SUPPORTING INFORMATION

A Simple and Expedient Method for the Preparation of N-Chlorinated Hydantoins

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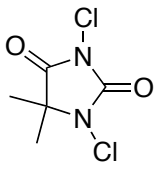
General: All commercially available hydantoins and trichloroisocyanuric acid (TCCA) were purchased from Aldrich and used without purification. Chiral hydantoin starting materials **S1, S3,** and **S5** were prepared by known methods.[1-3] Solvents were purchased from either Fisher Scientific or Mallinckrodt Chemicals and used without purification. ^{1}H and ^{13}C NMR spectra were collected on a 300 MHz NMR spectrometer (VARIAN INOVA) using CD_3CN, or CD_3Cl. Chemical shifts are reported in parts per million (ppm). Spectra are referenced to residual solvent peaks. Infrared spectra were collected on a Mattson Galaxy Series FTIR 3000. Samples were prepared as KBr pellets. Elemental analyses were performed on a Perkin Elmer Series II CHNS/O analyzer 2400. Melting points were measured on a Mel-Temp II capillary apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer Polarimeter 341. Flash silica gel (32-63 μm) from Dynamic Adsorbents, Inc. was used for filtration. In all cases, X-Ray quality crystals were obtained directly from the recrystallization crop from chloroform/hexanes, with the exception of compound **8**. X-ray quality crystals for compound **8** were obtained on slow evaporation from benzene and hexanes.

Experimental:

General Procedure for the N-chlorination of hydantoins:

The appropriate hydantoin (3 mmol) was suspended in acetonitrile (10 mL) in a 20 mL screw-top vial equipped with a magnetic stir bar. TCCA (6 mmol, 2 equiv) was added in one portion and the resulting slurry was stirred for 30 min, during which time the mixture became uniform and clear. The acetonitrile was removed by rotary evaporation to give a white solid, which was triturated in hot chloroform. The remaining solids were removed by filtration with suction, and the filtrate was then filtered with suction through a 1-cm thick pad of silica gel packed with chloroform in a 50 mL fritted funnel. The silica gel pad was subsequently washed with chloroform and the combined organics were concentrated by rotary evaporation to provide the crude chlorinated product. The crude isolate was purified by recrystallization from chloroform/hexanes. The mother liquor was then concentrated and the residue was re-subjected to recyrstallization to provide a second crop of products.

Analytical Data for Compounds 3-12



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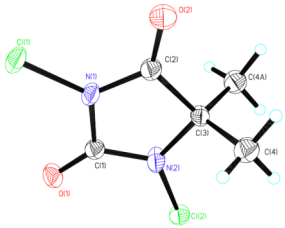
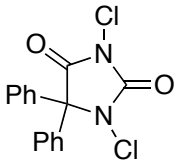


3, 1,3-Dichloro-5,5-dimethylhydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 1.48 (s, 6H); ^{13}C NMR (75 MHz, CD_3CN): δ 171.3, 151.6, 68.7, 22.4; IR (KBr, νcm^{-1}): 1755, 1734; Elemental Analysis: Calc.: C: 30.48%, H: 3.07%, N: 14.22%; Found: C: 30.47%, H: 2.96%, N: 14.06%; mp = 133-135^{o} C.



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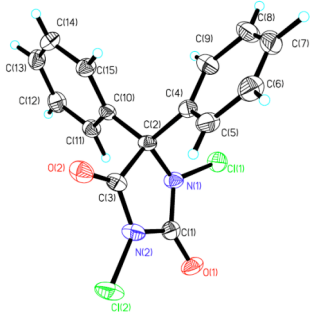
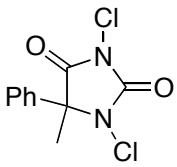


4, 1,3-Dichloro-5,5-phenylhydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 7.51 (m, 6H), 7.35 (m, 4H); ^{13}C NMR (75 MHz; CD_3CN): δ 168.5, 151.5, 135.5, 130.5, 129.8, 129.4; IR (KBr, νcm^{-1}): 1797, 1746; Elemental Analysis: Calc.: C: 56.10%, H: 3.14%, N: 8.72%; Found: C: 55.96%, H: 2.92%, N: 8.69%; mp = 159-161^{o} C.



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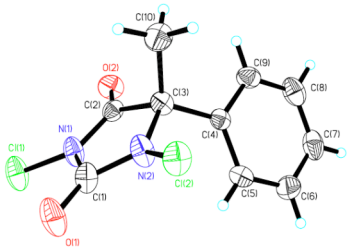
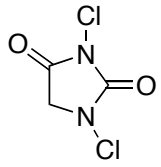


5, 1,3-Dichloro-5-methyl-5-phenylhydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 7.45 (s, 5H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 169.6, 151.9, 130.6, 130.1, 127.3, 72.3, 21.1; IR (KBr, νcm^{-1}): 1794, 1747; Elemental Analysis: Calc.: C: 46.36%, H: 3.11%, N: 10.81%; Found: C: 46.13%, H: 3.15%, N: 10.80%; mp = 127-128^{o} C.



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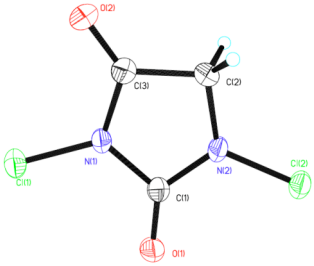
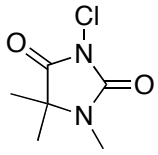


6, 1,3-Dichlorohydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 4.26 (s, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ 165.1, 154.6, 57.6; IR (KBr, νcm^{-1}): 1740; Elemental Analysis: Calc.: C: 21.33%, H: 1.19%, N: 16.58%; Found: C: 21.41%, H: 1.16%, N: 16.60%; mp = 115-117^{o} C.



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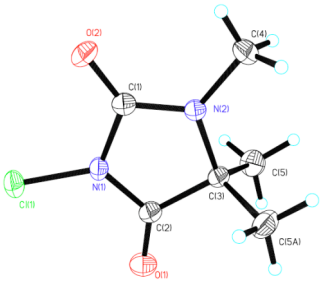
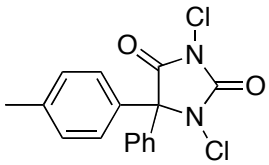


7, 3-Chloro-1,5,5-trimethylhydantion:

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.91 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 151.1, 62.8, 25.3, 22.3; IR (KBr, νcm^{-1}): 1744, 1725; Elemental Analysis: Calc.: C: 40.81%, H: 5.14%, N: 15.86%; Found: C: 40.73%, H: 5.34%, N: 15.94%; mp = 165-168^{o} C.



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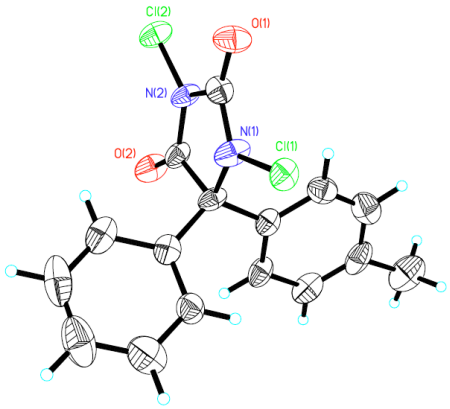
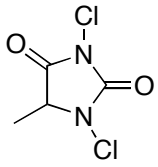


8, 1,3-Dichloro-5-(4-methylphenyl)-5-phenylhydantoin

^{1}H NMR (300 MHz, CD_3CN): δ 7.46 (m, 3H), 7.32 (m, 2H), 7.26 (m, 2H), 7.18 (m, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ 168.6, 151.5, 141.2, 135.5, 132.6, 130.8, 130.4, 129.7, 129.34, 129.32, 79.8, 21.2; IR (KBr, νcm^{-1}): 1796, 1759; Elemental Analysis: Calc.: C: 57.33%, H: 3.61%, N: 8.36%; Found: C: 57.14%, H: 3.63%, N: 8.24%; mp = 130-131^{o} C.



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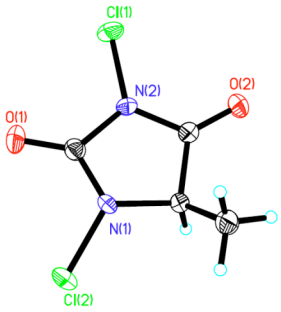
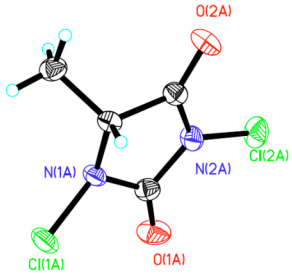
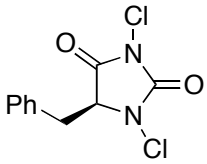




9, 1,3-Dichloro-5-methylhydantoin

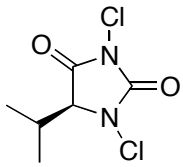
^{1}H NMR (300 MHz, CD_3CN): δ 4.34 (q, J = 7.2 Hz, 1H), 1.47 (d, J = 7.2 Hz 2H); ^{13}C NMR (75 MHz, CD_3CN): δ 168.3, 156.6, 64.3, 14.6; IR (KBr, νcm^{-1}): 1795, 1756, 1738; Elemental Analysis: Calc.: C: 26.25%, H: 2.20%, N: 15.31%; Found: C: 26.34%, H: 2.20%, N: 15.08%; mp = 94-96^{o} C.



10

10, (S)-1,3-Dichloro-5-benzylhydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 7.29 (m, 3H), 7.21 (m, 2H), 4.60 (m, 1H), 3.24 (m, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ 167.1, 153.3, 134.8, 130.7, 129.5, 128.5, 69.0, 34.9; IR (KBr, νcm^{-1}): 1742; Elemental Analysis: Calc.: C: 46.36%, H: 3.11%, N: 10.81%; Found: C: 46.12%, H: 3.13%, N: 10.88%; mp = 114-116^{o} C; $[\alpha]_D^{20}$ = + 27.5^{o} (c = 1.01, $CHCl_3$).



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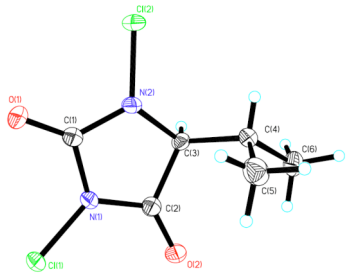
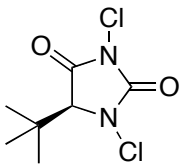


11, (S)-1,3-Dichloro-5-(*iso*-propyl)hydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 4.21 (d, J = 3.3 Hz, 1H), 2.35 (doublet of a septet, J_1 = 3.3 Hz, J_2 = 6.9 Hz, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.00, (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ 167.2, 154.3, 73.0, 29.9, 17.2; IR (KBr, νcm^{-1}): 1804, 1740; Elemental Analysis: Calc.: C: 34.15%, H: 3.82%, N: 13.27%; Found: C: 34.42%, H: 3.99%, N: 13.35%; mp = 130-132^{o} C; $[\alpha]_D^{20}$ = + 23.5^{o} (c = 1.15, $CHCl_3$).



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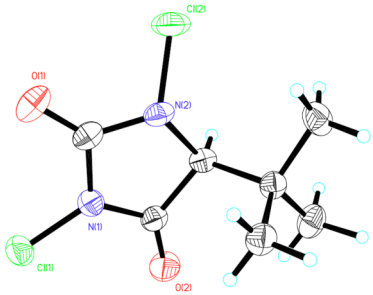


12, (S)-1,3-Dichloro-5-(*tert*-butyl)hydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ 3.99 (s, 1H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN): δ 167.4, 155.9, 77.7, 36.7, 26.2; IR (KBr, νcm^{-1}): 1802, 1746; Elemental Analysis: Calc.: C: 37.35%, H: 4.48%, N: 12.45%; Found: C: 37.90%, H: 4.59%, N: 12.57%; mp = 85-87^{o} C; $[\alpha]_D^{20}$ = + 7.2^{o} (c = 1.02, $CHCl_3$).

REFERENCES

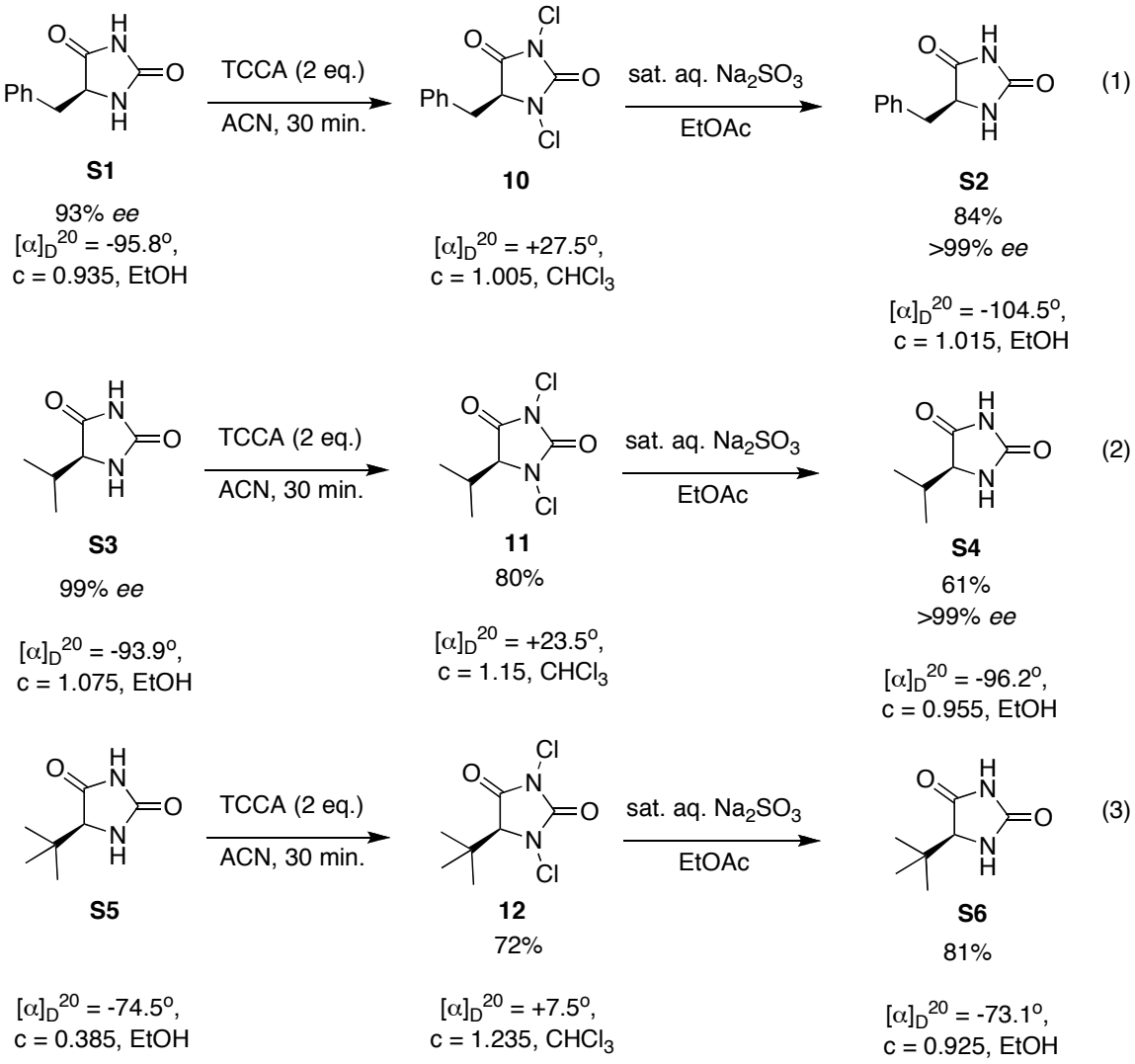
(1) Anteunis, M .J. O.; Spiessens, L.; Dewitte, M.; Callens, R.; Reyniers, F. *Bull. Soc. Chim. Belg.* **1987**, *96*, 459-465.

(2) Reist, M.; Carrupt, P. A.; Testa, B.; Lehmann, S.; Hansen, J. J. *Helv. Chim. Acta*, **1996**, *79*, 767-778.

(3) Lickefett, H.; Krohn, K.; Konig, W. A.; Gehrcke, B.; Syldatk, C. *Tetrahedron: Asymmetry* **1993**, *4*, 1129-1135.

(4) Reduction of chiral N-chlorinated hydantoins and confirmation of optical purity:

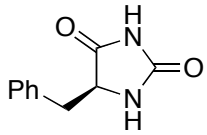
Chiral N-chlorohydantoins **10-12** were converted back to their parent chiral hydantoins by washing an ethyl acetate solution with saturated aqueous sodium sulfite. The optical rotation of the re-isolated, *non-recrystallized* parent hydantoin was in agreement with that of the starting chiral hydantoins prior to chlorination, thus confirming that the chlorination event does not errode the optical purity of the starting hydantoins:



Representative Procedure: Conversion of 10 to S2

(S)-5-Benzyl-1,3-dichlorohydantoin **10** (100 mg, 0.39 mmol) was dissolved in ethyl acetate (5 mL) in a 60 mL separatory funnel and washed with saturated aqueous sodium sulfite (5 mL) followed by saturated brine (5 mL). The organics were then dried over sodium sulfate and concentrated to give 62 mg (84%) of the reduced (S)-5-benzylhydantoin **S2**.

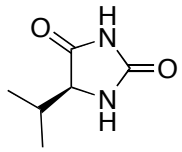
Analytical Data:



S2

S2, (S)-5-Benzylhydantoin:

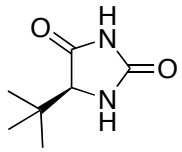
^{1}H NMR (300 MHz, CD_3CN): δ 8.43 (br s, 1H), 7.34 (m, 5H), 6.21 (br s, 1H), 4.29 (m, 1H), 3.00, (m, 2H); ^{13}C NMR (75 MHz, CD_3CN): δ 175.3, 157.47, 136.9, 130.6, 129.3, 127.9, 60.2, 37.8; $[\alpha]_D^{20}$ = -104.5° (c = 1.02, EtOH), synthetic (S)-5-benzylhydantoin **S1** (93% *ee*): -95.8° (c = 0.935, EtOH).



S4

S4, (S)-5-(*iso*-Propyl)hydantoin:

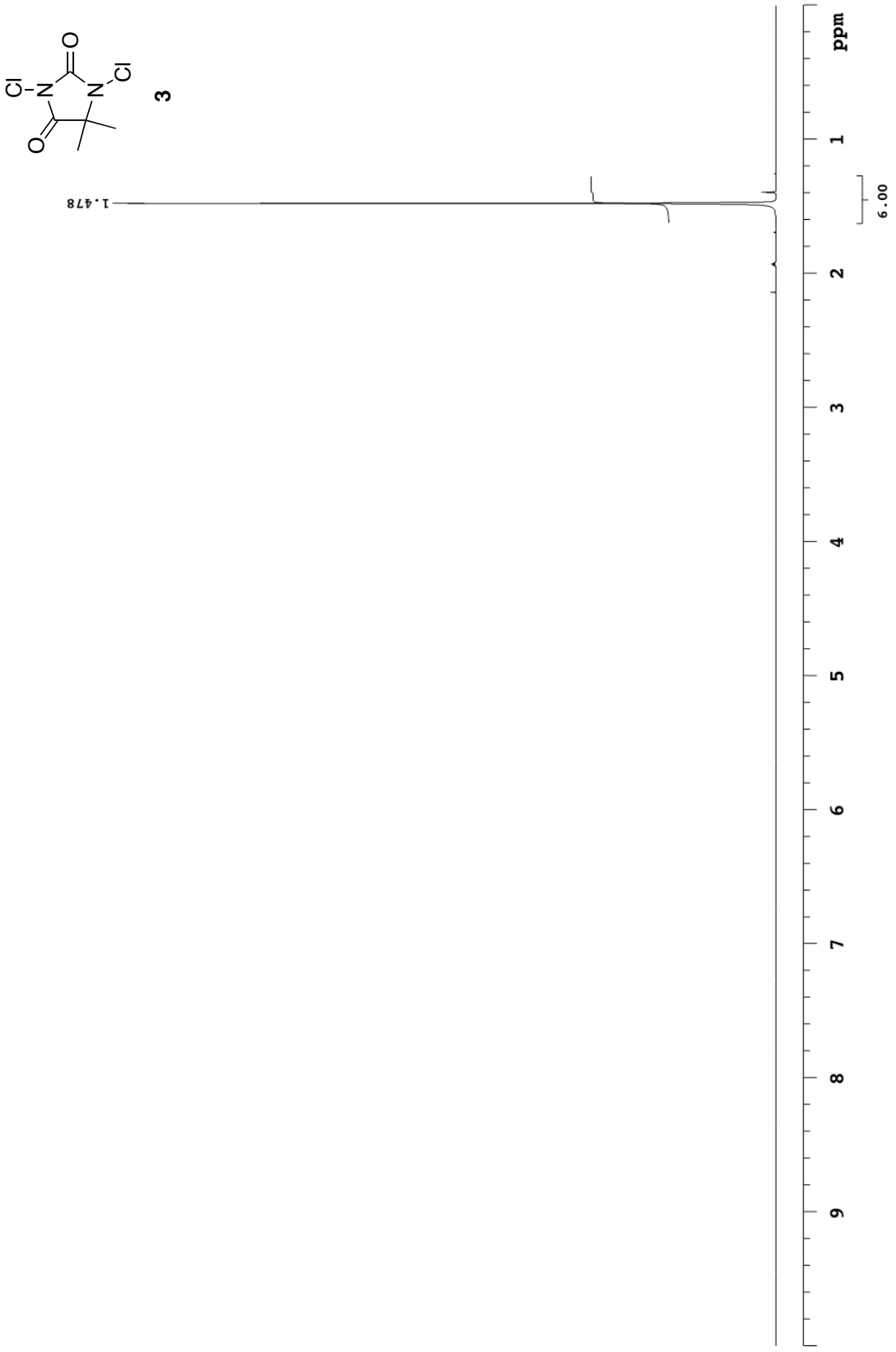
^{1}H NMR (300 MHz, CD_3CN): δ = 8.75 (br s, 1H), 6.35 (br s, 1H), 3.93 (dd, J_1 = 1.5 Hz, J_2 = 3.6 Hz, 1H), 2.08 (septet of doublets, J_1 = 3.6 Hz, J_2 = 6.6 Hz, 1H), 0.977 (d, J = 6.6, 3H), 0.863 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN): δ =175.8, 158.7, 64.4, 30.9, 18.9, 16.3; $[\alpha]_D^{20}$ = -96.2° (c = 0.955, EtOH), synthetic (S)-5-(*iso*-propyl)hydantoin **S3** (99% *ee*): -93.9° (c = 1.08, EtOH).



S6

S6, (S)-5-(*tert*-Butyl)hydantoin:

^{1}H NMR (300 MHz, CD_3CN): δ = 8.37 (br s, 1H), 6.18 (br s, 1H), 3.70 (d, J = 1.8 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN): δ = 174.9, 157.9, 67.5, 35.0, 25.7; $[\alpha]_D^{20}$ = -73.1° (c = 0.925, EtOH), synthetic (S)-5-(*tert*-butyl)hydantoin **S5**: -74.5° (c = 0.385, EtOH).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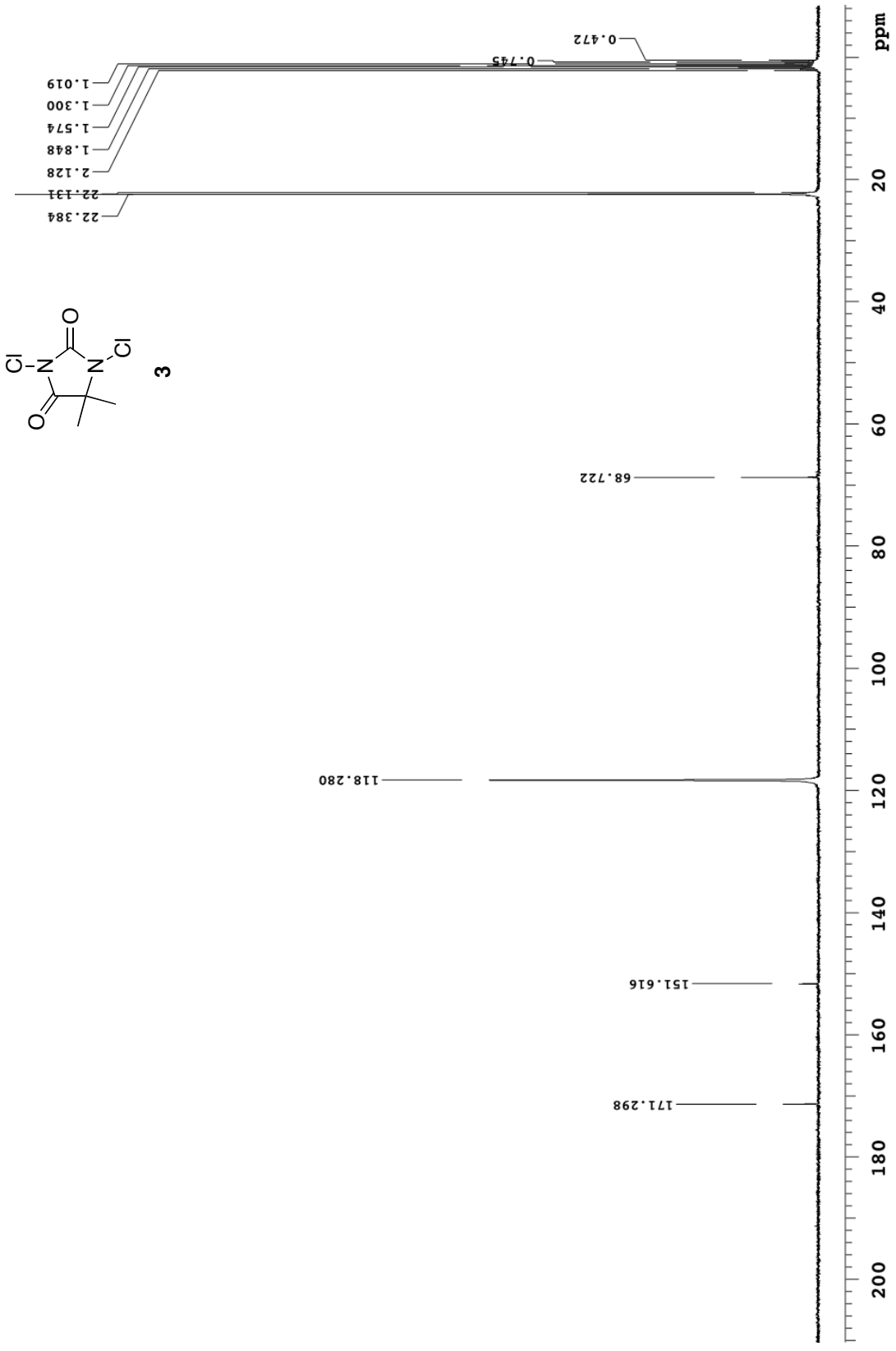
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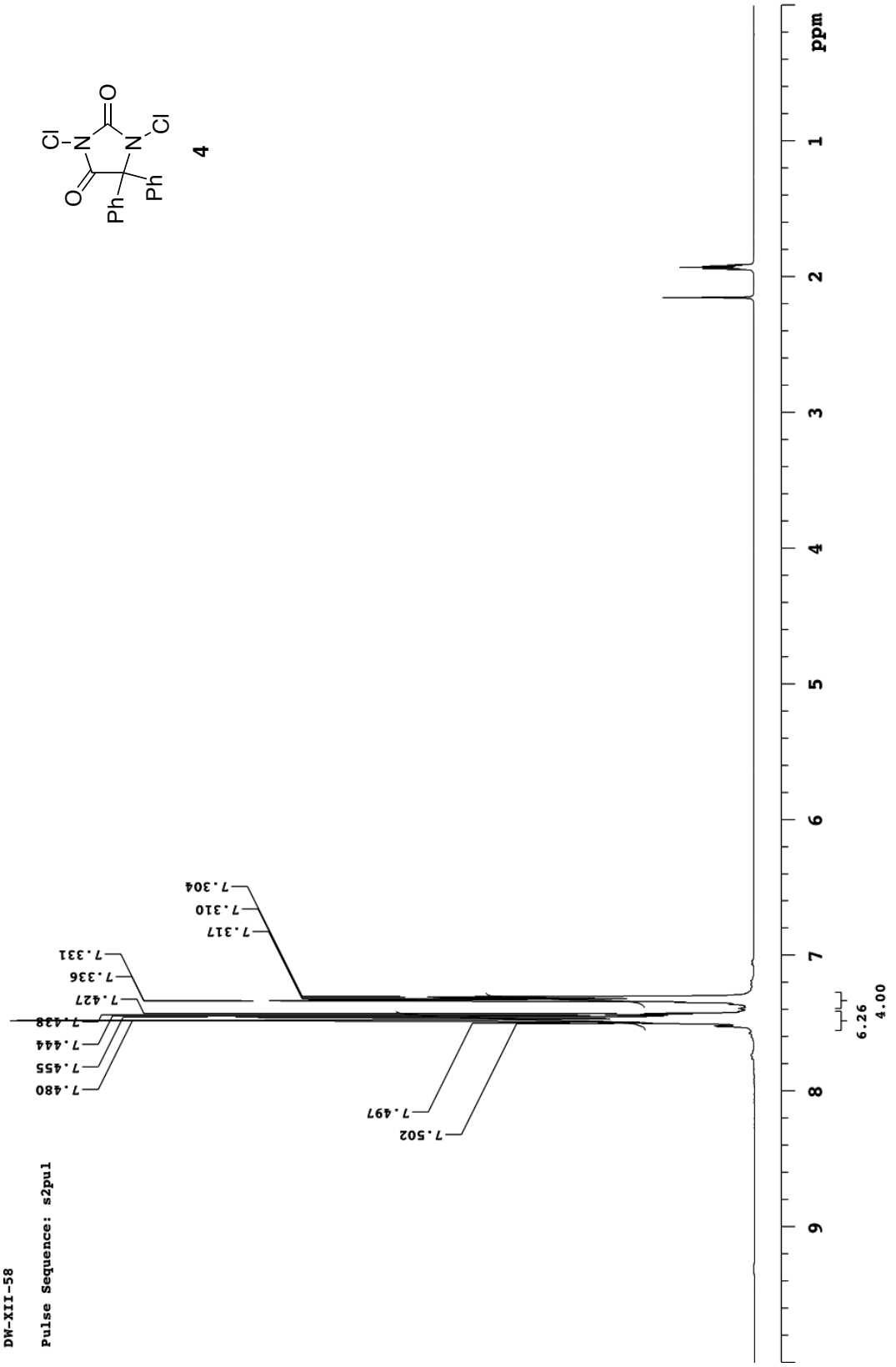
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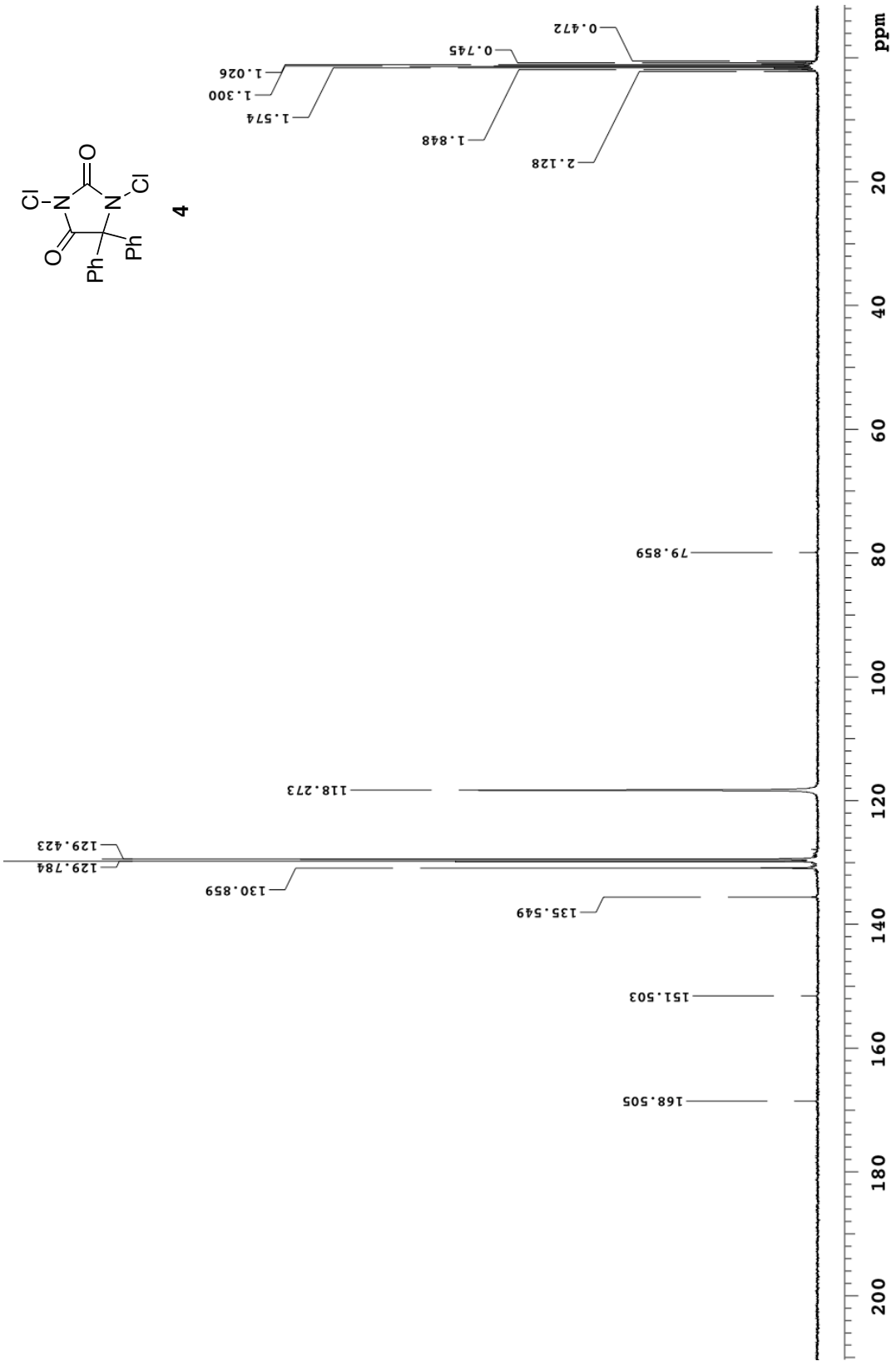
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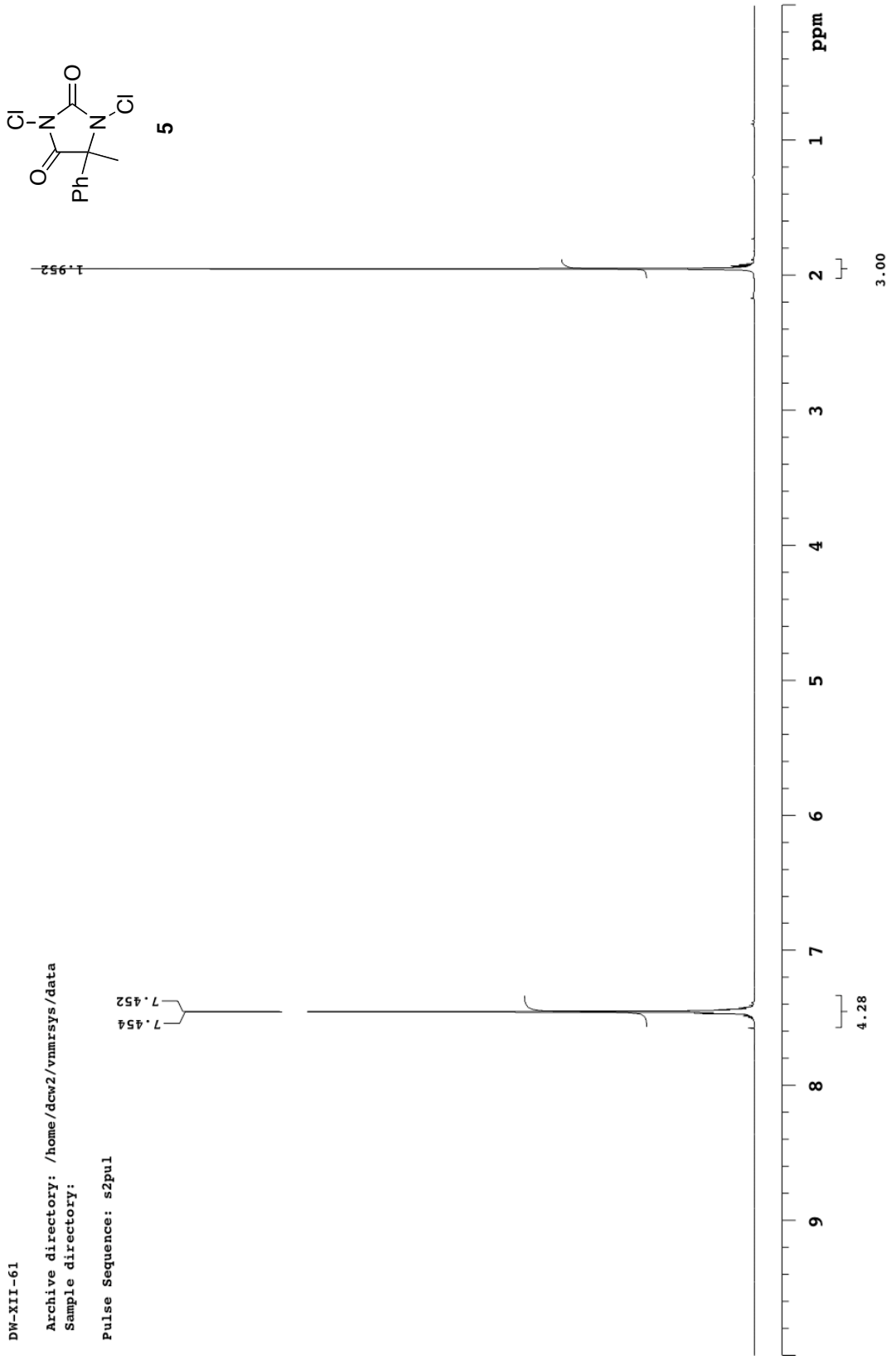
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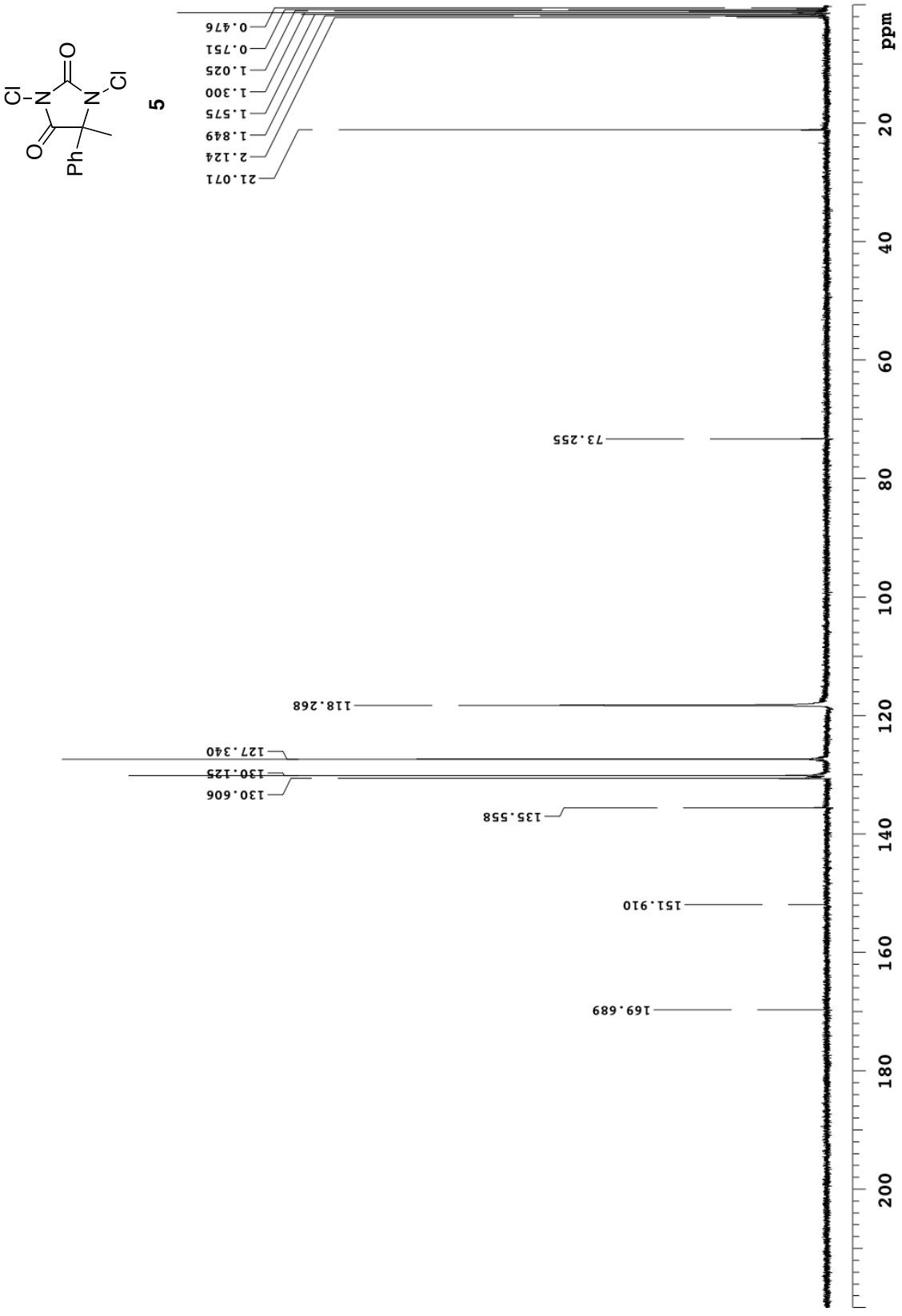
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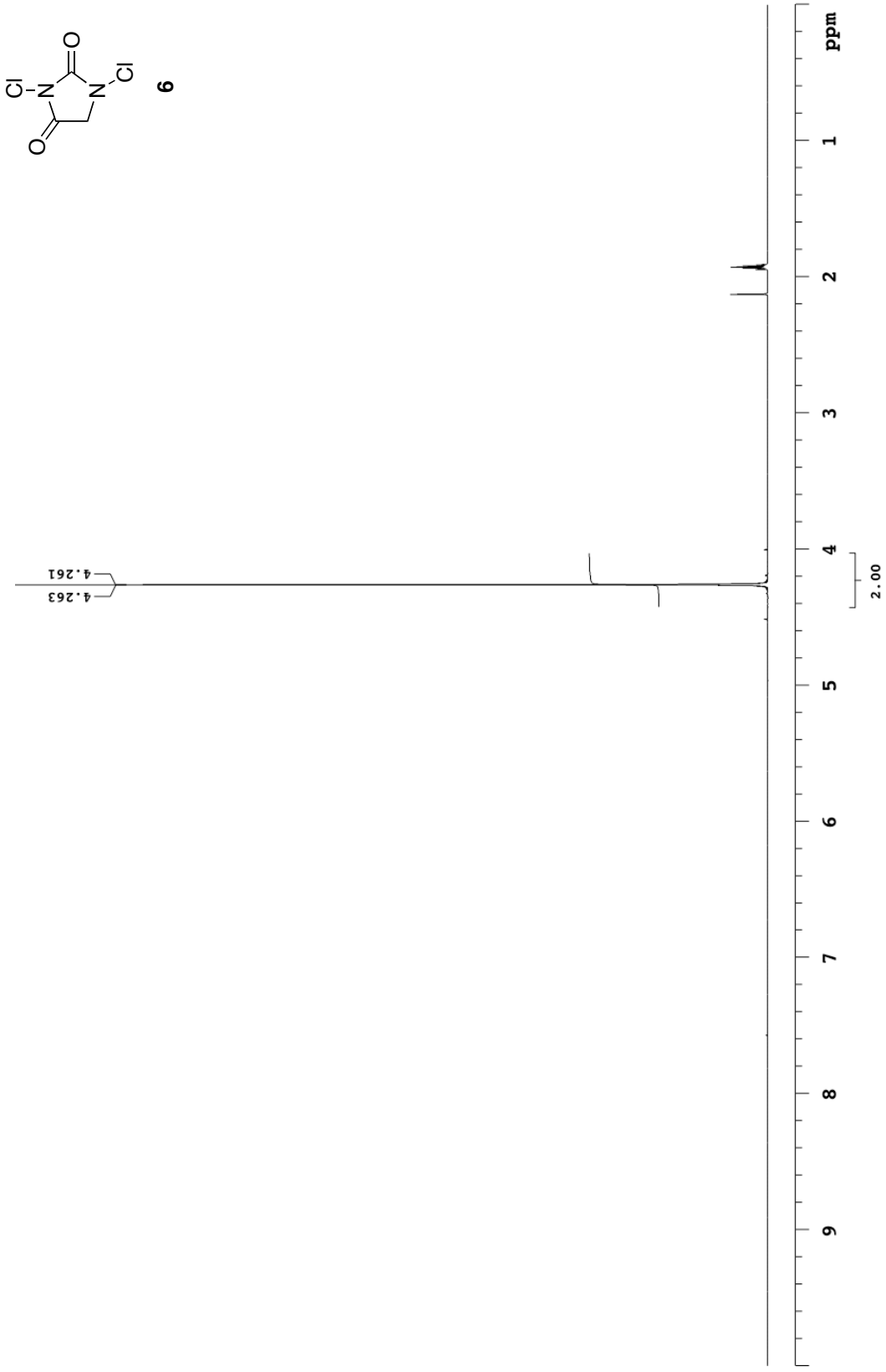
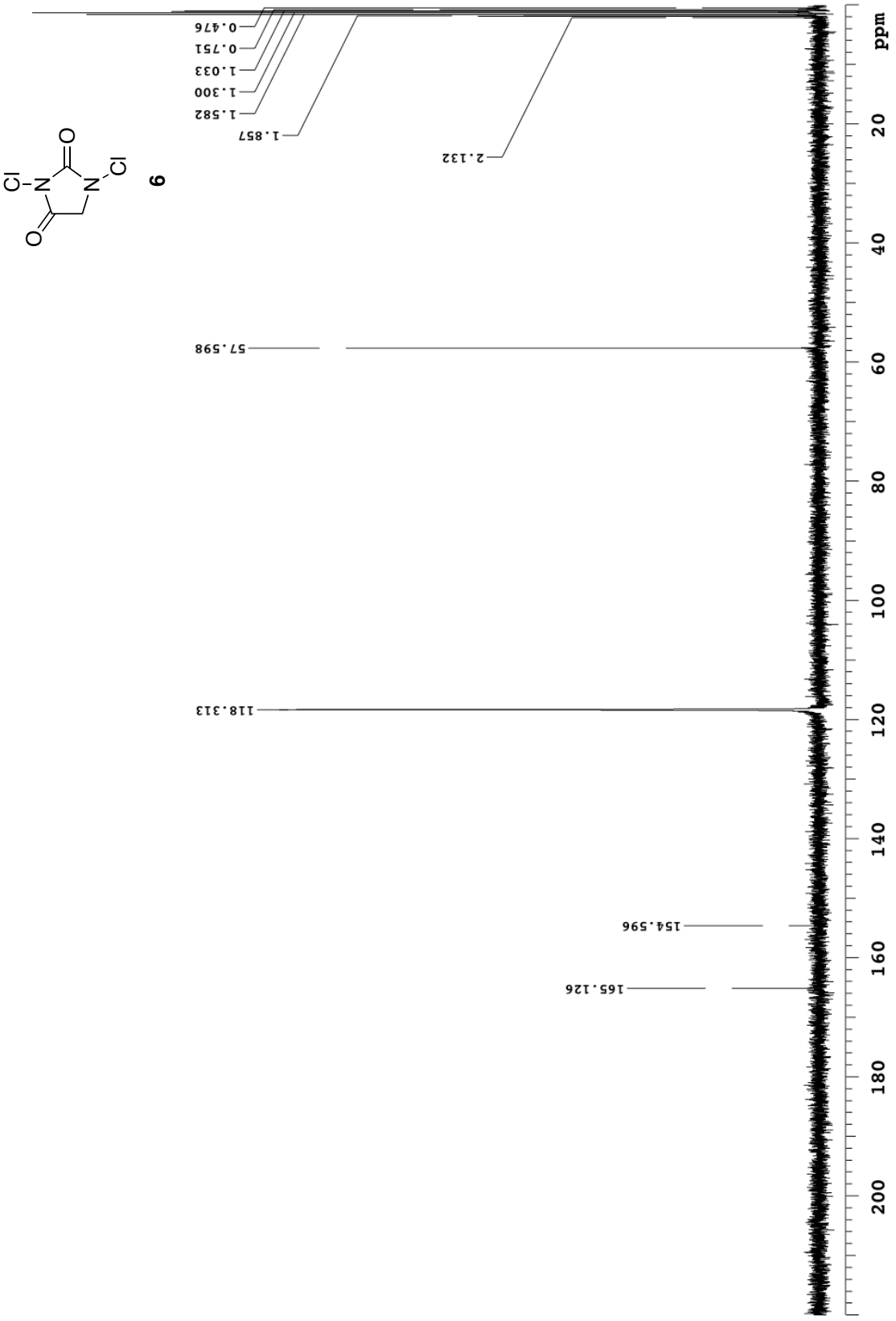
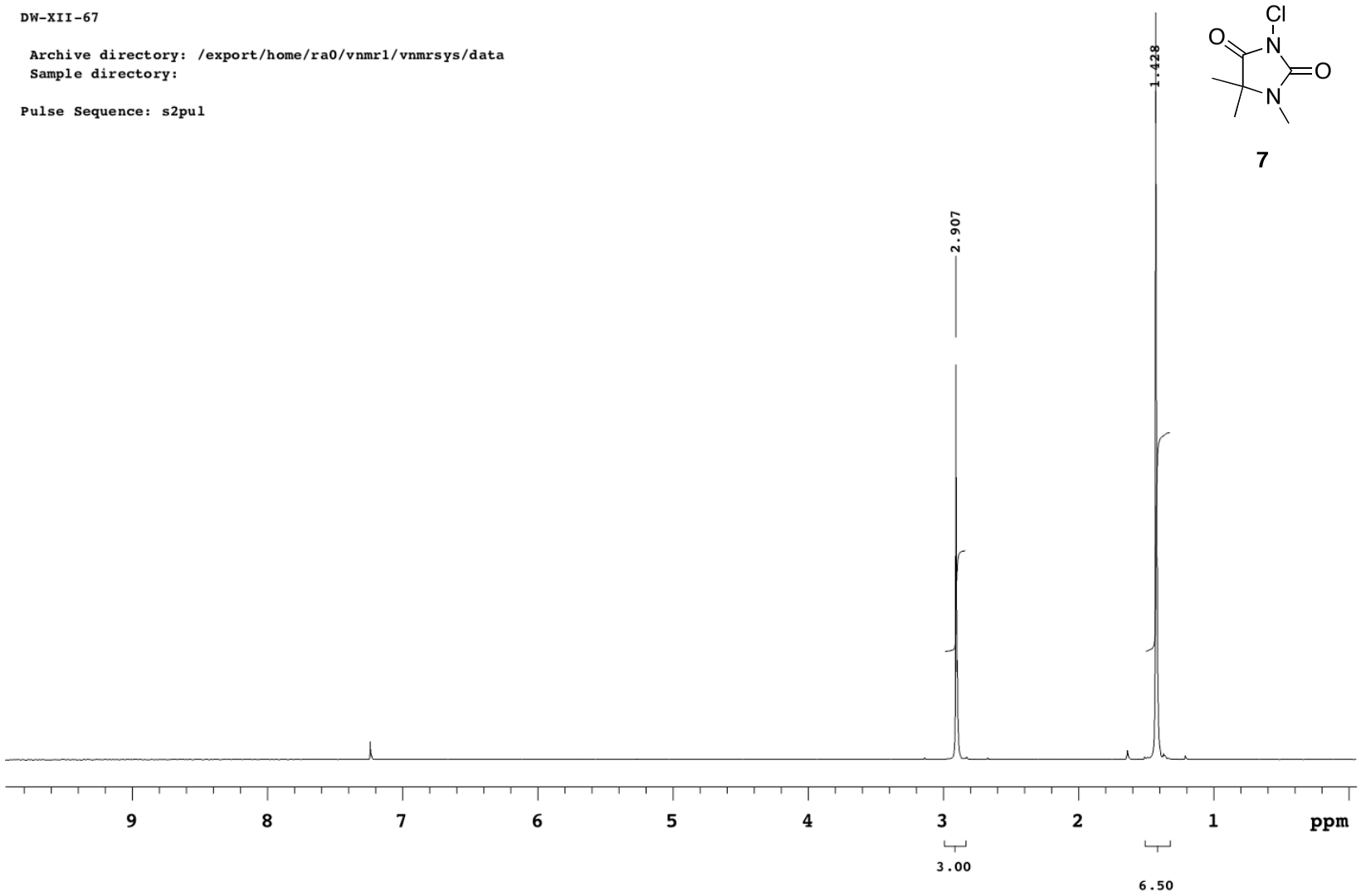
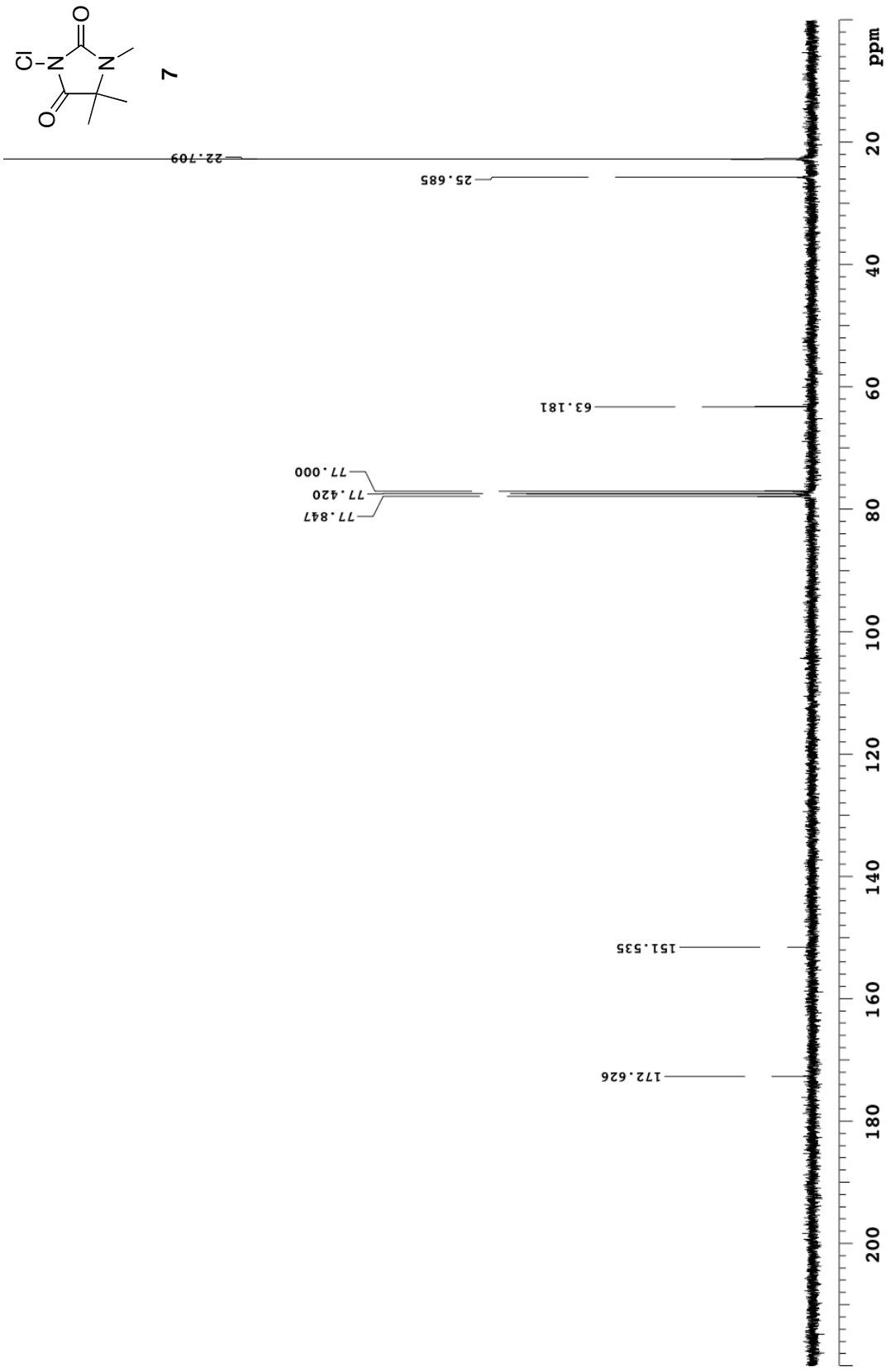
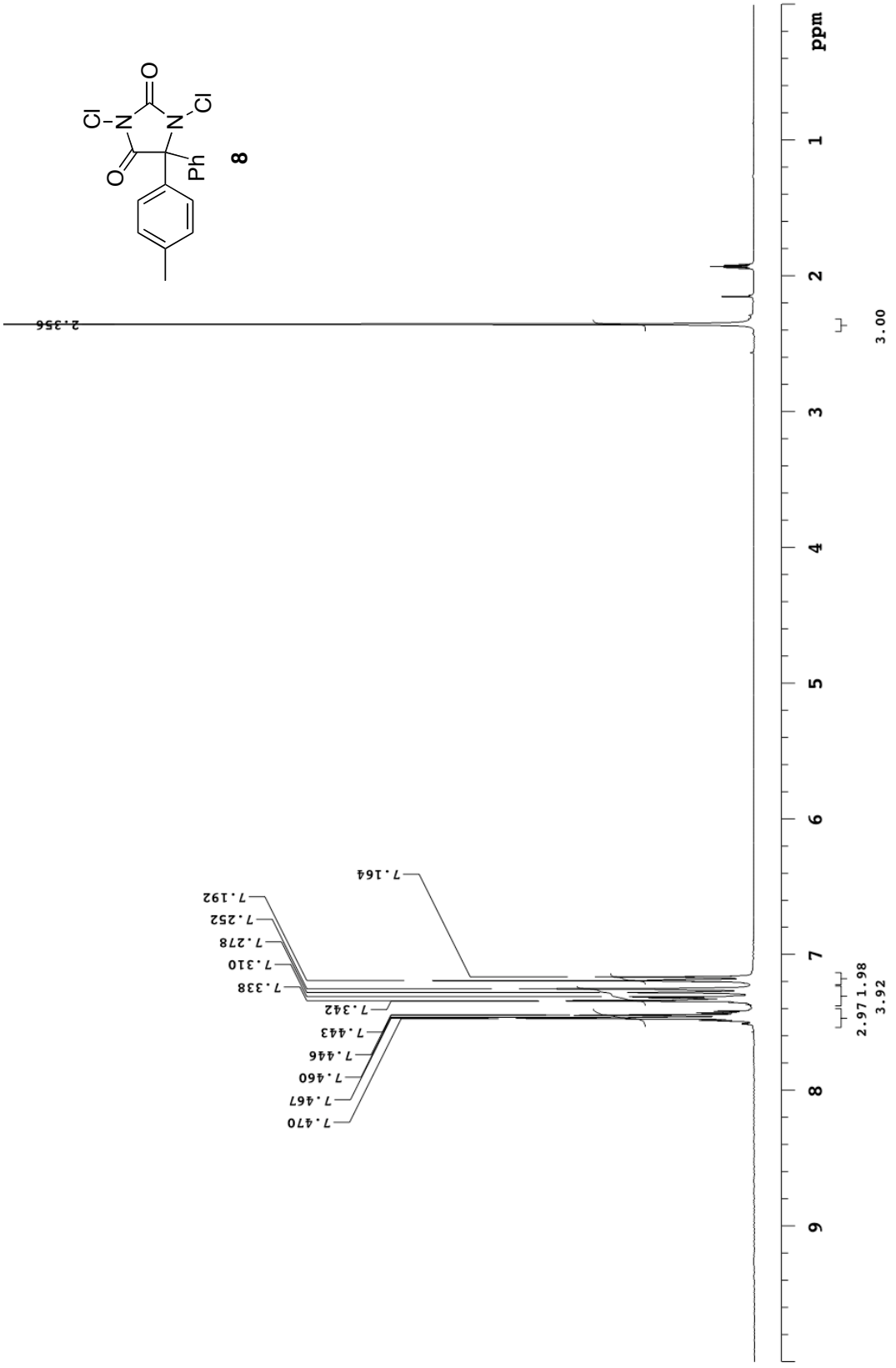
180
200

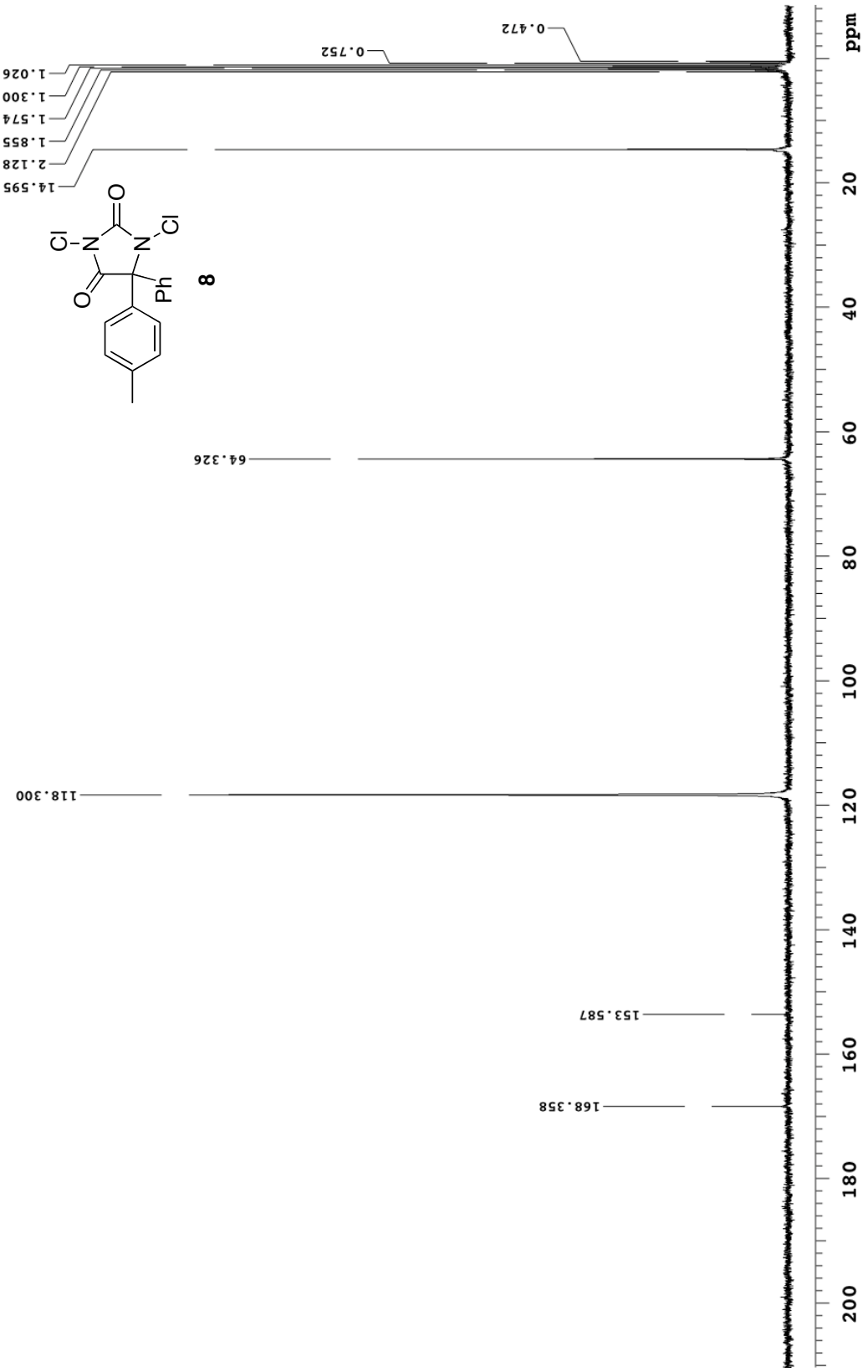

Cl
N
O
O
N
Cl
6
4.261
4.263
2.00
ppm
1
2
3
4
5
6
7
8
9

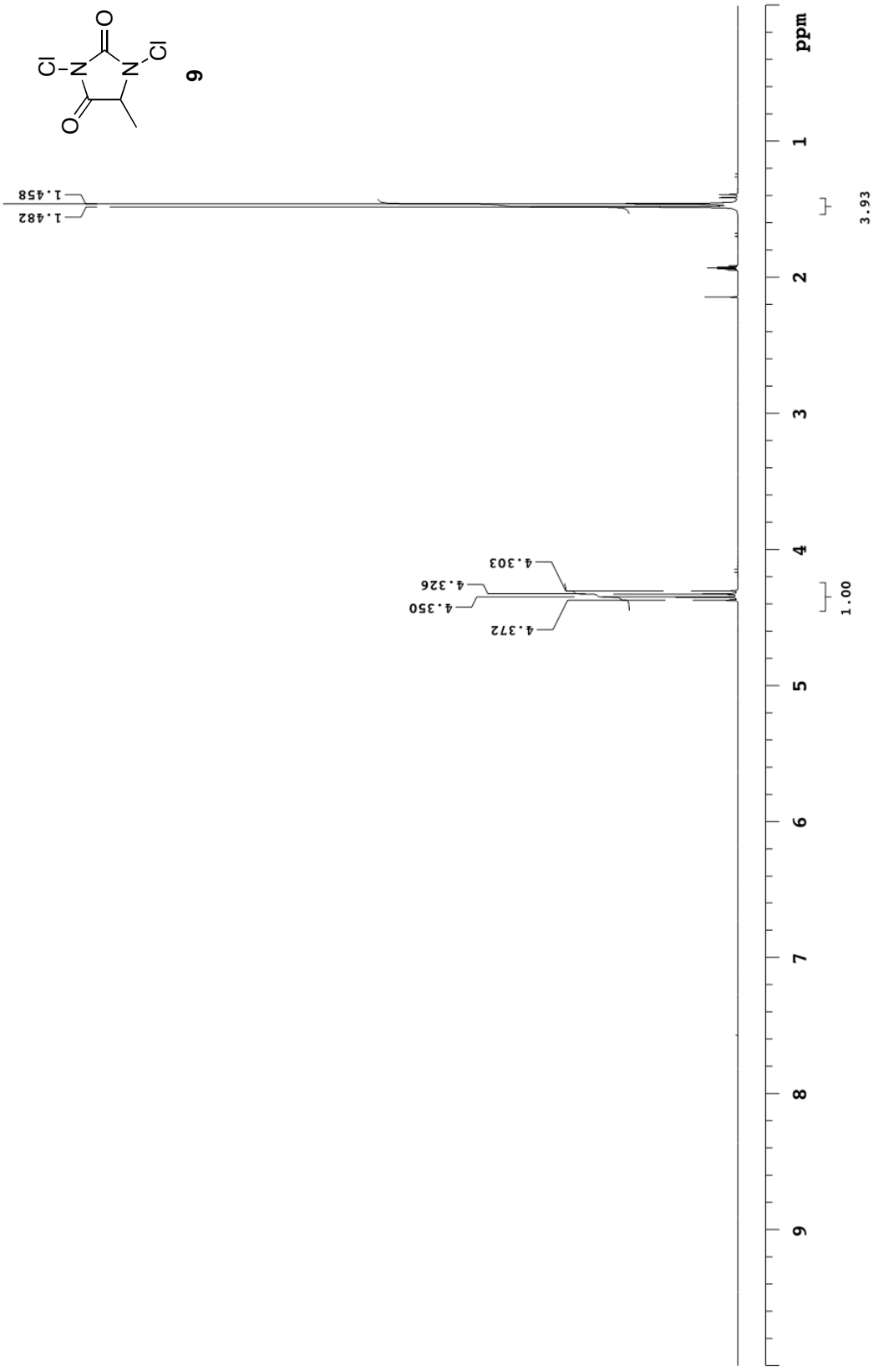

0.476
0.751
1.033
1.300
1.582
1.857
2.132
57.598
118.313
154.596
165.126
ppm
20
40
60
80
100
120
140
160
180
200
Cl
N
O
6


DW-XII-67
Archive directory: /export/home/ra0/vnmr1/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Cl
O
N
O
N
7
2.907
1.428
9
8
7
6
5
4
3
2
1
ppm
3.00
6.50

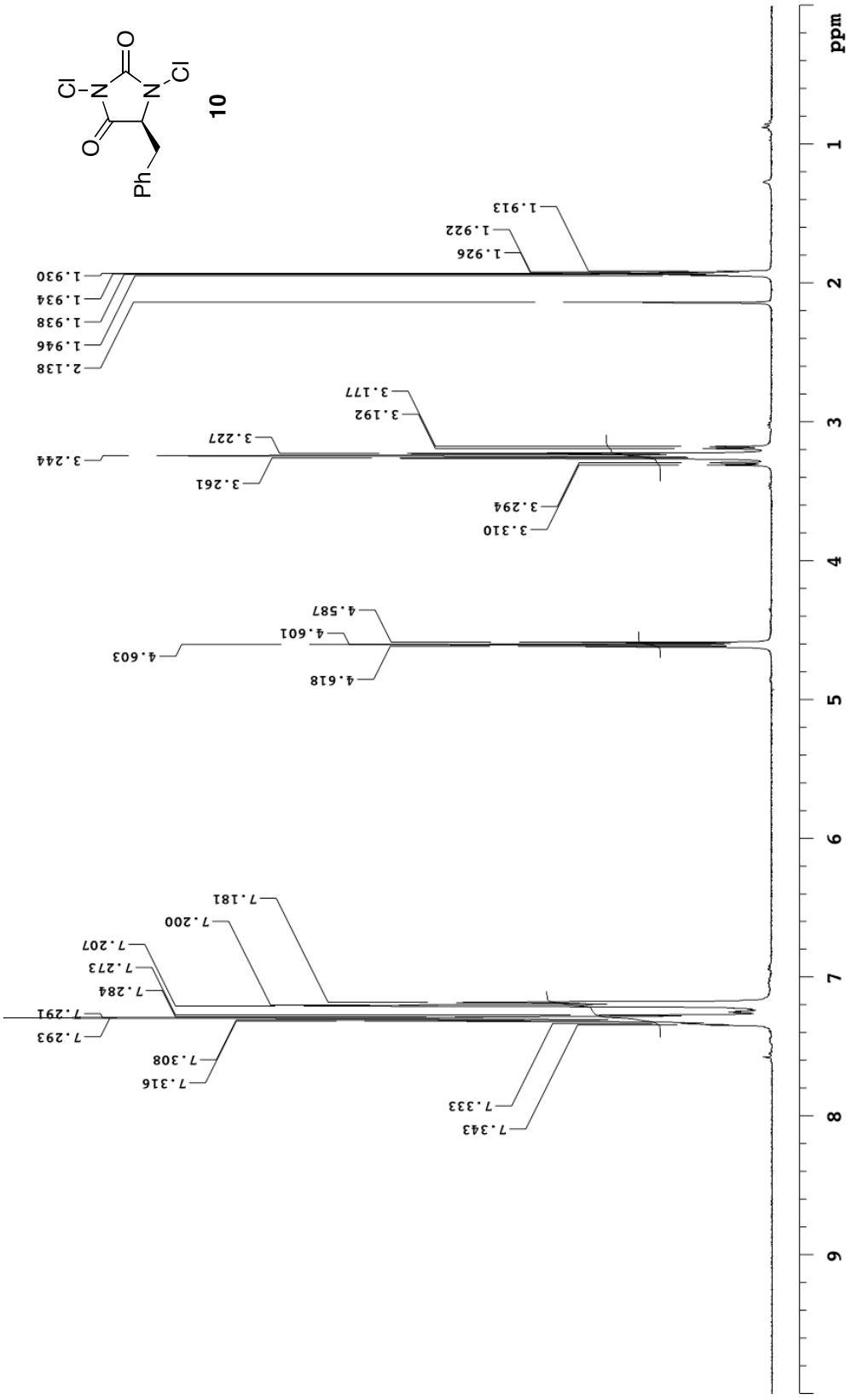

7
22.709
25.685
63.181
77.000
77.420
77.847
151.535
172.626
ppm
20
40
60
80
100
120
140
160
180
200

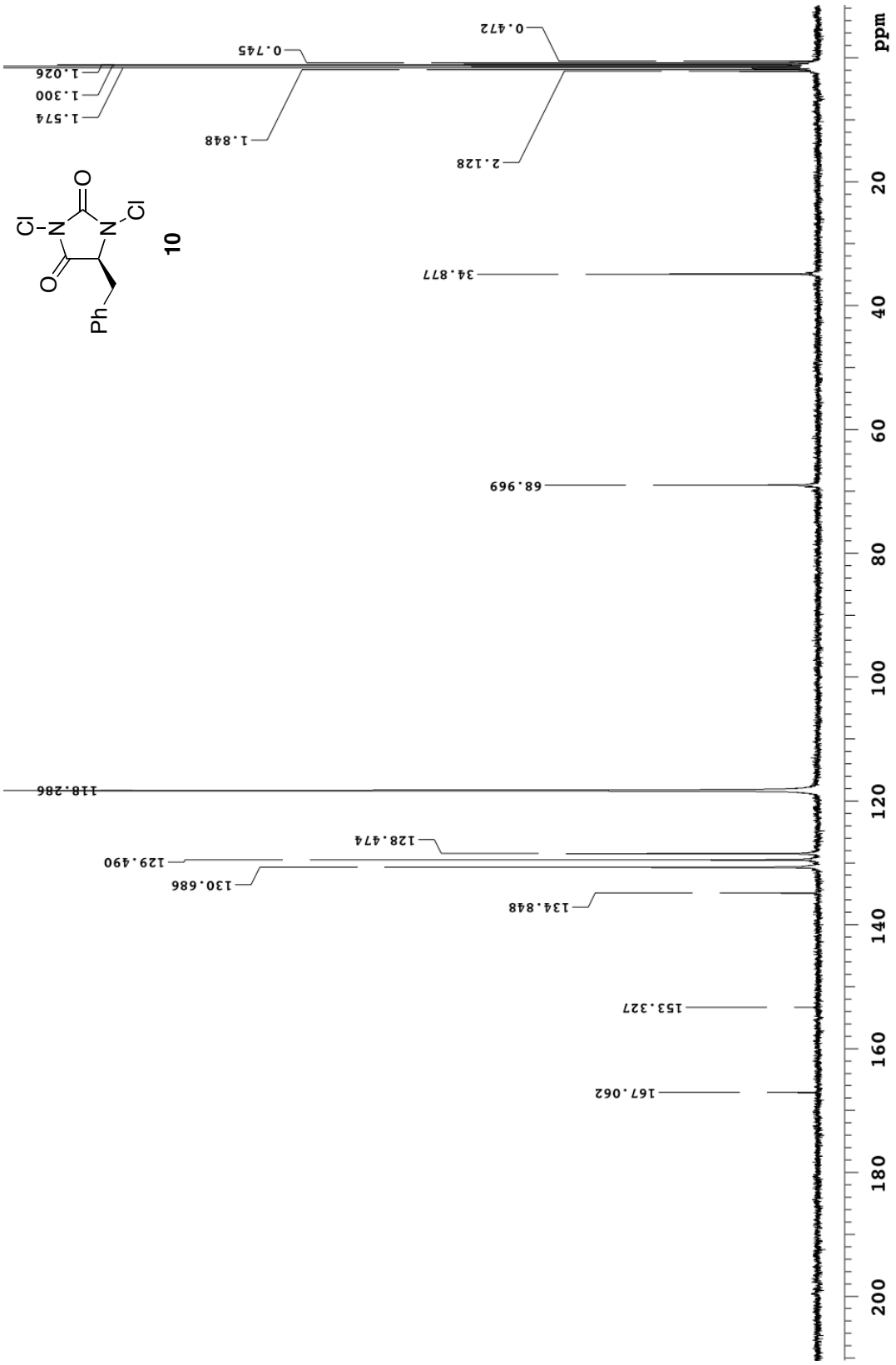

8
2.356
7.164
7.192
7.252
7.278
7.310
7.338
7.342
7.443
7.446
7.460
7.467
7.470
ppm
3.00
2.97
1.98
3.92

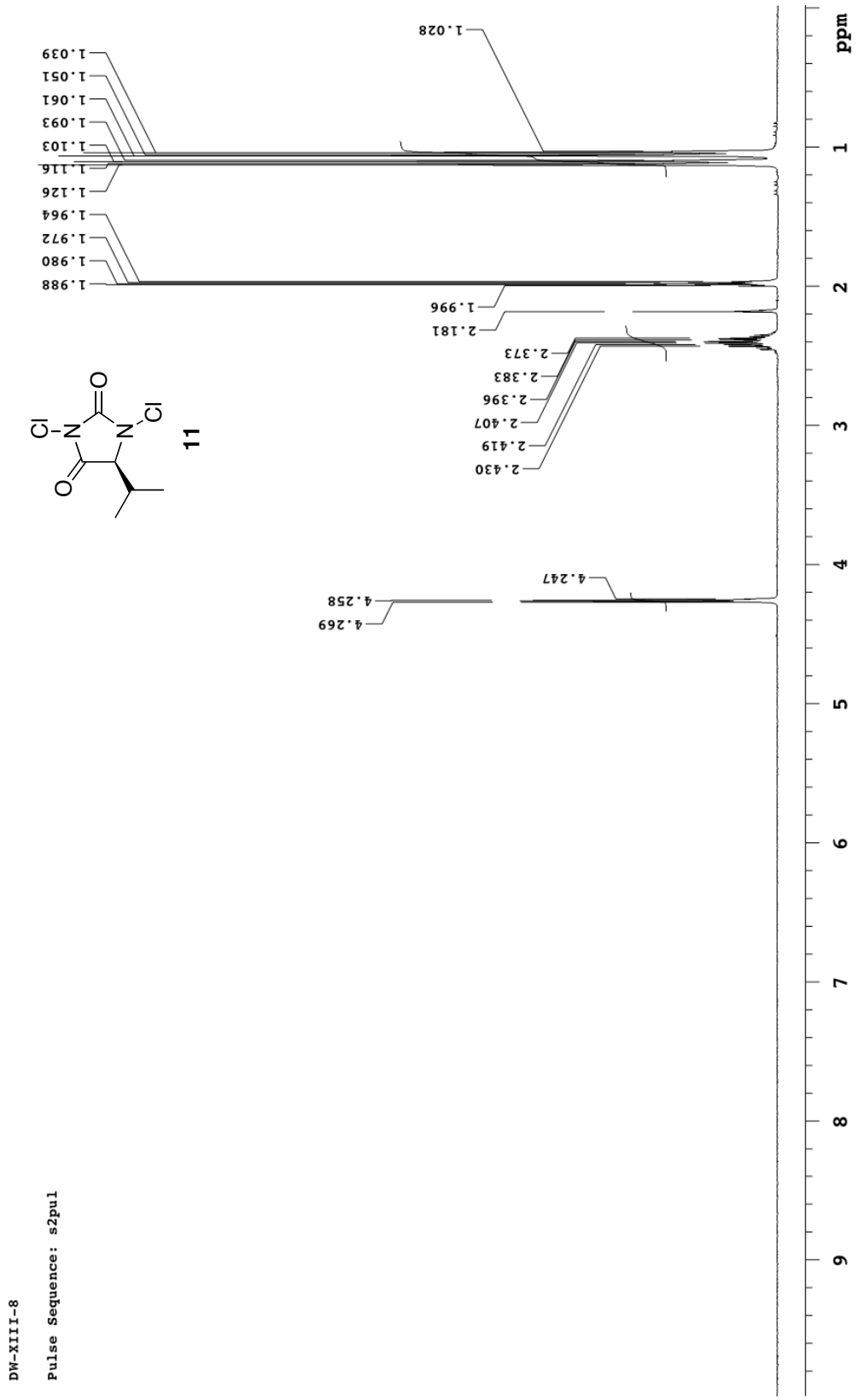

0.472
0.752
1.026
1.300
1.574
1.855
2.128
14.595
64.326
118.300
153.587
168.358
ppm
20
40
60
80
100
120
140
160
180
200
Cl
N
N
Cl
O
O
Ph
8

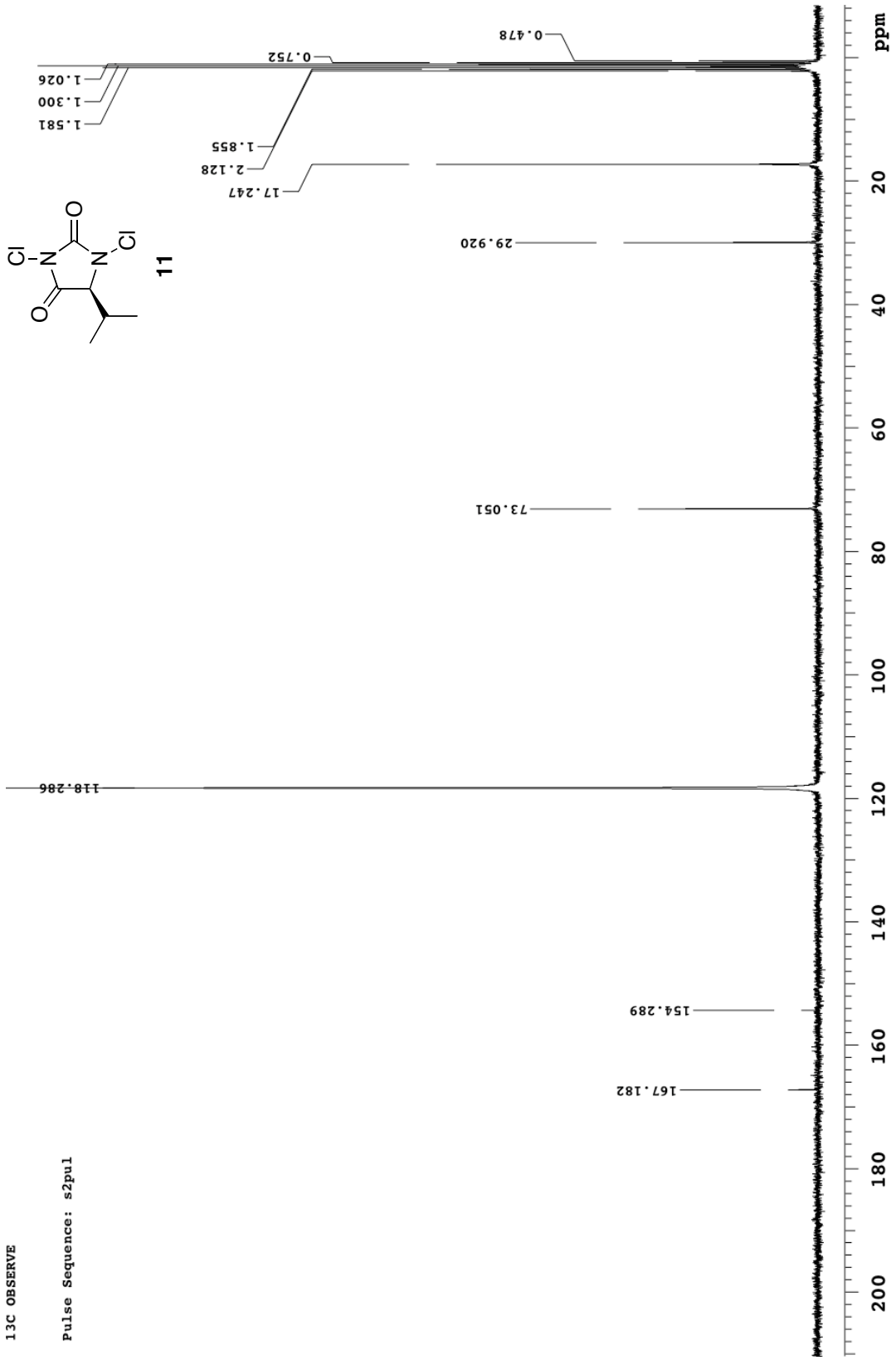

9
1.458
1.482
4.303
4.326
4.350
4.372
3.93
1.00
ppm

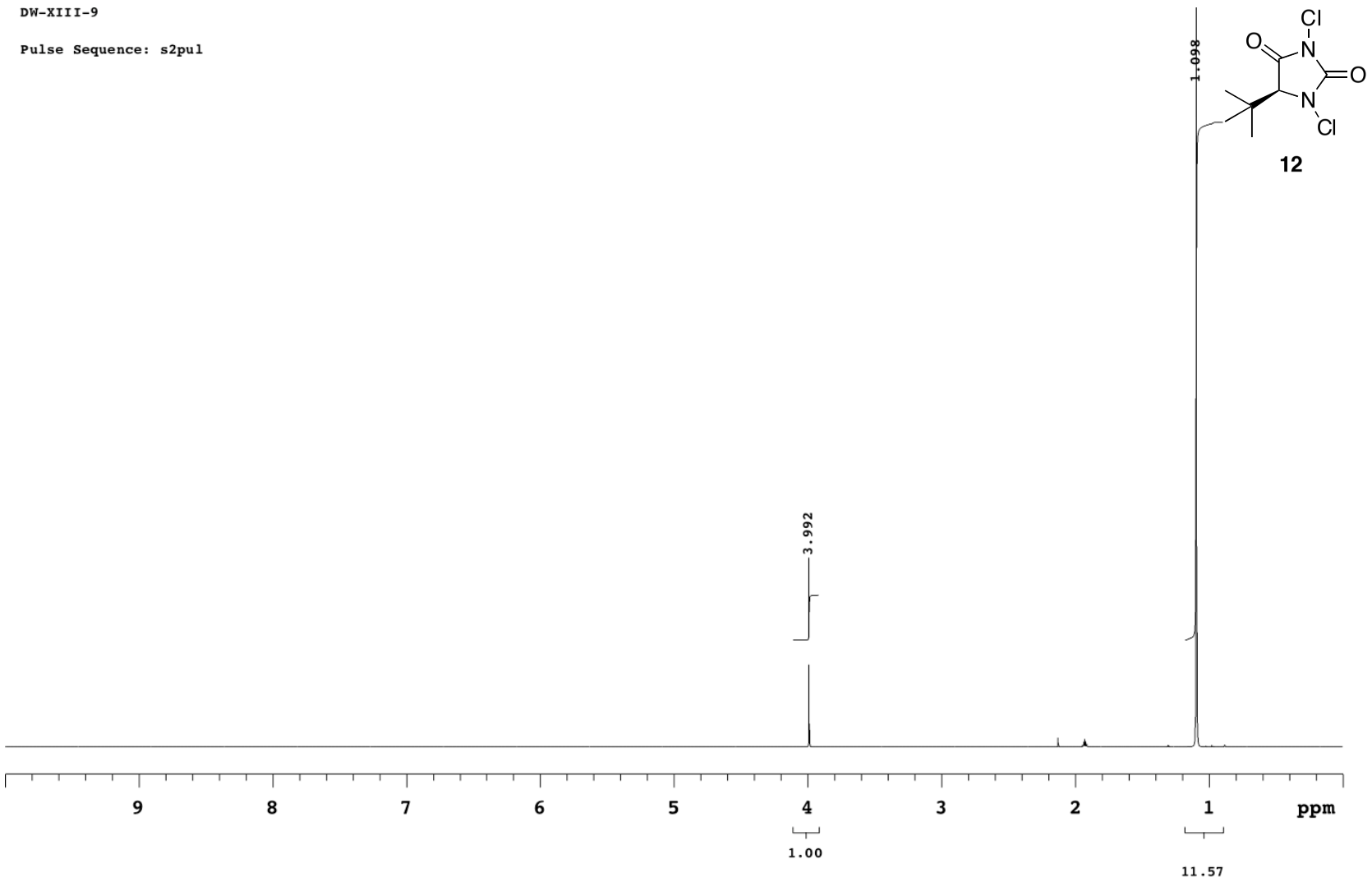
0.472
0.752
1.026
1.300
1.574
1.855
2.128
14.595
9
64.326
118.300
153.587
168.358
ppm
20
40
60
80
100
120
140
160
180
200

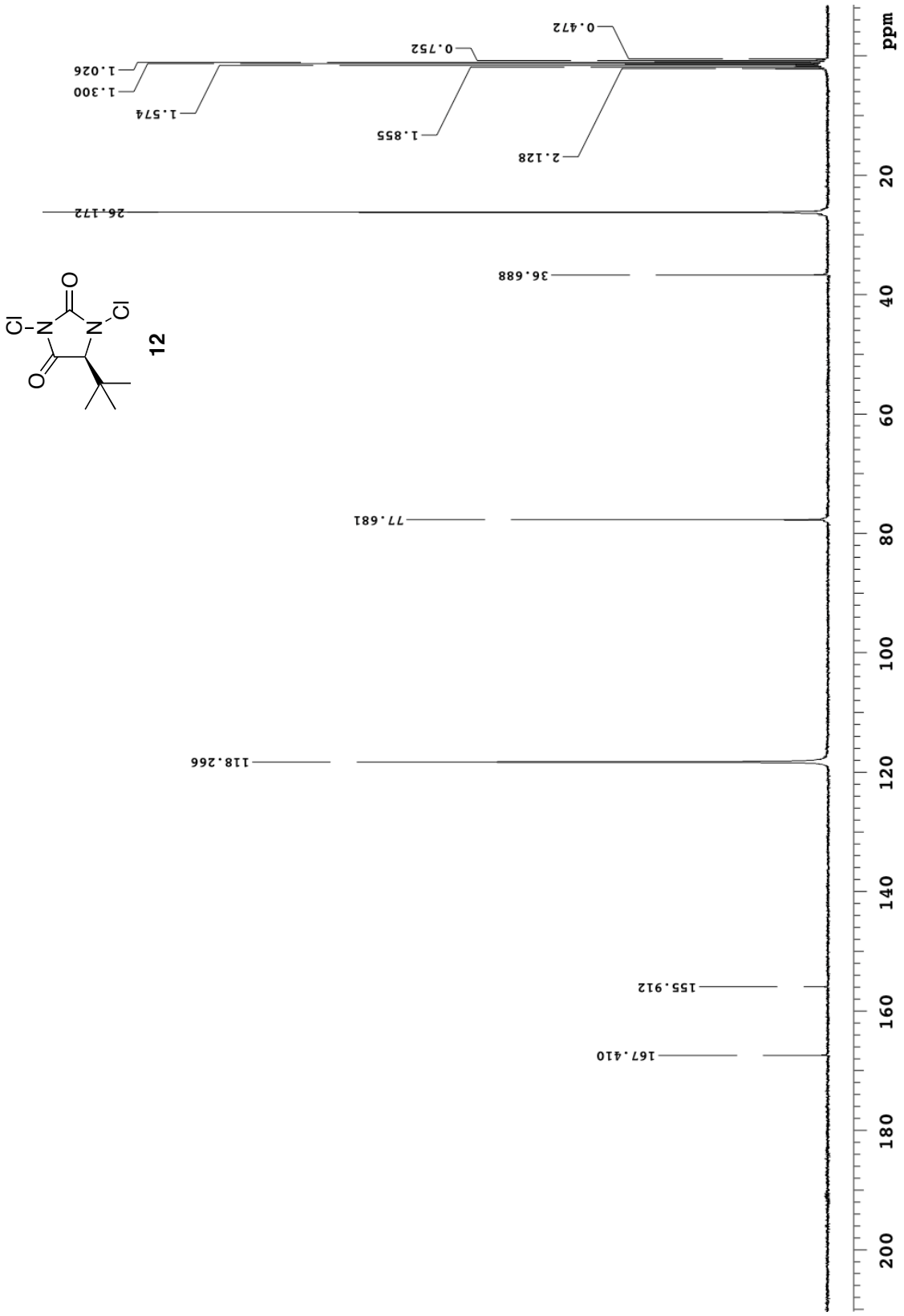

10
Cl
N
O
Ph
ppm
1.913
1.922
1.926
1.930
1.934
1.938
1.946
2.138
3.177
3.192
3.227
3.244
3.261
3.294
3.310
4.587
4.601
4.603
4.618
7.181
7.200
7.207
7.273
7.284
7.291
7.293
7.308
7.316
7.333
7.343


0.472
0.745
1.026
1.300
1.574
1.848
2.128
34.877
68.969
118.286
128.474
129.490
130.686
134.848
153.327
167.062
ppm
20
40
60
80
100
120
140
160
180
200
Cl
N
O
Ph
10


DW-XIII-8
Pulse Sequence: s2pul
11
1.028
1.039
1.051
1.061
1.093
1.103
1.116
1.126
1.964
1.972
1.980
1.988
1.996
2.181
2.373
2.383
2.396
2.407
2.419
2.430
4.247
4.258
4.269
ppm


13C OBSERVE
Pulse Sequence: s2pul
118.286
167.182
154.289
73.051
29.920
17.247
2.128
1.855
1.581
1.300
1.026
0.752
0.478
ppm
11


DW-XIII-9
Pulse Sequence: s2pul
1.098
3.992
9
8
7
6
5
4
3
2
1
ppm
1.00
11.57
Cl
O
N
O
N
Cl
12


0.472
0.752
1.026
1.300
1.574
1.855
2.128
26.172
36.688
77.681
118.266
155.912
167.410
ppm
20
40
60
80
100
120
140
160
180
200
Cl
N
O
O
N
Cl
12