Stereoselective Synthesis of Constrained Azacyclic Hydroxyethylene Isosteres as Aspartic Protease Inhibitors – Dipolar Cycloaddition and Related Methodologies Toward Branched Pyrrolidine and Pyrrolidinone Carboxylic Acids

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Supporting Information

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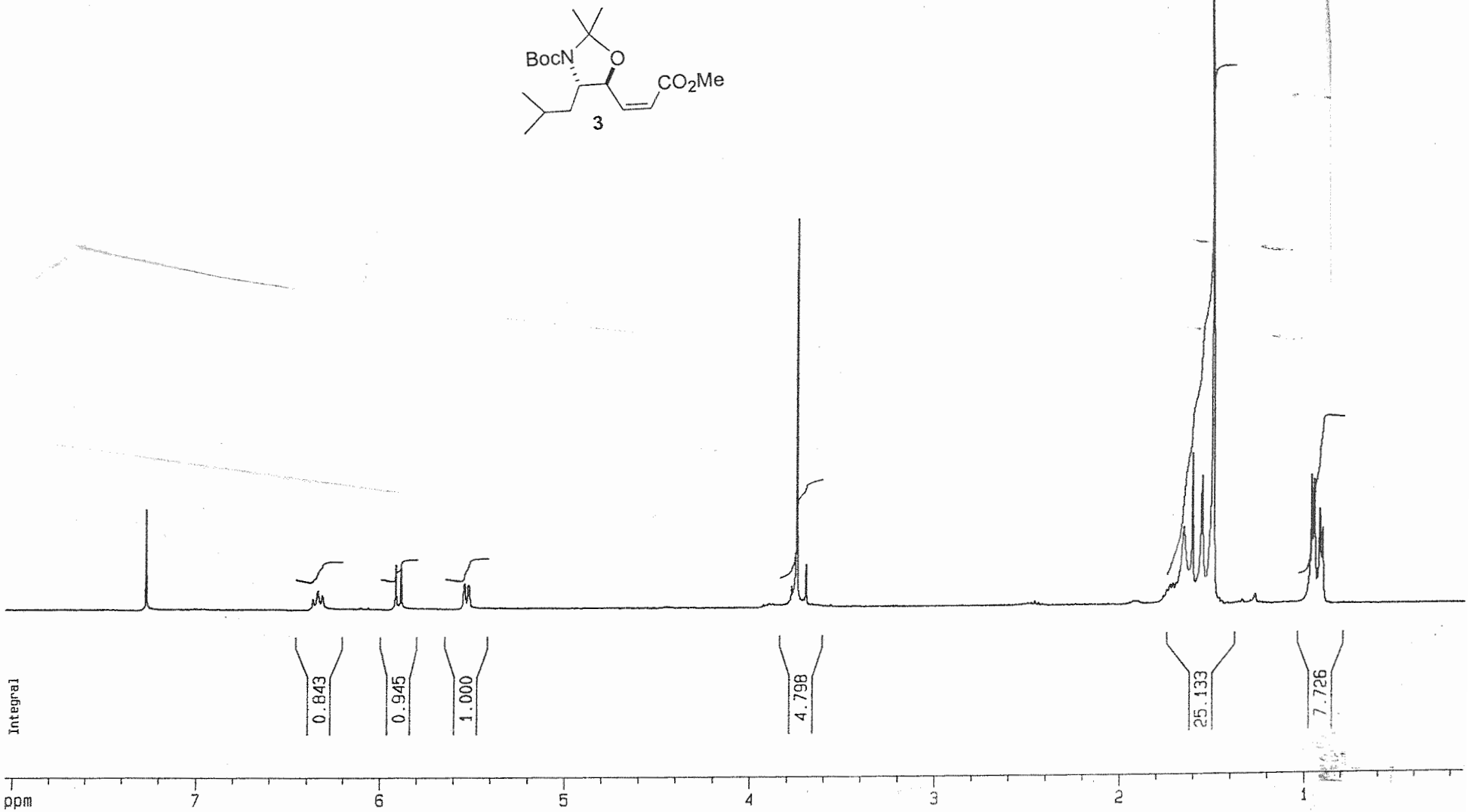
4. X-ray CIF files; compounds 6, 16

Experimental Section

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods; THF and ether, from Na/ benzophenone; CH_2Cl_2 and toluene, from CaH_2. All commercially available reagents were used without further purification. All reactions were performed under argon atmosphere. NMR (^1H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers in $CDCl_3$ or CD_3OD or D_2O with solvent resonance as the internal standard. Low- and high-resolution mass spectra were recorded on VG Micromass, AEIMS 902, or Kratos MS-50 spectrometers using fast atom bombardement (FAB). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck 60F 254 precoated silica gel plates. Flash column chromatography was performed using (40-60 μm) silica gel at increased pressure. All melting points are uncorrected. HPLC analysis was done on reverse phase O18 columns.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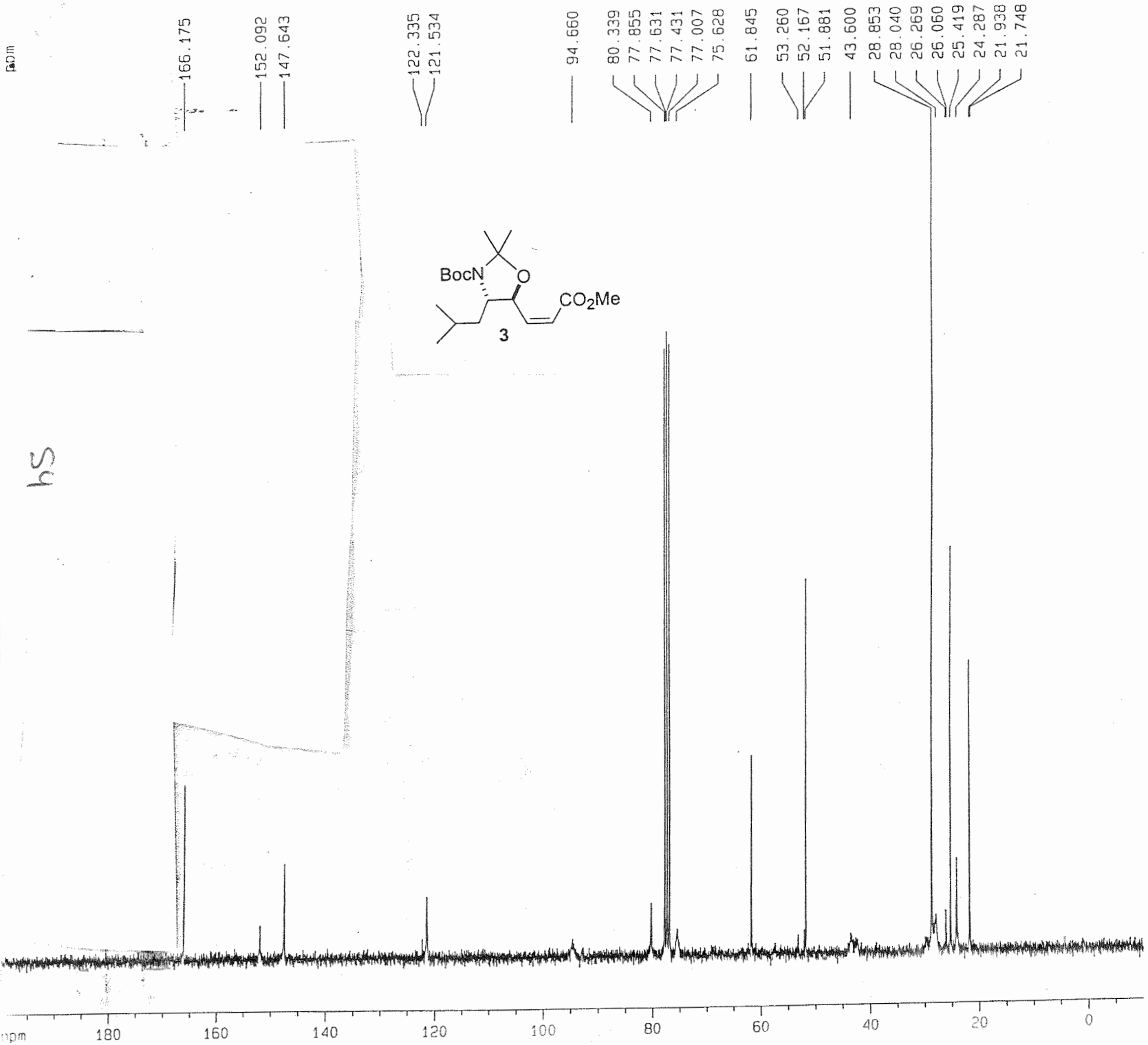
6
5
4
3
2
1

S3



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DE 37.93 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

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PL1 7.00 dB
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1D NMR plot parameters
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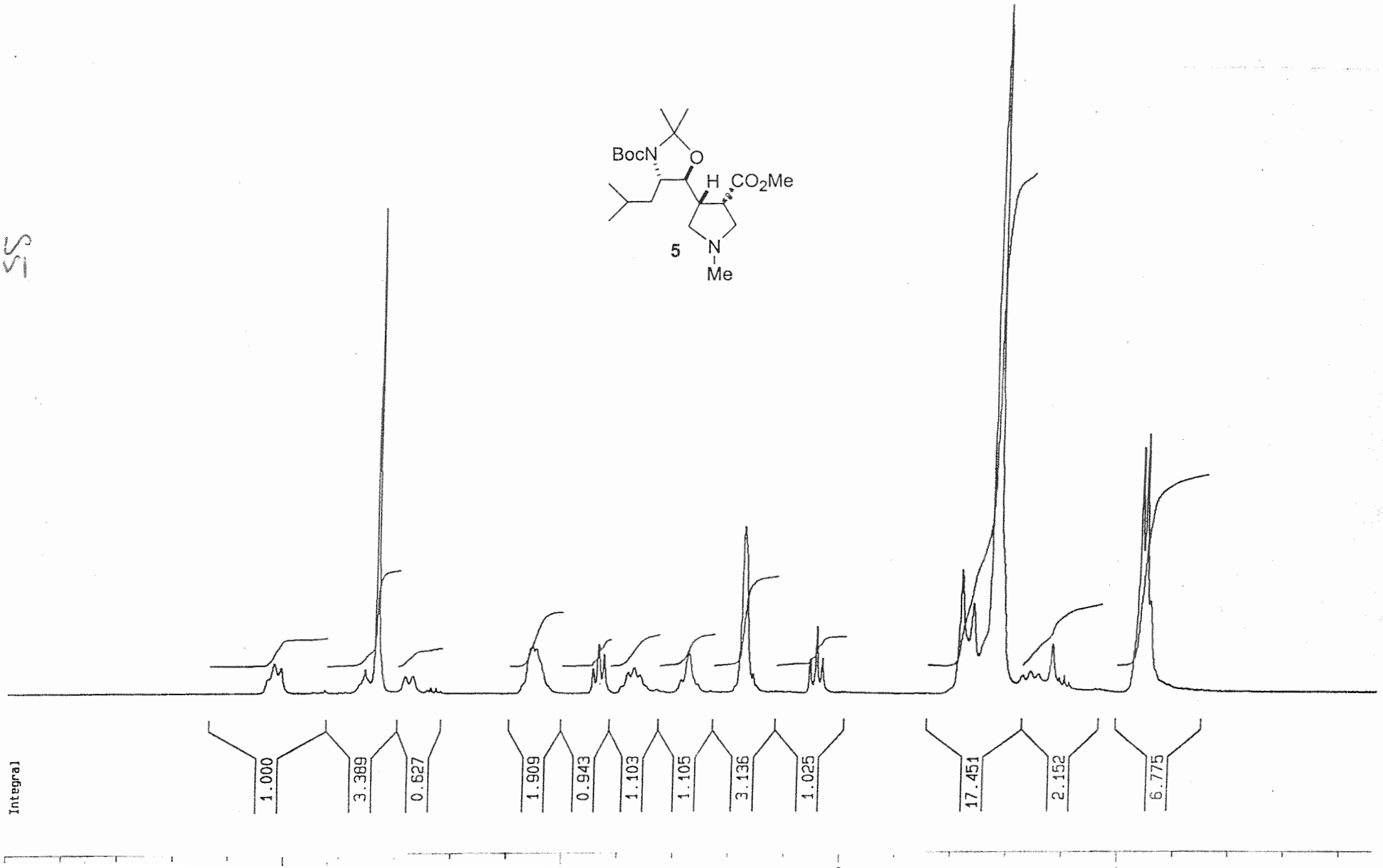
HZCM 720.37366 Hz/cm

S4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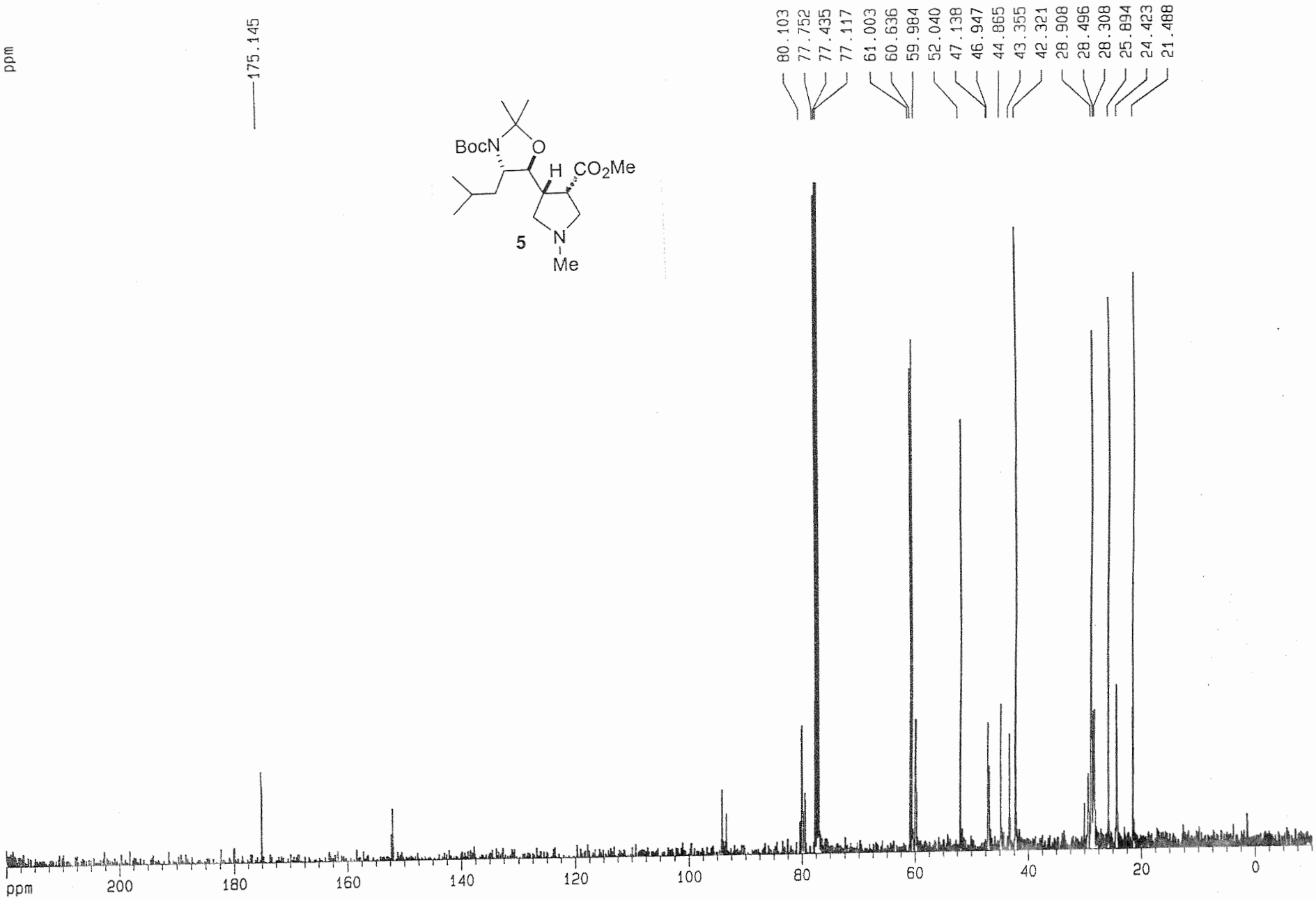
S5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Me
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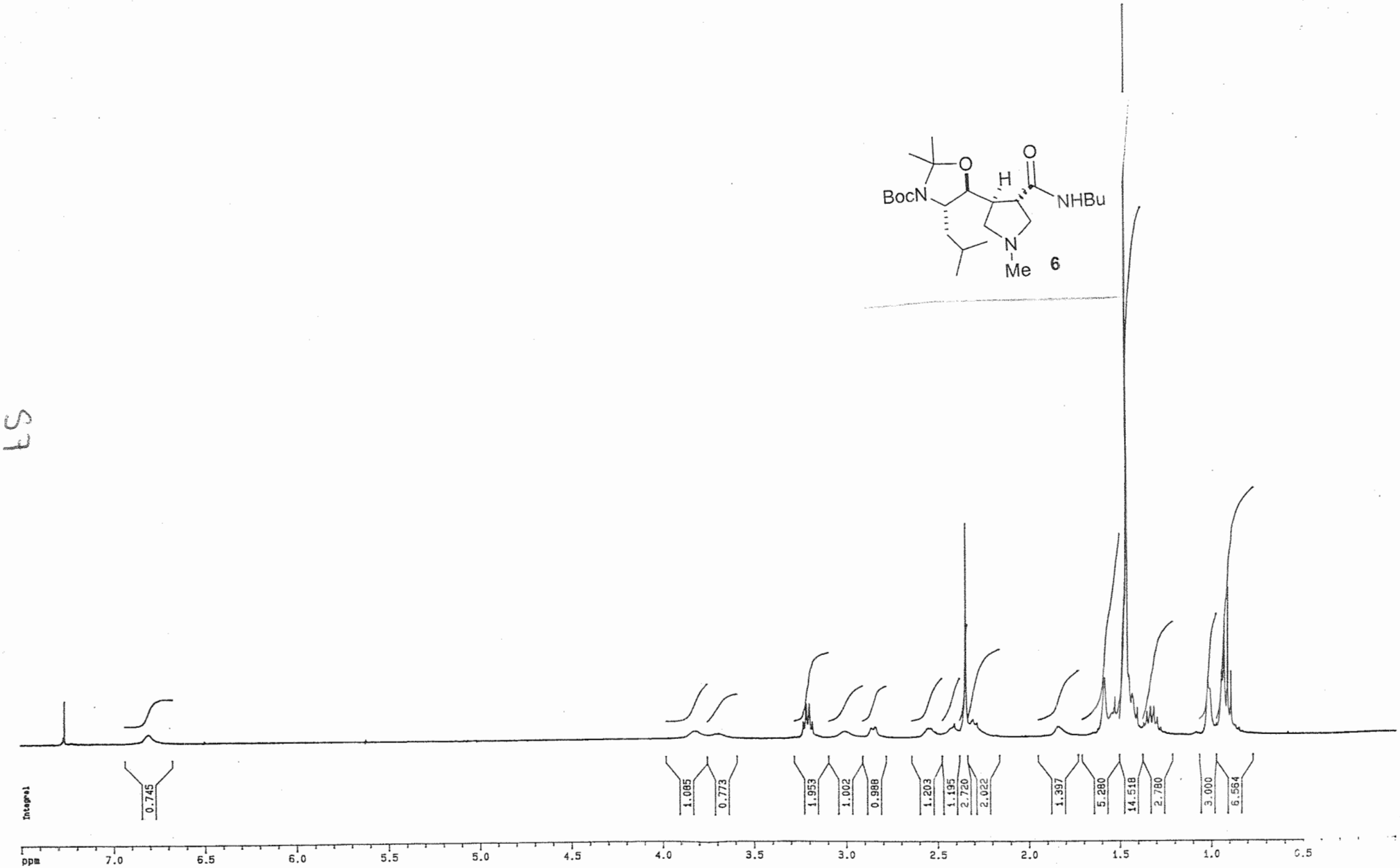
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O
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Me
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2.0
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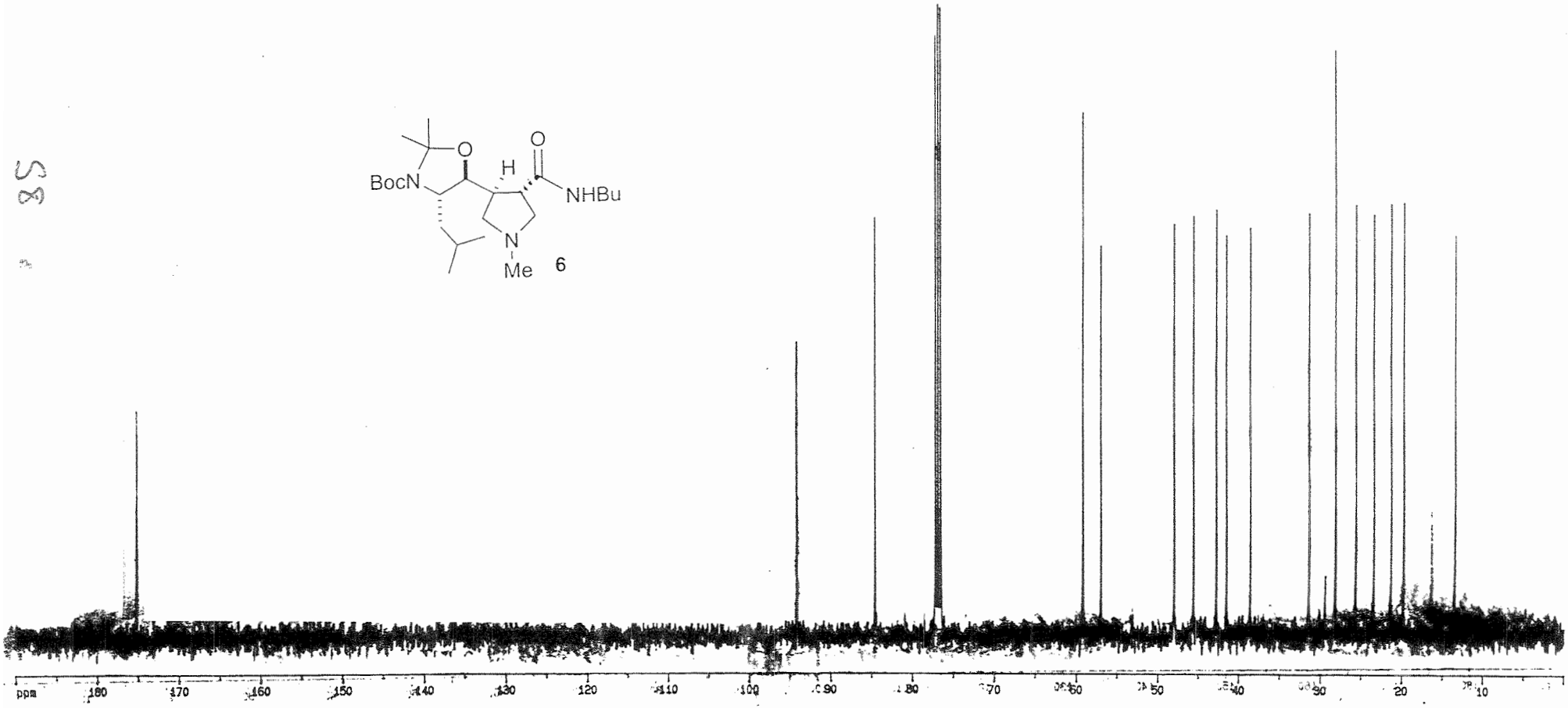
0.5

S1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H
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Me
6
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70
60
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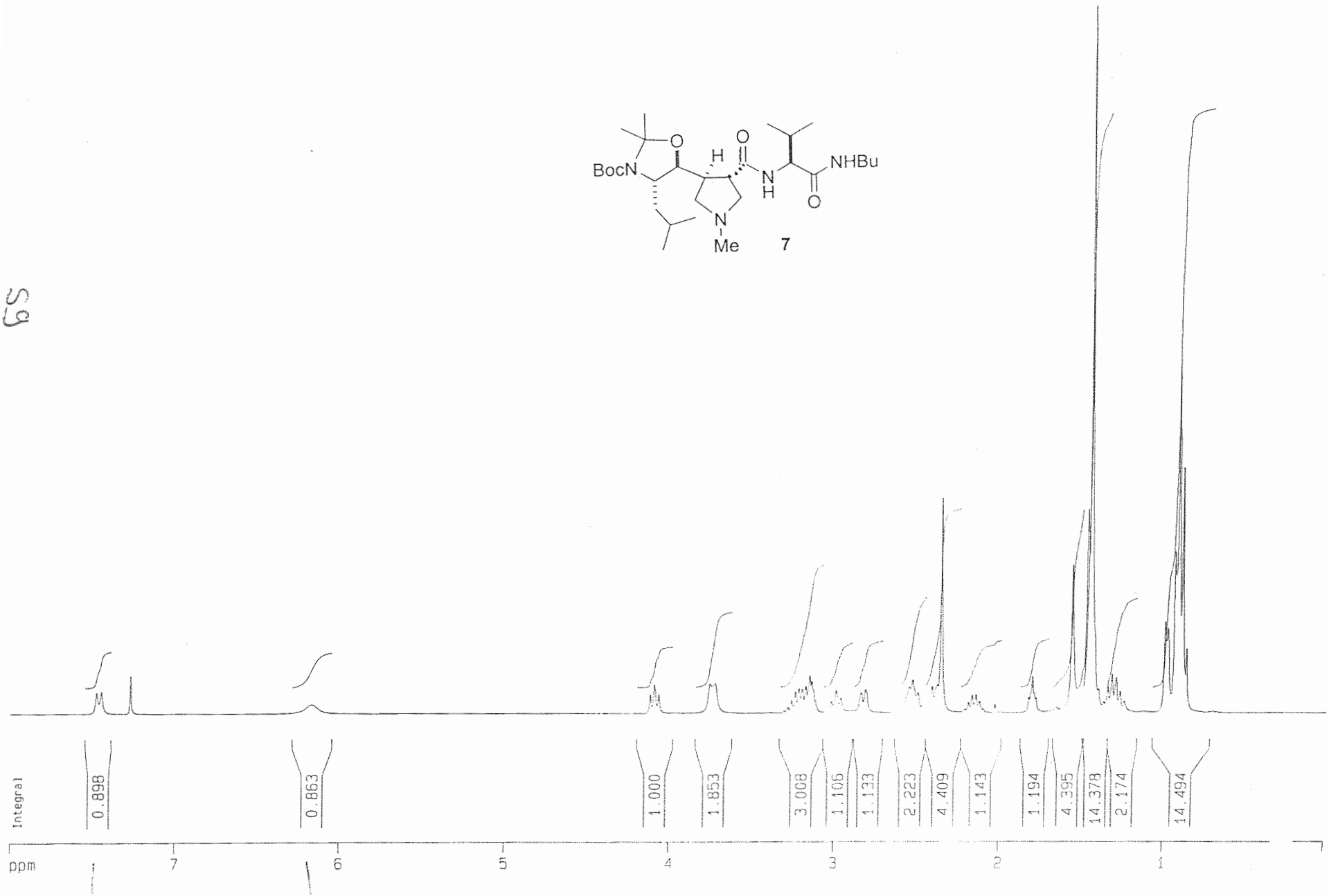
40
30
20
10

S8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O
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N
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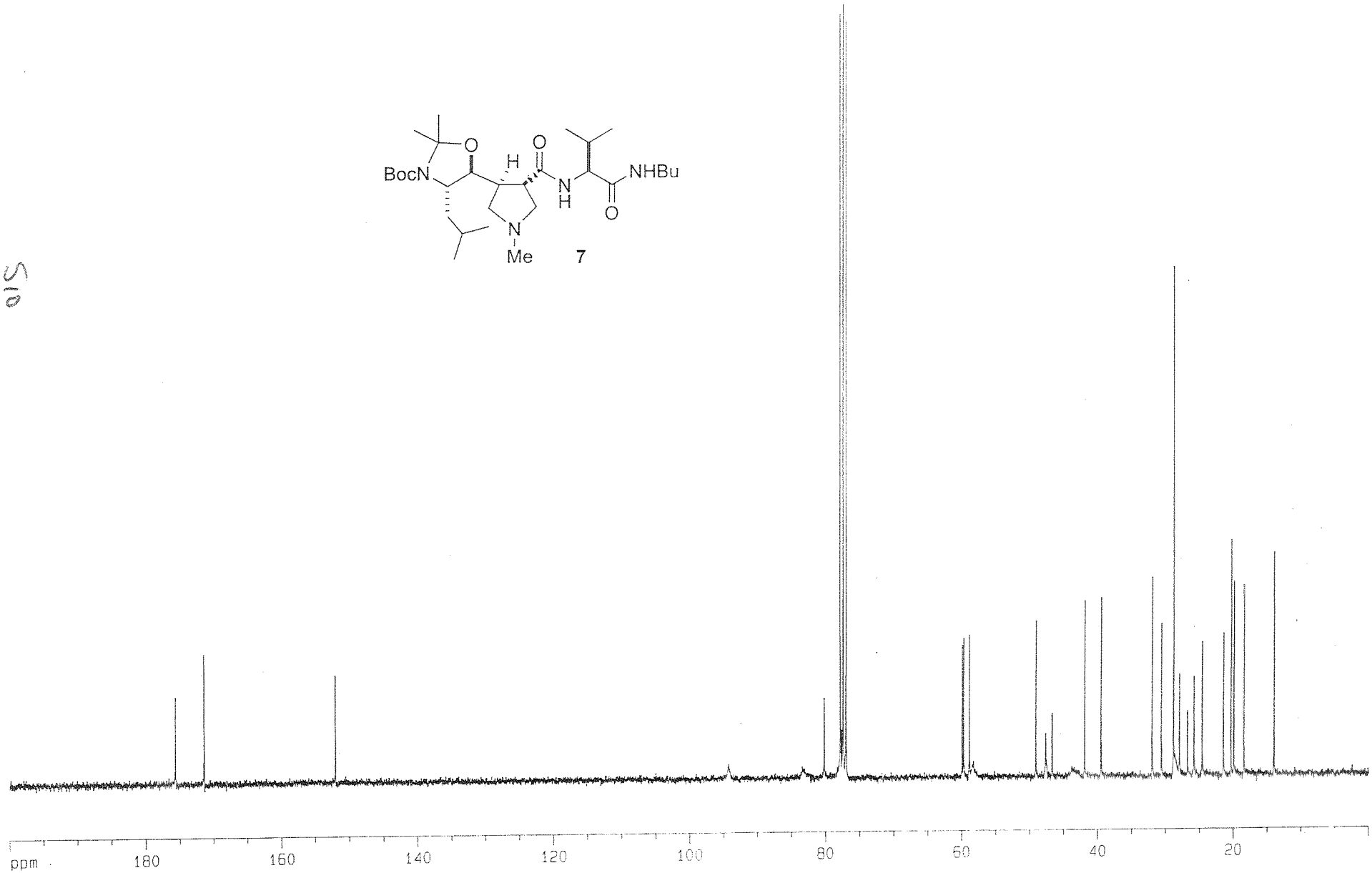
3
2
1

7



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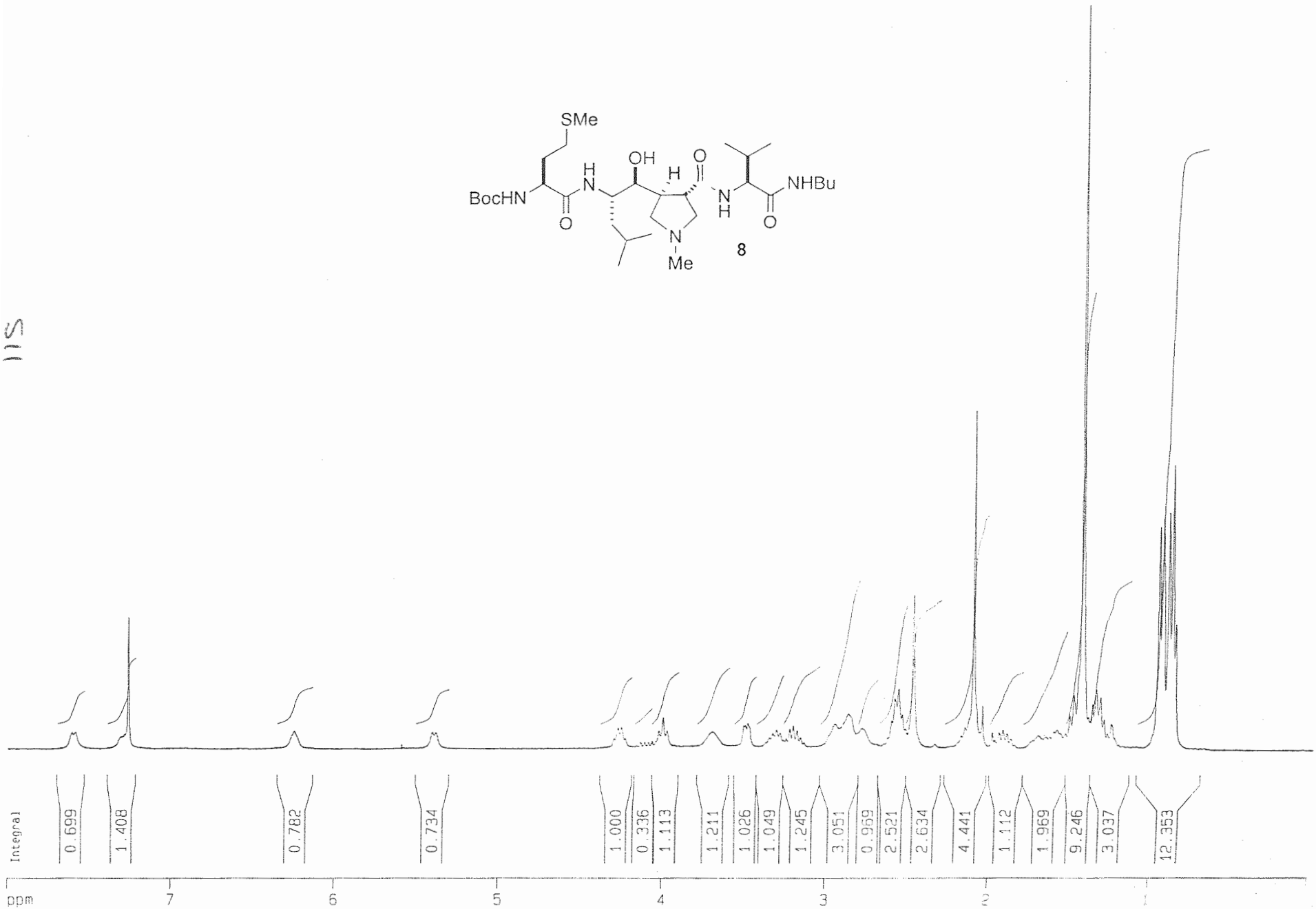
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BocHN
H
N
O
OH
H
O
N
H
NHBu
O
N
Me
8
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0.782
0.734
1.000
0.336
1.113
1.211
1.026
1.049
1.245
3.051
0.969
2.521
2.634
4.441
1.112
1.969
9.246
3.037
12.353
ppm
7
6
5
4
3
2
1

S11

SMe
BocHN
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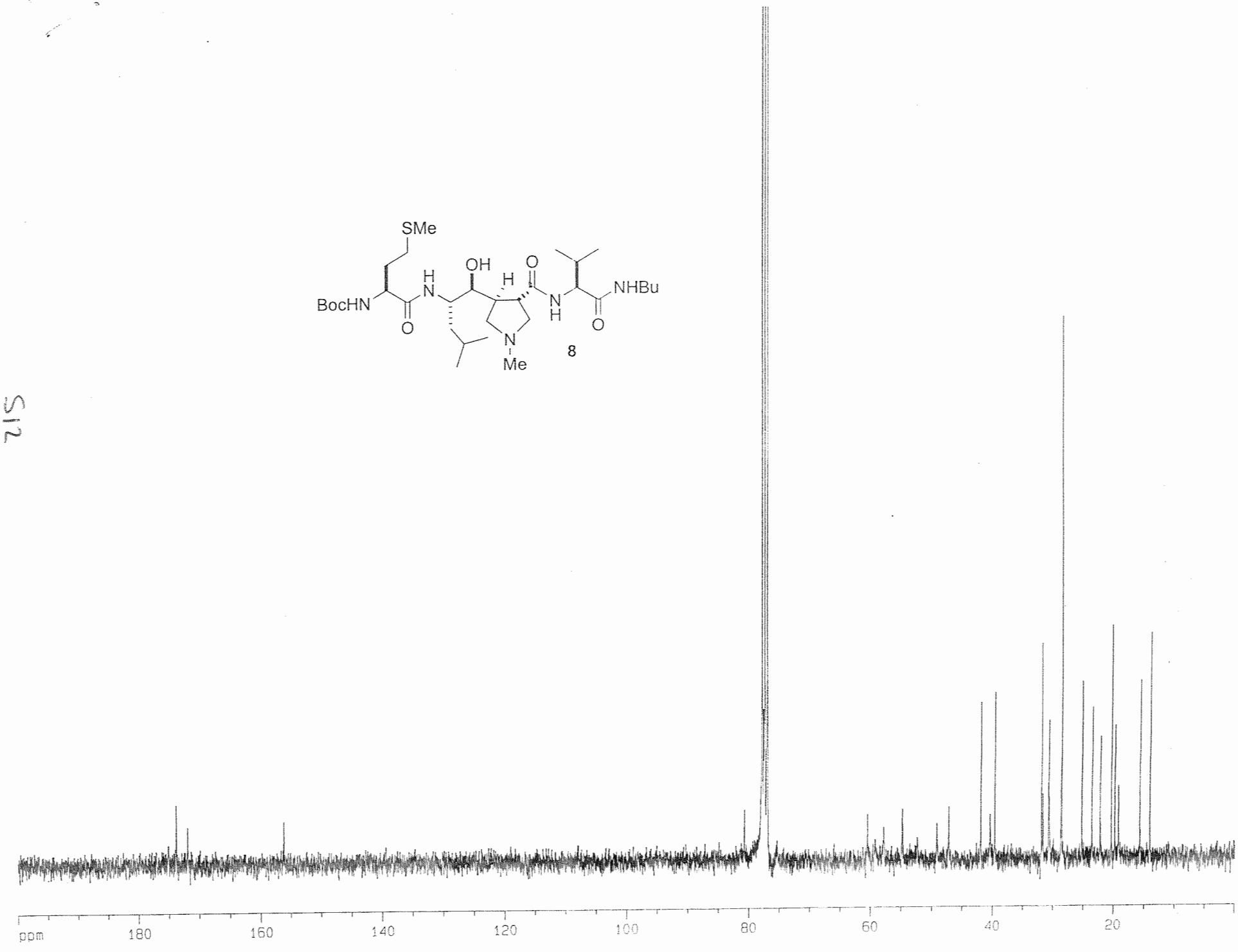
H
N
OH
H
O
N
H
NHBu
O
N
Me
8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40
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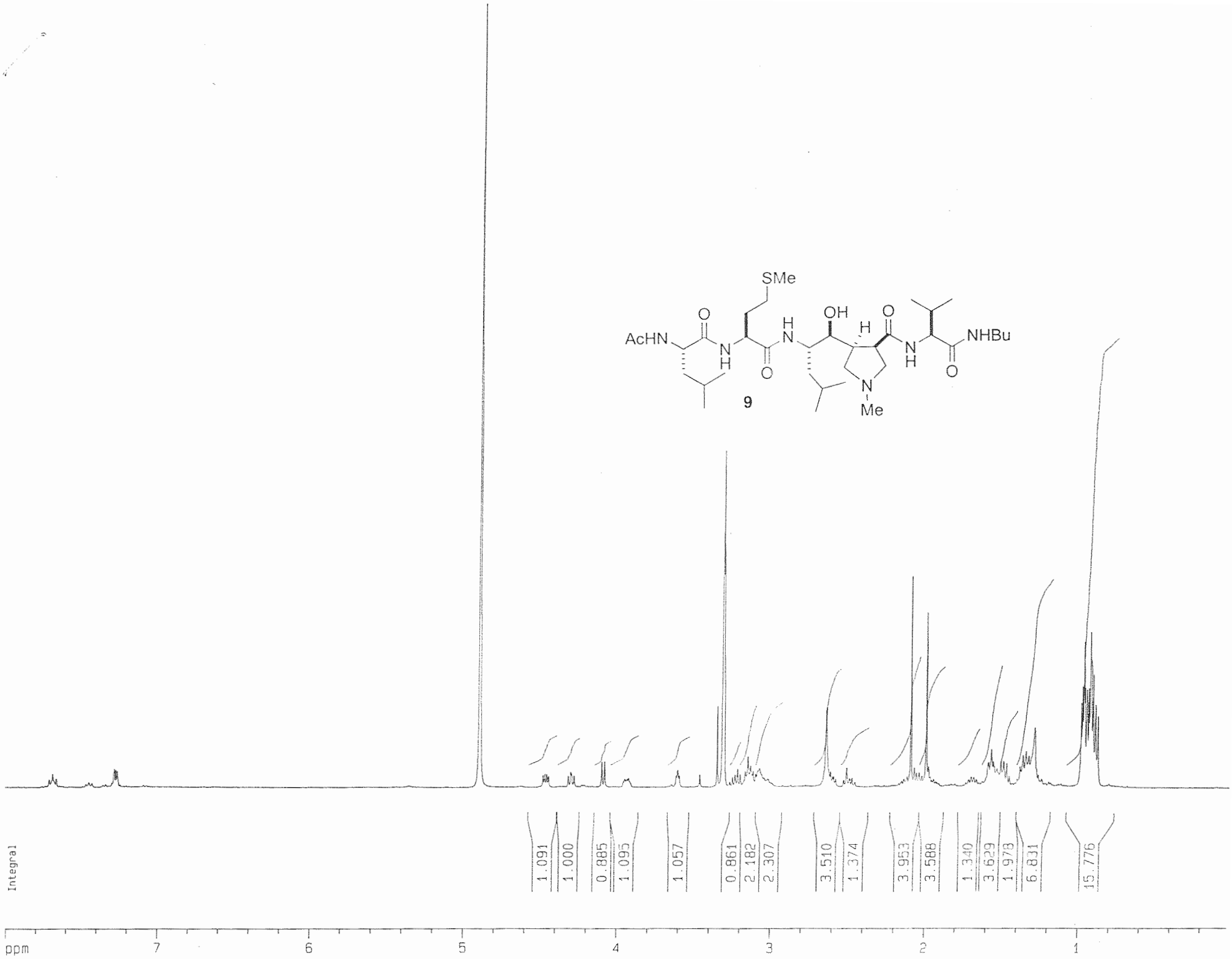
S12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AcHN
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N
H
O
H
N
OH
H
O
N
H
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O
N
Me
9
Integral
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1.000
0.885
1.095
1.057
0.861
2.182
2.307
3.510
1.374
3.953
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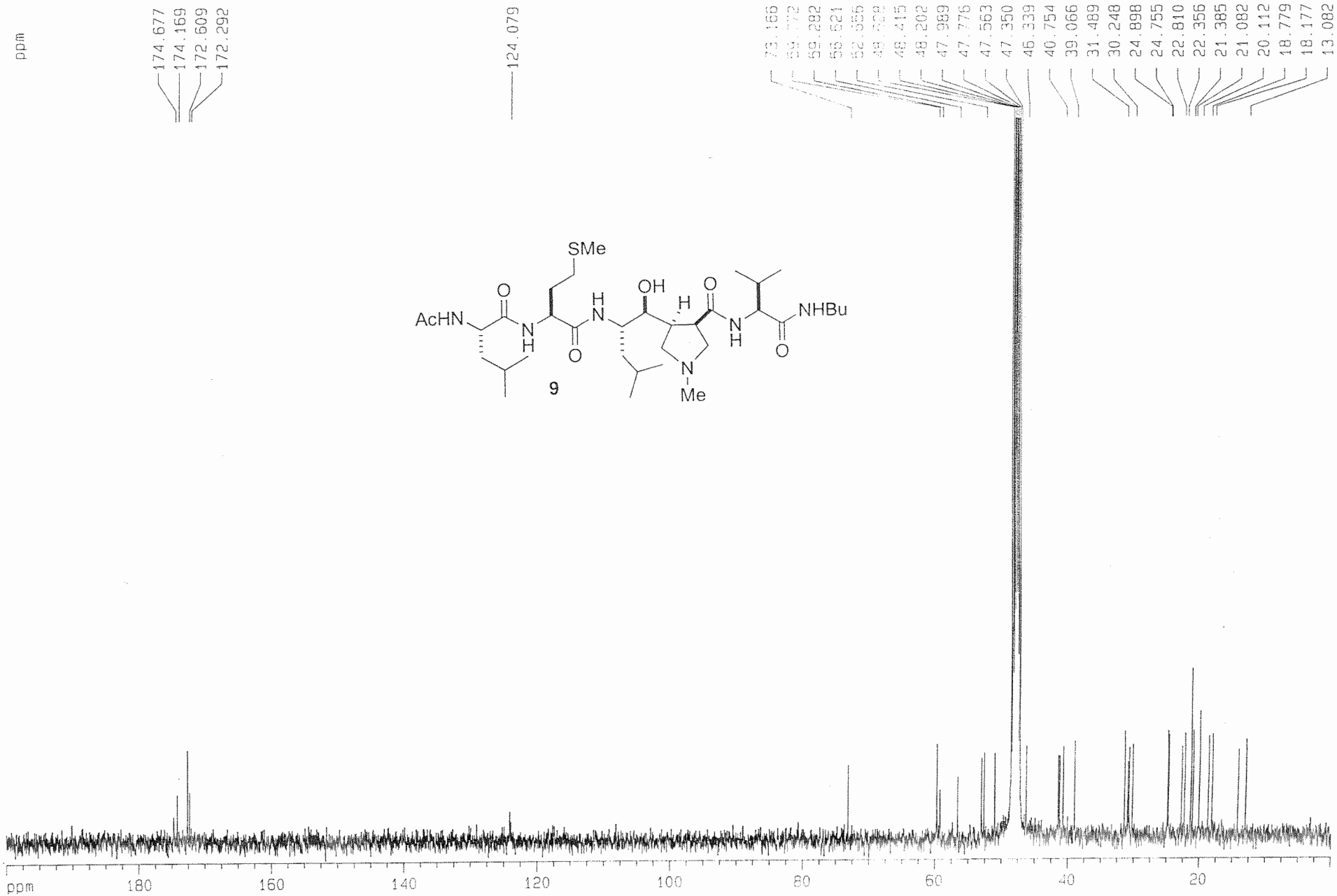
ppm
7
6
5
4
3
2
1

S13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47.350
46.339
40.754
39.066
31.489
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24.898
24.755
22.810
22.356
21.385
21.082
20.112
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18.177
13.082
SMe
AcHN
O
N
H
H
N
O
OH
H
O
N
H
NHBu
O
N
Me
9
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120
100
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60
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20

BocN
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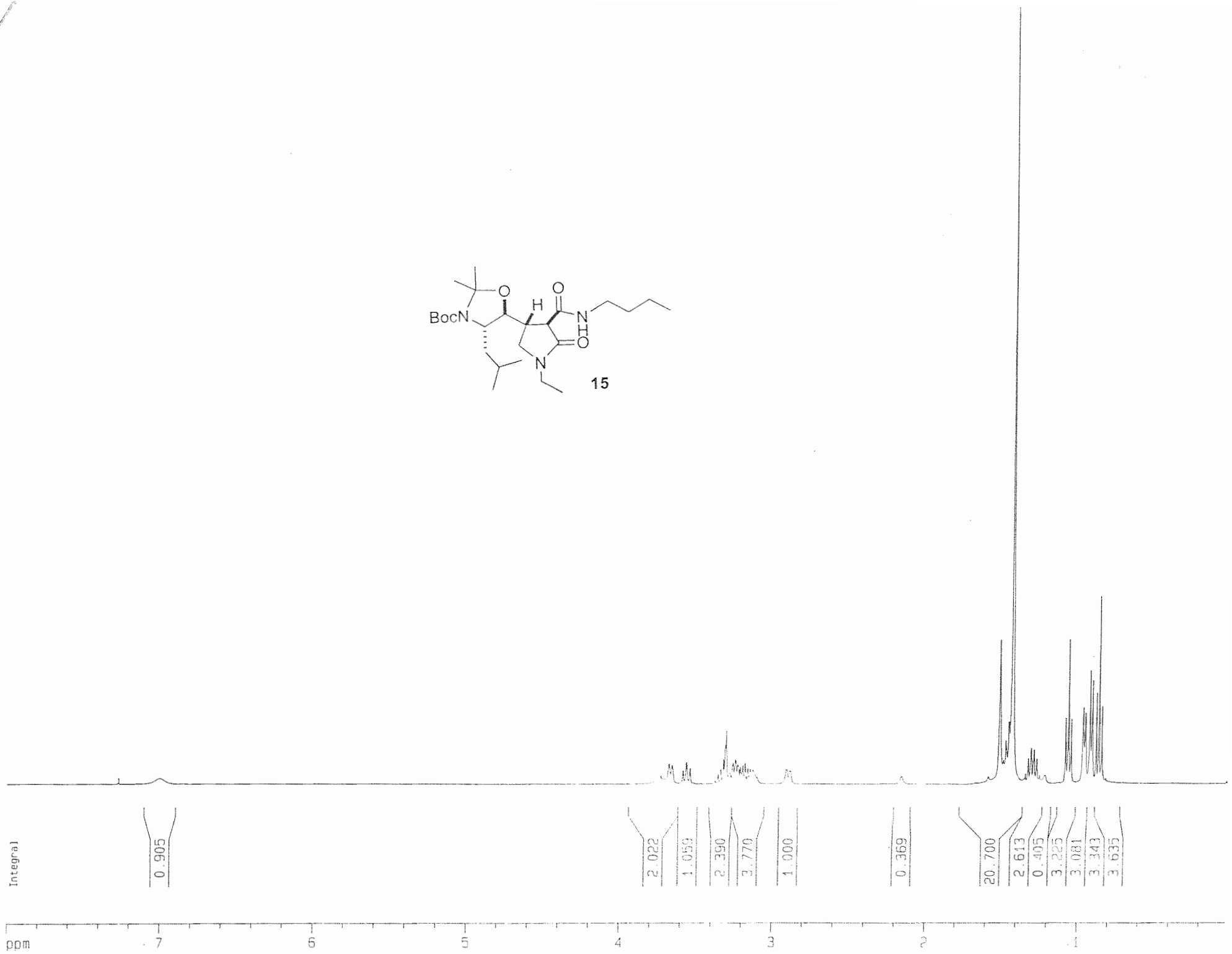
H
O
N
15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1

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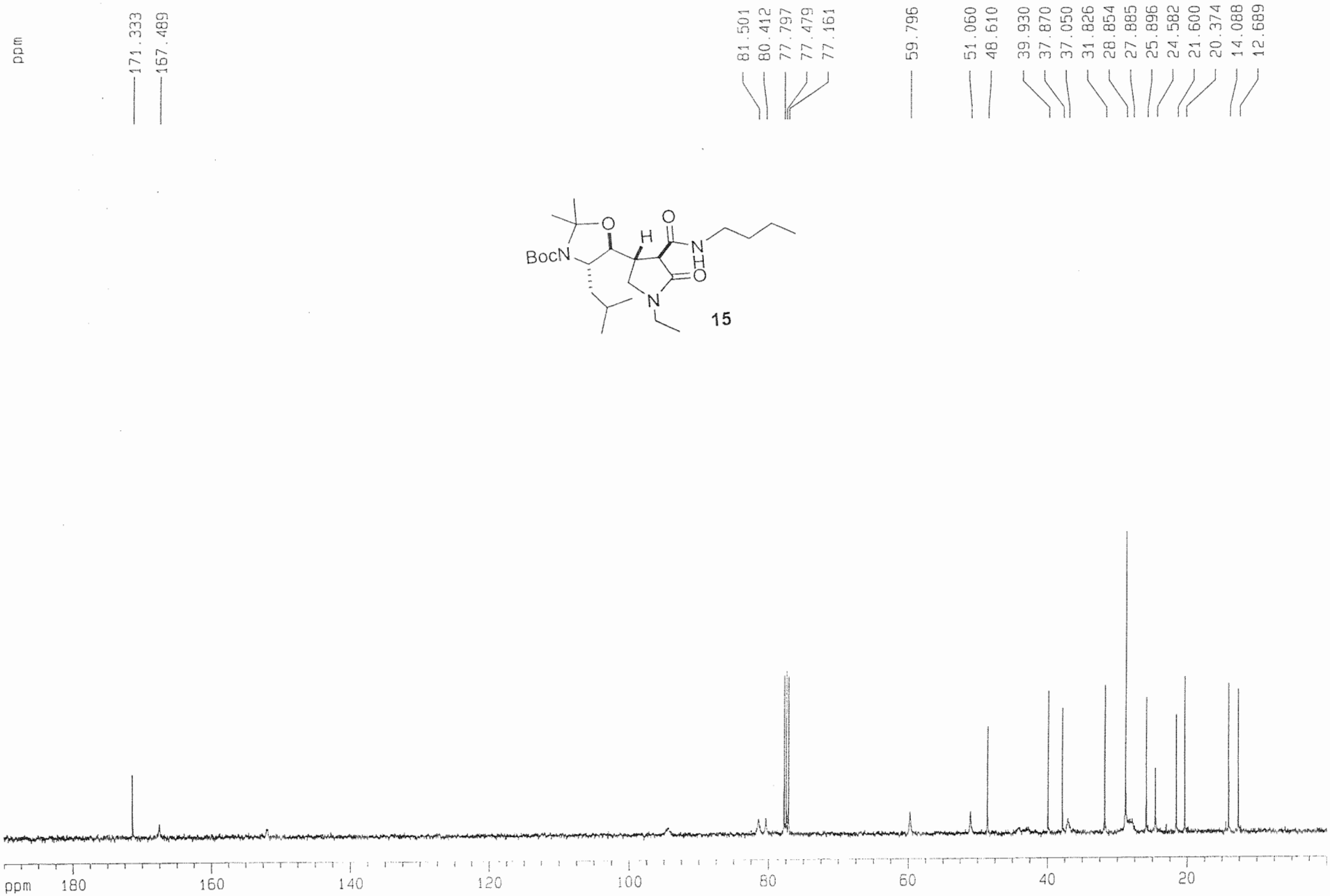
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31.826
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27.885
25.896
24.582
21.600
20.374
14.088
12.689
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N
O
O
N
15
ppm
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140
120
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80
60
40
20

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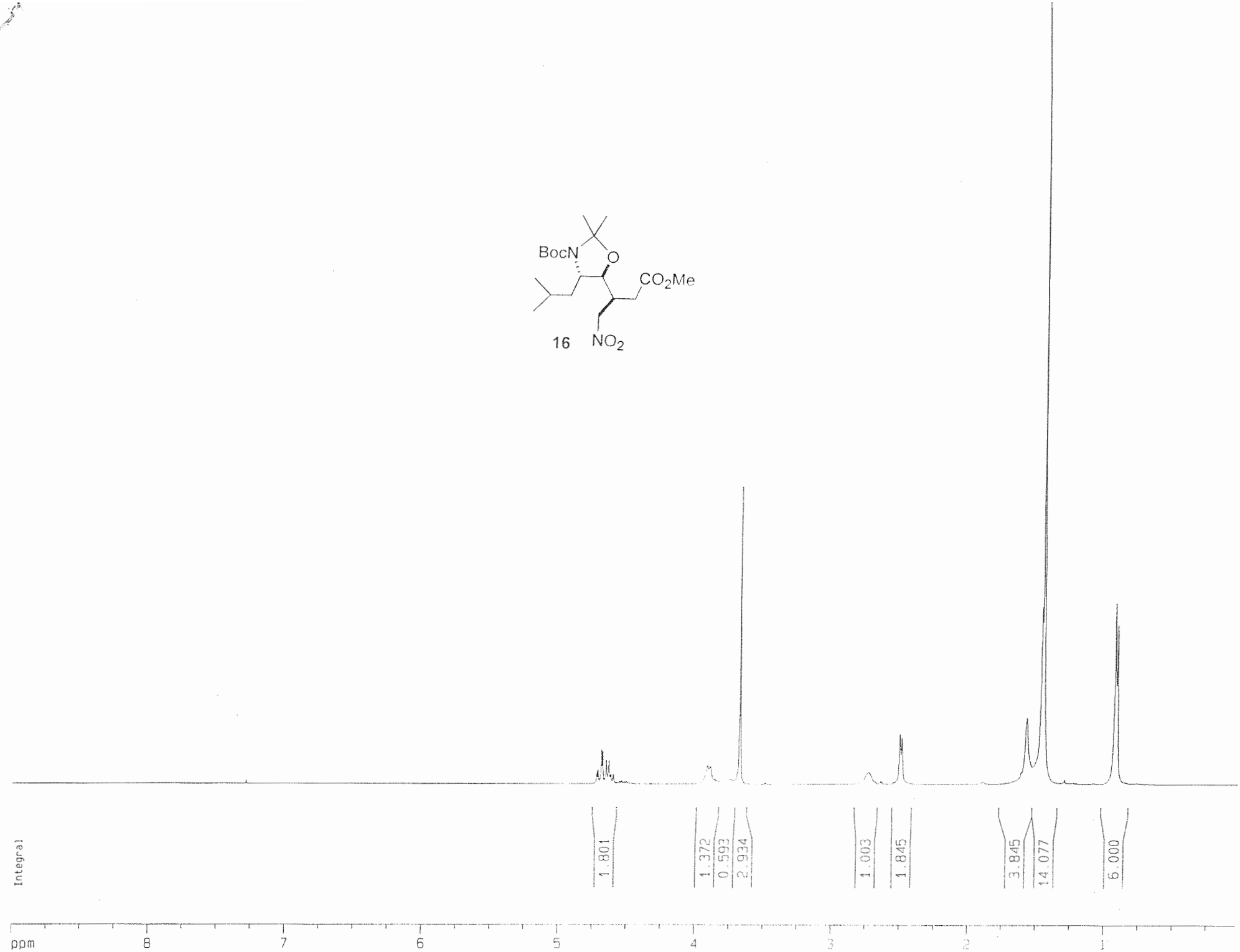
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7
6
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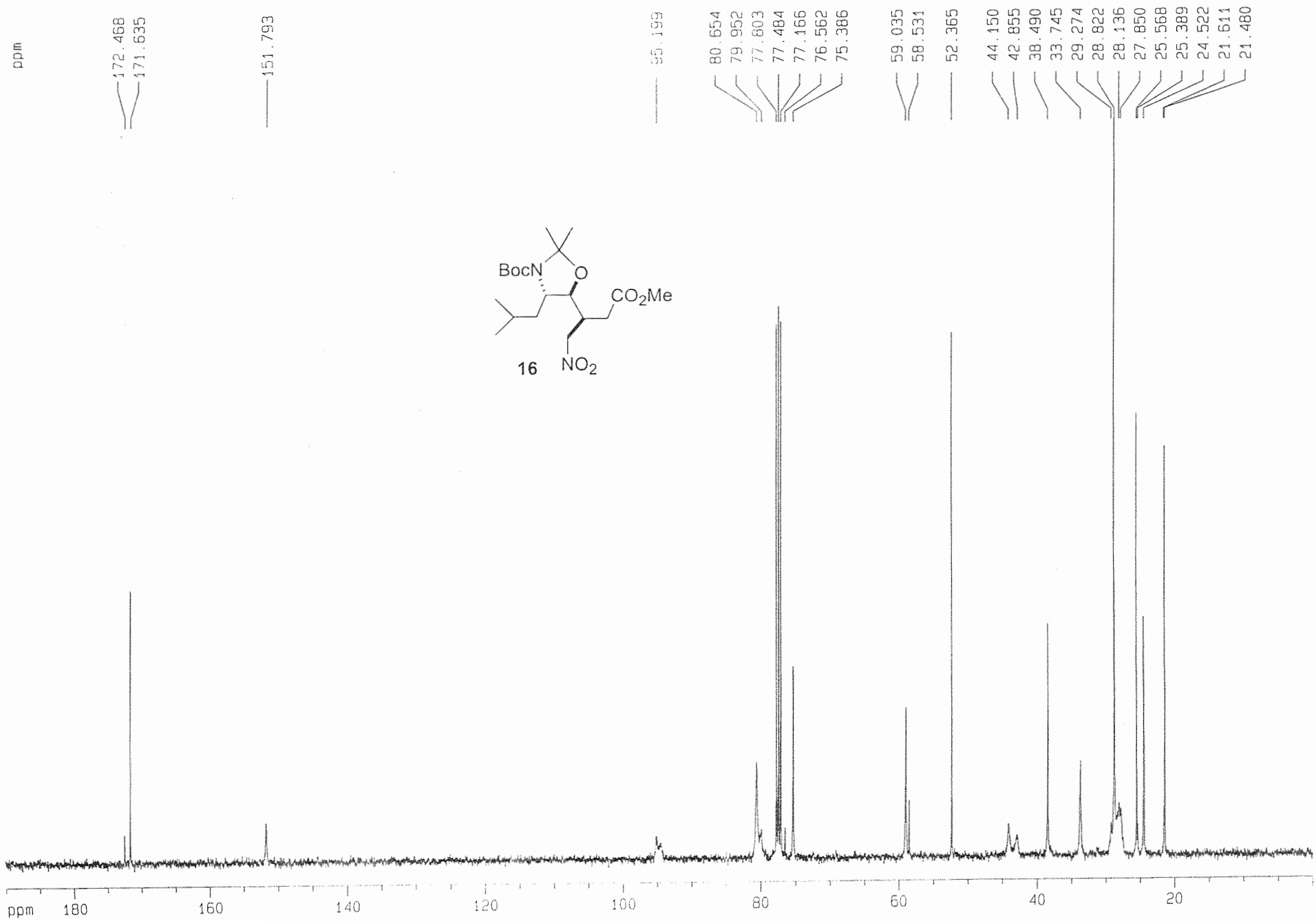
4
3
2
1

S17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52.365
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38.490
33.745
29.274
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28.136
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24.522
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80
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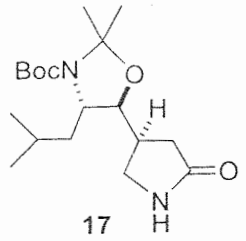
BocN
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H
O
N
H

17

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3
2
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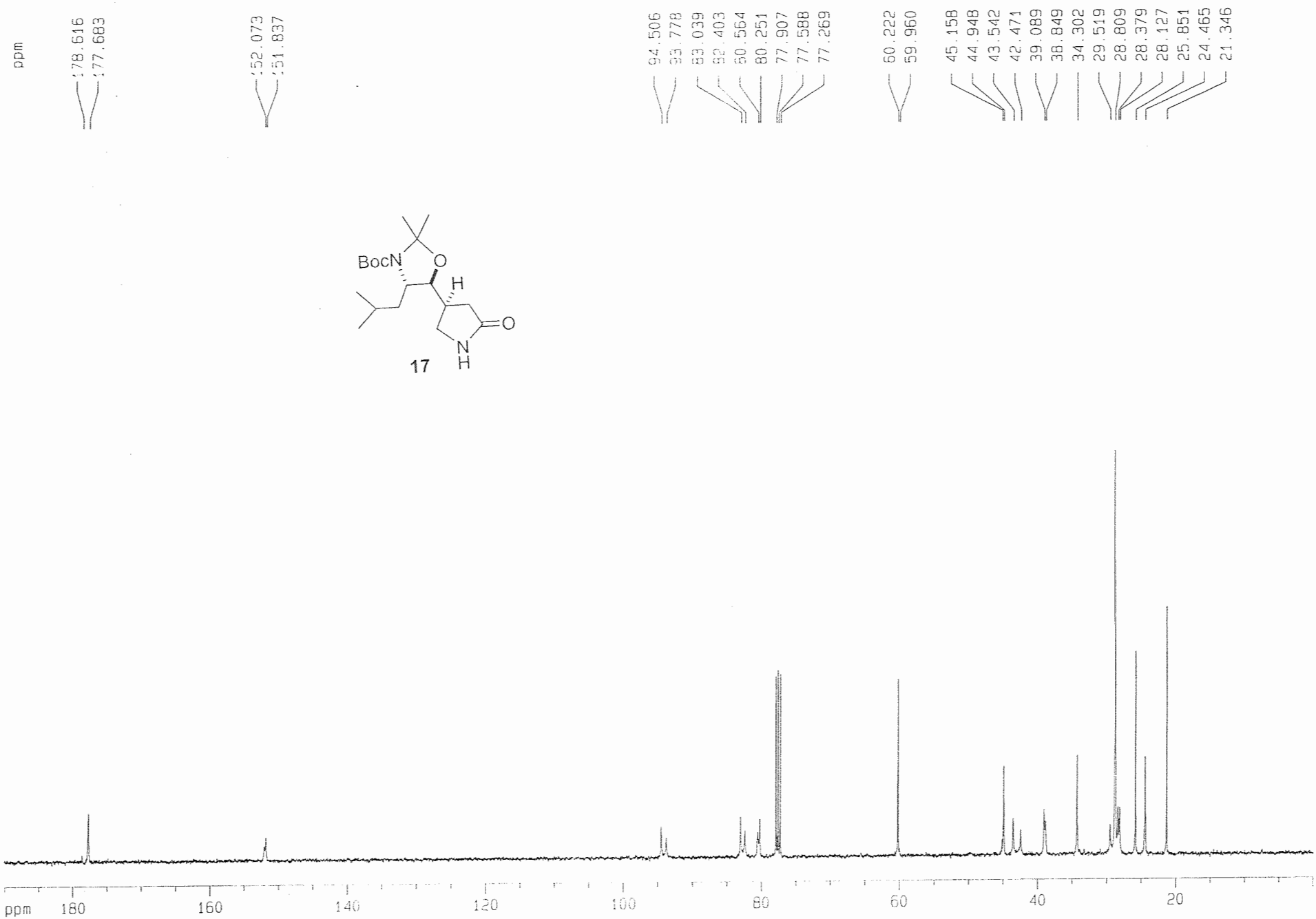
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29.519
28.809
28.379
28.127
25.851
24.465
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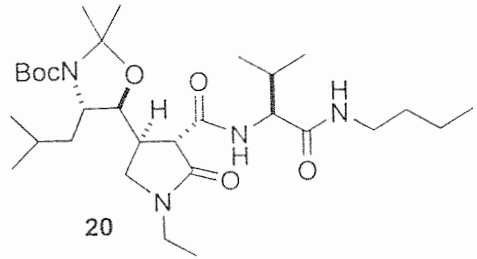
20

S20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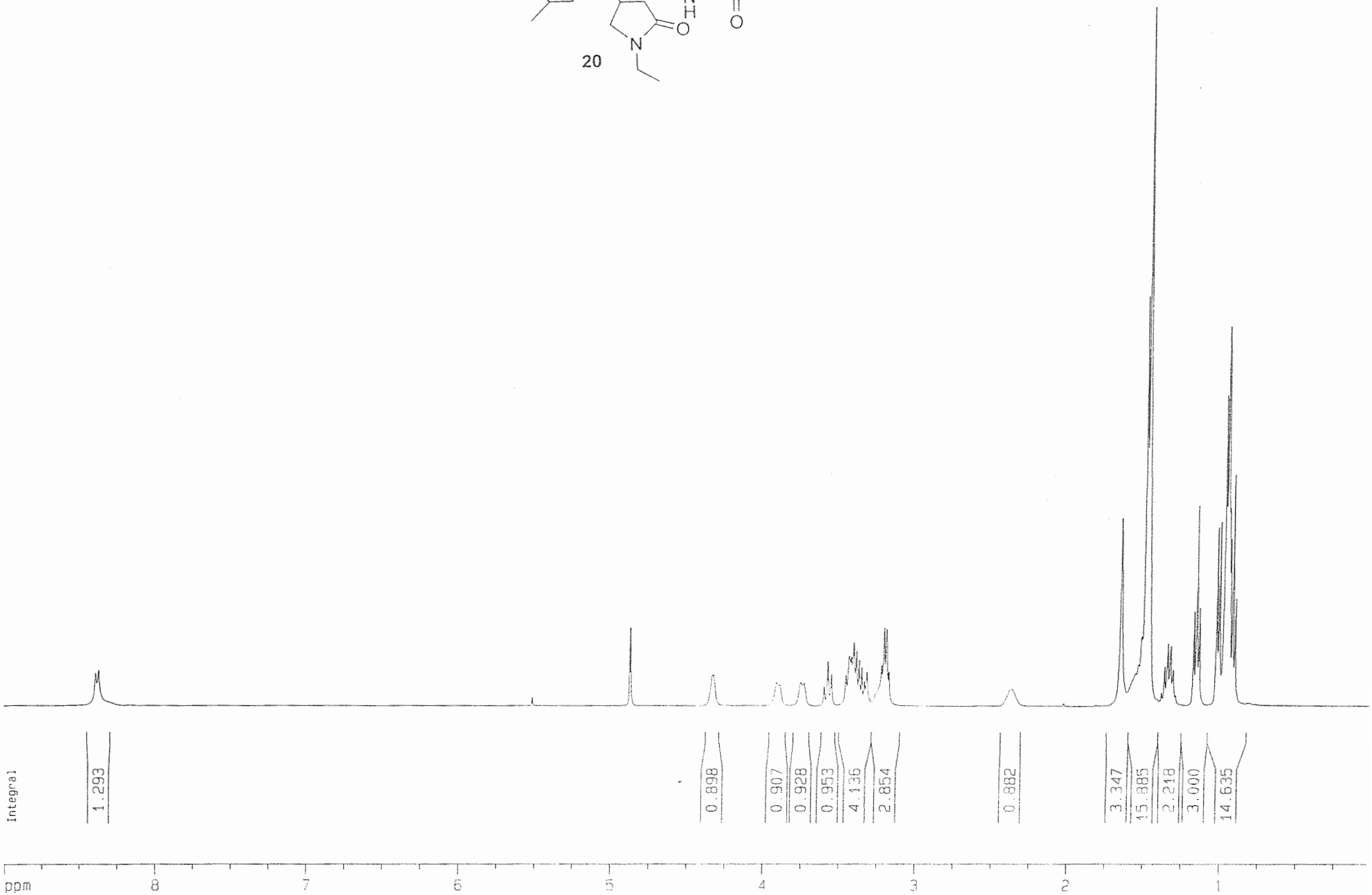
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7
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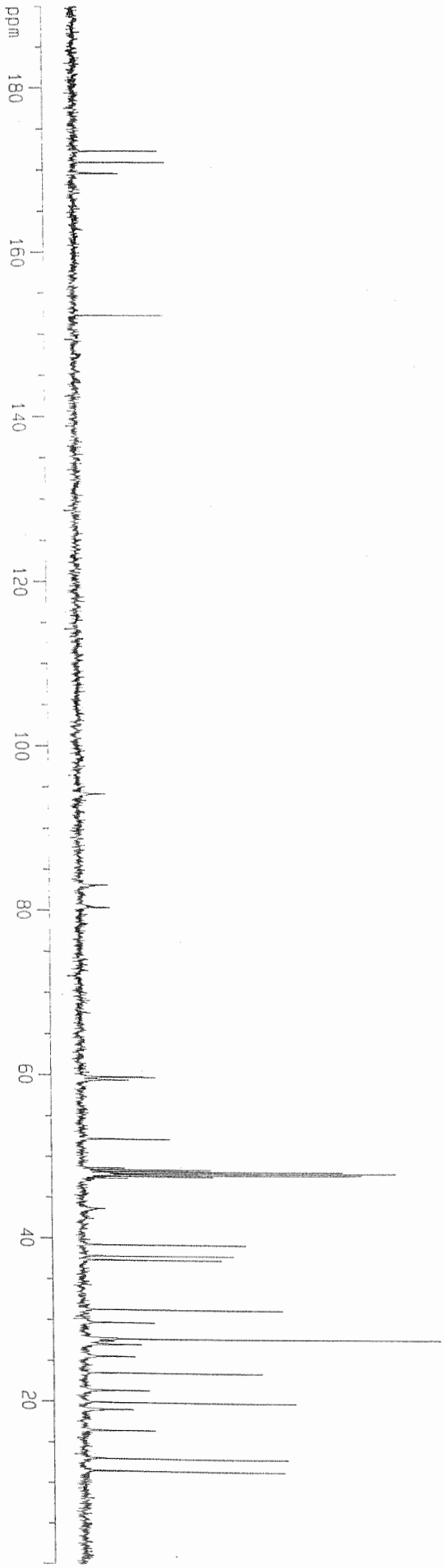
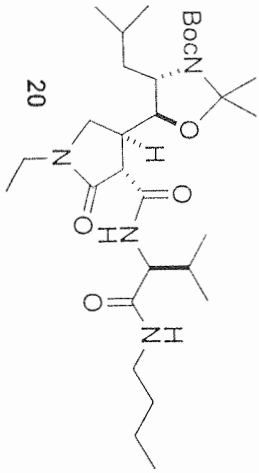
4
3
2
1





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169.529

152.236

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48.481
48.268
48.055
47.842
47.629
47.416
39.304
37.928
37.436
31.359
29.770
27.830
27.503
27.123
25.667
23.645
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20.055
19.191
16.608
13.173
11.643

SMe
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O
H
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OH
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O
N
O
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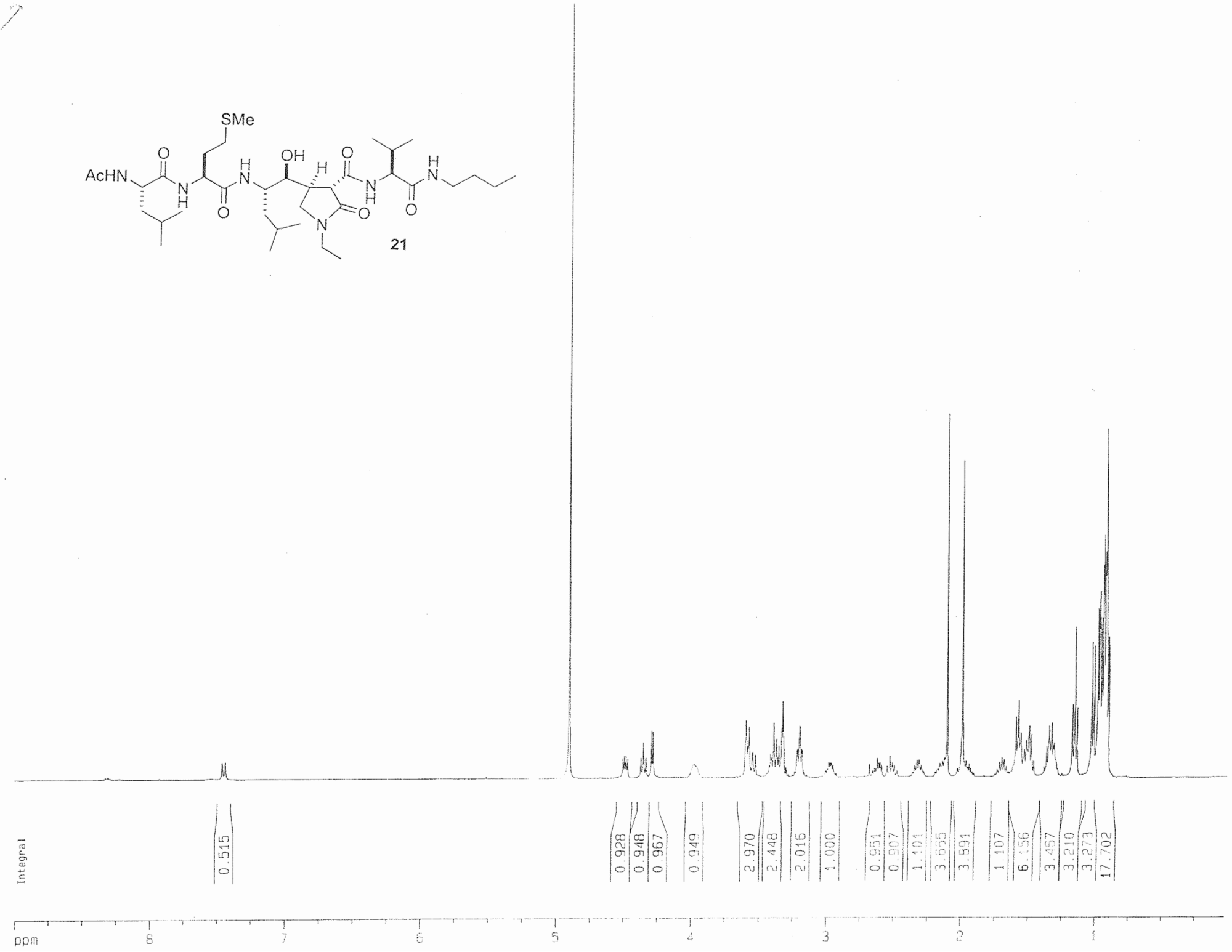
N
H
O
H
N

21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2.448
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3.991
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ppm
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7
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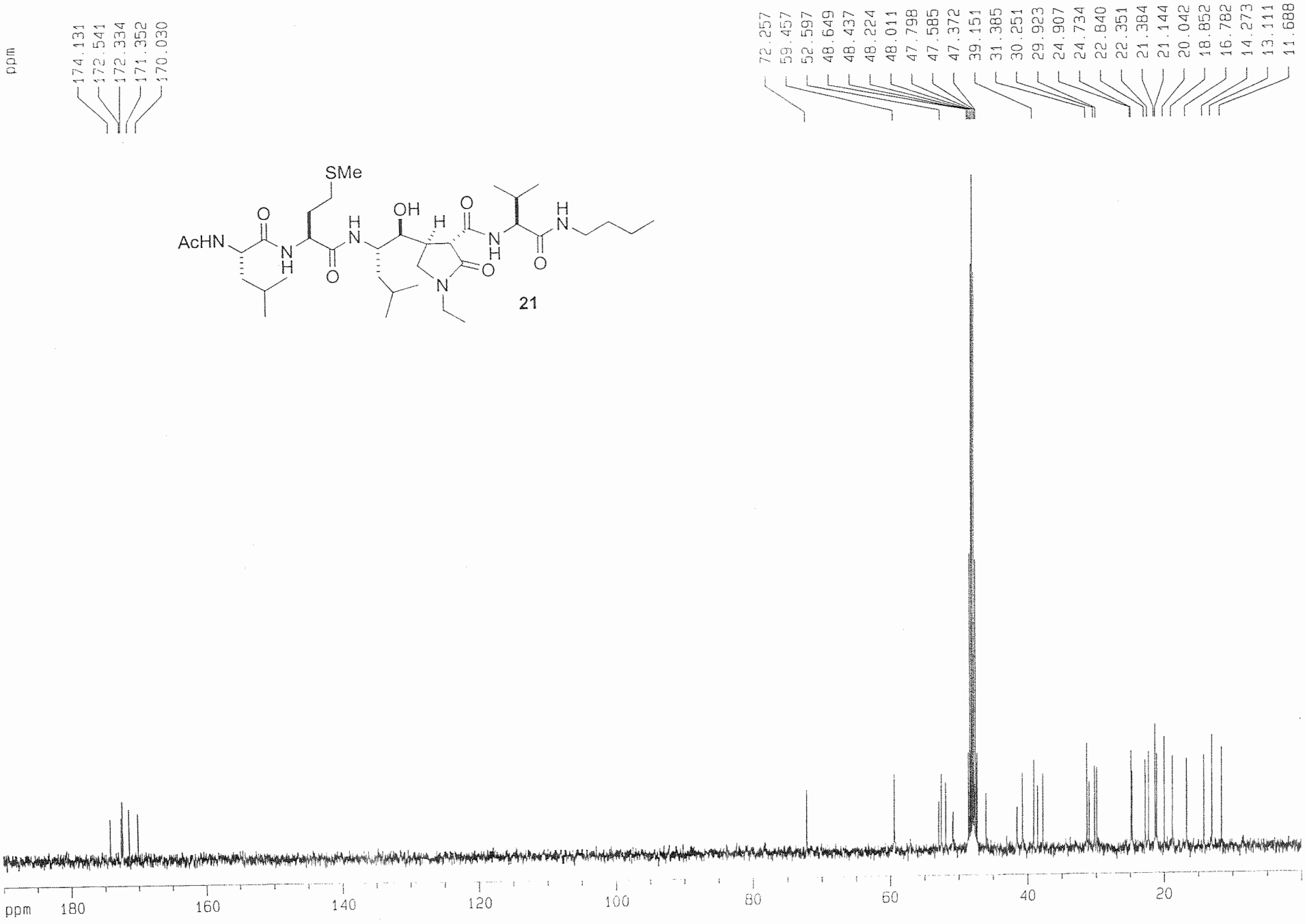
1

S23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47.585
47.372
39.151
31.385
30.251
29.923
24.907
24.734
22.840
22.351
21.384
21.144
20.042
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16.782
14.273
13.111
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SMe
AcHN
OH
21
ppm
180
160
140
120
100
80
60
40
20

S24

BocN
O
H
O
N
H
NHBu
O
NMe
O
27
Integral
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0.921
1.000
0.795
0.949
0.961
1.145
1.088
1.125
3.395
3.214
1.179
1.179
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2.958
1.493
18.464
ppm
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7
6
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4
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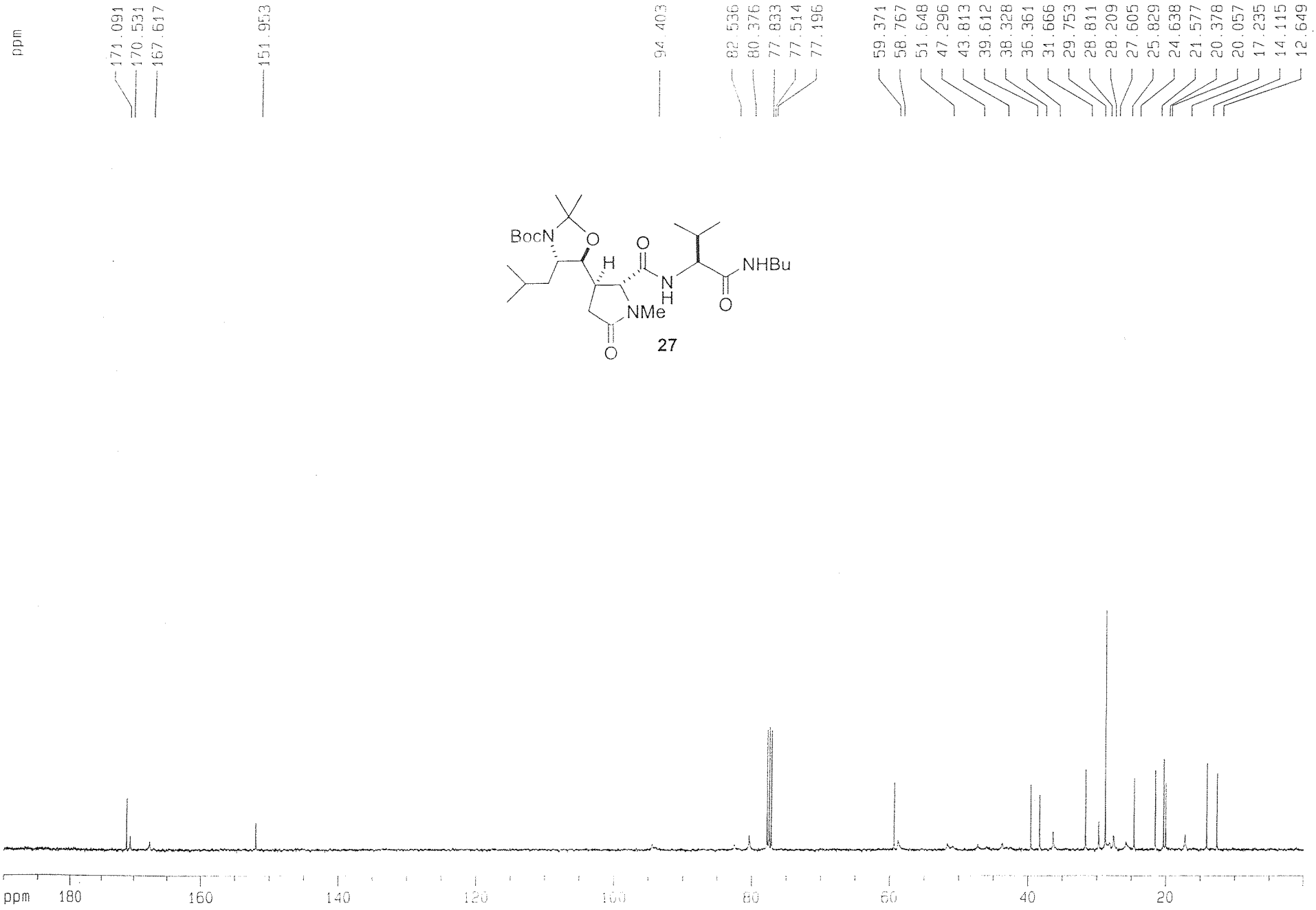
2
1

S25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77.196
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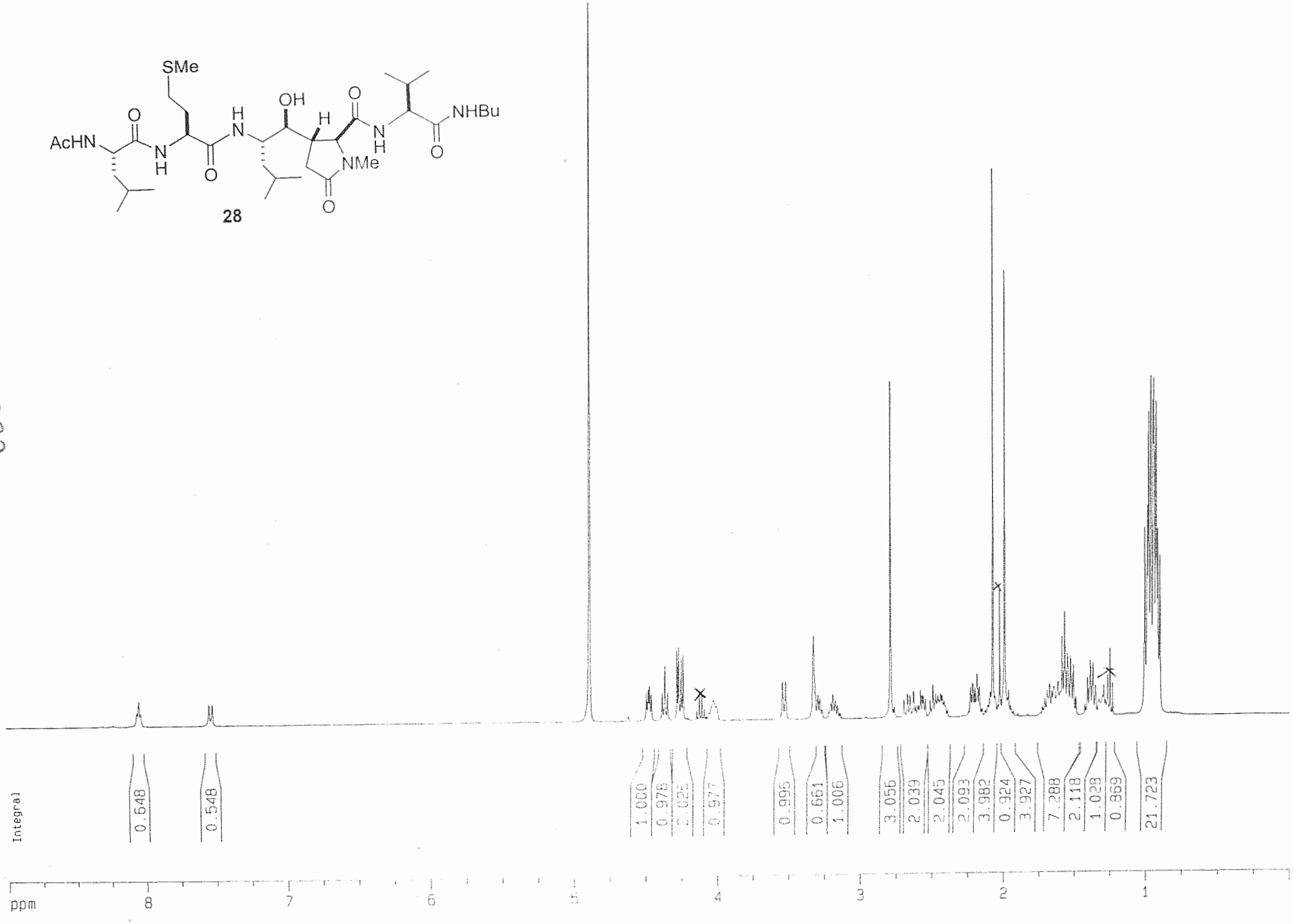
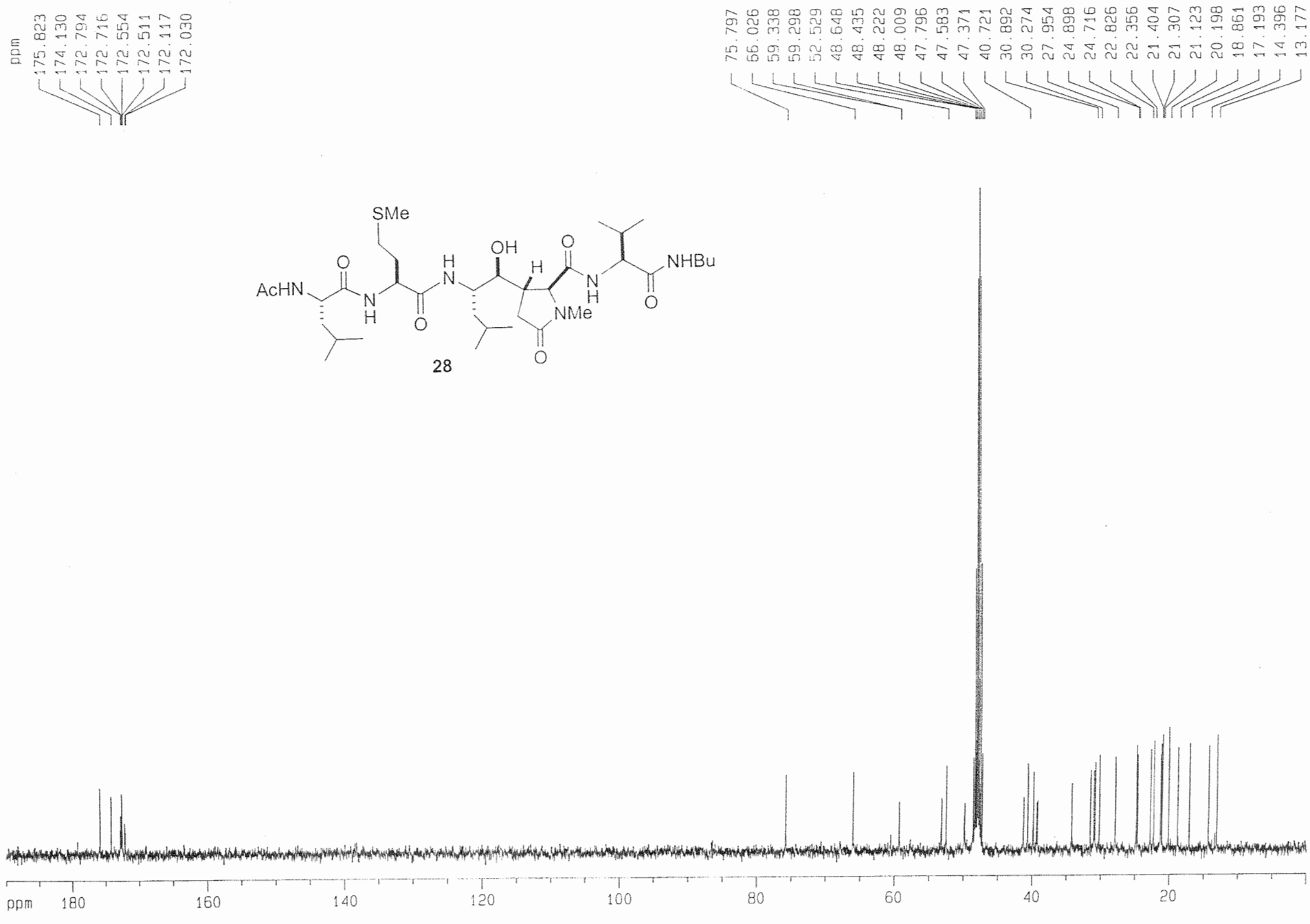
58.767
51.648
47.296
43.813
39.612
38.328
36.361
31.666
29.753
28.811
28.209
27.605
25.829
24.638
21.577
20.378
20.057
17.235
14.115
12.649
BocN
O
H
O
N
H
NHBu
O
NMe
O
27
ppm
180
160
140
120
100
80
60
40
20

S26

SMe
OH
O
NHBu
AcHN
H
N
H
O
H
N
H
O
NMe
O
O
28


Integral
0.648
0.548
1.000
0.978
2.022
0.977
0.996
0.661
1.006
3.056
2.039
2.045
2.093
3.982
0.924
3.927
7.288
2.118
1.028
0.869
21.723
ppm
8
7
6
5
4
3
2
1


ppm
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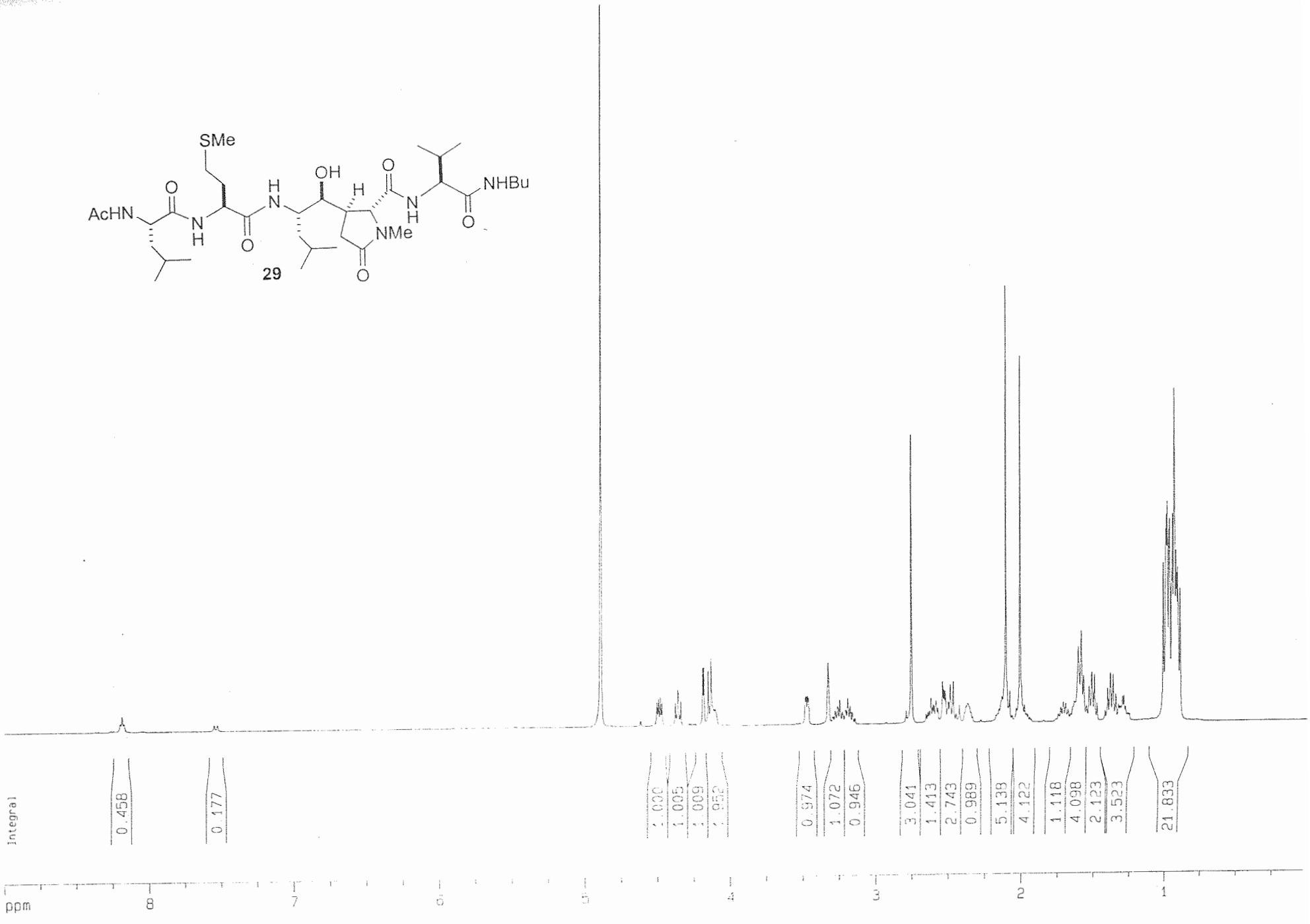
172.794
172.716
172.554
172.511
172.117
172.030
75.797
66.026
59.338
59.298
52.529
48.648
48.435
48.222
48.009
47.796
47.583
47.371
40.721
30.892
30.274
27.954
24.898
24.716
22.826
22.356
21.404
21.307
21.123
20.198
18.861
17.193
14.396
13.177
SMe
AcHN
O
N
H
O
H
N
OH
H
O
N
H
NMe
O
O
NHBu
O
28
ppm
180
160
140
120
100
80
60
40
20

SMe
AcHN
O
N
H
O
H
N
OH
H
O
N
H
NHBu
O
NMe
O
29


Integral
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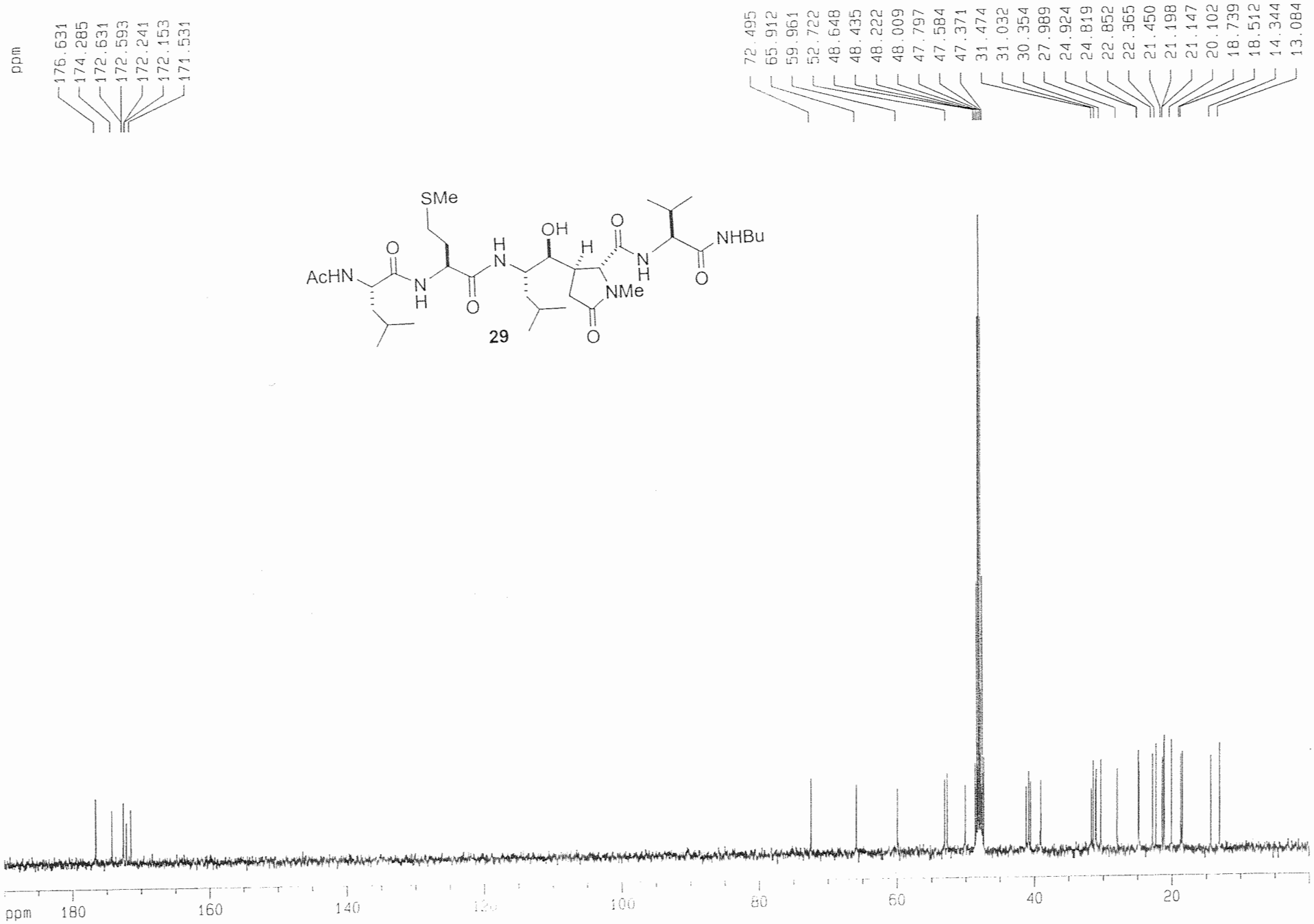
1.000
1.005
1.009
1.952
0.974
1.072
0.946
3.041
1.413
2.743
0.989
5.138
4.122
1.118
4.098
2.123
3.523
21.833
ppm
8
7
6
5
4
3
2
1


ppm
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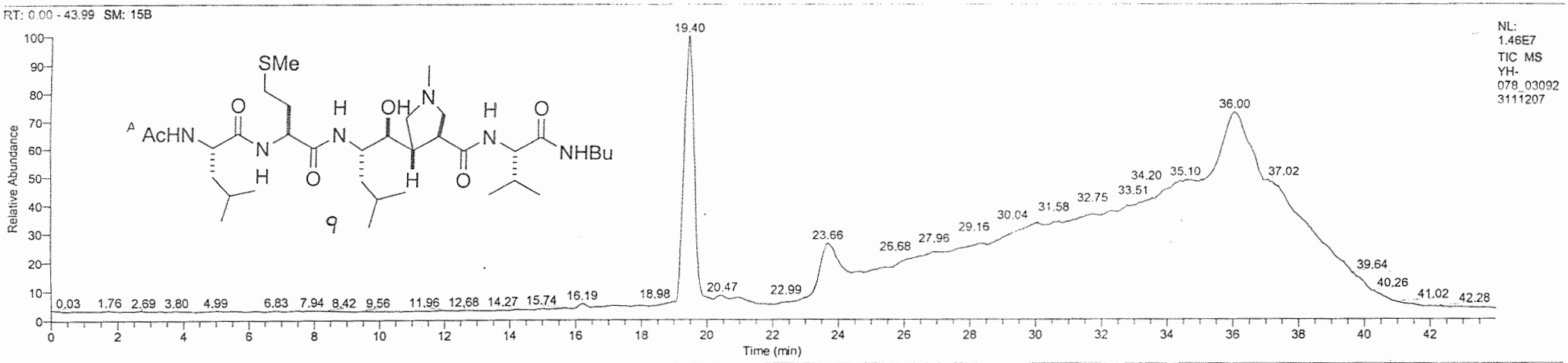
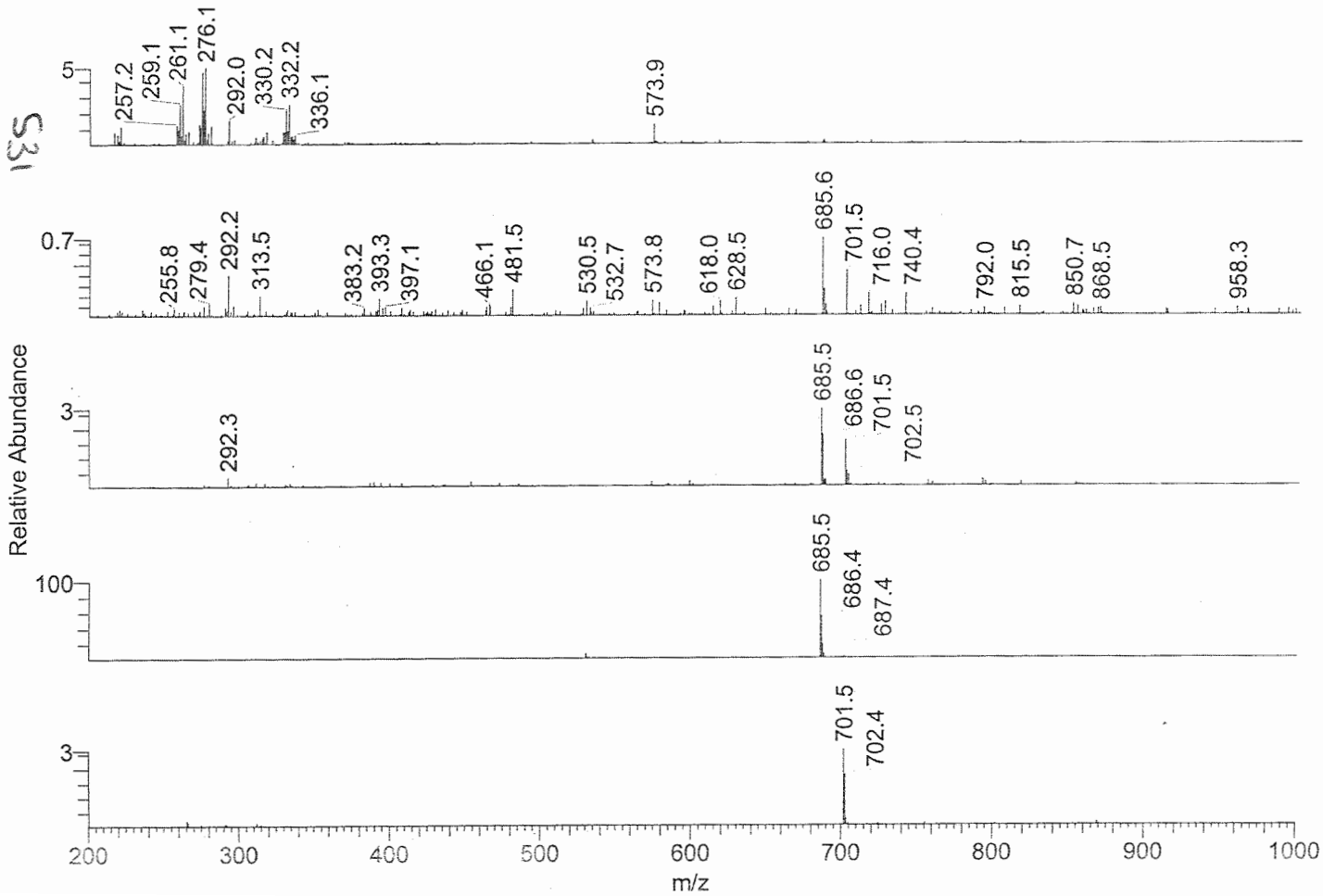
172.631
172.593
172.241
172.153
171.531
72.495
65.912
59.961
52.722
48.648
48.435
48.222
48.009
47.797
47.584
47.371
31.474
31.032
30.354
27.989
24.924
24.819
22.852
22.365
21.450
21.198
21.147
20.102
18.739
18.512
14.344
13.084
SMe
AcHN
O
N
H
O
H
N
OH
H
O
N
H
NMe
O
O
NHBu
O
29
ppm
180
160
140
120
100
80
60
40
20

S30

YH-078_030923111207 23/09/2003 11:12:07





YH-078_030923111207#1374 RT: 23.69 AV: 1 SB: 58 0.59-1.05 , 1.95-2.45 NL: 2.24E5 T: {0,0} + c ESI corona sid=50.00 det=1200.00 Full ms [200.00-1000.00]

YH-078_030923111207#1222 RT: 21.07 AV: 1 SB: 58 0.59-1.05 , 1.95-2.45 NL: 3.44E4 T: {0,0} + c ESI corona sid=50.00 det=1200.00 Full ms [200.00-1000.00]

YH-078_030923111207#1181 RT: 20.36 AV: 1 SB: 58 0.59-1.05 , 1.95-2.45 NL: 1.24E5 T: {0,0} + c ESI corona sid=50.00 det=1200.00 Full ms [200.00-1000.00]

YH-078_030923111207#1127 RT: 19.43 AV: 1 SB: 58 0.59-1.05 , 1.95-2.45 NL: 4.64E6 T: {0,0} + c ESI corona sid=50.00 det=1200.00 Full ms [200.00-1000.00]

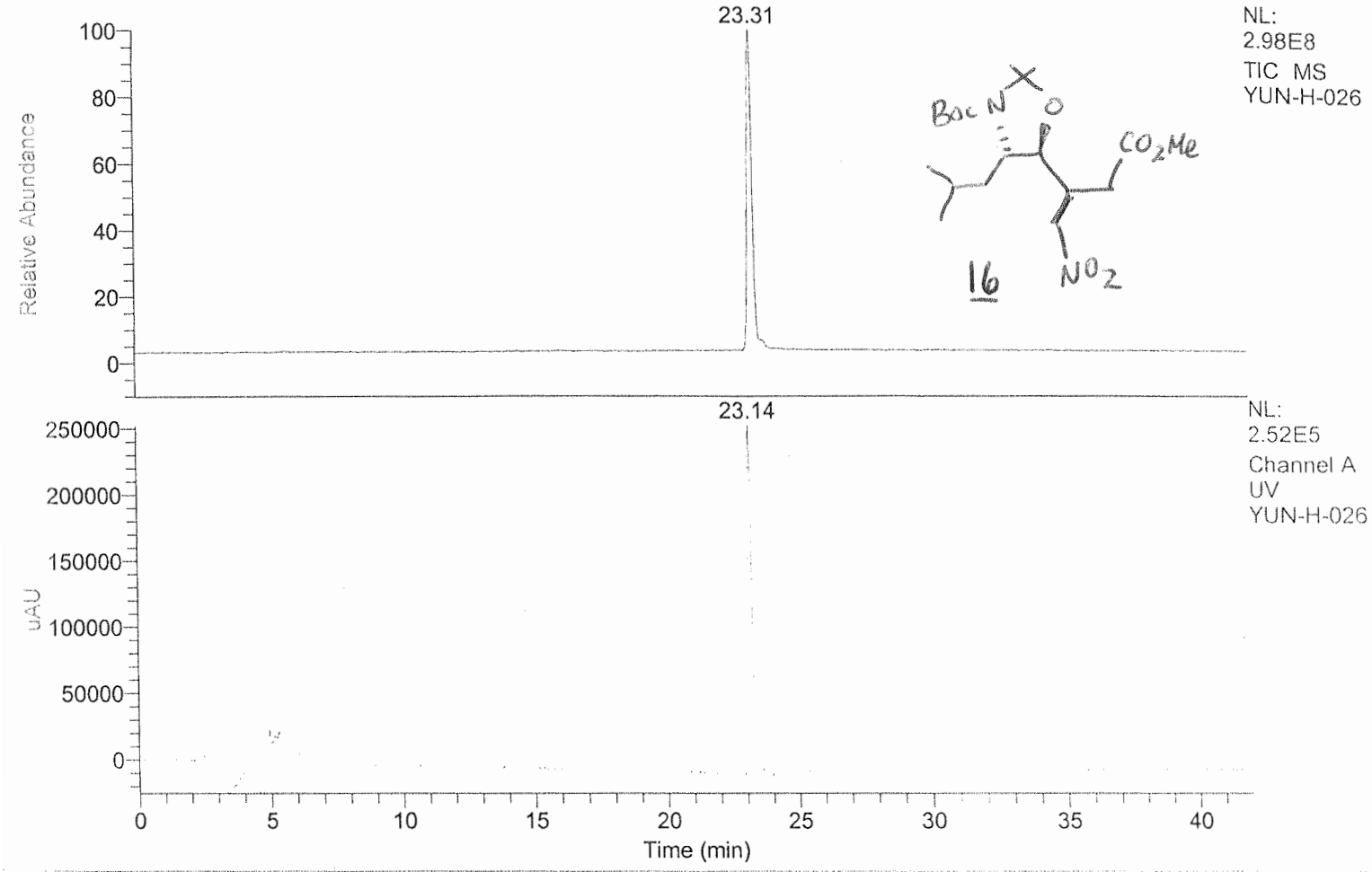
YH-078_030923111207#941 RT: 16.22 AV: 1 SB: 58 0.59-1.05 , 1.95-2.45 NL: 1.22E5 T: {0,0} + c ESI corona sid=50.00 det=1200.00 Full ms [200.00-1000.00]

S31

Ana LCMS\DATA\YUN-H-026 06/23/2004 06:12:18 PM

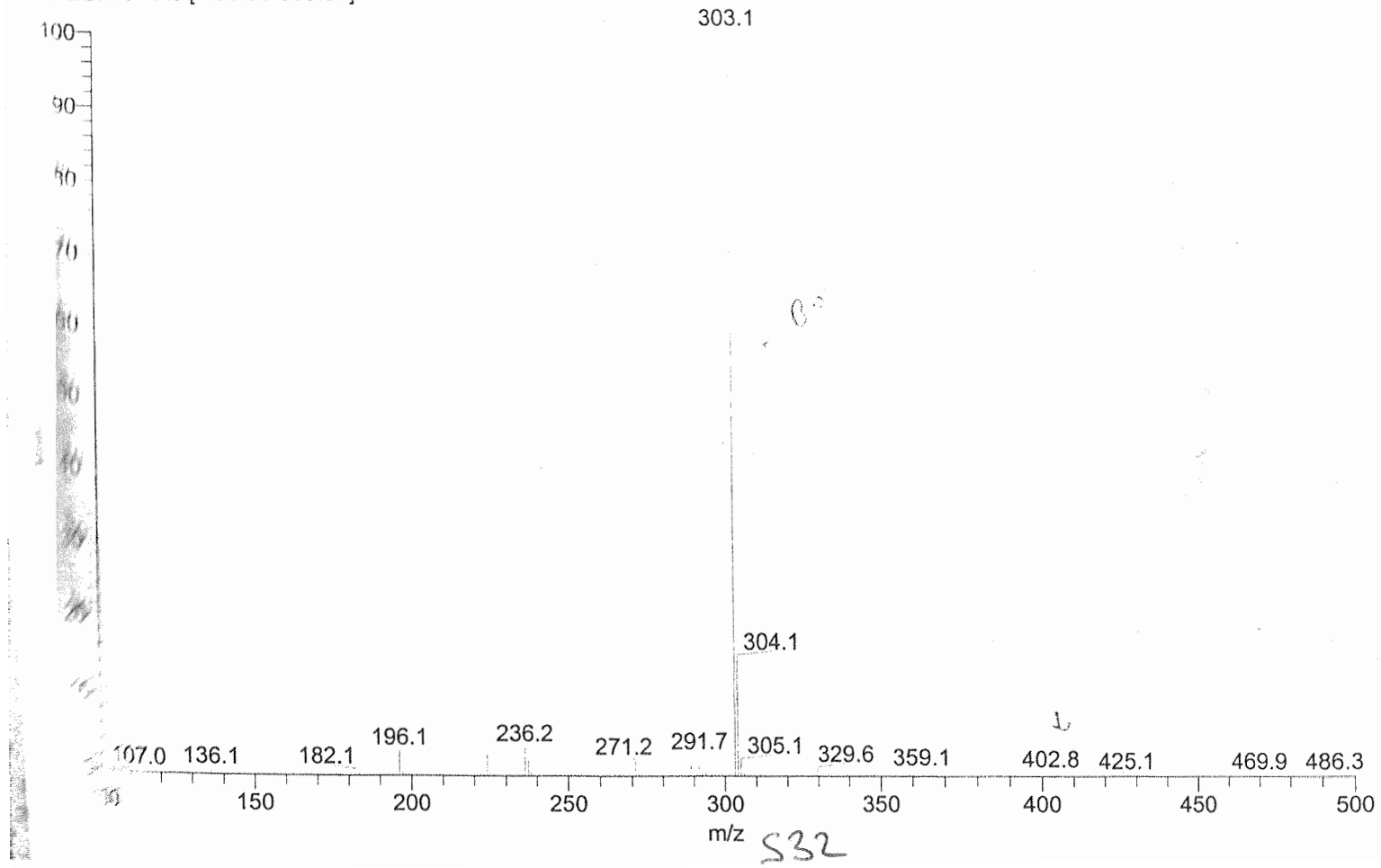
-90B%, over 20 min, A=0.1% TFA/H2O, B=0.1% TFA/ACN, Flow=0.5 ml/mn, inj vol :10uL, col:Prevail C18 250x4.6mm, Channel A =214, B=254, C =280

T: 0.00 - 42.00 SM: 7B



YUN-H-026 #1860-1896 RT: 23.17-23.49 AV: 37 NL: 1.22E8

T: + c ESI Full ms [100.00-500.00]

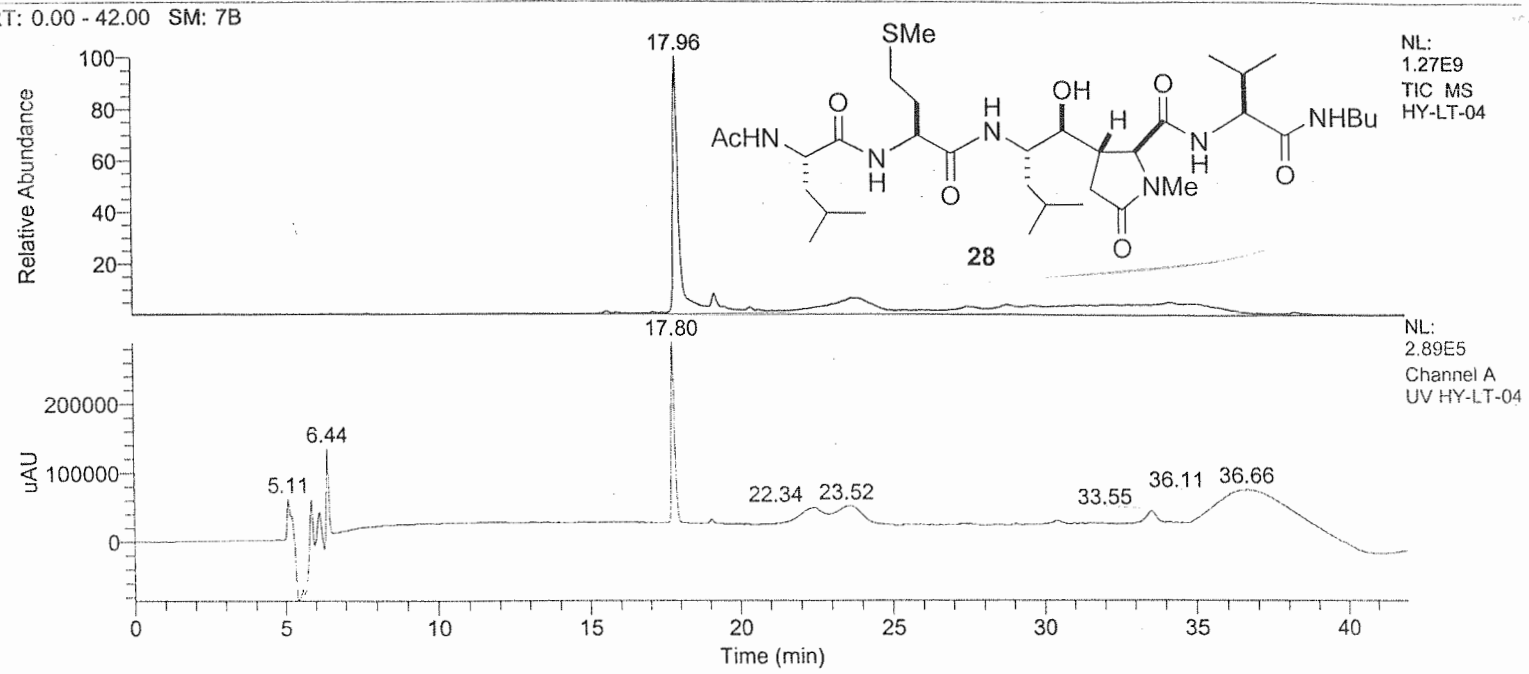


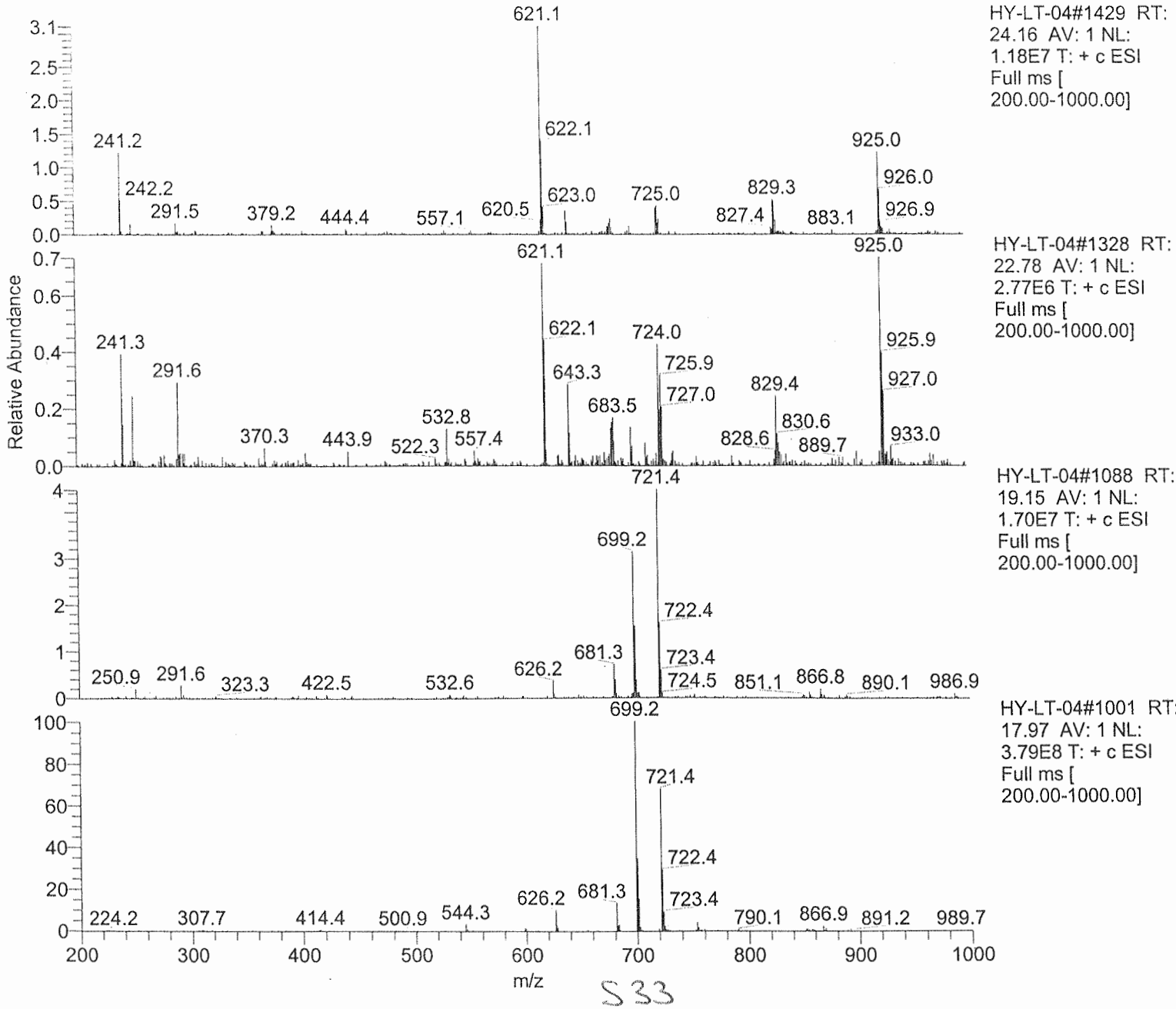
S32

C:\Ana LCMS\DATA\HY-LT-04 05/31/2004 09:41:19 PM

20-80B%over 20 min, A=0.1% TFA/H2O, B=0.1% TFA/ACN, Flow=0.5 ml/mn, inj vol :10uL, col:Prevail C18 250x4.6mm, Channel A =214, B=254, C =280

RT: 0.00 - 42.00 SM: 7B



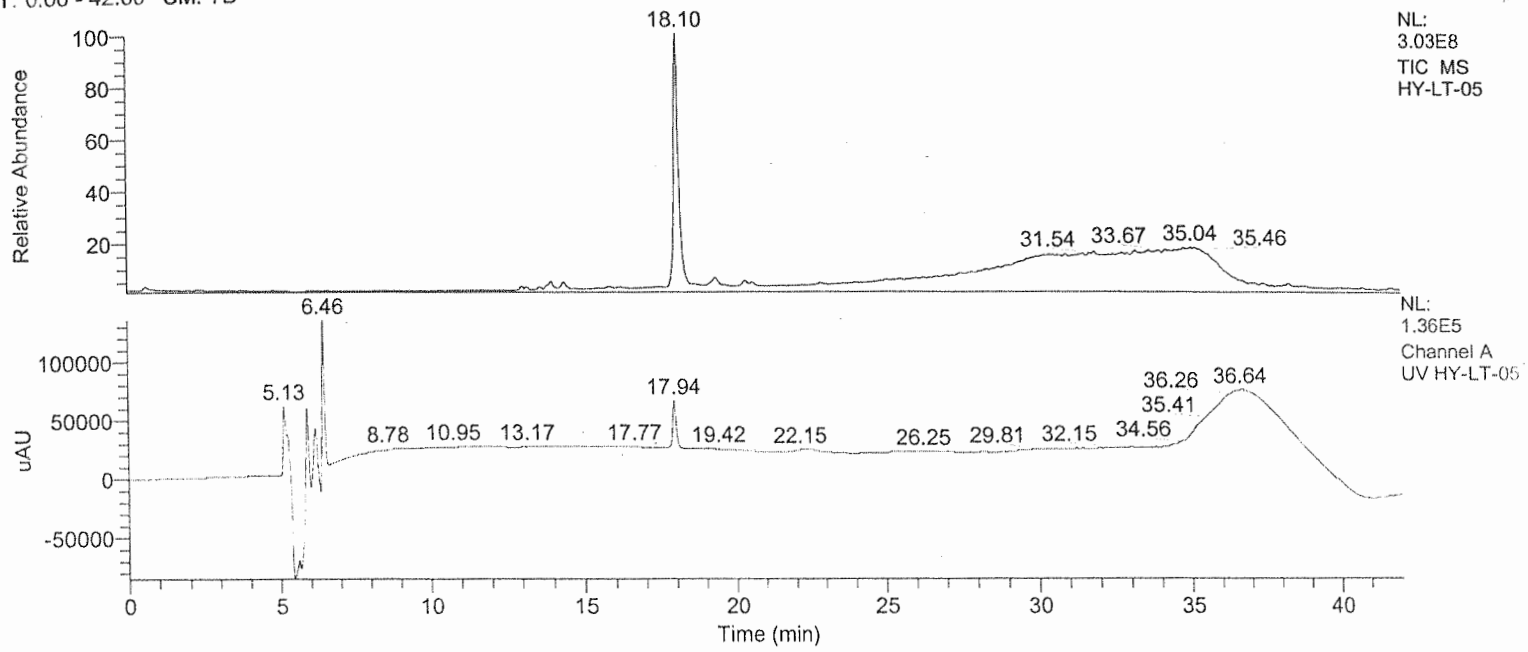


S33

C:\Ana LCMS\DATA\HY-LT-05 05/31/2004 10:27:23 PM

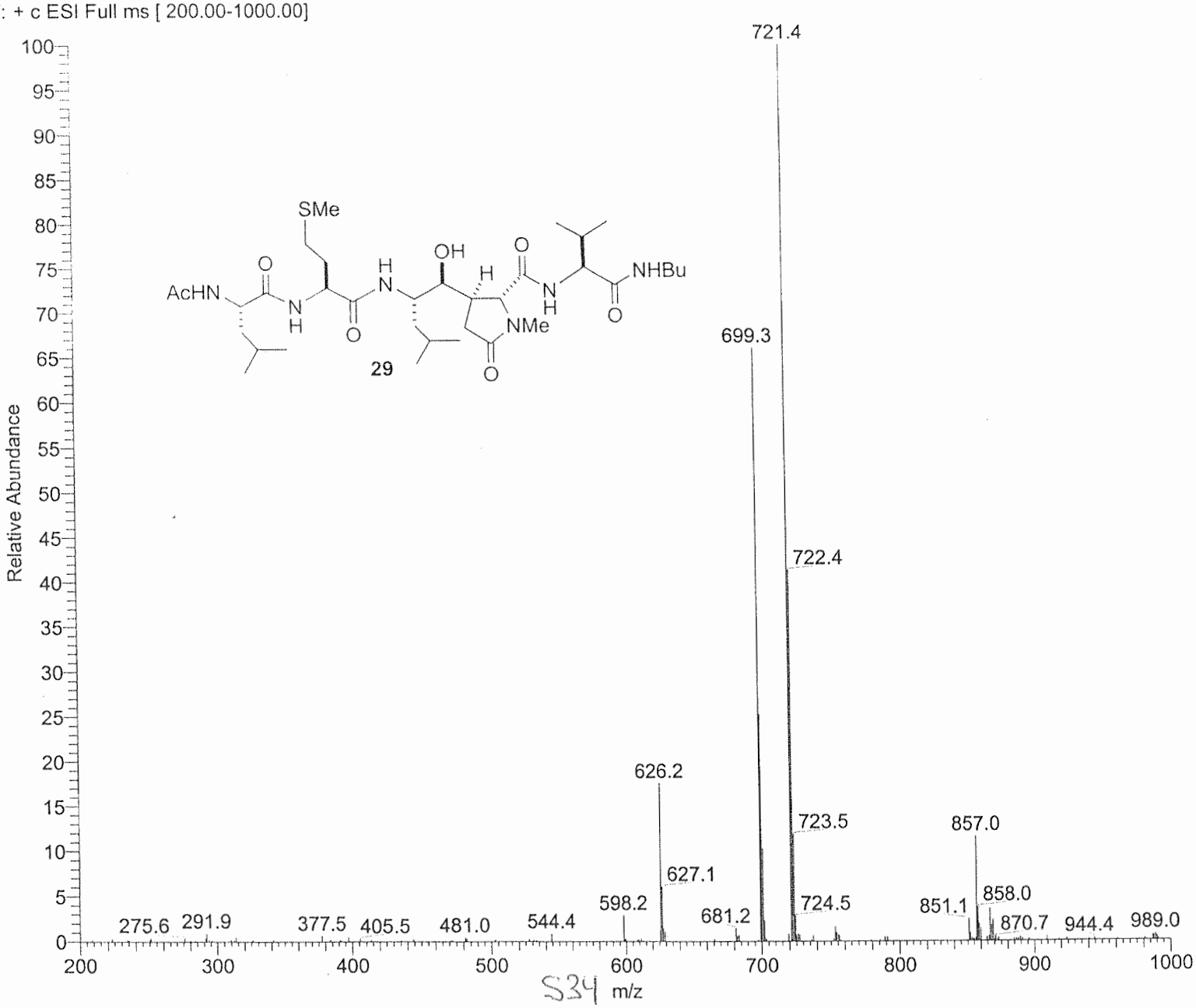
20-80B%over 20 min, A=0.1% TFA/H2O, B=0.1% TFA/ACN, Flow=0.5 ml/mn, inj vol :10uL, col:Prevail C18 250x4.6mm, Channel A =214, B=254, C =280

RT: 0.00 - 42.00 SM: 7B



HY-LT-05 #1003 RT: 18.10 AV: 1 NL: 1.03E8

T: + c ESI Full ms [200.00-1000.00]



S34