

Biomimetic Total Synthesis of (±)-Doitunggarcinone A and (+)-Garcibracteaton

Henry P. Pepper,[†] Stephen J. Tulip,[†] Yuji Nakano[‡] and Jonathan H. George^{*,†}

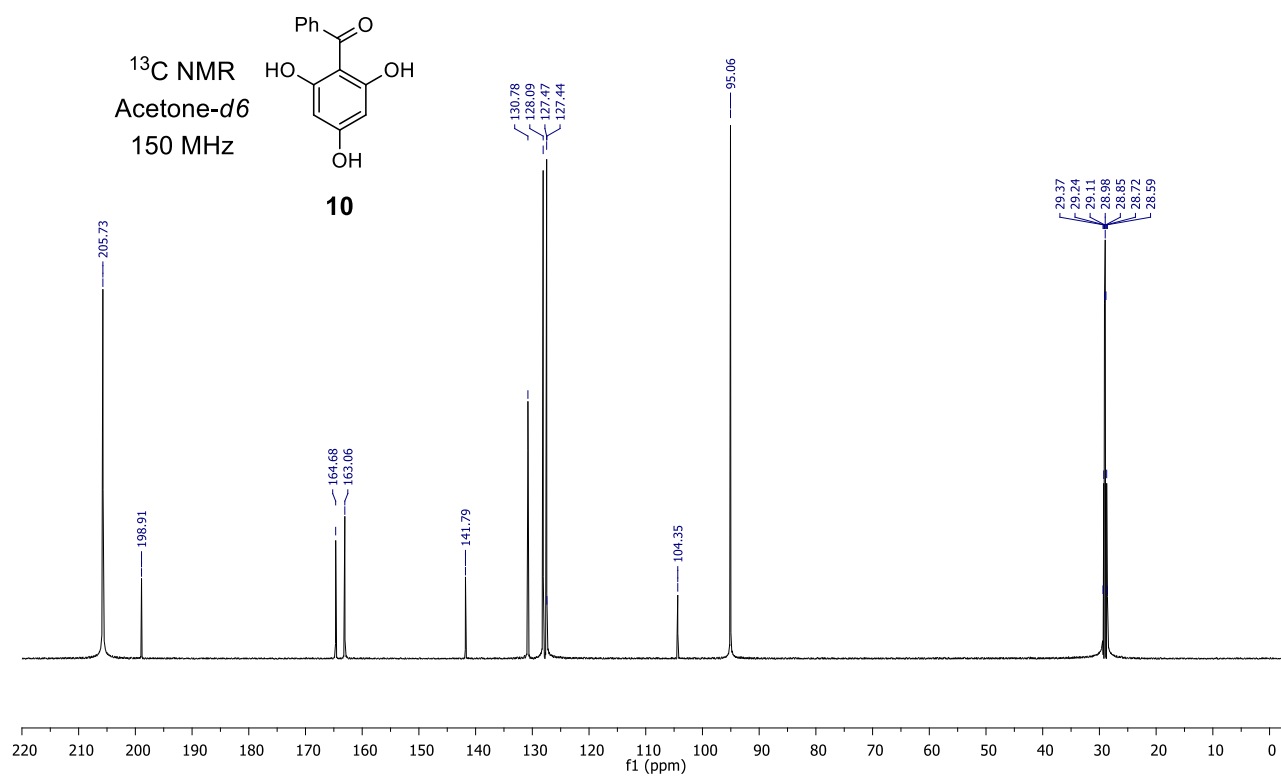
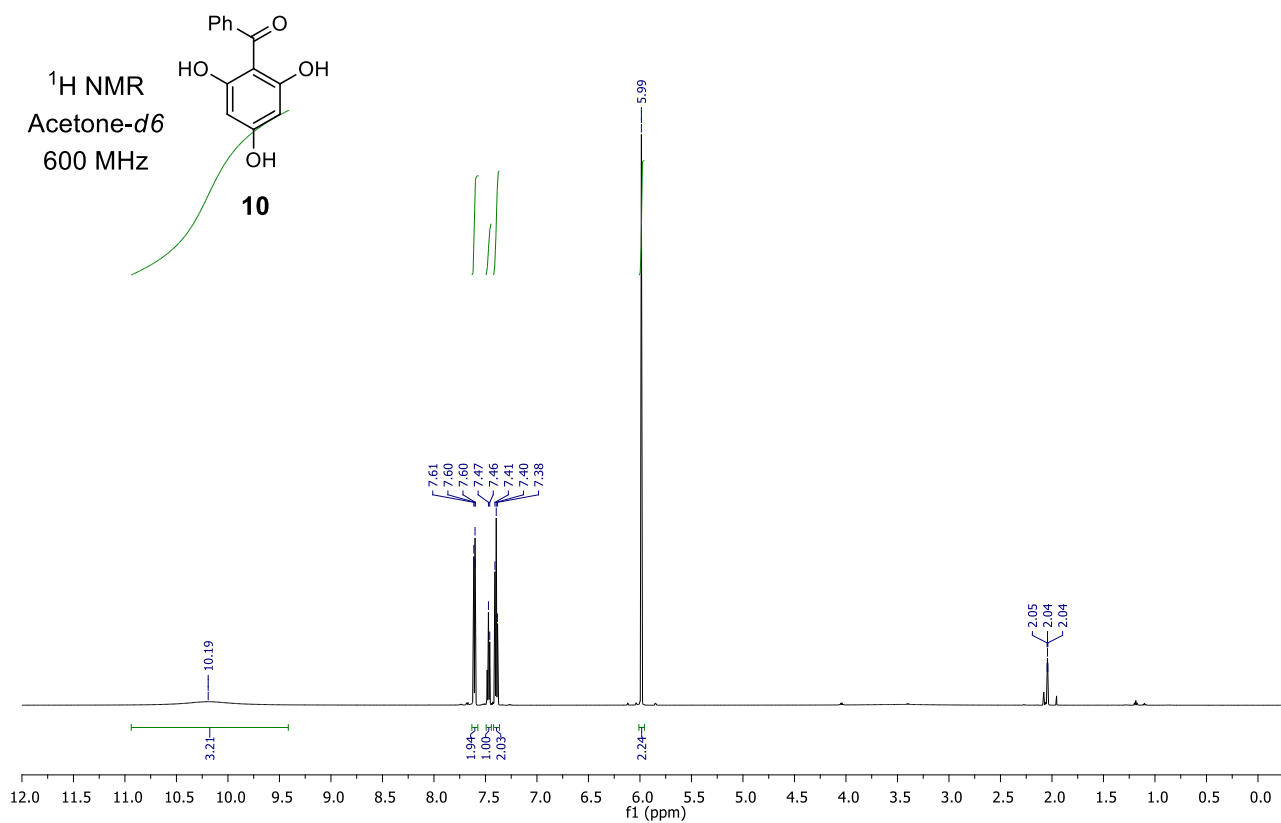
[†]School of Chemistry & Physics, University of Adelaide, Adelaide 5005, South Australia, Australia.

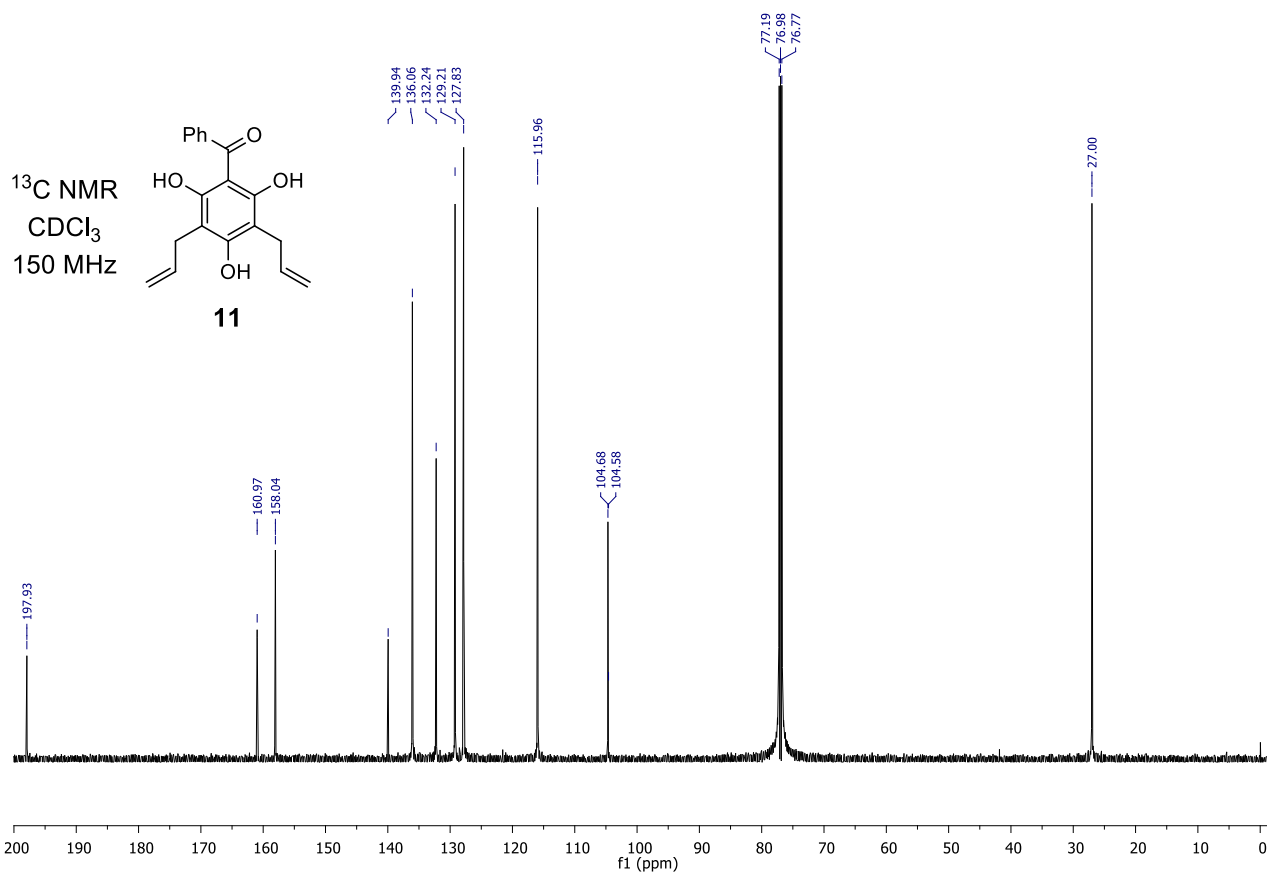
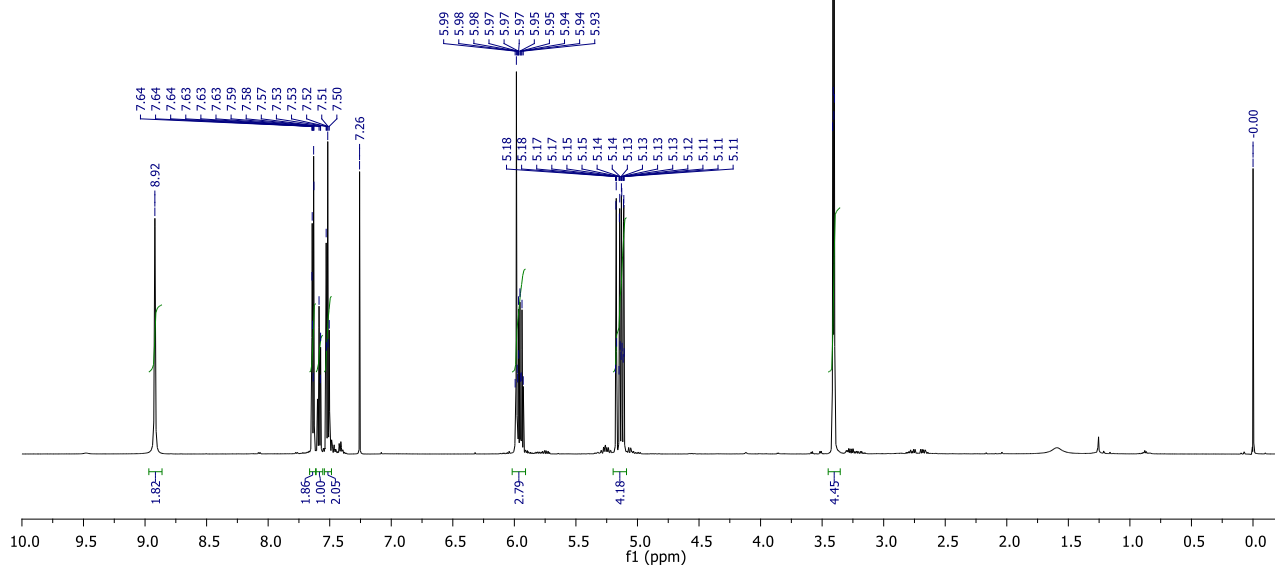
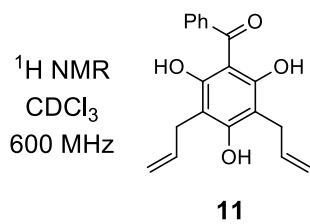
[‡]School of Chemistry, Monash University, Clayton 3800, Victoria, Australia.

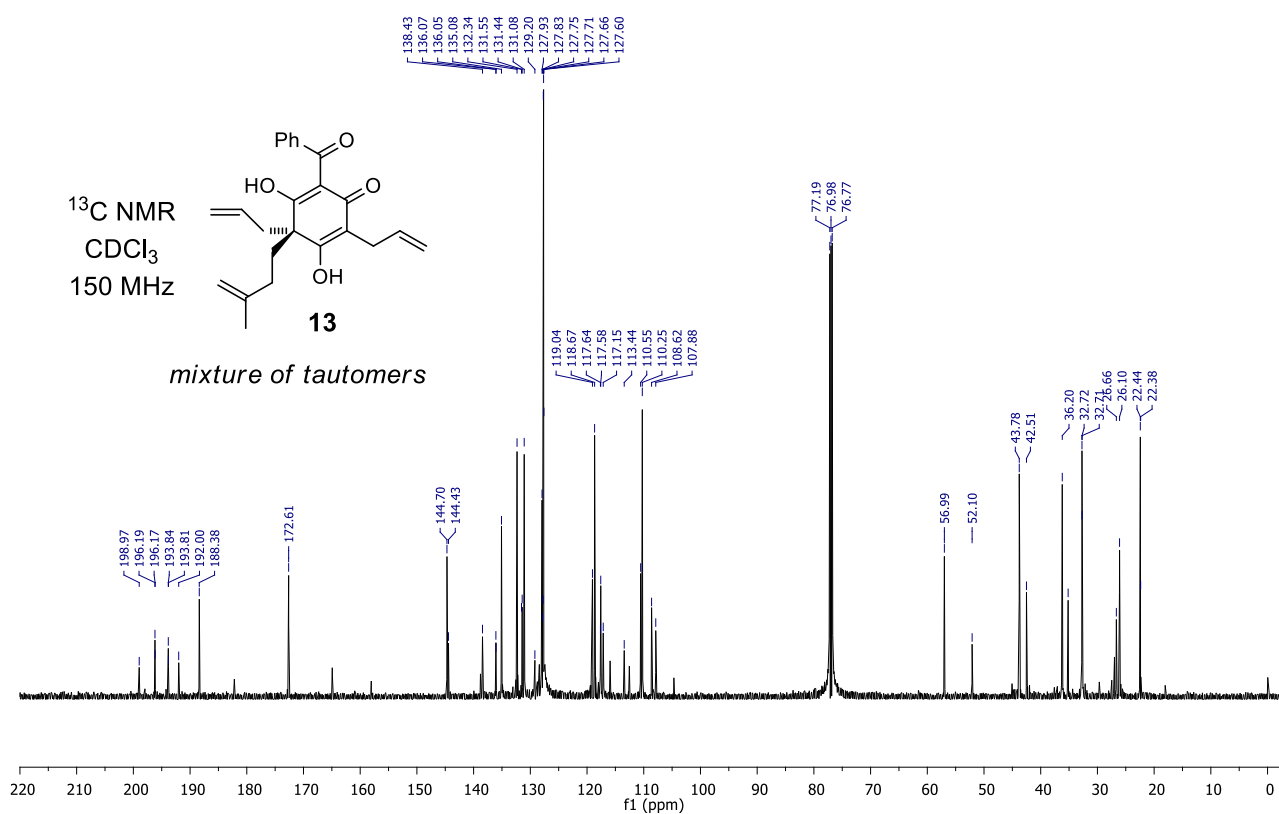
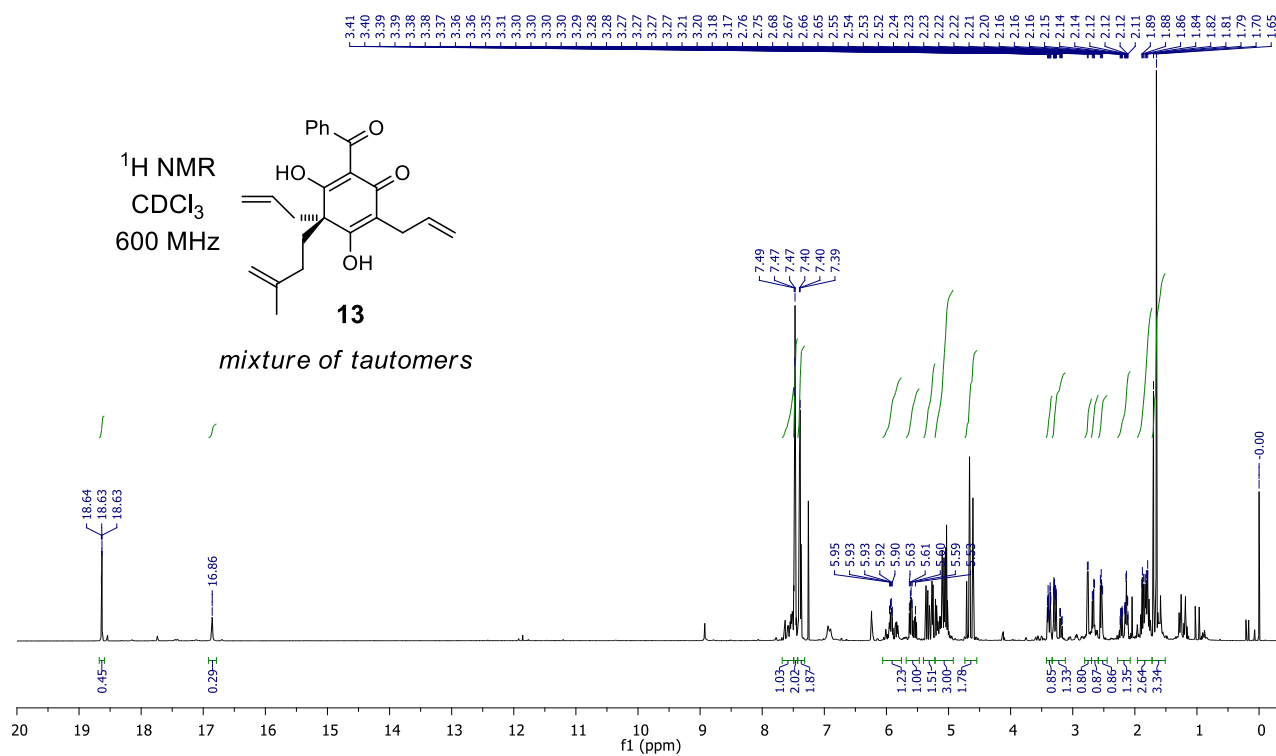
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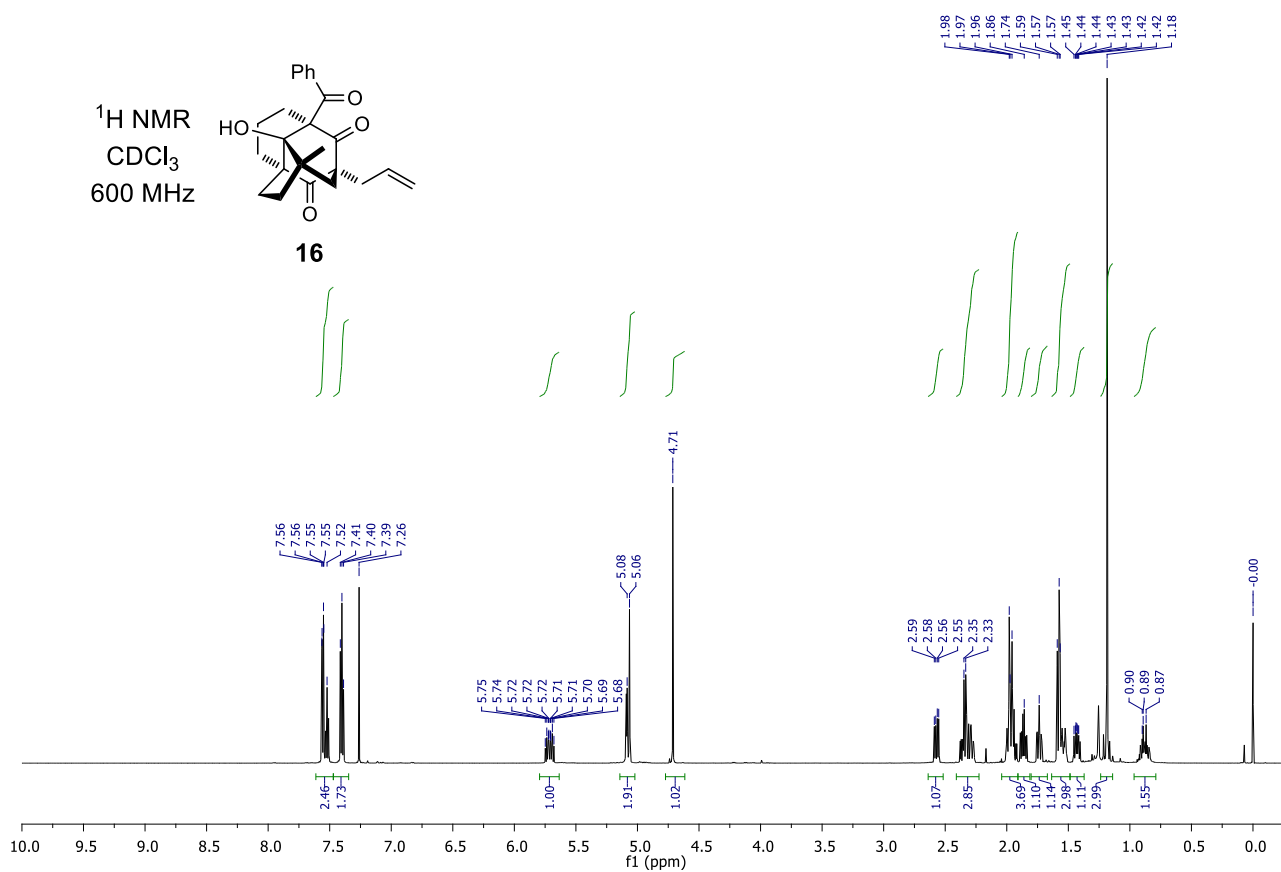
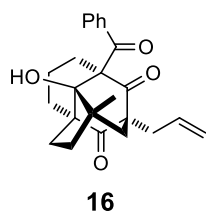
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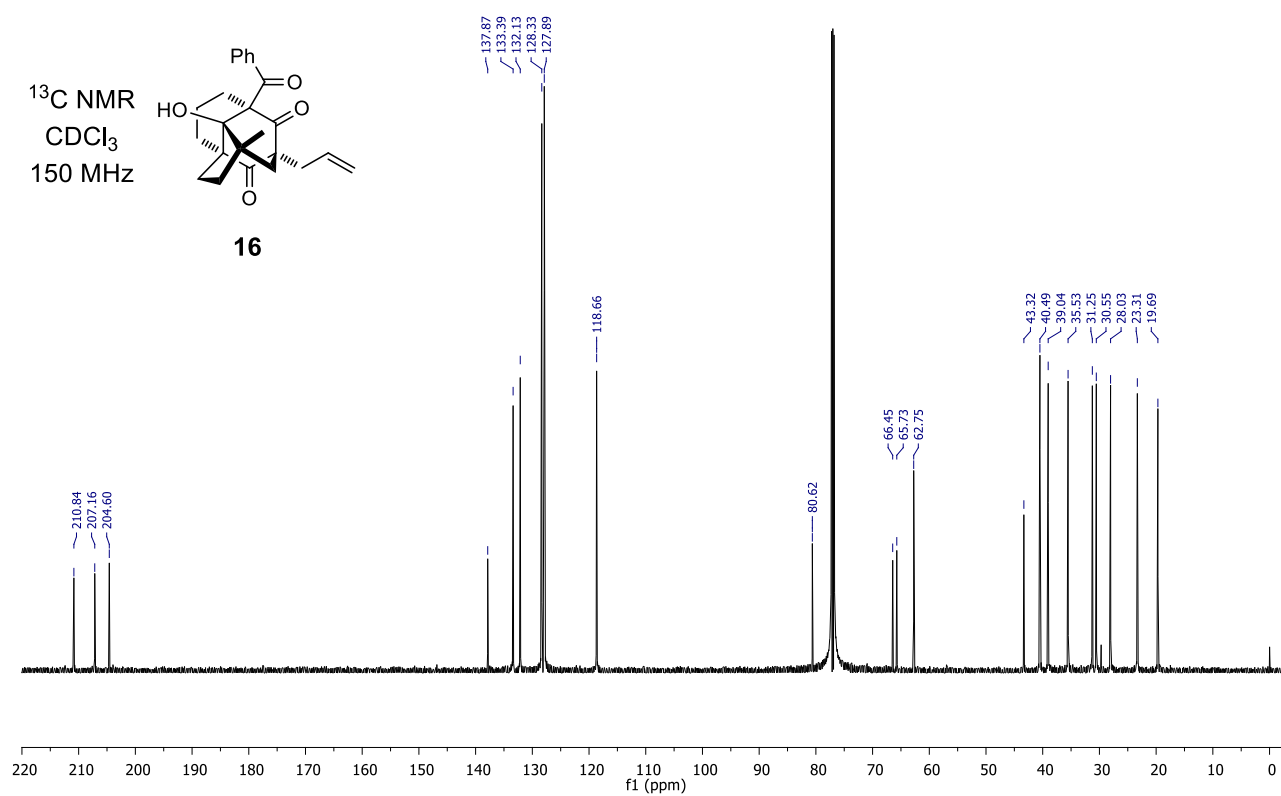
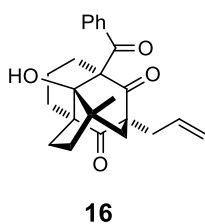


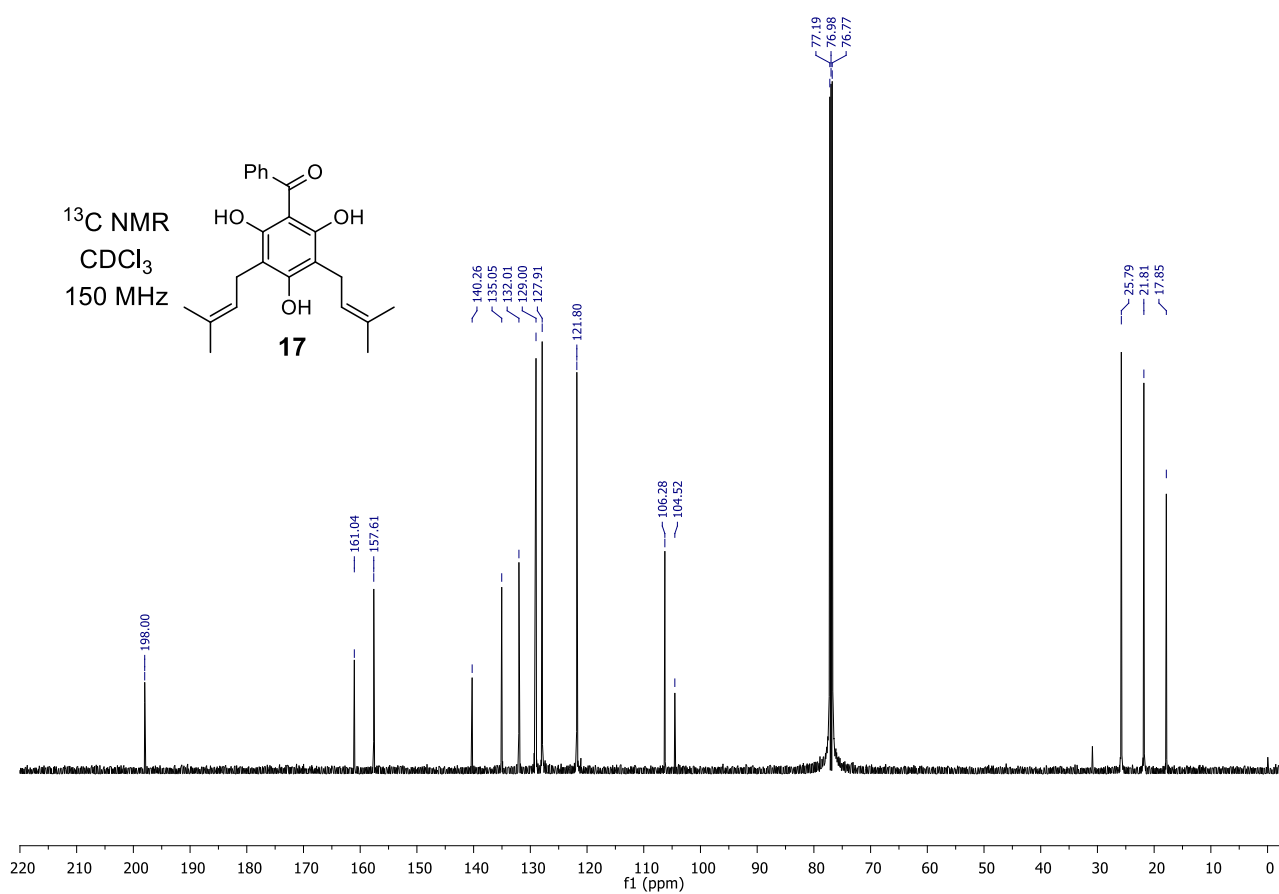
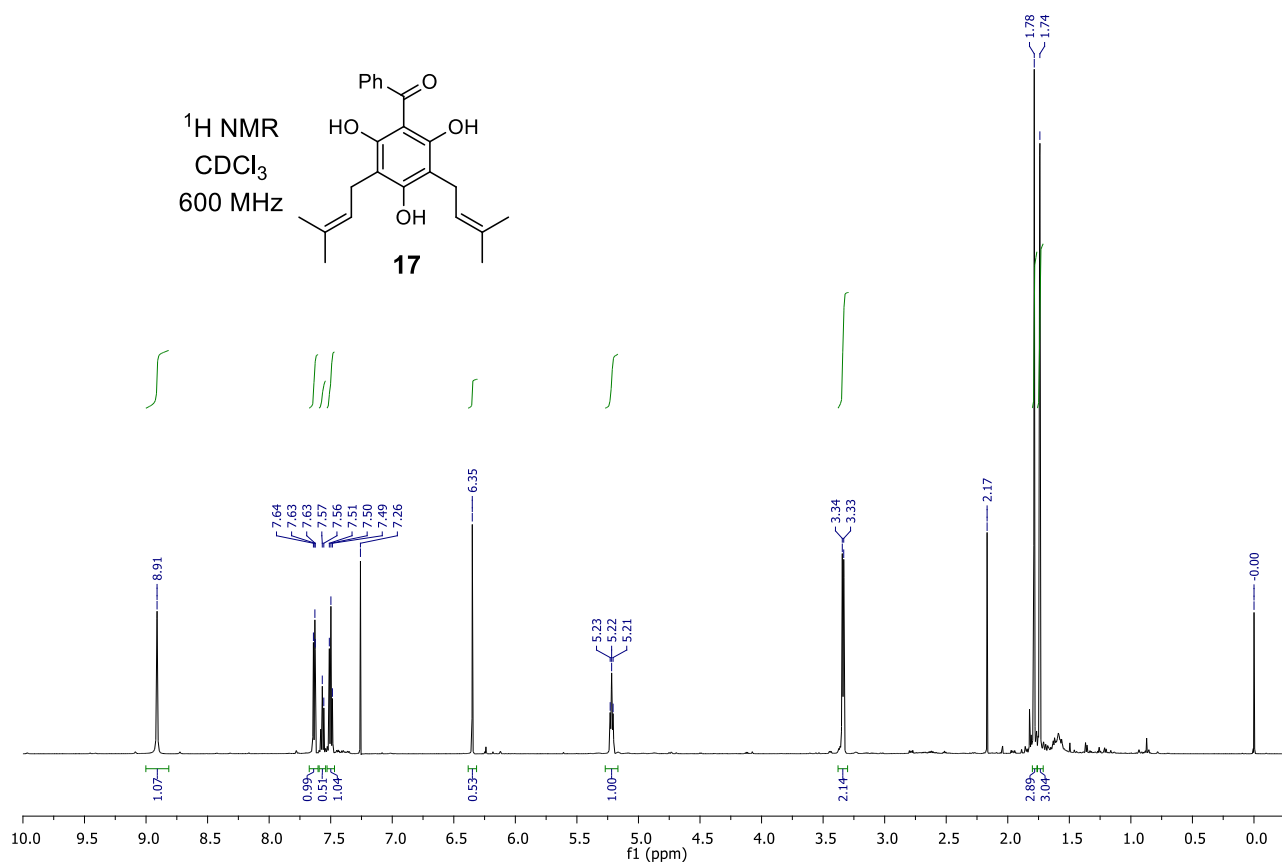


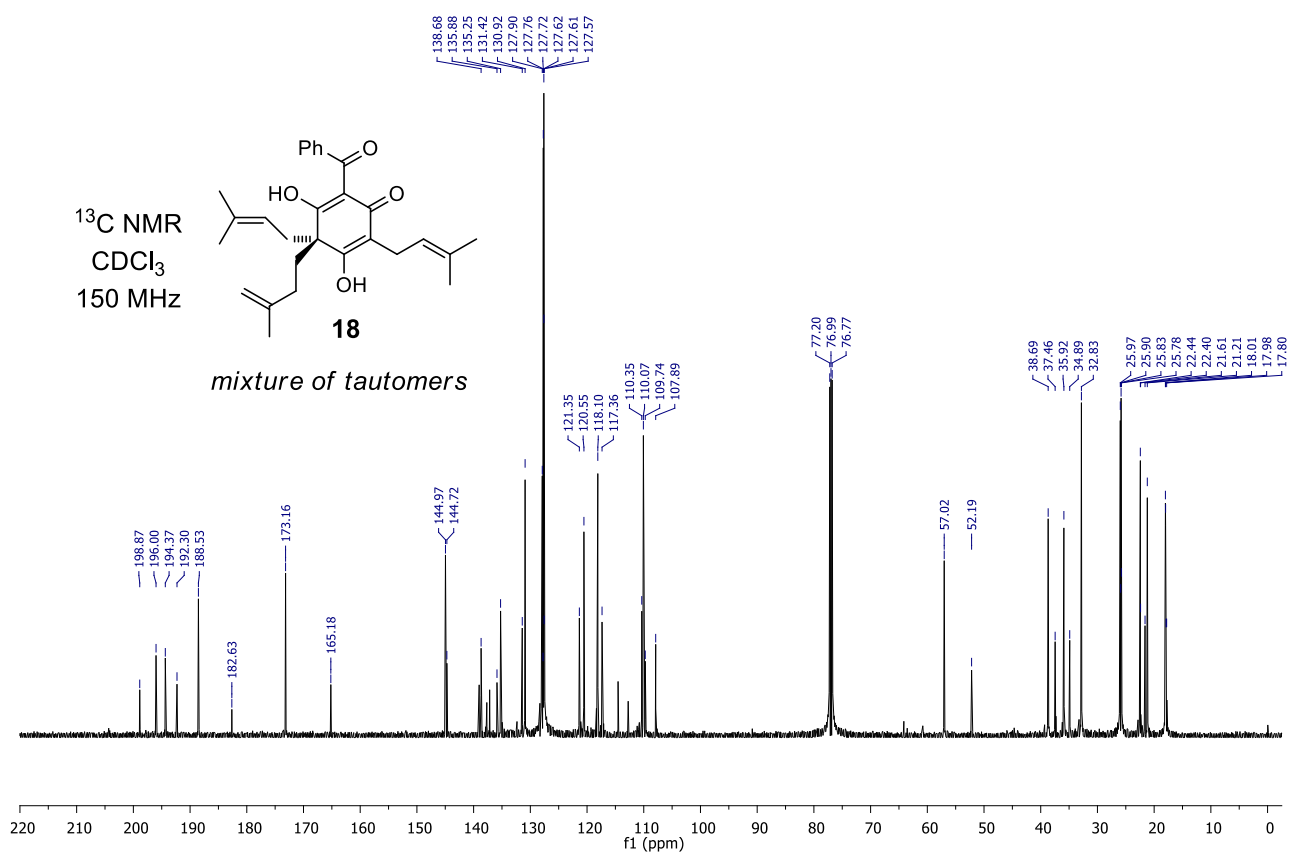
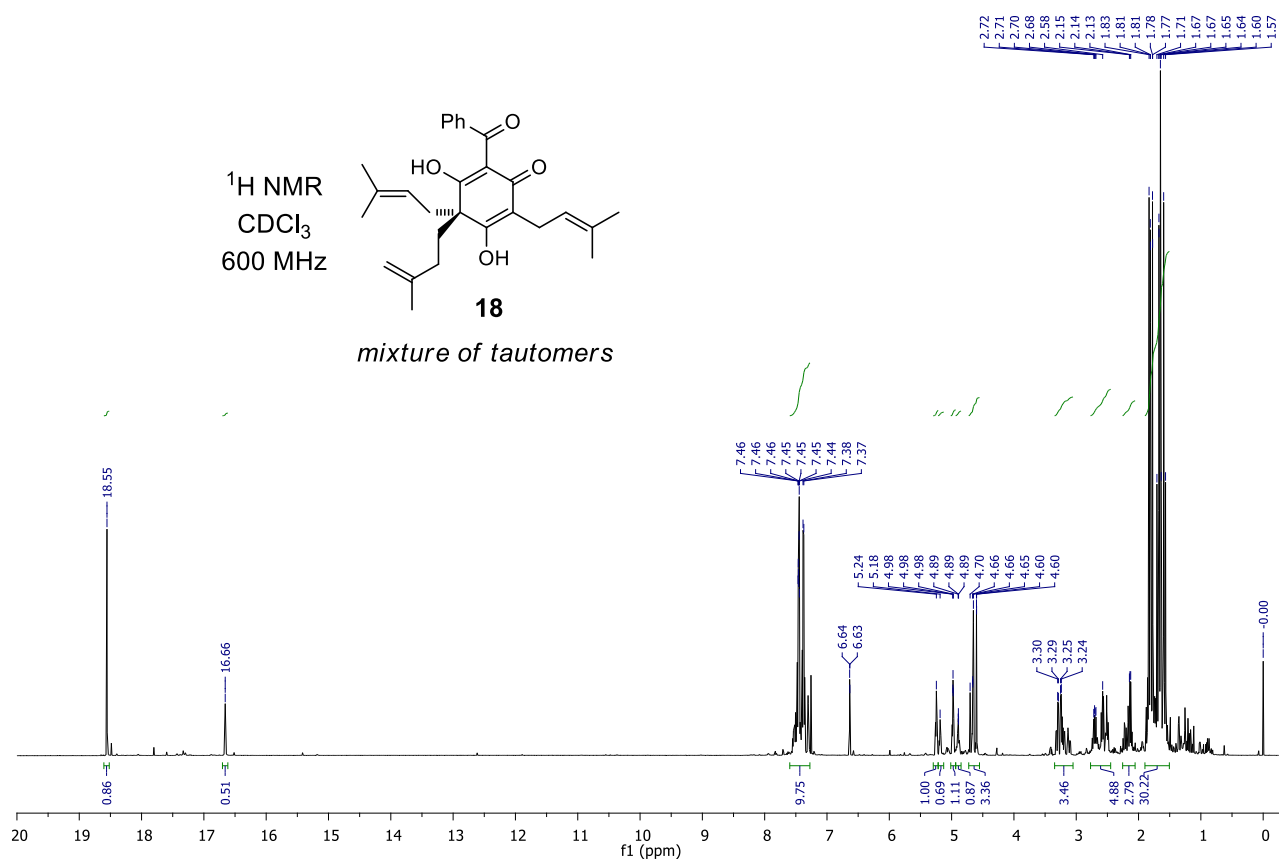
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 CDCl_3
 600 MHz

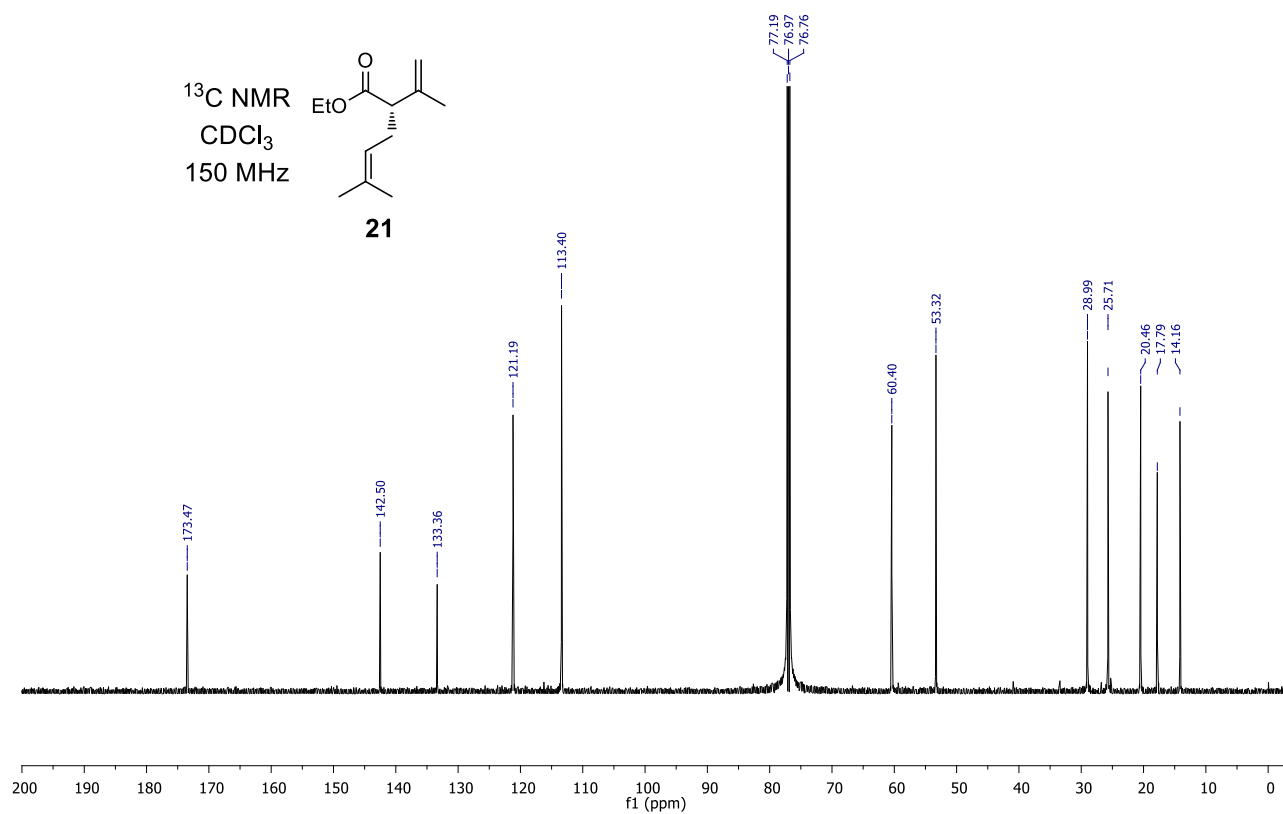
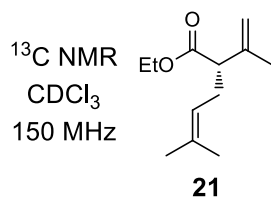
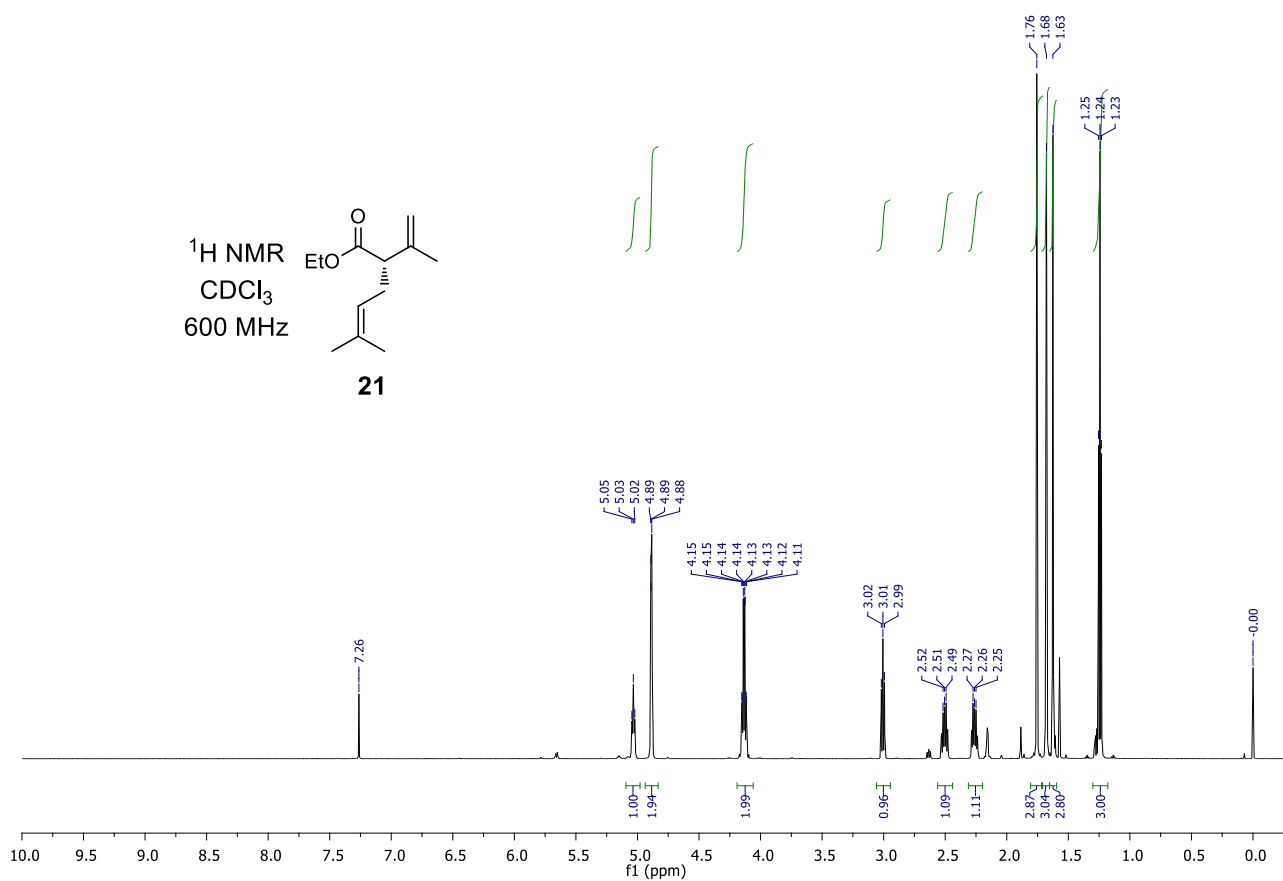
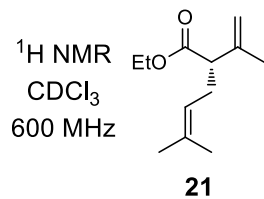


^{13}C NMR
 CDCl_3
 150 MHz

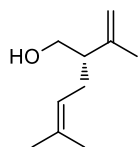




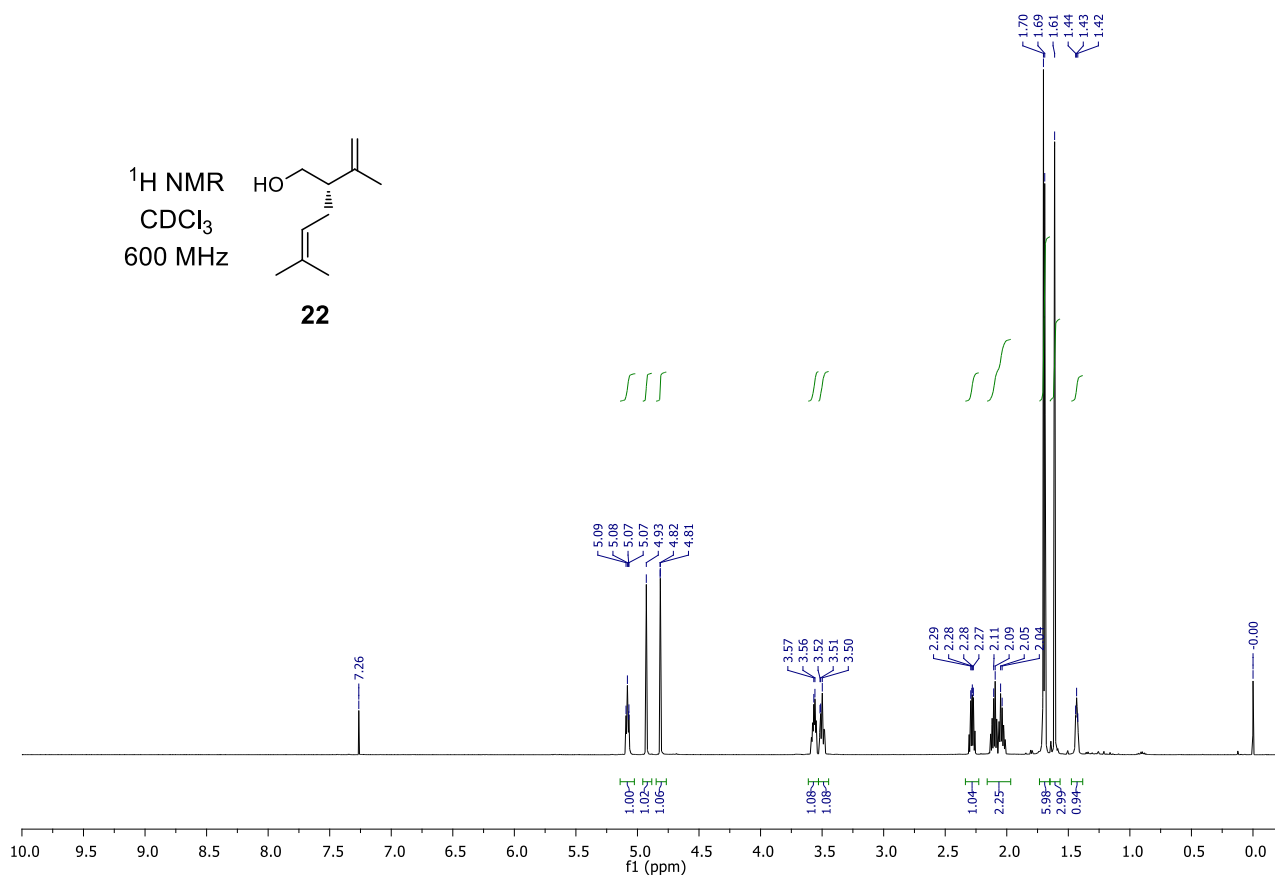




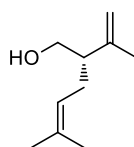
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CDCl₃
600 MHz



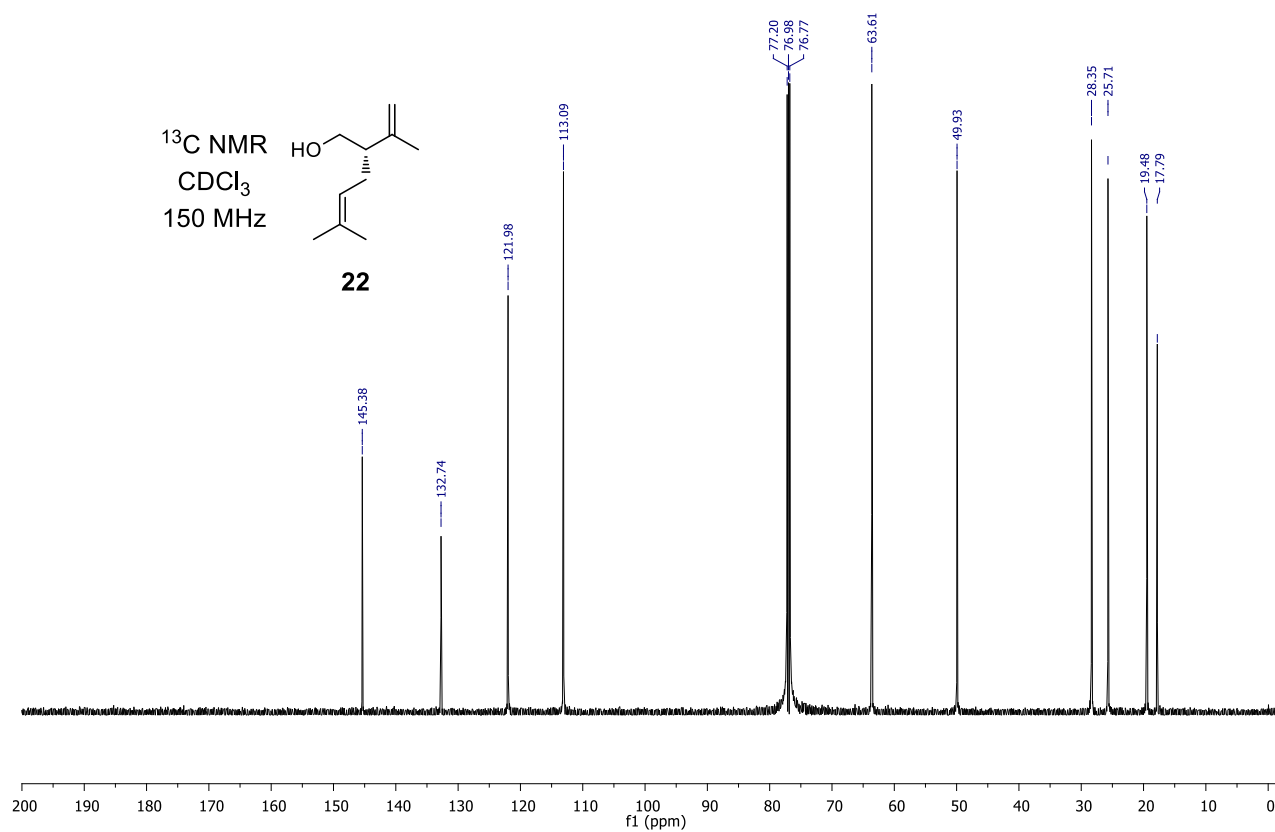
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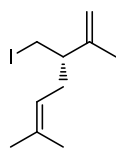
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150 MHz



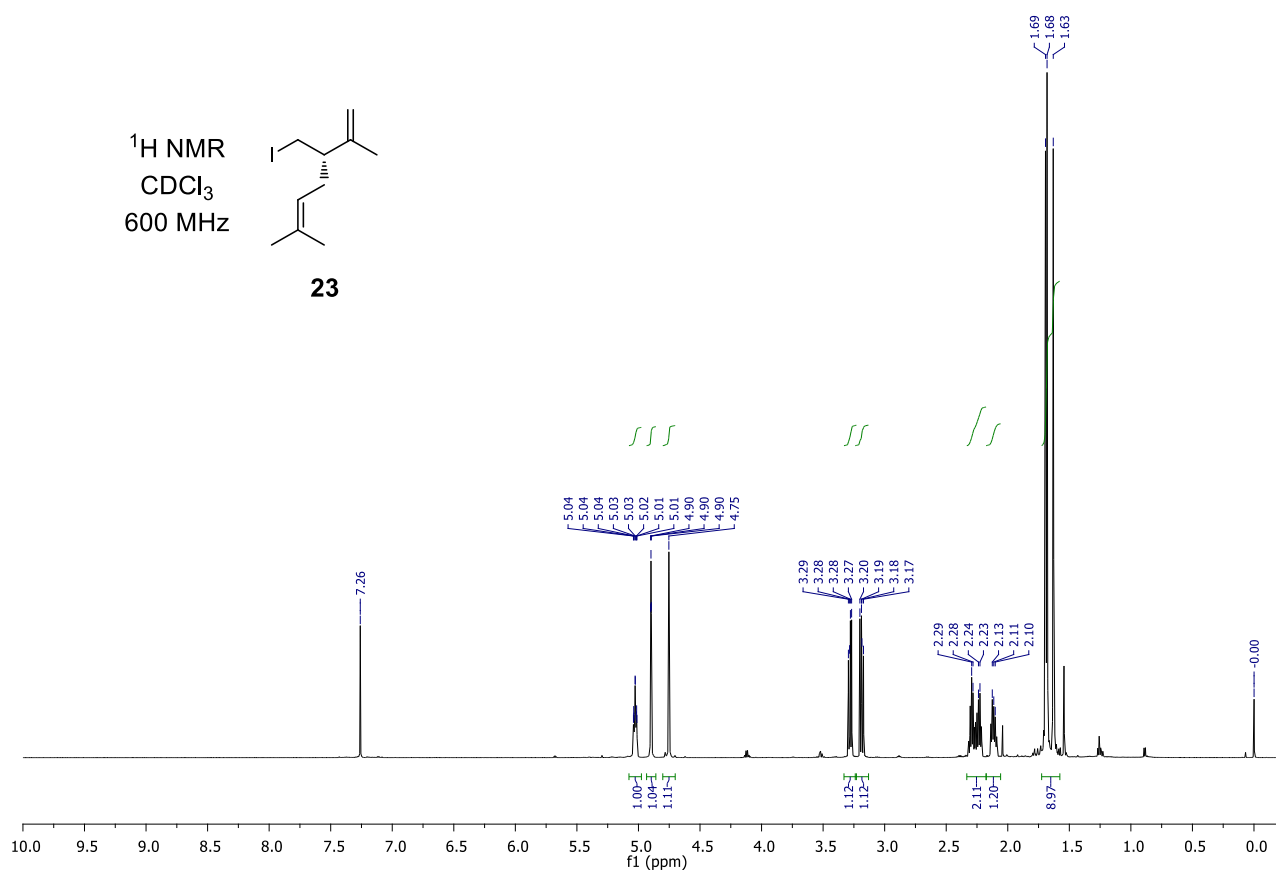
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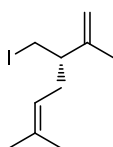
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 CDCl_3
 600 MHz



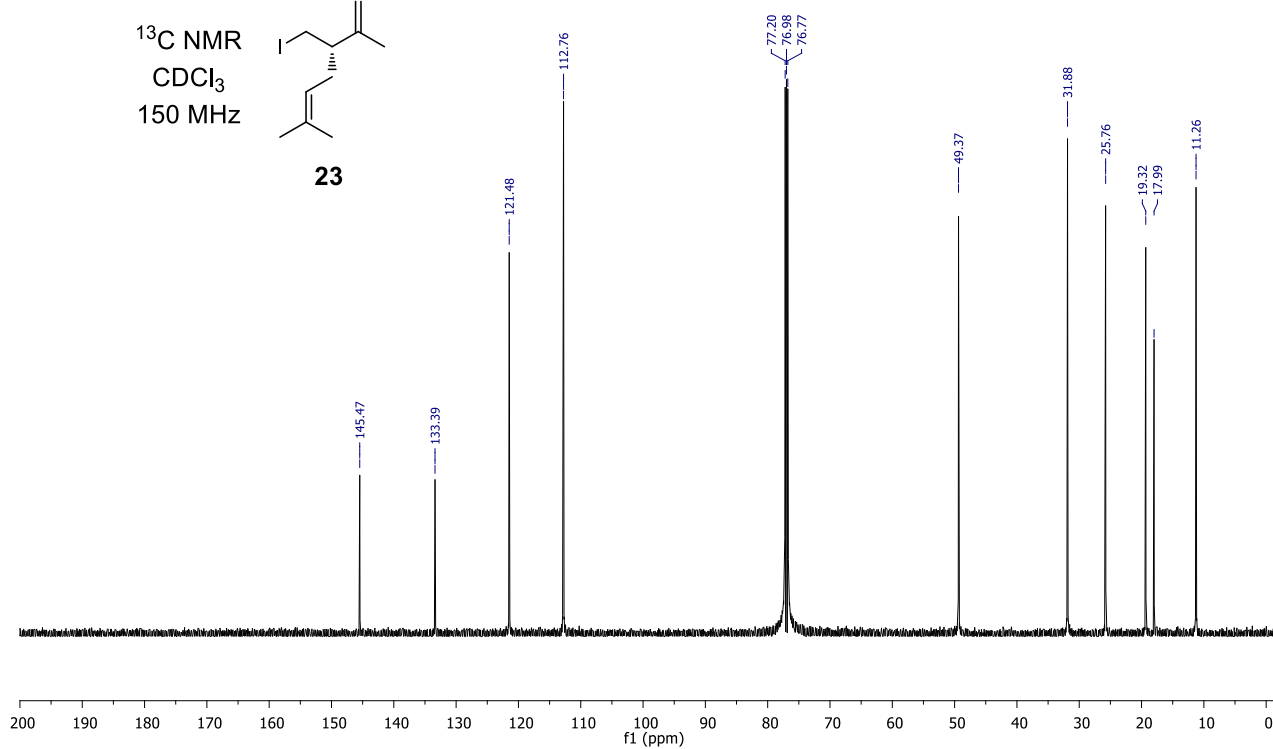
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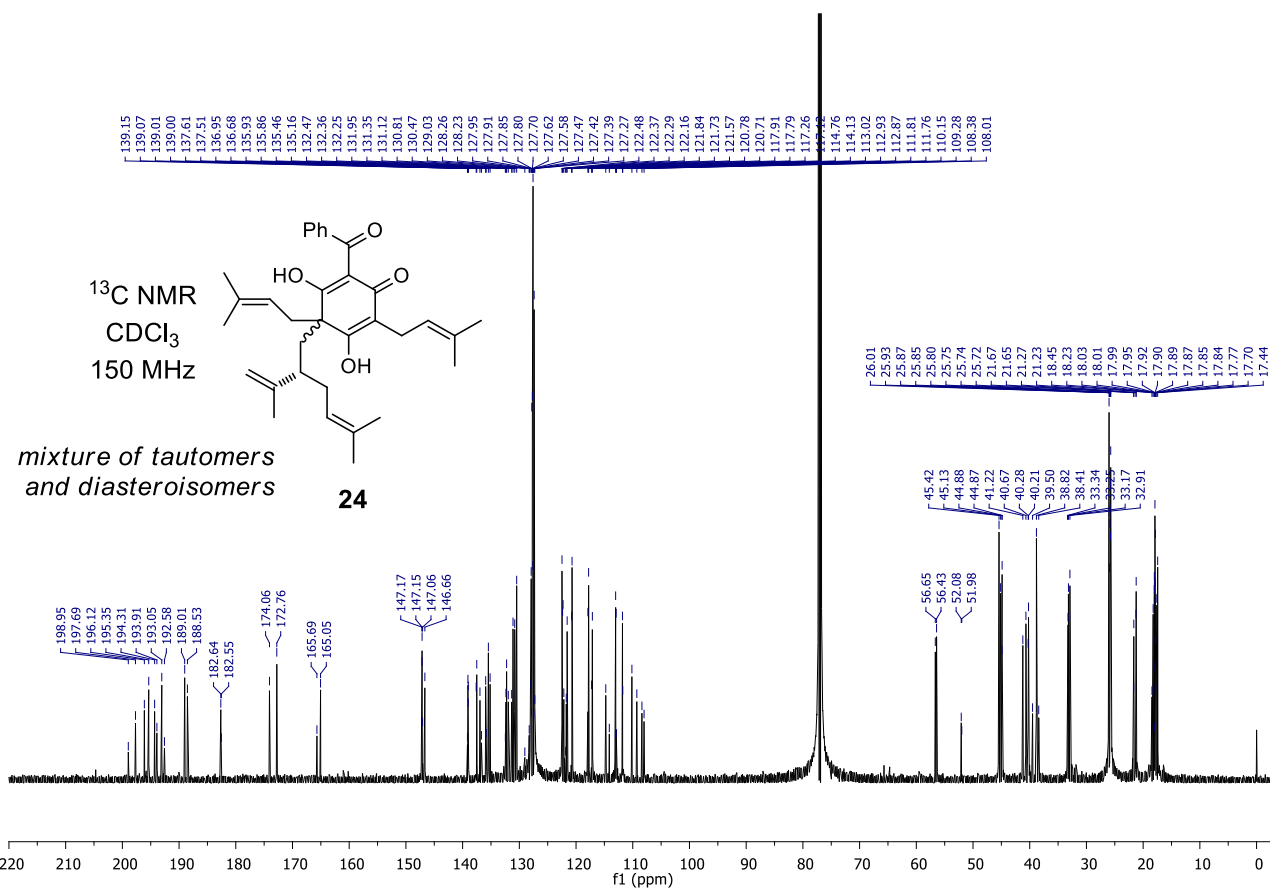


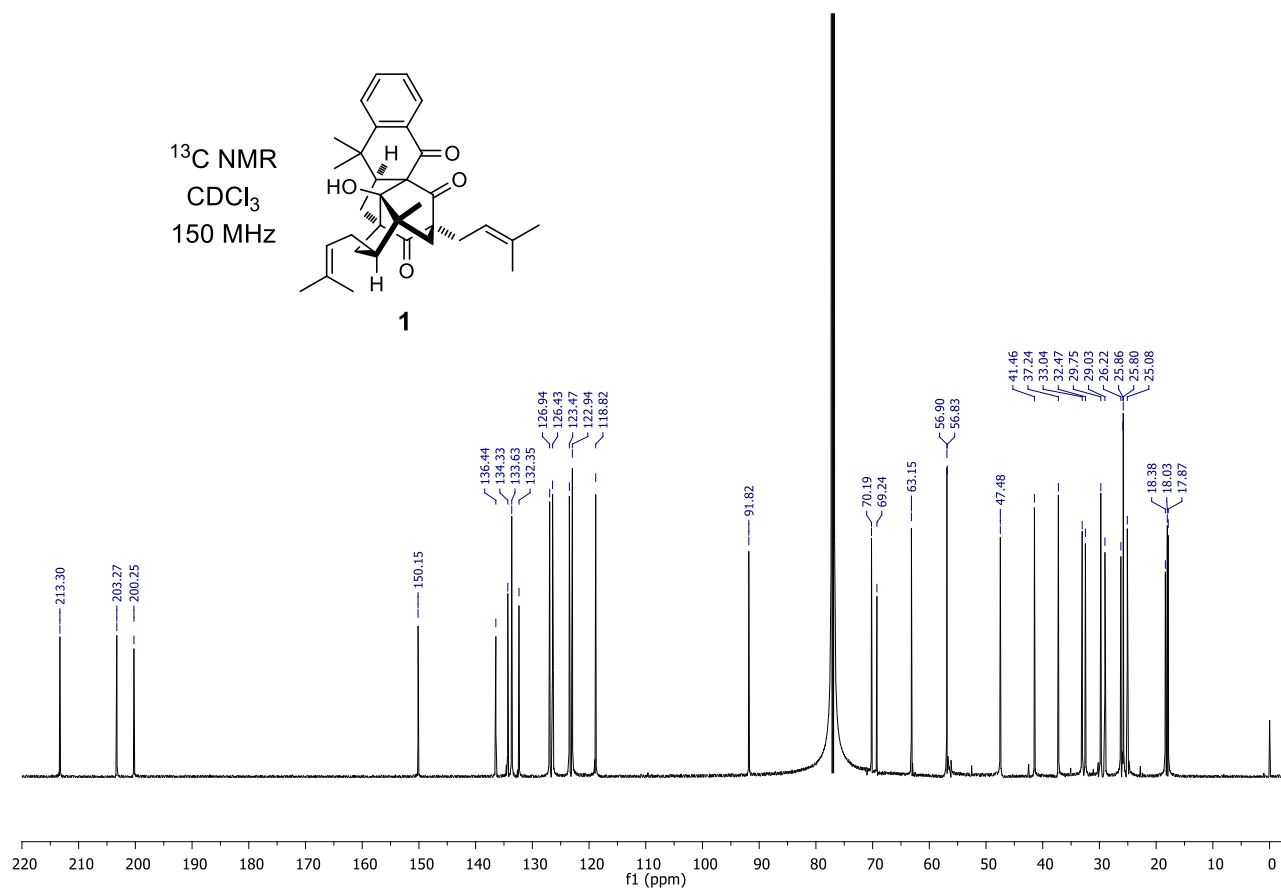
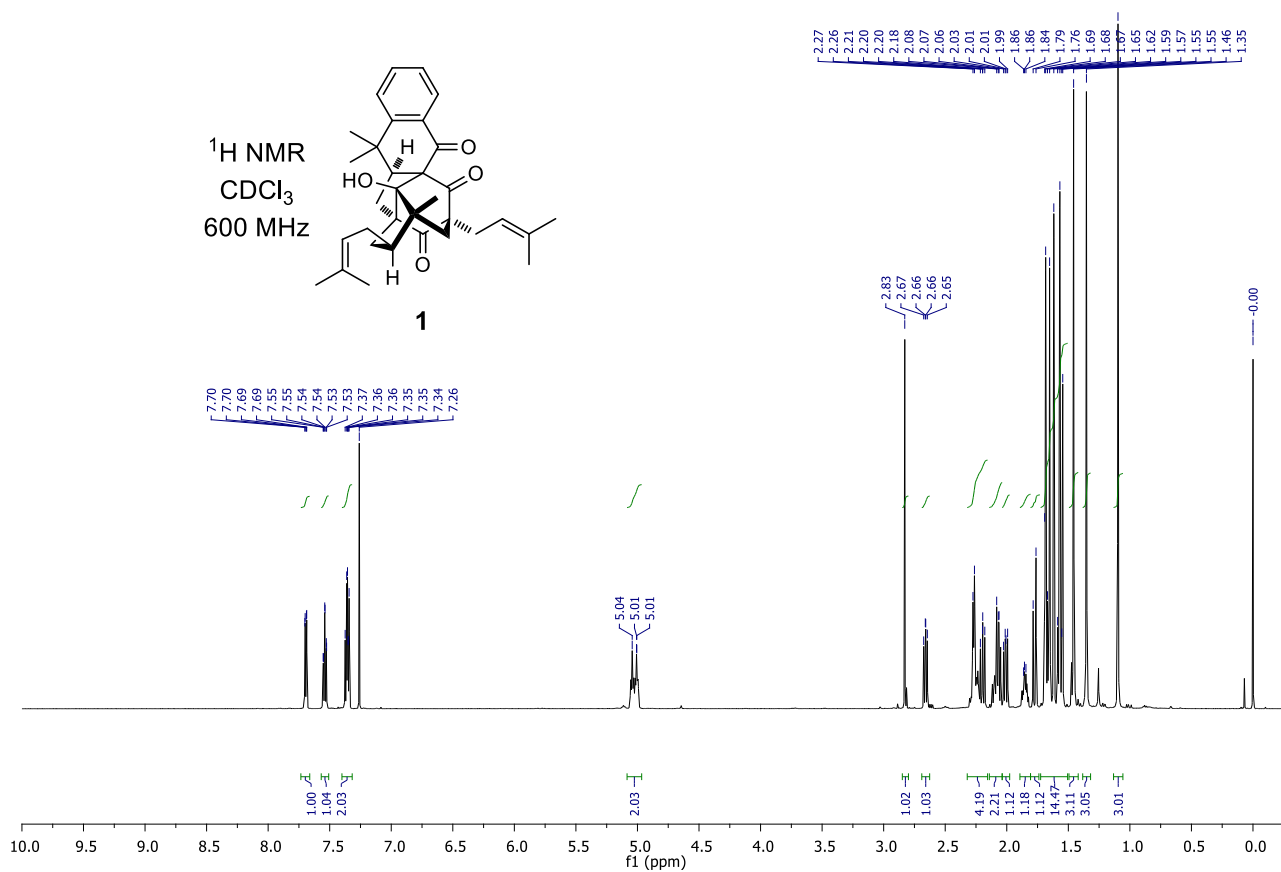
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 CDCl_3
 150 MHz

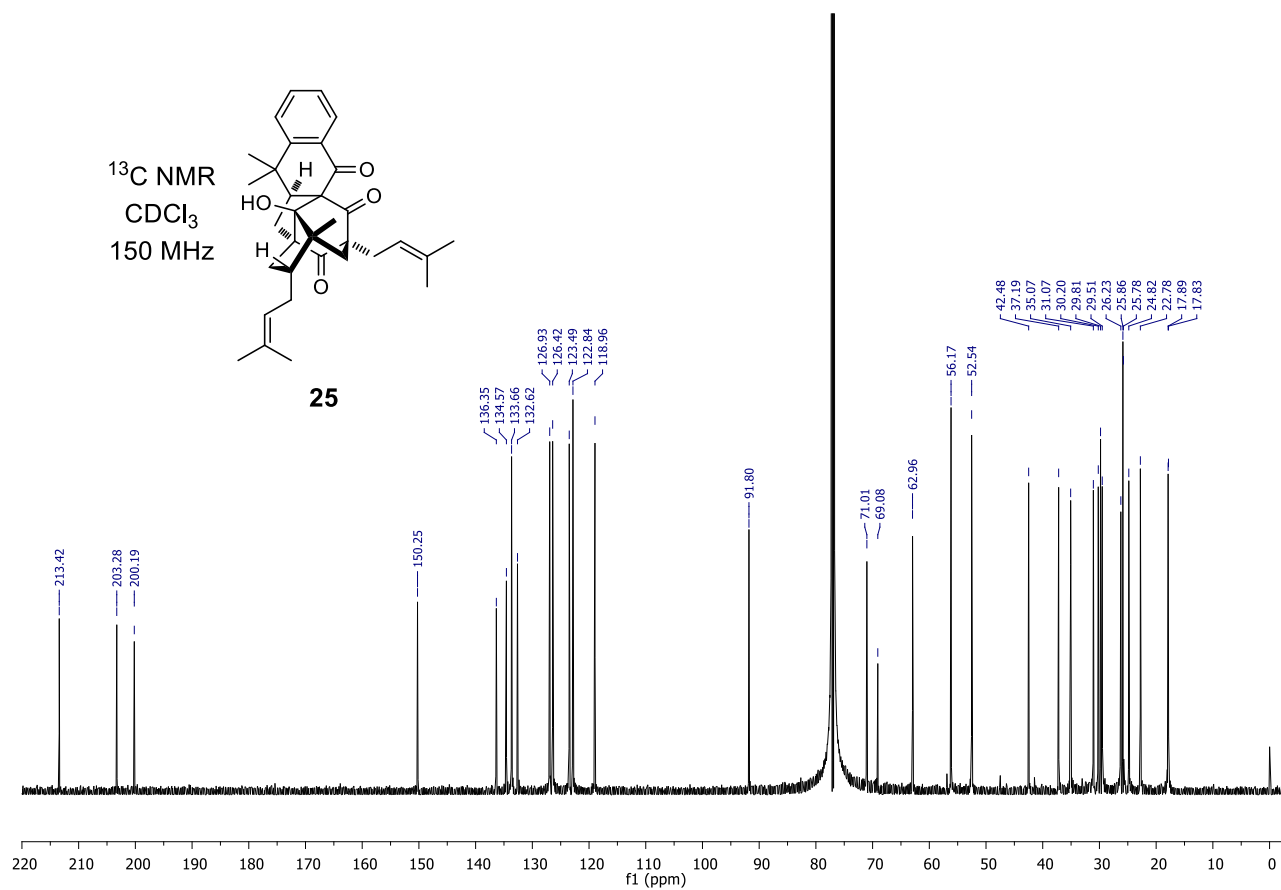
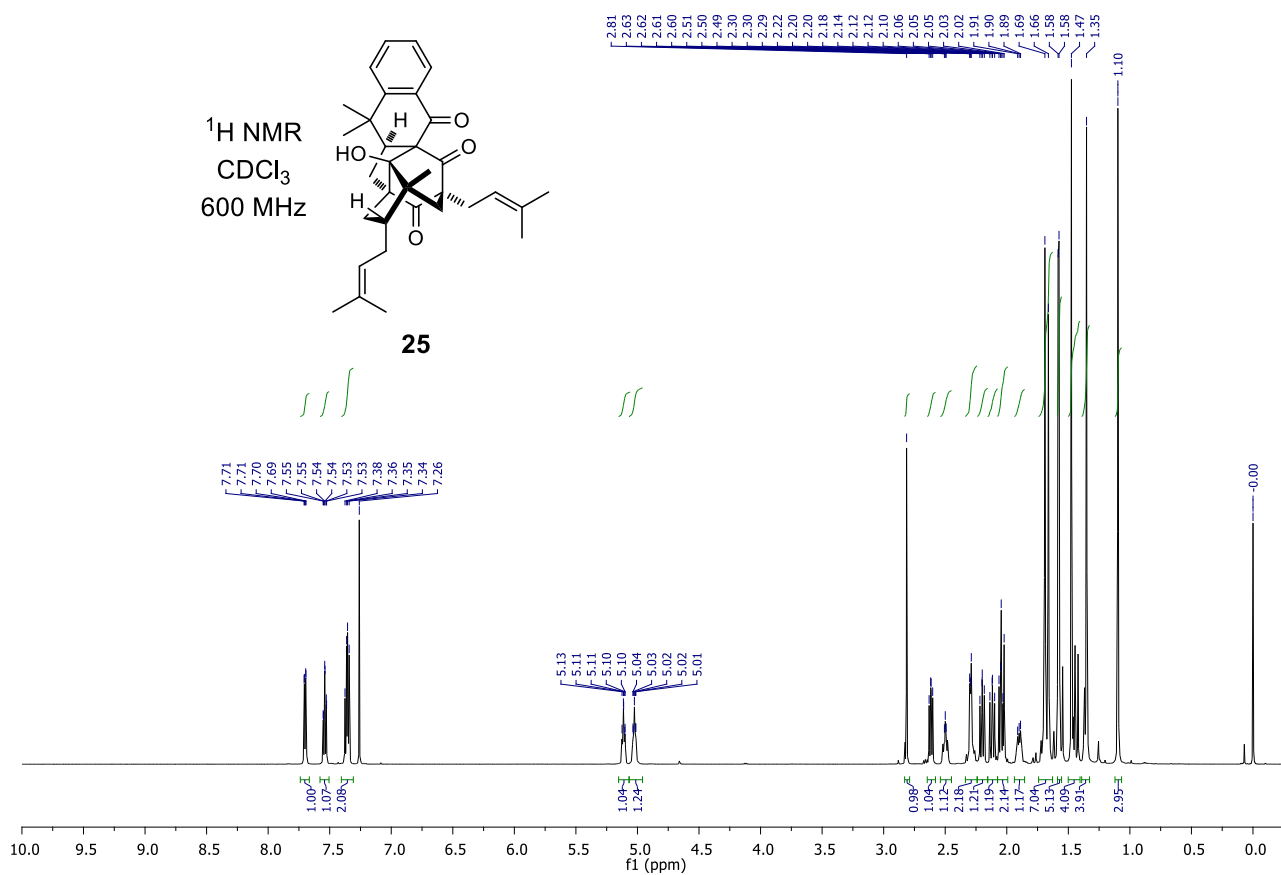


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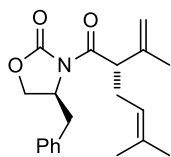




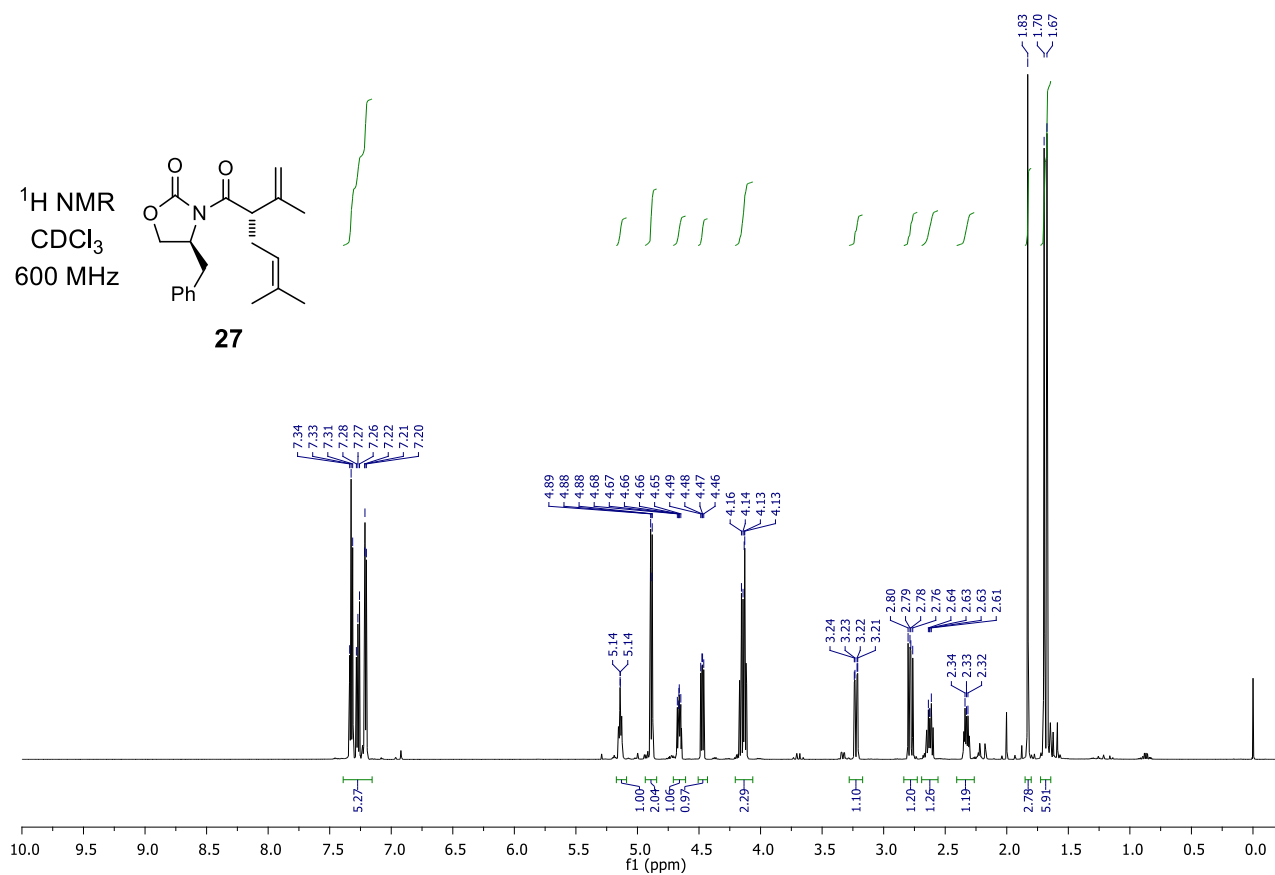




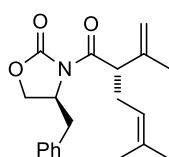
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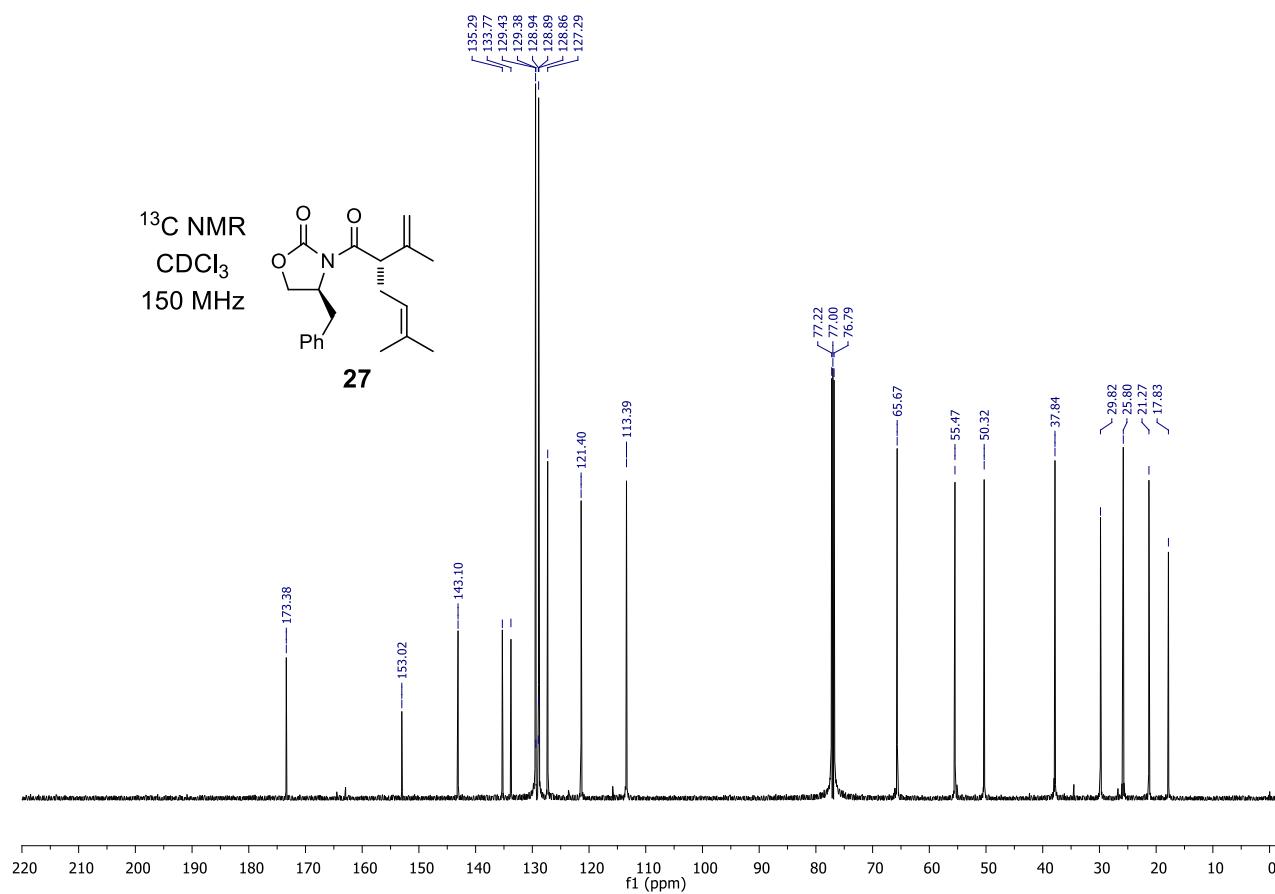
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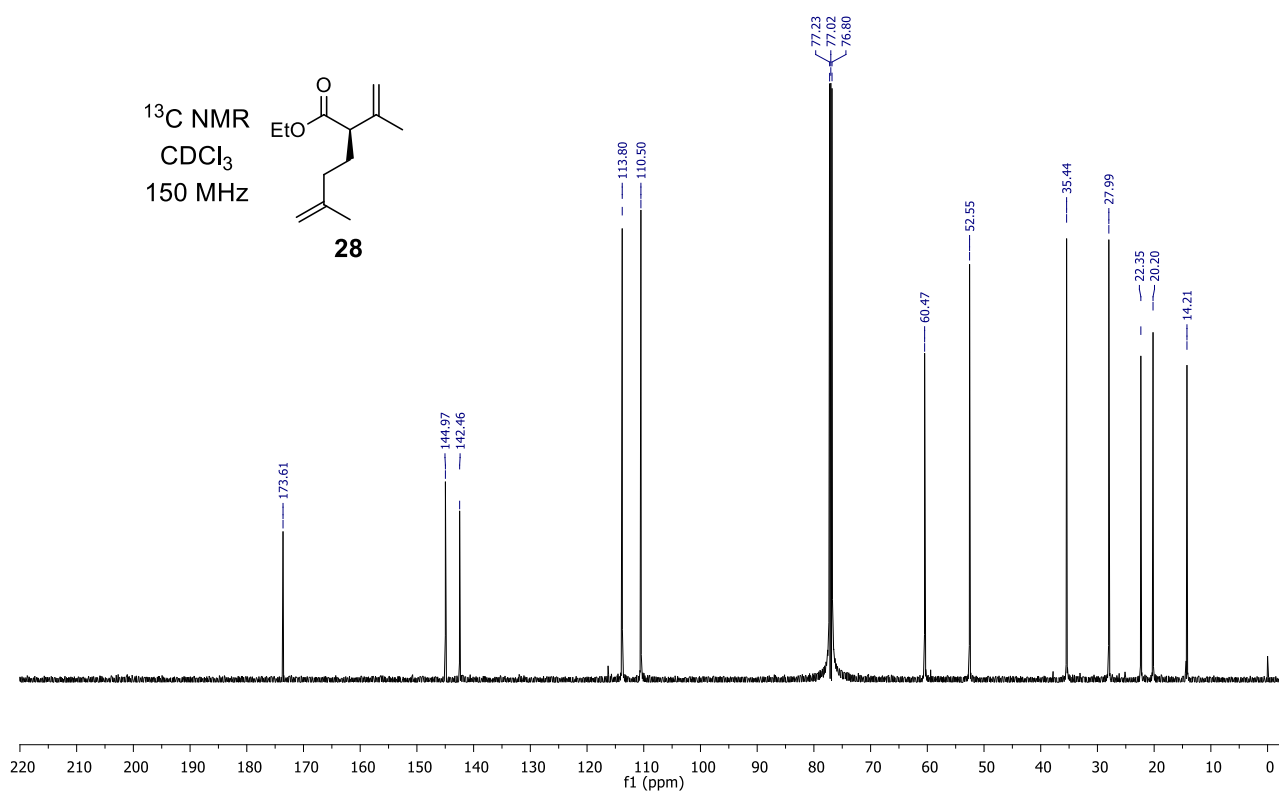
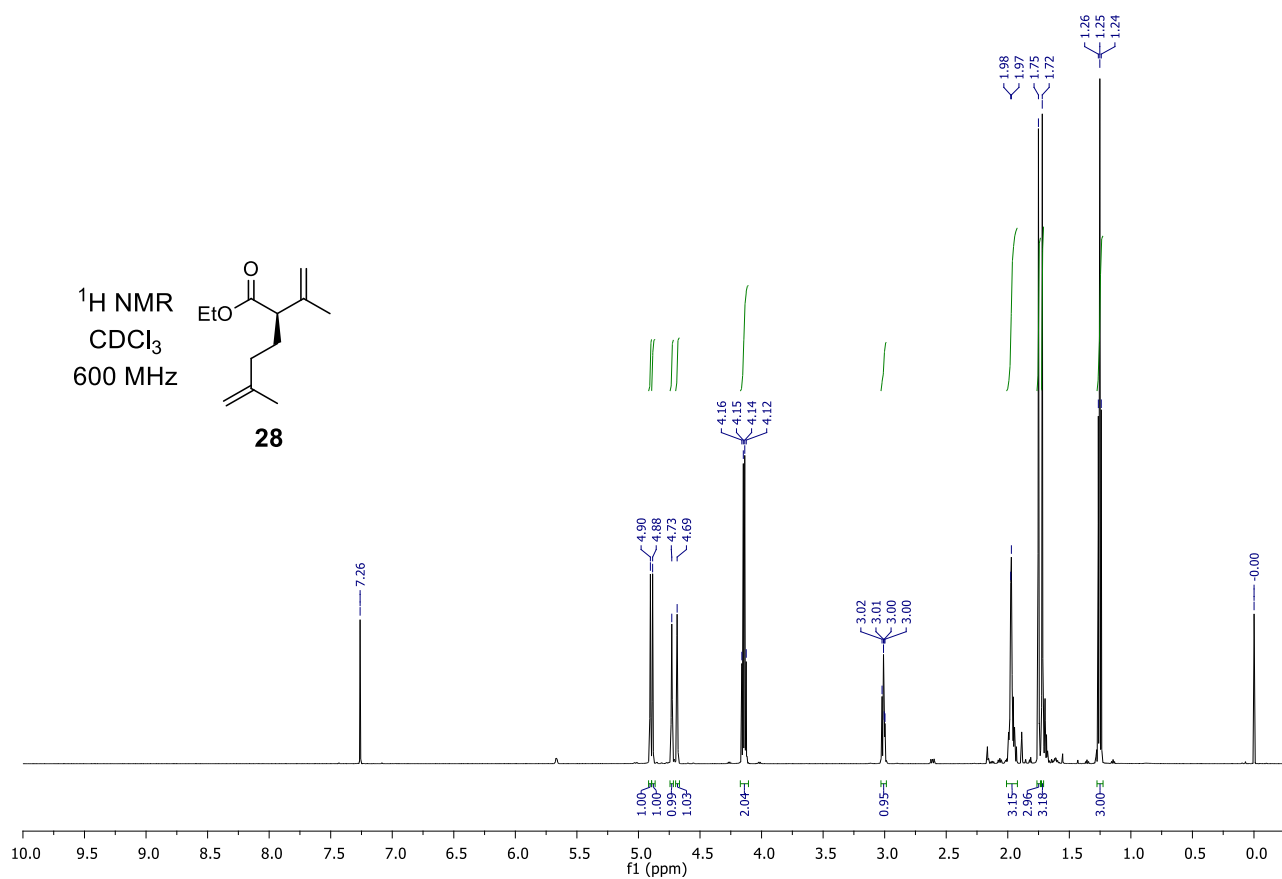


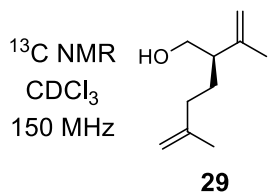
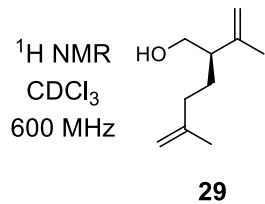
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CDCl₃
150 MHz

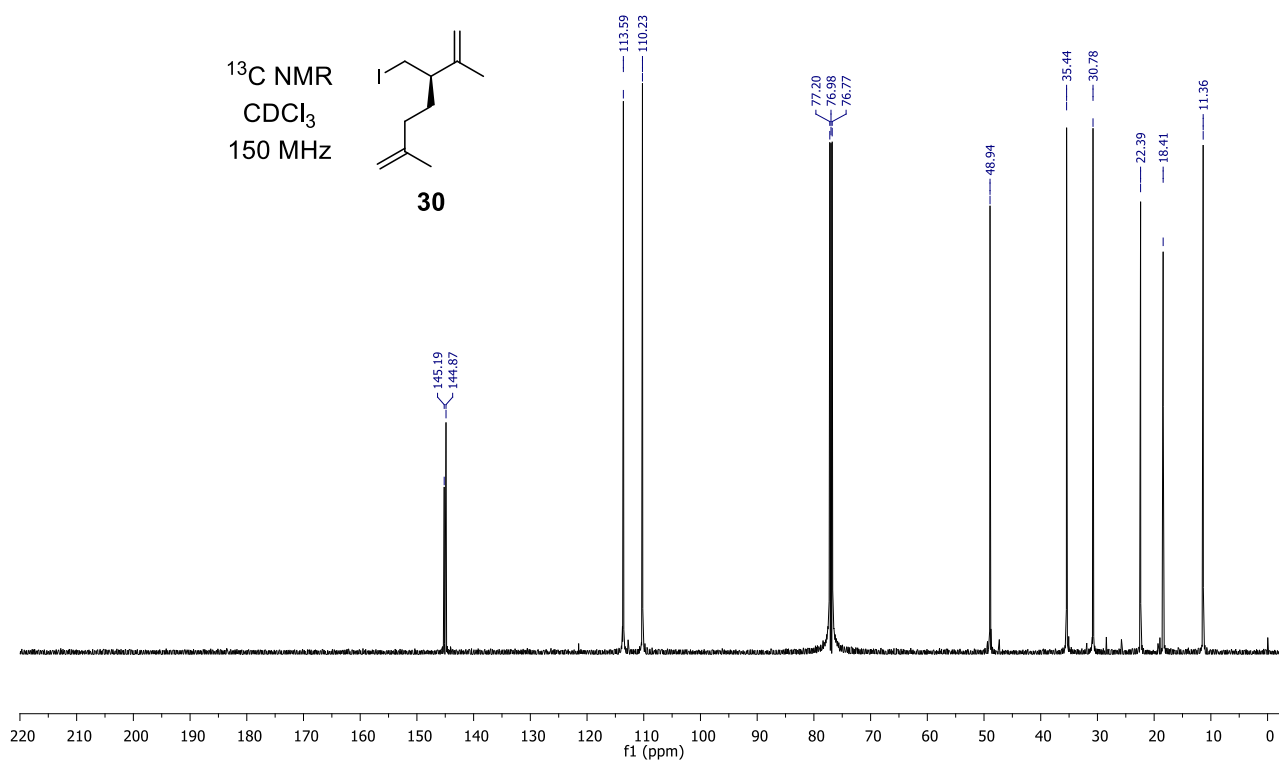
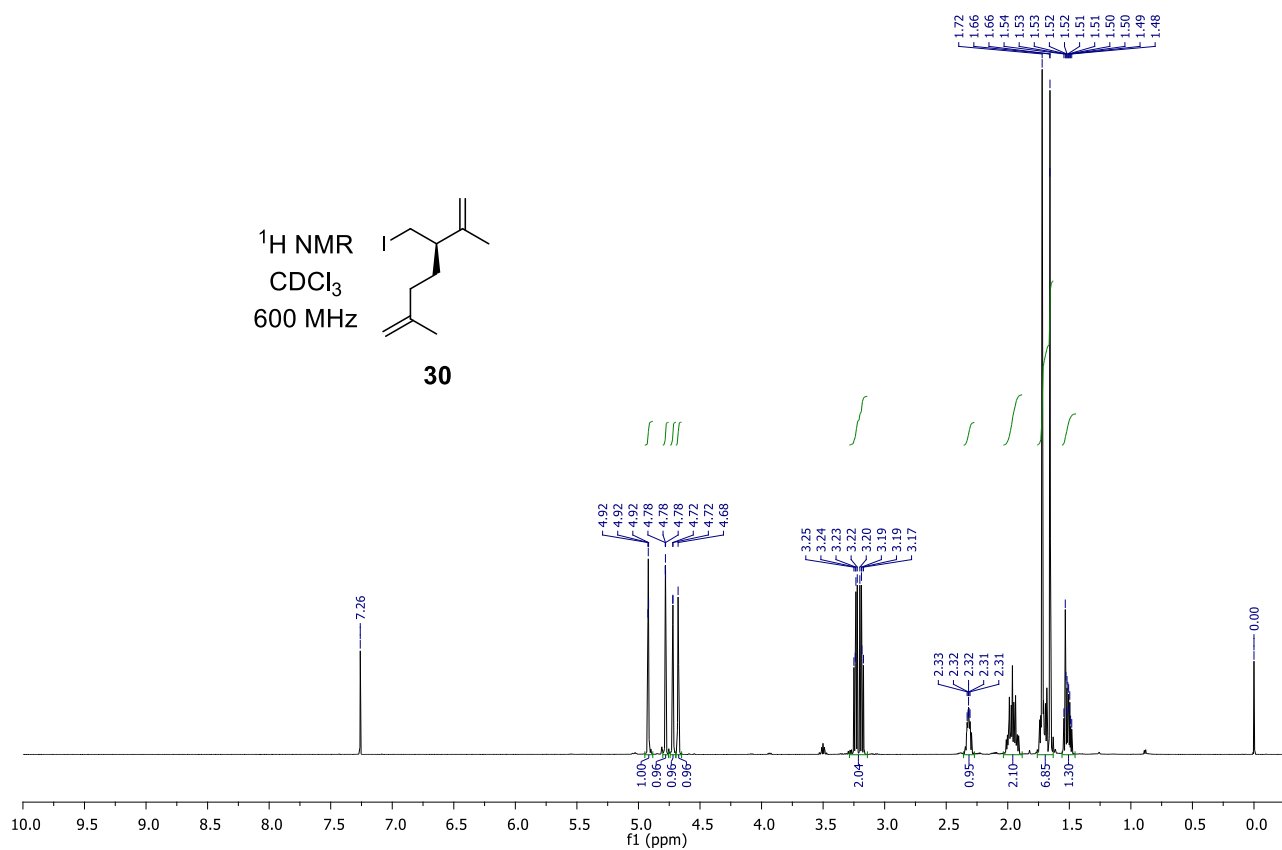


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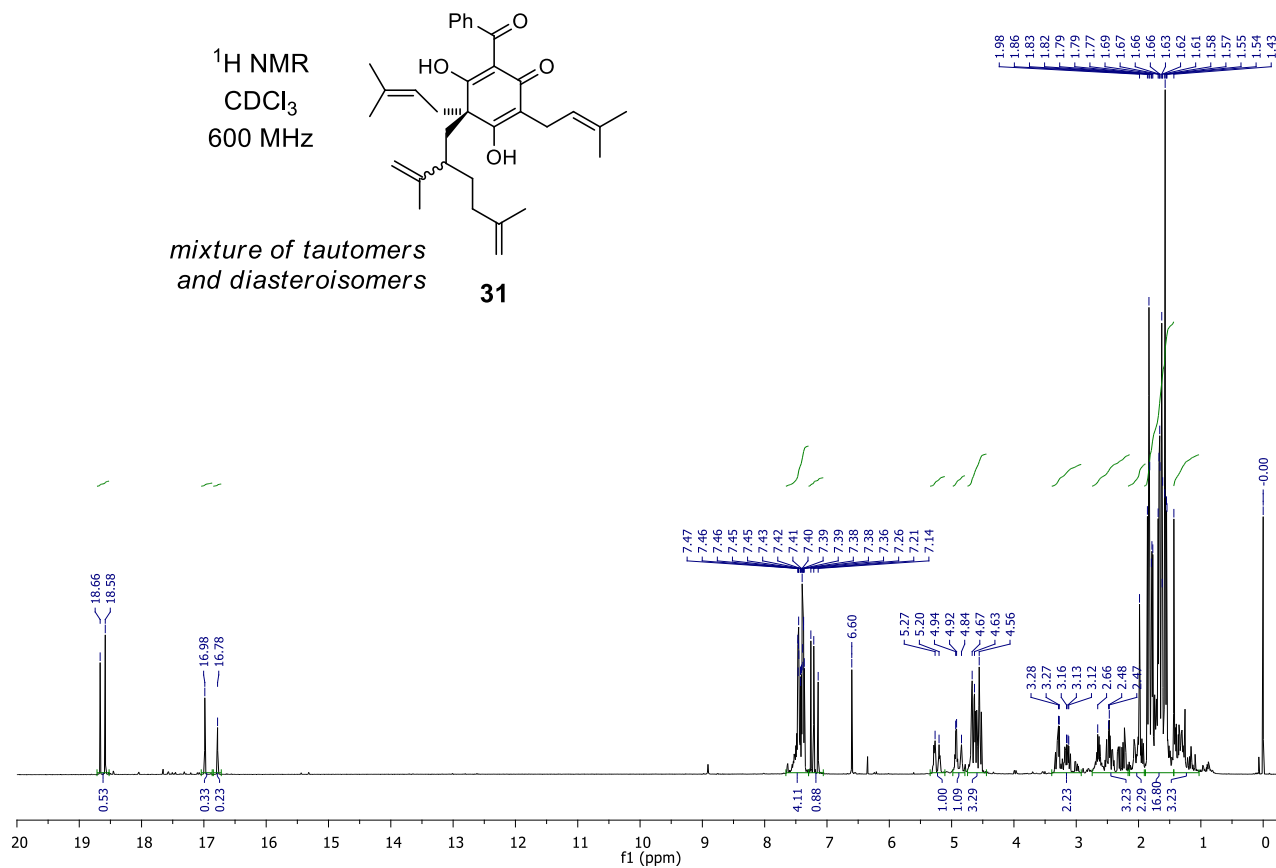




¹H NMR
CDCl₃
600 MHz

*mixture of tautomers
and diastereoisomers*

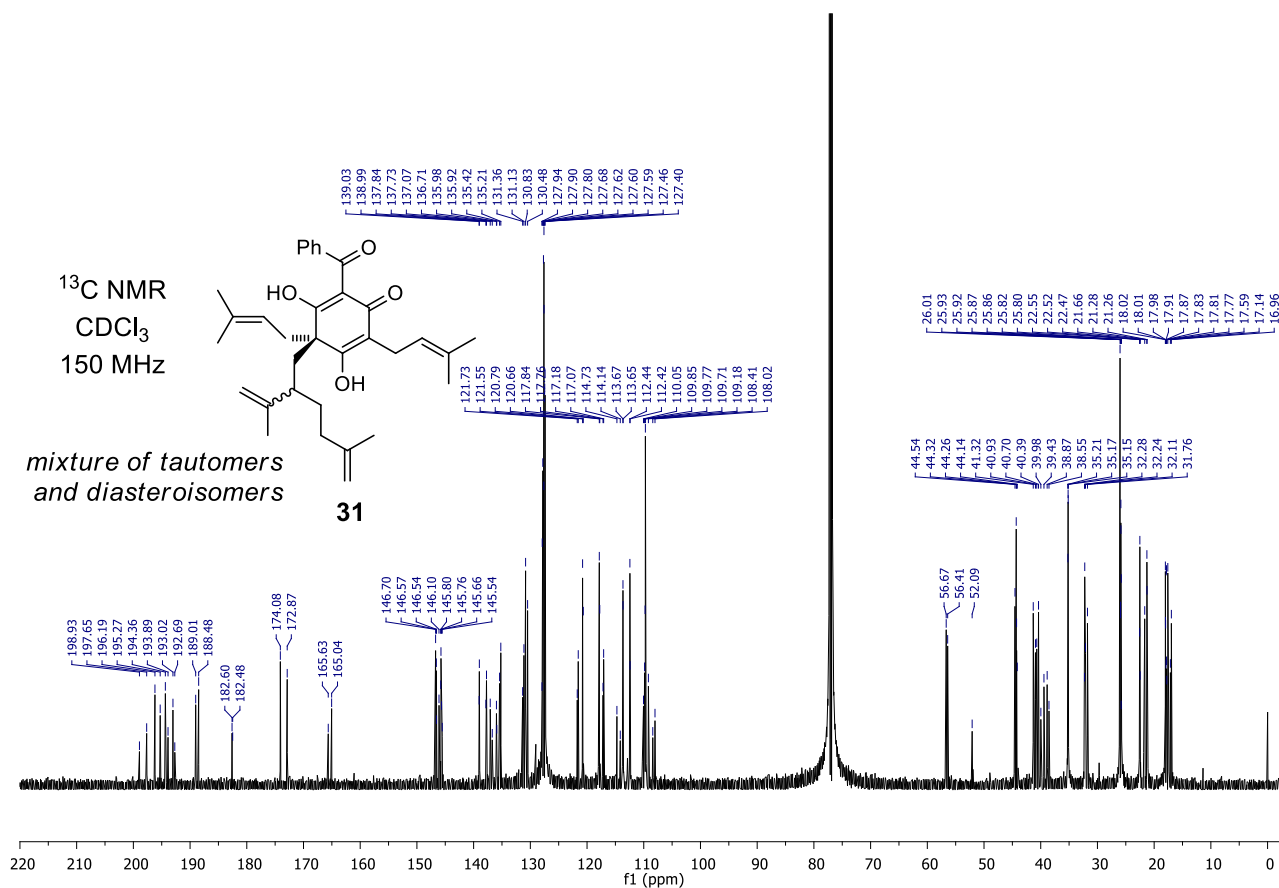
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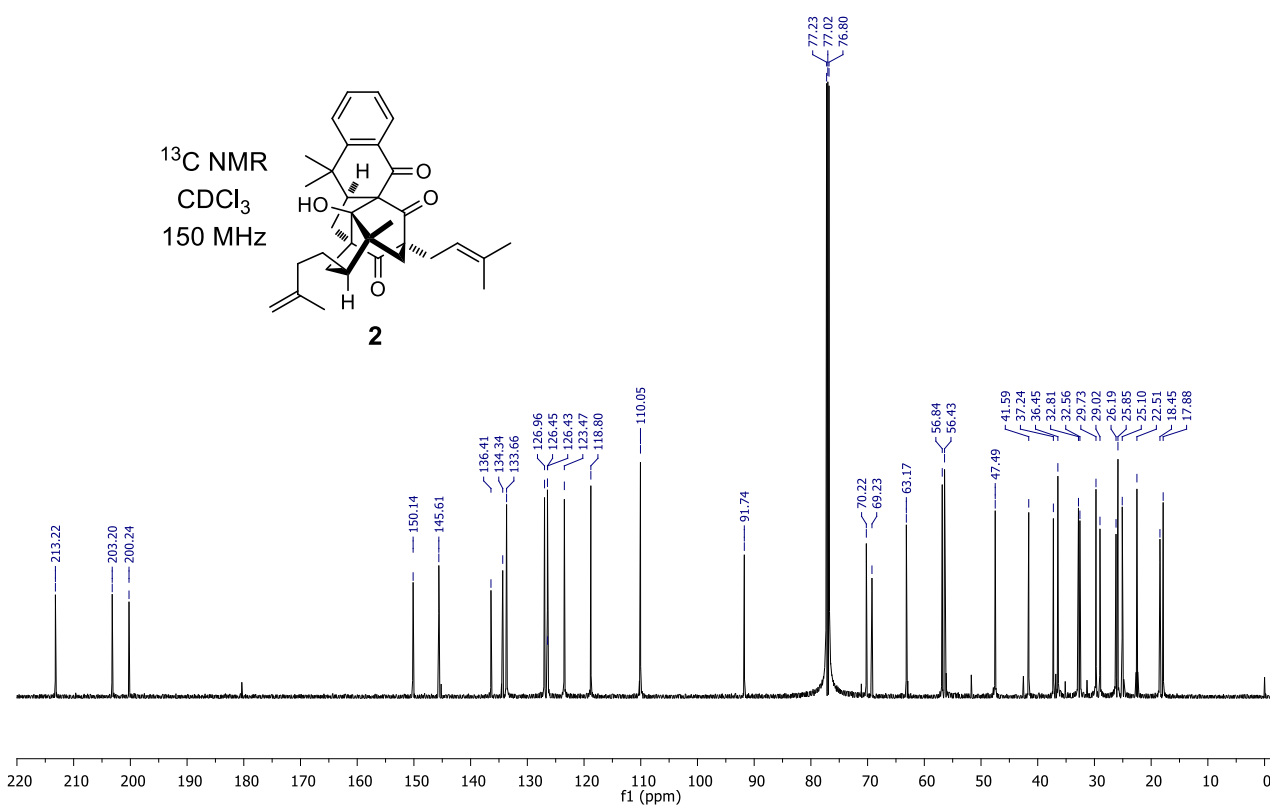
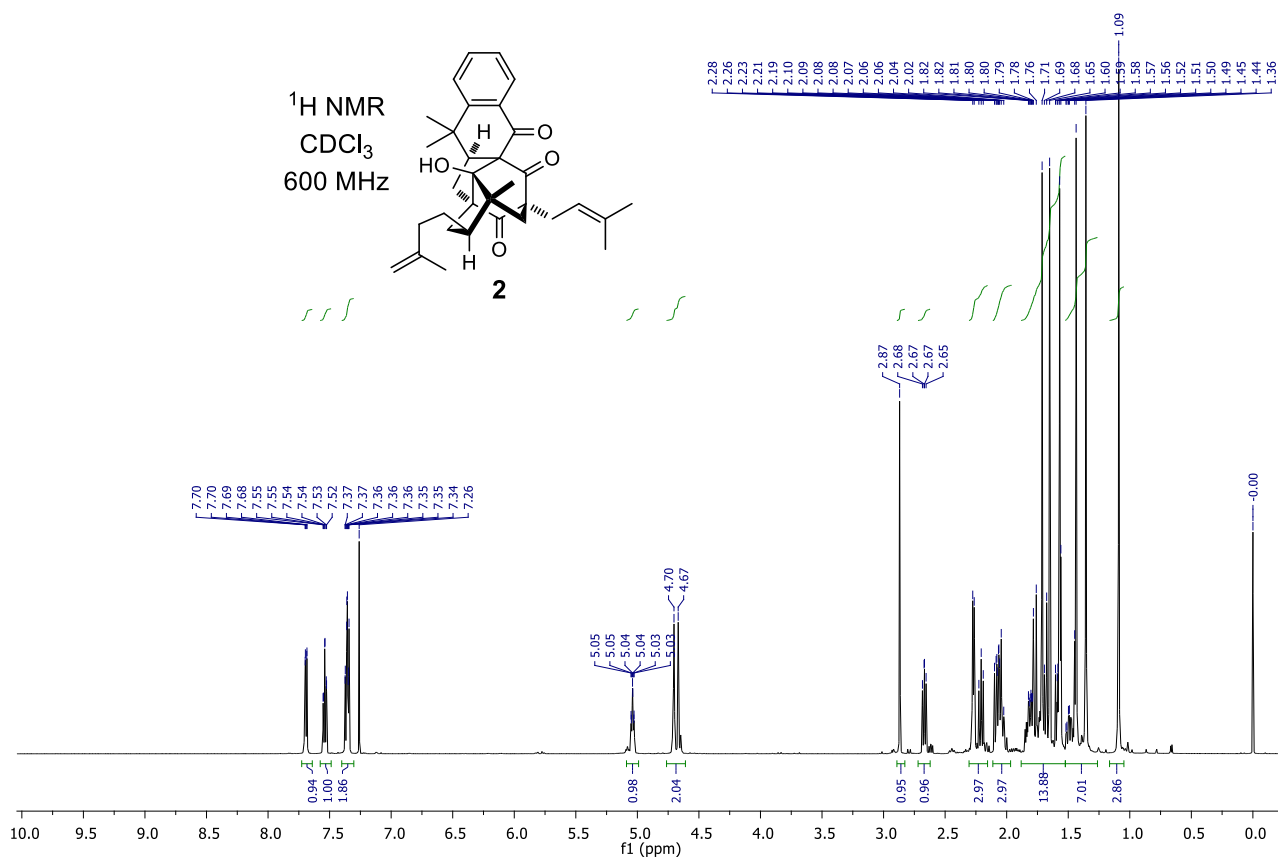


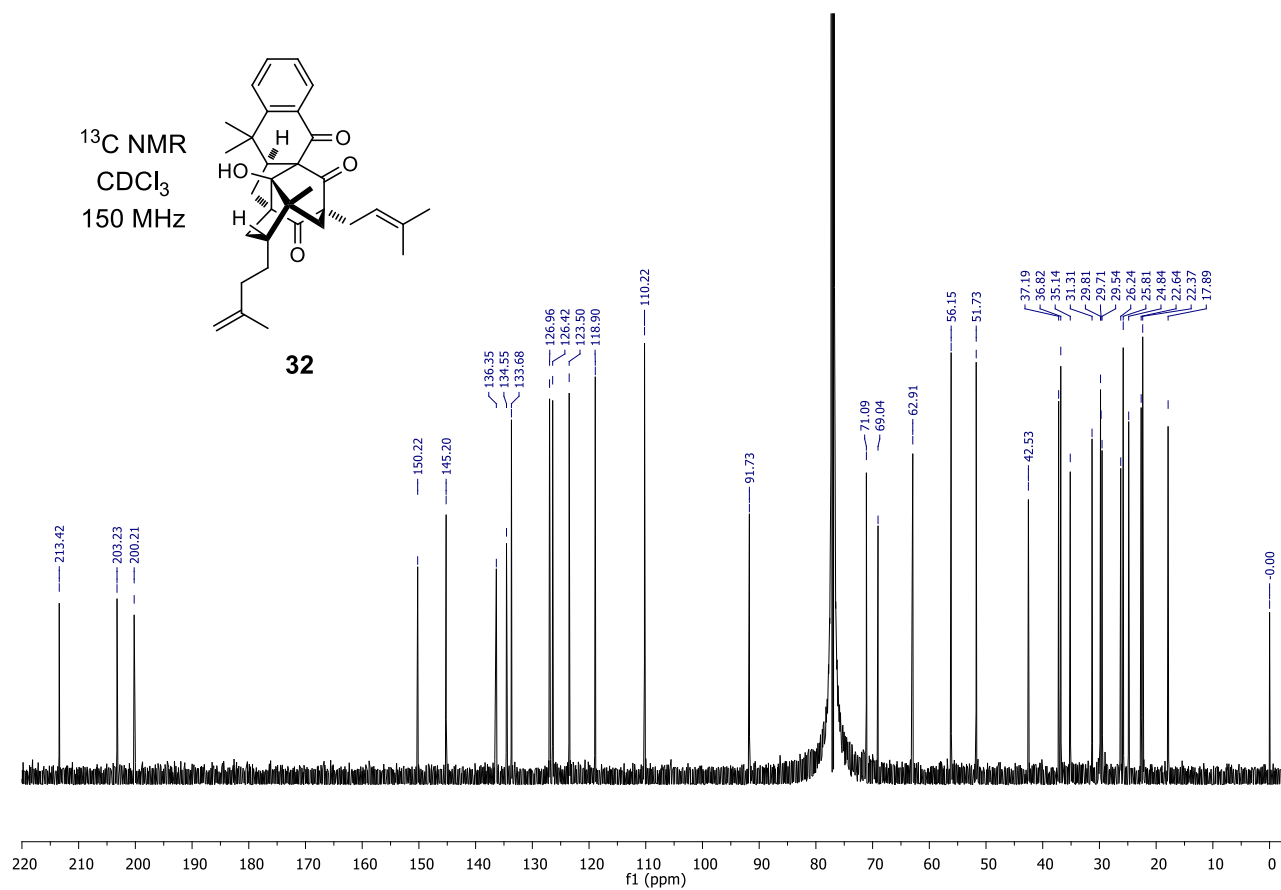
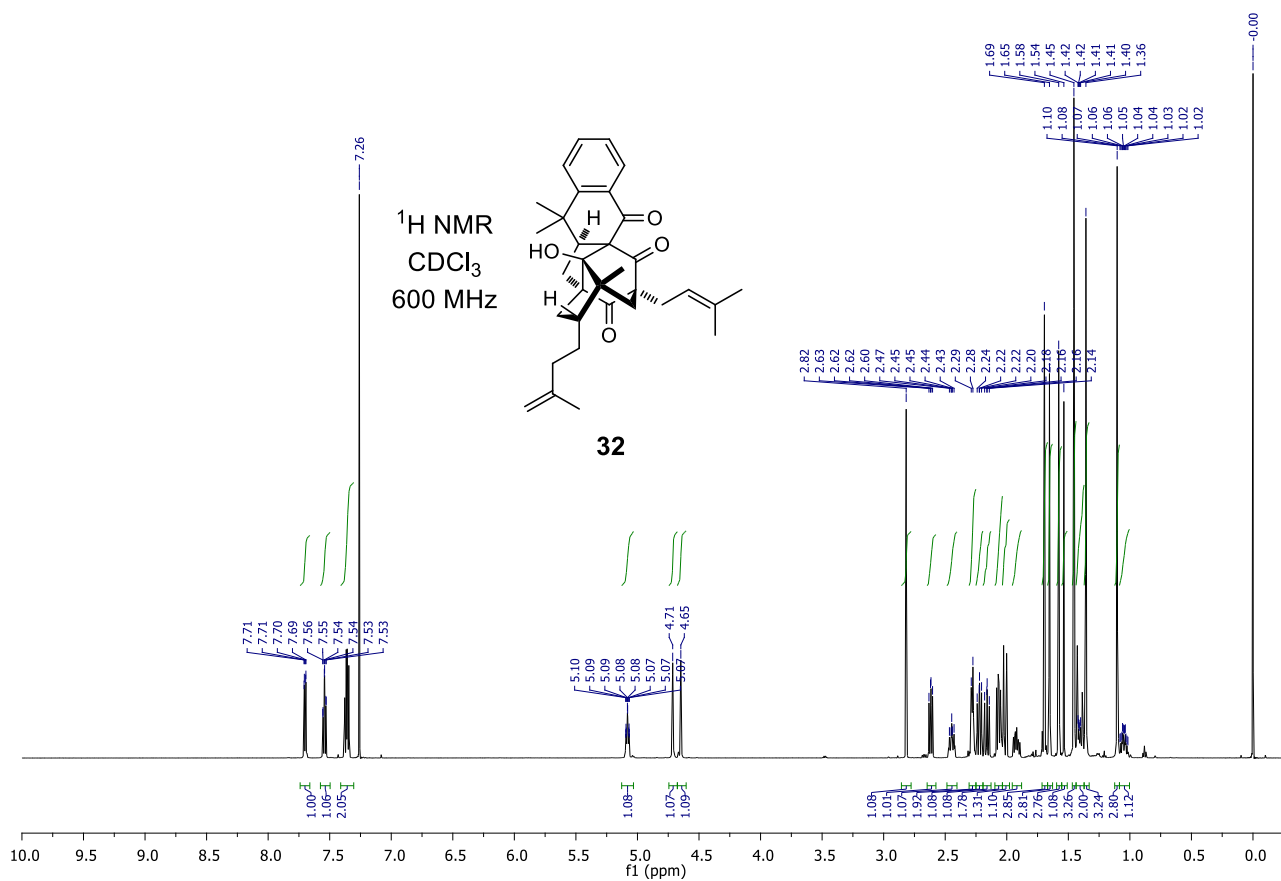
¹³C NMR
CDCl₃
150 MHz

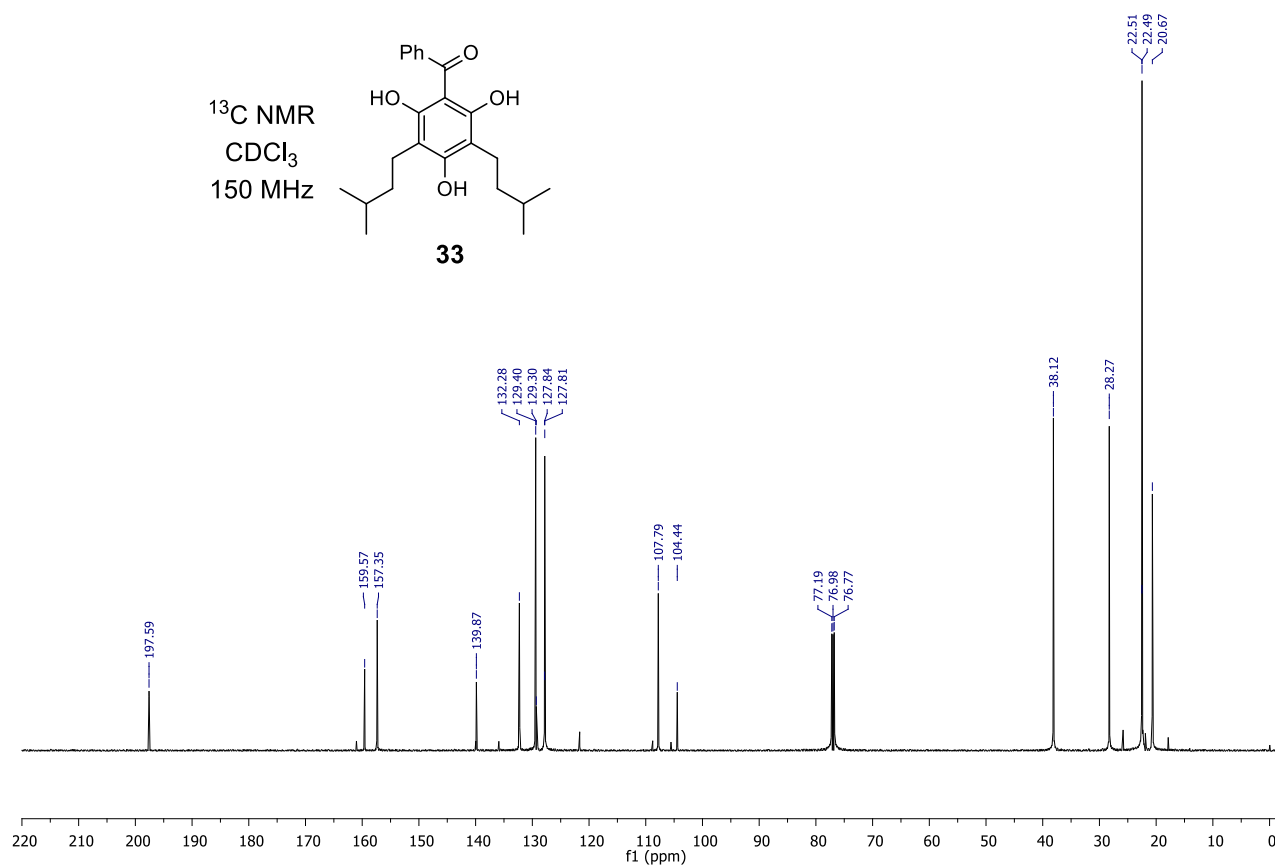
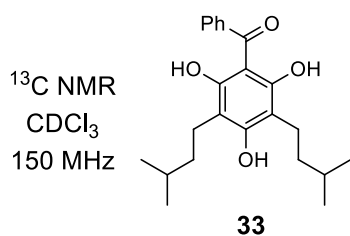
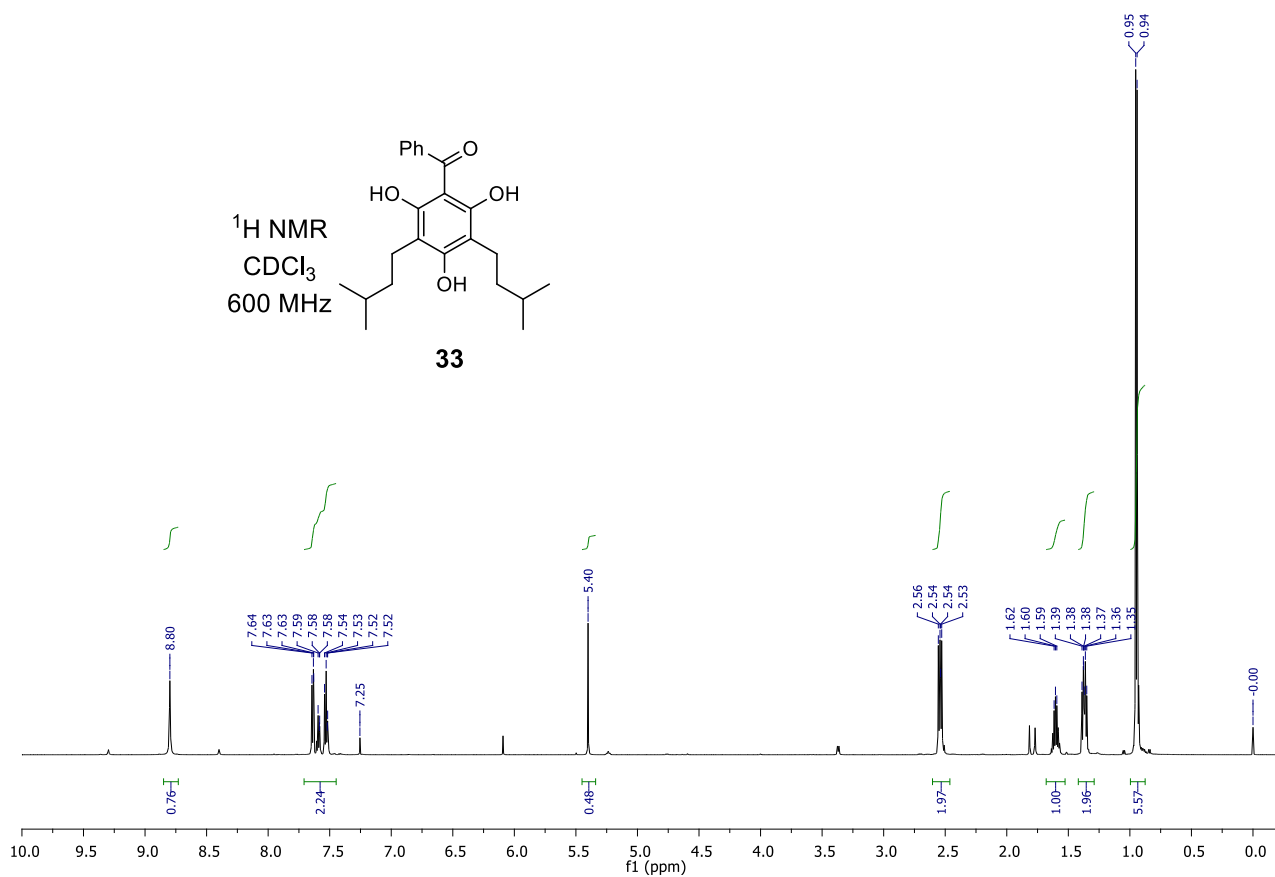
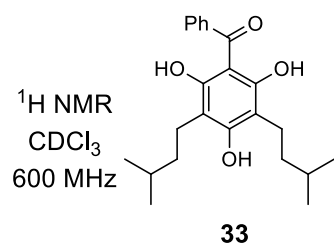
*mixture of tautomers
and diastereoisomers*

31









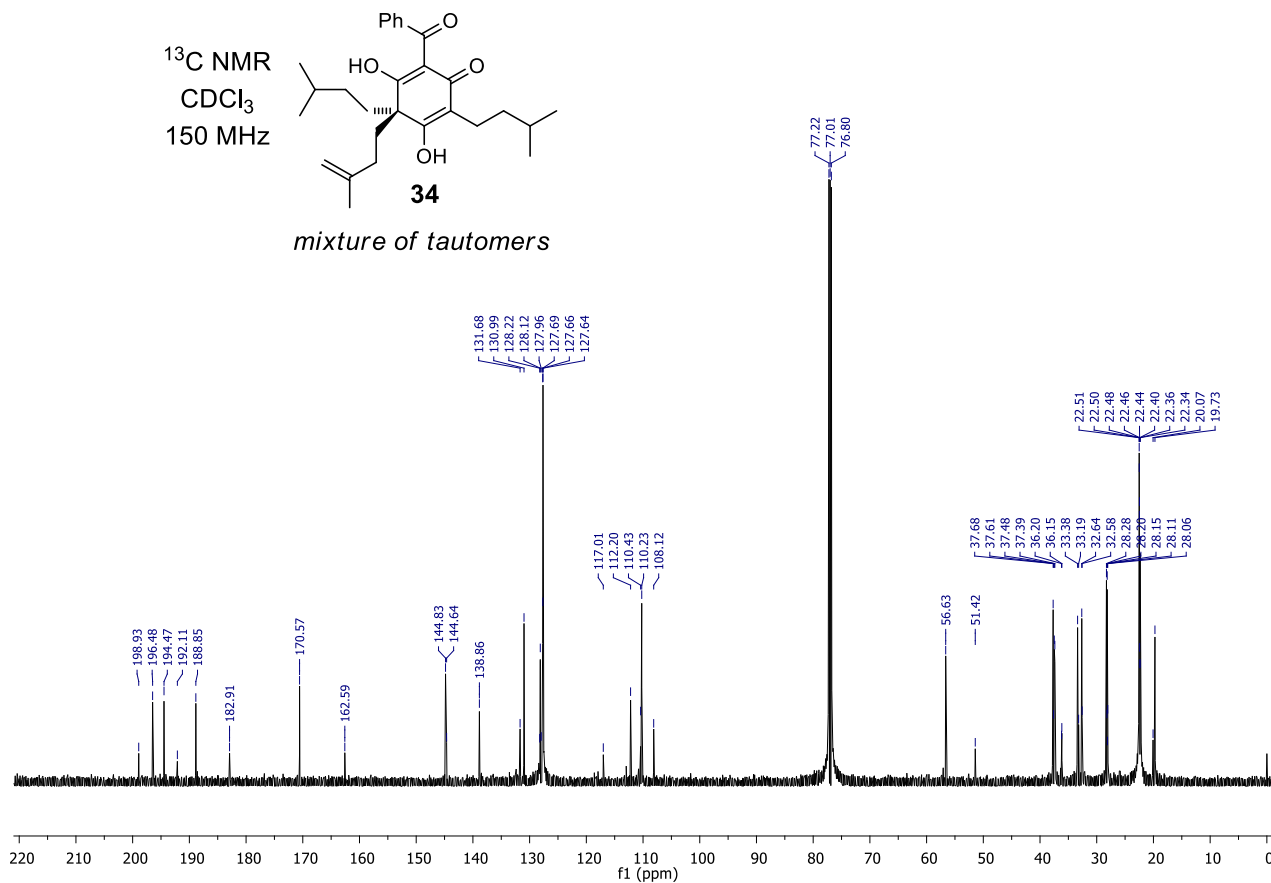
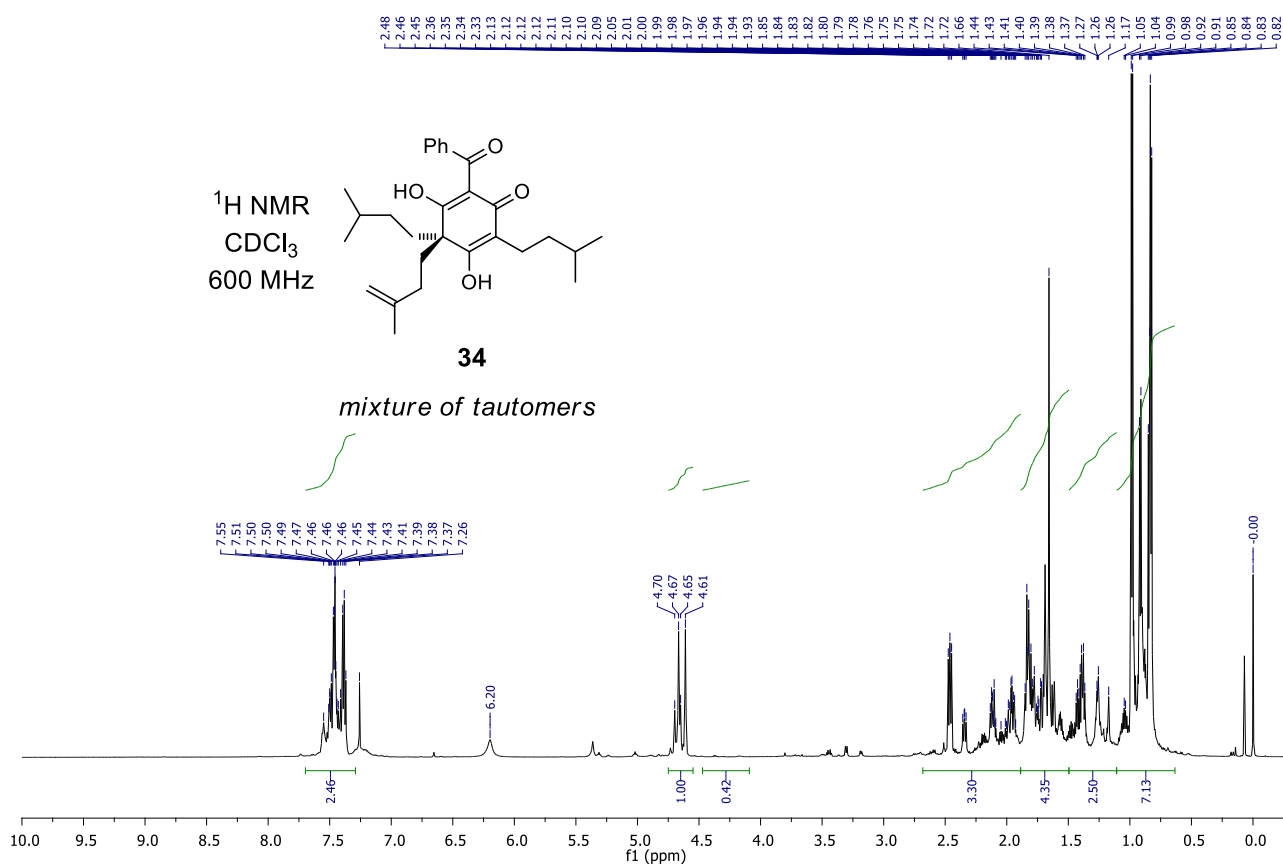


Table 1: ^{13}C NMR Spectral Data for *Garcinia* Natural Products

	nemorosonol ¹	garcibracteateone	5- <i>epi</i> - garcibracteateone	doitunggarcinone A	doitunggarcinone B ²
1	63.6	63.2	63.0	63.1	63.3
2	209.4	213.3	213.4	213.2	210.8
3	62.8	70.2	71.0	70.2	62.6
4	40.4	32.5	30.2	32.5	40.2
5	48.7	56.9	52.5	56.4	47.8
6	47.3	47.5	42.5	41.5	47.4
7	83.9	91.8	91.8	91.7	83.4
8	109.8	69.2	69.1	69.2	109.5
9	199.1	203.3	203.3	203.1	198.9
10	46.4	47.5	35.1	47.4	46.5
11	25.7	25.1	24.8	25.1	24.9
12	120.2	118.8	119.0	118.7	119.3
13	133.5	134.3	134.6	134.3	133.5
14	26.2	25.9	25.8	25.8	26.0
15	18.0	17.9	17.9	17.8	17.9
16	29.9	29.0	31.1	29.0	29.5
17	120.4	56.8	56.2	56.8	119.8
18	133.1	37.1	37.2	37.2	133.9
19	26.1	26.2	26.2	26.1	17.8
20	17.7	29.8	29.8	29.7	26.0
21	35.5	33.0	29.5	32.7	32.8
22	123.8	122.9	122.8	36.4	36.3
23	131.5	132.4	132.6	145.6	145.7
24	25.8	25.8	25.9	110.0	109.8
25	17.9	18.0	17.8	22.5	22.5
26	19.1	18.4	22.8	18.4	19.3
27	174.9	200.3	200.2	200.2	174.8
28	135.3	136.4	136.3	136.4	134.8
29	128.3	150.2	150.2	150.3	127.9
30	130.2	123.5	123.5	123.5	128.0
31	128.3	133.6	133.7	133.6	130.4
32	130.2	126.9	126.9	126.9	128.0
33	128.3	126.6	126.4	126.4	127.9
OH					

(1) Monache, F. D.; Monache, G. D.; Pinherio, R. M.; Radics, L. *Phytochemistry* **1988**, 27, 2305-2308.(2) Tantapakul, C.; Phakhodee, W.; Thunwadee, R.; Cheenpracha, S.; Prawat, U.; Deachathai, S.; Laphookhieo, S. *J. Nat. Prod.* **2012**, 75, 1660-1664.

Table 2: ¹H NMR Spectral Data for *Garcinia* Natural Products

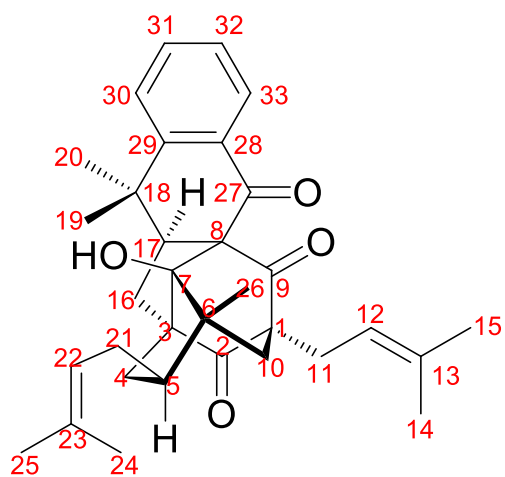
	nemorosonol ¹	garcibrateatone	5- <i>epi</i> - garcibracteatone	doitunggarcinone A	doitunggarcinone B ²
1					
2					
3					
4	2.05, 1.56	2.01 dd (11.8, 7.9) 1.56 m	2.12 dd (12.3, 10.9) 1.35 m	2.05, 1.60 m	1.97, 1.50 m
5	1.57	1.85 m	2.50 m	1.81 m	1.63 m
6					
7					
8					
9					
10	1.56, 1.48	1.77 d (13.9,) 1.68 d (13.8)	2.03 d (14.2) 1.43 d (14.5)	1.81, 1.60 m	1.68, 1.55 m
11	2.92, 2.88	2.27 d (7.3)	2.29 d (8.0)	2.26 m	2.45, 2.16 m
12	5.59	5.01 t (7.2)	5.02 t (7.2)	5.04 t (7.6, 7.2)	5.17 m
13					
14	1.71	1.65 s	1.66 s	1.65 s	1.64 s
15	1.64	1.57 s	1.58 s	1.55 s	1.51 s
16	2.61, 2.18	2.20 dd (11.3, 10.1) 2.07 m	1.9 m, 1.68 m	2.20, 2.06 m	2.45, 2.16 m
17	5.15	2.66 dd (9.8, 7.8)	2.62 dd (9.8, 7.7)	2.66 m	4.92 m
18					
19	1.54	1.35 s	1.35 s	1.35 s	1.64 s
20	1.40	1.10 s	1.10 s	1.08 s	1.71 s
21	2.10, 2.08	2.24 m, 2.05 dd (11.5, 7.8)	2.2 dd (11.2, 10.1) 2.05 t (9.5)	2.20, 2.06 m	2.16, 1.97 m
22	4.95	5.04 t (7.2)	5.11 t (7.2)	2.05, 1.81 m	1.97, 1.79 m
23					
24	1.63	1.68 s	1.69 s	4.70 brs 4.66 brs	4.66 brs 4.62 brs
25	1.49	1.62 s	1.58 s	1.71 s	1.67
26	0.90	1.46 s	1.47 s	1.45 s	1.15
27					
28					
29	7.04				7.47 m
30	7.47	7.35 d (7.6)	7.35 d (7.8)	7.34-7.38 m	7.44 m
31	7.04	7.54 td (7.6, 1.4)	7.54 td (7.6, 1.4)	7.54 dt (7.6, 0.8)	7.47 m
32	7.47	7.36 t (7.6)	7.36 t (7.6)	7.34-7.38 m	7.44 m
33	7.04	7.69 dd (7.6, 1.3)	7.70 dd (7.6, 1.2)	7.69 d (7.6)	7.47 m
OH	2.0, 16.0	2.83	2.81	2.82 brs	5.08, 15.32

Table 3: Comparison of ^1H NMR Spectral Data for Synthetic and Natural Doitunggarcinone A

	doitunggarcinone A (synthetic)	doitunggarcinone A (natural) ²
1		
2		
3		
4	2.04 m, 1.58 m	2.05, 1.60 m
5	1.80 m	1.81 m
6		
7		
8		
9		
10	1.77 d (14.0) 1.66 d (14.0)	1.81, 1.60 m
11	2.27 d (7.1)	2.26 m
12	5.04 t (7.2)	5.04 t (7.6, 7.2)
13		
14	1.65 s	1.65 s
15	1.57 s	1.55 s
16	2.21 dd (13.4, 11.5) 2.08 dd (13.4 11.5)	2.20, 2.06 m
17	2.67 dd (9.9, 7.8)	2.66 m
18		
19	1.36 s	1.35 s
20	1.09 s	1.08 s
21	1.72 m, 1.49 m	2.20, 2.06 m
22	2.04 m, 1.81 m	2.05, 1.81 m
23		
24	4.70 s 4.67 s	4.70 brs 4.66 brs
25	1.71 s	1.71 s
26	1.44 s	1.45 s
27		
28		
29		
30	7.36 td (7.6, 1.4)	7.34-7.38 m
31	7.54 dt (7.6, 1.4)	7.54 dt (7.6, 0.8)
32	7.35 d (7.6)	7.34-7.38 m
33	7.69 dd (7.6, 1.4)	7.69 d (7.6)
OH	2.87 s	2.82 brs

In reference 2 the authors misassigned the H-21 peaks of doitunggarcinone A. The correct peak shifts are given for synthetic doitunggarcinone A in the table above.

Garcibracteatone atom numbering:



Software Version : 6.3.1.0504
 Sample Name : natural garcibracteateone
 Instrument Name : Series 200 HPLC
 Rack/Vial : 1/2
 Sample Amount : 1.000000
 Cycle : 1

Date : 18/04/2013 1:18:28 PM
 Data Acquisition Time : 18/04/2013 10:09:30 AM
 Channel : A
 Operator : manager
 Dilution Factor : 1.000000

Result File :
 Sequence File : D:\Yuj\Sequence\garcibr.seq

Channel Parameters
 Data will be collected from channel A
 Delay Time : 0.00 min
 Run Time : 20.00 min
 Sampling Rate : 10.0000 pts/s

Channel A Channel B
 Signal Source LC200UV

Autosampler Method

Injection Source : Autosampler
 Injection volume : 10.0 µL
 Loop size : 100 µL
 Fixed mode : Off
 Excess volume : 1 µL
 Air cushion : 5 µL
 Sample syringe size : 250 µL
 Sample speed : Fast

Flush volume : 500 µL
 Flush speed : Medium
 Flush cycles : 2
 Pre-injection flush cycles : 0
 Post-injection flush cycles : 1
 Post-method flush cycles : 0

Needle level : 4.0 mm
 Inject delay time : 0.00 min
 Peltier tray temperature : OFF

Peltier tolerance (+/-) : 1°C

Detector Parameters

Step	Time	Wavelength	Autozero
1	20.0	254	Yes

Lamp off at end of run : No

Pump Parameters

Step	Time	Flow	A	B	Curve
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1	20.0	1.00	98	2	0.0

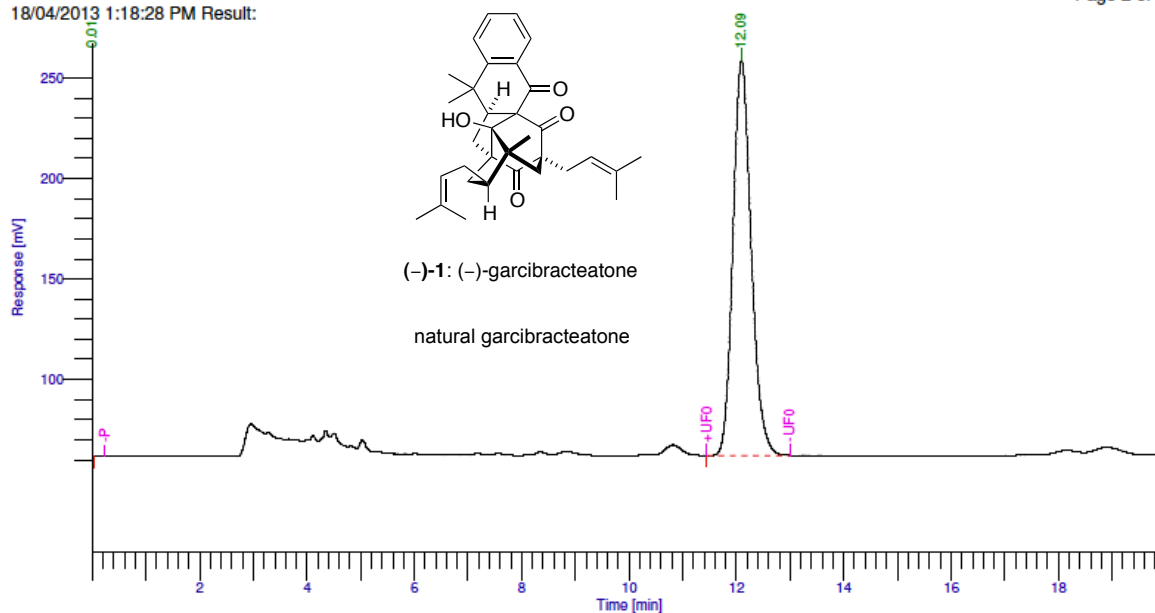
Ready Time : 500.0 min
 Standby Flow : 0.10 mL/min
 Saver Equ Time : 0.0 min
 Min Pressure : 0 PSI

Standby Time : 15.0 min
 Solvent Saver : No
 Shutdown : No
 Max Pressure : 6200 PSI

Timed Events

There are no timed events in the method

18/04/2013 1:18:28 PM Result:



DEFAULT REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]
1		0.01	17.13	22.33	0.00	0.00
2		12.09	4638562.47	196792.48	100.00	100.00
			4638579.60	196814.81	100.00	100.00

Software Version : 6.3.1.0504
 Sample Name : 3-HP-68a synthetic racemic
 Instrument Name : Series 200 HPLC
 Rack/Vial : 0/2
 Sample Amount : 1.000000
 Cycle : 1

Date : 18/04/2013 10:46:24 AM
 Data Acquisition Time : 18/04/2013 8:33:32 AM
 Channel : A
 Operator : manager
 Dilution Factor : 1.000000

Result File :
 Sequence File : C:\PenEx\TcWS\Ver6.3.1\Examples\3-HP-68a synthetic racemic.seq

Channel Parameters

Data will be collected from channel A
 Delay Time : 0.00 min
 Run Time : 60.00 min
 Sampling Rate : 10.0000 pts/s

Channel A Channel B
 Signal Source LC200UV

Autosampler Method

Injection Source : Autosampler
 Injection volume : 10.0 µL
 Loop size : 100 µL
 Fixed mode : Off
 Excess volume : 1 µL
 Air cushion : 5 µL
 Sample syringe size : 250 µL
 Sample speed : Fast

Flush volume : 500 µL
 Flush speed : Medium
 Flush cycles : 2
 Pre-injection flush cycles : 0
 Post-injection flush cycles : 1
 Post-method flush cycles : 0

Needle level : 4.0 mm
 Inject delay time : 0.00 min
 Peltier tray temperature : Off

Peltier tolerance (+/-) : 1°C

Detector Parameters

Step	Time	Wavelength	Autozero
1	60.0	254	Yes

Lamp off at end of run : No

Pump Parameters

Step	Time	Flow	A	B	Curve
0	0.5	1.00	98	2	0.0
1	60.0	1.00	98	2	0.0

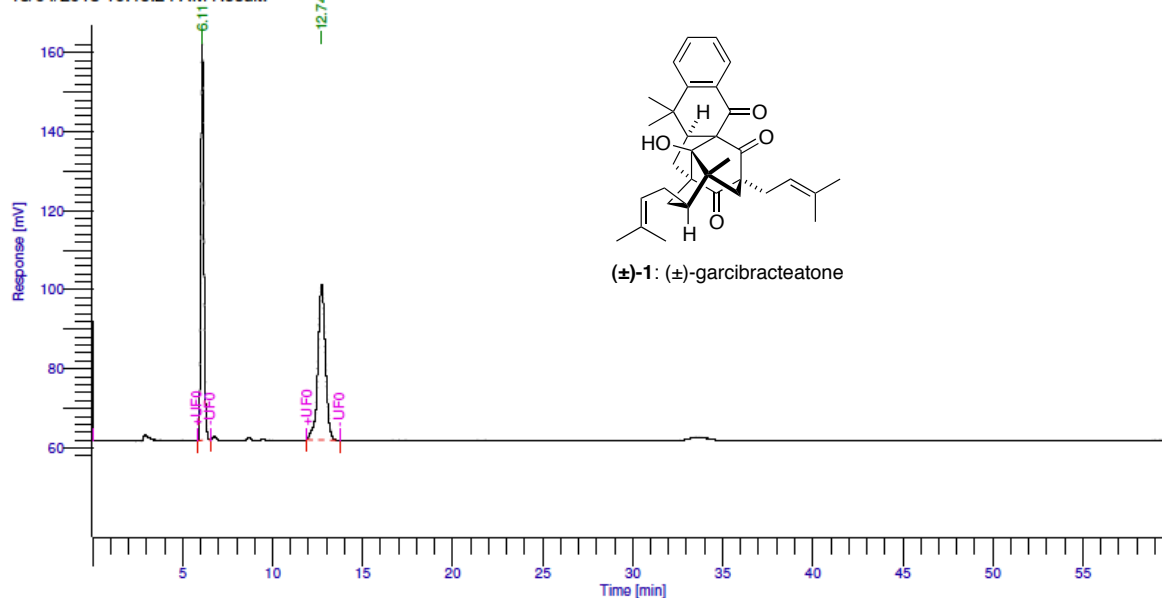
Ready Time : 500.0 min
 Standby Flow : 0.10 mL/min
 Saver Equ Time : 0.0 min
 Min Pressure : 0 PSI

Standby Time : 15.0 min
 Solvent Saver : No
 Shutdown : No
 Max Pressure : 6200 PSI

Timed Events

There are no timed events in the method

18/04/2013 10:46:24 AM Result:

**DEFAULT REPORT**

Peak #	Component Name	Time [min]	Area [µV*sec]	Height [µV]	Area [%]	Norm. Area [%]	BL	Raw Amount	Adjusted Amount
1		6.105	1092040.45	100560.32	48.90	48.90	MM	1.0920	1.0920
2		12.735	1141244.59	39415.02	51.10	51.10	MM	1.1412	1.1412
			2233285.04	139975.34	100.00	100.00		2.2333	2.2333

Software Version : 6.3.1.0504
 Sample Name : 4-HP-21a
 Instrument Name : Series 200 HPLC
 Rack/Vial : 1/3
 Sample Amount : 1.000000
 Cycle : 1

Date : 18/04/2013 1:14:26 PM
 Data Acquisition Time : 18/04/2013 10:30:14 AM
 Channel : A
 Operator : manager
 Dilution Factor : 1.000000

Result File :
 Sequence File : D:\Yujin\Sequence\garcibr.seq

Channel Parameters

Data will be collected from channel A
 Delay Time : 0.00 min
 Run Time : 20.00 min
 Sampling Rate : 10.0000 pts/s

	Channel A	Channel B
Signal Source	LC200UV	

Autosampler Method

Injection Source : Autosampler
 Injection volume : 10.0 µL
 Loop size : 100 µL
 Fixed mode : Off
 Excess volume : 1 µL
 Air cushion : 5 µL
 Sample syringe size : 250 µL
 Sample speed : Fast

Flush volume : 500 µL
 Flush speed : Medium
 Flush cycles : 2
 Pre-injection flush cycles : 0
 Post-injection flush cycles : 1
 Post-method flush cycles : 0

Needle level : 4.0 mm
 Inject delay time : 0.00 min
 Peltier tray temperature : OFF

Peltier tolerance (+/-) : 1°C

Detector Parameters

Step	Time	Wavelength	Autozero
1	20.0	254	Yes

Lamp off at end of run : No

Pump Parameters

Step	Time	Flow	A	B	Curve
0	0.5	1.00	98	2	0.0
1	20.0	1.00	98	2	0.0

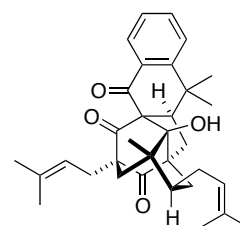
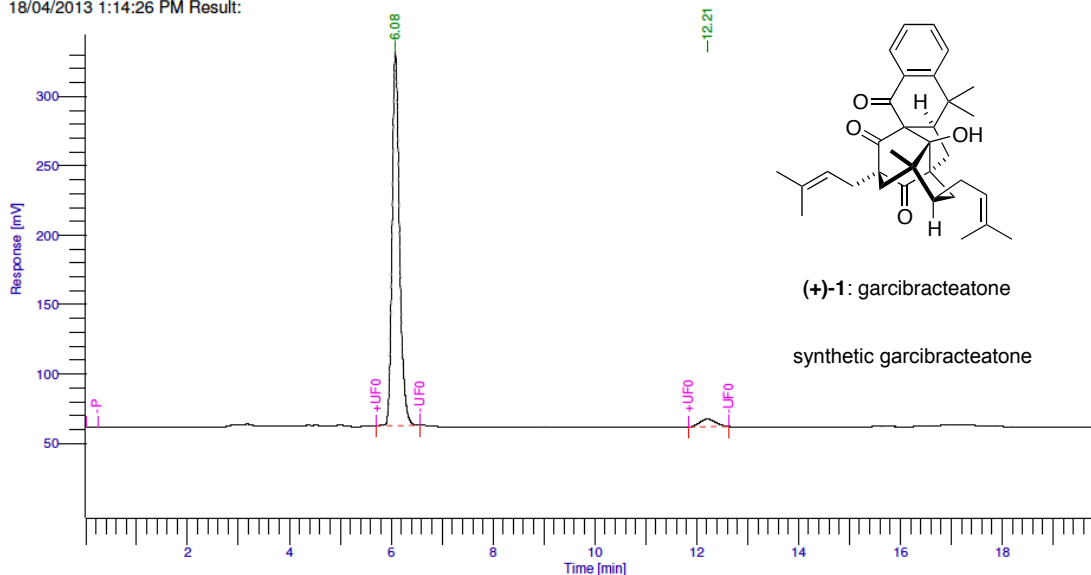
Ready Time : 500.0 min
 Standby Flow : 0.10 mL/min
 Saver Equ Time : 0.0 min
 Min Pressure : 0 PSI

Standby Time : 15.0 min
 Solvent Saver : No
 Shutdown : No
 Max Pressure : 6200 PSI

Timed Events

There are no timed events in the method

18/04/2013 1:14:26 PM Result:

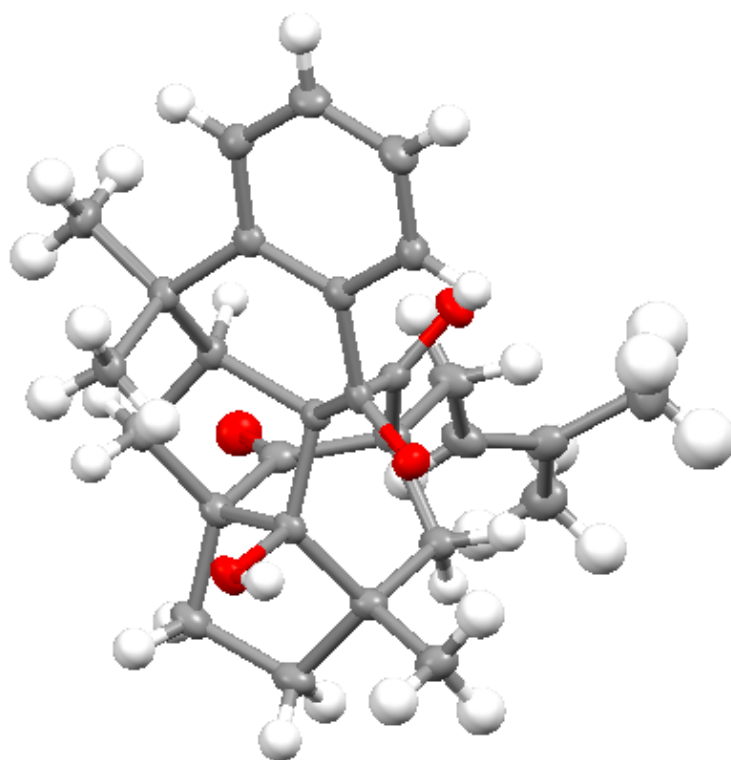


(+)-1: garcibracteateone

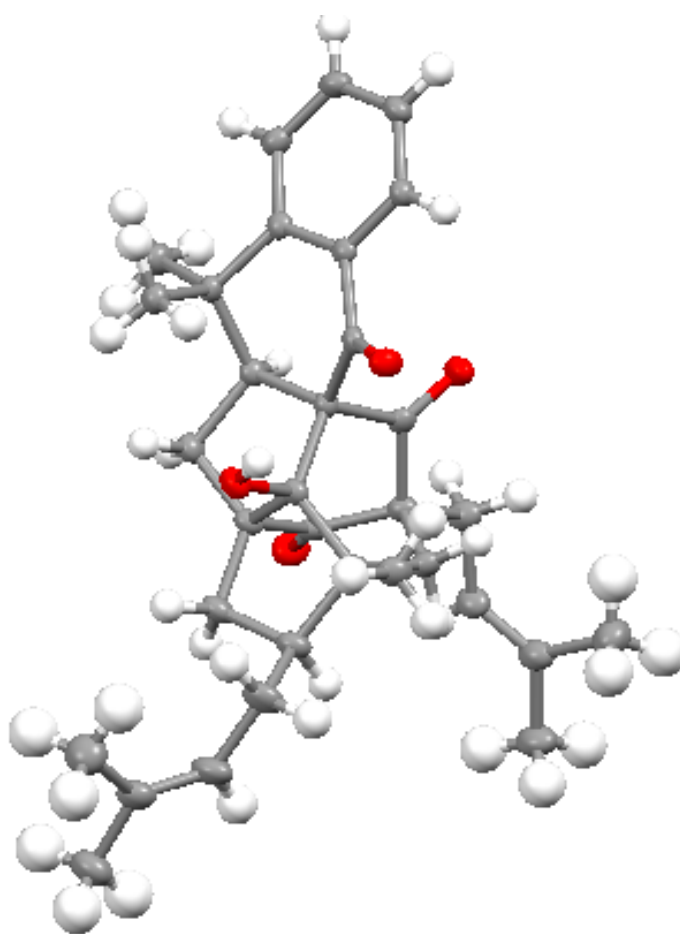
synthetic garcibracteateone

DEFAULT REPORT

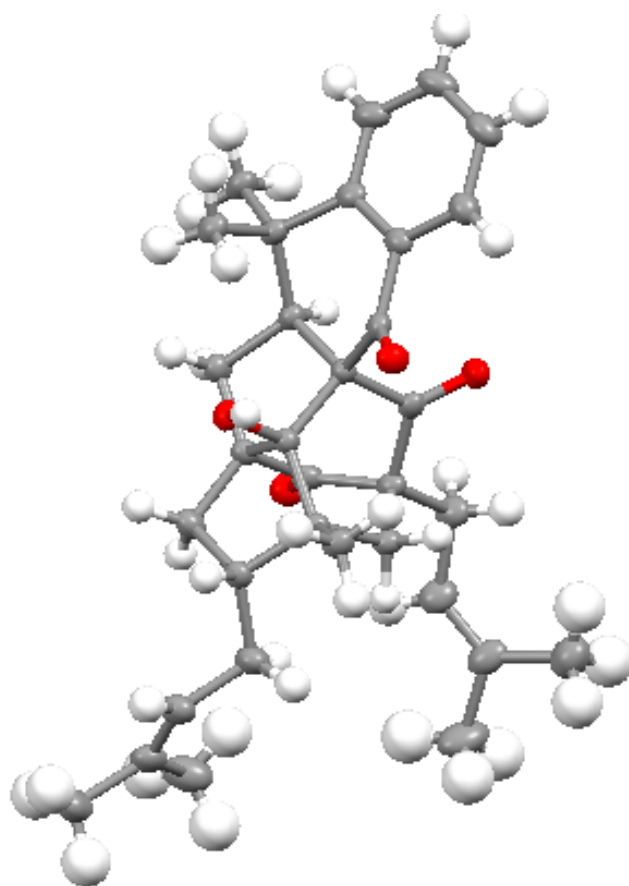
Peak #	Component Name	Time [min]	Area [µV*sec]	Height [µV]	Area [%]	Norm. Area [%]
1		6.08	2725610.28	269521.69	95.74	95.74
2		12.21	121396.90	5541.51	4.26	4.26
		2847007.17	275063.20	100.00	100.00	100.00



Thermal ellipsoid plot for compound 19



Thermal ellipsoid plot for garcibracteatone (1)



Thermal ellipsoid plot for 5-*epi*-garcibracteatone (25)