Total Synthesis of (–)-Ardeemin

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Contents of Supporting Information

Experimental methods

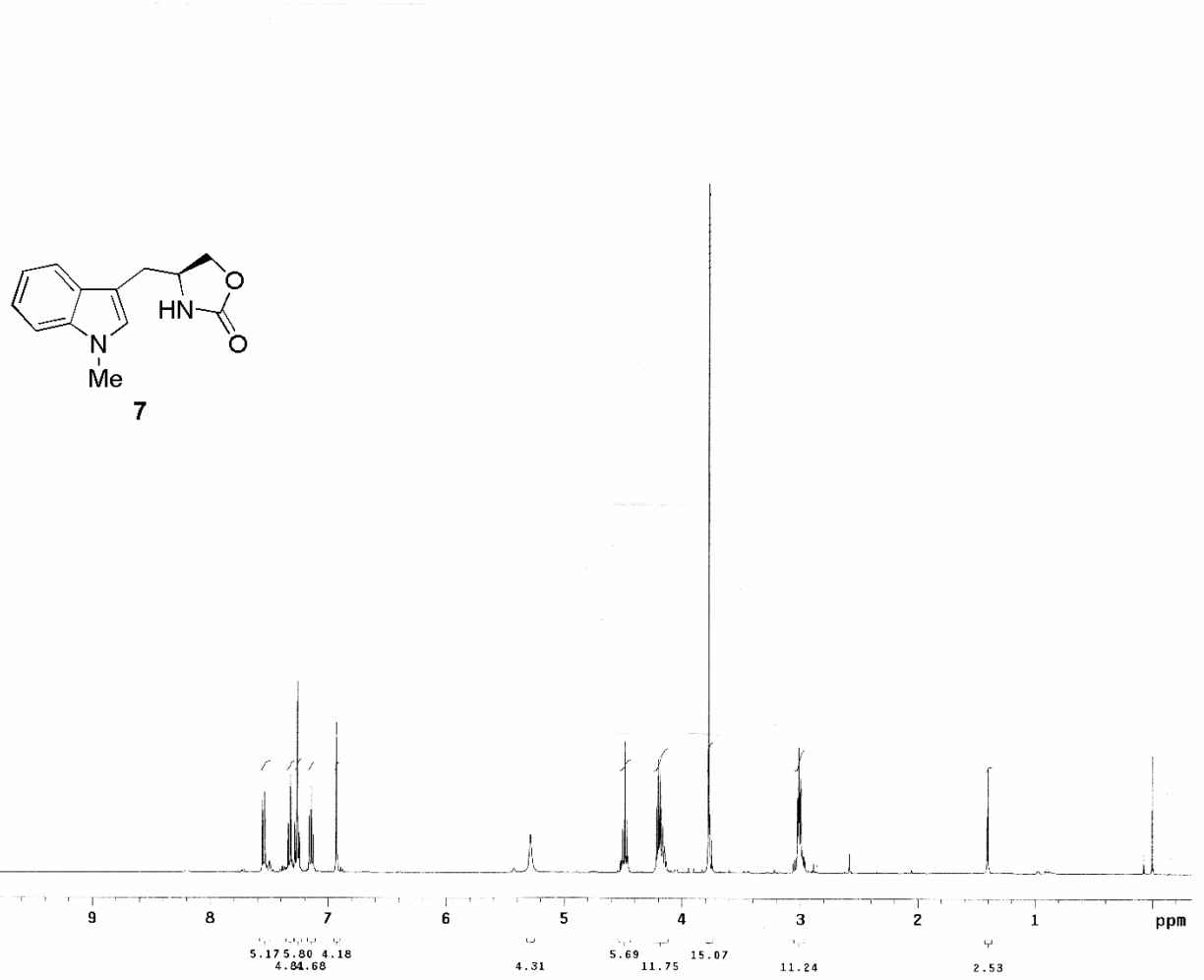
All commercially available reagents were used without further purification. All solvents were dried and distilled before use; THF and Et_2O were distilled from sodium/benzophenone ketyl; dichloromethane and acetonitrile were distilled from calcium hydride; methanol was distilled from Mg/I_2; $CHCl_3$ was distilled from P_2O_5. Column chromatography was conducted by using 200-300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (IR, 1H NMR, ^{13}C NMR, and HRMS). IR spectra were recorded on a FT IR spectrometer. NMR spectra were recorded on 600/400/200 MHz NMR spectrometers. HRMS spectra were obtained by the FAB method.

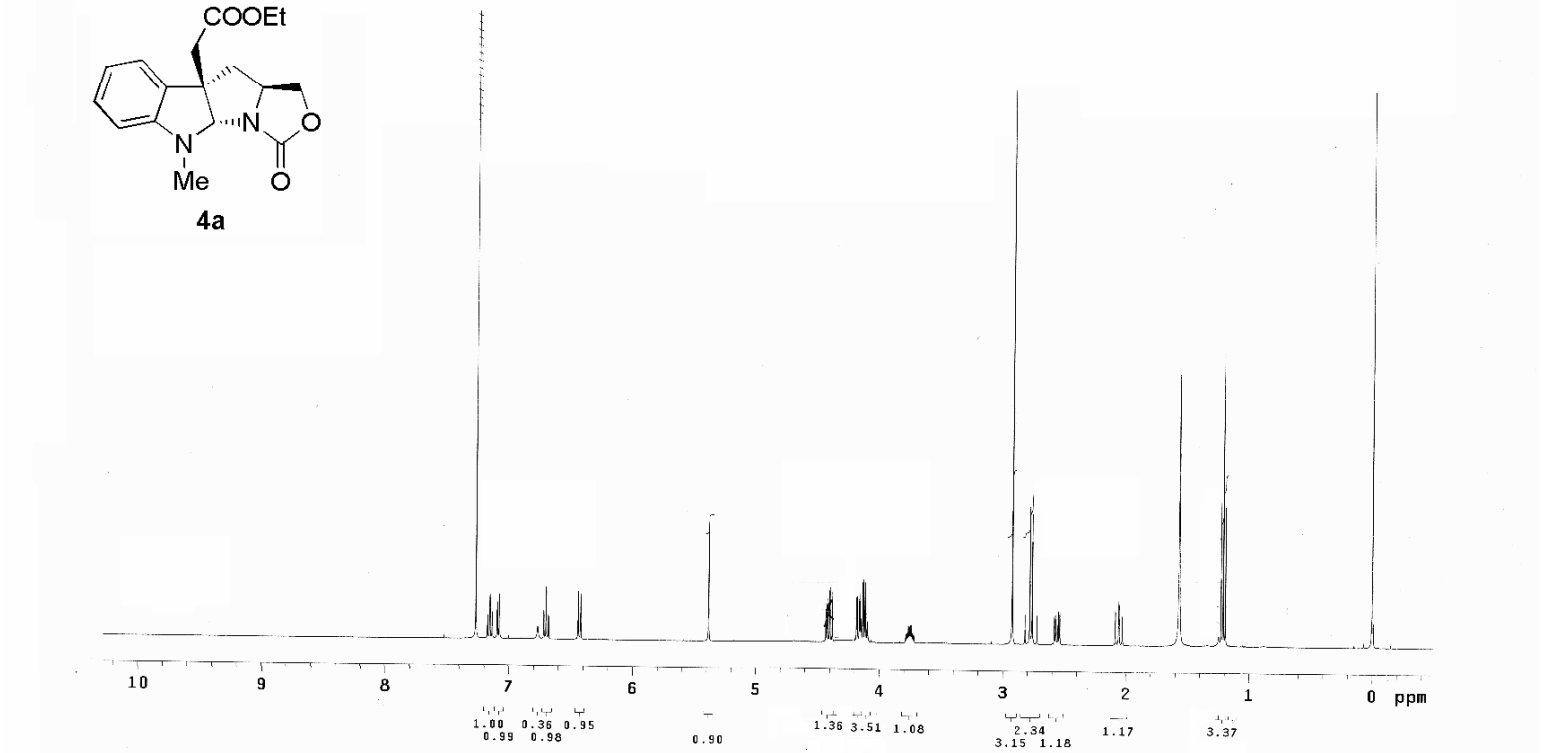
1-Methyltryptophan 11 was prepared according to the literature procedure.[1]

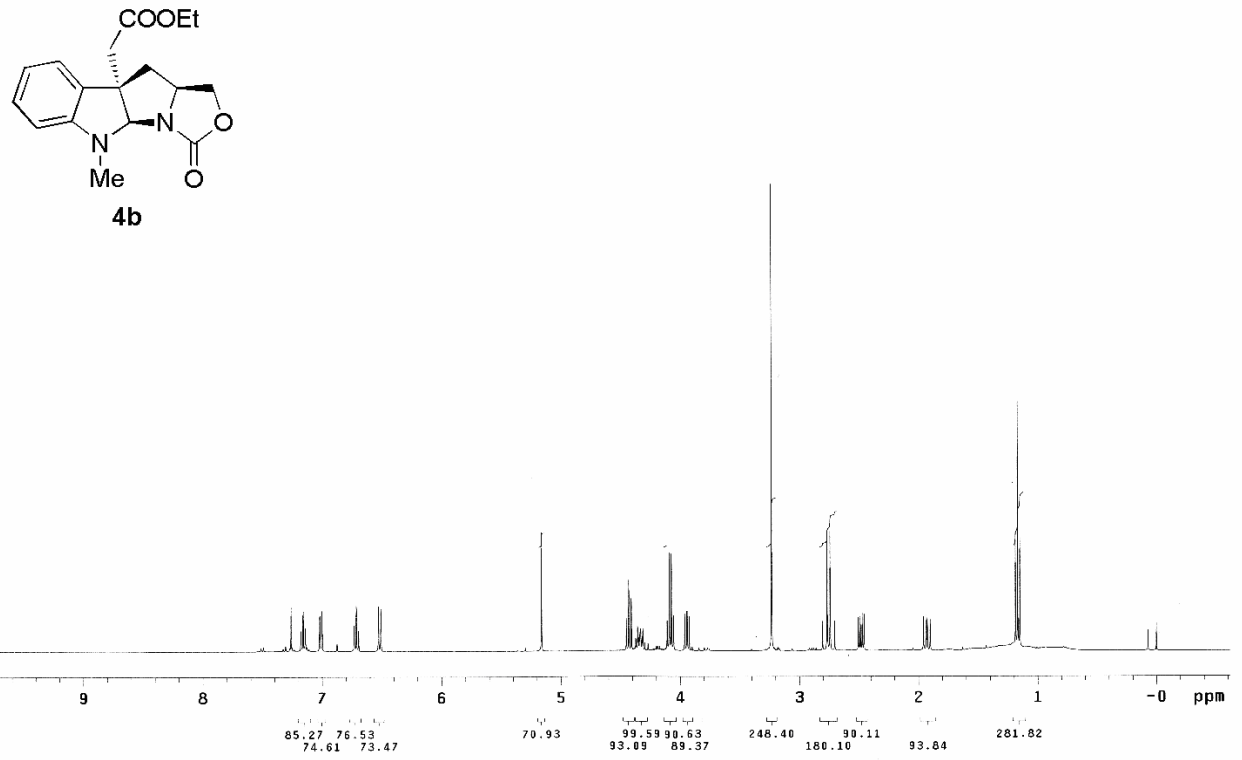
Metallic Na (52 g, 2.26 mol) was added with stirring in small pieces to liquid NH_3 (ca. 3,000 ml) containing ferric nitrate monohydrate (3.6 g) at –60 ^oC. After dissolution was completed, tryptophan (200 g, 1.10 mol) suspended in anhydrate Et_2O (appropriate amount) was added to the stirred mixture. After 30 min, MeI (182 g, 1.28 mol) was added dropwise over 30 min and stirring was continued till NH_3 was evaporated. Water (800 mL) was added to the residue and the mixture was heated to dissolve, filtered and adjusted to pH 5.0 with AcOH (ca. 120 mL), followed by the addition of EtOH (800 mL). The mixture was allowed to stand in a refrigerator overnight. The resultant white precipitates were collected and washed successively with H_2O (800 mL), 50% aq. EtOH (800 mL), EtOH (800 mL), and Et_2O (800 mL) to yield 1-methyltryptophan **11** as a colorless solid (196 g, 92% yield), m.p. 223–226 ^oC.

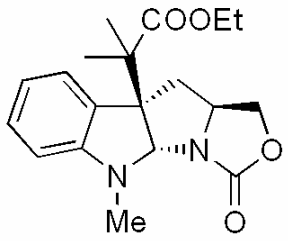
Reference

1) Yamada, S.; Shioiri, T.; Itaya, T.; Hara, T.; Matsueda, R. *Chem. Pharm. Bull.* **1965**, *13*, 88.

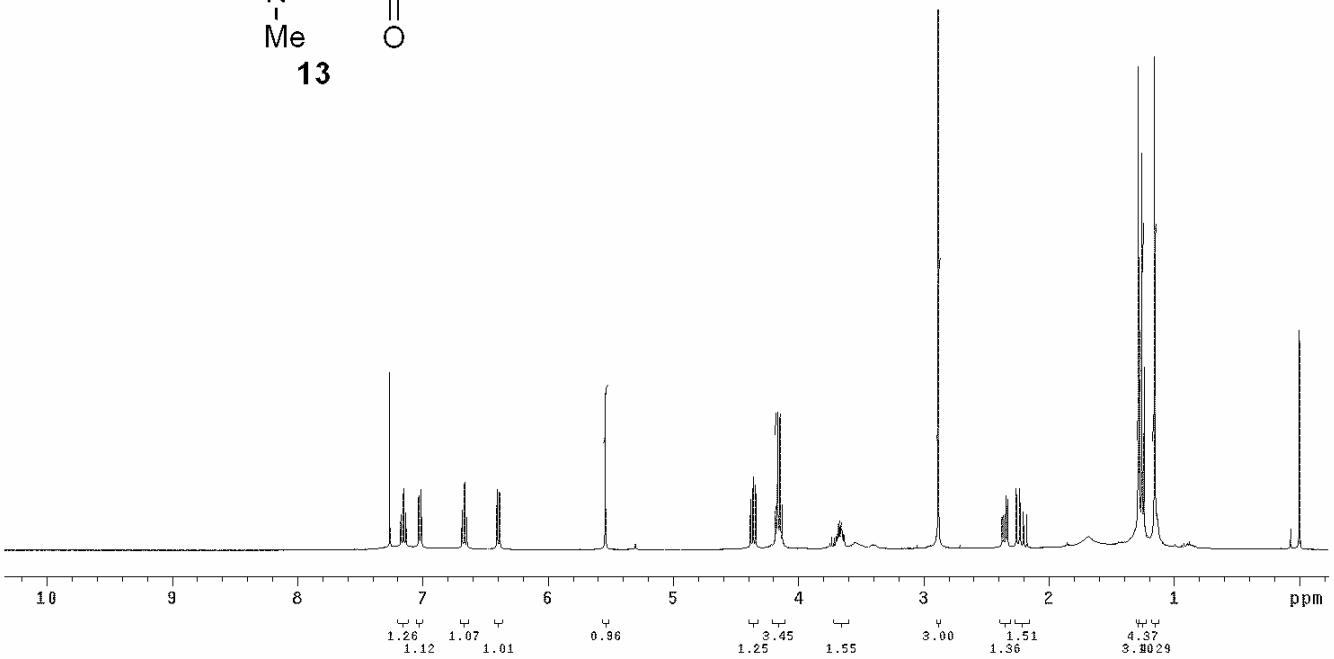

HN
O
O
N
Me
7
10
9
8
7
6
5
4
3
2
1
ppm
5.17
5.80
4.18
4.84
4.68
4.31
5.69
11.75
15.07
11.24
2.53

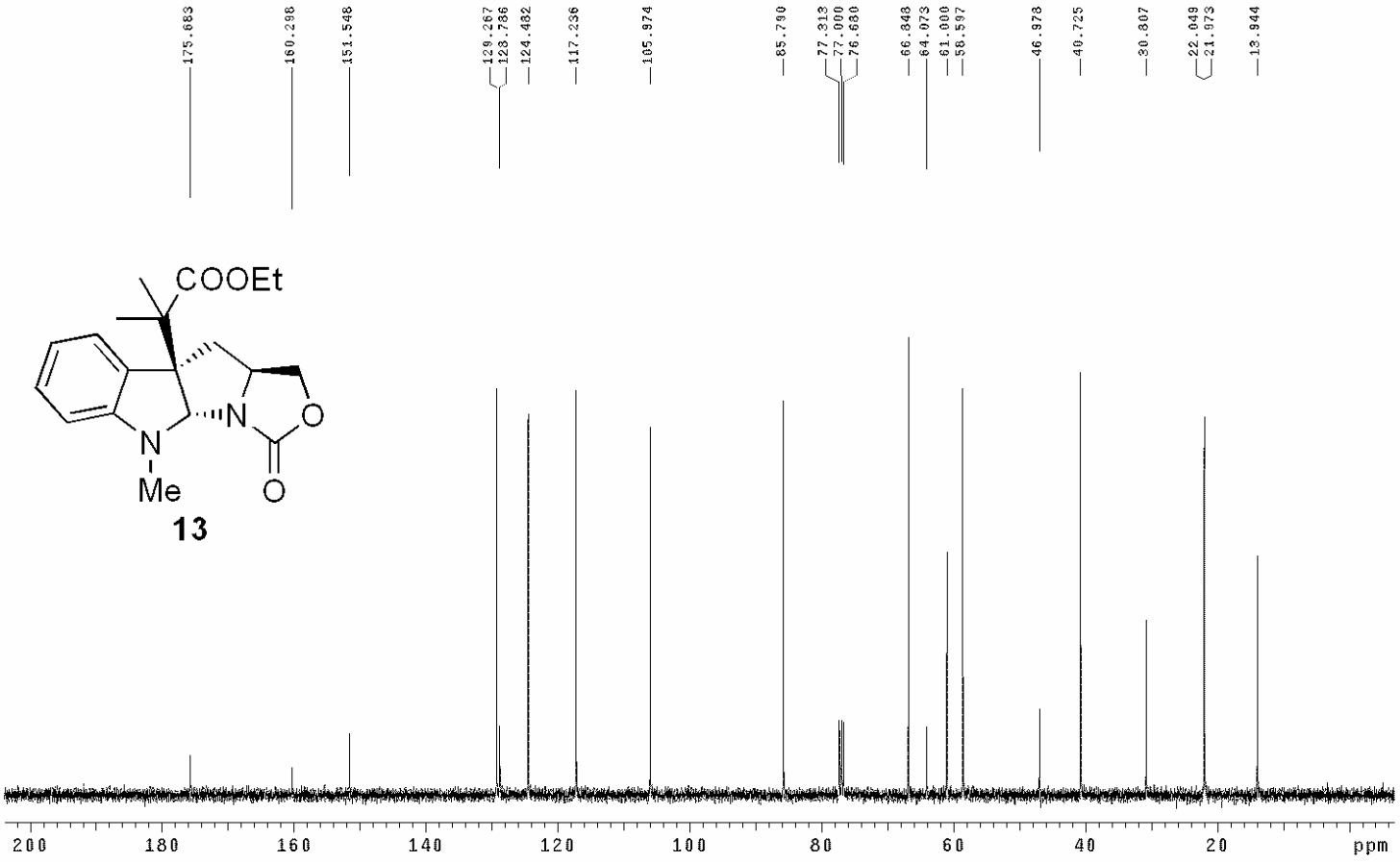

COOEt
N
Me
N
O
O
4a
10
9
8
7
6
5
4
3
2
1
0 ppm
1.00
0.99
0.36
0.98
0.95
0.90
1.36
3.51
1.08
2.34
3.15
1.18
1.17
3.37


COOEt
N
N
O
Me
O
4b
10
9
8
7
6
5
4
3
2
1
-0
ppm
85.27
74.61
76.53
73.47
70.93
99.59
93.09
90.63
89.37
248.40
180.10
90.11
93.84
281.82


COOEt
N
Me
N
O
O

13


10
9
8
7
6
5
4
3
2
1
ppm
1.26
1.12
1.07
1.01
0.96
3.45
1.25
1.55
3.00
1.51
1.36
4.37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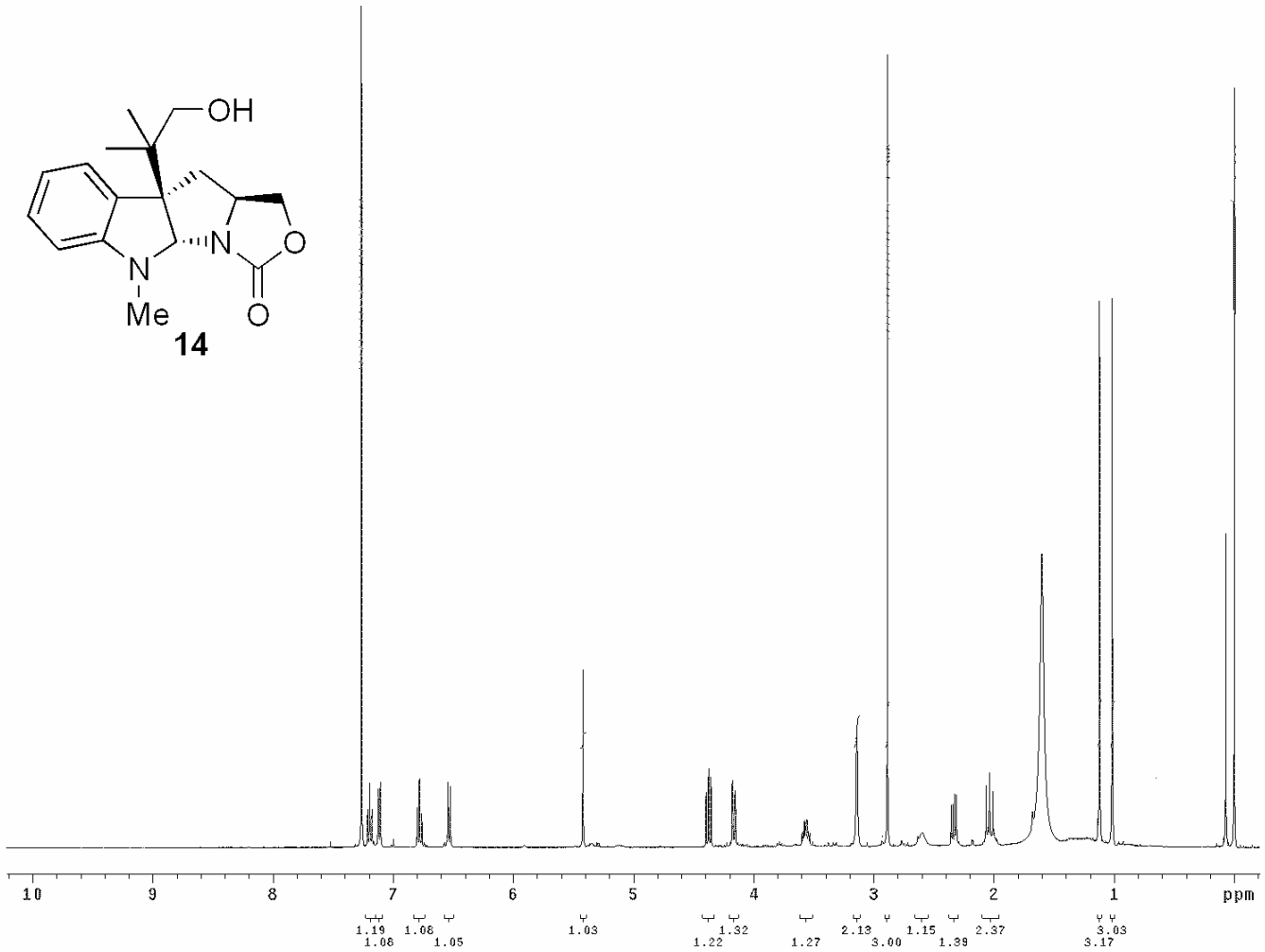
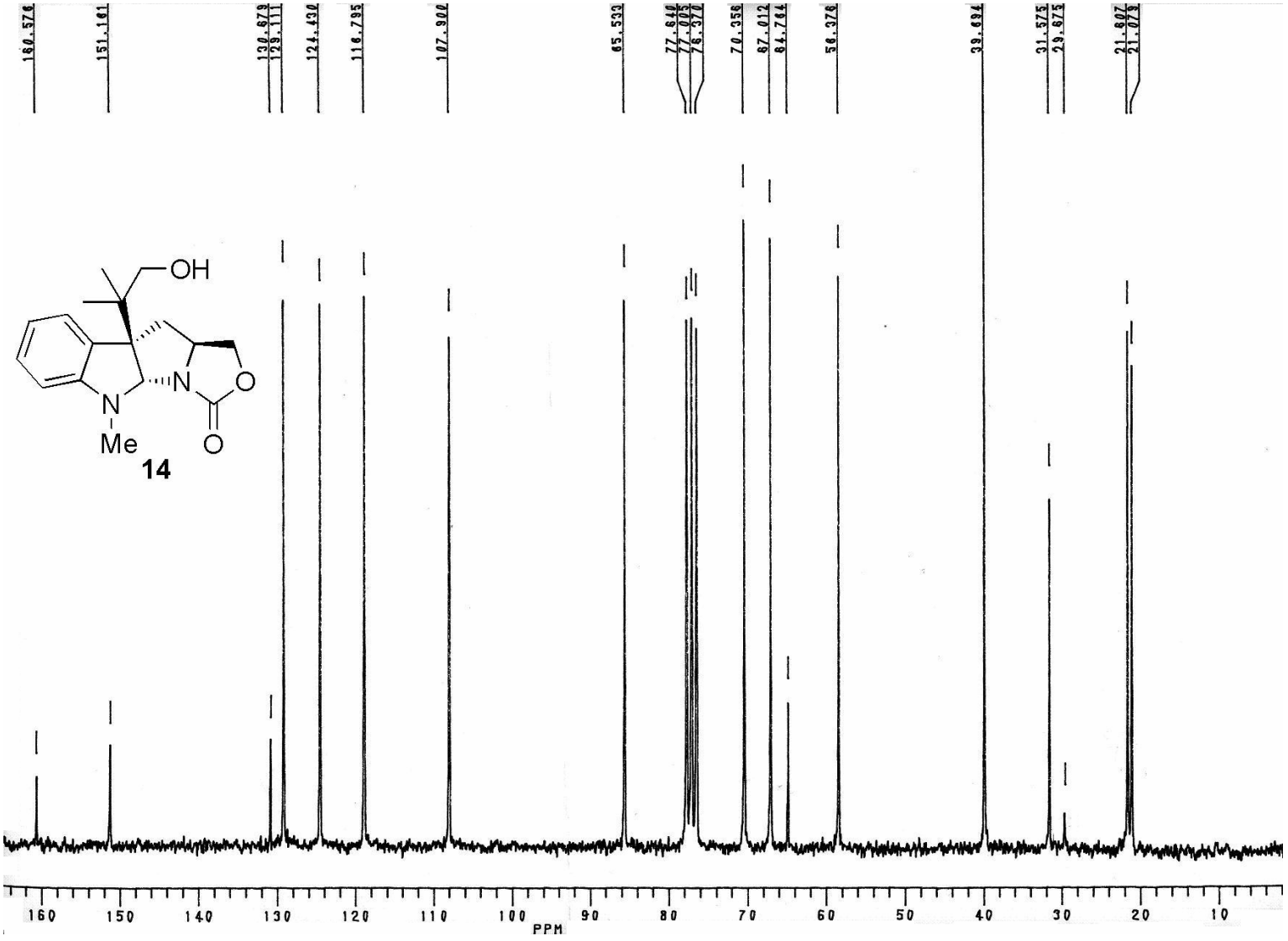
160.298
151.548
129.267
128.786
124.482
117.236
105.974
85.790
77.313
77.000
76.680
66.848
64.073
61.000
56.597
46.978
40.725
30.807
22.049
21.973
13.944
COOEt
N
O
N
Me
O
13
200
180
160
140
120
100
80
60
40
20
ppm


OH
N
Me
N
O
O
14
10
9
8
7
6
5
4
3
2
1
ppm
1.19
1.08
1.08
1.05
1.03
1.32
1.22
1.27
2.13
3.00
1.15
1.39
2.37
3.03
3.17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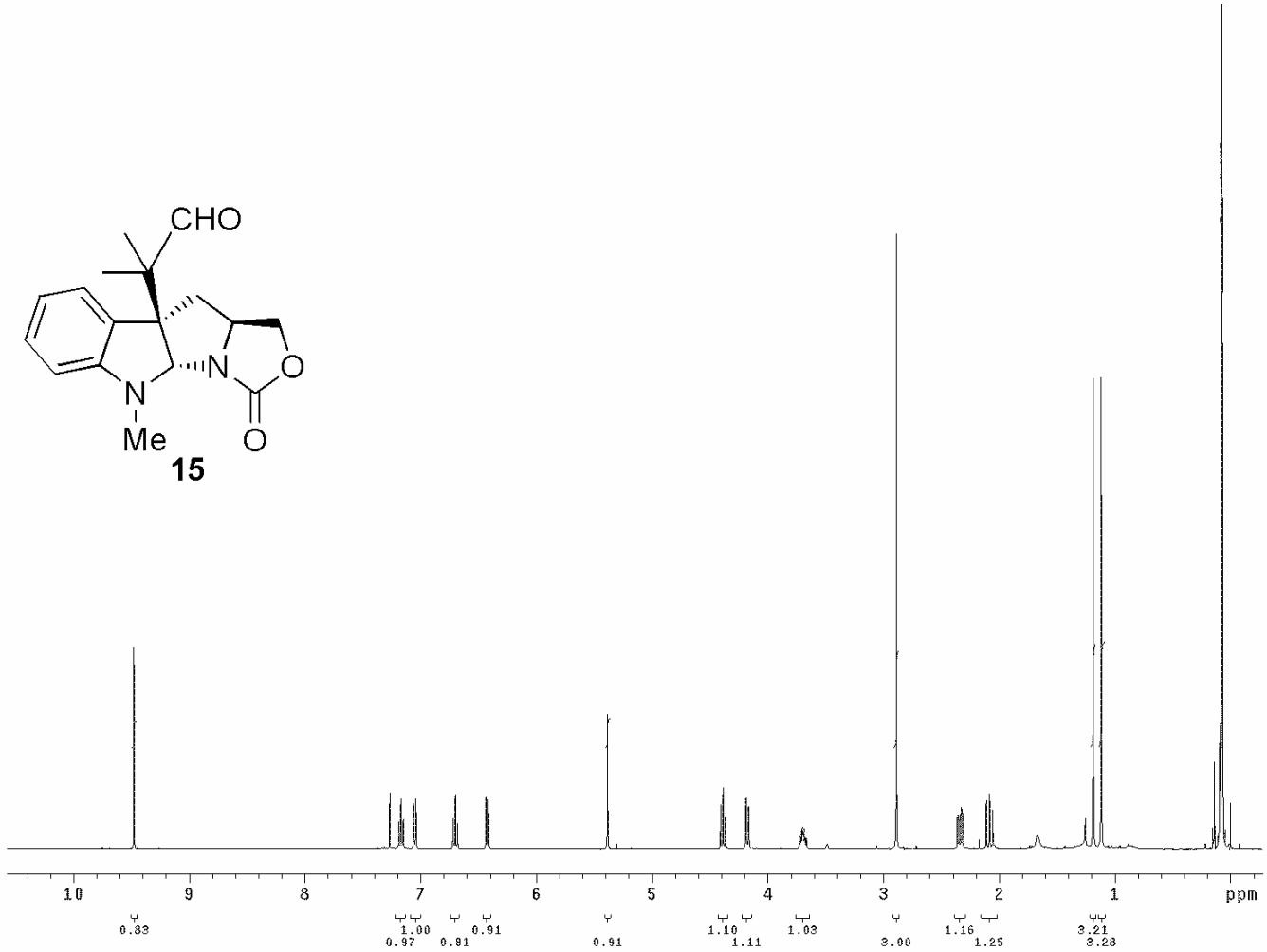
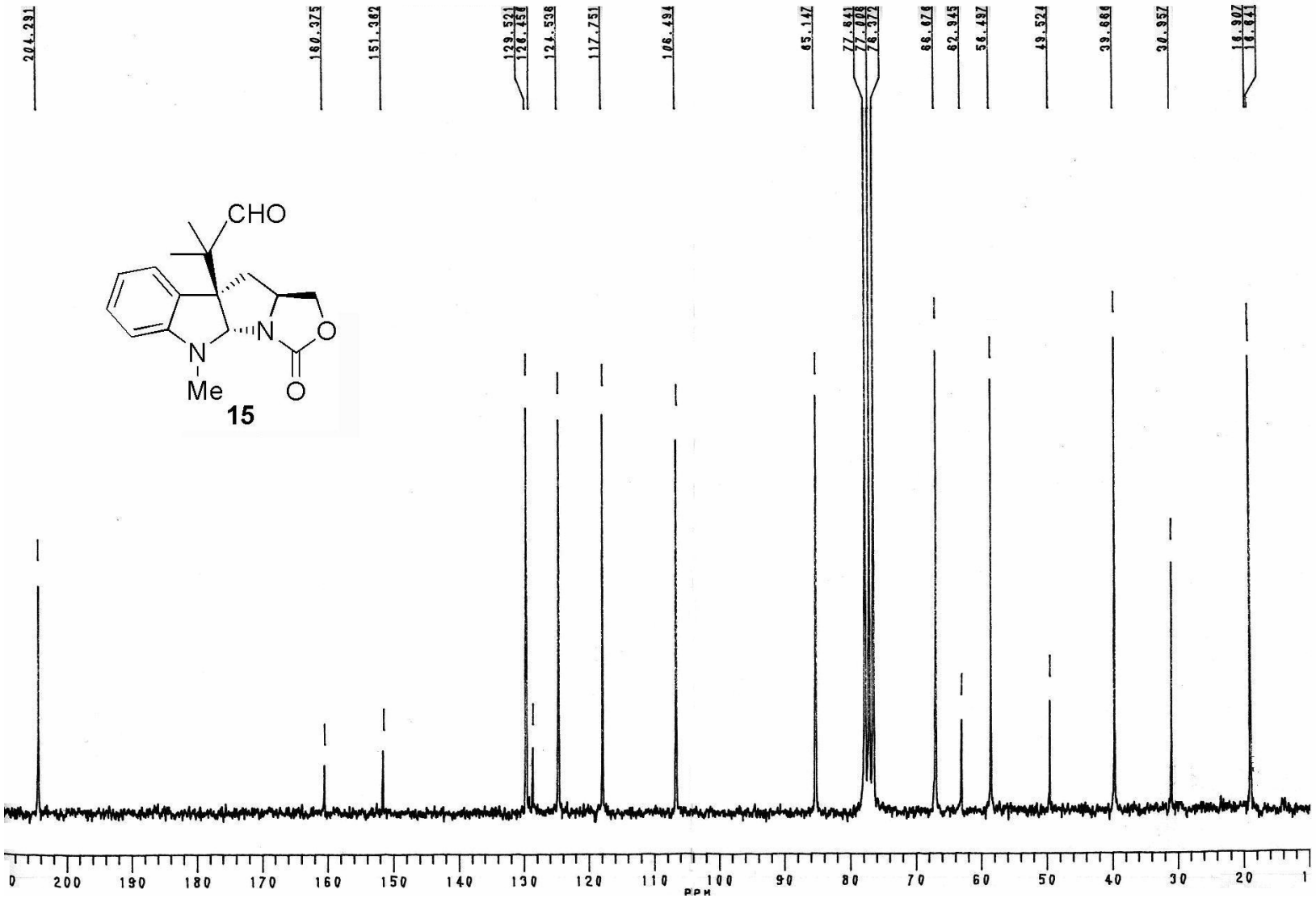
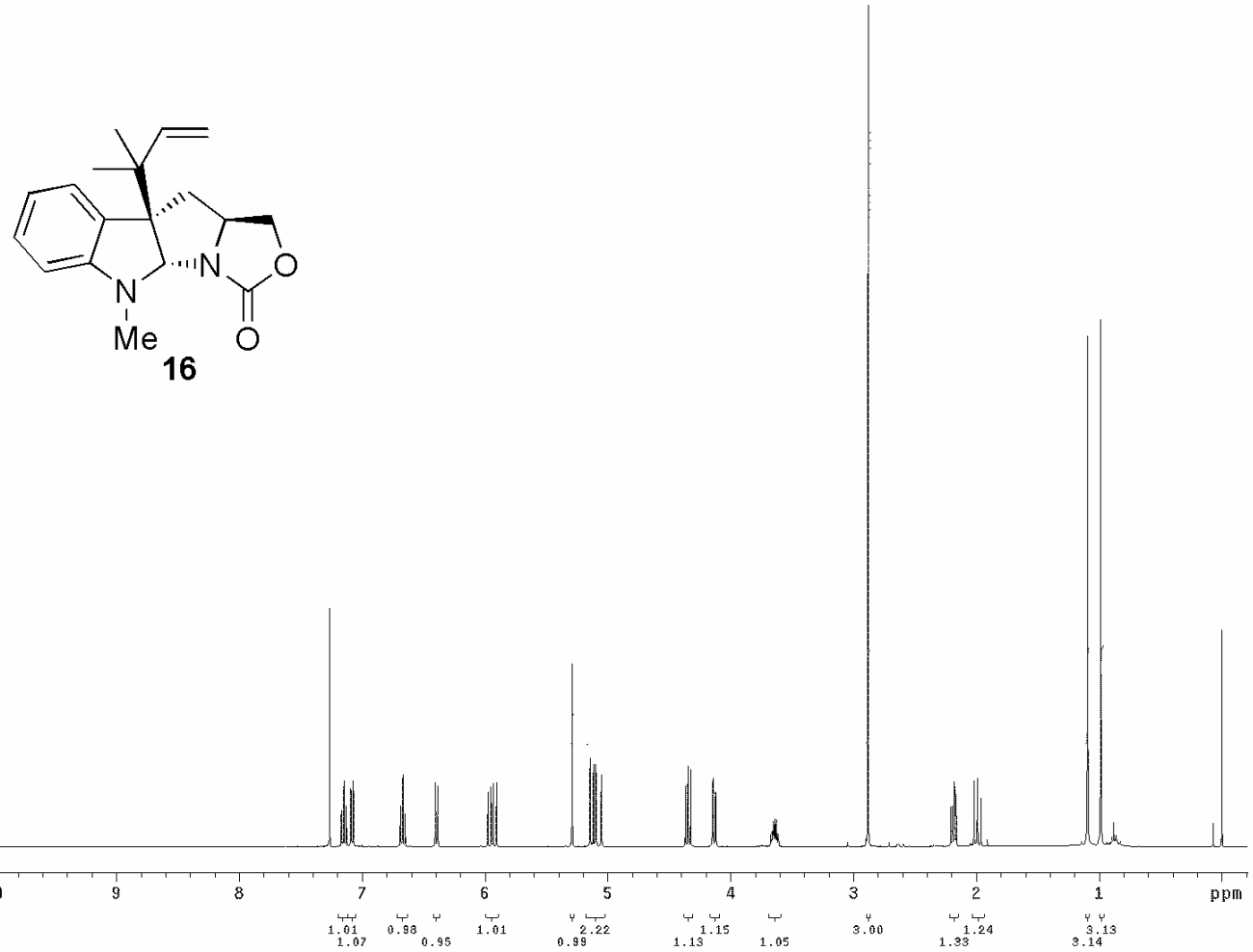
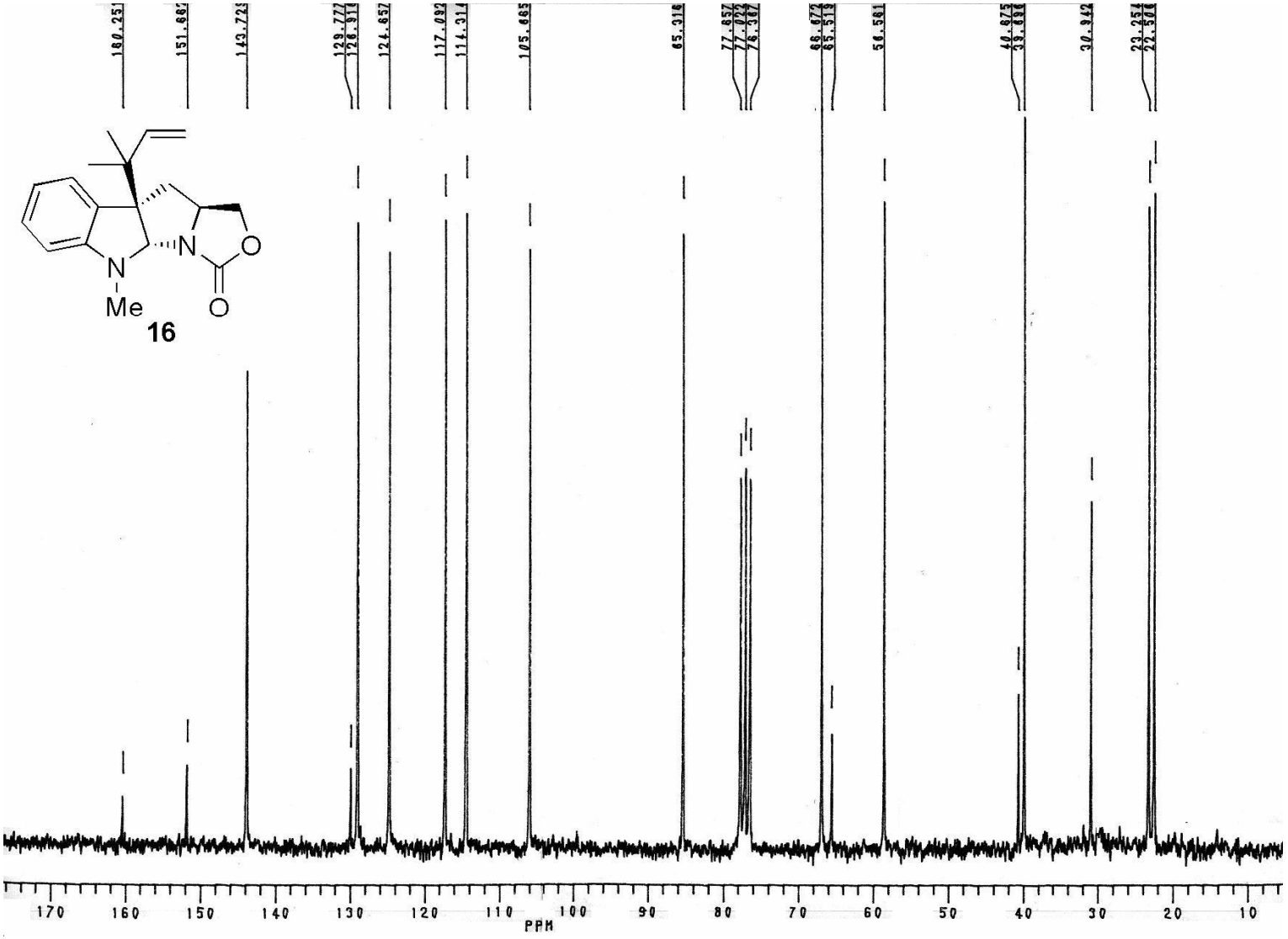
151.161
130.678
129.111
124.430
116.785
107.900
65.533
77.640
77.005
76.370
70.358
67.012
64.744
58.378
39.694
31.575
29.875
21.807
21.079
OH
N
O
N
Me
O
14
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
PPM


CHO
N
Me
N
O
O
15
10
9
8
7
6
5
4
3
2
1
ppm
0.83
1.00
0.97
0.91
0.91
0.91
1.10
1.11
1.03
3.00
1.16
1.25
3.21
3.28


204.291
160.375
151.362
129.521
128.457
124.538
117.751
106.494
65.147
77.641
77.408
77.372
68.078
62.945
58.497
49.524
39.684
30.957
18.907
18.041
CHO
N
O
N
Me
O
15
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
1
PPM


N
N
O
O
Me
16
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.07
0.98
0.95
1.01
2.22
0.99
1.15
1.13
1.05
3.00
1.24
1.33
3.13
3.14


180.251
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143.723
129.777
128.911
124.657
117.092
114.314
105.465
65.318
77.657
77.072
76.347
68.477
65.513
56.581
40.875
33.811
30.342
23.251
22.514
N
O
N
Me
O
16
170
160
150
140
130
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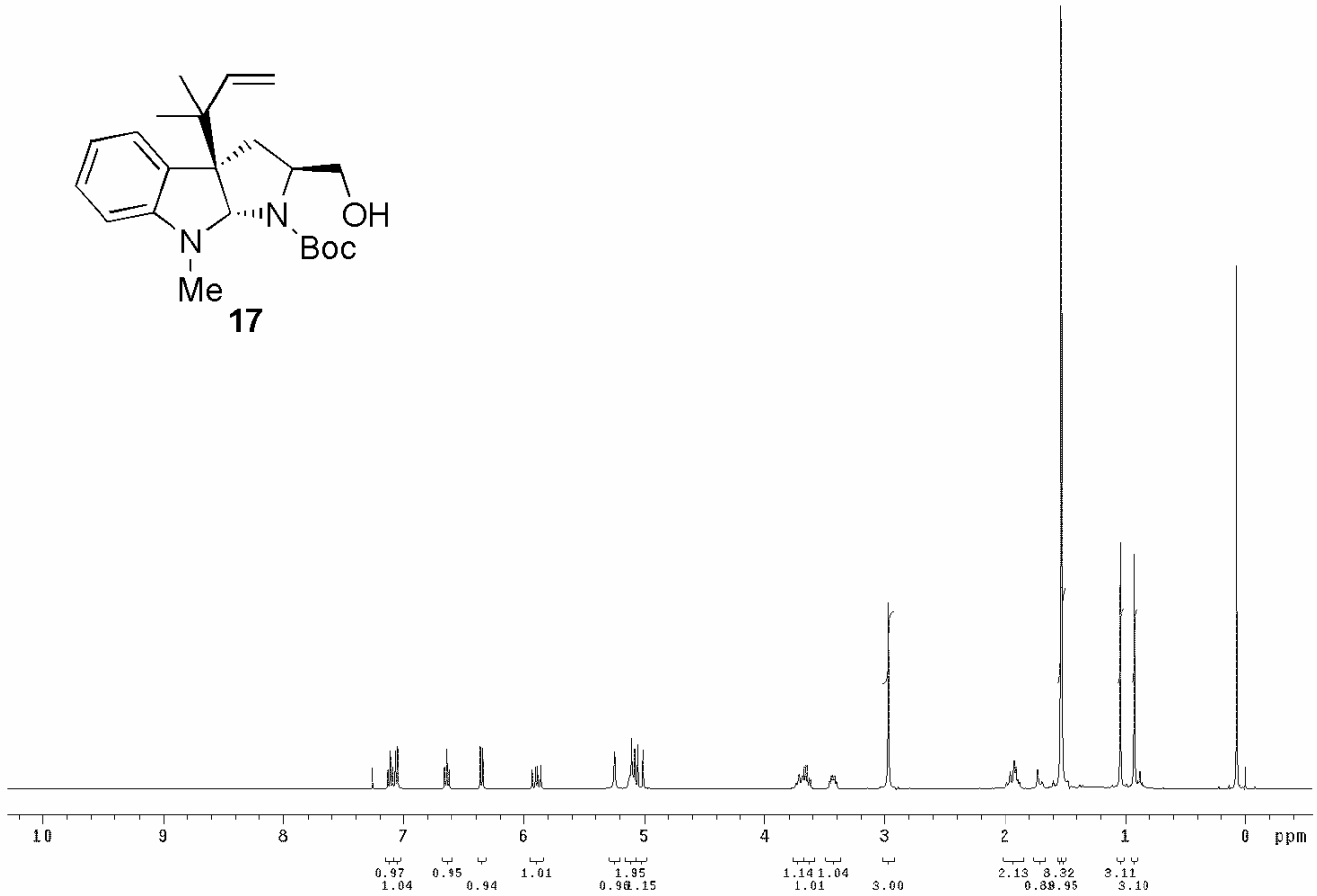
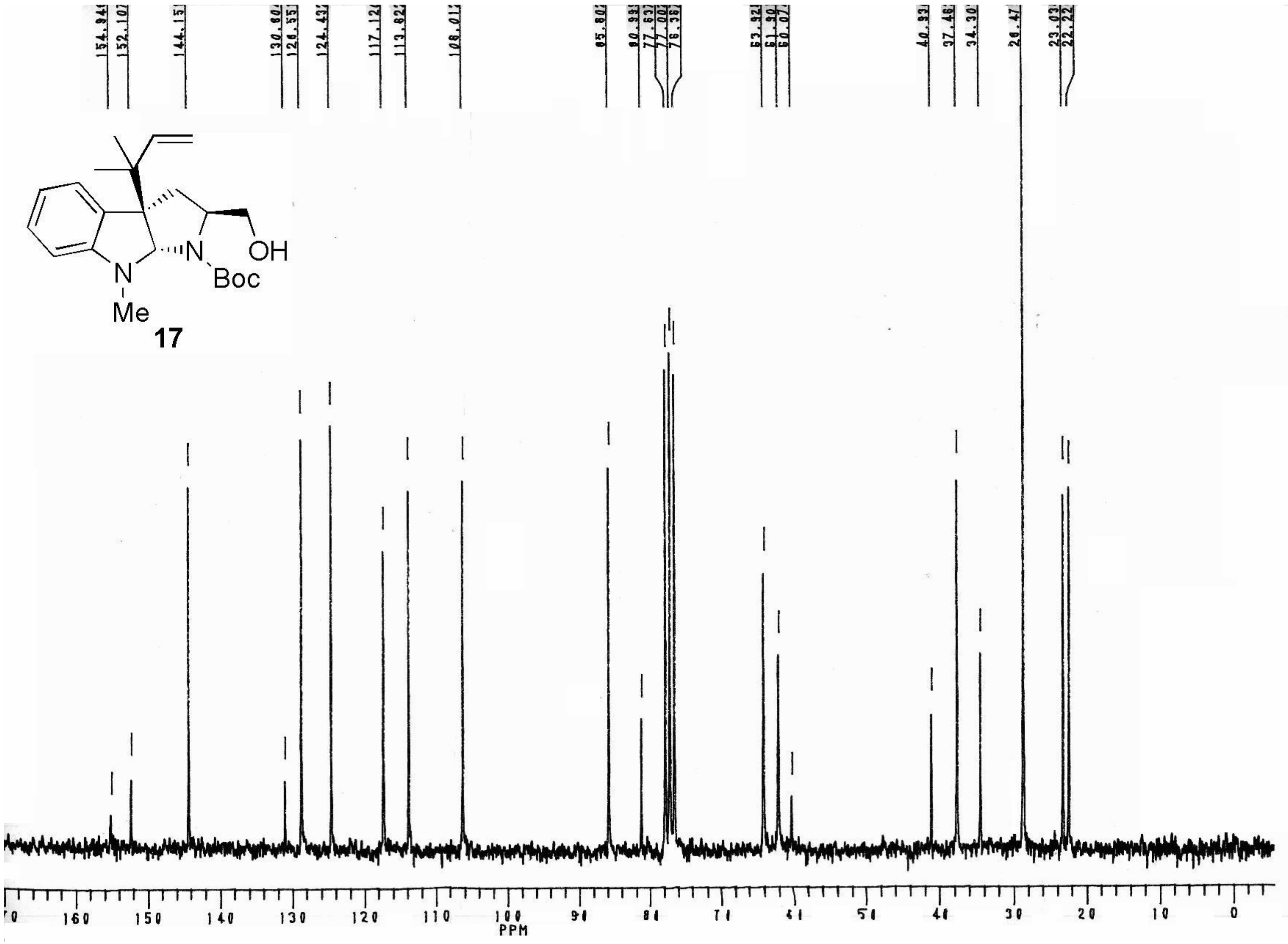
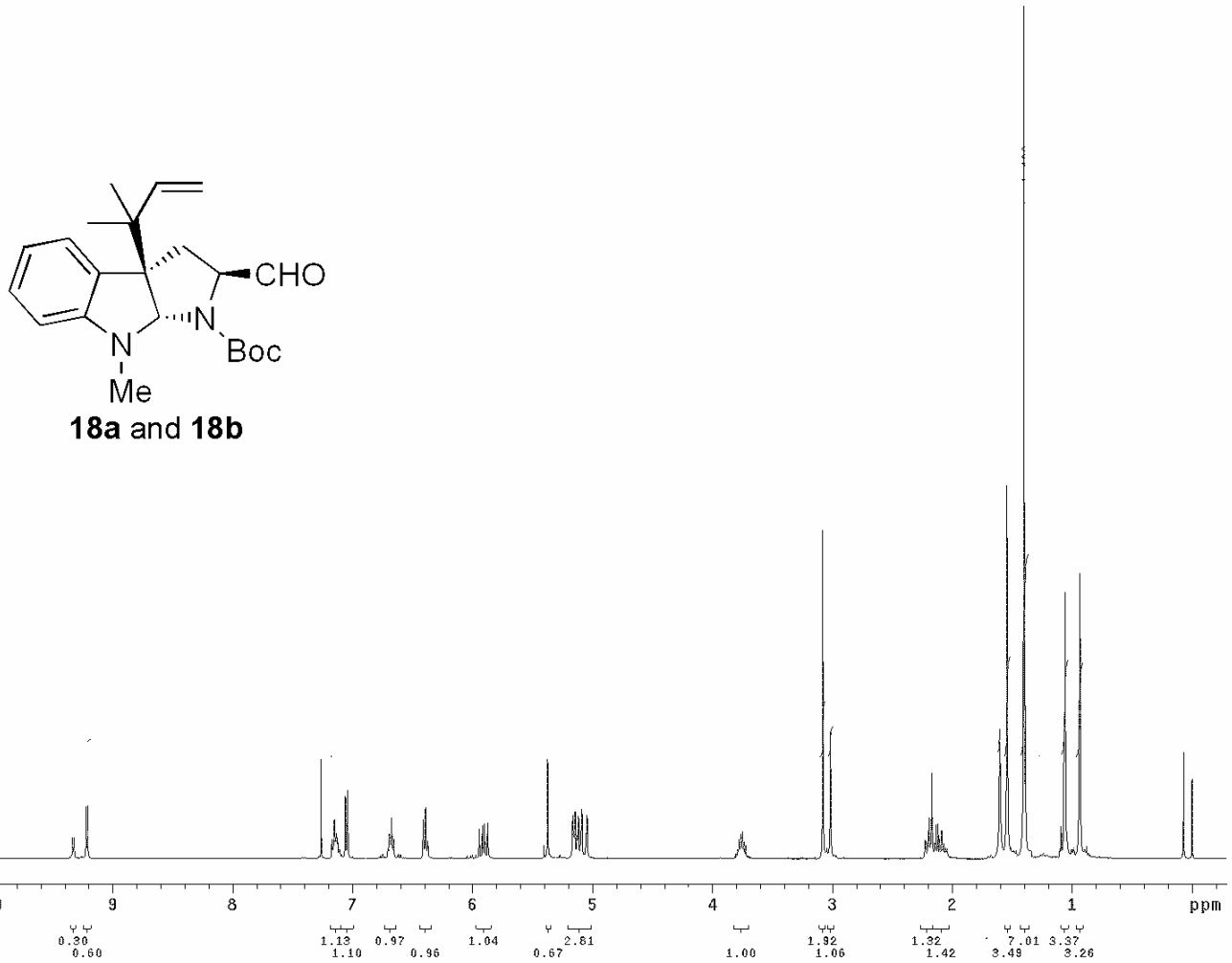
90
80
70
60
50
40
30
20
10
PPM


N
OH
N
Boc
Me
17
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.04
0.95
0.94
1.01
1.95
1.14
1.01
1.04
3.00
2.13
3.32
3.11
3.10


OH
N
Boc
N
Me
17
PPM


CHO
N
Boc
N
Me
10
9
8
7
6
5
4
3
2
1
ppm
0.30
0.60
1.13
1.10
0.97
0.96
1.04
0.67
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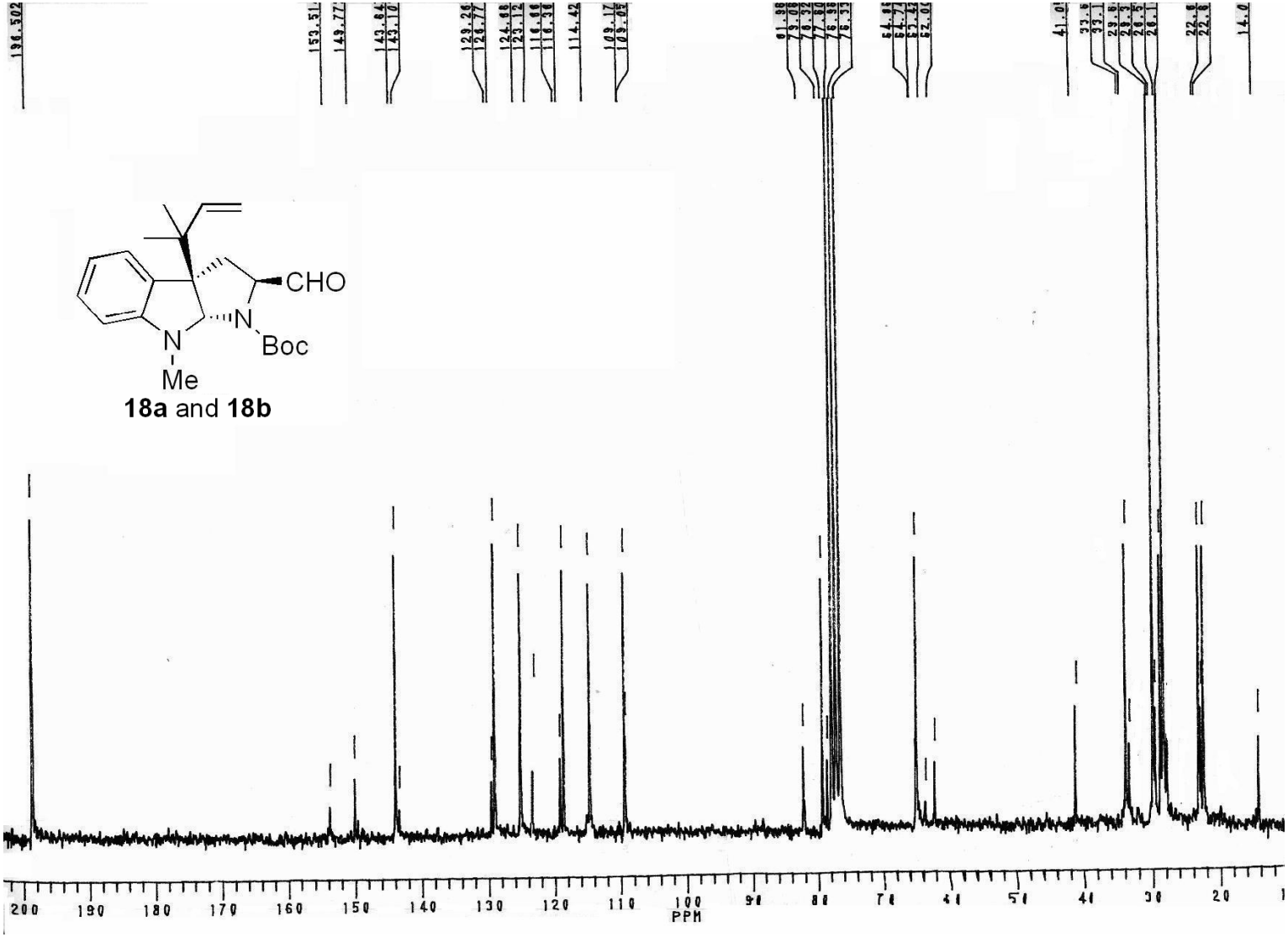
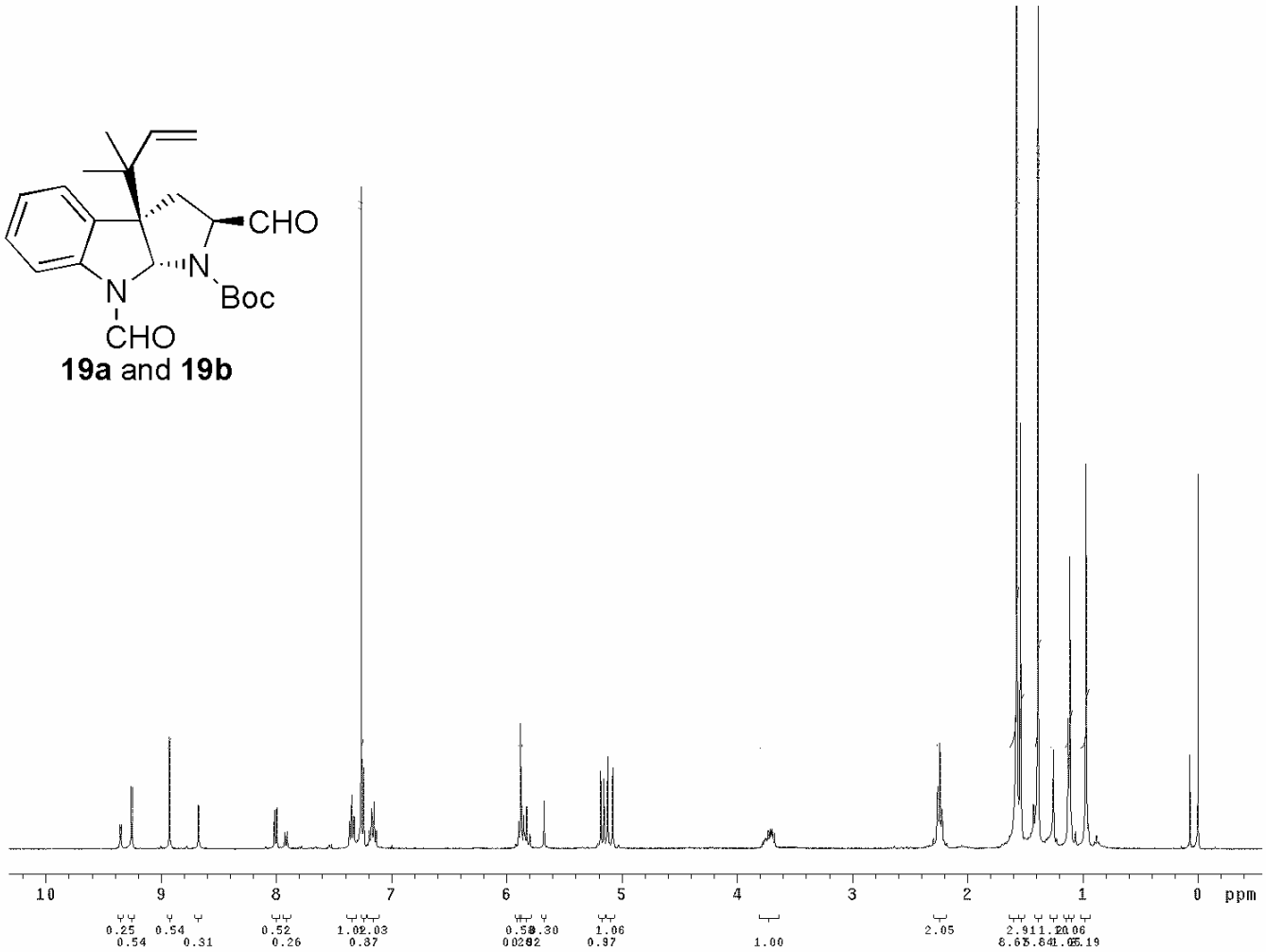
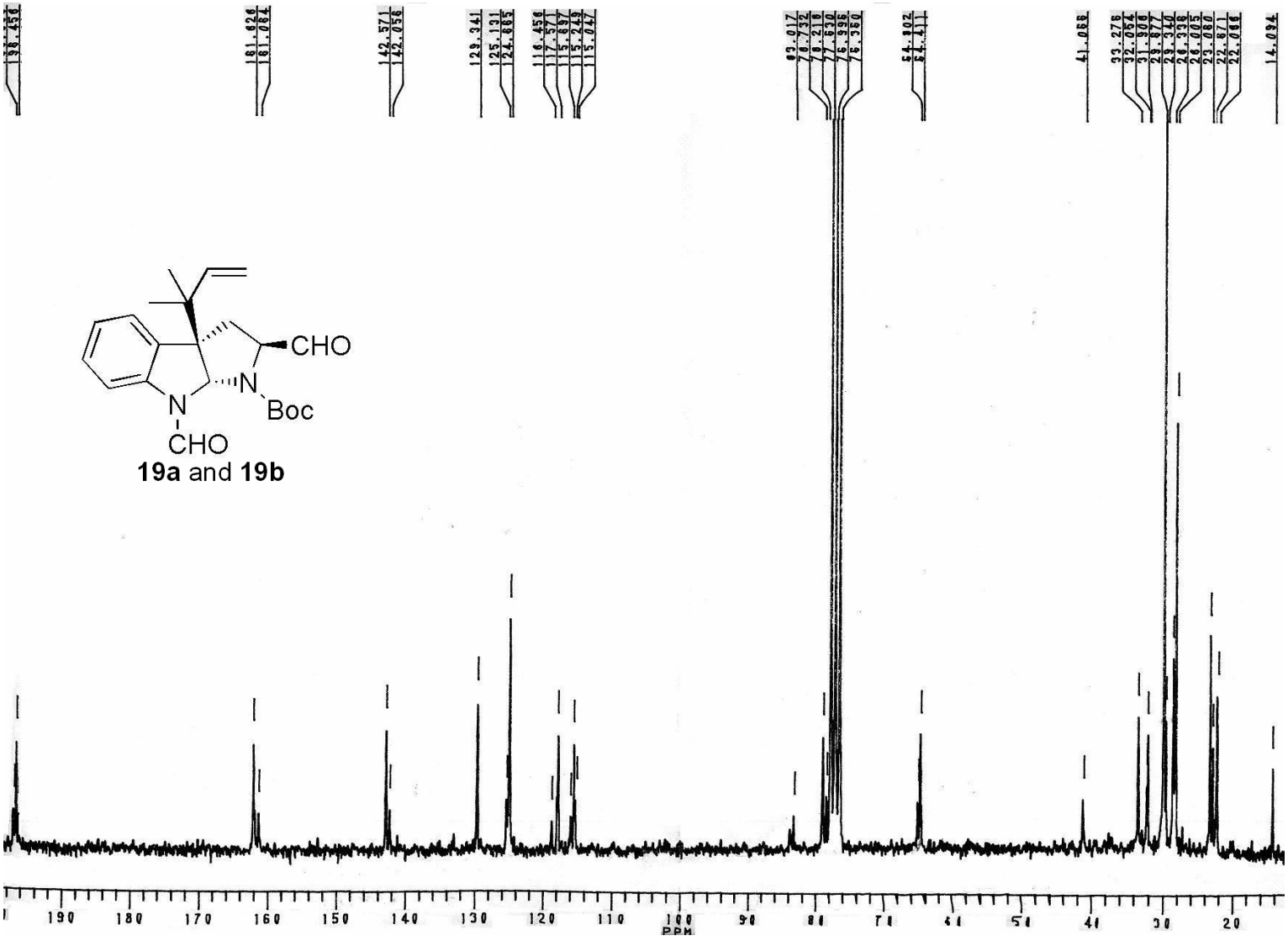
1.00
1.92
1.06
1.32
1.42
7.01
3.49
3.37
3.26

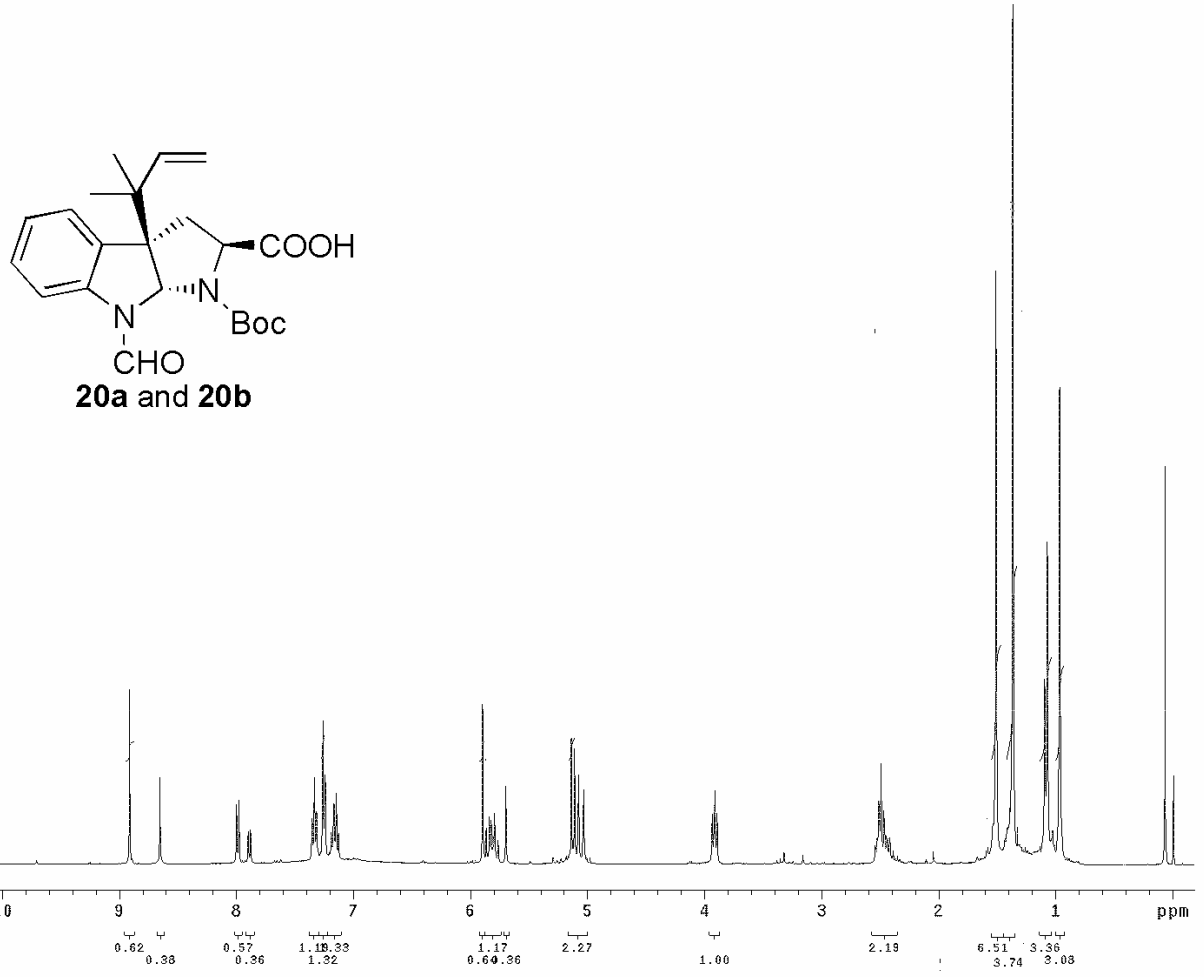
18a and **18b**

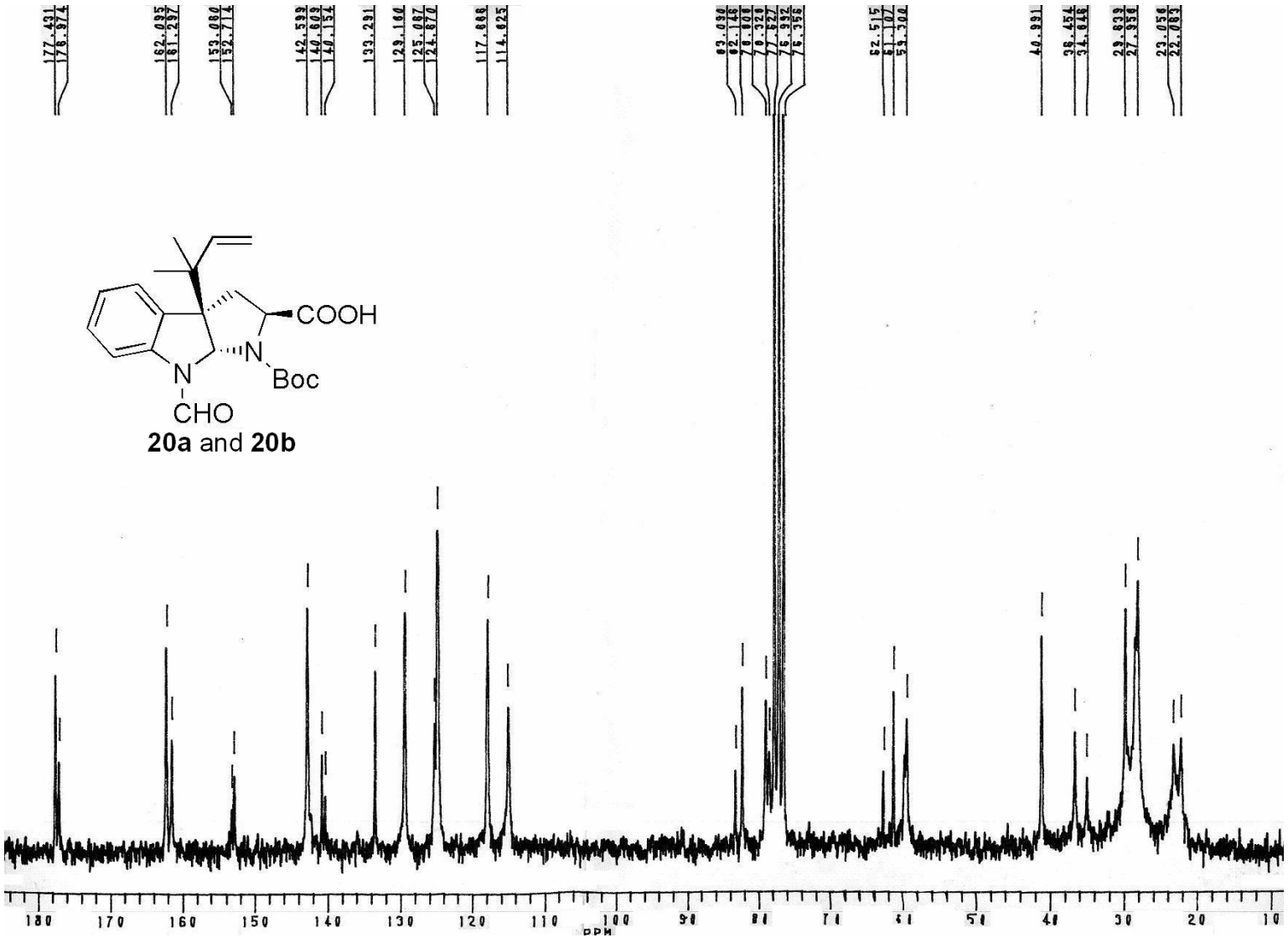

CHO
N
N
Boc
Me
18a and 18b
PPM

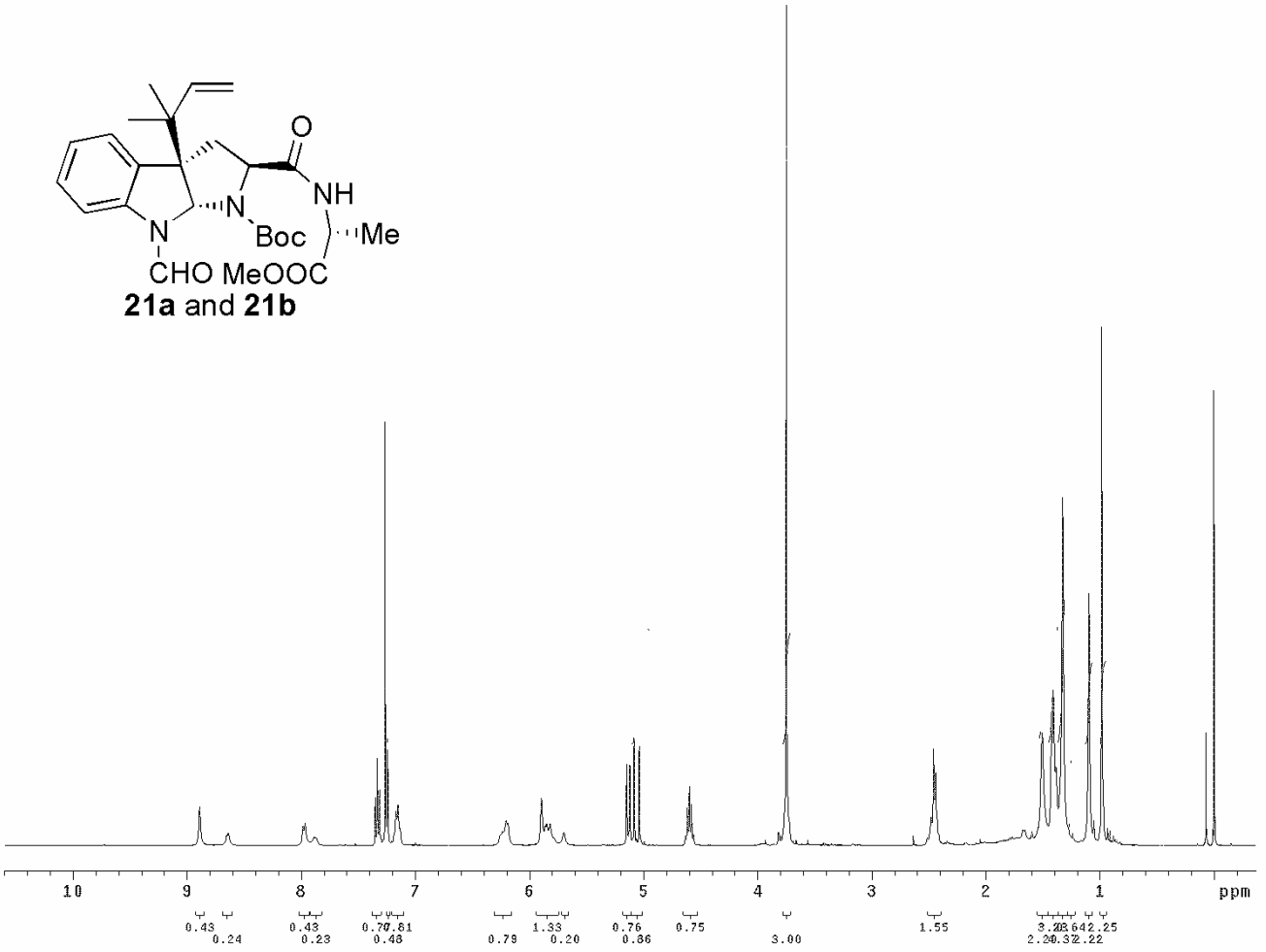


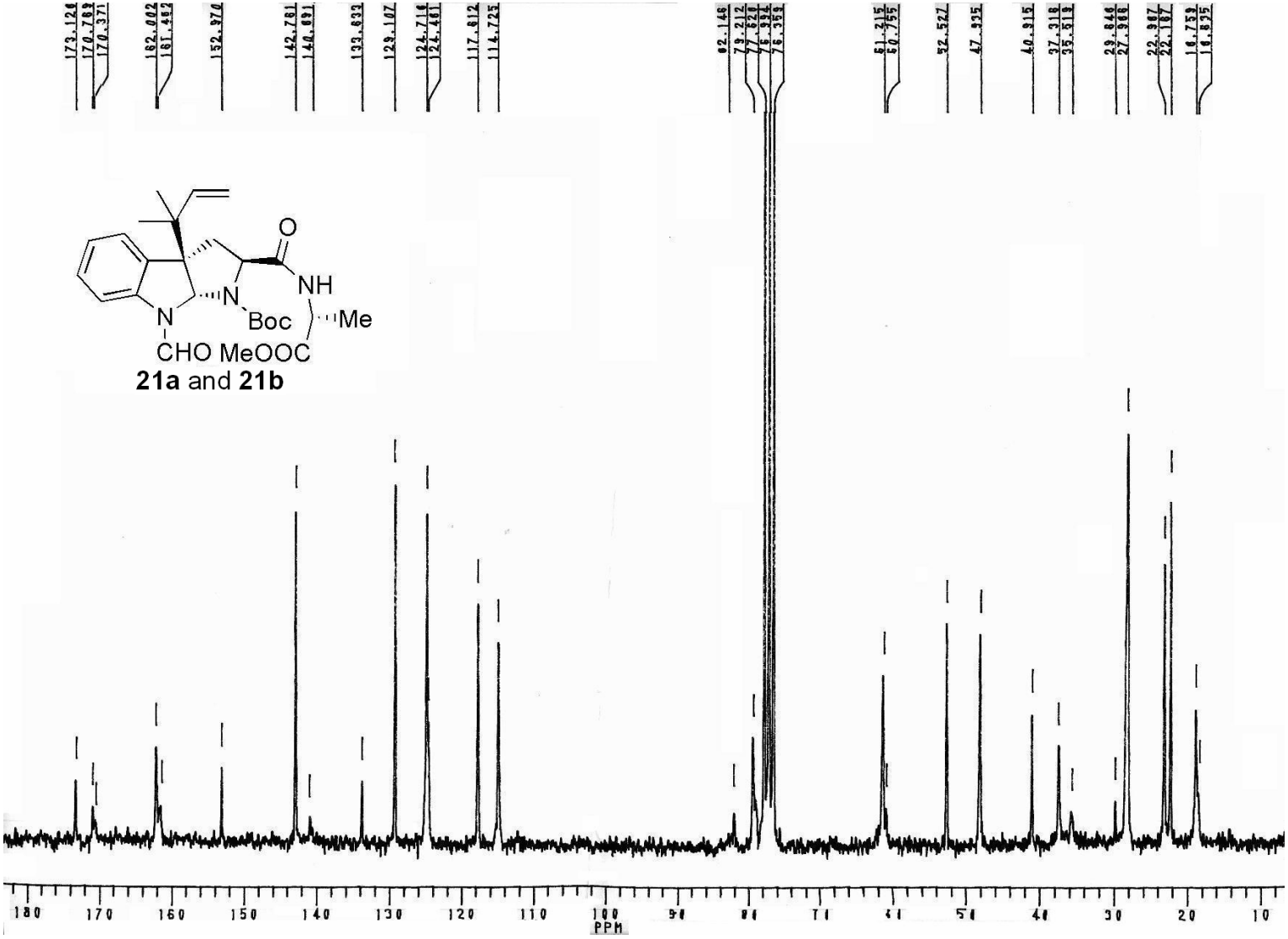
19a and **19b**

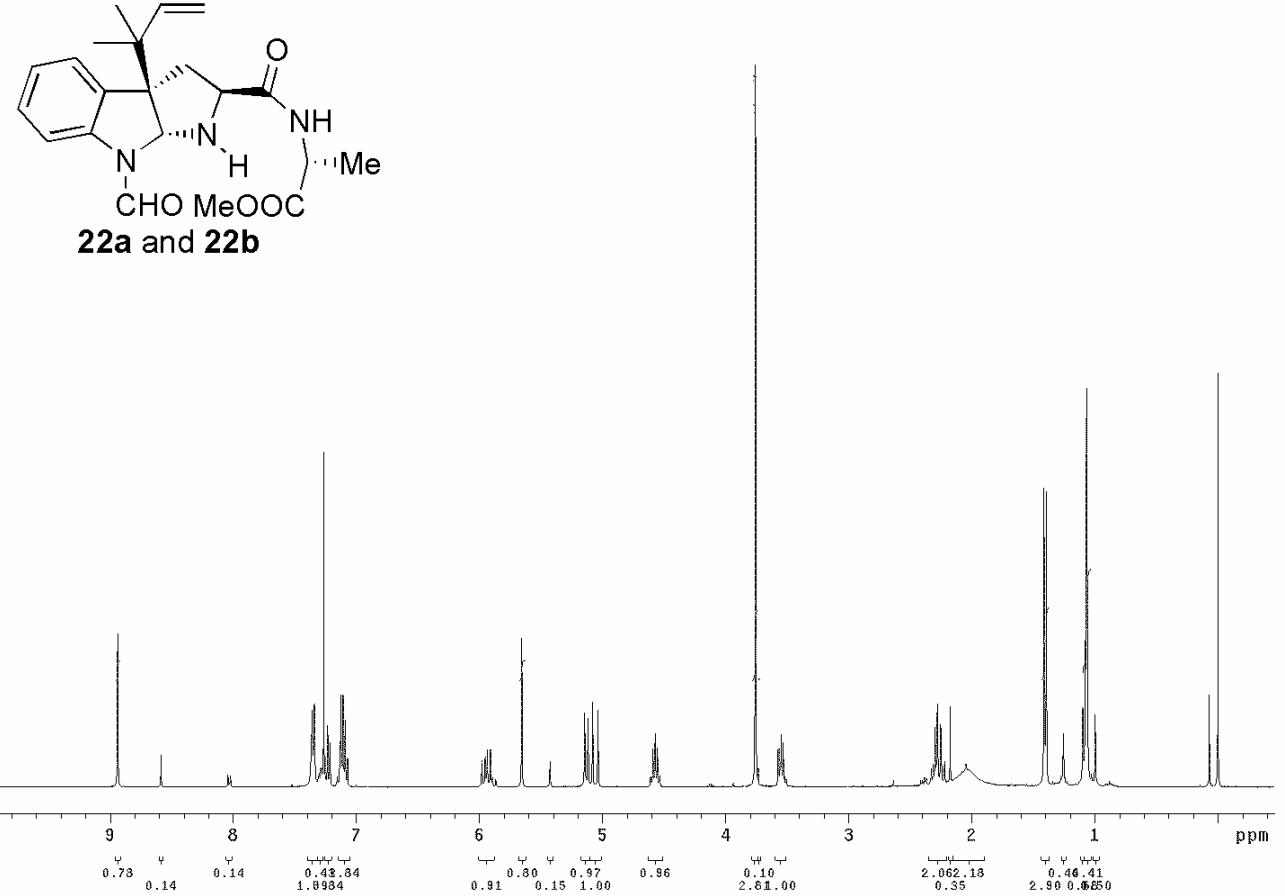

CHO
N
Boc
N
CHO
19a and 19b
198.454
181.624
181.084
142.571
142.058
129.341
125.131
124.885
116.456
117.571
115.897
115.245
115.047
83.017
78.732
78.218
77.610
76.998
76.350
54.102
54.411
41.088
33.278
32.064
31.908
29.877
29.440
28.338
28.005
23.860
22.871
22.088
14.094
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
PPM

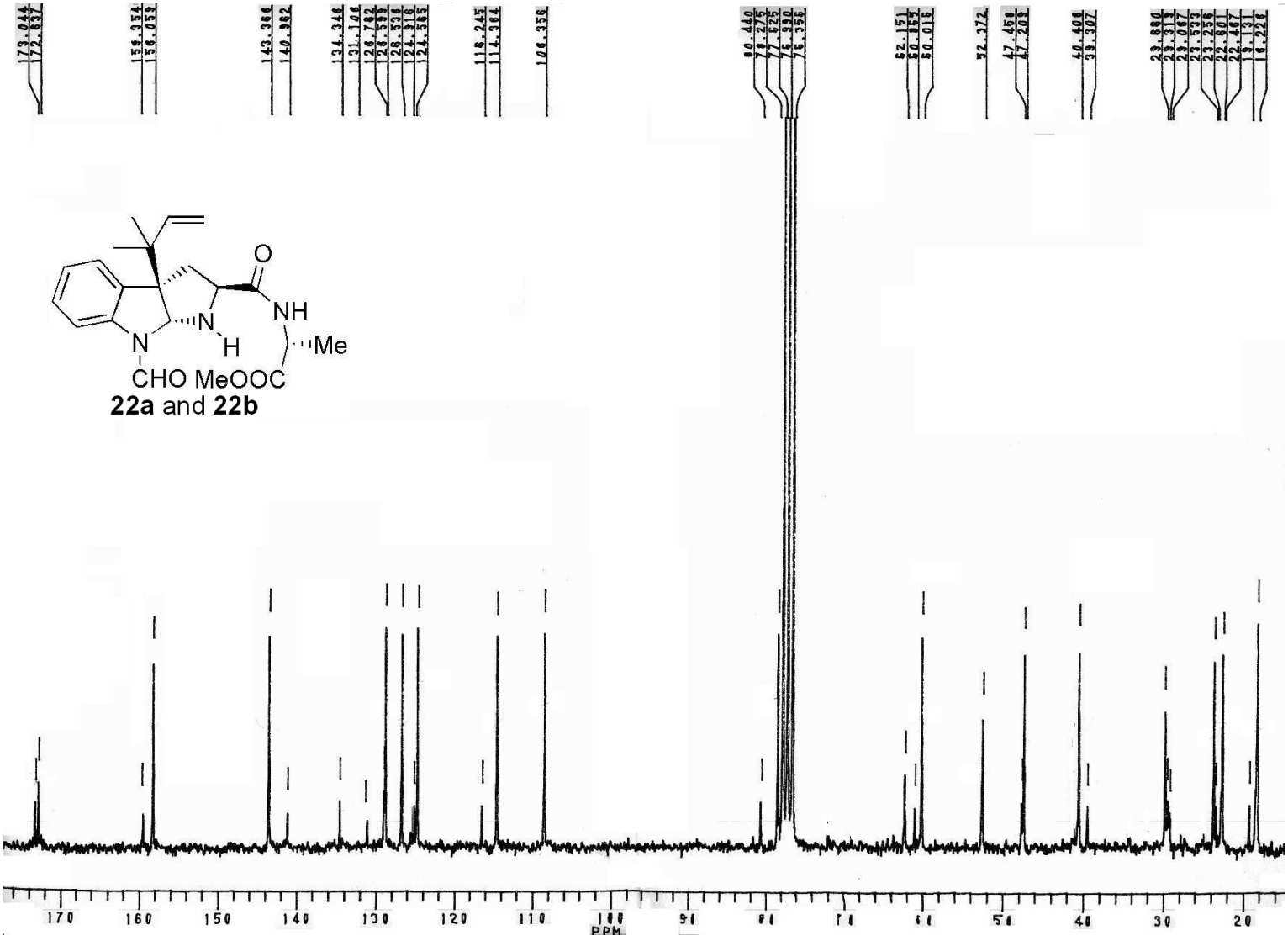

COOH
N
N
Boc
CHO
20a and 20b
10
9
8
7
6
5
4
3
2
1
ppm
0.62
0.38
0.57
0.36
1.17
0.64
0.36
2.27
1.00
2.19
6.51
3.74
3.36
3.08

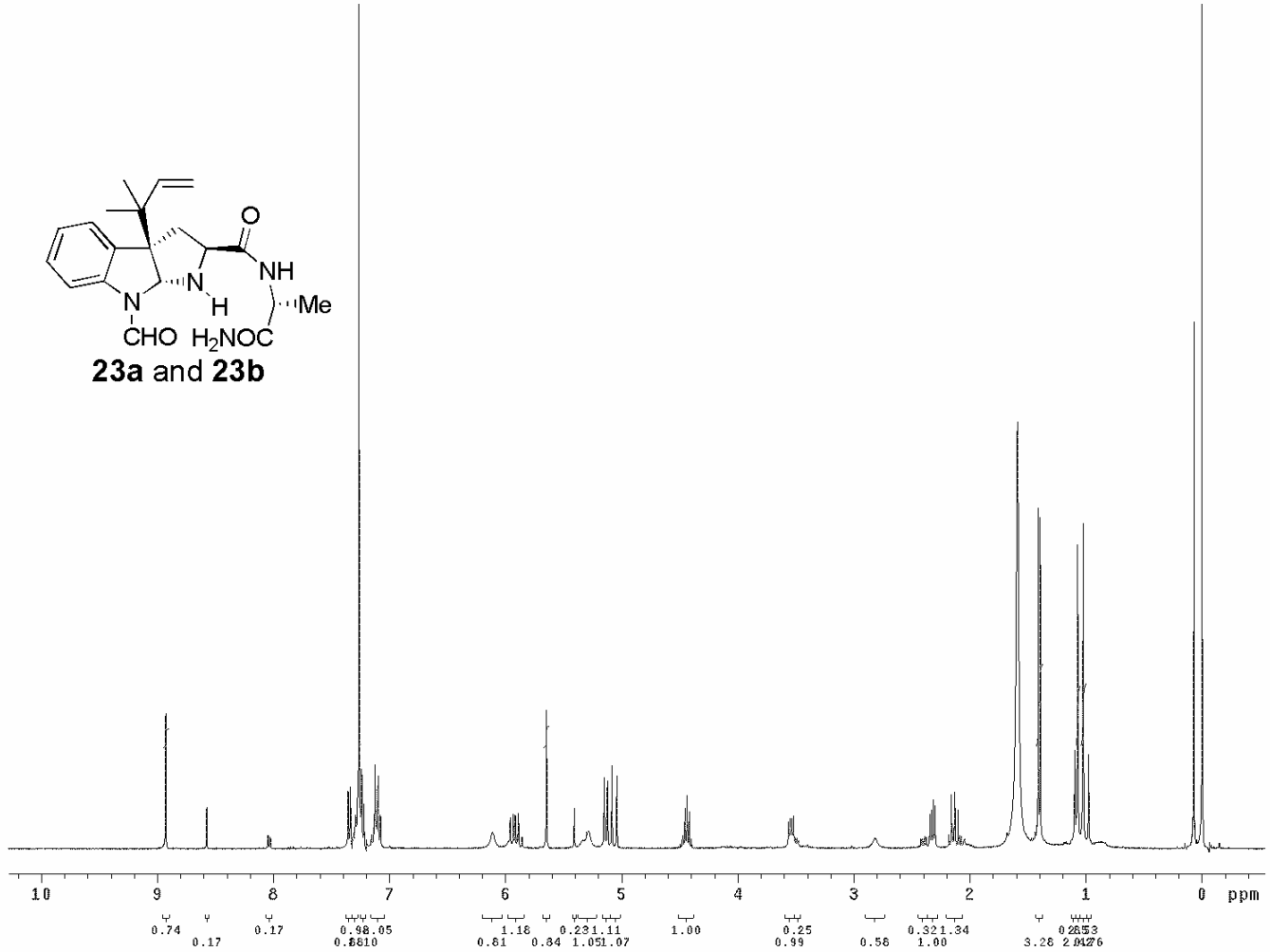

177.431
176.974
162.085
161.237
153.080
152.714
142.533
140.009
140.154
133.291
123.160
125.087
124.670
117.888
114.625
83.030
82.148
78.101
78.320
77.327
76.992
76.356
62.515
61.107
53.300
40.991
38.454
34.048
29.839
27.954
23.056
22.083
COOH
N
Boc
N
CHO
20a and 20b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
PPM

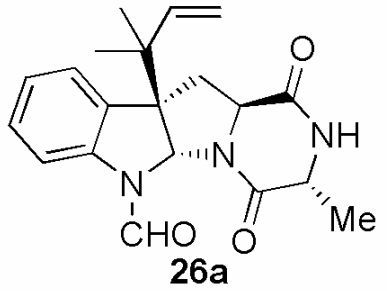

O
NH
N
N
Boc
Me
CHO MeOOC
21a and 21b
10
9
8
7
6
5
4
3
2
1
ppm
0.43
0.24
0.43
0.23
0.79
0.48
0.81
0.79
1.33
0.20
0.76
0.86
0.75
3.00
1.55
2.24
0.37
2.22
2.25


O
NH
N
N
Boc
Me
CHO MeOOC
21a and 21b
PPM

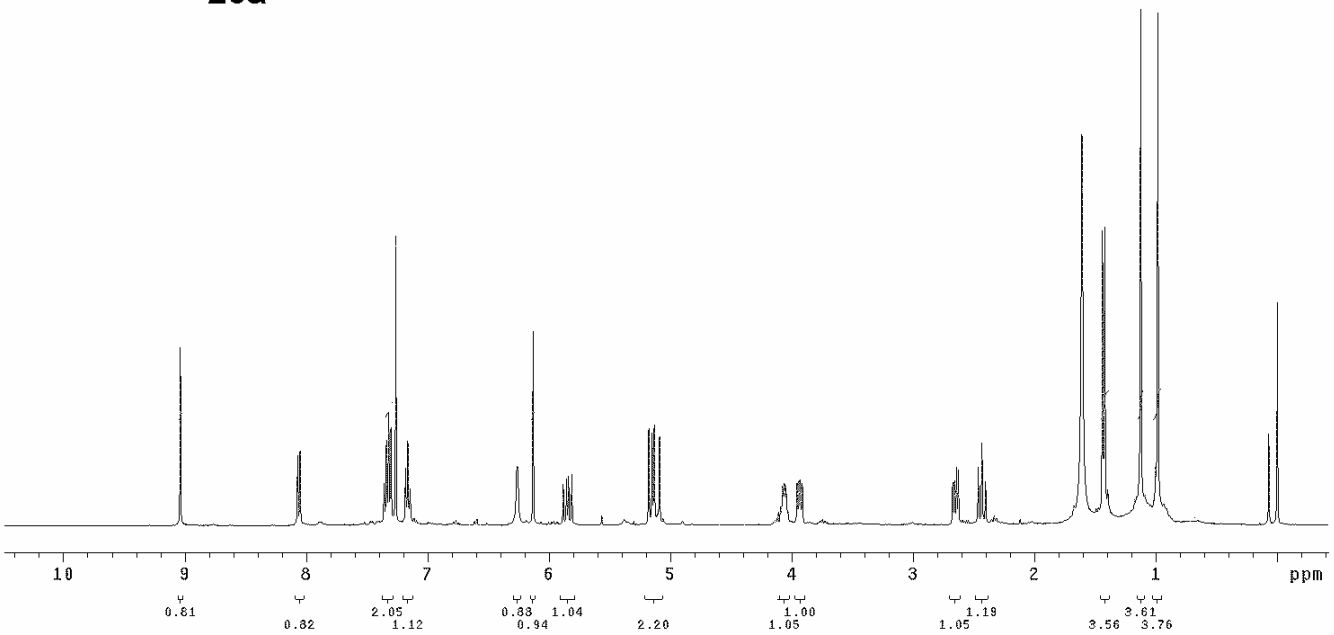

O
NH
N
H
Me
N
CHO MeOOC
22a and 22b
10
9
8
7
6
5
4
3
2
1
ppm

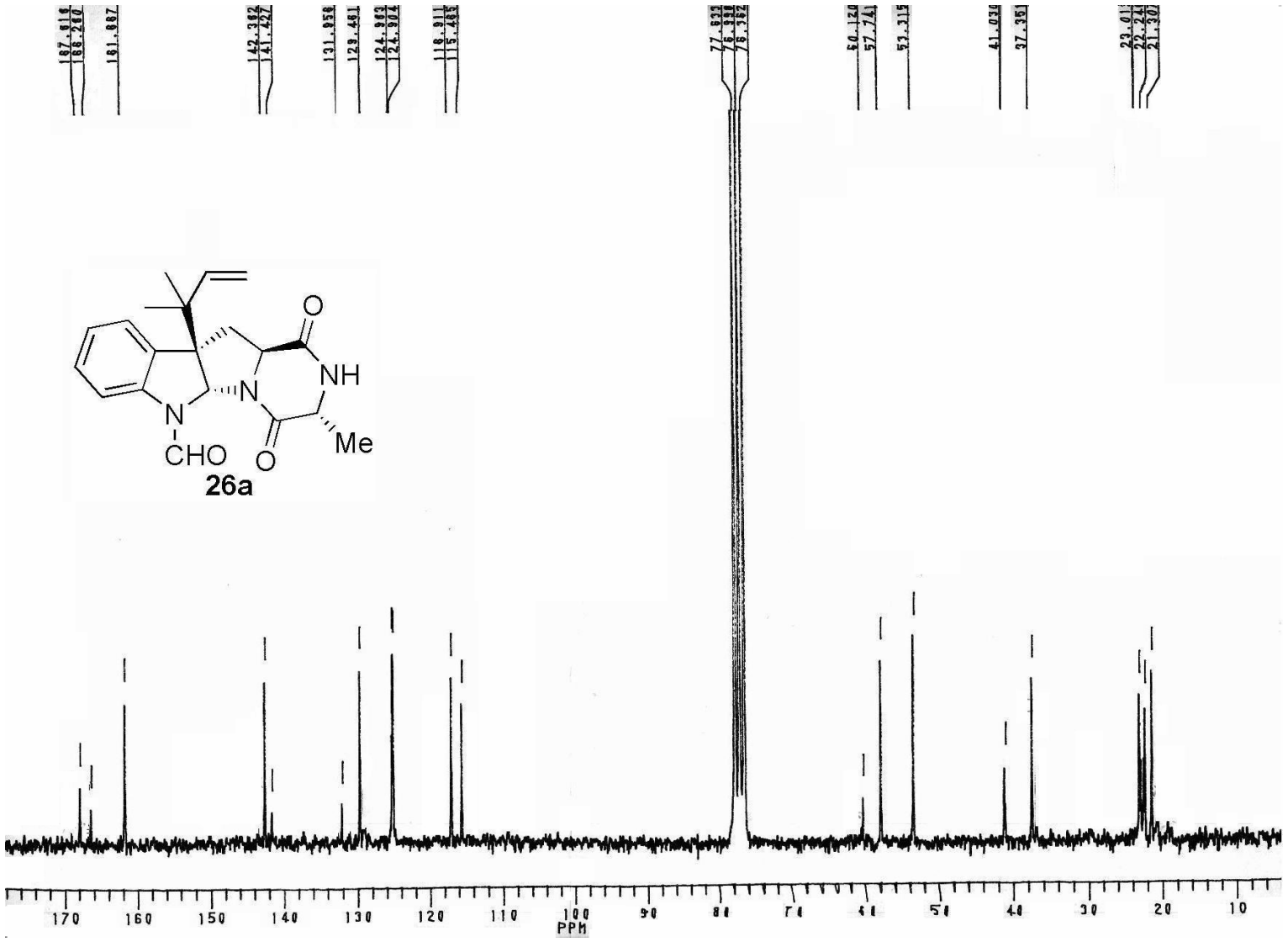

O
NH
N
H
Me
CHO MeOOC
22a and 22b
PPM

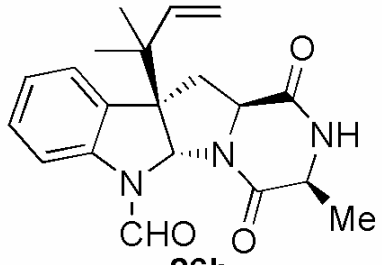

O
NH
N
H
Me
N
CHO
H2NOC
23a and 23b
10
9
8
7
6
5
4
3
2
1
0
ppm


O
NH
N
N
CHO
O
Me

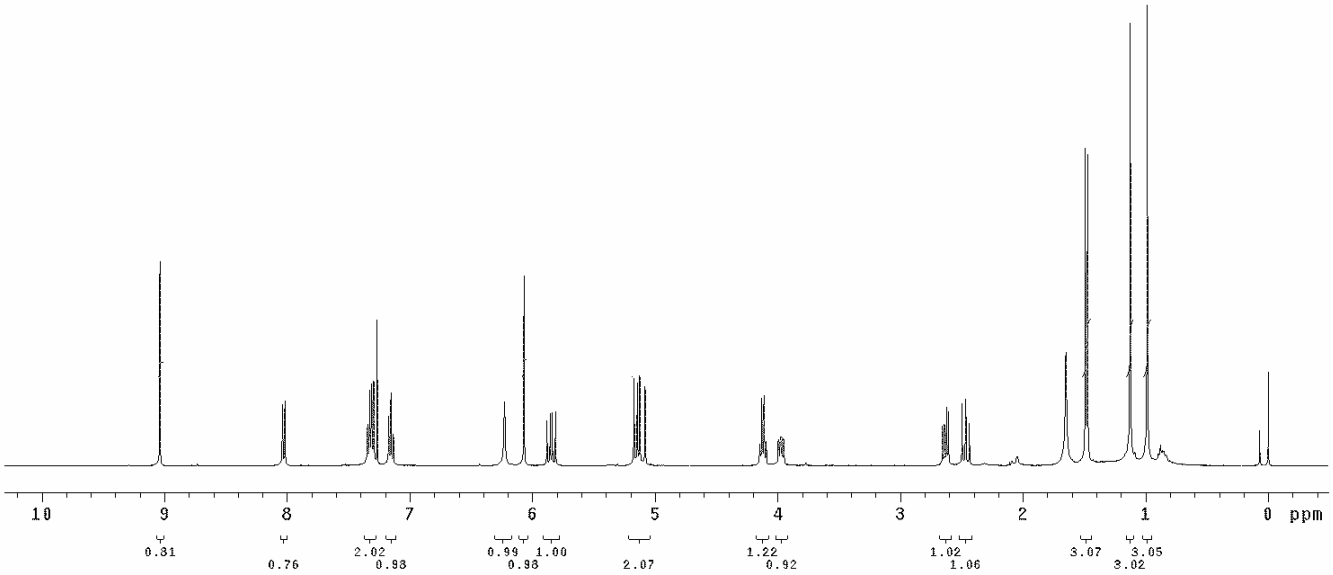
26a

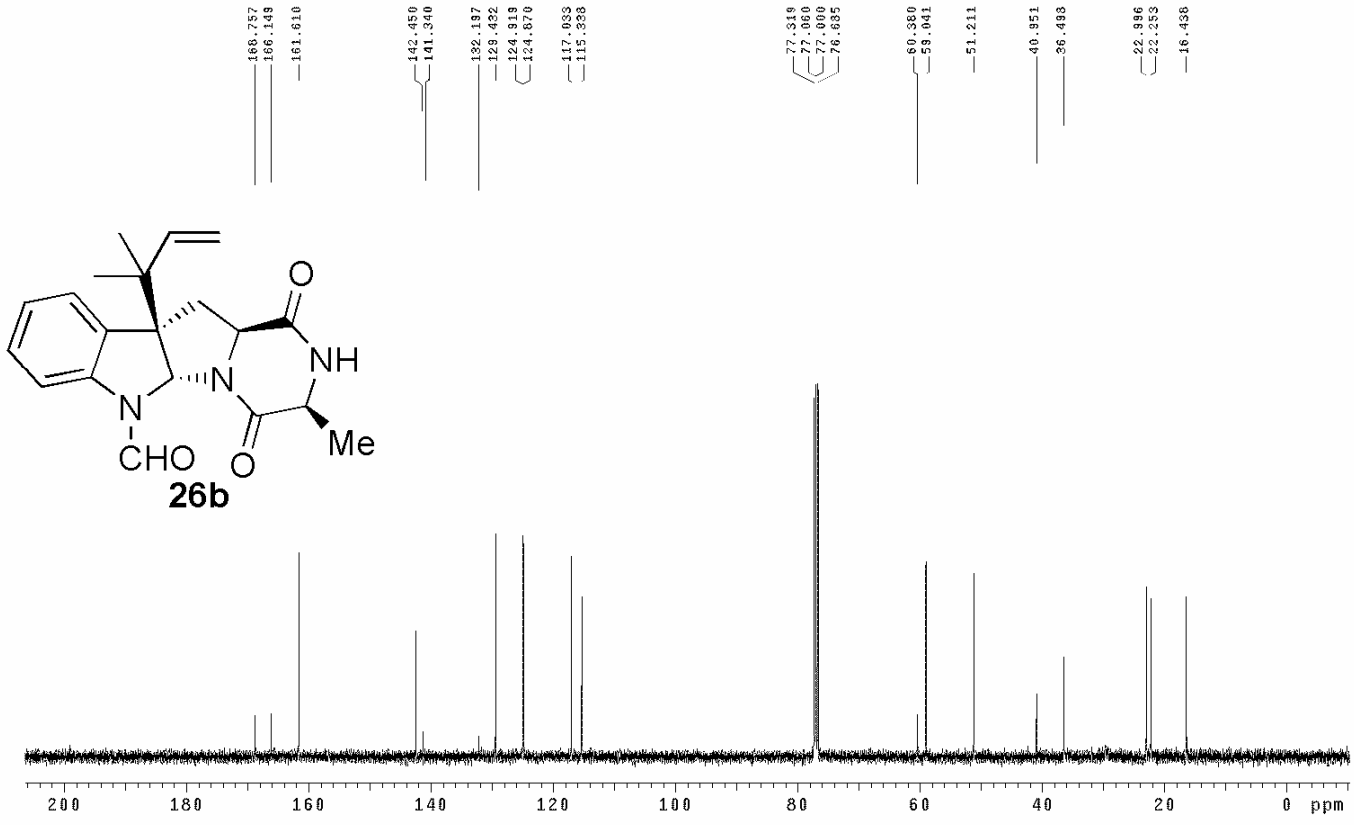

10
9
8
7
6
5
4
3
2
1
ppm
0.81
0.82
2.05
1.12
0.88
0.94
1.04
2.20
1.00
1.05
1.05
1.19
3.56
3.61
3.76


O
NH
N
N
CHO
O
Me
26a
PPM

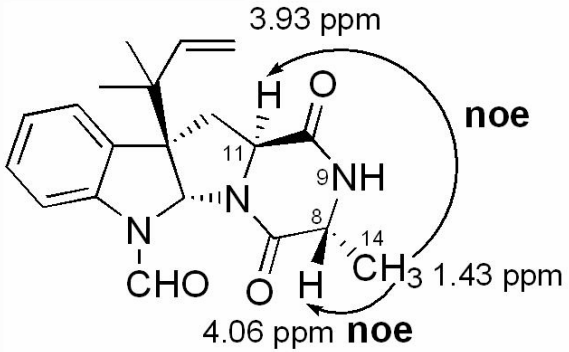

O
NH
N
N
CHO
O
Me

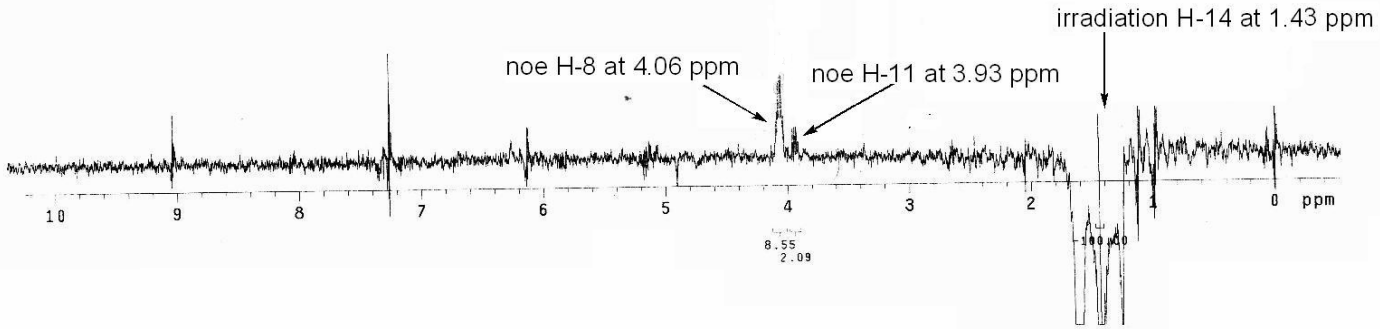
26b


10
9
8
7
6
5
4
3
2
1
0 ppm
0.31
0.76
2.02
0.98
0.99
1.00
0.98
2.07
1.22
0.92
1.02
1.06
3.07
3.05
3.02

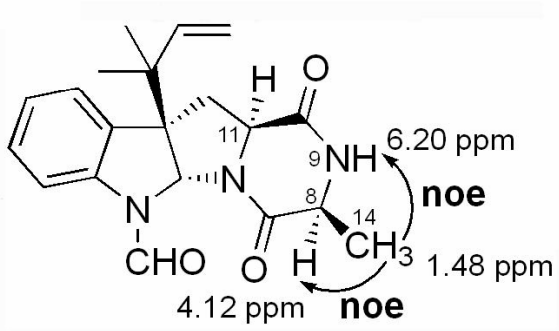

166.757
166.149
161.610
142.450
141.340
132.197
129.432
124.913
124.670
117.033
115.338
77.319
77.060
77.000
76.685
60.380
53.041
51.211
40.951
36.493
22.996
22.253
16.436
O
NH
N
N
Me
CHO
O
26b
200
180
160
140
120
100
80
60
40
20
0
ppm

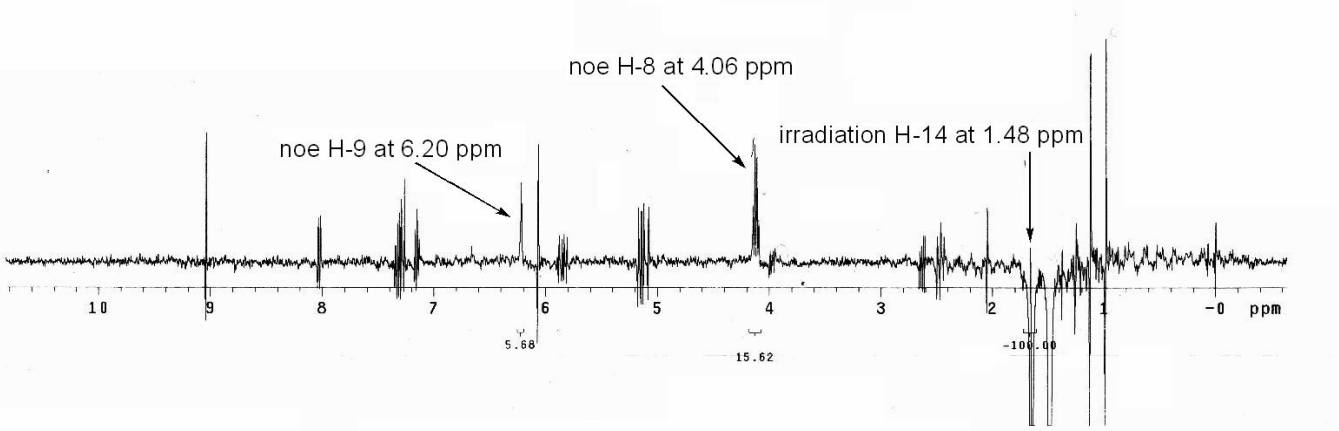
NOEDS Spectrum of Diketopiperazine **26a**

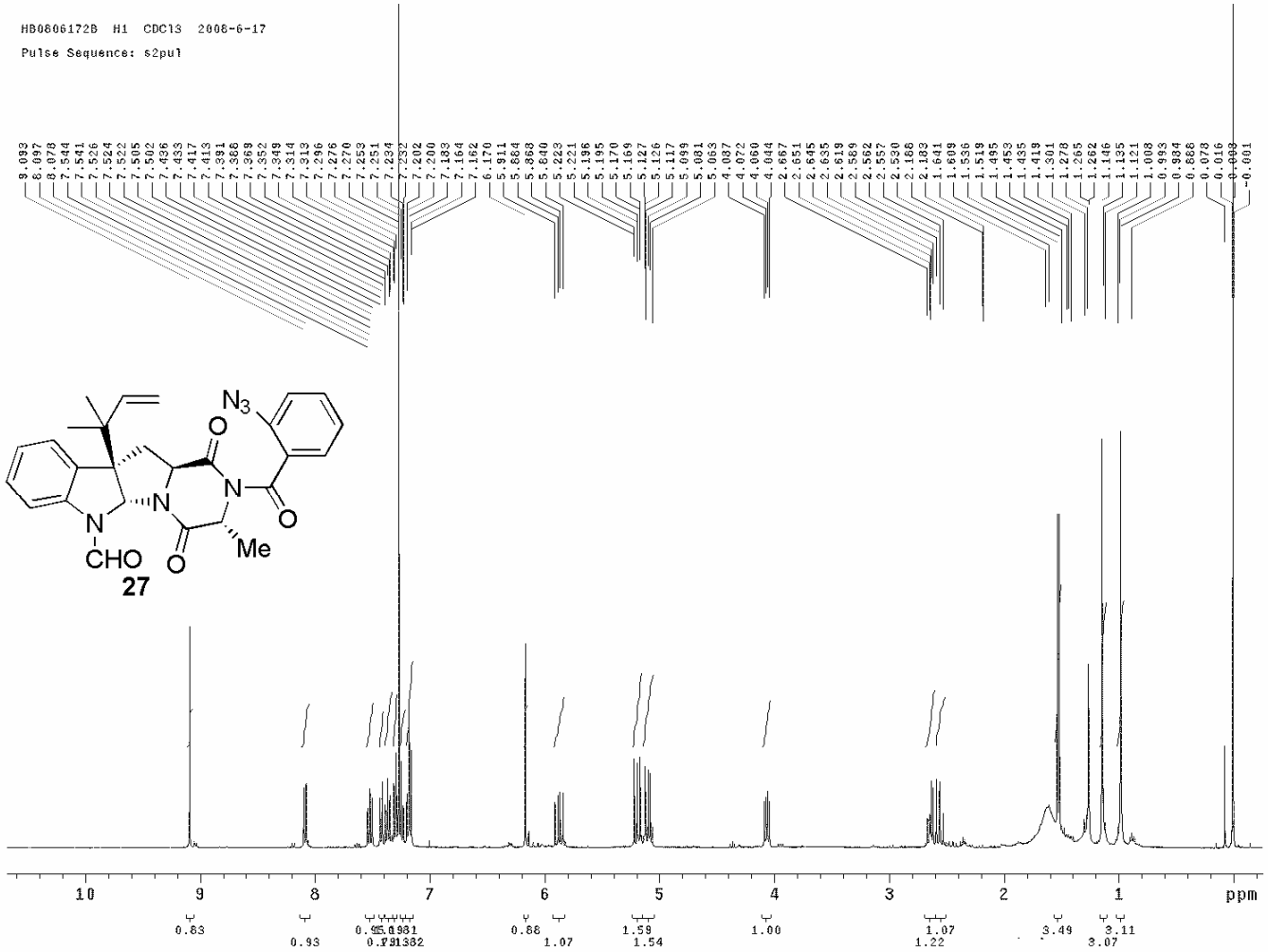


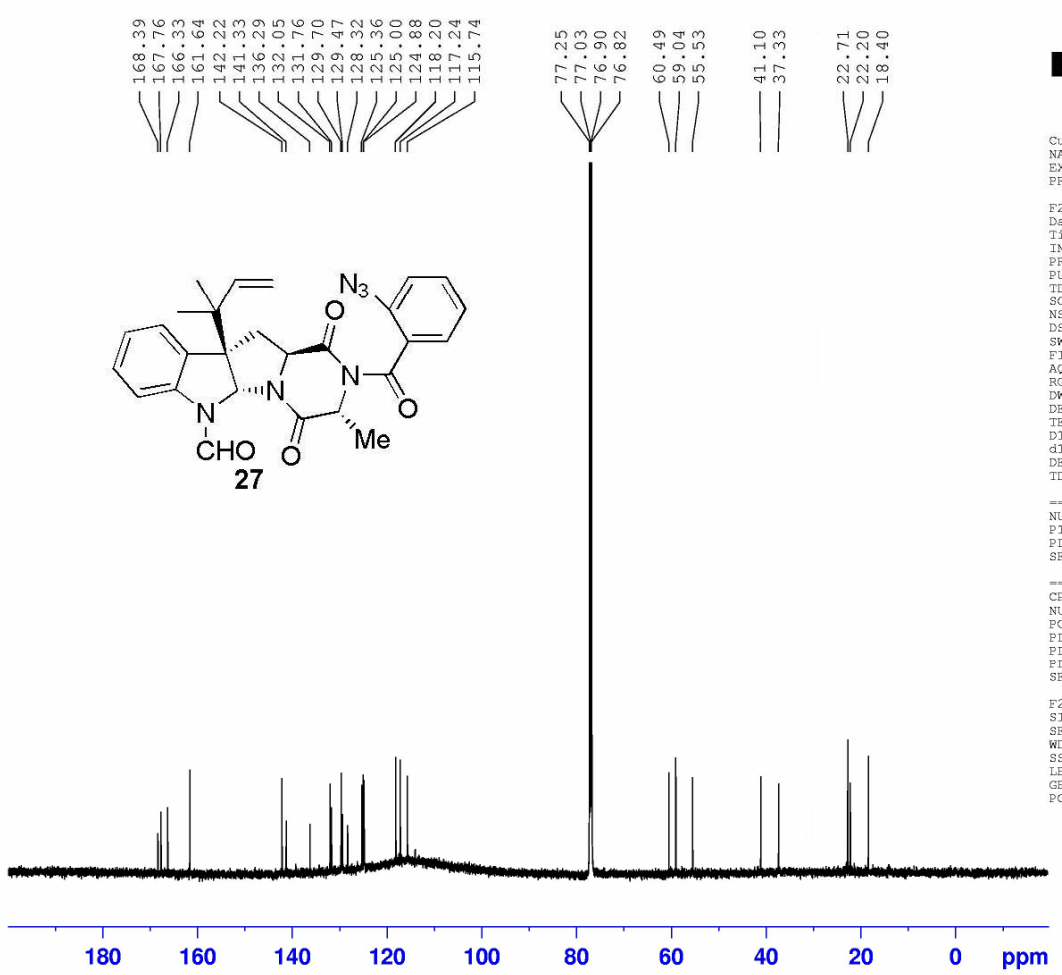


NOEDS Spectrum of Diketopiperazine **26b**



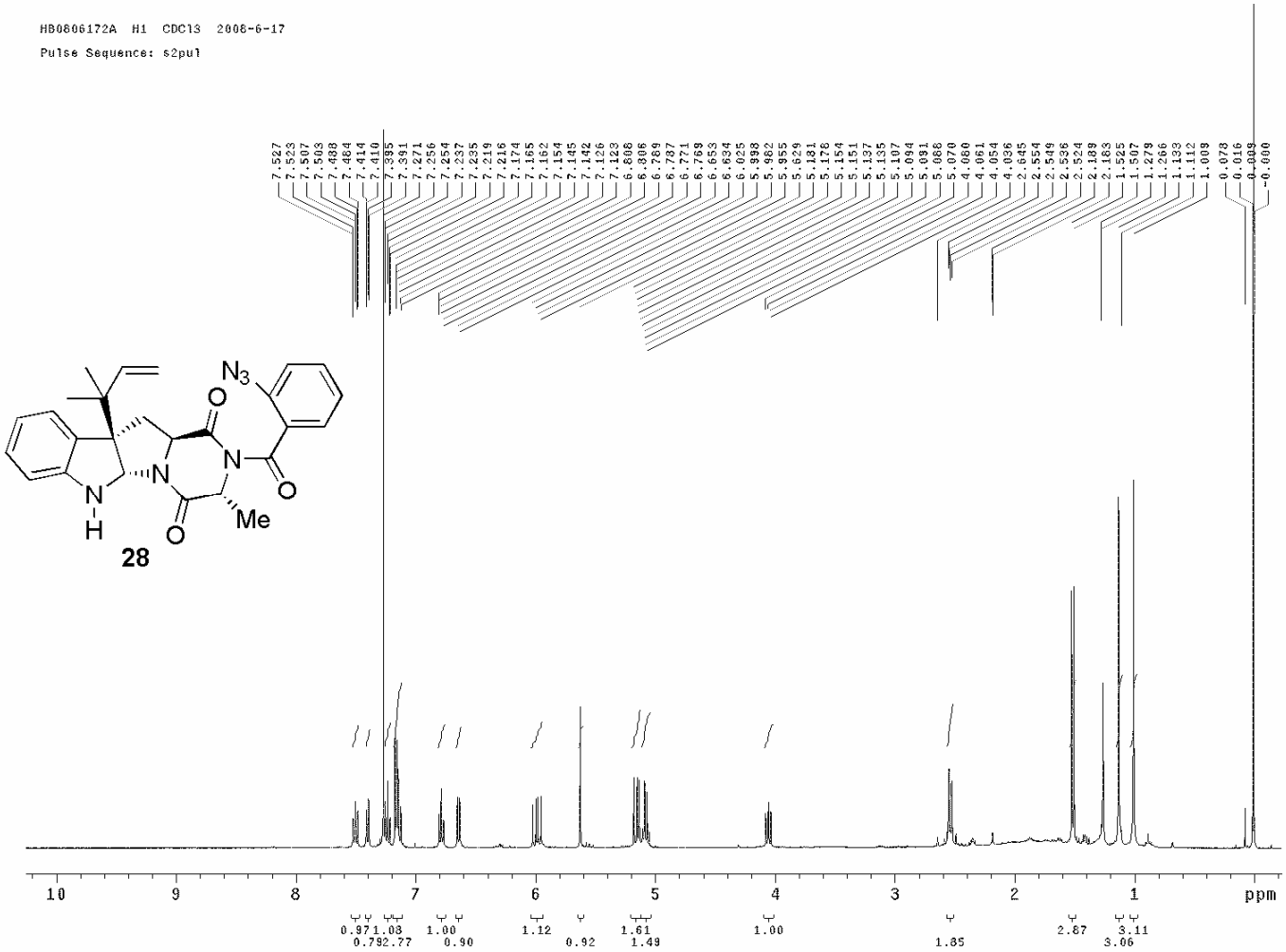


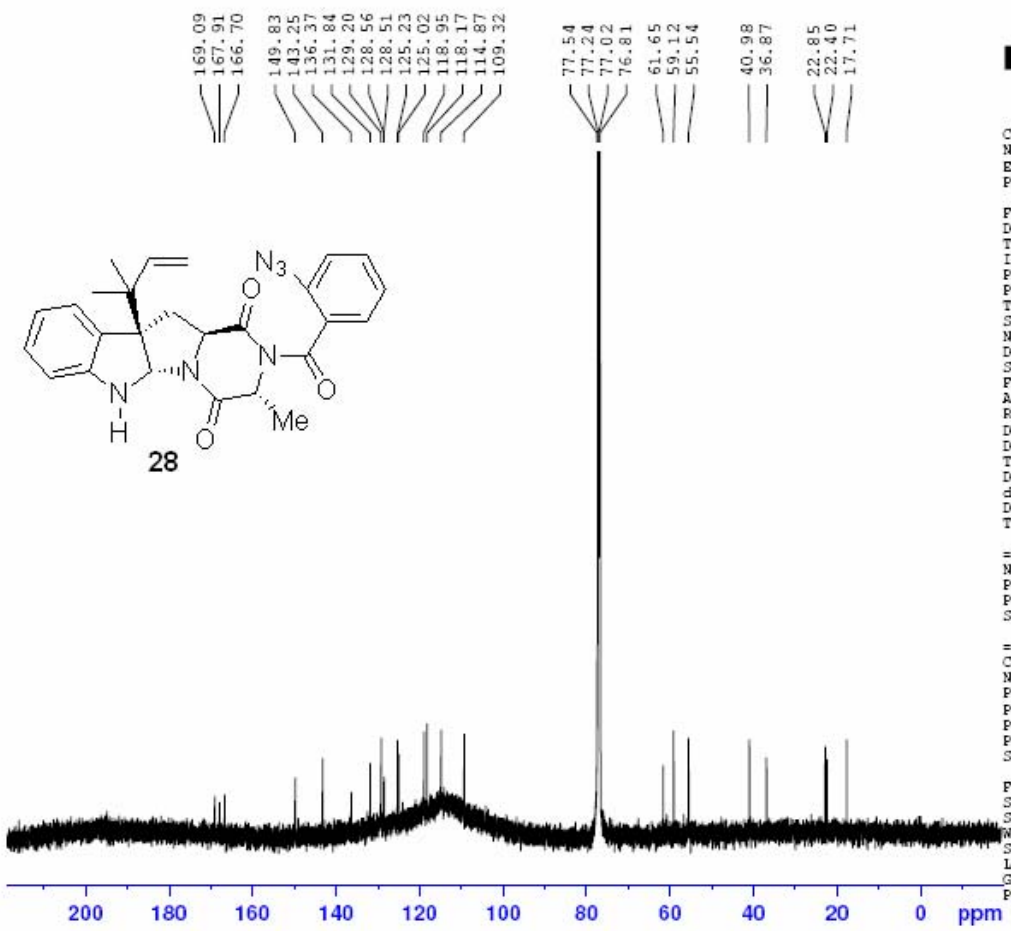

HB0806172B H1 CDCl3 2008-6-17
Pulse Sequence: s2pul
N3
O
N
O
N
CHO
O
O
Me
27
10
9
8
7
6
5
4
3
2
1
ppm



BRUKER

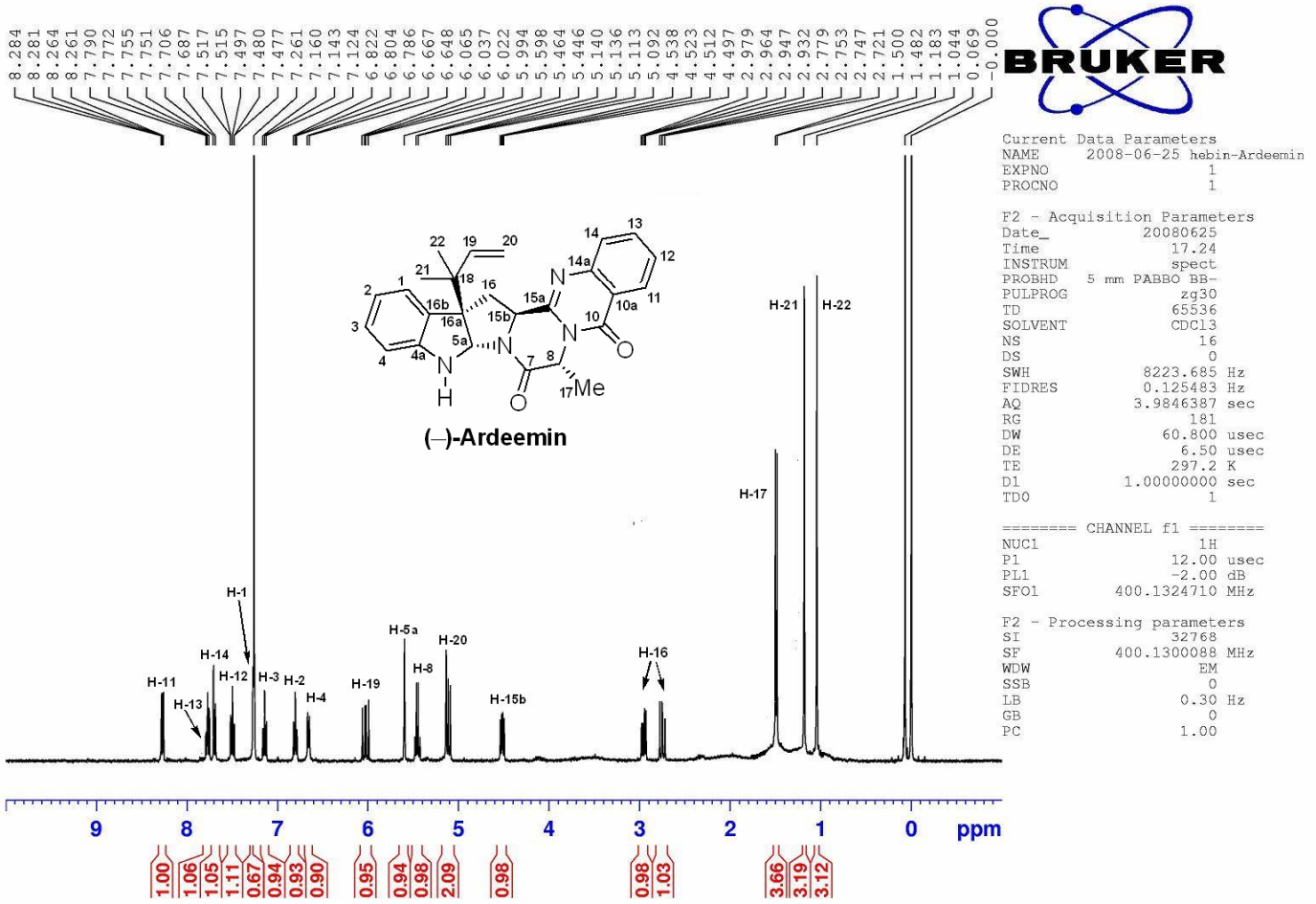
```
Current Data Parameters
NAME      2008-06-24 hebin-0806172B
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20080625
Time                3.12
INSTRUM            spect
PROBHD   5 mm PATXI 1H/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 8000
DS                    0
SWH           36057.691 Hz
FIDRES         0.550197 Hz
AQ            0.9088159 sec
RG                  181
DW               13.867 usec
DE                6.50 usec
TE                296.6 K
D1           5.00000000 sec
d11          0.03000000 sec
DELTA        4.90000010 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                 11.50 usec
PL1                -3.00 dB
SFO1        150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              80.00 usec
PL12               19.68 dB
PL13               19.50 dB
PL2                -1.00 dB
SFO2        600.1324005 MHz

F2 - Processing parameters
SI                  32768
SF          150.9028035 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```


HB0806172A H1 CDCl3 2008-6-17
Pulse Sequence: s2pul
28

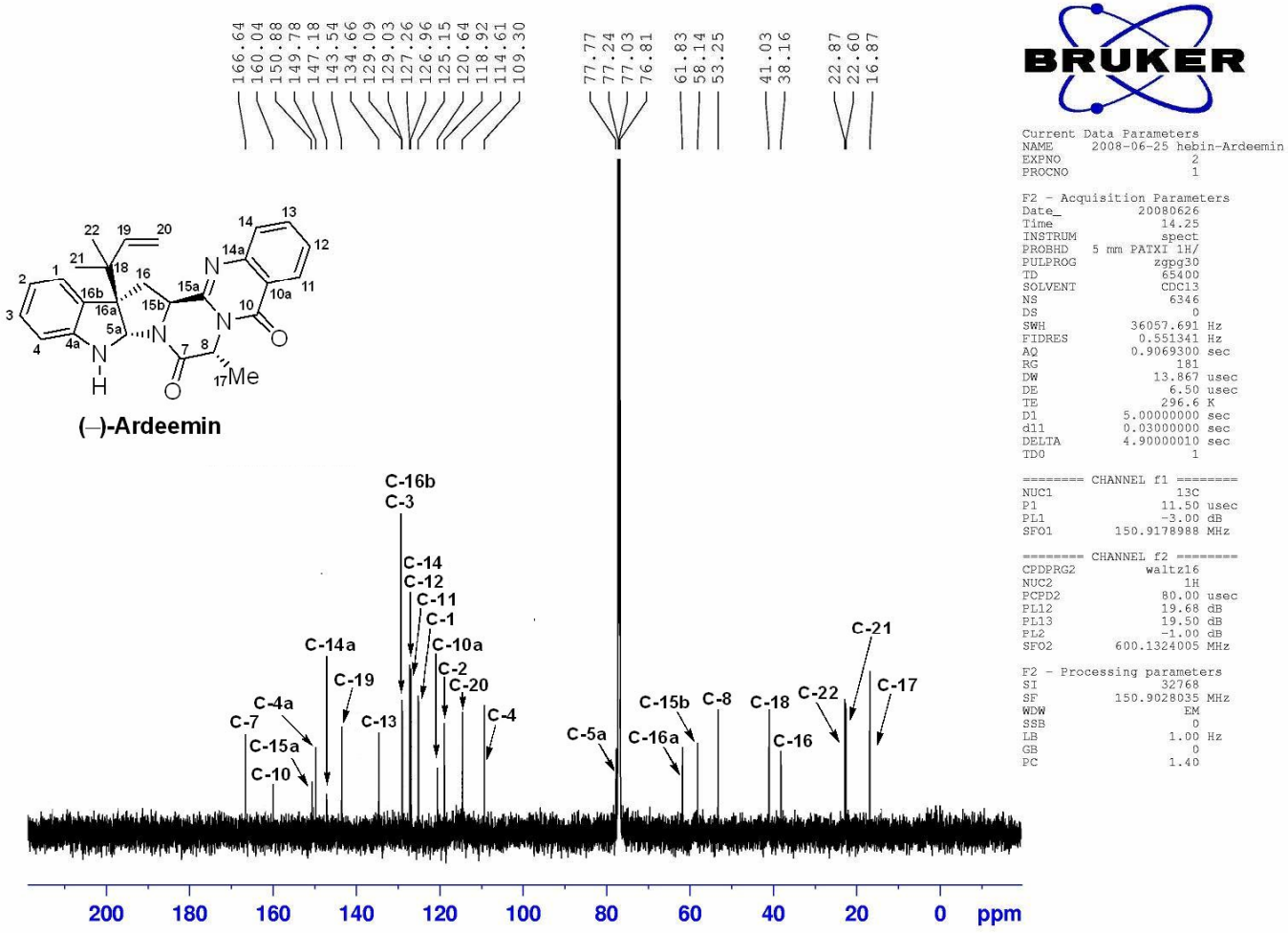


BRUKER

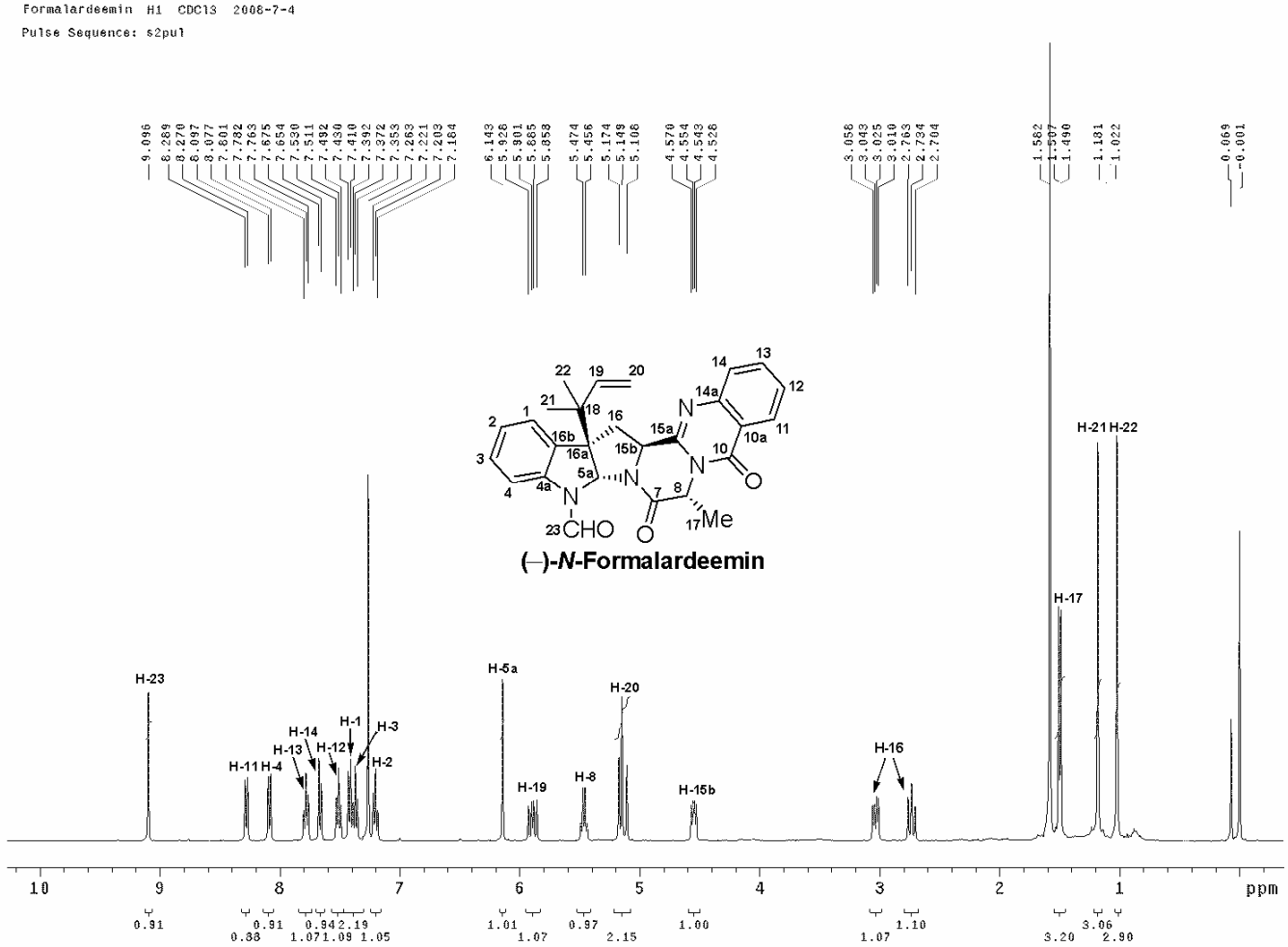
```
Current Data Parameters
NAME      2008-06-23 hebin
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20080623
Time               21.01
INSTRUM            spect
PROBHD   5 mm PATXI 1H/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 7819
DS                    0
SWH           36057.691 Hz
FIDRES        0.550197 Hz
AQ            0.9088159 sec
RG                  181
DW               13.867 usec
DE                6.50 usec
TE               297.9 K
D1            5.00000000 sec
d11           0.03000000 sec
DELTA         4.90000010 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                11.50 usec
PL1               -3.00 dB
SFO1        150.9179988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL12              19.68 dB
PL13              19.50 dB
PL2               -1.00 dB
SFO2        600.1324005 MHz

F2 - Processing parameters
SI                32768
SF          150.9028030 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

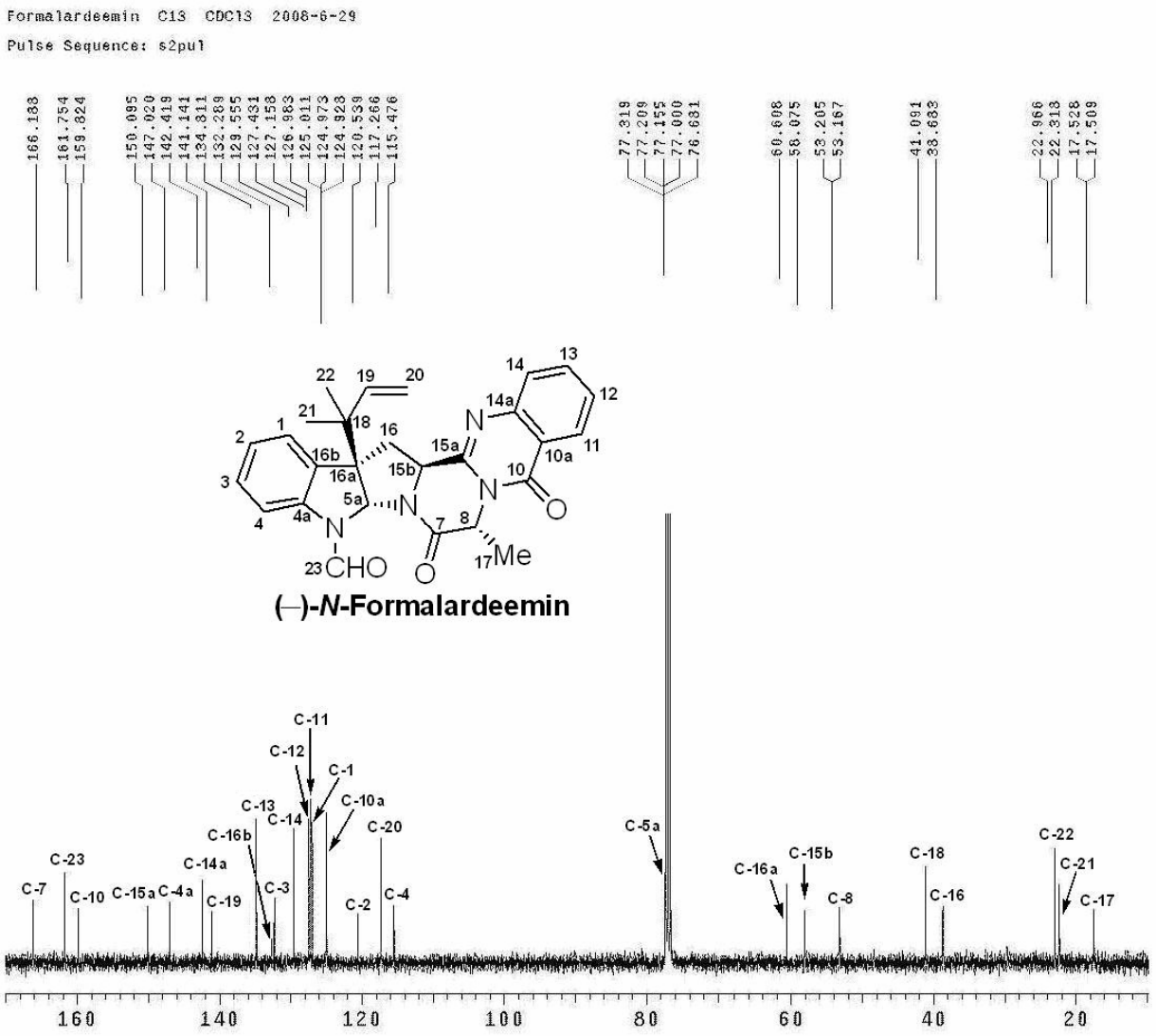


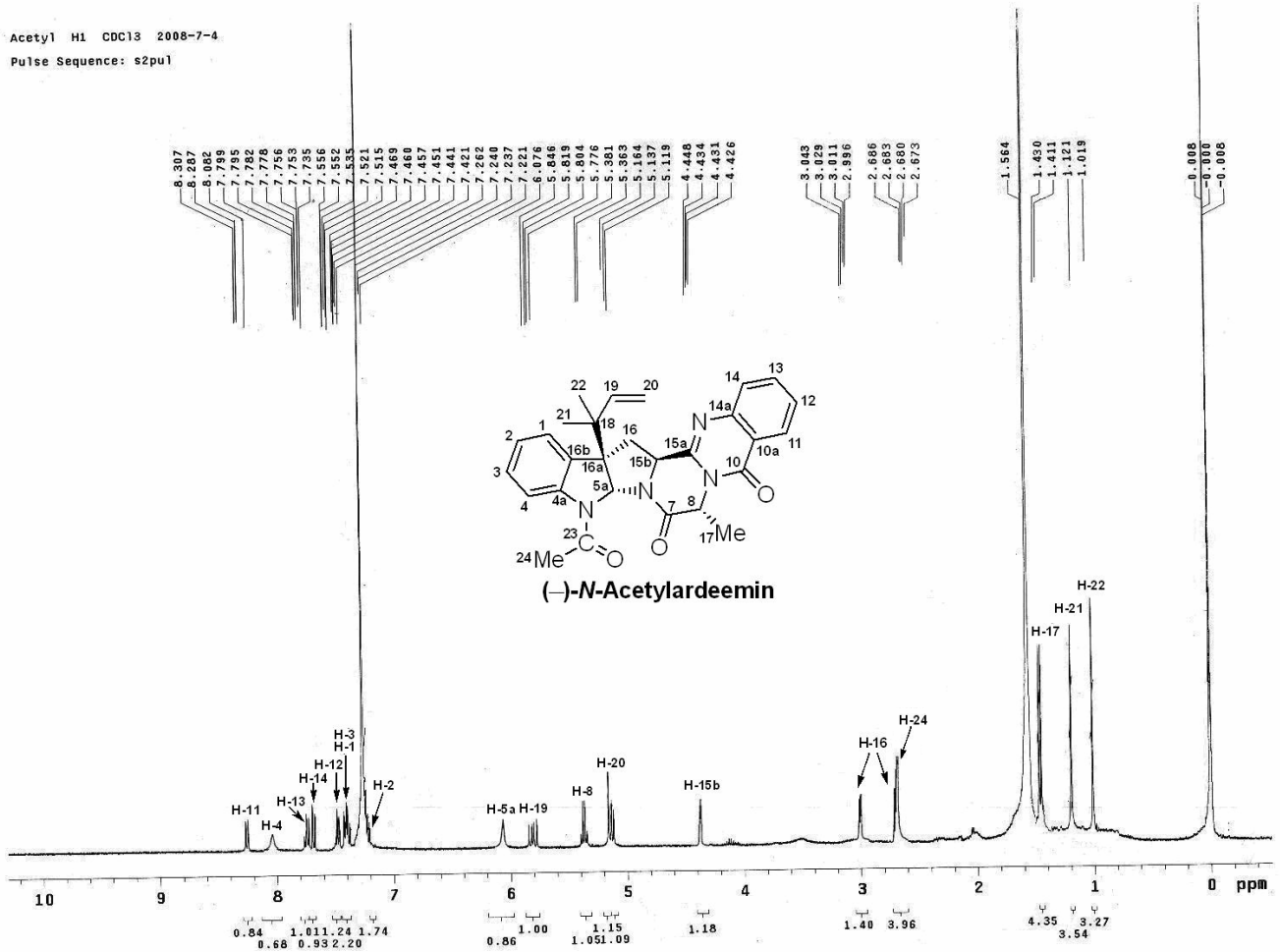

```
Current Data Parameters
NAME      2008-06-25 hebin-Ardeemin
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20080625
Time              17.24
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   0
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG                 181
DW              60.800 usec
DE               6.50 usec
TE              297.2 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1              12.00 usec
PL1             -2.00 dB
SFO1       400.1324710 MHz

F2 - Processing parameters
SI                32768
SF         400.1300088 MHz
WDW                  EM
SSB                   0
LB             0.30 Hz
GB                    0
PC             1.00
```




```
Current Data Parameters
NAME      2008-06-25 hebin-Ardeemin
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20080626
Time              14.25
INSTRUM           spect
PROBHD  5 mm PATXI 1H/
PULPROG        zgpg30
TD              65400
SOLVENT         CDCl3
NS               6346
DS                  0
SWH         36057.691 Hz
FIDRES        0.551341 Hz
AQ           0.9069300 sec
RG                181
DW             13.867 usec
DE              6.50 usec
TE             296.6 K
D1          5.00000000 sec
d11         0.03000000 sec
DELTA       4.90000010 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 13C
P1                11.50 usec
PL1               -3.00 dB
SFO1        150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             80.00 usec
PL12              19.68 dB
PL13              19.50 dB
PL2               -1.00 dB
SFO2        600.1324005 MHz

F2 - Processing parameters
SI                32768
SF          150.9028035 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```


Formalardeemin H1 CDCl3 2008-7-4
Pulse Sequence: s2pul
(–)-N-Formalardeemin
H-23
H-11
H-4
H-14
H-13
H-12
H-1
H-3
H-2
H-5a
H-19
H-8
H-20
H-15b
H-16
H-17
H-21
H-22
ppm


Formalardeemin C13 CDCl3 2008-6-29
Pulse Sequence: s2pul
166.183
161.754
159.824
150.095
147.020
142.419
141.141
134.811
132.289
129.555
127.431
127.158
126.983
125.011
124.973
124.928
120.539
117.266
115.476
77.319
77.209
77.155
77.000
76.681
60.608
58.075
53.205
53.167
41.091
38.683
22.966
22.313
17.528
17.509
(–)-N-Formalardeemin
C-11
C-12
C-1
C-13
C-14
C-10a
C-16b
C-20
C-23
C-14a
C-5a
C-15b
C-18
C-22
C-16a
C-21
C-7
C-10
C-15a
C-4a
C-19
C-3
C-2
C-4
C-8
C-16
C-17
160
140
120
100
80
60
40
20


Acetyl H1 CDCl3 2008-7-4
Pulse Sequence: s2pul
(–)-N-Acetylardeemin
H-11
H-4
H-13
H-14
H-12
H-3
H-1
H-2
H-5a
H-19
H-8
H-20
H-15b
H-16
H-24
H-17
H-21
H-22
ppm