Activation of Alcohols with Carbon Dioxide: Intermolecular Allylation of Weakly Acidic Pronucleophiles.

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Supporting Information

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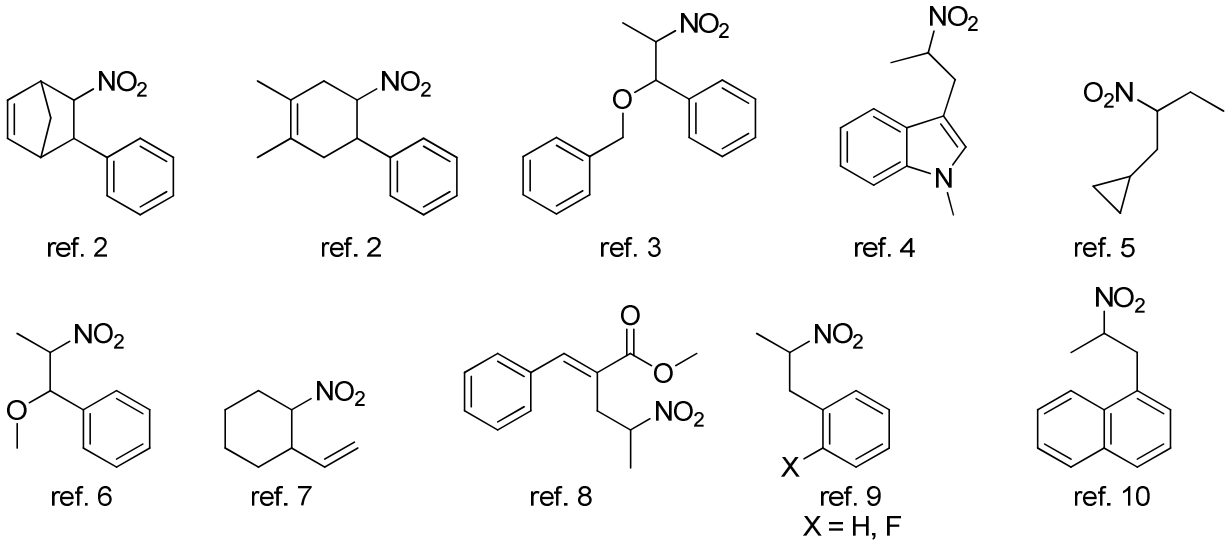
General Information:

All reactions were run in oven or flame dried 2.0 – 5.0 mL microwave vials from Biotage. DMSO was purchased from Sigma Aldrich and stored in a glove box. Allyl alcohol was purchased from Sigma Aldrich and stored over 3 Å mol sieves. All other allyl alcohols except 2-phenylprop-2-en-1-ol were commercially available and used as received. 2-Phenylprop-2-en-1-ol was prepared according to a literature procedure.[1] Palladium tetrakis(triphenylphosphine) was purchased from Strem, stored in a glovebox, and used as received. **2a, 2e, 2f, and 2i** were purchased and used as received. CO_2 was dispensed through a Matheson 3040 series regulator attached to a cylinder purchased from Lindweld.

TLC analysis was performed with silica gel HL TLC plates w/UV254 from Sorbent Technologies. 60 Å porosity, 230 x 400 mesh standard grade silica gel from Sorbent Technologies was used for column chromatography. GC/MS data was obtained using a Shimadzu GCMS-QP2010 SE. Microwave experiments were run in a Biotage Initiator. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on a Bruker Advance 500 DRX equipped with a QNP cryoprobe or a Bruker Advance 400. ^{19}F NMR spectra were referenced to trifluoromethyltoluene while ^{1}H and ^{13}C NMR spectra were referenced to residual protio solvent signals.

Nitroalkanes were prepared according to literature procedures:



Procedure A (synthesis of 2b and 2c):[11]

To a glass sleeve, the respective phenylacetonitrile (16.5 mmol) was added to dimethyl carbonate (25 mL, 16 equiv.), and K_2CO_3 (4.5 g, 2 equiv.). The sleeve was placed in a stainless steel Parr reactor, sealed, heated to 160 ^oC and stirred for 3 hr. The reaction was then quenched by turning off the heating source and allowing the apparatus to cool to room temperature. After removal of the glass sleeve, the contents were subjected to a water workup (200 mL), extracted with EtOAc (100 mL), and purified by flash chromatography over silica in 2% EtOAc:Hexanes.

Procedure B (synthesis of substrates 2d):[12]

In a 100 mL flame-dried Schlenk flask under Ar, dry THF (13 mL) was added. The solvent was then placed in a dry ice/acetone bath and cooled to -78 ^oC. *n*-BuLi (8.0 mL, solution 1.6 M/Hex from Aldrich) was added dropwise and the solution was stirred for 10 min. The solution was then warmed to room temperature, stirred for 5 minutes then cooled to -78 ^oC. Next, commercially available 4-methoxyphenylacetonitrile (1.85 g, 12.6 mmol) was added dropwise over 10 minutes. The solution was stirred for 1 hr before benzyl bromide (2.15 g ,1 equiv) was added dropwise. The resulting solution was stirred for 30 min., warmed to room temperature, and stirred overnight. The reaction was quenched with aq. NH_4Cl (20 mL), subjected to a water workup (2 x 50 mL), and extracted with EtOAc (50 mL) and dried over $MgSO_4$. The solution was then filtered and concentrated via rotary evaporation to yield a light yellow oil that solidified upon standing. The solid was then purified via recrystallization by heating the solid in 50 mL EtOH until dissolved then placed in the freezer. The product was collected via vacuum filtration as an off-white solid.

Procedure C (synthesis of substrate 2h):[13]

A 100 mL round bottom flask was charged with benzyl cyanide (.94 g, 8 mmol), 1-methylindole-3-carboxaldehyde (1.27 g, 8 mmol), sodium methoxide (0.04 g, 0.8 mmol) and EtOH (12 mL) and stirred at room temperature overnight. The reaction mixture was then concentrated *in vacuo* followed by an aqueous workup in water (2 x 50 mL), extracted with EtOAc (100 mL), and dried over $MgSO_4$. After concentration via rotary evaporation, the crude product was heated until dissolved in 20 mL EtOH to

yield 4-(1-methyl-1*H*-indol-3-yl)-2-phenylbut-3-enenitrile as an orange solid (1.25 g, 4.8 mmol). The solid was then dissolved in THF (5 mL) and cooled to 0 ^{o}C followed by the addition of $NaBH_4$ (0.2 g, 4.8 mmol). The solution was allowed to warm to room temperature and stirred overnight followed by quenching with NH_4Cl (10 mL), aqueous workup (3 x 20 mL), extraction with EtOAc (20 mL), and purification via column chromatography in 2% EtOAc:Hexane to provide **2h**.

References:

1. Duan et al. *J. Org. Chem.* **2009**, *74*, 9191-9194.

2. Gates et al. *J. Org. Chem.* **1943**, *8*, 373-379.

3. Kamimura et al. *J. Org. Chem.* **1990**, *55*, 2437-2442.

4. Szmuszkovicz et al. *J. Org. Chem.* **1960**, *25*, 1548-1558. See ref. 9 method B for reduction conditions (1 eq $NaBH_4$ used).

5. B. Quiclet-Sire and S. Z. Zard. *Synthesis.* **2005**, *19*, 3319-3326. See ref 9 method B for reduction conditions of the nitroalkene (2 eq $NaBH_4$ used).

6. M. Osorio-Olivares et al. *Bioorg. Med. Chem.* **2004**, *12*, 4055-4066.

7. H. Estreicher and E. J. Corey. *J. Am. Chem. Soc.* **1978**, *100*, 6294-6295.

8. J. S. Rao and D. Basavaiah. *Tetrahedron Letters.* **2004**, *45*, 1621-1625.

9. Kabalka et al. *Tetrahedron*. **1990**, *46*, 7443-7457. (Method B was used).

10 Vilvhes- Herrea et al. *Bioorg. Med. Chem.* **2009**, *17*, 2452-2460. See ref 9 method B for reduction conditions of the nitroalkene (2 eq $NaBH_4$ used).

11. A.J. Grenning and J.A. Tunge. *Org. Lett.* **2010**, *12*, 740-742.

12. Tundo, P. *Pure Appl. Chem.* **2000**, *72*, 1793.

13. Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 2803.

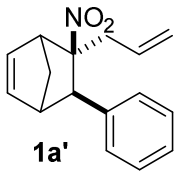
14. Ebitani, K.; Motokura, K.; Mori, K.; Mizugaki, T.; Kaneda, K. *J. Org. Chem.* **2006**, *71*, 5440.

Representative procedure for the CO_2 catalyzed activation of allyl alcohol towards allylation of nitroalkanes:

A 2.0 – 5.0 mL microwave vial (Biotage #351521) dried in an oven was charged with a stir bar and taken into a glove box. $Pd(PPh_3)_4$ (10 mol %, 0.035 g) was added along with DMSO (1.75 mL) and the vial capped using a vial cap (Biotage #352298) and a manual cap crimper (Biotage #353671). The vial was removed from the glovebox and substrate (0.30 mmol) and allyl alcohol (0.45 mmol, 0.026 g) were added sequentially via syringe. CO_2 was then bubbled through the solvent using a long 20G needle connected to a balloon and a separate 25.5G needle to vent. After 6 min. the vent needle was removed

followed by the CO_2 needle and the top of the vial is wrapped in parafilm "M". The vial was then placed in an oil bath at room temperature and heated/stirred at 80 ^oC for 14 hours.

After 14 hours the vial was removed from the bath, and allowed to cool to room temperature. The contents were taken up in EtOAc (10 mL) and transferred to a separatory funnel and were washed with 30 mL DI water 3x. The organic layer was dried over $MgSO_4$, filtered, and the solvent evaporated *in vacuo* followed by purification via silica gel column chromatography using 1:20 EtOAc:Pentanes as an eluent.



1a'

dr = 95:5 ; Stereochemistry assigned by inference. See Ref. 11.

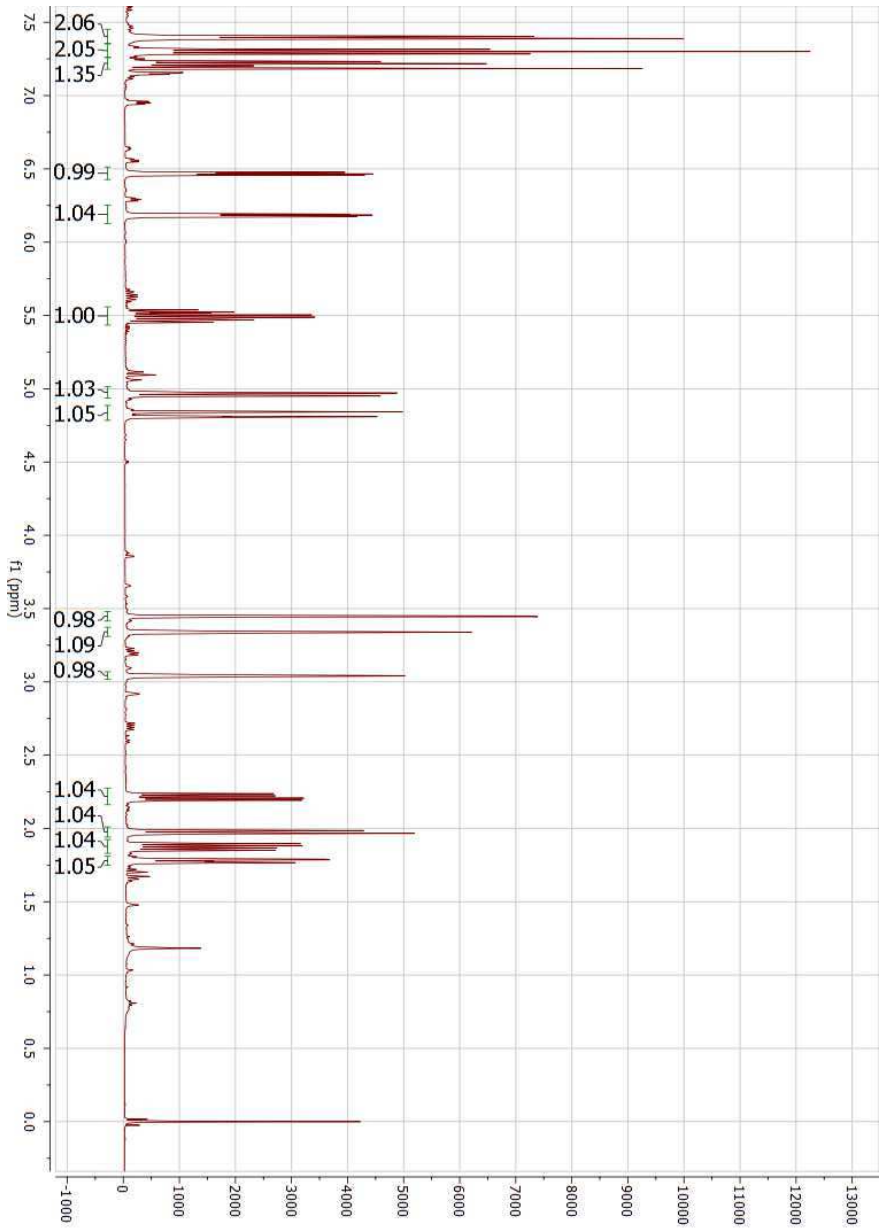
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

(major diastereomer) δ 7.47 (d, *J* = 7.43 Hz, 2H), 7.37 (t, *J* = 7.40 Hz, 2H), 7.30 (m, 1H), 6.54 (dd, *J* = 5.66, 3.22 Hz, 1H), 6.26 (dd, *J* = 5.67, 2.82 Hz, 1H), 5.57 (m, 1H), 5.04 (dt, *J* = 10.2, 0.95 Hz 1H), 4.90 (dq, *J* = 16.9 Hz, 1.50 Hz, 1H), 3.52 (d, *J* = 2.63 Hz, 1H), 3.41 (s, 1H), 3.12 (s, 1H), 2.29 (ddt, *J* = 15.0, 6.97, 1.20 Hz, 1H), 2.05 (d, *J* = 9.60 Hz, 1H), 1.95 (dd, *J* = 15.0, 7.60 Hz, 1H), 1.85 (dq, *J* = 9.56, 2.07 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$):

(major diastereomer) δ 139.79, 138.18, 135.82, 130.21, 127.45, 126.06, 118.66, 100.40, 52.03, 47.13, 45.67, 44.58, 42.14.

GC/MS Data: 255.1 (M^+, 1 %), 66.1, base peak.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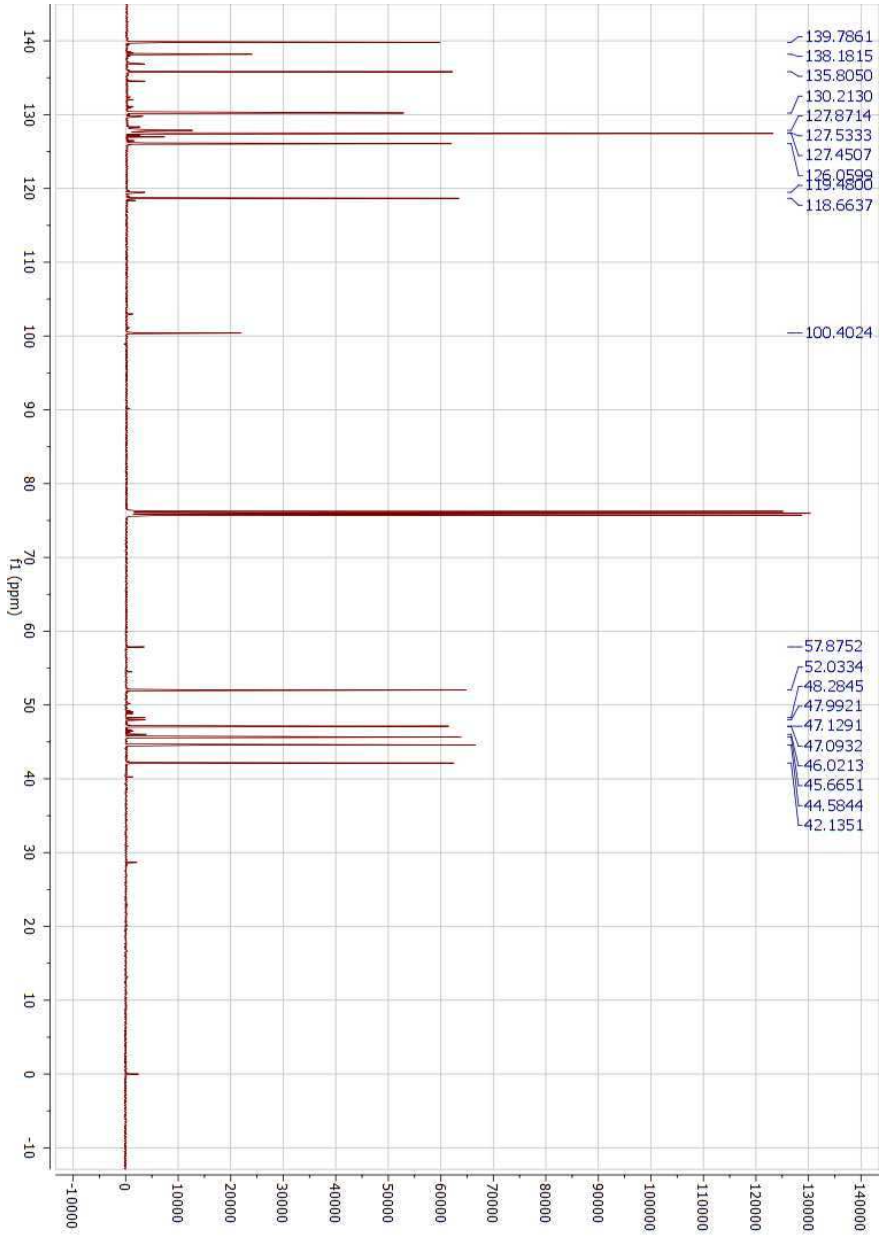
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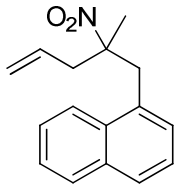


1b

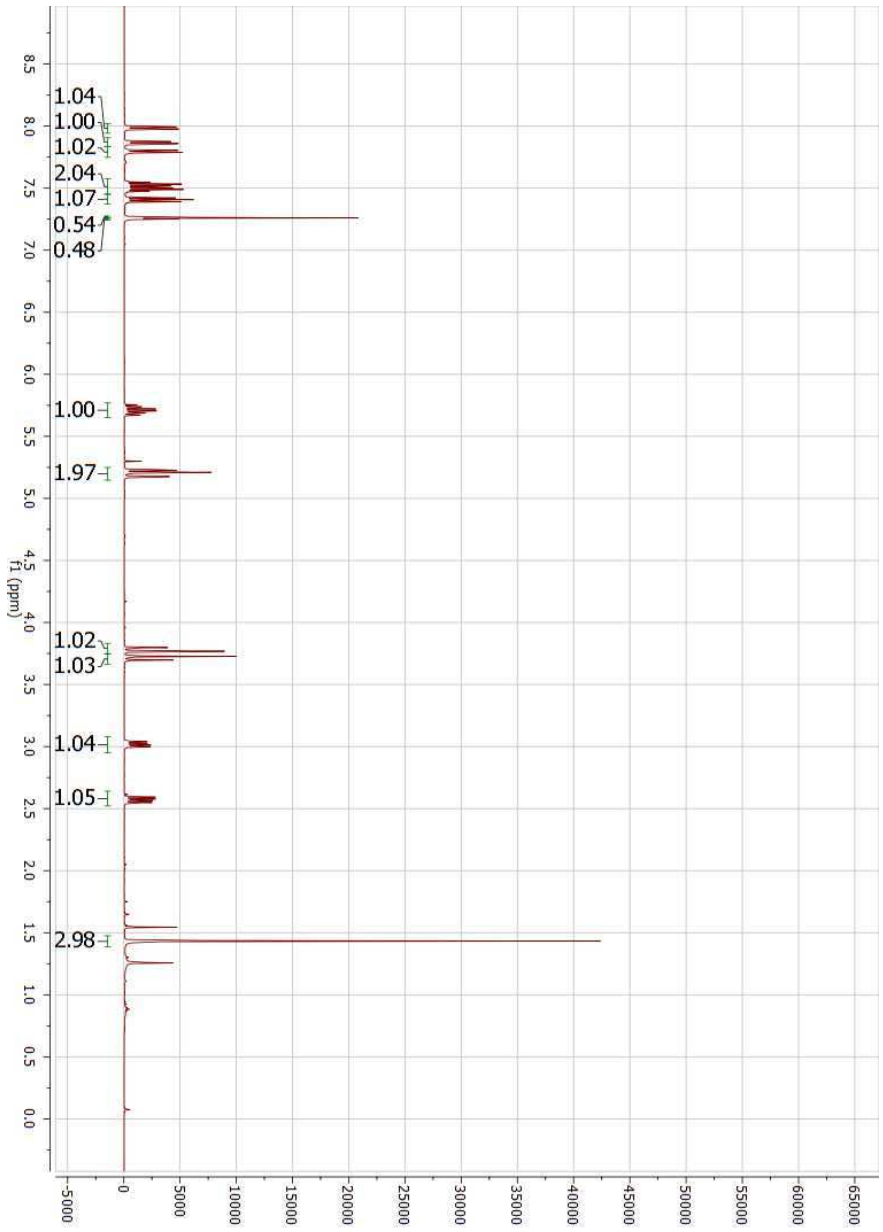
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.99 (d, *J* = 8.66 Hz, 1H), 7.87 (d, *J* = 8.08 Hz, 1H), 7.80 (d, *J* = 8.40 Hz, 1H), 7.44 (m, 2H), 7.51 (t, *J* = 7.65 Hz, 1H), 7.26 (d, *J* = 6.22 Hz, 1H), 5.71 (m, 1H), 5.21 (m, 2H), 3.78 (d, *J* = 14.7 Hz, 1H), 3.71 (d, *J* = 14.6 Hz, 1H), 3.02 (dd, *J* = 14.2, 6.86 Hz, 1H), 2.57 (dd, *J* = 14.2, 7.76 Hz, 1H), 1.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 133.91, 132.66, 131.15, 130.92, 129.01, 128.47, 128.38, 126.27, 125.67, 125.38, 123.63, 120.93, 92.43, 44.36, 41.09, 21.31.

GC/MS data: 255.1 (M^+, 8 %), 141.1, base peak.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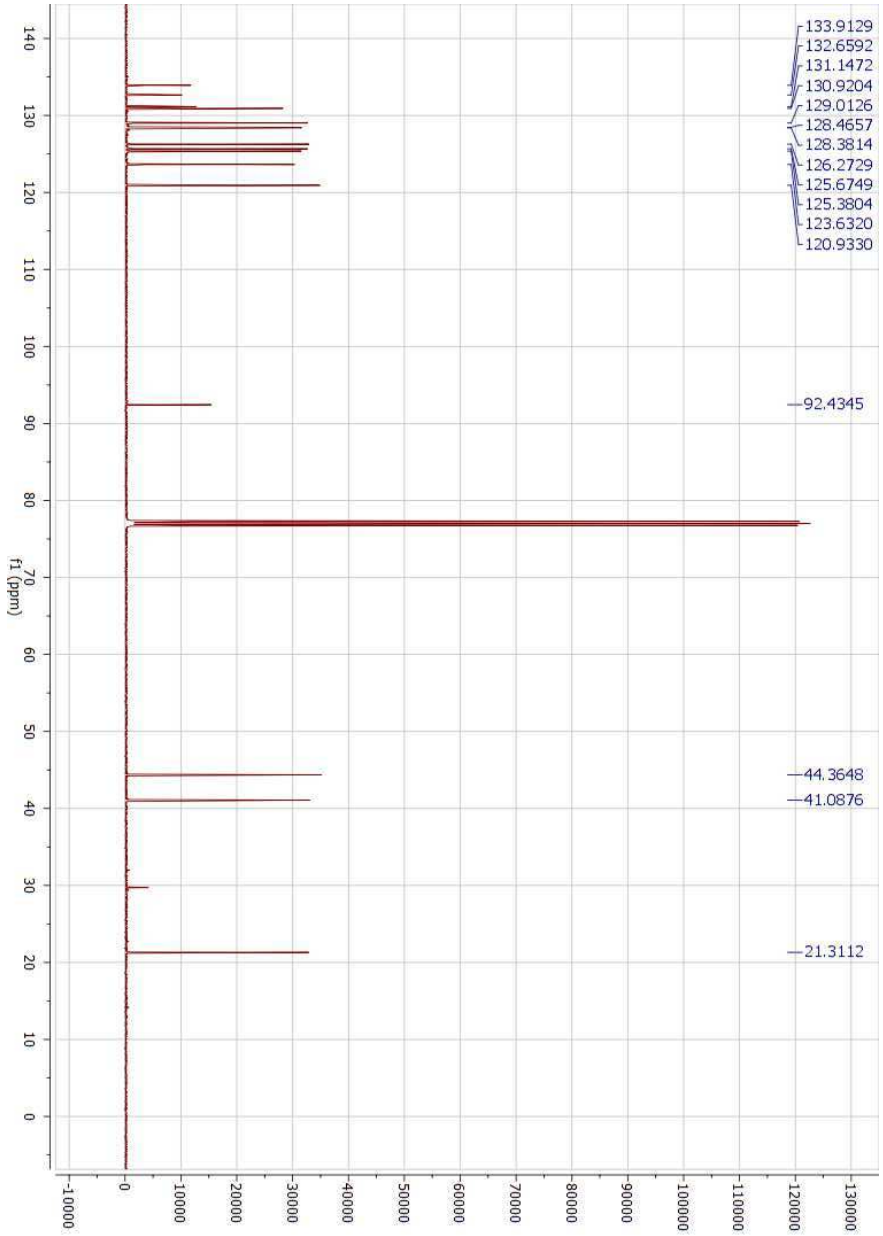
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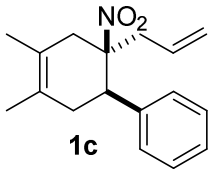


1c

dr > 95:5; Stereochemistry assigned by inference. See Ref. 11.

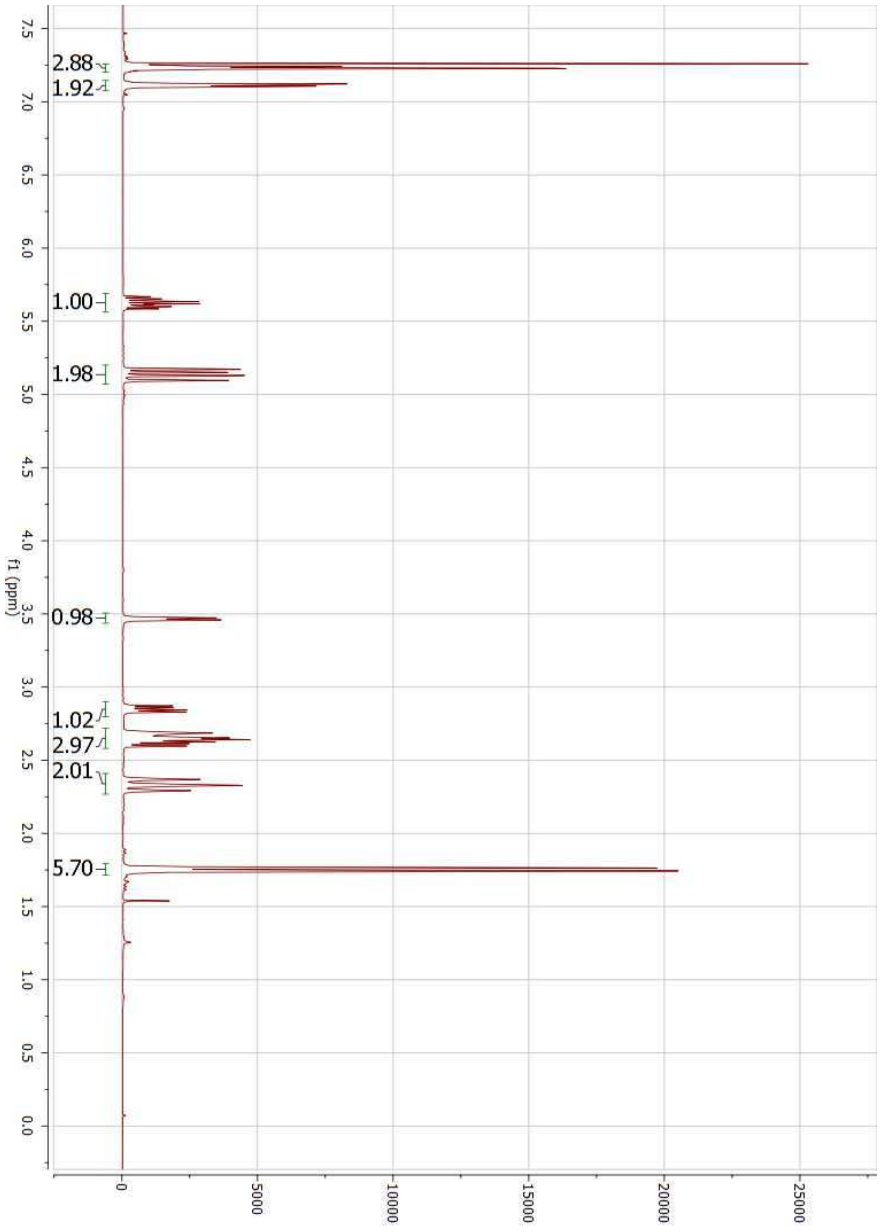
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.23 (m, 3H), 7.11 (m, 2H), 5.63 (m, 1H), 5.14 (m, 2H), 3.47 (d, *J* = 6.82 Hz, 1H), 2.85 (dd, *J* = 14.1, 6.81 Hz, 1H), 2.64 (m, 3H), 2.34 (m, 2H), 1.75 (d, *J* = 10.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 140.27, 130.99, 128.47, 128.27, 127.53, 124.40, 123.72, 120.64, 92.98, 46.8, 41.80, 36.6, 33.35, 19.36, 18.30.

GC/MS data: 225.2 (M – NO_2, 8%), 183.1, base peak.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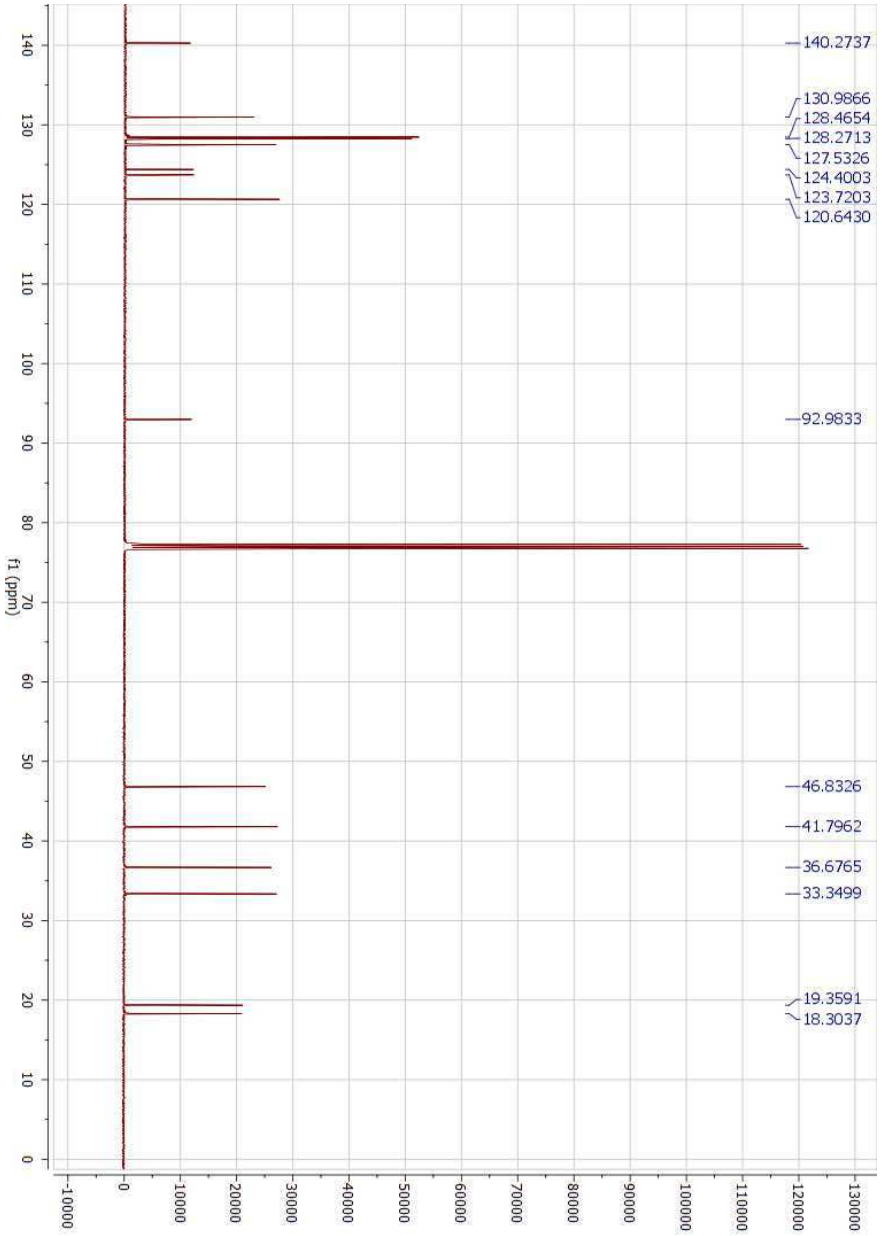
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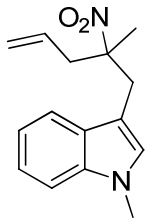


1d

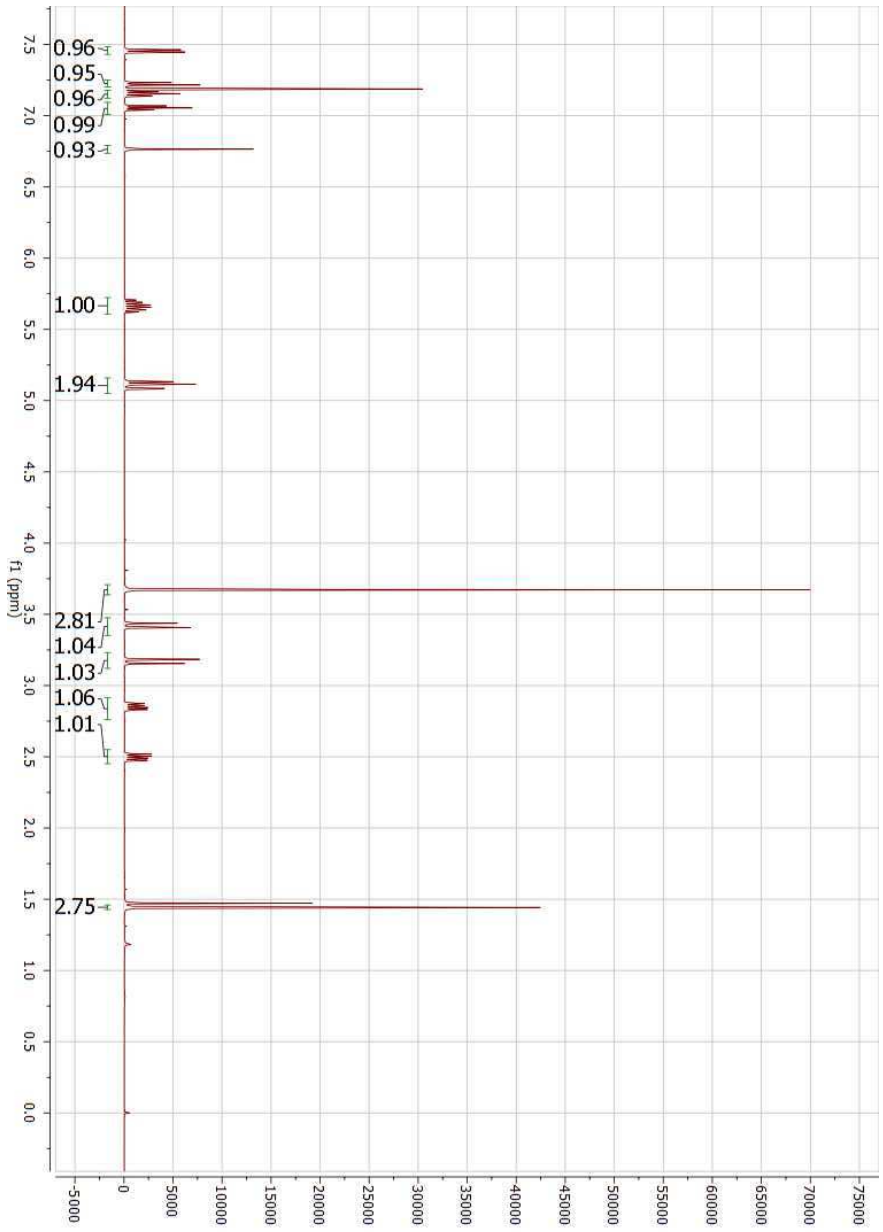
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.53 (dt, *J* = 7.97, 0.92 Hz, 1H), 7.30 (dt, *J* = 8.31, 0.91 Hz, 1H), 7.23 (ddd, *J* = 8.18, 6.99, 1.11 Hz, 1H), 7.13 (ddd, *J* = 7.99, 6.94, 1.08 Hz, 1H), 6.84 (s, 1H), 5.74 (m, 1H), 5.19 (m, 2H), 3.75 (s, 3H), 3.49 (d, *J* = 14.8 Hz, 1H), 3.24 (d, *J* = 14.8 Hz, 1H), 2.92 (dd, *J* = 14.2, 7.05 Hz, 1H), 2.57 (dd, *J* = 14.1, 7.62 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 136.62, 131.19, 128.48, 128.45, 121.69, 120.50, 119.32, 118.74, 109.37, 107.48, 92.63, 44.04, 35.61, 32.78, 21.50.

GC/MS data: 258.1 (M^+, 14%) 144.1, base peak.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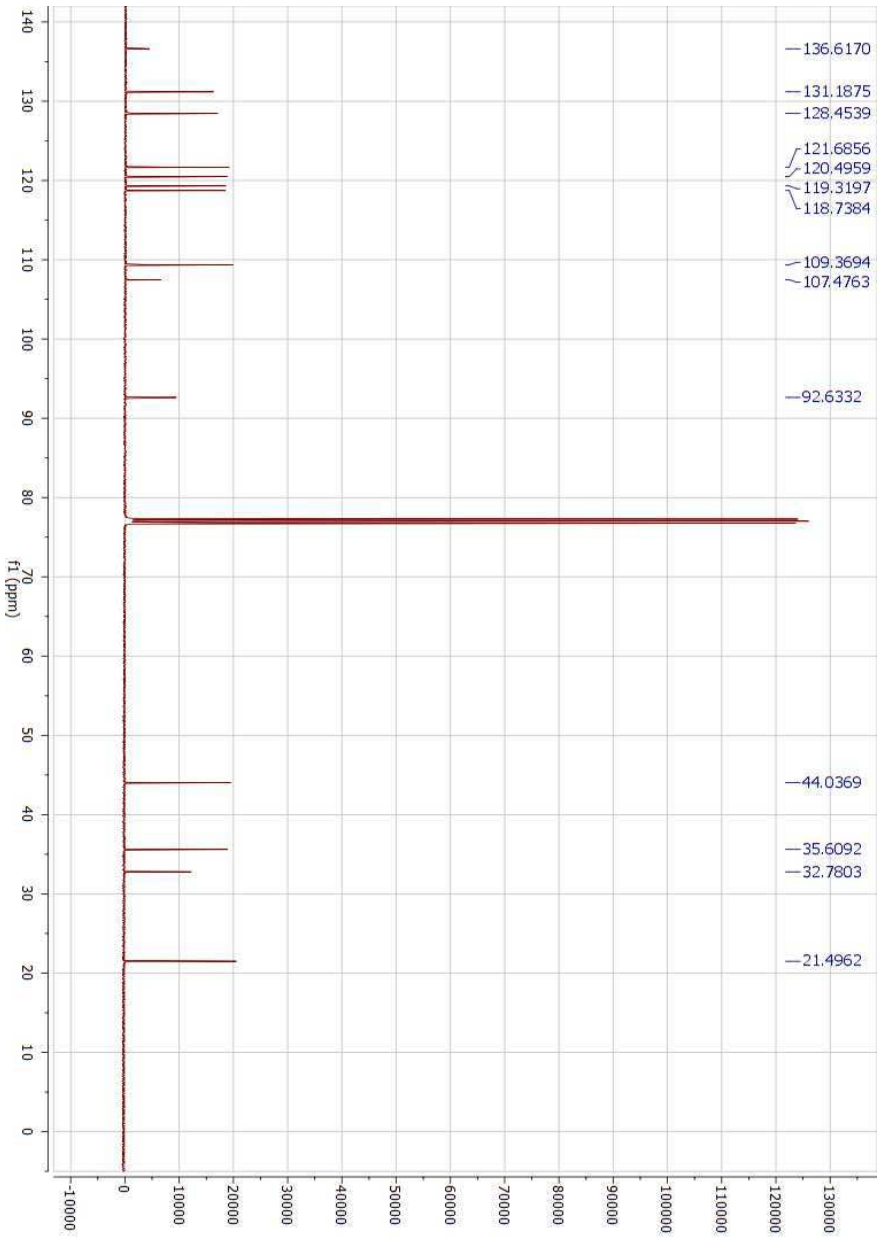
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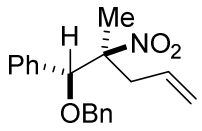


1e

dr = 88:12; Relative stereomchemistry assigned via x-ray structure of corresponding amine salt.

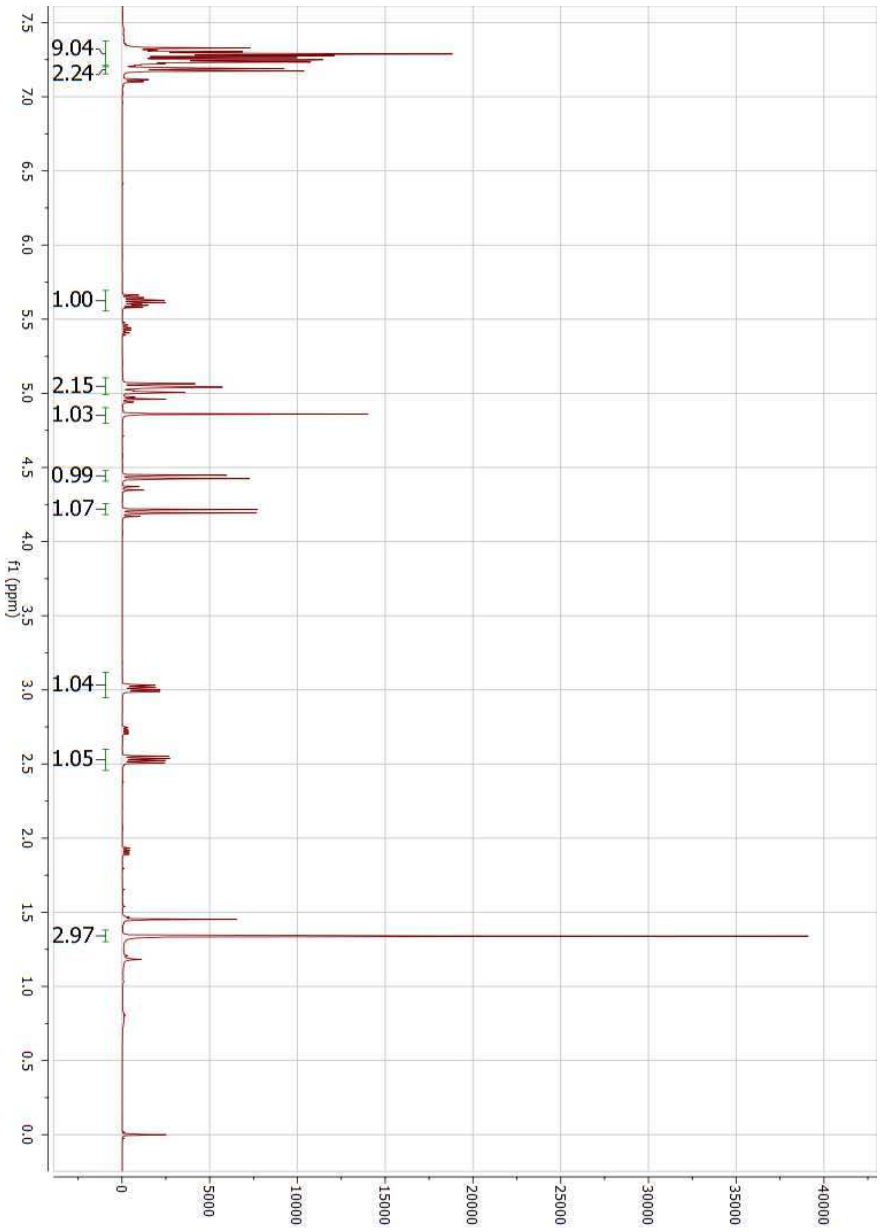
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

(major diastereomer) δ 7.30 (m, 8H), 7.18 (m, 2H), 5.62 (m, 1H), 5.04 (m, 2H), 4.86 (s, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.20 (d, *J* = 11.5, 1H), 3.01 (dd, *J* = 14.5, 6.63 Hz, 1H), 2.53 (dd, *J* = 14.6, 7.89 Hz, 1H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

(major diastereomer) δ 136.19, 134.15, 130.31, 127.82, 127.43, 127.40, 127.33, 126.88, 119.34, 93.20, 83.66, 70.43, 39.01, 16.74.

GC/MS data: 221.1 (M – toluene, 1%), 91.1, base peak.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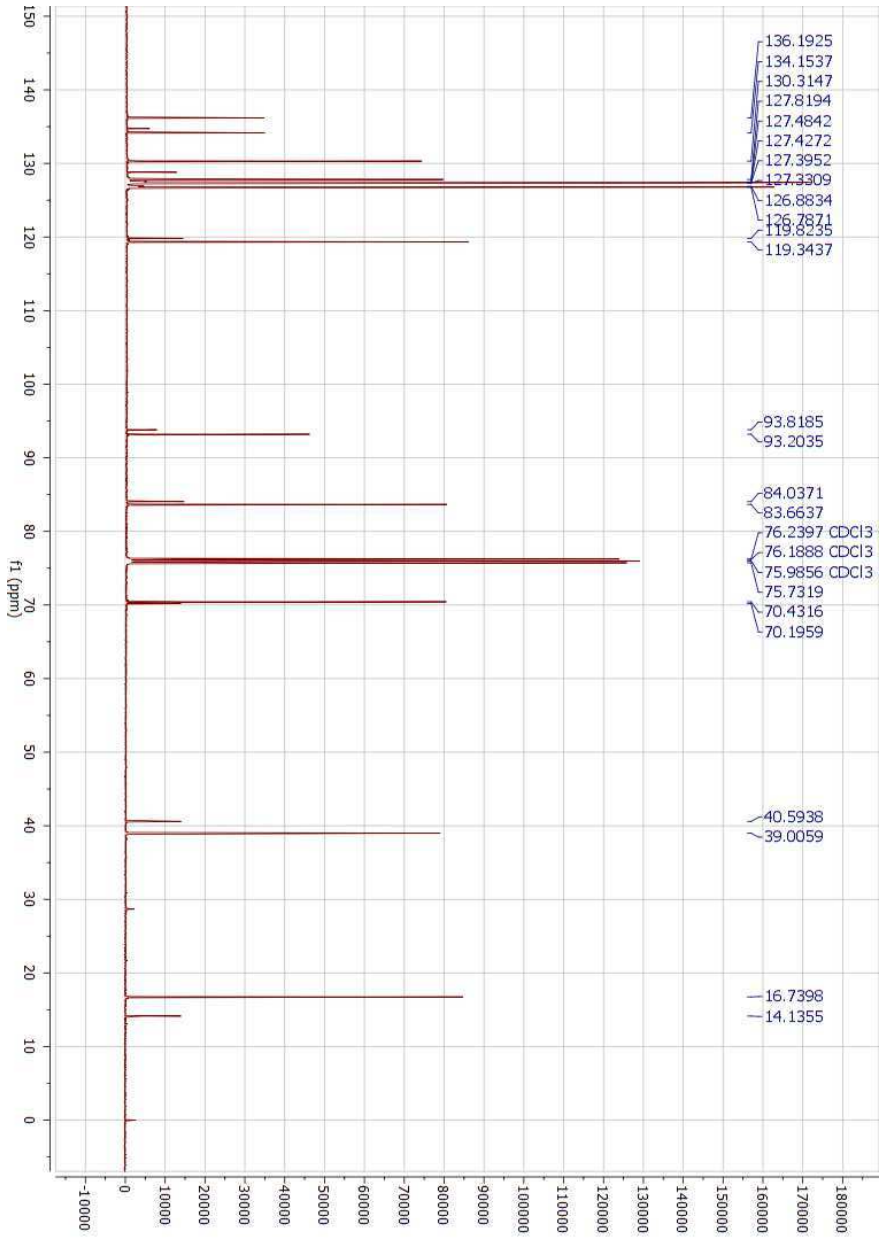
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119.3437
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93.2035
84.0371
83.6637
76.2397 CDCl3
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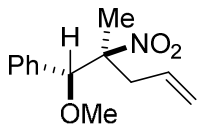


1f

dr = 88:12; Relative stereochemistry assigned based on the x-ray structure of the 1e salt.

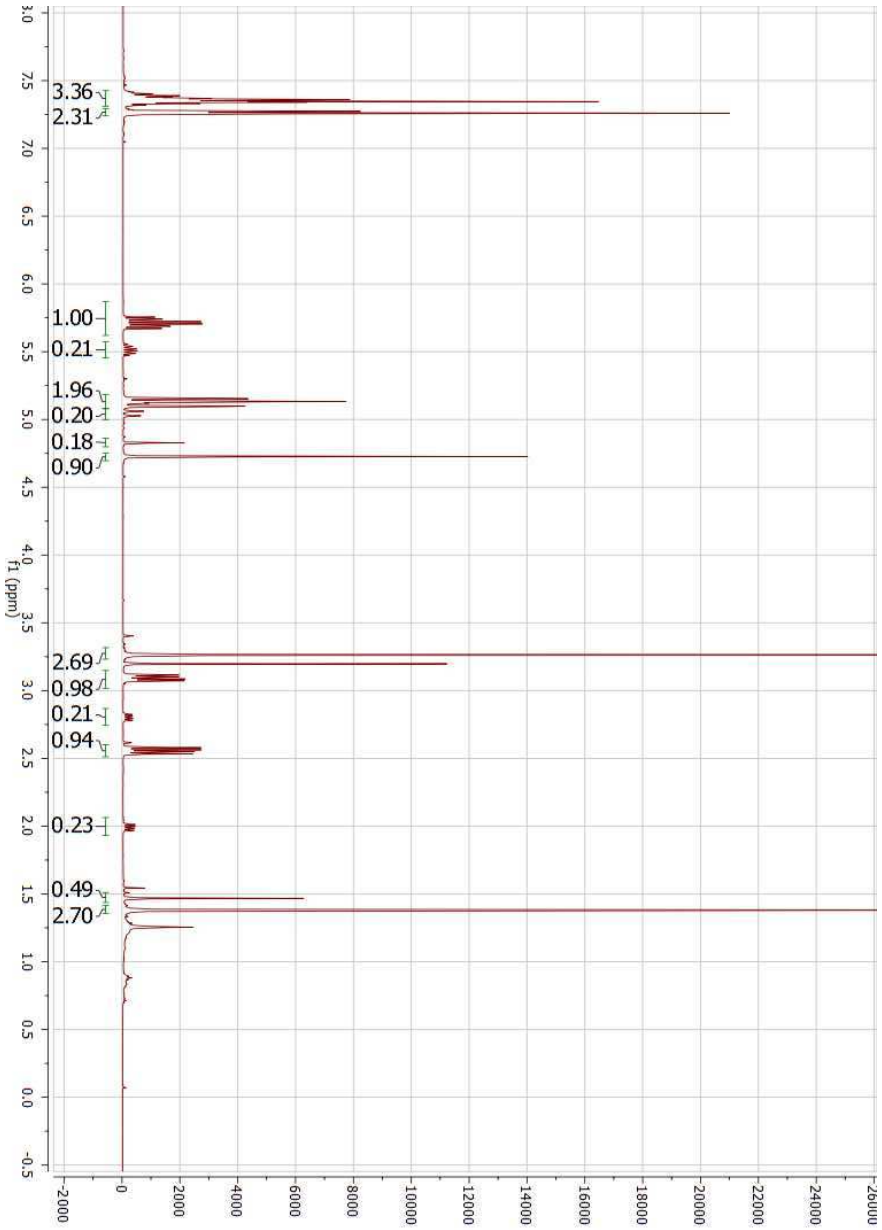
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

(major diastereomer) δ 7.35 (m, 3H), 7.27 (m, 2H), 5.71 (m, 1H), 5.13 (m, 2H), 4.73 (s, 1H), 3.26 (s, 3H), 3.09 (dd, *J* = 14.1, 6.75 Hz, 1H), 2.56 (dd, *J* = 14.5, 7.90 Hz, 1H), 1.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

(major diastereomer) δ 135.17, 131.41, 128.75, 128.37, 128.22, 120.32, 94.18, 87.23, 57.84, 39.83, 17.85.

GC/MS data: 121.1 base peak.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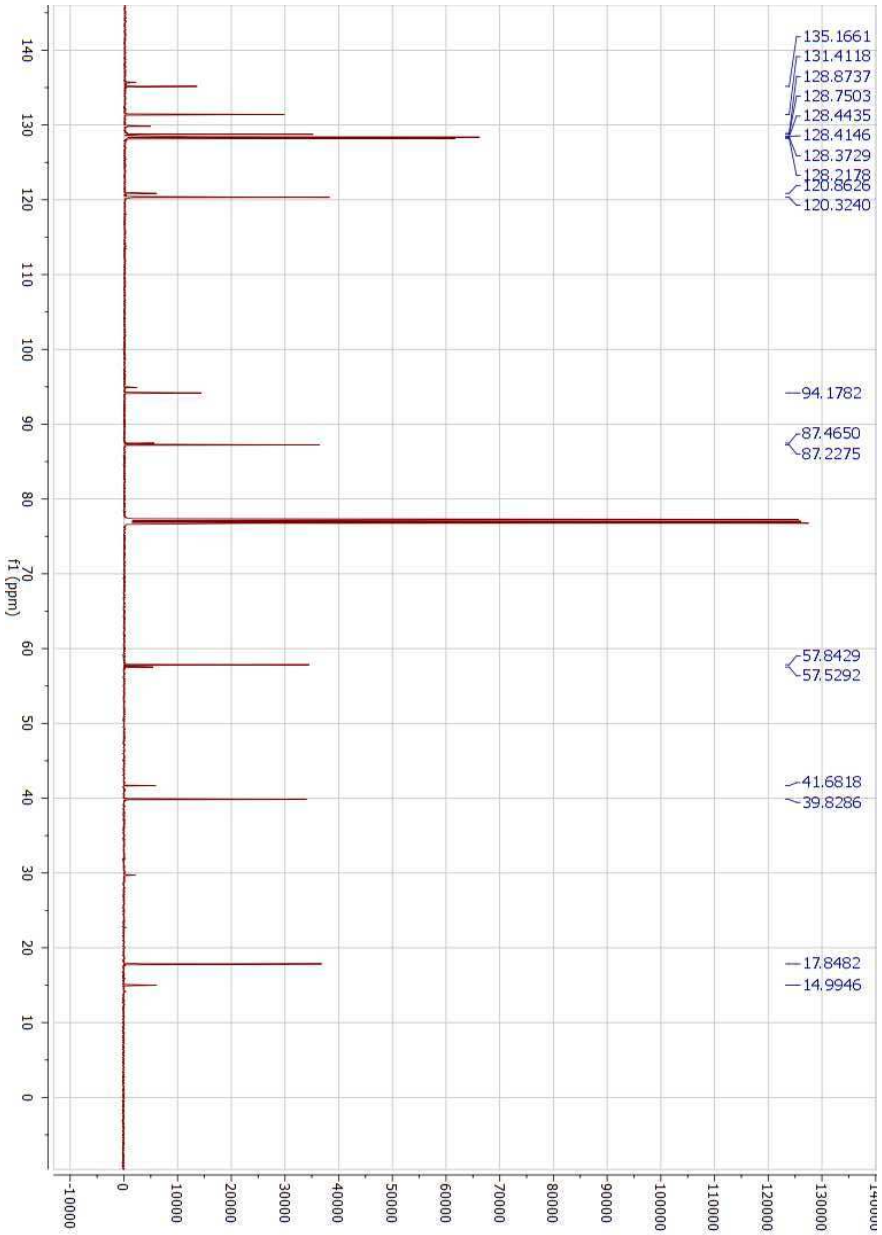
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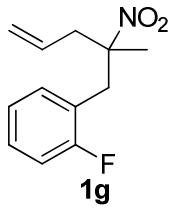


1g

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

δ 7.27 (m, 1H), 7.07 (m, 3H), 5.70 (m, 1H), 5.20 (m, 2H), 3.33 (d, J = 14.3 Hz, 1H), 3.25 (d, J = 14.2 Hz, 1H), 2.89 (dd, J = 14.1, 6.93 Hz, 1H), 2.53 (dd, J = 14.2, 7.68 Hz, 1H), 1.48 (s, 3H).

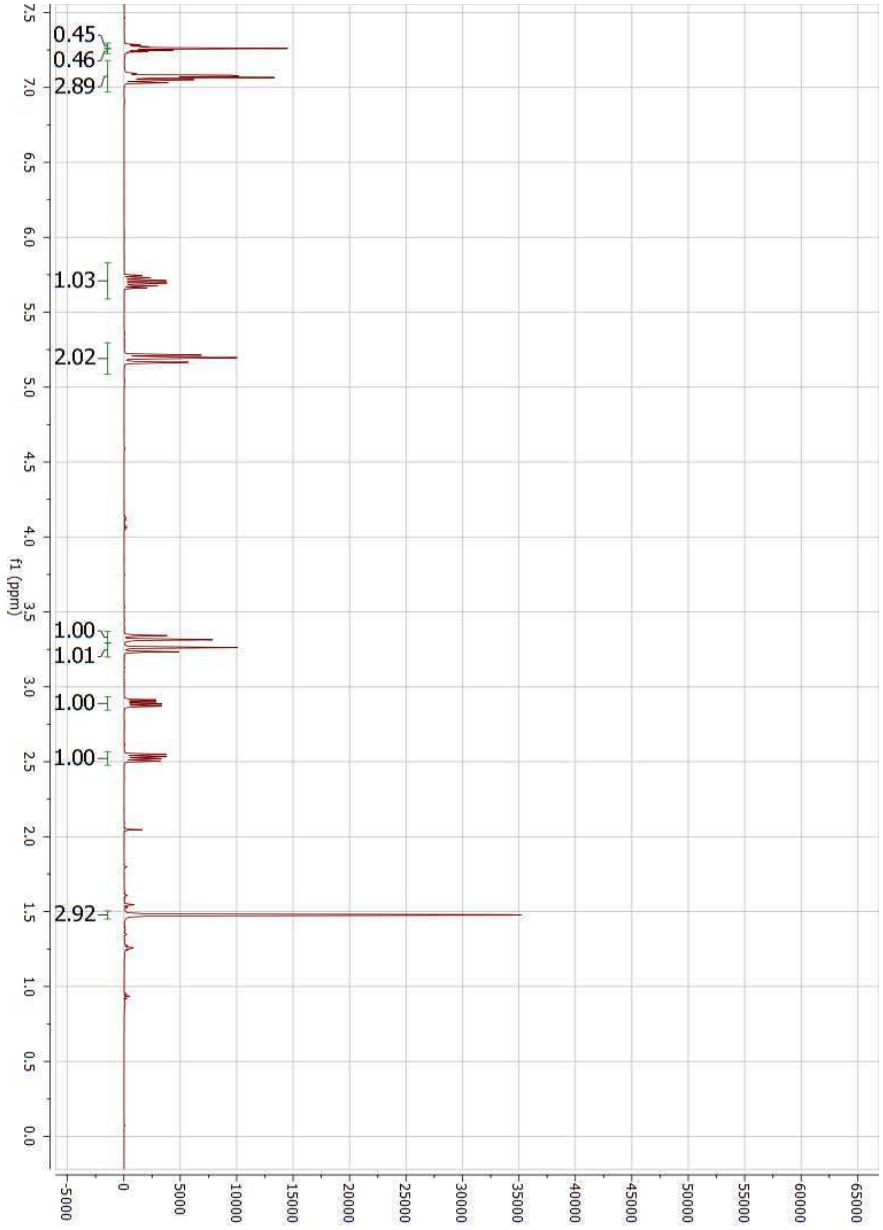
^{13}C NMR (126 MHz, $CDCl_3$):

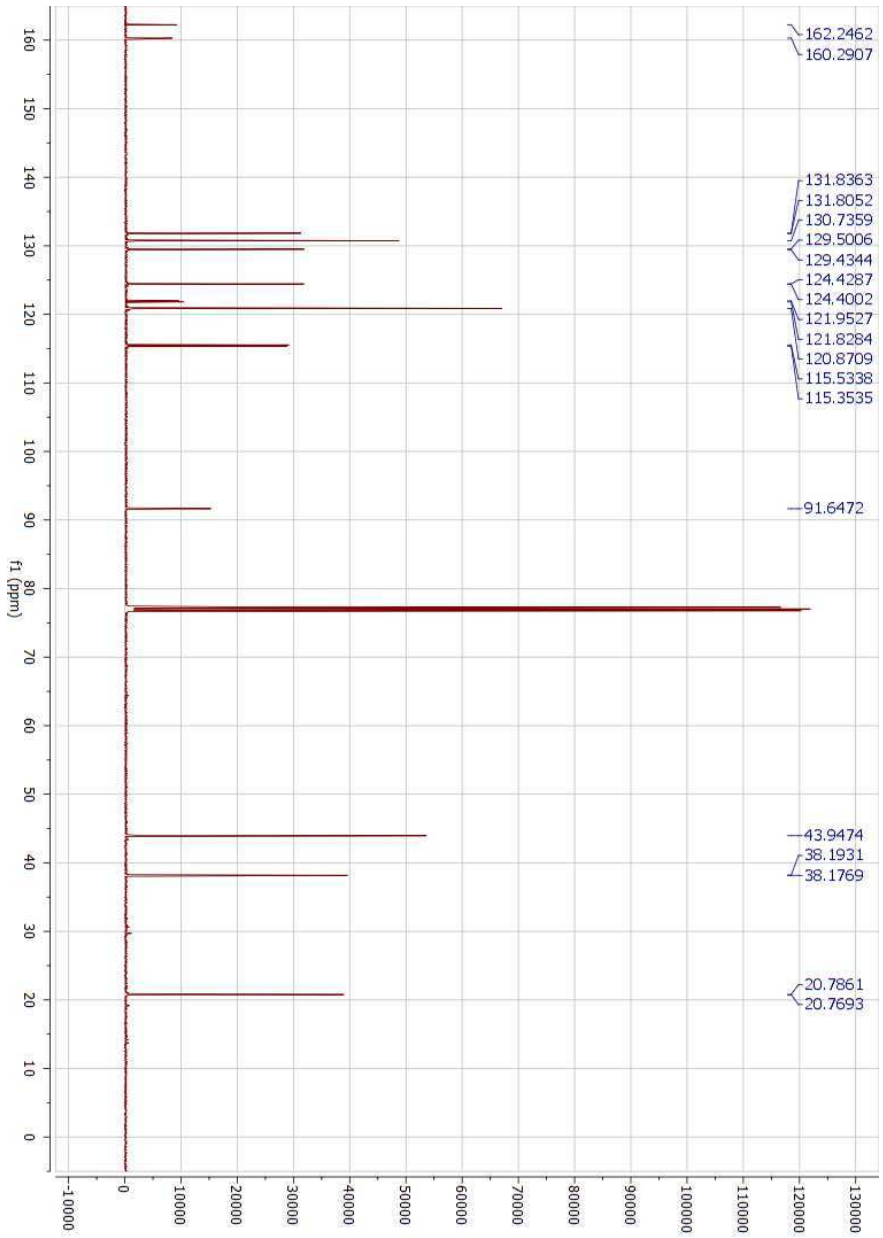
δ 161.27 (d, J_{CF} = 246 Hz), 131.82 (d, J_{CF} = 3.91 Hz), 130.74, 129.47 (d, J_{CF} = 8.32 Hz), 124.41 (d, J_{CF} = 3.60 Hz), 121.89 (d, J_{CF} = 15.7 Hz), 120.87, 115.44 (d, J_{CF} = 22.7 Hz), 91.65, 43.95, 38.19, 20.78.

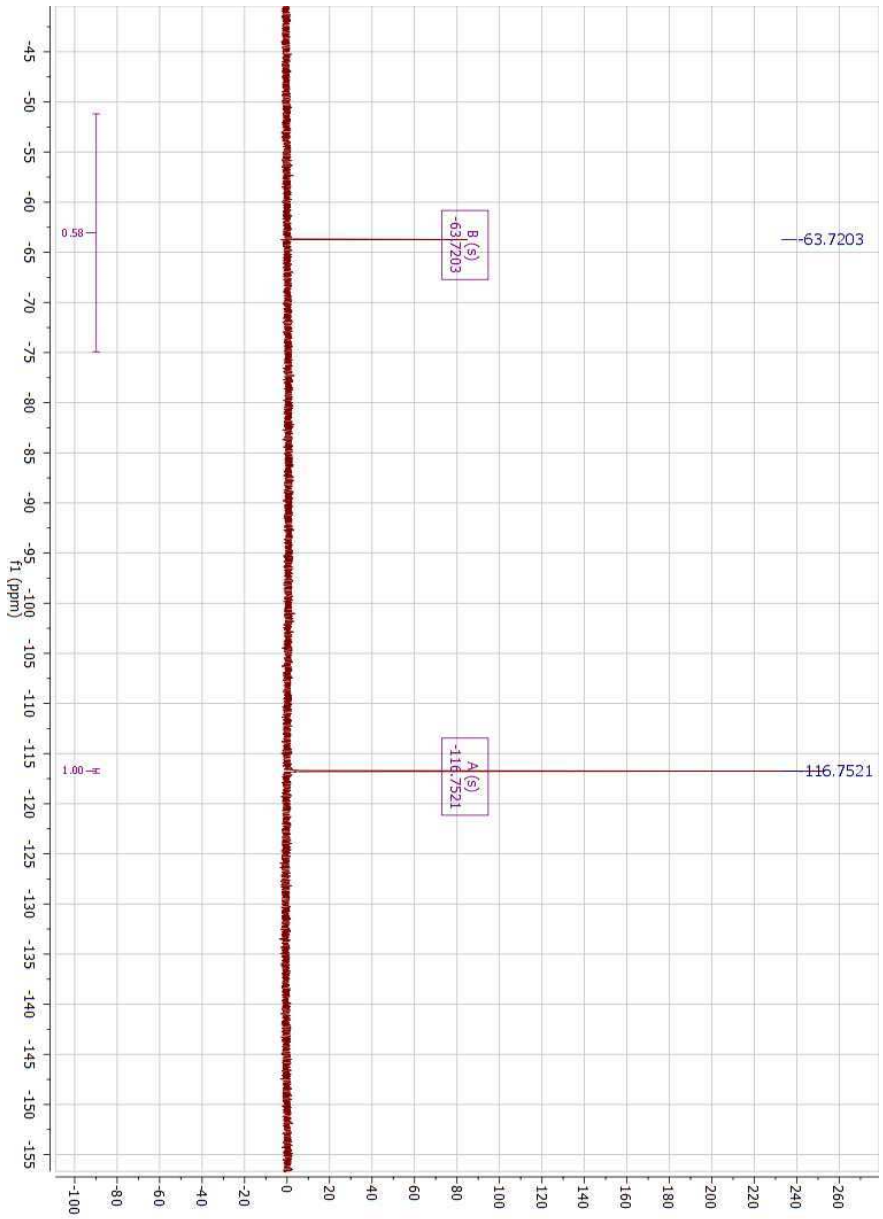
^{19}FNMR (376 MHz, $CDCl_3$):

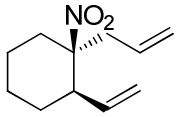
δ -116.75.

GC/MS data: 223.05 (M^+ 0.1 %), 109.1, base peak.


0.45
0.46
2.89
1.03
2.02
1.00
1.01
1.00
1.00
2.92
f1 (ppm)


162.2462
160.2907
131.8363
131.8052
130.7359
129.5006
129.4344
124.4287
124.4002
121.9527
121.8284
120.8709
115.5338
115.3535
91.6472
43.9474
38.1931
38.1769
20.7861
20.7693
f1 (ppm)


f1 (ppm)
0.58
1.00
B (s)
-63.7203
A (s)
-116.7521
-63.7203
116.7521



1h

dr = 85:15; Stereochemistry assigned by inference. See Ref. 11.

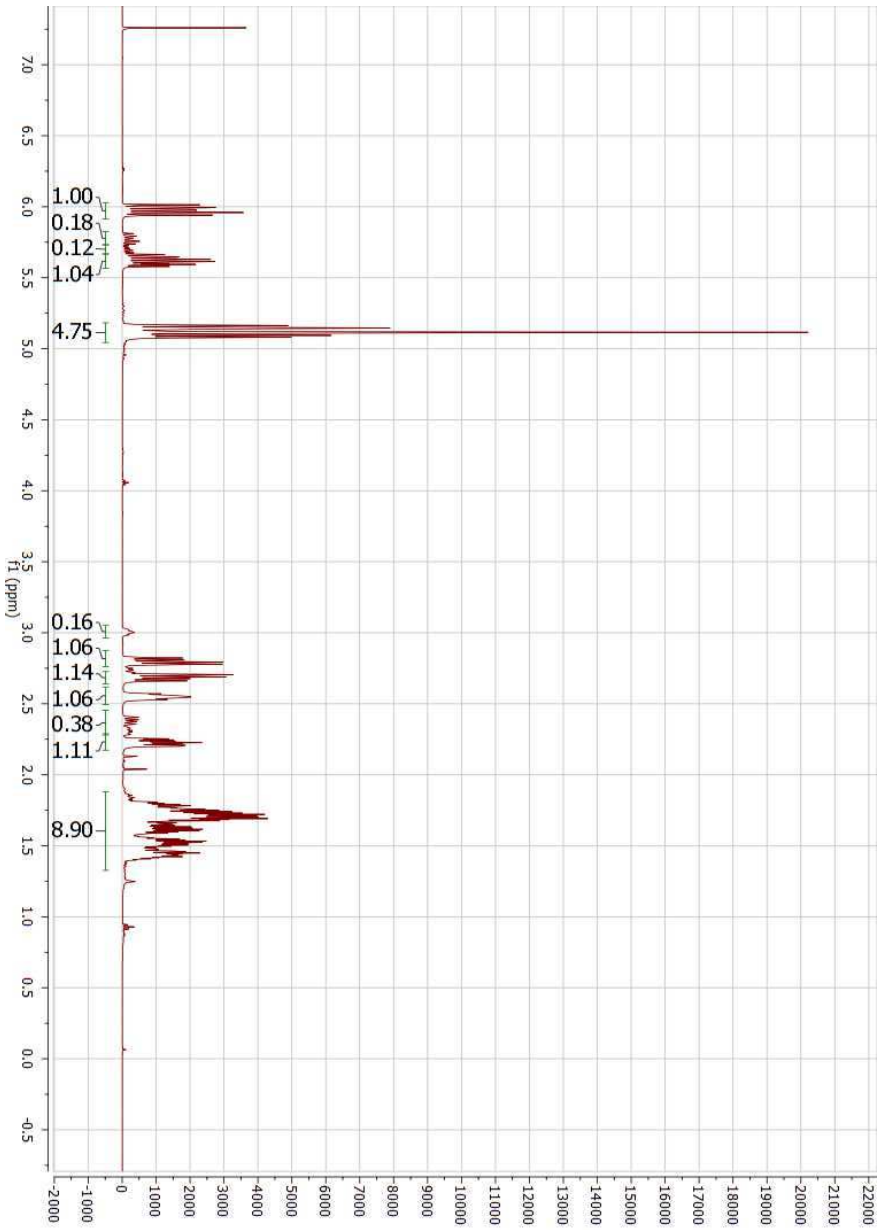
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

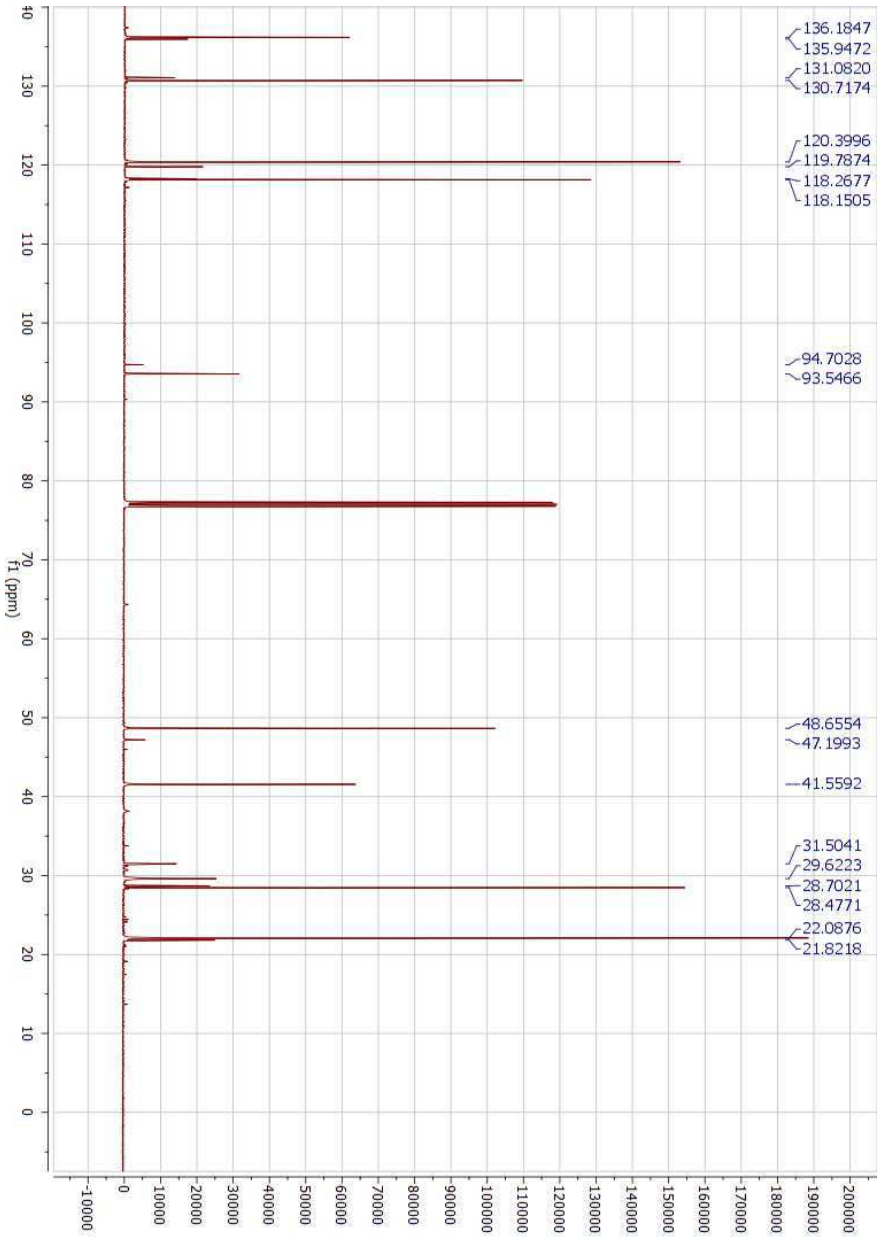
(major diastereomer) δ 5.98 (m, 1H), 5.62 (m, 1H), 5.13 (m, 4H), 2.80 (dd, *J* = 15.1 Hz, 7.08 Hz, 1H), 2.69 (dd, *J* = 14.1, 7.60 Hz, 1H), 2.55 (m, 1H), 2.23 (ddd, *J* = 13.8, 8.62, 3.78 Hz, 1H), 1.60 (m, 8H).

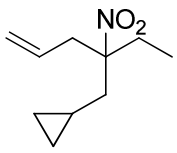
^{13}C NMR (126 MHz, $CDCl_3$):

(major diastereomer) δ 136.18, 130.72, 120.40, 118.15, 93.55, 48.66, 41.56, 29.62, 28.48, 22.09.

GC/MS data: 149.2 (M – NO_2, 5%), 81.1 (base peak).


1.00
0.18
0.12
1.04
4.75
0.16
1.06
1.14
1.06
0.38
1.11
8.90
f1 (ppm)


136.1847
135.9472
131.0820
130.7174
120.3996
119.7874
118.2677
118.1505
94.7028
93.5466
48.6554
47.1993
41.5592
31.5041
29.6223
28.7021
28.4771
22.0876
21.8218
f1 (ppm)



1i

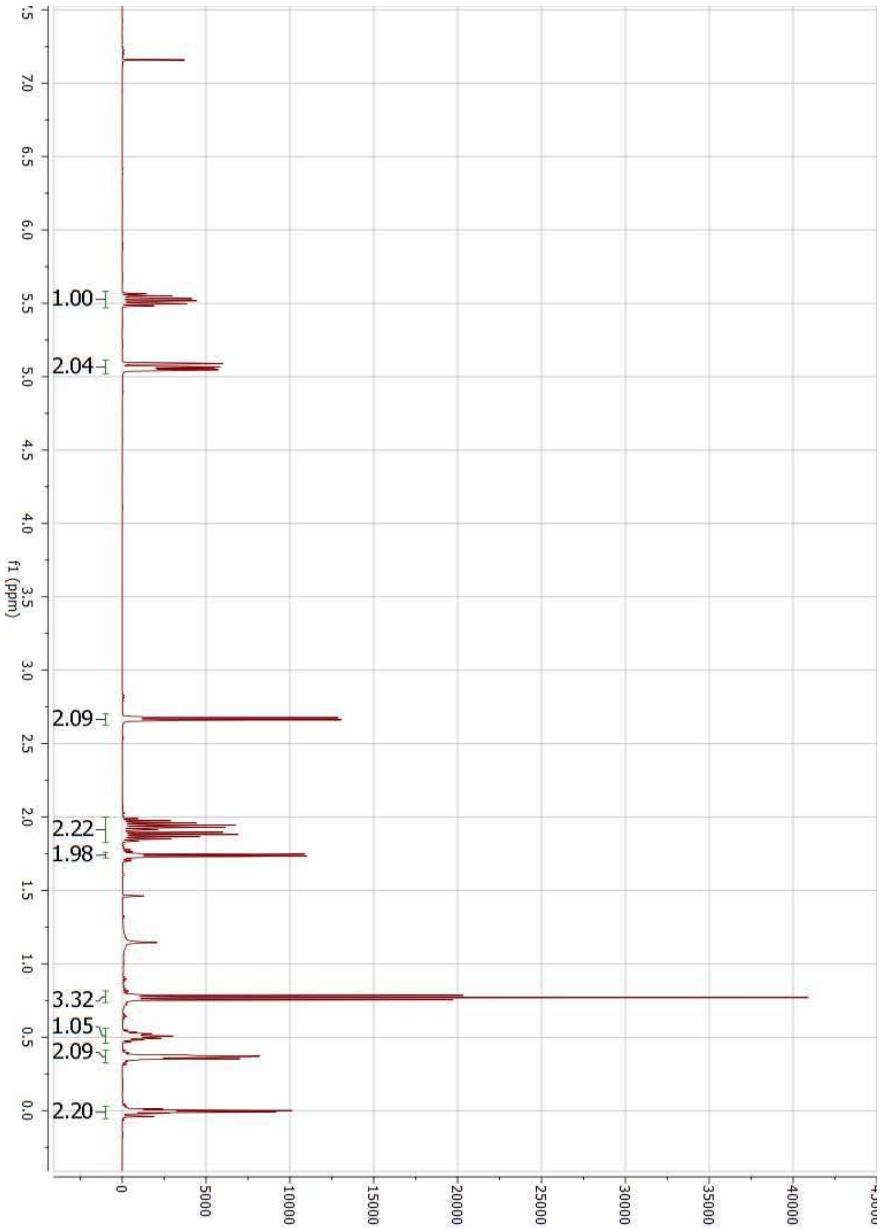
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

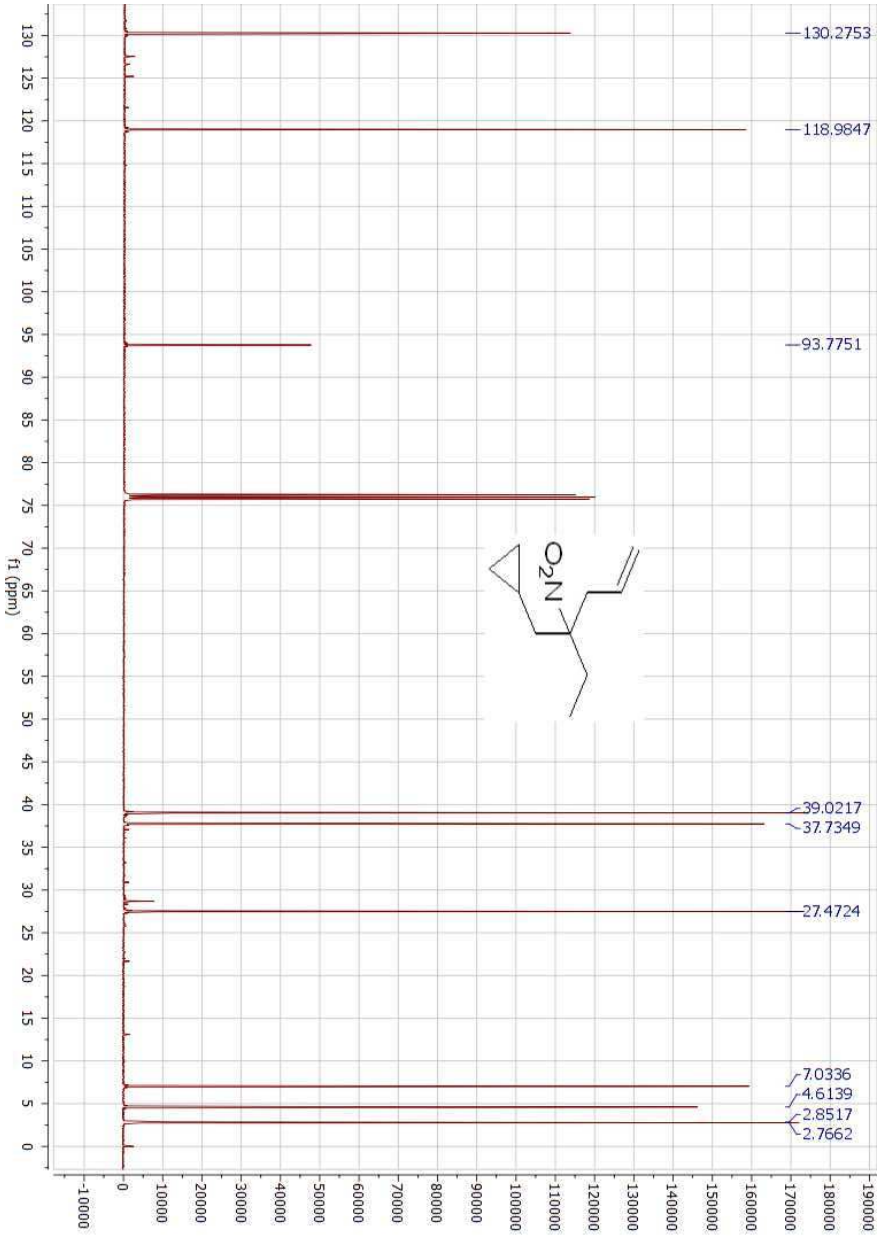
δ 5.63 (ddt, *J* = 17.3, 10.1, 7.30 Hz, 1H), 5.17 (m, 2H), 2.77 (dt, *J* = 7.30, 1.24 Hz, 2H), 2.01 (m, 2H), 1.84 (dd, *J* = 6.8, 1.46 Hz, 2H), 0.87 (t, *J* = 7.45 Hz, 3H), 0.61 (m, 1H), 0.46 (m, 2H), 0.10 (m, 2H).

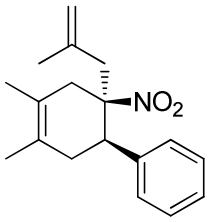
^{13}C NMR (126 MHz, $CDCl_3$):

δ 130.28, 118.98, 93.78, 39.02, 37.73, 28.68, 7.03, 4.61, 2.85, 2.78.

GC/MS data: 154.1 (M – ethyl, 0.4 %), 55.1, base peak.


f1 (ppm)
1.00
2.04
2.09
2.22
1.98
3.32
1.05
2.09
2.20


130.2753
118.9847
93.7751
39.0217
37.7349
27.4724
7.0336
4.6139
2.8517
2.7662
O2N
f1 (ppm)



1j

dr = 90:10; Stereochemistry assigned by inference. See Ref. 11.

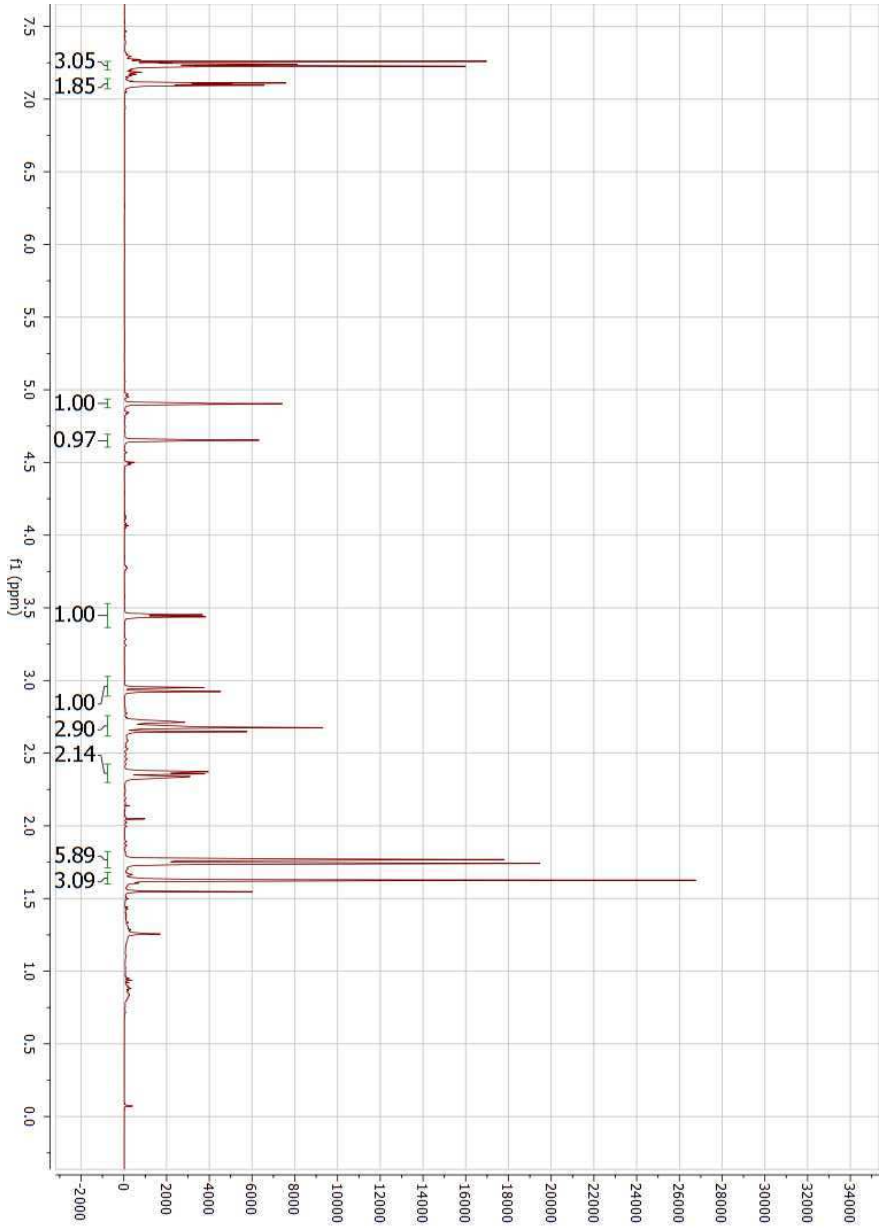
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

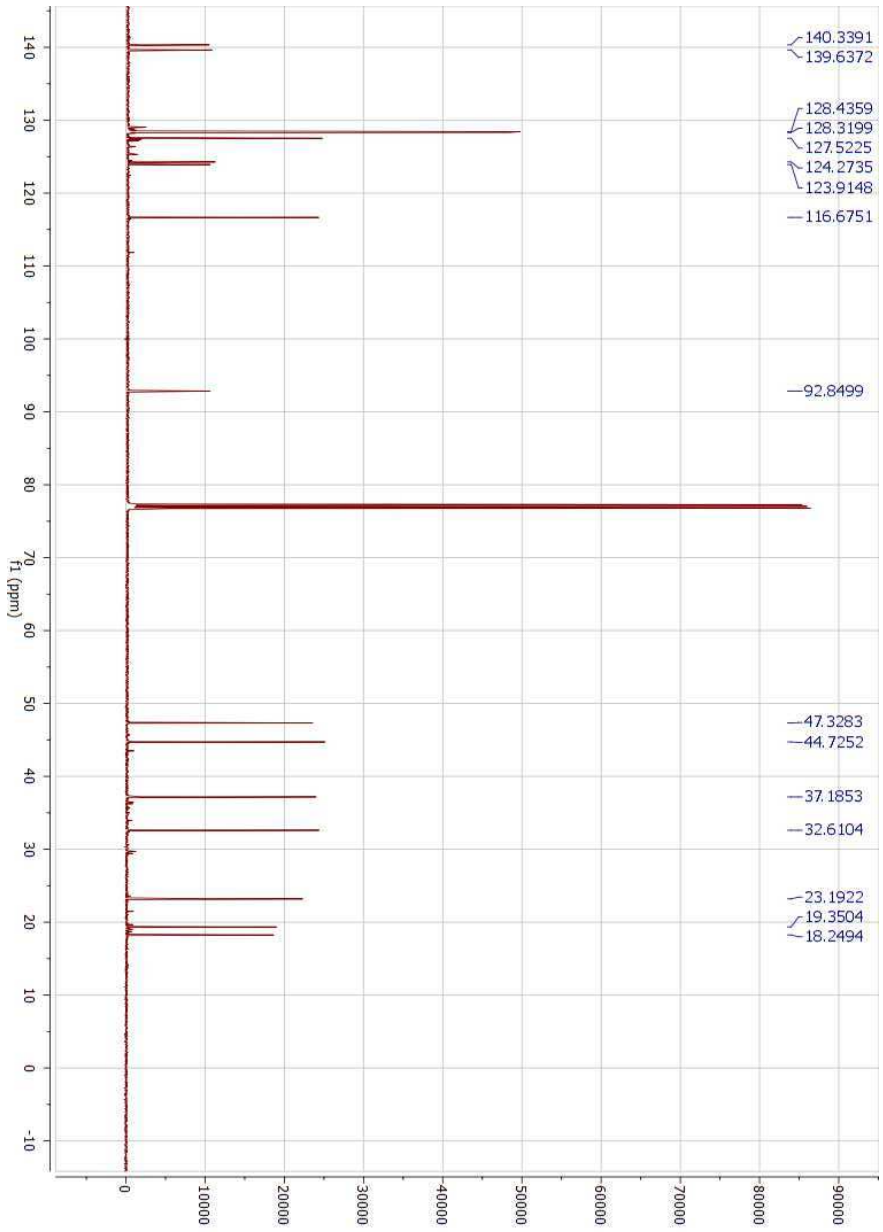
δ 7.23 (m, 3H), 7.10 (m, 2H), 4.90 (t, *J* = 1.70 Hz, 1H), 4.65 (d, *J* = 1.05 Hz, 1H), 3.44 (d, *J* = 7.17 Hz, 1H), 2.93 (d, *J* = 14.0 Hz, 1H), 2.69 (m, 3H), 2.36 (m, 2H), 1.75 (d, *J* = 13.6 Hz, 6H), 1.63 (s, 3H).

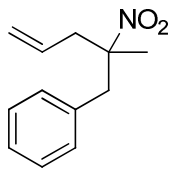
^{13}C NMR (126 MHz, $CDCl_3$):

δ 140.34, 139.64, 128.44, 128.32, 127.52, 124.27, 123.91, 116.68, 92.85, 47.33, 44.73, 37.19, 32.61, 23.19, 19.35, 18.25.

GC/MS data: 239.2 ($M - NO_2$), 197.1 183.1, base peak.


3.05
1.85
1.00
0.97
1.00
1.00
2.90
2.14
5.89
3.09
f1 (ppm)


140.3391
139.6372
128.4359
128.3199
127.5225
124.2735
123.9148
116.6751
92.8499
47.3283
44.7252
37.1853
32.6104
23.1922
19.3504
18.2494
f1 (ppm)



1k

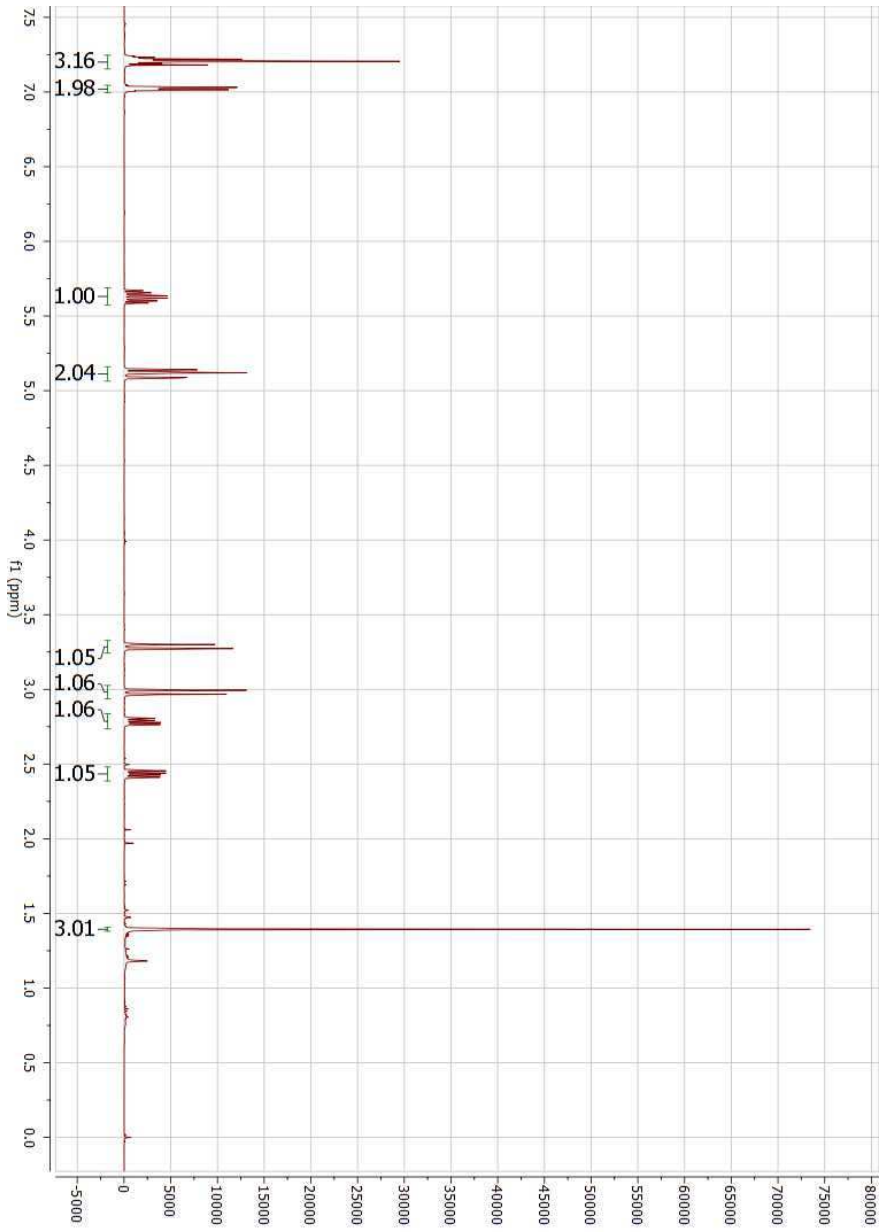
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

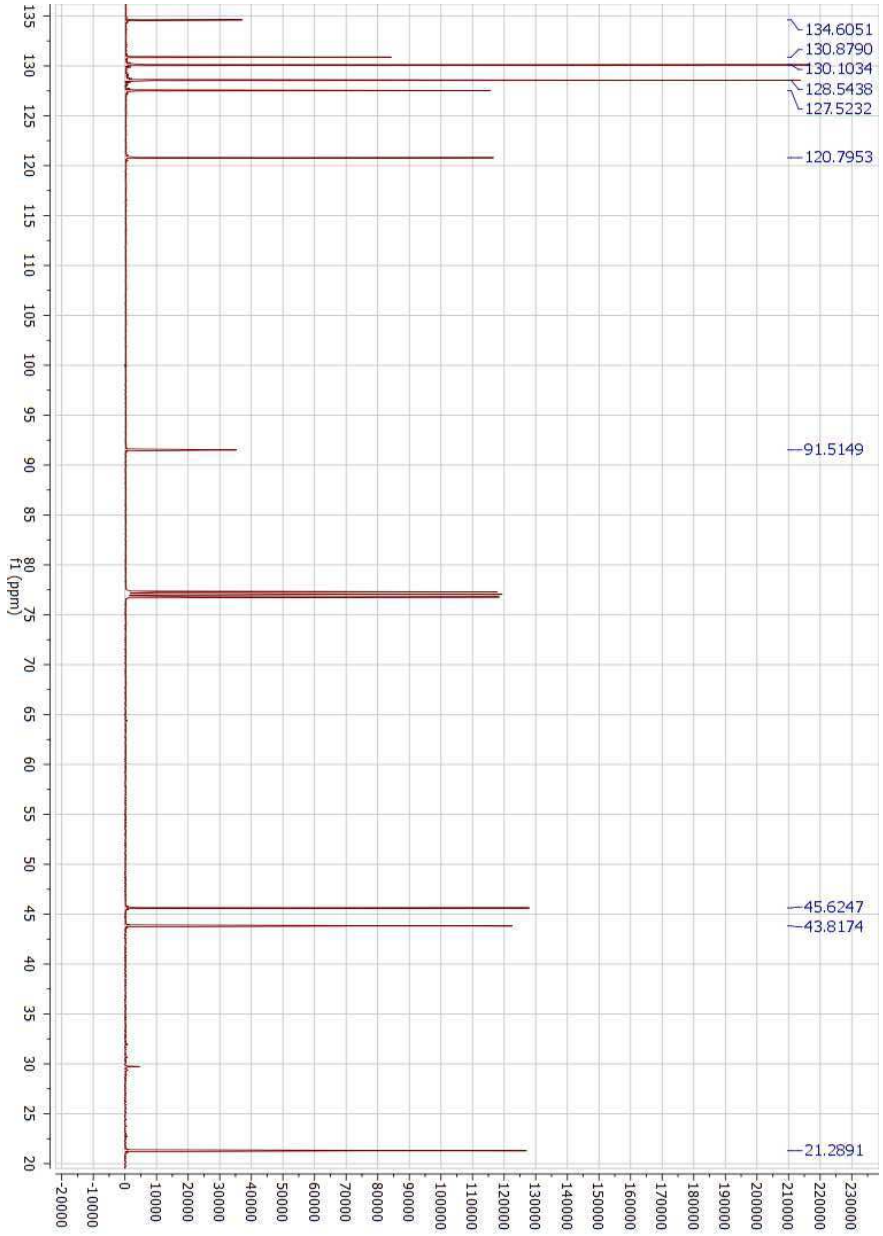
δ 7.30 (m, 3H), 7.02 (dd, *J* = 7.52, 1.90 Hz, 2H), 5.63 (dddd, *J* = 17.1, 10.2, 7.61, 6.96 Hz, 1H), 5.12 (m, 2H), 3.29 (d, *J* = 13.9 Hz, 1H), 2.98 (d, *J* = 13.9 Hz, 1H), 2.79 (dd, *J* = 14.2, 6.97 Hz, 1H), 2.43 (dt, *J* = 14.2, 7.68, 1.07 Hz, 1H), 1.39 (s, 3H).

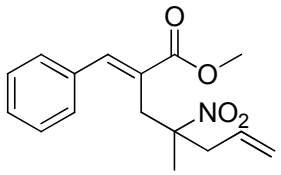
^{13}C NMR (126 MHz, $CDCl_3$):

δ 134.60, 130.88, 130.10, 128.54, 127.52, 120.80, 91.51, 45.62, 43.82, 21.29.

GC/MS data: 159.1 (M- NO_2, 4%), 91.1, base peak.


3.16
1.98
1.00
2.04
1.05
1.06
1.06
1.05
3.01
f1 (ppm)


134.6051
130.8790
130.1034
128.5438
127.5232
120.7953
91.5149
45.6247
43.8174
21.2891
f1 (ppm)



1l

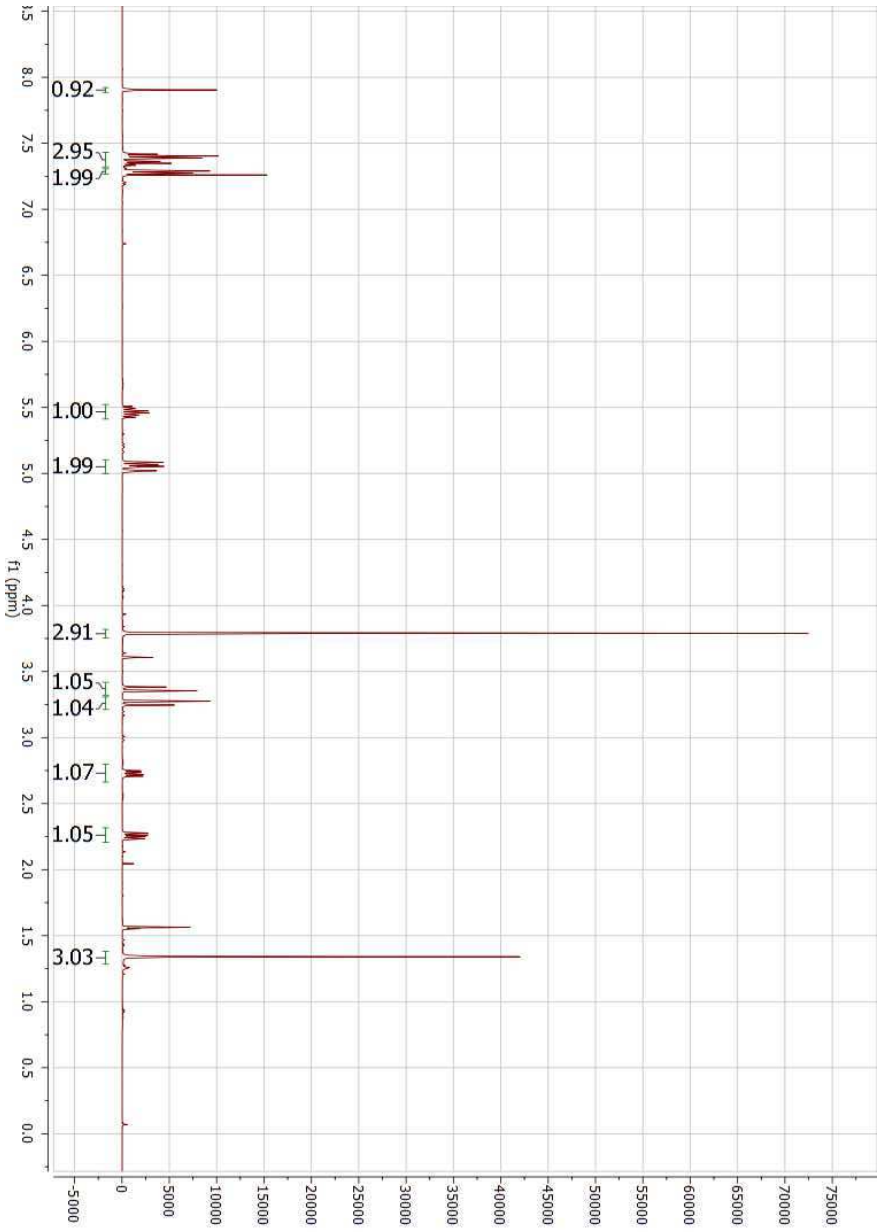
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

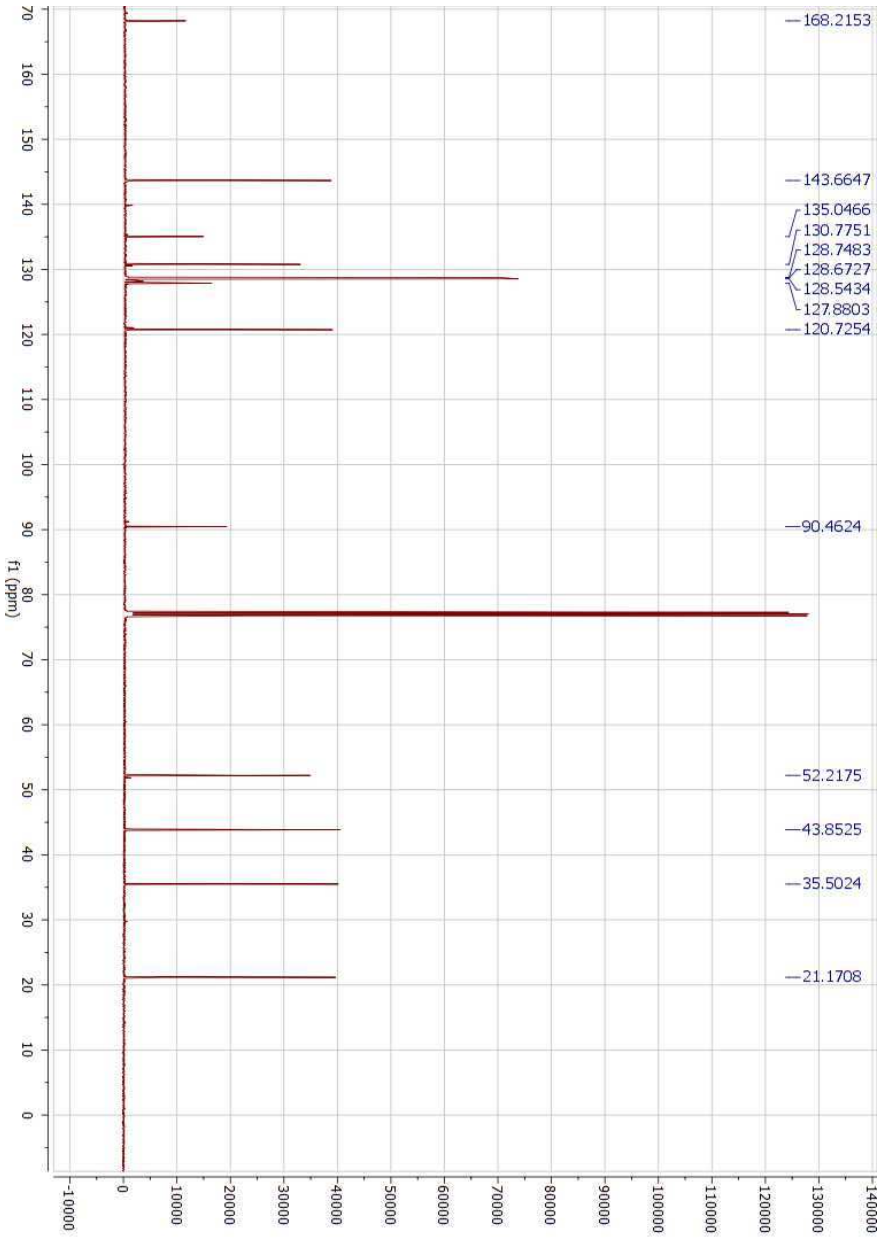
δ 7.90 (s, 1H), 7.39 (m, 3H), 7.28 (m, 2H), 5.47 (m, 1H), 5.06 (m, 2H), 3.79 (s, 3H), 3.37 (d, *J* = 16.5 Hz, 1H), 3.26 (d, *J* = 14.6 Hz, 1H), 2.73 (dd, *J* = 14.1, 6.78 Hz, 1H), 2.26 (dd, *J* = 14.2, 8.00 Hz, 1H), 1.34 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):

δ 168.22, 143.67, 135.05, 130.78, 128.75, 128.67, 128.54, 127.88, 120.73, 90.46, 52.21, 43.85, 35.50, 21.17.

GC/MS data: 289.1 (M^+, 1%), 115.1, base peak.

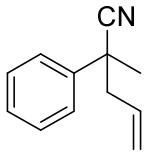

0.92
2.95
1.99
1.00
1.99
2.91
1.05
1.04
1.07
1.05
3.03
f1 (ppm)


168.2153
143.6647
135.0466
130.7751
128.7483
128.6727
128.5434
127.8803
120.7254
90.4624
52.2175
43.8525
35.5024
21.1708
f1 (ppm)

Representative procedure for the CO_2 catalyzed activation of allylic alcohol towards allylation of nitriles:

A 2.0 – 5.0 mL microwave vial (Biotage #351521) was flame dried and charged with the nitrile substrate (if solid, 0.3 mmol) and a stir bar. In the glove box, $Pd(PPh_3)_4$ (2.5 mol %, 0.0086 g) was added along with DMSO (2 mL) and the vial was capped using a vial cap (Biotage #352298) and a manual cap crimper (Biotage #353671). The vial was then removed from the glove box and substrate (if liquid, 0.3 mmol) and allyl alcohol (0.6 mmol, 0.035 g) were added sequentially via syringe. CO_2 was then bubbled through the solvent using a long 20G needle connected to a balloon and a separate 25.5G needle to vent. After 5 minutes, the vent needle is removed followed by the CO_2 needle and the top of the vial was wrapped in parafilm. The vial was then placed in an oil bath at room temperature and heated/stirred at 90 ^oC for 14 hours.

After 14 hours the vial was removed from the bath, and allowed to cool to room temperature. An aliquot was then diluted in DCM and subjected to GC/MS analysis to determine conversion. The remaining solution was subjected to purification via silica gel column chromatography using 1:50 EtOAc:Pentanes as an eluent.



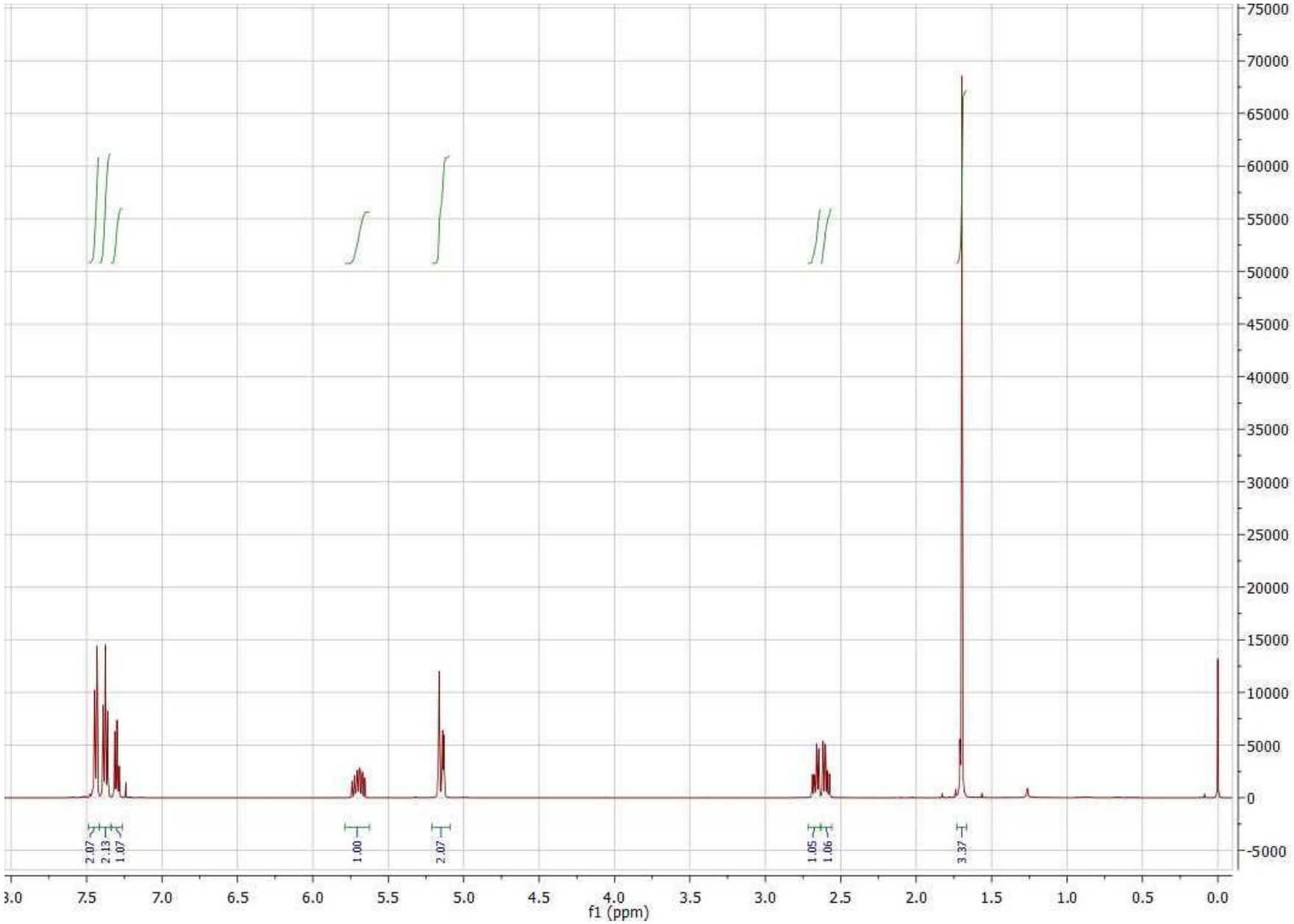
2a

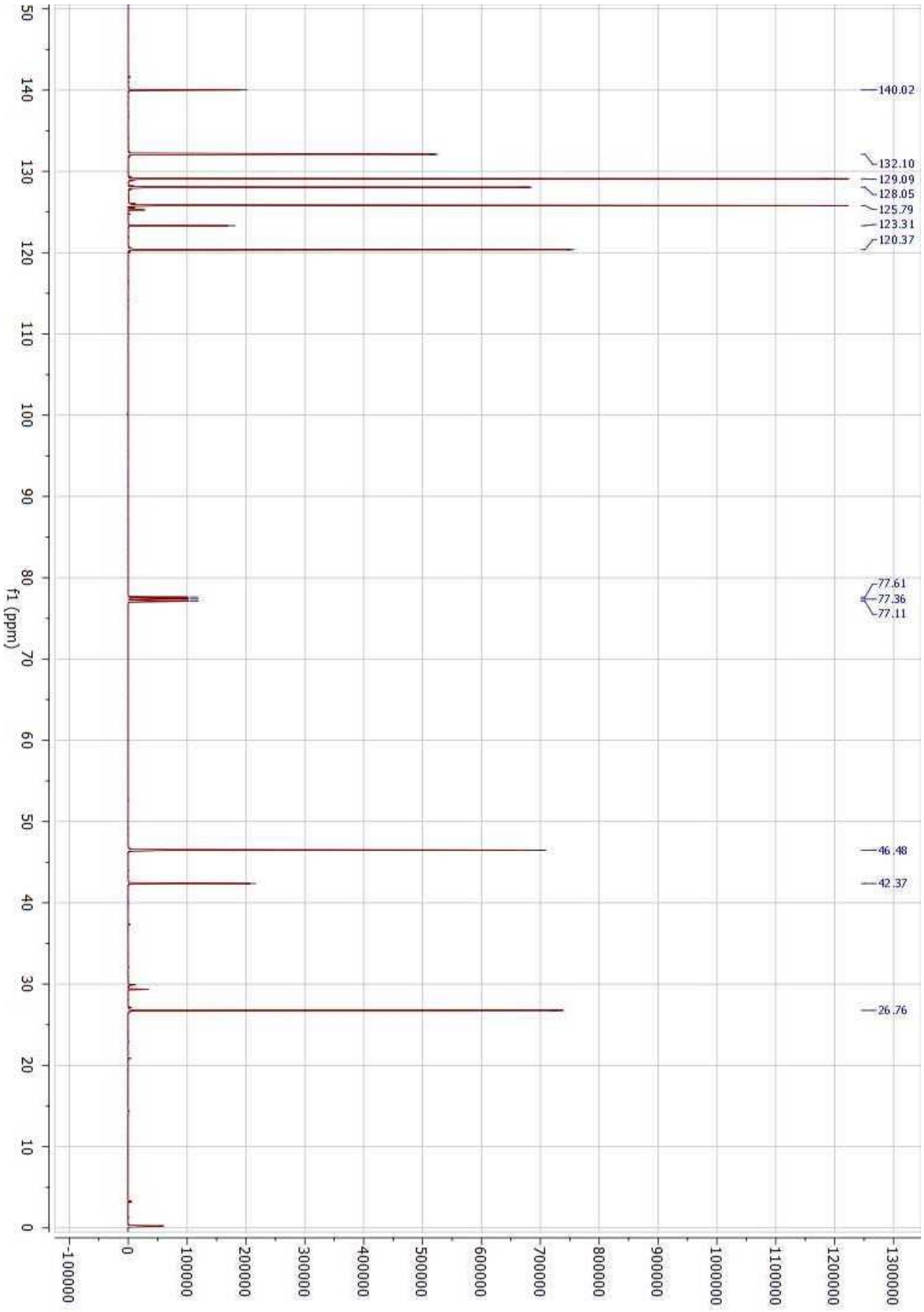
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

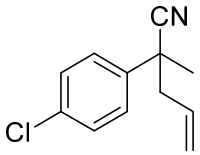
δ 7.44 (m, 2H), 7.38 (m, 2H), 7.30 (m, 1H), 5.70 (m, 1H), 5.15 (m, 2H), 2.67 (ddt, *J* = 13.9, 6.7, 1.3 Hz, 1H), 2.60 (ddt, *J* = 13.9, 7.8, 1.0 Hz, 1H), 1.7 (s, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 140.02, 132.10, 129.09, 128.05, 125.79, 123.31, 120.37, 46.48, 42.37, 26.76.


2.07
2.13
1.07
1.00
2.07
1.05
1.06
3.37
f1 (ppm)


140.02
132.10
129.09
128.05
125.79
123.31
120.37
77.61
77.36
77.11
46.48
42.37
26.76
f1 (ppm)



2b

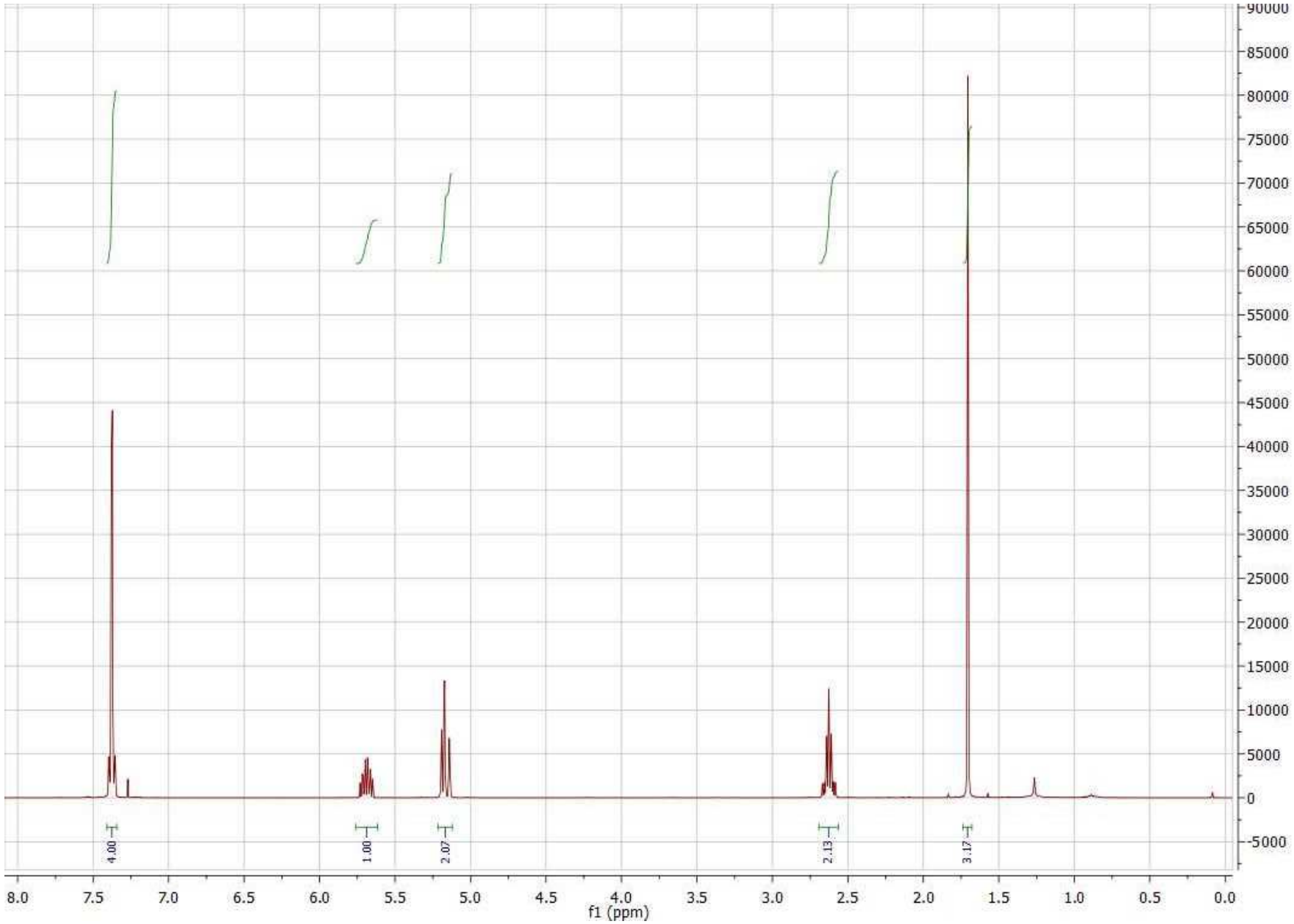
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

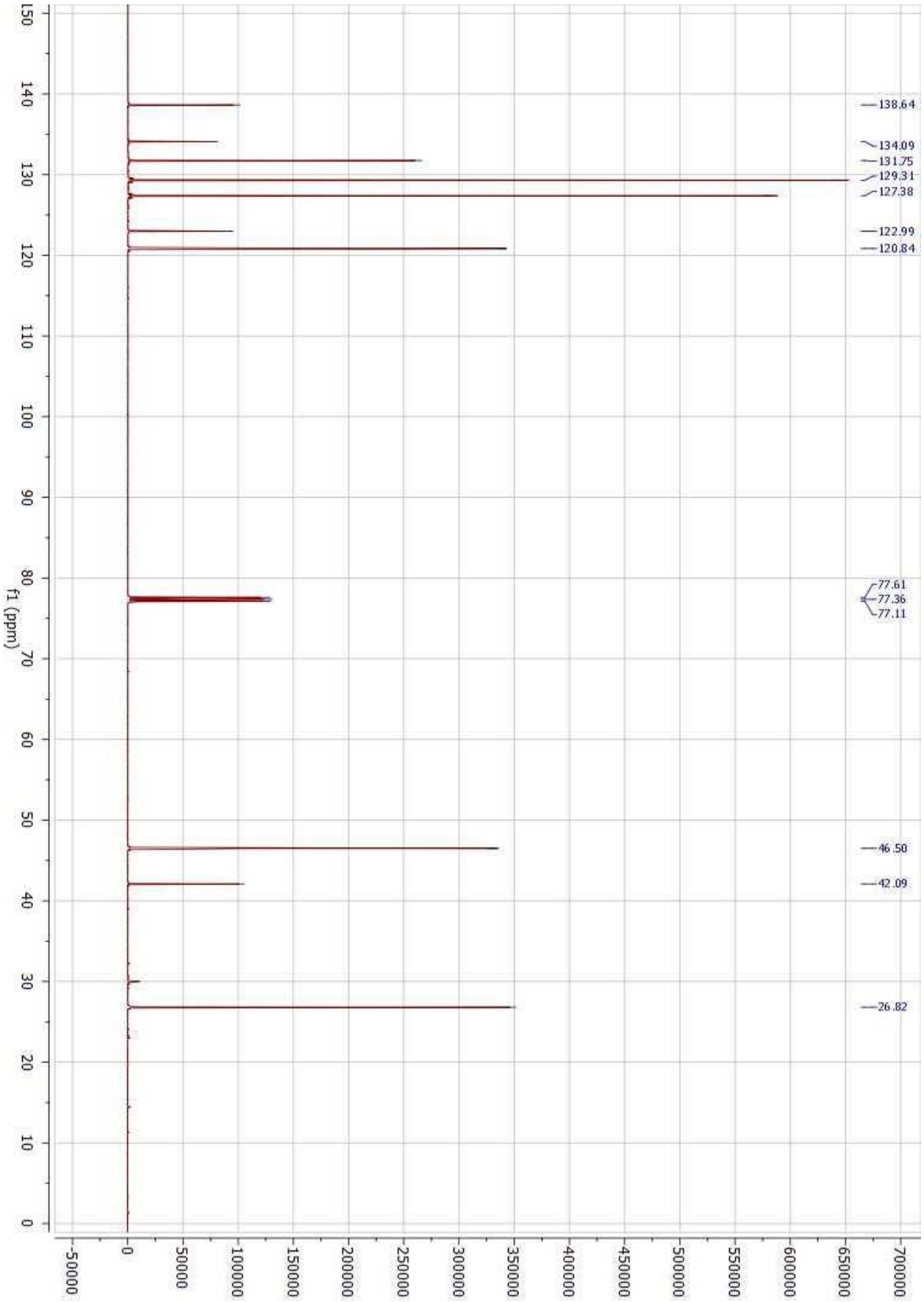
δ 7.38 (m, 4H), 5.69 (dddd, *J* = 17.0, 10.2, 7.6, 6.9 Hz, 1H), 5.17 (m, 2H), 2.62 (m, 2H), 1.71 (s, 3H).

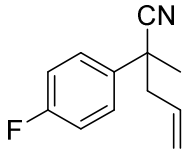
^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 138.64, 134.09, 131.75, 129.31, 127.38, 122.99, 120.84, 46.50, 42.09, 26.82.

GC/MS data: 205.1 (M^+), 164.1 (base peak).


4.00
1.00
2.07
2.13
3.17
f1 (ppm)


138.64
134.09
131.75
129.31
127.38
122.99
120.84
77.61
77.36
77.11
46.50
42.09
26.82
f1 (ppm)



2c

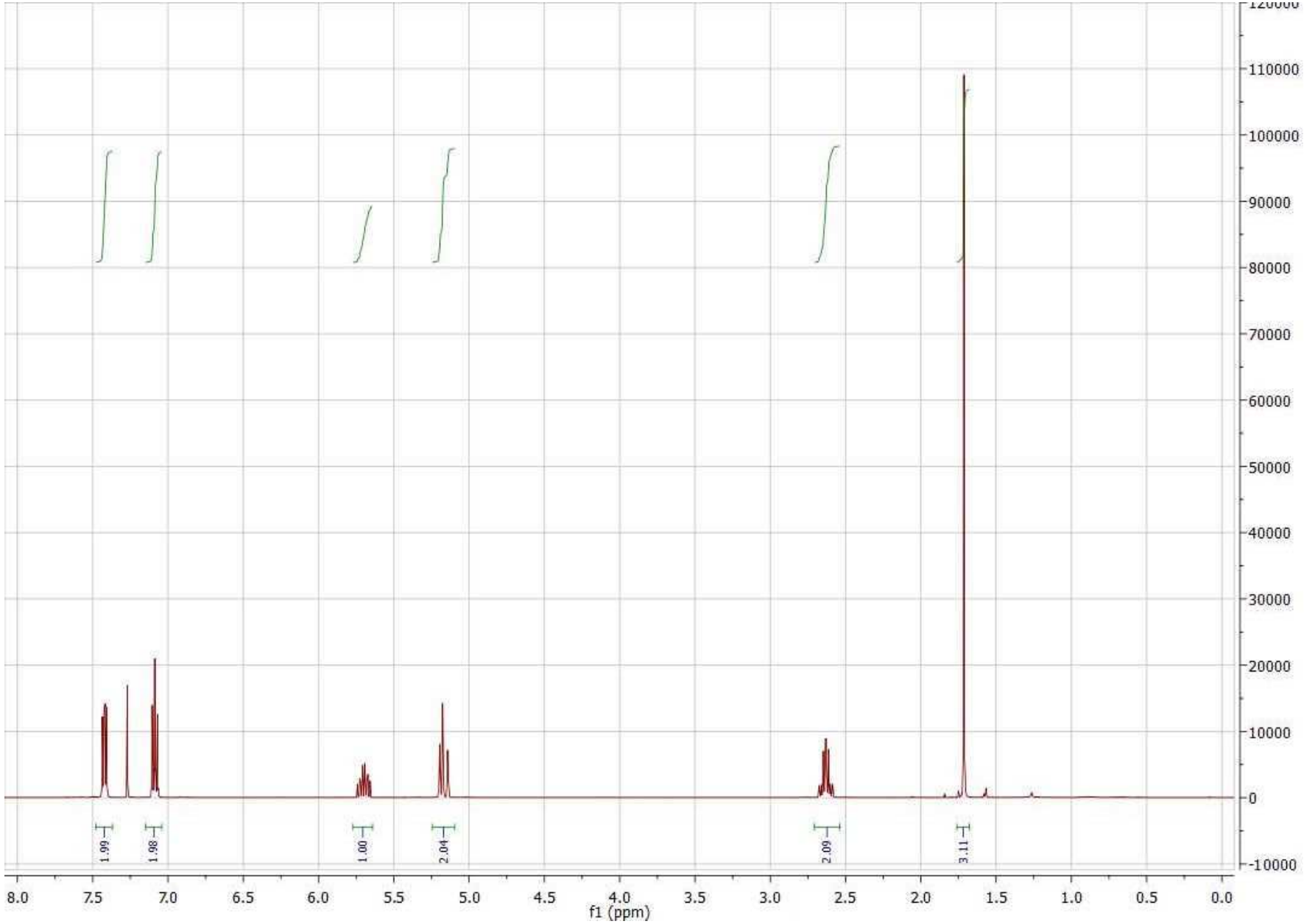
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

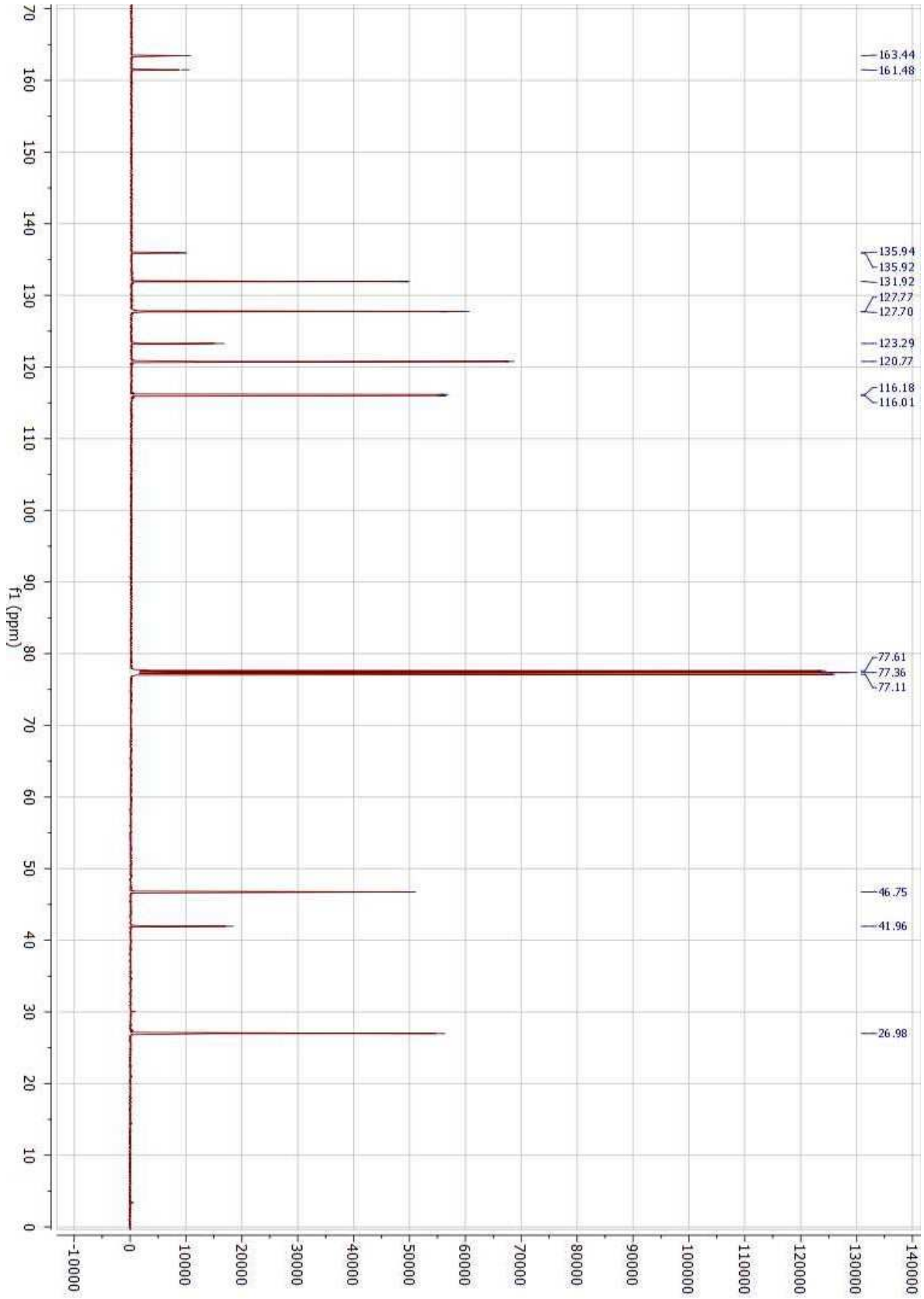
δ 7.42 (m, 2H), 7.09 (m, 2H), 5.70 (dddd, *J* = 17.0, 10.2, 7.6, 6.9 Hz, 1H), 5.18 (m, 2H), 2.63 (m, 2H), 1.71 (s, 3H).

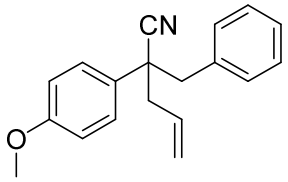
^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 163.44, 161.48, 135.94, 135.92, 131.92, 127.77, 127.70, 123.29, 120.77, 116.18, 116.01, 46.75, 41.96, 26.98.

GC/MS data: 189.1 (M^+), 148.1 (base peak).


1.99
1.98
1.00
2.04
2.09
3.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000


163.44
161.48
135.94
135.92
131.92
127.77
127.70
123.29
120.77
116.18
116.01
77.61
77.36
77.11
46.75
41.96
26.98
f1 (ppm)



2d

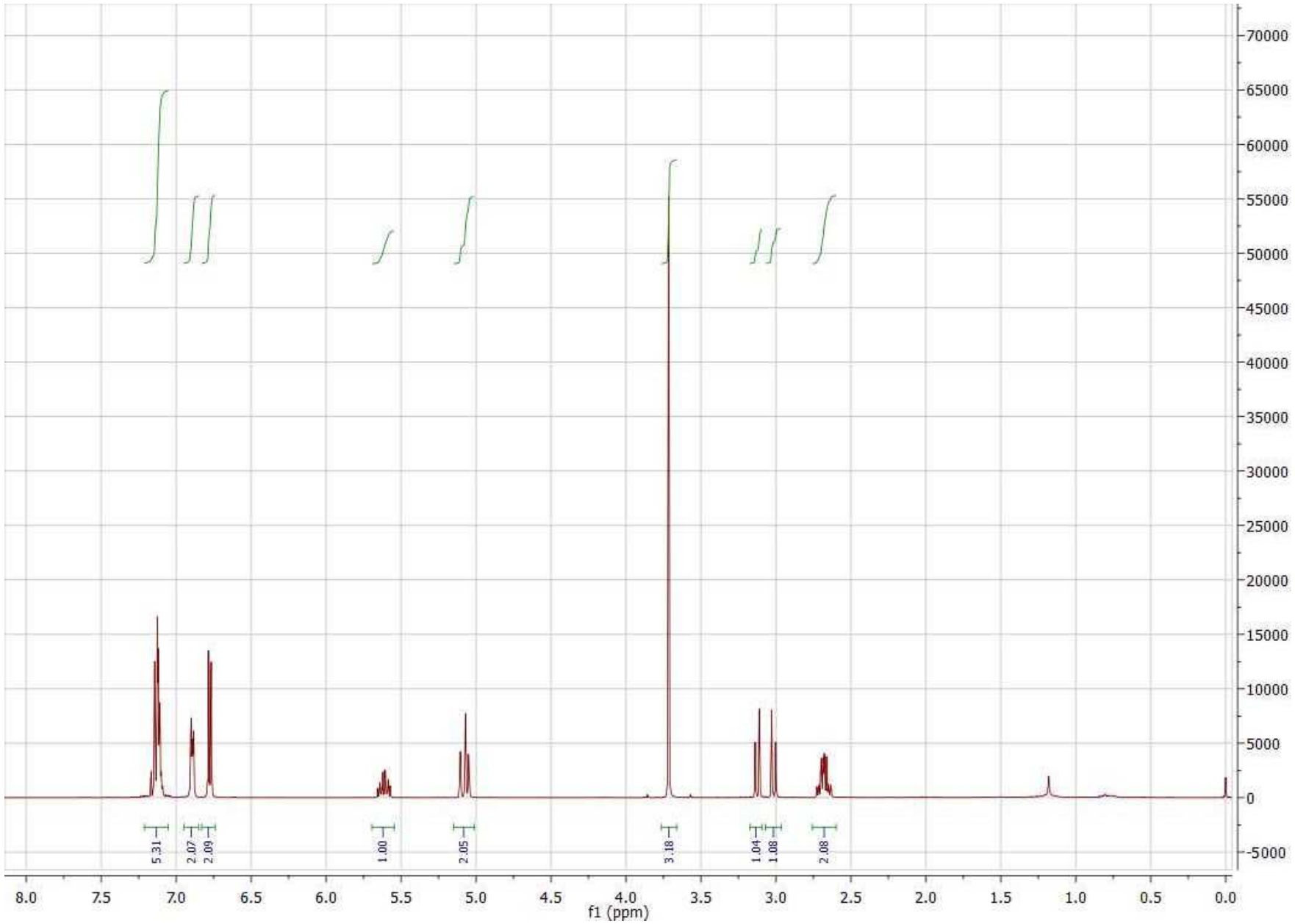
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

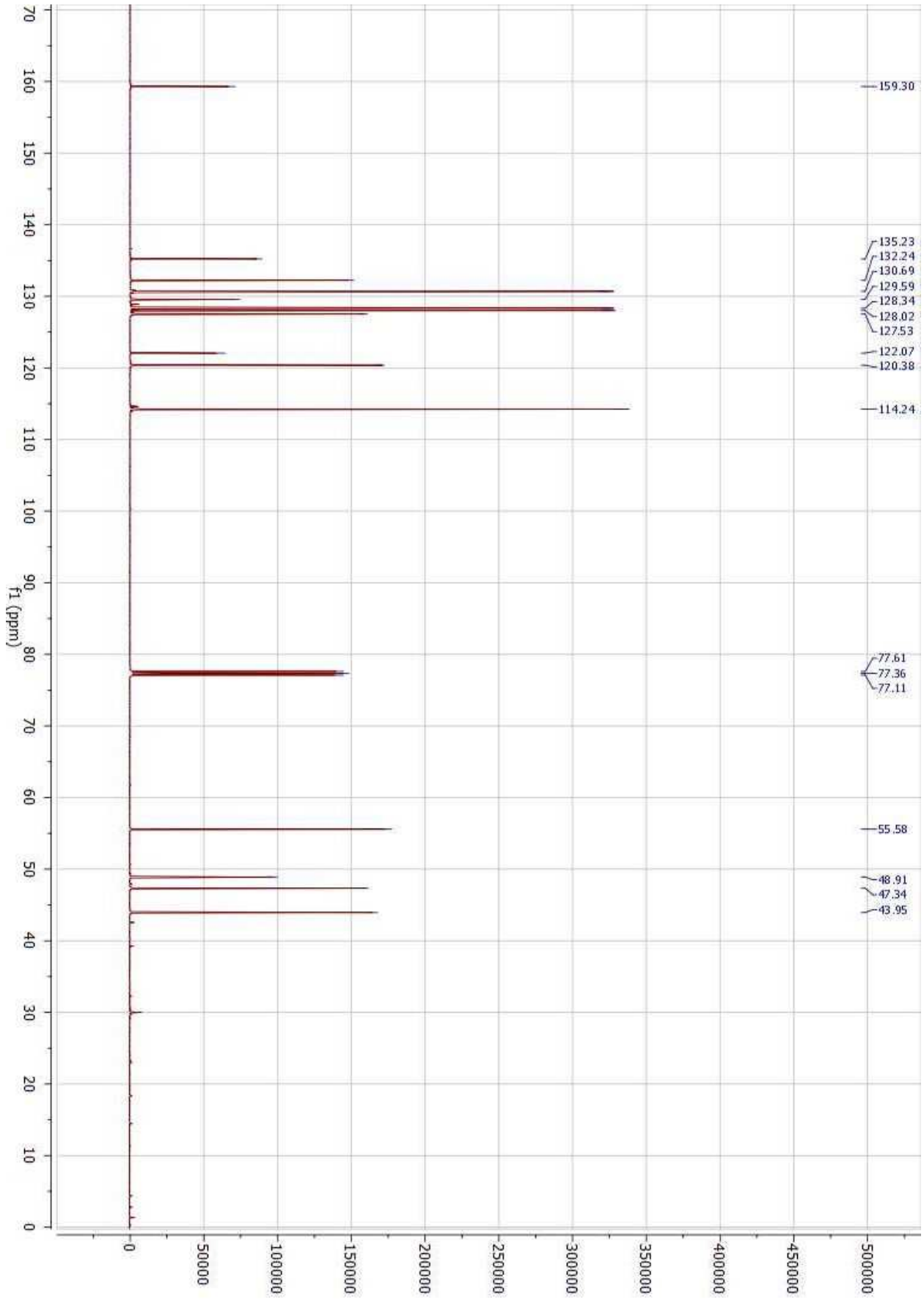
δ 7.13 (m, 5H), 6.89 (m, 2H), 6.78 (m, 2H), 5.61 (dddd, *J* = 16.9, 10.2, 7.6, 6.5 Hz, 1H), 5.07 (m, 2H), 3.72 (s, 3H), 3.12 (d, *J* = 13.5 Hz, 1H), 3.02 (d, *J* = 13.5 Hz, 1H), 2.68 (m, 2H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 159.30, 135.23, 132.24, 130.69, 129.59, 128.34, 128.02, 127.53, 122.07, 120.38, 114.24, 55.58, 48.91, 47.34, 43.95.

GC/MS data: 277.2 (M^+), 186.10 (base peak).


70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
5.31
2.07
2.09
1.00
2.05
3.18
1.04
1.08
2.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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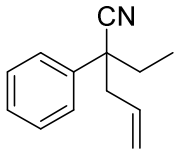
55.58
48.91
47.34
43.95
f1 (ppm)



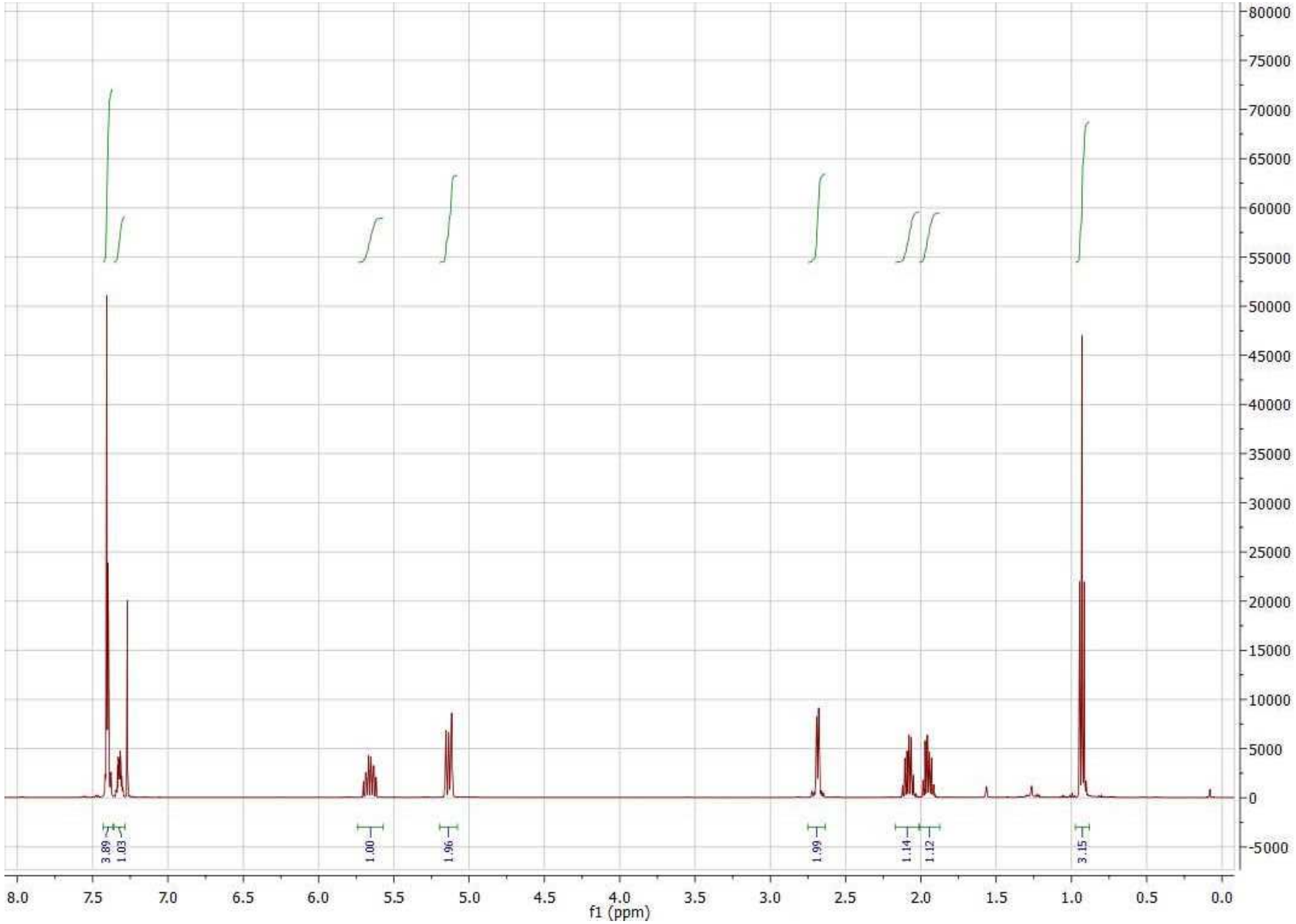
2e

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

δ 7.40 (m, 4H), 7.32 (m, 1H), 5.66 (m, 1H), 5.13 (m, 2H), 2.69 (ddt, *J* = 7.0, 2.0, 1.1 Hz, 2H), 2.08 (m, 1H), 1.96 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 138.14, 132.25, 129.15, 128.06, 126.52, 122.31, 120.19, 49.14, 45.34, 33.44, 9.92.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35000
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20000
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5000
0
-5000
3.89
1.03
1.00
1.96
1.99
1.14
1.12
3.15
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
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1.0
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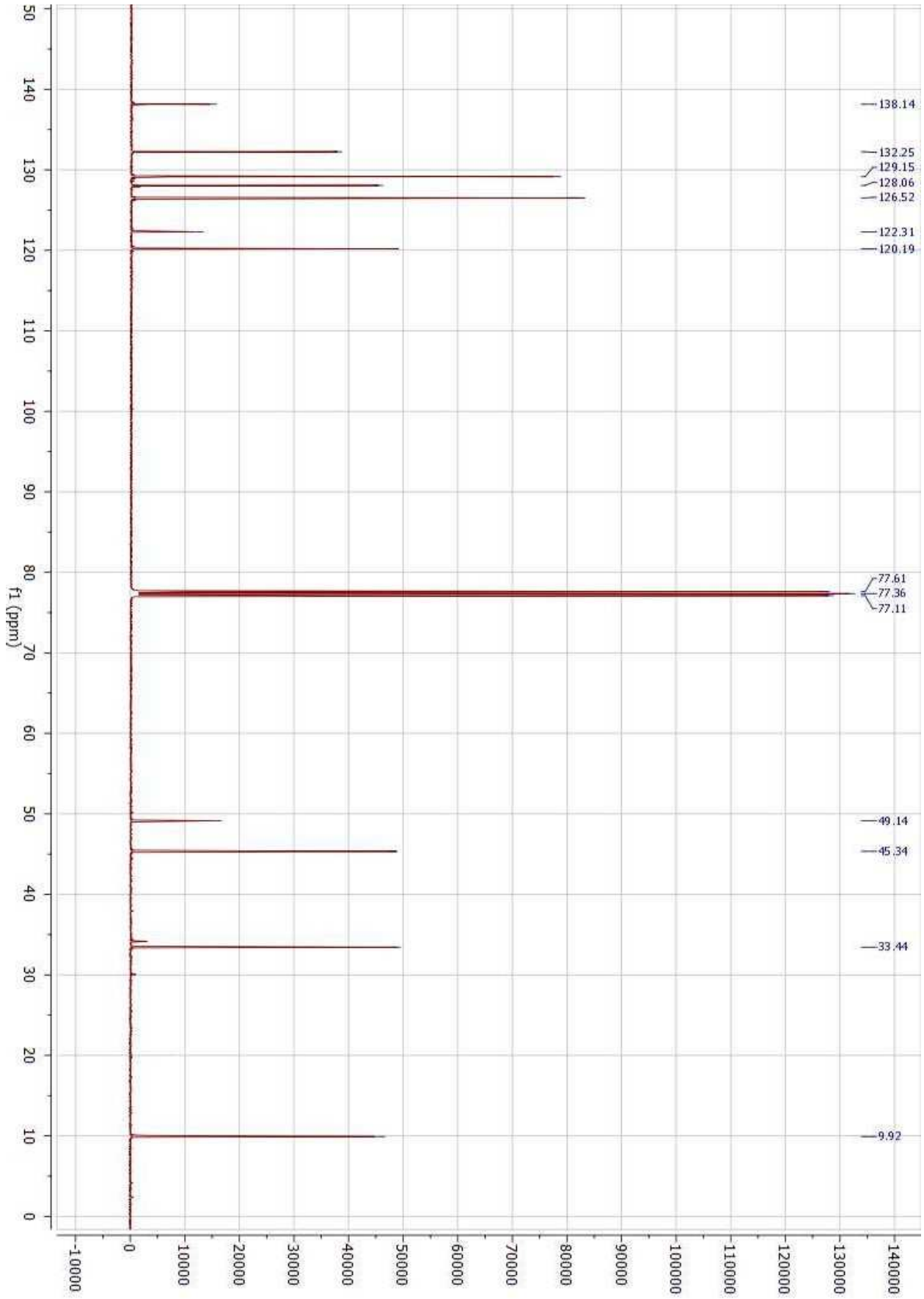
0.0
f1 (ppm)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132.25
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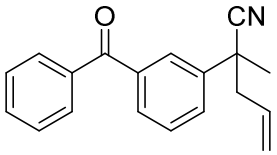
77.61
77.36
77.11
49.14
45.34
33.44
9.92
f1 (ppm)



2f

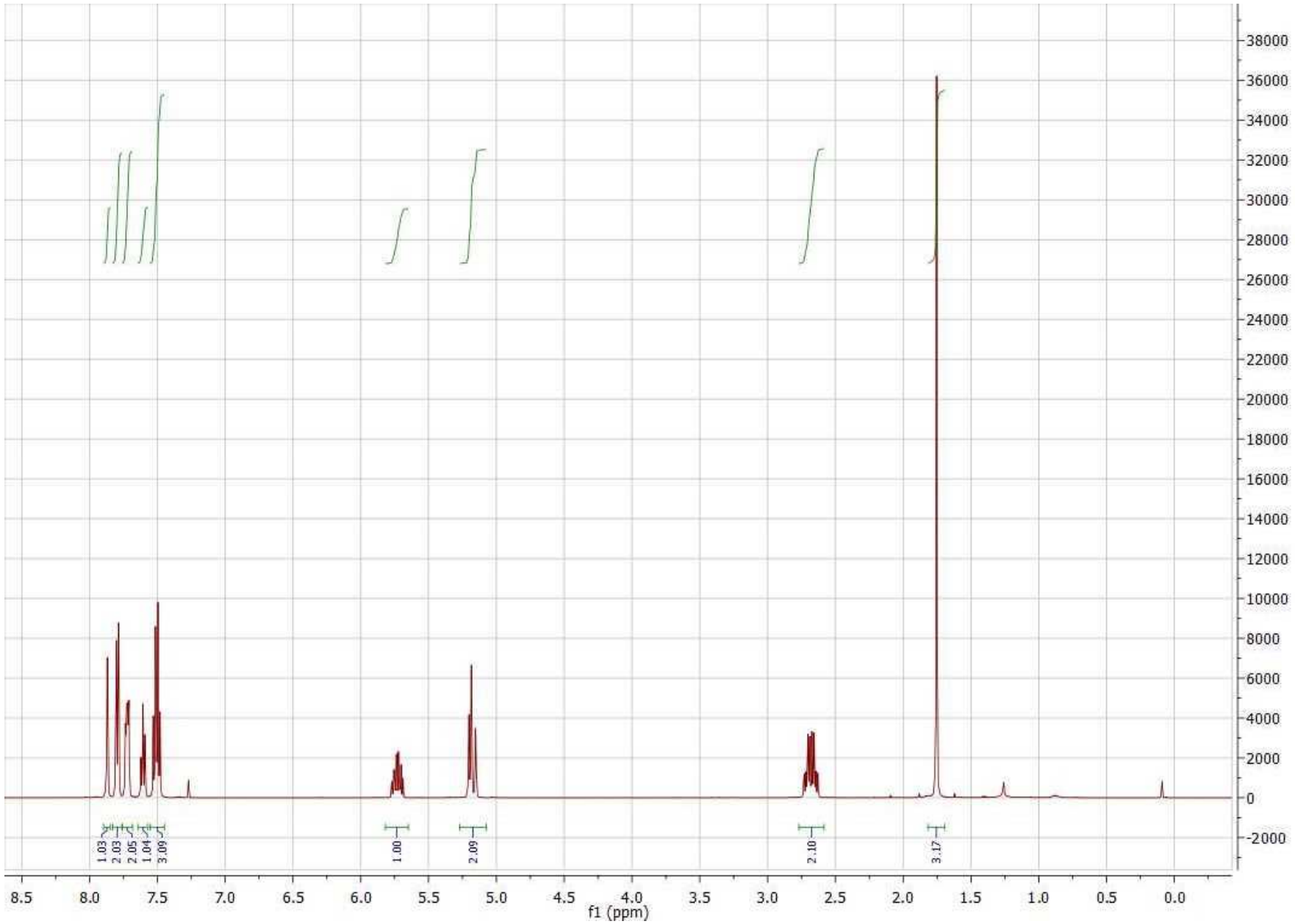
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.87 (t, *J* = 1.9 Hz, 1H), 7.80 (m, 2H), 7.72 (m, 2H), 7.60 (m, 1H), 7.51 (m, 3H), 5.73 (ddt, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.18 (m, 2H), 2.68 (m, 2H), 1.75 (s, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 196.29, 140.61, 138.46, 137.37, 133.03, 131.72, 130.28, 130.13, 129.91, 129.08, 128.66, 127.00, 122.91, 120.86, 46.35, 42.34, 26.68.

GC/MS data: 275.1 (M^+), 234.10 (base peak).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20000
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6000
4000
2000
0
-2000
1.03
2.03
2.05
1.04
3.09
1.00
2.09
2.10
3.17
8.5
8.0
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7.0
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6.0
5.5
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4.5
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1.5
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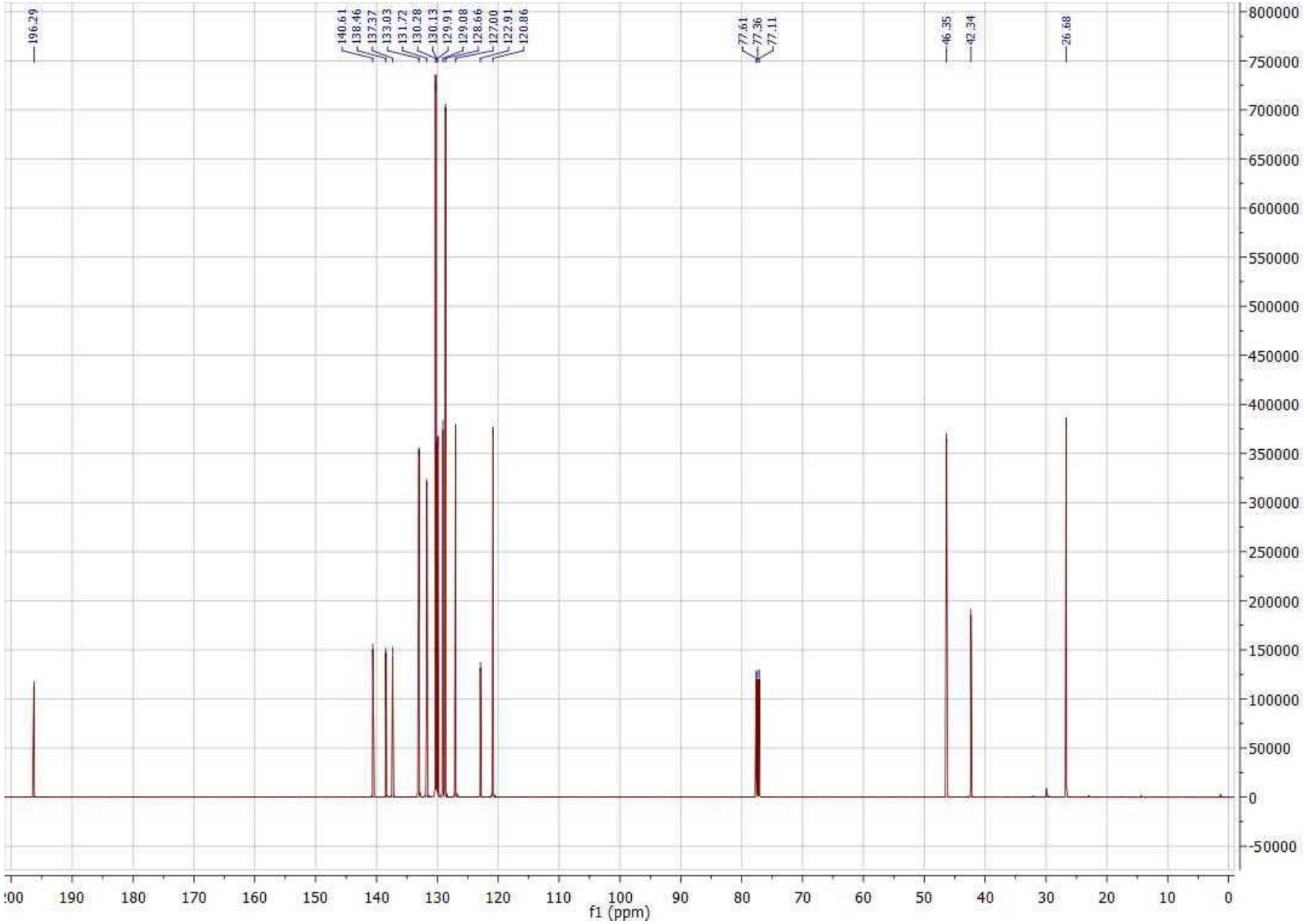
0.0
f1 (ppm)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137.37
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130.13
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129.08
128.66
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77.11
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42.34
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750000
700000
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
200
190
180
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90
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50
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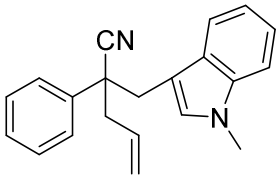
f1 (ppm)



2h

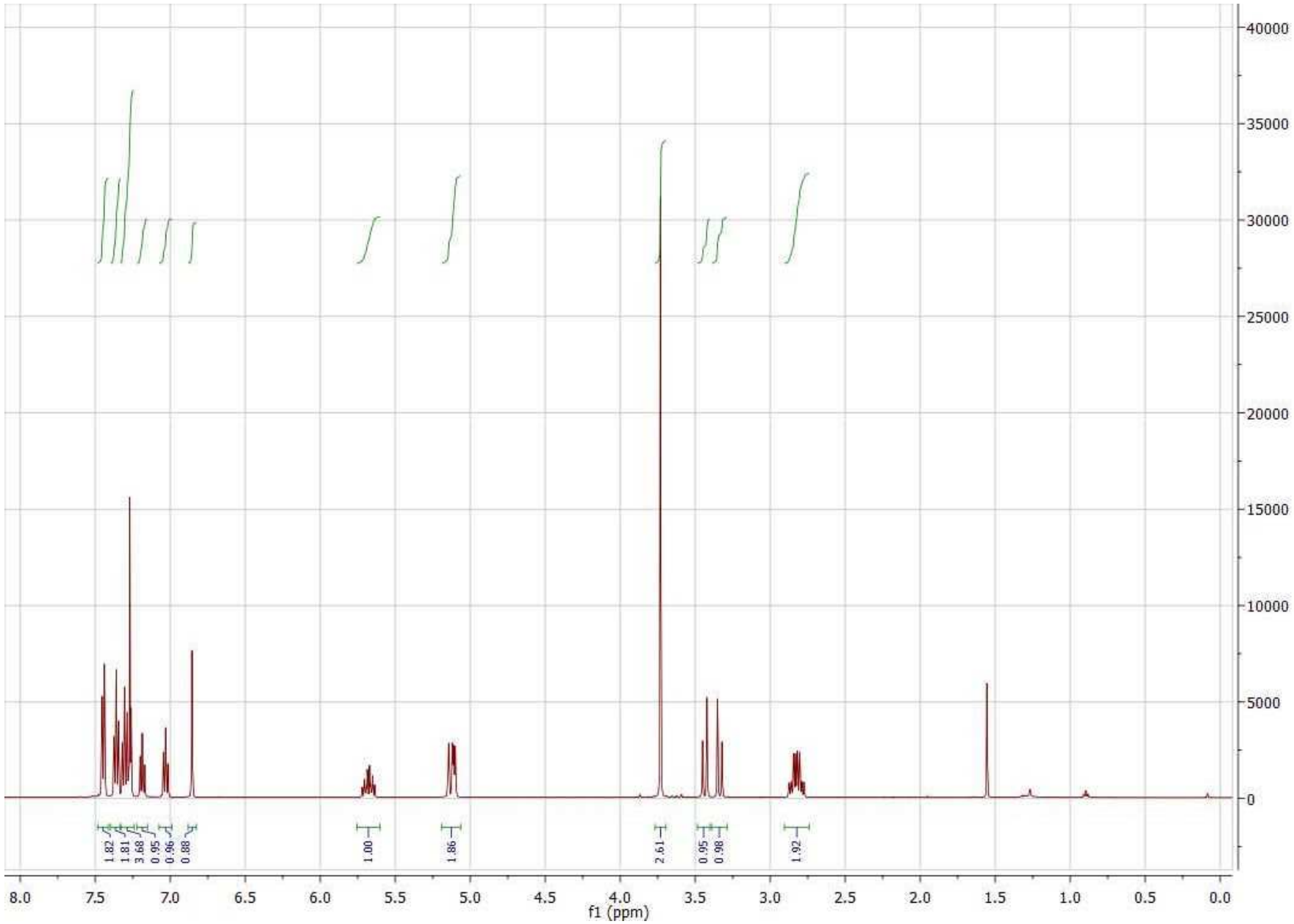
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.45 (m, 2H), 7.36 (m, 2H), 7.29 (m, 3H), 7.19 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.03 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.85 (s, 1H), 5.68 (dddd, *J* = 17.1, 10.3, 7.6, 6.6 Hz, 1H), 5.12 (m, 2H), 3.73 (s, 3H), 3.44 (d, *J* = 14.7 Hz, 1H), 3.34 (d, *J* = 14.6 Hz, 1H), 2.82 (m, 2H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 138.66, 136.72, 132.47, 129.10, 129.05, 128.84, 128.12, 126.89, 122.82, 121.80, 120.23, 119.39, 119.00, 109.48, 108.26, 50.20, 43.47, 37.39, 33.12.

GC/MS data: 300.2 (M^+), 144.15 (base peak).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0.88
1.00
1.86
2.61
0.95
0.98
1.92
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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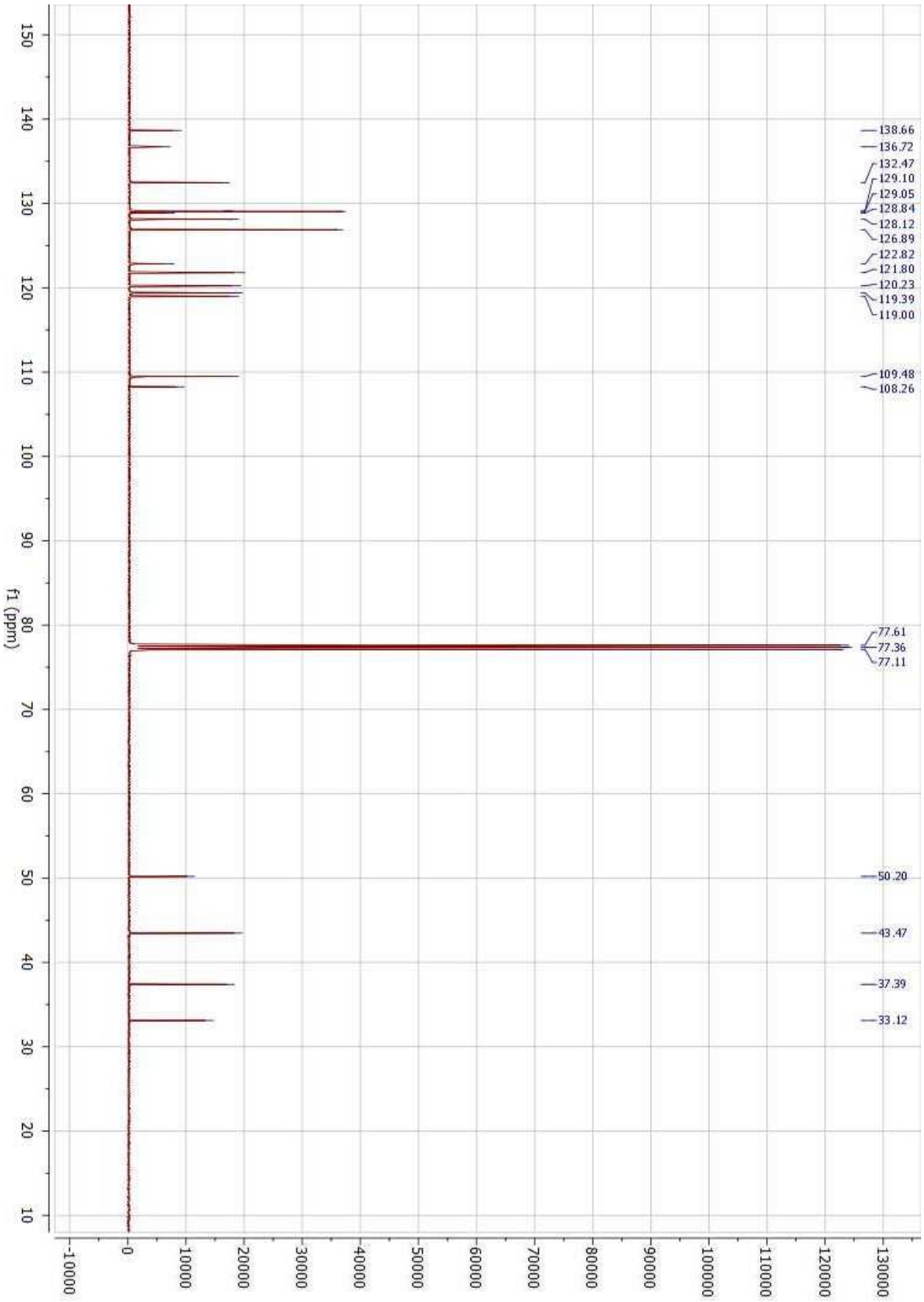
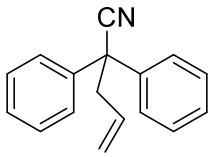
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


138.66
136.72
132.47
129.10
129.05
128.84
128.12
126.89
122.82
121.80
120.23
119.39
119.00
109.48
108.26
77.61
77.36
77.11
50.20
43.47
37.39
33.12
f1 (ppm)



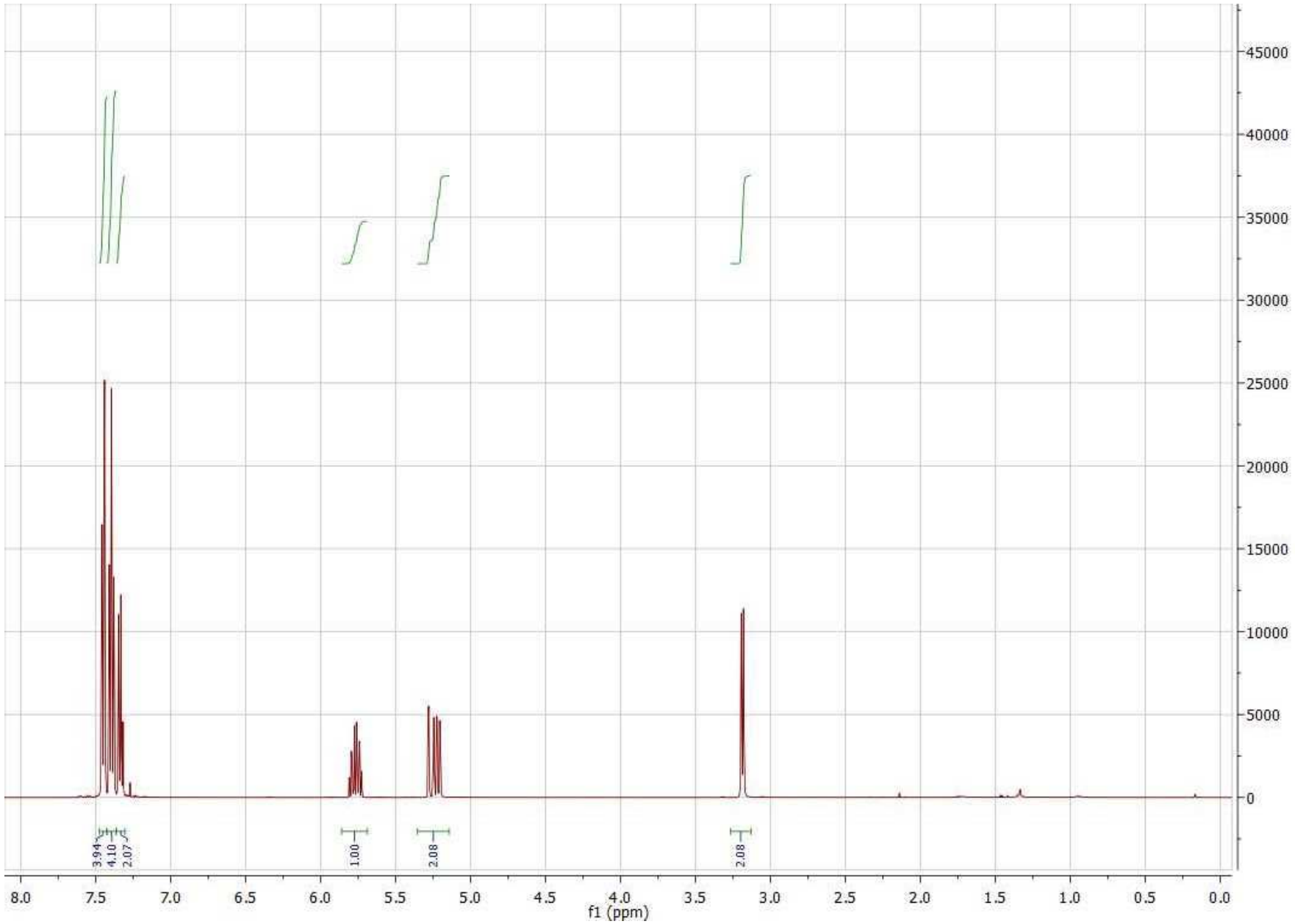
2i

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

δ 7.45 (m, 4H), 7.39 (ddd, *J* = 7.8, 6.8, 1.3 Hz, 4H), 7.34 (m, 2H), 5.77 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.23 (m, 2H), 3.19 (dt, *J* = 7.1, 1.2 Hz, 2H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 139.94, 132.00, 129.08, 128.17, 127.25, 122.19, 120.64, 51.94, 44.13.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2.07
1.00
2.08
2.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.0
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2.0
1.5
1.0
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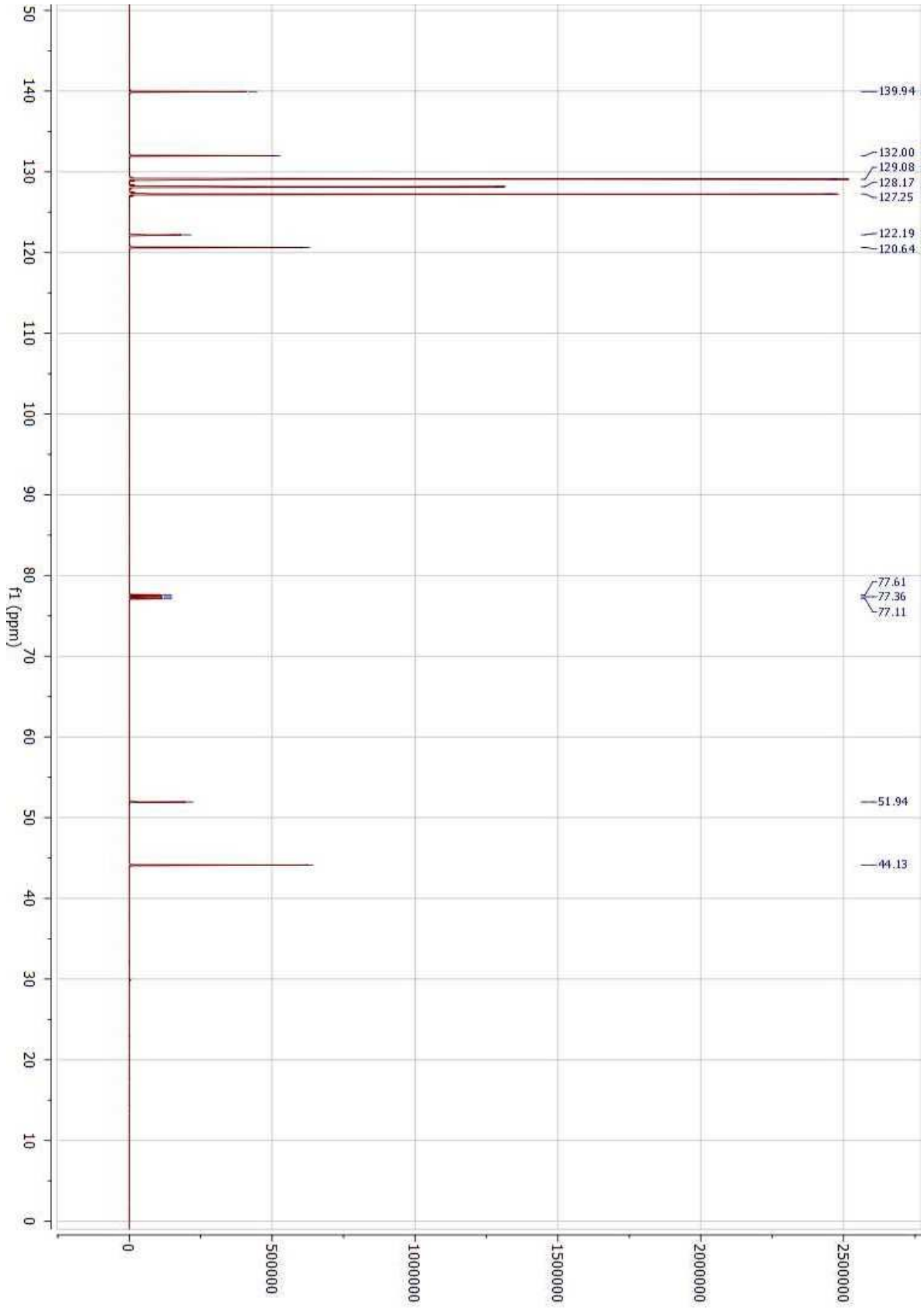
0.0
f1 (ppm)


f1 (ppm)
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130
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90
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50
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10
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1000000
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2000000
2500000
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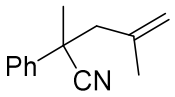
129.08
128.17
127.25
122.19
120.64
77.61
77.36
77.11
51.94
44.13



3a

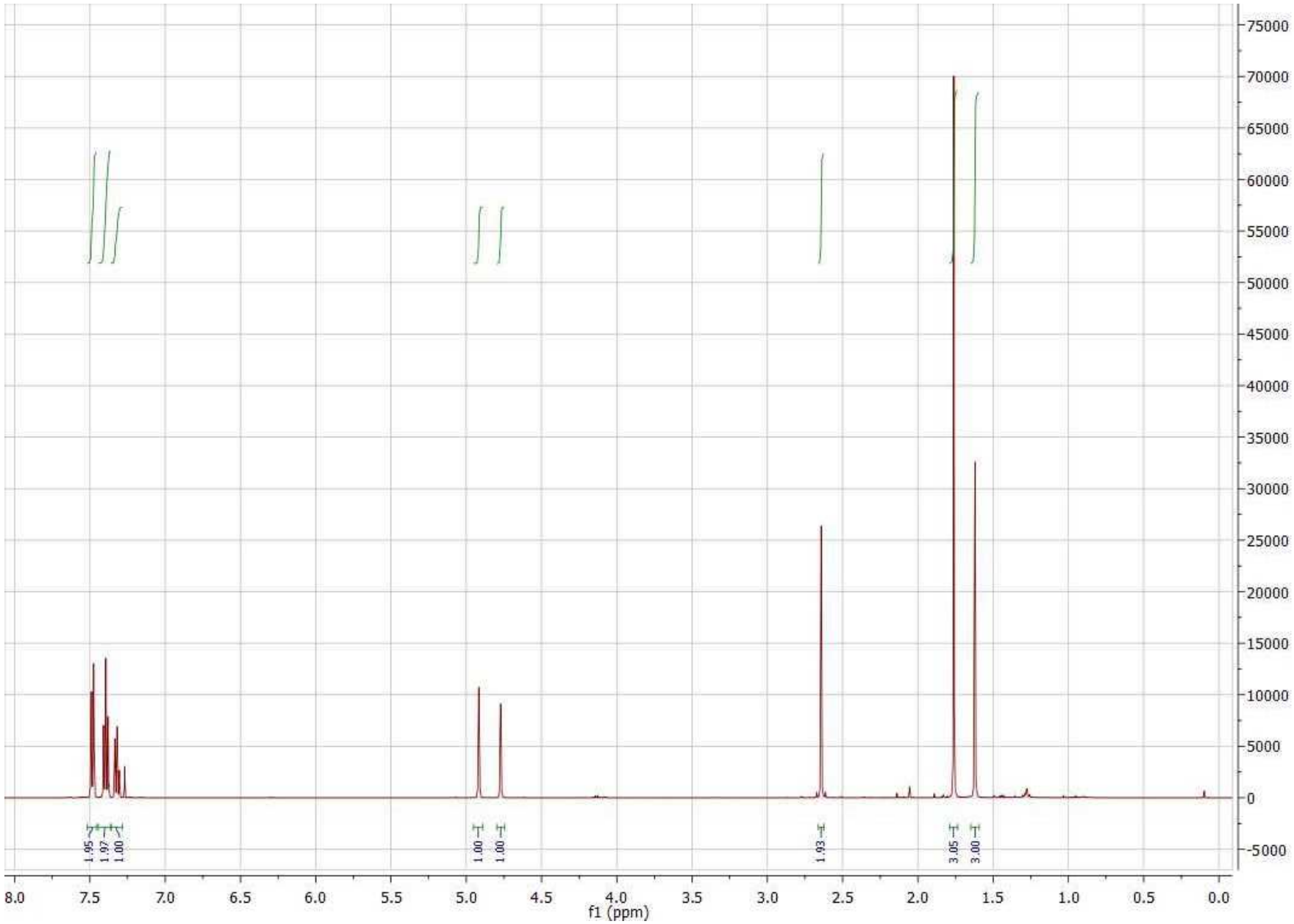
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.48 (m, 2H), 7.39 (m, 2H), 7.33 (m, 1H), 4.92 (p, *J* = 1.6 Hz, 1H), 4.77 (dq, *J* = 1.8, 1.0 Hz, 1H), 2.64 (t, *J* = 1.0 Hz, 2H), 1.76 (s, 3H), 1.62 (m, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 140.37, 140.27, 129.07, 128.05, 125.89, 123.88, 116.94, 50.08, 42.03, 27.83, 23.84.

GC/MS data: 185.1 (M^+), 130.1 (base peak).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-5000
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1.97
1.00
1.00
1.00
1.93
3.05
3.00
8.0
7.5
7.0
6.5
6.0
5.5
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2.0
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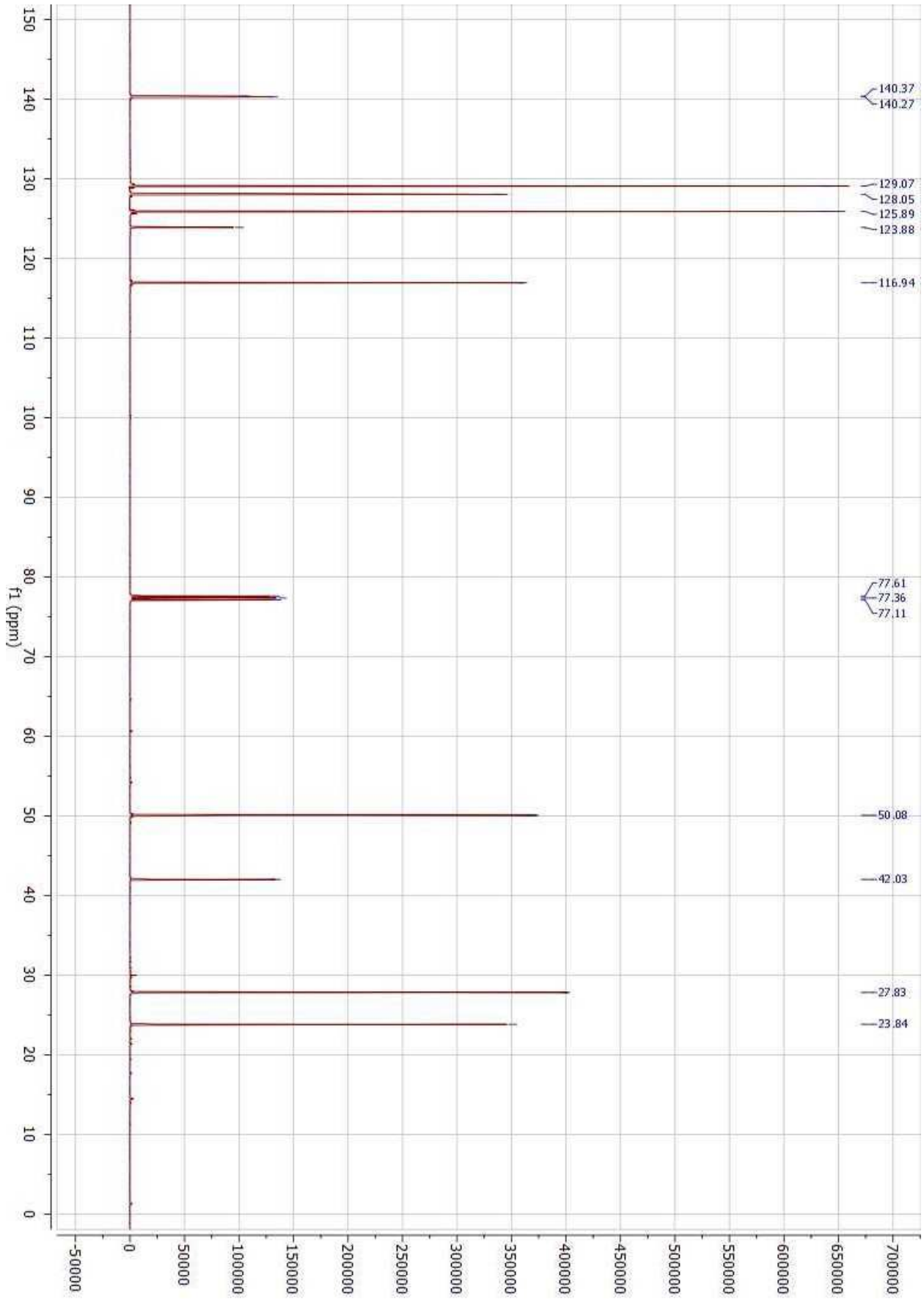
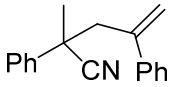
0.0
f1 (ppm)


140.37
140.27
129.07
128.05
125.89
123.88
116.94
77.61
77.36
77.11
50.08
42.03
27.83
23.84
f1 (ppm)



3b

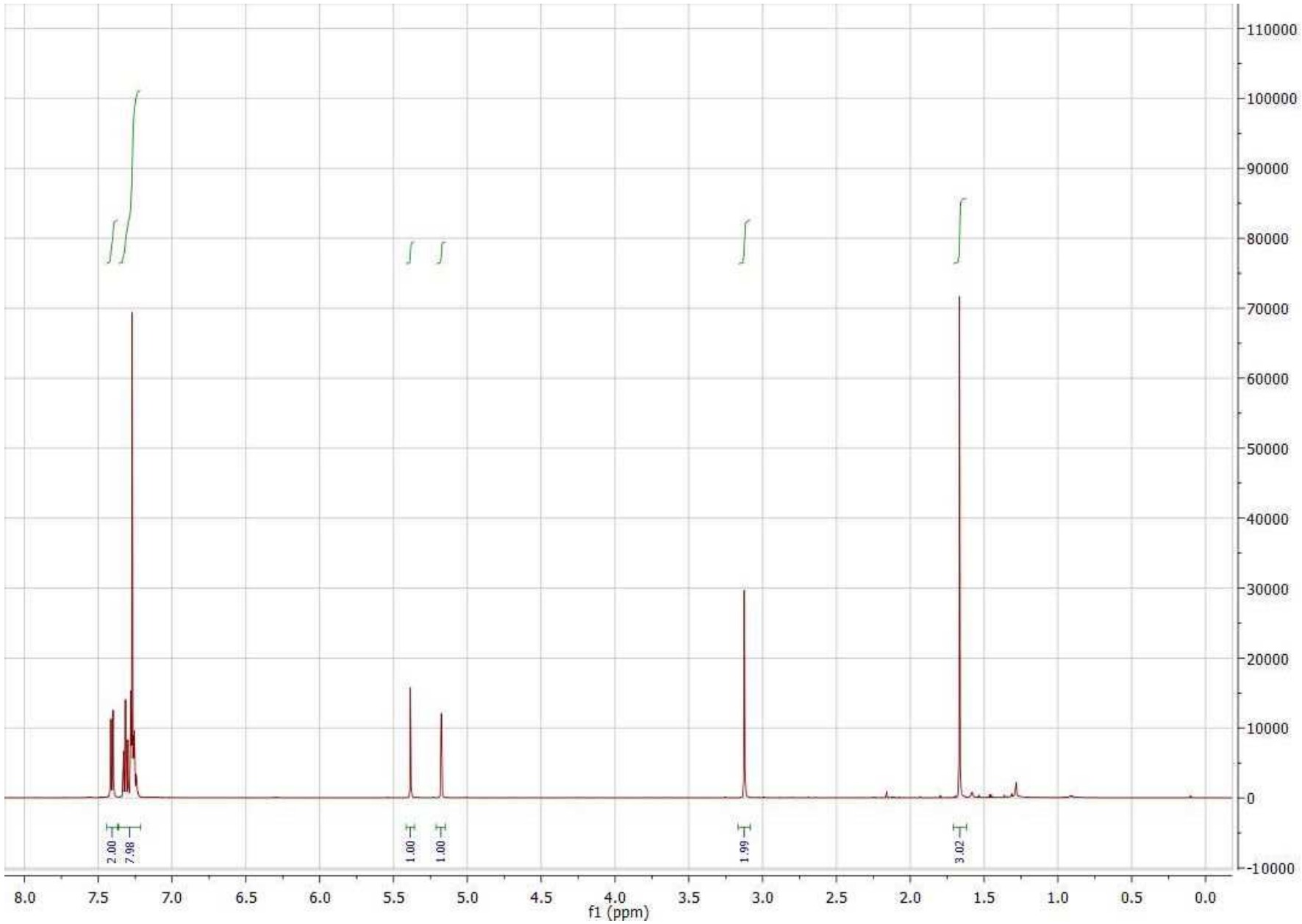
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.41 (m, 2H), 7.28 (m, 3H), 5.39 (d, *J* = 1.1 Hz, 1H), 5.18 (q, *J* = 1.0 Hz, 1H), 3.12 (d, *J* = 1.0 Hz, 2H), 1.67 (s, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 143.85, 141.74, 140.21, 128.98, 128.58, 128.04, 127.87, 126.81, 126.01, 123.33, 119.21, 47.46, 43.13, 27.28.

GC/MS data: 247.1 (M^+), 139.1 (base peak).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1.00
1.99
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6.0
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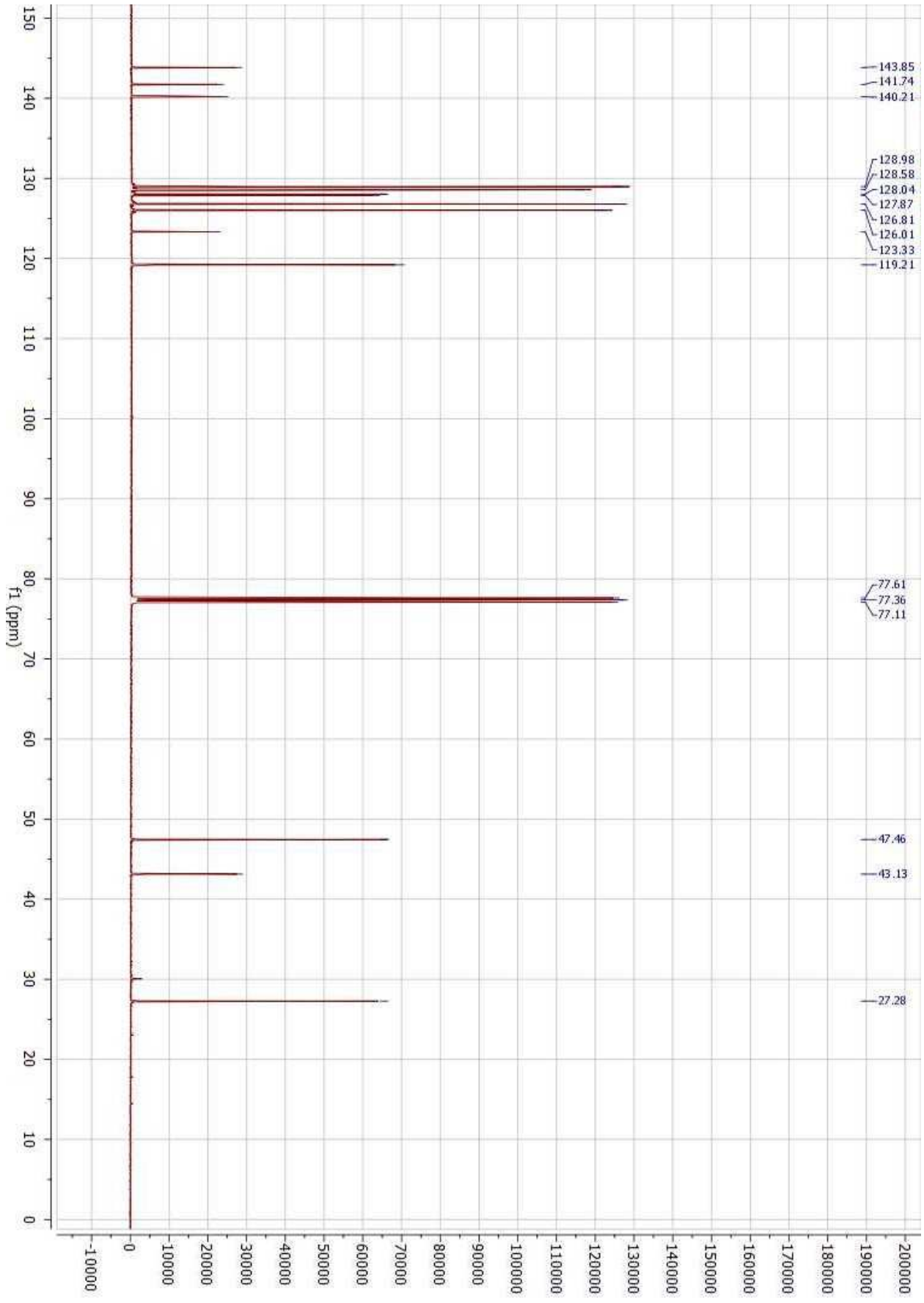
0.0
f1 (ppm)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128.04
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123.33
119.21
77.61
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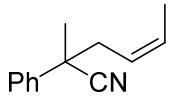
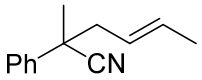
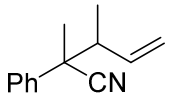
77.11
47.46
43.13
27.28
f1 (ppm)



● linear Z diasteromer residues



■ = linear E diastereomer residues



▲ = branched residues (both diastereomers)

3c (l : b, 2 : 1) (cis : trans, 1 : 2.5)

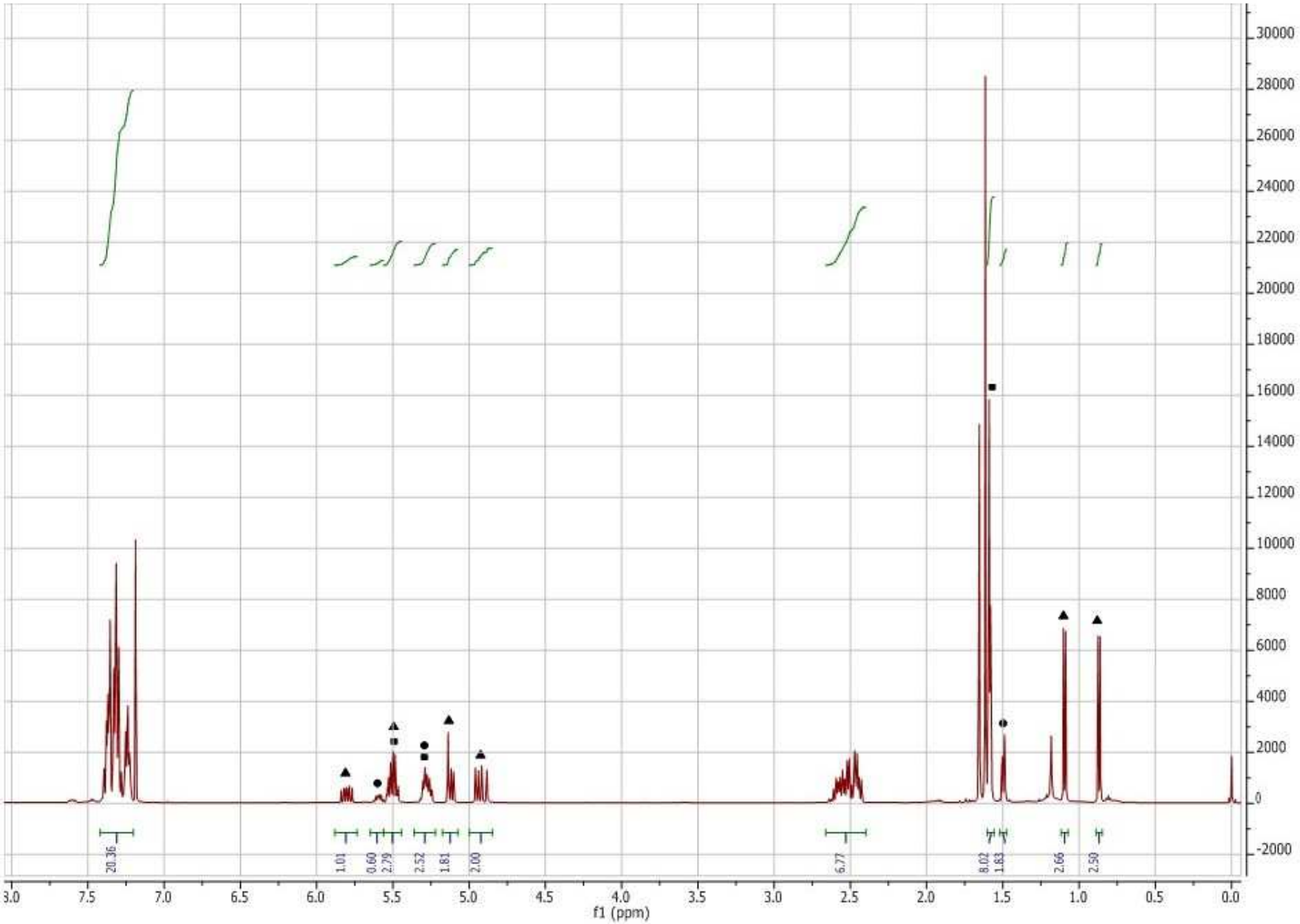
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

δ 7.40 (m, 5H (Ph-H_{linear}), 5H (Ph-$H_{branched}$)), 5.89 (ddd, J = 16.6, 10.5, 8.8 Hz, 1H branched), 5.68 (m, 1H *cis*-linear), 5.59 (m, 1H (*trans*-linear), 1H (branched)), 5.36 (m, 1H (*cis*-linear), 1H (*trans*-linear)), 5.20 (m, 2H, branched), 5.01 (m, 2H, branched), 2.59 (m, (2H *cis*-linear), (2H *trans*-linear), (1H branched)), 1.66 (d, J = 7.1 Hz, 3H, *trans*-linear), 1.57 (d, J = 7.1 Hz, 3H, *cis*-linear), 1.17 (d, J = 6.8 Hz, 3H, branched), 0.94 (d, J = 6.8 Hz, 2H, branched).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 140.49, 140.36, 140.05, 139.26, 138.79, 138.16, 131.40, 129.23, 129.13, 128.85, 128.09, 128.04, 126.74, 126.22, 125.98, 125.95, 124.71, 123.93, 123.70, 123.07, 122.34, 117.99, 117.63, 48.69, 47.66, 47.04, 46.74, 45.60, 42.83, 42.59, 39.63, 26.77, 26.56, 24.57, 18.33, 17.21, 15.99, 13.38.

Isomers assigned by TOCSY NMR spectroscopy experiments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2.79
2.52
1.81
2.00
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8.02
1.83
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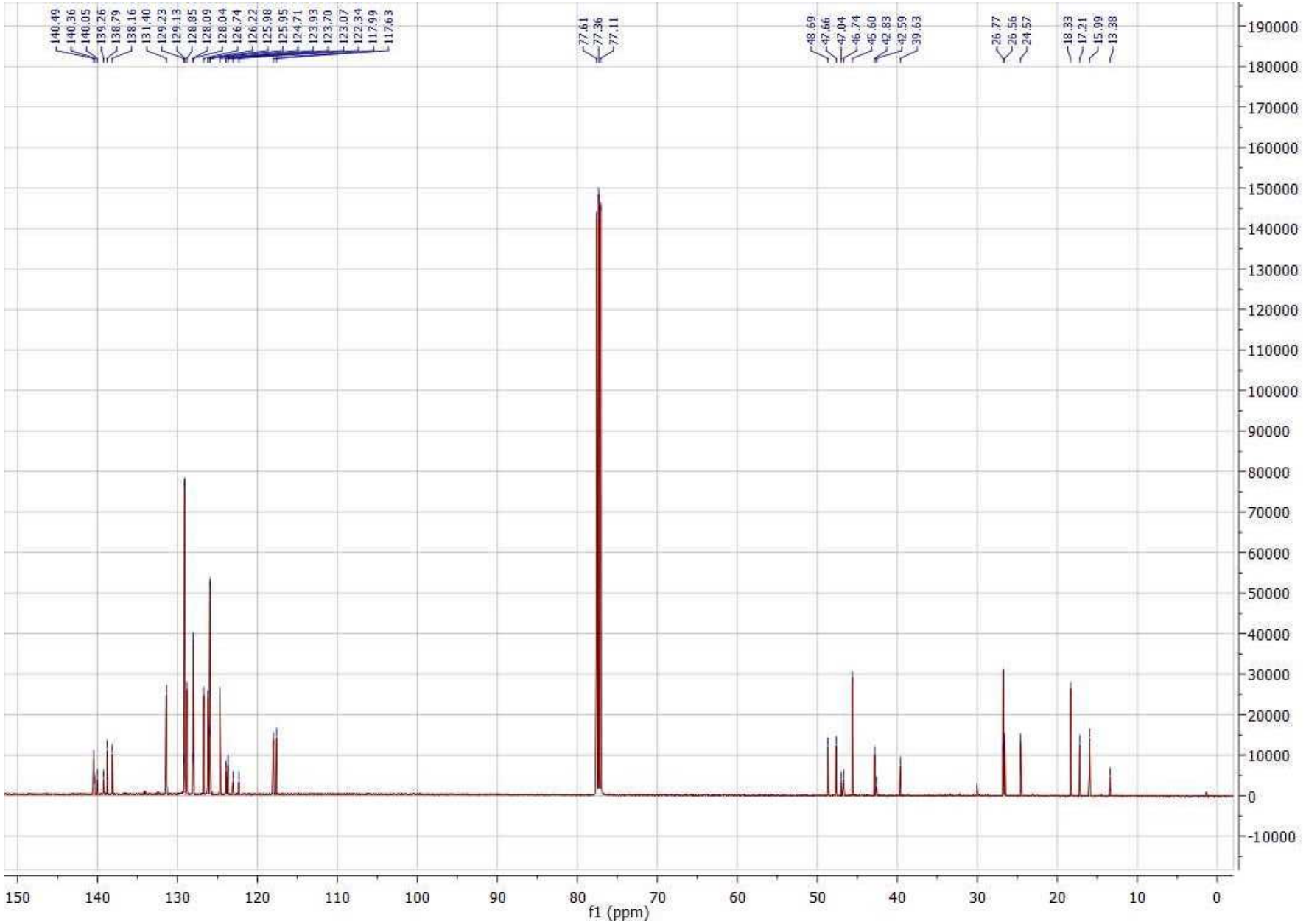
f1 (ppm)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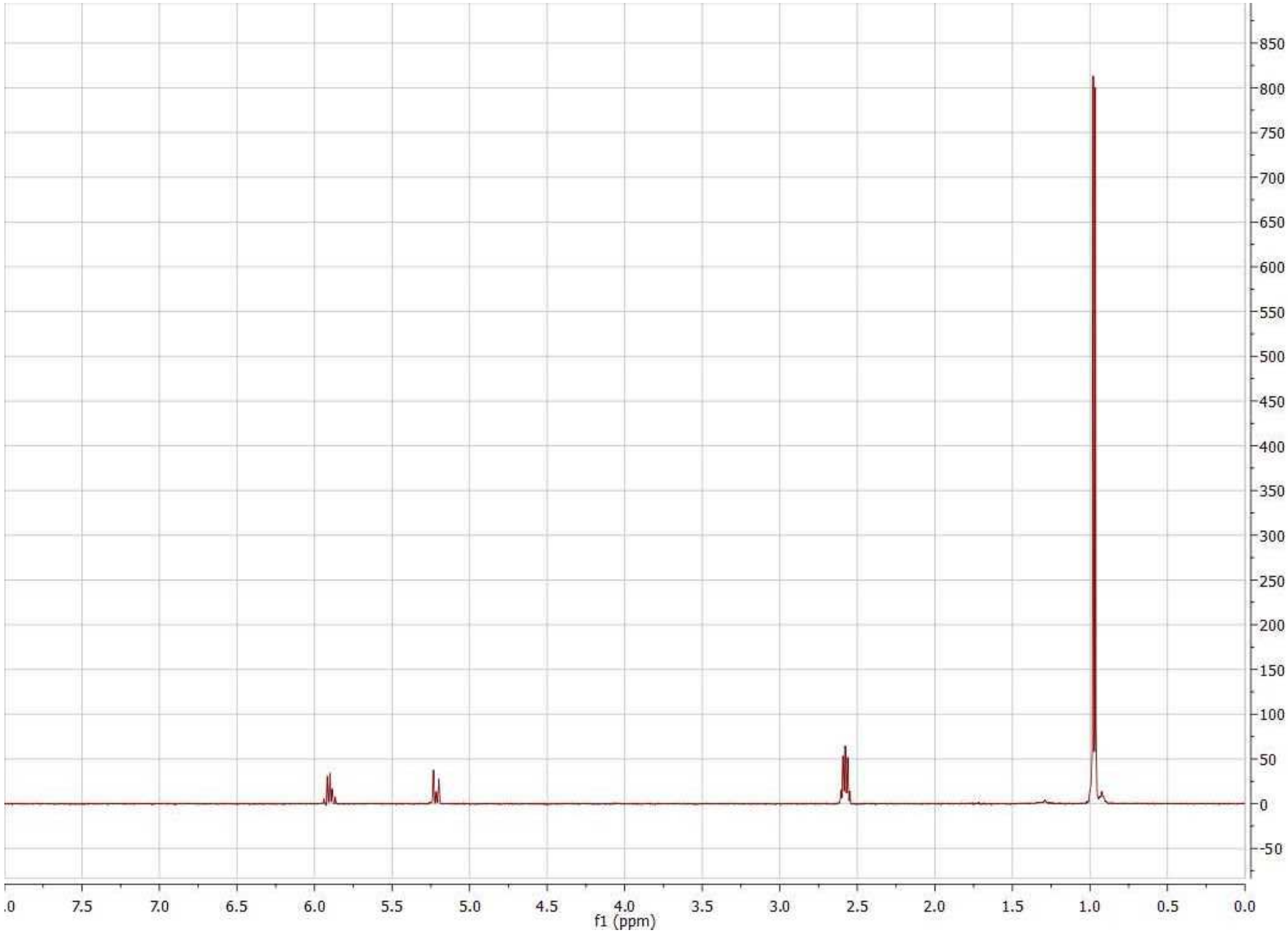
f1 (ppm)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6.0
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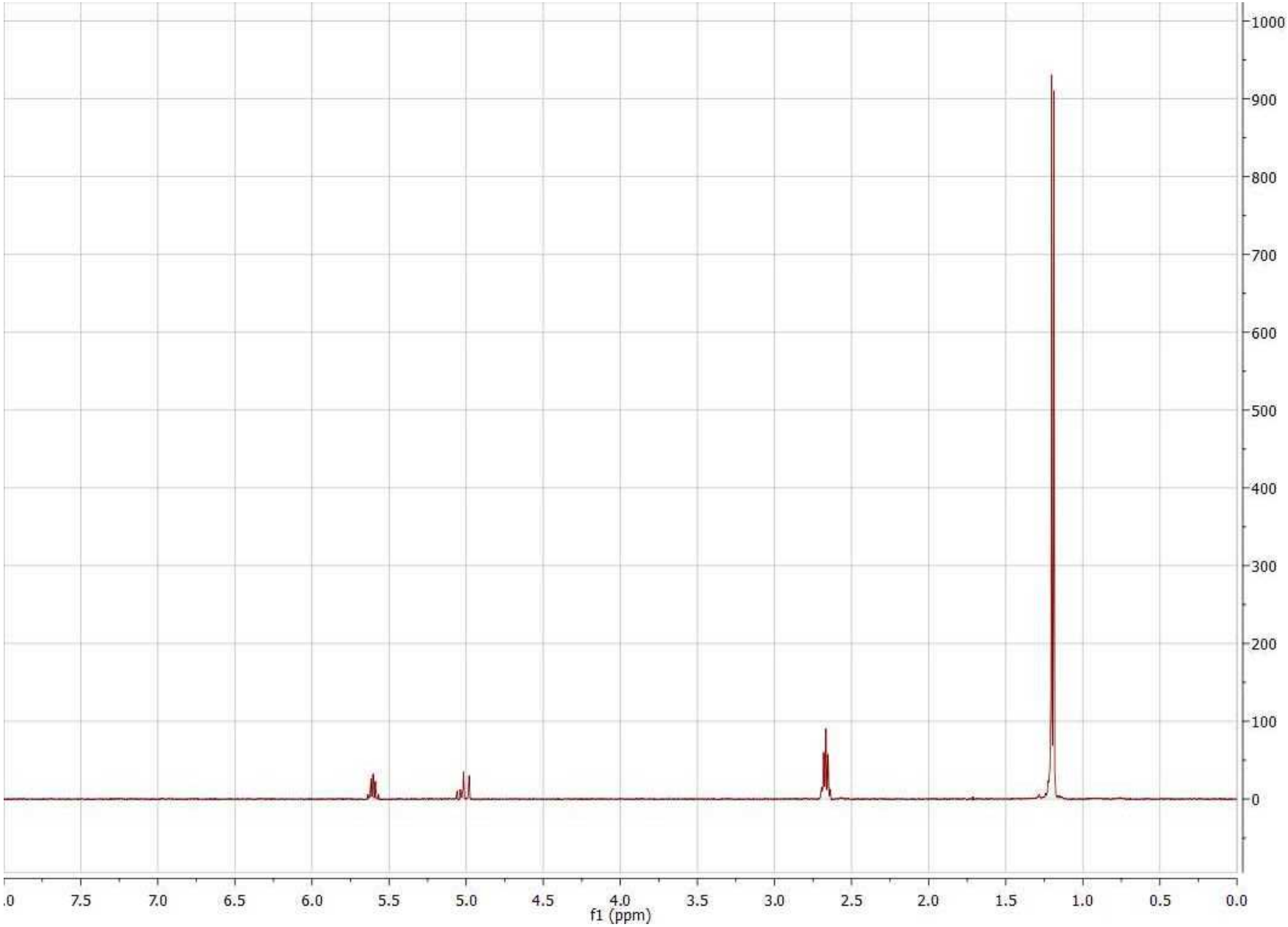
f1 (ppm)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300
200
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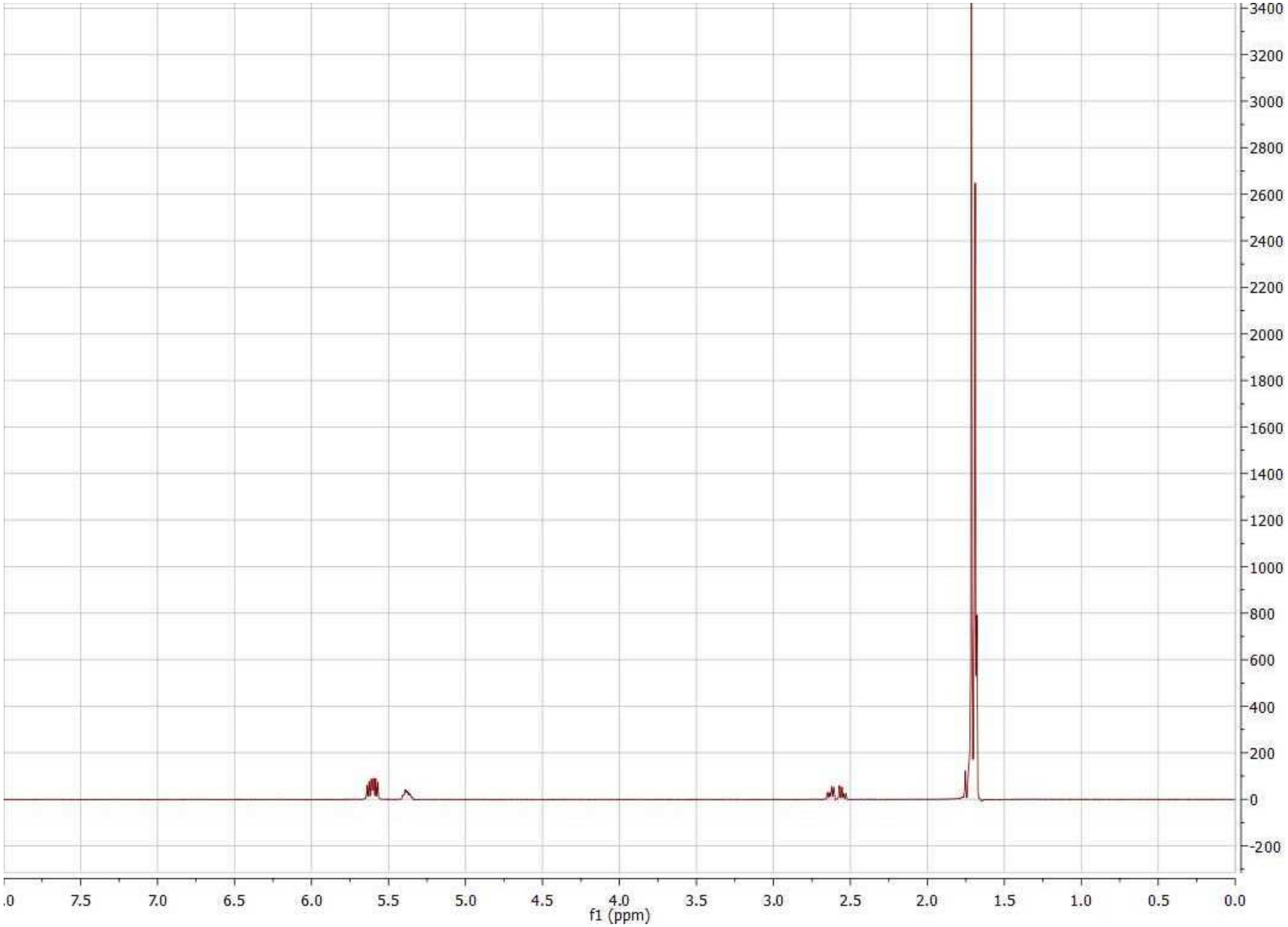
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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2400
2200
2000
1800
1600
1400
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1000
800
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400
200
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-200
7.5
7.0
6.5
6.0
5.5
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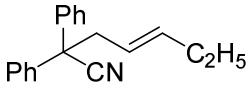
0.0
f1 (ppm)



3d (l : b, 10.5 : 1)

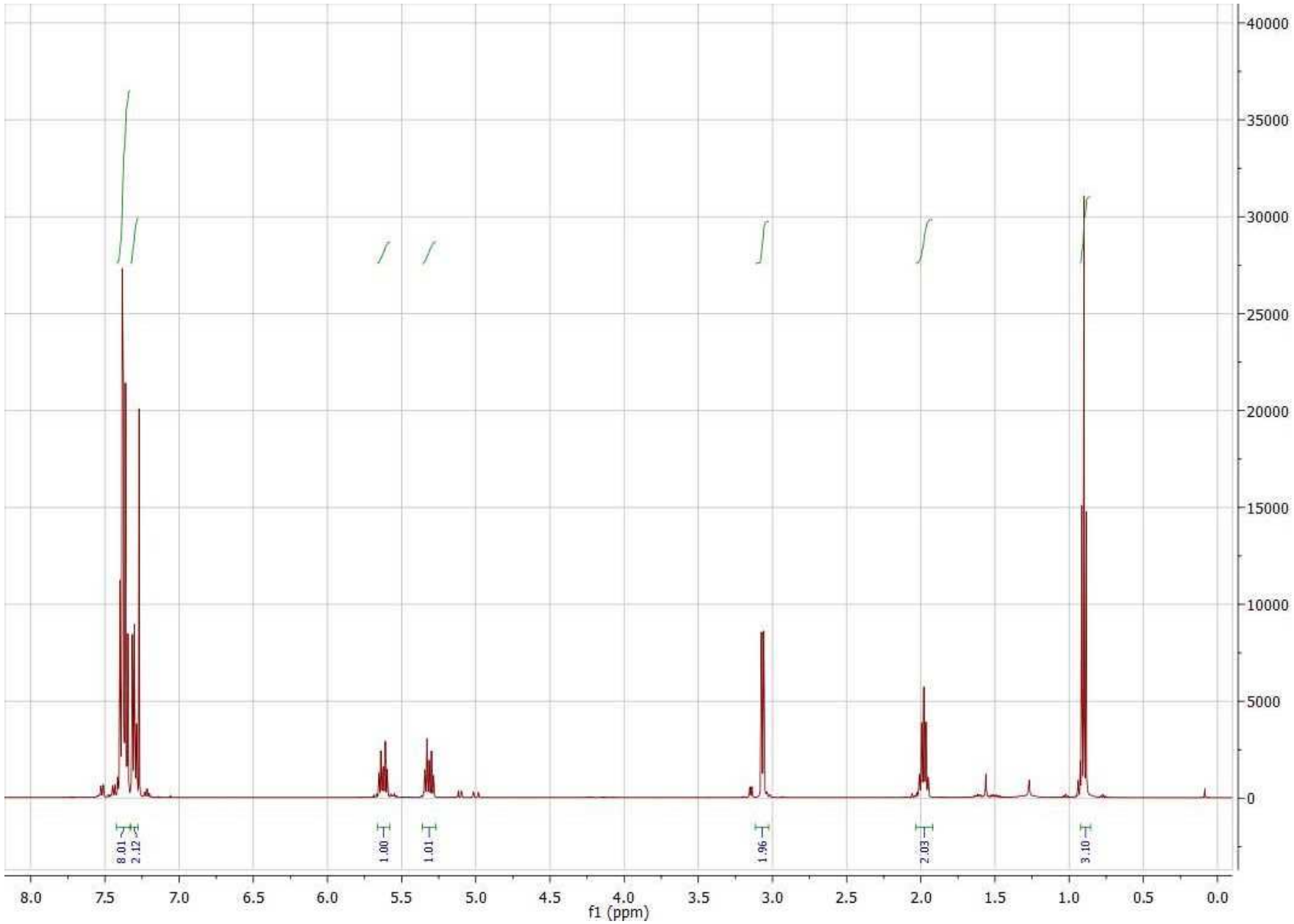
^{1}H NMR Spectra (500 MHz, $CDCl_3$):

(Major linear diastereomer) δ 7.37 (m, 8H), 7.30 (m, 2H), 5.63 (dtt, *J* = 15.4, 6.5, 1.2 Hz, 1H), 5.31 (dtt, *J* = 15.5, 7.1, 1.6 Hz, 1H), 3.07 (dq, *J* = 7.2, 1.1 Hz, 2H), 1.98 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

(Major linear diasteromer) δ 140.33, 138.83, 129.08, 128.14, 127.47, 122.47, 122.32, 52.48, 43.18, 25.96, 13.89.

GC/MS data: 261.2 (M^+), 193.1 (base peak).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6.0
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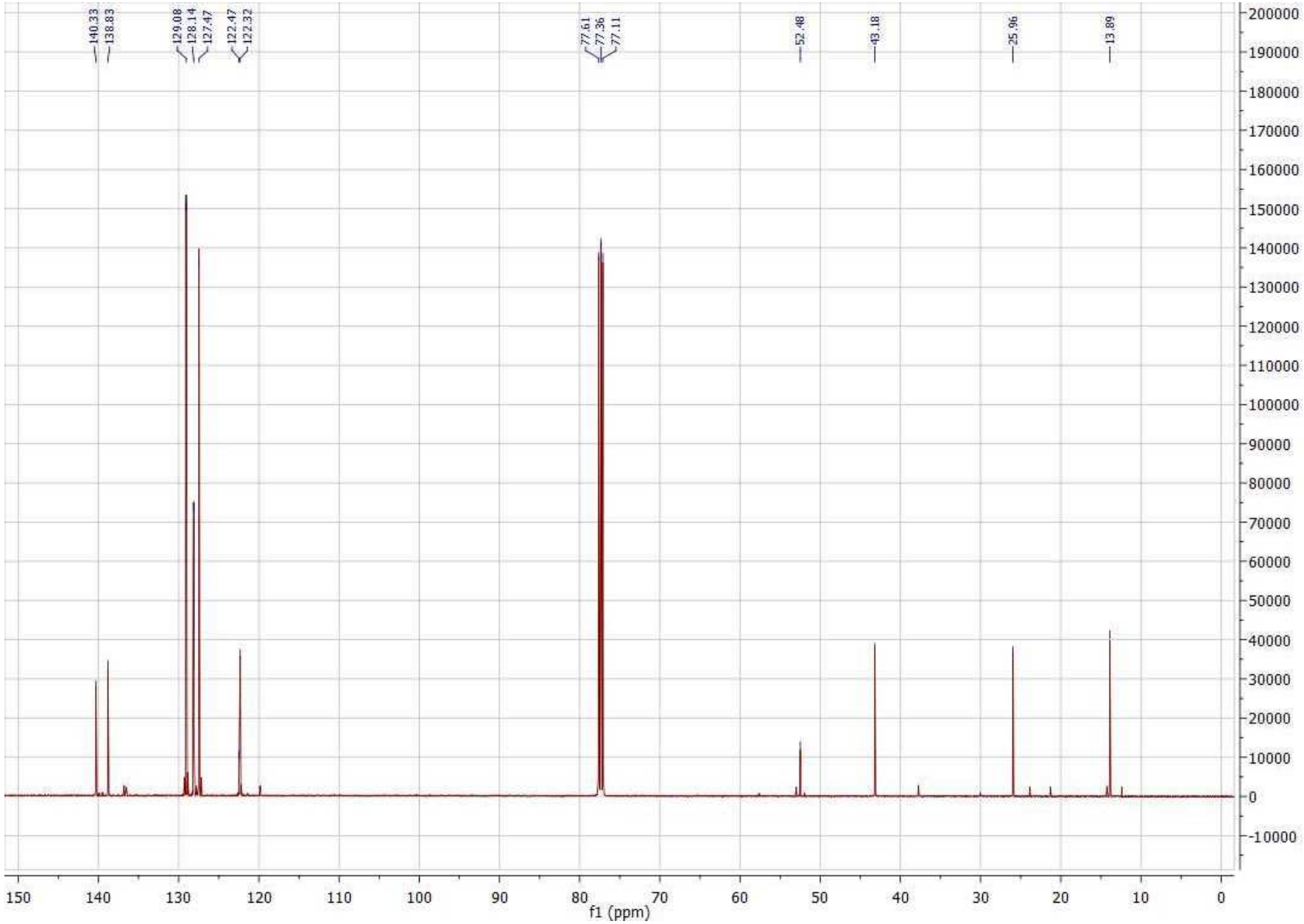
f1 (ppm)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138.83
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122.47
122.32
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43.18
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13.89
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190000
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170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
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100
90
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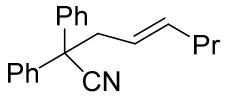
70
60
50
40
30
20
10
0
f1 (ppm)



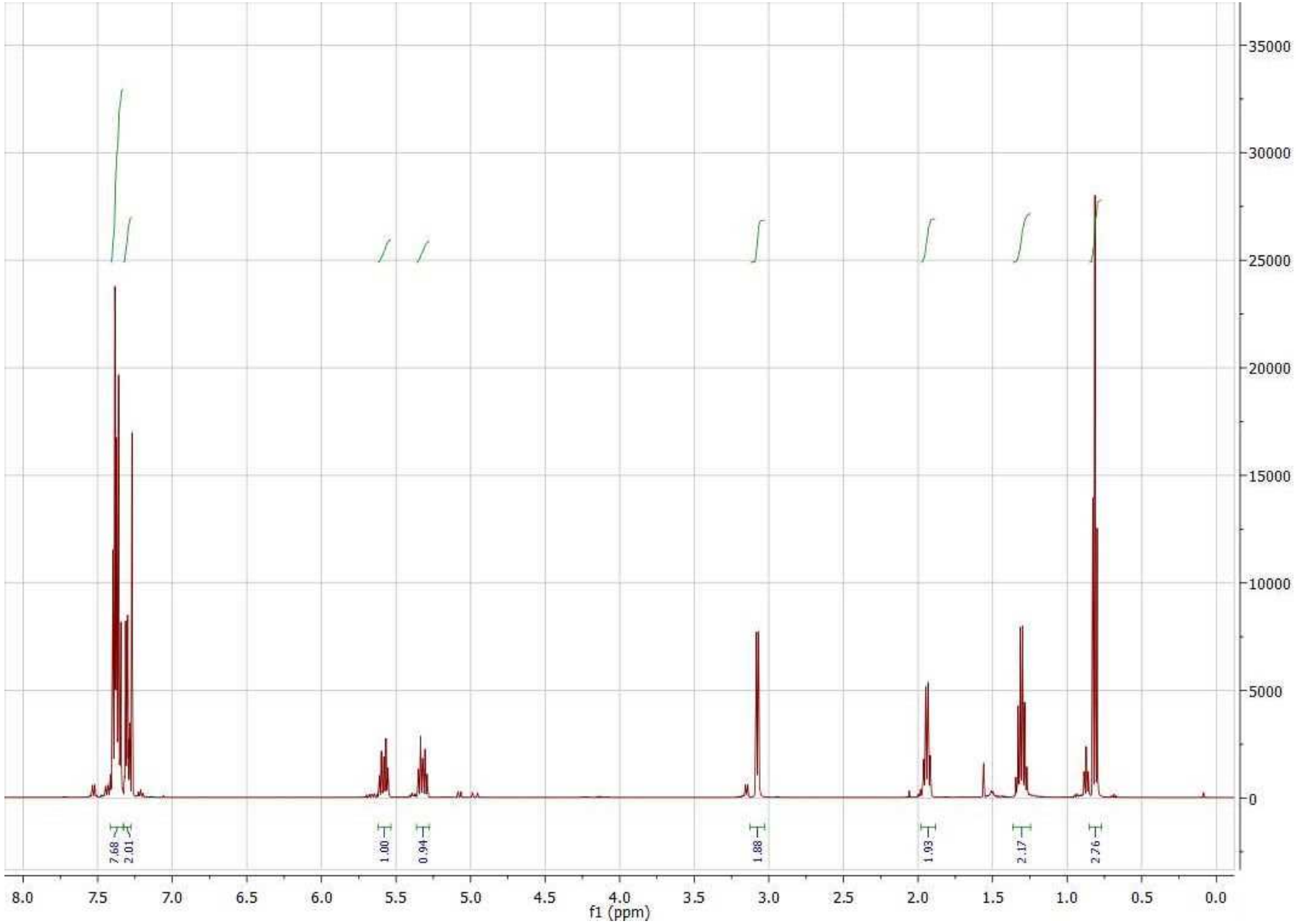
3e (l : b, 11.2 : 1) (cis : trans, 1 : 14.3)

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

(Major linear diastereomer) δ 7.38 (m, 8H), 7.30 (m, 2H), 5.58 (dtt, *J* = 15.0, 6.8, 1.3 Hz, 1H), 5.32 (dtt, *J* = 15.4, 7.1, 1.4 Hz, 1H), 3.08 (dq, *J* = 7.1, 1.0 Hz, 2H), 1.94 (m, 2H), 1.31 (h, *J* = 7.3 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

(Major linear diastereomer) δ 140.32, 137.14, 129.08, 128.13, 127.46, 123.47, 122.48, 52.46, 43.29, 34.91, 22.63, 13.83.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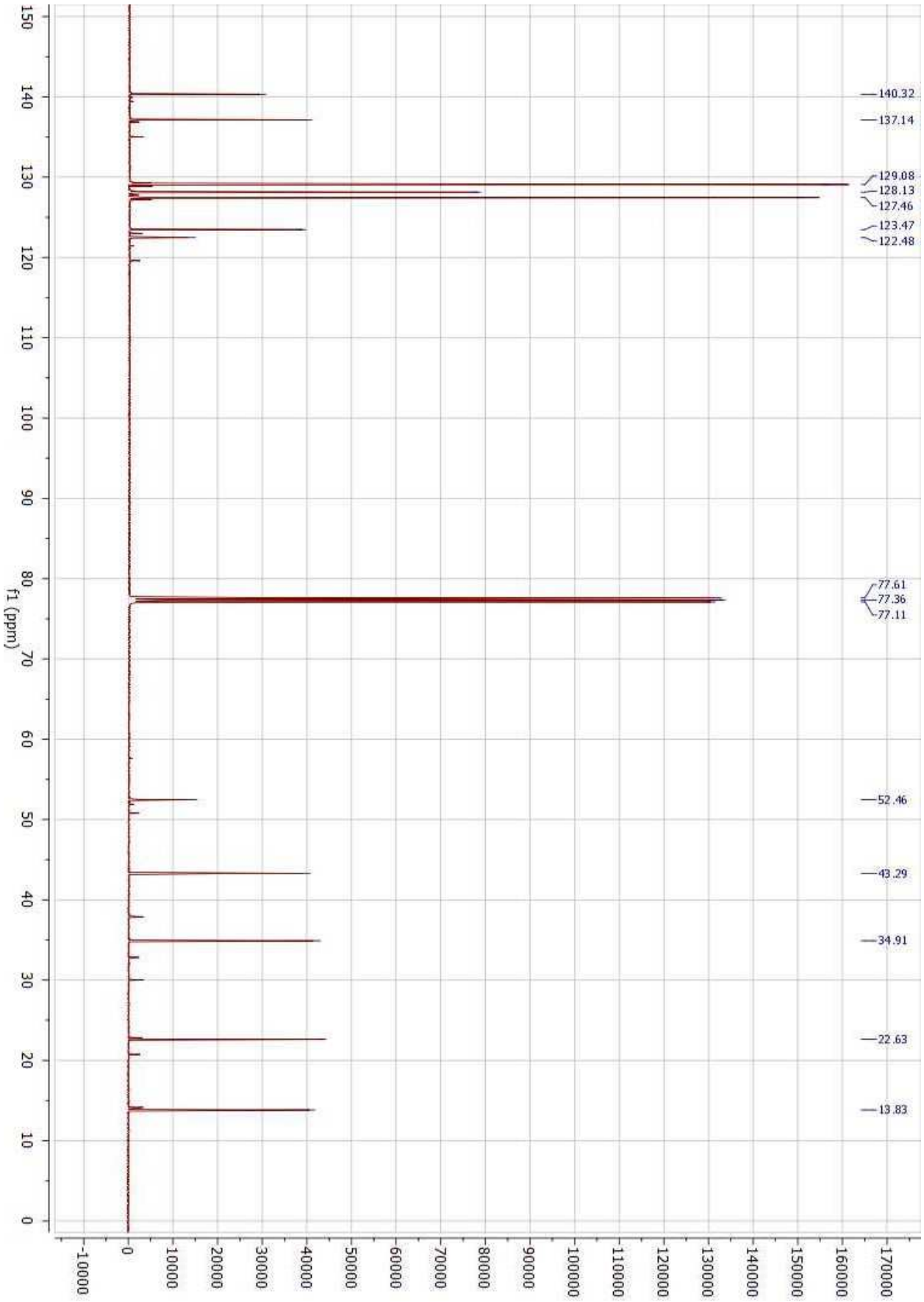
f1 (ppm)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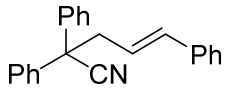
128.13
127.46
123.47
122.48
77.61
77.36
77.11
52.46
43.29
34.91
22.63
13.83
f1 (ppm)



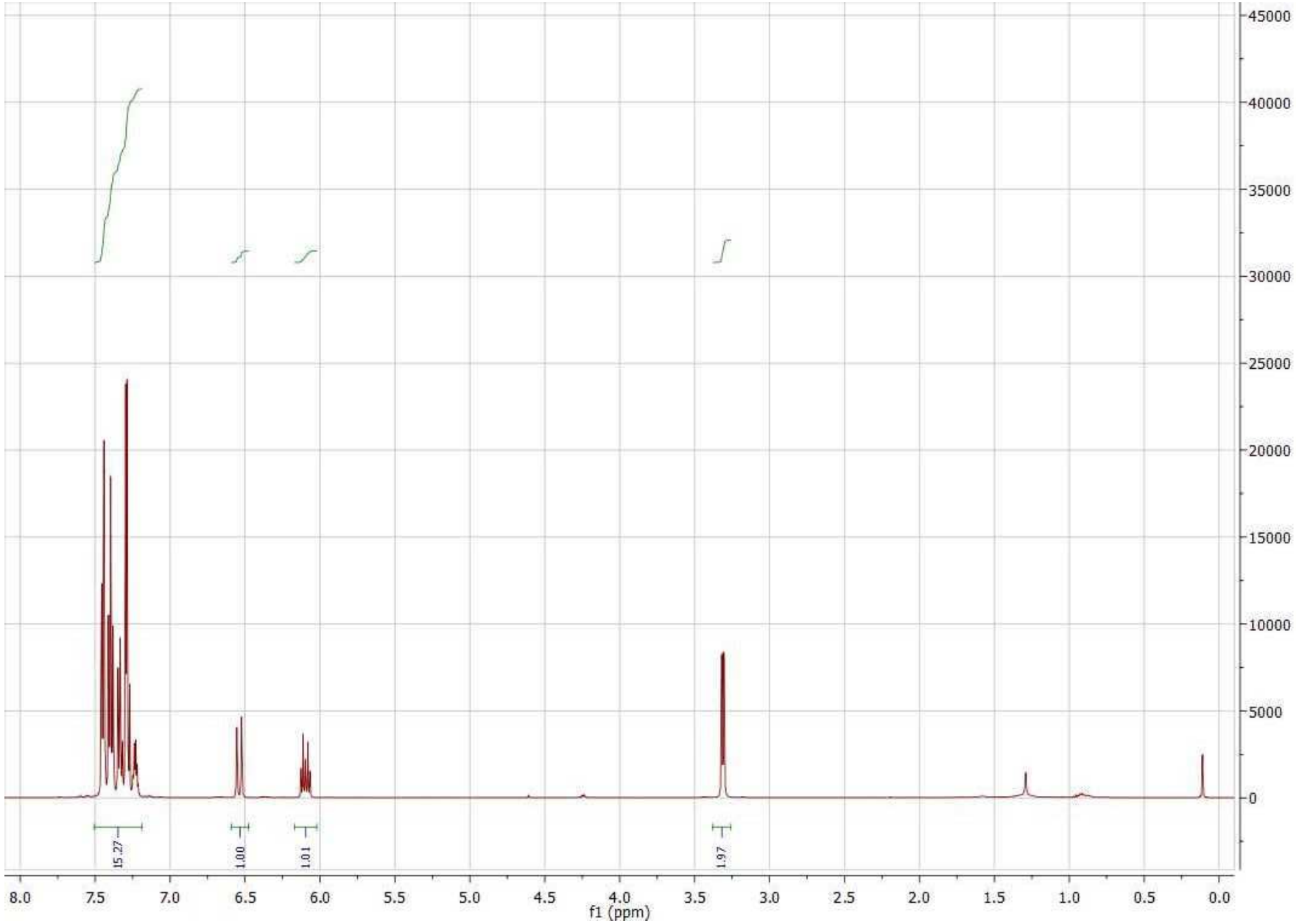
3f

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

δ 7.37 (m, 15H), 6.54 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.10 (dt, *J* = 15.7, 7.2 Hz, 1H), 3.31 (dd, *J* = 7.4, 1.3 Hz, 2H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 140.07, 137.05, 135.53, 129.20, 128.79, 128.31, 127.94, 127.41, 126.70, 123.39, 122.34, 52.36, 43.56.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1.01
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7.0
6.5
6.0
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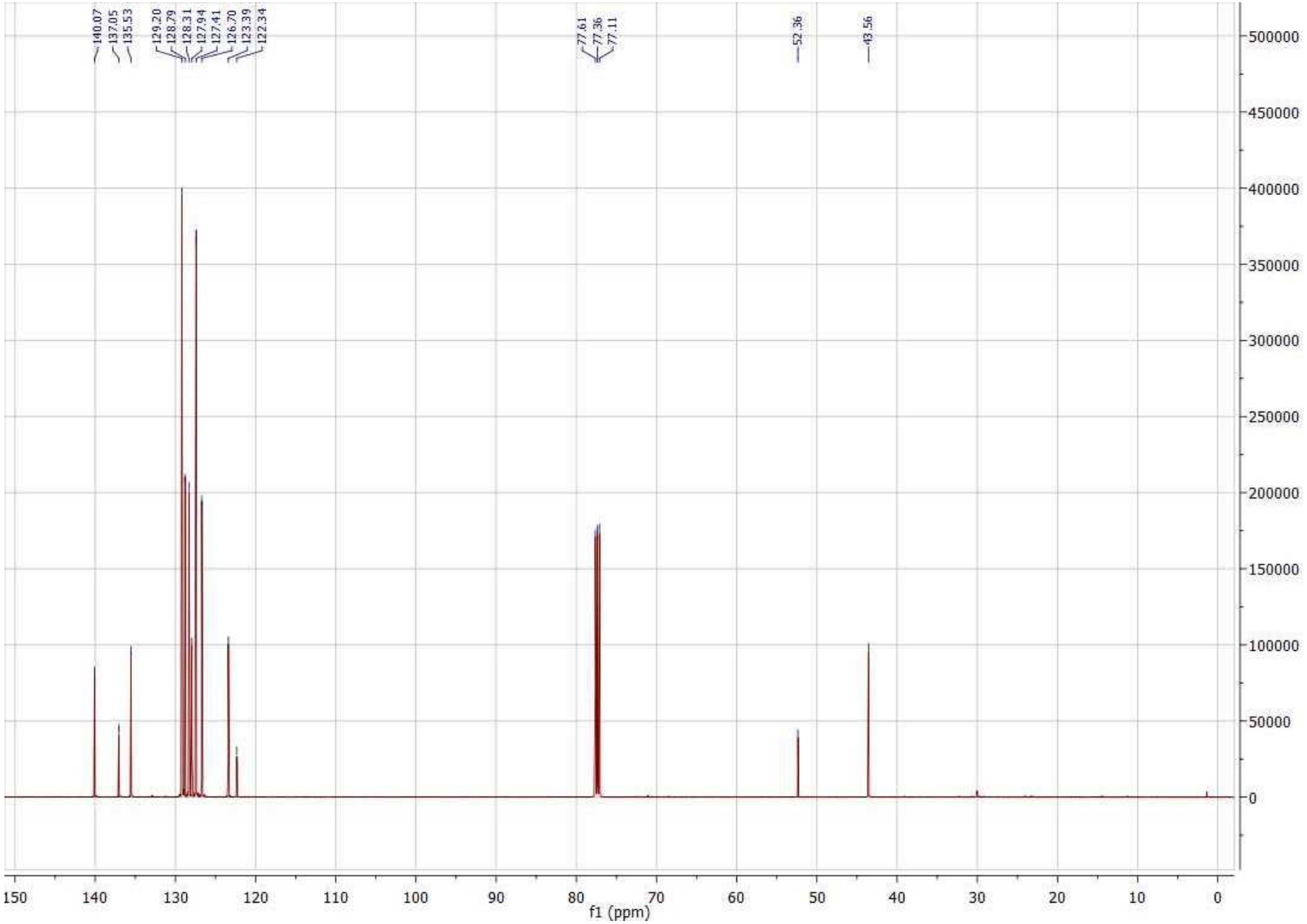
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


140.07
137.05
135.53
129.20
128.79
128.31
127.94
127.41
126.70
123.39
122.34
77.61
77.36
77.11
52.36
43.56
500000
450000
400000
350000
300000
250000
200000
150000
100000
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100
90
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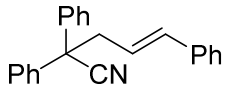
50
40
30
20
10
0
f1 (ppm)



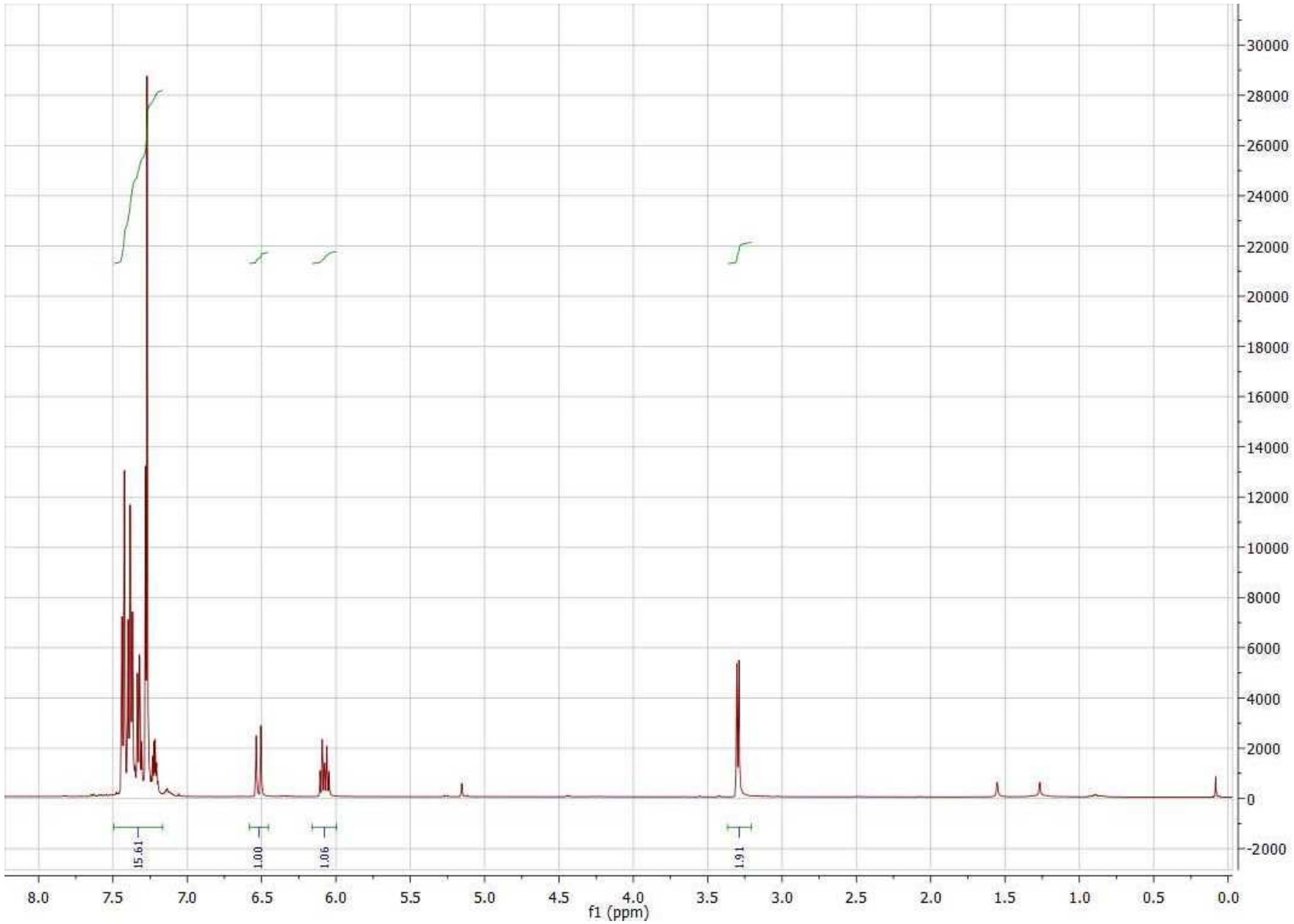
3g

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

δ 7.37 (m, 15H), 6.54 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.10 (dt, *J* = 15.7, 7.2 Hz, 1H), 3.31 (dd, *J* = 7.4, 1.3 Hz, 2H).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 140.10, 137.08, 135.55, 129.23, 128.81, 128.33, 127.97, 127.44, 126.73, 123.42, 122.36, 52.39, 43.60.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4000
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1.00
1.06
1.91
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7.0
6.5
6.0
5.5
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3.0
2.5
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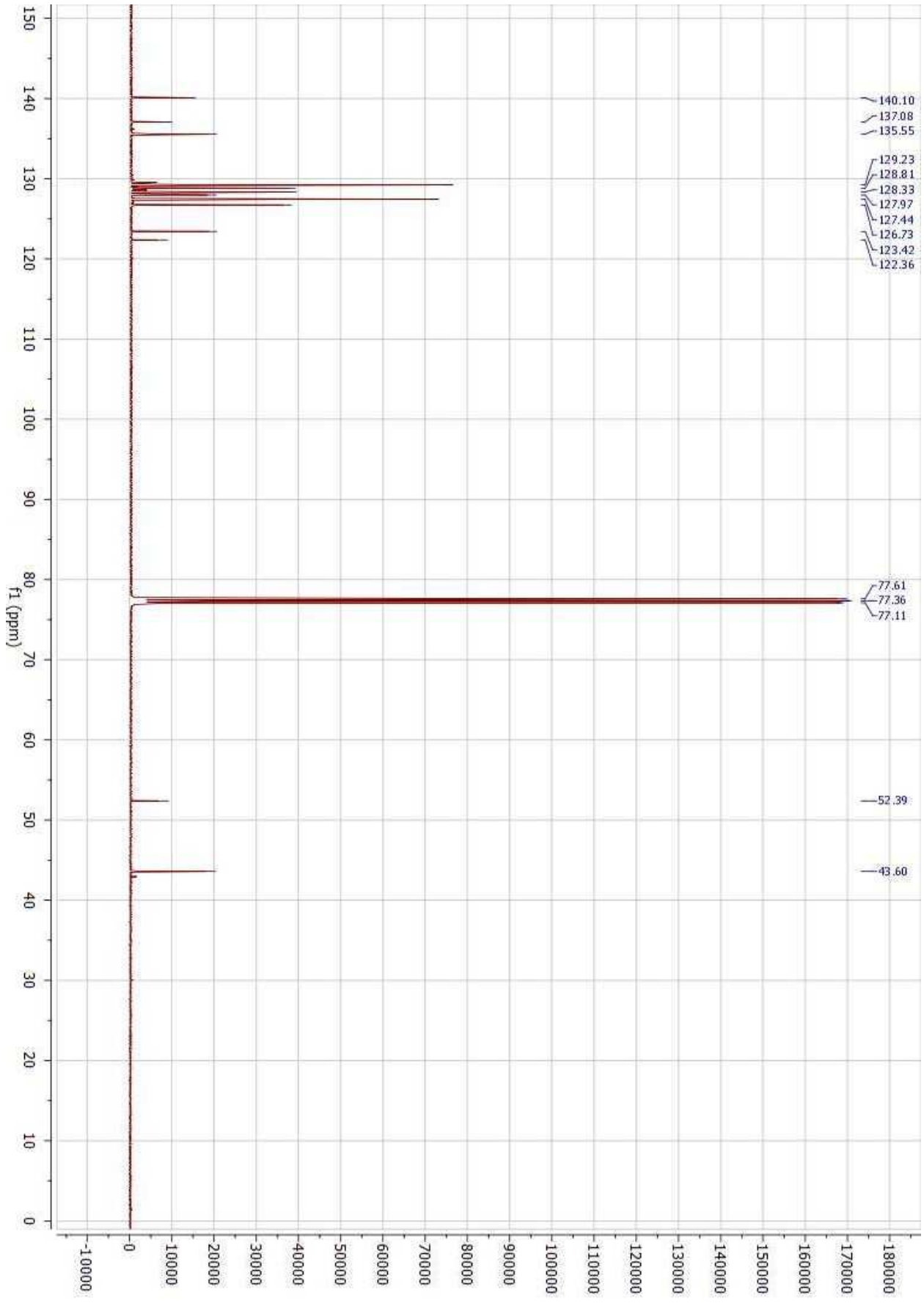
1.5
1.0
0.5
0.0
f1 (ppm)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77.11
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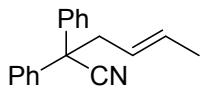
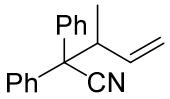
43.60
f1 (ppm)





■ = Major linear diastereomer residues **▲ = Branched residues**

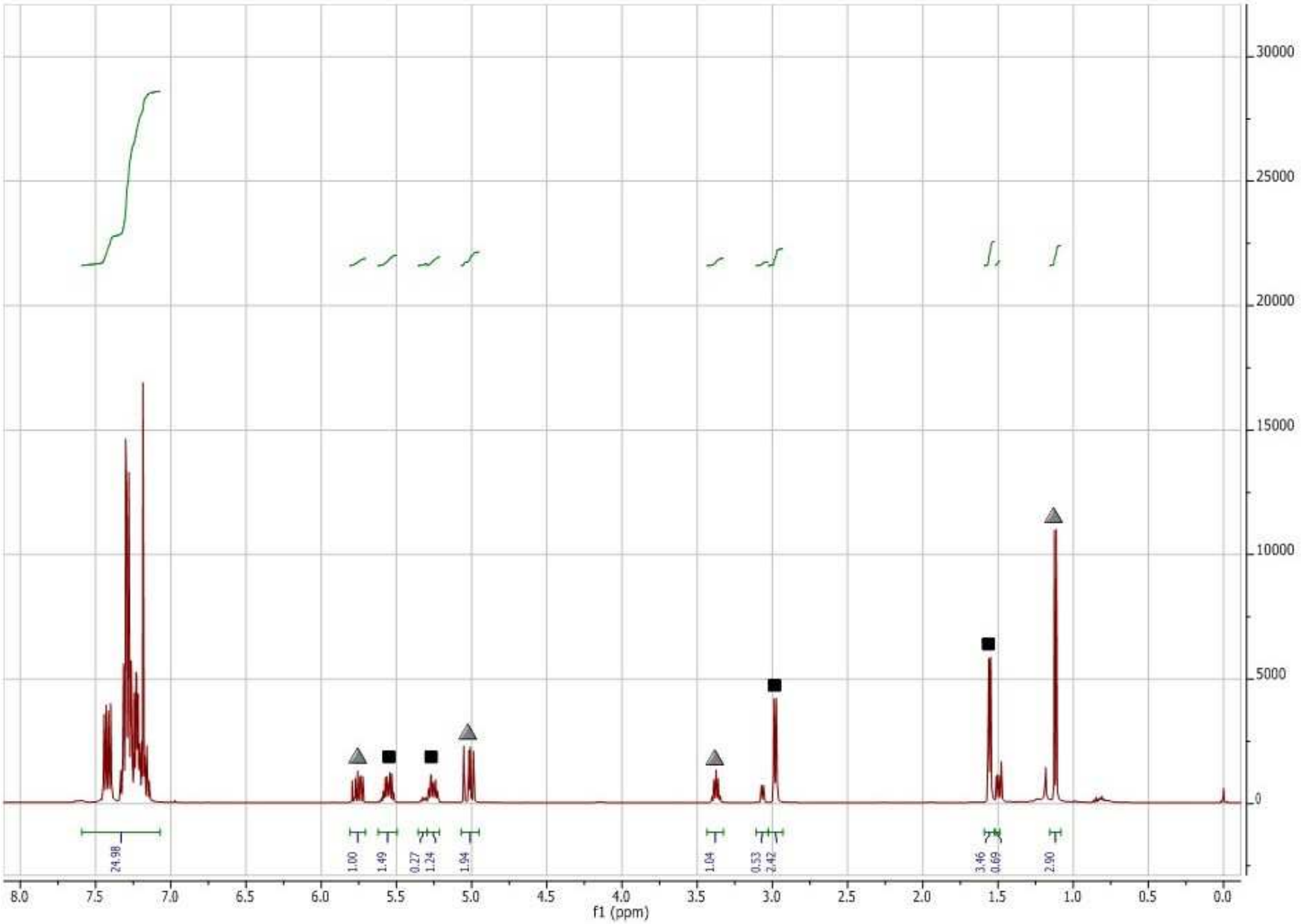
3h (l : b, 1.4 : 1) (cis : trans, 1 : 4.6)

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

δ 7.38 (m, 10H (Ph-H_{linear}), 10H (Ph-$H_{branched}$)), 5.84 (ddd, J = 17.1, 10.5, 7.6 Hz, 1H, branched), 5.64 (m, 1H, linear), 5.34 (m, 1H, linear), 5.32 (m, 1H, linear diastereomer), 5.10 (m, 2H, branched), 3.45 (m, 1H, branched), 3.07 (dt, J = 7.3, 1.2 Hz, 2H, linear diatereomer) 2.98 (dt, J = 7.0, 1.2 Hz, 2H, linear), 1.64 (dq, J = 6.7, 1.2 Hz, 3H, linear), 1.50 (ddt, J = 6.9, 1.87, 0.94 Hz, 3H, linear diastereomer), 1.20 (d, J = 6.7 Hz, 3H, branched).

^{13}C NMR Spectra (126 MHz, $CDCl_3$):

δ 140.30, 139.63, 139.50, 138.53, 131.70, 129.24, 129.12, 129.10, 129.01, 128.20, 128.15, 128.04, 127.94, 127.49, 127.42, 127.13, 124.49, 123.95, 122.50, 121.12, 117.85, 58.19, 52.48, 51.88, 44.51, 43.25, 37.52, 18.37, 17.33, 13.48.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7.0
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6.0
5.5
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4.5
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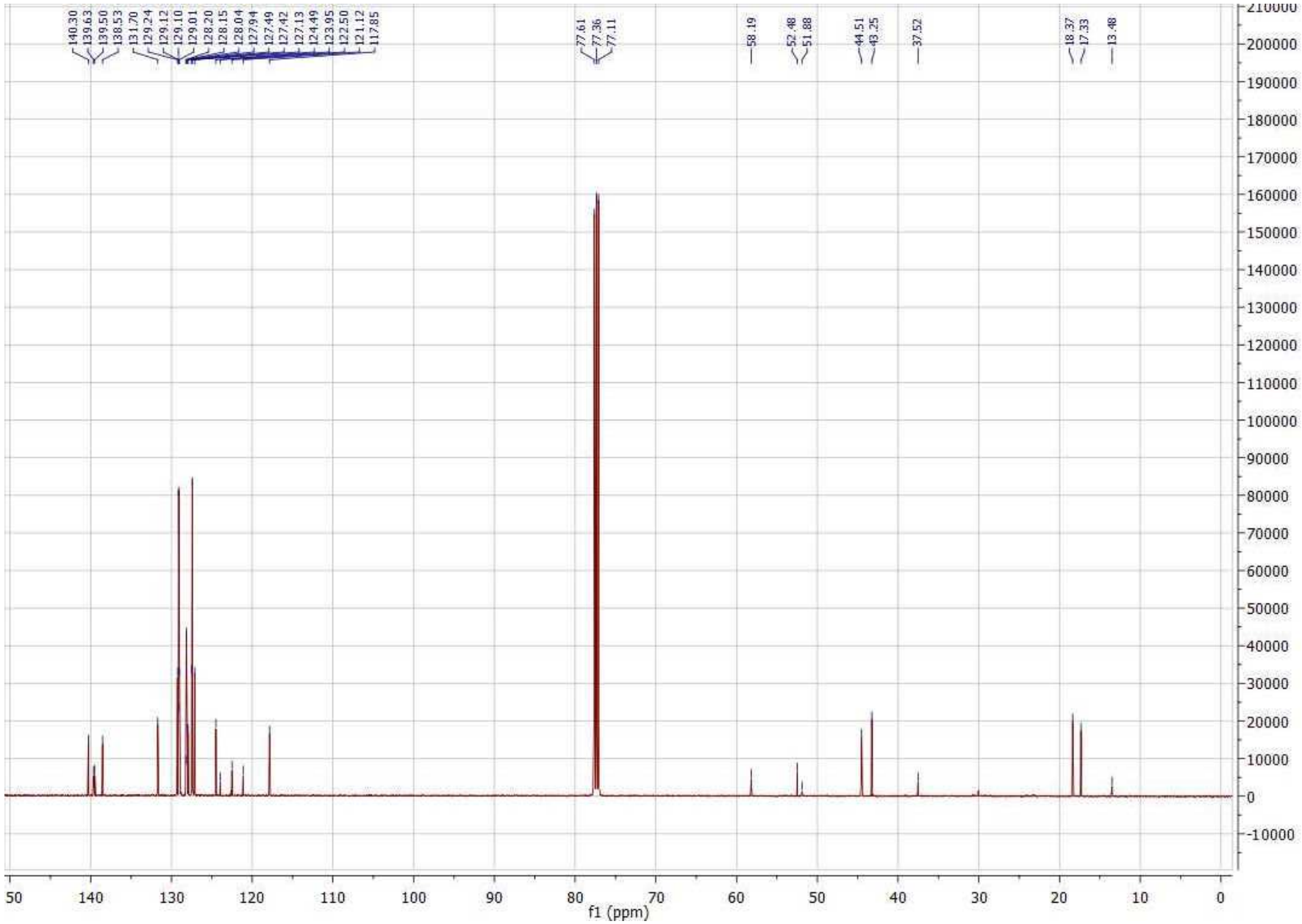
1.5
1.0
0.5
0.0
f1 (ppm)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127.94
127.49
127.42
127.13
124.49
123.95
122.50
121.12
117.85
77.61
77.36
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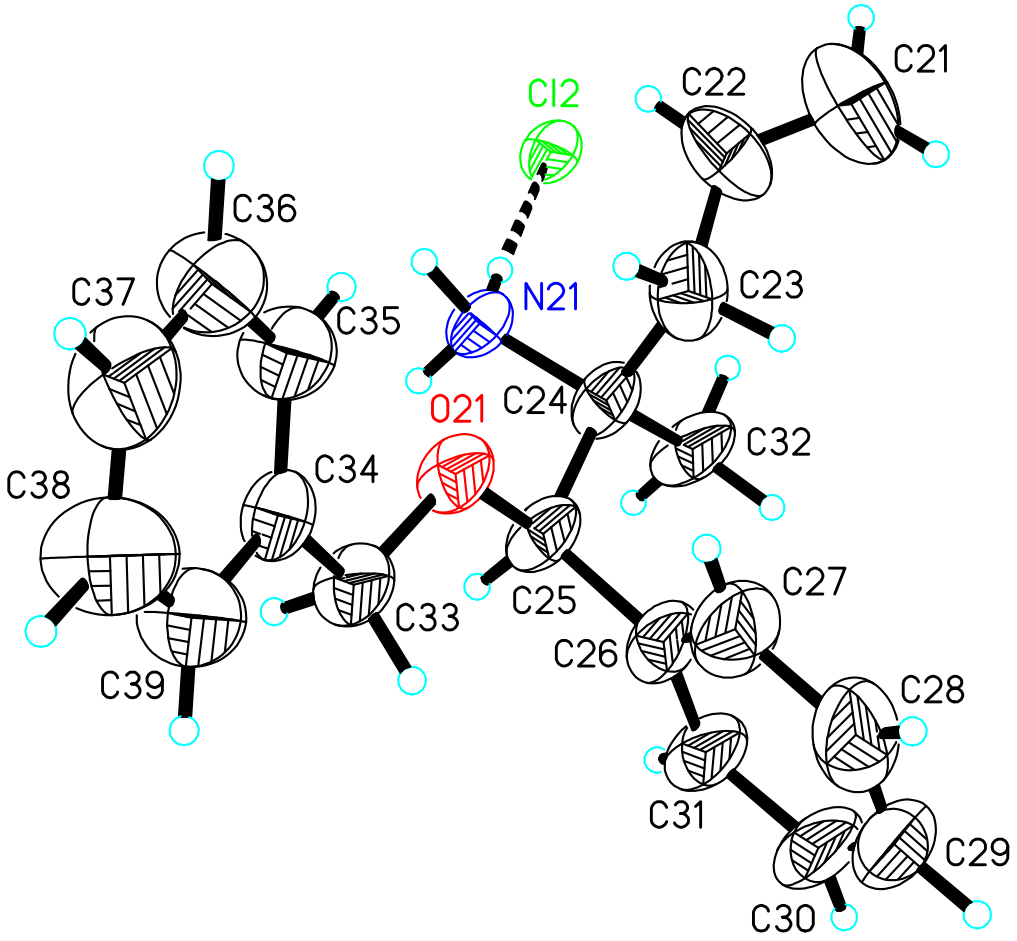
17.33
13.48
f1 (ppm)



1e was reduced to the amine and crystals of the amine-HCl salt were collected as follows:

Detailed description of x-ray crystal structure determination for [C19H24NO][Cl] :

The alignment reflections for determining the preliminary unit cell for the crystal of [C19H24NO][Cl] (**1)** indexed quite well as a C-centered monoclinic lattice. The crystal was therefore believed to utilize a monoclinic space group and intensity data were collected accordingly. The monoclinic R_{sym} was 0.105 and the most probable space group appeared to be centrosymmetric C2/m. When the structure would not solve in C2/m, the intensity data were

further analyzed and this indicated the possible presence of a c-glide. The structure solved straightforwardly in the centrosymmetric space group C2/c with an asymmetric unit containing two [C19H24NO][Cl] cation/anion pairs. When this structure failed to refine below $R_1 = 0.153$, the possibility of it being a triclinic structure that was pseudomerohedrally twinned to look monoclinic was considered. This turned out to be the case and the final centrosymmetric triclinic asymmetric unit has four nearly identical, but crystallographically-independent [C19H24NO][Cl] cation/anion pairs, related by non-crystallographic pseudosymmetry. The crystals utilize the centro-symmetric triclinic space group $C\bar{1}$ [a nonstandard setting of $P\bar{1}$ – C_i^1 (No. 2)] with lattice constants at 100K of: $\boldsymbol{a}$ =26.96214(19)Å, $\boldsymbol{b}$ = 12.68483(10)Å, $\boldsymbol{c}$ = 21.88641(18)Å, $\boldsymbol{\alpha}$ = 90.4219(6)°, $\boldsymbol{\beta}$ = 104.5435(4)°, $\boldsymbol{\gamma}$ = 89.7970(4)°, V = 7245.3(1)Å^3 and Z = 16 [C19H24NO][Cl] moieties. The crystals are pseudomerohedrally (68%/32%) twinned with the two domains related by a 180° rotation about the $\boldsymbol{b}$ axis.

The final centrosymmetric triclinic asymmetric unit contains four cation/anion pairs. All nonhydrogen atoms were included in the structural model with variable anisotropic thermal parameters. All twelve hydrogens for the protonated amine groups were located from difference Fourier syntheses and incorporated into the structural model as individual isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. Mild restraints were applied to the anisotropic thermal parameters of two carbon atoms [C(78) and C(79)] and three of the ammonium hydrogens were fixed at values 1.2 times the equivalent isotropic thermal parameter of their nitrogen atom. The remainder of the hydrogen atoms were placed at idealized sp^2- or sp^3-hybridized positions with C-H bond lengths of 0.95 - 1.00 Å and isotropic thermal parameters fixed at values 1.20 (nonmethyl) or 1.50 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they are bonded. Methyl groups were placed at

idealized "staggered" positions. The terminal ethylene group for the first cation is 57%/43% disordered between two conformations and both of these were restrained to have metrical parameters similar to that group in the fourth cation.

The final least-squares refinement cycles for **1** in space group $C\bar{1}$ utilized anisotropic thermal parameters for all nonhydrogen atoms, isotropic thermal parameters for all hydrogen atoms, 867 variables, 51 restraints and 11861 reflections having $2\theta(CuK\alpha) < 140.10°$. Final agreement factors at convergence for **1** are: R_1(unweighted, based on F) = 0.078 for 10457 independent absorption-corrected "observed" reflections having $2\theta(CuK\alpha) < 140.10°$ and $I>2\sigma(I)$; R_1(unweighted, based on F) = 0.086 and wR_2(weighted, based on F^2) = 0.213 for all 11861 independent absorption-corrected reflections having $2\theta(CuK\alpha) < 140.10°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.59 and -0.56 $e^-/Å^3$, respectively.