Metal-Free Decarboxylative Hetero-Diels-Alder Synthesis of 3-Hydroxypyridines: a Rapid Access to *N*-fused Bicyclic Hydroxypiperidine Scaffolds

Supporting Information

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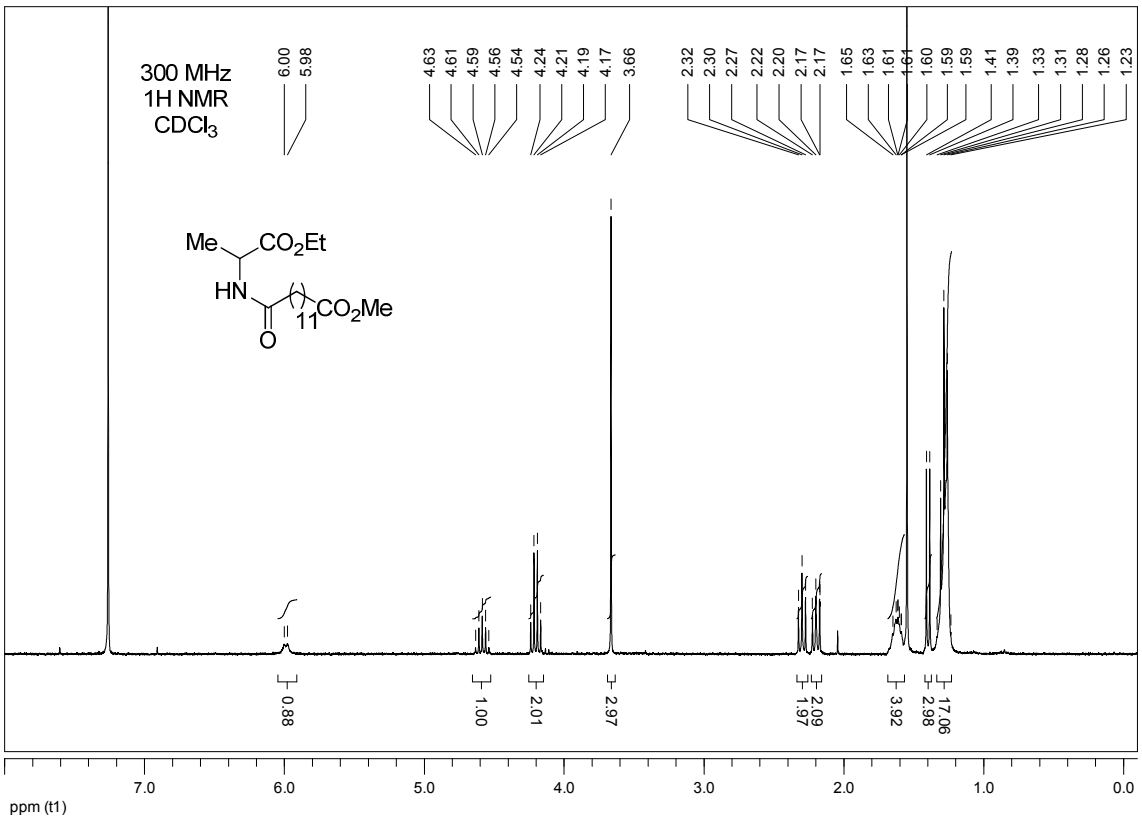
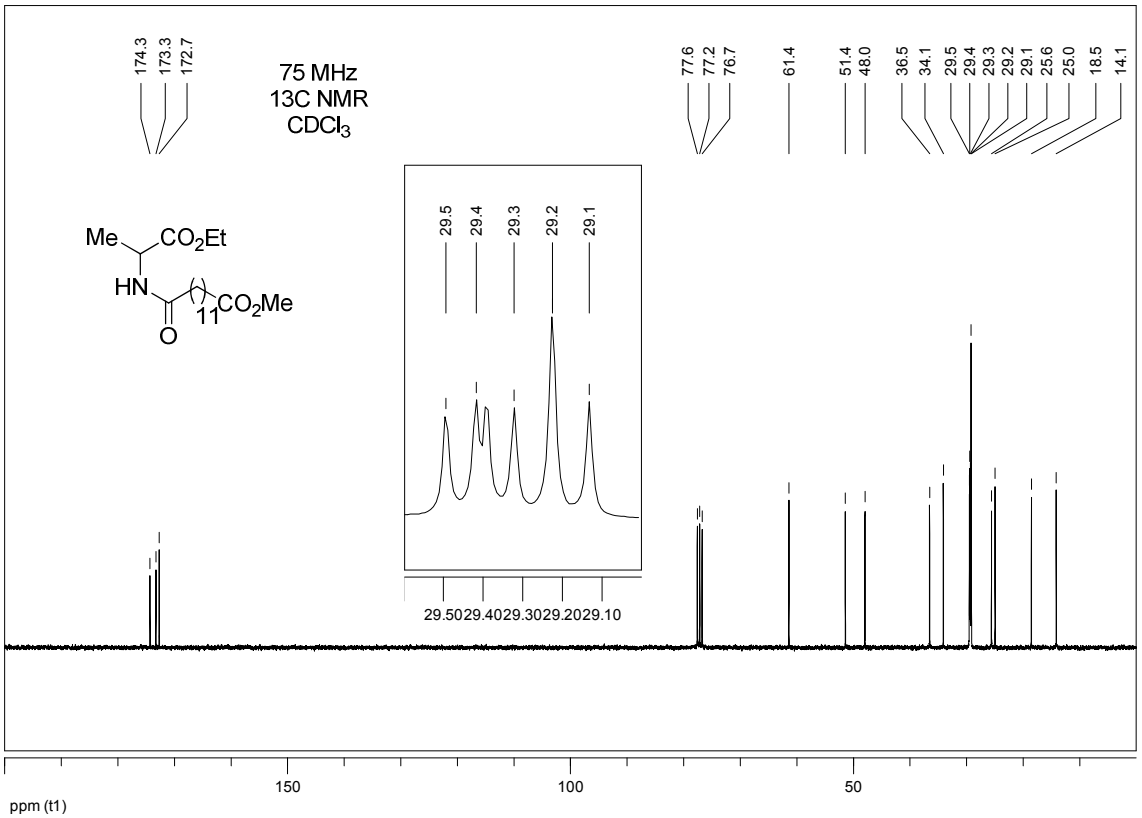
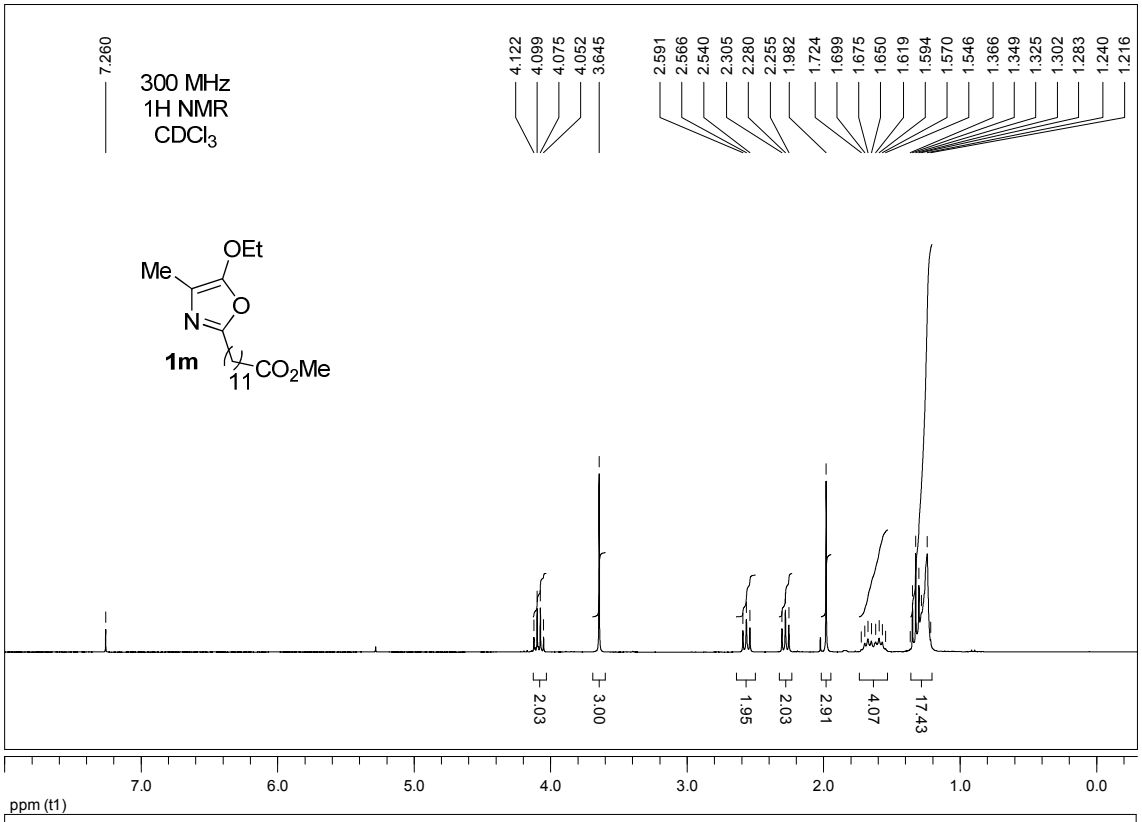
II. Copies of ^{1}H and ^{13}C NMR spectra



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2.280
2.255
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1.724
1.699
1.675
1.650
1.619
1.594
1.570
1.546
1.366
1.349
1.325
1.302
1.283
1.240
1.216
OEt
Me
O
N
1m
11
CO2Me
2.03
3.00
1.95
2.03
2.91
4.07
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3.0
2.0
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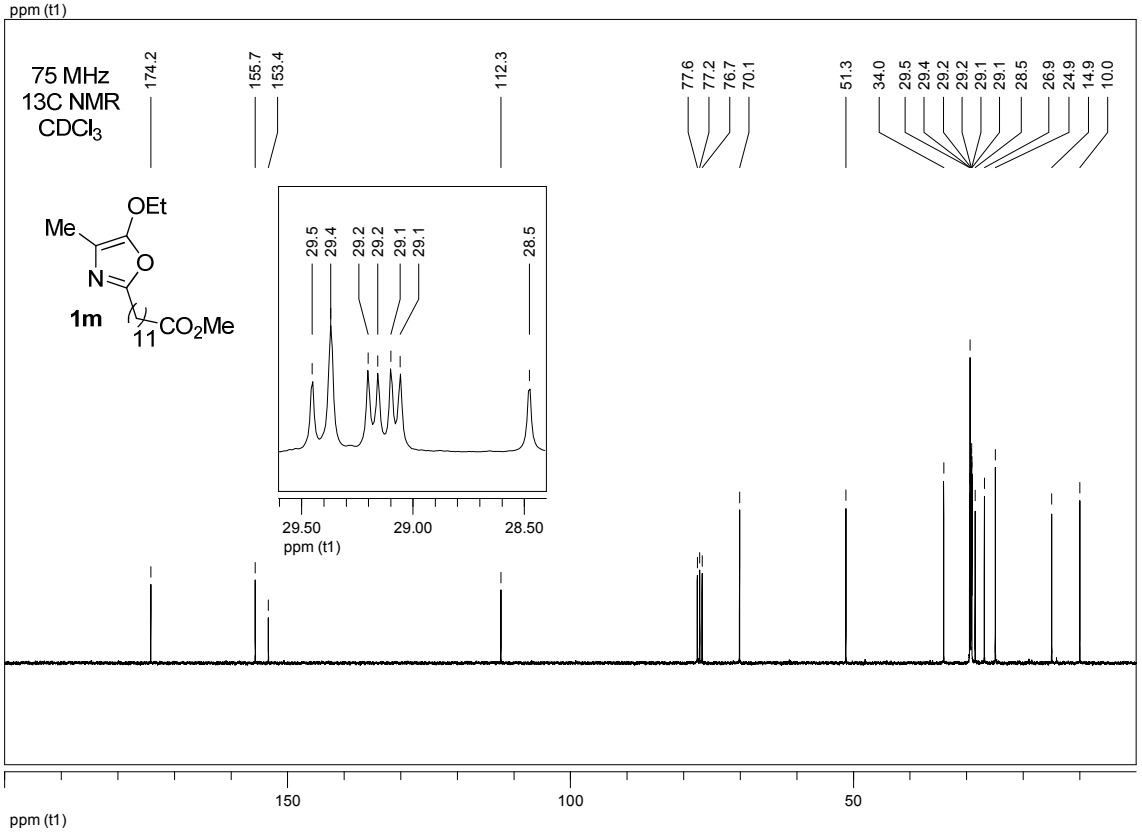
ppm (t1)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153.4
112.3
77.6
77.2
76.7
70.1
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34.0
29.5
29.4
29.2
29.2
29.1
29.1
28.5
26.9
24.9
14.9
10.0
OEt
Me
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N
1m
11
CO2Me
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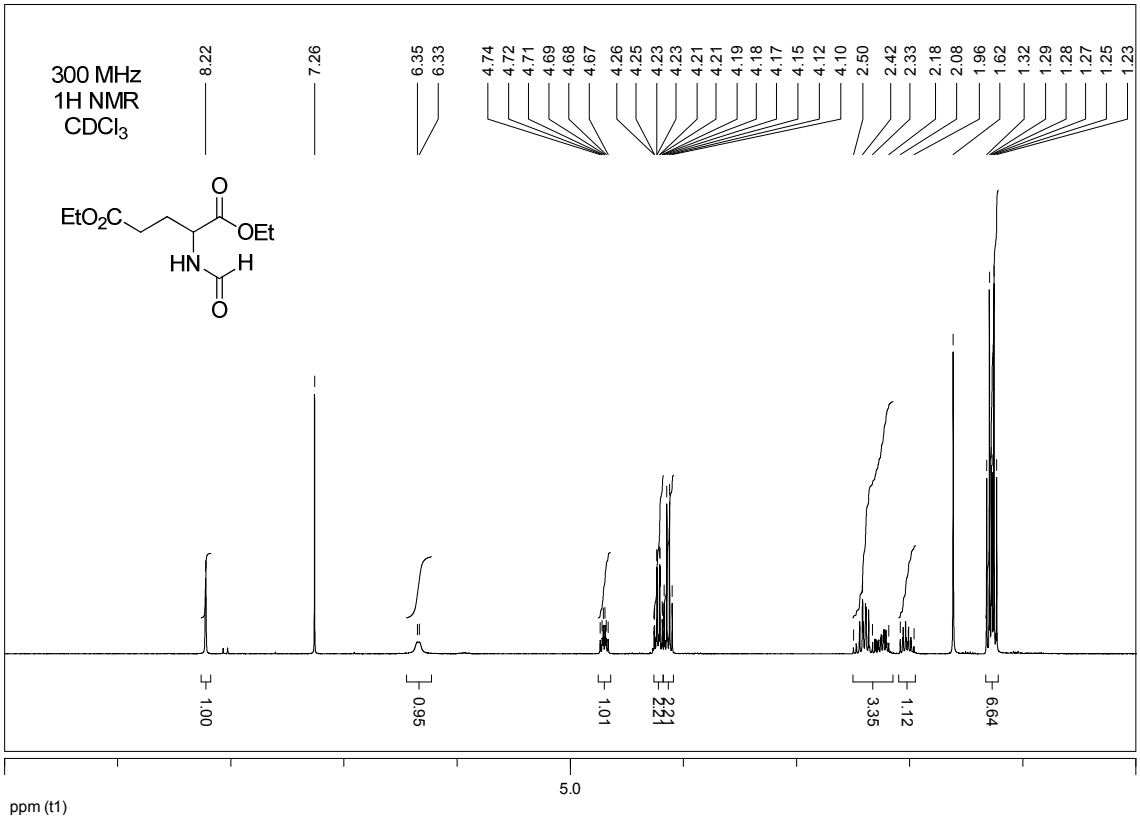
ppm (t1)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4.67
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4.25
4.23
4.23
4.21
4.21
4.19
4.18
4.17
4.15
4.12
4.10
2.50
2.42
2.33
2.18
2.08
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1.62
1.32
1.29
1.28
1.27
1.25
1.23
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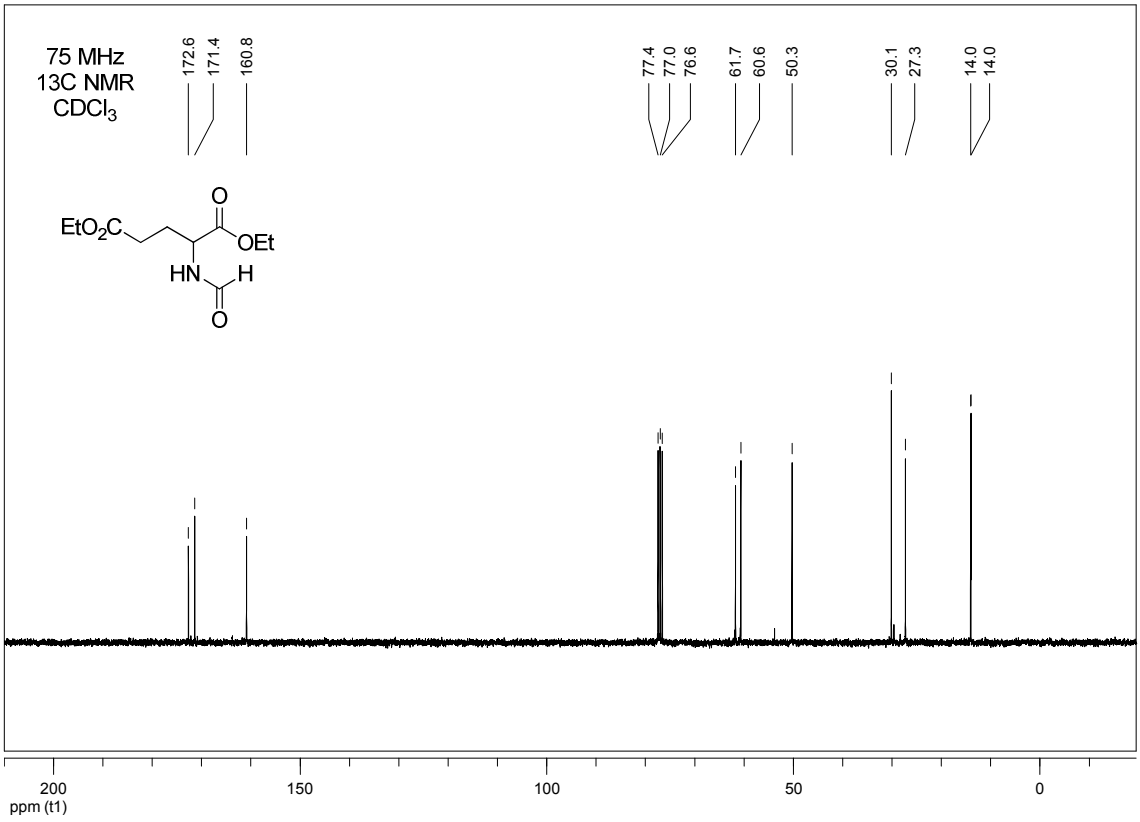
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H
O
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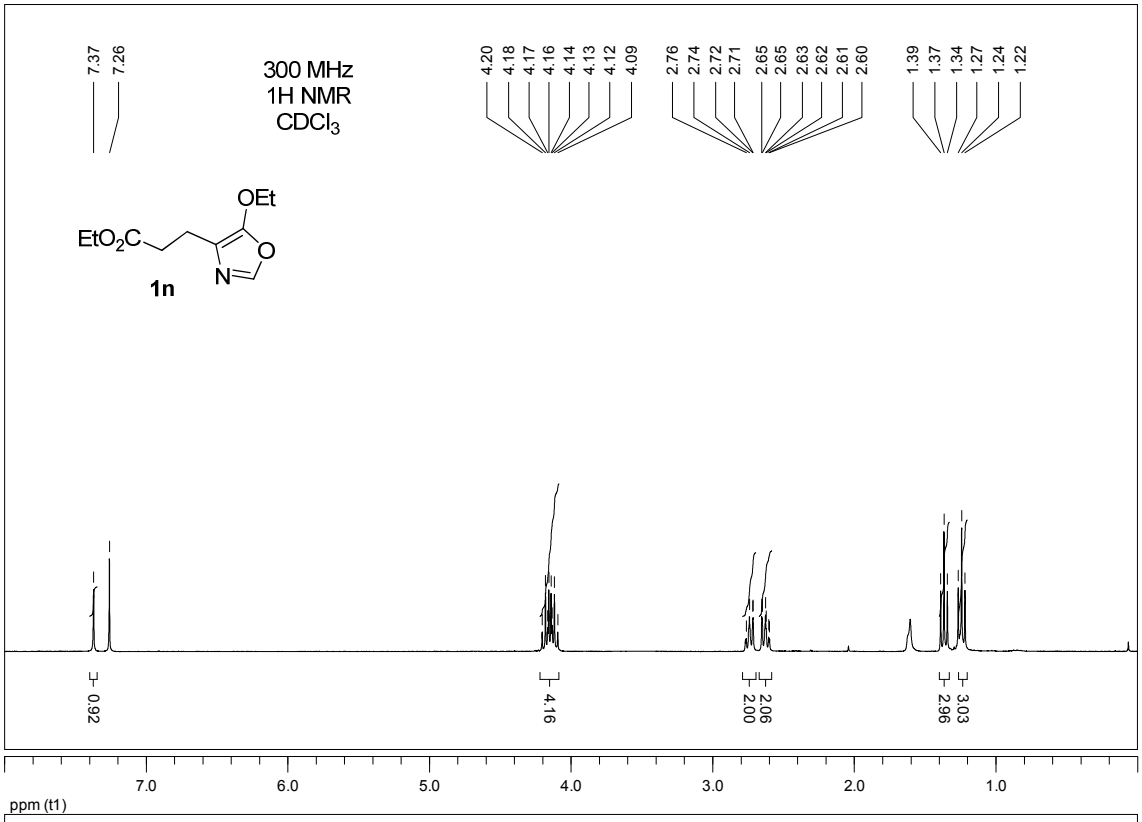
ppm (t1)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4.12
4.09
2.76
2.74
2.72
2.71
2.65
2.65
2.63
2.62
2.61
2.60
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1.34
1.27
1.24
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EtO2C
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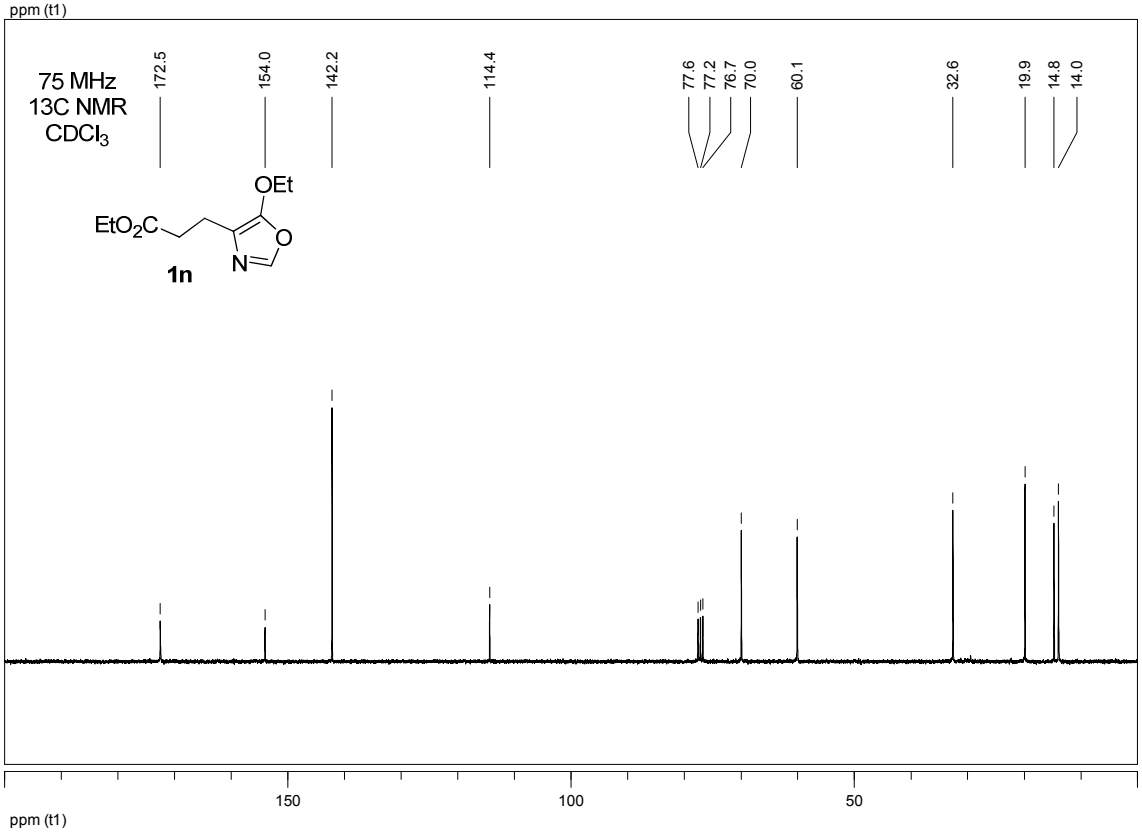
ppm (t1)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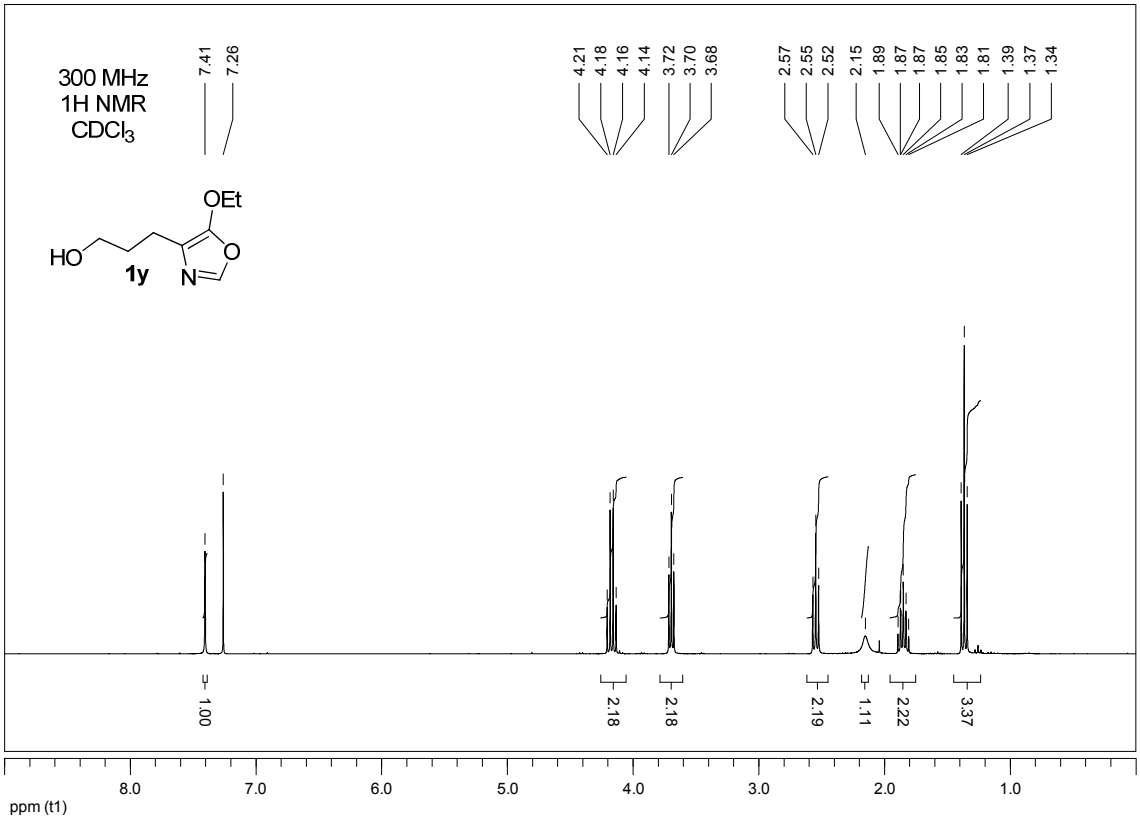
EtO2C
O
N
1n
150
100
50
ppm (t1)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2.57
2.55
2.52
2.15
1.89
1.87
1.87
1.85
1.83
1.81
1.39
1.37
1.34
OEt
HO
1y
O
N
1.00
2.18
2.18
2.19
1.11
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3.0
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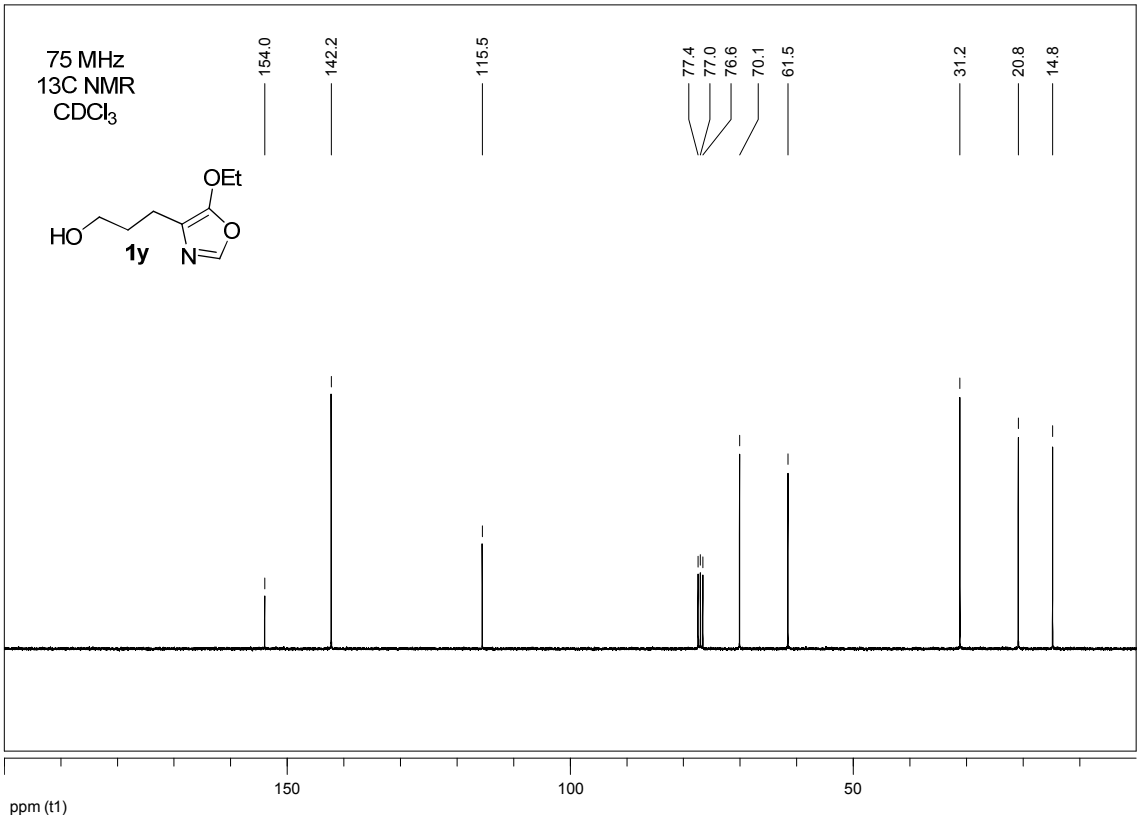
1.0
ppm (t1)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14.8
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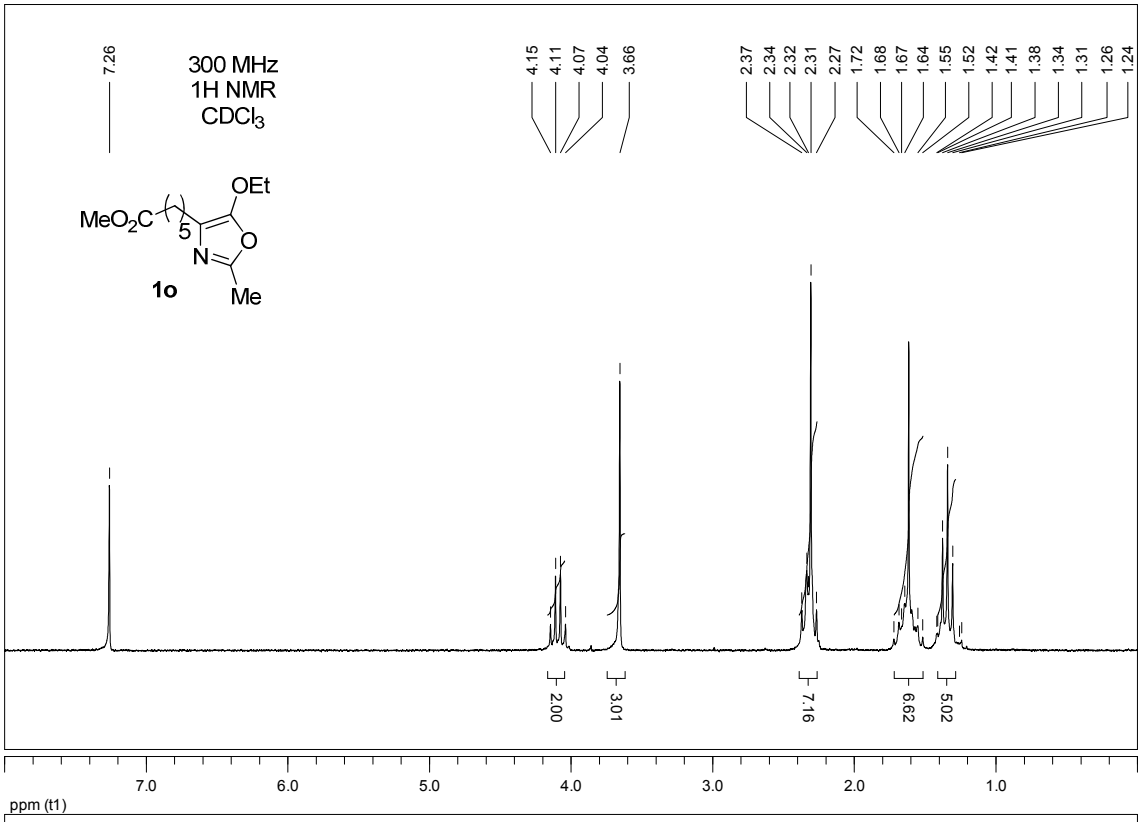
1y
O
N
150
100
50
ppm (t1)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4.07
4.04
3.66
2.37
2.34
2.32
2.31
2.27
1.72
1.68
1.67
1.64
1.55
1.52
1.42
1.41
1.38
1.34
1.31
1.26
1.24
OEt
MeO2C
5
O
N
Me
1o
2.00
3.01
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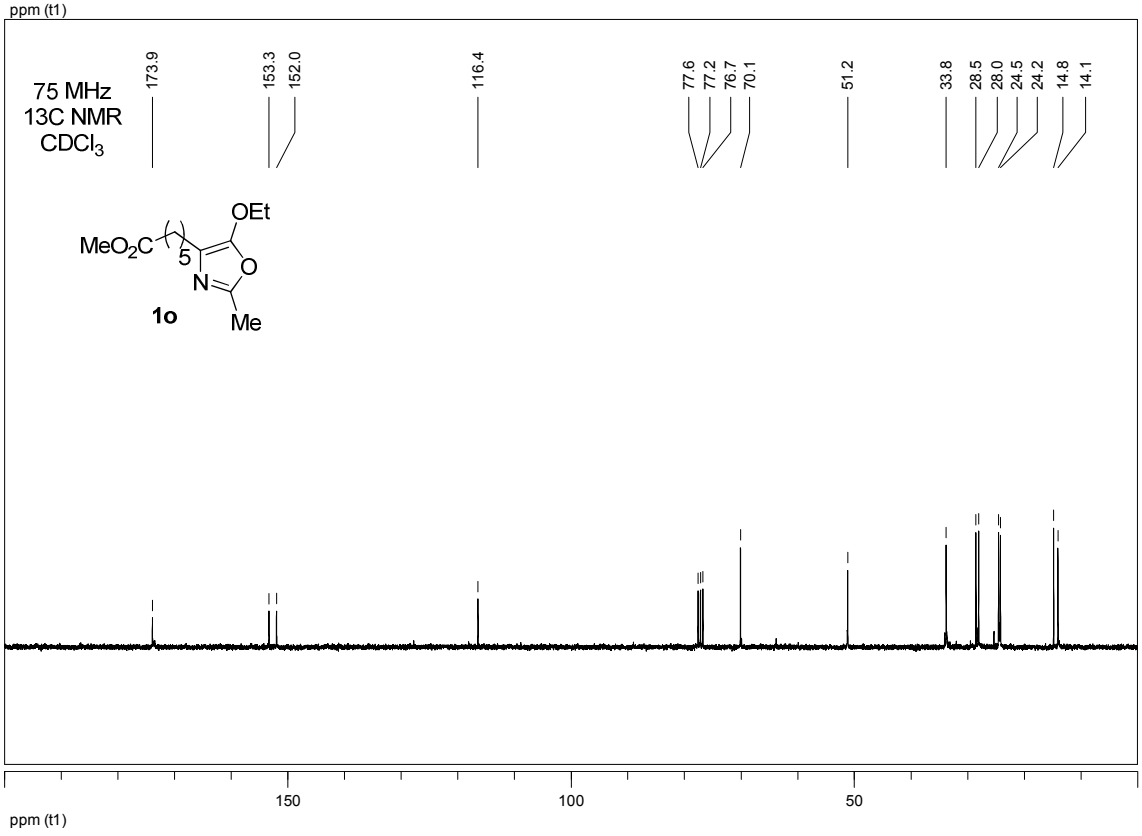
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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152.0
116.4
77.6
77.2
76.7
70.1
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33.8
28.5
28.0
24.5
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14.1
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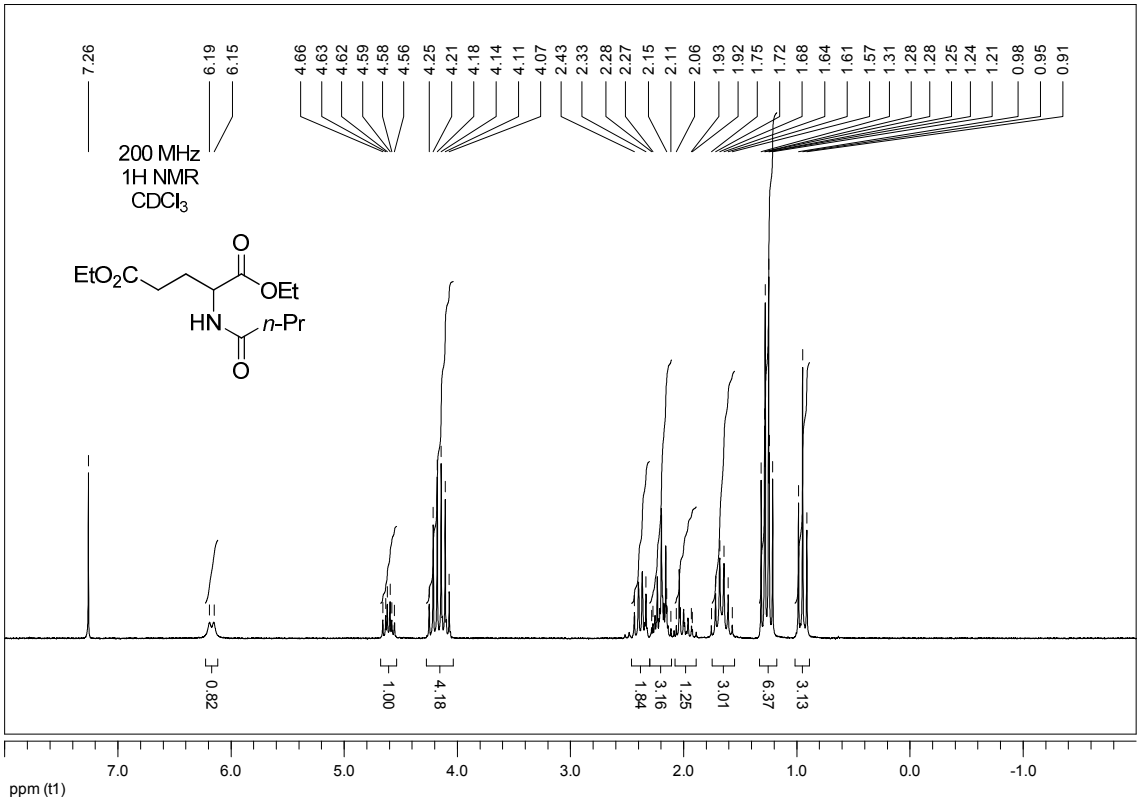
MeO2C
5
O
N
Me
1o
150
100
50
ppm (t1)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4.14
4.11
4.07
2.43
2.33
2.28
2.27
2.15
2.11
2.06
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1.92
1.75
1.72
1.68
1.64
1.61
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1.31
1.28
1.28
1.25
1.24
1.21
0.98
0.95
0.91
200 MHz
1H NMR
CDCl3
EtO2C
O
OEt
HN
n-Pr
O
0.82
1.00
4.18
1.84
3.16
1.25
3.01
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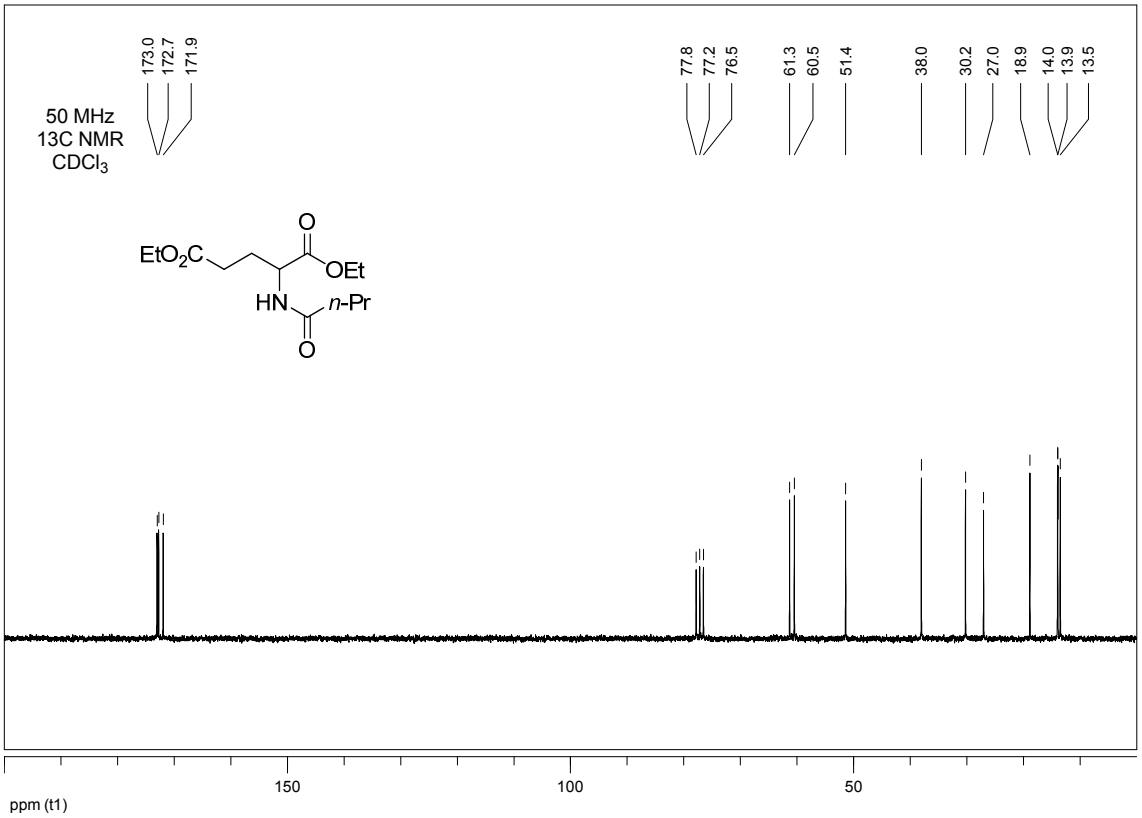
ppm (t1)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18.9
14.0
13.9
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50 MHz
13C NMR
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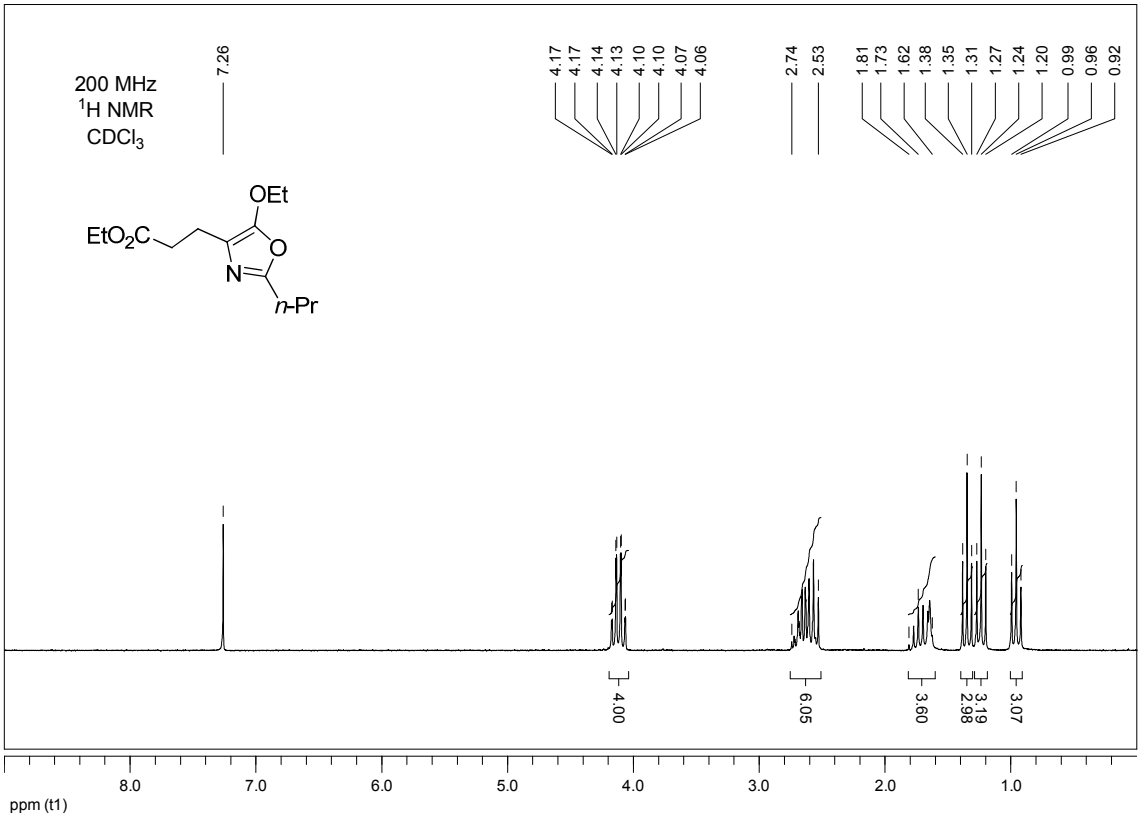
EtO2C
O
OEt
HN
n-Pr
O
150
100
50
ppm (t1)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4.17
4.14
4.13
4.10
4.10
4.07
4.06
2.74
2.53
1.81
1.73
1.62
1.38
1.35
1.31
1.27
1.24
1.20
0.99
0.96
0.92
OEt
EtO_2C
O
N
n-Pr
4.00
6.05
3.60
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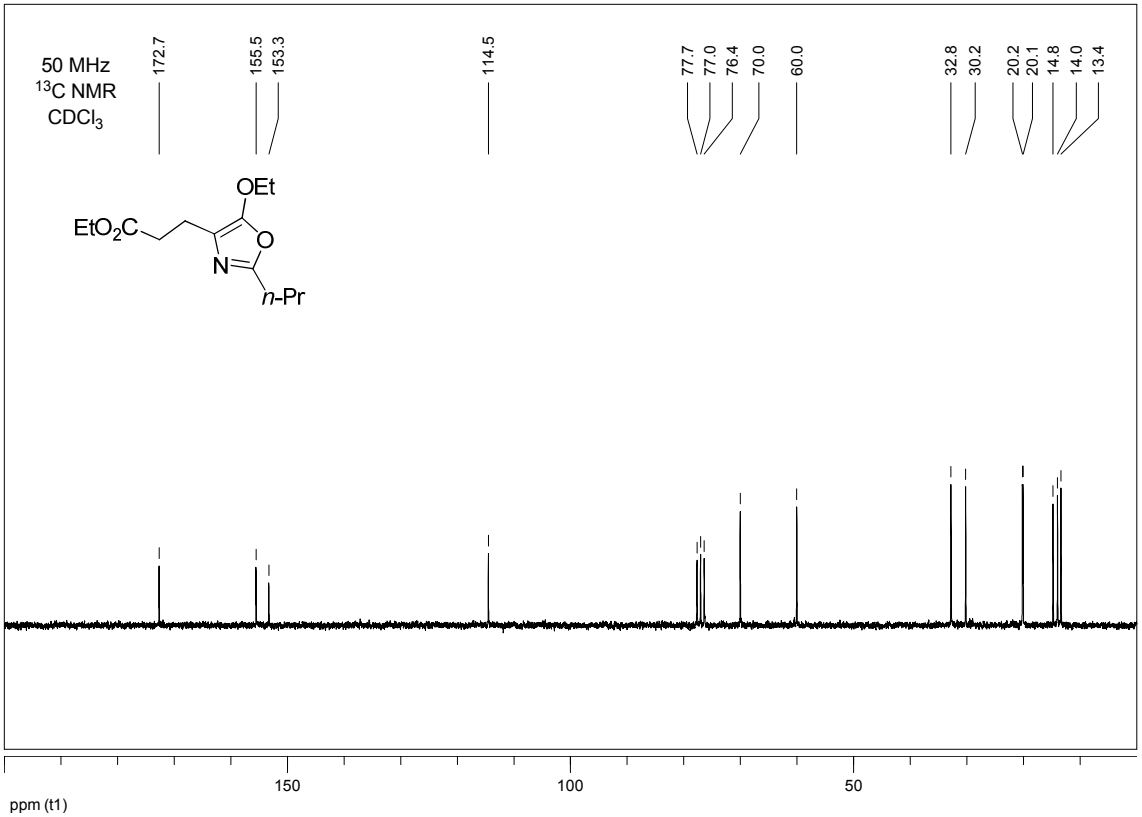
ppm (t1)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155.5
153.3
114.5
77.7
77.0
76.4
70.0
60.0
32.8
30.2
20.2
20.1
14.8
14.0
13.4
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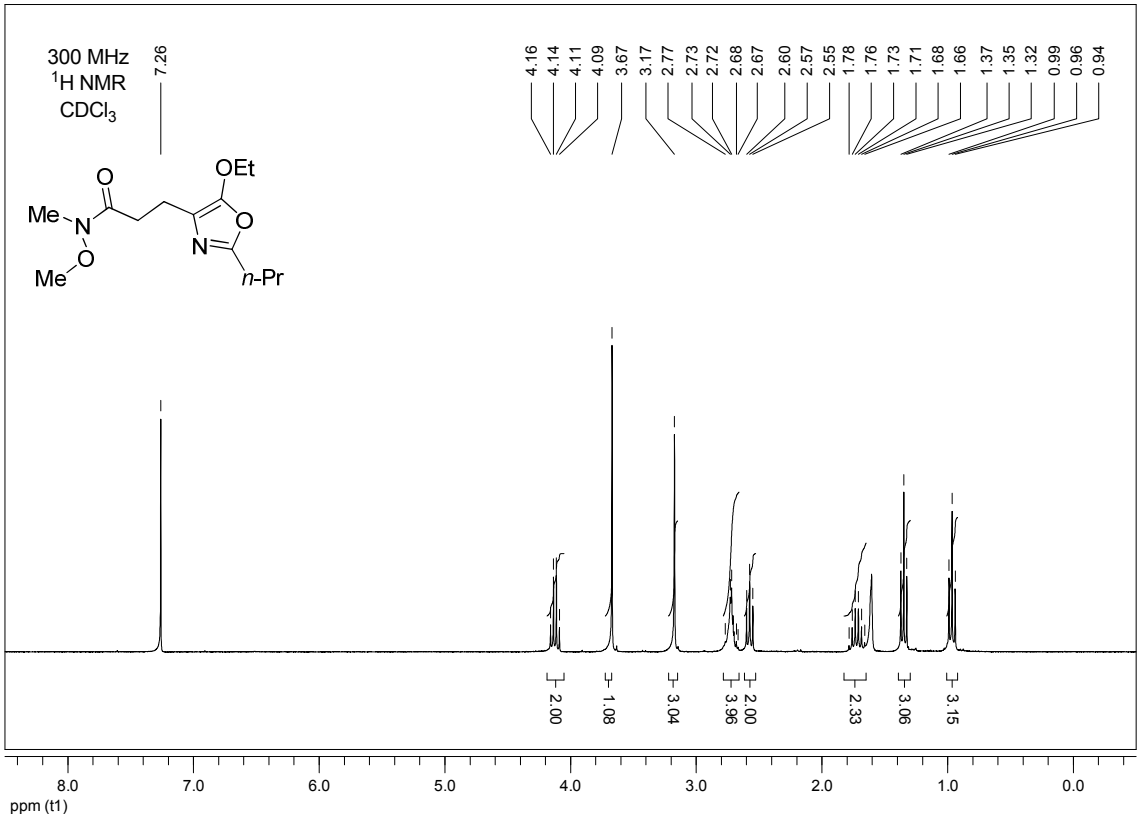
EtO_2C
O
N
n-Pr
150
100
50
ppm (t1)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4.14
4.11
4.09
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2.77
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2.72
2.68
2.67
2.60
2.57
2.55
1.78
1.76
1.73
1.71
1.68
1.66
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1.35
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0.94
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1.08
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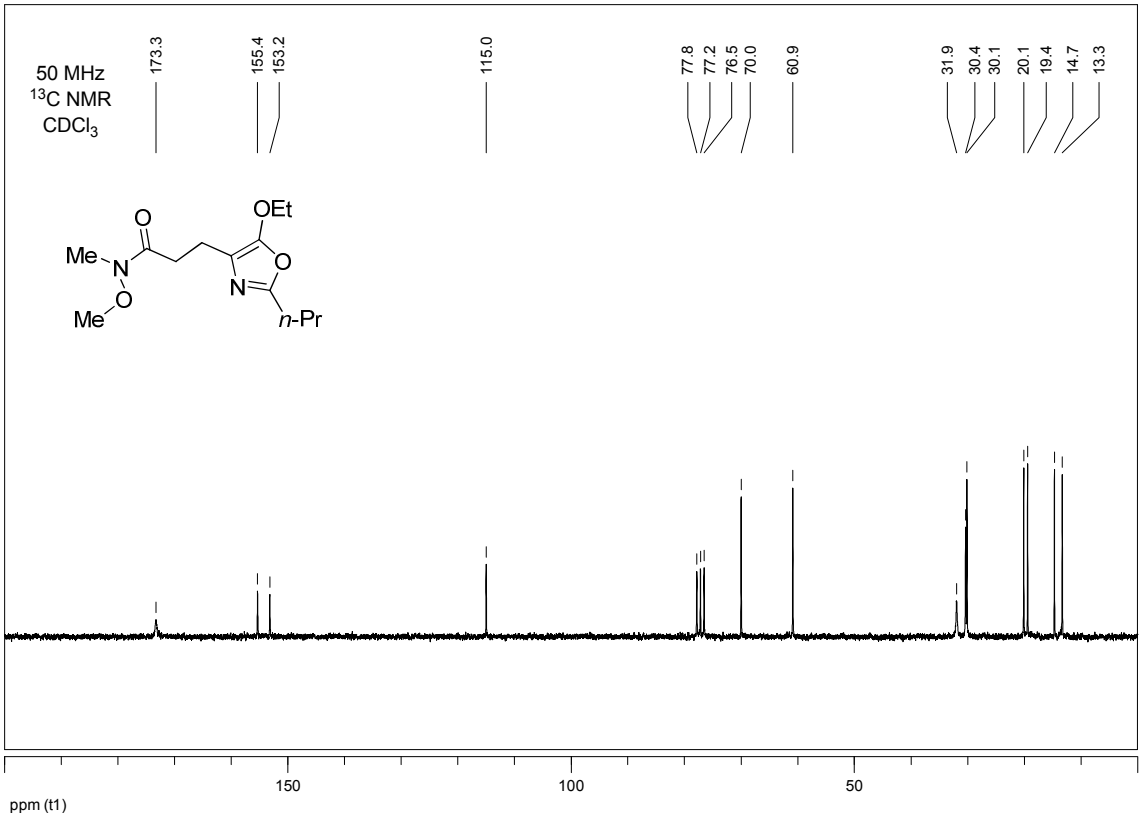
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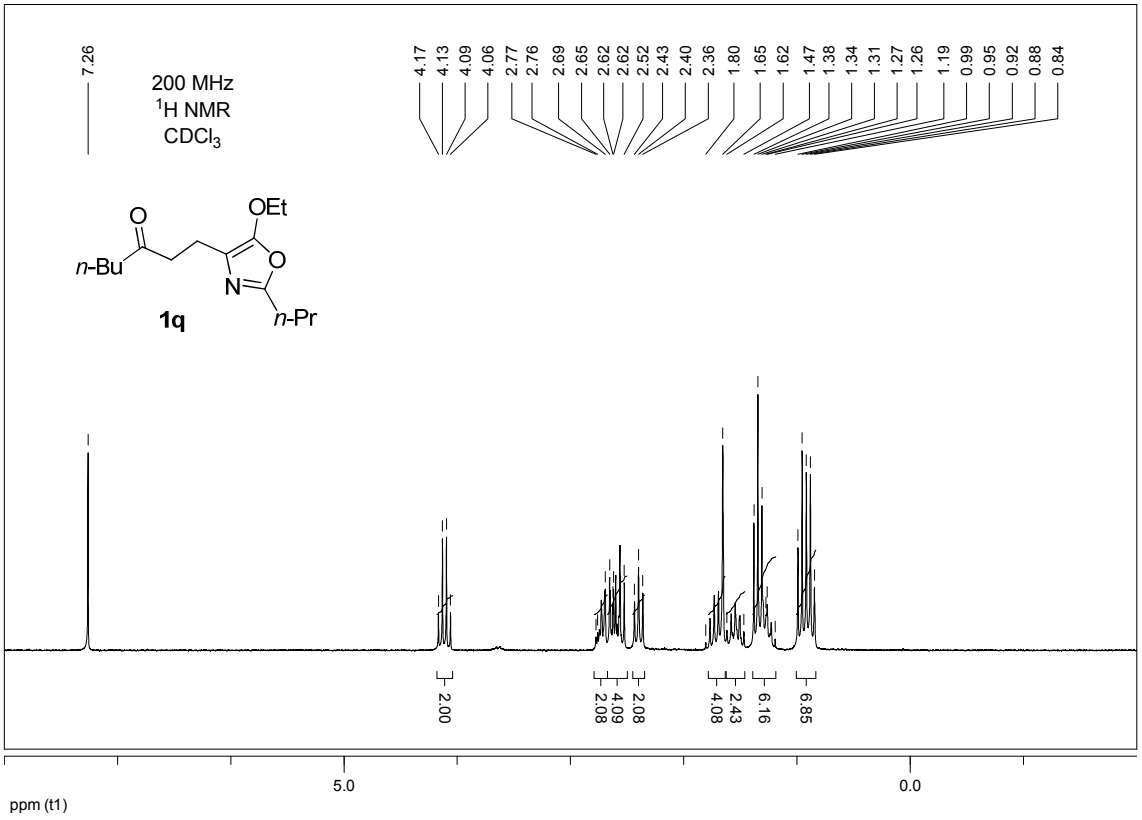
173.3
155.4
153.2
115.0
77.8
77.2
76.5
70.0
60.9
31.9
30.4
30.1
20.1
19.4
14.7
13.3
OEt
O
Me
N
O
Me
O
N
n-Pr
150
100
50
ppm (t1)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4.13
4.09
4.06
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2.76
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2.65
2.62
2.62
2.52
2.43
2.40
2.36
1.80
1.65
1.62
1.47
1.38
1.34
1.31
1.27
1.26
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0.99
0.95
0.92
0.88
0.84
OEt
O
n-Bu
N
O
n-Pr
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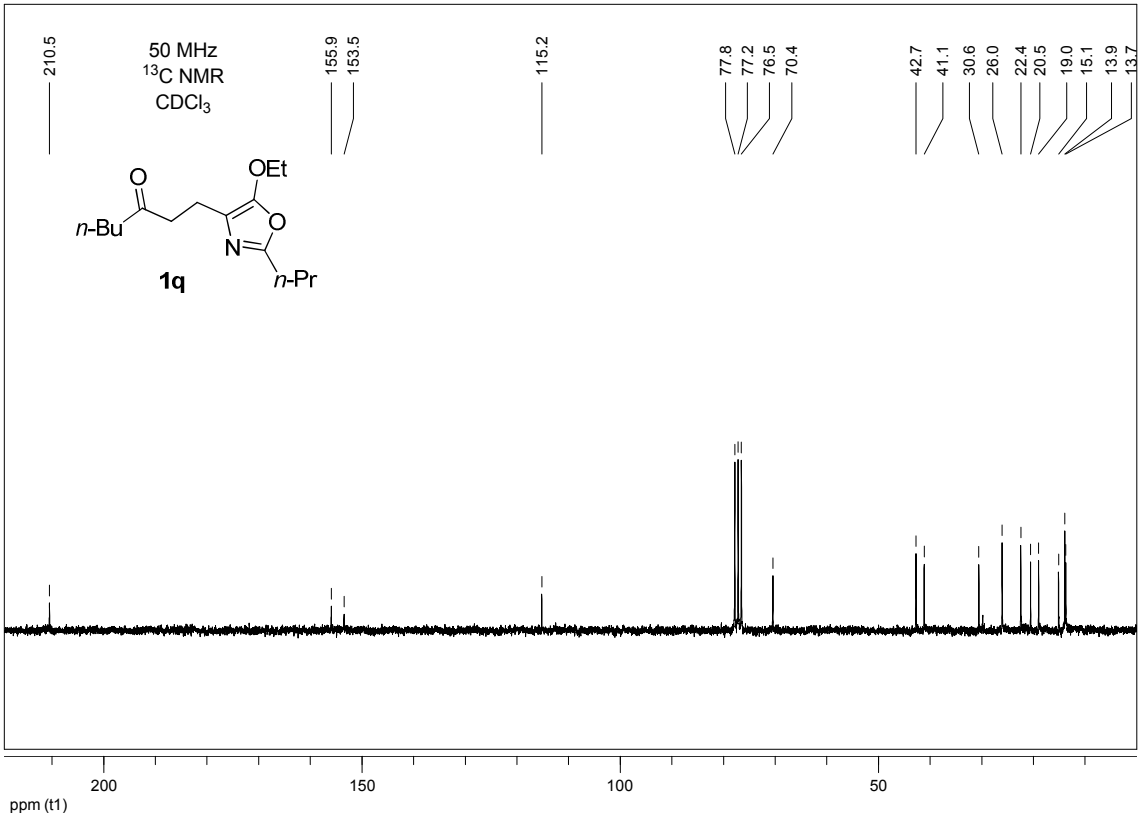
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77.2
76.5
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41.1
30.6
26.0
22.4
20.5
19.0
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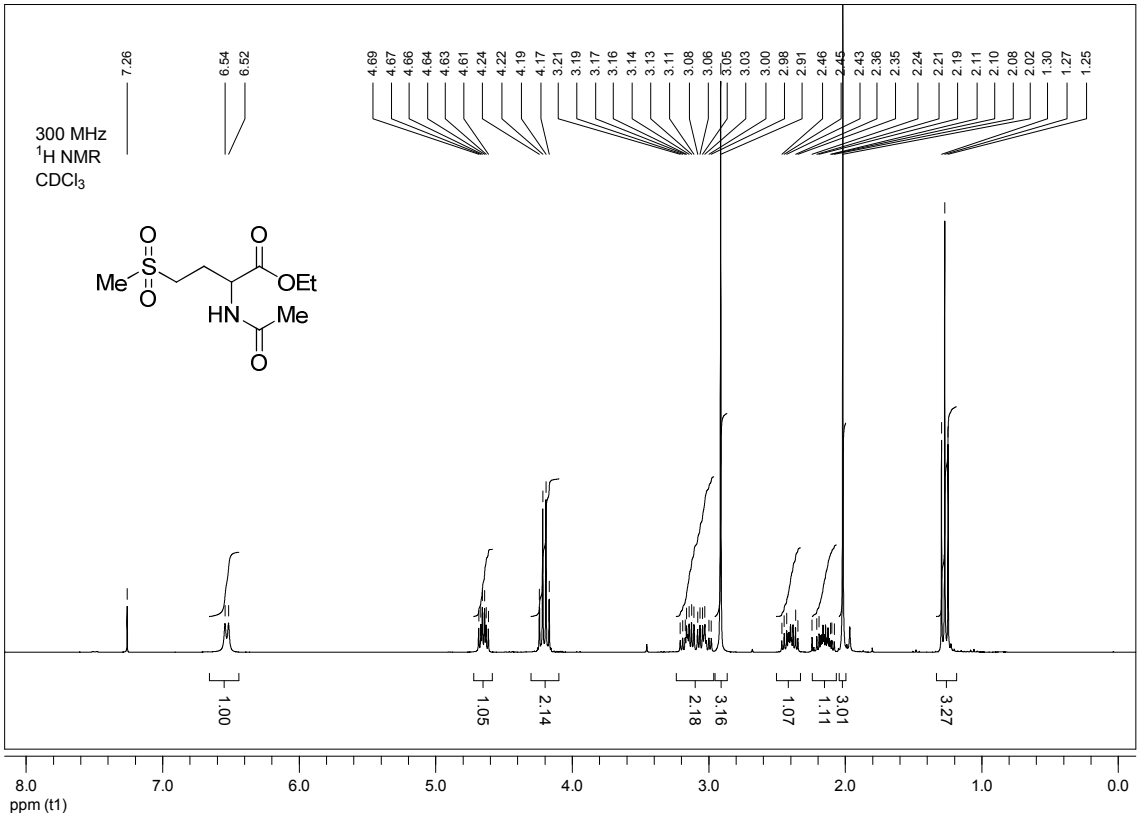
ppm (t1)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4.66
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4.63
4.61
4.24
4.22
4.19
4.17
3.21
3.19
3.17
3.16
3.14
3.13
3.11
3.08
3.06
3.05
3.03
3.00
2.98
2.91
2.46
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2.43
2.36
2.35
2.24
2.21
2.19
2.11
2.10
2.08
2.02
1.30
1.27
1.25
1.00
1.05
2.14
2.18
3.16
1.07
1.11
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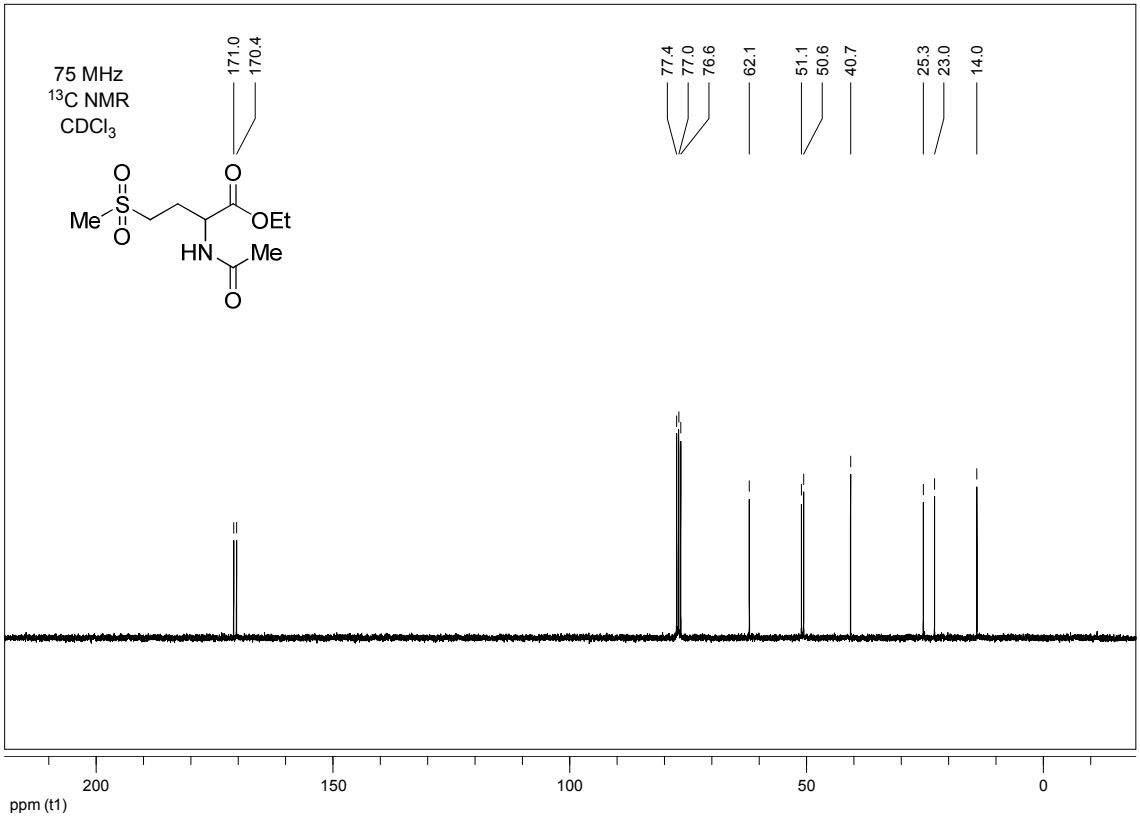
ppm (t1)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170.4
77.4
77.0
76.6
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50.6
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25.3
23.0
14.0
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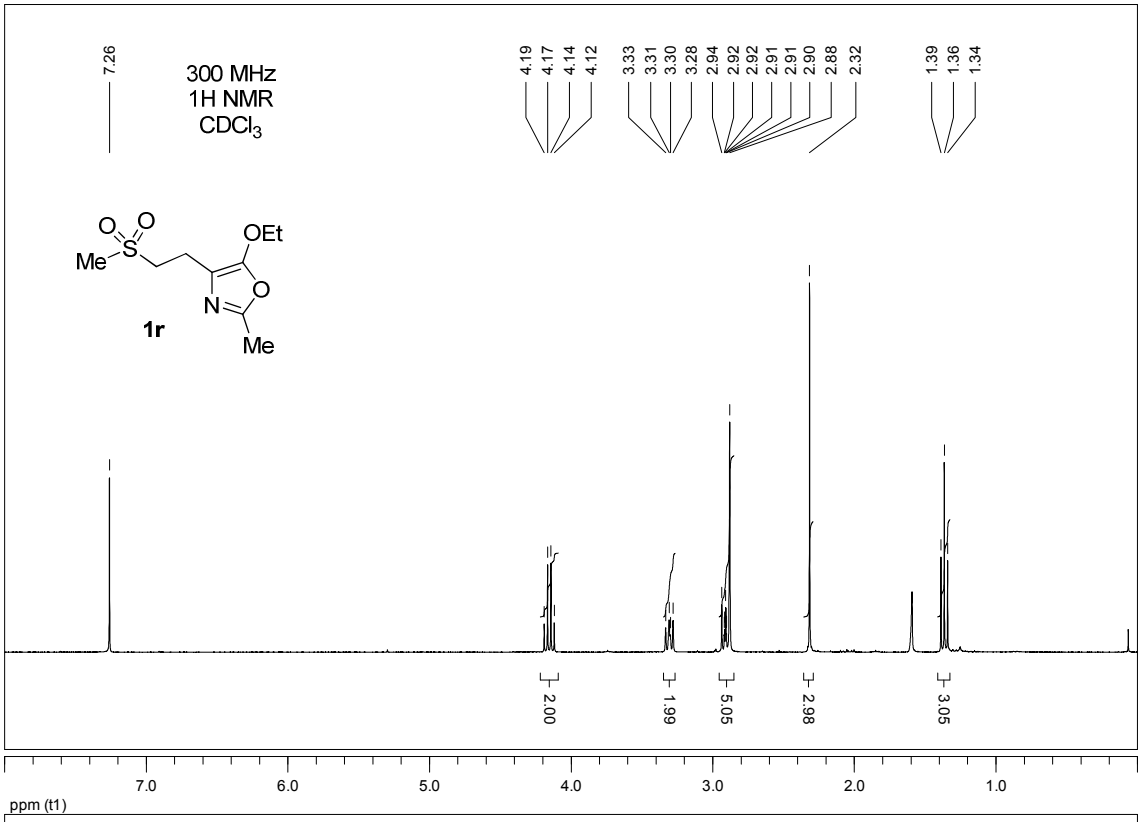
ppm (t1)


7.26
300 MHz
1H NMR
CDCl3
4.19
4.17
4.14
4.12
3.33
3.31
3.30
3.28
2.94
2.92
2.92
2.91
2.91
2.90
2.88
2.32
1.39
1.36
1.34
Me
O
O
S
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N
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1r
2.00
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7.0
6.0
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3.0
2.0
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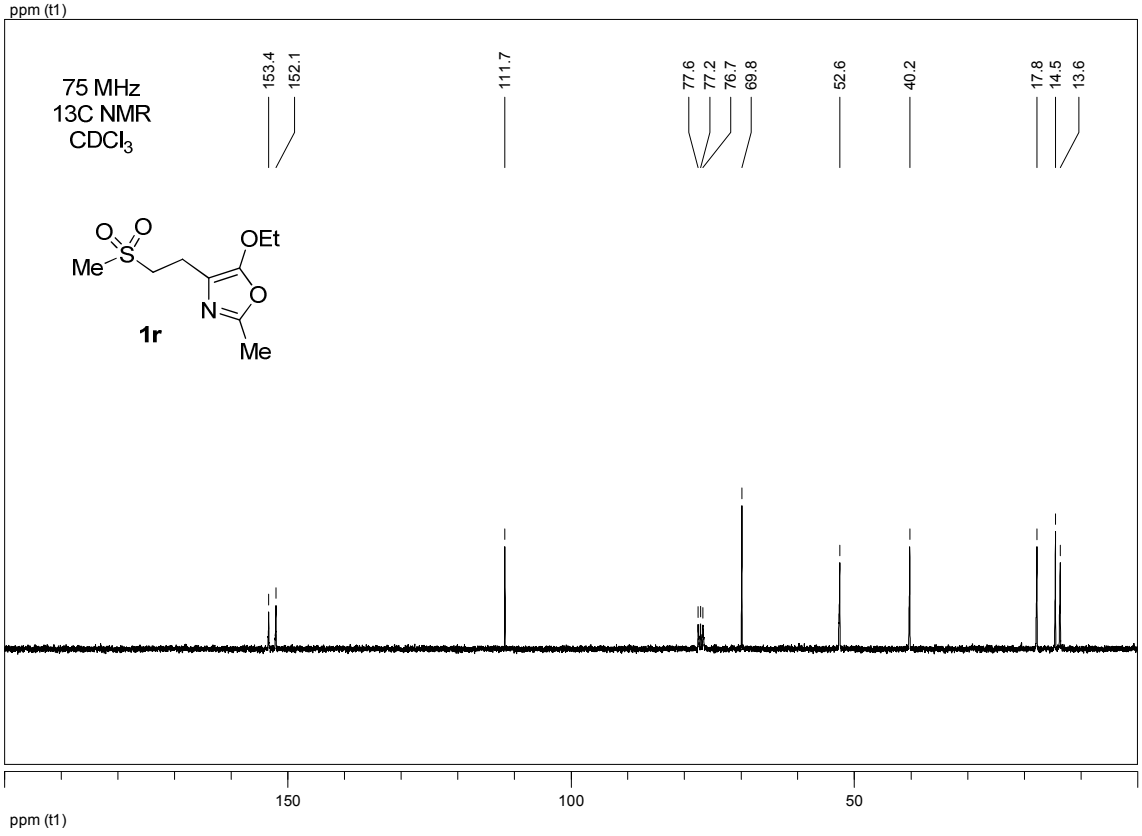
ppm (t1)


75 MHz
13C NMR
CDCl3
153.4
152.1
111.7
77.6
77.2
76.7
69.8
52.6
40.2
17.8
14.5
13.6
Me
O
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S
OEt
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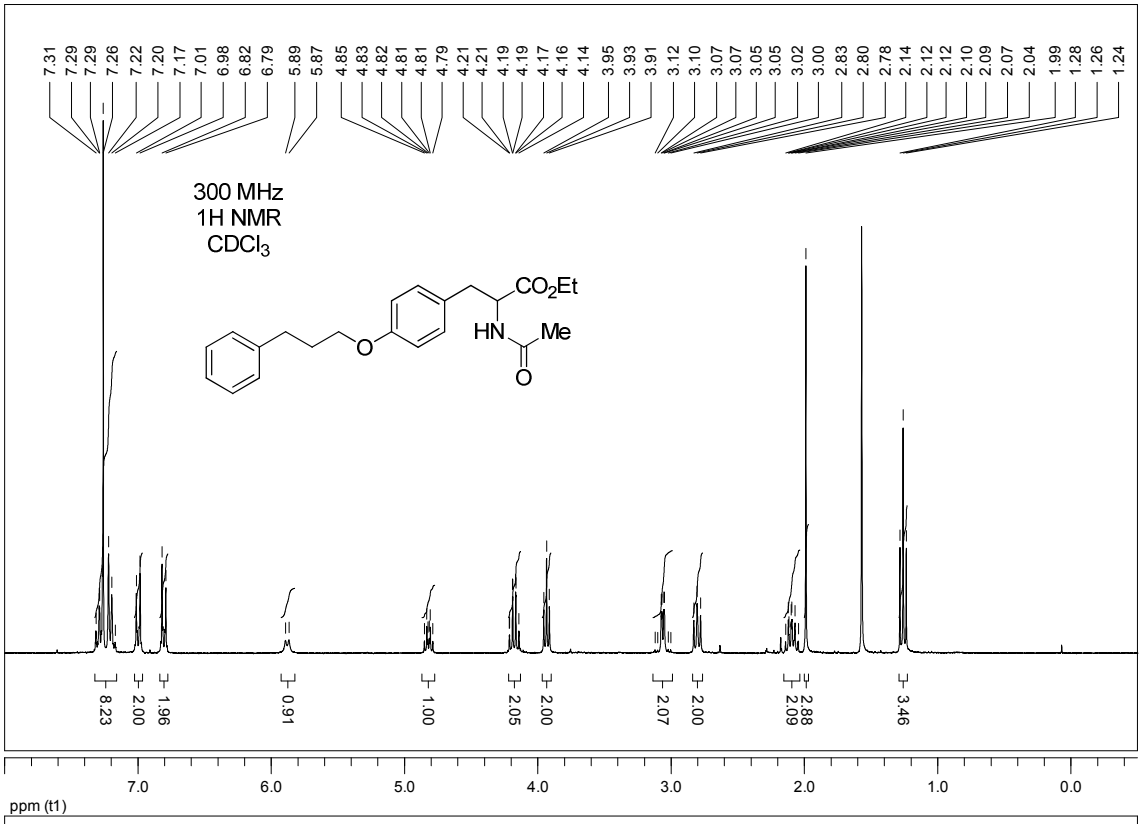
O
Me
1r
150
100
50
ppm (t1)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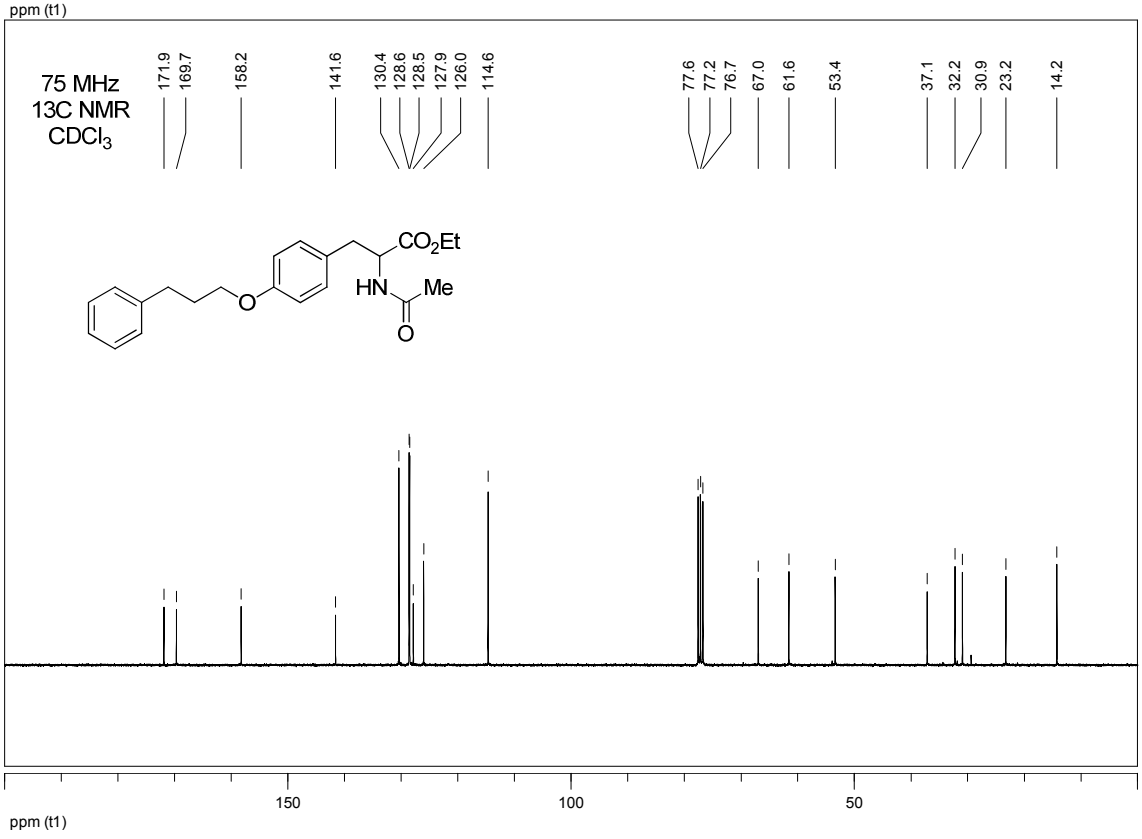
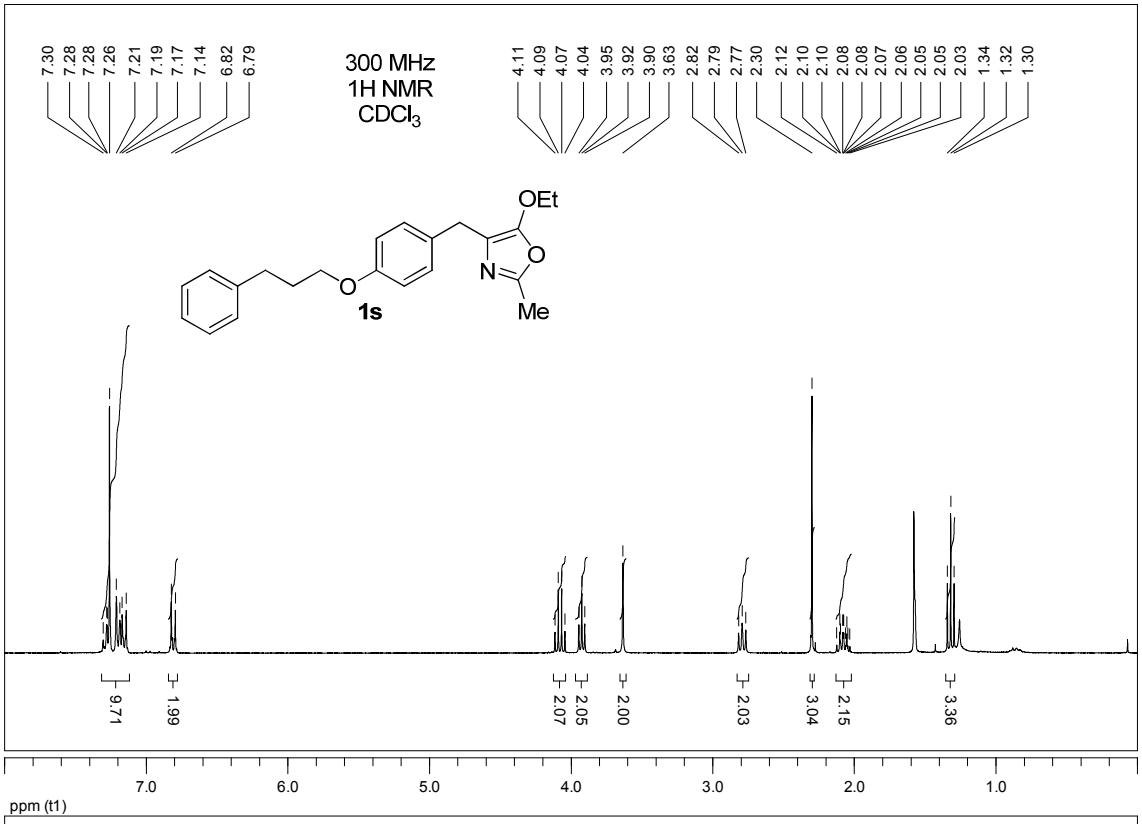
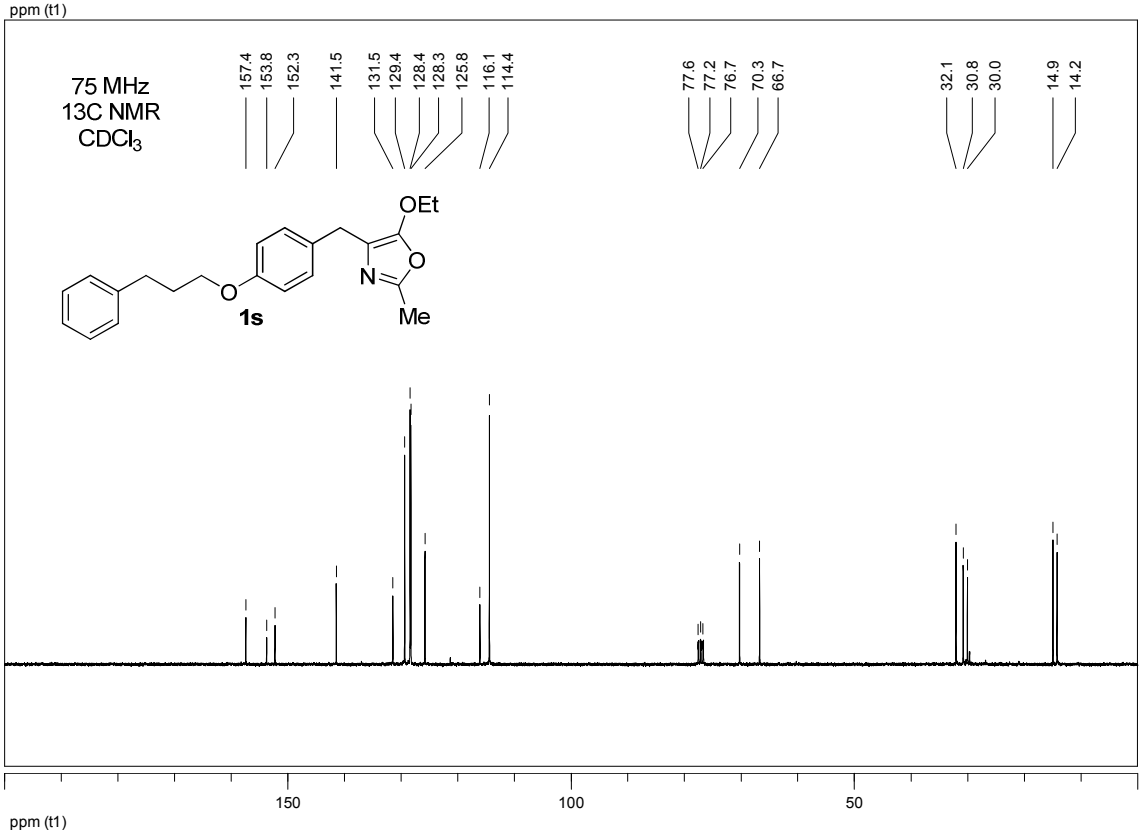
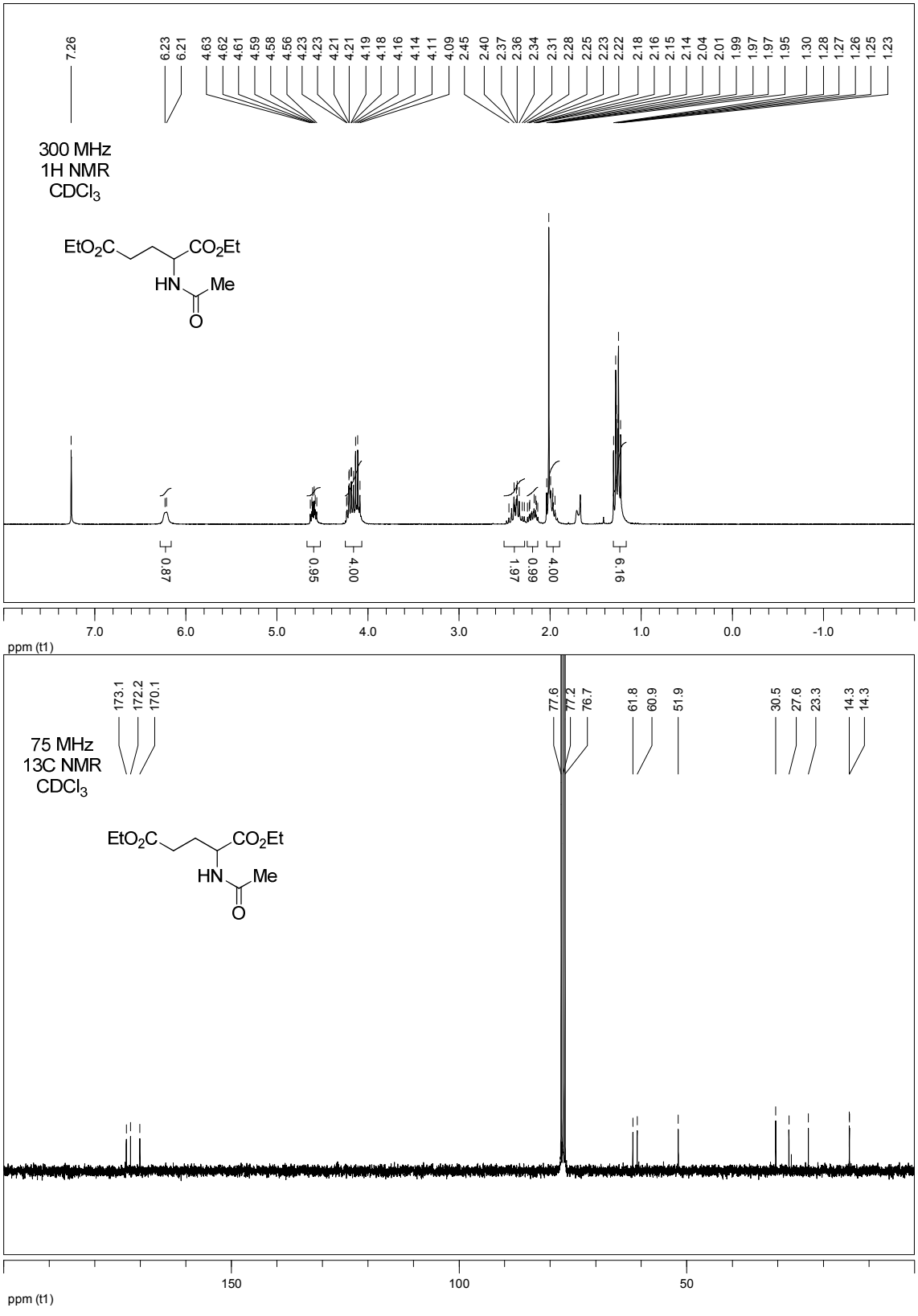
300 MHz
1H NMR
CDCl3
CO2Et
HN
Me
O
O
8.23 2.00 1.96 0.91 1.00 2.05 2.00 2.07 2.00 2.09 3.46
7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (t1)


75 MHz
13C NMR
CDCl3
171.9 169.7 158.2 141.6 130.4 128.6 128.5 127.9 126.0 114.6 77.6 77.2 76.7 67.0 61.6 53.4 37.1 32.2 30.9 23.2 14.2
CO2Et
HN
Me
O
O
150 100 50
ppm (t1)


7.30
7.28
7.28
7.26
7.21
7.19
7.17
7.14
6.82
6.79
300 MHz
1H NMR
CDCl3
4.11
4.09
4.07
4.04
3.95
3.92
3.90
3.63
2.82
2.79
2.77
2.30
2.12
2.10
2.10
2.08
2.08
2.07
2.06
2.05
2.05
2.03
1.34
1.32
1.30
OEt
O
N
O
Me
1s
9.71
1.99
2.07
2.05
2.00
2.03
3.04
2.15
3.36
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
157.4
153.8
152.3
141.5
131.5
129.4
128.4
128.3
125.8
116.1
114.4
77.6
77.2
76.7
70.3
66.7
32.1
30.8
30.0
14.9
14.2
OEt
O
N
O
Me
1s
150
100
50
ppm (t1)


7.26
6.23
6.21
4.63
4.62
4.61
4.59
4.58
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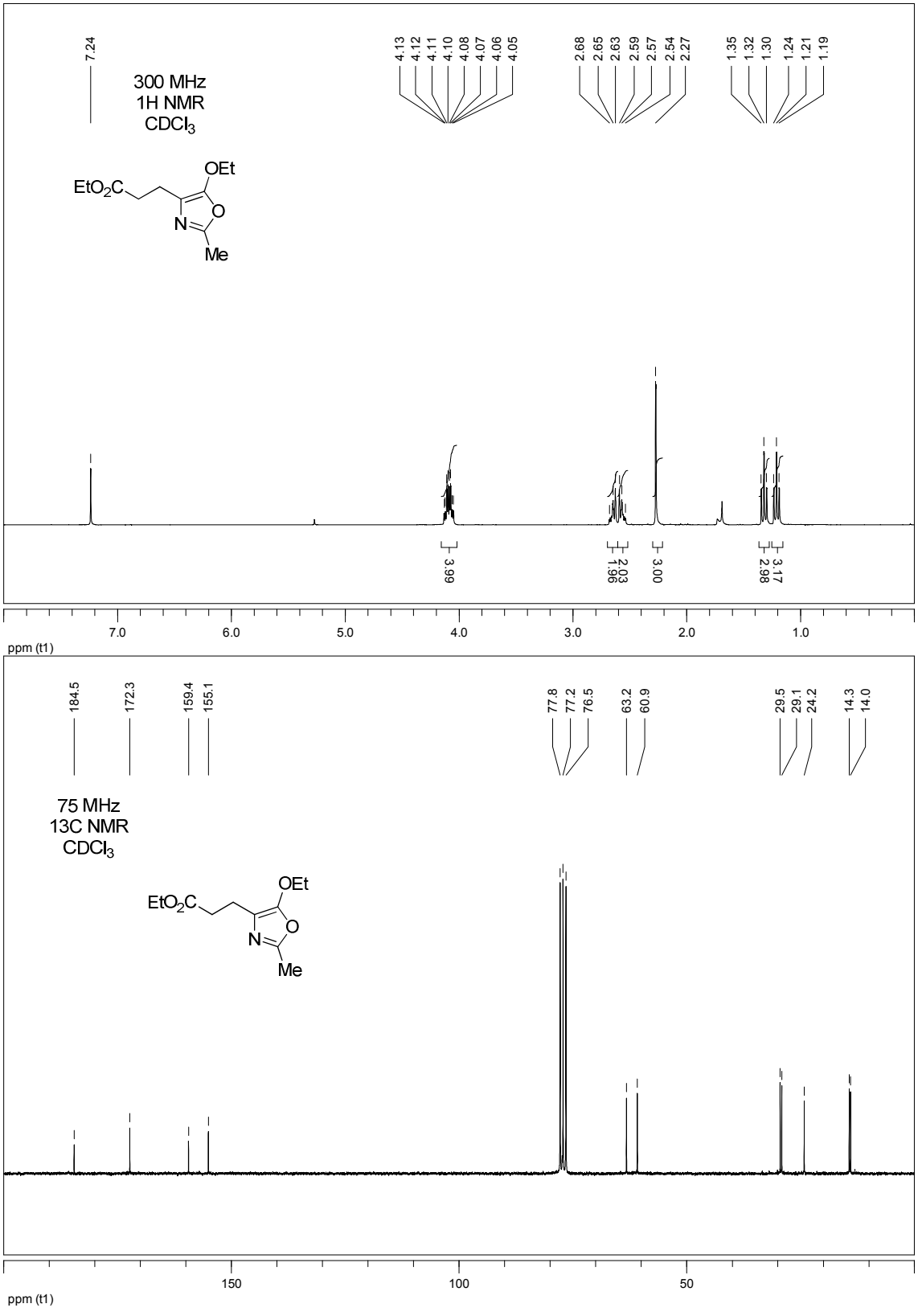
4.23
4.23
4.21
4.21
4.19
4.18
4.16
4.14
4.11
4.09
2.45
2.40
2.37
2.36
2.34
2.31
2.28
2.25
2.23
2.22
2.18
2.16
2.15
2.14
2.04
2.01
1.99
1.97
1.97
1.95
1.30
1.28
1.27
1.26
1.25
1.23
300 MHz
1H NMR
CDCl3
EtO2C
CO2Et
HN
Me
O
0.87
0.95
4.00
1.97
0.99
4.00
6.16
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm (t1)
173.1
172.2
170.1
77.6
77.2
76.7
61.8
60.9
51.9
30.5
27.6
23.3
14.3
14.3
75 MHz
13C NMR
CDCl3
EtO2C
CO2Et
HN
Me
O
150
100
50
ppm (t1)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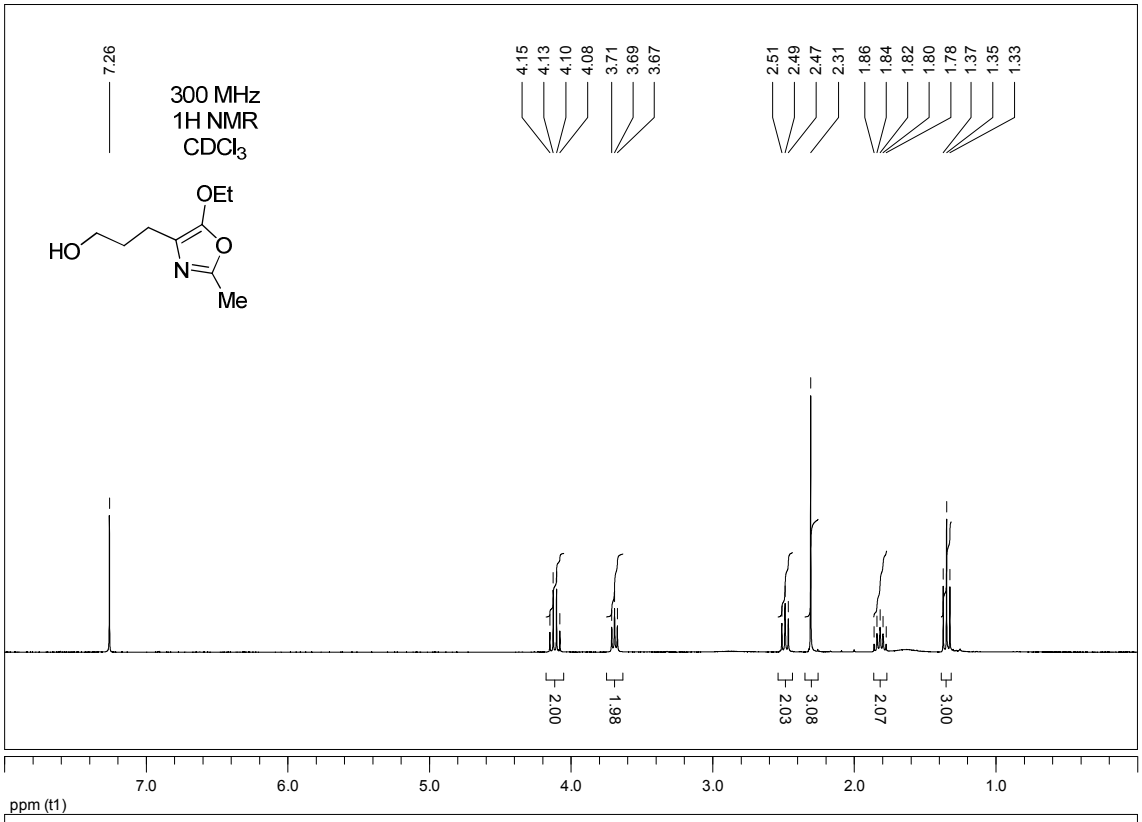
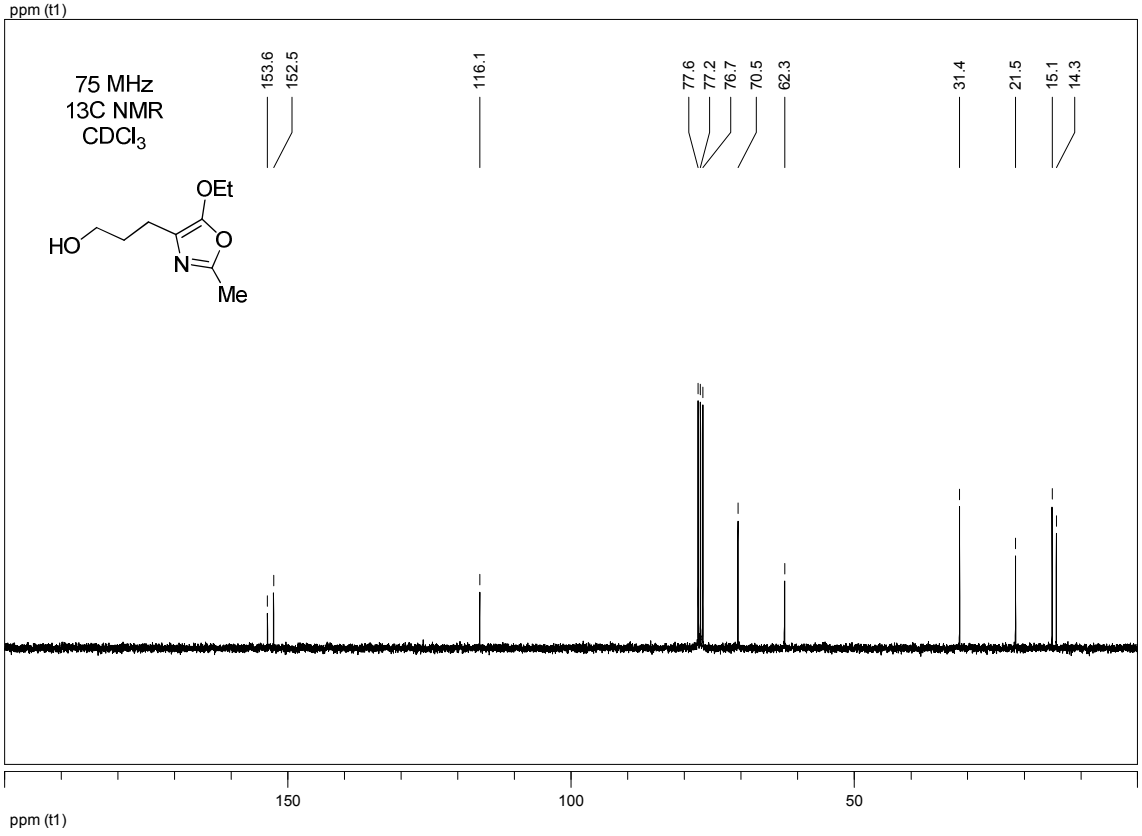
4.13
4.12
4.11
4.10
4.08
4.07
4.06
4.05
2.68
2.65
2.63
2.59
2.57
2.54
2.27
1.35
1.32
1.30
1.24
1.21
1.19
300 MHz
1H NMR
CDCl3
EtO2C
OEt
O
N
Me
3.99
2.03
1.96
3.00
2.98
3.17
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)
184.5
172.3
159.4
155.1
77.8
77.2
76.5
63.2
60.9
29.5
29.1
24.2
14.3
14.0
75 MHz
13C NMR
CDCl3
150
100
50
ppm (t1)


7.26
300 MHz
1H NMR
CDCl3
4.15
4.13
4.10
4.08
3.71
3.69
3.67
2.51
2.49
2.47
2.31
1.86
1.84
1.82
1.80
1.78
1.37
1.35
1.33
OEt
HO
O
N
Me
2.00
1.98
2.03
3.08
2.07
3.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
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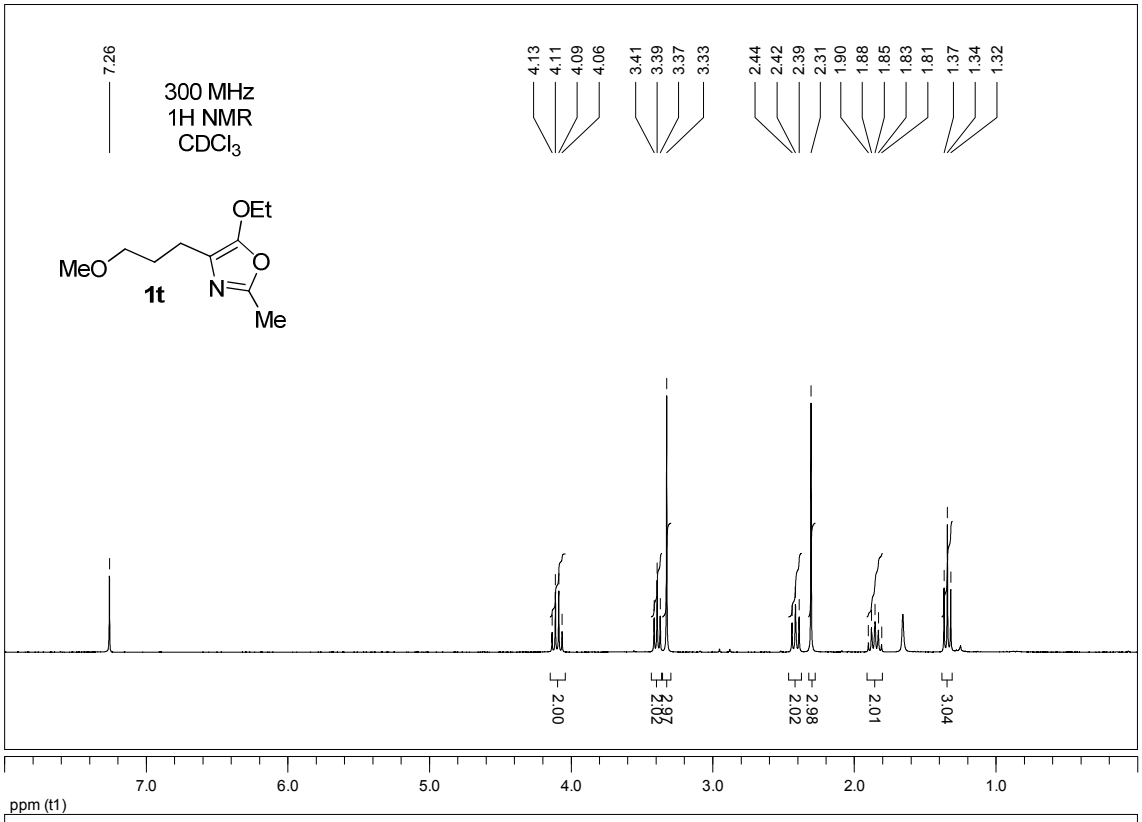
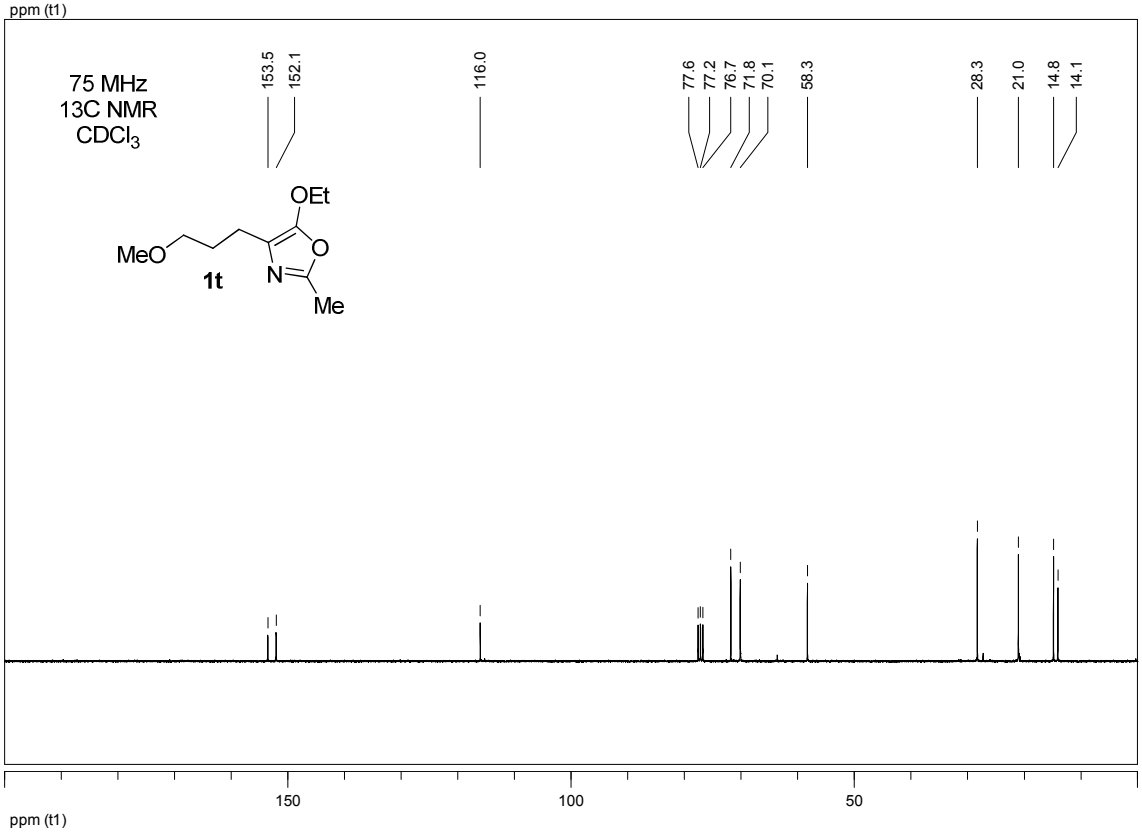
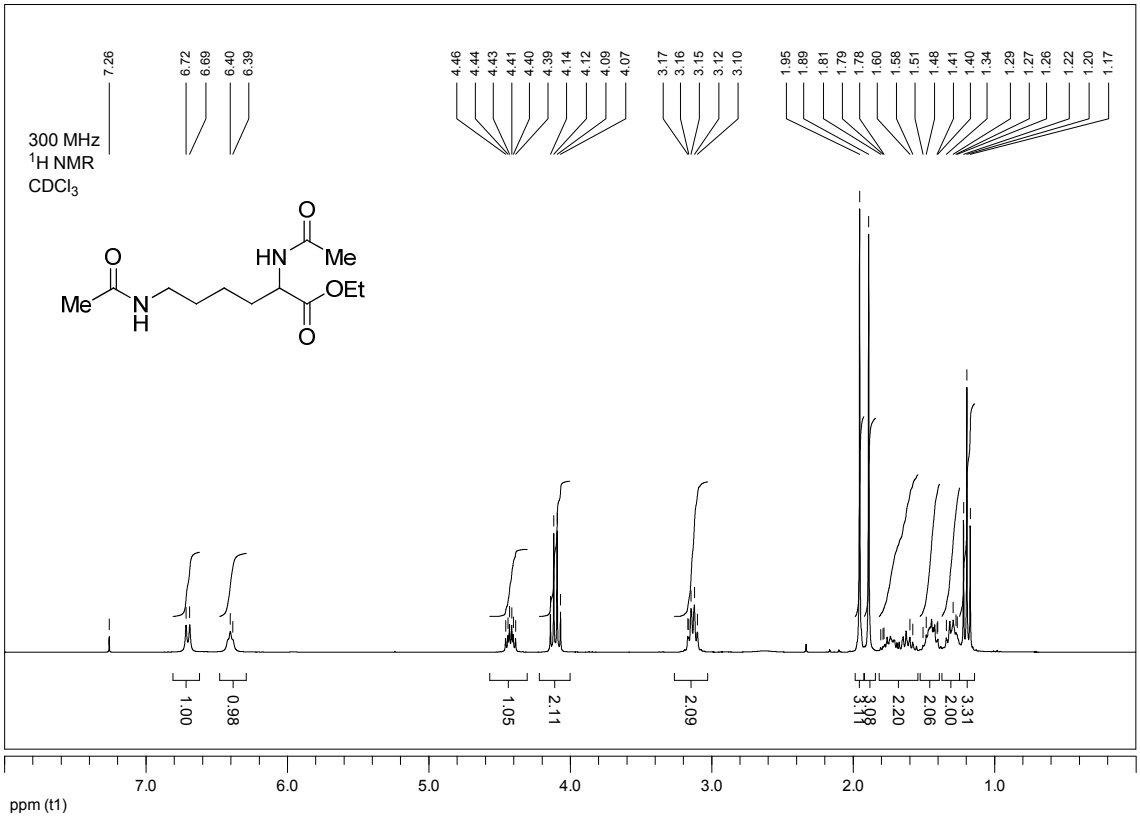
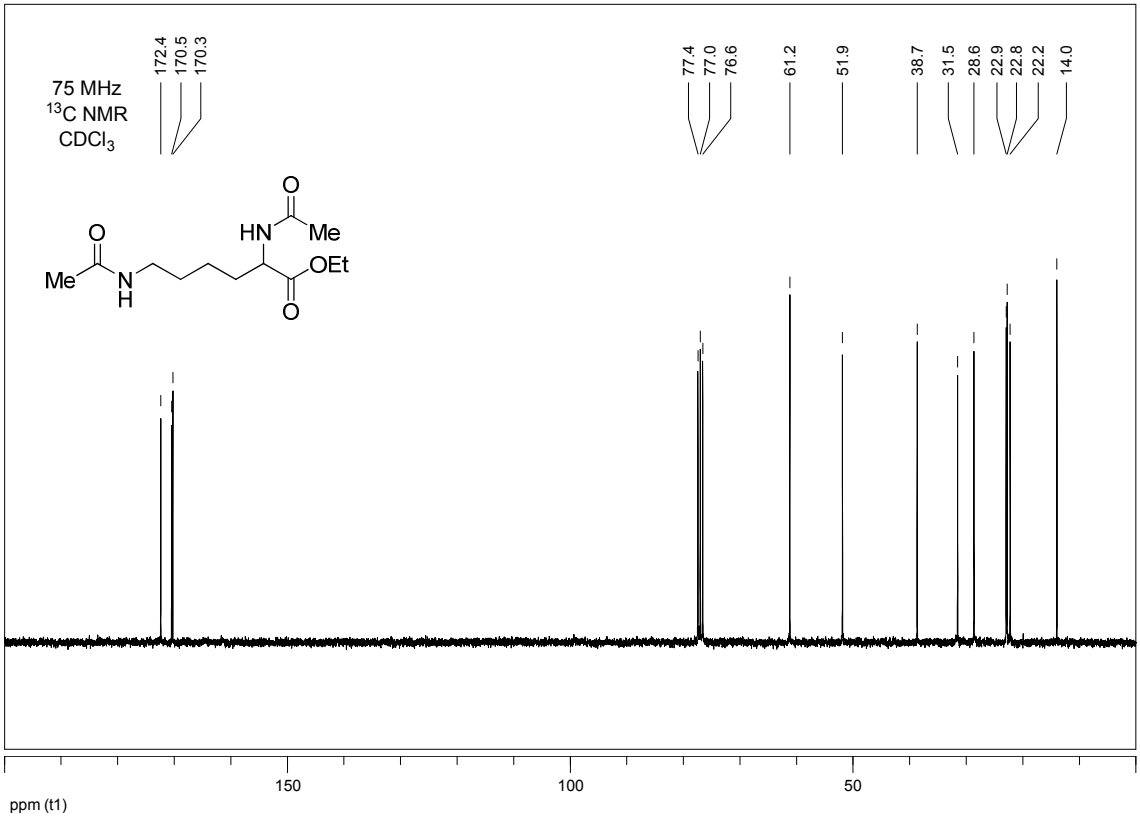
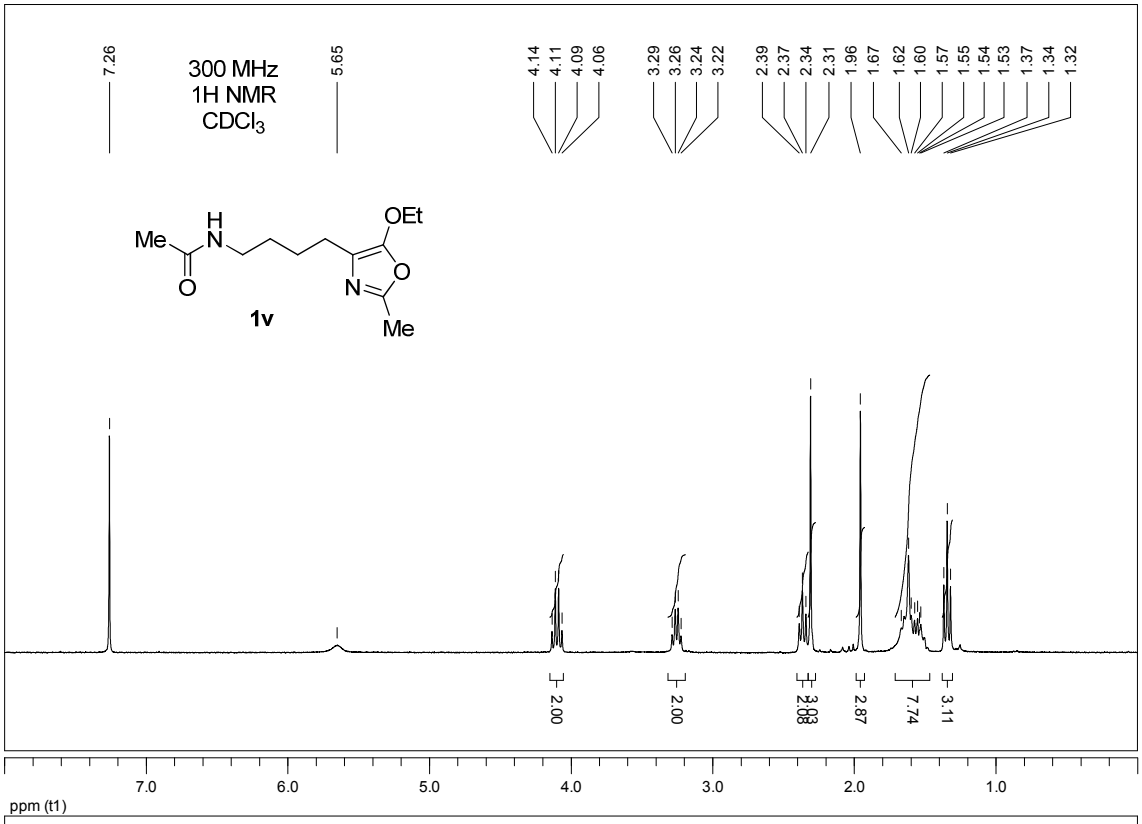
152.5
116.1
77.6
77.2
76.7
70.5
62.3
31.4
21.5
15.1
14.3
OEt
HO
O
N
Me
150
100
50
ppm (t1)

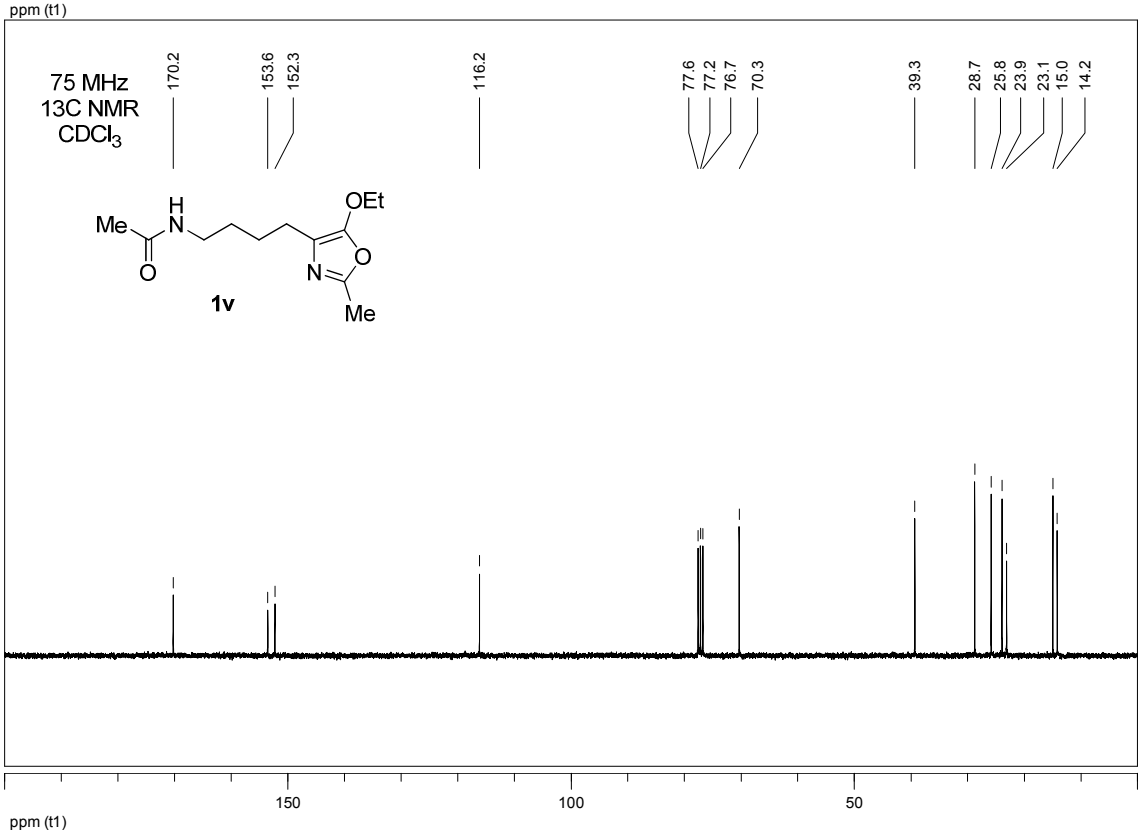

7.26
300 MHz
1H NMR
CDCl3
4.13
4.11
4.09
4.06
3.41
3.39
3.37
3.33
2.44
2.42
2.39
2.31
1.90
1.88
1.85
1.83
1.81
1.37
1.34
1.32
OEt
MeO
O
N
Me
1t
2.00
2.87
2.02
2.98
2.01
3.04
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

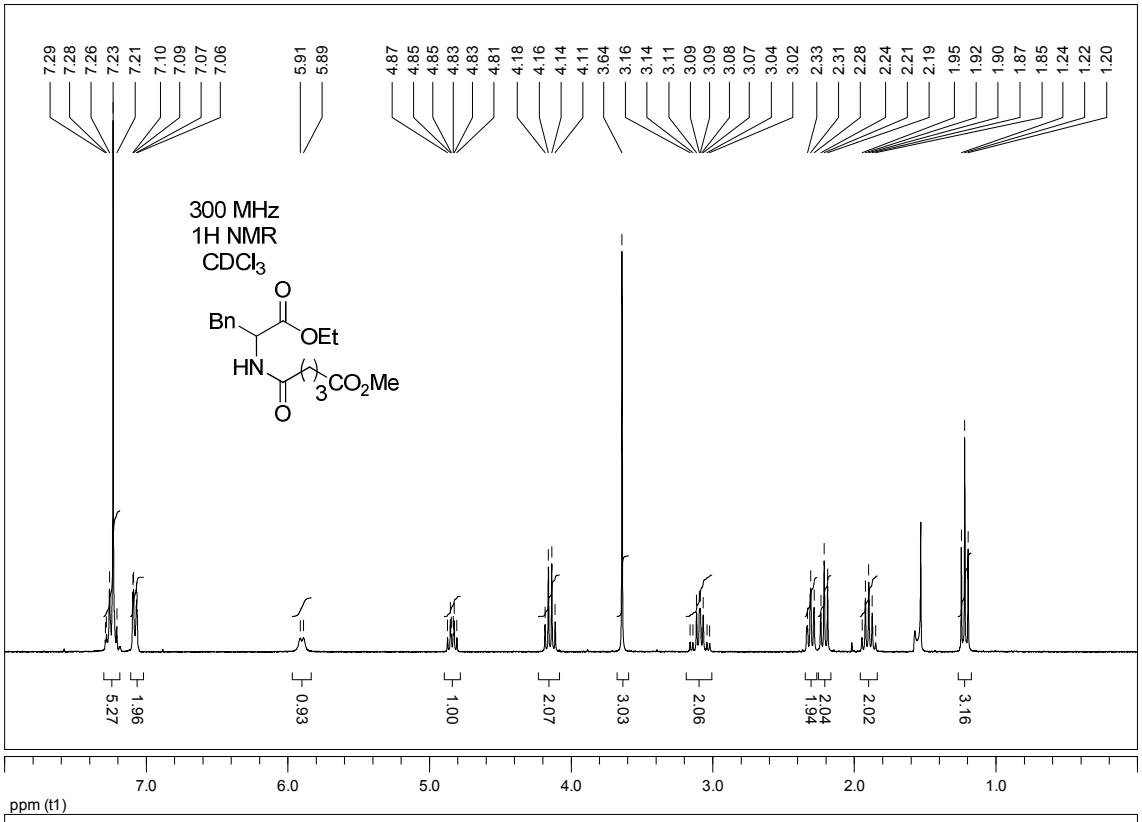

75 MHz
13C NMR
CDCl3
153.5
152.1
116.0
77.6
77.2
76.7
71.8
70.1
58.3
28.3
21.0
14.8
14.1
OEt
MeO
O
N
Me
1t
150
100
50
ppm (t1)

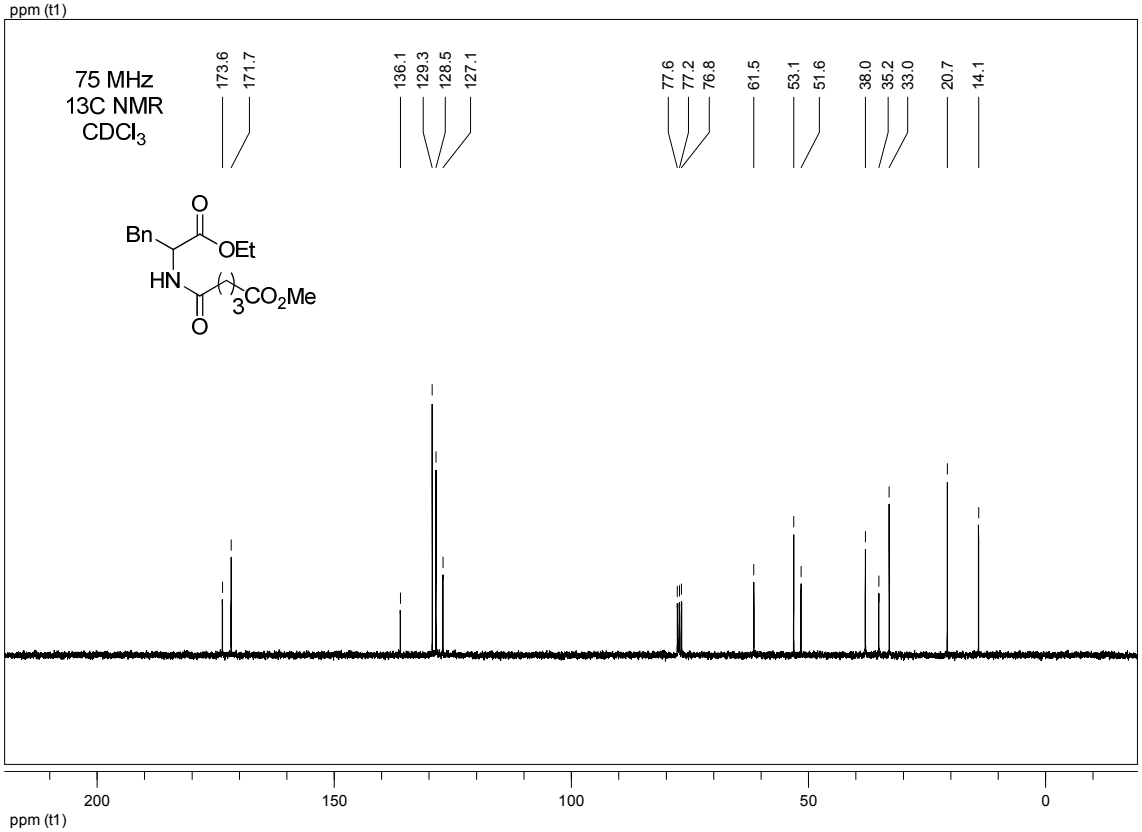

7.26
6.72
6.69
6.40
6.39
4.46
4.44
4.43
4.41
4.40
4.39
4.14
4.12
4.09
4.07
3.17
3.16
3.15
3.12
3.10
1.95
1.89
1.81
1.79
1.78
1.60
1.58
1.51
1.48
1.41
1.40
1.34
1.29
1.27
1.26
1.22
1.20
1.17
300 MHz
1H NMR
CDCl3
O
HN
Me
O
Me
N
H
OEt
O
1.00
0.98
1.05
2.11
2.09
3.08
3.11
2.20
2.06
2.00
3.31
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

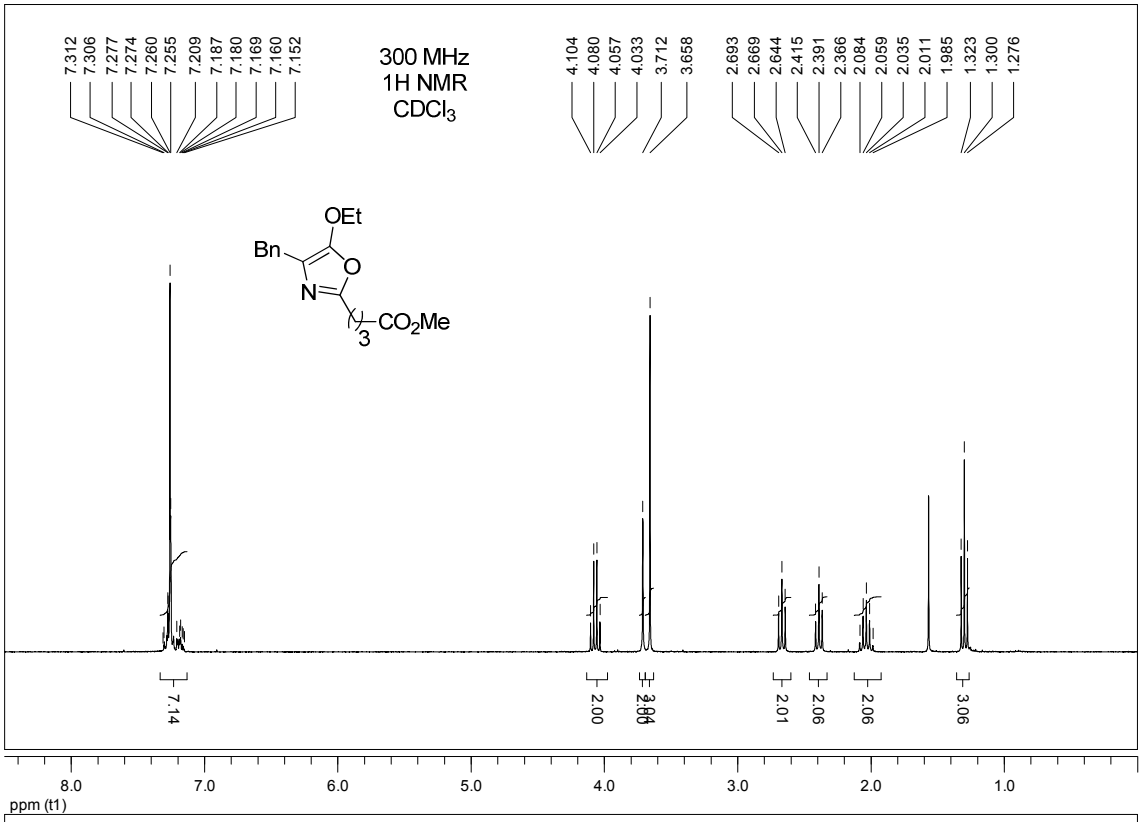

172.4
170.5
170.3
77.4
77.0
76.6
61.2
51.9
38.7
31.5
28.6
22.9
22.8
22.2
14.0
75 MHz
13C NMR
CDCl3
O
HN
Me
O
Me
N
H
OEt
O
150
100
50
ppm (t1)


300 MHz
1H NMR
CDCl3
7.26
5.65
4.14
4.11
4.09
4.06
3.29
3.26
3.24
3.22
2.39
2.37
2.34
2.31
1.96
1.67
1.62
1.60
1.57
1.55
1.54
1.53
1.37
1.34
1.32
Me
H
N
O
OEt
O
N
Me
1v
2.00
2.00
3.08
2.87
7.74
3.11
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
170.2
153.6
152.3
116.2
77.6
77.2
76.7
70.3
39.3
28.7
25.8
23.9
23.1
15.0
14.2
Me
H
N
O
OEt
O
N
Me
1v
150
100
50
ppm (t1)


7.29
7.28
7.26
7.23
7.21
7.10
7.09
7.07
7.06
5.91
5.89
4.87
4.85
4.85
4.83
4.83
4.81
4.18
4.16
4.14
4.11
3.64
3.16
3.14
3.11
3.09
3.09
3.08
3.07
3.04
3.02
2.33
2.31
2.28
2.24
2.21
2.19
1.95
1.92
1.90
1.87
1.85
1.24
1.22
1.20
300 MHz
1H NMR
CDCl3
Bn
OEt
HN
3
CO2Me
O
5.27
1.96
0.93
1.00
2.07
3.03
2.06
1.94
2.04
2.02
3.16
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
173.6
171.7
136.1
129.3
128.5
127.1
77.6
77.2
76.8
61.5
53.1
51.6
38.0
35.2
33.0
20.7
14.1
Bn
OEt
HN
3
CO2Me
O
200
150
100
50
0
ppm (t1)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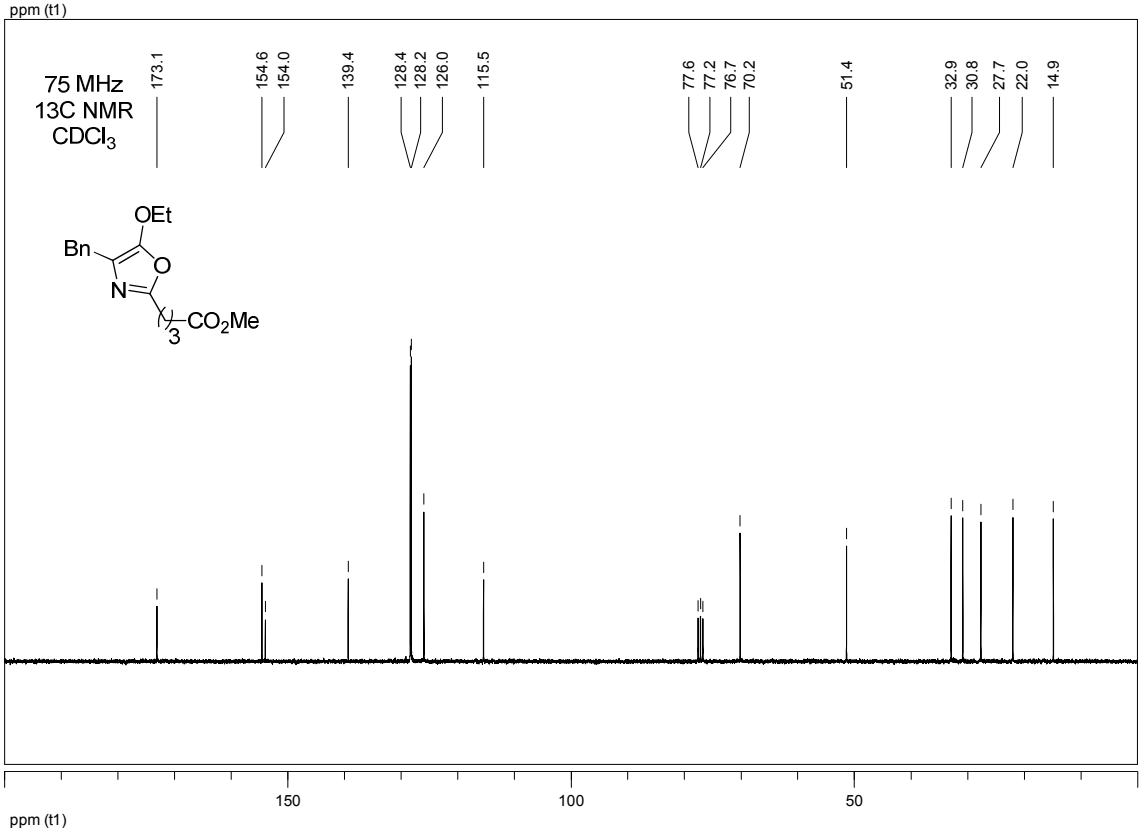
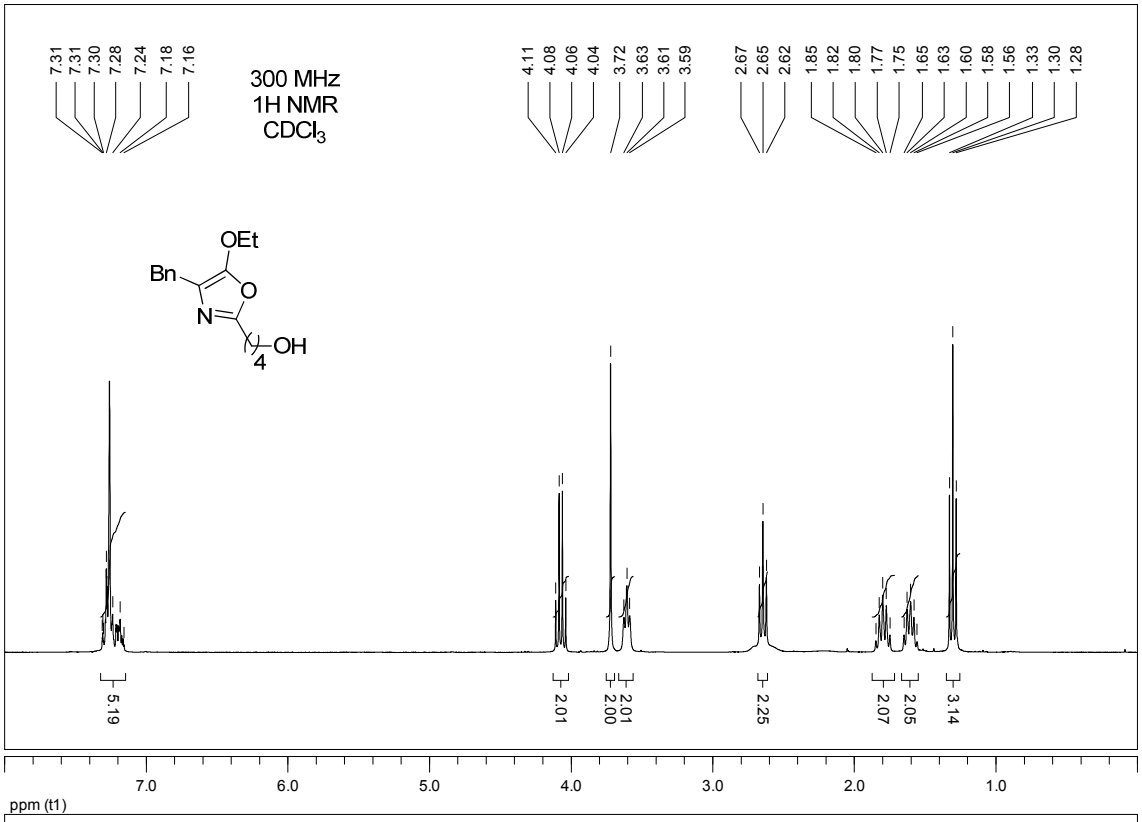
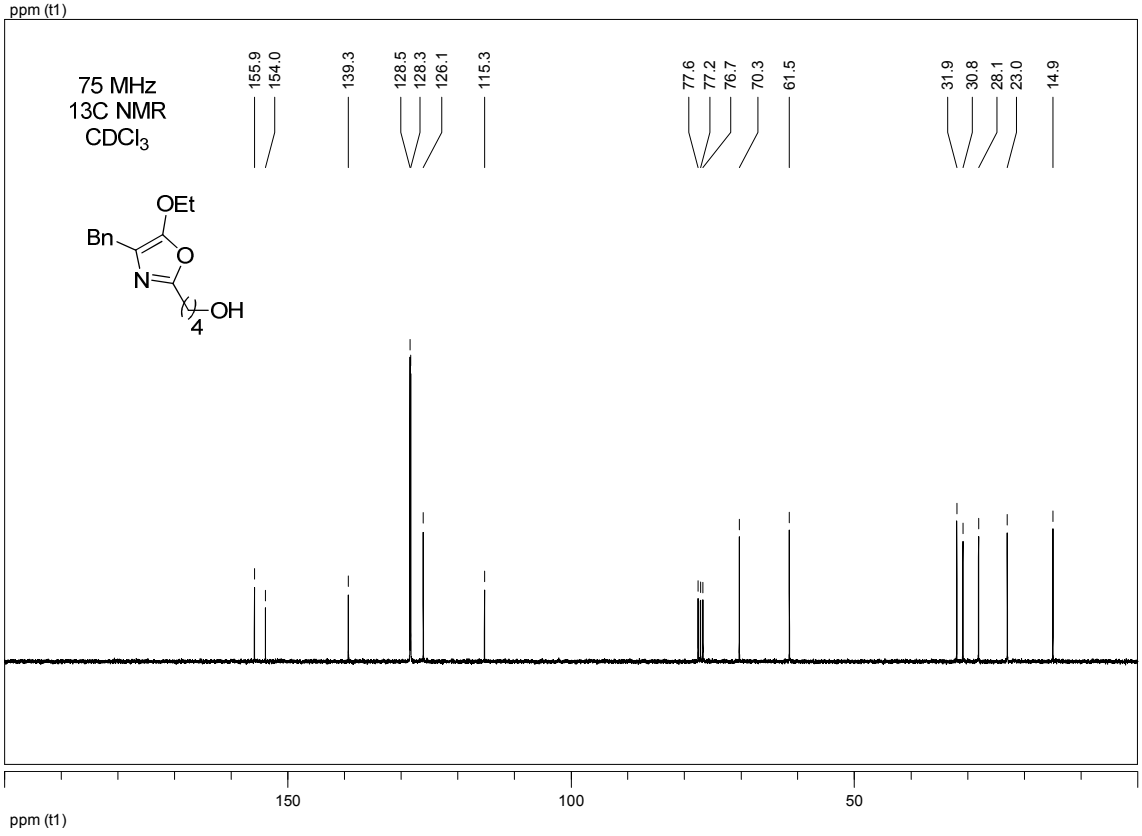
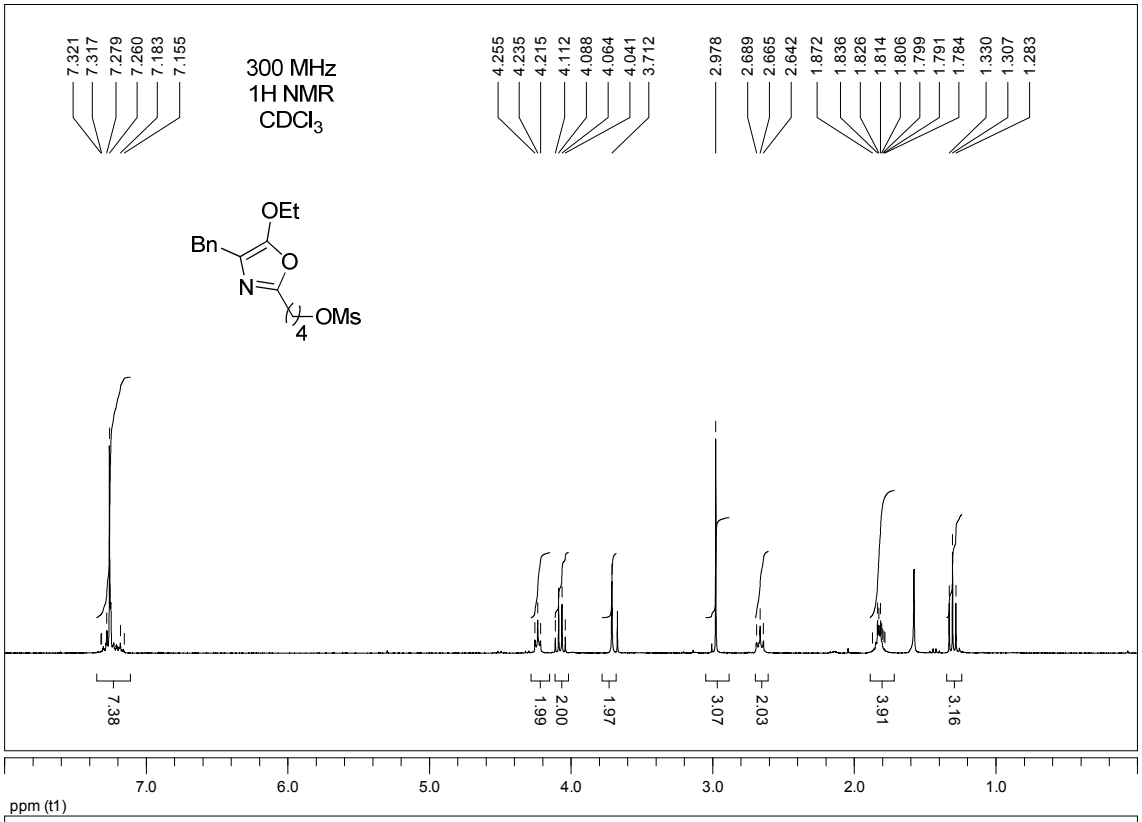
7.306
7.277
7.274
7.260
7.255
7.209
7.187
7.180
7.169
7.160
7.152
300 MHz
1H NMR
CDCl3
4.104
4.080
4.057
4.033
3.712
3.658
2.693
2.669
2.644
2.415
2.391
2.366
2.084
2.059
2.035
2.011
1.985
1.323
1.300
1.276
OEt
Bn
O
N
CO2Me
3
7.14
2.00
2.00
2.01
2.06
2.06
3.06
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
173.1
154.6
154.0
139.4
128.4
128.2
126.0
115.5
77.6
77.2
76.7
70.2
51.4
32.9
30.8
27.7
22.0
14.9
OEt
Bn
O
N
CO2Me
3
150
100
50
ppm (t1)


7.31
7.31
7.30
7.28
7.24
7.18
7.16
300 MHz
1H NMR
CDCl3
4.11
4.08
4.06
4.04
3.72
3.63
3.61
3.59
2.67
2.65
2.62
1.85
1.82
1.80
1.77
1.75
1.65
1.63
1.60
1.58
1.56
1.33
1.30
1.28
OEt
Bn
O
N
OH
4
5.19
2.01
2.00
2.01
2.25
2.07
2.05
3.14
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
155.9
154.0
139.3
128.5
128.3
126.1
115.3
77.6
77.2
76.7
70.3
61.5
31.9
30.8
28.1
23.0
14.9
OEt
Bn
O
N
OH
4
150
100
50
ppm (t1)


7.321
7.317
7.279
7.260
7.183
7.155
300 MHz
1H NMR
CDCl3
4.255
4.235
4.215
4.112
4.088
4.064
4.041
3.712
2.978
2.689
2.665
2.642
1.872
1.836
1.826
1.814
1.806
1.799
1.791
1.784
1.330
1.307
1.283
OEt
Bn
O
N
OMs
4
7.38
1.99
2.00
1.97
3.07
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3.16
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6.0
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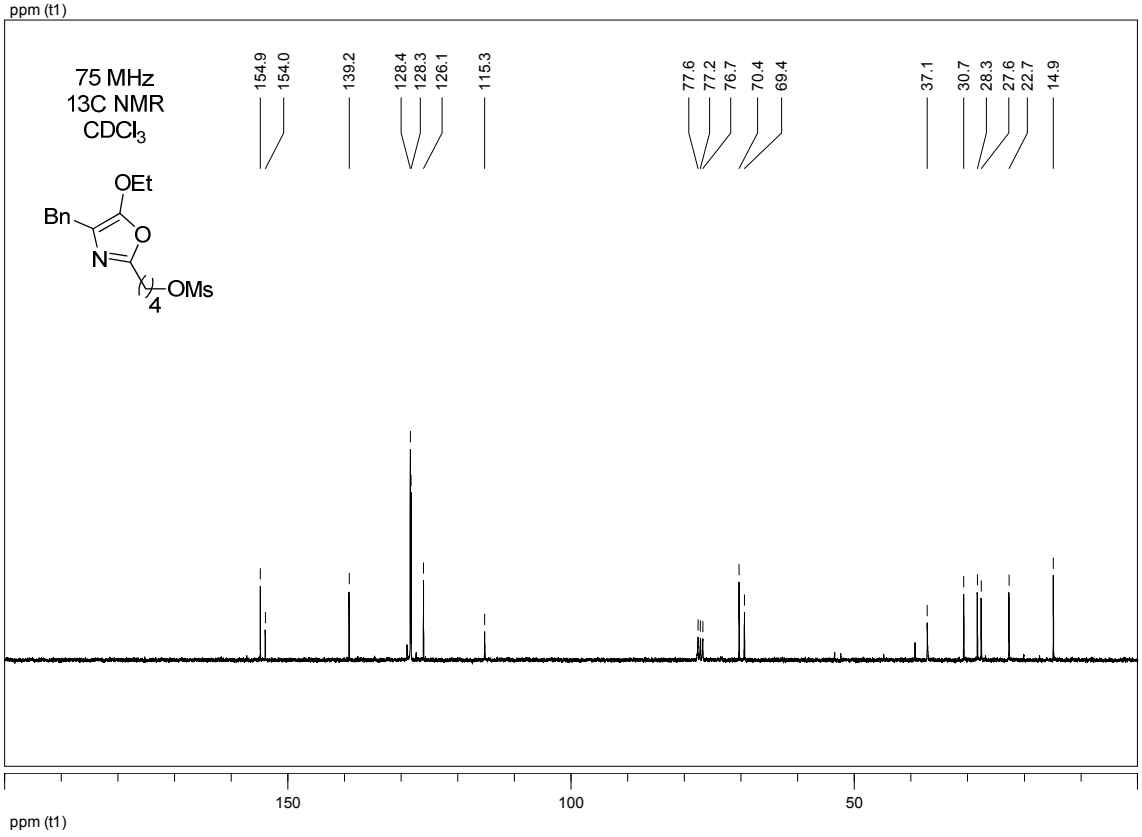
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
13C NMR
CDCl3
154.9
154.0
139.2
128.4
128.3
126.1
115.3
77.6
77.2
76.7
70.4
69.4
37.1
30.7
28.3
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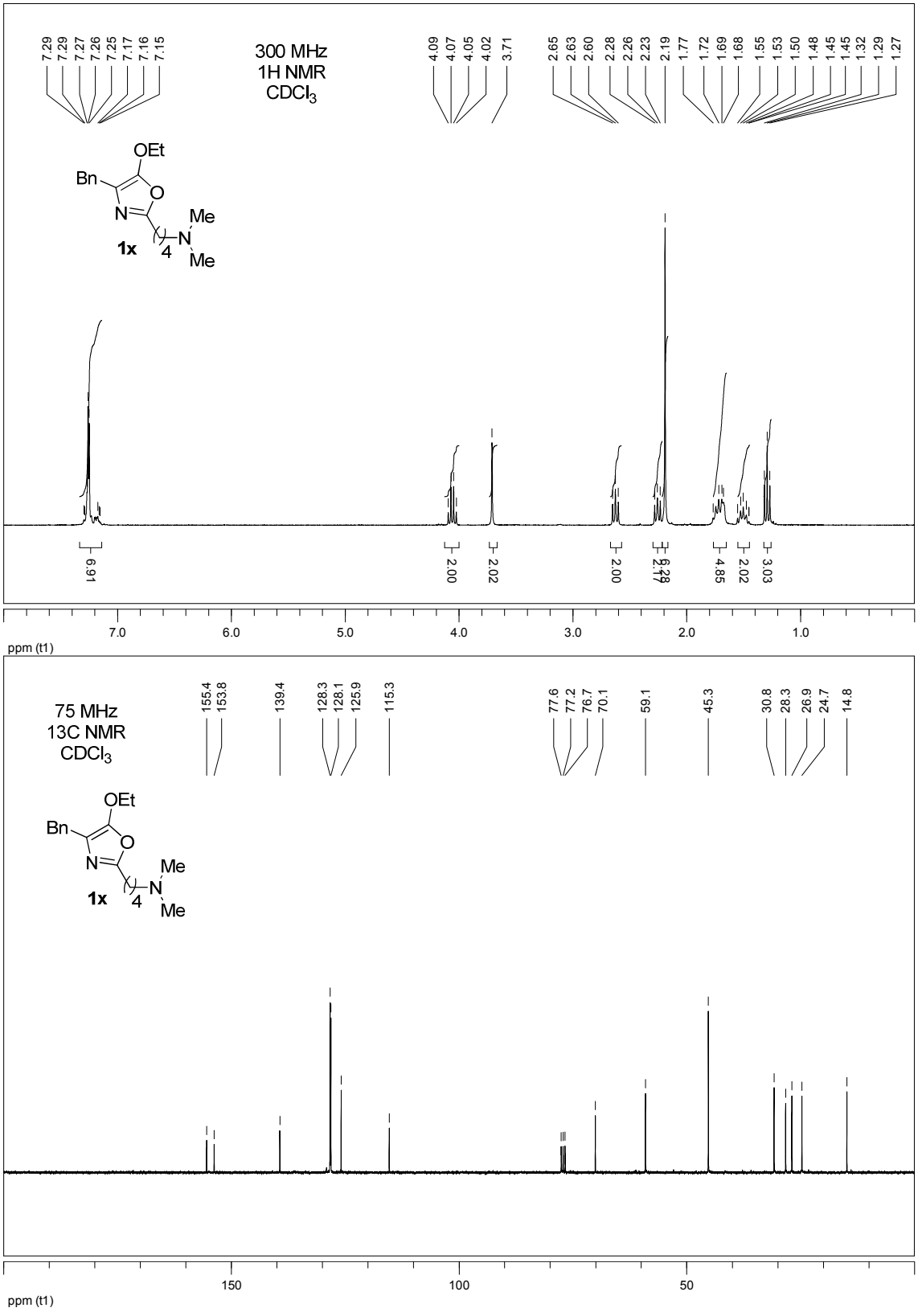
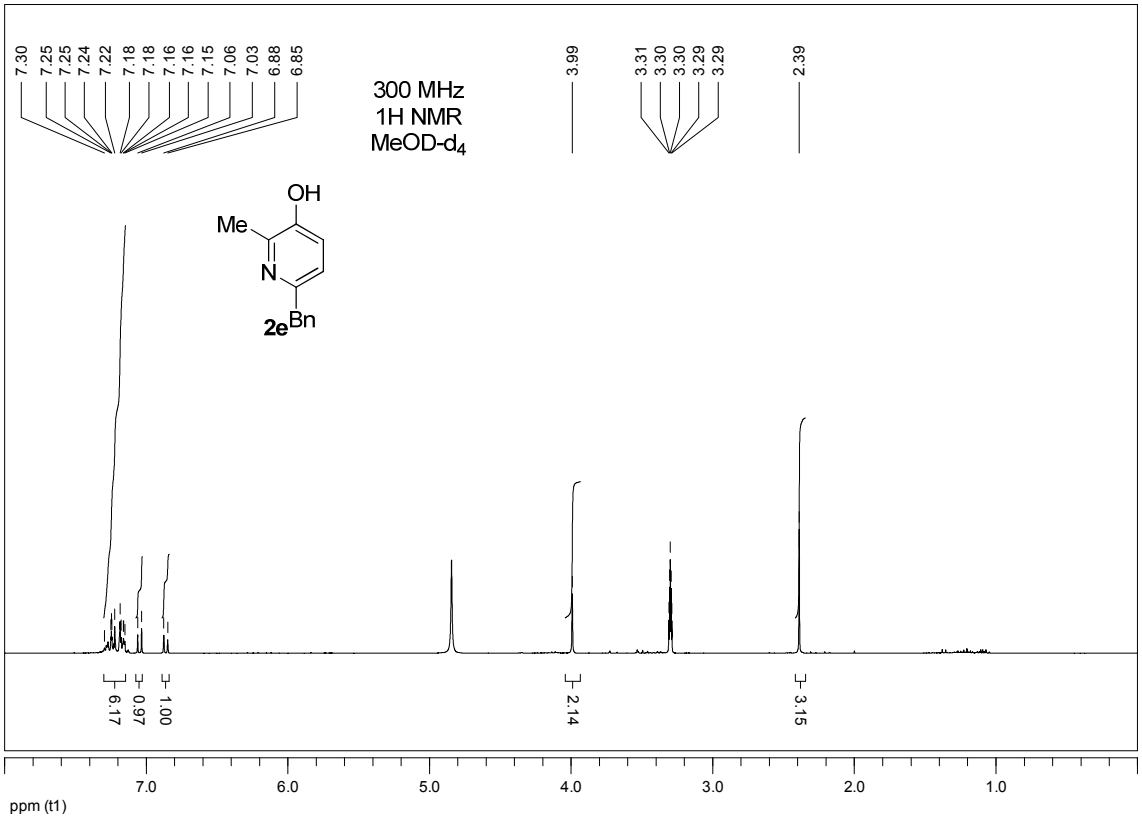
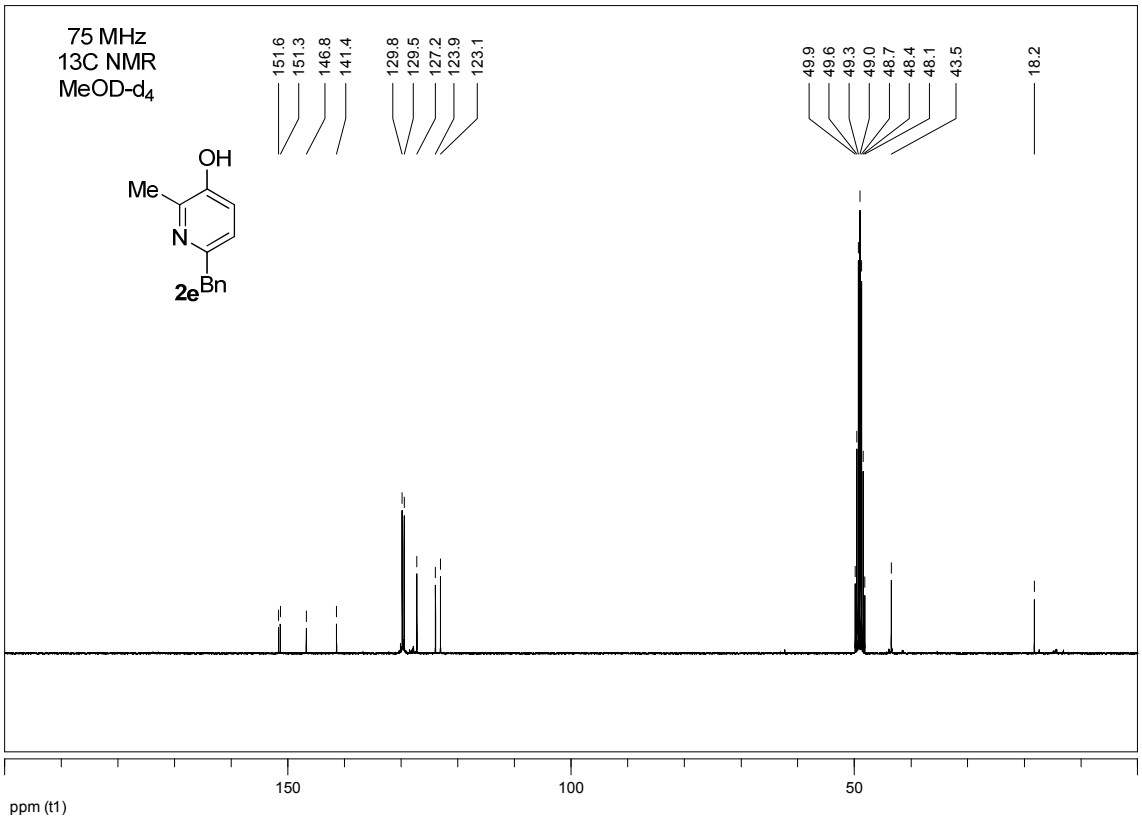
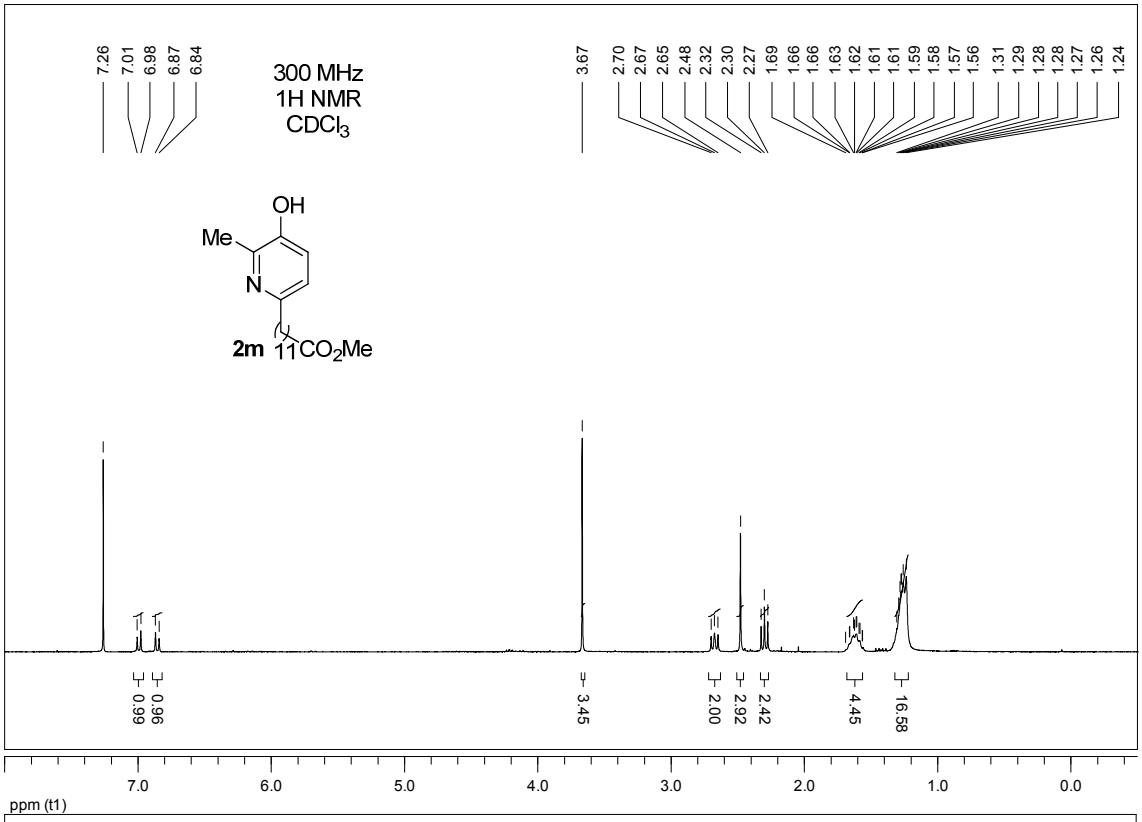
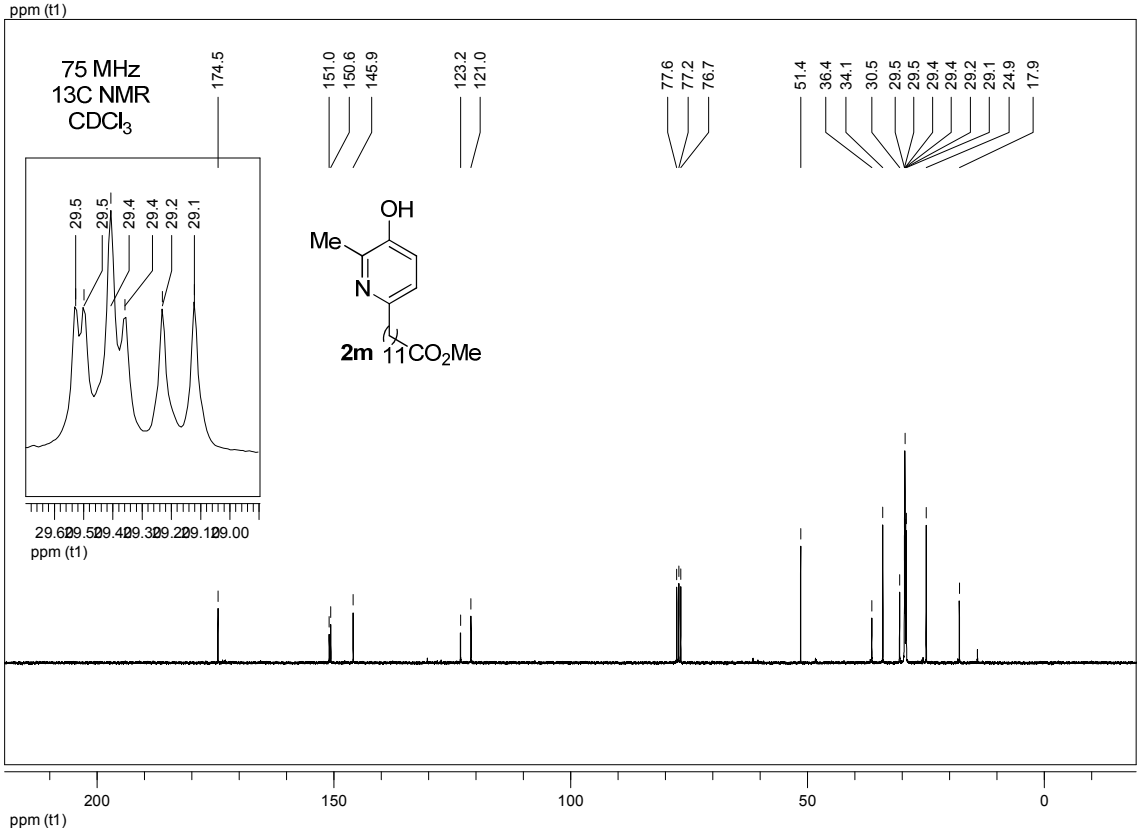
22.7
14.9
OEt
Bn
O
N
OMs
4
150
100
50
ppm (t1)

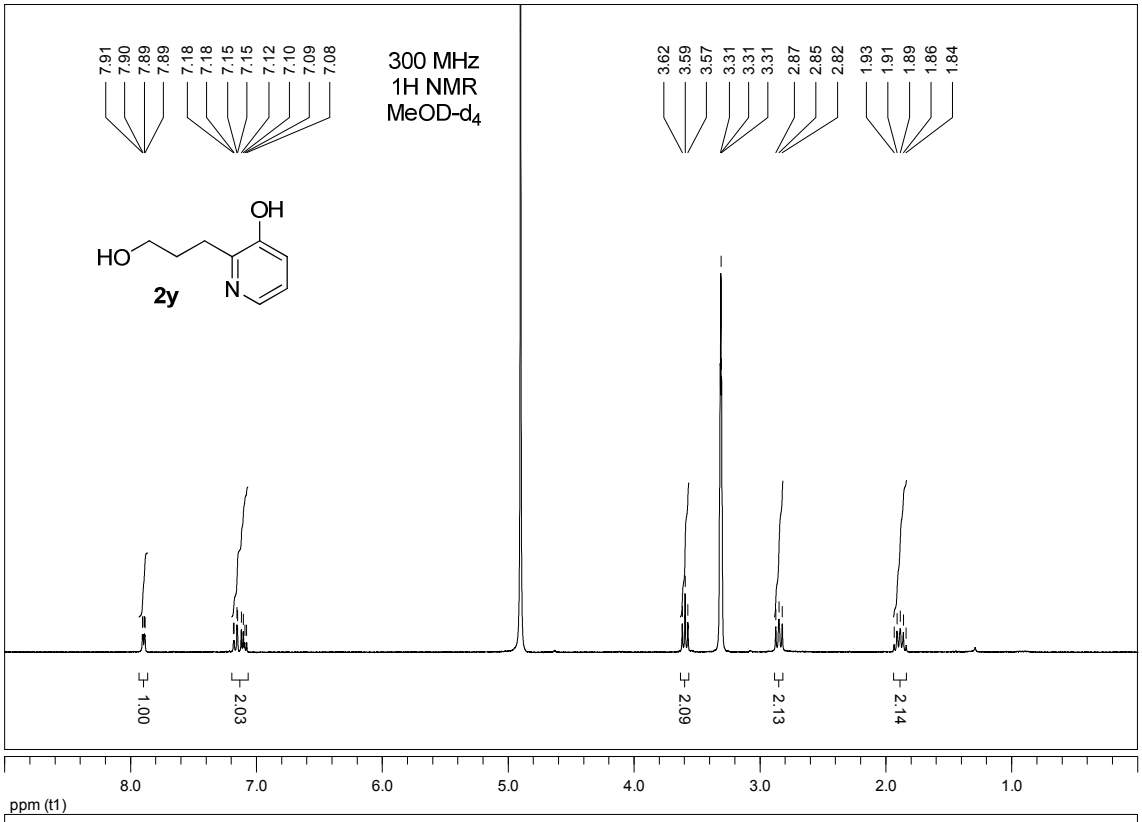

300 MHz
1H NMR
CDCl3
7.29
7.29
7.27
7.26
7.25
7.17
7.16
7.15
4.09
4.07
4.05
4.02
3.71
2.65
2.63
2.60
2.28
2.26
2.23
2.19
1.77
1.72
1.69
1.68
1.55
1.53
1.50
1.48
1.45
1.45
1.32
1.29
1.27
OEt
Bn
O
N
Me
N
Me
4
1x
6.91
2.00
2.02
2.00
2.17
4.85
2.02
3.03
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)
75 MHz
13C NMR
CDCl3
155.4
153.8
139.4
128.3
128.1
125.9
115.3
77.6
77.2
76.7
70.1
59.1
45.3
30.8
28.3
26.9
24.7
14.8
OEt
Bn
O
N
Me
N
Me
4
1x
150
100
50
ppm (t1)

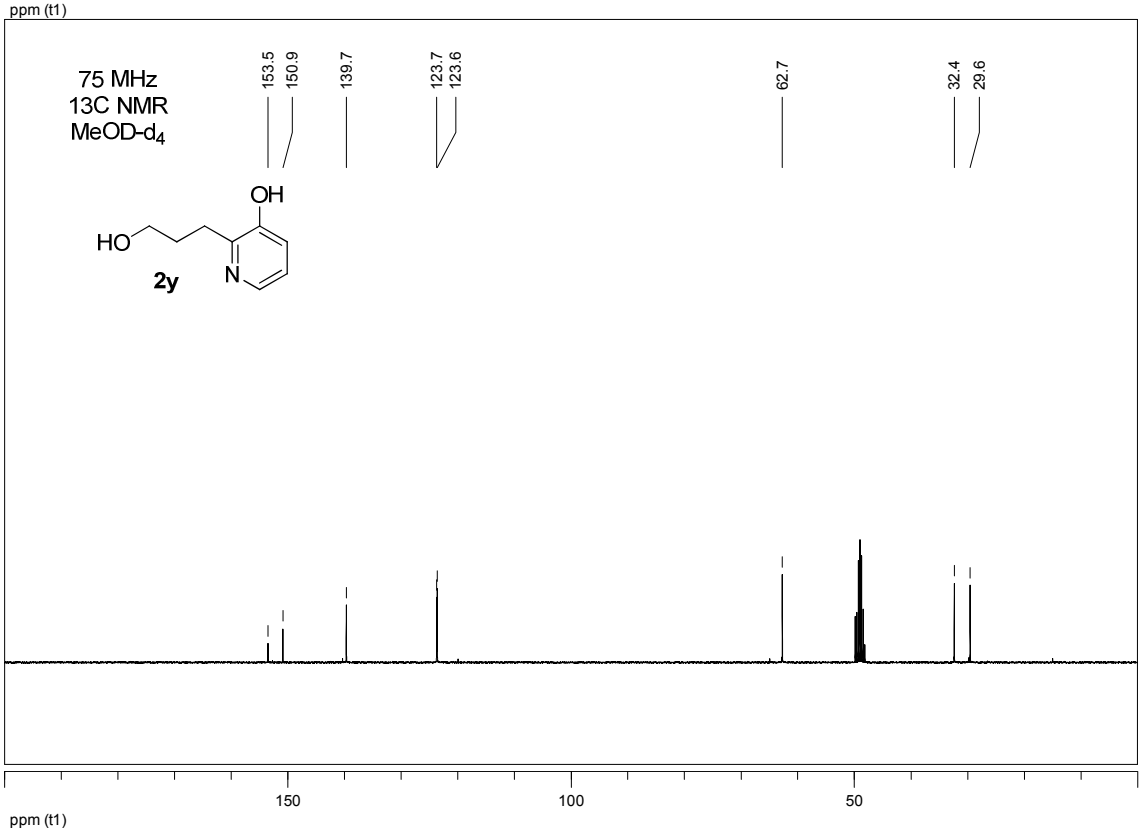

7.30
7.25
7.25
7.24
7.22
7.18
7.18
7.16
7.16
7.15
7.06
7.03
6.88
6.85
300 MHz
1H NMR
MeOD-d4
3.99
3.31
3.30
3.30
3.29
3.29
2.39
OH
Me
N
2eBn
9.17
0.97
1.00
2.14
3.15
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

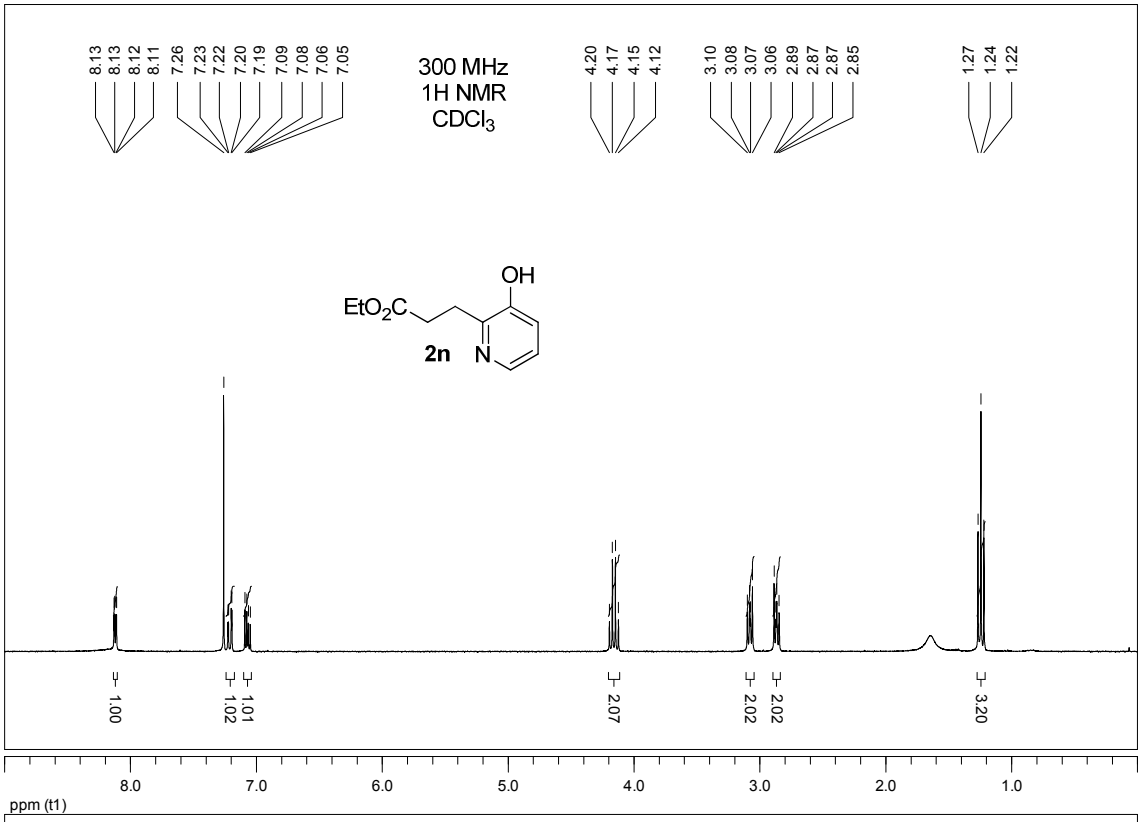

75 MHz
13C NMR
MeOD-d4
151.6
151.3
146.8
141.4
129.8
129.5
127.2
123.9
123.1
49.9
49.6
49.3
49.0
48.7
48.4
48.1
43.5
18.2
OH
Me
N
2eBn
150
100
50
ppm (t1)

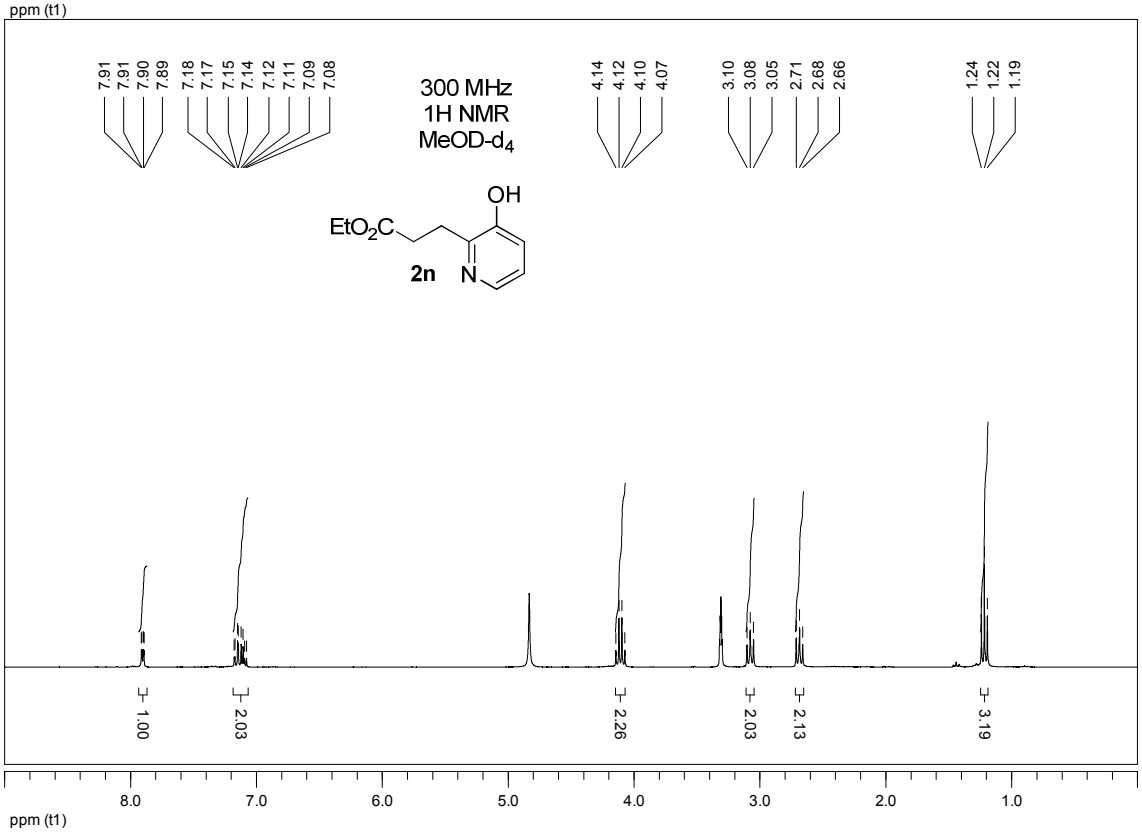

7.26
7.01
6.98
6.87
6.84
300 MHz
1H NMR
CDCl3
3.67
2.70
2.67
2.65
2.48
2.32
2.30
2.27
1.69
1.66
1.66
1.63
1.62
1.61
1.61
1.59
1.58
1.57
1.56
1.31
1.29
1.28
1.28
1.27
1.26
1.24
OH
Me
N
2m 11CO2Me
0.99
0.96
3.45
2.00
2.92
2.42
4.45
16.58
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

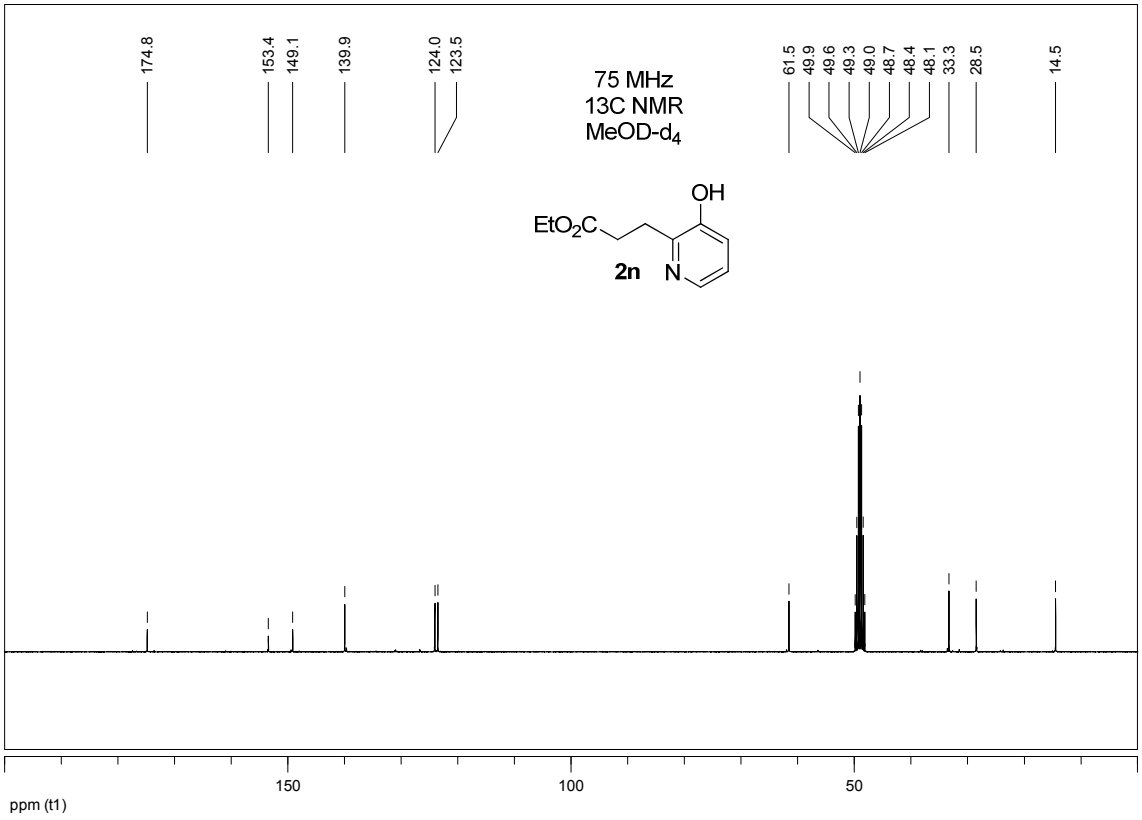

75 MHz
13C NMR
CDCl3
174.5
151.0
150.6
145.9
123.2
121.0
77.6
77.2
76.7
51.4
36.4
34.1
30.5
29.5
29.5
29.4
29.4
29.2
29.1
24.9
17.9
29.5
29.5
29.4
29.4
29.2
29.1
OH
Me
N
2m 11CO2Me
29.60
29.50
29.40
29.30
29.20
29.10
29.00
ppm (t1)
200
150
100
50
0
ppm (t1)

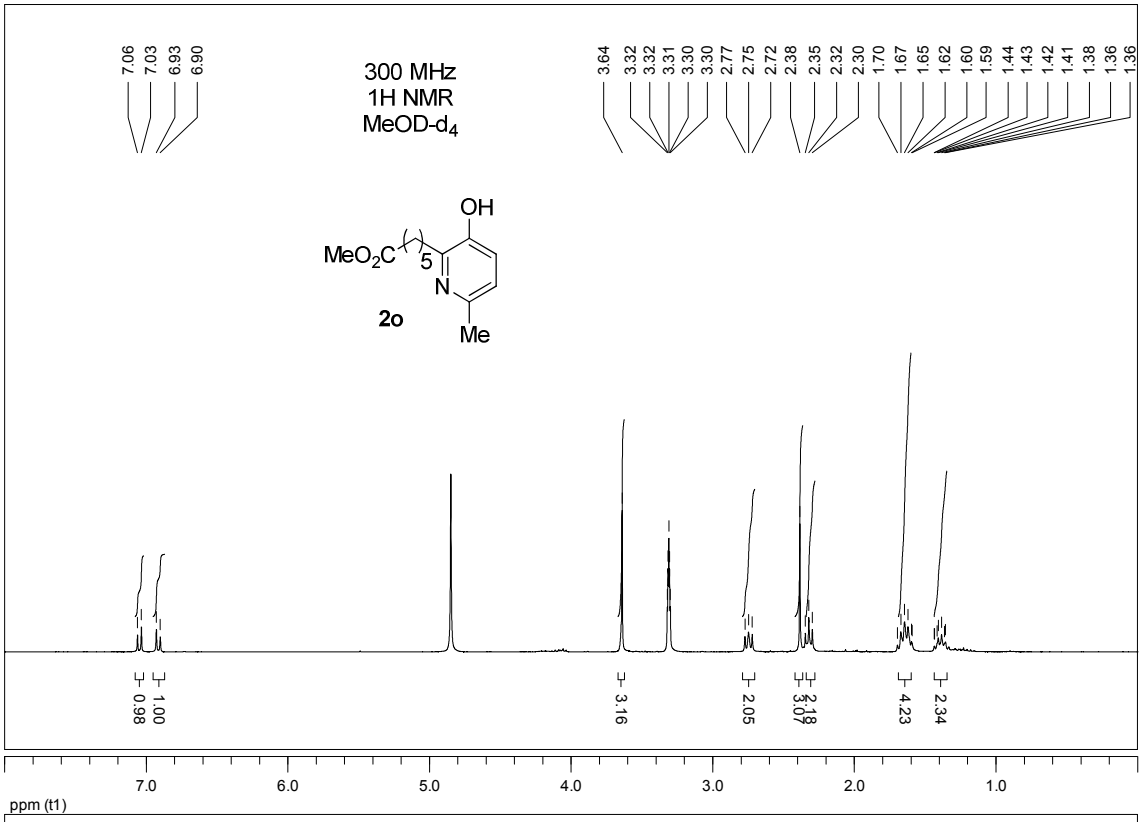

7.91
7.90
7.89
7.89
7.18
7.18
7.15
7.15
7.12
7.10
7.09
7.08
300 MHz
1H NMR
MeOD-d4
3.62
3.59
3.57
3.31
3.31
3.31
2.87
2.85
2.82
1.93
1.91
1.89
1.86
1.84
OH
HO
N
2y
1.00
2.03
2.09
2.13
2.14
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

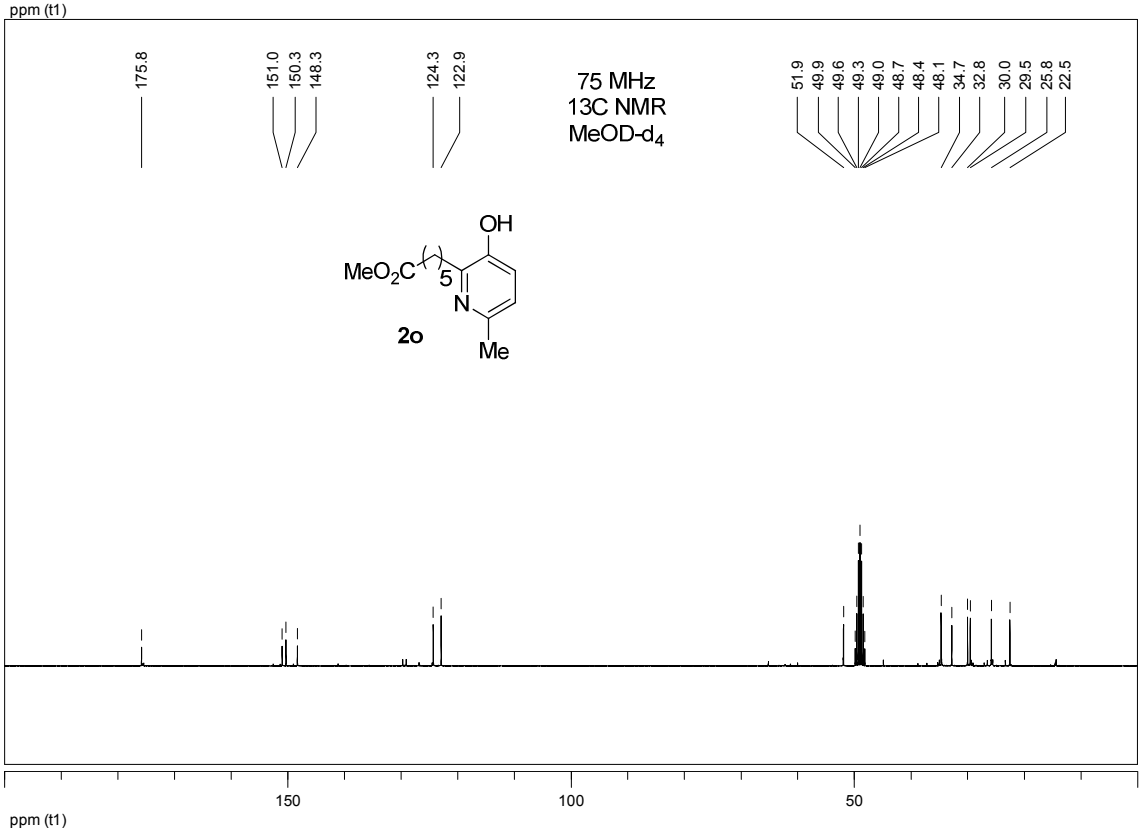

75 MHz
13C NMR
MeOD-d4
153.5
150.9
139.7
123.7
123.6
62.7
32.4
29.6
OH
HO
N
2y
150
100
50
ppm (t1)

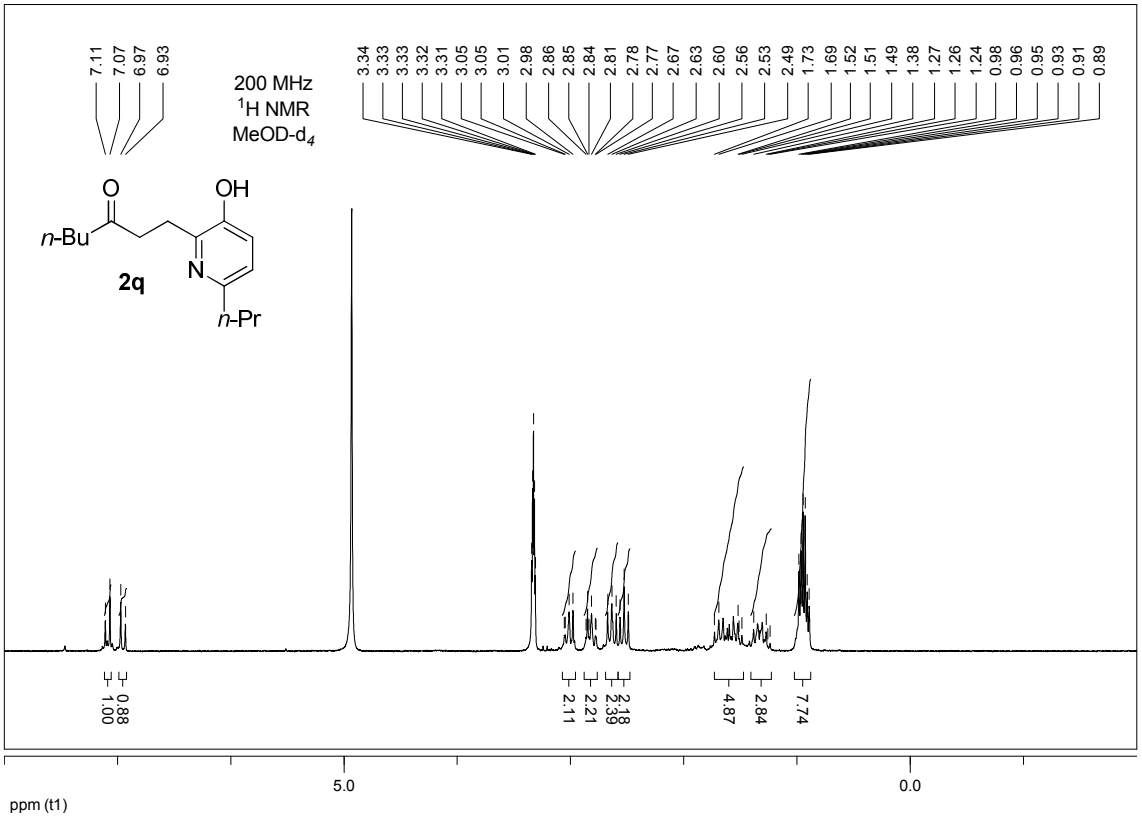

8.13
8.13
8.12
8.11
7.26
7.23
7.22
7.20
7.19
7.09
7.08
7.06
7.05
300 MHz
1H NMR
CDCl3
4.20
4.17
4.15
4.12
3.10
3.08
3.07
3.06
2.89
2.87
2.87
2.85
1.27
1.24
1.22
OH
EtO2C
2n
N
1.00
1.02
1.01
2.07
2.02
2.02
3.20
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

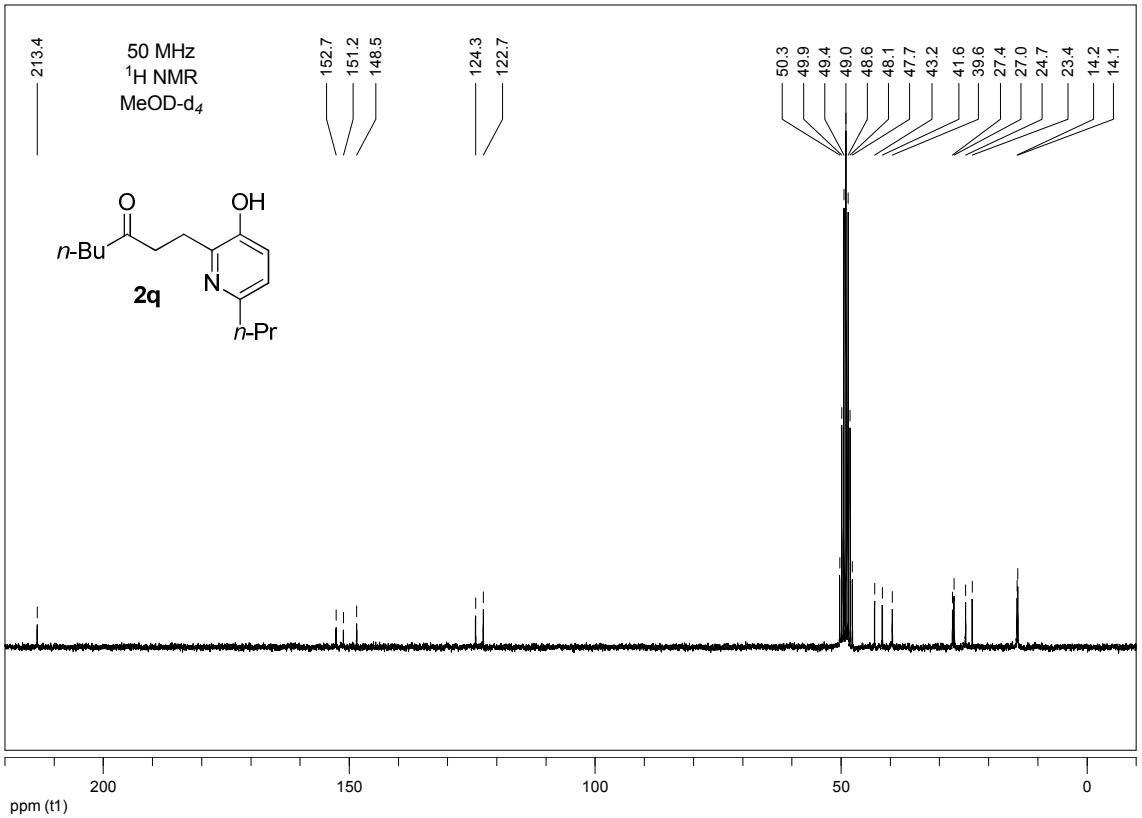

7.91
7.91
7.90
7.89
7.18
7.17
7.15
7.14
7.12
7.11
7.09
7.08
300 MHz
1H NMR
MeOD-d4
4.14
4.12
4.10
4.07
3.10
3.08
3.05
2.71
2.68
2.66
1.24
1.22
1.19
OH
EtO2C
2n
N
1.00
2.03
2.26
2.03
2.13
3.19
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

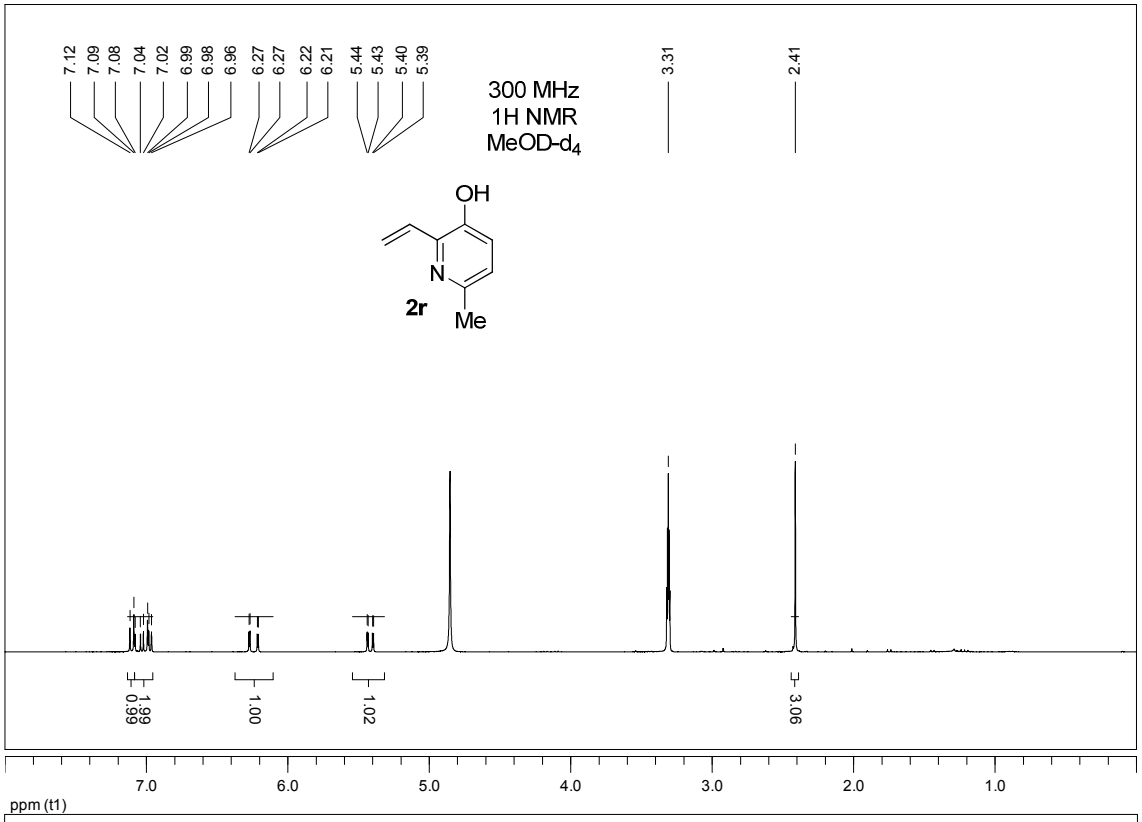

174.8
153.4
149.1
139.9
124.0
123.5
75 MHz
13C NMR
MeOD-d4
61.5
49.9
49.6
49.3
49.0
48.7
48.4
48.1
33.3
28.5
14.5
OH
EtO2C
2n
N
150
100
50
ppm (t1)

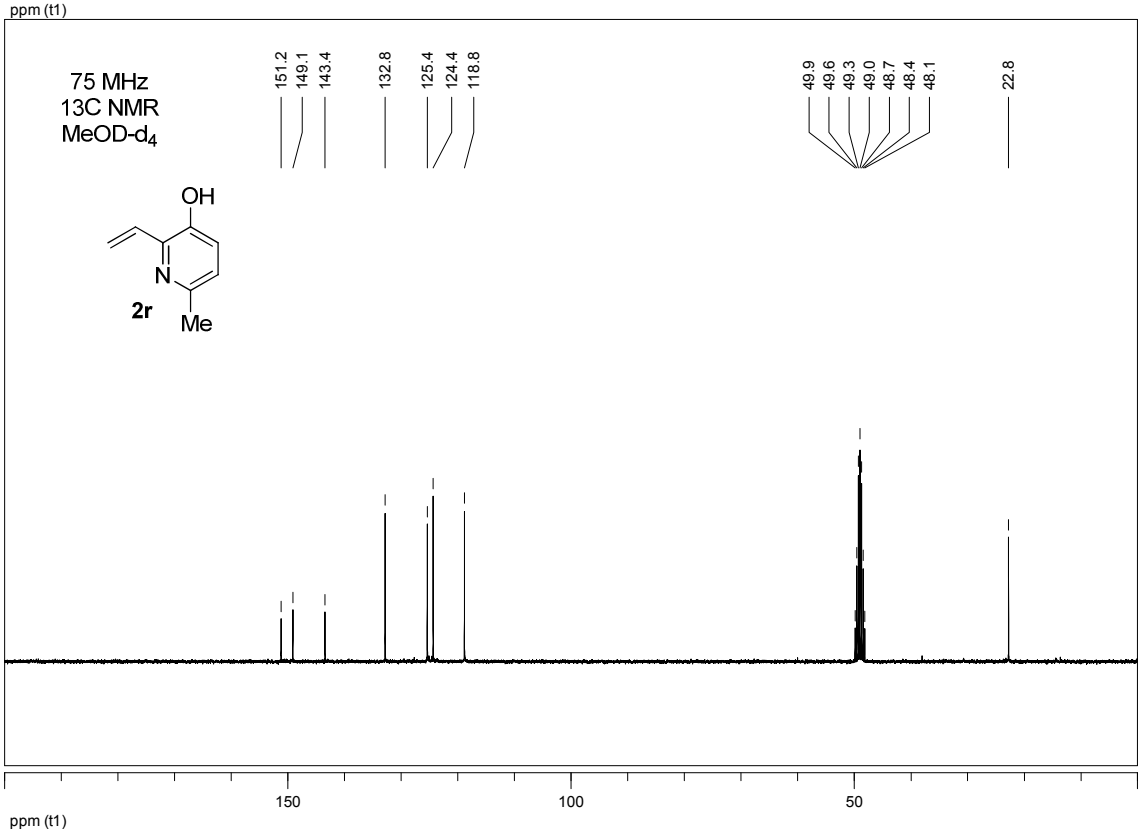

7.06
7.03
6.93
6.90
300 MHz
1H NMR
MeOD-d4
3.64
3.32
3.32
3.31
3.30
3.30
2.77
2.75
2.72
2.38
2.35
2.32
2.30
1.70
1.67
1.65
1.62
1.60
1.59
1.44
1.43
1.42
1.41
1.38
1.36
1.36
OH
MeO2C
5
N
2o
Me
0.98
1.00
3.16
2.05
2.18
3.07
4.23
2.34
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

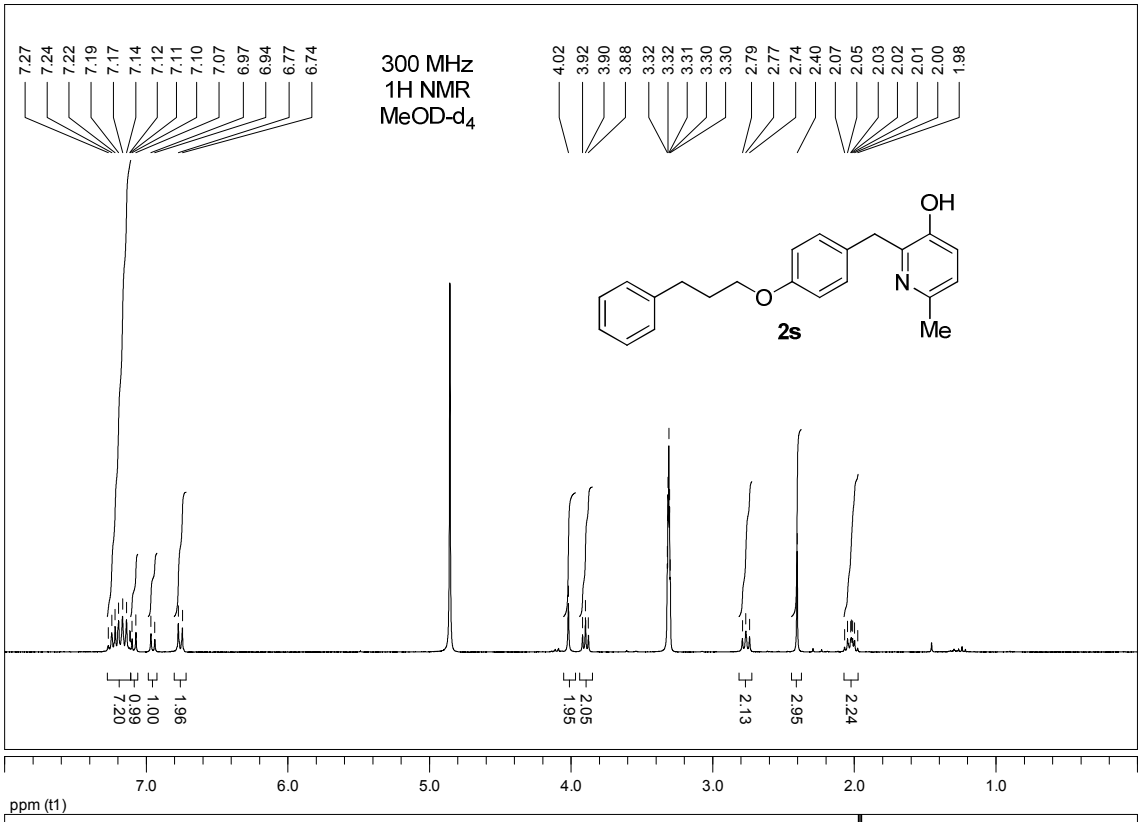

175.8
151.0
150.3
148.3
124.3
122.9
75 MHz
13C NMR
MeOD-d4
51.9
49.9
49.6
49.3
49.0
48.7
48.4
48.1
34.7
32.8
30.0
29.5
25.8
22.5
OH
MeO2C
5
N
2o
Me
150
100
50
ppm (t1)

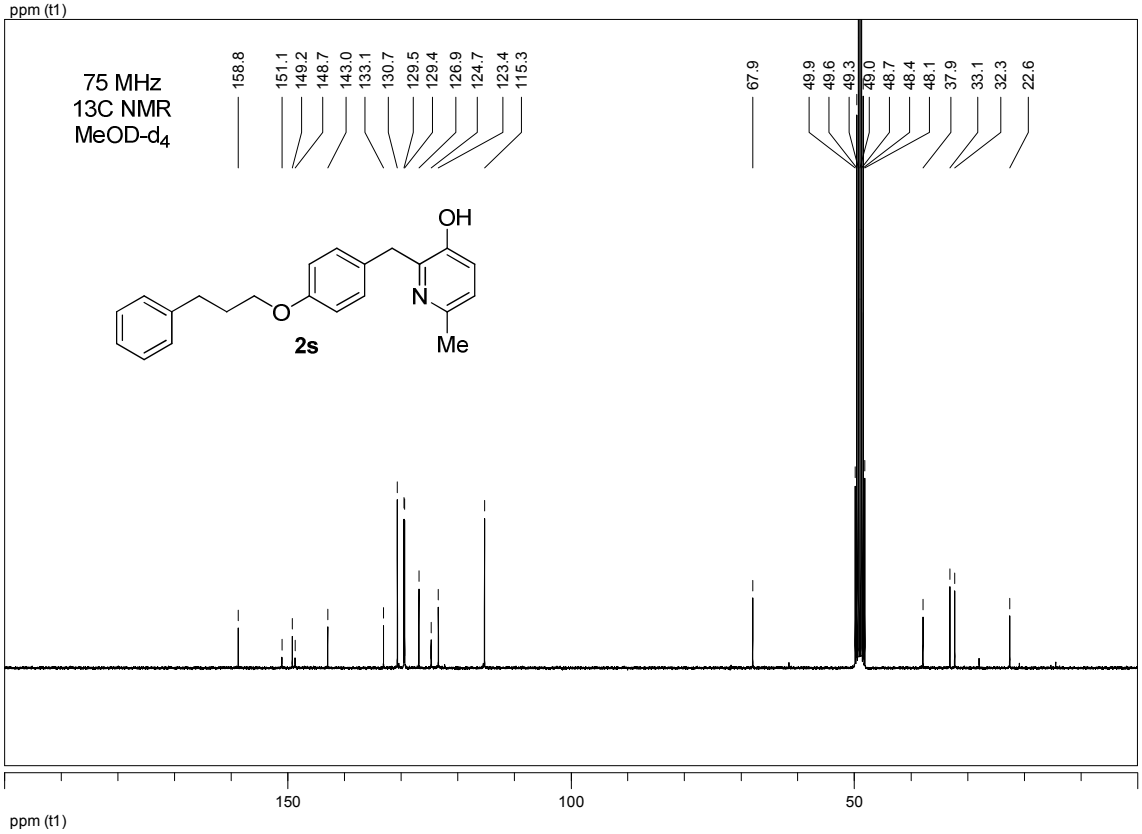

7.11
7.07
6.97
6.93
200 MHz
^{1}H NMR
MeOD-d_4
3.34
3.33
3.33
3.32
3.31
3.05
3.05
3.01
2.98
2.86
2.85
2.84
2.81
2.78
2.77
2.67
2.63
2.60
2.56
2.53
2.49
1.73
1.69
1.52
1.51
1.49
1.38
1.27
1.26
1.24
0.98
0.96
0.95
0.93
0.91
0.89
O
OH
n-Bu
N
n-Pr
2q
1.00
0.88
2.11
2.21
2.18
2.38
4.87
2.84
7.74
5.0
0.0
ppm (t1)

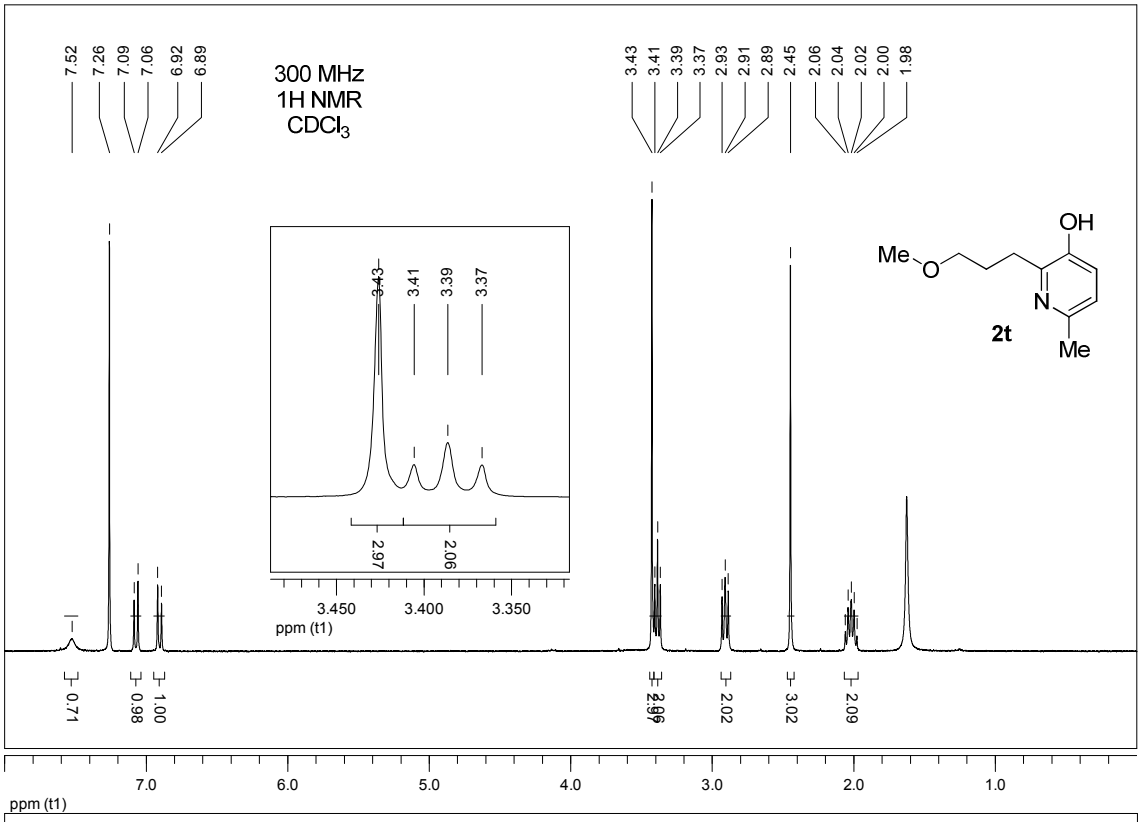

213.4
50 MHz
^{1}H NMR
MeOD-d_4
152.7
151.2
148.5
124.3
122.7
50.3
49.9
49.4
49.0
48.6
48.1
47.7
43.2
41.6
39.6
27.4
27.0
24.7
23.4
14.2
14.1
O
OH
n-Bu
N
n-Pr
2q
200
150
100
50
0
ppm (t1)

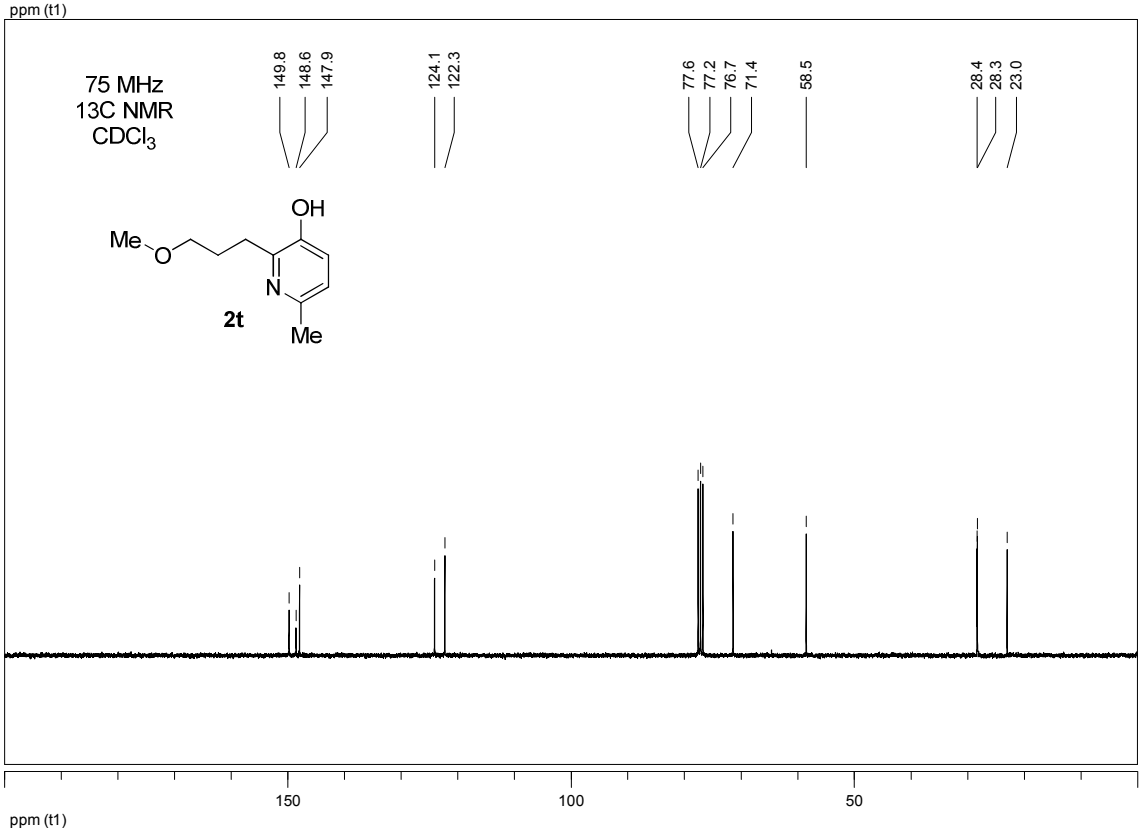

7.12
7.09
7.08
7.04
7.02
6.99
6.98
6.96
6.27
6.27
6.22
6.21
5.44
5.43
5.40
5.39
3.31
2.41
300 MHz
1H NMR
MeOD-d4
OH
N
2r
Me
0.99
1.96
1.00
1.02
3.06
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

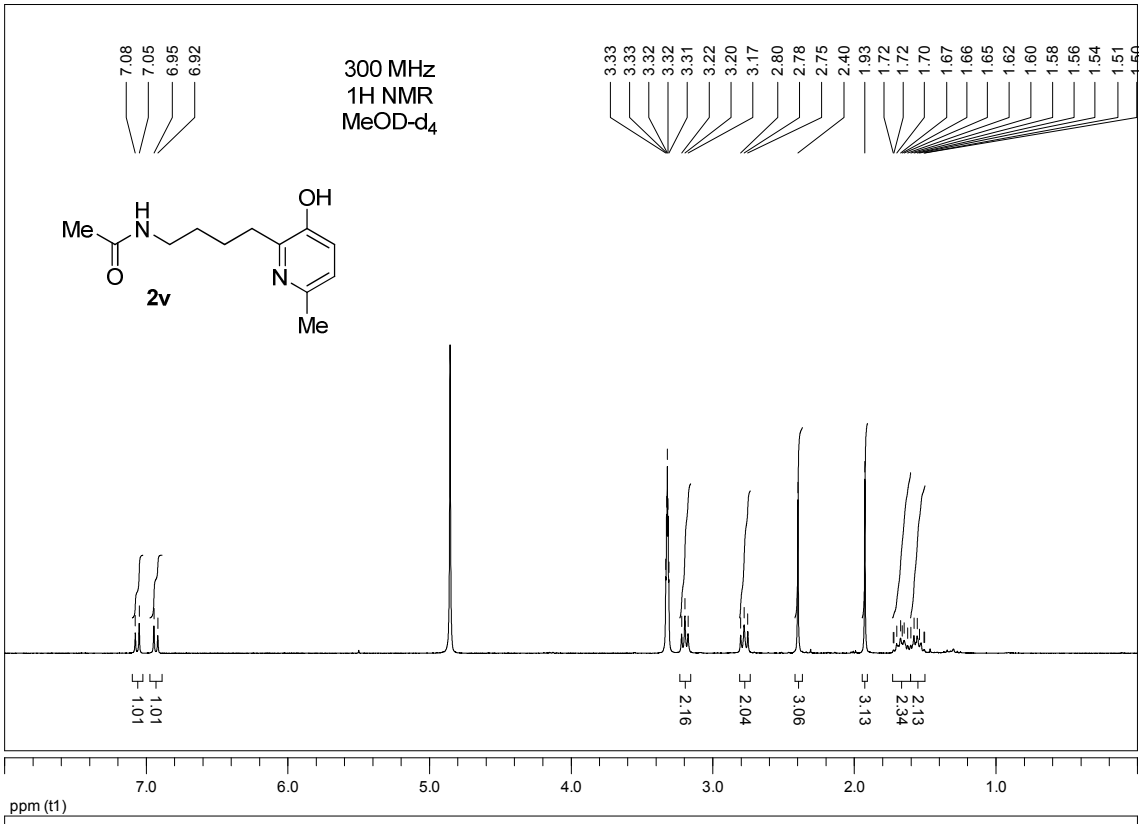

75 MHz
13C NMR
MeOD-d4
151.2
149.1
143.4
132.8
125.4
124.4
118.8
49.9
49.6
49.3
49.0
48.7
48.4
48.1
22.8
OH
N
2r
Me
150
100
50
ppm (t1)

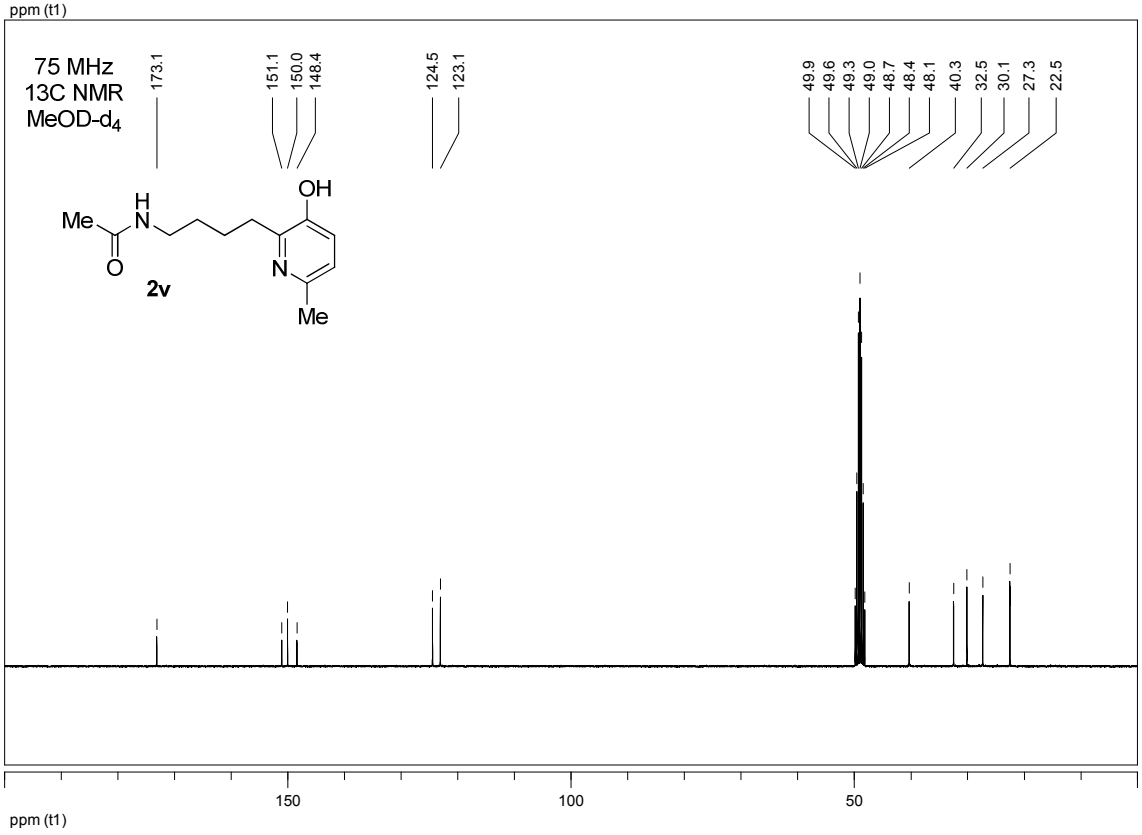

7.27
7.24
7.22
7.19
7.17
7.14
7.12
7.11
7.10
7.07
6.97
6.94
6.77
6.74
300 MHz
1H NMR
MeOD-d4
4.02
3.92
3.90
3.88
3.32
3.32
3.31
3.30
3.30
2.79
2.77
2.74
2.40
2.07
2.05
2.03
2.02
2.01
2.00
1.98
OH
N
O
2s
Me
7.20
0.99
1.00
1.96
1.95
2.05
2.13
2.95
2.24
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

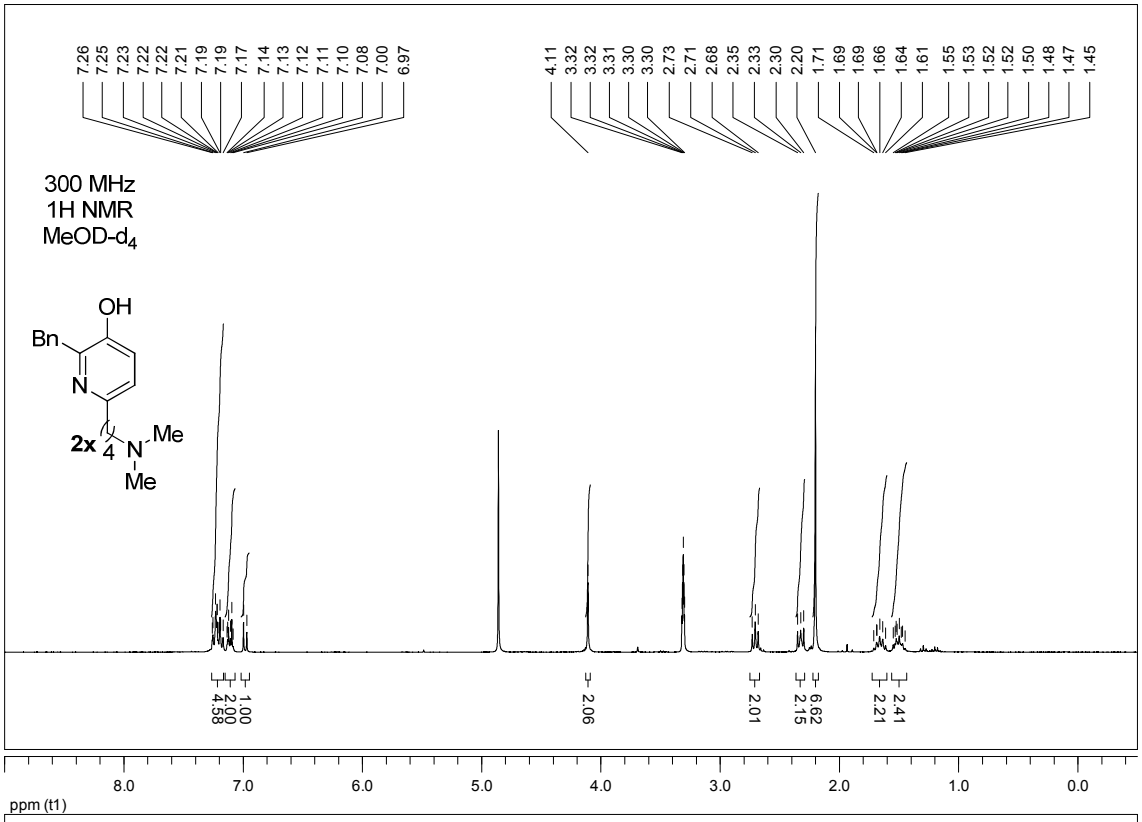

75 MHz
13C NMR
MeOD-d4
158.8
151.1
149.2
148.7
143.0
133.1
130.7
129.5
129.4
126.9
124.7
123.4
115.3
97.9
49.9
49.6
49.3
49.0
48.7
48.4
48.1
37.9
33.1
32.3
22.6
OH
N
O
2s
Me
150
100
50
ppm (t1)

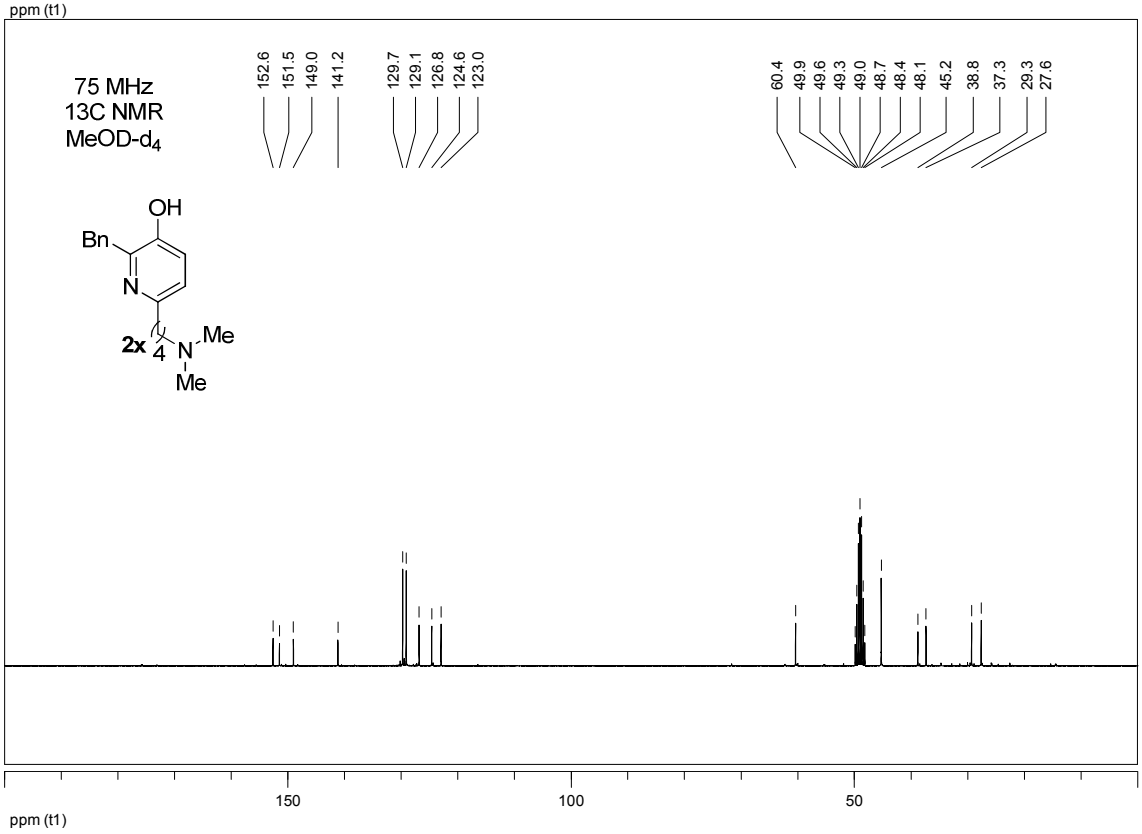

300 MHz
1H NMR
CDCl3
7.52
7.26
7.09
7.06
6.92
6.89
3.43
3.41
3.39
3.37
2.93
2.91
2.89
2.45
2.06
2.04
2.02
2.00
1.98
0.71
0.98
1.00
2.07
2.02
3.02
2.09
2.97
2.06
3.450
3.400
3.350
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)
OH
Me
O
N
Me
2t

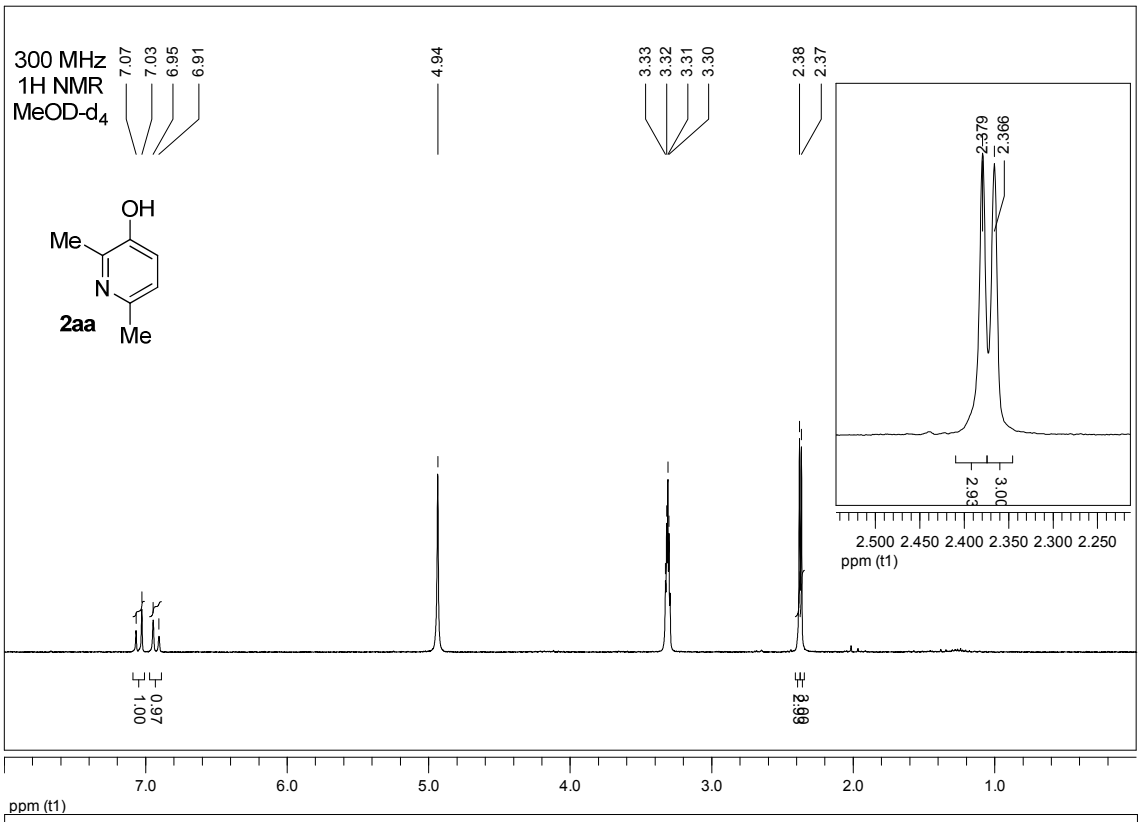

75 MHz
13C NMR
CDCl3
149.8
148.6
147.9
124.1
122.3
77.6
77.2
76.7
71.4
58.5
28.4
28.3
23.0
OH
Me
O
N
Me
2t
150
100
50
ppm (t1)

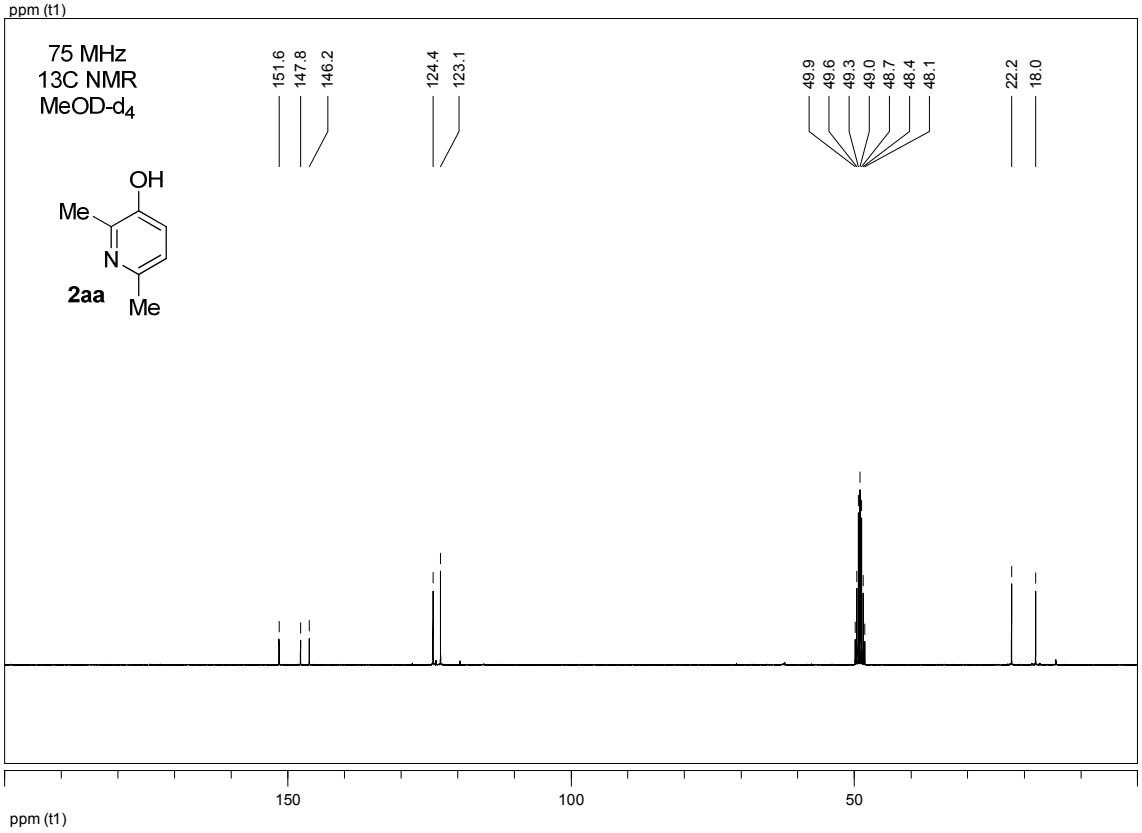

300 MHz
1H NMR
MeOD-d4
7.08
7.05
6.95
6.92
3.33
3.33
3.32
3.32
3.31
3.22
3.20
3.17
2.80
2.78
2.75
2.40
1.93
1.72
1.72
1.70
1.67
1.66
1.65
1.62
1.60
1.58
1.56
1.54
1.51
Me
H
N
O
OH
N
Me
2v
1.01
1.01
2.16
2.04
3.06
3.13
2.34
2.13
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

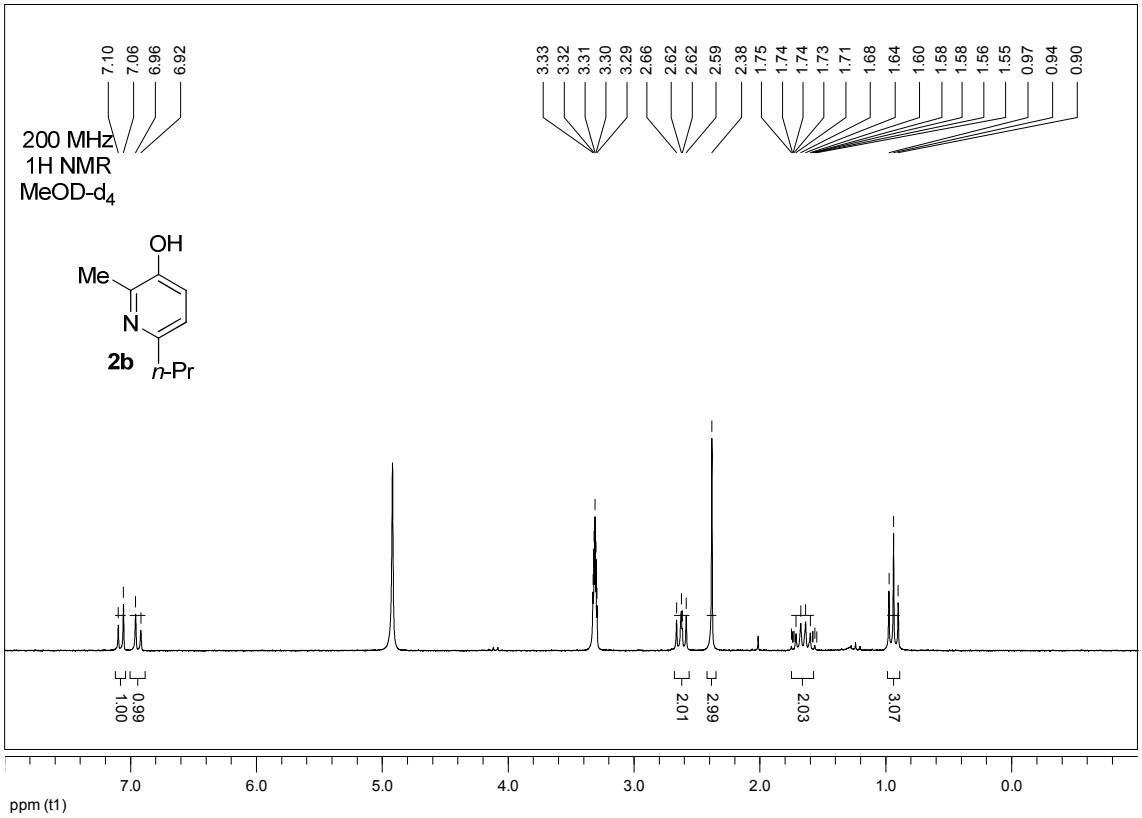

75 MHz
13C NMR
MeOD-d4
173.1
151.1
150.0
148.4
124.5
123.1
49.9
49.6
49.3
49.0
48.7
48.4
48.1
40.3
32.5
30.1
27.3
22.5
Me
H
N
O
OH
N
Me
2v
150
100
50
ppm (t1)

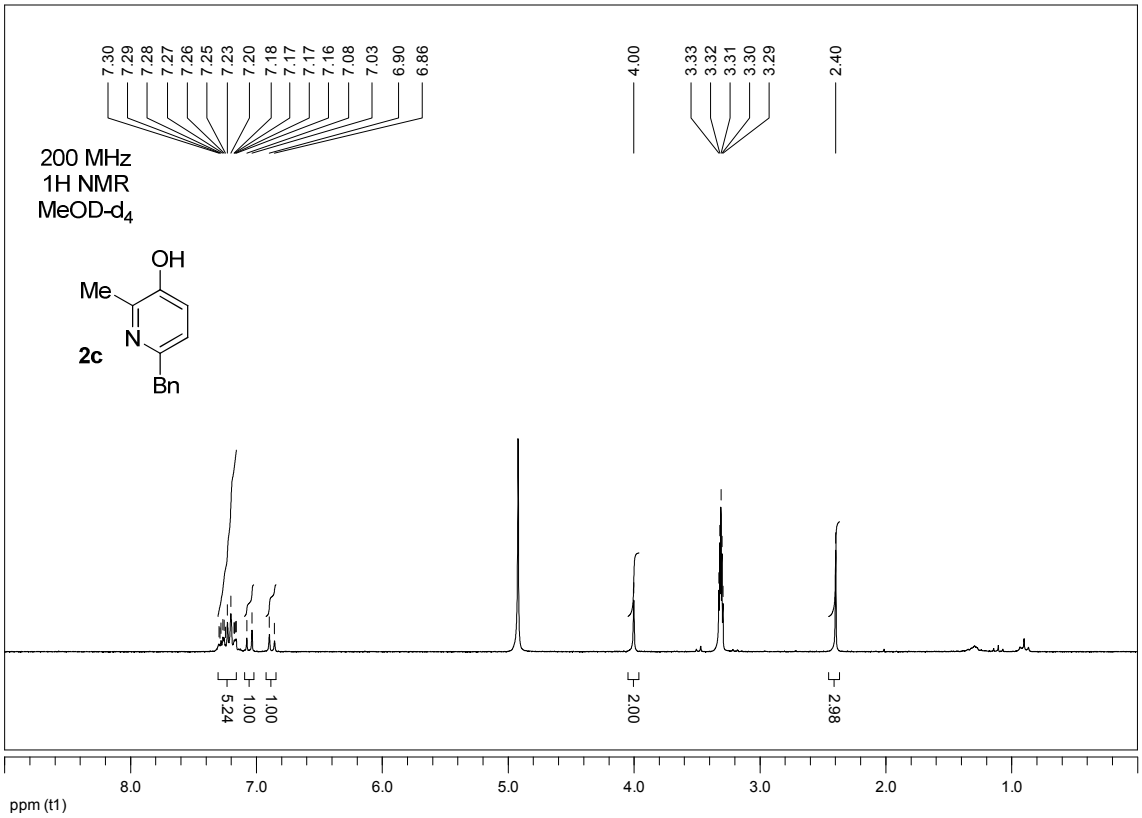

7.26
7.25
7.23
7.22
7.22
7.21
7.19
7.19
7.17
7.14
7.13
7.12
7.11
7.10
7.08
7.00
6.97
4.11
3.32
3.32
3.31
3.30
3.30
2.73
2.71
2.68
2.35
2.33
2.30
2.20
1.71
1.69
1.69
1.66
1.64
1.61
1.55
1.53
1.52
1.52
1.50
1.48
1.47
1.45
300 MHz
1H NMR
MeOD-d4
OH
Bn
N
2x
4
N
Me
Me
4.58
2.00
1.00
2.06
2.01
2.15
6.62
2.21
2.41
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

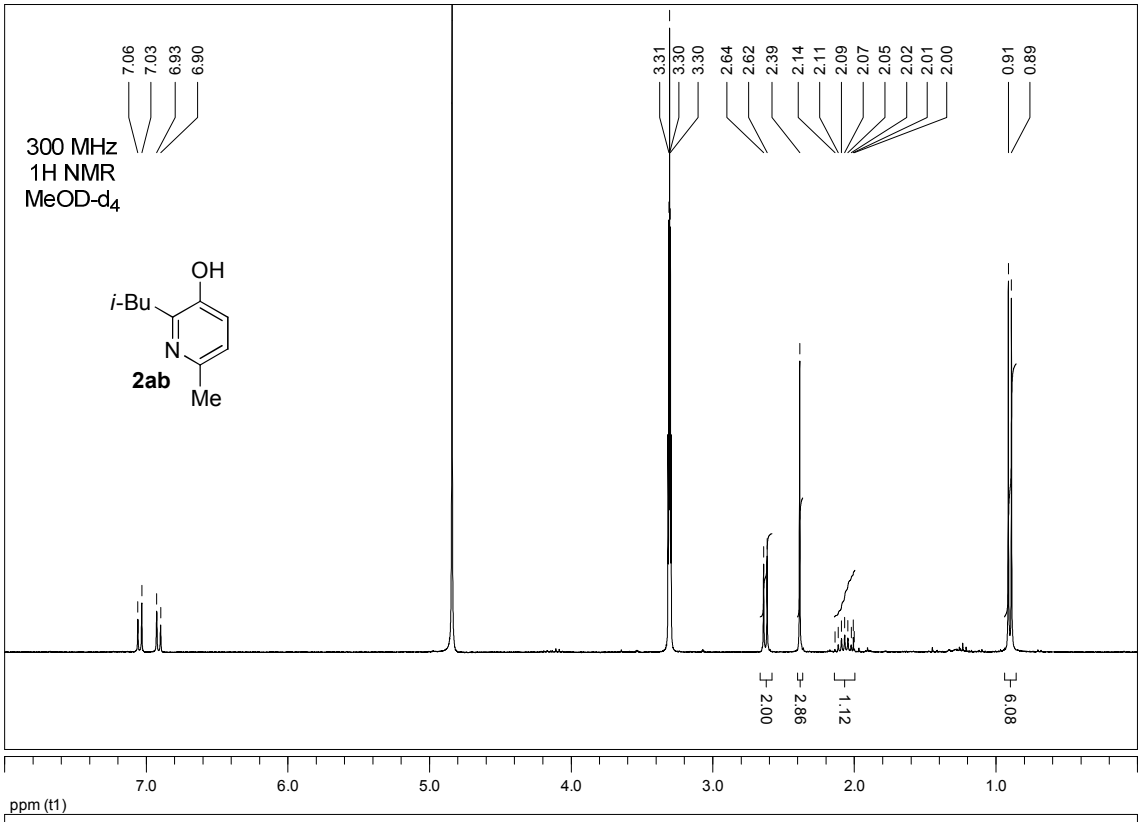

75 MHz
13C NMR
MeOD-d4
152.6
151.5
149.0
141.2
129.7
129.1
126.8
124.6
123.0
60.4
49.9
49.6
49.3
49.0
48.7
48.4
48.1
45.2
38.8
37.3
29.3
27.6
OH
Bn
N
2x
4
N
Me
Me
150
100
50
ppm (t1)

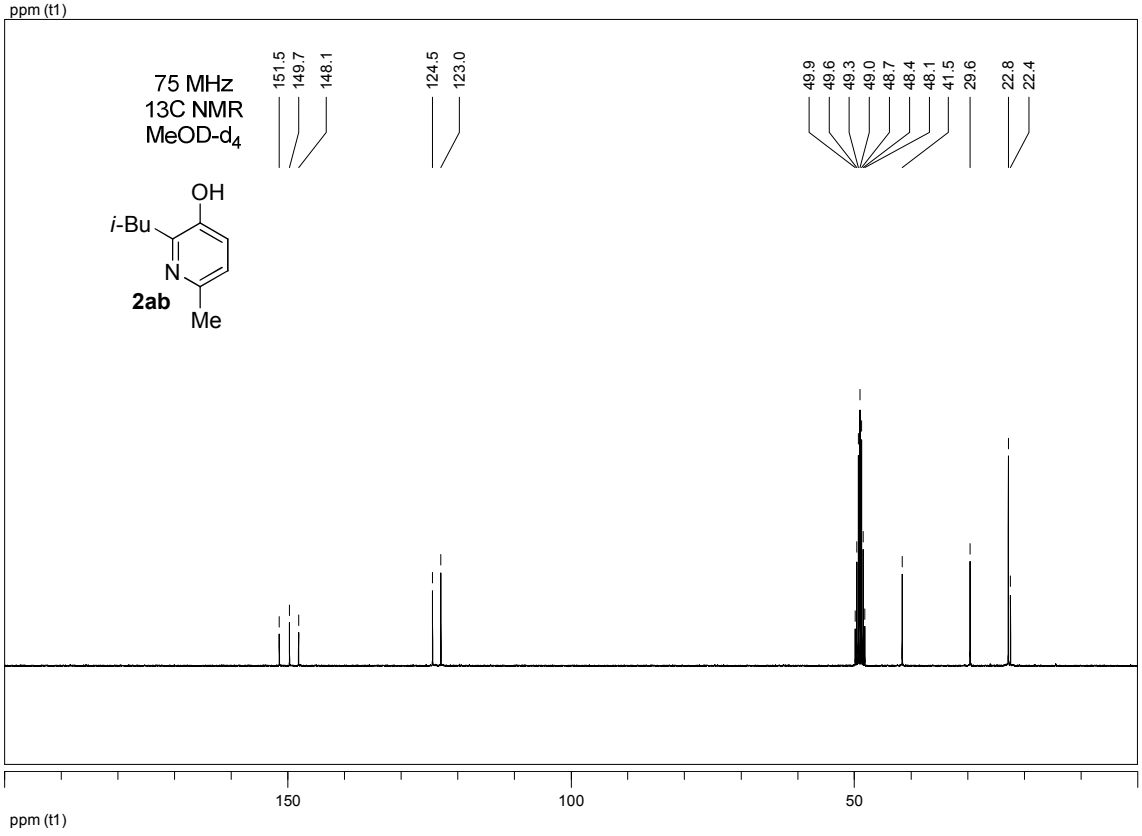

300 MHz
1H NMR
MeOD-d4
7.07
7.03
6.95
6.91
4.94
3.33
3.32
3.31
3.30
2.38
2.37
2.379
2.366
OH
Me
N
2aa
Me
1.00
0.97
2.98
3.00
2.500 2.450 2.400 2.350 2.300 2.250
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

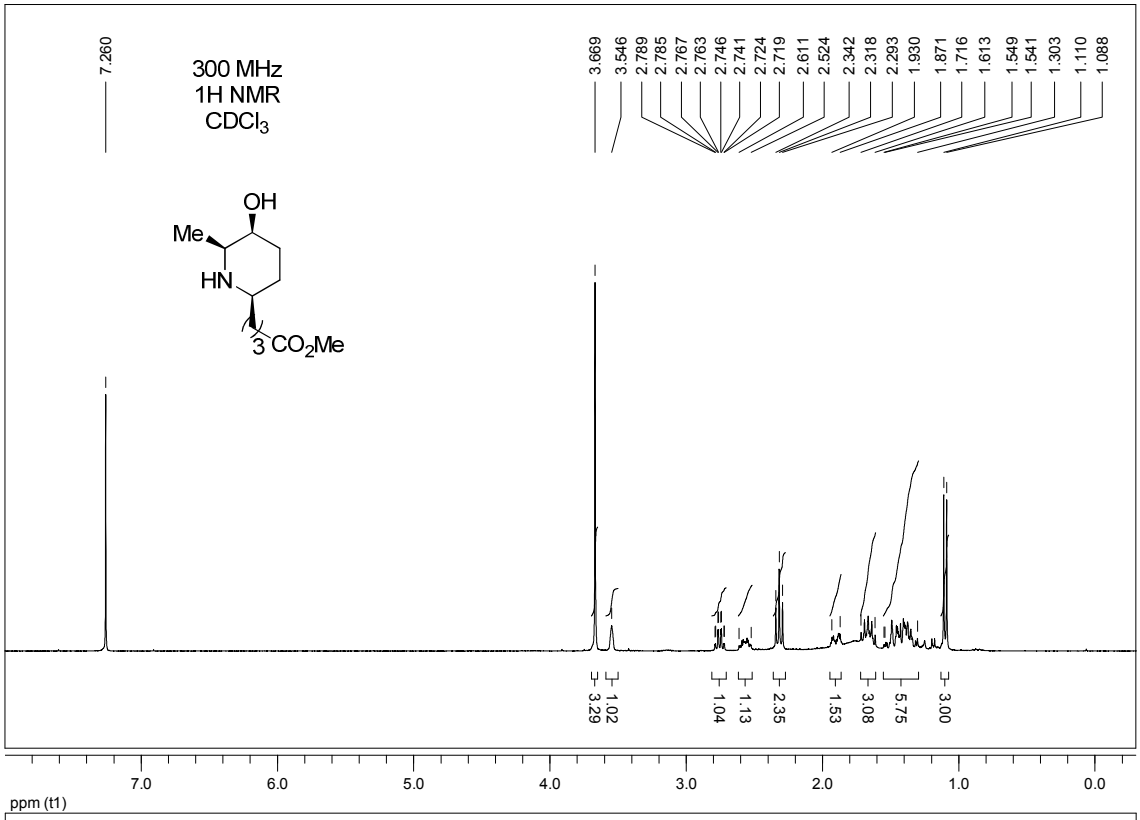

75 MHz
13C NMR
MeOD-d4
151.6
147.8
146.2
124.4
123.1
49.9
49.6
49.3
49.0
48.7
48.4
48.1
22.2
18.0
OH
Me
N
2aa
Me
150
100
50
ppm (t1)

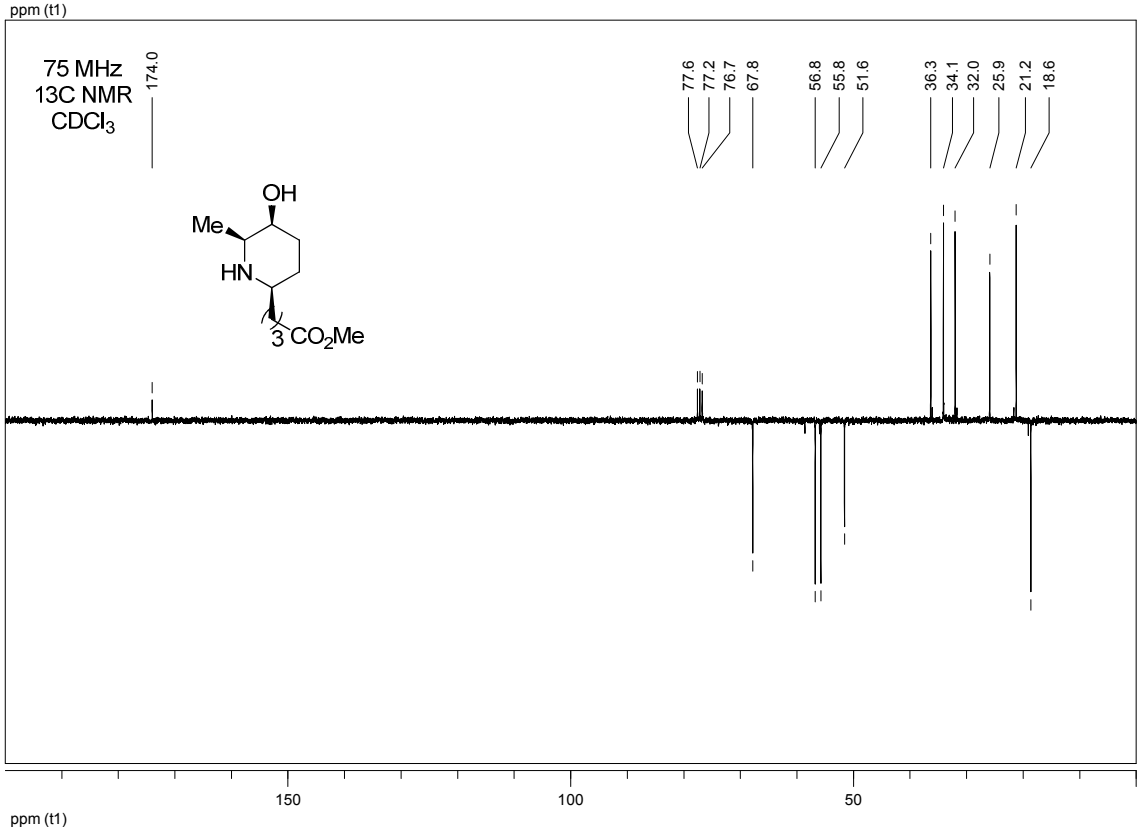

7.10
7.06
6.96
6.92
3.33
3.32
3.31
3.30
3.29
2.66
2.62
2.62
2.59
2.38
1.75
1.74
1.74
1.73
1.71
1.68
1.64
1.60
1.58
1.58
1.56
1.55
0.97
0.94
0.90
200 MHz
1H NMR
MeOD-d4
OH
Me
N
2b
n-Pr
1.00
0.99
2.01
2.99
2.03
3.07
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

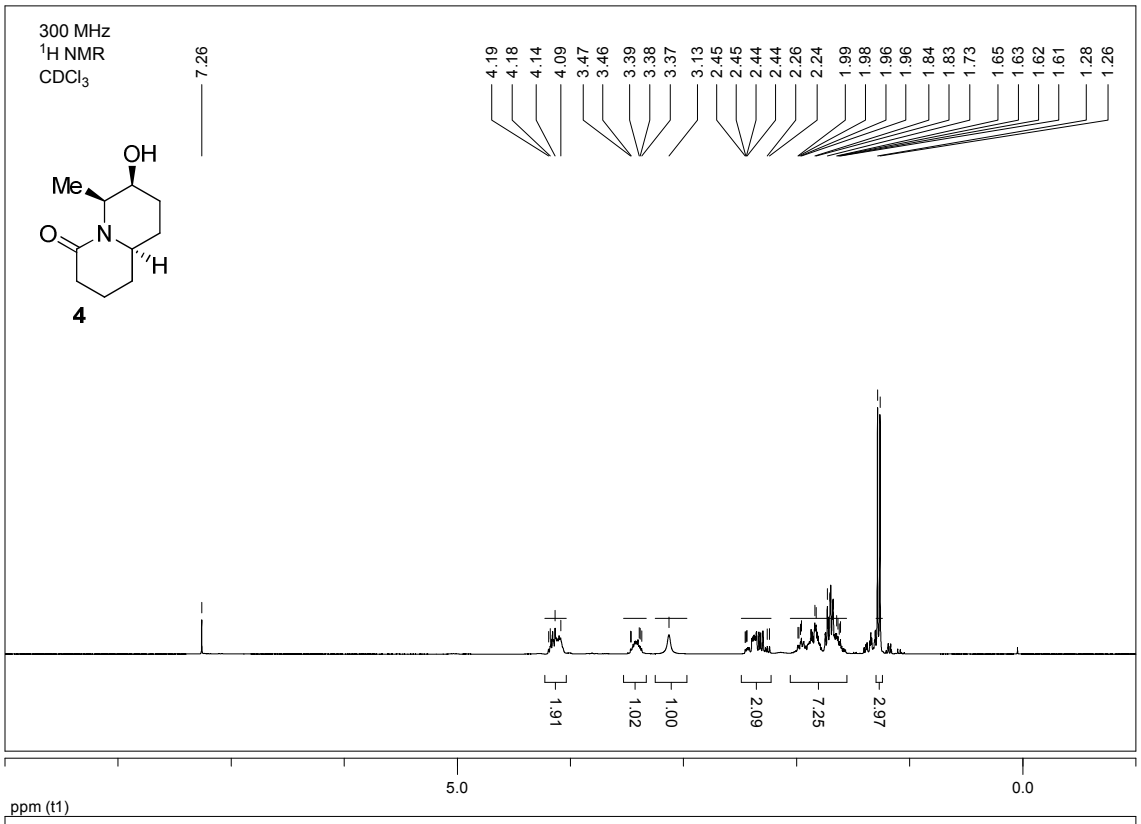

7.30
7.29
7.28
7.27
7.26
7.25
7.23
7.20
7.18
7.17
7.17
7.16
7.08
7.03
6.90
6.86
4.00
3.33
3.32
3.31
3.30
3.29
2.40
200 MHz
1H NMR
MeOD-d4
OH
Me
N
2c
Bn
5.24
1.00
1.00
2.00
2.98
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

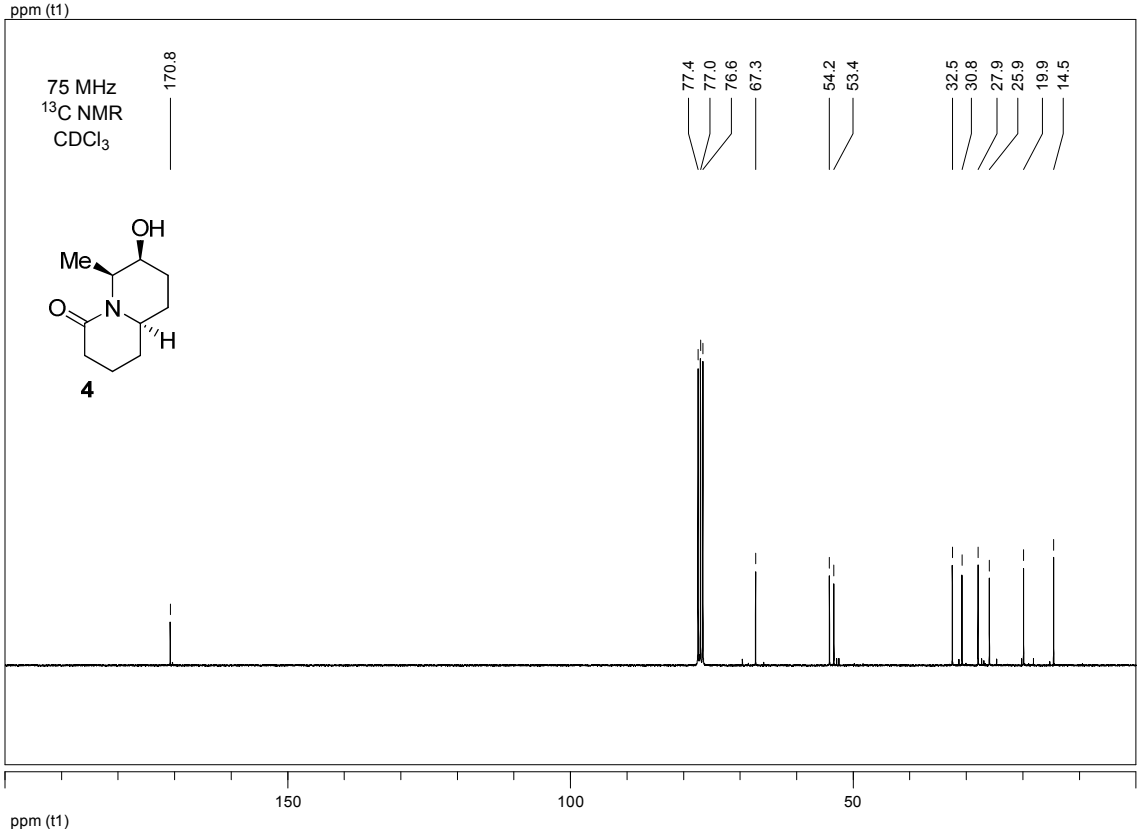

7.06
7.03
6.93
6.90
3.31
3.30
3.30
2.64
2.62
2.39
2.14
2.11
2.09
2.07
2.05
2.02
2.01
2.00
0.91
0.89
300 MHz
1H NMR
MeOD-d4
OH
i-Bu
N
2ab
Me
2.00
2.86
1.12
6.08
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

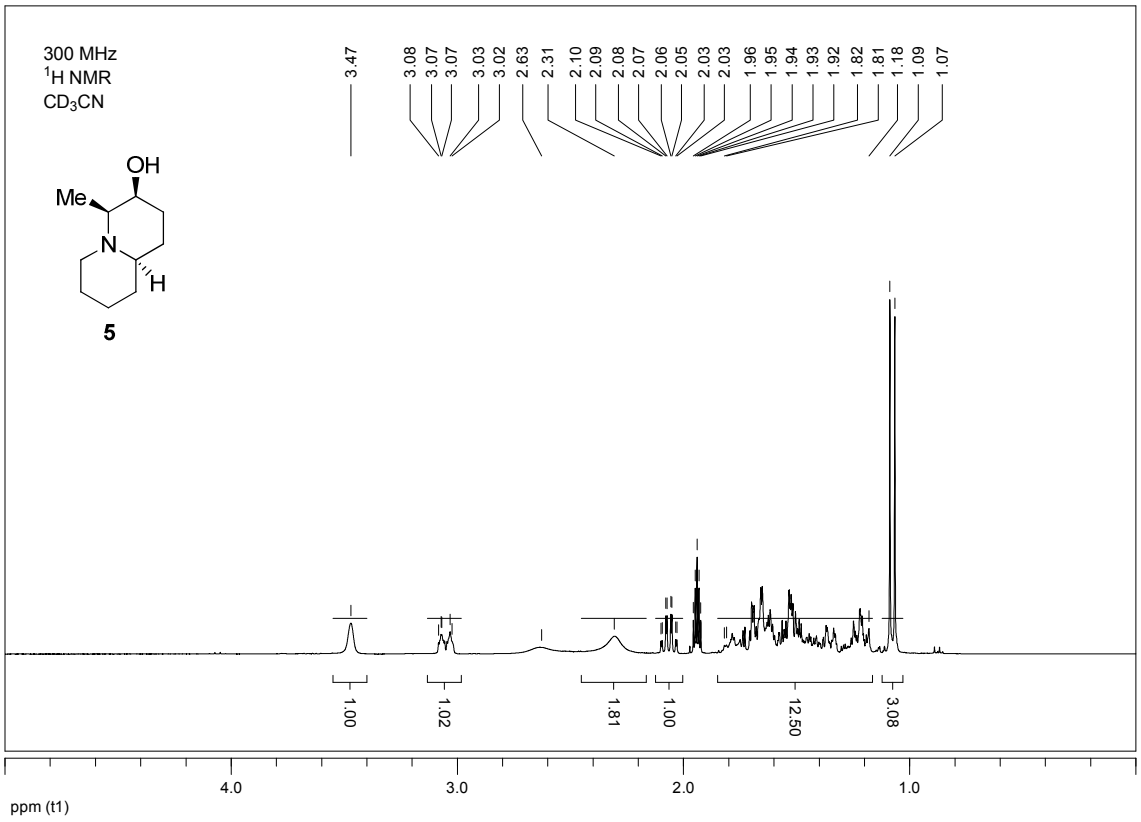

151.5
149.7
148.1
124.5
123.0
49.9
49.6
49.3
49.0
48.7
48.4
48.1
41.5
29.6
22.8
22.4
75 MHz
13C NMR
MeOD-d4
OH
i-Bu
N
2ab
Me
150
100
50
ppm (t1)

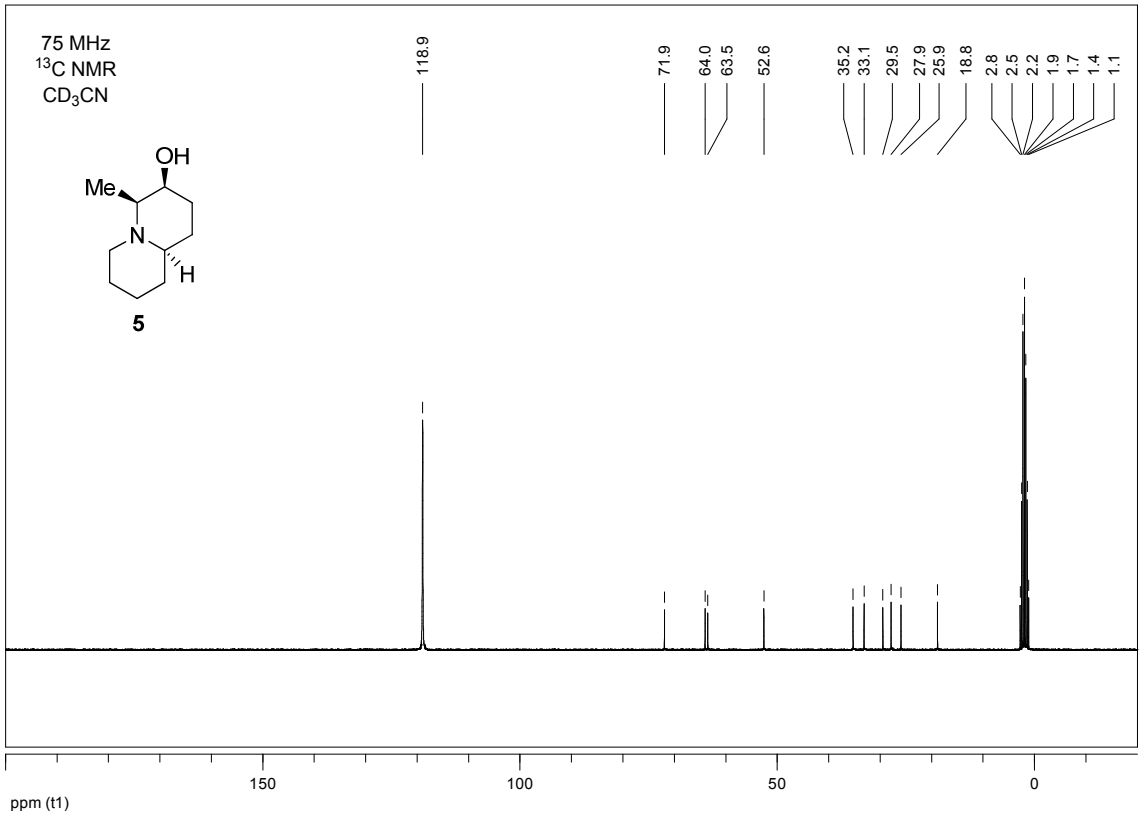

300 MHz
1H NMR
CDCl3
7.260
3.669
3.546
2.789
2.785
2.767
2.763
2.746
2.741
2.724
2.719
2.611
2.524
2.342
2.318
2.293
1.930
1.871
1.716
1.613
1.549
1.541
1.303
1.110
1.088
OH
Me
HN
3
CO2Me
3.29
1.02
1.04
1.13
2.35
1.53
3.08
5.75
3.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

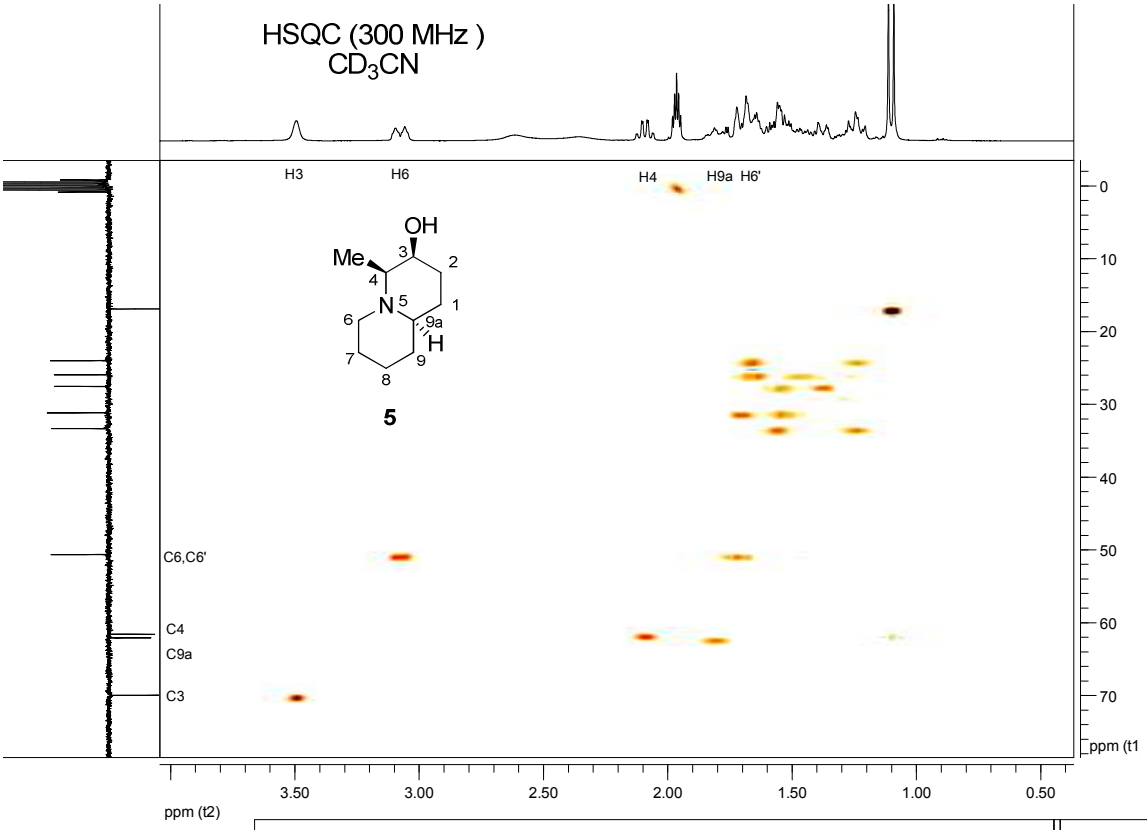

75 MHz
13C NMR
CDCl3
174.0
77.6
77.2
76.7
67.8
56.8
55.8
51.6
36.3
34.1
32.0
25.9
21.2
18.6
OH
Me
HN
3
CO2Me
150
100
50
ppm (t1)

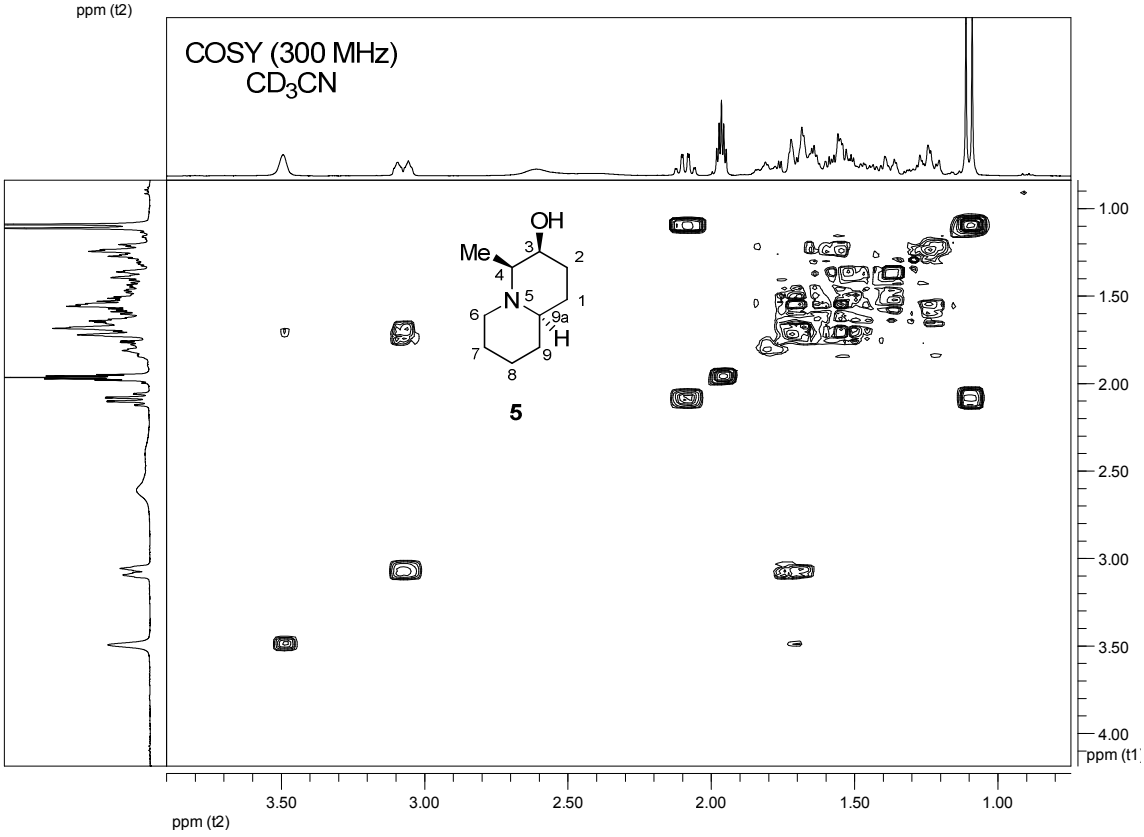

300 MHz
1H NMR
CDCl3
7.26
4.19
4.18
4.14
4.09
3.47
3.46
3.39
3.38
3.37
3.13
2.45
2.45
2.44
2.44
2.26
2.24
1.99
1.98
1.96
1.96
1.84
1.83
1.73
1.65
1.63
1.62
1.61
1.28
1.26
OH
Me
O
N
H
4
1.91
1.02
1.00
2.09
7.25
2.97
5.0
0.0
ppm (t1)

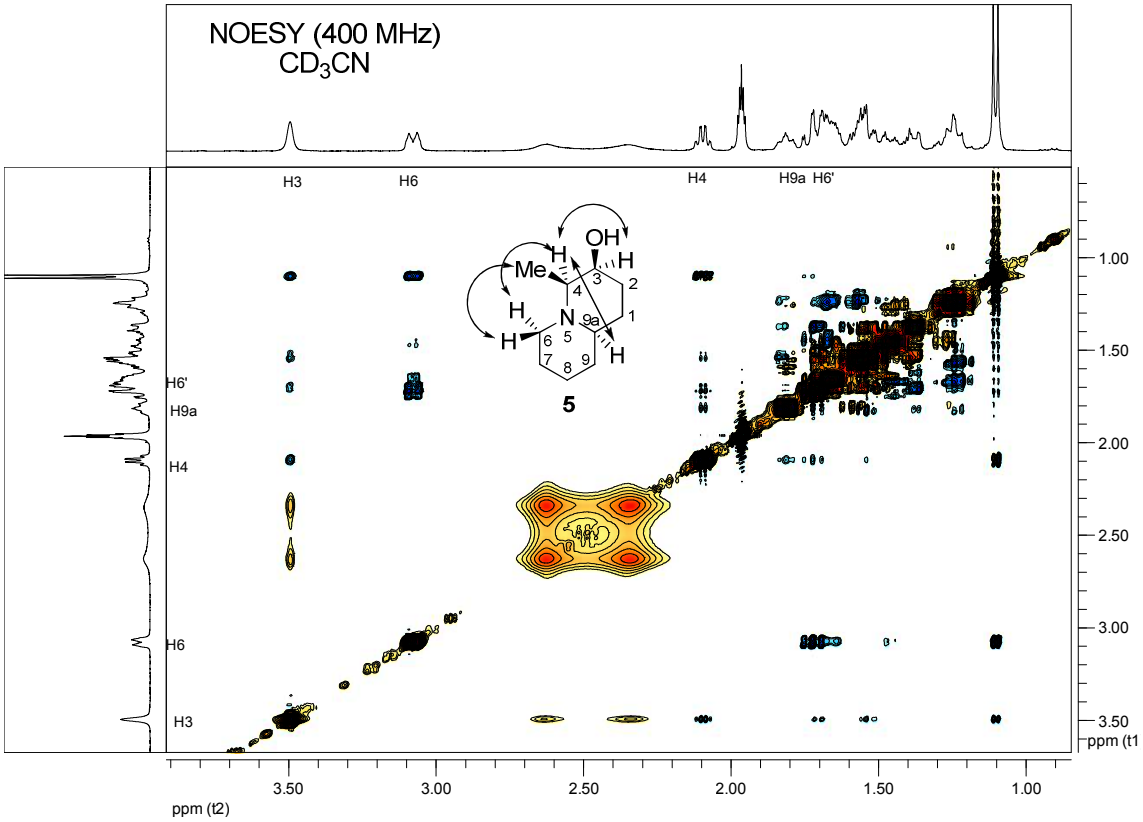

75 MHz
13C NMR
CDCl3
170.8
77.4
77.0
76.6
67.3
54.2
53.4
32.5
30.8
27.9
25.9
19.9
14.5
OH
Me
O
N
H
4
150
100
50
ppm (t1)

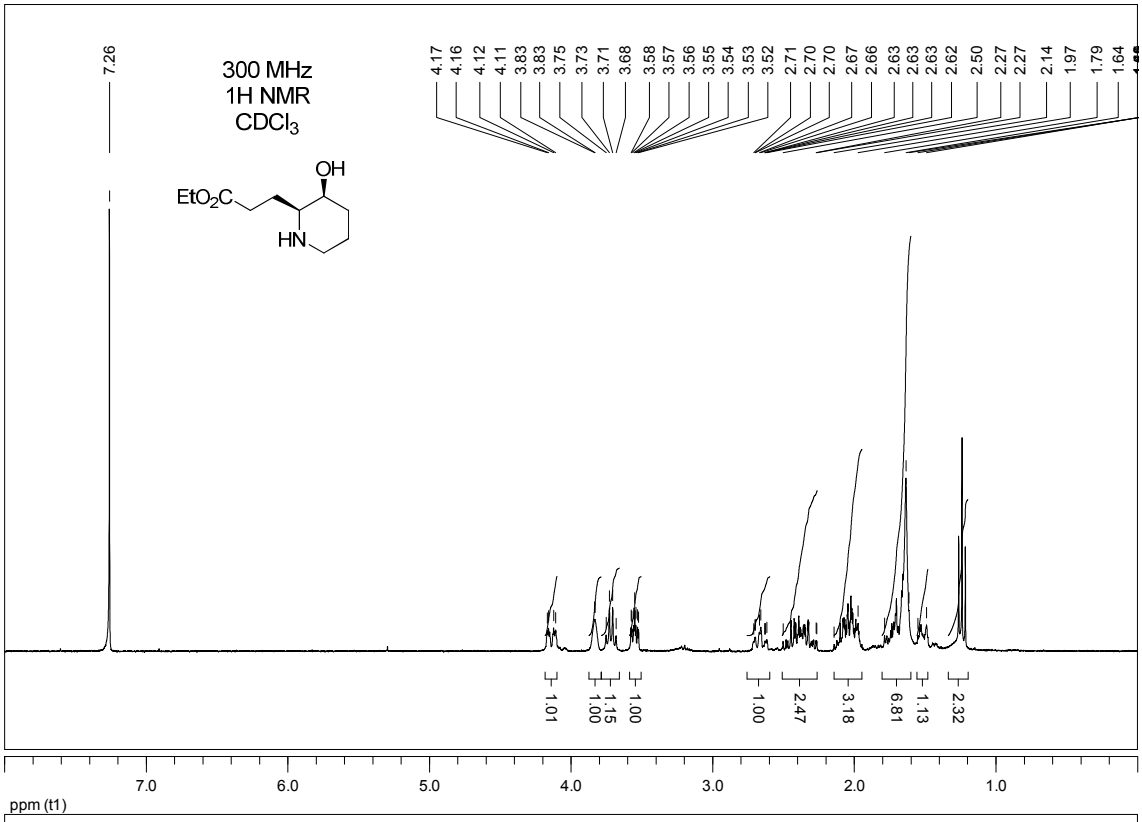

300 MHz
1H NMR
CD3CN
3.47
3.08
3.07
3.07
3.03
3.02
2.63
2.31
2.10
2.09
2.08
2.07
2.06
2.05
2.03
2.03
1.96
1.95
1.94
1.93
1.92
1.82
1.81
1.18
1.09
1.07
OH
Me
N
H
5
1.00
1.02
1.81
1.00
12.50
3.08
4.0
3.0
2.0
1.0
ppm (t1)

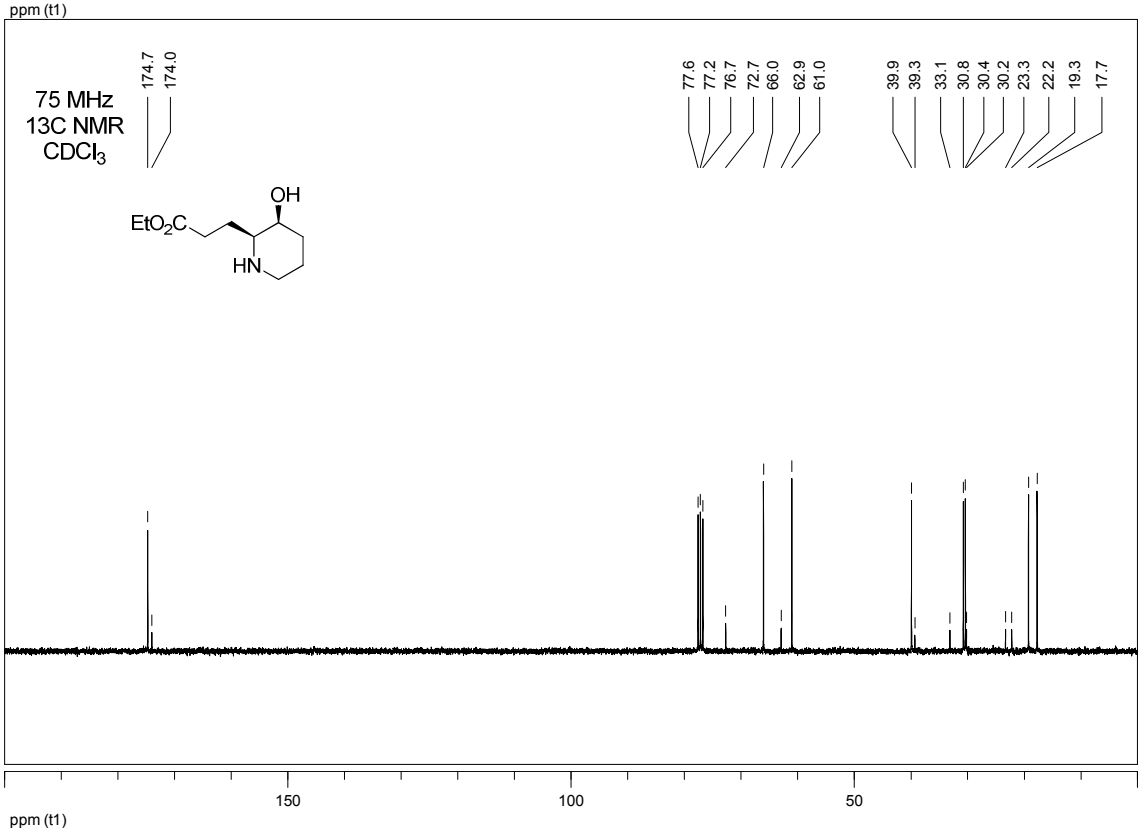

75 MHz
13C NMR
CD3CN
118.9
71.9
64.0
63.5
52.6
35.2
33.1
29.5
27.9
25.9
18.8
2.8
2.5
2.2
1.9
1.7
1.4
1.1
OH
Me
N
H
5
150
100
50
0
ppm (t1)

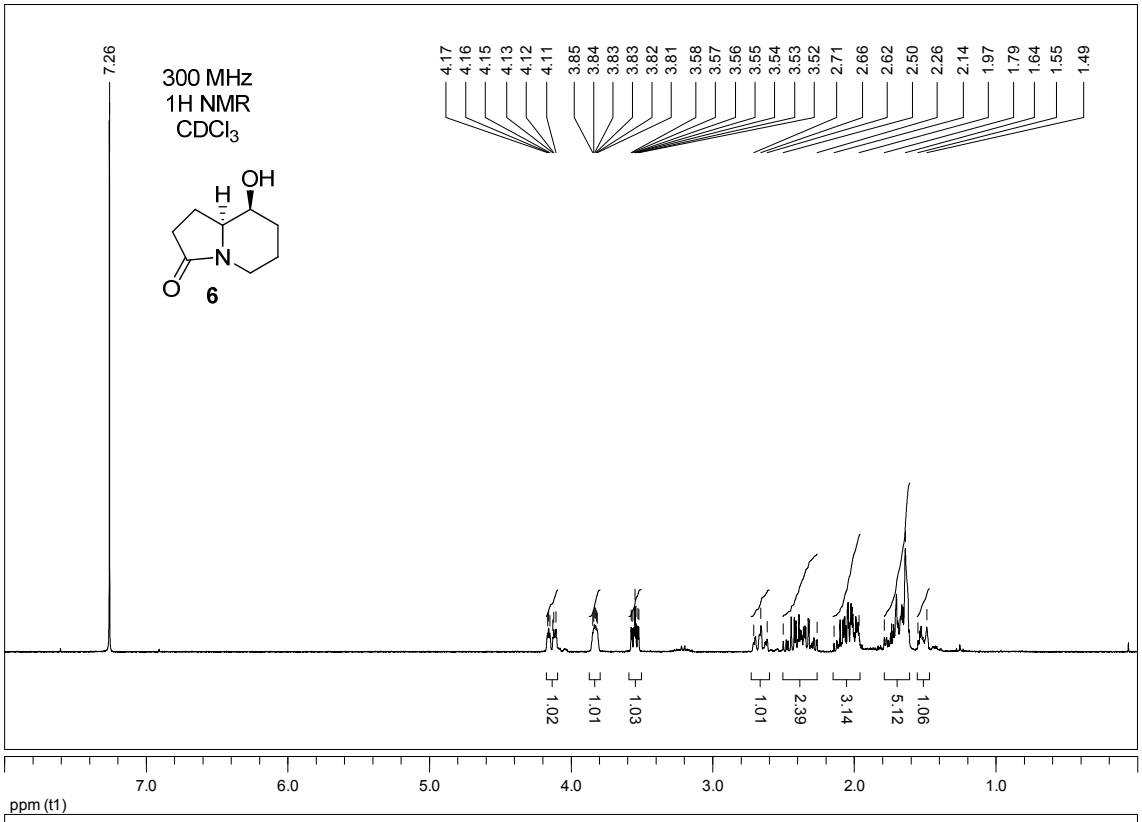

HSQC (300 MHz)
CD3CN
H3
H6
H4
H9a
H6'
OH
Me
N
H
5
C6,C6'
C4
C9a
C3
ppm (t1
ppm (t2)

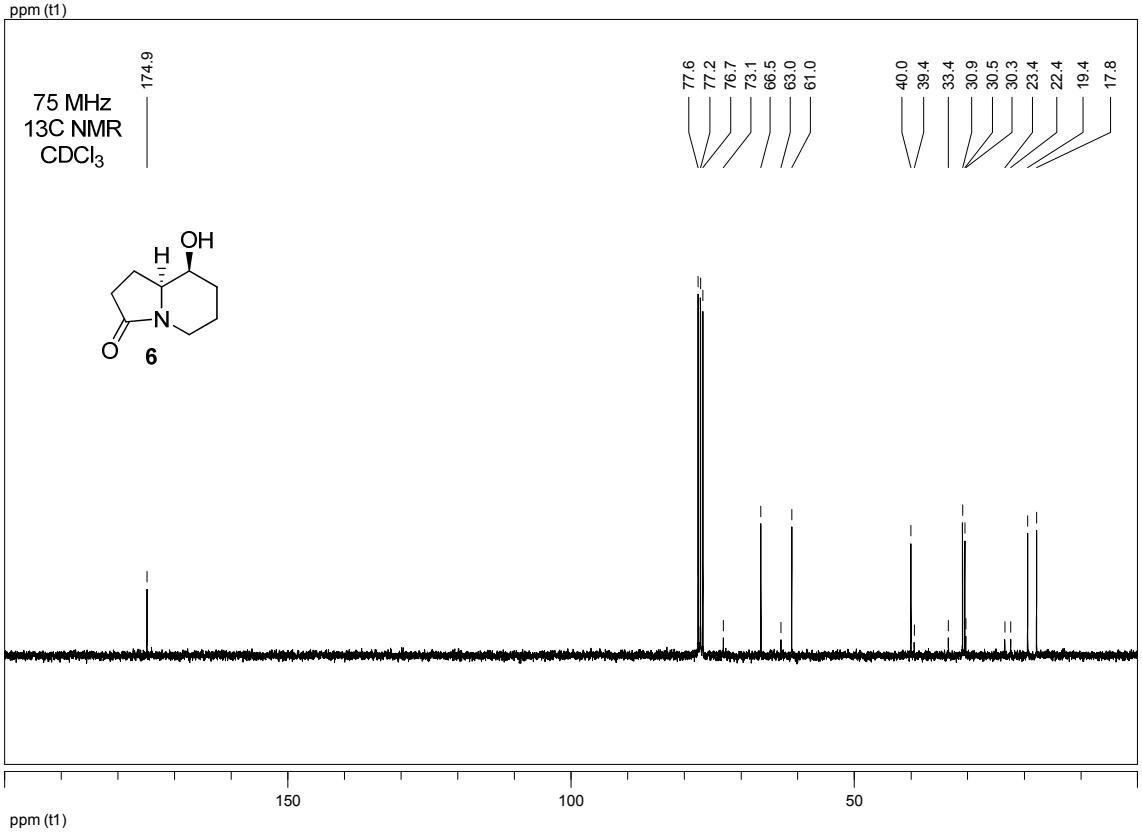

COSY (300 MHz)
CD3CN
OH
Me
N
H
5
ppm (t1)
ppm (t2)

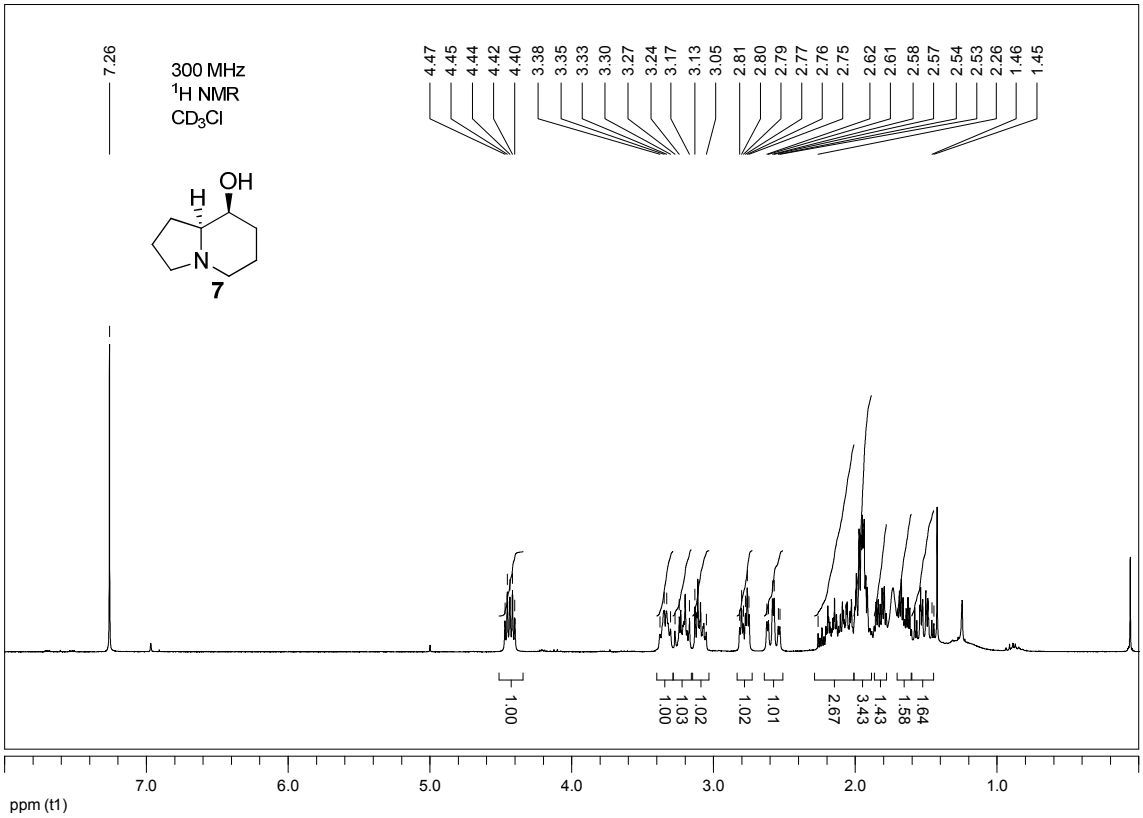

NOESY (400 MHz)
CD3CN
H3
H6
H4
H9a H6'
H6'
H9a
H4
H6
H3
OH
Me
H
N
9a
5
1.00
1.50
2.00
2.50
3.00
3.50
ppm (t1
3.50
3.00
2.50
2.00
1.50
1.00
ppm (t2)

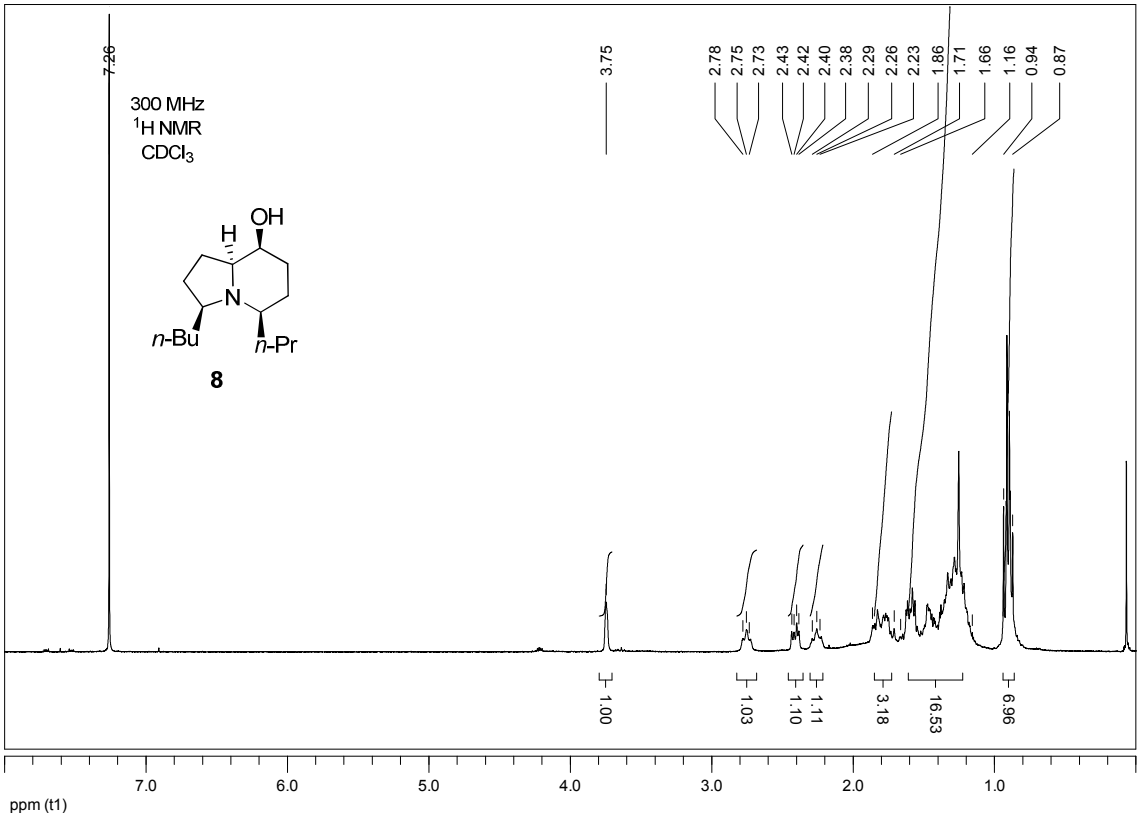

300 MHz
1H NMR
CDCl3
7.26
4.17
4.16
4.12
4.11
3.83
3.83
3.75
3.73
3.71
3.68
3.58
3.57
3.56
3.55
3.54
3.53
3.52
2.71
2.70
2.70
2.67
2.66
2.63
2.63
2.63
2.62
2.50
2.27
2.27
2.14
1.97
1.79
1.64
1.01
1.00
1.15
1.00
1.00
2.47
3.18
6.81
1.13
2.32
OH
EtO2C
HN
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

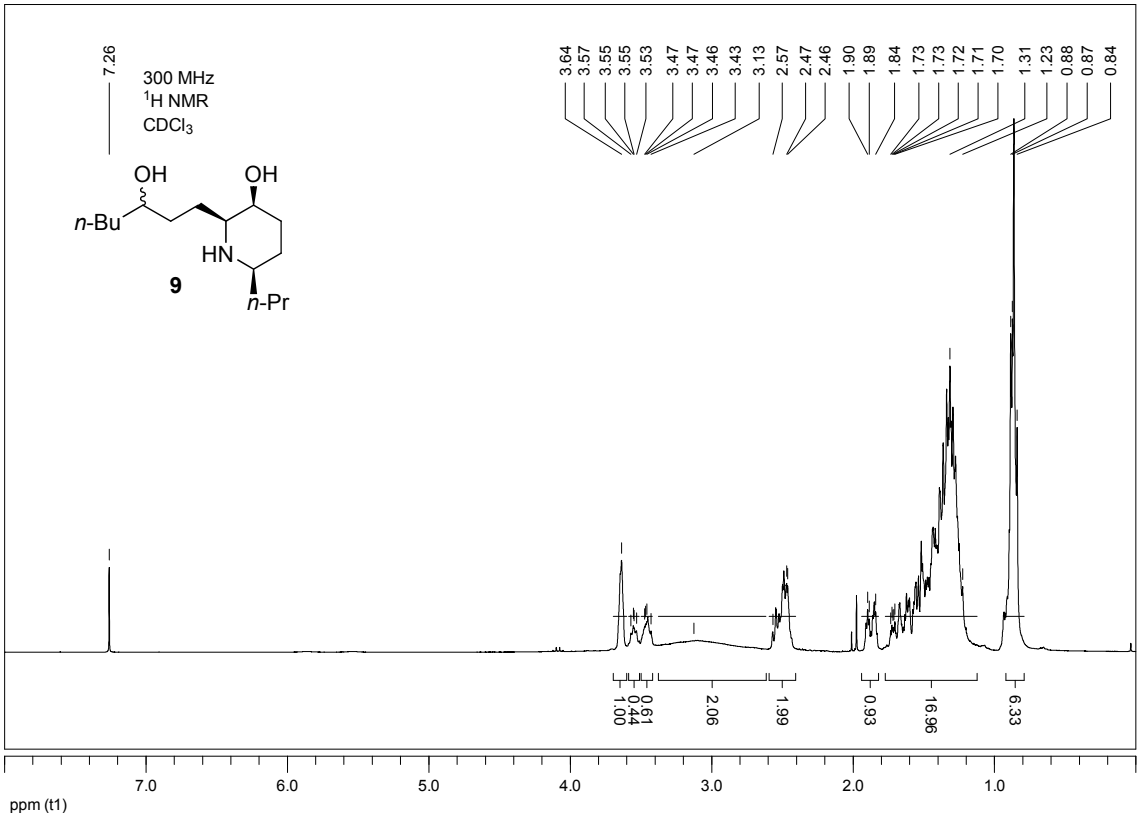

75 MHz
13C NMR
CDCl3
174.7
174.0
77.6
77.2
76.7
72.7
66.0
62.9
61.0
39.9
39.3
33.1
30.8
30.4
30.2
23.3
22.2
19.3
17.7
OH
EtO2C
HN
150
100
50
ppm (t1)

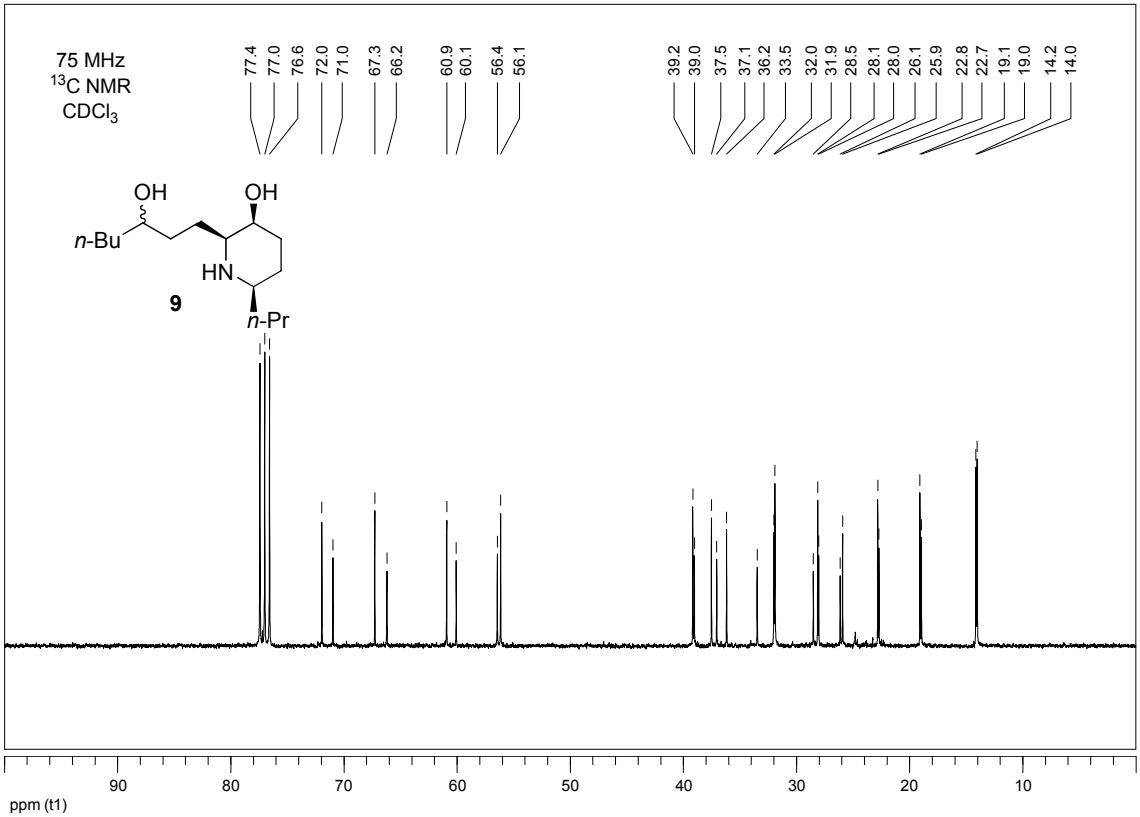

7.26
300 MHz
1H NMR
CDCl3
OH
H
N
O
6
4.17
4.16
4.15
4.13
4.12
4.11
3.85
3.84
3.83
3.83
3.82
3.81
3.58
3.57
3.56
3.55
3.54
3.53
3.52
2.71
2.66
2.62
2.50
2.26
2.14
1.97
1.79
1.64
1.55
1.49
1.02
1.01
1.03
1.01
2.39
3.14
5.12
1.06
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

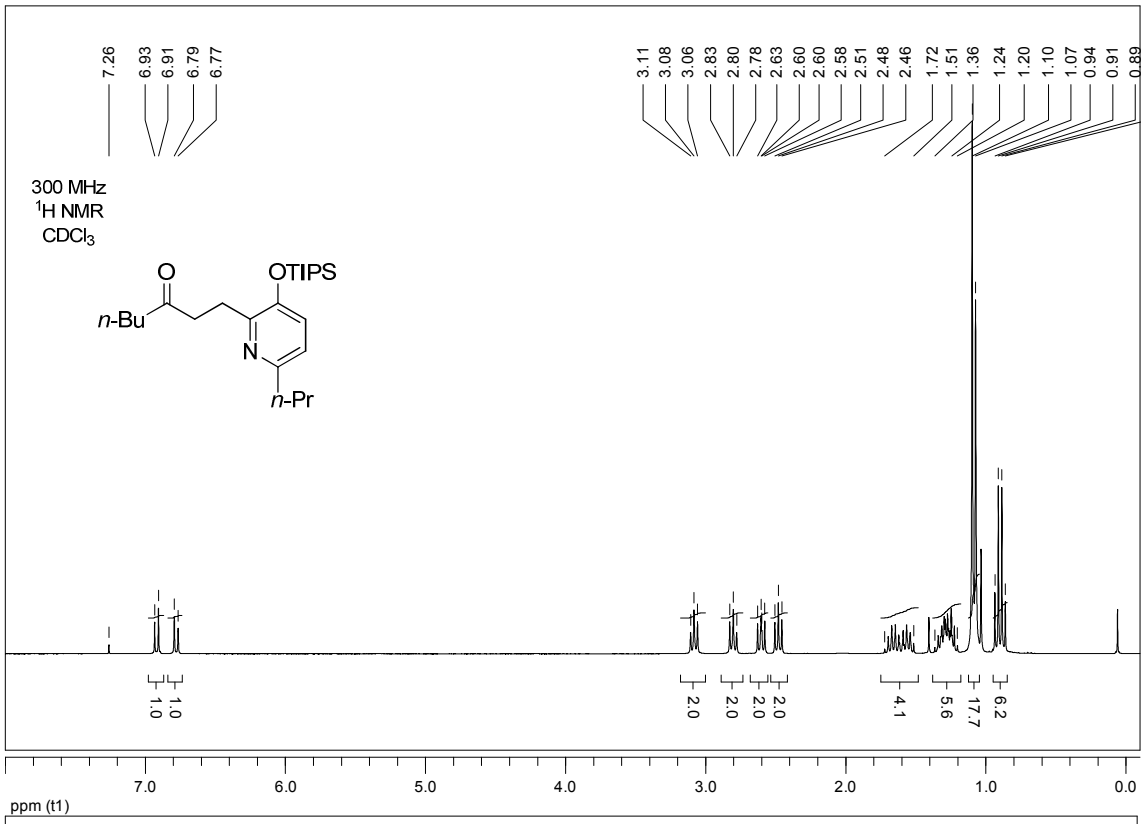

174.9
75 MHz
13C NMR
CDCl3
OH
H
N
O
6
77.6
77.2
76.7
73.1
66.5
63.0
61.0
40.0
39.4
33.4
30.9
30.5
30.3
23.4
22.4
19.4
17.8
150
100
50
ppm (t1)

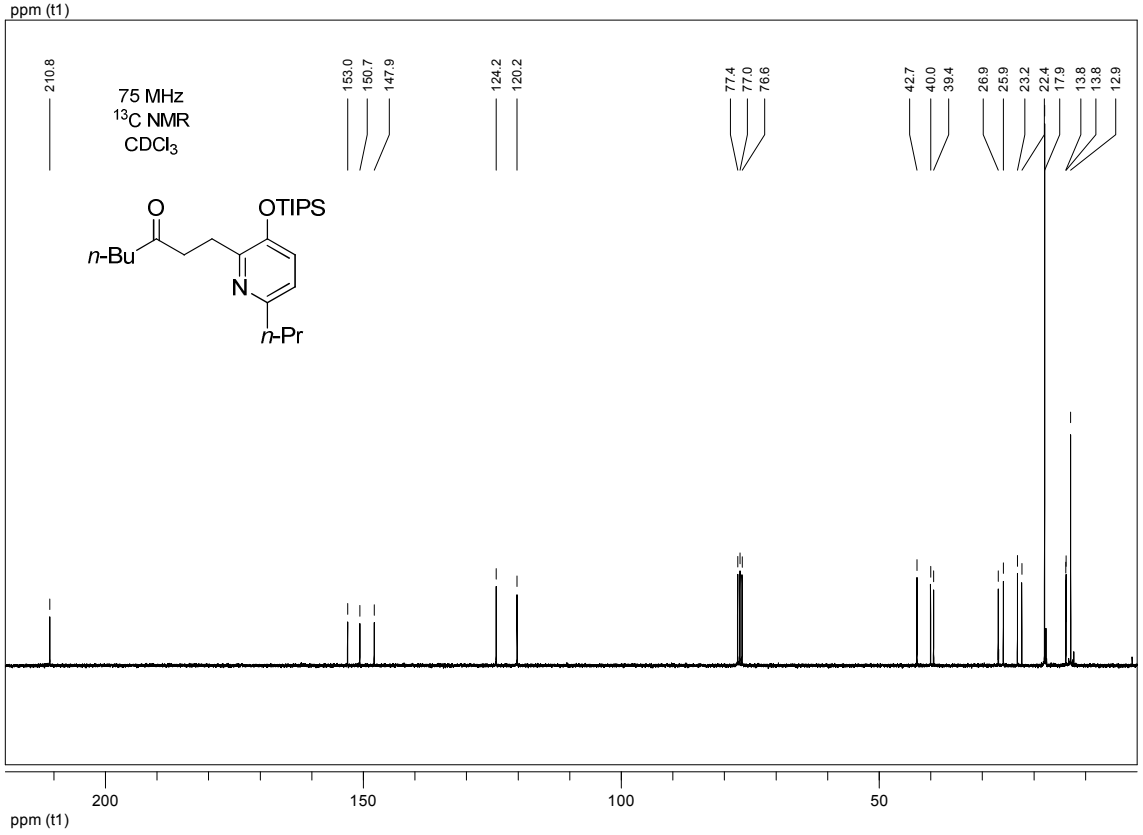

7.26
300 MHz
1H NMR
CD3Cl
4.47
4.45
4.44
4.42
4.40
3.38
3.35
3.33
3.30
3.27
3.24
3.17
3.13
3.05
2.81
2.80
2.79
2.77
2.76
2.75
2.62
2.61
2.58
2.57
2.54
2.53
2.26
1.46
1.45
H
OH
N
7
1.00
1.00
1.03
1.02
1.02
1.01
2.67
3.43
1.43
1.58
1.64
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

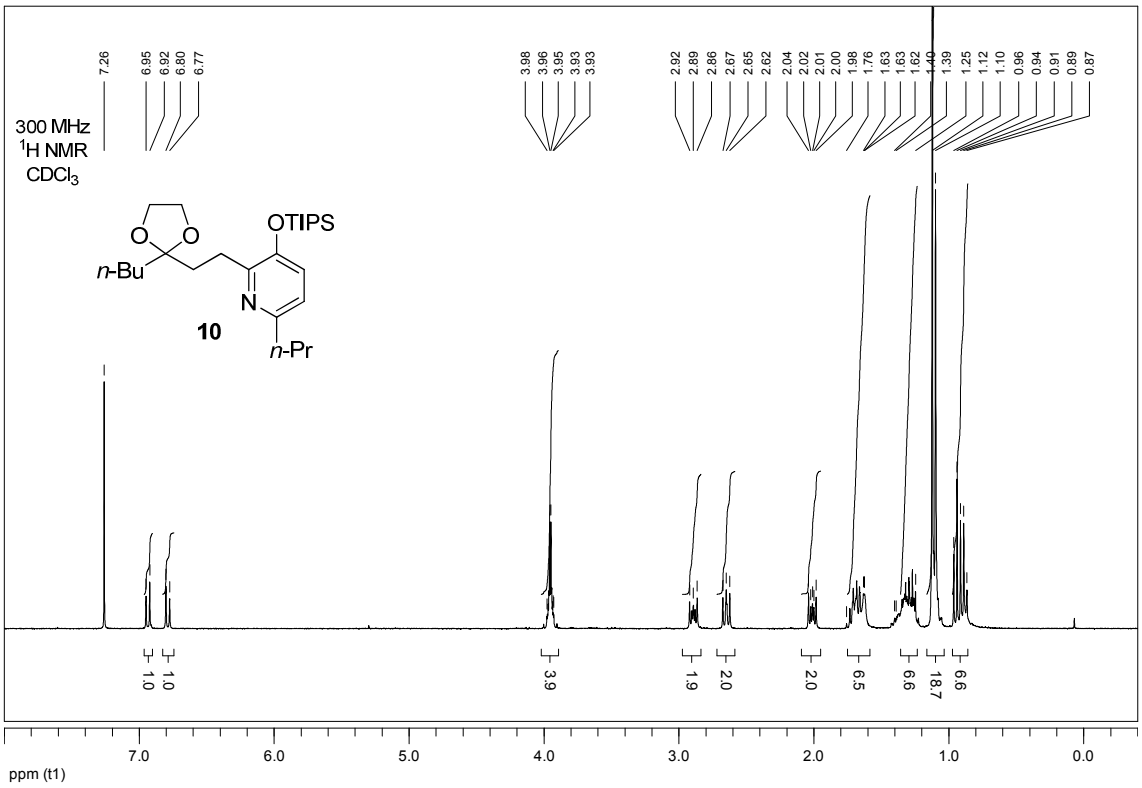

7.26
300 MHz
1H NMR
CDCl3
OH
H
N
n-Bu
n-Pr
8
3.75
2.78
2.75
2.73
2.43
2.42
2.40
2.38
2.29
2.26
2.23
1.86
1.71
1.66
1.16
0.94
0.87
1.00
1.03
1.10
1.11
3.18
16.53
6.96
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

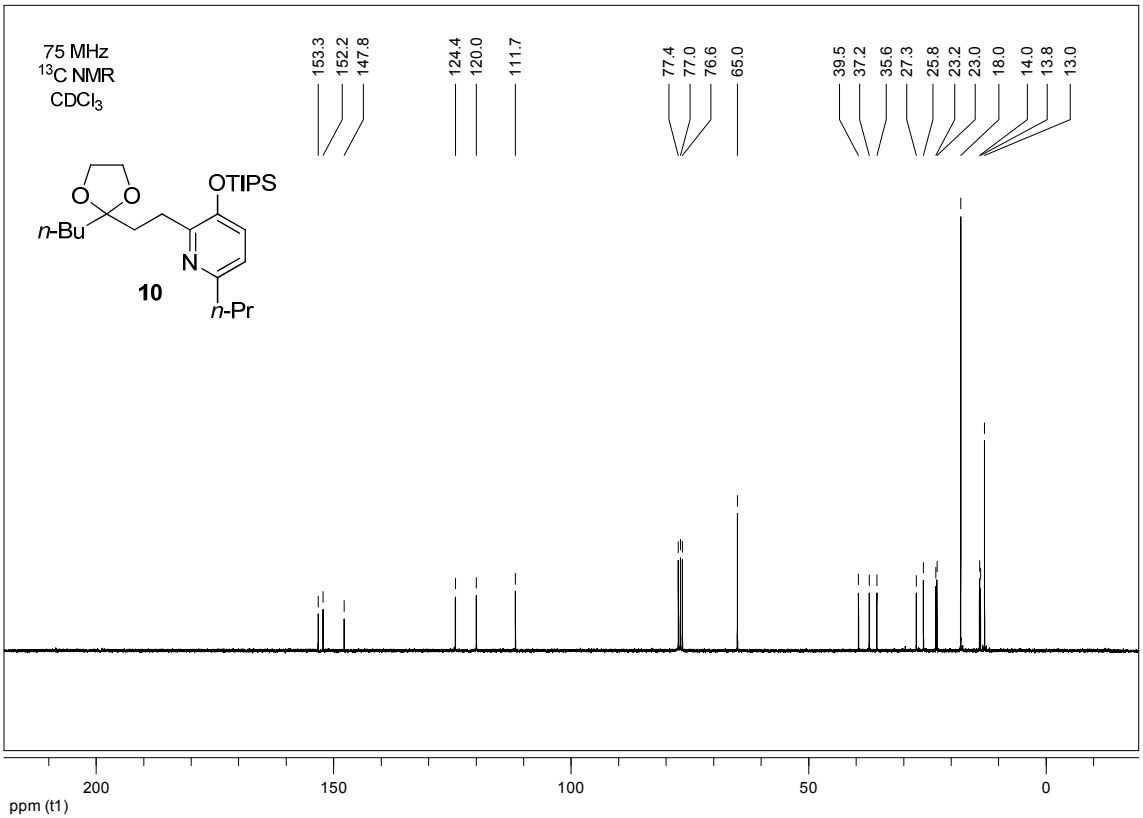

7.26
300 MHz
^{1}H NMR
$CDCl_3$
OH
OH
n-Bu
HN
9
n-Pr
3.64
3.57
3.55
3.55
3.53
3.47
3.47
3.46
3.43
3.13
2.57
2.47
2.46
1.90
1.89
1.84
1.73
1.73
1.72
1.71
1.70
1.31
1.23
0.88
0.87
0.84
1.00
0.91
0.44
0.90
2.06
1.69
0.93
16.96
6.33
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

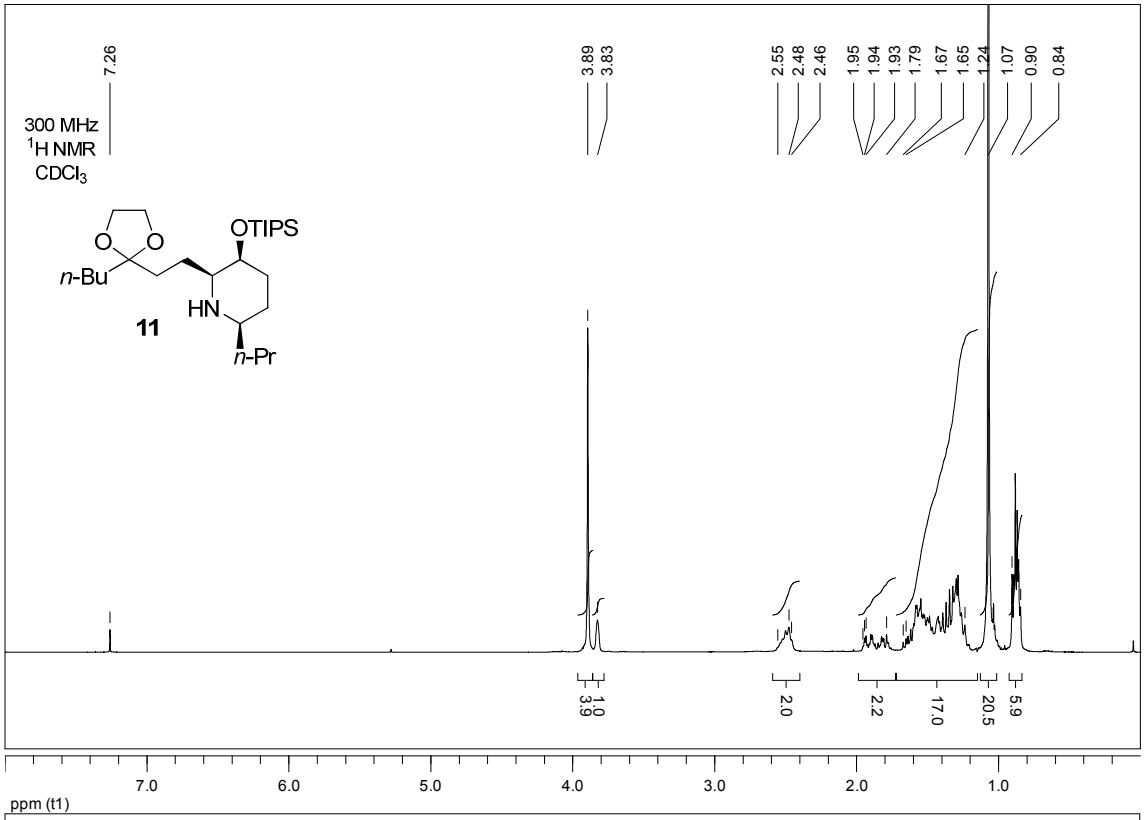

75 MHz
^{13}C NMR
$CDCl_3$
OH
OH
n-Bu
HN
9
n-Pr
77.4
77.0
76.6
72.0
71.0
67.3
66.2
60.9
60.1
56.4
56.1
39.2
39.0
37.5
37.1
36.2
33.5
32.0
31.9
28.5
28.1
28.0
26.1
25.9
22.8
22.7
19.1
19.0
14.2
14.0
90
80
70
60
50
40
30
20
10
ppm (t1)


7.26
6.93
6.91
6.79
6.77
3.11
3.08
3.06
2.83
2.80
2.78
2.63
2.60
2.60
2.58
2.51
2.48
2.46
1.72
1.51
1.36
1.24
1.20
1.10
1.07
0.94
0.91
0.89
300 MHz
1H NMR
CDCl3
O
OTIPS
n-Bu
N
n-Pr
1.0
1.0
2.0
2.0
2.0
2.0
4.1
5.6
17.7
6.2
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


210.8
153.0
150.7
147.9
124.2
120.2
77.4
77.0
76.6
42.7
40.0
39.4
26.9
25.9
23.2
22.4
17.9
13.8
13.8
12.9
75 MHz
13C NMR
CDCl3
O
OTIPS
n-Bu
N
n-Pr
200
150
100
50
ppm (t1)


300 MHz
1H NMR
CDCl3
7.26
6.95
6.92
6.80
6.77
3.98
3.96
3.95
3.93
3.93
2.92
2.89
2.86
2.67
2.65
2.62
2.04
2.02
2.01
2.00
1.98
1.76
1.63
1.63
1.62
1.40
1.39
1.25
1.12
1.10
0.96
0.94
0.91
0.89
0.87
OTIPS
n-Bu
N
10
n-Pr
1.0
1.0
3.9
1.9
2.0
2.0
9.5
6.6
18.7
9.6
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


75 MHz
13C NMR
CDCl3
153.3
152.2
147.8
124.4
120.0
111.7
77.4
77.0
76.6
65.0
39.5
37.2
35.6
27.3
25.8
23.2
23.0
18.0
14.0
13.8
13.0
OTIPS
n-Bu
N
10
n-Pr
200
150
100
50
0
ppm (t1)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300 MHz
1H NMR
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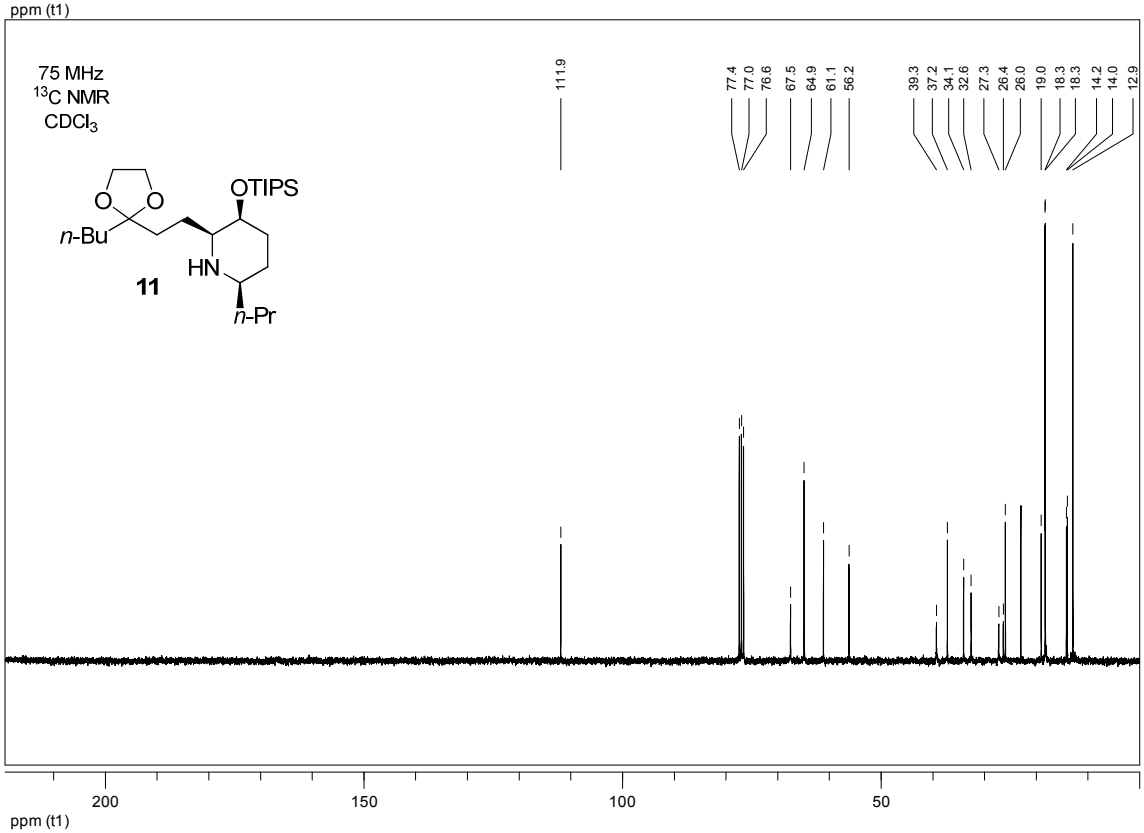
3.89
3.83
2.55
2.48
2.46
1.95
1.94
1.93
1.79
1.67
1.65
1.24
1.07
0.90
0.84
OTIPS
n-Bu
HN
n-Pr
11
1.0
3.9
2.0
2.2
17.0
20.5
5.9
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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13C NMR
CDCl3
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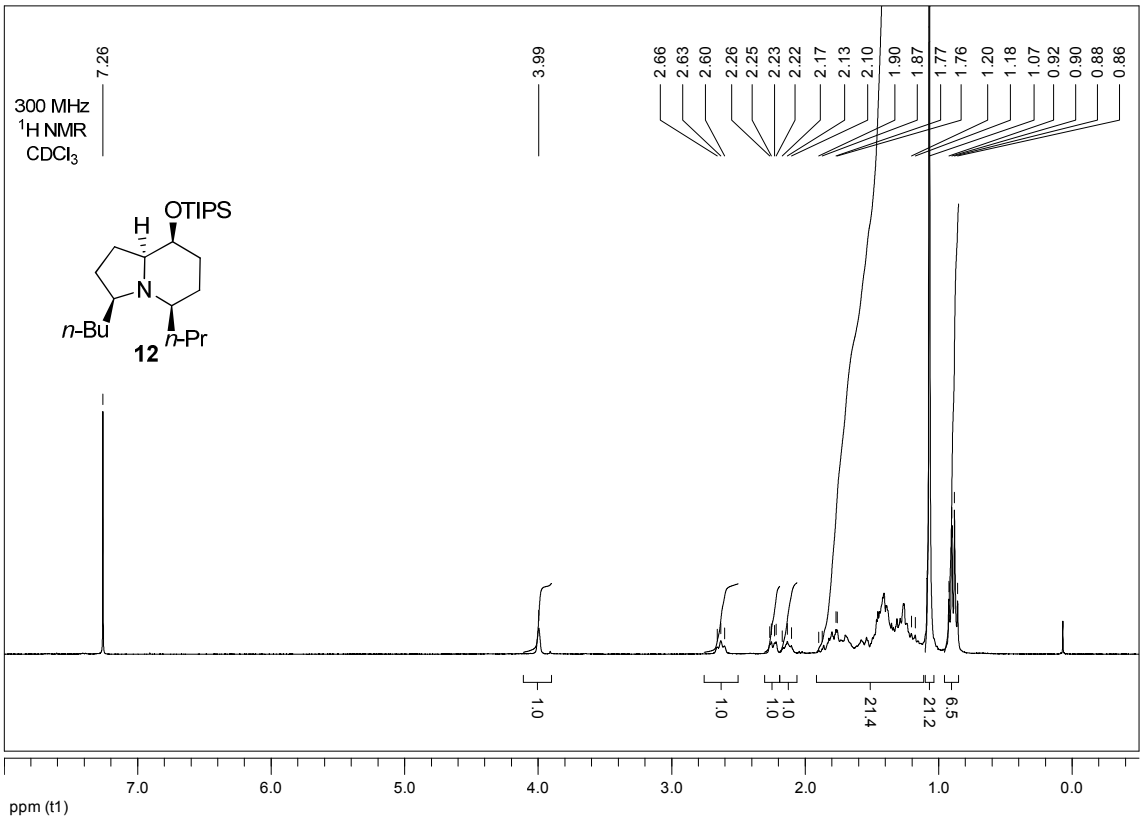
77.0
76.6
67.5
64.9
61.1
56.2
39.3
37.2
34.1
32.6
27.3
26.4
26.0
19.0
18.3
18.3
14.2
14.0
12.9
OTIPS
n-Bu
HN
n-Pr
11
200
150
100
50
ppm (t1)


300 MHz
^{1}H NMR
$CDCl_3$
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3.99
2.66
2.63
2.60
2.26
2.25
2.23
2.22
2.17
2.13
2.10
1.90
1.87
1.77
1.76
1.20
1.18
1.07
0.92
0.90
0.88
0.86
OTIPS
H
N
n-Bu
n-Pr
12
1.0
1.0
1.0
1.0
21.4
21.2
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7.0
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5.0
4.0
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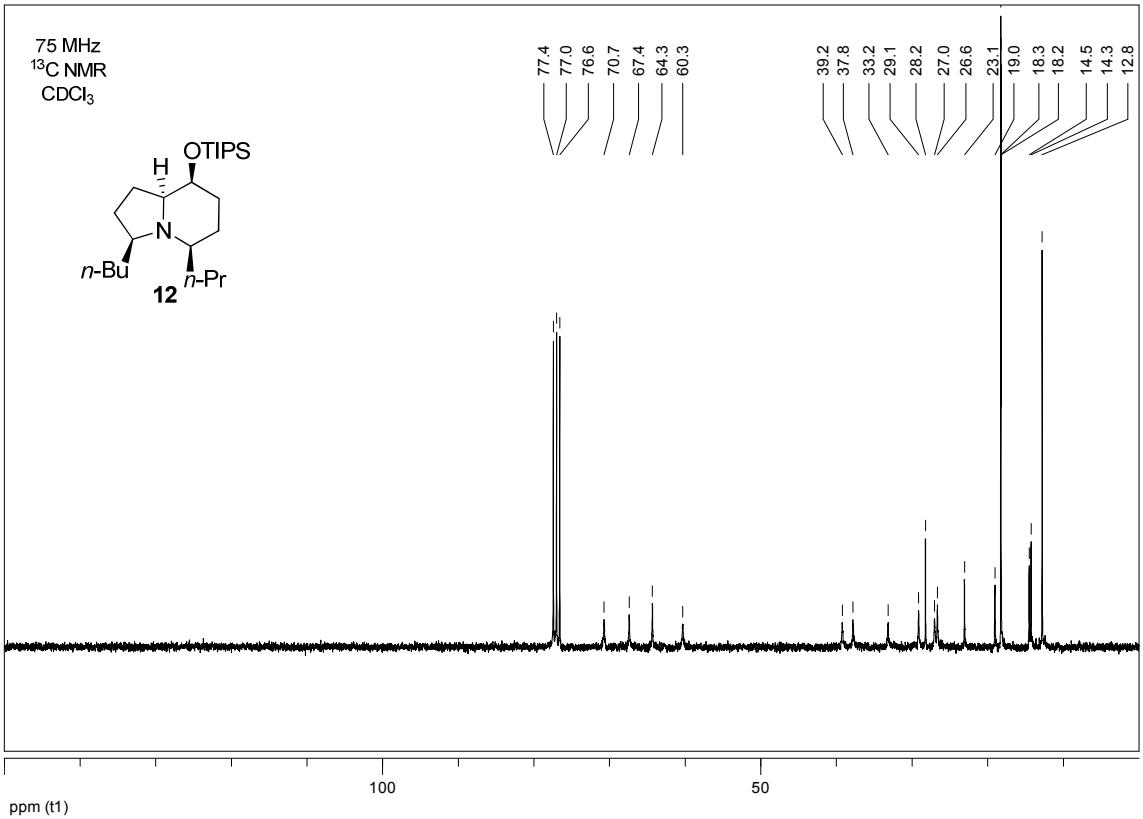
1.0
0.0
ppm (t1)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^{13}C NMR
$CDCl_3$
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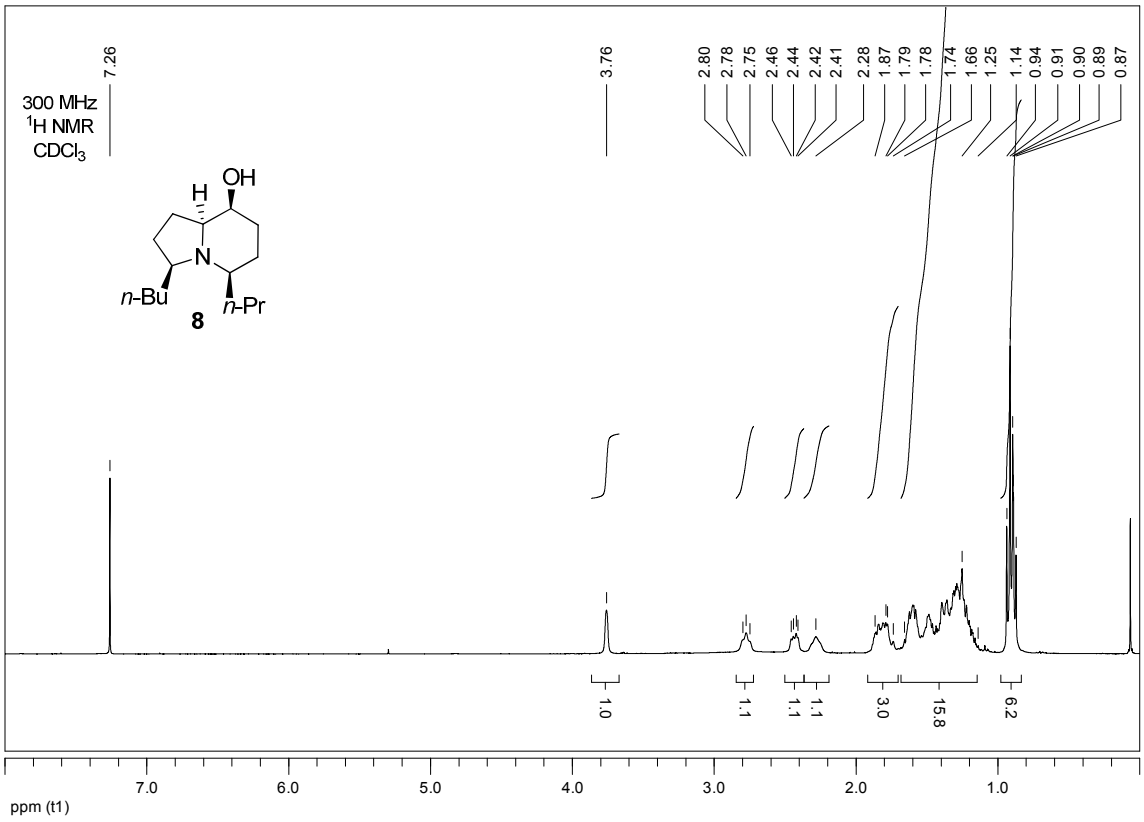
77.0
76.6
70.7
67.4
64.3
60.3
39.2
37.8
33.2
29.1
28.2
27.0
26.6
23.1
19.0
18.3
18.2
14.5
14.3
12.8
OTIPS
H
N
n-Bu
n-Pr
12
100
50
ppm (t1)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^{1}H NMR
$CDCl_3$
7.26
3.76
2.80
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2.44
2.42
2.41
2.28
1.87
1.79
1.78
1.74
1.66
1.25
1.14
0.94
0.91
0.90
0.89
0.87
H
OH
N
n-Bu
n-Pr
8
1.0
1.1
1.1
1.1
3.0
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7.0
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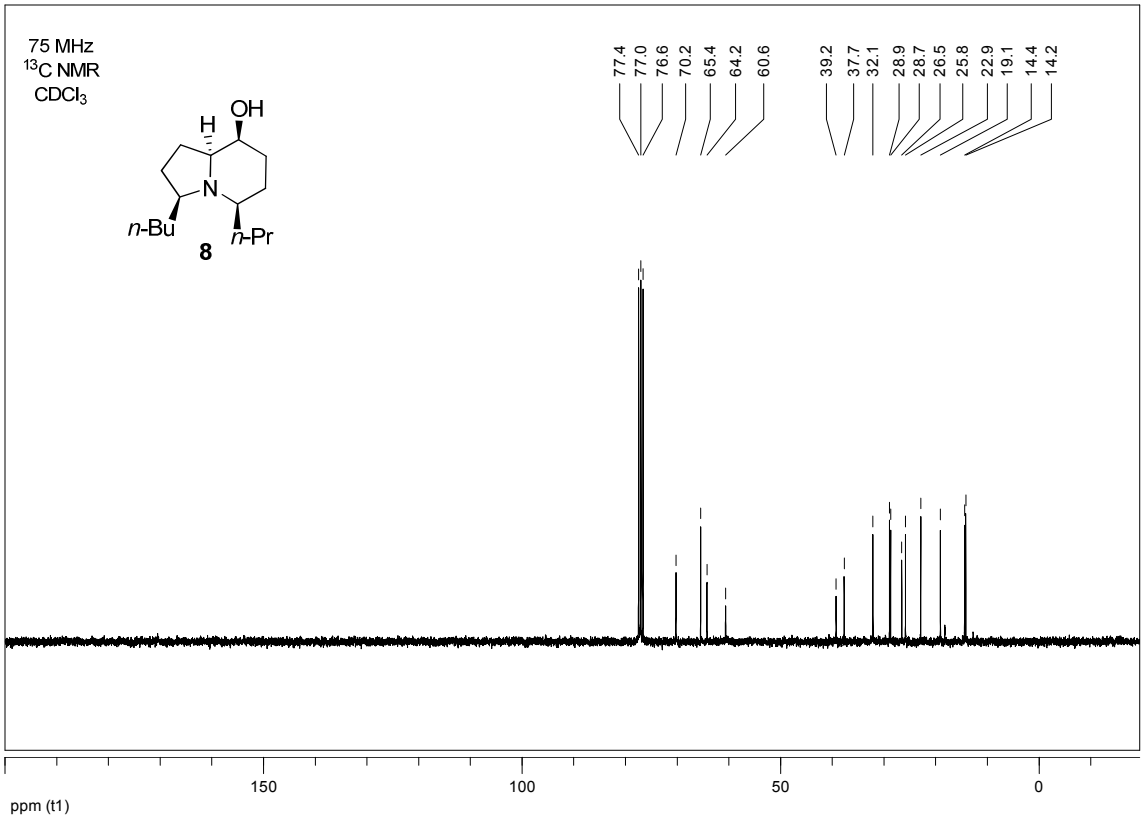
4.0
3.0
2.0
1.0
ppm (t1)


75 MHz
^{13}C NMR
$CDCl_3$
77.4
77.0
76.6
70.2
65.4
64.2
60.6
39.2
37.7
32.1
28.9
28.7
26.5
25.8
22.9
19.1
14.4
14.2
H
OH
N
n-Bu
n-Pr
8
150
100
50
0
ppm (t1)

II. Theoretical complementary details

State specific dual descriptors are real space functions defined by:[1]

$$\Delta f_i(\vec{r}) = \rho^{ESi}(\vec{r}) - \rho^{GS}(\vec{r}), \qquad \text{(S1)}$$

where ρ^{ESi} denotes the electron density of the ith excited state and ρ^{GS} that of the electronic ground state. They were obtained at the Time Dependent Density Functional Theory (TDDFT) level using 10 states and incorporating implicit solvent effects using the default IEFPCM implementation.

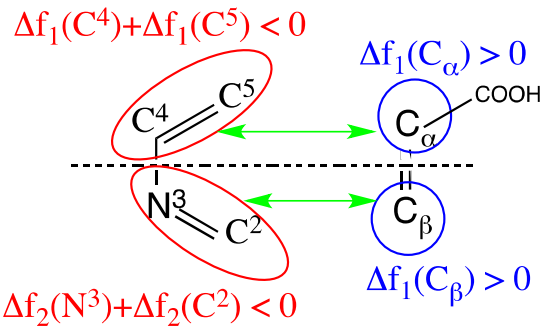
As generalization of the usual dual descriptor,[2] they provide information about the electrophilic (where they take positive values) and nucleophilic (regions of negative values) behaviours from a pure density point of view. Such descriptors are local in the sense that they are calculated at each space point. They can be "translated" in the language of reactive sites by the so-called condensation procedure ("coarse grained" view of chemical reactivity). To this aim, we apply an adaptation of the widespread Yang-Mortier scheme,[3] using Bader's Atoms-in-Molecules atomic charges q:[4]

$$\Delta f_i(atomA) = q^{GS}(atomA) - q^{ESi}(atomA). \qquad \text{(S2)}$$

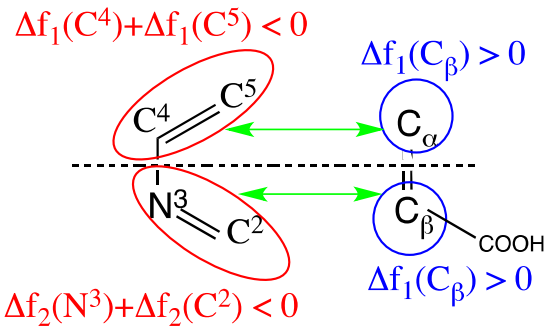
If one wants to compare two different molecules (and not only two reactive sites on the same molecule), one has to shift towards grand canonical description (derivative with respect to the electronic chemical potential instead of the electron number). The simplest way[5] for achieving this is to multiply the dual descriptors values by the squared global softness S^2 (where $S = \left(\frac{\partial N}{\partial \mu}\right)_{v(\vec{r})}$). In this work, S was computed using finite difference linearization involving the ionization potential and the electron affinity of the studied molecule.

A reaction will be favored in terms of electro/nucleophilicity if the main interactions are between atoms exhibiting opposite reactivities, in other words, if the product of the

corresponding condensed descriptors are negative. As explained in the article, and as represented in Figure S2, the nucleophilicity of the C^4=C^5 bond is described by the Δf_1 state-specific dual descriptor, while the nucleophilicty of the N^3=C^2 bond is accounted for by Δf_2. As for the electrophilicity of C_α=C_β bond in acrylic acid, it is satisfactorily traced by Δf_1. The two possible orientation for the Diels-Alder addition (**A** and **B**) can be schematically represented as above, where the green arrows identify the favored interactions in terms of electro/nucleophilicities:



Orientation of **A** type



Orientation of **B** type

In order to compare the two orientations by only considering the intrinsic reactants properties as intended in conceptual DFT (*i.e.* without the need to know anything about the corresponding transition state), the two following simple combinations can be proposed:

$$Pref\,\Delta f(A) = \overbrace{\left[\Delta f_1(C^4) + \Delta f_1(C^5)\right]}^{oxazole} \times \overbrace{\Delta f_1(C_\alpha)}^{acrylic\ acid} + \left[\Delta f_2(N^3) + \Delta f_2(C^2)\right] \times \Delta f_1(C_\beta), \quad \text{(S3)}$$

$$Pref\,\Delta f(B) = \left[\Delta f_1(C^4) + \Delta f_1(C^5)\right] \times \Delta f_1(C_\beta) + \left[\Delta f_2(N^3) + \Delta f_2(C^2)\right] \times \Delta f_1(C_\alpha). \quad \text{(S4)}$$

Similarly, if one is interested in reactivity from the electrostatic point of view, the GS atomic charges will play the role of the condensed dual descriptors:

$$PrefQ(A)=\left[q\left(C^4\right)+q\left(C^5\right)\right]\times q\left(C_\alpha\right)+\left[q\left(N^3\right)+q\left(C^2\right)\right]\times q\left(C_\beta\right), \quad \text{(S5)}$$

$$PrefQ(A)=\left[q\left(C^4\right)+q\left(C^5\right)\right]\times q\left(C_\beta\right)+\left[q\left(N^3\right)+q\left(C^2\right)\right]\times q\left(C_\alpha\right). \quad \text{(S6)}$$

Generally, philicity (coming from the energy variations with respect to the electron number) has strong links with the so-called "orbital control" (it can be shown that in most cases Δf_1 is close to ρ^{LUMO}-ρ^{HOMO}), while the "charge control" is connected to energetic variations due to changes to the external potential.[6]

In Bader's Atoms-in-Molecules theory,[4] bond critical points (BCPs) are points where the electron density gradient vanishes, the union of the two special gradient paths that originate from a BCP and that end at the two nuclei defining the bond path between them. In general, the density (ρ_c) and the laplacian ($\square^2\rho_c$ measures the charge accumulation ($\square^2\rho_c<0$) or depletion ($\square^2\rho_c>0$)) values at these points characterize the nature (covalent, ionic…) and the strength of the corresponding bond.

The source function[7] enables to evaluate to what extent each atomic basin Ω (we recall that atomic basins are separated by density gradient zero-flux surfaces) contributes to the density at a given point: the density can be actually decomposed into a sum of source function contributions, each of them being related to only one basin, according to:

$$\rho_c=\sum_\Omega \underbrace{-\frac{1}{4\pi}\int_\Omega \frac{\nabla^2\rho(\vec{r}')}{\|\vec{r}_c-\vec{r}'\|}d^3r'}_{S(\Omega)}=\sum_\Omega S(\Omega) \quad . \quad \text{(S7)}$$

Summing up over all atoms of the functional group directly enables to evaluate the source contribution of this substituents at a given real space point.

As Bader's atoms constitute an exhaustive partition of real space by non-overlapping domains, the total energy of the molecule can be properly decomposed, as shown by Pendás and coworkers,[8,9] into intra-atomic contributions and pair interactions, the last ones being equal to:

$$E_{AB}^{\text{int}} = E_{AB}^{nn} + E_{AB}^{en} + E_{AB}^{ne} + E_{AB}^{ee}, \qquad \text{(S8)}$$

where E_{AB}^{en} denotes the repulsion between the two nuclei, and E_{AB}^{ee} corresponds to the repulsion between the electrons in Ω_A and the ones in Ω_B. This last contribution can be rigorously splitted into a classical electrostatic contribution and an exchange-correlation one, the latter being linked to covalency, so that S8 can be cast in the following final form:

$$E_{AB}^{\text{int}} = E_{AB}^{\textit{total classical electrostatics}} + E_{AB}^{\text{"covalency"}}. \qquad \text{(S8)}$$

Delocalization indexes[10] are used here as a kind of "bond orders".[11]

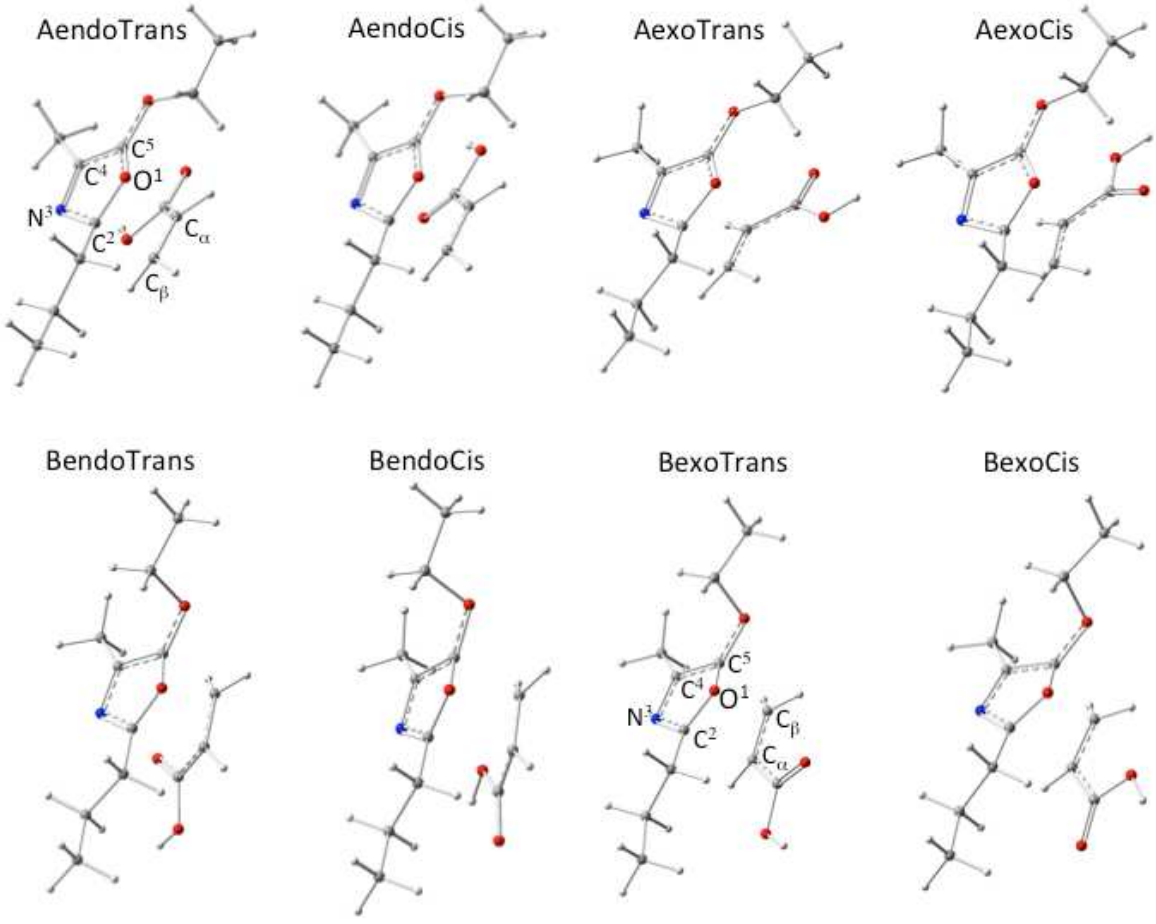


Figure S1. Views of the eight optimized transition states for the HDA step, depending on the relative orientation of the reactants. H in white, C in grey, N in blue, O in red.

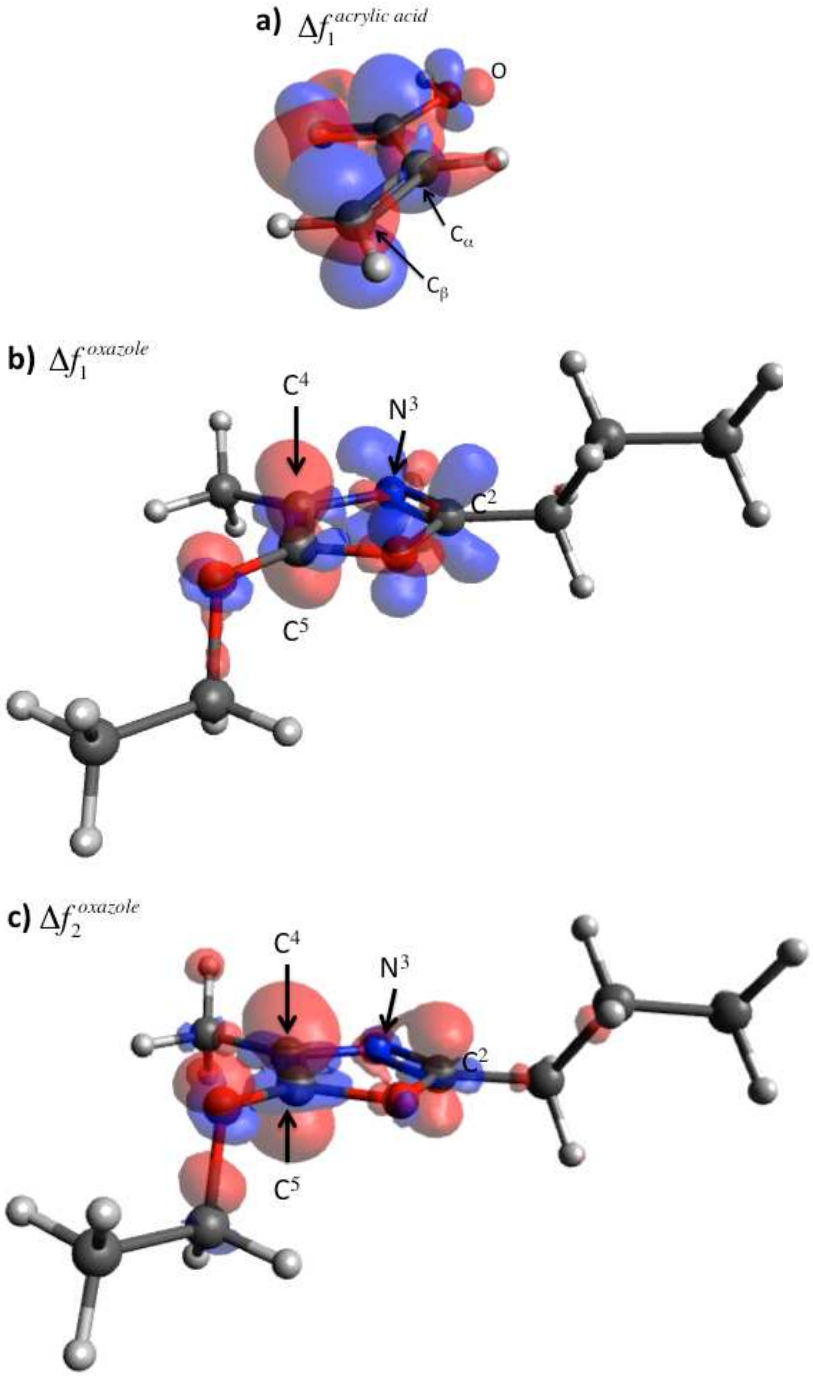


Figure S2. Views of : a) Δf_1 for acrylic acid (isovalue 0.004 a.u.), b) Δf_1 for oxazole, c) Δf_2 for oxazole (isovalue : 0.005 a.u. for b) and c)). Blue corresponds to positive values an indicates electrophilic regions, while red correspnds to negative values, indicating nucleophilic regions. H in white, C in grey, N in blue, O in red. These figures were generated with the Avogadro software (http://avogadro.openmolecules.net/).

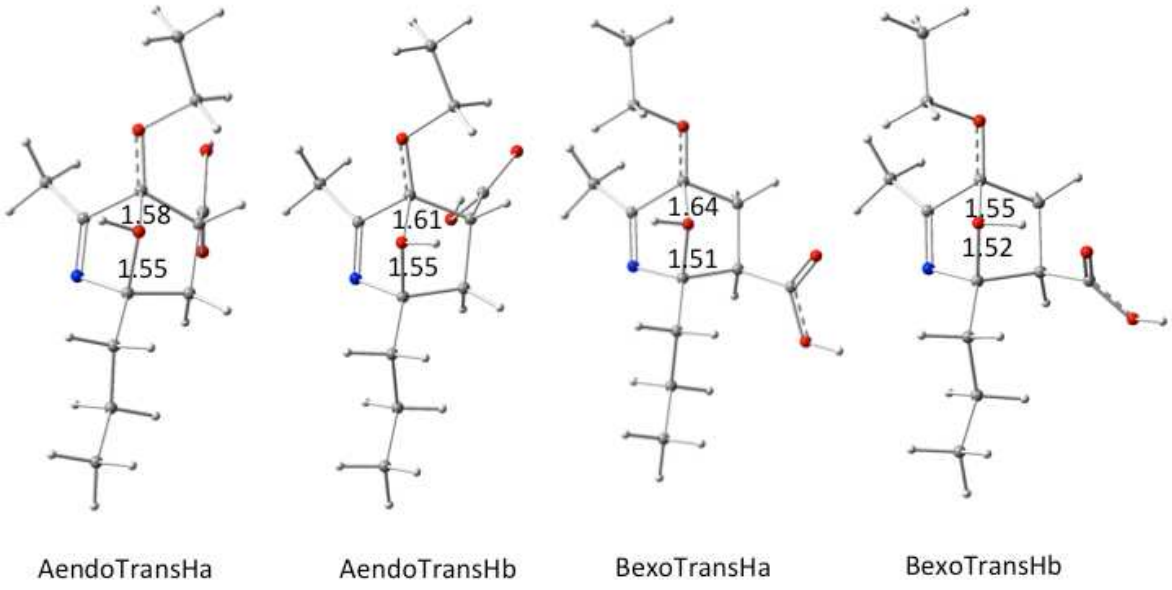


Figure S3. Views of the possible protonated bicyclic products. H in white, C in grey, N in blue, O in red.

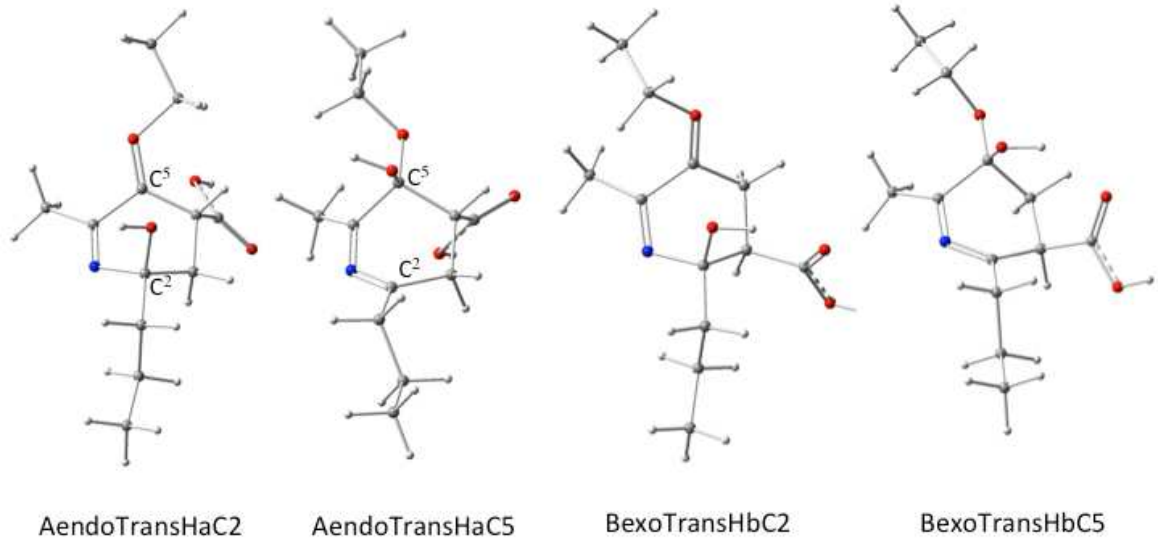


Figure S4. Views of the possible openings of the protonated bicyclic products. H in white, C in grey, N in blue, O in red.

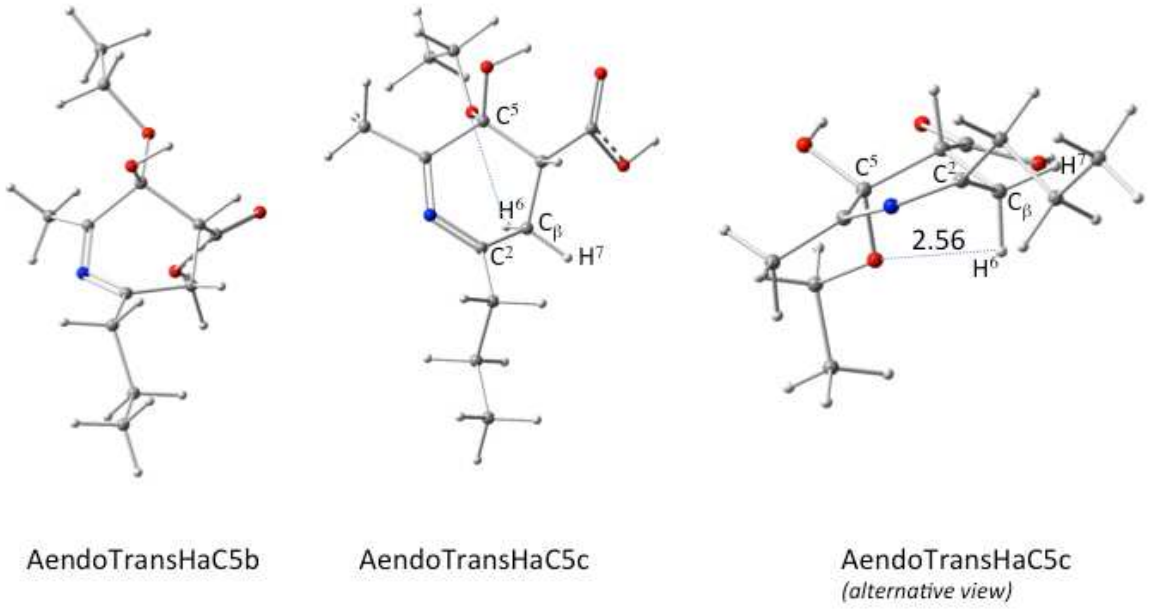


Figure S5. Successive isomerizations of compound **Aendo1HaC1**. H in white, C in grey, N in blue, O in red.

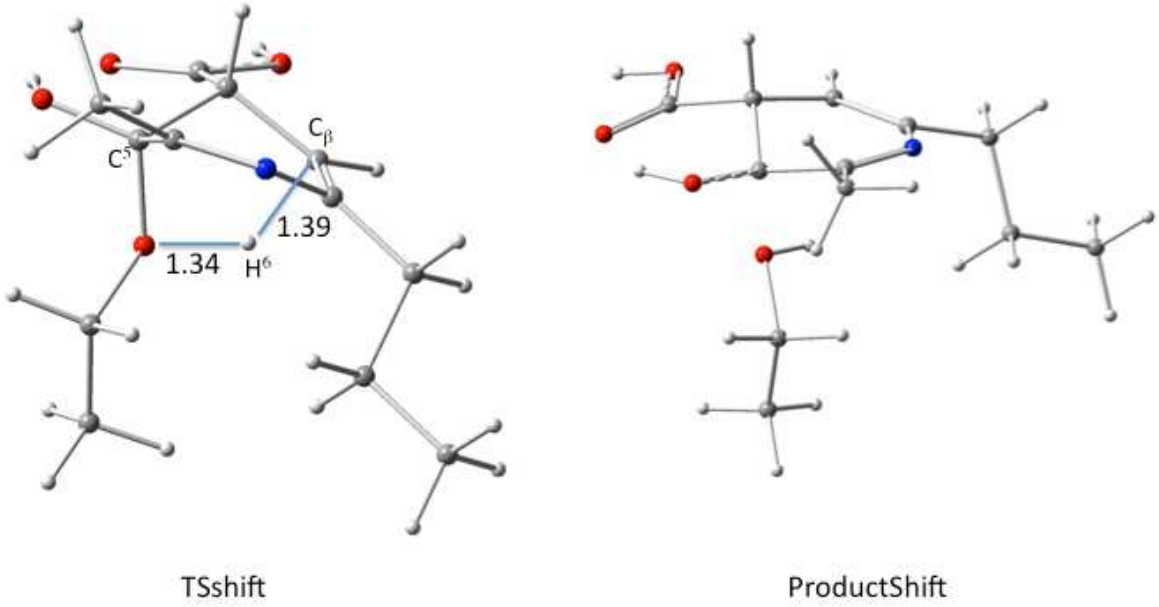


Figure S6. View of proton shift from **Aendo1HaC1c**. H in white, C in grey, N in blue, O in red.

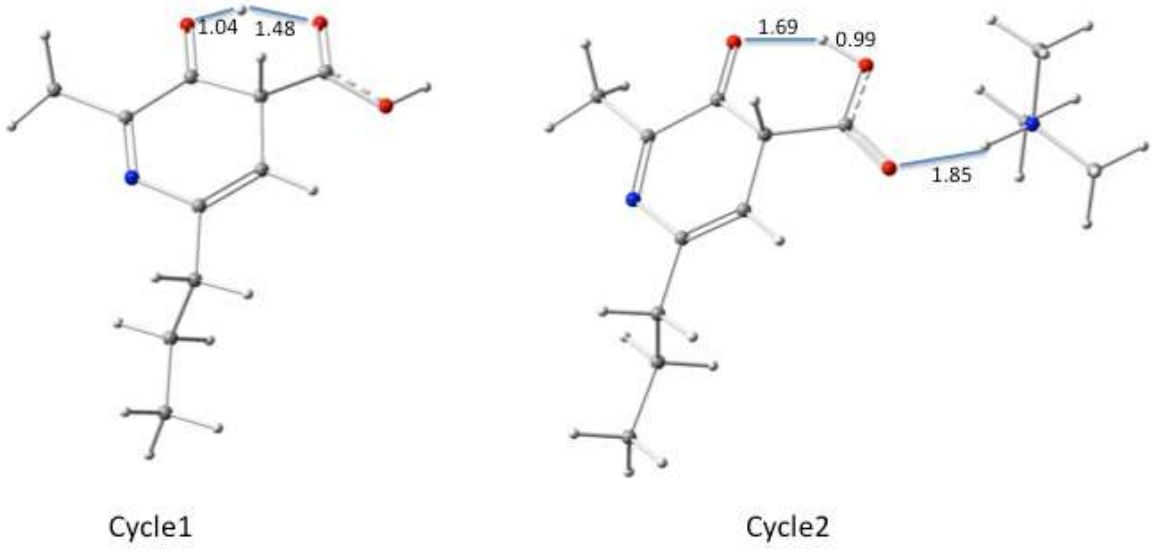


Figure S7. Views of the cyclic product after ethanol elimination in absence and in presence of trimethylamine. H in white, C in grey, N in blue, O in red.

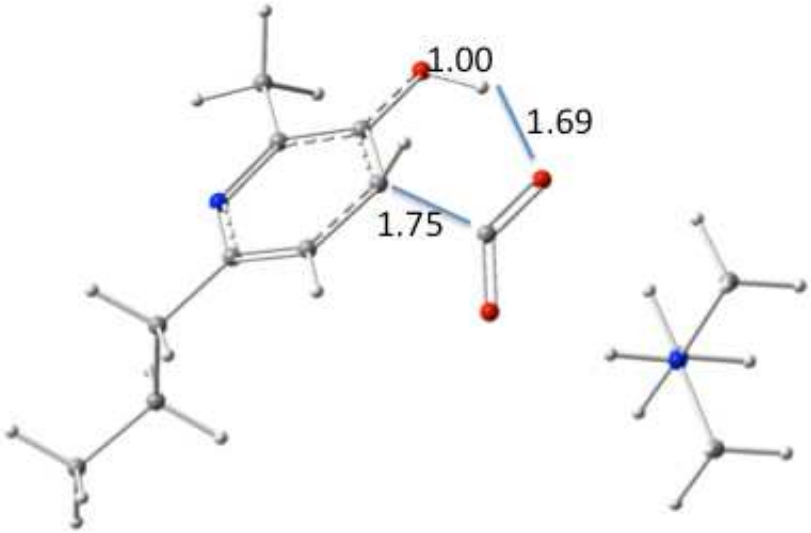


Figure S8. View of the optimized transition state leading to CO_2 release (final rearomatization step). H in white, C in grey, N in blue, O in red.

Full Gaussian 09 reference:
Gaussian 09, Revision B.01,

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G.E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.;Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian, Inc., Wallingford CT, 2010.

References

[1] V. Tognetti, C. Morell, P. W. Ayers, L. Joubert, H. Chermette, *Phys. Chem. Chem. Phys.* **2013**, *15*, 14465.

[2] C. Morell, A. Grand, A. Toro-Labbé, *J. Phys. Chem. A* **2005**, *109*, 205.

[3] W. Yang, W. Mortier, *J. Am. Chem. Soc.* **1986**, *108*, 5708.

[4] R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Oxford University Press, **1990**.

[5] J. Padmanabhan, R. Parthasarathi, M. Elango, V. Subramanian, B. S. Krishnamoorthy, S. Gutierrez-Oliva, A. Toro-Labbé, D. R. Roy, P. K. Chattaraj, *J. Phys. Chem. A* **2007**, *111*, 9130.

[6] F. Zielinski, V. Tognetti, L. Joubert, *J. Mol. Model.* **2013**, *19*, 4049.

[7] R. F. W. Bader, C. Gatti, *Chem. Phys. Lett.* **1998**, *287*, 233.

[8] M. A. Blanco, A. M. Pendás, E. Francisco, *J. Chem. Theory Comput.* **2005**, *1*, 1096.

[9] A. M. Pendás, M. A. Blanco, E. Francisco, *J. Chem. Phys.* **2004**, *120***,** 4581.

[10] X. Fradera X, M. A. Austen, R. F. W. Bader RFW, *J. Phys. Chem. A* **1999**, *103*, 304.

[11] C. L. Firme, O. A. C. Antunes, P. M. Esteves, *J. Phys. Chem. A* **2007**, *111*, 11904.