Stereoselective Total Synthesis of (–)-(2*S*,4*R*)-3'-Methoxyl Citreochlorol: Preparation and Use of New Proline Based Auxiliary for Asymmetric Acetate Aldol Reaction.

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Supplementary Information

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Conditions for demethylation:

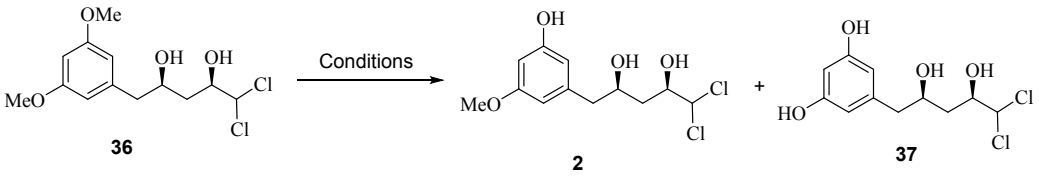


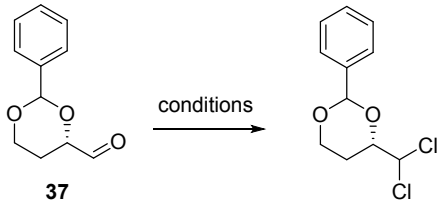
Table 1:

s.no	Reaction conditions	2 : 37 : 36
1	BBr_3, DCM,-78 ^oC - rt, 16 h	0 : 0 : 79% [a, 1]
2	$AlCl_3$, DCM, 0 ^oC - rt, 28 h	0 : 0 : 68% [a, 2]
3	$HPPh_2$, n-BuLi, THF, 0 ^oC - rt, 8 h	0 : 0 : 0[c, 3]
4	$AlCl_3$ (6eq), DCM:EtSH(5:1), -10 ^oC - rt, 24 h	0 : 0 : 80% [a]
5	$AlCl_3$(exess) ,DCM:EtSH(1:1), -10 ^oC – rt, 1 h	0 : 55%[b]: 0 [a]
6	LiCl, DMF, 150 ^oC,12 h	0 : 0 : 91% [a]
7	TMS-I, $CHCl_3$, 0 ^oC – rt, 12 h	0 : 0 : 0 [c, 4]
8	NaH, EtSH, DMF, Reflux, 12 h	0 : 0 : 0[c]
9	Al, I_2, DMSO, MeCN, 80 ^oC, 12 h	0 : 0 : 69% [a, 5]
10	KI, TFA, 40 ^oC, 12 h	0 : 0 : 0 [c]
11	$AlCl_3$, thiourea, DCM, 0 ^oC – rt, 12 h	0 : 0 : 93% [a]
12	$MeSO_3H$, TFA, 40 ^oC, 12 h	0 : 0 : 0 [c]

a. We observed some unidentified products with starting compound.

b. 55% yield with some other impurities. c. Unidentified products

Conditions for deoxy dichlorination of aldehydes:



37

Table 2:

Entry	**Reaction conditions**	**Result**[a]
1	$(PPh_2)Cl$, NCS, DCM, 0 ^oC – rt, 6h	complex mixture[6]
2	(a) $H_2N\text{-}NH_2.H_2O$, MeOH (b) $CuCl_2$, Et_3N, MeOH, 0 ^oC – rt, 4h	complex mixture[7]
3	$P(OPh)_3$, Cl_2, Et_3N, DCM, -78 ^oC, 8h	complex mixture[8]
4	PCl_5, DCM, -78 ^oC, 3h	complex mixture[9]
5	(a) $H_2N\text{-}NH_2.H_2O$, MeOH (b) $CuCl_2$, DIPEA, MeOH, 0 ^oC – rt, 4h	complex mixture[7]
6	(a) $H_2N\text{-}NH_2.H_2O$, MeOH (b) $CuCl_2$, pyrrolidine, MeOH, 0 ^oC – rt, 4h	complex mixture[7]
7	(a) $H_2N\text{-}NH_2.H_2O$, MeOH (b) $CuCl_2$, tBuOLi, MeOH,0 ^oC – rt, 4h	complex mixture[7]
8	TBAI, PPh_3, DCE, 80 ^oC, 12h	complex mixture[5]
9	PCl_5, CCl_4, 0 ^oC - rt, 5h	complex mixture
10	PCl_5, $CaCl_2$, CCl_4, -20 ^oC – 0 ^oC, 1h	complex mixture

a. TLC analysis shows several compounds, GC and NMR shows no desired signals.

Crystallographic Data of Compound 1:

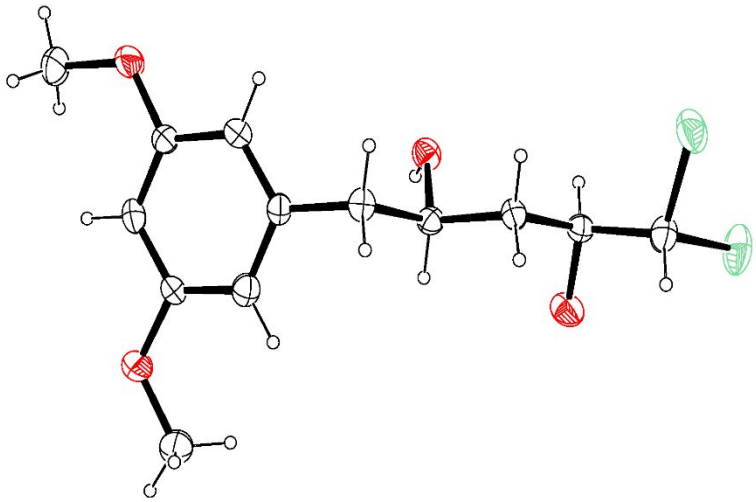


Figure S1. ORTEP structure of for (–)-(2*S*, 4*R*)-3`-methoxy citreochlorol. The thermal ellipsoid plots are drawn at 30% probability level. Hydrogen atoms on carbons are omitted for clarity. Selected bond distances (Å) and angles (°). The coumpound was crystallised in hexane dichloromethane solvent mixture at -20 °C.

Table 3. Crystal data and structure refinement for (–)-(2*S*, 4*R*)-3`-methoxy citreochlorol.

Identification code	shelx	
Empirical formula	C13 H20 Cl2 O5	
Formula weight	327.19	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.682(2) Å	α= 90°.
	b = 6.4255(14) Å	β= 100.179(8)°.
	c = 26.074(6) Å	γ = 90°.
Volume	1596.6(6) $Å^3$	
Z	4	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	0.421 mm^{-1}	

F(000)	688
Crystal size	0.210 x 0.075 x 0.025 mm^3
Theta range for data collection	0.793 to 24.996°.
Index ranges	-11<=h<=11, -7<=k<=7, -31<=l<=31
Reflections collected	21317
Independent reflections	5629 [R(int) = 0.0594]
Completeness to theta = 24.996°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.990 and 0.917
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5629 / 1 / 379
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0805, wR2 = 0.2178
R indices (all data)	R1 = 0.1381, wR2 = 0.2670
Absolute structure parameter	-0.03(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.629 and -0.798 $e.Å^{-3}$

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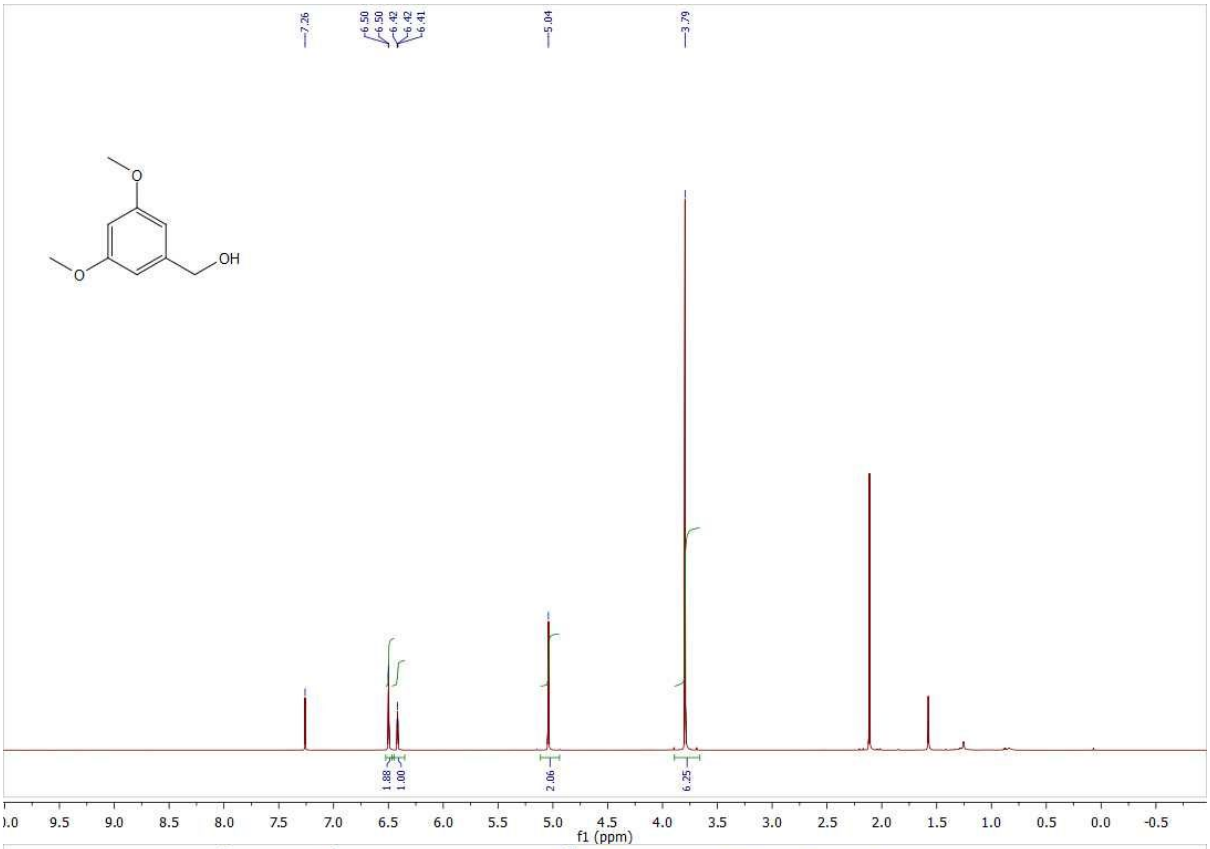
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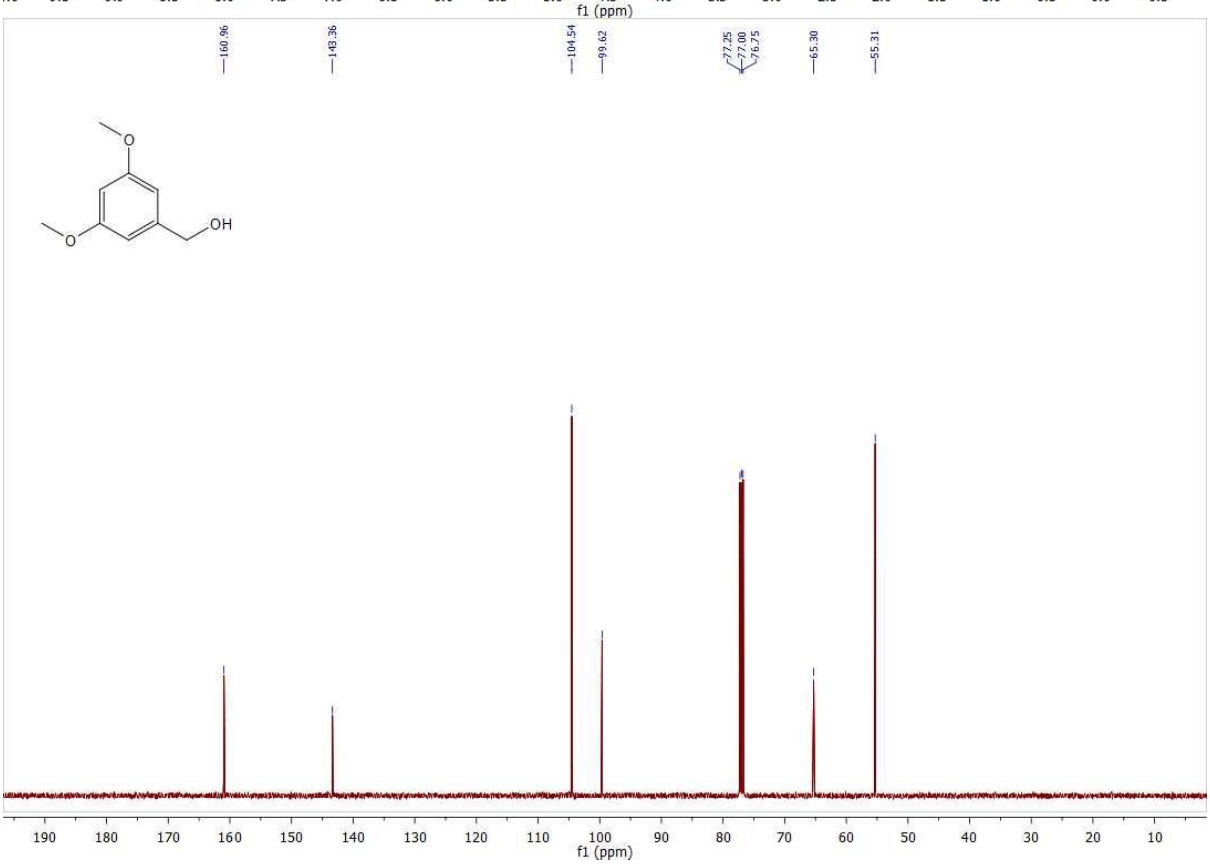
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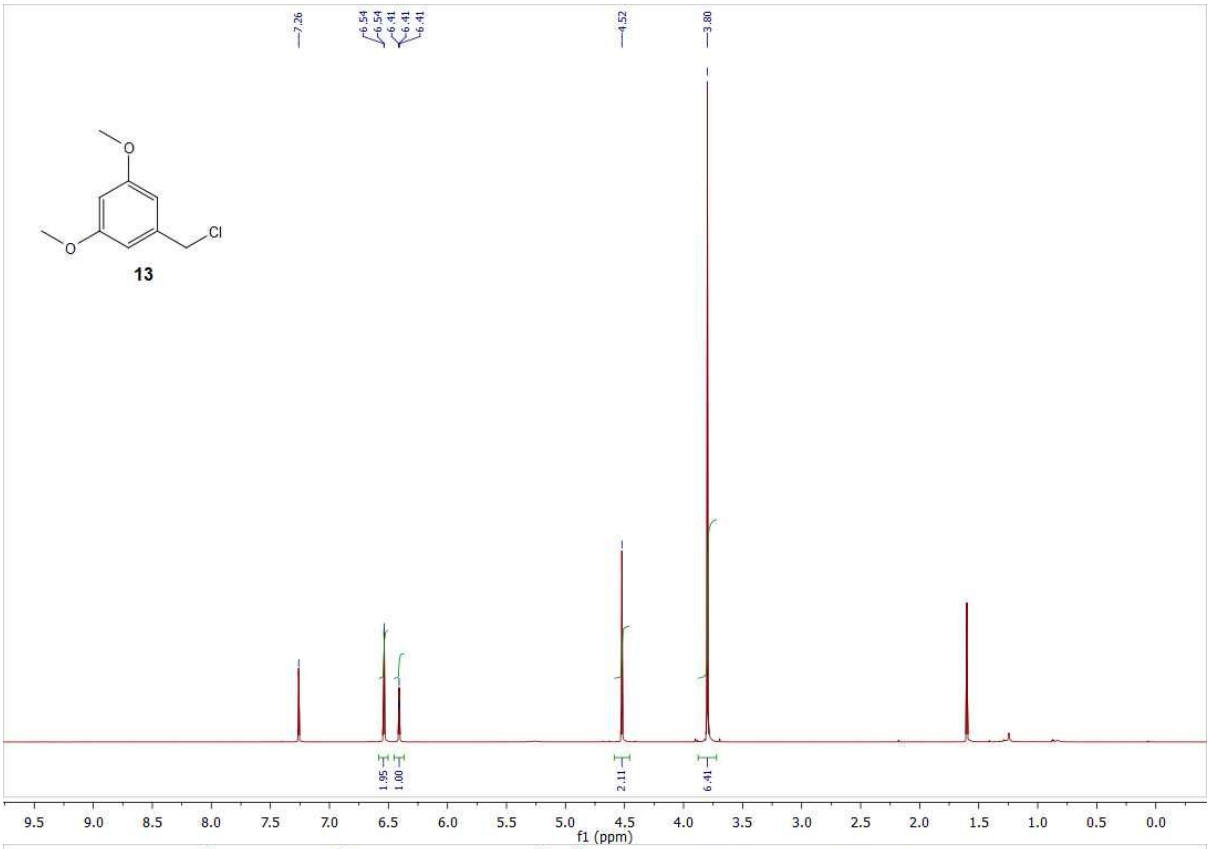
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6.41
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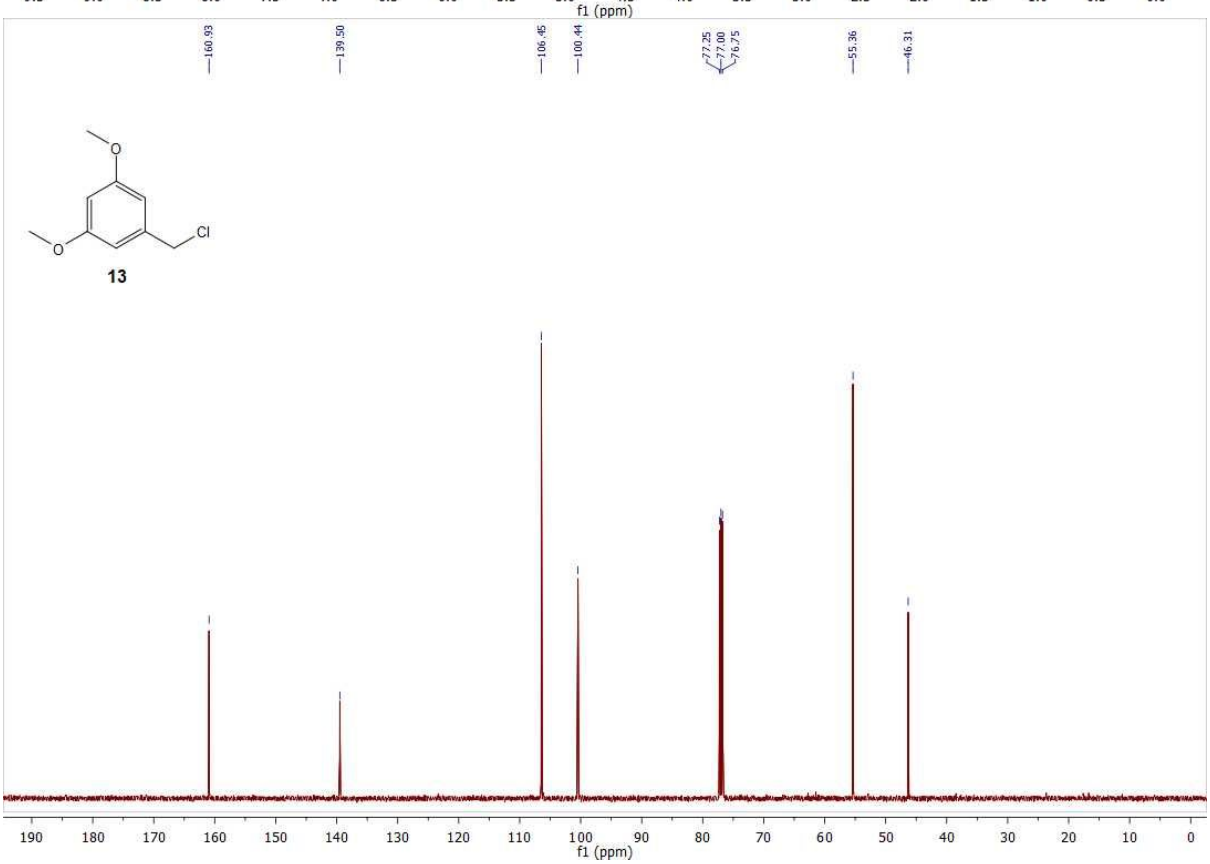
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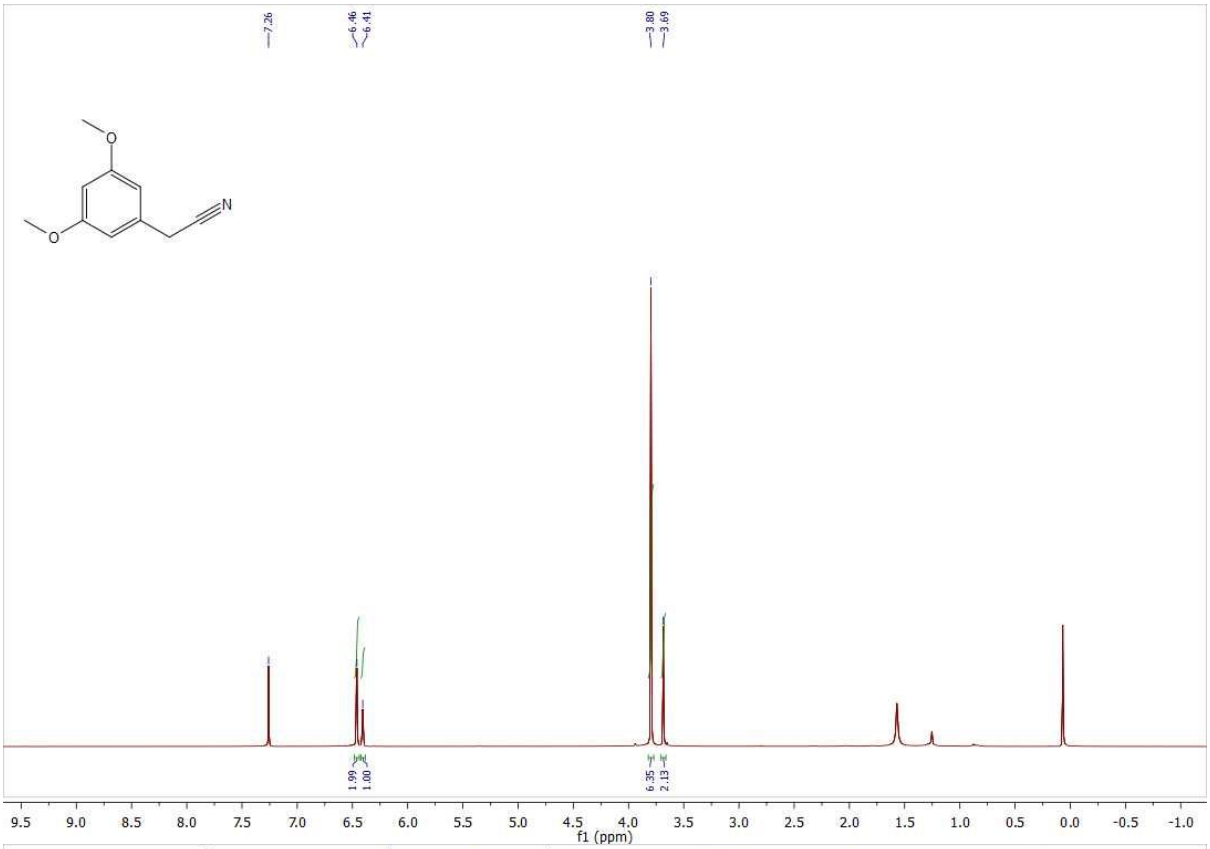
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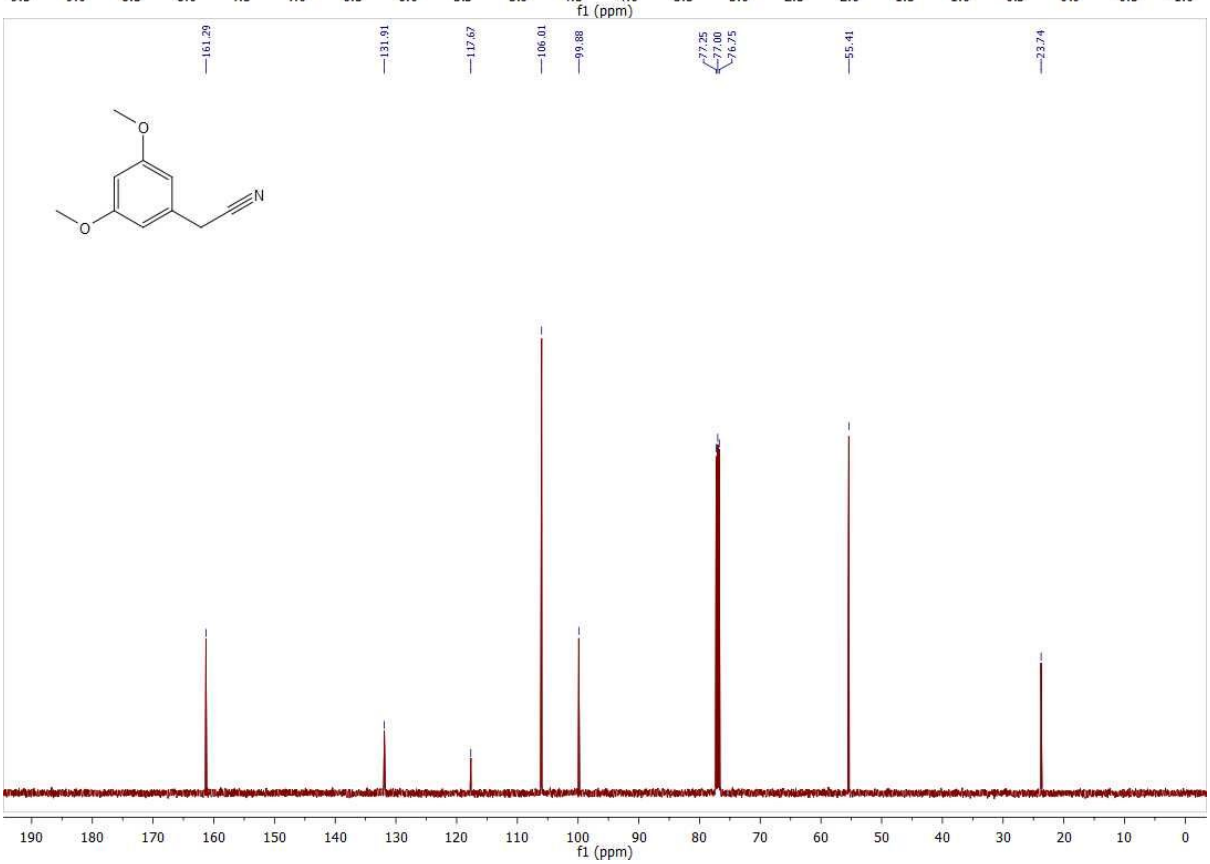
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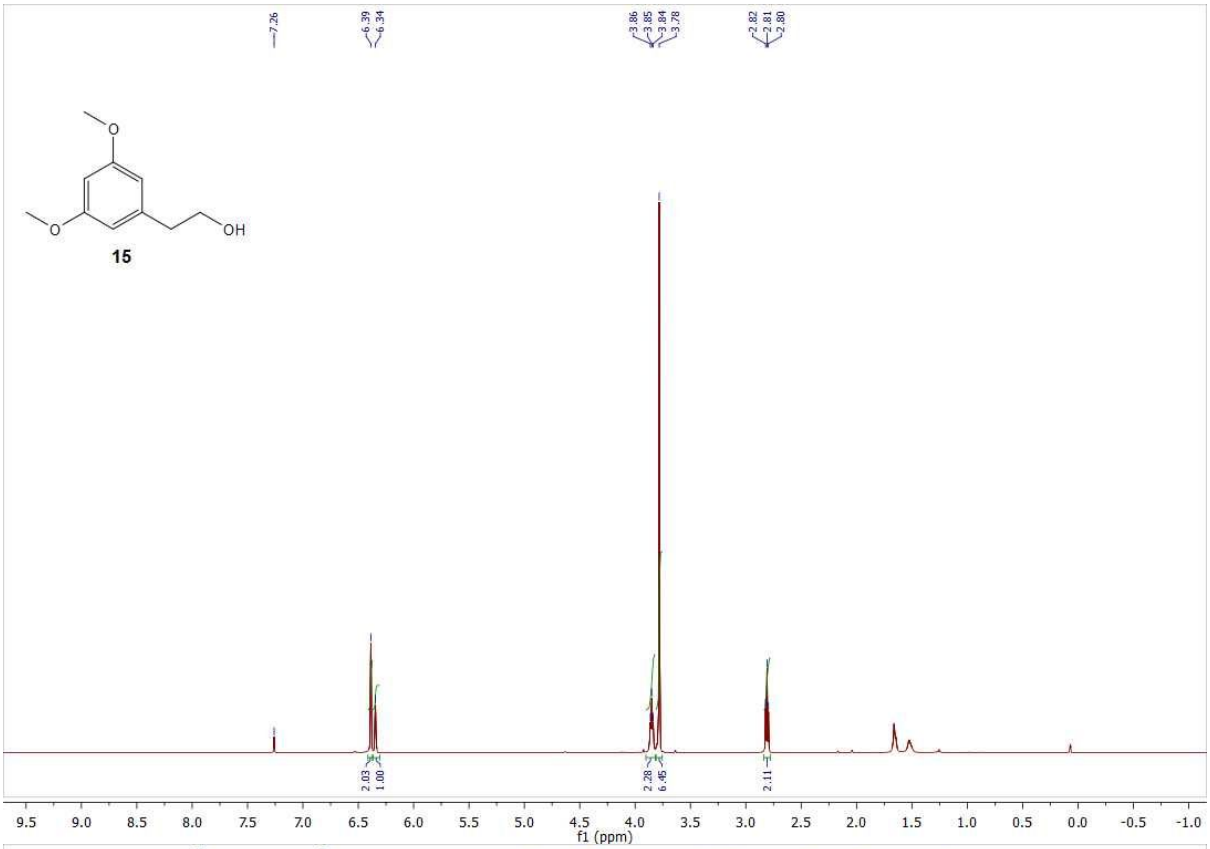
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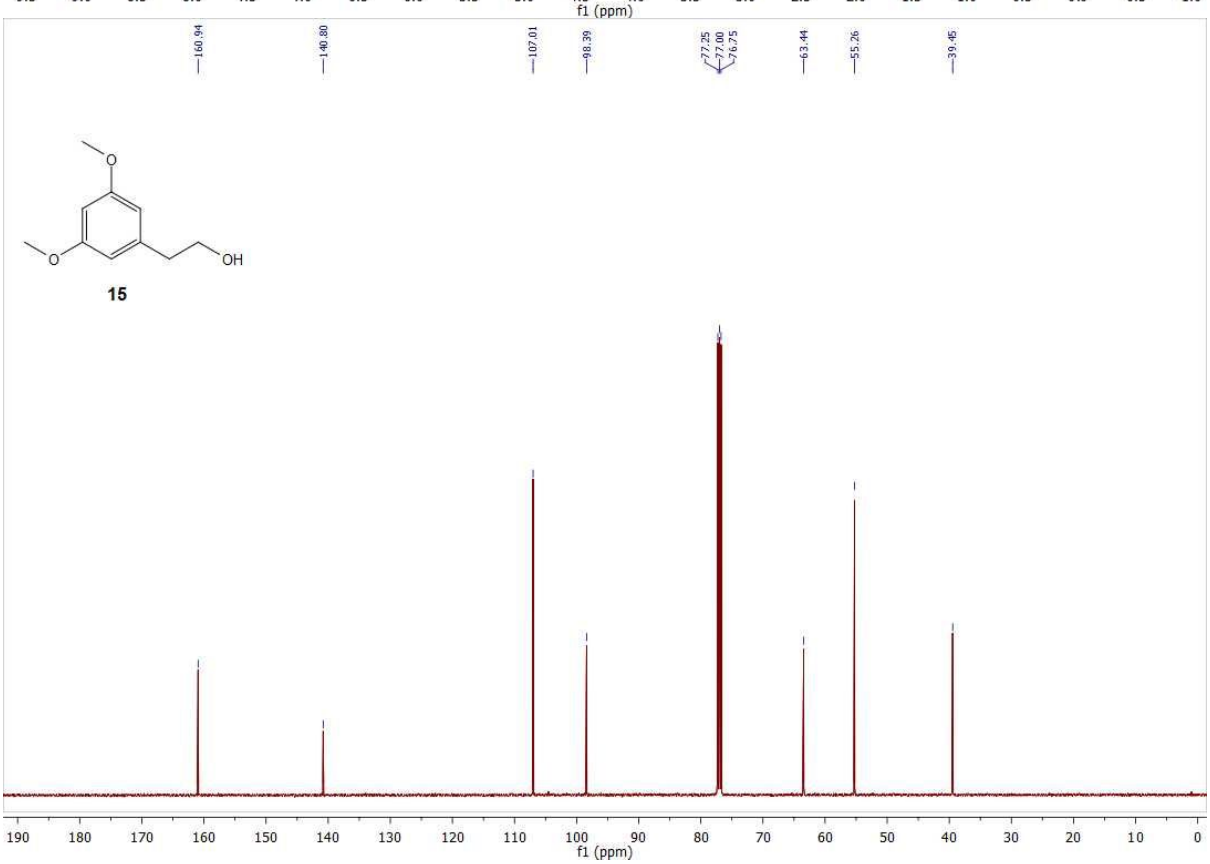
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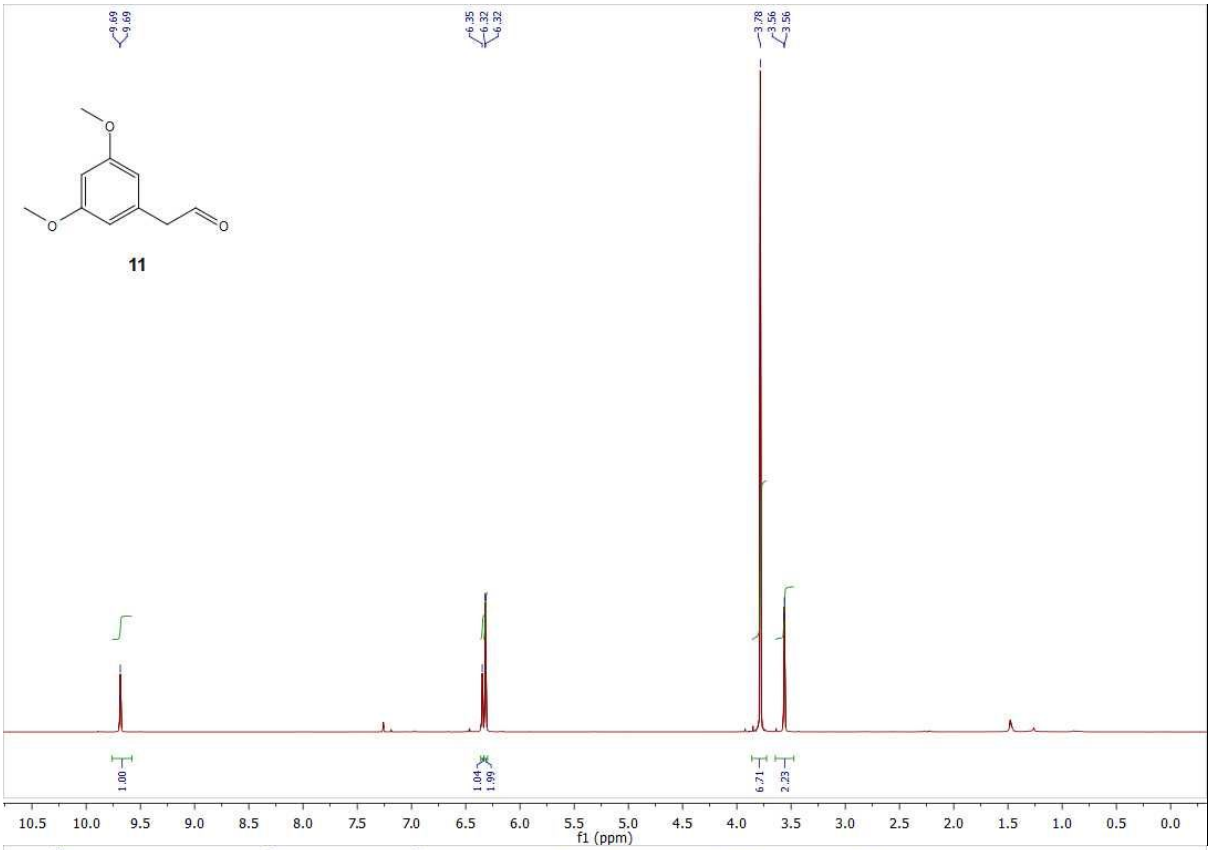
f1 (ppm)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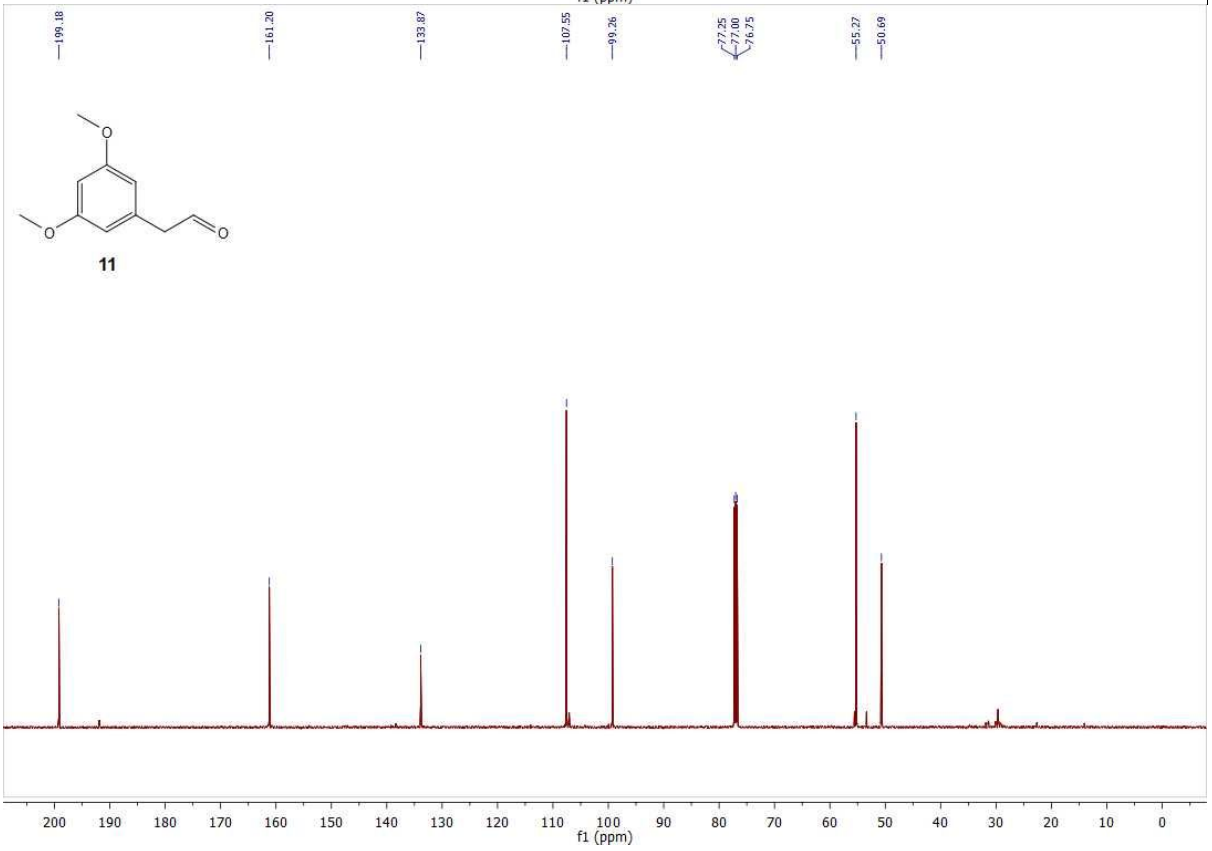
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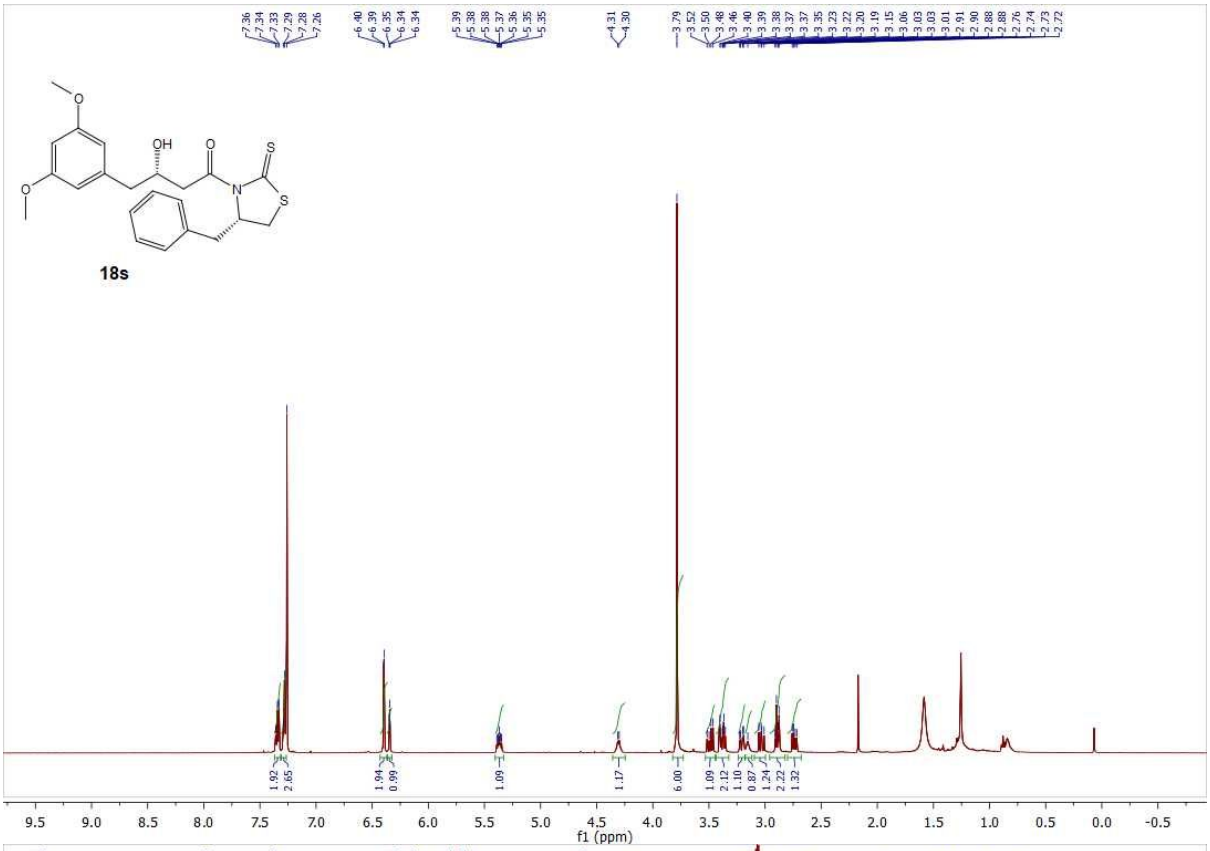
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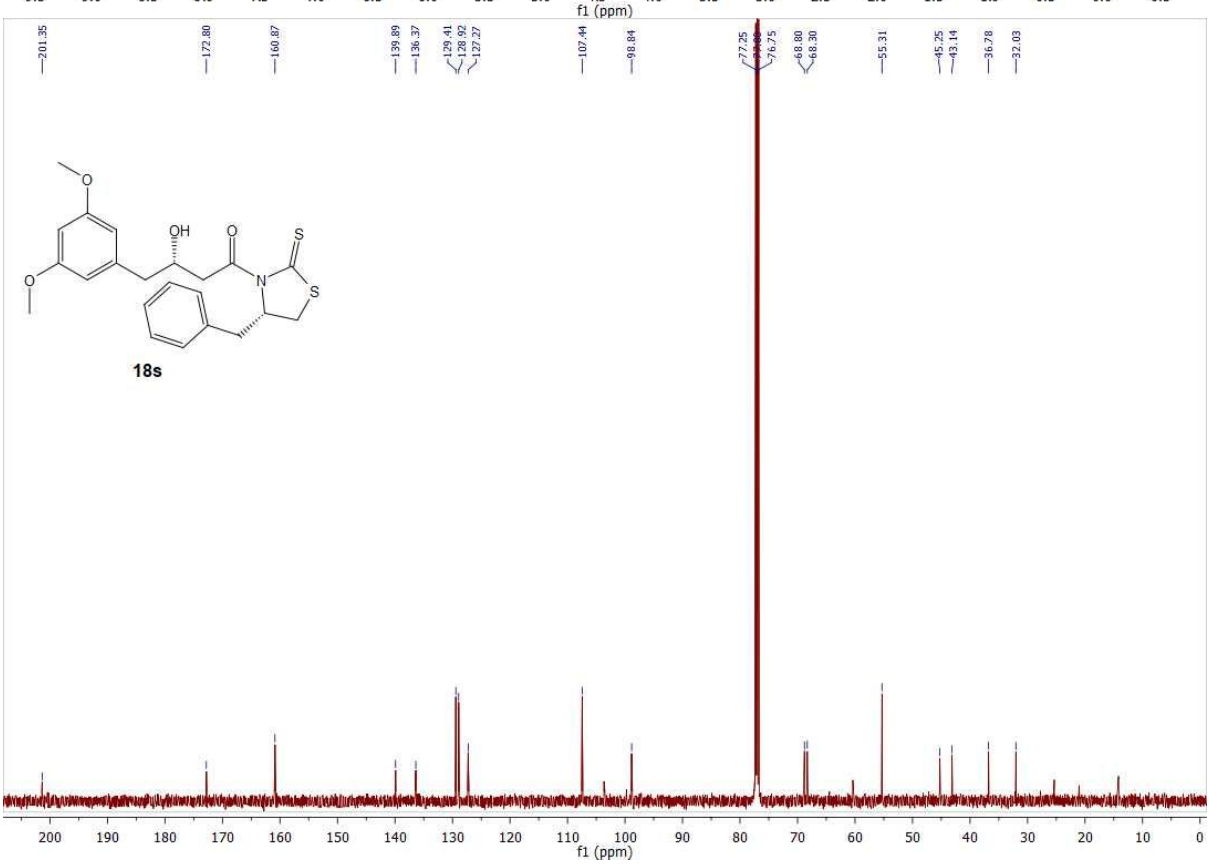
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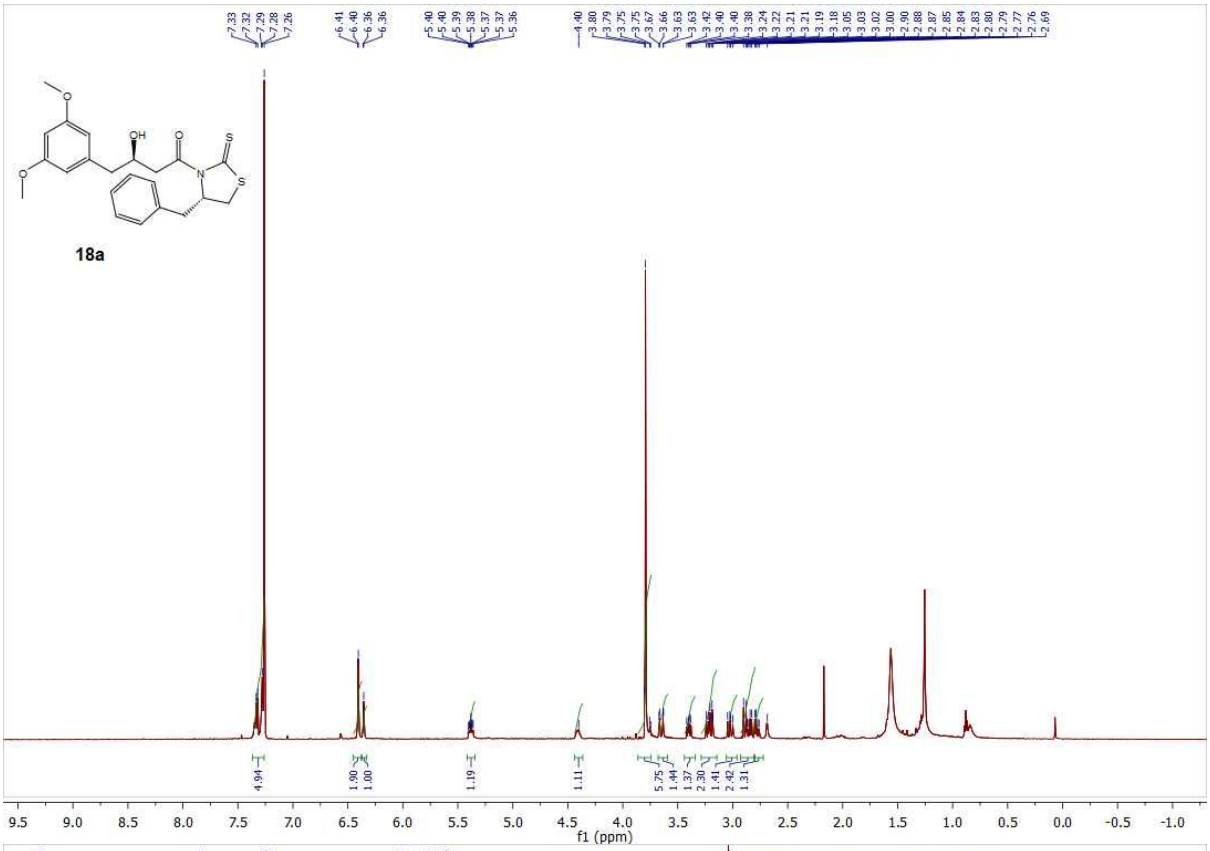
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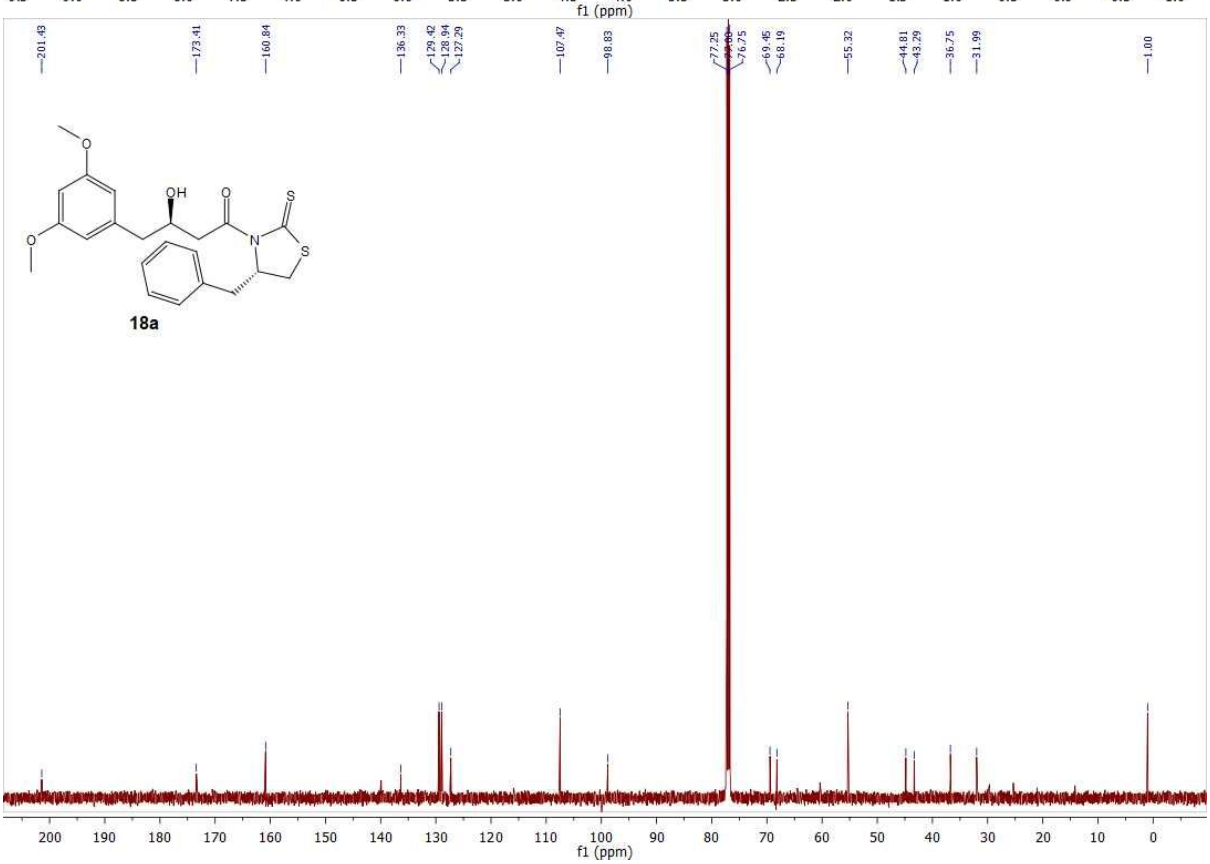
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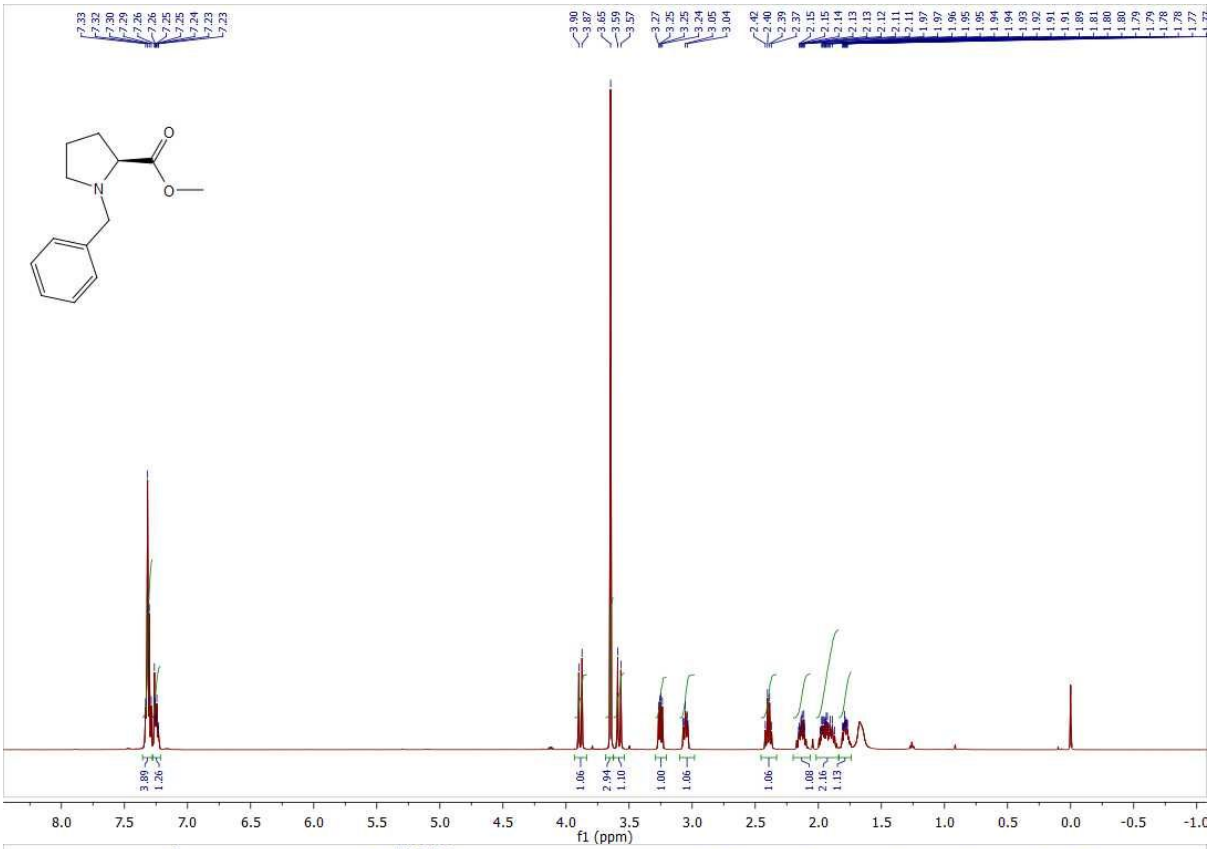
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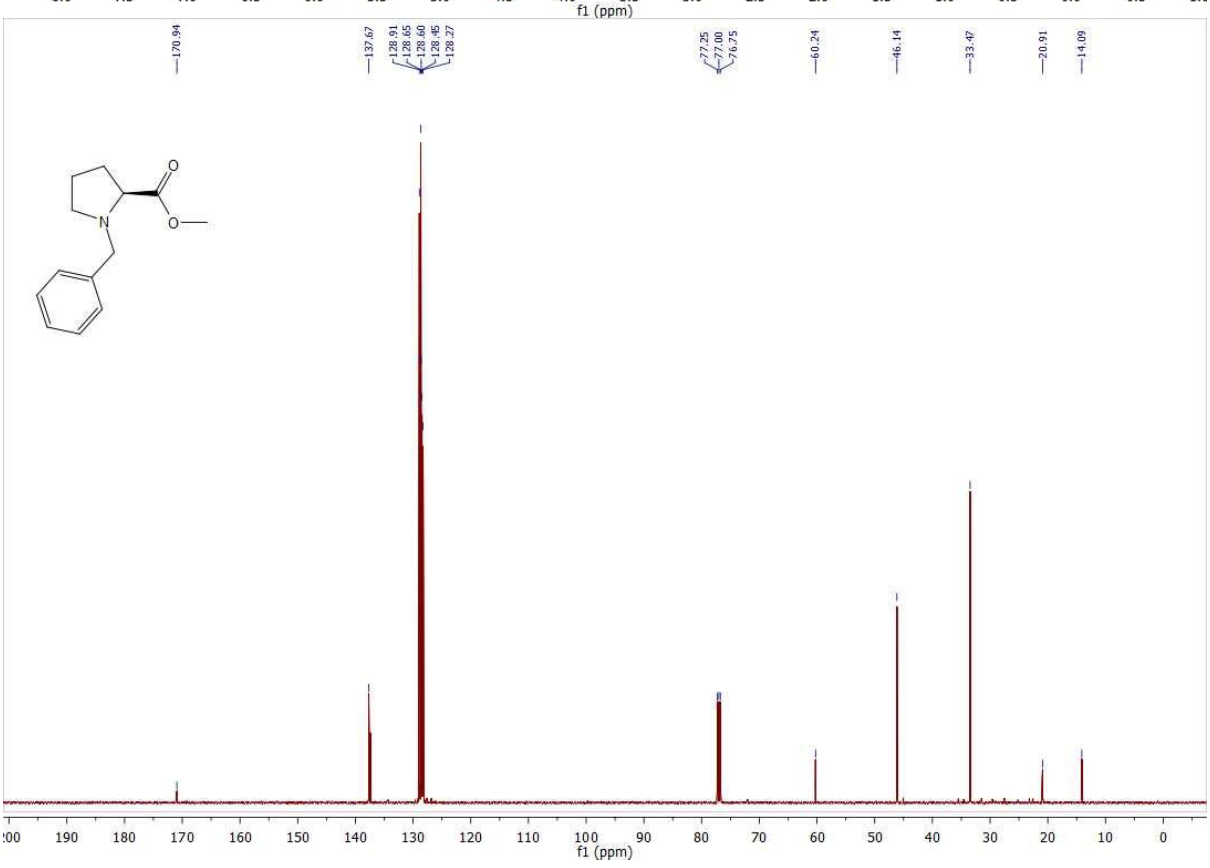
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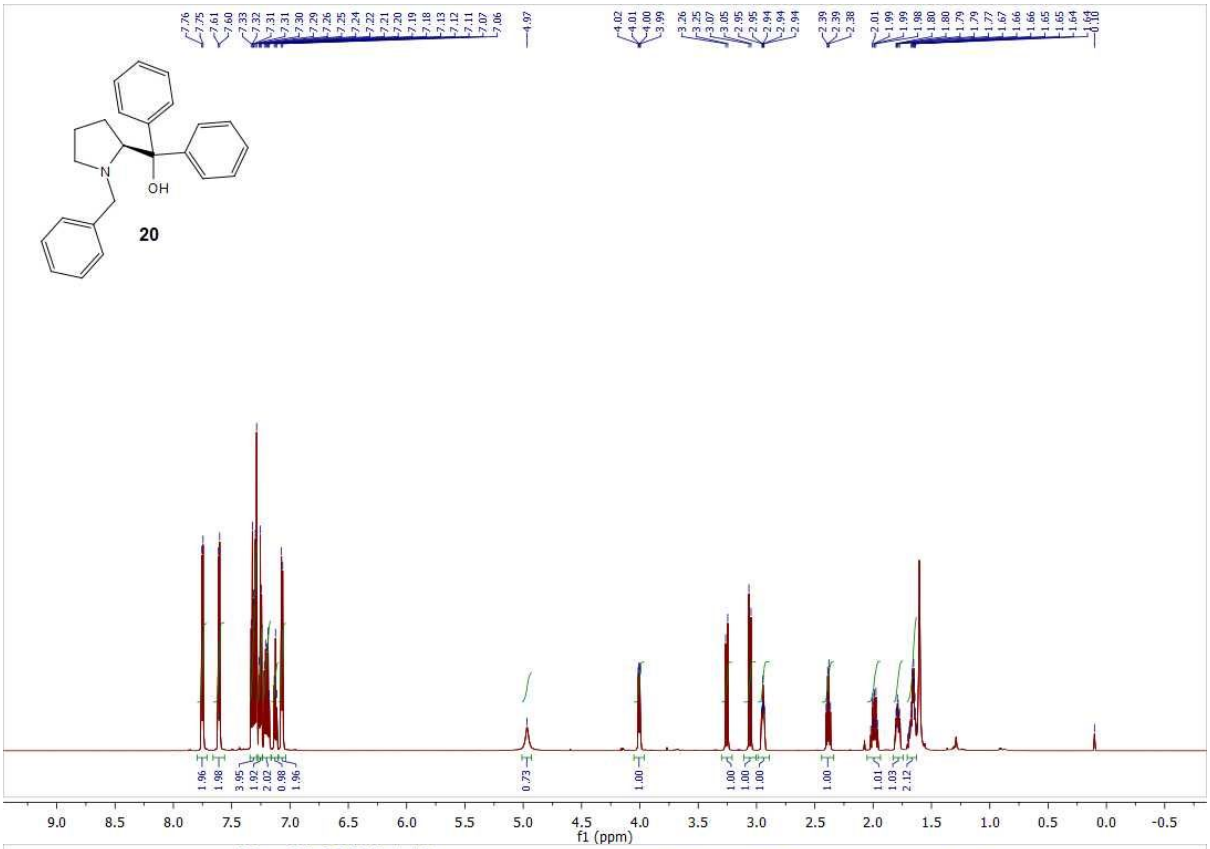
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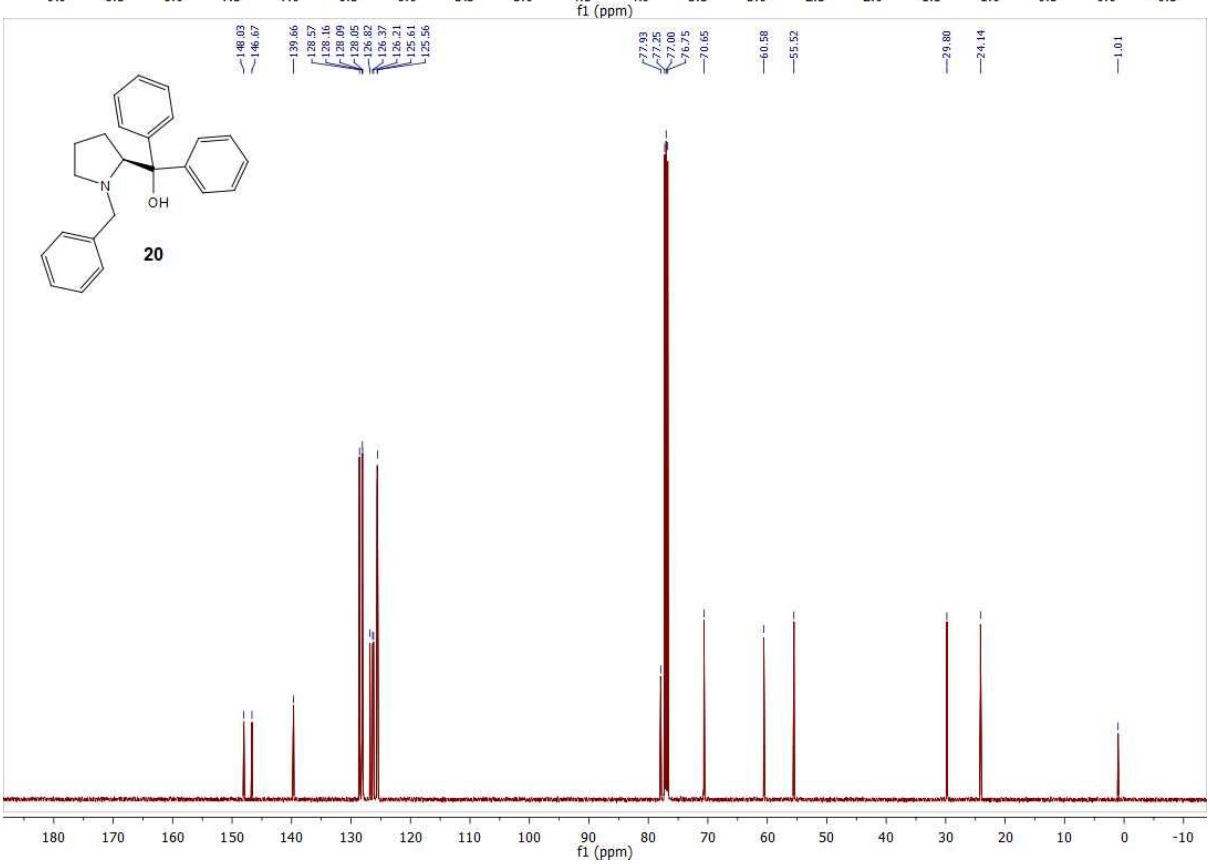
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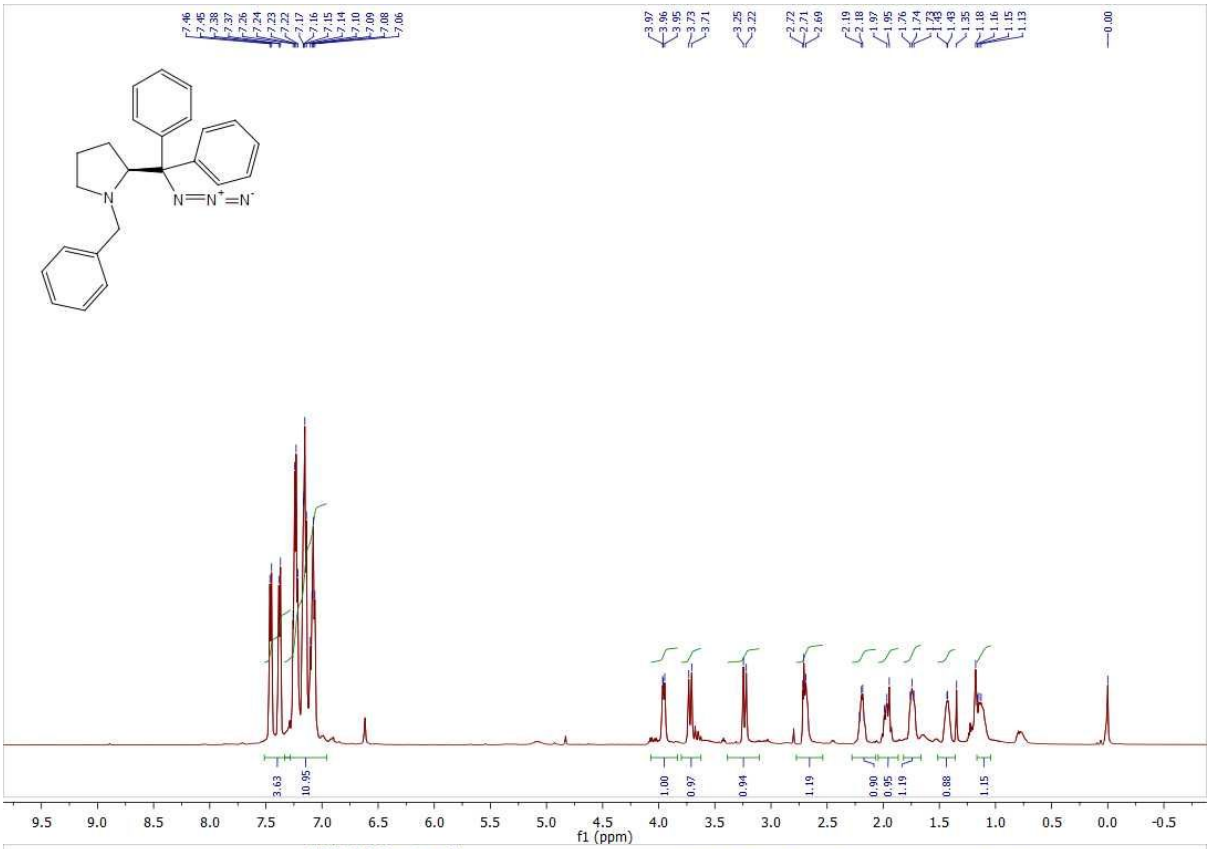
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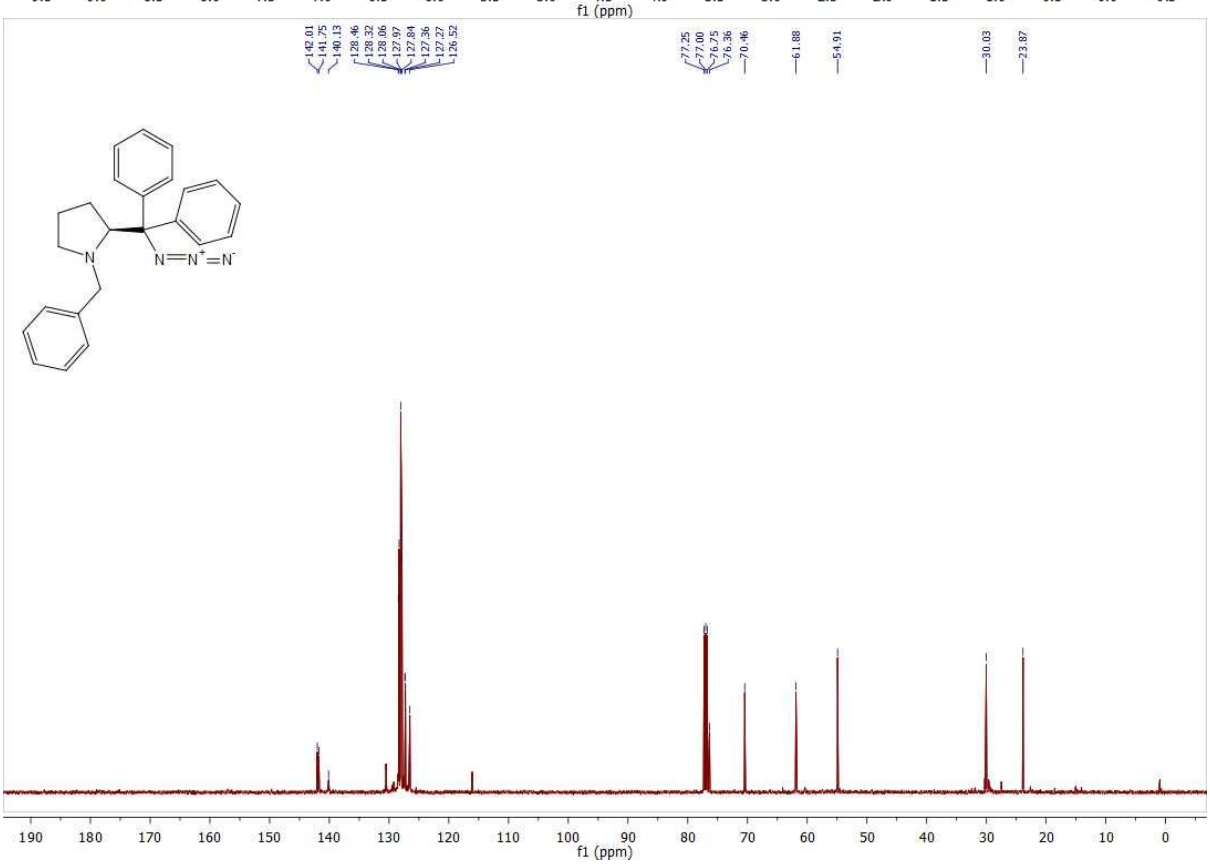
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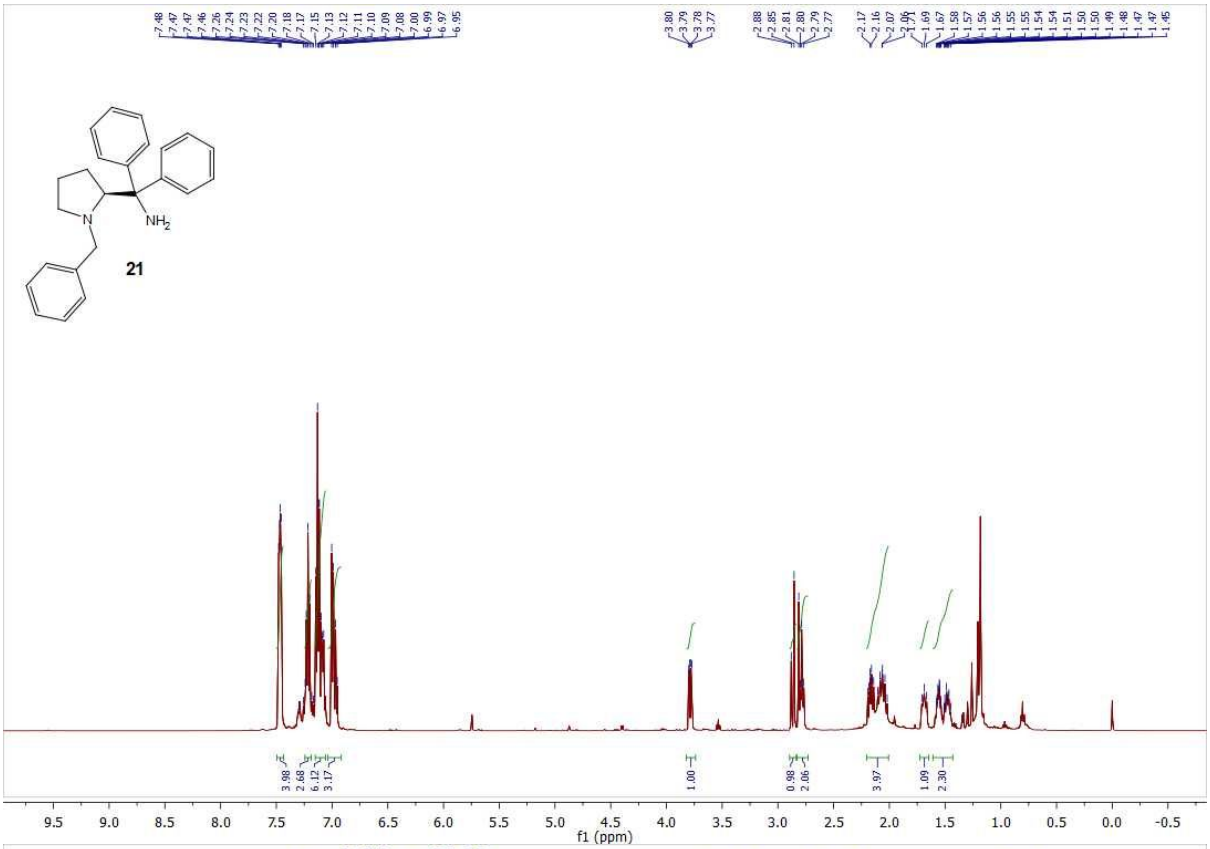
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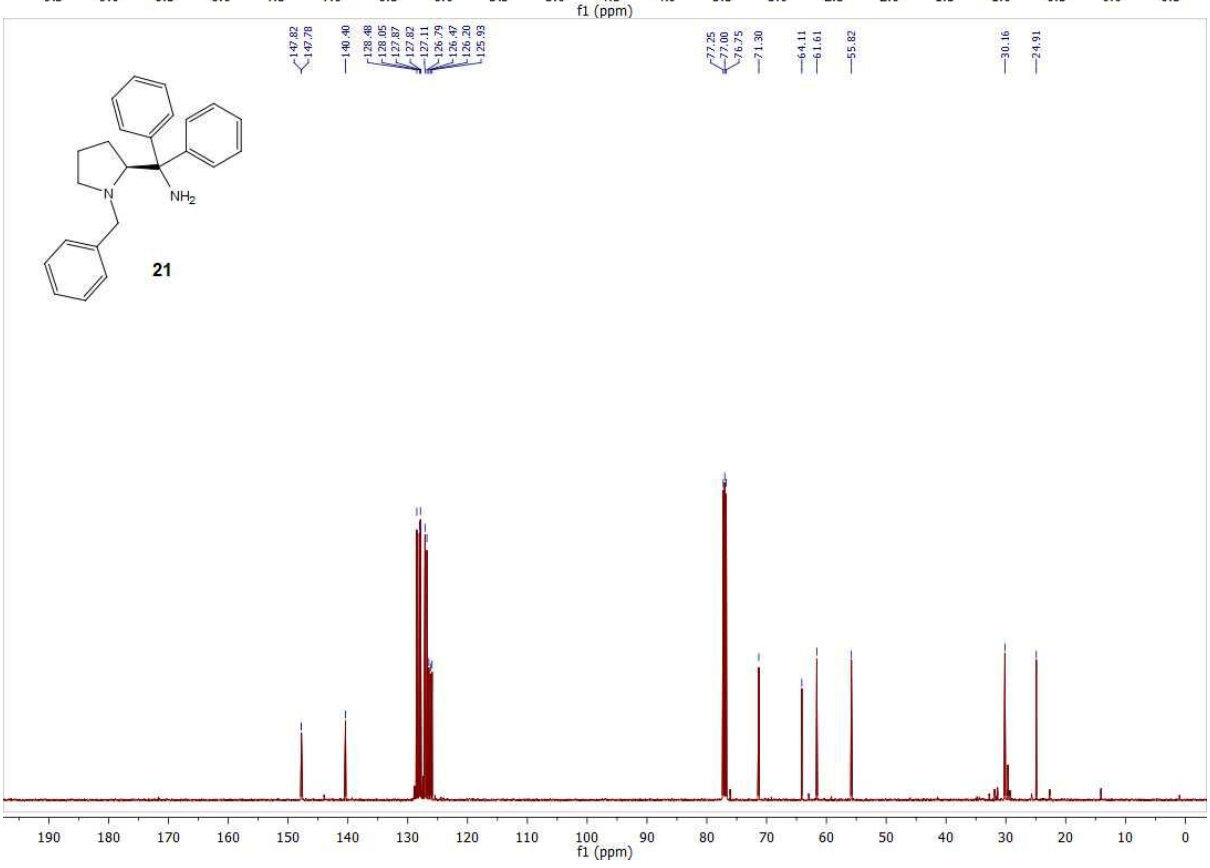
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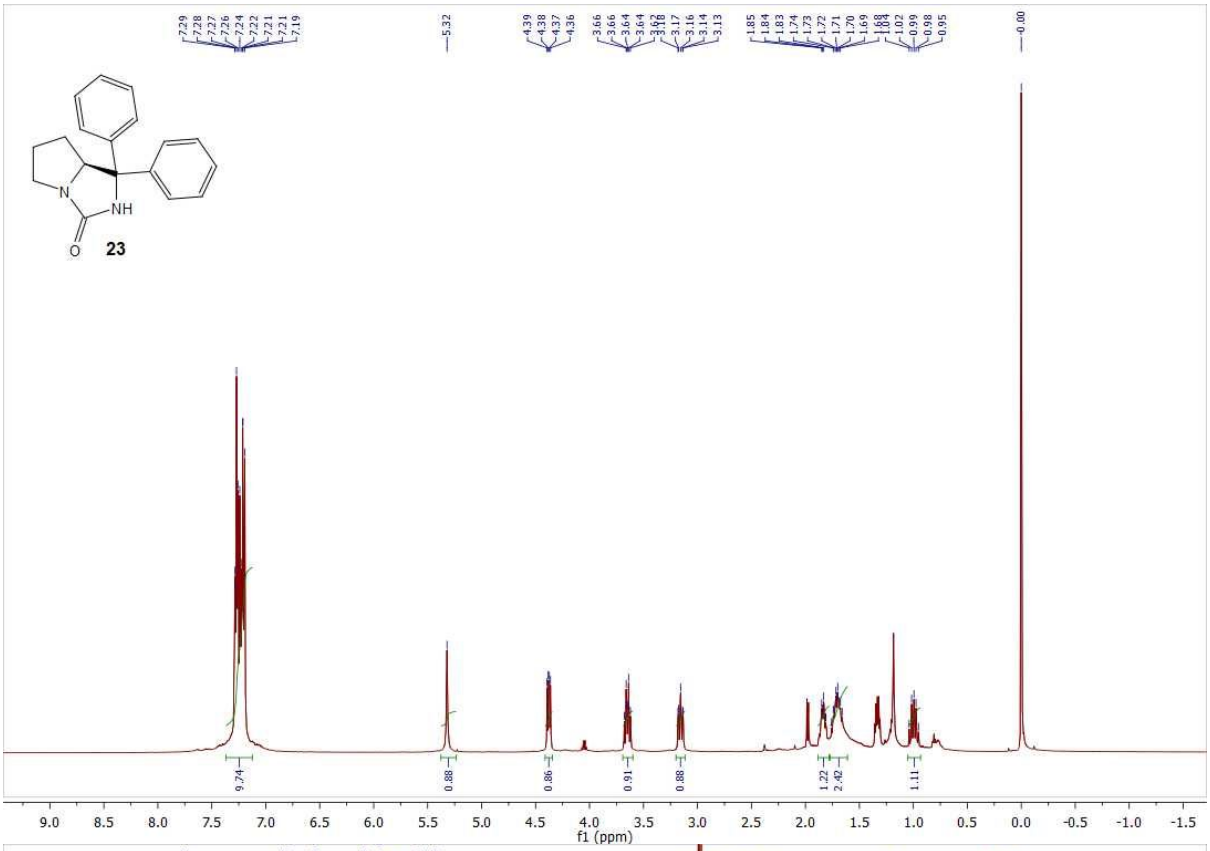
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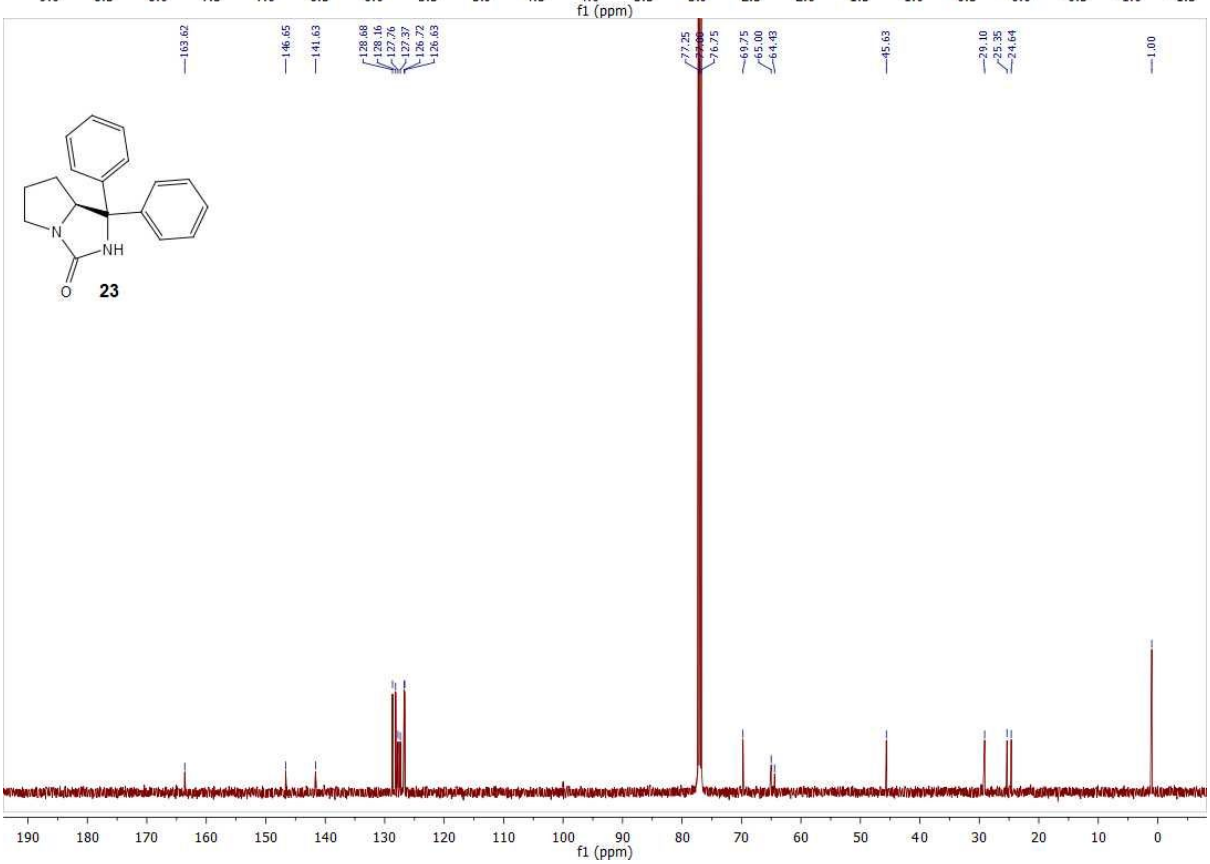
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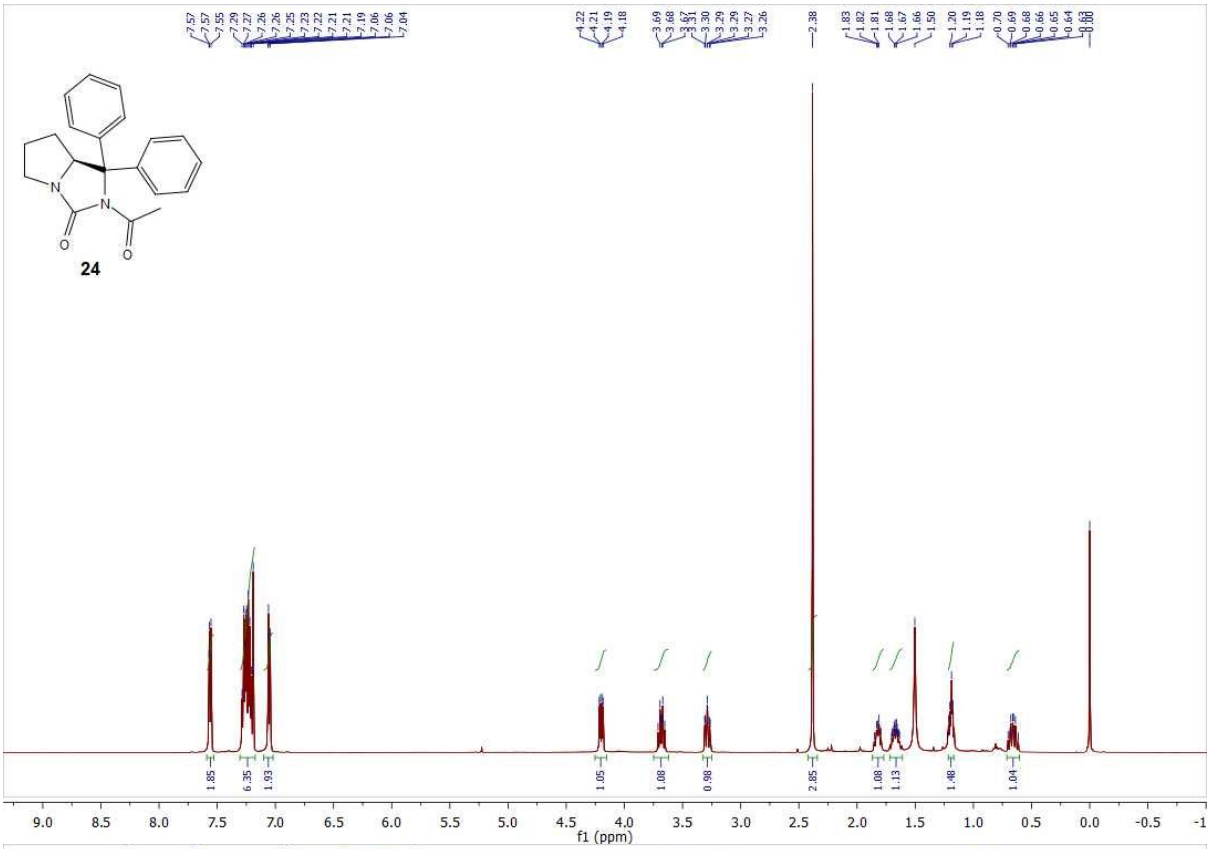
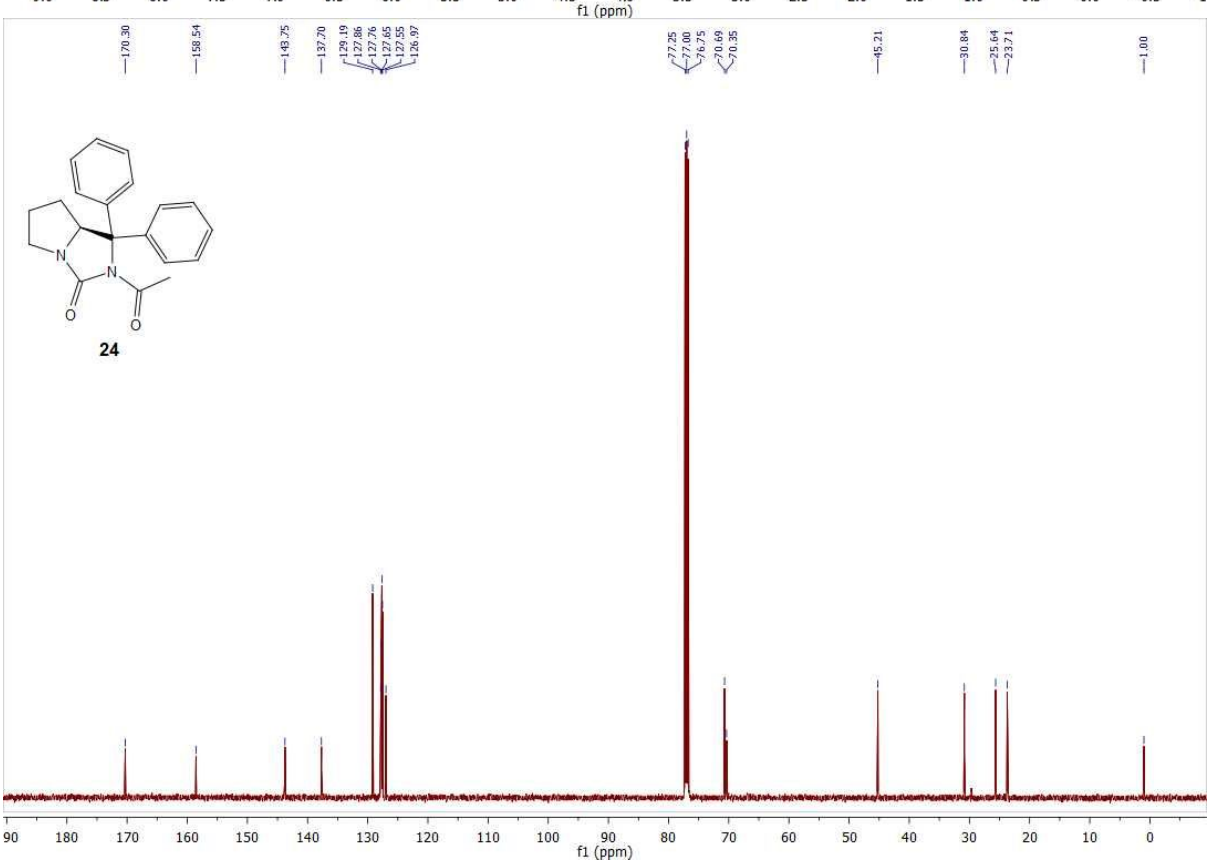
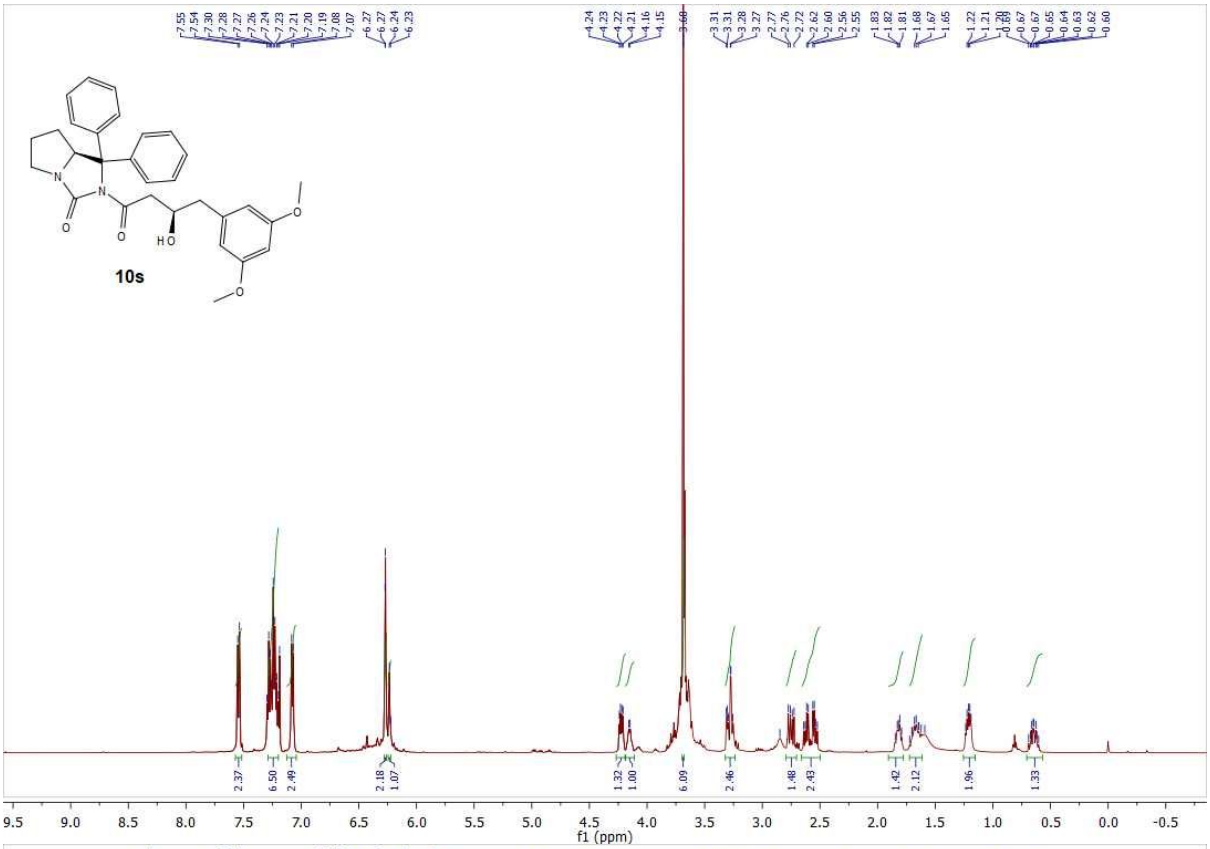
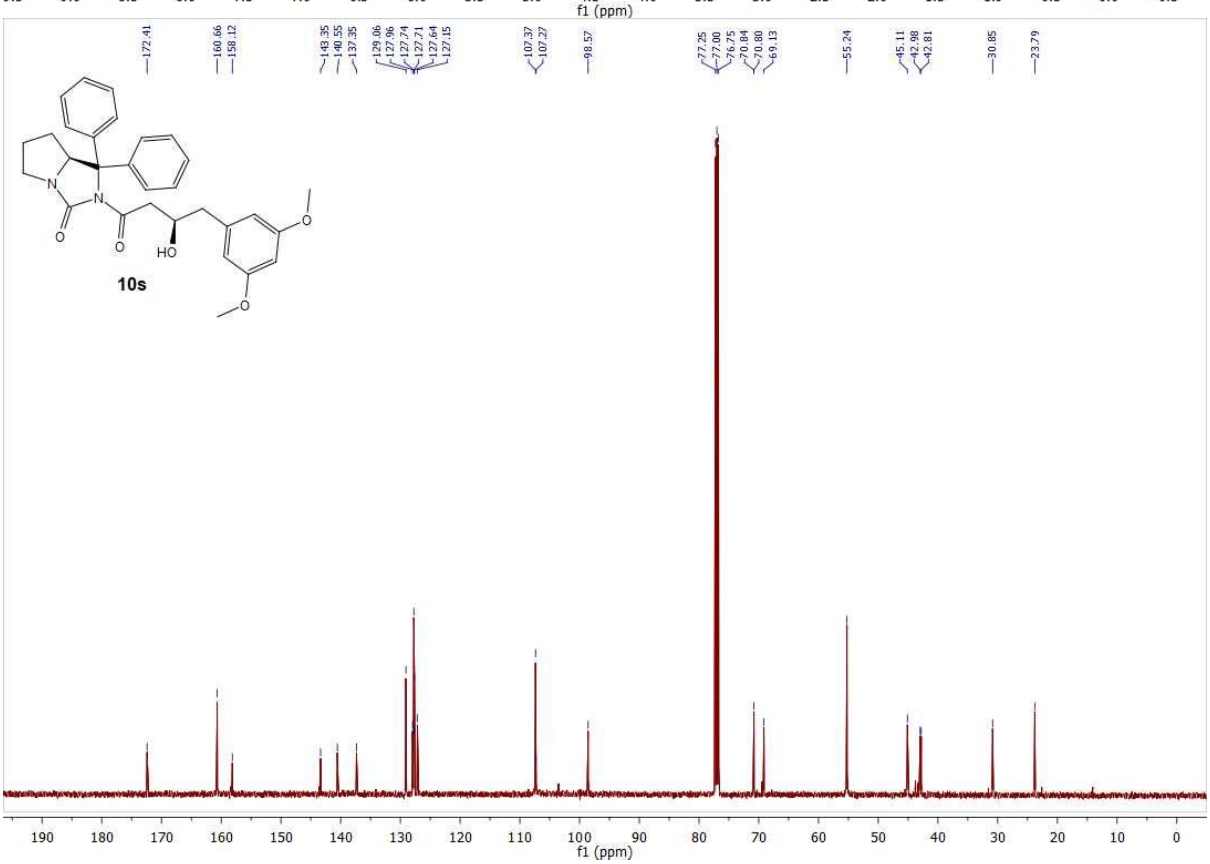
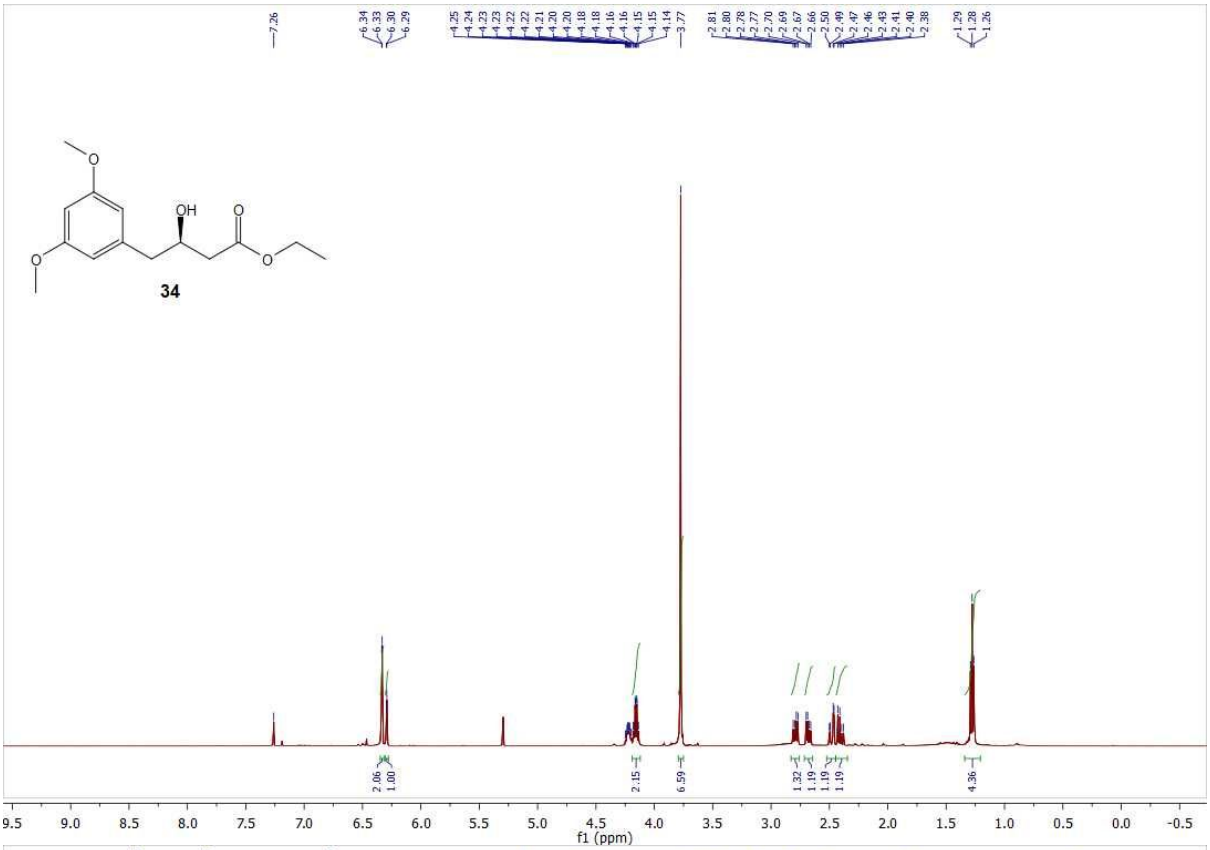
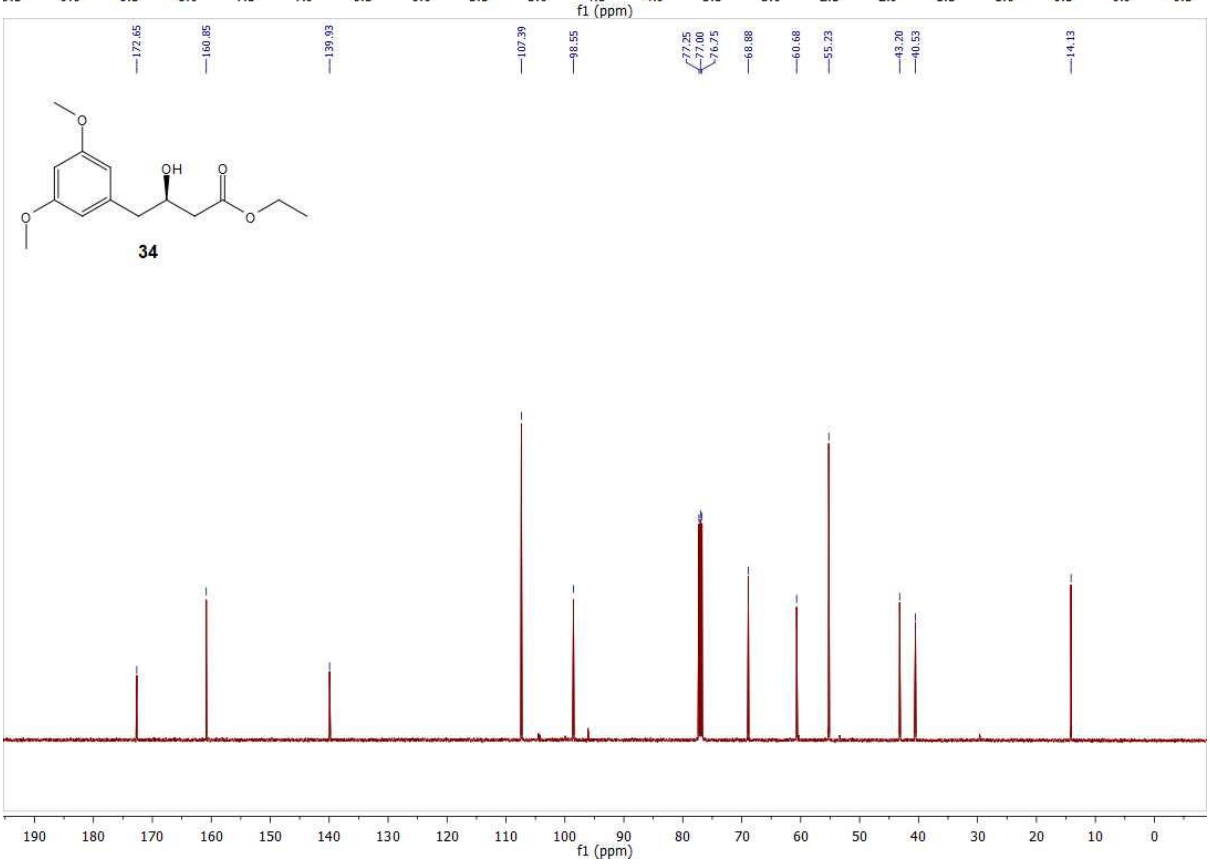

24
f1 (ppm)

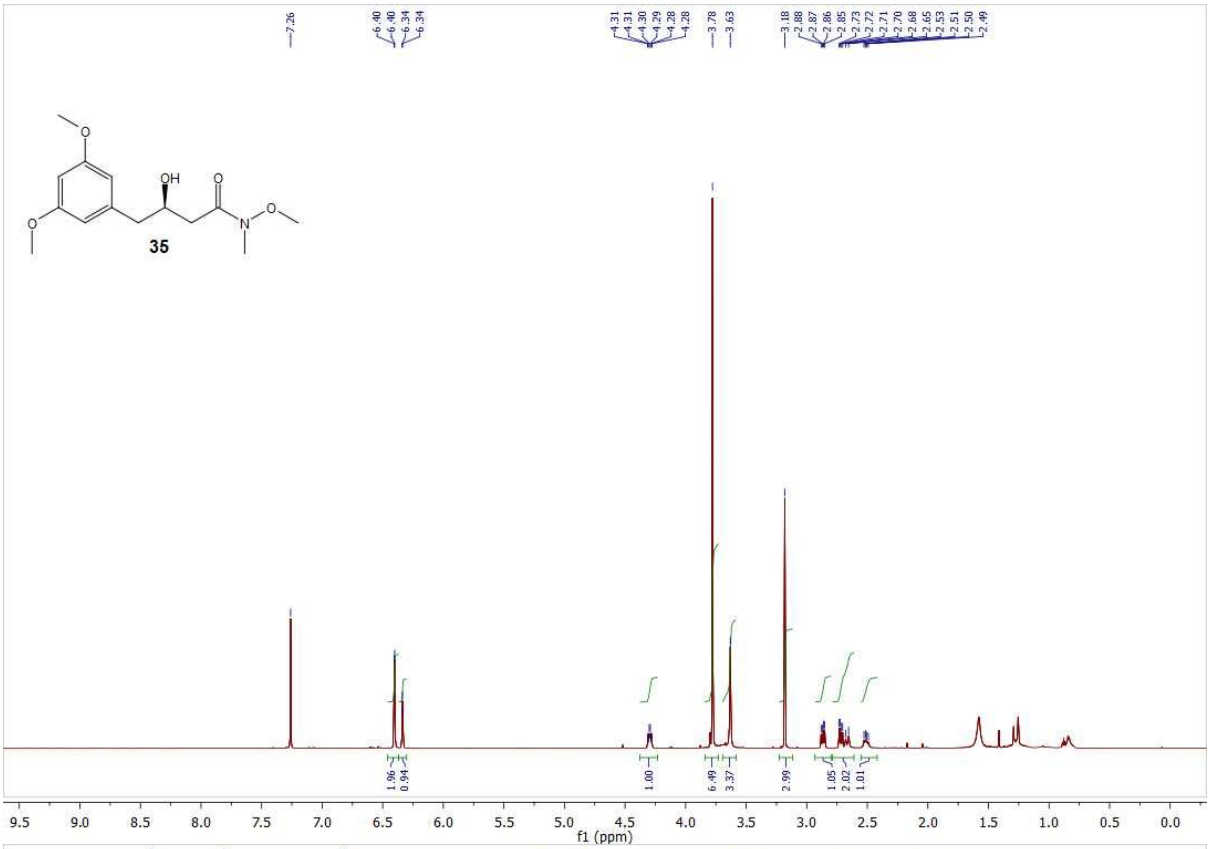

24
f1 (ppm)

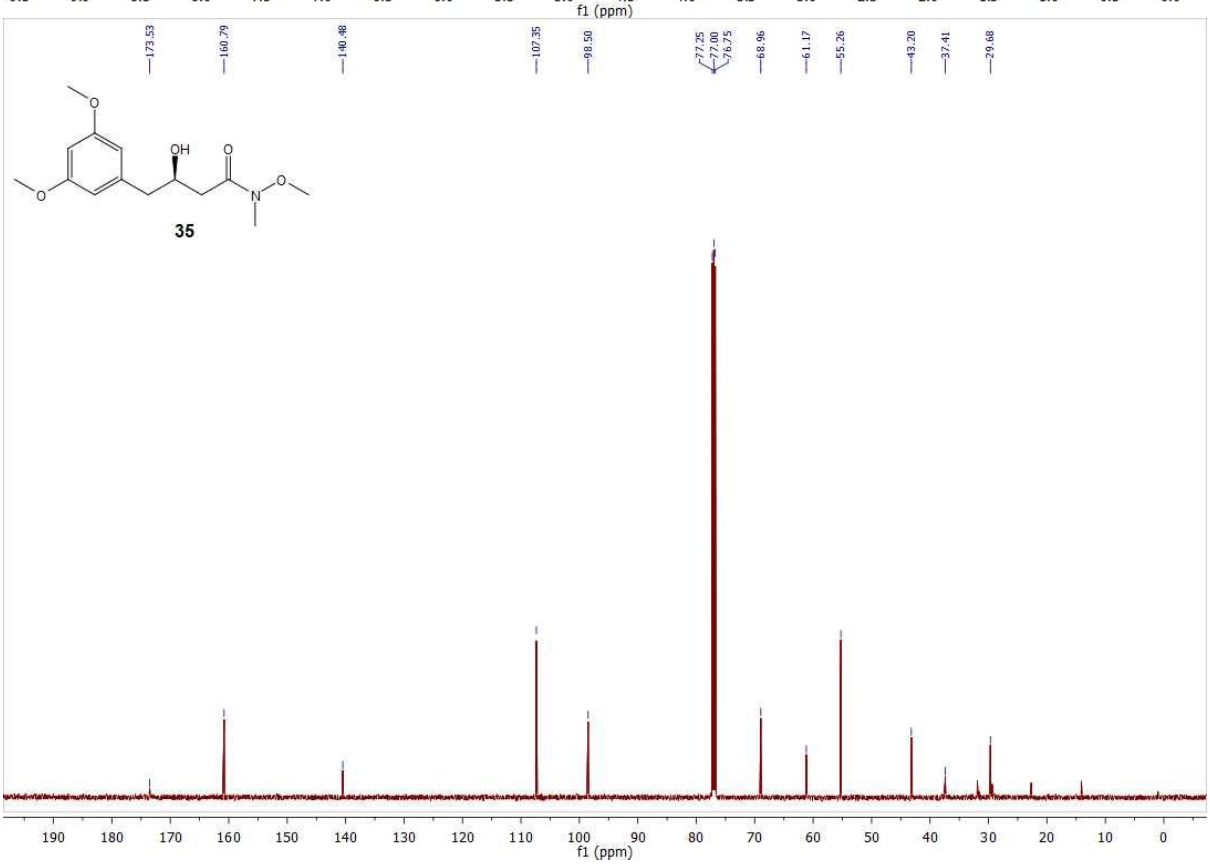

10s
f1 (ppm)

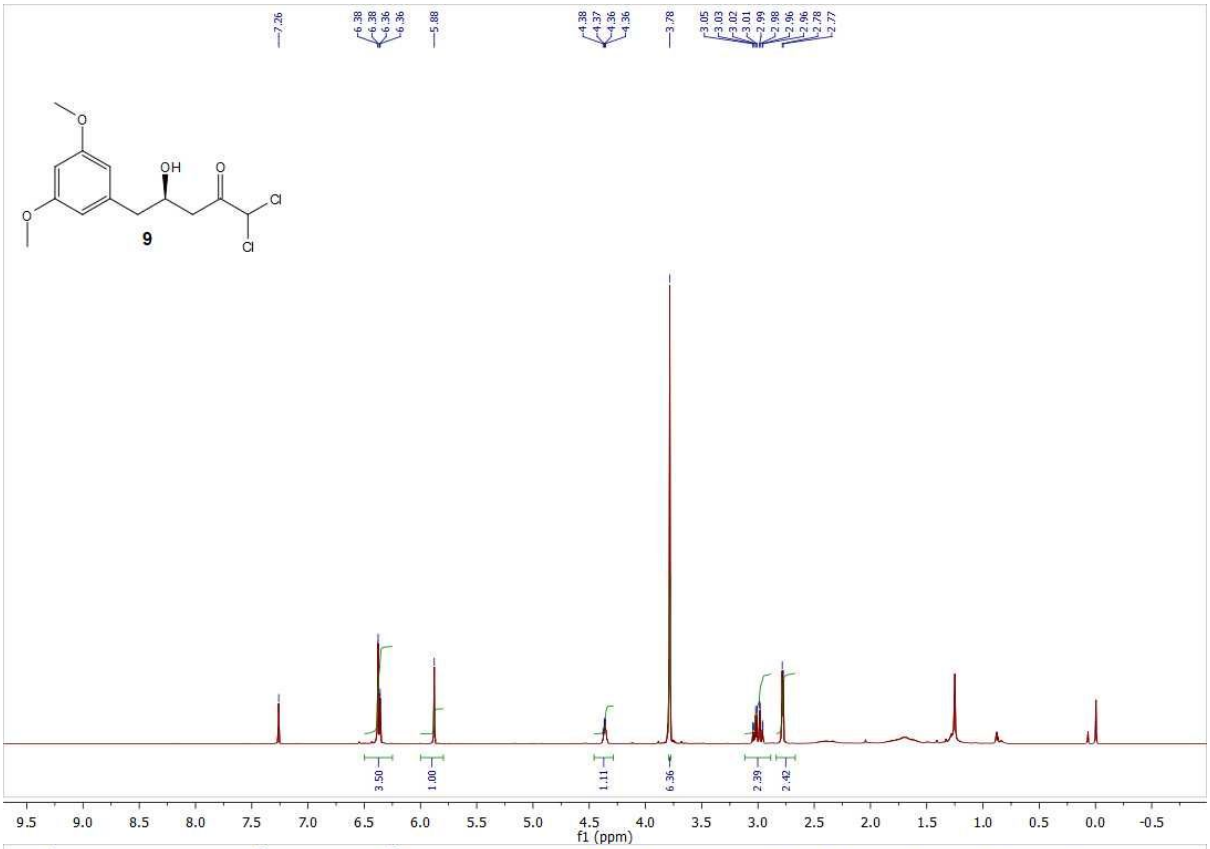

10s
f1 (ppm)

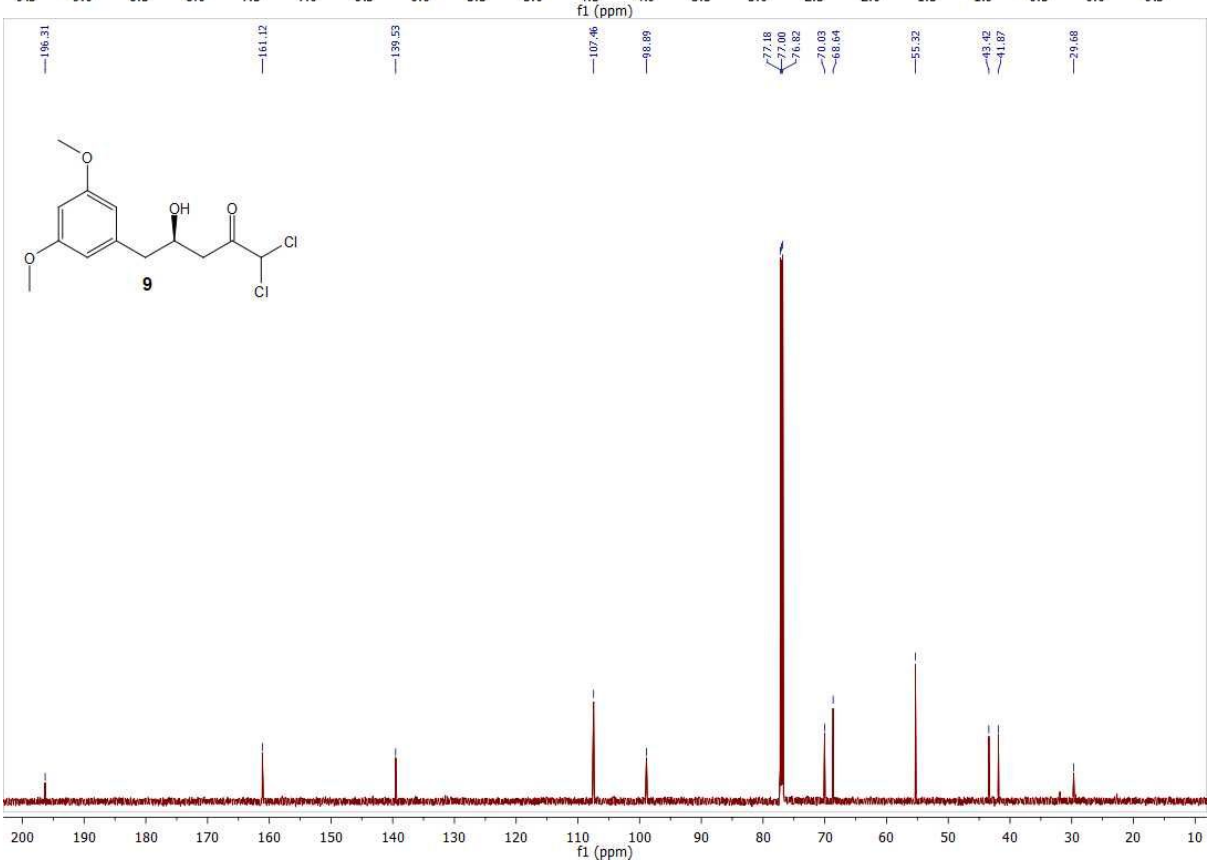

34
f1 (ppm)

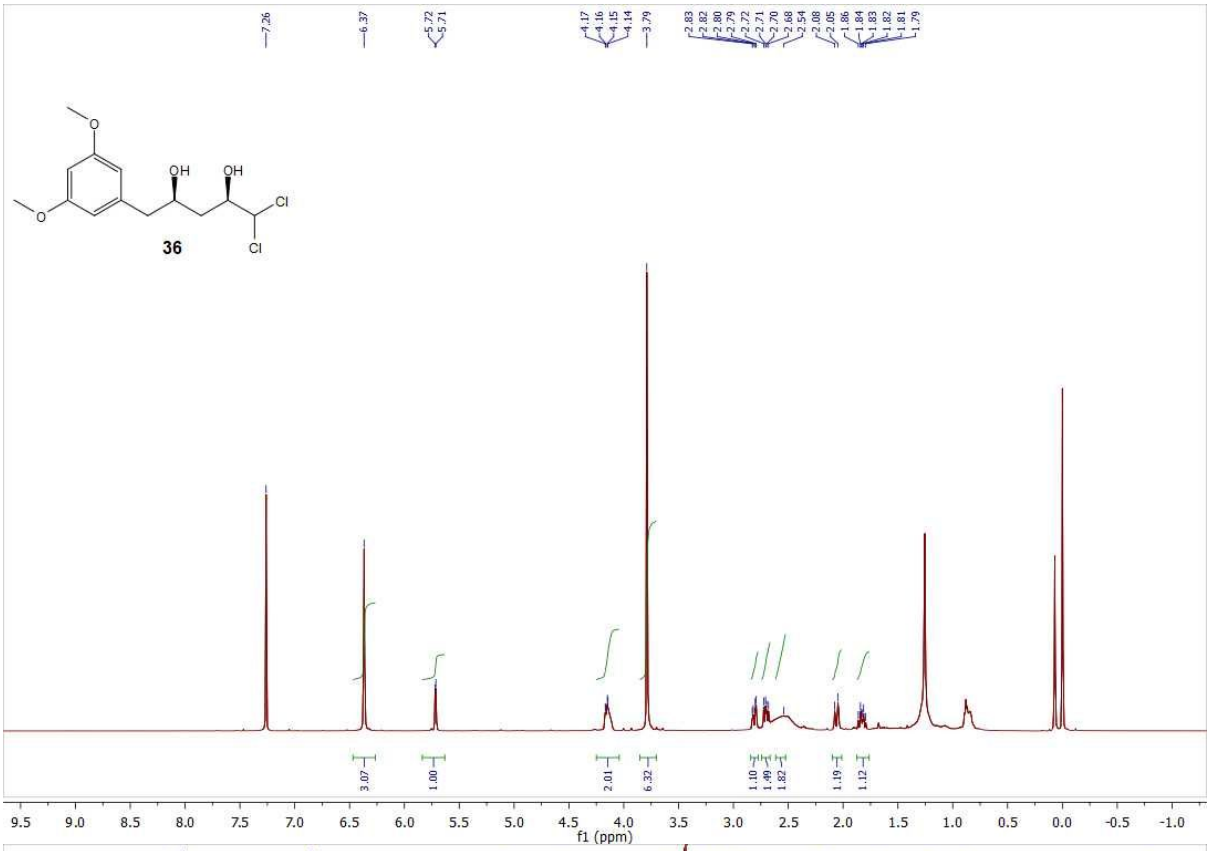

34
f1 (ppm)

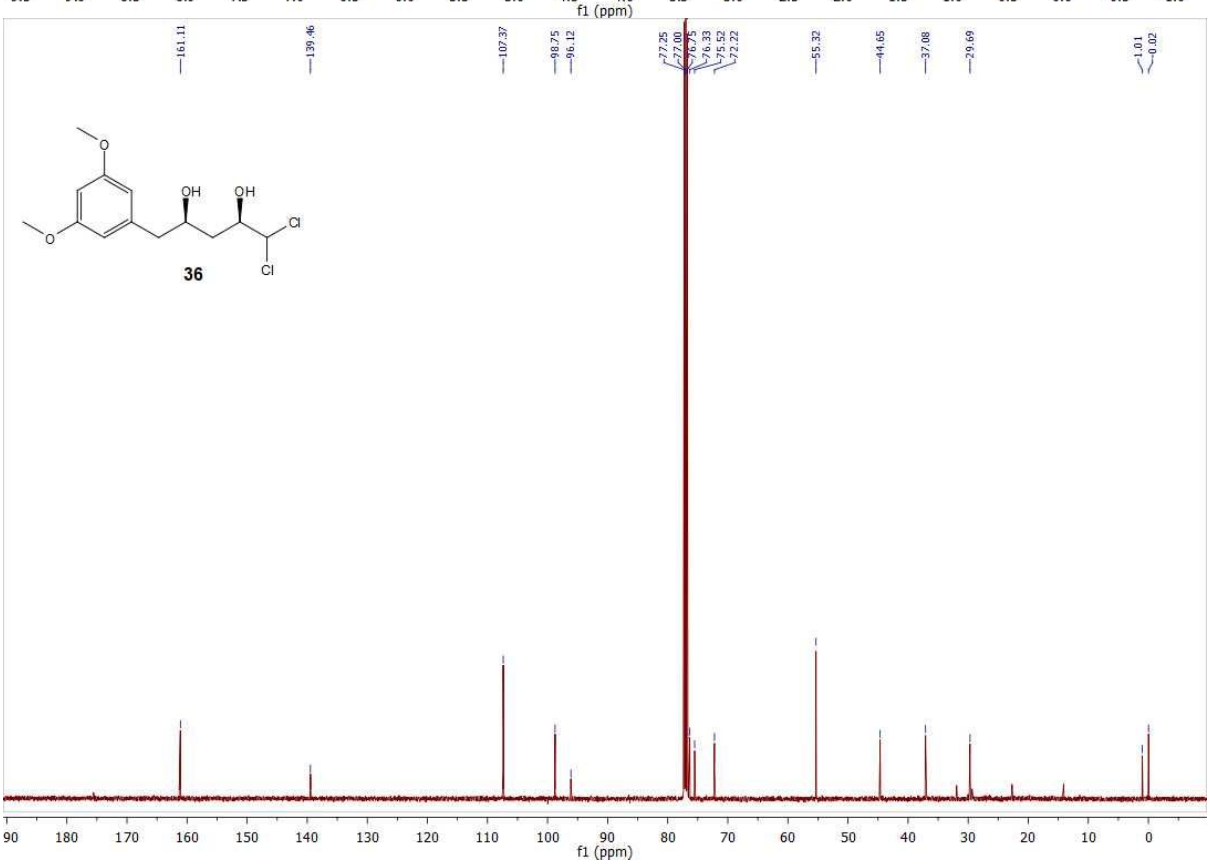

35
f1 (ppm)

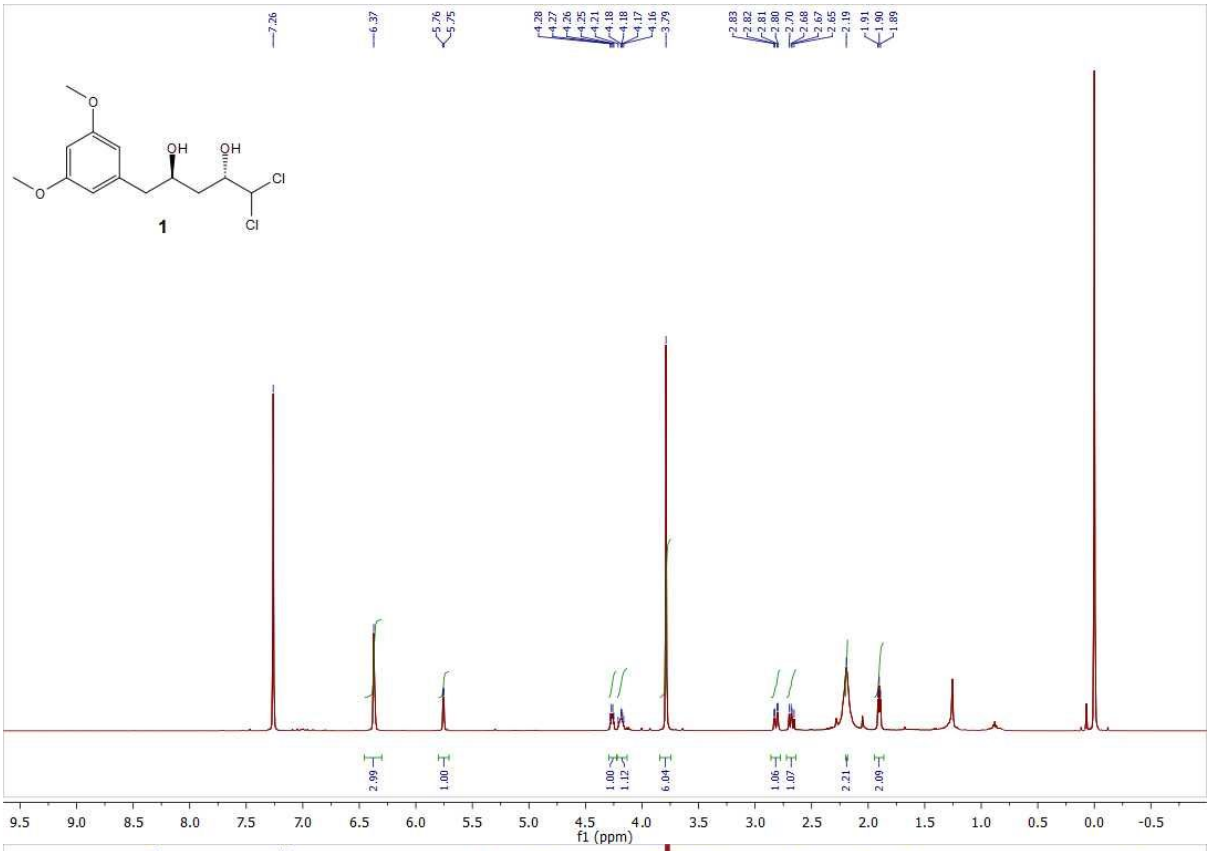

35
f1 (ppm)

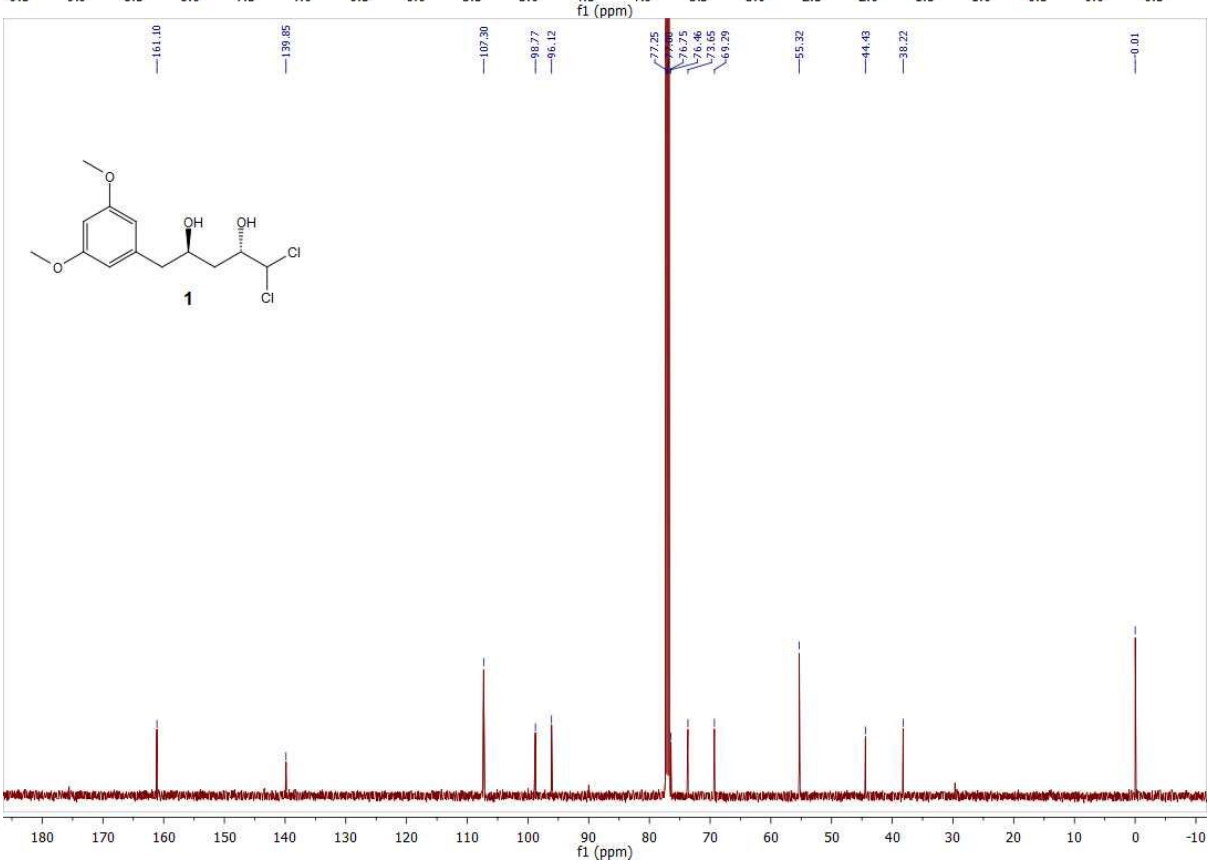

7.26
6.38
6.38
6.36
6.36
5.88
4.38
4.37
4.36
4.36
3.78
3.05
3.03
3.02
3.01
2.99
2.98
2.96
2.96
2.78
2.77
OH
O
Cl
Cl
O
O
9
3.50
1.00
1.11
6.36
2.39
2.42
f1 (ppm)


196.31
161.12
139.53
107.46
98.89
77.18
77.00
76.82
70.03
68.64
55.32
43.42
41.87
29.68
OH
O
Cl
Cl
O
O
9
f1 (ppm)


7.26
6.37
5.72
5.71
4.17
4.16
4.15
4.14
3.79
2.83
2.82
2.80
2.79
2.72
2.71
2.70
2.68
2.54
2.08
2.05
1.86
1.84
1.83
1.82
1.81
1.79
OH
OH
Cl
Cl
O
O
36
3.07
1.00
2.01
6.32
1.10
1.49
1.82
1.19
1.12
f1 (ppm)


161.11
139.46
107.37
98.75
96.12
77.25
77.00
76.75
76.33
75.52
72.22
55.32
44.65
37.08
29.69
1.01
0.02
OH
OH
Cl
Cl
O
O
36
f1 (ppm)


7.26
6.37
5.76
5.75
4.28
4.27
4.26
4.25
4.21
4.18
4.18
4.17
4.16
3.79
2.83
2.82
2.81
2.80
2.70
2.68
2.67
2.65
2.19
1.91
1.90
1.89
O
OH
OH
Cl
Cl
O
1
2.99
1.00
1.00
1.12
6.84
1.06
1.07
2.21
2.09
f1 (ppm)


161.10
139.85
107.30
98.77
96.12
77.25
76.75
76.46
73.65
69.29
55.32
44.43
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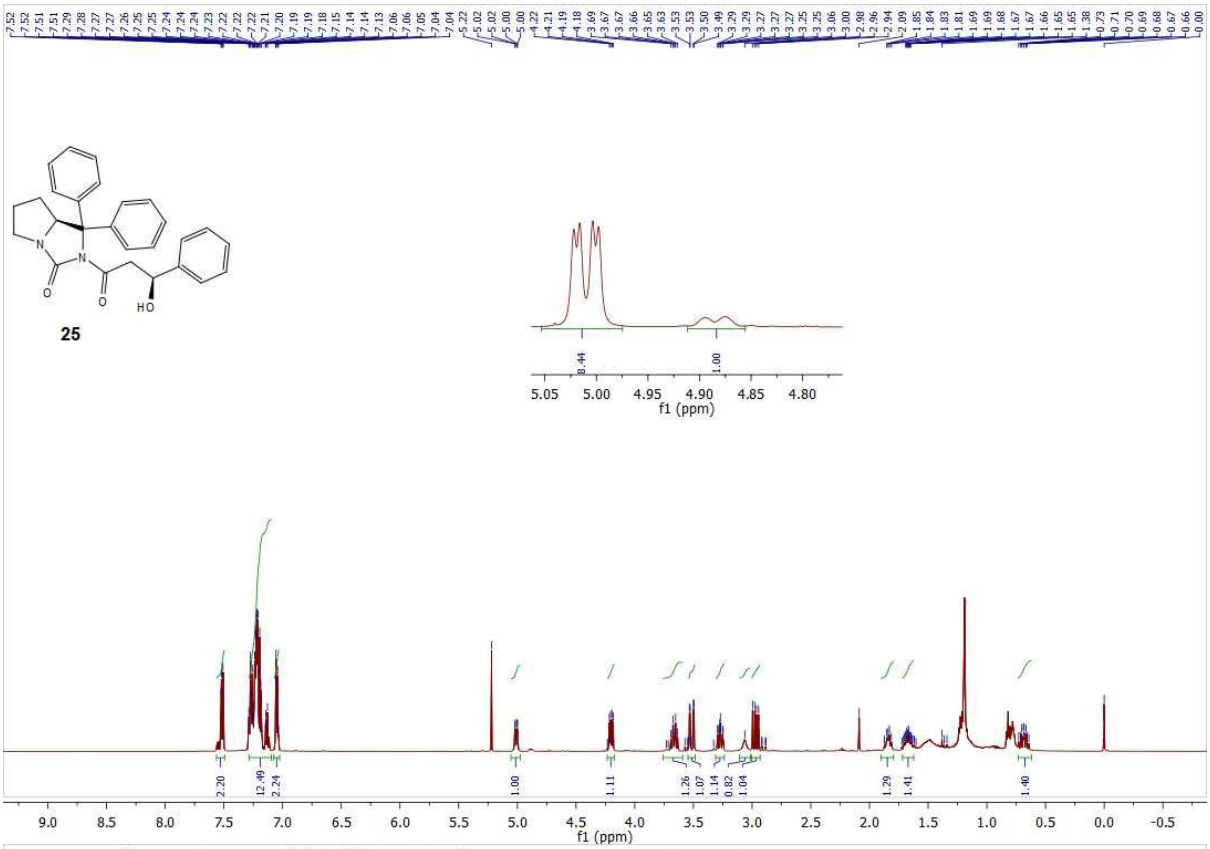
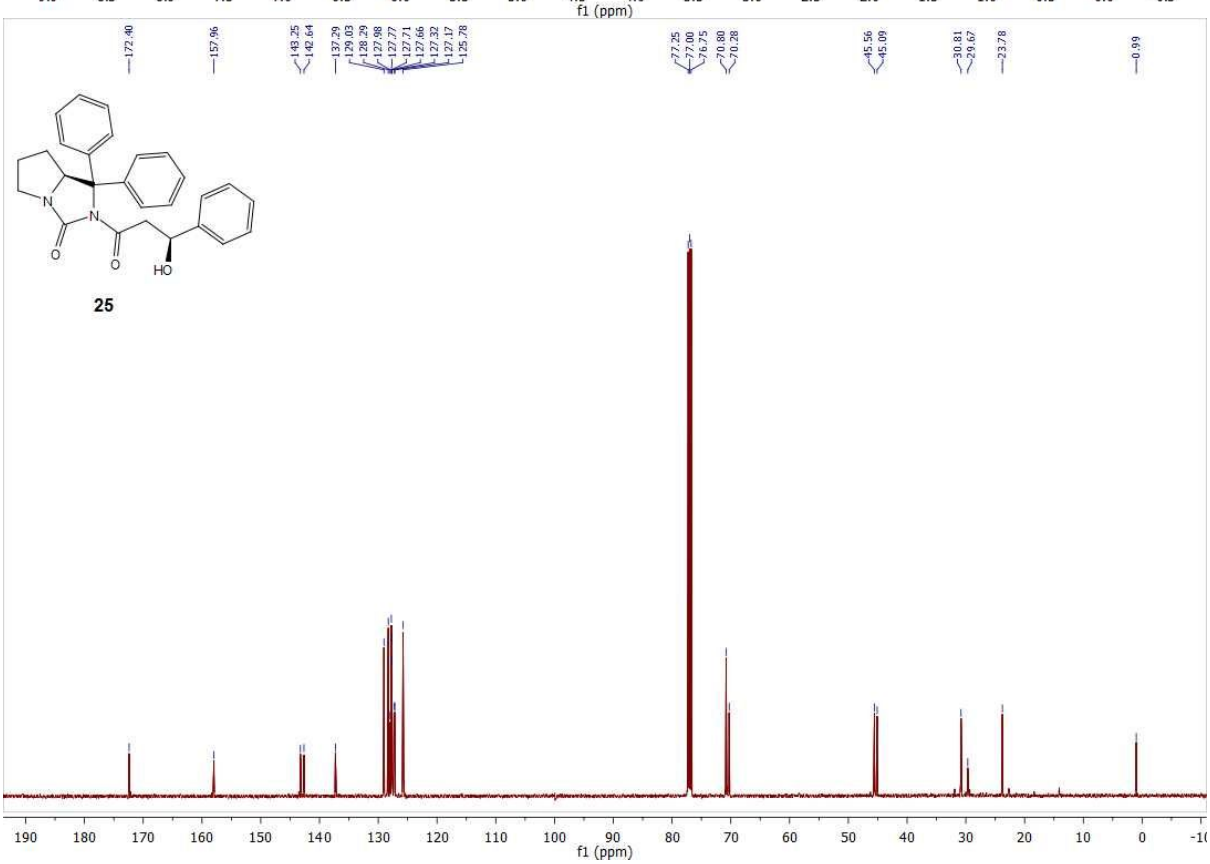
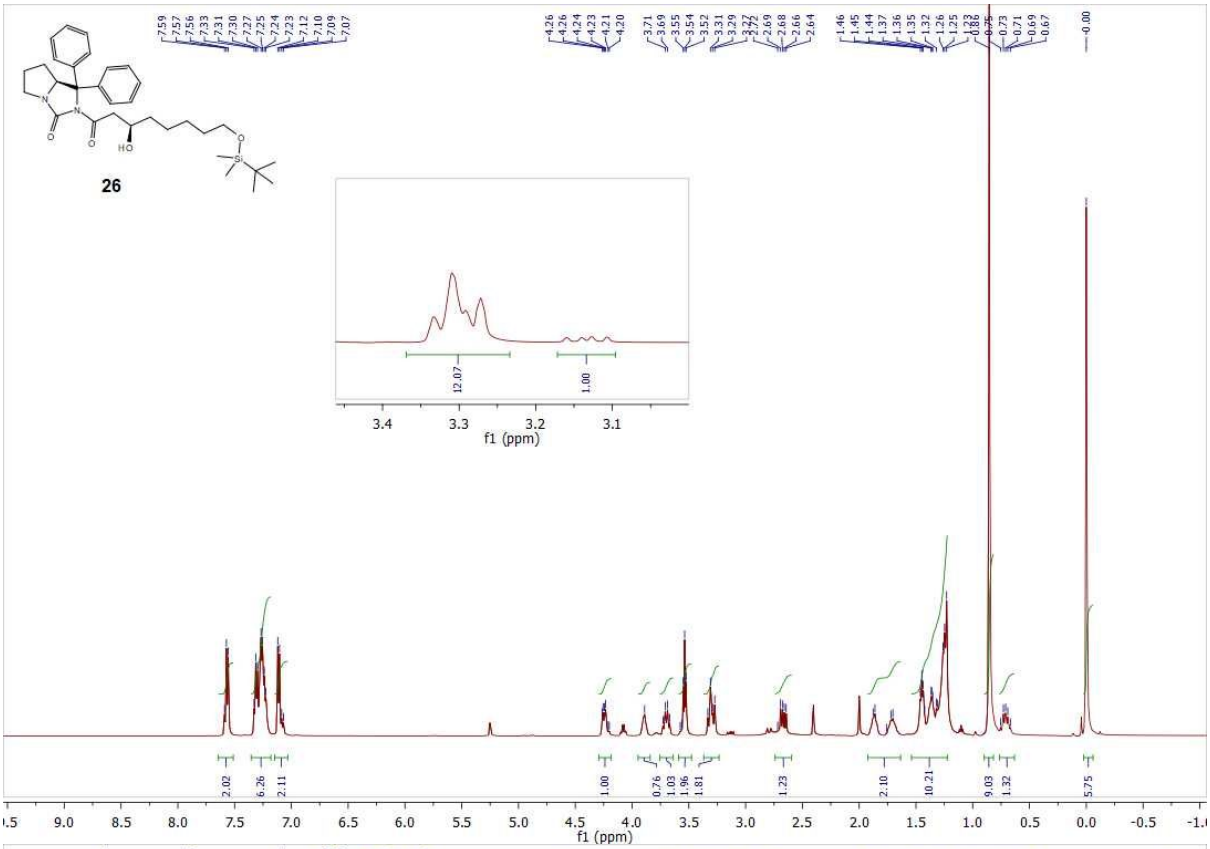
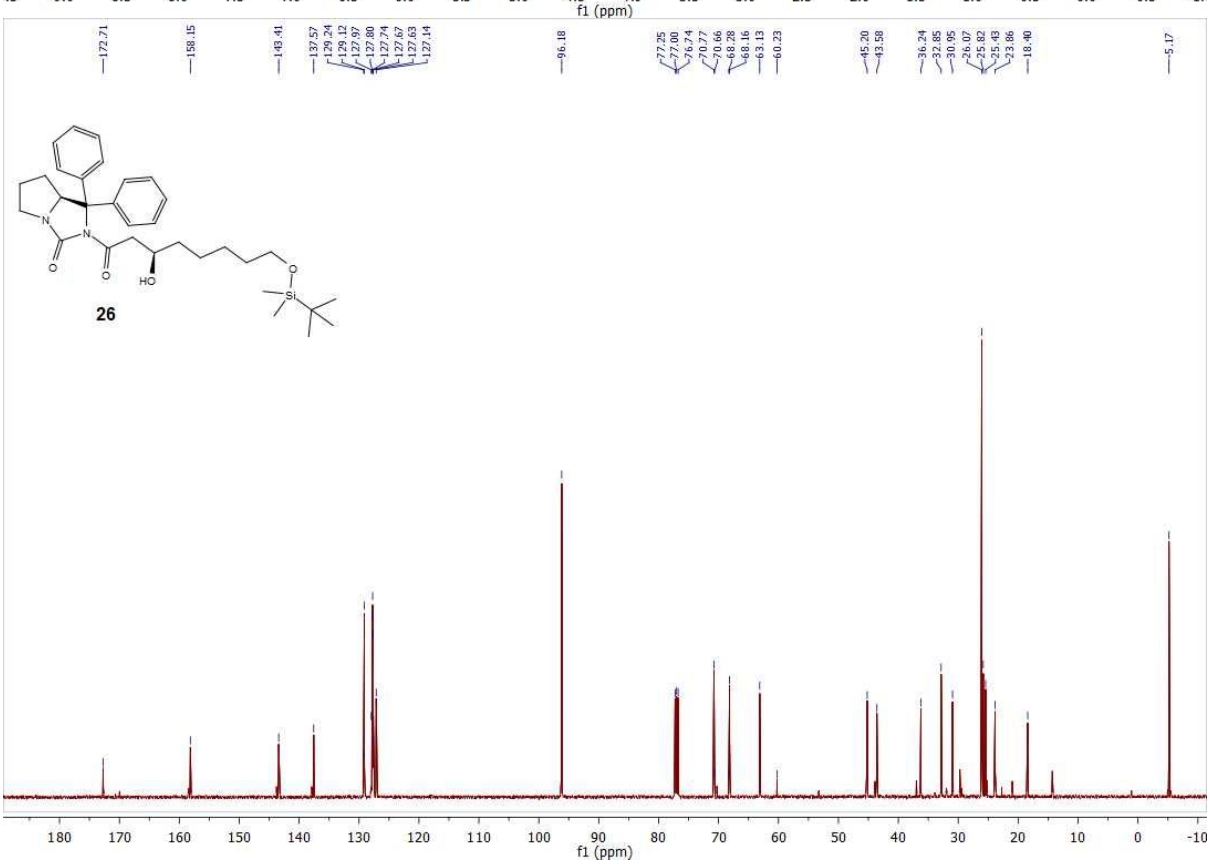
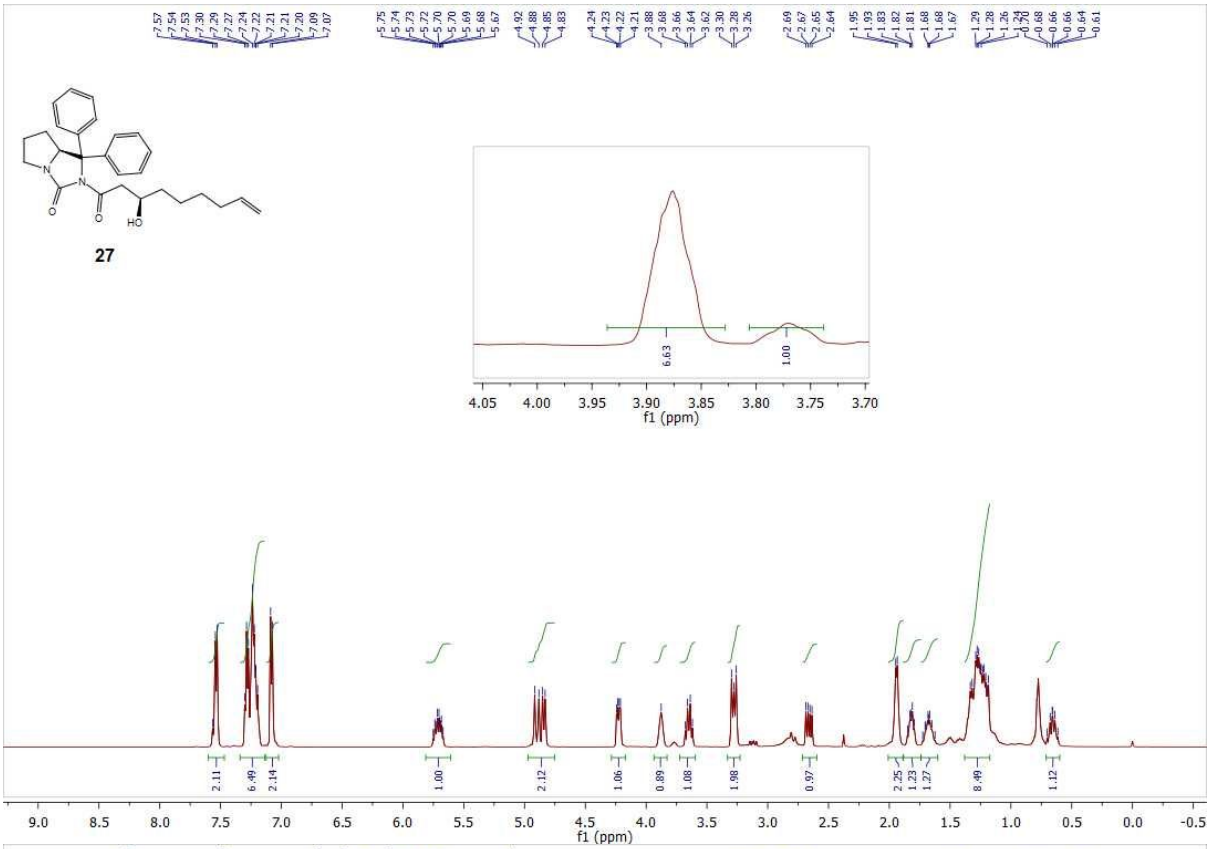
O
OH
OH
Cl
Cl
O
1
f1 (ppm)

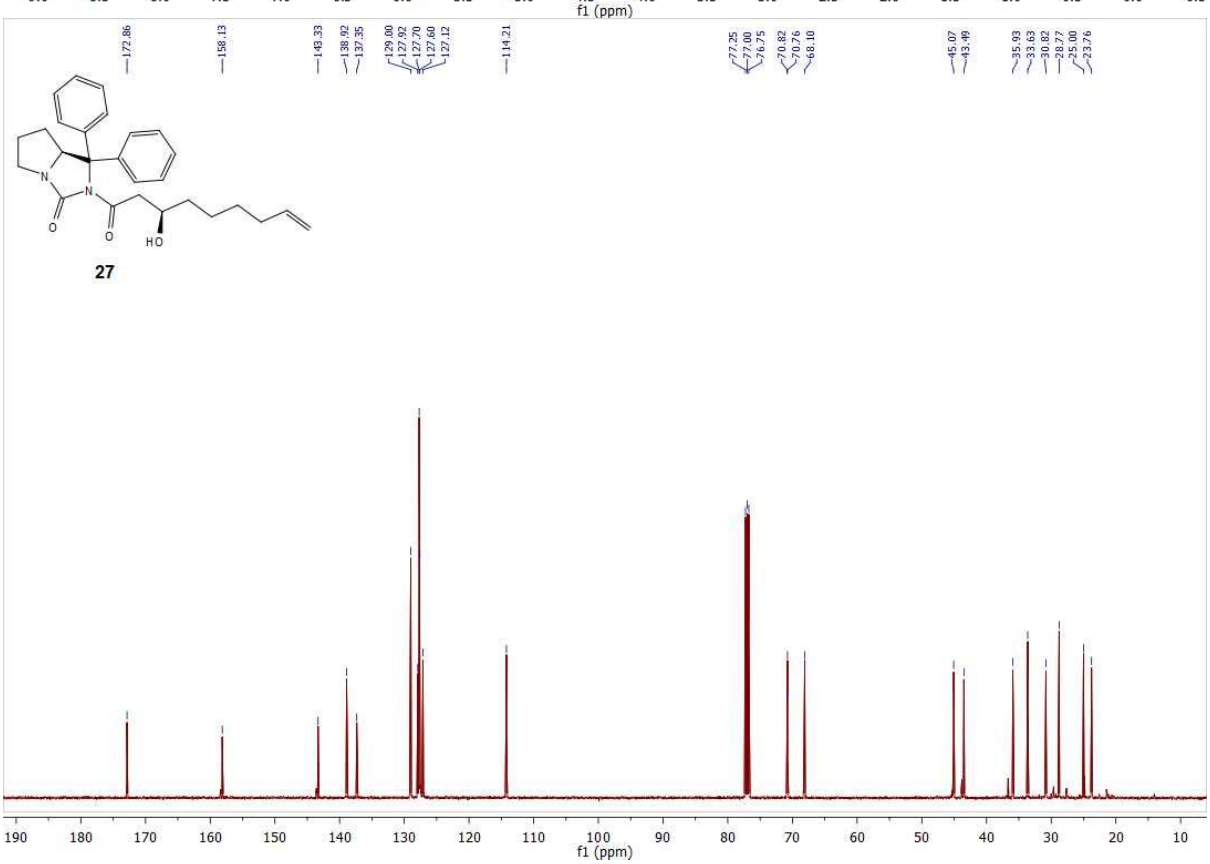

25
f1 (ppm)

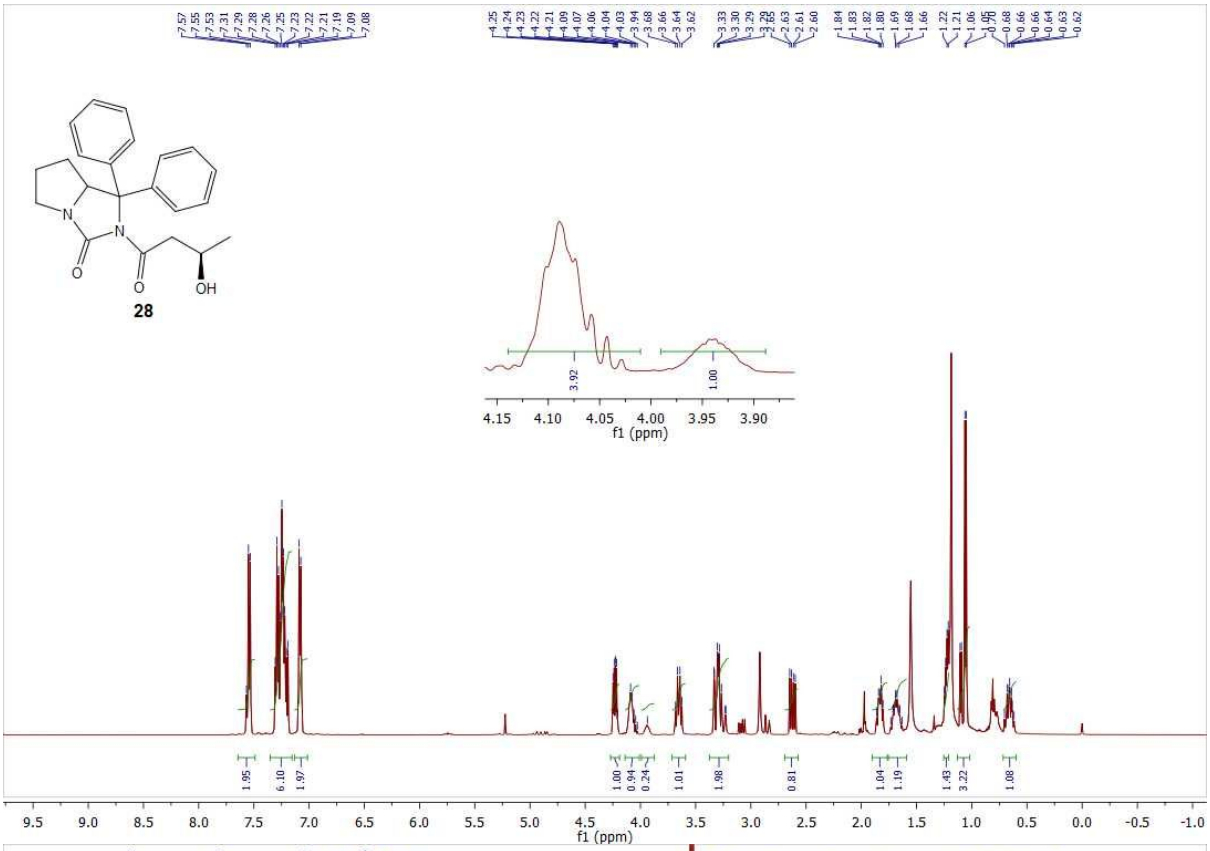

25
f1 (ppm)

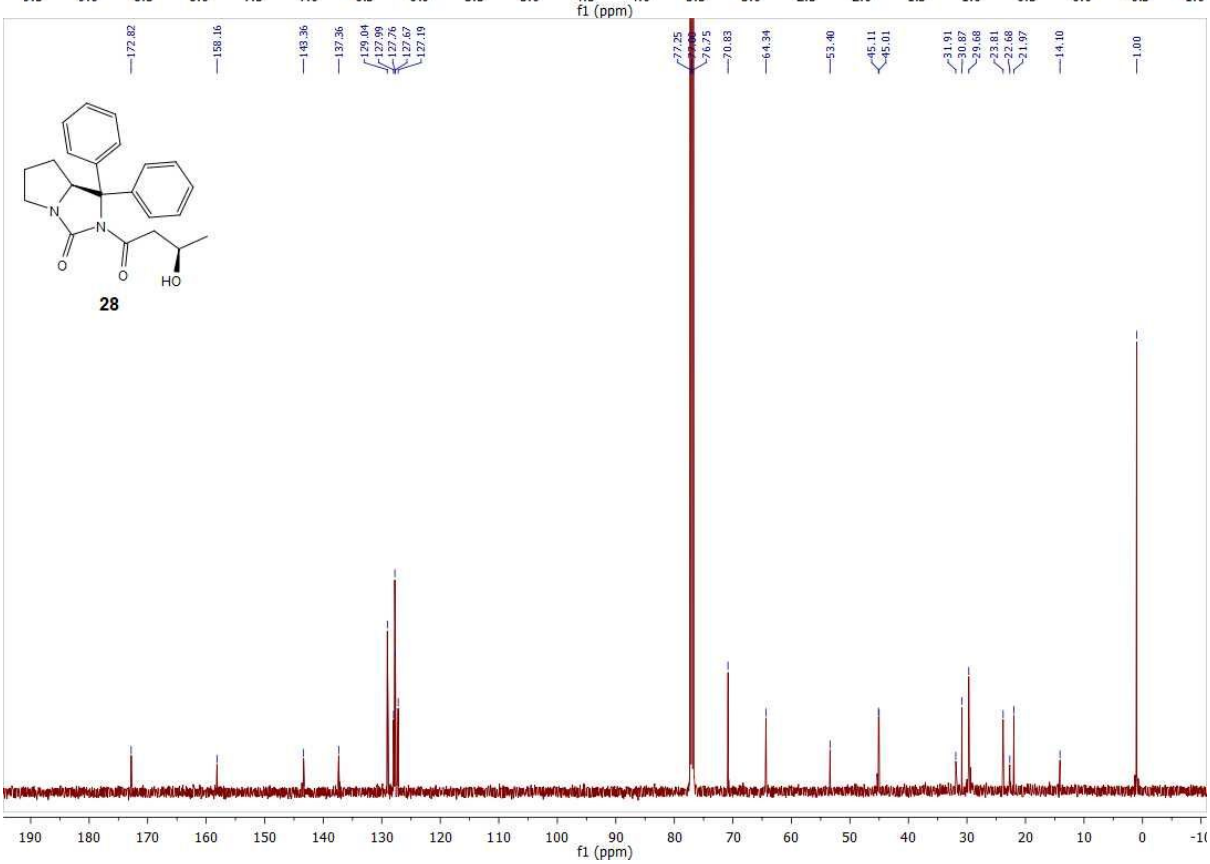

26
f1 (ppm)

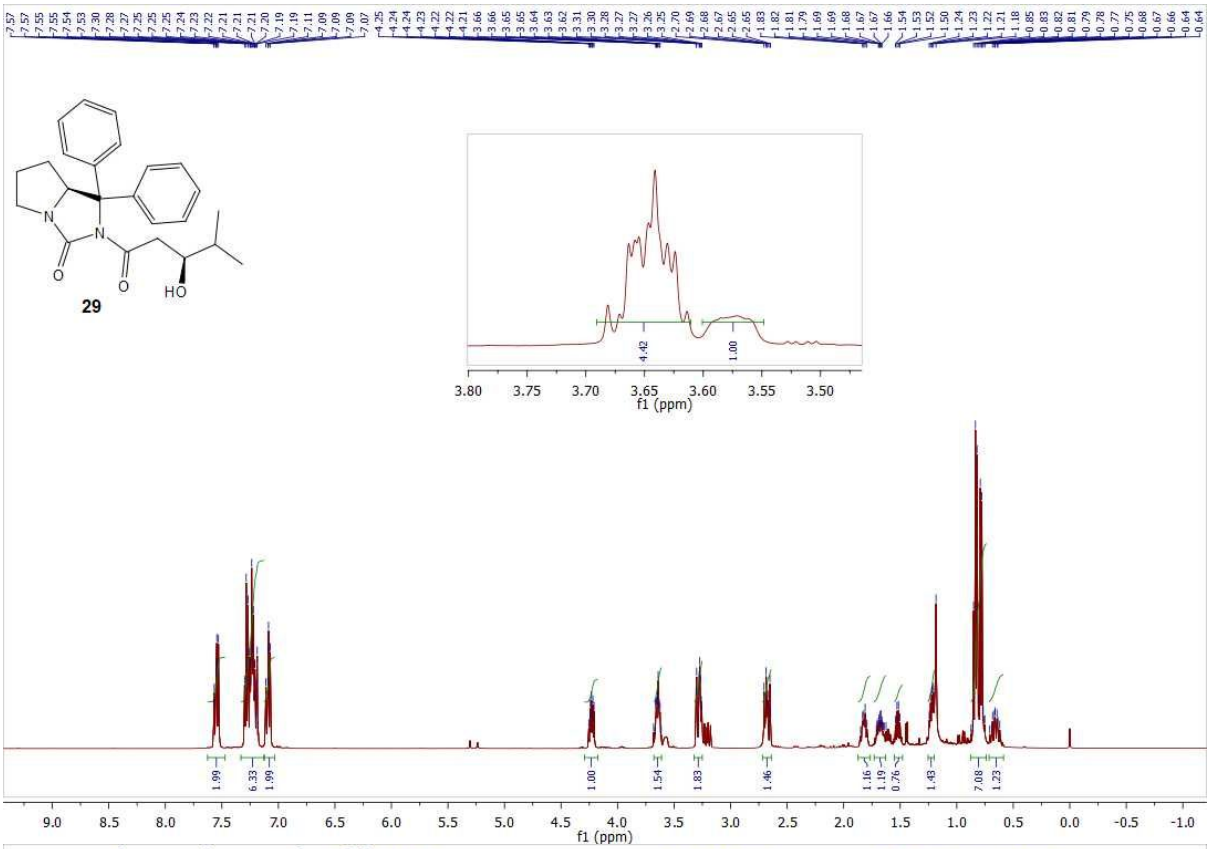

26
f1 (ppm)

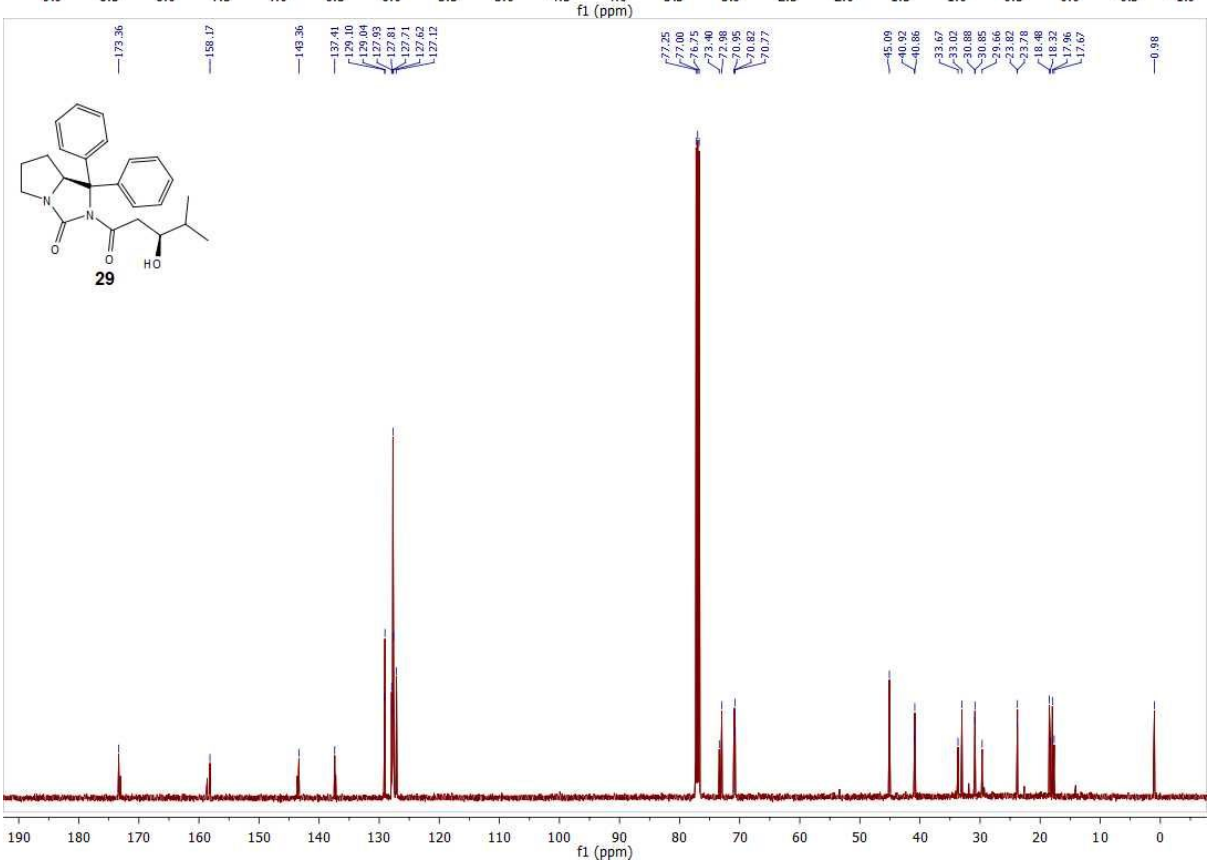

27
6.63
1.00
4.05 4.00 3.95 3.90 3.85 3.80 3.75 3.70
f1 (ppm)
2.11 6.49 2.14 1.00 2.12 1.06 0.89 1.08 1.98 0.97 2.25 1.23 1.27 8.49 1.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

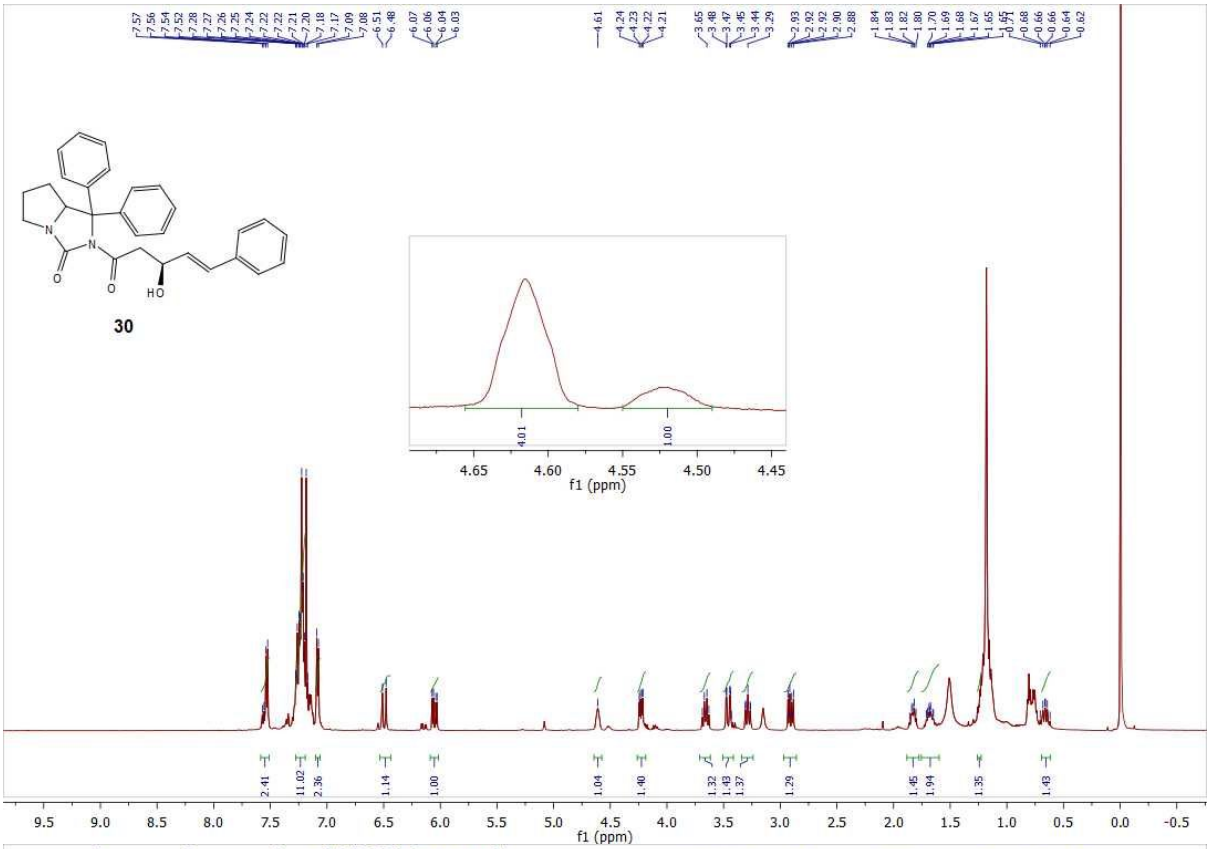

27
172.86
158.13
143.33
138.92
137.35
129.00
127.92
127.70
127.60
127.12
114.21
77.25
77.00
76.75
70.82
70.76
68.10
45.07
43.49
35.93
33.63
30.82
28.77
25.00
23.76
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

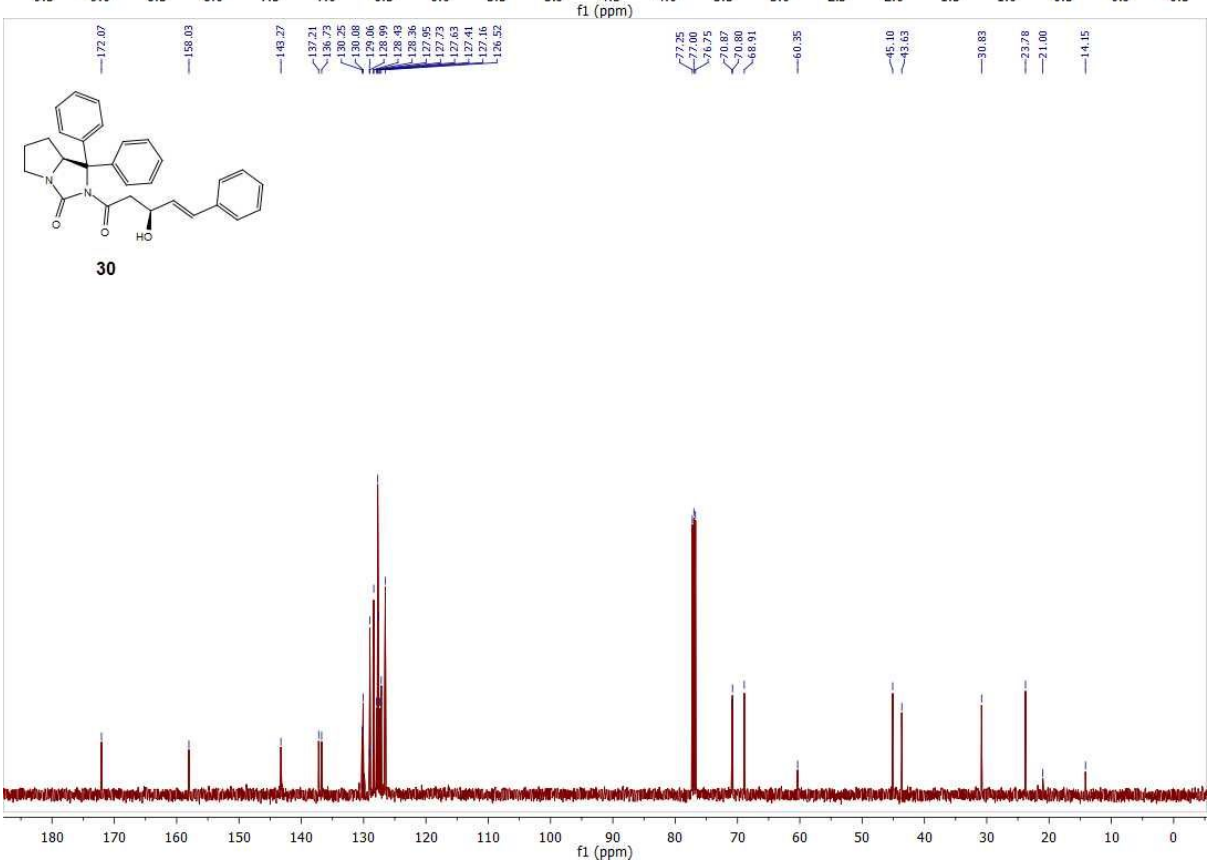

28
f1 (ppm)

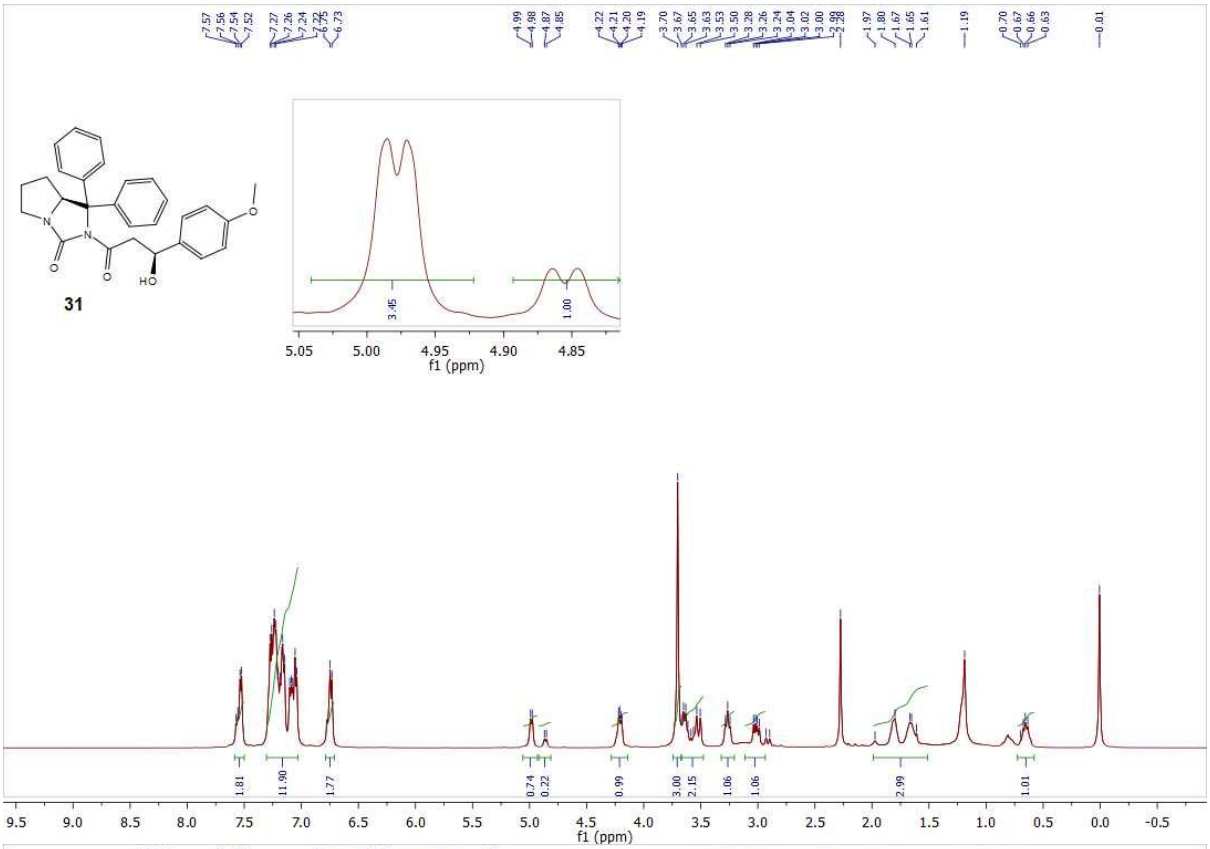

28
f1 (ppm)

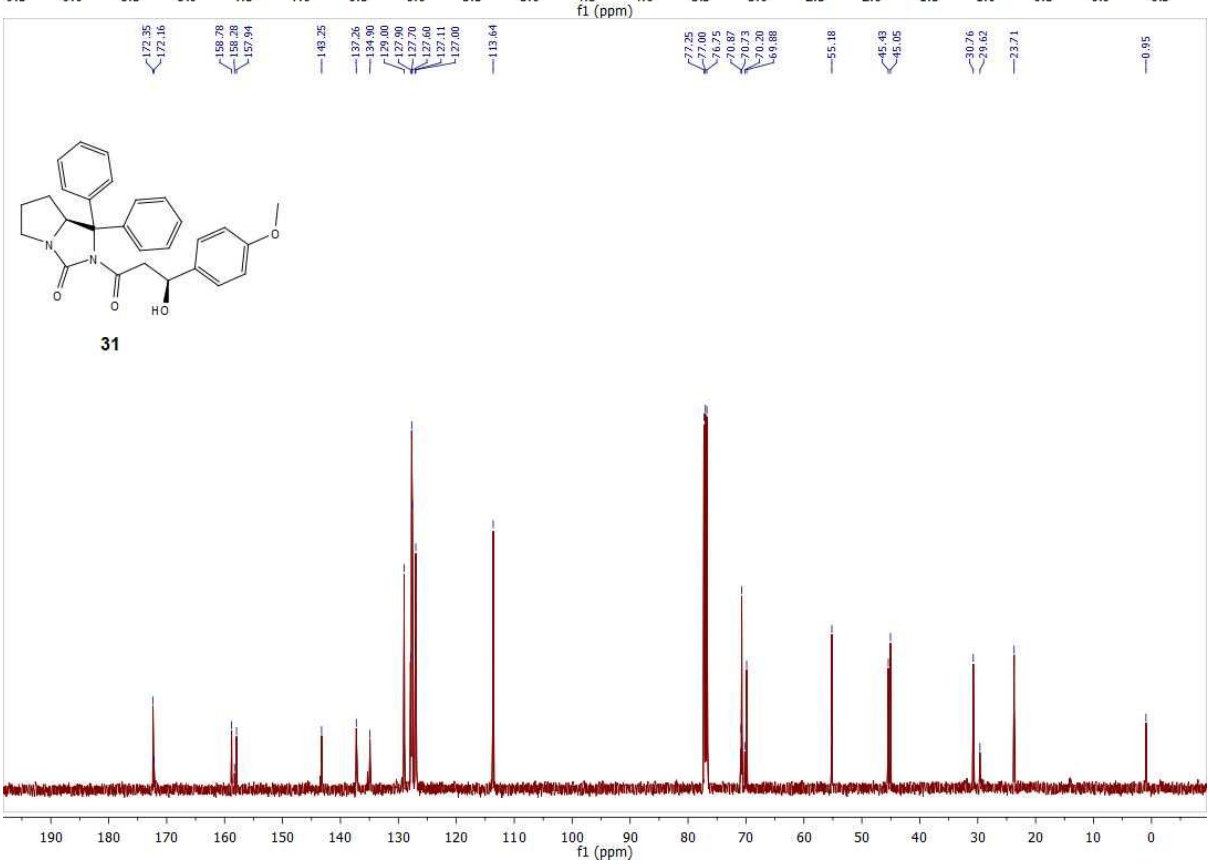

29
4.42
1.00
f1 (ppm)
1.99
6.33
1.99
1.00
1.54
1.83
1.46
1.16
1.19
0.76
1.43
7.08
1.23
f1 (ppm)

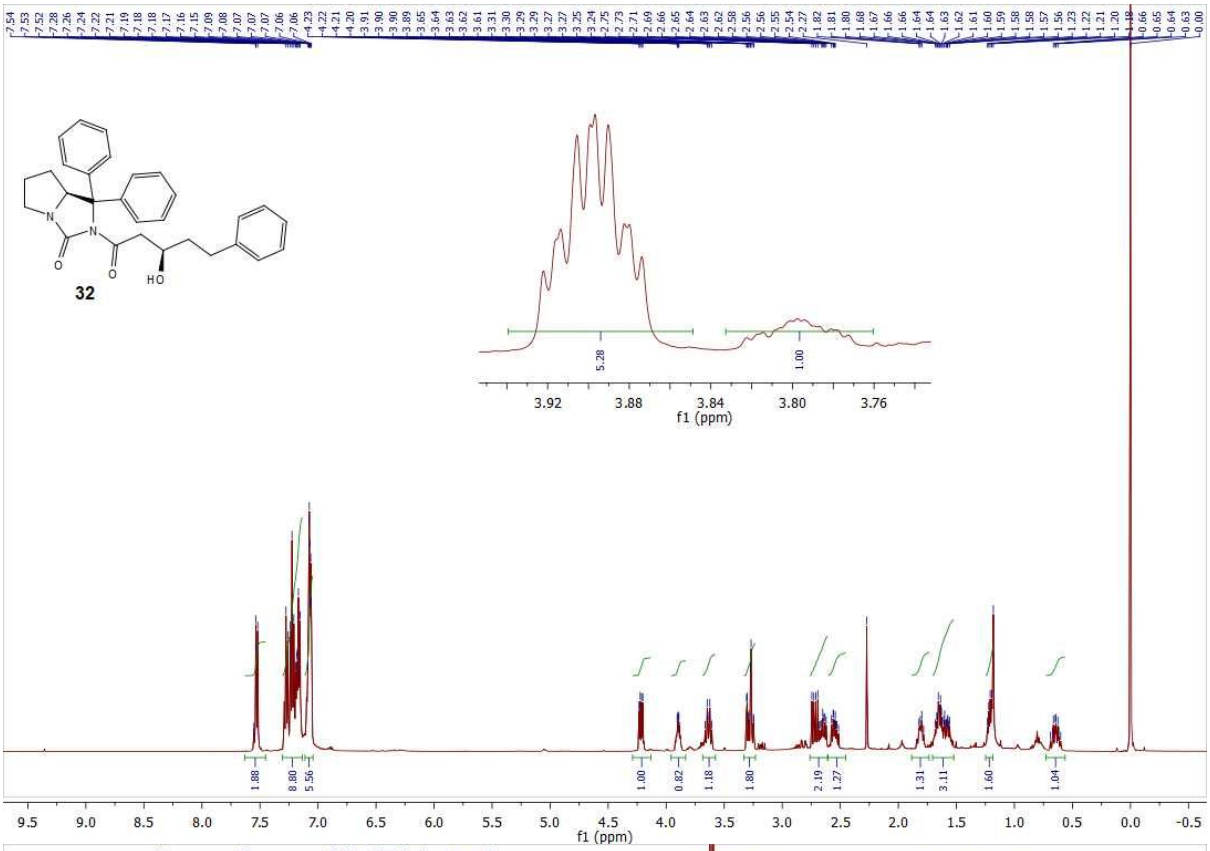

29
f1 (ppm)

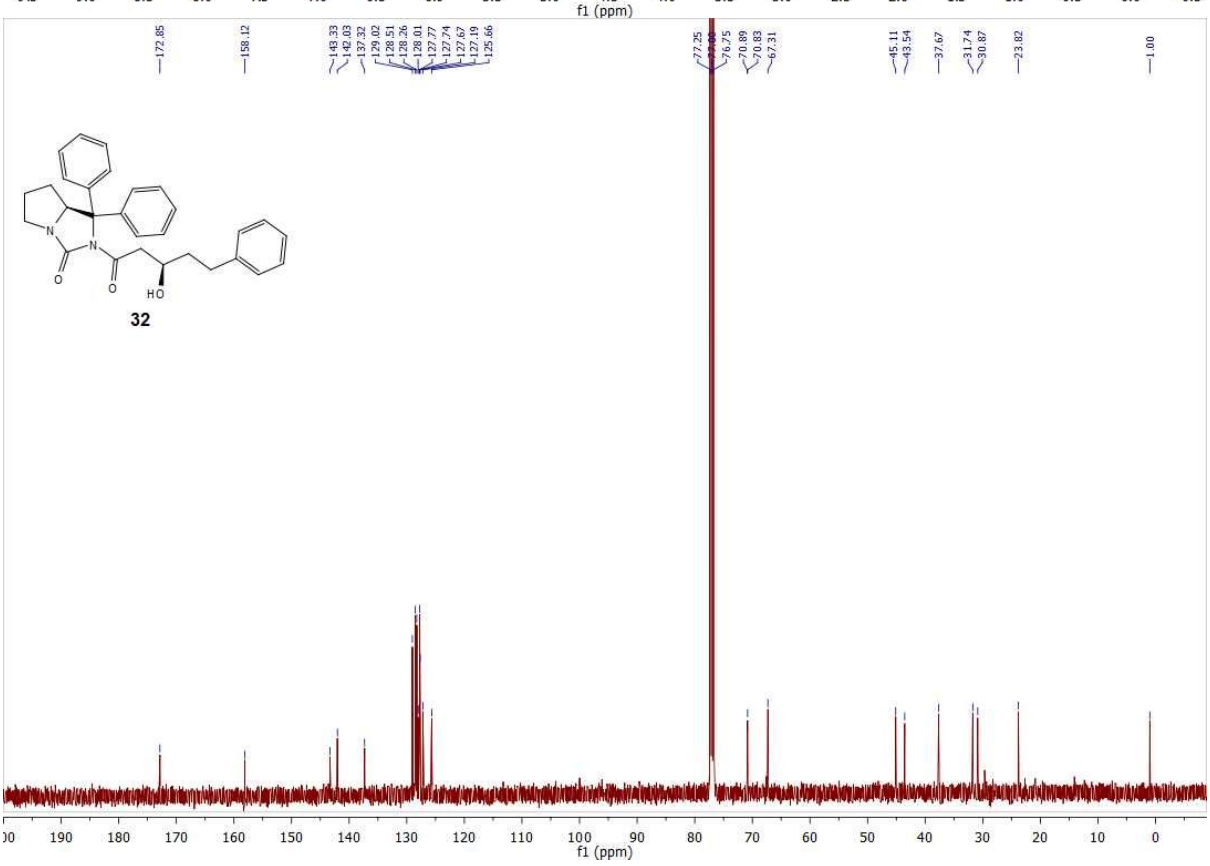

30
f1 (ppm)


30
f1 (ppm)


31
3.45
1.00
5.05
5.00
4.95
4.90
4.85
f1 (ppm)
1.81
11.90
1.77
0.74
0.22
0.99
3.00
2.15
1.06
1.06
2.99
1.01
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
0.0
-0.5
f1 (ppm)


31
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


32
5.28
1.00
3.92
3.88
3.84
3.80
3.76
f1 (ppm)
1.88
8.80
5.56
1.00
0.82
1.18
1.80
2.19
1.27
1.31
3.11
1.60
1.04
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
0.0
-0.5
f1 (ppm)


32
172.85
158.12
143.33
142.03
137.32
129.02
128.51
128.26
128.01
127.77
127.74
127.67
127.19
125.66
77.25
76.75
70.89
70.83
67.31
45.11
43.54
37.67
31.74
30.87
23.82
1.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)