Lithiathion of *N*-Alkyl-(*o*-tolyl)aziridine: Stereoselective Synthesis of Isochromans.

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SUPPORTING INFORMATION

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Experimental

General

All reactions involving air-sensitive reagents were performed in oven-dried glassware under an atmosphere of nitrogen using syringe-septum cap technique. Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere over sodium / benzophenone. Hexane was freshly distilled under a nitrogen atmosphere over finely powdered CaH_2.

Column chromatography was performed using the solvent systems indicated. Petroleum ether refers to the fraction boiling at 30–40 °C. The stationary phase used was silica gel 60 unless otherwise indicated.

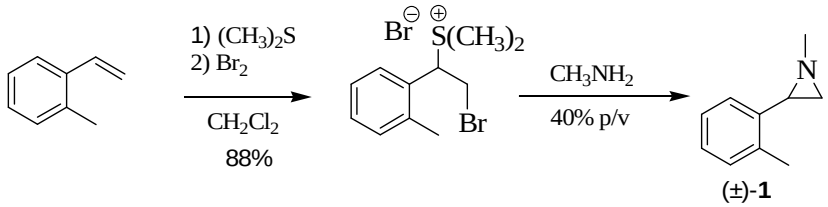
^{1}H NMR and ^{13}C NMR spectra were recorded at 400, 500, 600 MHz and 75, 100, 125, 150 MHz respectively with $CDCl_3$ as solvent. Data are expressed as chemical shifts in parts per million (ppm) relative to residual chloroform $CDCl_3$ (^{1}H δ 7.27), (^{13}C δ 77.0). The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; ddt, doublet of doublet of triplets; t, triplet; br, broad; m multiplet. Coupling constants *J* are given in Hz. Infra-red spectra of the compounds were recorded as a film or KBr disc as indicated. Low resolution mass spectra were obtained by GC-MS analysis using a gas chromatography with a BPX_5 column-HP 6890 plus (30 m, 0.25 mm i.d.) equipped with a 5973 mass selective detector operating at 70 eV (flow rate (He) = 1 mL/min). Specific rotations $[\alpha]_D$ were measured using a polarimeter with a cell of path length 1.0 dm, at 20 °C. Concentrations (c) are given in g/100 mL. Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; detection was accomplished by UV light (254 nm), by exposing to I_2 vapours and spraying a solution of (5% W/V) ammonium molibdate and 0.2% W/V cerium(III)sulphate in 100 ml 17.6% aq. sulphuric acid and heating to 200 °C for some time until blue spots appear.

N,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2. Commercial solutions of *n*-BuLi (2.5 M hexane solution) and *sec*-BuLi (1.3 M cyclohexane solution) were titrated by using *N*-pivaloyl-*o*-toluidine prior use.[1]

All other chemicals were of commercial grade and used without further purification.

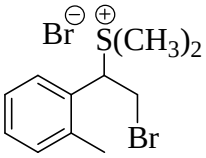
[1] Suffert, J. *J. Org. Chem.* **1989**, *54*, 509-510.

Procedure for the preparation of aziridine (±)-1.



(±)-**1**

Aziridine **(±)-1** was prepared using dimethyl-[2-bromo-1-(o-tolyl)ethyl]sulphonium bromide as intermediate, which was easily generated by reaction of bromine, dimethyl sulphide (*ca.* 1:5 molar ratio in CH_2Cl_2) and *o*-tolylstyrene.[2] A commercially available aqueous solution (40% p/v) of $MeNH_2$ (20 mmol) was added dropwise at 0 °C to the sulphonium bromide (1 mmol) and the resulting mixture was stirred overnight. The mixture was poured into 20 mL of saturated brine, extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Kugelrohr distillation furnished the desired aziridine with 95% yield. Spectroscopic data for **(±)-1** have been reported.[3]



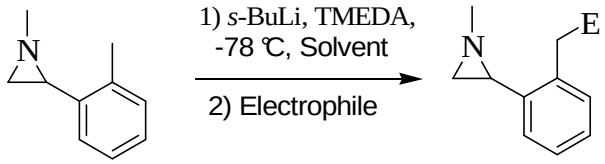
[2-Bromo-1-(*o*-tolyl)ethyl]dimethylsulphonium bromide: white solid, mp 119–120 °C, 88%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 4.87 (s, 3 H), 5.12 (s, 3 H), 5.45 (s, 3 H), 6.55 (t, *J* = 11.0 Hz, 1 H), 6.65 (dd, *J* = 5.5, 11.0 Hz, 1 H), 7.08 (q, *J* = 5.5 Hz, 1 H), 9.82–9.96 (m, 4 H). C^{13}-NMR ($CDCl_3$, 500 MHz) δ 21.5, 25.5, 26.4, 31.4, 129.9, 131.0, 133.2, 134.2, 141.4. ESI-MS *m/z* (%): 197 (43), 118 (64). FT-IR (KBr, cm^{-1}): 3423, 2981, 2932, 2915, 1493, 1440, 1207, 1004, 737. Anal calcd for $C_{11}H_{16}Br_2S$: C, 38.84; H, 4.74%. Found: C, 37.79; H, 4.59%.

(*S*)-1 ($[\alpha]_D^{20}$ = +144 (c = 1.0, $CHCl_3$), er > 98:2, 63% yield) was prepared by lithiation/MeI-trapping sequence from *S*-(+)-1-methyl-2-phenylaziridine ($[\alpha]_D^{20}$ = + 177 (c = 0.5, $CHCl_3$), er > 98:2) according a reported procedure.[3] *S*-(+)-1-methyl-2-phenylaziridine (40% yield) was synthetized starting from commercially available (*R*)-styrene oxide, by ring-opening reaction with $MeNH_2$ and a subsequent Mitsunobu ring-closure of the correspondent aminoalcohols.[4,5,6] The

[2] Chow, Y. L.; Bakker, B. H.; Iwai, K. *J. Chem. Soc. Chem. Comm.* **1980**, 521–522.
[3] Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005,** *7*, 17, 3749-3752.
[4] a) Sawamura, M; Hamashima, H; Ito, Y. *J. Org. Chem*. **1990**, 55, 5935.16. b) Huszthy, P; Oue, M; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem*. **1992**, 57, 5383-5394.
[5] Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1986**, *29*, 2241 – 2249.
[6] Fujita, S.; Imamura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1975-1977.

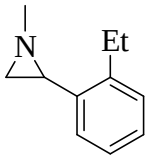
enantiomeric purity of the aziridine derivatives was ascertained by ^{1}H-NMR in presence of Mosher's acid (See page S28-S29).

Procedure for the lithiation/trapping sequence of aziridine 1:

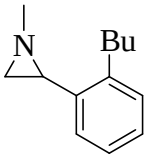


1 **2a-j**

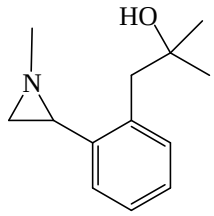
To a stirred solution of aziridine **(±)-1** (100 mg, 0.68 mmol) and TMEDA (204.0 µL, 1.36 mmol) in THF (4 mL) at -78 °C a solution of *sec*-BuLi (1.4 M in hexane, 972 µL, 1.36 mmol) was added dropwise . After 30 minutes at -78 °C the electrophile (1.36 mmol) was added neat if liquid and in 2.0 ml of solvent if solid. After 2 hours at -78 °C, the mixture was allowed to warm slowly to room temperature and the reaction mixture was poured in saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography (AcOEt/petroleum ether, 3/7) afforded the substituted aziridines **2a-j**. The same procedure was used for *S*-(+)-1-methyl-2-(*o*-tolyl)aziridine using hexane as the solvent.



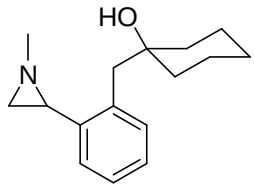
2-(2-Ethylphenyl)-1-methylaziridine (2b): colourless oil, 95%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.26 (t, *J* = 7.6 Hz, 3 H), 1.61 (d, *J* = 6.5 Hz, 1 H), 1.85 (d, *J* = 3.5 Hz, 1 H), 2.39 (dd, *J* = 3.5, 6.5 Hz, 1 H), 2.51 (s, 3 H), 2.76 (dd, *J* = 2.0, 7.4 Hz, 1 H), 2.79 (dd, *J* = 2.0, 7.4 Hz, 1 H), 7.09-7.22 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 25.7, 38.0, 40.0, 48.0, 58.6, 125.7, 125.9, 126.8, 127.8, 137.3, 142.4. GC-MS *m/z* (%): 161 [M^+, 18], 160 (100), 146 (98), 131 (58), 117 (96), 91 (29). FT-IR **(**film, cm^{-1}): 3047, 2967, 2849, 1491, 1459, 1383, 1191, 1013, 800, 753, 732.



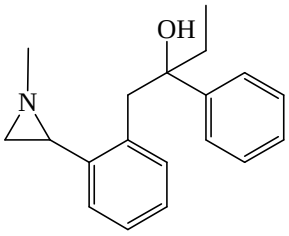
2-(2-Butylphenyl)- 1-methylaziridine (2c): yellow oil, 95%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, *J* = 7.4 Hz, 3 H), 1.41-1.48 (m, 2 H), 1.61-1.67 (m, 3 H), 1.87 (d, *J* = 3.4 Hz, 1 H), 2.41 (dd, *J* = 3.4, 6.5 Hz, 2 H), 2.52 (s, 3 H), 2.72-2.82 (m, 2 H), 7.13-7.26 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.0, 22.7, 32.5, 33.0, 38.0, 40.0, 47.9, 125.7, 125.9, 126.6, 128.7, 137.4, 141.1. GC-MS *m/z* (%): 189 [M^+, 12], 188 (54), 174 (35), 160 (36), 145 (43), 144 (54), 131 (39), 117 (100), 91 (25). FT-IR **(**film, cm^{-1}): 2955, 2927, 2870, 1491, 1458, 1259, 1029, 759.



2-Methyl-1-[2-(1-methylaziridin-2-yl)phenyl]propan-2-ol (2d): waxy solid, 57%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 3 H), 1.31 (s, 3 H), 1.60 (d, *J* = 6.7 Hz, 1 H), 1.90 (d, *J* = 3.6 Hz, 1 H), 2.42 (dd, *J* = 4.4, 7.4 Hz, 1 H), 2.44 (s, 3 H), 2.70 (d, *J* = 13.6 Hz, 1 H), 2.99 (d, *J* = 13.6 Hz, 1 H), 7.04-7.13 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 28.1, 32.1, 36.4, 41.5, 45.5, 46.5, 69.3, 126.3, 126.7, 128.2, 131.5, 137.1, 138.2. ESI-MS *m/z* (%): 228 [M-Na$^+$] (100). FT-IR **(**film, cm^{-1}): 3385, 2959, 1452, 1379, 1139, 744. Anal calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82%; Found: C, 75.96; H, 9.24; N, 6.71;

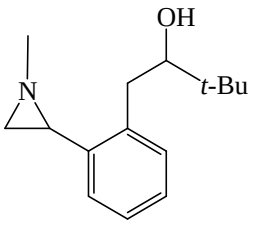


1-[2-(1-Methylaziridin-2-yl)benzyl]cyclohexanol (2e). waxy solid, 21%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.23-1.71 (m, 10 H), 1.66 (d overlapping m at 1.23-1.71 ppm, *J* = 6.7 Hz, 1 H), 1.98 (d, *J* = 3.6 Hz, 1 H), 2.48 (dd overlapping s at 2.50 ppm, *J* = 3.0, 6.5 Hz, 1 H), 2.50 (s, 3 H), 2.80 (d, *J* = 13.6 Hz, 1 H), 2.93 (d, *J* = 13.6 Hz, 1 H), 5.28 (br s, 1 H), 7.09-7.18 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 22.2, 22.6, 26.1, 36.3, 36.4, 40.7, 41.7, 44.7, 46.6, 69.9, 126.3, 126.7, 128.4, 131.5, 136.8, 138.3. GC-MS *m/z* (%): 245 [M$^+$, 10], 227 (53), 202 (18), 147 (100), 115 (20). FT-IR (film, cm^{-1}): 3059, 2932, 2854, 1448, 1380, 1264, 986, 735. Anal calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71; Found: C, 78.12; H, 9.38; N, 5.65.



1-[2-(1-Methylaziridin-2-yl)phenyl]-2-phenylbutan-2-ol (2g). Mixture of diastereoisomers (dr = 70:30). Overall yield 74%.

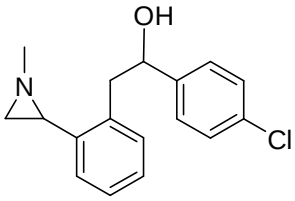
Major diastereoisomer: yellow solid, mp 71-72 °C, 52%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.66 (t, *J* = 7.3 Hz, 3 H), 1.68 (d, *J* = 6.7 Hz, 1 H), 1.84-1.99 (m, 2 H), 2.10 (d, *J* = 3.6 Hz, 1 H), 2.24 (s, 3 H), 2.37 (dd, *J* = 3.8, 6.5 Hz, 1 H), 3.20 (AB system, 2 H), 7.19-7.28 (m, 5 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 8.0, 33.2, 35.5, 41.8, 46.0, 46.1, 74.8, 125.4, 125.9, 126.4, 127.0, 127.8, 129.0, 131.7, 137.2, 138.2, 149.2. GC-MS *m/z* (%): 281 [M$^+$, 10], 280 (11), 252 (29), 237 (15), 219 (21), 179 (22), 146 (100), 132 (59), 105(17), 103 (28), 91 (35), 77 (41), 44 (41). FT-IR **(**KBr, cm^{-1}): 3140, 2961, 2953, 2931, 2850, 1442, 1378, 1199, 1020, 774, 753, 704. Anal calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8,24; N, 4.98%. Found: C, 81.03; H, 8.33%; N, 4.76%.



3,3-Dimethyl-1-[2-(1-methylaziridin-2-yl)phenyl]butan-2-ol (2h). Separable mixture of diastereoisomers (dr = 80:20).

Major diastereoisomer **(*R**,*R**)-2h**: white solid, mp 38-40 °C, 55%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 1.68 (d, *J* = 6.7 Hz, 1 H), 1.98 (d, *J* = 3.6 Hz, 1 H), 2.51 (dd, *J* = 3.6, 6.6 Hz, 1 H), 2.53 (s, 3 H), 2.81 (dd, *J* = 10.5, 13.4 Hz, 1 H), 2.86 (dd, *J* = 2.9, 13.4 Hz, 1 H), 3.26 (dd, *J* = 2.9, 7.6 Hz, 1 H), 7.12-7.24 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.9, 34.4, 35.6, 41.4, 46.7, 81.5, 125.8, 127.5, 128.5, 129.7, 137.4, 140.2. GC-MS *m/z* (%): 233 [M^+, 3], 176 (100), 144 (24), 134 (39), 131 (37), 117 (25), 103 (27), 57 (22), 44 (51). FT-IR **(**KBr, cm^{-1}): 3212, 2951, 2866, 1479, 1452, 1380, 1361, 1077, 1015, 805, 758. Anal calcd for $C_{15}H_{23}NO$: C, 77.21; N, 6.00; H, 9.93%. Found: C, 77.58; N, 6.17; H, 9.92 %.

Minor diastereoisomer **(*R**,*S**)-2h**: colourless oil, 27%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9 H), 1.59 (d, *J* = 6.6 Hz, 1 H), 1.93 (d, *J* = 3.5 Hz, 1 H), 2.40 (dd, *J* = 2.9, 6.5 Hz, 1 H), 2.51 (s, 3 H), 2.62 (dd, *J* = 10.7, 13.8 Hz, 1 H), 2.99 (dd, *J* = 2.0, 13.8 Hz, 1 H), 3.43 (dd, *J* = 2.0, 10.7 Hz, 1 H), 7.12-7.24 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.8, 34.7, 35.1, 37.7, 40.9, 47.9, 80.0, 126.5, 126.9, 130.2, 138.0, 138.3. GC-MS *m/z* (%): 233 [M^+ 4], 218 (15), 176 (100), 134 (45), 131 (42), 117 (28), 103 (32), 44 (57). FT-IR (film, cm^{-1}): 3383, 3061, 2952, 2867, 1463, 1454, 1385, 1361, 1069, 1013, 739. Anal calcd for $C_{15}H_{23}NO$: C, 77.21; N, 6.00; H, 9.93%. Found: C, 77.58; N, 6.17; H, 9.92 %.

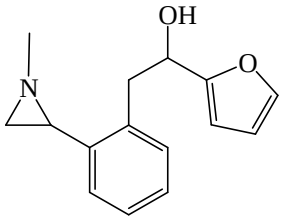


1-(4-Chlorophenyl)-2-[2-(1-methylaziridin-2-yl)-phenyl]-ethanol (2i). Separable mixture of diastereoisomers (dr = 70:30).

Major diastereoisomer **(*R**,*R**)-2i**: white solid, mp 135-137 °C, 59%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.72 (d, *J* = 6.7 Hz, 1 H), 2.03 (d, *J* = 3.6 Hz, 1 H), 2.48 (dd, *J* =3.8, 6.5 Hz, 1 H), 2.53 (s, 3 H), 3.00 (dd, *J* =3.9, 13.8 Hz, 1 H), 3.06 (dd, *J* =10.6, 13.8 Hz, 1 H), 4.74 (dd, *J* = 3.8, 10.4 Hz, 1 H), 7.19-7.47 (m, 8 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 36.1, 41.3, 43.3, 46.4, 74.5, 126.4, 126.7, 127.8, 127.9, 128.3, 128.7, 129.6, 132.2, 137.5, 138.4, 145.0. GC-MS *m/z* (%): 287 [M^+, 3], 243 (8), 178 (15), 146 (20), 103 (19), 77 (14), 44 (100). ESI-MS *m/z* (%): 288 [M-H^+] (100). FT-IR (KBr, cm^{-1}): 3357, 3060, 2950, 2855, 1489, 1089, 819, 737. Anal calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6,30; N, 4.87%. Found: C, 70.76; H, 6.35; N, 4.93%. The enantiomeric purity of **(1*S*,2'*S*)-2i** ($[\alpha]^{20}_D$ = + 46.4, c 0.5, $CHCl_3$) was determined by HPLC analysis (OD-H chiral column; hexane:*i*PrOH 99:1; flow: 1.0 ml/min; for racemic **(*R**,*R**)-2i** t_1 = 9. min, t_2 = 48.2 min; for **(1*S*,2'*S*)-2i** t = 48.2 min).

Minor diastereoisomer **(*R**,*S**)-2i**: yellow oil, 26%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.64 (d, *J* = 6.7 Hz, 1 H), 1.96 (d, *J* = 3.4 Hz, 1 H), 2.33 (dd, *J* = 3.9, 6.4 Hz, 1 H), 2.48 (s, 3 H), 2.98 (dd, *J* = 5.4

Hz, 13.7 Hz, 1 H), 3.28 (dd, *J* = 5.5, 13.7 Hz, 1 H), 4.99 (t, *J* = 5.3 Hz, 1 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 7.02-7.46 (m, 8 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 36.5, 41.3, 41.8, 46.8, 72.3, 126.5, 126.7, 127.5, 127.8, 132.4, 135.5, 137.9, 142.8. GC-MS *m/z* (%): 287 [M^+, 5], 243 (21), 146 (68), 131 (26), 103 (32), 77 (26), 44 (100). ESI-MS *m/z* (%): 288 [$M-H^+$] (100). FT-IR **(**film, cm^{-1}): 3351, 3061, 2950, 2856, 1489, 1454, 1090, 1014, 738. The enantiomeric purity of **(1*R*,2'*S*)-2i** ($[\alpha]^{20}_D$ = + 76.6, c 1.0, $CHCl_3$) was determined by HPLC analysis (OD-H chiral column; hexane:*i*PrOH 95:5; flow: 1.0 ml/min; for racemic **(*R**,*S**)-2i** t_1 = 9.3 min, t_2 = 10.5 min; for **(1*R*,2'*S*)-2i** t = 10.5 min).



1-(Furan-2-yl)-2-[2-(1-methylaziridin-2-yl)phenyl]ethanol (2j). Separable mixture of diastereoisomers (dr = 70:30).

Major diastereoisomer **(*R**,*R**)-2j**: yellow oil, 56%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.67 (d, *J* = 6.6 Hz, 1 H), 2.00 (d, *J* = 3.6 Hz, 1 H), 2.46 (dd, *J* = 3.6, 6.5 Hz, 1 H), 2.51 (s, 3 H), 3.05 (dd, *J* = 3.7, 13.7 Hz, 1 H), 3.26 (dd, *J* = 11.4, 13.6 Hz, 1 H), 4.66 (dd, *J* = 3.8, 11.3 Hz, 1 H), 6.24-6.29 (m, 2 H), 7.10-7.11 (m, 2 H), 7.18-7.25 (m, 2 H), 7.33-7.35 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 35.8, 39.2, 41.5, 46.0, 68.6, 104.7, 110.0, 126.4, 127.8, 128.7, 129.4, 137.8, 138.1, 141.4, 158.5. GC-MS *m/z* (%): 243 [M^+, 7], 228 (10), 182(17), 144 (26), 132 (22), 115 (26), 95 (23), 44 (100). FT-IR **(**film, cm^{-1}): 3353, 3115, 3061, 2950, 2854, 1451, 1381, 1144, 1064, 1012, 735. Anal calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76;%. Found: C, 74.28; H, 6.97; N, 5.65 %.

Minor diastereoisomer **(*R**,*S**)-2j**: yellow oil, 24%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.55 (d, *J* = 6.6 Hz , 1 H), 1.88 (d, *J* = 3.6 Hz, 1 H), 2.31 (dd, *J* = 3.6, 6.6 Hz, 1 H), 2.39 (s, 3 H), 3.08 (dd, *J* = 5.6, 13.9 Hz, 2 H), 3.24 (dd, *J* = 5.3, 13.9 Hz, 1 H), 4.94 (t, *J* = 5.4 Hz, 1 H), 5.96-5.07 (m, 1 H), 6.17-6.18 (m, 1 H), 6.63 (d, *J* = 7.5 Hz, 1 H), 6.94-7.05 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 36.6, 38.7, 41.3, 46.9, 67.8, 106.1, 110.2, 126.5, 126.9, 127.6, 130.5, 135.9, 137.9, 141.2, 156.4. GC-MS *m/z* (%): 243 [M^+, 5], 182 (15), 144 (21), 132 (20), 115 (25), 95 (26), 44 (100). FT-IR **(**film, cm^{-1}): 3359, 3117, 2949, 1733, 1604, 1492, 1454, 1384, 1145, 1050, 1012, 807, 738.

General procedure for the preparation of aminomethylisochromans: A solution of the hydroxyalkylated phenylaziridine (1.0 mmol) in 3.0 mL of acetic acid was stirred at room temperature until the substrate disappeared (TLC monitoring, AcOEt/petroleum ether, 8/2). The resulting reaction mixture was poured into 20 mL of $NaOH_{aq}$ (10%), extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixture was purified by flash-chromatography (silica gel; CH_2Cl_2/MeOH, 9/1) to give the corresponding isochromans showing the following data:

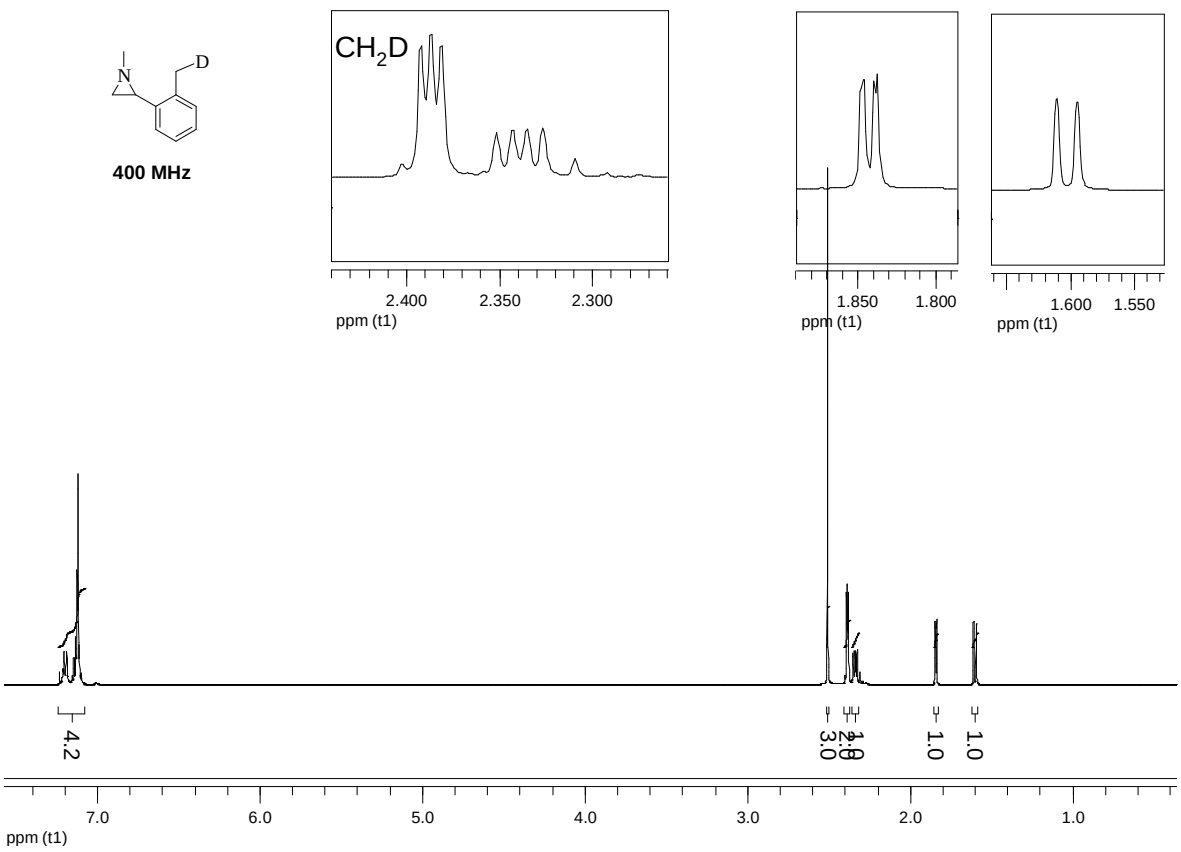
Spiro[cyclohexane-1,3'-(1'-methylamino)-3,4-dihydro-1*H*-isochromene] (3a): colourless oil, 80%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.16-1.58 (m, 7 H), 1.69-1.81 (m, 3H), 2.54 (d, *J* = 15.6 Hz, 1 H), 2.60 (s, 3 H), 2.76 (d, *J* = 15.6 Hz, 1 H), 2.87 (dd, *J* = 9.0, 12.1 Hz, 1 H), 3.27 (dd, *J* = 2.4, 12.1 Hz, 1 H), 4.28 (br s, 1H), 4.96 (d, *J* = 7.8 Hz, 1 H), 7.02–7.07 (m, 2 H), 7.13-7.16 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.9, 22.0, 26.0, 35.3, 38.9, 39.5, 53.4, 56.1, 68.3, 72.2, 123.8, 126.1, 126.9, 129.5, 133.3, 134.5. ESI-MS *m/z* (%): 246 $[M-H]^+$ (100). GC-MS *m/z* (%): 201 $[M^+ - 44]$, 183 (76), 141 (100), 117 (23). FT-IR (film, cm^{-1}): 2934, 2855, 1627, 1450, 1259, 1075, 742.

1-Methylaminomethyl-3-*tert*-butyl-3,4-dihydro-1*H*-isochromene (*R,*S**)-3c**: yellow oil, 80%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.0 (s, 9 H), 2.50 (s, 3 H), 2.59 (dd, *J* = 1.8, 15.7 Hz, 1 H), 2.73–2.85 (m, 2 H), 3.19 (dd, *J* = 2.9, 12.0 Hz, 1 H), 3.28 (dd, *J* = 2.6, 11.3 Hz, 1 H), 4.9 (d, *J* = 8.0 Hz, 1 H), 7.03–7.15 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 25.8, 29.3, 34.0, 36.1, 55.2, 56.5, 75.8, 81.6, 123.6, 126.0, 126.4, 129.3, 135.0, 136.3. ESI-MS *m/z* (%): 234 $[M-H]^+$ (100). FT-IR (film, cm^{-1}): 2954, 1478, 1362, 1100, 744.

1-Methylaminomethyl-3-*tert*-butyl-3,4-dihydro-1*H*-isochromene (*R,*R**)-3c**: yellow oil, 80%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.0 (s, 9 H), 2.52 (s, 3 H), 2.58 (dd, *J* = 2.8, 16.0 Hz, 1 H), 2.69 (dd, *J* = 2.9, 12.8 Hz, 1 H), 2.99 (dd, *J* = 1.8, 12.6 Hz, 1 H), 3.42 (dd, *J* = 2.8, 11.3 Hz, 1 H), 4.97 (dd, *J* = 2.8, 10.7 Hz, 1 H), 7.03–7.29 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 25.9, 28.9, 33.8, 36.1, 55.2, 74.2, 74.6, 125.2, 125.8, 126.5, 129.1, 134.4, 135.9. ESI-MS *m/z* (%): 234 $[M-H]^+$ (100), FT-IR (film, cm^{-1}): 2954, 1478, 1362, 1100, 744.

1-Methylaminomethyl-3-(4-chlorophenyl)-3,4-dihydro-1*H*-isochromene (*R,*S**)-3d**: colourless oil, 43%. ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.9 (br s, 1 H), 2.49 (s, 3 H), 2.93-3.07 (m, 3 H), 3.22 (dd, *J* = 2.9, 12.5 Hz, 1 H), 4.75 (dd, *J* = 2.9, 11.0 Hz, 1 H), 5.15 (d, *J* = 7.7 Hz, 1 H), 7.09–7.25 (m, 5 H), 7.34 (m, 3 H). ^{13}C-MNR ($CDCl_3$, 100 MHz) δ 36.5, 36.9, 57.0, 75.3, 76.6, 124.1, 126.6, 126.6, 126.7, 127.3, 128.5, 128.9, 133.3, 134.0, 135.8, 140.7. ESI-MS *m/z* (%): 288 $[M-H]^+$ (100). GC-MS *m/z* (%): 245 [M^+-H, 3], 243 (28), 178 (82), 131 (76), 103 (100).FT-IR (film, cm^{-1}): 3435, 2962, 1437, 1262, 1090, 802. The enantiomeric purity of **(1*R*,3*S*)-3d** ($[\alpha]^{20}_D$ = -19.3, c 0.2, $CHCl_3$) was determined by HPLC analysis (OD-H chiral column; hexane:*i*PrOH 95:5; flow: 1.5 ml/min; for racemic **(*R**,*S**)-3d** t_1 = 4.90 min, t_2 = 7.13 min; for **(1*R*,3*S*)-3d** resulted t = 4.90 min).

1-Methylaminomethyl-3-(4-chlorophenyl)-3,4-dihydro-1*H*-isochromene (*R,*R**)-3d:** yellow oil, 32%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.34 (br s, 1 H), 2.47 (s, 3 H), 2.84 (dd, *J* = 2.9, 13.2 Hz, 1 H), 2.94 (d, *J* = 6.6 Hz, 1 H), 3.12 (dd, *J* = 10.2, 12.9 Hz, 2 H), 4.89 (t, *J* = 6.6 Hz, 1 H), 5.11 (dd, *J* = 2.6, 10.1 Hz, 1 H), 7.06–7.19 (m, 4 H), 7.30-7.36 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 36.0, 36.0_2, 55.4, 69.3, 74.2, 125.2, 126.4, 126.8, 127.5, 128.6, 128.7, 133.3, 133.3_2, 135.2, 140.4. ESI-MS *m/z* (%): 288 $[M-H]^+$ (100). FT-IR (film, cm^{-1}): 2929, 1490, 1085, 749. The enantiomeric purity of **(1*R*,3*R*)-3d** ($[\alpha]^{20}_D$ = +6, c 0.5, $CHCl_3$) was determined by HPLC analysis (OD-H chiral column; hexane:*i*PrOH 95:5; flow: 1.5 ml/min; for racemic **(*R**,*R**)-3d** t_1 = 6.3 min, t_2 = 10.0 min; for **(1*R*,3*R*)-3d** t = 6.3 min).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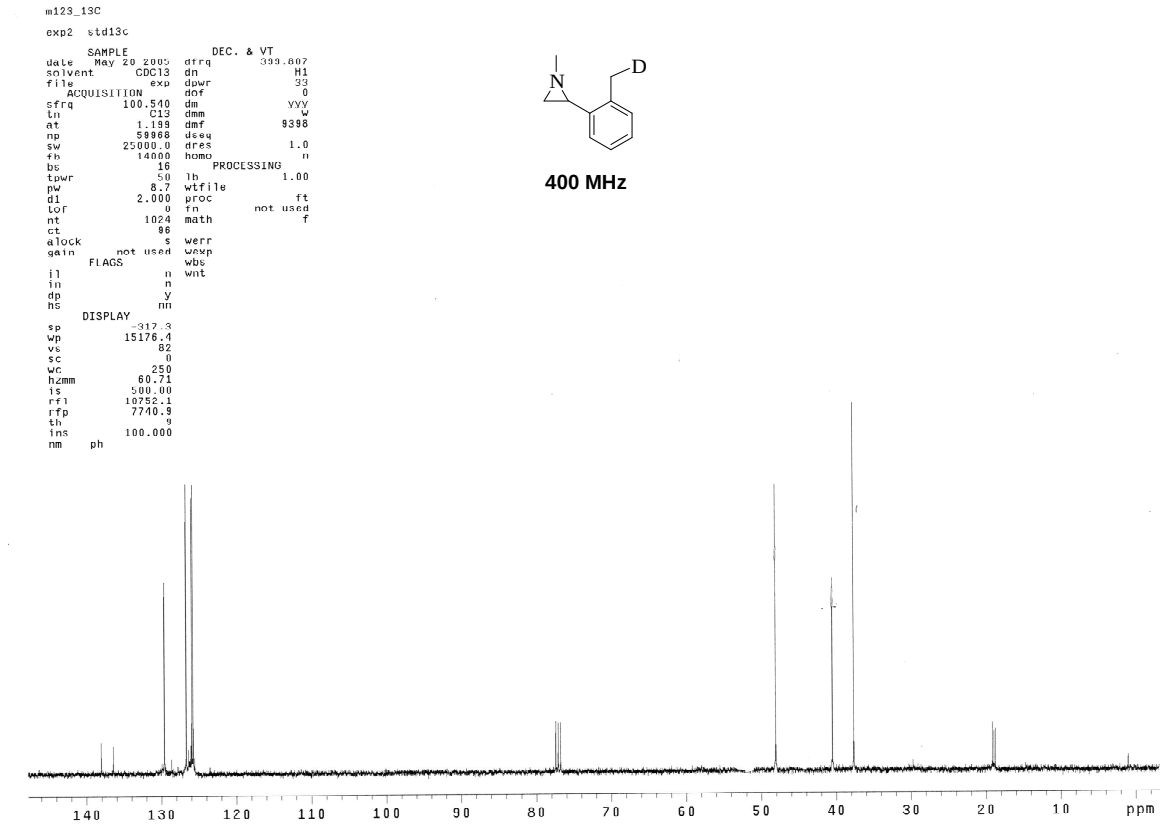
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proc ft
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math f
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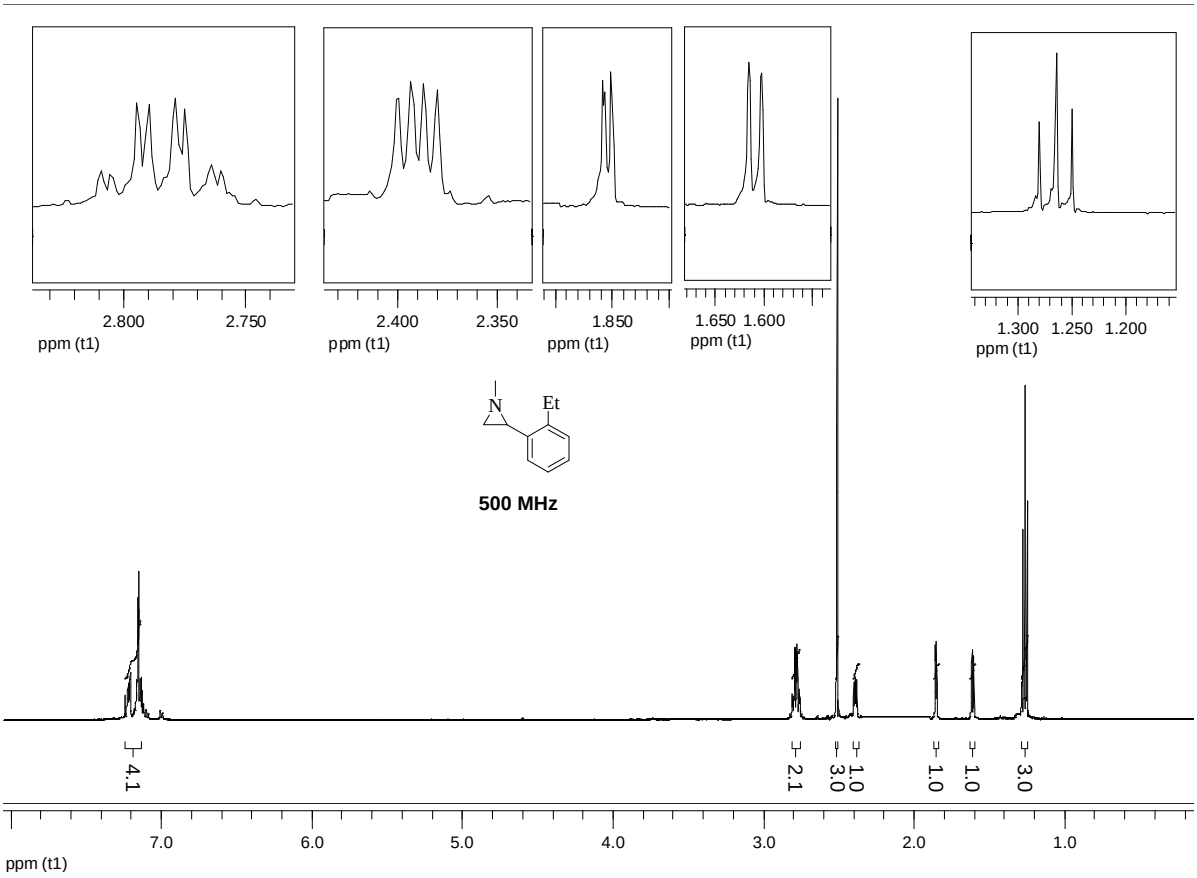
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2.1
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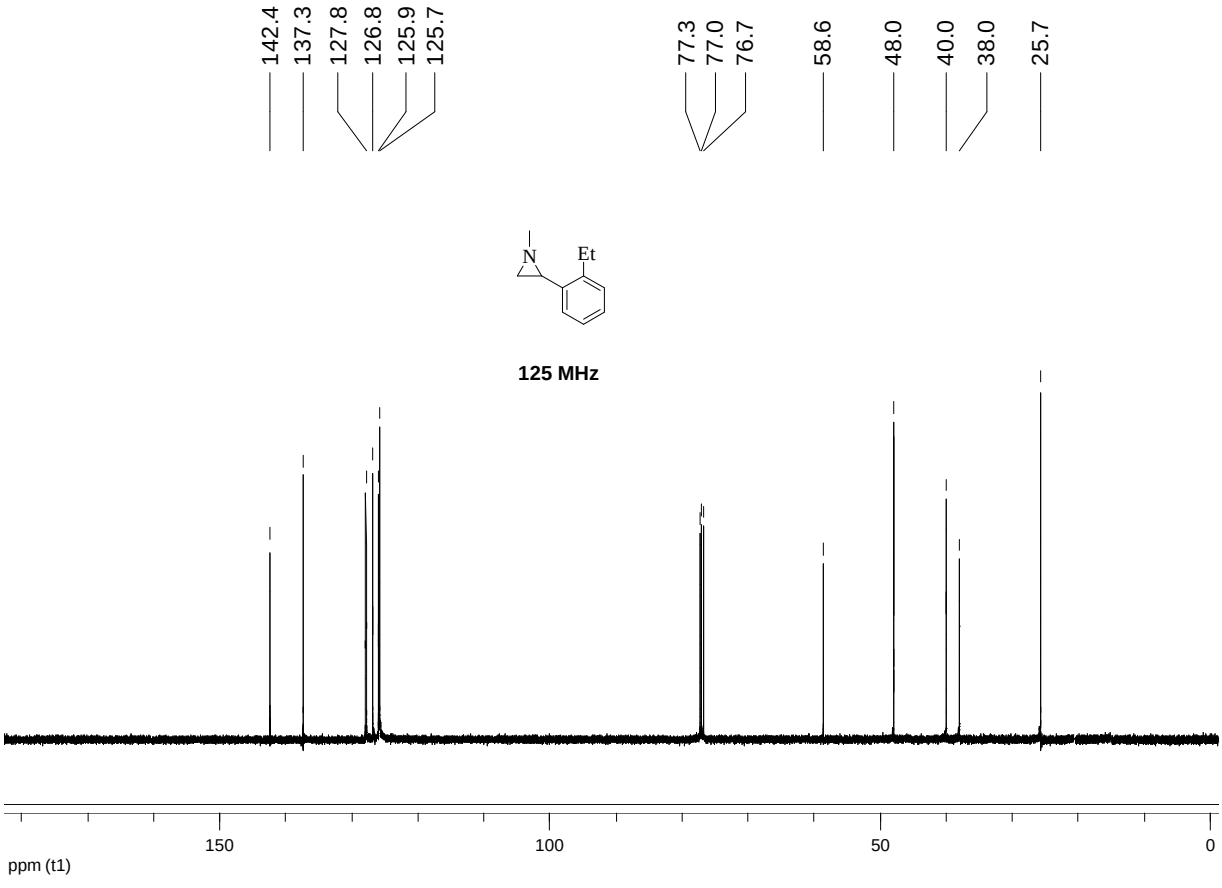
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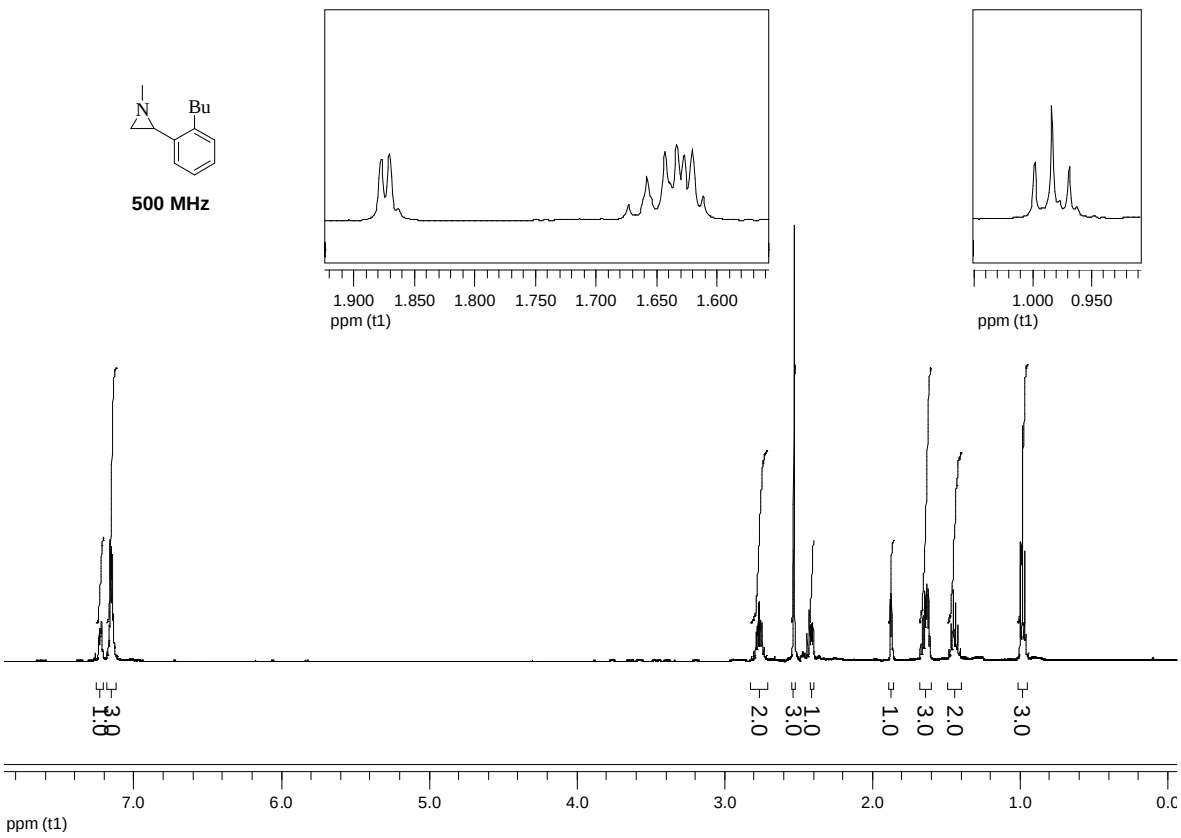
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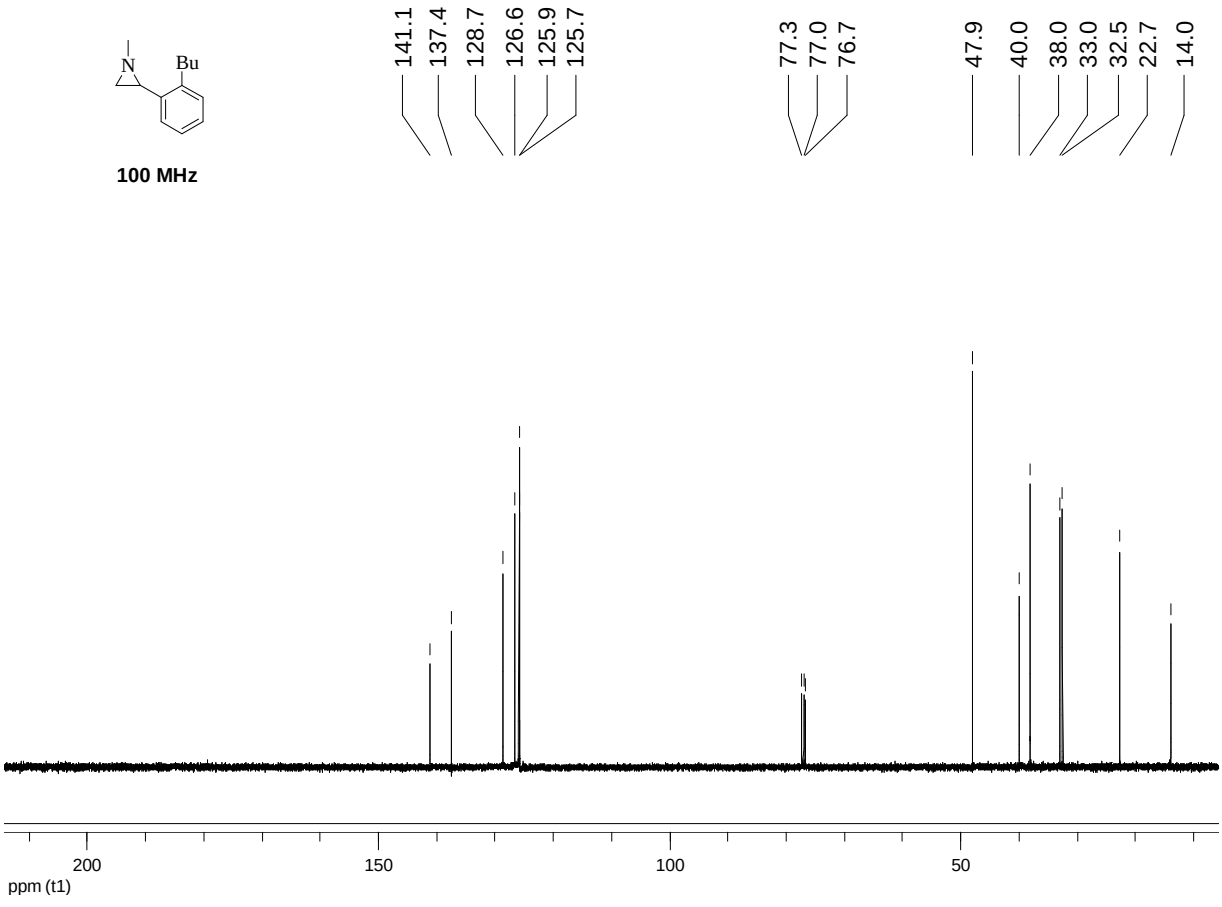
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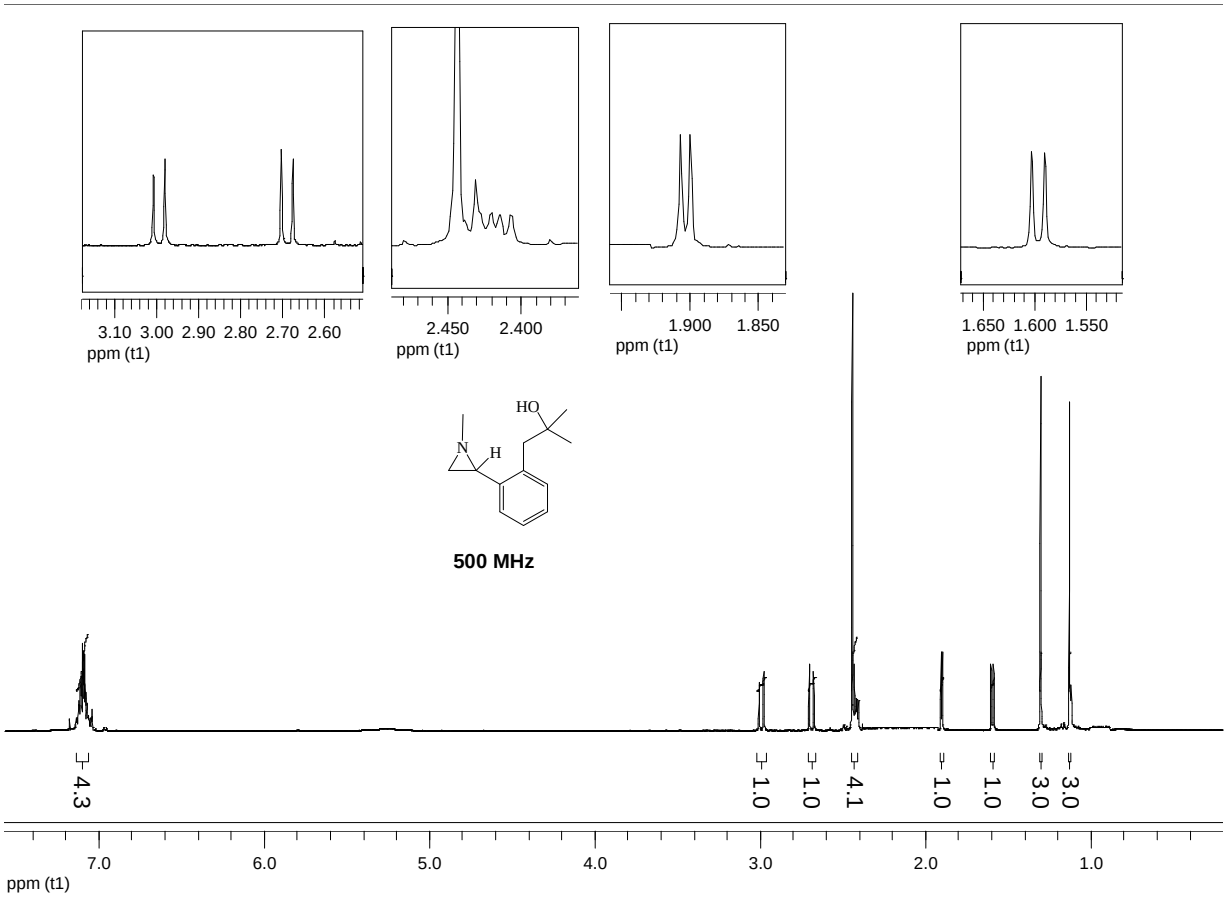
ppm (t1)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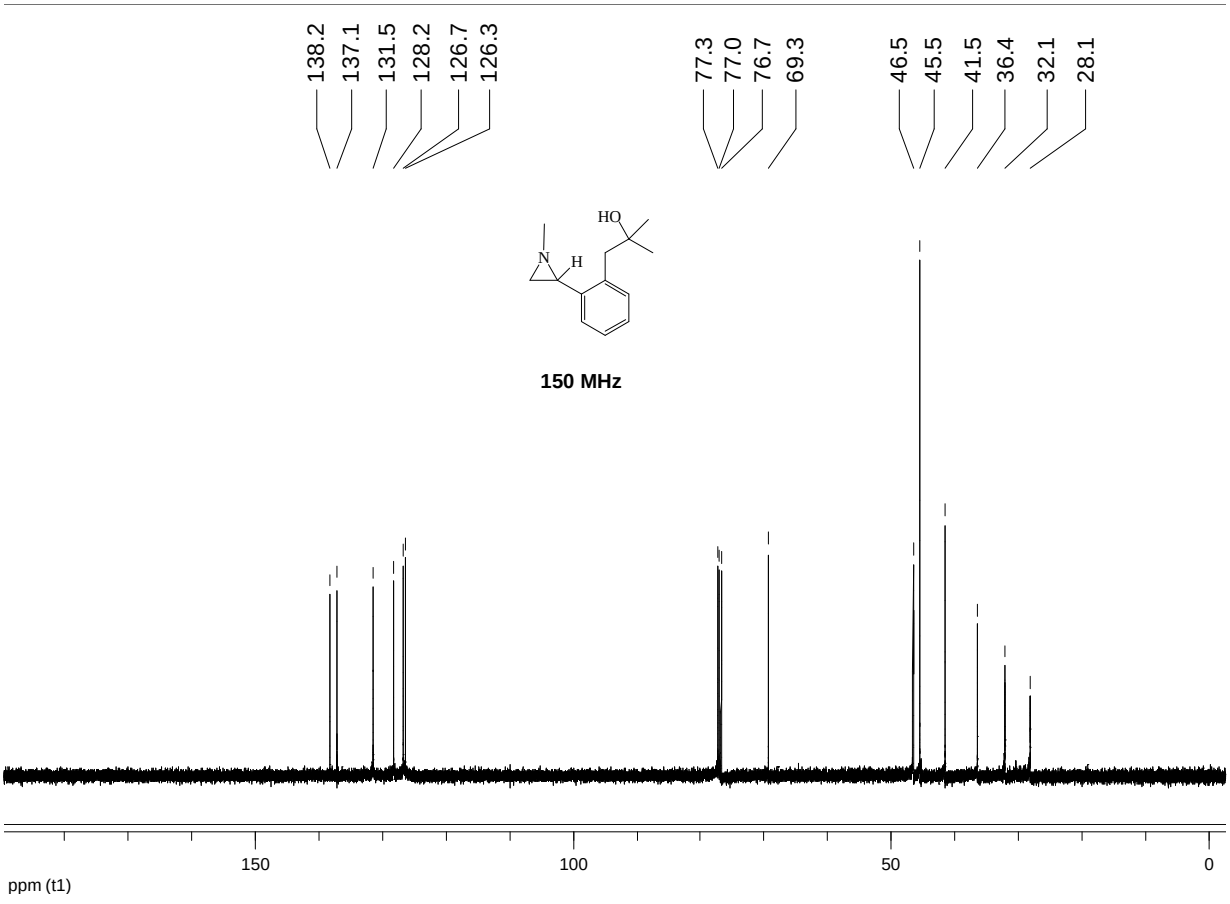
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H
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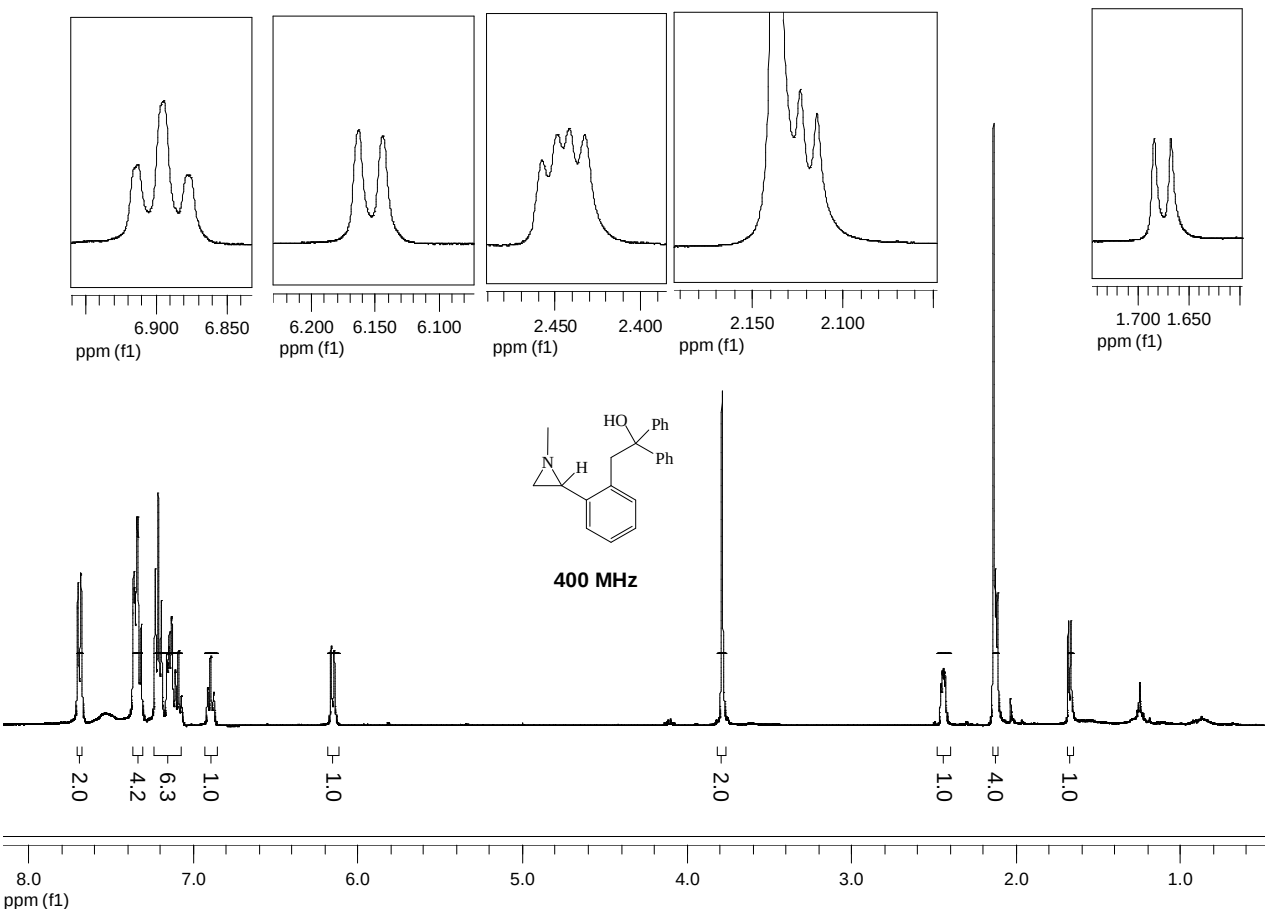
50
0
ppm (t1)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ppm (f1)
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Ph
Ph
N
H
400 MHz
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1.0
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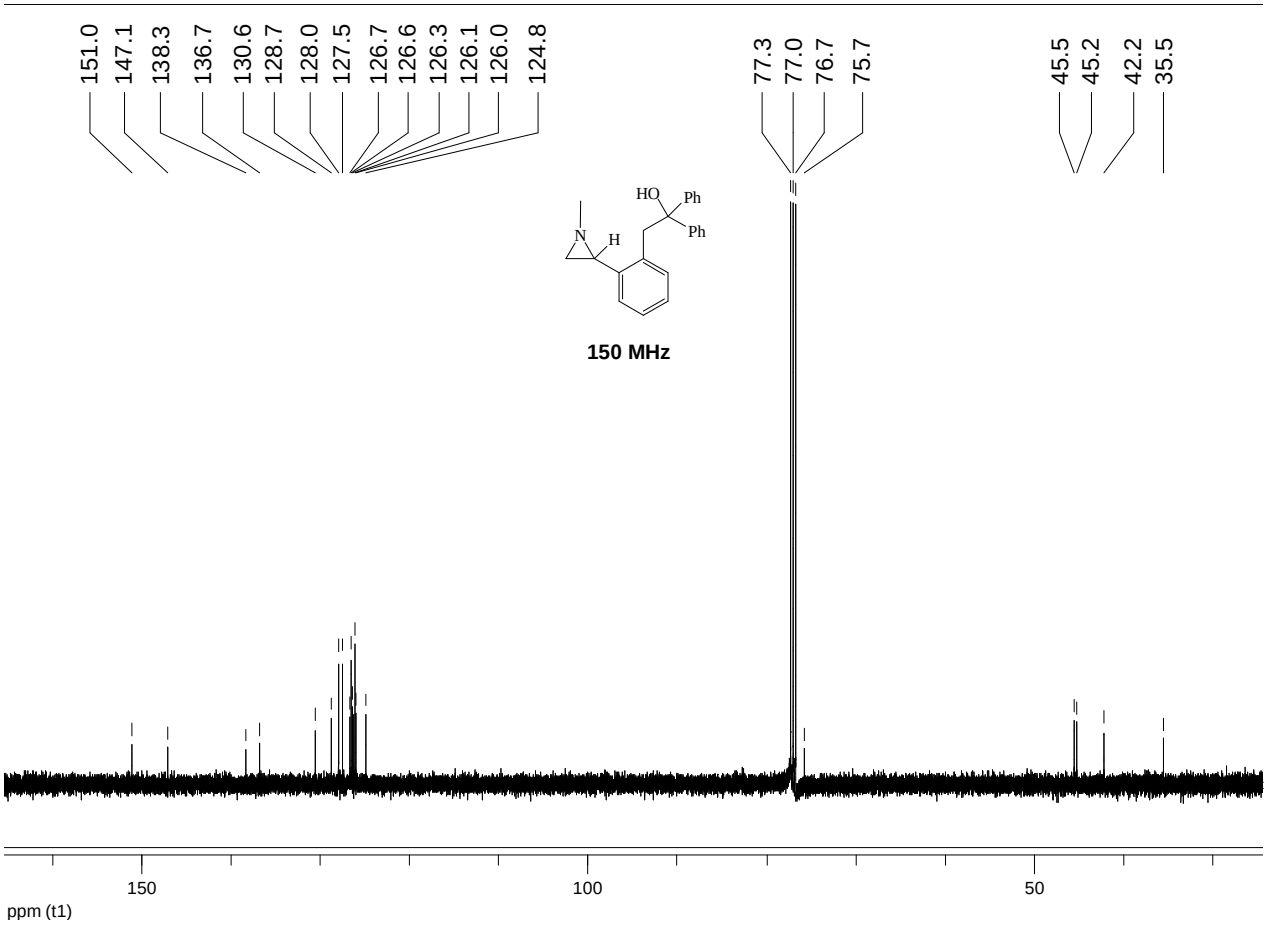
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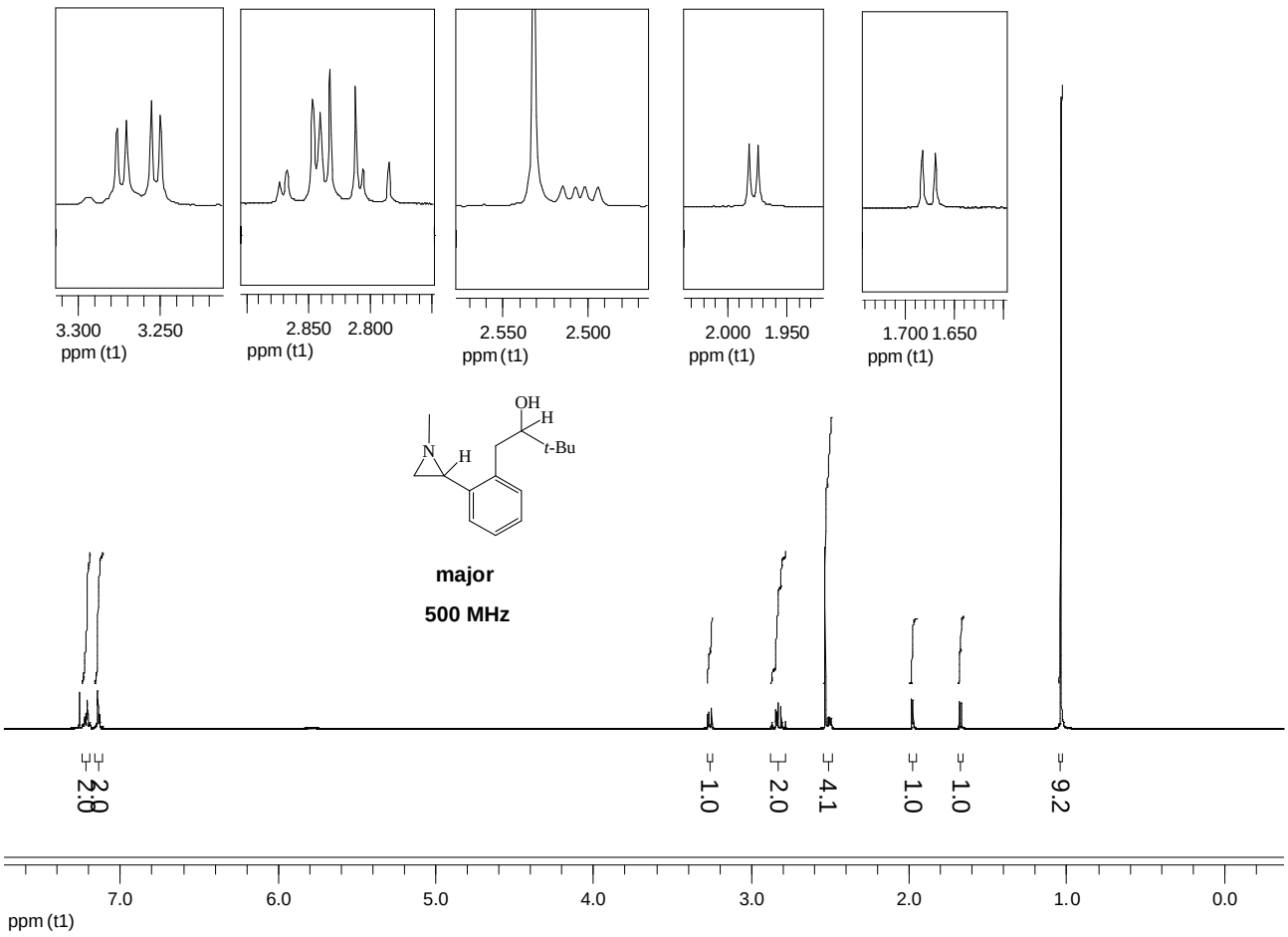
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t-Bu
N
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major
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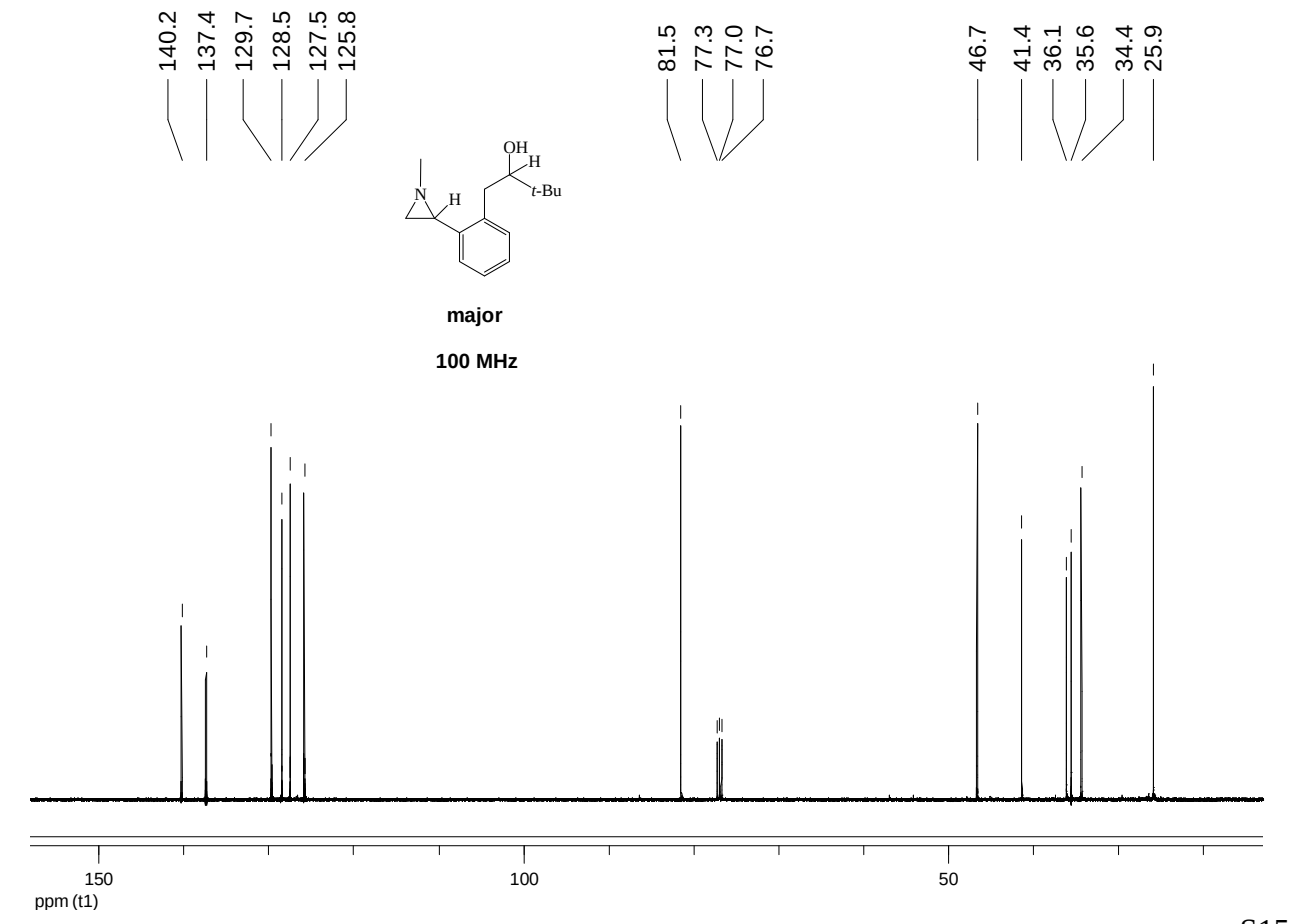
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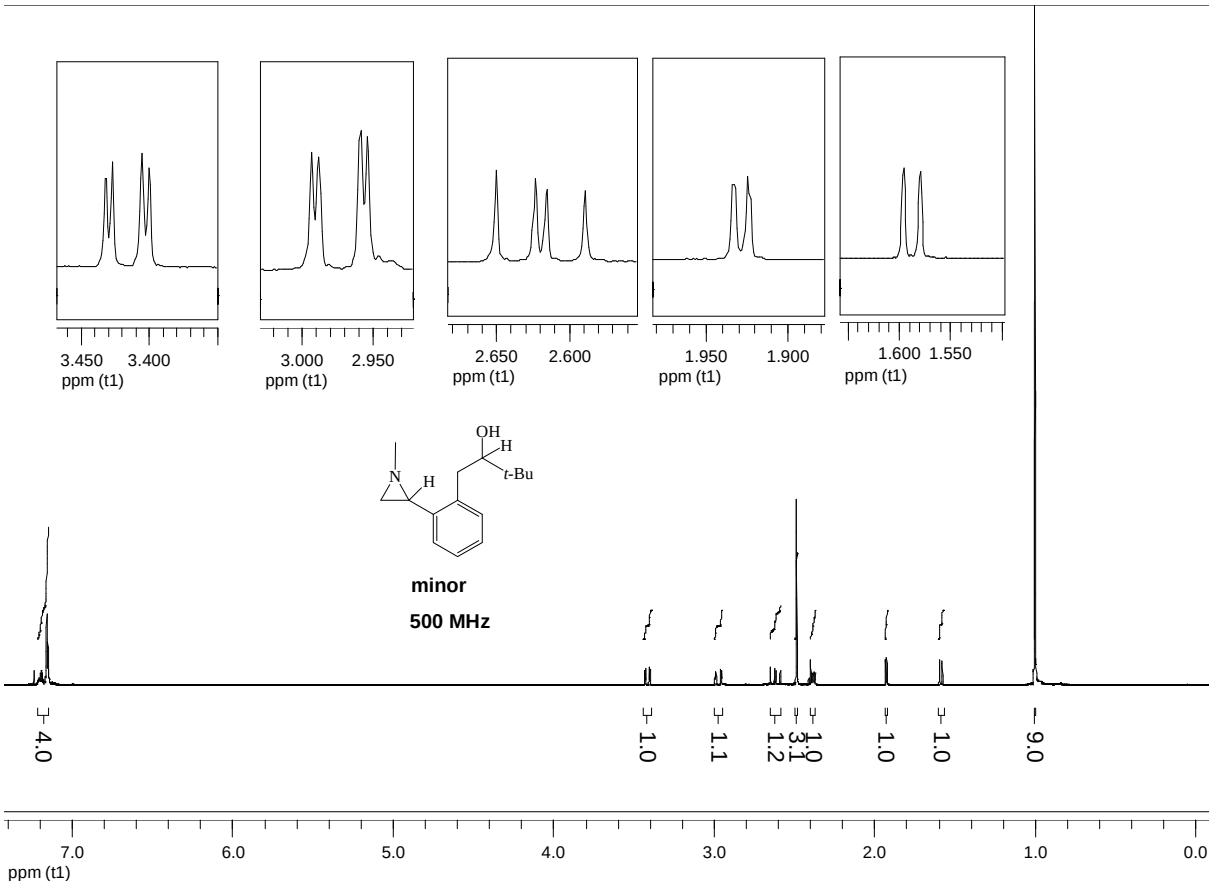
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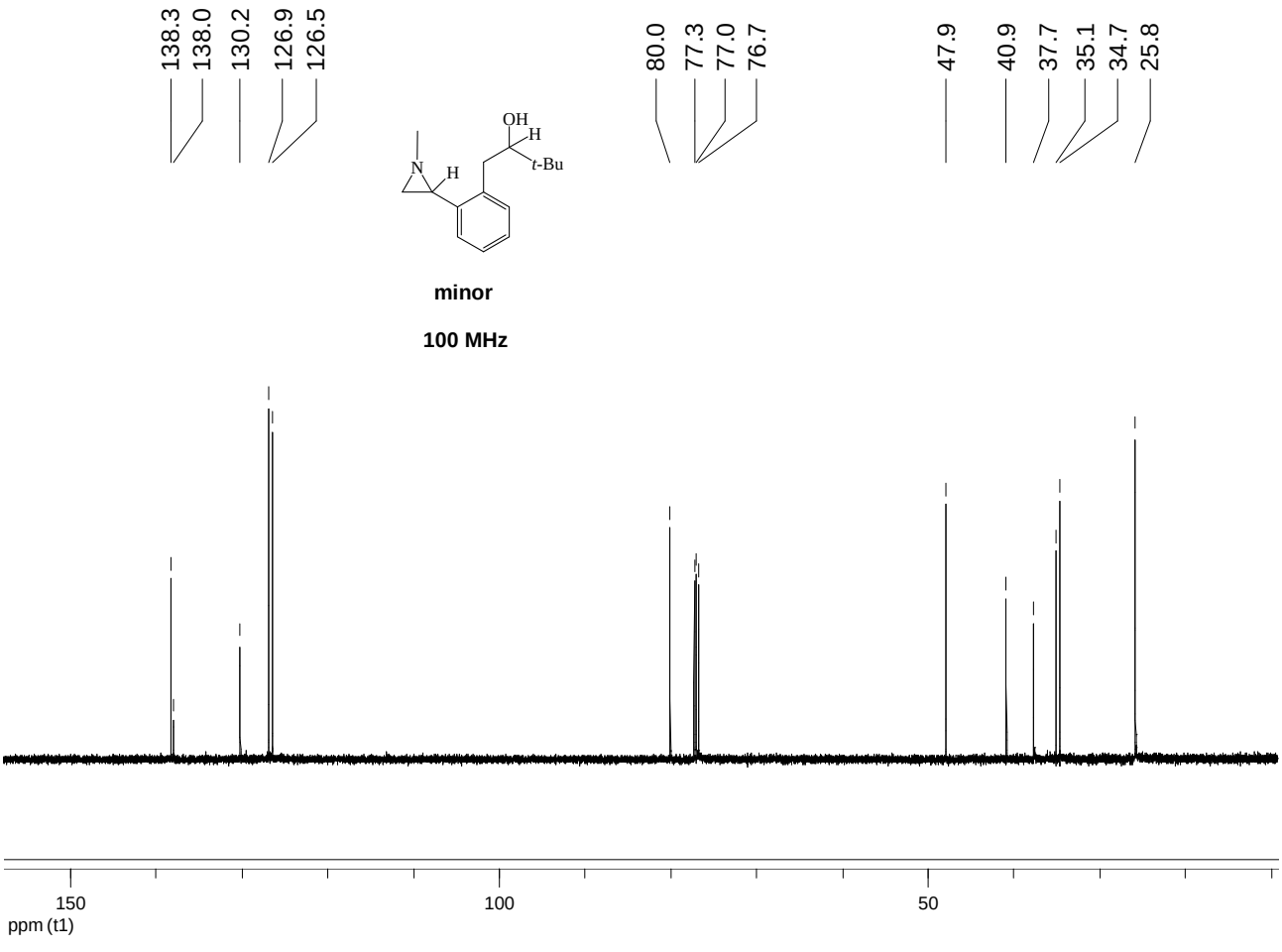
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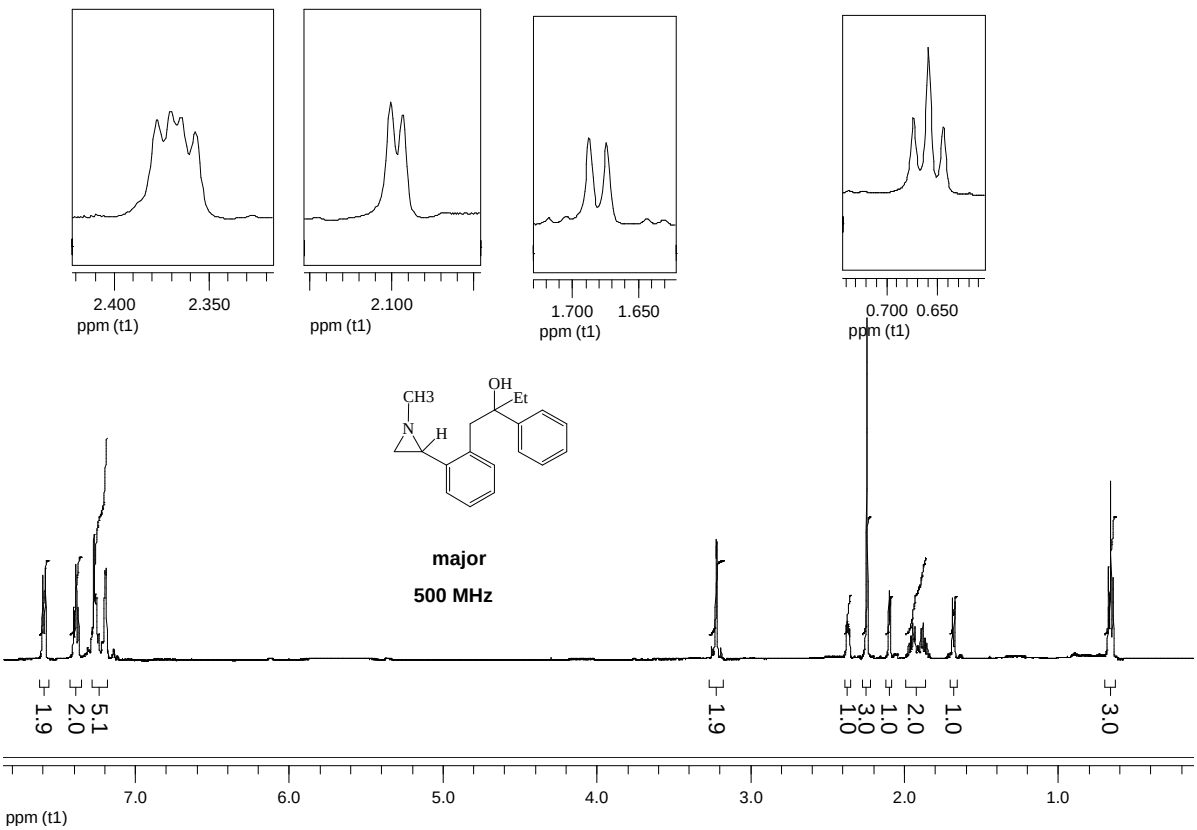
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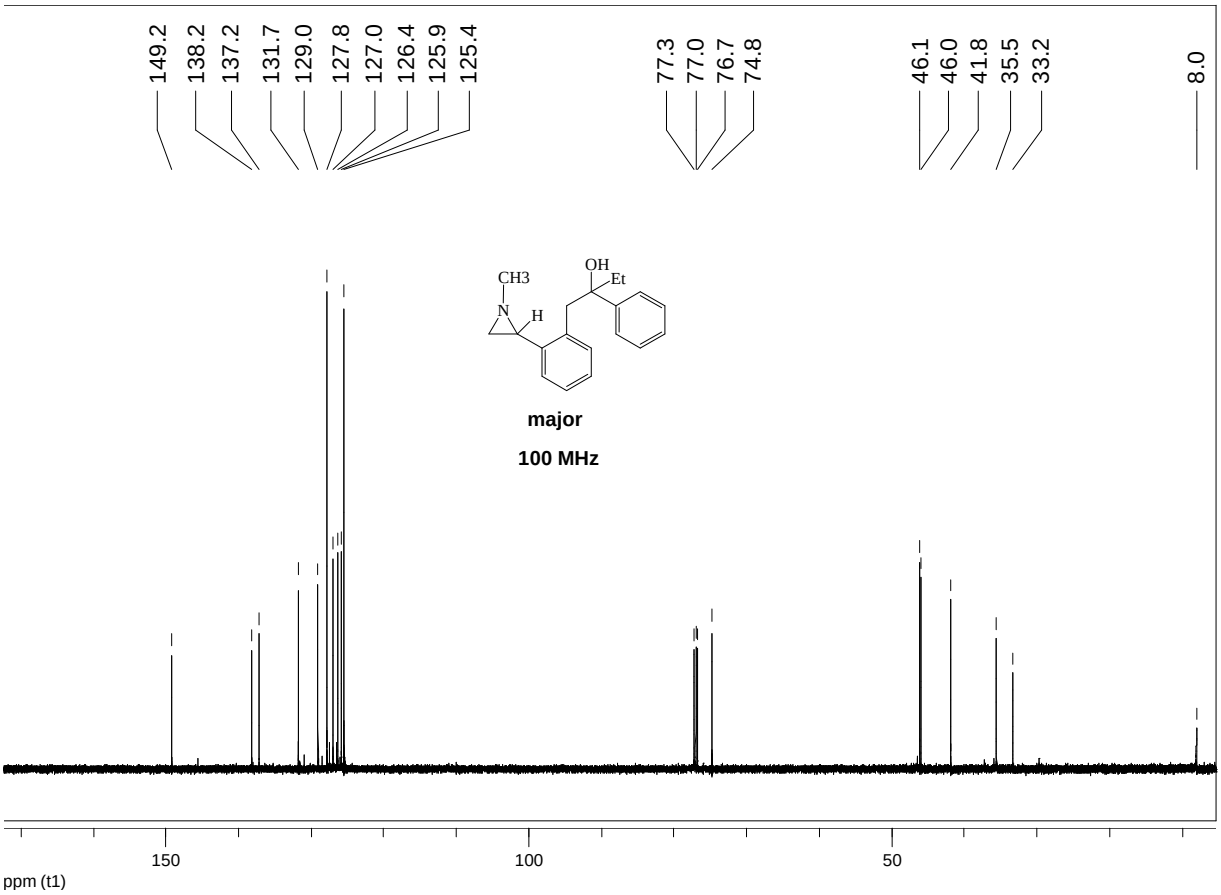
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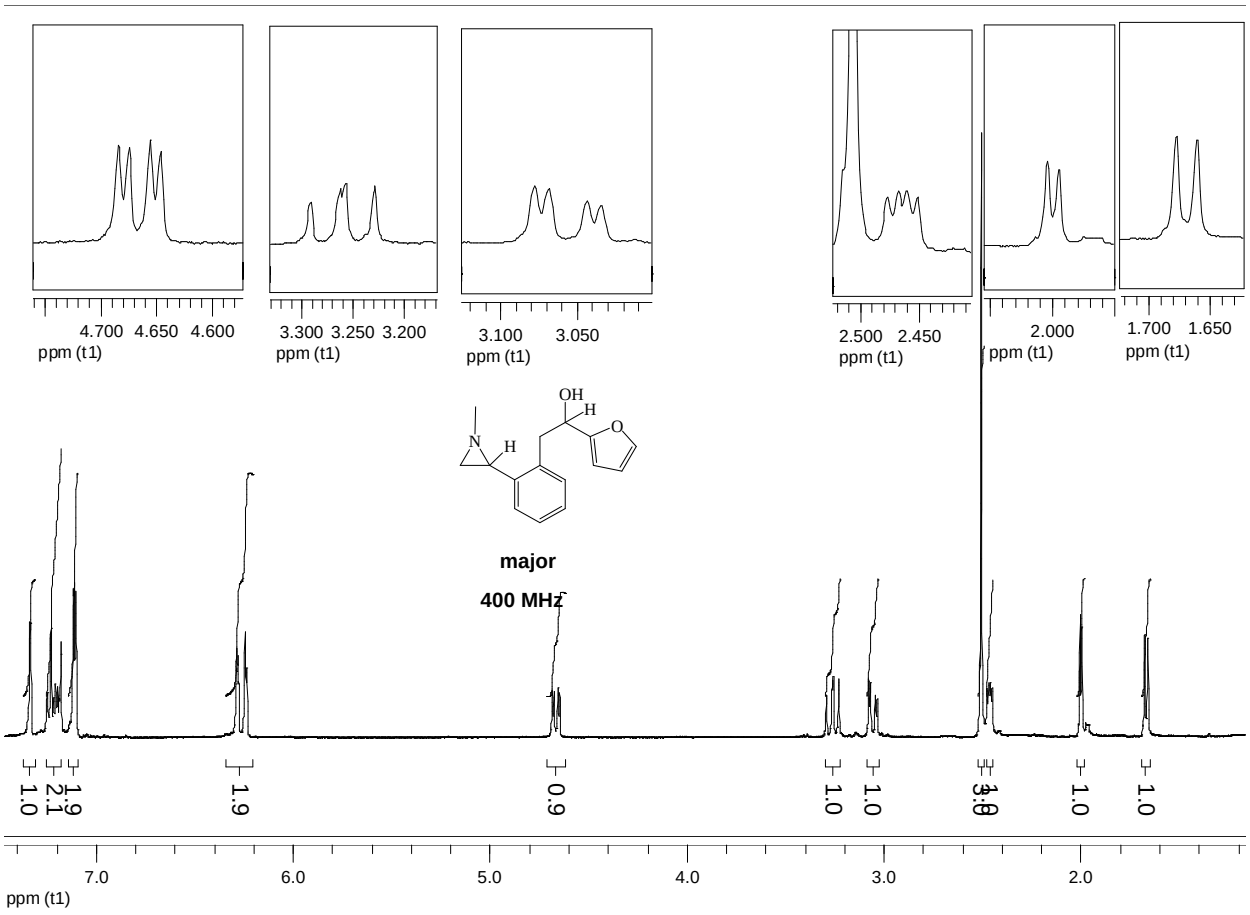
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N
H
O
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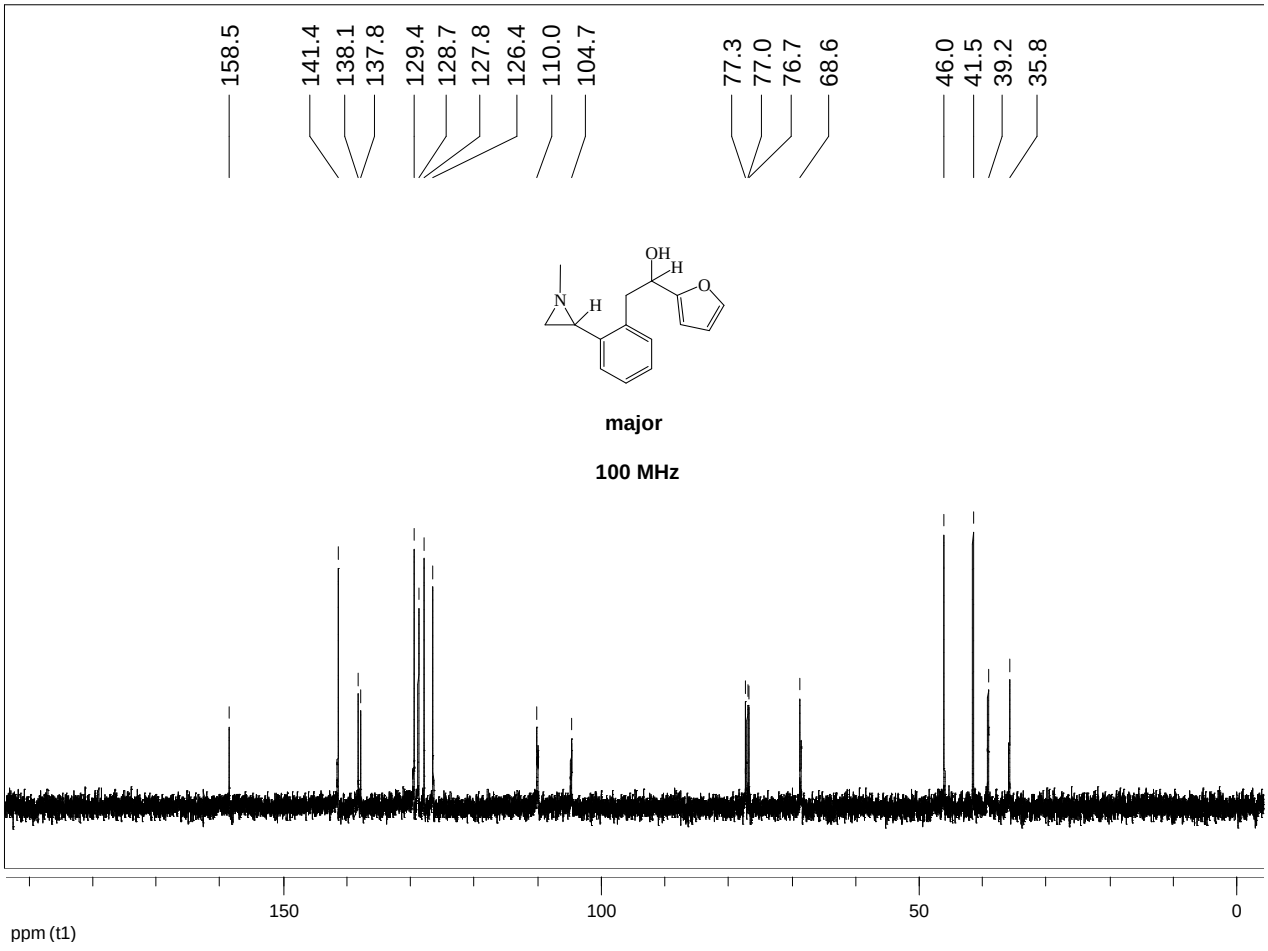
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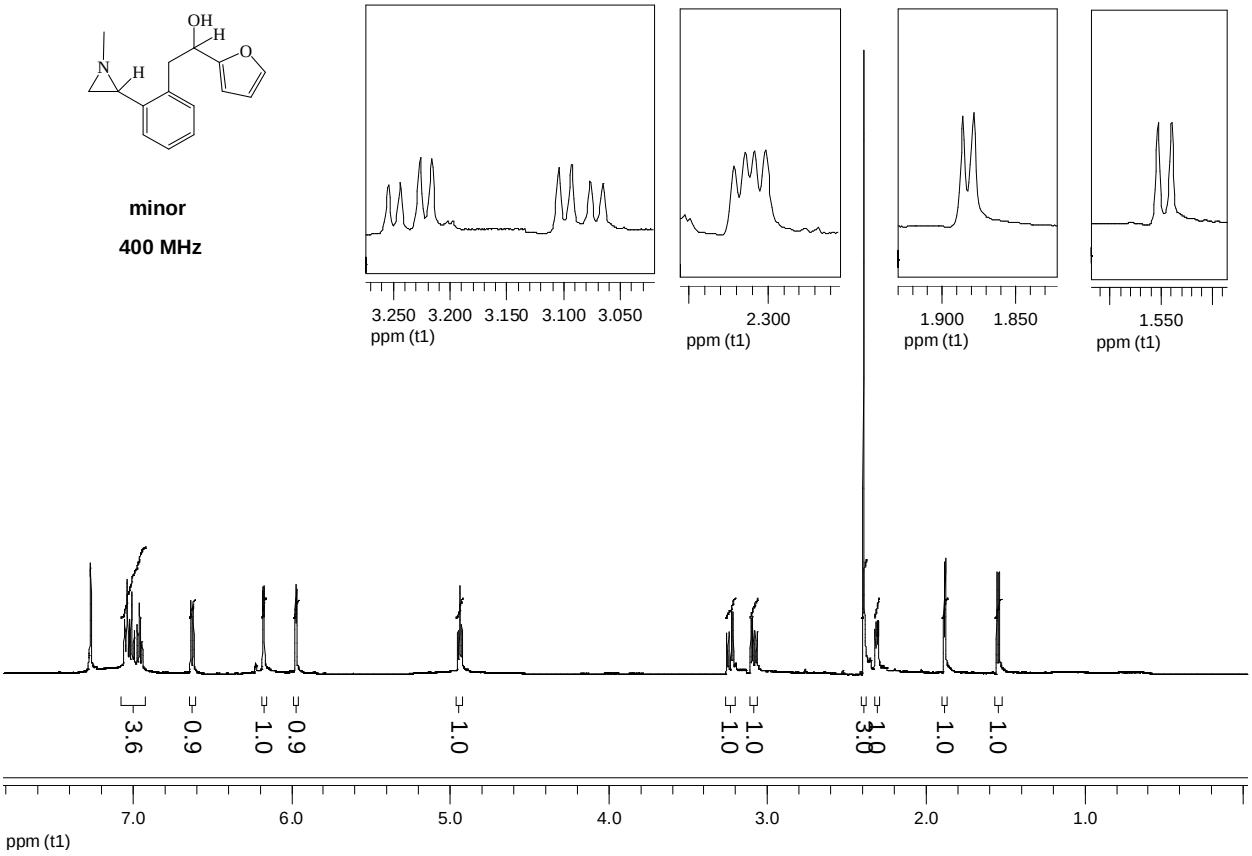
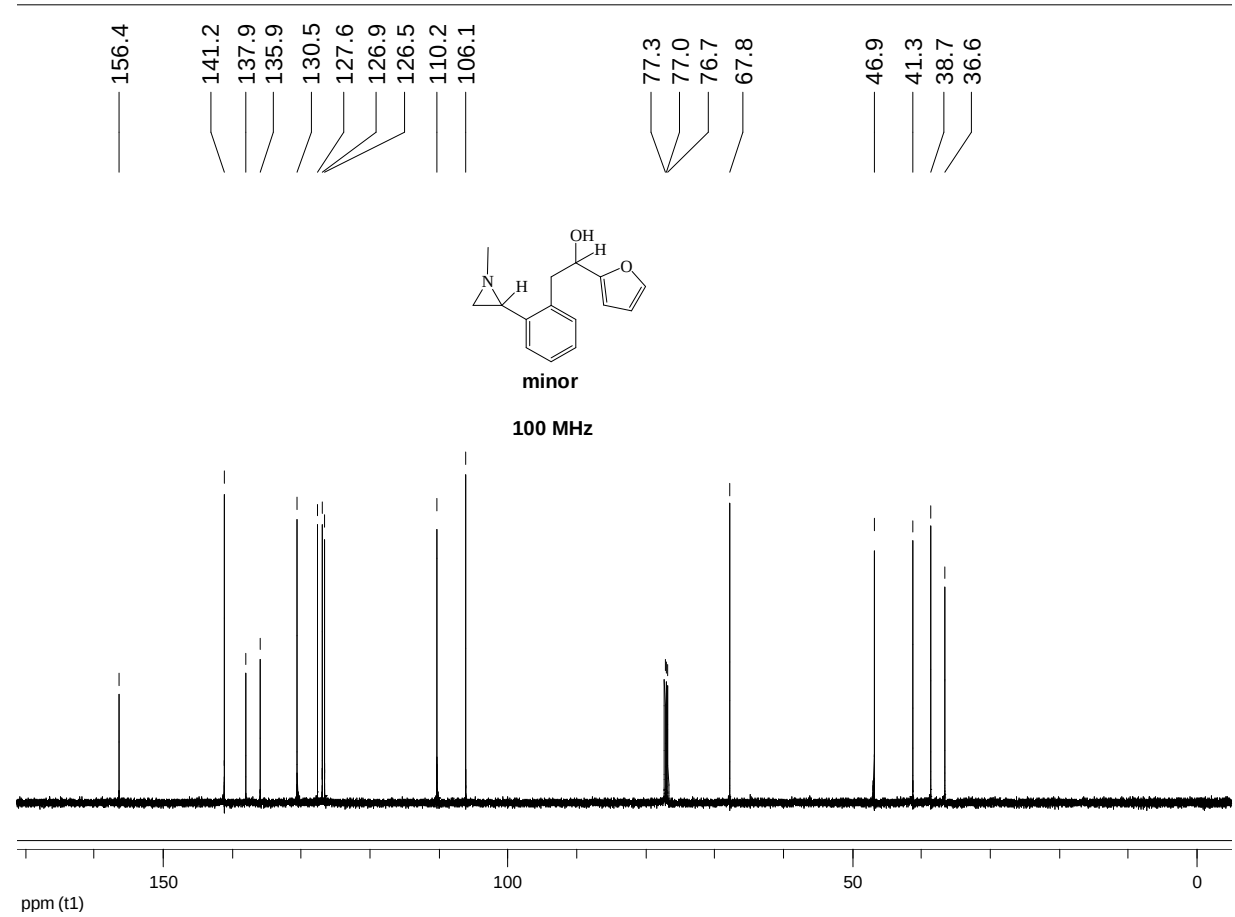
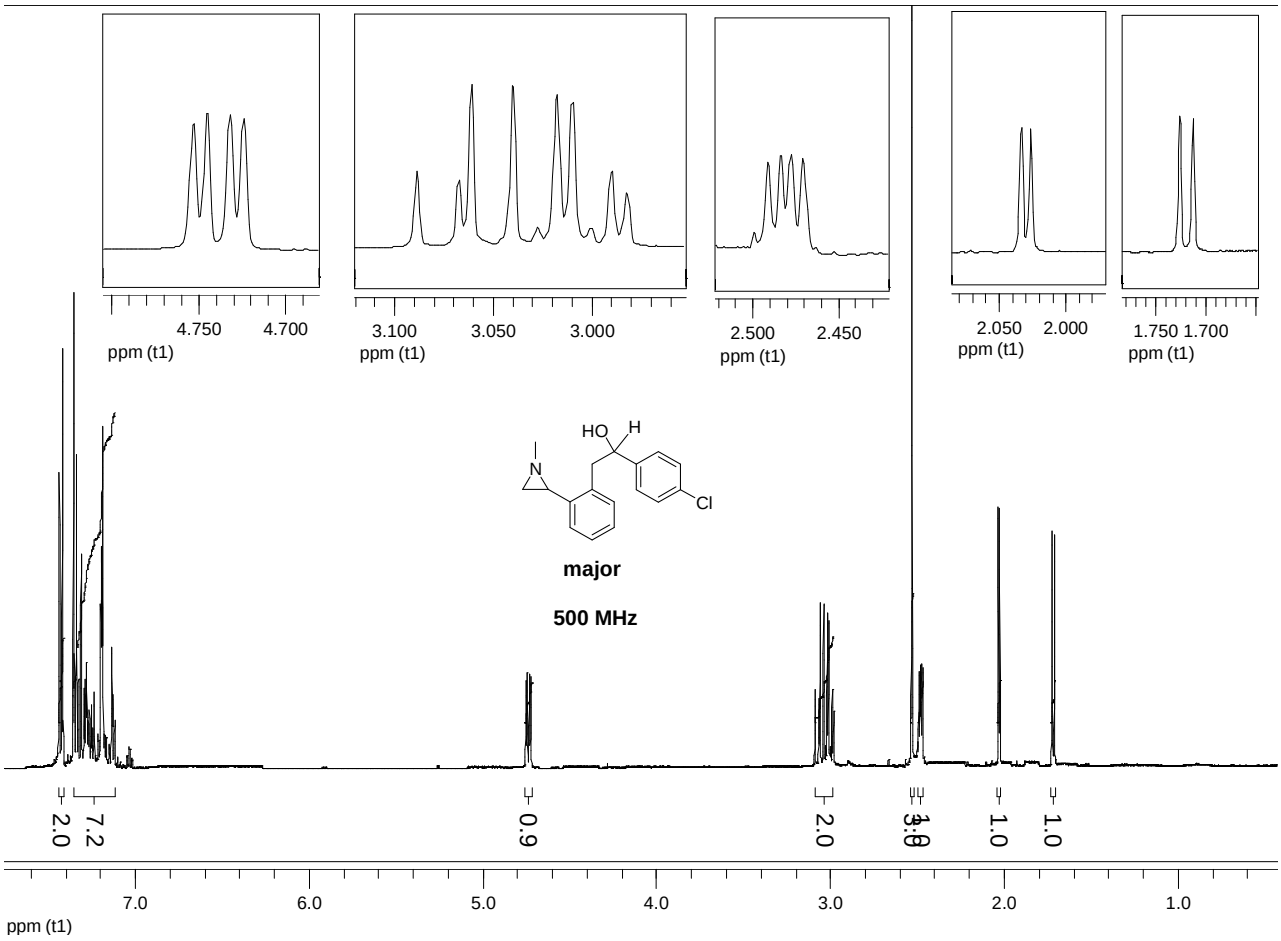
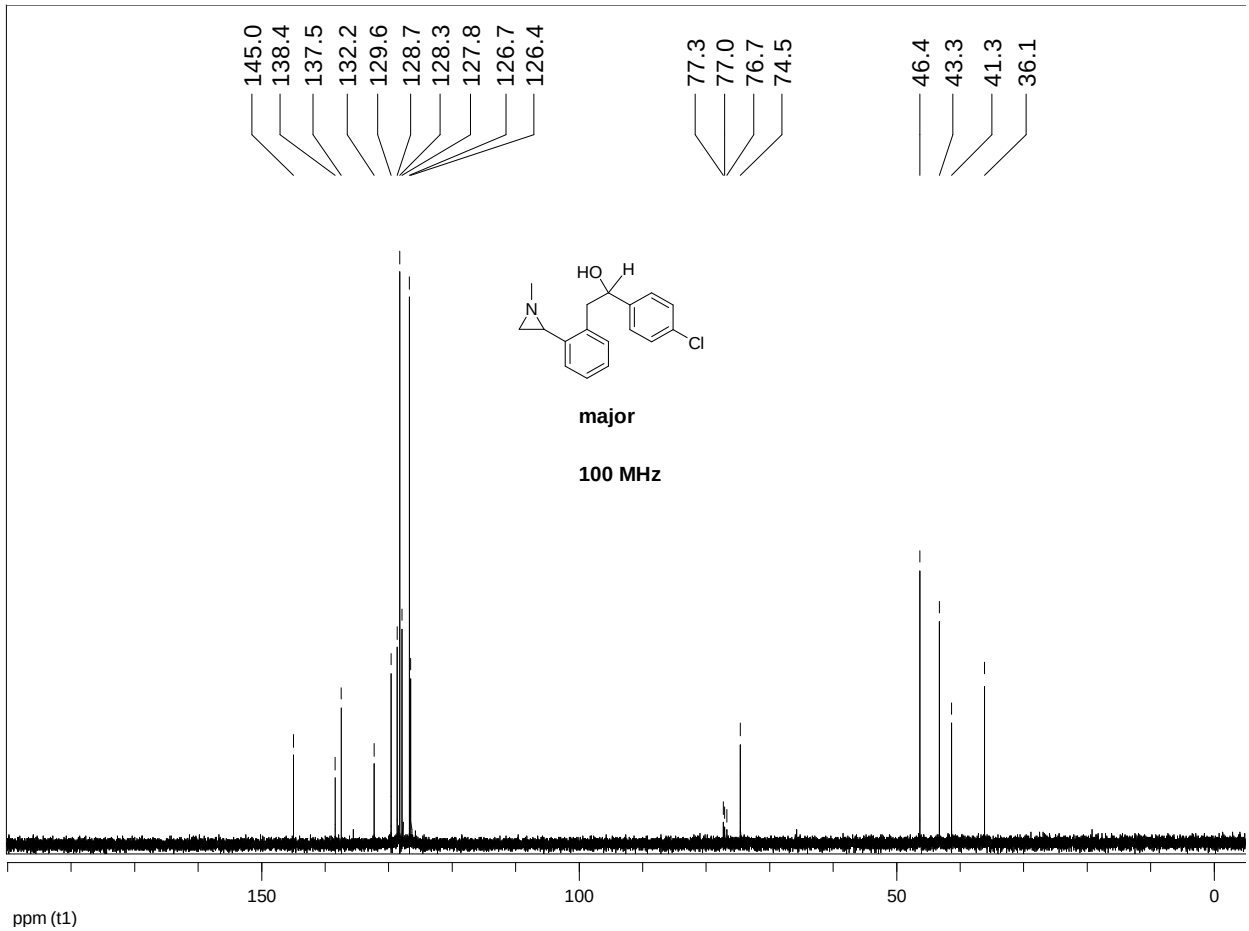
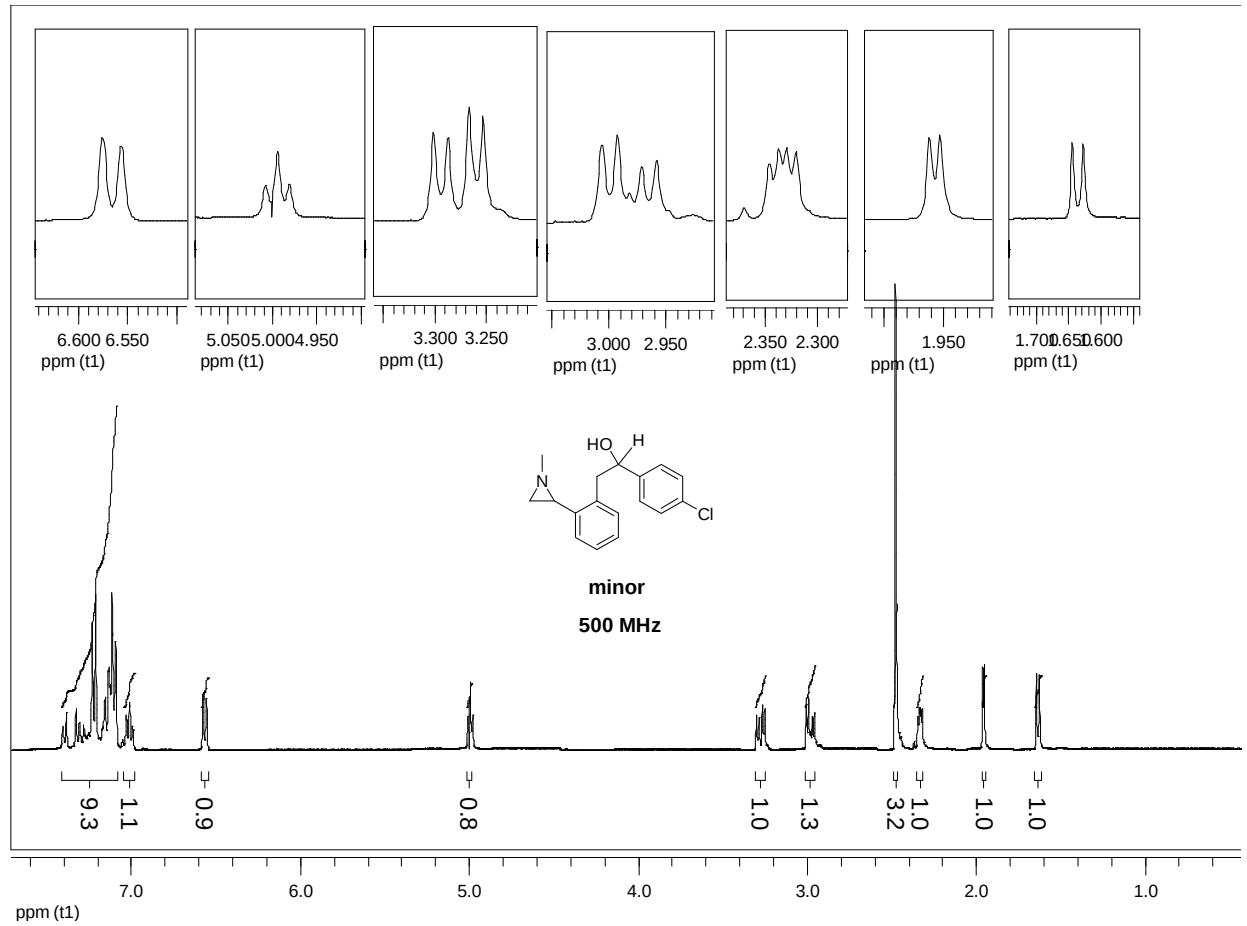
104.7
77.3
77.0
76.7
68.6
46.0
41.5
39.2
35.8
OH
H
N
H
O
major
100 MHz
150
100
50
0
ppm (t1)

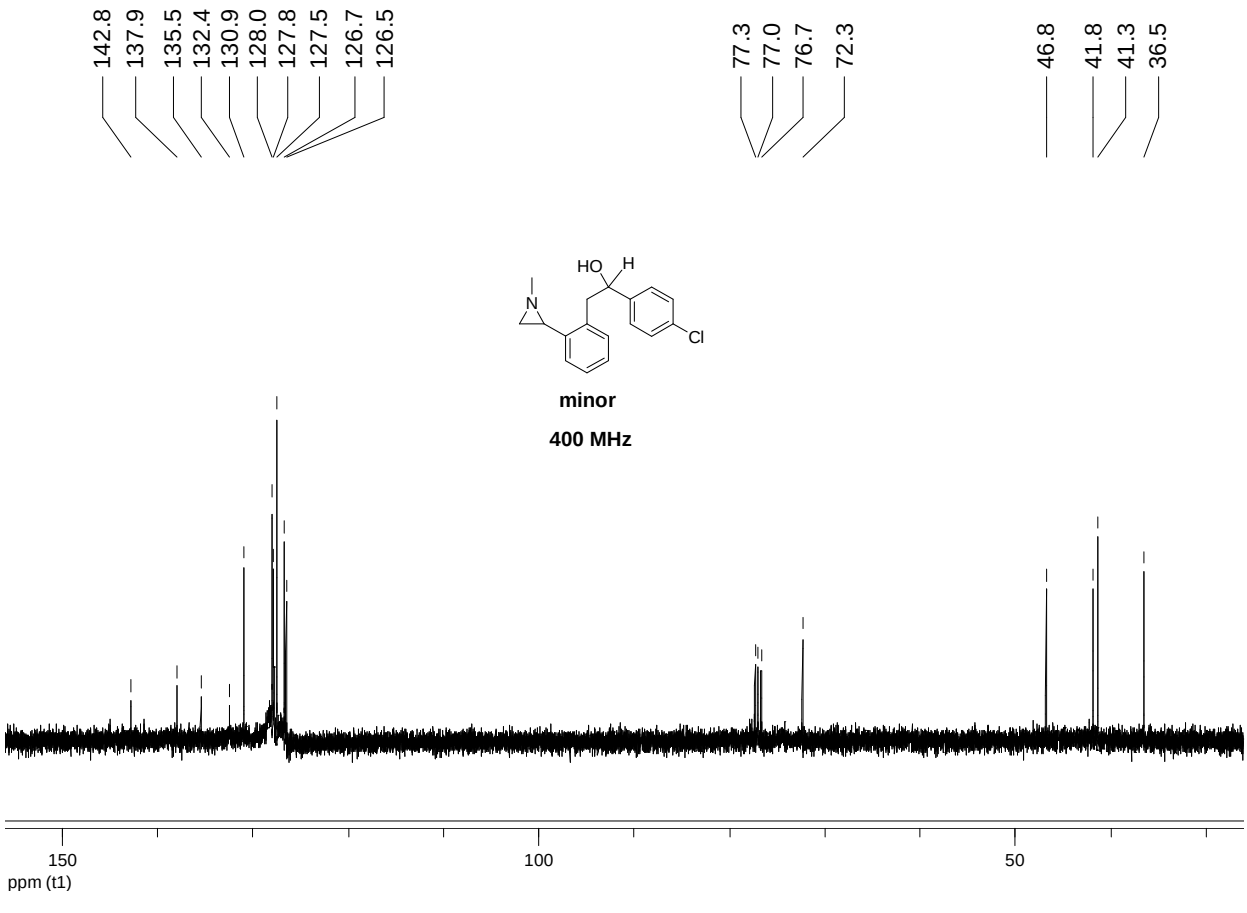

OH
H
N
H
O
minor
400 MHz
3.250 3.200 3.150 3.100 3.050
ppm (t1)
2.300
ppm (t1)
1.900 1.850
ppm (t1)
1.550
ppm (t1)
3.6
0.9
1.0
0.9
1.0
1.0
1.0
3.0
1.0
1.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

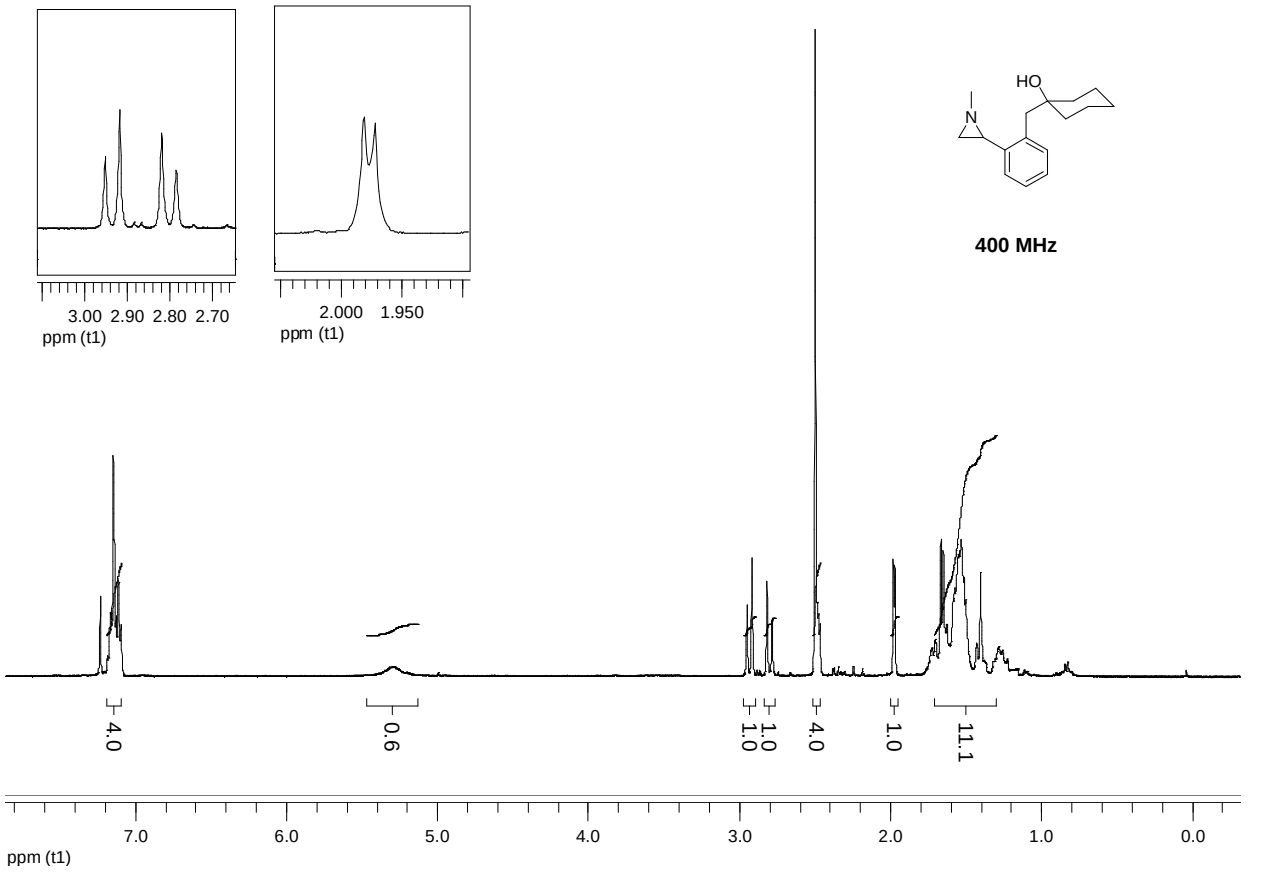

156.4
141.2
137.9
135.9
130.5
127.6
126.9
126.5
110.2
106.1
77.3
77.0
76.7
67.8
46.9
41.3
38.7
36.6
OH
H
N
H
O
minor
100 MHz
150
100
50
0
ppm (t1)

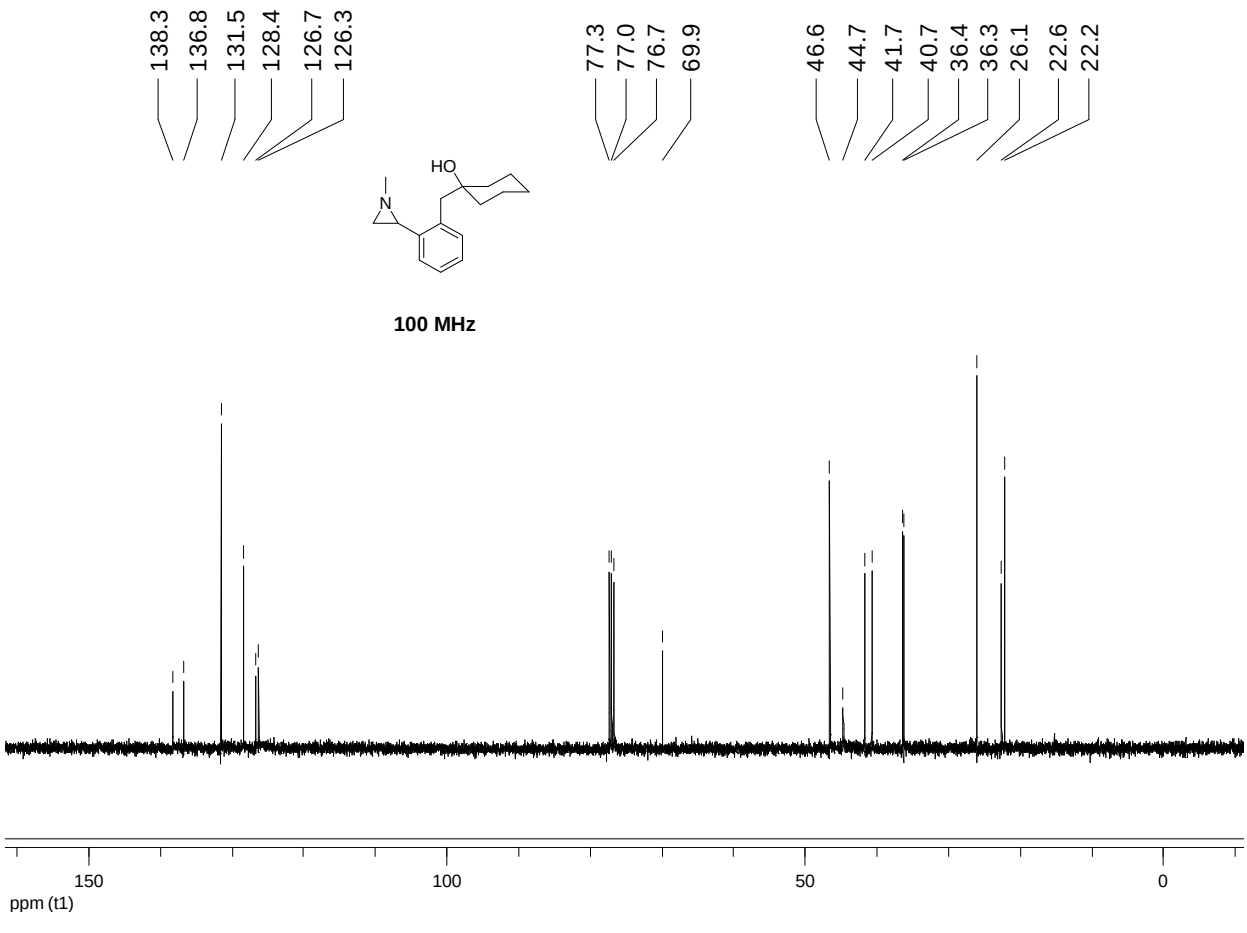

4.750 4.700
ppm (t1)
3.100 3.050 3.000
ppm (t1)
2.500 2.450
ppm (t1)
2.050 2.000
ppm (t1)
1.750 1.700
ppm (t1)
HO
H
N
Cl
major
500 MHz
2.0
7.2
0.9
2.0
3.0
1.0
1.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

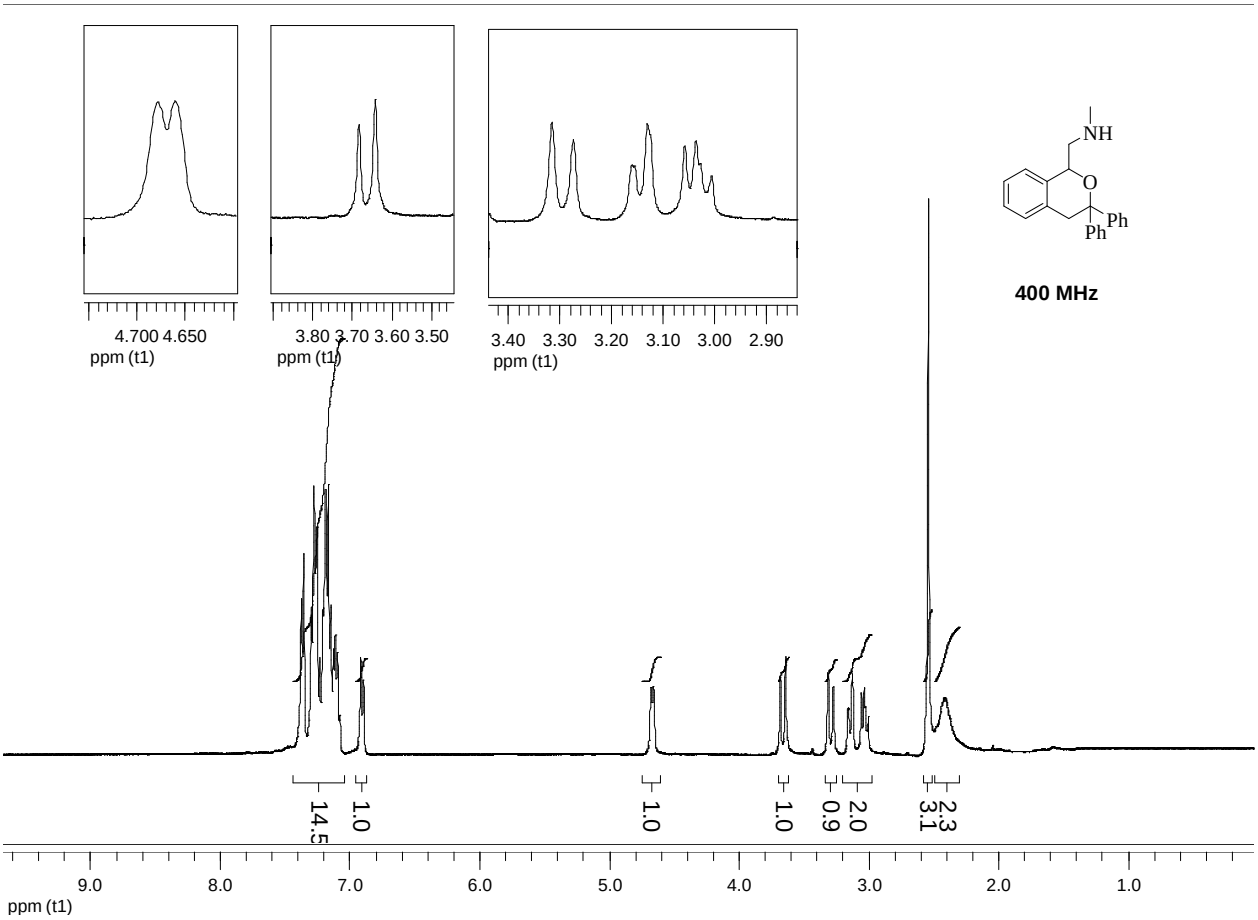

145.0
138.4
137.5
132.2
129.6
128.7
128.3
127.8
126.7
126.4
77.3
77.0
76.7
74.5
46.4
43.3
41.3
36.1
HO
H
N
Cl
major
100 MHz
150
100
50
0
ppm (t1)

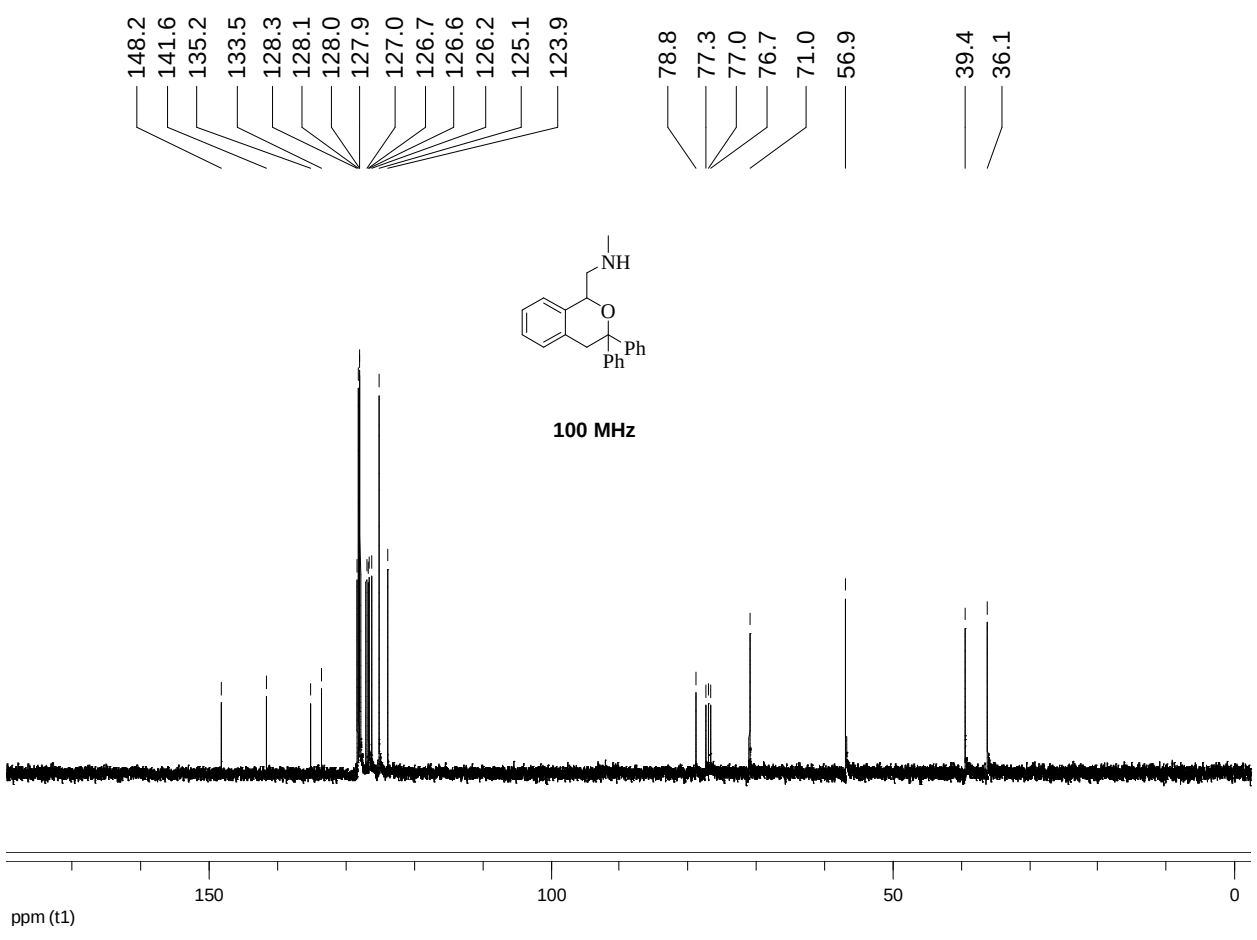

6.600 6.550
ppm (t1)
5.0505.0004.950
ppm (t1)
3.300 3.250
ppm (t1)
3.000 2.950
ppm (t1)
2.350 2.300
ppm (t1)
1.950
ppm (t1)
1.700 1.650 1.600
ppm (t1)
HO
H
N
Cl
minor
500 MHz
6.3
1.1
0.9
0.8
1.0
1.3
3.2
1.0
1.0
1.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

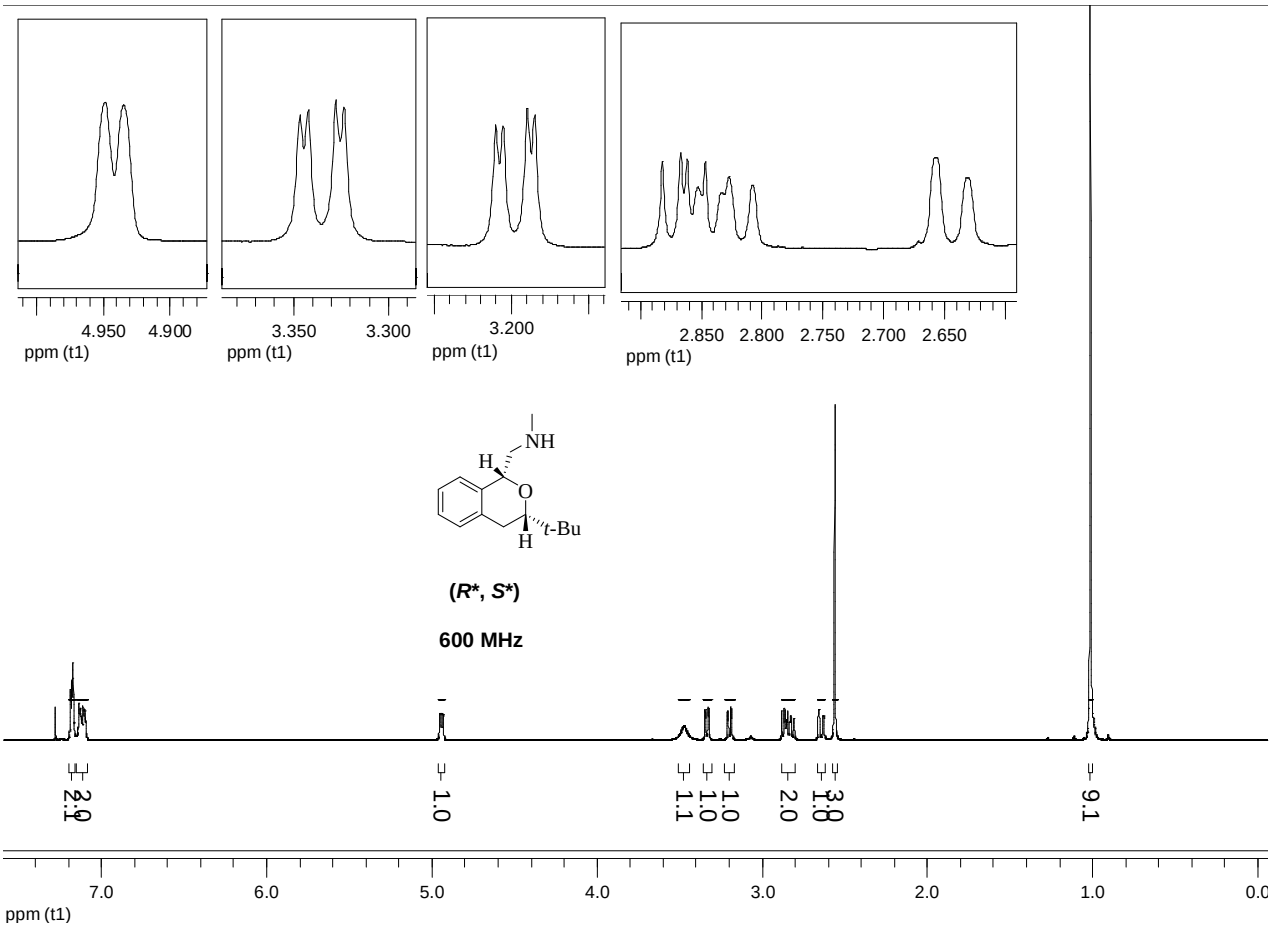

142.8
137.9
135.5
132.4
130.9
128.0
127.8
127.5
126.7
126.5
77.3
77.0
76.7
72.3
46.8
41.8
41.3
36.5
HO
H
N
Cl
minor
400 MHz
150
100
50
ppm (t1)

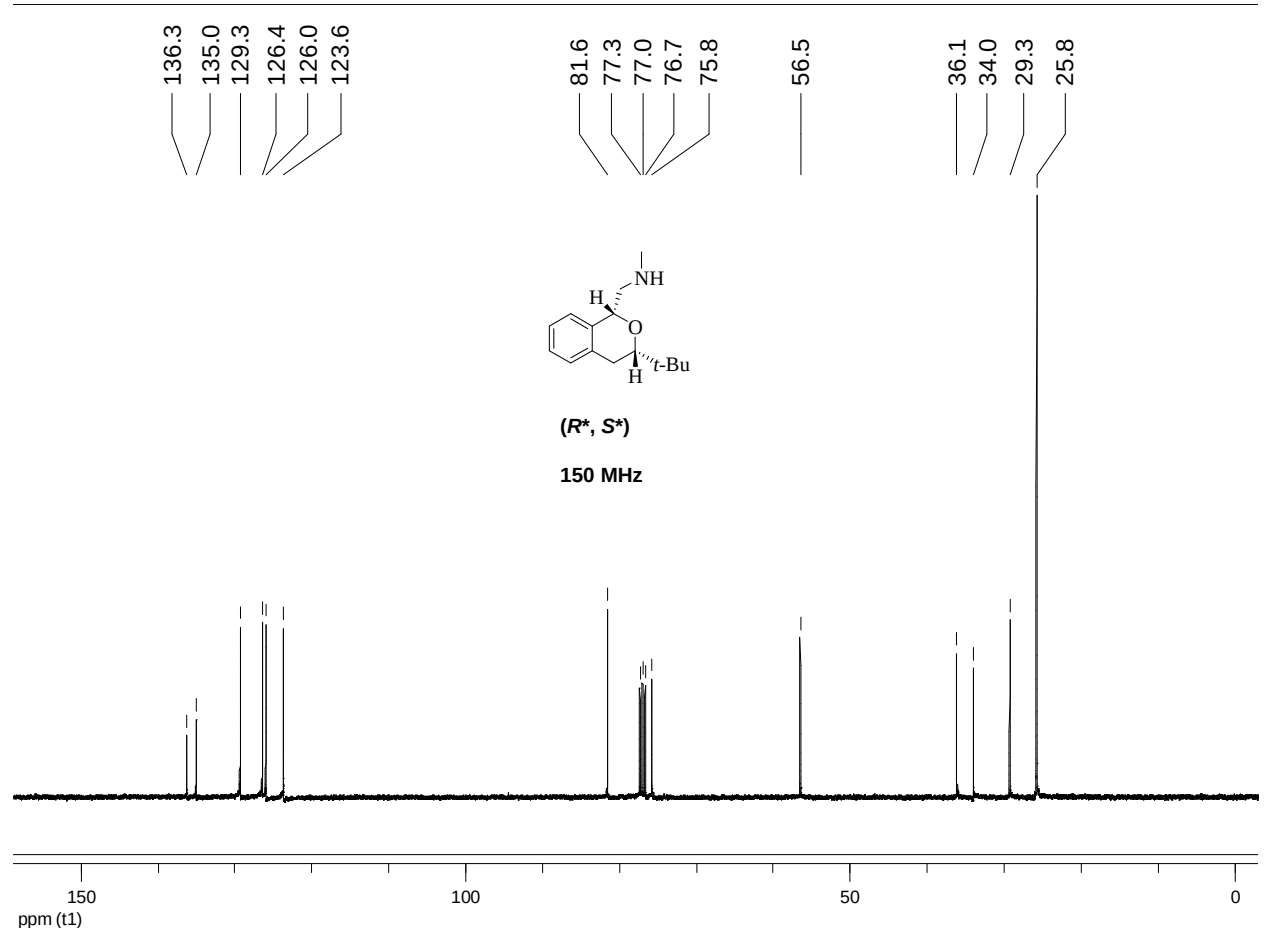

3.00 2.90 2.80 2.70
ppm (t1)
2.000 1.950
ppm (t1)
HO
N
400 MHz
4.0
0.6
1.0
1.0
4.0
1.0
11.1
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

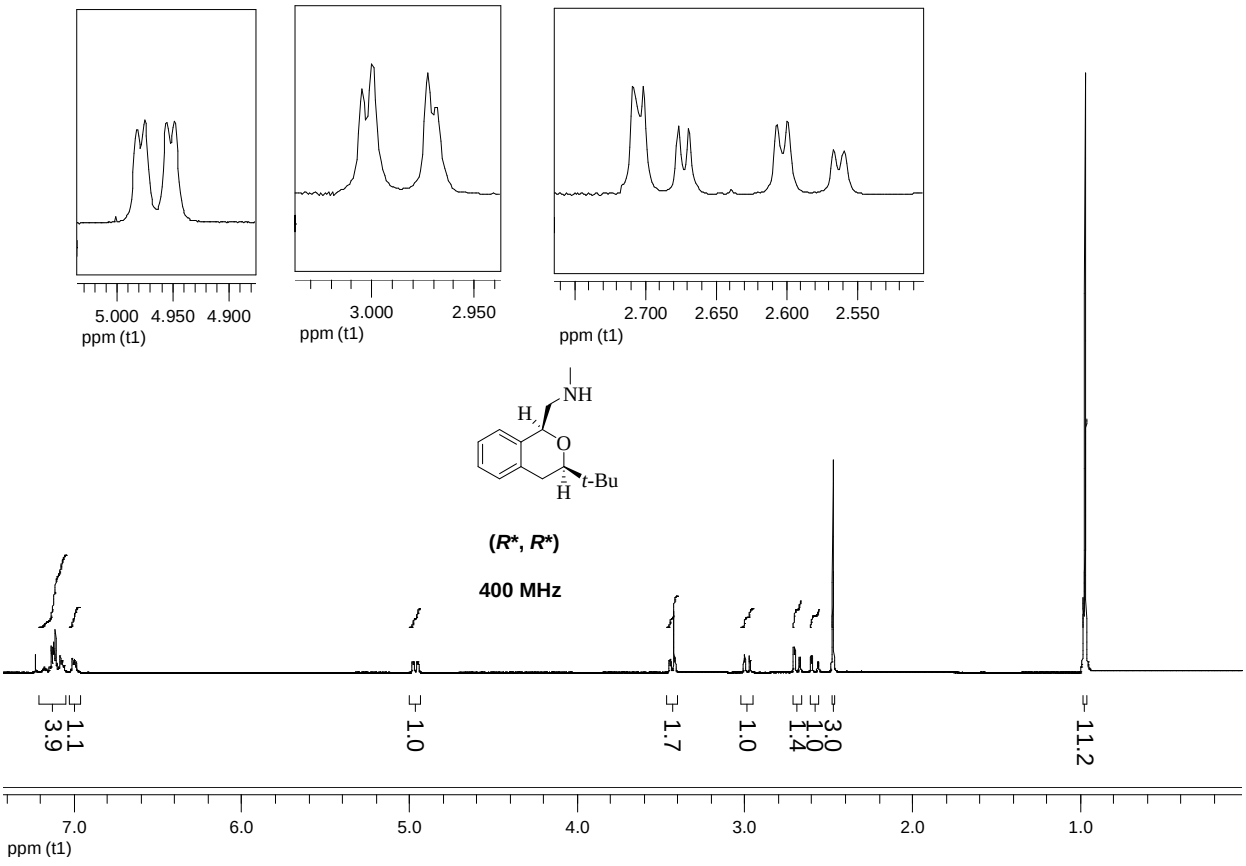

138.3
136.8
131.5
128.4
126.7
126.3
77.3
77.0
76.7
69.9
46.6
44.7
41.7
40.7
36.4
36.3
26.1
22.6
22.2
HO
N
100 MHz
150
100
50
0
ppm (t1)

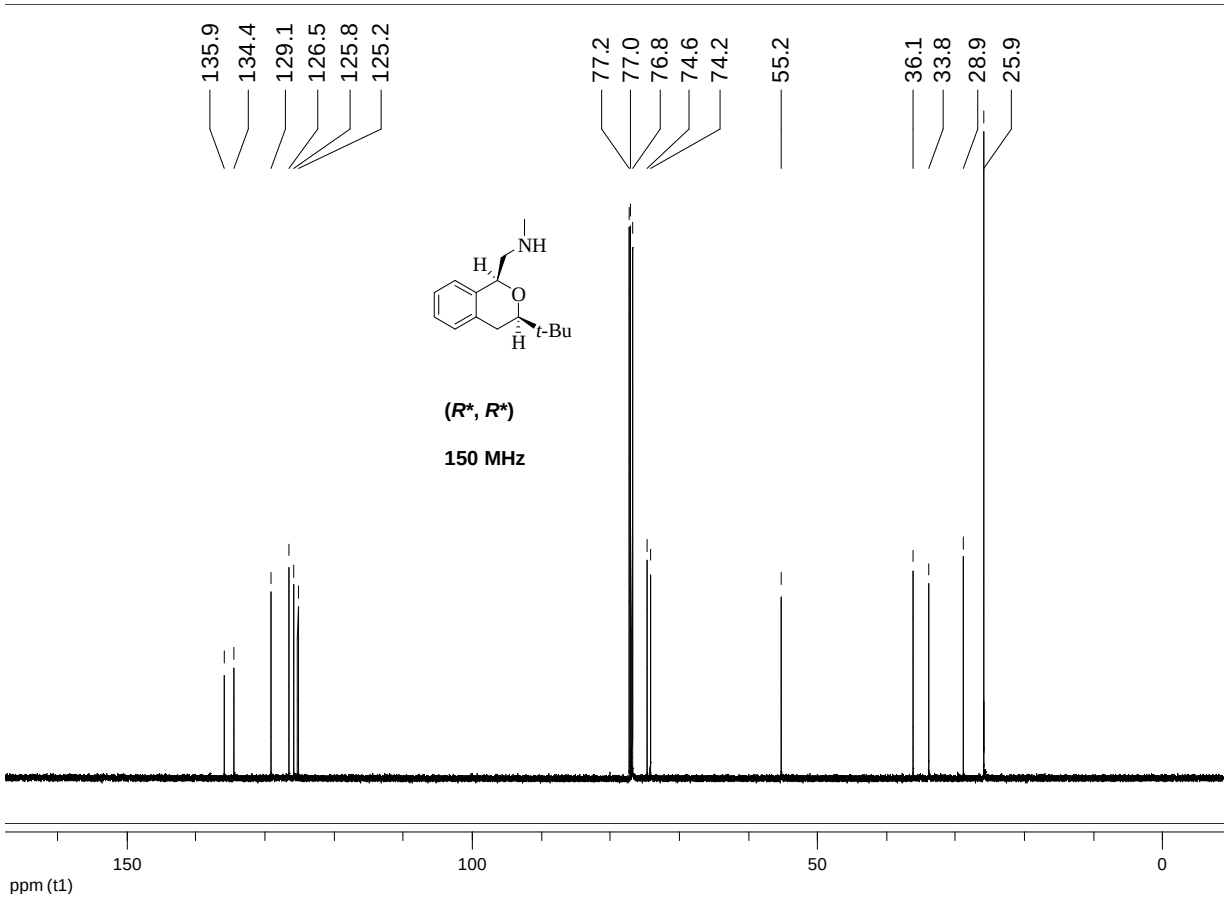

NH
O
Ph
Ph
400 MHz
4.700 4.650
ppm (t1)
3.80 3.70 3.60 3.50
ppm (t1)
3.40 3.30 3.20 3.10 3.00 2.90
ppm (t1)
14.5
1.0
1.0
1.0
0.9
2.0
2.3
3.1
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (t1)

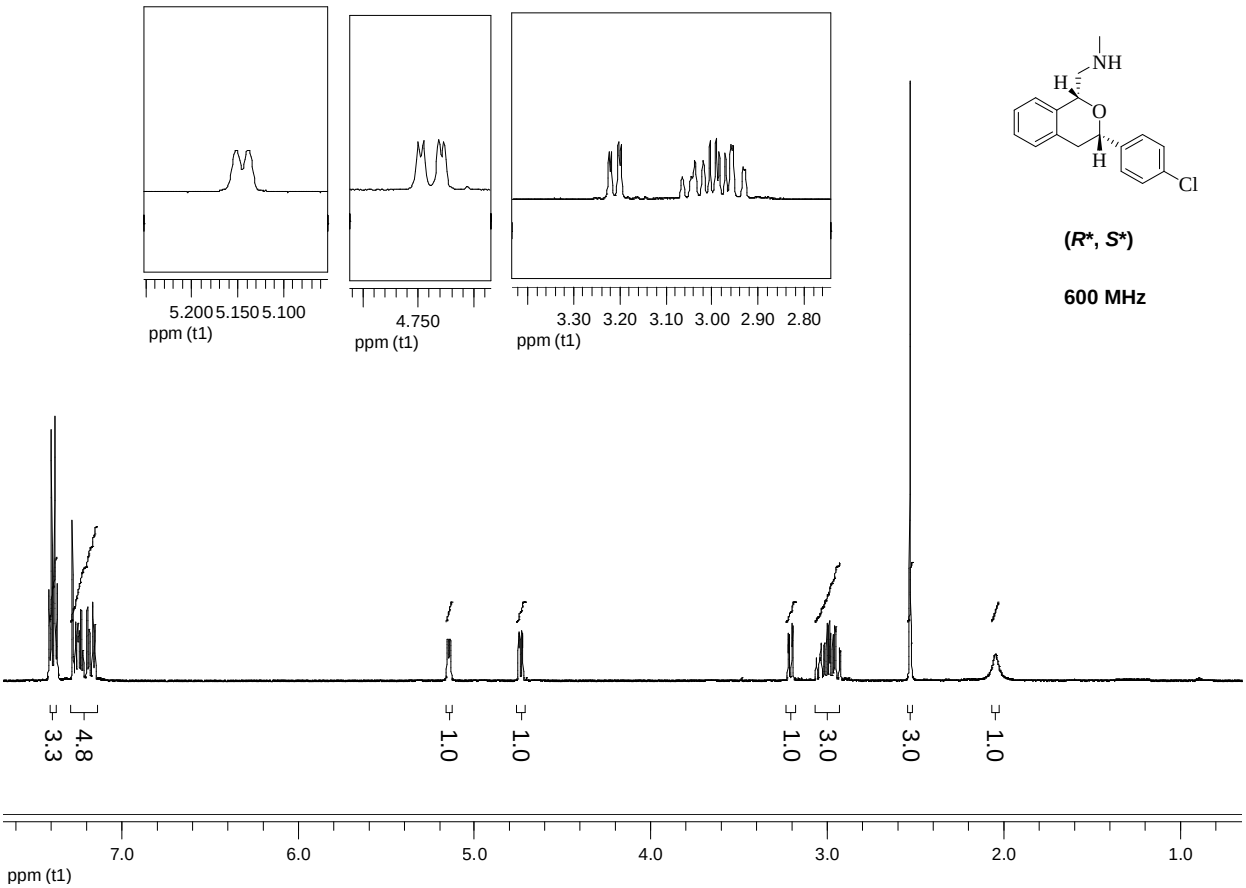

148.2
141.6
135.2
133.5
128.3
128.1
128.0
127.9
127.0
126.7
126.6
126.2
125.1
123.9
78.8
77.3
77.0
76.7
71.0
56.9
39.4
36.1
NH
O
Ph
Ph
100 MHz
150 100 50 0
ppm (t1)

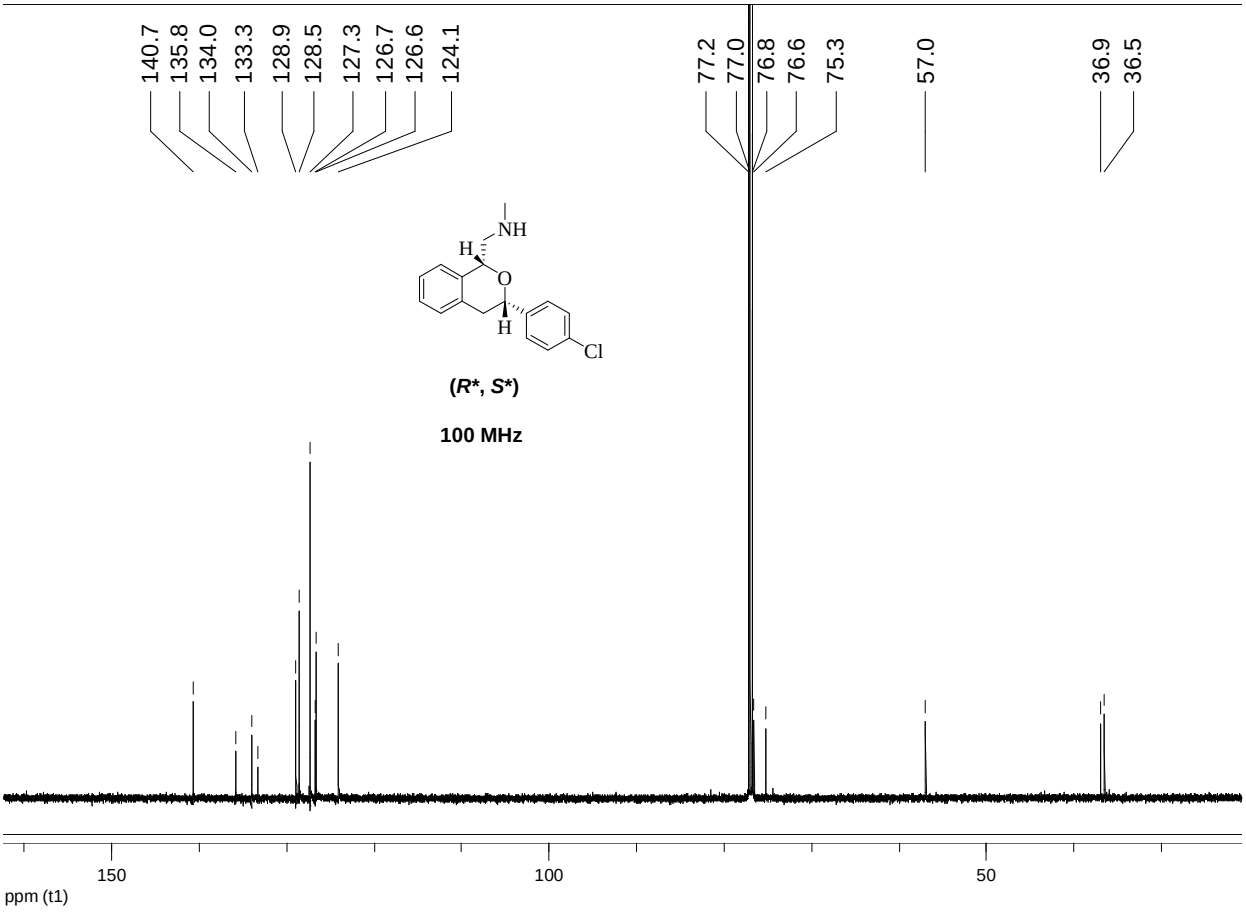

4.950
4.900
ppm (t1)
3.350
3.300
ppm (t1)
3.200
ppm (t1)
2.850
2.800
2.750
2.700
2.650
ppm (t1)
NH
H
O
t-Bu
H
(R*, S*)
600 MHz
2.0
1.0
1.1
1.0
1.0
2.0
3.0
9.1
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

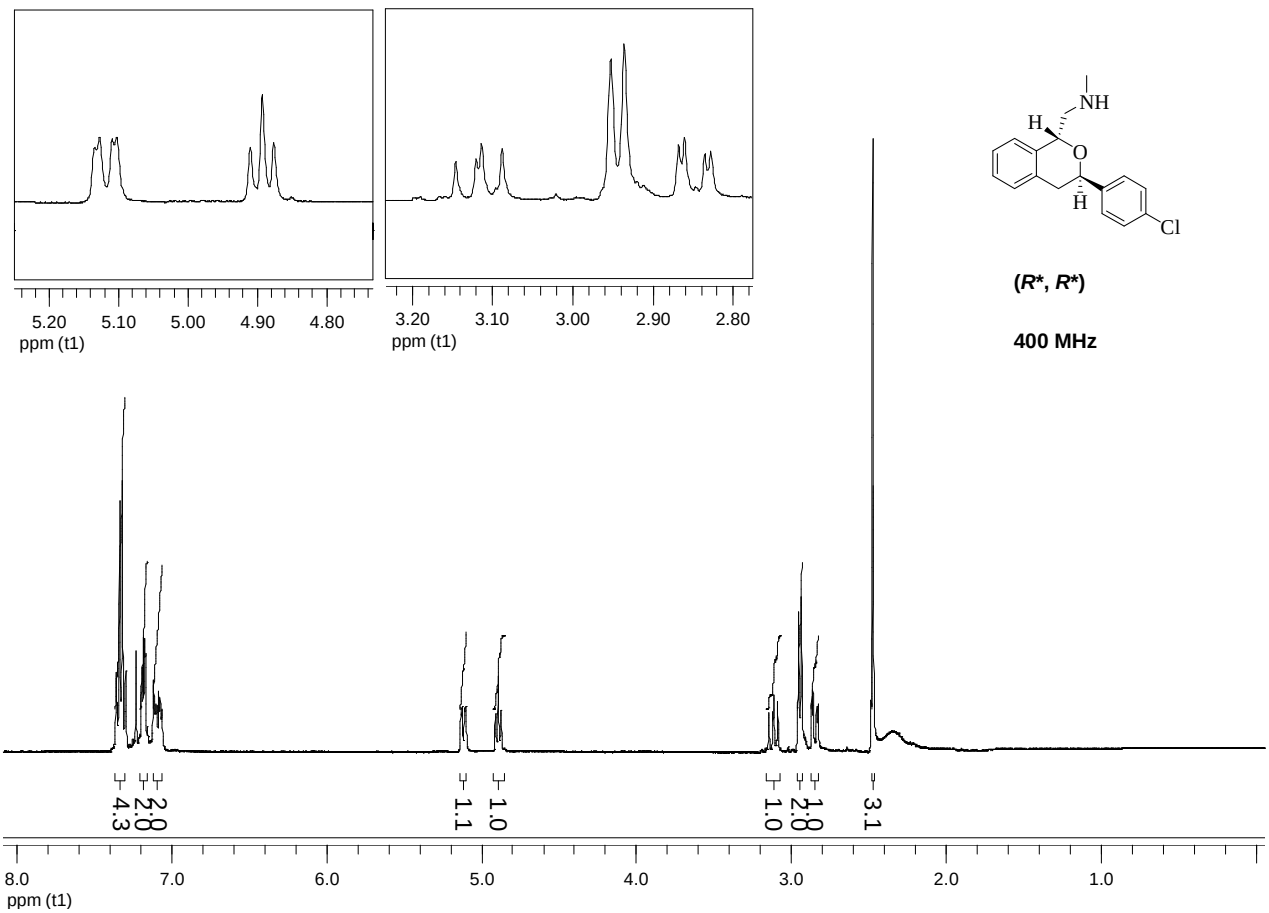

136.3
135.0
129.3
126.4
126.0
123.6
81.6
77.3
77.0
76.7
75.8
56.5
36.1
34.0
29.3
25.8
NH
H
O
t-Bu
H
(R*, S*)
150 MHz
150
100
50
0
ppm (t1)

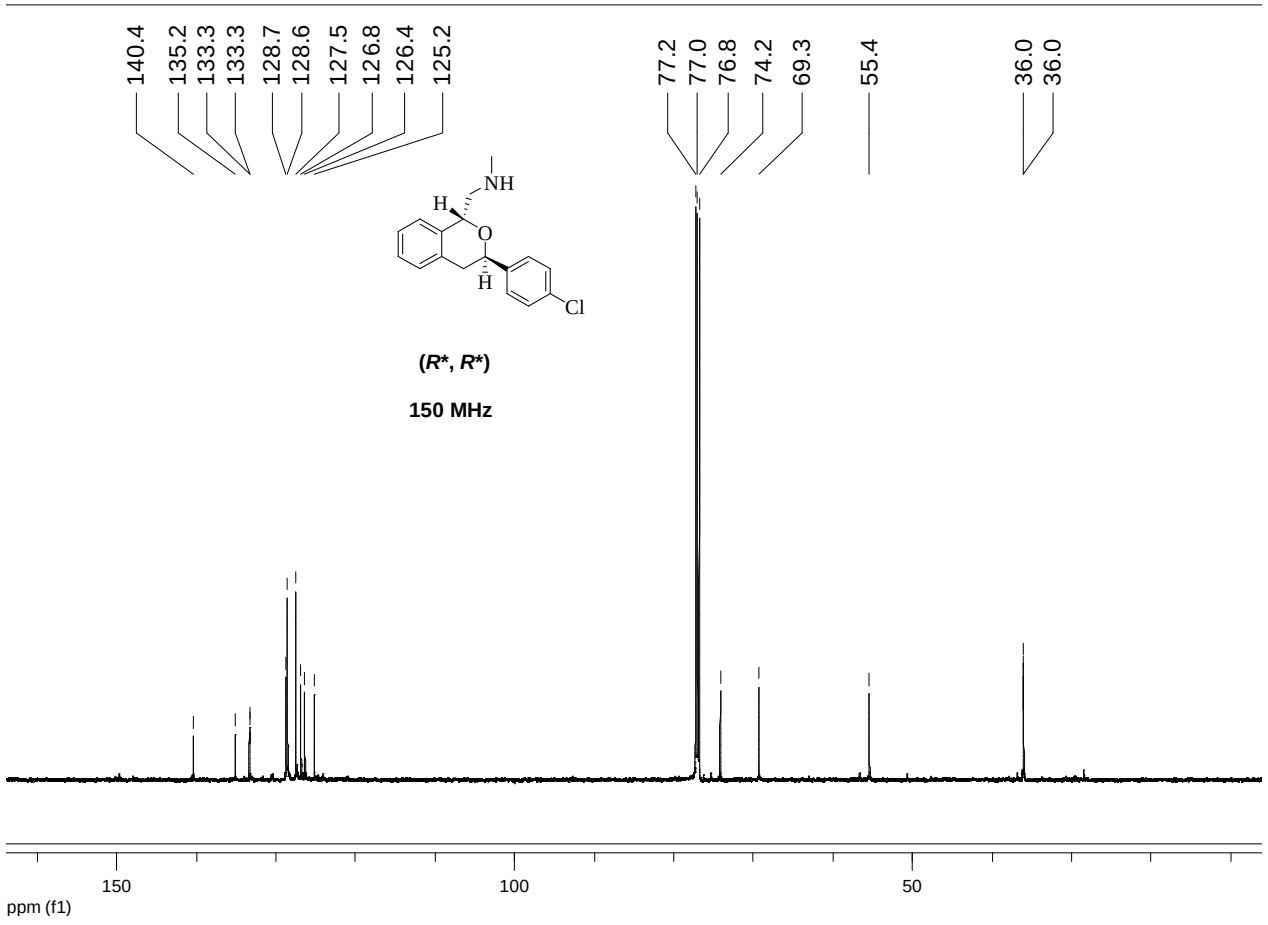

5.000 4.950 4.900
ppm (t1)
3.000 2.950
ppm (t1)
2.700 2.650 2.600 2.550
ppm (t1)
NH
H
O
H
t-Bu
(R*, R*)
400 MHz
3.9
1.1
1.0
1.7
1.0
1.4
1.0
3.0
11.2
7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm (t1)

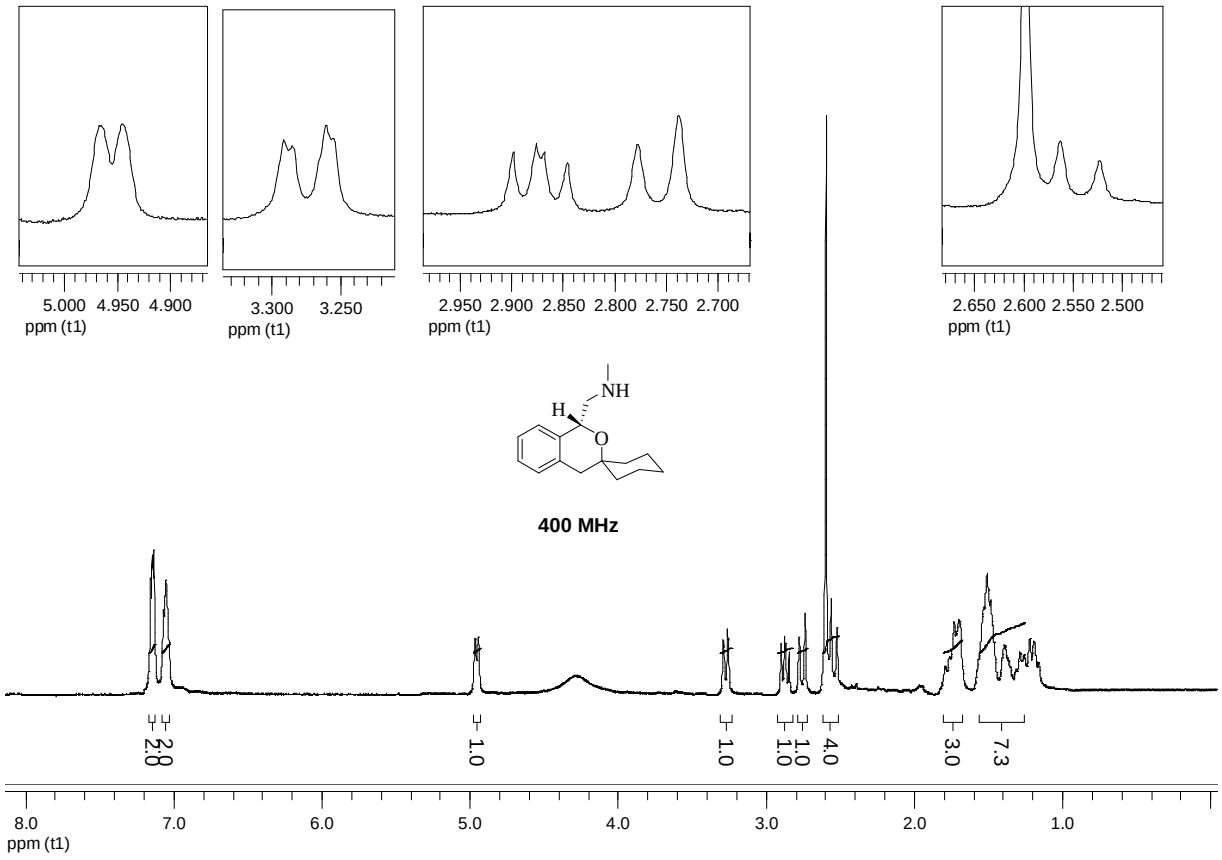

135.9
134.4
129.1
126.5
125.8
125.2
77.2
77.0
76.8
74.6
74.2
55.2
36.1
33.8
28.9
25.9
NH
H
O
H
t-Bu
(R*, R*)
150 MHz
150 100 50 0
ppm (t1)

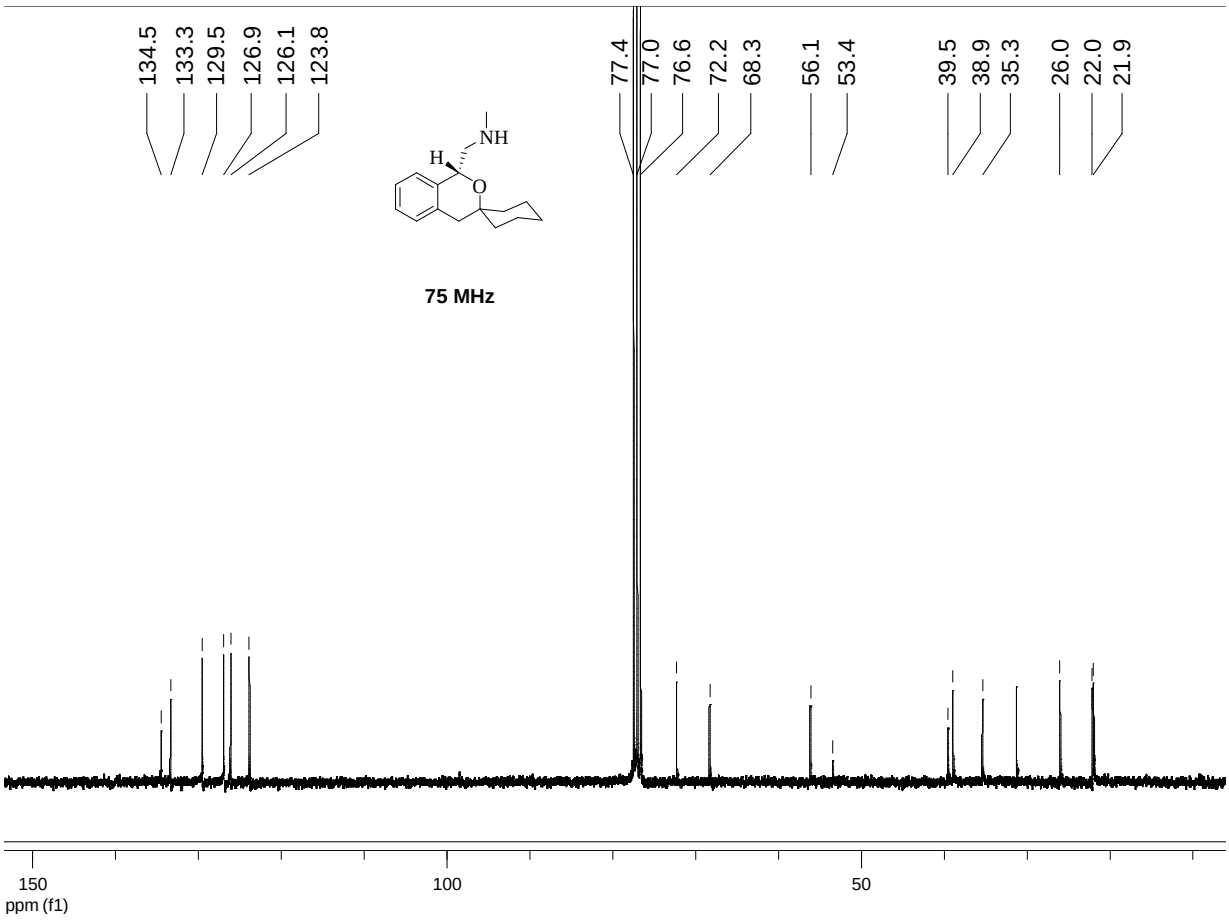

5.200 5.150 5.100
ppm (t1)
4.750
ppm (t1)
3.30 3.20 3.10 3.00 2.90 2.80
ppm (t1)
NH
H
O
H
Cl
(R*, S*)
600 MHz
3.3
4.8
1.0
1.0
1.0
3.0
3.0
1.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

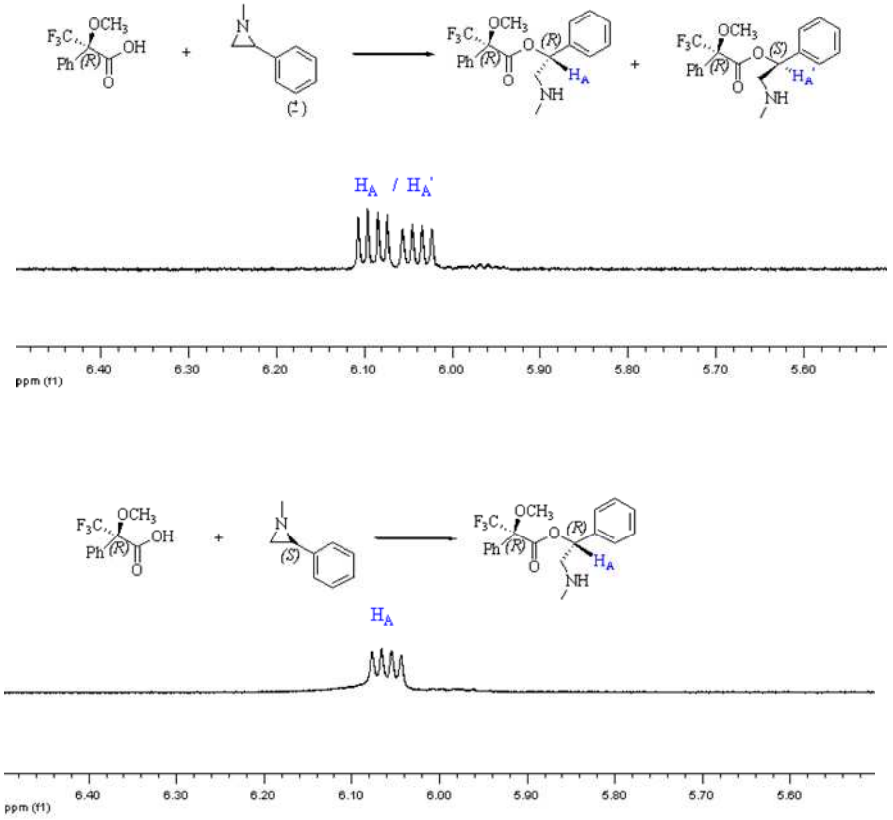

140.7
135.8
134.0
133.3
128.9
128.5
127.3
126.7
126.6
124.1
77.2
77.0
76.8
76.6
75.3
57.0
36.9
36.5
NH
H
O
H
Cl
(R*, S*)
100 MHz
150
100
50
ppm (t1)


5.20
5.10
5.00
4.90
4.80
ppm (t1)
3.20
3.10
3.00
2.90
2.80
ppm (t1)
NH
H
O
H
Cl
(R*, R*)
400 MHz
4.3
2.0
2.0
1.1
1.0
1.0
1.8
3.1
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

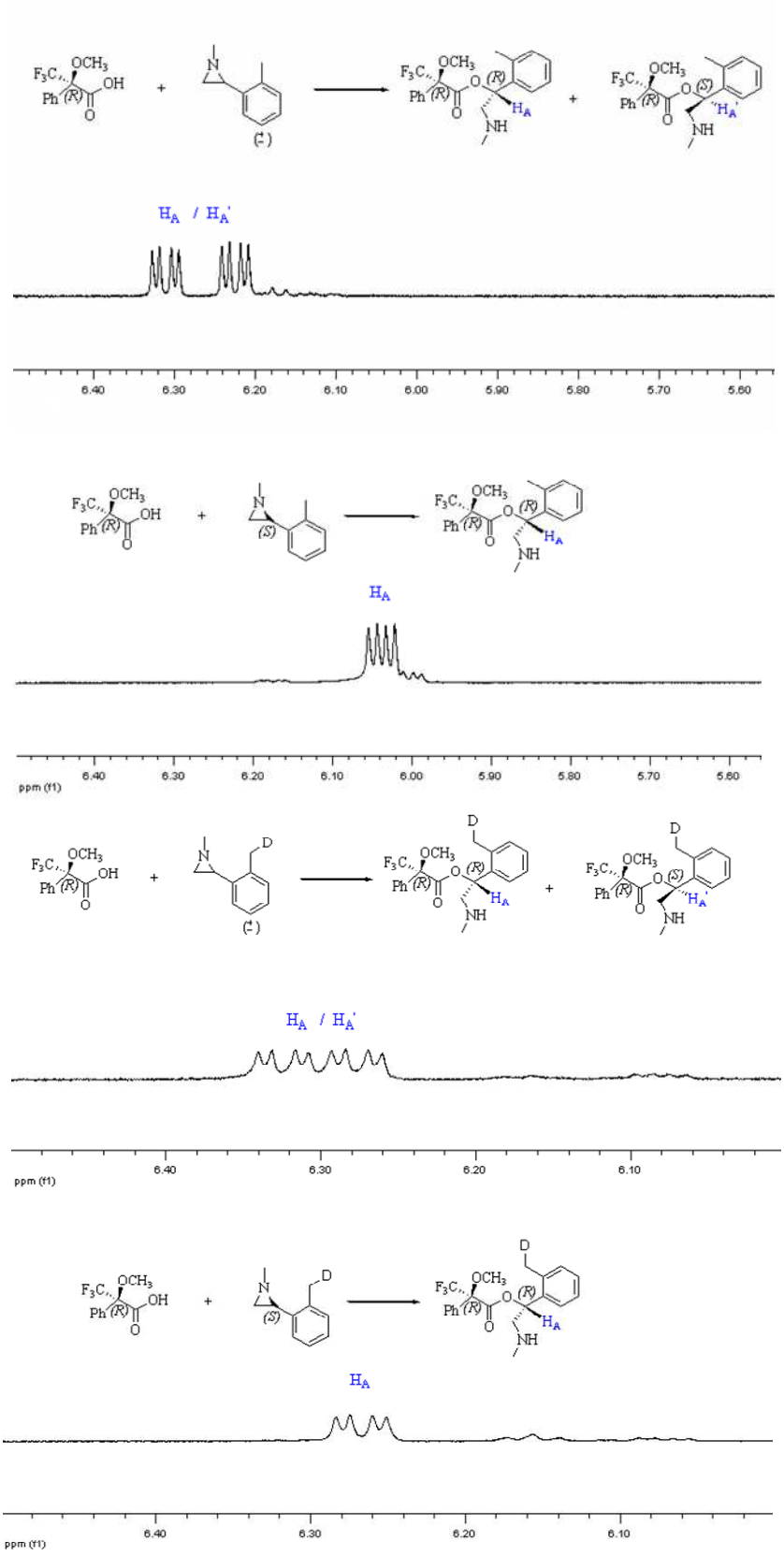

140.4
135.2
133.3
133.3
128.7
128.6
127.5
126.8
126.4
125.2
77.2
77.0
76.8
74.2
69.3
55.4
36.0
36.0
NH
H
O
H
Cl
(R*, R*)
150 MHz
150
100
50
ppm (f1)


5.000 4.950 4.900
ppm (t1)
3.300 3.250
ppm (t1)
2.950 2.900 2.850 2.800 2.750 2.700
ppm (t1)
2.650 2.600 2.550 2.500
ppm (t1)
NH
H
O
400 MHz
2.0
2.0
1.0
1.0
1.0
1.0
4.0
3.0
7.3
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


134.5
133.3
129.5
126.9
126.1
123.8
77.4
77.0
76.6
72.2
68.3
56.1
53.4
39.5
38.9
35.3
26.0
22.0
21.9
NH
H
O
75 MHz
150
100
50
ppm (f1)

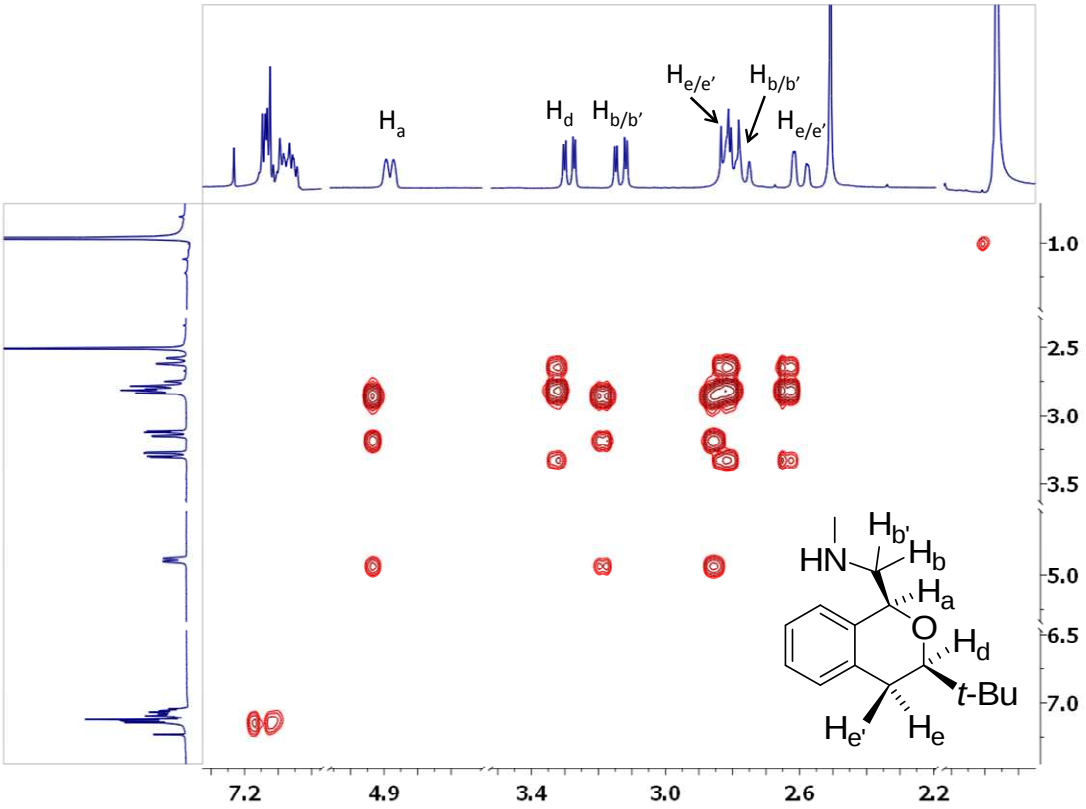


Enantiomeric purity of aziridine **(*S*)-4**.

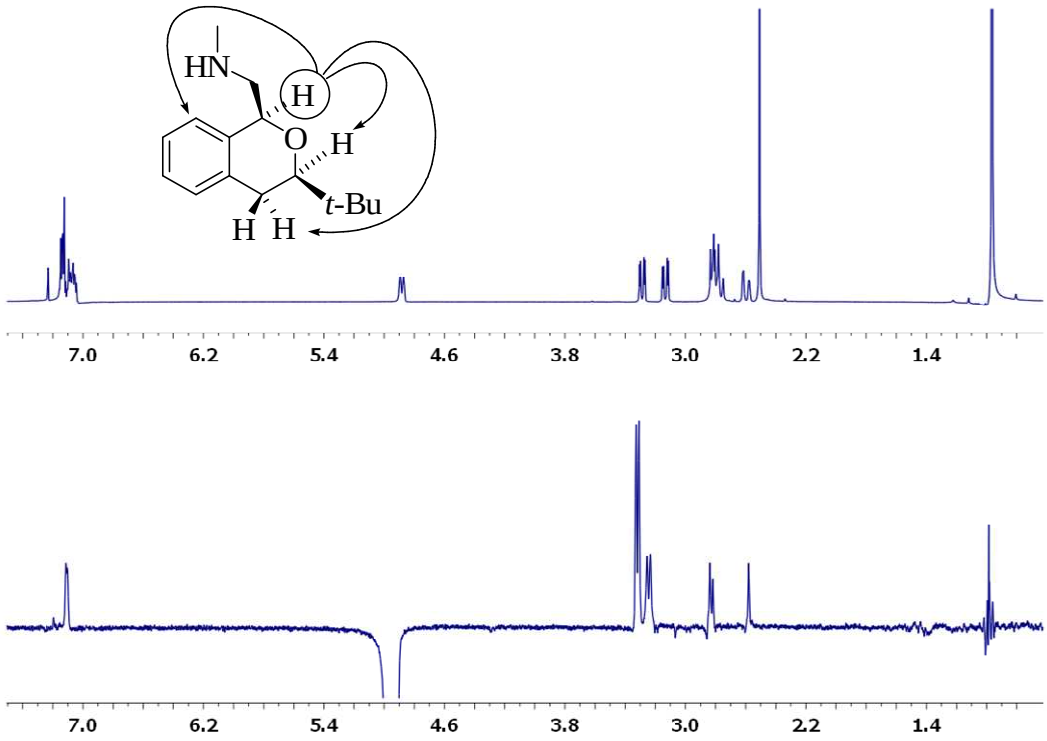


Enantiomeric purity of aziridine **(*S*)-1** and **(*S*)-2a**.

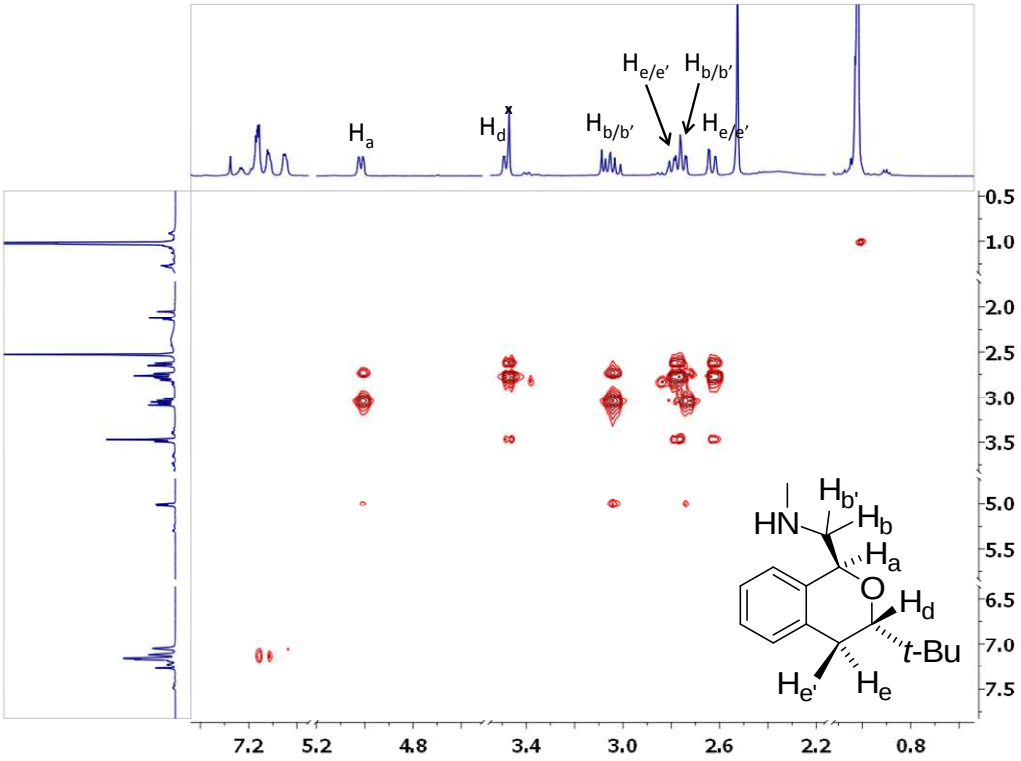
Stereochemical analysis on isochromans **3**



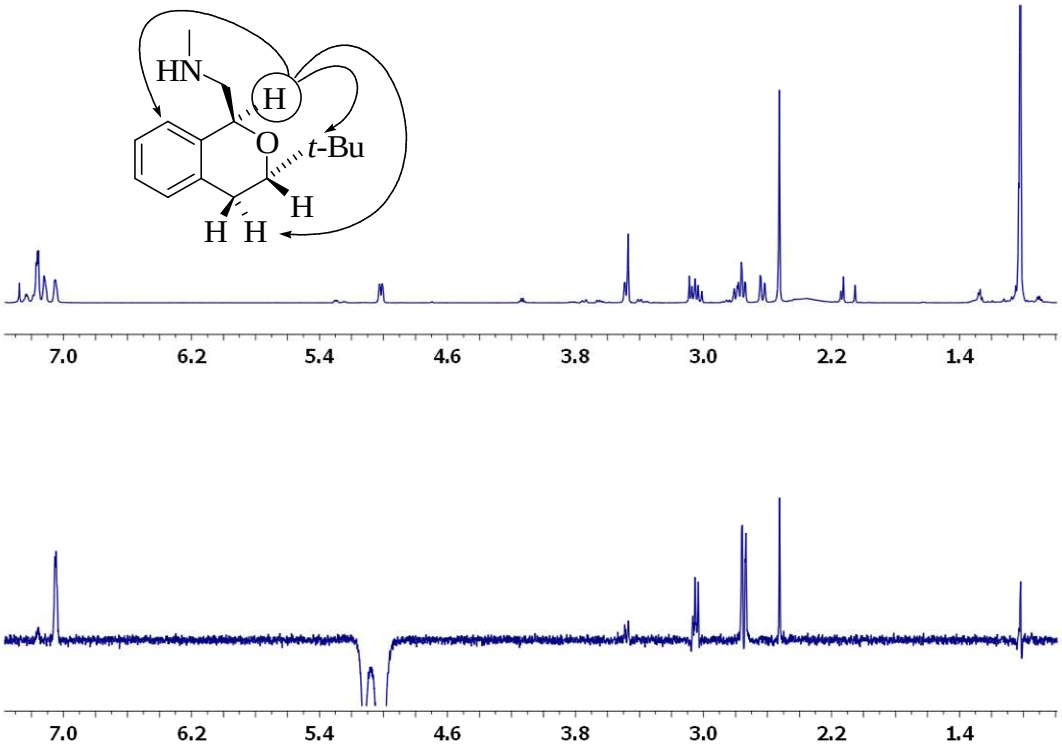
COSY experiment (600 MHz) of **(*R**,*S**)-3c**.



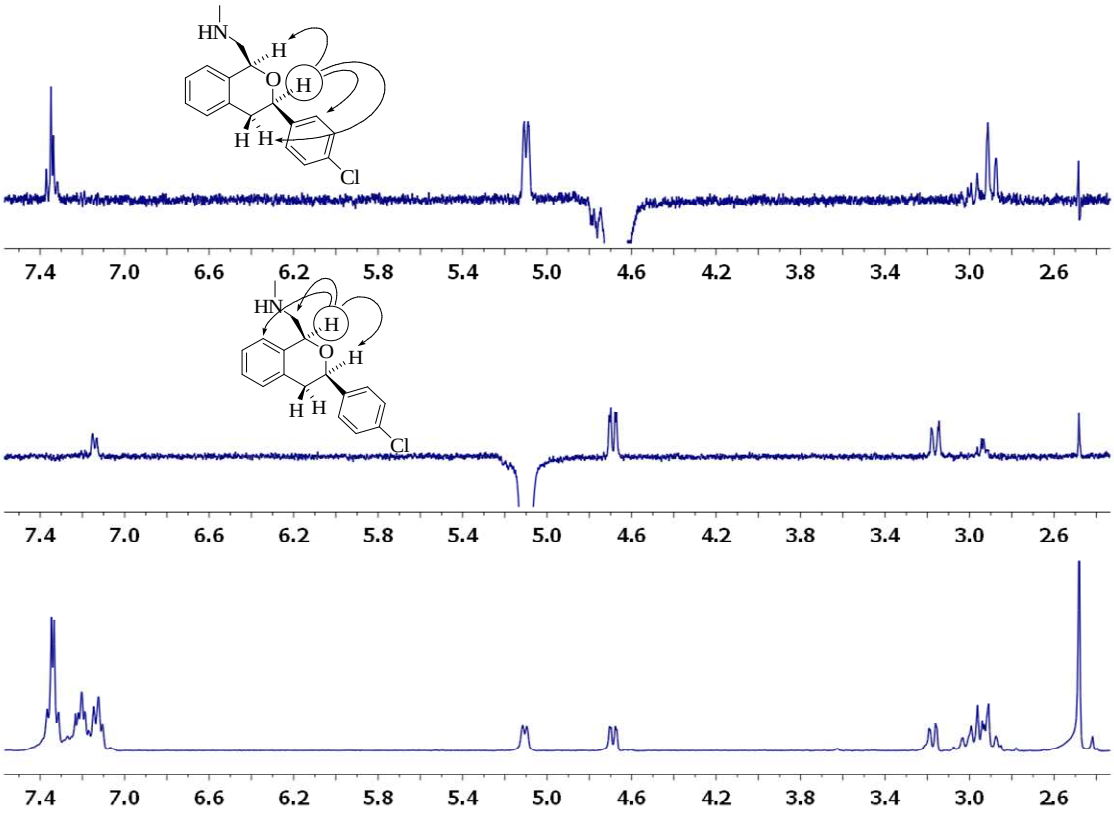
Selective NOESY experiment (600 MHz) of **(*R**,*S**)-3c**.



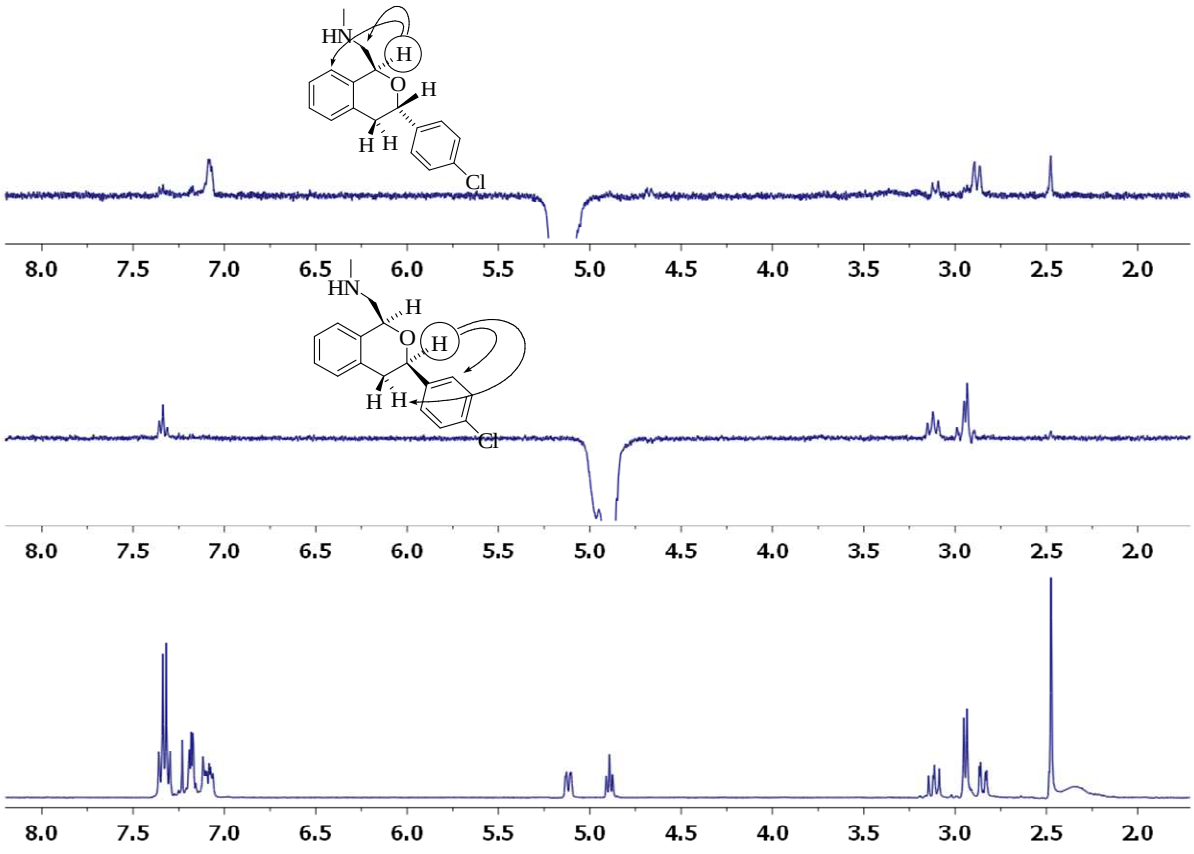
COSY experiment (600 MHz) of **(*R**,*R**)-3c**.



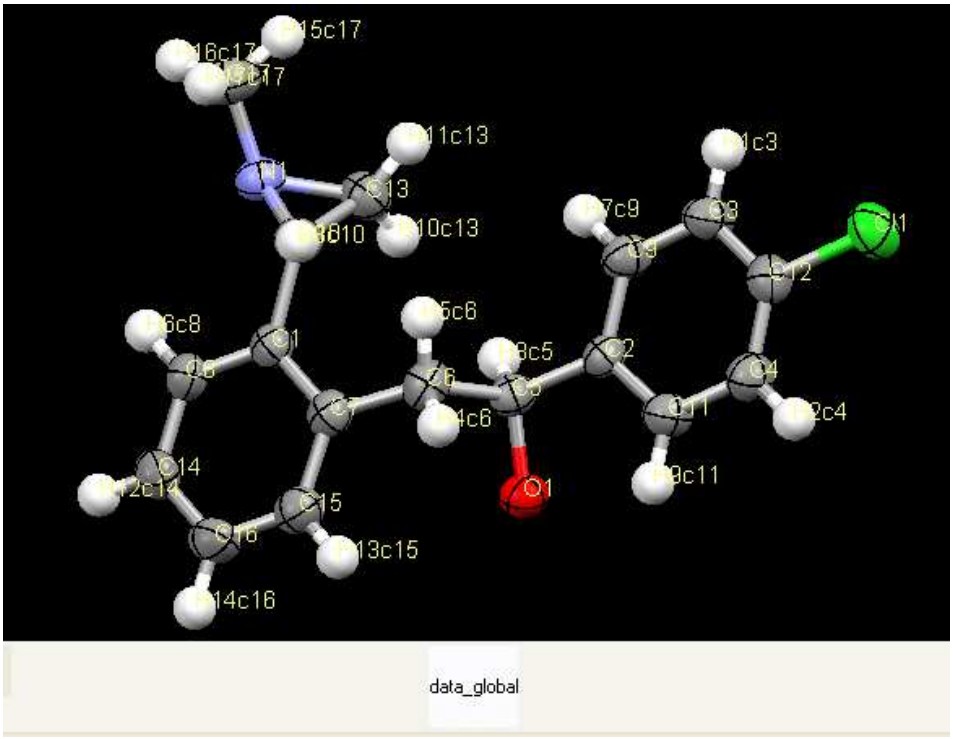
Selective NOESY experiment (600 MHz) of **(*R**,*R**)-3c.**



Selective NOESY experiment (600 MHz) of **(*R**,*S**)-3d.**



Selective NOESY experiment (600 MHz) of **(*R**,*R**)-3d.**



X-ray crystal structure of **(*R**,*R**)-2i** (50% ellipsoid probability)