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Supplementary Material

Six-step total syntheses of (−)-galanthamine and (−)-*N*-norgalanthamine

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Supplementary Material

for

Six-Step Total Syntheses of (–)-Galanthamine and (–)-*N*-Norgalanthamine

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Contents

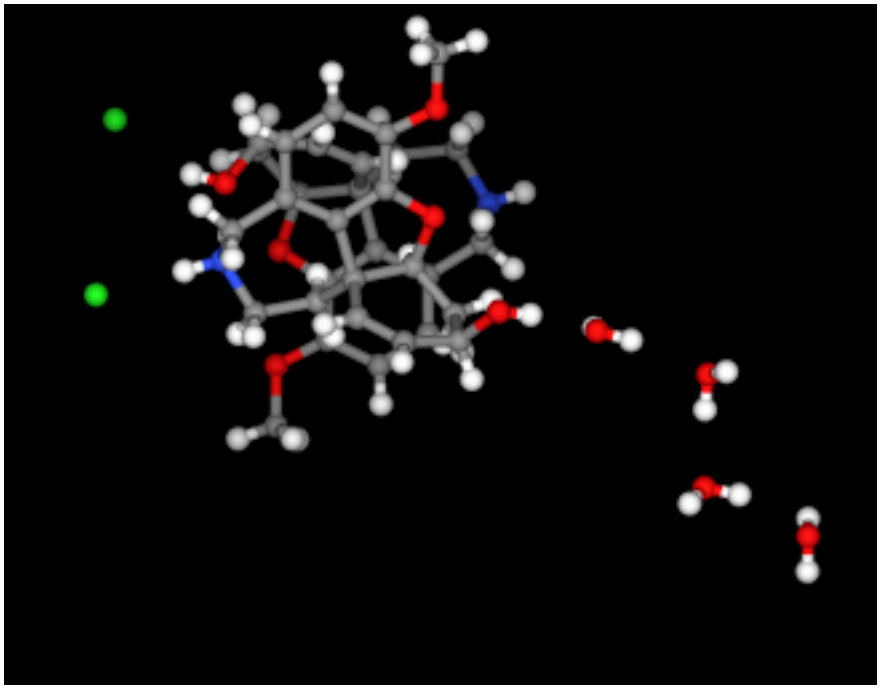


Figure S1: Plot derived from the single-crystal X-ray analysis of compound **2** (CCDC 2175431) showing two molecules of the hydrochloride salt and four molecules of water (crystal grown from fractions obtained after flash chromatographic purification on silica gel using 20:1 v/v dichloromethane/methanol as the eluting solvent).

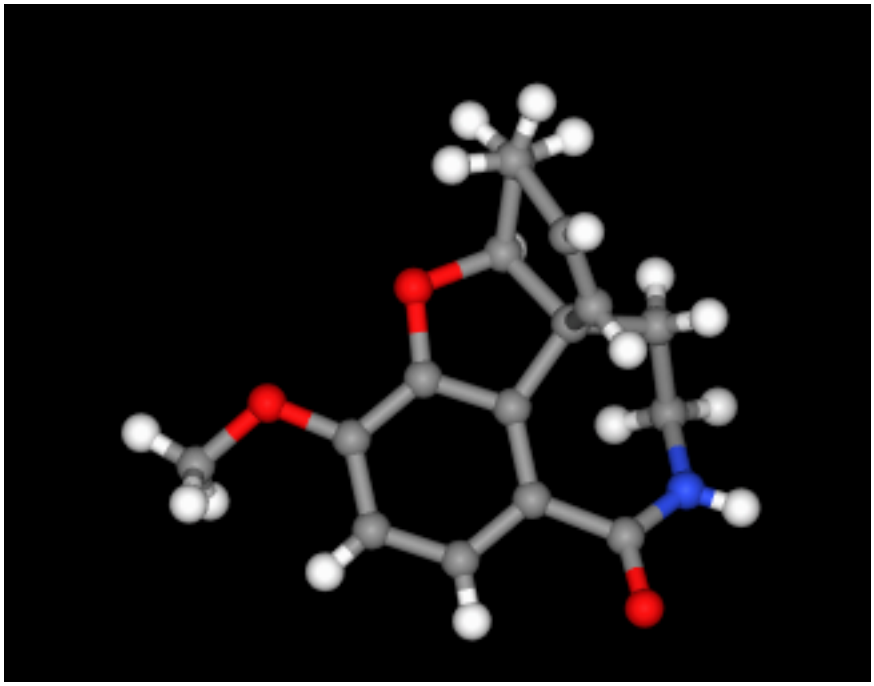


Figure S2: Plot derived from the single-crystal X-ray analysis of compound **11** (CCDC 2175430) (crystal grown using the vapour diffusion technique conducted at ambient temperatures and a dichloromethane/hexane solvent system).

Table 1: ^{13}C NMR Spectral Comparisons for Galanthamine (1)

Galanthamine[a,b] δ_C	Authentic Sample[b,c] δ_C	Compound **1**[b,d] δ_C	$\Delta\delta_C$[e]
146.0	145.8	145.8	0
144.3	144.1	144.2	+0.1
133.2	133.0	132.9	–0.1
129.2	129.1	128.4	–0.7
127.8	127.6	127.7	+0.1
126.9	126.8	126.6	–0.2
122.3	122.1	122.3	+0.2
114.4	111.2	111.2	0
88.9	88.7	88.7	0
62.2	62.0	62.0	0
60.7	60.6	60.3	–0.3
56.1	55.9	55.9	0
54.0	53.8	53.6	–0.2
48.4	48.2	48.1	–0.1
42.2	42.0	41.6	–0.4
33.9	33.7	33.5	–0.2
30.1	29.9	29.9	0

[a]data reported in ref. 1 for (±)-**1**; [b]recorded in $CDCl_3$; [c]commercially-derived (–)-galanthamine; [d]sample prepared using the route shown in Schemes 1 and 2; [e]difference between chemical shift observed for the authentic and synthetic samples.

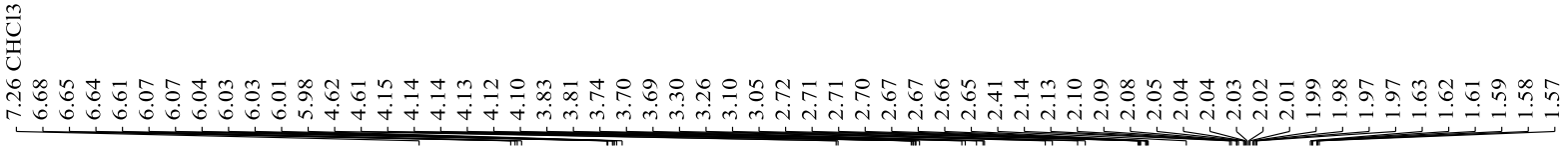
Table 2: ^{13}C NMR Spectral Comparisons for *N*-Norgalanthamine (2)

Norgalanthamine[a,b] δ_C	Authentic Sample[b,c] δ_C	Compound **2**[b,d] δ_C	$\Delta\delta_C$[e]
146.2	146.2	146.3	+0.1
143.9	144.1	144.1	0
133.1	133.2	133.2	0
133.0	133.0	133.0	0
127.6	127.7	127.7	0
127.0	127.1	127.0	–0.1
120.5	120.7	120.8	+0.1
111.0	111.1	111.1	0
88.5	88.6	88.6	0
61.9	62.0	62.0	0
55.8	55.9	56.0	+0.1
53.8	53.9	53.9	0
48.7	48.7	48.7	0
47.0	47.1	47.1	0
40.3	40.2	40.2	0
29.9	29.9	29.9	0

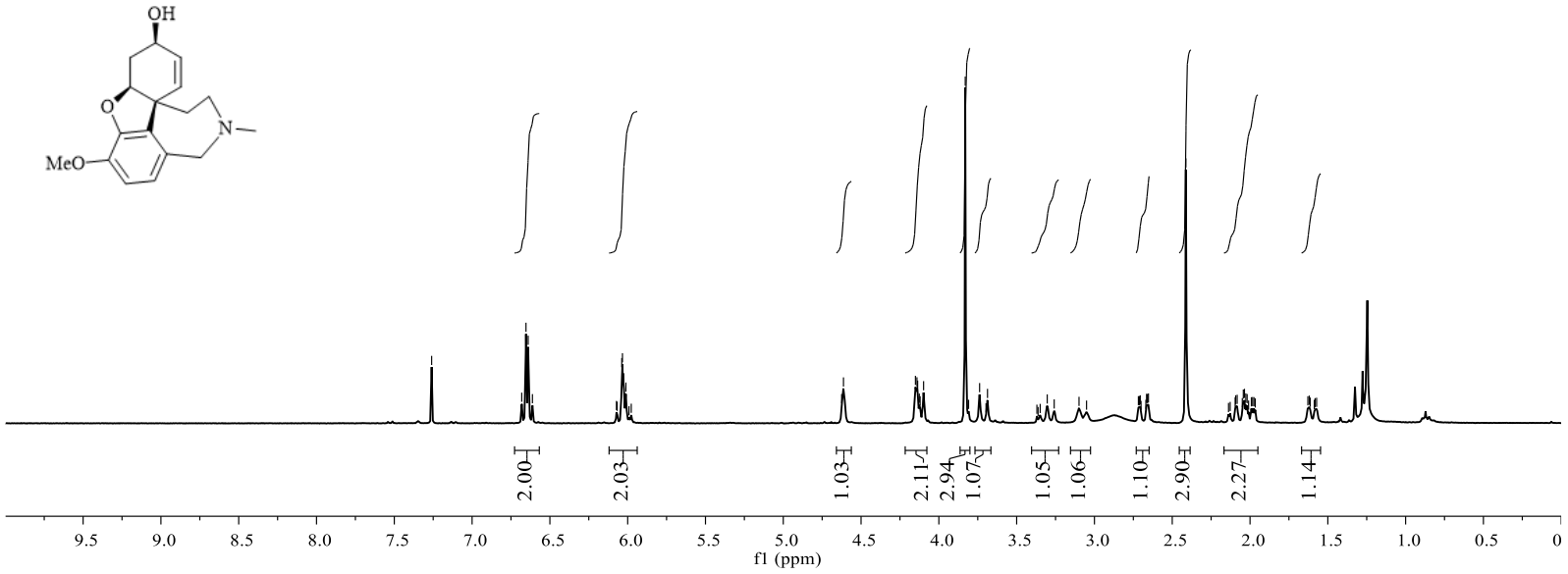
[a]data reported in ref. 2 for (–)-**2**; [b]recorded in $CDCl_3$; [c]sample prepared by Dr Yu-Tao He by *N*-demethylation of commercially-derived (–)-galanthamine; [d]sample prepared by Mr Nan Hu using the route shown in Schemes 1 and 3; [e]differences in chemical shift observed for the authentic and synthetic samples.

References

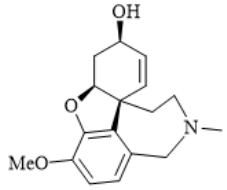
1. Nugent, J.; Banwell, M. G. An Eleven-step Synthesis of Galanthamine from Commercially Available Materials. *Eur. J. Org. Chem*. **2016**, 5862-5867.
2. Jordis, U.; Treu, M.; Hirnscahll, M.; Frohlich, J.; Crollner, L.; Kalz, B.; Kalz, T.; Kuhnhackl, P. Methods for Producing Norgalanthamine, As Well As Isomers, Salts and Hydrates Thereof. US 2006/0069251 A1 patent, Mar. 30, **2006**.

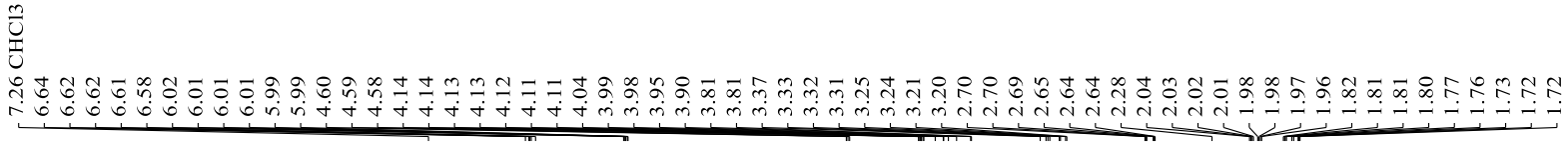


300 MHz ^{1}H NMR Spectrum of Compound **1** (recorded in $CDCl_3$)



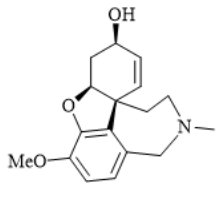
75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **1** (recorded in $CDCl_3$)





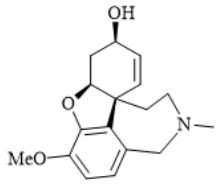
300 MHz ^{1}H NMR Spectrum of Compound **1·D/HCl**

(recorded in $CDCl_3$)

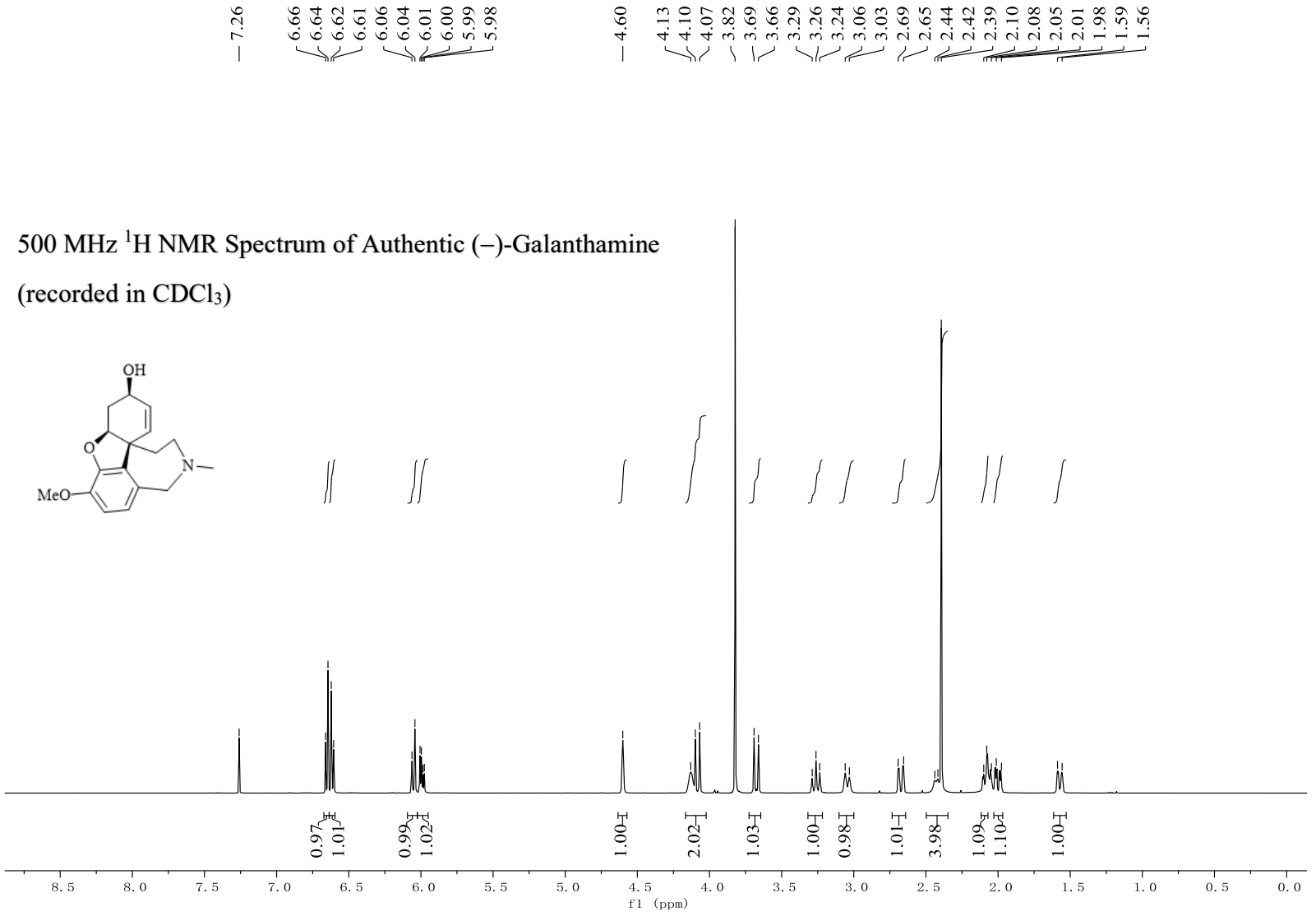


75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **1·D/HCl**

(recorded in $CDCl_3$)



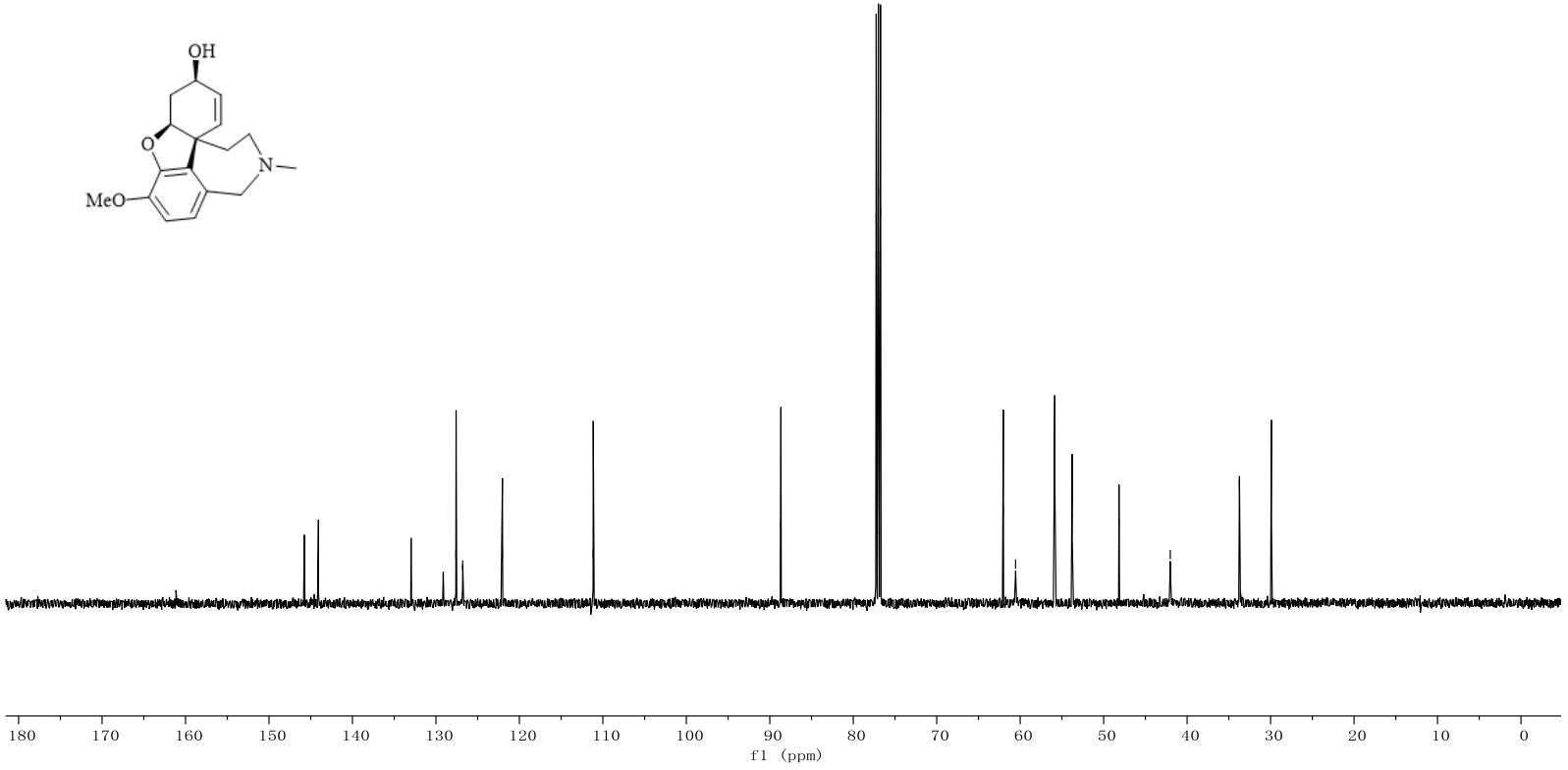
·D/HCl

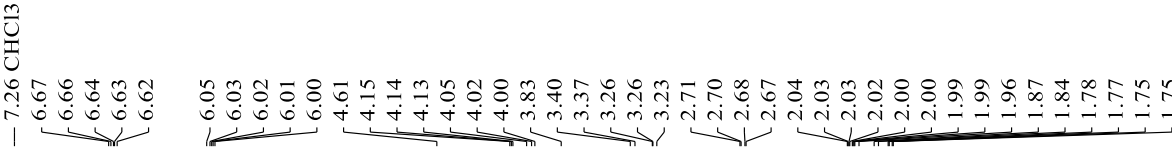

7.26
6.66
6.64
6.62
6.61
6.06
6.04
6.01
6.00
5.99
5.98
4.60
4.13
4.10
4.07
3.82
3.69
3.66
3.29
3.26
3.24
3.06
3.03
2.69
2.65
2.44
2.42
2.39
2.10
2.08
2.05
2.01
1.98
1.59
1.56
500 MHz ^{1}H NMR Spectrum of Authentic (−)-Galanthamine
(recorded in $CDCl_3$)
OH
O
N
MeO
0.97
1.01
0.99
1.02
1.00
2.02
1.03
1.00
0.98
1.01
3.98
1.09
1.10
1.00
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
f1 (ppm)

145.78
144.09
132.99
129.13
127.60
126.79
122.05
111.16
88.68
77.25
77.00
76.75
62.03
60.55
55.87
53.78
48.17
42.02
33.73
29.90

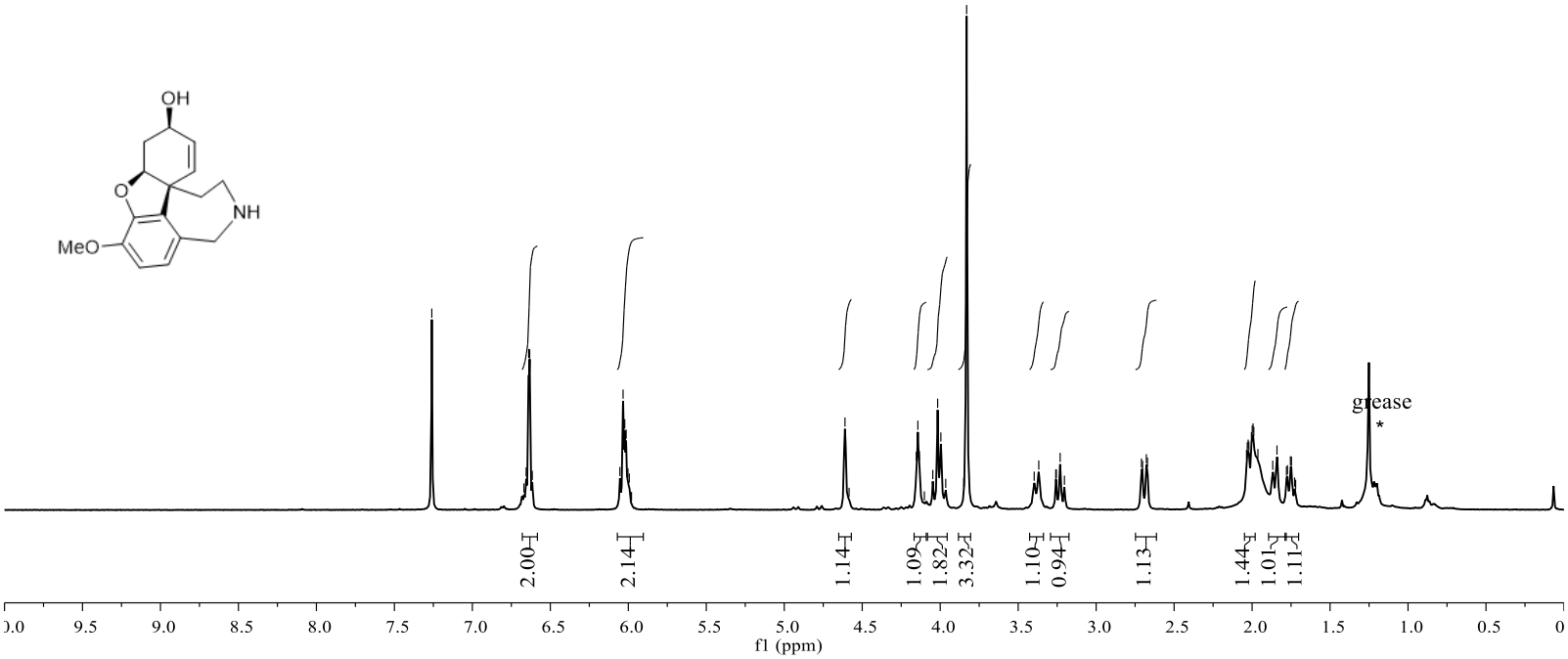
126 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Authentic (–)-Galanthamine

(recorded in $CDCl_3$)

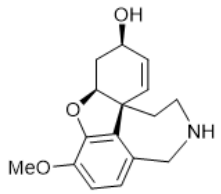




300 MHz ^{1}H NMR Spectrum of Synthetically-derived Compound **2** (recorded in $CDCl_3$)

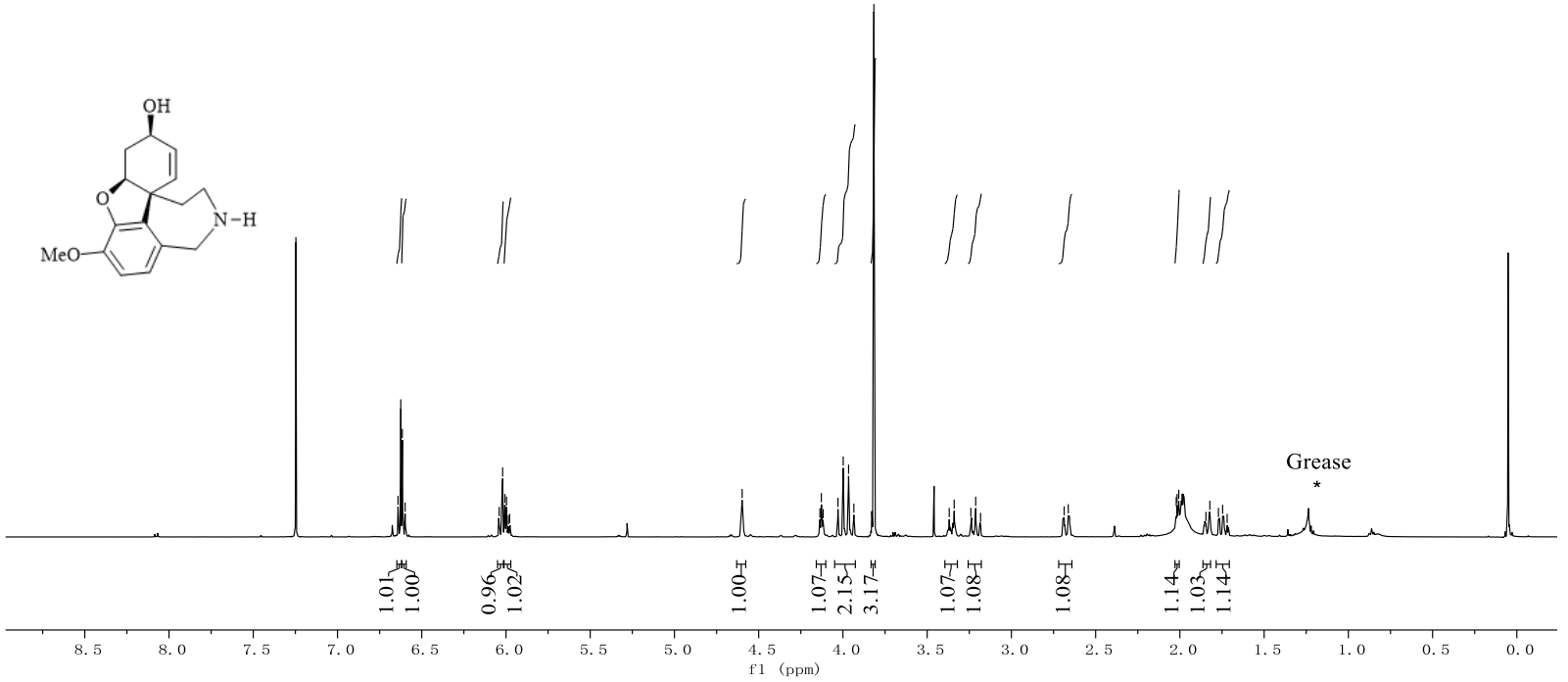


75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Synthetically-derived Compound **2** (recorded in $CDCl_3$)

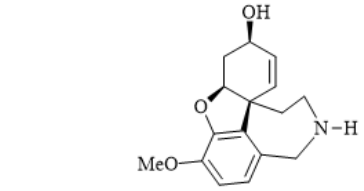


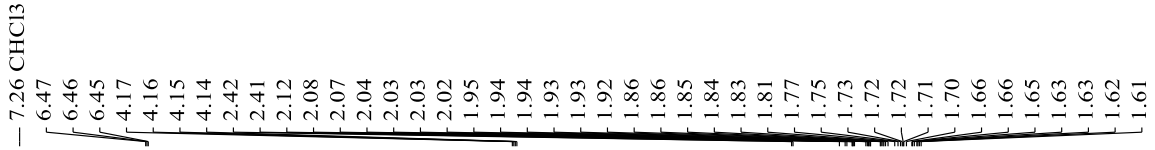
500 MHz ^{1}H NMR Spectrum of Compound **2** Derived

from Authentic (–)-Galanthamine (recorded in $CDCl_3$)

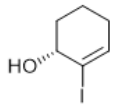


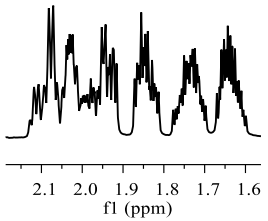
126 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **2** Derived from Authentic (–)-Galanthamine (recorded in $CDCl_3$)

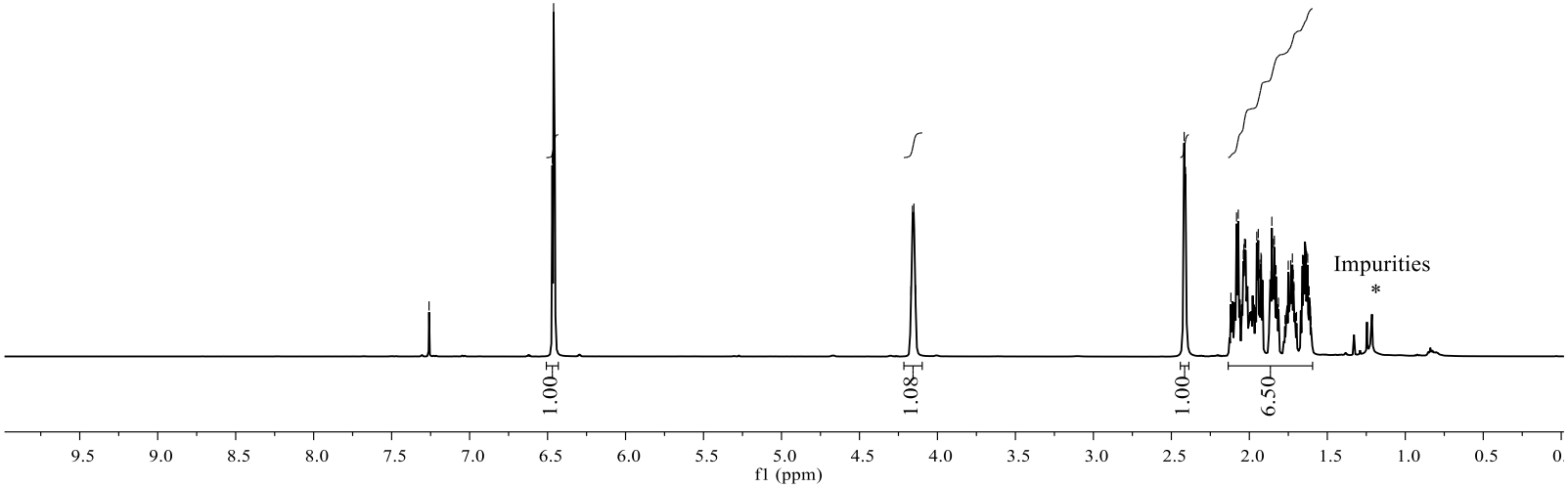




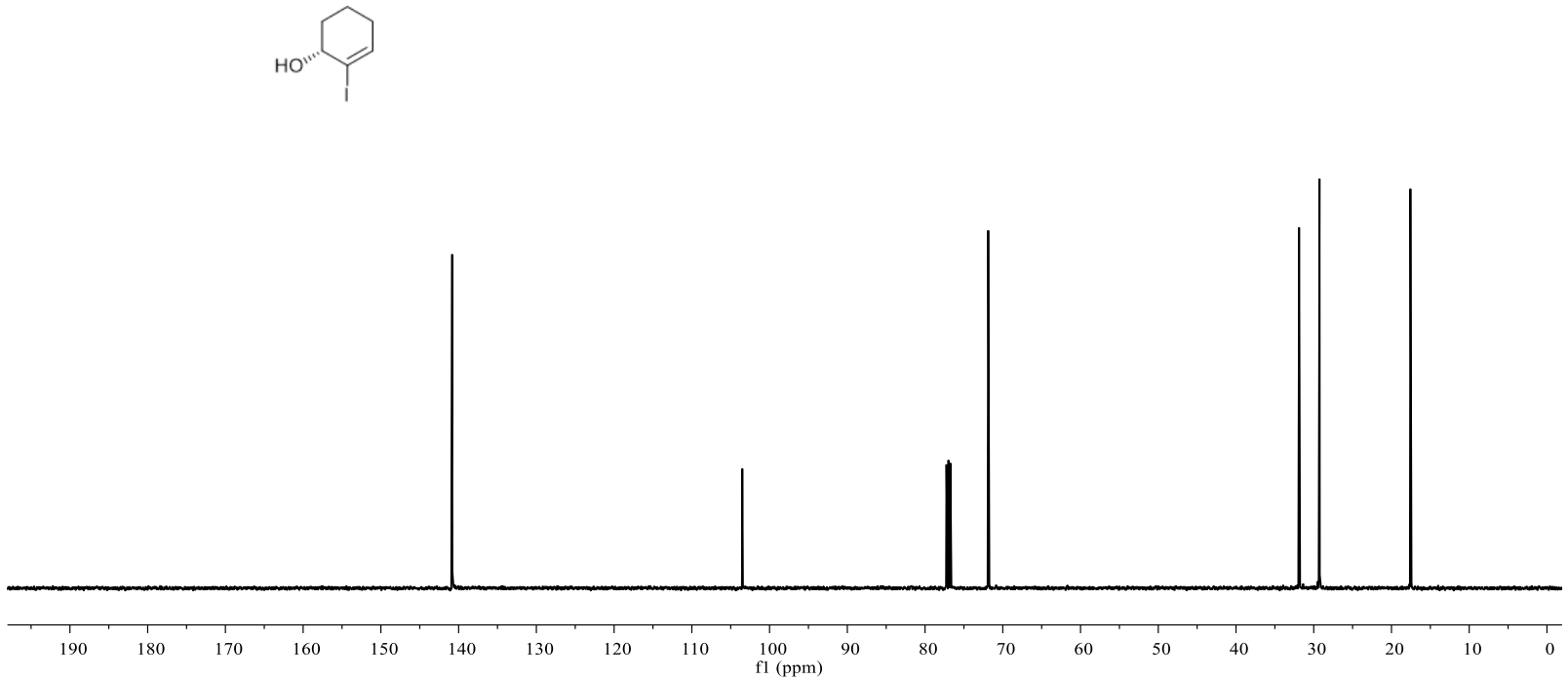
500 MHz ^{1}H NMR Spectrum of Compound **3** (recorded in $CDCl_3$)

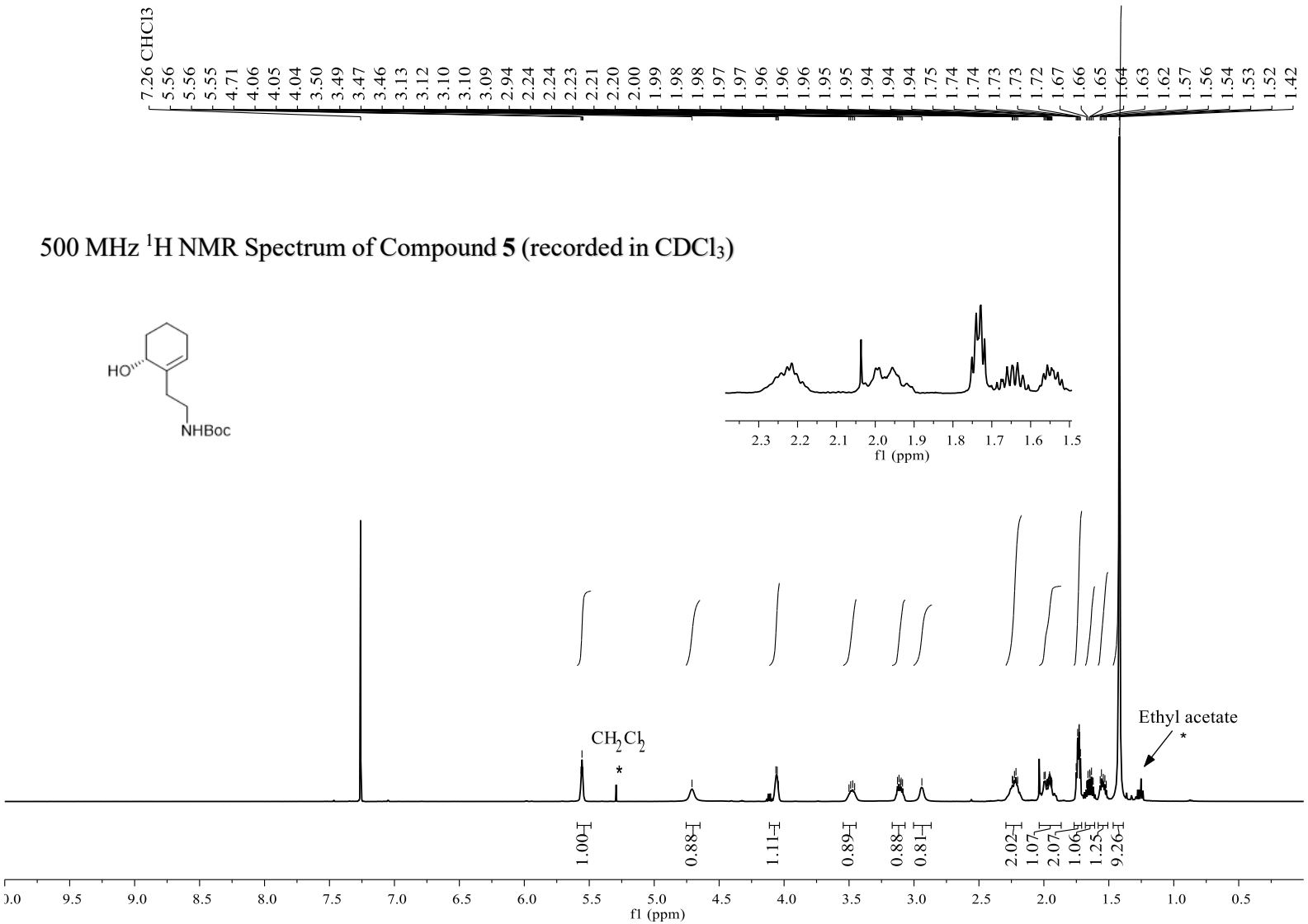






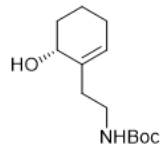
126 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **3** (recorded in $CDCl_3$)

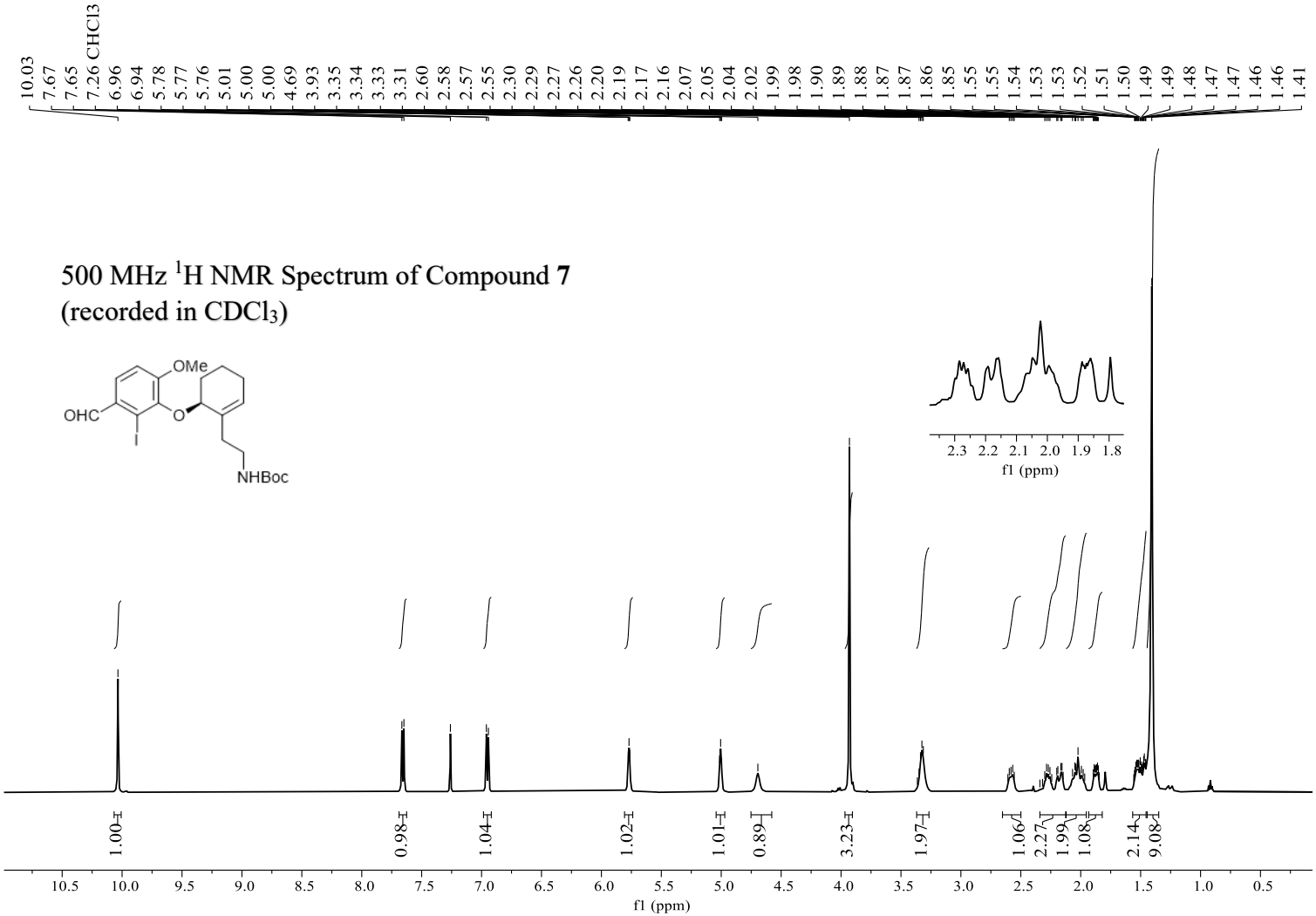




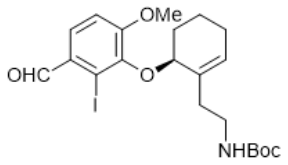
500 MHz ^{1}H NMR Spectrum of Compound **5** (recorded in $CDCl_3$)

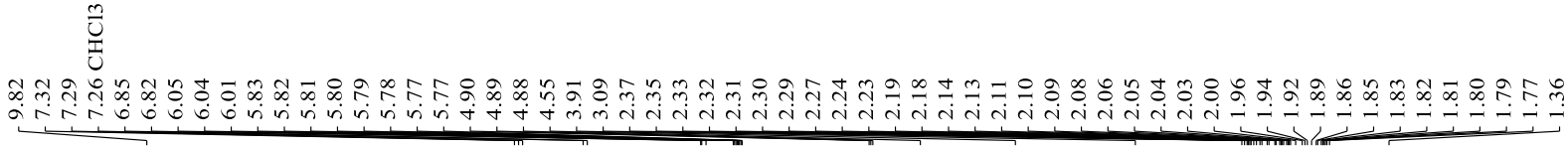
126 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)



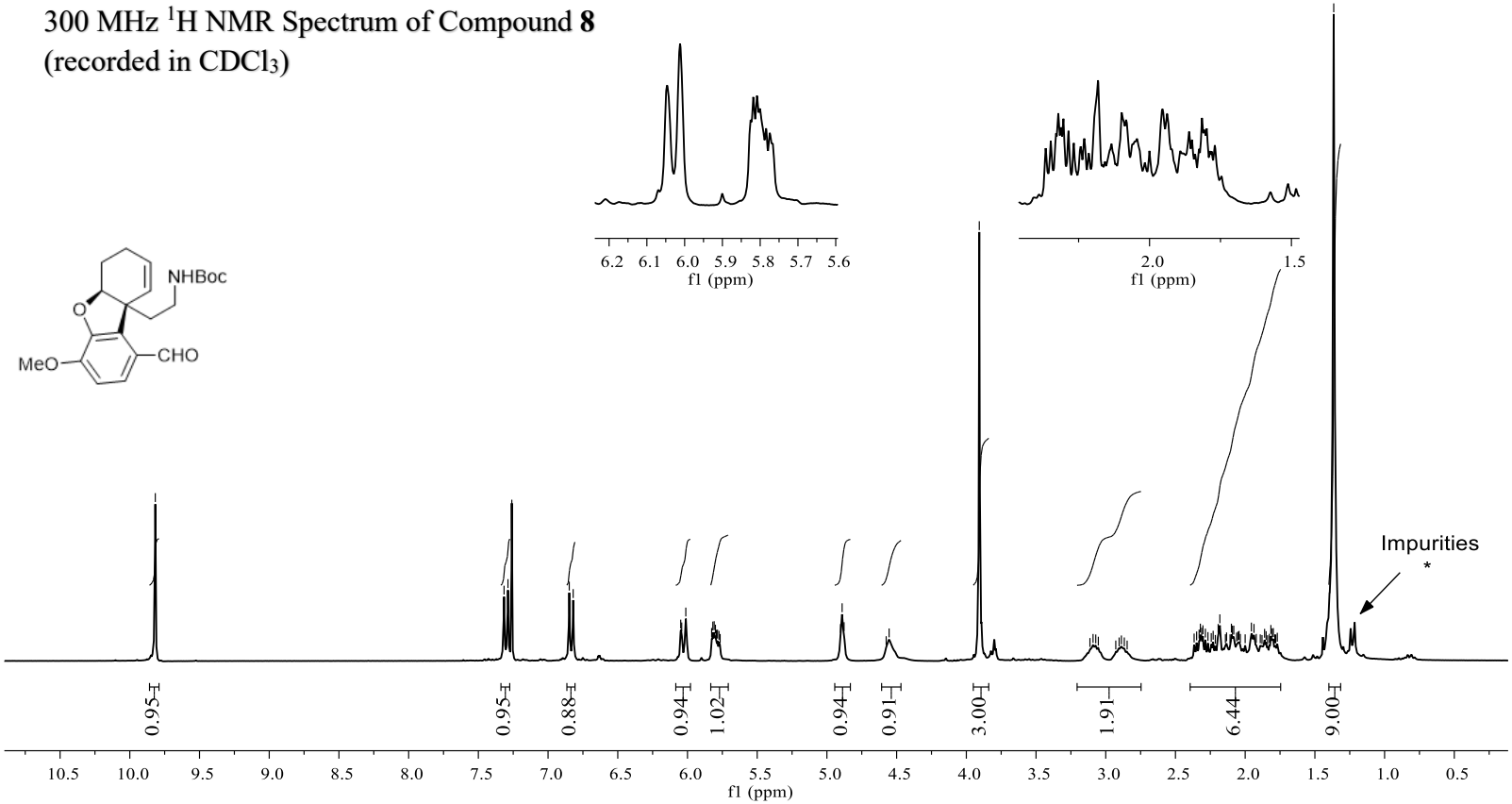

10.03
7.67
7.65
7.26 CHCl3
6.96
6.94
5.78
5.77
5.76
5.01
5.00
5.00
4.69
3.93
3.35
3.34
3.33
3.31
2.60
2.58
2.57
2.55
2.30
2.29
2.27
2.26
2.20
2.19
2.17
2.16
2.07
2.05
2.04
2.02
1.99
1.98
1.90
1.89
1.88
1.87
1.87
1.86
1.85
1.55
1.55
1.54
1.53
1.53
1.52
1.51
1.50
1.49
1.49
1.48
1.47
1.47
1.46
1.46
1.41
500 MHz 1H NMR Spectrum of Compound 7
(recorded in CDCl3)
OMe
OHC
O
I
NHBoc
2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
1.00
0.98
1.04
1.02
1.01
0.89
3.23
1.97
1.06
2.27
1.99
1.08
2.14
9.08
10.5 10.0 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)

126 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)



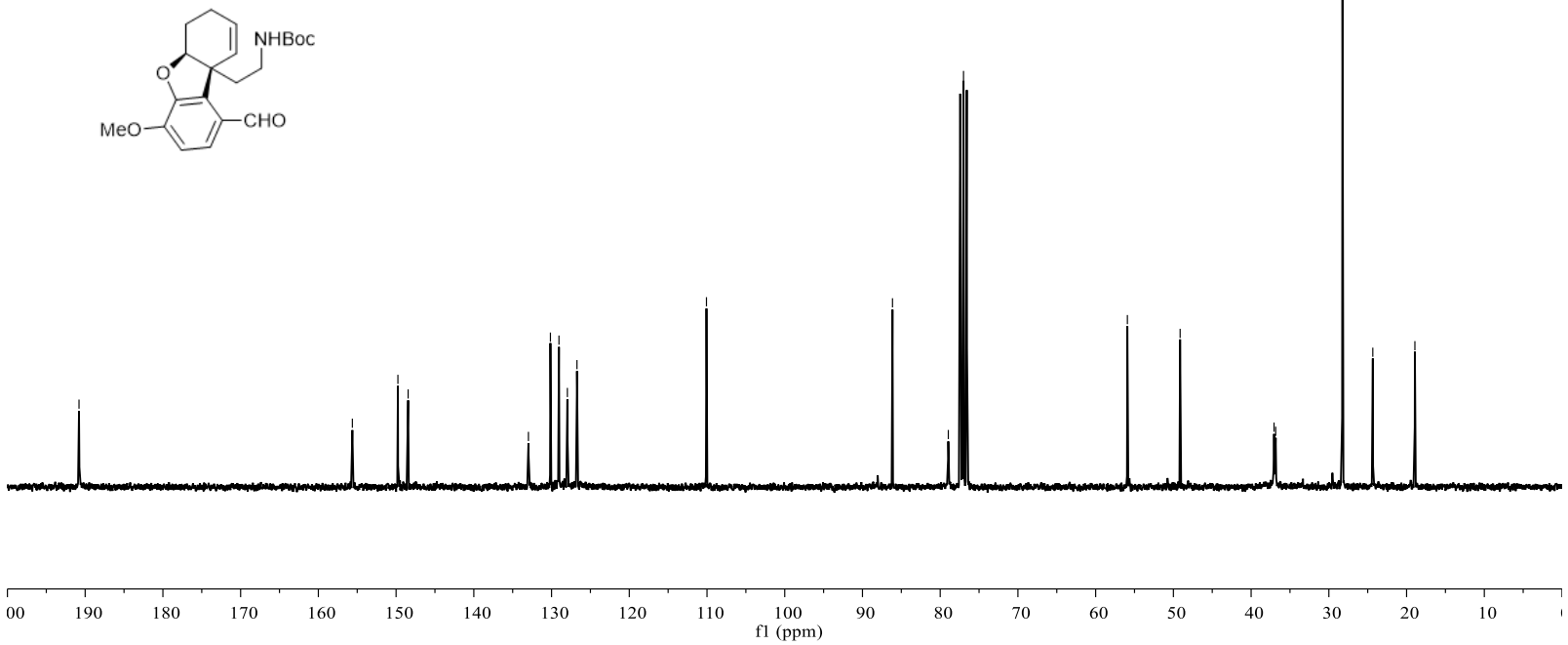


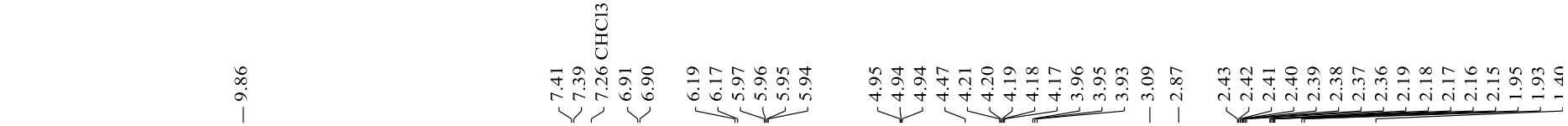
300 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



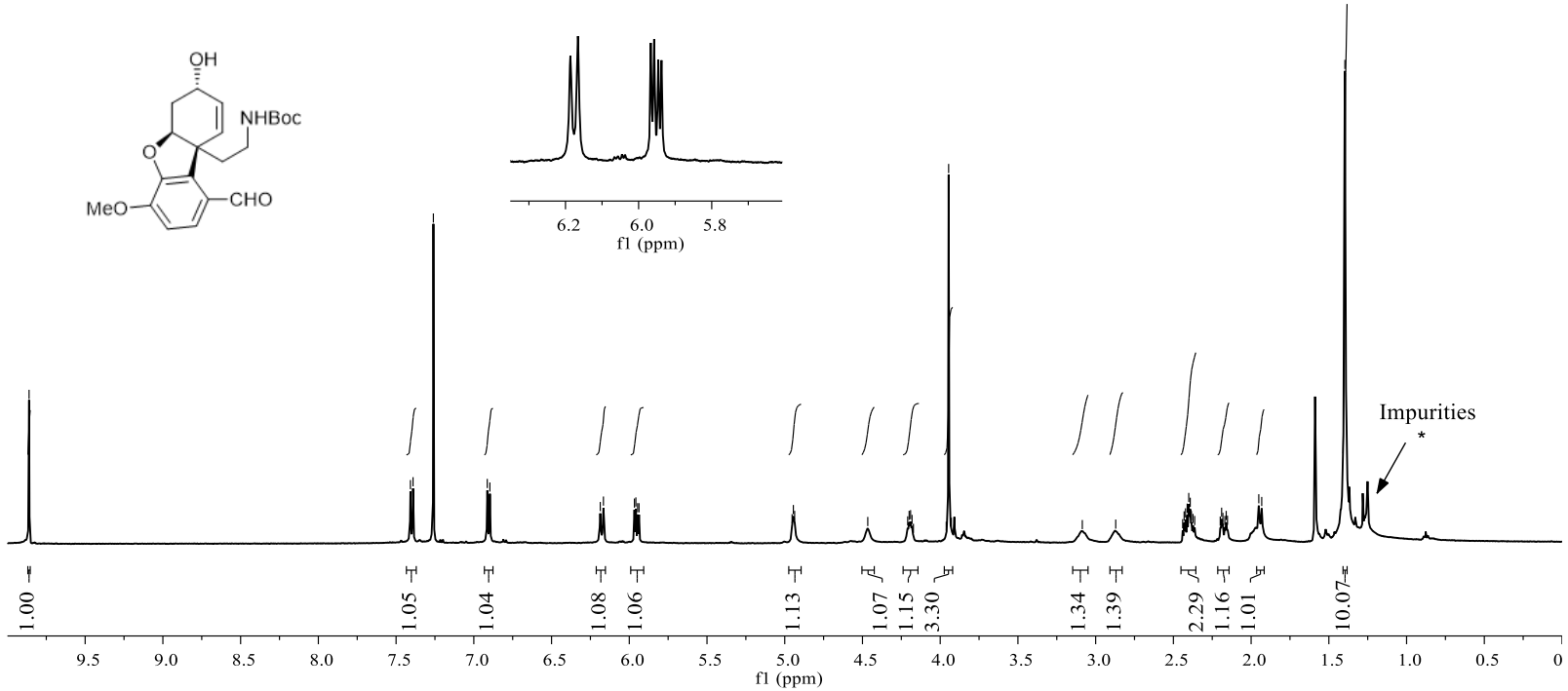
190.79
155.62
149.76
148.45
132.97
130.14
129.04
127.96
126.73
110.07
86.14
78.96
77.00 CDCl3
55.92
49.13
37.05
36.84
28.25
24.35
18.93

75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)

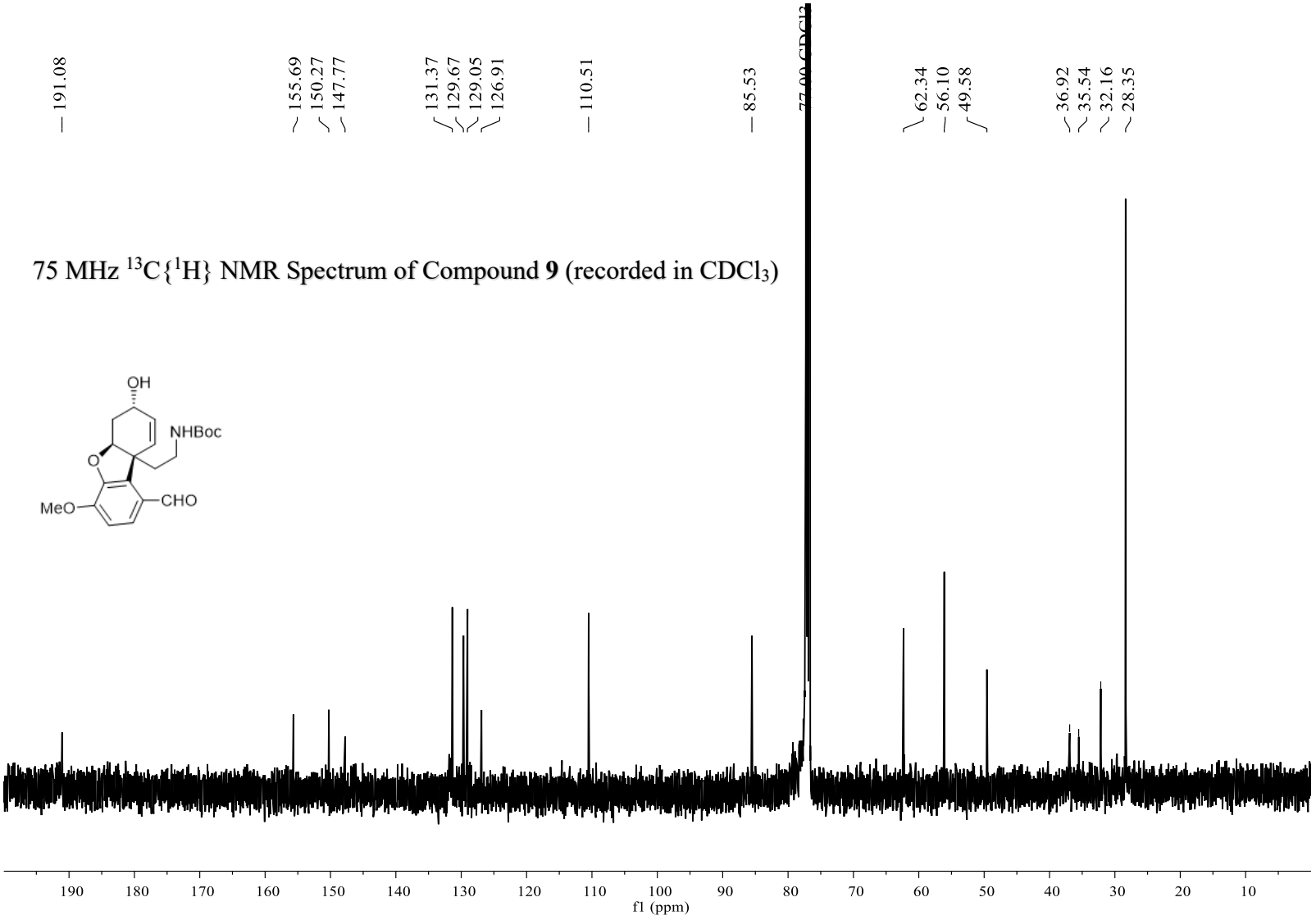


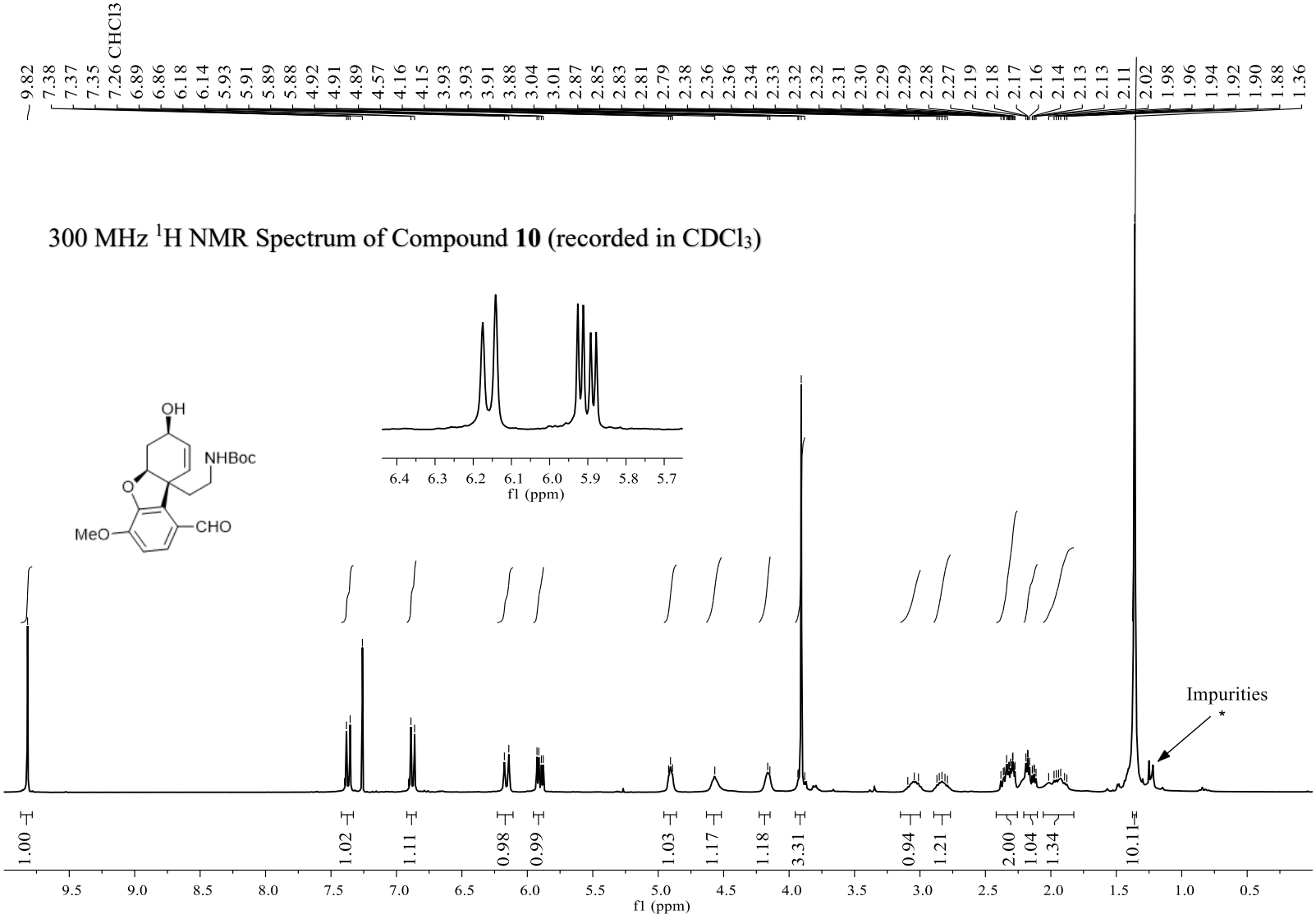


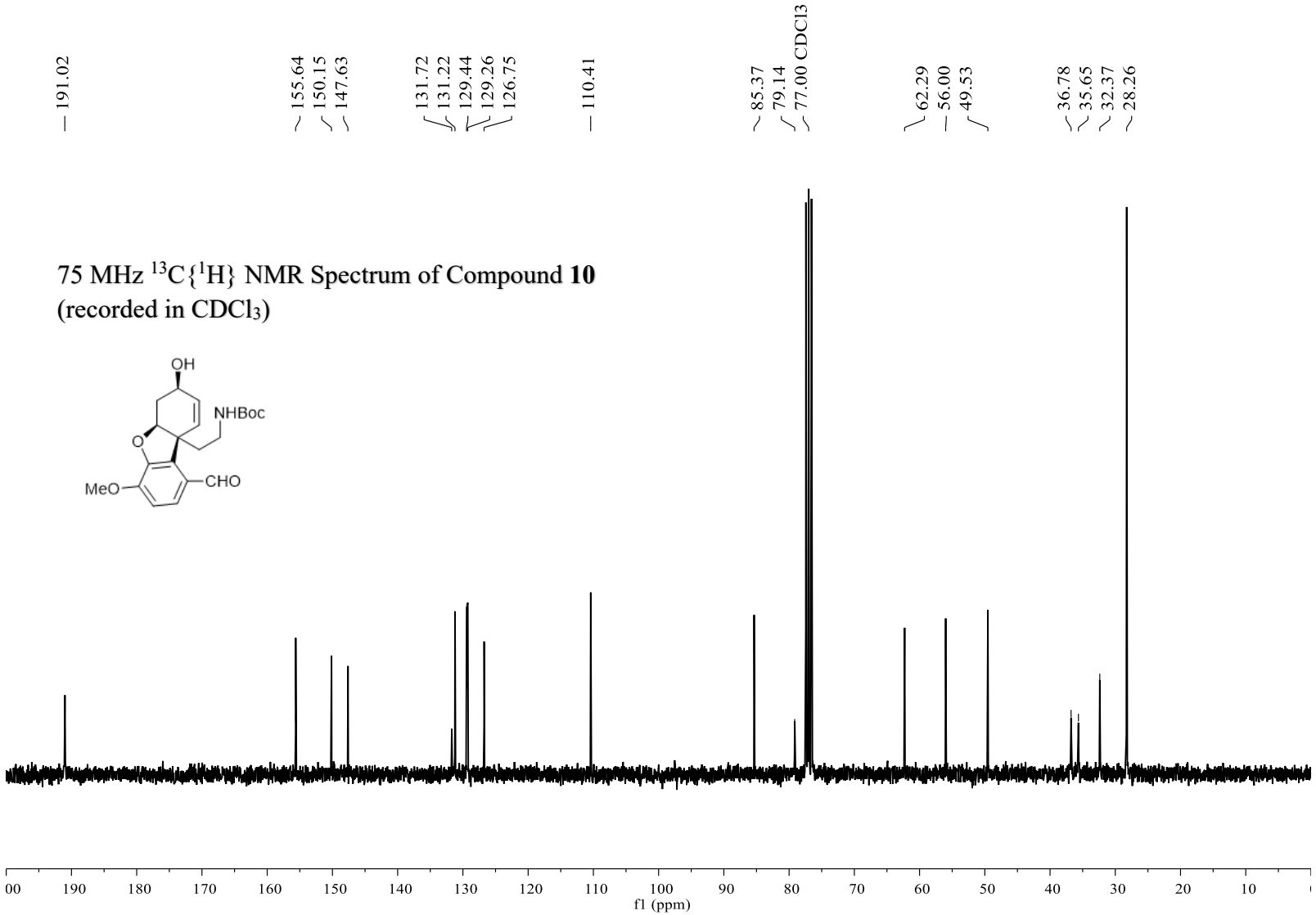
300 MHz ^{1}H NMR Spectrum of Compound **9** (recorded in $CDCl_3$)



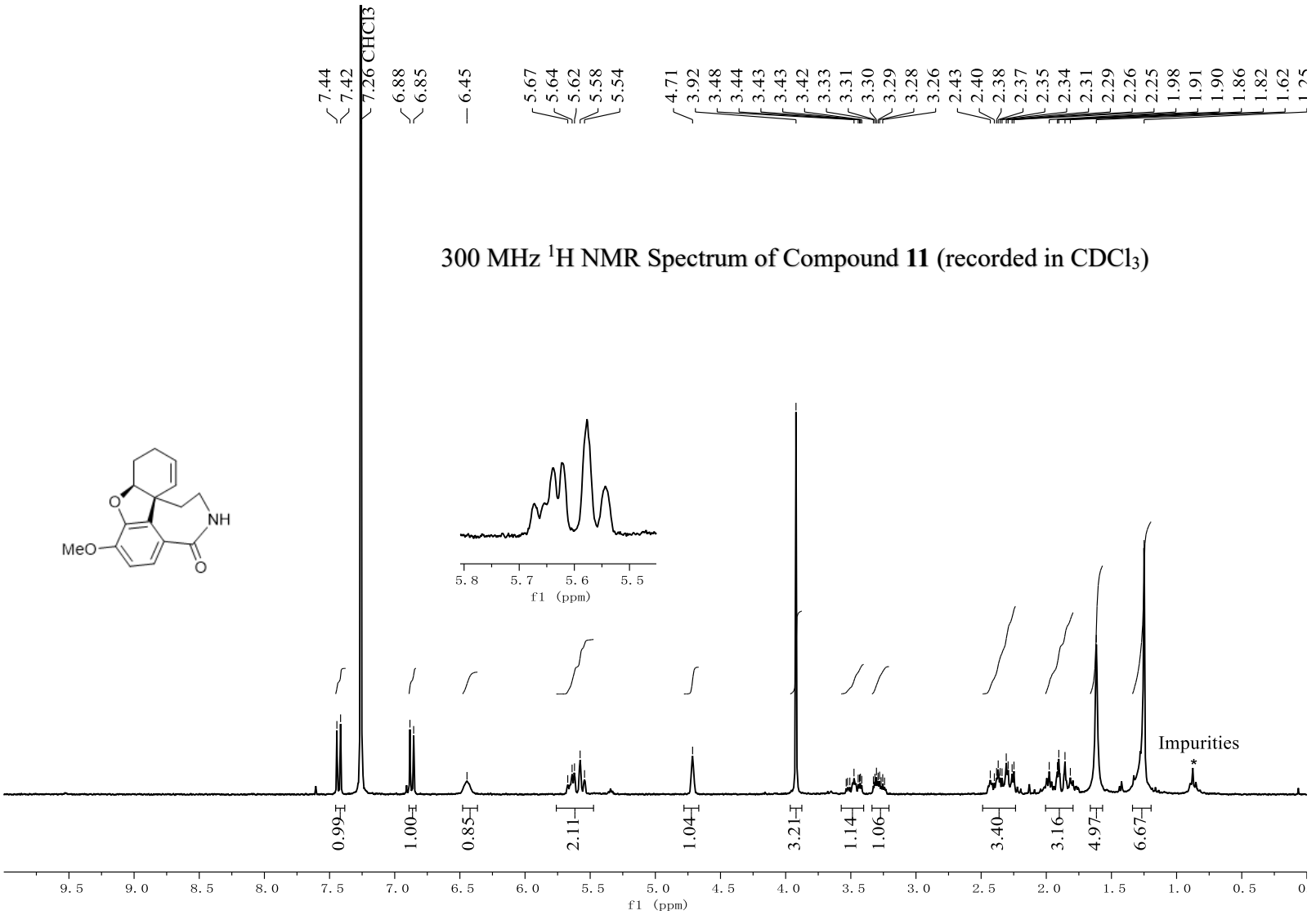
75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **9** (recorded in $CDCl_3$)




9.82
7.38
7.37
7.35
7.26 CHCl3
6.89
6.86
6.18
6.14
5.93
5.91
5.89
5.88
4.92
4.91
4.89
4.57
4.16
4.15
3.93
3.93
3.91
3.88
3.04
3.01
2.87
2.85
2.83
2.81
2.79
2.38
2.36
2.36
2.34
2.33
2.32
2.32
2.31
2.30
2.29
2.29
2.28
2.27
2.19
2.18
2.17
2.16
2.14
2.13
2.13
2.11
2.02
1.98
1.96
1.94
1.92
1.90
1.88
1.36
300 MHz ^{1}H NMR Spectrum of Compound **10** (recorded in $CDCl_3$)
OH
NHBoc
O
MeO
CHO
6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7
f1 (ppm)
Impurities
*
1.00
1.02
1.11
0.98
0.99
1.03
1.17
1.18
3.31
0.94
1.21
2.00
1.04
1.34
10.11
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)



75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)



300 MHz ^{1}H NMR Spectrum of Compound **11** (recorded in $CDCl_3$)

75 MHz $^{13}C\{^{1}H\}$ NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)