Modular Synthesis of β-Amino Boronate Peptidomimetics

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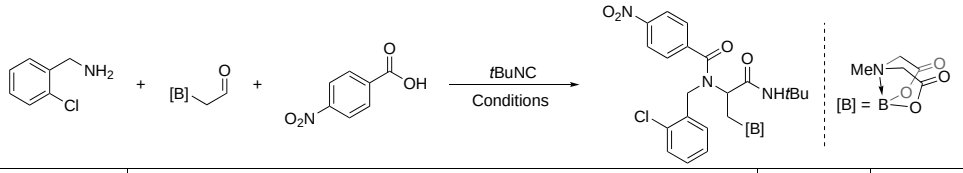
Reaction Optimization

Table S1. Optimization experiments for the Ugi-reaction with α-borylaldehydes.

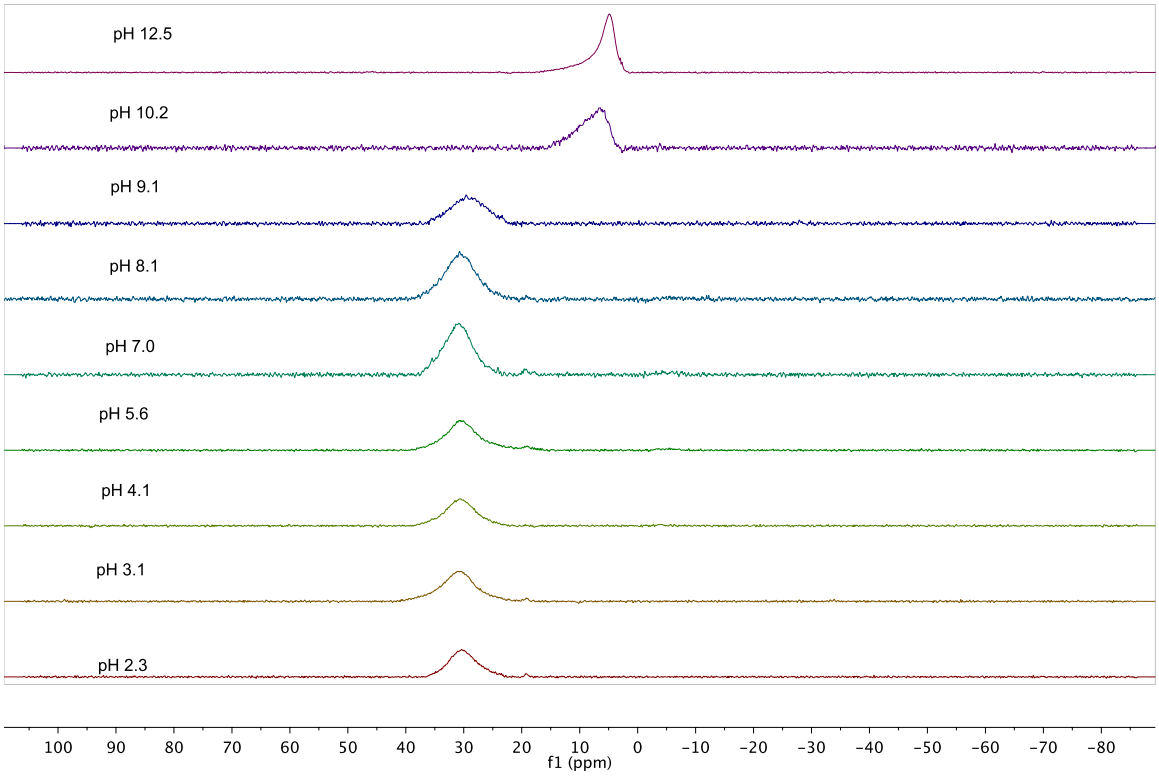


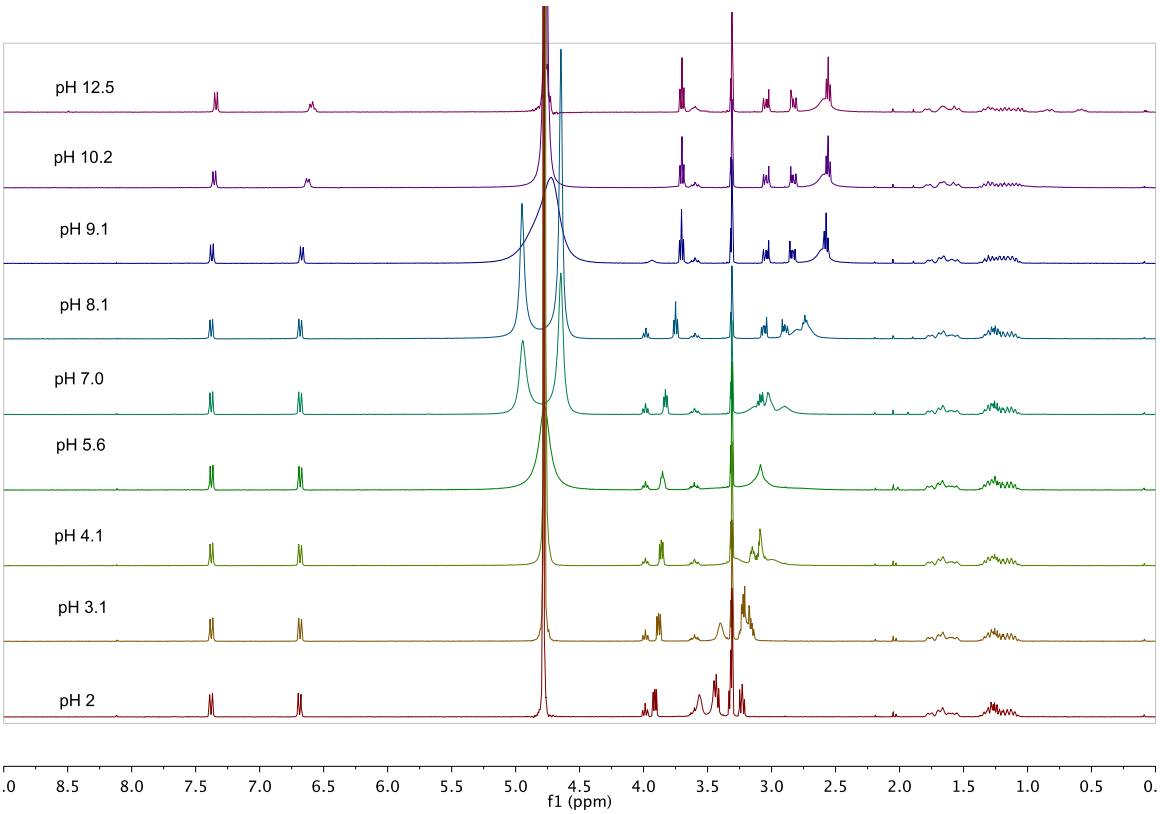
Entry	Solvent (M)	Conditions	T (^{o}C)	Time (h)	Yield[a]
1	MeCN (1.0 M)	1.0 equiv amine and carboxylic acid, 1.0 equiv isocyanide	25	24	0%
2	MeCN (0.5 M)	1.0 equiv amine and carboxylic acid, 1.0 equiv isocyanide	25	24	50%
3	DMSO (0.2 M)	1.0 equiv of amine and carboxylic acid, 1.2 equiv isocyanide	120, µwave	2	16%
4	DMSO (1.0 M)	1.0 equiv of amine and carboxylic acid, 1.2 equiv isocyanide	100, µwave	3	29%
5	MeCN (0.1 M)	1.2 equiv amine and carboxylic acid, 2.0 equiv isocyanide	60	24	75%

[a]NMR yield of the desired product.

pH Titration

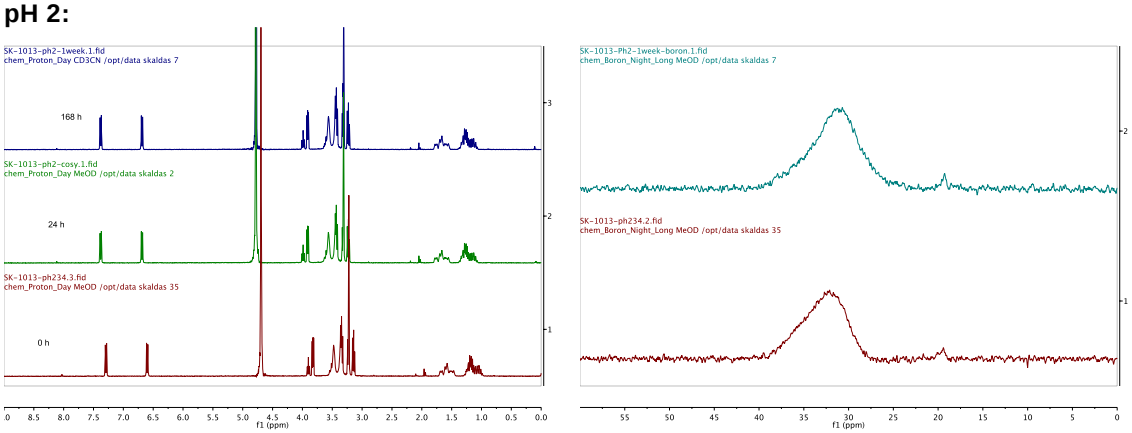
General Procedure: To a solution compound **3b** (20. mg, 0.05 mmol) in 2.0 ml of CD_3OD was added 0.6 ml of HEPES buffer (0.10 M in D_2O) and was left to stir for 5 min. The pH was adjusted to ~3 by dropwise addition of 2.0 M $HClO_4$ in D_2O. A 200 µL aliquot was taken for ^{1}H and ^{11}B NMR. The pH was increased by ~1 pH unit by addition of 2.0 M NaOH(aq) in D_2O until a pH of ~12.5 was reached. At each pH, a 200 µL aliquot was taken for NMR. This experiment was repeated in duplicate.



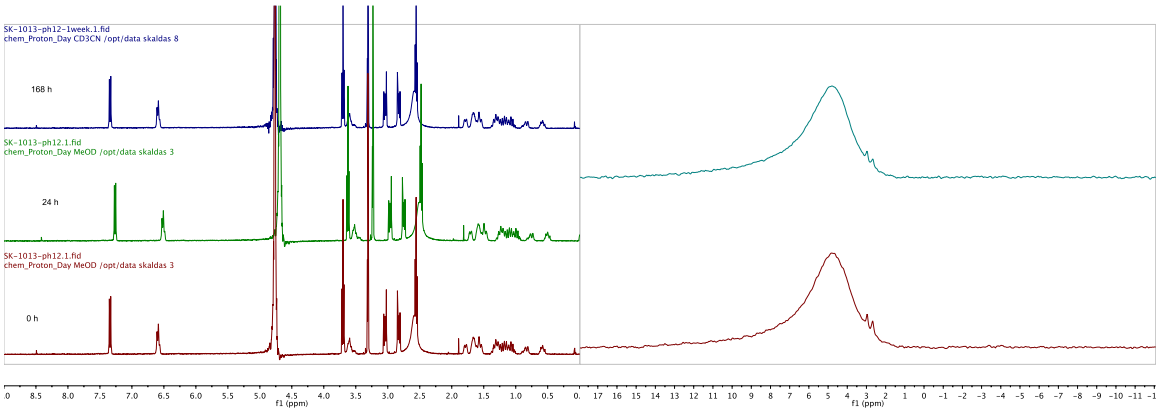


After 1 week at pH 2 and pH 12 in CD_3OD there was no observable decomposition by proton or boron NMR.

pH 2:

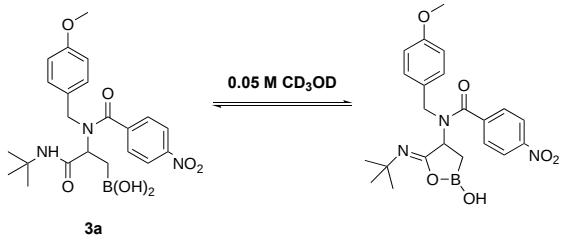


pH 12:

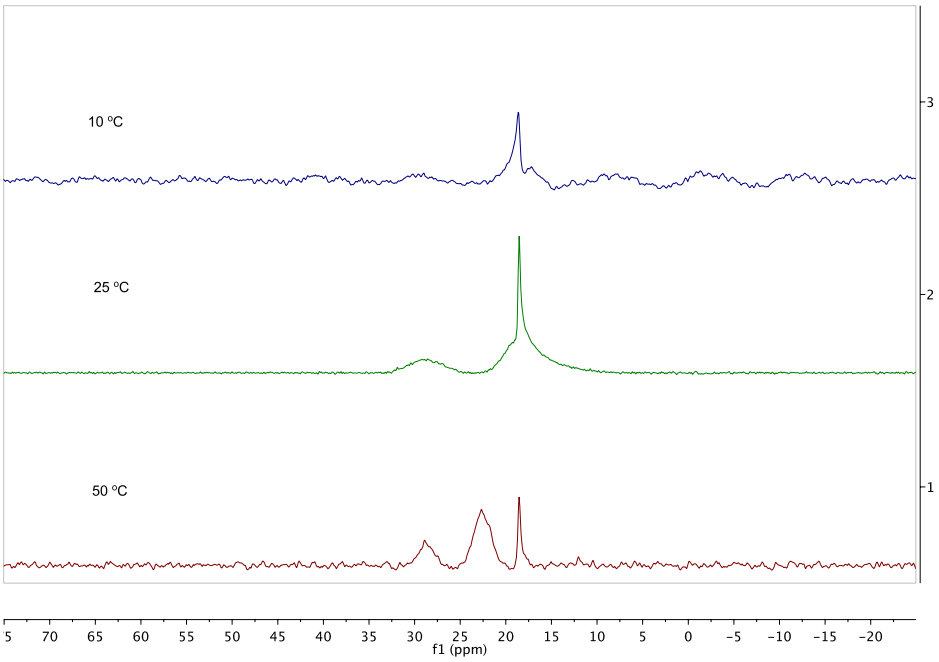


Oxaborolane Study

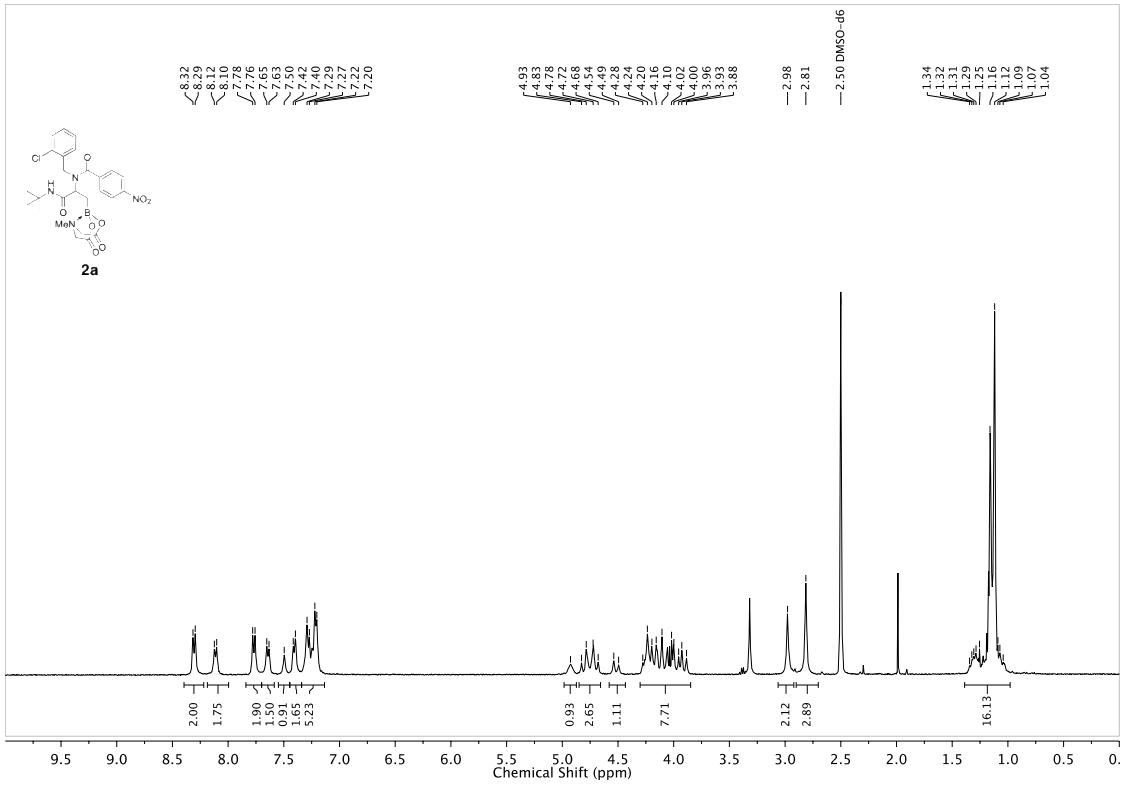
General Procedure: Compound **3a** was dissolved in deuterated methanol (0.05 M) and ^{11}B NMR (128 MHz) analysis was carried out a 10 ^{o}C, 25 ^{o}C, and 50 ^{o}C.



3a



NMR Spectra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7.20
4.93
4.83
4.78
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4.49
4.28
4.24
4.20
4.16
4.10
4.02
4.00
3.96
3.93
3.88
2.98
2.81
2.50 DMSO-d6
1.34
1.32
1.31
1.29
1.25
1.16
1.12
1.09
1.07
1.04
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1.50
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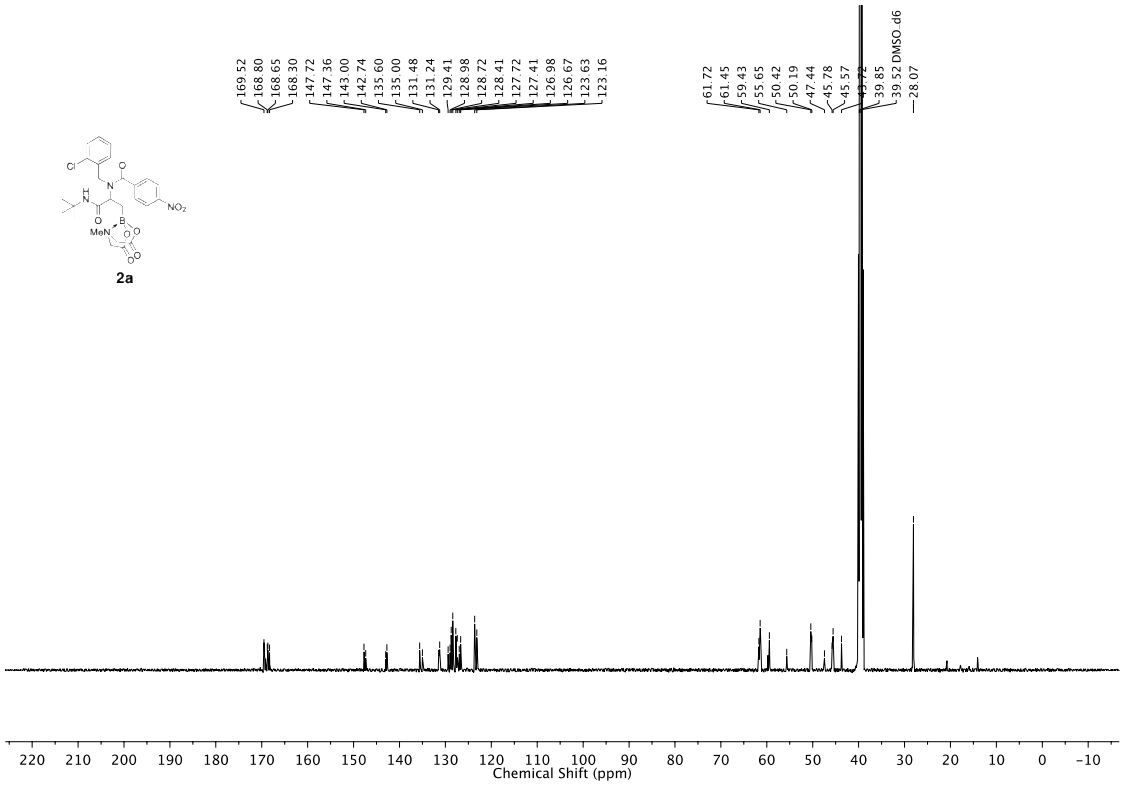
Chemical Shift (ppm)
2a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127.41
126.98
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Chemical Shift (ppm)
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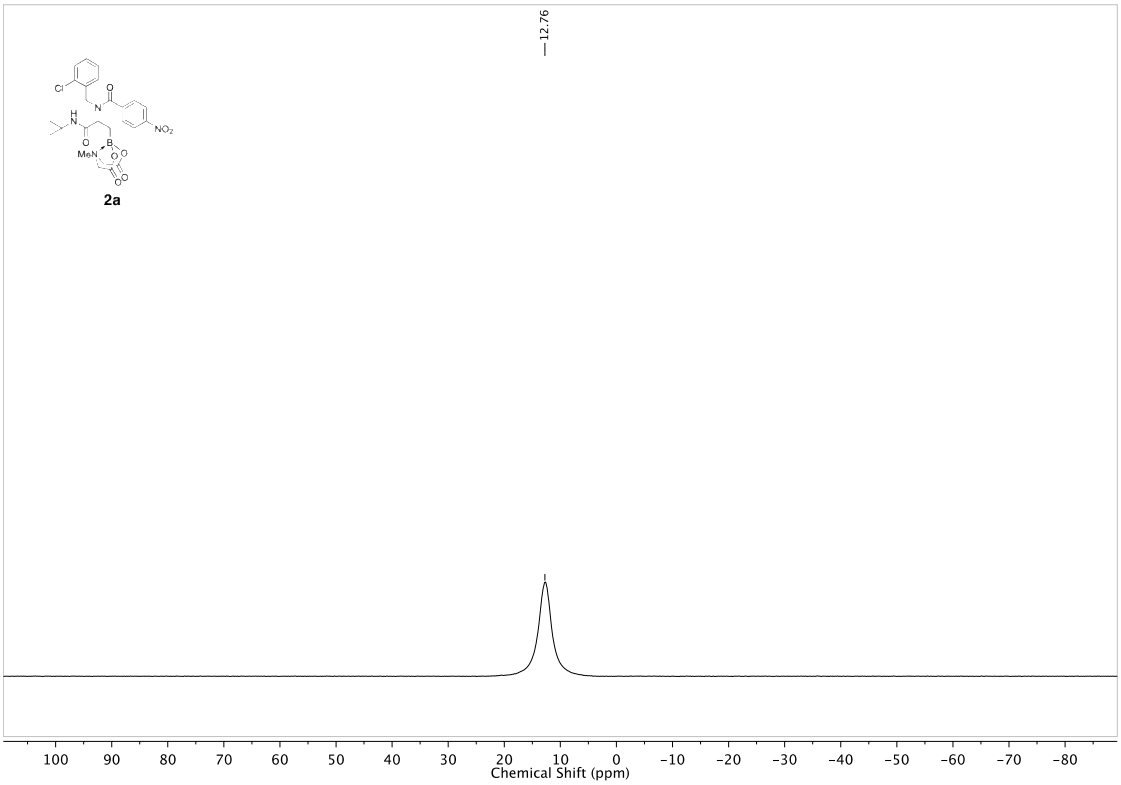
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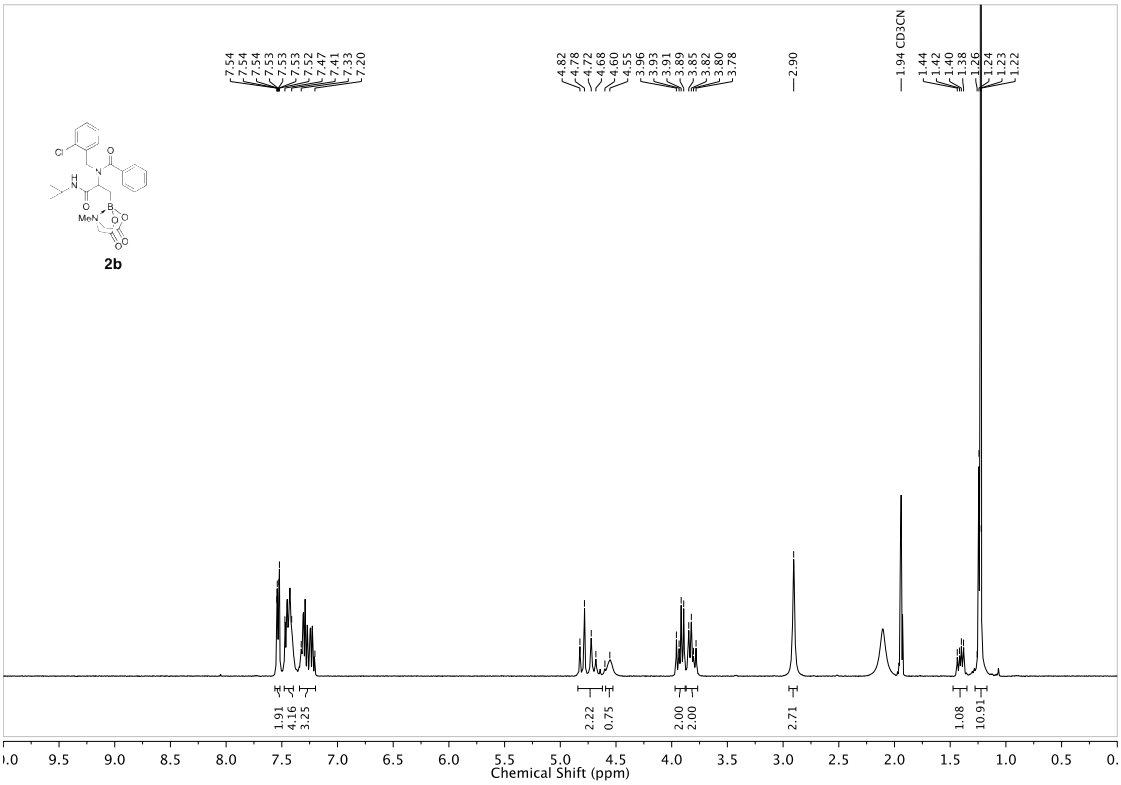
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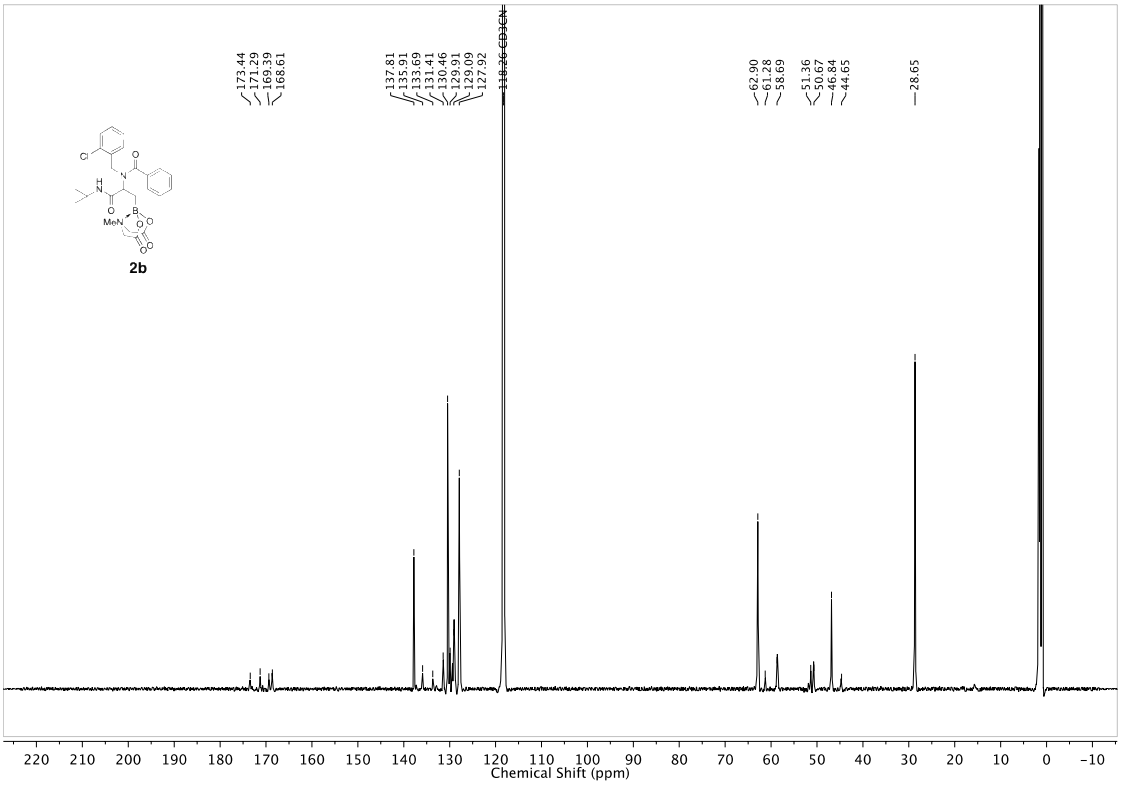
4.68
4.60
4.55
3.96
3.93
3.91
3.89
3.85
3.82
3.80
3.78
2.90
1.94 CD3CN
1.44
1.42
1.40
1.38
1.26
1.24
1.23
1.22
2b
1.91
4.16
3.25
2.22
0.75
2.00
2.00
2.71
1.08
10.91
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
Chemical Shift (ppm)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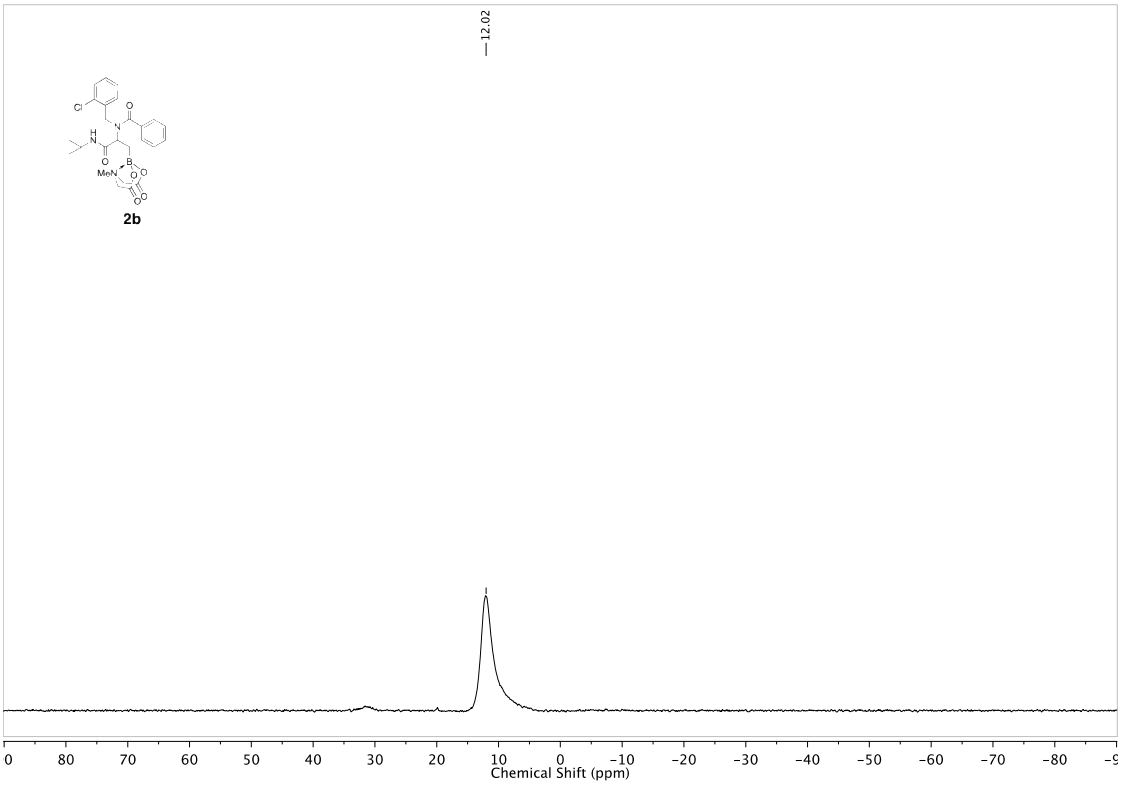
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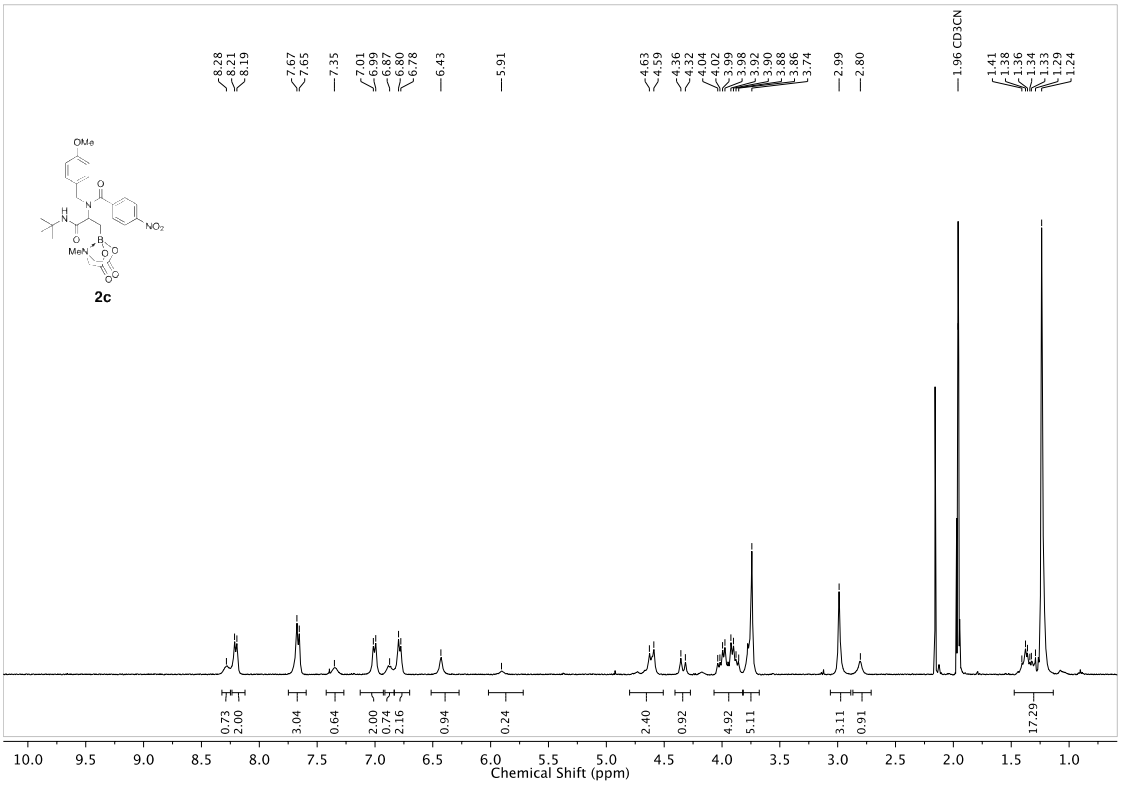
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4.32
4.04
4.02
3.99
3.98
3.92
3.90
3.88
3.86
3.74
2.99
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1.96 CD3CN
1.41
1.38
1.36
1.34
1.33
1.29
1.24
OMe
NO2
MeN
2c
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0.64
2.00
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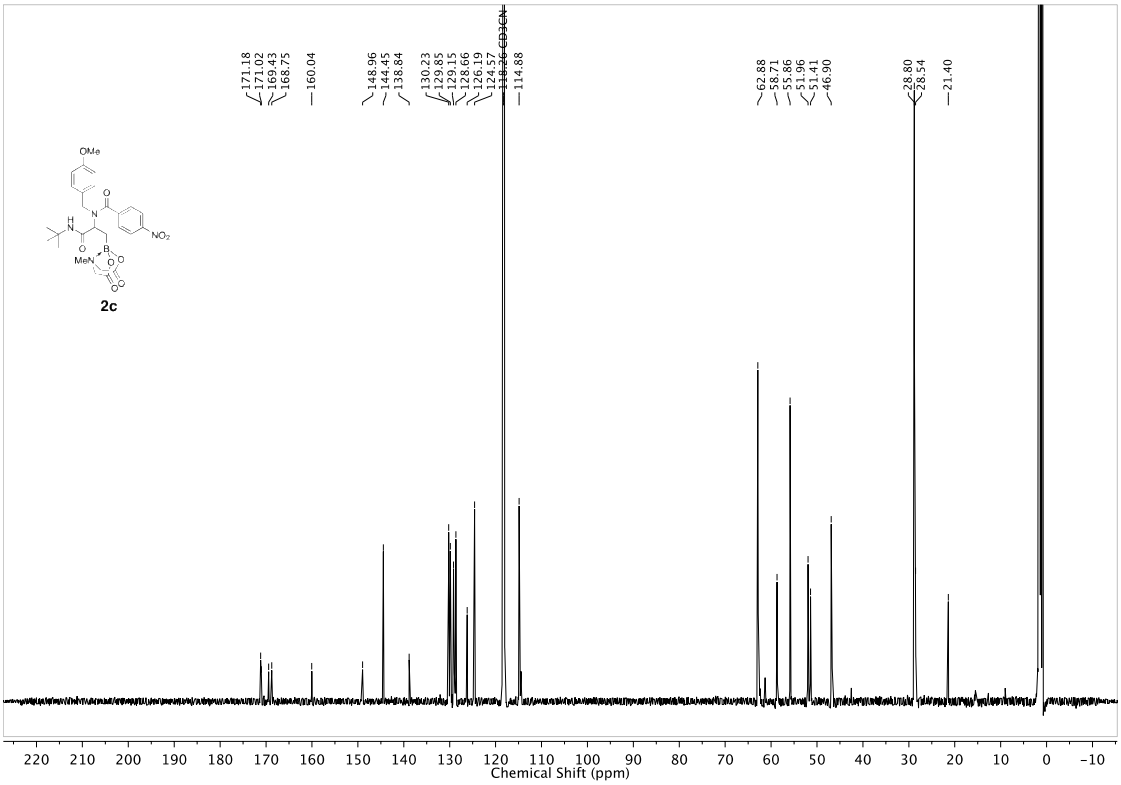
17.29
Chemical Shift (ppm)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114.88
62.88
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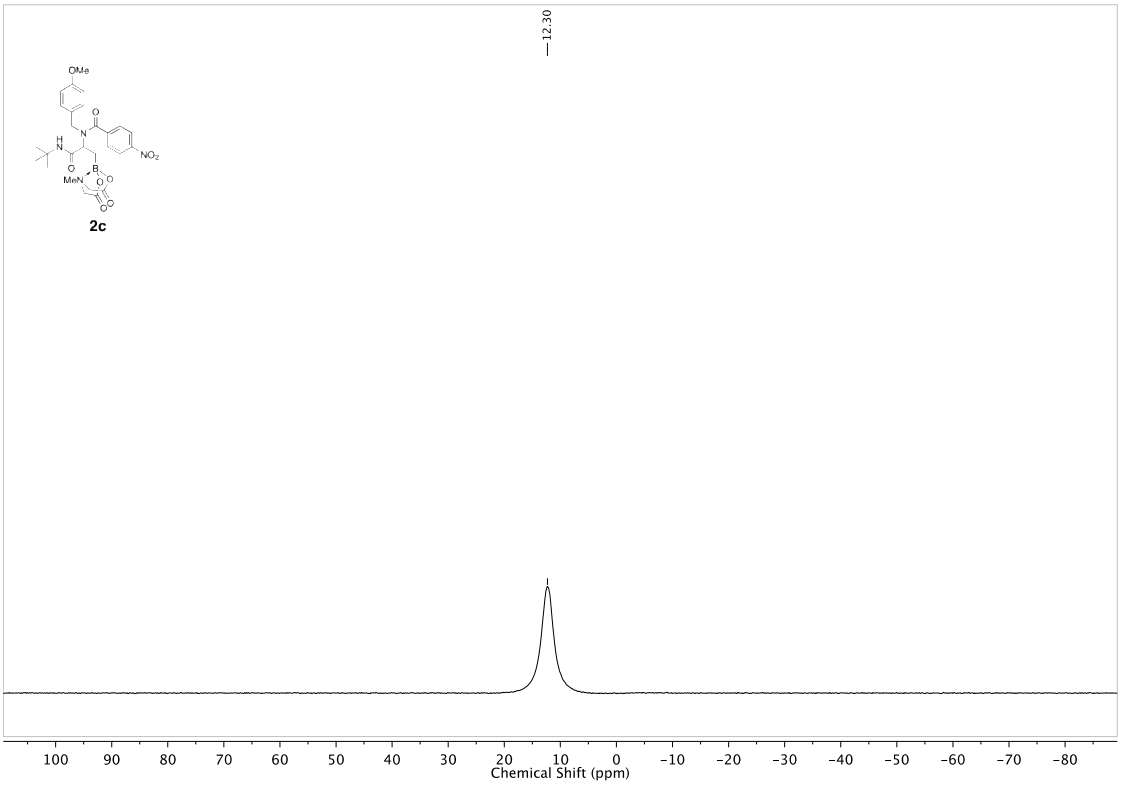
OMe
NO2
MeN
2c
Chemical Shift (ppm)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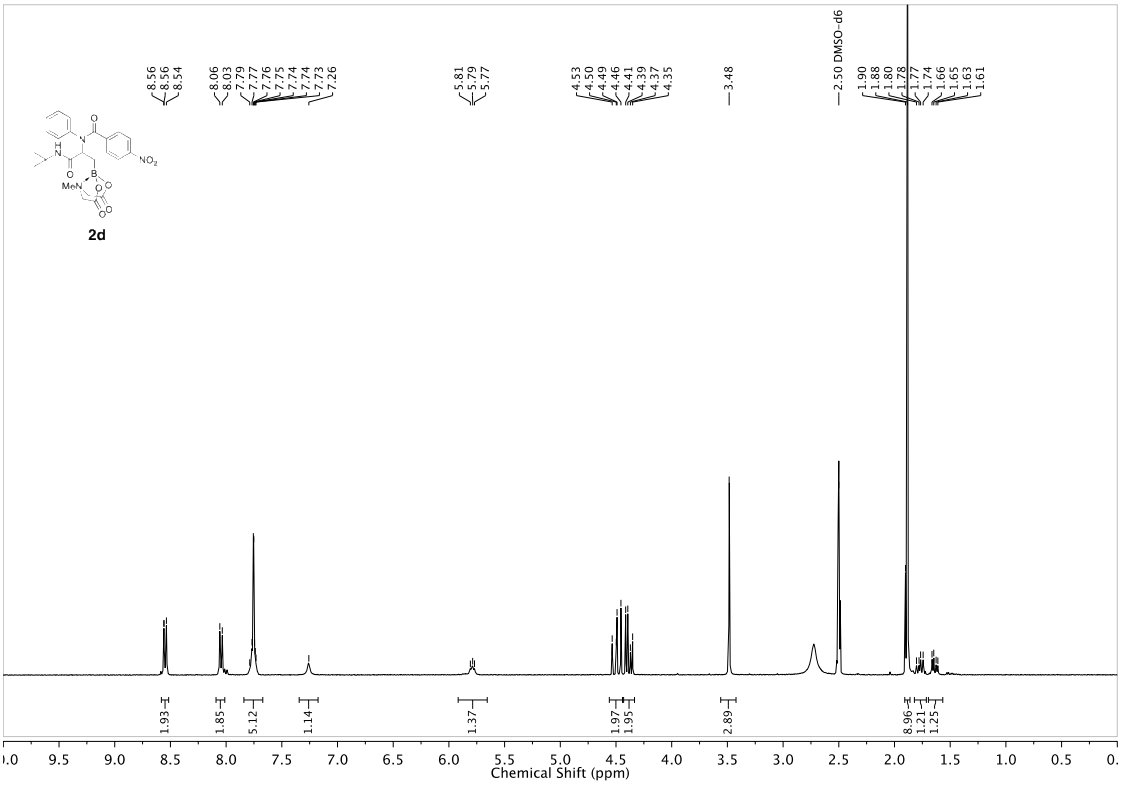
Chemical Shift (ppm)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2.89
8.96
1.21
1.25
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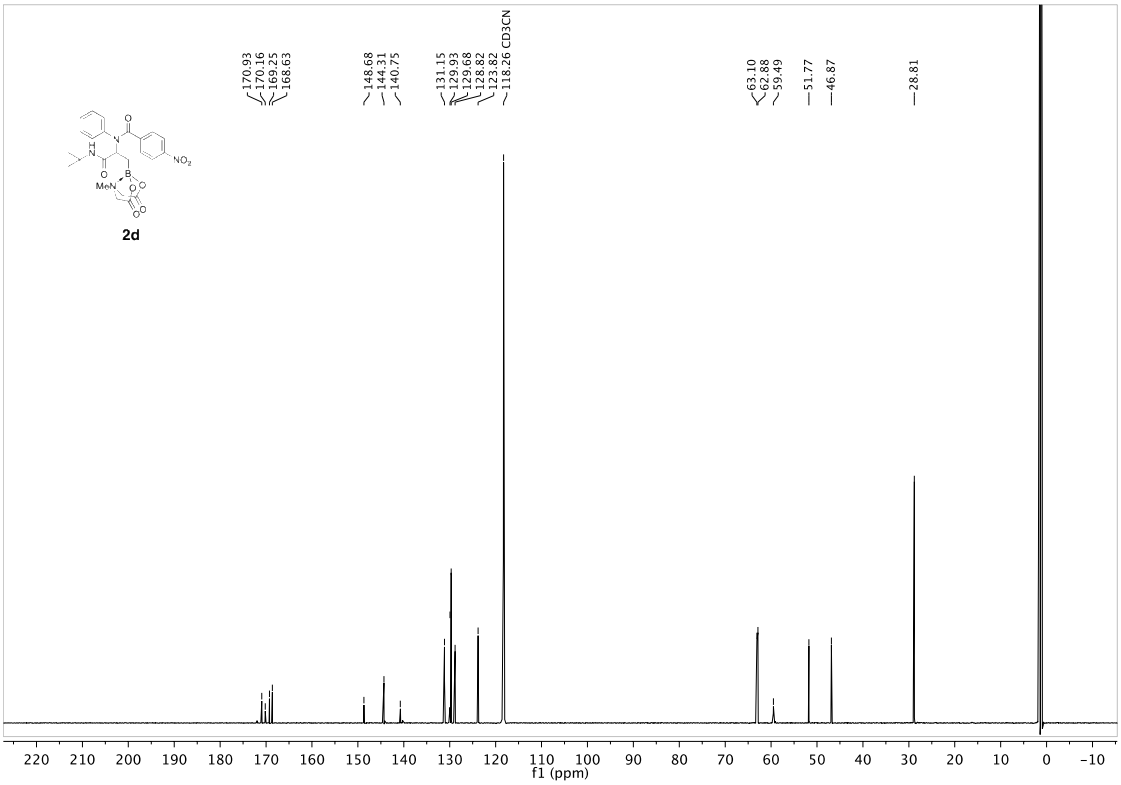
Chemical Shift (ppm)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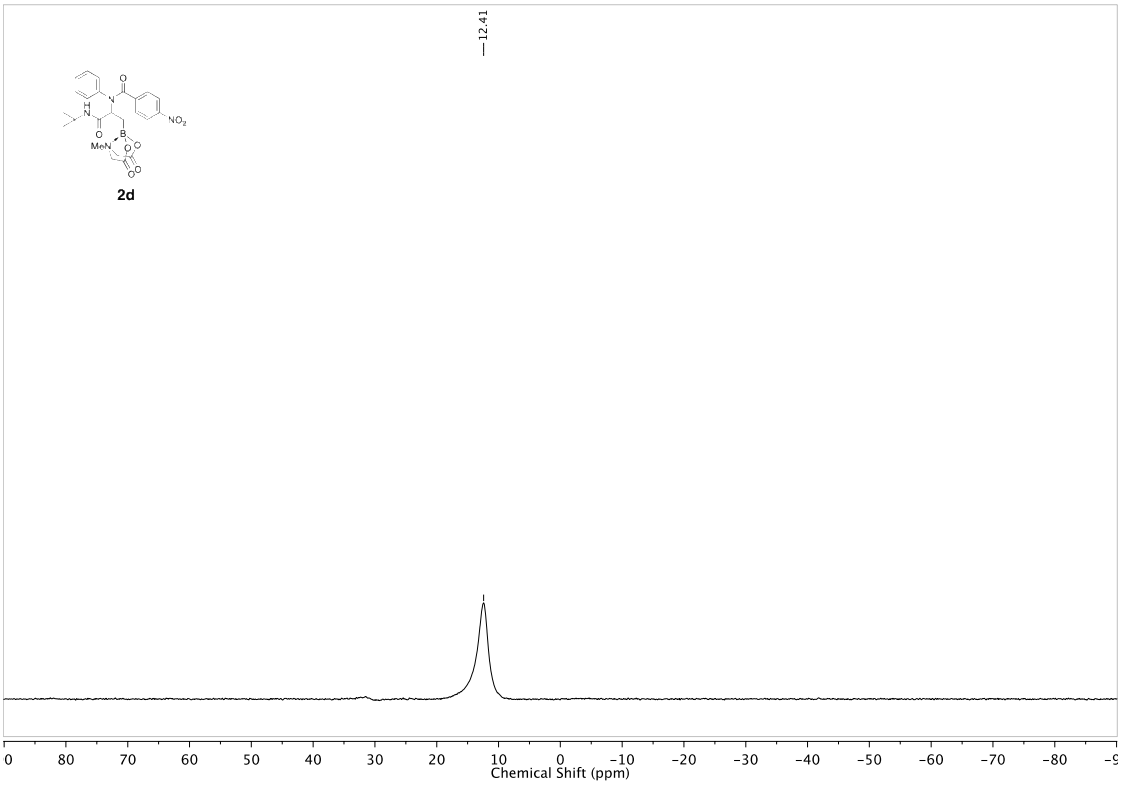
2d
f1 (ppm)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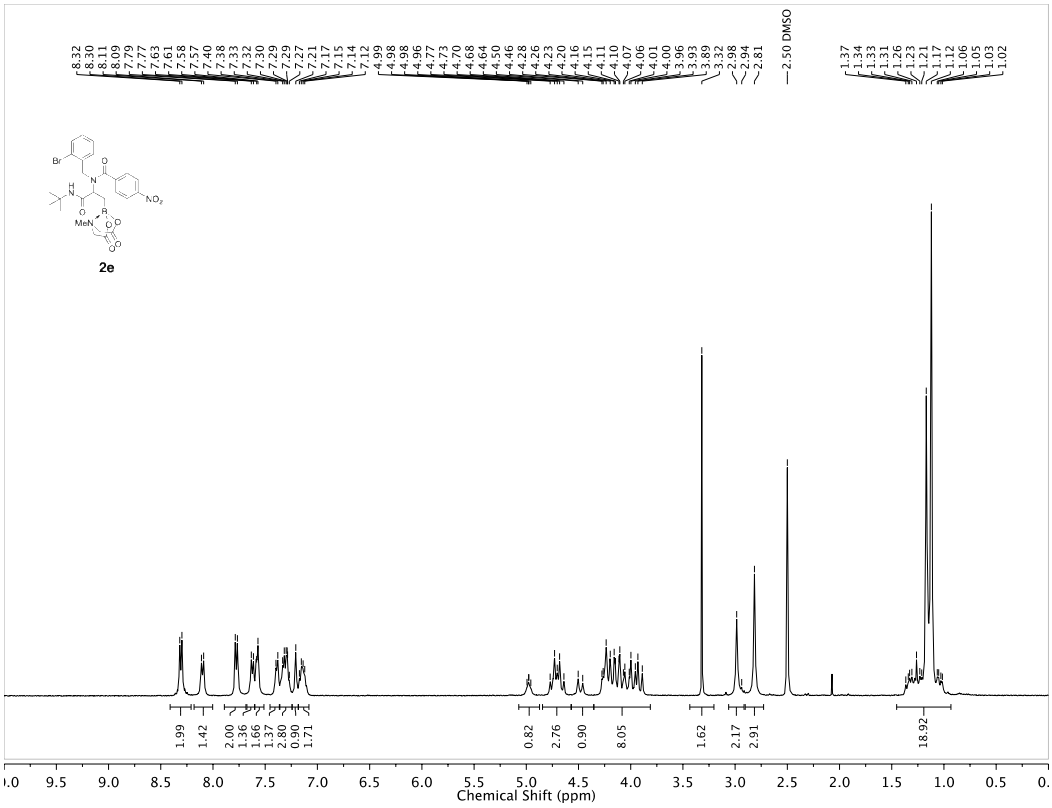
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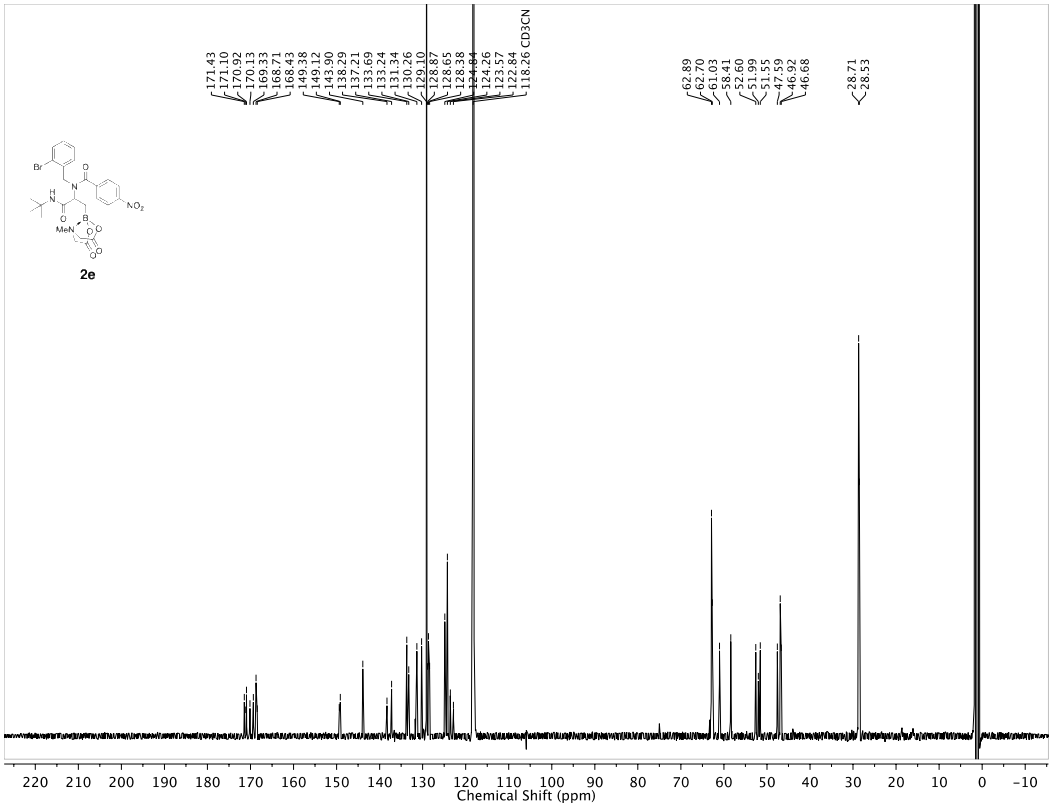
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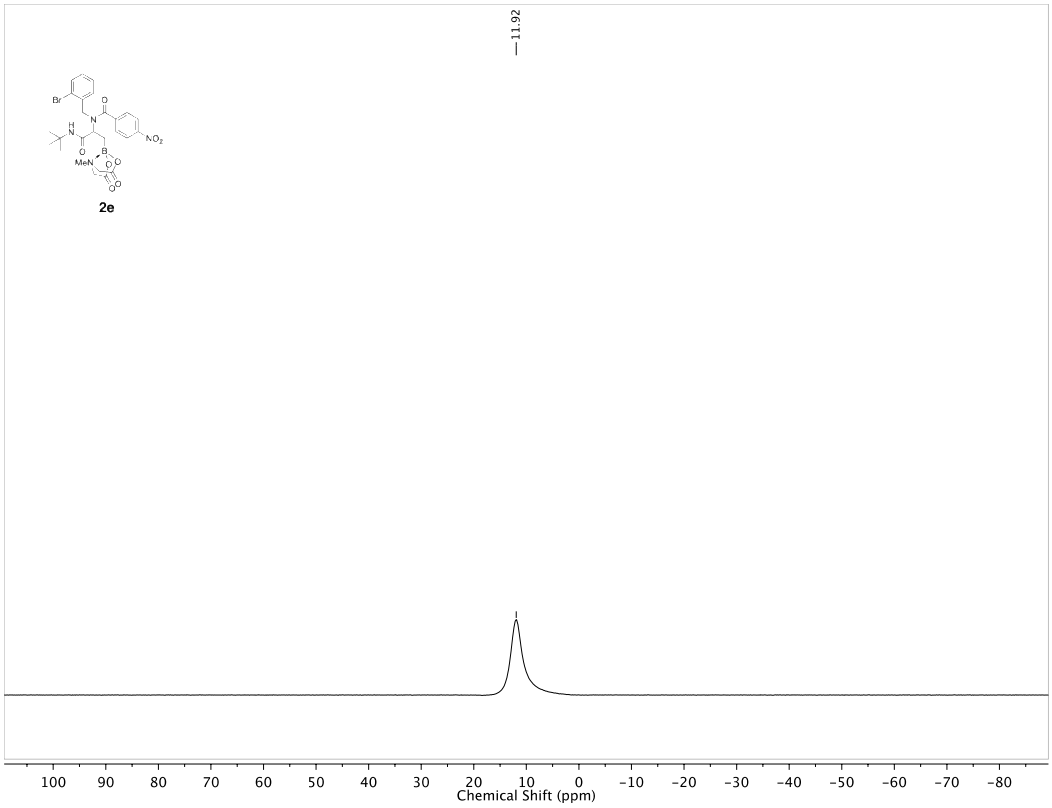
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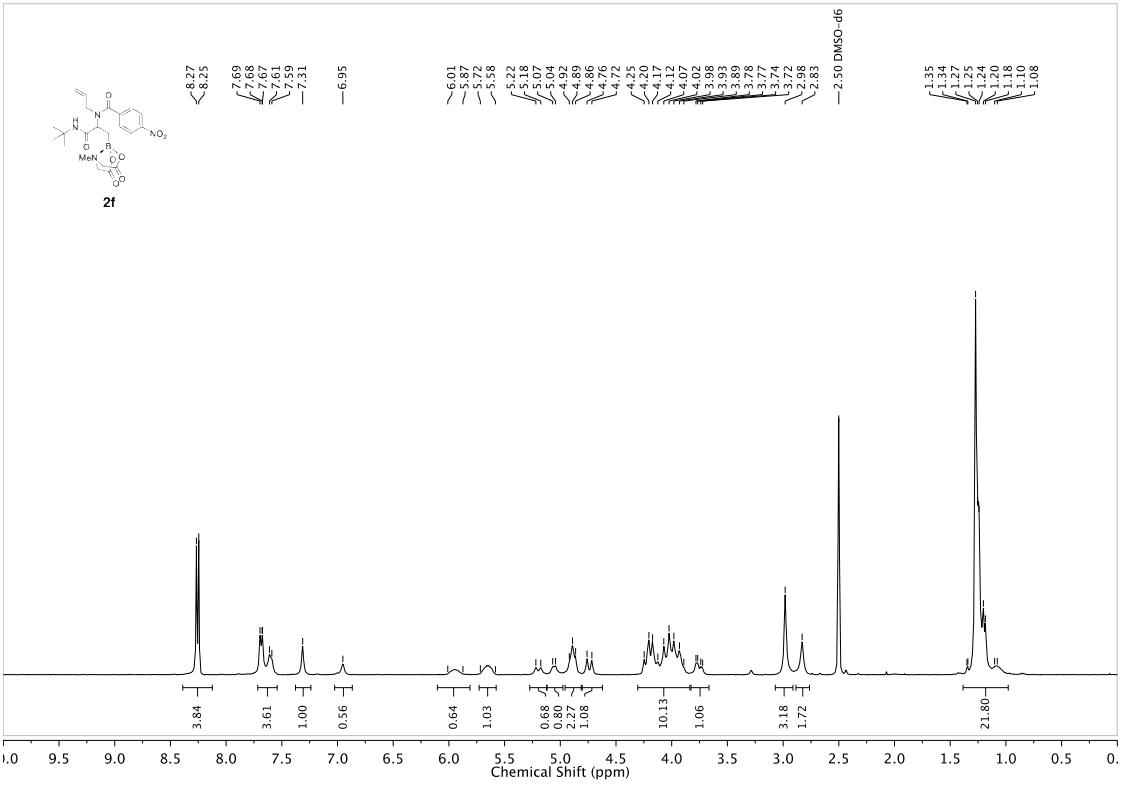
Chemical Shift (ppm)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21.80
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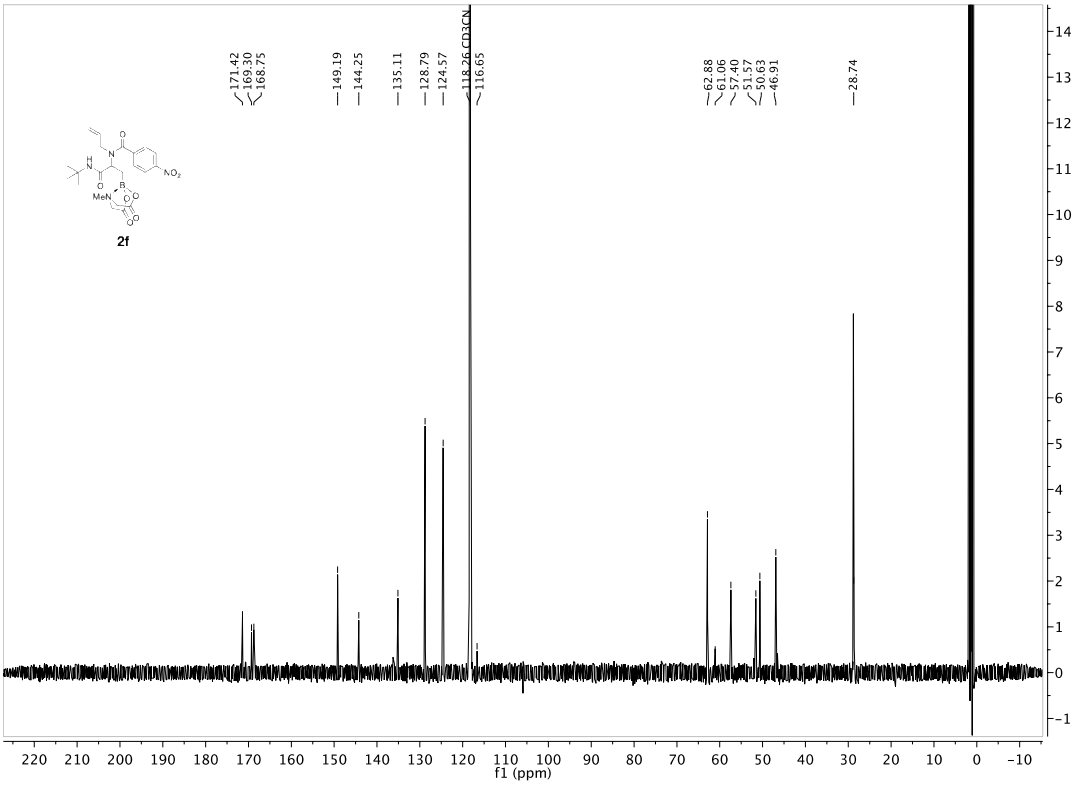
Chemical Shift (ppm)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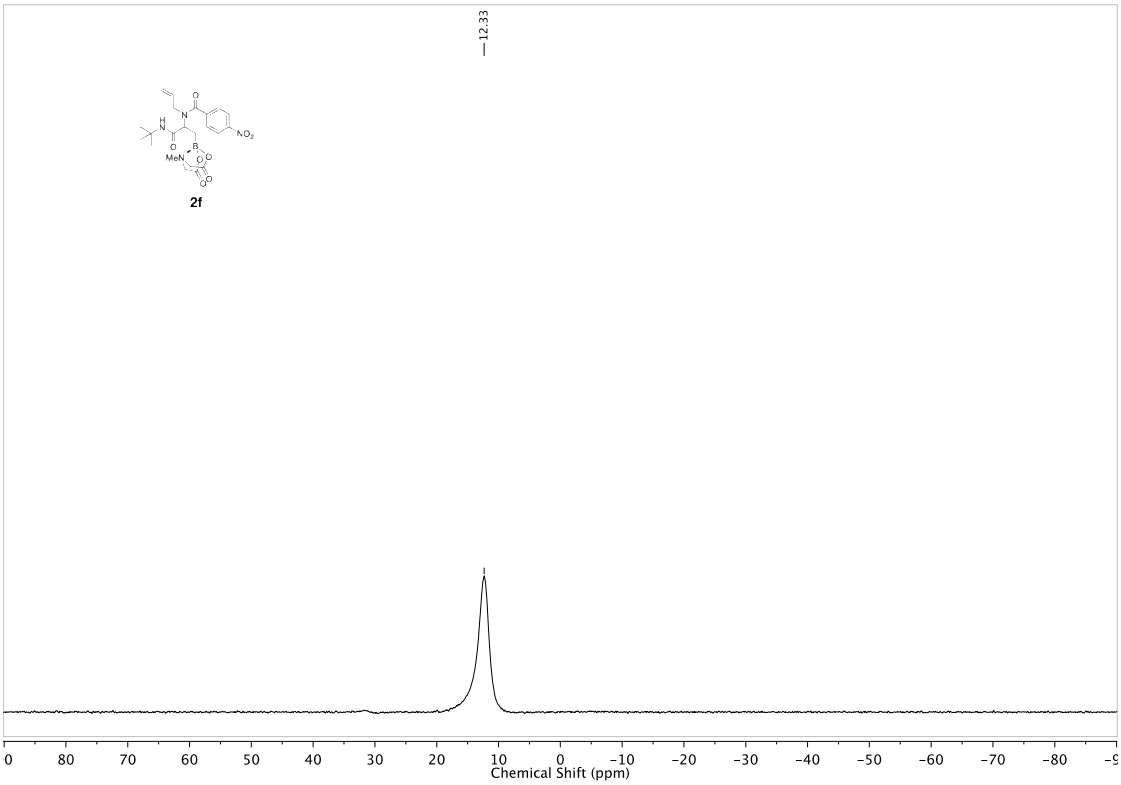
2f
f1 (ppm)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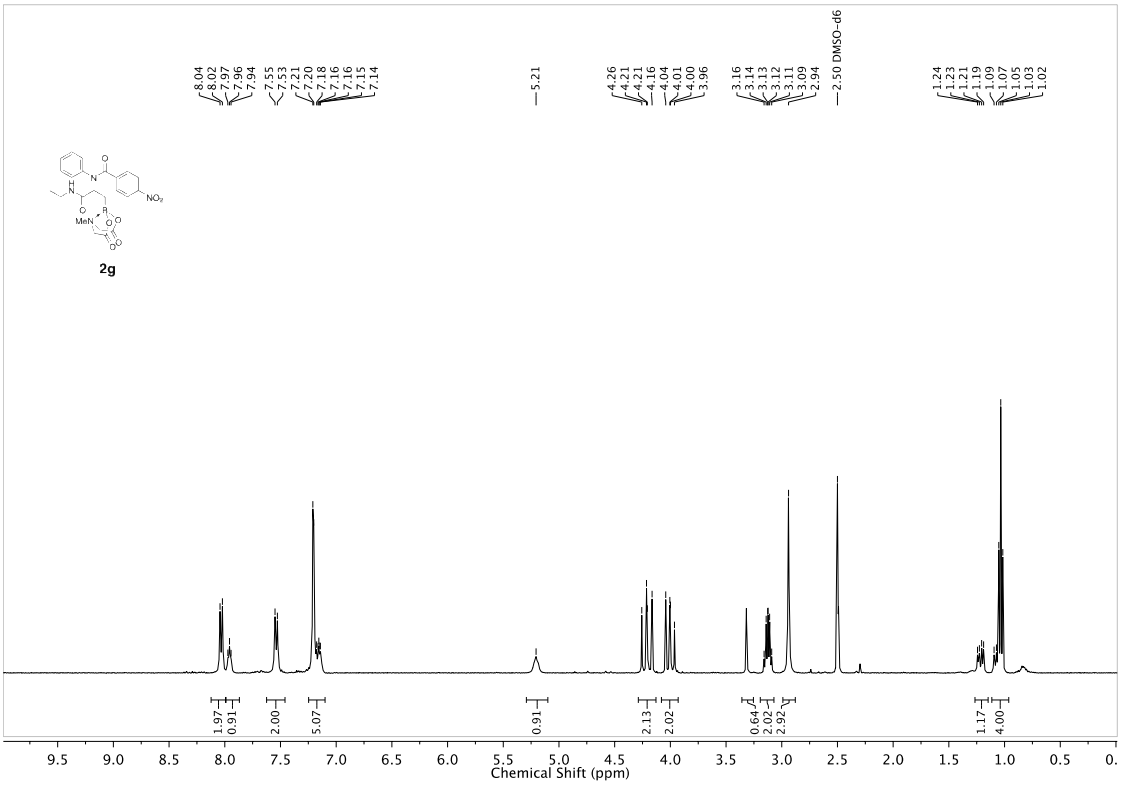
Chemical Shift (ppm)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7.14
5.21
4.26
4.21
4.21
4.16
4.04
4.01
4.00
3.96
3.16
3.14
3.13
3.12
3.11
3.09
2.94
2.50 DMSO-d6
1.24
1.23
1.21
1.19
1.09
1.07
1.05
1.03
1.02
1.97
0.91
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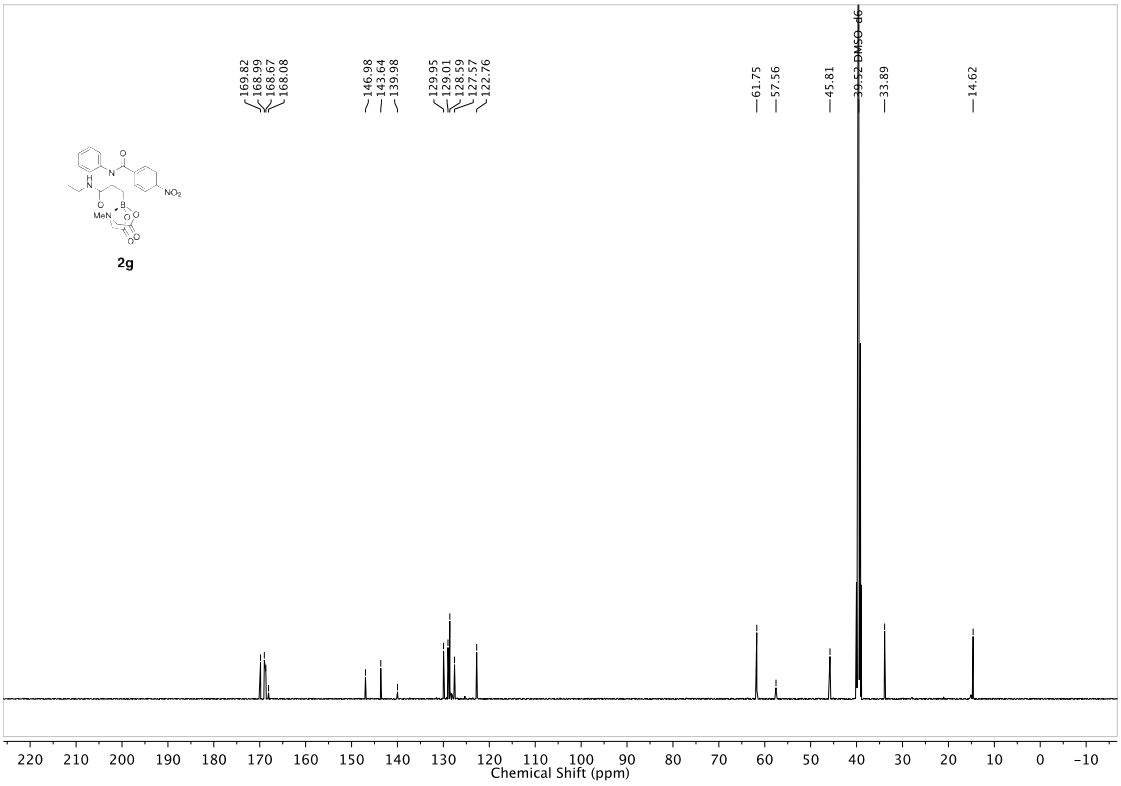
1.17
4.00
Chemical Shift (ppm)
2g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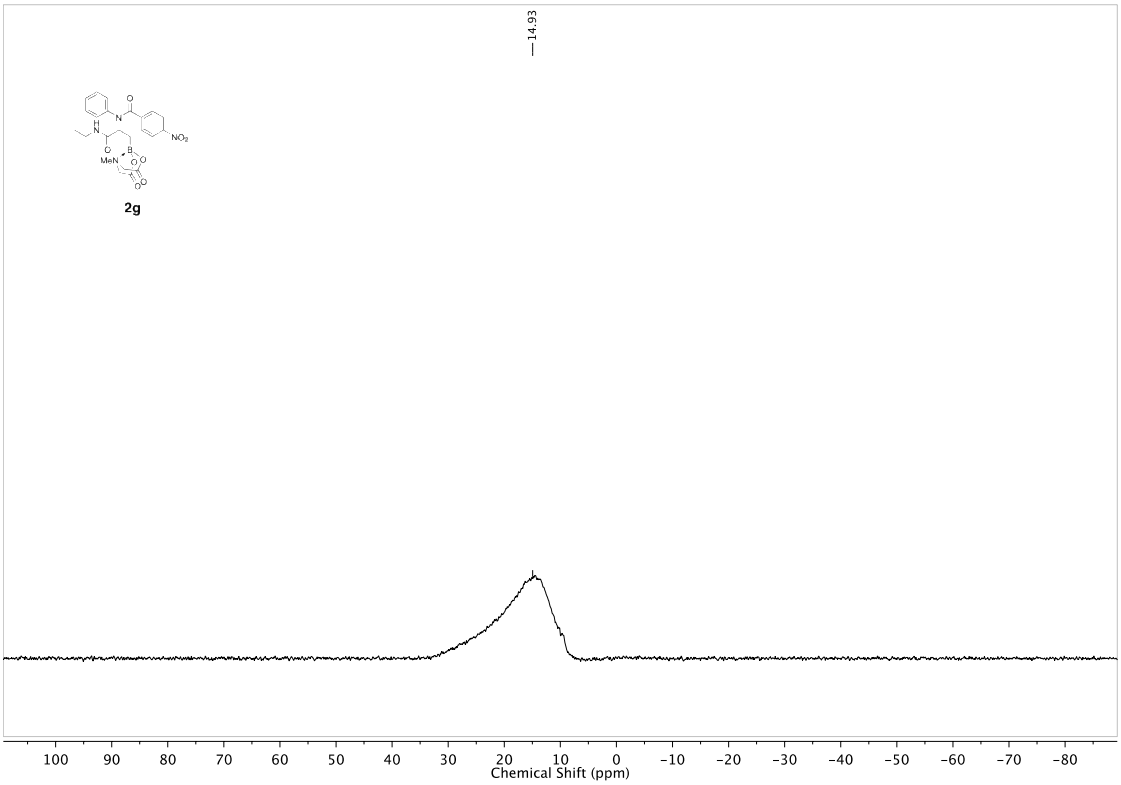
Chemical Shift (ppm)
2g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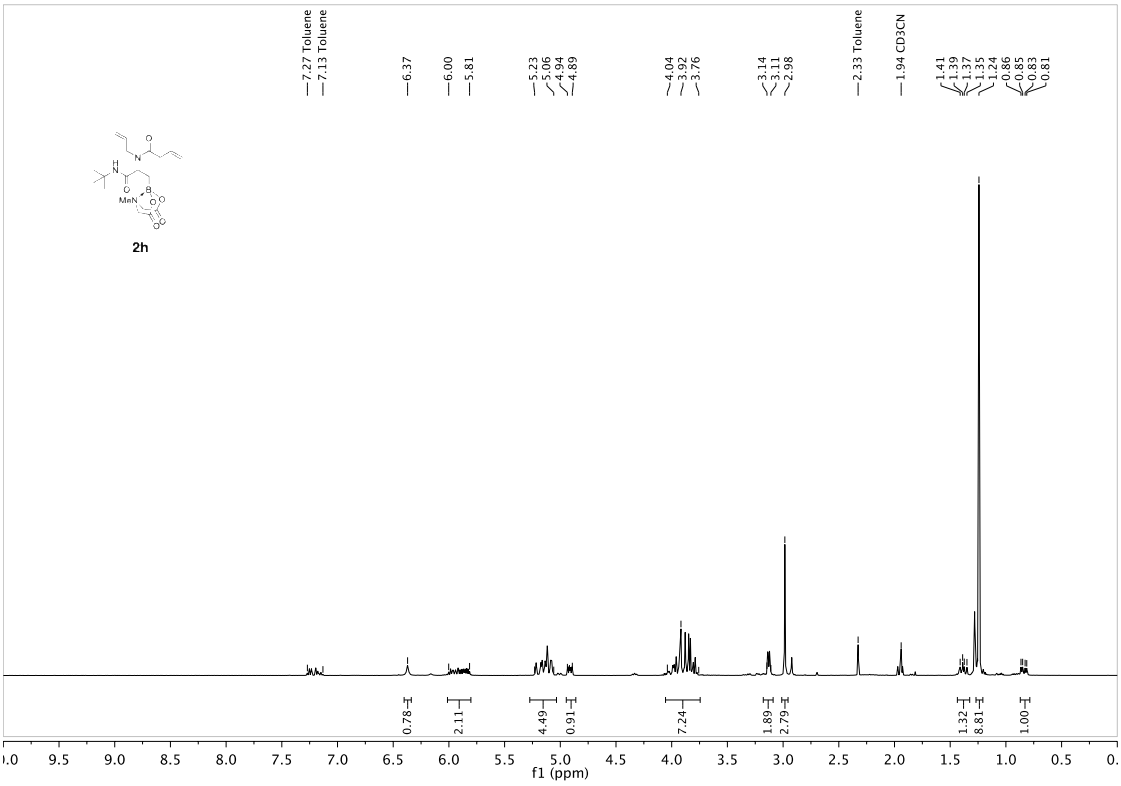
Chemical Shift (ppm)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3.14
3.11
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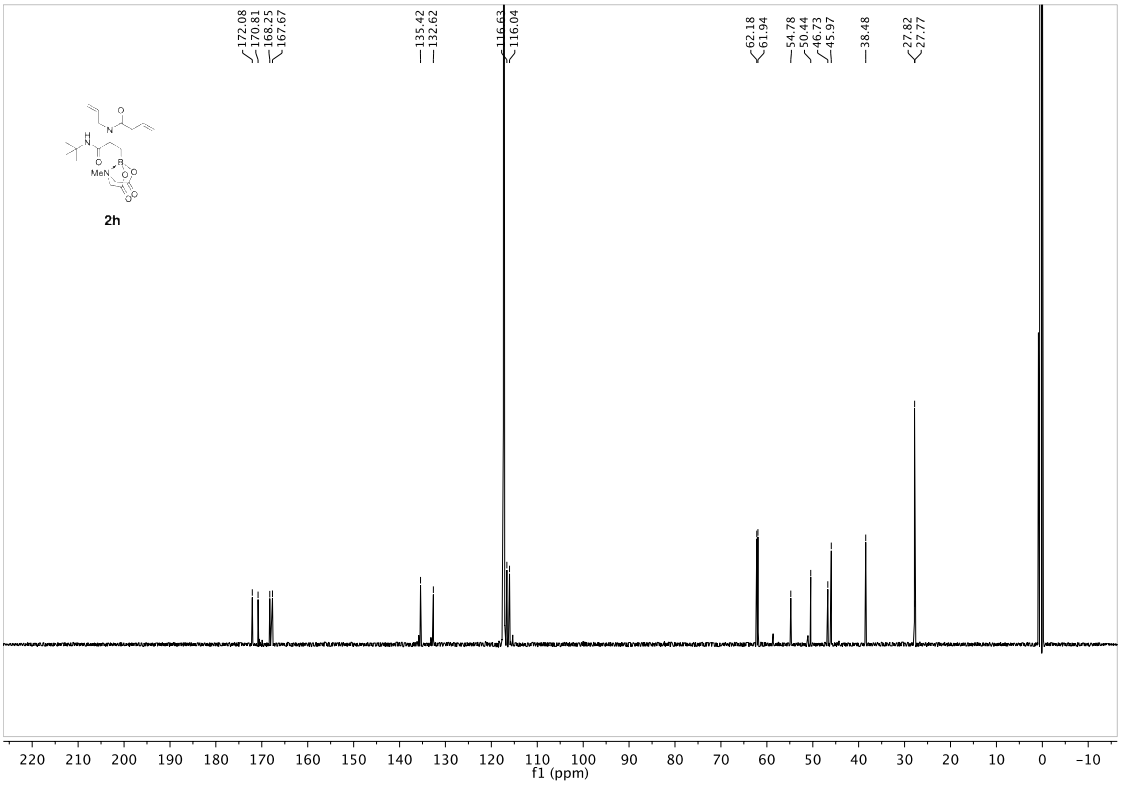
f1 (ppm)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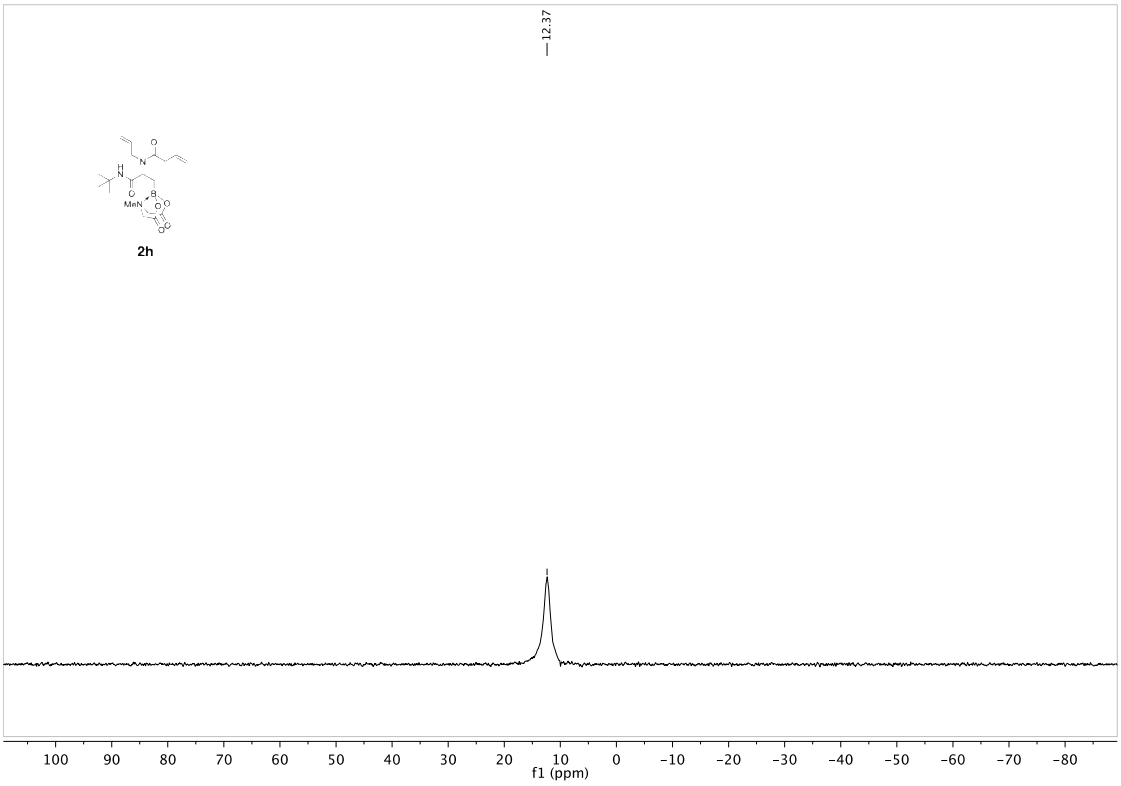
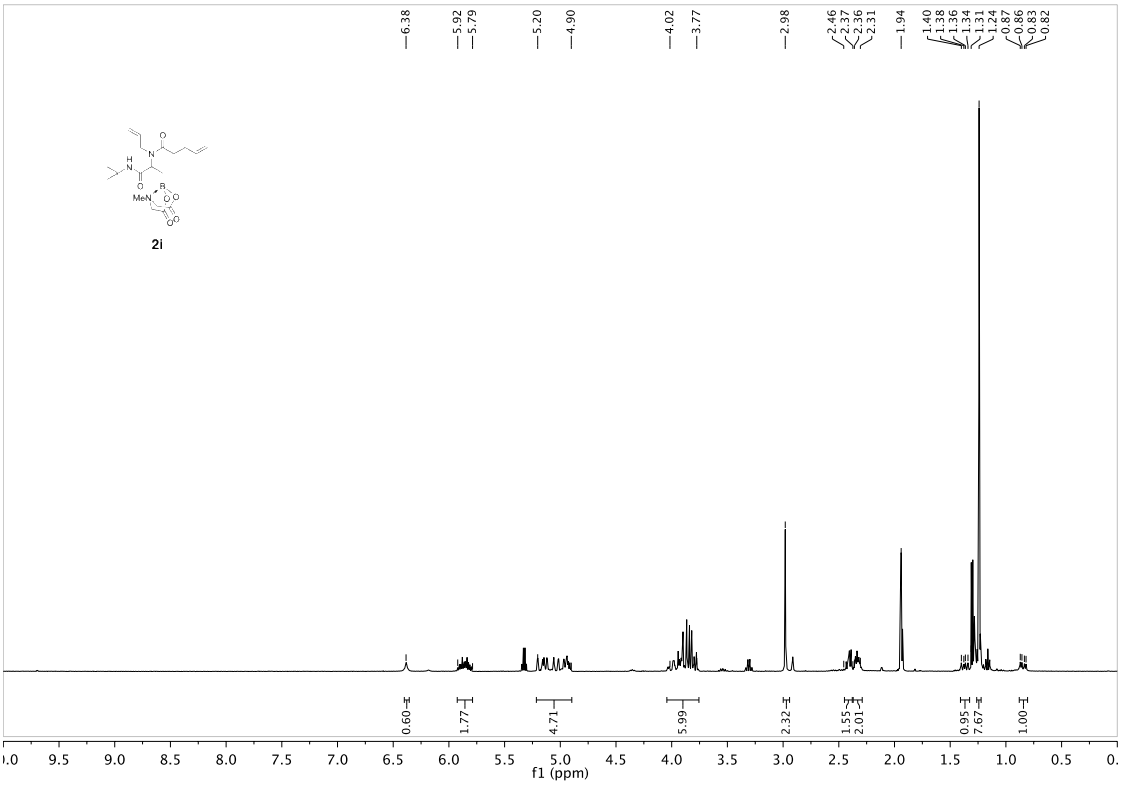
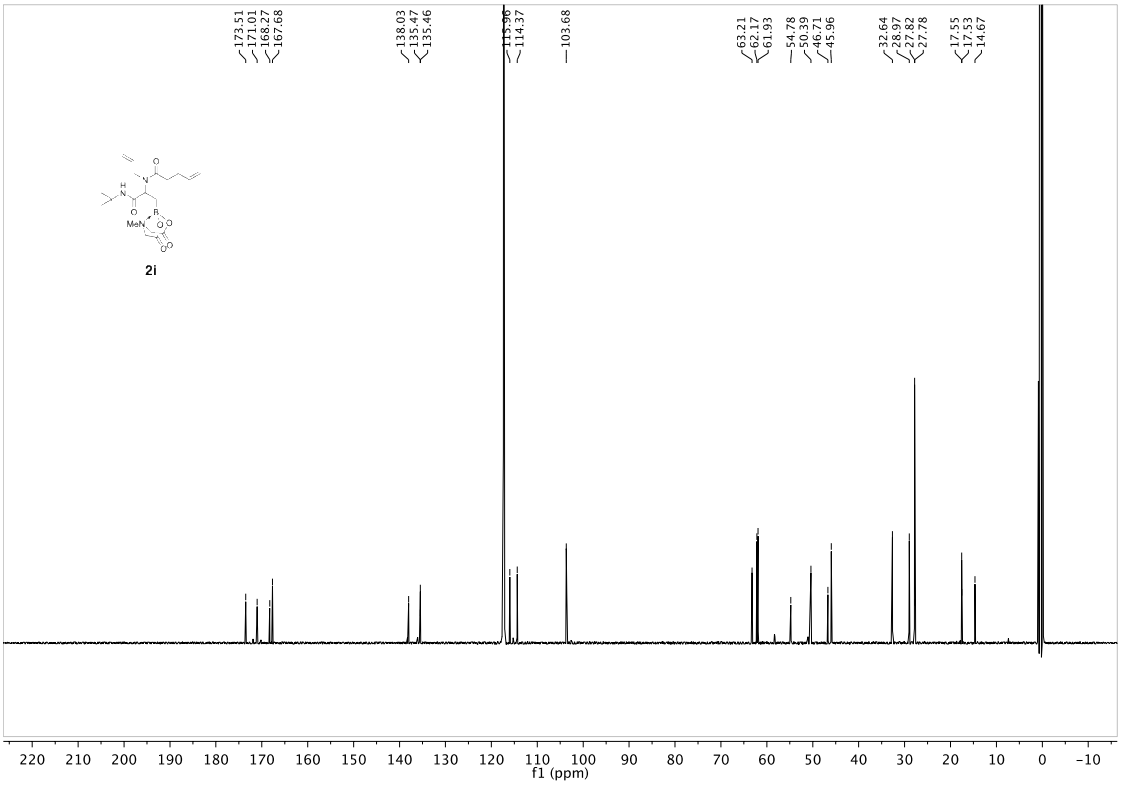
38.48
27.82
27.77
2h
f1 (ppm)

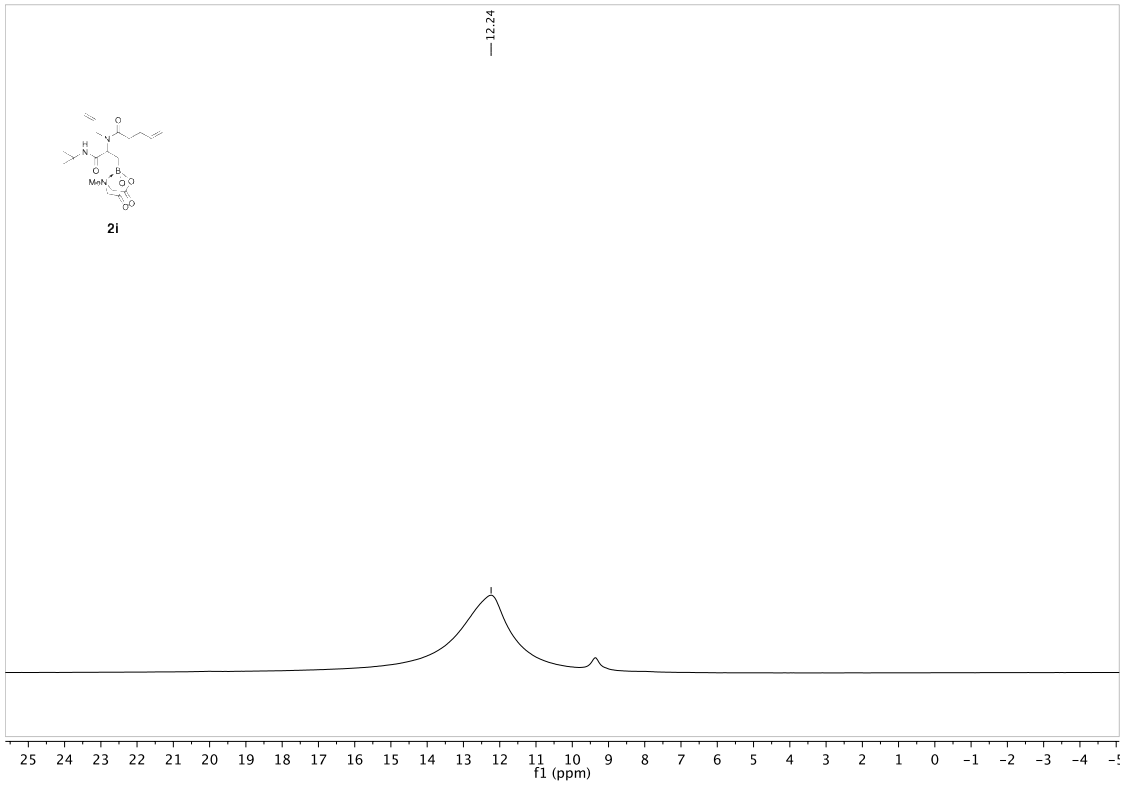

12.37
2h
f1 (ppm)

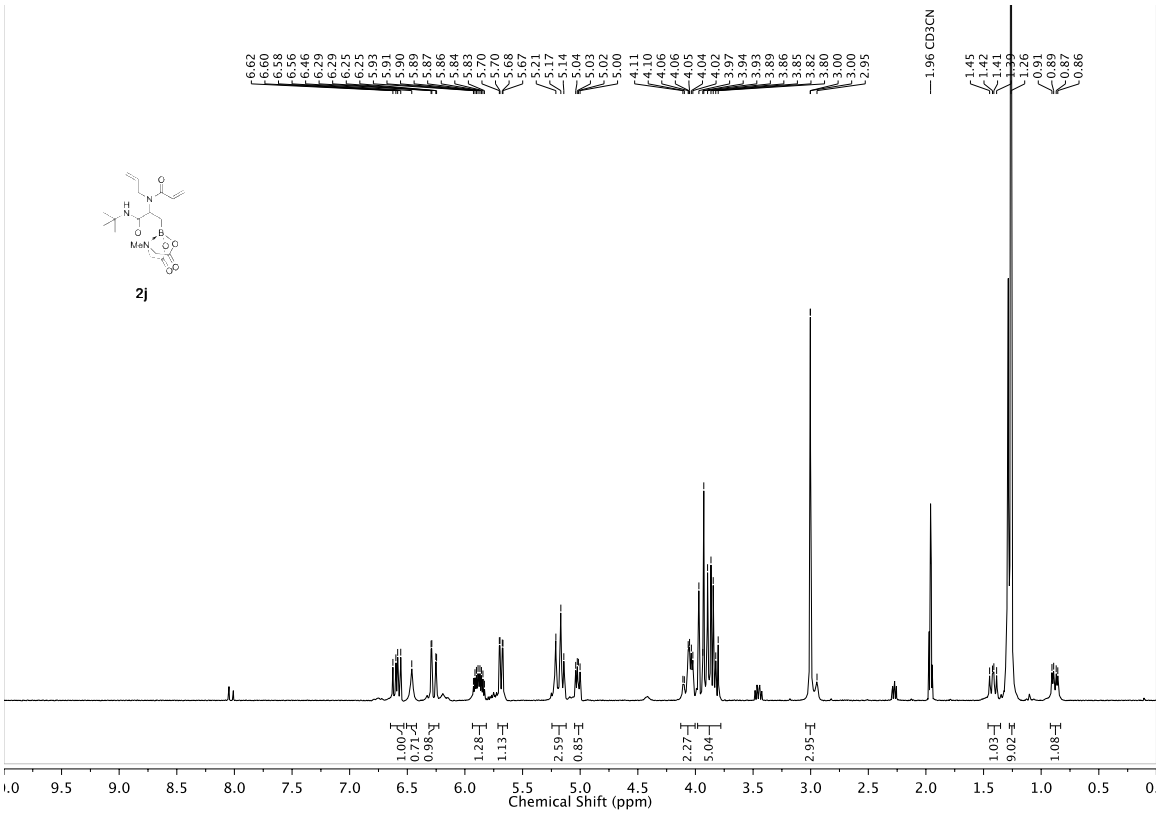

6.38
5.92
5.79
5.20
4.90
4.02
3.77
2.98
2.46
2.37
2.36
2.31
1.94
1.40
1.38
1.36
1.34
1.31
1.24
0.87
0.86
0.83
0.82
0.60
1.77
4.71
5.99
2.32
1.55
2.01
0.95
7.67
1.00
f1 (ppm)

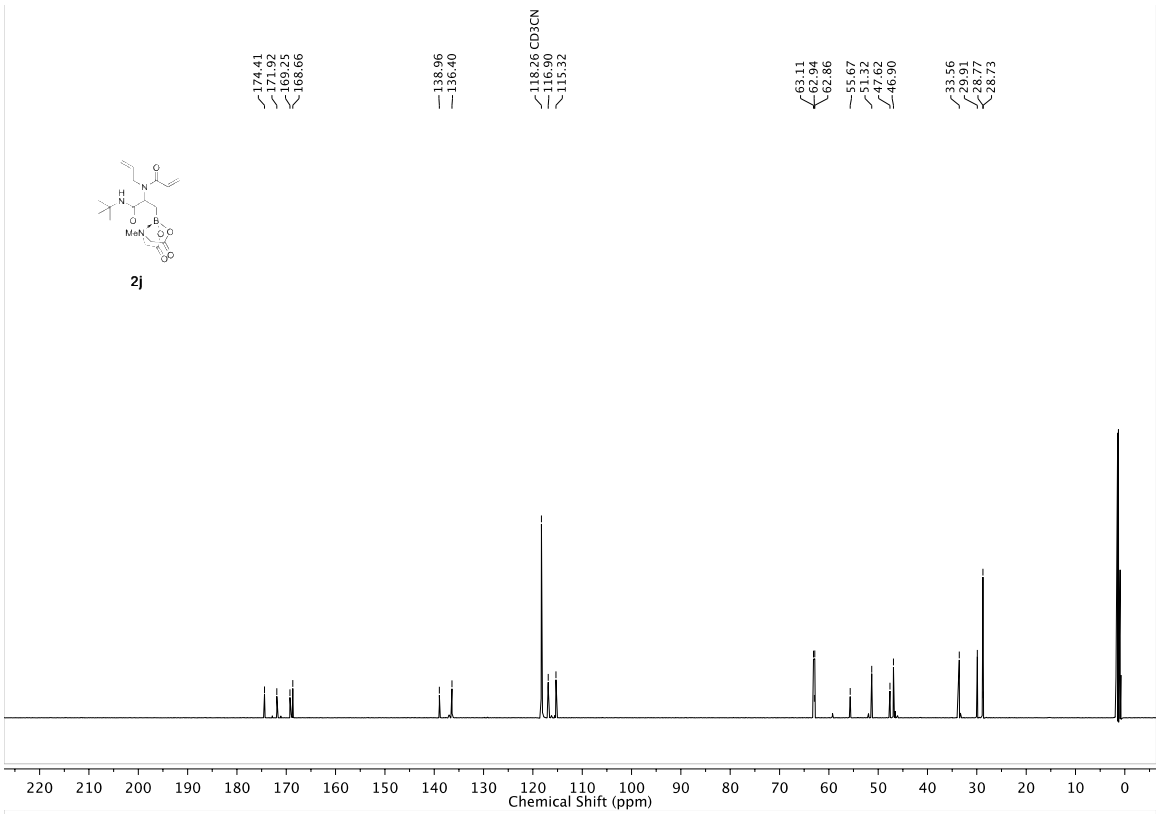
2i

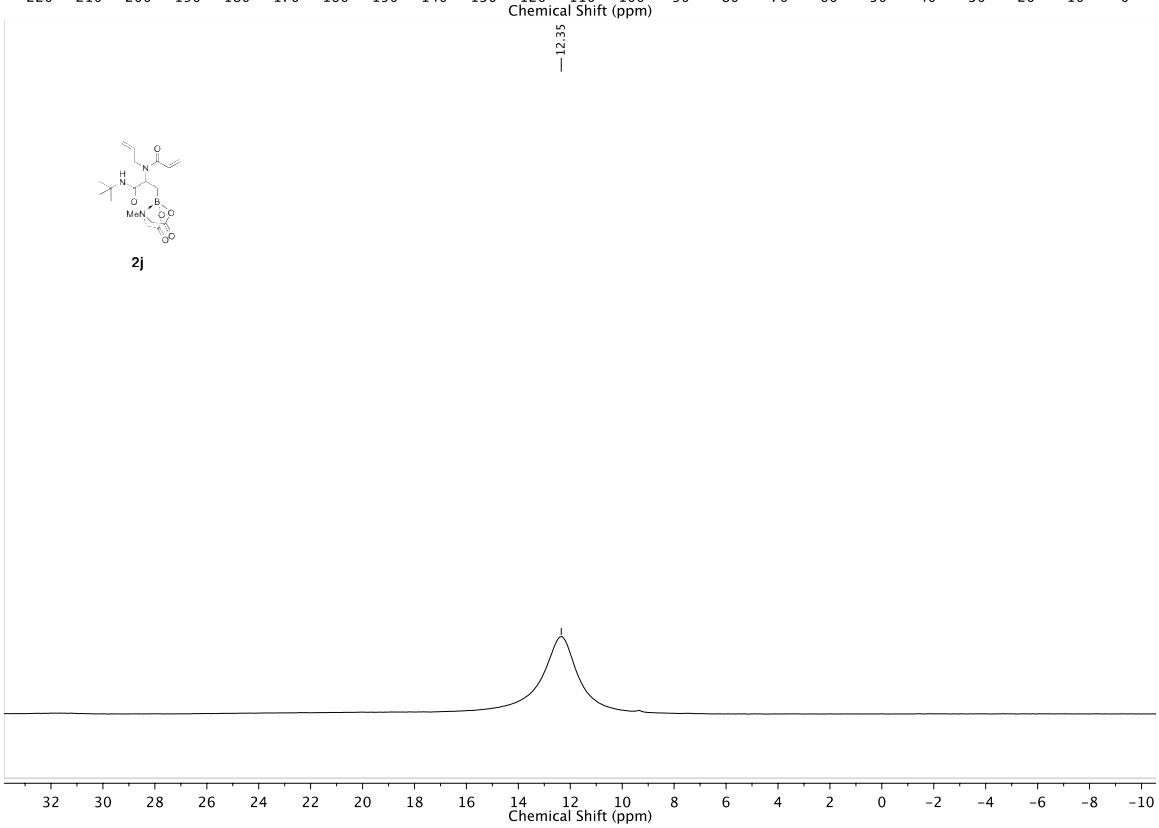

173.51
171.01
168.27
167.68
138.03
135.47
135.46
115.96
114.37
103.68
63.21
62.17
61.93
54.78
50.39
46.71
45.96
32.64
28.97
27.82
27.78
17.55
17.53
14.67
f1 (ppm)

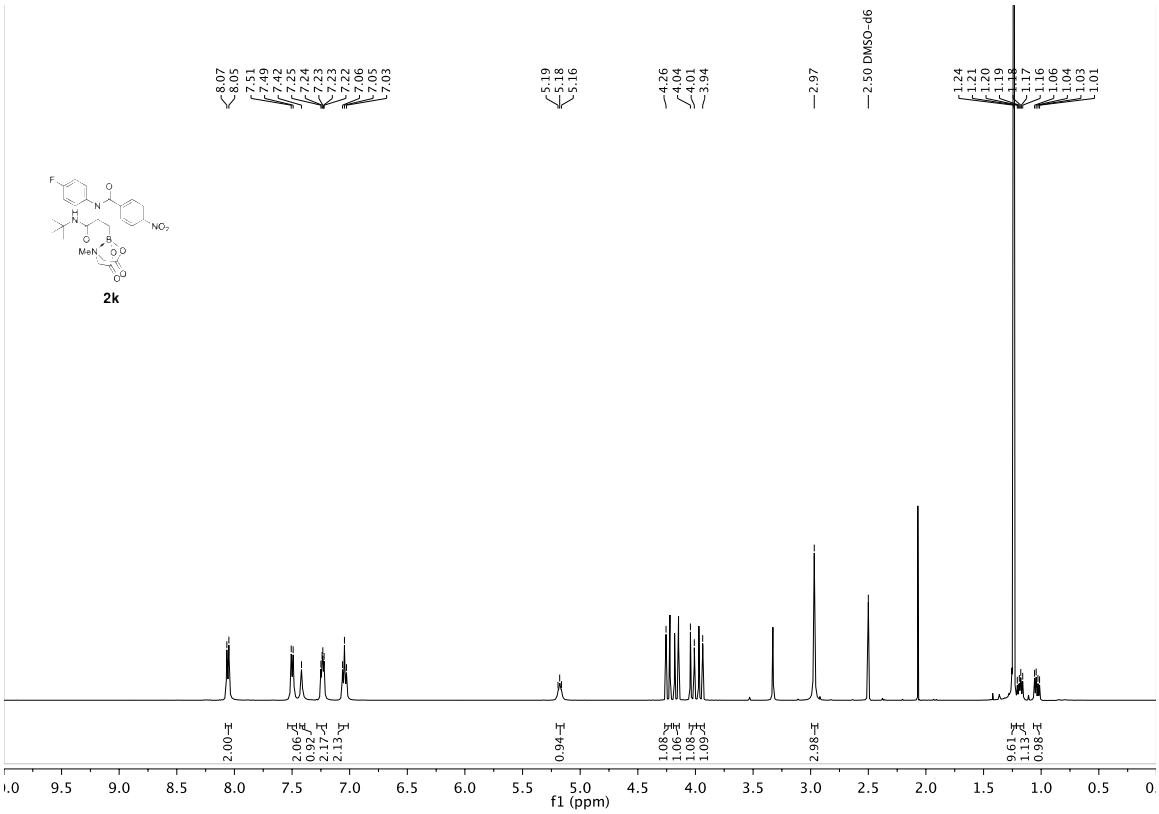
2i


12.24
2i
f1 (ppm)

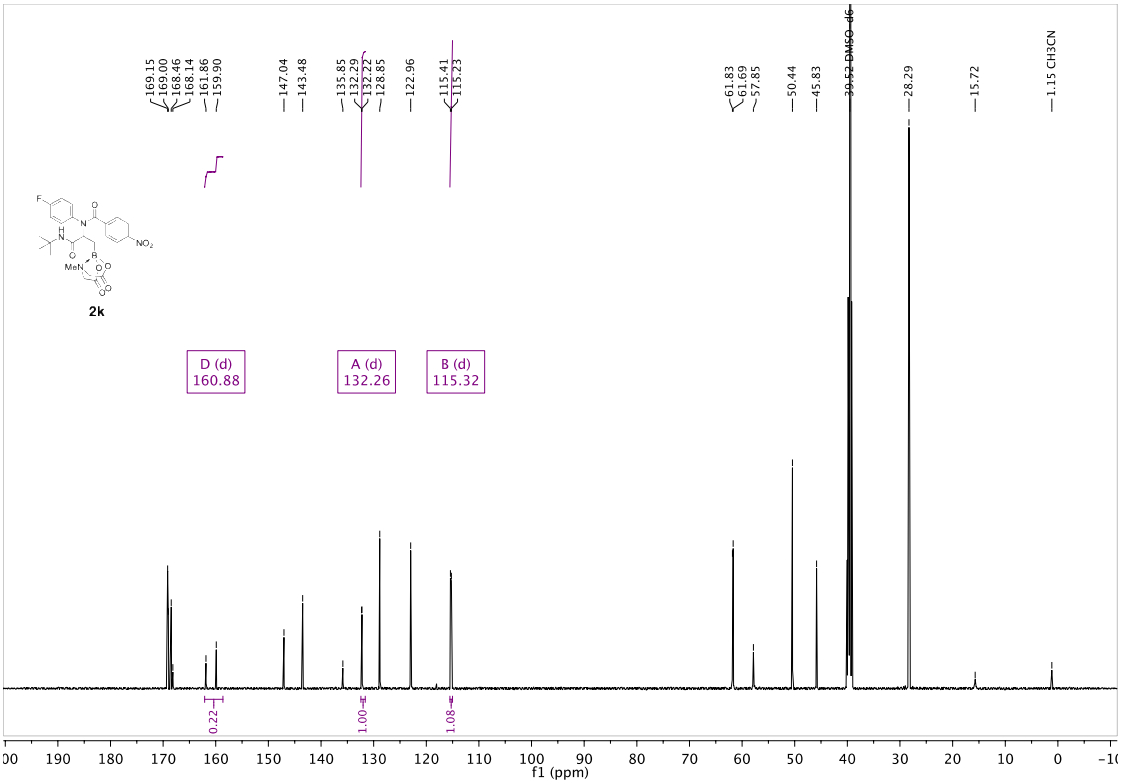

1.96 CD3CN
2j
Chemical Shift (ppm)


174.41
171.92
169.25
168.66
138.96
136.40
118.26 CD3CN
116.90
115.32
63.11
62.94
62.86
55.67
51.32
47.62
46.90
33.56
29.91
28.77
28.73
2j
Chemical Shift (ppm)

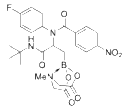

12.35
2j
Chemical Shift (ppm)


8.07
8.05
7.51
7.49
7.42
7.25
7.24
7.23
7.23
7.22
7.06
7.05
7.03
5.19
5.18
5.16
4.26
4.04
4.01
3.94
2.97
2.50 DMSO-d6
1.24
1.21
1.20
1.19
1.18
1.17
1.16
1.06
1.04
1.03
1.01
2.00
2.06
0.92
2.17
2.13
0.94
1.08
1.06
1.08
1.09
2.98
9.61
1.13
0.98
f1 (ppm)

2k

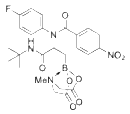

169.15
169.00
168.46
168.14
161.86
159.90
147.04
143.48
135.85
132.29
132.22
128.85
122.96
115.41
115.23
61.83
61.69
57.85
50.44
45.83
39.52 DMSO-d6
28.29
15.72
1.15 CH3CN
D (d)
160.88
A (d)
132.26
B (d)
115.32
0.22
1.00
1.08
f1 (ppm)

2k



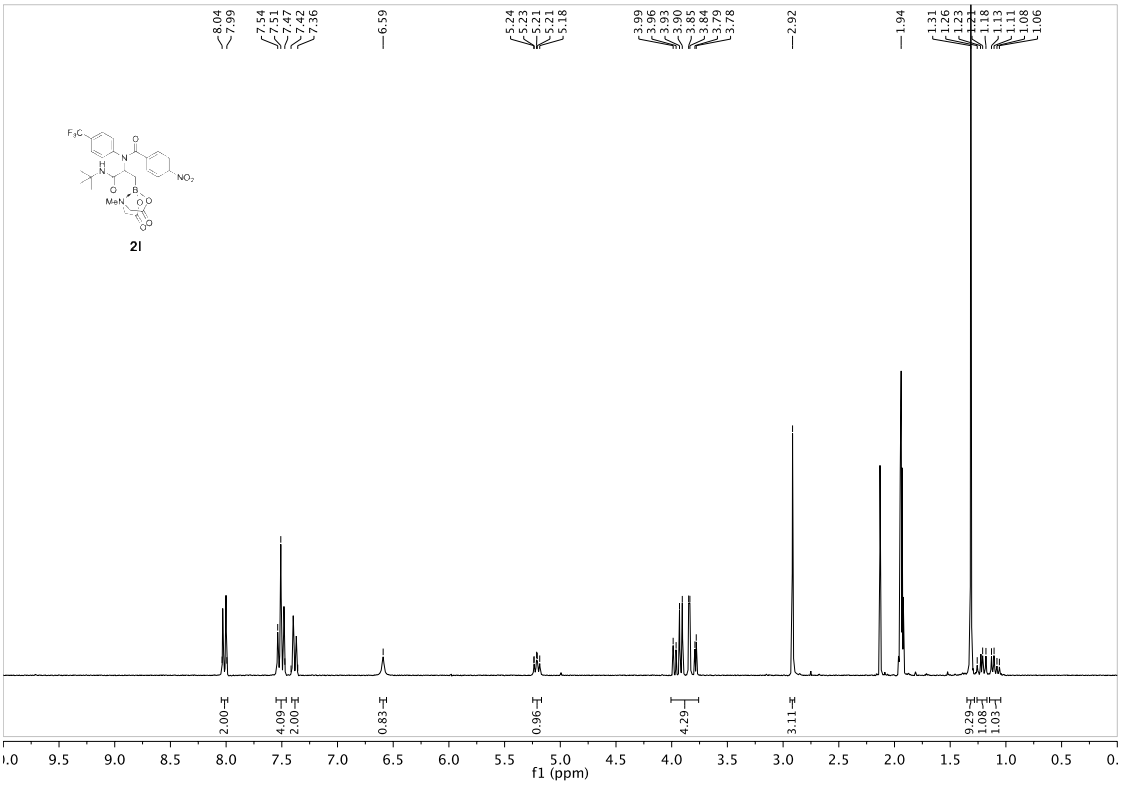
2k

12.26
100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80
f1 (ppm)

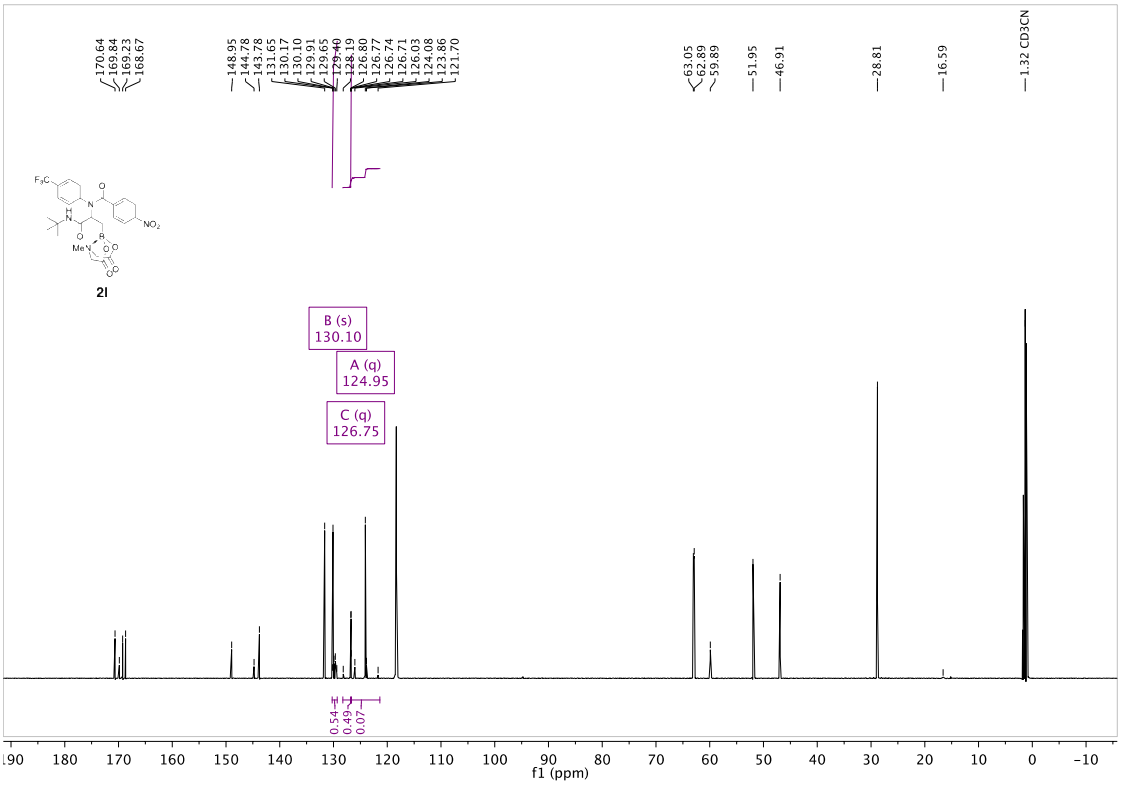


2k

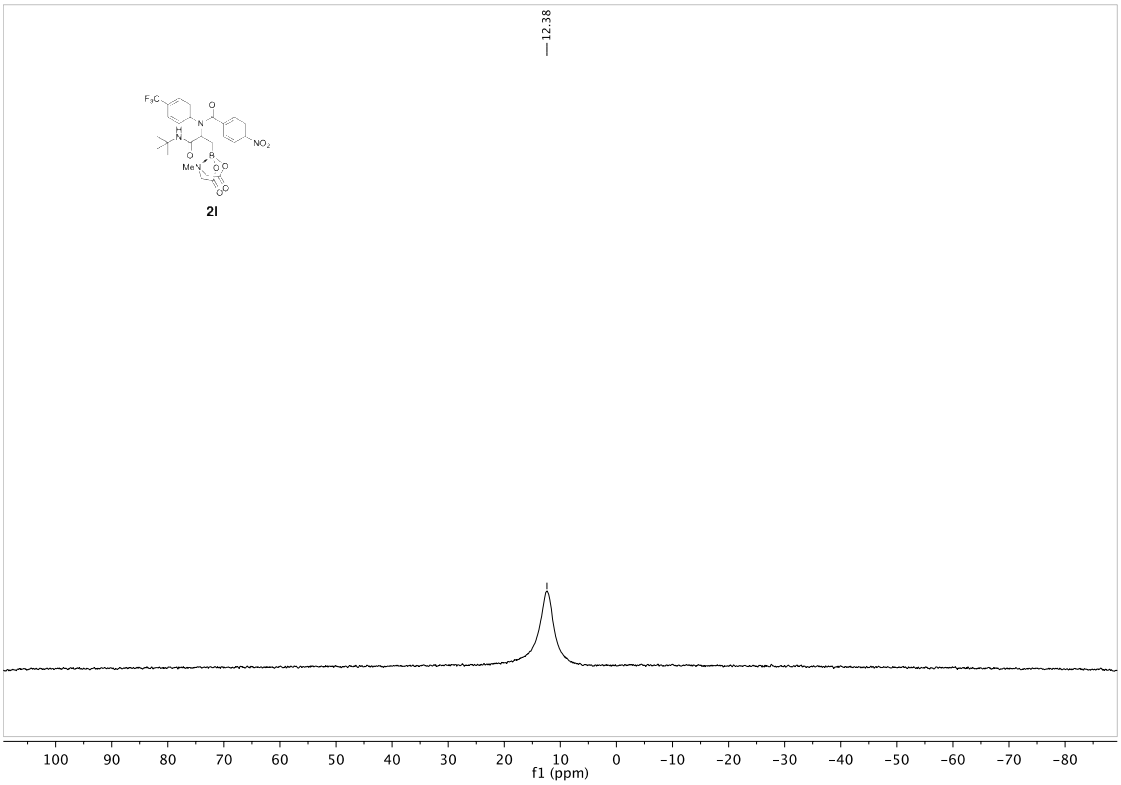
−113.97
100 80 60 40 20 0 −20 −40 −60 −80 −100 −120 −140 −160 −180 −200 −220 −240 −260 −280
f1 (ppm)

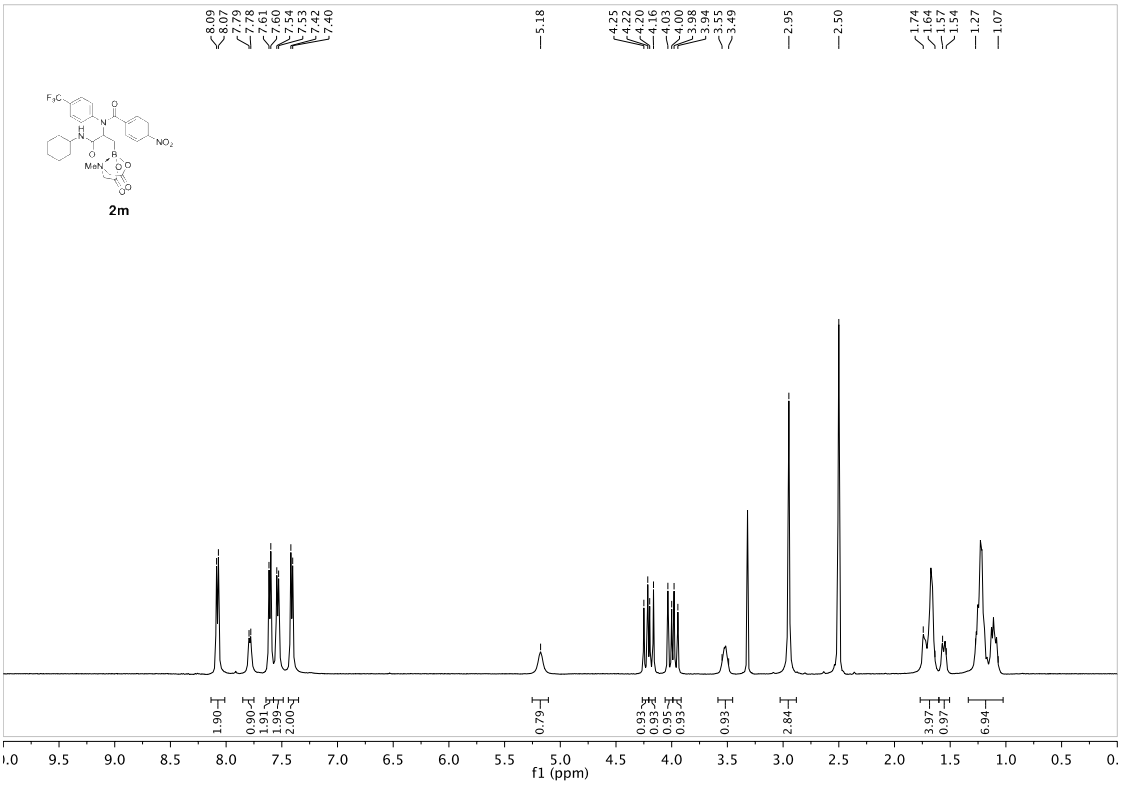

8.04
7.99
7.54
7.51
7.47
7.42
7.36
6.59
5.24
5.23
5.21
5.21
5.18
3.99
3.96
3.93
3.90
3.85
3.84
3.79
3.78
2.92
1.94
1.31
1.26
1.23
1.21
1.18
1.13
1.11
1.08
1.06
2.00
4.09
2.00
0.83
0.96
4.29
3.11
9.29
1.08
1.03
f1 (ppm)

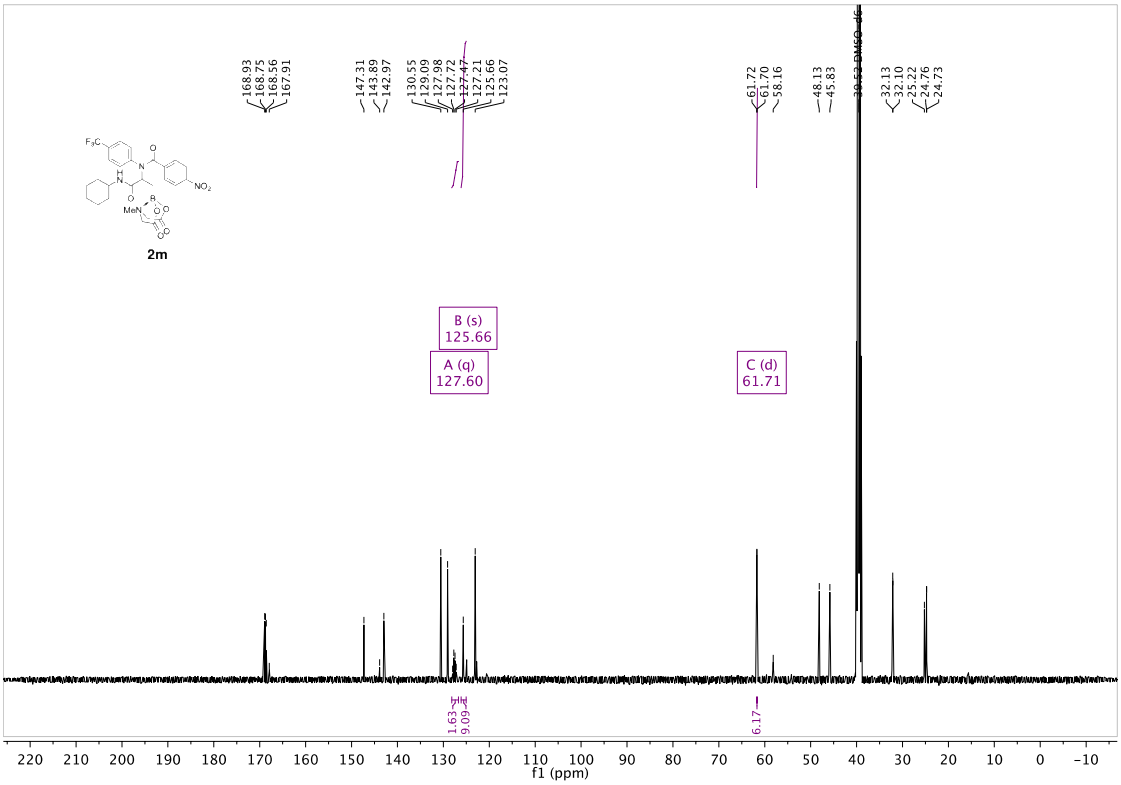
2l

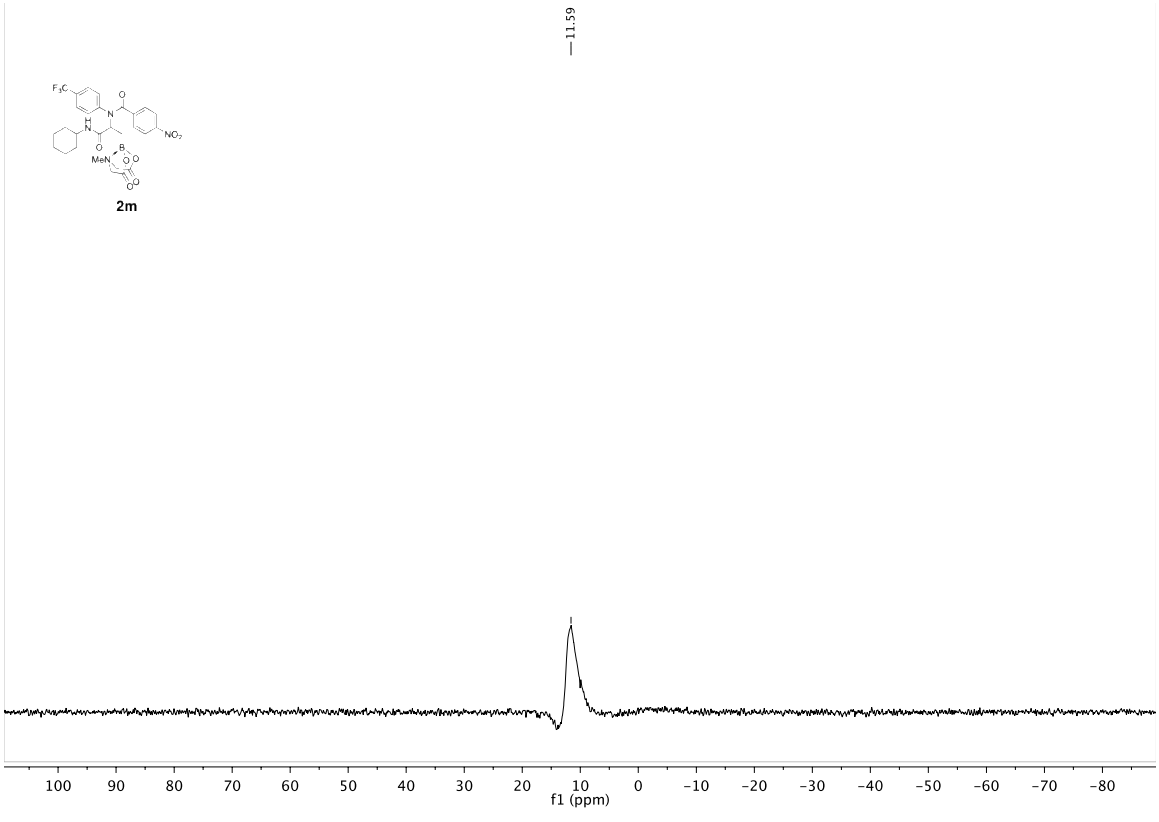

170.64
169.84
169.23
168.67
148.95
144.78
143.78
131.65
130.17
130.10
129.91
129.65
129.40
128.19
126.80
126.77
126.74
126.71
124.08
123.86
121.70
63.05
62.89
59.89
51.95
46.91
28.81
16.59
1.32 CD3CN
B (s)
130.10
A (q)
124.95
C (q)
126.75
0.54
0.49
0.07
f1 (ppm)

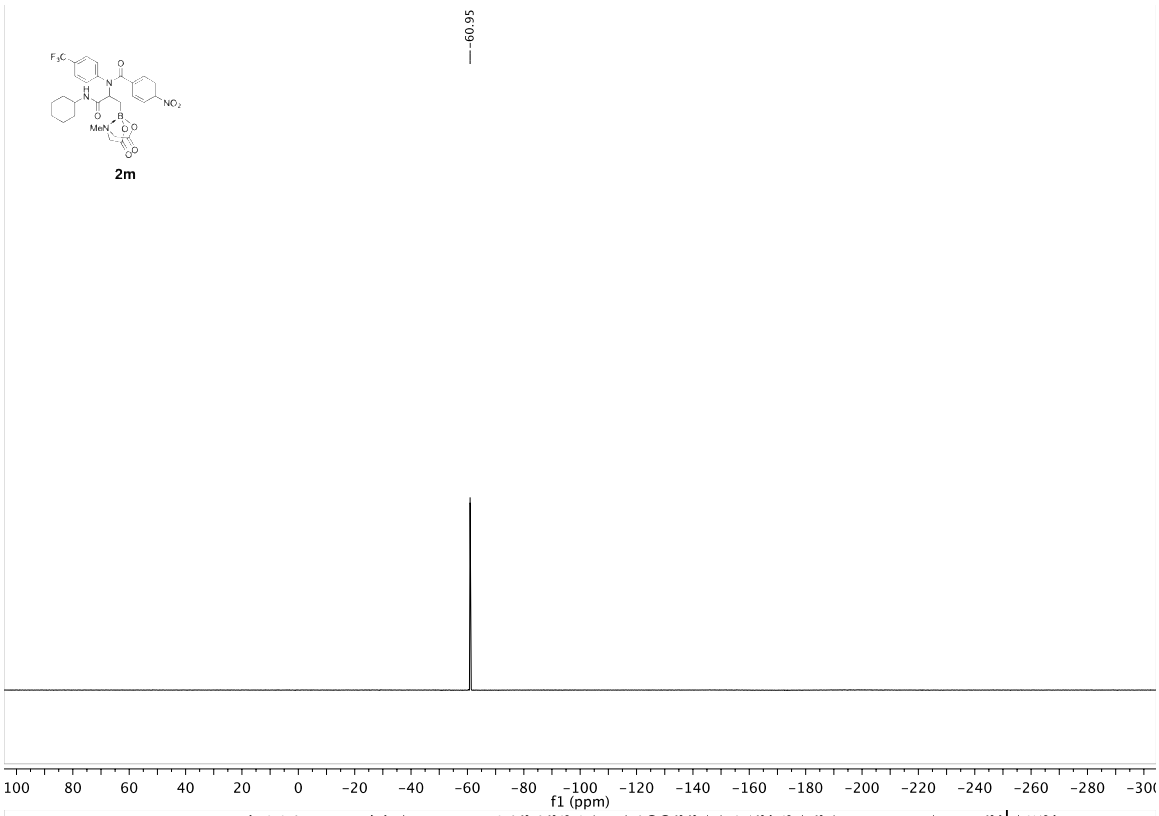
2l

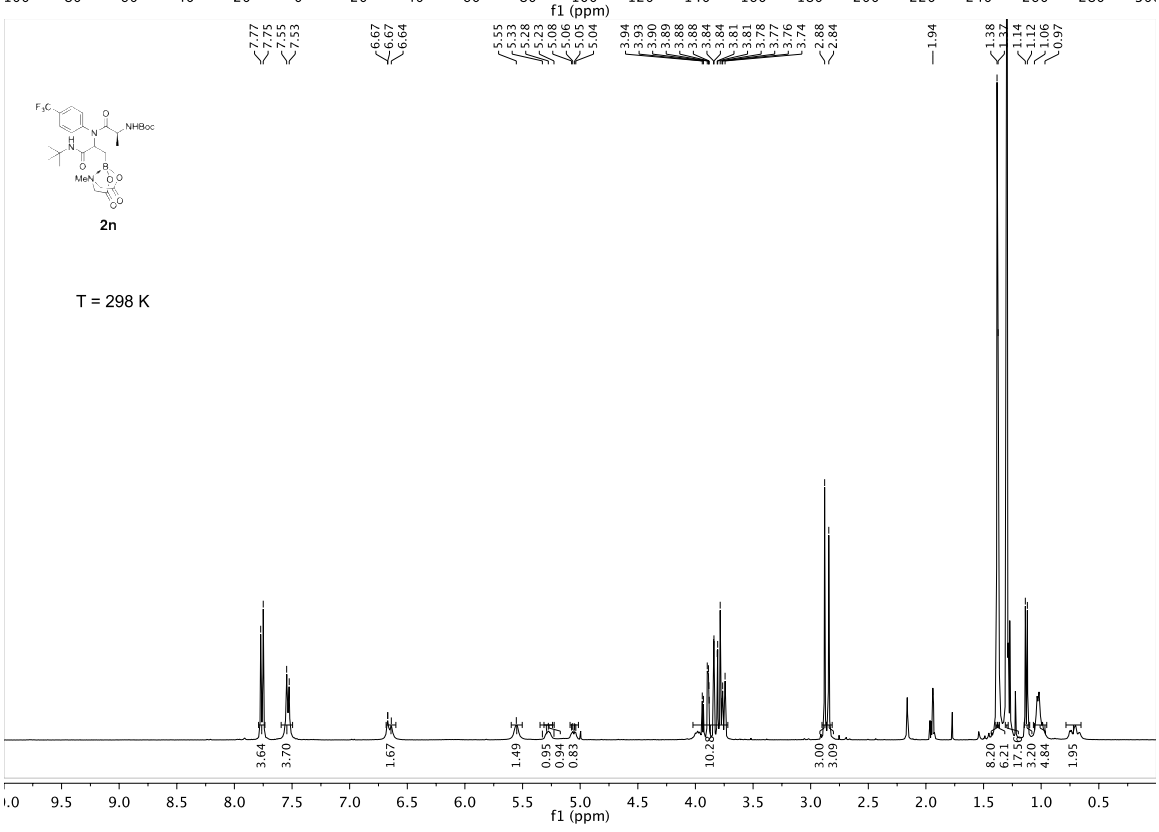

12.38
2l
100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80
f1 (ppm)

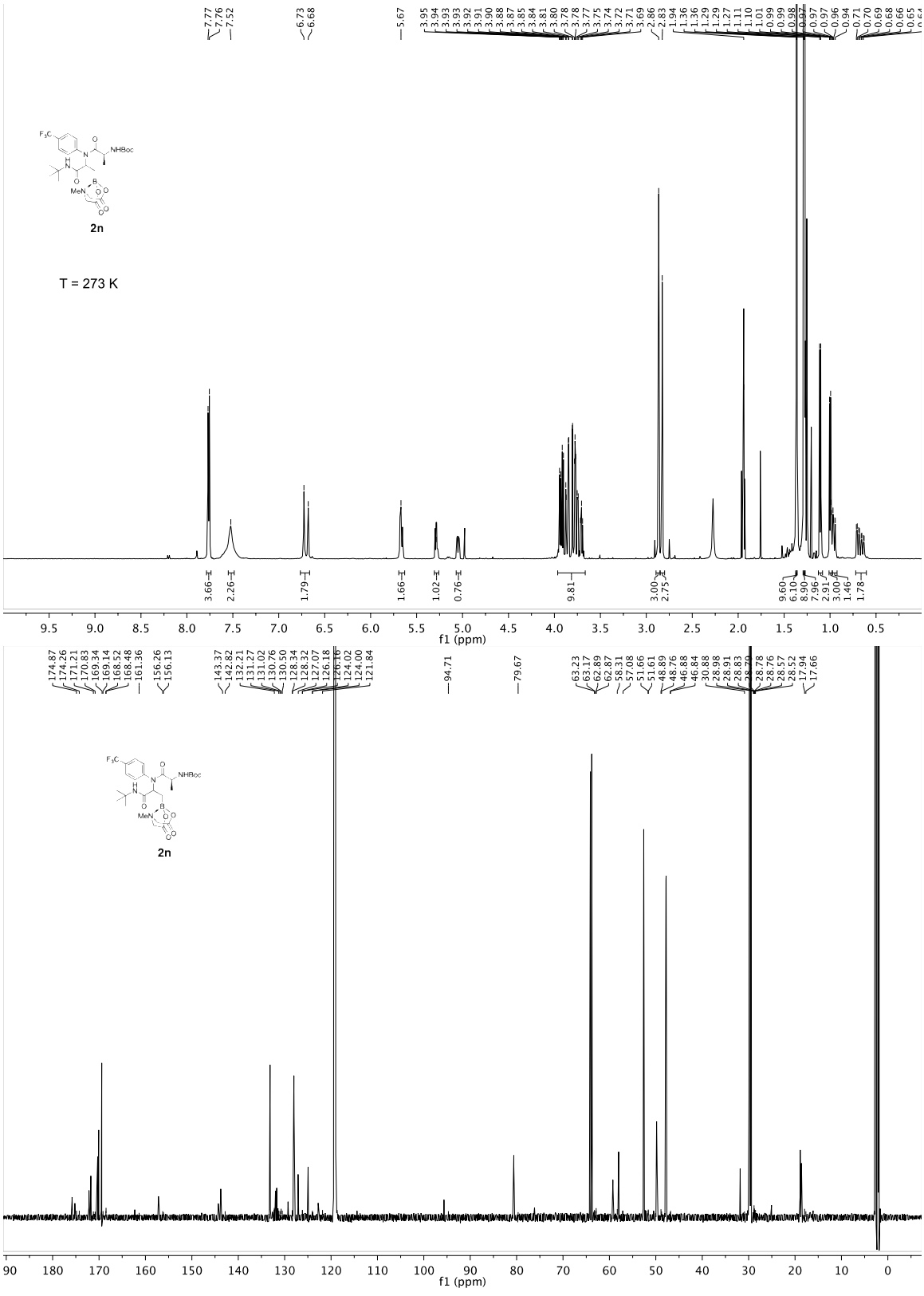

8.09
8.07
7.79
7.78
7.61
7.60
7.54
7.53
7.42
7.40
5.18
4.25
4.22
4.20
4.16
4.03
4.00
3.98
3.94
3.55
3.49
2.95
2.50
1.74
1.64
1.57
1.54
1.27
1.07
2m
1.90
0.90
1.91
1.99
2.00
0.79
0.93
0.93
0.93
0.93
2.84
3.97
0.97
6.94
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

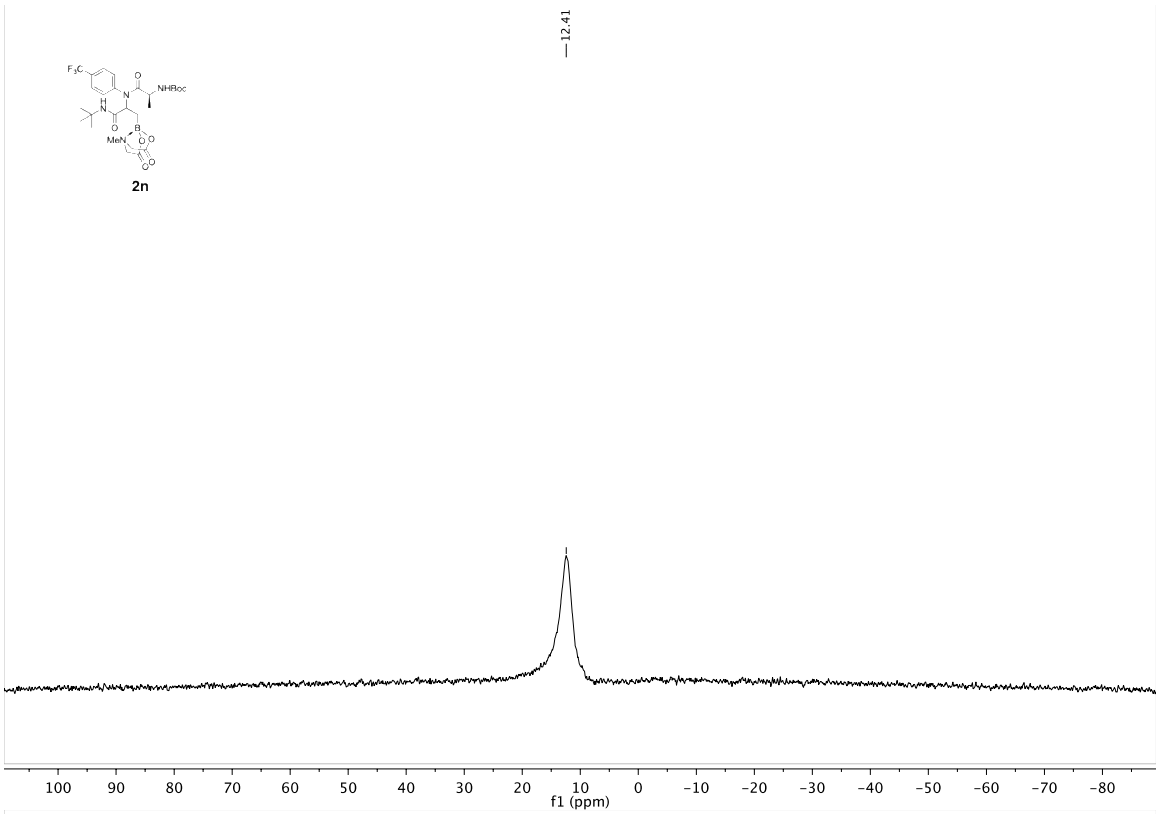

168.93
168.75
168.56
167.91
147.31
143.89
142.97
130.55
129.09
127.98
127.72
127.47
127.21
125.66
123.07
61.72
61.70
58.16
48.13
45.83
32.13
32.10
25.22
24.76
24.73
B (s)
125.66
A (q)
127.60
C (d)
61.71
1.63
9.09
6.17
f1 (ppm)
2m

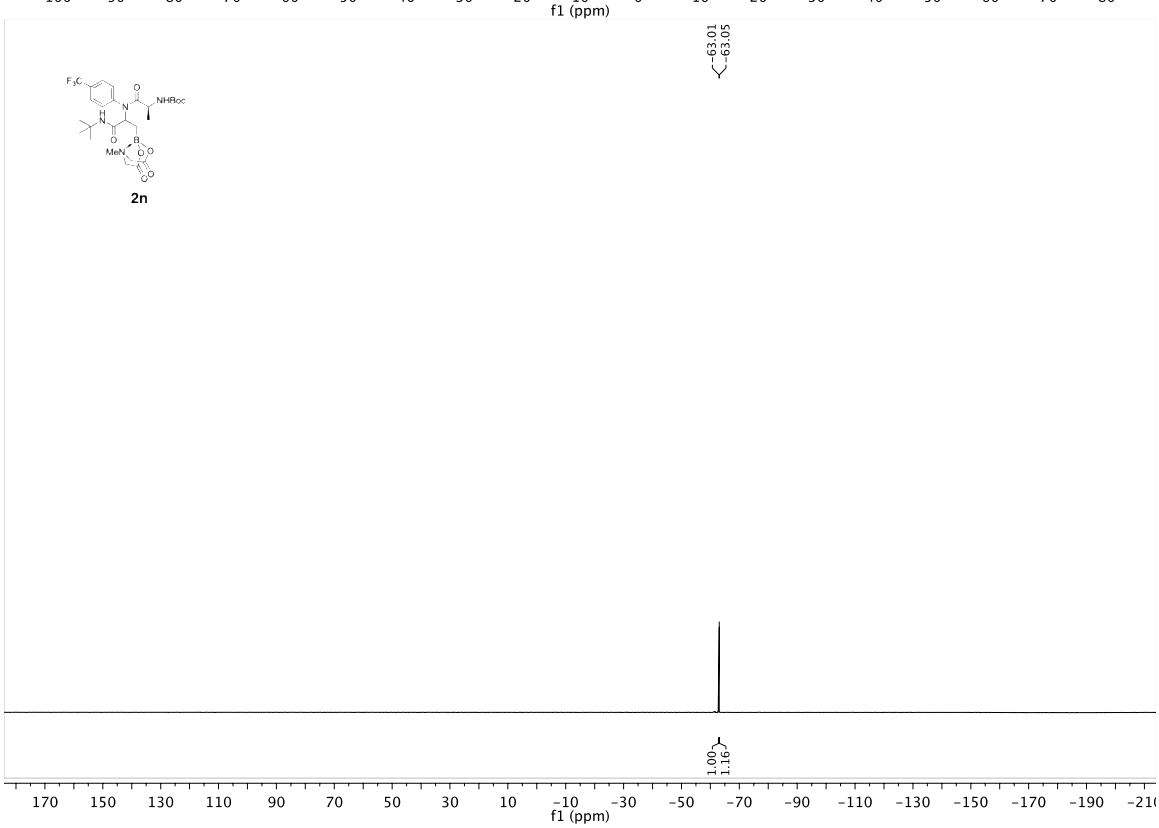

11.59
f1 (ppm)
2m

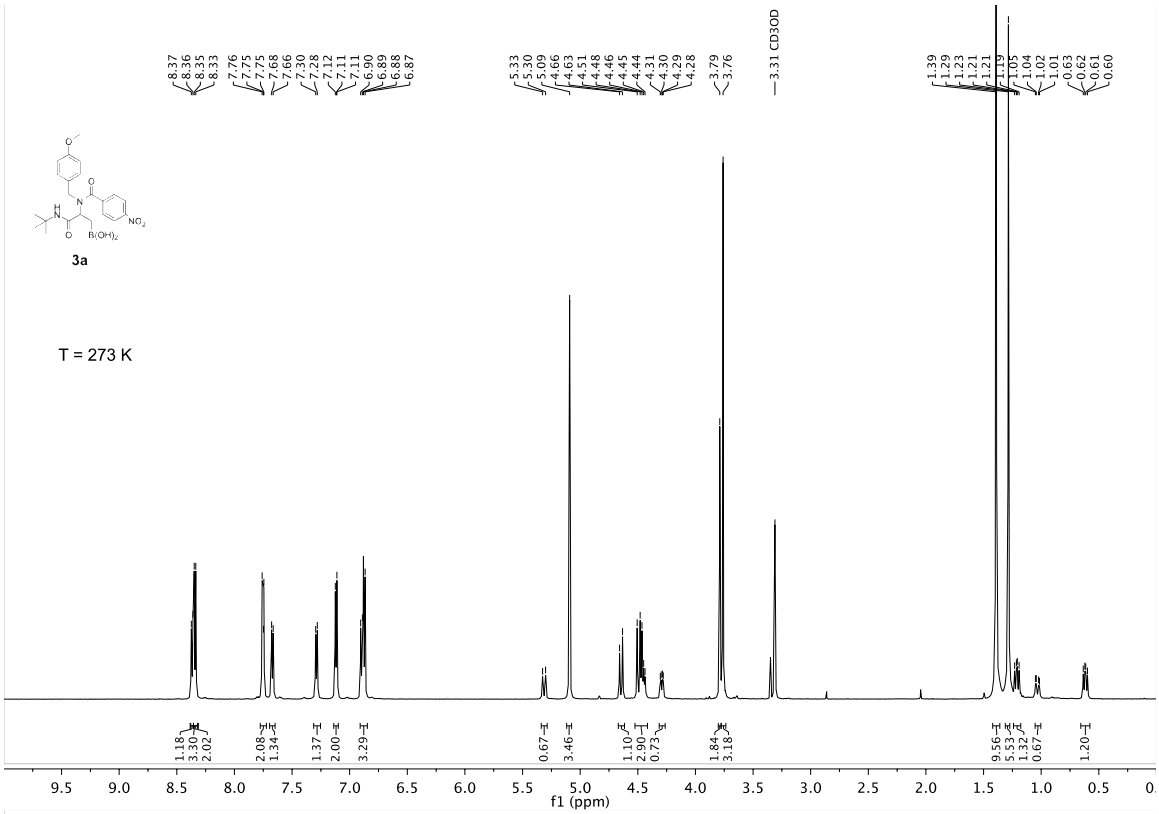

−60.95
2m
f1 (ppm)

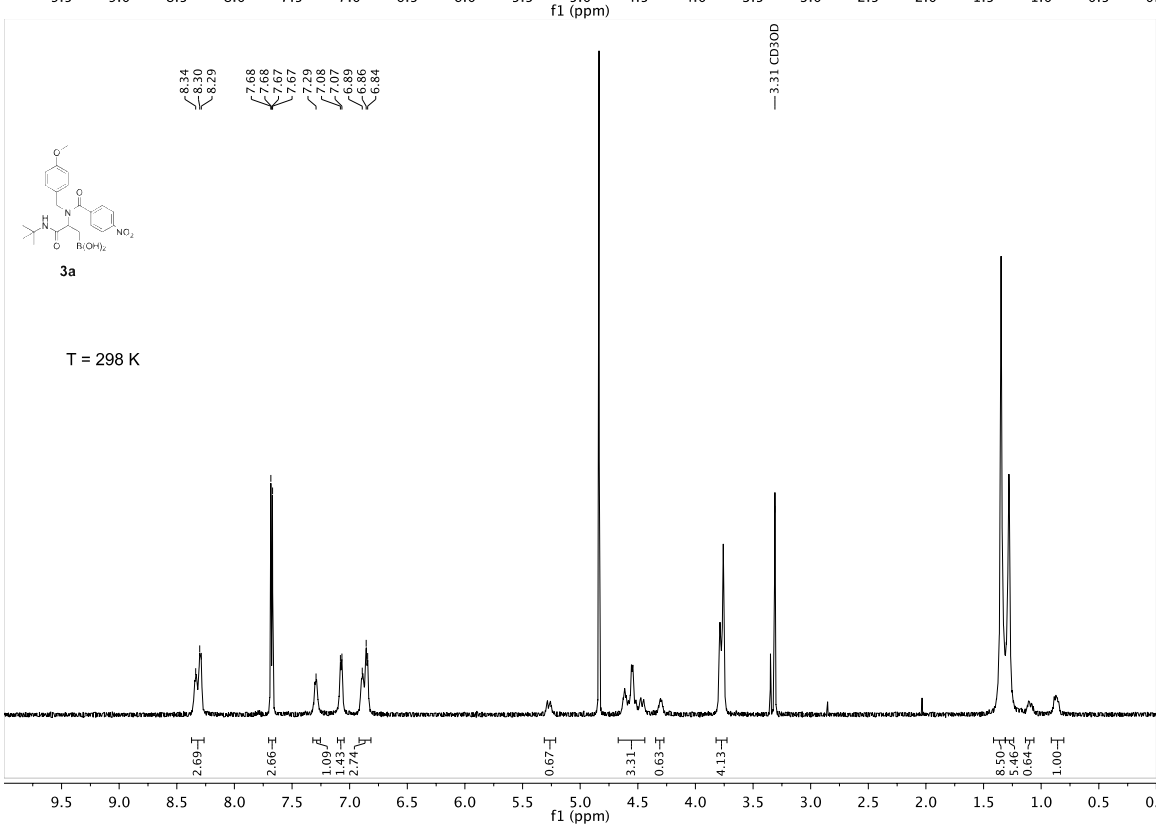

2n
T = 298 K
f1 (ppm)

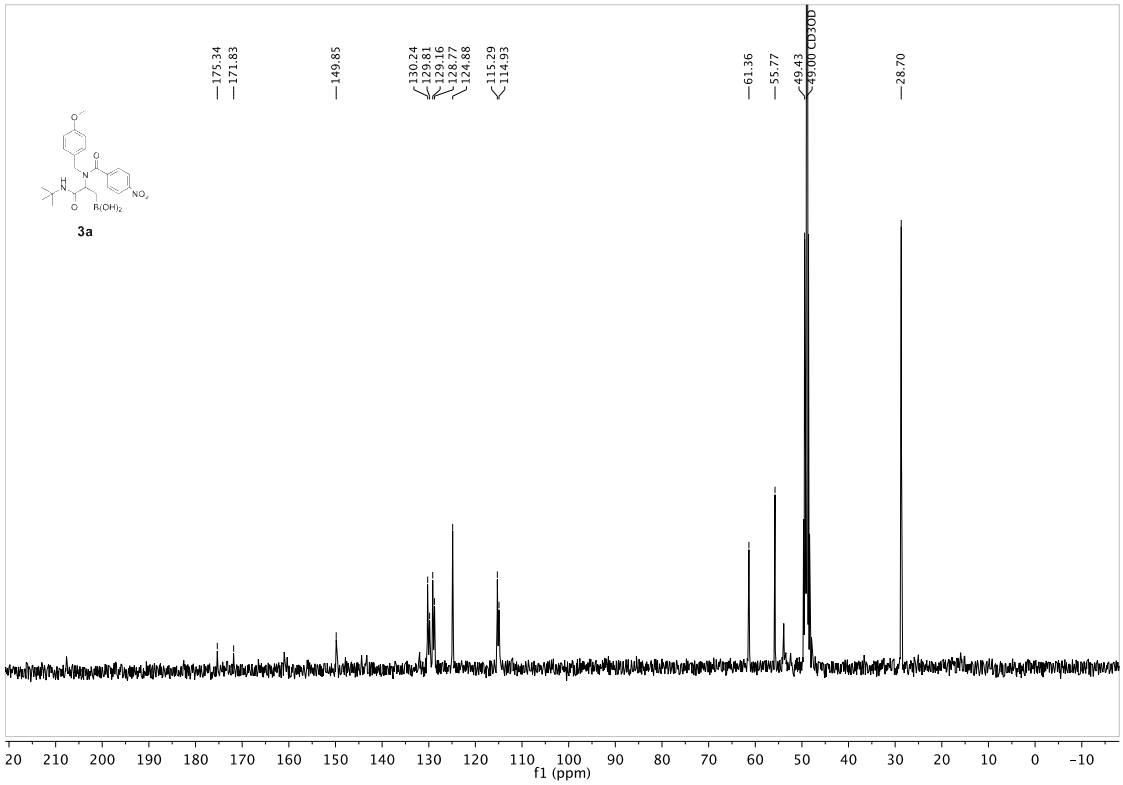

2n
T = 273 K
f1 (ppm)
2n
f1 (ppm)

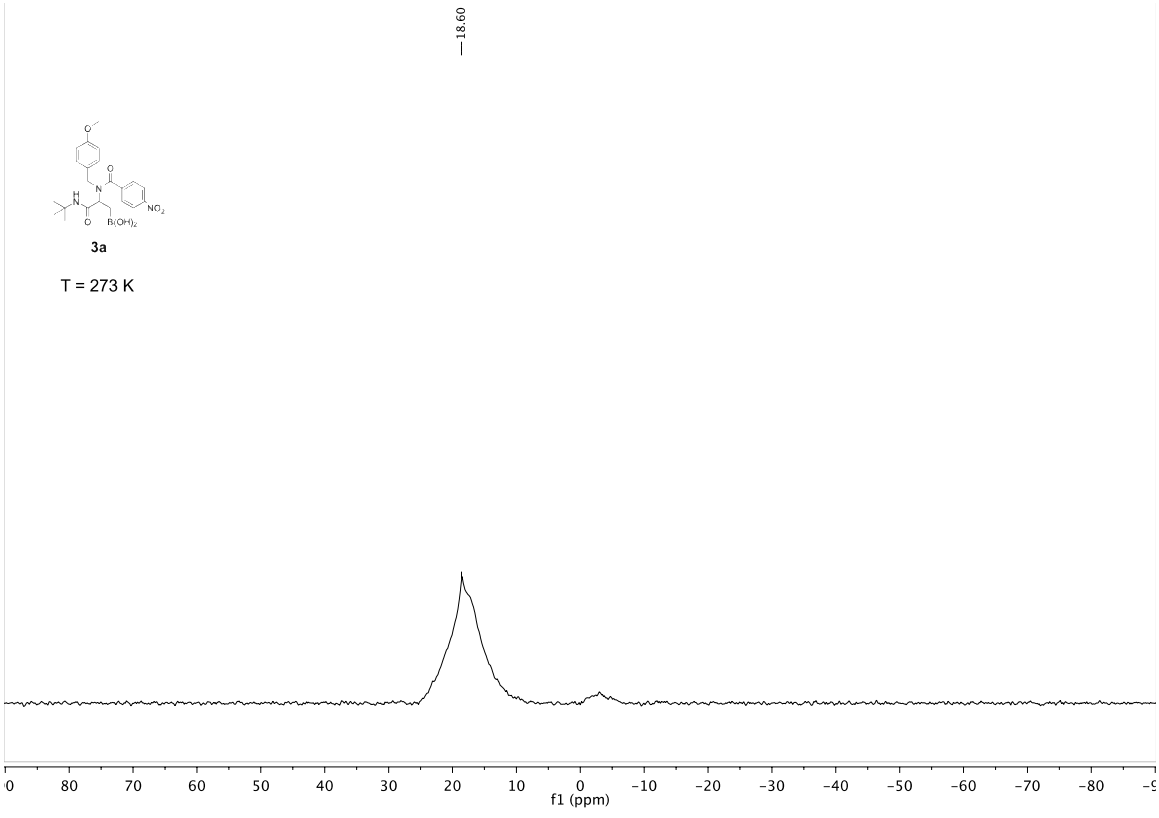

12.41
2n
100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80
f1 (ppm)

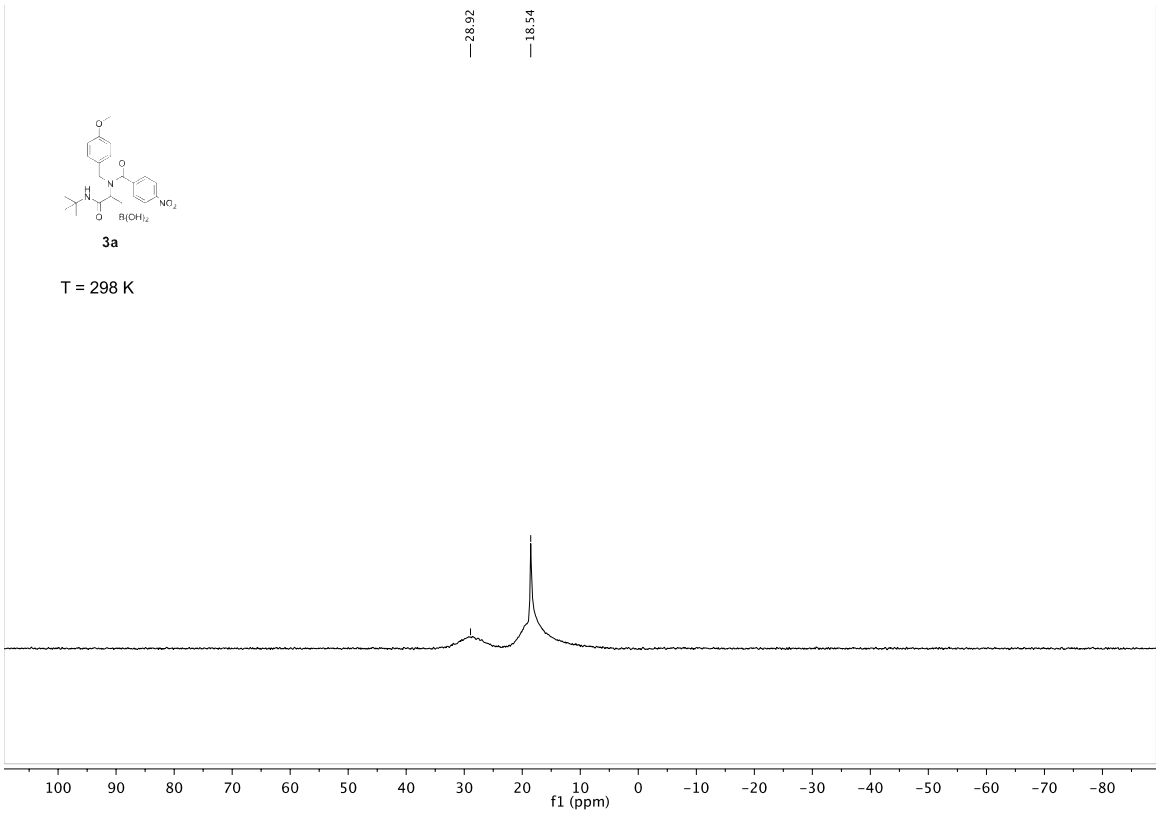

63.01
63.05
2n
1.00
1.16
170 150 130 110 90 70 50 30 10 −10 −30 −50 −70 −90 −110 −130 −150 −170 −190 −210
f1 (ppm)

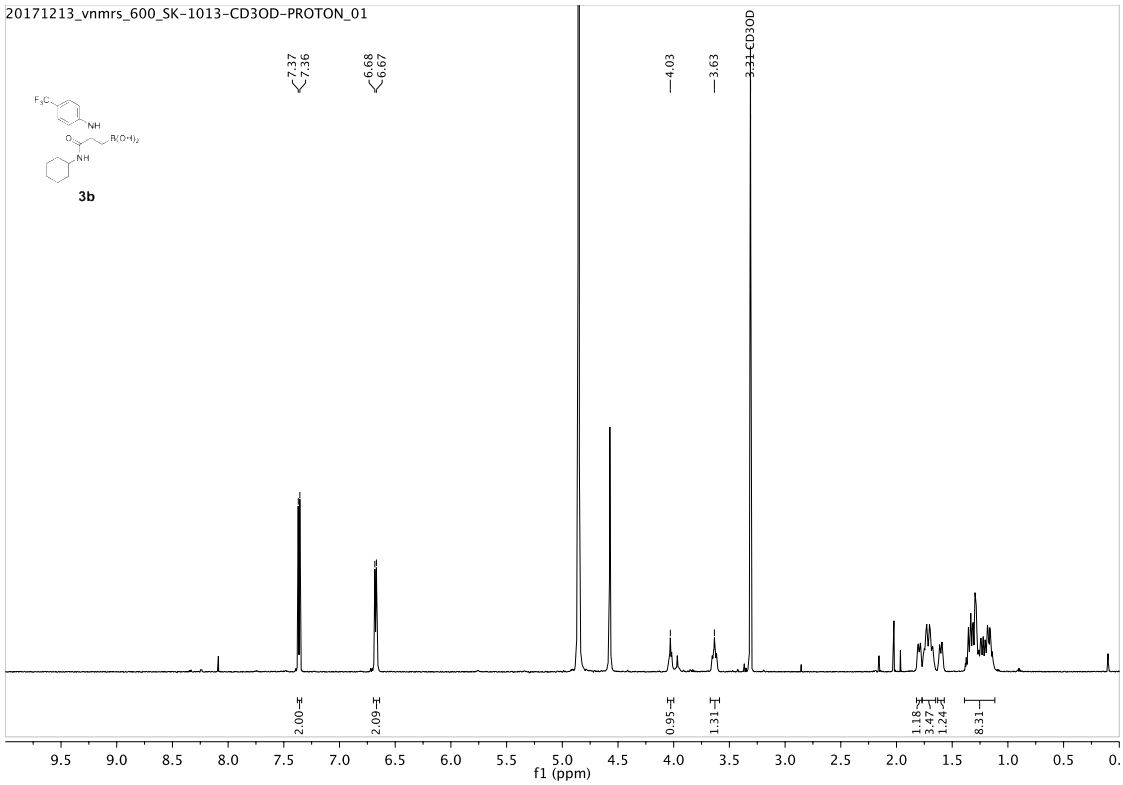

3a
T = 273 K
f1 (ppm)

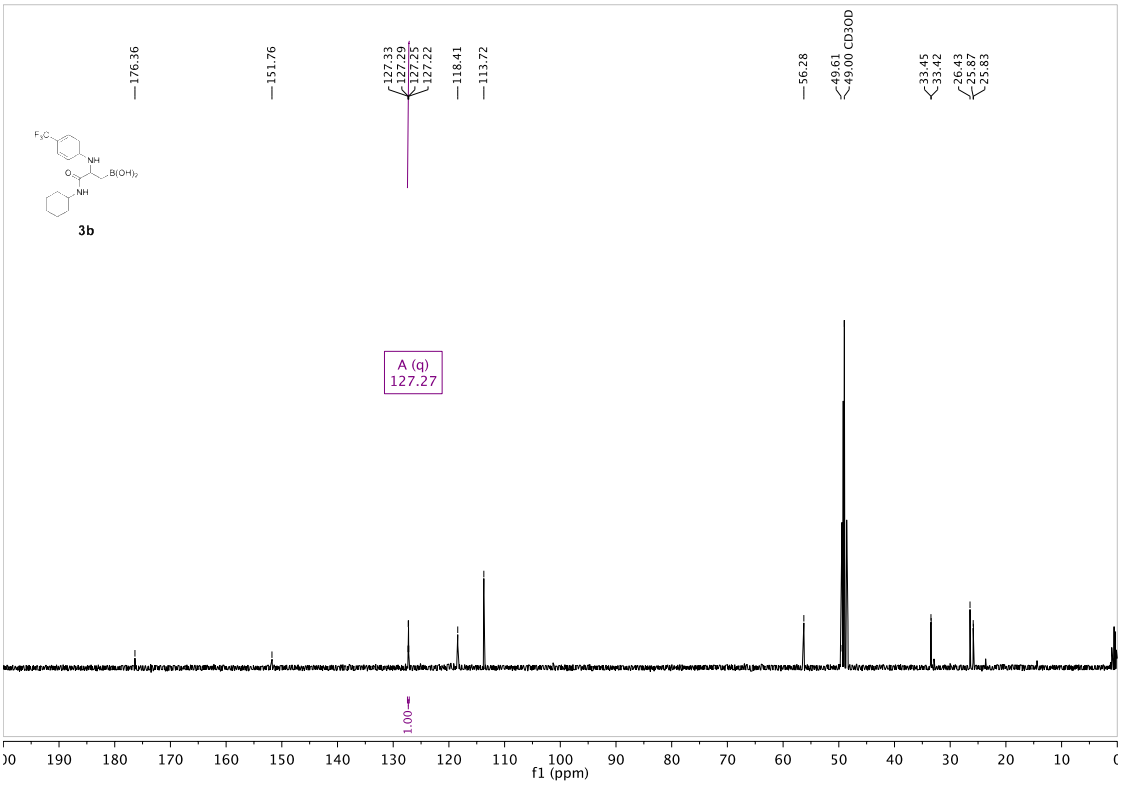

3a
T = 298 K
f1 (ppm)

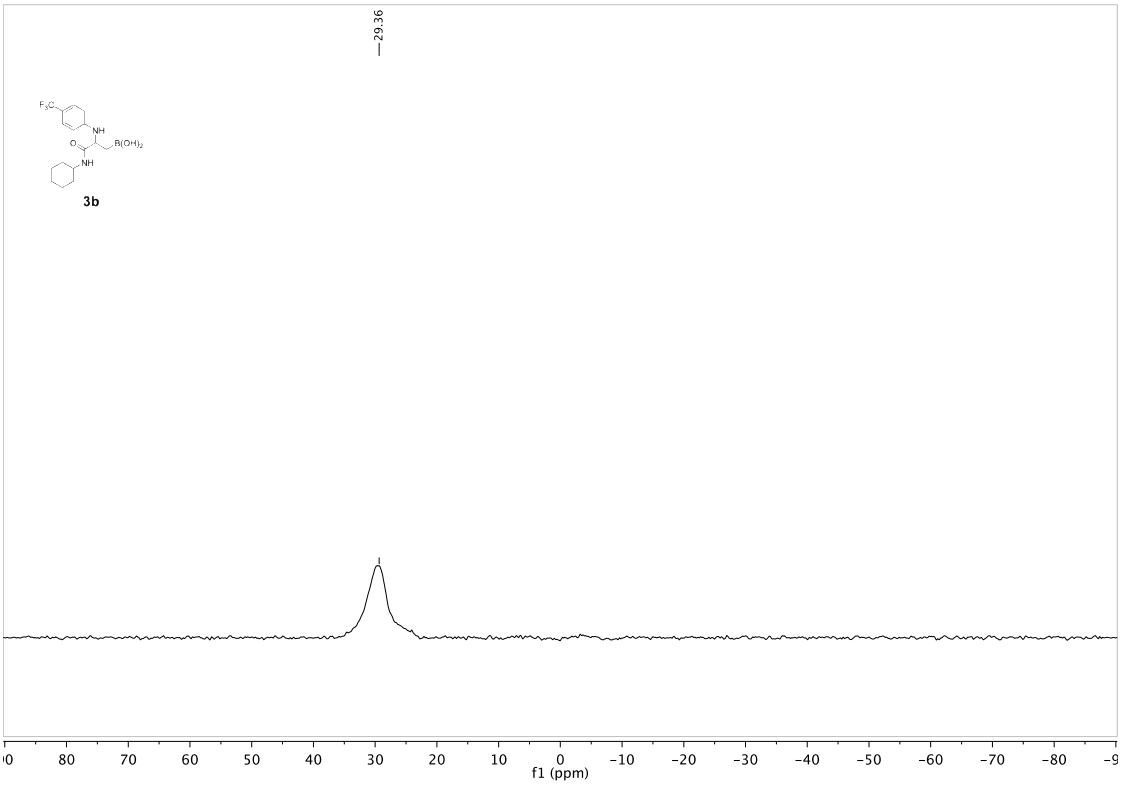

175.34
171.83
149.85
130.24
129.81
129.16
128.77
124.88
115.29
114.93
61.36
55.77
49.43
49.00 CD3OD
28.70
3a
f1 (ppm)

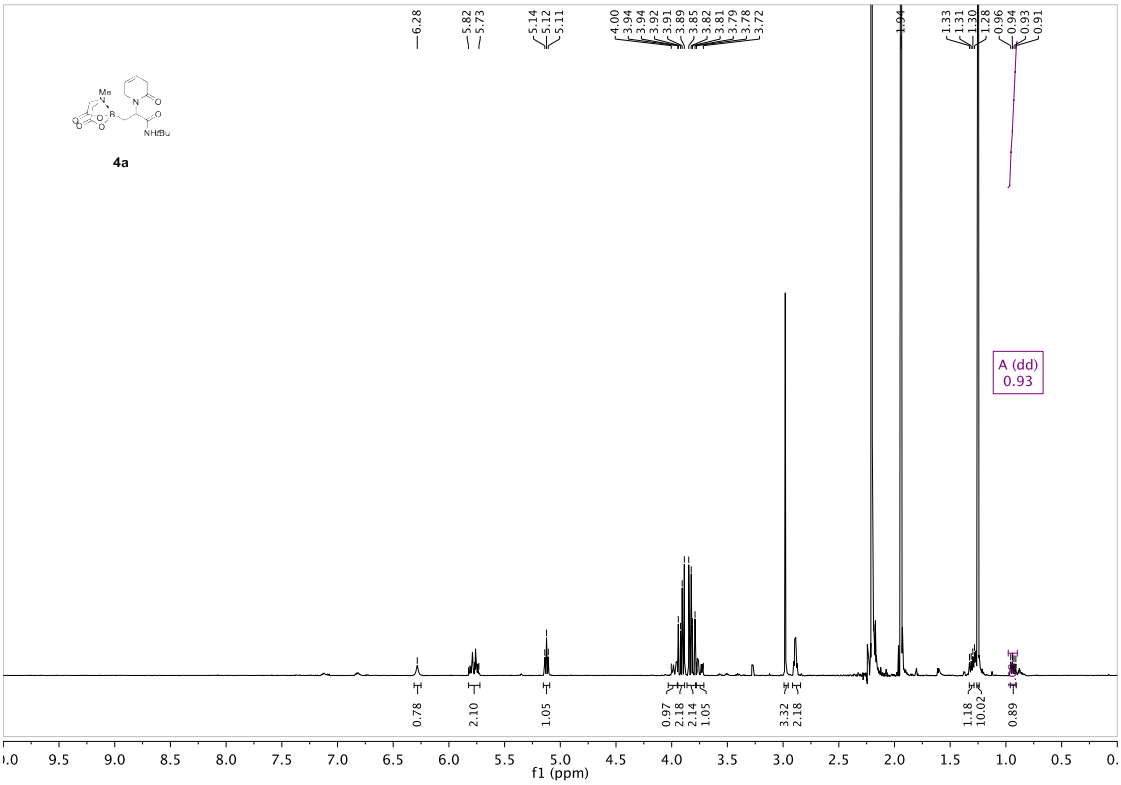

18.60
3a
T = 273 K
f1 (ppm)

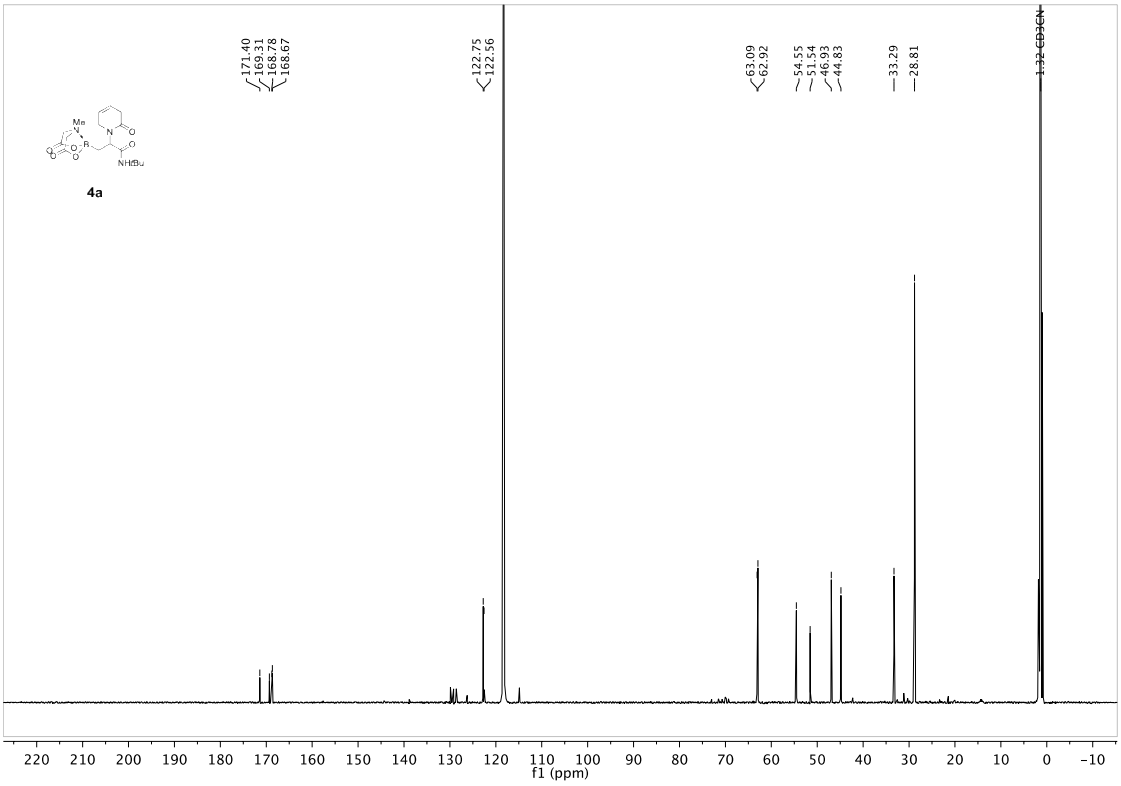

28.92
18.54
3a
T = 298 K
f1 (ppm)

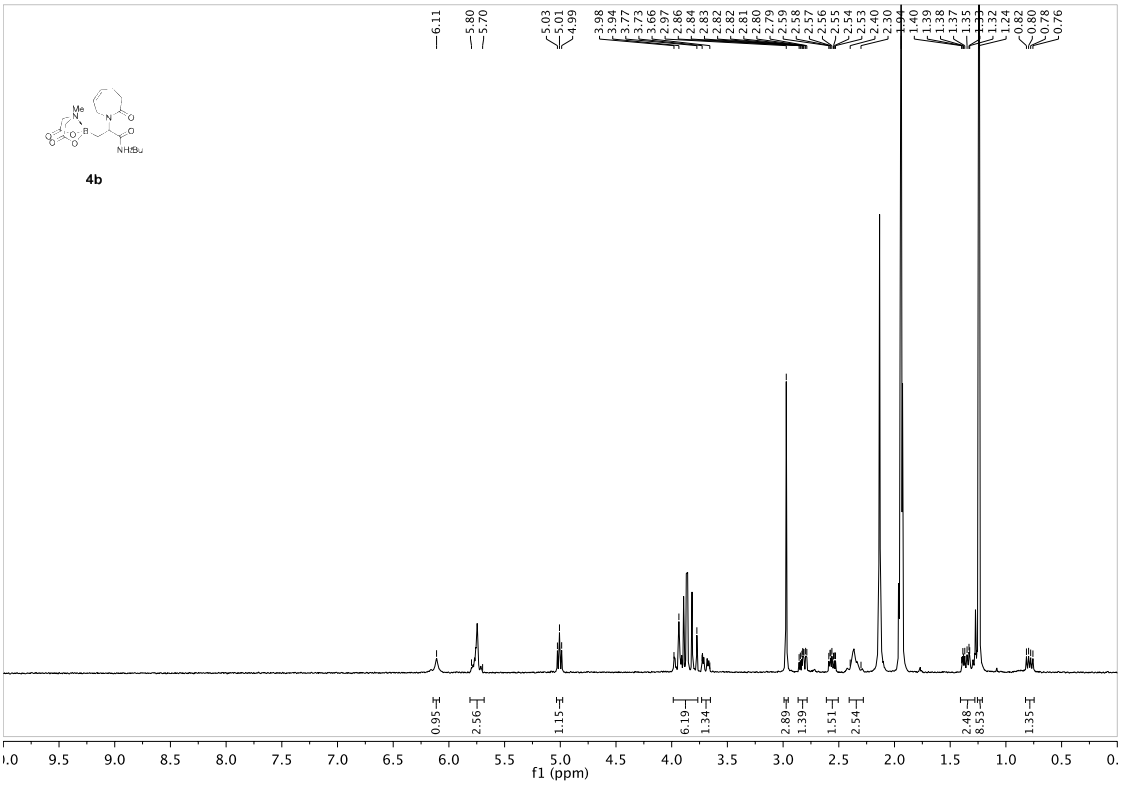

20171213_vnmrs_600_SK-1013-CD3OD-PROTON_01
7.37
7.36
6.68
6.67
4.03
3.63
3.31 CD3OD
3b
2.00
2.09
0.95
1.31
1.18
3.47
1.24
8.31
f1 (ppm)

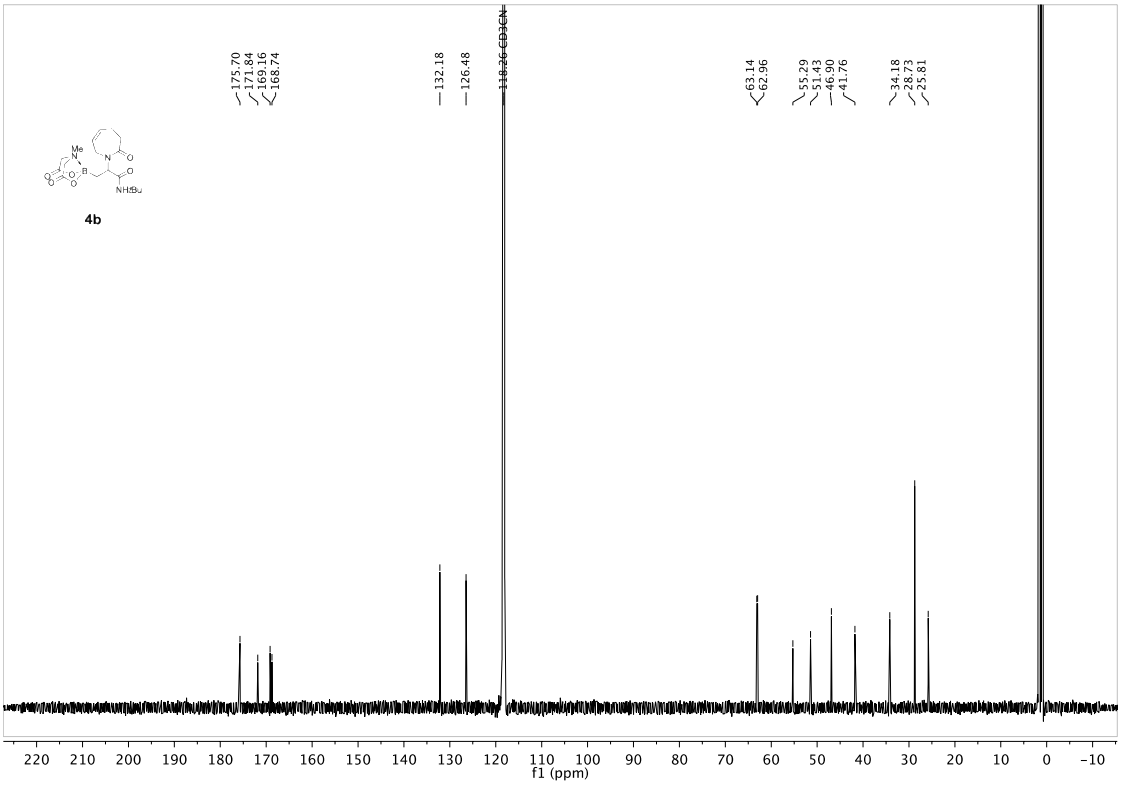

176.36
151.76
127.33
127.29
127.25
127.22
118.41
113.72
56.28
49.61
49.00 CD3OD
33.45
33.42
26.43
25.87
25.83
3b
A (q)
127.27
1.00
f1 (ppm)

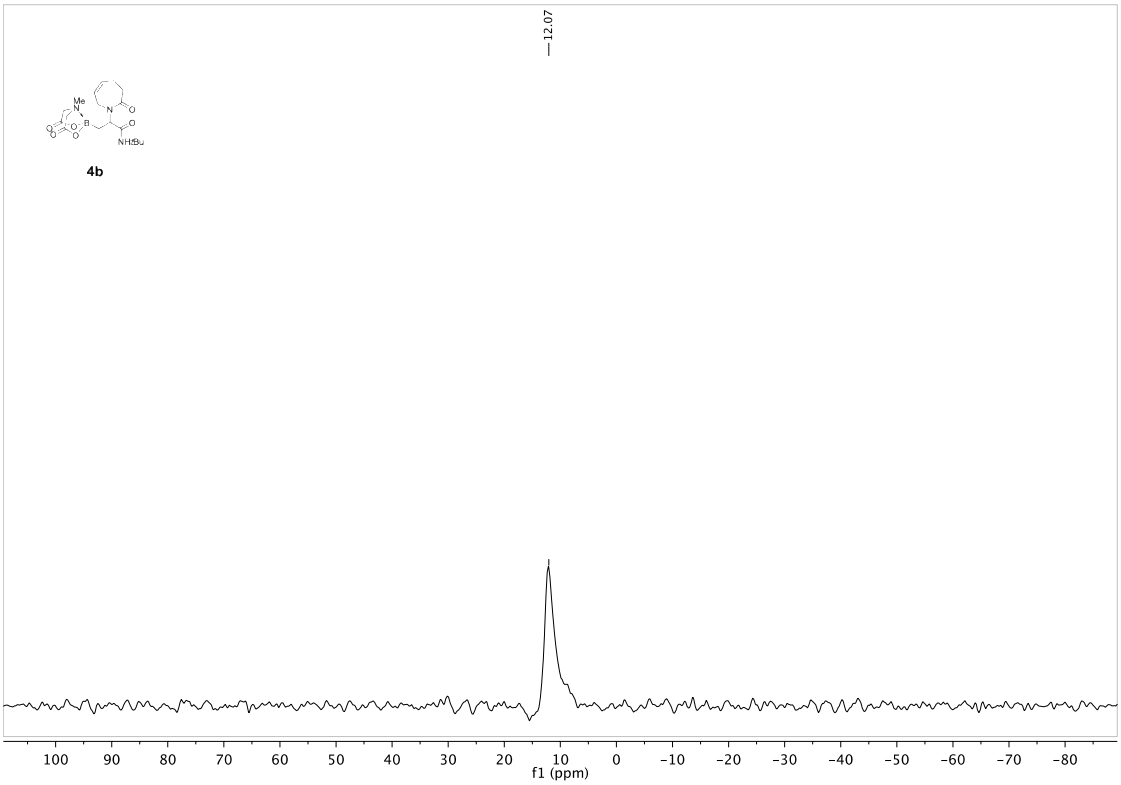

29.36
3b
f1 (ppm)

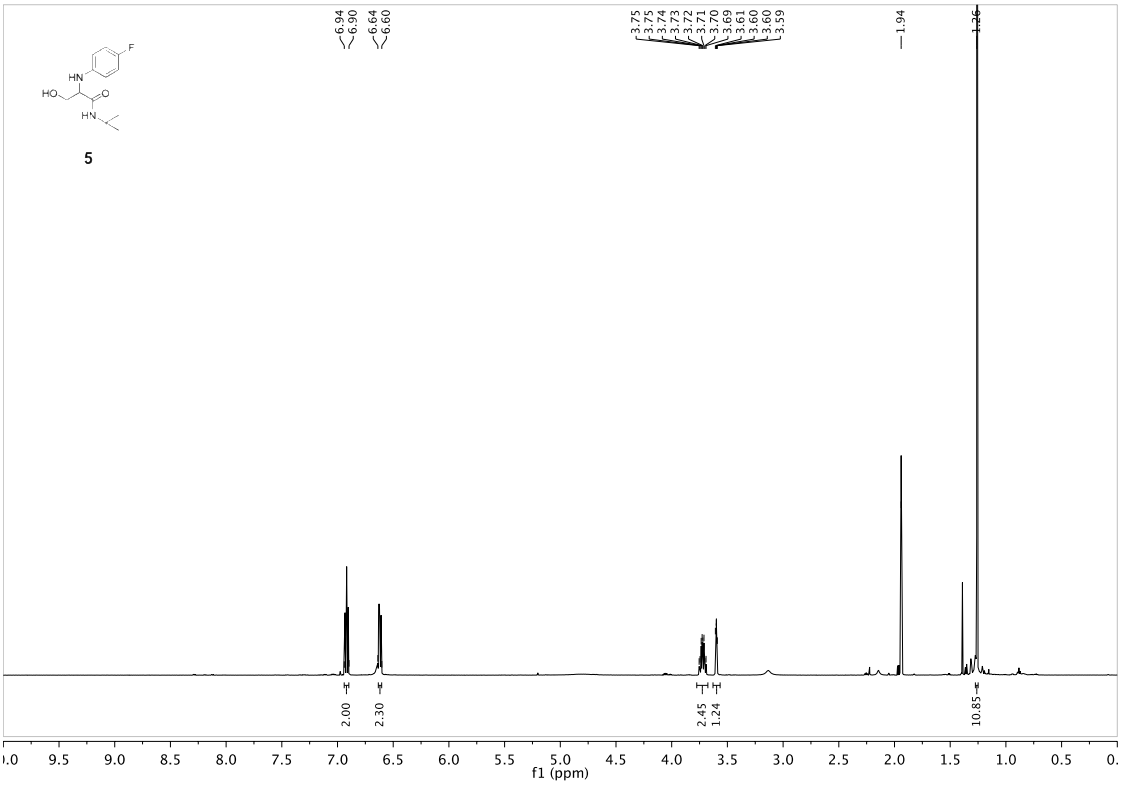

6.28
5.82
5.73
5.14
5.12
5.11
4.00
3.94
3.94
3.92
3.91
3.89
3.85
3.82
3.81
3.79
3.78
3.72
1.04
1.33
1.31
1.30
1.28
0.96
0.94
0.93
0.91
A (dd)
0.93
0.78
2.10
1.05
0.97
2.18
2.14
1.05
3.32
2.18
1.18
10.02
0.89
f1 (ppm)
4a

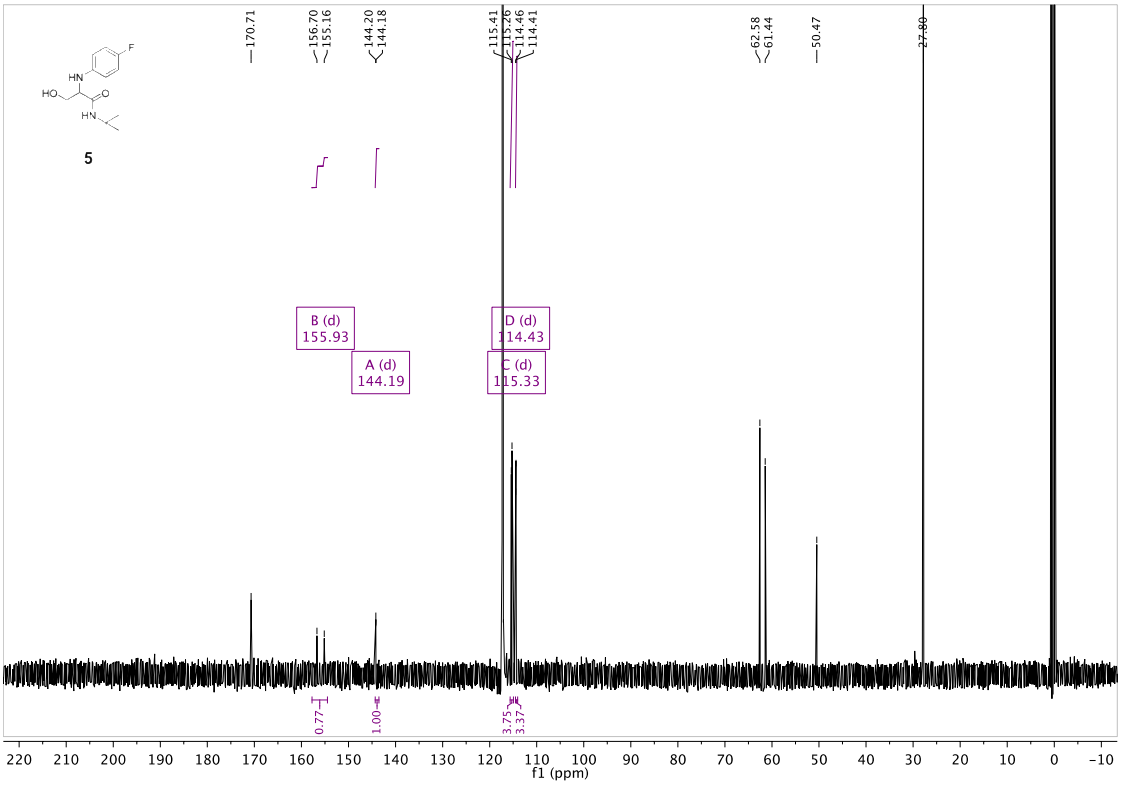

171.40
169.31
168.78
168.67
122.75
122.56
63.09
62.92
54.55
51.54
46.93
44.83
33.29
28.81
1.32 CD3CN
f1 (ppm)
4a

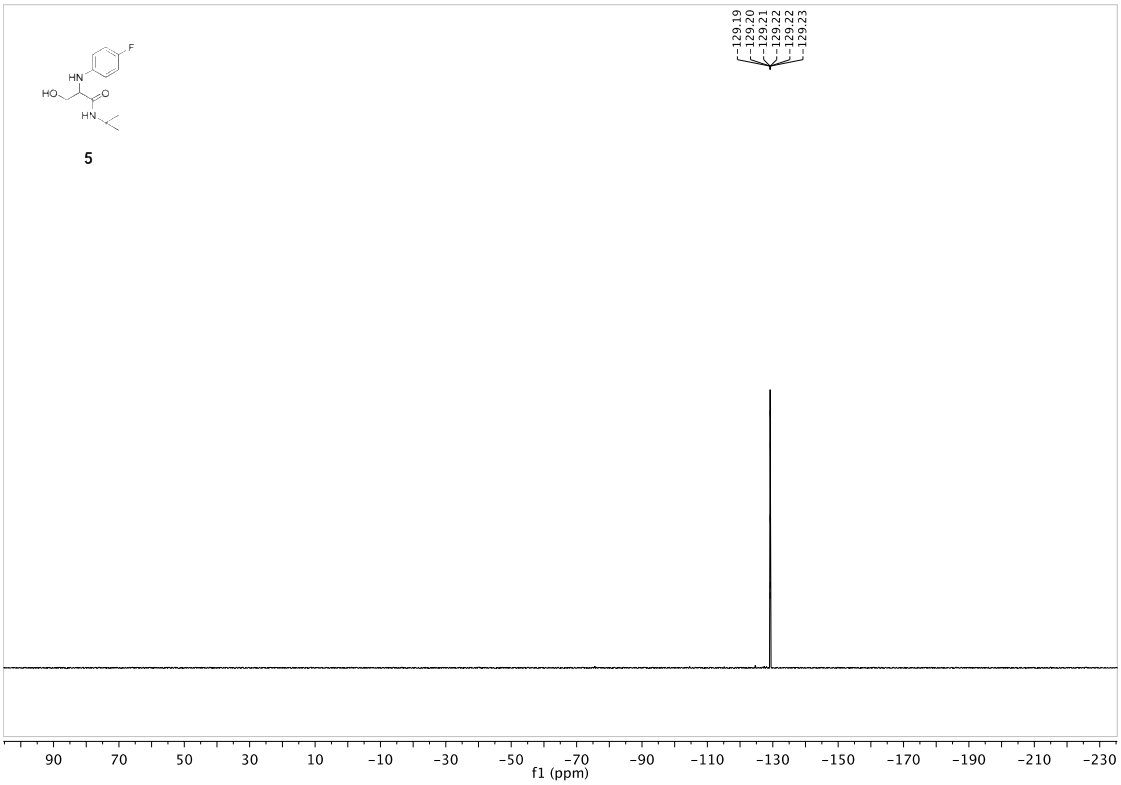

4b
f1 (ppm)


4b
f1 (ppm)


12.07
4b
100 90 80 70 60 50 40 30 20 10 0 −10 −20 −30 −40 −50 −60 −70 −80
f1 (ppm)


6.94
6.90
6.64
6.60
3.75
3.75
3.74
3.73
3.72
3.71
3.70
3.69
3.61
3.60
3.60
3.59
1.94
1.26
5
2.00
2.30
2.45
1.24
10.85
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


170.71
156.70
155.16
144.20
144.18
115.41
115.26
114.46
114.41
62.58
61.44
50.47
27.80
B (d)
155.93
A (d)
144.19
D (d)
114.43
C (d)
115.33
0.77
1.00
3.75
3.37
f1 (ppm)


-129.19
-129.20
-129.21
-129.22
-129.22
-129.23
f1 (ppm)