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Synthesis of Proteasome Inhibitor 6-Deoxy-Omuralide and Its Enantiomer Using Stereoselective Alkylation of Substituted Proline Ester

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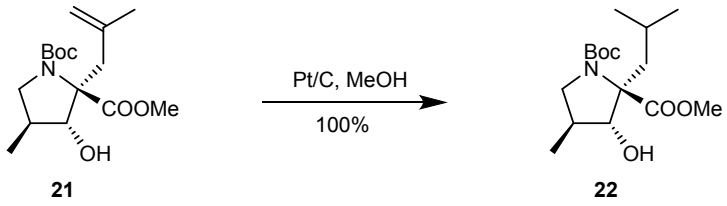
Supporting Information

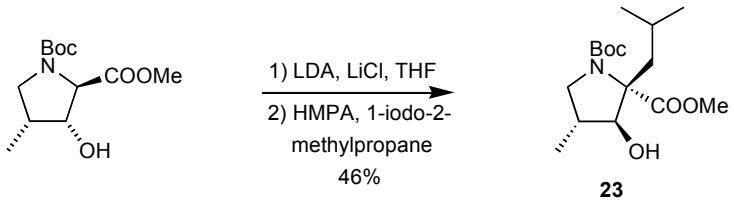


21 **22**

1-(tert-Butyl) 2-methyl (2*R*,3*R*,4*S*)-3-hydroxy-4-methyl-2-(2-methylallyl) pyrrolidine-1,2 -dicarboxylate (21)

1-(tert-Butyl) 2-methyl (2*R*,3*R*,4*S*)-3-hydroxy-2-isobutyl-4-methylpyrrolidine-1,2-dicarboxylate (22)

The olefin **21** (26 mg, 0.084 mmol) was dissolved in MeOH (1.5 mL) and hydrogenated (H_2, 4 bar) in the presence of Pt/C (10 mg, 10 %). After 3 h, the catalyst was filtered off and the filtrate was concentrated in vacuo (40 °C/300 mbar). The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 3.5 : 1) to yield the isobutyl pyrrolidine **22** (26.2 mg, 100 %) as a colourless, spectroscopically pure crystals; mp = 102-103 °C; $[\alpha]^{20}_D$ = + 12.1 (*c* 1.20, $CHCl_3$); IR (solid): υ 3393, 2951, 1741 (C=O), 1662 (C=O), 1432, 1408, 1369, 1337, 1236, 1160, 1123, 1102, 1074, 1017, 971, 910, 775, 687 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 1.11/1.14 (2 d, *J* = 6.3 Hz, 3H), 1.41/1.43 (2 s, 9H), 1.77-1.93 (m, 2.5H), 2.09 (dd, *J* = 14.4, 7.9 Hz, 0.5H), 2.21 (m, 1H), 2.86/2.90 (b, 1H), 2.98/2.99 (2 "t", *J* = 11.0, 11.0 Hz, 1H), 3.61/3.67 (2 dd, *J* = 10.6, 8.2 Hz, 1H), 3.69/3.70 (2 s, 3H), 3.81 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.3/15.4, 22.9/23.1, 24., 25.4/25.5, 28.3, 37.6/38.1, 37.7/38.4, 50.4/50.9, 52.2/53.4, 70.5, 79.6/80.3, 82.9/83.5, 153.8, 175.3/175.5; MS (FAB, pos.): *m/z* (%) 316 (52) $[M + H]^+$, 260 (56), 216 (100), 156 (28), 57 (56); HRMS (FAB, pos.): $[M + H]^+$ calcd for $C_{16}H_{30}NO_5$: 316.2124; found 316.2110.



23

1-(tert-Butyl) 2-methyl (2*S*,3*S*,4*R*)-3-hydroxy-2-isobutyl-4-methylpyrrolidine-1,2-dicarboxylate (23)

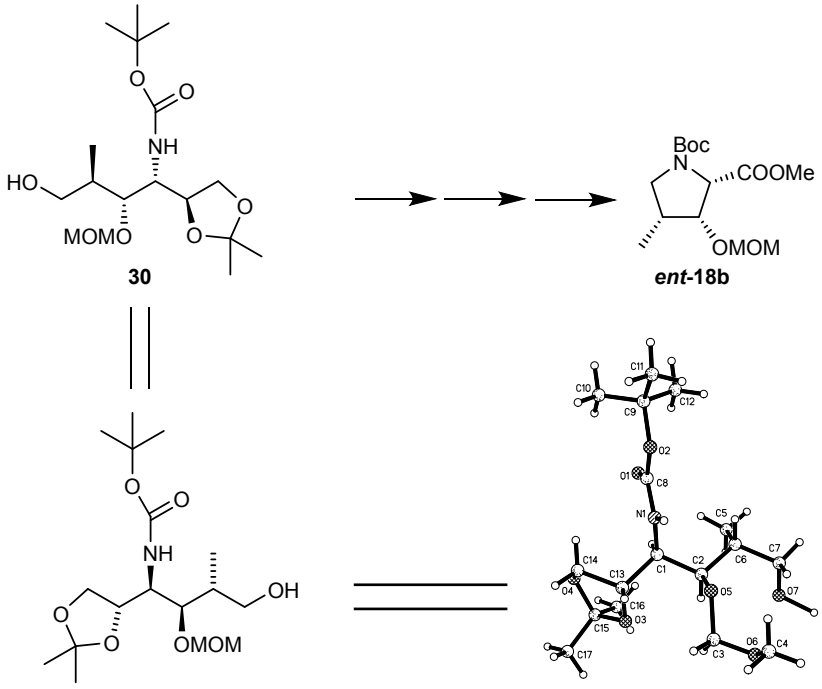
Diisopropylamine (71 mg, 0.70 mmol) was dissolved in dry THF (2.0 mL) and cooled down to 0 °C. A solution of *n*-BuLi (300 mg, 0.62 mmol, 1.58 M in hexane) was added dropwise. The solution was stirred for 30 min at 0 °C and then cooled to -50 °C. The substituted proline methyl ester (52 mg, 0.20 mmol) in THF (1.0 mL) was added dropwise via syringe. The resulting mixture was stirred for 50 min at 0 °C and LiCl (14 mg, 0.31 mmol) was added. The reaction mixture was stirred at 0 °C for additional 30 min, and then cooled to -50 °C. A solution of 1-iodo-2-methylpropane (91 mg, 0.50 mmol) in HMPA (90 mg, 0.50 mmol) was introduced in one portion. The reaction was allowed to proceed at 0 °C for further 5 h before being quenched with sat. NH_4Cl (1.5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (2 × 5 mL), dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 3 : 1) to afford the isobutyl pyrrolidine **23** (28.5 mg, 46 %) as colourless, analytically pure crystals (*dr* = 90 : 10 from ^{1}H NMR); mp = 101-102 °C; $[\alpha]^{20}_D$ = – 11.6 (*c* 1.50, $CHCl_3$); IR (solid): υ 3392, 2952, 1741 (C=O), 1663 (C=O), 1408, 1369, 1337, 1237, 1218, 1160, 1103, 1074, 1017, 972, 910, 861 cm^{-1}; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 1.12/1.14 (2 d, *J* = 6.4 Hz, 3H), 1.41/1.43 (2 s, 9H), 1.77-1.93 (m, 2.5H), 2.09 (dd, *J* = 14.5, 8.0 Hz, 0.5H), 2.21 (m, 1H), 2.85/2.90 (2 d, *J* = 5.9 Hz, 1H), 2.98/2.99 (2 "t", *J* = 11.0, 11.0 Hz, 1H), 3.61/3.66 (2 dd, *J* = 10.6, 8.2 Hz, 1H), 3.69/3.70 (2 s, 3H), 3.81 (dd, *J* = 10.3, 5.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.3/15.4, 22.9/23.1,

24.5, 25.4/25.5, 28.3, 37.6/38.1, 37.7/38.4, 50.4/50.9, 52.2/53.4, 70.5, 79.6/80.3, 82.9/83.5, 153.8, 175.3/175.5; Anal. Calcd for $C_{16}H_{29}NO_5$: C, 60.92; H, 9.27; N, 4.44. Found: C, 60.64; H, 9.23; N, 4.46.

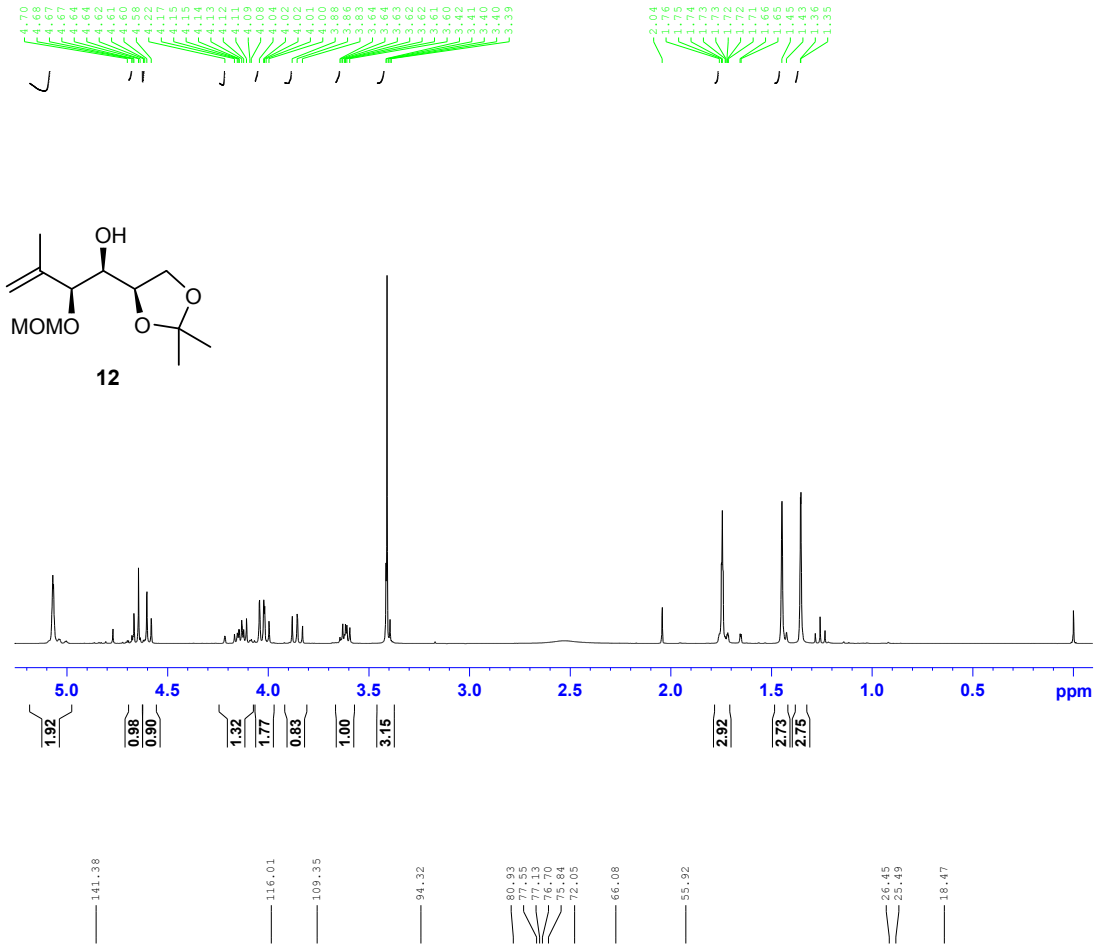
The precursor of *ent*-18

1-(tert-Butyl) 2-methyl (2S,3*R*,4*R*)-3-(methoxymethoxy)-4-methylpyrrolidine -1,2-dicarboxylate (*ent*-18b)

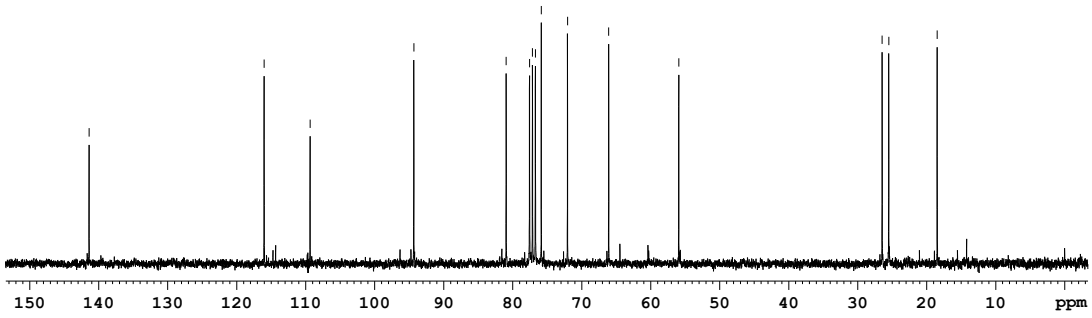
tert-Butyl((1*S*,2*R*,3*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-2-(methoxymethoxy)-3-methylbutyl)carbamate (30)

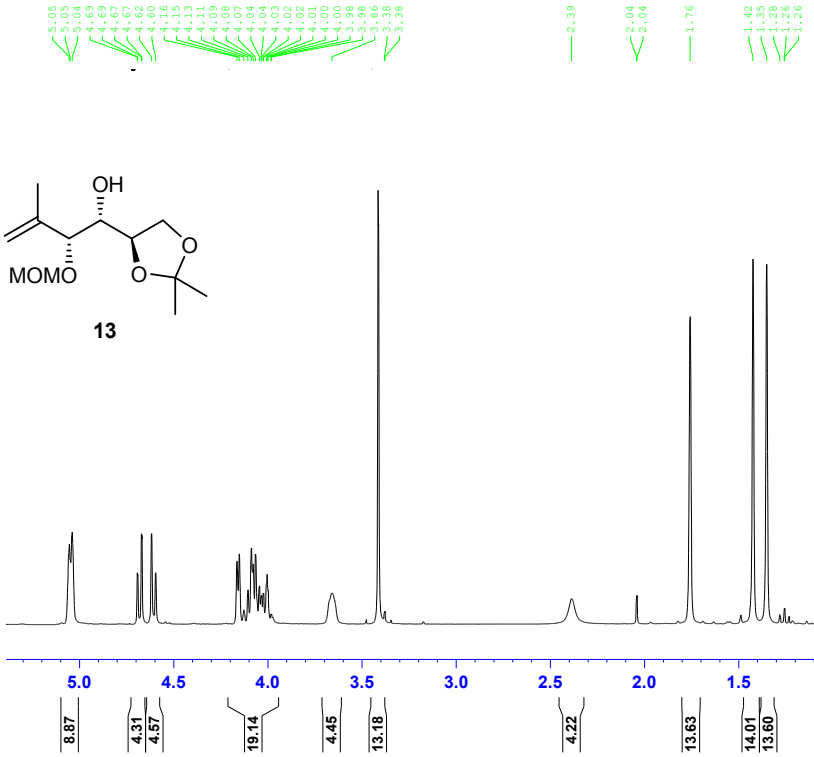


NMR Spectra



Compound **12**

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2.0
1.5
1.0
0.5
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ppm
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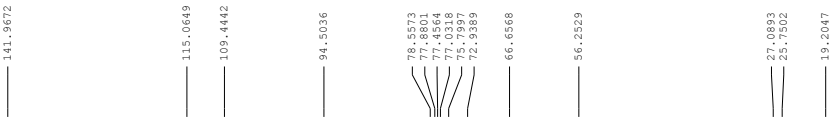
13.18
4.22
13.63
14.01
13.60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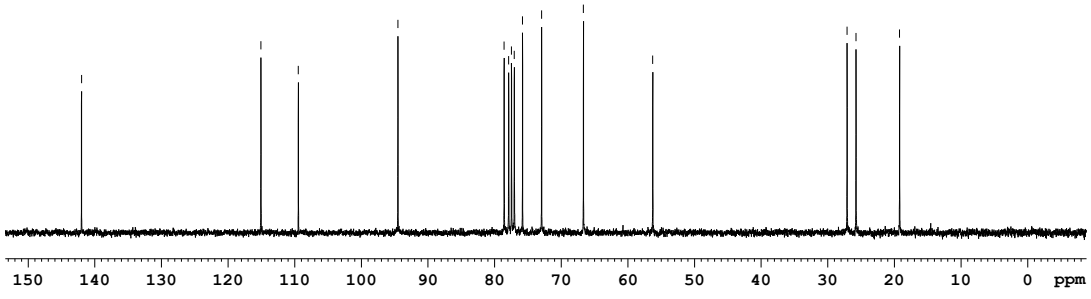
25.7502
19.2047

Compound **13**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40
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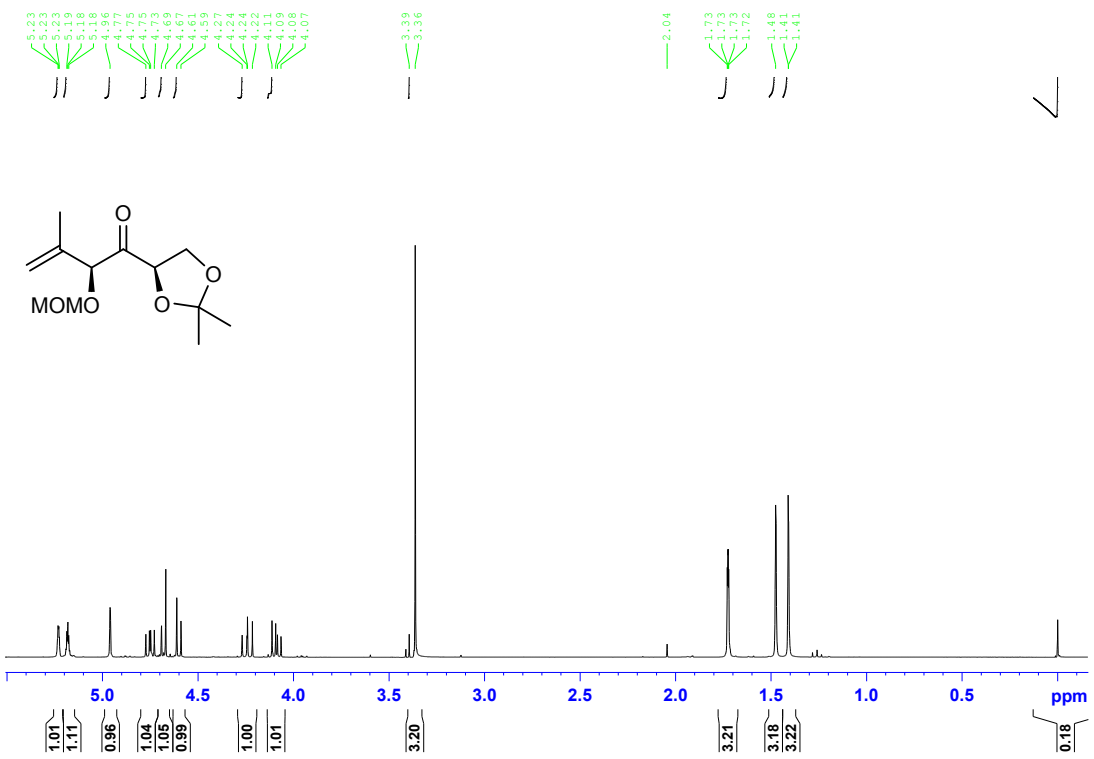
20
10
0
ppm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5.19
5.18
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4.75
4.75
4.73
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4.67
4.61
4.59
4.27
4.24
4.24
4.22
4.11
4.09
4.08
4.07
3.39
3.36
2.04
1.73
1.73
1.73
1.72
1.48
1.41
1.41
MOMO
O
O
O
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4.5
4.0
3.5
3.0
2.5
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1.5
1.0
0.5
ppm
1.01
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3.18
3.22
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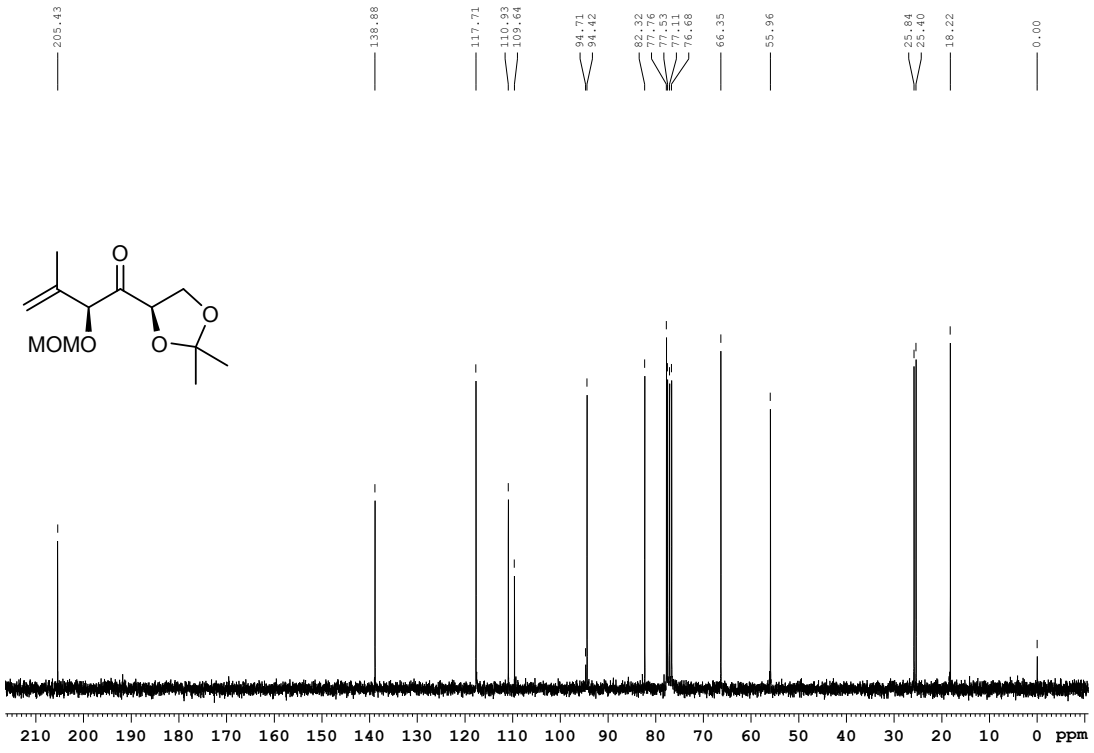
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77.53
77.11
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66.35
58.96
25.84
25.40
18.22
0.00
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O
O
O
210
200
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140
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100
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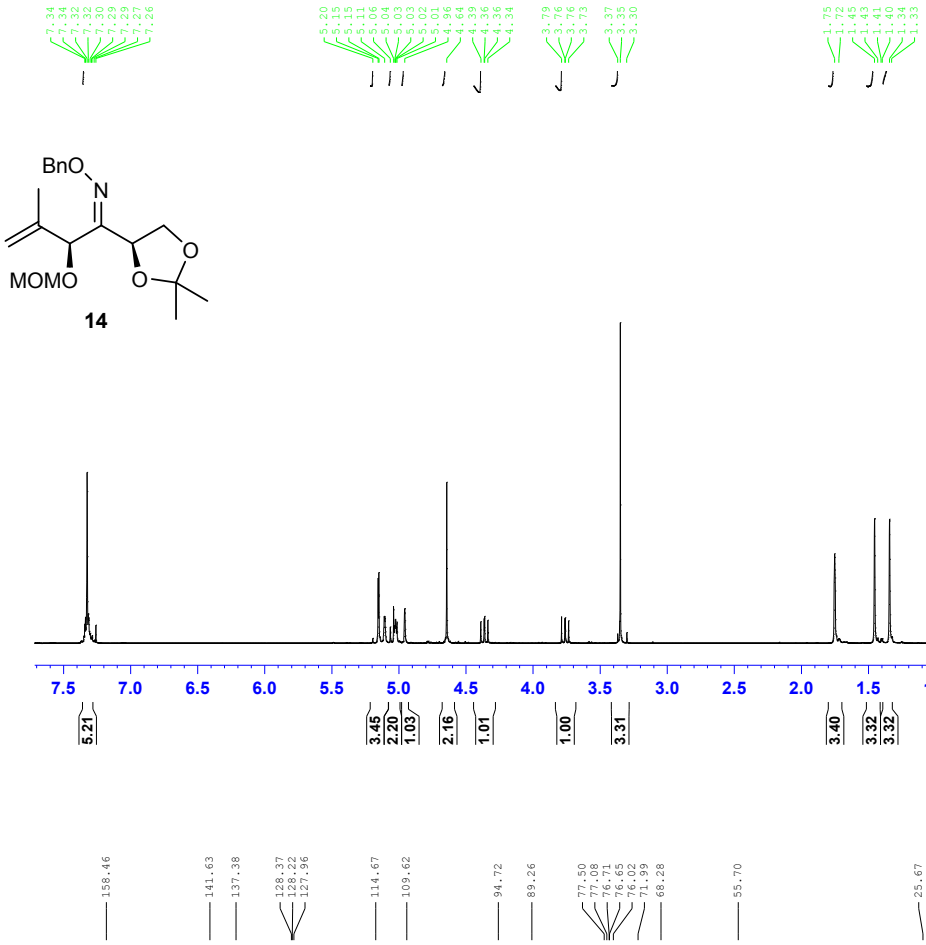
60
50
40
30
20
10
0
ppm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3.0
2.5
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1.0
0.5
ppm
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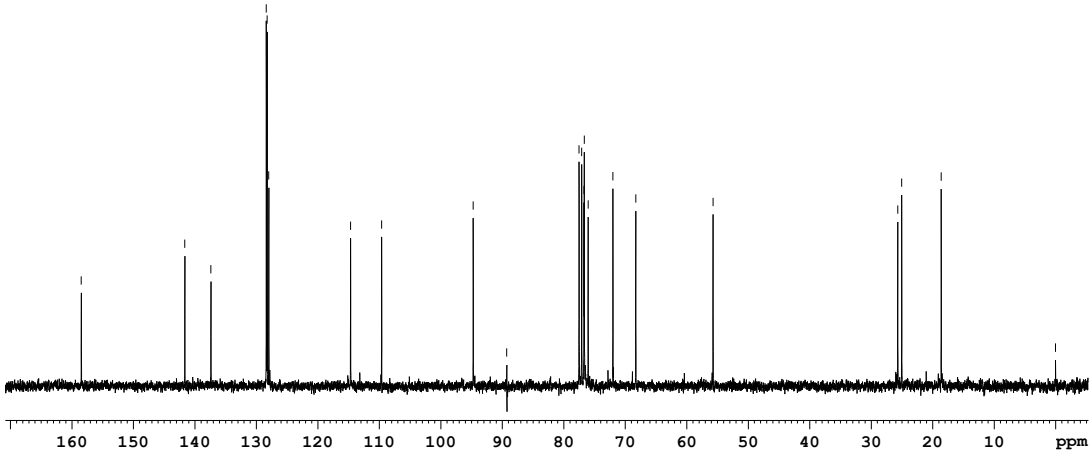
3.32

Compound **14**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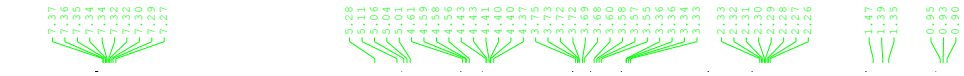
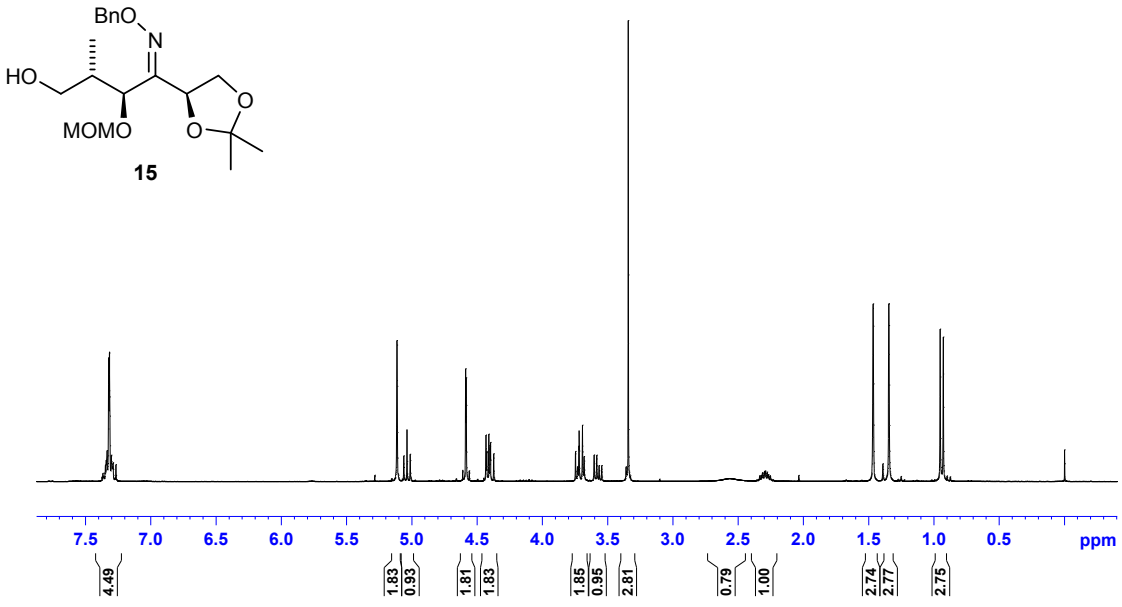
70
60
50
40
30
20
10
ppm

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6.5
6.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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2.74
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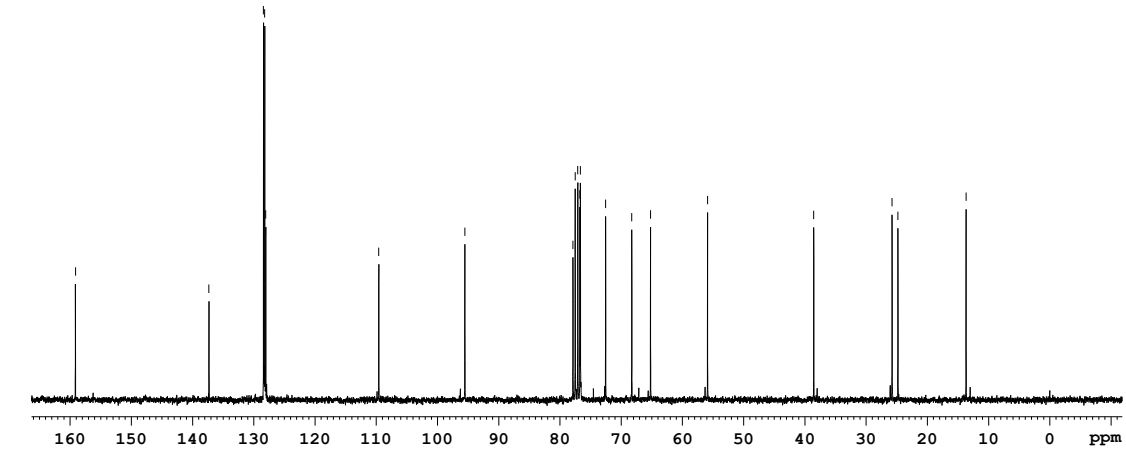
2.75

Compound **15**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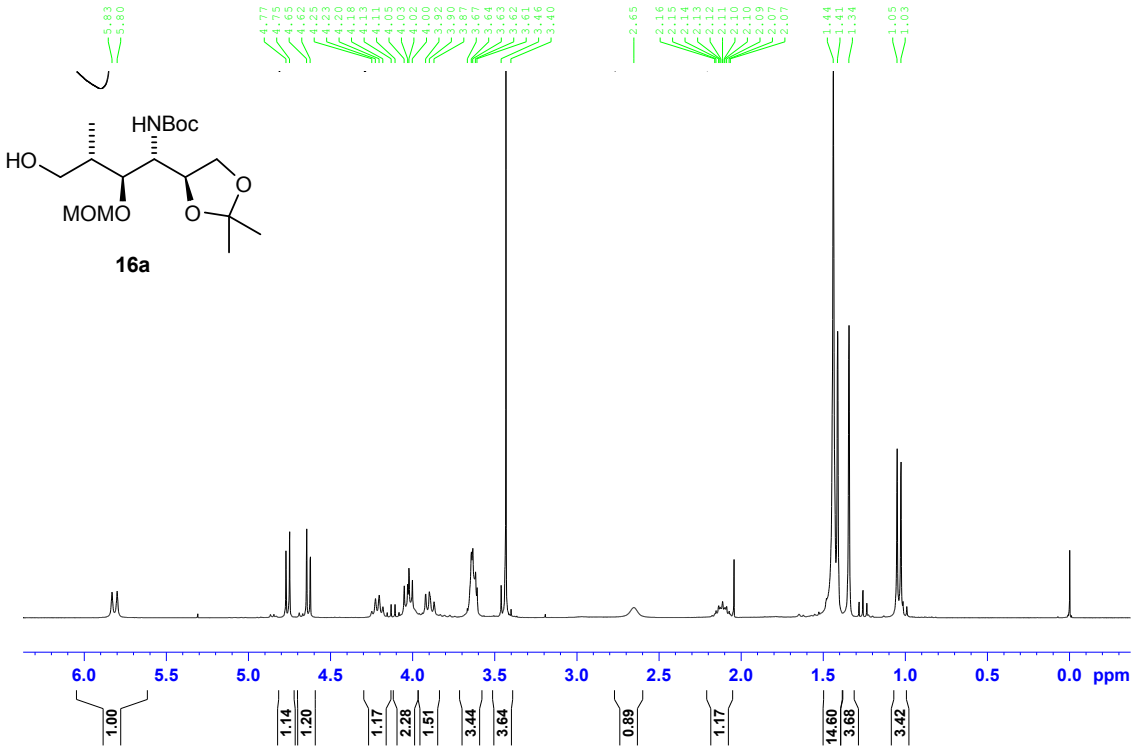
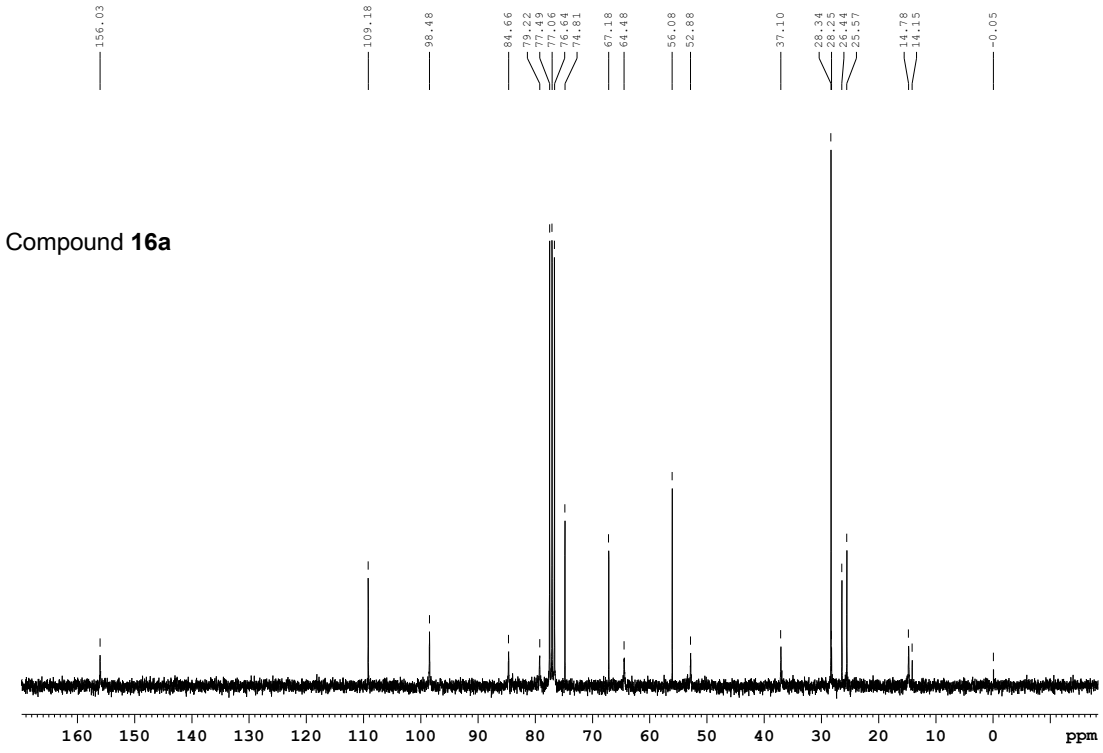
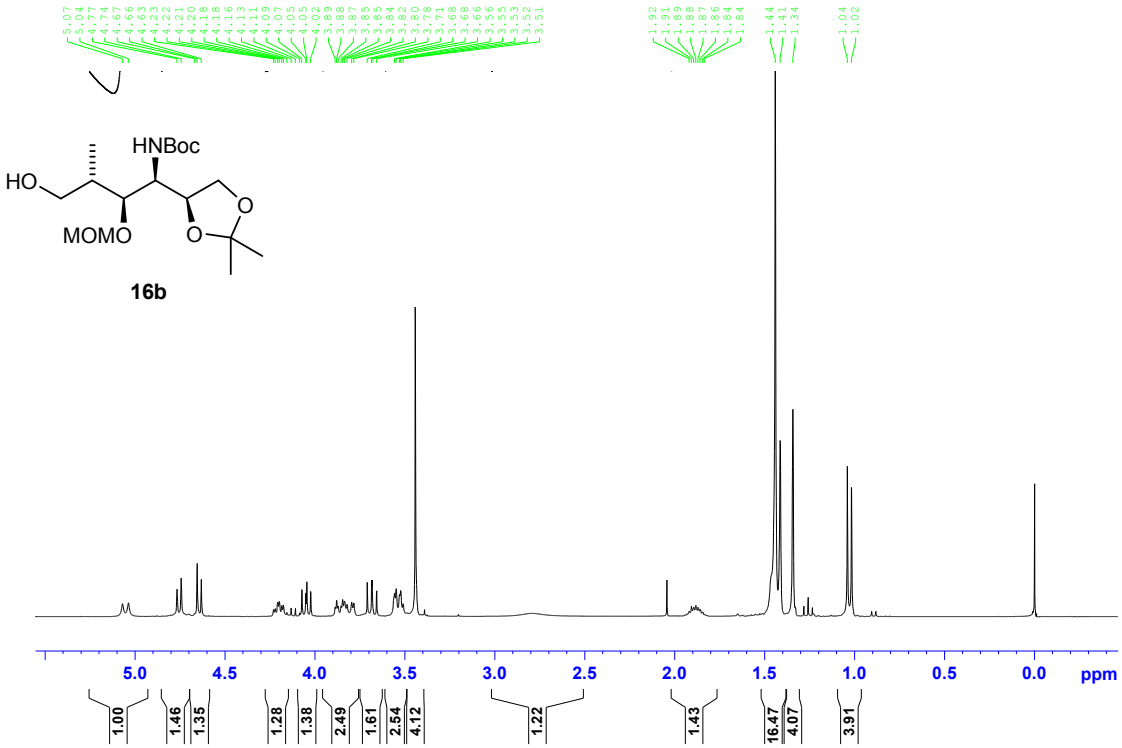
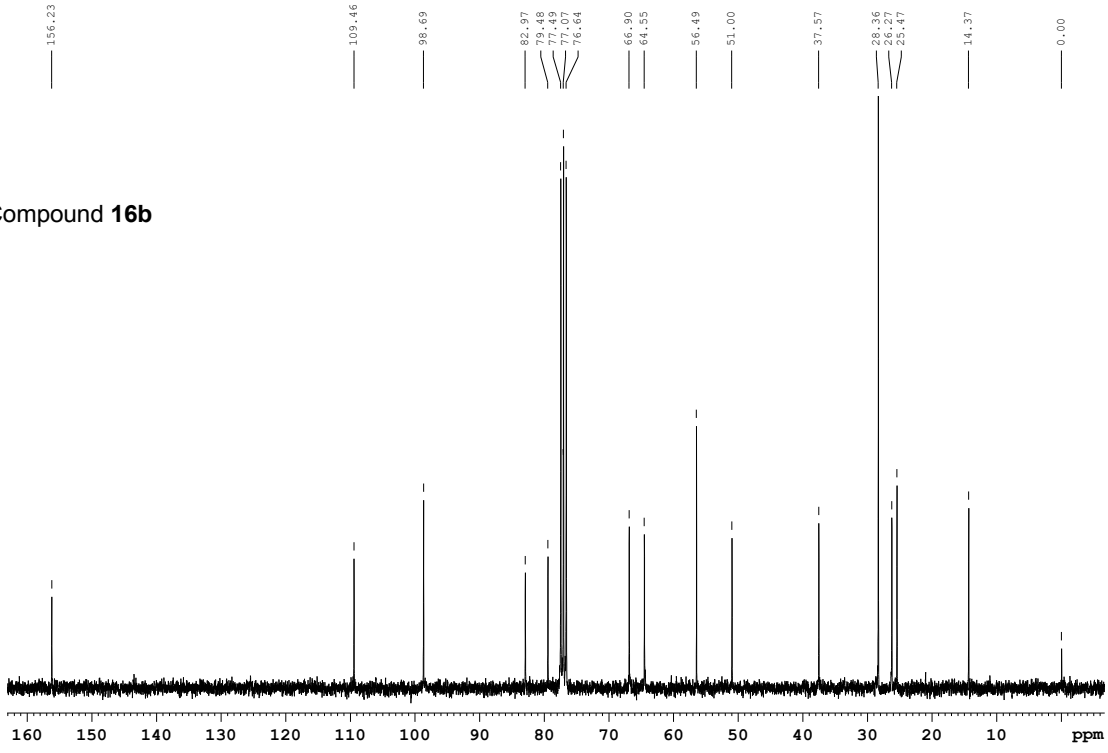
40
30
20
10
0
ppm



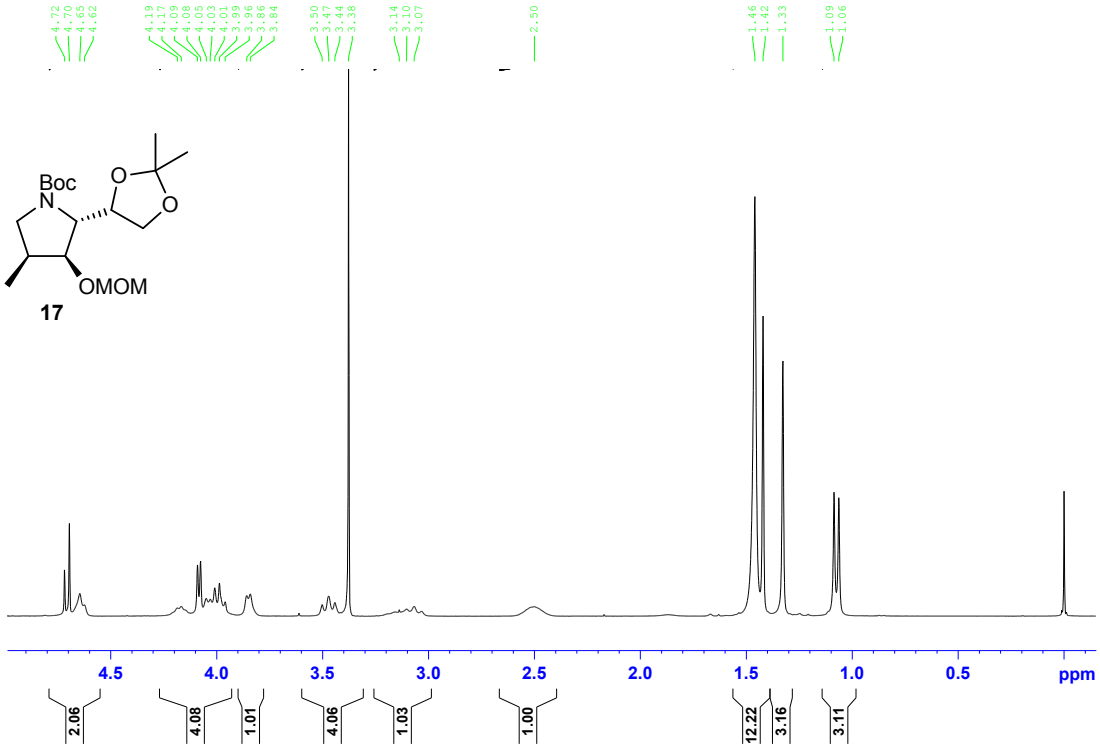


Compound **16a**





Compound **16b**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3.86
3.84
3.50
3.47
3.44
3.38
3.14
3.10
3.07
2.50
1.46
1.42
1.33
1.09
1.06
Boc
N
O
O
OMOM
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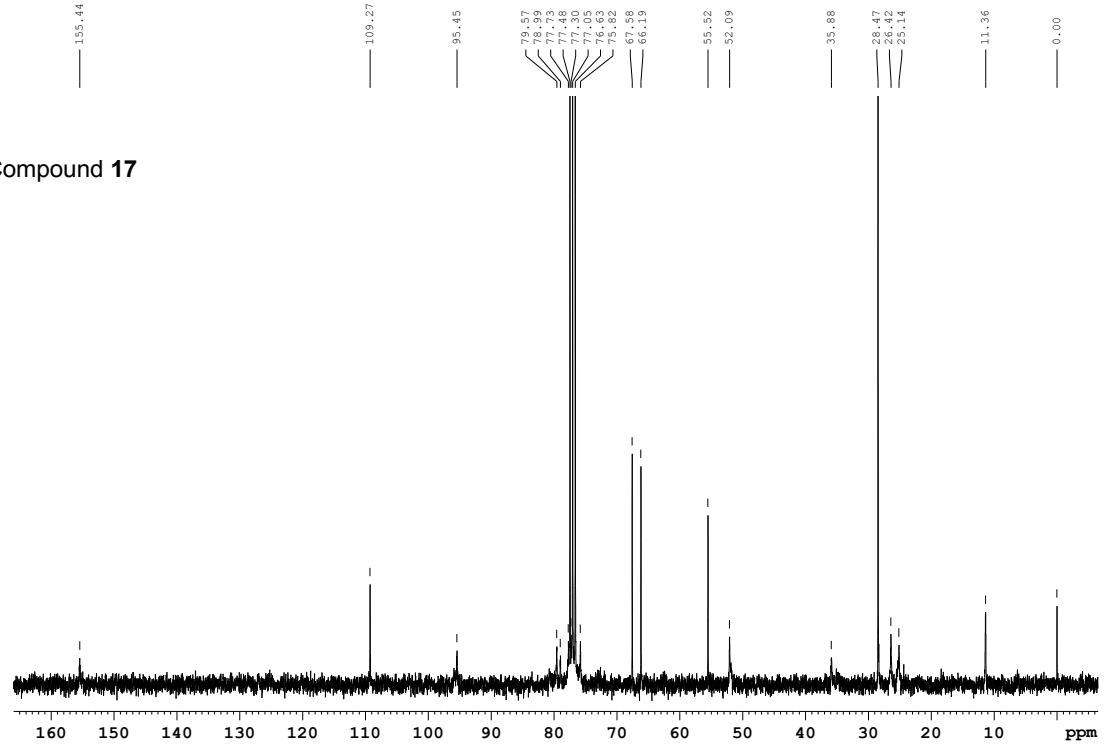
3.11

Compound **17**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77.30
77.05
76.63
75.82
67.58
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55.52
52.09
35.88
28.47
26.42
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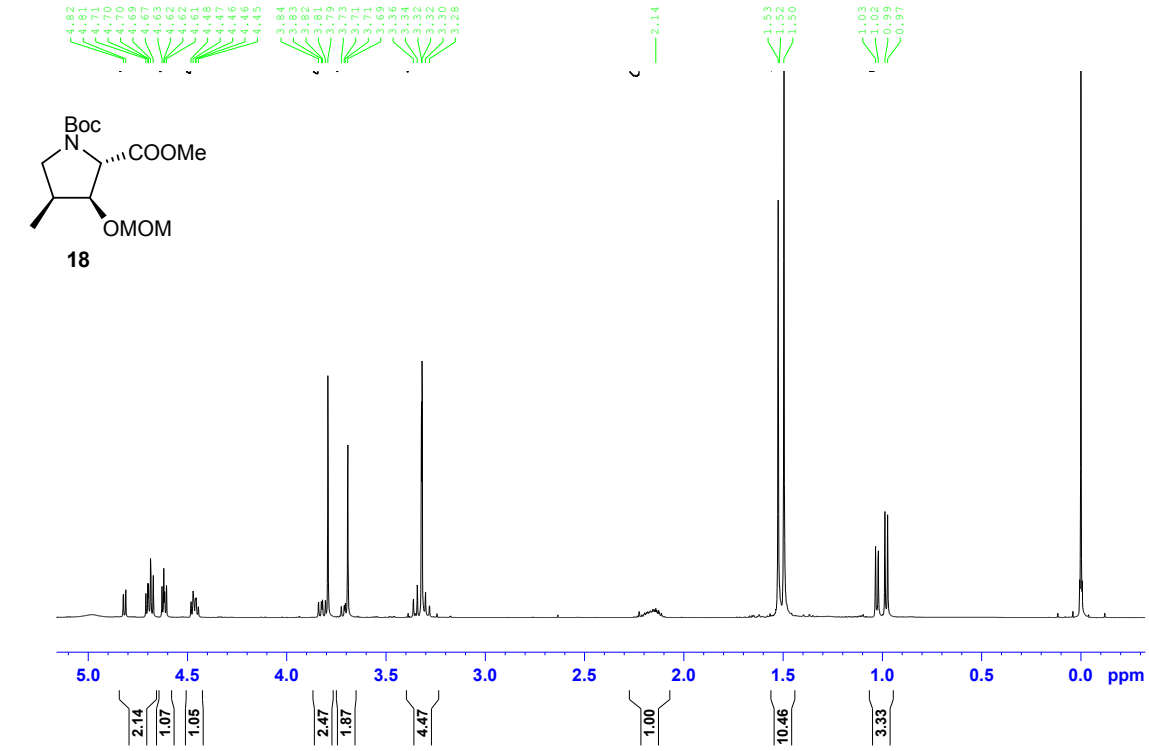
50
40
30
20
10
ppm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N
COOMe
OMOM
18
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3.84 3.83 3.82 3.81 3.79 3.73 3.71 3.71 3.69 3.36 3.34 3.32 3.32 3.30 3.28
2.14
1.53 1.52 1.50
1.03 1.02 0.99 0.97
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
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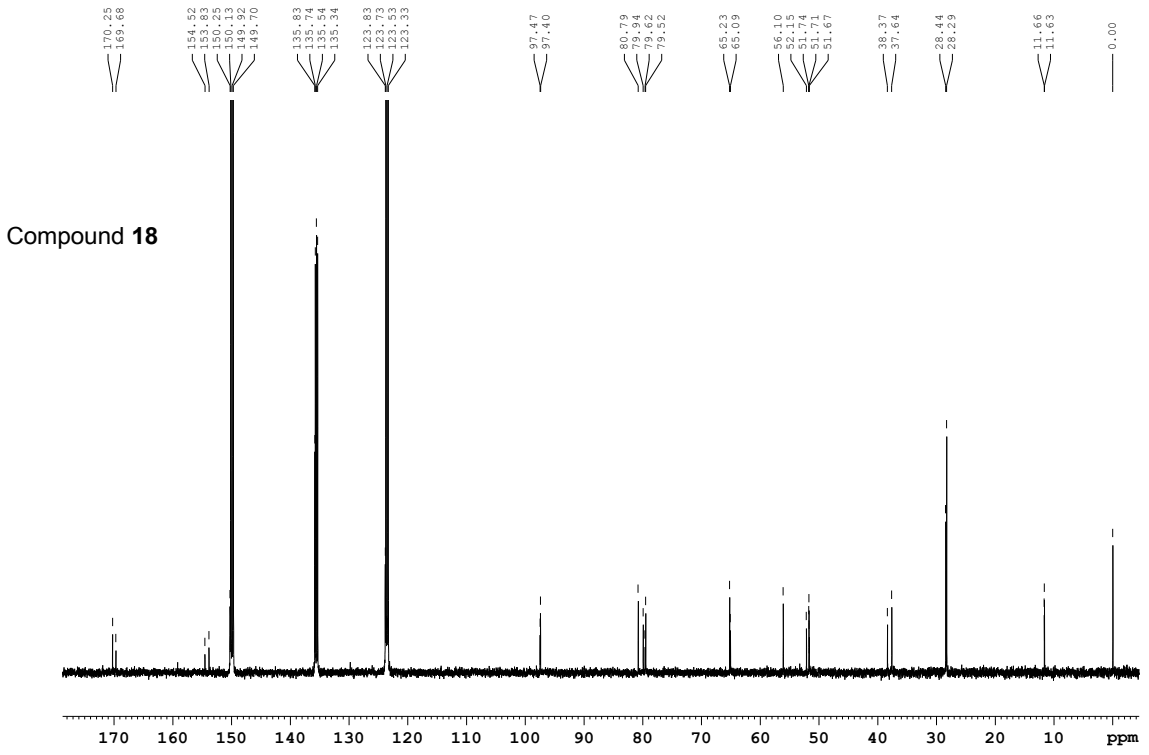
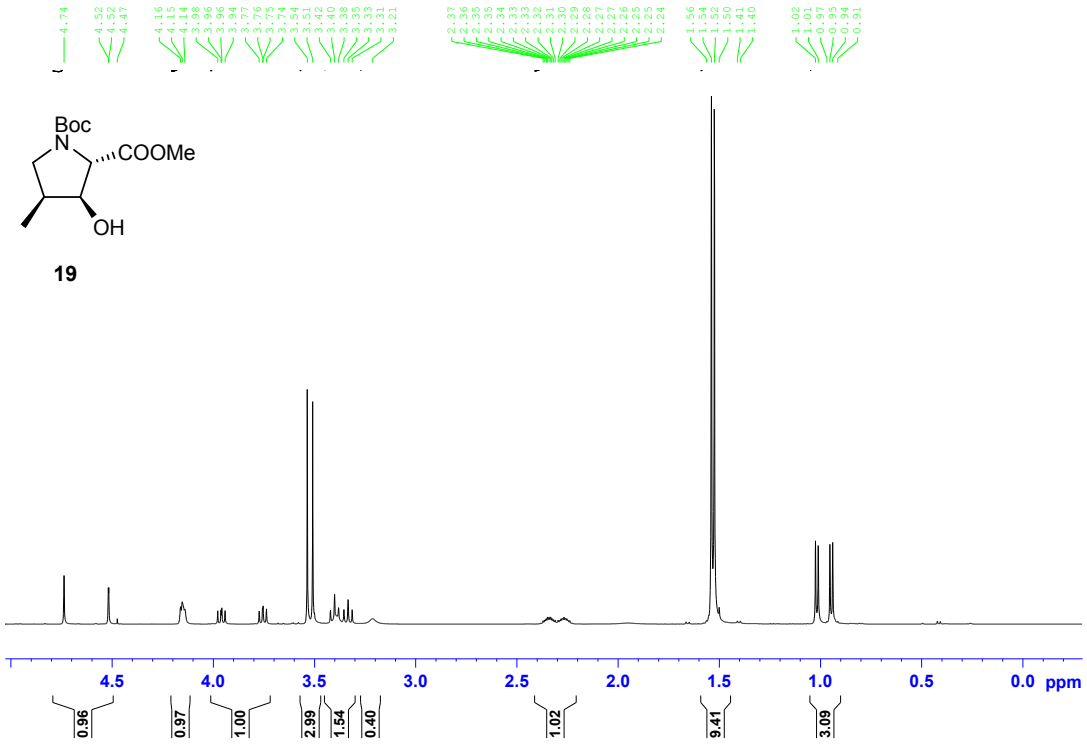
Compound **18**


170.25 169.68 154.52 153.83 150.25 150.13 149.92 149.70 135.83 135.74 135.54 135.34 123.83 123.73 123.53 123.33 97.47 97.40 80.79 79.94 79.62 79.52 65.23 65.09 56.10 52.15 51.74 51.71 51.67 38.37 37.64 28.44 28.29 11.66 11.63 0.00
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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COOMe
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1.5
1.0
0.5
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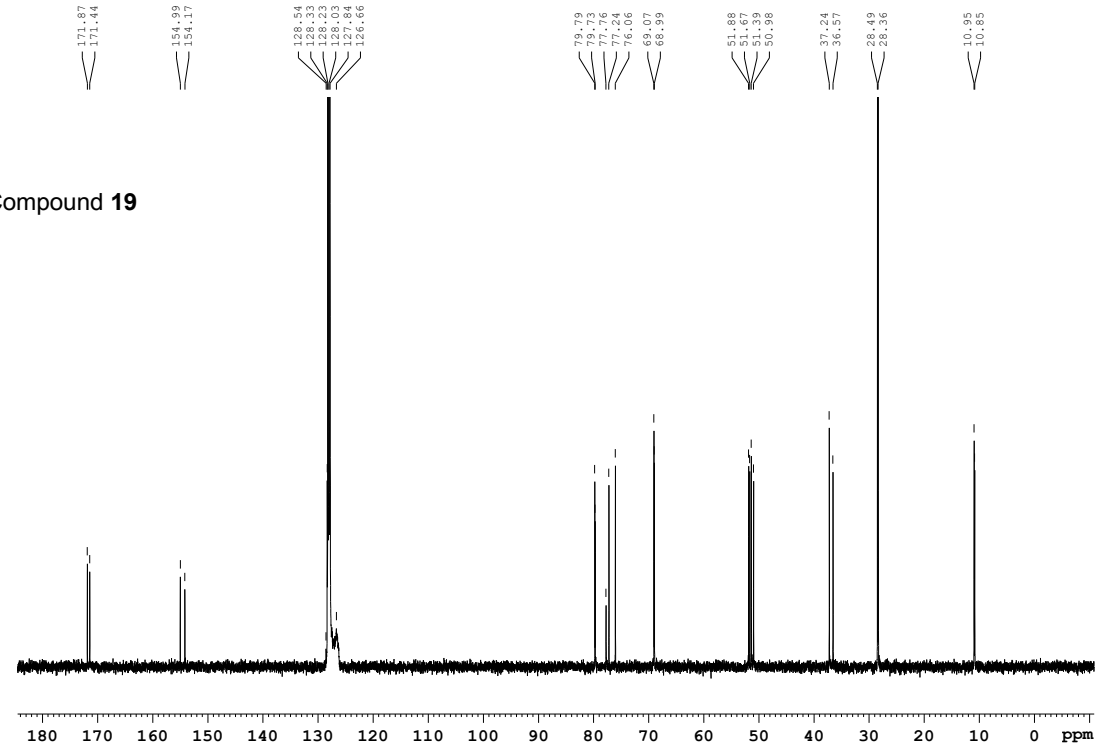
1.02
9.41
3.09

Compound **19**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110
100
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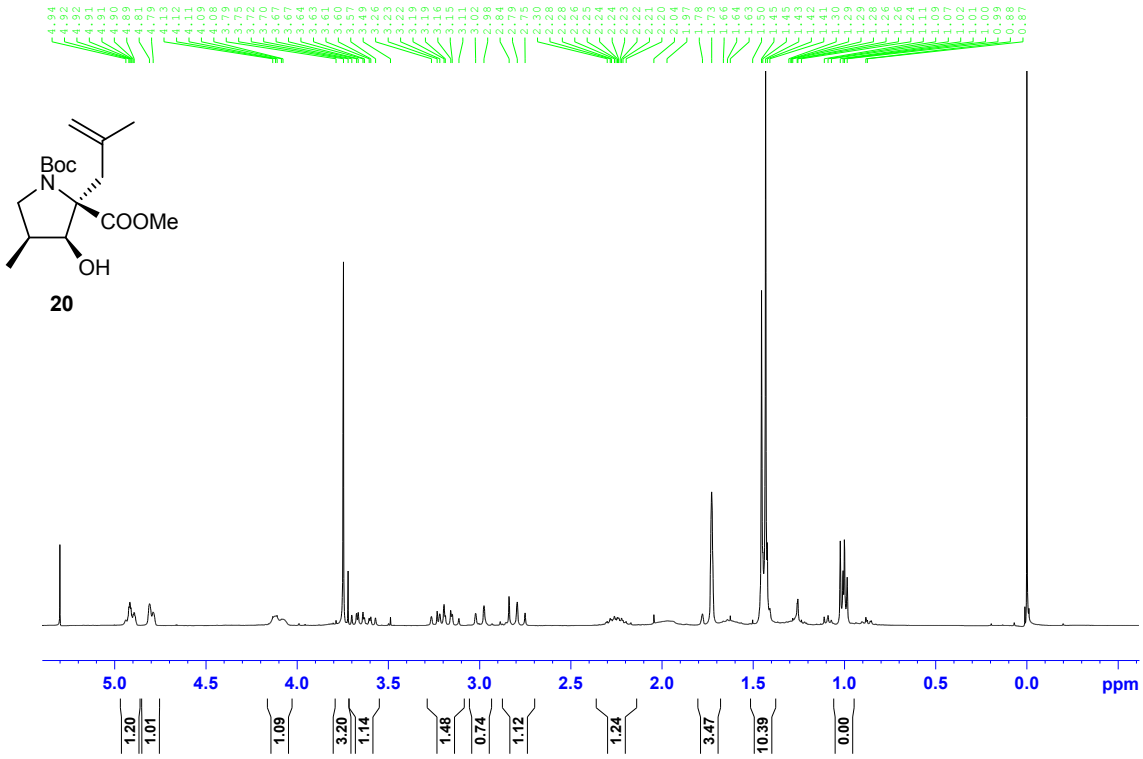
70
60
50
40
30
20
10
0
ppm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N
COOMe
OH
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4.5
4.0
3.5
3.0
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0.5
0.0
ppm
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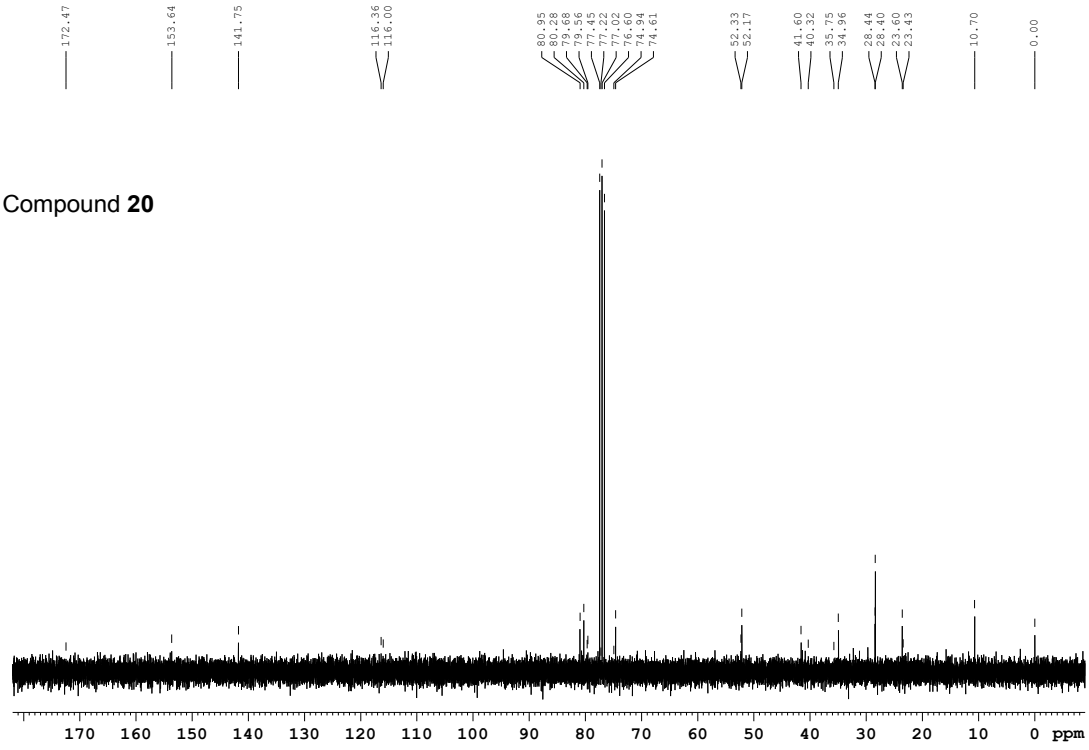
0.00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10
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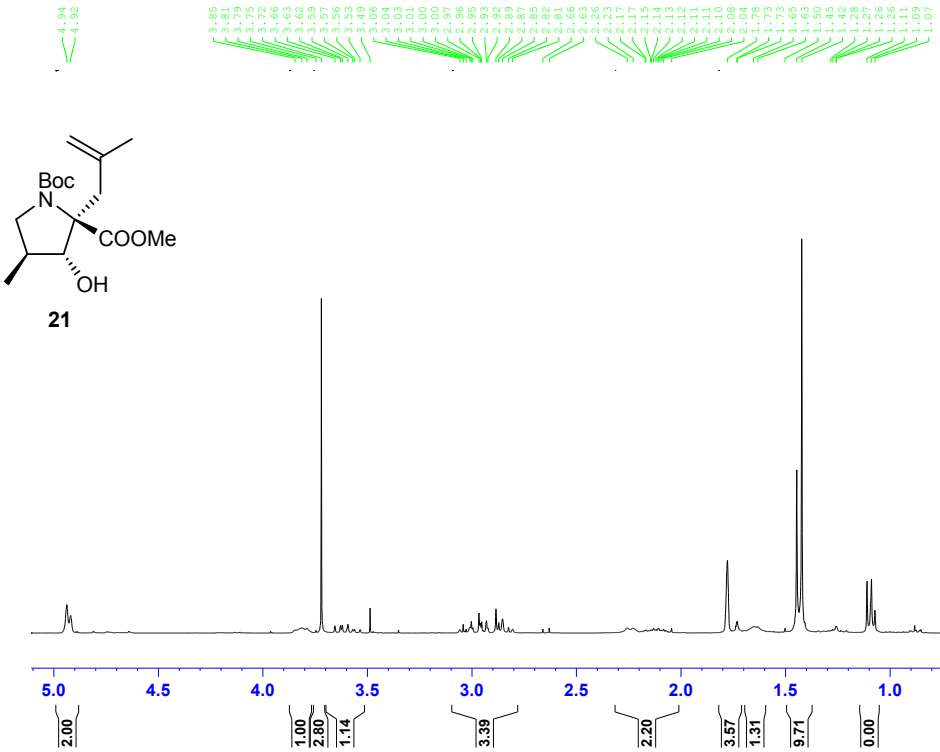
ppm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COOMe
OH
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4.0
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3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.00
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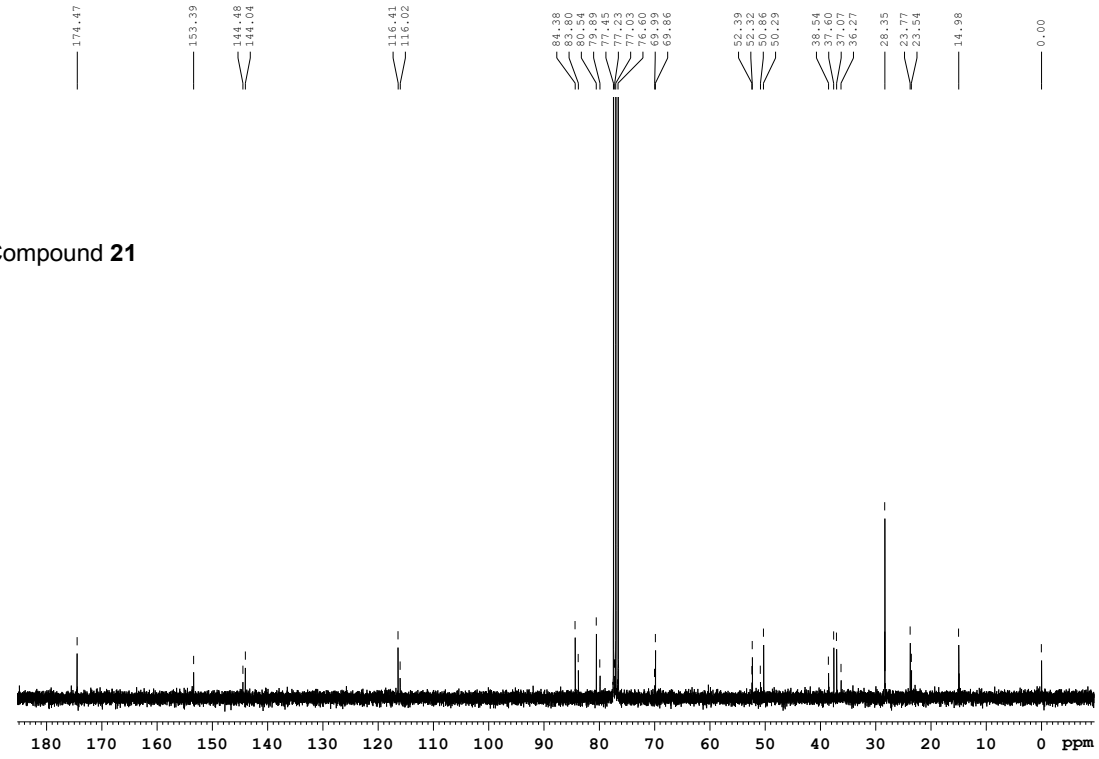
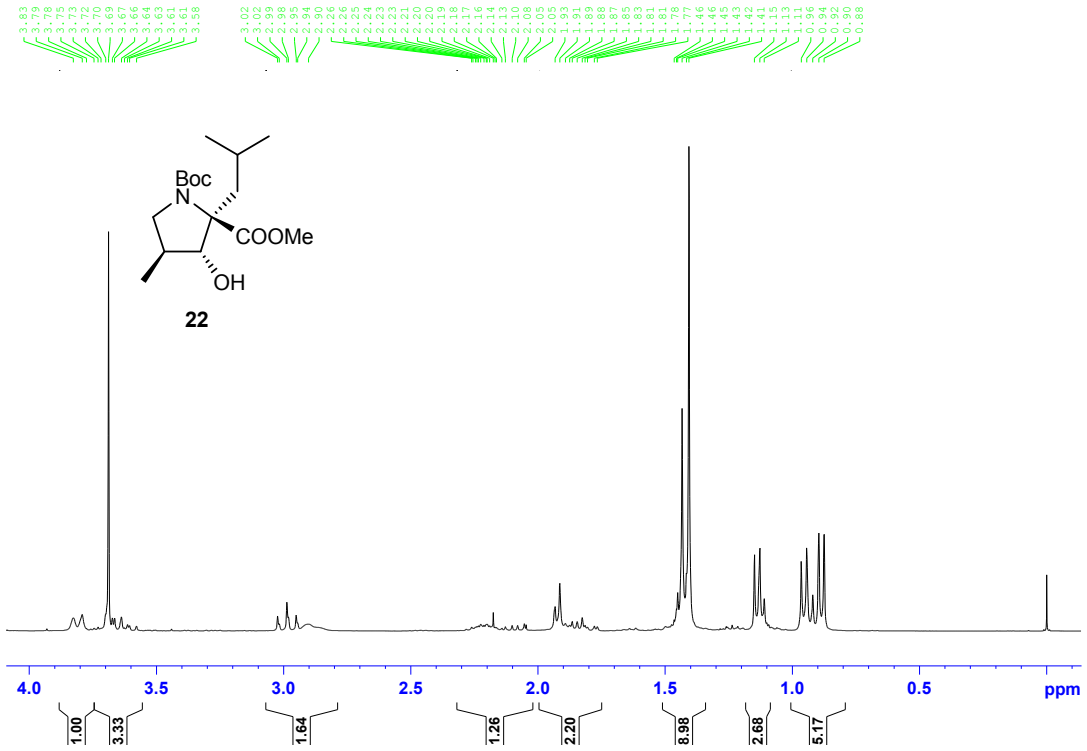
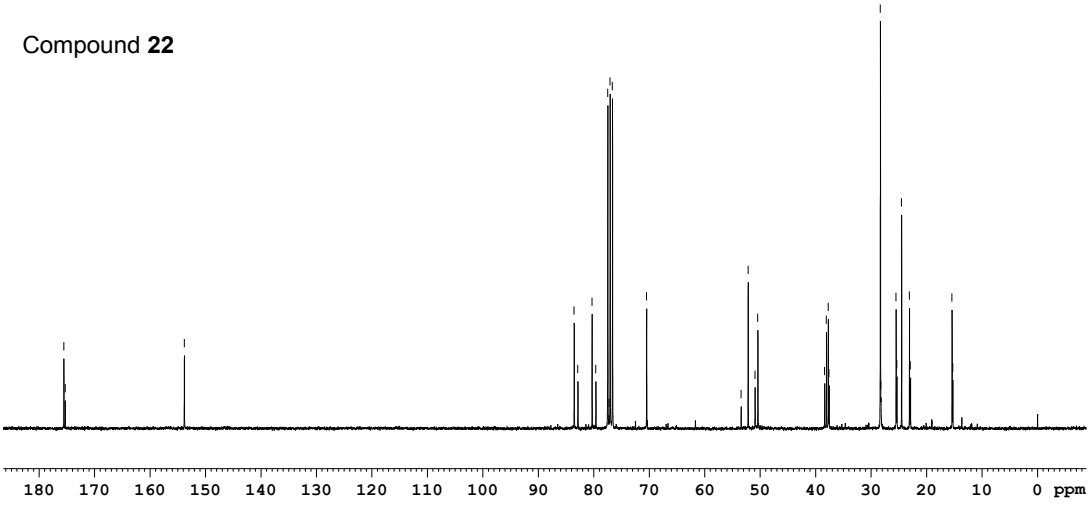
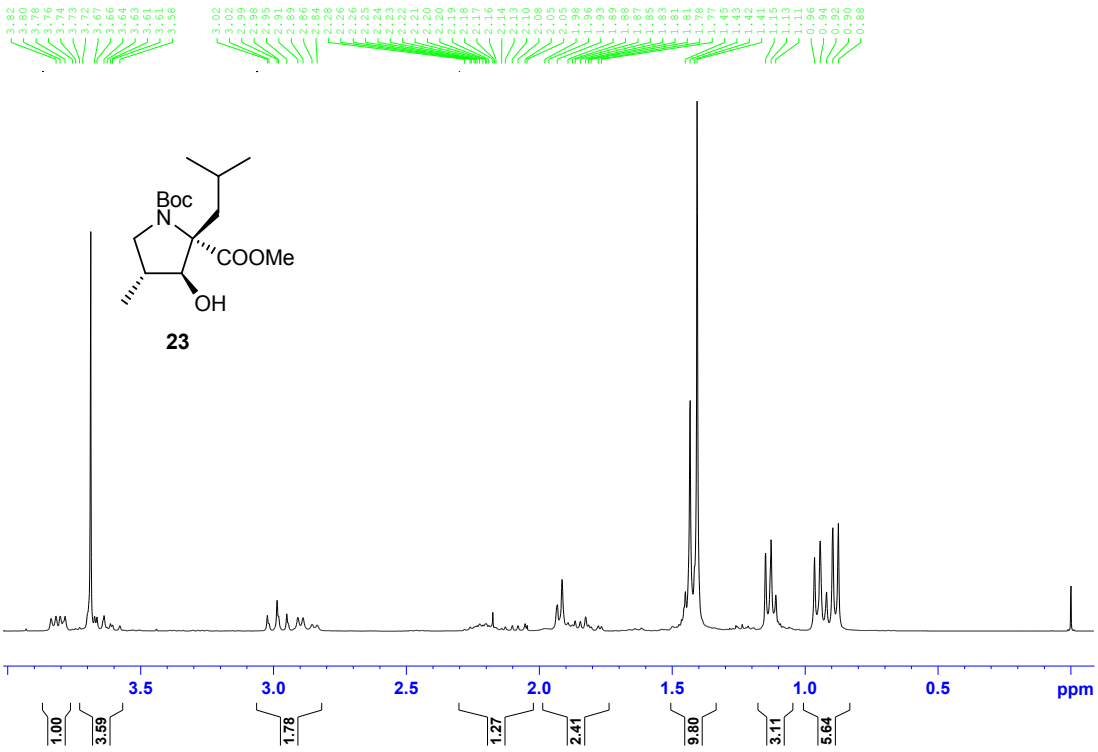
1.14
3.39
2.20
3.57
1.31
9.71
0.00

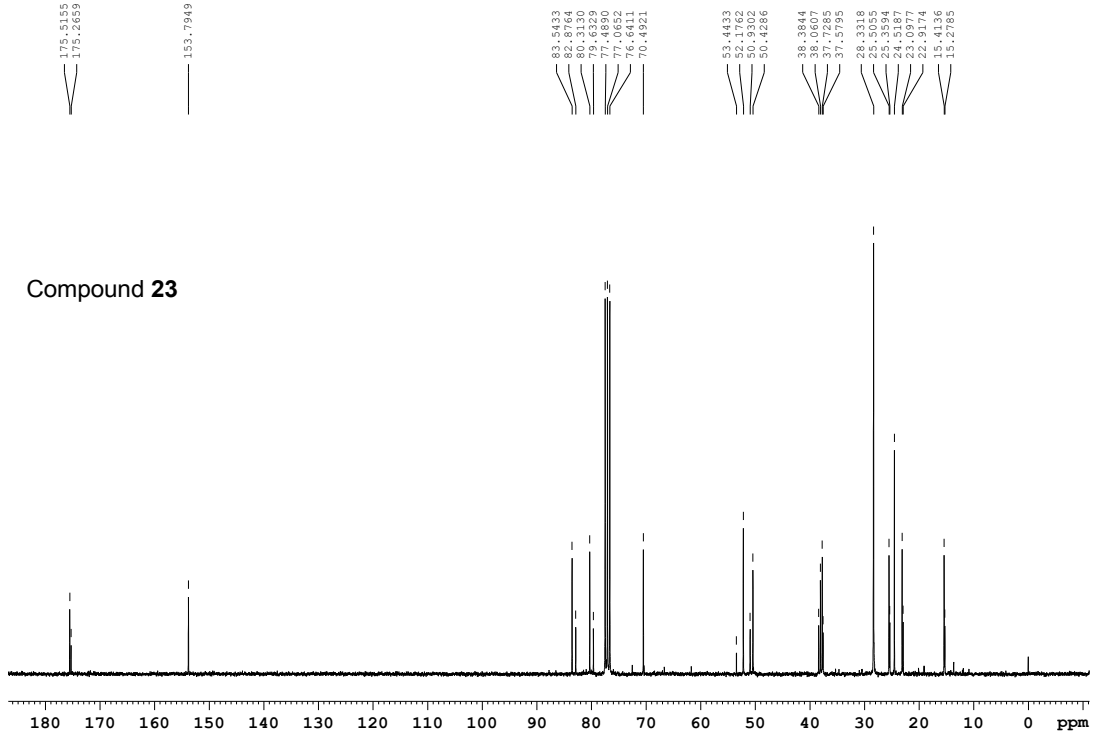

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

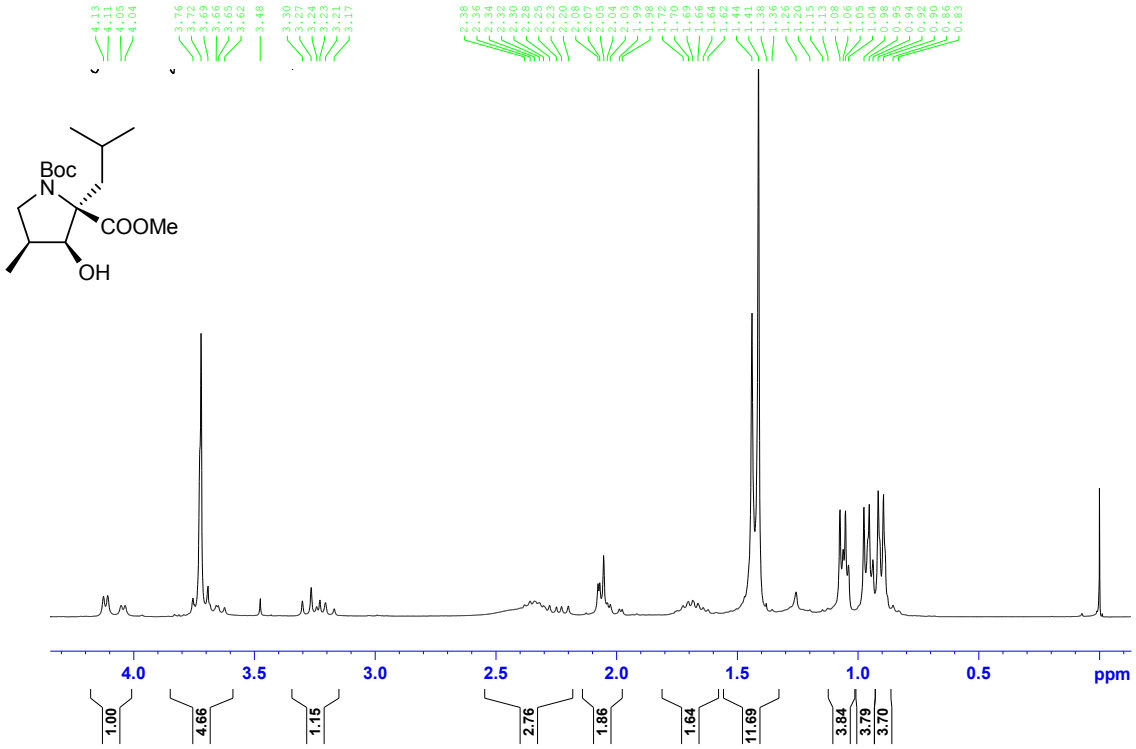
Compound **21**

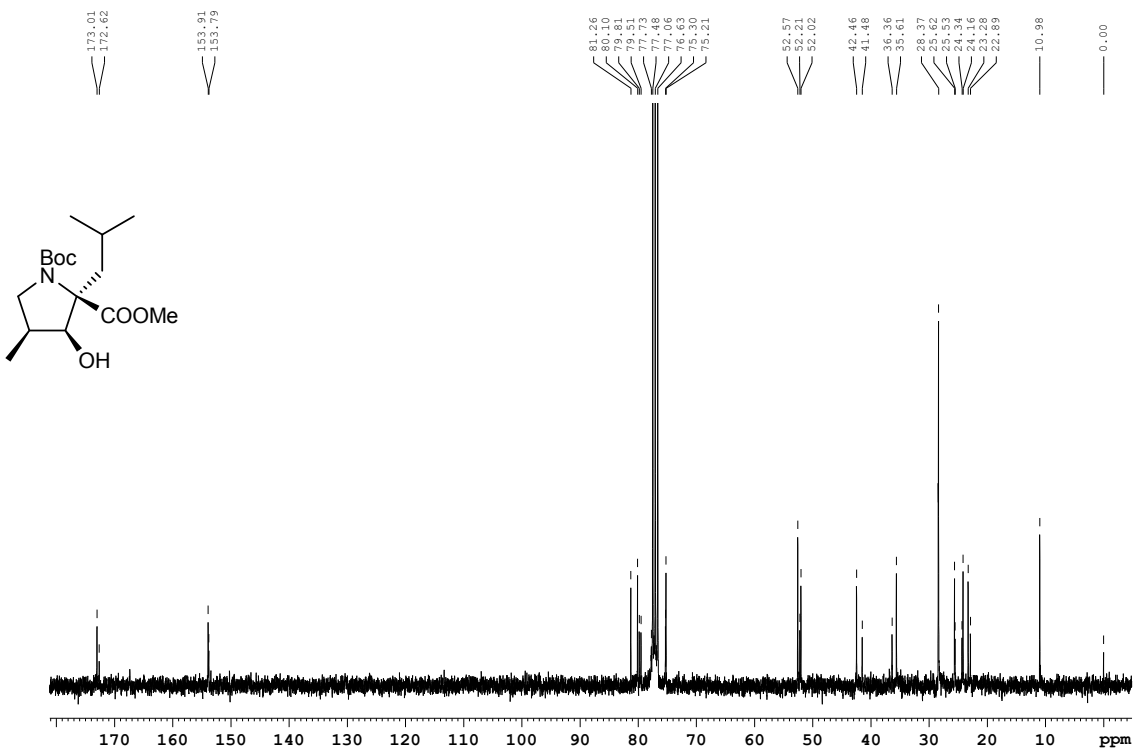

Boc
N
COOMe
OH
22
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
3.33
1.64
1.26
2.20
8.98
2.68
5.17

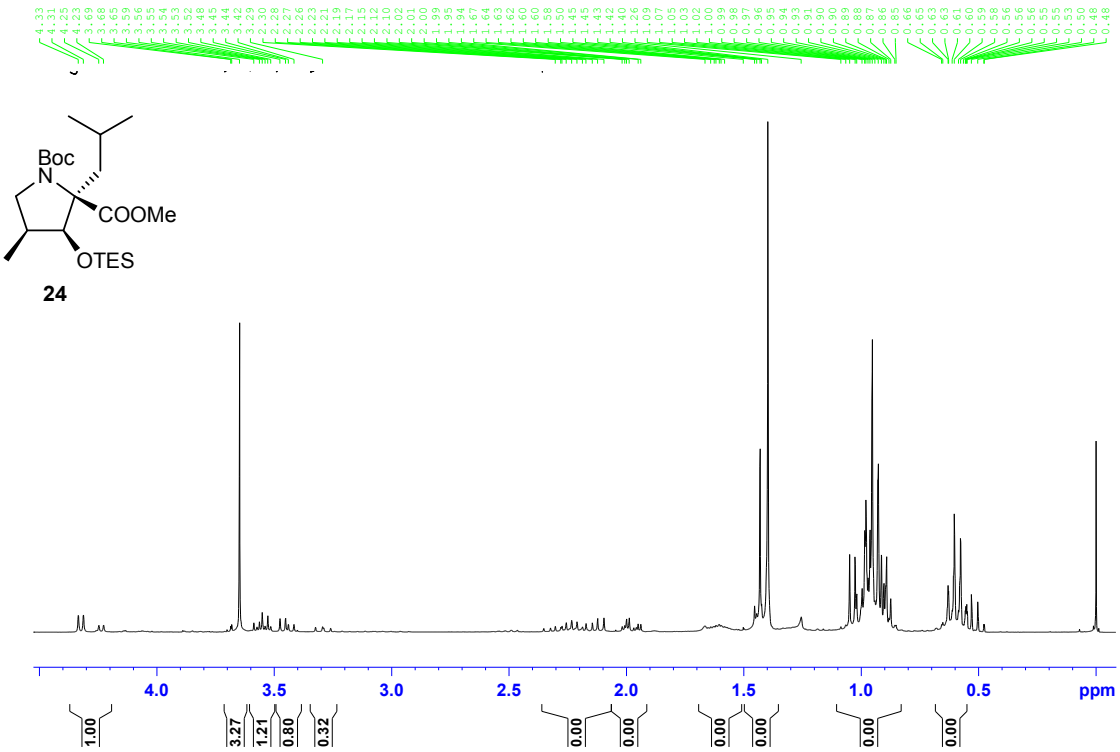

Compound 22
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

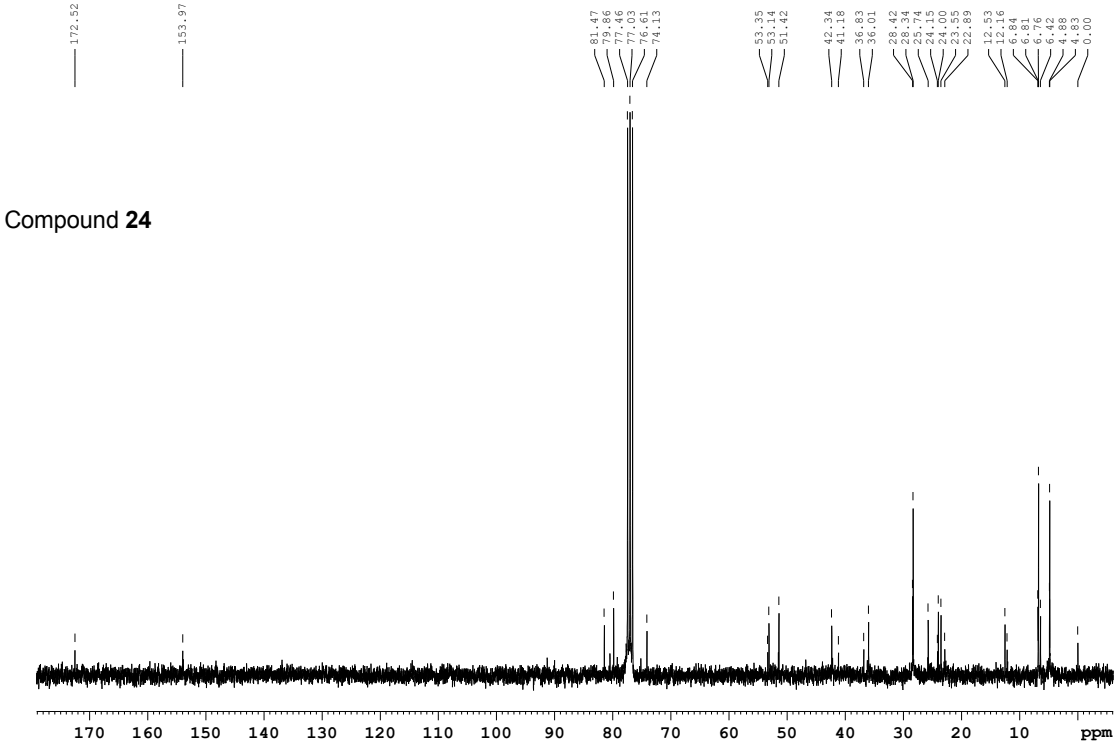

Boc
N
COOMe
OH
23
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
3.59
1.78
1.27
2.41
9.80
3.11
5.64


Compound 23
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

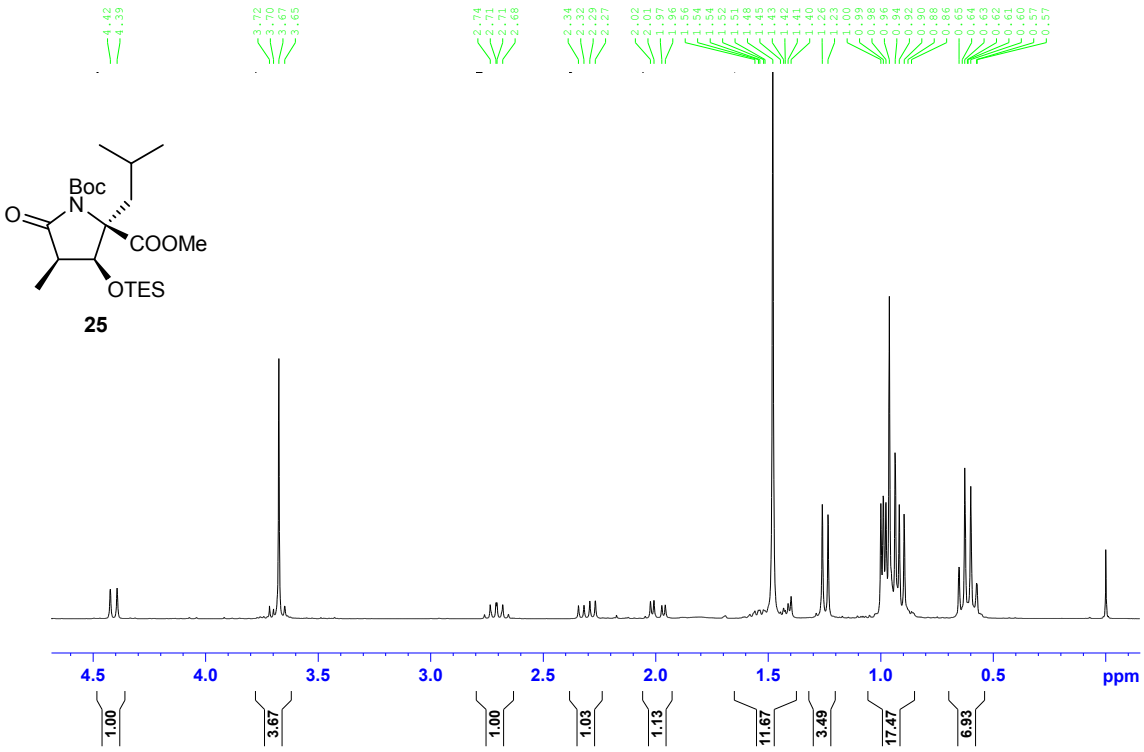

Boc
N
COOMe
OH
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
4.66
1.15
2.76
1.86
1.64
11.69
3.84
3.79
3.70


Boc
N
COOMe
OH
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

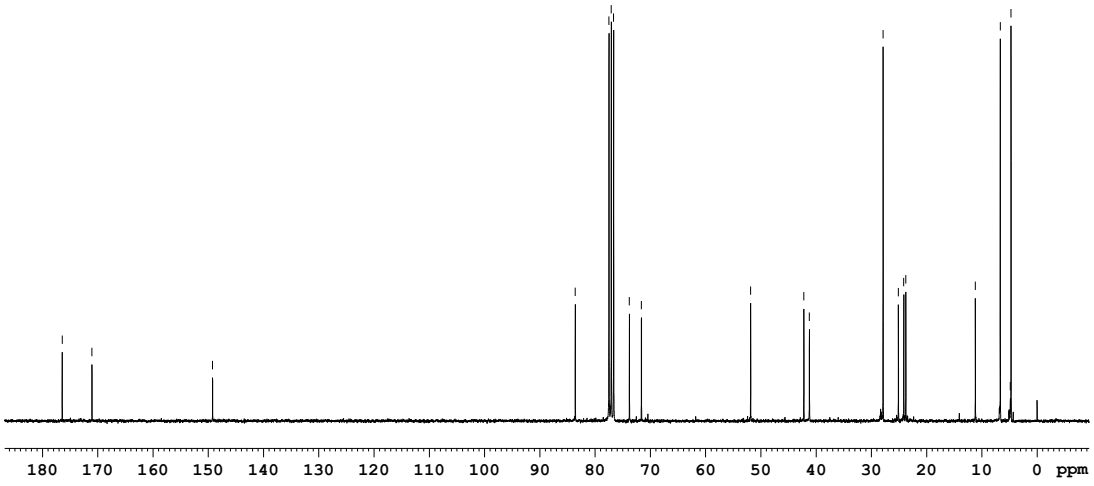

Boc
N
COOMe
OTES
24
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
3.27
1.21
0.80
0.32
0.00
0.00
0.00
0.00
0.00
0.00

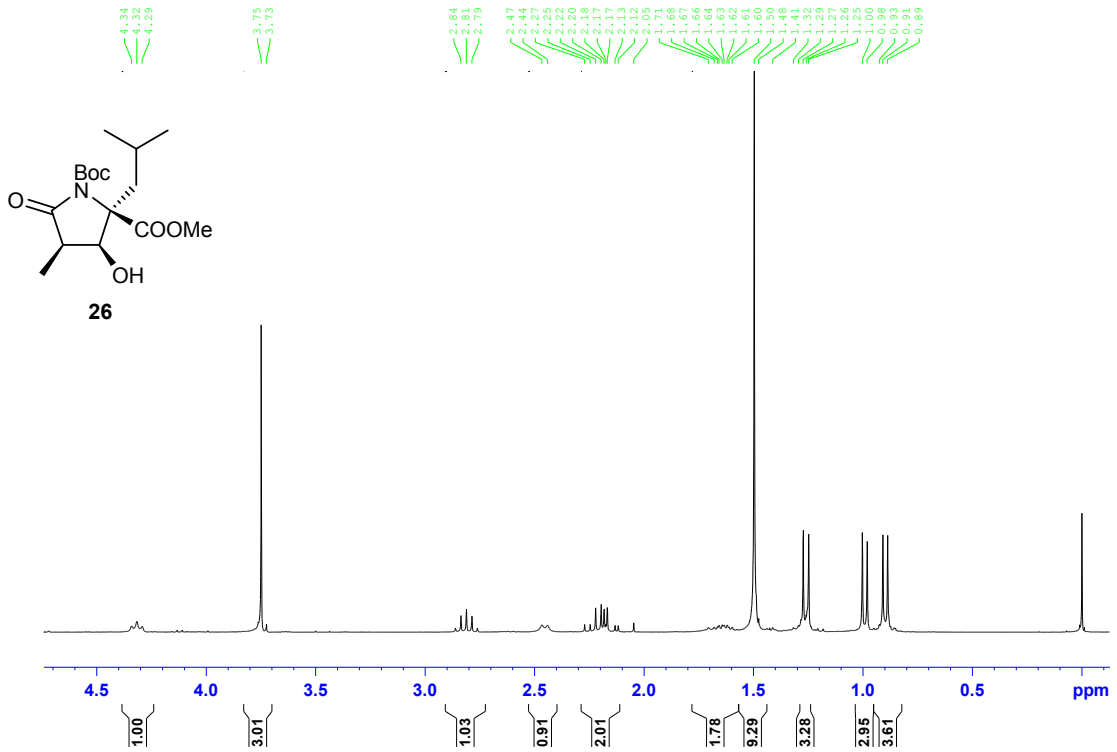

172.52
153.97
81.47
79.86
77.46
77.03
76.61
74.13
53.35
53.14
51.42
42.34
41.18
36.83
36.01
28.42
28.34
25.74
24.15
24.00
23.55
22.89
12.53
12.16
6.84
6.81
6.76
6.42
4.88
4.83
0.00
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

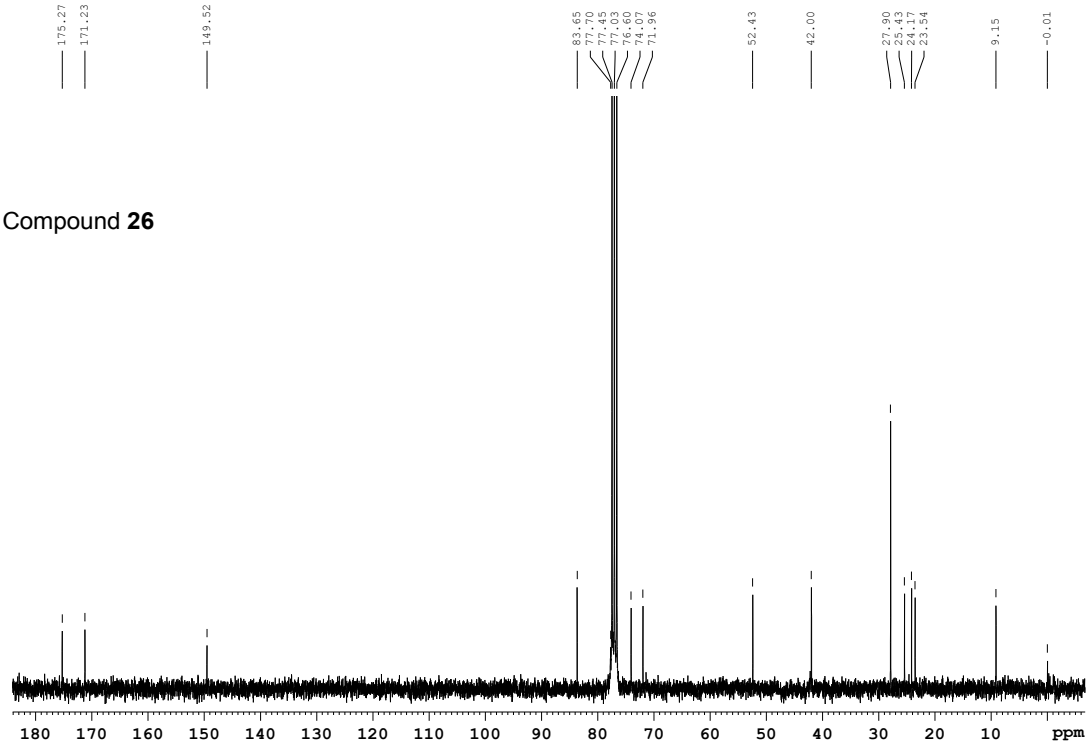
Compound **24**


Boc
N
O
COOMe
OTES
25
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
3.67
1.00
1.03
1.13
11.67
3.49
17.47
6.93

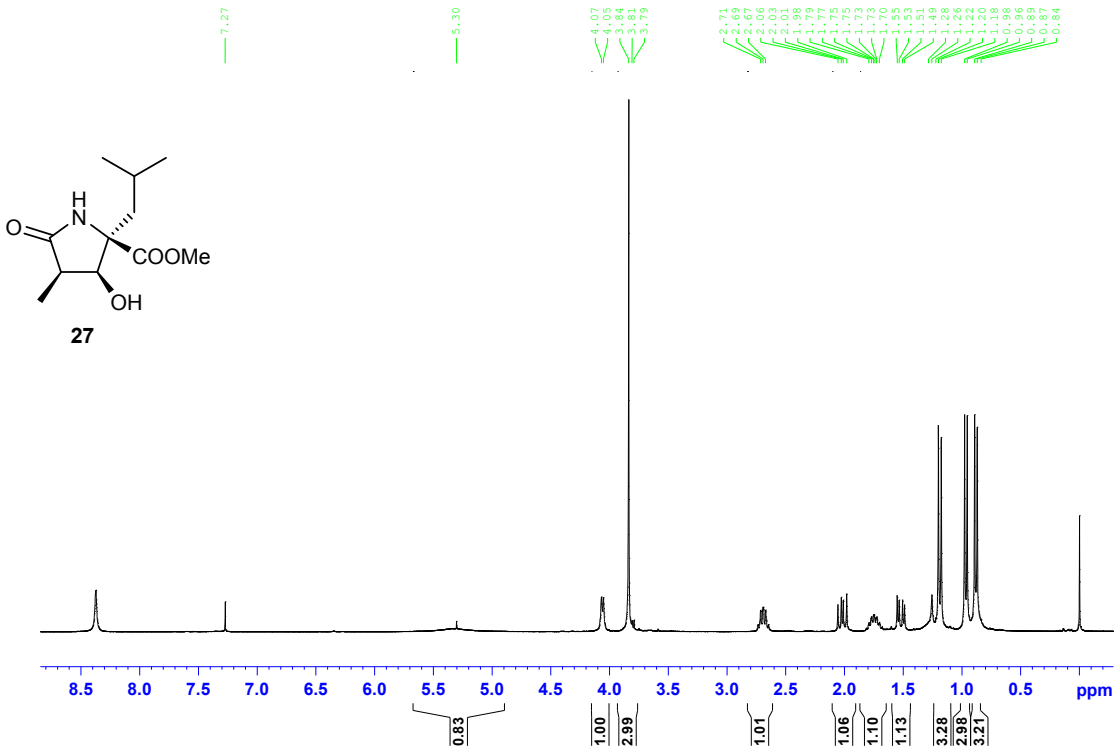
Compound **25**


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

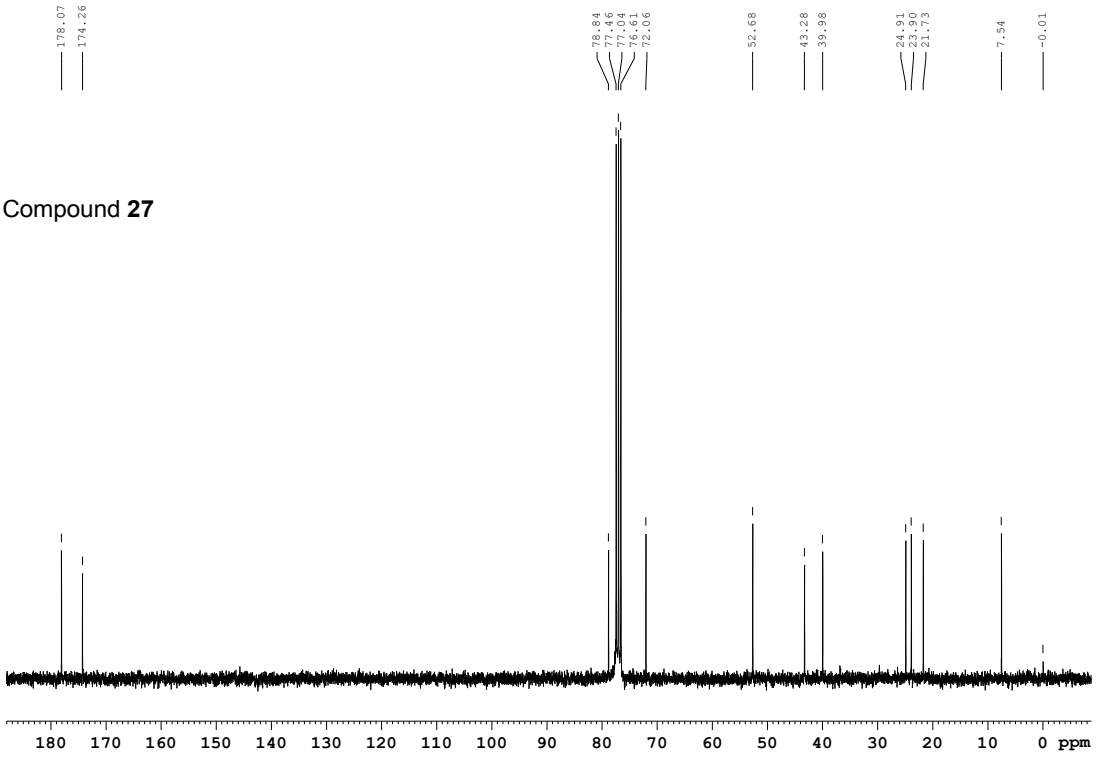

Boc
N
O
COOMe
OH
26
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


175.27
171.23
149.52
83.65
77.70
77.45
77.23
76.60
74.07
71.96
52.43
42.00
27.90
25.43
24.17
23.54
9.15
-0.01
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

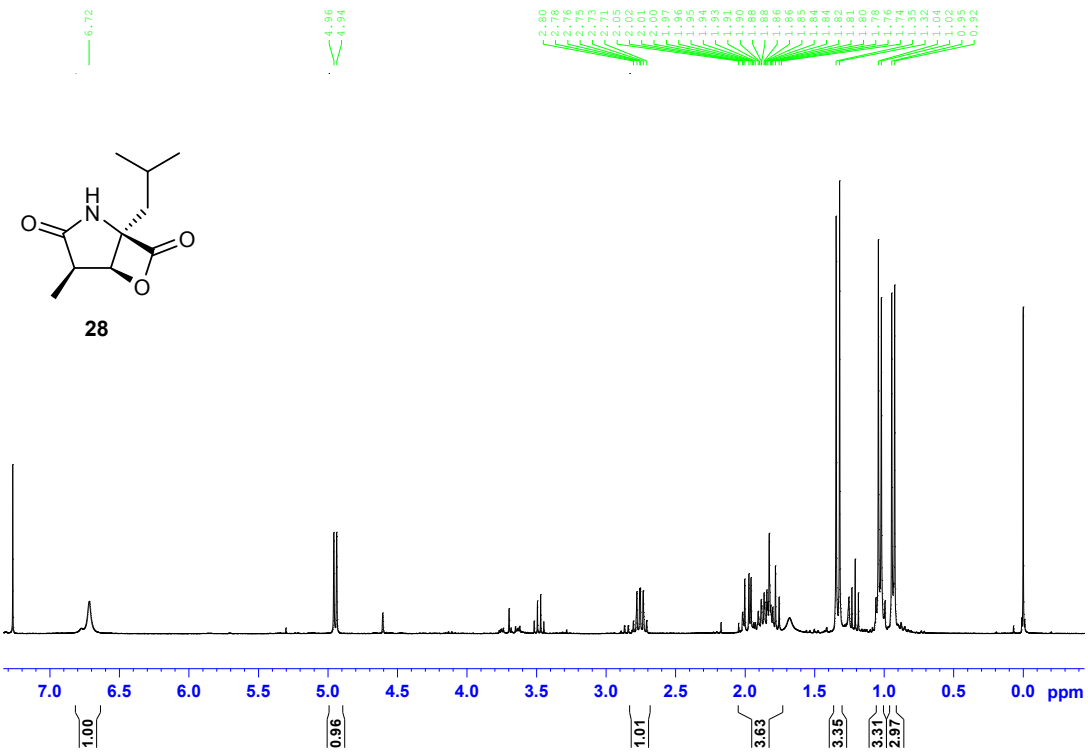
Compound **26**



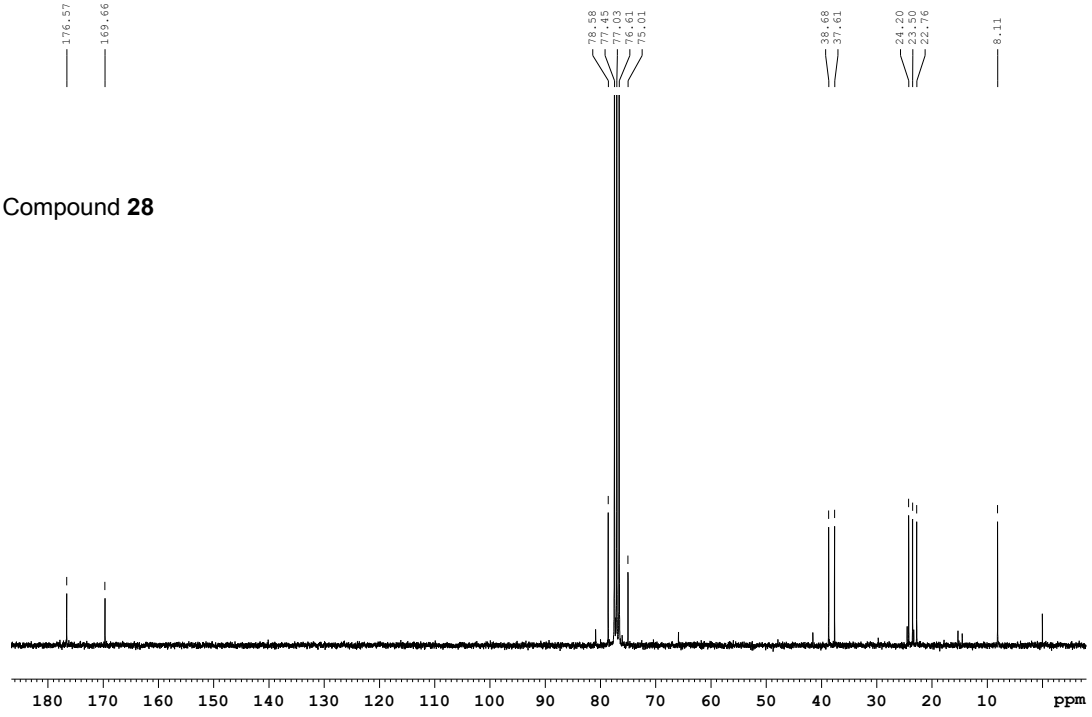
27



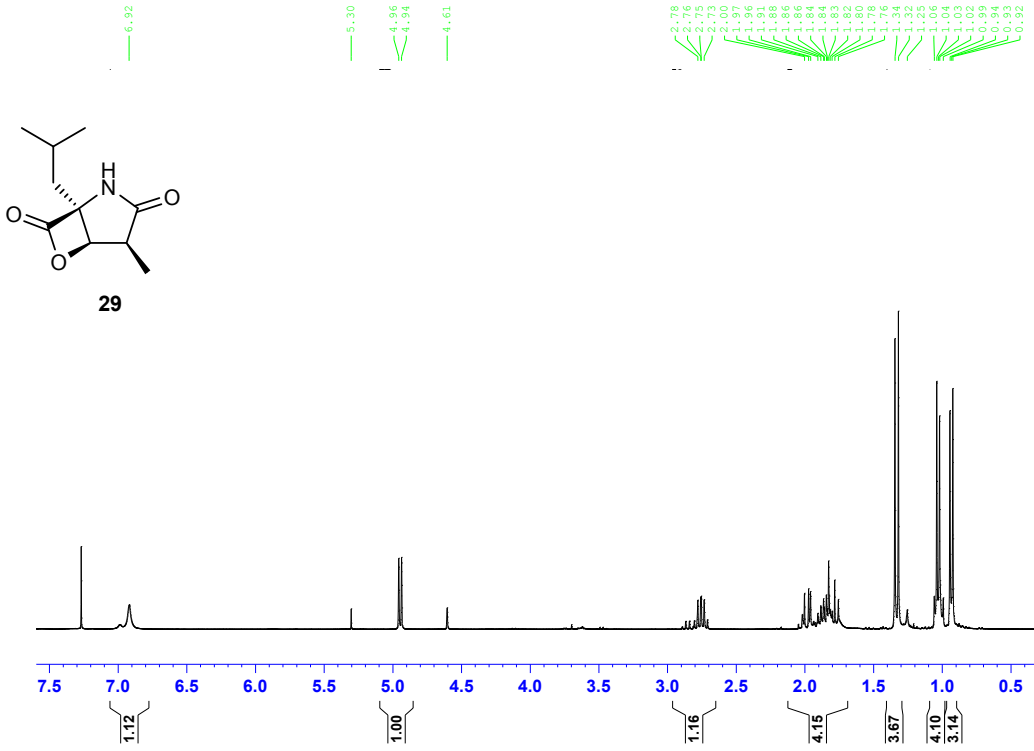
Compound **27**

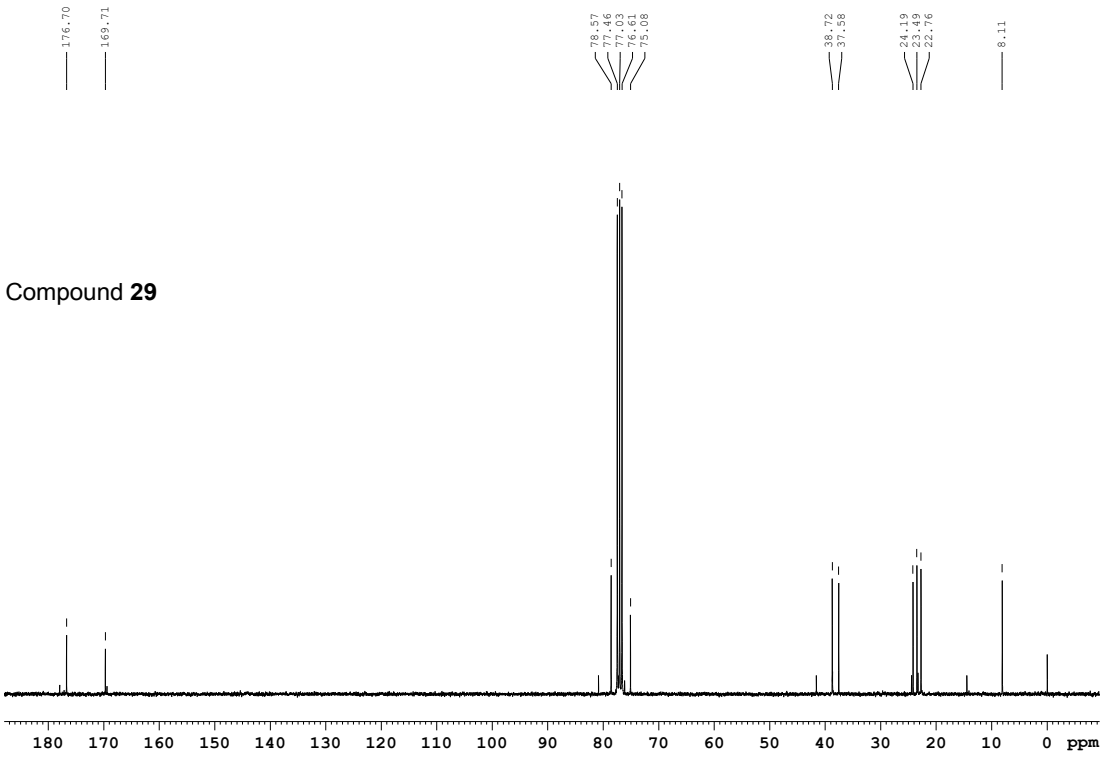


28



Compound **28**

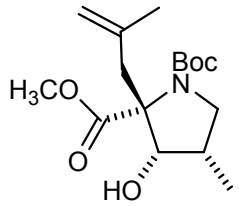

6.92
5.30
4.96
4.94
4.61
2.78
2.76
2.75
2.73
2.00
1.97
1.96
1.91
1.88
1.86
1.86
1.84
1.83
1.82
1.80
1.78
1.76
1.34
1.32
1.25
1.06
1.04
1.03
1.02
0.99
0.94
0.93
0.92
H
N
O
O
O
29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.12
1.00
1.16
4.15
3.67
4.10
3.14


176.70
169.71
78.57
77.46
77.03
76.61
75.08
38.72
37.58
24.19
23.49
22.76
8.11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

Compound **29**

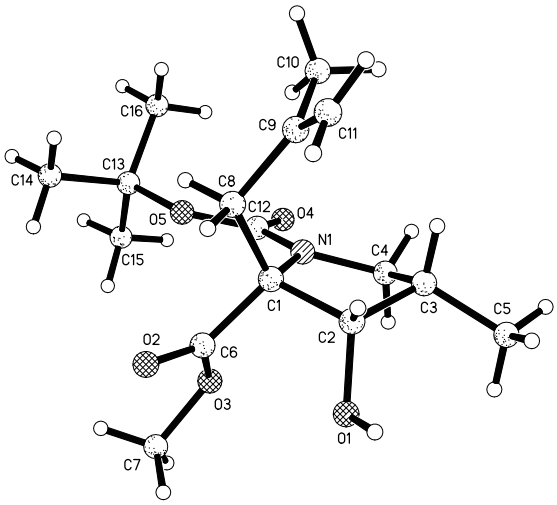
1-(tert-Butyl) 2-methyl (2R,3S,4S)-3-hydroxy-4-methyl-2-(2-methylallyl)pyrrolidine -

1,2-dicarboxylate (20)

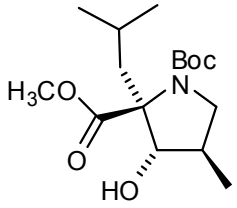


20

$C_{16}H_{27}NO_5$
Monoclinic $P2_1$
a = 9.098 (2) Å
b = 10.8457 (18) Å
c = 9.382 (2) Å
V = 901.0 (3) Å^3
α = 90°, β= 90°, γ = 90°
Z = 2, R*(F)* = 0.0833
Rw*(F^2)* = 0.2101
Crystal size: 0.35 × 0.10 × 0.10 mm
Calculated density: 1.155
2Θ-range for data collection: 4.84-64.91°
Independent reflections: 2077
Observed reflections: 1744
Contributing reflections to refinement: 1744
Refined parameters: 204

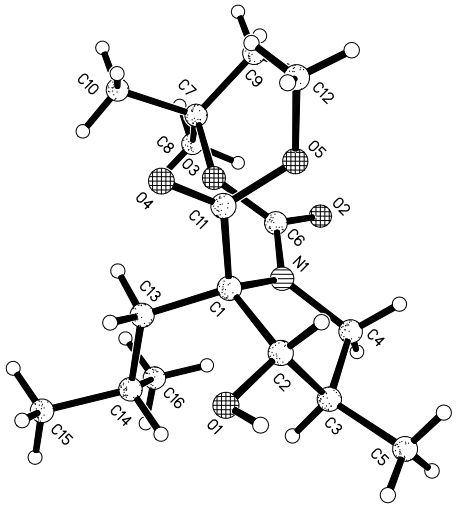


1-(tert-Butyl) 2-methyl (2S,3S,4R)-3-hydroxy-2-isobutyl-4-methylpyrrolidine -1,2-dicarboxylate (23)

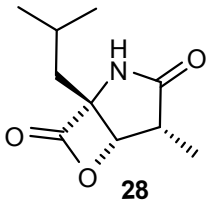


23

$C_{16}H_{29}NO_5$
Orthorhombic $P2_12_12_1$
a = 9.1627 (7) Å
b = 11.9106 (12) Å
c = 16.6391 (13) Å
V = 1815.9 (3) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0613
Rw*(F^2)* = 0.1564
Crystal size: 0.5 × 0.35 × 0.07 mm^3
Calculated density: 1.154 g/cm^3
2Θ-range for data collection: 4.57-67.91°
Independent reflections: 3284
Observed reflections: 2838
Contributing reflections to refinement: 2838
Refined parameters: 200

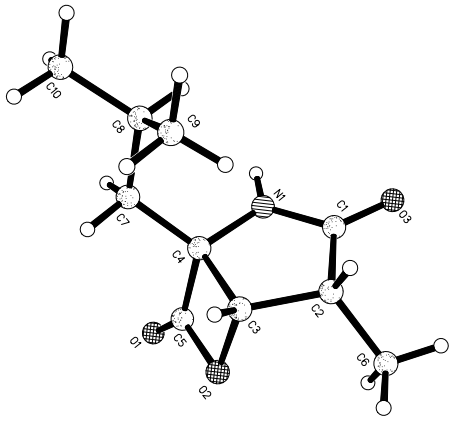


(1*R*,4*R*,5*S*)-1-Isobutyl-4-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione (28)



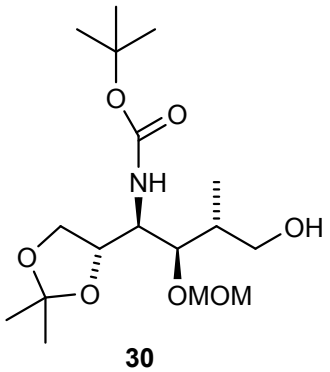
28

$C_{10}H_{15}NO_3$
Orthorhombic $P2_12_12_1$
a = 7.5269 (6) Å
b = 7.6821 (7) Å
c = 18.8867 (12) Å
V = 1105.78 (3) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0678
Rw*(F^2)* = 0.1594
Crystal size: 0.25 × 0.10 × 0.05 mm^3
Calculated density: 1.200 g/cm^3
2Θ-range for data collection: 2.15-30.00°
Independent reflections: 2079
Observed reflections: 1745
Contributing reflections to refinement: 1745
Refined parameters: 128



tert-Butyl ((1*S*,2*R*,3*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-

2-(methoxymethoxy)-3-methylbutyl)carbamate (30)



30

$C_{17}H_{33}NO_7$
Orthorhombic $P2_12_12_1$
a = 9.5027 (13) Å
b = 10.2463 (12) Å
c = 21.100 (2) Å
V = 2054.4 (4) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0764
Rw*(F^2)* = 0.1810
Crystal size: 0.5 × 0.35 × 0.04 mm^3
Calculated density: 1.175 g/cm^3
2Θ-range for data collection: 4.19-67.98°
Independent reflections: 3827
Observed reflections: 3335
Contributed reflections to refinement: 3335
Refined parameters: 236