Supporting Information

Asymmetric Synthesis of 3,4-Diaminocyclohexanol and *endo*-7-Azabicyclo[2.2.1]heptane-2-amine

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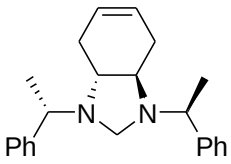
Table of contents

Experimental part

1. General Information

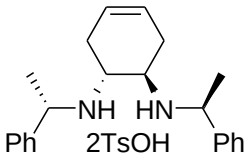
Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer digital polarimeter in a 1 dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on Varian MR 400 and Gemini 200 instruments. Chemical shifts are reported in ppm relative to the solvent residual peak of $CDCl_3$ (δ_H 7.26, δ_C 77.0) and of CD_3OD (δ_H 3.31, δ_C 49.0), *J*-values are given in Hz and in the assignments s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, br b = broad band. ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet FT-380 spectrometer and IR assignments are reported in wave numbers (cm^{-1}). MS spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5975 spectrometer with GLC injection (using an Agilent DB-5MS UI column, 30 m, ID 0.25 mm, 0.25 µm). Molecular weights were determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230-400 mesh) at medium pressure. All the organic, inorganic and organometallic reagents and anhydrous solvents were purchased from Aldrich.

2. (3a*R*,7a*R*)-1,3-bis[(1*S*)-1-phenylethyl]-2,3,3a,4,7,7a-hexahydro-1*H*-benzimidazole (9).



To a solution of **5** (160 mg, 0.49 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen atmosphere anhydrous $MgSO_4$ (480 mg), paraformaldehyde (300 mg, 10 mmol) and a catalytic amount of *p*-toluensulfonic acid were added. The reaction mixture was stirred at room temperature for 24 hours, then the solid residue was filtered off over Celite®. The clear solution was first neutralized with 5% sodium bicarbonate, then extracted with CH_2Cl_2, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to afford the product **9** as a white solid (160 mg, 0.48 mmol, 98%). M.p. = 115-117 °C. $[\alpha]^{20}_D$ = –83.0° (c 1.0, $CHCl_3$). IR (v^{-1}, KBr) = 3021, 2966, 2928, 2814, 1492, 1446, 1341, 1212, 1120, 1105, 1085, 1021, 766, 705, 678. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.37 (d, J= 7.0 Hz, 6H), 2.04- 2.16 (br m, 2H), 2.42-2.50 (m, 2H), 2.55-2.62 (br m, 2H), 3.50 (s, 2H), 3.81 (q, J = 7.0 Hz, 2H), 5.63 (br d, J_{app}= 3.1 Hz, 2H), 7.19-7.30 (m, 10 H). ^{13}C NMR (100.77 MHz, $CDCl_3$, 25 °C): δ 21.5, 33.3, 61.2, 63.4, 71.3, 125.8, 126.8, 127.6, 128.1, 143.4. MS (EI): m/z = 332 (26%), 331(82%), 227(37%), 123 (52%), 105 (100%), 79 (24%). MS (ES) m/z = 333.2 $[M + H]^+$. Anal. Calcd for $C_{23}H_{28}N_2$: C, 83.09; H, 8.49; N, 8.43. Found C, 83.21; H, 8.50; N, 8.42.

3. (1*R*,2*R*)-*N*,*N*'-[(1*S*)-1-phenylethyl]-4-cyclohexene-1,2-diaminium bis(4-methylbenzenesulfonate) (13).



To a vigorously stirred solution of **5** (150 mg, 0.47 mmol) in anhydrous diethyl ether (5 mL) a solution of *p*-toluenesulfonic acid (222 mg, 1.17 mmol) in anhydrous diethyl ether (5 mL) was slowly added. The supernatant was then removed by decantation and the solid salt washed twice with the same solvent. The hygroscopic and sticky solid salt was then well dried under vacuum to yield **13** as an off white crystalline solid (300 mg, 0.45 mmol, 96%). M.p. = 116-124 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.70 (d, J = 6.4 Hz, 6H), 2.40 (s, 6H), 2.43-2.48 (br m, 4H), 3.57 (br s, 2 H), 4.48 (br s, 2H), 5.35 (s, 2H), 7.22 (d, J = 8.0 Hz, 4H), 7.29-7.35 (m, 6H), 7.59-7.61 (m, 4H), 7.80 (d, J = 8.0 Hz, 4H), 9.00 (br b, 2H), 10.23 (br b, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ 21.1, 21.2, 25.5, 52.3, 57.5, 122.2, 126.0, 127.3, 128.8, 129.1, 129.4, 134.7, 140.6.

4. Hydroboration reaction with 9-borabicyclo[3.3.1]nonane (9-BBN)

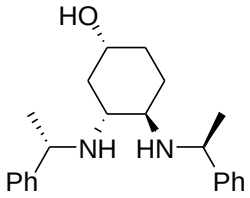
4.1. Preparation of 9-BBN:

A 1 M solution of 9-BBN in anhydrous THF was prepared accordingly to the reported procedure.[1]

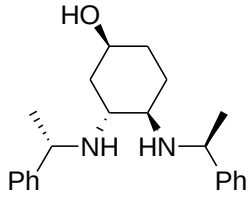
4.2. Synthesis of 8a and 8b from diaminocyclohexene derivative 5:

The diaminocyclohexene derivative **5** (100 mg, 0.31 mmol) was dissolved in anhydrous THF (1 mL) under nitrogen atmosphere. A 1 M solution of 9-BBN (3.1 mmol, 3.1 mL) was added at room temperature and the mixture stirred for 3 hours. An aqueous solution of 3 M NaOH (0.5 mL) was added dropwise at 0 °C followed by an aqueous solution of 30% H_2O_2 (0.5 mL). The mixture was stirred for 1 h and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The oily residue was prepurified by acid-base washing: NMR analysis showed an overall conversion of 98% (d.r. 75:25). The two diastereomers **8a** and **8b** were separated by column chromatography (silica gel, gradient of methanol in dichloromethane up to 15%) and characterized.

[1] Alexakis, A.; Tomassini, A; Chouillet, C; Roland, S; Mangeney, P; Bernardinelli, G. *Angew. Chem. Int. Ed*. **2000**, *39*, 4093-4095.



(1*R*,3*R*,4*R*)-3,4-bis[(1*S*)-phenylethylamino]cyclohexanol (8a). White solid. 65% yield. M.p. = 56-58 °C. $[\alpha]^{20}_{D}$ = –105.5° (c 0.9, $CHCl_3$). IR (KBr): ν 3300, 2927, 2857, 1451, 761, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 0.92-1.06 (m, 2H), 1.10-1.19 (m, 1H), 1.32 (d, J = 6.8Hz, 6H), 1.76-1.83 (m, 1H), 1.94-2.13 (m, 4H), 2.17-2.23 (m, 1H), 3.43-3.50 (m, 1H), 3.82 (q, J = 6.8 Hz, 1H), 3.86 (q, J = 6.8 Hz, 1H), 7.21-7.35 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25°C): δ 25.3, 26.7, 32.8, 38.4, 54.4, 54.7, 55.8, 56.9, 126.5, 126.8, 126.9, 128.3, 128.4, 145.3, 145.6. MS (ES) m/z = 339.0 $[M + H]^+$. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found C, 78.14; H, 8.95; N, 8.26.



(1*S*,3*R*,4*R*)-3,4-bis[(1*S*)-phenylethylamino]cyclohexanol (8b). White crystalline solid. 22% yield. M.p. = 124-126 °C. $[\alpha]^{20}_{D}$ = –86.5° (c 0.53, $CHCl_3$). IR (KBr): ν 3423, 2966, 2926, 1439, 773, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 1.18-1.28 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.31-1.42 (m, 1H), 1.65-1.69 (m, 1H), 1.84-1.88 (m, 1H), 2.03-2.08 (m, 1H), 2.10-2.17 (m, 1H), 2.2-2.8 (br b, NH+OH), 2.49 (ddd, J_1 = 4.0 Hz, J_2 = 3.2 Hz, J_3 = 10.8 Hz, 1H), 3.88 (q, J = 6.6 Hz, 1H), 3.89 (q, J = 6.6 Hz, 1H), 3.98 (br m, 1H), 7.24-7.39 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$, 25°C): δ 24.7, 25.1, 25.3, 31.0, 37.6, 53.1, 54.4, 54.7, 57.4, 66.1, 126.7, 126.9, 128.5, 145.2, 145.4. MS (ES) m/z = 339.0 $[M + H]^+$. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found C, 78.01; H, 8.92; N, 8.30.

5. Hydroboration reaction with $BH_3{\cdot}SMe_2$

5.1. Synthesis of 8a and 8b from diaminocyclohexene derivative 5:

The diaminocyclohexene derivative **5** (150 mg, 0.47 mmol) was dissolved in anhydrous tetrahydrofuran (4 mL) in a two-necked round bottomed flask under nitrogen atmosphere and $BH_3{\cdot}SMe_2$ complex (107 mg, 1.41 mmol) was added at room temperature and the reaction stirred for 5 hours. To the cooled mixture (0 °C) an aqueous solution of 3.0 M NaOH (0.5 mL) was slowly added followed by an aqueous solution of 30% H_2O_2 (0.5 mL) and left at room temperature for 1 hour. After extraction with ethyl acetate, the collected organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give a white sticky solid. After acid-base washing, the two diastereomers **8a** and **8b** (d.r. 65:35 from ^{1}H NMR of the crude) were separated on column as reported before (50% overall yield).

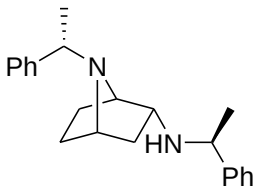
5.2. Synthesis of 8a and 8b from aminal derivative 9:

Same procedure was carried out on the aminal derivative **9** (160 mg, 0.48 mmol) using 2.5 equivalents of $BH_3{\cdot}SMe_2$. After purification on column (silica gel, gradient from ethyl acetate/cyclohexane 1:1 to ethyl acetate) the two diastereomers **10a** and **10b** (d.r. 60:40 from ^{1}H NMR) were collected together with a 70% overall yield. From the crude were also separated the two byproduct **11** (20% yield) and **12** (10% yield). The diastereomers mixture (120 mg, 0.34 mmol) was dissolved in THF (5 mL) and an aqueous solution of 2 M HCl (8 mL) was added. The mixture was heated at 80 °C for 5 hours, cooled to ambient temperature, basified with NaOH and extracted with ethyl acetate. After usual workup, the two diastereomers **8a** and **8b** (d.r. 60:40 from ^{1}H NMR of the crude) were separated on column as reported before (75% overall yield).

5.3. Synthesis of 8a and 8b from ditosylate derivative 13:

Same procedure was carried out on the ditosylate derivative **13** (315 mg, 0.43 mmol) using 6.0 equivalents of $BH_3{\cdot}SMe_2$. After usual workup, the two diastereomers **8a** and **8b** were obtained with a good purity (d.r. 1:1 from ^{1}H NMR) with a 75 % overall yield.

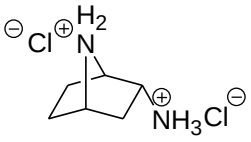
6. *N*,N'-bis[1(*S*)-phenylethyl]-7-azabicyclo[2.2.1]heptan-2-amine (7).



The diaminocyclohexanol **8a** (105 mg, 0.31 mmol) was dissolved in anhydrous toluene (3 mL) under nitrogen atmosphere and triphenylphosphine (PPh_3, 98 mg, 0.37 mmol) and then diisopropyl azodicarboxylate (DIAD, 75 mg, 0.37 mmol) were added at room temperature. After 2 hours 3 M NaOH was added and the mixture stirred for additional 3 hours. The organic layer was extracted three times with ethyl acetate and the solvent evaporated. After acid-base washing, the crude was purified on column (silica, gradient of methanol in ethyl acetate from 10 to 20%) affording the byproducts **5** (12%) and **14** (8%) and the product **7** as a colorless oil (65 mg, 0.20 mmol, 65% yield). $[\alpha]^{20}_D$ = –85.7° (c 0.65, $CHCl_3$). IR (neat): ν 3060, 3024, 2969, 2869, 1491, 1452, 1368, 1305, 1264, 1109, 761, 699. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 0.79 (dd, J_1 = 12.4 Hz, J_2 = 4.8 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.31-1.38 (m, 1H), 1.51-1.59 (m, 1H), 1.69-1.77 (m, 1H), 1.81-1.91 (m, 1H), 2.19-2.28 (br m, 1H), 2.86-2.88 (m, 1H), 3.15-3.20 (m, 1H), 3.41-3.45 (m, 1H), 3.46 (q, J = 6.4 Hz, 1H), 3.61 (q, J = 6.4 Hz, 1H), 7.17-7.34 (m, 10H). ^{13}C NMR (100.7 MHz, $CDCl_3$, 25°C): δ 19.2, 22.7, 23.2, 27.9, 38.4, 55.6, 56.7, 56.8, 57.8, 61.1, 126.6, 126.7, 126.9, 127.0, 128.2, 128.3, 145.9. MS (EI): m/z = 215

(14%), 173 (26%), 105 (100%), 69 (34%). MS (ES) m/z = 321.2 $[M + H]^+$. Anal. Calcd for $C_{22}H_{28}N_2$: C, 82.45; H, 8.81; N, 8.74. Found C, 82.59; H, 8.79; N, 8.72.

7. (–)-endo-7-Azabicyclo[2.2.1]heptane-2-amine bis-hydrochloride (1).



The bicyclic diamine **7** (48 mg, 0.15 mmol) was dissolved in freshly distilled methanol (4 mL) in a glass reactor, 6 M HCl (75 µL, 0.45 mmol) was added and the solution stirred for few minutes. 25 mg of 20% $Pd(OH)_2/C$ were then added and the apparatus submitted to a pressure of 6 bar H_2 for 6 hours. The catalyst was removed by filtration over Celite, then the solution concentrated to leave the product **1**-2HCl as an off-white solid (27 mg, 0.145 mmol, 97% yield). M.p. >220 °C (dec.). $[\alpha]^{20}_D$ = –2.5° (c 1.2, CH_3OH). IR (KBr): ν 3405, 2935, 2567, 1626, 1605, 1566, 1354, 1341, 1156. ^{1}H NMR (400 MHz, CD_3OD, 25°C): δ 1.69 (dd, J_1 = 14.0 Hz, J_2 = 4.8 Hz, 1H), 1.94-1.99 (m, 1H), 2.10 (br s, 3H), 2.47-2.58 (m, 1H), 3.91-3.97 (m, 1H), 4.33 (m, 1H), 4.48 (m, 1H). ^{13}C NMR (100.7 MHz, CD_3OD, 25°C): δ 21.3, 27.9, 32.8, 49.8, 60.7. MS (ES) m/z = 113.2 $[M – 2HCl + H]^+$. Anal. Calcd for $C_6H_{14}Cl_2N_2$: C, 38.93; H, 7.62; Cl, 38.31, N, 15.13. Found C, 38.88; H, 7.64; Cl, 38.26, N, 15.16.

NMR spectra of compounds

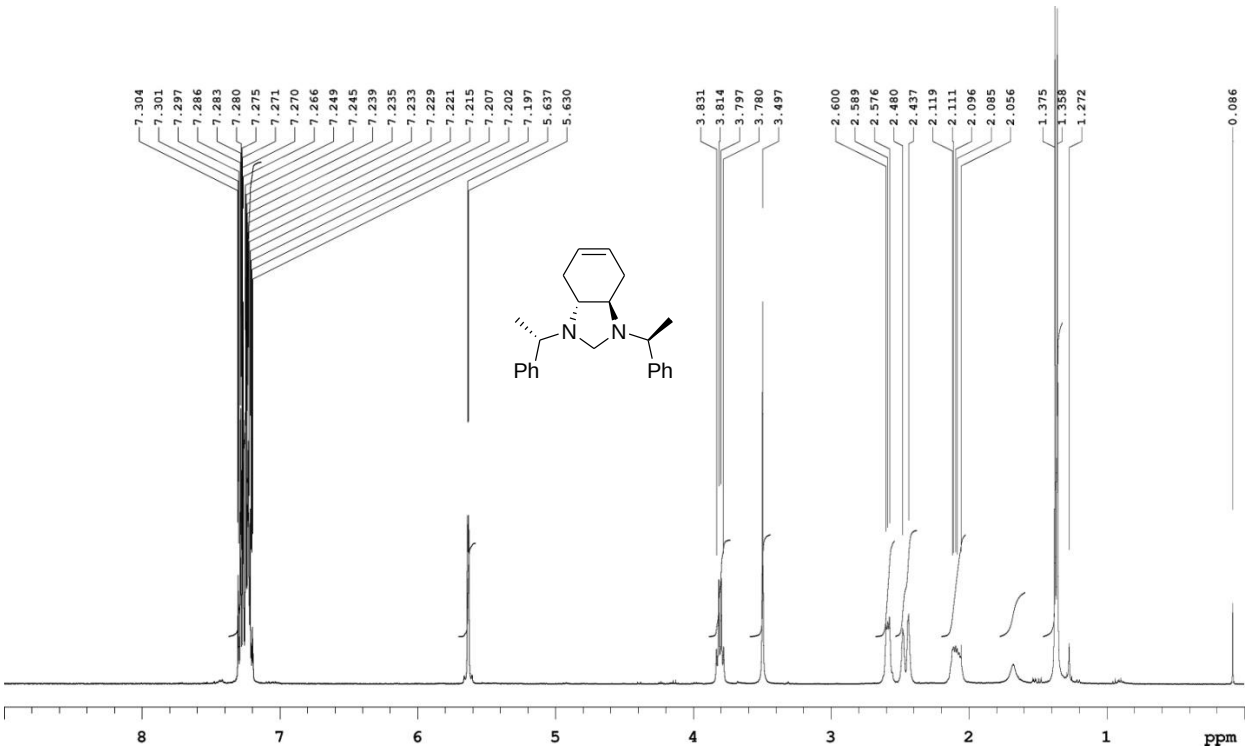


Figure S1: ^{1}H NMR of **9**

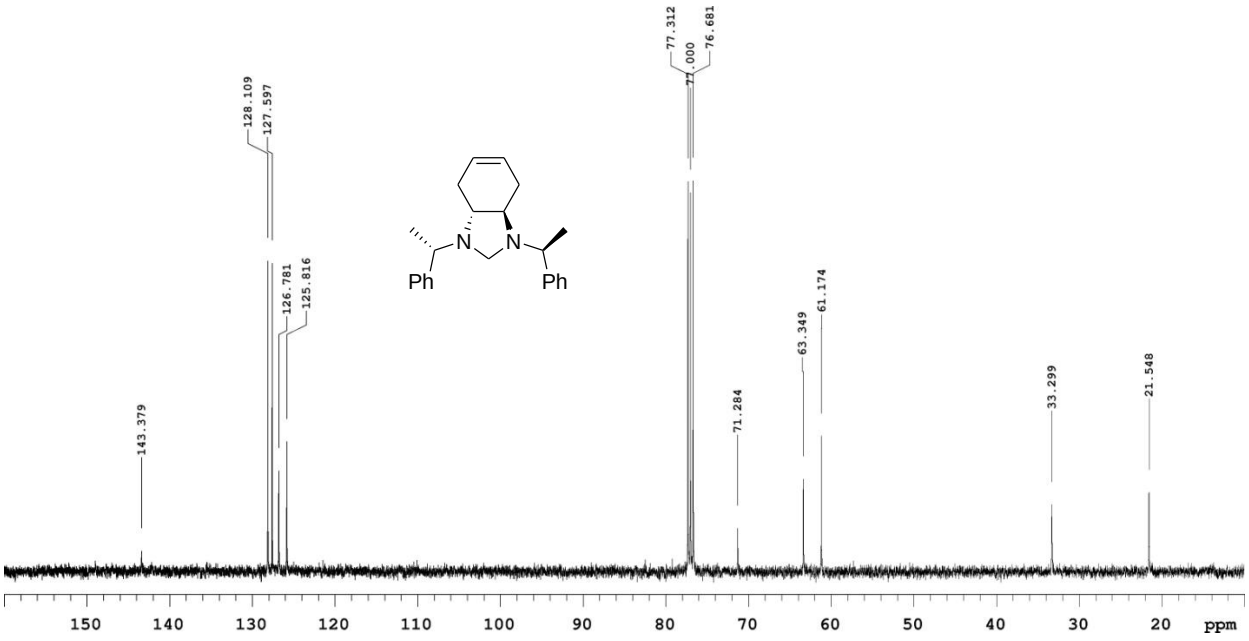


Figure S2: ^{13}C NMR of **9**

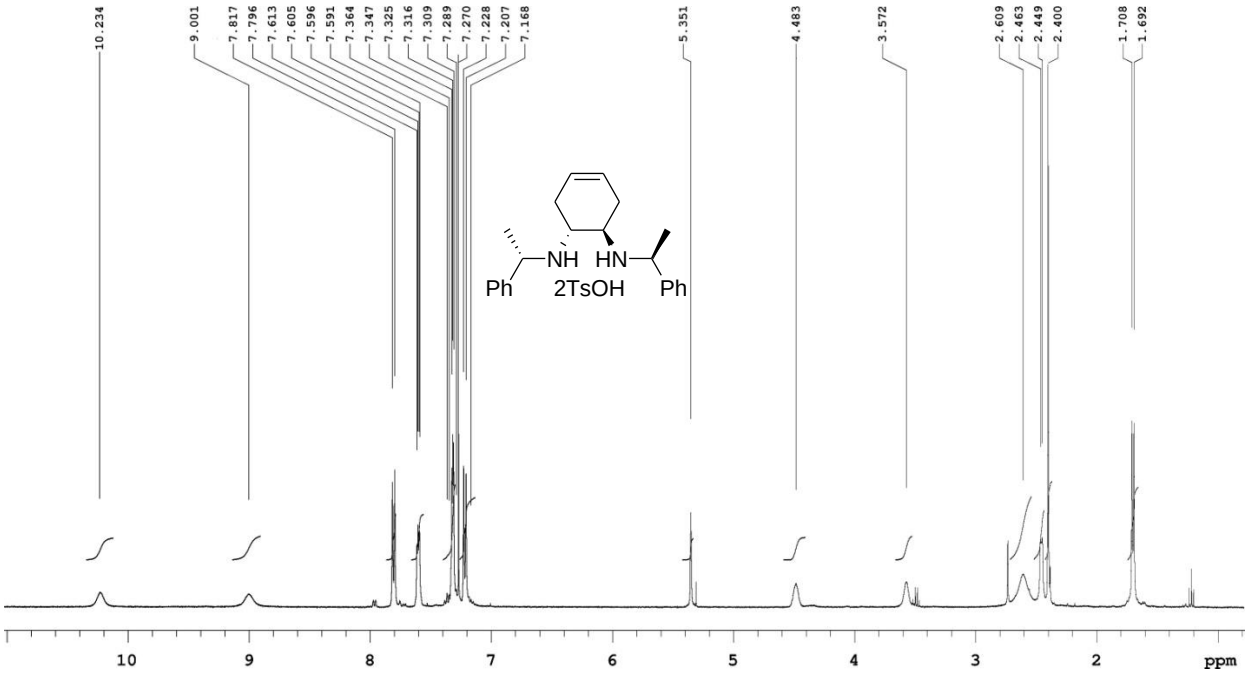


Figure S3: ^{1}H NMR of **13**

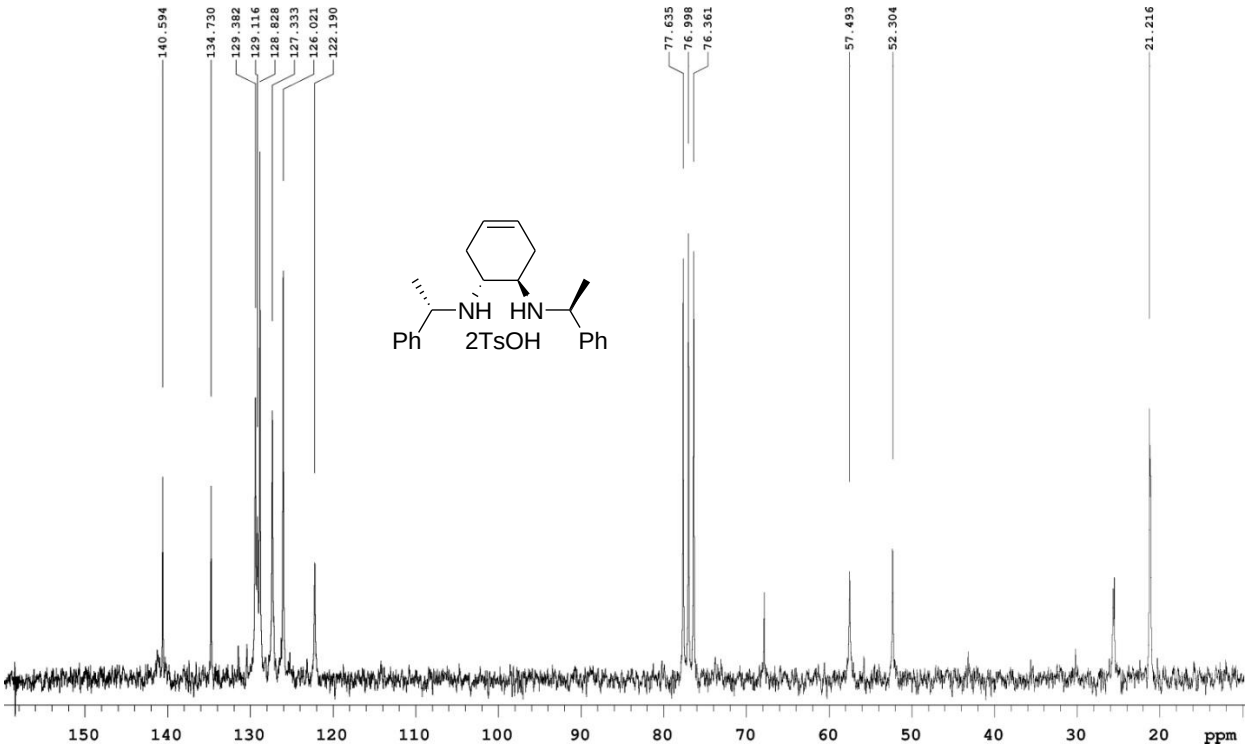


Figure S4: ^{13}C NMR of **13**

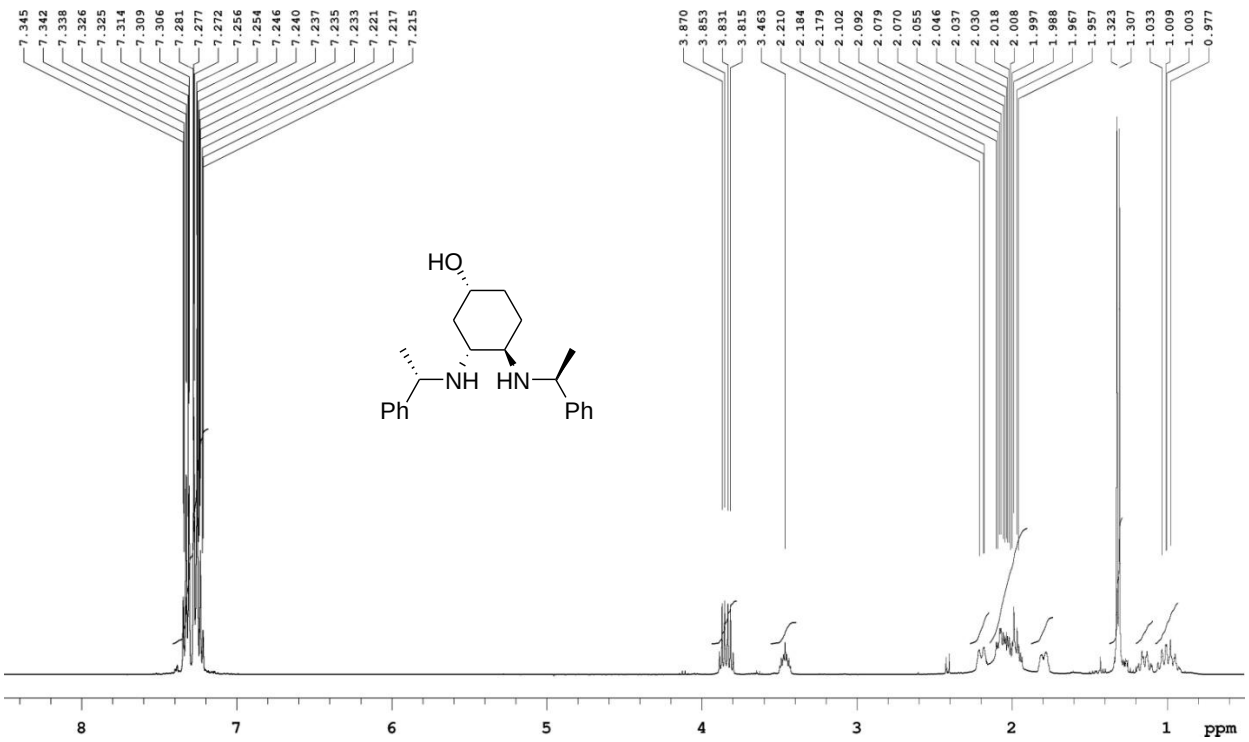


Figure S5: ^{1}H NMR of **8a**

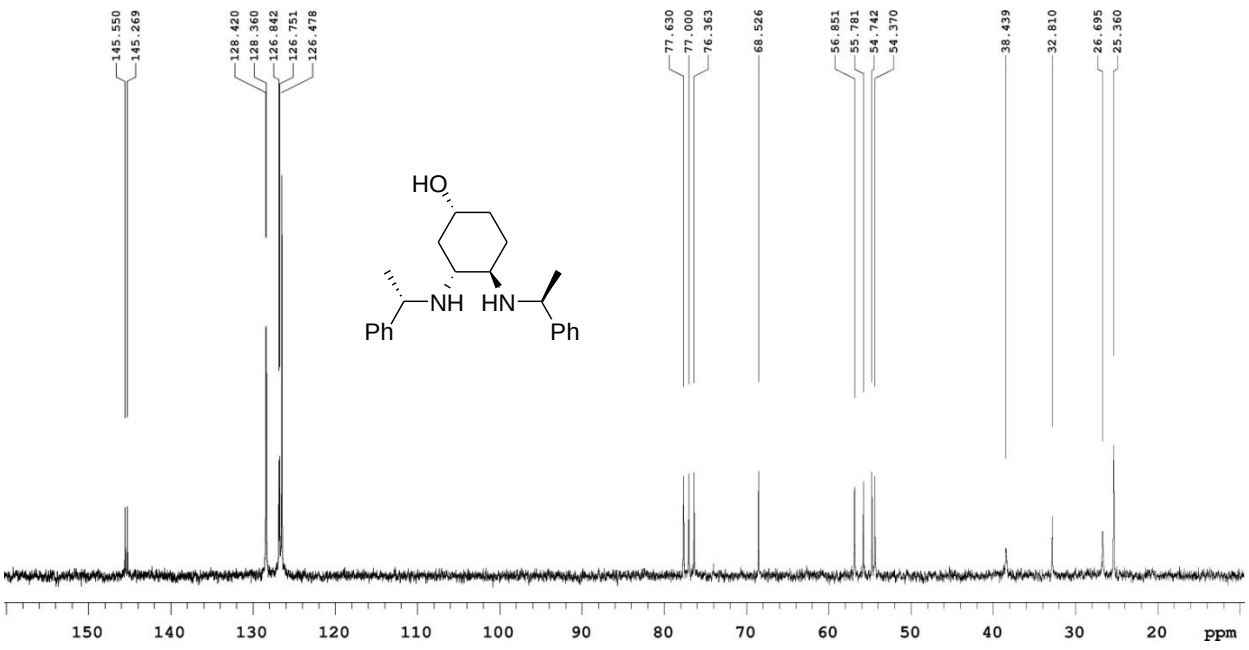


Figure S6: ^{13}C NMR of **8a**

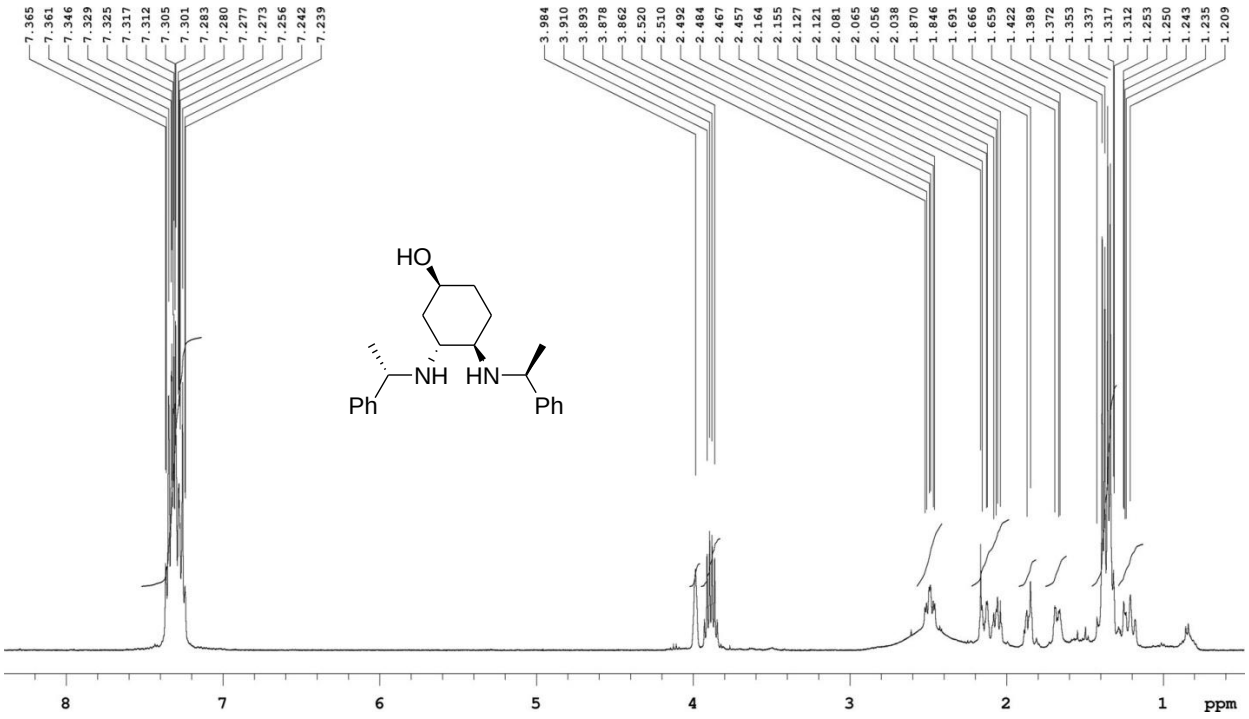


Figure S7: ^{1}H NMR of **8b**

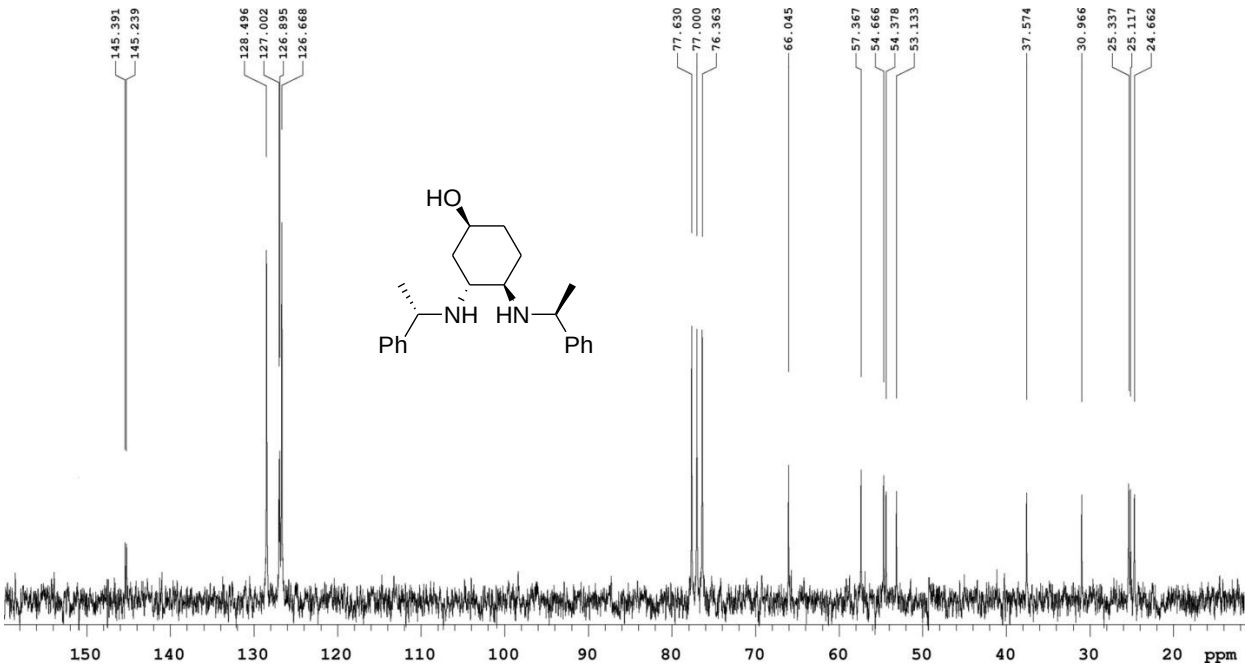


Figure S8: ^{13}C NMR of **8b**

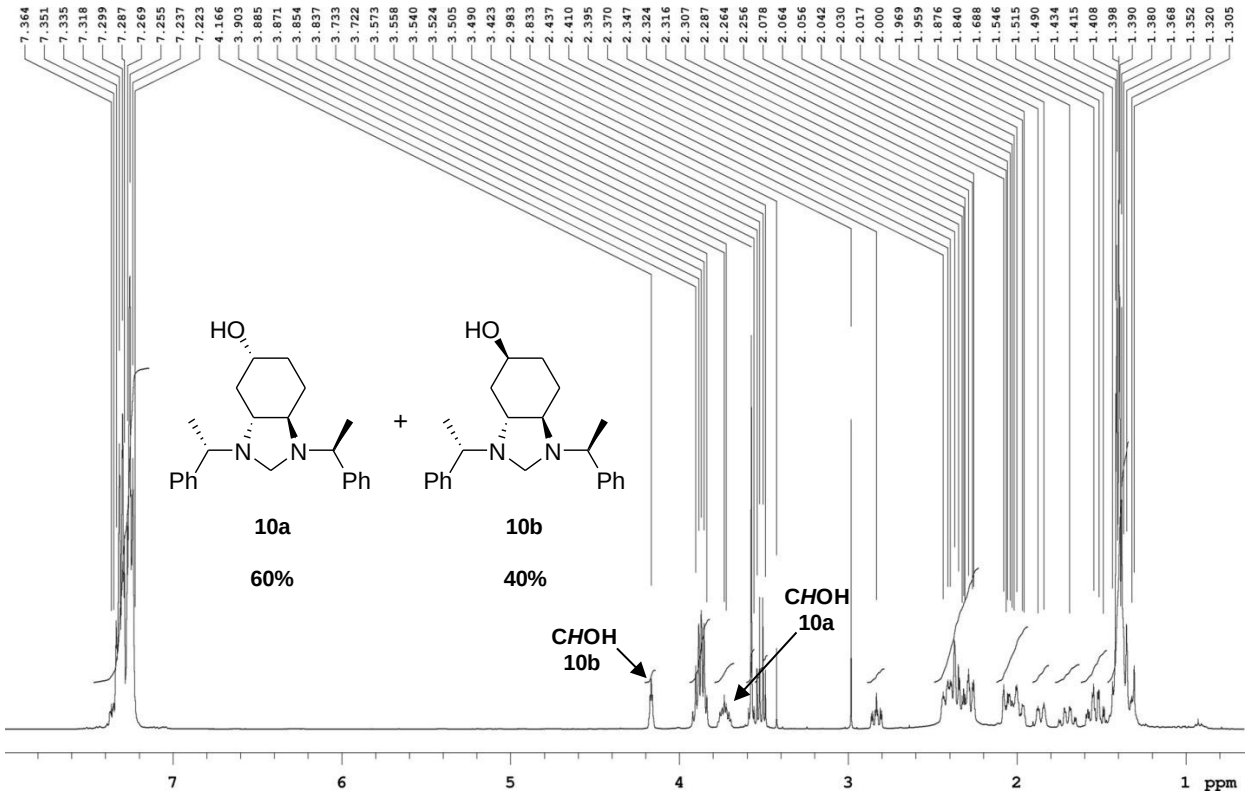


Figure S9: ^{1}H NMR of the mixture **10a**/**10b** (60:40)

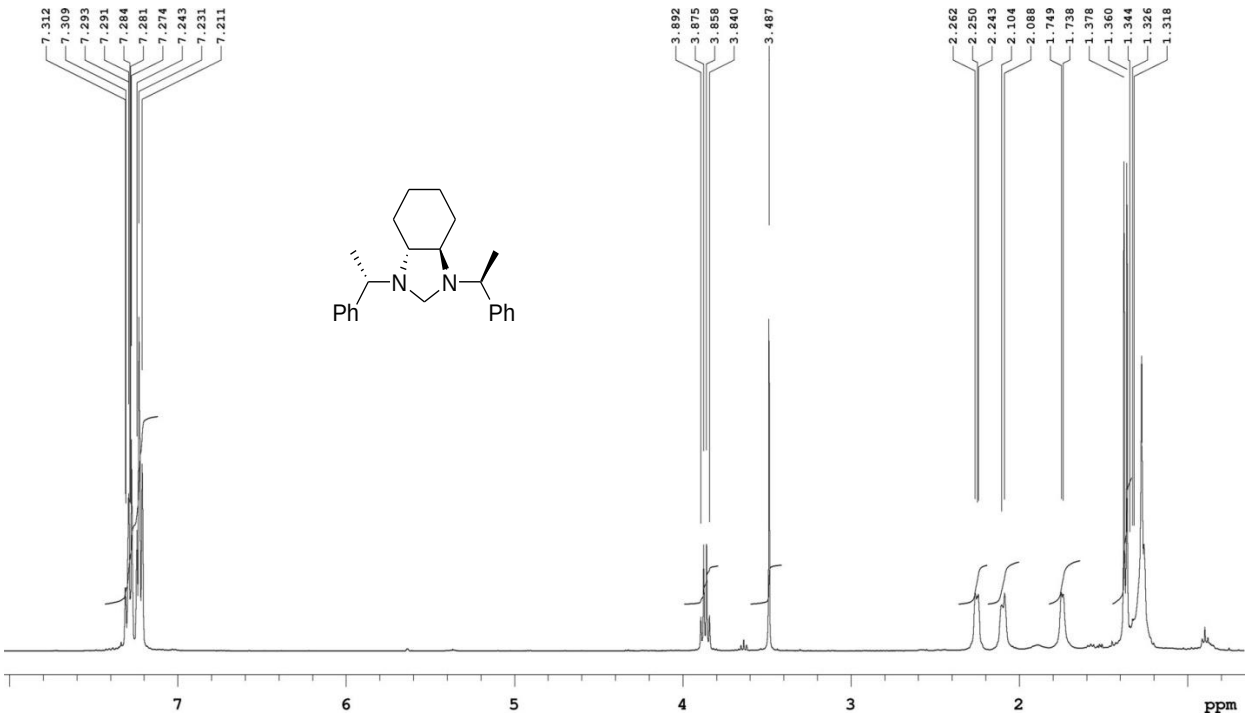


Figure S10: ^{1}H NMR of **11**

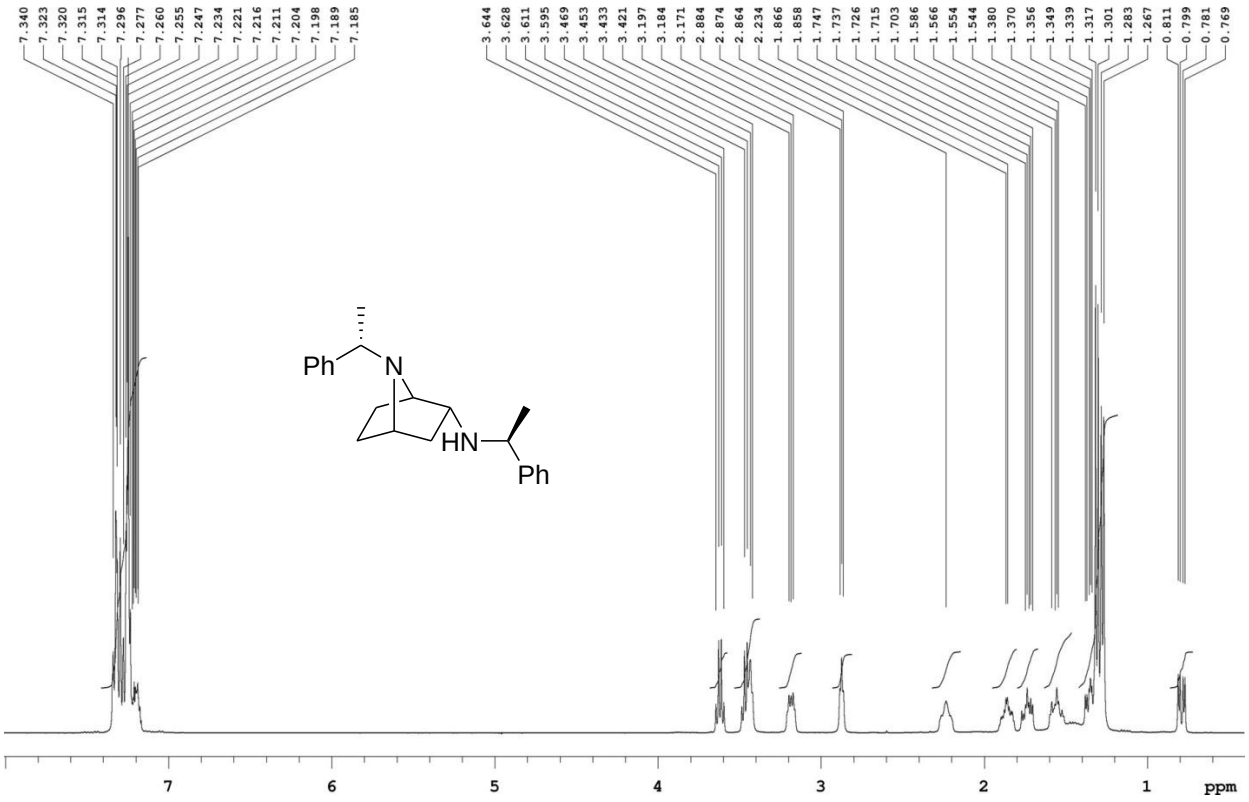


Figure S11: ^{1}H NMR of **7**

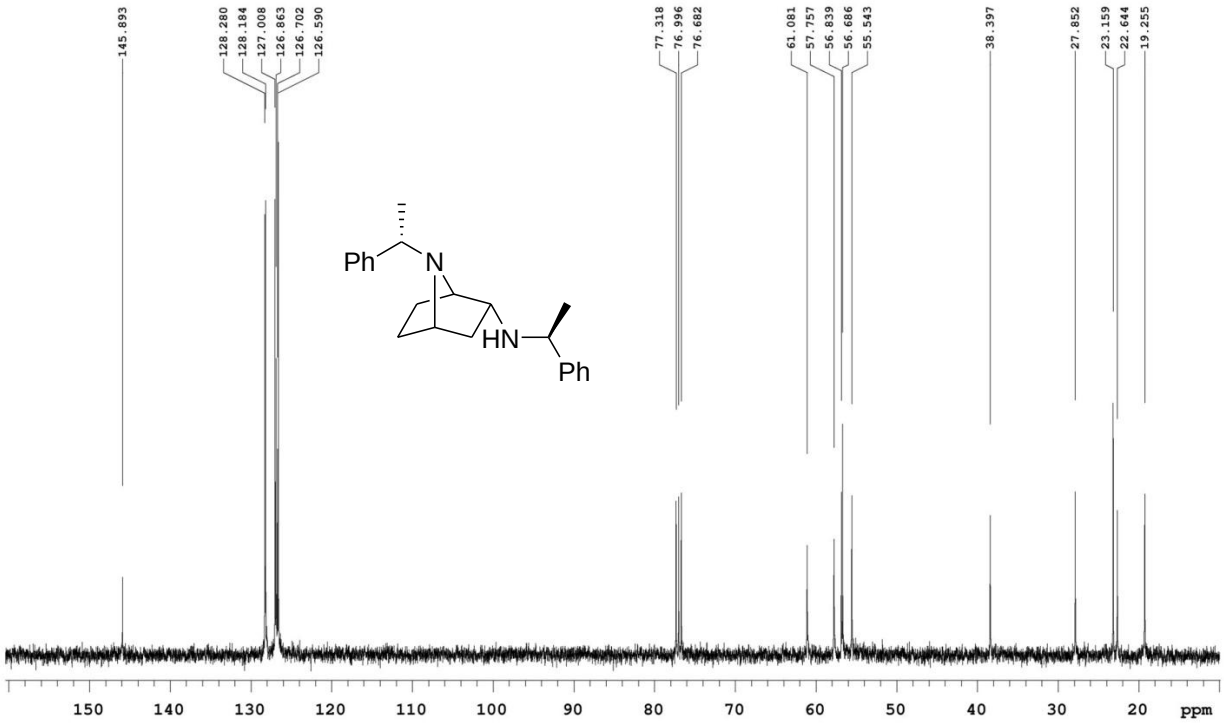


Figure S12: ^{13}C NMR of **7**

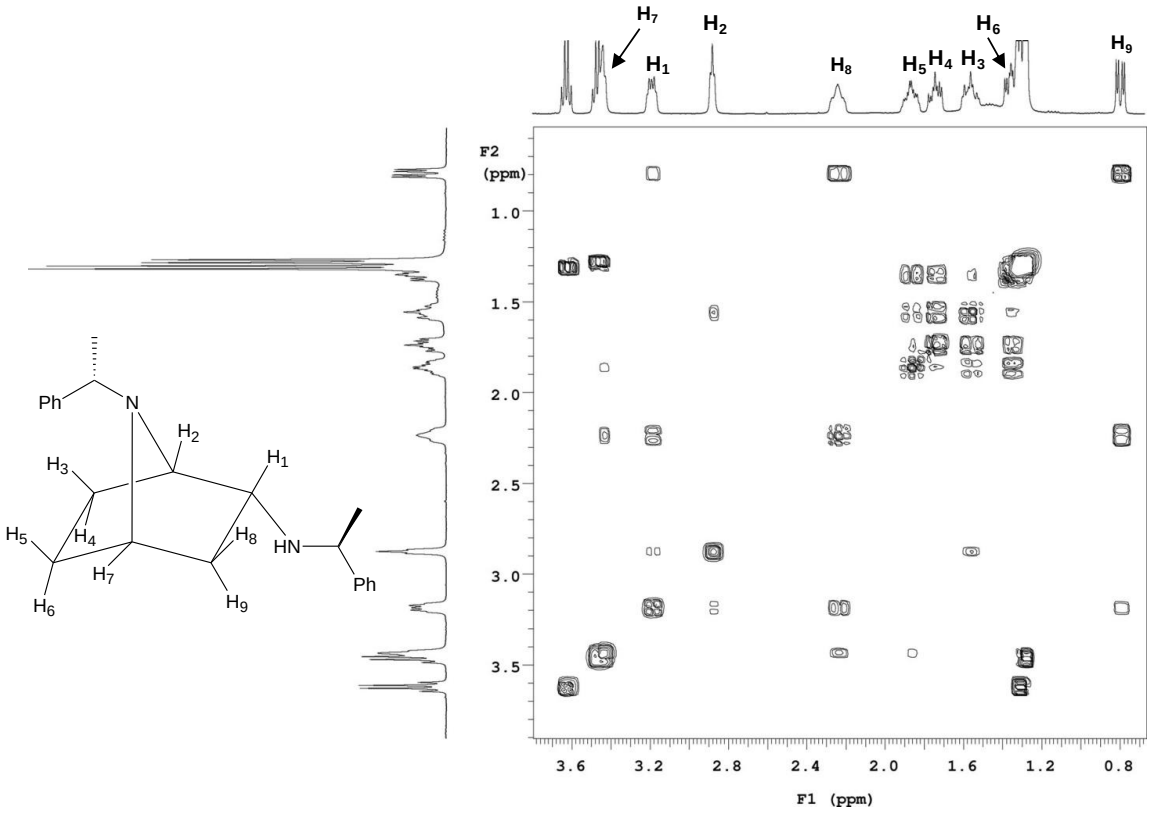


Figure S13: Partial ^{1}H-^{1}H gradient COSY spectrum (400 MHz, $CDCl_3$, 25 °C) of **7**

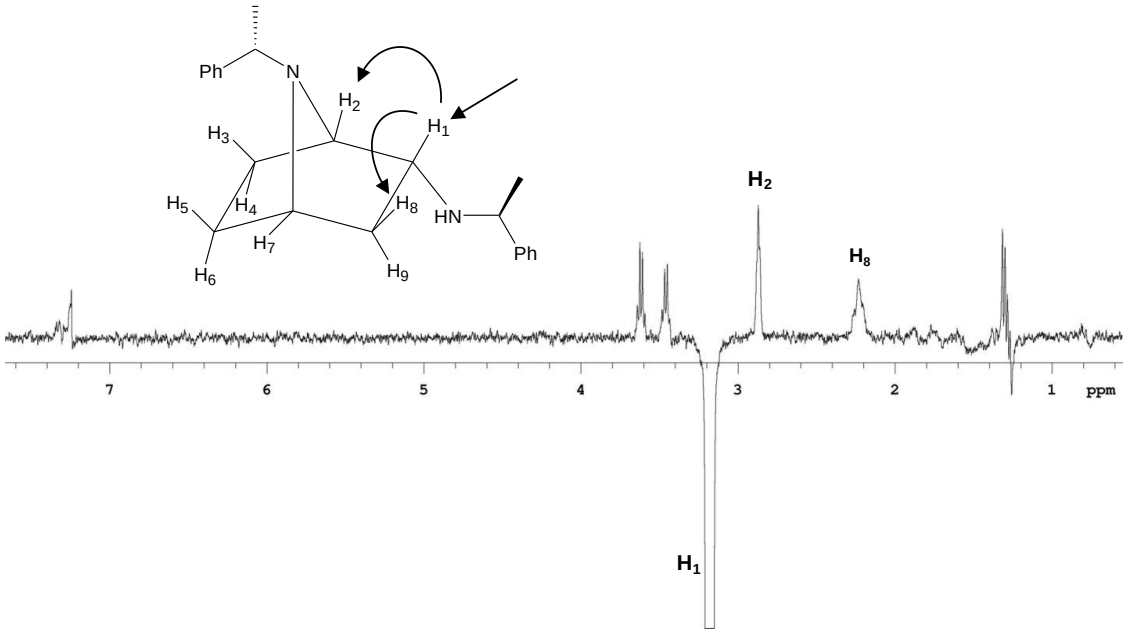


Figure S14: 1D-NOE spectrum (400 MHz, $CDCl_3$, 25 °C) of **7** obtained using a DPFGSE-NOE sequence with a 50 Hz 'r-snob' pulse and a mixing time of 2 seconds. Selective excitation of the proton H_1 shows a positive NOE on H_2, confirming the bicyclic structure.

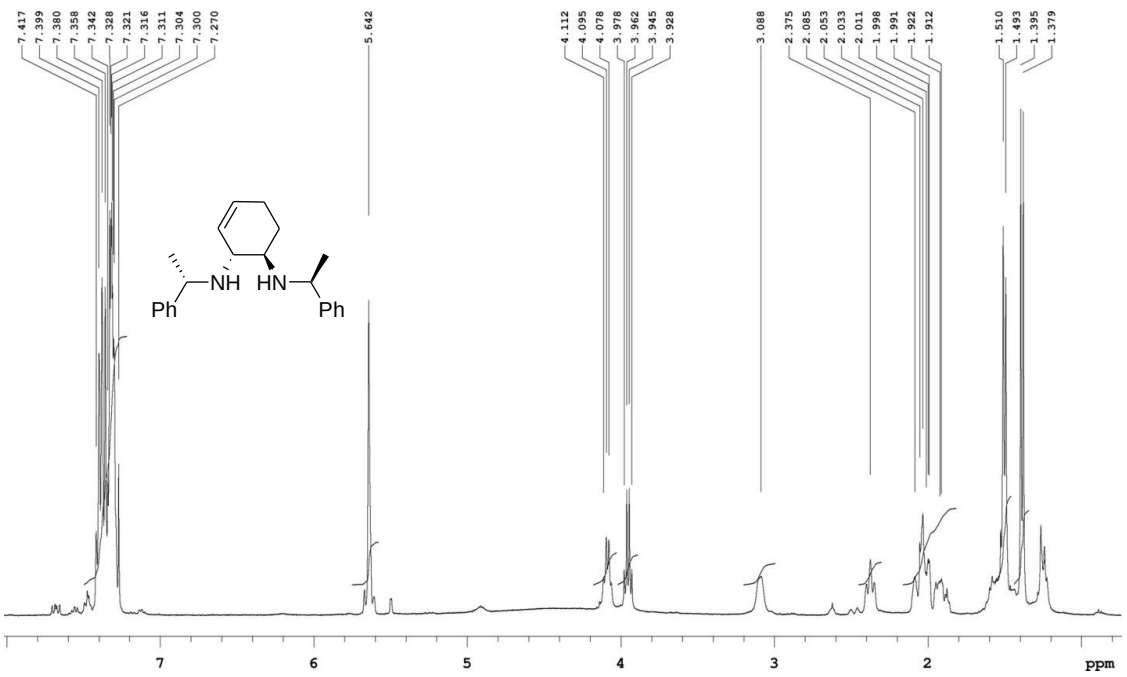


Figure S15: ^{1}H NMR of **14**

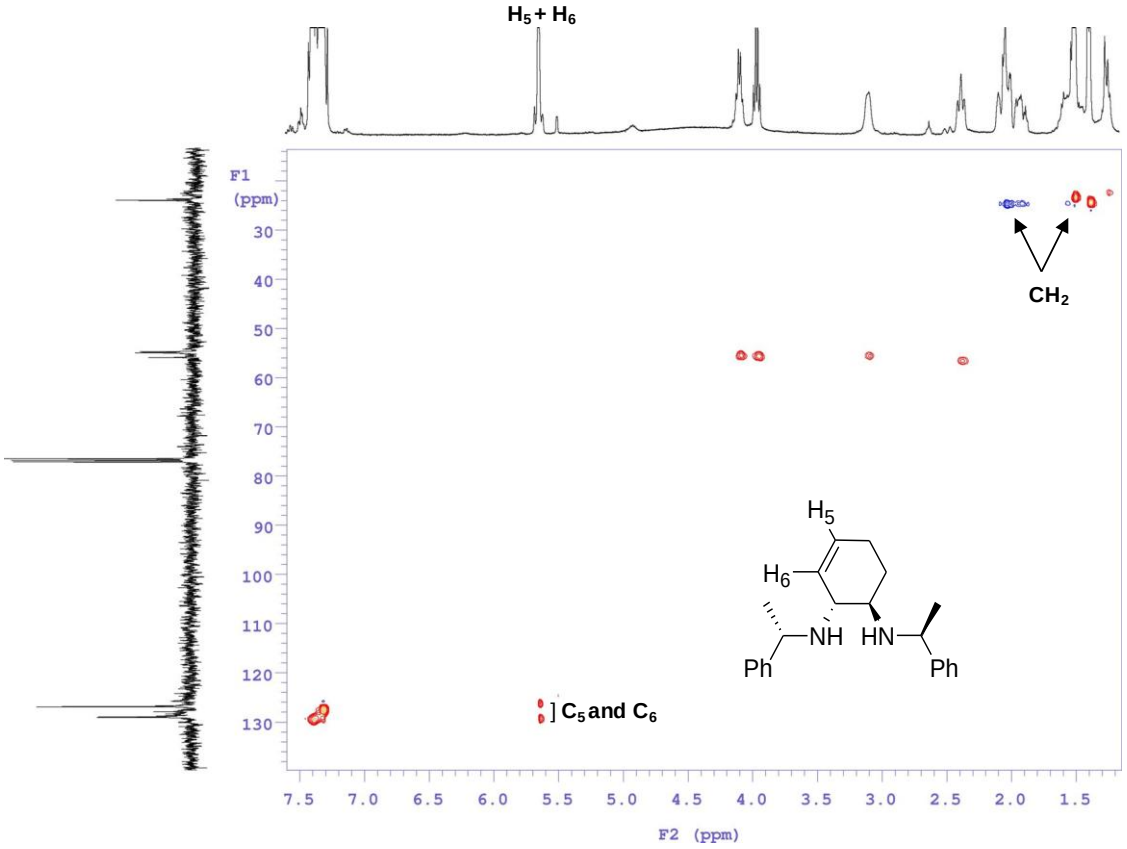


Figure S16: phase sensitive gradient HSQC spectrum (400 MHz, $CDCl_3$, 25 °C) of **14**. Although protons H_5 and H_6 are indistinguishable, showing a singlet at 5.64 ppm, the corresponding carbons are well separated confirming the non-symmetric structure (odd multiplicity in red, even multiplicity in blue)

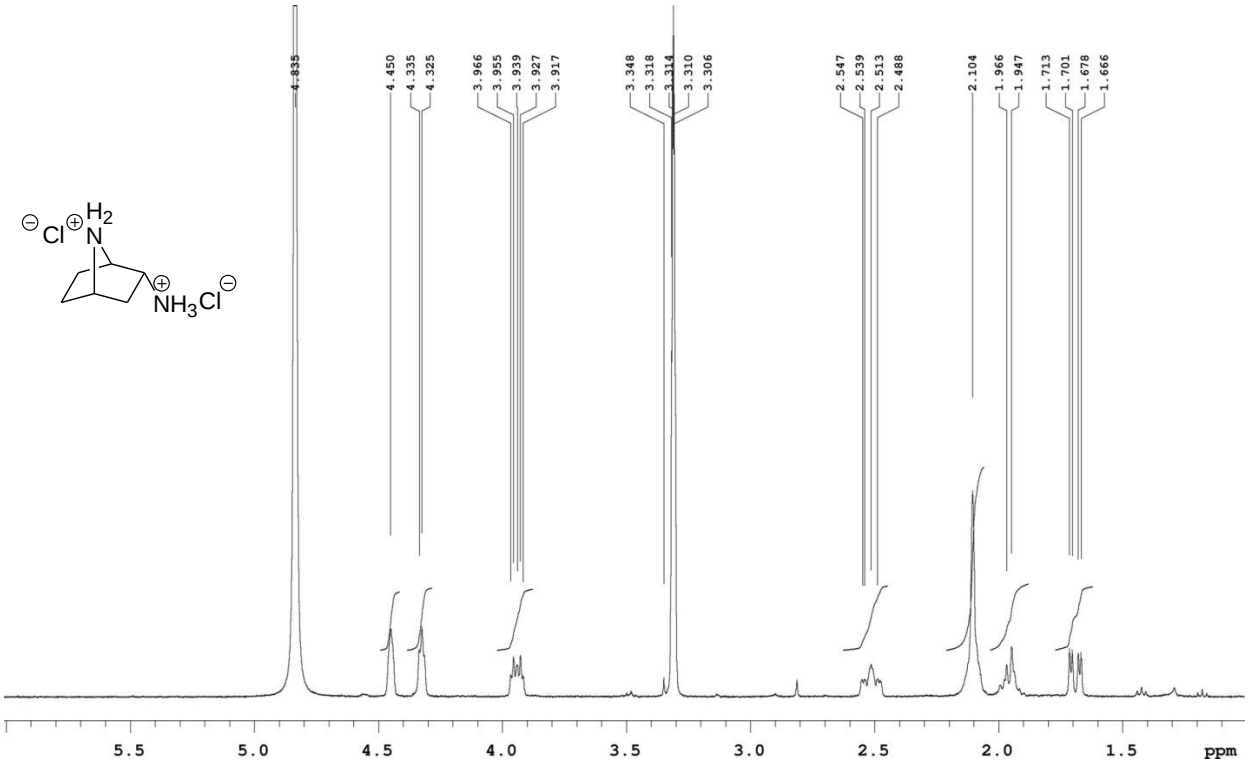


Figure S17: ^{1}H NMR (400 MHz, CD_3OD, 25 °C) of **1**-2HCl.

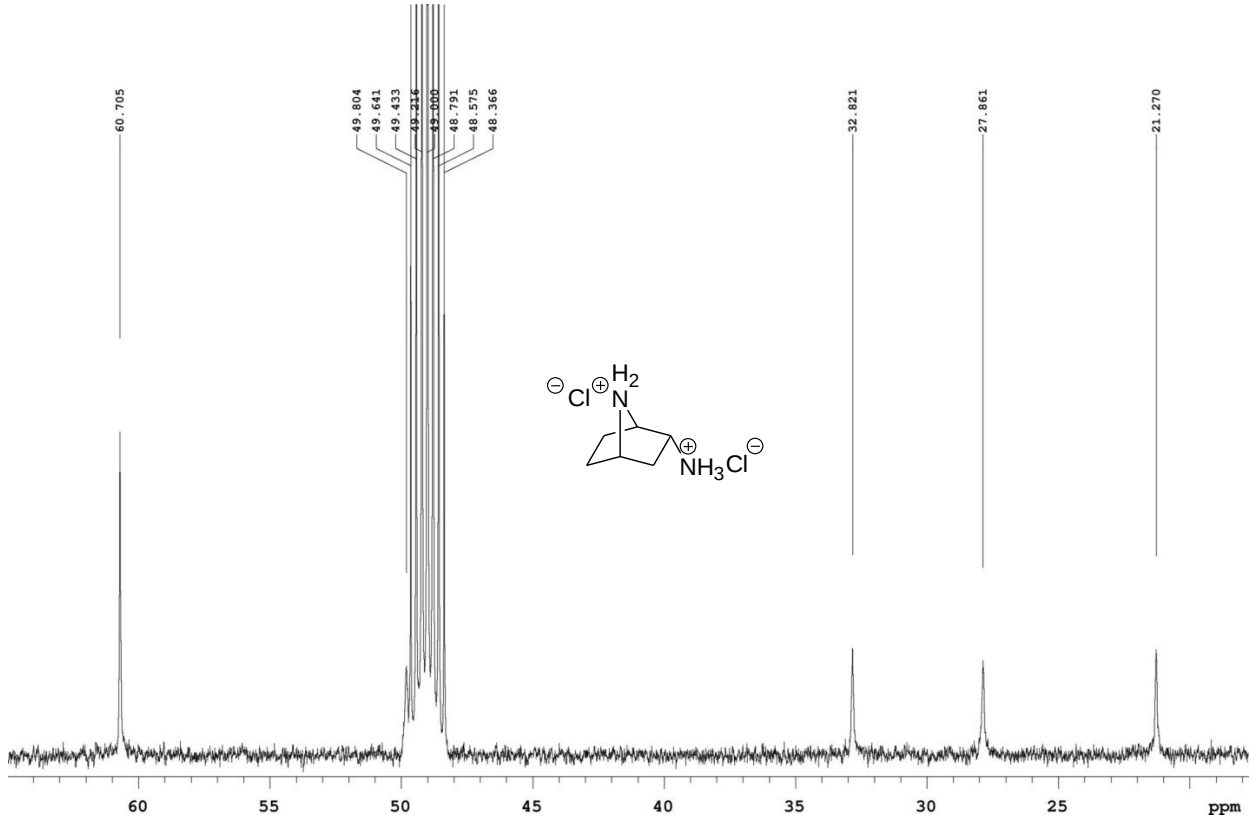


Figure S18: ^{13}C NMR (100.7 MHz, CD_3OD, 25 °C) of **1**-2HCl.

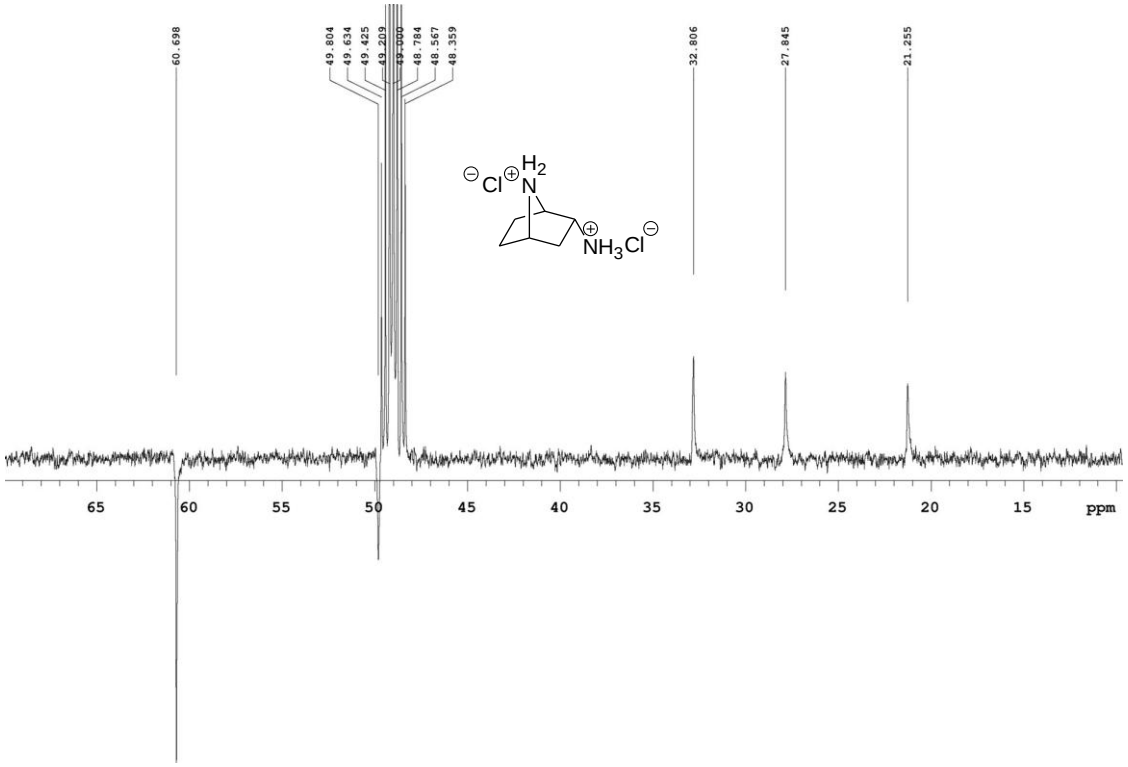


Figure S19: APT spectrum (100.7 MHz, CD_3OD, 25 °C) of **1**-2HCl.

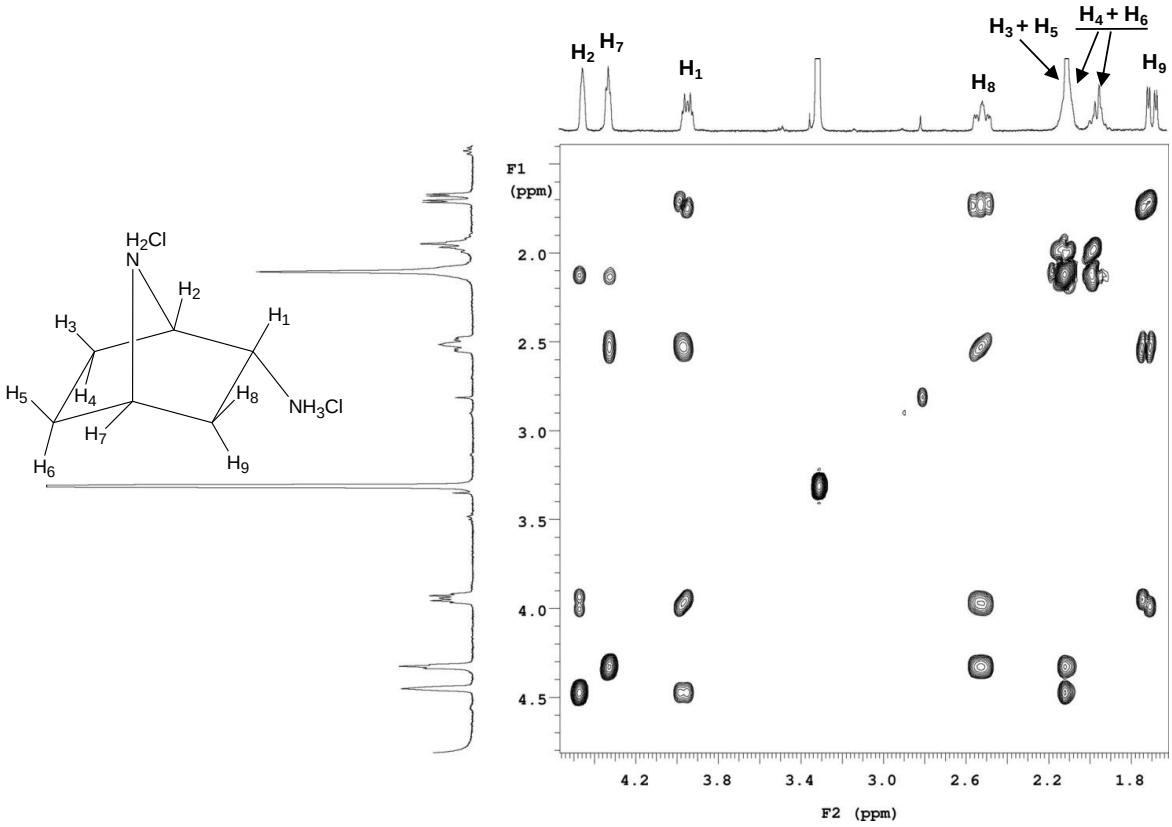


Figure S20: ^1H-^1H gradient COSY spectrum (400 MHz, CD_3OD, 25 °C) of **1**-2HCl.

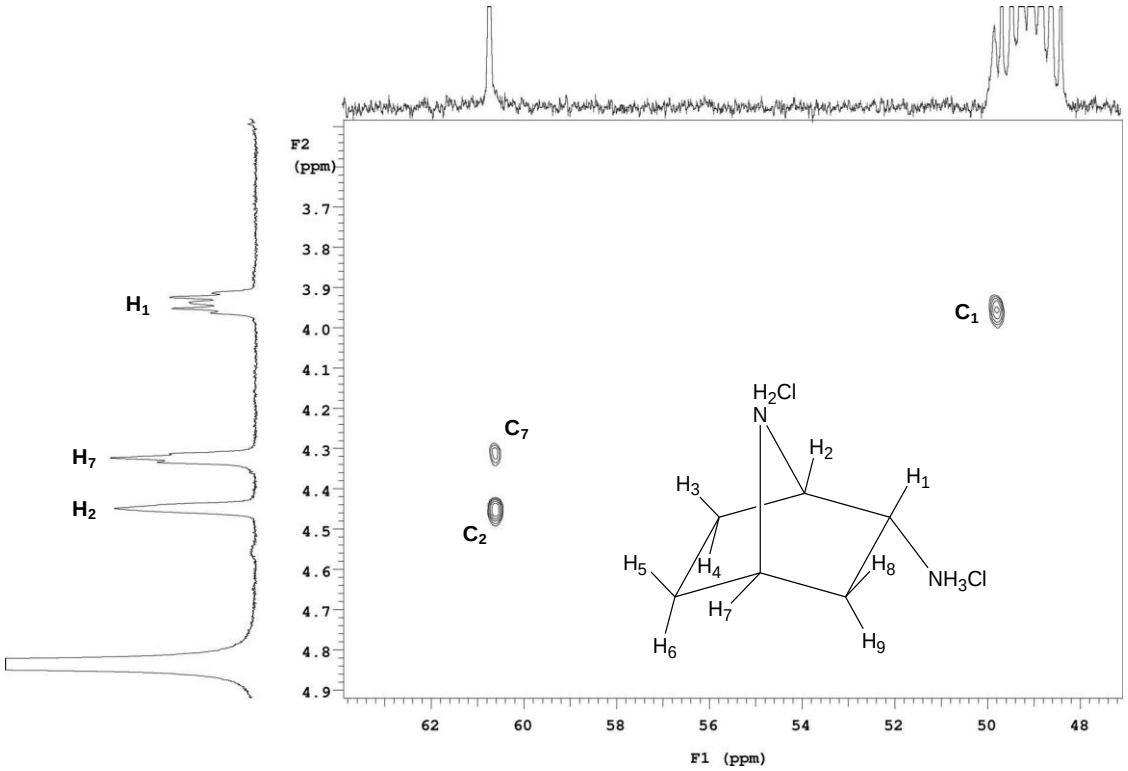


Figure S21: partial phase sensitive gradient HSQC spectrum (400 MHz, CD_3OD, 25 °C) of **1**-2HCl. The two methine carbons C_2 and C_7 are overlapped.