Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supplementary Information for:

Synthesis of substituted tetrahydroisoquinolines by lithiation then electrophilic quench

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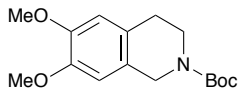
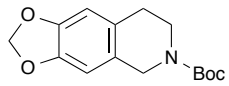
tert-Butyl 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 2



2

Di-*tert*-butyl dicarbonate (14.3 g, 66 mmol) was added to 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10.6 g, 55 mmol) in a mixture of water (60 mL) and 1,4-dioxane (120 mL) at 0 °C. After 4 h, the mixture was warmed to room temperature over 16 h. The mixture was extracted with Et_2O (3 x 100 mL), and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **2** (12.7 g, 79%) as a solid, m.p. 128–130 °C, lit.[1] 128–130 °C; spectroscopic data as reported.[1,2]

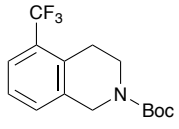
tert-Butyl 7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate 3



3

Di-*tert*-butyl dicarbonate (4.4 g, 20 mmol) was added to 5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (3.0 g, 17 mmol) in a mixture of water (20 mL) and 1,4-dioxane (40 mL) at 0 °C. After 4 h, the mixture was warmed to room temperature over 16 h. The mixture was extracted with Et_2O (3 x 30 mL), and the organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **3** (3.2 g, 68%) as an oil; R_f 0.5 [petrol–EtOAc (90:10)]; FTIR υ_{max} (film)/ cm^{-1} 2975, 2930, 2900, 1690; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.60–6.58 (2H, m, 2 x CH), 5.92 (2H, s, CH_2), 4.46 (2H, s, CH_2), 3.62 (2H, t, *J* 6, CH_2), 2.74 (2H, t, *J* 6, CH_2), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers, one aromatic C could not be observed) δ = 154.8, 146.1, 127.7, 108.5, 106.4, 106.1, 100.7, 79.8, 46.0 & 45.2, 41.8 & 40.6, 28.9, 28.4; HRMS (ES) Found: MNa^+, 300.1201. $C_{15}H_{19}NO_4Na$ requires MNa^+, 300.1212; LRMS *m/z* (ES) 300 (100%).

tert-Butyl 5-(Trifluoromethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 4

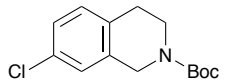


4

Di-*tert*-butyl dicarbonate (1.9 g, 8.9 mmol) was added to 5-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (1.5 g, 7.4 mmol) in a mixture of water (10 mL) and 1,4-dioxane (20 mL) at 0 °C. After 4 h, the mixture was warmed to room temperature over 16 h. The mixture was extracted with Et_2O (3 x 20 mL), and the organic

layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **4** (1.5 g, 67%) as an oil; R_f 0.41 [petrol–EtOAc (95:5)]; FT-IR υ_{max} (film)/ cm^{-1} 2975, 2930, 1695, 1420; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.51 (1H, m, CH), 7.29–7.28 (2H, m, 2 x CH), 4.63 (2H, s, CH_2), 3.65 (2H, t, *J* 6, CH_2), 3.10 (2H, t, *J* 6, CH_2), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) 154.6, 135.5, 133.6, 130.1, 126.2, 125.9, 124.1 (q, *J* 6), 124.4 (CF_3, q, *J* 274), 80.1, 46.1 & 45.1, 41.1 & 40.8, 28.4, 25.7; HRMS (ES) Found: MNa^+, 324.1201 $C_{15}H_{18}NO_2F_3Na$ requires MNa^+ 324.1187; LRMS *m/z* (ES) 324 (100%).

tert-Butyl 7-Chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate 5

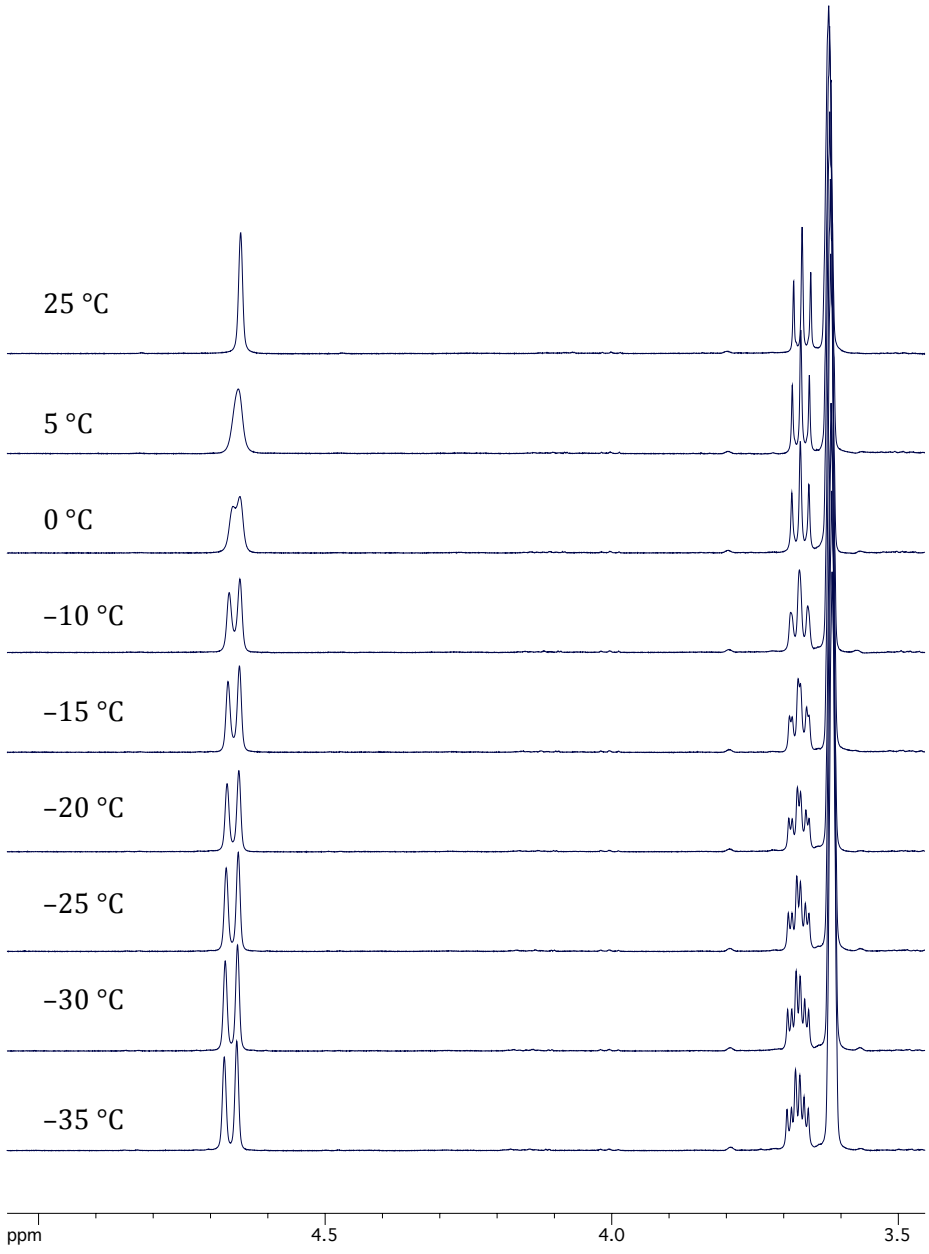


5

Di-*tert*-butyl dicarbonate (1.7 g, 7.9 mmol) was added to 7-chloro-1,2,3,4-tetrahydroisoquinoline (1.1 g, 6.6 mmol) in a mixture of water (8 mL) and 1,4-dioxane (16 mL) at 0 °C. After 4 h, the mixture was warmed to room temperature over 16 h. The mixture was extracted with Et_2O (3 x 20 mL), and the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **5** (1.48 g, 70%) as an oil; R_f 0.27 [petrol–EtOAc (95:5)]; FTIR υ_{max} (film)/ cm^{-1} 2980, 2935, 1670, 1420; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.16–7.07 (3H, m, 3 x CH), 4.55 (2H, s, CH_2), 3.65–3.63 (2H, m, CH_2), 2.80 (2H, t, *J* 5, CH_2), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.7, 135.4, 133.1, 131.7, 130.7, 129.3 & 129.1, 126.5 & 126.1, 80.0, 45.7 & 44.9, 41.5 & 40.5, 28.5, 28.3; HRMS (ES) Found: MNa^+, 290.0933 $C_{10}H_{11}NO_2{}^{35}ClNa$ requires MNa^+, 290.0924; LRMS m/z (ES), 292 (33%, ^{37}Cl), 290 (100, ^{35}Cl).

2. VT-NMR spectra and data

A sample of the tetrahydroisoquinoline **4** (15 mg) in D_8-THF (0.7 mL) was placed in an NMR tube; the tube was transferred to a cooled NMR spectrometer (400 MHz, temperature coil recording –35 °C). The NMR spectrometer was warmed gradually and spectra were recorded as shown below. Warming allowed coalescence of the signals for the benzylic NCH_2 protons at 4.67 ppm, which occurred at approximately 5 °C (only peaks in this region are shown below, which includes these signals plus the triplet for the other NCH_2 and the broad peak for some undeuterated THF).



From the spectra, coalescence for the benzylic CH_2 at 4.65 ppm occurred at T_c ~ 5 °C.

The difference in chemical shift ($\Delta\nu^{o}_{AB}$) between the rotamers at low temp. was ~8.9 Hz.

So, at 5 °C, k = (π x 8.9)/√2 = 19.8 s^{-1}

So, at 5 °C, $t_{1/2}$ = (ln2)/k = 0.035 s

And, at 5 °C, $\Delta G^{‡}$ = RT[ln(k_bT/h) - ln$k$] = 61.0 kJ/mol

These data compare very favourably with the parent *N*-Boc-tetrahydroisoquinoline,[2] which has a barrier to rotation of the Boc group, $\Delta G^{‡} \approx$ 60.8 kJ/mol at 5.5 °C.

Using line shape analysis, values for k were calculated using formulas shown below.[3]

pre-coalescence, slow exchange:

$$k = \frac{\pi}{\sqrt{2}}[(\Delta v_A)^e_{1/2} - (\Delta v_A)^0_{1/2}]$$

pre-coalescence, intermediate exchange:

$$k = \frac{\pi}{\sqrt{2}}[{\Delta v_0}^2 - {\Delta v_e}^2]^{1/2}$$

coalescence:

$$k = \frac{\pi \Delta v_0}{\sqrt{2}}$$

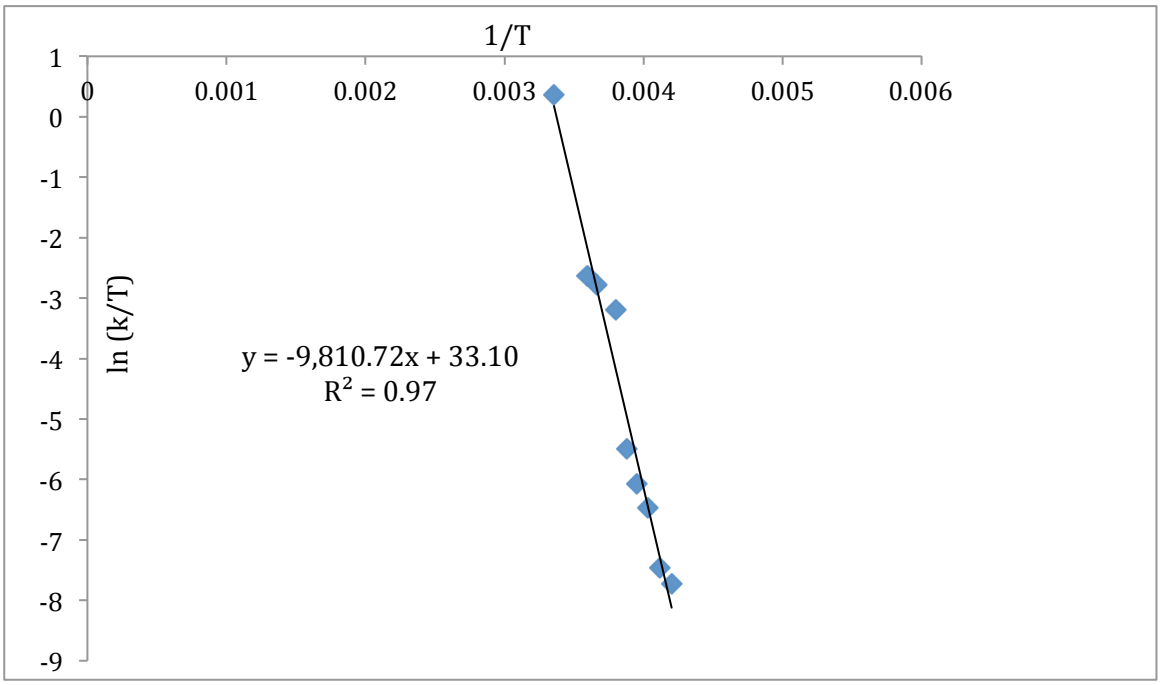
post-coalescence:

$$k = \frac{\pi {\Delta v_o}^2}{2} \frac{1}{(\Delta v_{1/2})^e - (\Delta v_A)^0_{1/2}}$$

Raw data:

T/K	1/T	Δv_0	$(\Delta v_A)^e_{1/2}$	$(\Delta v_A)^0_{1/2}$	Δv_e	k	ln(k/T)
238	0.004201	8.9	2.944	2.897		0.10441	-7.7317
243	0.004115	8.9	2.96	2.897		0.13995	-7.4595
248	0.004032	8.9	3.069	2.897		0.38209	-6.4755
253	0.003952	8.9	3.16	2.897		0.58424	-6.0708
258	0.003876	8.9	3.373	2.897		1.05740	-5.4971
263	0.003802	8.9	4.03	2.897	7.48	10.7136	-3.2006
273	0.003663	8.9	5.56	2.897	4.68	16.8167	-2.7870
278	0.003597	8.9	7.38	2.897		19.7708	-2.6434
298	0.003356	8.9	3.19	2.897		424.651	0.3542

Eyring plot of 1/T against ln(*k*/T):



These values provided the following (approximate) parameters:

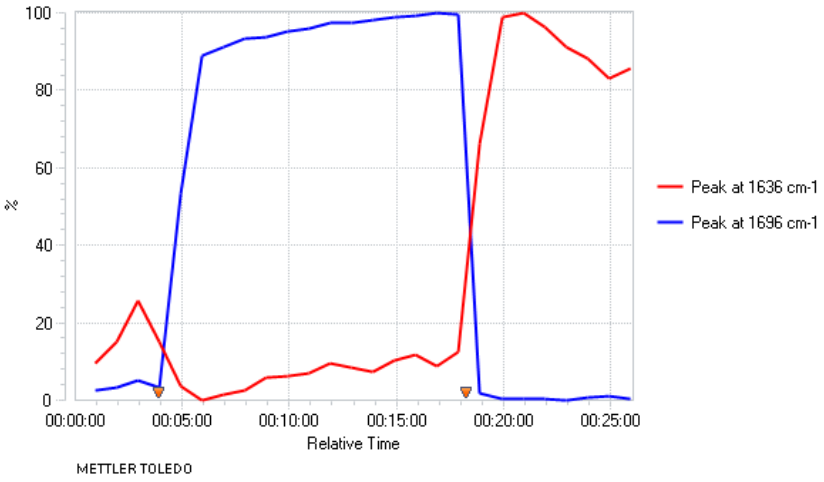
$\Delta H^{\ddagger} \approx 81$ kJ/mol

$\Delta S^{\ddagger} \approx 77$ J/K·mol

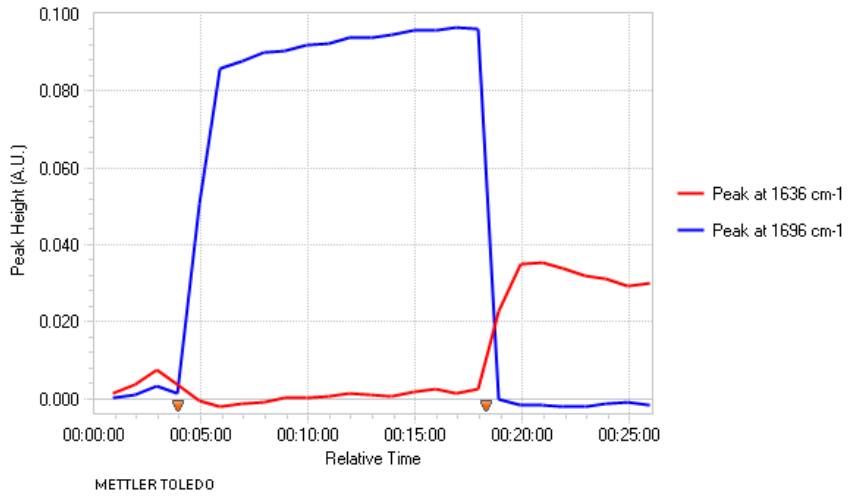
These values suggest that $\Delta G^{\ddagger} \approx 60$ kJ/mol at 5 °C and $\Delta G^{\ddagger} \approx 64$ kJ/mol at –50 °C.
This equates to $t_{1/2} \approx 2$ min at –50 °C. The lithiation reactions were carried out at –50 °C and we allow a few minutes for the rotation of the Boc group, so these data approximately match the experimental results and the ReactIR (see Section 3, page S-7).

3. ReactIR spectra

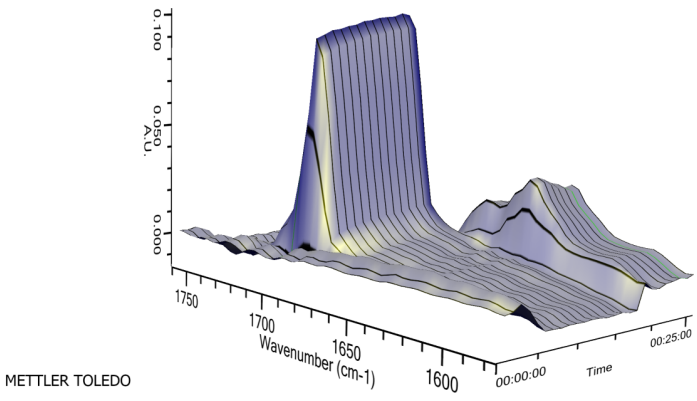
THF (12 mL) was added to a flask equipped with a stirrer bar and ReactIR™ probe at room temperature. After cooling to –50 °C, a solution of tetrahydroisoquinoline **3** (0.5 g, 2 mmol) in THF (2.0 mL) was added. The solution was stirred for about 10–15 min (to verify the stability of the signal readout). An IR peak at 1696 cm^{-1} was observed which was assigned to $\nu_{c=o}$ (blue line in 2D plots below). At ~18 min, *n*-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane) was added dropwise. A new peak at 1636 cm^{-1} was observed which was assigned to $\nu_{c=o}$ of the lithiated intermediate (red line in 2D plots below).



(Graph based on % peak height)



(Graph based on peak height)



(3D plot)

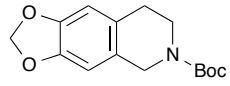
4. References

1. J. A. Hickin, A. Ahmed, K. Fucke, M. Ashcroft and K. Jones, *Chem. Commun.*, 2014, **50**, 1238.

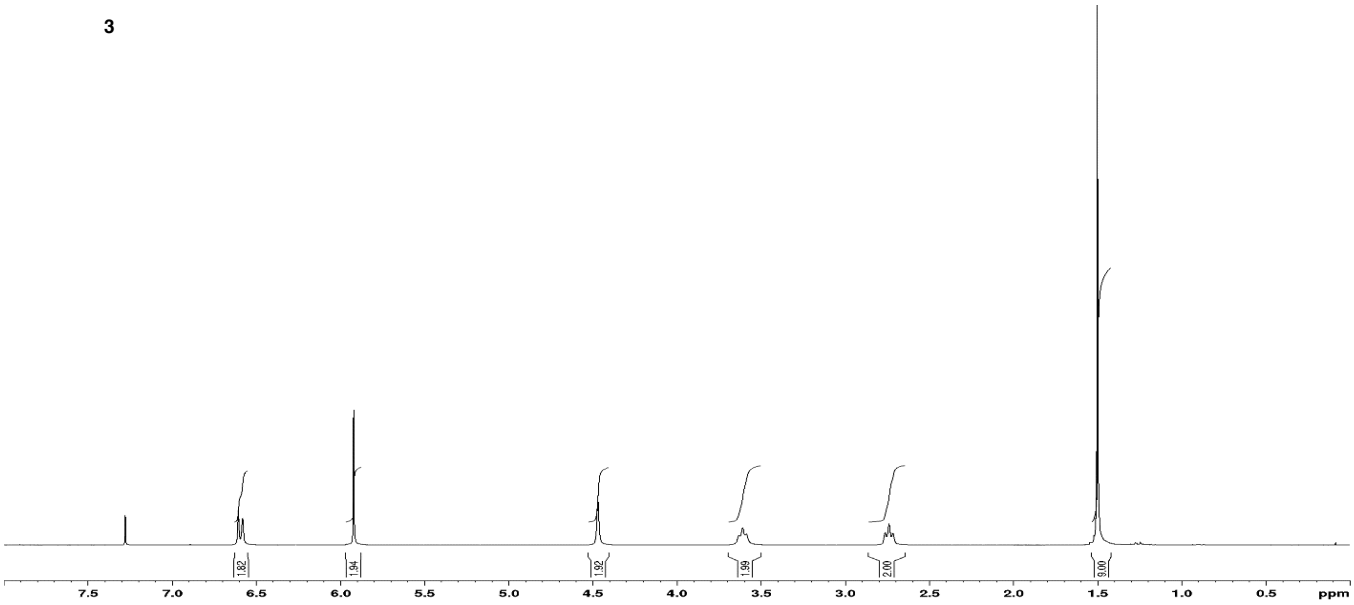
2. X. Li, D. Leonori, N. S. Sheikh and I. Coldham, *Chem. Eur. J.*, 2013, **19**, 7724.

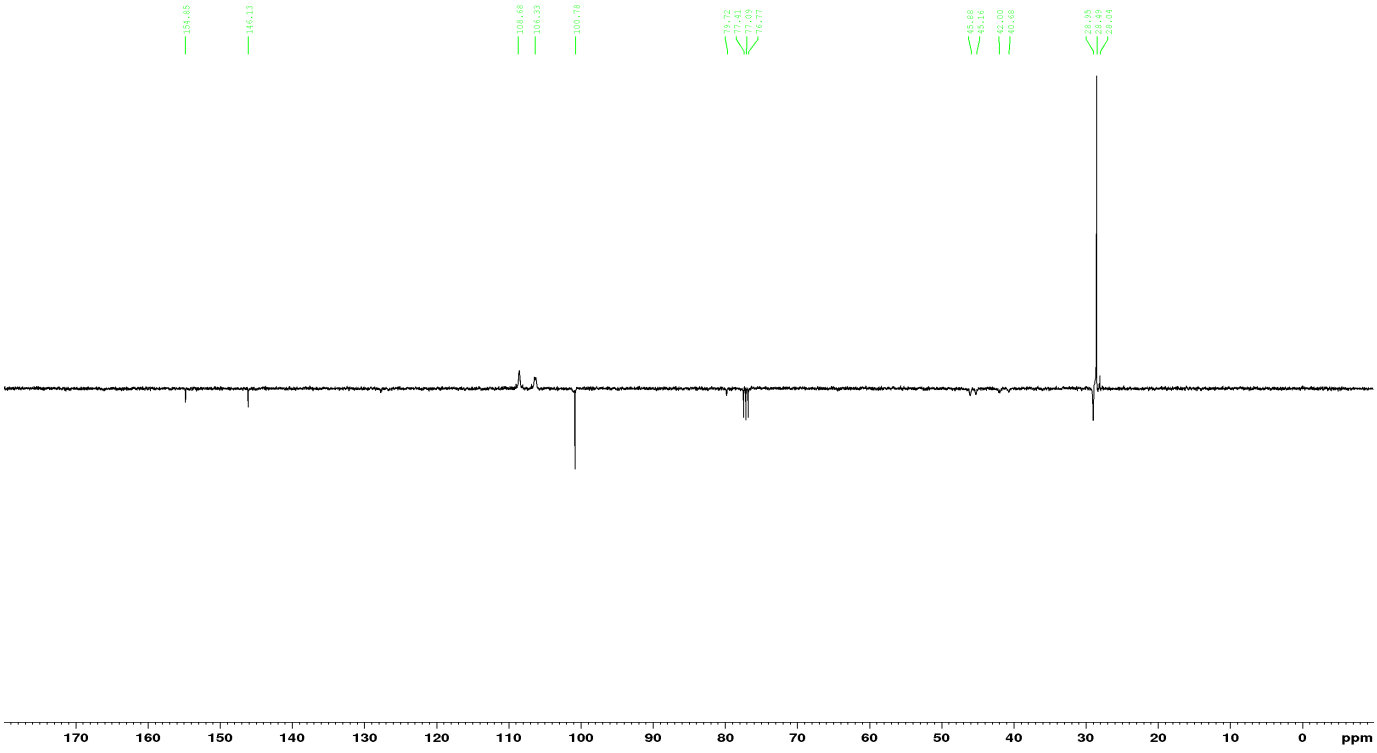
3. F. P. Gasparro and N. H. Kolodny, *J. Chem. Educ.* 1977, **54**, 258.

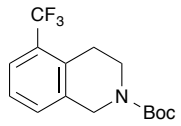
5. NMR spectra



3



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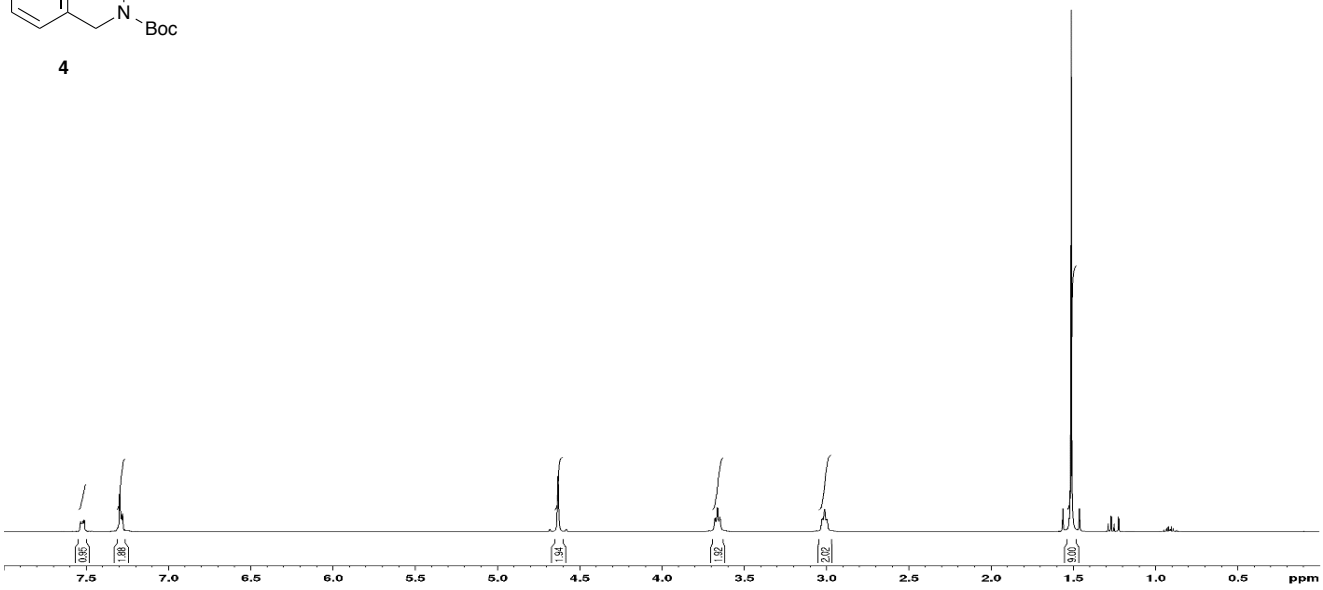
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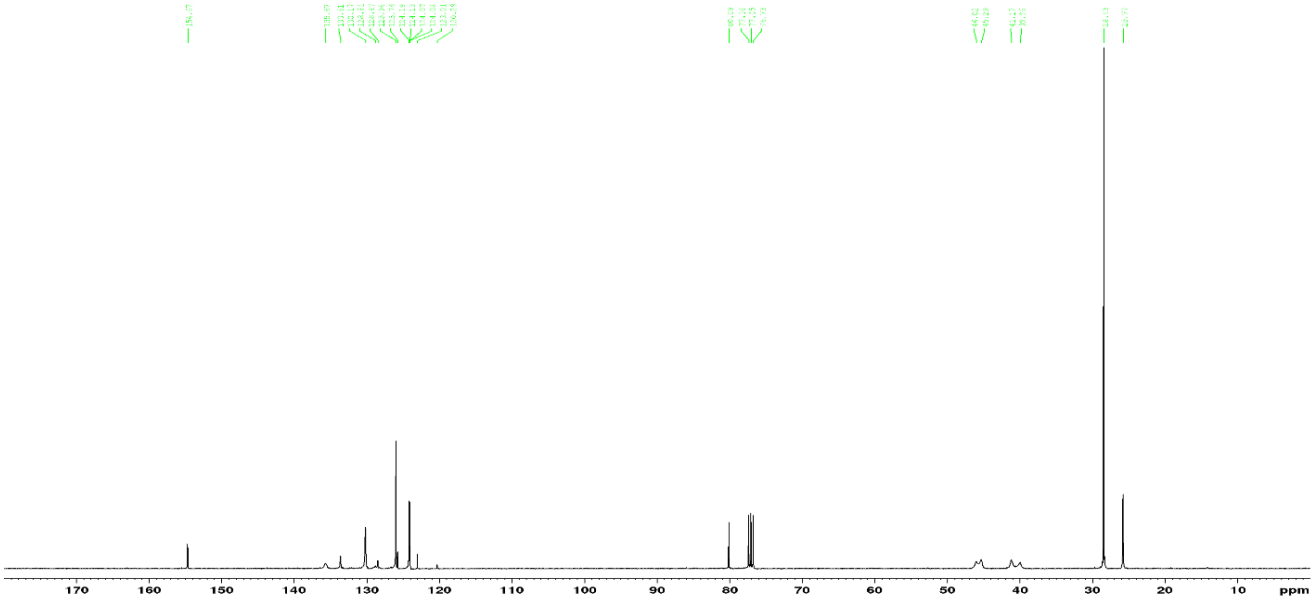
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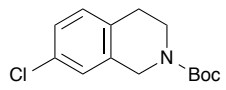
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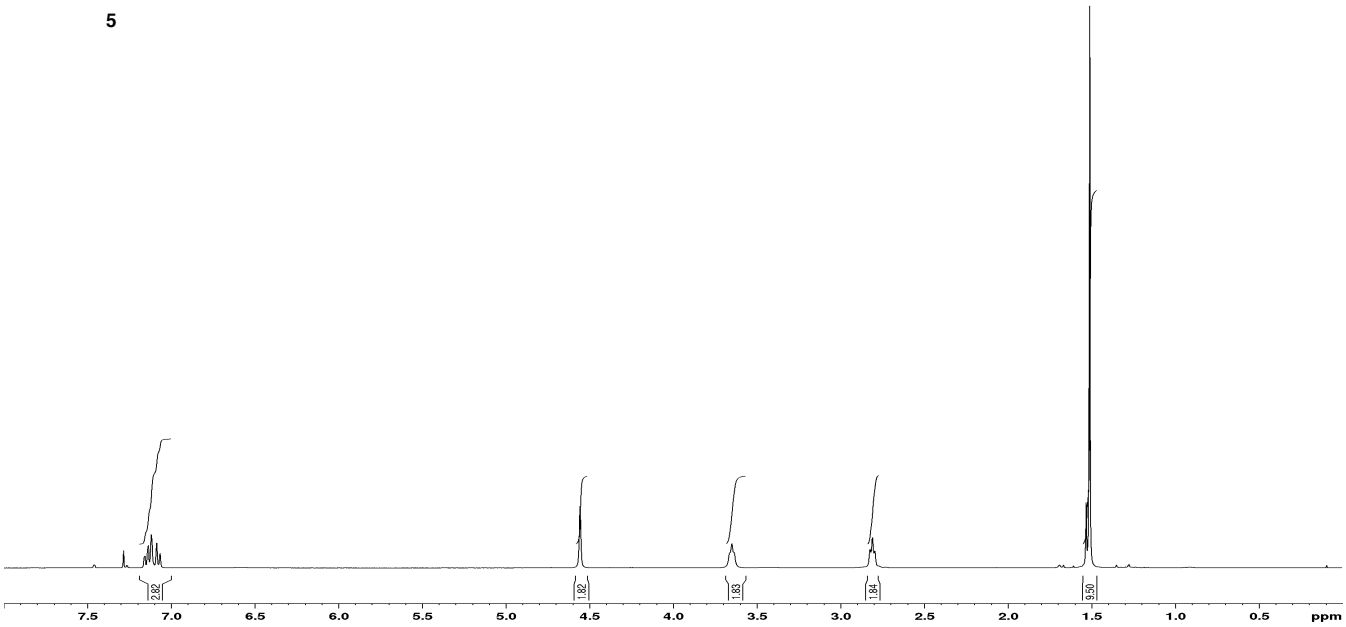
Boc

5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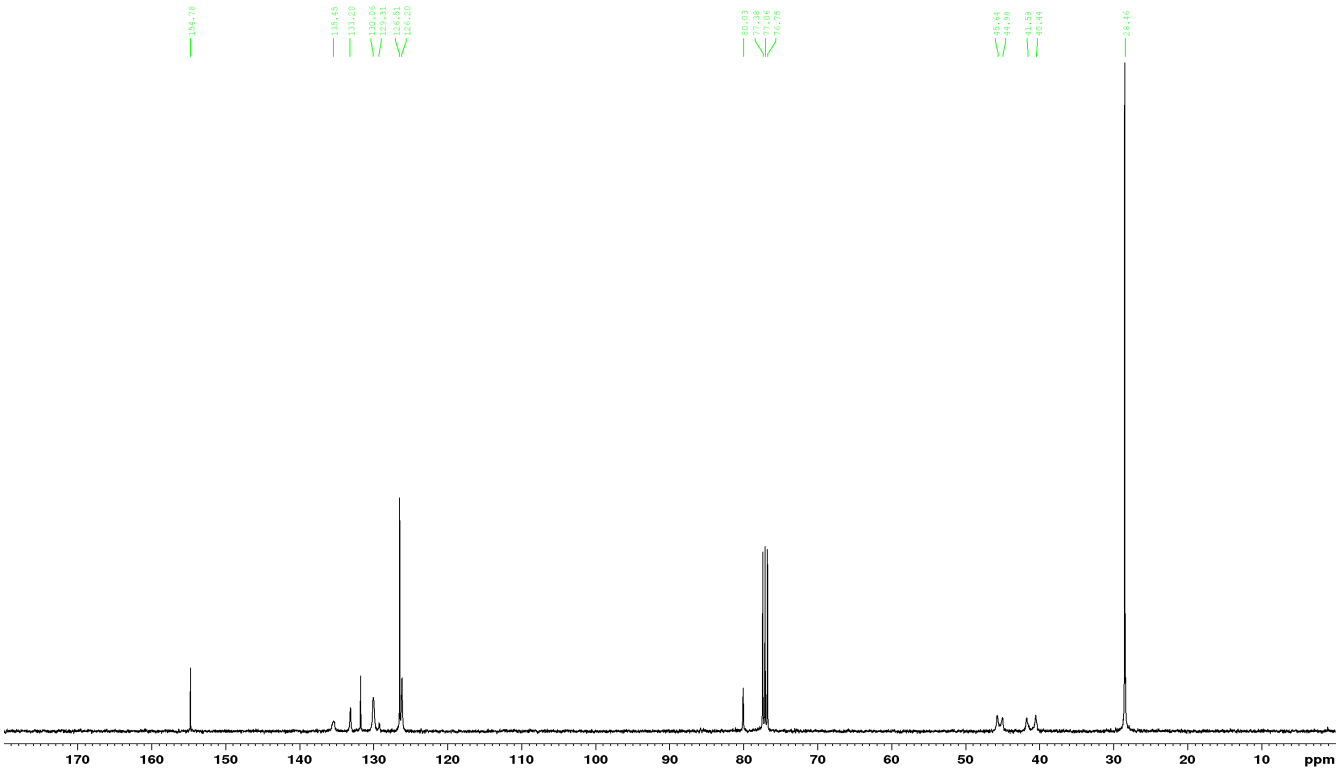
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41.59
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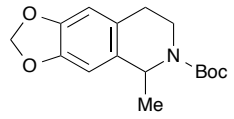

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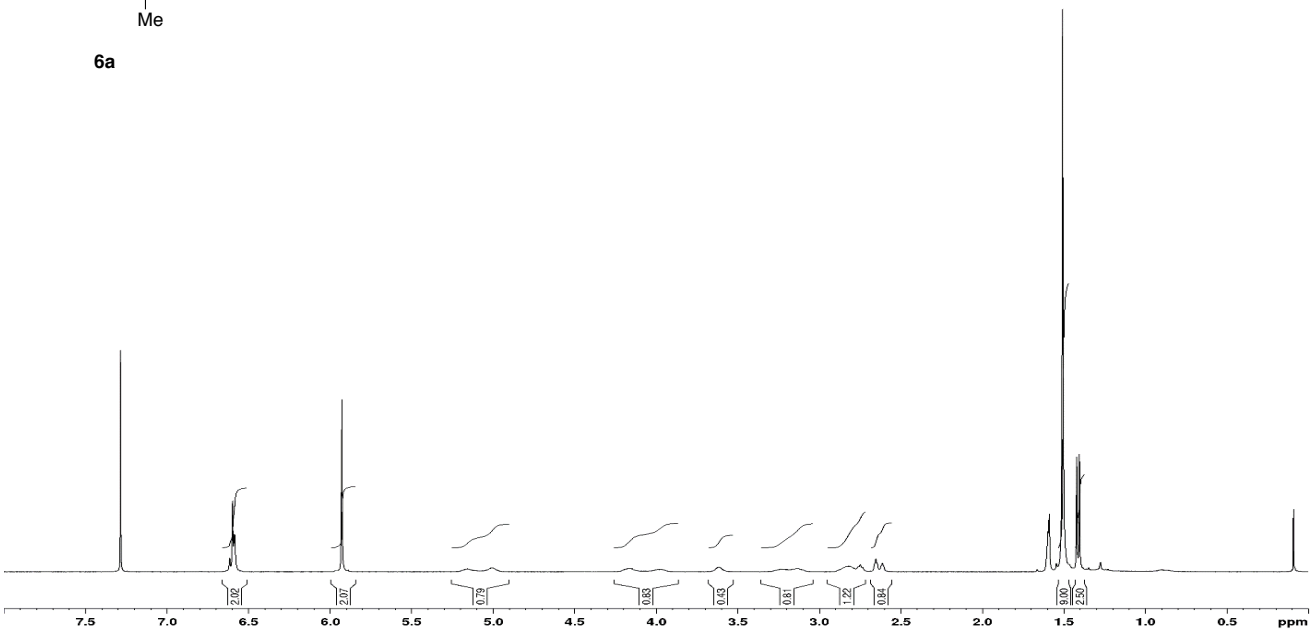
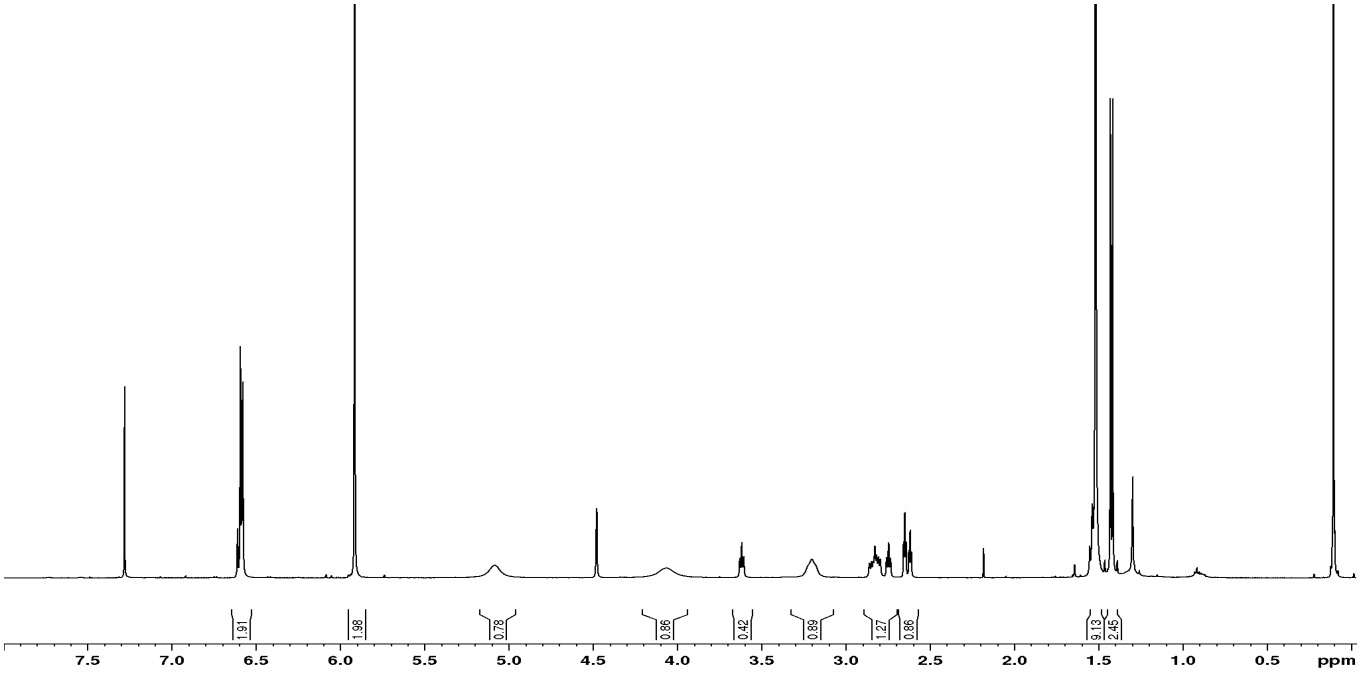
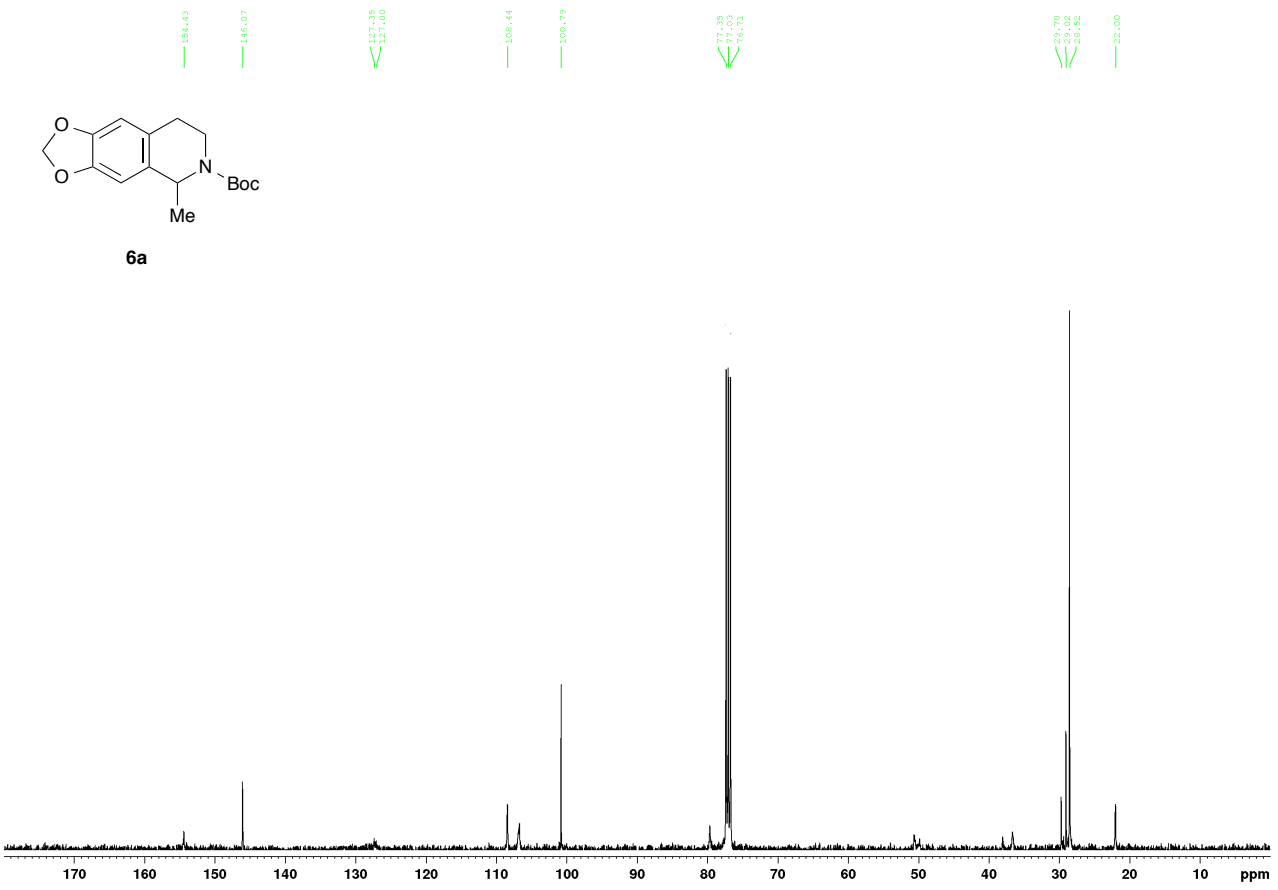


This ^{1}H NMR spectrum was also run at 50 °C in $CDCl_3$:

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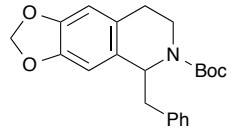
ppm

6a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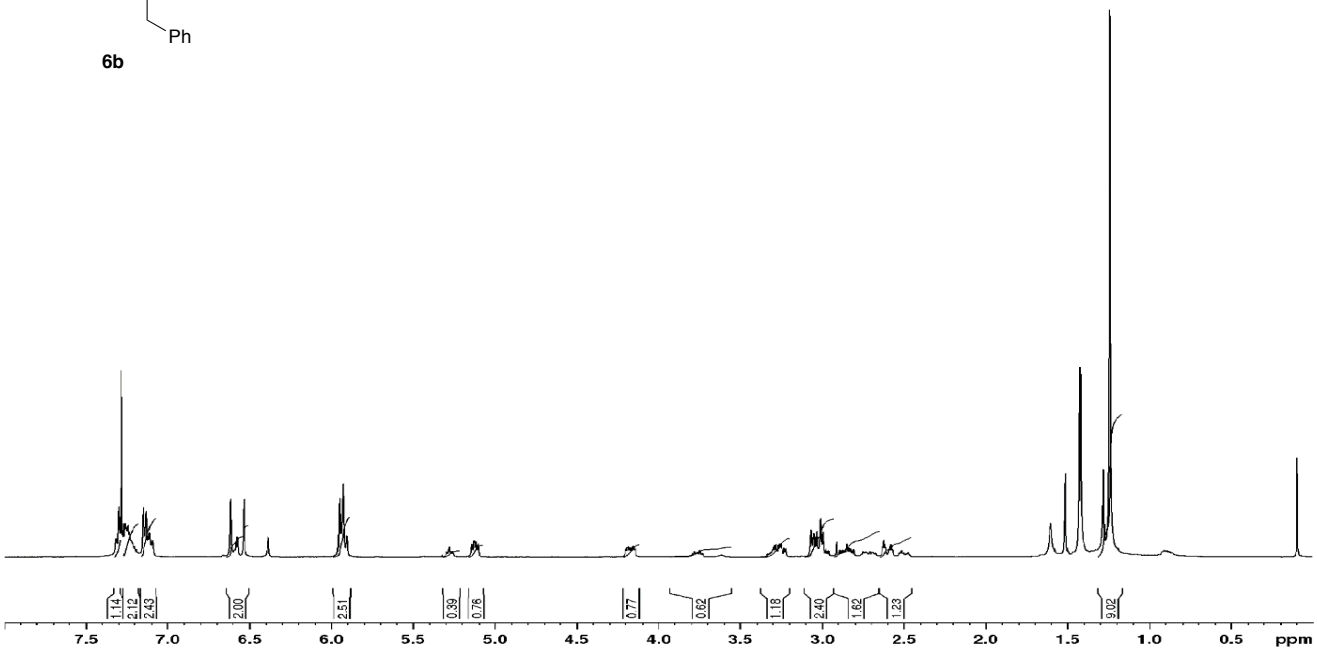
Ph

6b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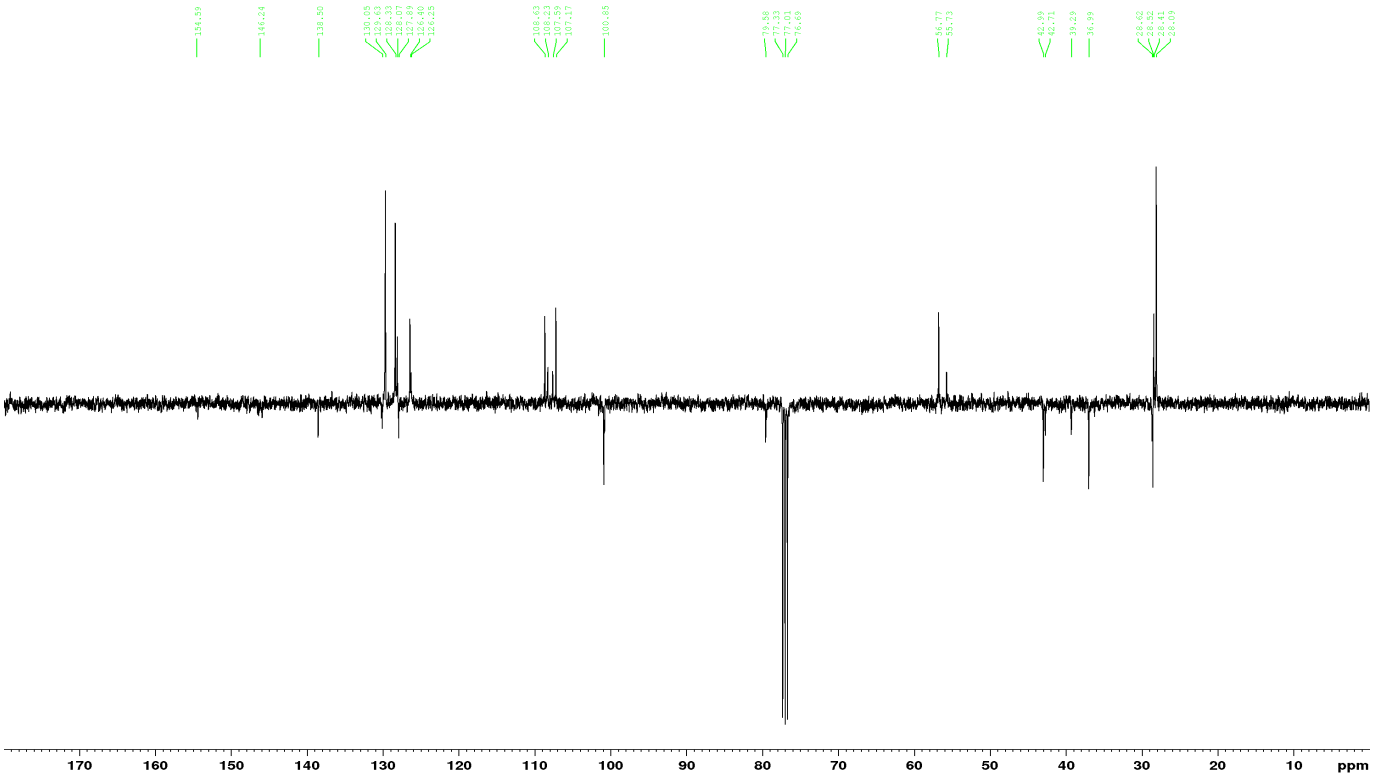
ppm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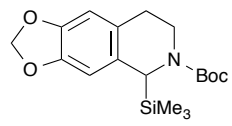
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SiMe3

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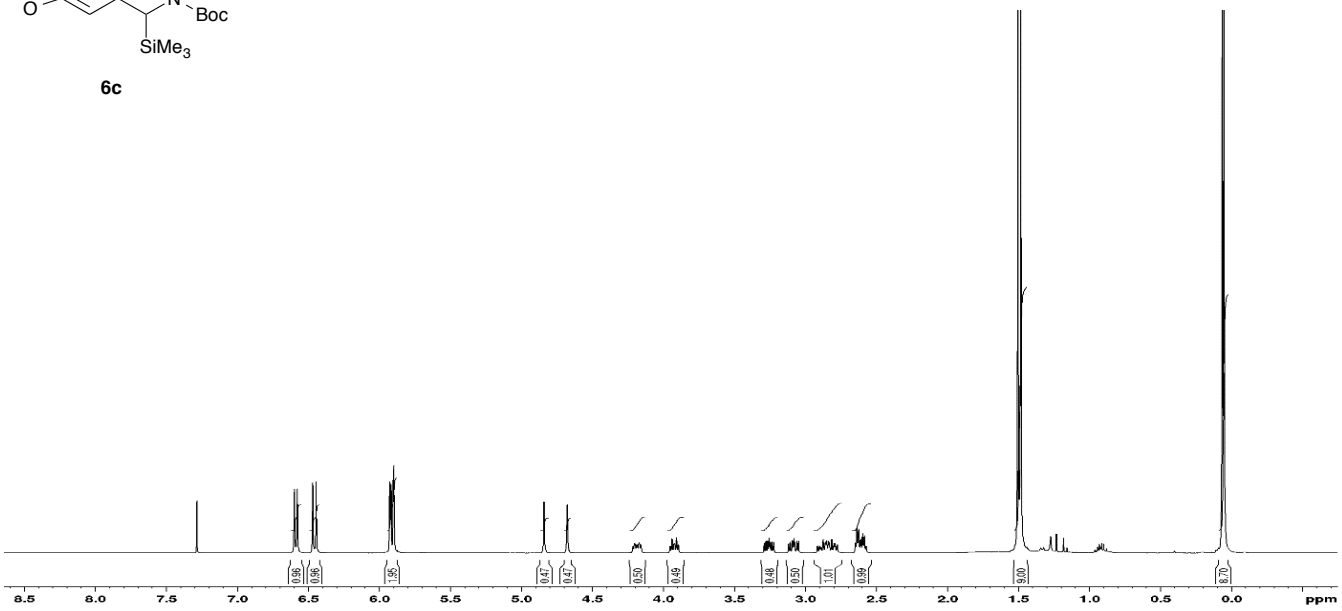
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7.5
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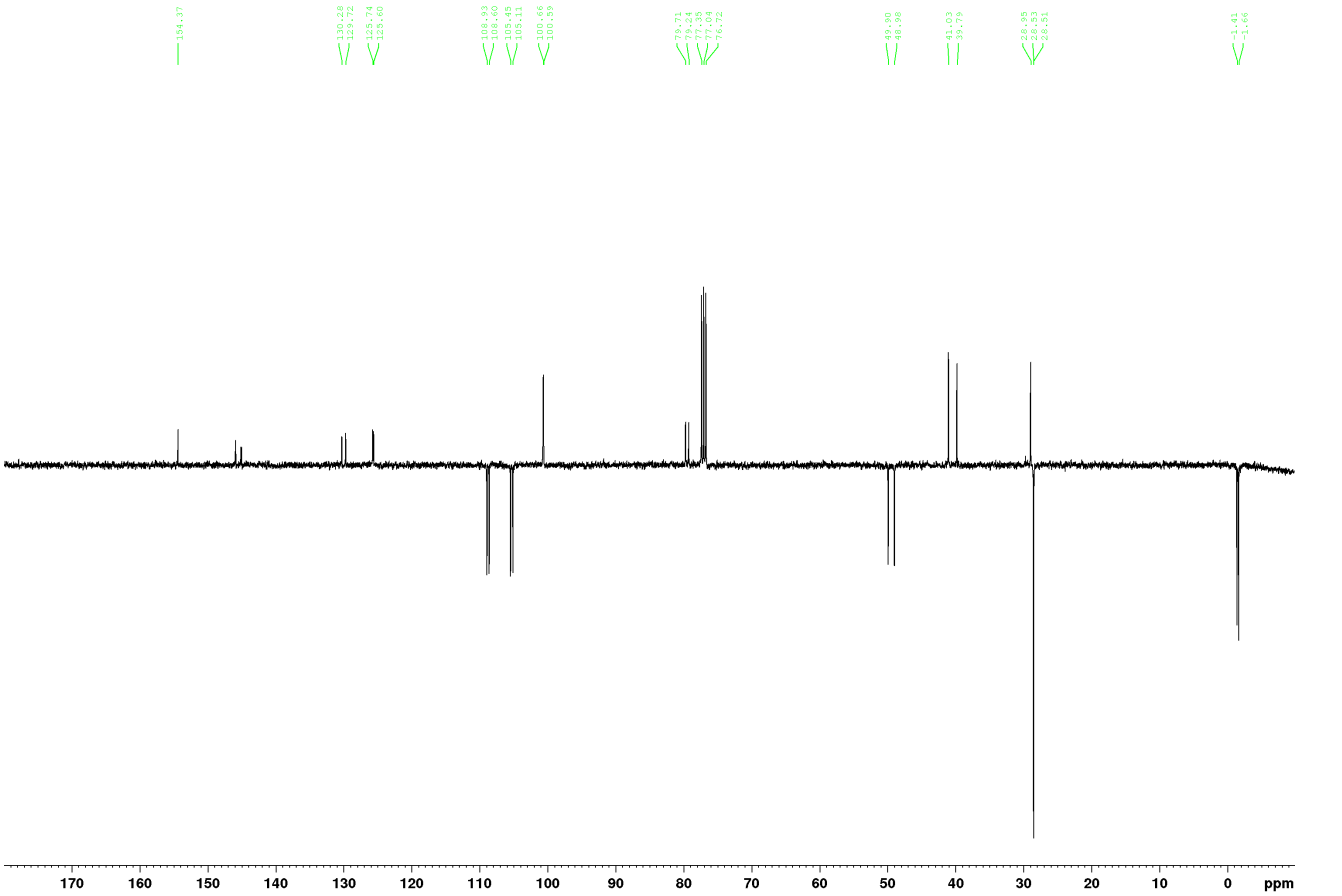
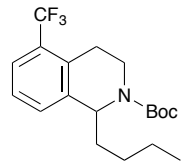
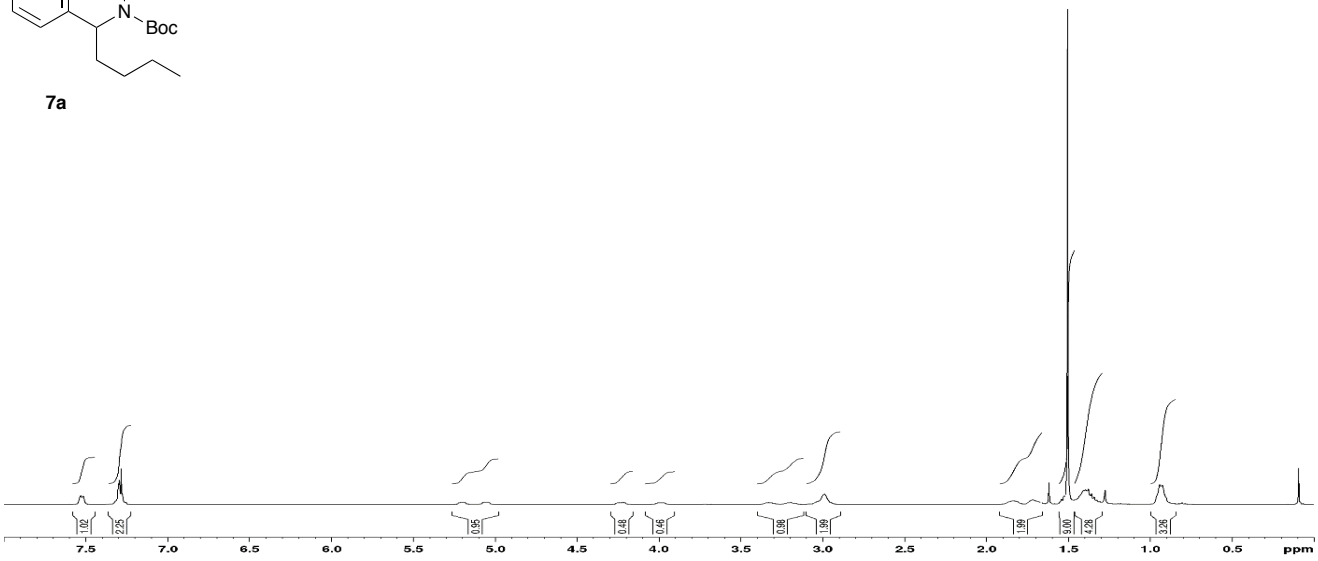
0.0
ppm

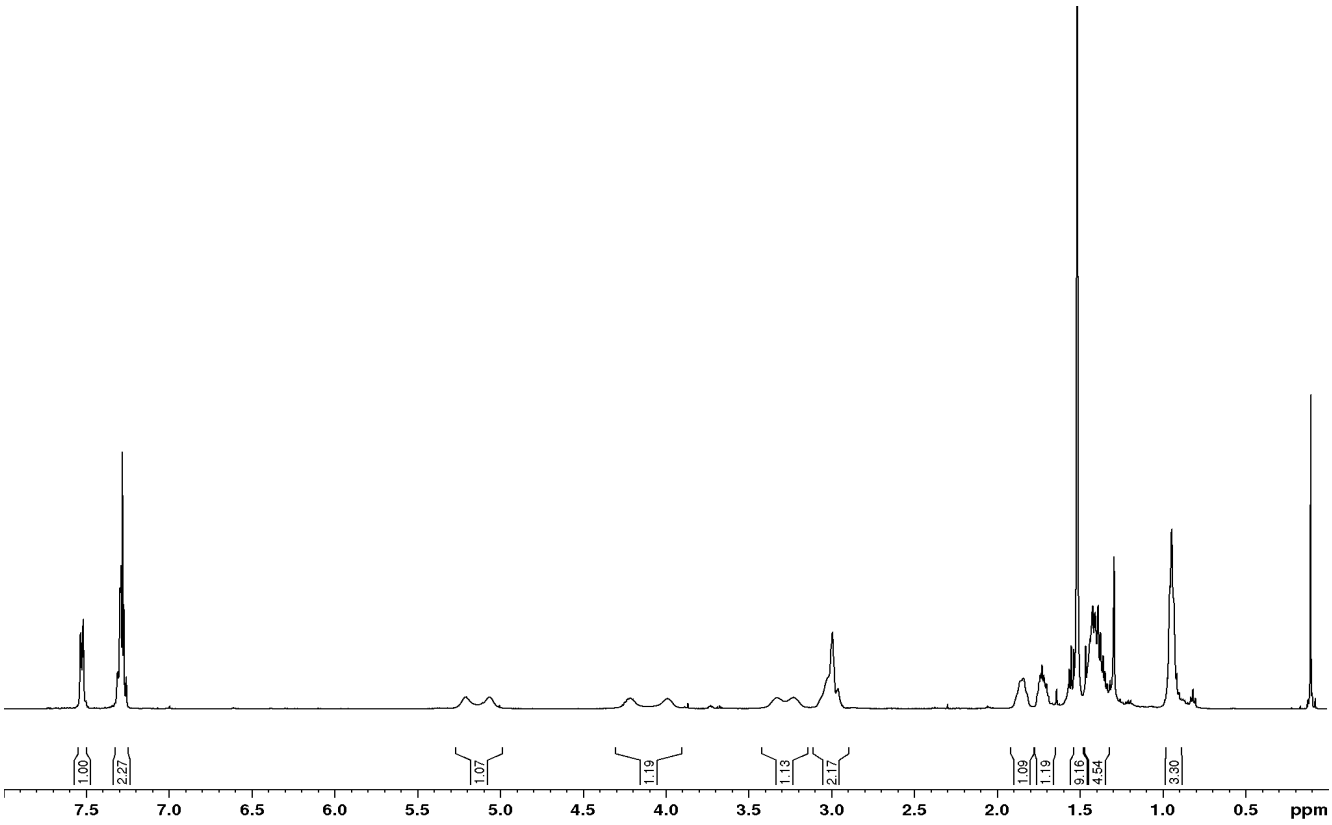

194.37
130.28
129.72
125.74
125.60
108.93
108.60
105.45
105.11
100.66
100.59
79.71
79.24
77.35
77.04
76.72
49.30
48.98
43.03
39.79
28.35
28.33
28.31
-1.41
-1.66
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

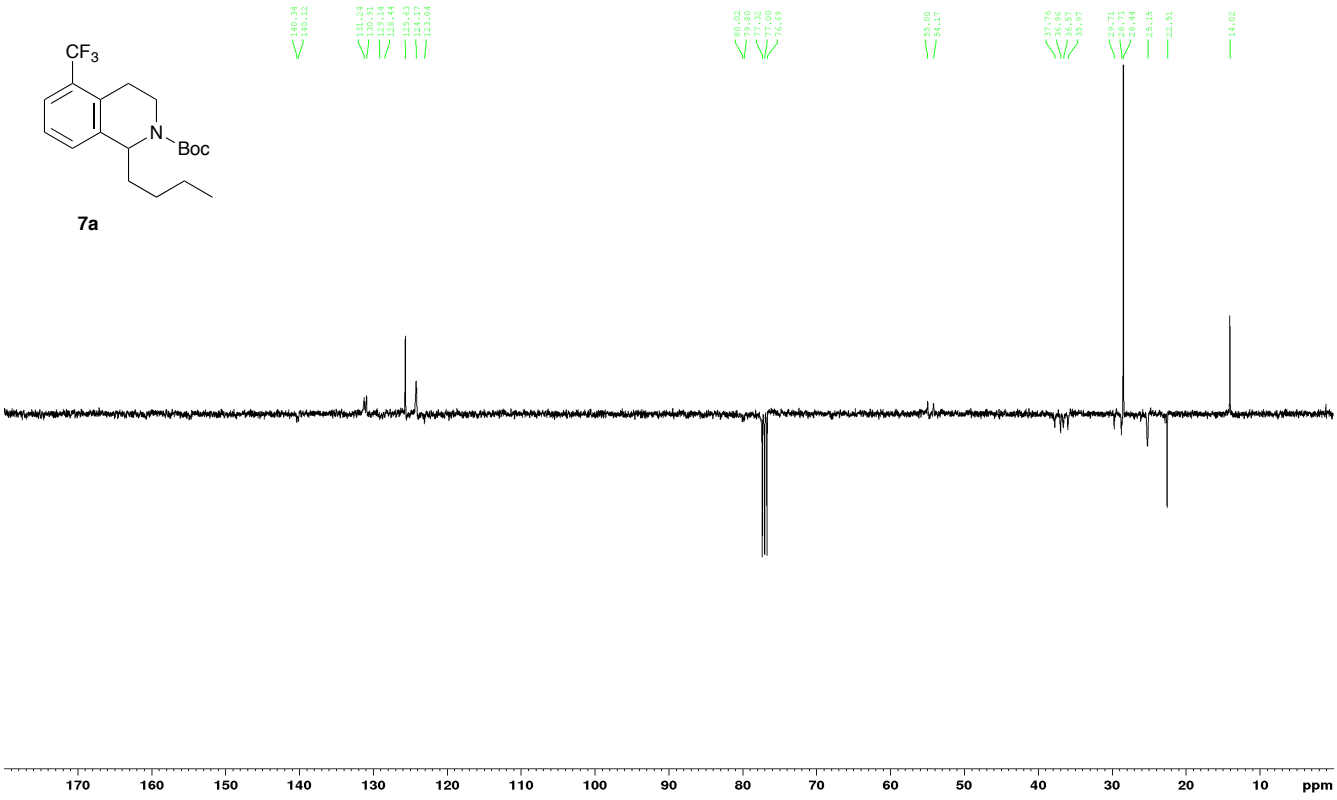


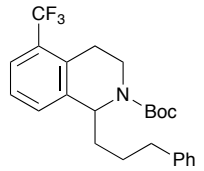
7a



This ^{1}H NMR spectrum was also run at 40 °C in $CDCl_3$:

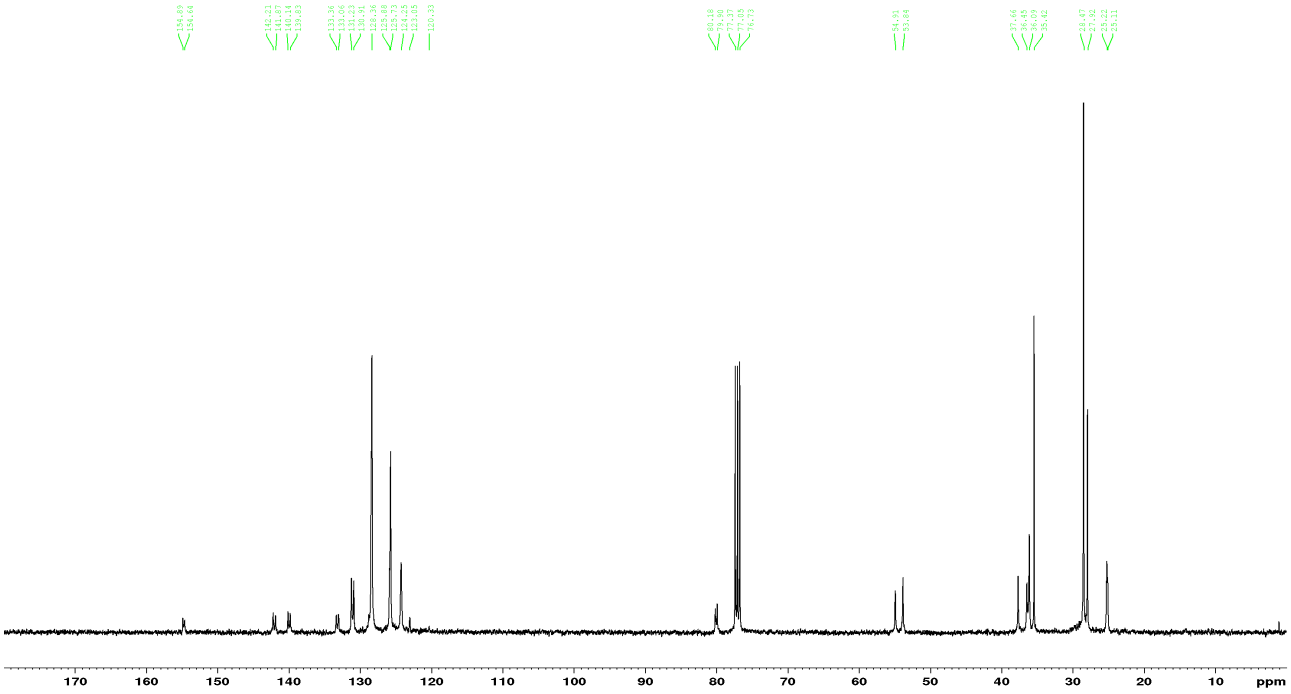


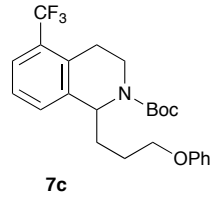

CF3
N
Boc
7a
140.34
140.12
131.24
130.71
129.14
128.44
125.63
124.17
123.04
80.02
79.60
77.32
77.00
76.69
55.00
54.17
37.76
36.66
36.57
35.97
29.71
28.71
28.44
25.15
22.81
14.02
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CF3
N
Boc
Ph

7b

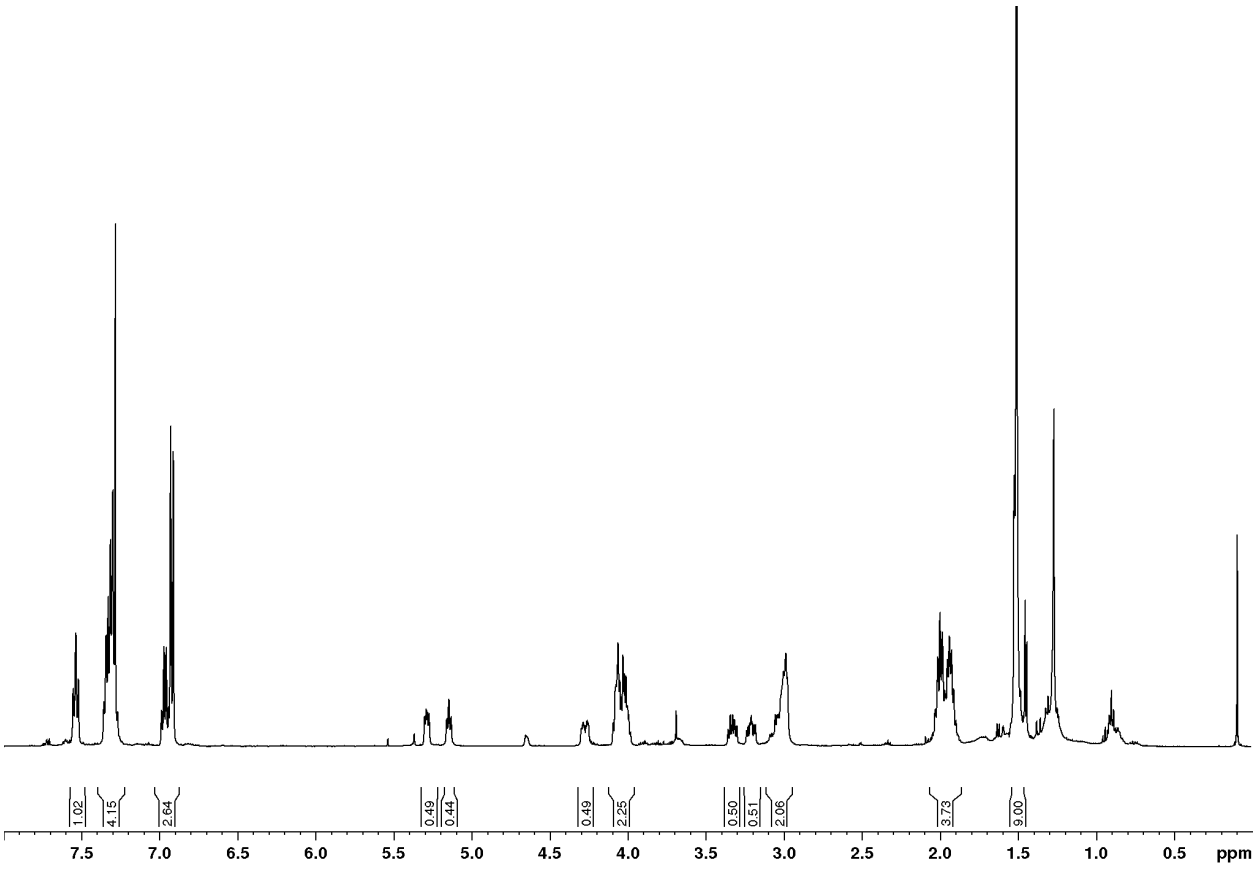
1.00
6.89
0.97
1.03
0.97
1.92
1.90
3.83
9.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

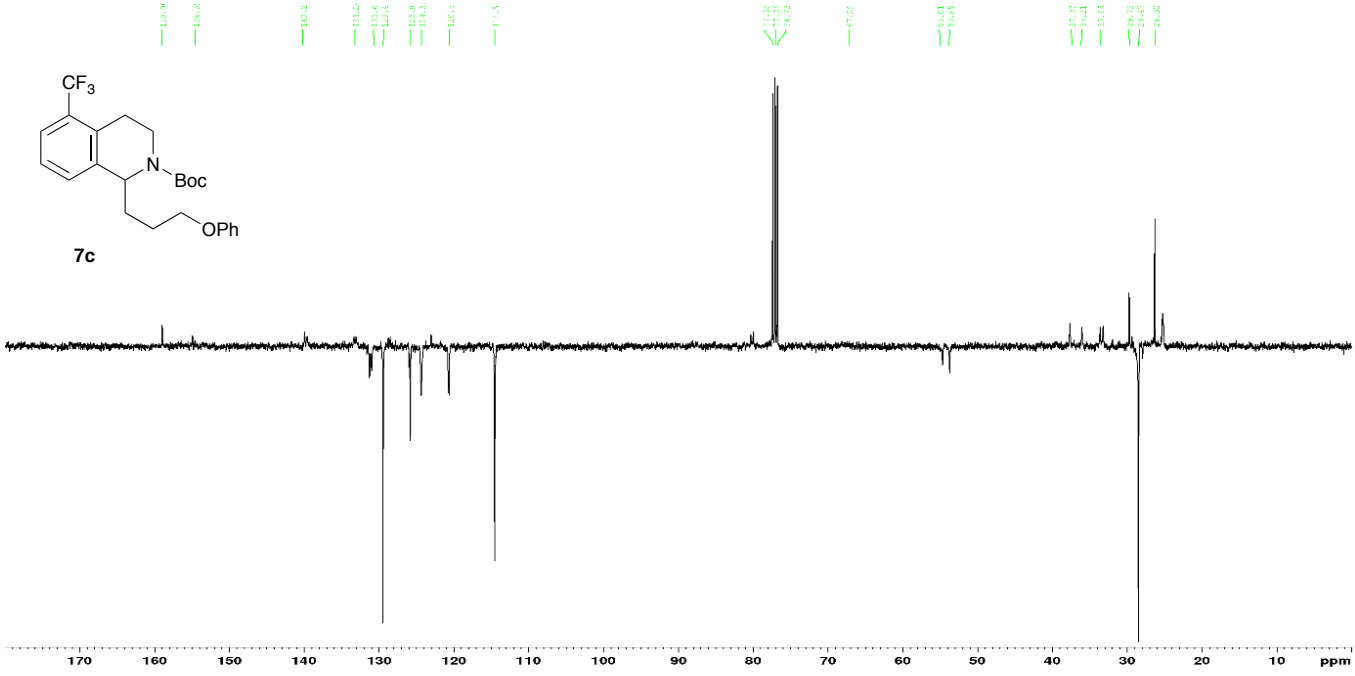

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

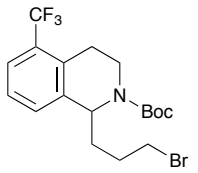


7c

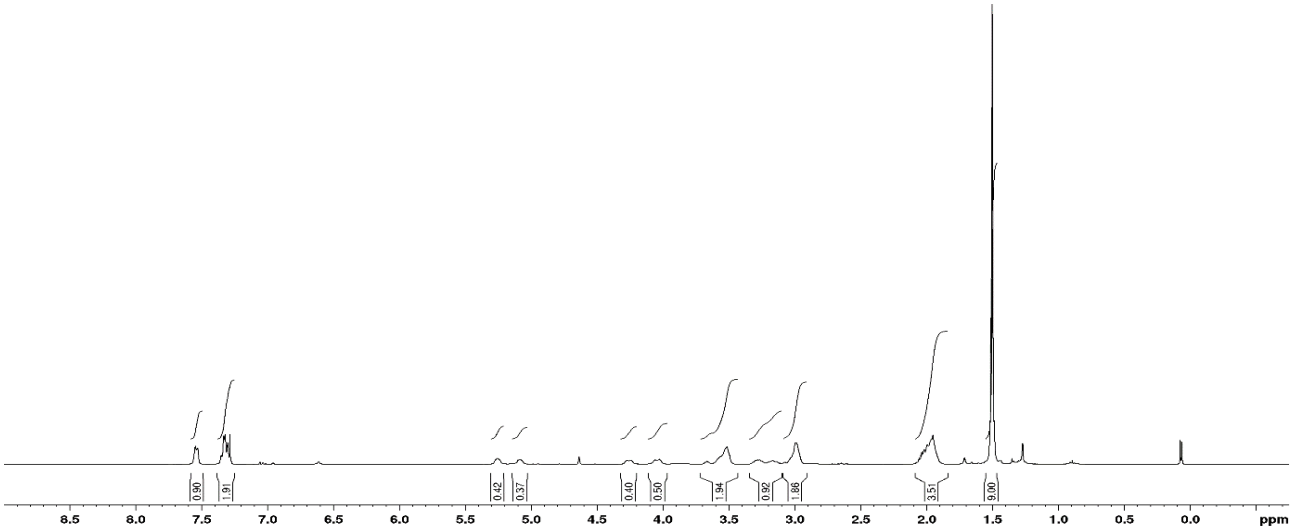
This ^{1}H NMR spectrum was also run at 5 °C in $CDCl_3$:

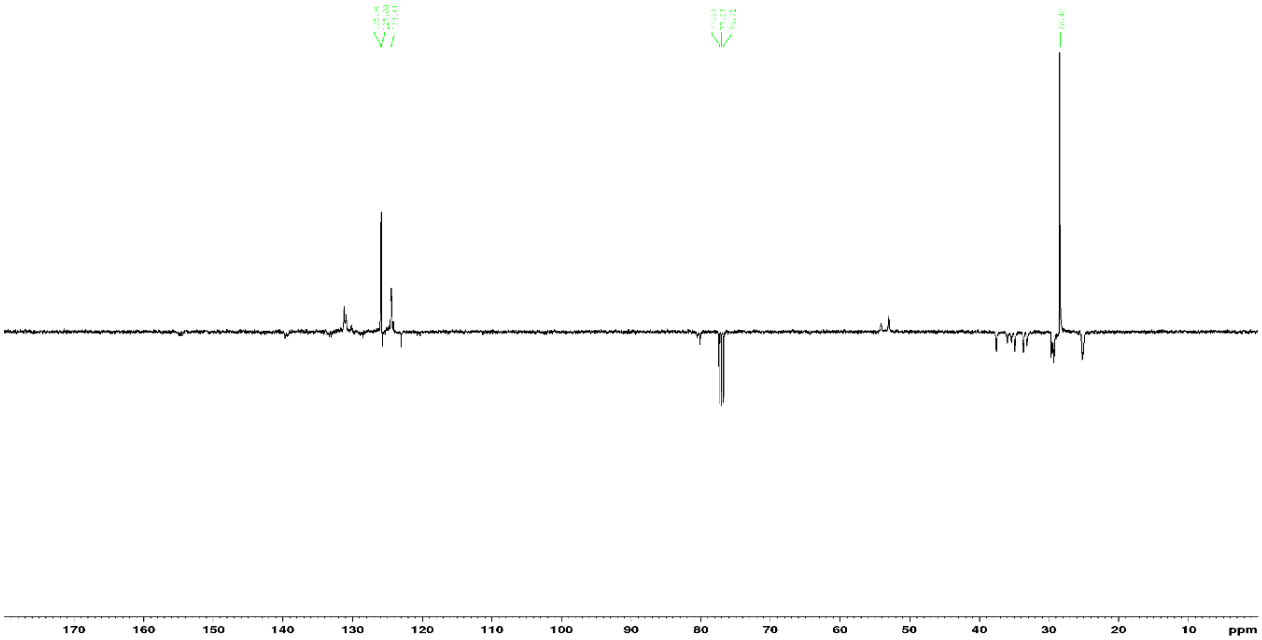


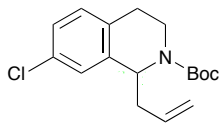

CF3
N
Boc
OPh
7c
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CF3
N
Boc
Br

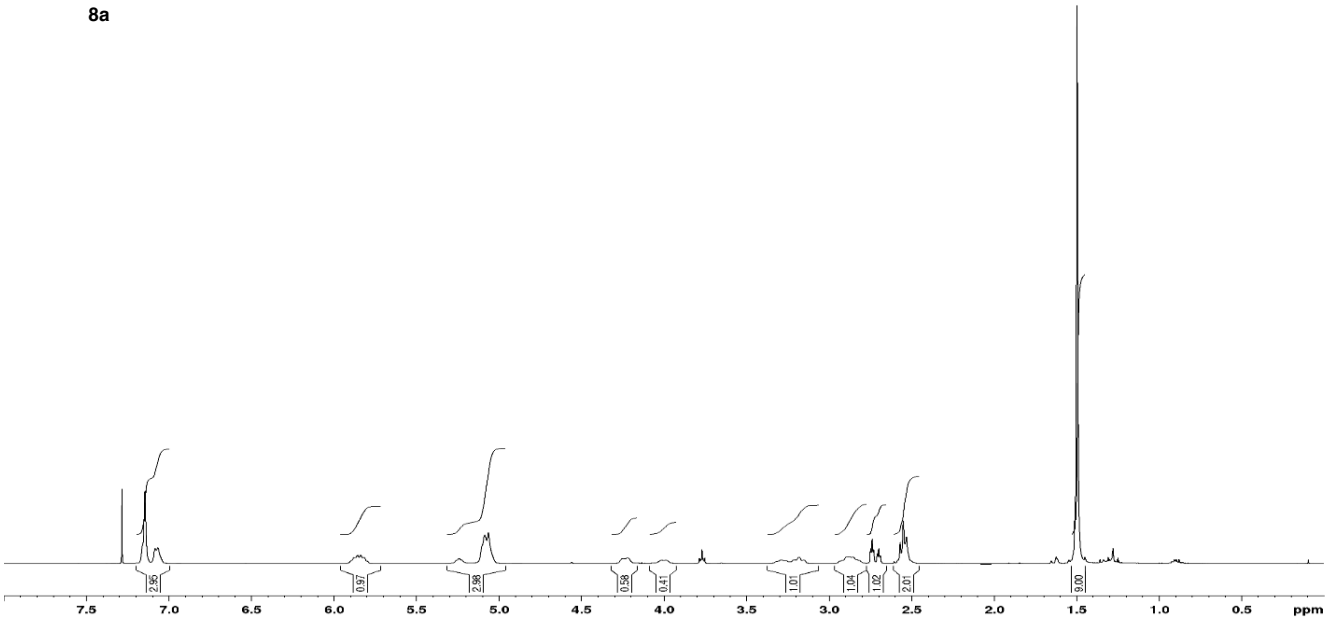
7d

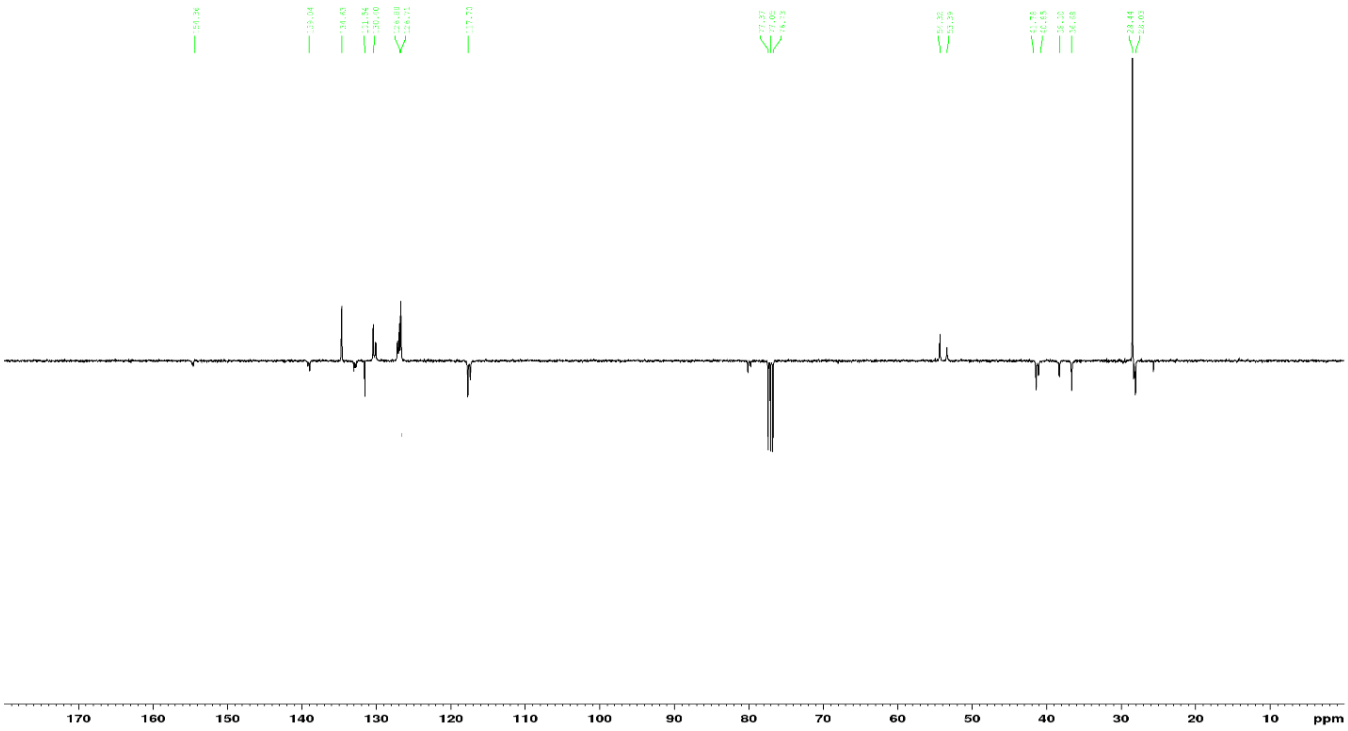

0.90
1.91
0.42
0.37
0.40
0.50
1.94
0.92
1.88
3.51
9.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

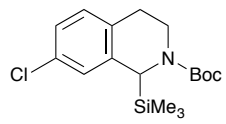

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Cl
N
Boc

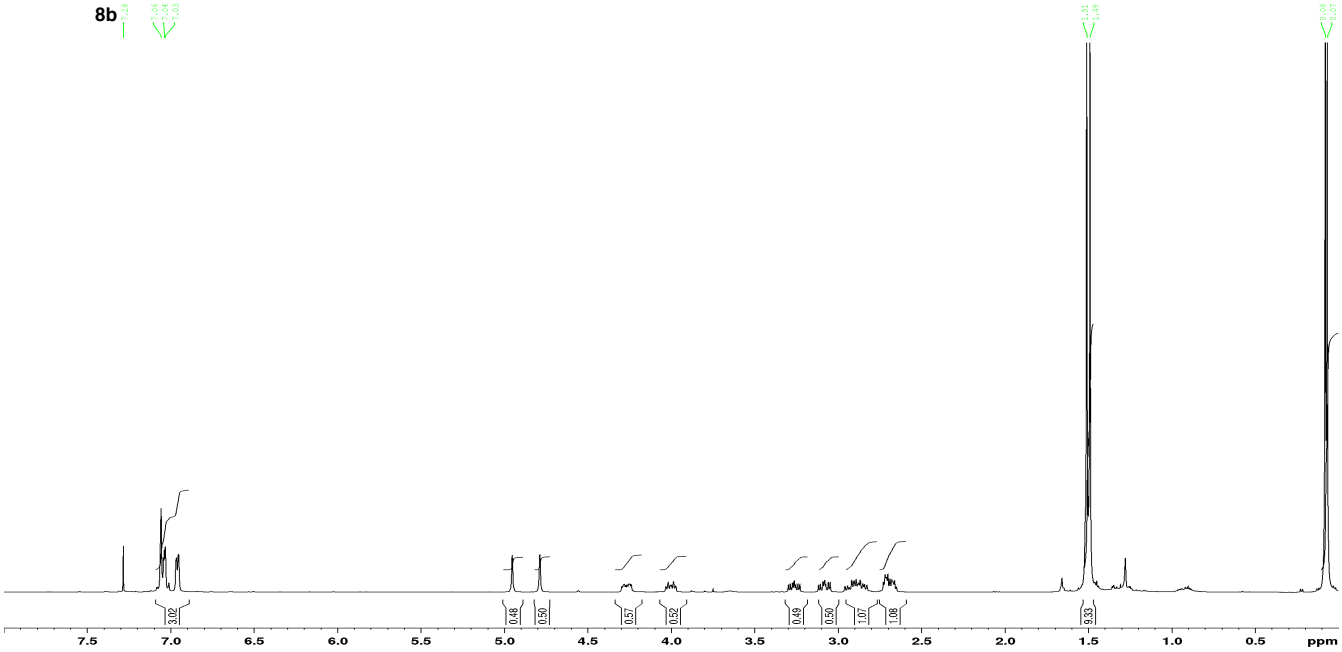
8a

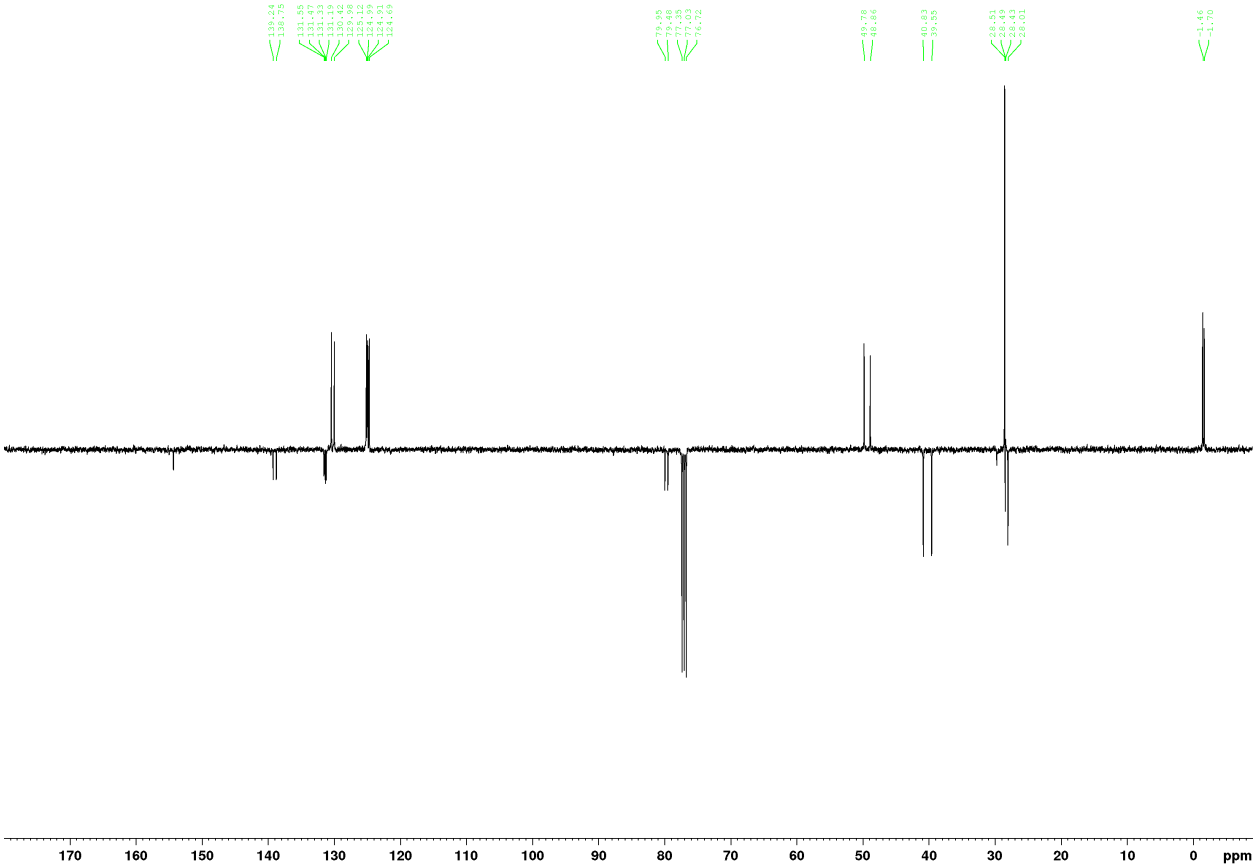

2.95
0.97
2.98
0.58
0.41
1.01
1.04
1.02
2.01
9.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

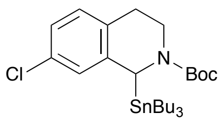

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Cl
N
Boc
SiMe3

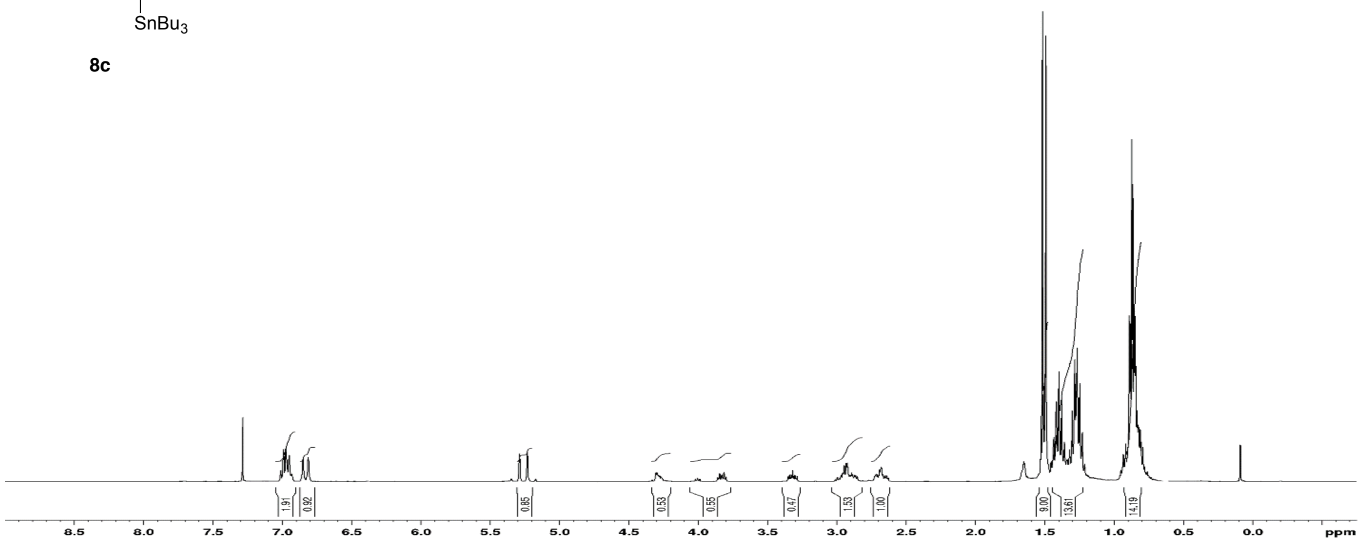
8b

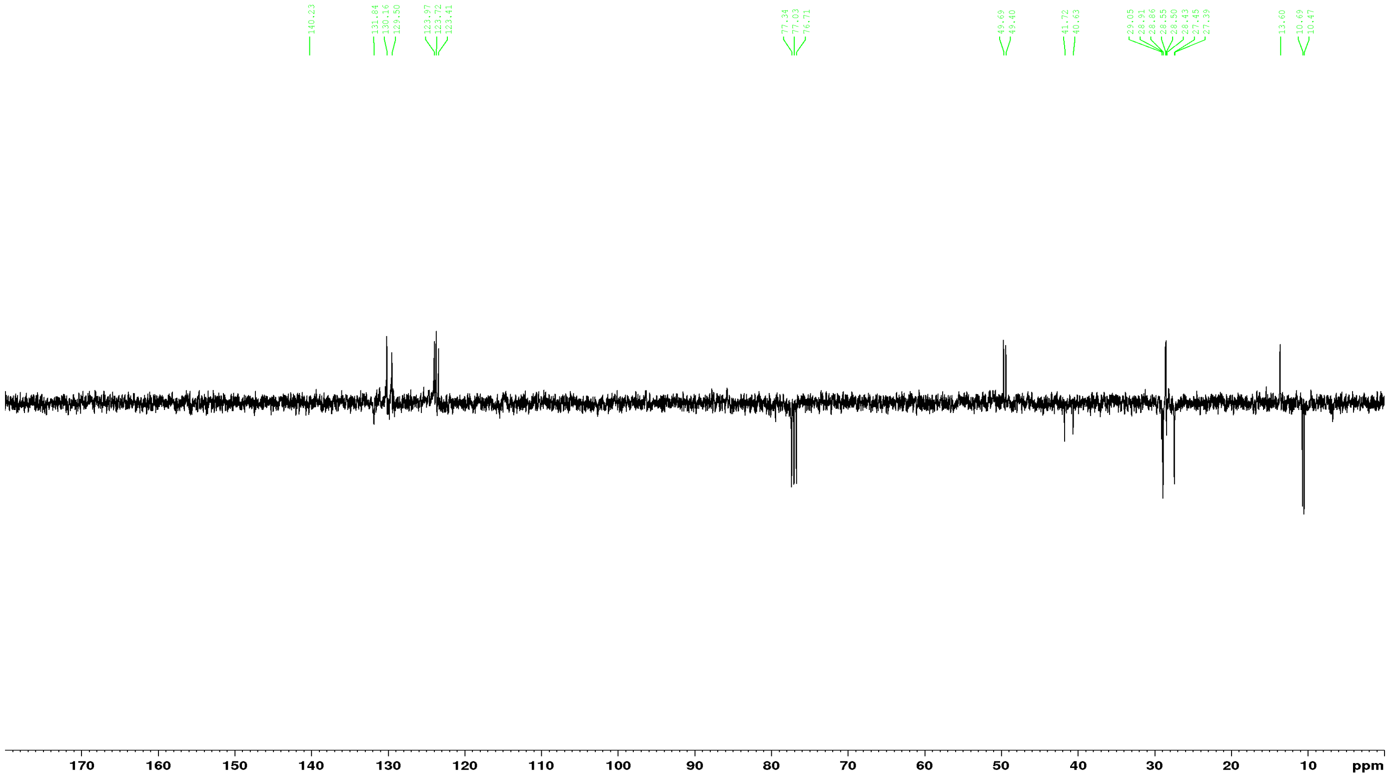

7.28
7.06
7.04
7.03
1.51
1.49
1.08
1.07
3.02
0.48
0.90
0.57
0.52
0.49
0.90
1.07
1.08
9.93
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

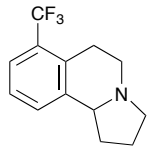

139.24
138.75
131.55
131.47
131.33
131.15
130.42
129.98
125.52
124.99
124.91
124.69
79.95
79.46
77.29
77.03
76.72
49.78
48.64
40.83
39.59
28.51
28.49
28.43
28.01
-1.46
-1.70
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



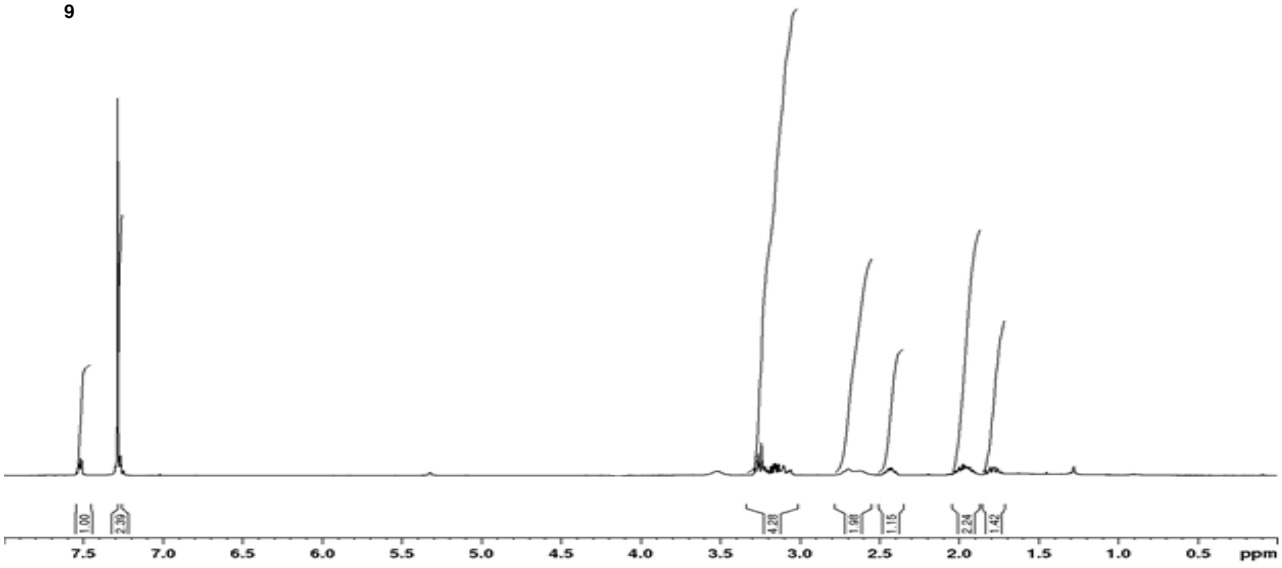
8c

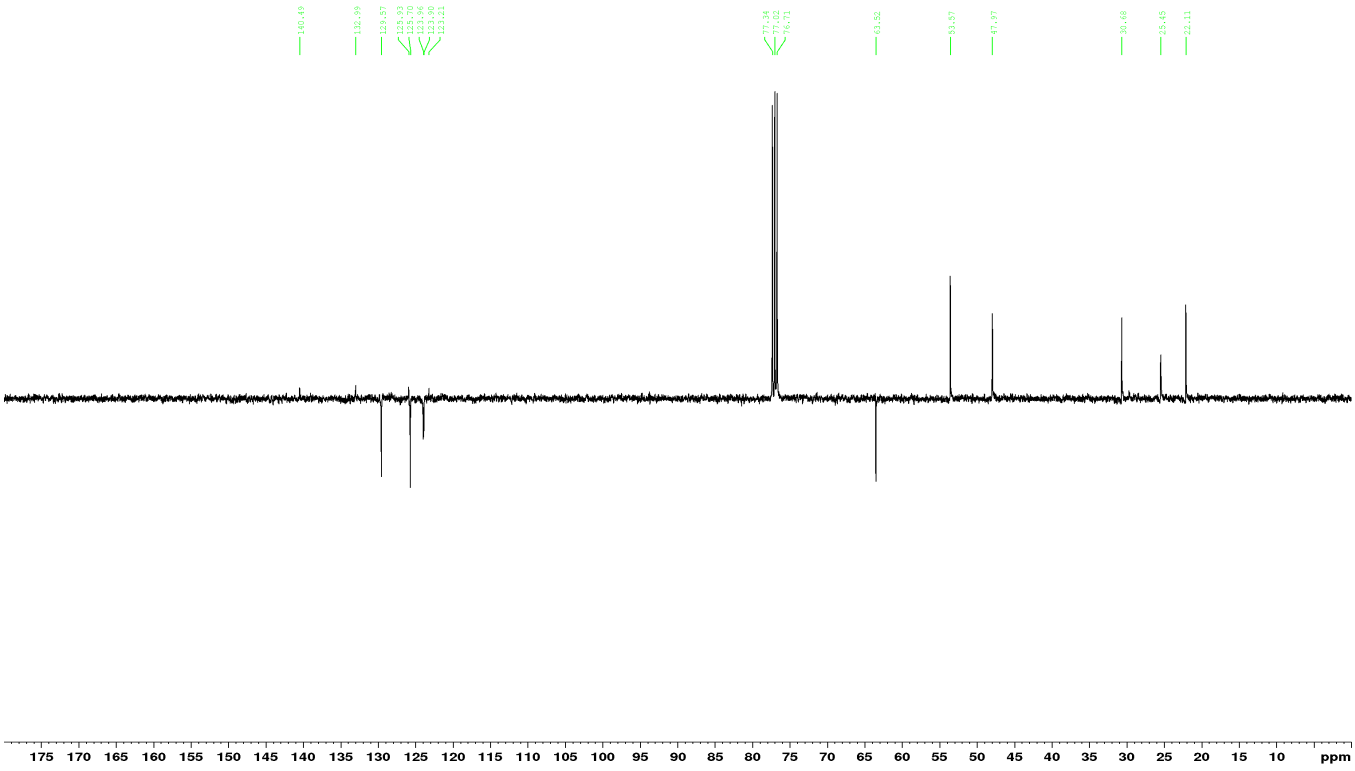


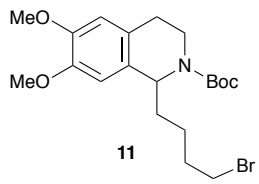



CF3
N

9

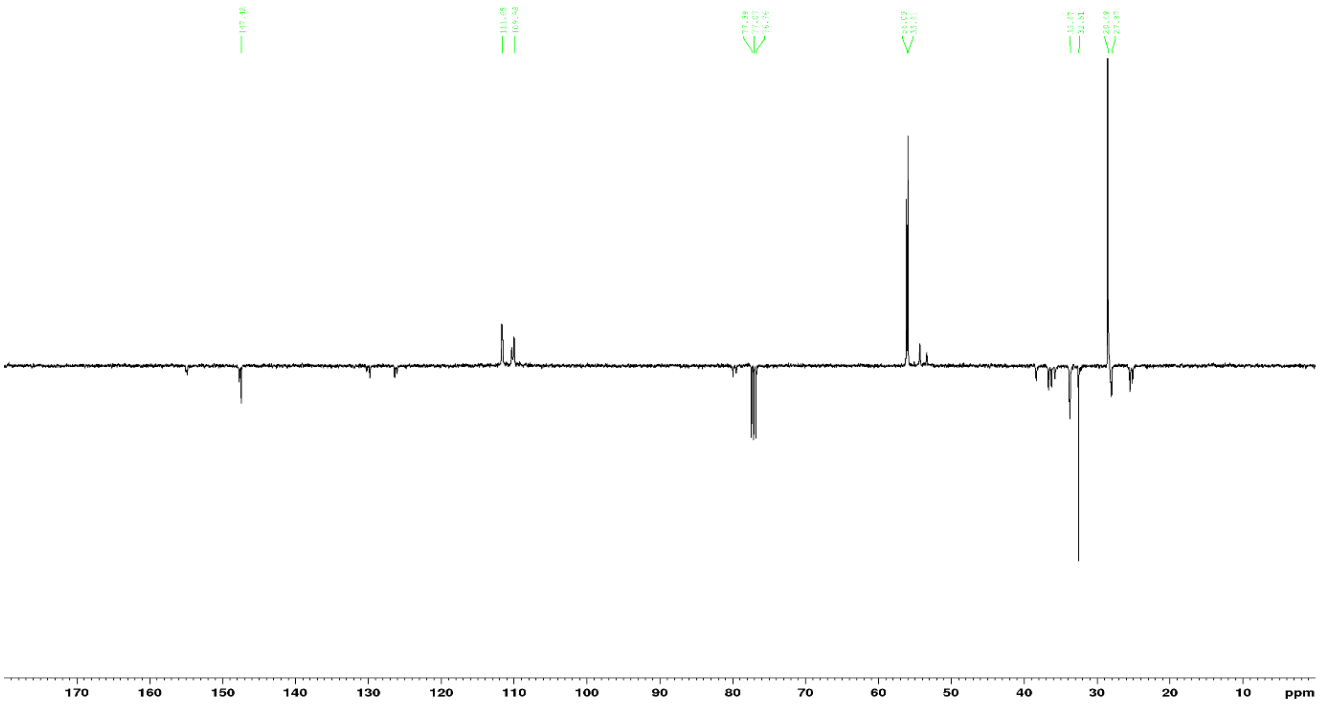

1.00
2.39
4.28
1.98
1.15
2.24
1.42
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

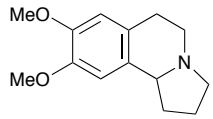

140.49
132.99
124.57
77.34
77.02
76.71
63.52
53.57
47.97
30.48
25.45
22.11
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
ppm


MeO
MeO
N
Boc
Br

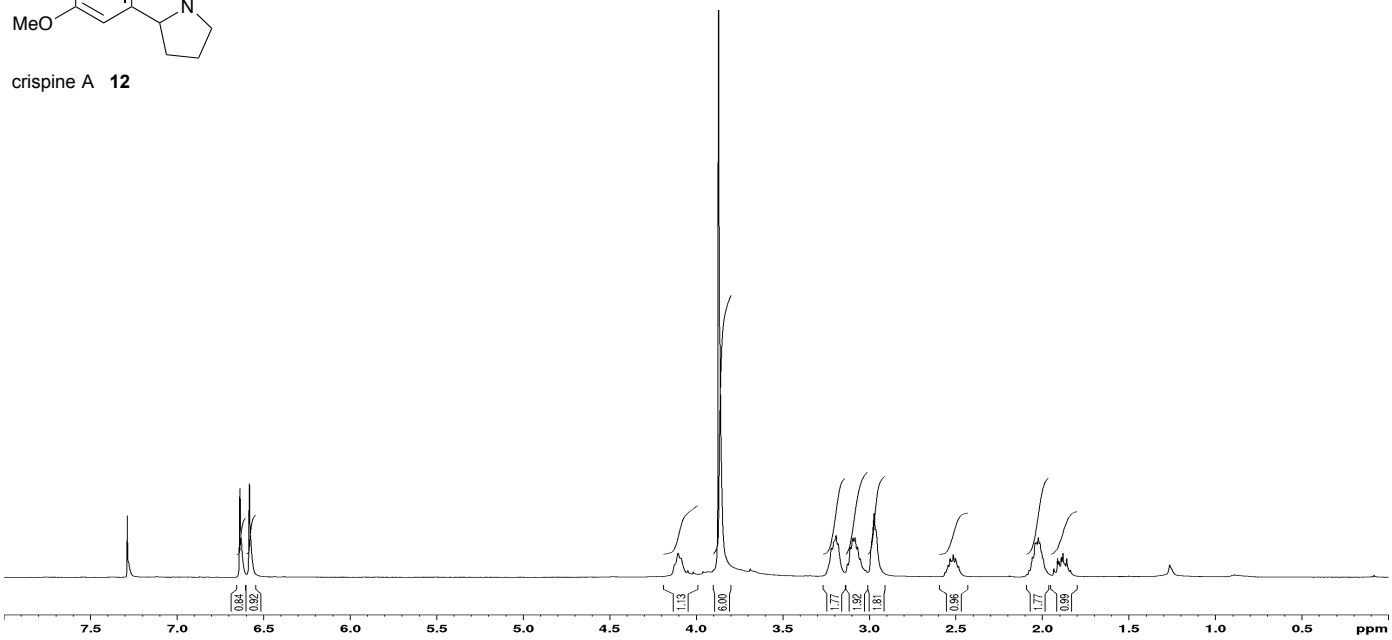
11

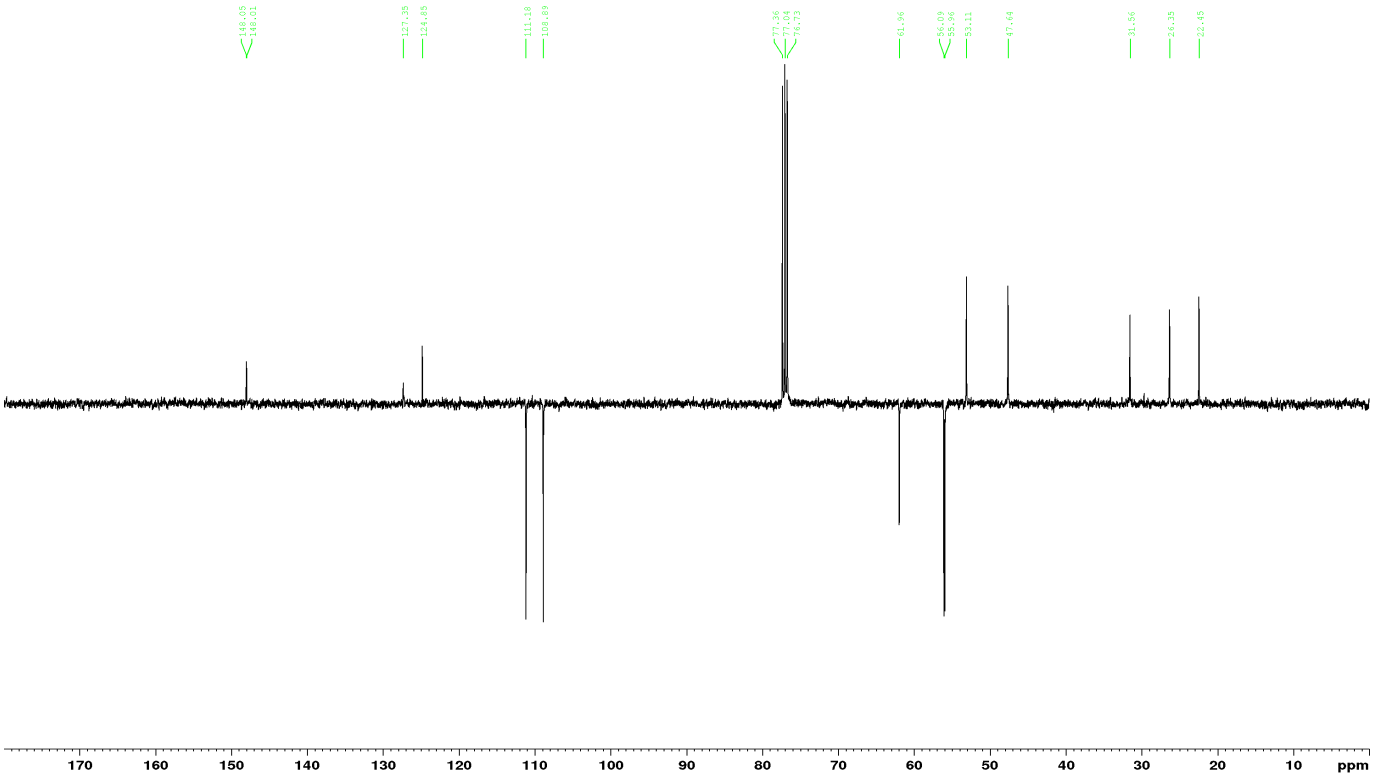
1.79
0.90
0.46
0.52
2.02
0.94
1.03
0.88
5.87
9.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

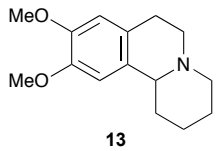

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



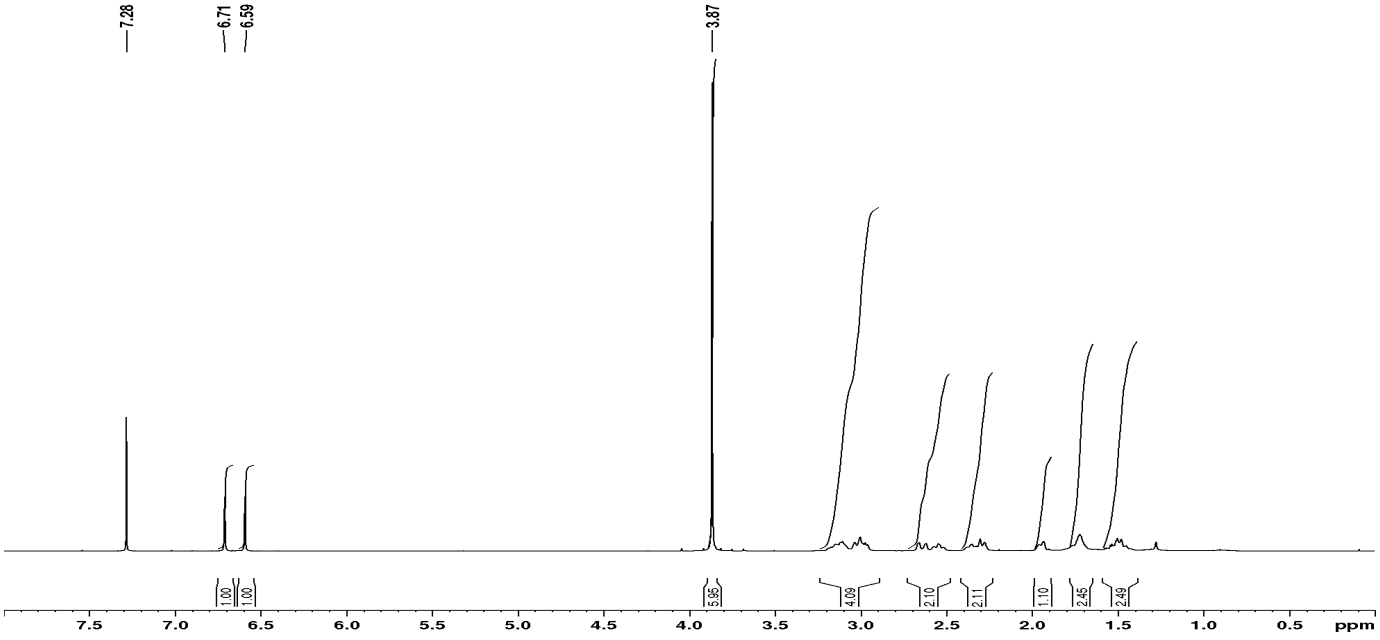
crispine A **12**

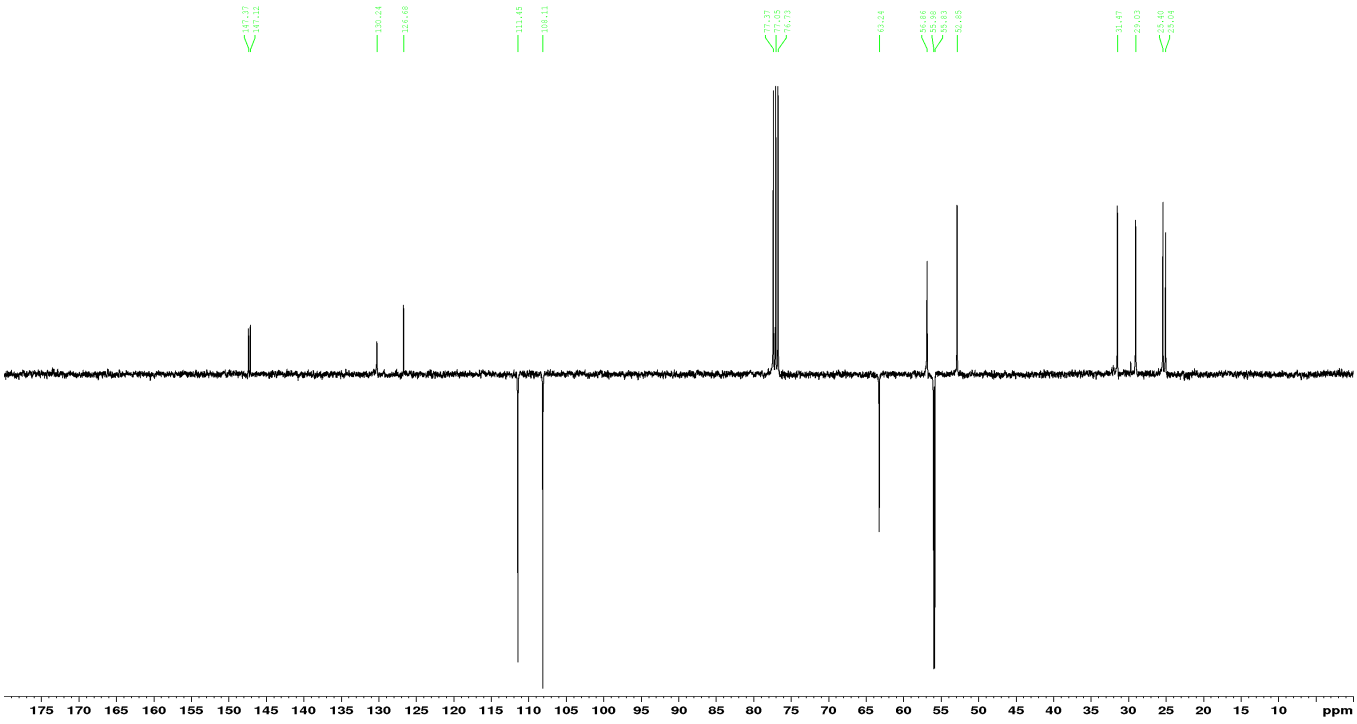


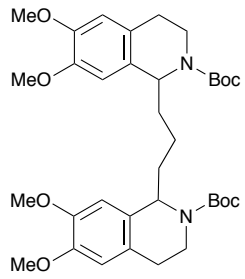



MeO
MeO
N

13

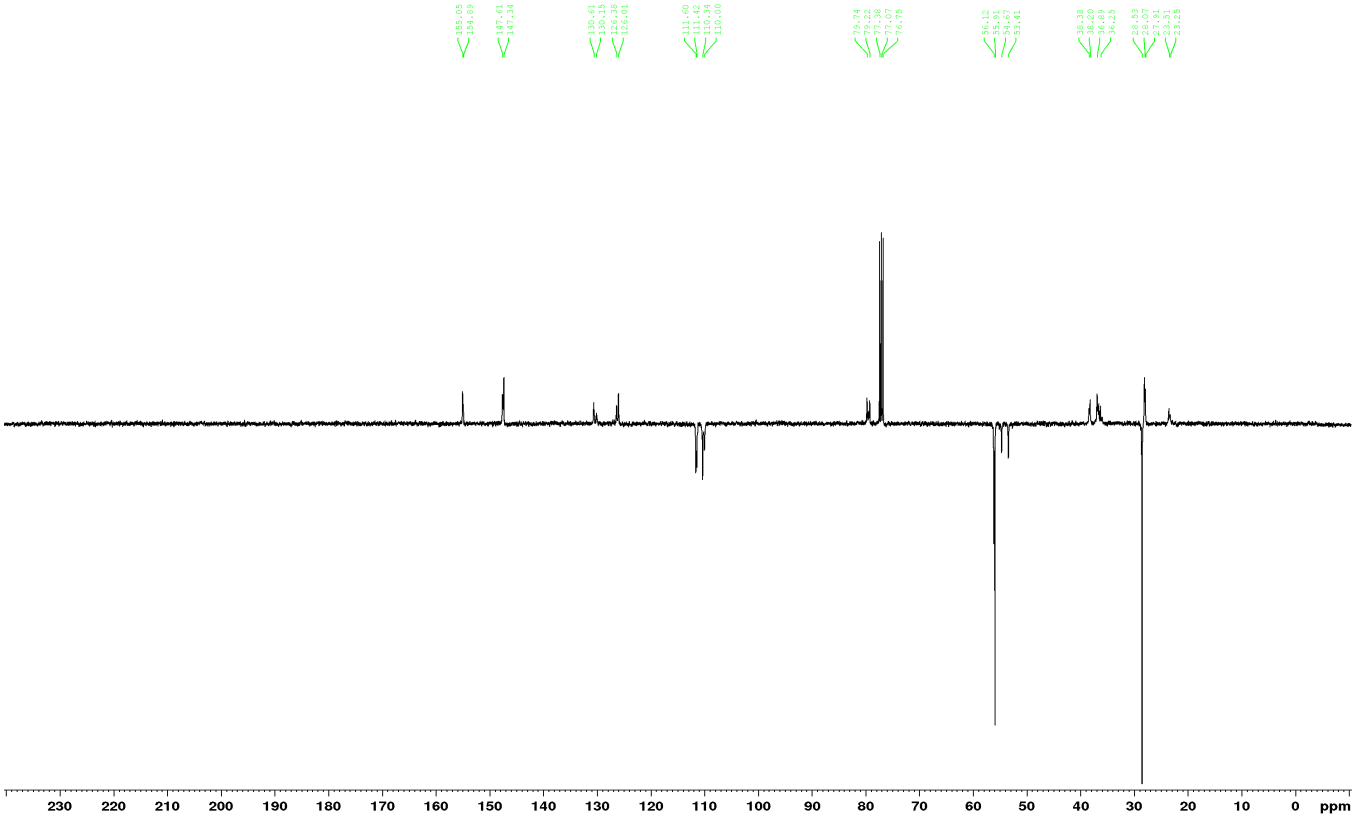

7.28
6.71
6.59
3.87
1.00
1.00
5.95
4.09
2.10
2.11
1.10
2.45
2.49
ppm

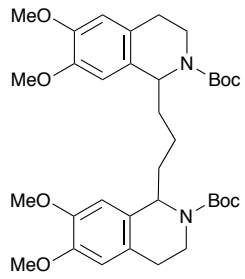

147.97
147.12
130.24
126.68
111.45
109.11
77.37
77.05
76.73
63.24
56.86
55.98
55.80
52.65
31.47
29.03
25.40
25.04
ppm


MeO
MeO
N
Boc
MeO
MeO
N
Boc

14a

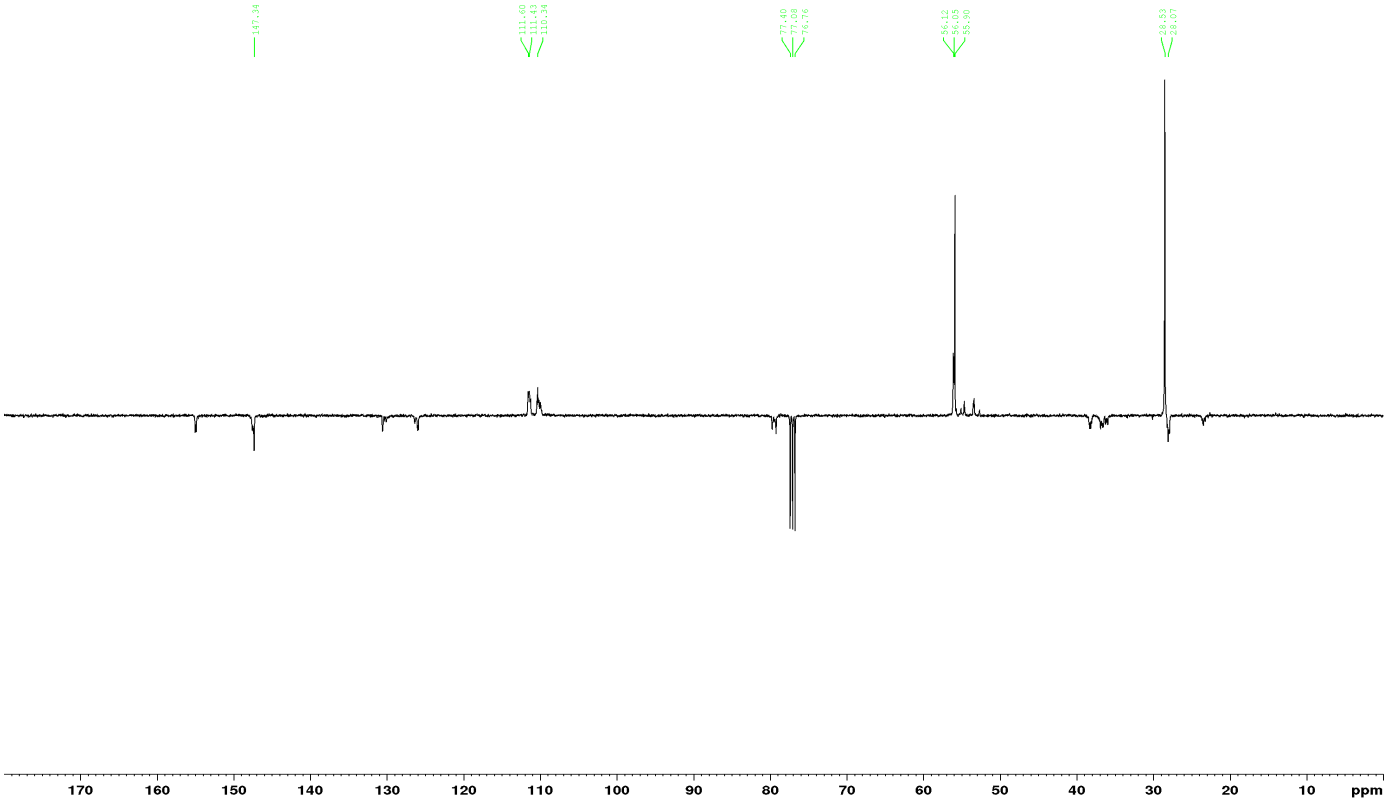
1.94
0.96
0.42
0.57
5.83
1.04
1.04
1.02
2.25
1.03
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

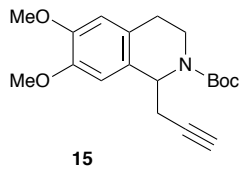

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


MeO
MeO
N
Boc
MeO
MeO
N
Boc

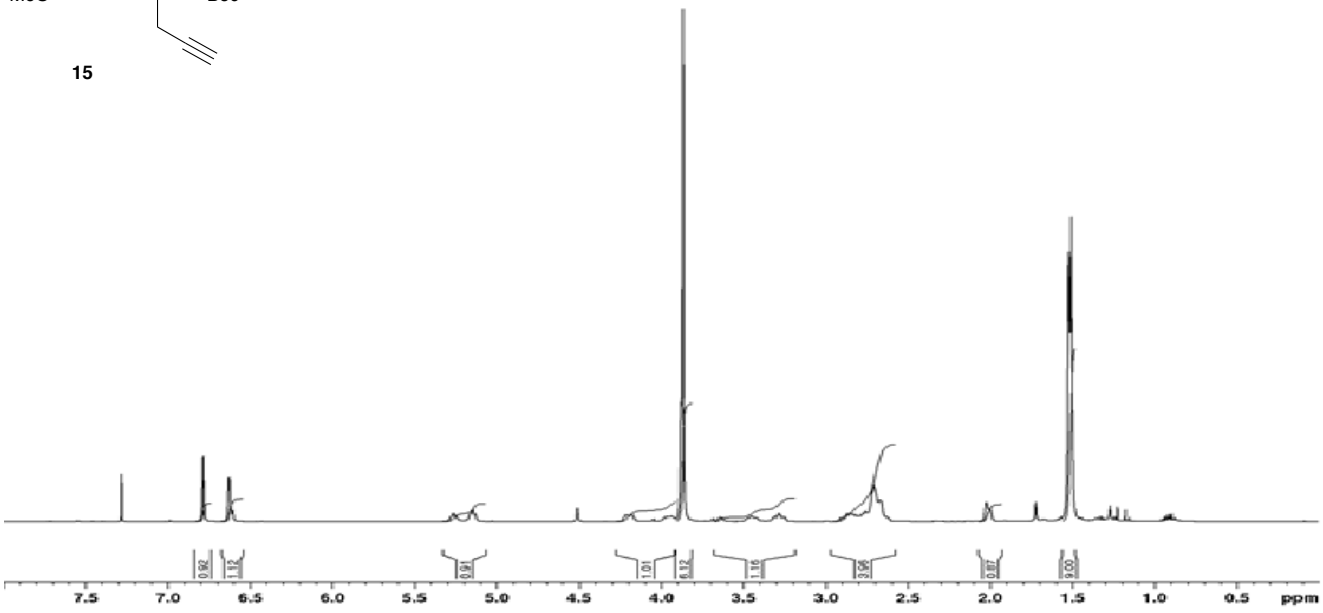
14b

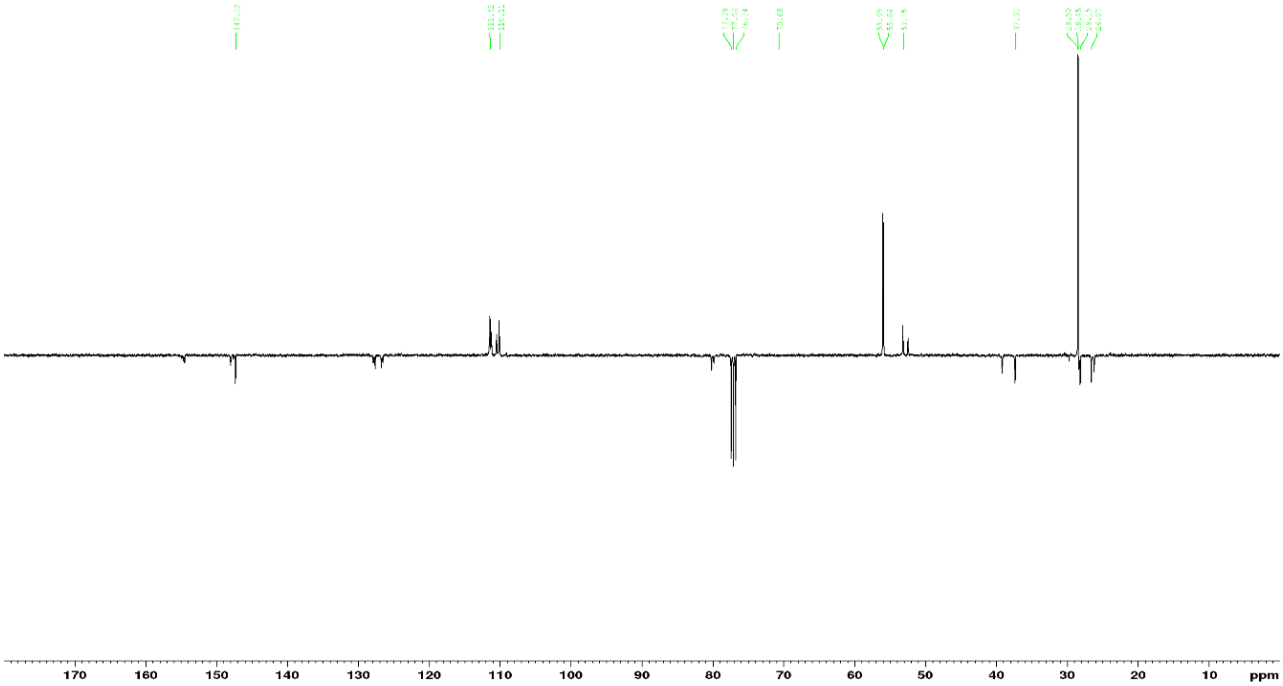
1.91
0.95
0.42
0.59
5.89
1.03
1.13
1.05
2.12
1.22
9.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

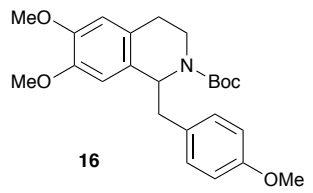

147.34
111.60
111.43
110.36
77.40
77.08
76.76
56.12
56.05
55.90
28.53
28.07
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
MeO
N
Boc

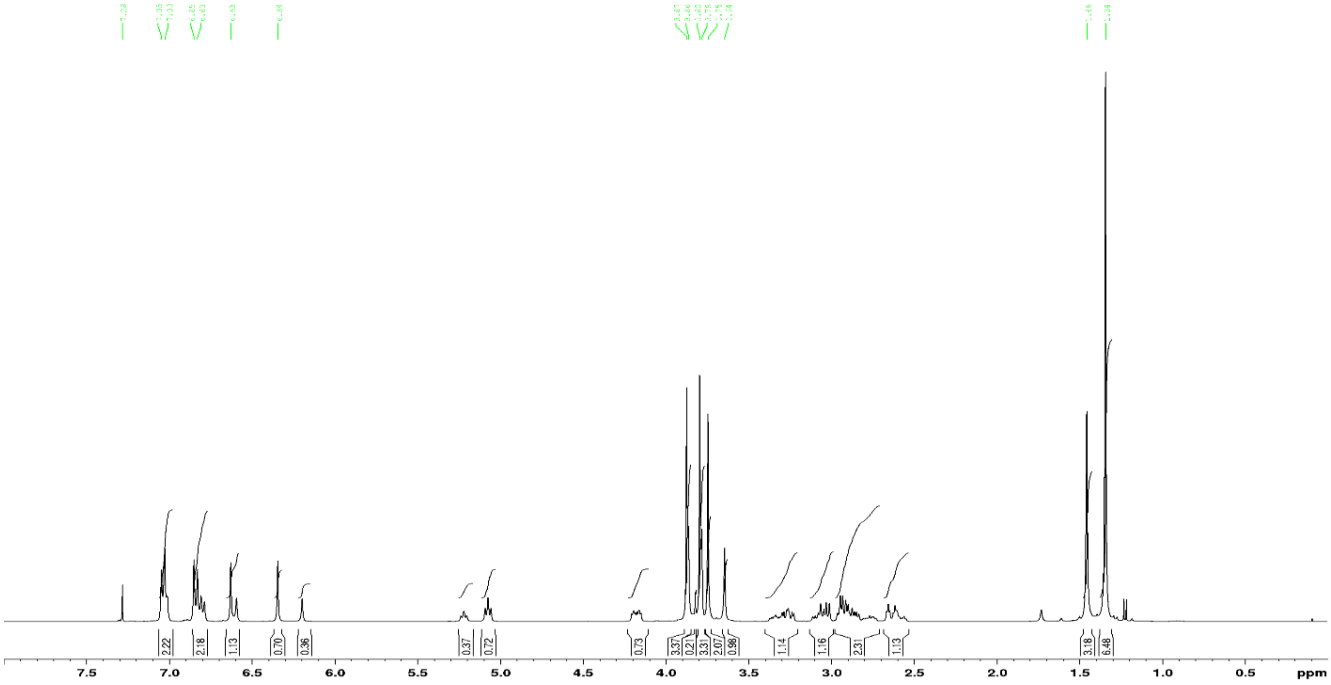
15

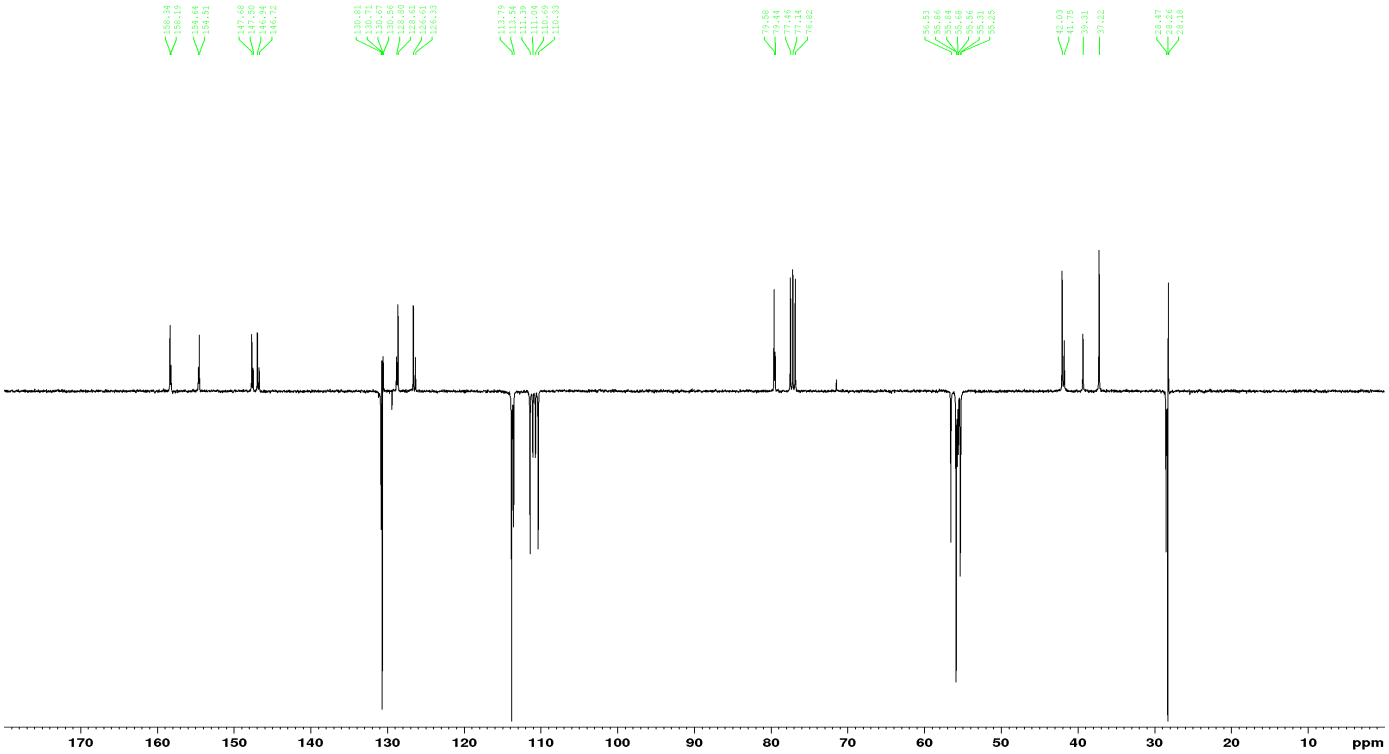

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

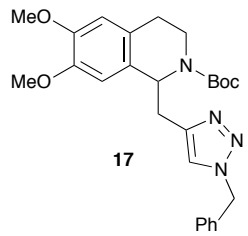

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
MeO
N
Boc
OMe

16

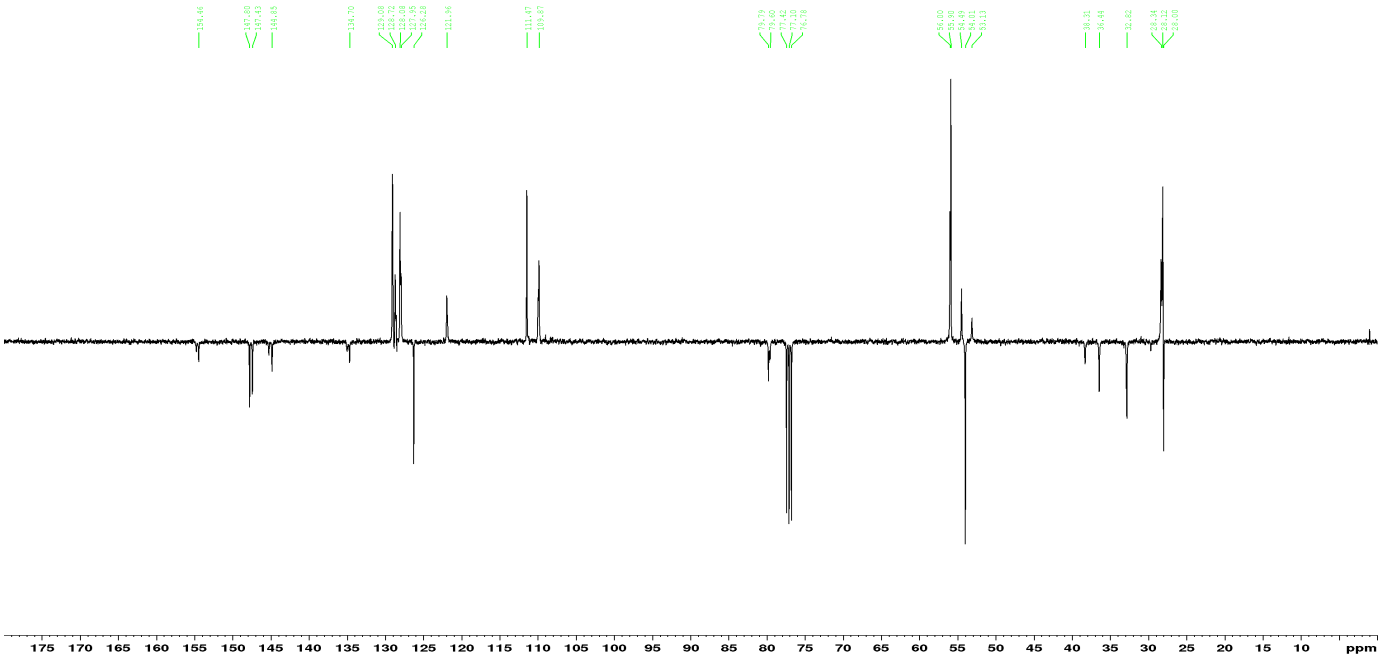

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

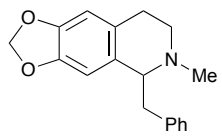

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
MeO
N
Boc
N
N
N
Ph

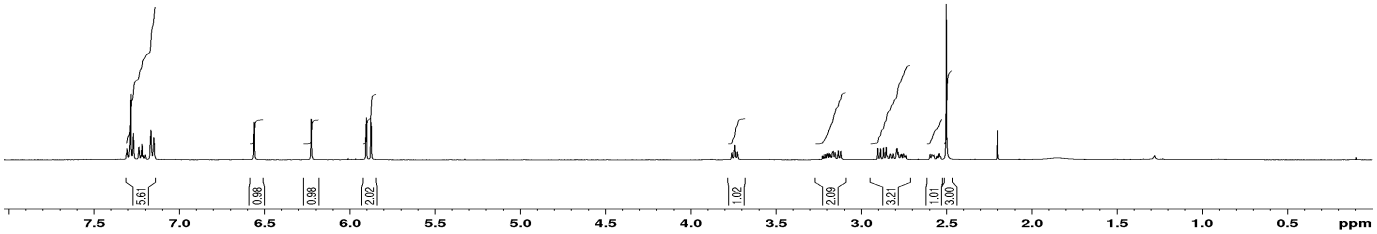
17

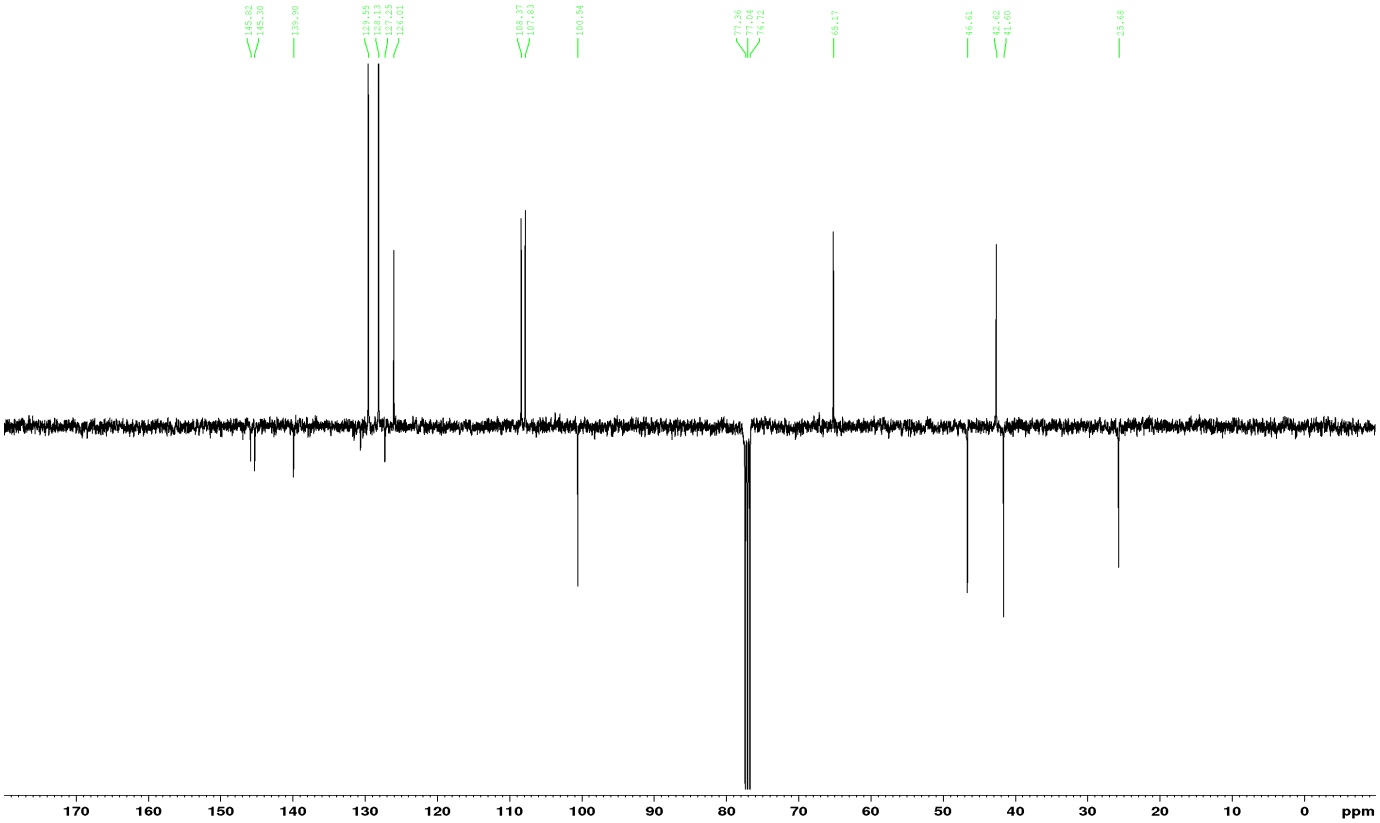
5.07
1.91
2.82
1.19
5.70
2.86
0.99
0.94
0.73
8.70
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

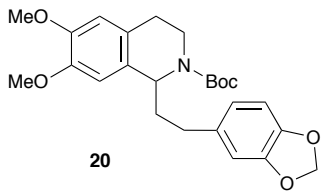

175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
ppm


O
O
N
Me
Ph

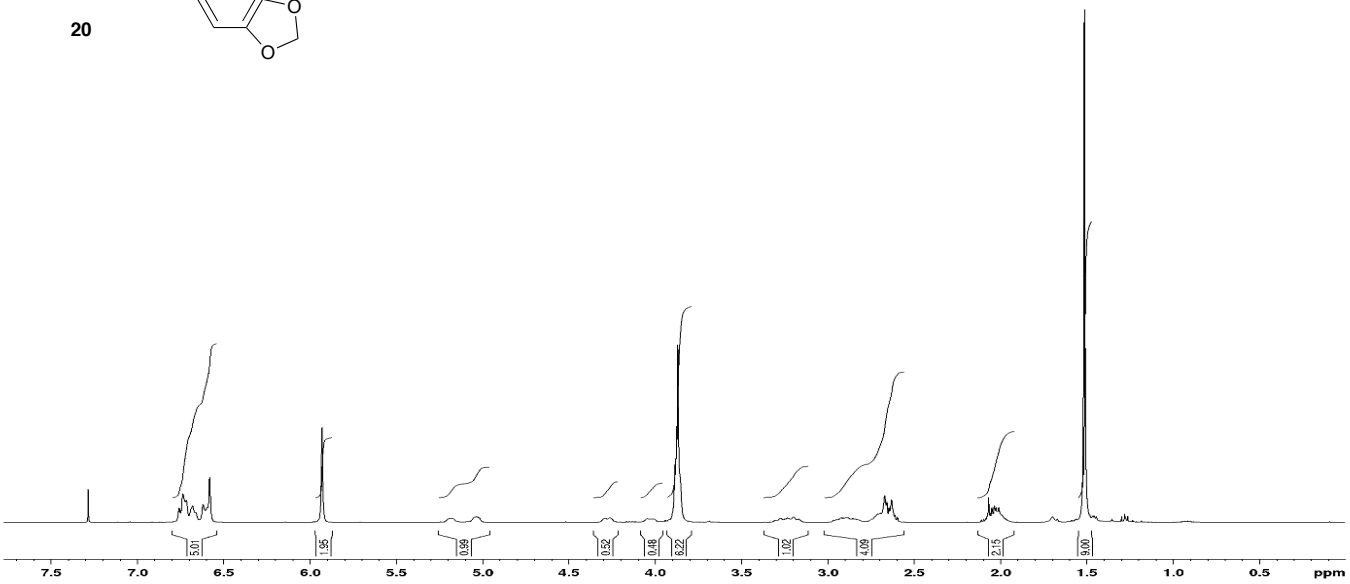
18

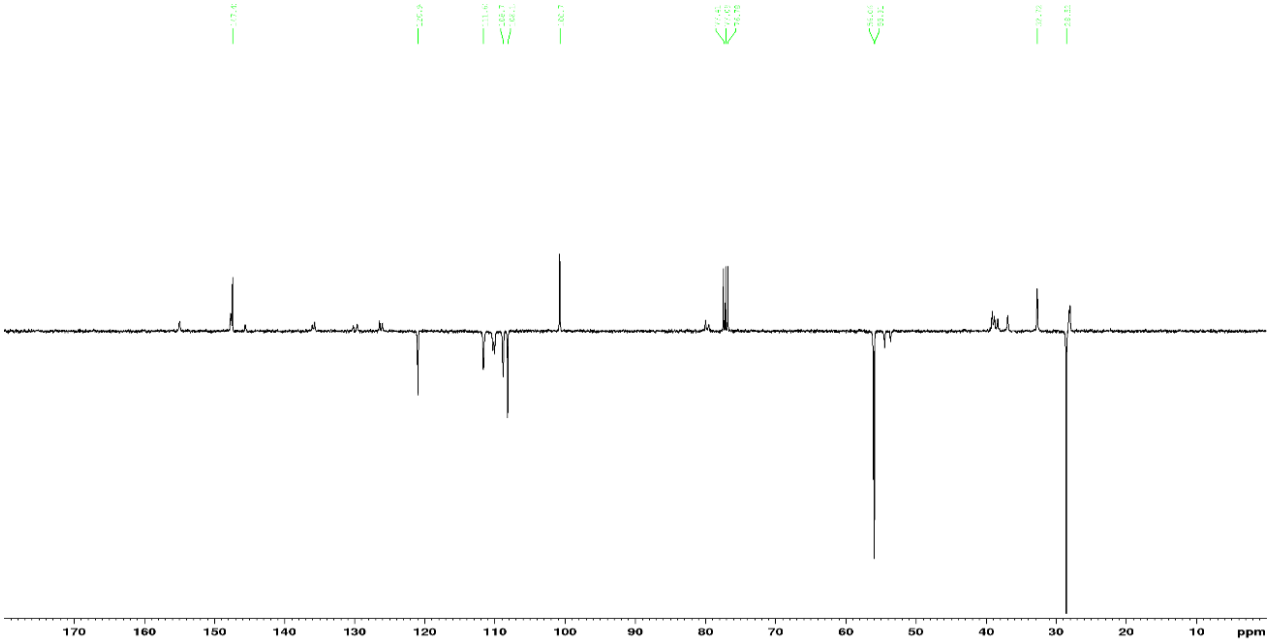

5.61
0.98
0.98
2.02
1.02
2.09
3.21
1.01
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

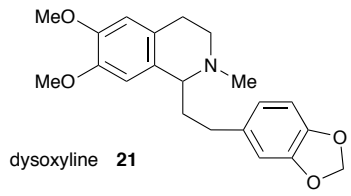

145.82
145.30
139.90
129.55
128.13
127.25
126.01
108.37
107.83
100.54
77.36
77.04
76.72
65.17
46.61
42.42
41.60
25.68
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


MeO
MeO
N
Boc
O
O

20


5.01
1.95
0.99
0.52
0.48
6.22
1.02
4.09
2.15
9.00
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


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



dysoxyline **21**