Macrolactamization versus macrolactonization: Total synthesis of FK228, the depsipeptide histone deacetylase inhibitor.

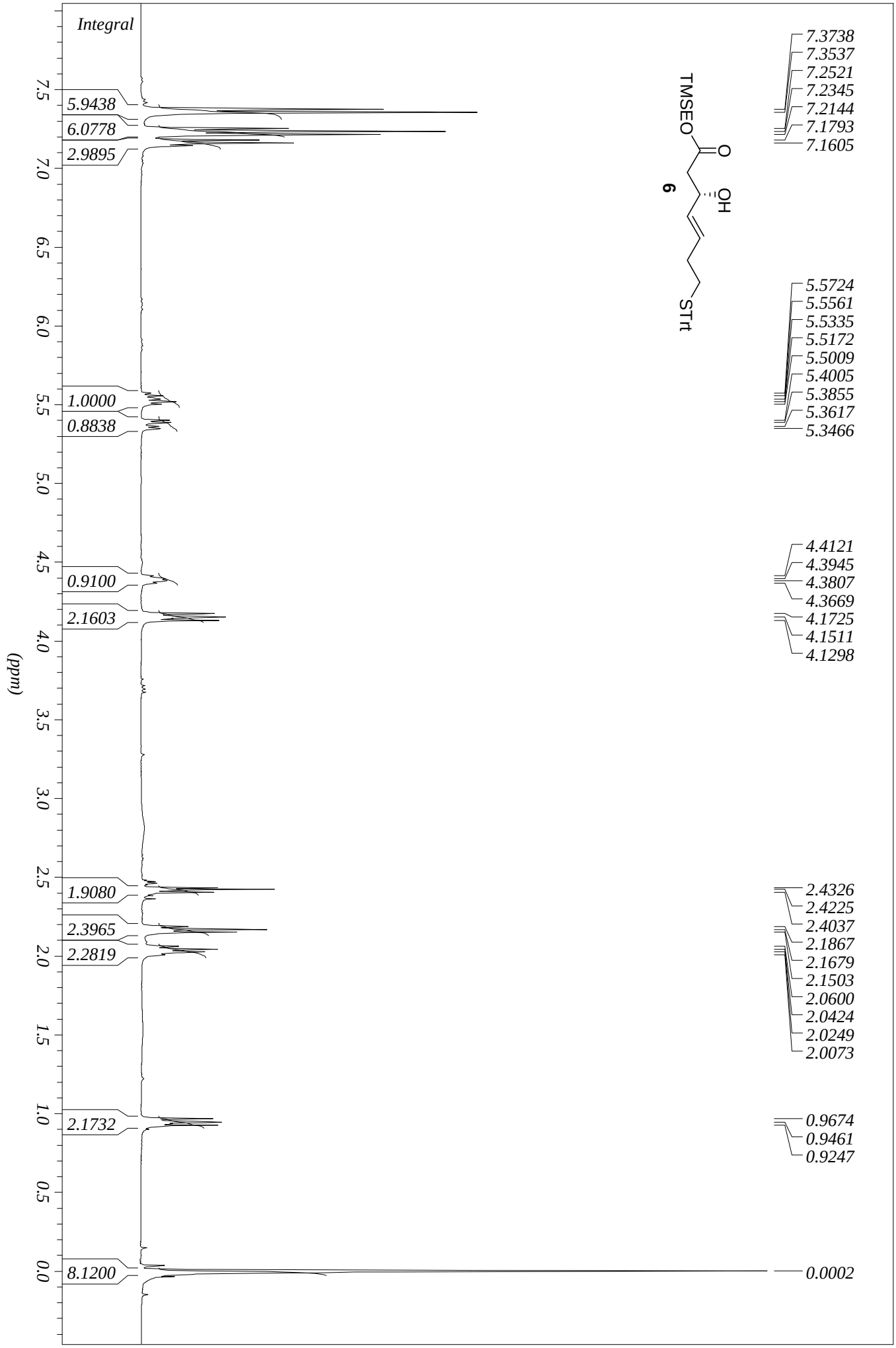
Shijun Wen, Graham Packham and A. Ganesan

Supporting Information

General experimental methods

Chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous dichloromethane was freshly distilled from calcium hydride and tetrahydrofuran from sodium wire with benzophenone as indicator. All other anhydrous solvents were purchased as Aldrich sure-seal® bottles. Analytical TLC was carried out on pre-coated plastic plates, normal phase Merck 60 F_{254} silica plates. Visualization was carried out either with short-wave UV, or staining with aqueous potassium permanganate or phosphomolybdic acid. Column chromatography was performed using silica (Apollo, 70-230 mesh). Melting points were taken on a hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz respectively. Chemical shifts are given in ppm. Characteristic splitting patterns due to spin spin coupling are expressed as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All coupling constants are measured in Hertz. Low resolution mass spectra were obtained by electrospray ionization and high resolution mass spectra by FT-ICR.

General workup for peptide coupling reactions. The reaction mixture was cooled (ice bath) followed by addition of sat aq NH_4Cl. The phases were separated and the aqueous phase extracted with dichloromethane or EtOAc. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography.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OH
STrt
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7.0
6.5
6.0
5.5
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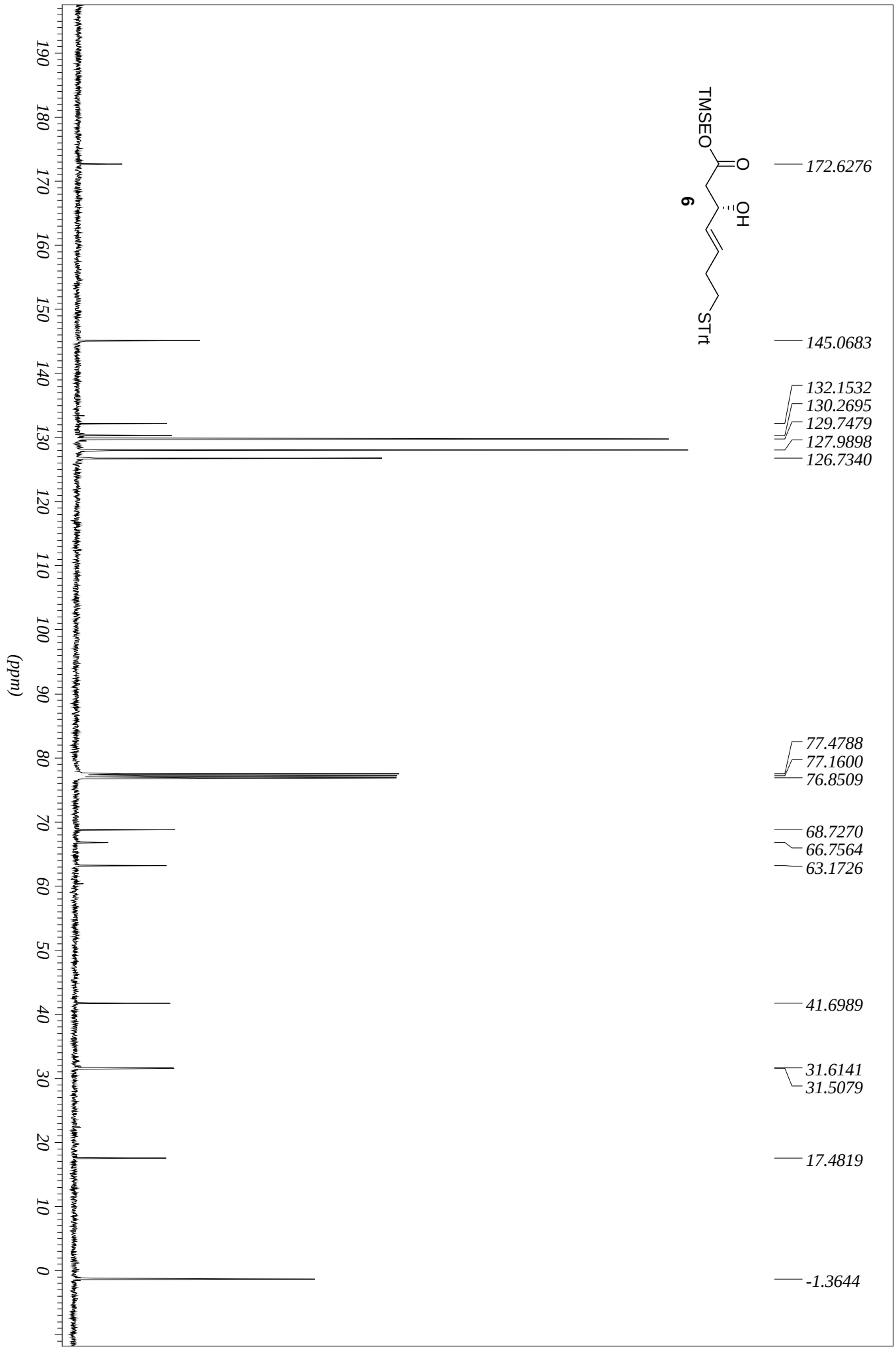
(ppm)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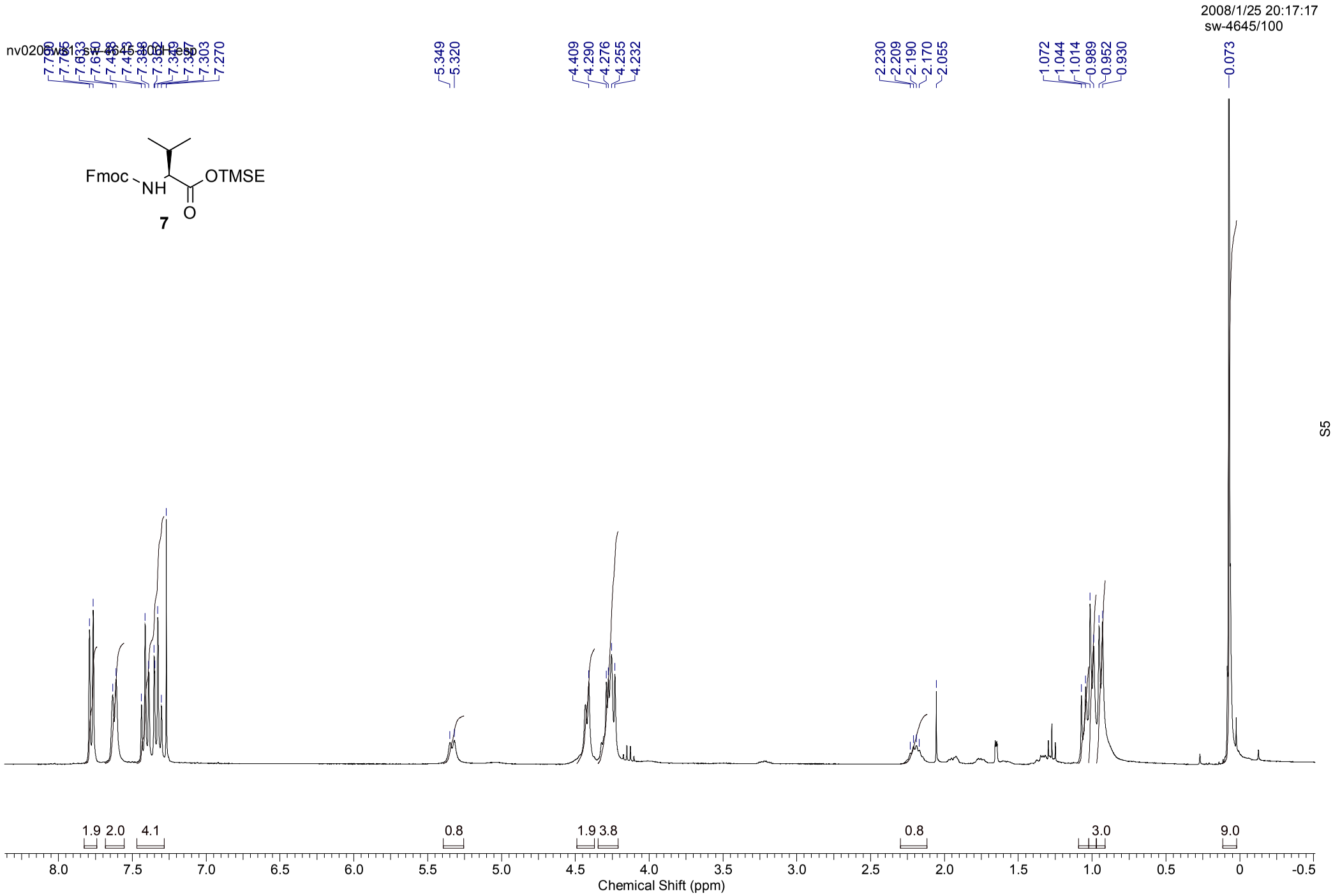
(ppm)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4.290
4.276
4.255
4.232
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2.209
2.190
2.170
2.055
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1.044
1.014
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NH
OTMSE
O
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4.1
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1.9
3.8
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3.0
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8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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2.0
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1.0
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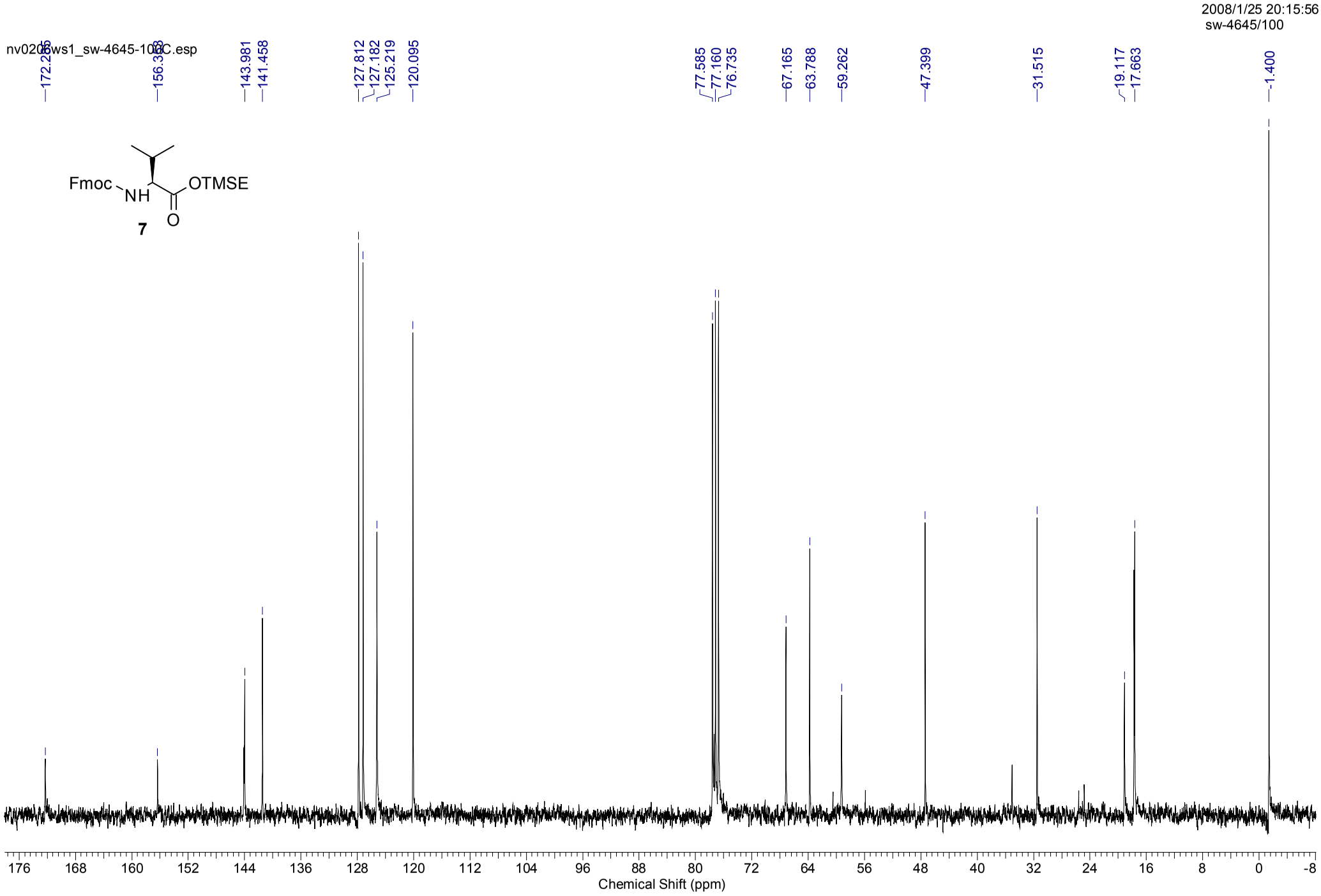
Chemical Shift (ppm)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NH
O
OTMSE
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S6
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160
152
144
136
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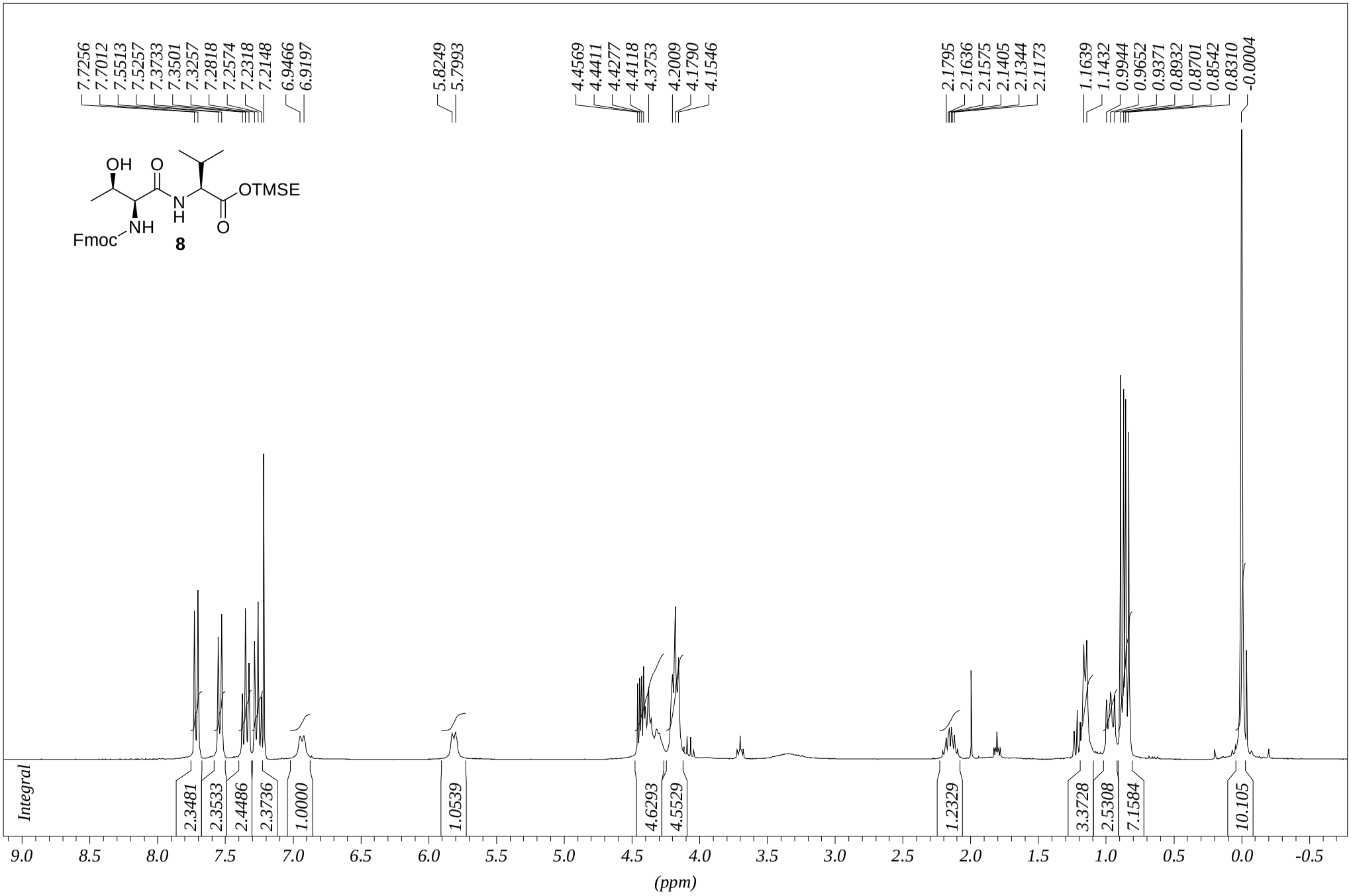
Chemical Shift (ppm)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6.0
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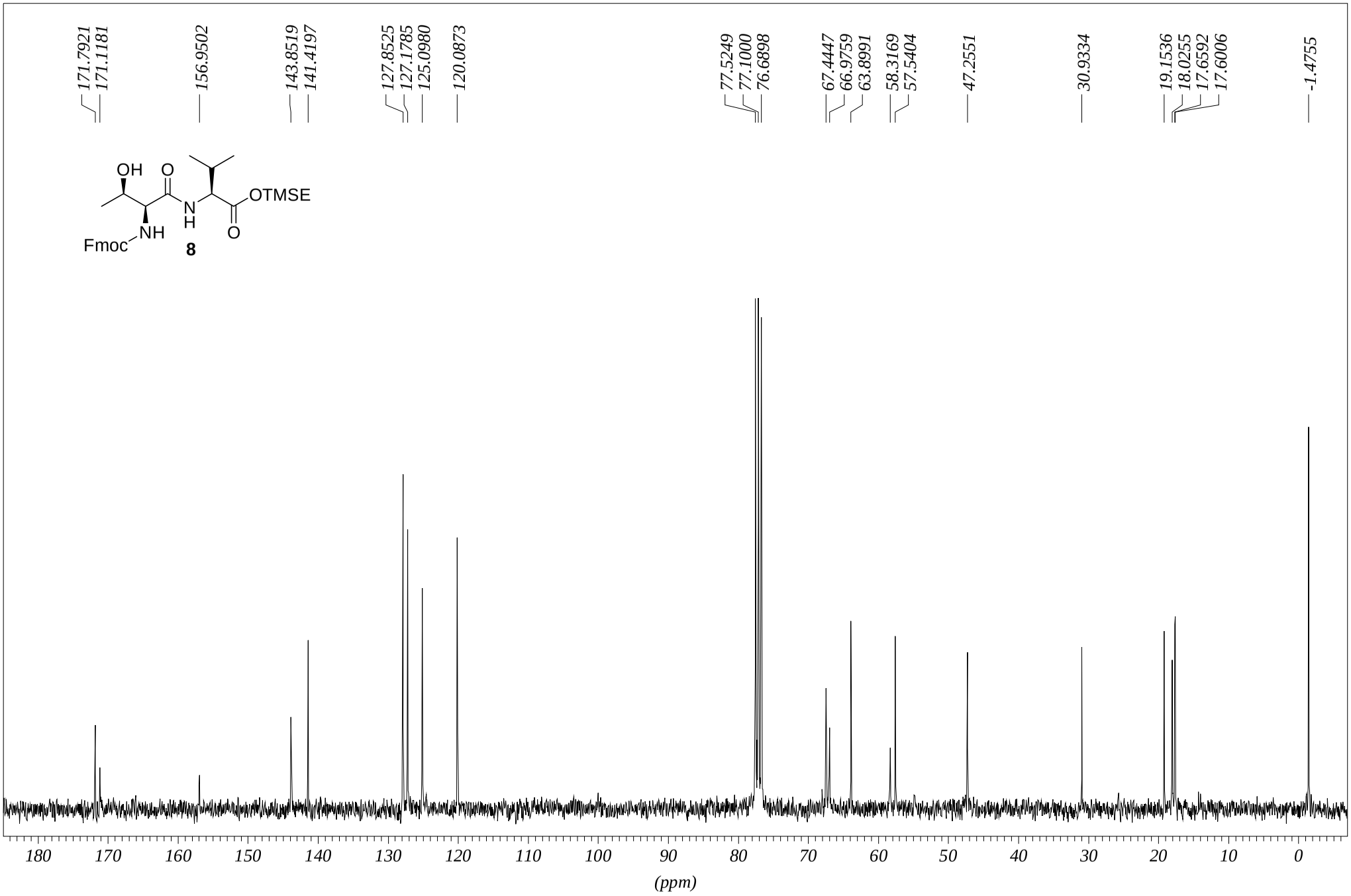
(ppm)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O
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H
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O
NH
Fmoc
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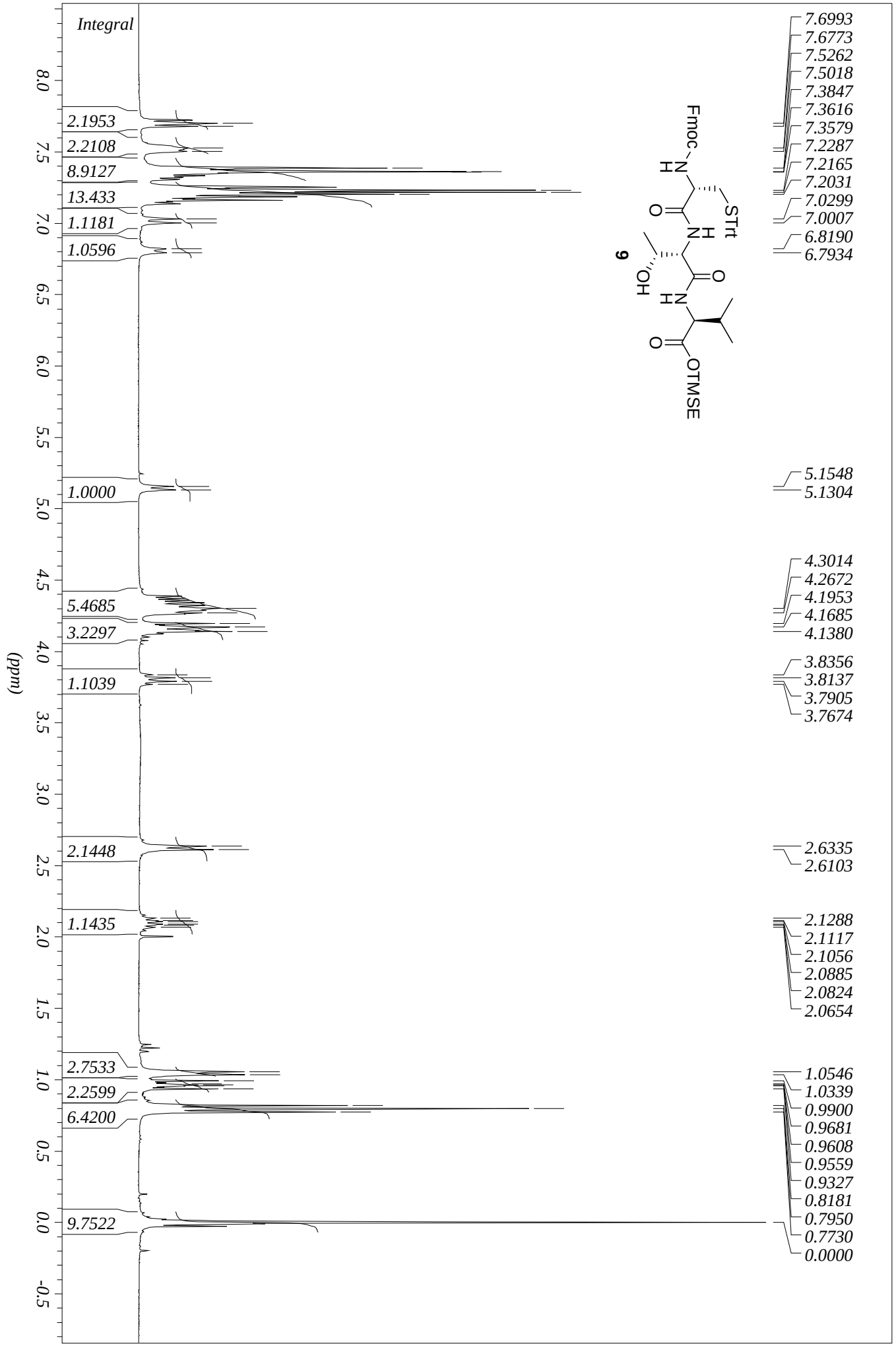
(ppm)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4.0
3.5
3.0
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2.0
1.5
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(ppm)
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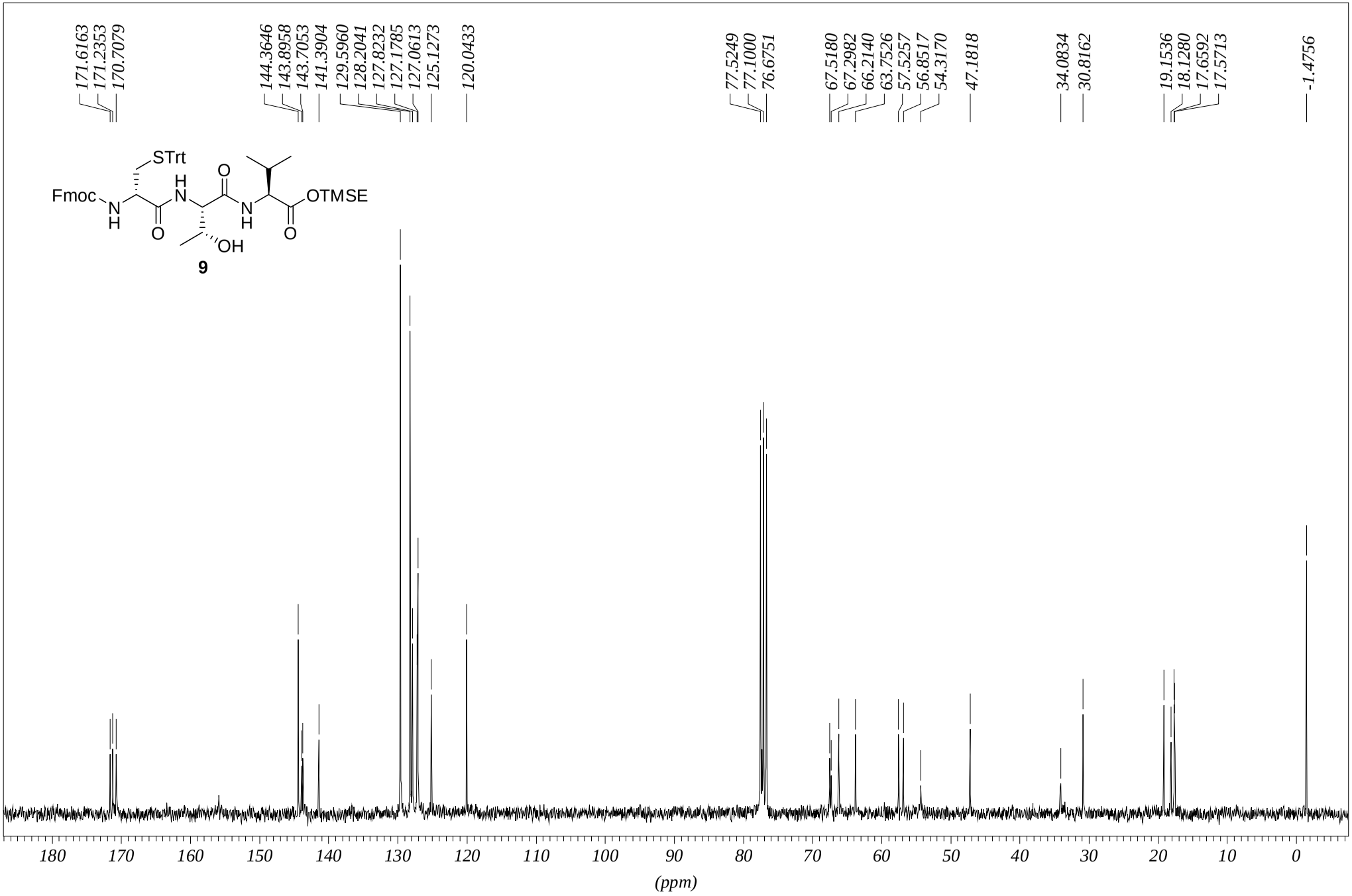
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H
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O
N
H
OTMSE
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9
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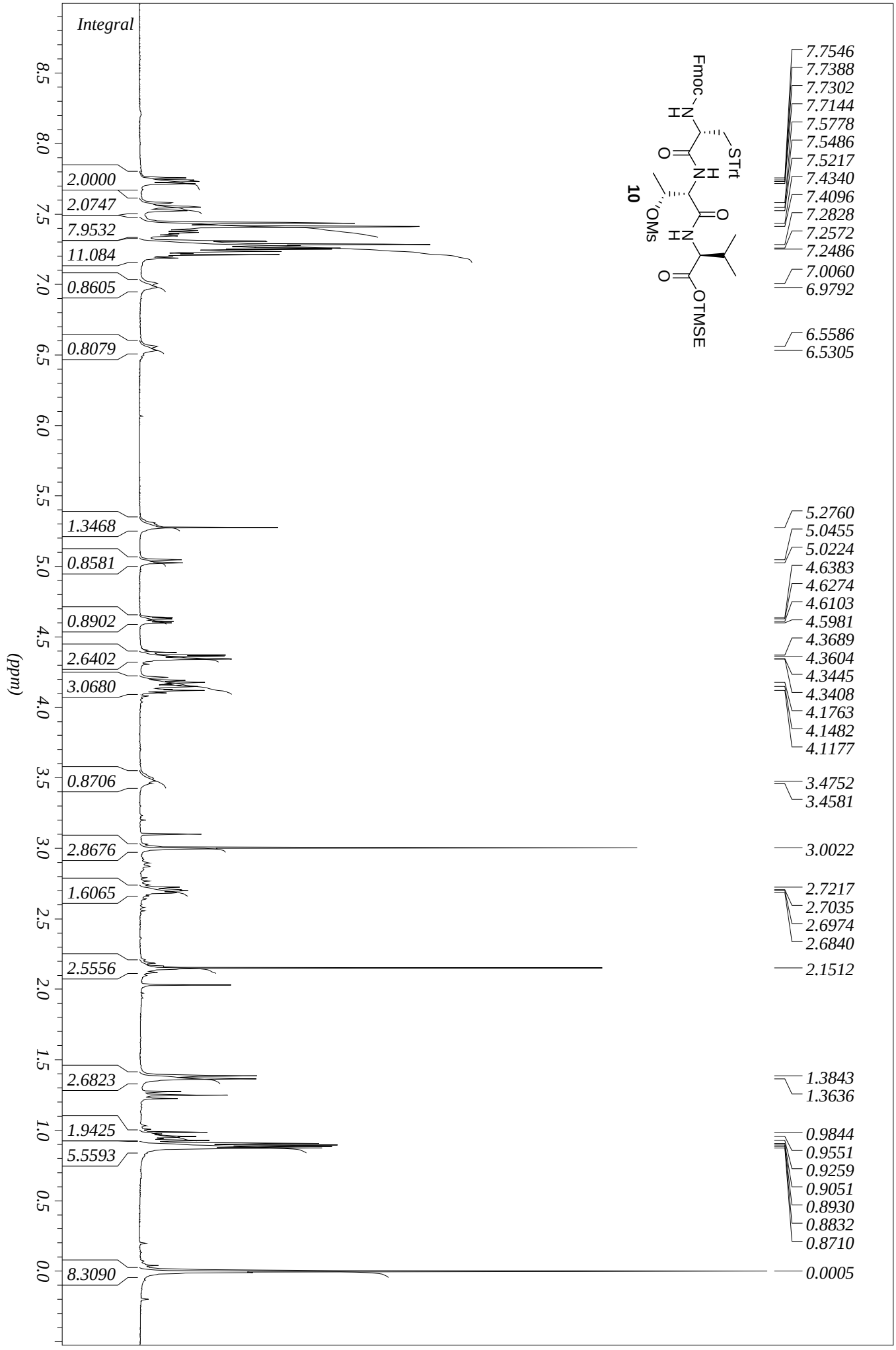
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STrt
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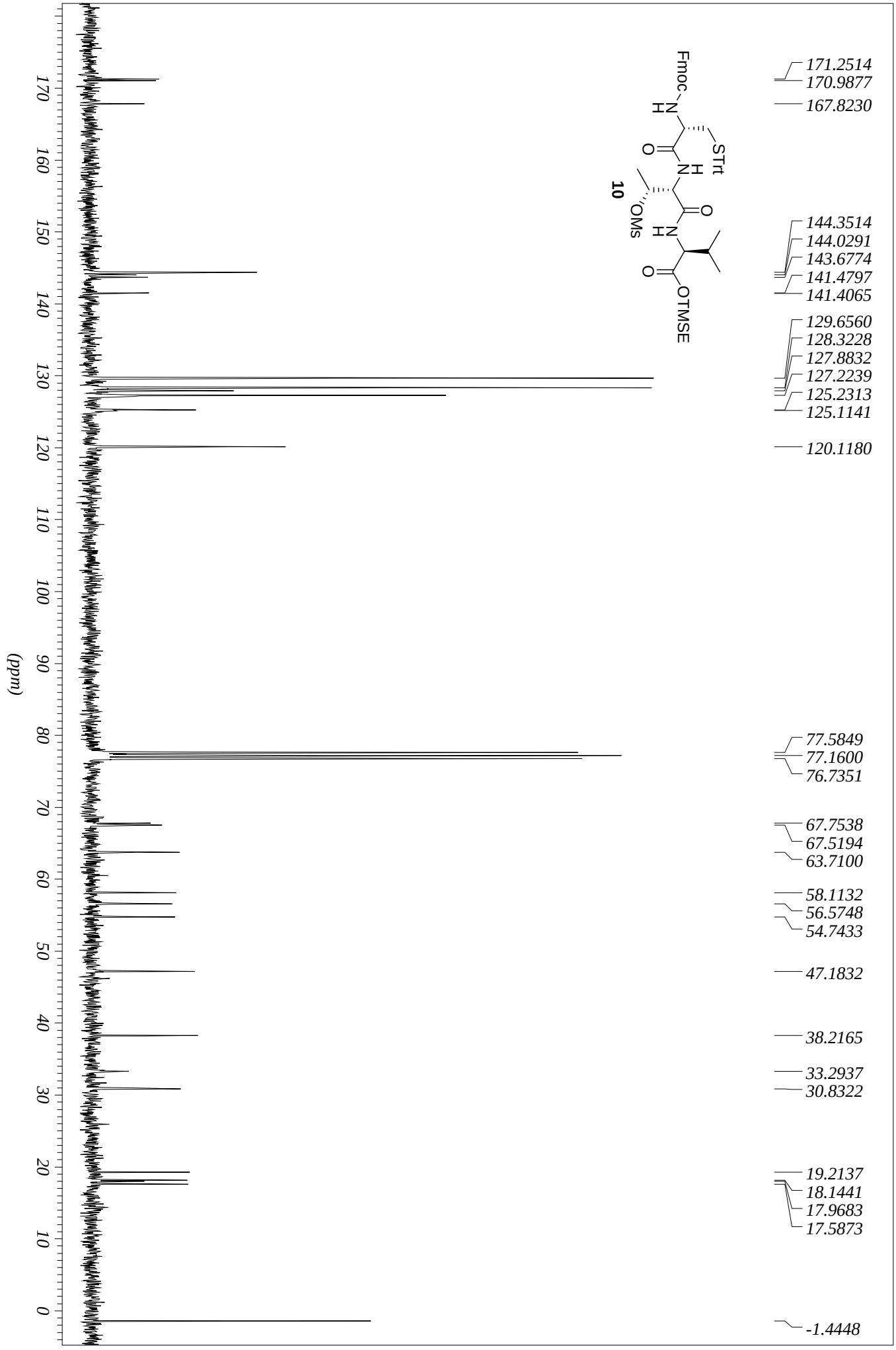
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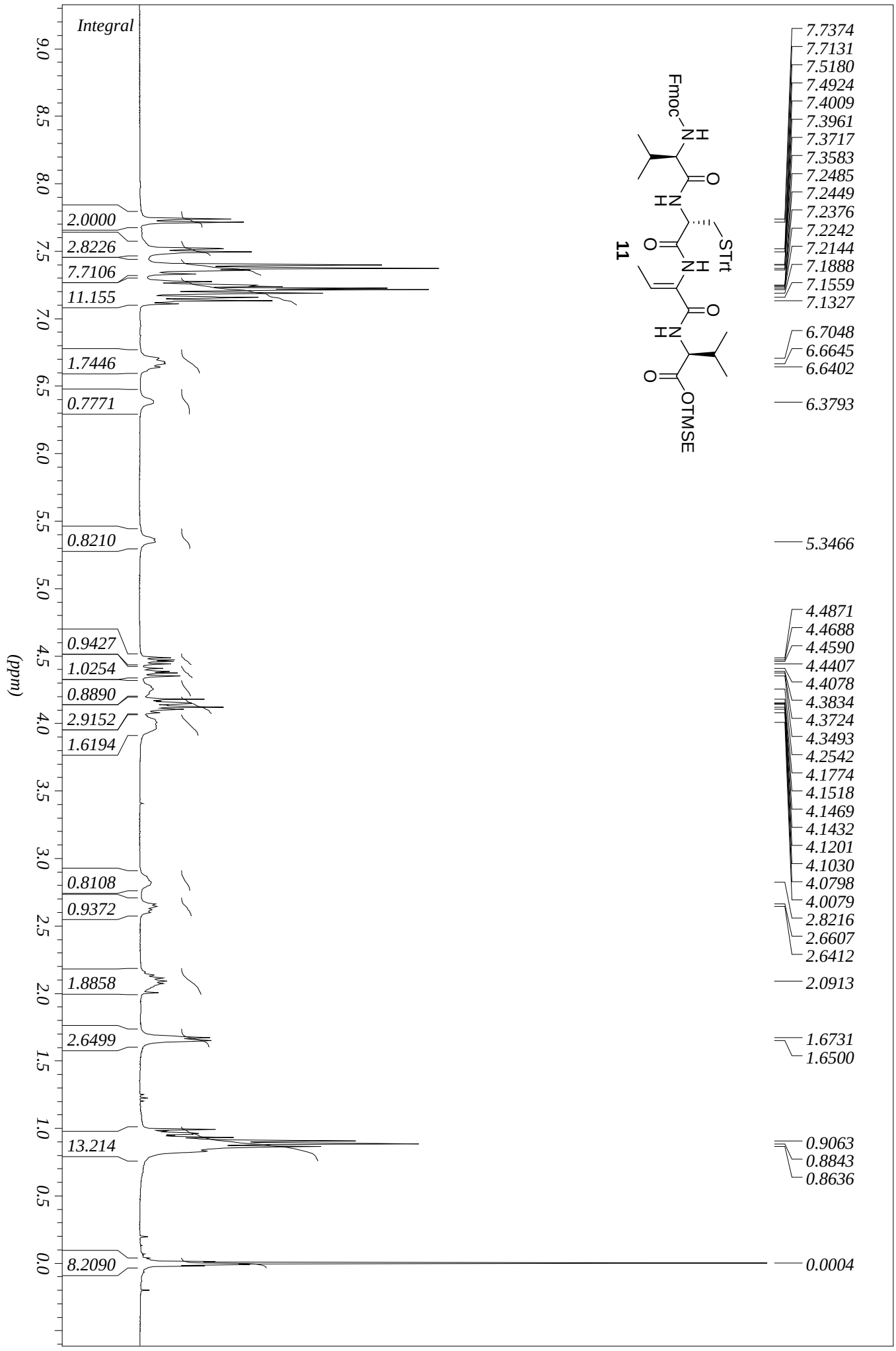
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(ppm)
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Fmoc
STrt
OTMSE
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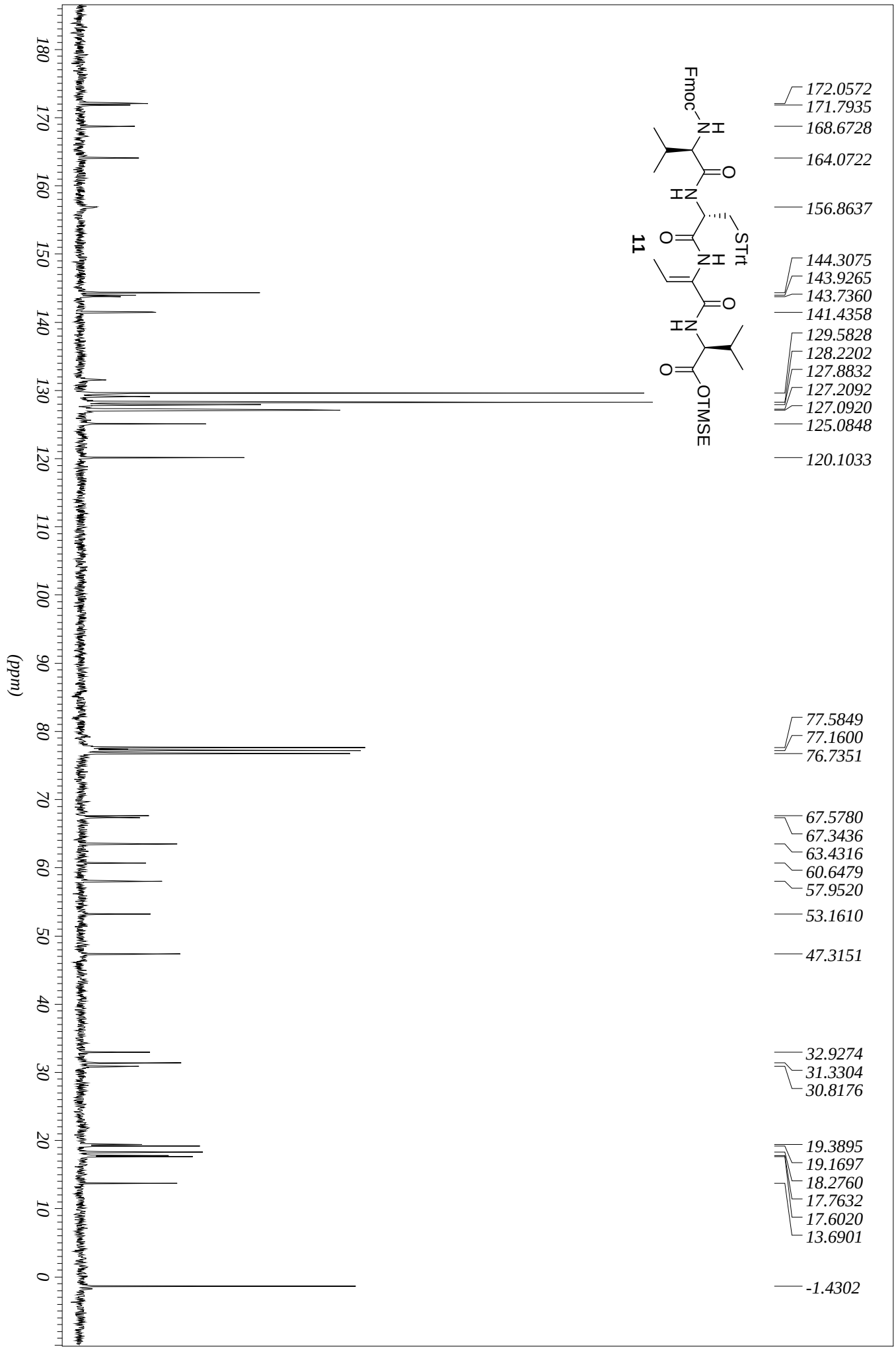
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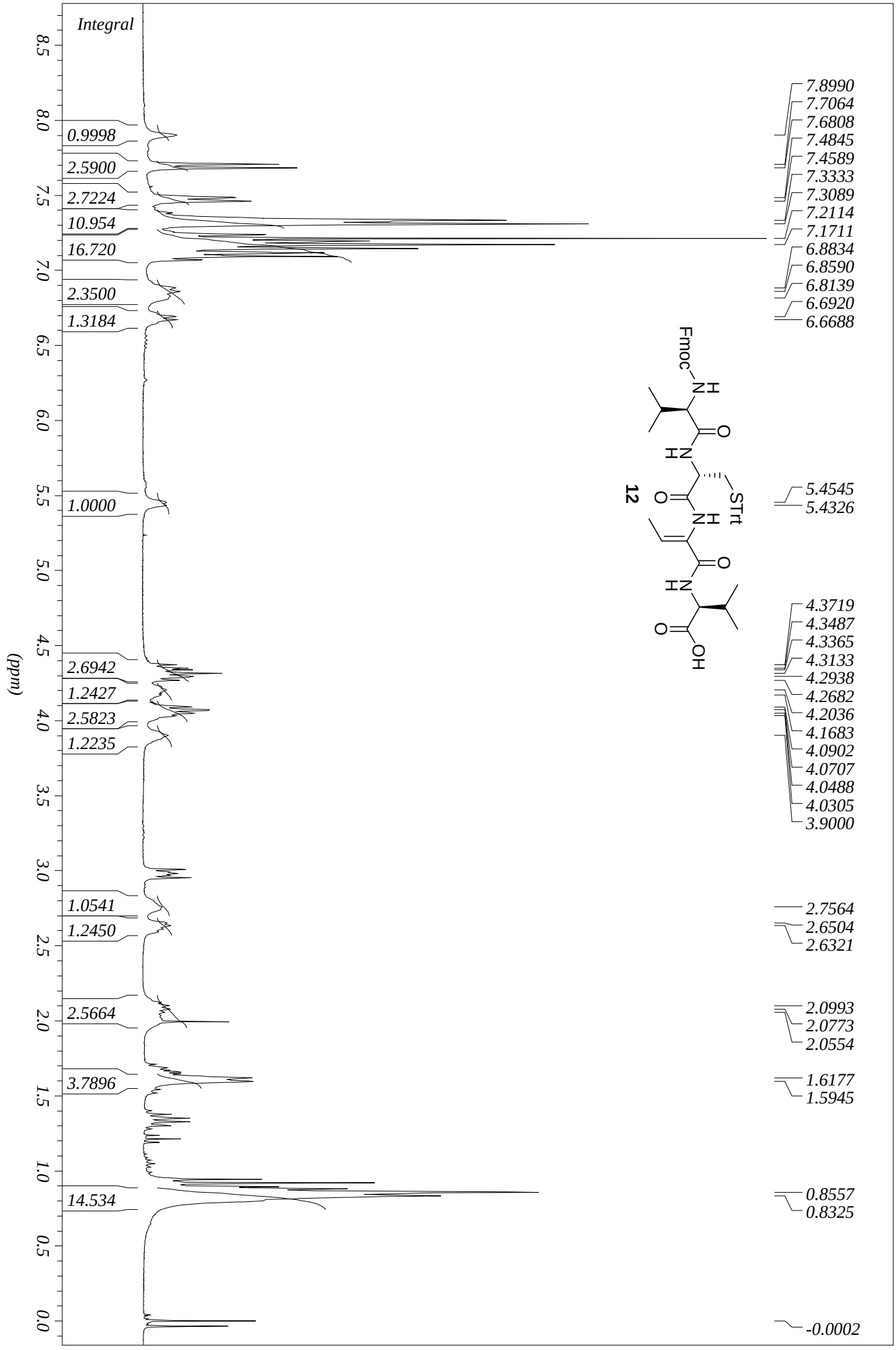
(ppm)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7.7064
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Fmoc
STrt
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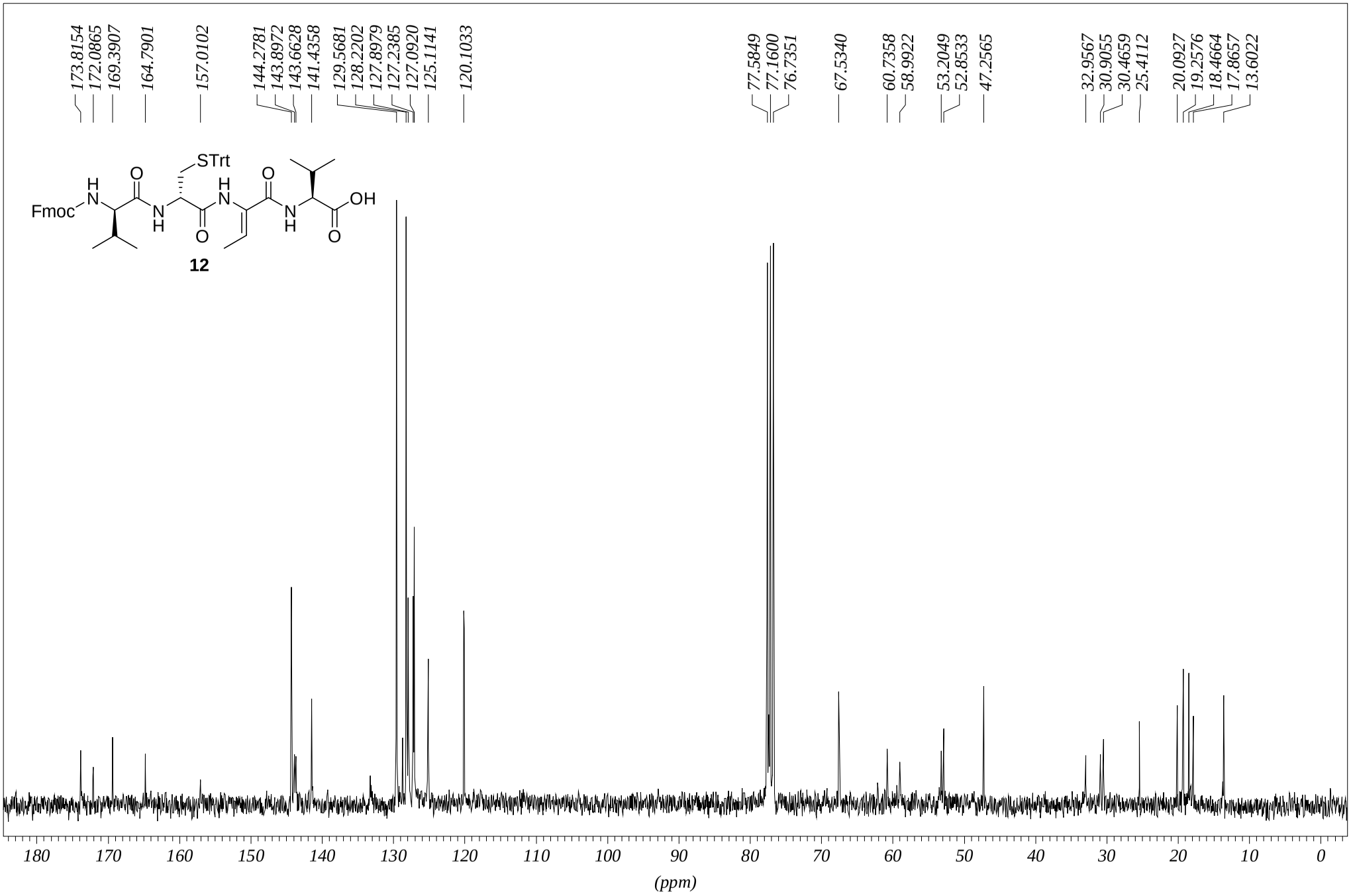
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47.2565
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STrt
Fmoc
OH
12
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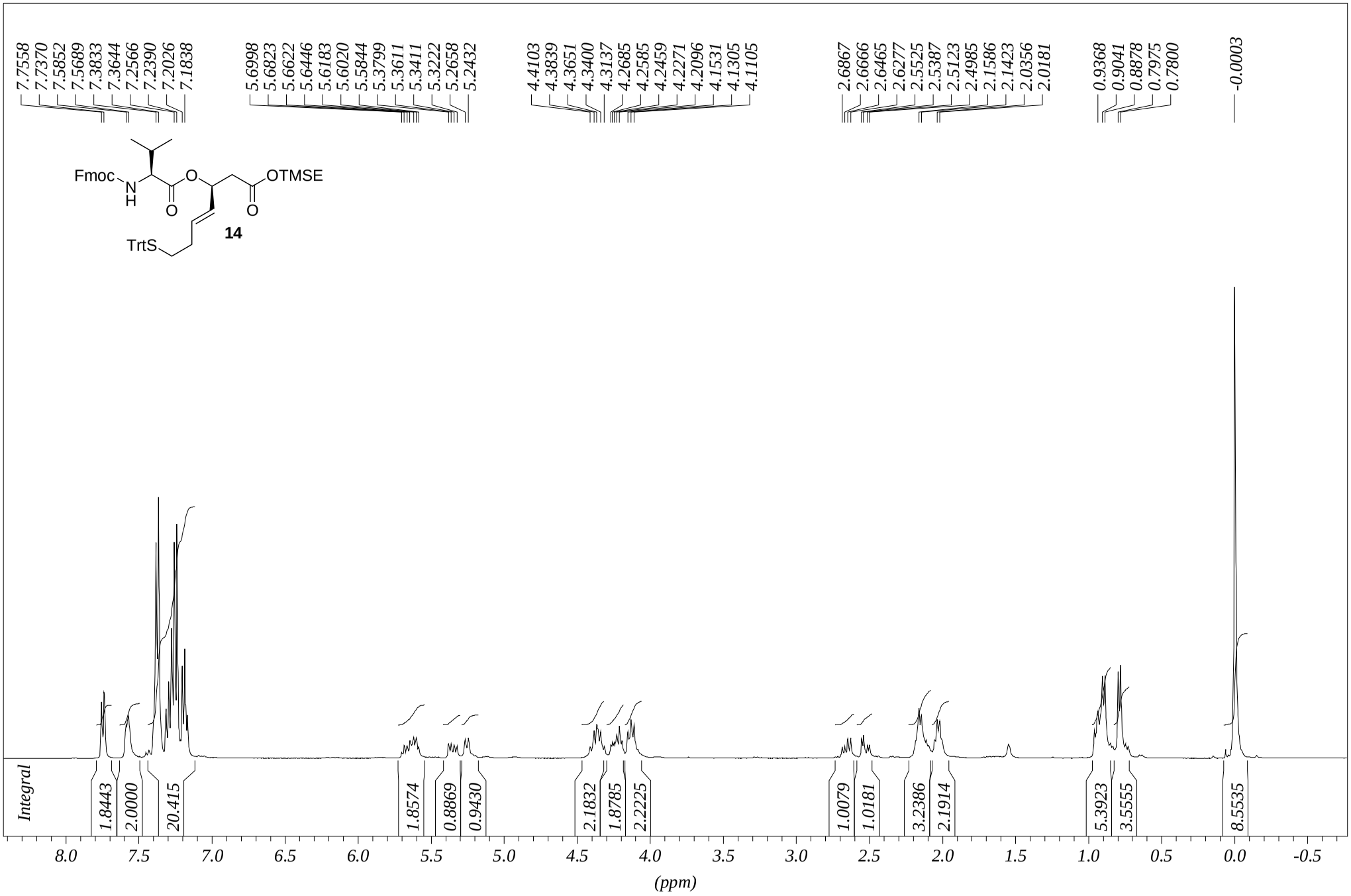
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Fmoc
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O
O
O
O
OTMSE
TrtS
14
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7.0
6.5
6.0
5.5
5.0
4.5
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2.0
1.5
1.0
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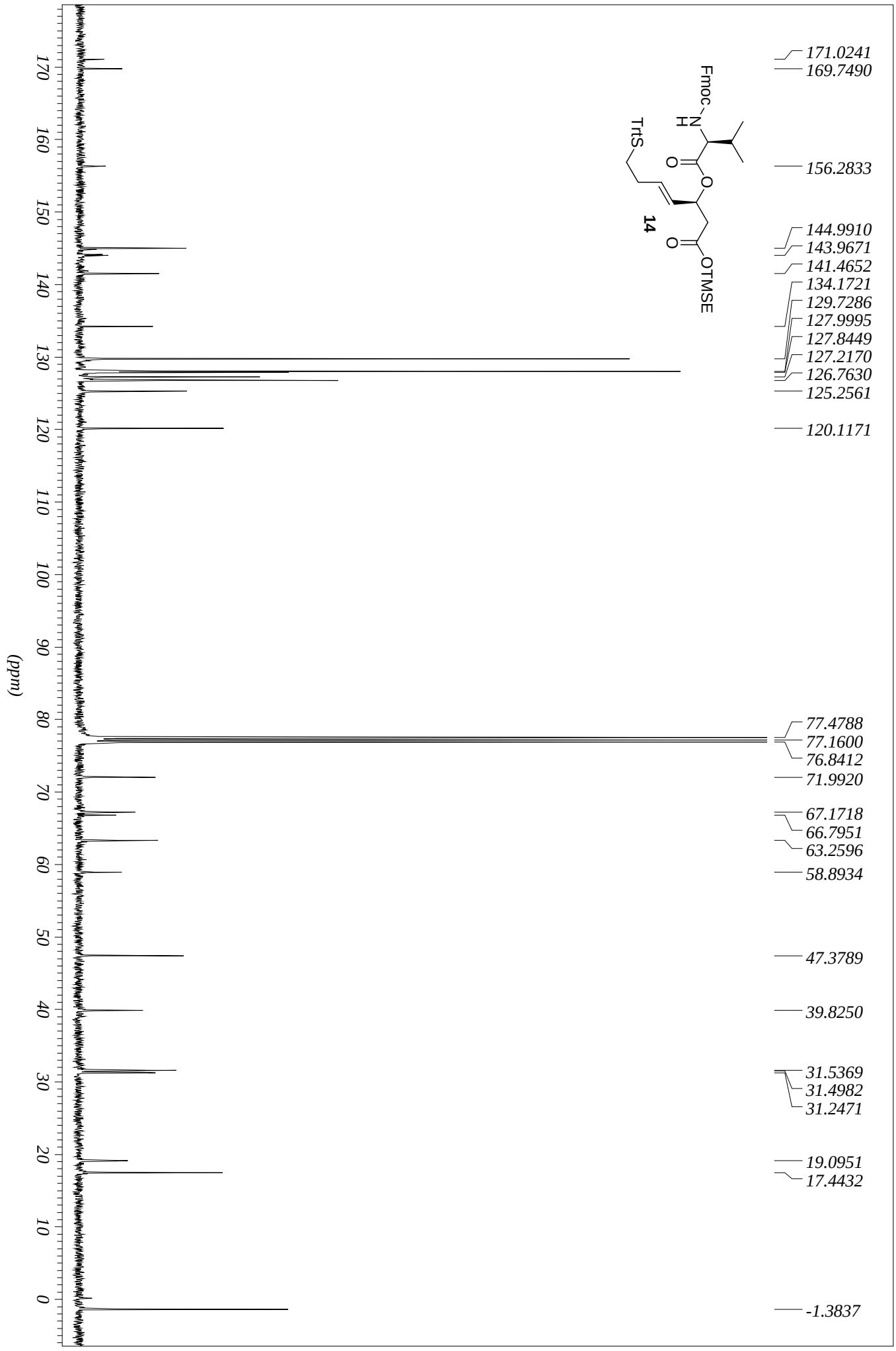
-0.5
(ppm)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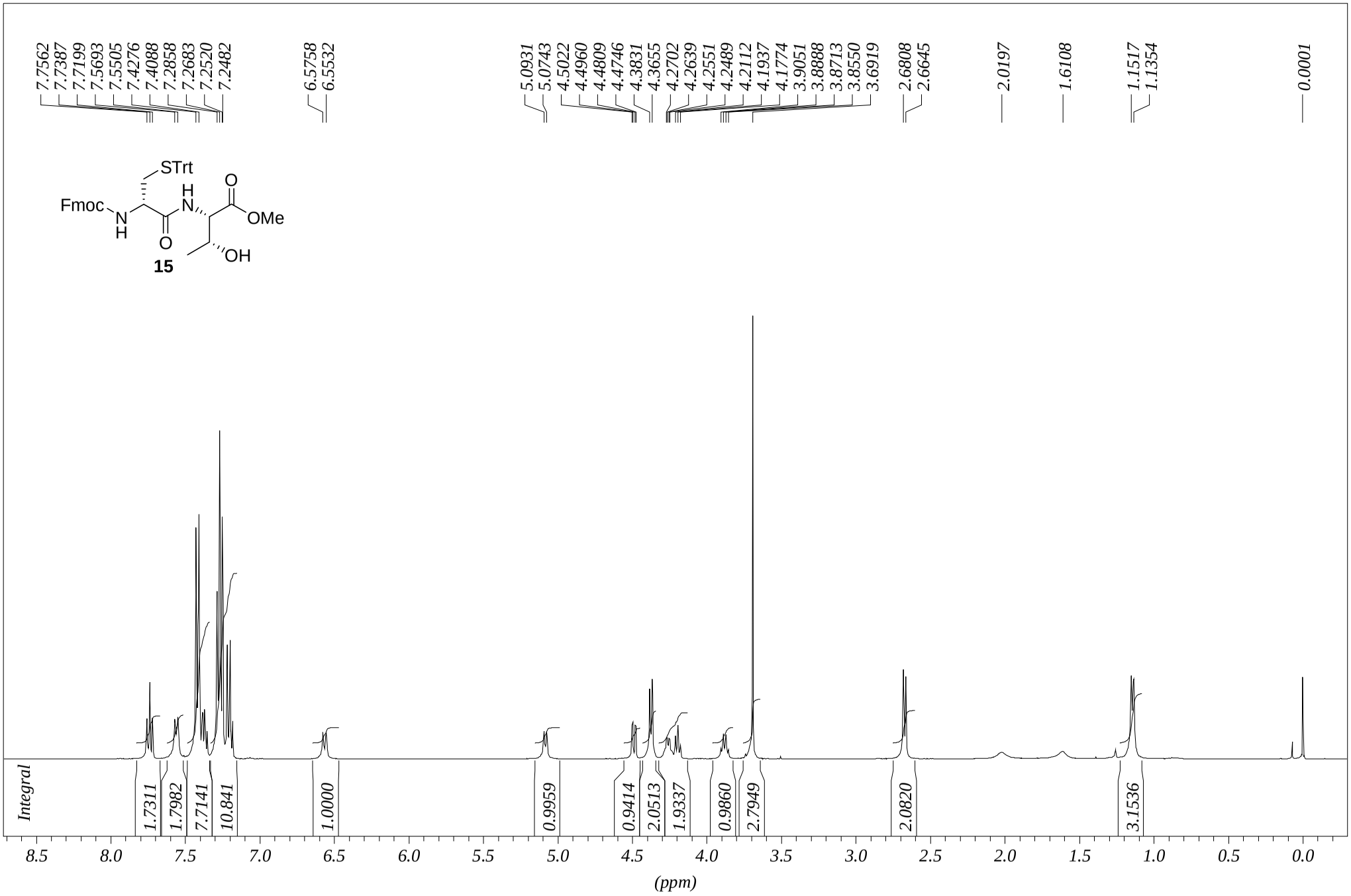
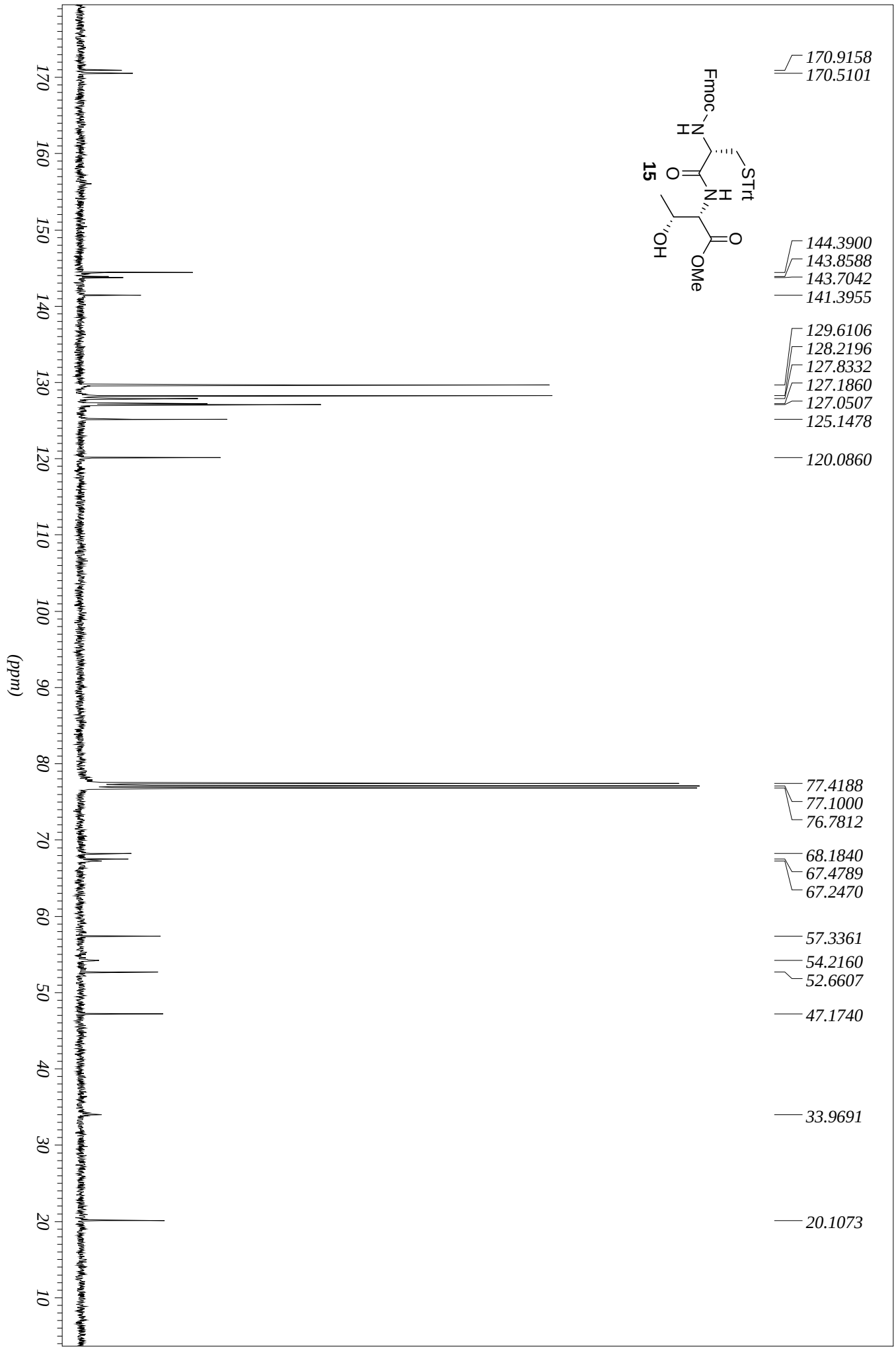
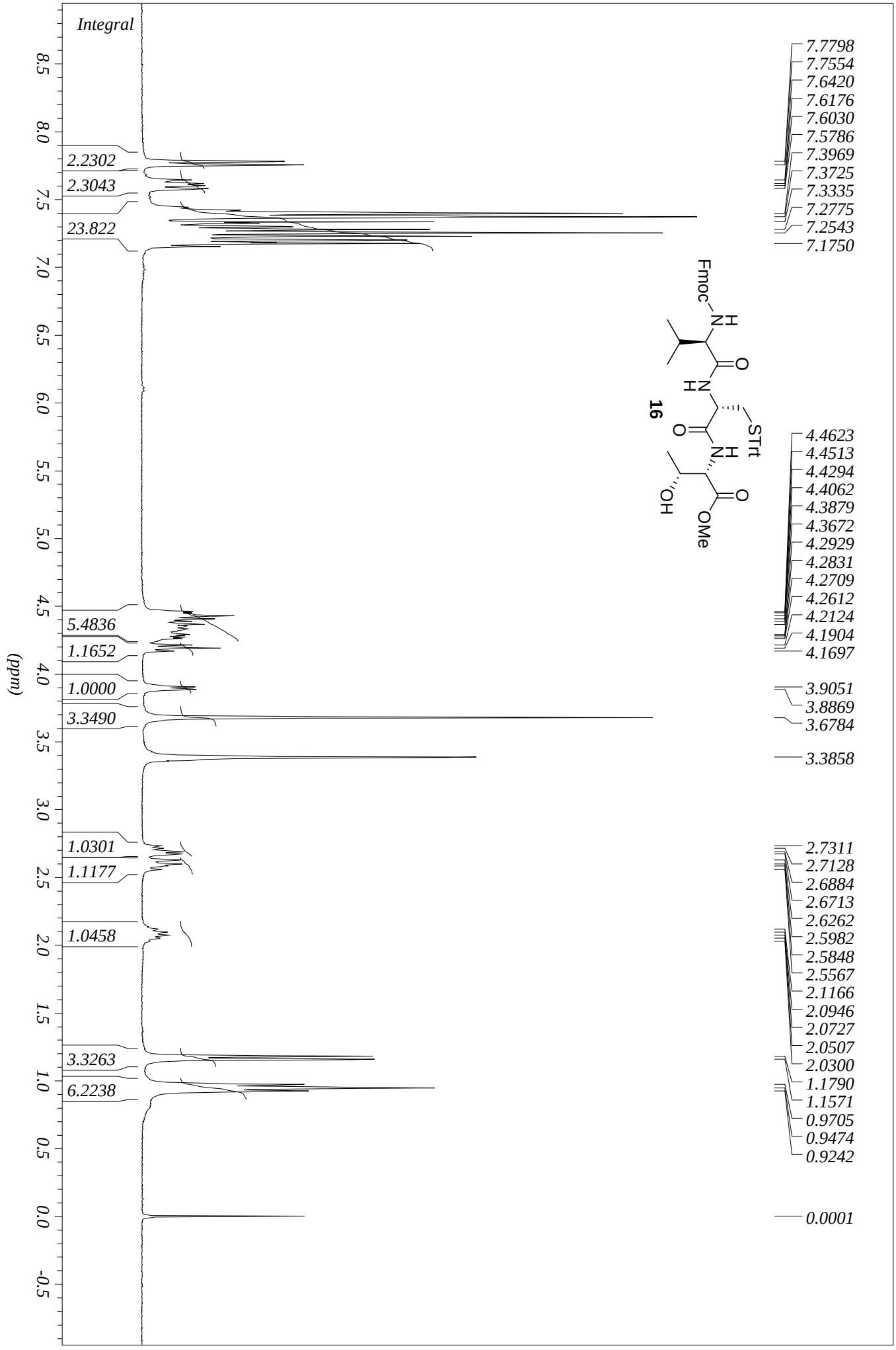
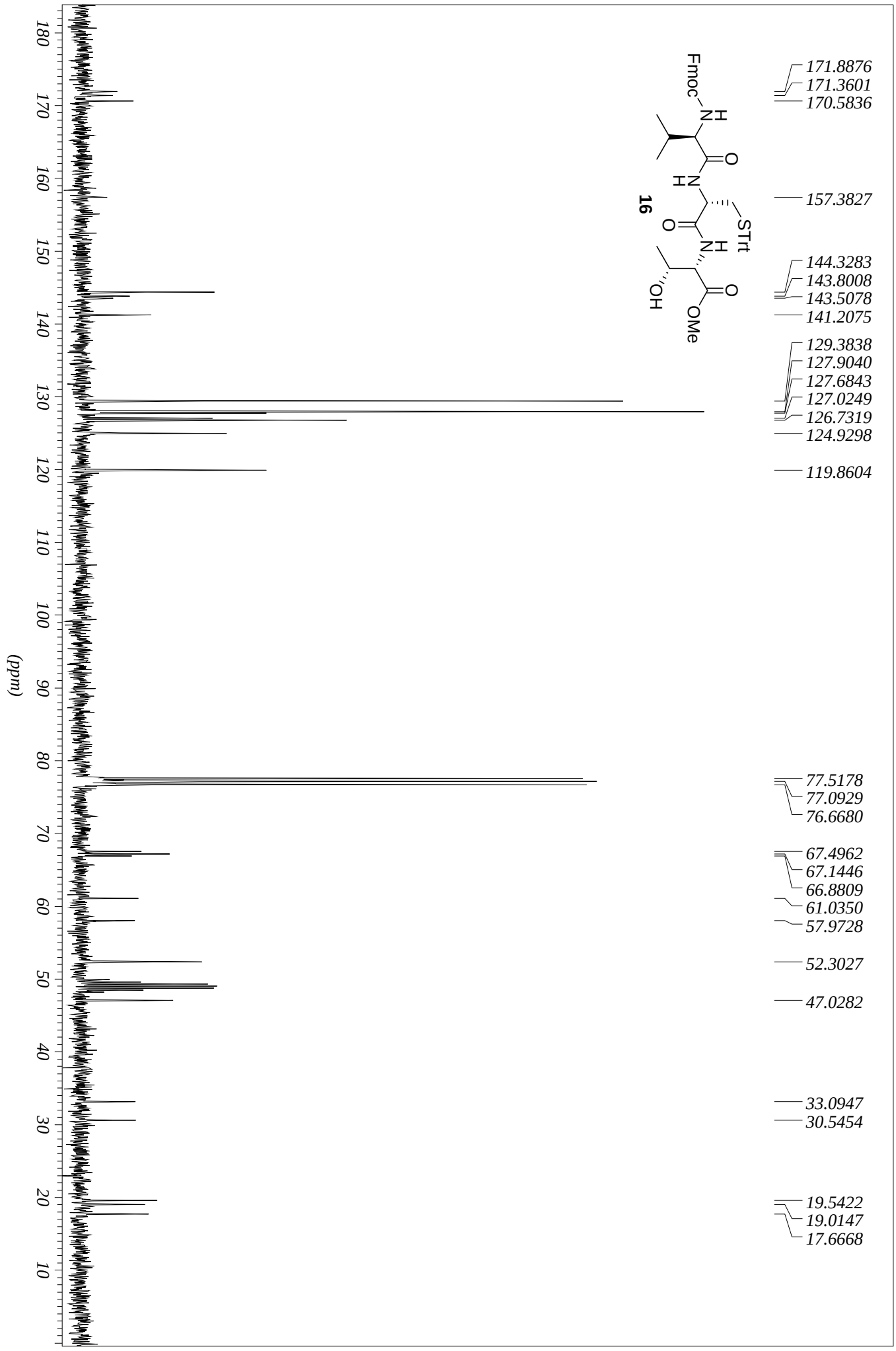
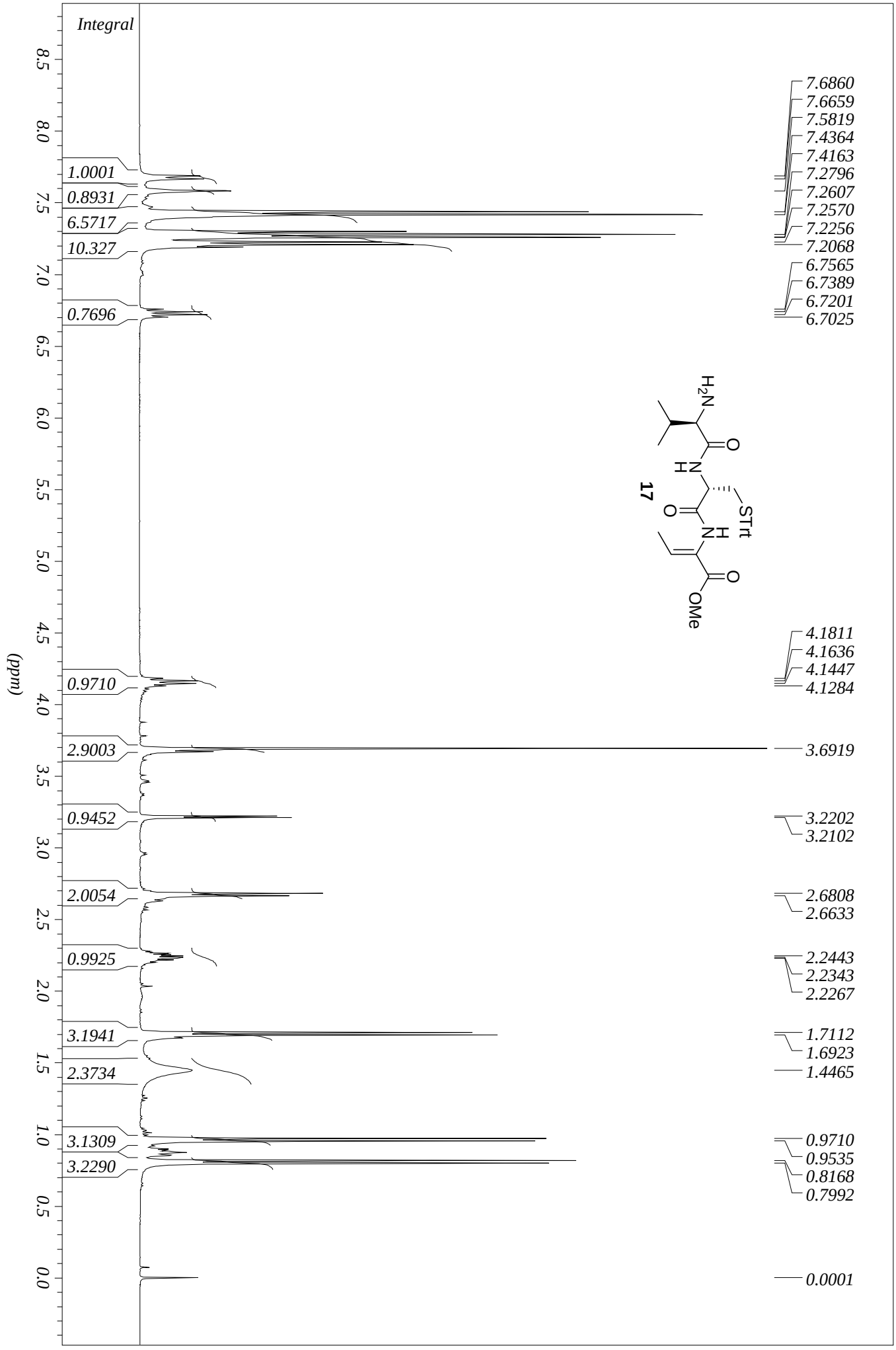
-1.3837
Fmoc
N
H
O
O
O
TrtS
14
OTMSE
(ppm)


7.7562
7.7387
7.7199
7.5693
7.5505
7.4276
7.4088
7.2858
7.2683
7.2520
7.2482
6.5758
6.5532
5.0931
5.0743
4.5022
4.4960
4.4809
4.4746
4.3831
4.3655
4.2702
4.2639
4.2551
4.2489
4.2112
4.1937
4.1774
3.9051
3.8888
3.8713
3.8550
3.6919
2.6808
2.6645
2.0197
1.6108
1.1517
1.1354
0.0001
STrt
Fmoc
N
H
H
N
O
O
OMe
O
OH
15
Integral
1.7311
1.7982
7.7141
10.841
1.0000
0.9959
0.9414
2.0513
1.9337
0.9860
2.7949
2.0820
3.1536
8.5
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
(ppm)

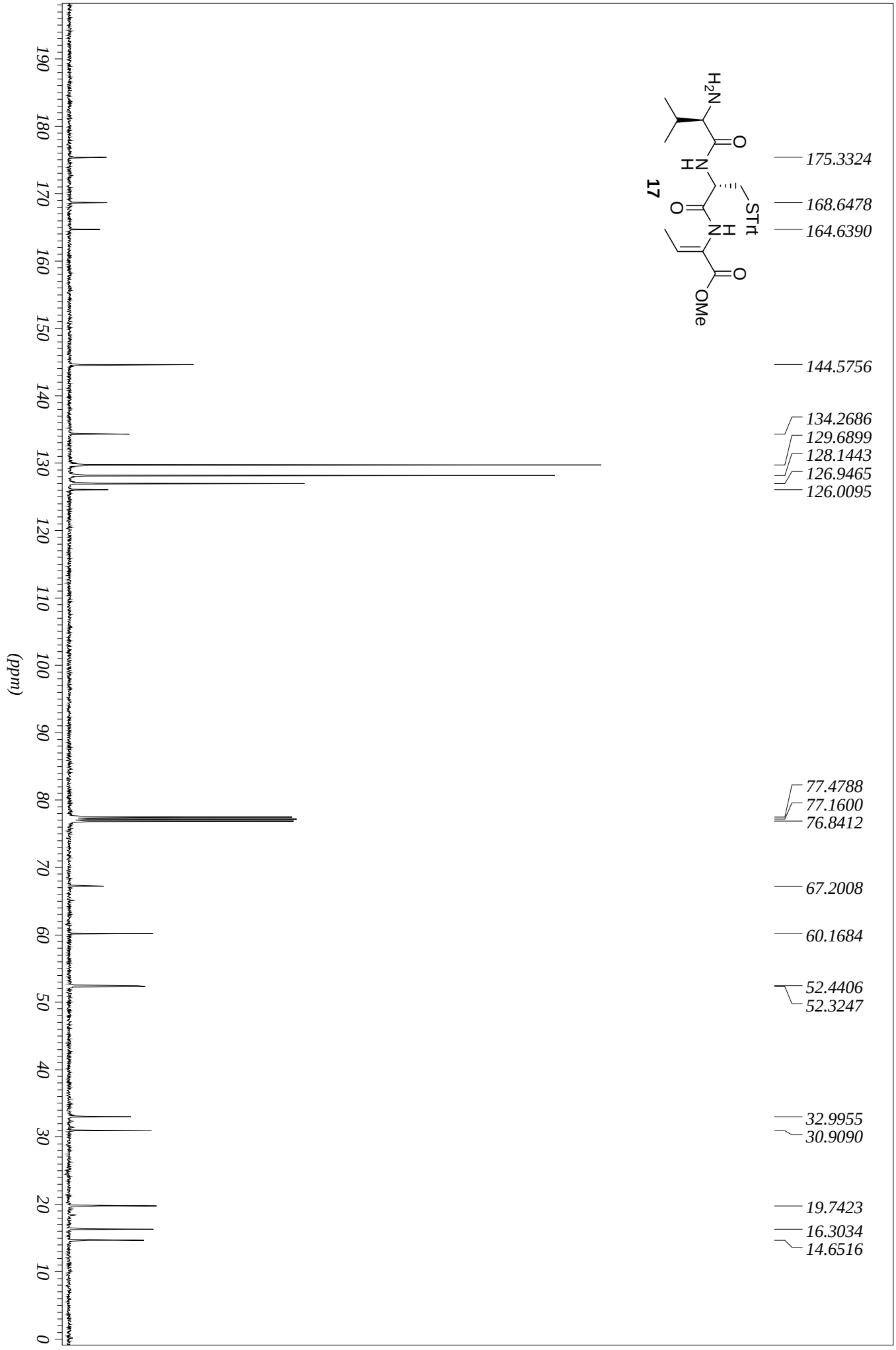

sw-4820/29
170.9158
170.5101
144.3900
143.8588
143.7042
141.3955
129.6106
128.2196
127.8332
127.1860
127.0507
125.1478
120.0860
77.4188
77.1000
76.7812
68.1840
67.4789
67.2470
57.3361
54.2160
52.6607
47.1740
33.9691
20.1073
(ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Fmoc
N
H
O
STrt
H
N
O
OH
O
OMe
15

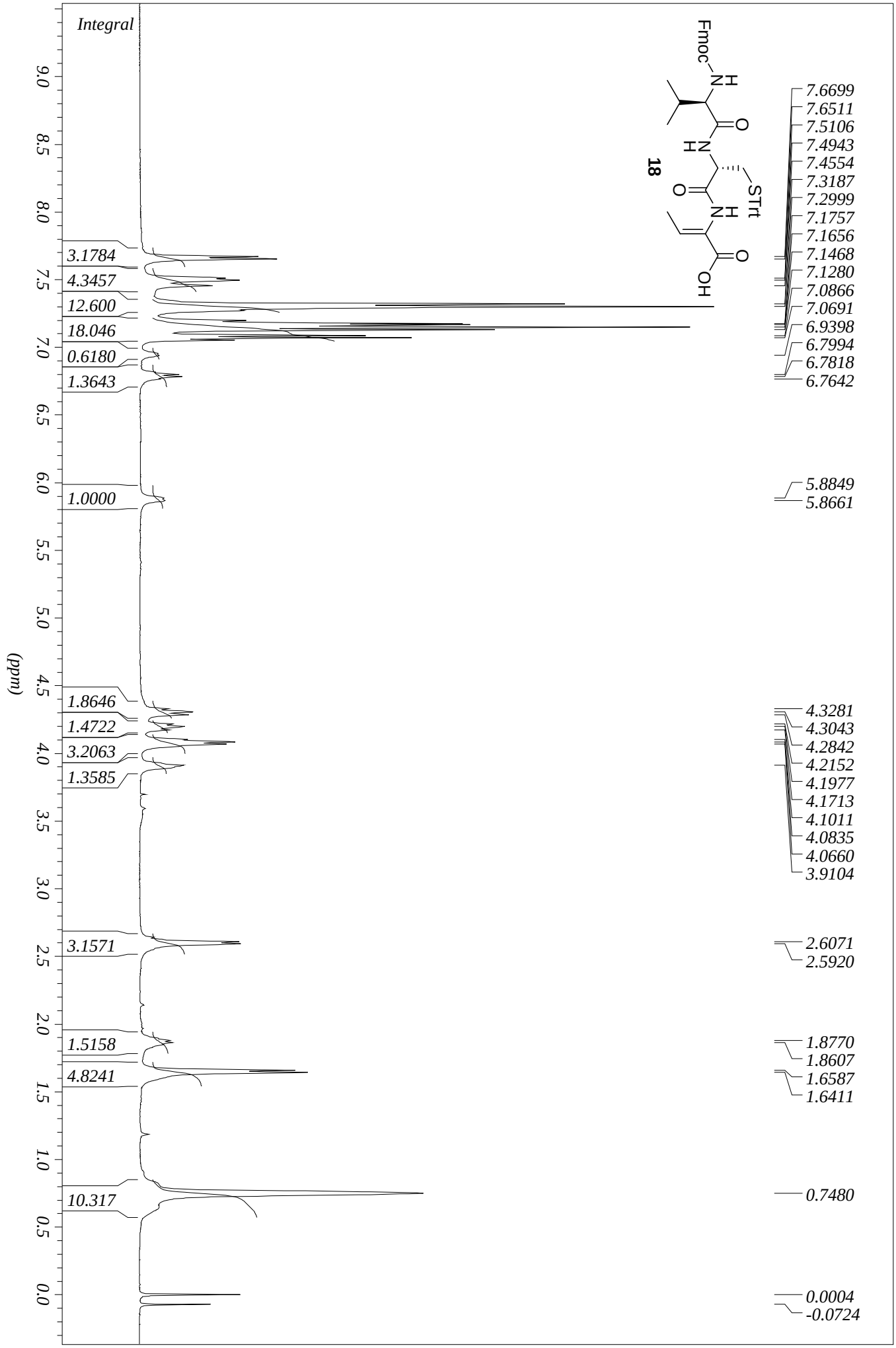

Integral
2.2302
2.3043
23.822
5.4836
1.1652
1.0000
3.3490
1.0301
1.1177
1.0458
3.3263
6.2238
(ppm)
7.7798
7.7554
7.6420
7.6176
7.6030
7.5786
7.3969
7.3725
7.3335
7.2775
7.2543
7.1750
4.4623
4.4513
4.4294
4.4062
4.3879
4.3672
4.2929
4.2831
4.2709
4.2612
4.2124
4.1904
4.1697
3.9051
3.8869
3.6784
3.3858
2.7311
2.7128
2.6884
2.6713
2.6262
2.5982
2.5848
2.5567
2.1166
2.0946
2.0727
2.0507
2.0300
1.1790
1.1571
0.9705
0.9474
0.9242
0.0001
Fmoc
STrt
OMe
OH
16

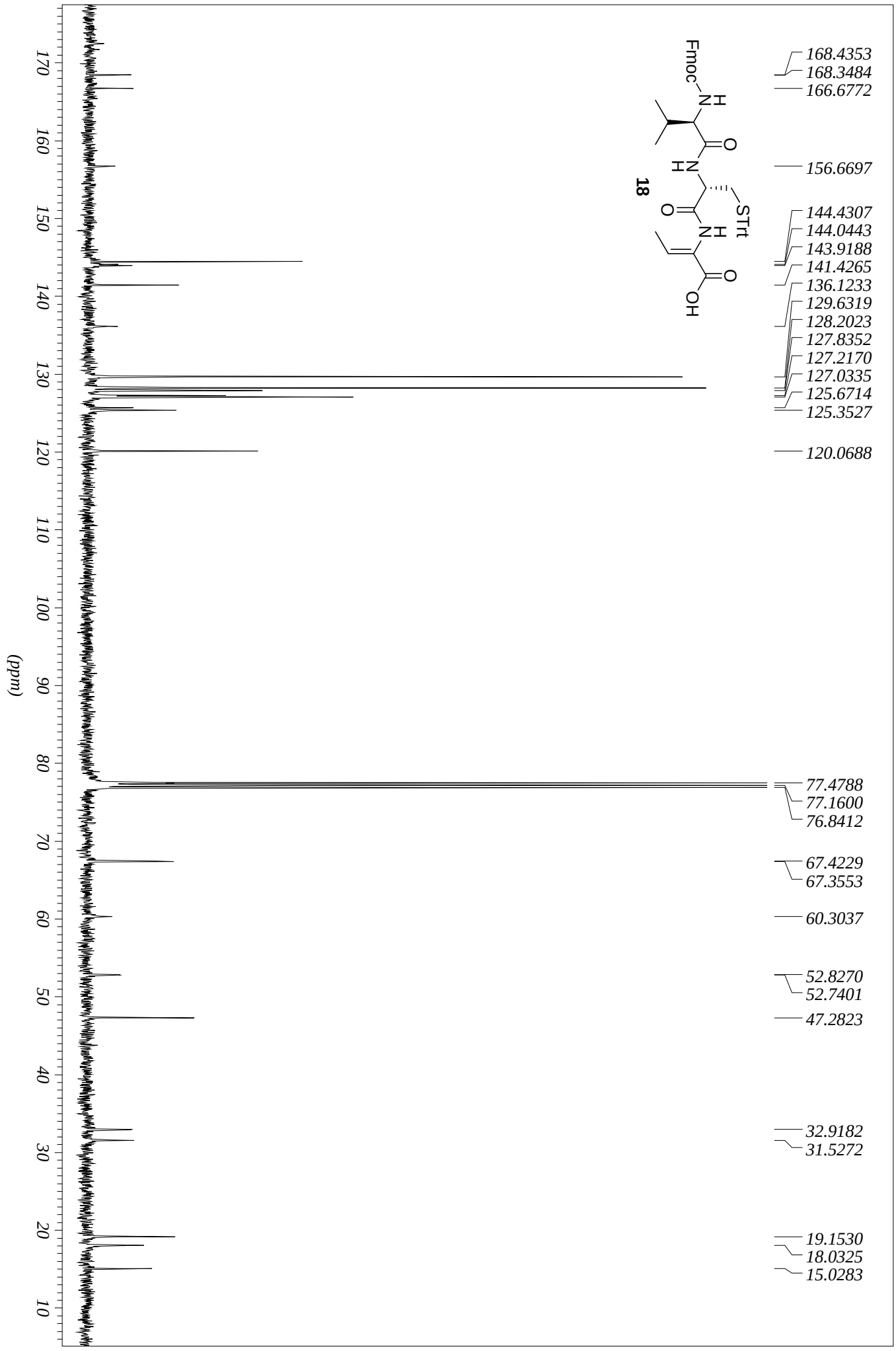

sw-4820/31
Fmoc
N
H
O
N
H
16
O
STrt
N
H
OH
O
OMe
171.8876
171.3601
170.5836
157.3827
144.3283
143.8008
143.5078
141.2075
129.3838
127.9040
127.6843
127.0249
126.7319
124.9298
119.8604
77.5178
77.0929
76.6680
67.4962
67.1446
66.8809
61.0350
57.9728
52.3027
47.0282
33.0947
30.5454
19.5422
19.0147
17.6668
(ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

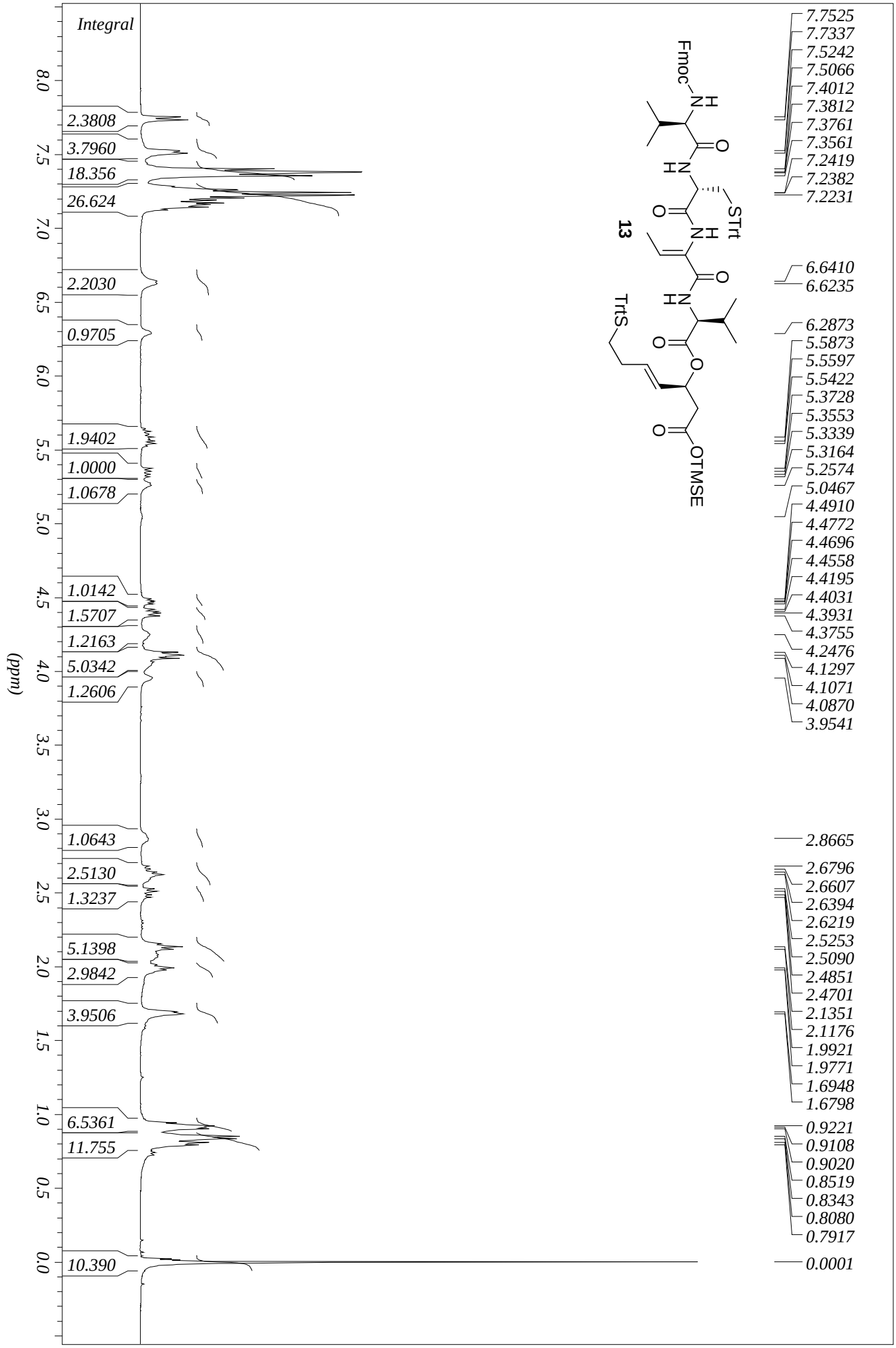

Integral
1.0001
0.8931
6.5717
10.327
0.7696
0.9710
2.9003
0.9452
2.0054
0.9925
3.1941
2.3734
3.1309
3.2290
7.6860
7.6659
7.5819
7.4364
7.4163
7.2796
7.2607
7.2570
7.2256
7.2068
6.7565
6.7389
6.7201
6.7025
4.1811
4.1636
4.1447
4.1284
3.6919
3.2202
3.2102
2.6808
2.6633
2.2443
2.2343
2.2267
1.7112
1.6923
1.4465
0.9710
0.9535
0.8168
0.7992
0.0001
(ppm)
8.5
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

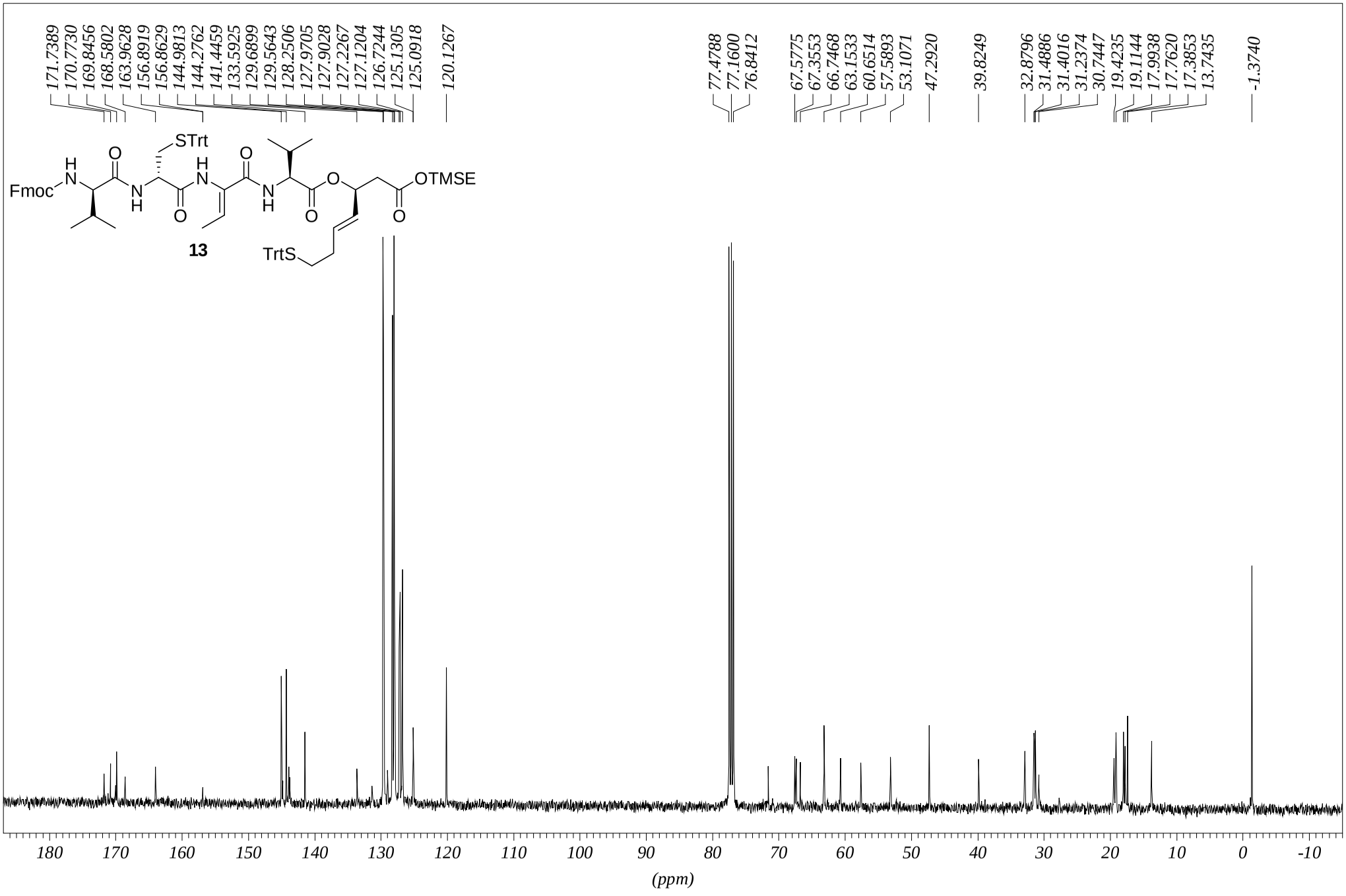
H2N
O
N
H
17
O
STrt
N
H
O
OMe

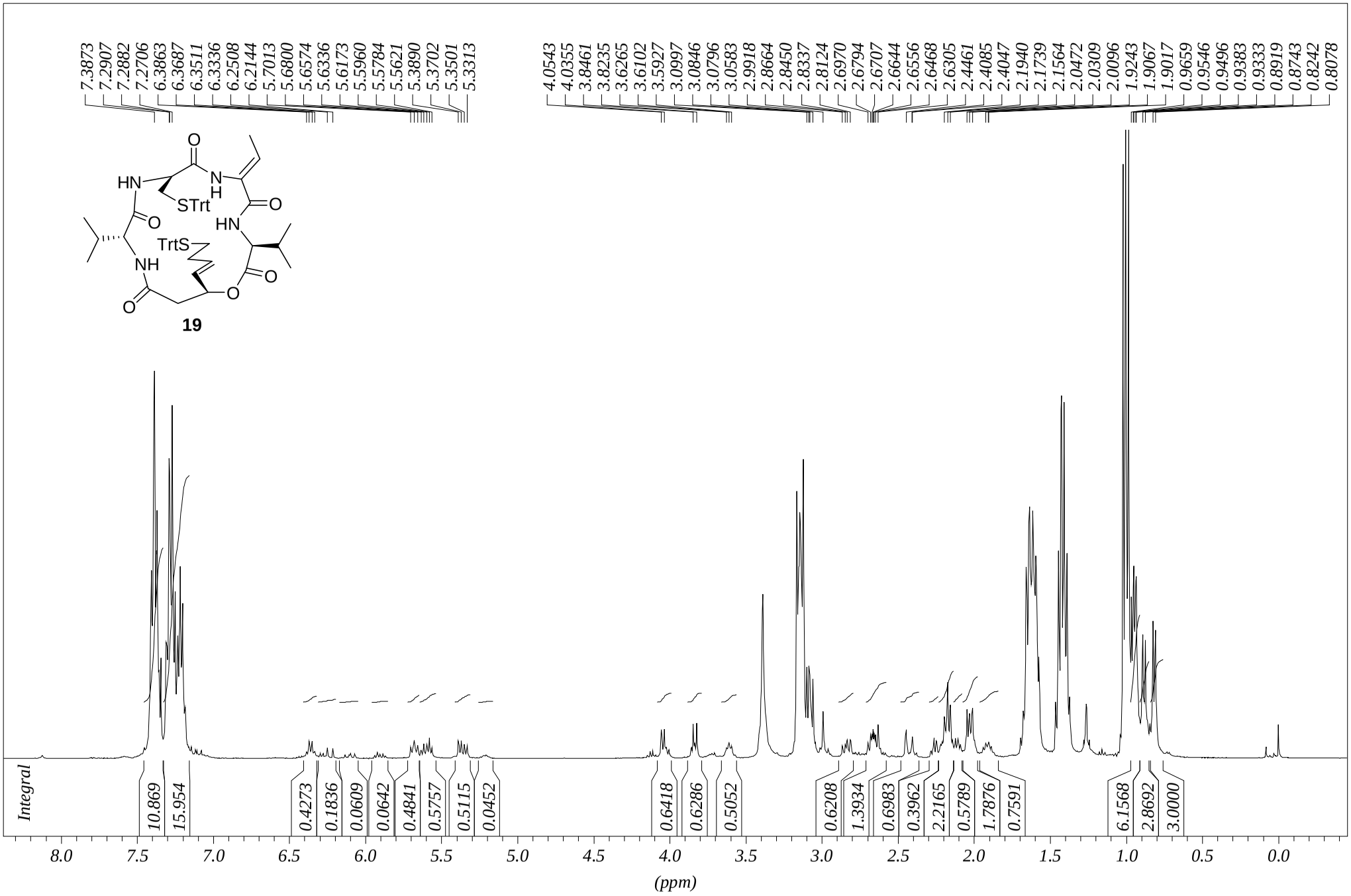

175.3324
168.6478
164.6390
144.5756
134.2686
129.6899
128.1443
126.9465
126.0095
77.4788
77.1600
76.8412
67.2008
60.1684
52.4406
52.3247
32.9955
30.9090
19.7423
16.3034
14.6516
17
(ppm)

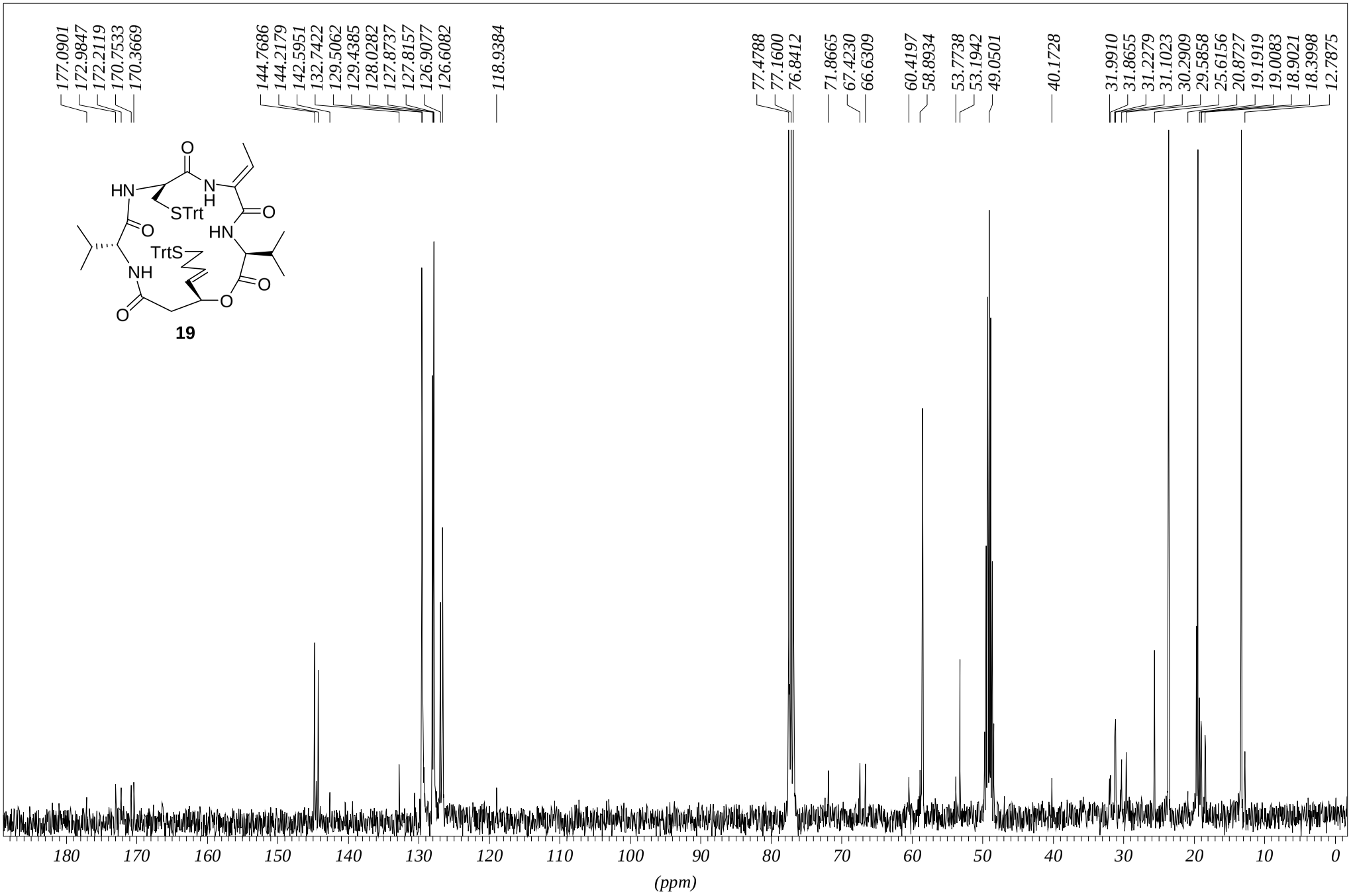

Integral
Fmoc
N
H
O
N
H
O
STrt
N
H
O
OH
18
7.6699
7.6511
7.5106
7.4943
7.4554
7.3187
7.2999
7.1757
7.1656
7.1468
7.1280
7.0866
7.0691
6.9398
6.7994
6.7818
6.7642
5.8849
5.8661
4.3281
4.3043
4.2842
4.2152
4.1977
4.1713
4.1011
4.0835
4.0660
3.9104
2.6071
2.5920
1.8770
1.8607
1.6587
1.6411
0.7480
0.0004
-0.0724
3.1784
4.3457
12.600
18.046
0.6180
1.3643
1.0000
1.8646
1.4722
3.2063
1.3585
3.1571
1.5158
4.8241
10.317
9.0
8.5
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
(ppm)

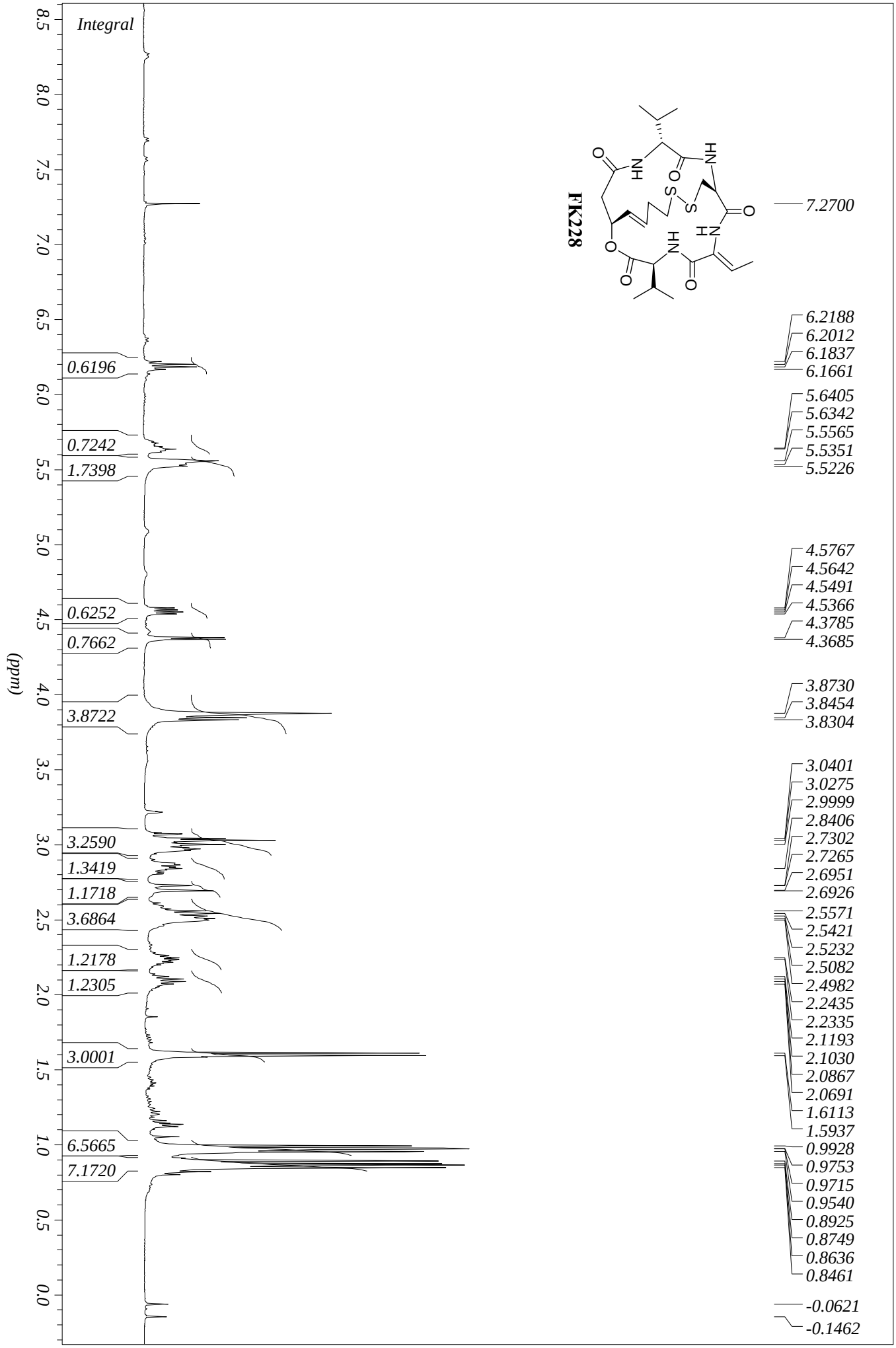

sw-4820/38
Fmoc
STrt
OH
18
168.4353
168.3484
166.6772
156.6697
144.4307
144.0443
143.9188
141.4265
136.1233
129.6319
128.2023
127.8352
127.2170
127.0335
125.6714
125.3527
120.0688
77.4788
77.1600
76.8412
67.4229
67.3553
60.3037
52.8270
52.7401
47.2823
32.9182
31.5272
19.1530
18.0325
15.0283
(ppm)

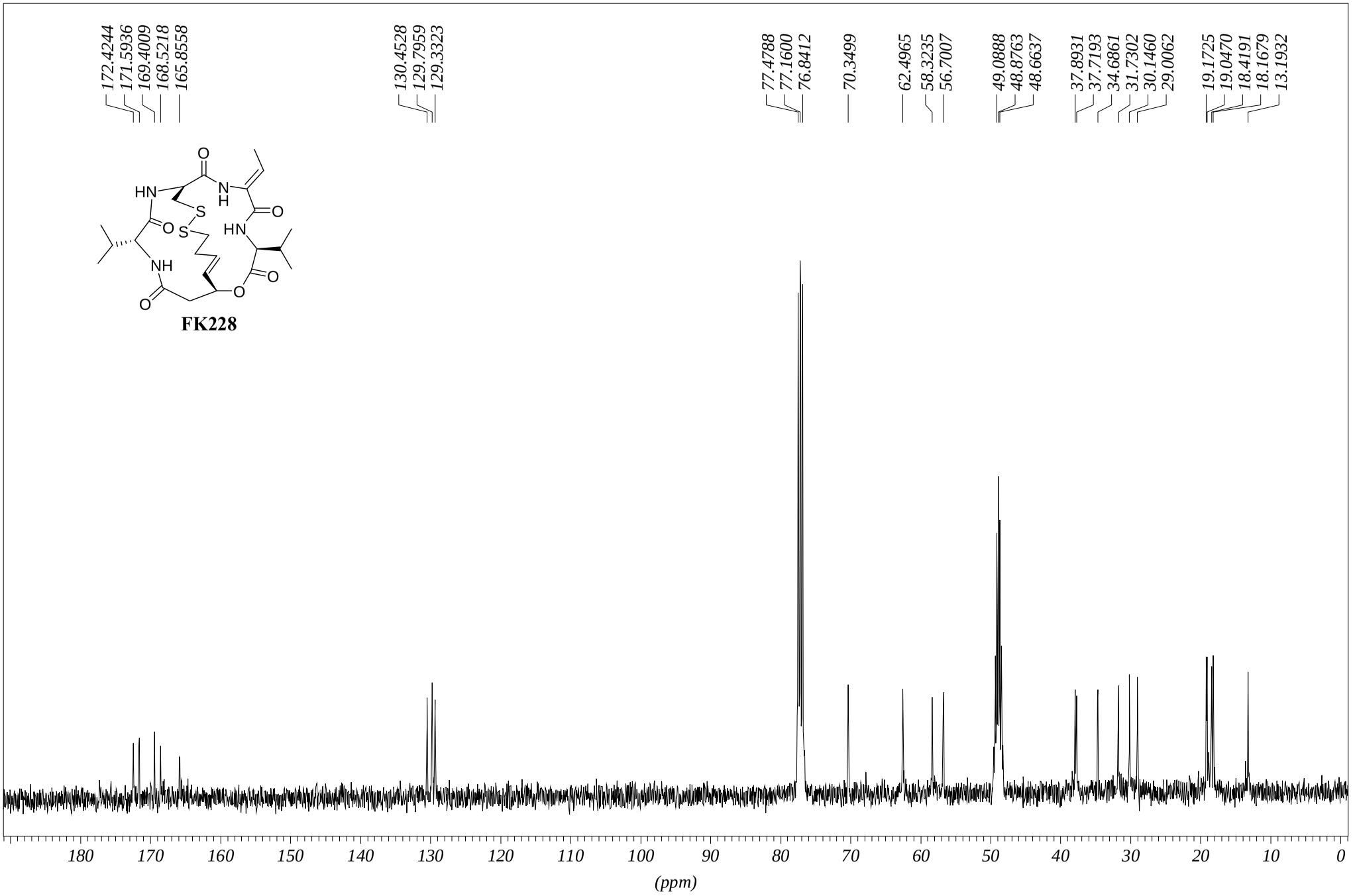

Integral
2.3808
3.7960
18.356
26.624
2.2030
0.9705
1.9402
1.0000
1.0678
1.0142
1.5707
1.2163
5.0342
1.2606
1.0643
2.5130
1.3237
5.1398
2.9842
3.9506
6.5361
11.755
10.390
(ppm)
Fmoc
STrt
TrtS
OTMSE
13
7.7525
7.7337
7.5242
7.5066
7.4012
7.3812
7.3761
7.3561
7.2419
7.2382
7.2231
6.6410
6.6235
6.2873
5.5873
5.5597
5.5422
5.3728
5.3553
5.3339
5.3164
5.2574
5.0467
4.4910
4.4772
4.4696
4.4558
4.4195
4.4031
4.3931
4.3755
4.2476
4.1297
4.1071
4.0870
3.9541
2.8665
2.6796
2.6607
2.6394
2.6219
2.5253
2.5090
2.4851
2.4701
2.1351
2.1176
1.9921
1.9771
1.6948
1.6798
0.9221
0.9108
0.9020
0.8519
0.8343
0.8080
0.7917
0.0001

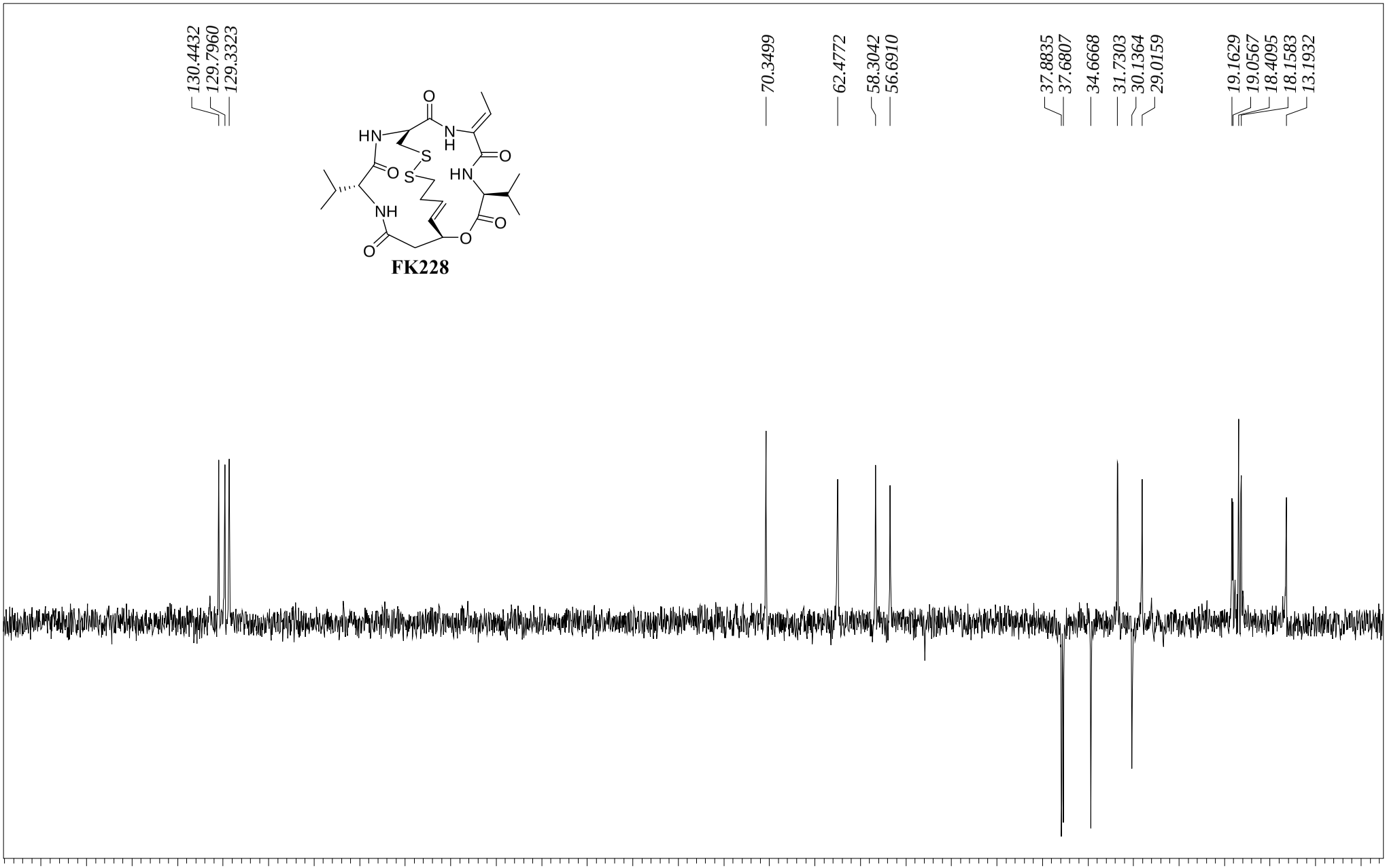

171.7389
170.7730
169.8456
168.5802
163.9628
156.8919
156.8629
144.9813
144.2762
141.4459
133.5925
129.6899
129.5643
128.2506
127.9705
127.9028
127.2267
127.1204
126.7244
125.1305
125.0918
120.1267
77.4788
77.1600
76.8412
67.5775
67.3553
66.7468
63.1533
60.6514
57.5893
53.1071
47.2920
39.8249
32.8796
31.4886
31.4016
31.2374
30.7447
19.4235
19.1144
17.9938
17.7620
17.3853
13.7435
-1.3740
Fmoc
STrt
OTMSE
TrtS
13
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)


7.3873
7.2907
7.2882
7.2706
6.3863
6.3687
6.3511
6.3336
6.2508
6.2144
5.7013
5.6800
5.6574
5.6336
5.6173
5.5960
5.5784
5.5621
5.3890
5.3702
5.3501
5.3313
4.0543
4.0355
3.8461
3.8235
3.6265
3.6102
3.5927
3.0997
3.0846
3.0796
3.0583
2.9918
2.8664
2.8450
2.8337
2.8124
2.6970
2.6794
2.6707
2.6644
2.6556
2.6468
2.6305
2.4461
2.4085
2.4047
2.1940
2.1739
2.1564
2.0472
2.0309
2.0096
1.9243
1.9067
1.9017
0.9659
0.9546
0.9496
0.9383
0.9333
0.8919
0.8743
0.8242
0.8078
HN
O
N
H
STrt
O
HN
O
TrtS
NH
O
O
O
O
19
Integral
10.869
15.954
0.4273
0.1836
0.0609
0.0642
0.4841
0.5757
0.5115
0.0452
0.6418
0.6286
0.5052
0.6208
1.3934
0.6983
0.3962
2.2165
0.5789
1.7876
0.7591
6.1568
2.8692
3.0000
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
(ppm)


177.0901
172.9847
172.2119
170.7533
170.3669
144.7686
144.2179
142.5951
132.7422
129.5062
129.4385
128.0282
127.8737
127.8157
126.9077
126.6082
118.9384
77.4788
77.1600
76.8412
71.8665
67.4230
66.6309
60.4197
58.8934
53.7738
53.1942
49.0501
40.1728
31.9910
31.8655
31.2279
31.1023
30.2909
29.5858
25.6156
20.8727
19.1919
19.0083
18.9021
18.3998
12.7875
O
HN
N
H
STrt
O
HN
TrtS
NH
O
O
O
O
19
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


Integral
FK228
7.2700
6.2188
6.2012
6.1837
6.1661
5.6405
5.6342
5.5565
5.5351
5.5226
4.5767
4.5642
4.5491
4.5366
4.3785
4.3685
3.8730
3.8454
3.8304
3.0401
3.0275
2.9999
2.8406
2.7302
2.7265
2.6951
2.6926
2.5571
2.5421
2.5232
2.5082
2.4982
2.2435
2.2335
2.1193
2.1030
2.0867
2.0691
1.6113
1.5937
0.9928
0.9753
0.9715
0.9540
0.8925
0.8749
0.8636
0.8461
-0.0621
-0.1462
0.6196
0.7242
1.7398
0.6252
0.7662
3.8722
3.2590
1.3419
1.1718
3.6864
1.2178
1.2305
3.0001
6.5665
7.1720
(ppm)


172.4244
171.5936
169.4009
168.5218
165.8558
130.4528
129.7959
129.3323
77.4788
77.1600
76.8412
70.3499
62.4965
58.3235
56.7007
49.0888
48.8763
48.6637
37.8931
37.7193
34.6861
31.7302
30.1460
29.0062
19.1725
19.0470
18.4191
18.1679
13.1932
FK228
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


130.4432
129.7960
129.3323
70.3499
62.4772
58.3042
56.6910
37.8835
37.6807
34.6668
31.7303
30.1364
29.0159
19.1629
19.0567
18.4095
18.1583
13.1932
HN
N
H
O
S
S
HN
O
NH
O
O
O
O
FK228
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)
S33