Supporting Information

Enantiospecific Synthesis and Biological Investigations of a Nuphar Alkaloid: Proposed Structure of a Castoreum Component

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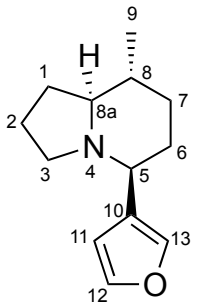
1. Comparison of ^{1}H and ^{13}C-NMR data from prior work



alkaloid **1**

^{1}H and ^{13}C NMR data of alkaloid 1 was summarized in the table below.

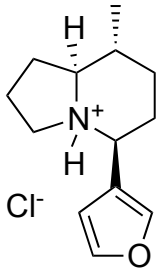
1. ^{1}H NMR data of Georg, Kunz, and Barluenga are similar to each other.

2. ^{13}C NMR data of Georg, Kunz, Barluenga, LaLonde are similar to each other.

3. Although Davis reports that their data of alkaloid **1** is identical with Barluenga's, we found that the ^{1}H NMR spectrum provided to us by Barluenga's lab was quite different from the Davis ^{1}H NMR, especially in the ~3.0 ppm region. Davis' spectrum of **1** seems not calibrated, which made it difficult for us to further decipher the spectrum.

4. In Davis' paper (*JOC*, **2006**, *71*, 4222), although the spectroscopic data of the intermediate #16 was identical to Barluenga's report (intermediate #10), we found that the two spectra were somewhat different. This led us to the speculation that they might have produced the stereochemical isomer of the alkaloid. The comparison of spectroscopic data of the intermediate **11** further supported this hypothesis (see below).

5. We synthesized the HCl salt of alkaloid **1** and examined its spectra, which was different from any of the reported spectra including the one by Davis'.



1•HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (bs, 1H), 7.68 (s, 1H), 7.41 (s, 1H), 7.09 (d, *J* = 1.4 Hz, 1H), 3.67 (t, *J* = 9.8 Hz, 1H), 3.44 (s, 1H), 2.75 – 2.47 (m, 4H), 2.26 (m, 3H), 2.05 (dd, *J* = 13.6, 2.8 Hz, 1H), 1.94 (m, 2H), 1.35 – 1.21 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 141.6, 121.1, 110.5, 73.9, 61.6, 51.9, 33.0, 32.9, 31.5, 27.5, 19.2, 18.6.

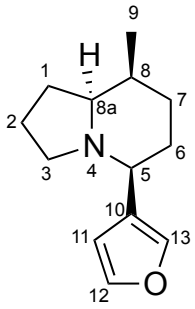
alkaloid1	Georg		Kunz		Barluenga	
Atom #	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1 (2H)	2.0-1.85 1.52-1.45	29.2	2.01-1.90 1.54-1.36	29	1.98-1.87 M	28.9
2 (2H)	1.76-1.50	20.3	1.68-1.55	20	M	20
3 (2H)	2.95-2.84 2.0-1.85	53.3	2.99-2.78 2.01-1.90	53.1	2.88 (td, 8.8, 2.2 Hz) 1.98-1.87	53.1
4	–	–	–	–	–	–
5	2.95-2.84	59.9	2.99-2.78	59.8	2.91 (dd, 8.4, 5.7Hz)	59.7
6	1.82-1.70	34.3	1.84-1.70	34	M	34
7 (2H)	1.18-1.01 1.82-1.70	34.1	1.14-1.01 1.84-1.70	33.8	1.13-1.02 M	33.8
8	1.50-1.35	36.6	1.54-1.36	36.3	M	36.2
8a	1.68-1.51	71.6	1.68-1.55	71.5	M	71.4
9	0.91 (d, 6.5 Hz)	19	0.91 (d, 6.5 Hz)	18.8	0.90 (d, 6.6 Hz)	18.8
10	–	128.4	–	128	–	128
11	6.44	109.9	6.47	109.7	6.44	109.6
12	7.34	139.5	7.35	139.4	7.33-7.26	139.3
13	7.34	142.8	7.35	142.8	7.33-7.26	142.6

M = 1.82-1.39, 8H

alkaloid1	Davis*		LaLonde		Tufariello	Bates
Atom #	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H/^{13}C	^{1}H/^{13}C
1 (2H)	1.98 N	Not provided.	Not provided.	29.2	Not provided. "confirmed by comparison of the H and C NMR spectra of **1** synthesized independently by LaLonde."	Not provided. Referred to Barluenga's data
2 (2H)	N			20.2		
3 (2H)	2.88 (td, 8.8, 2.2Hz) N			53.3		
4	–		–	–		
5	2.90 (dd, 8.4, 5.7Hz)		3.52 (dd, 8.0, 6.0 Hz)	60		
6	N		Not provided.	34.4		
7 (2H)	1.13 N			34.1		
8	N			36.5		
8a	N			71.6		
9	0.90 (d, 6.6Hz)		0.89 (d, 6 Hz)	18.2		
10	–		–	–		
11	6.42		6.45	–		
12	7.38		7.36	139.7		
13	7.38		7.36	143.1		

N = 1.39, 8H

*actual spectrum looks different from data here

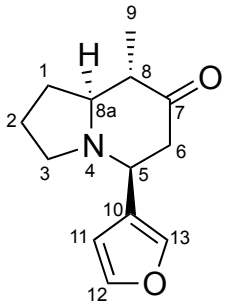


alkaloid **2**

Alkaloid 2	**Georg**[1]		**Kunz**		**Ban**	
Atom #	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1 (2H)	1.70-1.58	27 or 32.3	M	32.1	Not provided.	Not provided.
2 (2H)	1.72-1.52	20.3	M	20.1		
3 (2H)	2.90-2.83	53.6	2.91-2.82	53.4		
	1.87-1.75		1.88-1.75		3.1-2.7	
4	–	–	–	–	–	
5	2.90-2.83	61.1	2.91-2.82	60.9	3.1-2.7	
6 (2H)	1.52-1.45	29.1	1.52-1.45	28.9	Not provided.	
	1.87-1.75		1.88-1.75			
7 (2H)	1.72-1.52	27 or 32.3	M	26.8		
8	1.93 (td, 6.8, 2.8 Hz)	29.6	1.97-1.89	29.4		
8a	2.14-2.06	67.7	2.15-2.06	67.5		
9 (3H)	1.04 (d, 7.0 Hz)	12.4	1.04 (d, 7.0 Hz)	12.2	0.91 (d, 6 Hz)	
10	–	129	–	128.7	–	
11	6.43	109	6.43	109.7	6.46	
12	7.36-7.30	139.2	7.35-7.31	139.1	7.36-7.35	
13	7.36-7.30	142.7	7.35-7.31	142.6	7.36-7.36	

M=1.71-1.53, 6H

1. Our data match with ones by Kunz. However, we unable to decide on the assignments for the ^{13}C signals for atoms 1 and 7 (red).



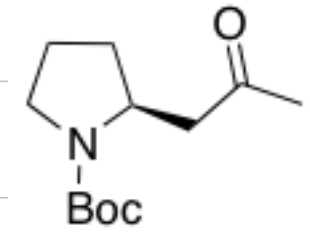
intermediate **11**

Int. 11	**Georg (solid)[1]**		**Tufariello**		**Davis (liquid)[2]**	
Atom #	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1 (2H)	2.09-1.97 1.79-1.58	30.5	Not provided.	Not provided.	1.04 (d, 6.3Hz), 1.48, 1.70, 1.91(2H), 2.38 (3H), 2.42 (q, 8.2Hz), 3.26, 3.68, 3.81, 6.42, 7.22, 7.38 (d, 7.2Hz)	10.5, 21.9, 30.6, 45.4, 49.7, 50.6, 52.4, 59.4, 110.3, 121.5, 140.7, 143.0, 211.3
2 (2H)	1.92-1.79 1.79-1.58	21.5				
3 (2H)	2.94 (dd, 12.4, 5.4 Hz) 2.09-1.97	52.2				
4	–	–				
5	3.34 (dd, 11.9, 3.2Hz)	58.1	3.30 (dd, 11.5, 3.6 Hz)			
6 (2H)	2.76-2.65 2.50-2.39	48.6				
7	–	209.8	Not provided.			
8	2.50-2.39	50.5				
8a	2.09-1.97	70.5				
9	1.04 (d, 6.6 Hz)	10.7	1.03 (d, 6.6 Hz)			
10	–	126.8				
11	6.47	109.1	Not provided.			
12	7.42-7.31	143.6				
13	7.42-7.32	139.6				

1. We confirmed the structure of **11** by X-ray.
2. The chemical shifts are noted in order from upfield to downfield region since it was not possible to make assignments of each H and C peak. This spectroscopic data clearly differs from ours.

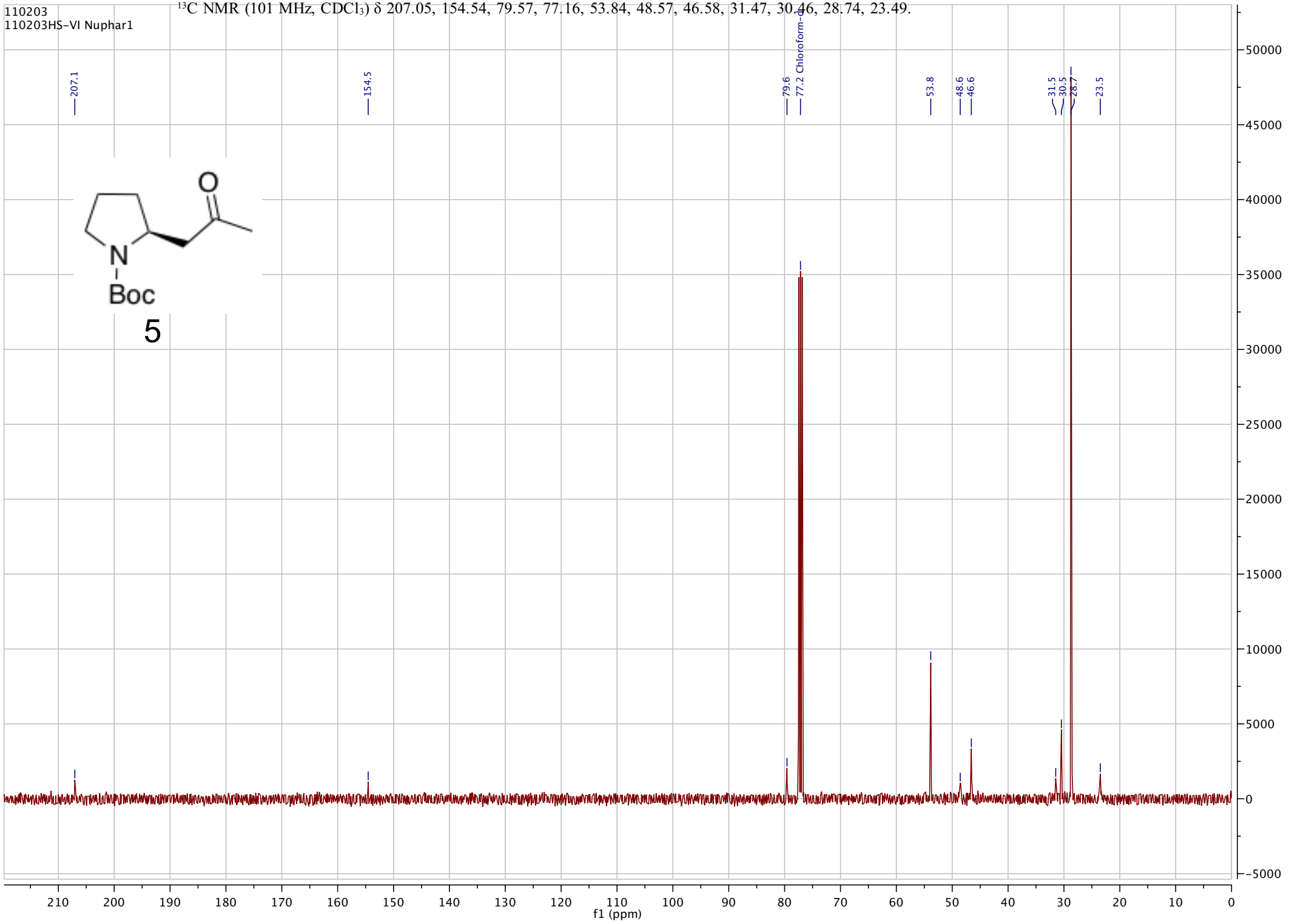
110203
110203HS-VI Nuphar1

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (ddd, *J* = 11.2, 7.4, 3.5 Hz, 1H), 3.33 (dt, *J* = 10.2, 5.6 Hz, 2H), 3.00 (s, 1H), 2.41 (dd, *J* = 15.8, 9.4 Hz, 1H), 2.13 (d, *J* = 3.1 Hz, 3H), 2.10 – 2.01 (m, 1H), 1.85 – 1.74 (m, 2H), 1.68 – 1.60 (m, 1H), 1.46 (s, 9H).



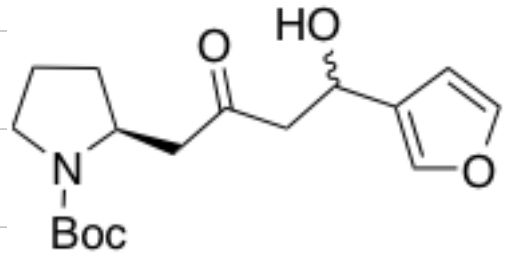
5

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.05, 154.54, 79.57, 77.16, 53.84, 48.57, 46.58, 31.47, 30.46, 28.74, 23.49.



110203
110203HS-VI Nuphar2

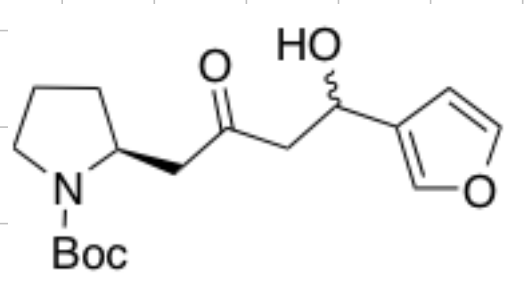
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 9.0, 1.1 Hz, 2H), 6.38 (s, 1H), 5.15 (s, 1H), 4.18 (s, 1H), 3.69 – 3.05 (m, 3H), 3.03 – 2.72 (m, 3H), 2.46 (dd, *J* = 15.6, 8.3 Hz, 1H), 2.08 (dq, *J* = 15.9, 8.0 Hz, 1H), 1.82 (d, *J* = 5.3 Hz, 2H), 1.65 (m, 1H), 1.45 (m, 9H).



6

110203
110203HS-VI Nuphar2

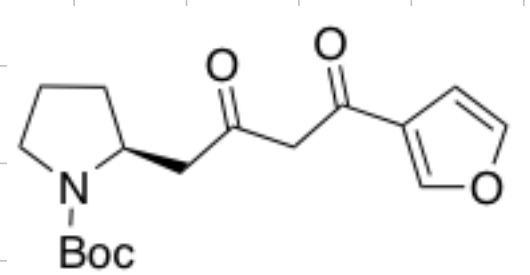
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.15, 208.90, 154.76, 143.46, 139.18, 128.14, 108.66, 79.82, 77.48, 77.16, 77.16, 76.84, 63.45, 63.29, 53.78, 50.91, 50.81, 48.66, 46.61, 31.65, 28.74, 23.63.



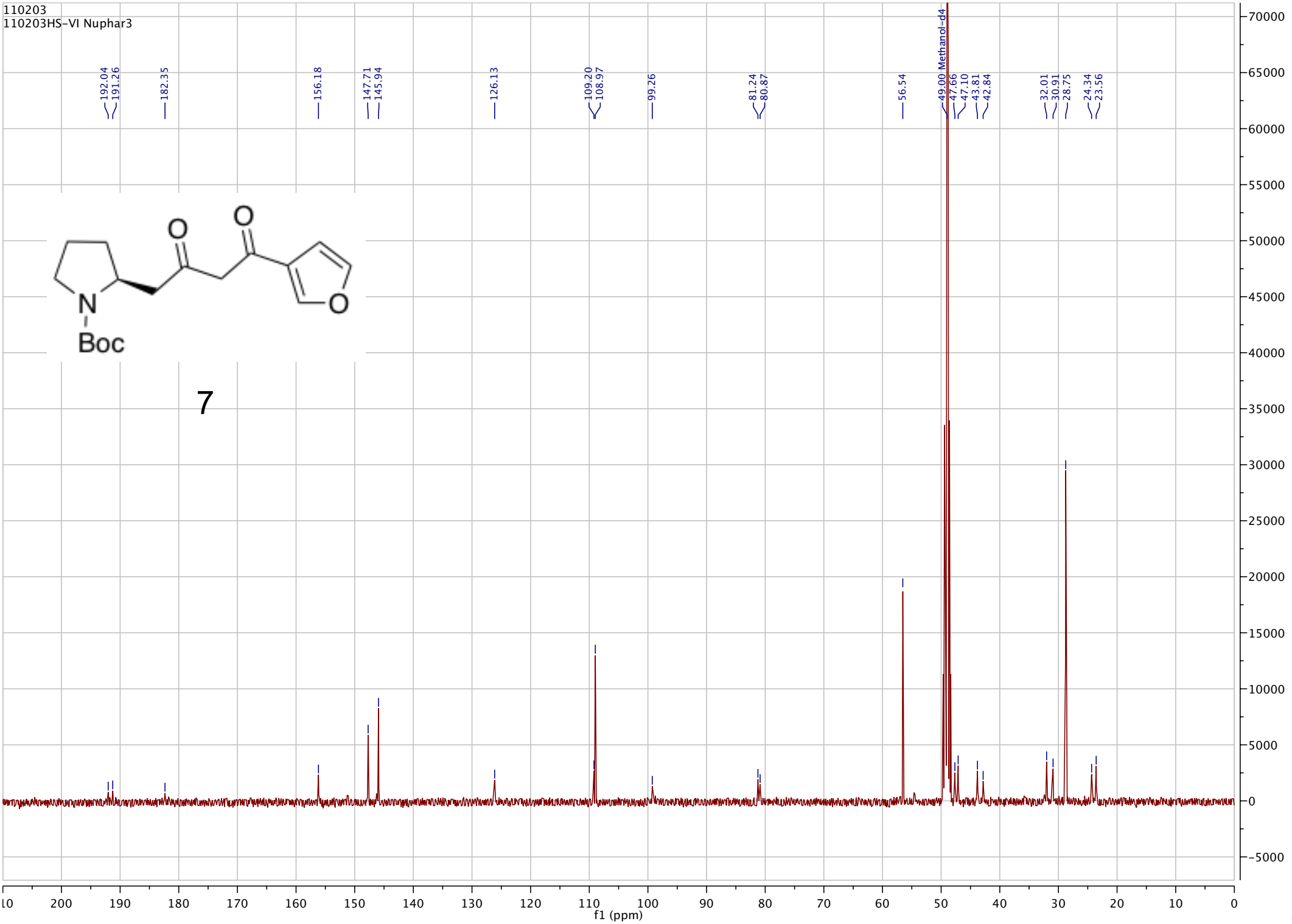
6

110203
110203HS-VI Nuphar3

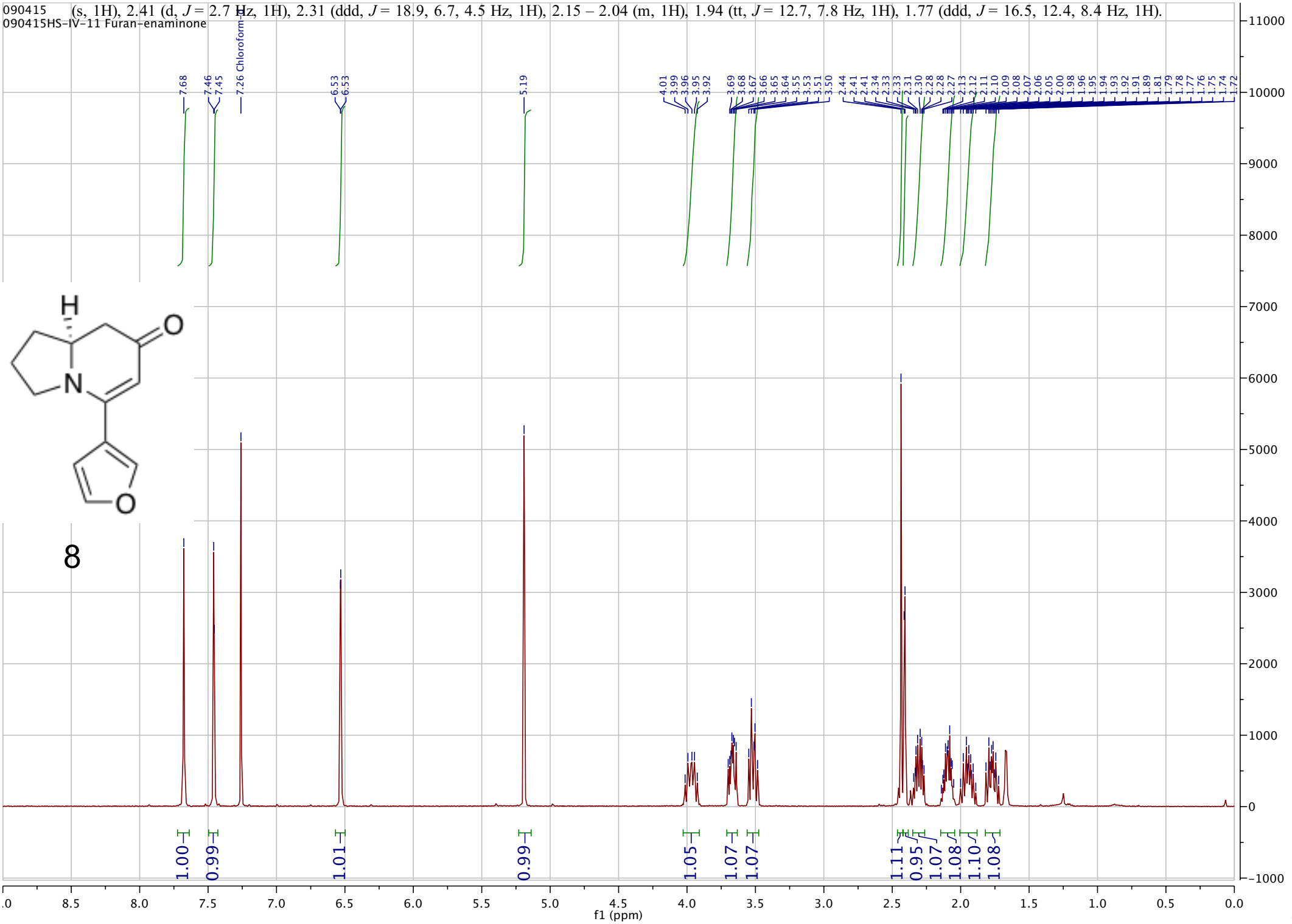
^{1}H NMR (400 MHz, MeOD) δ 8.23 (s, 1H), 7.61 (s, 1H), 6.81 (s, 1H), 6.07 (d, *J* = 14.5 Hz, 1H), 4.19 (s, 1H), 3.34 (d, *J* = 16.0 Hz, 3H), 2.83 (m, 1H), 2.41 (s, 1H), 1.95 (m, 4H), 1.46 (s, 9H).



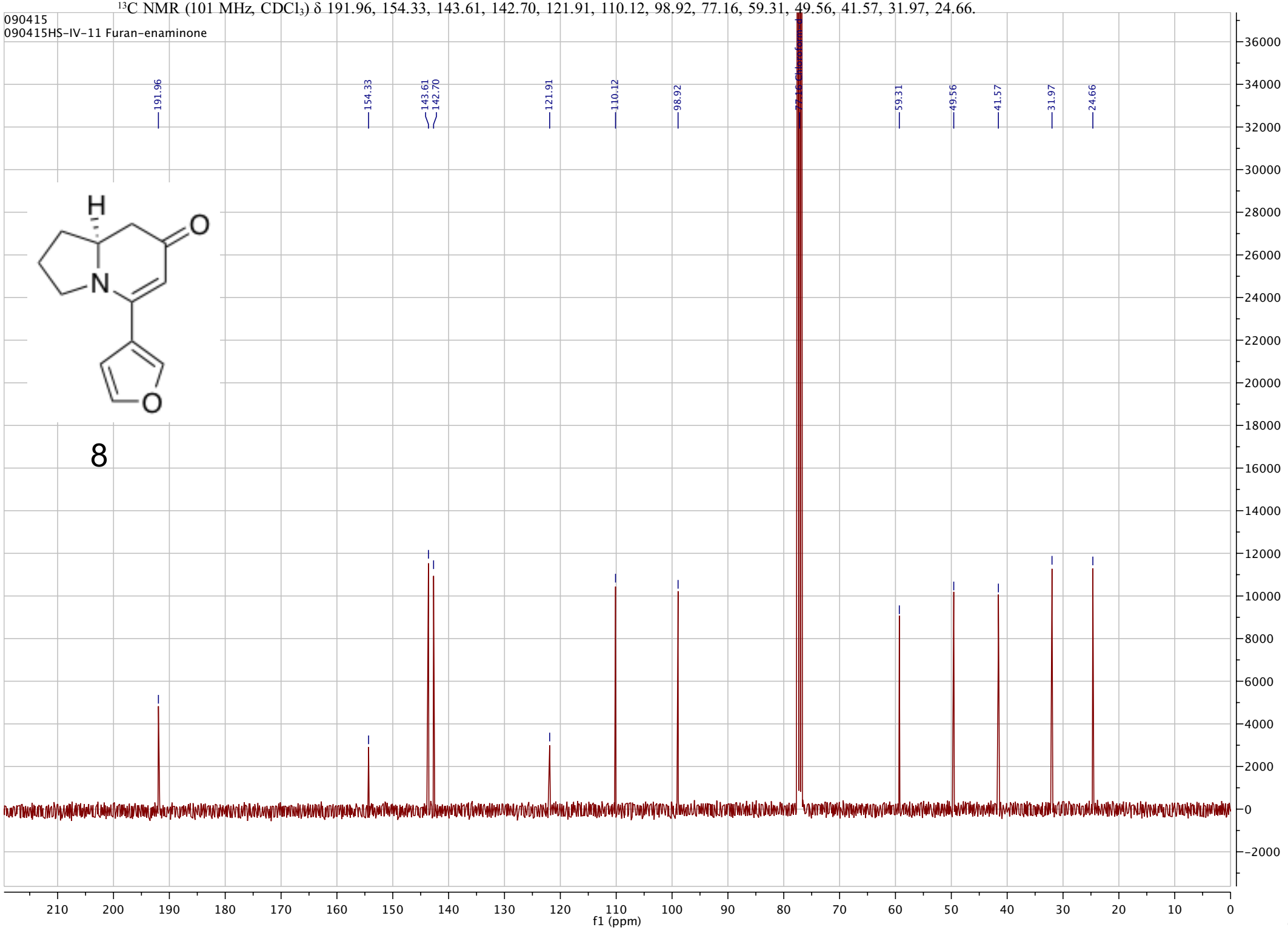
7


110203
110203HS-VI Nuphar3
192.04
191.26
182.35
156.18
147.71
145.94
126.13
109.20
108.97
99.26
81.24
80.87
56.54
49.00 Methanol-d4
47.66
47.10
43.81
42.84
32.01
30.91
28.75
24.34
23.56
O
O
N
Boc
O
7
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 6.53 (d, *J* = 1.0 Hz, 1H), 5.19 (s, 1H), 4.03 – 3.91 (m, 1H), 3.71 – 3.63 (m, 1H), 3.56 – 3.48 (m, 1H), 2.44 (s, 1H), 2.41 (d, *J* = 2.7 Hz, 1H), 2.31 (ddd, *J* = 18.9, 6.7, 4.5 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.94 (tt, *J* = 12.7, 7.8 Hz, 1H), 1.77 (ddd, *J* = 16.5, 12.4, 8.4 Hz, 1H).

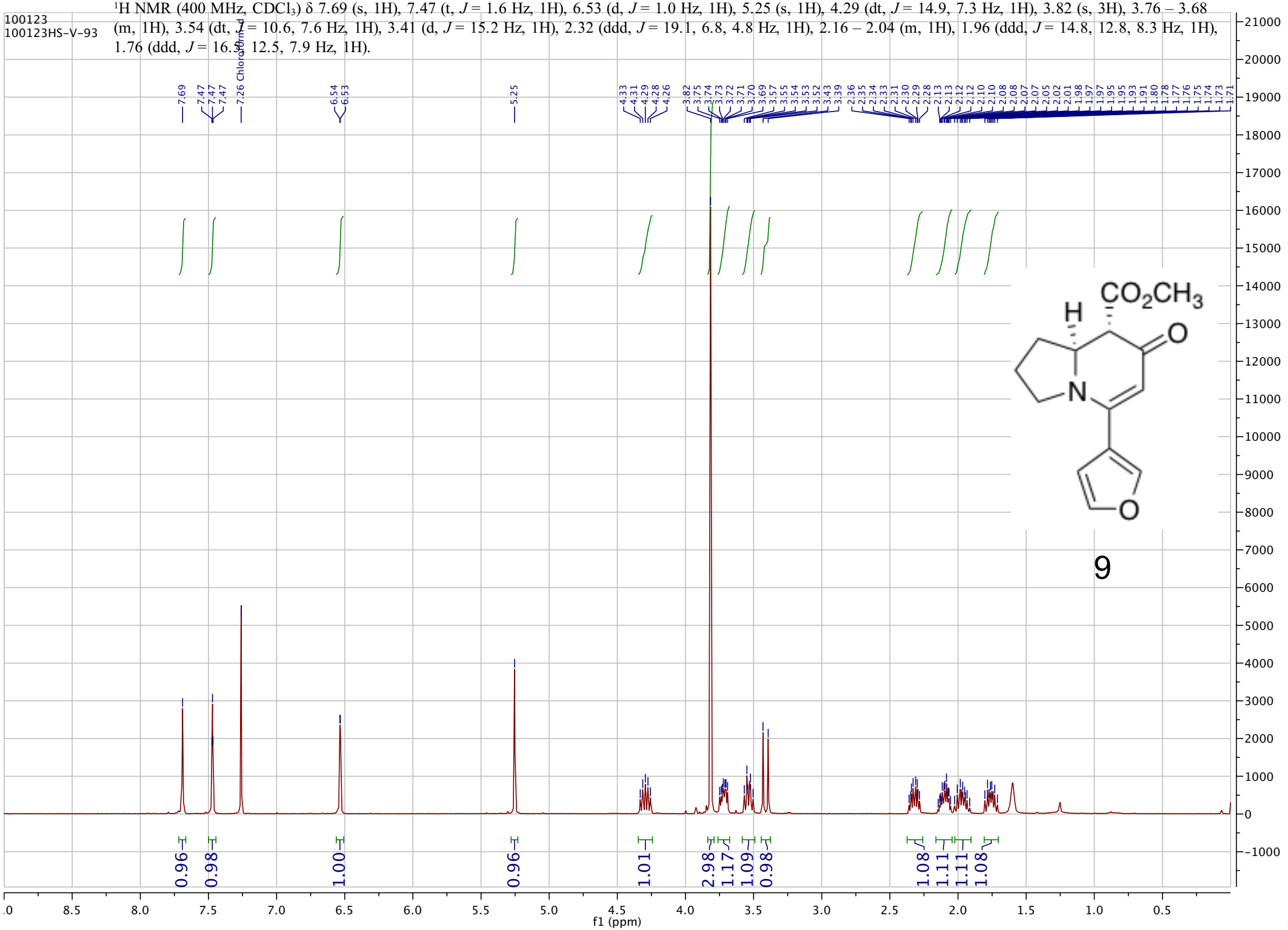


^{13}C NMR (101 MHz, $CDCl_3$) δ 191.96, 154.33, 143.61, 142.70, 121.91, 110.12, 98.92, 77.16, 59.31, 49.56, 41.57, 31.97, 24.66.



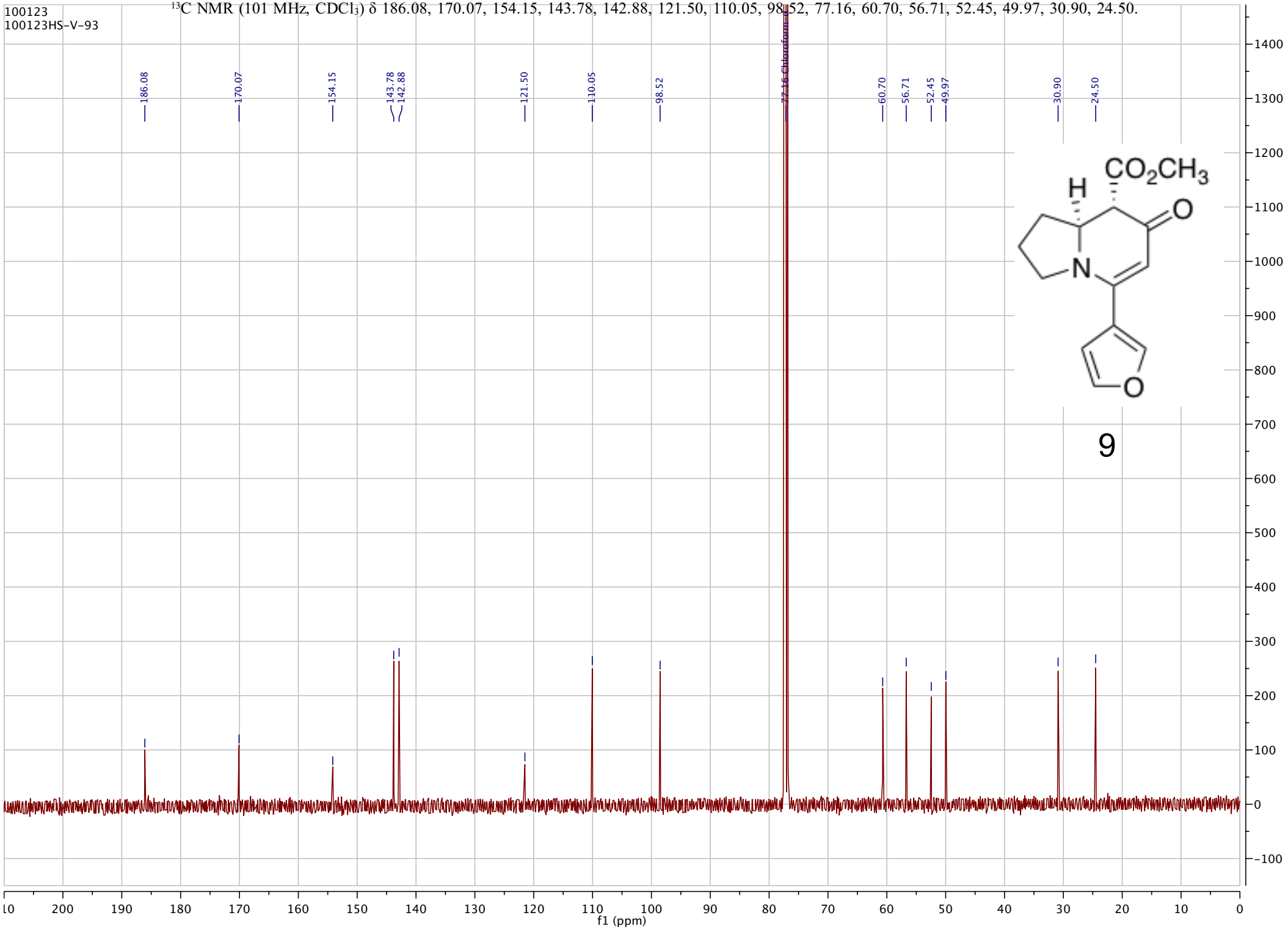
100123
100123HS-V-93

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.47 (t, *J* = 1.6 Hz, 1H), 6.53 (d, *J* = 1.0 Hz, 1H), 5.25 (s, 1H), 4.29 (dt, *J* = 14.9, 7.3 Hz, 1H), 3.82 (s, 3H), 3.76 – 3.68 (m, 1H), 3.54 (dt, *J* = 10.6, 7.6 Hz, 1H), 3.41 (d, *J* = 15.2 Hz, 1H), 2.32 (ddd, *J* = 19.1, 6.8, 4.8 Hz, 1H), 2.16 – 2.04 (m, 1H), 1.96 (ddd, *J* = 14.8, 12.8, 8.3 Hz, 1H), 1.76 (ddd, *J* = 16.5, 12.5, 7.9 Hz, 1H).



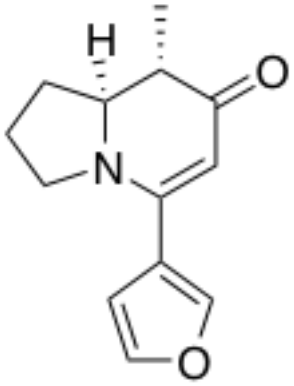
9

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.08, 170.07, 154.15, 143.78, 142.88, 121.50, 110.05, 98.52, 77.16, 60.70, 56.71, 52.45, 49.97, 30.90, 24.50.



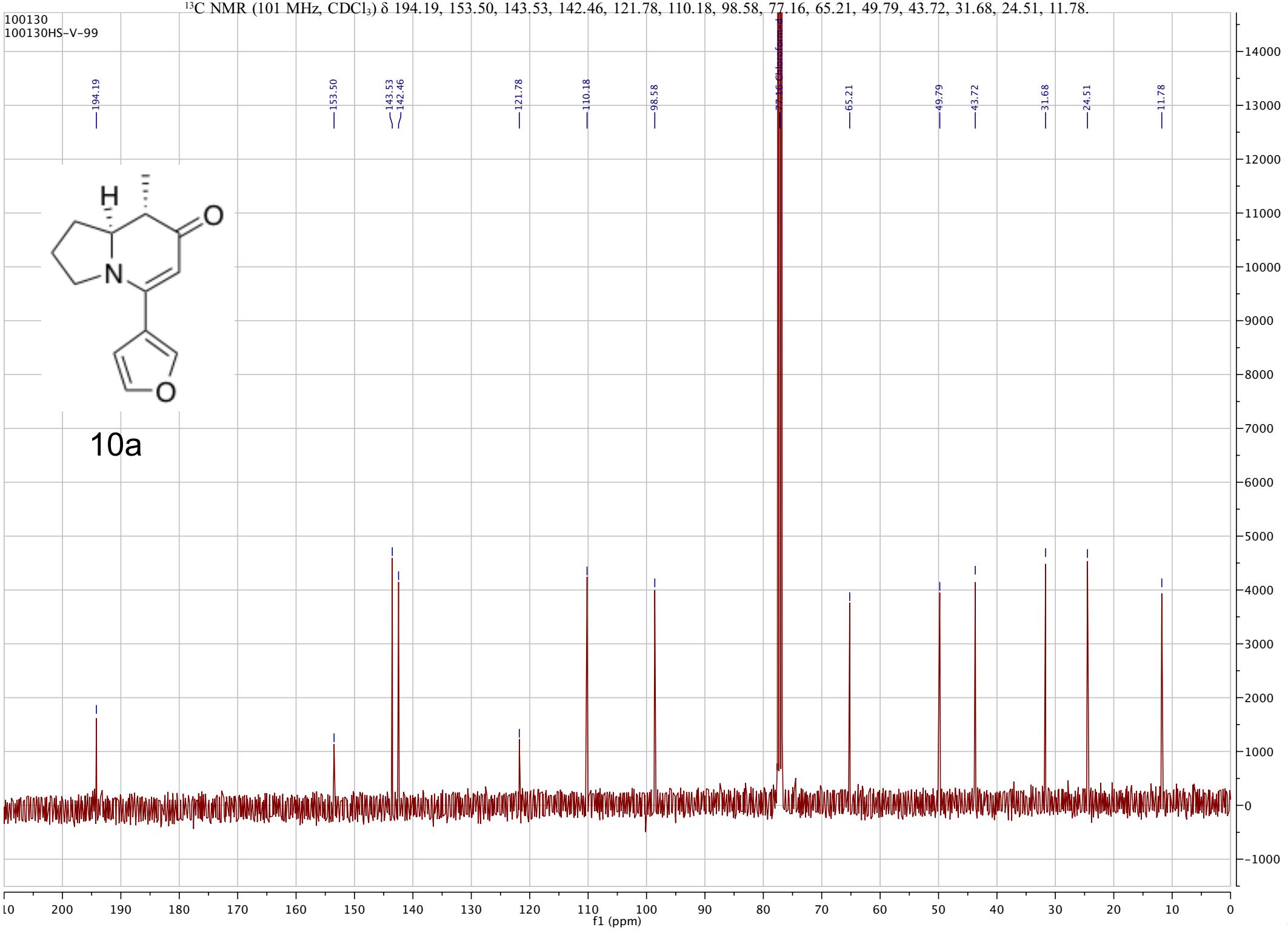
100130
100130HS-V-99

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 1H), 7.45 (t, *J* = 1.7 Hz, 1H), 6.53 (dd, *J* = 1.8, 0.8 Hz, 1H), 5.21 (s, 1H), 3.77 – 3.67 (m, 1H), 3.51 (ddd, *J* = 14.2, 13.8, 7.7 Hz, 2H), 2.33 (dtd, *J* = 12.6, 6.5, 3.2 Hz, 1H), 2.23 (dq, *J* = 13.7, 6.8 Hz, 1H), 2.09 (dddd, *J* = 14.1, 10.6, 7.2, 3.5 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.84 – 1.73 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H).



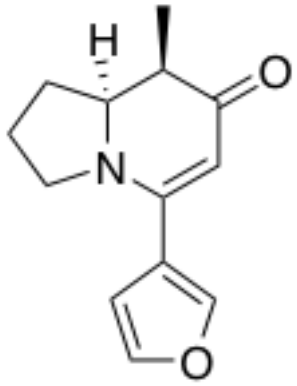
10a

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.19, 153.50, 143.53, 142.46, 121.78, 110.18, 98.58, 77.16, 65.21, 49.79, 43.72, 31.68, 24.51, 11.78.



110103
110103HS-VI-117 minor

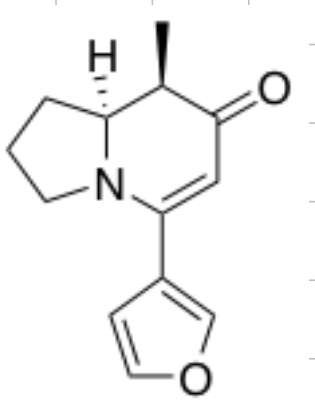
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.46 (t, *J* = 1.6 Hz, 1H), 6.57 – 6.52 (m, 1H), 5.12 (s, 1H), 4.04 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.74 – 3.67 (m, 1H), 3.54 (dt, *J* = 10.7, 6.9 Hz, 1H), 2.31 – 2.23 (qd, *J* = 7.3, 4.0 Hz, 1H), 2.14 – 2.03 (m, 2H), 2.01 – 1.90 (m, 2H), 1.04 (d, *J* = 7.3 Hz, 3H).



10b

110103
110103HS-VI-117 minor

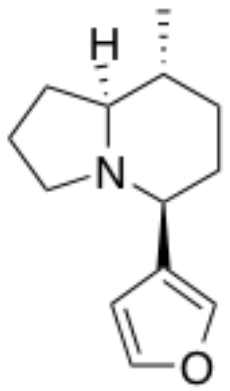
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.90, 153.31, 143.61, 142.59, 121.63, 110.10, 96.98, 77.16, 62.42, 49.89, 42.50, 27.08, 24.98, 10.95.



10b

101024
101024HS-VI-60

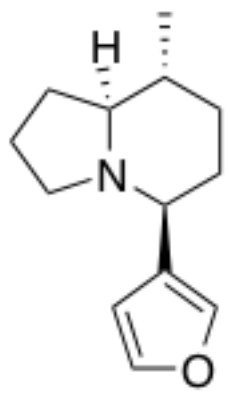
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 0.9 Hz, 2H), 6.44 (s, 1H), 2.95 – 2.84 (m, 2H), 1.93 (ddd, *J* = 23.6, 12.8, 7.4 Hz, 2H), 1.83 – 1.36 (m, 9H), 1.14 – 1.00 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H).



1

101024
101024HS-VI-60

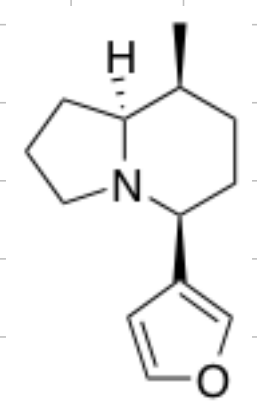
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.84, 139.45, 128.40, 109.88, 77.16, 71.58, 59.91, 53.31, 36.57, 34.32, 34.05, 29.21, 20.25, 18.98.



1

110112
110112HS-VI-124

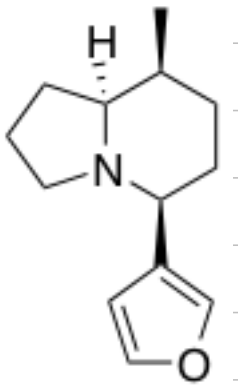
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 6.43 (s, 1H), 2.90 – 2.83 (m, 2H), 2.14 – 2.06 (m, 1H), 1.93 (td, *J* = 6.8, 2.8 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.70 – 1.53 (m, 7H), 1.52 – 1.45 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H).



2

110112
110112HS-VI-124

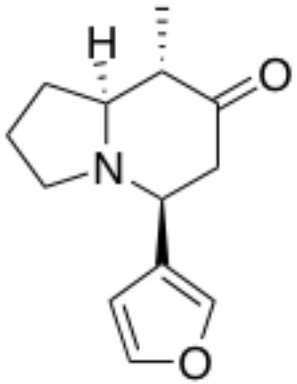
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.74, 139.21, 128.95, 109.89, 67.69, 61.07, 53.58, 32.34, 29.62, 29.14, 27.04, 20.27, 12.35.



2

100201
100201HS-V-102

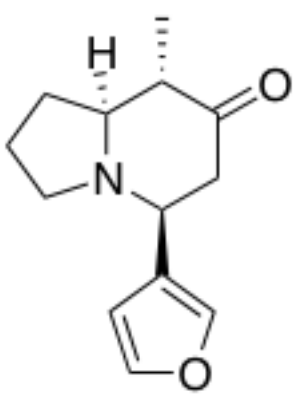
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H), 6.47 (s, 1H), 3.34 (dd, *J* = 11.9, 3.2 Hz, 1H), 2.94 (dd, *J* = 12.4, 5.4 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.50 – 2.39 (m, 2H), 2.09 – 1.97 (m, 3H), 1.92 – 1.58 (m, 3H), 1.04 (d, *J* = 6.6 Hz, 3H).



11

100201
100201HS-V-102

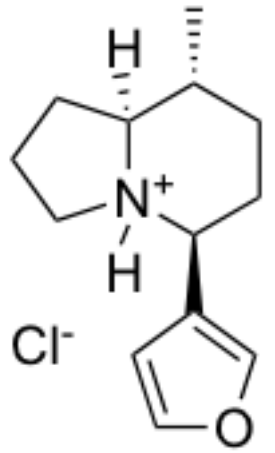
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.82, 143.57, 139.63, 126.81, 109.08, 70.53, 58.05, 52.24, 50.49, 48.60, 30.53, 21.50, 10.65.



11

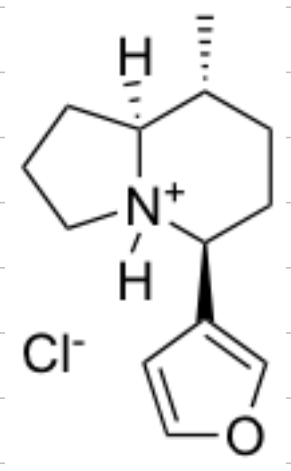
120104
120104 Nuphar HCl salt

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 7.68 (s, 1H), 7.41 (s, 1H), 7.09 (d, *J* = 1.4 Hz, 1H), 3.67 (t, *J* = 9.8 Hz, 1H), 3.44 (s, 1H), 2.75 – 2.47 (m, 4H), 2.26 (m Hz, 3H), 2.05 (dd, *J* = 13.6, 2.8 Hz, 1H), 1.94 (m, 2H), 1.35 – 1.21 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H).



120104
120104 Nuphar HCl salt

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.33, 141.56, 121.11, 110.48, 73.90, 61.62, 51.86, 32.99, 32.85, 31.47, 27.51, 19.22, 18.55, 0.13.



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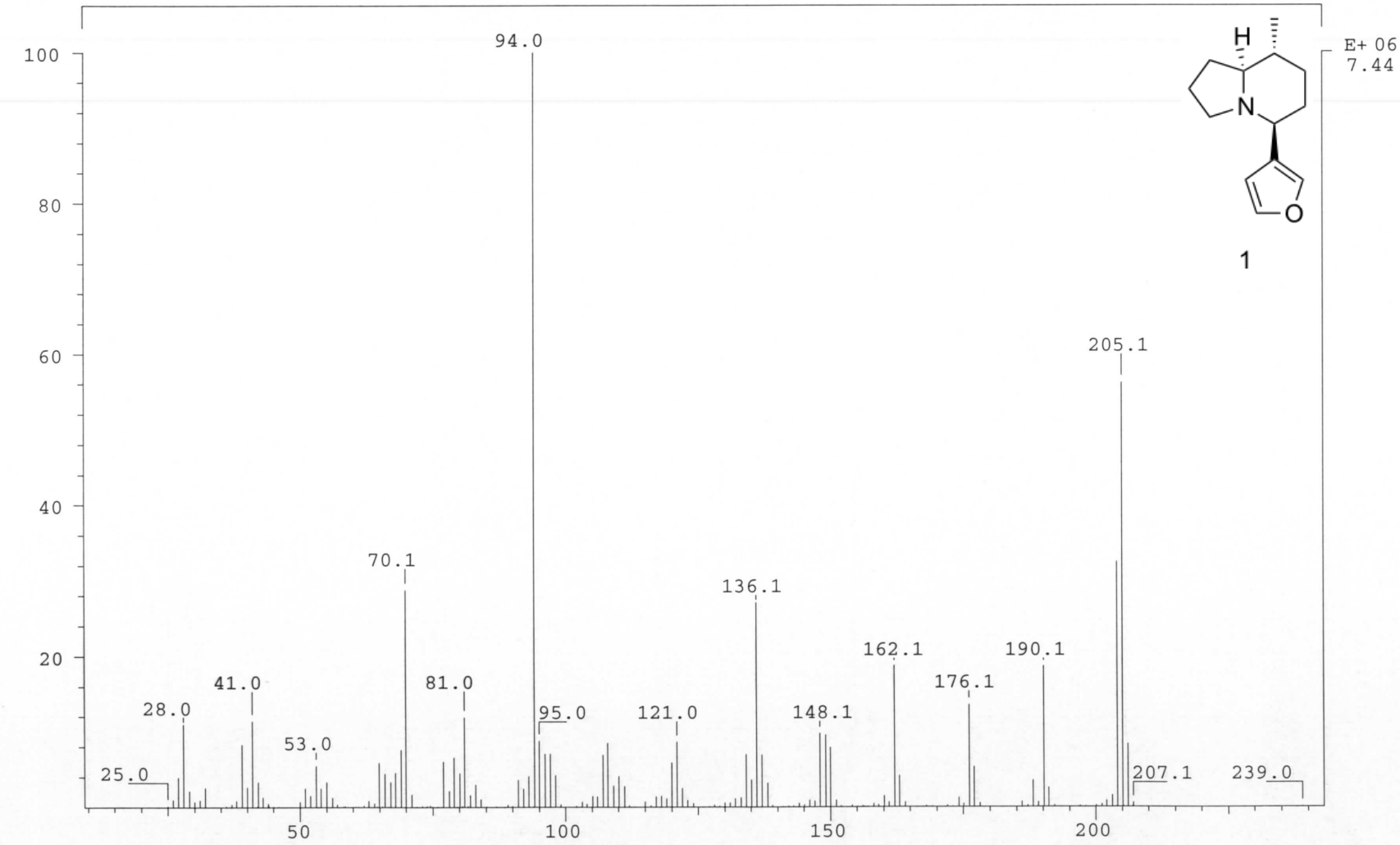
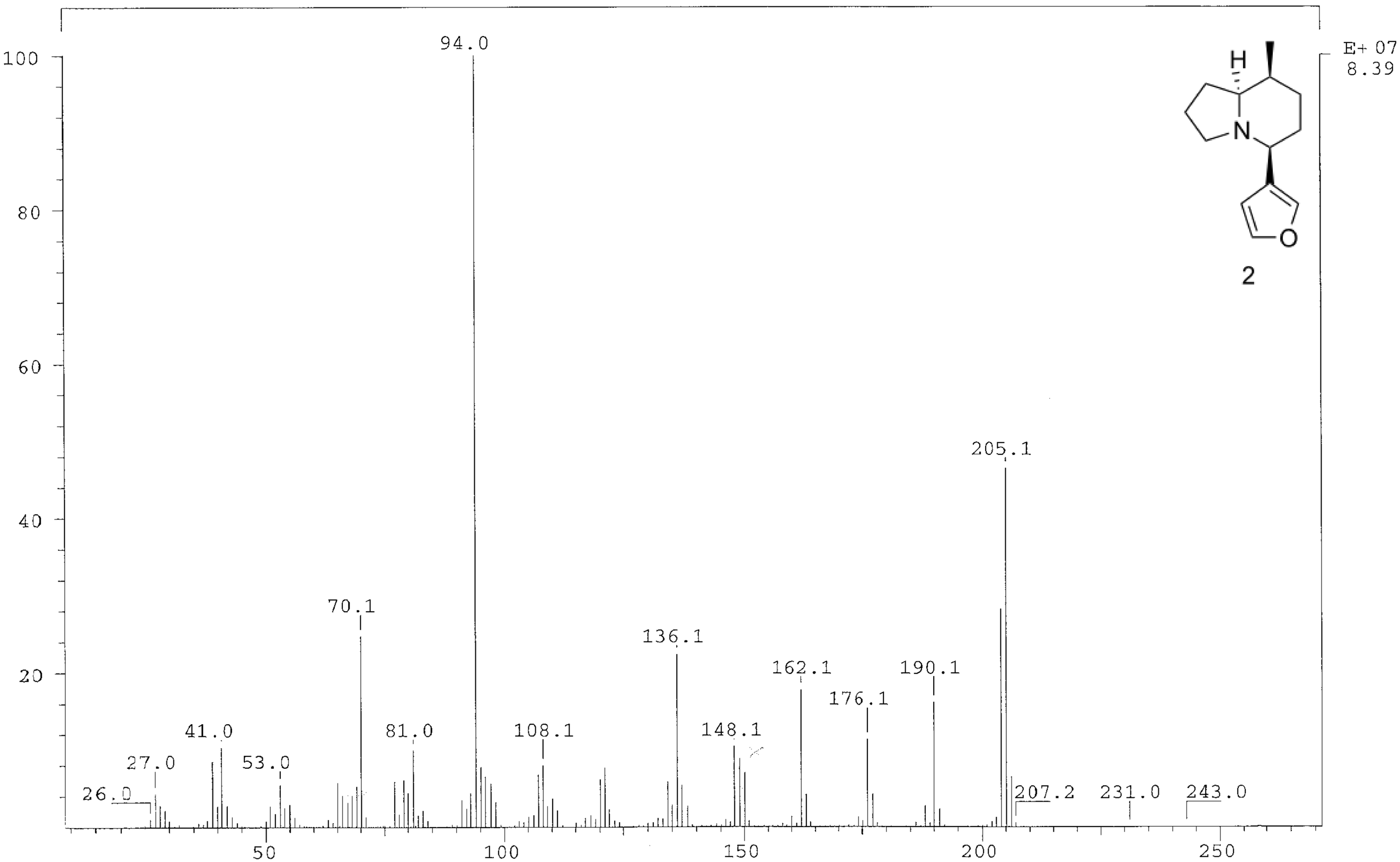
SPEC:  e94511ga                                03-May-11   Elapse:  10:25.4      764
Samp:  HS VI 219                                           Start :  13:39:22    3339
Comm:  70 eV LR EI GCMS D85 cap col [50(1)_15_320(5)] 1500 res
Mode:  EI +VE +LMR  BSCAN (EXP) UP LR NRM
Oper:                                                      Inlet :
Base:  94.0                 Inten :  7443870               Masses:  20 > 650
Norm:  94.0                 RIC   :  45999722              #peaks:  192
Peak:  0.00  mmu
```



1

SPEC: e94626gl 18-May-11 Elapse: 10:33.9 771
Samp: HSVI-119 Start : 10:35:15 1752
Comm: 70 eV LR EI GCMS D85 cap col [50(1)_15_320(5)] 1500 res
Mode: EI +VE +LMR BSCAN (EXP) UP LR NRM
Oper: Inlet :
Base: 94.0 Inten : 83909888 Masses: 20 > 650
Norm: 94.0 RIC : 463473432 #peaks: 292
Peak: 0.00 mmu



2