Supporting Information.

A Tandem Nucleophilic Addition/Cyclization Reaction in the Synthesis of Ketimine-type Iminosugars

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General details.

All reactions were performed under argon. The solvents were dried and distilled prior to use. The methyl and phenyl Grignard reagents were purchased from standard commercial sources and titrated in THF by menthol in the presence of orthophenanthroline. *n*-Butyl- (1.24 M) and *n*-decyl-MgBr (1.06 M) were prepared and titrated before use. Silica gel F254 (0.2 mm) was used for TLC plates, detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid or an aqueous solution of $KMnO_4$ (2%) / Na_2CO_3 (4%), followed by heating. Flash column chromatography was performed over silica gel M 9385 (40-63 μm) Kieselgel 60. NMR spectra were recorded on a 250 MHz or a 500 MHz spectrometer (250 MHz or 500 MHz for ^1H, 62.5 MHz or 125 MHz for ^{13}C, as indicated). Chemical shifts are expressed in parts per million (ppm) using TMS as internal standard. Coupling constants are in Hz and splitting pattern abbreviations are: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

General procedure for the synthesis of nitriles 6 and **7**

To a solution of hydroxylamine hydrochloride (8.33 g, 120 mmol) in a 1:1 mixture of ethanol and water (180 mL) was added sodium hydrogenocarbonate (8.76 g, 104 mmol). The solution was stirred at room temperature until evolution of CO_2 has ceased. Then a solution of the protected sugar **4** or **5** (26.1 mmol) in ethanol (50 mL) was slowly added and the mixture stirred for 24 h at room temperature. After concentration under reduced pressure, the residue was extracted with EtOAc (4 × 20 mL). Combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding oxime which was used in the next step without purification.

To a solution of methanesulfonylchloride (4.43 mL, 57.3 mmol) in dry pyridine (13 mL) at 0 °C was slowly added a solution of the crude oxime (8.15 mmol) in dry pyridine (13 mL). The mixture was stirred at 0 °C for 1 h and then for 3 h at room temperature. Cold water (80 mL) was slowly added and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (PE/EtOAc 7:3) gave pure nitriles **6** or **7** in 87% and 60% yield respectively (two steps).

5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-4-*O*-methanesulfonyl -*D*-ribononitrile (6)

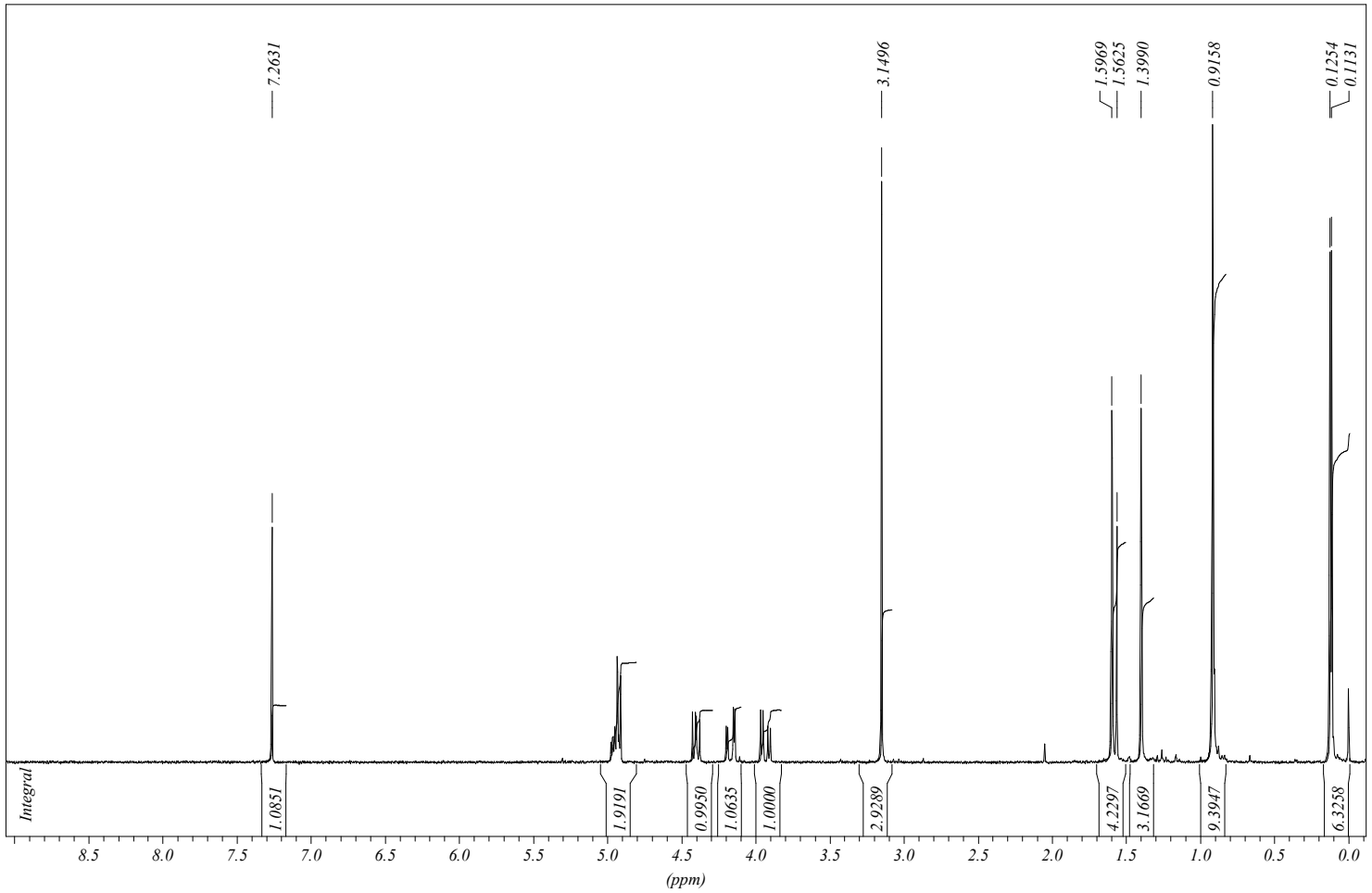
Colorless crystals mp = 79 °C; $[\alpha]_D^{20}$ = –54.2 (*c* 0.6, $CHCl_3$); IR (film) 2991, 2932, 2885, 2858, 1472, 1464, 1362, 1254, 1230 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) δ 0.11 (3 H, s), 0.12 (3 H, s), 0.91 (9 H, s), 1.40 and 1.59 (3 H, s), 3.15 (3 H, s), 3.93 (1 H, dd, *J* = 12.2, 4.0 Hz), 4.15 (1 H, dd, *J* = 12.2, 2.5 Hz), 4.40

(1 H, dd, J = 6.9, 5.2 Hz), 4.92 (1 H, d, J = 5.2 Hz), 4.94 (1 H, m); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ –5.7 (CH_3), –5.5 (CH_3), 18.2 (C), 25.7 (3 × CH_3), 25.7 (CH_3), 26.7 (CH_3), 38.8 (CH_3), 62.3 (CH_2), 66.3 (CH), 75.1, (CH), 79.4 (CH), 112.3 (C), 116.6 (C). Anal. Calcd for for $C_{15}H_{29}NO_6SiS$: C, 47.47; H, 7.70; N, 3.69. Found, C, 47.76; H, 7.82; N, 3.59. ESI-HRMS: calcd for $C_{15}H_{30}NO_6SiS$ $[M+H]^+$ 380.1563; found 380.1567.

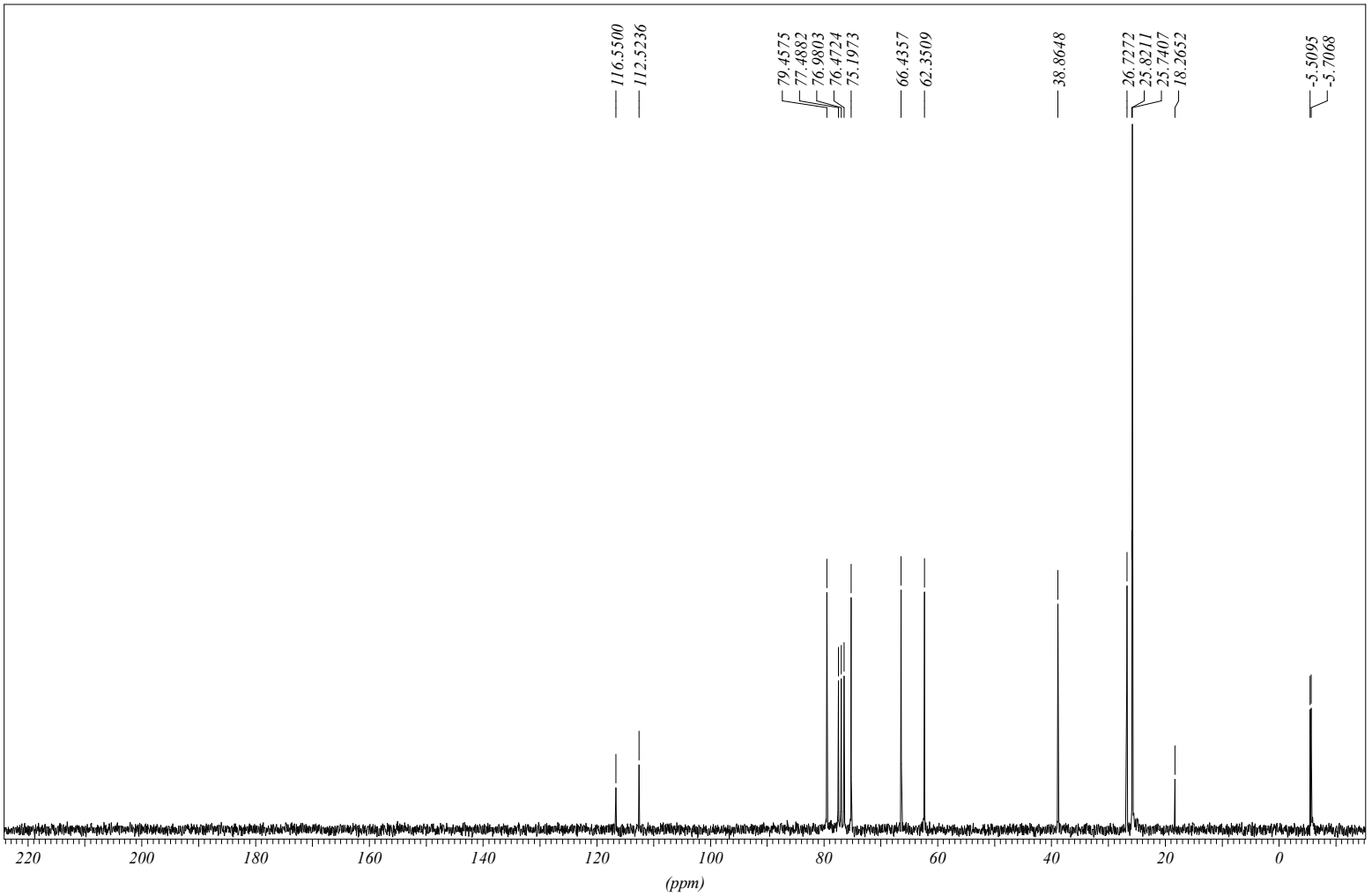
2,3-*O*-isopropylidene-4-*O*-methanesulfonyl-5-*O*-triphenylmethyl-*D*-lyxononitrile (7)

Colorless crystals mp = 145 °C; $[\alpha]_D^{20}$ = +12.3 (*c* 0.22, $CHCl_3$); IR (film) 3439, 3060, 2990, 2924, 2854, 1739, 1599, 1492, 1450, 1362, 1176 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.40 and 1.58 (3 H, s), 3.10 (3 H, s), 3.33 (1 H, dd, J = 11.3, 3.4 Hz), 3.63 (1 H, dd, J = 11.3, 4.2 Hz), 4.13 (1 H, bs), 4.39–4.50 (2 H, m), 4.96 (1 H, m), 7.20–7.50 (15 H, m, Ar-H); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 26.1 (CH_3), 27.1 (CH_3), 38.6 (CH_3), 63.2 (CH_2), 65.1 (CH), 77.7 (CH), 79.9 (CH), 87.8 (C), 112.9 (C), 116.0 (C), 127.3-128.8 and 142.7 (4 × Ar-*C*). Anal. Calcd for for $C_{28}H_{29}NO_6S$: C, 66.25; H, 5.76; N, 2.76. Found, C, 66.23; H, 5.83; N, 2.61. ESI-HRMS: calcd for $C_{28}H_{29}NO_6SNa$ $[M+Na]^+$ 530.1620; found 530.1613.

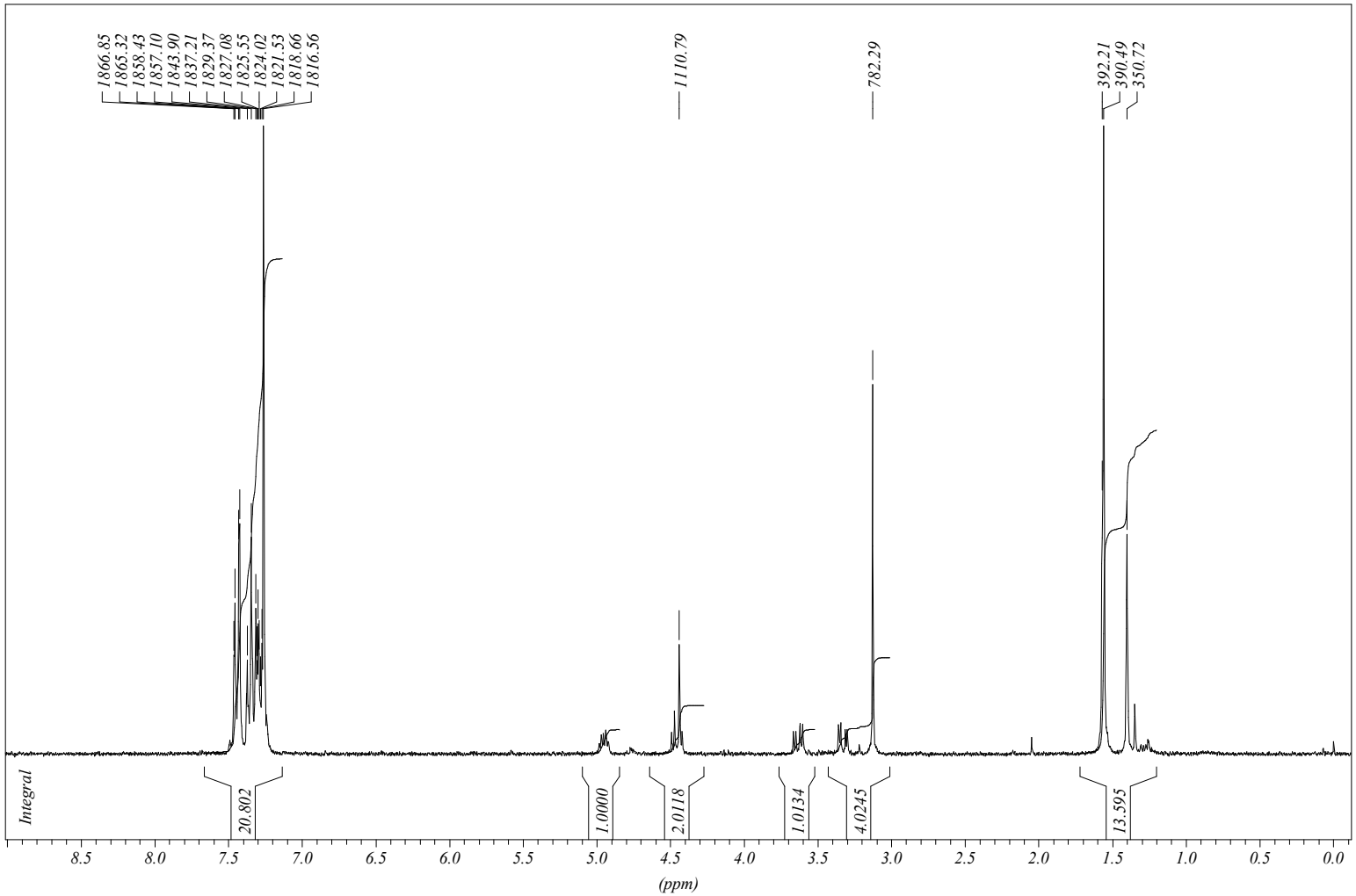
(^{1}H-NMR spectrum of **6** at 250 MHz in $CDCl_3$)



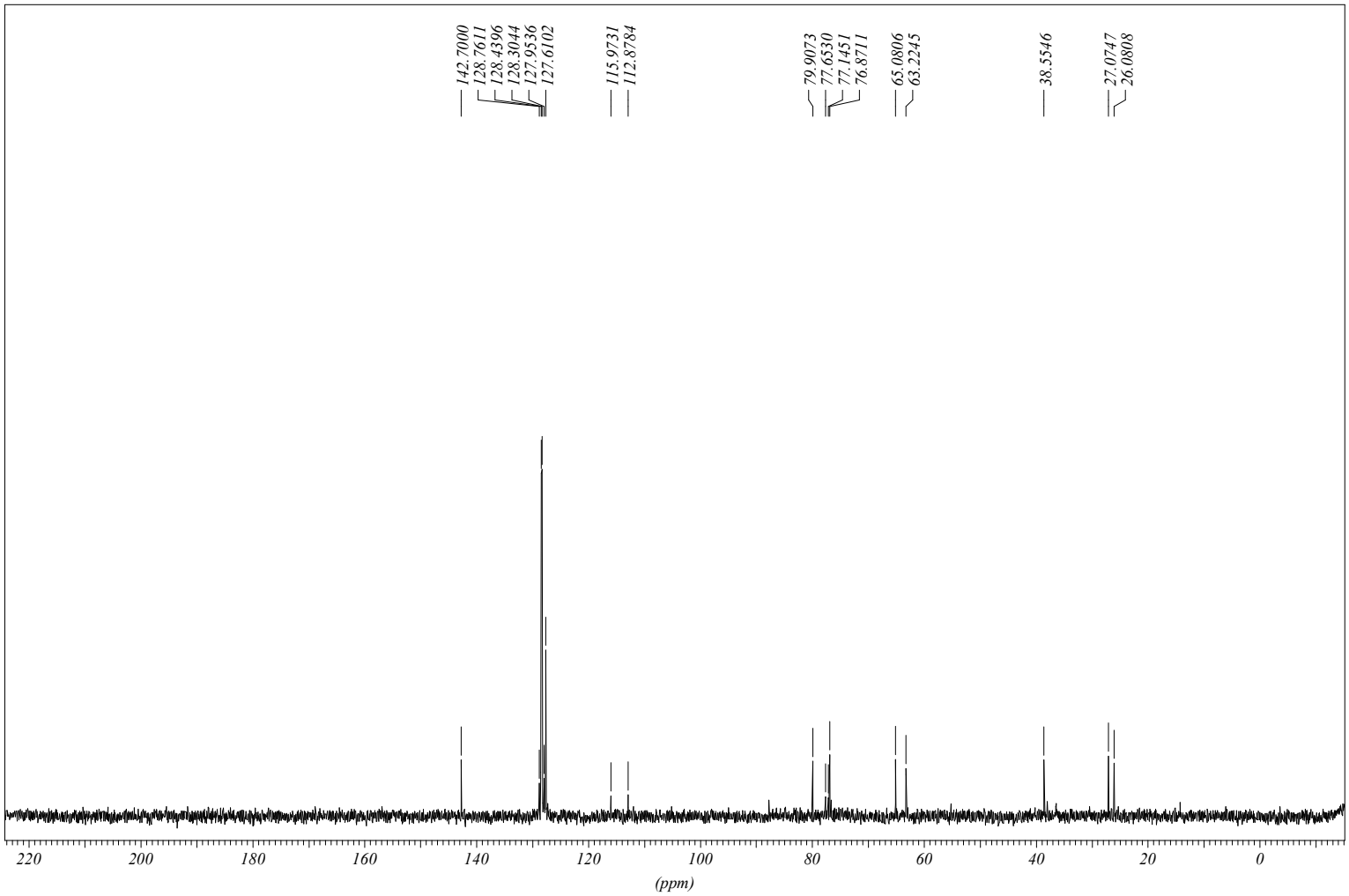
(^{13}C-NMR spectrum of **6** in $CDCl_3$)



(^{1}H-NMR spectrum of **7** at 250 MHz in $CDCl_3$)



(^{13}C-NMR spectrum of **7** in $CDCl_3$)



General procedure for the synthesis of cyclic ketimine sugars. A solution of glycononitrile (0.40 mmol) in toluene (7 mL) under argon was heated at 70 °C and the Grignard reagent (1.5 eq) was added dropwise. The solution was stirred at 70°C for 1.5 h and cooled to rt. Diethyl ether (20 mL) and a saturated solution of NH_4Cl (20 mL) were successively added and the resulting solution was extracted. The aqueous phase was extracted with Et_2O (2 × 20 mL) and the organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The crude sample of **1** was purified by silica gel chromatography to yield the pure compound.

For the synthesis of **1h**, THF (2 mL) was added to the reaction mixture after 1.5 h at 70 °C and the resulting solution was stirred at room temperature overnight. The reaction mixture was then treated as above.

The purification of 2-decyl-1-pyrroline **1d** required three successive chromatographic separations to remove the Würtz-type by-products.

(3R, 4R, 5S)-3,4-dibenzyloxy-5-benzyloxymethyl-2-methyl-1-pyrroline (1a)

Colorless oil (55%), R_f = 0.50 (PE/EtOAc 6:4); $[\alpha]_D^{20}$ = –67.1 (*c* 1.1, $CHCl_3$); IR (film) 3063, 3030, 2920, 2861, 1646, 1496, 1454, 1363 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 2.13 (3 H, s), 3.80 (2 H, d, *J* = 4.2 Hz), 4.22–4.35 (2 H, m), 4.59 (1 H, m), 4.55–4.72 (6 H, m), 7.25–7.45 (15 H, m, Ar-*H*); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 18.4 (CH_3), 68.8 (CH_2), 70.8 (CH), 73.0 (CH_2), 73.1 (CH_2), 73.8 (CH_2), 84.4 (CH), 89.4 (CH), 127.8–128.9 (Ar-CH), 138.3 (Ar-C), 138.4 (Ar-C), 138.9 (Ar-C), 175.8 (C); ESI-HRMS: calcd for $C_{27}H_{30}NO_3$ $[M+H]^+$ 416.2226; found 416.2219.

(3R, 4R, 5S)-3,4-dibenzyloxy-5-benzyloxymethyl-2-phenyl-1-pyrroline (1b)

yellow oil (61%), R_f = 0.45 (PE/Et_2O 6:4); $[\alpha]_D^{20}$ = –1.4 (*c* 0.66, $CHCl_3$); IR (film) 3415, 3062, 3030, 2919, 2864, 1615, 1496, 1454, 1365 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 3.92 (1 H, dd, *J* = 9.4, 7.0 Hz), 4.08 (1 H, dd, *J* = 9.4, 4.4 Hz), 4.40 (1 H, dd, *J* = 3.1, 1.6 Hz), 4.52 (1 H, m), 4.60–4.75 (6 H, m), 5.21 (1 H, d, *J* = 1.6 Hz), 7.30–7.50 (m, 18 H, Ar-*H*), 7.87 (2 H, d, *J* = 7.0 Hz, Ar-H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 68.6 (CH_2), 72.0 (CH), 72.6 (CH_2), 73.6 (CH_2), 82.0 (CH), 87.0 (CH), 127.1–128.6 (CH), 130.8 (CH), 133.2, 137.4, 138.1 and 138.5 (4 × Ar-C), 171.8 (C); MS (ESI) *m/*z : 478 (100%, MH^+); ESI-HRMS: calcd for $C_{32}H_{32}NO_3$ $[M+H]^+$ 478.2382; found 478.2381.

(3R, 4R, 5S)-3,4-dibenzyloxy-5-benzyloxymethyl-2-butyl-1-pyrroline (1c)

yellow oil (56%). R_f = 0.33 (PE/Et_2O 6:4); $[\alpha]_D^{20}$ = –10.9 (*c* 0.36, $CHCl_3$); IR (film) 3063, 3030, 2956, 2928, 2869, 1497, 1454, 1362 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 0.84 (3 H, t, *J* = 7.3 Hz), 1.22–1.36 (2 H, m), 1.50 (2 H, m), 2.45 (2 H, m), 3.73 (2 H, d, *J* = 4.8 Hz), 4.21 (1 H, dd, *J* = 6.4, 4.8Hz), 4.24 (1 H,

m), 4.58 (1 H, d, J = 4.8 Hz), 4.52–4.66 (6 H, m), 7.25–7.37 (m, 15 H, Ar-*H*); ^{13}C NMR (125 MHz; $CDCl_3$) δ 12.8 (CH_3), 21.5 (CH_2), 26.9 (CH_2), 30.3 (CH_2), 67.2 (CH_2), 69.0 (CH), 71.5, 71.7 and 72.3 (3 × CH_2), 83.1 (CH), 86.8 (CH), 126.3–127.4 (Ar-CH), 136.8, 137.0 and 137.5 (3 × Ar-C), 177.6 (C); MS (ESI) *m/*z : 458 (100%, MH^+); ESI-HRMS: calcd for $C_{30}H_{36}NO_3$ $[M+H]^+$ 458.2695; found 458.2685.

(3R, 4R, 5S)-3,4-dibenzyloxy-5-benzyloxymethyl-2-decyl-1-pyrroline (1d)

Colorless oil (38%). R_f = 0.30 (PE/Et_2O 5:5); $[\alpha]_D^{20}$ = –58.1 (*c* 0.60, $CHCl_3$); IR (film) 3064, 3031, 2923, 2854, 1641, 1454, 1363; ^{1}H NMR (250 MHz; $CDCl_3$) 0.80 (3 H, t, J = 7.3 Hz), 1.20–1.30 (14 H, m), 1.49 (2 H, m), 2.30 (2 H, t, J = 7.6 Hz), 3.72 (2 H, d, J = 4.0 Hz), 4.22 (2 H, m), 4.57 (1 H, m), 4.44–4.52 (6 H, m), 7.13–7.35 (m, 15 H); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 14.6 (CH_3), 23.1, 26.2, 29.3–30.0, 32.1 and 32.4 (CH_2), 68.7 (CH_2), 70.5 (CH), 72.9, 73.1 and 73.8 (3 × CH_2), 84.5 (CH), 88.2 (CH), 127.8–129.2 (Ar-CH), 138.3, 138.5 and 139.0 (3 × Ar-C), 179.1 (C); ESI-HRMS: calcd for $C_{36}H_{48}NO_3$ $[M+H]^+$ 542.3634, found 542.3637.

(3S, 4R, 5S)-3,4-isopropylidenedioxy-5-[(*O-tert*-butyldimethylsilyl)hydroxymethyl]-2-methyl-1-pyrroline (1e)

Colorless oil (45%), R_f = 0.45 (PE/EtOAc 5:5); IR (film) 2954, 2930, 2857, 1649, 1472, 1463, 1381, 1372, 1256, 1092 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.09 (6 H, s), 0.92 (9 H, s), 1.36 and 1.41 (3 H, s), 2.07 (3 H, s), 3.89 (1 H, t, J = 7.9 Hz), 3.92 (1 H, m), 4.00 (1 H, dd, J = 7.9, 4.4 Hz), 4.71 (1 H, dd, J = 5.3, 3.8 Hz), 4.87 (1 H, d, J = 5.3 Hz); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ –5.3 (CH_3), –5.2 (CH_3), 16.9 (CH_3), 18.6 (C), 26.1 (3 × CH_3), 26.2 (CH_3), 27.1 (CH_3), 61.8 (CH_2), 74.1 (CH), 78.3 (CH), 87.7 (CH), 112.1 (C), 174.8 (C); ESI-HRMS: calcd for $C_{15}H_{30}NO_3Si$ $[M+H]^+$ 300.1995; found 300.1999.

(3S, 4R, 5S)-3,4-isopropylidenedioxy-5-[(*O- tert*-butyldimethylsilyl)hydroxymethyl]-2-phenyl-1-pyrroline (1f)

Colorless oil (53%), R_f = 0.70 (PE/EtOAc 8:2); $[\alpha]_D^{20}$ = –110.9 (*c* 0.44, $CHCl_3$); IR (film) 2987, 2953, 2930, 2883, 1613, 1472, 1463, 1449, 1381, 1372, 1346, 1216 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.13 (3 H, s), 0.14 (3 H, s), 0.92 (9 H, s), 1.26 and 1.40 (3 H, s), 3.99 (1 H, t, J = 10.8 Hz), 4.15 (2 H, m), 4.89 (1 H, dd, J = 5.4, 4.0 Hz), 5.50 (1 H, d, J = 5.4 Hz), 7.40–7.50 (3 H, m, Ar-H), 8.00 (2 H, m, Ar-H); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ –5.3 (CH_3), –5.2 (CH_3), 18.5 (C), 26.0 (CH_3), 26.2 (3 × CH_3), 27.0 (CH_3), 62.0 (CH_2), 74.2 (CH), 78.3 (CH), 86.1 (CH), 112.2 (C), 129.2–133.4 (Ar-C), 171.8 (C); ESI-HRMS: calcd for $C_{20}H_{32}NO_3Si$ $[M+H]^+$ 362.2151, found 362.2150.

(3R, 4S, 5S)-3,4-isopropylidenedioxy-2-methyl-5-[(*O*-triphenylmethyl)hydroxymethyl]-1-pyrroline (1g)

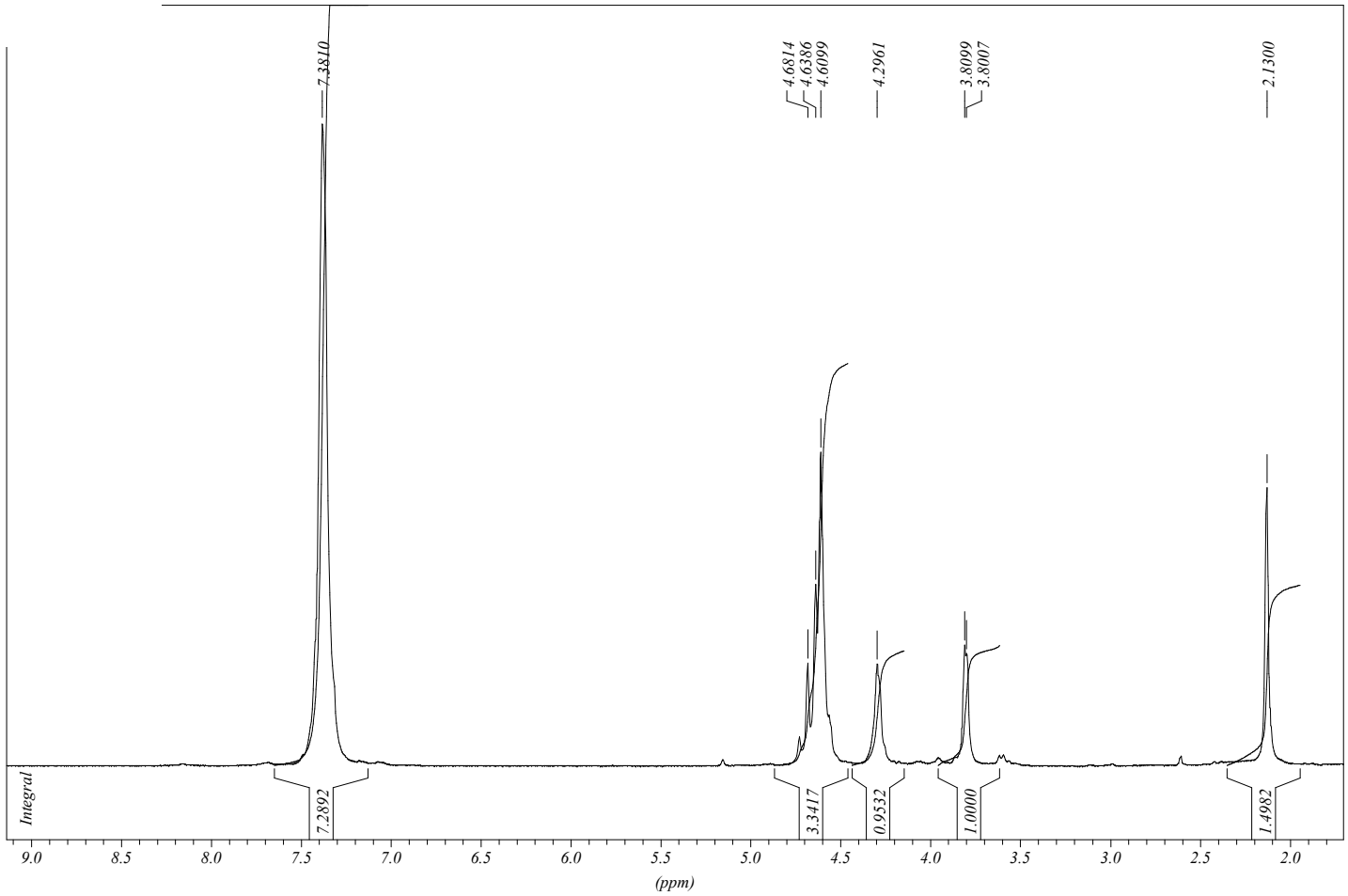
Colorless oil (88%), R_f = 0.63 (PE/EtOAc 7:3); $[\alpha]_D^{20}$ –43.1 (*c* 1.24, $CHCl_3$); IR (film) 3059, 2988, 2931, 2875, 1651, 1597, 1489, 1449, 1372, 1206, 1080 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.25 and 1.28 (3 H, s), 2.11 (3 H, s), 3.12 (1 H, dd, J = 9.4, 3.0 Hz), 3.40 (1 H, dd, J = 9.4, 3.6 Hz), 4.13 (1 H, bs), 4.31 (1 H,

d, J = 5.3 Hz), 4.97 (1 H, d, J = 5.3 Hz), 7.10–7.32 (15 H, m, Ar-H); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 17.5 (CH_3), 26.4 (CH_3), 27.5 (CH_3), 63.6 (CH_2), 76.6 (CH), 81.5 (CH), 87.5 (C), 87.9 (CH), 112.1 (C), 127.5, 128.3, 129.0 and 144.2 (4 × Ar-*C*), 176.1 (C); ESI-HRMS: calcd for $C_{28}H_{30}NO_3$ (MH^+) 428.2226; found 428.2222.

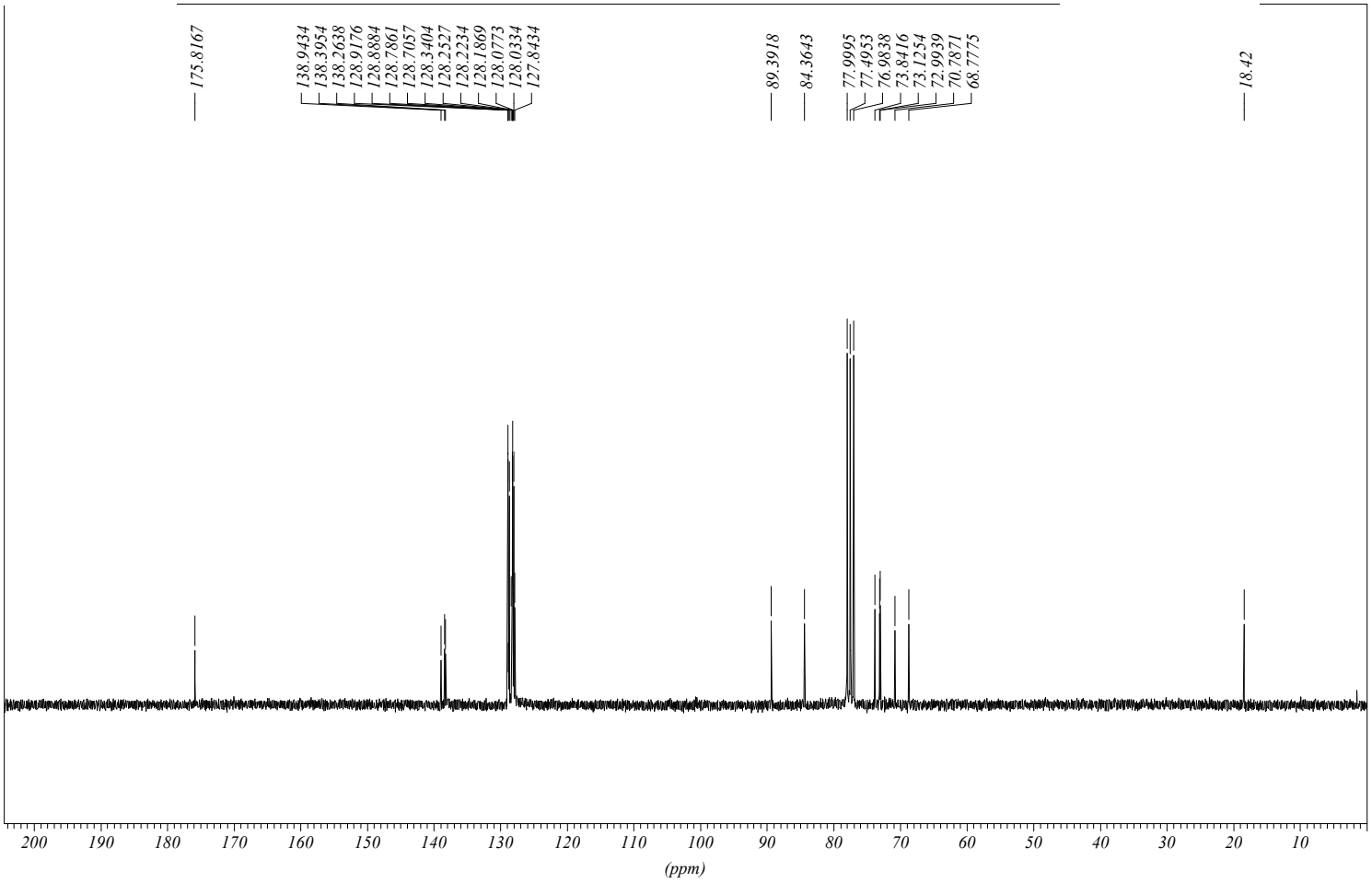
(3R, 4R, 5R)-3,4-dibenzyloxy-5-benzyloxymethyl-2-phenyl-1-pyrroline (1h)

Yellow oil (50%), R_f = 0.45 (PE/Et_2O 6:4); $[\alpha]_D^{20}$ = +14.6 (*c* 0.8, $CHCl_3$); IR (film) 3062, 3030, 2861, 1615, 1495, 1454, 1360 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.47 (1 H, dd, J = 9.7, 8.0 Hz), 3.91 (1 H, dd, J = 9.7, 4.4 Hz), 4.26 (1 H, t, J = 2.0 Hz), 4.45 (1 H, ddd, J = 8.0, 4.4, 2.0 Hz), 4.53 (2 H, bs), 4.56 (1 H, d, J = 11.9 Hz), 4.61 (1 H, d, J = 11.9 Hz), 4.63 (1 H, d, J = 11.9 Hz), 4.69 (1 H, d, J = 11.9 Hz), 5.06 (1 H, d, J = 2.0 Hz), 7.22–7.45 (m, 18 H, Ar-*H*), 7.84 (2 H, m, Ar-H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 71.51, 71.52 (CH_2), 71.6 (CH_2), 73.5 (CH_2), 76.5 (CH), 83.5 (CH), 89.1 (CH), 127.5–128.6 (Ar-CH), 130.9 (Ar-CH), 133.0, 137.3, 138.1, 138.3 (4 × Ar-C), 171.5 (C); ESI-HRMS: calcd for $C_{32}H_{32}NO_3$ $[M+H]^+$ 478.2383, found 478.2372.

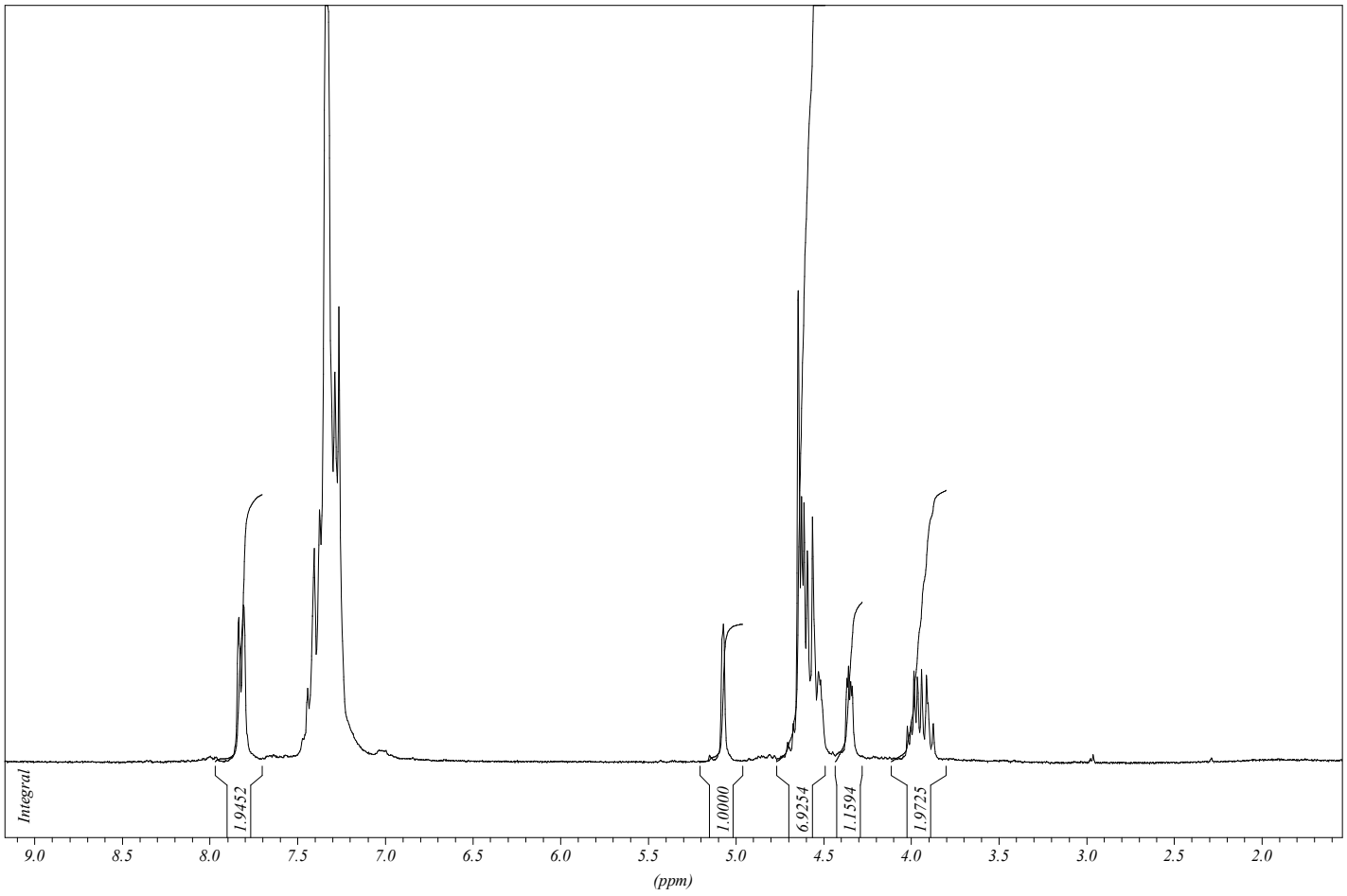
(^{1}H-NMR spectrum of **1a** at 250 MHz in $CDCl_3$)



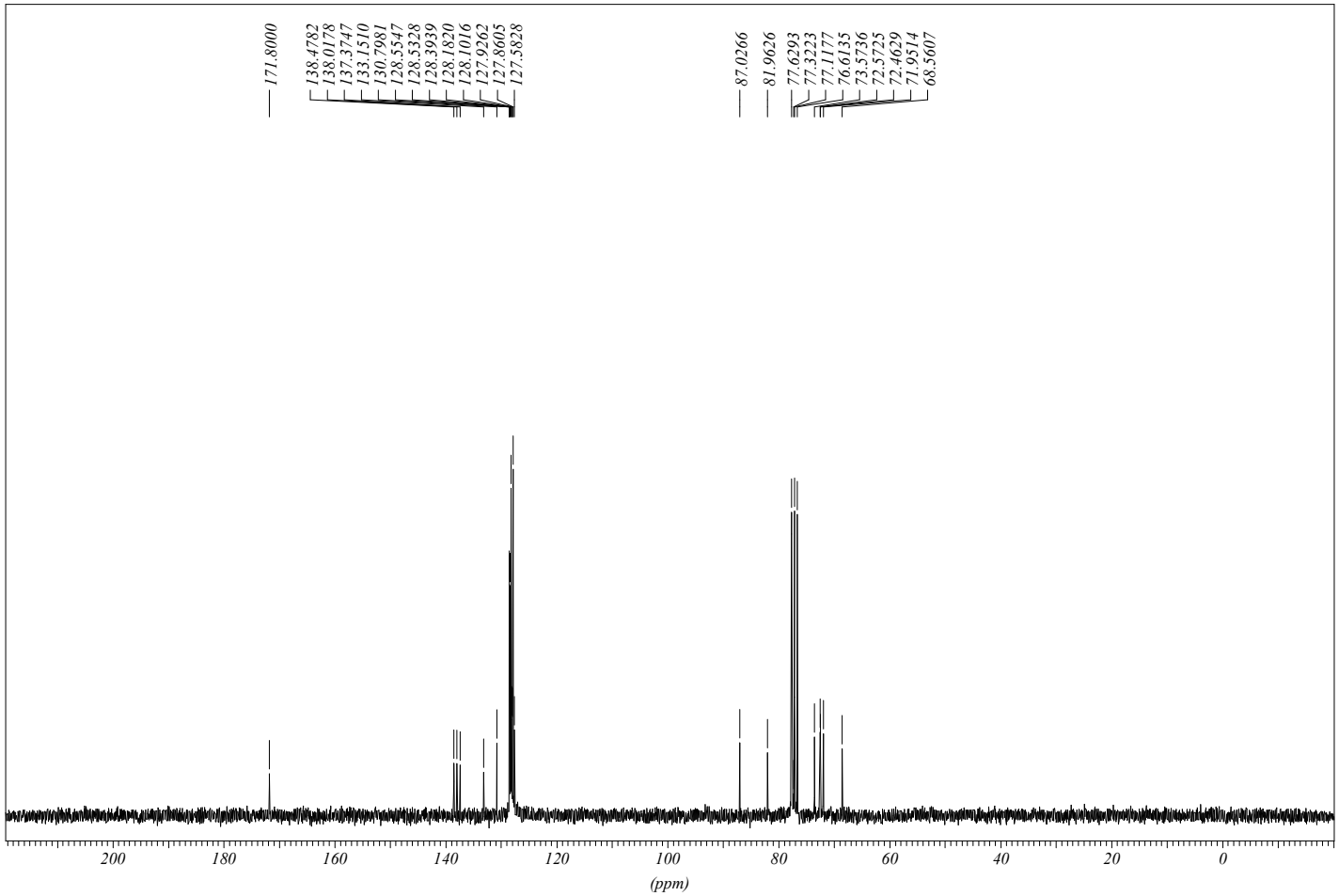
(^{13}C-NMR spectrum of **1a** in $CDCl_3$)



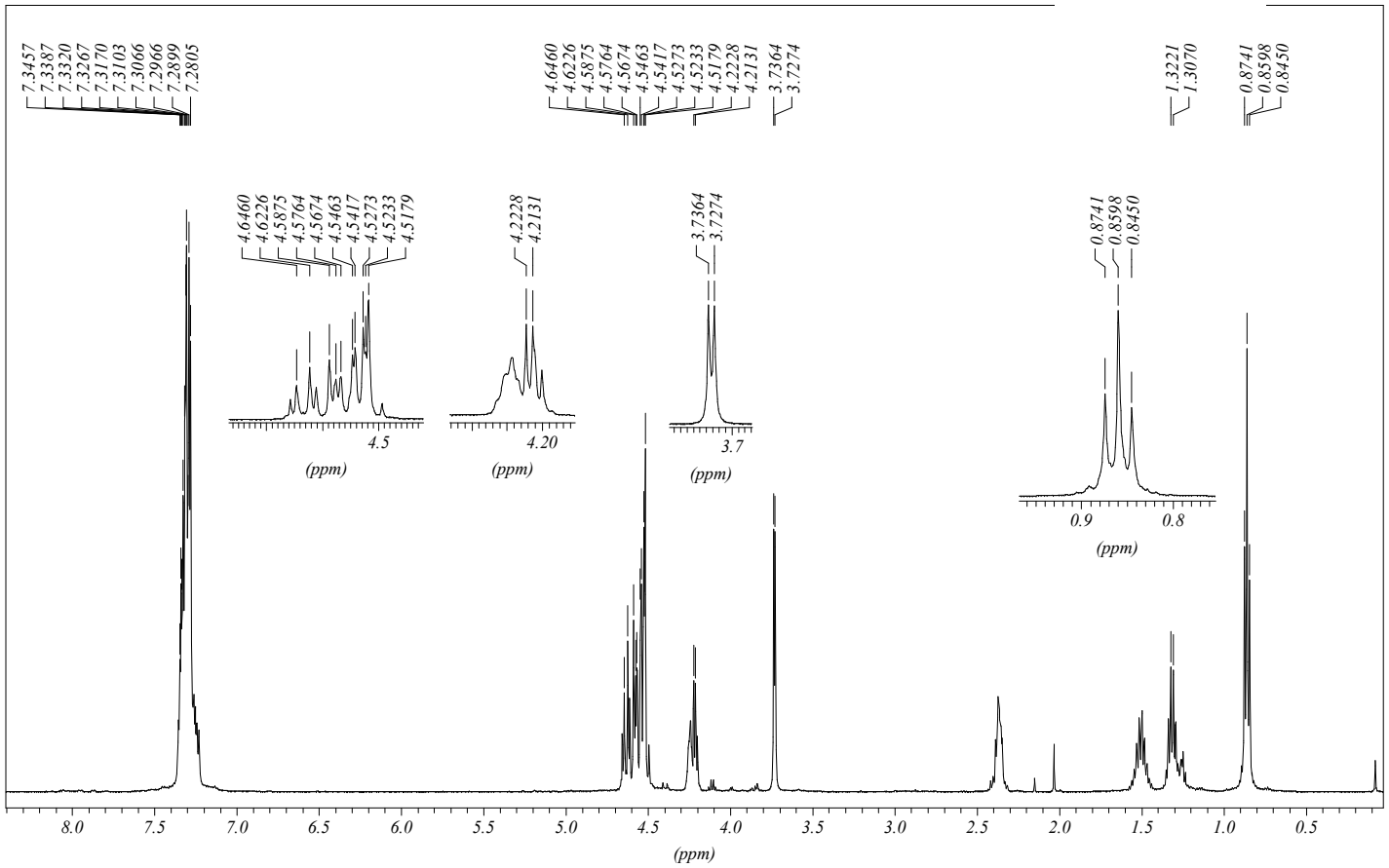
(^{1}H-NMR spectrum of **1b** at 250 MHz in $CDCl_3$)



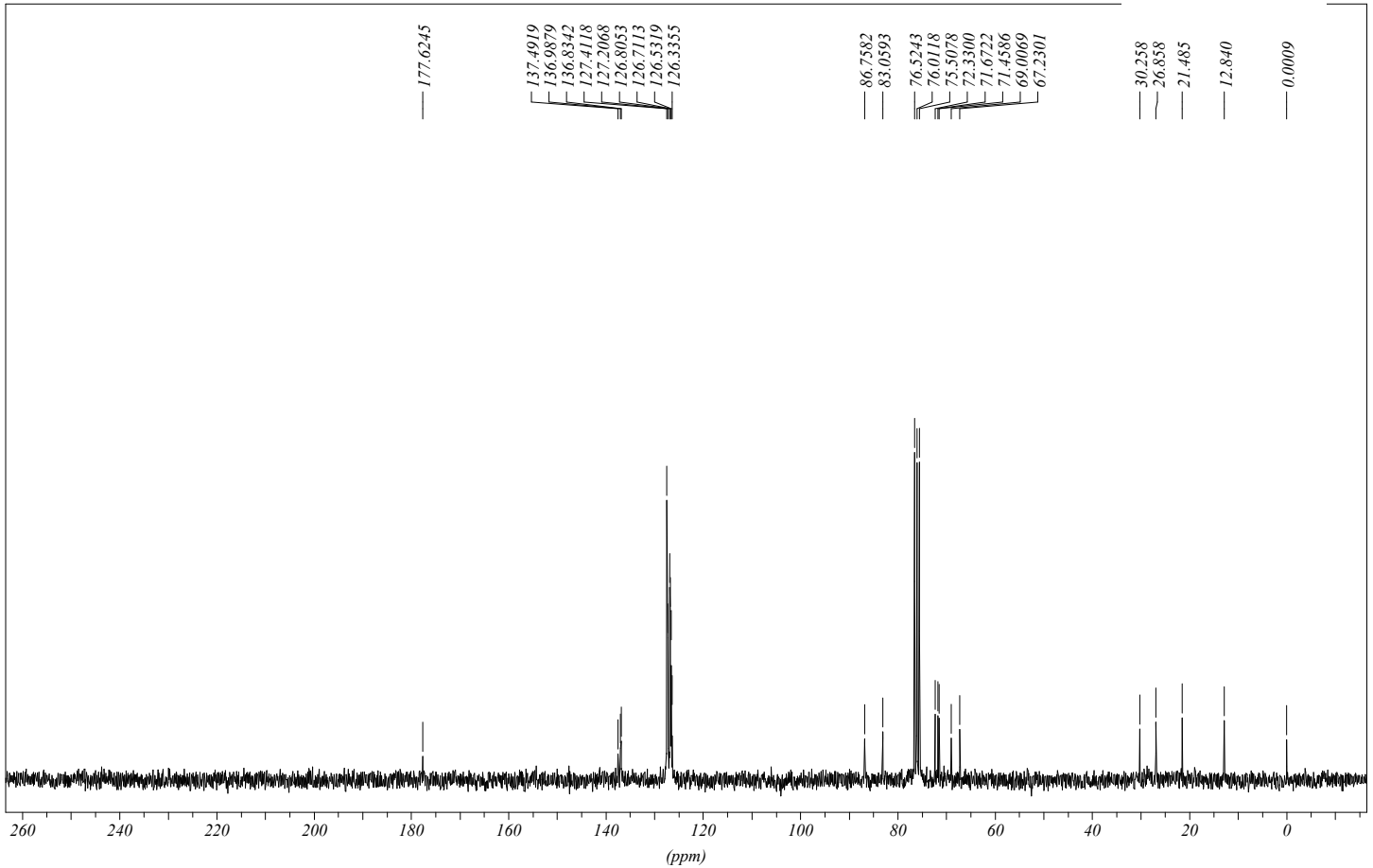
(^{13}C-NMR spectrum of **1b** in $CDCl_3$)



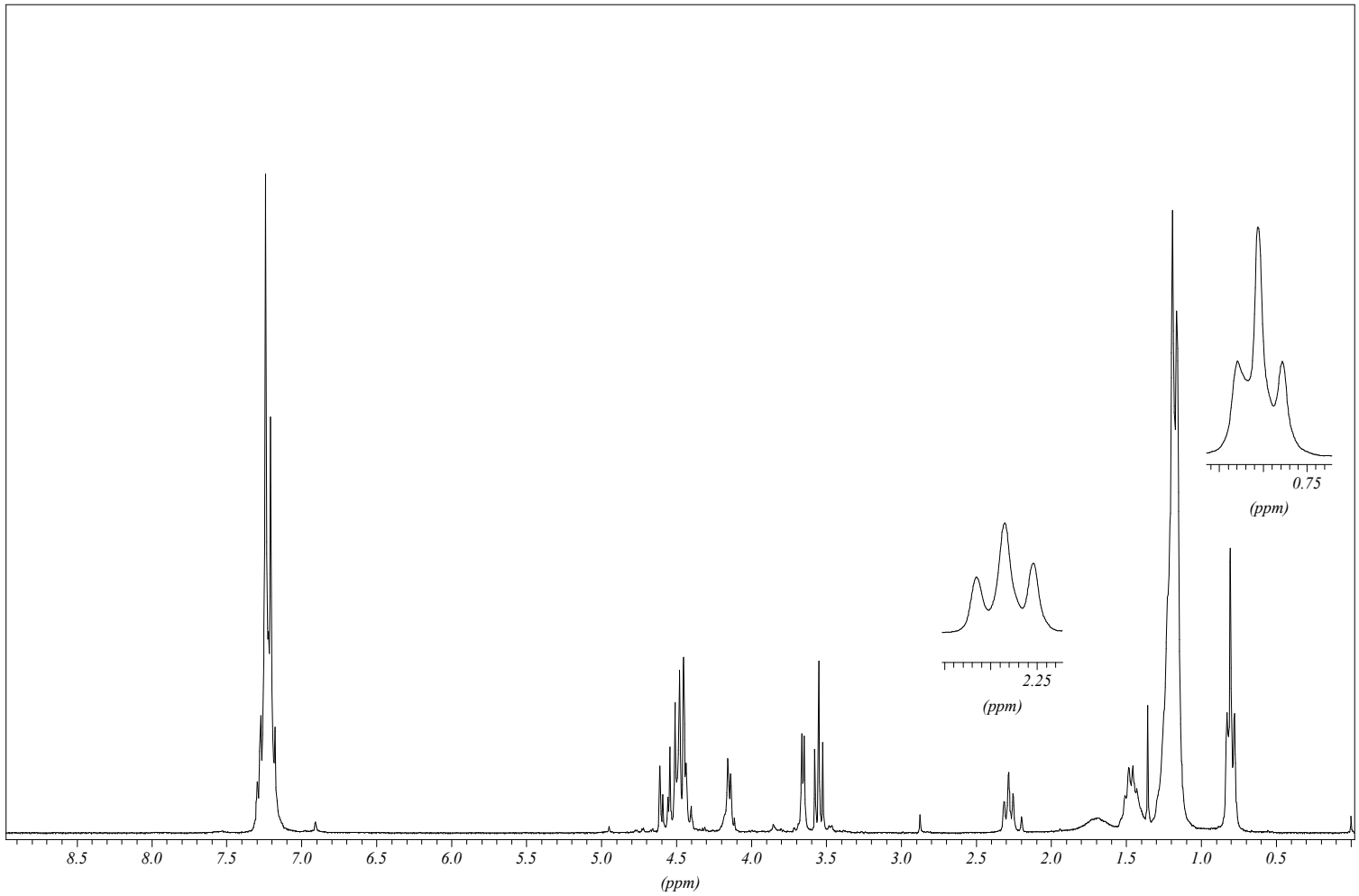
(^{1}H-NMR spectrum of **1c** at 250 MHz in $CDCl_3$)



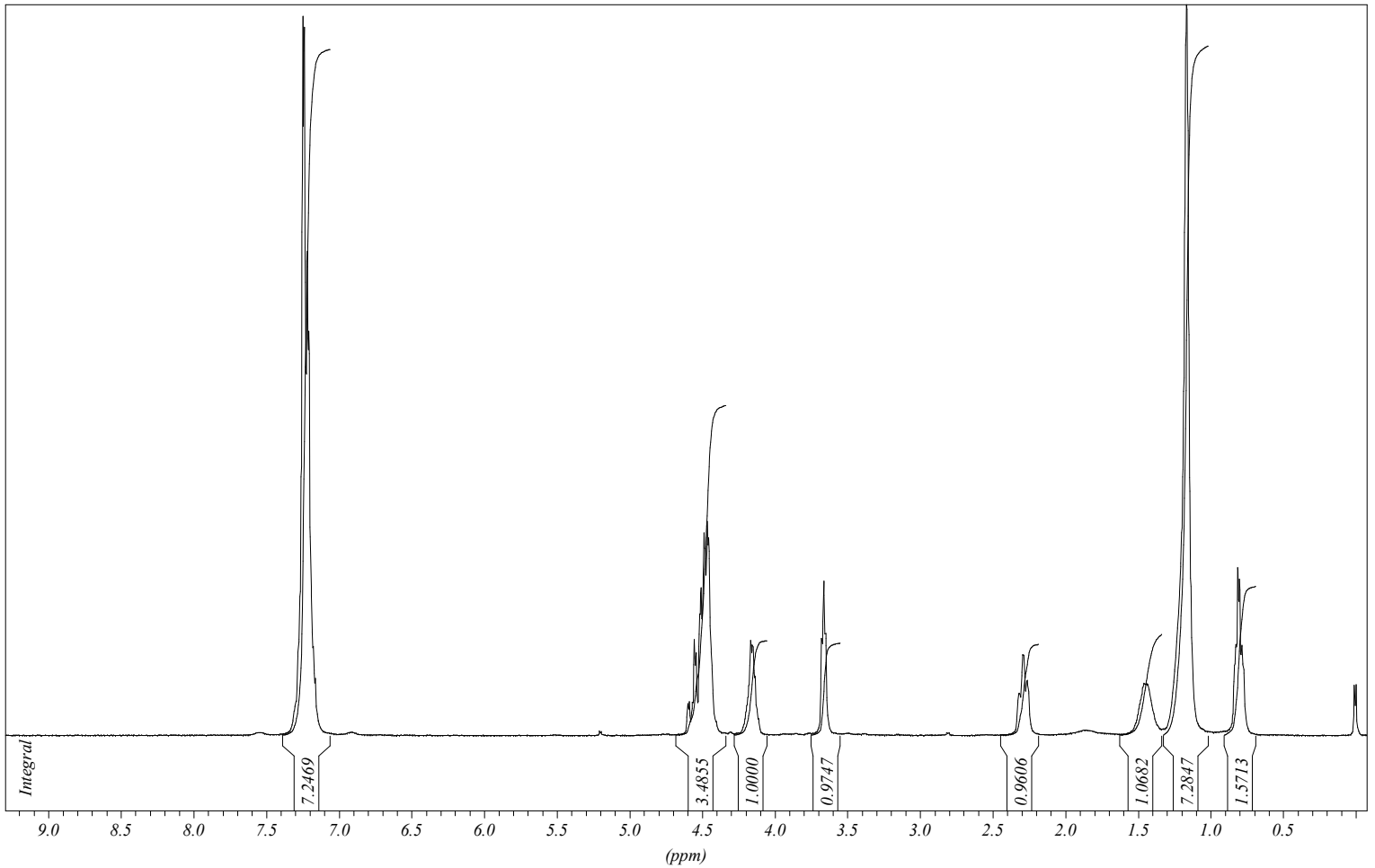
(^{13}C-NMR spectrum of **1c** in $CDCl_3$)



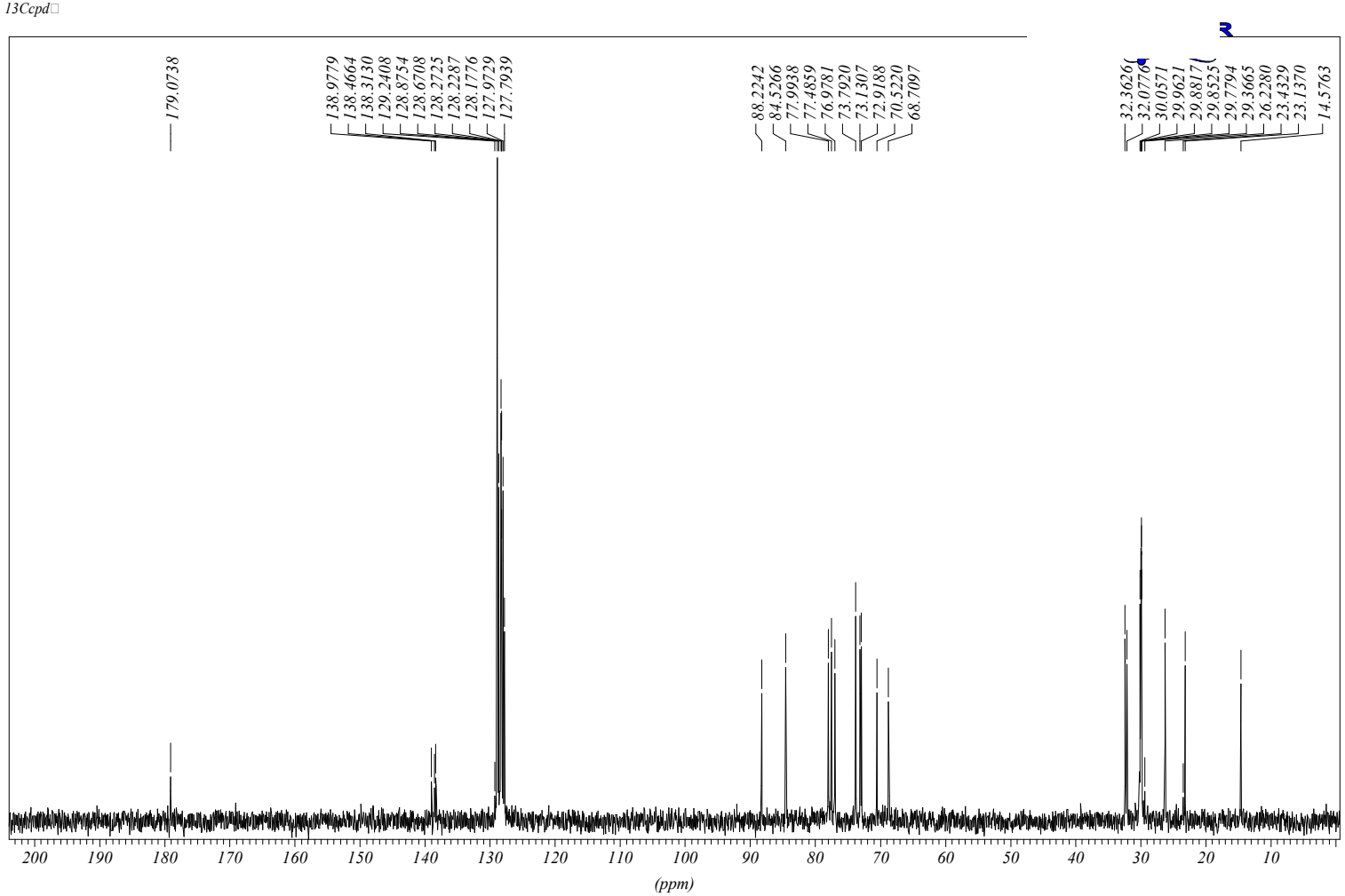
(^{1}H-NMR spectrum of **1d** at 250 MHz, after a second purification)



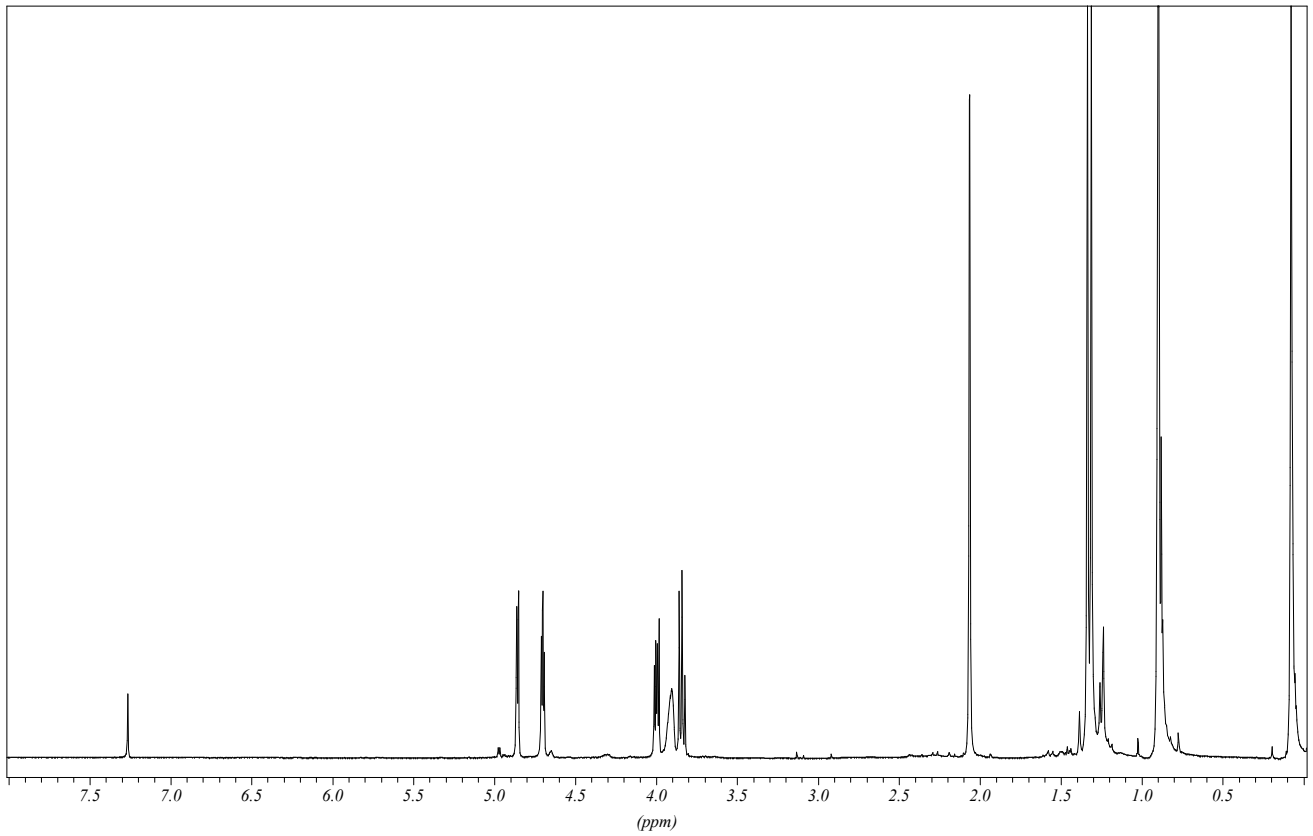
(^{1}H-NMR spectrum of **1d** after three purifications , in $CDCl_3$ at 250 MHz)



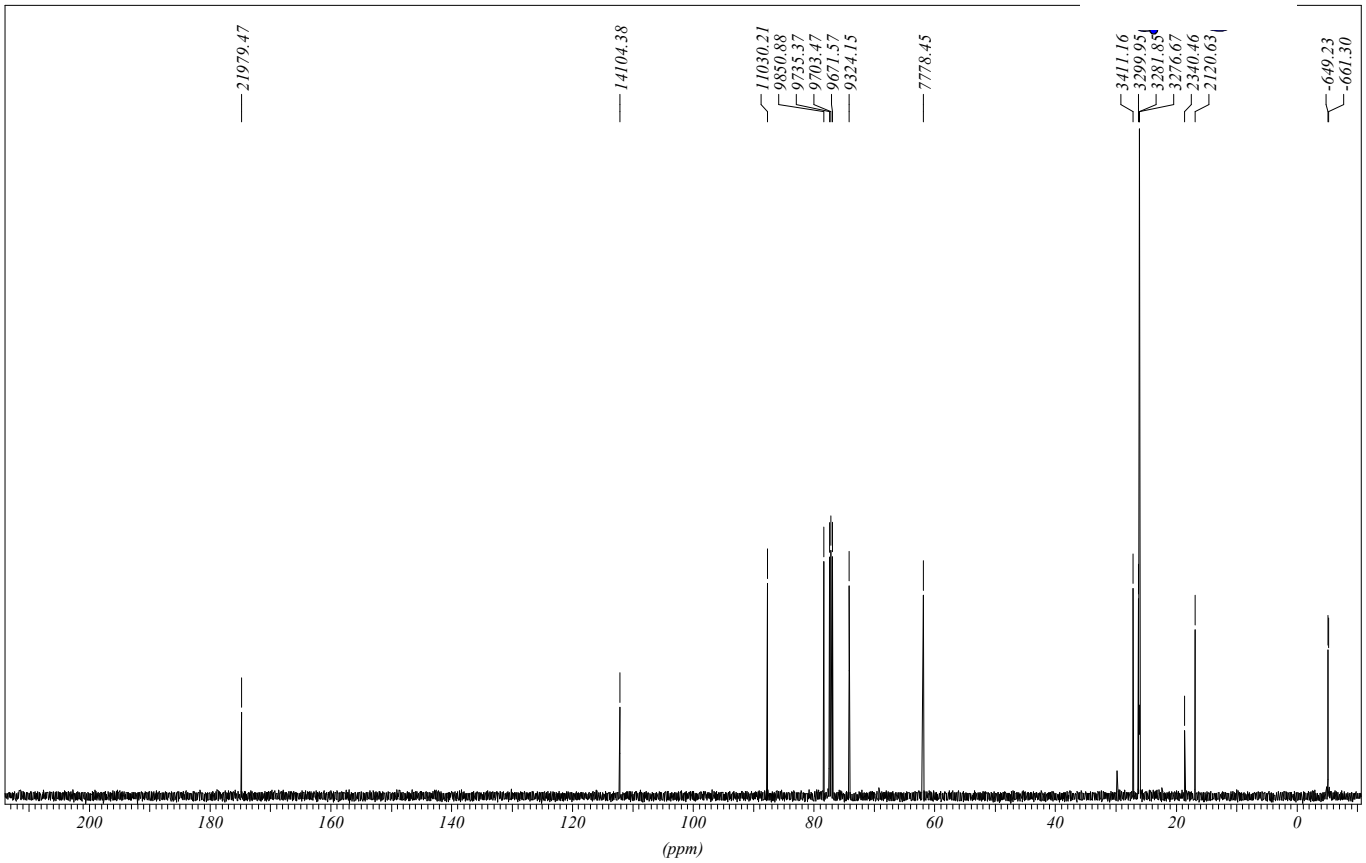
(^{13}C-NMR spectrum of **1d** in $CDCl_3$)



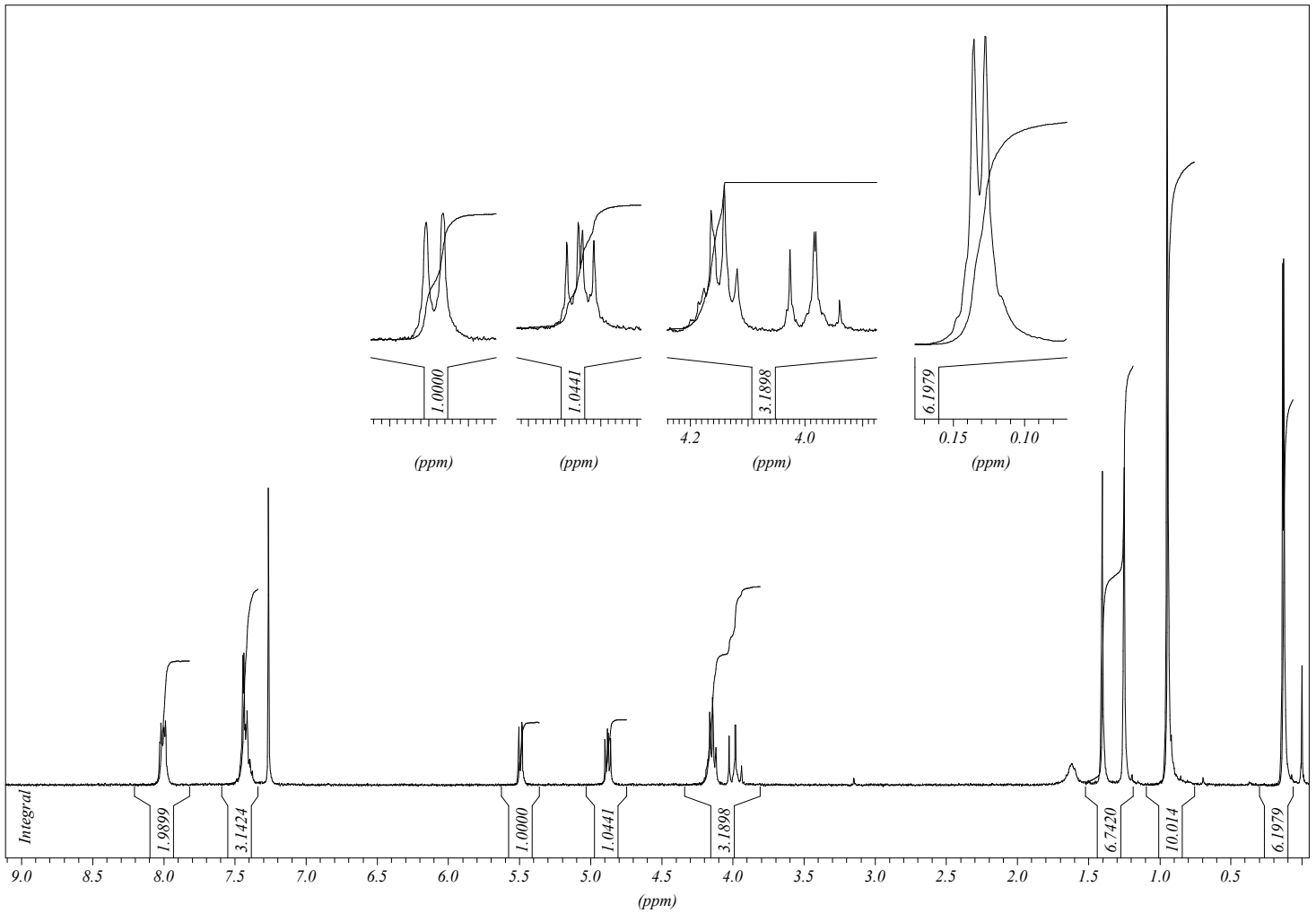
(^{1}H-NMR spectrum of **1e** at 250 MHz in $CDCl_3$)



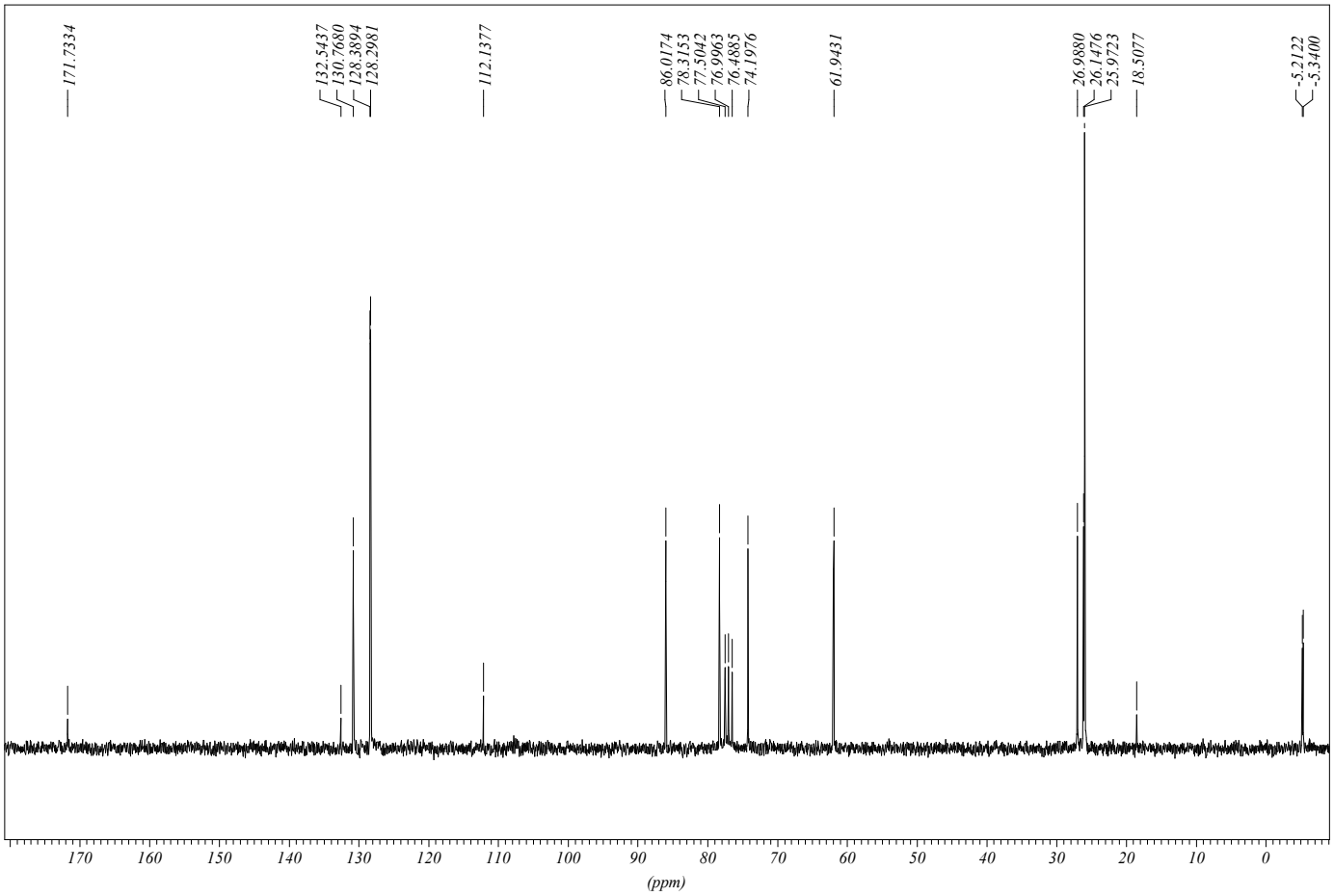
(^{13}C-NMR spectrum of **1e** in $CDCl_3$)



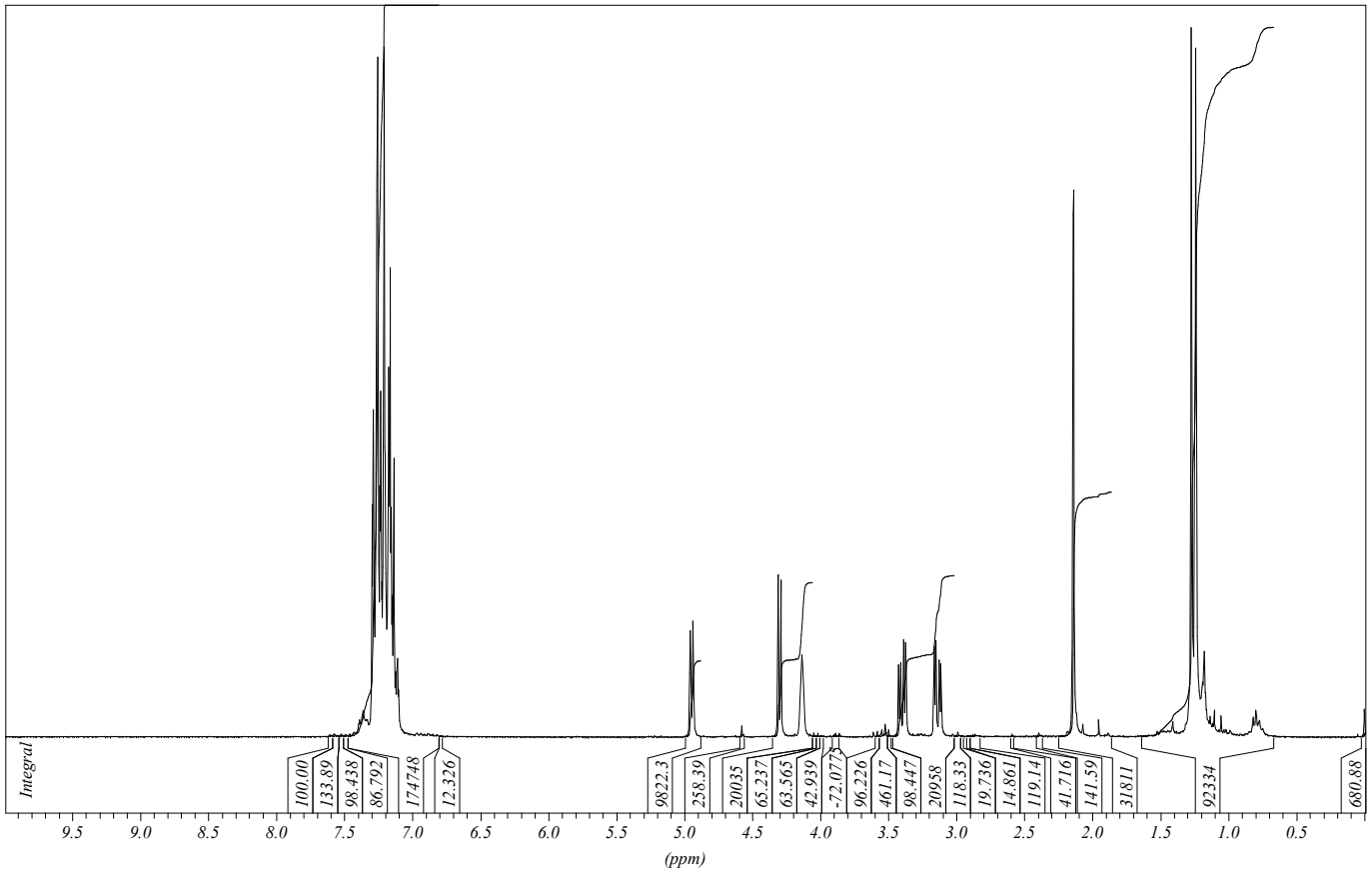
(^{1}H-NMR spectrum of **1f** at 250 MHz in $CDCl_3$)



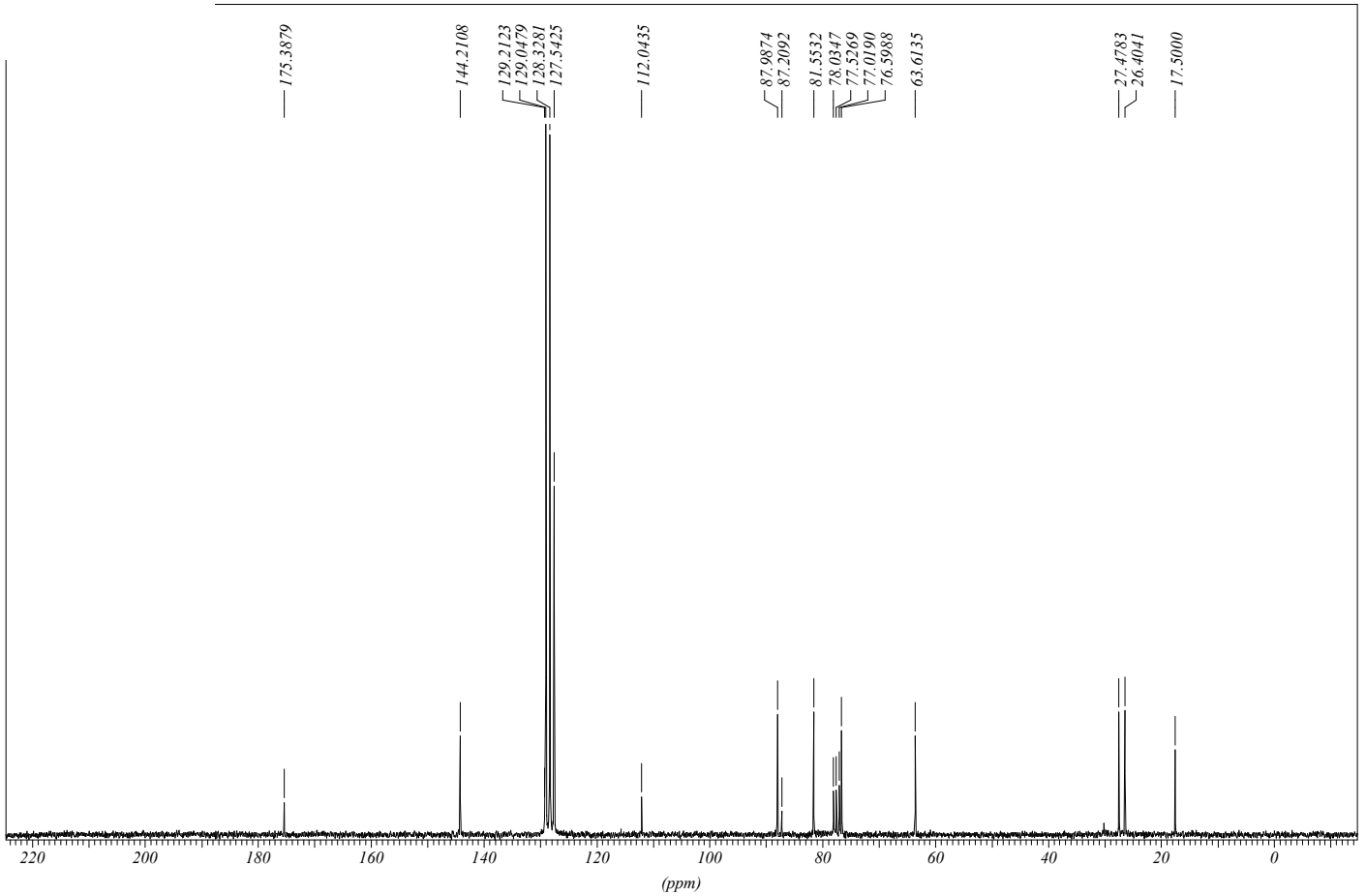
(^{13}C-NMR spectrum of **1f** in $CDCl_3$)



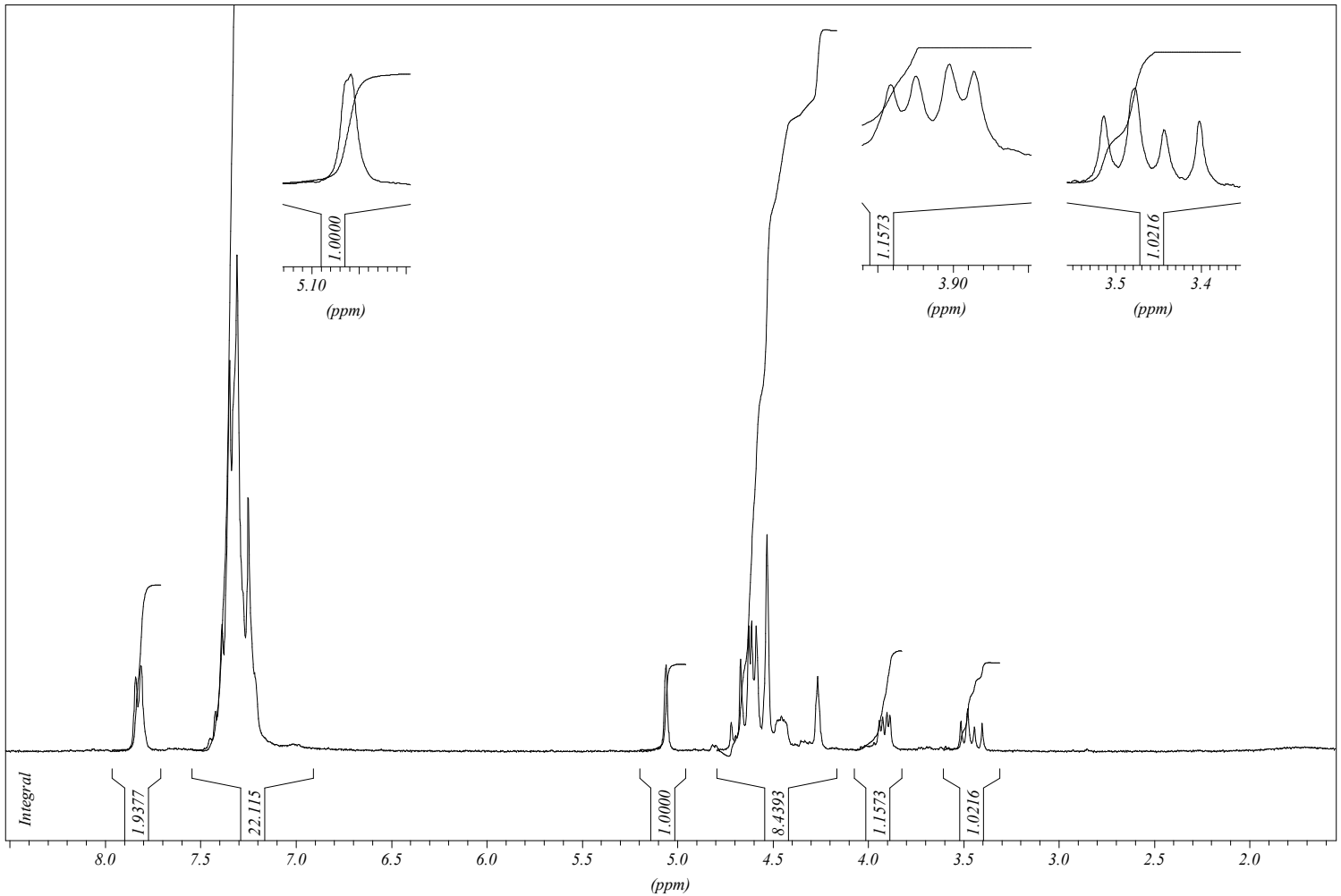
(^{1}H-NMR spectrum of **1g** at 250 MHz in $CDCl_3$)



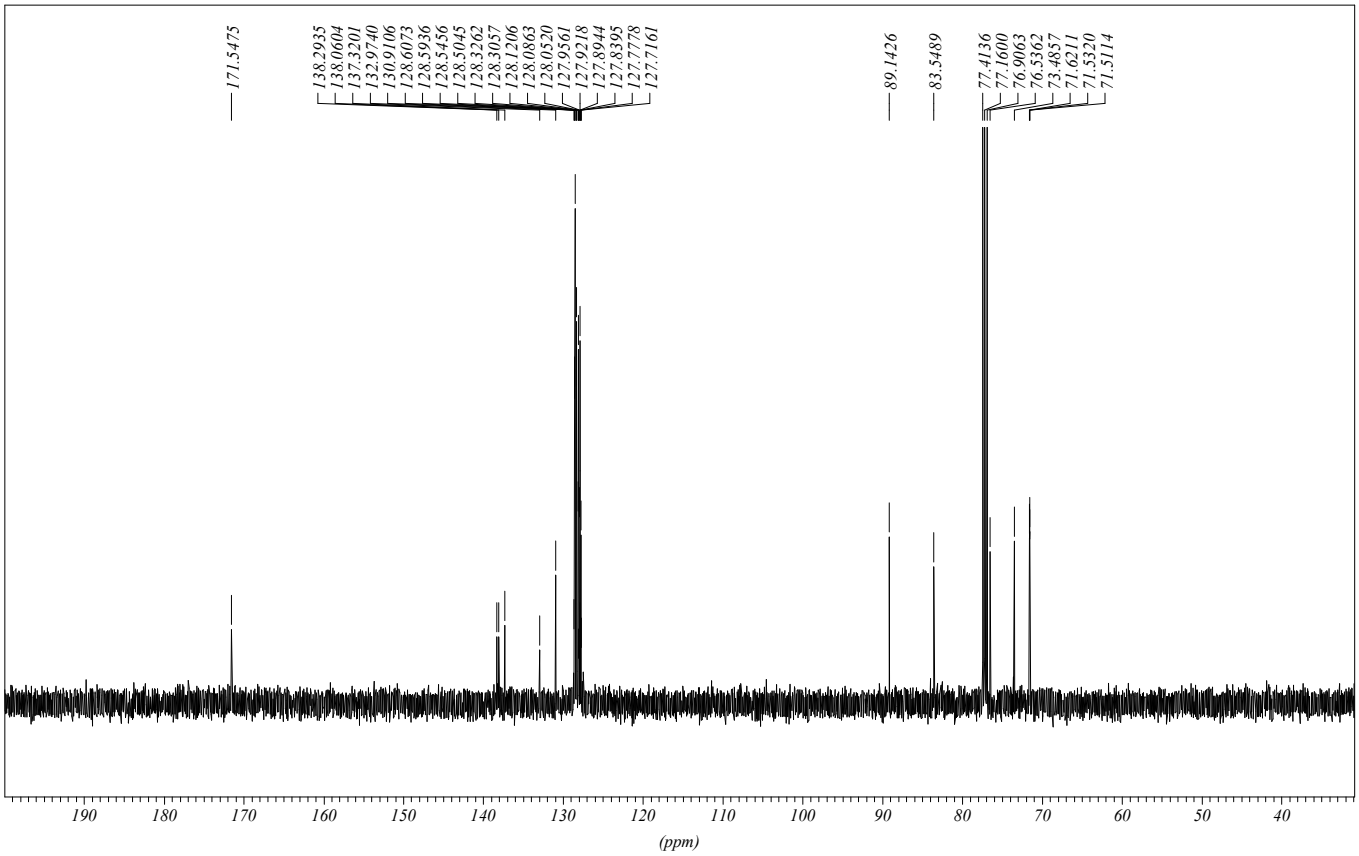
(^{13}C-NMR spectrum of **1g** in $CDCl_3$)



(^{1}H-NMR spectrum of **1h** at 250 MHz in $CDCl_3$)



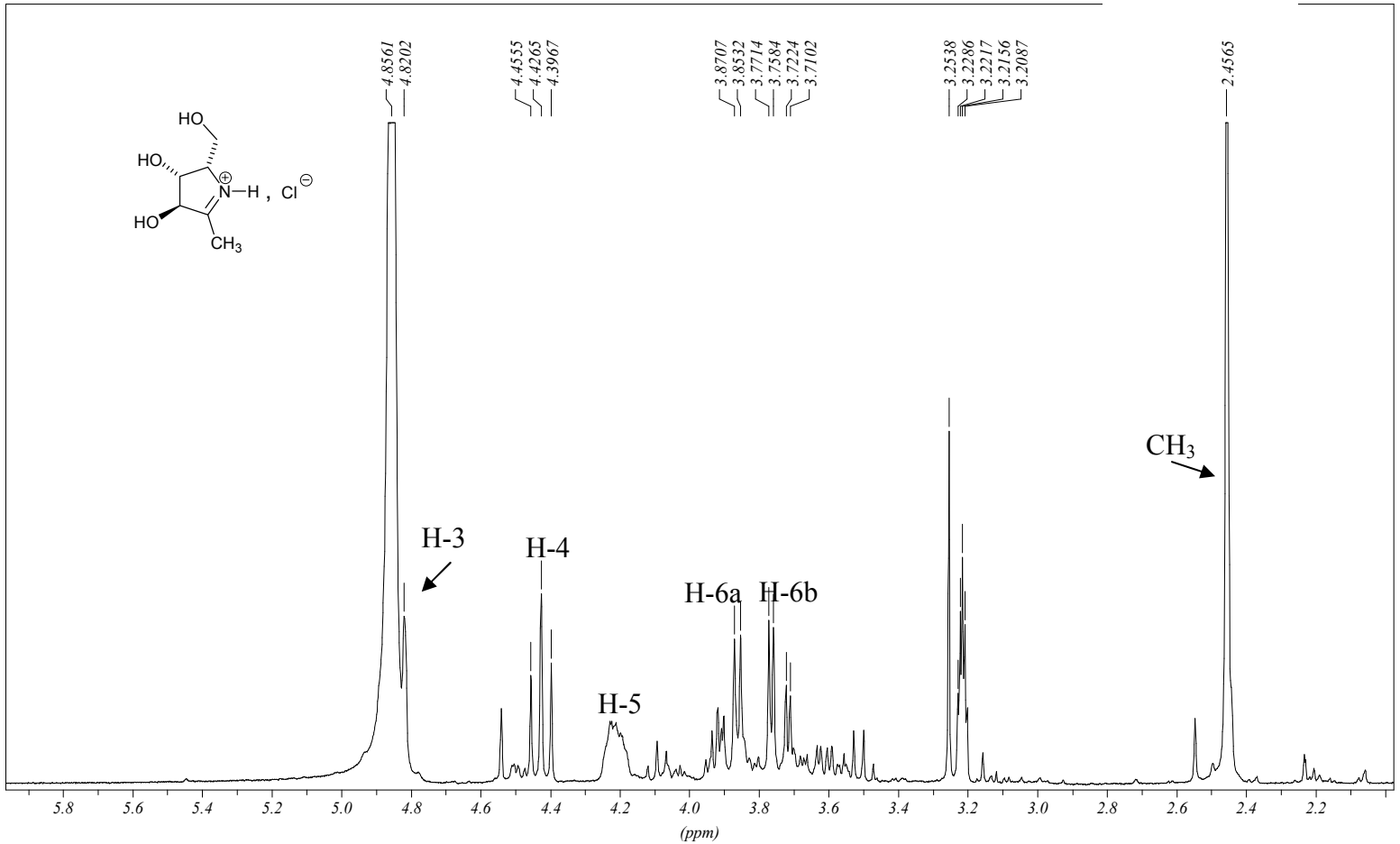
(^{13}C-NMR spectrum of **1h** in $CDCl_3$)



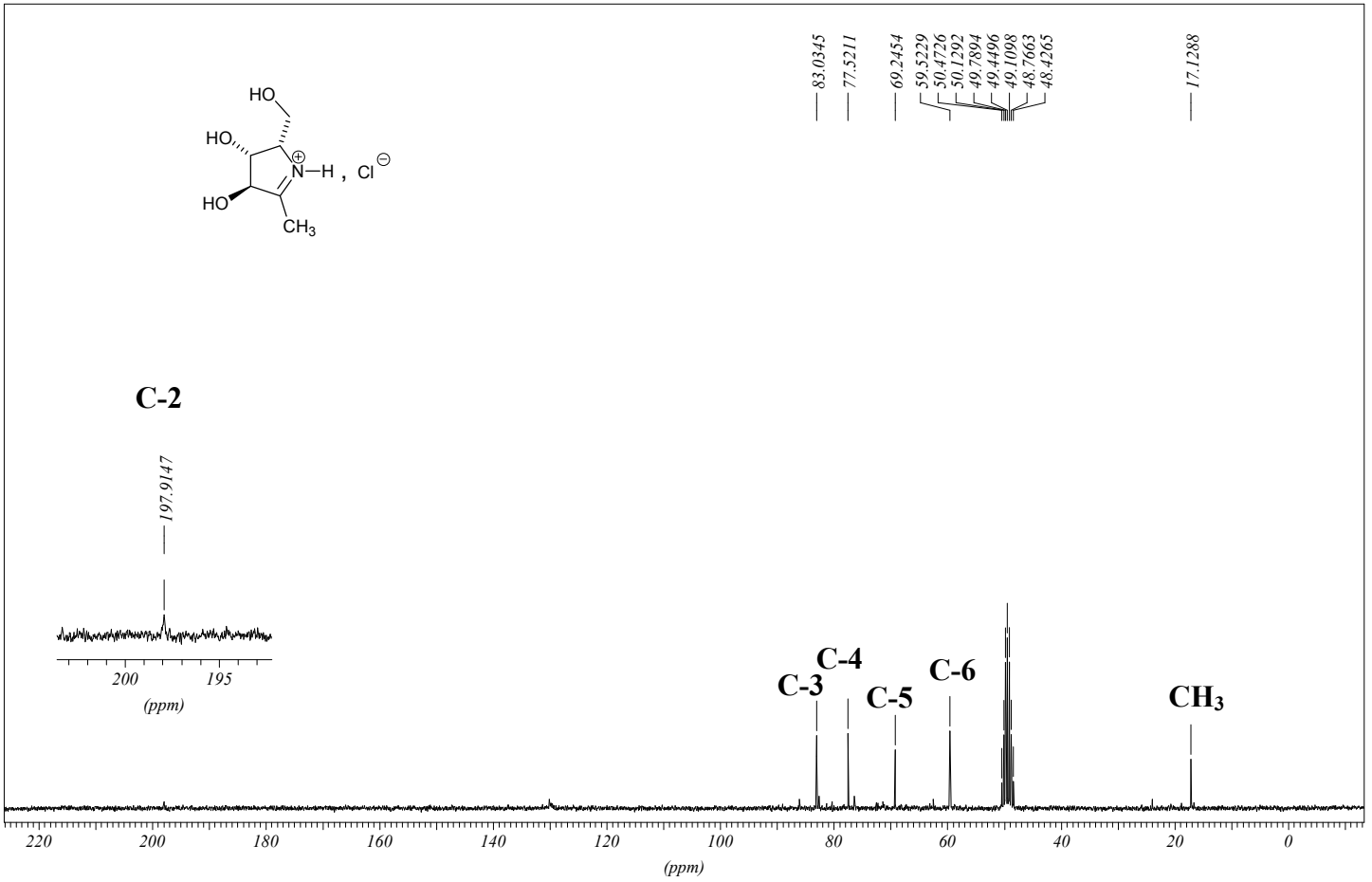
Deprotection of 1a :

To a solution of **1a** (100 mg, 0.24 mmol) in dry CH_2Cl_2 (1.0 mL) at –60 °C was added a 1M solution of BCl_3 in CH_2Cl_2 (1.2 mL, 1.2 mmol) under argon atmosphere. The resulting mixture was stirred for 8 h at –60 °C. Methanol (1.0 mL) was then added and the solution was slowly warmed to rt. Evaporation of the solvents gave an orange oil which was successively washed with Et_2O (2 × 2 mL) and $CHCl_3$ (2 × 2 mL) to remove the by-products. Compound **9** (36 mg, 84%) was isolated as its iminium chloride as deduced from the ^{13}C-NMR spectrum (δ, 197.9, C-2). Purification was performed by chromatography on a hydrophobic HP20 support (Prolabo) (eluent, 1 mM HCl) to give **9** as a colourless foam : ^{1}H NMR (250 MHz; CD_3OD) δ 2.46 (3 H, s), 3.73 (1 H, dd, J = 12.2, 3.2 Hz), 3.88 (1 H, dd, J = 12.2, 4.4 Hz), 4.20 (1 H, m), 4.41 (1 H, t, J = 7.3 Hz), 4.80 (1 H, d); ^{13}C NMR (125 MHz; CD_3OD) δ 17.1 (CH_3), 59.5 (CH_2), 69.2 (CH), 77.5 (CH), 83.0 (CH), 197.9 (C); MS (ESI) *m/z* : 146 (100%, MH^+); ESI-HRMS: calcd for $C_6H_{12}NO_3$ $[M+H]^+$ 146.0817, found 146.0815.

(^{1}H-NMR spectrum of **9** in CD_3OD)

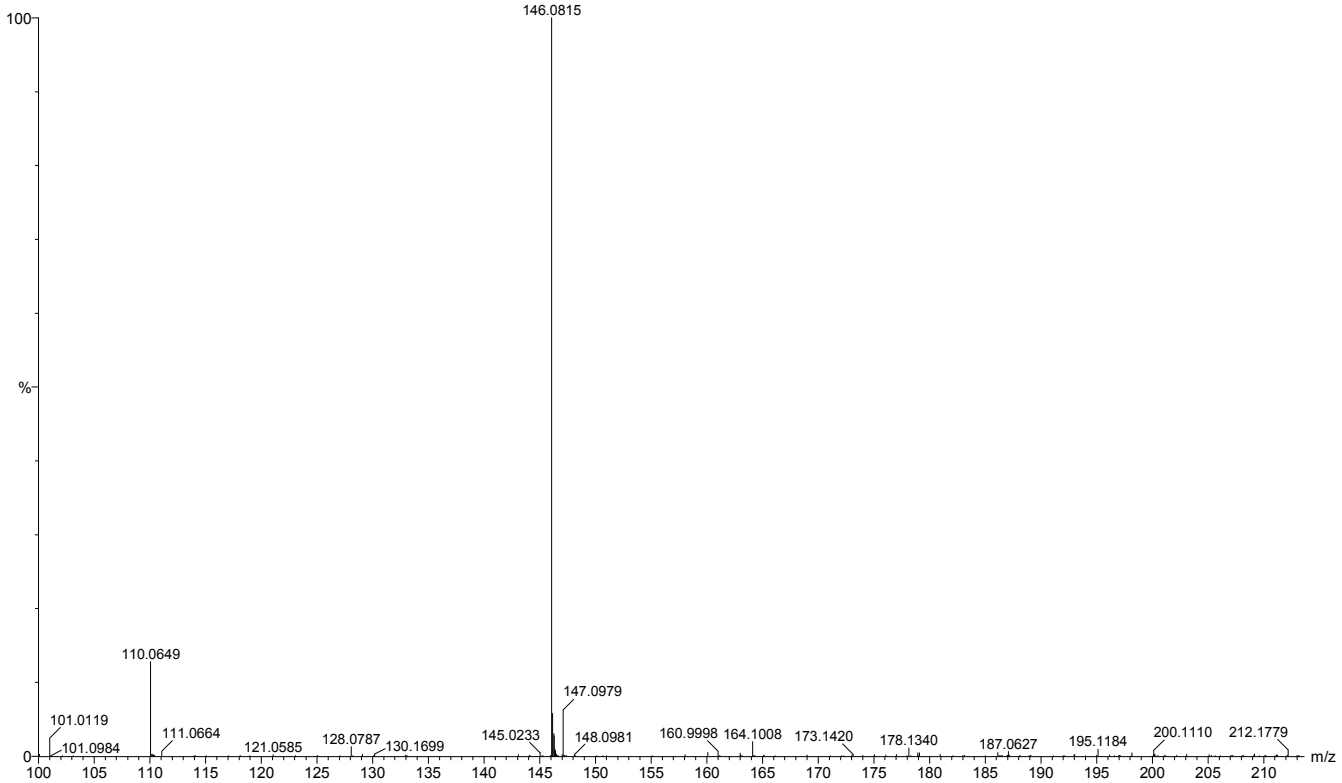


(^{13}C-NMR spectrum of **9** in CD_3OD)

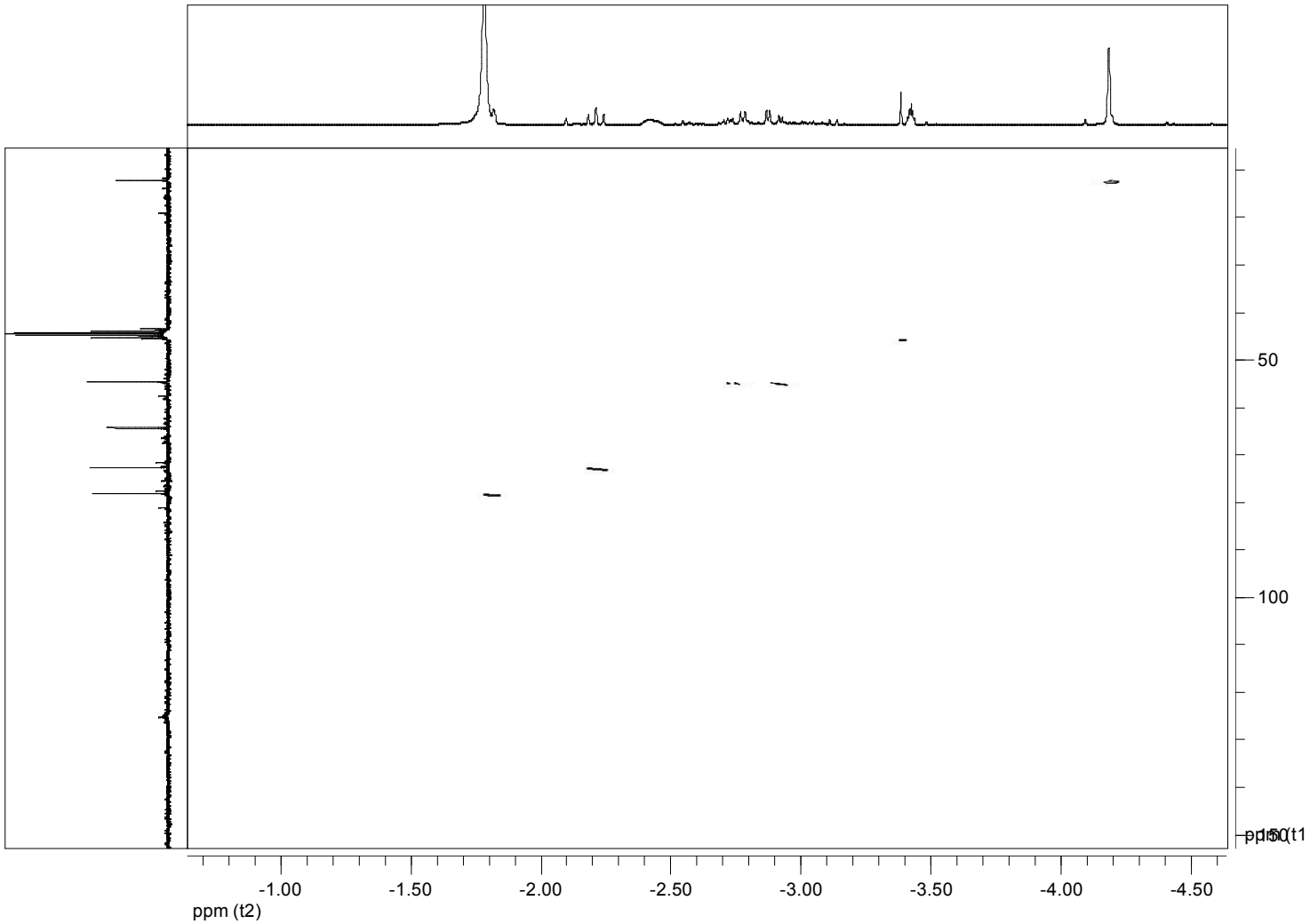


ESI-HRMS spectrum of **9**.

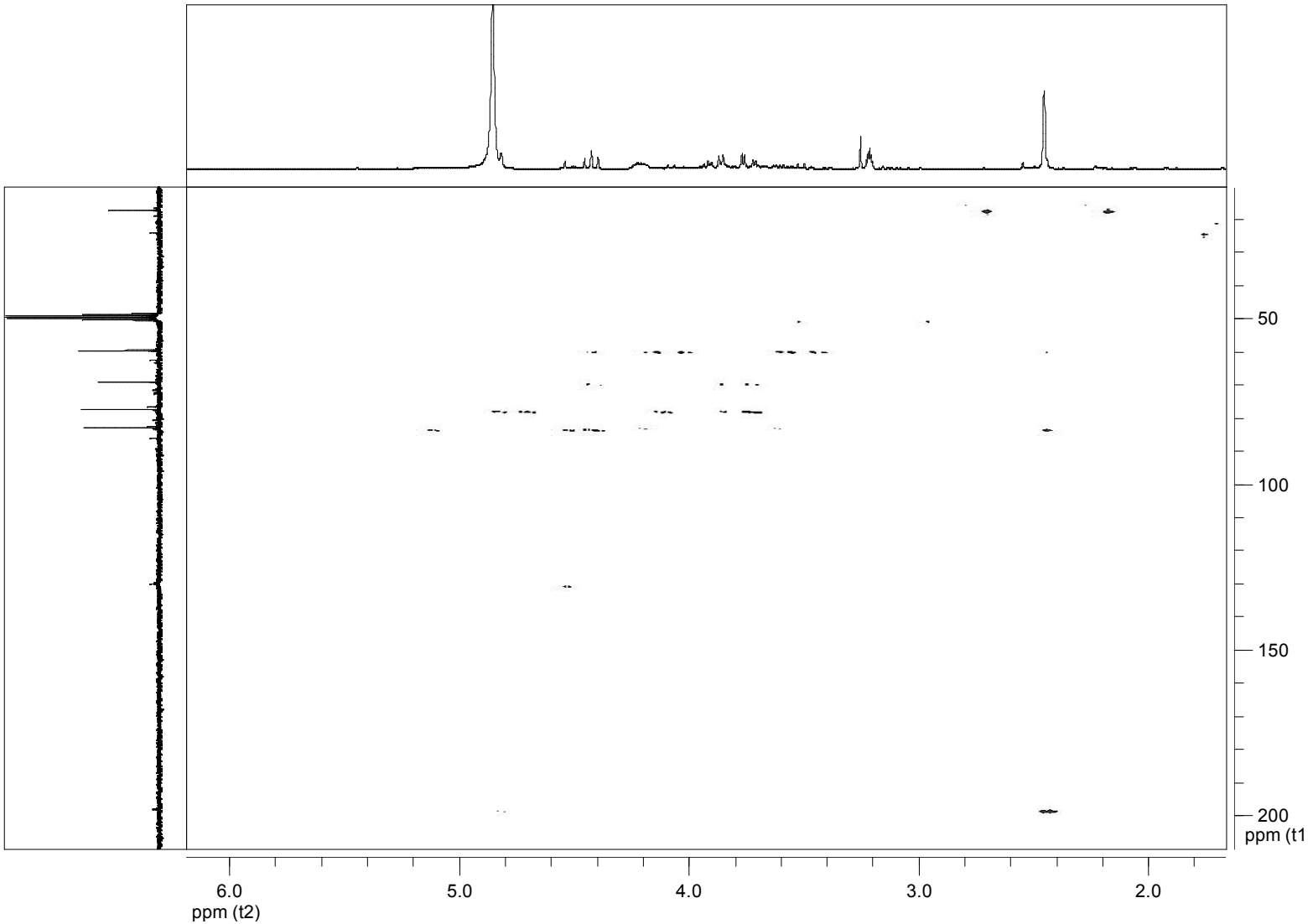
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
146.0815	146.0817	-0.2	-1.3	1.5	1	C6 H12 N O3



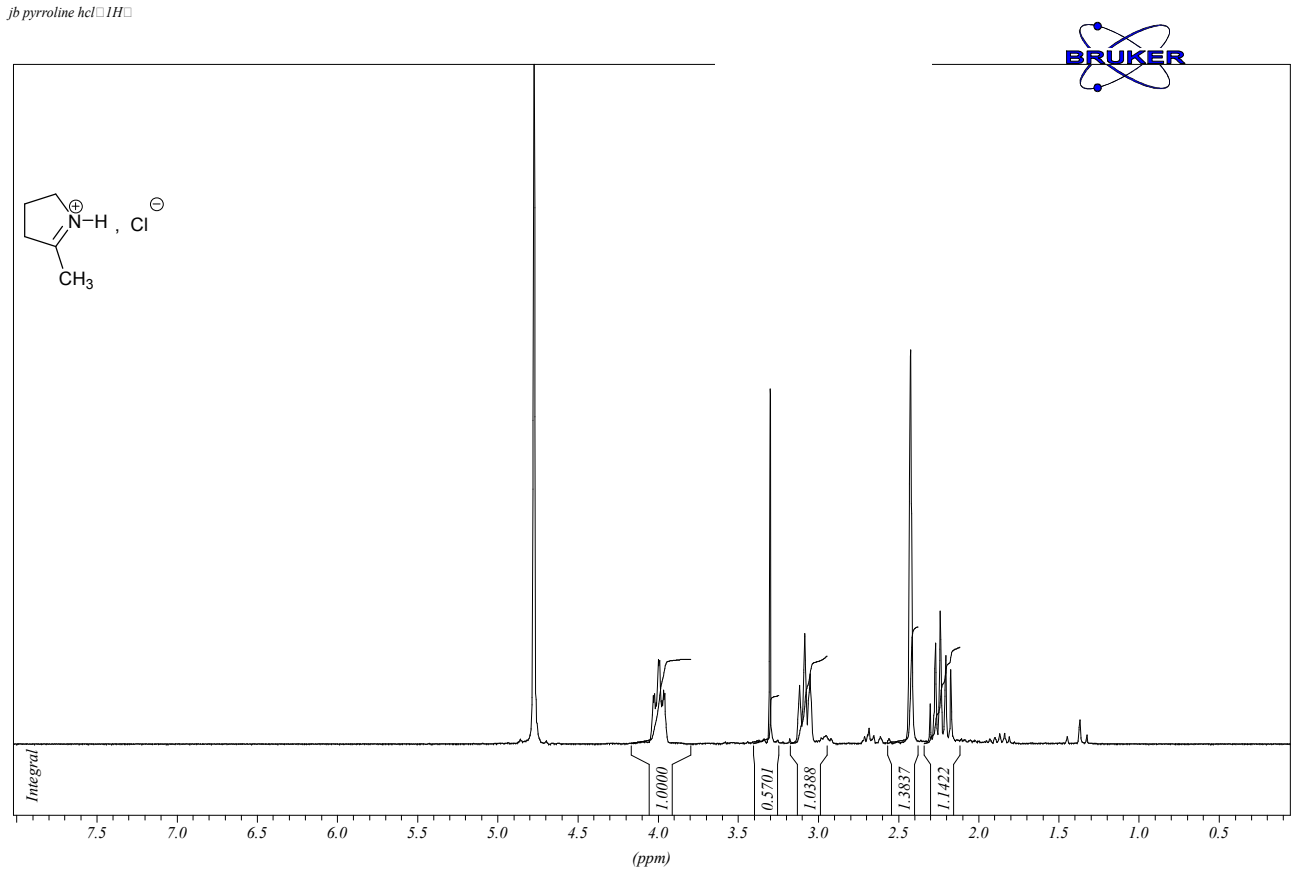
HMQC spectrum of **9**



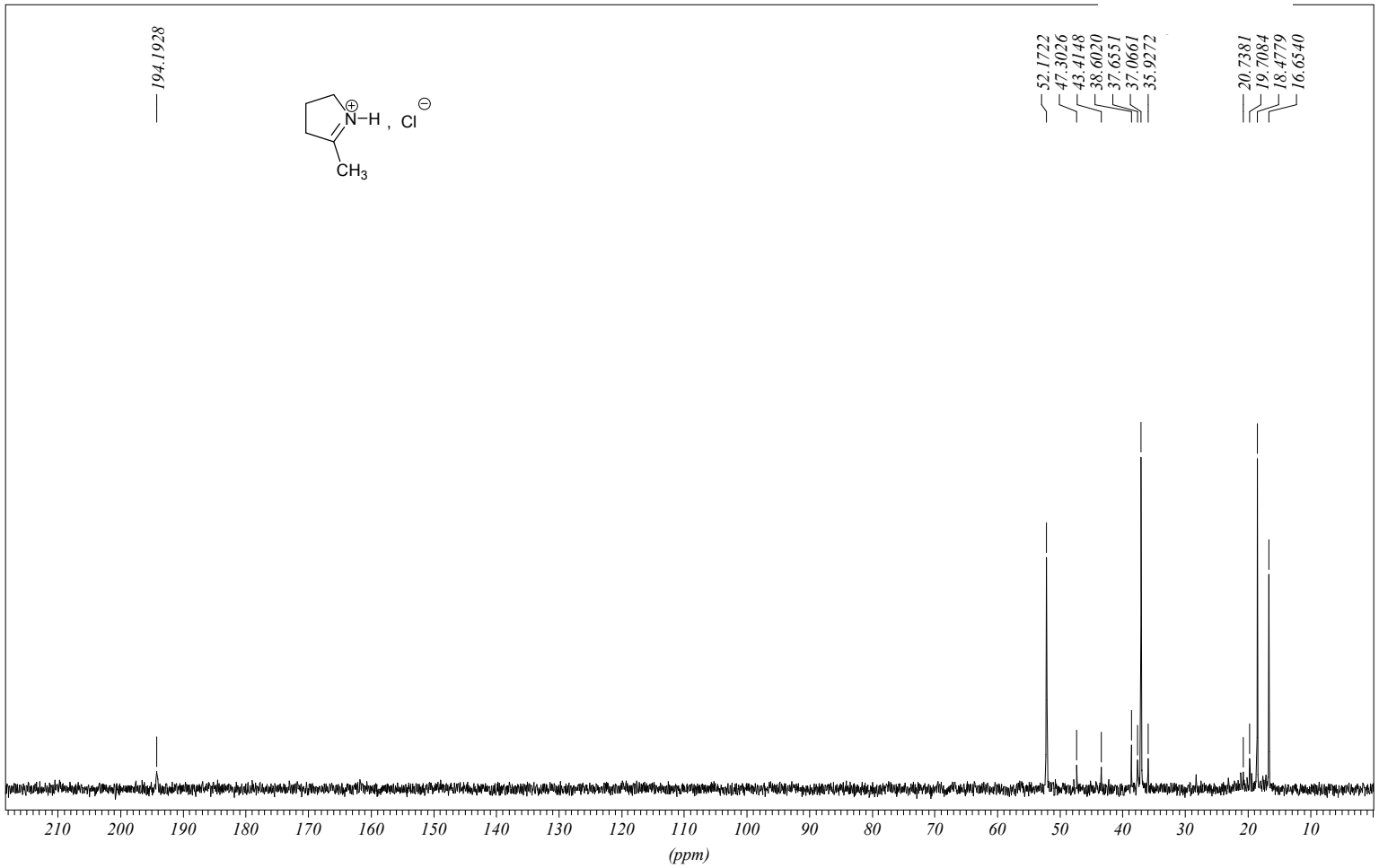
HMBC spectrum of **9**



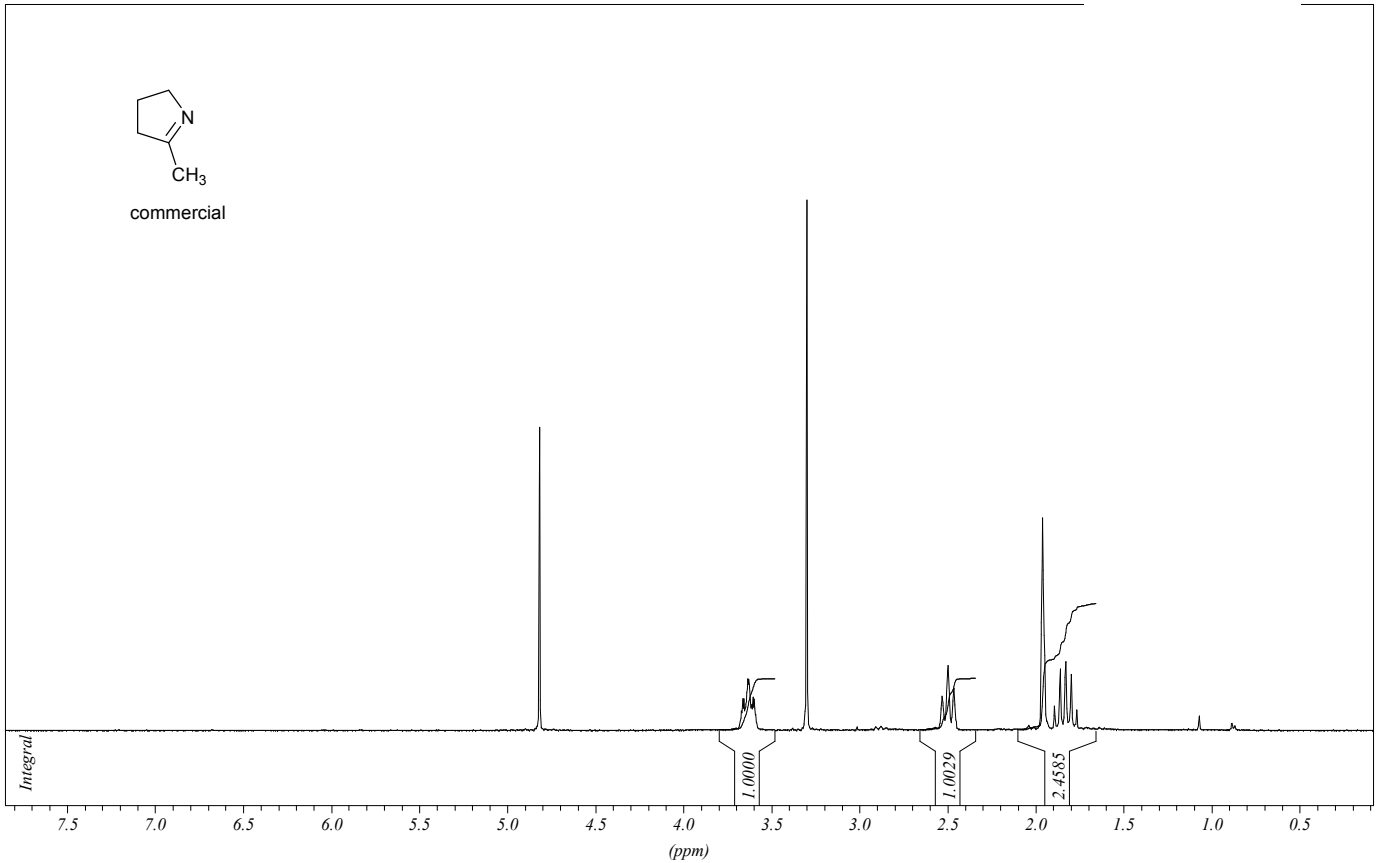
(^{1}H-NMR spectrum of crude 2-methylpyrroline hydrochloride in D_2O – CH_3OH used as a reference)



(^{13}C-NMR spectrum of crude 2-methylpyrroline hydrochloride in D_2O)



(^{1}H-NMR spectrum of commercial 2-methylpyrroline in D_2O – CH_3OH used as a reference)



(^{13}C-NMR spectrum of commercial 2-methylpyrroline in D_2O)