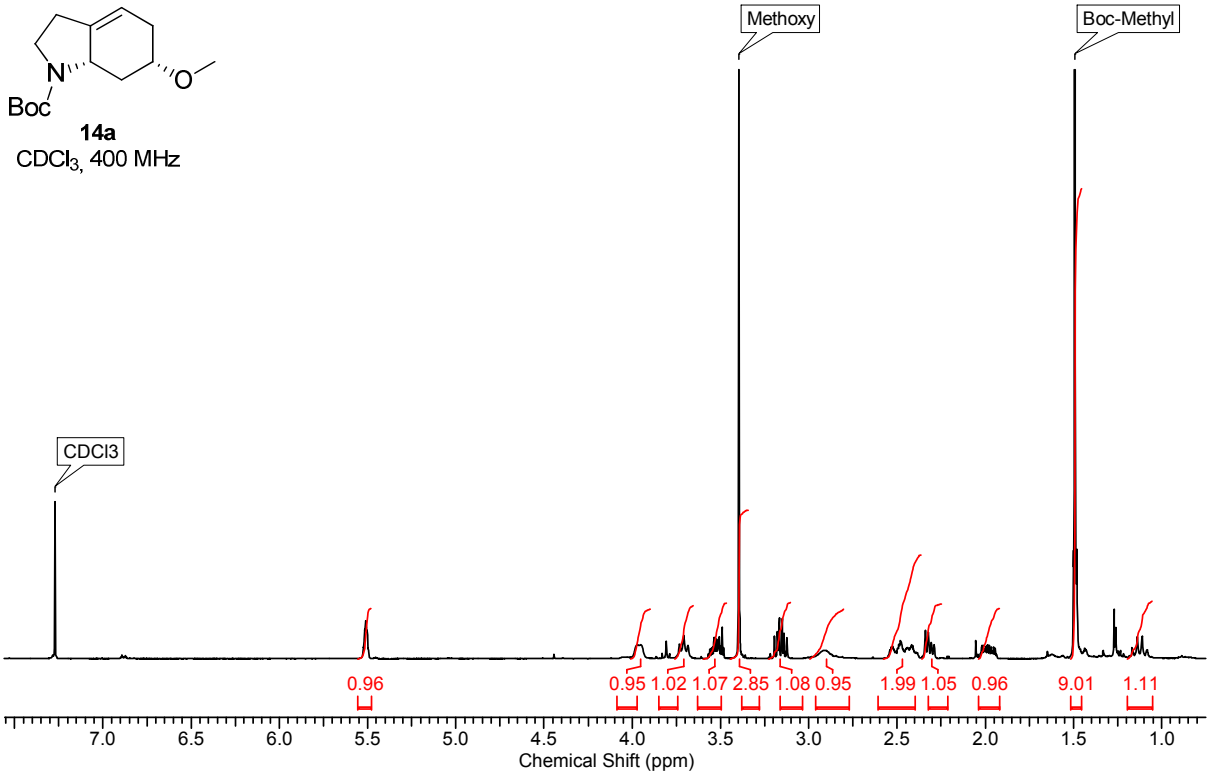
13

$CDCl_3$, 400 MHz

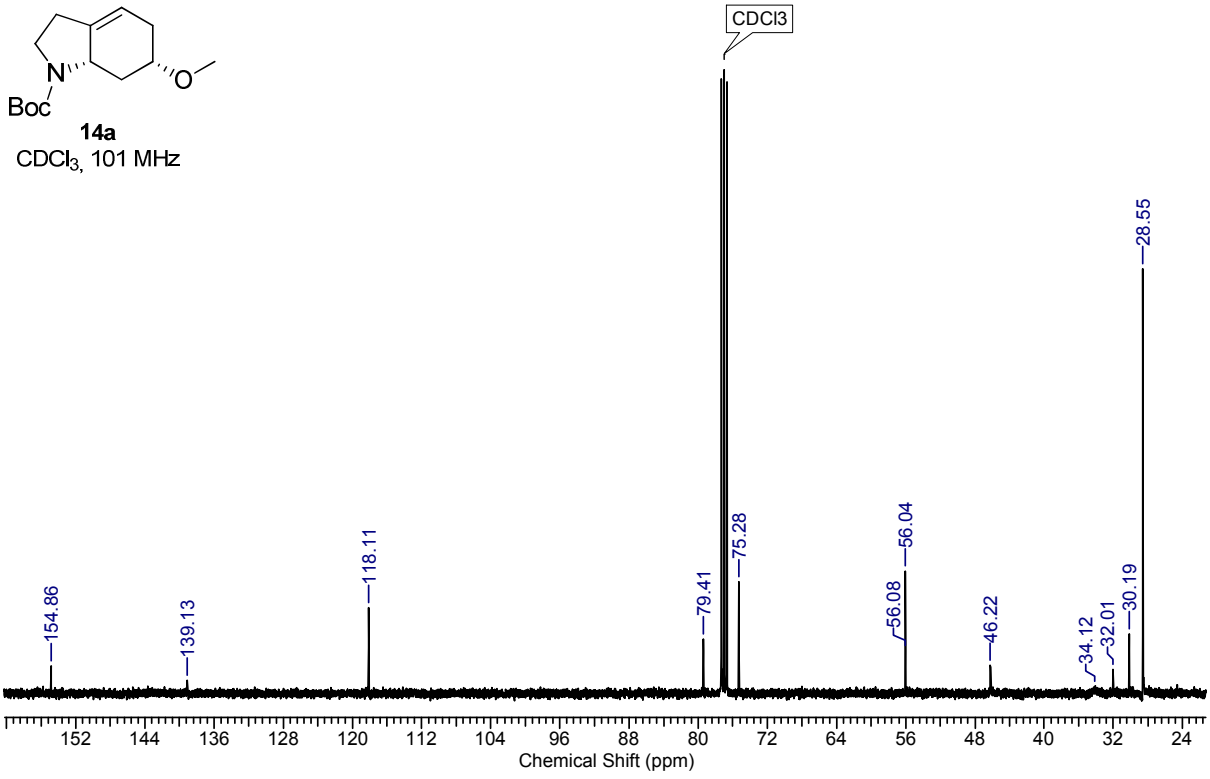


13

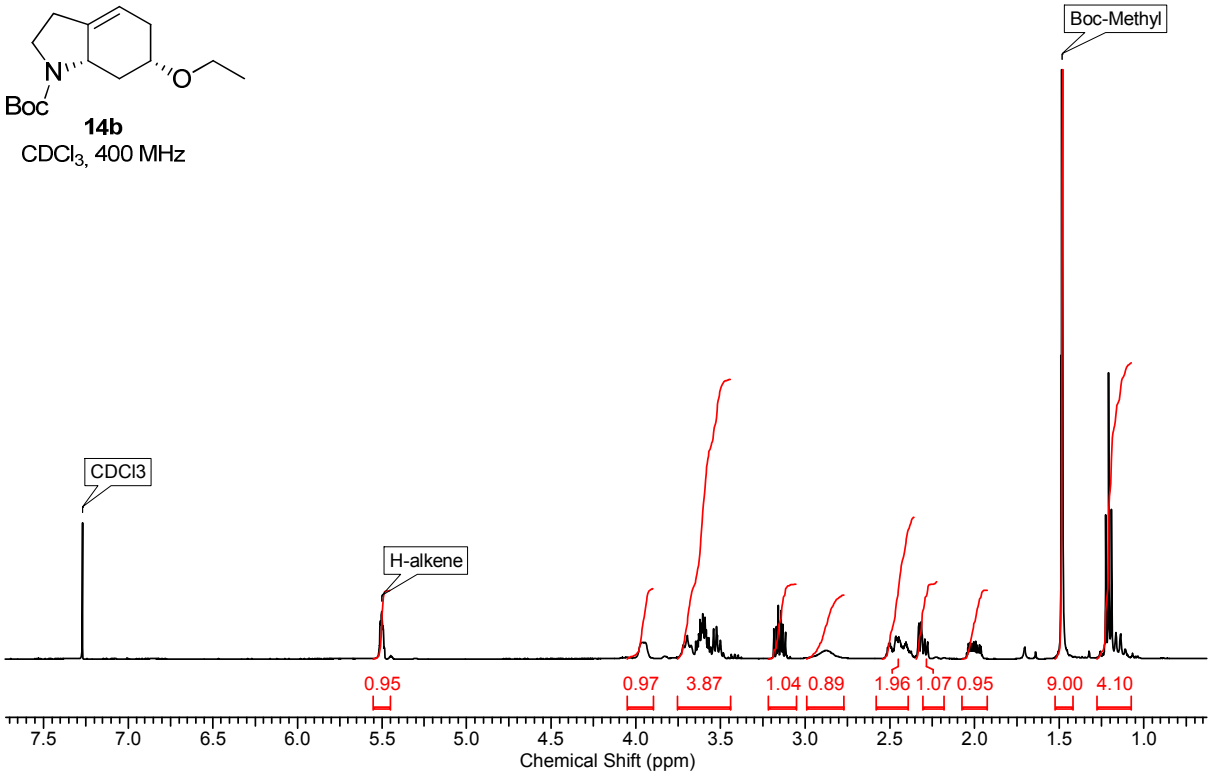
$CDCl_3$, 101 MHz

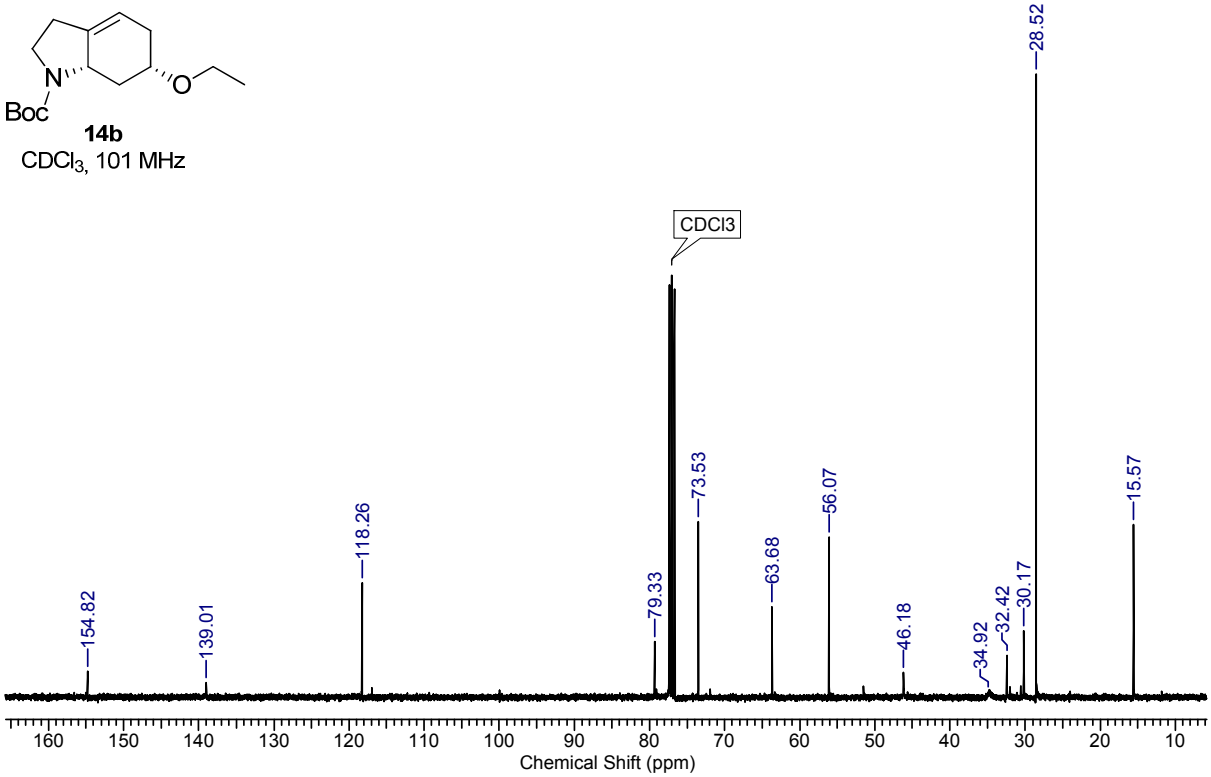


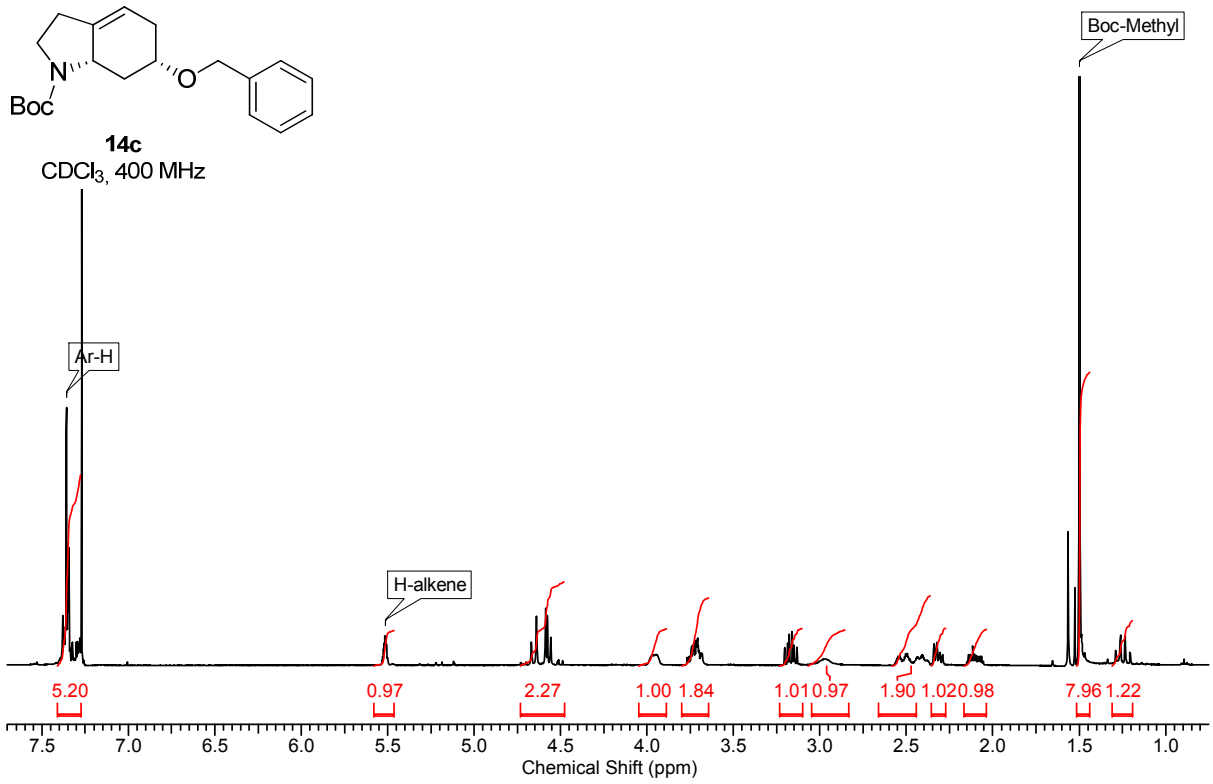
14a
$CDCl_3$, 400 MHz

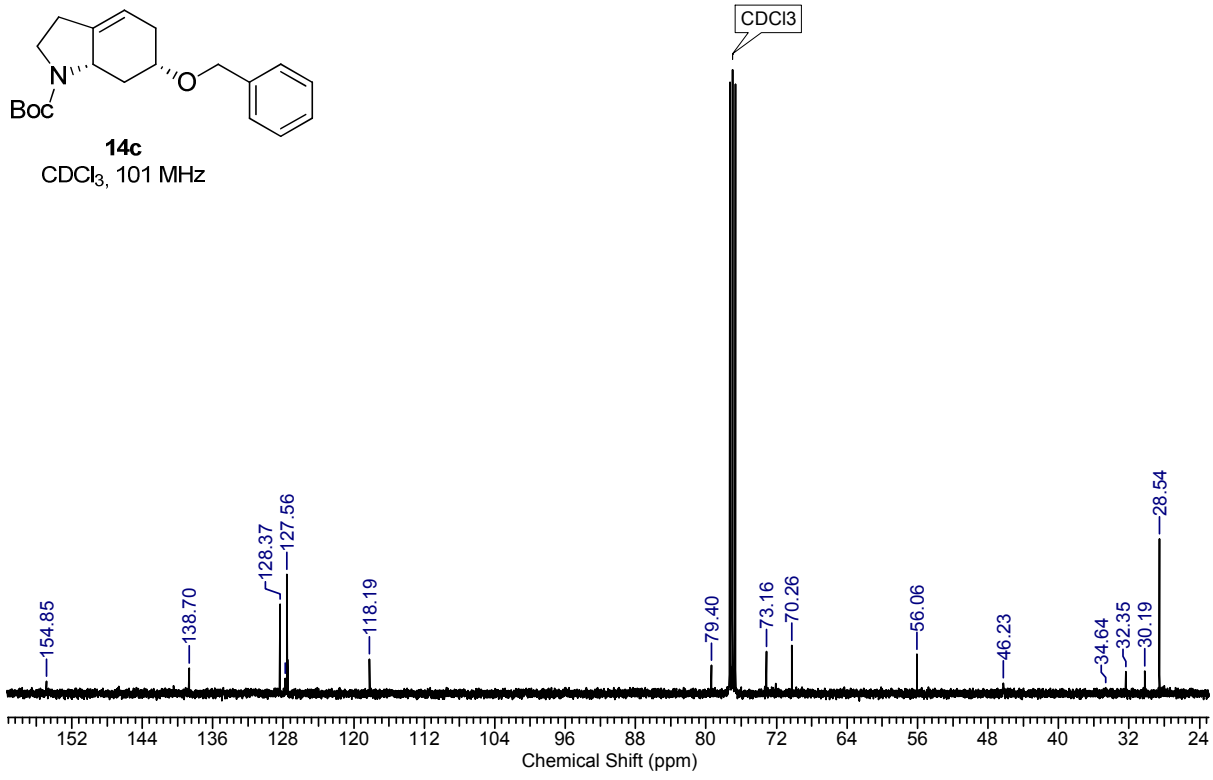


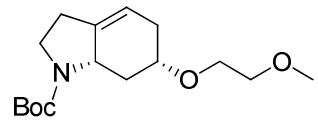
14a
$CDCl_3$, 101 MHz


Boc
14b
CDCl3, 400 MHz
Boc-Methyl
CDCl3
H-alkene
0.95
0.97
3.87
1.04
0.89
1.96
1.07
0.95
9.00
4.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


Boc
14b
CDCl3, 101 MHz
CDCl3
28.52
73.53
56.07
118.26
63.68
15.57
79.33
154.82
139.01
46.18
34.92
32.42
30.17
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

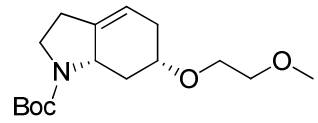

Boc
N
O
14c
CDCl3, 400 MHz
Boc-Methyl
Ar-H
H-alkene
5.20
0.97
2.27
1.00
1.84
1.01
0.97
1.90
1.02
0.98
7.96
1.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


Boc
N
O
14c
CDCl3, 101 MHz
CDCl3
154.85
138.70
128.37
127.56
118.19
79.40
73.16
70.26
56.06
46.23
34.64
32.35
30.19
28.54
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
Chemical Shift (ppm)



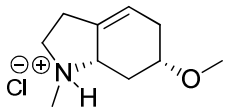
14d

$CDCl_3$, 400 MHz

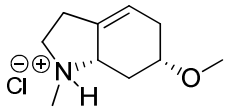


14d

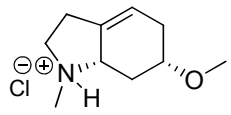
$CDCl_3$, 101 MHz



2a
D_2O, 400 MHz

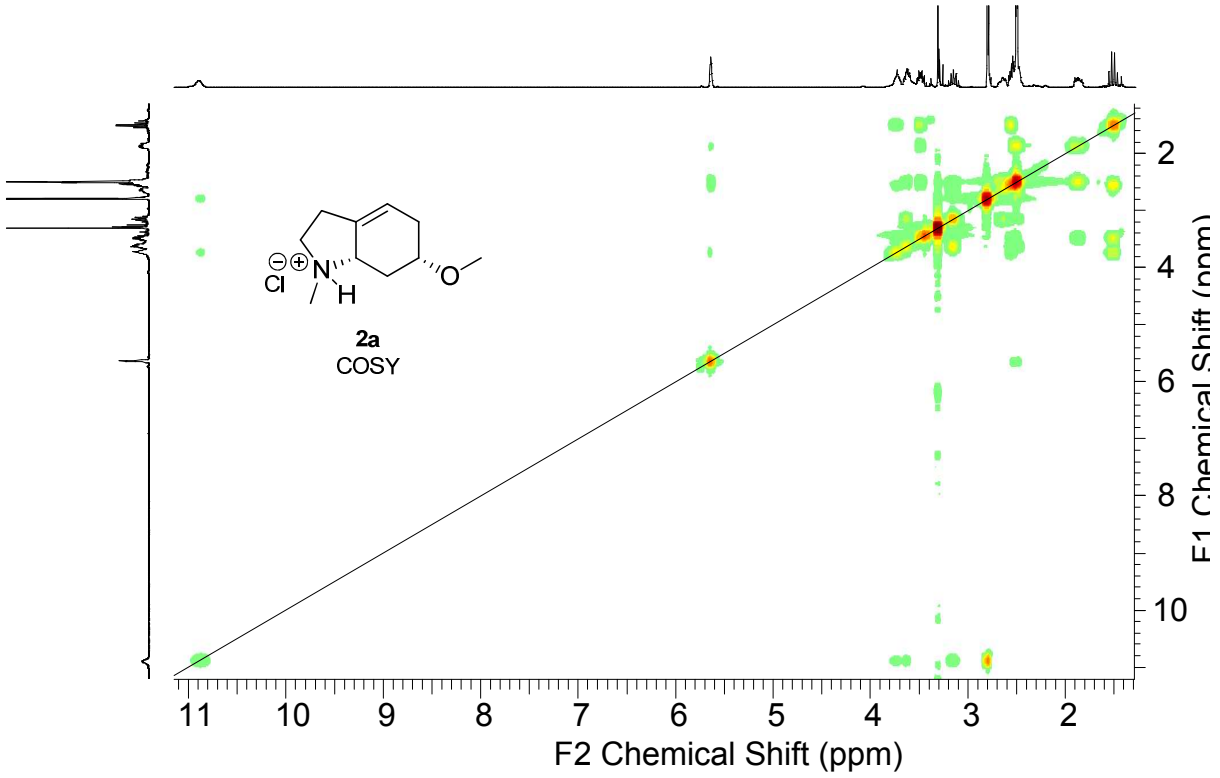


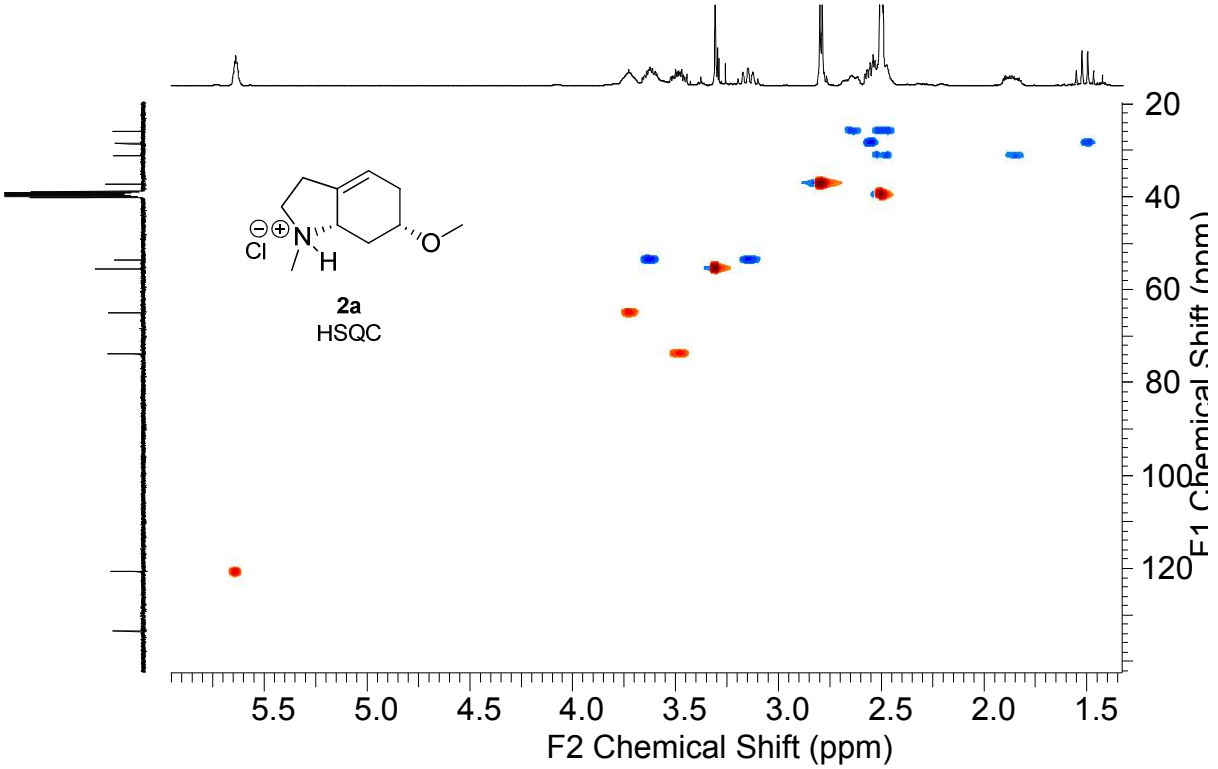
2a
DMSO-d_6, 400 MHz

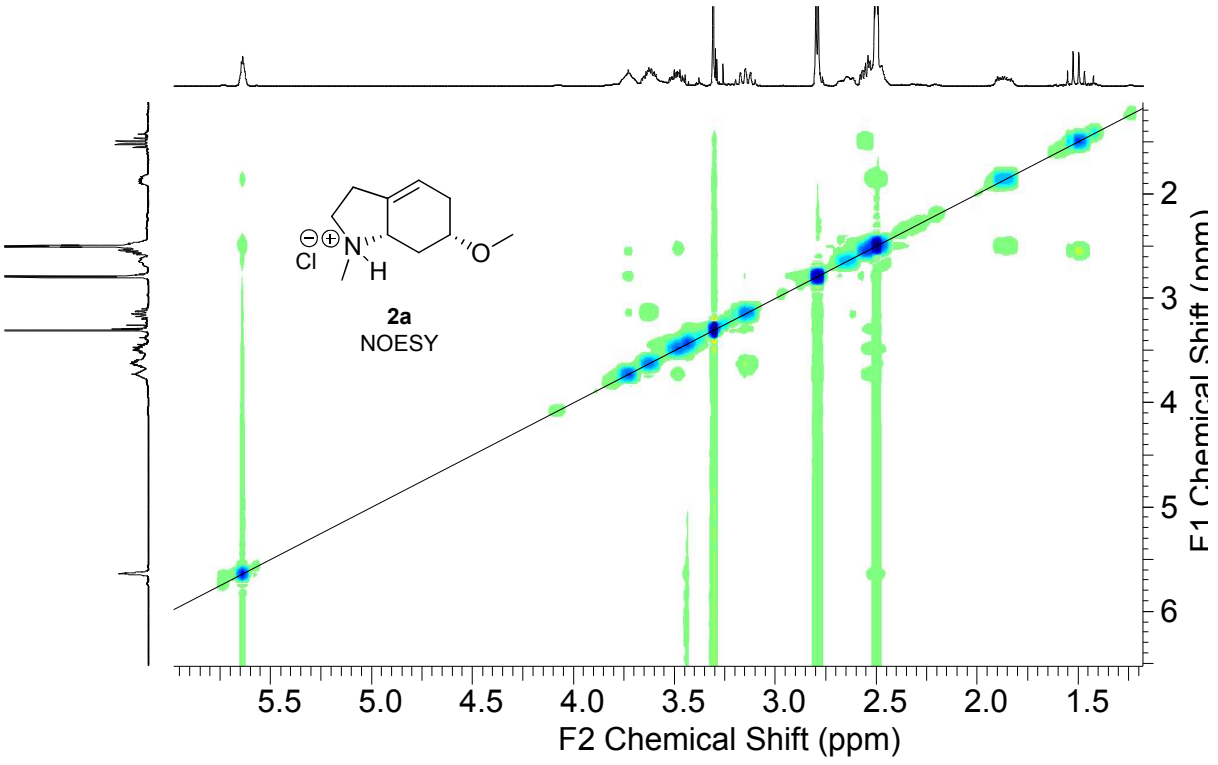


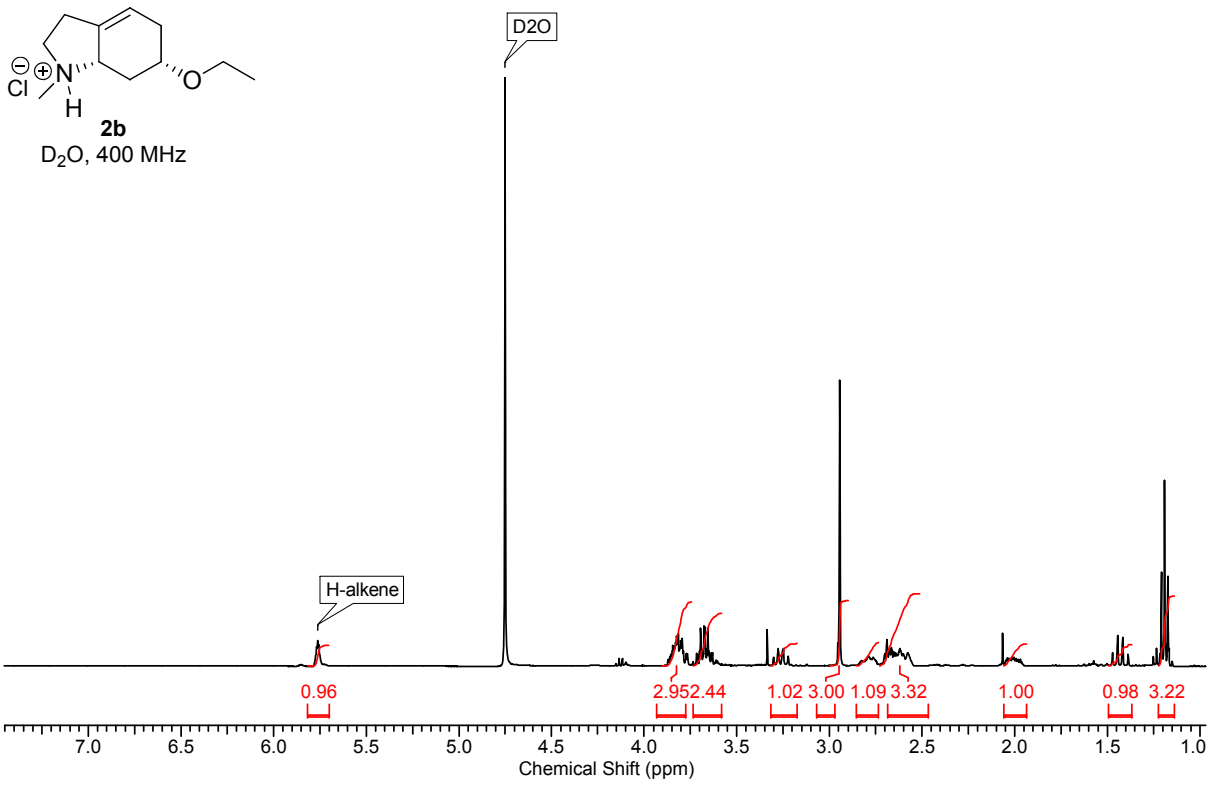
2a

DMSO-d_6, 101 MHz



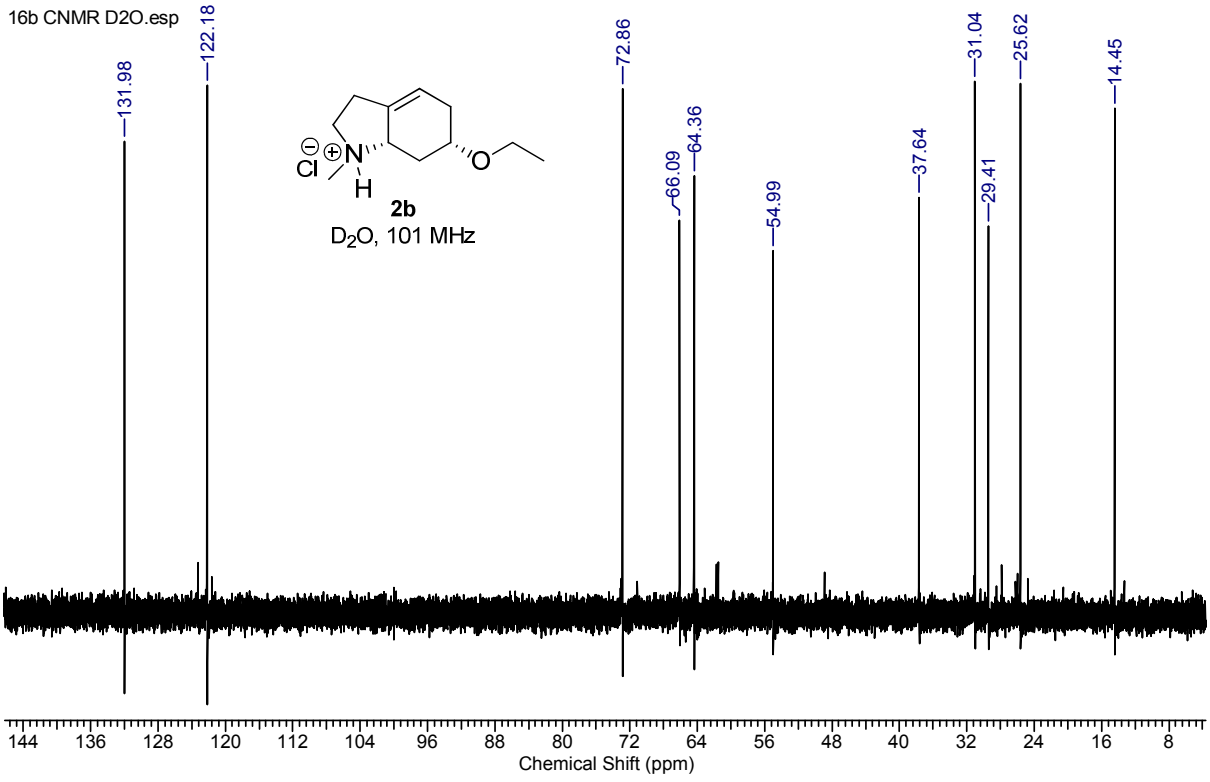

Cl
N
H
O
2a
HSQC
20
40
60
80
100
120
F1 Chemical Shift (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F2 Chemical Shift (ppm)


Cl
N
H
O
2a
NOESY
2
3
4
5
6
F1 Chemical Shift (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F2 Chemical Shift (ppm)



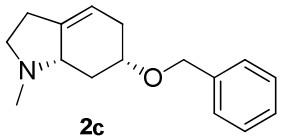
2b

D_2O, 400 MHz



2b

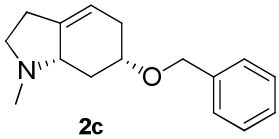
D_2O, 101 MHz



2c

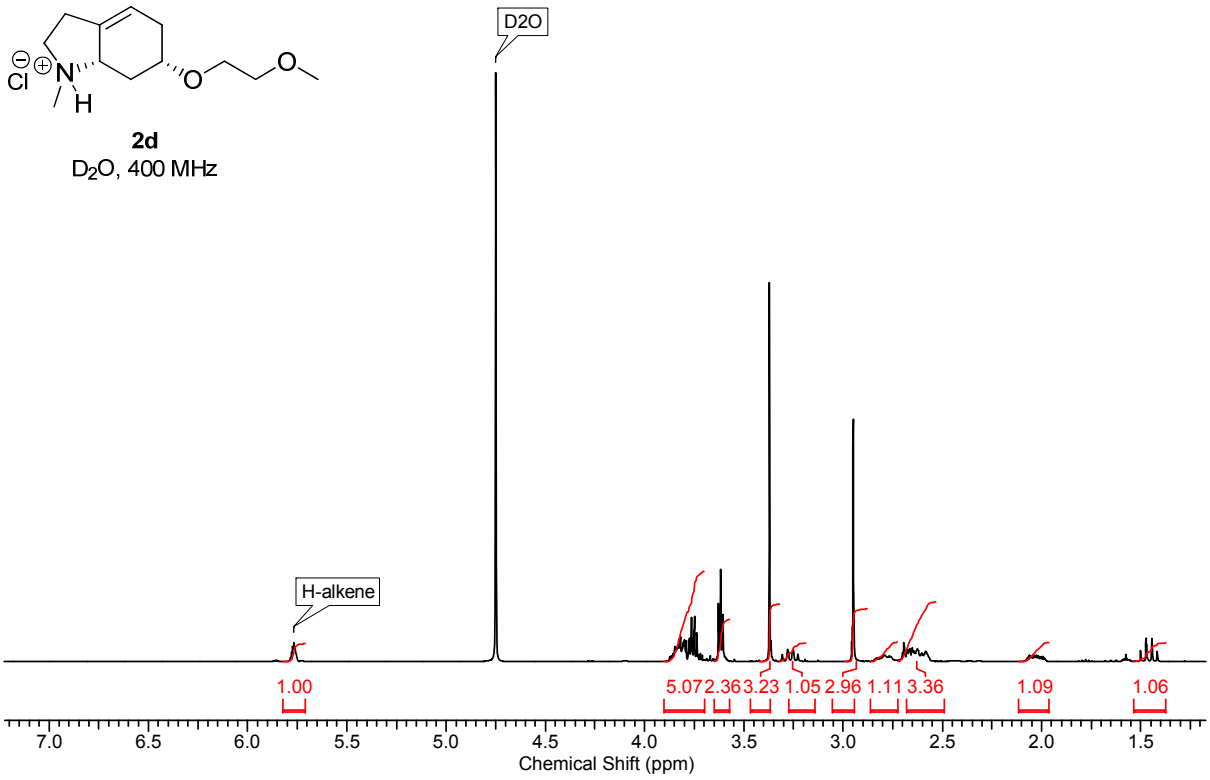
$CDCl_3$, 400 MHz

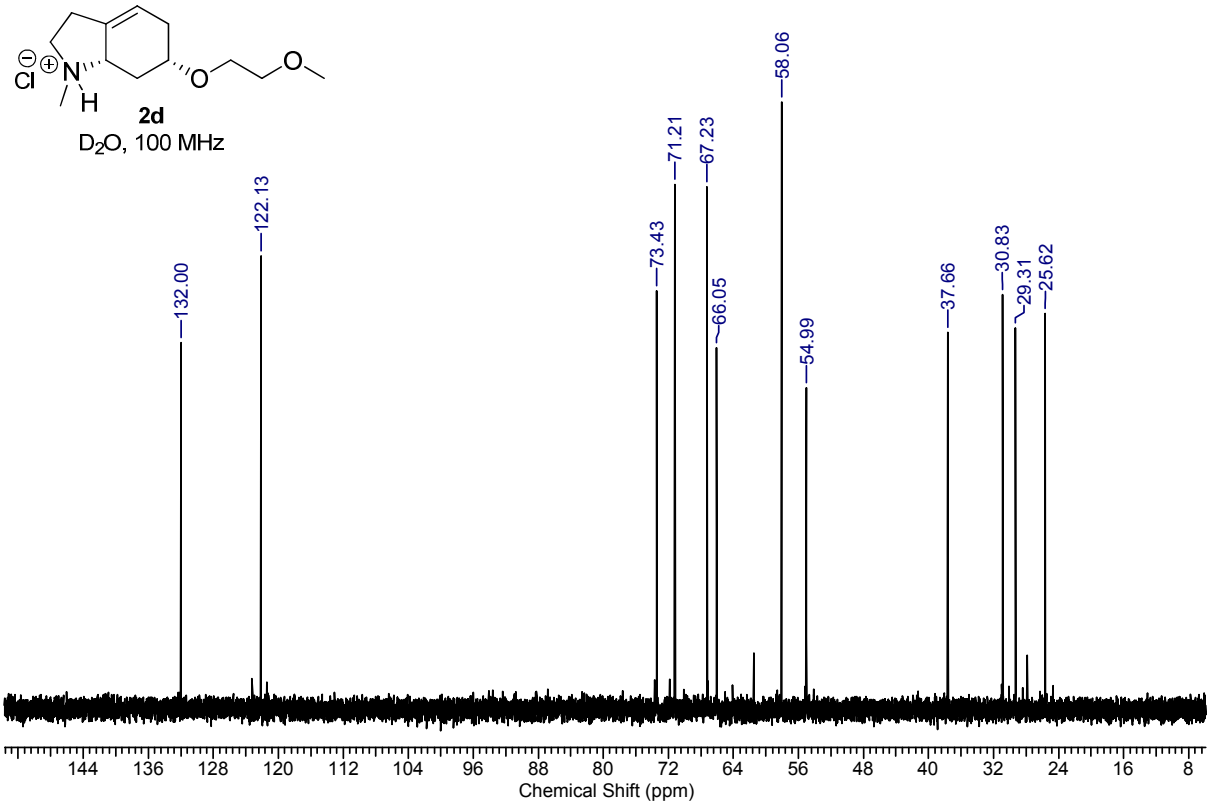
16c CNMR.esp

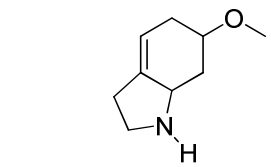


2c

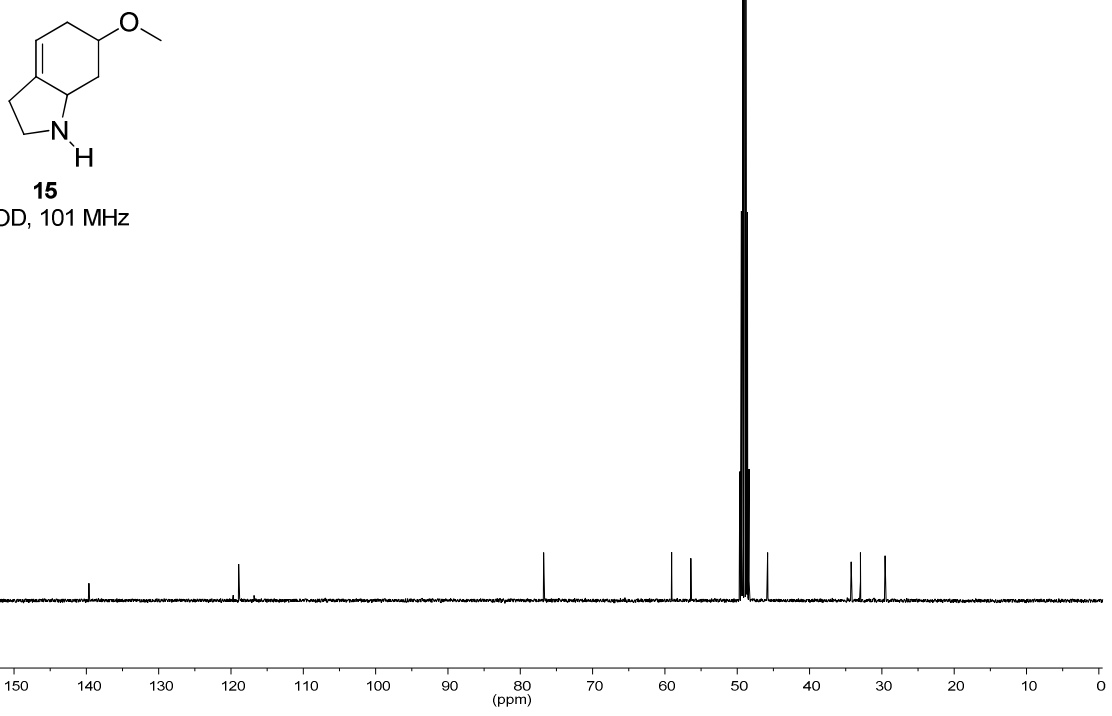
$CDCl_3$, 101 MHz


2d
D2O, 400 MHz
D2O
H-alkene
1.00
5.07
2.36
3.23
1.05
2.96
1.11
3.36
1.09
1.06
Chemical Shift (ppm)

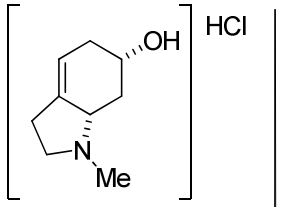

2d
D2O, 100 MHz
132.00
122.13
73.43
71.21
67.23
66.05
58.06
54.99
37.66
30.83
29.31
25.62
Chemical Shift (ppm)



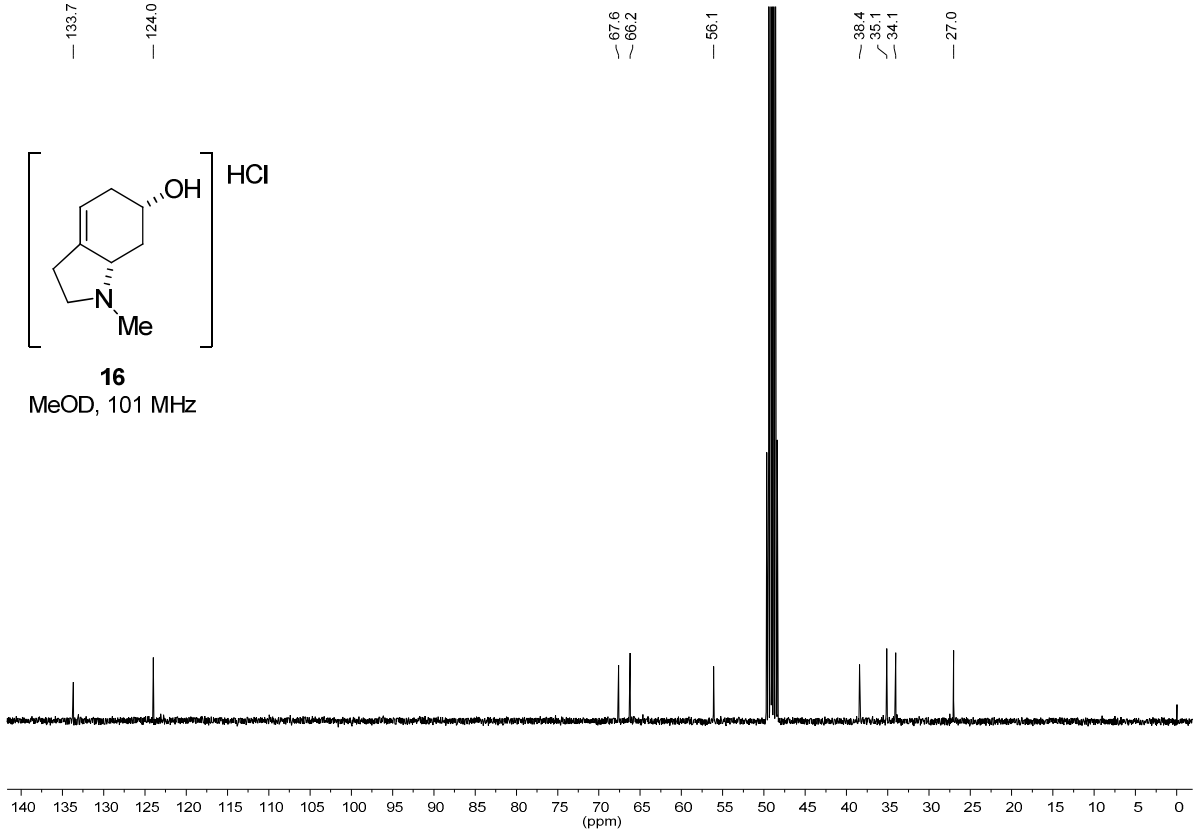
15
MeOD, 400 MHz



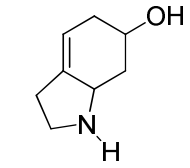
15
MeOD, 101 MHz



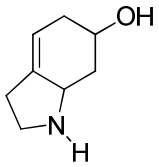
16
MeOD, 400 MHz



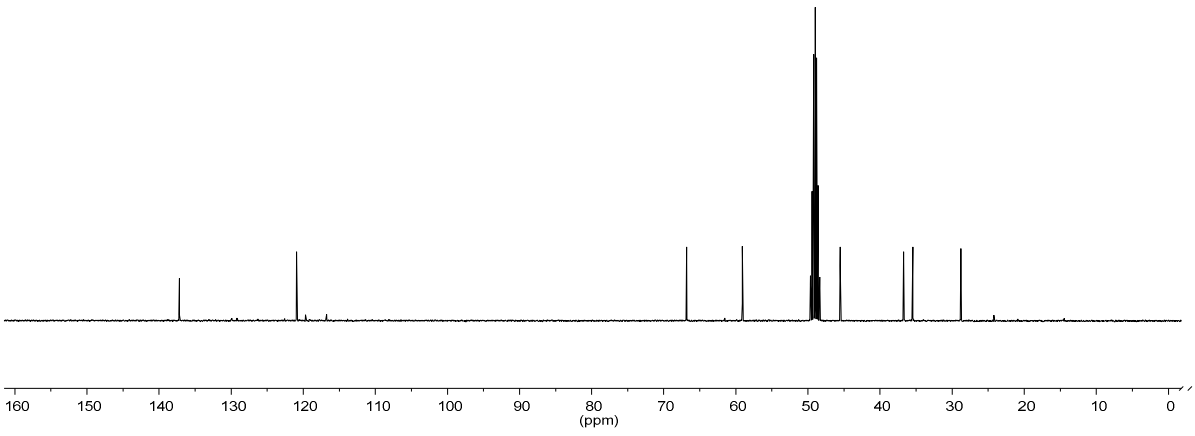
16
MeOD, 101 MHz

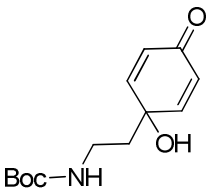


17
MeOD, 400 MHz



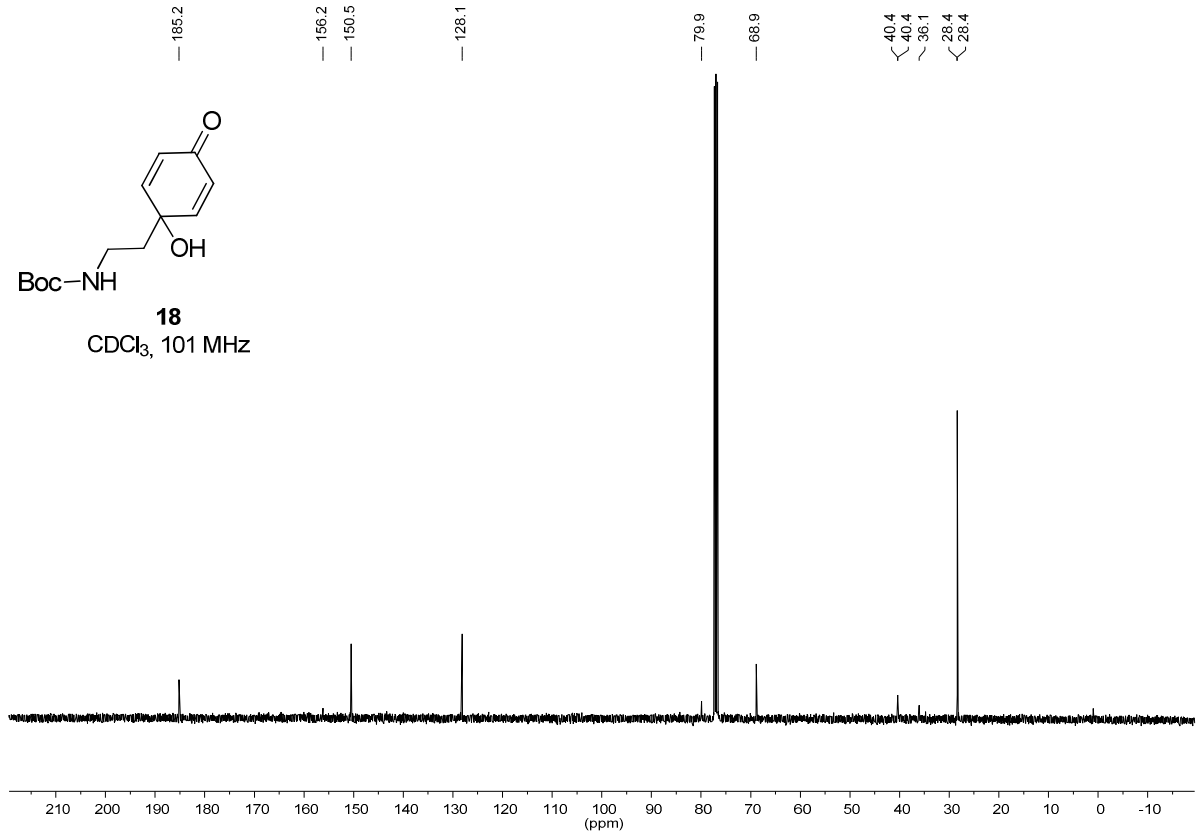
17
MeOD, 101 MHz





18

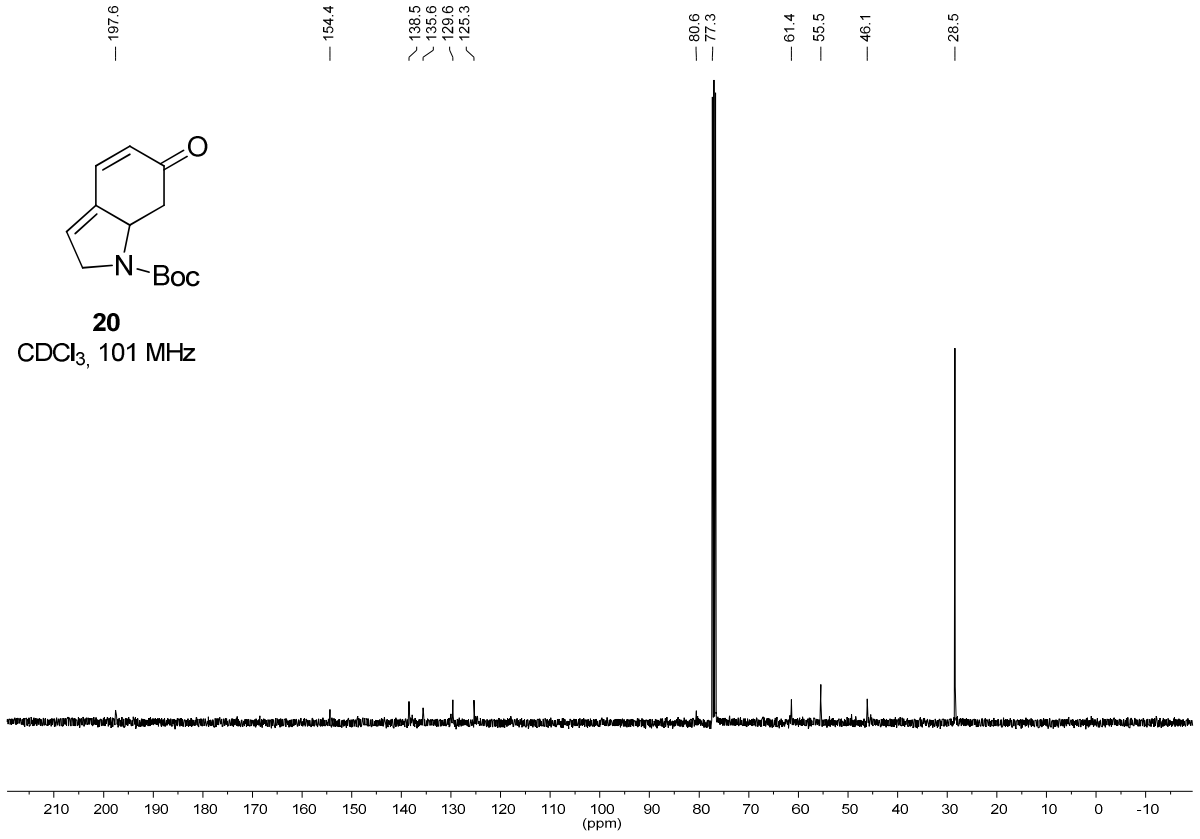
$CDCl_3$, 400 MHz



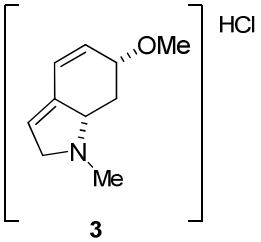
18

$CDCl_3$, 101 MHz

20
$CDCl_3$, 400 MHz

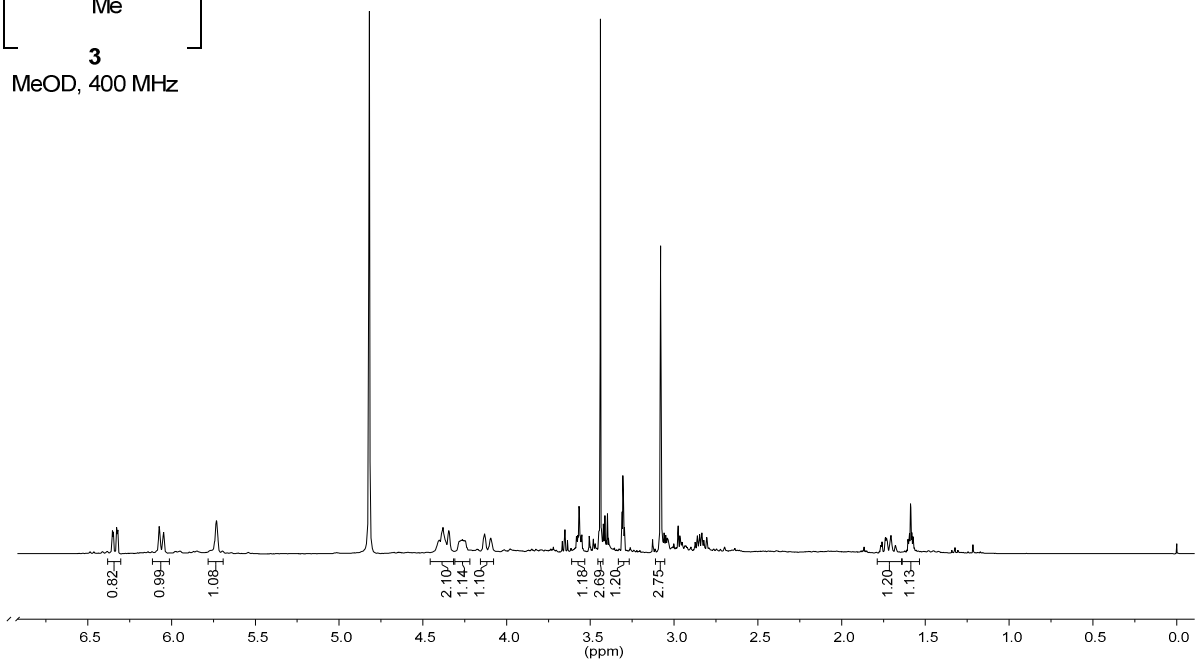


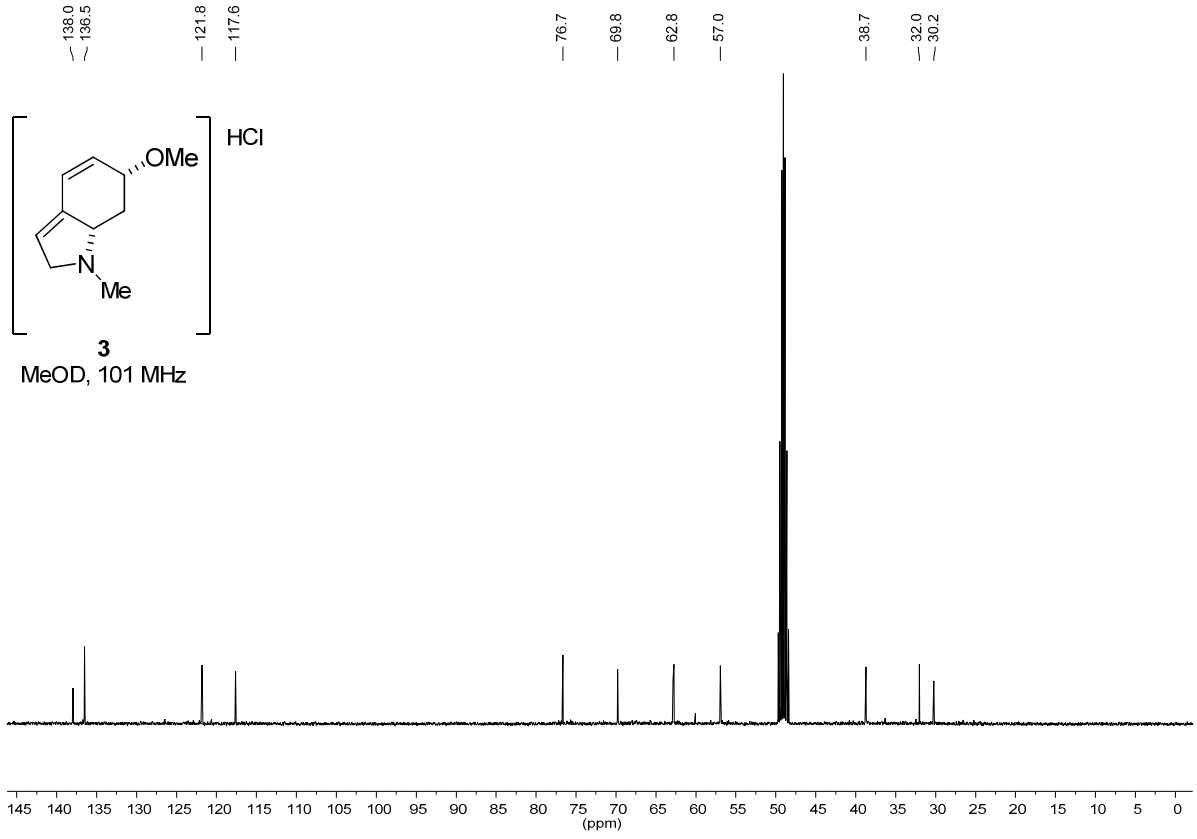
20
$CDCl_3$, 101 MHz



3

MeOD, 400 MHz





3

MeOD, 101 MHz