Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information for

Total syntheses of (-)-15-oxopuupehenol and (+)-puupehenone and formal syntheses of (-)-puupehenol and (+)-puupehedione

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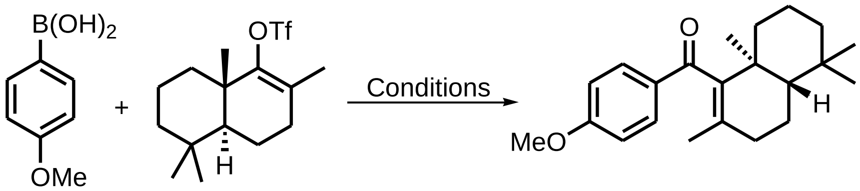
Contents

1. Optimization of the Suzuki carbonylative coupling reaction

As shown in Table S1, the commercially available (4-methoxyphenyl) boronic acid **12a** and bicyclic triflate **11** were used as models to screen the conditions of the planed Suzuki carbonylative coupling reaction. Various Pd catalysts ($PdCl_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, $Pd(dppf)_2Cl_2$, $Pd_2(dba)_3$ and $Pd(CH_3CN)_2Cl_2$), the reaction temperature (80°C *vs* 100°C) and the solvents (DMF or dioxane) were screened. Then the optimized reaction conditions were thus identified to be entry 9:

Table S1. Screening the conditions of Suzuki carbonylative coupling reaction[a]



12a **11** **18a**

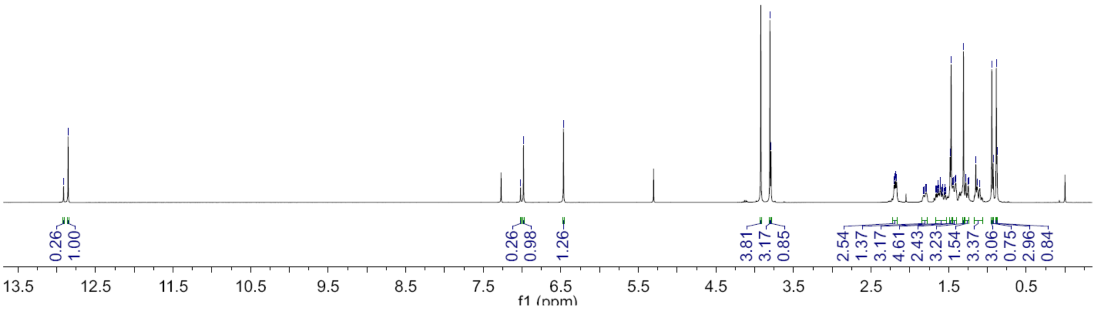
Entry	Pd catalyst	Temperature(°C)	Solvents	Yields(%)
1	$PdCl_2$, PPh_3	100	DMF	31
2	$Pd(PPh_3)_2Cl_2$	100	DMF	30
3	$Pd(OAc)_2$, PPh_3	100	DMF	-
4	$Pd(dppf)Cl_2$	100	DMF	30
5	$Pd_2(dba)_3$	100	DMF	-
6	$Pd(PPh_3)_4$	100	DMF	30
7	$Pd(CH_3CN)_2Cl_2$	100	DMF	-
8	$PdCl_2$, PPh_3	80	DMF	40
9[b]	$PdCl_2$, PPh_3	80	DMF	60
10[b]	$PdCl_2$, PPh_3	80	1,4-dioxane	-
11[b]	$PdCl_2$, PPh_3	60	DMF	-

[a] All the reactions were performed on 0.2 mmol scale, using 0.2 equiv. Pd as catalyst and 3 equiv. K_2CO_3 as base.
[b] 0.3 equiv. $PdCl_2$ and 0.6 equiv. PPh_3 were used.

2. Determination of the structure of Compounds 13a

Compounds **13** and **13a** are inseparable by column chromatography on silica gel and **13** and **13a**'s mixed NMR spectra (^{1}H , ^{13}C, and ^{13}C DEPT 135) and Mass spectra (LCMS) are obtained.

(1) ^{1}H NMR Spectra of inseparable mixture (**13** and **13a**)



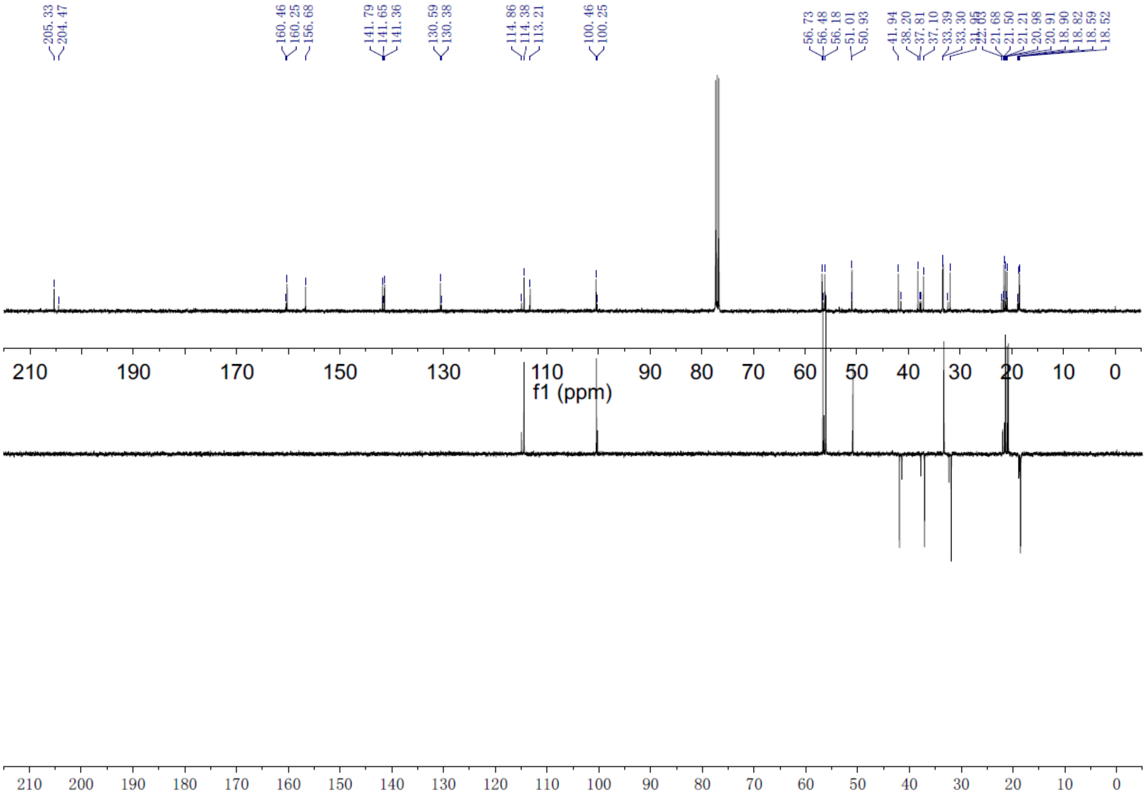
From the mixed ^{1}H NMR Spectra, we can deduce the following items:

a. The amounts of 13a and 13 is in 1:4 ratio (0.26 : 1 ≈ 1 : 4, ArO-H; 0.26 : 0.98 ≈ 1 : 4, Ar-H; 0.85 : 3.17 ≈ 1 : 4, ArO-CH_3).

b. There is a strong Hydrogen bond between the phenol and its ortho-carbonyl group in 13a which makes its phenolic hydrogen appeared in 12.91 ppm.

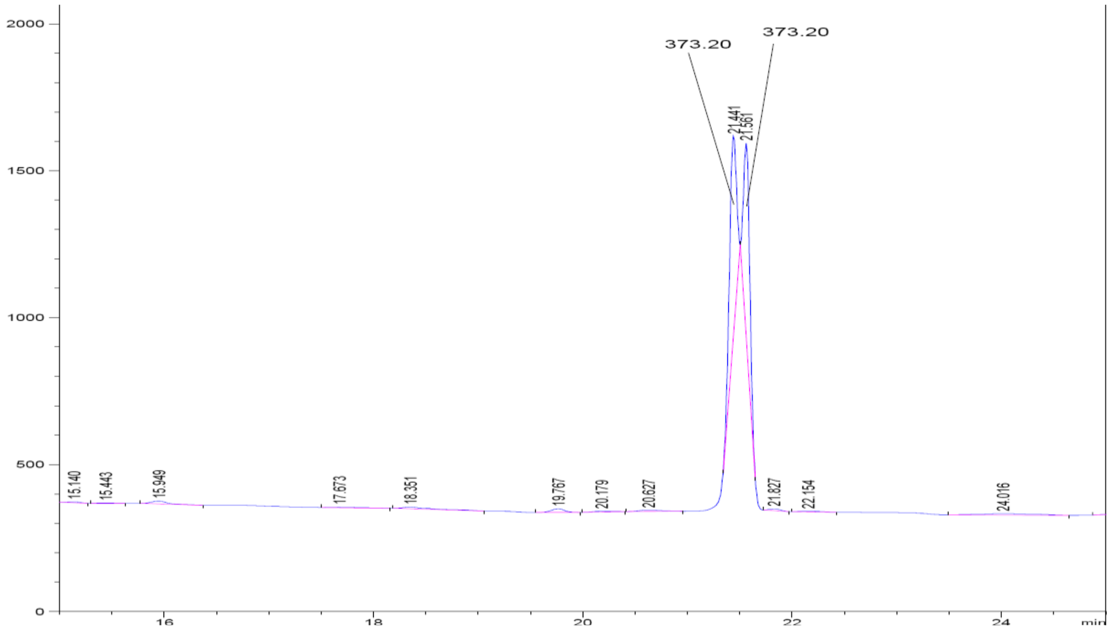
c. There are two aromatic hydrogen atoms in 13a (6.47 ppm, 1.26 Ar-H vs 6.98, 7.02 ppm, (0.26+0.98) Ar-H vs 12.91, 12.85ppm, (0.26+1.00) ArO-H)

(2) ^{13}C and DEPT 135 NMR spectra of inseparable mixture (**13** and **13a**)



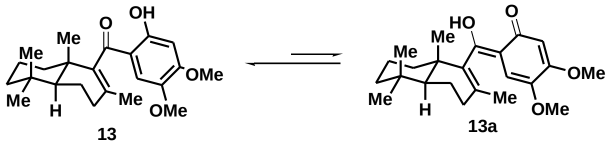
(3) Mass spectra (LCMS) of inseparable mixture (**13** and **13a**)

LC/MS data was obtained on Agilent Technologies 1260 Infinity II with C18 silica gel columns and Agilent G6125B Series LC/MSD mass detector. As eluent, a mixture of MeCN (HPLC grade) with H_2O (Mili-Q Integral Water Purification System) and 0.1 vol-% formic acid as additive was employed.



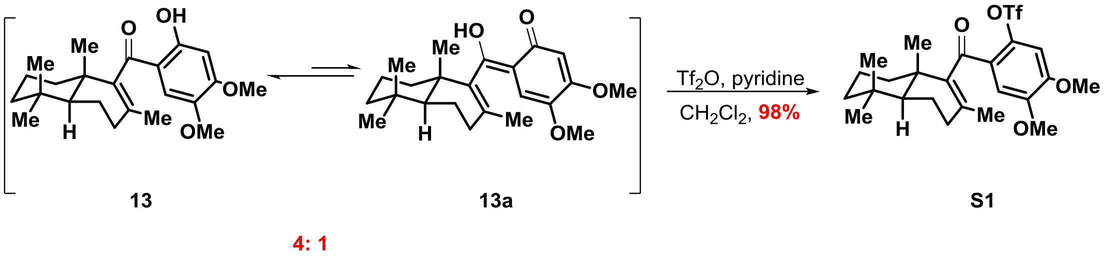
According to the Mass spectra, **13** and **13a** has the same molecular ionic peak (Found : 373.20 （$(M+H)^+$) at a very close retention time which indicate they have a same molecular composition ($C_{23}H_{32}O_4$).

Based on the above obtained spectra data, **13a** is deduced to be the ketone/enol tautomer of **13**.



When the inseparable mixture of **13** and **13a** (4 : 1 ratio according to the obtained ^1H NMR spectra indicates that the amount of **13** is about 80%) was submitted to the optimal cyclization reaction (Table 1, entry 6), the desired cyclization product **19** was obtained in 86% yield. The high yield indicates that **13a** can be partially transformed into **13** or directly yields in **19**.

When the mixture of **13** and **13a** (4 : 1 ratio according to ^1H NMR) was treated with Tf_2O/pyridine in CH_2Cl_2, a single acylation product **S1** was obtained in 98% yield. This result supports our speculation that **13** and **13a** are tautermeric to each other due to the presence of a strong hydrogen bond.

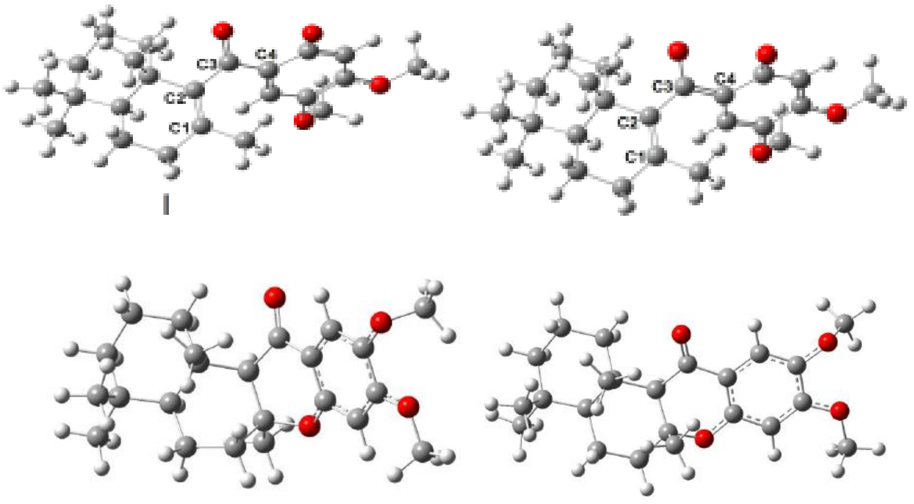


3. DFT Calculations

3.1 Computational details

All the computational works were performed using Gaussian 16 suite of programs.[S1] Geometry optimizations were carried out at M062X[S2]/6-31G (d,p) level of theory. Vibrational frequencies were calculated at the same level to ensure the optimized structures are energy minima (no imaginary frequency).

3.2 Calculation results



I

I′

19

8-*epi*-19

Fig The optimized geometries of **I**, **I′**, **19** and 8-*epi*-**19**

Table SX. The calculated total energies (E) and the relative total energies (ΔE) of **I** and **I′**, **19** and 8-*epi*-**19**.

isomer	E (a.u.)	ΔE (kJ/mol)
I	−1194.913985	0
I′	−1194.913982	0.008
19	−1196.13073347	34.95
8-epi-19	−1196.14405886	0

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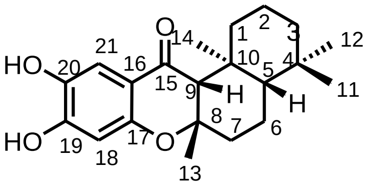
[S2] Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group

Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-class Functionals and 12 other Functionals. *Theor. Chem. Acc.* 2008, *120*, 215.

4. Comparison of the spectra data of synthetic and those of natural product

4.1 Comparisons of the spectra data of synthetic (-)-15-oxopuupehenol and those of natural one



(-)-15-oxopuupehenol (6)

4.1.1 Comparisons of their ^{13}C NMR spectra data (ppm)

number	Synthetic (-)-15-oxopuupehenol	Natural (-)-15-oxopuupehenol[1]	△
1	40.1	40.1	0
2	18.4	18.4	0
3	41.6	41.6	0
4	33.4	33.4	0
5	54.2	54.2[a]	0
6	18.2	18.2	0
7	39.9	39.9	0
8	80.4	80.4	0
9	64.5	64.5	0
10	38.7	38.6[b]	0.1
11	33.8	33.8	0
12	22.0	22.0	0
13	26.6	26.6	0
14	15.2	15.2	0
15	195.6	195.5[c]	0.1
16	114.8	114.7[d]	0.1
17	157.1	156.9[e]	0.2
18	103.7	103.7	0
19	153.5	153.5[f]	0
20	138.5	138.8[g]	- 0.3

21	110.8	110.6[h]	0.2

[C] In the article, the ^{13}C NMR spectra data for C15 is 194.3 ppm, however, it reads as 195.5 ppm in the spectra provide by the isolation author in the SI. So 195.5 was adopted to compare with the data of synthetic one's. The same situations were found at C5, 10, 16, 17, 19, 20, 21.

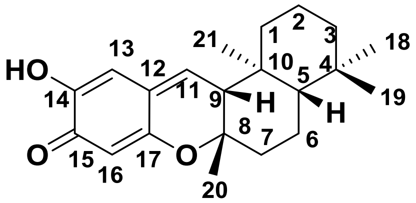
4.1.2 Comparisons of their partial ^{1}H NMR spectra data (ppm)

number	Synthetic (-)-15-oxopuupehenol	Natural (-)-15-oxopuupehenol[1]	∆
1	1.68 (m) 2.21 (d, *J* = 14.2 Hz)	1.67 (m) 2.21 (dt, *J* = 14.5, 3.2 Hz)	0.01 0
2	1.71 (m) 1.64 (m)	1.70 (m) 1.62(m)	0.01 0.02
3	1.19 (m) 1.39 (m)	1.17 (m) 1.41 (m)	0.02 - 0.02
5	0.88 (d, *J* = 1.4 Hz, 1H)	0.91 (m)	- 0.03
6	1.52 (m) 1.41 (m)	1.52 (m) 1.41 (m)	0 0
7	1.53 (m) 1.21 (m)	1.53 (m) 1.22 (m)	0 -0.01
9	1.91(s)	1.88 (s)	0.03
11	0.91 (s)	0.92 (s)	-0.01
12	0.84 (s)	0.84 (s)	0
13	1.23 (s)	1.23 (s)	0
14	0.85 (s)	0.85 (s)	0
18	6.43 (s)	6.42 (s)	0.01
19	-	6.60 (s)	
20	-	6.29 (s)	
21	7.55 (s)	7.47 (s)	0.08

4.1.3 Comparisons of their physical data and MS data

data	Synthetic (-)-15-oxopuupehenol	Reported values (-)-15-oxopuupehenol
$[\alpha]_D$	- 102.0 (c = 0.5 M, CH_3OH)	-106 (c = 0.52 M, CH_3OH)[1] -94.3 (c = 0.01M, CH_3OH)[2]
MS	345.2066($M+H^+$)	344.1980[1]

4.2 Comparisons of the spectra data of synthetic Puupehenone and those of Natural one



Puupehenone (1)

4.2.1 Comparisons of their ^{13}C NMR spectra data (ppm)

number	Synthetic Puupehenone	Natural Puupehenone[5]	△
1	39.2	39.2	0
2	18.1	18.1	0
3	41.6	41.6	0
4	33.3	33.3	0
5	53.8	53.8	0
6	18.4	18.4	0
7	40.0	40.0	0
8	78.8	78.9	- 0.1
9	54.8	54.8	0
10	40.7	40.7	0
11	140.4	140.7	- 0.3
12	129.3	129.2	0.1
13	105.0	105.2	- 0.2
14	147.4	147.5	-0.1
15	182.0	182.1	-0.1
16	106.0	106.0	0
17	162.8	162.8	0
18	33.7	33.7	0
19	21.9	21.9	0
20	28.0	28.0	0
21	15.0	15.0	0

4.2.2 Comparisons of their partial ^{1}H NMR spectra data (ppm)

number	Synthetic Puupehenone	Natural Puupehenone[5]	△
1	1.57 (m) 2.17 (m)	1.57 (m) 2.17 (m)	0 0
2	1.43 (m)	1.43 (m)	0
3	1.19 (m) 1.40 (m)	1.21 (m) 1.41 (m)	- 0.02 - 0.01
5	0.94 (m)	0.94 (m)	0

6	1.52 (m)	1.54 (m)	- 0.02
7	1.16 (m) 1.68 (m)	1.16 (m) 1.67 (m)	0 0.01
9	2.04 (d, *J* = 6.9 Hz)	2.04 (d, *J* = 7.0 Hz)	0
11	6.65 (d, *J* = 6.9 Hz)	6.65 (brd, J = 7.0 Hz)	0
13	6.20 (s)	6.20 (s)	0
16	5.85 (d, *J* = 1.0 Hz)	5.85 (d, J = 1.1 Hz)	- 0.01
18	0.91 (s)	0.90 (s)	0.01
19	0.84 (s)	0.83 (s)	0.01
20	1.23 (s)	1.21 (s)	0.02
21	0.82 (s)	0.80 (s)	0.02

4.2.3 Comparisons of their physical data and MS data

data	Synthetic Puupehenone	Reported values Puupehenone
$[\alpha]_D$	278.0 (c = 0.5 M, $CHCl_3$) 180.0 (c = 0.1M, CH_2Cl_2)	315 (c =1.64, CCl_4)[3] 297.0(c = 0.44, CCl_4)[4] 59 (c = 0.1, CH_3OH)[5] 98 (c = 0.5, $CHCl_3$)[5] 189(c = 1.08, CCl_4)[6] 113 (c=1.79, $CHCl_3$)[6]
MS	351.1937 ($M+Na^+$)	351.1948 ($M+Na^+$)[5]

5. References

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6. NMR spectra of all synthetic new compounds.

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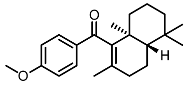
STANDARD 1H OBSERVE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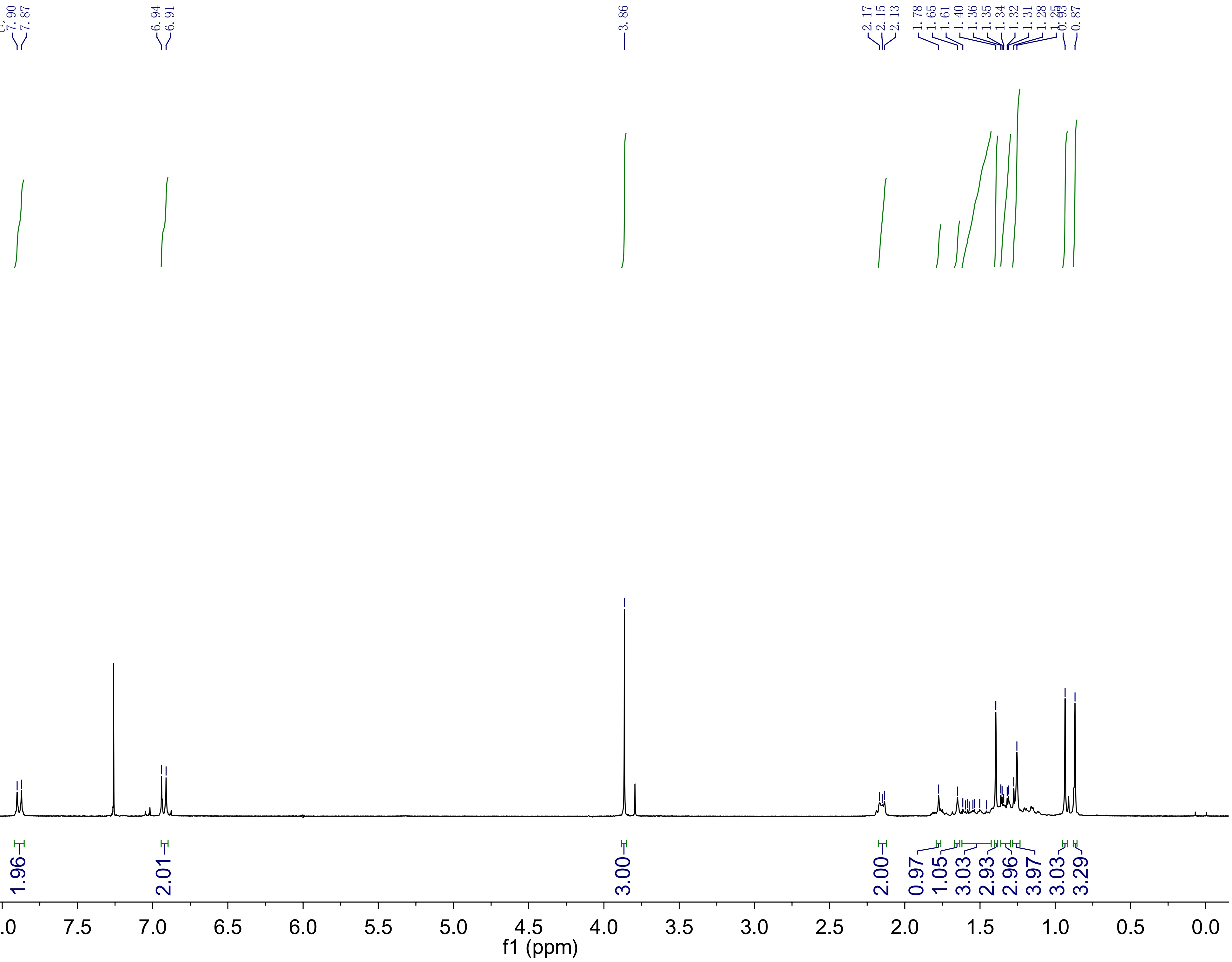

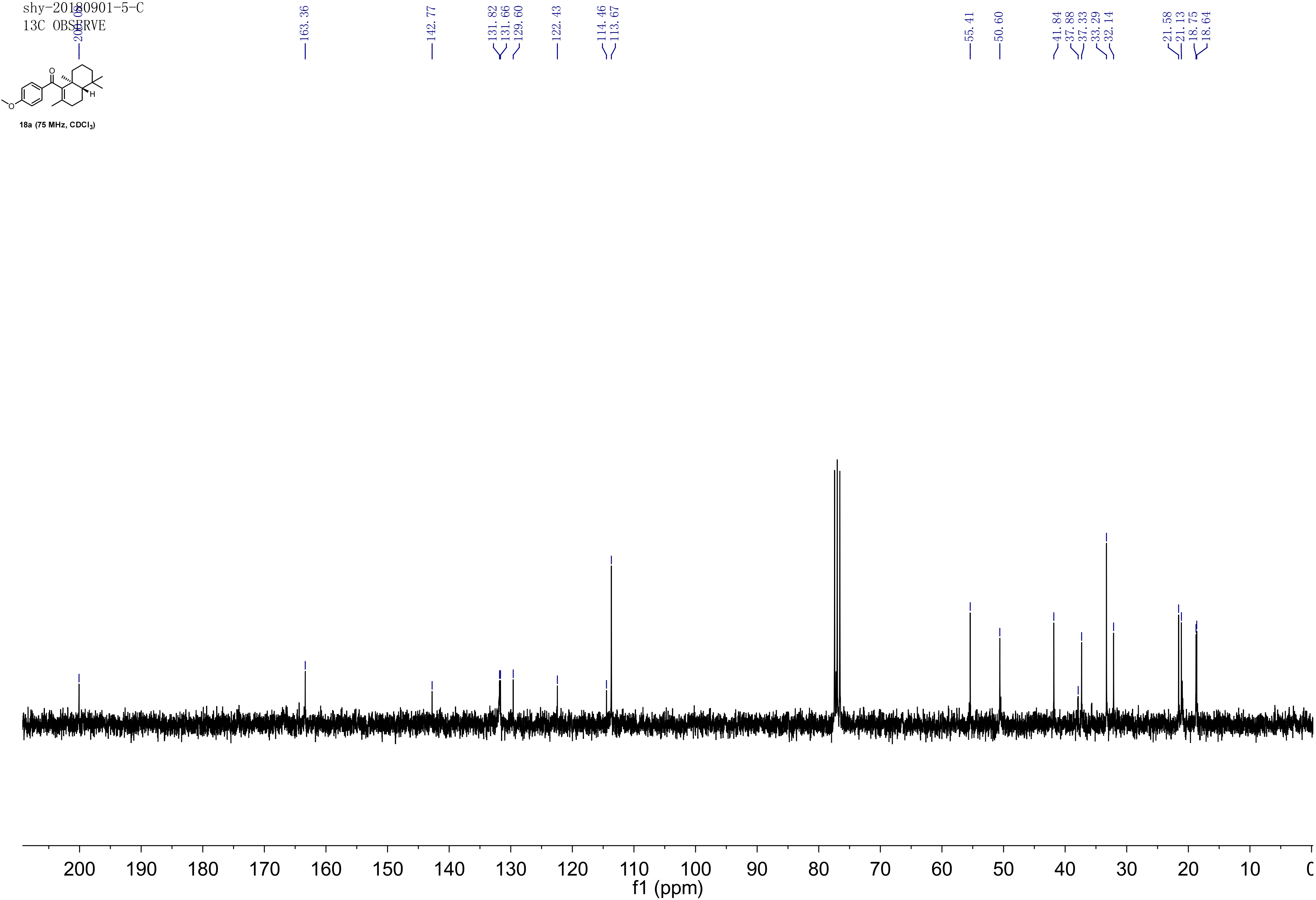

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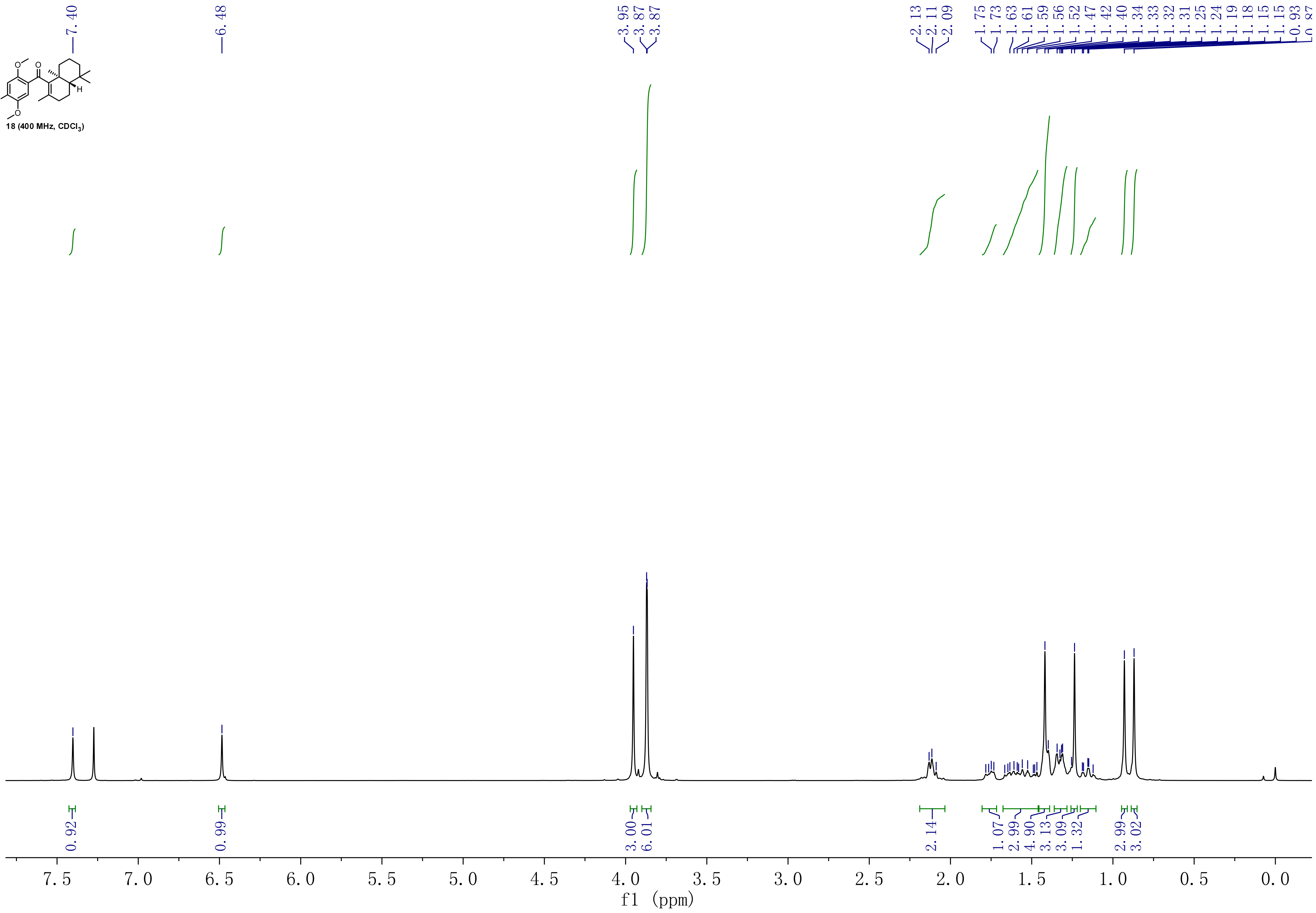
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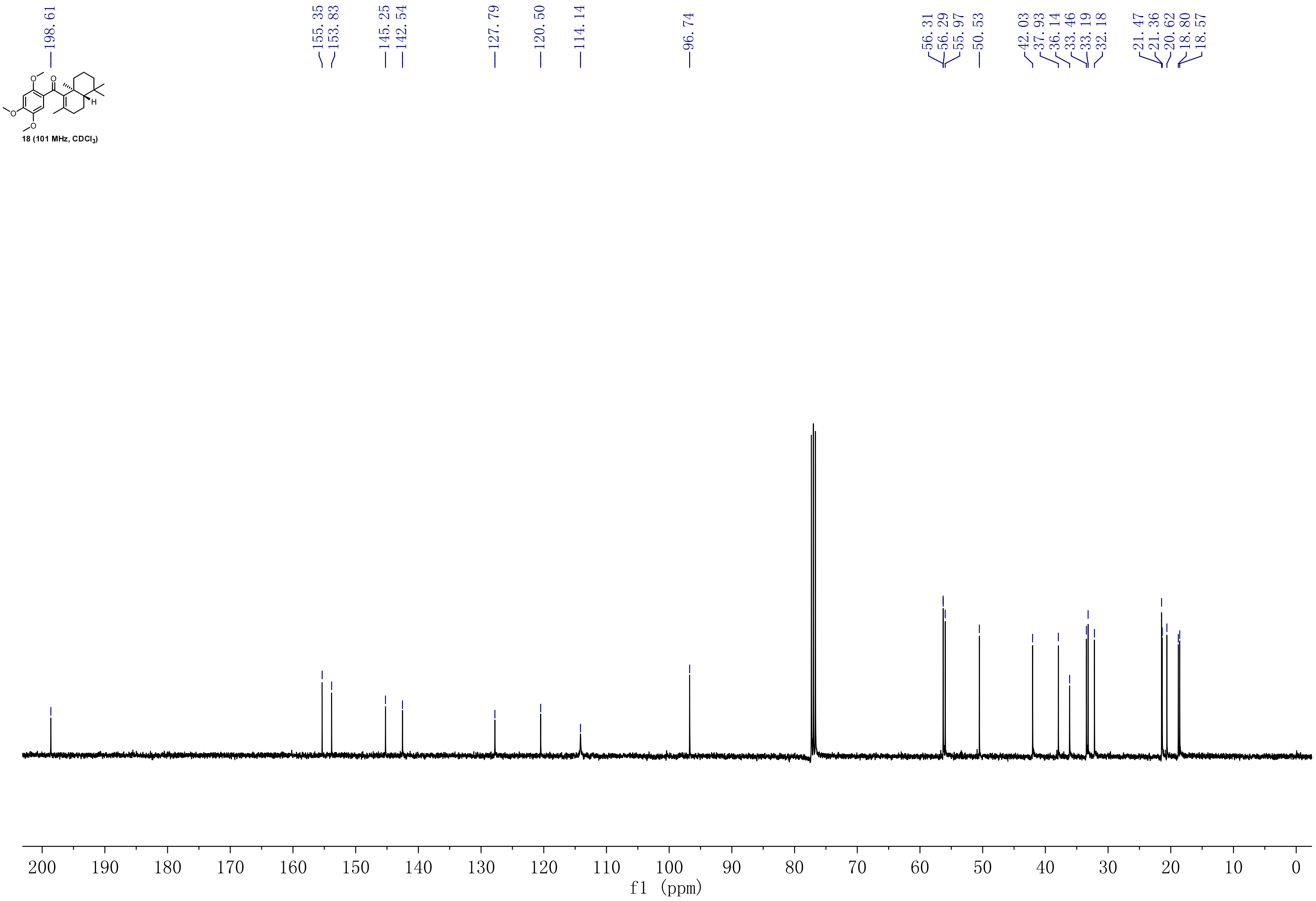

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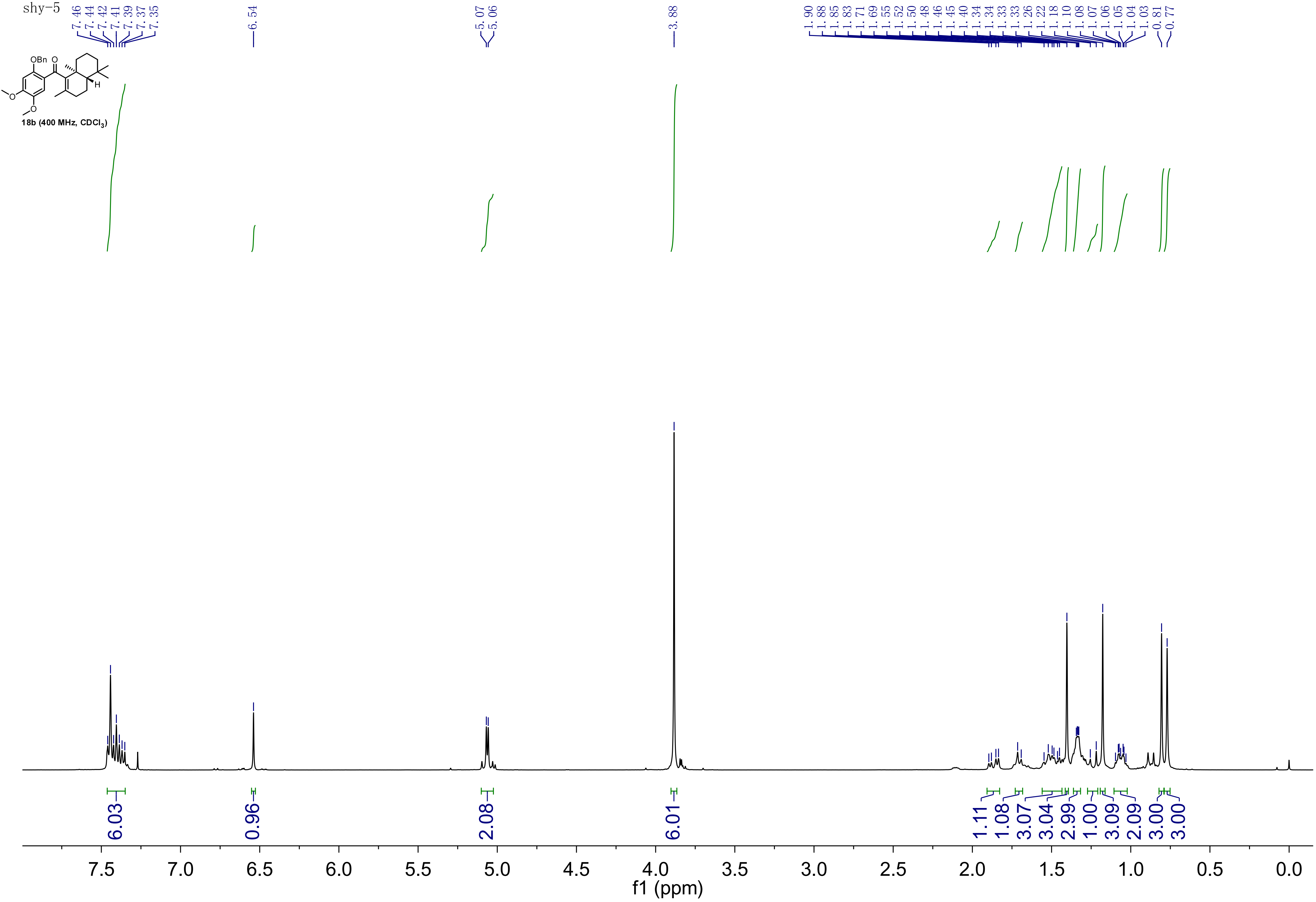

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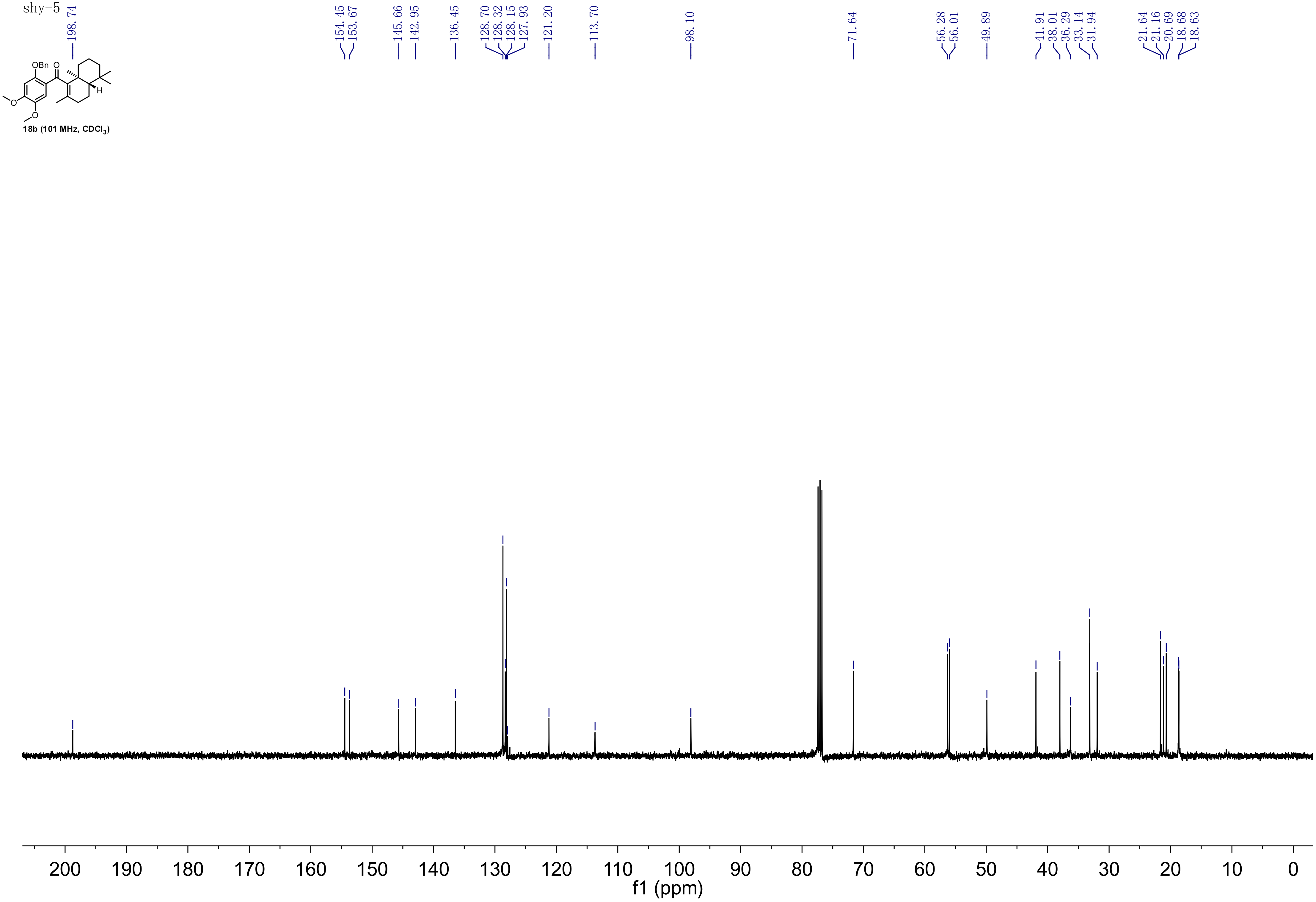
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128.32
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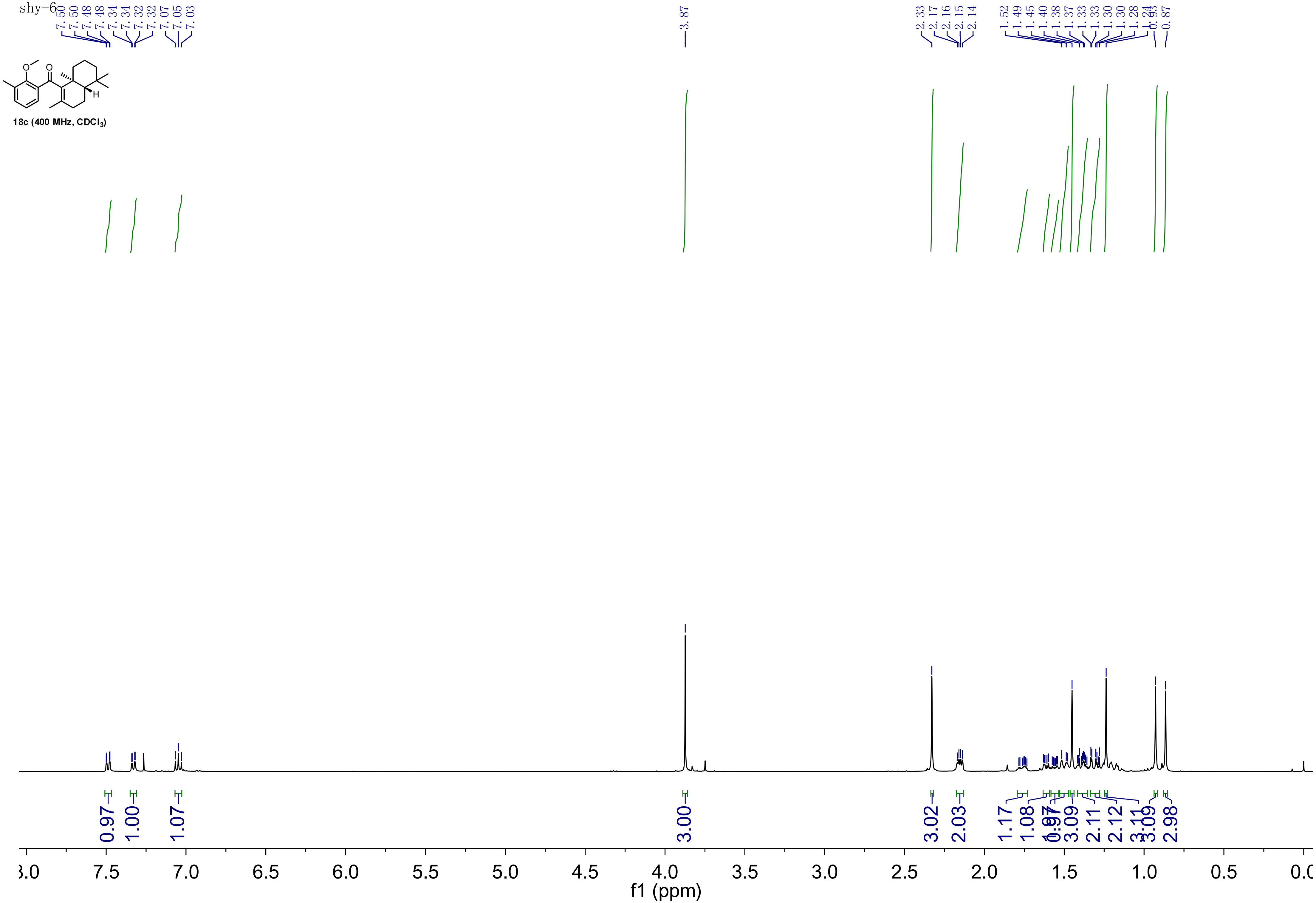
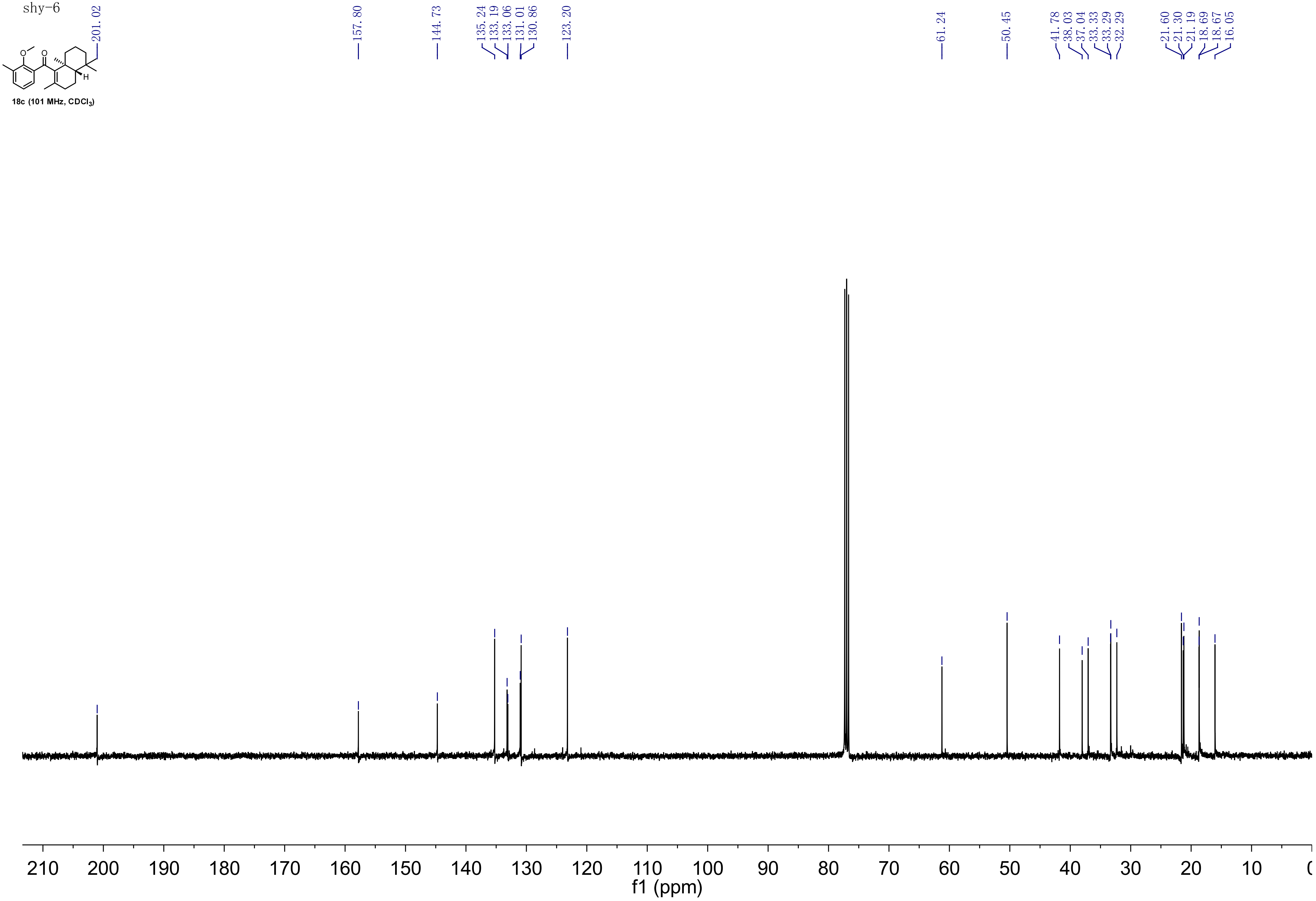
127.93
121.20
113.70
98.10
71.64
56.28
56.01
49.89
41.91
38.01
36.29
33.14
31.94
21.64
21.16
20.69
18.68
18.63
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

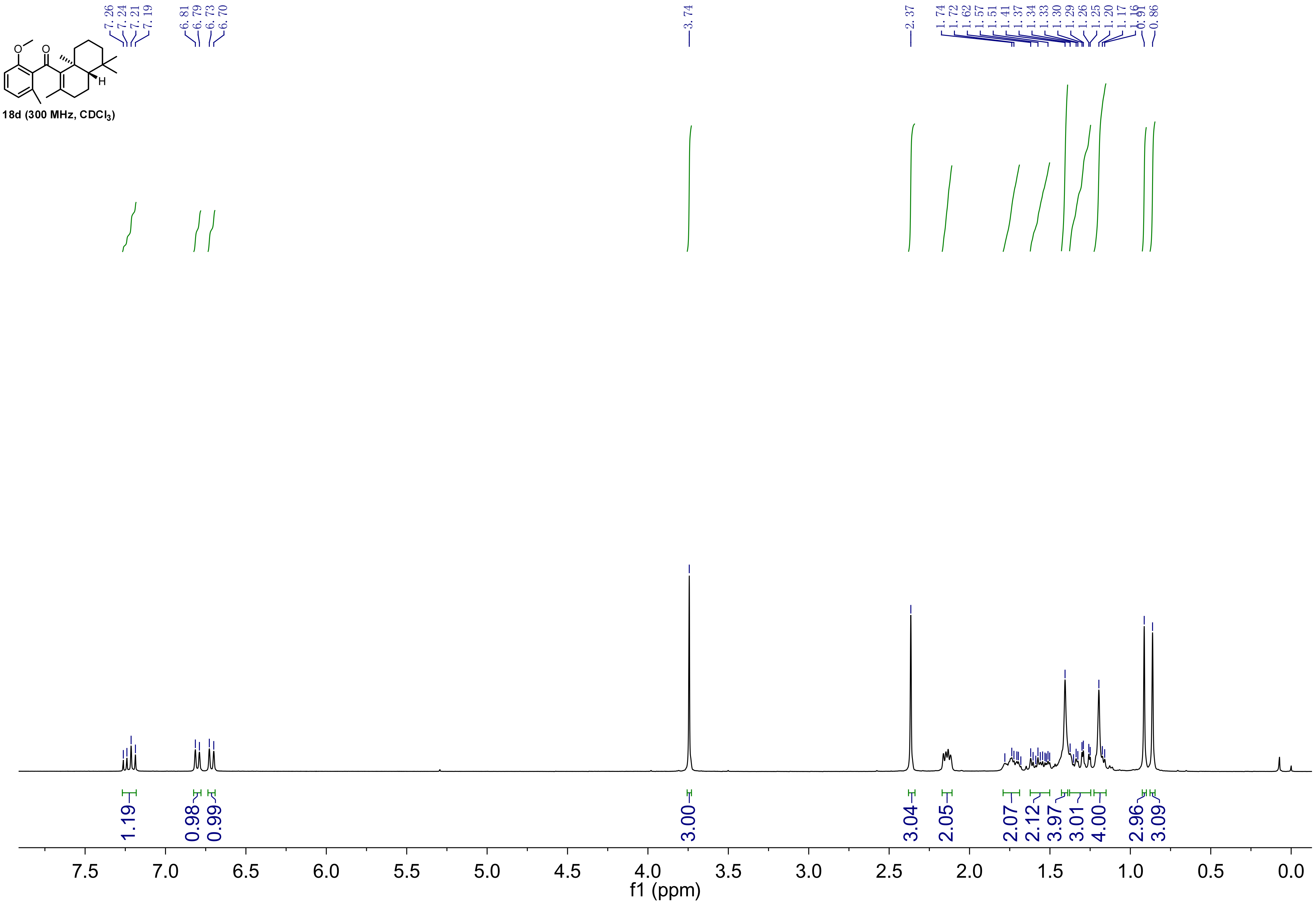


18c (400 MHz, $CDCl_3$)

shy-6



18c (101 MHz, CDCl$_3$)



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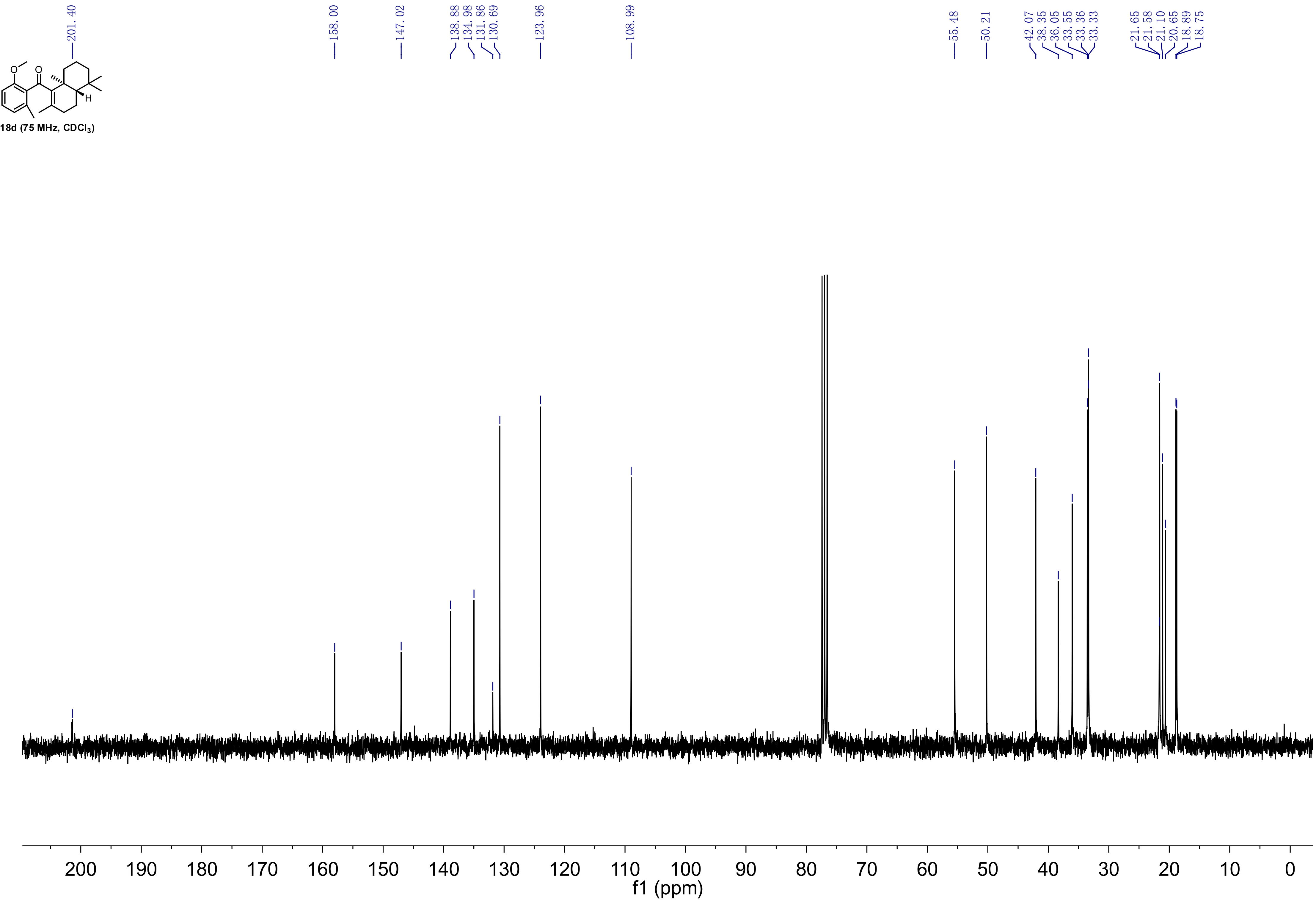

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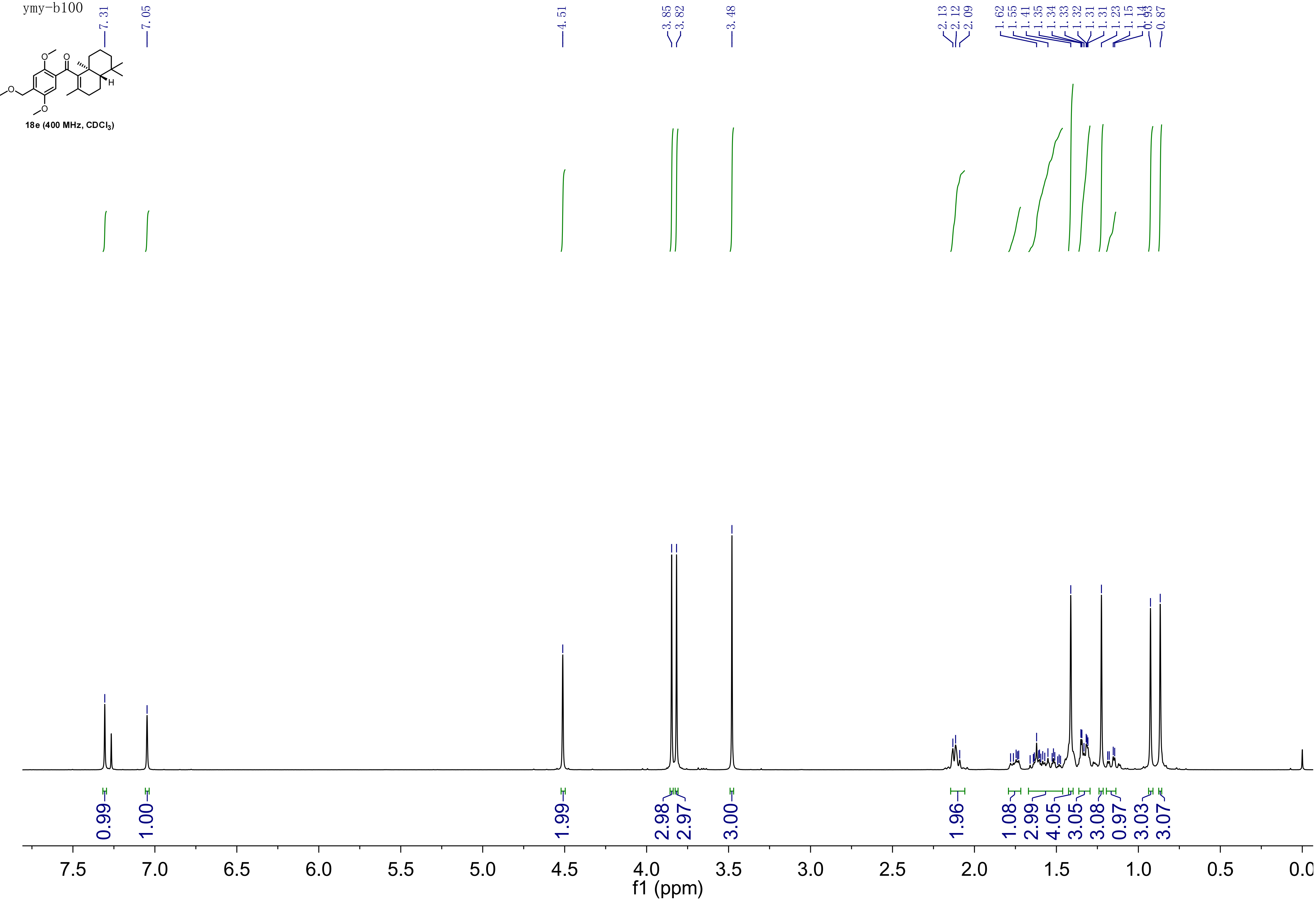

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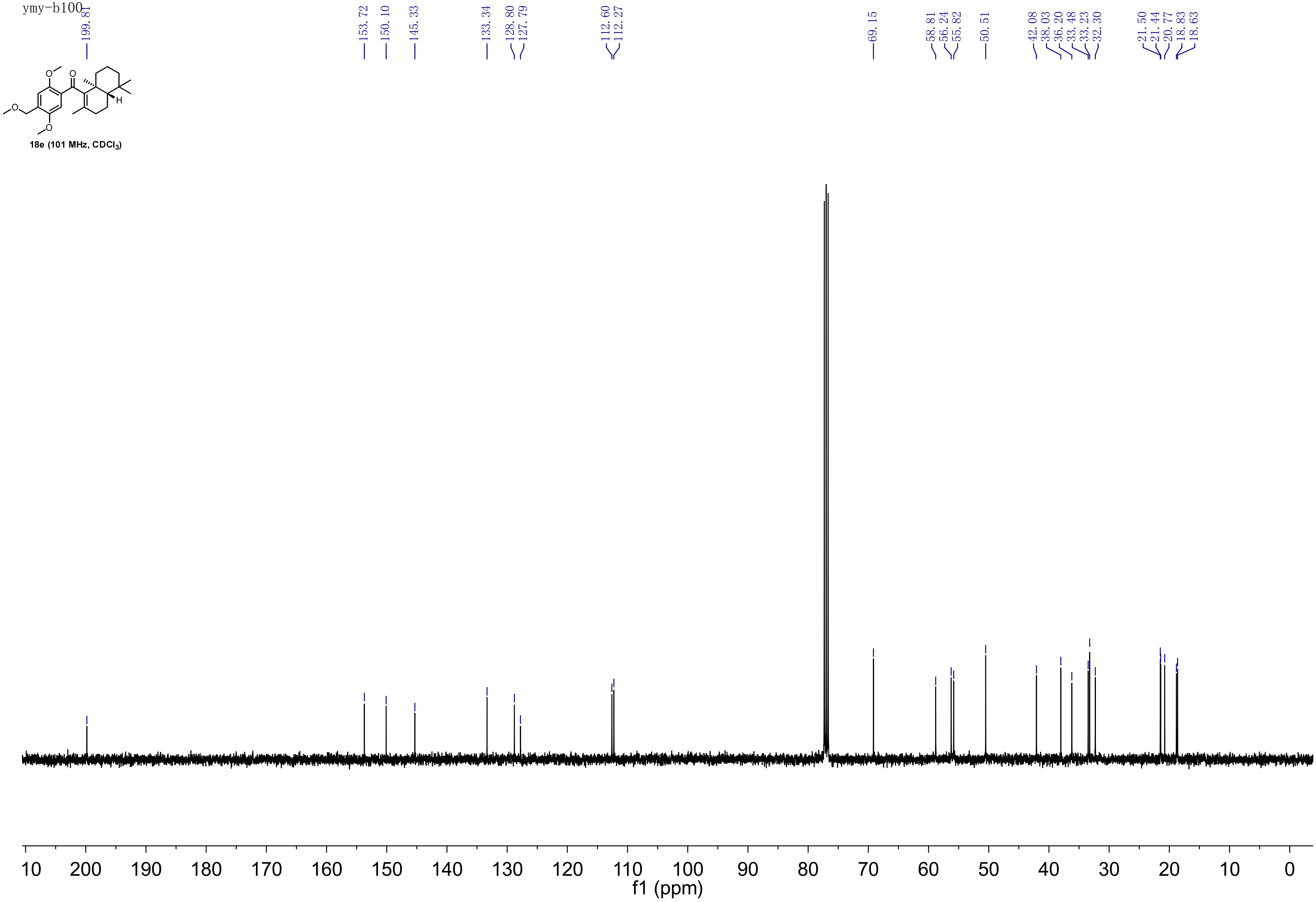
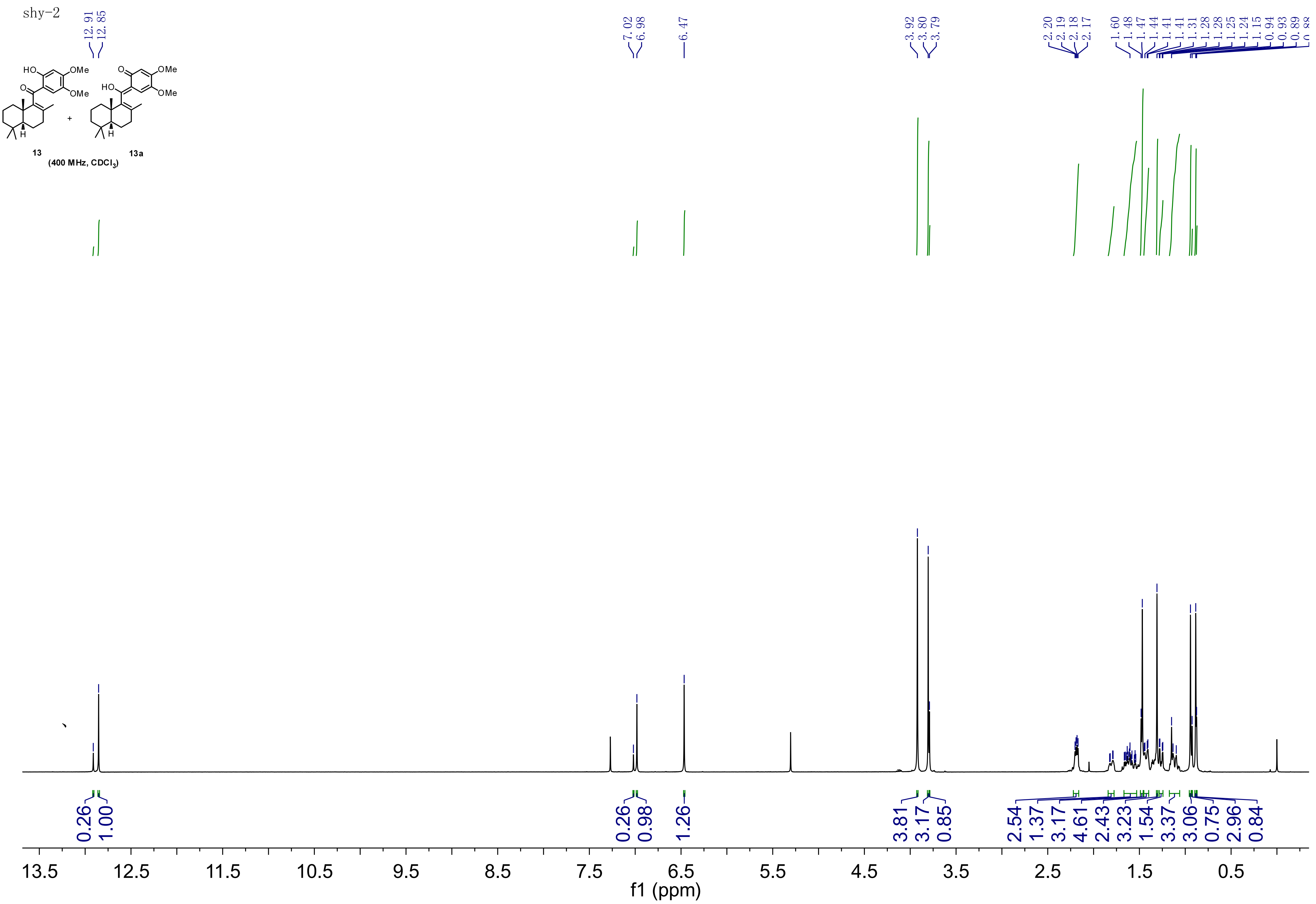


18e (101 MHz, $CDCl_3$)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13a
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6.98
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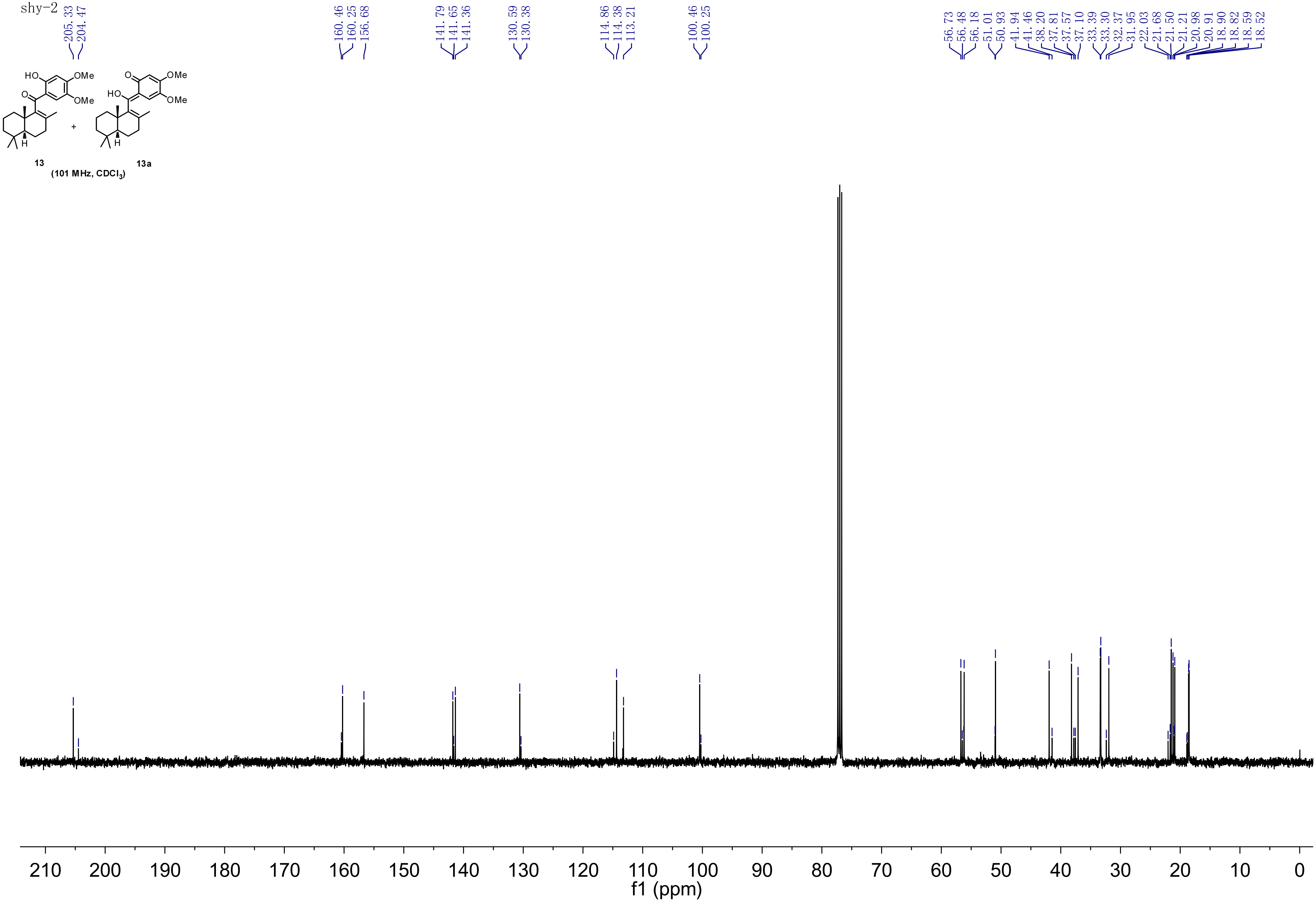
0.5
f1 (ppm)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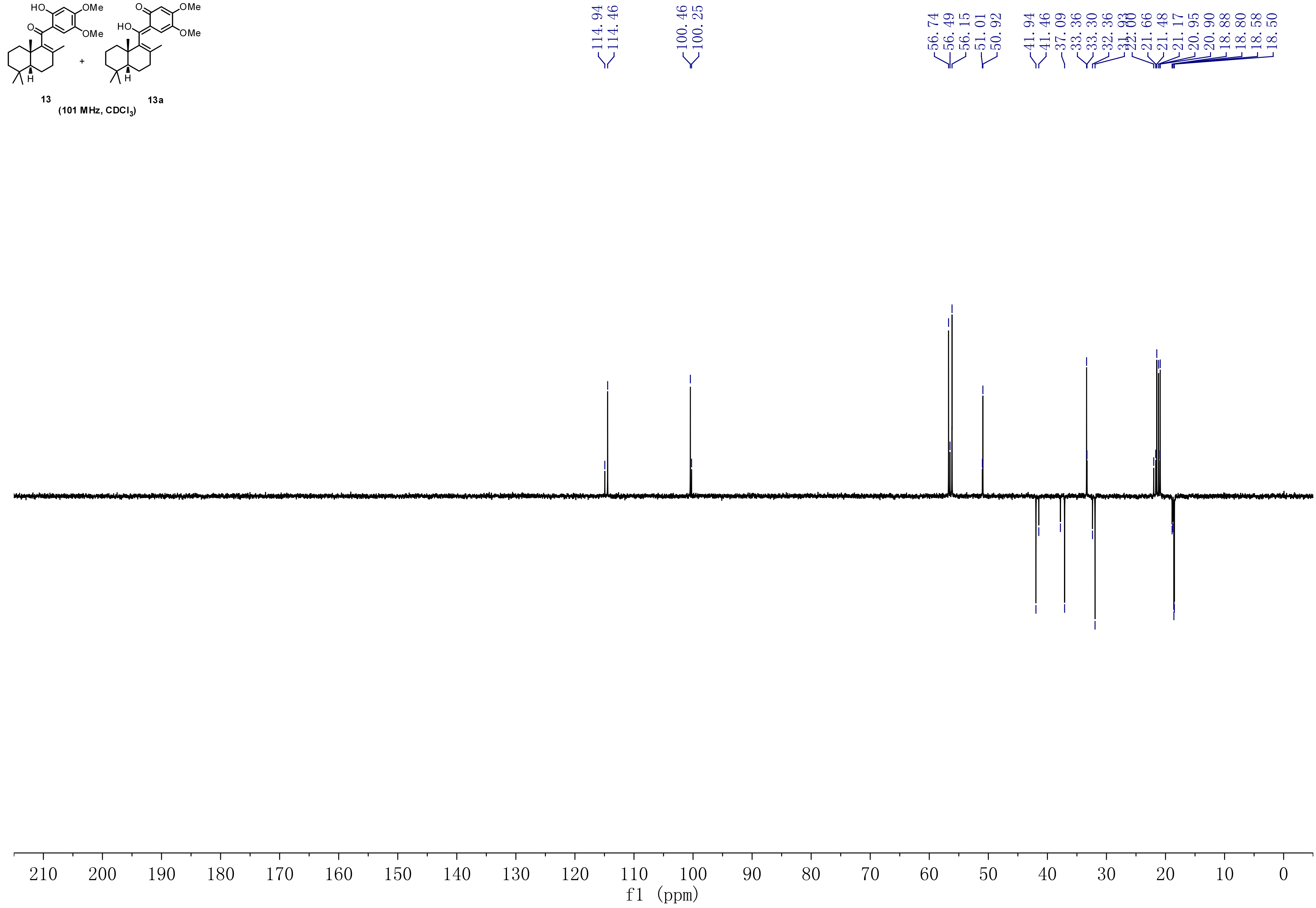
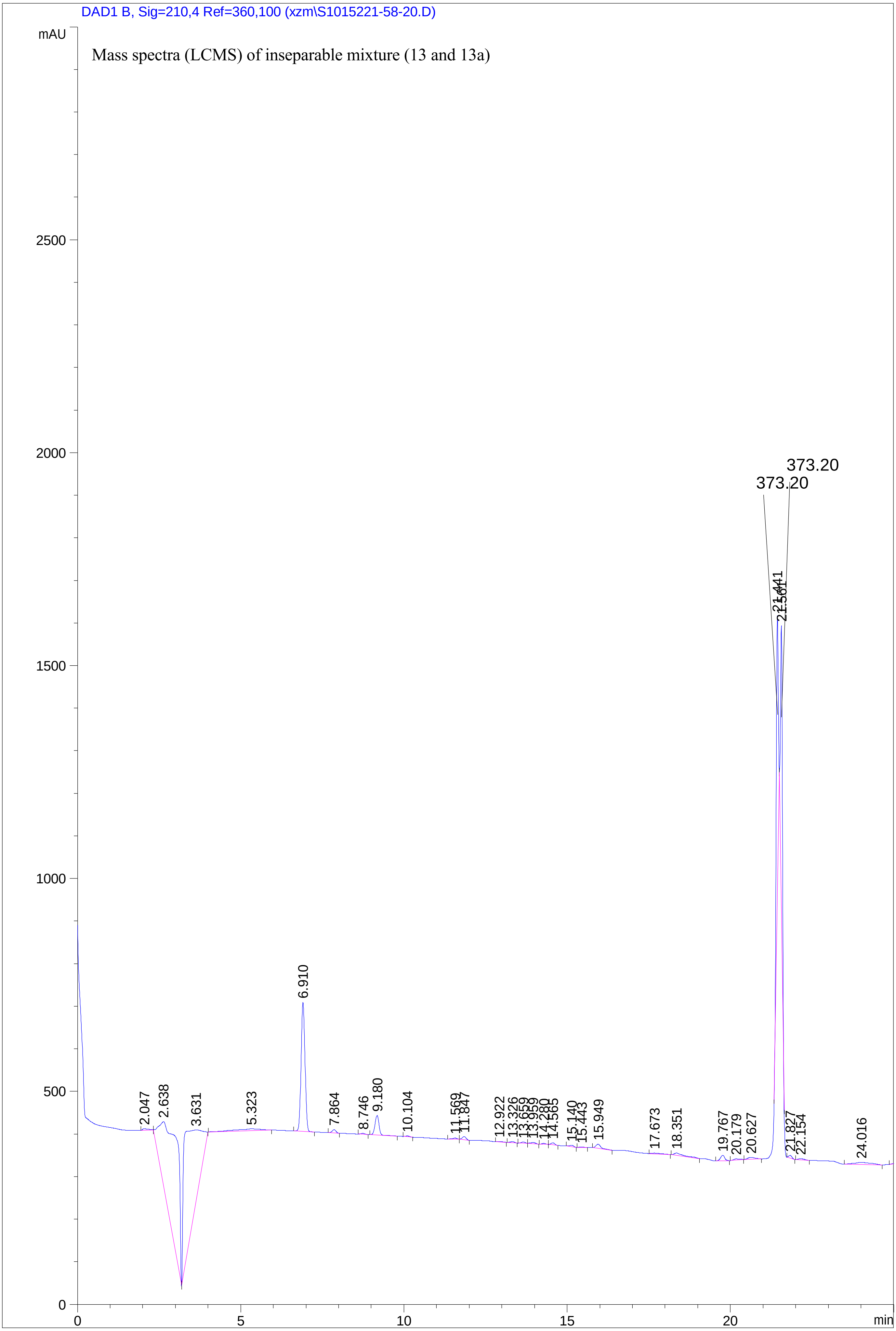
56.48
56.18
51.01
50.93
41.94
41.46
38.20
37.81
37.57
37.10
33.39
33.30
32.37
31.95
22.03
21.68
21.50
21.21
20.98
20.91
18.90
18.82
18.59
18.52
HO
OMe
O
OMe
H
13
+
O
OMe
HO
OMe
H
13a
(101 MHz, CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



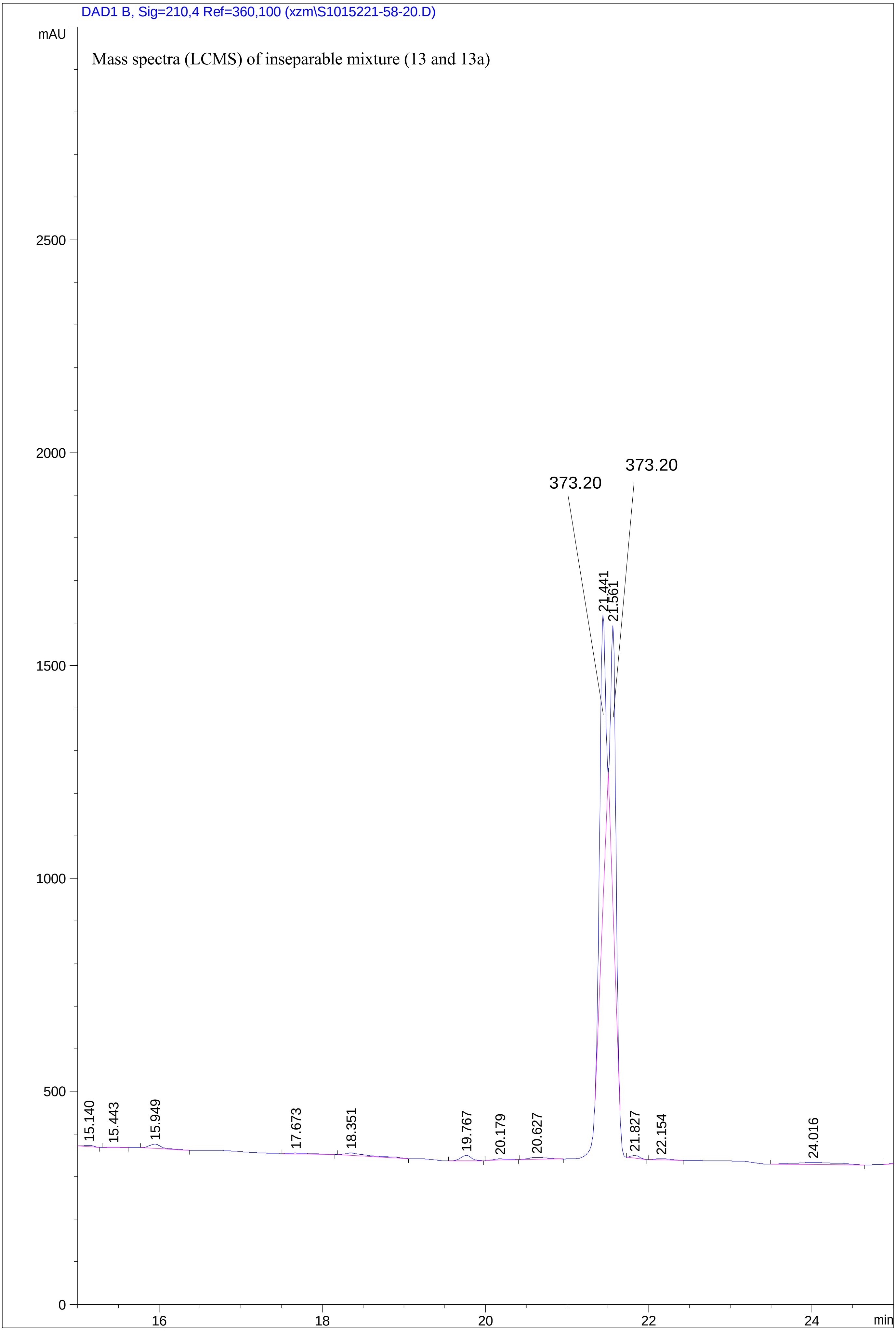
13 + 13a (101 MHz, $CDCl_3$)

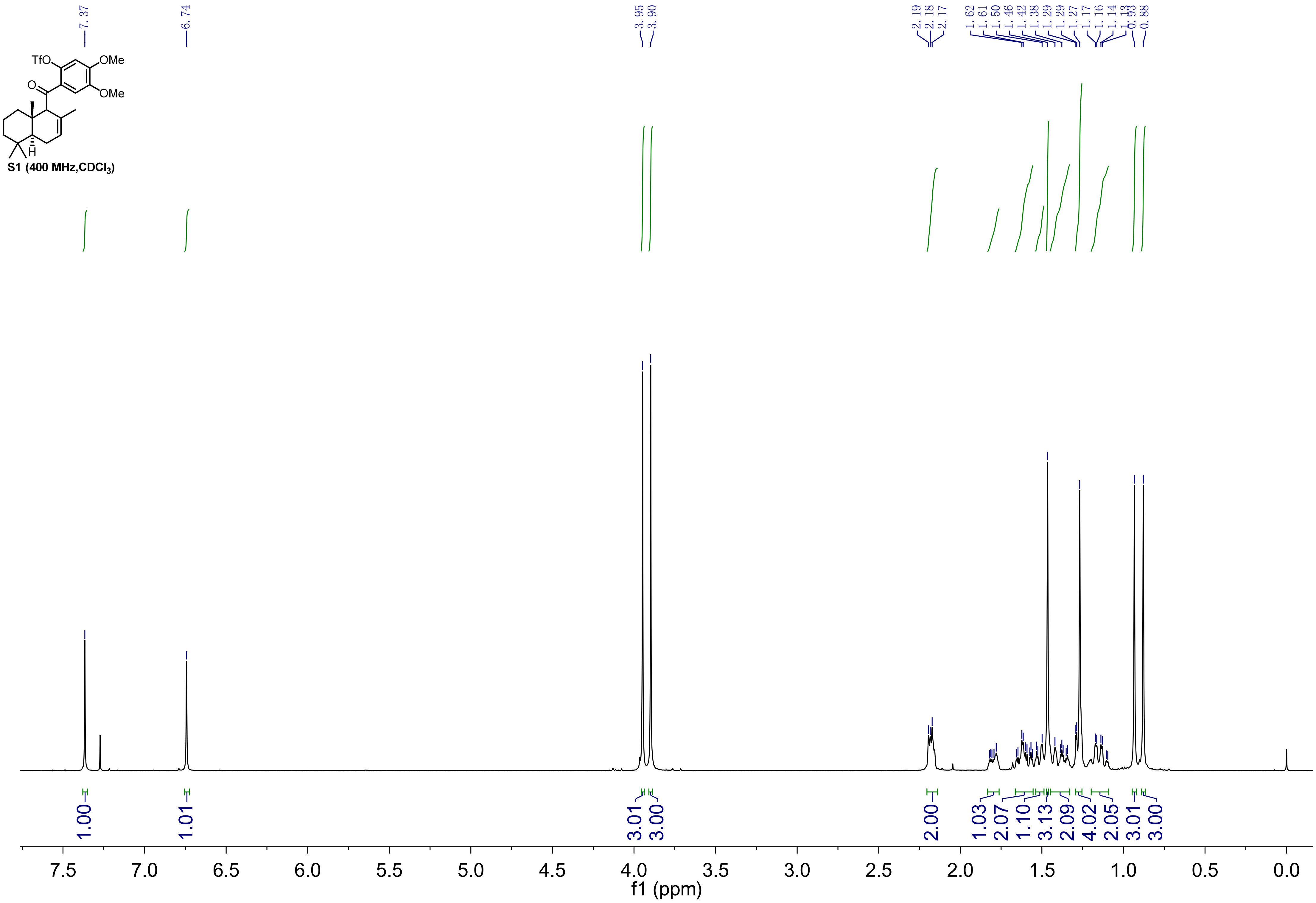
当前色谱图

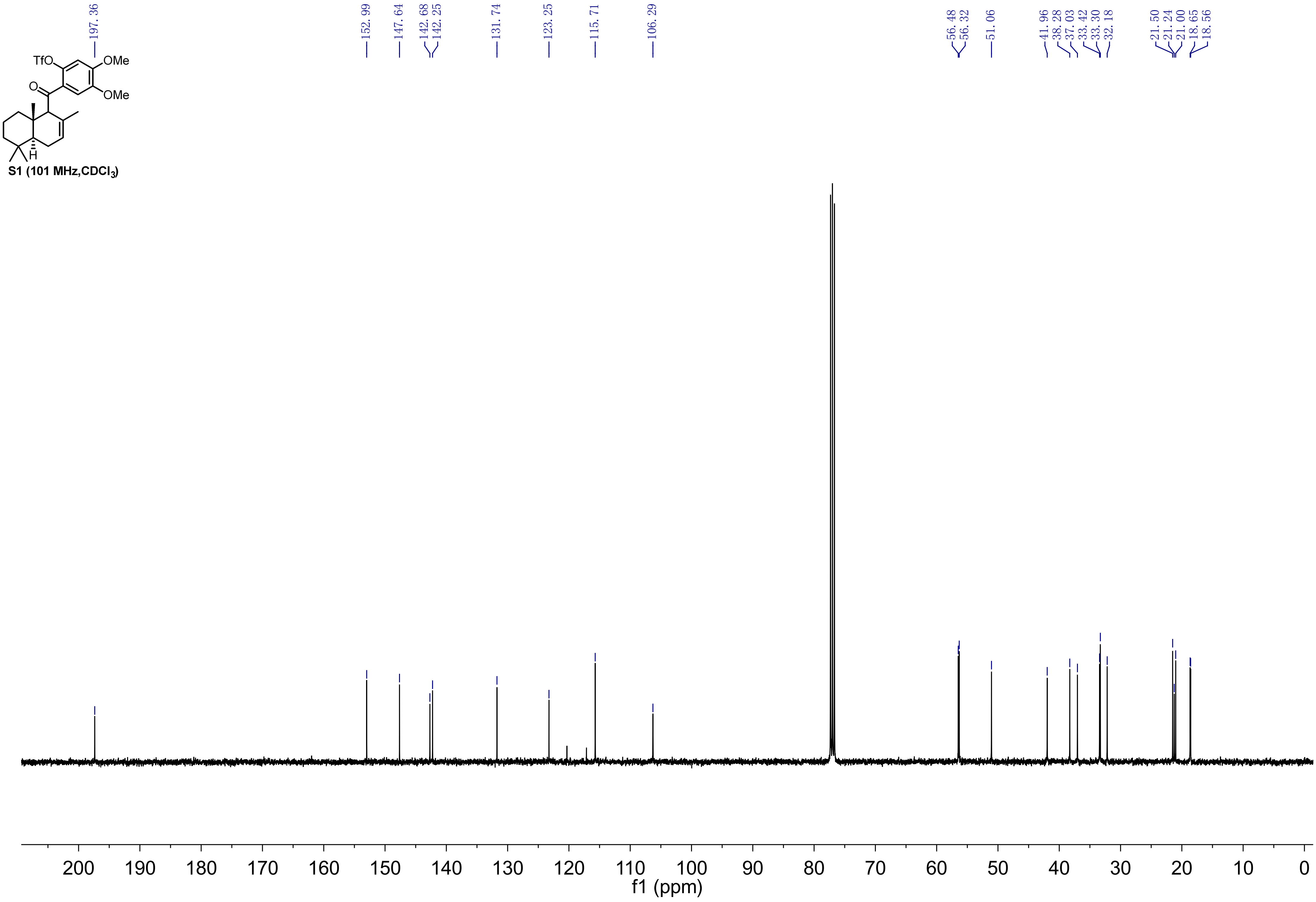


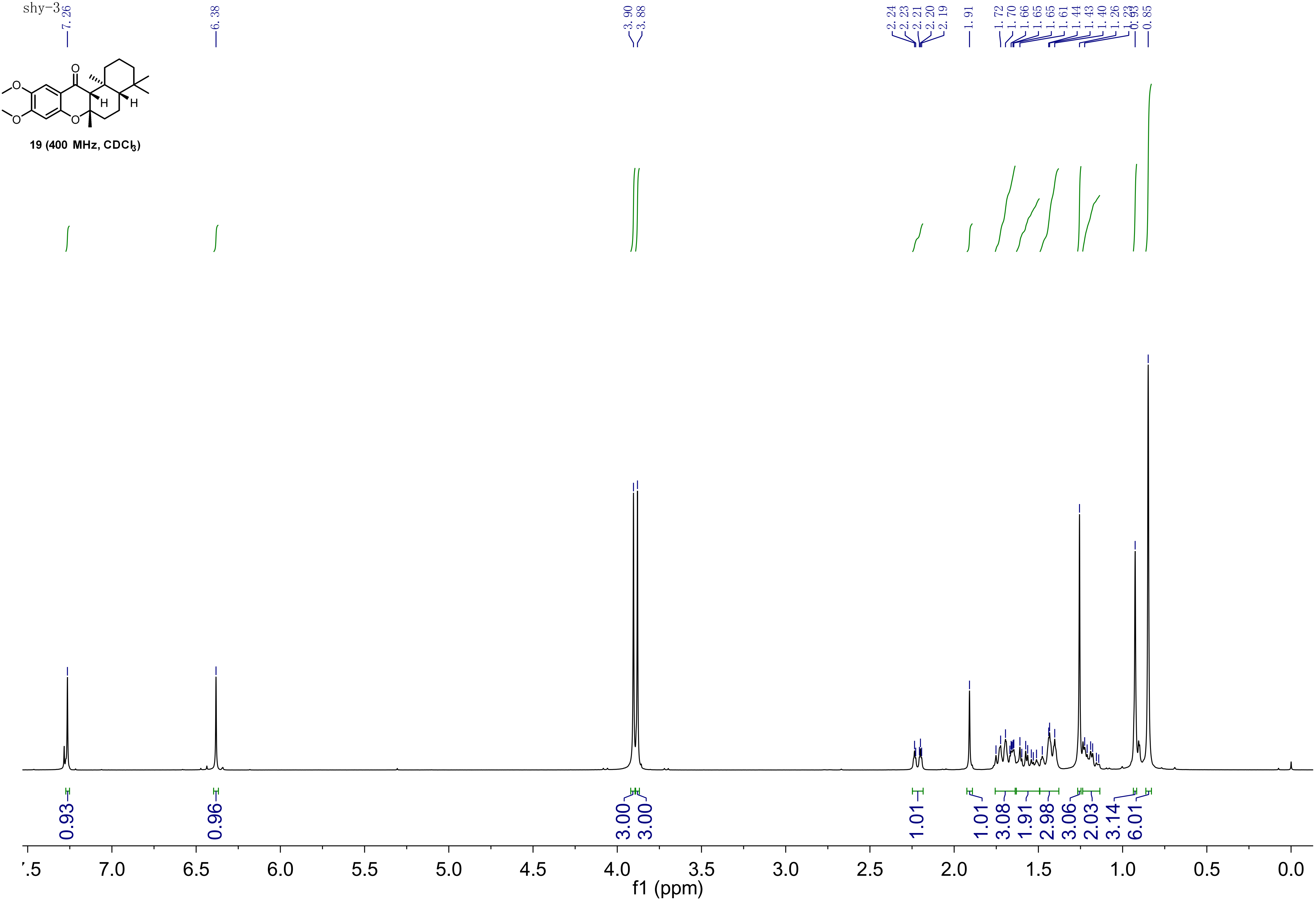
Mass spectra (LCMS) of inseparable mixture (13 and 13a)

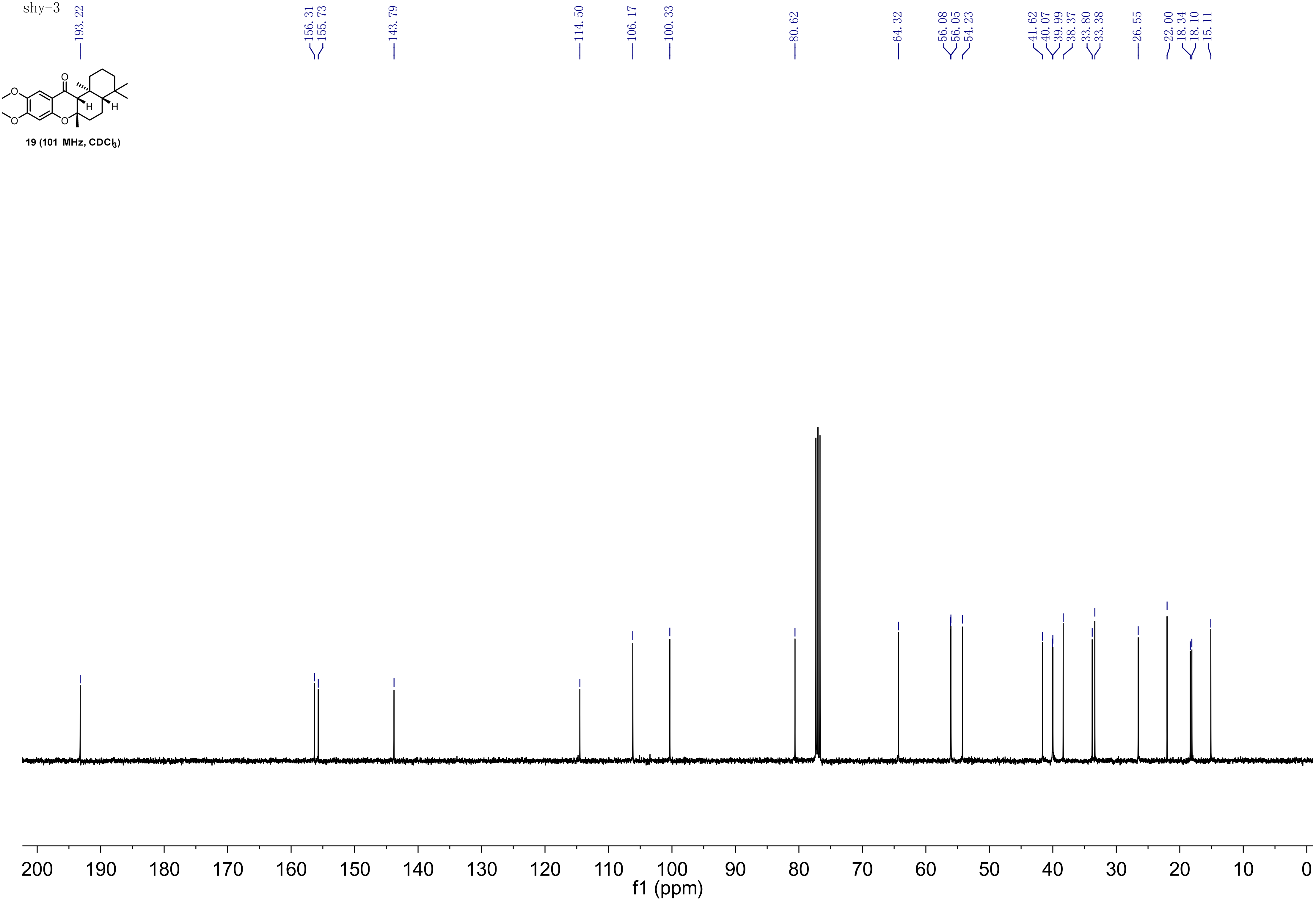
当前色谱图


DAD1 B, Sig=210,4 Ref=360,100 (xzm\S1015221-58-20.D)
mAU
Mass spectra (LCMS) of inseparable mixture (13 and 13a)
2500
2000
1500
1000
500
0
373.20
373.20
21.441
21.561
15.140
15.443
15.949
17.673
18.351
19.767
20.179
20.627
21.827
22.154
24.016
16
18
20
22
24
min

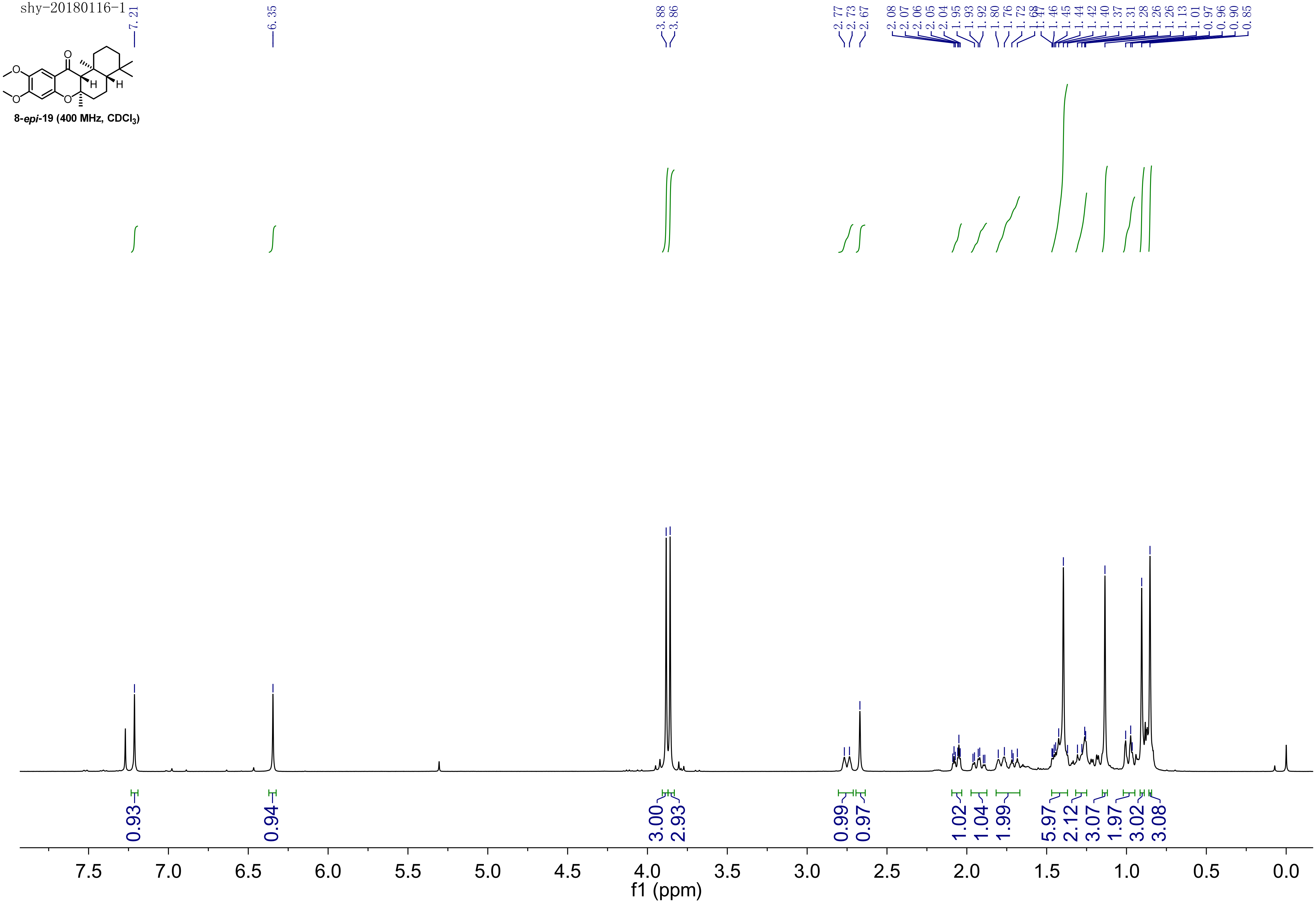

TfO
OMe
O
OMe
H
S1 (400 MHz,CDCl$_3$)
7.37
6.74
3.95
3.90
2.19
2.18
2.17
1.62
1.61
1.50
1.46
1.42
1.38
1.29
1.29
1.27
1.17
1.16
1.14
1.13
0.93
0.88
1.00
1.01
3.01
3.00
2.00
1.03
2.07
1.10
3.13
2.09
4.02
2.05
3.01
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

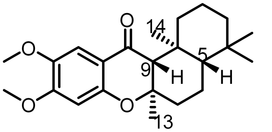

S1 (101 MHz,CDCl$_3$)


shy-3
7.26
6.38
3.90
3.88
2.24
2.23
2.21
2.20
2.19
1.91
1.72
1.70
1.66
1.65
1.65
1.61
1.44
1.43
1.40
1.26
1.23
0.93
0.85
19 (400 MHz, CDCl3)
O
O
O
O
H
H
0.93
0.96
3.00
3.00
1.01
1.01
3.08
1.91
2.98
3.06
2.03
3.14
6.01
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)

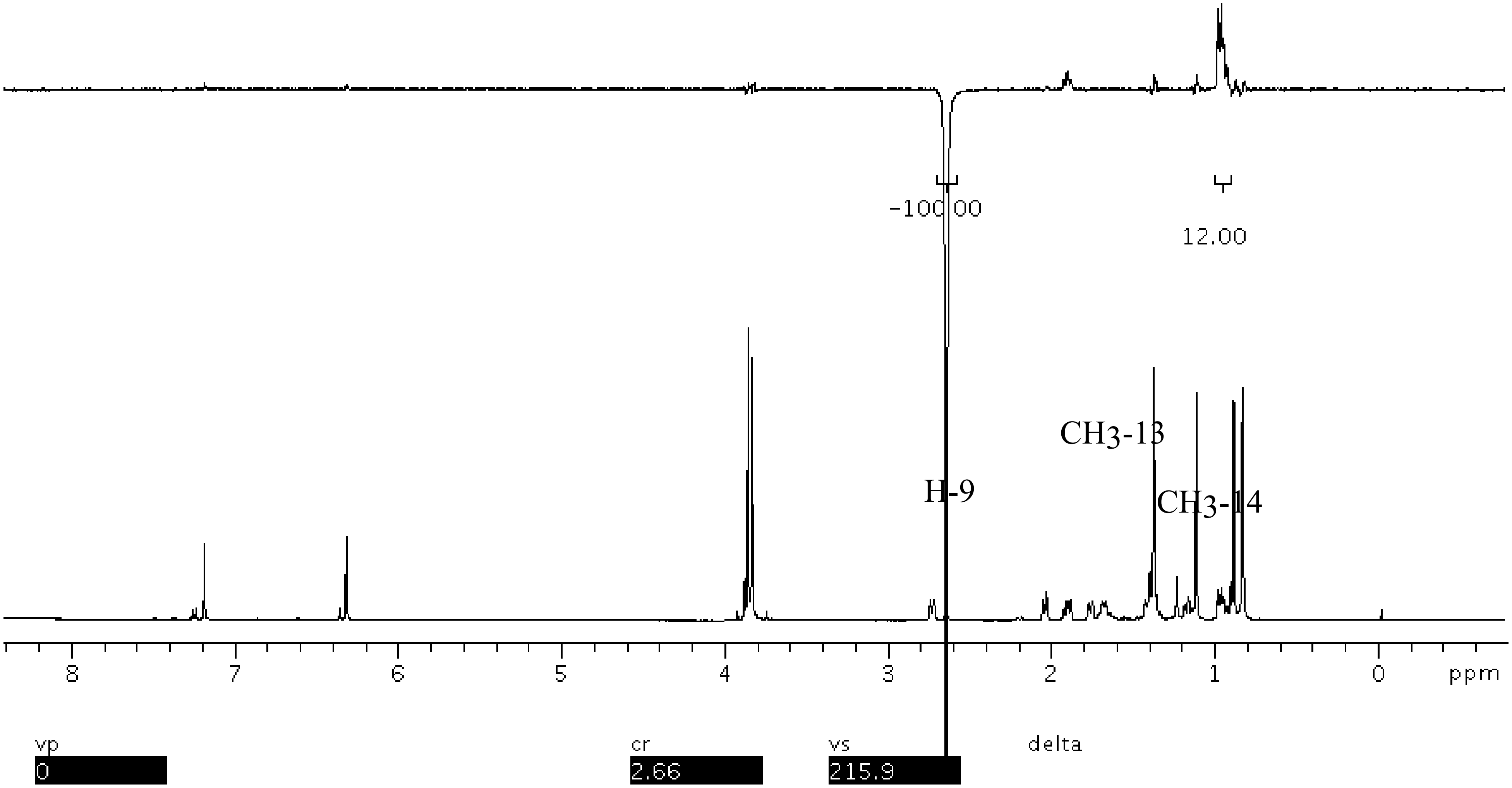


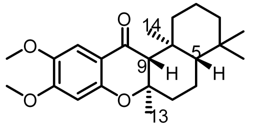
19 (101 MHz, $CDCl_3$)


shy-20180116-1
8-*epi*-19 (400 MHz, CDCl3)
7.21
6.35
3.88
3.86
2.77
2.73
2.67
2.08
2.07
2.06
2.05
2.04
1.95
1.93
1.92
1.80
1.76
1.72
1.68
1.47
1.46
1.45
1.44
1.42
1.40
1.37
1.31
1.28
1.26
1.13
1.01
0.97
0.96
0.90
0.85
0.93
0.94
3.00
2.93
0.99
0.97
1.02
1.04
1.99
5.97
2.12
3.07
1.97
3.02
3.08
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)

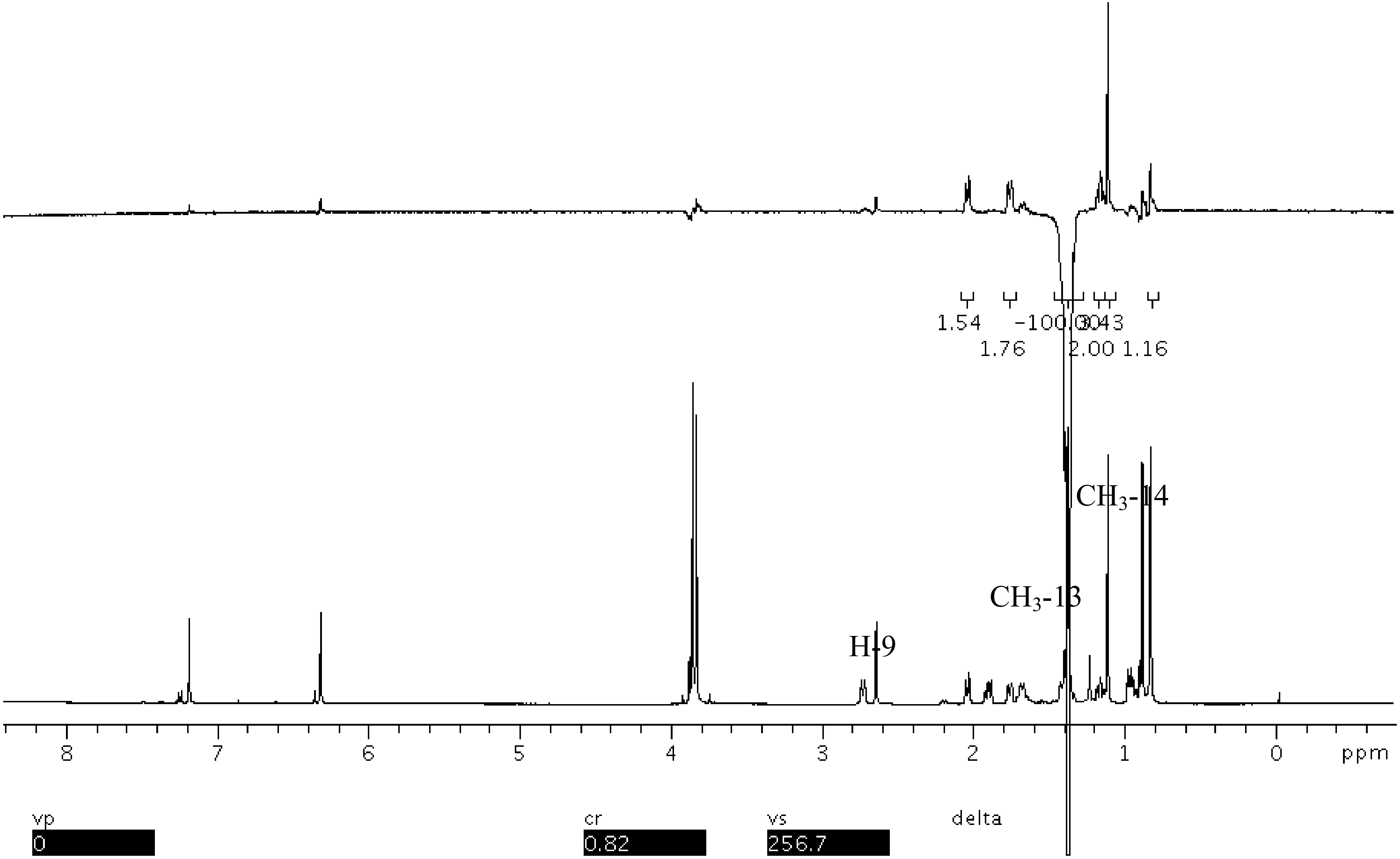


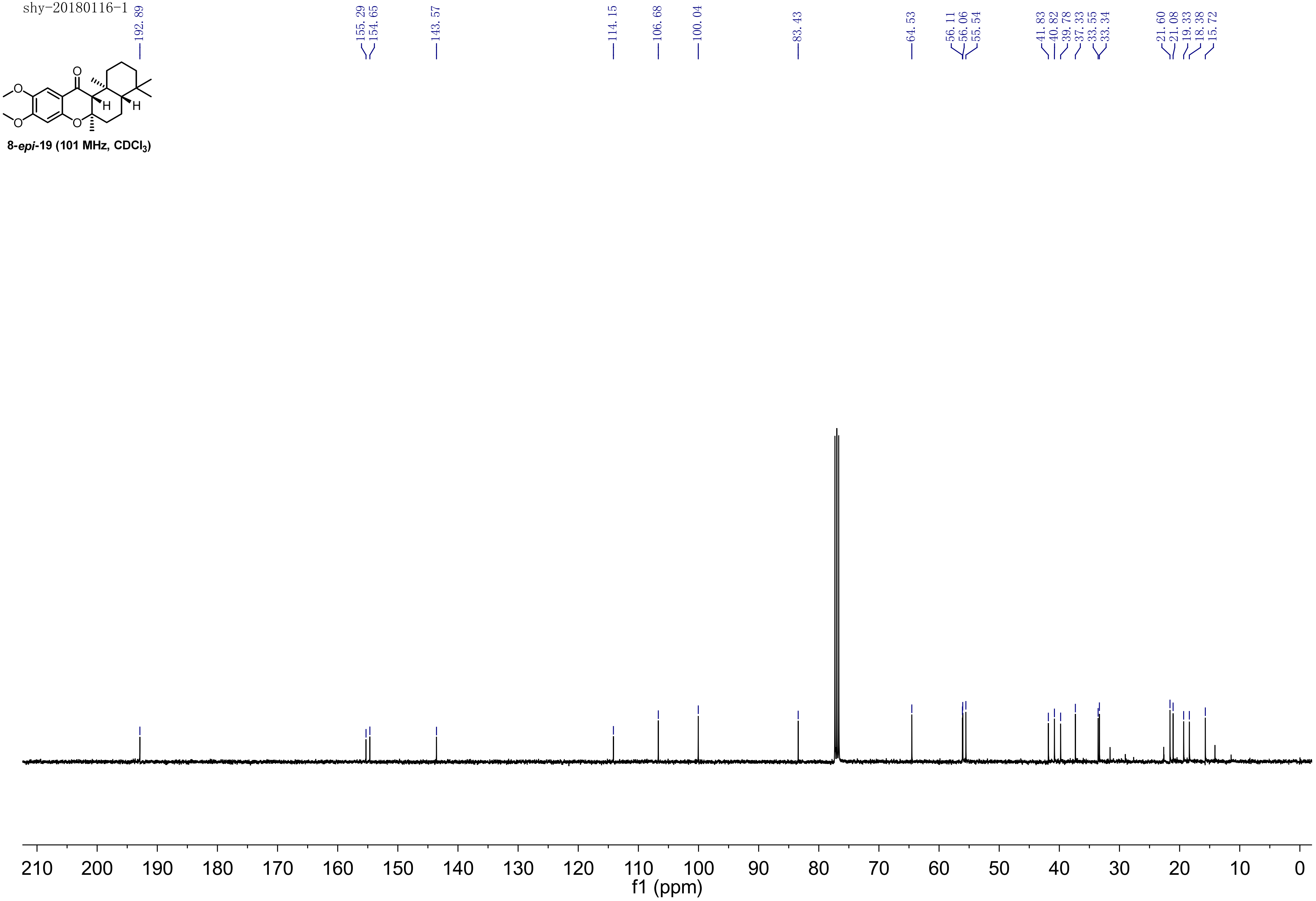
8-*epi*-19 (600 MHz, $CDCl_3$)



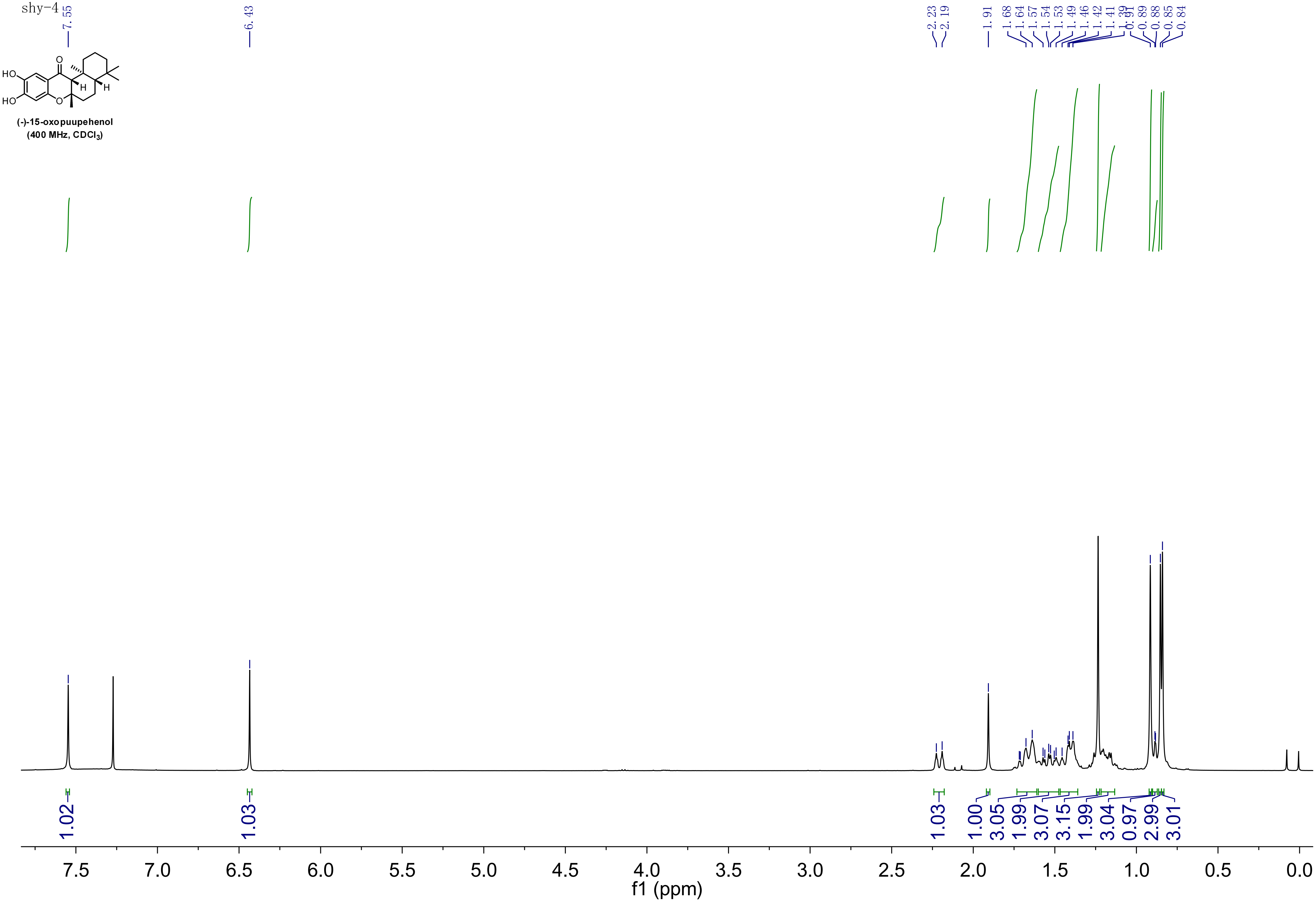


8-*epi*-19 (600 MHz, $CDCl_3$)

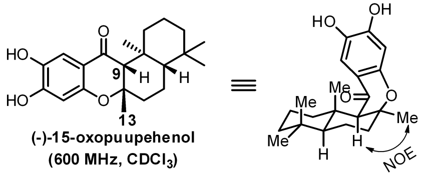




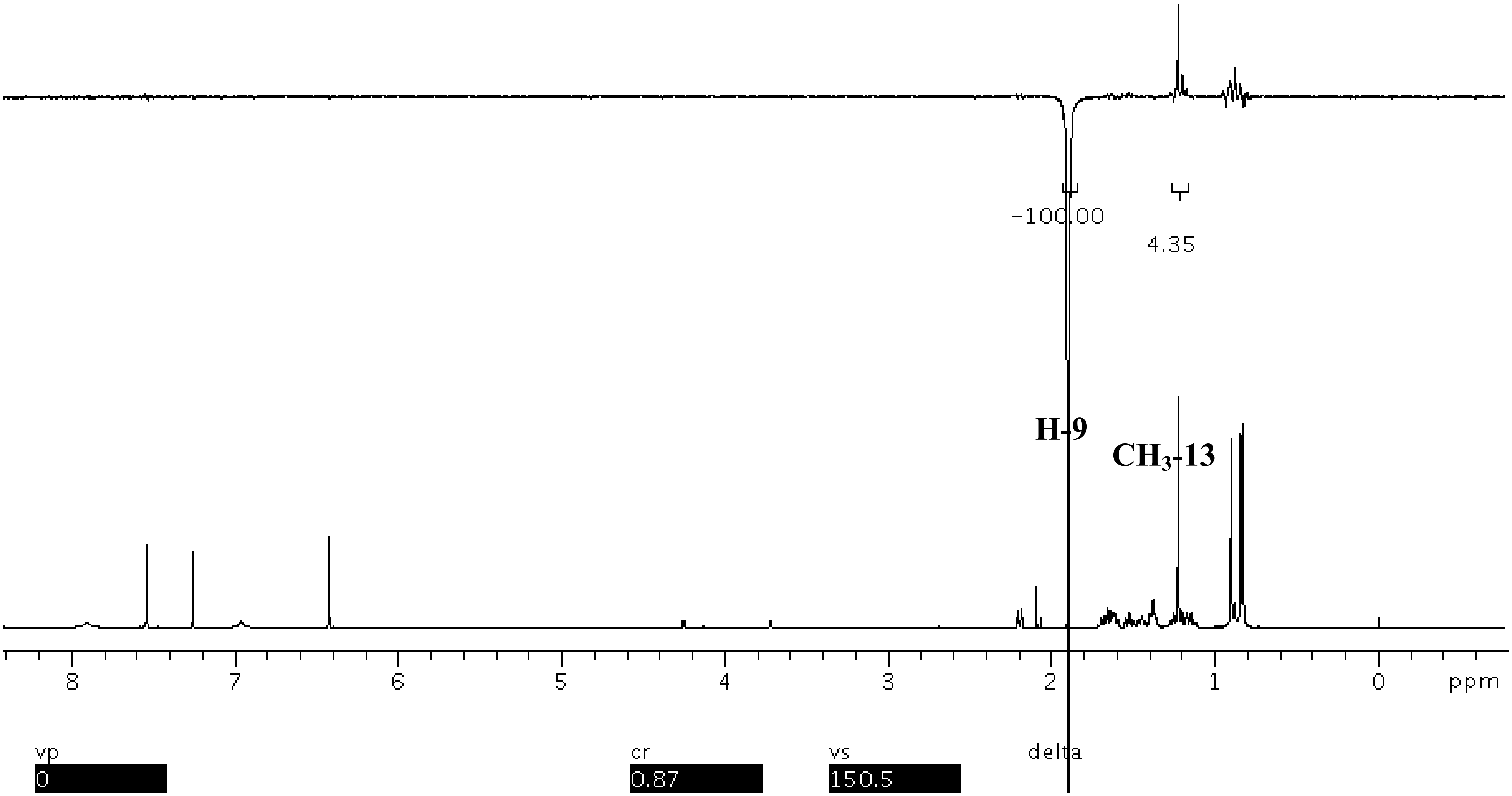
8-*epi*-19 (101 MHz, $CDCl_3$)

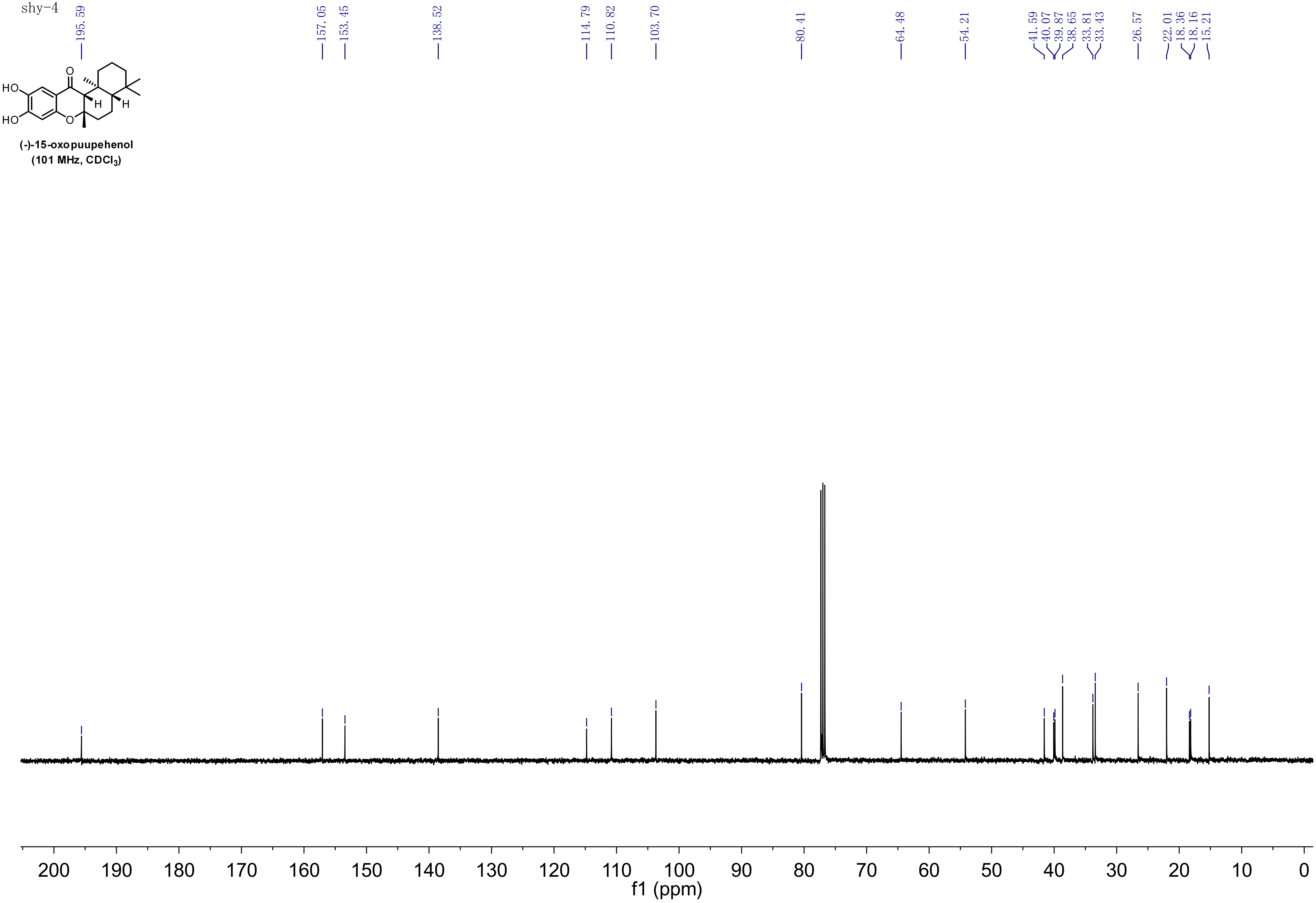


(-)-15-oxopuupehenol
(400 MHz, $CDCl_3$)

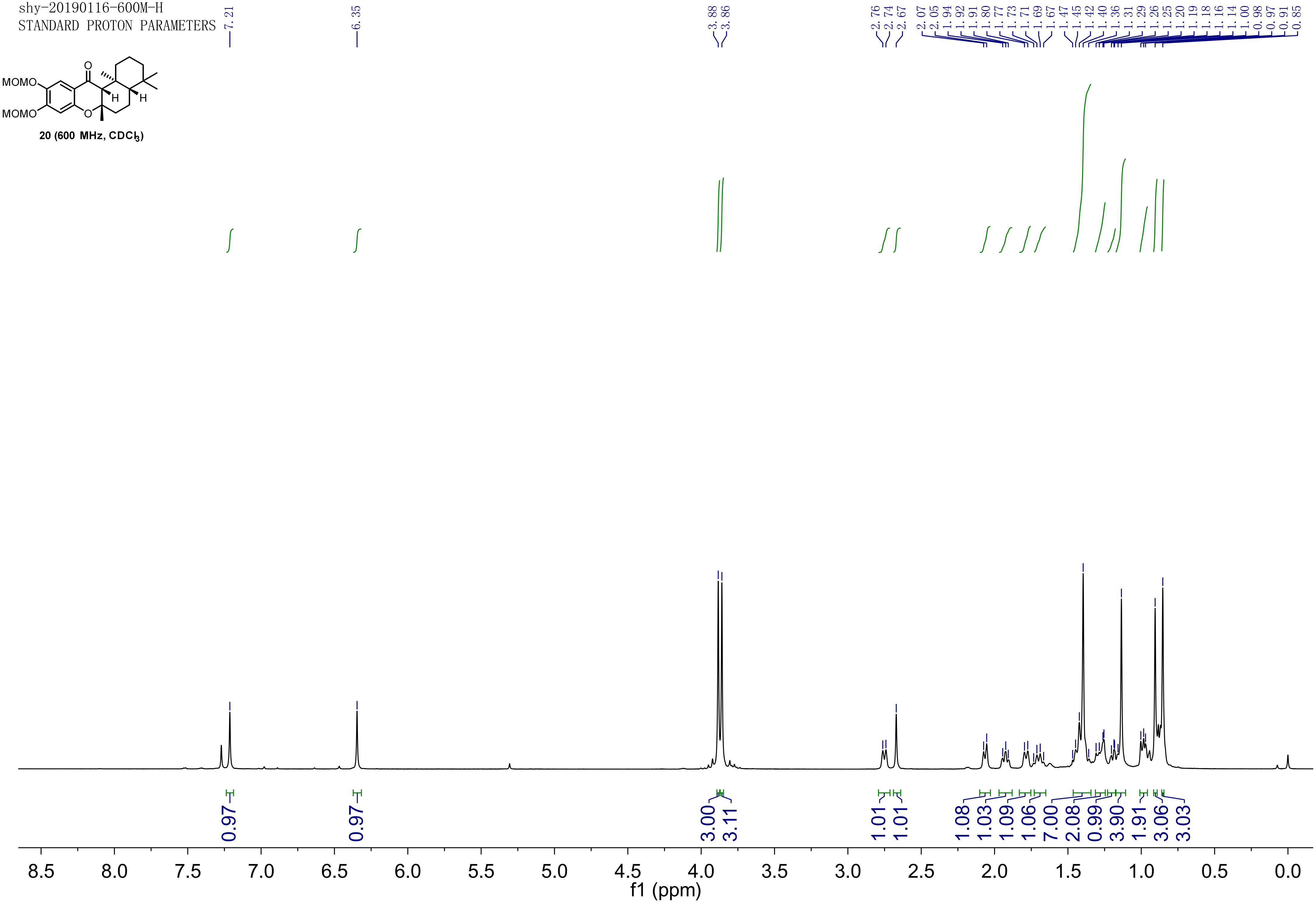


(-)-15-oxopuupehenol
(600 MHz, $CDCl_3$)

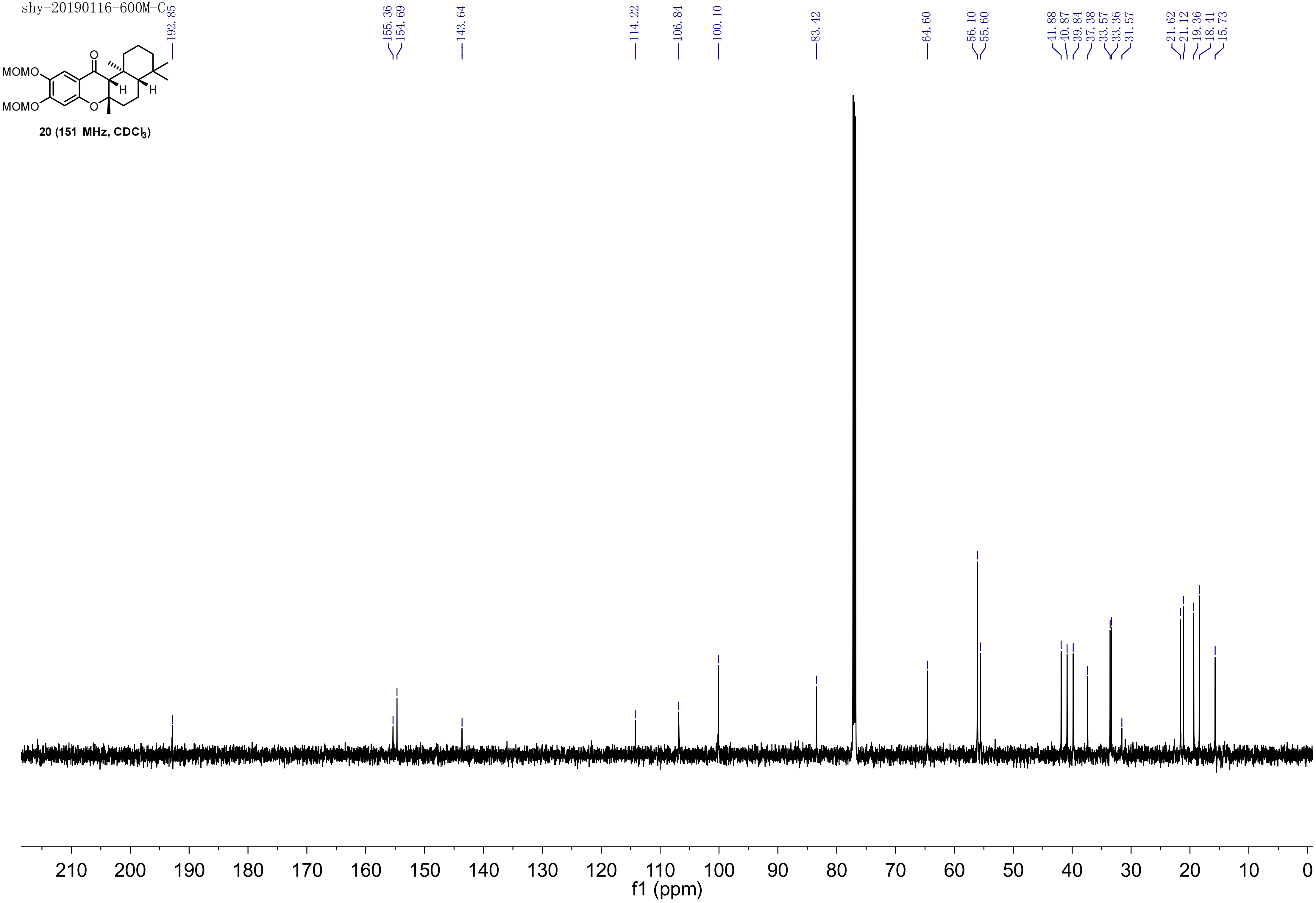


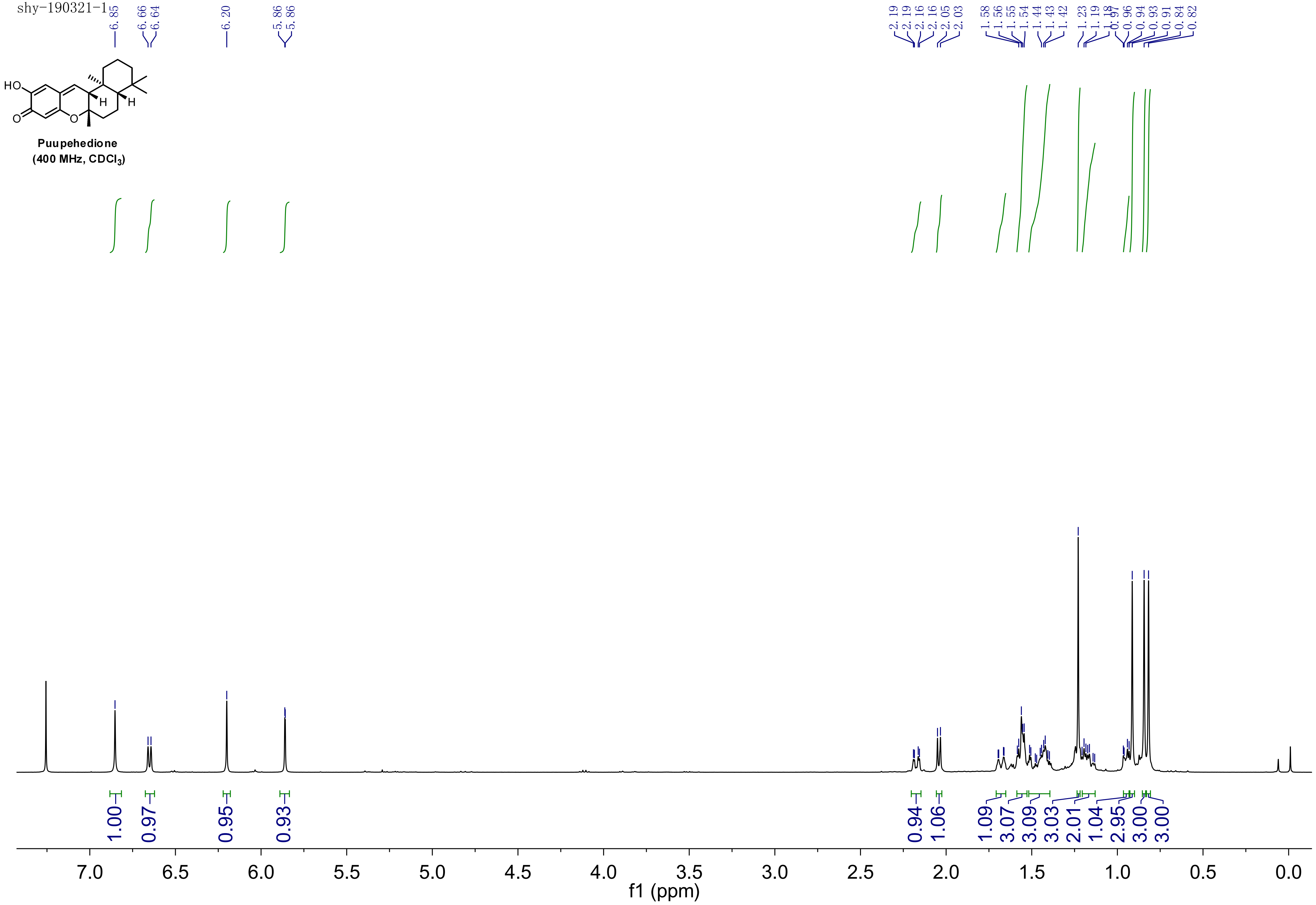


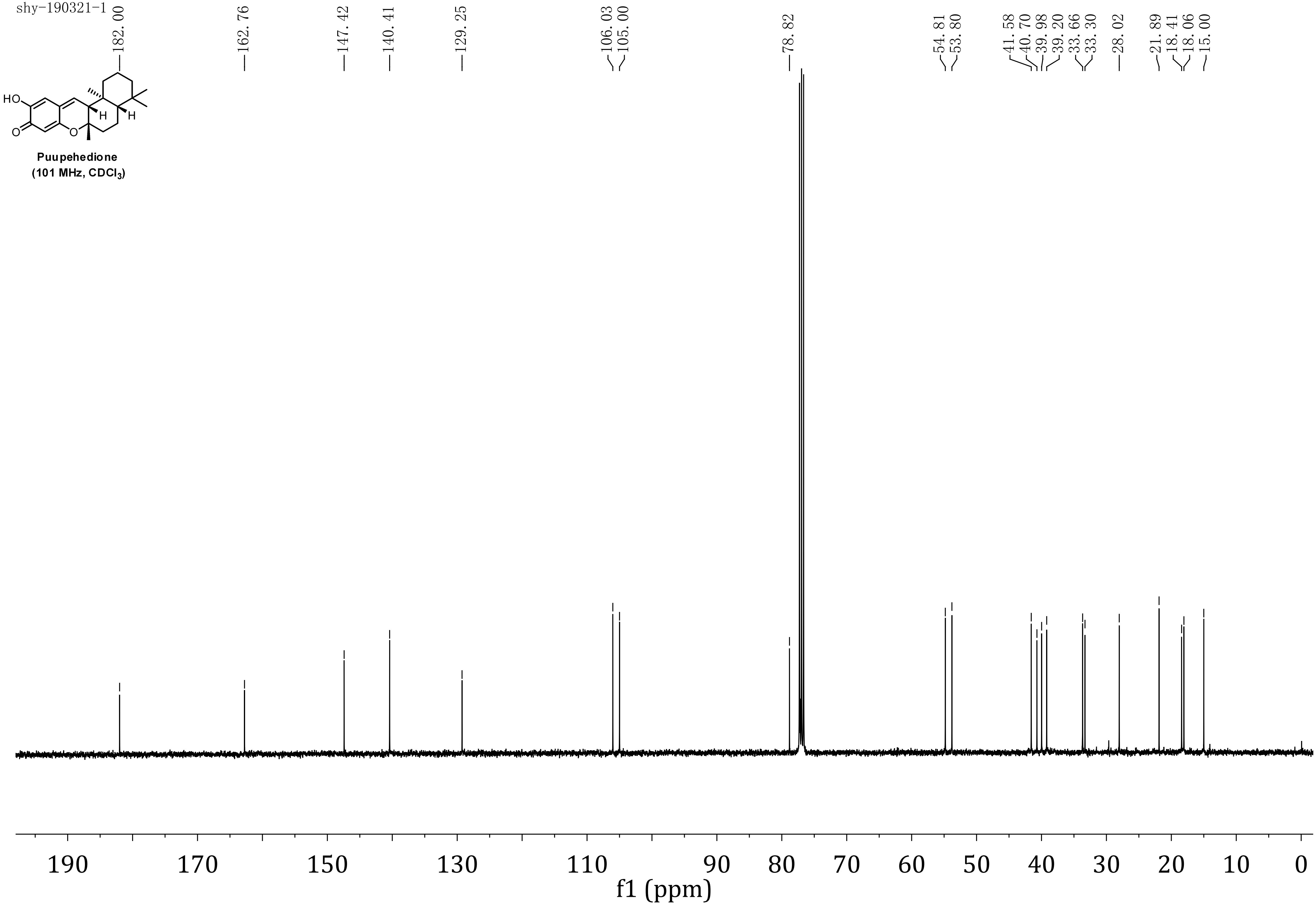
(-)-15-oxopuupehenol
(101 MHz, $CDCl_3$)



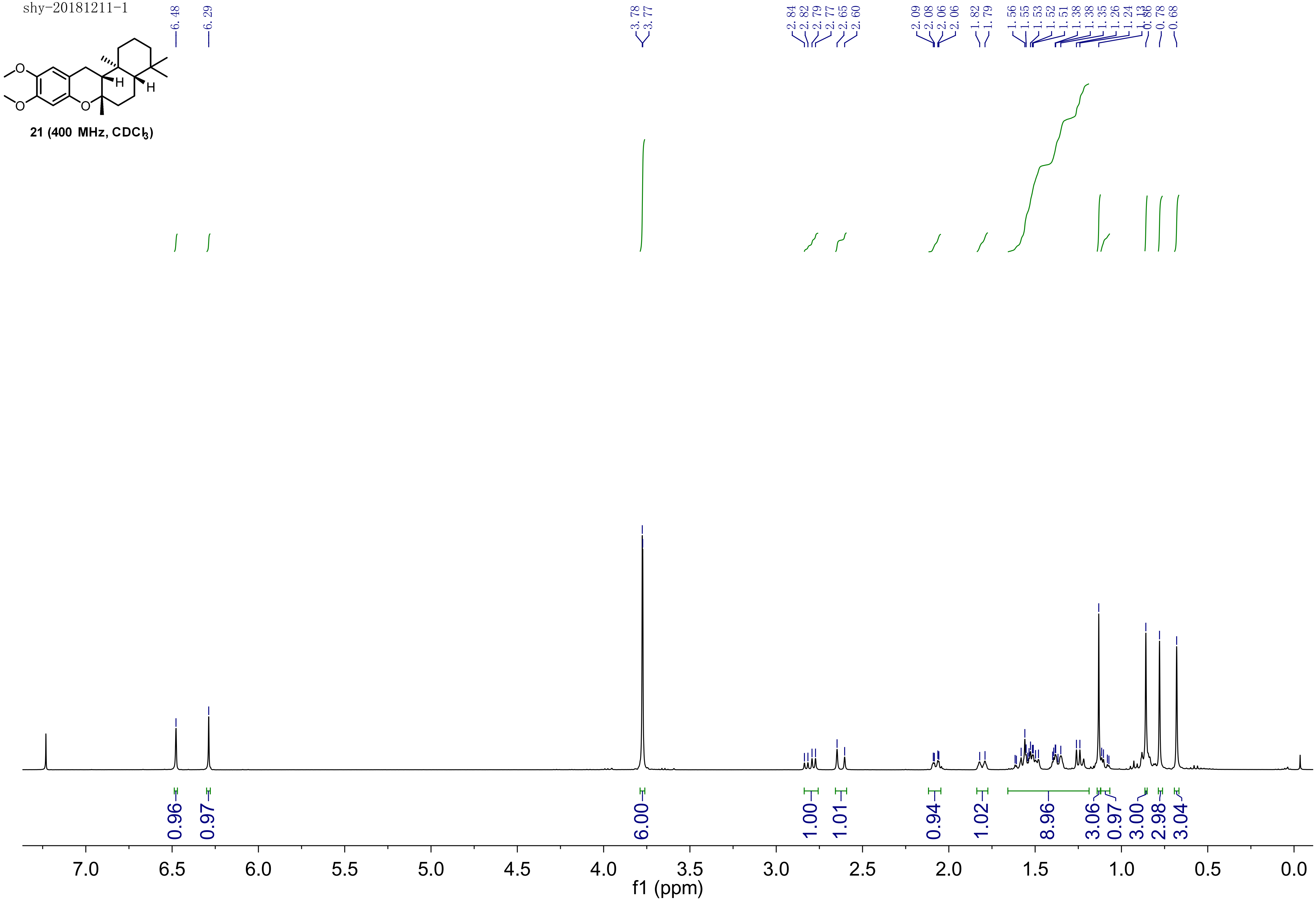
20 (600 MHz, $CDCl_3$)


20 (151 MHz, CDCl$_3$)

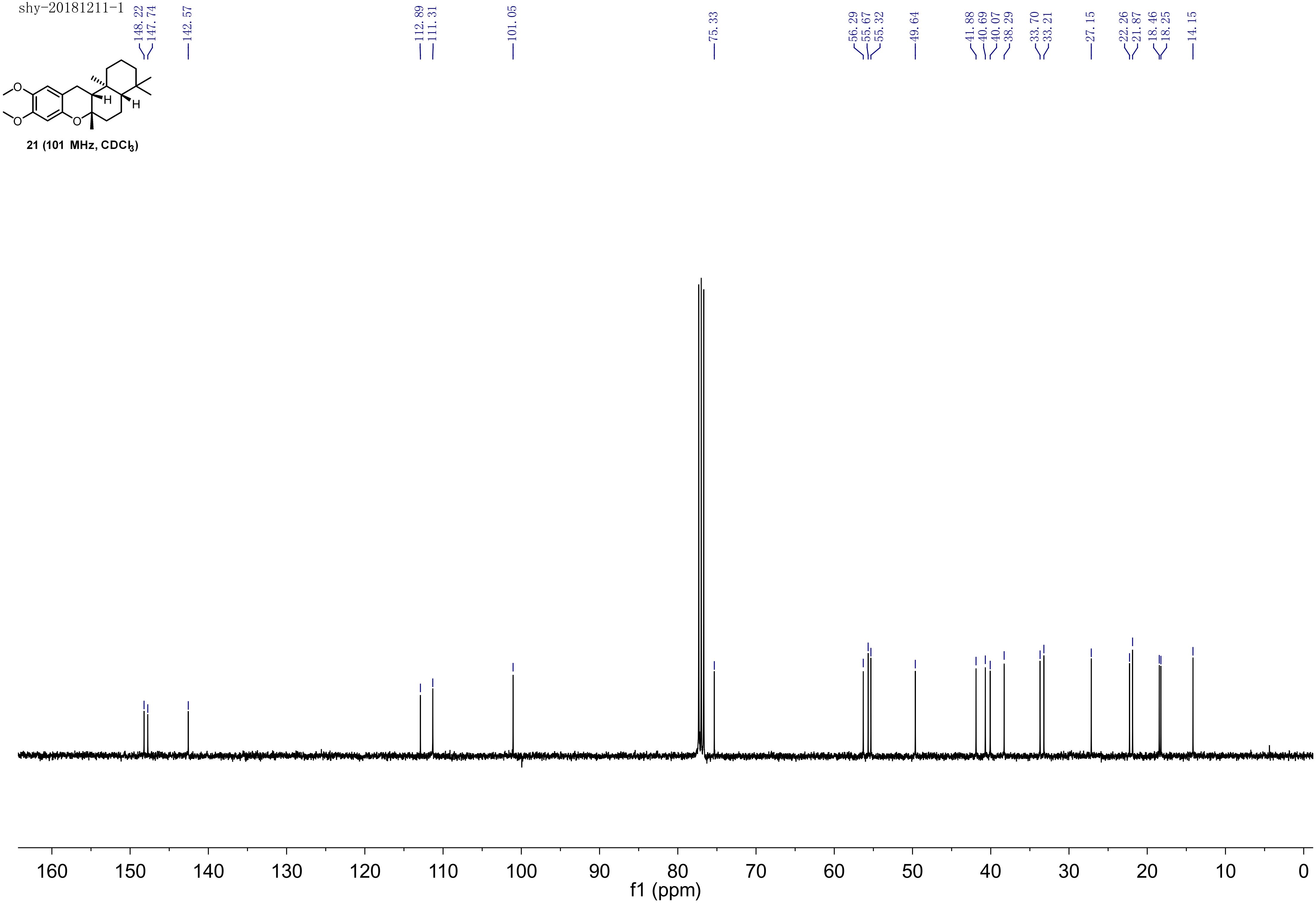

shy-190321-1
6.85
6.66
6.64
6.20
5.86
5.86
2.19
2.19
2.16
2.16
2.05
2.03
1.58
1.56
1.55
1.54
1.44
1.43
1.42
1.23
1.19
1.18
0.97
0.96
0.94
0.93
0.91
0.84
0.82
HO
O
O
H
H
Puupehedione
(400 MHz, CDCl$_3$)
1.00
0.97
0.95
0.93
0.94
1.06
1.09
3.07
3.09
3.03
2.01
1.04
2.95
3.00
3.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



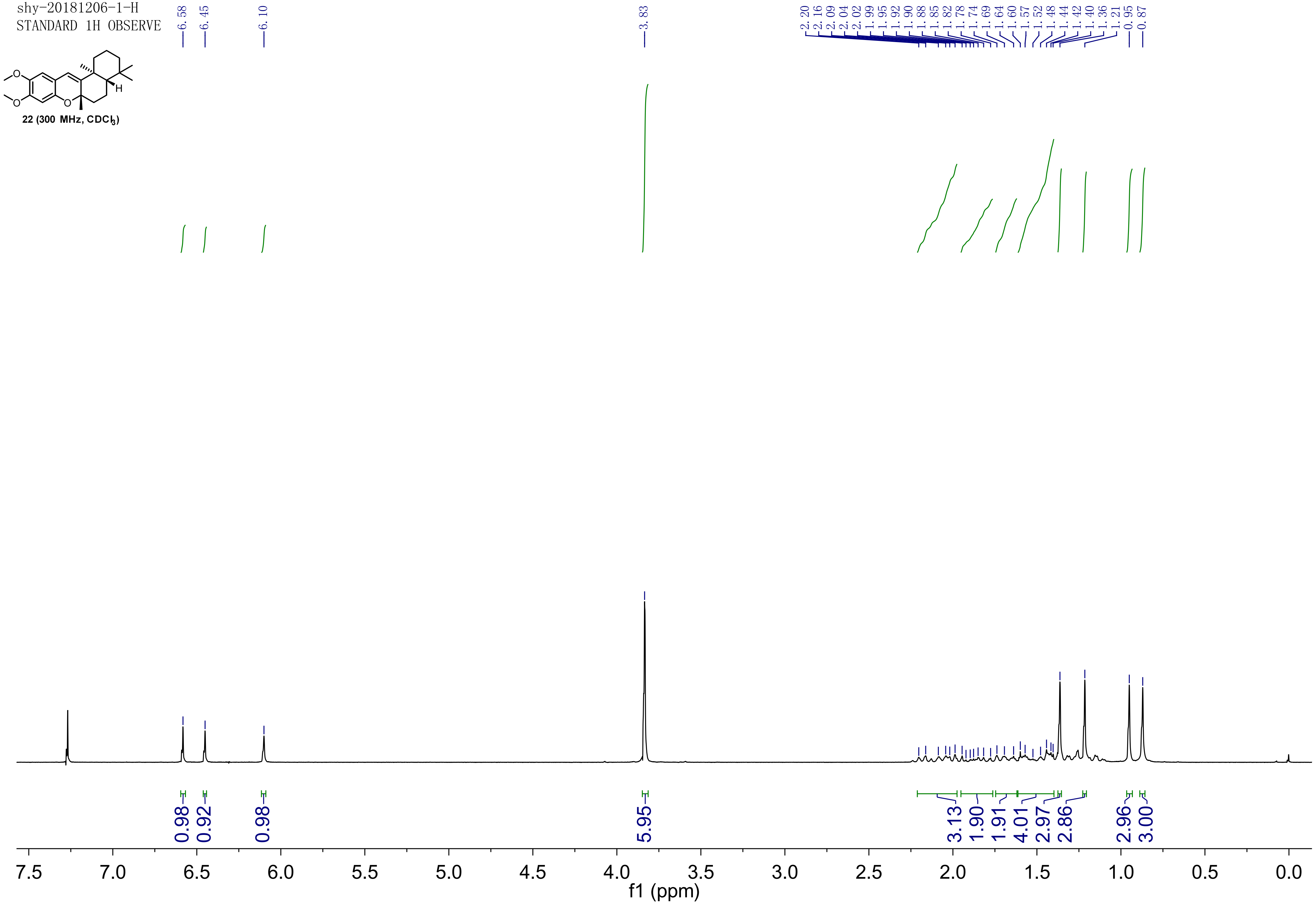
Puupehedione
(101 MHz, $CDCl_3$)

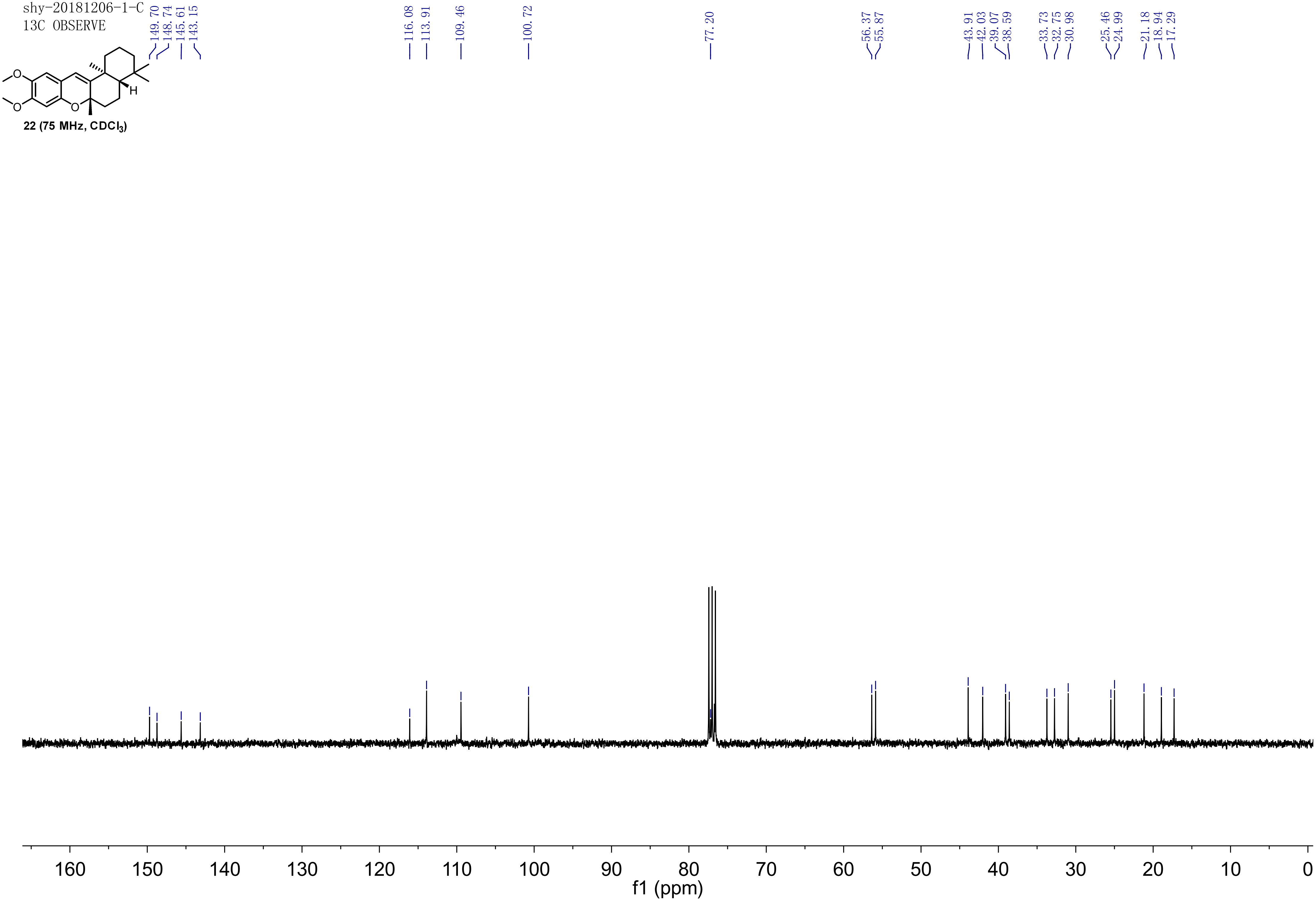


21 (400 MHz, $CDCl_3$)



21 (101 MHz, $CDCl_3$)


shy-20181206-1-H
STANDARD 1H OBSERVE
22 (300 MHz, CDCl$_3$)
6.58
6.45
6.10
3.83
2.20
2.16
2.09
2.04
2.02
1.99
1.95
1.92
1.90
1.88
1.85
1.82
1.78
1.74
1.69
1.64
1.60
1.57
1.52
1.48
1.44
1.42
1.40
1.36
1.21
0.95
0.87
0.98
0.92
0.98
5.95
3.13
1.90
1.91
4.01
2.97
2.86
2.96
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
0.0
f1 (ppm)



22 (75 MHz, $CDCl_3$)