Aryne Compatible Solvents are not Always Innocent

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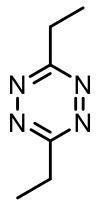
General Information

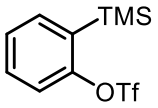
All commercial reagents and solvents were used as received. Flash column chromatography was performed using Silicycle silica gel (55−65 Å pore diameter). Thin-layer chromatography was performed on Sorbent Technologies silica plates (250 μm thickness). Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) and Carbon nuclear magnetic resonance spectroscopy (^{13}C NMR) spectra were recorded on a Bruker DMX 500 ^{1}H NMR. High-resolution mass spectra were obtained by Dr. Rakesh Kohli at the University of Pennsylvania's Mass Spectrometry Service Center on a on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using electrospray ionization. X-ray diffraction data obtained and solved by Dr. Patrick Carroll at the University of Pennsylvania. High performance liquid chromatography analysis was performed using a Jasco HPLC instrument equipped with a Phenomenex column (Luna 5u C18(2) 100A; 250 × 4.60 mm, 5 μm).

Experimental Procedures



1

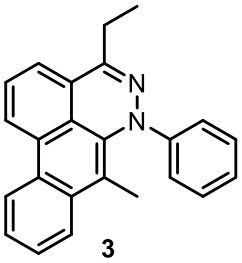
3,6-diethyl-1,2,4,5-tetrazine (1): Synthetic method and characterization data of **1** have been reported in our previous publication.[1]



2

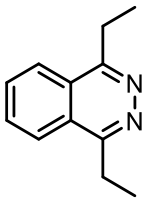
2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2): 2 was prepared according to the literature procedure.[2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.52 (m, 1H), 7.47-7.41 (m, 1H), 7.37-7.32 (m, 2H), 0.37 (s, 9H).



3

4-ethyl-7-methyl-6-phenyl-6H-dibenzo[de,g]cinnoline (3): Synthetic method and characterization data of **3** have been reported in our previous publication.[1]



4

1,4-diethylphthalazine (4): A vial was charged with 8.0 mmol of **1** (1.10 g) and 4.0 mmol of **2** (0.97 mL) in 4.0 mL of dichloromethane at 24 ˚C, and 1 M TBAF in THF (4.4 mmol, 4.4 mL) was slowly added to the solution over the course of 20 minutes. After the addition, the solution was concentrated in vacuo, and filtered on the silica gel, and purified by flash column chromatography (hexanes/ethyl acetate 1:3) to afford **4** (0.27 g). The data for this compound was previously reported in the literature.[3,4]

Isolated Yield: 37 %.

Physical Property: White solid.

TLC: R_f = 0.17 (silica gel, 25% ethyl acetate/hexanes).

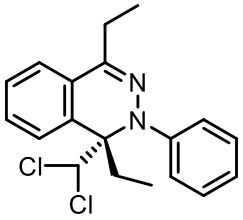
^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.05 (dd, 2H, J = 6.3, 3.3 Hz), 7.80 (dd, 2H, J = 6.3, 3.3 Hz), 3.30 (q, 4H, 7.5 Hz), 1.44 (t, 6H, 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 159.9, 131.5, 125.3, 124.5, 26.3, 13.1.

HRMS (ESI) calculated for $C_{12}H_{14}N_2Na^+$ $[M+Na]^+$ 209.1049, found 209.1064.



rac-**5a**

(*R*)- and (*S*)-1-(dichloromethyl)-1,4-diethyl-2-phenyl-1,2-dihydrophthalazine (*rac*-5a): A 4 mL vial was charged with 48 μmol of 1,4-diethylphthalazine **4** (9.0 mg), 480 μmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (140 mg) in 50 μL of dichloromethane at 24 °C, 1 M TBAF in THF (530 μmol, 53 μL) was slowly added to the solution over the course of 5 minutes. After the addition, the solution was concentrated in vacuo, and filtered on the silica gel, and purified by flash column chromatography (ethyl acetate/hexanes 1:10) to afford *rac*-**5a** (2.2 mg).

Isolated Yield: 13 %

Physical Property: White solid, m.p. = 111-112 ˚C.

TLC: R_f = 0.70 (silica gel, ethyl acetate/hexanes 1:4).

^{1}H NMR (500 MHz, CD_2Cl_2)

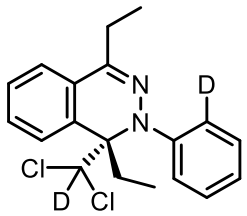
δ 7.59-7.54 (m, 1H), 7.54-7.50 (m, 2H), 7.49-7.46 (m, 3H), 7.43-7.37 (m, 2H), 7.29 (tt, 1H, J = 7.4, 0.9 Hz), 5.77 (s, 1H), 2.79-2.55 (m, 3H), 2.04-1.95 (m, 1H), 1.22 (t, 3H, J = 7.5 Hz), 1.07 (t, 3H, J = 7.2 Hz).

^{13}C NMR (125 MHz, CD_2Cl_2)

δ 145.5, 142.4, 129.2, 128.6, 128.5, 127.9, 127.84, 127.80, 127.0, 126.3, 123.6, 122.7, 77.3, 69.8, 28.2, 25.4, 11.6, 9.9.

IR (neat): 2973, 2929, 2869, 1596, 1492, 1446, 1093, 1034, 753, 699 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{21}N_2Cl_2^+$ $[M+H]^+$ 347.1076, found 347.1083.



rac-[D_2]-**5a**

(*R*)- and (*S*)-1-(dichloromethyl-*d*)-1,4-diethyl-2-(phenyl-2-*d*)-1,2-dihydrophthalazine (*rac*-[D_2]-**5a):** A vial was charged with 19 mg (0.10 mmol) of **4** and 300 mg (1.0 mmol) of **2** in 100 µL of dichloromethane at 24 ˚C, and 1 M TBAF in THF (1.1 mmol, 1.1 mL) was slowly added to the solution over the course of 5 minutes. After the addition, the solution was concentrated in vacuo, and filtered on the silica gel, and purified by flash column chromatography (ethyl acetate/hexanes 1:10) to afford *rac*-[D_2]-**5a** (1.2 mg).

Isolated Yield: 3 %.

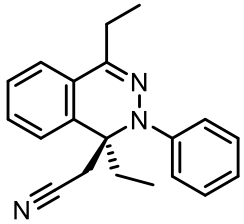
Physical Property: White solid, m.p. = 112-113 ˚C.

TLC: R_f = 0.70 (silica gel, ethyl acetate/hexanes 1:4).

^{1}H NMR (500 MHz, CD_2Cl_2)

δ 7.59-7.54 (m, 1H), 7.54-7.50 (m, 1H), 7.49-7.46 (m, 3H), 7.43-7.37 (m, 2H), 7.29 (tt, 1H, J = 7.4, 0.9 Hz), 2.79-2.55 (m, 3H), 2.04-1.95 (m, 1H), 1.22 (t, 3H, J = 7.5 Hz), 1.07 (t, 3H, J = 7.2 Hz).

HRMS (ESI) calculated for $C_{19}H_{18}D_2N_2Cl_2^+$ $[M+H]^+$ 349.1202, found 349.1204.



rac-**5b**

(*R*)- and (*S*)-2-(1,4-diethyl-2-phenyl-1,2-dihydrophthalazin-1-yl)acetonitrile (*rac*-**5b), Procedure I (Scheme 2, eq 6):** A 4 mL vial was charged with 48 µmol of 1,4-diethylphthalazine **4** (9.0 mg), 480 µmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (140 mg) in 50 µL of dichloromethane at 24 ^oC, 1 M TBAF in THF (530 µmol, 530 µL) was slowly added to the solution over the course of 5 minutes. After the addition, the solution was concentrated in vacuo, and filtered on the silica gel, and purified by flash column chromatography (ethyl acetate/hexanes 1:10) to afford *rac*-**5b** (1.2 mg).

(*R*)- and (*S*)-2-(1,4-diethyl-2-phenyl-1,2-dihydrophthalazin-1-yl)acetonitrile (*rac*-**5b), Procedure II:** A 4.0 mL vial was charged with 48 µmol of 1,4-diethylphthalazine **4** (9.0 mg), 480 µmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (140 mg), 530 µmol of anhydrous CsF (81 mg) in 50 µL of acetonitrile was heated to 80 ^oC. After 2 hours, the solution was cooled down, concentrated in vacuo and purified by flash column

chromatography (ethyl acetate/hexanes 1:10) to afford *rac*-**5b** (3.6 mg).

Isolated Yield: 8% (Procedure I), 25 % (Procedure II).

Physical Property: Pale yellow solid, m.p. = 135-136 ˚C.

TLC: R_f = 0.38 (silica gel, ethyl acetate/hexanes 1:4).

^{1}H NMR (500 MHz, CD_2Cl_2)

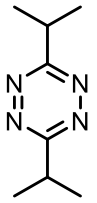
δ 7.54-7.40 (m, 7H), 7.39-7.36 (m, 1H), 7.34-7.30 (m, 1H), 2.83-2.68 (m, 4H), 2.10-1.95 (m, 2H), 1.26 (t, 3H, J = 7.6 Hz), 0.97 (t, 3H, J = 7.3 Hz).

^{13}C NMR (125 MHz, CD_2Cl_2)

δ 146.1, 146.0, 132.9, 130.1, 128.6, 128.4, 128.2, 126.6, 125.2, 123.3, 117.6, 63.4, 27.7, 25.8, 25.4, 11.6, 8.9.

IR (neat): 2973, 2032, 2877, 1594, 1492, 1472, 1446, 1210, 1119, 756, 702 cm^{-1}.

HRMS (ESI) calculated for $C_{20}H_{22}N_3^+$ $[M+H]^+$ 304.1808, found 304.1808.



3,6-diisopropyl-1,2,4,5-tetrazine: 3,6-diisopropyl-1,2,4,5-tetrazine was prepared according to the literature procedure from commercially available isobutyronitrile.[5] The product was purified by flash column chromatography (ethyl acetate/hexanes = 6.25%).

Isolated Yield: 56 %.

Physical Property: Red oil.

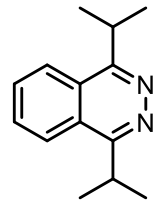
TLC: R_f = 0.46 (silica gel, 25% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (sep, 2H, J = 7.0 Hz), 1.25 (d, 12H, J = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 33.9, 21.0.

IR (neat): 2973, 2934, 2877, 1472, 1461, 1383, 1365, 1336, 1286, 1250, 1072, 899, 883 cm^{-1}.

HRMS (ESI) calculated for $C_8H_{14}N_4^+$ $[M]^+$ 166.1213, found 166.1222.



6

1,4-diisopropylphthalazine (6): A vial was charged with 0.117 mmol of 3,6-diisopropyl-1,2,4,5-tetrazine (19.5 mg) and 1.17 mmol of **2** (350 mg) in 0.1 mL of dichloromethane at 24 ˚C, and 1 M TBAF in THF (1.30 mmol, 1.30 mL) was slowly added to the solution over the course of 5 minutes. After the addition, the solution was concentrated in vacuo, and filtered on the silica gel, and purified by flash column chromatography (hexanes/ethyl acetate 1:3) to afford **6** (18.6 mg).

Isolated Yield: 74 %.

Physical Property: White solid, m.p. = 85-86 ˚C.

TLC: R_f = 0.19 (silica gel, ethyl acetate/hexanes 1:4).

^{1}H NMR (500 MHz, $CDCl_3$)

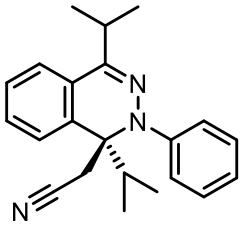
δ 8.18 (dd, 2H, J = 6.3, 3.3 Hz), 7.86 (dd, 2H, J = 6.3, 3.3 Hz), 3.86 (sep, 2H, 6.8 Hz), 1.53 (d, 12H, 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 162.5, 131.3, 125.0, 124.3, 30.2, 22.0.

IR (neat): 2968, 2930, 2873, 1540, 1566, 1472, 1457, 1386, 1264, 1087, 1035, 991, 774, 735, 703, 668 cm^{-1}.

HRMS (ESI) calculated for $C_{22}H_{16}N_2^+$ $[M+H]^+$ 215.1543, found 215.1554.



rac-**7**

(*R*)- and (*S*)-2-(1,4-diisopropyl-2-phenyl-1,2-dihydrophthalazin-1-yl)acetonitrile (*rac*-7): A 4 mL vial was charged with 0.13 mmol of 1,4-diisopropylphthalazine **6** (28 mg), 1.3 mmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (390 mg), 1 M TBAF in THF (1.4 mmol, 1.4 mL) in 50 µL of dichloromethane was heated to 80 ^{o}C. After 2 hours, the solution was cooled down, concentrated in vacuo and purified by flash column chromatography (ethyl acetate/hexanes 1:10) to afford *rac*-**7** (0.60 mg).

Isolated Yield: 1 %.

Physical Property: White solid, m.p. = 140-141 ˚C.

TLC: R_f = 0.38 (silica gel, ethyl acetate/hexanes 1:4).

^{1}H NMR (500 MHz, CD_2Cl_2)

δ 7.60-7.40 (m, 7H), 7.35-7.28 (m, 1H), 7.24-7.18 (m, 1H), 3.37 (d, 1H, J = 17.6 Hz), 3.28-3.18 (m, 1H), 2.85 (d, 1H, J = 17.6 Hz), 2.19-2.09 (m, 1H), 1.25-1.21 (m, 6H), 0.90 (d, 3H, J = 6.8 Hz), 0.74 (d, 3H, J = 6.8 Hz).

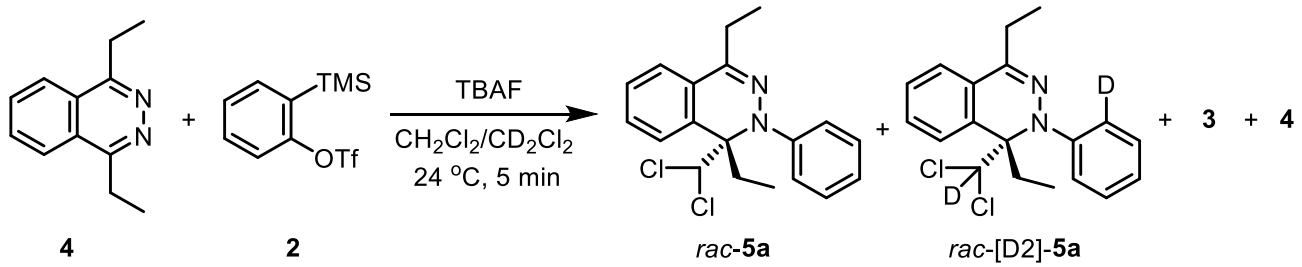
^{13}C NMR (125 MHz, CD_2Cl_2)

δ 146.5, 146.2, 130.2, 129.4, 128.7, 128.5, 128.1, 126.4, 126.0, 125.7, 122.8, 118.1, 66.6, 37.0, 29.1, 27.6, 21.3, 19.7, 19.2, 17.6.

IR (neat): 2960, 2921, 2849, 1262, 1096, 1028, 803 cm^{-1}.

HRMS (ESI) calculated for $C_{22}H_{26}N_3^+$ $[M+H]^+$ 332.2121, found 332.2121.

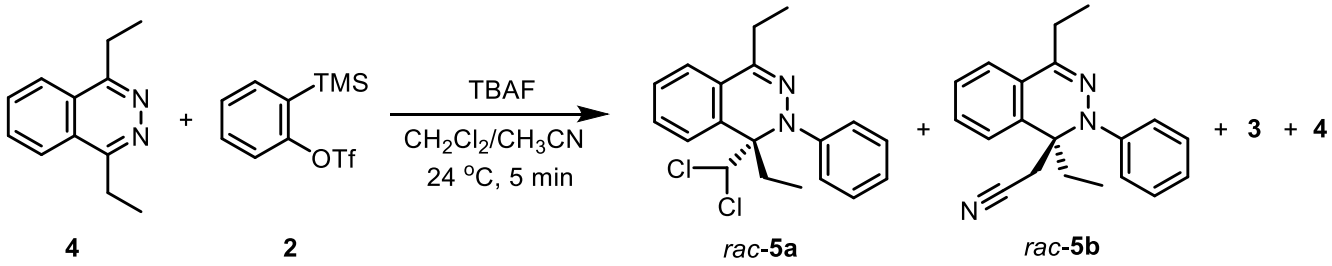
Crossover Experiment in Scheme 2.



4 **2** *rac*-**5a** *rac*-[D2]-**5a**

Each vial was charged with 0.10 mmol of phthalazine **4** (19 mg) and 1.0 mmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (300 mg) in 100 μL of CH_2Cl_2, CD_2Cl_2, CH_2Cl_2/CD_2Cl_2 (1:1), and CCl_4 at 24 ˚C, and 1 M TBAF in THF (1.1 mmol, 1.1 mL) was slowly added to the solution over the course of 5 minutes. After the addition, the solution was concentrated in vacuo, and filtered on the silica gel, and purified by flash column chromatography (ethyl acetate/hexanes 1:10 to straight ethyl acetate) to afford **3**, **4**, and *rac*-**5a** (or *rac*-[D_2]-**5a**).

Crossover Experiment in Scheme 4 (eq 7).



4 **2** *rac*-**5a** *rac*-**5b**

Each vial was charged with 10 μmol of phthalazine **4** (1.9 mg) and 100 μmol of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (30 mg) in CH_3CN and CH_2Cl_2 in different molar ratios (total 5.0 mmol) at 24˚C, and 1 M TBAF in THF (110 μmol, 110 μL) was slowly added to each solution over the course of 5 minutes. After the addition, the solutions and 9,10-diphenylanthracene as an internal standard were directly subjected to HPLC for analysis.

References

1) Suh, S.-E.; Barros, S. A.; Chenoweth, D. M. *Chem. Sci.* **2015**, *6*, 5128.

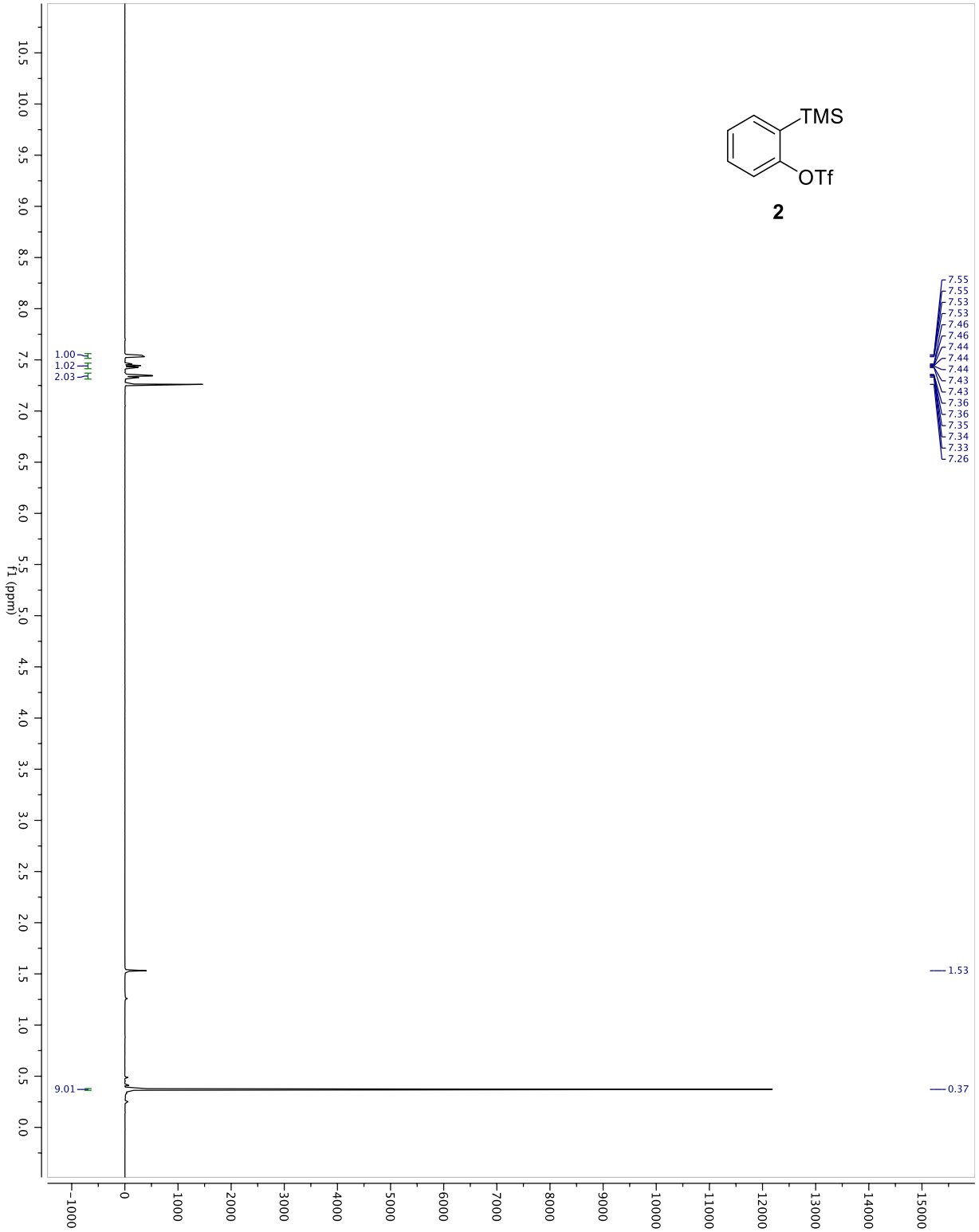
2) Shaibu, B. S.; Kawade, R. K.; Liu, R.-S. *Org. Biomol. Chem.* **2012**, *10*, 6834.

3) Hayashi, E.; Iinuma, M.; Utsunomiya, I.; Iijima, C.; Oishi, E.; Higashino, T. *Chem. Pharm. Bull.* **1977**, *25*, 579.

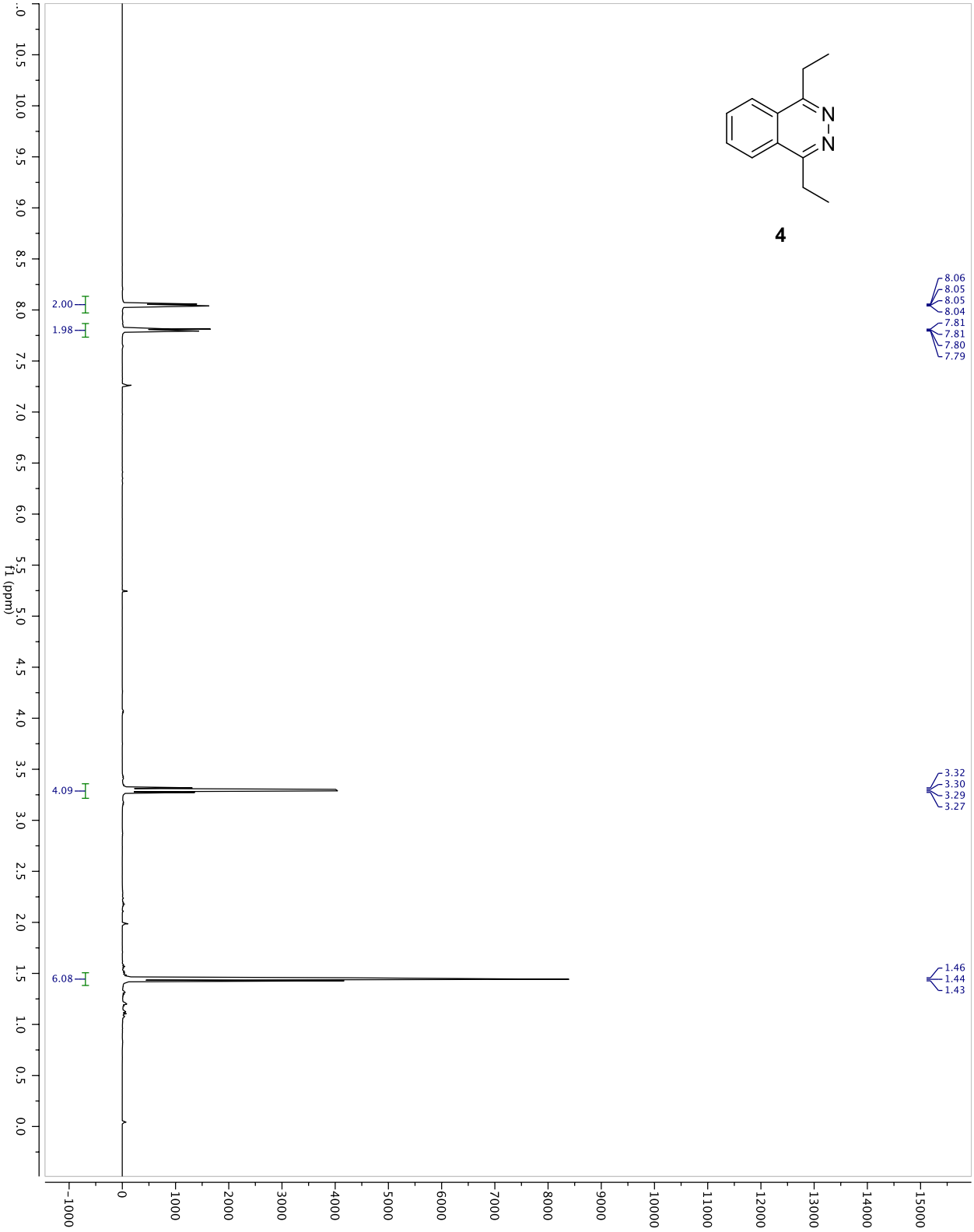
4) Stephenson, L.; Walker, T.; Warburton, W. K.; Webb, G. B. *J. Chem. Soc*. **1962**, 1282.

5) Yang, J.; Karver, M. R.; Li, W.; Sahu, S.; Devaraj, N. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 5222.

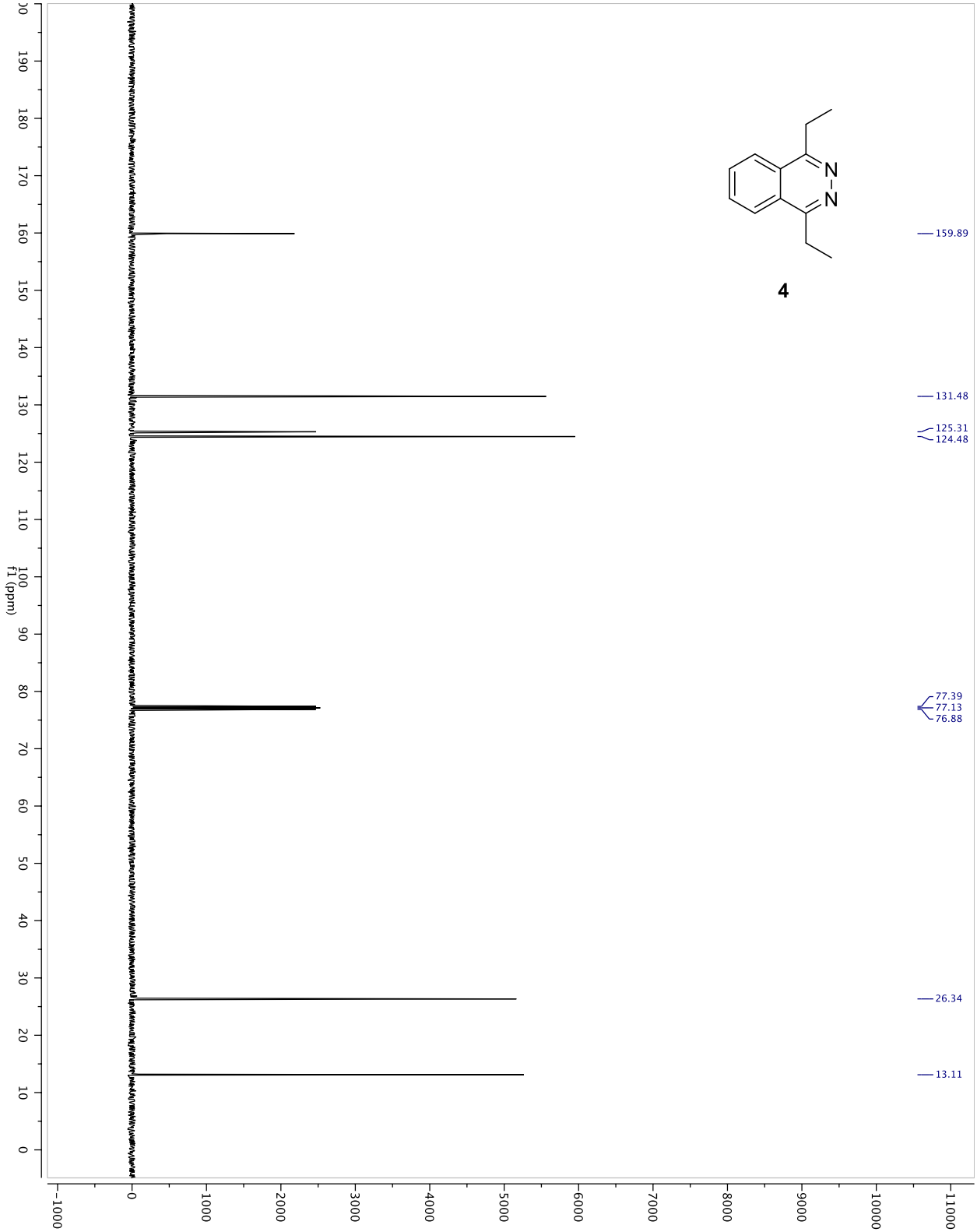
^{1}H NMR spectrum of **2** in $CDCl_3$ (500 MHz).



^{1}H NMR spectrum of **4** in $CDCl_3$ (500 MHz).

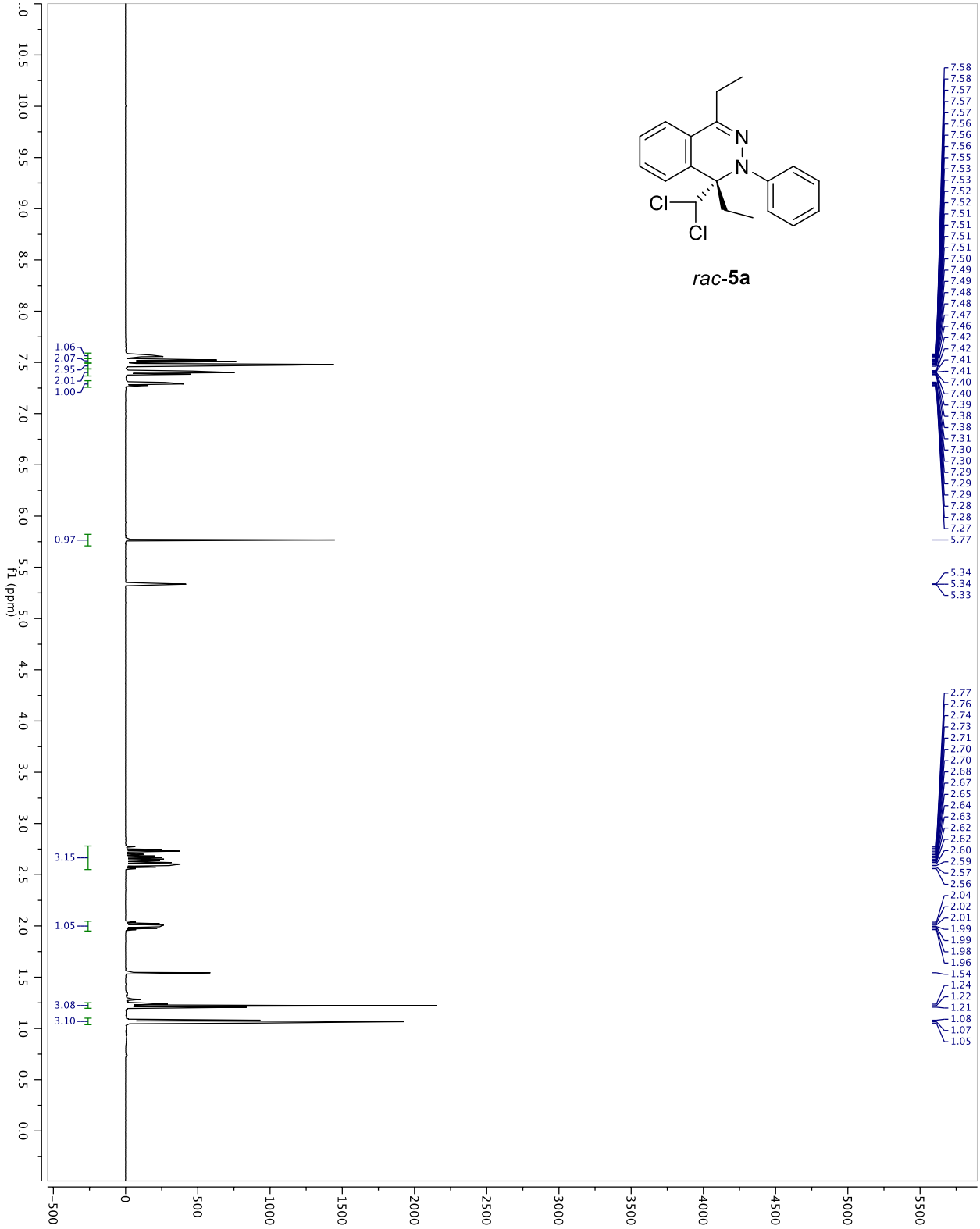


^{13}C NMR spectrum of **4** in $CDCl_3$ (125 MHz).

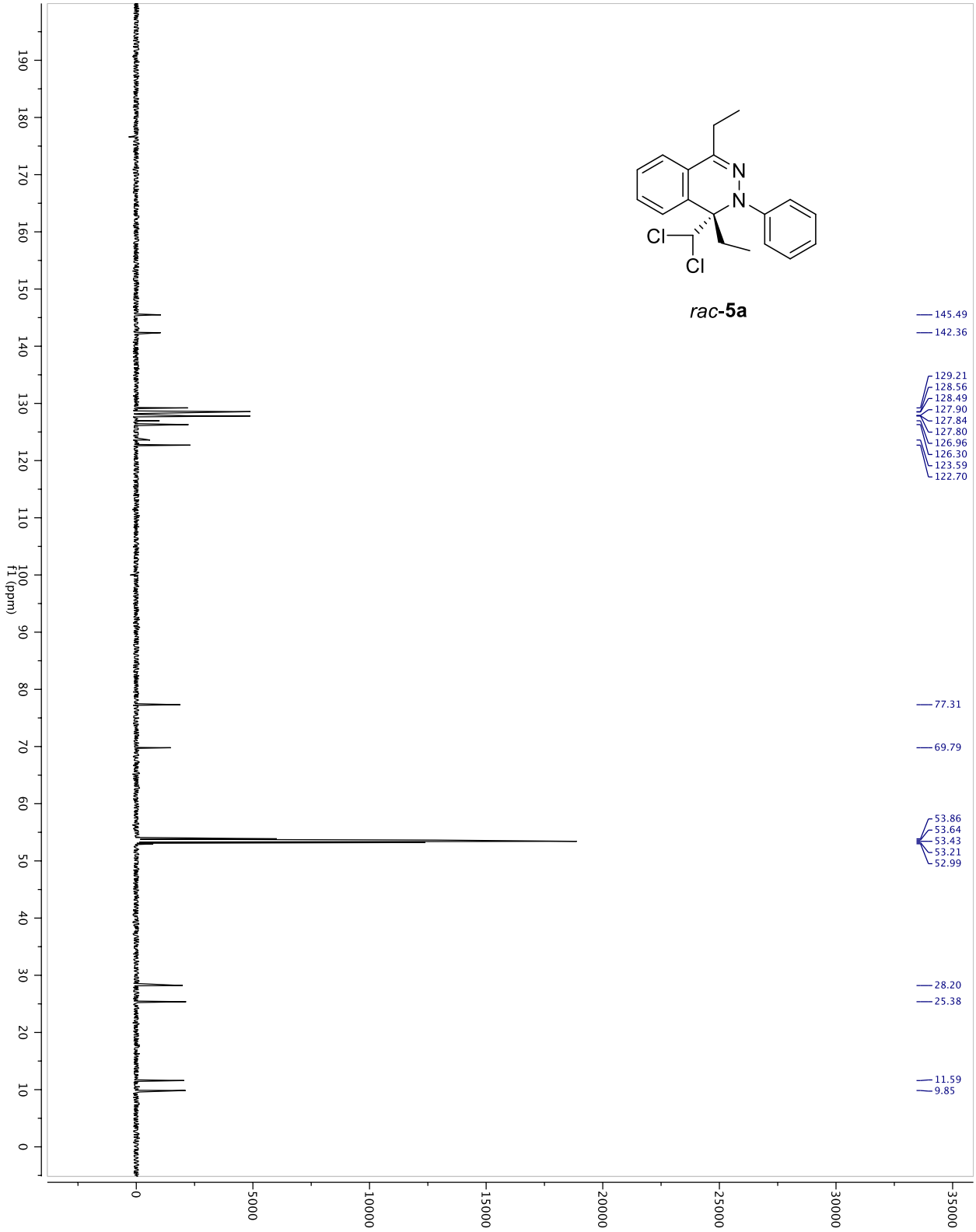


4

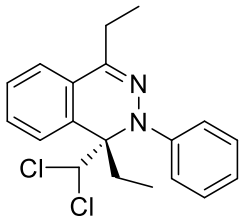
^{1}H NMR spectrum of *rac*-**5a** in CD_2Cl_2 (500 MHz).



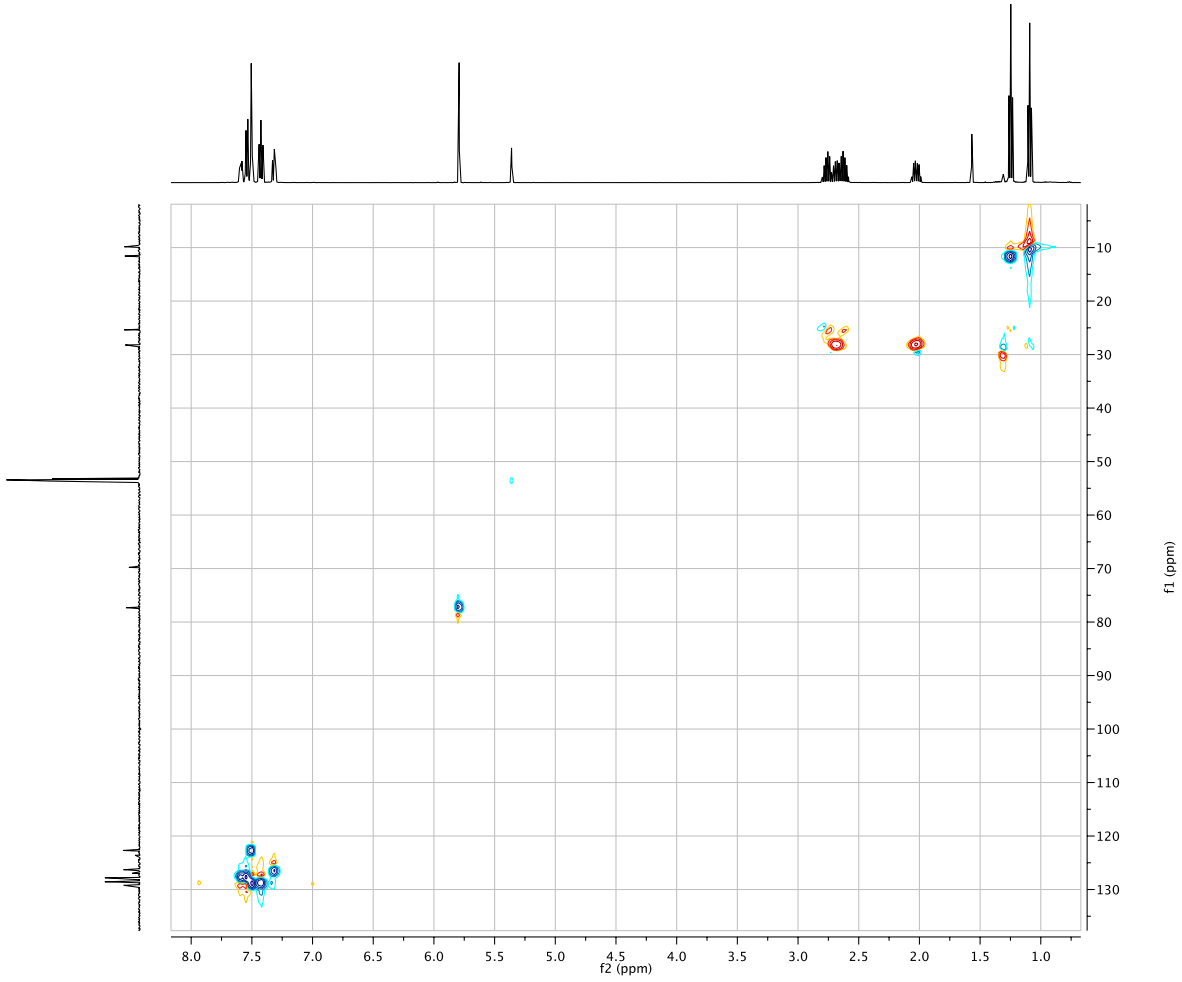
^{13}C NMR spectrum of *rac*-**5a** in CD_2Cl_2 (125 MHz).



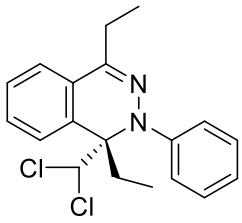
HSQC spectrum of *rac*-**5a** in CD_2Cl_2.



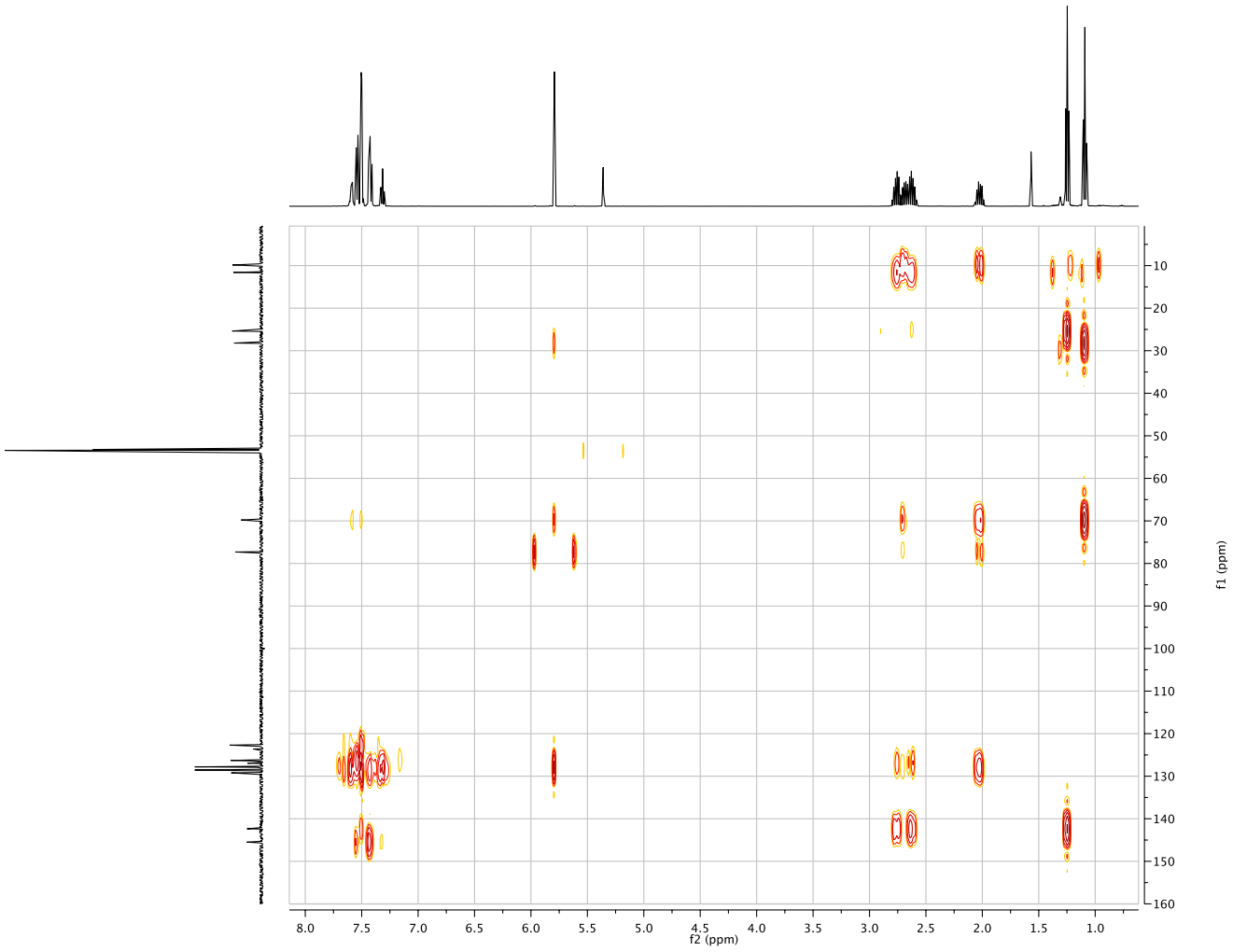
rac-**5a**



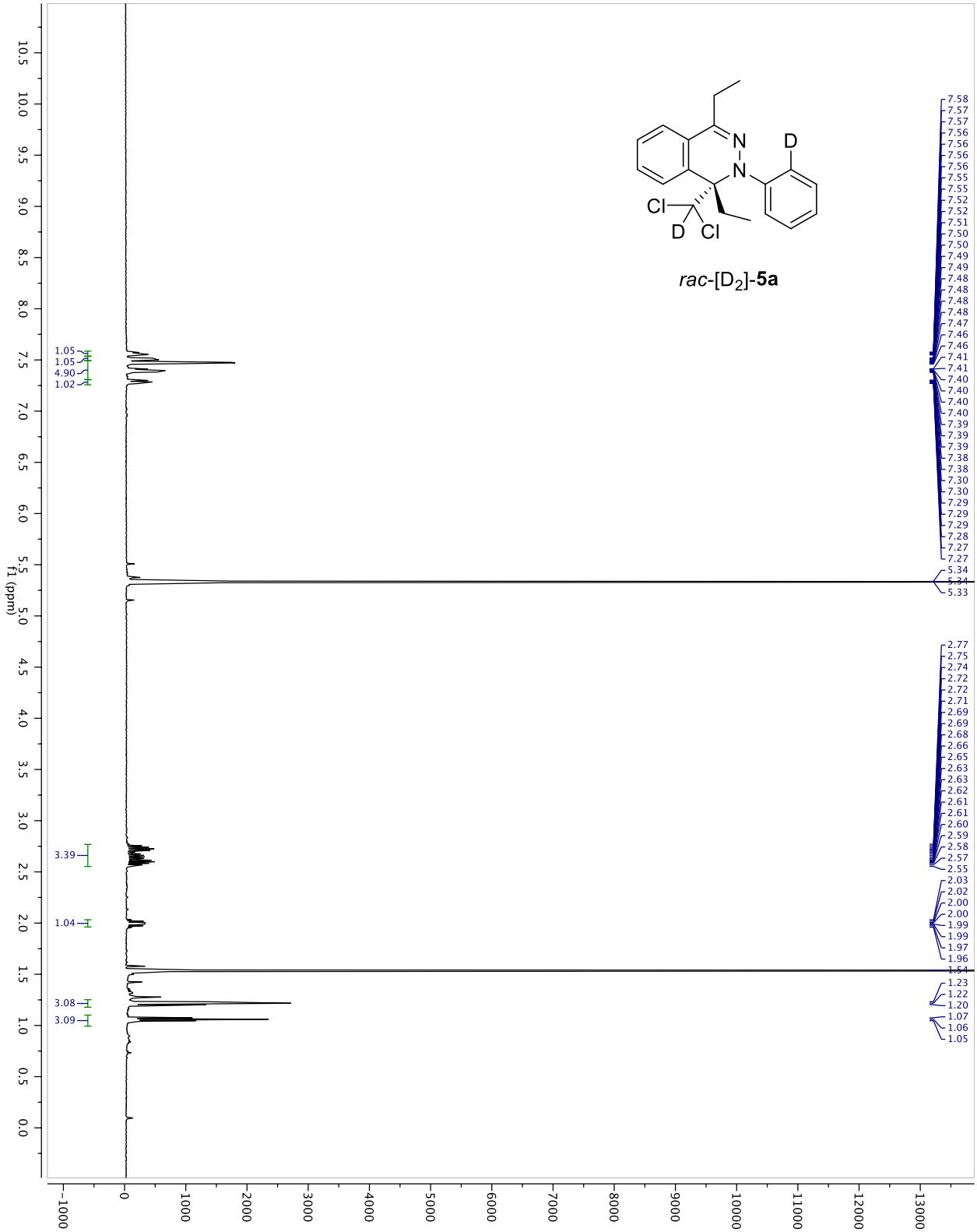
HMBC spectrum of *rac*-**5a** in CD_2Cl_2.



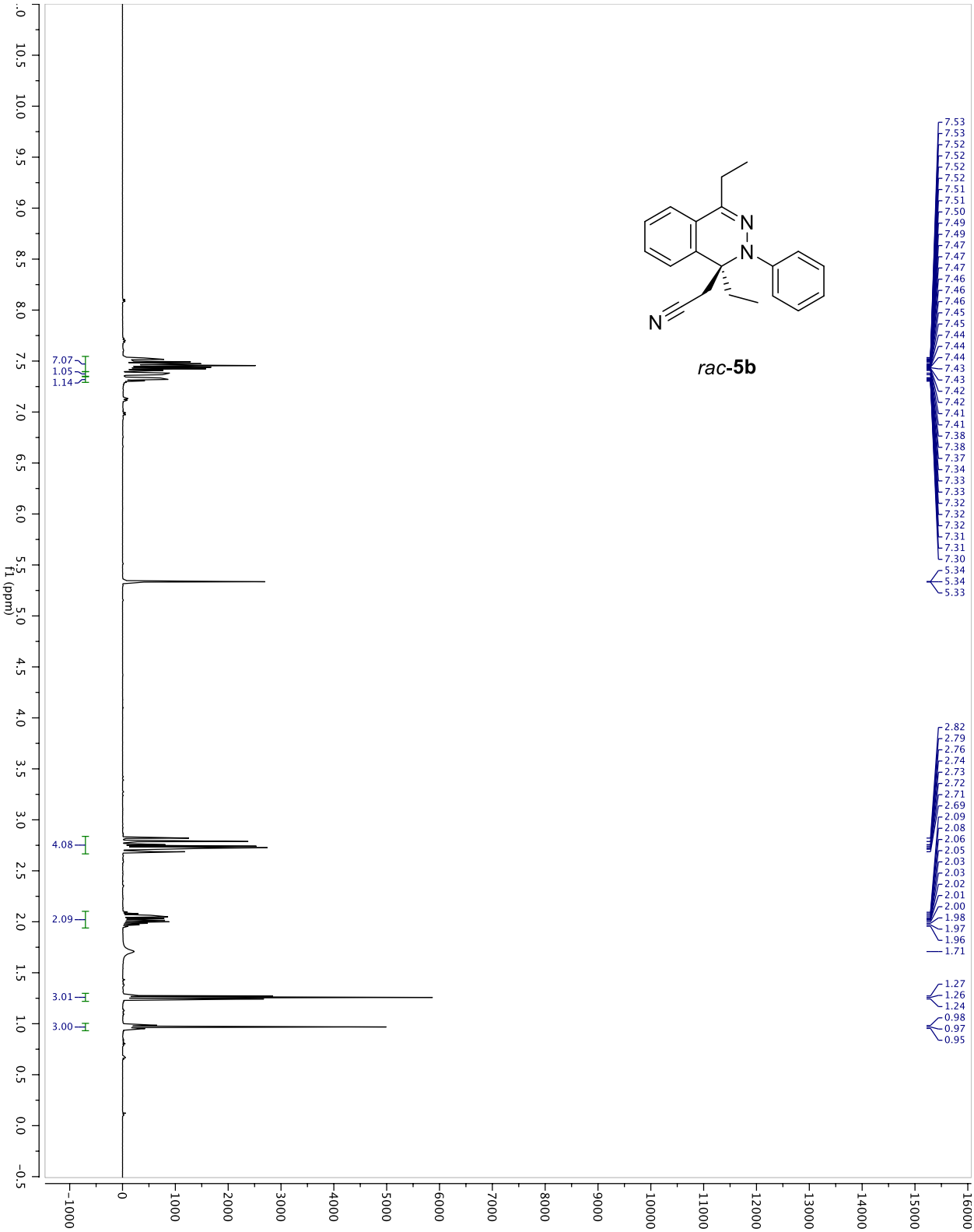
rac-**5a**



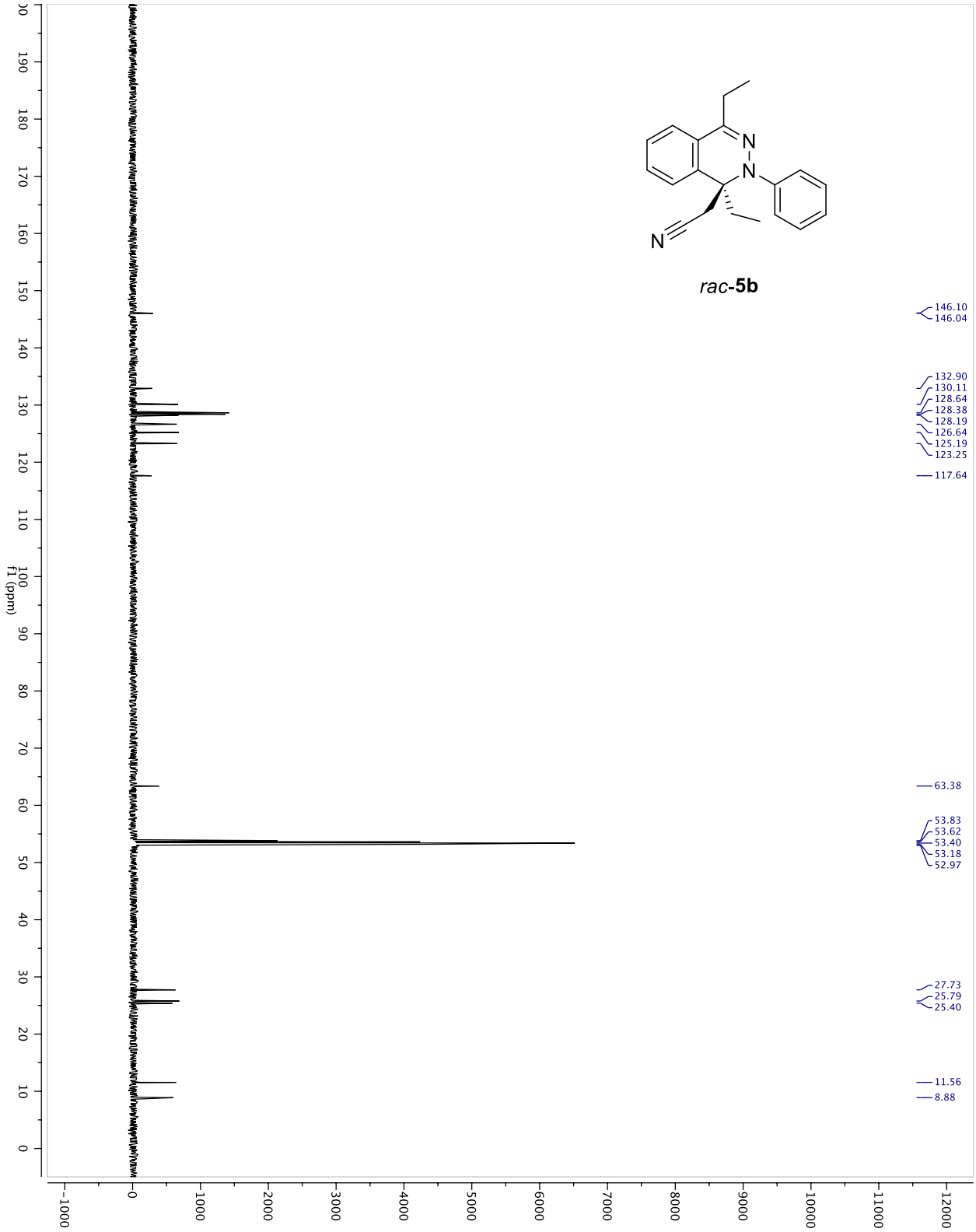
^{1}H NMR spectrum of *rac*-[D_2]-**5a** in CD_2Cl_2 (500 MHz).



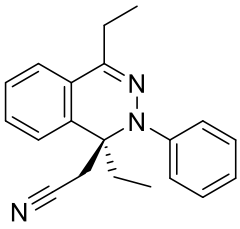
^{1}H NMR spectrum of *rac*-**5b** in CD_2Cl_2 (500 MHz).



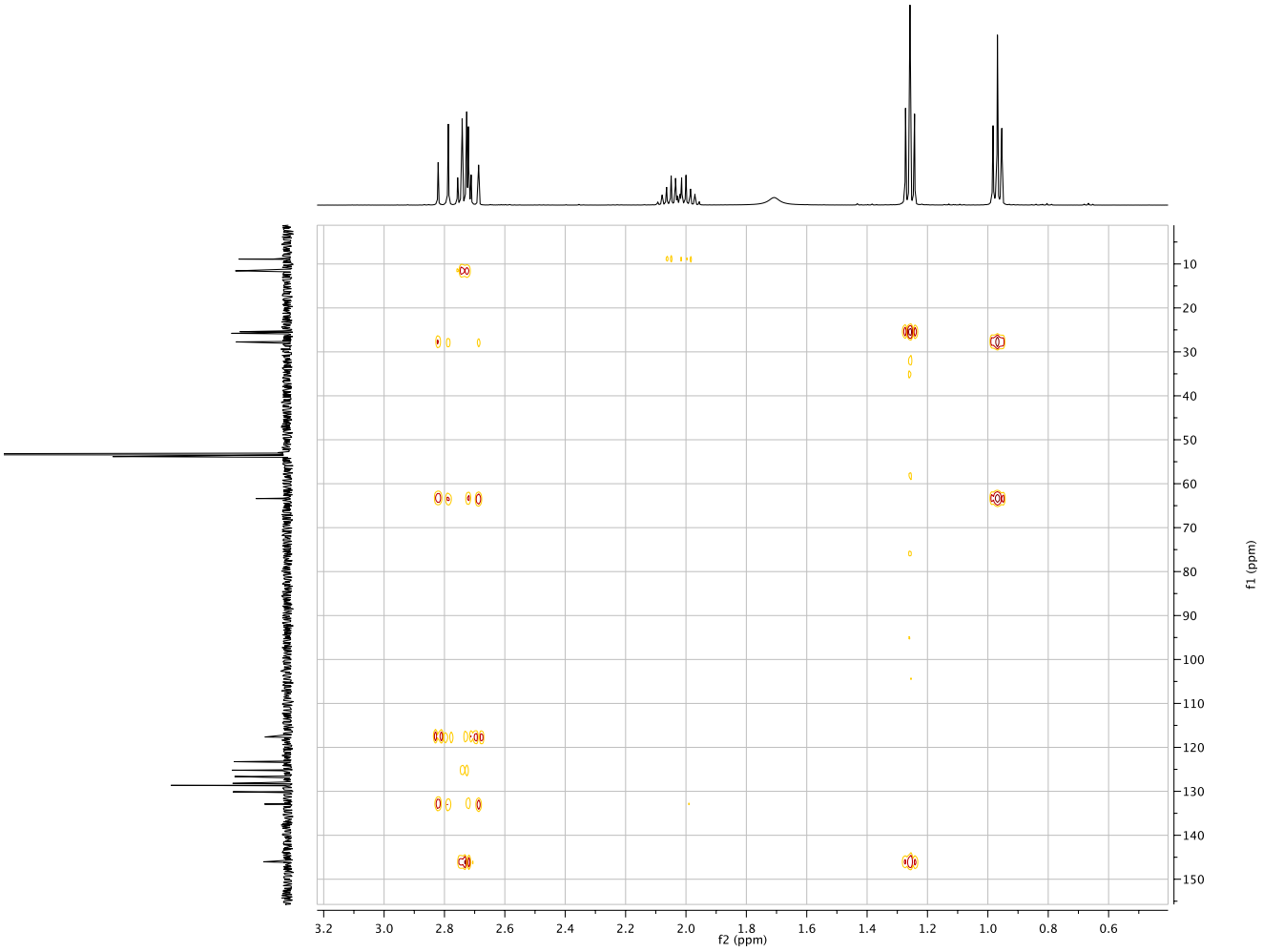
^{13}C NMR spectrum of *rac*-**5b** in CD_2Cl_2 (125 MHz).



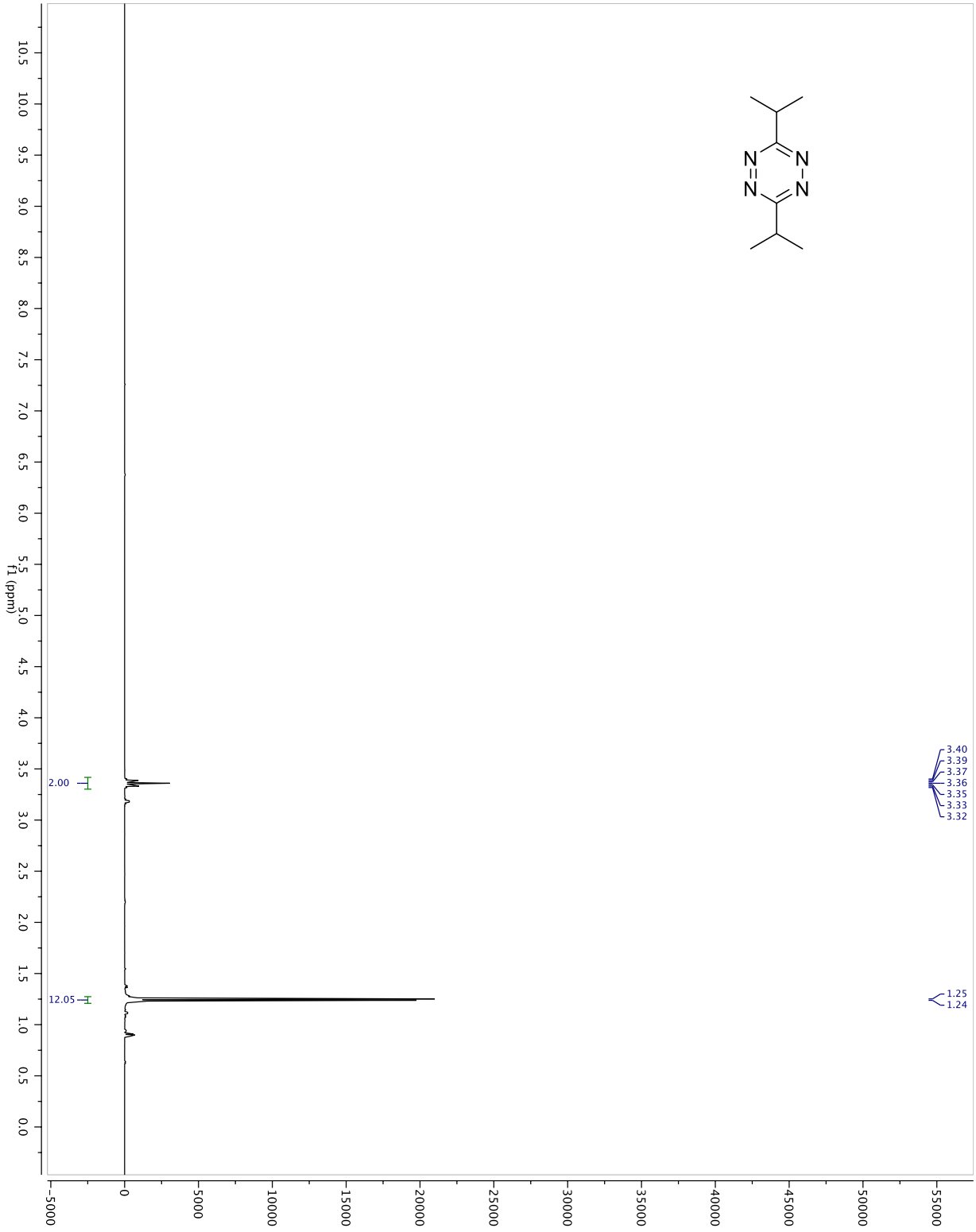
HMBC spectrum of *rac*-**5b** in CD_2Cl_2.



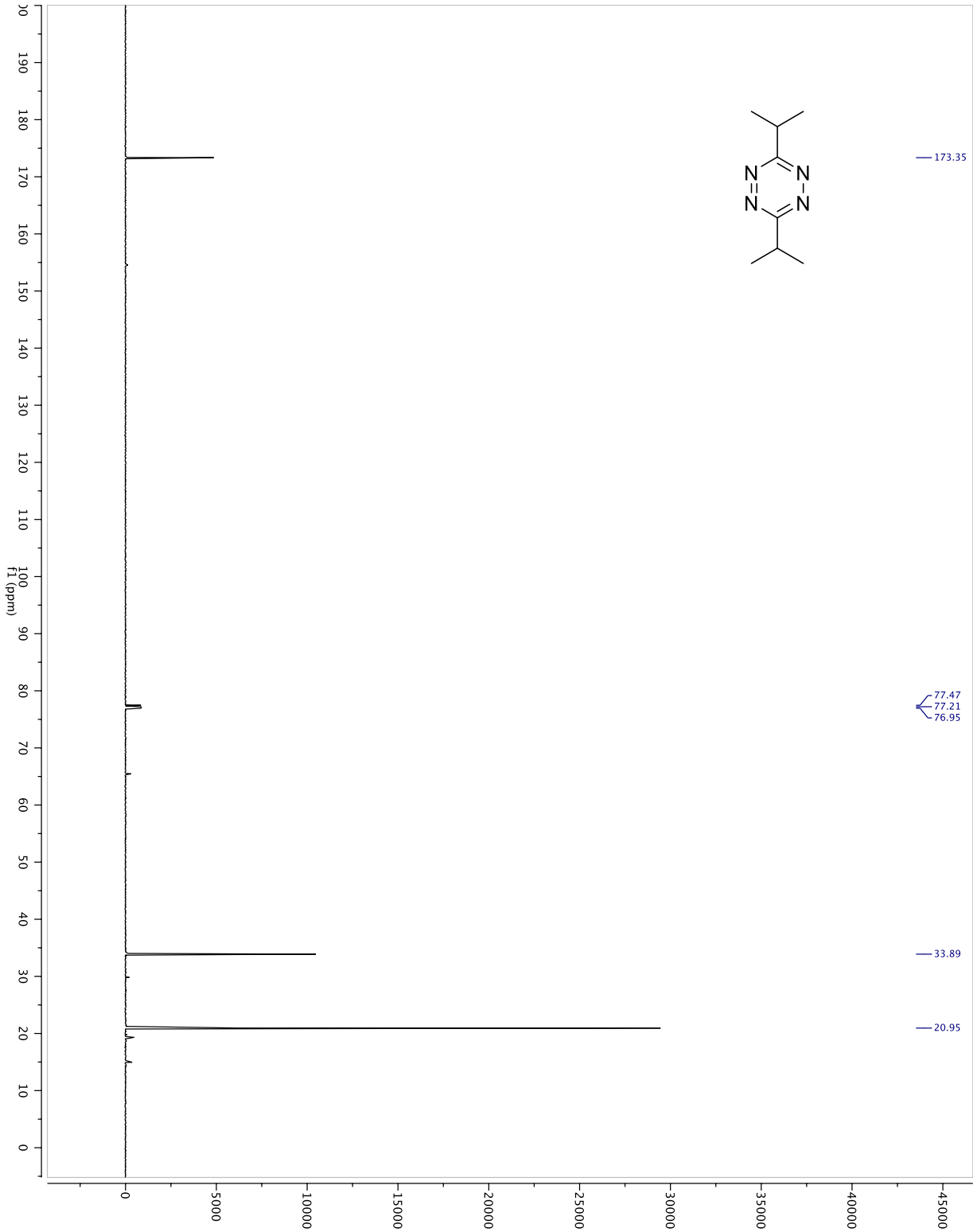
rac-**5b**



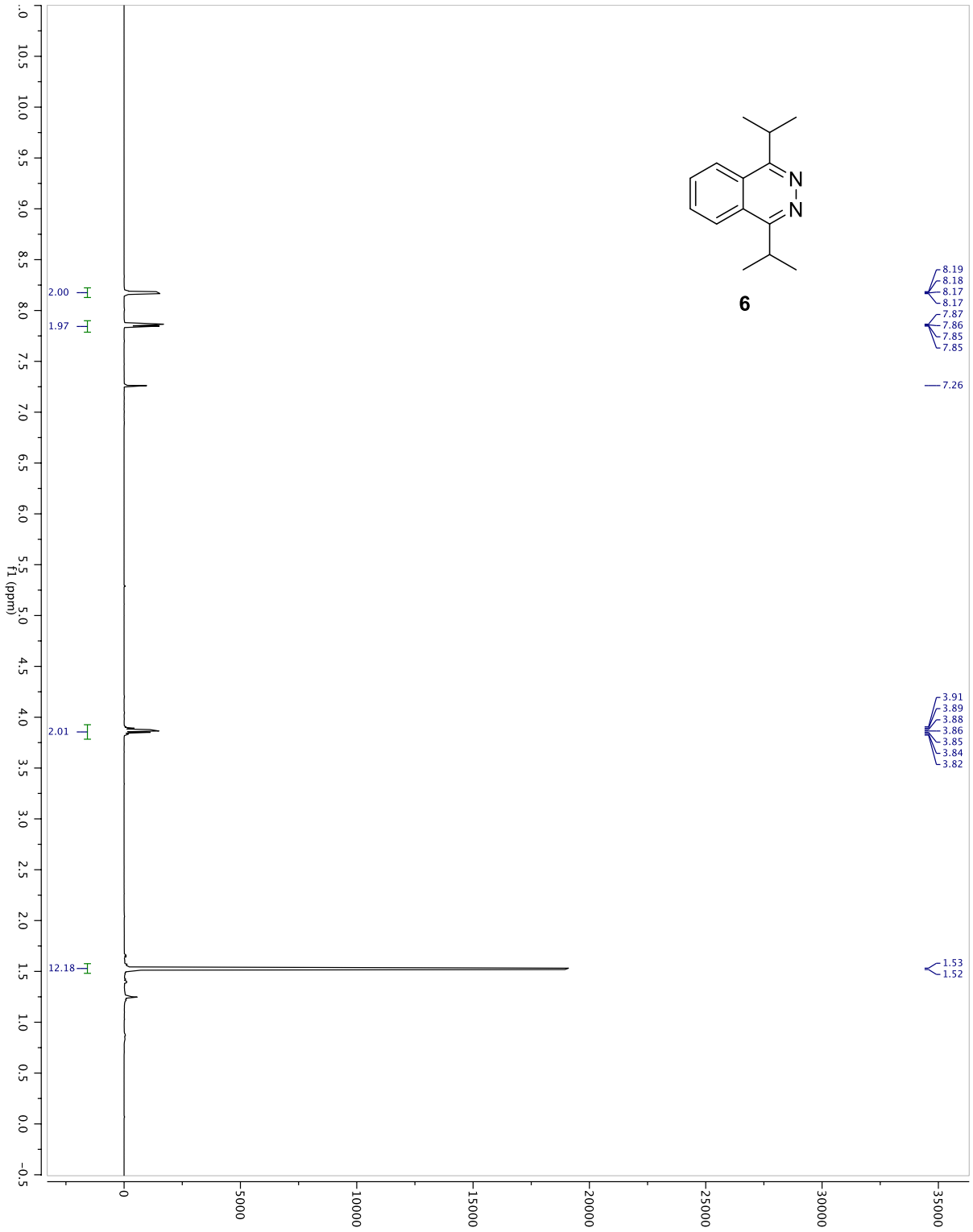
^{1}H NMR spectrum of 3,6-diisopropyl-1,2,4,5-tetrazine in $CDCl_3$ (500 MHz).



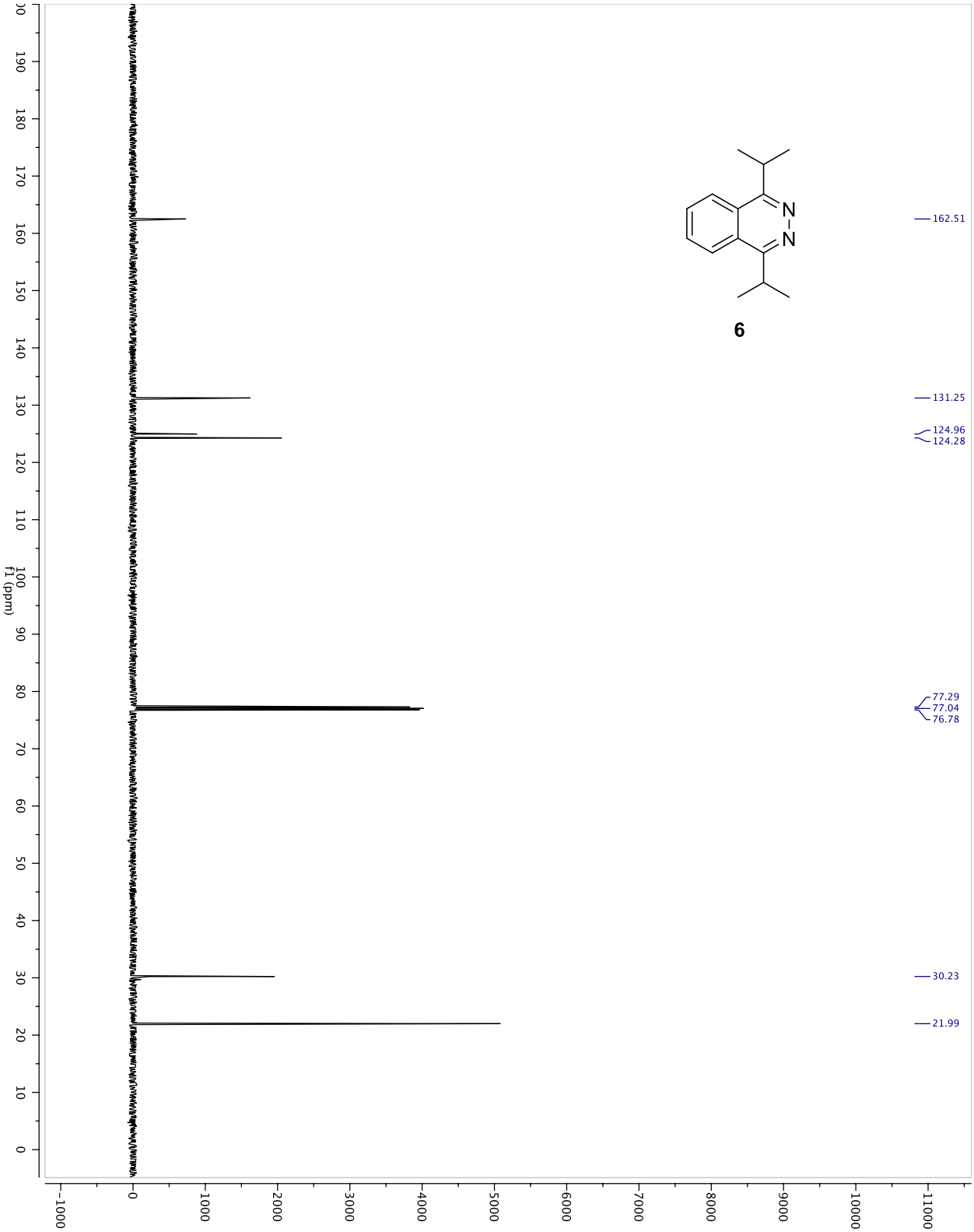
^{13}C NMR spectrum of 3,6-diisopropyl-1,2,4,5-tetrazine in $CDCl_3$ (125 MHz).



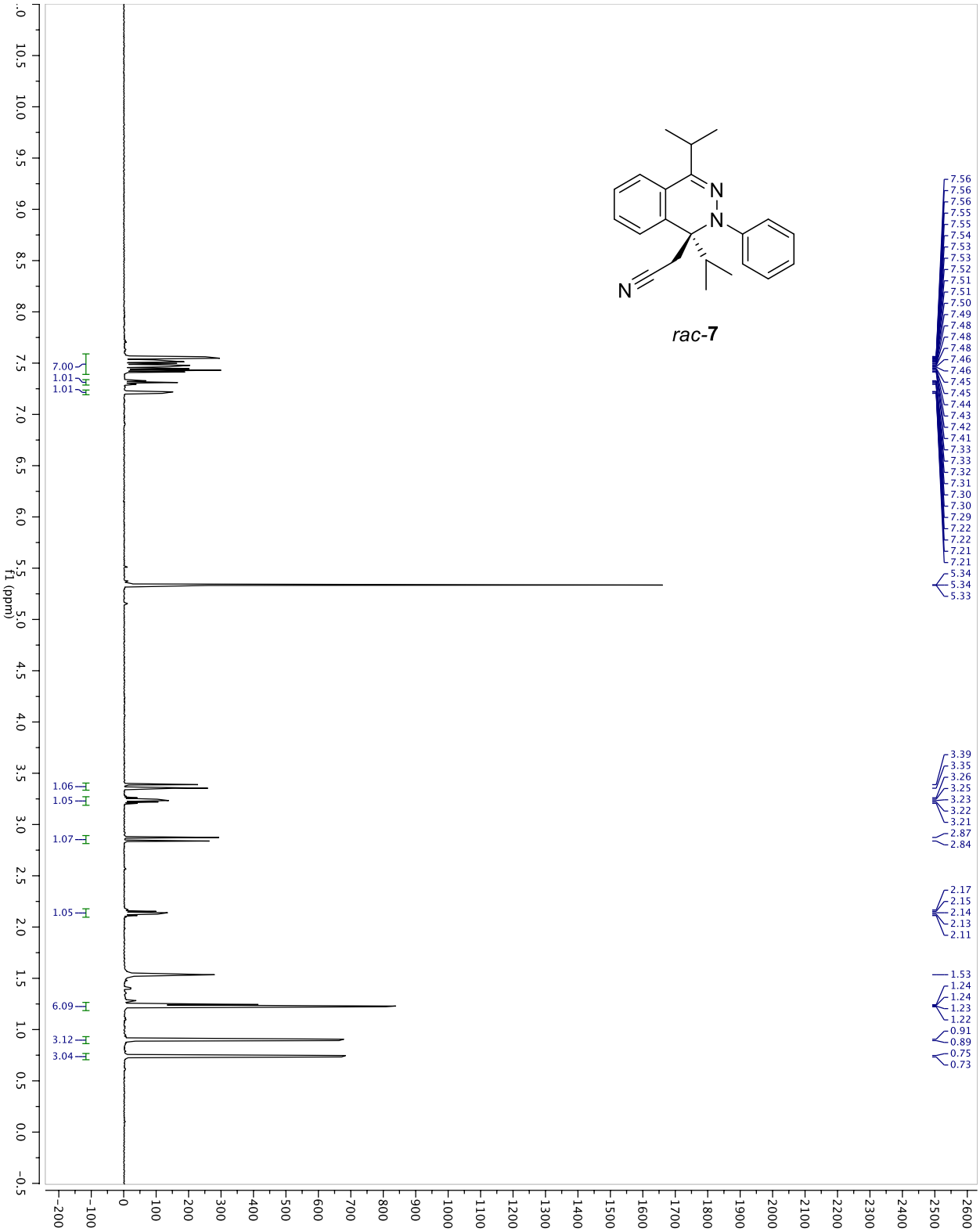
^{1}H NMR spectrum of **6** in $CDCl_3$ (500 MHz).



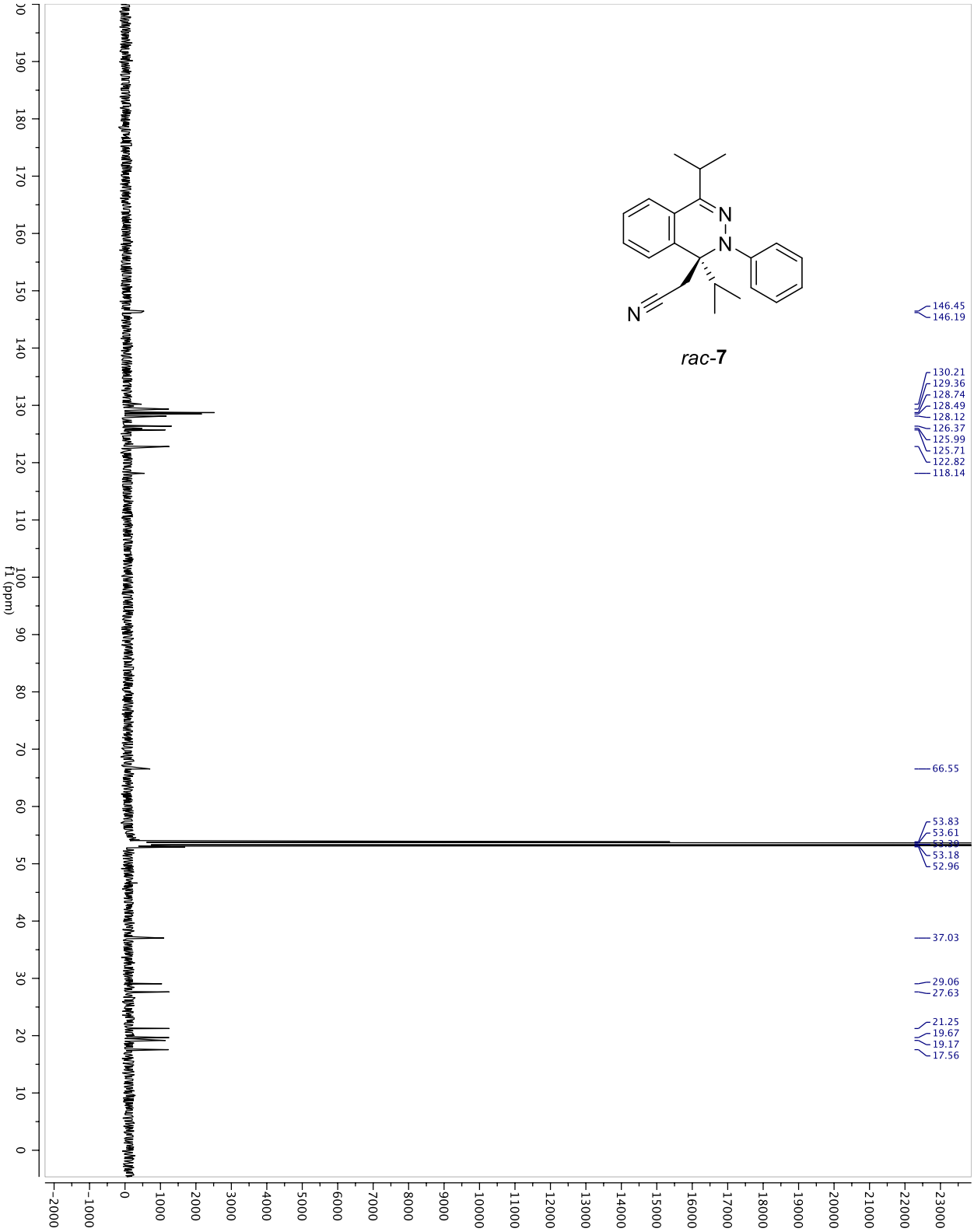
^{13}C NMR spectrum of **4c** in $CDCl_3$ (125 MHz).



^{1}H NMR spectrum of *rac*-**7** in CD_2Cl_2 (500 MHz).



^{13}C NMR spectrum of *rac*-**6c** in CD_2Cl_2 (125 MHz).



CCDC Number of X-ray crystal structures of **5a** and **5b**.

5a

Summary of Data CCDC 1425956

Compound Name:
Formula: C19 H20 Cl2 N2,()n,(C1)n,0.85(H1 Cl1),0.15(Cl1)
Unit Cell Parameters: a 8.5618(10) b 8.6657(9) c 22.783(3) P212121

5b

Summary of Data CCDC 1425957

Compound Name:
Formula: C20 H21 N3
Unit Cell Parameters: a 7.1149(3) b 26.5631(11) c 8.5150(4) P21

Crystal data and structure refinement for **5a**.

Empirical formula	$C_{19}H_{20}N_2Cl_2$
Formula weight	347.27
Temperature	100(1) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell constants:	
a	8.5618(10) Å
b	8.6657(9) Å
c	22.783(3) Å
Volume	1690.4(3) $Å^3$
Z	4
Density (calculated)	1.365 Mg/m^3
Absorption coefficient	0.385 mm^{-1}
F(000)	728
Crystal size	0.32 x 0.22 x 0.12 mm^3
Theta range for data collection	2.51 to 25.39°
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-27 \leq l \leq 27$
Reflections collected	22569
Independent reflections	3110 [R(int) = 0.0433]
Completeness to theta = 25.39°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.4705
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3110 / 67 / 275
Goodness-of-fit on F^2	1.237
Final R indices [I>2sigma(I)]	R1 = 0.0764, wR2 = 0.1911
R indices (all data)	R1 = 0.0769, wR2 = 0.1913
Absolute structure parameter	0.49(19)
Largest diff. peak and hole	0.600 and -0.640 $e.Å^{-3}$

Crystal data and structure refinement for **5b**.

Empirical formula	$C_{20}H_{21}N_3$
Formula weight	303.40
Temperature	100(1) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1$
Cell constants:	
a	7.1149(3) Å
b	26.5631(11) Å
c	8.5150(4) Å
β	90.955(3)°
Volume	1609.06(12) $Å^3$
Z	4
Density (calculated)	1.252 Mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	648
Crystal size	0.12 x 0.12 x 0.05 mm^3
Theta range for data collection	1.53 to 25.48°
Index ranges	$-8 \leq h \leq 8$, $-31 \leq k \leq 32$, $-10 \leq l \leq 10$
Reflections collected	29916
Independent reflections	5858 [R(int) = 0.0402]
Completeness to theta = 25.48°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6245
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5858 / 1 / 420
Goodness-of-fit on F^2	1.080
Final R indices [I>2sigma(I)]	R1 = 0.0632, wR2 = 0.1647
R indices (all data)	R1 = 0.0748, wR2 = 0.1719
Absolute structure parameter	2(3)
Largest diff. peak and hole	0.485 and -0.238 $e.Å^{-3}$