Supplementary Information

Total Synthesis and Target Identification of Marine Cyclopiane Diterpenes

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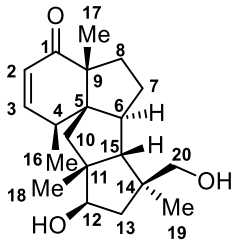
2. Comparison of natural and synthetic Cyclopiane diterpenes

Table S1. Comparison of natural and synthetic 12β-hydroxy Conidiogenone C (9) ($[\alpha]_D^{20}$)

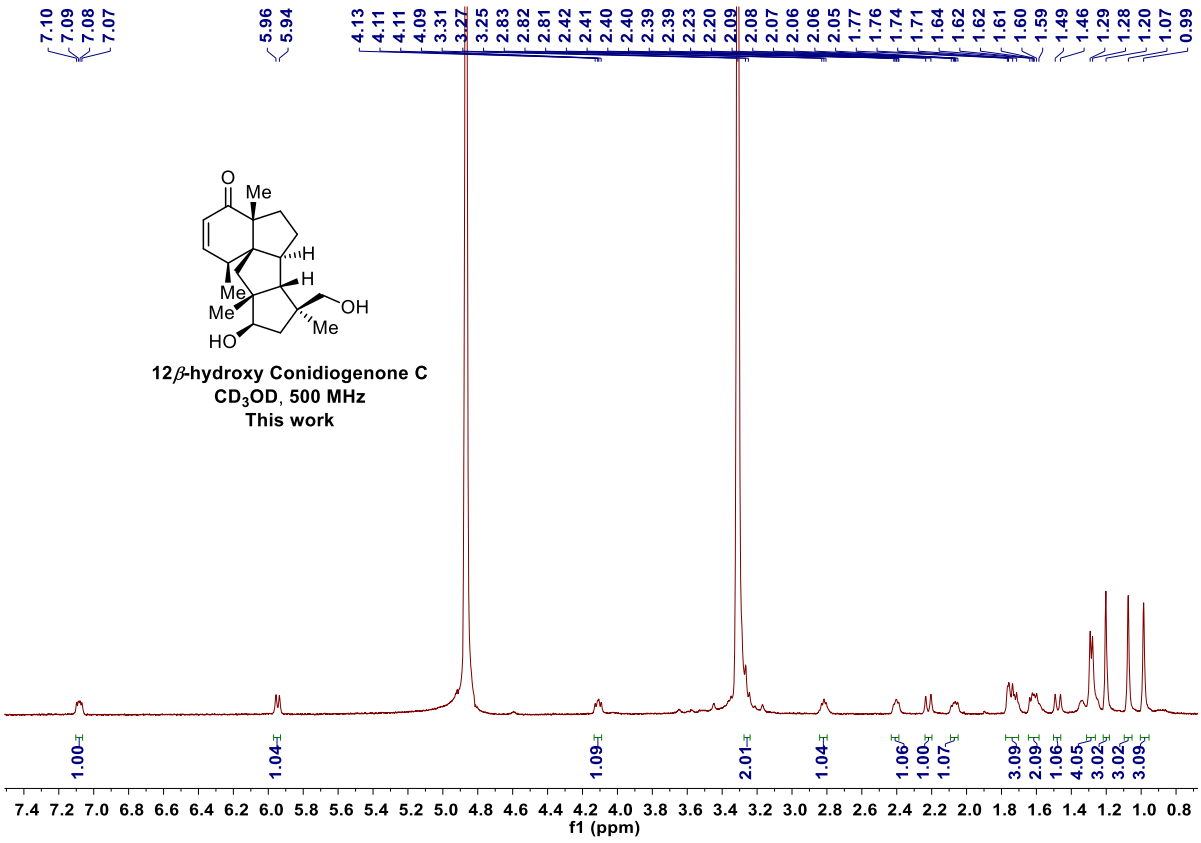
	$[\alpha]_D^T$
Natural[1]	$[\alpha]_D^{25} = -0.22$ (*c* = 1, MeOH)
Synthetic	$[\alpha]_D^{20} = -6.0$ (*c* = 0.5, MeOH)

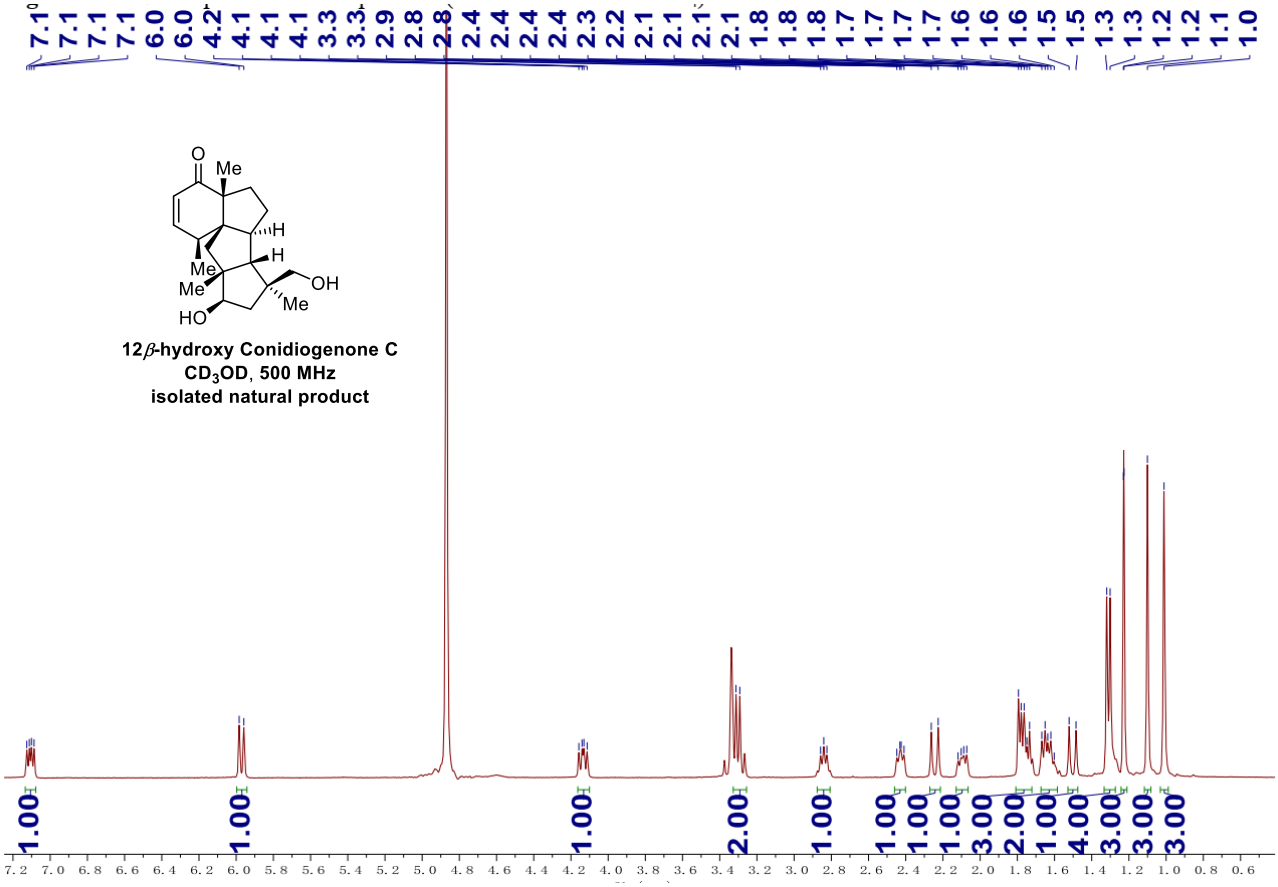
Table S2. Comparison of natural and synthetic 12β-hydroxy Conidiogenone C (9)

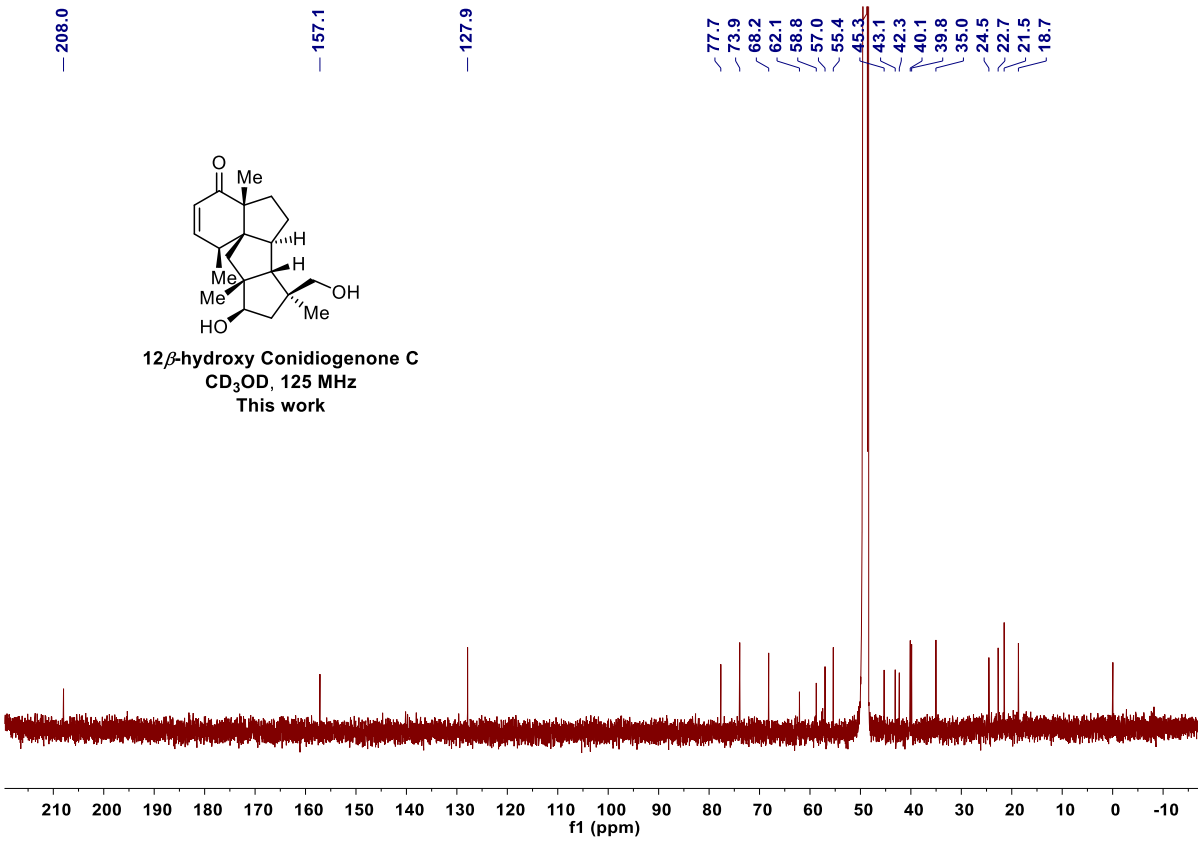


12β-hydroxy conidiogenone C

	^{1}H NMR (CD_3OD)		^{13}C NMR (CD_3OD)		
No.	Our sample (500 Hz)	Natural[1] (400 Hz)	Our sample (125 Hz)	Natural[1] (100 Hz)	Different (Δ ppm)
1			208.0	208.2	–0.2
2	5.95 (d, *J* = 10.0 Hz, 1H)	5.97 (d, *J* = 10.0 Hz)	127.9	127.9	0
3	7.08 (dd, *J* = 9.9, 5.3 Hz, 1H)	7.11 (dd, *J* = 10.0, 5.5 Hz, 1H)	157.1	157.1	0
4	2.82 (p, *J* = 6.2 Hz, 1H)	2.84 (p, *J* = 7.0 Hz, 1 H)	40.1	40.1	0
5			62.1	62.1	0
6	2.42 – 2.39 (m, 1H)	2.43, (m, 1 H)	55.4	55.4	0
7	1.64 – 1.59 (m, 2H); 1.29 – 1.28 (m, 1H)	1.63, (m, 1 H); 1.29, (m, 1 H)	35.0	35.0	0
8	2.09 – 2.05 (m, 1H); 1.77 – 1.71 (m, 2H)	2.09, (m, 1 H); 1.76, (m, 1H)	39.8	39.8	0
9			58.8	58.7	0.1
10	2.22 (d, *J* = 14.9 Hz, 1H)	2.24 (d, *J* = 14.8 Hz, 1 H)	43.1	43.1	0
11			57.0	57.0	0
12	4.11 (dd, *J* = 10.5, 7.1 Hz, 1H)	4.14 (d, *J* = 11.0, 6.9 Hz, 1H)	77.7	77.7	0
13	1.77 – 1.71 (m, 2H); 1.64 – 1.59 (m, 2H)	1.76, (m, 1 H); 1.63, (m, 1H)	45.3	45.3	0
14			42.3	42.3	0
15	1.76 (d, *J* = 5.8 Hz, 1 H)	1.79 (d, *J* = 5.8 Hz, 1 H)	68.2	68.2	0
16	1.29 (d, *J* = 7.1 Hz, 3H)	1.32 (d, *J* = 7.2 Hz, 3 H)	18.7	18.7	0
17	1.20 (s, 3H)	1.23, (s, 3 H)	21.5	21.5	0
18	1.07 (s, 3H)	1.10, (s, 3 H)	22.7	22.7	0
19	0.99 (s, 3H),	1.01, (s, 3 H)	24.5	24.5	0
20	3.31– 3.25 (m, 2H)	3.30, (m, 2 H)	73.9	73.9	0
-OH	1.48 (d, *J* = 15.0 Hz, 1H)				


12β-hydroxy Conidiogenone C
CD3OD, 500 MHz
This work
f1 (ppm)


12β-hydroxy Conidiogenone C
CD3OD, 500 MHz
isolated natural product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77.7
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68.2
62.1
58.8
57.0
55.4
45.3
43.1
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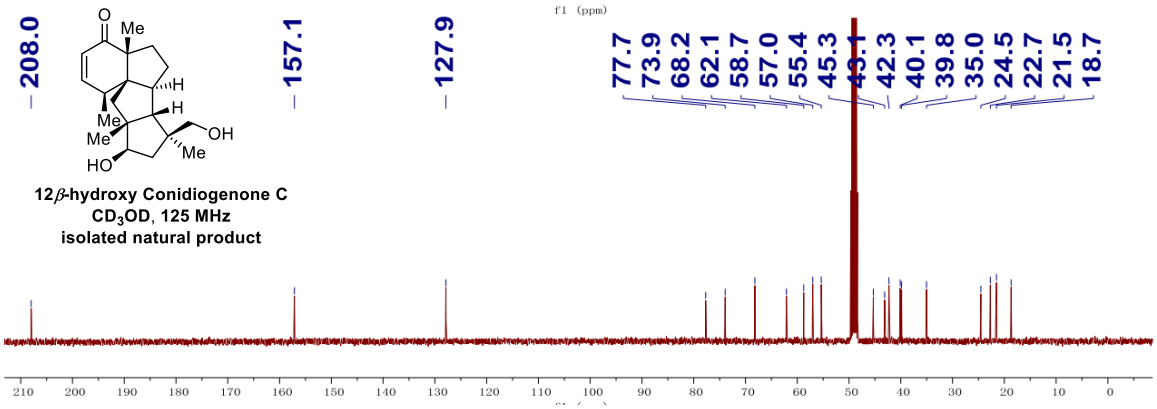
40.1
39.8
35.0
24.5
22.7
21.5
18.7
O
Me
H
H
Me
Me
OH
Me
HO
12β-hydroxy Conidiogenone C
CD3OD, 125 MHz
This work
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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157.1
127.9
77.7
73.9
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62.1
58.7
57.0
55.4
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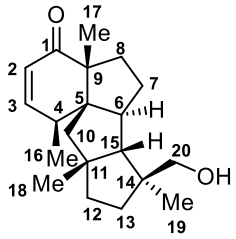
43.1
42.3
40.1
39.8
35.0
24.5
22.7
21.5
18.7
O
Me
H
H
Me
Me
OH
Me
HO
12β-hydroxy Conidiogenone C
CD3OD, 125 MHz
isolated natural product
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Table S3. Comparison of natural and synthetic Conidiogenone C (4) ($[\alpha]_D^{20}$)

	$[\alpha]_D^T$
Natural[2]	$[\alpha]_D^{20} = -11.9$ (*c* = 0.04, MeOH)
Synthetic	$[\alpha]_D^{20} = -8.6$ (*c* = 1, MeOH)

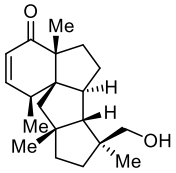
Table S4. Comparison of natural and synthetic Conidiogenone C (4)



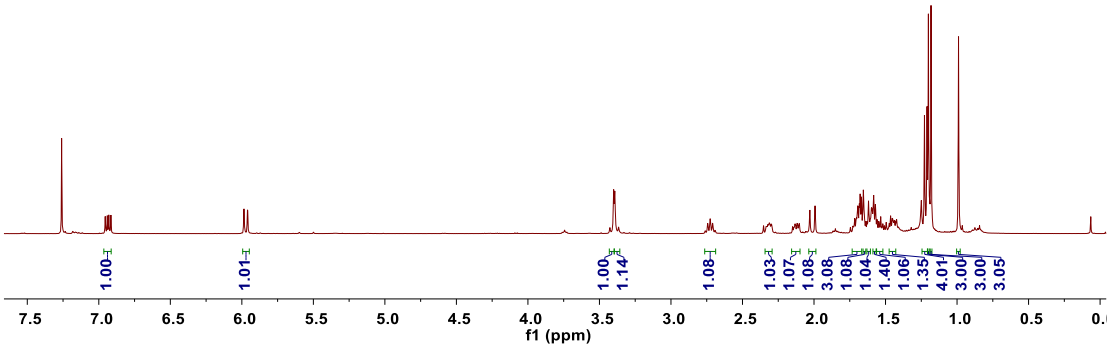
Conidiogenone C

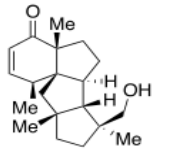
No.	Our sample (400 Hz)	Snyder's sample[3] (500 Hz)	Natural[2] (600 Hz)
2	5.97 (dd, *J* = 10.0, 1.1 Hz, 1 H)	5.97 (dd, *J* = 10.0, 1.2 Hz, 1 H)	5.97 (dd, *J* = 9.9, 1.1 Hz)
3	6.94 (dd, *J* = 10.0, 5.8 Hz, 1 H)	6.93 (dd, *J* = 10.0, 5.8 Hz, 1 H)	6.93 (dd, *J* = 9.9, 6.1 Hz)
4	2.69 – 2.76 (m, 1 H)	2.69 – 2.76, (m, 1 H)	2.70 – 2.75, m
6	2.30 – 2.34 (m, 1 H)	2.29 – 2.34, (m, 1 H)	2.32 (dd, *J* = 8.2, 4.9 Hz)
7a	1.67 – 1.73 (m, 3 H)	1.65 – 1.73, (m, 3 H)	1.70 – 1.73, m
7b	1.20 – 1.23 (m, 1 H)	1.20 – 1.23, (m, 1 H)	1.20 – 1.23, m
8a	2.15 – 2.10 (m, 1 H)	2.13 (ddd, *J* = 11.7, 5.5, 2.3 Hz, 1 H)	2.13 (ddd, *J* = 11.5, 5.5, 1.7 Hz)
8b	1.67 – 1.73 (m, 3 H)	1.65 – 1.73, (m, 3 H)	1.66 – 1.69, m
10a	2.01 (d, *J* = 14.7 Hz, 1 H)	2.01 (d, *J* = 14.6 Hz, 1 H)	2.01 (d, *J* = 14.8 Hz)
10b	1.66 – 1.64 (m, 1 H)	1.64 (d, *J* = 14.6 Hz, 1 H)	1.64 (d, *J* = 14.8 Hz)
12a	1.67 – 1.73 (m, 3 H)	1.65 – 1.73, (m, 3 H)	1.65 – 1.68, m
12b	1.60 – 1.63 (m, 1 H)	1.60 – 1.63, (m, 1 H)	1.60 – 1.63, m
13a	1.52 – 1.56 (m, 1 H)	1.52 – 1.56, (m, 1 H)	1.52 – 1.55, m
13b	1.43 – 1.47 (m, 1 H)	1.43 – 1.47, (m, 1 H)	1.43 – 1.47, m
15	1.58 (d, *J* = 5.0 Hz, 1 H)	1.58 (d, *J* = 5.1 Hz, 1 H)	1.58 (d, *J* = 4.9 Hz)
16	1.22 (d, *J* = 7.3 Hz, 3 H)	1.22 (d, *J* = 7.3 Hz, 3 H)	1.22 (d, *J* = 7.1 Hz)
17	1.18 (s, 3 H)	1.18 (s, 3 H)	1.19, s
18	1.20 (s, 3 H)	1.20 (s, 3 H)	1.21, s
19	0.99 (s, 3 H)	0.99 (s, 3 H)	0.99, s
20a	3.41 (d, *J* = 10.6 Hz, 1 H)	3.41 (d, *J* = 11.0 Hz, 1 H)	3.41 (d, *J* = 11.0 Hz)
20b	3.38 (d, *J* = 10.7 Hz, 1 H)	3.38 (d, *J* = 11.0 Hz, 1 H)	3.38 (d, *J* = 11.0 Hz)

No.	Our sample (100 Hz)	Snyder's sample[3] (125 Hz)	Natural[2] (150 Hz)	Different (Δ ppm)
1	205.7	205.7	205.7	0
2	127.4	127.3	127.3	0.1
3	154.2	154.2	154.2	0
4	37.8	37.8	37.8	0
5	59.9	59.9	59.9	0
6	54.7	54.7	54.7	0
7	34.2	34.2	34.2	0
8	38.8	38.7	38.7	–0.1
9	57.5	57.5	57.5	0
10	46.5	46.5	46.5	0
11	52.8	52.7	52.7	0.1
12	38.4	38.4	38.4	0
13	36.6	36.6	36.6	0
14	48.1	48.1	48.1	0
15	68.2	68.2	68.2	0
16	18.6	18.5	18.5	0.1
17	21.1	21.1	21.1	0
18	31.1	31.1	31.1	0
19	22.5	22.5	22.5	0
20	72.0	71.9	71.9	0.1

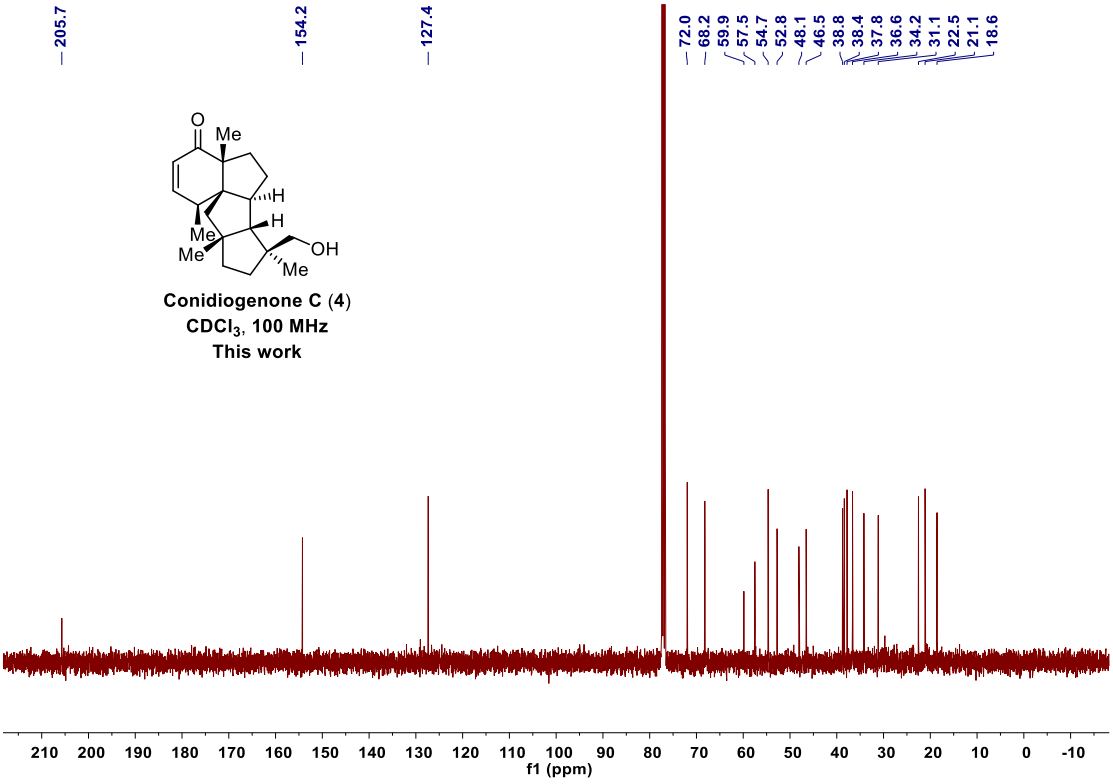


Conidiogenone C (4)
$CDCl_3$, 400 MHz
This work





11 conidiogenone C
($CDCl_3$, 500 MHz)
Snyder Synthetic Sample


205.7
154.2
127.4
72.0
68.2
59.9
57.5
54.7
52.8
48.1
46.5
38.8
38.4
37.8
36.6
34.2
31.1
22.5
21.1
18.6
Conidiogenone C (4)
CDCl3, 100 MHz
This work
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f1 (ppm)

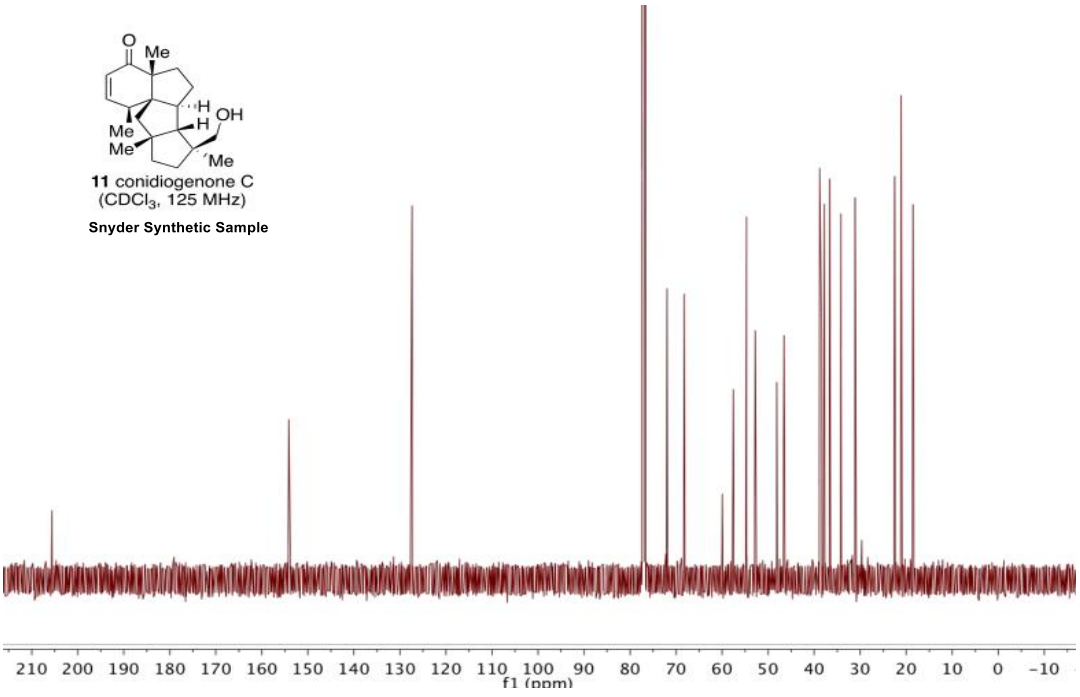
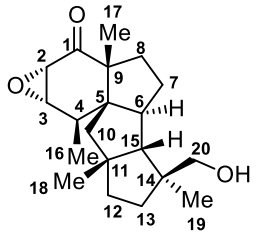

11 conidiogenone C
(CDCl3, 125 MHz)
Snyder Synthetic Sample
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Table S5. Comparison of natural and synthetic Conidiogenone K (8) ($[\alpha]_D^{20}$)

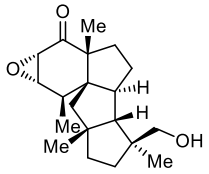
	$[\alpha]_D^T$
Natural[4]	$[\alpha]_D^{25} = -30.9$ (*c* = 0.28, MeOH)
Synthetic	$[\alpha]_D^{20} = -56.6$ (*c* = 1, MeOH)

Table S6. Comparison of natural and synthetic Conidiogenone K (8)

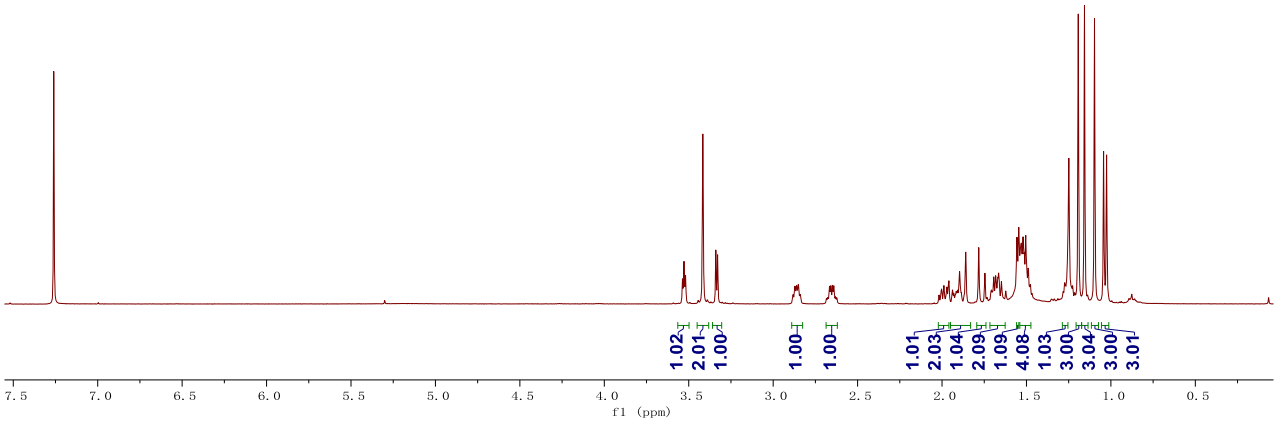


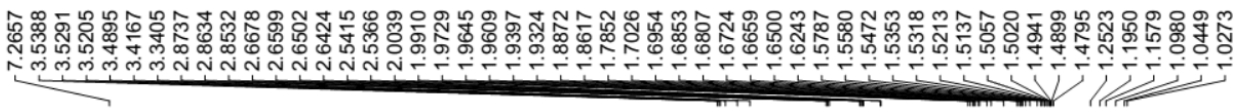
Conidiogenone K

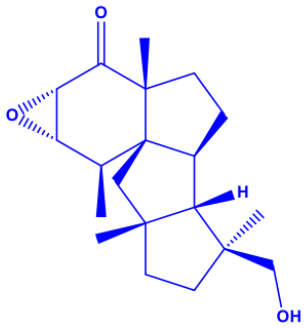
No.	^{1}H NMR ($CDCl_3$)		^{13}C NMR ($CDCl_3$)		
	Our sample (400 Hz)	Natural[4] (400 Hz)	Our sample (100 Hz)	Natural[4] (100 Hz)	Different (Δ ppm)
1			212.5	212.6	– 0.1
2	3.33 (d, *J* = 4.2 Hz, 1H)	3.34 (d, *J* = 4.1 Hz)	53.5	53.5	0
3	3.53 (t, *J* = 3.7 Hz, 1H)	3.53 (t, *J* = 3.8 Hz, 1 H)	61.2	61.2	0
4	2.65 (dq, *J* = 7.1, 3.2 Hz, 1H)	2.65 (dq, *J* = 7.2, 3.1 Hz, 1 H)	35.1	35.0	0.1
5			59.6	59.6	0
6	2.86 (dt, *J* = 8.8, 4.6 Hz, 1H)	2.86 (m, 1 H)	55.7	55.7	0
7	1.94– 1.90 (m, 1H); 1.28 – 1.23 (m, 1H)	1.92 (m, 1 H); 1.26 (m, 1 H)	34.1	34.0	0.1
8	2.02 – 1.96 (m, 1H); 1.54 – 1.52 (m, 1H)	1.99, (m, 1 H); 1.52, (m, 1H)	40.1	40.1	0
9			56.9	56.8	0.1
10	1.88 (d, *J* = 14.6 Hz, 1H); 1.76 (d, *J* = 14.6 Hz, 1H)	1.88 (d, *J* = 14.6 Hz, 1 H); 1.76 (d, *J* = 14.6 Hz, 1 H)	48.0	48.0	0
11			52.1	52.1	0
12	1.72 – 1.67 (m, 1H); 1.52 – 1.47 (m, 1H)	1.67 (m, 1 H); 1.52 (m, 1 H)	38.3	38.2	0.1
13	1.67 – 1.62 (m, 1H); 1.52 – 1.47 (m, 1H)	1.67 (m, 1 H); 1.52 (m, 1 H)	36.6	36.6	0
14			48.2	48.2	0
15	1.55 (d, *J* = 4.4 Hz, 1 H)	1.55 (d, *J* = 4.3 Hz, 1 H)	65.7	65.6	0.1
16	1.03 (d, *J* = 7.1 Hz, 3H)	1.04 (d, *J* = 7.1 Hz, 3 H)	15.2	15.1	0.1
17	1.16 (s, 3H)	1.16, (s, 3 H)	22.3	22.3	0
18	1.19 (s, 3H)	1.21, (s, 3 H)	31.7	31.7	0
19	1.10 (s, 3H),	1.10, (s, 3 H)	22.4	22.4	0
20	3.42 (s, 2H)	3.42, (s, 2 H)	72.0	72.0	0



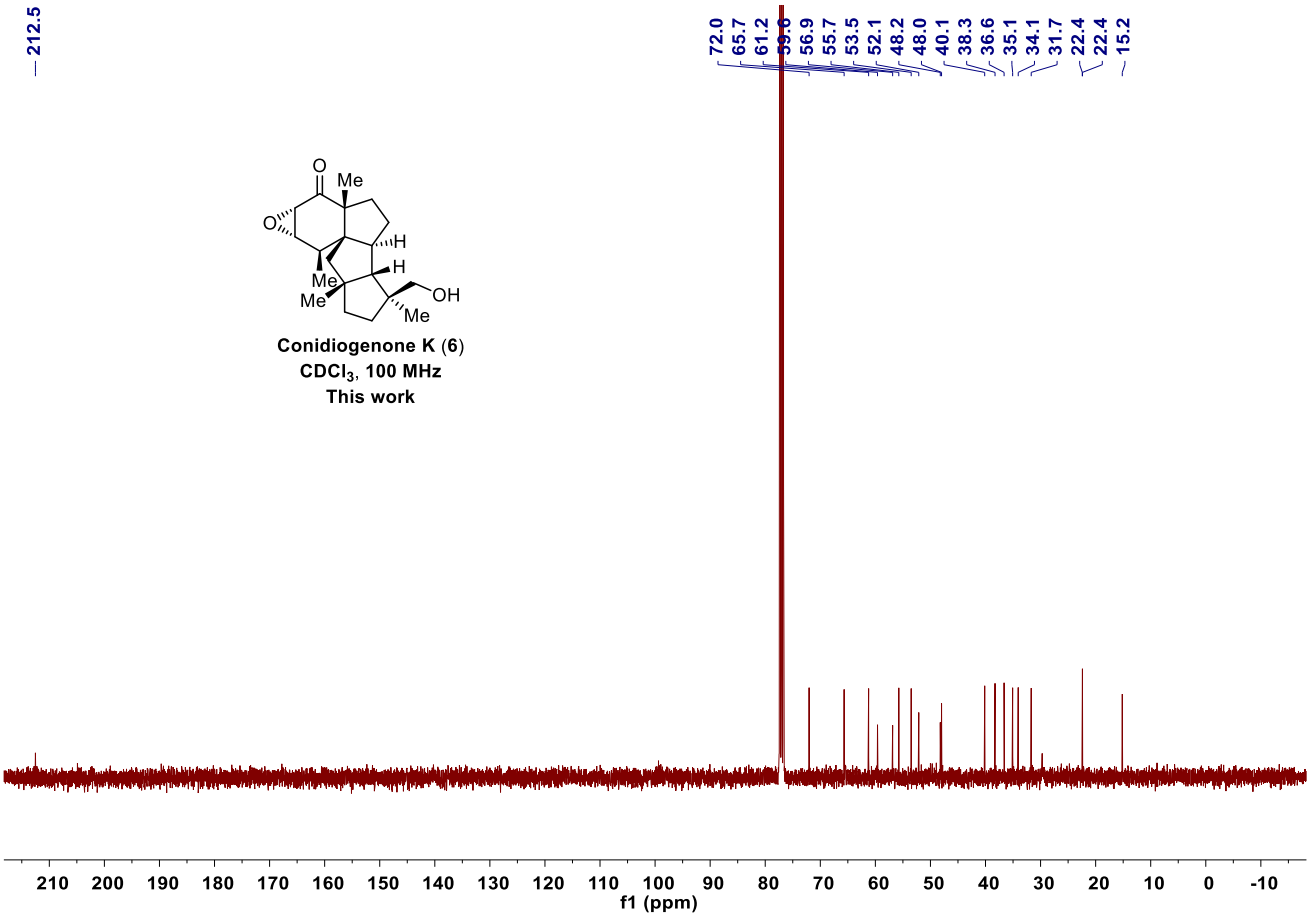
Conidiogenone K (6)
$CDCl_3$, 400 MHz
This work

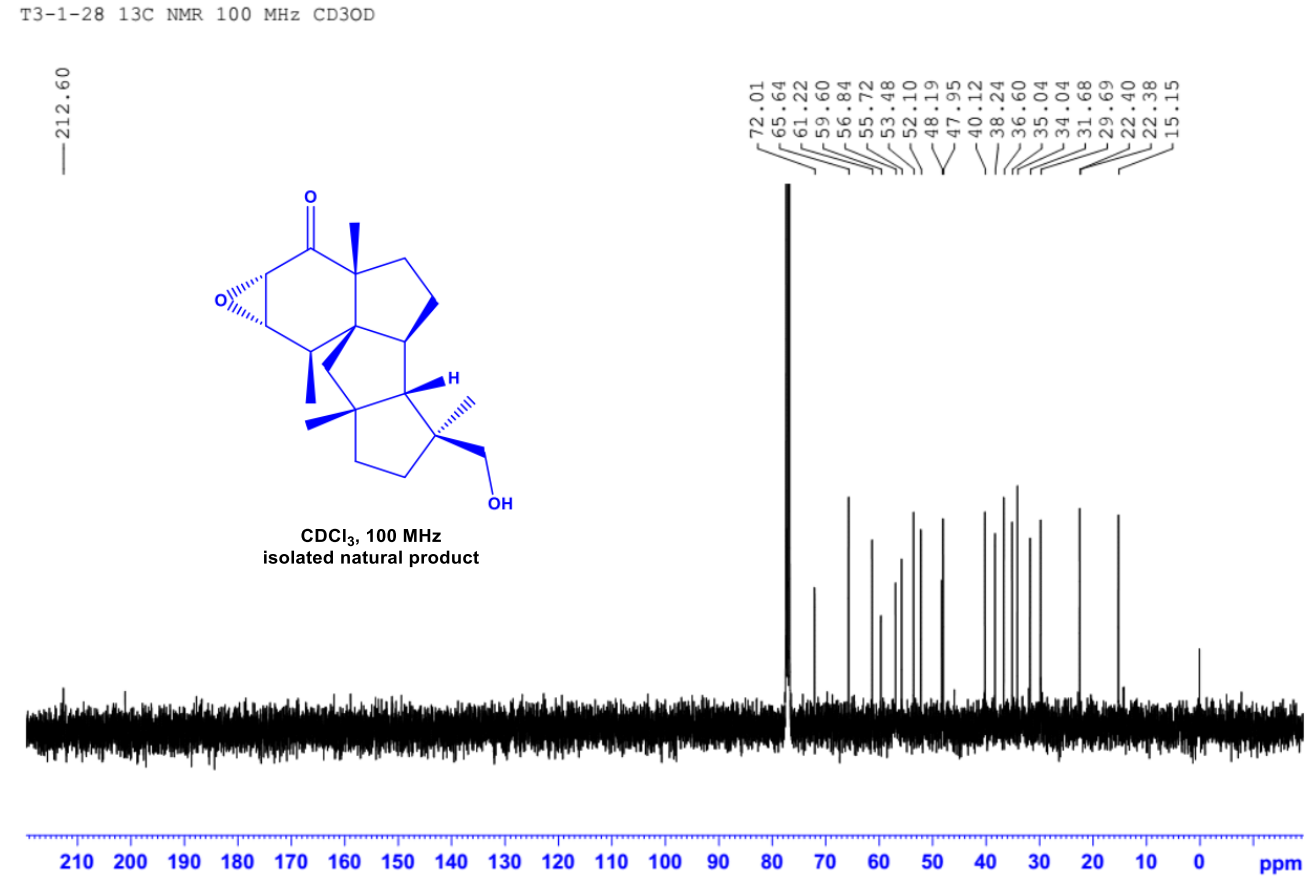






$CDCl_3$, 400 MHz
isolated natural product


212.5
72.0
65.7
61.2
59.6
56.9
55.7
53.5
52.1
48.2
48.0
40.1
38.3
36.6
35.1
34.1
31.7
22.4
22.4
15.2
O
Me
O
H
H
Me
Me
OH
Me
Conidiogenone K (6)
CDCl3, 100 MHz
This work
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


T3-1-28 13C NMR 100 MHz CD3OD
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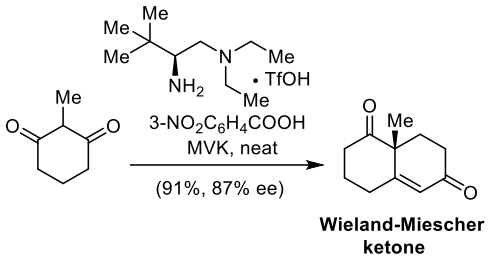
72.01
65.64
61.22
59.60
56.84
55.72
53.48
52.10
48.19
47.95
40.12
38.24
36.60
35.04
34.04
31.68
29.69
22.40
22.38
15.15
O
O
H
OH
CDCl3, 100 MHz
isolated natural product
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

3. Experimental Procedures

3.1 Total Synthesis of 12*β*-hydroxy Conidiogenone C

Synthesis of (–)-Wieland-Miecher ketone



(*S*)-N^1, N^1-diethyl-3,3-dimethylbutane-1,2-diamine (56.8 mg, 0.32 mmol), Trifluoromethanesulfonic acid (28.3 μL, 0.32 mmol), 2-methylcyclohexane-1,3- dione (2 g, 15.8 mmol), *m*-nitrobenzoic acid (26.7 mg, 0.16 mmol) and methyl vinyl ketone (2 mL) were added to a 10 mL sealed tube at room temperature. Then the mixture was stirred at 60 ℃ for 12 h. After completing the reaction, the mixture was concentrated and purified via flash chromatography (EtOAc / petroleum ether = 1/3) to afford (–)-Wieland-Miescher ketone (2.57 g, 14.43 mmol, 91% yield, 87% ee) as a yellow oil.

R_f = 0.21 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

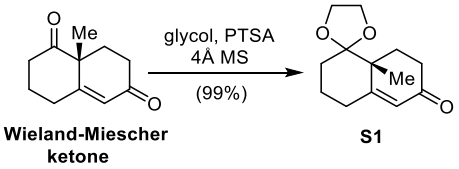
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (d, *J* = 1.8 Hz, 1H), 2.74 – 2.63 (m, 2H), 2.51 – 2.40 (m, 4H), 2.16 – 2.07 (m, 3H), 1.68 (qt, *J* = 13.3, 4.4 Hz, 1H), 1.42 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 211.0, 198.3, 165.9, 125.8, 50.6, 37.7, 33.6, 31.7, 29.7, 23.3, 22.9;

HRMS ESI Calcd for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886, found 201.0887;

$[\alpha]_D^{20}$ = – 89.2 (*c* = 1, C_6H_6), reported $[\alpha]_D^{20}$ = – 96.0 (*c* = 1, C_6H_6) [5].

Synthesis of ketal compound S1



To a stirred solution of (–)-Wieland-Miescher ketone (10 g, 56.1 mmol) in ethylene glycol (280 mL, 0.2 M) at room temperature was added 4 Å molecular sieves and *p*-toluenesulfonic acid (10.67 g, 56.1 mmol). The reaction mixture stirred at room temperature for 23 min before being poured into saturated aqueous $NaHCO_3$ (600 mL) and ice water (300 mL). Then the aqueous layer was extracted with EtOAc (3 × 400 mL), and the combined organic layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc / petroleum ether = 1/3) to afford **S1** (12.34 g, 55.51 mmol, 99%) as a colorless oil.

R_f = 0.28 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

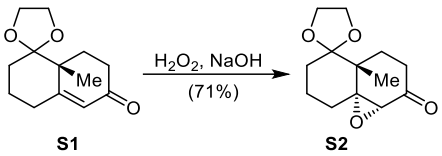
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (d, *J* = 1.8 Hz, 1H), 3.98 – 3.91 (m, 4H), 2.45 – 2.35 (m, 3H), 2.30 – 2.23 (m, 2H), 1.91 – 1.84 (m, 1H), 1.80 – 1.74 (m, 1H), 1.71 – 1.63 (m, 3H), 1.33 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*) δ 199.2, 167.8, 125.7, 112.4, 65.4, 65.1, 45.1, 33.9, 31.5, 30.1, 26.9, 21.8, 20.5;

HRMS ESI Calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 245.1148, found 245.1148;

$[\alpha]_D^{20}$ = – 84.4 (*c* = 0.5, C_6H_6), reported $[\alpha]_D^{25}$ = – 77 (*c* = 1, C_6H_6) [5].

Synthesis of compound S2



To a stirred solution of ketal **S1** (10 g, 44.98 mmol) in methanol (103 mL, 0.44 M) was added hydrogen peroxide aqueous solution (15.29 mL, 134.94 mmol, 30 % (w/w)) dropwise and sodium hydroxide aqueous solution (8.996 mL, 22.49 mmol, 10 % (w/w), dropwise at 0 °C over 30 min. The reaction mixture was stirred at 15°C for 3 d. Additional hydrogen peroxide aqueous solution (5.10 mL, 44.98 mmol) was added dropwise after each 24 h period. After 3d, the reaction mixture was added saturated sodium thiosulfate aqueous solution (200 mL), and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Subsequently, the resulting crude mixture was purified by flash column chromatography (EtOAc / petroleum ether = 1/3) to afford **S2** (7.61 g, 31.94 mmol, 71%) as a colorless soild.

R_f = 0.27 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

Mp 130.5 – 132.5 °C;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.01 (td, *J* = 6.5, 4.6 Hz, 1H), 3.91 – 3.82 (m, 3H), 3.07 (s, 1H), 2.32 – 2.26 (m, 2H), 2.19 (dd, *J* = 13.3, 4.3 Hz, 1H), 1.87 – 1.74 (m, 3H), 1.72 – 1.60 (m, 4H), 1.25 (s, 3H);

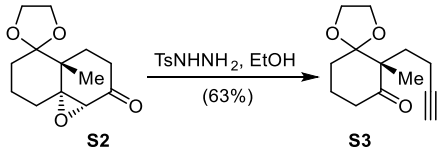
^{13}C NMR (100 MHz, Chloroform-*d*) δ 207.4, 113.4, 68.9, 65.3, 64.1, 63.1, 42.6, 34.3, 30.0, 29.4, 25.2, 21.5, 20.0;

HRMS ESI calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$ 261.1097, found 261.1099;

IR (neat) Vmax 2946, 2306, 1705, 1523, 1062, 755 cm^{-1};

$[\alpha]_D^{20}$ = – 124.2 (*c* = 0.5, $CHCl_3$).

Synthesis of compound S3



To a stirred solution of **S2** (280 mg, 1.17 mmol) in ethanol (11.8 mL) was added 4 Å molecular sieves and *p*-toluenesulfonyl hydrazide (219.4 mg, 1.17 mmol) at room temperature. Then the reaction mixture was heated to 50 °C and stirred overnight. After completing the reaction, the reaction mixture was quickly filtered with silica gel, and poured into saturated aqueous $NaHCO_3$. Subsequently, the aqueous layer was extracted with EtOAc (3 × 20 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (EtOAc / petroleum ether = 1/8) to afford **S3** (164 mg, 0.74 mmol, 63%) as a colorless oil.

R_f = 0.39 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.95-3.94 (m, 4H), 2.51 – 2.45 (m, 1H), 2.38 – 2.33 (m, 1H), 2.24 – 2.18 (m, 1H), 2.15 – 1.98 (m, 3H), 1.96 – 1.93 (m, 2H), 1.82 – 1.78 (m, 2H), 1.76 – 1.70 (m, 1H), 1.05 (s, 3H);

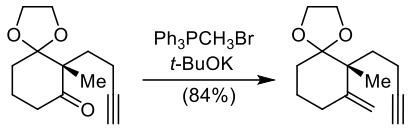
^{13}C NMR (125 MHz, Chloroform-*d*) δ 211.6, 113.6, 84.1, 68.6, 65.4, 65.2, 58.5, 37.2, 33.8, 29.6, 19.4, 13.9, 13.6;

HRMS ESI calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 245.1148, found 245.1148;

IR (neat) Vmax 2954, 2886, 1709, 1138, 1068, 1030 cm^{-1};

$[\alpha]_D^{20}$ = – 115.4 (*c* = 0.5, $CHCl_3$).

Synthesis of compound 11



S3 **11**

Prior to the reaction set-up, methyltriphenylphosphoniumbromide (12.54 g, 35.1 mmol) was heated to 110 °C and stirred overnight. To a solution of the above dry methyltriphenylphosphoniumbromide in THF (35 mL) was added potassium tert-butoxide (3.94 g, 35.1 mmol) and the resulting solution was stirred at 0 °C for 40 min, followed by the addition of **S3** (1.95 g, 8.77 mmol) in THF (5 mL, final concentration 0.2 M) via cannula at 0 °C. After being stirred for 12 h at room temperature, the resulting mixture was added saturated NH_4Cl aqueous solution (150 mL) and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the resulting crude mixture was purified by flash column chromatography (EtOAc / petroleum ether = 1/30) to yield compound **11** (1.65 g, 7.49 mmol, 84%) as a colorless soild.

R_f = 0.42 (silica, EtOAc: petroleum ether = 1: 30, stains with PMA);

Mp: 61.2 – 63.5 °C;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.91 (d, *J* = 1.6 Hz, 1H), 4.71 (d, *J* = 1.6 Hz, 1H), 3.97 – 3.91 (m, 4H), 2.17 – 2.14 (m, 2H), 2.03 – 2.01 (m, 2H), 1.91 – 1.90 (m, 2H), 1.88 – 1.81 (m, 2H), 1.72 – 1.67 (m, 1H), 1.65 – 1.61 (m, 1H), 1.55 – 1.46 (m, 1H), 1.01 (s, 3H);

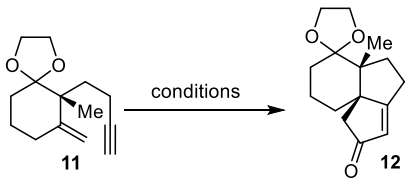
^{13}C NMR (125 MHz, Chloroform-*d*) δ 150.6, 112.9, 110.7, 85.2, 67.9, 65.3, 65.1, 49.1, 33.7, 31.7, 30.2, 23.4, 15.5, 13.4;

HRMS ESI calcd for $C_{14}H_{20}O_2Na$ $[M+Na]^+$ 243.1356, found 243.1359;

IR (neat) Vmax 3257, 2950, 2884, 1081, 899, 685 cm^{-1};

$[\alpha]_D^{20}$ = – 42.9 (*c* = 1, $CHCl_3$).

Synthesis of compound 12



Entry	Reagent	Additive	Solvent	Temp(°C)	Yield (%)[a]
1	$Co_2(CO)_8$ (1.0 eq)	TMANO	toluene	110	50
2	$Co_2(CO)_8$ (0.3 eq)	TMTU	toluene	110	11
3	$CoBr_2$ (0.1 eq) Zn (1.0 eq)	TMTU	toluene	70	0
4	$[Rh(CO)_2Cl]_2$ (0.1 eq)	none	DCE	80	0
5	$Co_2(CO)_8$ (0.8 eq)	4A MS	toluene	110	46
6	$Co_2(CO)_8$ (1.0 eq)	NMO	toluene	110	60
7	$Co_2(CO)_8$ (0.8 eq)	NMO	toluene	110	60

[a]Isolated yield

To a solution of the compound **11** (945 mg, 4.29 mmol) in toluene (30 mL) was added $Co_2(CO)_8$ (1.17 g, 3.43 mmol) under 1 atm of CO, the mixture was stirred at rt for 2 h. After the complete transformation of the starting material, the reaction mixture was added NMO (1.512 g, 12.87 mmol) and heated at 110 °C for 18 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel (EtOAc / petroleum ether = 1 / 8) to give product **12** (639 mg, 2.57 mmol, 60%) as a colorless oil.

R_f = 0.21 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.75 (t, *J* = 1.7 Hz, 1H), 3.95 – 3.90 (m, 4H), 2.78 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.44 (d, *J* = 17.9 Hz, 2H), 2.13 (d, *J* = 18.1 Hz, 1H), 1.76 – 1.71 (m, 2H), 1.68 – 1.61 (m, 4H), 1.13 – 1.08 (m, 1H), 0.75 (s, 3H);

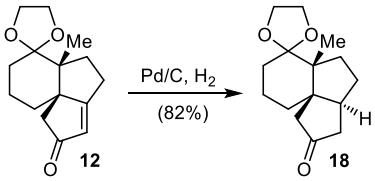
^{13}C NMR (125 MHz, Chloroform-*d*) δ 211.5, 193.3, 124.0, 111.2, 65.2, 65.1, 58.7, 48.1, 44.9, 34.5, 34.1, 30.4, 23.6, 21.8, 15.6;

HRMS ESI calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1305, found 271.1305;

IR (neat) Vmax 2938, 2873, 1705, 1628, 1146, 1115, 1030 cm^{-1};

$[\alpha]_D^{20}$ = 79.2 (*c* = 0.5, $CHCl_3$).

Synthesis of compound 18



To a solution of the compound **12** (445 mg, 1.79 mmol) in methanol (8 mL) were added 10% Pd/C (44.5 mg). The mixture was hydrogenated with a H_2 balloon until the starting material disappeared on TLC. Then the catalyst

was filtered off, the solvent was evaporated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (EtOAc / petroleum ether = 1 / 8) to give product **18** (367 mg, 1.47 mmol, 82%) as a colorless soild.

R_f = 0.40 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

Mp 41.2 – 43.1 °C;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.99 – 3.89 (m, 4H), 2.84 (q, *J* = 8.6 Hz, 1H), 2.39 (dd, *J* = 19.9, 8.8 Hz, 1H), 2.33 (d, *J* = 18.5 Hz, 1H), 2.16 – 2.11 (m, 2H), 1.92 (ddd, *J* = 14.2, 10.0, 4.4 Hz, 1H), 1.83 (d, *J* = 18.3 Hz, 1H), 1.65 (d, *J* = 11.9 Hz, 1H), 1.60 (dd, *J* = 12.5, 3.6 Hz, 1H), 1.56 – 150 (m, 3H), 1.44 (ddd, *J* = 13.5, 11.5, 5.8 Hz, 1H), 1.36 (ddd, *J* = 17.4, 12.7, 4.6 Hz, 1H), 1.25 (dt, *J* = 12.6, 5.6 Hz, 1H), 1.03 (s, 3H);

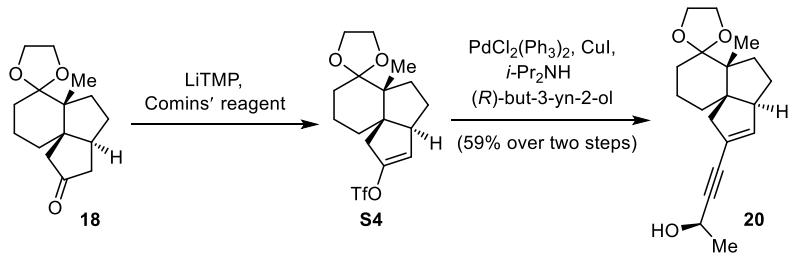
^{13}C NMR (125 MHz, Chloroform-*d*) δ 220.7, 112.7, 65.1(2C), 63.9, 55.2, 51.9, 49.5, 44.4, 41.6, 33.1, 31.2, 30.2, 19.5, 19.2;

HRMS ESI calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1461, found 273.1460;

IR (neat) Vmax 2945, 2904, 1738, 1169, 1129, 1049, 953, 910 cm^{-1};

$[\alpha]_D^{20}$ = – 29.6 (*c* = 1, $CHCl_3$).

Synthesis of compound 20



Entry	Conditions	Yield (%)[a]	Ratio
1	N_2H_4•H_2O, Et_3N/ I_2, TMG	81	3:2
2	N_2H_4•H_2O, DBU/ I_2, TMG	38	2:1
3	KHMDS, Comins' reagent	91	2.1:1
4	LiTMP, Comins' reagent	87	3:1

[a]Isolated yield

To a stirred solution of HTMP (0.20 mL, 1.2 mmol) in anhydrous THF (8 mL) at –78 °C under argon was added *n*-BuLi (0.75 mL, 1.2 mmol, 1.6 M in hexane) and the solution was stirred at –78 °C for 40 min. Then the freshly prepared LiTMP was added a solution of **18** (150 mg, 0.6 mmol) in anhydrous THF (4 mL). After stirred at 0°C for an hour, a solution of Comins' reagent (589 mg, 1.5 mmol) in dry THF (4 mL) was added to reaction mixture. After 3 h, the reaction mixture was quenched by saturated NH_4Cl aqueous solution (20 mL) and extract with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, concentrated and purified by flash chromatography (EtOAc / petroleum ether = 1 / 8) to afford product **S4** as a colorless oil.

To a solution of vinyl triflate **S4** (149.5 mg, 0.39 mmol) in dry THF (6 mL) was added diisopropylamine (0.734 mL, 5.2 mmol), (R)-but-3-yn-2-ol (0.045 mL, 0.52 mmol), $PdCl_2(PPh_3)_2$ (7.3 mg, 0.0104 mmol) and CuI (4.0 mg, 0.0208 mmol) under argon. The resulting mixture was stirred at ambient temperature for 2 h before being treated with H_2O (20 mL) and diluted with EtOAc (3 × 20 mL). Then the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified

through flash column chromatography (EtOAc / petroleum ether = 1 / 8) to yield enynyl alcohol **20** (106.9 mg, 0.35 mmol, 59% for two steps) as a colorless oil.

R_f = 0.27 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.93 (q, *J* = 2.2 Hz, 1H), 4.65 (q, *J* = 6.7 Hz, 1H), 3.96 – 3.86 (m, 4H), 2.95 – 2.91 (m, *J* = 8.1, 5.7, 2.8 Hz, 1H), 2.76 (dt, *J* = 16.3, 2.2 Hz, 1H), 1.99 – 1.90 (m, 3H), 1.87 (s, 1H), 1.65 (ddd, *J* = 21.6, 10.3, 6.1 Hz, 2H), 1.57 – 1.55 (m, 2H), 1.52 – 1.46 (m, 2H), 1.46 (d, *J* = 6.5 Hz, 3H), 1.43 – 1.39 (m, 2H), 0.94 (s, 3H);

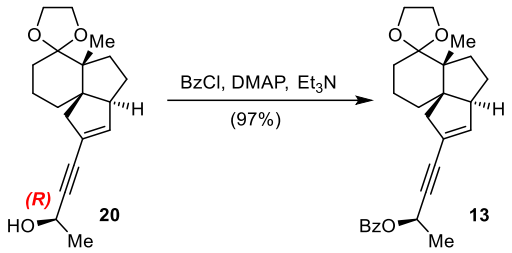
^{13}C NMR (125 MHz, Chloroform-*d*) δ 142.4, 121.8, 113.1, 91.4, 81.6, 64.8, 64.5, 58.9, 58.1, 56.3, 51.5, 46.2, 35.4, 35.0, 30.9, 28.7, 24.5, 20.6, 17.2;

HRMS ESI calcd for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1774, found 325.1775;

IR (neat) Vmax 3456, 2936, 2876, 1788, 1706, 1114, 1080, 1051 cm^{-1};

$[\alpha]_D^{20}$ = – 5.9 (*c* = 1, $CHCl_3$).

Synthesis of compound 13



To a solution of enynyl alcohol **20** (675 mg, 2.23 mmol) in dry DCM (11 mL) was added DMAP (54 mg, 0.446 mmol), Et_3N (0.34 mL, 2.45 mmol), BzCl (0.28 mL, 2.45 mmol) under argon. Then the resulting mixture was stirred at ambient temperature for 2 h. After completing the reaction, the mixture was quenched by H_2O (10 mL) and diluted with DCM (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Afterwards, the residue was purified through flash column chromatography (EtOAc / petroleum ether = 1 / 8) to yield **13** (880 mg, 2.16 mmol, 97%) as a colorless oil.

R_f = 0.31 (silica, EtOAc: petroleum ether = 1: 30, stains with PMA);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.57 – 7.54 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 5.98 (q, *J* = 2.3 Hz, 1H), 5.85 (q, *J* = 6.6 Hz, 1H), 3.9 6 – 3.85 (m, 4H), 2.95 – 2.91 (m, 1H), 2.77 (dt, *J* = 16.4, 2.2 Hz, 1H), 1.99 – 1.97 (m, 1H), 1.96 – 1.91 (m, 2H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.57 (dd, *J* = 6.9, 3.9 Hz, 4H), 1.50 – 1.38 (m, 4H), 0.94 (s, 3H);

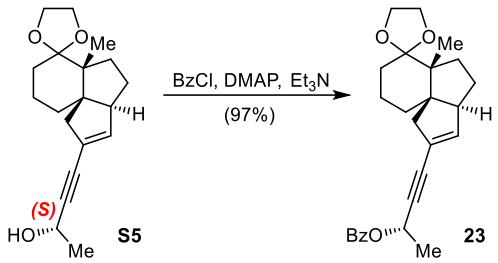
^{13}C NMR (125 MHz, Chloroform-*d*) δ 165.5, 143.1, 133.0, 130.2, 129.8, 128.3, 121.6, 113.1, 87.8, 82.4, 64.8, 64.5, 61.6, 58.2, 56.2, 51.5, 46.1, 35.5, 34.9, 30.9, 28.7, 21.7, 20.5, 17.2;

HRMS ESI calcd for $C_{26}H_{30}O_4Na$ $[M+Na]^+$ 429.2036, found 429.2037;

IR (neat) Vmax 2937, 2874, 1722, 1266, 1100, 1074, 1049, 1023, 713 cm^{-1};

$[\alpha]_D^{20}$ = – 7.7 (*c* = 1, $CHCl_3$).

Synthesis of compound 23



To a solution of enynyl alcohol **S5** (100 mg, 0.33 mmol) in dry DCM (1.5 mL) was added DMAP (8.1 mg, 0.066 mmol), Et_3N (0.05 mL, 0.36 mmol), BzCl (0.042 mL, 0.36 mmol) under argon. Then the resulting mixture was stirred at ambient temperature for 2 h. After completing the reaction, the mixture was quenched by H_2O (3 mL) and diluted with DCM (3 × 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Afterwards, the residue was purified through flash column chromatography (EtOAc / petroleum ether = 1 / 8) to yield **23** (130 mg, 0.32 mmol, 97%) as a colorless oil.

R_f = 0.31 (silica, EtOAc: petroleum ether = 1: 30, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.98 (d, *J* = 2.4 Hz, 1H), 5.85 (q, *J* = 6.6 Hz, 1H), 3.96 – 3.86 (m, 4H), 2.93 – 2.91 (m, 1H), 2.77 (dt, *J* = 16.3, 2.3 Hz, 1H), 1.99 – 1.91 (m, 3H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 4H), 1.50 – 1.38 (m, 4H), 0.94 (s, 3H).

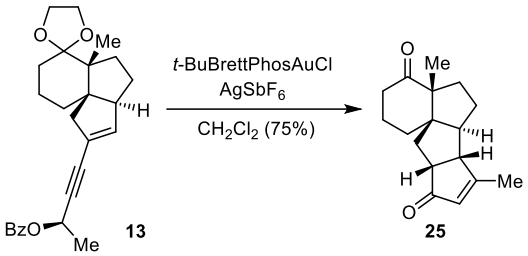
^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.5, 143.2, 133.0, 130.1, 129.8, 128.3, 121.5, 113.1, 87.8, 82.3, 64.8, 64.5, 61.6, 58.1, 56.2, 51.4, 46.0, 35.4, 34.9, 30.9, 28.7, 21.7, 20.6, 17.2.

HRMS ESI calcd for $C_{26}H_{30}O_4Na$ $[M+Na]^+$ 429.2036, found 429.2035;

IR (neat) Vmax 2943, 1714, 1264, 1094, 1029 cm^{-1};

$[\alpha]_D^{20}$ = – 0.8 (*c* = 2, $CHCl_3$).

Synthesis of compound 25



Weighing *t*-BuBrettPhosAuCl (3.46 mg, 0.00485 mmol, 5 mol%) and $AgSbF_6$ (3.33 mg, 0.0097 mmol, 10 mol%) into 10 mL round-bottom flask. 1 mL wet DCM was added. The mixture was stirred at room temperature for 10 min and a solution of **13** (40 mg, 0.0984 mmol) in 1 mL wet DCM was added. Subsequently, the mixture was stirred at room temperature until the reaction was completed monitored by TLC, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc / petroleum ether = 1 / 5) to afford **25** (19 mg, 0.073 mmol, 75%) as a colorless soild.

R_f = 0.24 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

Mp 112.6 – 114.4 °C;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.83 (t, *J* = 1.5 Hz, 1H), 3.03 (d, *J* = 6.2 Hz, 1H), 2.92 (ddd, *J* = 11.1, 6.2, 1.5 Hz, 1H), 2.50 – 2.43 (m, 2H), 2.23 – 2.16 (m, 2H), 2.11 (s, 3H), 2.06 – 2.01 (m, 1H), 1.85 – 1.82 (m, 1H), 1.79 (dq, *J* = 6.6, 3.5 Hz, 1H), 1.71 – 1.63 (m, 2H), 1.54 (tt, *J* = 13.4, 4.1 Hz, 1H), 1.44 – 1.37 (m, 2H), 1.33-1.26 (m, 1H), 1.11 (s, 3H);

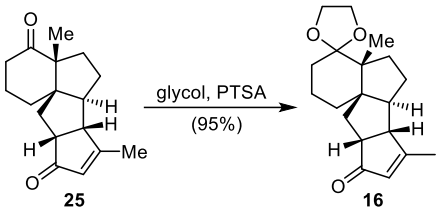
^{13}C NMR (125 MHz, Chloroform-*d*) δ 214.4, 212.6, 181.1, 130.3, 61.9, 60.4, 60.0, 51.4, 43.9, 38.1, 38.0, 31.5, 30.7, 30.5, 22.7, 19.5, 18.1;

HRMS ESI calcd for $C_{17}H_{22}O_2Na$ $[M+Na]^+$ 281.1512, found 281.1511;

IR (neat) Vmax 2947, 2876, 1699, 1614, 1456, 1313, 1271, 1113, 716 cm^{-1};

$[\alpha]_D^{20}$ = – 30.2 (*c* = 1, $CHCl_3$).

Synthesis of compound 11



To a stirred solution of **25** (94 mg, 0.364 mmol) in benzene (3.6 mL) were added ethylene glycol (0.2 mL, 3.640 mmol) and PTSA (6.9 mg, 0.036 mmol) at room temperature. Then the reaction mixture was heated to 80 ℃. After 9 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 ×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc / petroleum ether = 1 / 8) to produce **16** (104 mg, 0.34 mmol, 95%) as a colorless oil.

R_f = 0.22 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (s, 1H), 3.96 – 3.88 (m, 4H), 3.04 (d, *J* = 5.9 Hz, 1H), 2.89 – 2.85 (m, 1H), 2.62 (t, *J* = 8.8 Hz, 1H), 2.15 (s, 3H), 2.02 (t, *J* = 12.1 Hz, 1H), 1.74 (t, *J* = 10.1 Hz, 1H), 1.64 (d, *J* = 13.7 Hz, 1H), 1.50 (s, 1H), 1.45 – 1.35 (m, 5H), 1.31 – 1.28 (m, 1H), 1.22 – 1.13 (m, 2H), 1.01 (s, 3H);

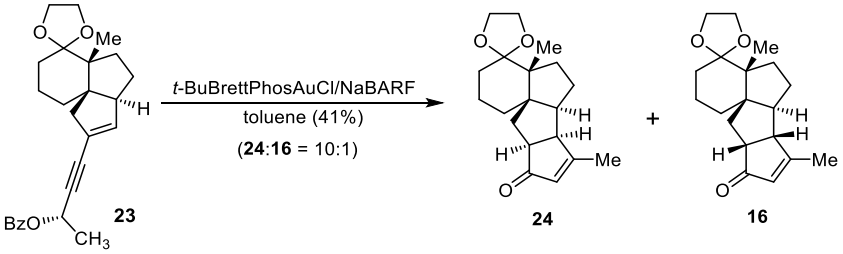
^{13}C NMR (100 MHz, Chloroform-*d*) δ 213.6, 182.0, 130.4, 113.0, 65.0, 63.9, 59.7, 59.6, 53.4, 50.9, 44.6, 39.1, 33.0, 32.0, 31.7, 30.3, 19.7, 18.5, 18.2;

HRMS ESI calcd for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1774, found 325.1771;

IR (neat) Vmax 2946, 2880,1692, 1616, 1463, 1437, 1376, 1191, 1139, 1119, 1035 cm^{-1};

$[\alpha]_D^{20}$ = – 49.9 (*c* = 1, $CHCl_3$).

Synthesis of compound 24



Weighing *t*-BuBrettPhosAuCl (3.48 mg, 0.00487 mmol, 5 mol%) and NaBARF (4.31 mg, 0.00487 mmol, 5 mol%) into 10 mL round-bottom flask. Later, 1.5 mL toluene was added. The mixture was stirred at room temperature for 10 mins and a solution of **23** (39.6 mg, 0.0974 mmol) in 1.5 mL toluene was added. Subsequently, the mixture was stirred at room temperature until the reaction was completed monitored by TLC, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc / petroleum ether = 1 / 8) to afford a mixture of **24** and **16** (24:**16** = 10:1, 12.3 mg, 0.041 mmol, 41%) as a colorless oil.

R_f = 0.23 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.77 (s, 1H), 4.00 – 3.89 (m, 4H), 3.38 (t, *J* = 7.6 Hz, 1H), 2.88 (dd, *J* = 17.0, 9.6 Hz, 1H), 2.80 (dd, *J* = 18.0, 8.8 Hz, 1H), 2.03 (s, 3H), 1.76 (ddd, *J* = 13.5, 10.2, 3.4 Hz, 1H), 1.64 – 1.52 (m, 4H), 1.54 – 1.47 (m, 4H), 1.38 – 1.28 (m, 3H), 1.03 (s, 3H);

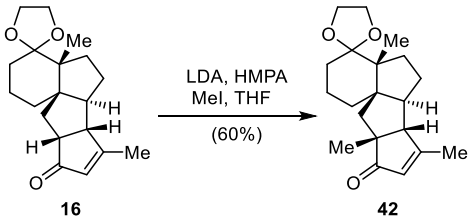
^{13}C NMR (100 MHz, Chloroform-*d*) δ 213.4, 179.9, 129.9, 112.9, 65.1, 63.9, 63.8, 54.4, 52.2, 50.6, 44.0, 36.3, 31.5, 30.3, 29.1, 24.4, 19.4, 18.9, 18.8;

HRMS ESI calcd for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1774, found 325.1773;

IR (neat) Vmax 2944, 2874, 1696, 1616, 1456, 1376, 1190, 1129, 1045 cm^{-1};

$[\alpha]_D^{20}$ = – 20.9 (*c* = 2, $CHCl_3$).

Synthesis of compound 42



16 **42**

To a stirred solution of diisopropylamine (85.6 µL, 0.576 mmol) in anhydrous THF (1.15 mL) at –78 °C under argon was added *n*-BuLi (0.36 mL, 0.576 mmol, 1.6 M in hexane) and the solution was stirred at –78 °C for 40 min. Then the freshly prepared LDA was added a solution of **16** (29 mg, 0.096 mmol) in anhydrous THF (1.15 mL). After being stirred at 0°C for an hour, HMPA (0.12 mL, 0.691 mmol) and MeI (0.076 mL, 1.200 mmol) were added to the reaction mixture. Then the mixture was warmed up to 25 °C and stirred for 2 hours. The reaction was quenched by saturated NH_4Cl aqueous solution and extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc: petroleum ether = 1 / 8) to provide **42** (18.2 mg, 0.058 mmol, 60%) as a colorless oil.

R_f = 0.27 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.80 (s, 1H), 3.95 – 3.87 (m, 4H), 2.64 – 2.59 (m, 2H), 2.15 (s, 3H), 2.03 (t, *J* = 10.6 Hz, 1H), 1.74 (t, *J* = 8.9 Hz, 1H), 1.64 (d, *J* = 13.2 Hz, 2H), 1.59 (s, 2H), 1.49 – 1.35 (m, 6H), 1.22 (s, 3H), 0.99 (s, 3H);

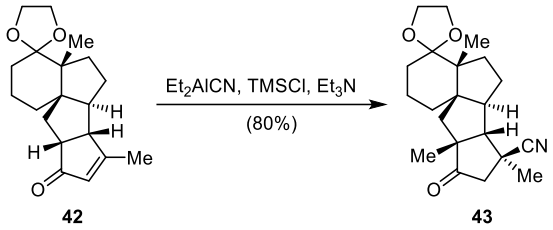
^{13}C NMR (100 MHz, Chloroform-*d*) δ 215.4, 180.5, 129.1, 113.0, 67.0, 65.0, 63.8, 59.9, 55.5, 53.6, 47.6, 44.5, 33.5, 31.7, 30.8, 30.3, 25.3, 19.5, 18.4, 18.2;

HRMS ESI calcd for $C_{20}H_{28}O_3Na$ $[M+Na]^+$ 339.1931, found 339.1930;

IR (neat) Vmax 2952, 2869,1703, 1618, 1464, 1140, 1072 cm^{-1};

$[\alpha]_D^{20}$ = – 22.8 (*c* = 1, $CHCl_3$).

Synthesis of compound 43



42 **43**

Preparation of Nagata reagent: To a solution of Et_3Al (1.01 mL, 1.0 M in toluene, 1.01 mmol) was added TMSCN (125 µL 1.01 mmol) at 0 °C. Then the solution was heated to 110 °C. After 1 h, the formed Nagata reagent was cooled down to room temperature and used for next step.

To a stirred solution of **42** (64 mg, 0.202 mmol) in dry THF (3.1 mL) was added above Et_2AlCN (1.01 mL, 1.0 M in toluene, 1.01 mmol) at room temperature. After 15 min, Et_3N (0.084 mL, 0.606 mmol) was added, followed by TMSCl (0.052 mL, 0.606 mmol). After overnight, the reaction was quenched by saturated $NaHCO_3$ and diluted with *t*-BuOMe (3 × 15 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 8) to provide **43** (55.5 mg, 0.16 mmol, 80%) as a colorless oil.

R_f = 0.20 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.90 – 3.80 (m, 4H), 2.85 (d, *J* = 19.5, 1H), 2.41 (d, *J* = 10.0 Hz, 1H), 2.31 (d, *J* = 19.5 Hz, 1H), 2.07 (q, *J* = 11.2, 1H), 1.98 – 1.88 (m, 3H), 1.71 (td, *J* = 9.6, 5.1 Hz, 1H), 1.66 – 1.54 (m, 3H), 1.49 – 1.39 (m, 7H), 1.34 – 1.27 (m, 4H), 0.93 (s, 3H);

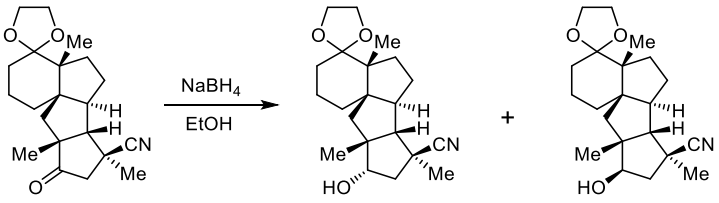
^{13}C NMR (100 MHz, Chloroform-*d*) δ 219.4, 125.8, 112.5, 65.1, 65.0, 64.8, 62.8, 57.5, 56.8, 50.7, 46.0, 42.9, 39.0, 37.8, 33.2, 30.1, 29.4, 23.4, 22.6, 21.4, 17.5;

HRMS ESI calcd for $C_{21}H_{29}NO_3Na$ $[M+Na]^+$ 366.2040, found 366.2039;

IR (neat) Vmax 2930, 2878, 1739, 1634, 1128, 1069 cm^{-1};

$[\alpha]_D^{20}$ = – 71.59 (*c* = 1, $CHCl_3$).

Synthesis of compound 44 and 45



43 **44** (33%) **45** (49%)

Entry	Conditions	Ratio	Yield (%)[a]
1	MeOH, rt	1.4:1	44% **44**, 33% **45**
2	MeOH, 0 °C	4:1	60% **44**, 15% **45**
3	MeOH, 40 °C	1.6:1	42% **44**, 26% **45**
4	EtOH, – 20 °C	1:1.5	33% **44**, 49% **45**

[a]Isolated yield

To a stirred solution of compound **43** (34.5 mg, 0.10 mmol) in EtOH (3 mL) at room temperature was added $NaBH_4$ (11.3 mg, 0.30 mmol). The reaction mixture stirred at –20 °C for 3 h before being quenched with H_2O. The aqueous layer was extracted with EtOAc (3 × 10 mL). Subsequently, the combined organic layers were washed

with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (EtOAc / petroleum ether = 1 / 3) to afford product **44** (11.9 mg, 0.034 mmol, 33%) and **45** (16.6 mg, 0.048 mmol, 49%) as a colorless soild.

Data for 44:

R_f = 0.32 (silica, EtOAc: petroleum ether = 1: 1, stains with PMA);

Mp 134.8 – 135.9 °C;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.15 (q, *J* = 8.0 Hz, 1H), 3.96 – 3.90 (m, 4H), 2.31 – 2.28 (m, 1H), 2.23 (dd, *J* = 15.6, 8.6 Hz, 2H), 2.17 – 2.09 (m, 2H), 2.02 (dd, *J* = 10.2, 5.0 Hz, 1H), 1.94 (d, *J* = 14.5 Hz, 2H), 1.69 – 1.66 (m, 1H), 1.63 – 1.59 (m, 3H), 1.52 – 1.49 (m, 5H), 1.39 (s, 3H), 1.22 (s, 3H), 0.99 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*) δ 127.7, 112.7, 78.9, 68.1, 65.0, 64.7, 59.0, 58.4, 56.6, 51.1, 45.6, 43.0, 41.0, 38.0, 34.4, 30.3, 29.3, 23.9, 21.6, 19.2, 17.6;

HRMS ESI calcd for $C_{21}H_{31}NO_3Na$ $[M+Na]^+$ 368.2196, found 368.2195;

IR (neat) Vmax 2928, 2869, 2232, 1456, 1336, 1080, 1040, 750 cm^{-1};

$[\alpha]_D^{20}$ = – 6.7 (*c* = 1, $CHCl_3$).

Data for 45:

R_f = 0.41 (silica, EtOAc: petroleum ether = 1: 1, stains with PMA);

Mp 192.5 – 194.3 °C;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.94 (m, 5H), 2.59 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.24 (d, *J* = 9.7 Hz, 1H), 2.15 (td, *J* = 11.4, 8.9 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.96 (dd, *J* = 13.0, 9.2 Hz, 1H), 1.86 (d, *J* = 2.0 Hz, 2H), 1.77 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.71 – 1.64 (m, 3H), 1.58 – 1.50 (m, 5H), 1.44 – 1.39 (m, 4H), 1.32 (s, 3H), 1.03 (s, 3H);

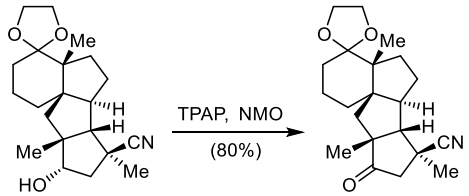
^{13}C NMR (100 MHz, Chloroform-*d*) δ 127.1, 113.0, 80.0, 69.8, 65.0, 64.7, 59.3, 58.8, 56.8, 51.2, 46.6, 40.6, 38.0, 37.2, 36.7, 30.5, 29.8, 28.3, 22.6, 21.7, 17.8;

HRMS ESI calcd for $C_{21}H_{31}NO_3Na$ $[M+Na]^+$ 368.2196, found 368.2197;

IR (neat) Vmax 2939, 2191, 1456, 1256, 1077, 1046, 732 cm^{-1};

$[\alpha]_D^{20}$ = – 5.2 (*c* = 2, $CHCl_3$).

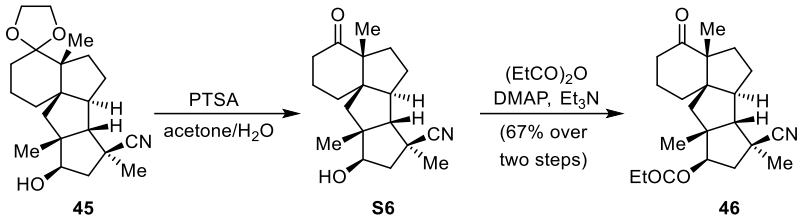
Recycle compound 43 from 44



44 **43**

To a stirred solution of compound **44** (20 mg, 0.058 mmol) in dry CH_2Cl_2 (4 mL) was added 4Å MS (20 mg), followed by NMO (27.1 mg, 0.232 mmol) and TPAP (6.1 mg, 0.017 mmol). After 40 min, the reaction mixture was purified directly by flash chromatography (EtOAc / petroleum ether = 1 / 8) to afford product **43** (15.9 mg, 0.046 mmol, 80%) as a colorless oil.

Synthesis of ester 46



A solution of compound **45** (35 mg, 0.102 mmol) in acetone/H_2O (2 mL / 2 mL) was added PTSA (17.5 mg, 0.102 mmol). The reaction mixture was heated to 40 ℃. After 60 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 8 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (EtOAc / petroleum ether = 1 / 8) to afford **S6**.

To a solution of compound **S6** (25 mg, 0.083 mmol) in dry DCM (3 mL) was added DMAP (1 mg, 0.0083 mmol), Et_3N (30 μL, 0.207 mmol), $(EtCO)_2O$ (15 μL, 0.166 mmol) under argon. Then the resulting mixture was stirred at ambient temperature for 2 h. After completing the reaction, the mixture was quenched by H_2O (10 mL) and diluted with DCM (3 × 8 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Afterwards, the residue was purified through silica gel flash column chromatography (EtOAc / petroleum ether = 1 / 3) to yield compound **46** (24.2 mg, 0.067 mmol, 67% for two steps) as a colorless oil.

R_f = 0.29 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

^{1}H NMR (**400 MHz, Chloroform-*d***) δ 5.16 – 5.13 (m, 1H), 2.40 – 2.34 (m, 5H), 2.27 (d, *J* = 5.5 Hz, 1H), 2.23 (d, J = 10.3 Hz, 1H), 2.18 – 2.13 (m, 1H), 1.87 – 1.76 (m, 6H), 1.74 – 1.66 (m, 1H), 1.61 (s, 1H), 1.48 – 1.37 (m, 5H), 1.29 (s, 3H), 1.15 (t, *J* = 7.5 Hz, 3H), 1.11 (s, 3H);

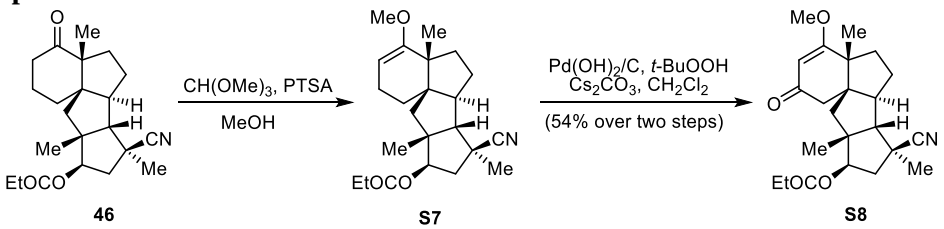
^{13}C NMR (**100 MHz, Chloroform-*d***) δ 215.2, 174.4, 126.4, 79.7, 69.3, 60.1, 59.0, 57.2, 52.4, 48.0, 43.7, 38.2, 37.1, 36.9, 36.3, 32.0, 27.7, 23.1, 22.6, 22.4, 20.0, 9.1;

HRMS ESI calcd for $C_{22}H_{32}NO_3$ $[M+H]^+$ 358.2377 found 358.2371;

IR (neat) Vmax 2932, 2866, 2232, 1701, 1629, 1187, 1078, 1028, 803 cm^{-1};

$[\alpha]_D^{20}$ = – 11.9 (*c* = 1, $CHCl_3$).

Synthesis of compound S8



To a stirred solution of compound **46** (13.6 mg, 0.038 mmol) in anhydrous MeOH (2 mL) at room temperature was added $CH(OMe)_3$ (67.4 μL, 0.646 mmol) and PTSA (5.42 mg, 0.028 mmol). The mixture was refluxed for 2 hours. After cooled to room temperature, the reaction mixture was diluted with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with EtOAc (3 × 8 mL). Subsequently, the combined organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The

crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 8) to provide **S7** as a colorless oil which was directly used for next step.

To a stirred solution of above compound **S7** (10 mg, 0.027 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at 25 ℃ was added 20% $Pd(OH)_2/C$ (4 mg), Cs_2CO_3 (44 mg, 0.135 mmol) and *t*-BuO_2H (25 μL, 0.135 mmol, 5.5 M in decane). After stirred at 25 ℃ for 19 hours, 20% $Pd(OH)_2/C$ (4 mg), Cs_2CO_3 (44 mg, 0.135 mmol.) and *t*-BuO_2H (25 μL, 0.135 mmol, 5.5 M in decane) was added to the reaction and stirred at 25 ℃ for 8 hours, the reaction mixture was filtered through a plug of Celite. Then the filtrate was concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 1) to give **S8** (7.9 mg, 0.020 mmol, 54% for two steps) as a colorless oil.

R_f = 0.27 (silica, EtOAc: petroleum ether = 1:1, stains with PMA);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.38 (s, 1H), 5.12 (dd, *J* = 7.5, 2.6 Hz, 1H), 3.68 (s, 3H), 2.57 (d, *J* = 16.4 Hz, 1H), 2.48 (d, *J* = 16.4 Hz, 1H), 2.38 (q, *J* = 7.7 Hz, 2H), 2.28 (d, *J* = 14.8 Hz, 1H), 2.21 – 2.15 (m, 3H), 2.09 (dd, *J* = 8.9, 5.8 Hz, 1H), 1.87 (s, 2H), 1.58 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 1.16 (t, *J* = 7.6 Hz, 3H);

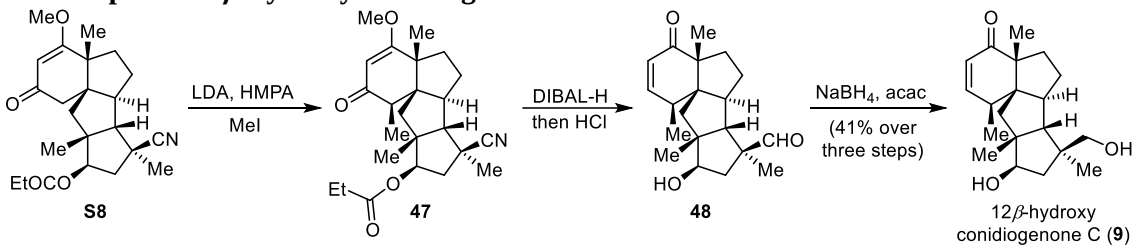
^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.2, 181.3, 174.2, 126.0, 102.5, 80.3, 71.0, 56.7, 56.3, 56.0, 51.8, 50.8, 49.4, 45.3, 44.3, 38.9, 34.4, 33.3, 27.7, 24.1, 22.5, 18.0, 9.1;

HRMS ESI calcd for $C_{23}H_{32}NO_4$ $[M+H]^+$ 386.2326, found 386.2329;

IR (neat) Vmax 2928, 2861, 2234, 1797, 1735, 1659, 1600, 1456, 1363, 1237, 1028, 752 cm^{-1};

$[\alpha]_D^{20}$ = –12,2 (*c* = 1, $CHCl_3$).

Synthesis of compound 12*β*-hydroxy Conidiogenone C



To a stirred solution of diisopropylamine (71 μL, 0.48 mmol) in anhydrous THF (1.3 mL) at –78 °C under argon was added *n*-BuLi (300 μL, 0.48 mmol, 1.6 M in hexane) and the solution was stirred at –78 °C for 40 mins. Then the freshly prepared LDA was added a solution of compound **S8** (10 mg, 0.027 mmol) in anhydrous THF (1.3 mL). After stirred at 0°C for an hour, HMPA (90 μL, 0.513 mmol) and MeI (87 μL, 1.37 mmol) was added to the reaction mixture. Then the mixture was warmed up to 25 °C and stirred for 2 hours. The reaction was quenched by saturated NH_4Cl aqueous solution and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 1) to provide **47** as a colorless oil.

To a stirred solution of above compound **47** (7 mg, 0.018 mmol) in dry toluene (1.5 mL) at – 78 °C was added DIBAL-H (90 μL, 0.090 mmol, 1.0 M solution in toluene). After stirred at – 78 °C for 30 min, the reaction mixture was quenched by 1N HCl (2 mL) and stirred for 2 h at ambient temperature. Then the aqueous layere was extracted

with *t*-BuOMe (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified with flash chromatography (EtOAc / petroleum ether = 1 / 3) to afford crude aldehyde which was directly used for the next step.

To a stirred solution of aldehyde **48** (4.2 mg, 0.0132 mmol) in dry THF (1 mL) at 0 °C was added $NaBH_4$·acac (7.4 mg, 0.0538 mmol). After being stirred at 0 °C for 10 min, the reaction mixture was quenched by H_2O. The aqueous layer was extracted with EtOAc (3 × 5 mL). Later, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified with flash chromatography (EtOAc / petroleum ether = 1 / 3) to afford 12*β*-hydroxy Conidiogenone C (**9**) (3.3 mg, 0.0104 mmol, 41% for three steps).

R_f = 0.22 (silica, EtOAc: petroleum ether = 2:1, stains with PMA);

Mp 80.3 – 82.2 °C;

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.08 (dd, *J* = 9.9, 5.3 Hz, 1H), 5.95 (d, *J* = 10.0 Hz, 1H), 4.11 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.31– 3.25 (m, 2H), 2.82 (p, *J* = 6.2 Hz, 1H), 2.42 – 2.39 (m, 1H), 2.22 (d, *J* = 14.9 Hz, 1H), 2.09 – 2.05 (m, 1H), 1.77 – 1.71 (m, 3H), 1.64 – 1.59 (m, 2H), 1.48 (d, *J* = 15.0 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 4H), 1.20 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H);

^{13}C NMR (125 MHz, Methanol-d_4) δ 208.0, 157.1, 127.9, 77.7, 73.9, 68.2, 62.1, 58.8, 57.0, 55.4, 45.3, 43.1, 42.3, 40.1, 39.8, 35.0, 24.5, 22.7, 21.5, 18.7;

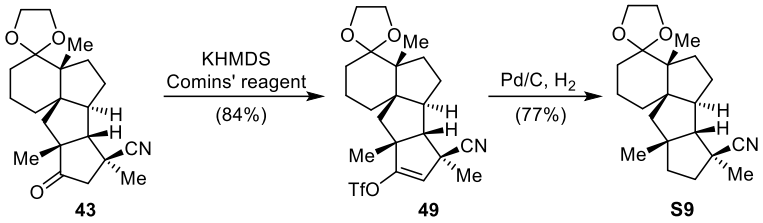
HRMS ESI calcd for $C_{20}H_{30}O_3Na$ $[M+Na]^+$ 341.2087, found 341.2090;

IR (neat) Vmax 2929, 2863, 1454, 1262, 1090, 1027, 802 cm^{-1};

$[\alpha]_D^{20}$ = – 6.0 (c = 0.5, MeOH), reported **$[\alpha]_D^{25}$** = – 0.22 (c = 1, MeOH)[1].

3.2 Total Synthesis of Conidiogenone C and K

Synthesis of compound S9



Entry	Conditions	Yield (%)[a]
1	N_2H_4•H_2O / $TsNHNH_2$	Decompose (form **43**)
2	LiCl, $Pd(PPh_3)_4$, *n*-Bu_3SnH	0 (form **49**)
3	HCOOH, $Pd(OAc)_2$, Et_3N	0 (form **49**)
4	PtO_2, H_2 (1 atm)	Decompose (form **49**)
5	Pd/C, H_2 (1 atm)	77 (form **49**)

[a]Isolated yield

A solution of **43** (35 mg, 0.102 mmol) in dry THF (2 mL) at – 78℃ was added dropwise the KHMDS (0.204 mL, 1.0 M solution in THF, 0.204 mmol). After 40 min, a solution of Comins' reagent (80.1 mg, 0.204 mmol) in dry THF (1.3 mL) was added. The reaction mixture was stirred at – 78℃ for 2 h. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (3 × 8 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc / petroleum ether = 1 / 8) to give **49.**

To a solution of the vinyl triflate **49** (34 mg, 0.071 mmol) in dry methanol (4 mL) were added 10% Pd/C (6.8 mg) as the catalyst. The mixture was hydrogenated at 1 atm of H_2 until the starting material disappeared on TLC. Then the catalyst was filtered off and the solvent was evaporated *in vacuo*. At last, the residue was purified by flash column chromatography on silica gel (EtOAc / petroleum ether = 1 / 8) to give product **S9** (18 mg, 0.055 mmol, 54% for two steps) as a colorless oil.

R_f = 0.52 (silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (500 MHz, Benzene-d_6) δ 3.62 – 3.55 (m, 4H), 2.28 (d, *J* = 14.7 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.08 – 2.00 (m, 2H), 1.84 (dd, *J* = 12.7, 8.1 Hz, 1H), 1.73 – 1.67 (m, 3H), 1.63 (dd, *J* = 12.8, 3.0 Hz, 2H), 1.59 – 1.54 (m, 3H), 1.51 (s, 3H), 1.48 – 1.45 (m, 2H), 1.39 (td, *J* = 13.2, 12.7, 3.7 Hz, 2H), 1.30 (dt, *J* = 11.3, 7.9 Hz, 1H), 1.13 (s, 3H), 1.07 (s, 3H);

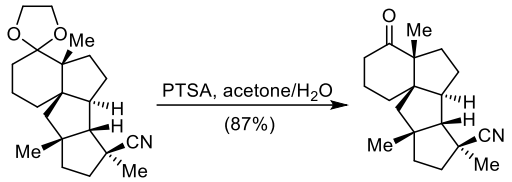
^{13}C NMR (125 MHz, Benzene-d_6) δ 126.6, 112.5, 69.3, 64.6, 64.3, 58.2, 56.6, 55.4, 51.1, 47.9, 40.6, 40.4, 40.0, 38.0, 36.9, 30.3, 29.3, 28.9, 22.3, 21.6, 17.8;

HRMS ESI calcd for $C_{21}H_{31}NO_2Na$ $[M+Na]^+$ 352.2247, found 352.2245;

IR (neat) Vmax 2927, 2233, 1742, 1459 cm^{-1};

$[\alpha]_D^{20}$ = 16.1 (*c* = 1, $CHCl_3$).

Synthesis of compound 50



A solution of **S9** (30 mg, 0.091 mmol) in acetone/H_2O (3 mL, 1/1) was added PTSA (17.3 mg, 0.091 mmol). The reaction mixture was heated to 40 ℃. After 60 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (EtOAc / petroleum ether = 1 / 8) to afford compound **50** (22.6 mg, 0.079 mmol, 87%) as a colorless oil.

R_f = 0.31(silica, EtOAc: petroleum ether = 1: 8, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.44 – 2.27 (m, 3H), 2.21 – 2.15 (m, 1H), 2.07 – 2.00 (m, 2H), 1.91 – 1.59 (m, 12H), 1.42 (s, 3H), 1.38 (s, 3H), 1.09 (s, 3H);

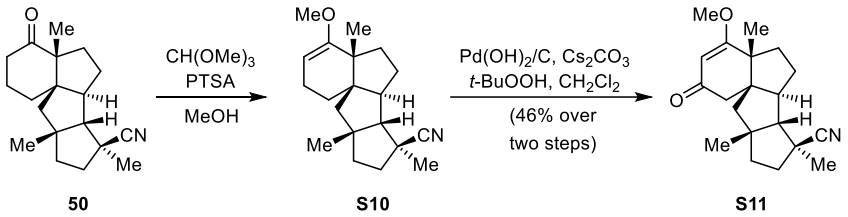
^{13}C NMR (100 MHz, Chloroform-*d*) δ 215.5, 126.7, 70.4, 59.4, 59.3, 52.6, 52.5, 50.9, 41.3, 39.0, 38.6, 38.2, 34.7, 34.5, 32.8, 31.2, 22.2, 22.1, 19.7;

HRMS ESI calcd for $C_{19}H_{28}NO$ $[M+H]^+$ 286.2165, found 286.2164;

IR (neat) Vmax 2934, 2868, 1701, 1456 cm^{-1};

$[\alpha]_D^{20}$ = 12.5 (*c* = 0.5, $CHCl_3$).

Synthesis of compound S11



To a stirred solution of **50** (30 mg, 0.105 mmol) in anhydrous MeOH (3 mL) at room temperature was added $CH(OMe)_3$ (195 μL, 1.785 mmol) and PTSA (14 mg, 0.079 mmol). The mixture was refluxed for 2 hours. After cooled to room temperature, the reaction mixture was diluted with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with EtOAc (3 × 10 mL). Subsequently, the combined organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 8) to provide **S10** as a colorless oil.

To a stirred solution of compound **S10** (21.4 mg, 0.0715 mmol) in anhydrous CH_2Cl_2 (2 mL) at 25 ℃ was added 20% $Pd(OH)_2$/C (5 mg), Cs_2CO_3 (116.5 mg, 0.357 mmol) and *t*-BuO_2H (64.1 μL, 0.357 mmol, 5.5 M in decane). After stirred at 25 ℃ for 19 hours, 20% $Pd(OH)_2$/C (5 mg), Cs_2CO_3 (116.5 mg, 0.357 mmol) and *t*-BuO_2H (64.1 μL, 0.357 mmol, 5.5 M in decane) was added to the reaction. After stirred at 25 ℃ for 8 hours, the reaction mixture was filtered through a plug of Celite. Then the filtrate was concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 3) to give **S11** (15 mg, 0.048 mmol, 46% for two steps) as a colorless oil.

R_f = 0.18 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.38 (s, 1H), 3.67 (s, 3H), 2.52 (d, *J* = 16.5 Hz, 1H), 2.45 (d, *J* = 16.5 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.02 – 1.95 (m, 2H), 1.91 – 1.85 (m, 2H), 1.82 – 1.73 (m, 2H), 1.60 – 1.56 (m, 5H), 1.41 (s, 3H), 1.39 (s, 3H), 1.20 (s, 3H);

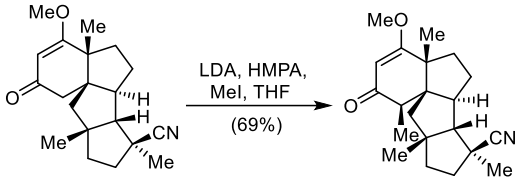
^{13}C NMR (100 MHz, Chloroform-*d*) δ 197.8, 181.7, 126.4, 102.5, 70.7, 56.2, 55.4, 52.7, 51.9, 51.5, 49.6, 44.4, 41.8, 38.4, 38.3, 34.1, 33.3, 31.9, 21.8, 17.8;

HRMS ESI calcd for $C_{20}H_{28}NO_2$ $[M+H]^+$ 314.2115, found 314.2114;

IR (neat) Vmax 2942, 2875, 1658, 1599, 1458, 1351, 1212 cm^{-1};

$[\alpha]_D^{20}$ = – 7.6 (*c* = 1, $CHCl_3$).

Synthesis of compound S12



S11 **S12**

To a stirred solution of diisopropylamine (101.5 μL, 0.682 mmol) in anhydrous THF (1.3 mL) at –78 °C under argon was added *n*-BuLi (426.3 μL, 0.682 mmol, 1.6 M in hexane) and the solution was stirred at –78 °C for 40 min. Then the freshly prepared LDA was added a solution of **S11** (12 mg, 0.038 mmol) in anhydrous THF (1.3 mL). After stirred at 0°C for an hour, HMPA (126.4 μL, 0.722 mmol) and MeI (123.5 μL, 1.93 mmol) were added to the reaction mixture. Then the mixture was warmed up to 25 °C and stirred for 2 hours. The reaction was quenched by saturated NH_4Cl aqueous solution and extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 3) to provide **S12** (8.6 mg, 0.026 mmol, 69%) as a colorless oil.

R_f = 0.23 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.31 (s, 1H), 3.69 (s, 3H), 2.42 (q, *J* = 7.4 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.07 – 2.00 (m, 2H), 1.92 (s, 2H), 1.88 – 1.77 (m, 2H), 1.74 – 1.68 (m, 2H), 1.64 – 1.58 (m, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.24 (d, *J* = 7.3 Hz, 3H);

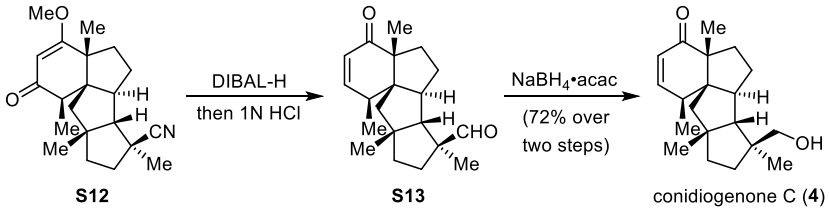
^{13}C NMR (100 MHz, Chloroform-*d*) δ 203.2, 180.1, 126.5, 100.4, 70.0, 57.2, 56.1, 53.0, 51.8, 50.5, 48.5, 46.9, 41.6, 38.3, 37.7, 36.8, 32.8, 31.9, 21.8, 19.9, 17.0;

HRMS ESI calcd for $C_{21}H_{30}NO_2$ $[M+H]^+$ 328.2271, found 328.2271;

IR (neat) Vmax 2924, 2860, 1658, 1601, 1458, 1367, 1169, 744 cm^{-1};

$[\alpha]_D^{20}$ = – 18.2 (*c* = 1, $CHCl_3$).

Synthesis of compound Conidiogenone C (4)



To a stirred solution of compound **S12** (10 mg, 0.031 mmol) in dry toluene (1.5 mL) at – 78 °C was added DIBAL-H (93 μL, 0.093 mmol, 1.0 M solution in toluene). After stirred at – 78 °C for 30 min, the reaction mixture was quenched by 1N HCl (1 mL) and stirred for 2h. Then the aqueous layere was extracted with MTBE (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified with flash chromatography (EtOAc / petroleum ether = 1 / 3) to afford compound **S13**.

To a stirred solution of ester compound **S13** (7.2 mg, 0.0240 mmol) in dry THF (1 mL) at 0 °C was added $NaBH_4$·acac (6.6 mg, 0.048 mmol). After stirred at 0 °C for 10 min, the reaction mixture was quenched by H_2O. The aqueous layer was extracted with EtOAc (3 × 5 mL). Later, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified with flash chromatography (EtOAc / petroleum ether = 1 / 3) to afford Conidiogenone C (**4**) (6.6 mg, 0.022 mmol, 72% for two steps).

R_f = 0.29 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (dd, *J* = 10.0, 5.8 Hz, 1H), 5.97 (dd, *J* = 10.0, 1.1 Hz, 1H), 3.41 (d, *J* = 10.6 Hz, 1H), 3.38 (d, *J* = 10.7 Hz, 1H), 2.76 – 2.69 (m, 1H), 2.34 – 2.30 (m, 1H), 2.15 – 2.10 (m, 1H), 2.01 (d, *J* = 14.7 Hz, 1H), 1.73 – 1.67 (m, 3H), 1.66 – 1.64 (m, 1H), 1.63 – 1.60 (m, 1H), 1.58 (d, *J* = 5.0 Hz, 1H), 1.56 – 1.52 (m, 1H), 1.47 – 1.43 (m, 1H), 1.23 – 1.20 (m, 1H), 1.22 (d, *J* = 7.3 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H);

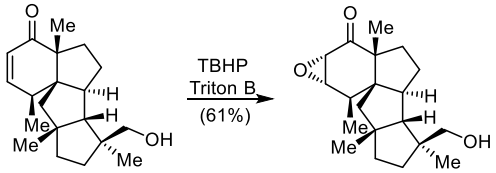
^{13}C NMR (100 MHz, Chloroform-*d*) δ 205.7, 154.2, 127.4, 72.0, 68.2, 59.9, 57.5, 54.7, 52.8, 48.1, 46.5, 38.8, 38.4, 37.8, 36.6, 34.2, 31.1, 22.5, 21.1, 18.6;

HRMS ESI calcd for $C_{20}H_{31}O_2$ $[M+H]^+$ 303.2319, found 303.2319;

IR (neat) Vmax 2926, 2860, 1655, 1601, 1459, 1032 cm^{-1};

$[\alpha]_D^{20}$ = – 8.6 (*c* = 1, MeOH), reported **$[\alpha]_D^{20}$** = – 11.9 (c = 0.04, MeOH) [3].

Synthesis of compound Conidiogenone K (8)



To a stirred solution of compound **4** (6 mg, 0.0198 mmol) in anhydrous THF (1 mL) at 25 °C was added Triton B (6.25 μL, 0.0396 mmol,40% wt in MeOH) and *t*-BuO_2H (72 μL, 0.396 mmol, 5.5 M in decane). After stirred at 25 °C for 30 min, the reaction was quenched by saturated NH_4Cl aqueous solution and extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Finally, the crude product was purified via flash chromatography (EtOAc / petroleum ether = 1 / 3) to provide Conidiogenone K (**8**) (3.8 mg, 0.012 mmol, 61%) as a colorless oil.

R_f = 0.31 (silica, EtOAc: petroleum ether = 1: 3, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.53 (dd, *J* = 4.04 Hz, 1H), 3.41 (s, 2H), 3.33 (d, *J* = 4.2 Hz, 1H), 2.86 (dt, *J* = 8.7, 4.6 Hz, 1H), 2.65 (dq, *J* = 7.0, 3.1 Hz, 1H), 2.01 – 1.91 (m, 3H), 1.88 (d, *J* = 14.4 Hz, 1H), 1.76 (d, *J* = 14.6 Hz, 1H), 1.71 – 1.65 (m, 2H), 1.57 – 1.49 (m, 5H) 1.28 – 1.27 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*) δ 212.5, 72.0, 65.7, 61.2, 59.6, 56.9, 55.7, 53.5, 52.1, 48.2, 48.0, 40.1, 38.3, 36.6, 35.1, 34.1, 31.7, 22.4, 22.3, 15.2;

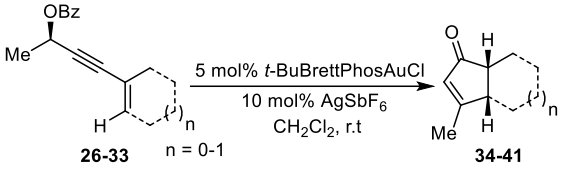
HRMS ESI calcd for $C_{20}H_{30}O_3Na$ $[M+Na]^+$ 341.2087, found 341.2091;

IR (neat) Vmax 2941, 2872, 1691, 1460, 1029 cm^{-1};

$[\alpha]_D^{20}$ = – 56.6 (c = 1, MeOH), reported **$[\alpha]_D^{25}$** = – 30.9 (c = 0.28, MeOH)[4].

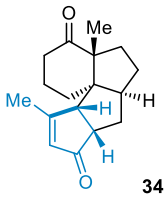
3.3 Stereocontrolled cyclopentenone construction

General procedure



Weighing *t*-BuBrettPhosAuCl (5 mol%) and $AgSbF_6$ (10 mol%) into 10 mL round-bottom flask. wet DCM was added. The mixture was stirred at room temperature for 10 min and a solution of enynyl benzoate in wet DCM was added. Subsequently, the mixture was stirred at room temperature until the reaction was completed monitored by TLC, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography to afford product.

Synthesis of compound 34



34

compound 34 (42 mg) was prepared as colorless oil according to the General procedure in 74% yield.

R_f = 0.25 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.91 (p, *J* = 1.3 Hz, 1H), 3.20 (d, *J* = 7.6 Hz, 1H), 3.18 – 3.11 (m, 1H), 2.61 (ddd, *J* = 13.2, 10.0, 3.1 Hz, 1H), 2.53 (td, *J* = 13.8, 6.5 Hz, 1H), 2.40 (dt, *J* = 10.9, 6.6 Hz, 1H), 2.27 (ddt, *J* = 14.0, 4.2, 2.2 Hz, 1H), 1.92 (d, *J* = 9.6 Hz, 1H), 1.90 – 1.85 (m, 2H), 1.72 – 1.65 (m, 2H), 1.63 – 1.58 (m, 2H), 1.44 (ddd, *J* = 13.5, 11.6, 7.5 Hz, 1H), 1.34 (s, 3H), 1.28 – 1.24 (m, 1H).

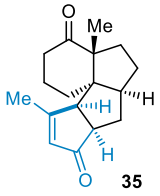
^{13}C NMR (100 MHz, Chloroform-*d*) δ 213.6, 211.5, 176.3, 132.7, 60.8, 60.2, 56.1, 52.8, 48.7, 37.7, 30.8, 29.6, 26.8, 24.5, 22.5, 22.4, 21.4.

HRMS ESI calcd for $C_{17}H_{22}O_2Na$ $[M+Na]^+$ 281.1512, found 281.1513;

IR (neat) Vmax 2938, 1716, 1452, 1318, 1263, 1094, 713 cm^{-1};

$[\alpha]_D^{20}$ = –14.5 (*c* = 1, $CHCl_3$).

Synthesis of compound 35



35

compound 35 (23 mg) was prepared as colorless oil according to the General procedure in 75% yield.

R_f = 0.25 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.91 (s, 1H), 3.21 – 3.12 (m, 2H), 2.61 (ddd, *J* = 13.3, 10.0, 3.1 Hz, 1H), 2.53 (td, *J* = 13.8, 6.6 Hz, 1H), 2.40 (dt, *J* = 10.9, 6.7 Hz, 1H), 2.27 (ddt, *J* = 14.3, 4.3, 2.1 Hz, 1H), 2.23 (s, 3H), 1.93 – 1.84 (m, 3H), 1.72 – 1.65 (m, 2H), 1.57 (dd, *J* = 13.3, 4.3 Hz, 1H), 1.42 (ddt, *J* = 19.1, 8.1, 3.7 Hz, 2H), 1.34 (s, 3H), 1.29 – 1.25 (m, 1H).

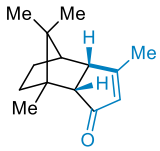
^{13}C NMR (100 MHz, Chloroform-*d*) δ 213.6, 211.5, 176.4, 132.7, 60.8, 60.1, 56.1, 52.8, 48.7, 37.7, 30.8, 29.6, 26.8, 24.5, 22.5, 22.4, 21.4;

HRMS ESI calcd for $C_{17}H_{22}O_2Na$ $[M+Na]^+$ 281.1512, found 281.1512;

IR (neat) Vmax 2945, 1688, 1603, 1461, 1311, 995, 868 cm^{-1};

$[\alpha]_D^{20}$ = –23.1 (*c* = 1, $CHCl_3$).

Synthesis of compound 36



36

compound 36 (75 mg) was prepared as colorless oil according to the General procedure in 73% yield.

R_f = 0.15 (silica, EtOAc: petroleum ether = 1: 30, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.82 (s, 1H), 3.18 (t, *J* = 6.2 Hz, 1H), 2.50 (dd, *J* = 7.1, 2.7 Hz, 1H), 1.99 (s, 3H), 1.92 (t, *J* = 4.7 Hz, 1H), 1.58 (ttd, *J* = 11.6, 4.8, 2.0 Hz, 1H), 1.36 (tdd, *J* = 12.1, 4.4, 2.8 Hz, 1H), 130 – 1.24 (m, 1H), 1.03 (s, 3H), 1.00 (s, 3H), 0.98 – 0.94 (m, 1H), 0.90 (s, 3H).

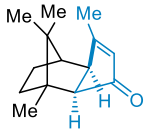
^{13}C NMR (100 MHz, Chloroform-*d*) δ 212.0, 179.5, 132.1, 58.0, 53.2, 51.9, 49.9, 46.5, 30.8, 22.4, 19.9, 18.5, 18.4, 15.3;

HRMS ESI calcd for $C_{14}H_{20}ONa$ $[M+Na]^+$ 227.1406, found 227.1407;

IR (neat) Vmax 2943, 1681, 1612, 1442, 1377, 1283, 1191 cm^{-1};

$[\alpha]_D^{20}$ = –13.4 (*c* = 1, $CHCl_3$).

Synthesis of compound 37



37

compound 37 (64 mg) was prepared as colorless oil according to the General procedure in 70% yield.

R_f = 0.15 (silica, EtOAc: petroleum ether = 1: 30, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.84 (q, *J* = 2.9, 2.2 Hz, 1H), 2.61 (d, *J* = 6.0 Hz, 1H), 2.20 (d, *J* = 6.0 Hz, 1H), 2.14 (s, 3H), 2.03 (d, *J* = 4.4 Hz, 1H), 1.88 (ddt, *J* = 20.7, 12.1, 4.6 Hz, 1H), 1.56 (dd, *J* = 11.8, 4.0 Hz, 1H), 131 – 1.28 (m, 1H), 120 – 1.16 (m, 1H), 1.14 (s, 3H), 0.79 (s, 3H), 0.76 (s, 3H).

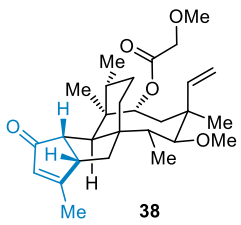
^{13}C NMR (100 MHz, Chloroform-*d*) δ 211.7, 180.8, 133.2, 60.2, 56.4, 50.8, 48.0, 46.5, 38.1, 29.3, 23.0, 20.1, 18.1, 12.1;

HRMS ESI calcd for $C_{14}H_{20}ONa$ $[M+Na]^+$ 227.1406, found 227.1407;

IR (neat) Vmax 2945, 1693, 1452, 1374, 1047 cm^{-1};

$[\alpha]_D^{20}$ = –8.5 (c = 1, $CHCl_3$).

Synthesis of compound 38



38

compound 38 (15 mg) was prepared as colorless oil according to the General procedure in 59% yield.

R_f = 0.21 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.32 (dd, *J* = 17.4, 11.1 Hz, 1H), 5.83 (s, 1H), 5.55 (d, *J* = 9.1 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 5.16 (d, *J* = 17.4 Hz, 1H), 3.96 (d, *J* = 16.3 Hz, 1H), 3.85 (d, *J* = 16.4 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.12 – 3.07 (m, 2H), 2.70 (d, *J* = 5.9 Hz, 1H), 2.27 – 2.20 (m, 2H), 2.11 (s, 3H), 2.09 – 2.06 (m, 1H), 1.83– 1,77 (m, 1H), 1.59 (d, *J* = 16.9 Hz, 1H), 1.45 (s, 3H), 1.42 – 1.33 (m, 2H), 1.28-1.25 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 1H), 1.16 (s, 3H), 1.12 – 1.04 (m, 1H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H).

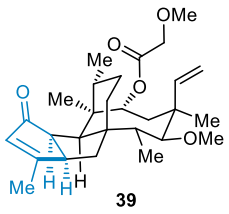
^{13}C NMR (100 MHz, Chloroform-*d*) δ 211.7, 179.9, 168.8, 140.3, 131.2, 115.7, 86.3, 71.1, 70.5, 61.2, 59.4, 54.4, 53.8, 47.8, 47.3, 45.6, 45.2, 41.5, 37.3, 35.3, 33.8, 32.1, 27.5, 26.7, 18.0, 17.4, 16.4, 11.9;

HRMS ESI calcd for $C_{28}H_{42}O_5Na$ $[M+Na]^+$ 481.2925, found 481.2927;

IR (neat) Vmax 2936, 1740, 1692, 1456, 1371, 1201, 1120 cm^{-1};

$[\alpha]_D^{20}$ = –36.5 (c = 1, $CHCl_3$).

Synthesis of compound 39



39

compound 39 (18 mg) was prepared as colorless oil according to the General procedure in 62% yield.

R $_f$ = 0.21 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.32 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.82 (s, 1H), 5.55 (d, *J* = 9.1 Hz, 1H), 5.22 (dd, *J* = 11.1, 1.6 Hz, 1H), 5.16 (dd, *J* = 17.4, 1.6 Hz, 1H), 3.96 (d, *J* = 16.3 Hz, 1H), 3.85 (d, *J* = 16.3 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.11 – 3.06 (m, 2H), 2.96 (s, 1H), 2.88 (s, 1H), 2.70 (d, *J* = 5.9 Hz, 1H), 2.24 (t, *J* = 6.4 Hz, 2H), 2.11 (s, 3H), 2.09 – 2.05 (m, 1H), 1.59 (s, 2H), 1.45 (s, 3H), 1.42 – 1.39 (m, 2H), 1.26 (d, *J* = 3.7 Hz, 2H), 1.16 (s, 3H), 0.83 (d, *J* = 7.2 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H).

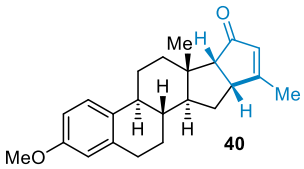
^{13}C NMR (100 MHz, Chloroform-*d*) δ 211.7, 179.9, 168.8, 140.3, 131.2, 115.7, 86.3, 71.1, 70.5, 61.2, 59.4, 54.4, 53.8, 47.8, 47.3, 45.6, 45.2, 41.5, 37.3, 35.3, 33.8, 32.1, 27.5, 26.7, 18.0, 17.4, 16.4, 11.9;

HRMS ESI calcd for $C_{28}H_{42}O_5Na$ $[M+Na]^+$ 481.2925, found 481.2925;

IR (neat) Vmax 2937, 1740, 1455, 1368, 1210, 1122 cm^{-1};

$[\alpha]_D^{20}$ = –43.8 (c = 1, $CHCl_3$).

Synthesis of compound 40



40

compound 40 (22 mg) was prepared as white soild according to the General procedure in 68% yield.

R$_f$ = 0.13 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 5.91 (s, 1H), 3.77 (s, 3H), 3.22 (dd, *J* = 9.9, 5.5 Hz, 1H), 2.87 – 2.82 (m, 2H), 2.45 (d, *J* = 5.4 Hz, 1H), 2.31 (dq, *J* = 13.1, 3.9 Hz, 1H), 2.13 (s, 3H), 2.00 (dt, *J* = 13.3, 3.4 Hz, 1H), 1.85 (ddd, *J* = 12.7, 5.7, 2.8 Hz, 1H), 1.74 (dd, *J* = 13.3, 5.2 Hz, 2H), 1.63 – 1.59 (m, 1H), 1.50 (dd, *J* = 12.7, 3.9 Hz, 1H), 1.45 – 1.42 (m, 1H), 1.40 – 1.24 (m, 2H), 1.17 (ddd, *J* = 13.0, 10.7, 6.3 Hz, 1H), 0.94 (s, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 209.8, 179.8, 157.5, 137.7, 132.6, 132.4, 126.4, 113.8, 111.4, 62.0, 55.2, 48.3, 48.2, 43.4, 43.2, 38.4, 34.2, 29.8, 28.2, 28.0, 26.3, 20.8, 18.2;

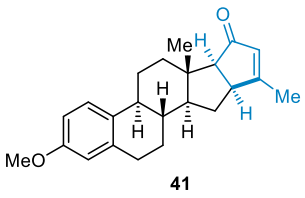
HRMS ESI calcd for $C_{23}H_{28}O_2Na$ $[M+Na]^+$ 359.1982, found 359.1983;

IR (neat) Vmax 2926, 1691, 1500, 1452, 1369, 1245, 1042 cm^{-1};

$[\alpha]_D^{20}$ = –29.6 (*c* = 1, $CHCl_3$).

Synthesis of compound 41

compound 41 (27 mg) was prepared as white soild according to the General procedure in 71% yield.



41

R_f = 0.13 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.62 (d, *J* = 2.9 Hz, 1H), 5.74 (p, *J* = 1.4 Hz, 1H), 3.77 (s, 3H), 3.27 – 3.21 (m, 1H), 2.88 – 2.82 (m, 2H), 2.56 (d, *J* = 7.0 Hz, 1H), 2.32 – 2.28 (m, 1H), 2.26 – 2.23 (m, 1H), 2.08 (s, 3H), 1.93 – 1.87 (m, 1H), 1.65 – 1.63 (m, 1H), 1.59 – 1.55 (m, 2H), 1.49 – 1.40 (m, 2H), 1.32 – 1.28 (m, 1H), 1.26 – 1.20 (m, 2H), 0.71 (s, 3H).

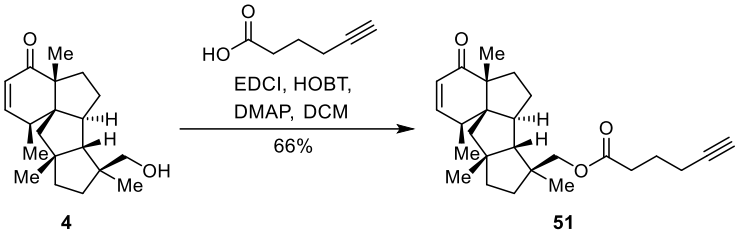
^{13}C NMR (100 MHz, Chloroform-*d*) δ 210.1, 179.8, 157.5, 137.7, 132.5, 130.4, 126.3, 113.8, 111.4, 62.9, 57.6, 55.2, 49.8, 43.7, 42.3, 39.3, 38.4, 29.7, 27.9, 27.7, 26.2, 17.6, 14.3;

HRMS ESI calcd for $C_{23}H_{28}O_2Na$ $[M+Na]^+$ 359.1982, found 359.1981;

IR (neat) Vmax 2931, 1692, 1617, 1500, 1446, 1246, 1040 cm^{-1};

$[\alpha]_D^{20}$ = –17.5 (*c* = 1, $CHCl_3$).

3.4 Preparation of Conidiogenone C Probe 51



EDCI (3.8 mg, 0.020 mmol), HOBT (2.7 mg, 0.020 mmol), DMAP (2.4 mg, 0.020 mmol), and 5-hexynoic acid (2.2 mg, 0.020 mmol) were added to a stirring solution of compound **4** (2.9 mg, 0.010 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After 4 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), and washed with brine (3 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc / petroleum ether = 1 / 6) to afford compound **51**(2.6 mg, 0.0066 mmol, 66%) as a colorless viscous oil.

R_f = 0.48 (silica, EtOAc: petroleum ether = 1: 5, stains with PMA);

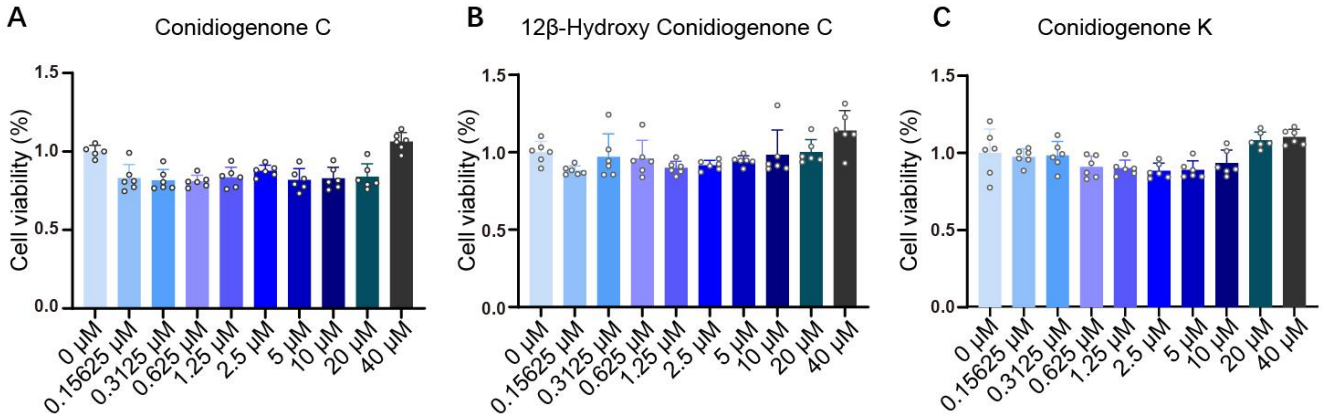
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.93 (dd, *J* = 10.0, 5.8 Hz, 1H), 5.98 (d, *J* = 10.0 Hz, 1H), 3.93 (d, *J* = 10.6 Hz, 1H), 3.85 (d, *J* = 10.7 Hz, 1H), 2.76-2.67 (m, 1H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.35-2.30 (m, 1H), 2.26 (td, *J* = 6.9, 2.6 Hz, 2H), 2.16-2.10 (m, 1H), 2.02 (d, *J* = 14.7 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.89-1.82 (m, 2H), 1.74-1.64 (m, 4H), 1.64-1.59 (m, 2H), 1.55-1.45 (m, 2H), 1.25 (s, 1H), 1.22 (d, *J* = 7.3 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*) δ 205.7, 173.4, 154.3, 127.5, 83.3, 73.0, 69.3, 68.9, 60.0, 57.6, 54.7, 53.0, 46.5, 46.2, 38.9, 38.3, 38.0, 37.2, 34.4, 33.1, 31.1, 23.8, 23.2, 21.2, 18.7, 18.0;

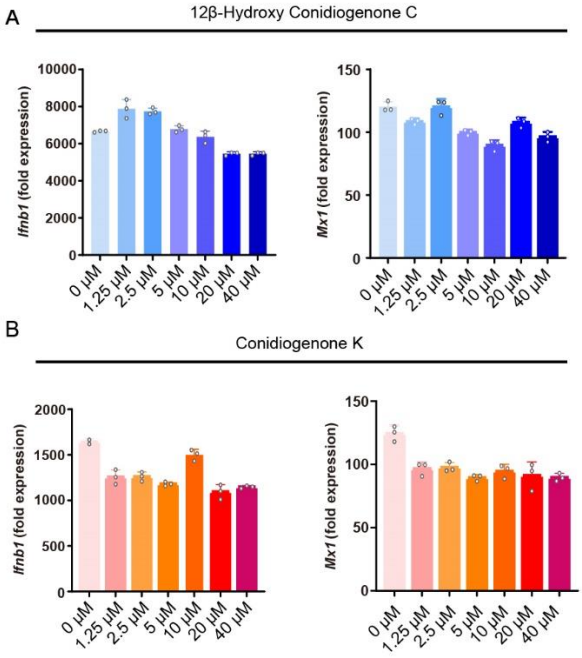
HRMS ESI calcd for $C_{26}H_{37}O_3$ $[M + H]^+$ 397.2743, found: 397.2740;

$[\alpha]_D^{20}$ = −9.3 (c = 0.2, MeOH).

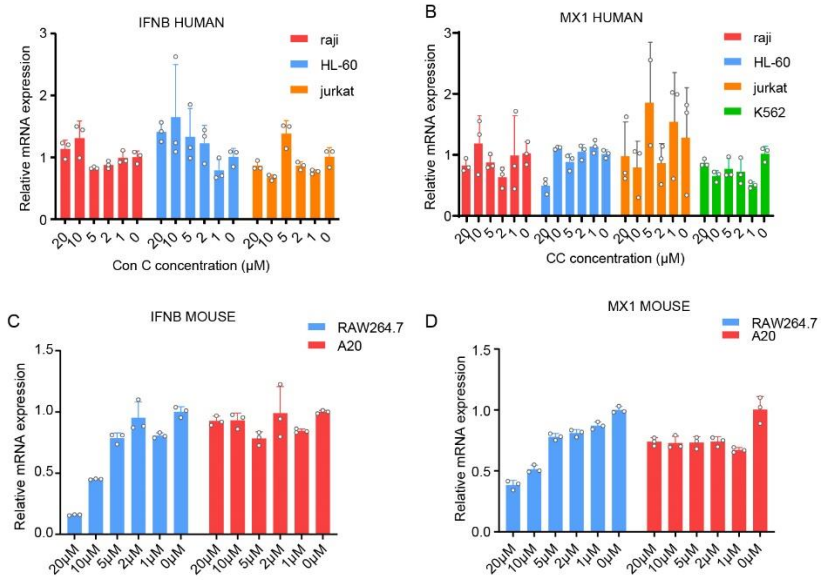
4. Supplementary figures and tables for target identification



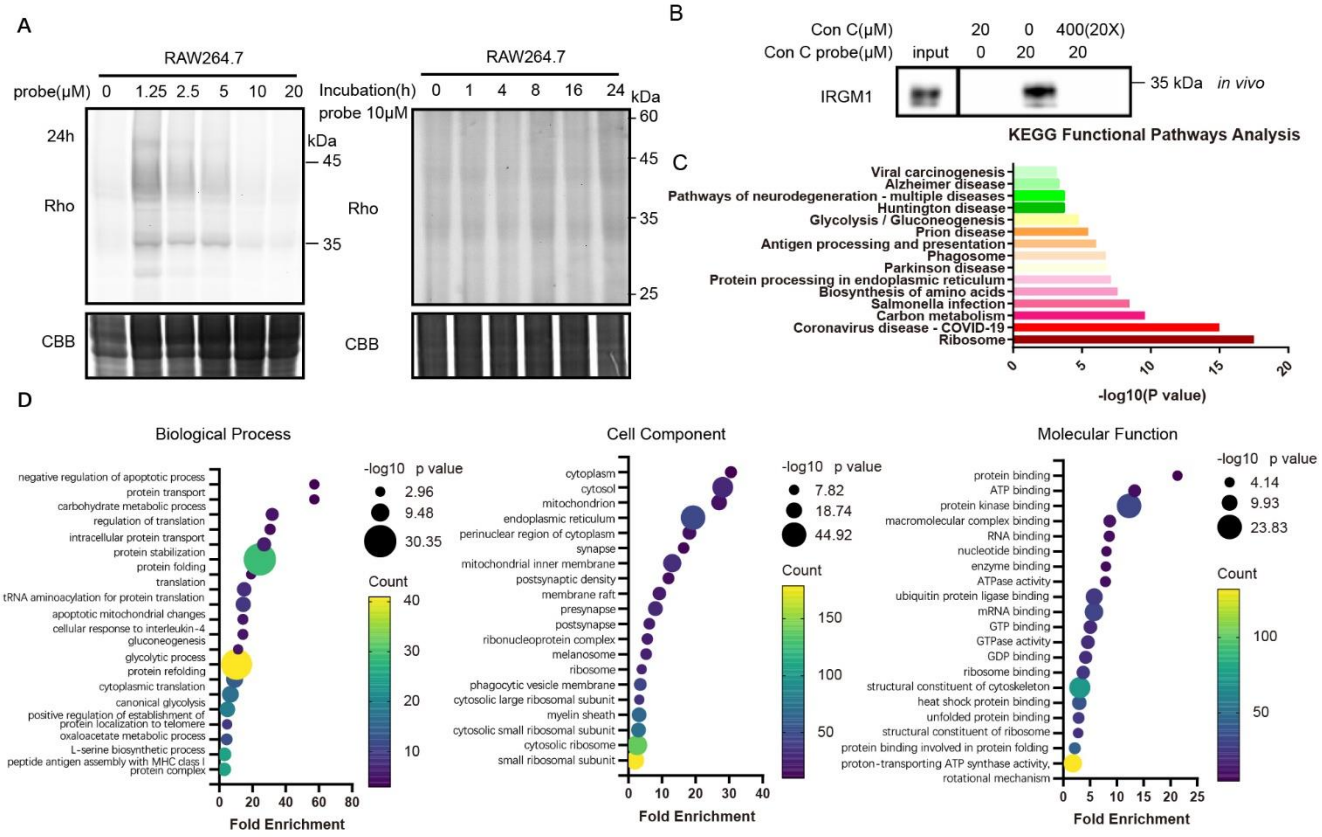
Supplementary Fig. S1 The Cytotoxicity of Conidiogenone C (A), 12β-Hydroxy Conidiogenone C (B) and Conidiogenone K (C) (0-40 μM) on the viability of HL60 cells, evaluated by CCK-8 kit. All measurements are presented as mean ± SD for 5 biological replicates. Source data are provided as a Source Data file.



Supplementary Fig. S2 Inhibitory effects of 12*β*-Hydroxy Conidiogenone C, Conidiogenone K in LPS-stimulated Raw264.7 cells. (A) *Ifnb1* and *Mx1* expression in Raw264.7 treated with 12*β*-Hydroxy Conidiogenone C (0-40 μM) by qPCR . (B) *Ifnb1* and *Mx1* expression in Raw264.7 treated with Conidiogenone K (0-40 μM) by qRT-PCR. All measurements are presented as mean ± SD for 3 biological replicates. Source data are provided as a Source Data file.

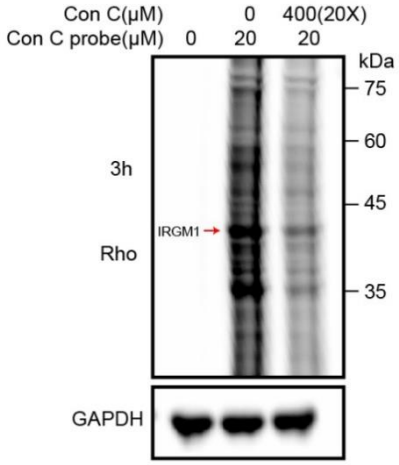


Supplementary Fig. S3 IFN-stimulated genes (ISGs) (Ifnb, Mx1) expression in in different cell lines. (A) *Ifnb1* and *Mx1* expression in human cell lines treated with conidiogenone C detected by qPCR . (B) *Ifnb1* and *Mx1* expression in mouse cell lines treated with conidiogenone C detected by qPCR. All measurements are presented as mean ± SD for 3 biological replicates. Source data are provided as a Source Data file.

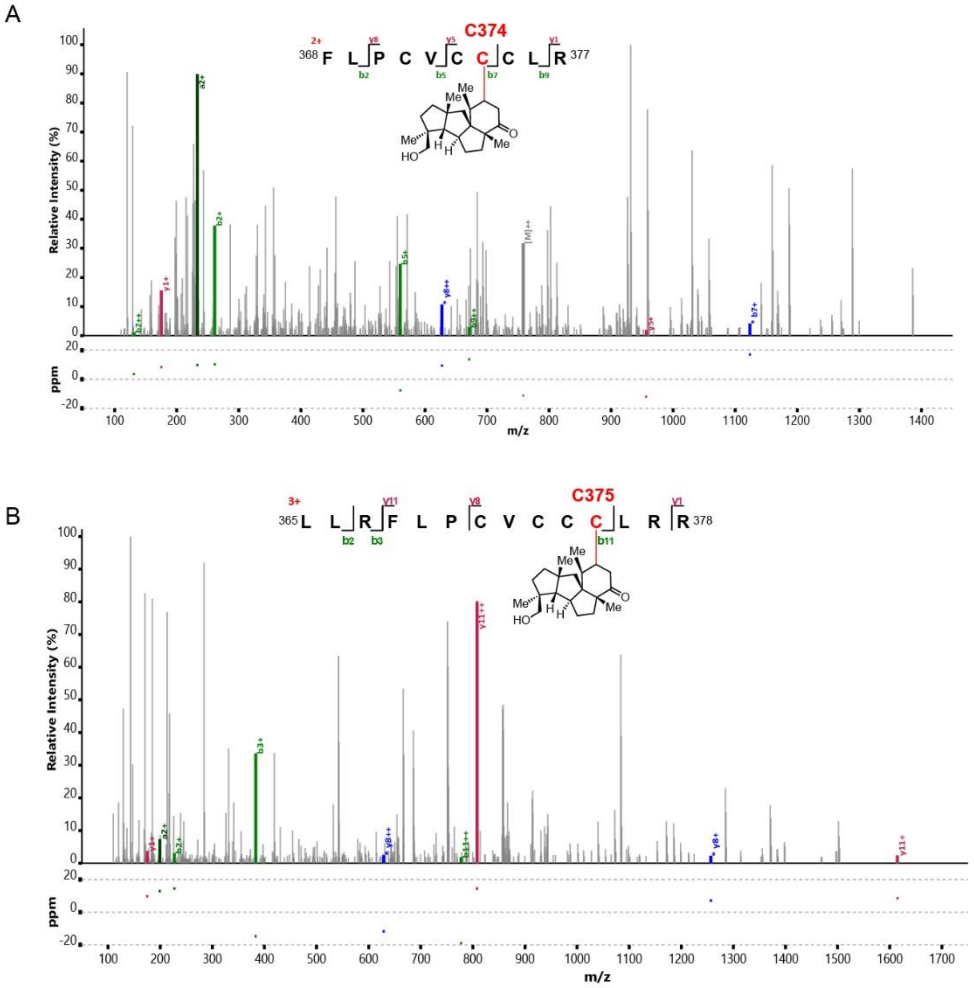


Supplementary Fig. S4 Evaluation of Conidiogenone C probe labeling in living Raw264.7 and analysis of the targets profiling in Raw264.7 cell lysates. (A) Concentration- and time-dependent labeling of Conidiogenone C

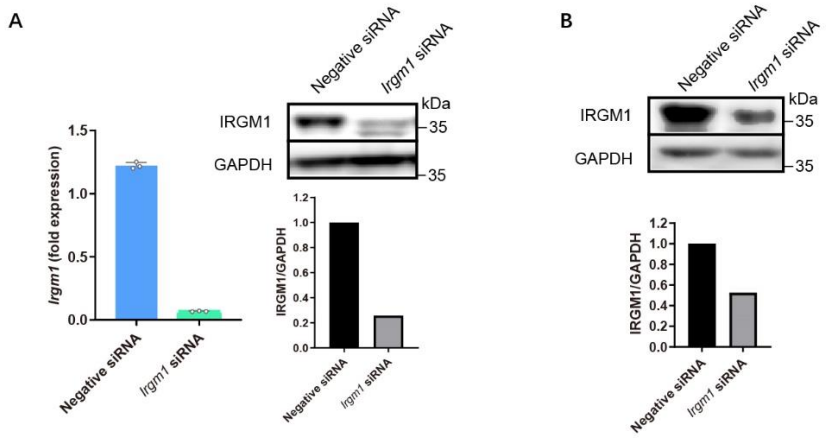
probe in living Raw264.7. The labeled lysates were reacted with azide-rhodamine (Rho) via CuAAC and the fluorescent intensity was determined by in-gel fluorescence scanning. Coomassie Brilliant Blue (CBB) staining demonstrates the equal labeling. (B) *In vivo* competitive pull-down assay using conidiogenone C probe, followed by western blot to confirm that conidiogenone C directly binds to IRGM1 protein in cell lysates. (C) KEGG functional pathways analysis of 59 target proteins identified by Conidiogenone C probe. (D) Gene ontology analysis Analysis of 59 target proteins identified by Conidiogenone C probe.



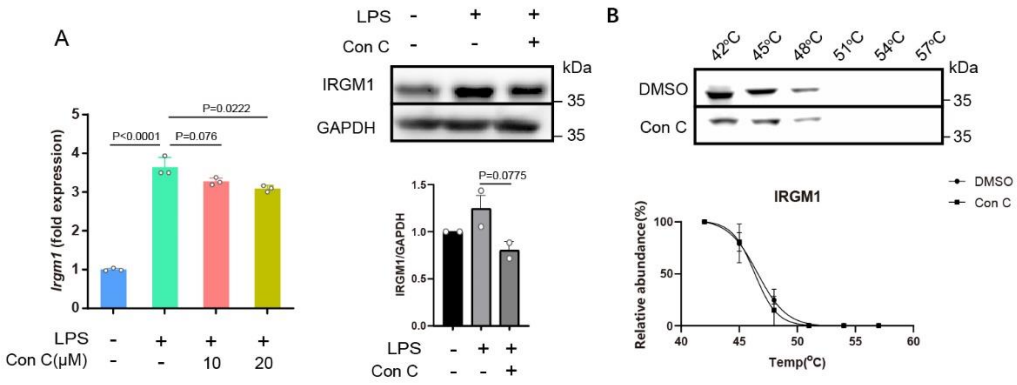
Supplementary Fig. S5 In-gel fluorescence profiling of conidiogenone C probe, followed by western blot to confirm the outstanding band in the gel is IRGM1, n=2 independent experiments with similar results.



Supplementary Fig. S6 Representative MS/MS spectrum for the identification of conidiogenone C-labeled IRGM1 peptides containing two binding residues C374 (A) and C375 (B), n=3 independent experiments with similar results.



Supplementary Fig. S7 Silencing efficiency for siRNAs against *IRGM1* with (B) or without (A) LPS-stimulation. All measurements are presented as mean ± SD. Source data are provided as a Source Data file.



Supplementary Fig. S8 Conidiogenone C did not decrease the expression of IRGM1 or affect the thermal stability of IRGM1. (A) The gene expression and protein level of IRGM1 in Raw264.7 treated with or without Conidiogenone C. (B) The interactions between Conidiogenone C and IRGM1 confirmed by CETSA-WB. Con C = conidiogenone C. All measurements are presented as mean ± SD for three(a, left; b) or two(a, right) biological replicates. Statistical differences were determined by by a two-sided Student's t-test. Source data are provided as a Source Data file.

Table S7. List of the overlap of the target proteins identified by Conidiogenone C probe in three biological replicates.

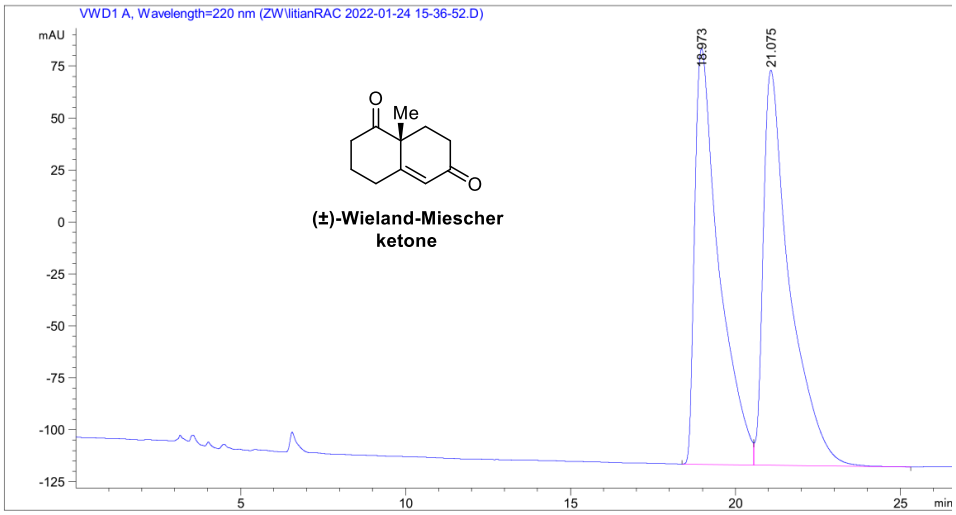
Protein name	Uniprot accession	Description
RAB18	P35293	Ras-related protein Rab-18
XPO1	Q6P5F9	Exportin-1
IF4A1	P60843	Eukaryotic initiation factor 4A-I
EF1A1	P10126	Elongation factor 1-alpha 1
TBB5	P99024	Tubulin beta-5 chain
CH60	P63038	60 kDa heat shock protein
AT1A1	Q8VDN2	Sodium/potassium-transporting ATPase subunit alpha-1
ACTB	P60710	Actin
PLSL	Q61233	Plastin-2
IMB1	P70168	Importin subunit beta-1
EF2	P58252	Elongation factor 2
TBA1B	P05213	Tubulin alpha-1B chain
G3P	P16858	Glyceraldehyde-3-phosphate dehydrogenase
IRGM1	Q60766	Immunity-related GTPase family M protein 1
GNAI2	P08752	Guanine nucleotide-binding protein G(i) subunit alpha-2
TCPQ	P42932	T-complex protein 1 subunit theta
TCPH	P80313	T-complex protein 1 subunit eta
TNPO1	Q8BFY9	Transportin-1
DHB12	O70503	Very-long-chain 3-oxoacyl-CoA reductase
HS90A	P07901	Heat shock protein HSP 90-alpha
RL7A	P12970	60S ribosomal protein L7a
ADT1	P48962	ADP/ATP translocase 1
ANXA5	P48036	Annexin A5
ARF3	P61205	ADP-ribosylation factor 3
IRG1	P54987	Cis-aconitate decarboxylase
MDHM	P08249	Malate dehydrogenase
VDAC2	Q60930	Voltage-dependent anion-selective channel protein 2
HS90B	P11499	Heat shock protein HSP 90-beta
ENOA	P17182	Alpha-enolase
ADT2	P51881	ADP/ATP translocase 2
RS5	P97461	40S ribosomal protein S5
PGK1	P09411	Phosphoglycerate kinase 1
TCPG	P80318	T-complex protein 1 subunit gamma
LDHA	P06151	L-lactate dehydrogenase A chain
EF1G	Q9D8N0	Elongation factor 1-gamma
CALX	P35564	Calnexin
ENPL	P08113	Endoplasmin
ATPA	Q03265	ATP synthase subunit alpha
RAB7A	P51150	Ras-related protein Rab-7a
CALR	P14211	Calreticulin
GLYM	Q9CZN7	Serine hydroxymethyltransferase
S61A1	P61620	Protein transport protein Sec61 subunit alpha isoform 1
RAC2	Q05144	Ras-related C3 botulinum toxin substrate 2
RS8	P62242	40S ribosomal protein S8

RL4	Q9D8E6	60S ribosomal protein L4
MPRD	P24668	Cation-dependent mannose-6-phosphate receptor
COX2	P00405	Cytochrome c oxidase subunit 2
RS4X	P62702	40S ribosomal protein S4
RS3	P62908	40S ribosomal protein S3
PRDX1	P35700	Peroxiredoxin-1
PDIA3	P27773	Protein disulfide-isomerase A3
RS11	P62281	40S ribosomal protein S11
RL6	P47911	60S ribosomal protein L6
BIP	P20029	Endoplasmic reticulum chaperone BiP
RAB1B	Q9D1G1	Ras-related protein Rab-1B
RL7	P14148	60S ribosomal protein L7
RS3A	P97351	40S ribosomal protein S3a
RS15A	P62245	40S ribosomal protein S15a
M2OM	Q9CR62	Mitochondrial 2-oxoglutarate/malate carrier protein

Table S8. List of primers for qRT-PCR

	Sense 5'-3'	Antisense 5'-3'
Irgm1	TGCTCCACTACTCCCCAACAT	GCTCCTACTGACCTCAGGTAAC
Gapdh	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA
Ifnb	GCACTACAGGCTCCGAGATGAAC	TTGTCGTTGCTTGGTTCTCCTTGT
Mx1	GACCATAGGGGTCTTGACCAA	AGACTTGCTCTTTCTGAAAAGCC

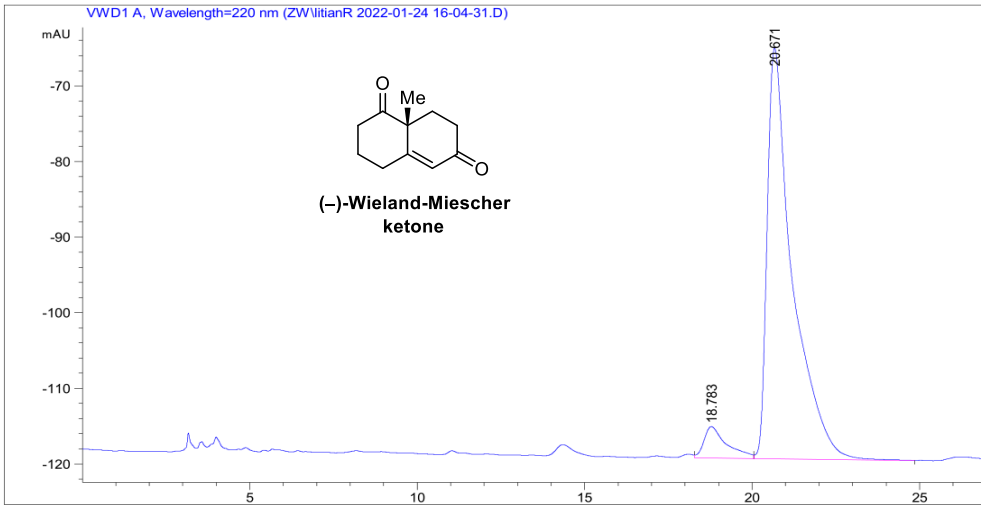
5. HPLC Spectra of Wieland-Miescher ketone



Peak Table

VWD1 A, Wavelength = 220 nm

Peak#	Ret. Time	Type	[min]	Area	Height	Area (%)
1	18.973	BV	0.7383	1.02498e4	199.85507	49.1108
2	21.075	VB	0.8022	1.062110e4	189.98506	50.8892
Total				2.08708e4	389.84013	100



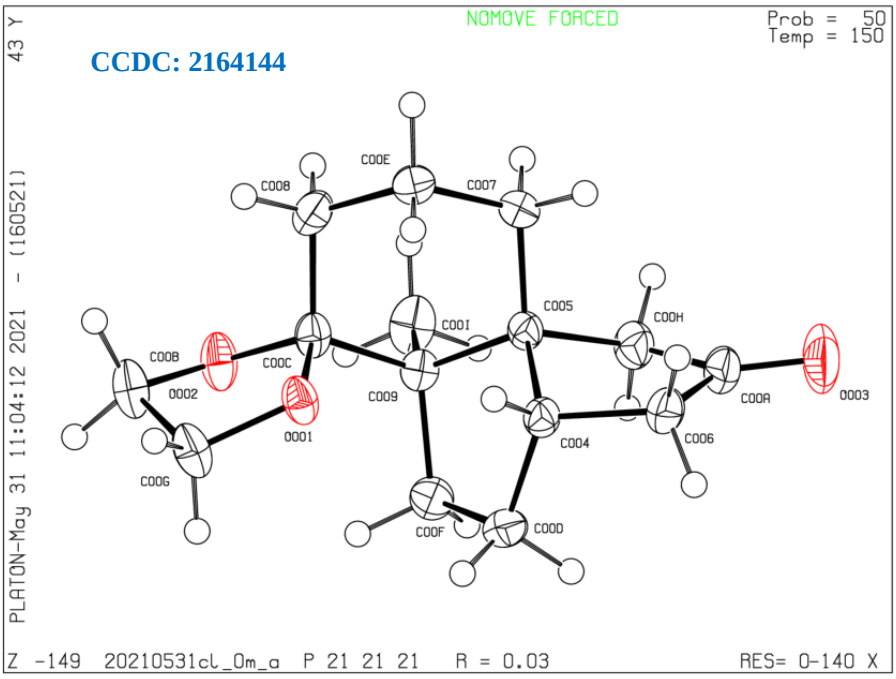
Peak Table

VWD1 A, Wavelength = 220 nm

Peak#	Ret. Time	Type	[min]	Area	Height	Area (%)
1	18.783	VV	0.6679	194.61844	4.14529	6.4061
2	20.671	VB	0.7424	2843.39233	54.34420	93.5939
Total				3038.01077	58.48949	100

Supplementary Fig. S9. HPLC Spectra of (–)-Wieland-Miescher ketone

6. Crystallographic Data



Bond precision: C-C = 0.0021 A Wavelength=1.34139

Cell: a=7.5163(3) b=7.9585(3) c=21.9789(8)
alpha=90 beta=90 gamma=90
Temperature: 150 K

	Calculated	Reported
Volume	1314.74(9)	1314.74(9)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C15 H22 O3	C15 H22 O3
Sum formula	C15 H22 O3	C15 H22 O3
Mr	250.33	250.32
Dx,g cm-3	1.265	1.265
Z	4	4
Mu (mm-1)	0.441	0.445
F000	544.0	544.0
F000'	545.23	
h,k,lmax	9,9,26	9,9,26
Nref	2507[1477]	2473
Tmin,Tmax	0.938,0.956	0.620,0.751
Tmin'	0.915	

Correction method= # Reported T Limits: Tmin=0.620 Tmax=0.751
AbsCorr = MULTI-SCAN

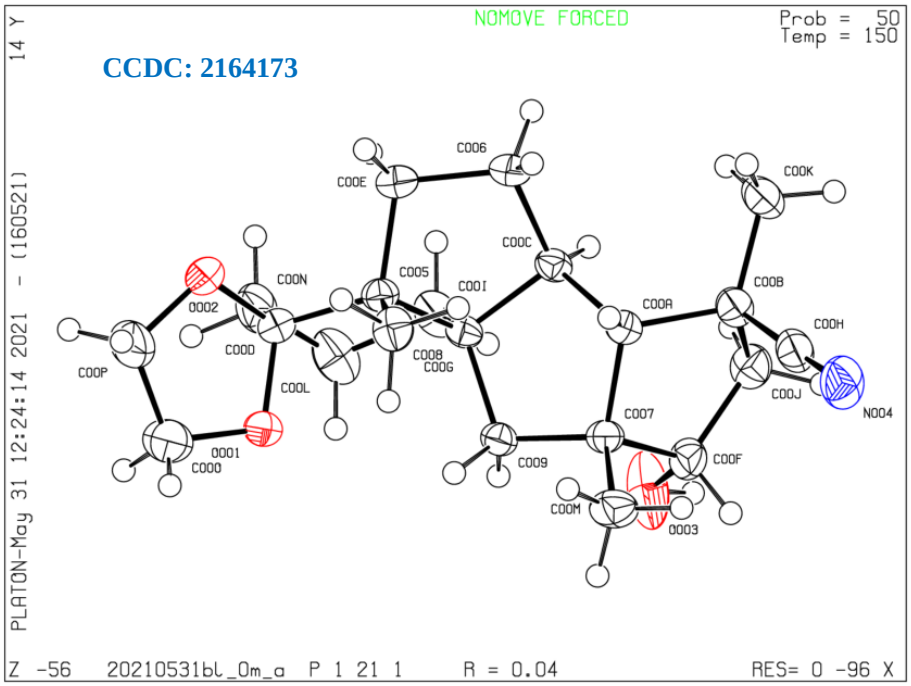
Data completeness= 1.67/0.99 Theta(max)= 54.901

R(reflections)= 0.0279(2429) wR2(reflections)= 0.0758(2473)

S = 1.078 Npar= 164

0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
0 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
10 **ALERT level G** = General information/check it is not something unexpected

Supplementary Fig. S10. Crystallographic Data of Compound 18

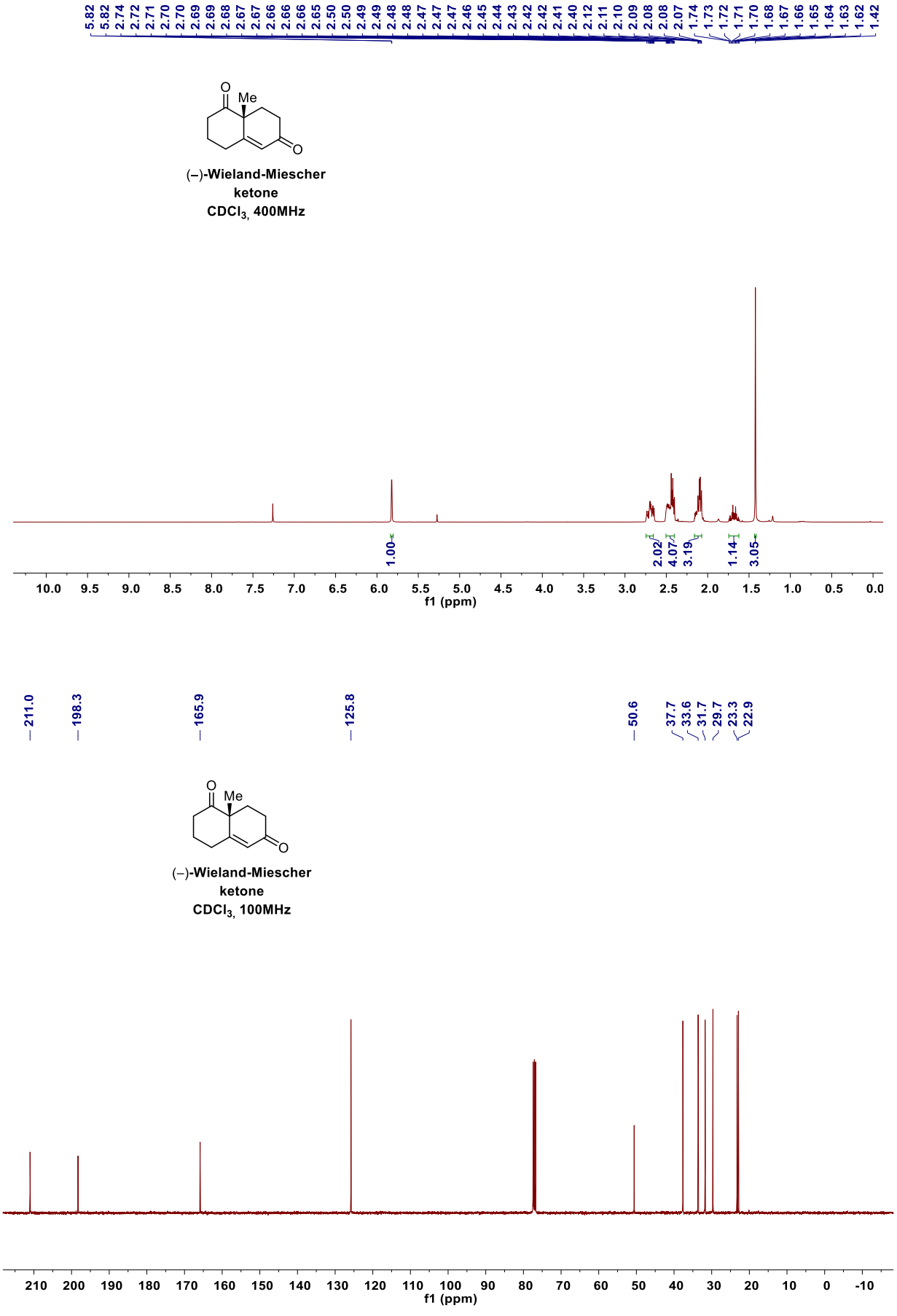



```
Bond precision:  C-C = 0.0033 A          Wavelength=1.34139

Cell:            a=8.1338(5)     b=11.7106(7)        c=9.8396(6)
                 alpha=90        beta=91.636(2)      gamma=90
Temperature:     150 K

                 Calculated                  Reported
Volume           936.86(10)                  936.86(10)
Space group      P 21                        P 1 21 1
Hall group       P 2yb                       P 2yb
Moiety formula   C21 H31 N O3                C21 H31 N O3
Sum formula      C21 H31 N O3                C21 H31 N O3
Mr               345.47                      345.47
Dx,g cm-3        1.225                       1.225
Z                2                           2
Mu (mm-1)        0.407                       0.411
F000             376.0                       376.0
F000'            376.81
h,k,lmax         9,13,11                     9,13,11
Nref             3169[ 1671]                 3087
Tmin,Tmax        0.906,0.921                 0.559,0.750
Tmin'            0.884

Correction method= # Reported T Limits: Tmin=0.559 Tmax=0.750
AbsCorr = MULTI-SCAN

Data completeness= 1.85/0.97      Theta(max)= 51.790

R(reflections)= 0.0370( 3023)     wR2(reflections)= 0.0986( 3087)

S = 1.065                 Npar= 231
```

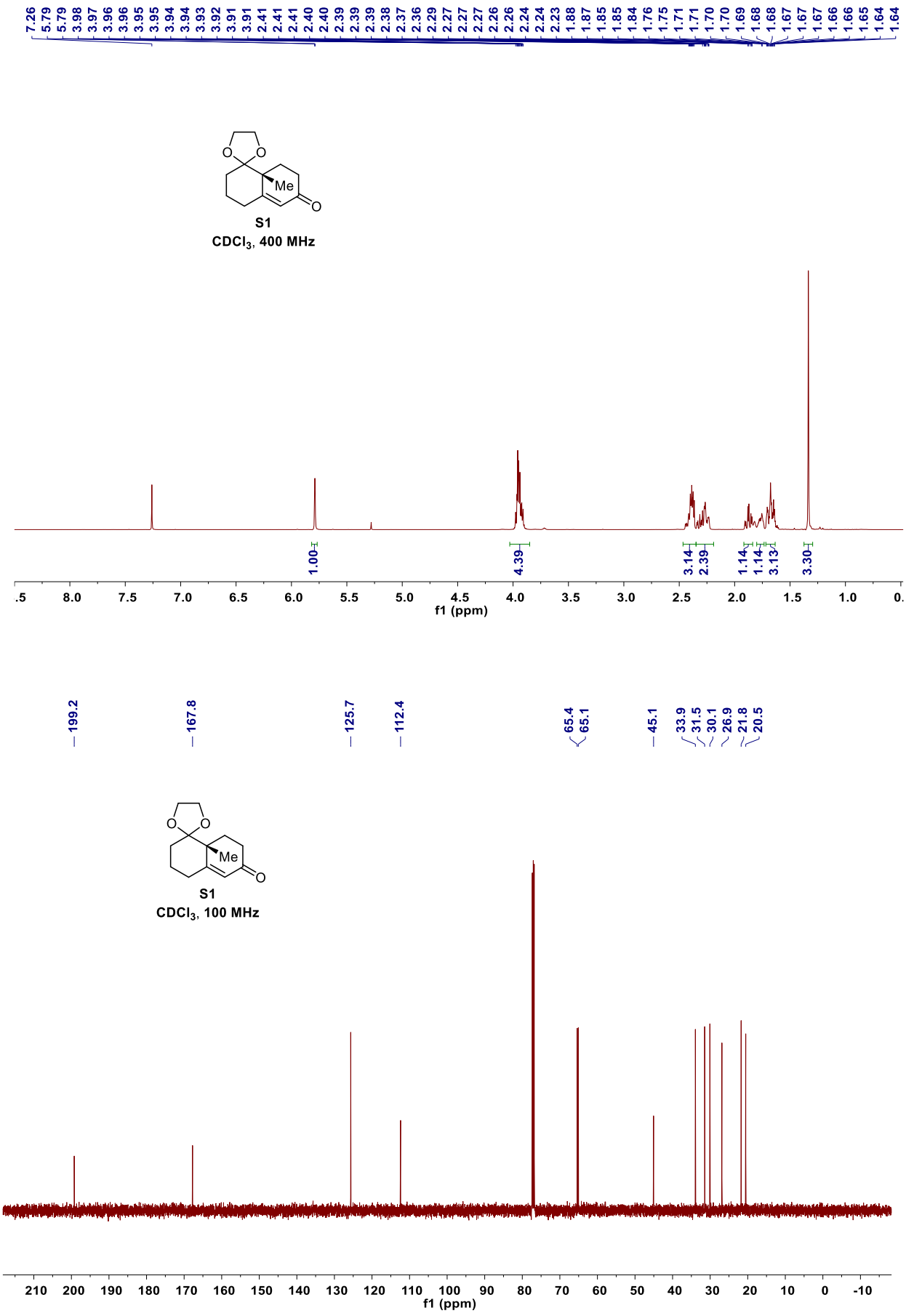
```
 0 ALERT level A = Most likely a serious problem - resolve or explain
 0 ALERT level B = A potentially serious problem, consider carefully
 4 ALERT level C = Check. Ensure it is not caused by an omission or oversight
18 ALERT level G = General information/check it is not something unexpected
```

Supplementary Fig. S11. Crystallographic Data of Compound 45

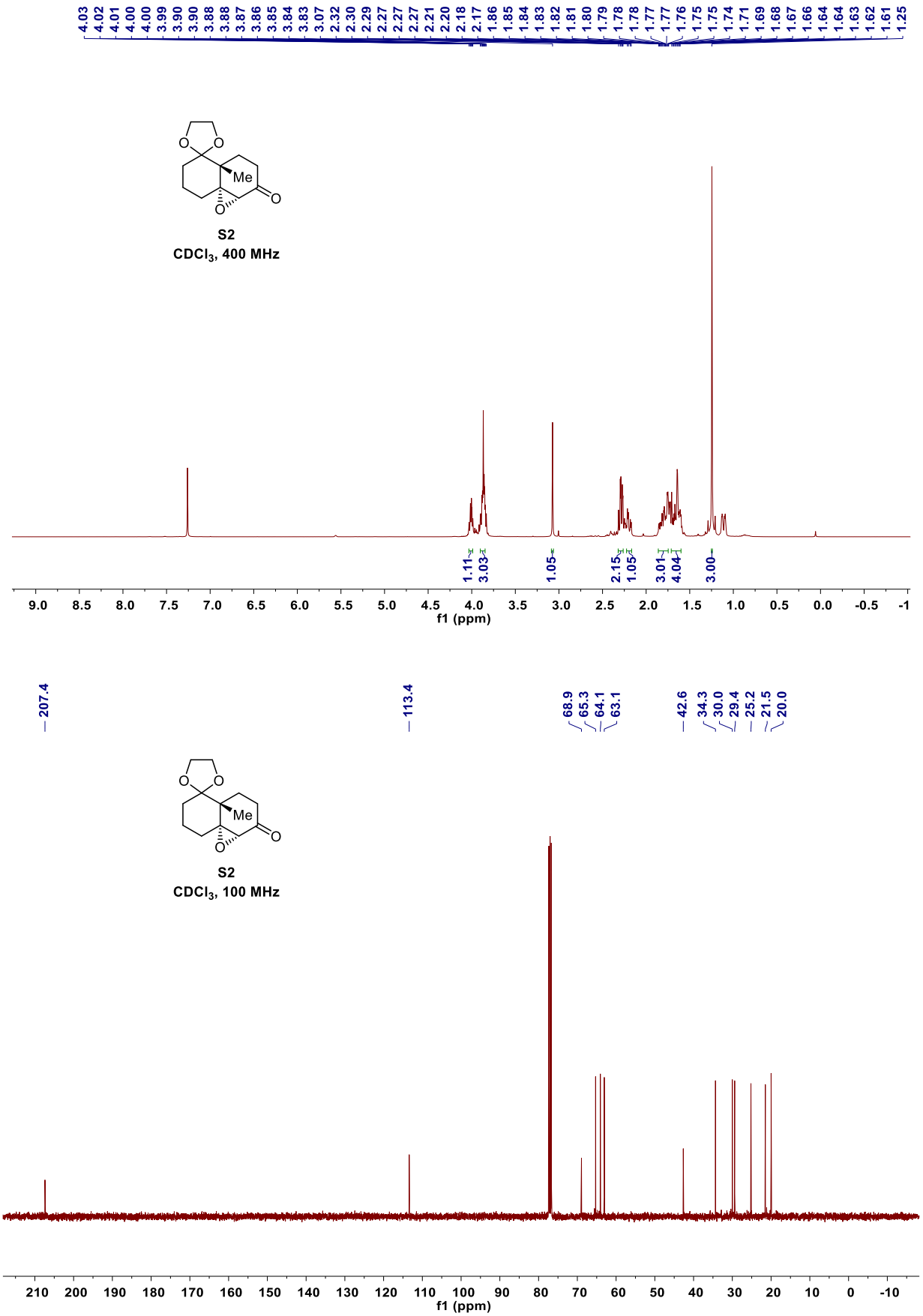
7. ^{1}H and ^{13}C NMR Spectra



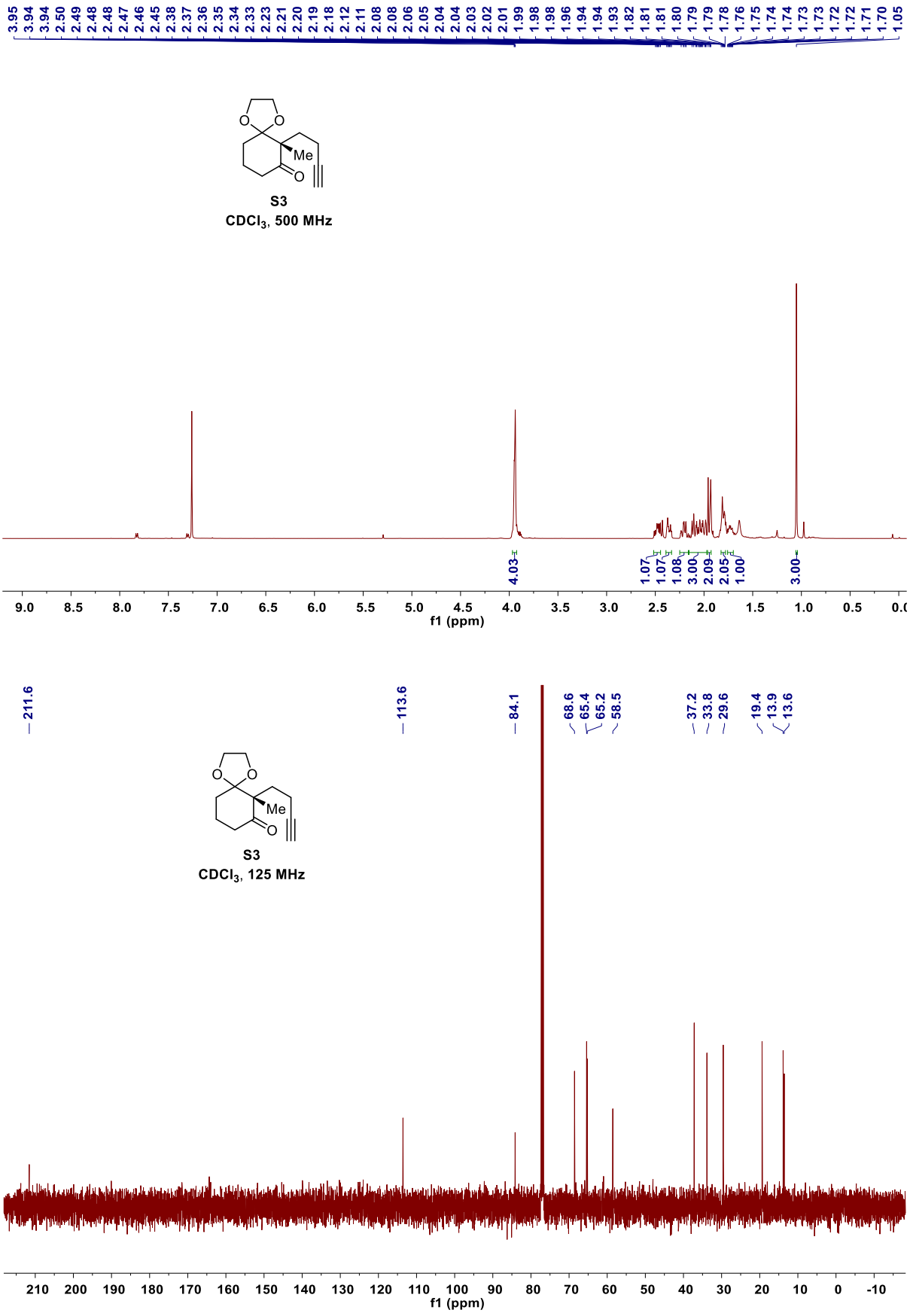
Supplementary Fig. S12. ^{1}H and ^{13}C NMR Spectra of (–)-Wieland-Miescher ketone



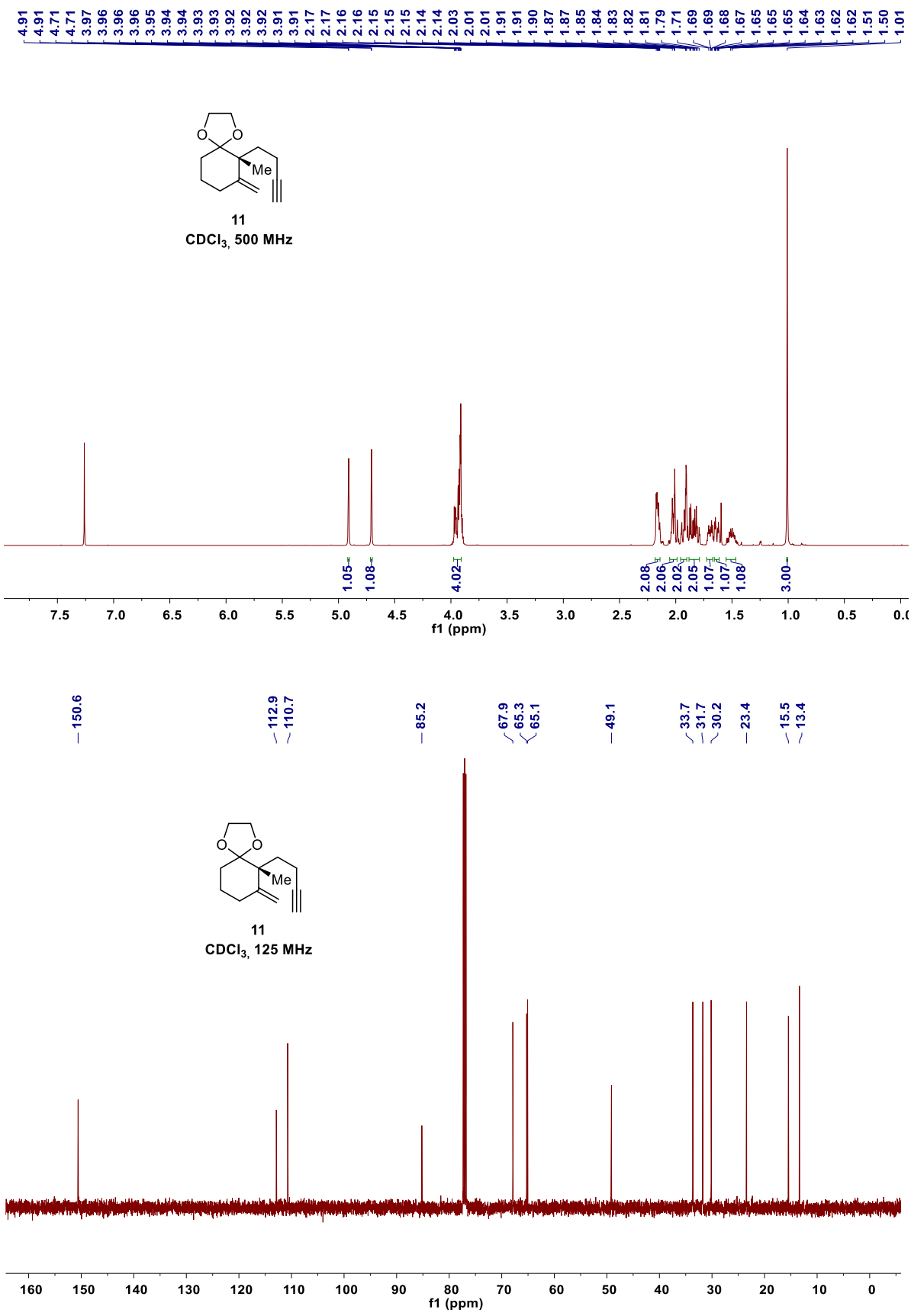
Supplementary Fig. S13. ^{1}H and ^{13}C NMR Spectra of S1



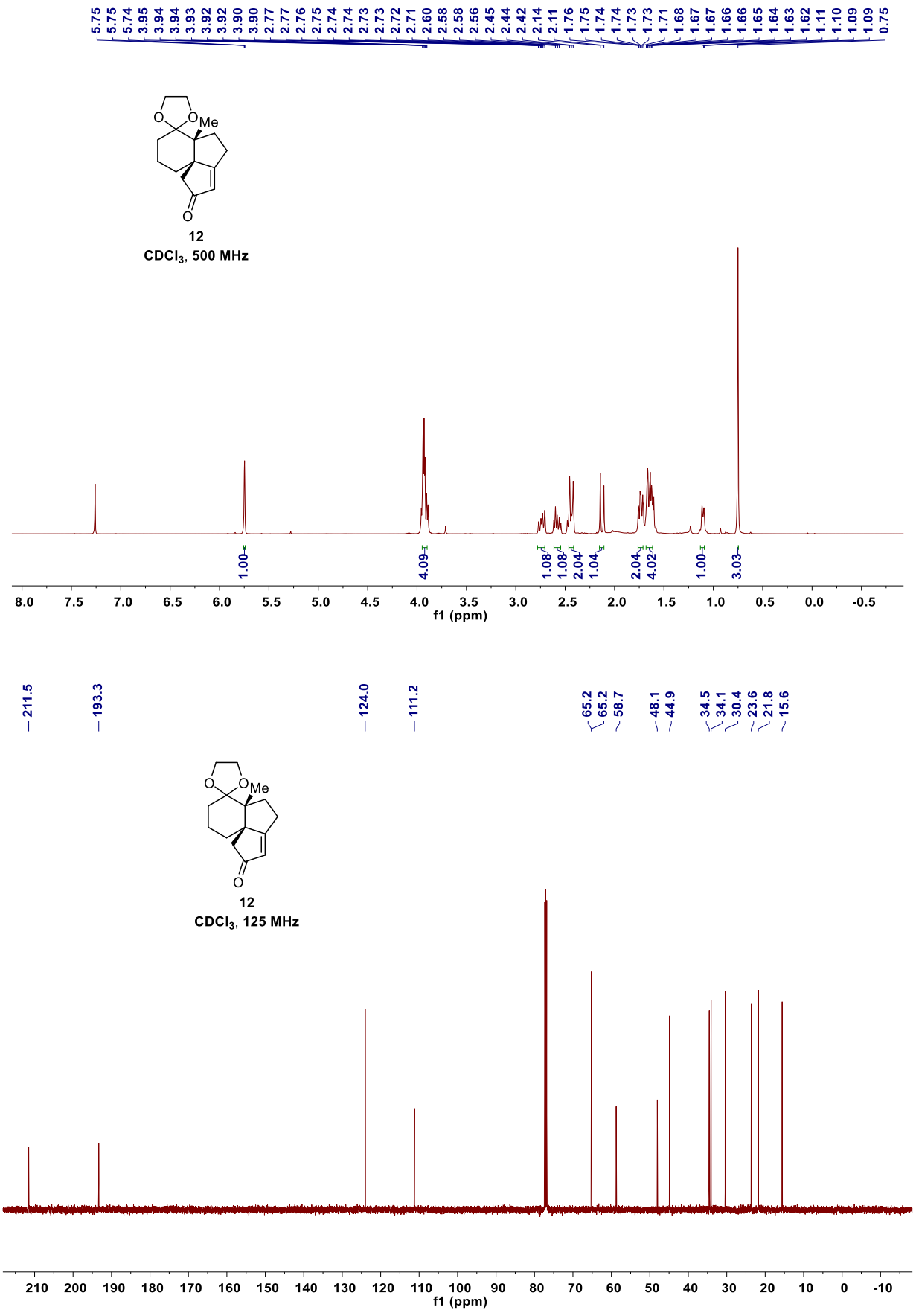
Supplementary Fig. S14. ^{1}H and ^{13}C NMR Spectra of S2



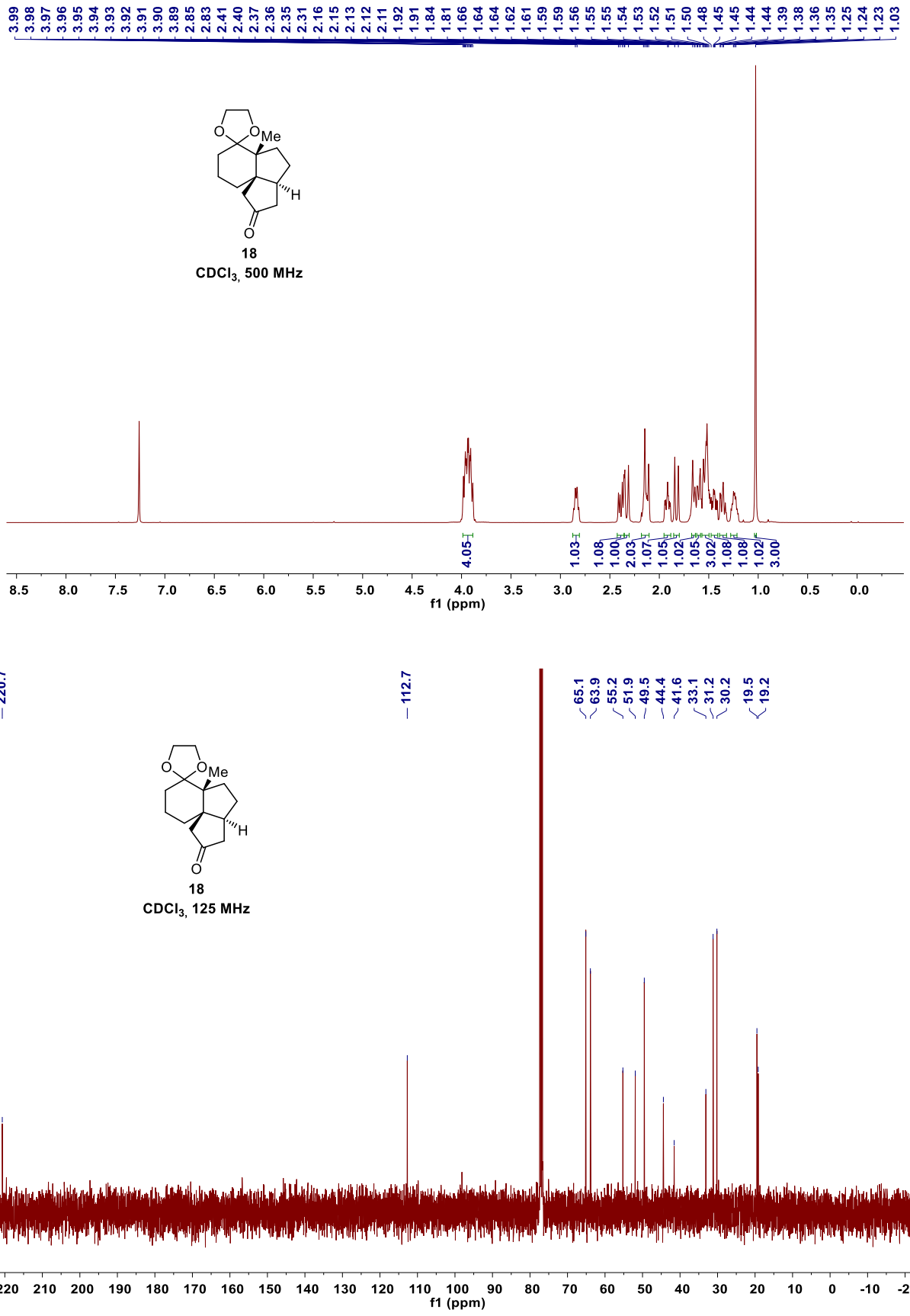
Supplementary Fig. S15. ^{1}H and ^{13}C NMR Spectra of S3



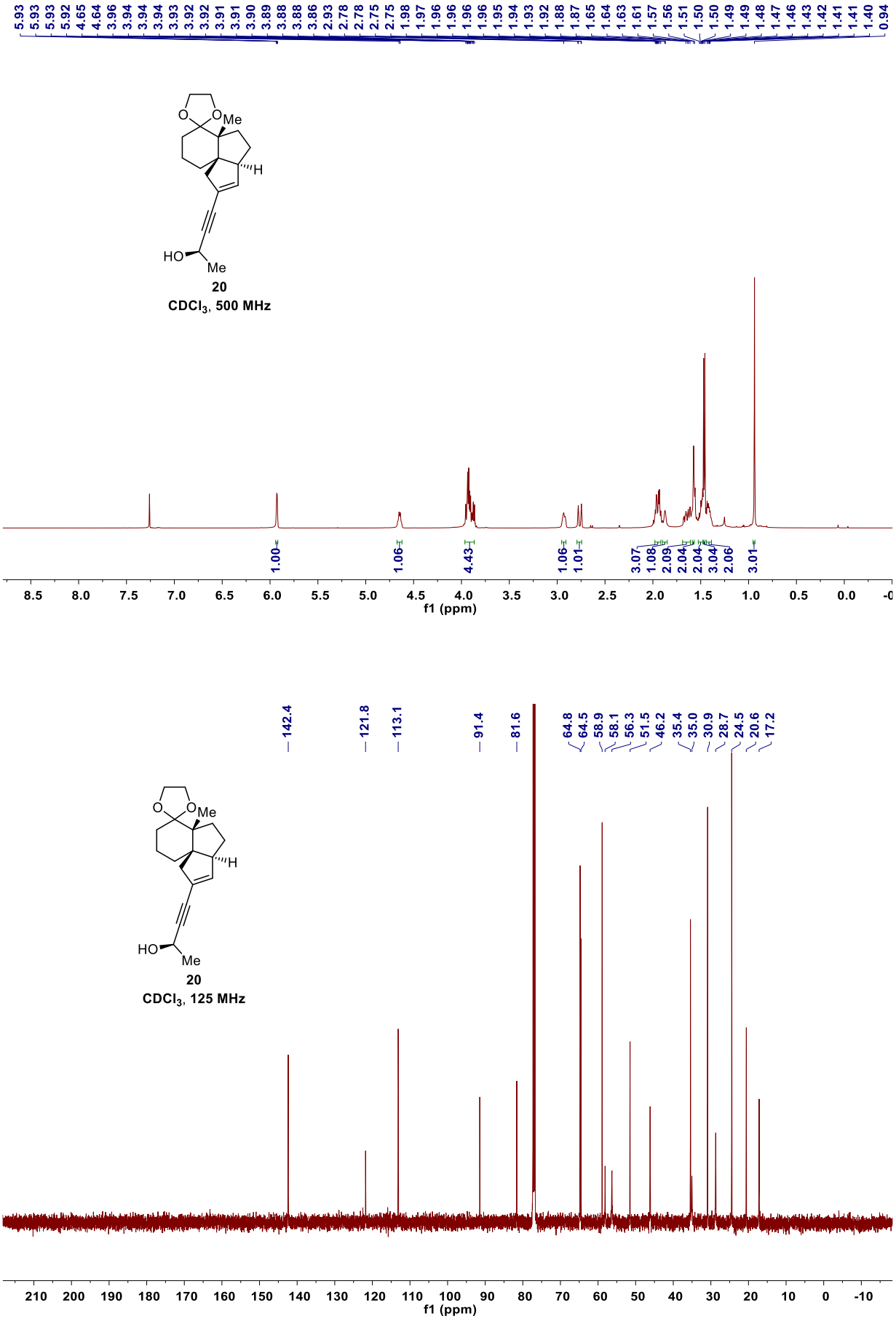
Supplementary Fig. S16. ^{1}H and ^{13}C NMR Spectra of 11



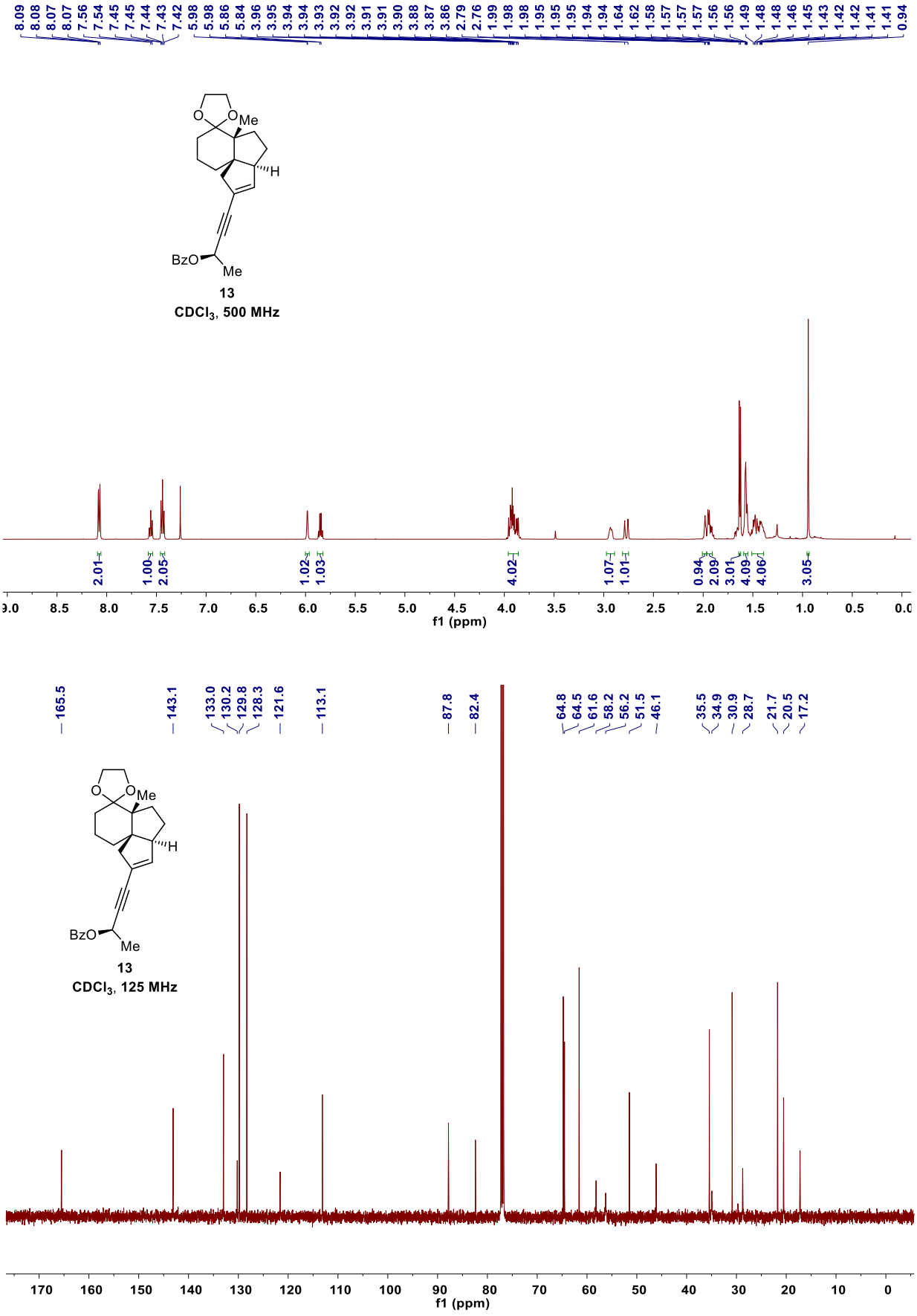
Supplementary Fig. S17. ^{1}H and ^{13}C NMR Spectra of 12



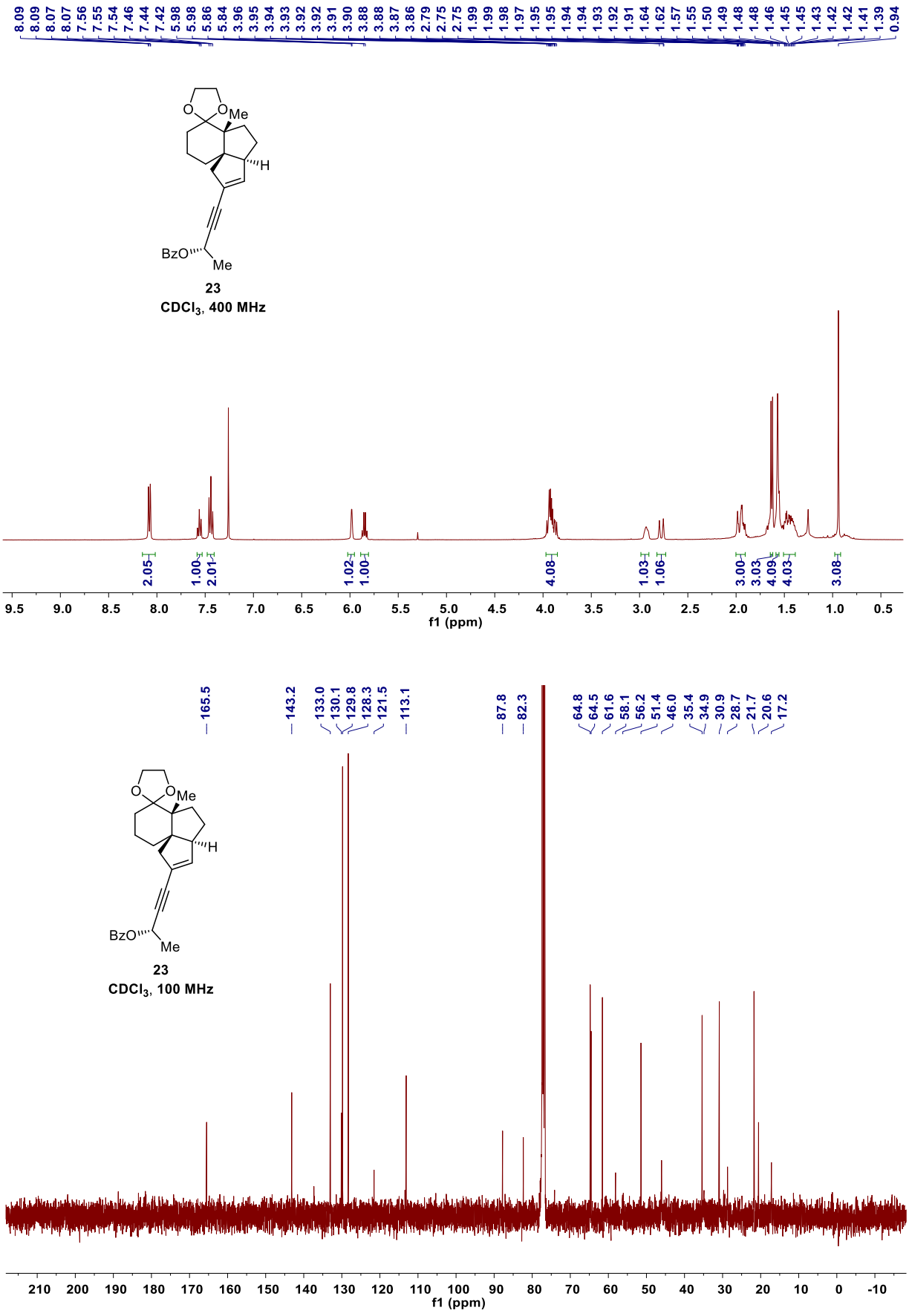
Supplementary Fig. S18. ^{1}H and ^{13}C NMR Spectra of 18



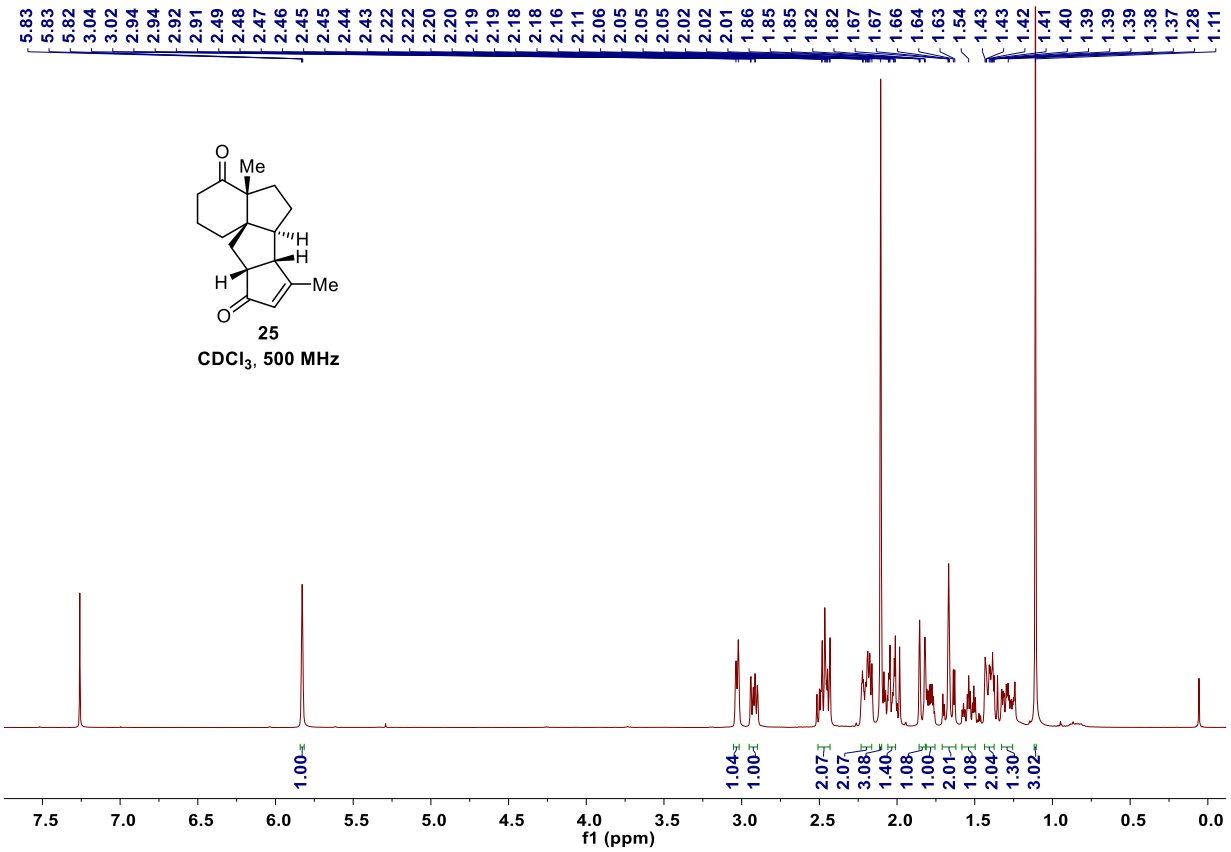
Supplementary Fig. S19. ^{1}H and ^{13}C NMR Spectra of 20

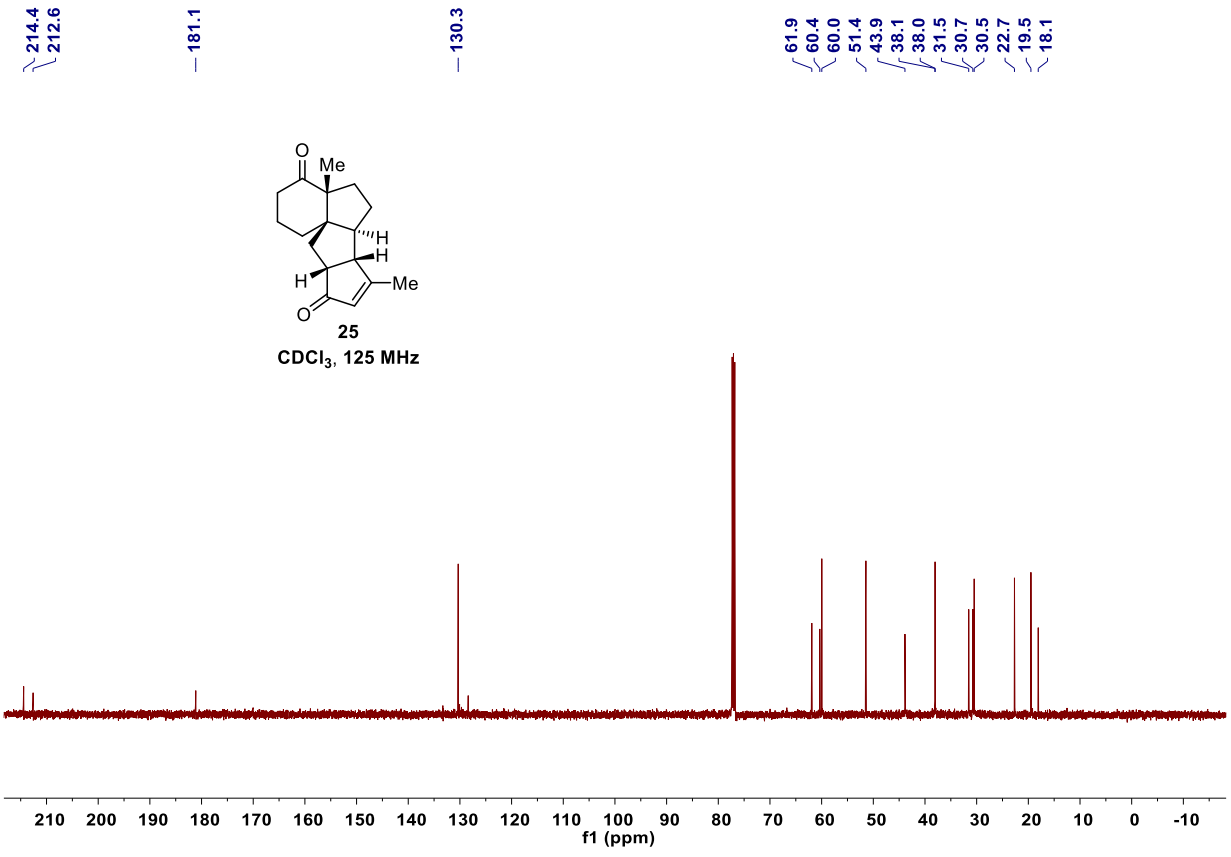


Supplementary Fig. S20. ^{1}H and ^{13}C NMR Spectra of 13

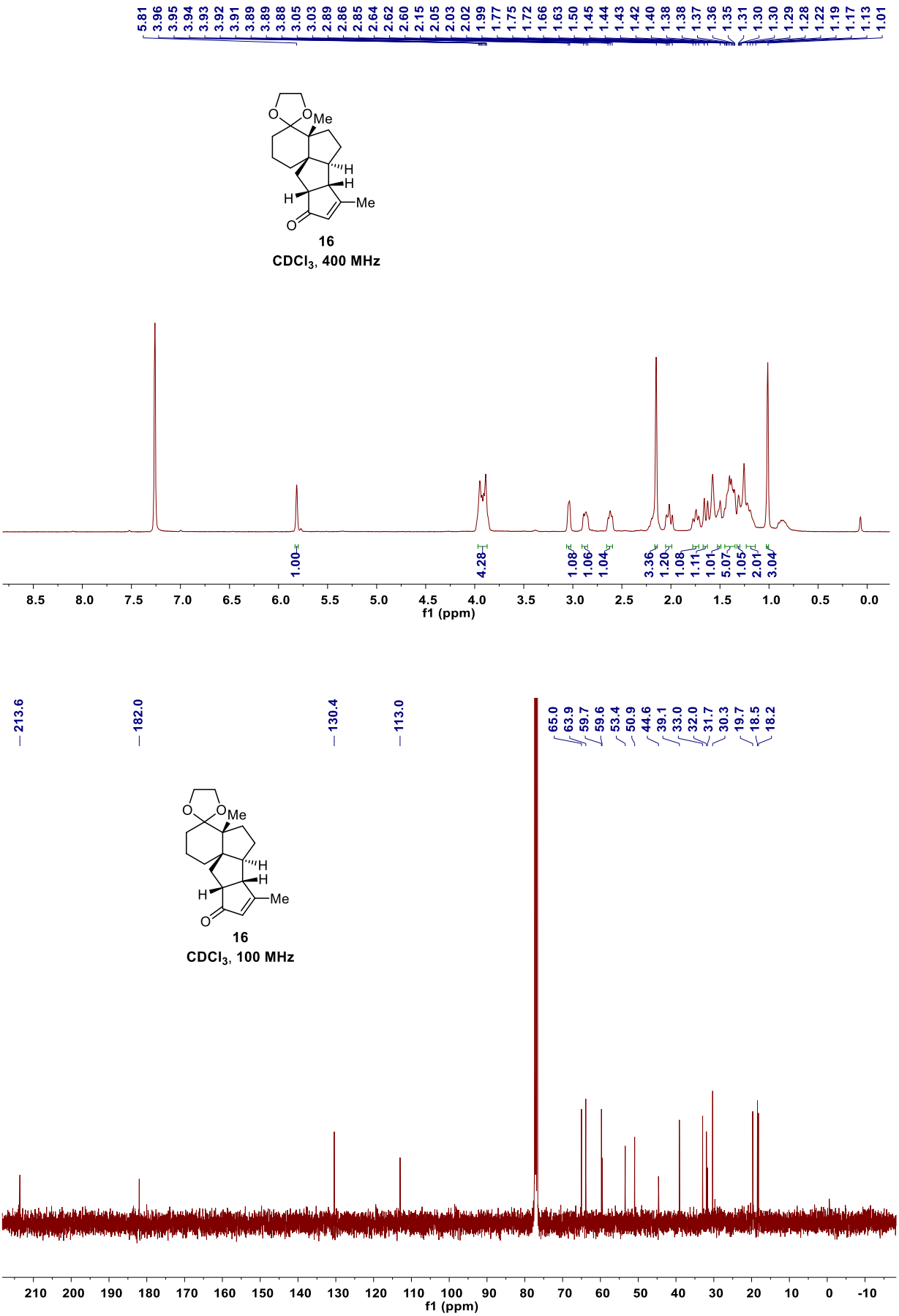


Supplementary Fig. S21. ^{1}H and ^{13}C NMR Spectra of 23

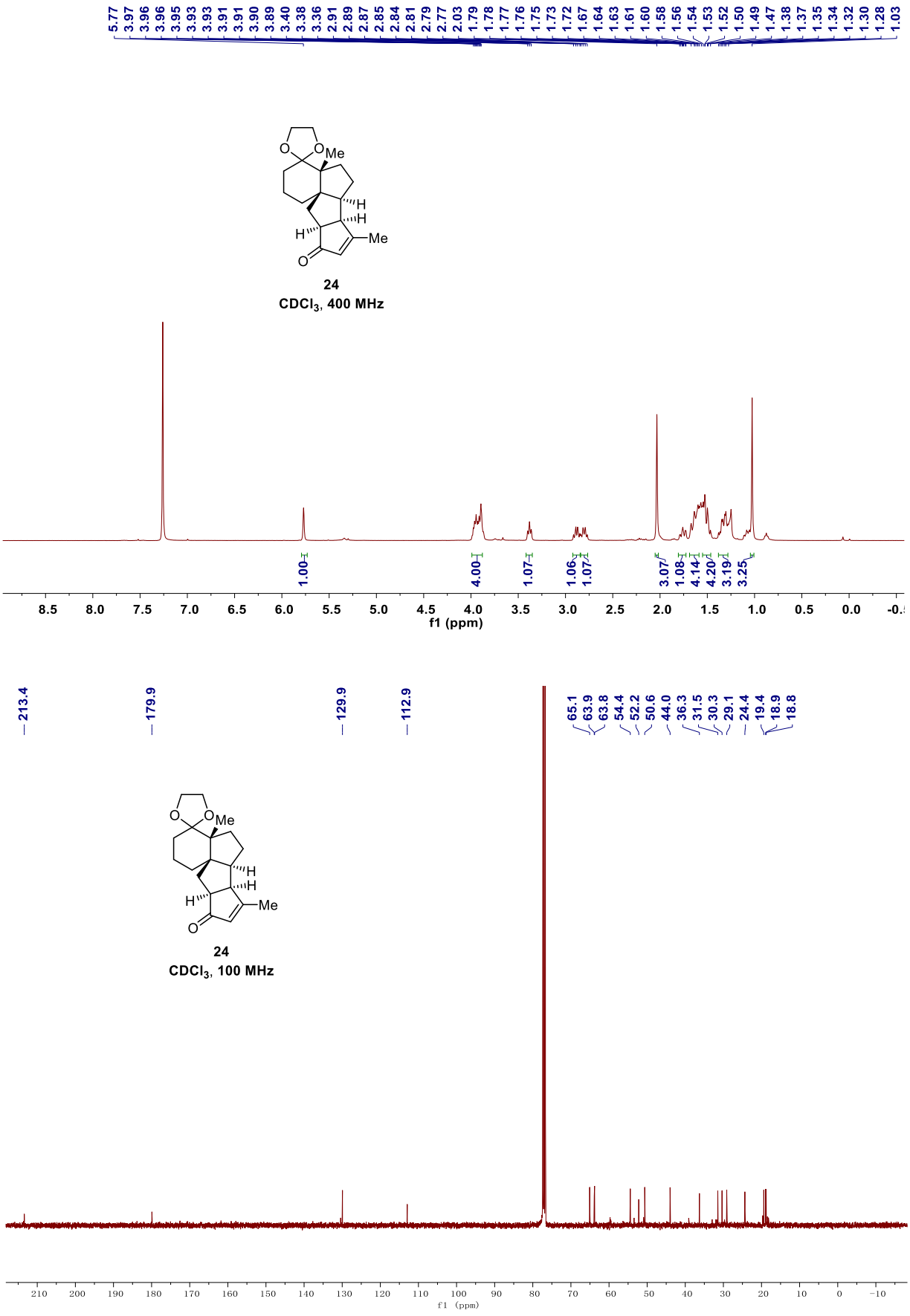




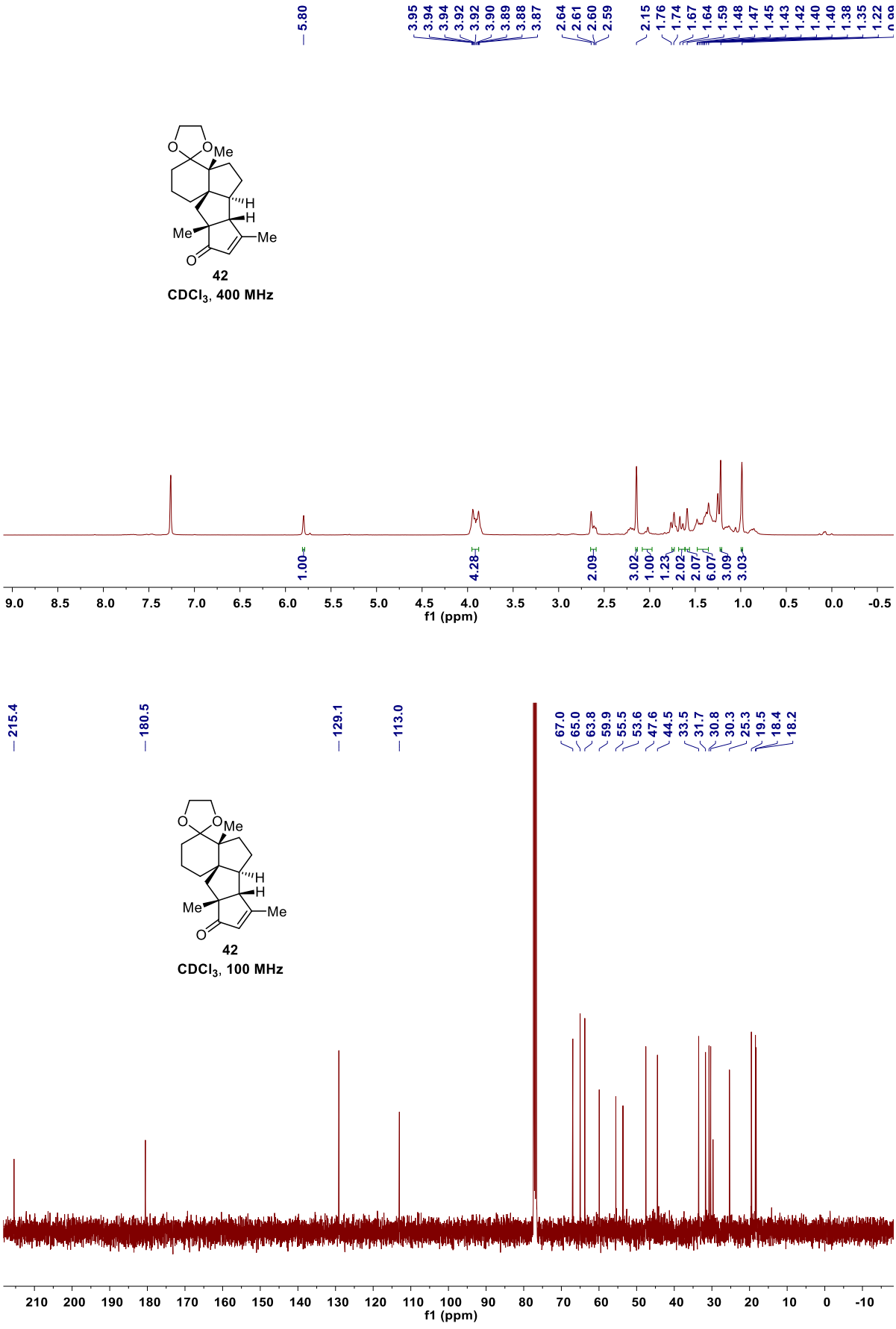
Supplementary Fig. S22. ^{1}H and ^{13}C NMR Spectra of 25



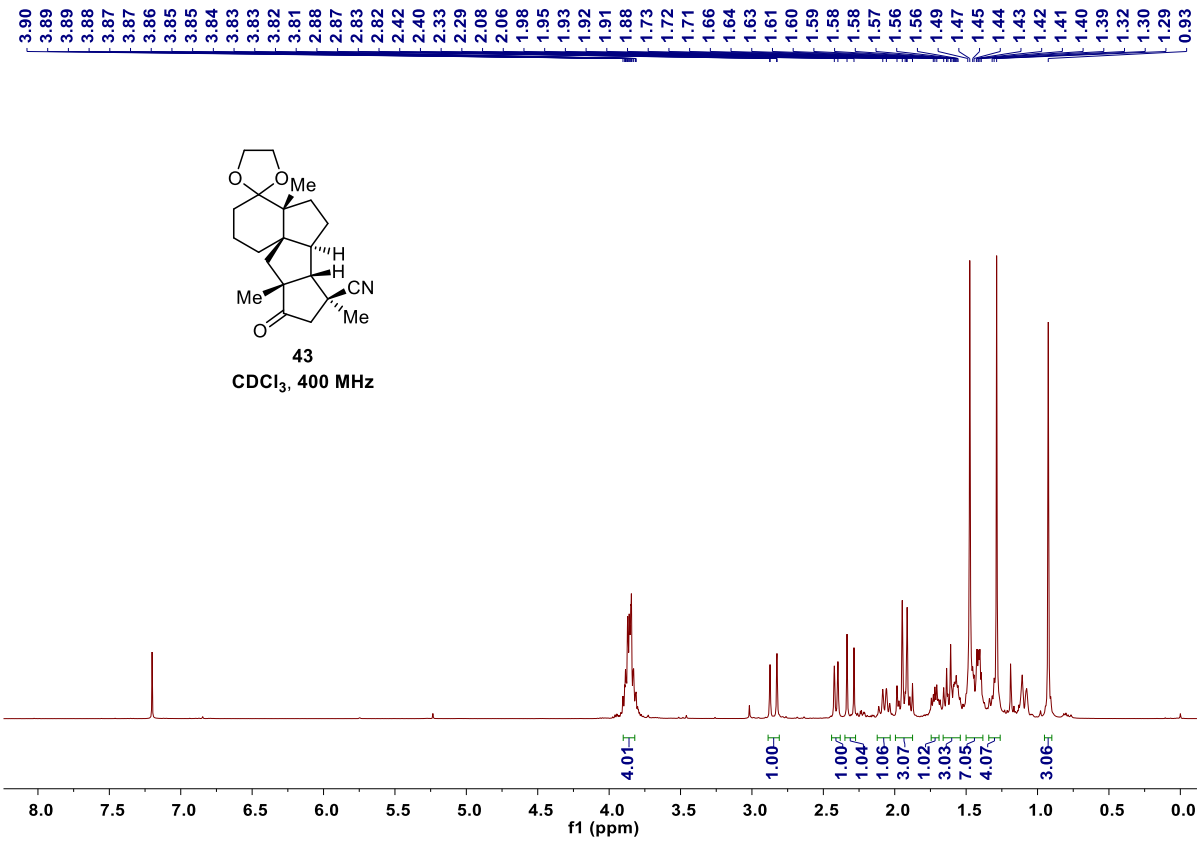
Supplementary Fig. S23. ^{1}H and ^{13}C NMR Spectra of 16

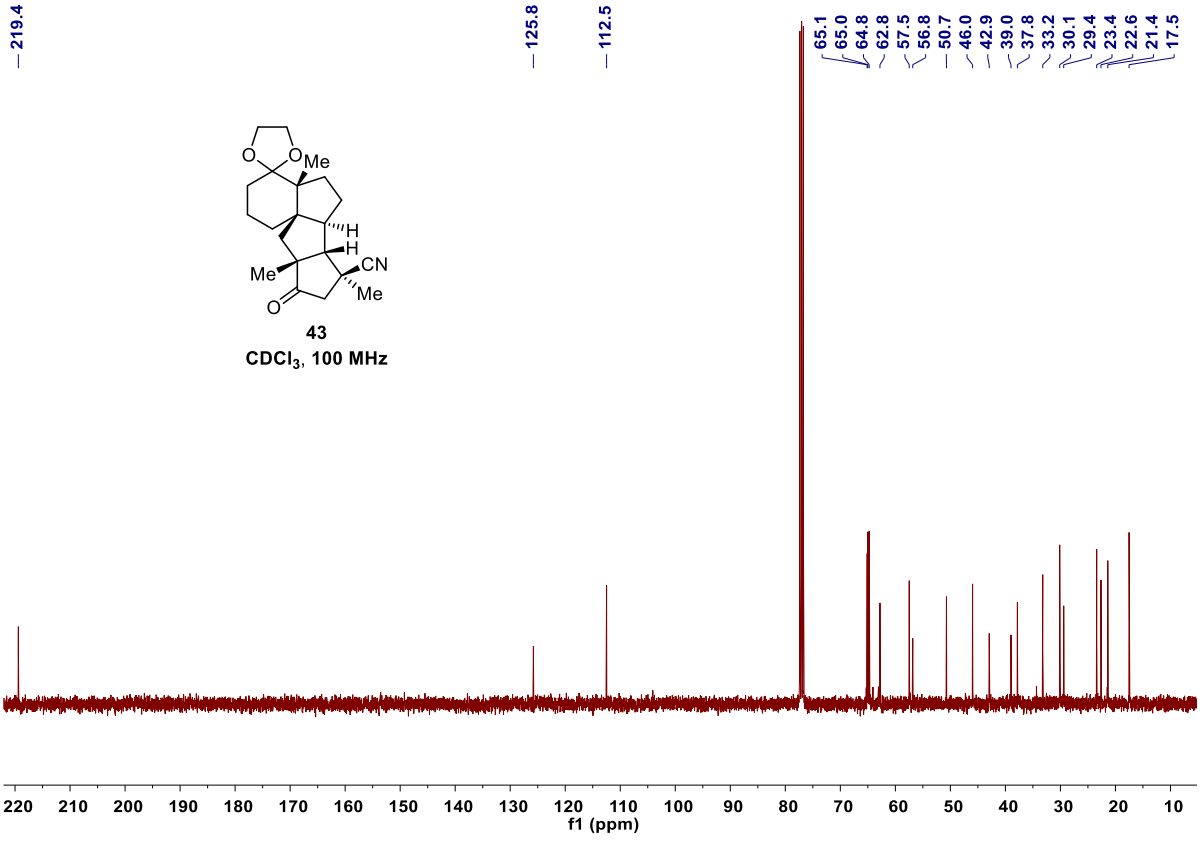


Supplementary Fig. S24. ^{1}H and ^{13}C NMR Spectra of 24

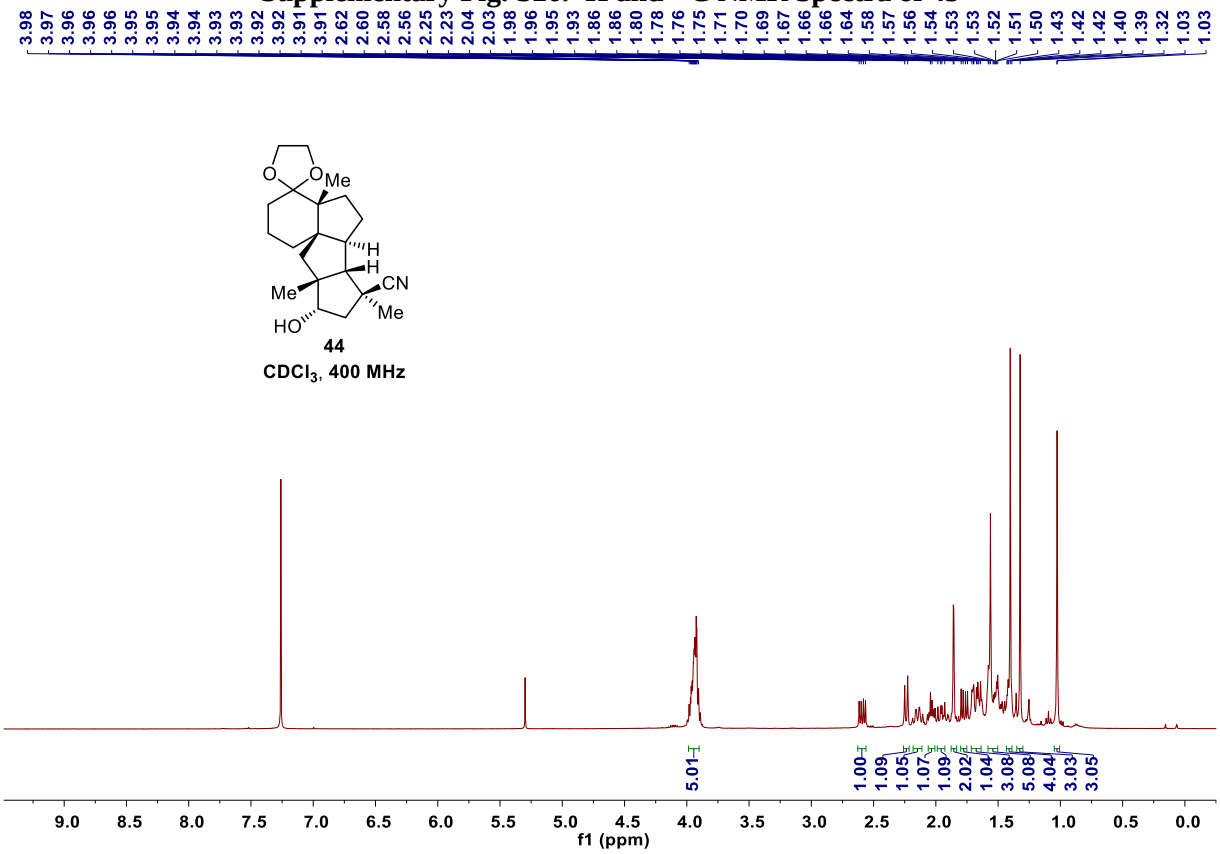


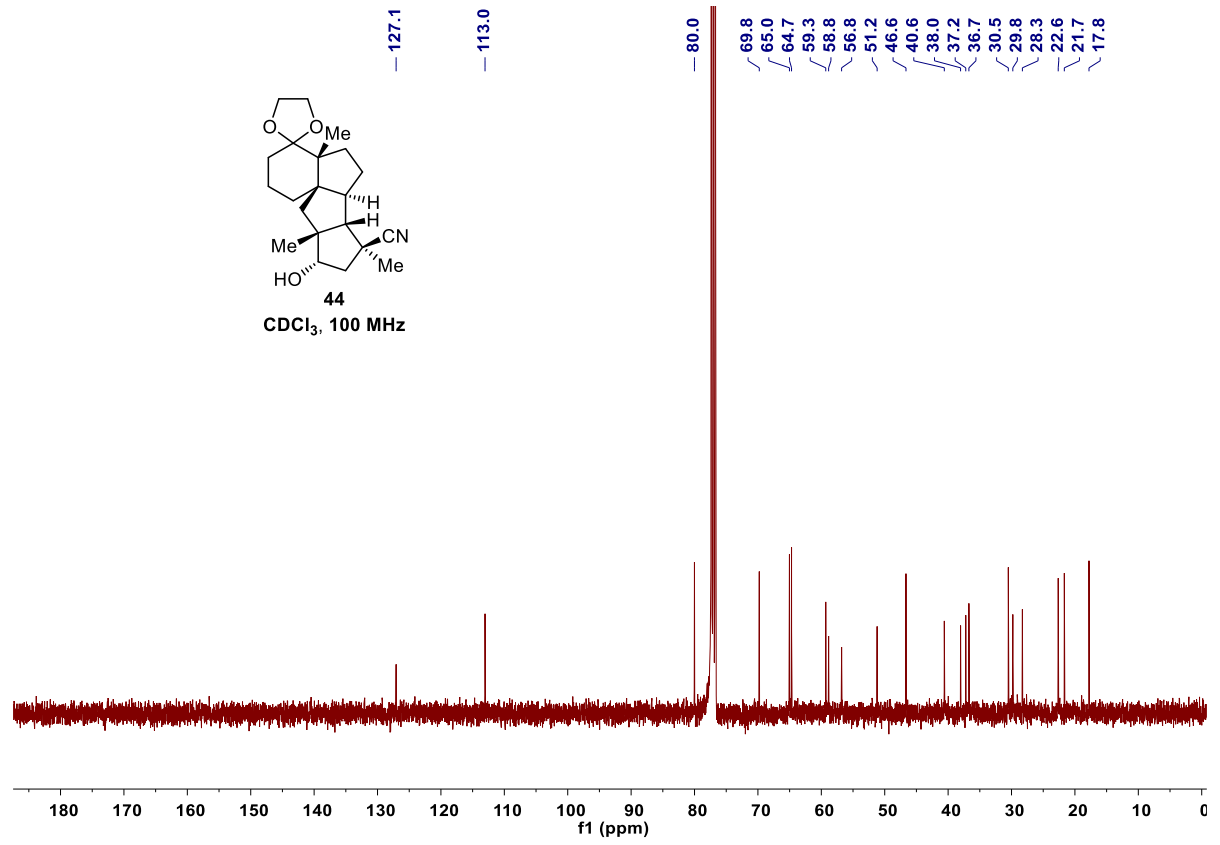
Supplementary Fig. S25. ^{1}H and ^{13}C NMR Spectra of 42


3.90 3.89 3.89 3.88 3.87 3.87 3.86 3.85 3.85 3.84 3.83 3.83 3.82 3.81 2.88 2.87 2.83 2.82 2.42 2.40 2.33 2.29 2.08 2.06 1.98 1.95 1.93 1.92 1.91 1.88 1.73 1.72 1.71 1.66 1.64 1.63 1.61 1.60 1.59 1.58 1.58 1.57 1.56 1.56 1.49 1.47 1.45 1.44 1.43 1.42 1.41 1.40 1.39 1.32 1.30 1.29 0.93
Me
H
H
CN
Me
Me
O
O
43
CDCl3, 400 MHz
4.01 1.00 1.00 1.04 1.06 3.07 1.02 3.03 7.05 4.07 3.06
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)

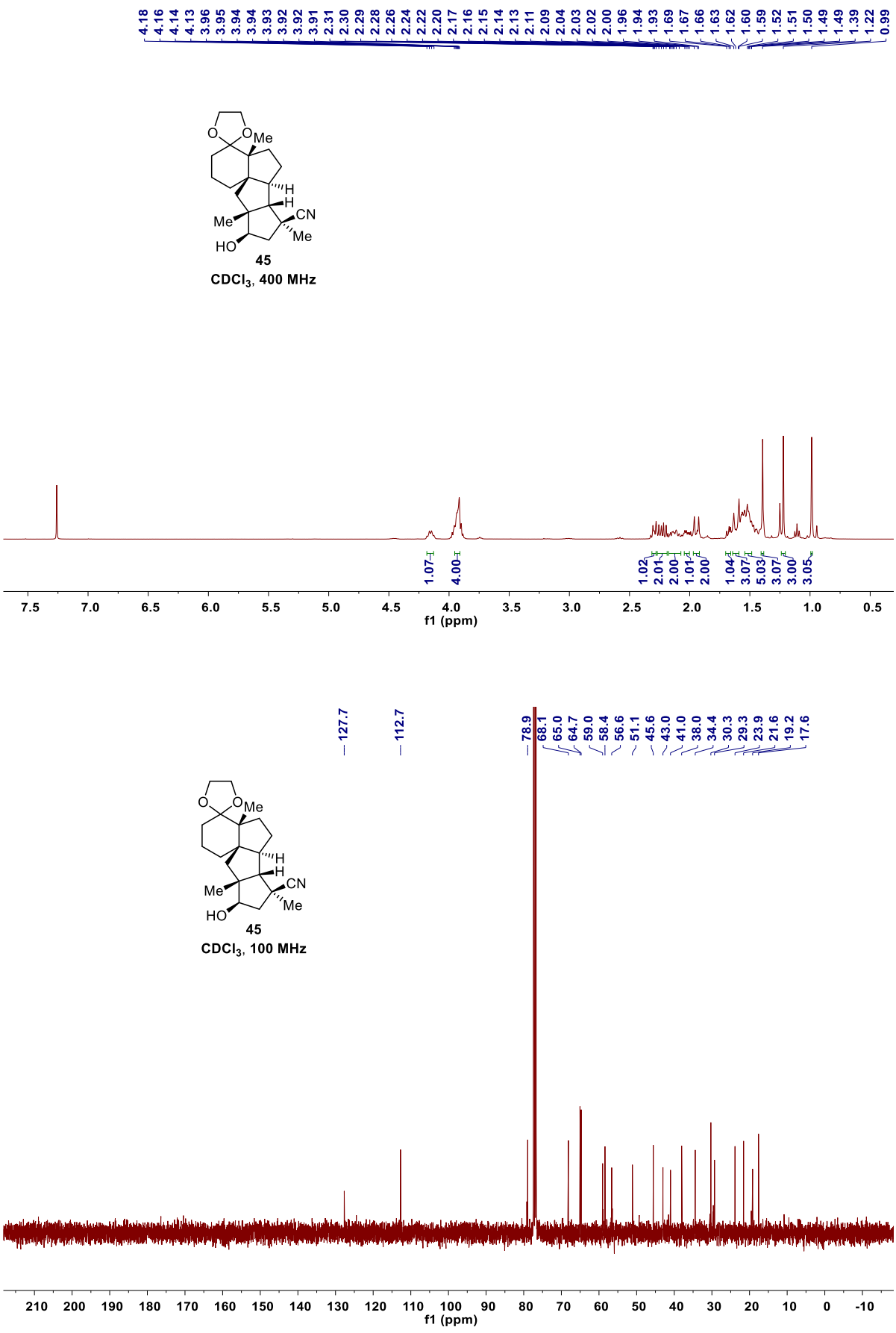

219.4
125.8
112.5
65.1 65.0 64.8 62.8 57.5 56.8 50.7 46.0 42.9 39.0 37.8 33.2 30.1 29.4 23.4 22.6 21.4 17.5
Me
H
H
CN
Me
Me
O
O
43
CDCl3, 100 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

Supplementary Fig. S26. ^{1}H and ^{13}C NMR Spectra of 43

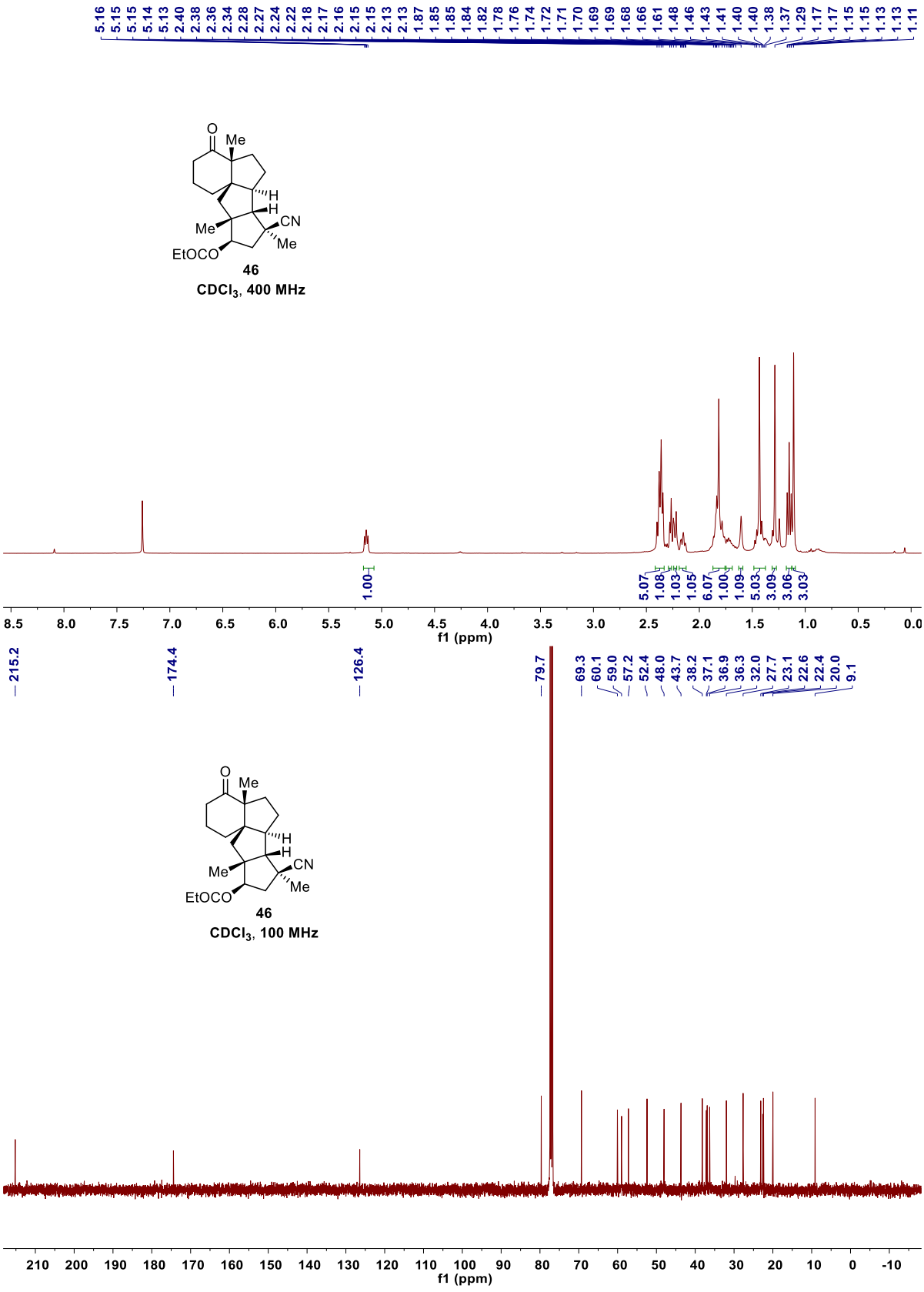




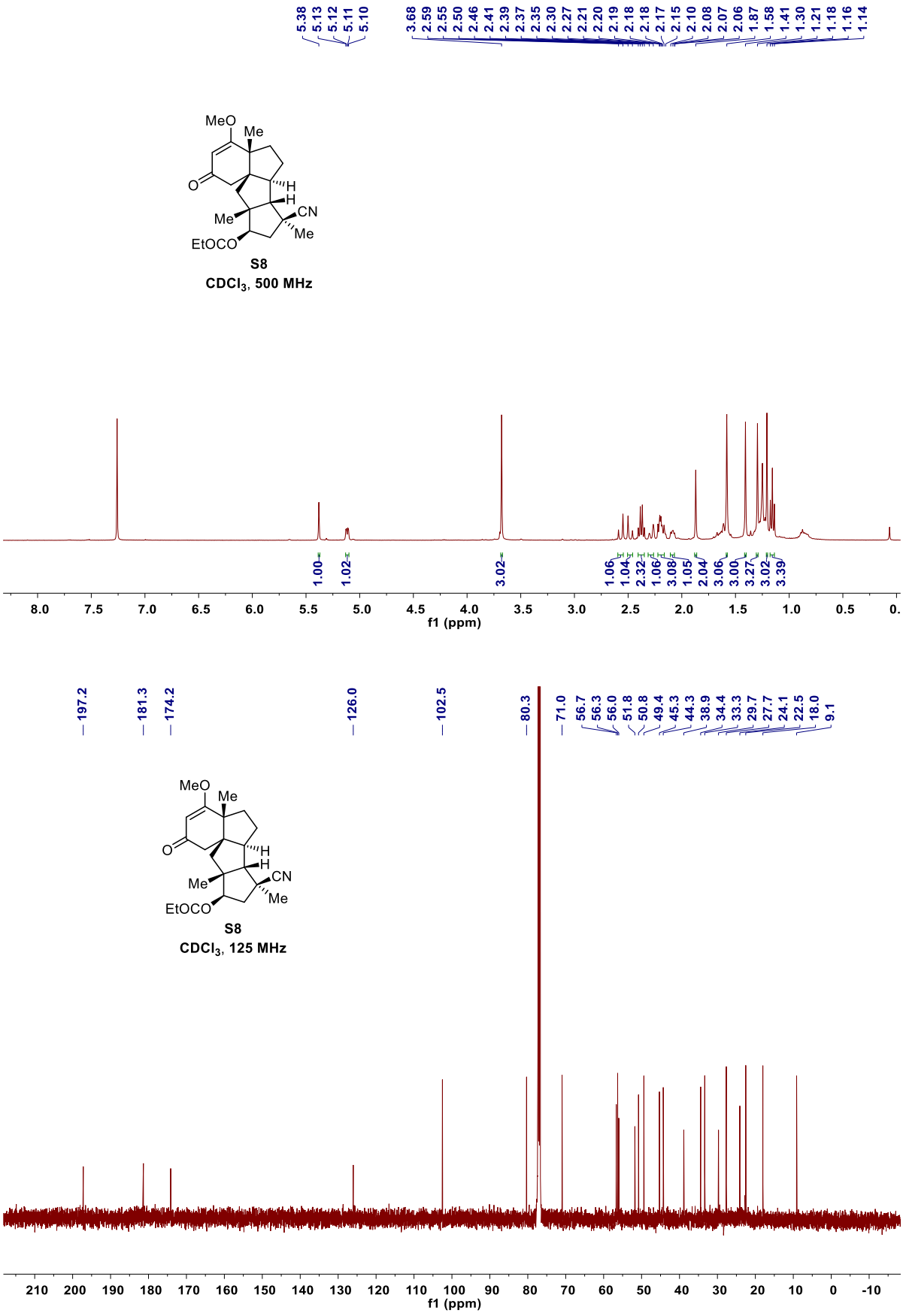
Supplementary Fig. S27. ^{1}H and ^{13}C NMR Spectra of 44



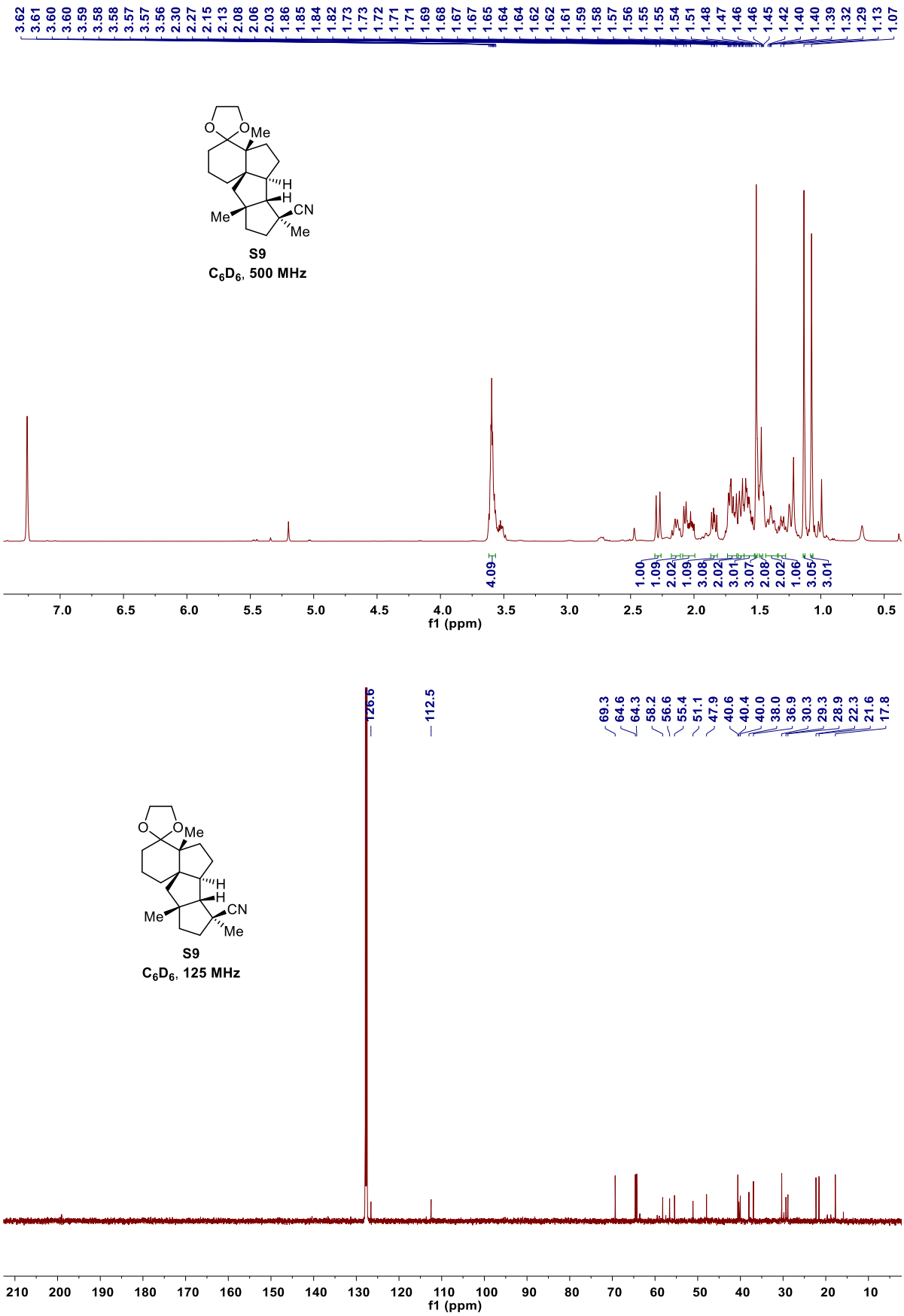
Supplementary Fig. S28. ^{1}H and ^{13}C NMR Spectra of 45



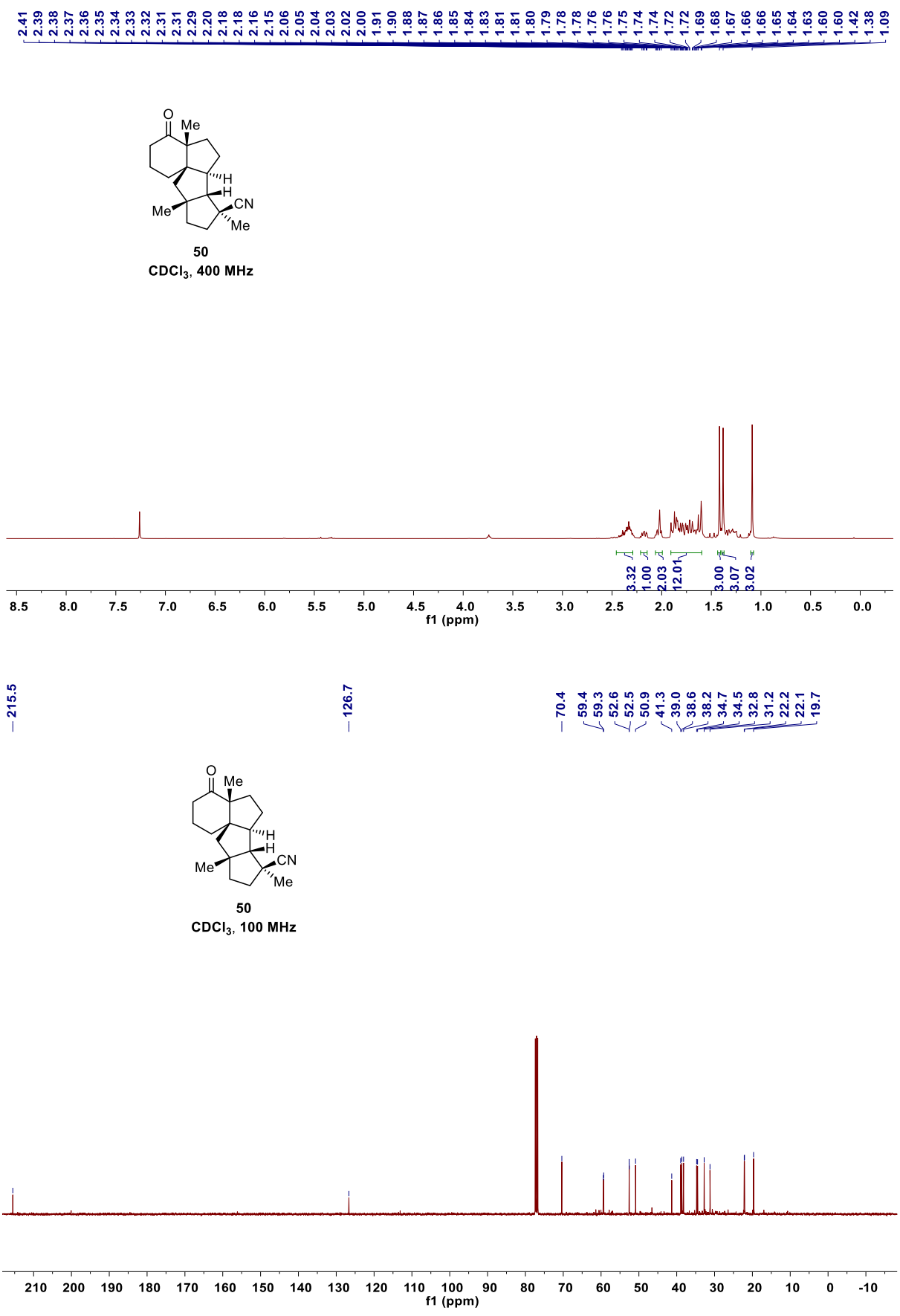
Supplementary Fig. S29. ^{1}H and ^{13}C NMR Spectra of 46



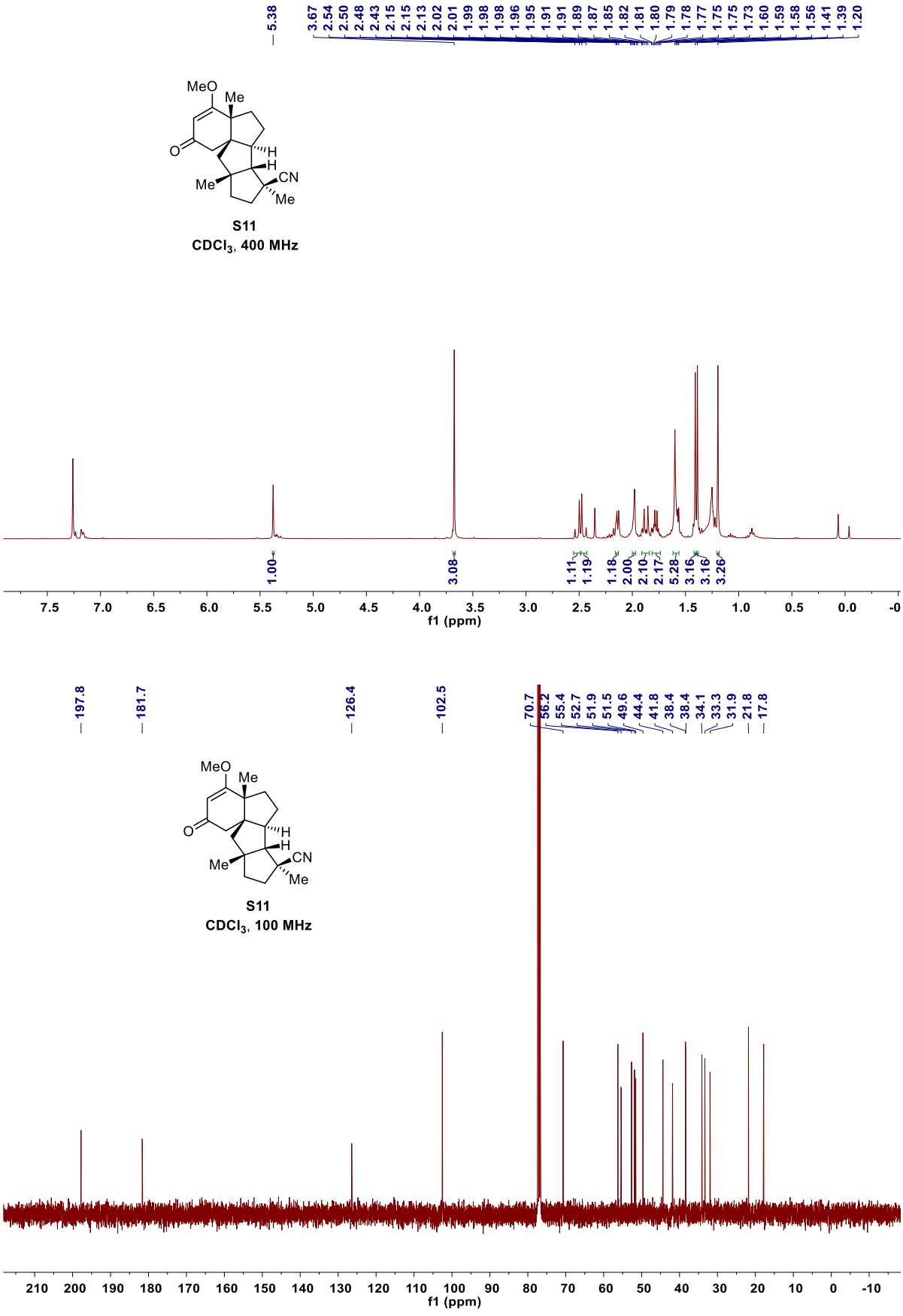
Supplementary Fig. S30. ^{1}H and ^{13}C NMR Spectra of S8



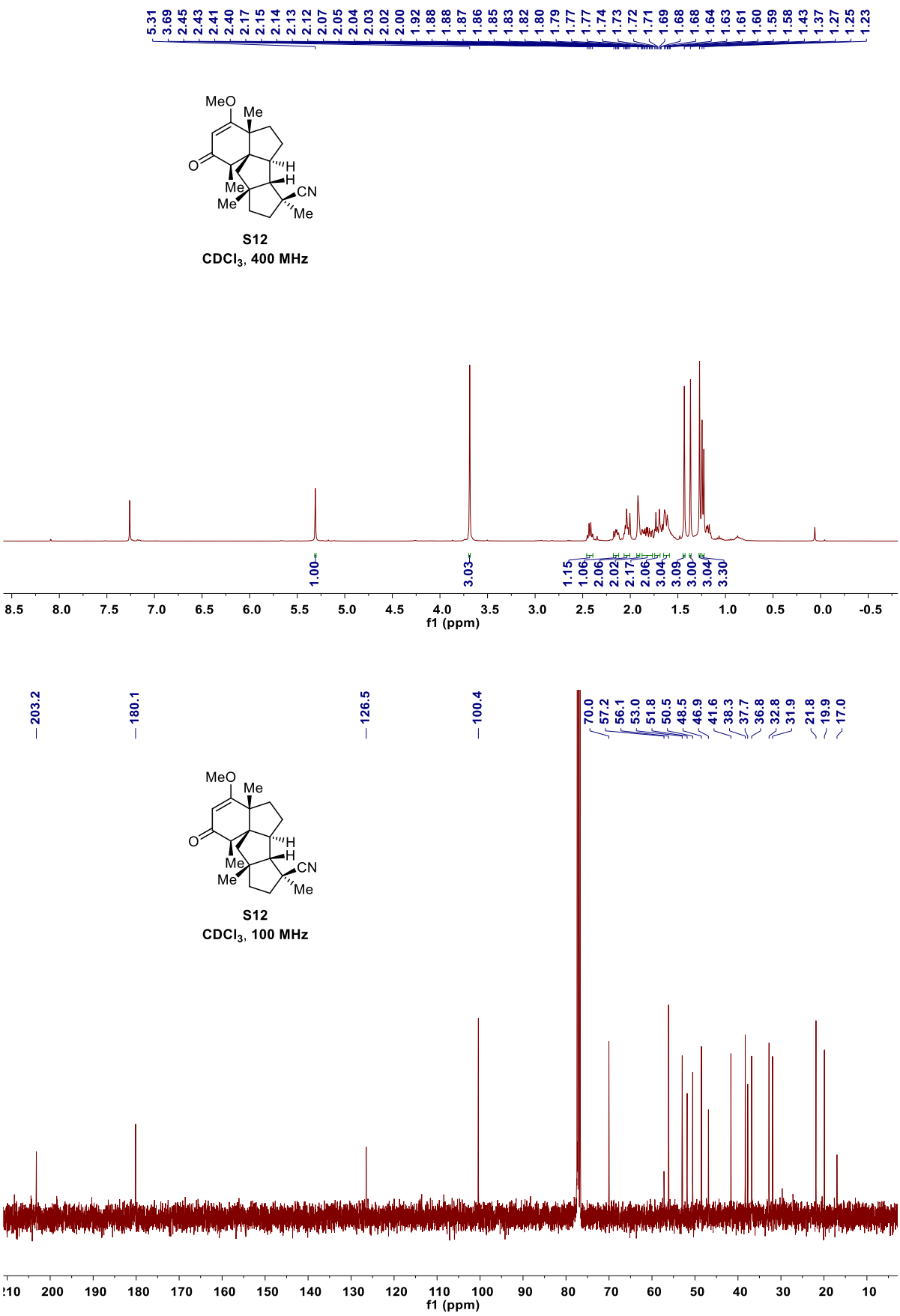
Supplementary Fig. S31. ^{1}H and ^{13}C NMR Spectra of S9



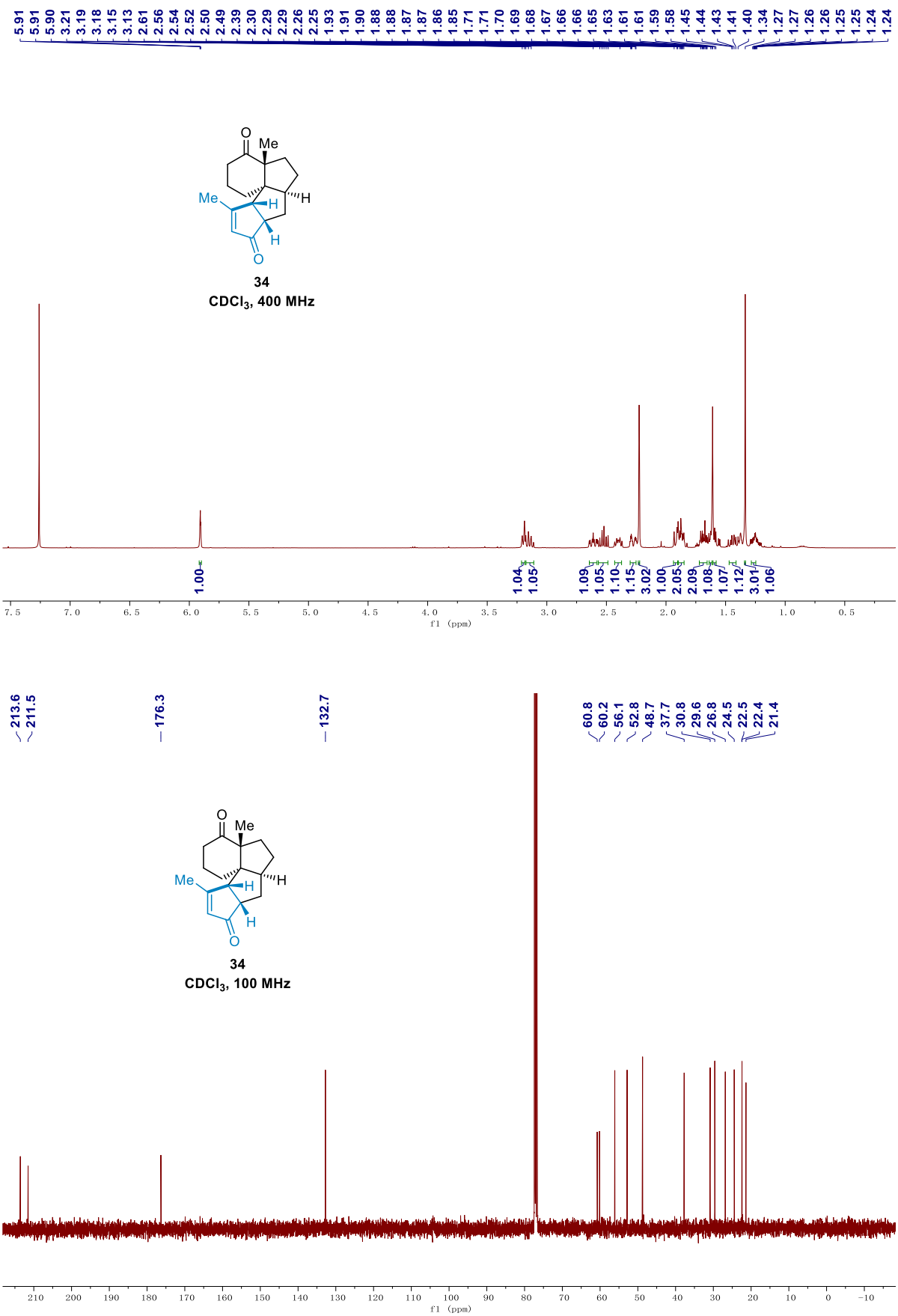
Supplementary Fig. S32. ^{1}H and ^{13}C NMR Spectra of 50



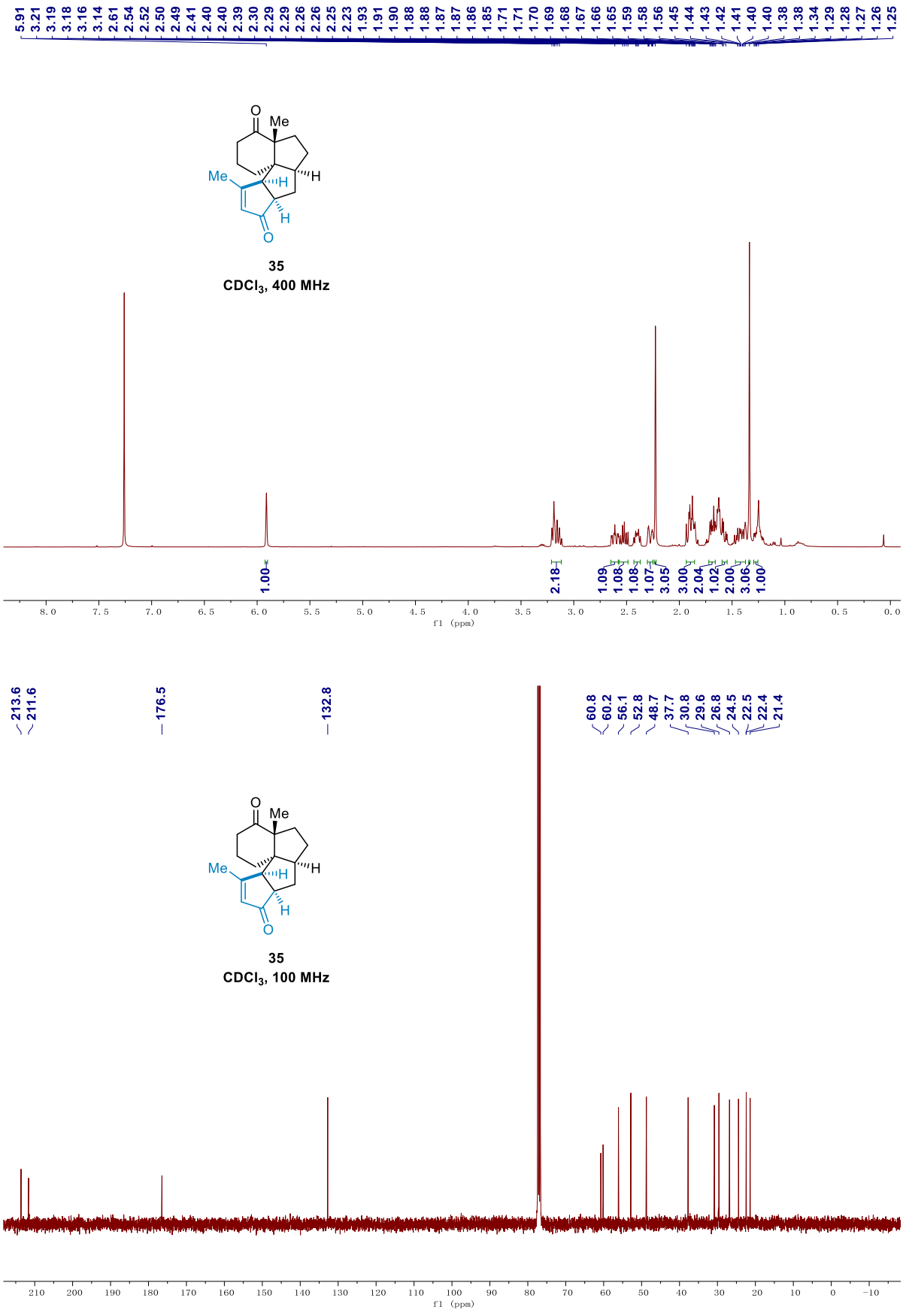
Supplementary Fig. S33. ^{1}H and ^{13}C NMR Spectra of S11



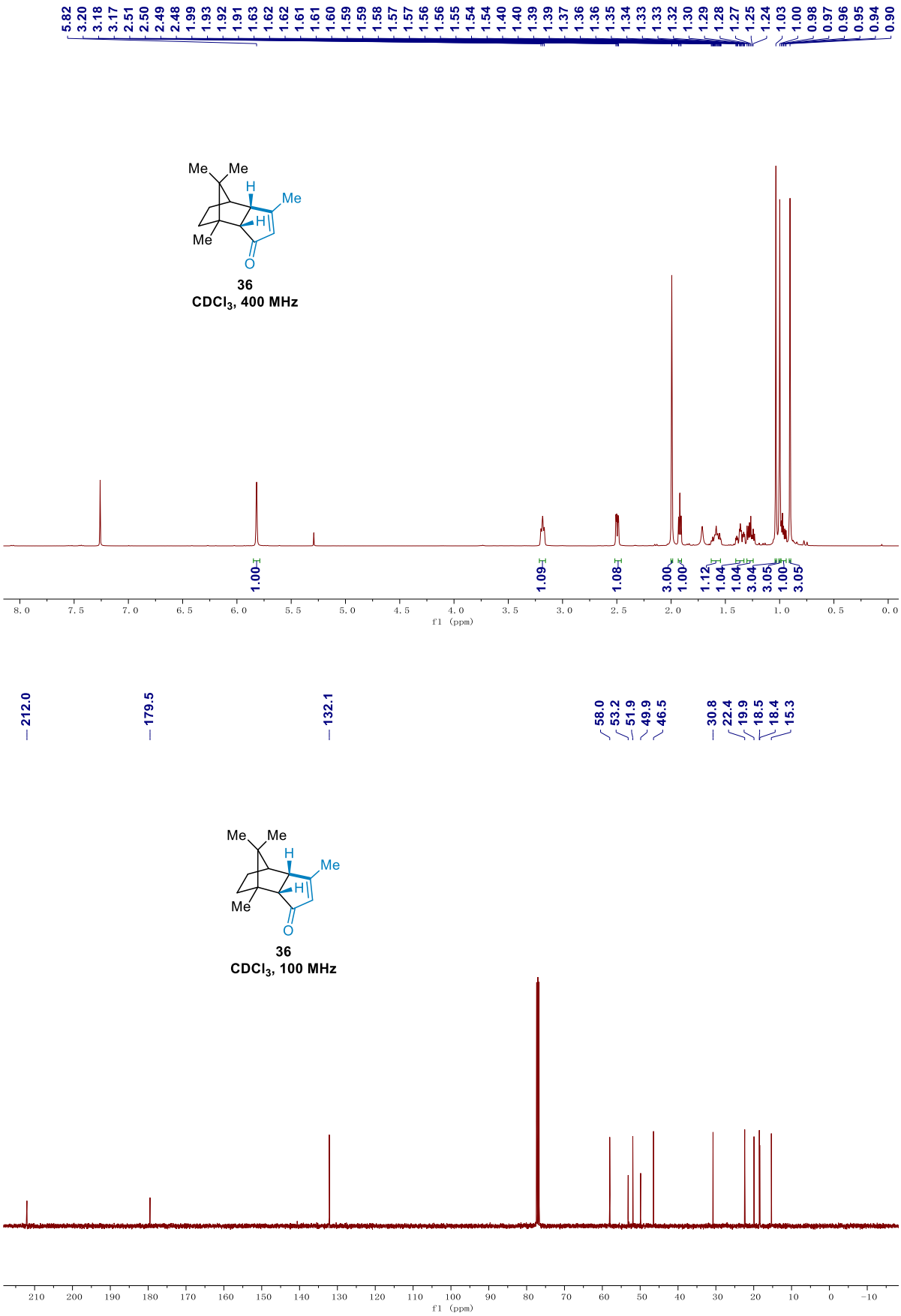
Supplementary Fig. S34. ^{1}H and ^{13}C NMR Spectra of S12



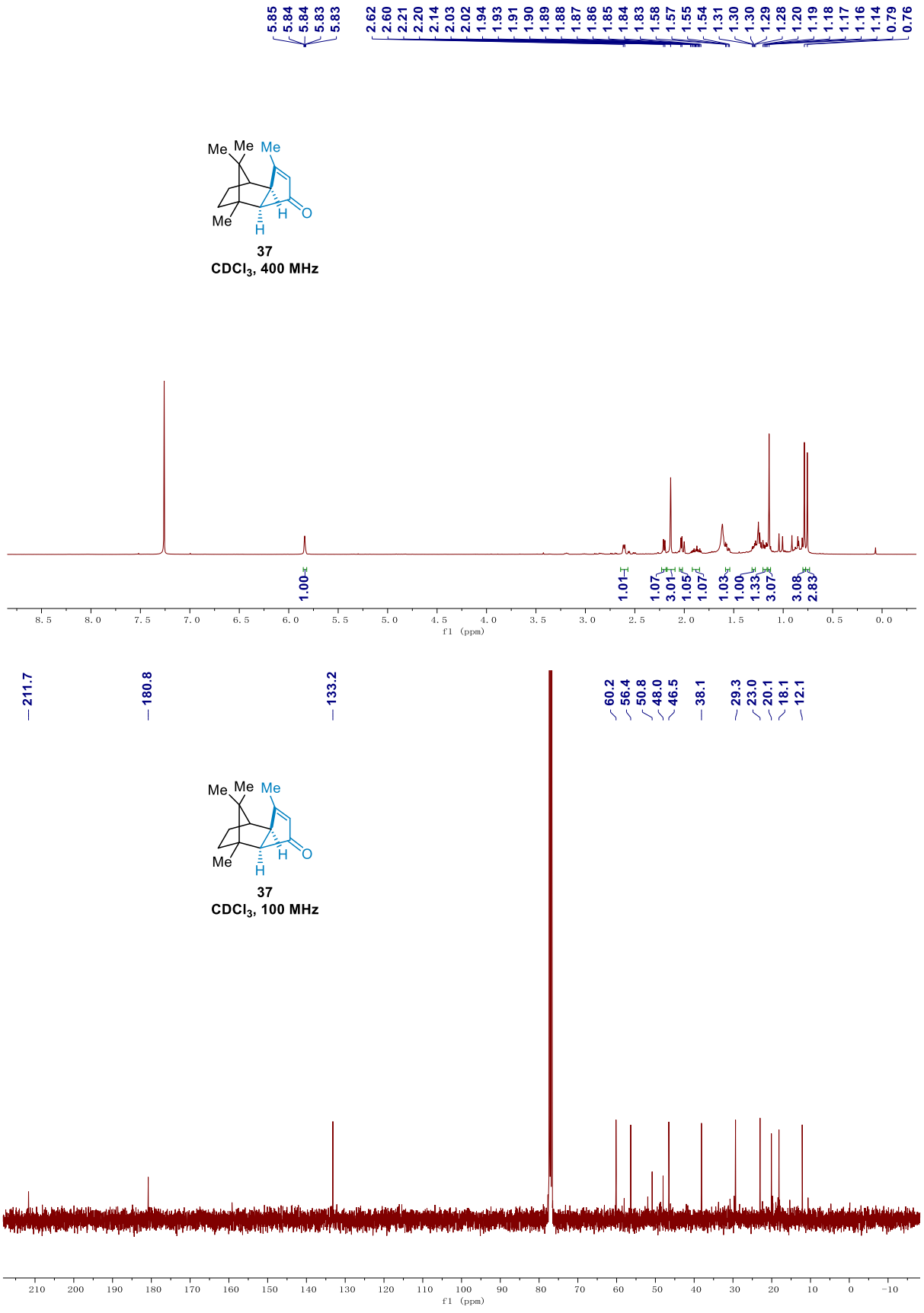
Supplementary Fig. S35. ^{1}H and ^{13}C NMR Spectra of 34



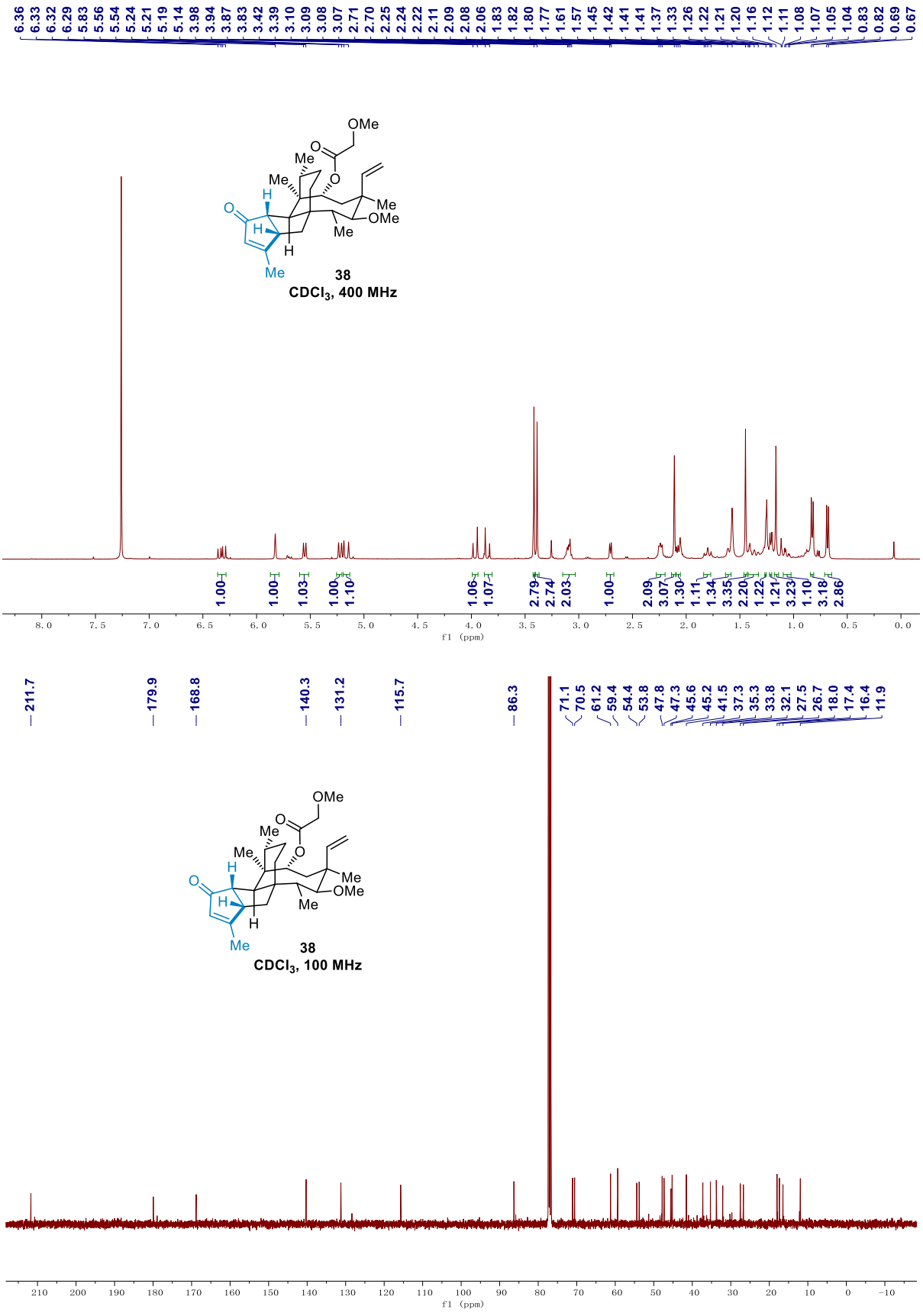
Supplementary Fig. S36. ^{1}H and ^{13}C NMR Spectra of 35



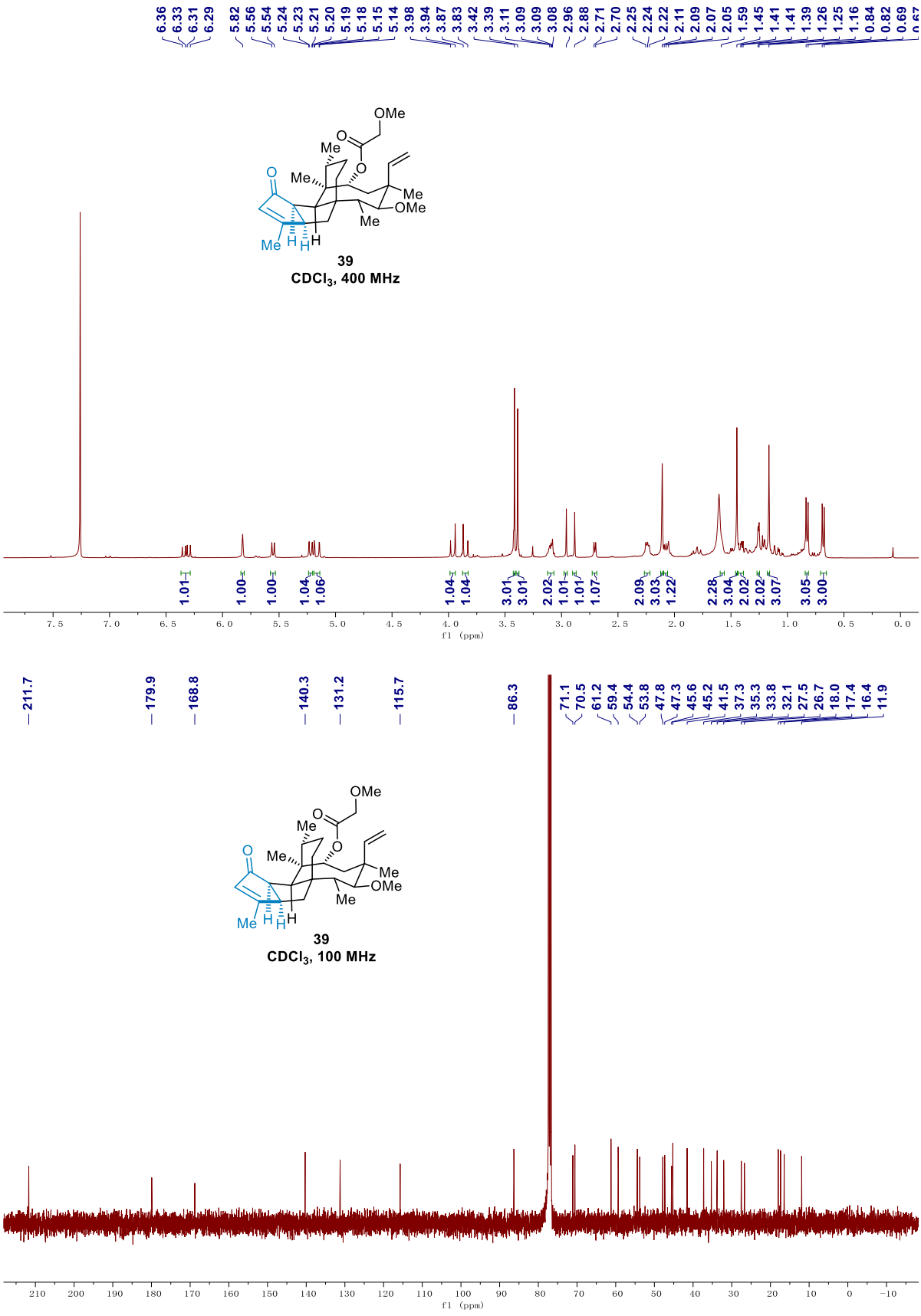
Supplementary Fig. S37. ^{1}H and ^{13}C NMR Spectra of 36



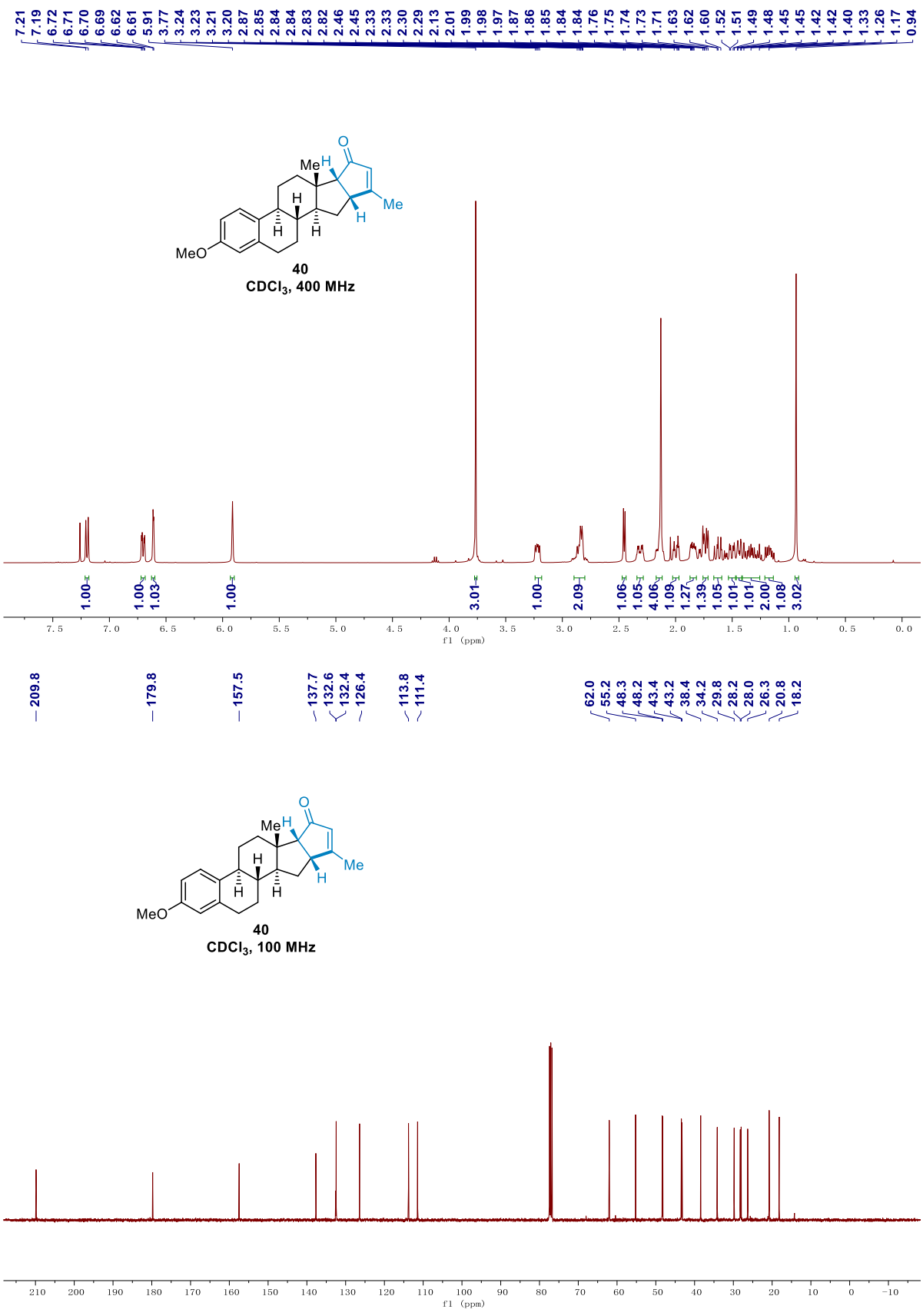
Supplementary Fig. S38. ^{1}H and ^{13}C NMR Spectra of 37



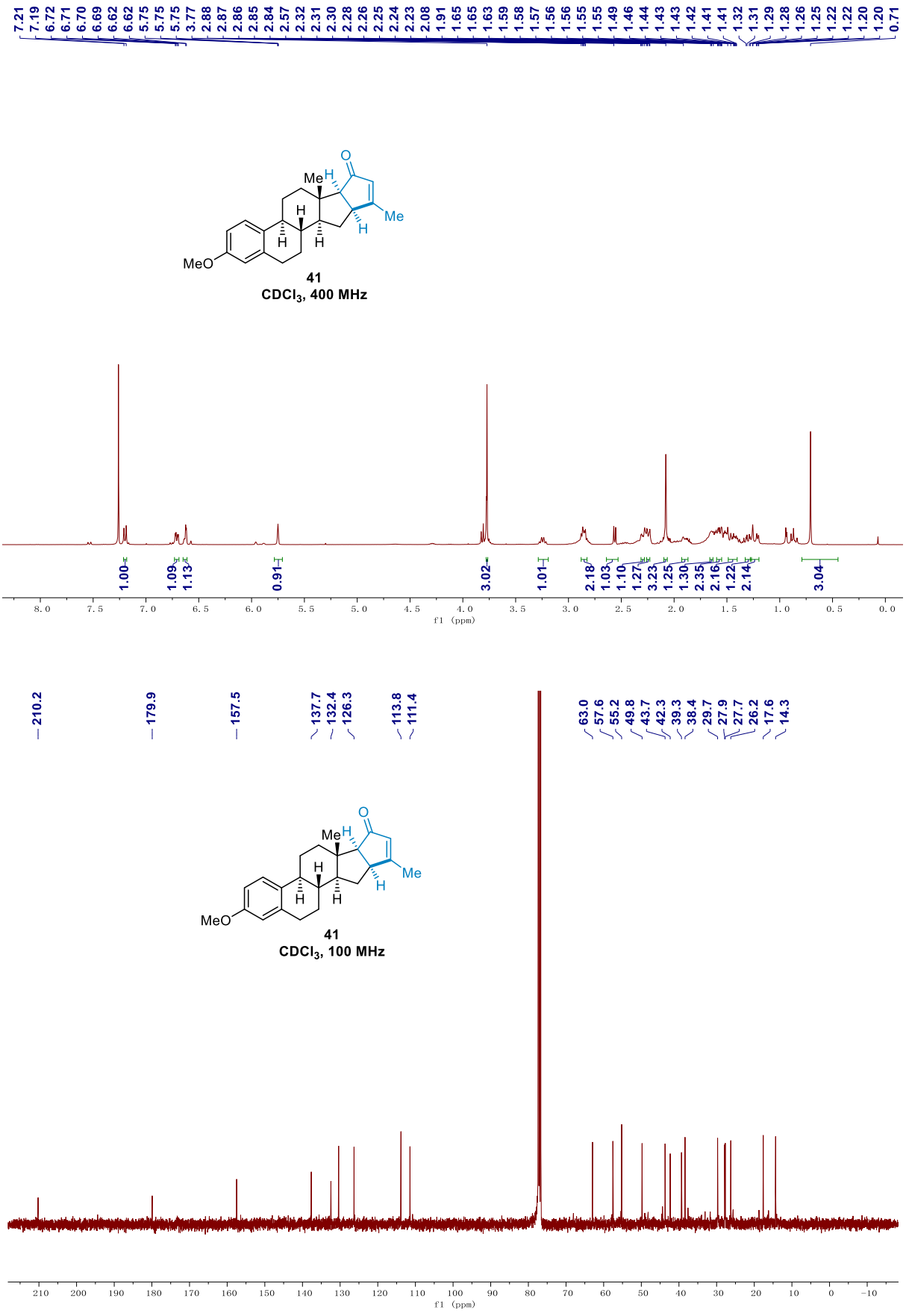
Supplementary Fig. S39. ^{1}H and ^{13}C NMR Spectra of 38



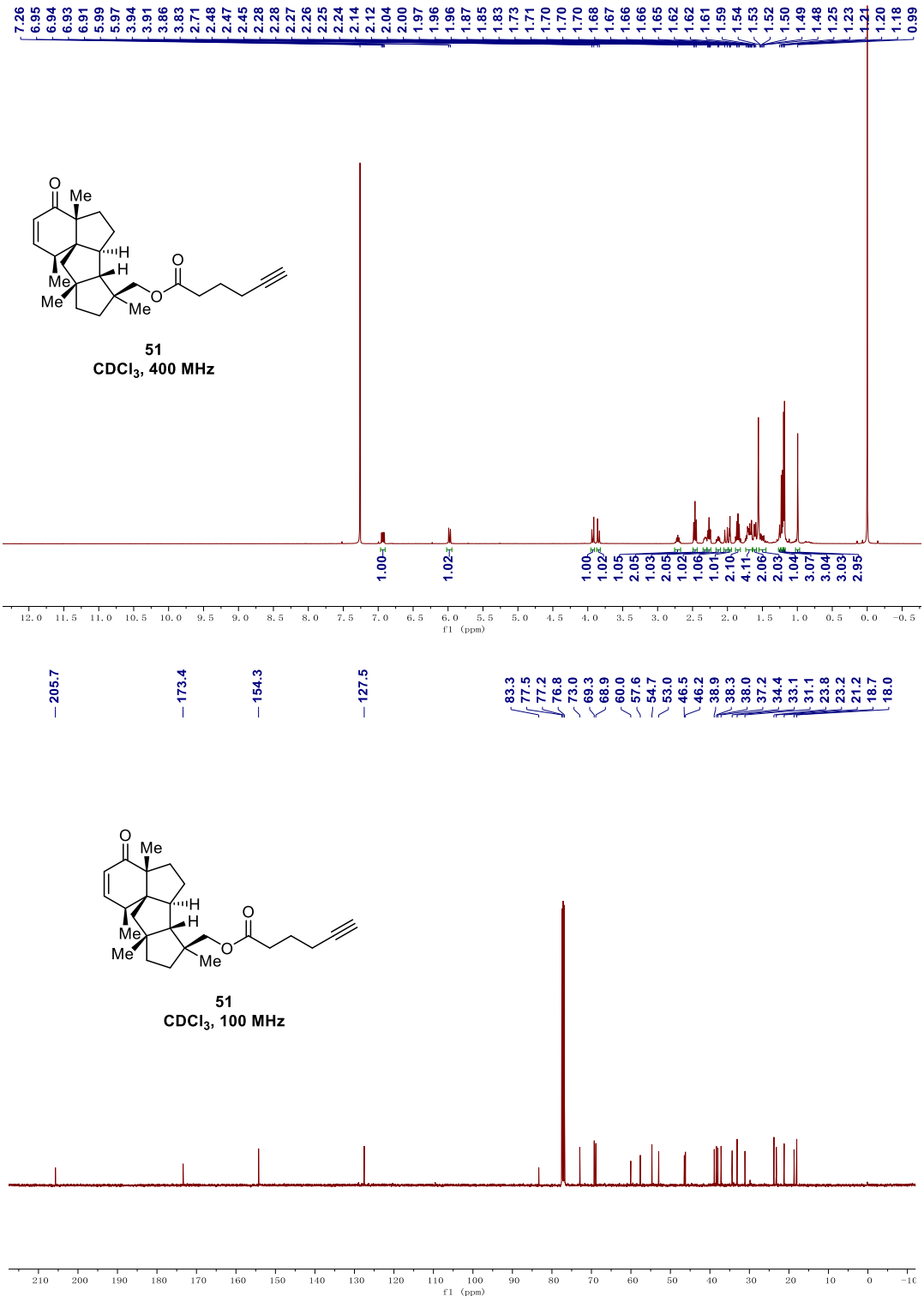
Supplementary Fig. S40. ^{1}H and ^{13}C NMR Spectra of 39



Supplementary Fig. S41. ^{1}H and ^{13}C NMR Spectra of 40



Supplementary Fig. S42. ^{1}H and ^{13}C NMR Spectra of 41



Supplementary Fig. S43. ^{1}H and ^{13}C NMR Spectra of 51

8. References

[1] Li, F.-L., Sun, W.-G., Zhang, S.-T., Gao, W.-X., Lin, S., Yang, B.-Y., Chai, C.-W., Li, H.-Q., Wang, J.-P., Hu, Z.-X. & Zhang, Y.-H. New Cyclopiane Diterpenes with Anti-inflammatory Activity from the Sea Sediment-Derived Fungus *Penicillium sp*. TJ403-2. *Chin. Chem. Lett*. **31**, 197–201 (2020).

[2] Du, L., Li, D.-H., Zhu, T.-J., Cai, S.-X., Wang, F.-P., Xiao, X. & Gu, Q.-Q. New Alkaloids and Diterpenes from a Deep Ocean Sediment Derived Fungus *Penicillium sp*. *Tetrahedron* **65**, 1033–1039 (2009).

[3] Hu, P.-F., Chi, H.-M., DeBacker, K. C., Gong, X., Keim, J. H., Hsu, I. T. & Snyder, S. A. Quaternary-Centre-Guided Synthesis of Complex Polycyclic Terpenes. *Nature* **569**, 703–707 (2019).

[4] Niu, S.-W., Fan, Z.-W., Tang, X.-X., Liu, Q.-M., Shao, Z.-Z., Liu, G.-M. & Yang, X-W. Cyclopiane-type Diterpenes from The Deep-Sea-Derived Fungus *Penicillium commune* MCCC 3A00940. *Tetrahedron Lett*. **59**, 375–378 (2018).

[5] Ling, T.; Chowdhury, C.; Kramer, B.; Vong, B. G.; Palladino, M. A.; Theodorakis, E. A. Enantioselective Synthesis of the Antiinflammatory Agent (–)-Acanthoic Acid. *J. Org. Chem*. **66**, 8843-8853 (2001).