A general protocol to afford enantioenriched linear homoprenylic amines

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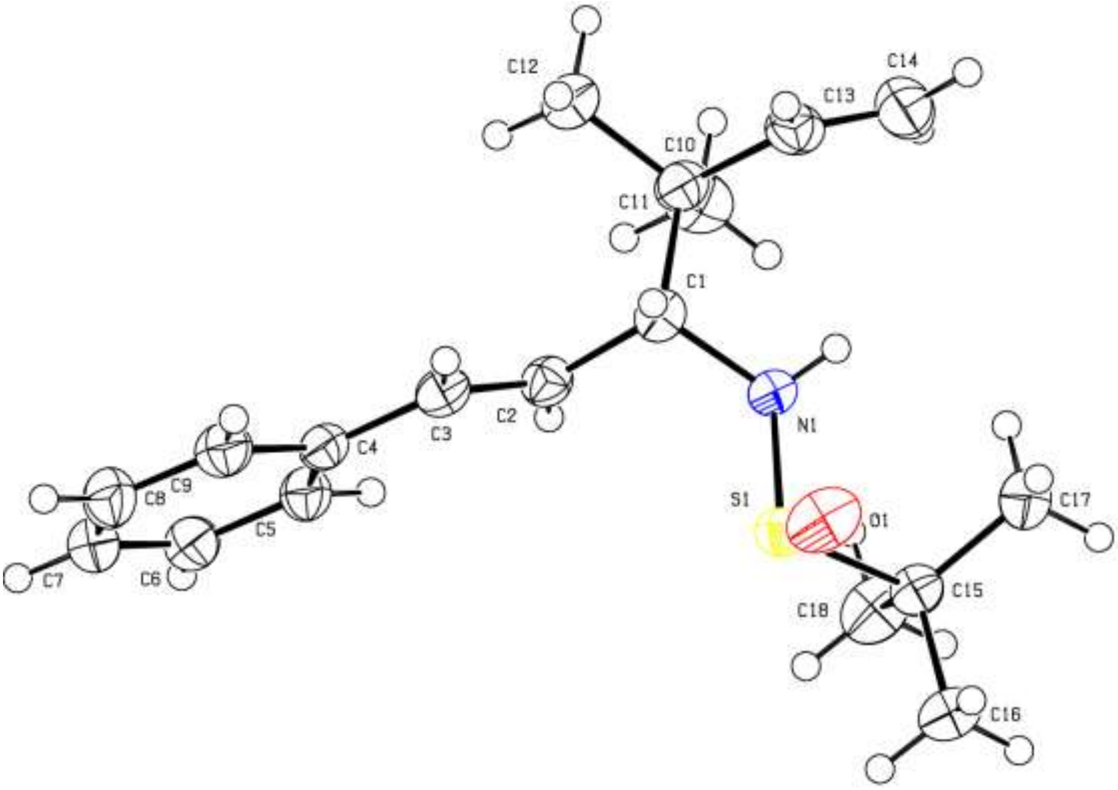
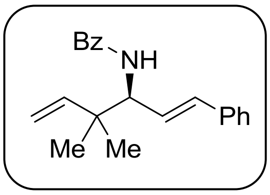
1. X-ray crystal structure for compound *ent*-2b



2. Determination of the enantiomeric and diastereomeric ratios.

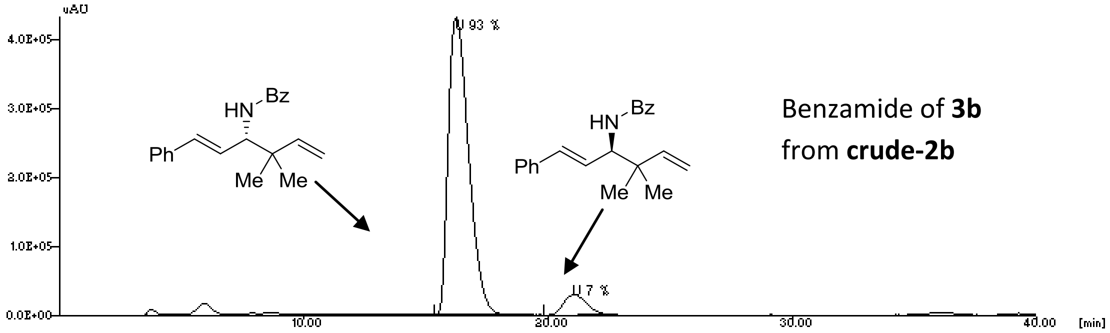
2.1. Determination of the enantiomeric ratio of donor 3b.

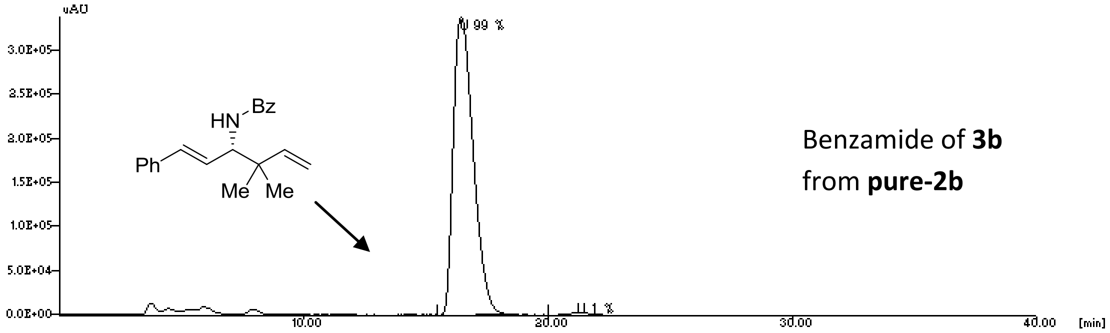


To a solution of crude compound **2b** (30 mg, 0.10 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise a solution of HCl in 1,4-dioxane (4 M, 0.40 mmol, 100µL) at 0 ºC under Ar atmosphere. After 1h the deprotection was finished (according TLC) and the solvent and volatiles (*t*-$BuSO_2Me$) were carefully removed under reduced pressure. To the obtained crude **3b** was added dry CH_2Cl_2 (0.2 mL) and the resulting solution was cooled to 0 ºC. A 2M solution of NaOH (150 µL) was added to the reaction mixture, followed by a dropwise addition of Benzoyl chloride (23 µL, 0.2 mmol). The reaction mixture was stirred for 12 h at room temperature before being quenched with an aqueous solution of NaOH (2M, 0.5 mL). Phase separation was followed by extraction of the aqueous layer with EtOAc (3 x 3 mL) and the combined organic layers were washed with NaOH (2M) followed by brine. Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure giving the expected product (31 mg, 95%, 92:8 er by chiral HPLC on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, λ=220 nm).

Pure product **2b** was submitted to the same procedure described above for crude **2b**, obtaining Benzamide of **3b** (29 mg, 95%, 99:1 er by chiral HPLC on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, λ=220 nm): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 2H), 7.55 – 7.40 (m, 3H), 7.40 – 7.28 (m, 4H), 7.25 – 7.17 (m, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.25 (d, *J* = 7.1 Hz, 1H), 6.20 (d, *J* = 7.0 Hz, 1H), 5.97 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.28 – 5.09 (m, *J* = 29.4 Hz, 2H), 4.77 – 4.66 (m, 1H), 1.17 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 144.0 (CH), 136.7 (C), 134.8 (C), 132.4 (CH), 131.5 (CH), 128.7 (CH), 128.5 (CH), 127.6

(CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 114.5 (CH_2), 58.8 (C), 41.3 (CH), 25.0 (CH_3), 23.7 (CH_3).





2.2. Determination of the enantiomeric ratio of amines 4a, 4c, 4f – 4l , 4n and 4o.

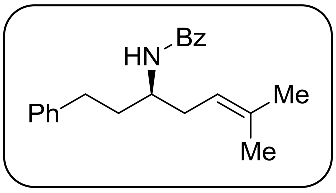
General procedure for benzoylation:

A solution of the corresponding free amine **4** (0.10 mmol) in CH_2Cl_2 (0.2 mL) was cooled to 0 ºC and a solution of NaOH (100 µL, 2 M) was added to the reaction mixture, followed by the dropwise addition of Benzoyl chloride (23 µL, 0.2 mmol). After being stirred for 12 h at room temperature, an aqueous solution of NaOH (0.5 mL, 2 M) was added and the aqueous layer was extracted with EtOAc (3 x 3 mL) and the combined organic layers were washed with NaOH (2 M) and brine. Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the expected product quantitatively, which was directly submitted to HPLC analysis.

This table summarizes the HPLC results obtained for the obtained benzamides, using a Chiracel ODH column (detection at λ=220 nm).

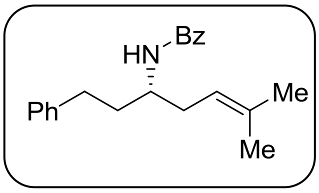
Benzamide	Solvent system *n*-Hexane/*i*-PrOH	Flow (mL/min)	t_R major (min)	t_R minor (min)	er (**4**/*ent*-**4**)
Benzamide of **4a**	95:5	1.0	30.4	23.9	88(*R*):12(*S*)
Benzamide of **4c**	95:5	0.5	20.8	18.5	82(*S*):18(*R*)
Benzamide of **4f**	95:5	1.0	37.7	42.0	89(*E*,*S*):11(*E*,*R*)
Benzamide of **4g**	95:5	1.0	18.4	14.9	92(*S*):8(*R*)
Benzamide of **4h**	95:5	1.0	29.5	18.9	89(*S*):11(*R*)
Benzamide of **4i**	95:5	1.0	32.8	21.4	89(*S*):11(*R*)
Benzamide of **4j**	95:5	1.0	31.8	20.8	89(*S*):11(*R*)
Benzamide of **4k**	90:10	1.0	36.5	30.1	90(*S*):10(*R*)
Benzamide of **4l**	95:5	1.0	37.8	28.0	94(*S*):6(*R*)
Benzamide of **4n**	95:5	1.0	20.5	30.1	85(*R*):15(*S*)
Benzamide of **4o**	98:2	1.0	17.0	20.8	86(2*R*,7*R*):14(2*S*,7*S*)

Benzamide of (*R*)-4a.

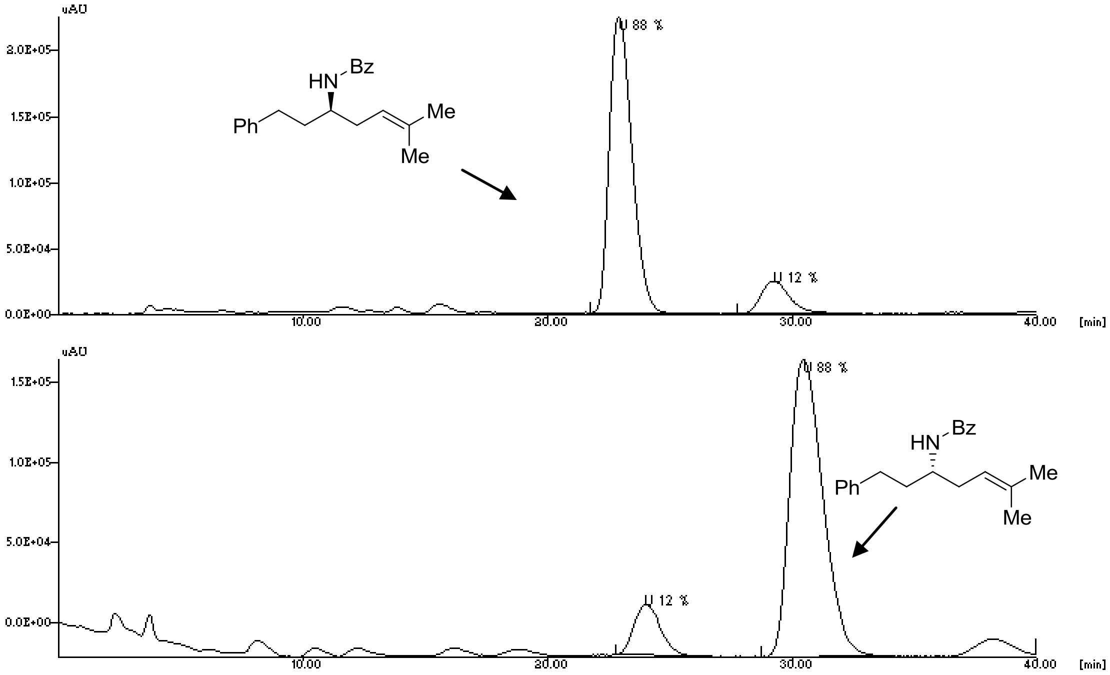


Following the general procedure for benzoylation from compound (*R*)-**4a**, Benzamide of (*R*)-**4a** was obtained as a white solid; R_f = 0.61 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.13 (m, 1H), 7.74 – 7.64 (m, 2H), 7.60 – 7.38 (m, 3H), 7.33 – 7.27 (m, 1H), 7.25 – 7.13 (m, 3H), 5.90 (d, *J* = 8.8 Hz, 1H), 5.19 (t, *J* = 7.4 Hz, 1H), 4.35 – 4.17 (m, 1H), 2.73 (t, *J* = 8.0 Hz, 2H), 2.49 – 2.20 (m, 2H), 2.09 – 1.75 (m, 2H), 1.72 (s, 3H), 1.63 (s, 3H); GC t_R = 18.45 min; LRMS (EI) *m/z* (%) 307 (M^+, 0.1), 238 (41), 186 (10), 122 (33), 117 (16), 105 (100), 95 (14), 77 (29).

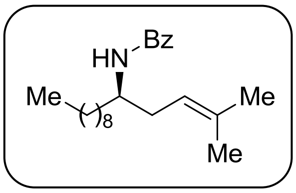
Benzamide of (*S*)-4a.



Following the general procedure for benzoylation from compound (*S*)-**4a**, Benzamide of (*S*)-**4a** was obtained as a white solid showing spectroscopical data identical to the one described for Benzamide of (*R*)-**4a**.

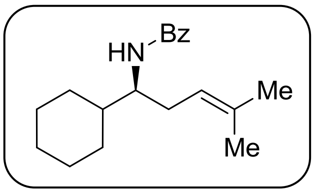


Benzamide of (*R*)-4b.

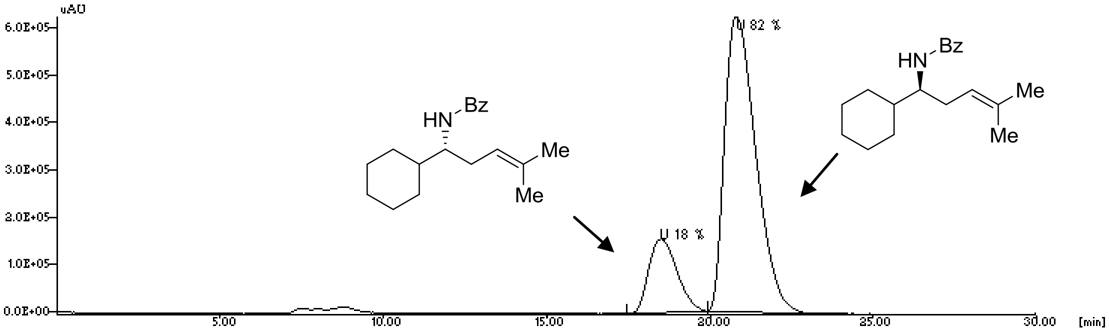


Following the general procedure for benzoylation from compound (*R*)-**4b**, Benzamide of (*R*)-**4b** was obtained as a yellow oil. In this case the HPLC analysis was unsuccessful and the ratio was determined by ^{1}H-NMR analysis of the MPA derivative (MPA-**4b**): R$_f$ = 0.37 (9:1 Hexane/EtOAc); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.76 – 7.70 (m, 2H), 7.53 – 7.39 (m, 3H), 5.86 (d, *J* = 9.1 Hz, 1H), 5.18 (t, *J* = 7.4 Hz, 1H), 4.14 (dt, *J* = 14.3, 7.0 Hz, 1H), 2.35 (dt, *J* = 13.6, 6.7 Hz, 1H), 2.28 – 2.15 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.44 – 1.35 (m, *J* = 4.9 Hz, 2H), 1.35 – 1.14 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H); GC t_R = 18.27 min; LRMS (EI) *m/z* (%) 328 (M^+, 0.1), 261 (10), 260 (48), 208 (6), 122 (6), 106 (10), 105 (100), 77(14).

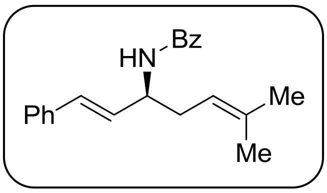
Benzamide of (*S*)-4c.



Following the general procedure for benzoylation from compound (*S*)-**4c**, Benzamide of (*S*)-**4c** was obtained as a white solid; R_f = 0.61 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.33 (m, 5H), 5.88 (d, *J* = 9.1 Hz, 1H), 5.16 (t, *J* = 7.2 Hz, 1H), 4.14 – 3.94 (m, 1H), 2.48 – 2.29 (m, 1H), 2.29 – 2.11 (m, 1H), 1.76 (d, *J* = 10.2 Hz, 4H), 1.70 (s, 3H), 1.61 (s, 3H), 1.51 (ddd, *J* = 14.7, 9.9, 3.2 Hz, 1H), 1.35 – 0.95 (m, 6H); GC t_R = 17.19 min; LRMS (EI) *m/z* (%) 285 (M^+, 0.1), 217 (15), 216 (95), 134 (3), 122 (11), 106 (8), 105 (100), 77 (25).

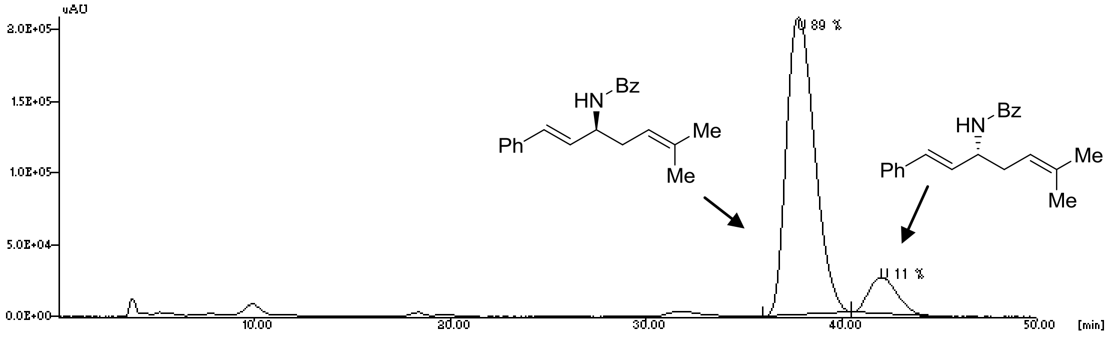


Benzamide of (*E*, *S*)-4f.

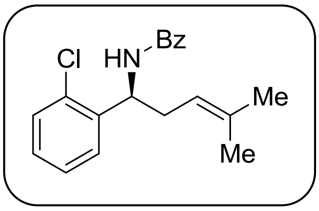


Following the general procedure for benzoylation from compound (*E*,*S*)-**4f**, Benzamide of (*E*,*S*)-**4f** was obtained as a white solid; R_f = 0.56 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.57 – 7.41 (m, 4H), 7.41 – 7.28 (m, 4H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 5.9 Hz, 1H), 6.17 (d, *J* = 7.9 Hz, 1H), 5.23 (t, *J* = 7.5 Hz, 1H), 4.99 – 4.85 (m, 1H), 2.49

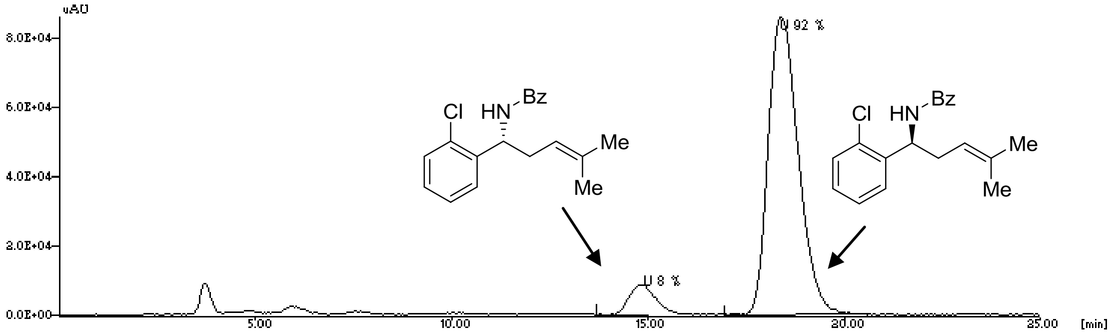
(qt, *J* = 15.1, 7.4 Hz, 2H), 1.74 (s, 3H), 1.68 (s, 3H); GC t_R = 19.34 min; LRMS (EI) *m/z* (%) 305 (M^+, 0.6), 237 (13), 236 (71), 169 (3), 115 (7), 106 (8), 105 (100), 77 (27).



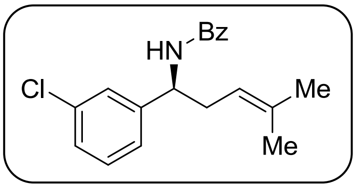
Benzamide of (*S*)-4g.



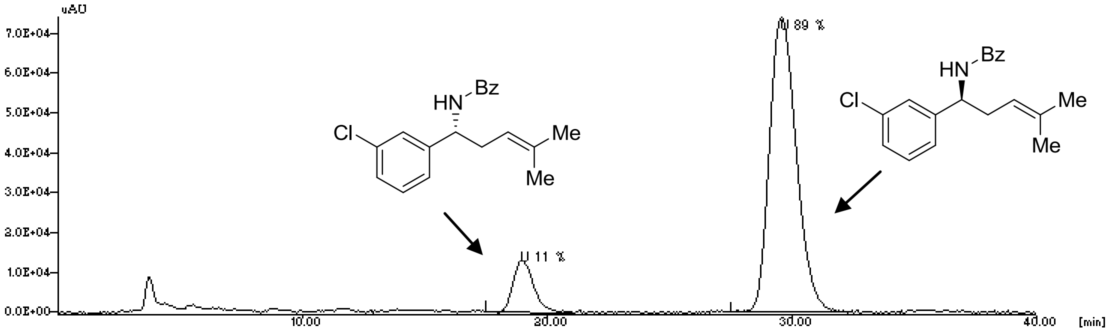
Following the general procedure for benzoylation from compound (*S*)-**4g**, Benzamide of (*S*)-**4g** was obtained as a white solid; R_f = 0.51 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.03 (m, 2H), 7.84 – 7.33 (m, 8H), 6.67 (d, *J* = 7.4 Hz, 1H), 5.48 (dd, *J* = 14.0, 7.4 Hz, 1H), 5.18 – 5.05 (m, 1H), 2.78 – 2.54 (m, 5H), 1.70 (d, *J* = 1.0 Hz, 3H), 1.62 (s, 3H); GC t_R = 18.41 min; LRMS (EI) *m/z* (%) 314 (M^+, 0.3), 246 (12), 245 (5), 244 (30), 192 (7), 177 (4), 106 (9), 105 (100), 77 (29).



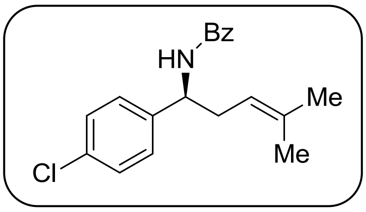
Benzamide of (*S*)-4h.



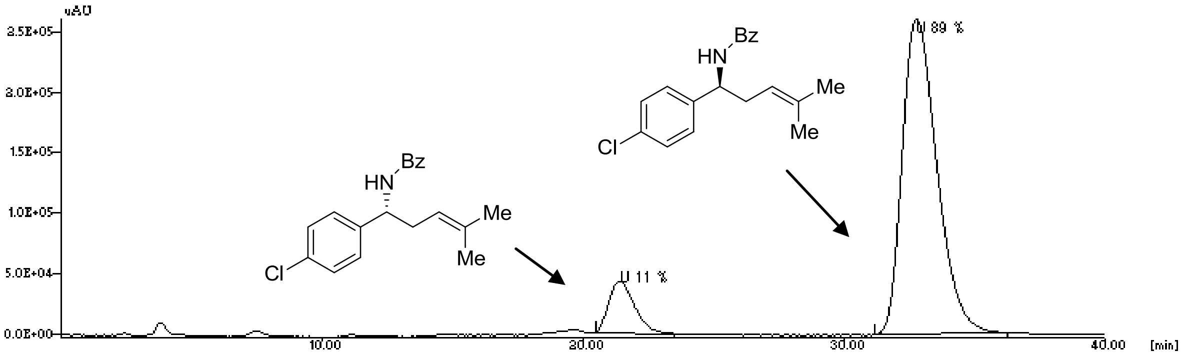
Following the general procedure for benzoylation from compound (*S*)-**4h**, Benzamide of (*S*)-**4h** was obtained as a white solid; R_f = 0.60 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H), 7.56 – 7.40 (m, 3H), 7.35 – 7.30 (m, 1H), 7.26 – 7.17 (m, 2H), 6.38 (br d, *J* = 7.1 Hz, 1H), 5.16 (dd, *J* = 14.0, 6.9 Hz, 1H), 5.08 (t, *J* = 7.2 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.71 (d, *J* = 0.9 Hz, 3H), 1.64 (br s, 5H); GC t_R = 18.15 min; LRMS (EI) *m/z* (%) 314 (M^+, 0.3), 246 (11), 245 (5), 244 (33), 192 (7), 177 (4), 106 (8), 105 (100), 77 (29).



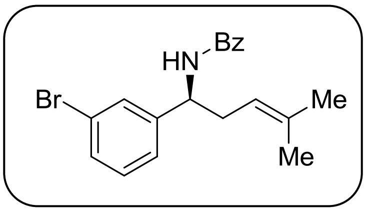
Benzamide of (*S*)-4i.



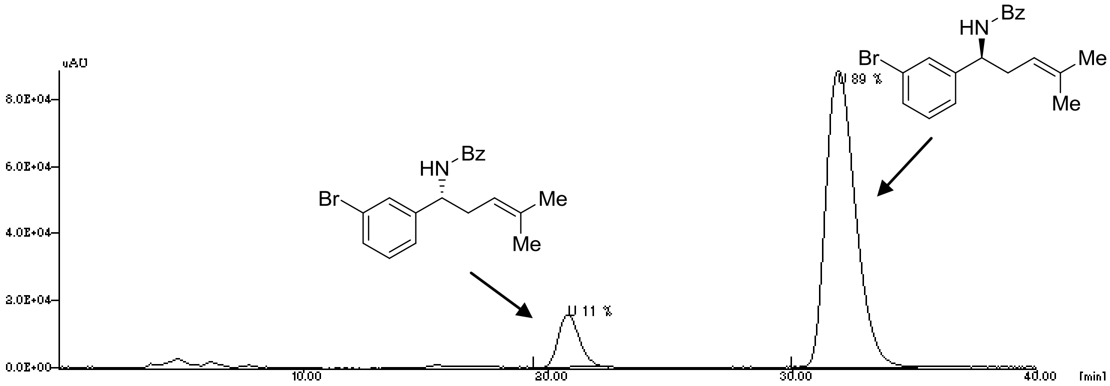
Following the general procedure for benzoylation from compound (*S*)-**4i**, Benzamide of (*S*)-**4i** was obtained as a white solid; R_f = 0.60 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.70 (m, 2H), 7.62 – 7.36 (m, 3H), 7.36 – 7.27 (m, 4H), 6.38 (d, *J* = 7.5 Hz, 1H), 5.16 (q, *J* = 6.9 Hz, 1H), 5.07 (dddd, *J* = 7.2, 5.9, 2.7, 1.3 Hz, 2H), 2.59 (t, *J* = 7.0 Hz, 3H), 1.70 (d, *J* = 1.0 Hz, 1H), 1.63 (s,3H); GC t_R = 18.44 min; LRMS (EI) *m/z* (%) 314 (M^+, 0.3), 246 (11), 245 (7), 244 (31), 192 (7), 177 (5), 106 (8), 105 (100), 77 (30).



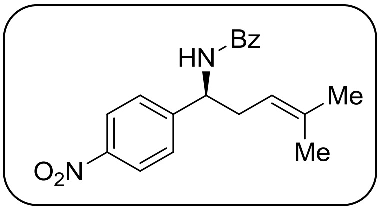
Benzamide of (*S*)-4j.



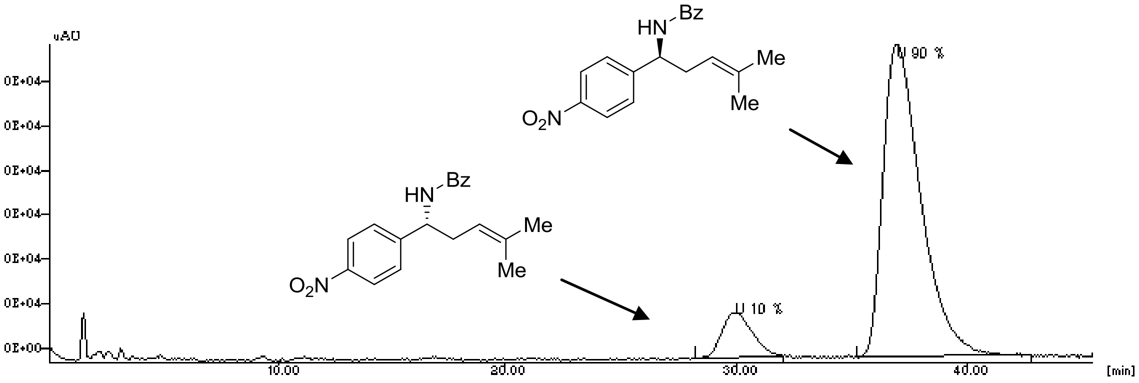
Following the general procedure for benzoylation from compound (*S*)-**4j**, Benzamide of (*S*)-**4j** was obtained as a white solid; $R_f = 0.55$ (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 2H), 7.62 – 7.34 (m, 6H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.37 (d, *J* = 7.4 Hz, 1H), 5.15 (dd, *J* = 14.2, 7.0 Hz, 1H), 5.12 – 5.02 (m, 1H), 2.60 (d, *J* = 6.5 Hz, 2H), 1.71 (d, *J* = 0.9 Hz, 3H), 1.63 (s, 3H); GC t_R = 18.90 min; LRMS (EI) *m/z* (%) 291 (3), 290 (16), 289 (3), 288 (16), 238 (4), 236 (4), 184 (2), 182 (2), 142 (4), 106 (8), 105 (100), 77 (29).



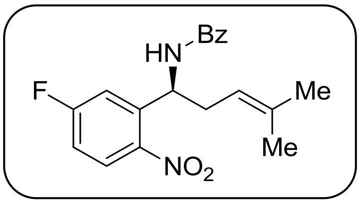
Benzamide of (*S*)-4k.



Following the general procedure for benzoylation from compound (*S*)-**4k**, Benzamide of (*S*)-**4k** was obtained as a white solid; R_f = 0.47 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 2H), 7.80 – 7.74 (m, 2H), 7.57 – 7.42 (m, 5H), 6.52 (d, *J* = 6.6 Hz, 1H), 5.22 (q, *J* = 6.8 Hz, 1H), 5.07 (t, *J* = 7.3 Hz, 1H), 2.62 (tq, *J* = 14.5, 7.2 Hz, 2H), 1.72 (d, *J* = 0.7 Hz, 3H), 1.64 (s, 3H); GC t_R = 22.93 min; LRMS (EI) *m/z* (%) 256 (9), 255 (43), 204 (2), 203 (13), 156 (2), 142 (4), 106 (8), 105 (100), 78 (3), 77 (27).

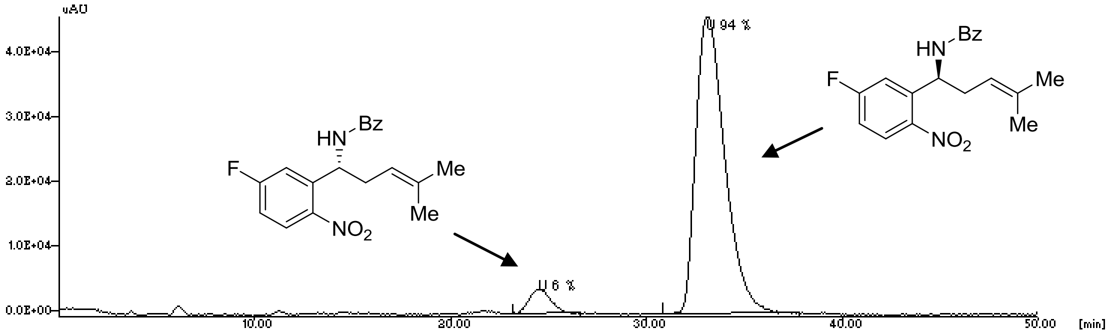


Benzamide of (*S*)-4l.

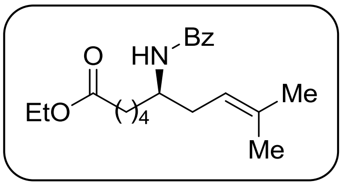


Following the general procedure for benzoylation from compound (*S*)-**4l**, Benzamide of (*S*)-**4l** was obtained as a white solid; R_f = 0.49 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.53 – 7.40 (m, 3H), 7.22 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.07 (ddd, *J* = 9.1, 7.1, 2.8 Hz, 1H), 6.75 (d, *J* = 6.0 Hz, 1H), 5.63 (dd, *J* = 13.9, 6.1 Hz, 1H), 5.15 (dddd, *J* = 7.4, 6.1, 2.7, 1.4 Hz, 1H), 2.83 – 2.70 (m, 1H), 2.68 – 2.51 (m, 1H), 1.74 (d, *J* = 0.9

Hz, 3H), 1.66 (s, 3H); GC t_R = 18.95 min; LRMS (EI) *m/z* (%) 342 (M^+, 0.08), 274 (3), 273 (15), 188 (3), 148 (3), 137 (3), 122 (6), 106 (8), 105 (100), 77 (27).

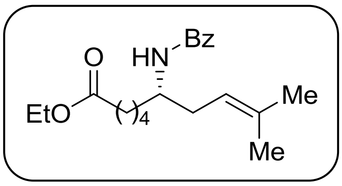


Benzamide of (*R*)-4n.

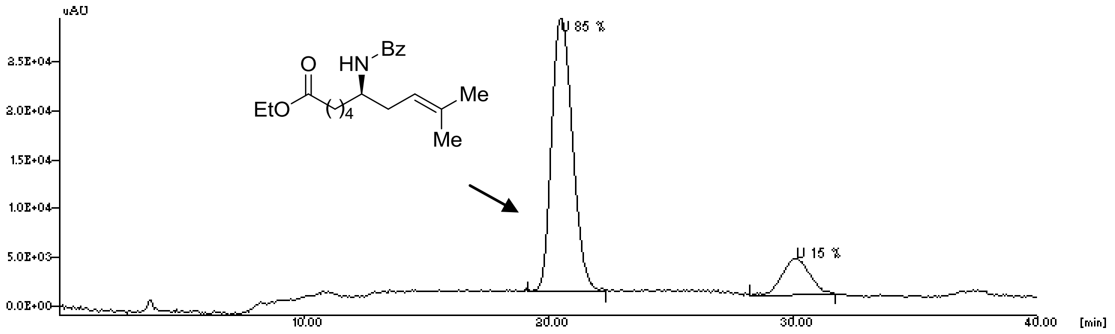


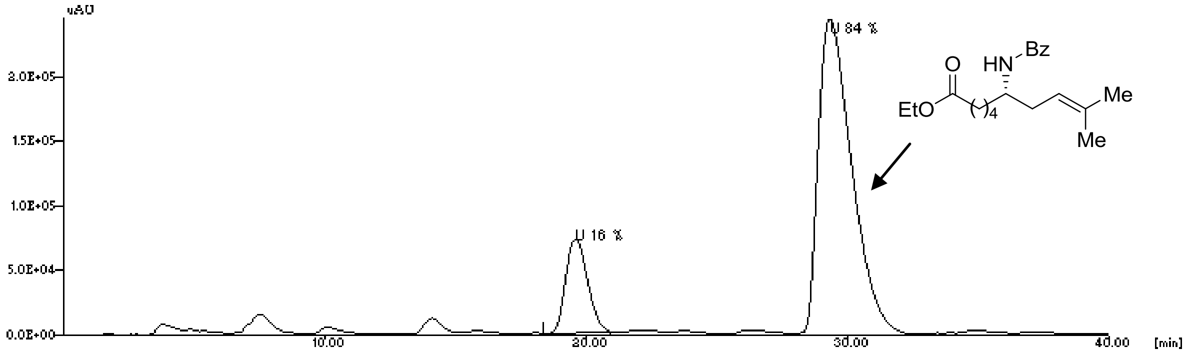
Following the general procedure for benzoylation from compound (*R*)-**4n**, Benzamide of (*R*)-**4n** was obtained as a yellow oil; R_f = 0.50 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.64 (m, 2H), 7.54 – 7.39 (m, 3H), 5.89 (br d, *J* = 8.9 Hz, 1H), 5.17 (t, *J* = 7.4 Hz, 1H), 4.27 – 3.94 (m, 3H), 2.44 – 2.12 (m, 4H), 1.72 (s, 3H), 1.66 (d, *J* = 5.1 Hz, 1H), 1.62 (s, 3H), 1.53 – 1.33 (m, 2H), 1.27 – 1.18 (m, 6H); GC t_R = 18.67 min; LRMS (EI) *m/z* (%) 331 (M^+, 0.2), 263 (8), 262 (47), 216 (16), 164 (8), 122 (6), 106 (8), 105 (100), 77 (18).

Benzamide of (*S*)-4n.

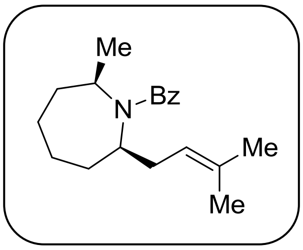


Following the general procedure for benzoylation from compound (*S*)-**4n**, Benzamide of (*S*)-**4n** was obtained with identical spectroscopical data as the one described for Benzamide of **(*R*)-4n**.



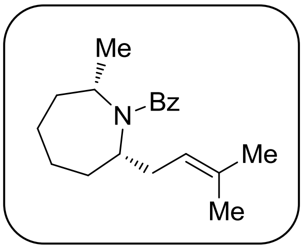


Benzamide of (2*R*, 7*R*)-4o.

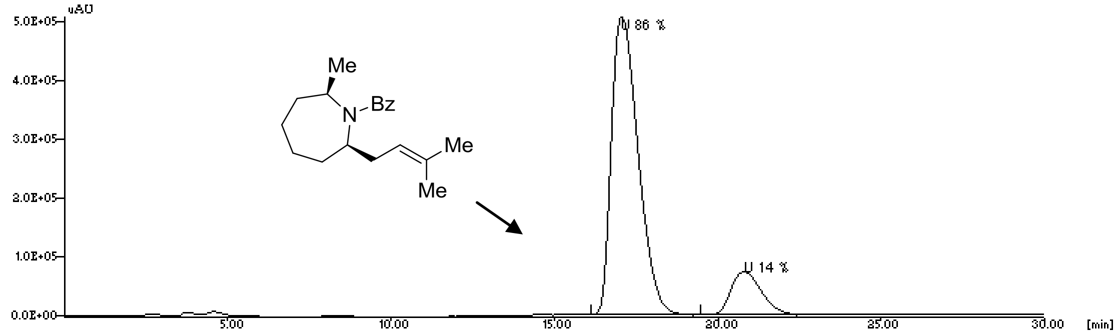


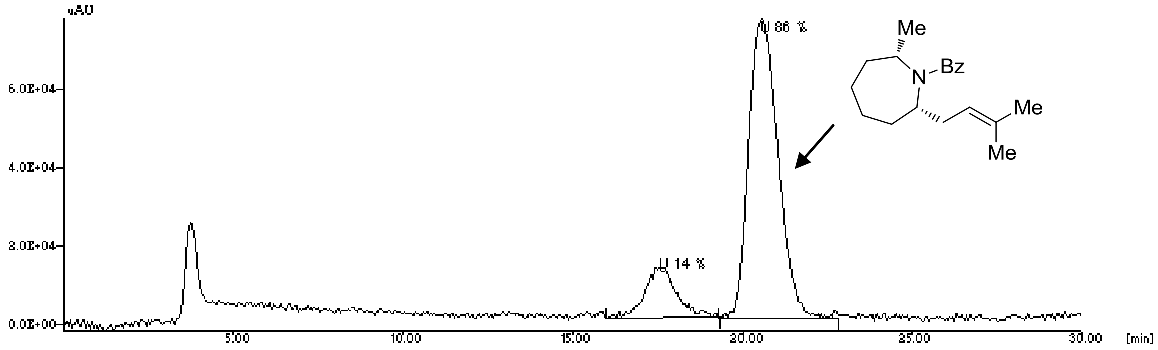
Following the general procedure for benzoylation from compound (2*R*, 7*R*)-**4o**, Benzamide of (2*R*, 7*R*)-**4o** was obtained as a white solid: R_f = 0.33 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.36 (m, 5H), 5.23 (br s, 0.5H), 5.03 – 4.85 (m, 1H), 4.85 – 4.74 (m, 0.5H), 4.18 – 4.04 (m, 0.5H), 3.97 – 3.82 (m, 0.5H), 2.60 – 2.20 (m, 2H), 2.17 – 1.88 (m, 2H), 1.85 – 1.24 (m, 14H); GC t_R = 16.84 min; LRMS (EI) *m/z* (%) 285 (M^+, 0.2), 217 (11), 216 (75), 105 (100), 77 (19).

Benzamide of (2*S*, 7*S*)-4o.



Following the general procedure for benzoylation from compound (2*S*, 7*S*)-**4o**, Benzamide of (2*S*, 7*S*)-**4o** was obtained with identical spectroscopical data as the one described for Benzamide of (2*R*, 7*R*)-**4o.**

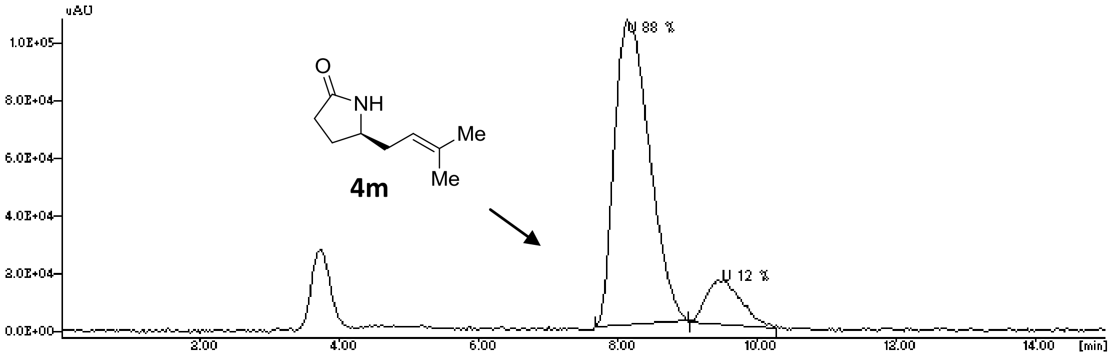


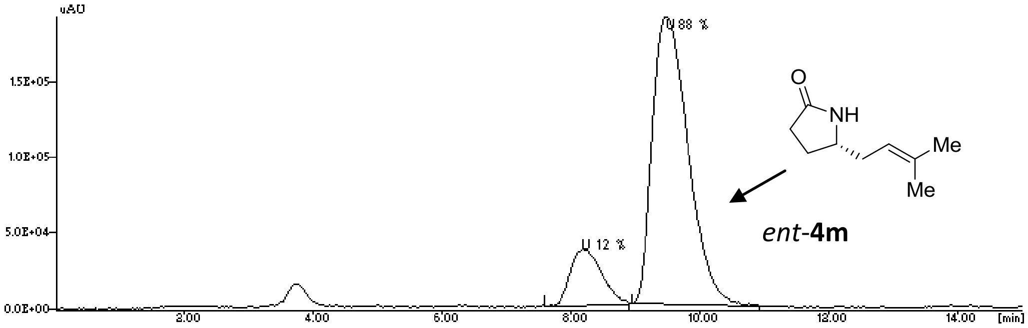


2.3. Determination of the enantiomeric ratio of lactam 4m.

Lactam **4m** was directly submitted to HPLC analysis without further derivatization. This table summarizes the HPLC results obtained for the obtained benzamide, using a Chiracel ODH column (UV detection at λ=220 nm).

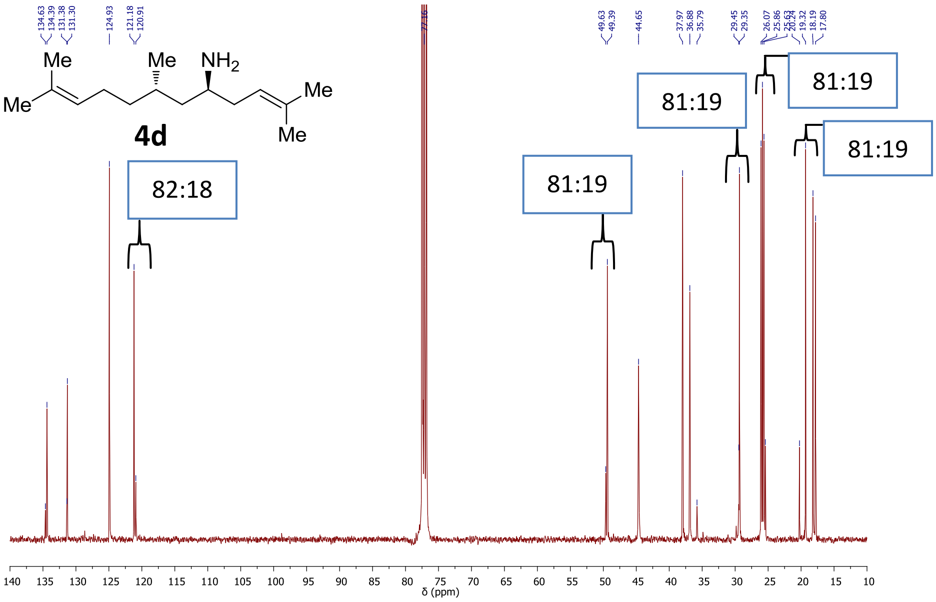
Lactam	Solvent system *n*-Hexane/*i*-PrOH	Flow (mL/min)	t_R (*R*) (min)	t_R (*S*) (min)	er (*R*)/(*S*)
4m	90:10	1.0	8.1	9.5	88:12

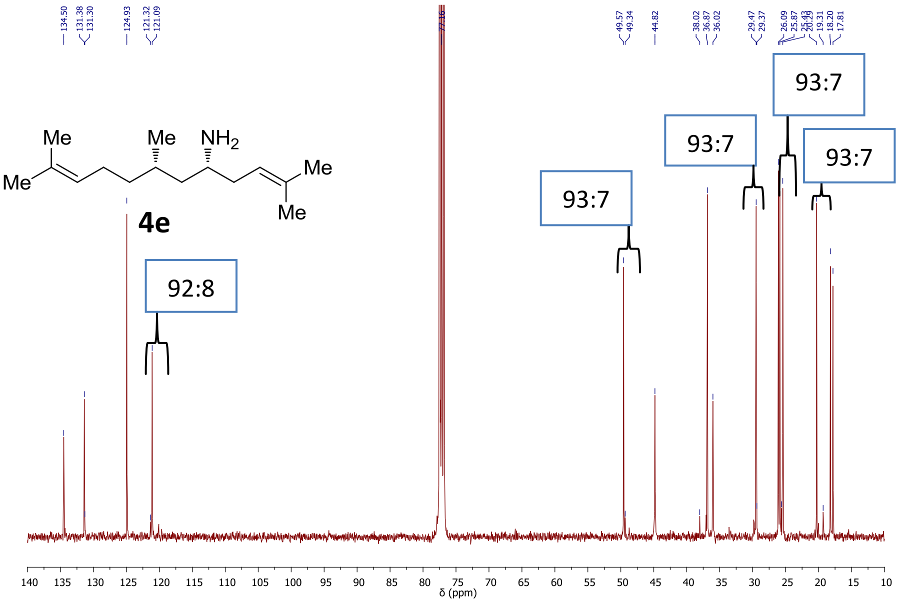




2.4. Determination of the diastereomeric ratio of amines 4d and 4e.

For these two compounds the diastereomeric ratio was estimated by comparing the ^{13}C-NMR spectra of both diastereoisomers. The relative height was measured for each pair of signals corresponding to the same carbon and the average of well resolved pair of signals (see below) was taken as diastereomeric ratio of amines **4d** (81:19 dr) and **4e** (93:7 dr).





3. Determination of the absolute configuration of amines 4a, 4b and 4k.

General procedure for the formation of MPA amides:

To a solution of (*R*)-α-Methoxyphenylacetic acid (83 mg, 0.5 mmol) in dry CH_2Cl_2 (2 mL) were added the corresponding free amine (0.5 mmol), DMPA (61 mg, 0.5 mmol) and EDC (115 mg, 0.6 mmol). The reaction mixture was stirred for 2 h at 23 ºC. The organic layer was washed sequentially with water, HCl (1 M), water, saturated $NaHCO_3$ aqueous solution and brine. The residue was dried over $MgSO_4$, filtered and concentrated at reduced pressure without further purification.

As described by the group of Riguera,[1] the addition of Ba^{2+} to the NMR sample of MPA amides should shift the equilibrium from an antiperiplanar to a synperiplanar conformation, which lead to an increase shielding of the vinylic signals by the phenyl group of the MPA auxiliary. Following this protocol, two experiments of ^1H NMR in CD_3CN were performed for each amide, before and after the addition of $Ba(ClO_4)_2$. The most relevant signals for the determination of absolute configuration of the selected amides are shown below (for copies of full spectra, see below).

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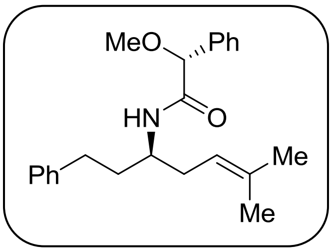
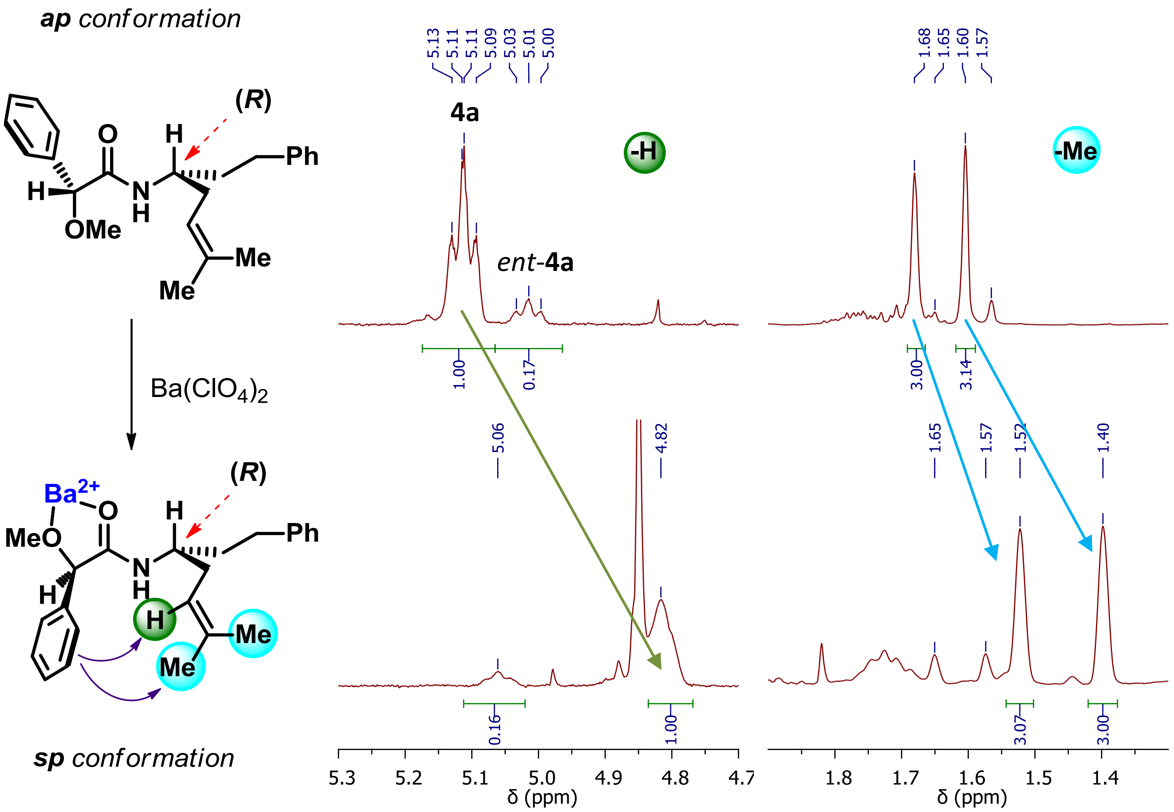
[1] R. García, J. M. Seco, S. A. Vázquez, E. Quiñoá, R. Riguera, *J. Org. Chem.* 2006, **71**, 1119.

(*R*)-MPA-4a.

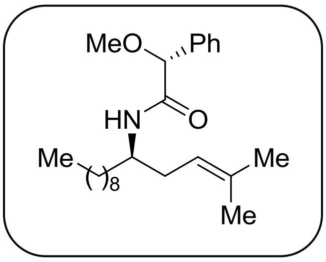


Following the general procedure of formation of MPA amides from amine **4a**, compound MPA-**4a** was obtained as a colorless oil:

^{1}H NMR (400 MHz, CD$_3$CN) δ 7.46 – 7.02 (m, 10H), 6.89 (d, *J* = 9.1 Hz, 1H), 5.11 (dd, *J* = 8.0, 6.7 Hz, 1H), 4.57 (s, 1H), 3.89 – 3.72 (m, 1H), 3.34 (s, 3H), 2.55 – 2.36 (m, 2H), 2.30 – 2.13 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H); *after the addition of 100 mg of Ba(ClO$_4$)$_2$*: ^{1}H NMR (400 MHz, CD$_3$CN) δ 7.54 – 7.07 (m, 10H), 6.84 (d, *J* = 9.3 Hz, 1H), 4.81 (s, 1H), 4.76 (br s, 1H), 3.86 – 3.76 (m, 1H), 3.31 – 3.23 (m, 3H), 2.59 – 2.39 (m, 2H), 2.18 – 1.96 (m, 4H), 1.47 (s, 3H), 1.35 (s, 3H).



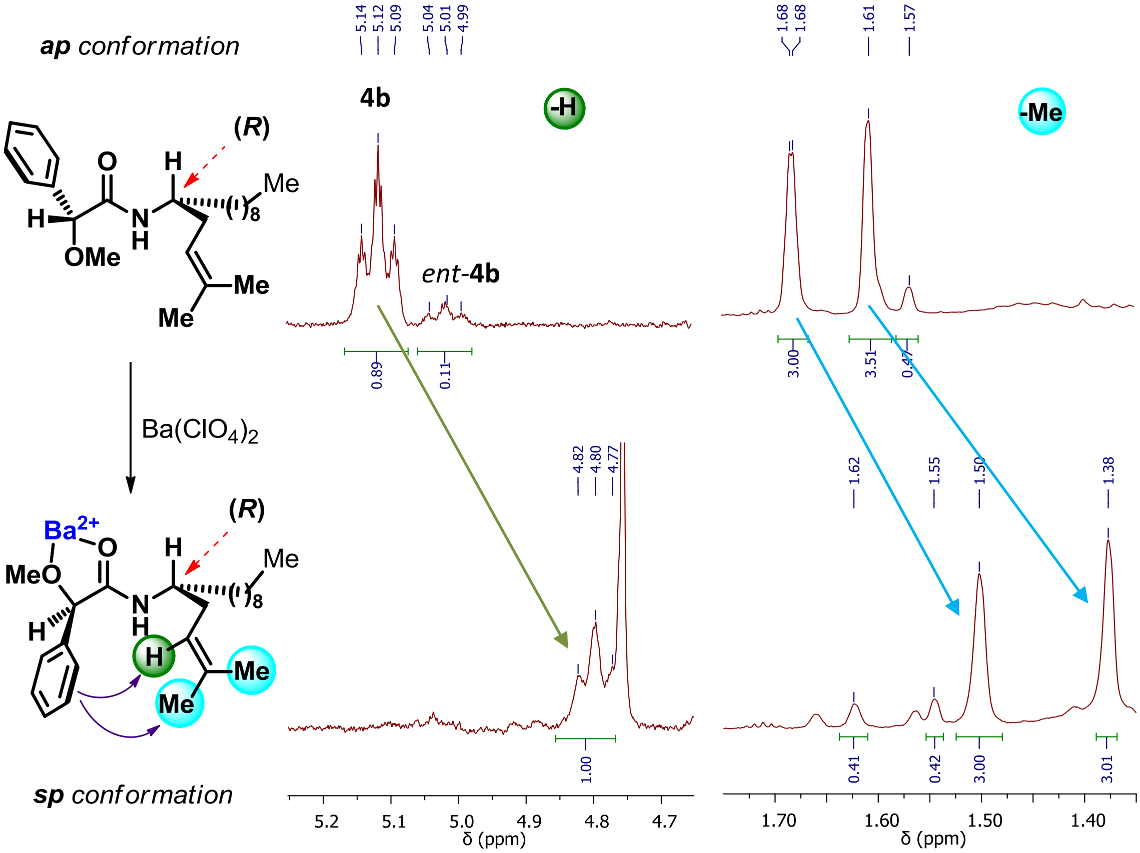
(*R*)-MPA-4b.



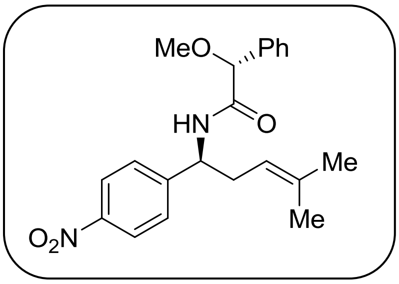
Following the general procedure of formation of MPA amides from amine **4b**, compound MPA-**4b** was obtained as a colorless oil:

^{1}H NMR (400 MHz, CD_3CN) δ 7.42 – 7.30 (m, 5H), 6.76 (d, *J* = 8.9 Hz, 1H), 5.19 – 5.04 (m, 1H), 4.53 (s, 1H), 3.85 – 3.69 (m, 1H), 3.32 (s, 3H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.61 (s, 3H), 1.33 – 1.07 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); *after the addition of 100 mg of* $Ba(ClO_4)_2$: ^{1}H NMR (400 MHz, CD_3CN) δ 7.48 – 7.31 (m, 5H), 6.78 (d, *J* = 9.2 Hz, 1H), 4.80 (t, *J* = 7.7 Hz, 1H), 4.76 (s, 1H), 3.85 – 3.66 (m, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.31 – 1.07 (m, 18H), 0.85 (t, *J* = 6.7 Hz, 3H).

In this case, the enantiomeric ratio of the free amine **4b** was taken directly from the diastereomeric ratio of the corresponding (*R*)-MPA derivatives-**4b** (89:11 dr).

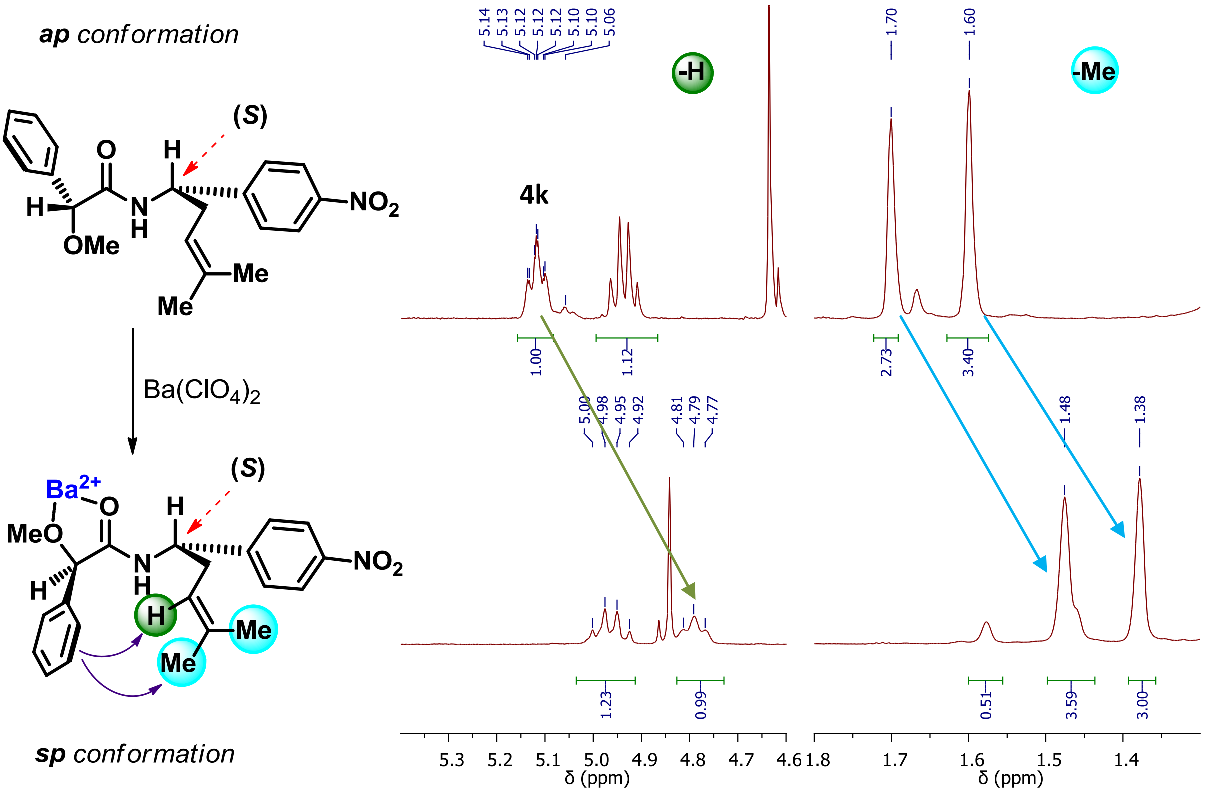


(*R*)-MPA derivative of 4k.

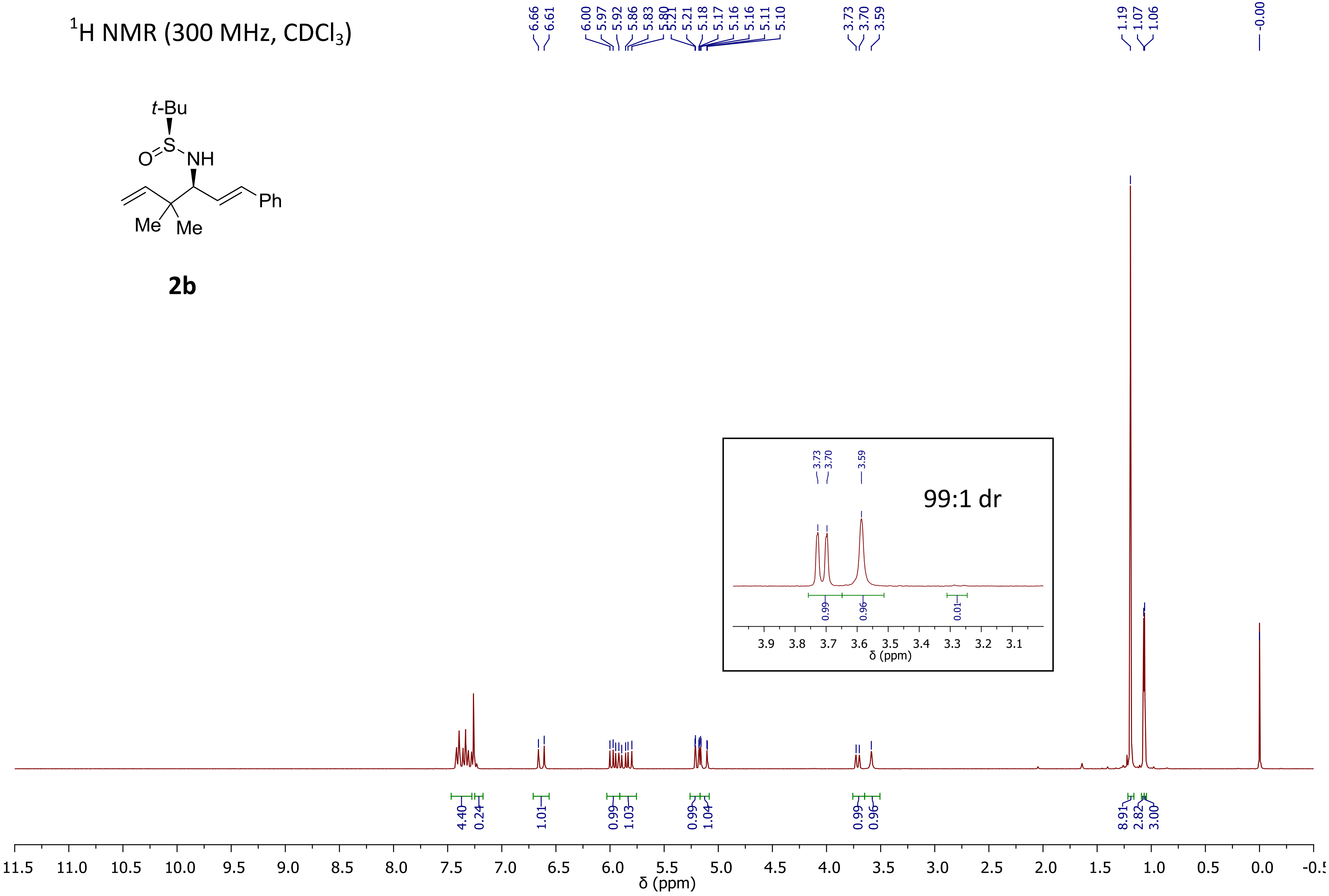


Following the general procedure of formation of MPA amides from amine **4k**, compound MPA-**4k** was obtained as a colorless oil:

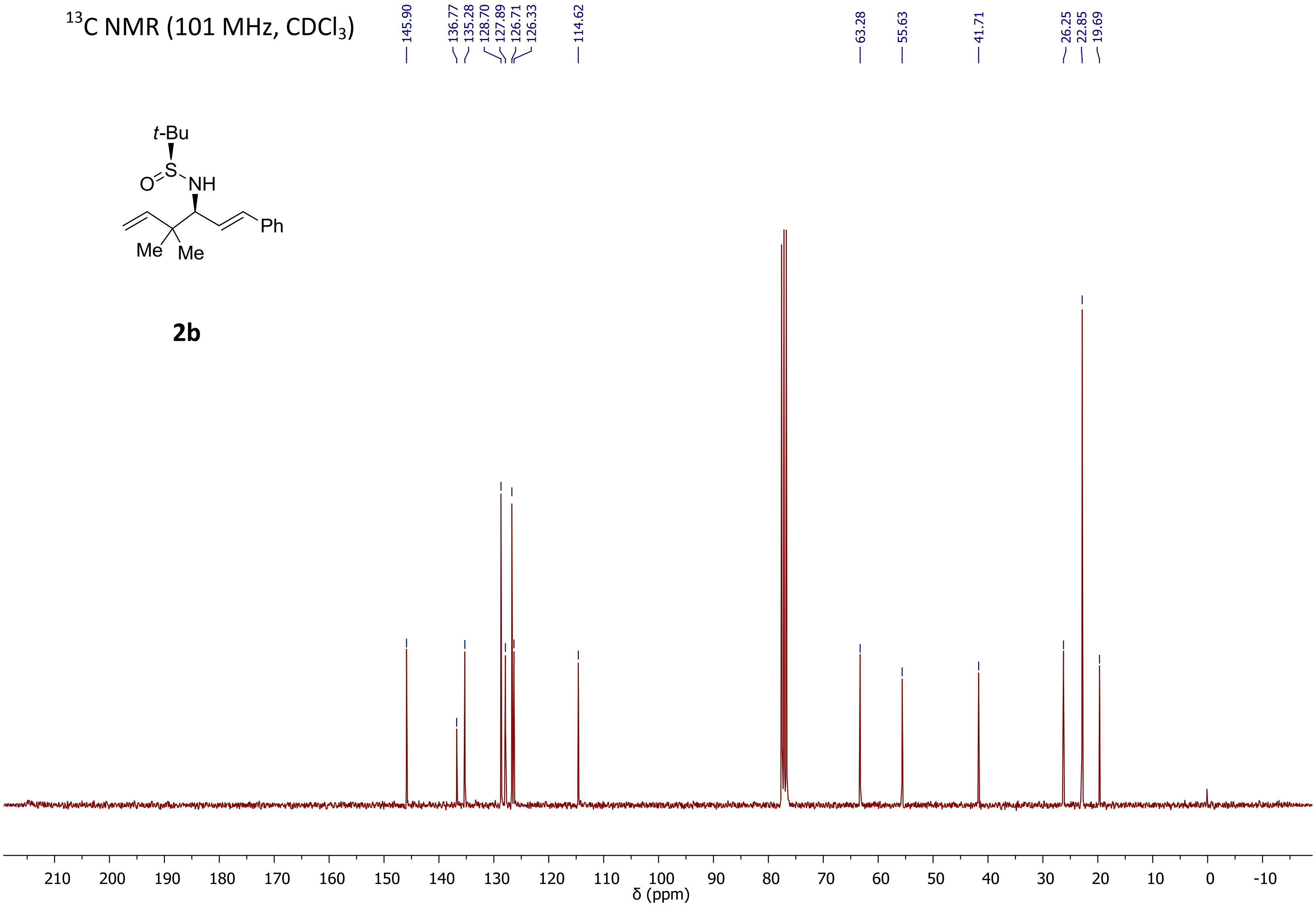
^{1}H NMR (400 MHz, CD_3CN) δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.43 – 7.23 (m, 6H), 5.12 (ddd, *J* = 7.2, 5.9, 1.4 Hz, 1H), 4.94 (q, *J* = 7.4 Hz, 1H), 4.64 (s, 1H), 3.39 (s, 3H), 2.54 (t, *J* = 7.2 Hz, 2H), 1.70 (s, 3H), 1.60 (s, 3H); *after the addition of 100 mg of Ba(ClO_4)$_2$*: ^{1}H NMR (400 MHz, CD_3CN) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50 – 7.28 (m, 6H), 4.96 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.84 (s, 1H), 4.79 (t, *J* = 6.8 Hz, 1H), 3.27 (s, 3H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.48 (s, 3H), 1.38 (s, 3H).



^{1}H NMR (300 MHz, $CDCl_3$)

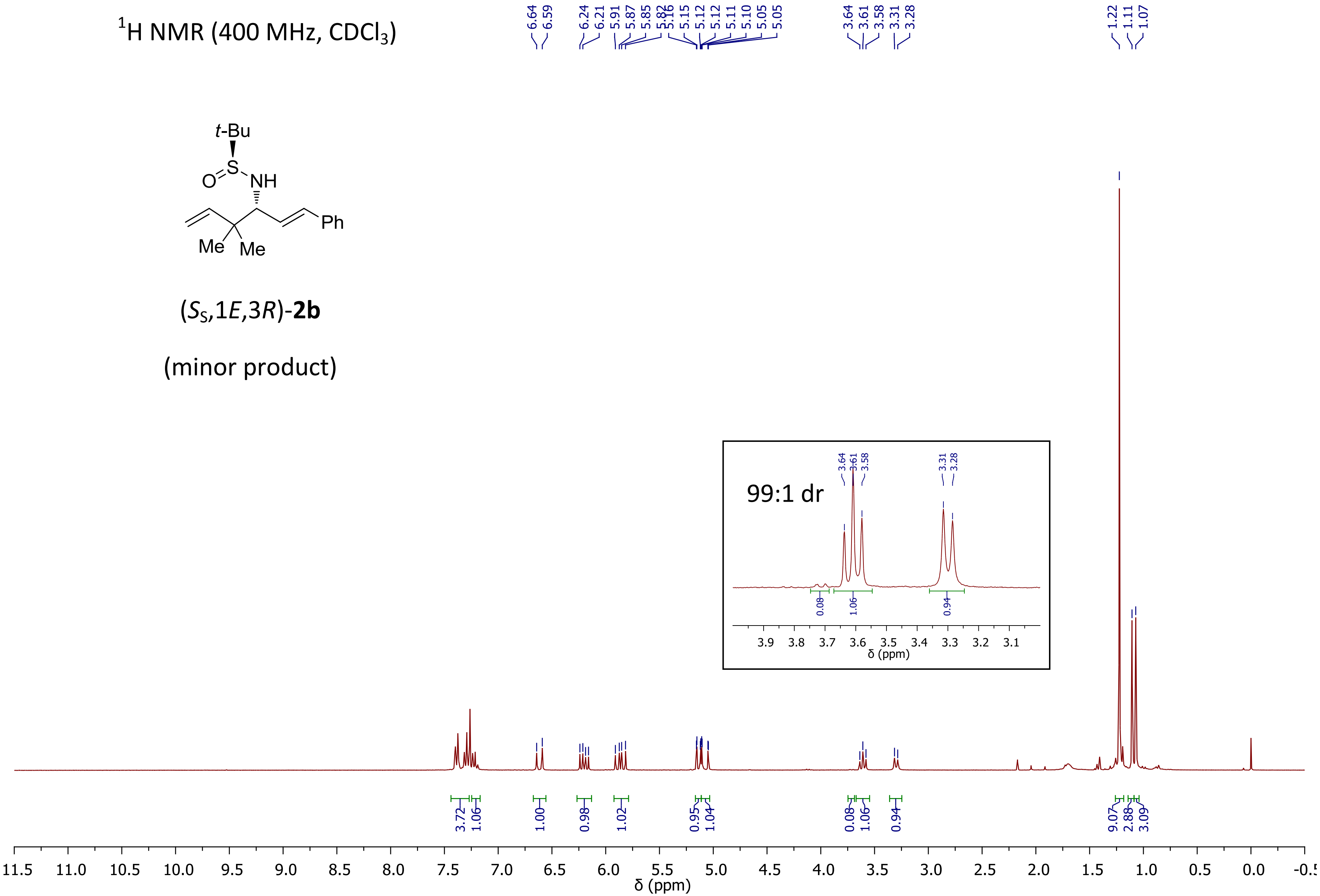


2b


^{13}C NMR (101 MHz, $CDCl_3$)
145.90
136.77
135.28
128.70
127.89
126.71
126.33
114.62
63.28
55.63
41.71
26.25
22.85
19.69
t-Bu
S
O
NH
Ph
Me
Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
δ (ppm)

2b

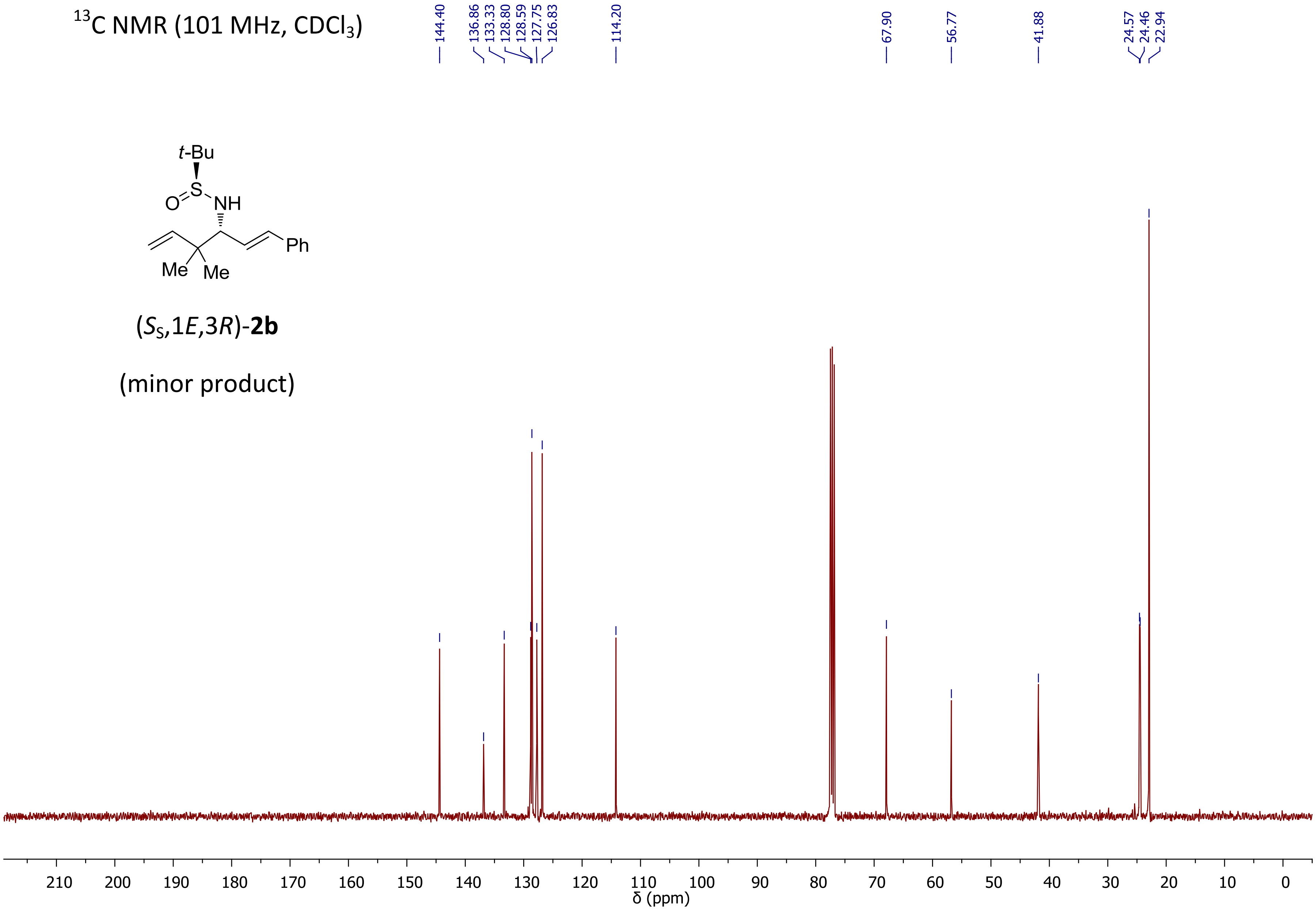
^{1}H NMR (400 MHz, $CDCl_3$)



(S_S,1*E*,3*R*)-**2b**

(minor product)

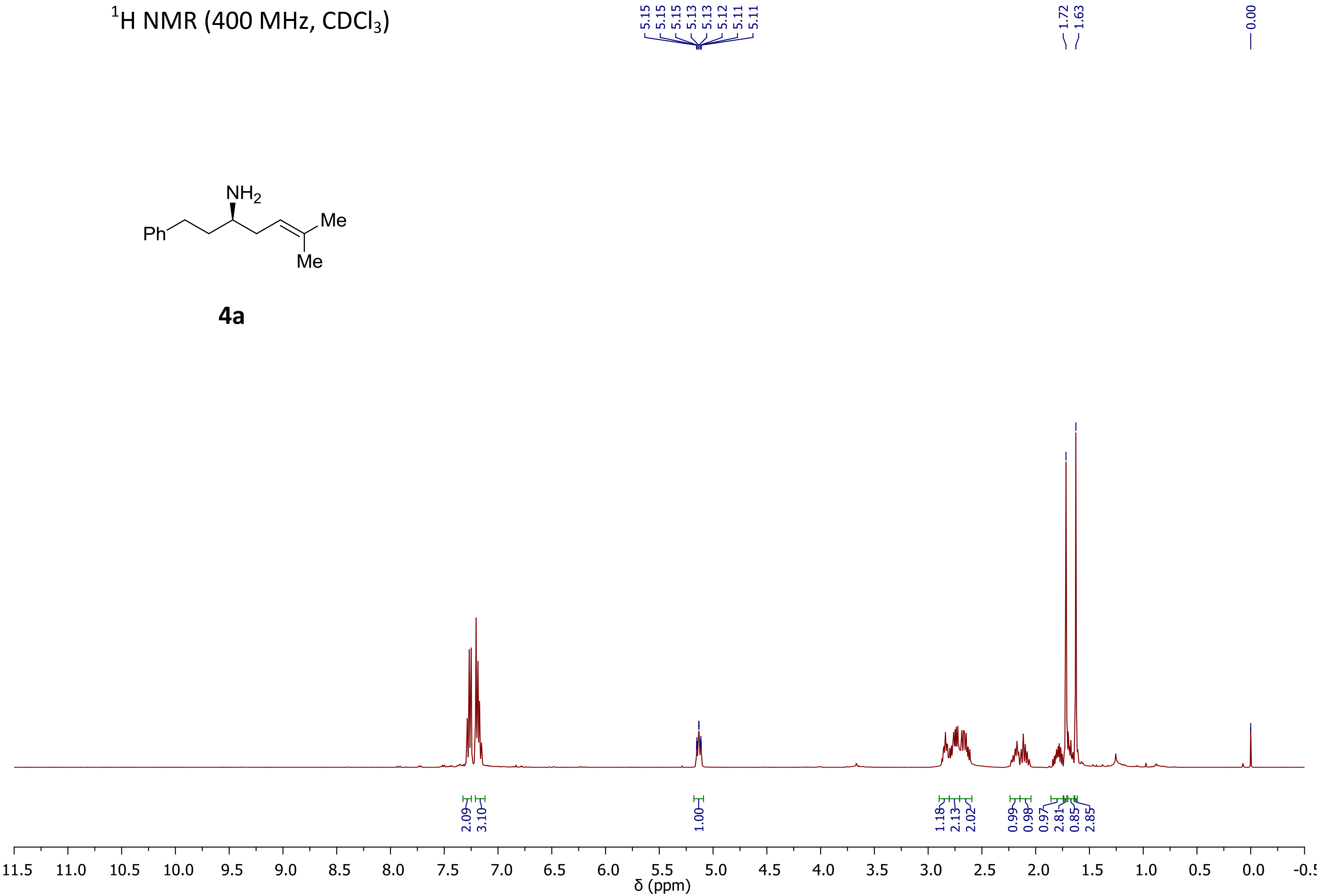
^{13}C NMR (101 MHz, CDCl$_3$)

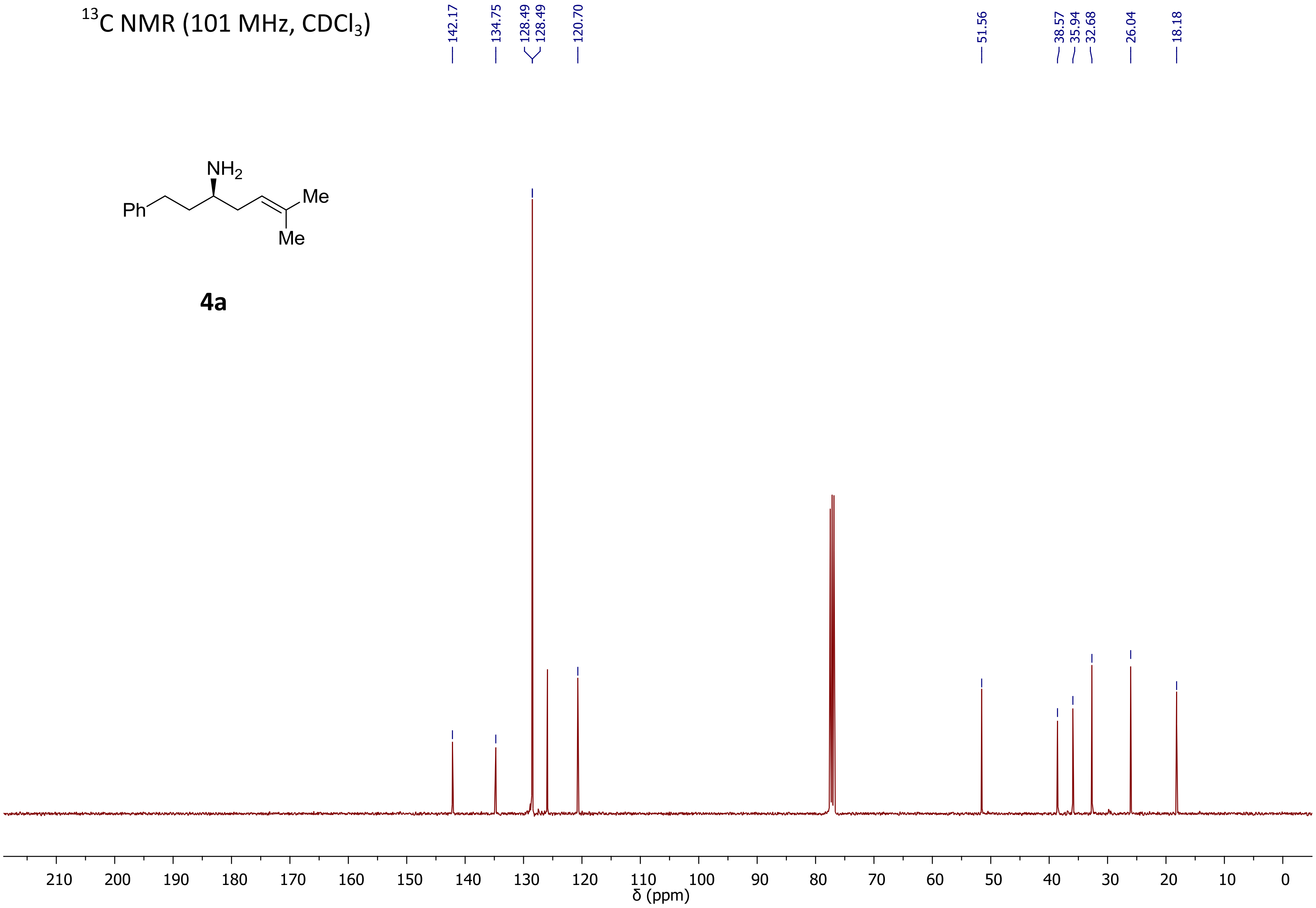


(S_S,1E,3R)-**2b**

(minor product)

^{1}H NMR (400 MHz, CDCl$_3$)

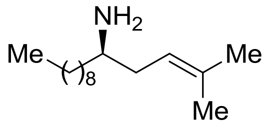




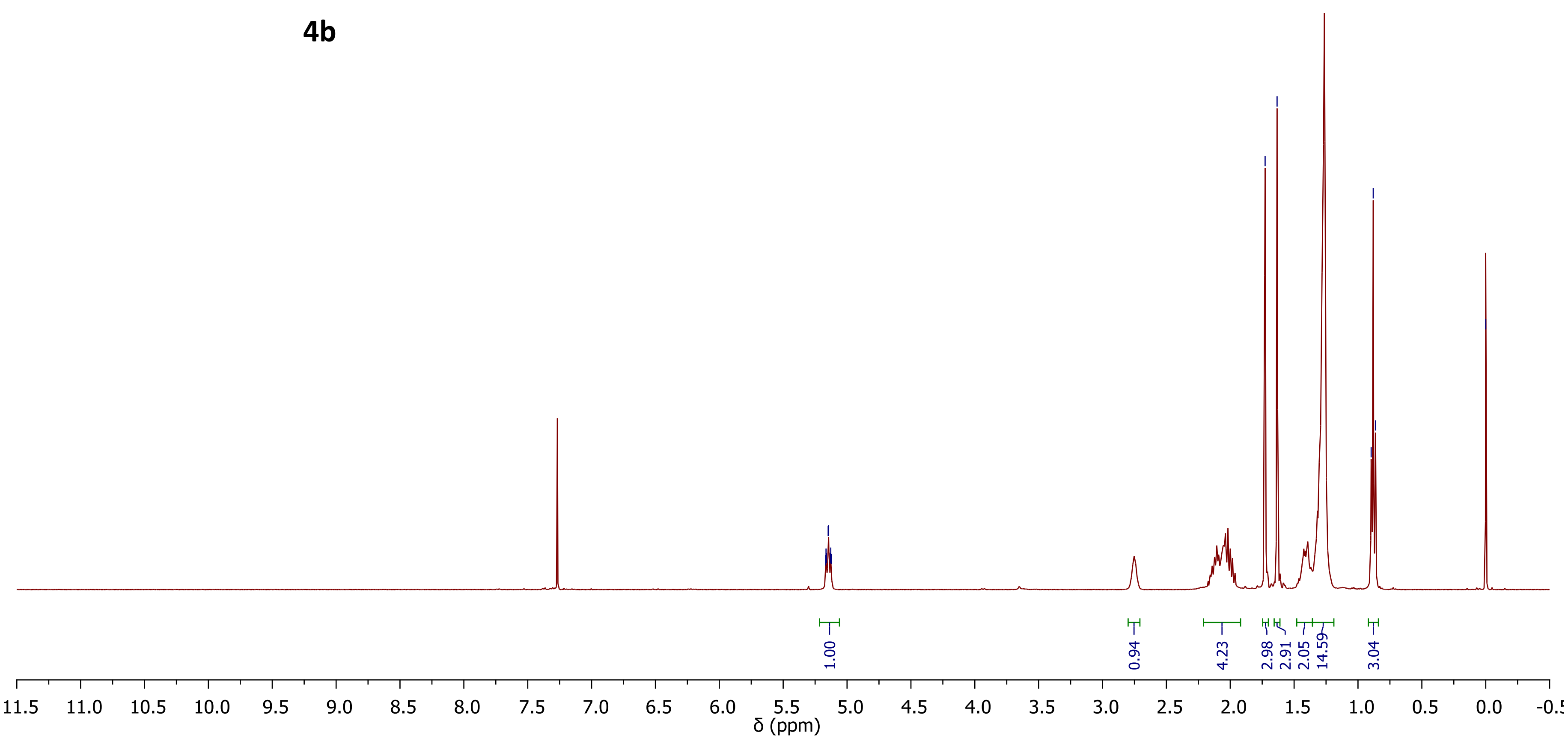
^{13}C NMR (101 MHz, CDCl$_3$)

4a

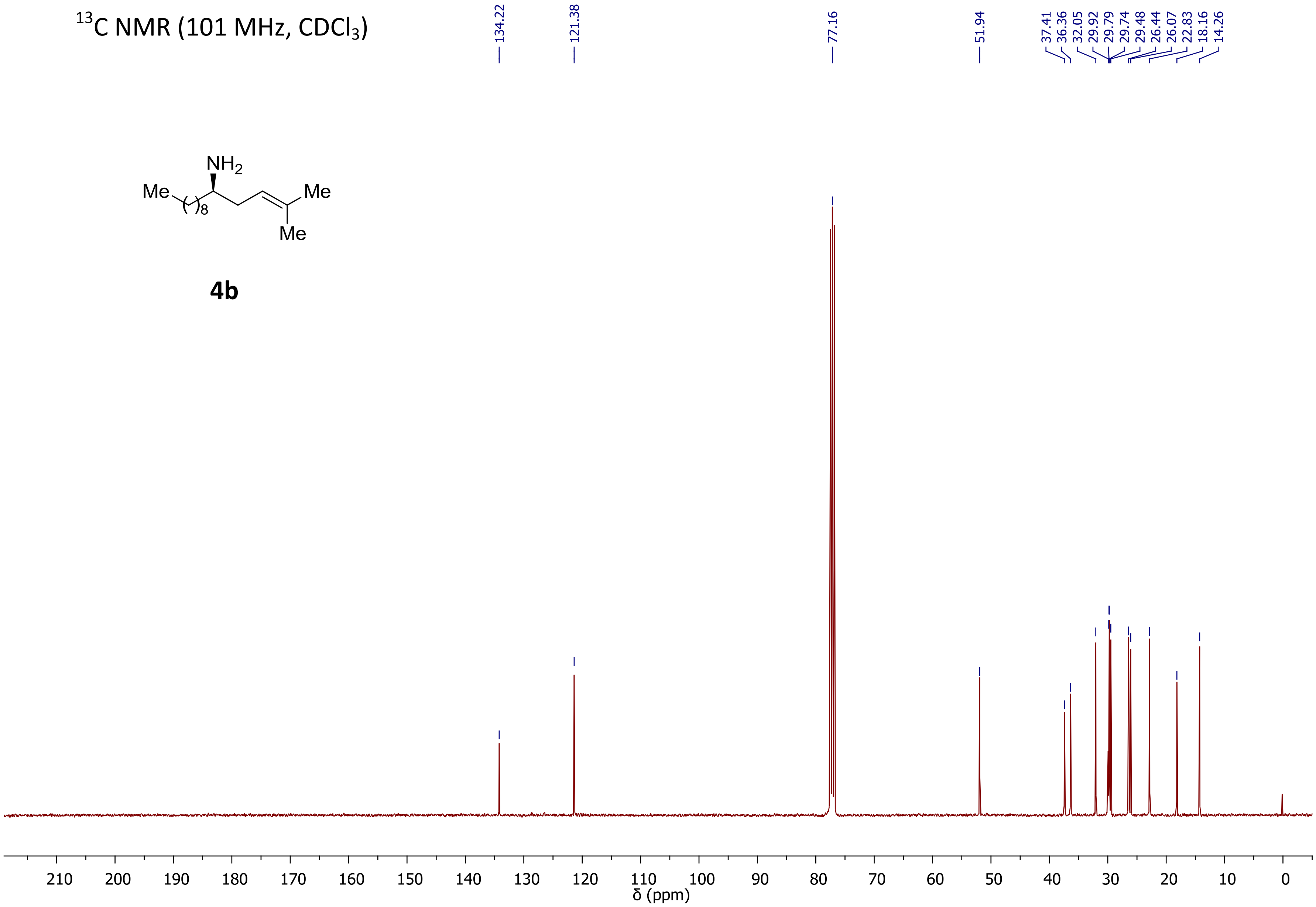
^{1}H NMR (400 MHz, CDCl$_3$)



4b

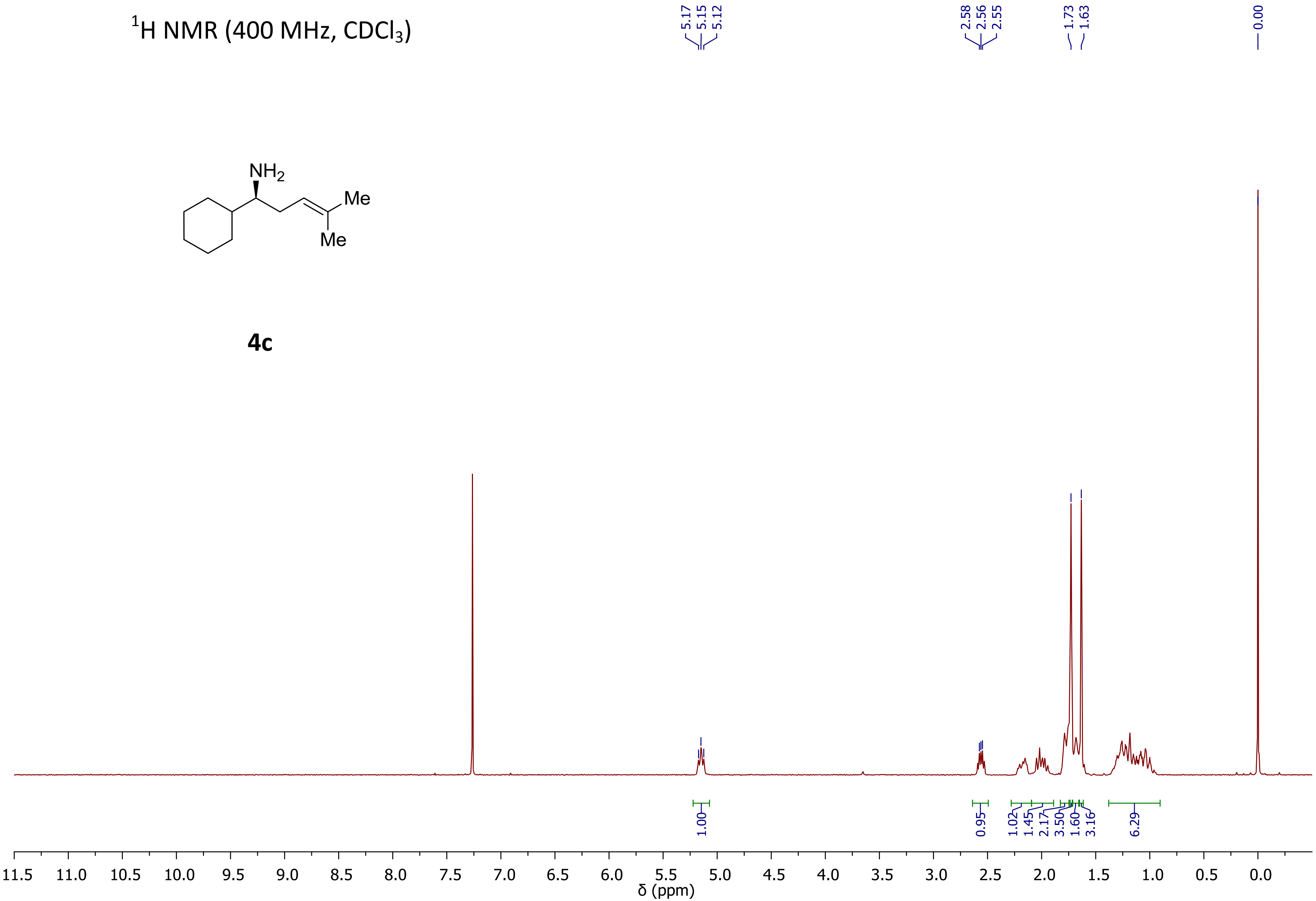


^{13}C NMR (101 MHz, CDCl$_3$)

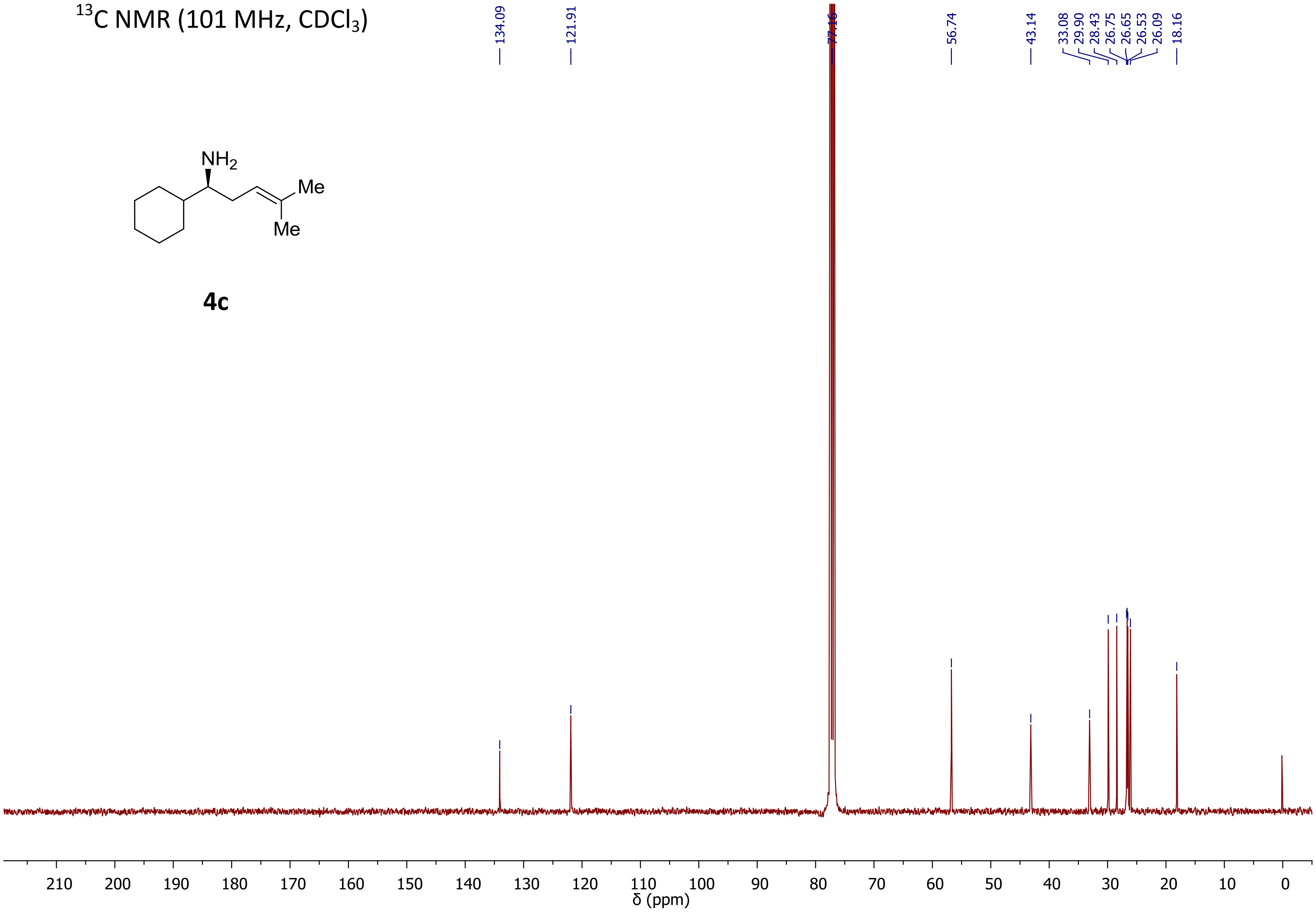


4b

^{1}H NMR (400 MHz, $CDCl_3$)

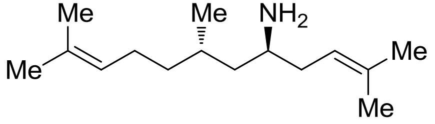


4c

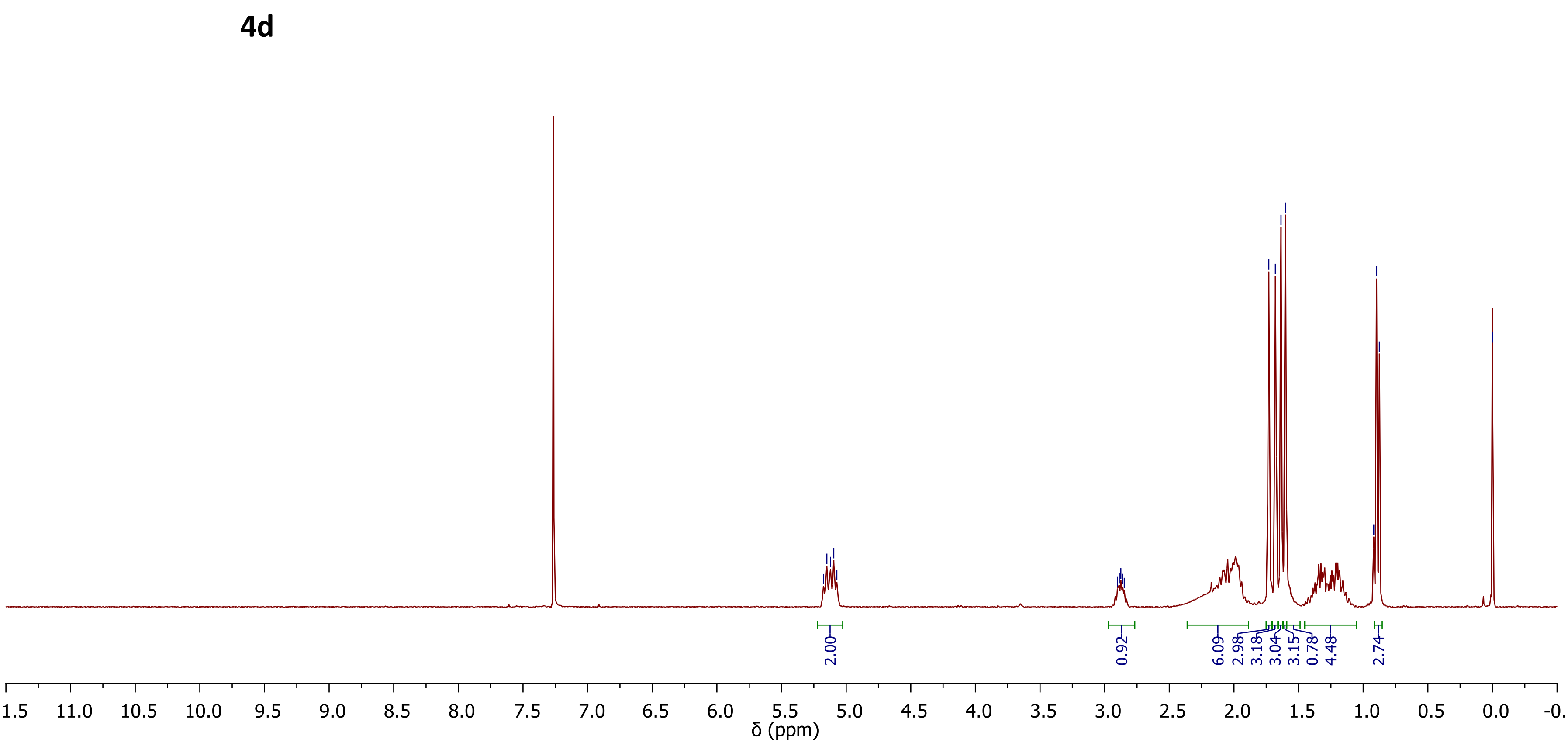

^{13}C NMR (101 MHz, $CDCl_3$)
NH2
Me
Me
134.09
121.91
77.16
56.74
43.14
33.08
29.90
28.43
26.75
26.65
26.53
26.09
18.16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

4c

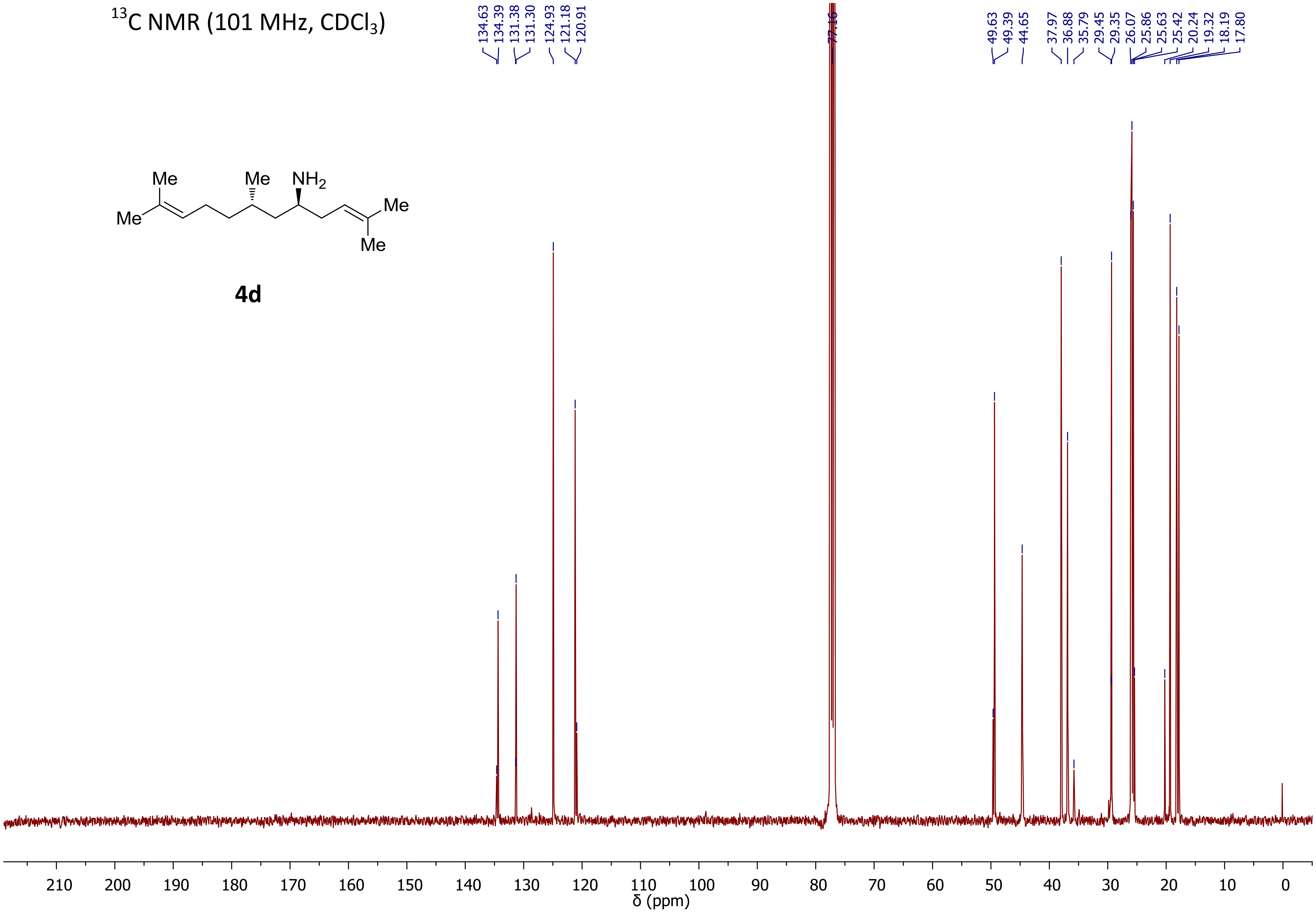
^{1}H NMR (300 MHz, $CDCl_3$)



4d

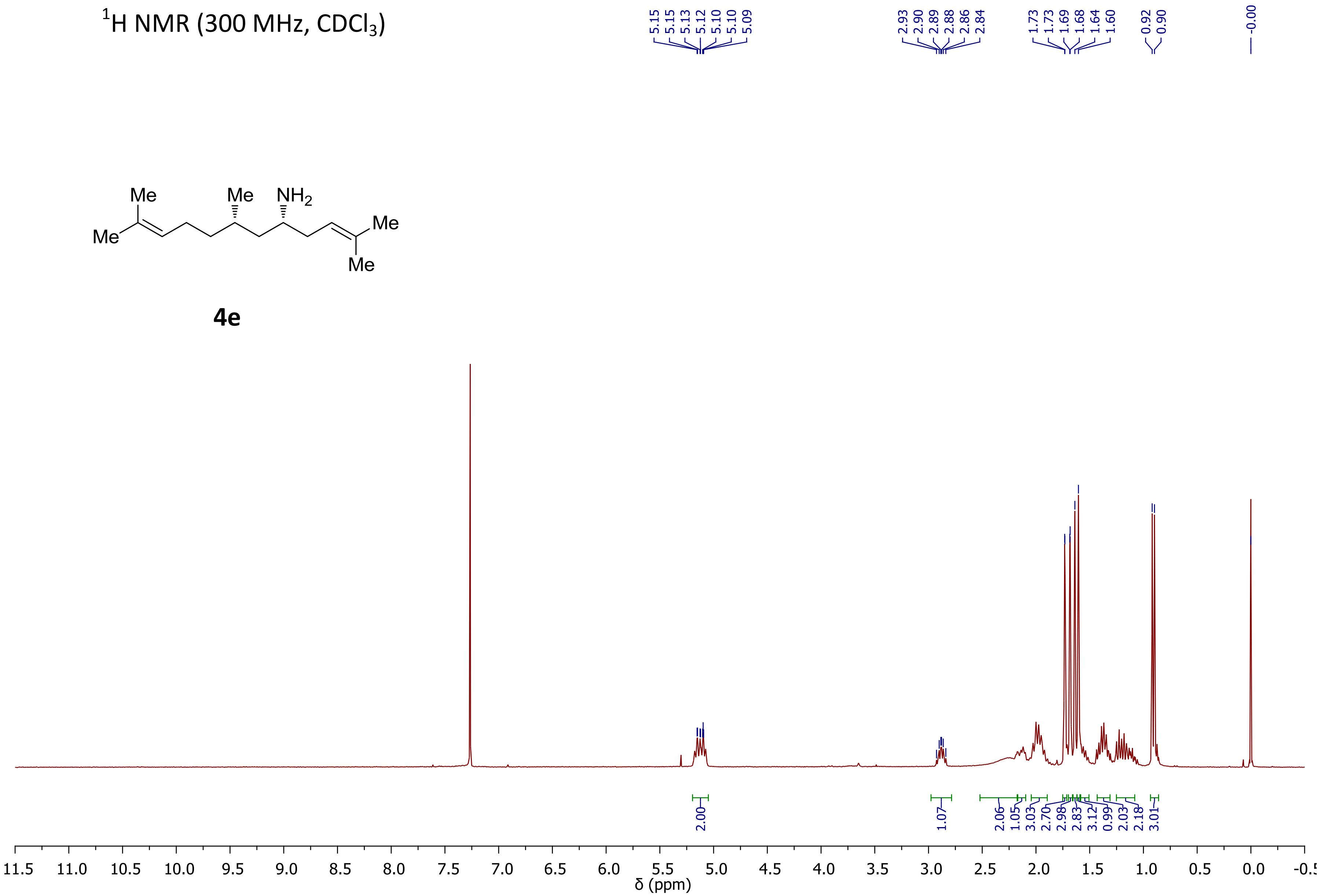


^{13}C NMR (101 MHz, $CDCl_3$)

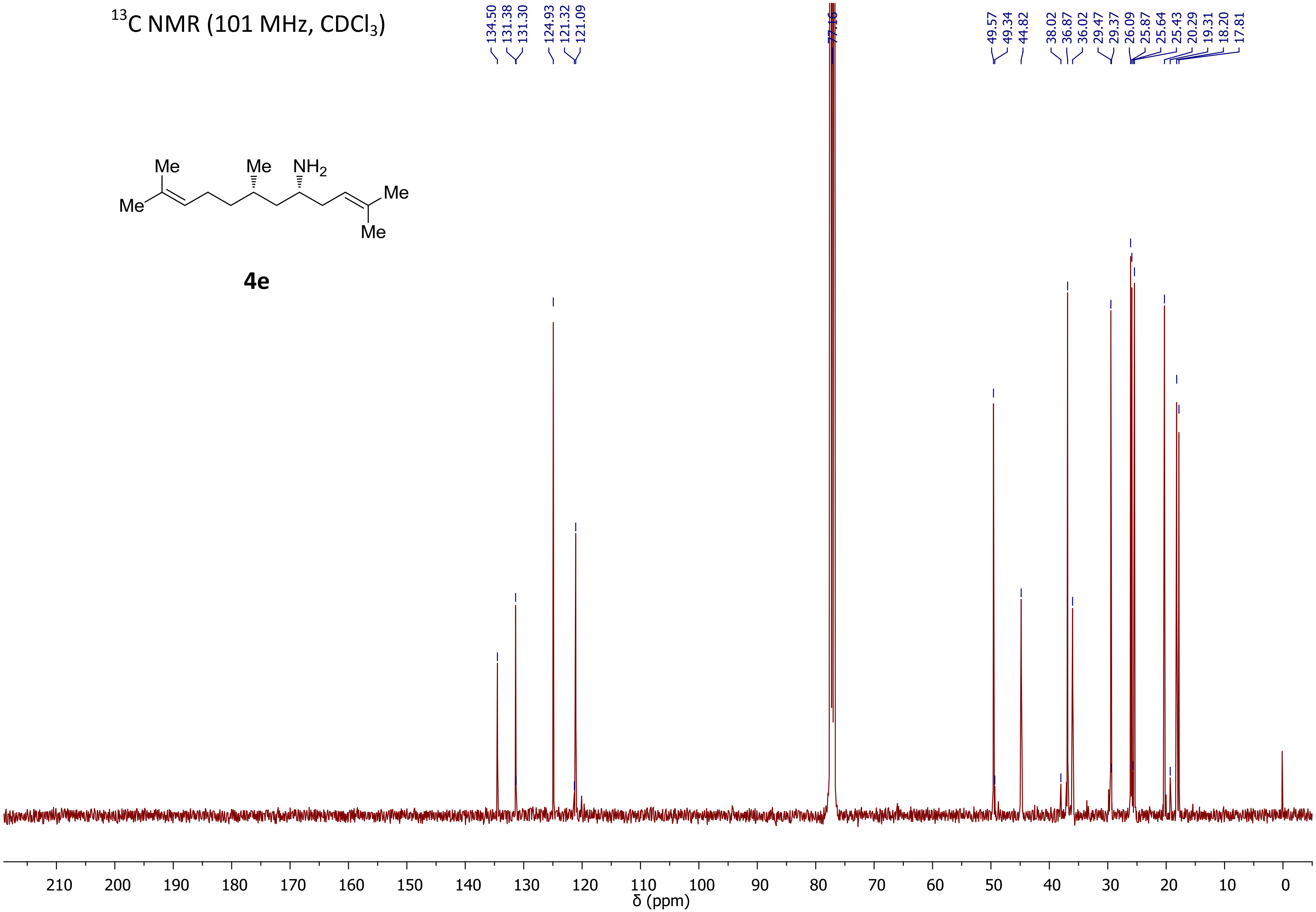


4d

^{1}H NMR (300 MHz, $CDCl_3$)



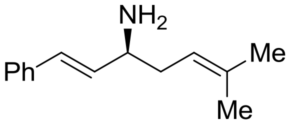
4e



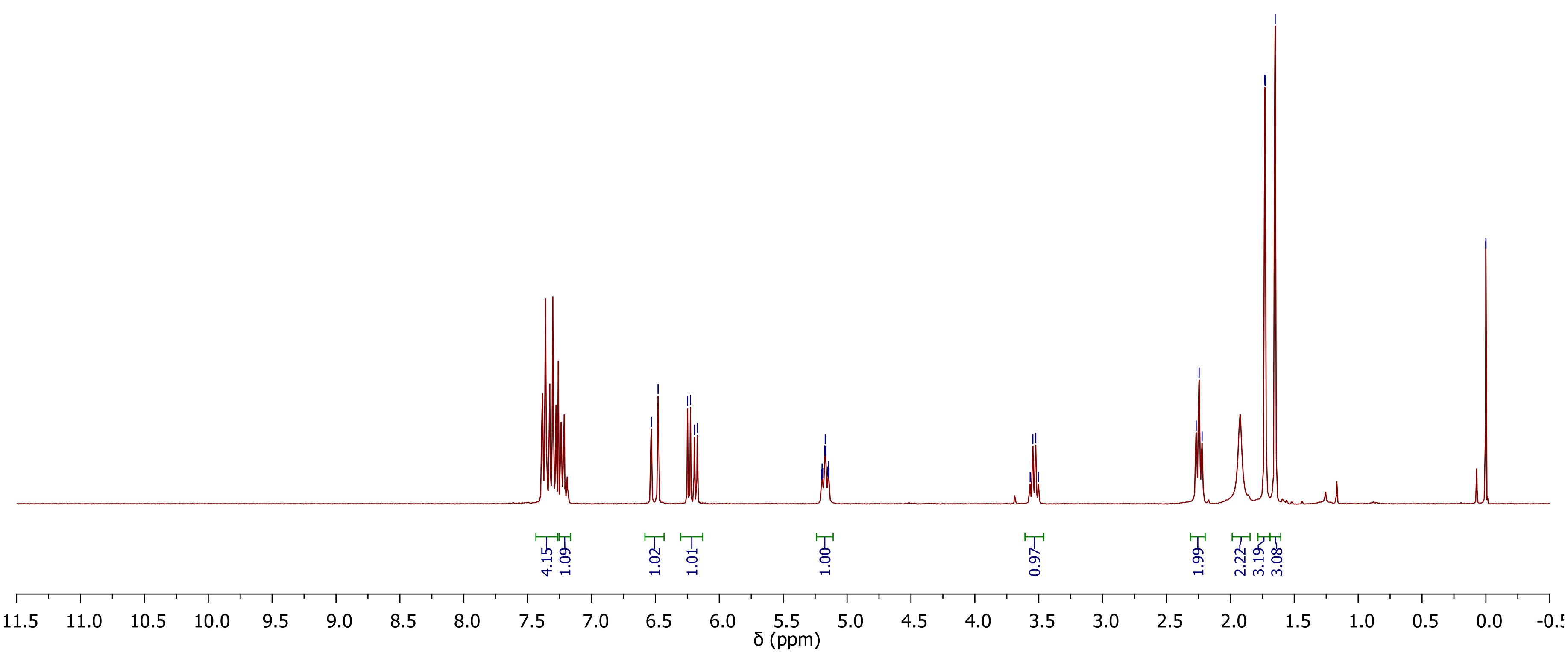
^{13}C NMR (101 MHz, CDCl$_3$)

4e

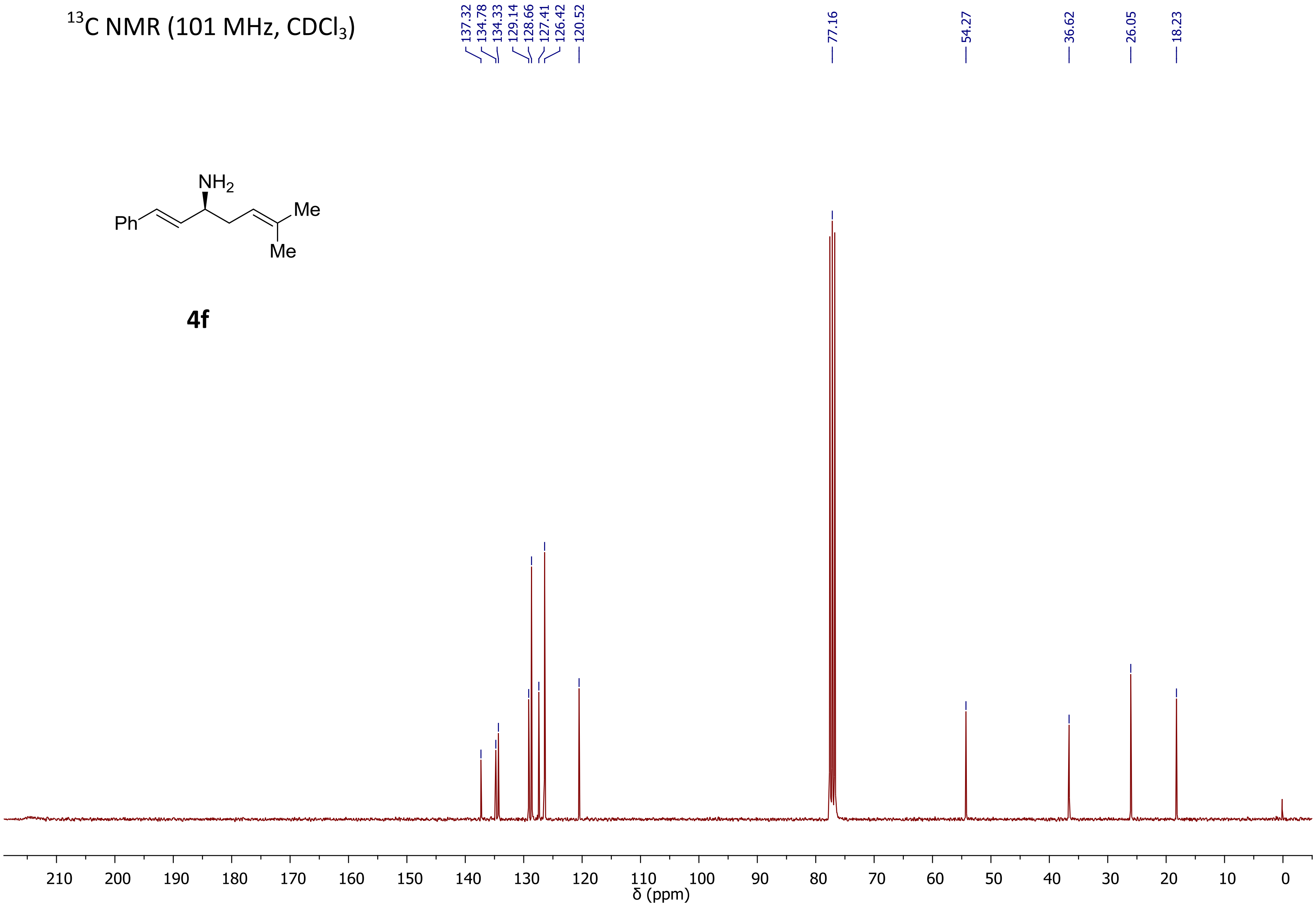
^{1}H NMR (400 MHz, $CDCl_3$)



4f



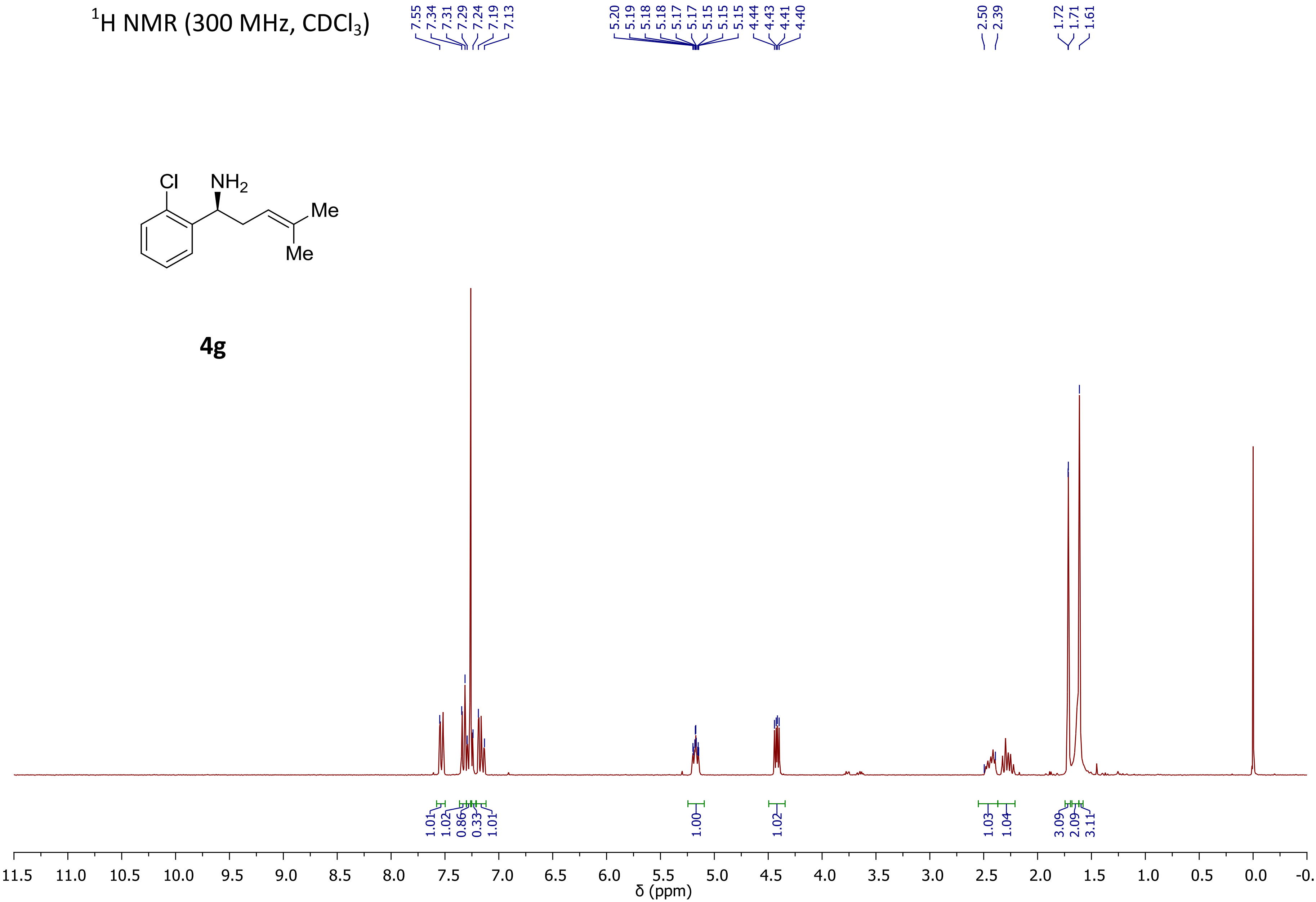
^{13}C NMR (101 MHz, CDCl$_3$)



4f

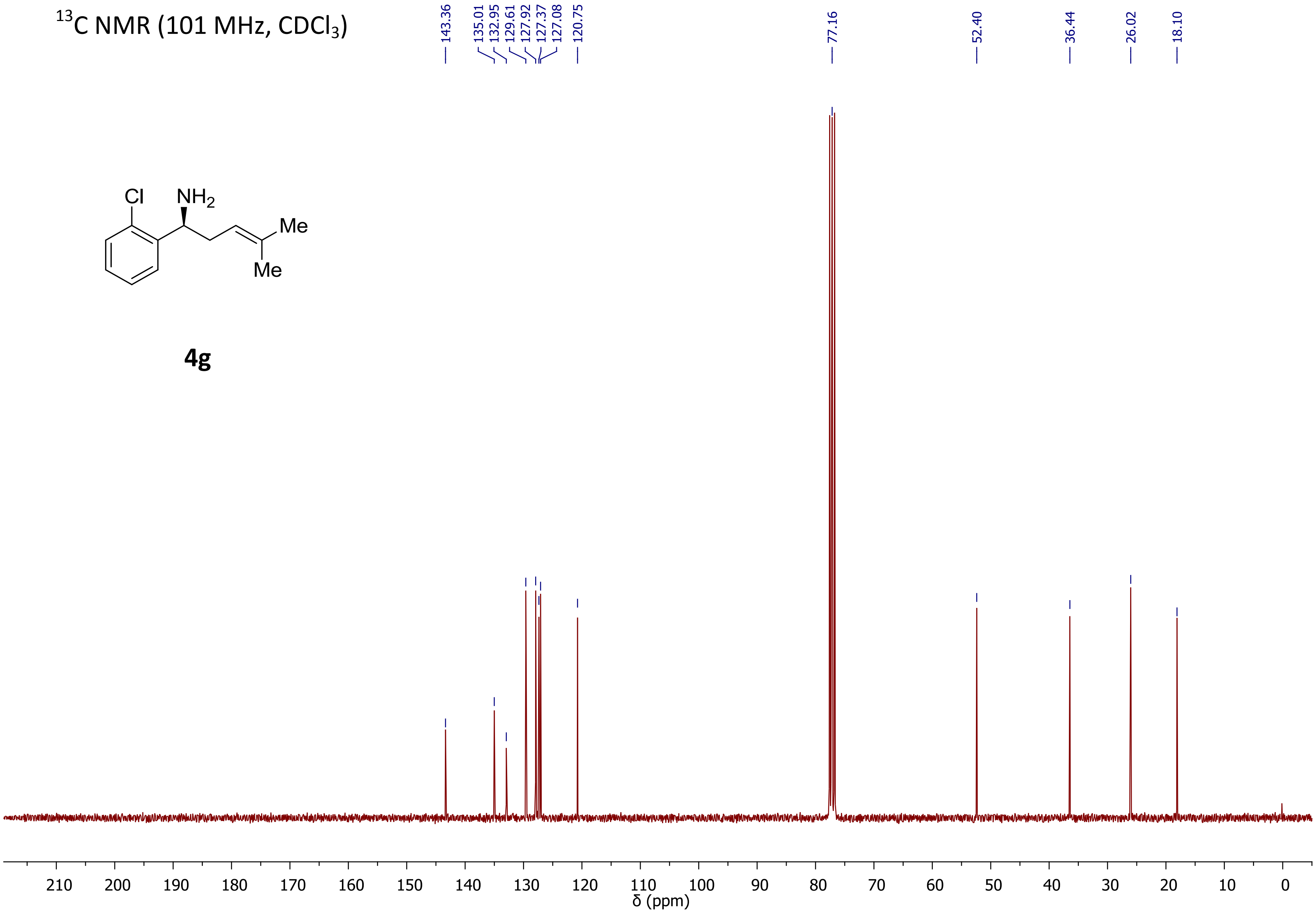
^{1}H NMR (300 MHz, $CDCl_3$)

4g



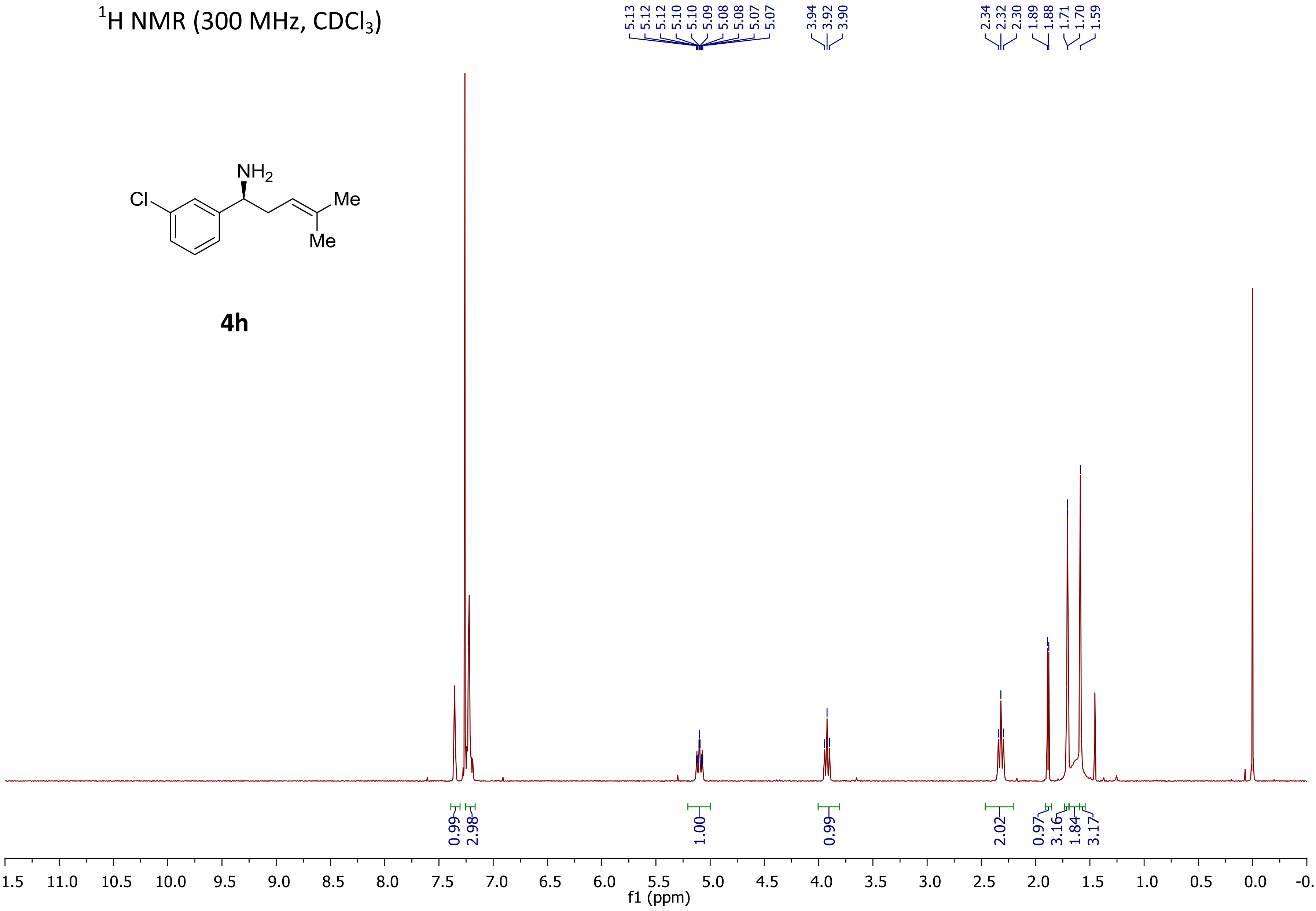
^{13}C NMR (101 MHz, CDCl$_3$)

4g

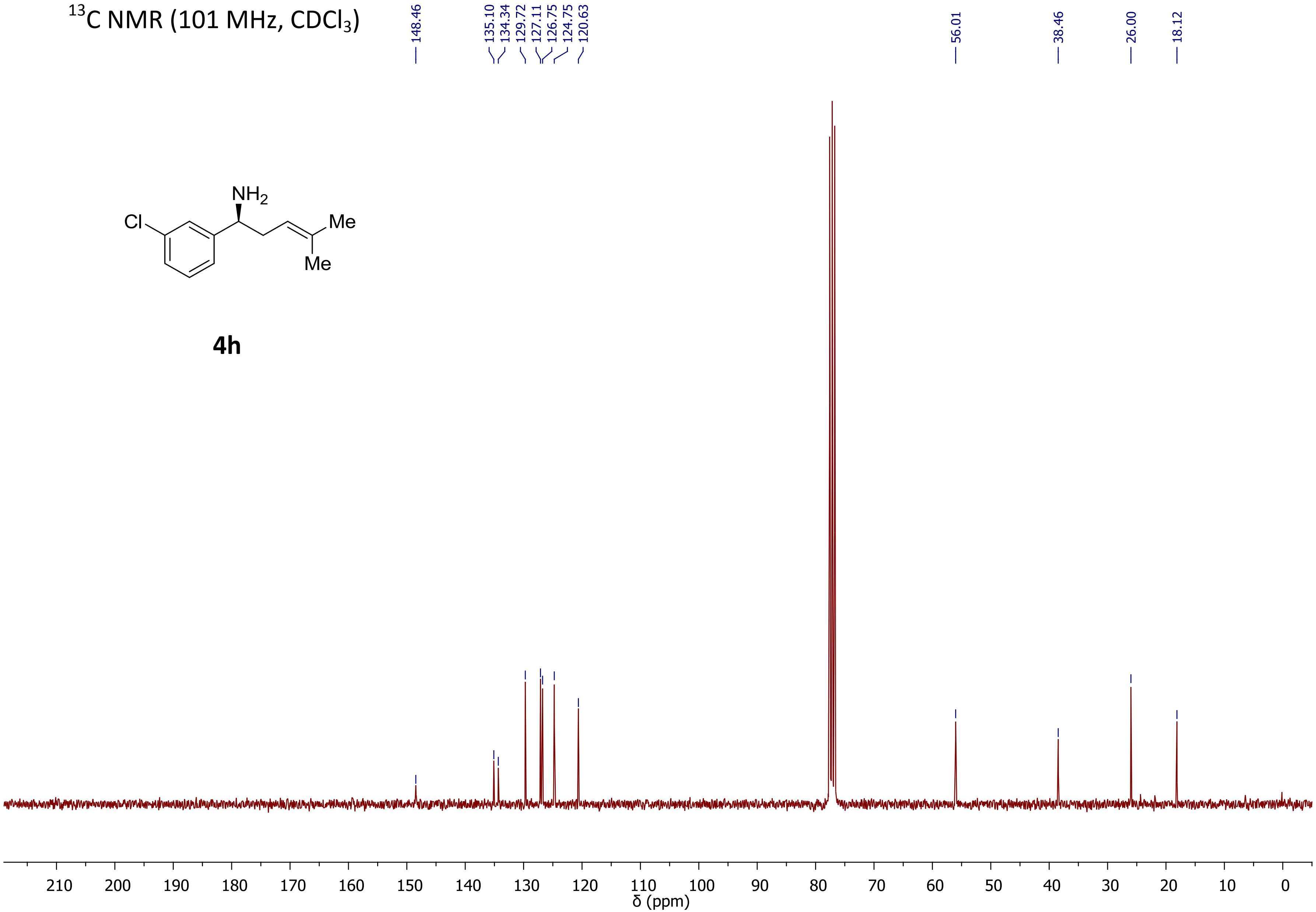


^{1}H NMR (300 MHz, $CDCl_3$)

4h

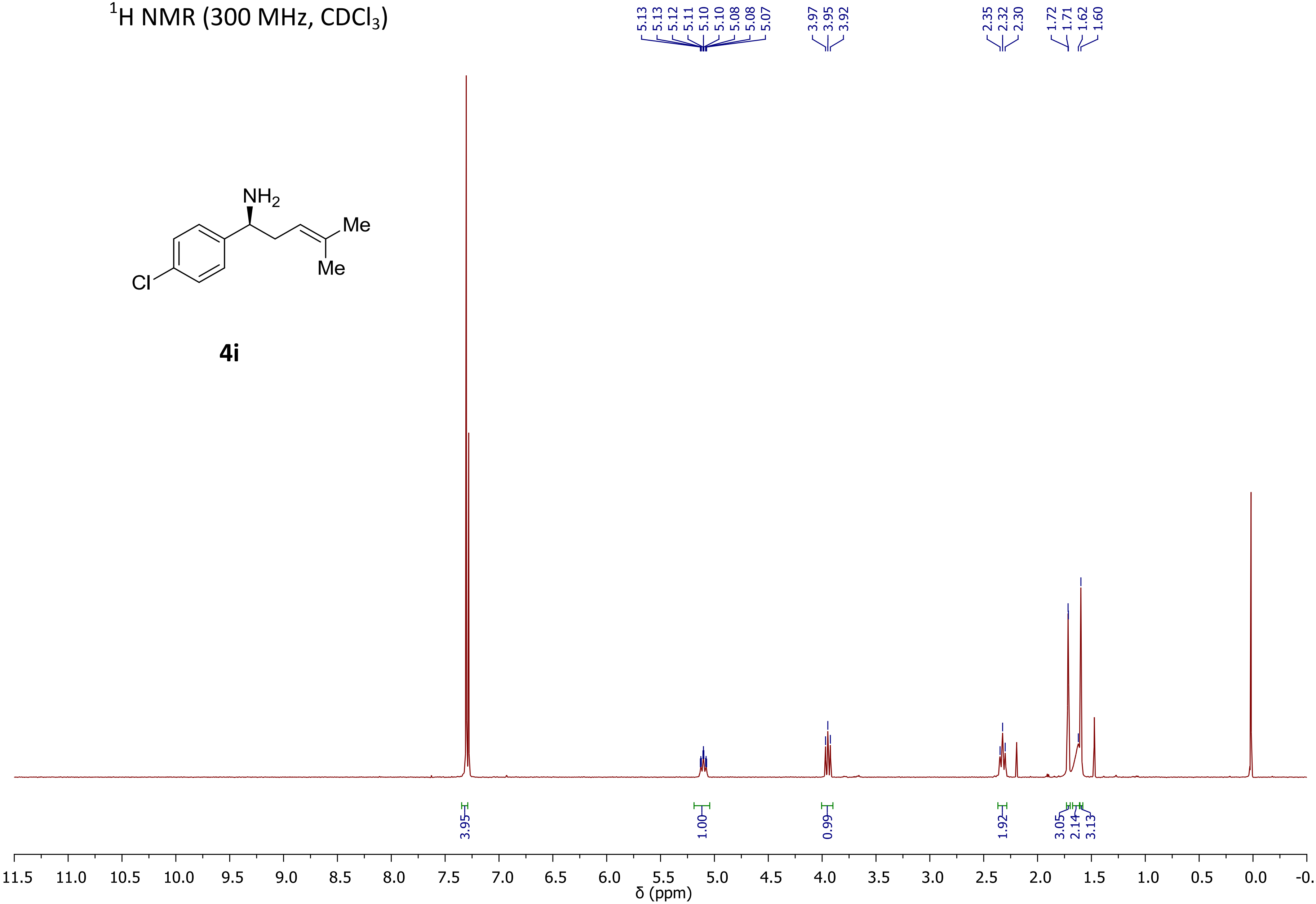


^{13}C NMR (101 MHz, $CDCl_3$)



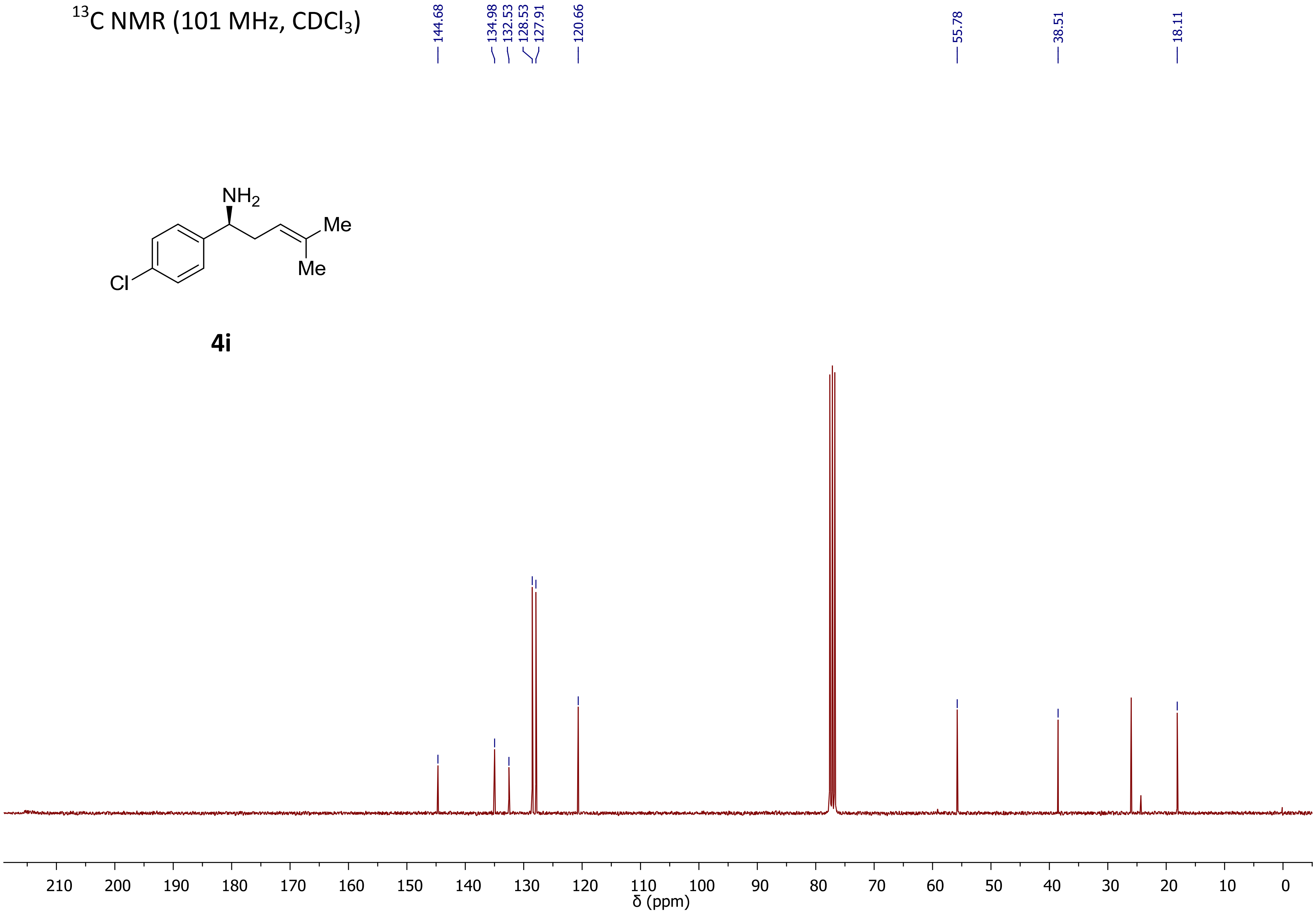
4h

^{1}H NMR (300 MHz, $CDCl_3$)



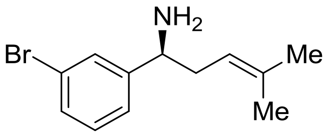
4i

^{13}C NMR (101 MHz, $CDCl_3$)

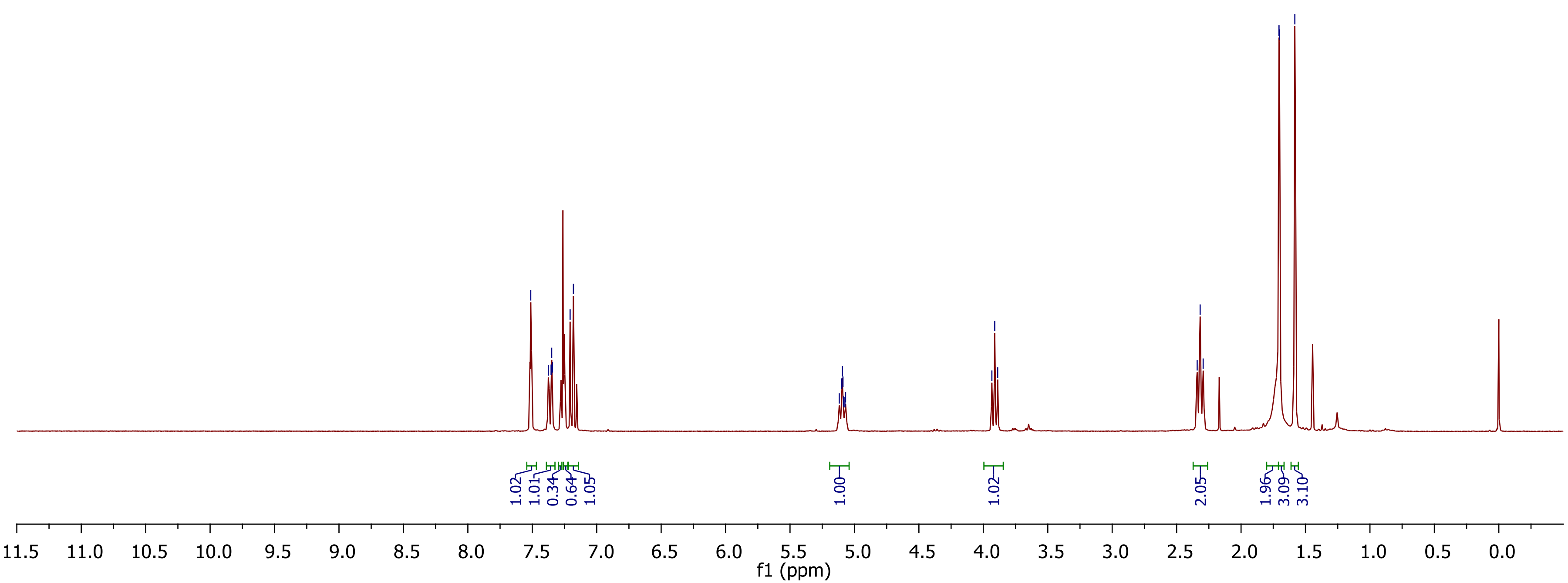


4i

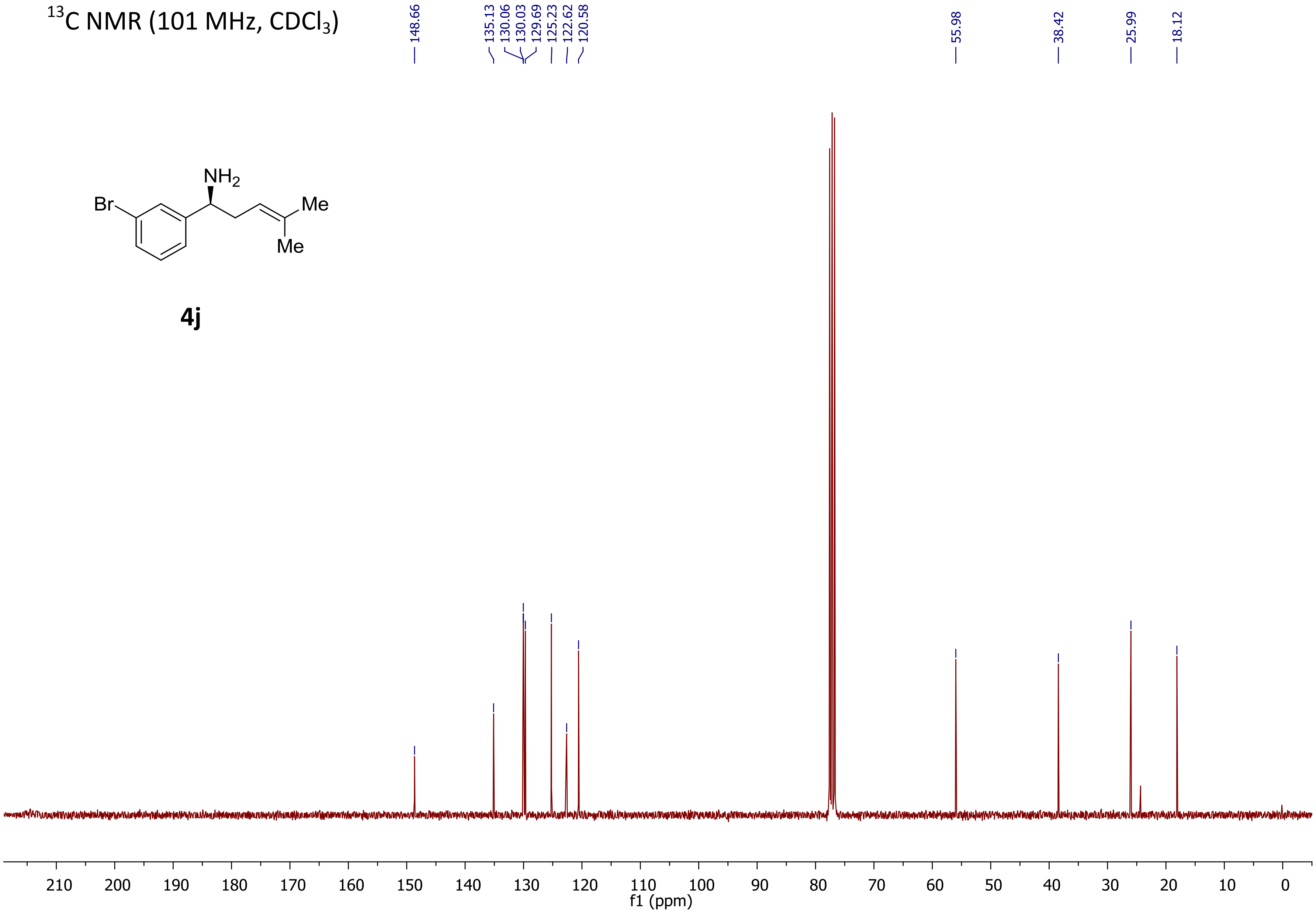
^{1}H NMR (300 MHz, CDCl$_3$)



4j

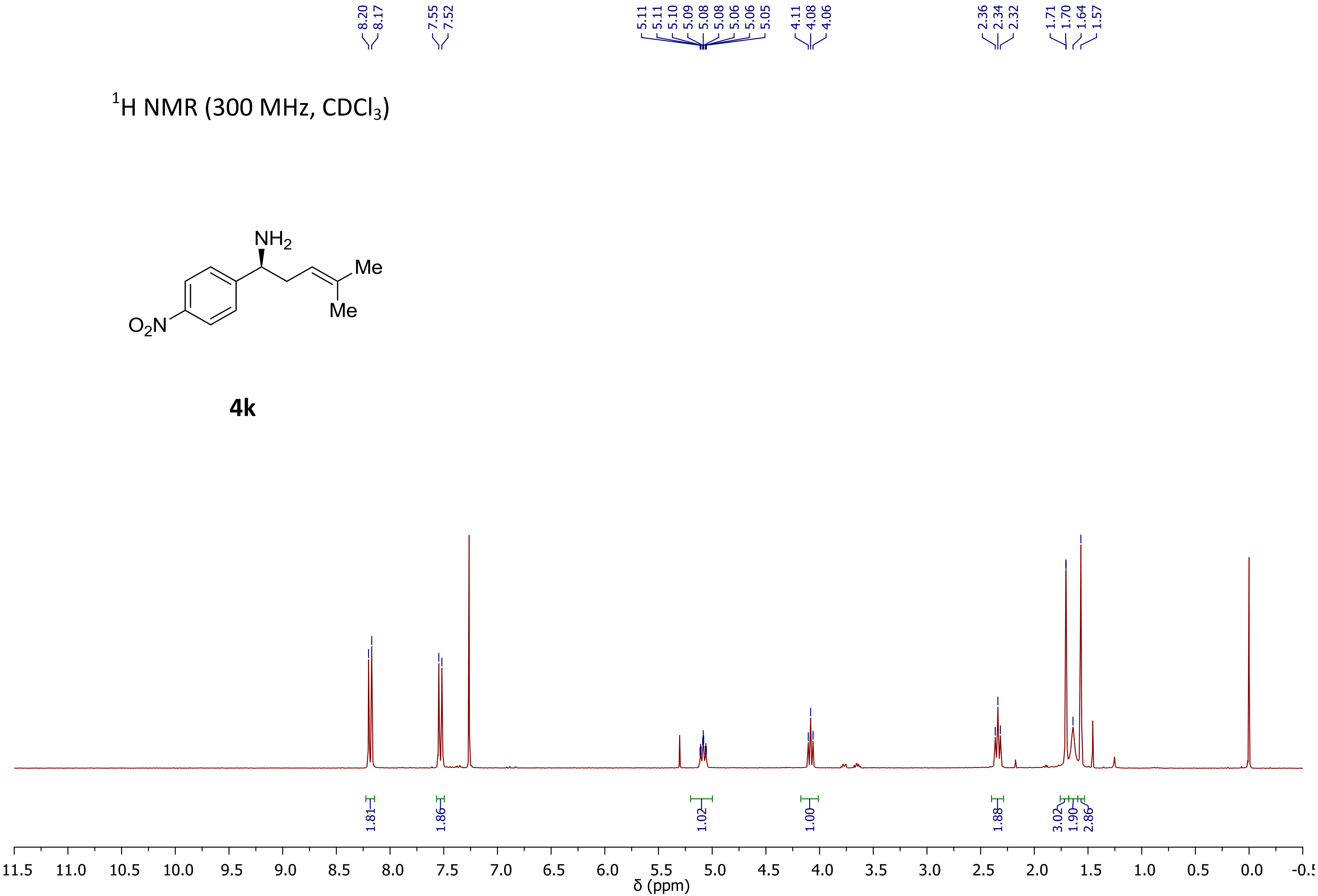


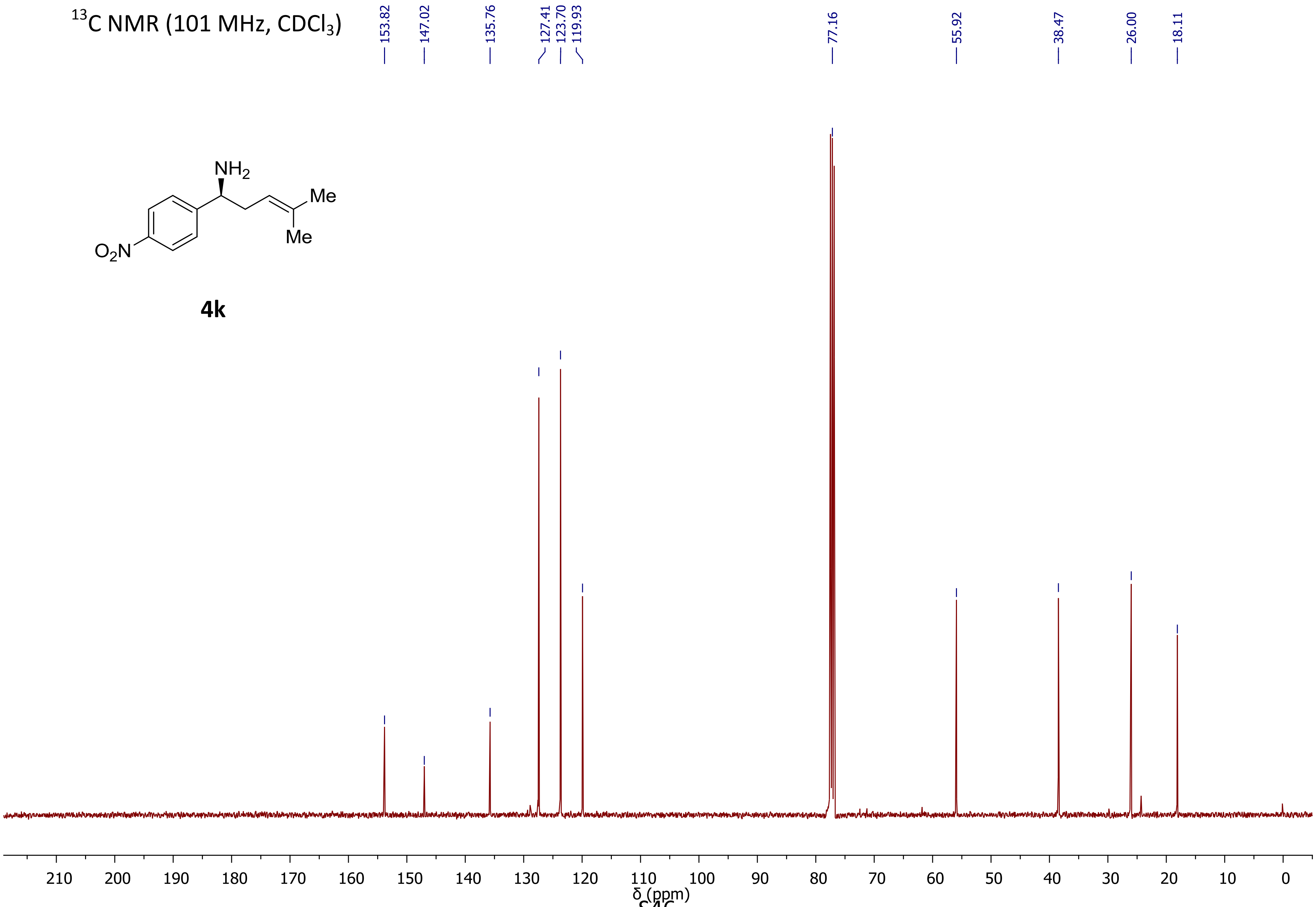
^{13}C NMR (101 MHz, CDCl$_3$)



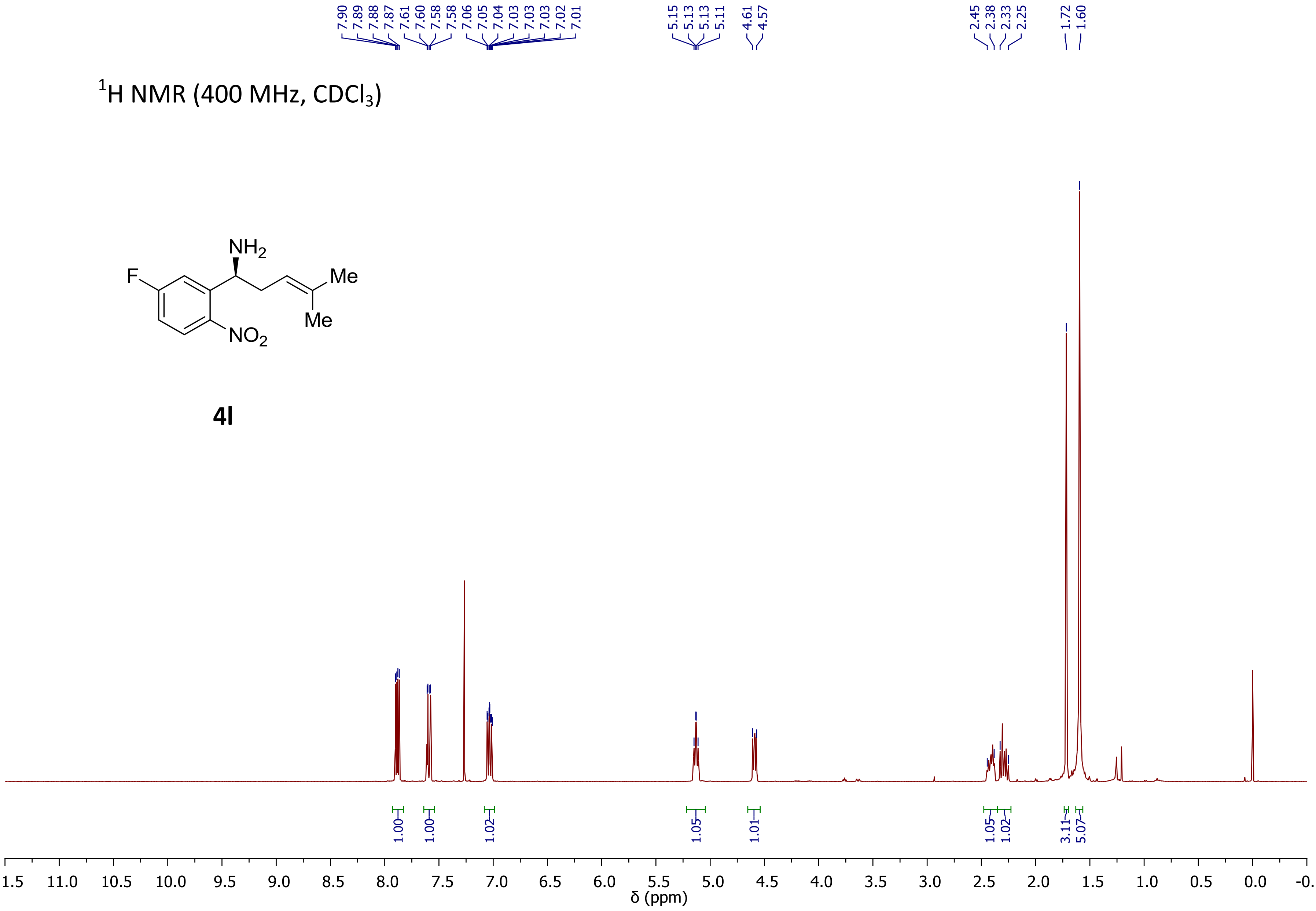
4j

^{1}H NMR (300 MHz, $CDCl_3$)

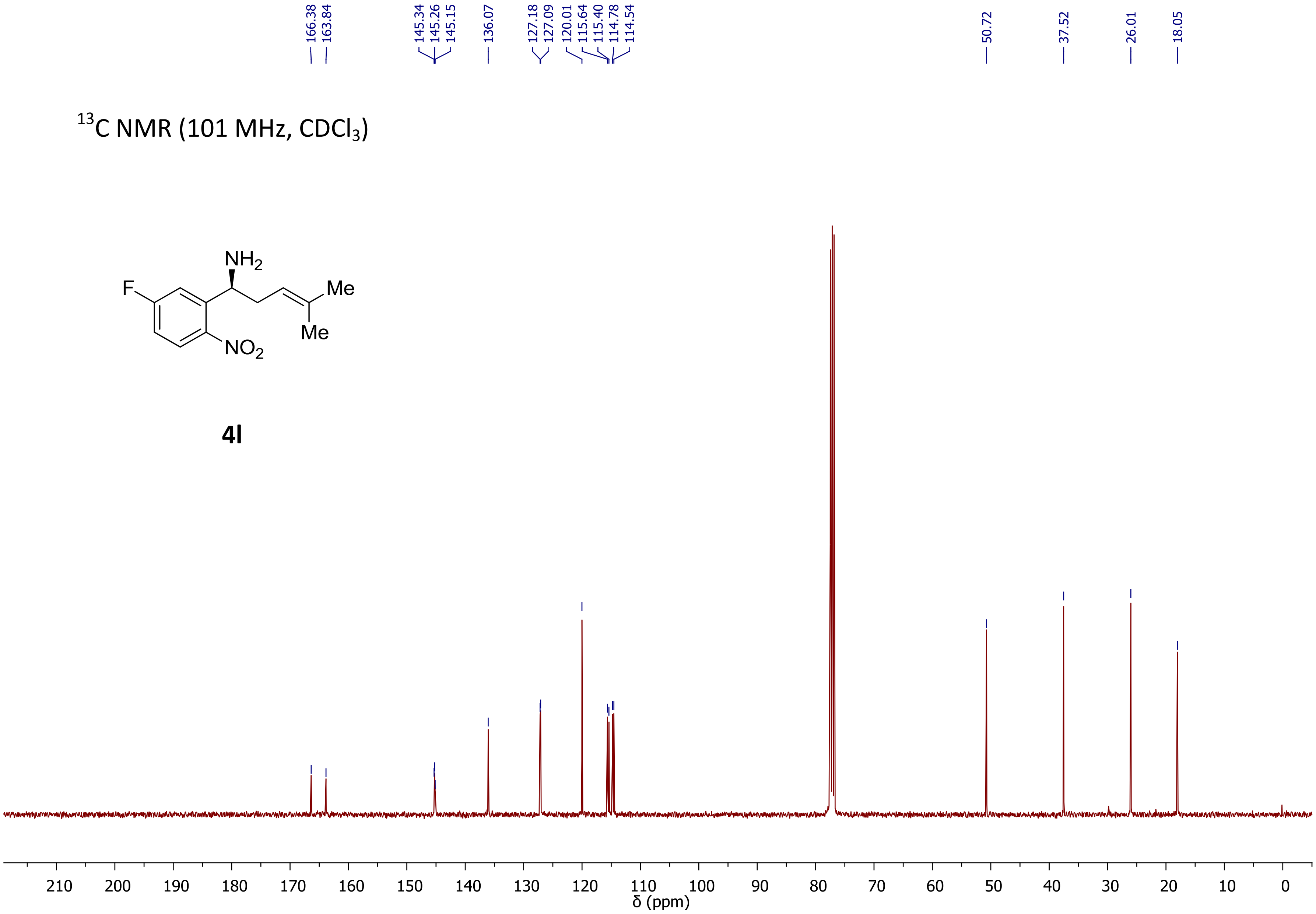



^{13}C NMR (101 MHz, CDCl$_3$)
153.82
147.02
135.76
127.41
123.70
119.93
77.16
55.92
38.47
26.00
18.11
NH$_2$
Me
Me
O$_2$N
4k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



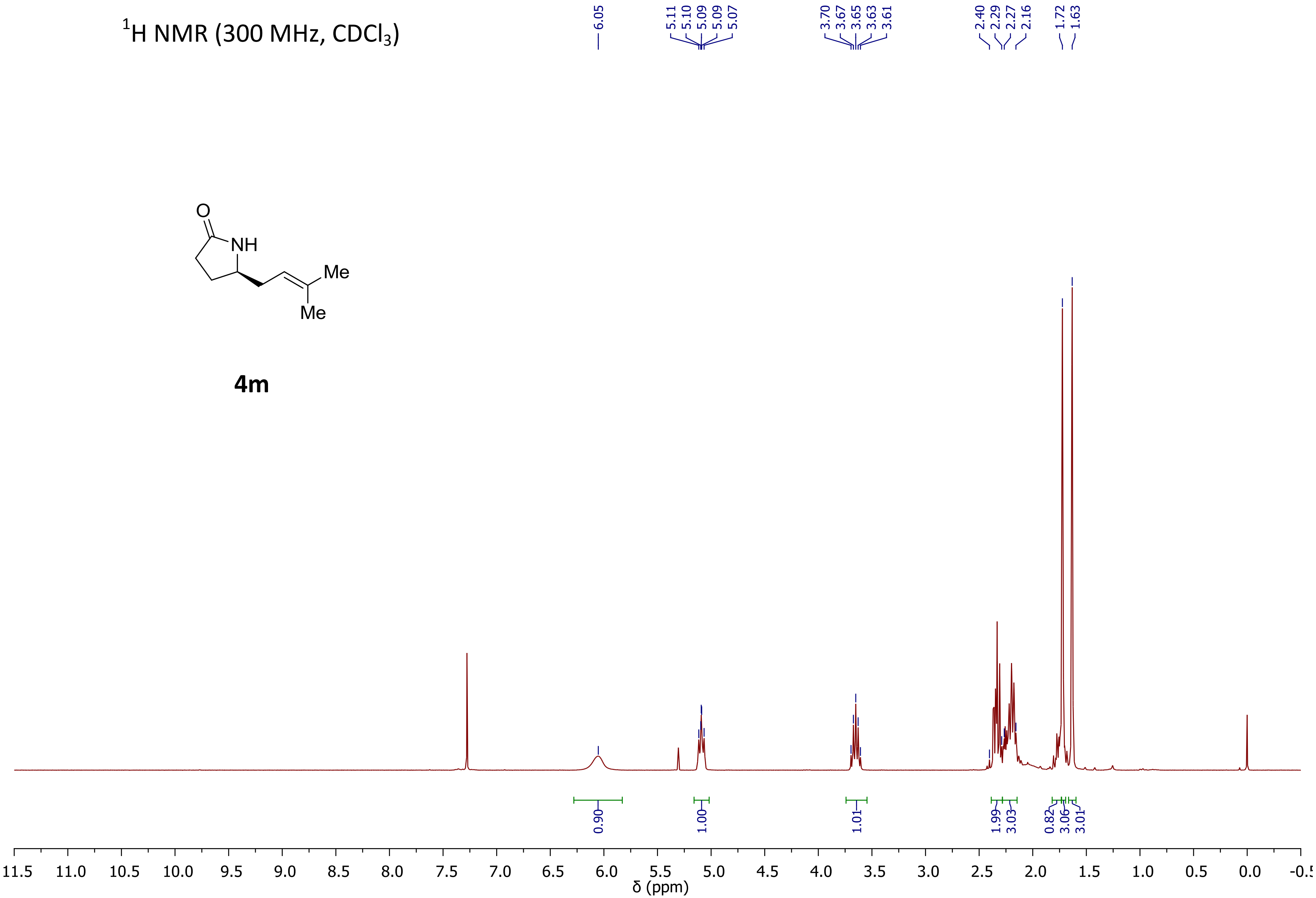
4l



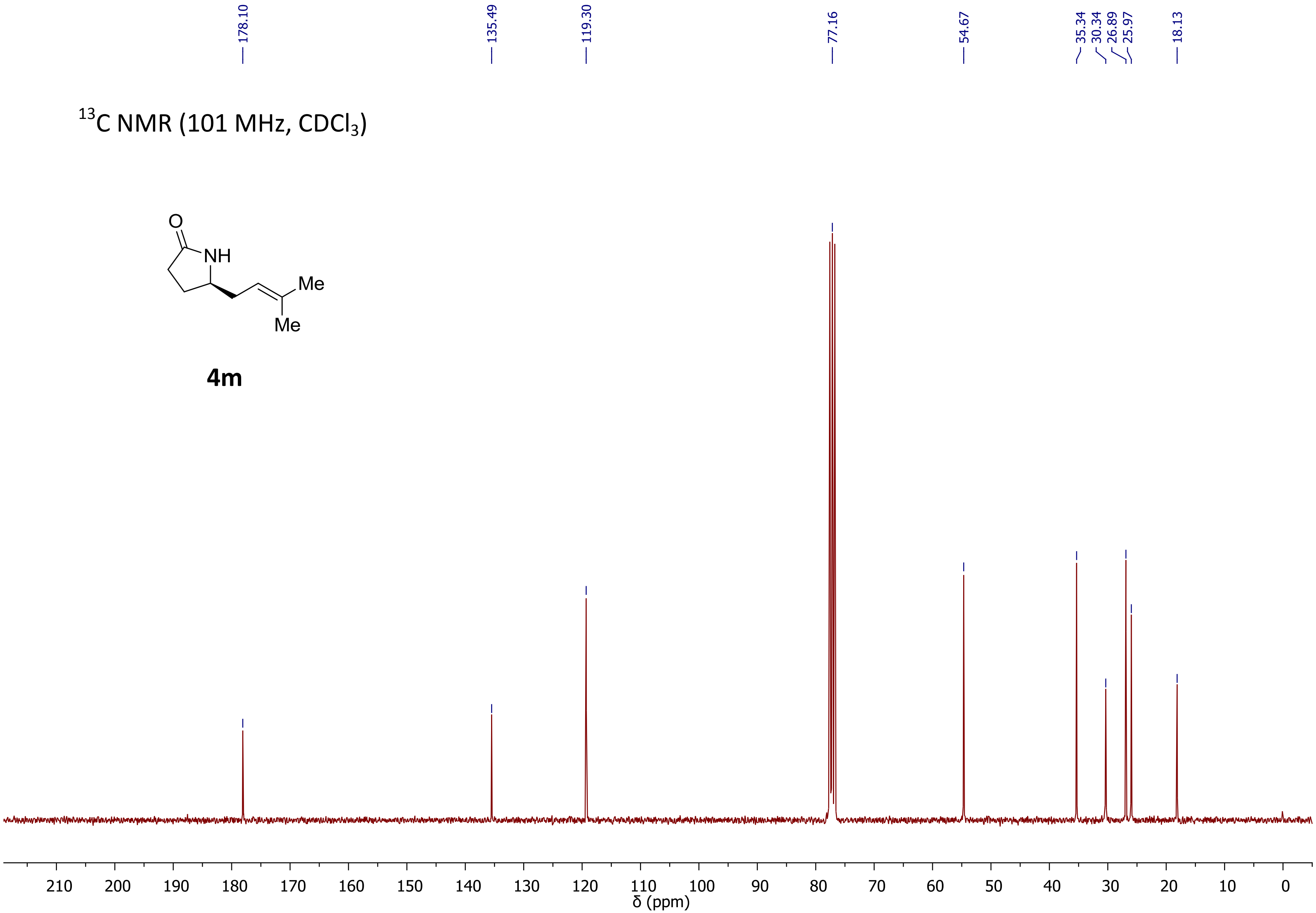
^{13}C NMR (101 MHz, CDCl$_3$)

4l

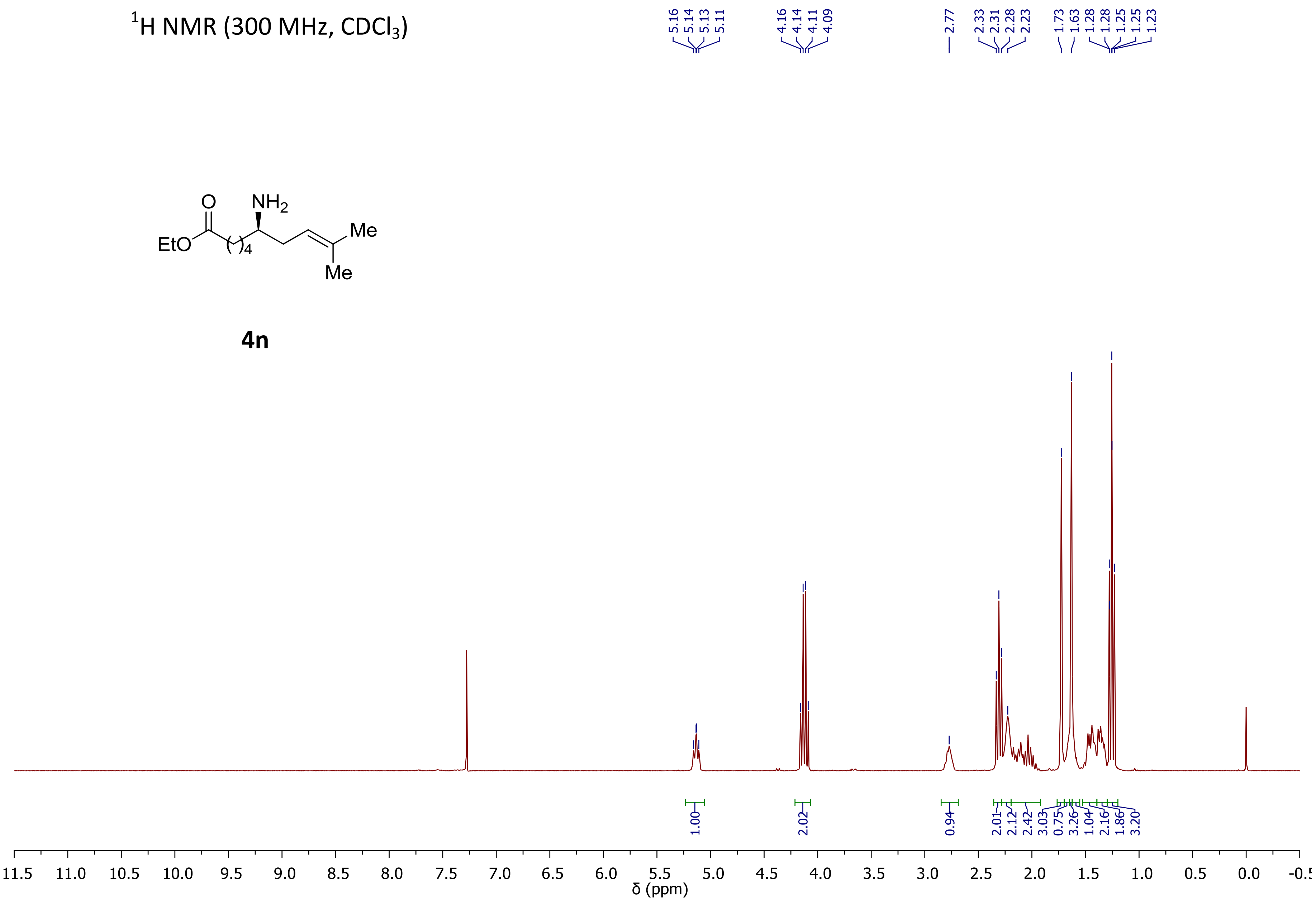
^{1}H NMR (300 MHz, $CDCl_3$)



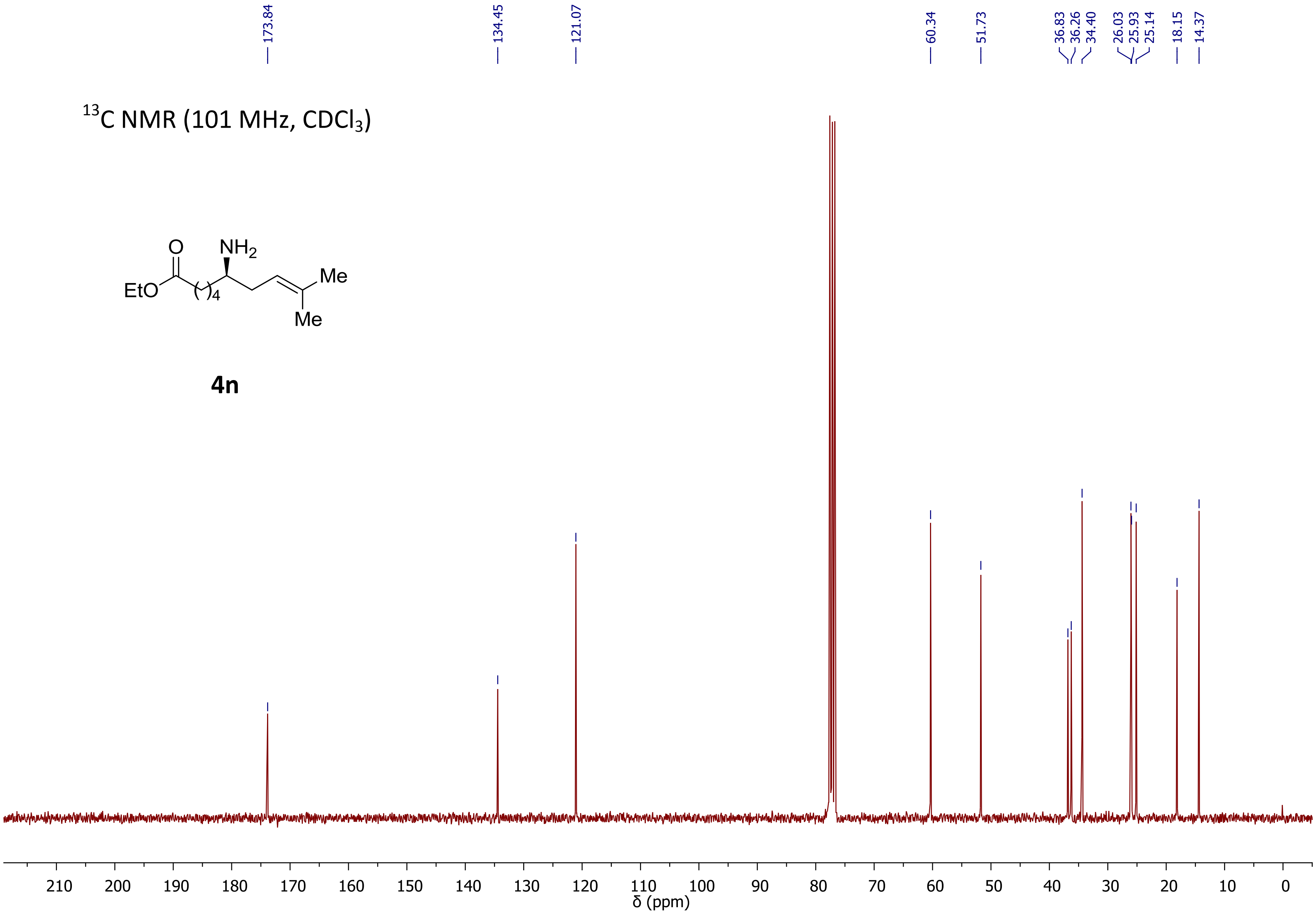
4m


178.10
135.49
119.30
77.16
54.67
35.34
30.34
26.89
25.97
18.13
^{13}C NMR (101 MHz, CDCl$_3$)
O
NH
Me
Me
4m
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



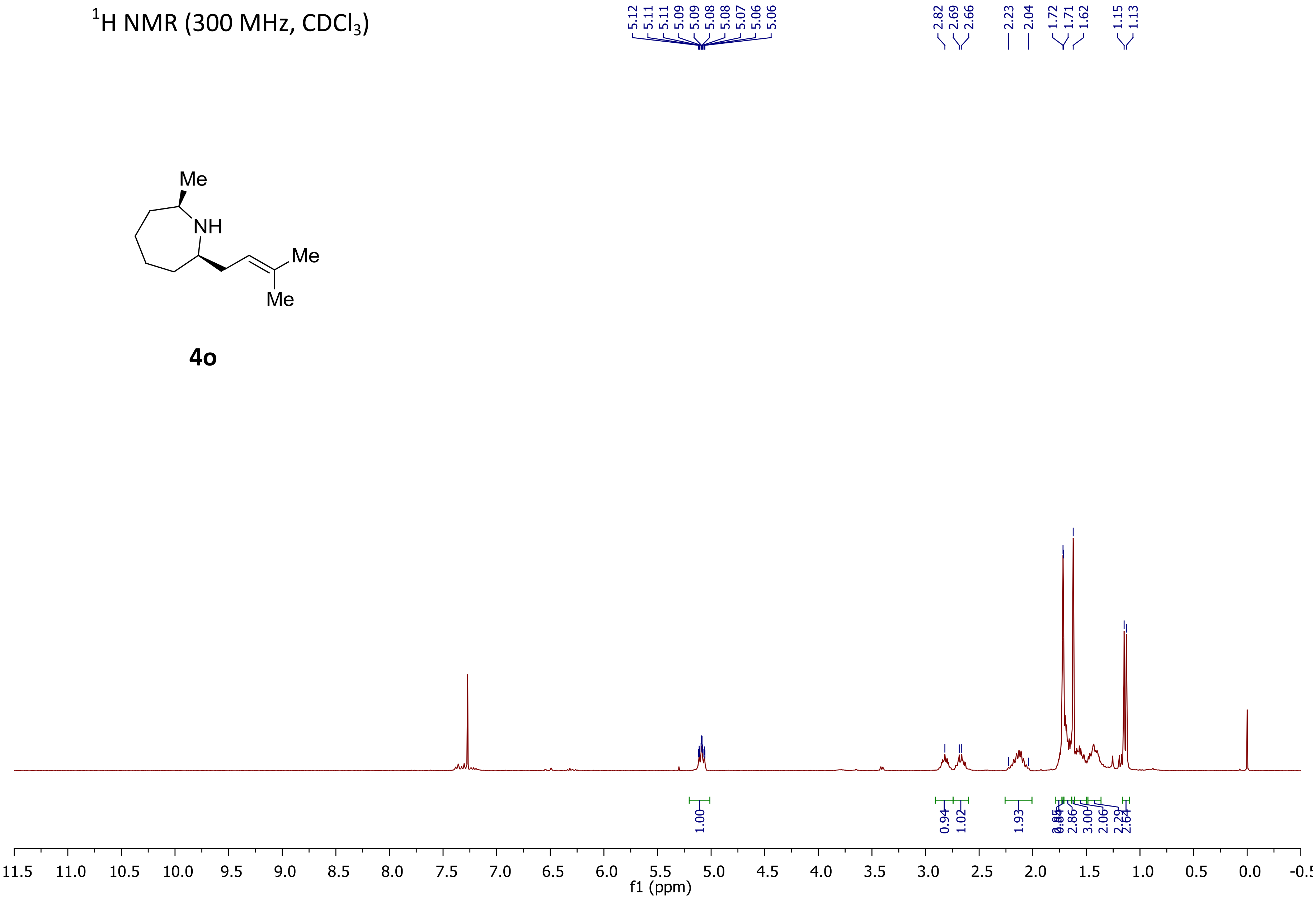
4n



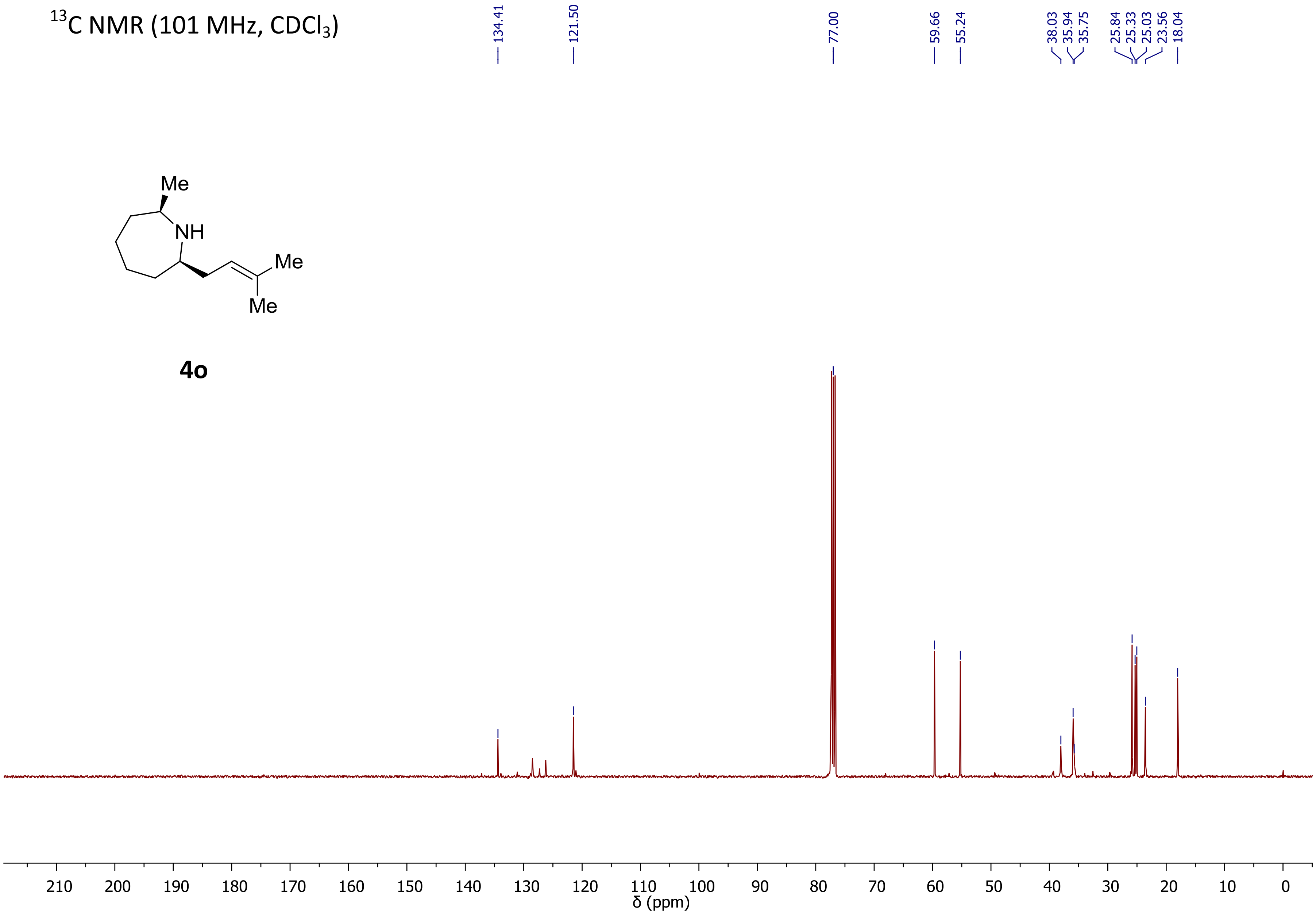
^{13}C NMR (101 MHz, CDCl$_3$)

4n

^{1}H NMR (300 MHz, $CDCl_3$)

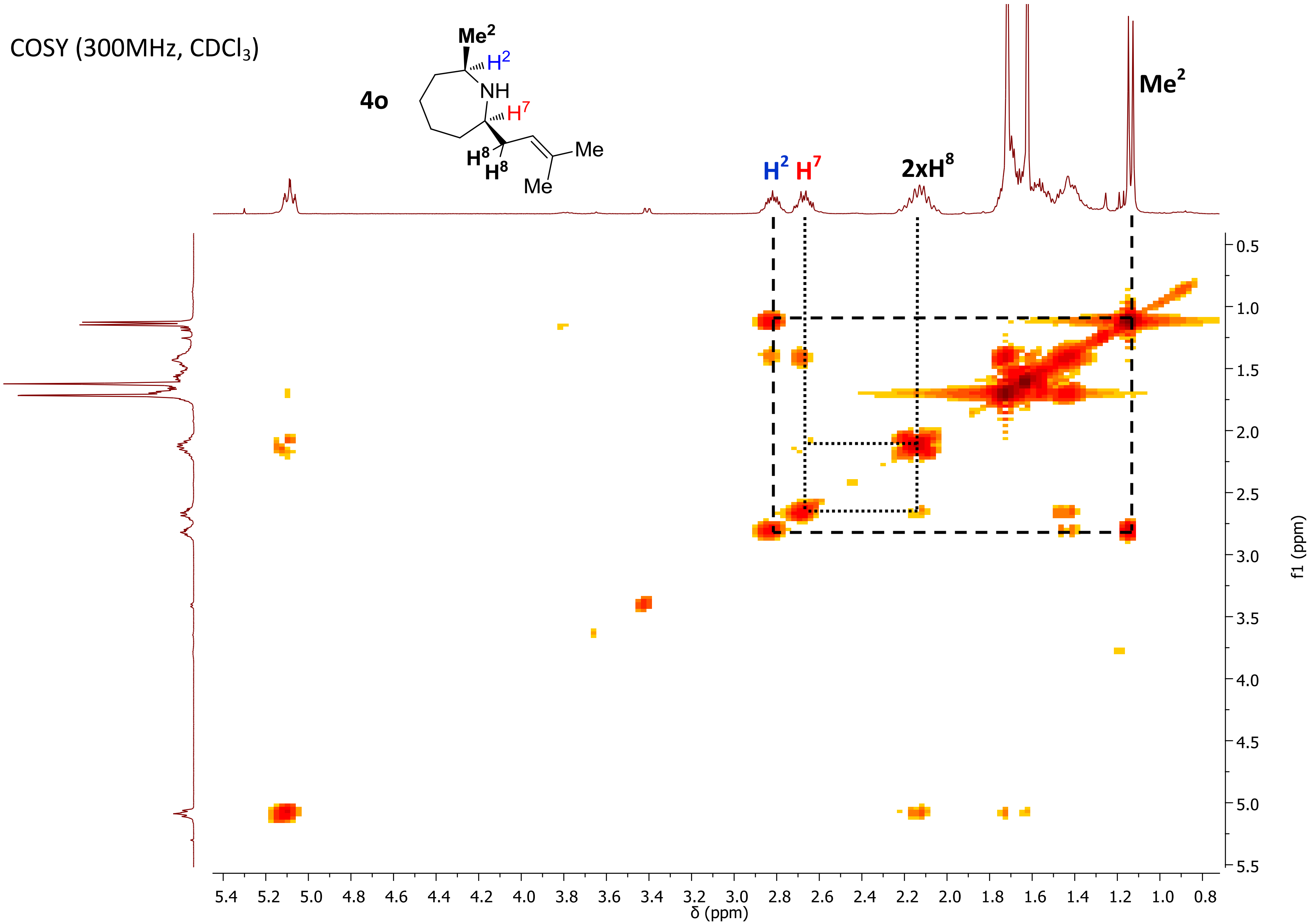


4o


^{13}C NMR (101 MHz, CDCl$_3$)
Me
NH
Me
Me
4o
134.41
121.50
77.00
59.66
55.24
38.03
35.94
35.75
25.84
25.33
25.03
23.56
18.04
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

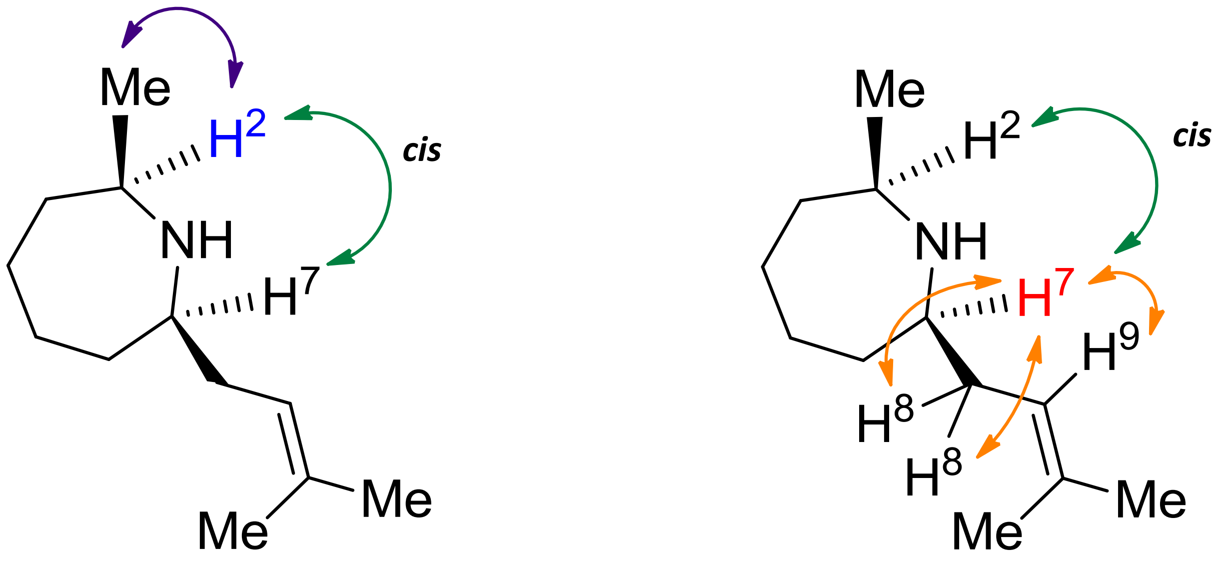
COSY (300MHz, $CDCl_3$)

4o



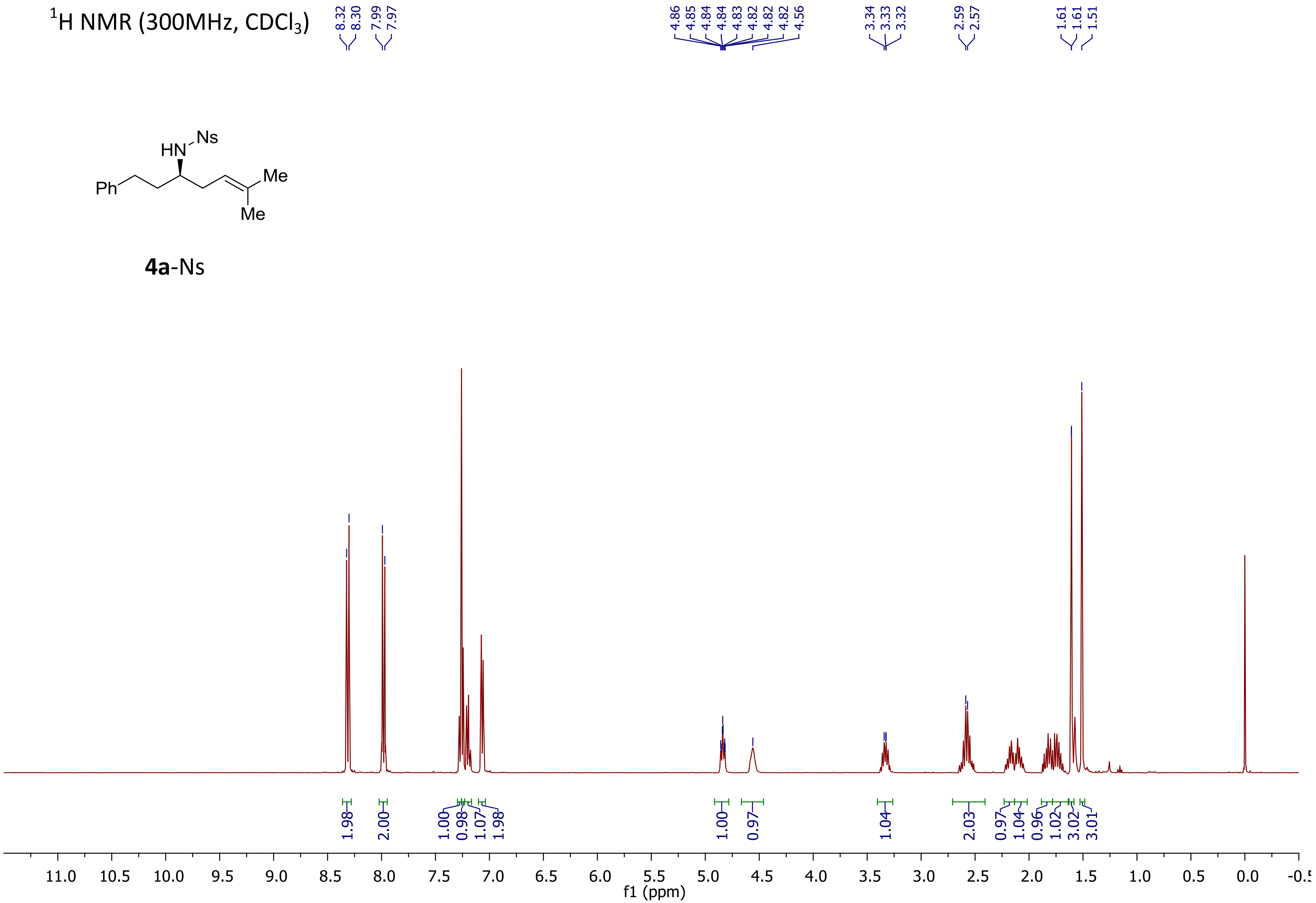
The most relevant observed nOes are shown in these two structures of azepane **4o**. Both hydrogens were found to be in a relative ***cis*** configuration.

Irradiation at 2.82 ppm (H^2)   **Irradiation at 2.67 ppm (H^7)**



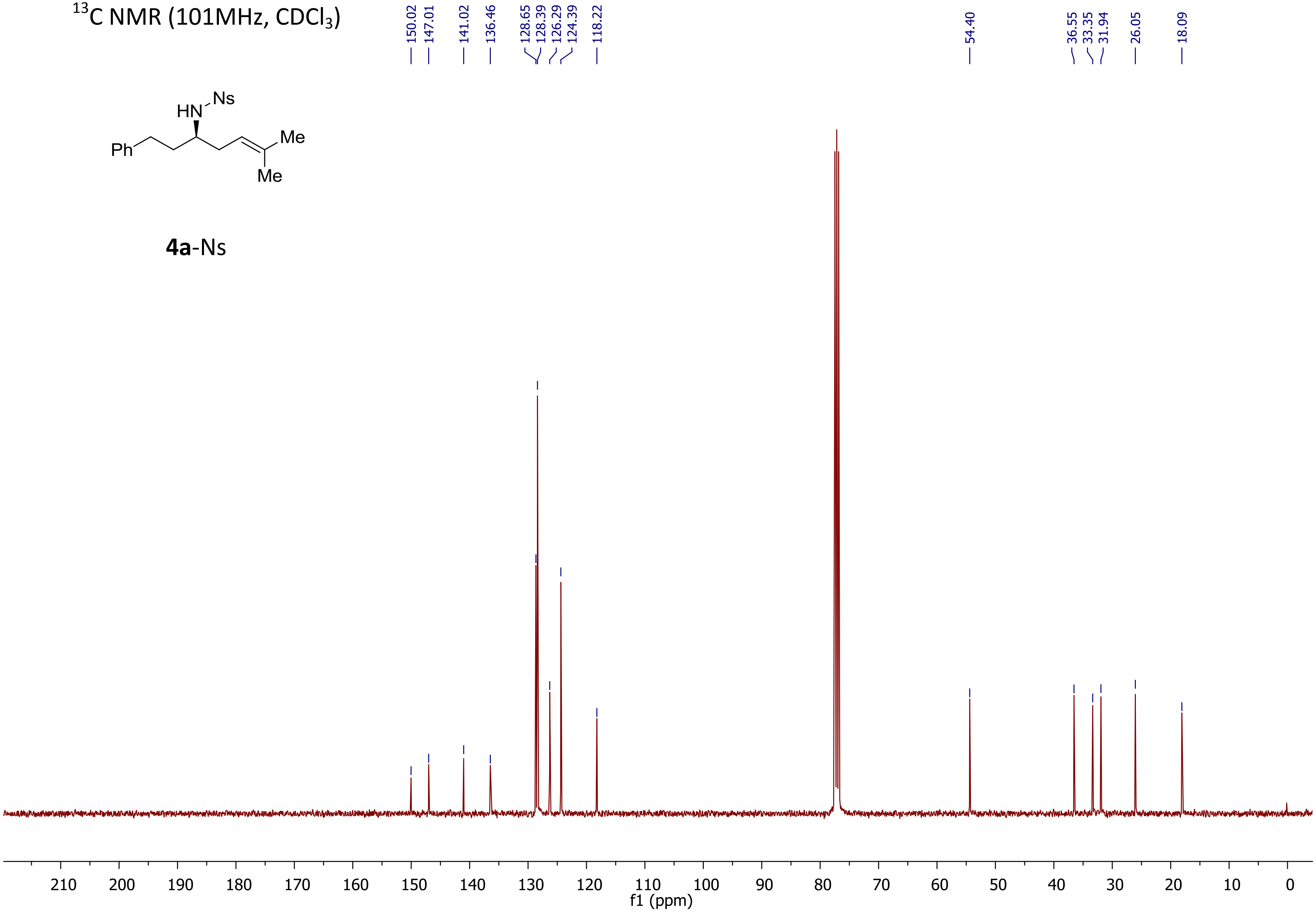
Azepane 4o

^{1}H NMR (300MHz, CDCl$_3$)

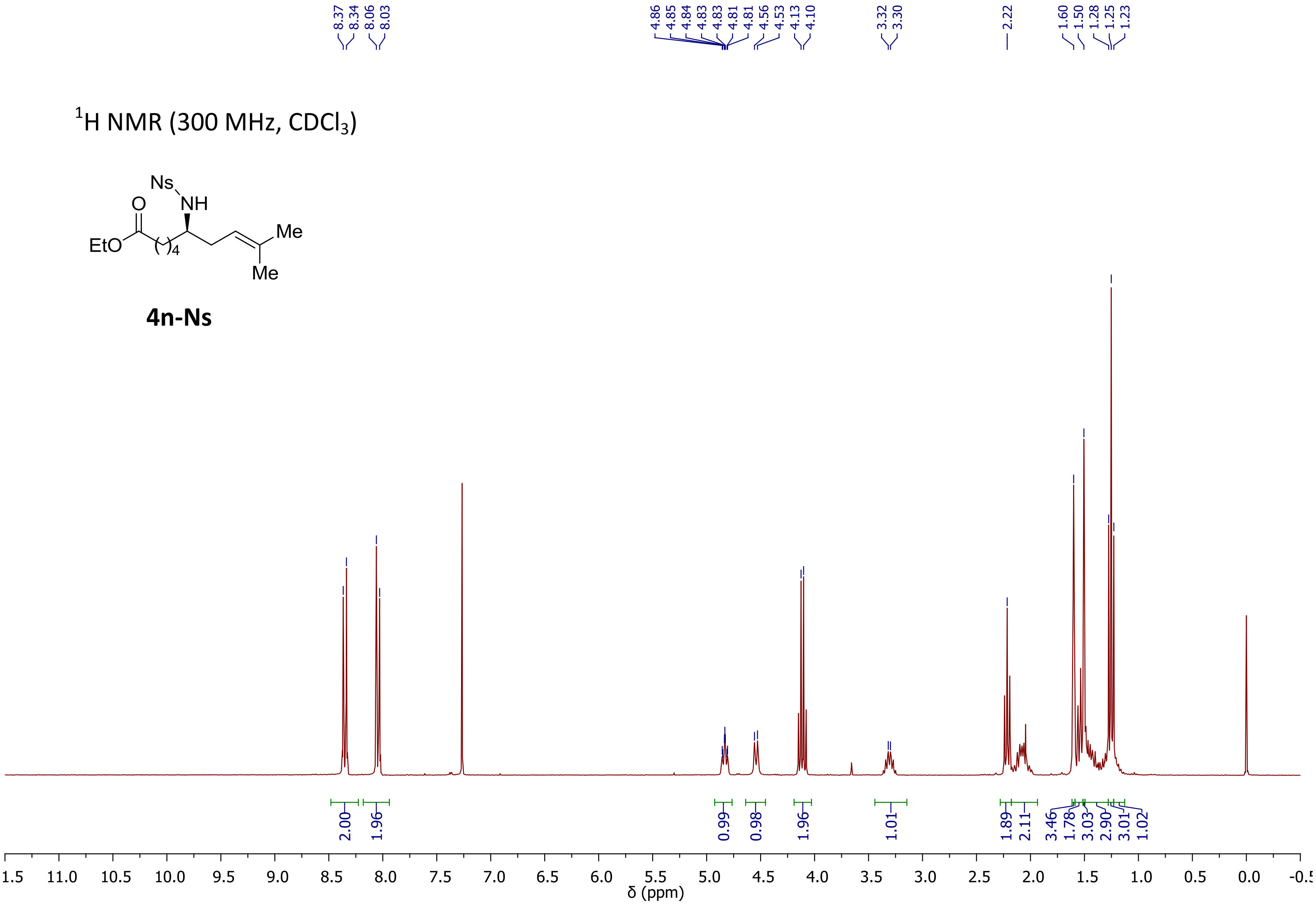


4a-Ns

^{13}C NMR (101MHz, CDCl$_3$)

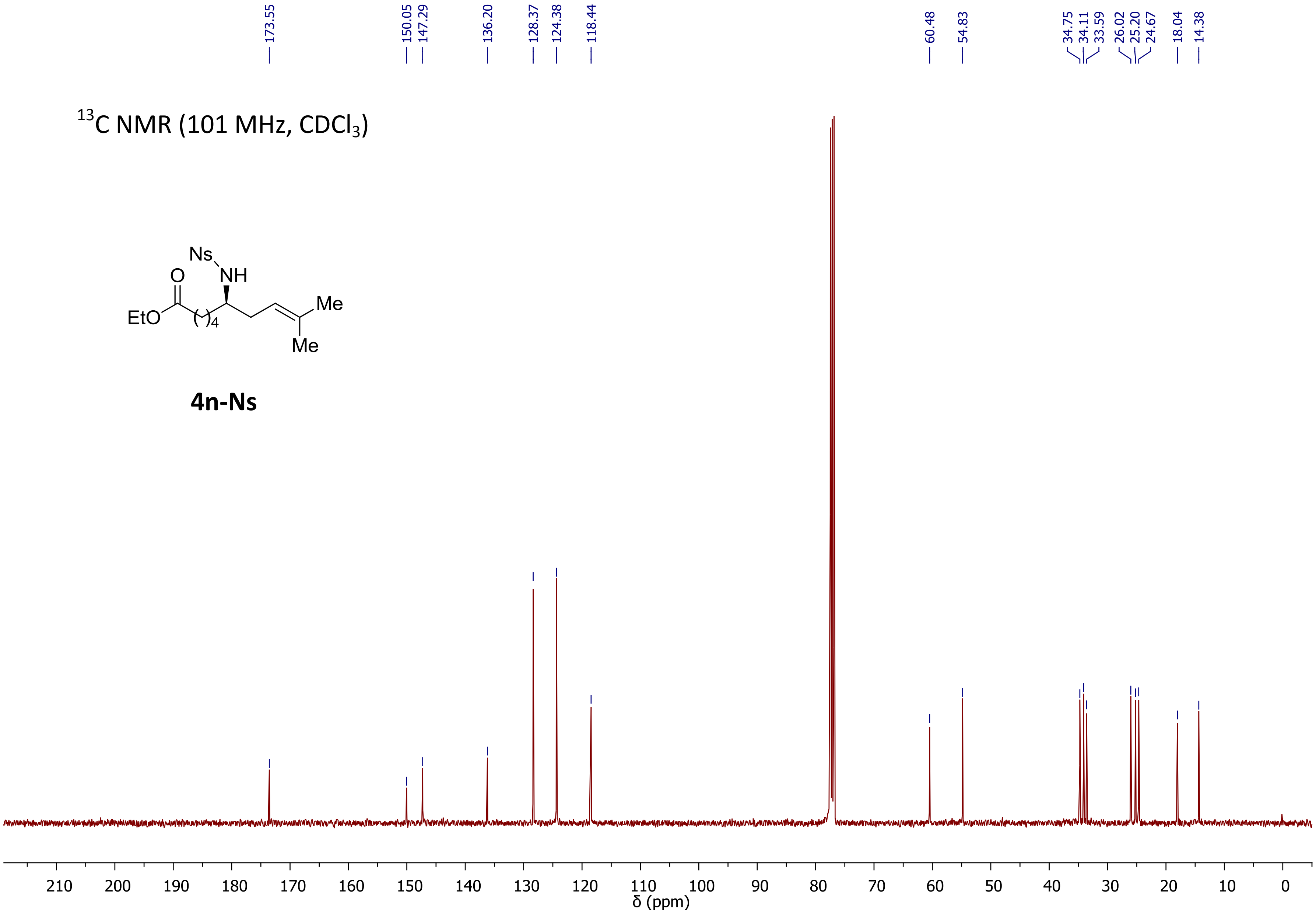


4a-Ns



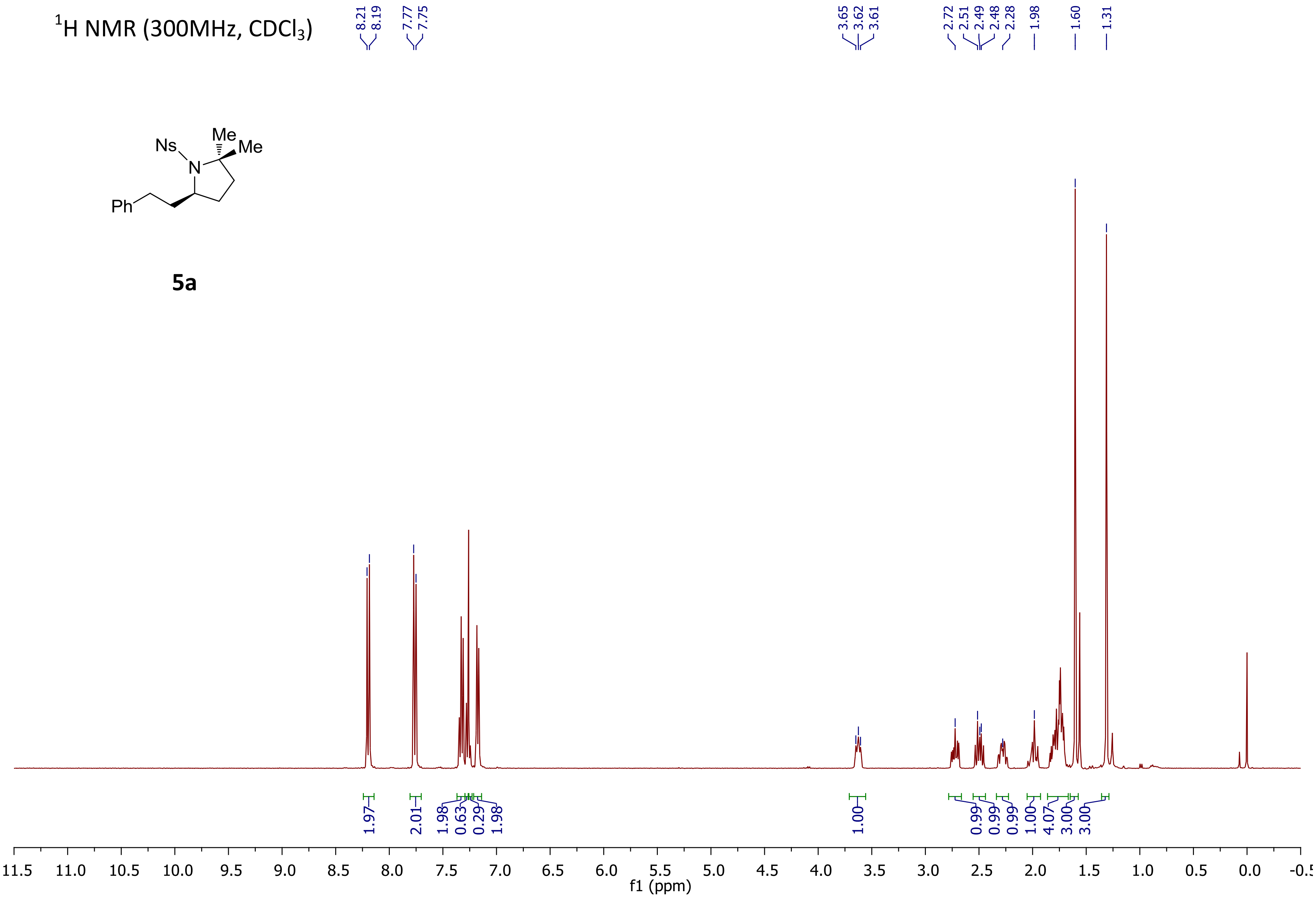
^{1}H NMR (300 MHz, $CDCl_3$)

4n-Ns


173.55
150.05
147.29
136.20
128.37
124.38
118.44
60.48
54.83
34.75
34.11
33.59
26.02
25.20
24.67
18.04
14.38
^{13}C NMR (101 MHz, CDCl$_3$)
Ns
NH
O
EtO
4
Me
Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

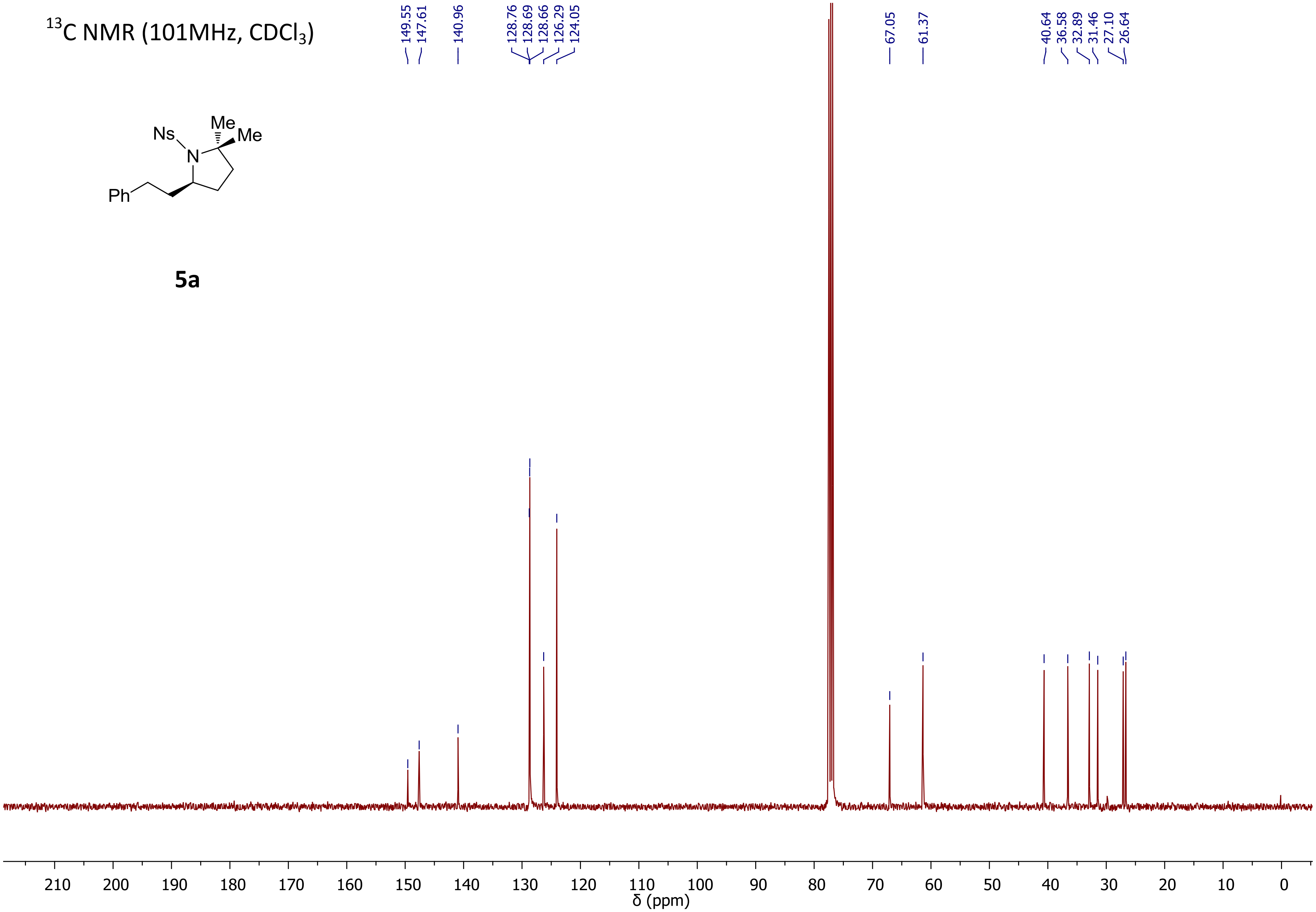
4n-Ns

^{1}H NMR (300MHz, CDCl$_3$)



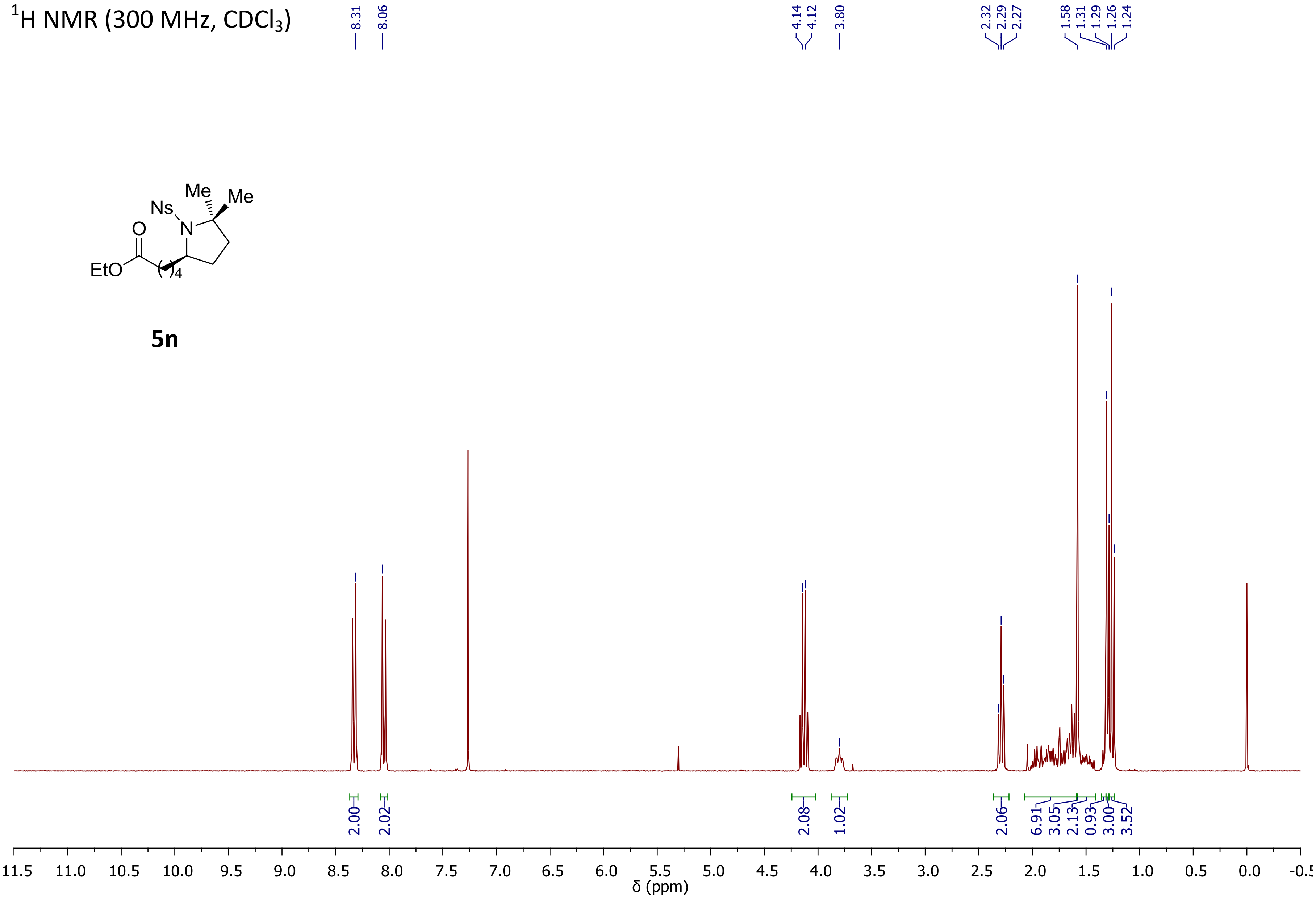
5a

^{13}C NMR (101MHz, $CDCl_3$)

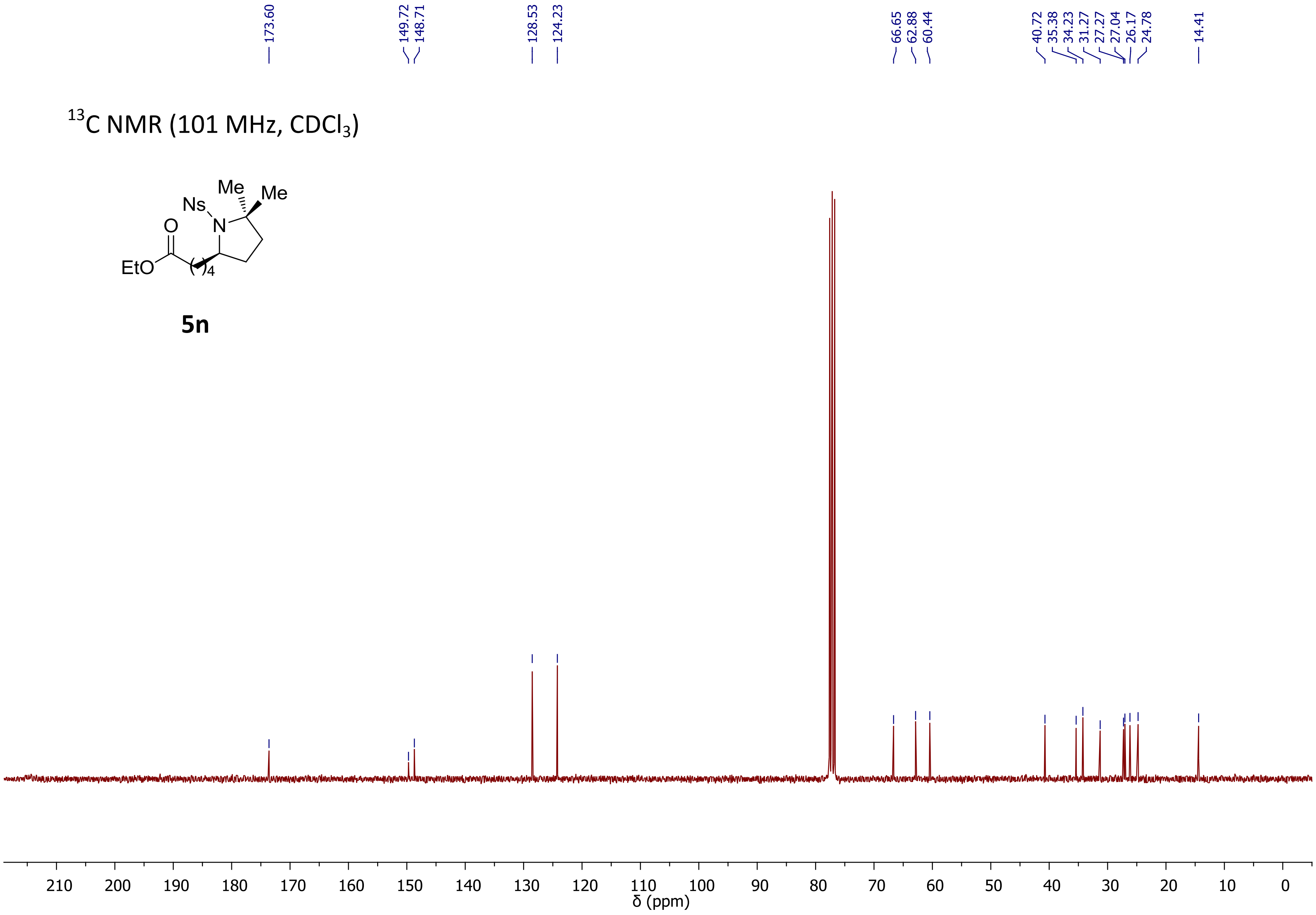


5a

^{1}H NMR (300 MHz, CDCl$_3$)



5n

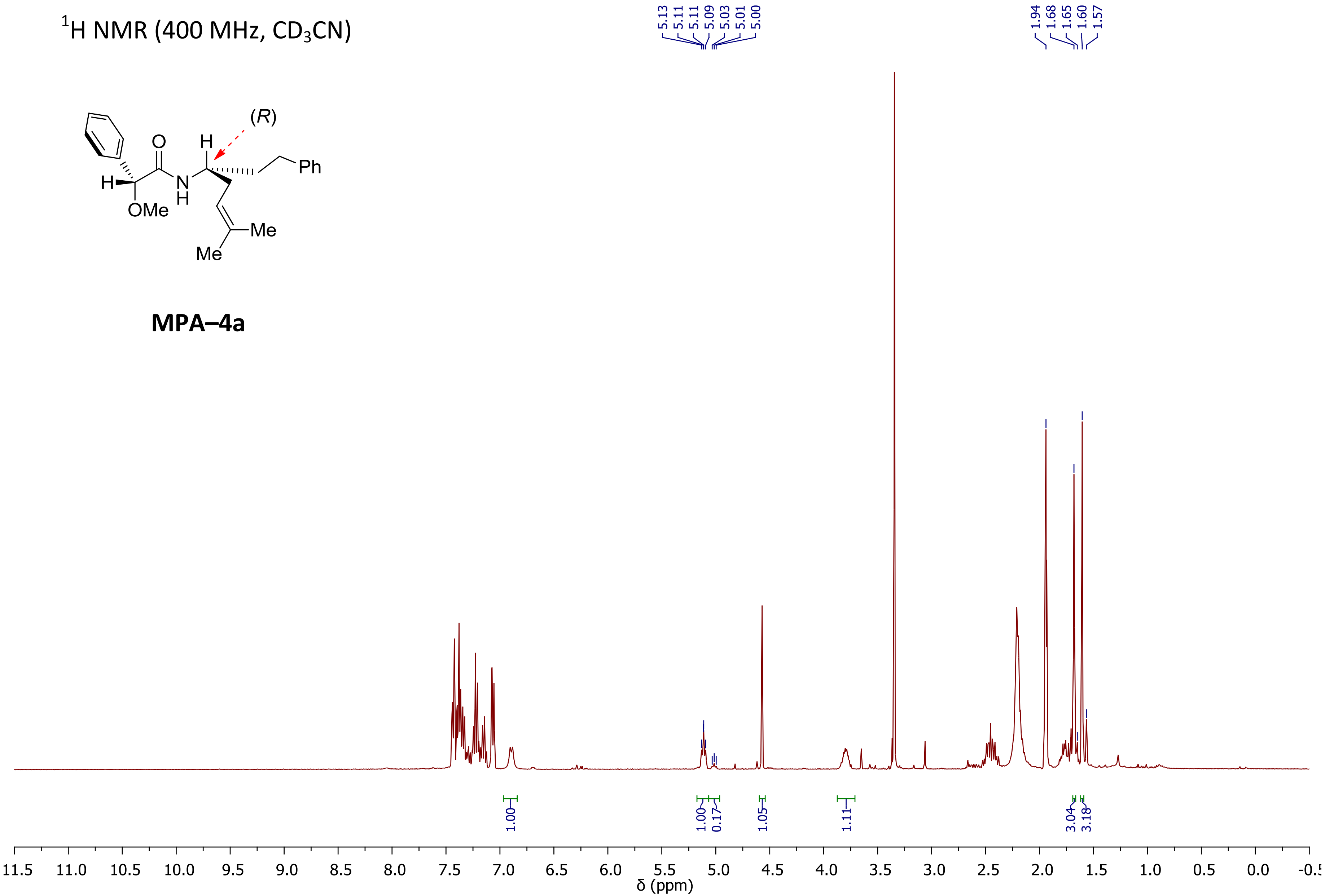


^{13}C NMR (101 MHz, CDCl$_3$)

5n

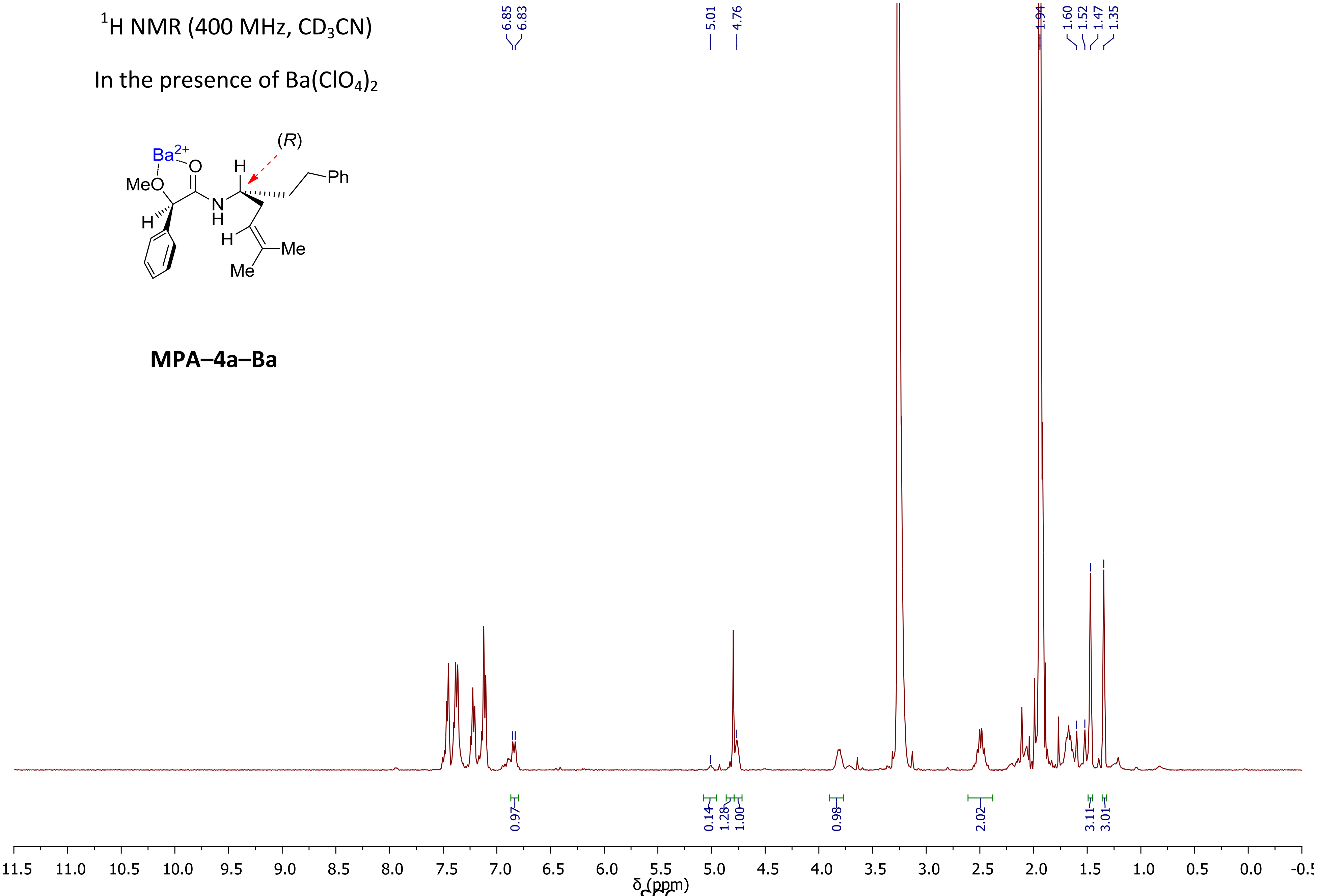
^{1}H NMR (400 MHz, CD$_3$CN)

MPA–4a



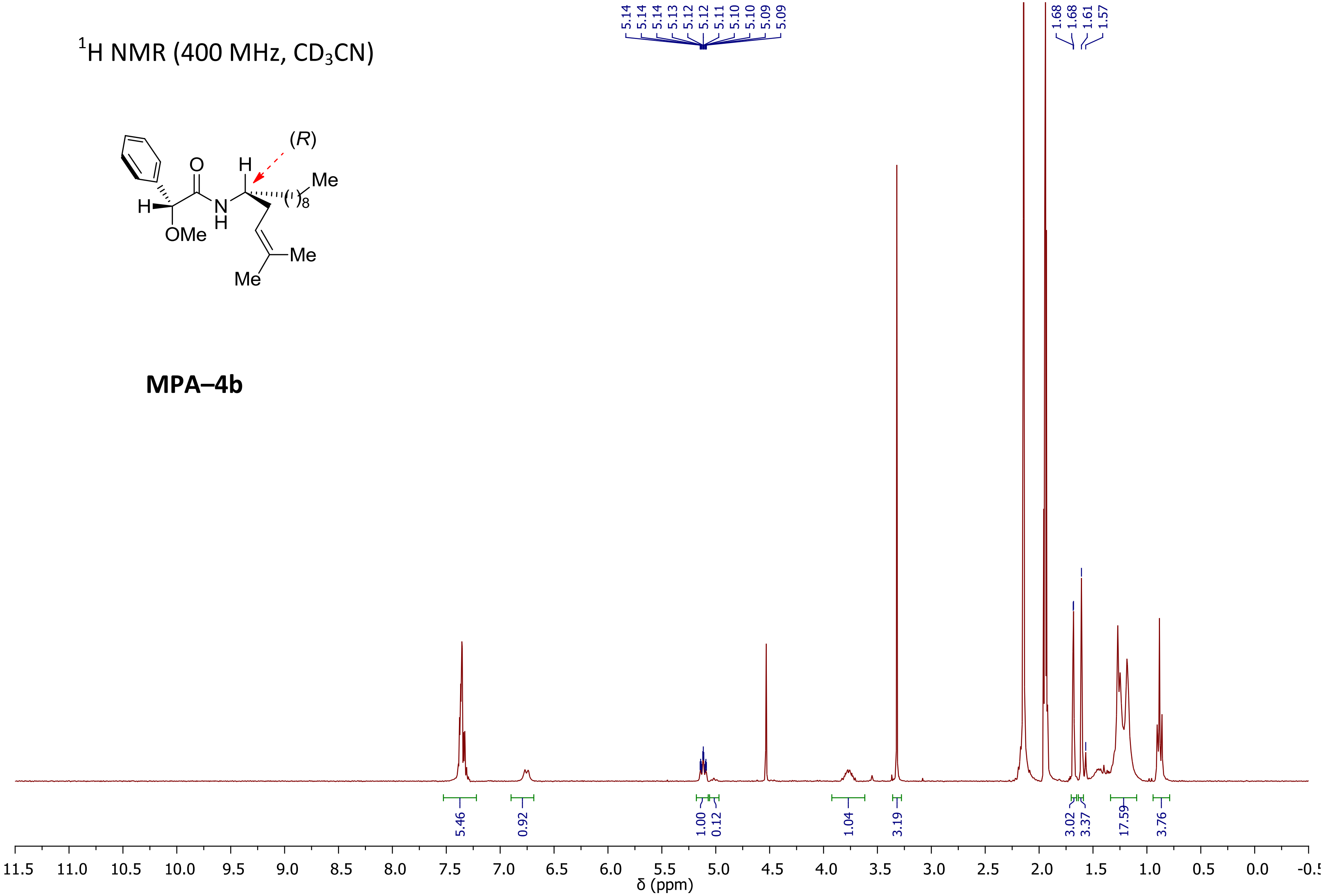
^{1}H NMR (400 MHz, CD_3CN)

In the presence of $Ba(ClO_4)_2$



MPA–4a–Ba

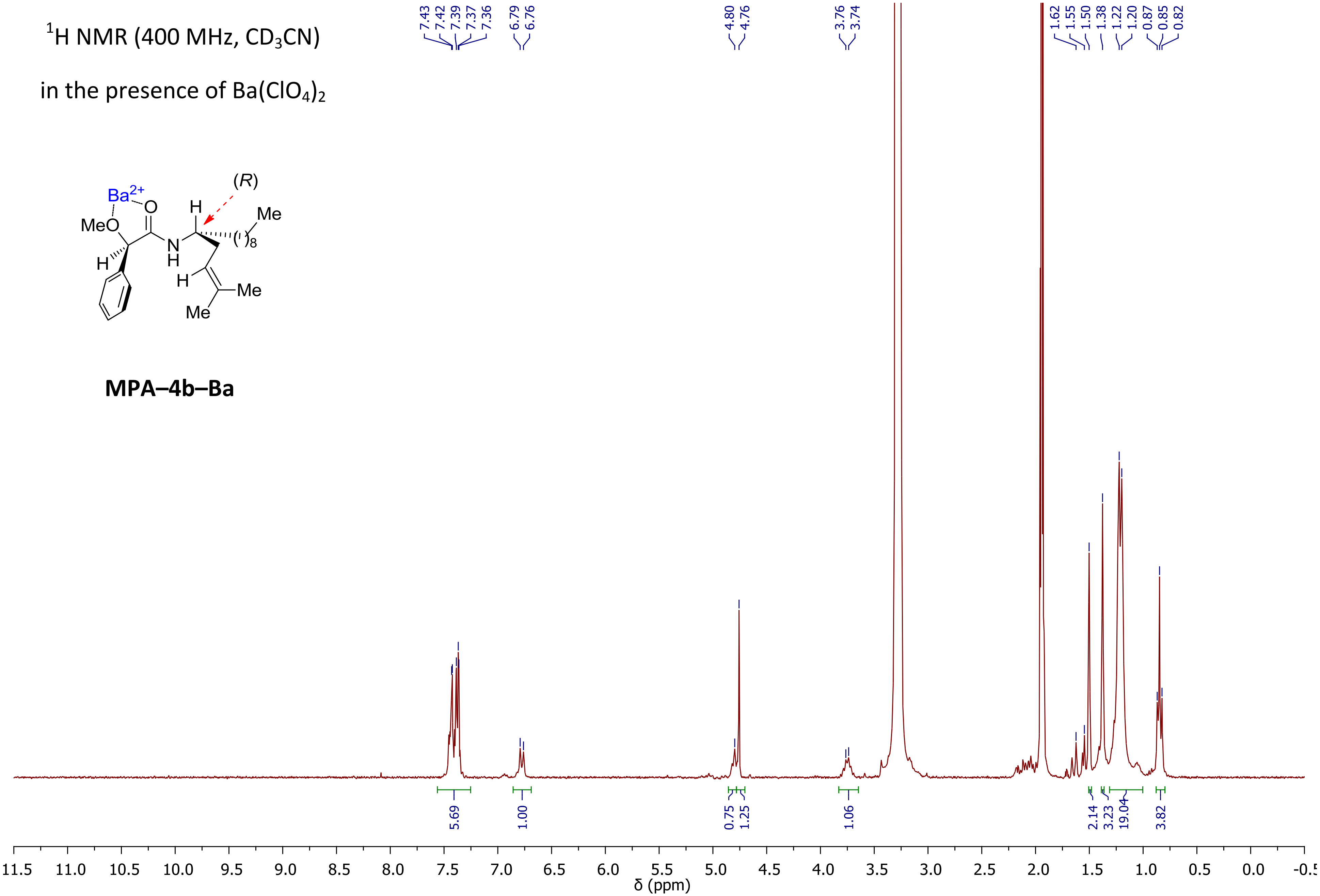
^{1}H NMR (400 MHz, CD_3CN)



MPA–4b

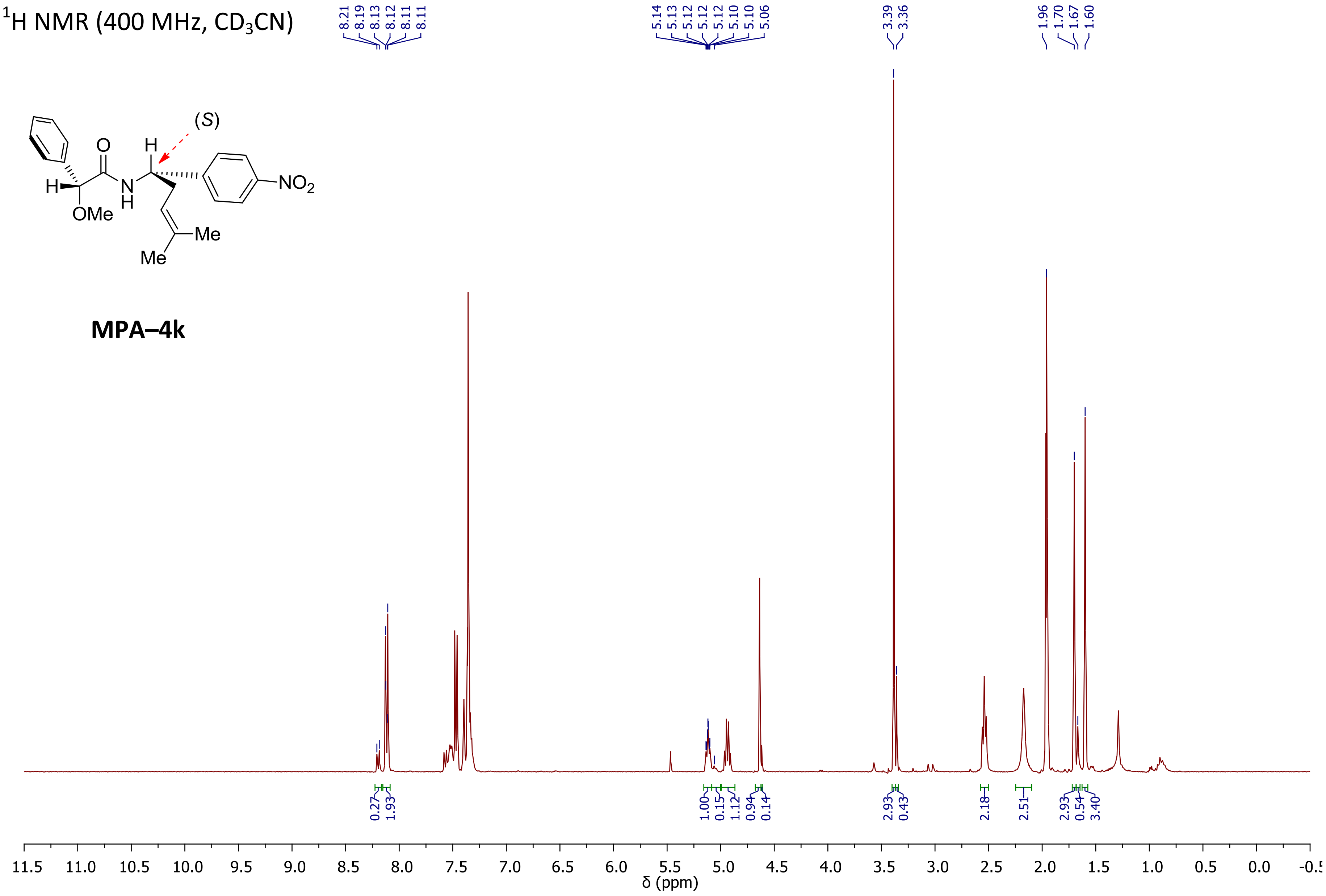
^{1}H NMR (400 MHz, CD_3CN)

in the presence of $Ba(ClO_4)_2$



MPA–4b–Ba

^{1}H NMR (400 MHz, CD_3CN)



MPA–4k

^{1}H NMR (400 MHz, CD_3CN)

In the presence of $Ba(ClO_4)_2$

MPA–4k–Ba