

Supporting information – NMR spectra, HPLC analysis and crystal data for *ent*-17a

Synthetic Study of Natural Metabolites Containing a Benzo[*c*]oxepine Skeleton: Heterocornol C and D

Ján Gettler,[†] Tomáš Čarný,[†] Martin Markovič,^{‡} Peter Koóš,^{*‡} Erika Samolová,[#]
Ján Moncol[§] and Tibor Gracza[†]*

[†]Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia

[‡] Georganics Ltd., Koreničova 1, SK-811 03 Bratislava, Slovakia

[#] Institute of Physics of the Czech Academy of Science, Na Slovance 2, 182 21 Prague 8, Czech Republic

[§]Department of Inorganic Chemistry, Institute of Inorganic Chemistry, Technology and Materials, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia

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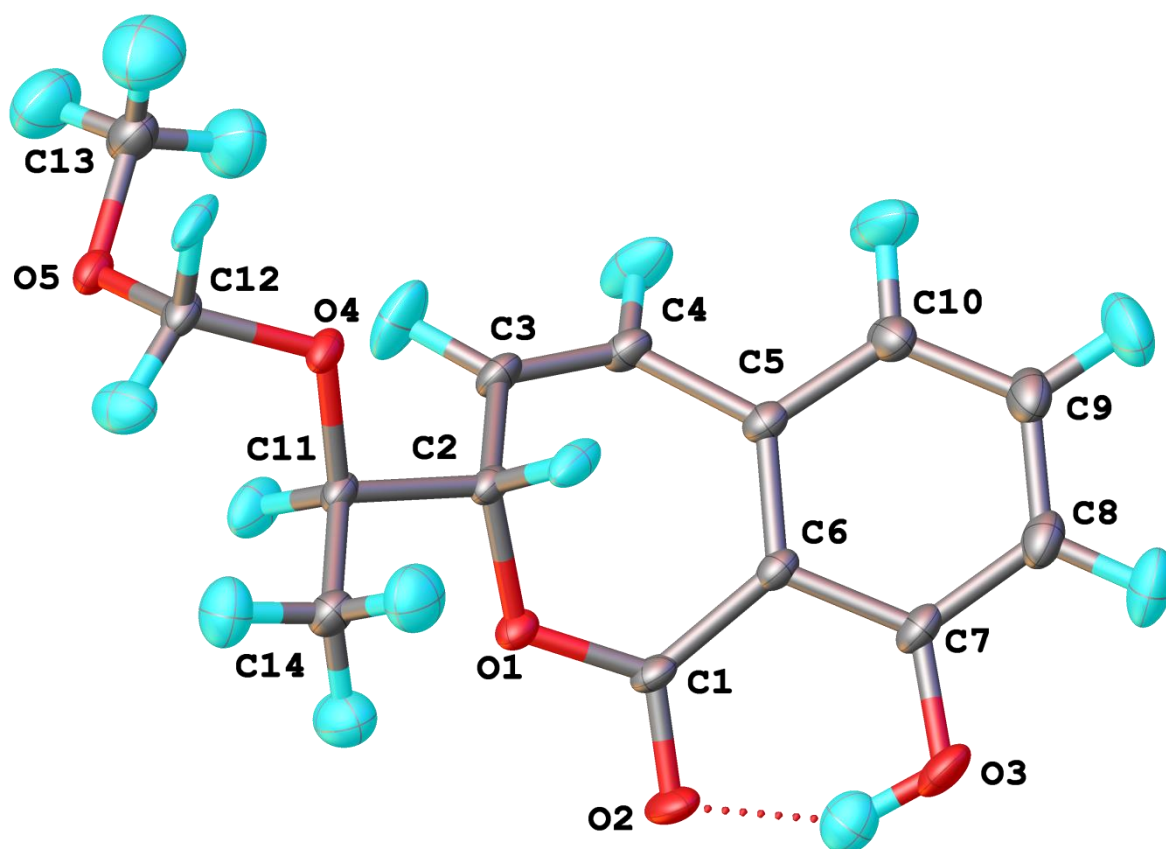


Figure S1. An ORTEP view of *ent*-17a showing the atom-numbering scheme of non-hydrogen atoms. Displacement ellipsoids are plotted at the 50% probability level.

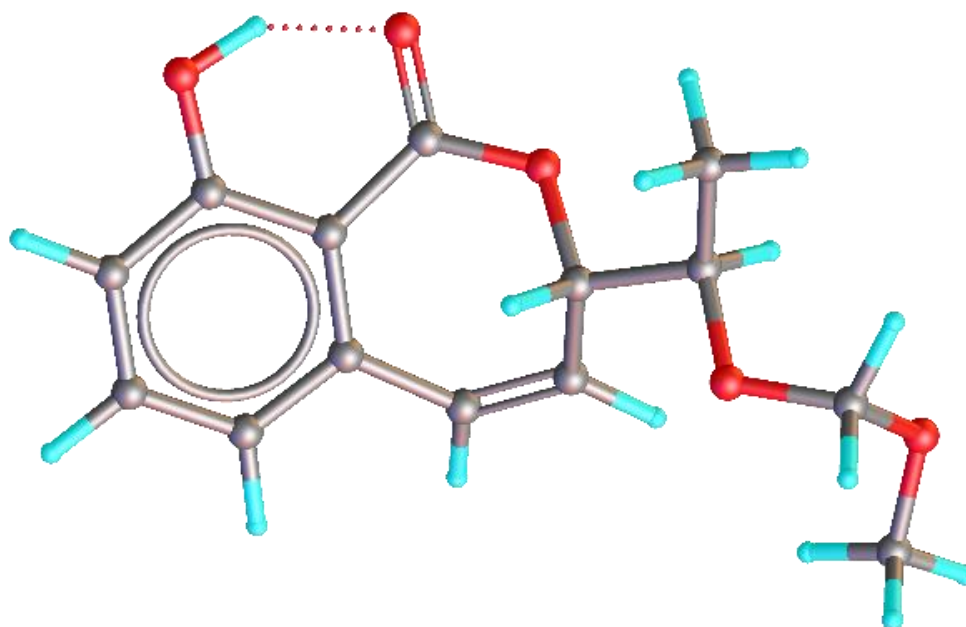


Figure S2. A ball-and-stick view of crystal structure of *ent*-17a.

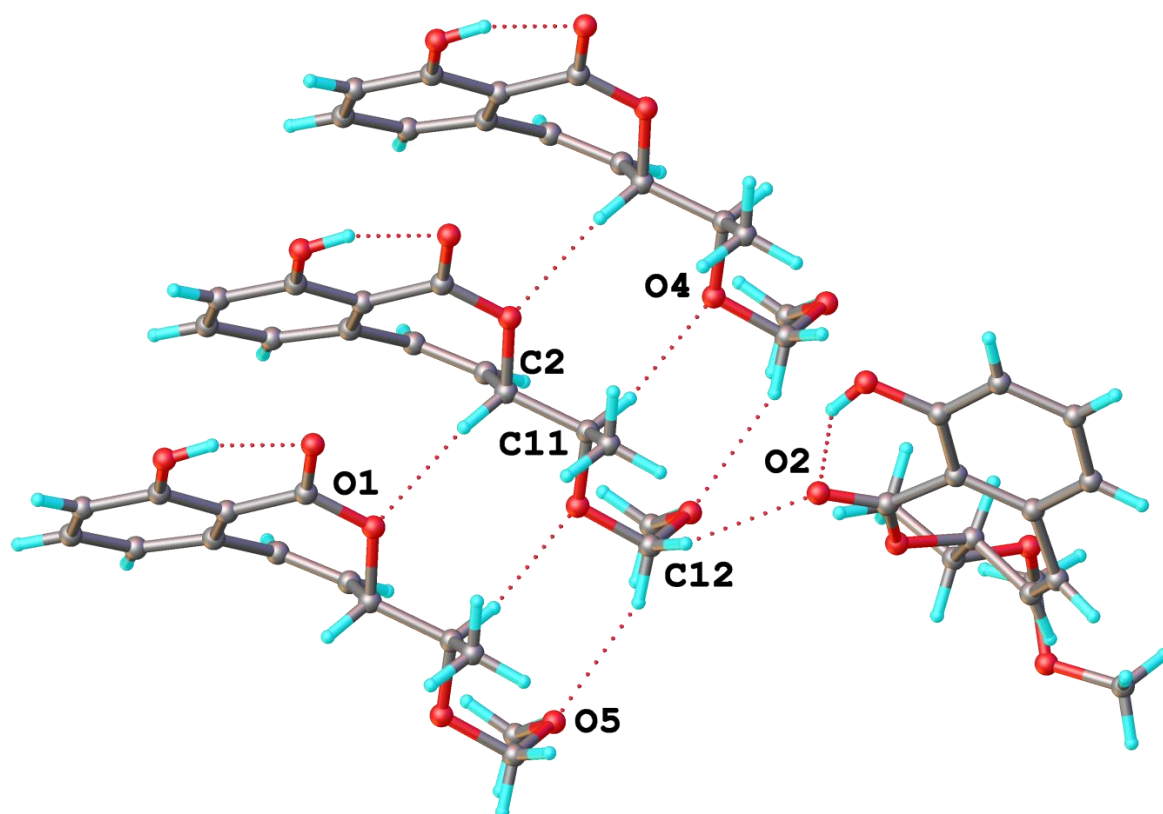


Figure S3. Crystal structure of *ent*-17a showing C–H···O hydrogen bonds.

Crystal Data for *ent*-17a: C₁₄H₁₆O₅ (*M* = 264.27 g/mol): monoclinic, space group *P*2₁ (no. 4), *a* = 4.27815(5) Å, *b* = 12.64187(14) Å, *c* = 11.93812(17) Å, β = 98.3328(15)°, *V* = 638.843(17) Å³, *Z* = 2, *T* = 95 K, μ (CuK α) = 0.873 mm^{−1}, *D*_{calc} = 1.374 g/cm³, 12519 reflections measured (7.484° ≤ 2 Θ ≤ 147.14°), 2520 unique (*R*_{int} = 0.0377, *R*_{sigma} = 0.0266) which were used in all calculations. IAM: The final *R*₁ was 0.0269 (*I* > 2 σ (*I*)) and *wR*₂ was 0.0675 (all data). CCDC no. 2222838. HAR: The final *R*₁ was 0.0184 (*I* > 2 σ (*I*)) and *wR*₂ was 0.0404 (all data). CCDC no. 2222839. The Flack parameters for the IAM and HAR model have the value of *x* = 0.01(7) and 0.07(7), respectively. The Hooft parameter has a value of *y* = 0.04(6) for both models.

Table S1. Hydrogen Bonds for *ent*-17a (IAM).

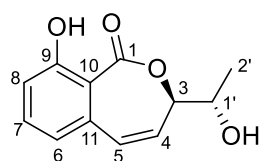
D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O3	H3	O2	0.8400	1.8161(17)	2.5503(15)	145.03(13)
C11	H11	O4 ¹	1.0000	2.4857(17)	3.4719(17)	168.75(3)
C2	H2	O1 ²	1.0000	2.5860(16)	3.5763(16)	170.62(4)
C12	H12a	O5 ²	0.9900	2.4544(16)	3.3739(16)	154.31(3)
C12	H12b	O2 ³	0.9900	2.5997(16)	3.4750(17)	147.41(4)

¹-1+*X*,+*Y*,+*Z*; ²1+*X*,+*Y*,+*Z*; ³1-*X*,1/2+*Y*,1-*Z*

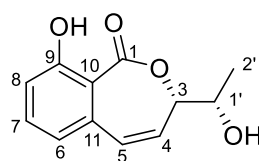
Table S2. Hydrogen Bonds for *ent*-**17a** (HAR).

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O3	H3	O2	0.990(9)	1.664(11)	2.5451(11)	145.9(13)
C11	H11	O4 ¹	1.104(8)	2.387(8)	3.4763(12)	168.8(9)
C2	H2	O1 ²	1.105(8)	2.488(8)	3.5814(12)	170.0(9)
C12	H12a	O5 ²	1.099(8)	2.327(8)	3.3774(12)	159.2(8)
C12	H12b	O2 ³	1.109(8)	2.472(9)	3.4762(12)	149.8(10)

¹-1+X,+Y,+Z; ²1+X,+Y,+Z; ³1-X,1/2+Y,1-Z

Table S3. Comparison of the NMR data of synthetic and natural heterocornol D.

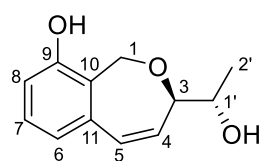
heterocornol D

diastereoisomer (**3b**)

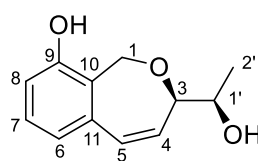
position	natural (Lei et al. ⁸)	synthetic	
	δ_{H} (m, J [Hz])	heterocornol D (3a) δ_{H} (m, J [Hz])	diastereoisomer 3b δ_{H} (m, J [Hz])
1	-	-	-
3	4.45 (brt, 5.8)	4.46 (ddd, 5.8, 4.7, 1.8)	4.46 (td, 5.8, 1.7)
4	6.42 (dd, 10.3, 5.8)	6.41 (dd, 10.4, 5.8)	6.34 (dd, 10.3, 5.9)
5	6.97 (brd, 10.3)	6.98 (brd, 10.4)	6.95 (brd, 10.4)
6	6.88 (d, 8.1)	6.88 (d, 7.6)	6.88 (d, $J = 7.5$)
7	7.45 (t, 7.9)	7.45 (t, 7.9)	7.45 (t, 7.9)
8	6.97 (d, 7.9)	6.98 – 6.96 (m)	6.97 (dd, 8.2, 1.1)
9	-	-	-
10	-	-	-
11	-	-	-
1'	4.08 (m)	4.10 – 4.05 (m)	4.06 (quint., 6.4)
2'	1.27 (d, 6.4)	1.27 (d, 6.5)	1.28 (d, 6.5)

position	natural (Lei et al. ⁸)	synthetic	
	δ_{C}	heterocornol D (3a) δ_{C}^*	diastereoisomer 3b δ_{C}
1	171.0, C	172.5	172.5
3	77.5, CH	79.0	79.1
4	135.3, CH	136.8	136.8
5	129.7, CH	131.2	131.4
6	120.3, CH	121.8	121.8
7	133.2, CH	134.7	134.7
8	116.9, CH	118.3	118.4
9	160.3, C	161.8	161.8
10	115.0, C	116.5	116.5
11	136.9, C	138.4	138.3
1'	66.8, CH	68.3	68.1
2'	17.4, CH ₃	18.8	18.6

* the difference of + 1.4 ppm in shifts for all signals compared to natural compound was caused by different locking of NMR spectra. The ¹³C NMR spectrum of synthetic compound was locked to residual solvent peak (MeOH 49.00 ppm).

Table S4. Comparison of the NMR data of synthetic and natural heterocornol C.

heterocornol C

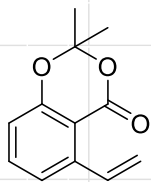
diastereoisomer **18**

position	natural (Lei et al. ⁸)	synthetic	
	δ_{H} (m, <i>J</i> [Hz])	heterocornol C (1) δ_{H} (m, <i>J</i> [Hz])	diastereoisomer 18 δ_{H} (m, <i>J</i> [Hz])
1	5.23 (d, 13.7)	5.23 (d, 13.8)	5.25, (d, 13.8)
3	4.35 (m)	4.35 (dt, 5.0, 2.4)	4.40 (dt, 5.0, 2.4)
4	5.96, dd (12.4, 2.0)	5.96 (dd, 12.4, 2.5)	5.89 (dd, 12.5, 2.5)
5	6.50 (brd, 12.4)	6.50 (dd, 12.5, 2.3)	6.54 (dd, 12.5, 2.3)
6	6.72 (d, 7.5)	6.72 (d, 7.5)	6.73, d (7.5)
7	7.02 (t, 7.5)	7.03 (t, 7.8)	7.03, t (7.8)
8	6.66 (d, 7.5)	6.67 (d, 8.1)	6.67, d (8.1)
9	-	-	-
10	4.44 (d, 13.7)	4.45 (d, 13.8)	4.46, (d, 13.8)
11	-	-	-
1'	3.76 (m)	3.77 (qd, 6.4, 5.3)	3.85 (qd, 6.4, 5.3)
2'	1.19 (d, 6.4)	1.19 (d, 6.4)	1.15 (d, 6.4)

position	natural (Lei et al. ⁸)	synthetic	
	δ_{C}	heterocornol C (1) δ_{C}^*	diastereoisomer 18 δ_{C}
1	63.5, CH ₂	64.9, CH ₂	64.8, CH ₂
3	86.1, CH	87.4, CH	87.3, CH
4	132.2, CH	133.6, CH	133.0, CH
5	130.1, CH	131.4, CH	132.1 CH
6	121.8, CH	123.2, CH	123.1, CH
7	127.6, CH	129.0, CH	129.0, CH
8	113.8, CH	115.1, CH	115.2, CH
9	153.5, C	154.9, C	155.1, C
10	125.7, C	127.1, C	127.2, C
11	137.6, C	139.0, C	139.0, C
1'	69.4, CH	70.8, CH	70.3, CH
2'	17.7, CH ₃	19.1, CH ₃	18.7, CH ₃

* the difference of + 1.4 ppm in shifts for all signals compared to natural compound was caused by different locking of NMR spectra. The ¹³C NMR spectrum of synthetic compound was locked to residual solvent peak (MeOH 49.00 ppm).

¹H NMR (300MHz, CDCl₃)



8

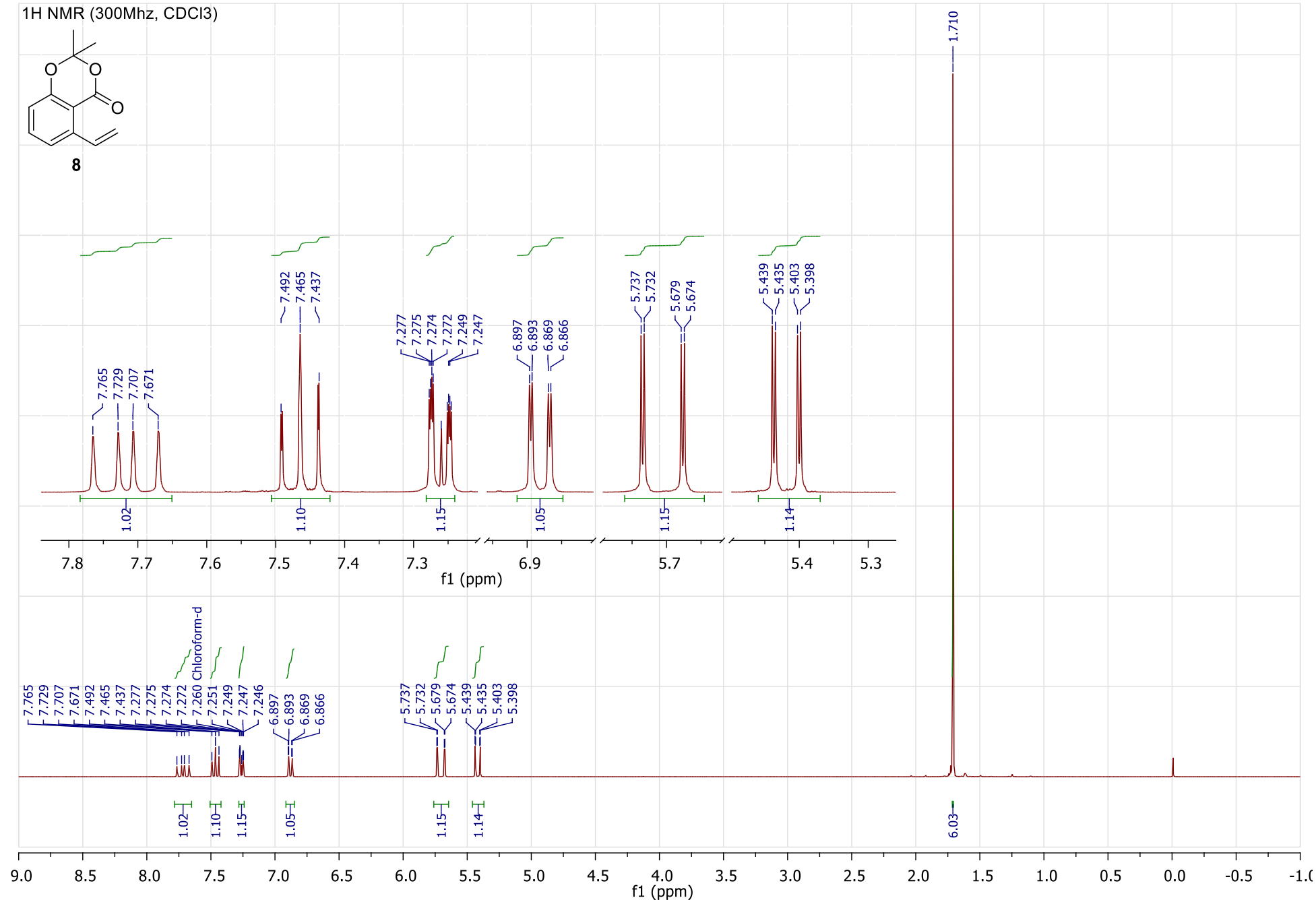


Figure S4. ¹H NMR spectrum of **8**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)

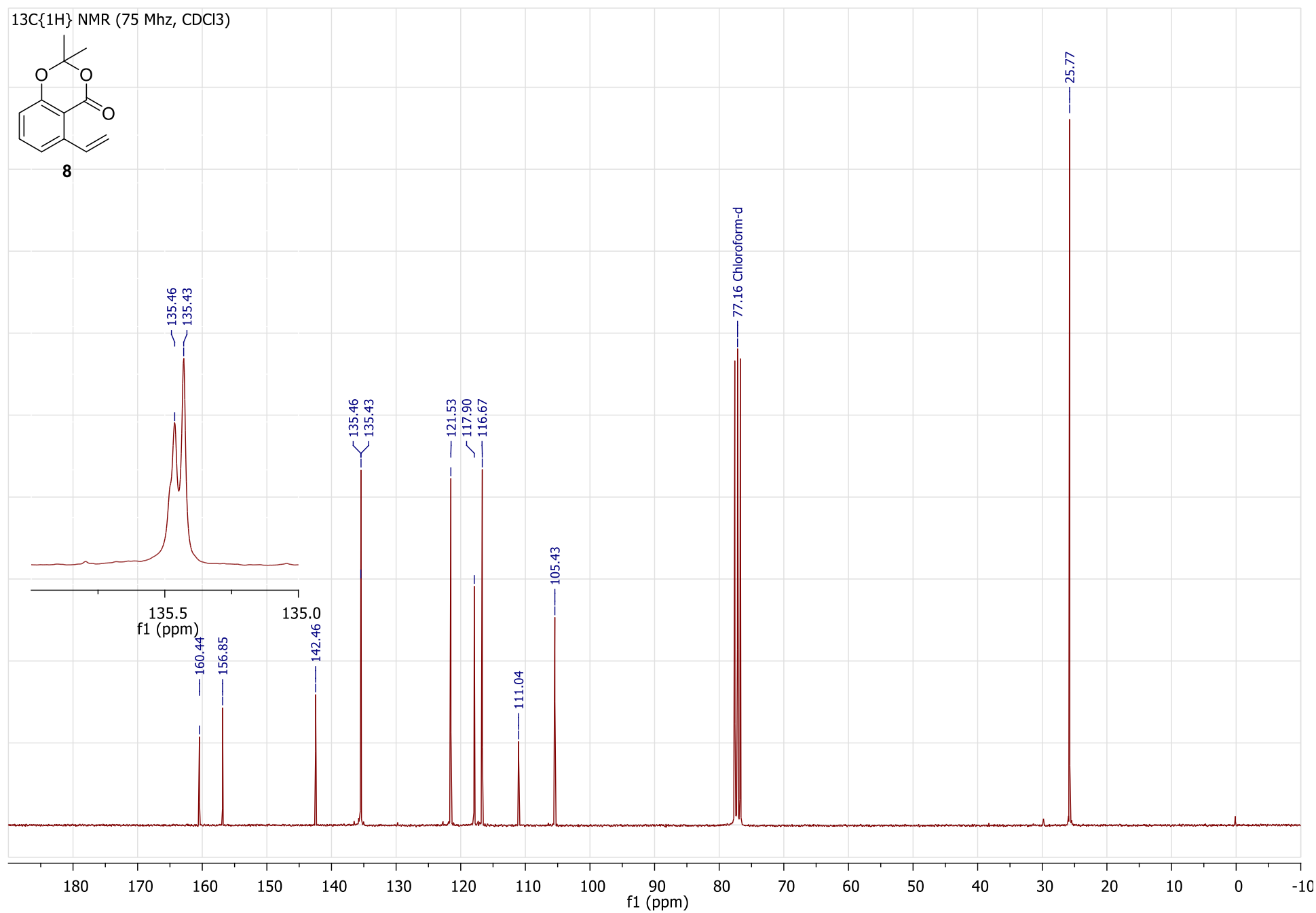
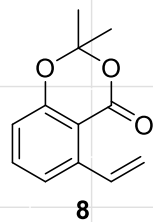


Figure S5. ^{13}C NMR spectrum of **8**.

¹H NMR (CDCl₃, 300 MHz)

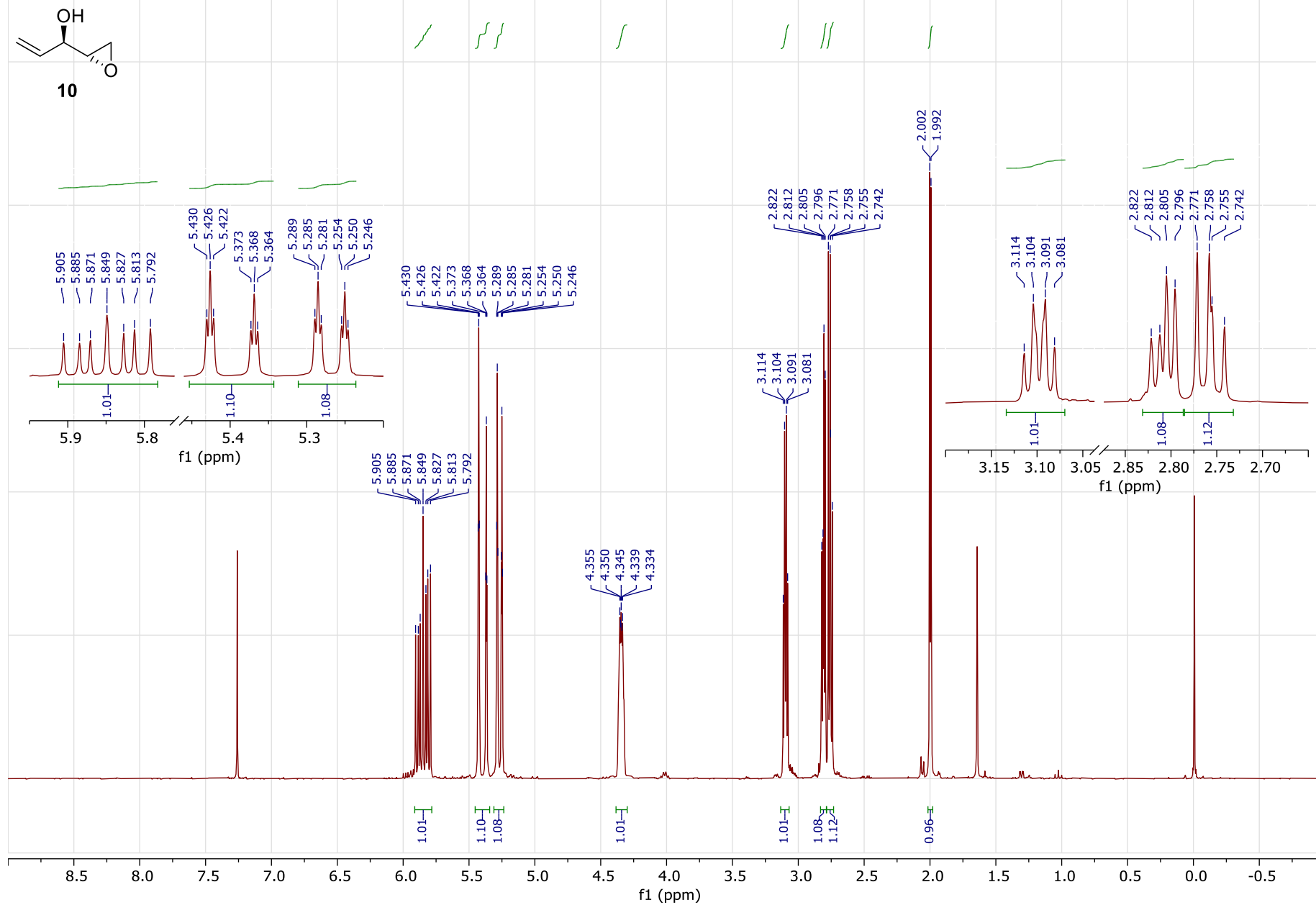


Figure S6. ¹H NMR spectrum of **10**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)

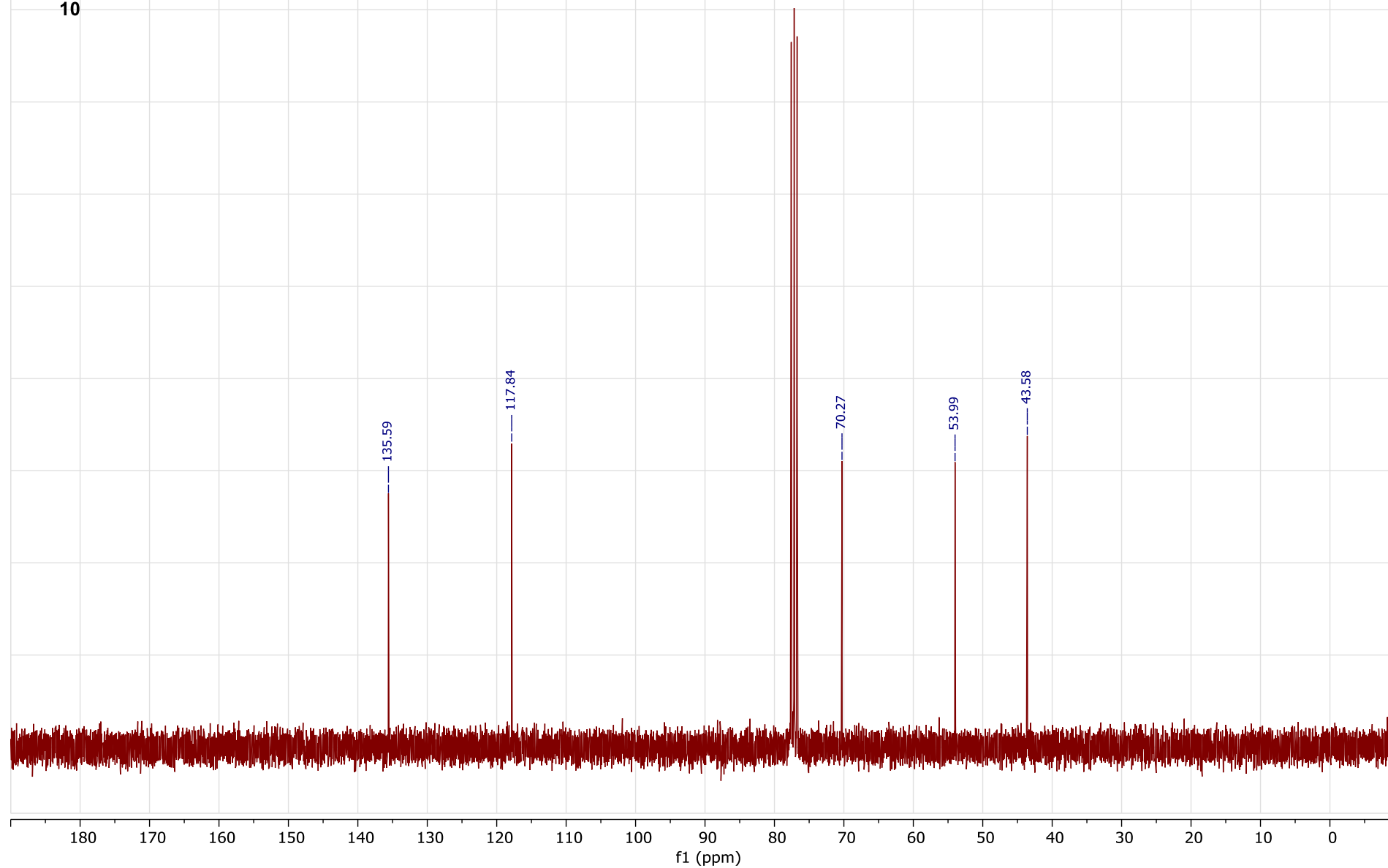
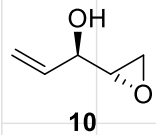


Figure S7. ^{13}C NMR spectrum of **10**.

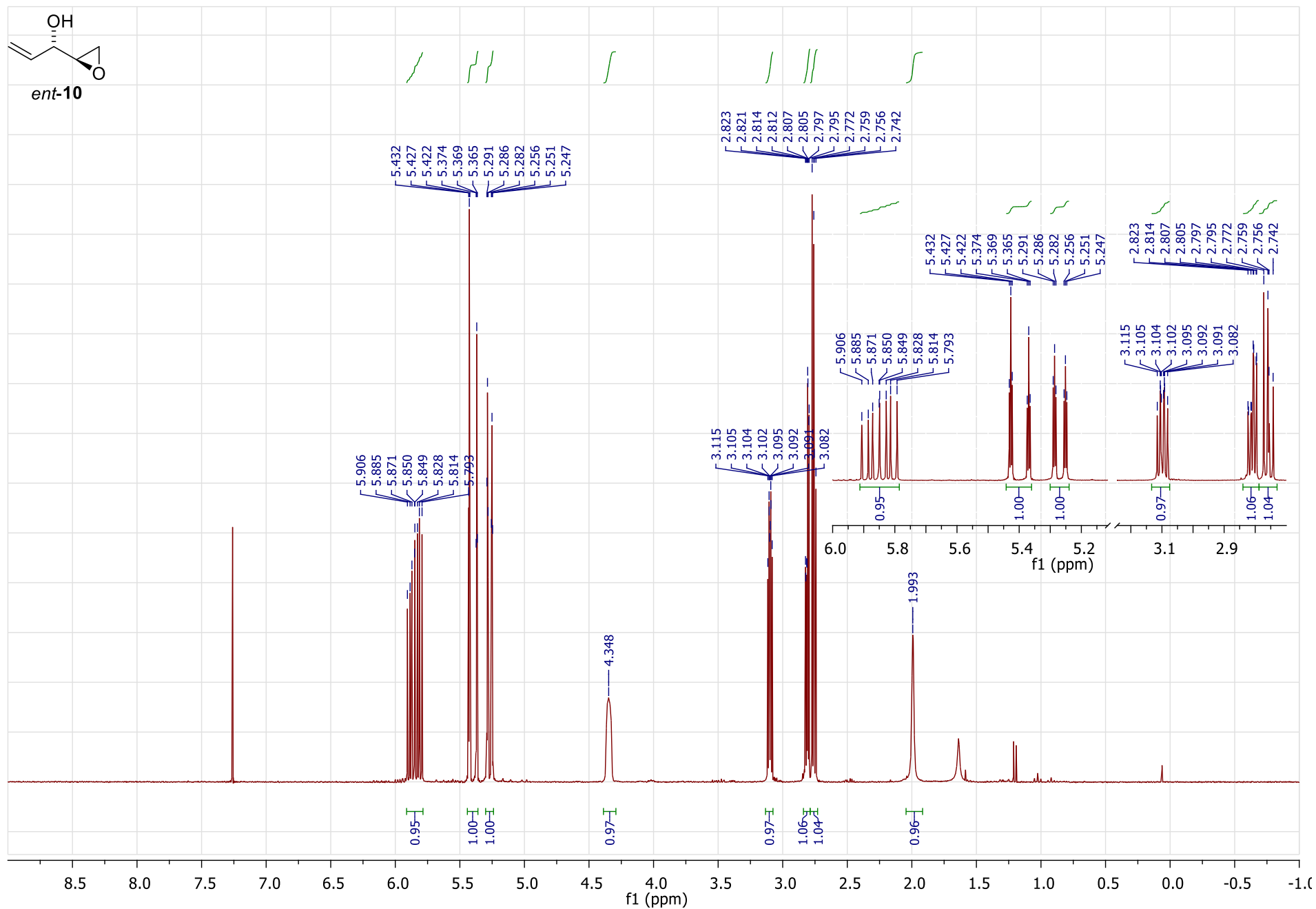


Figure S8. ^1H NMR spectrum of *ent-10*.

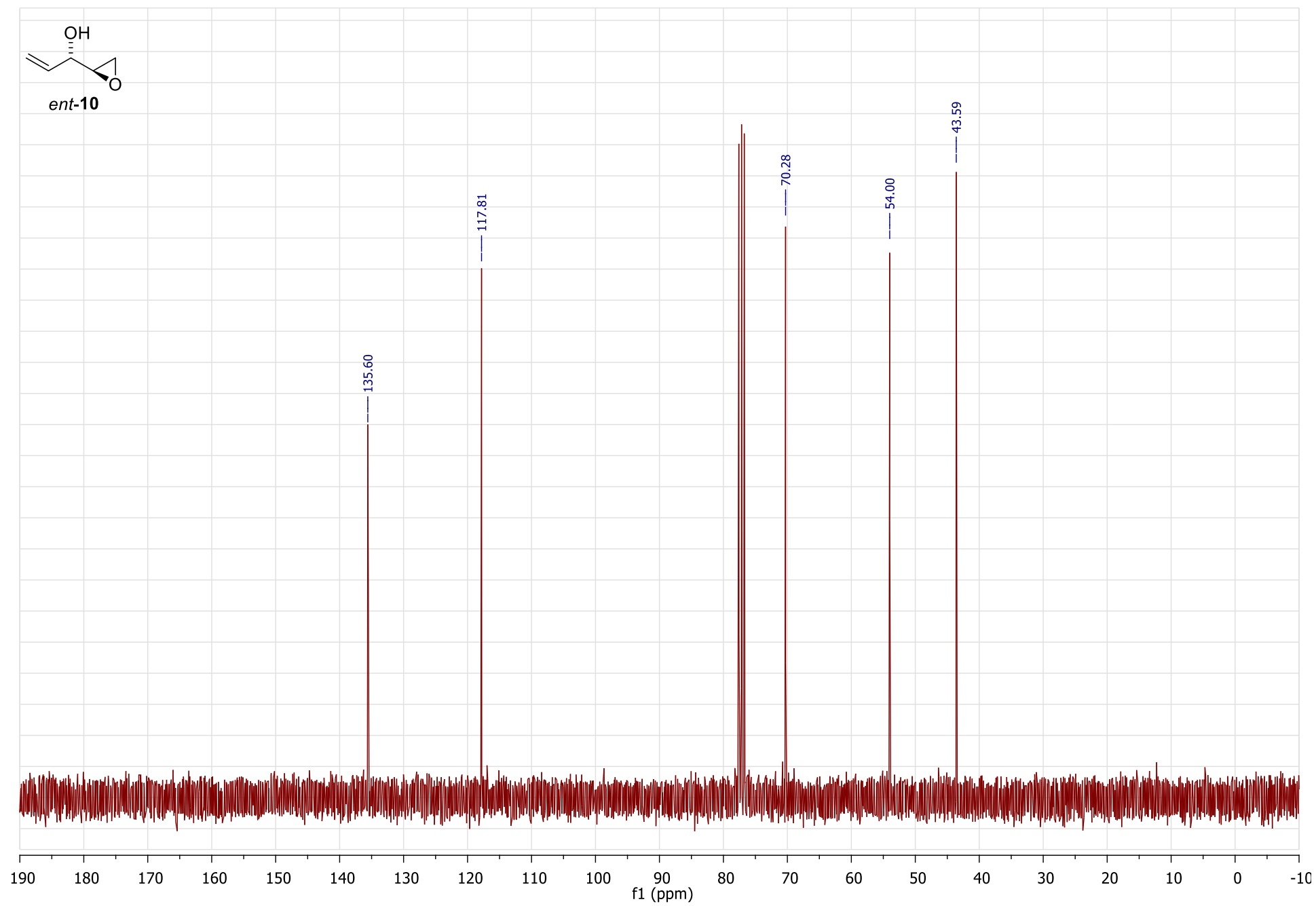
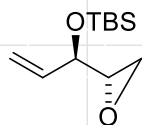


Figure S9. ^{13}C NMR spectrum of *ent-10*.

¹H NMR (300 Mhz, CDCl₃)



11

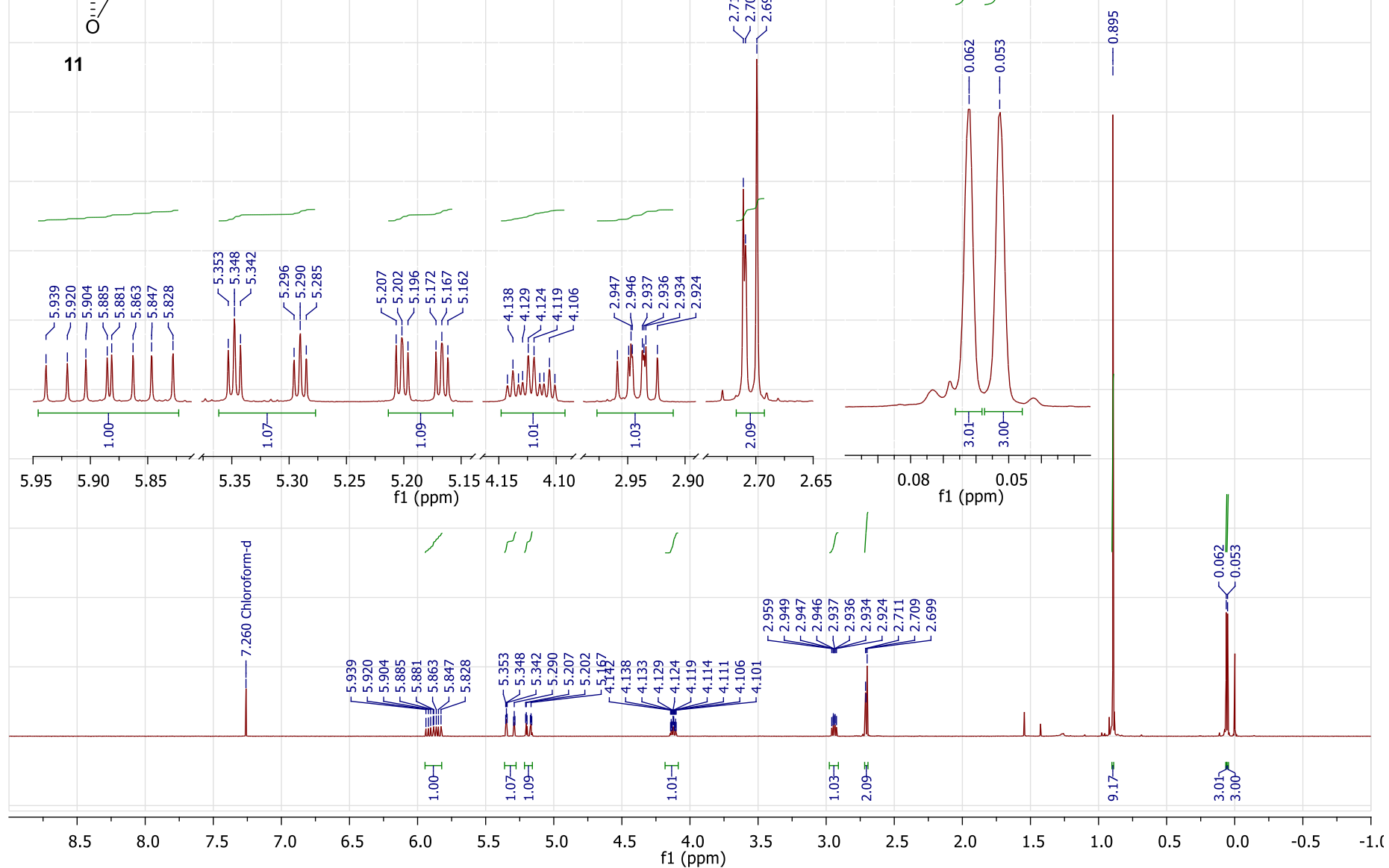


Figure S10. ¹H NMR spectrum of **11**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)

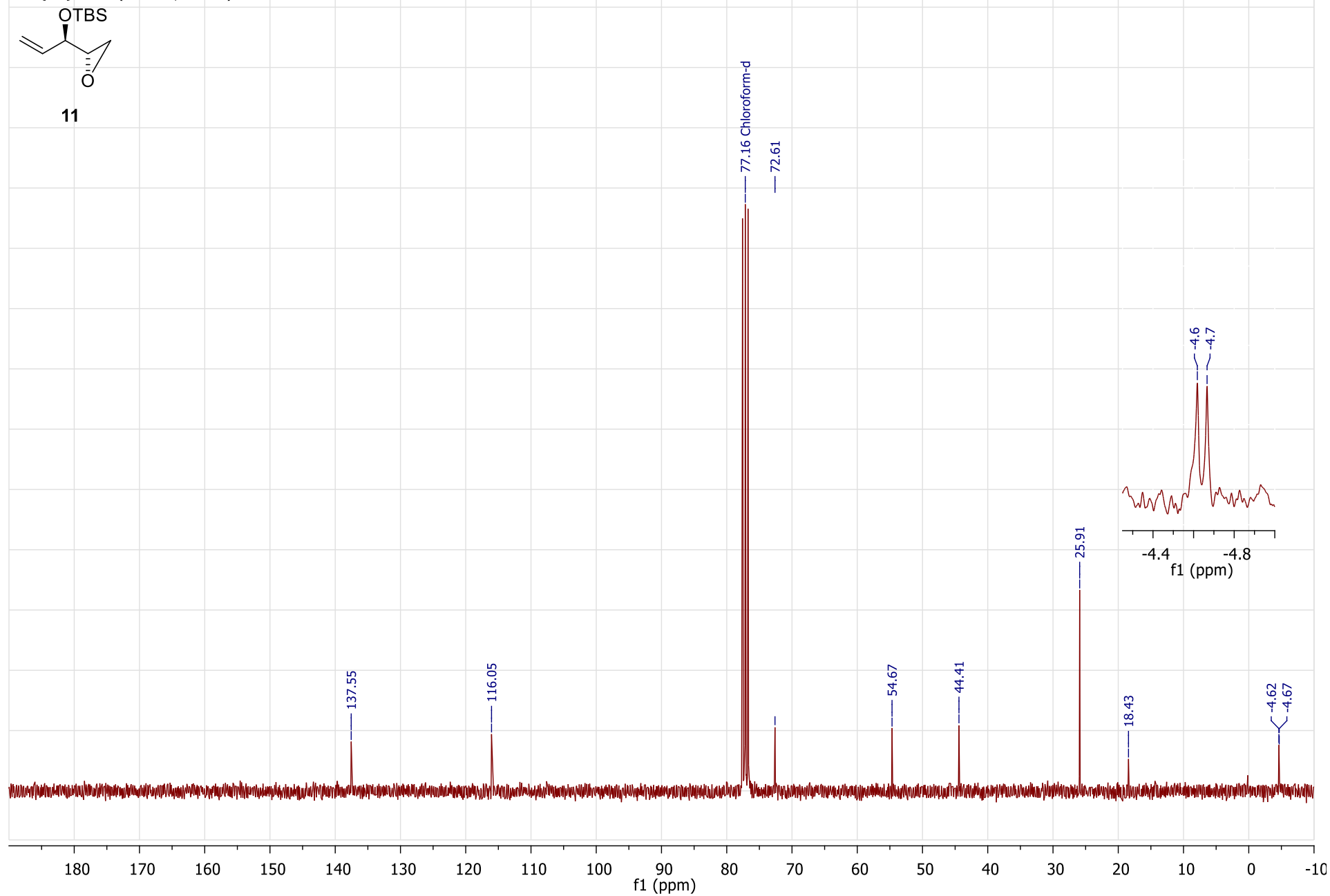
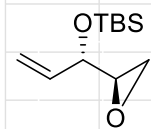


Figure S11. ^{13}C NMR spectrum of **11**.

¹H NMR (300 Mhz, CDCl₃)



ent-11

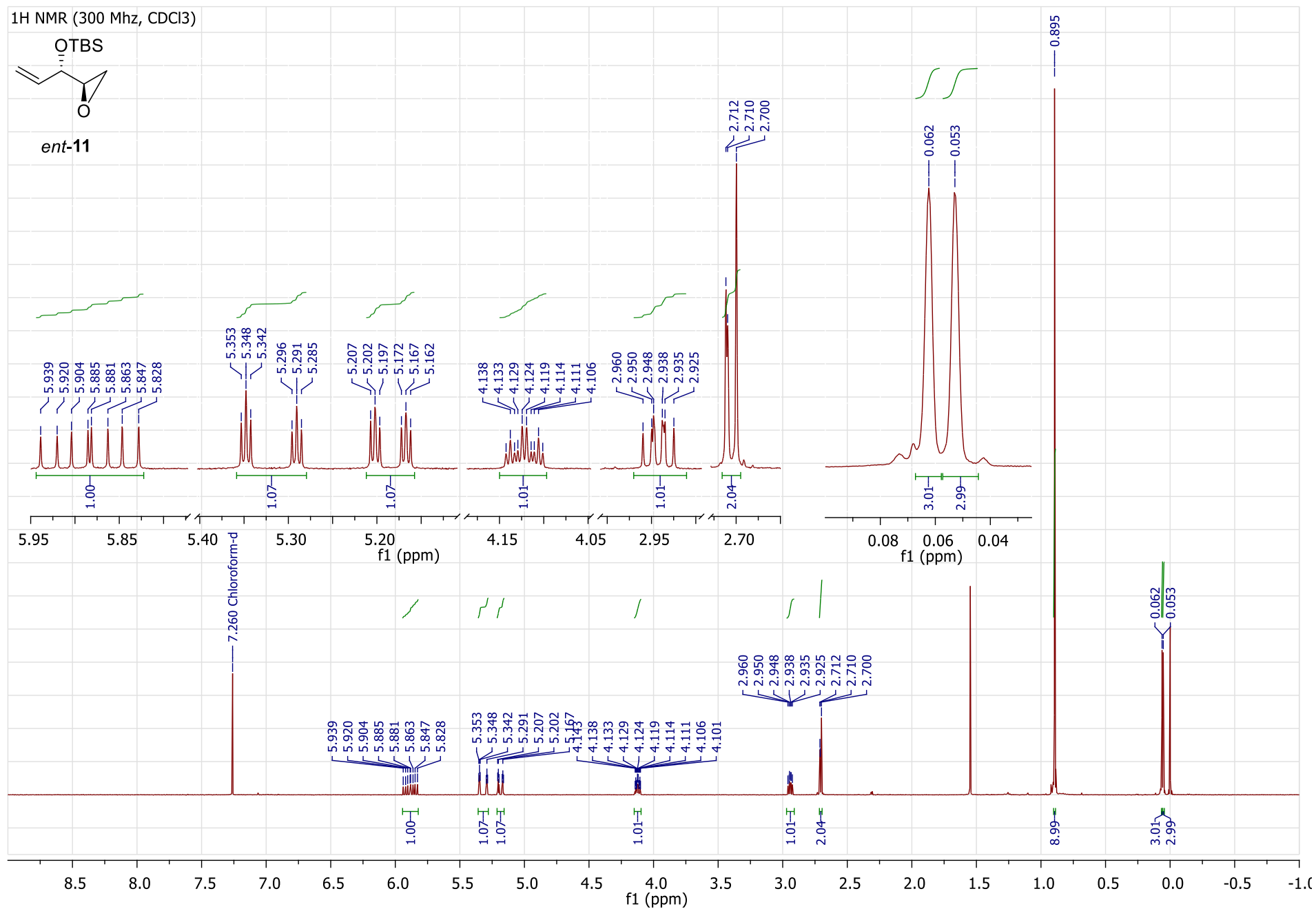


Figure S12. ¹H NMR spectrum of *ent*-11.

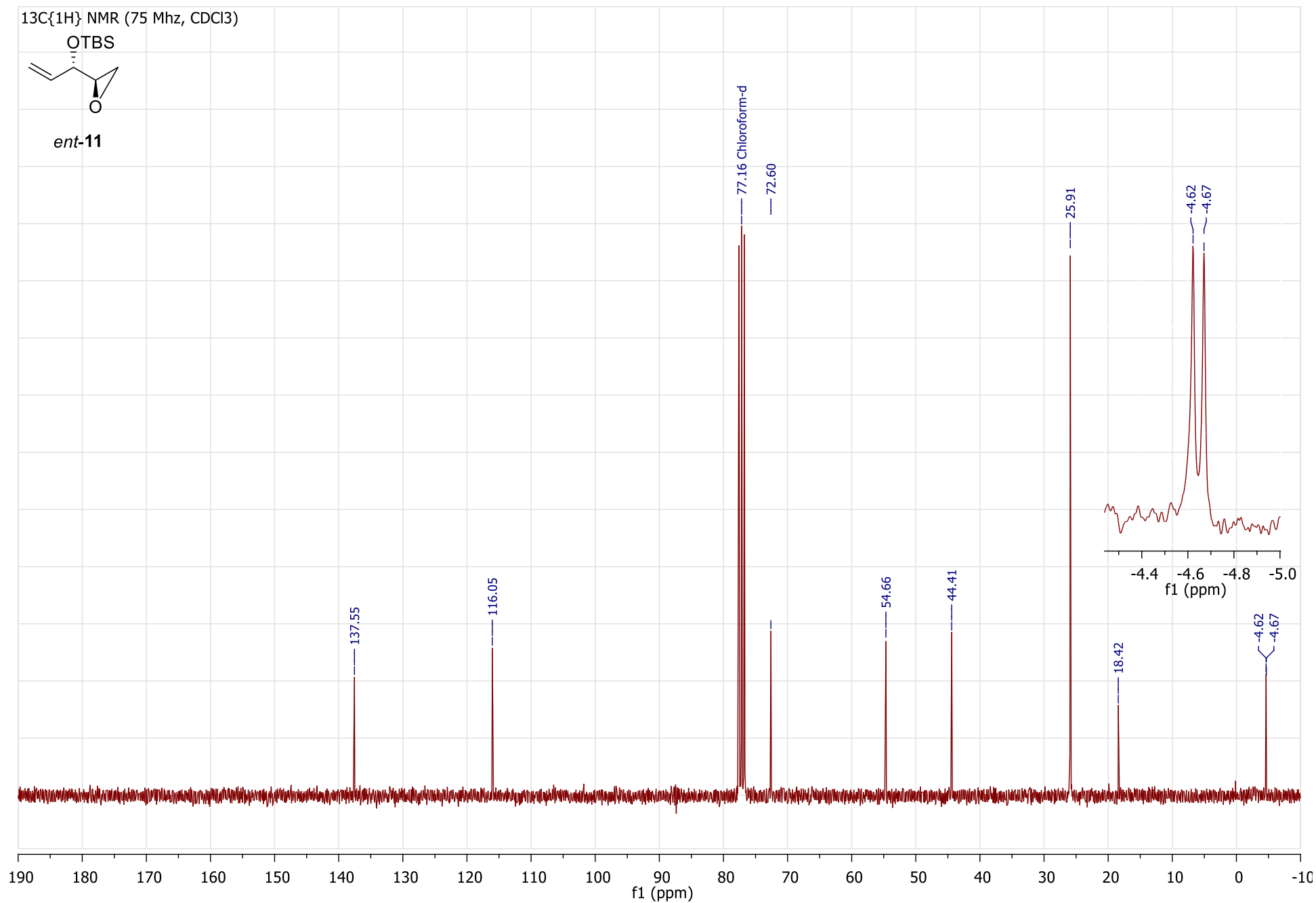


Figure S13. ^{13}C NMR spectrum of *ent*-11.

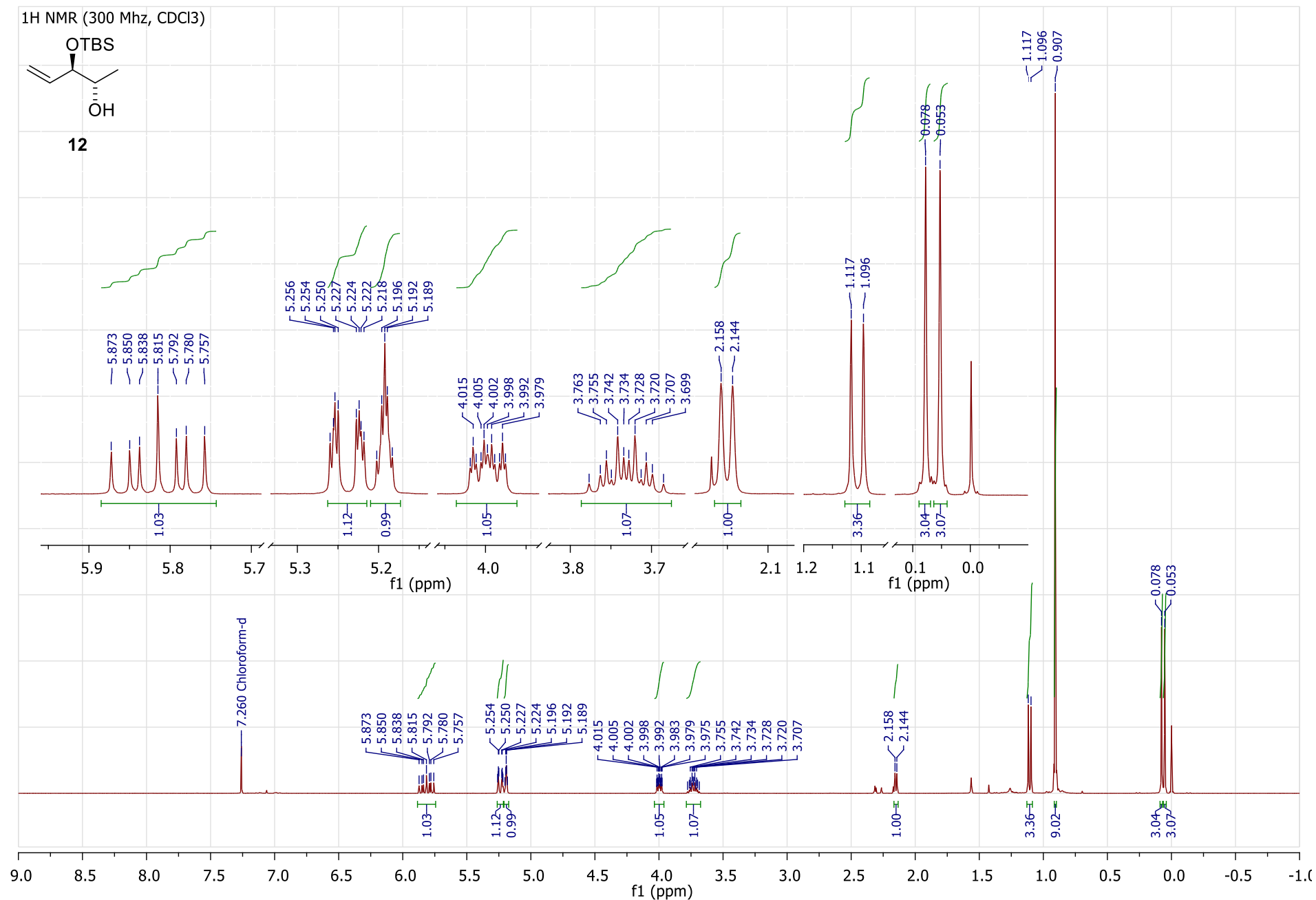


Figure S14. ¹H NMR spectrum of **12**.

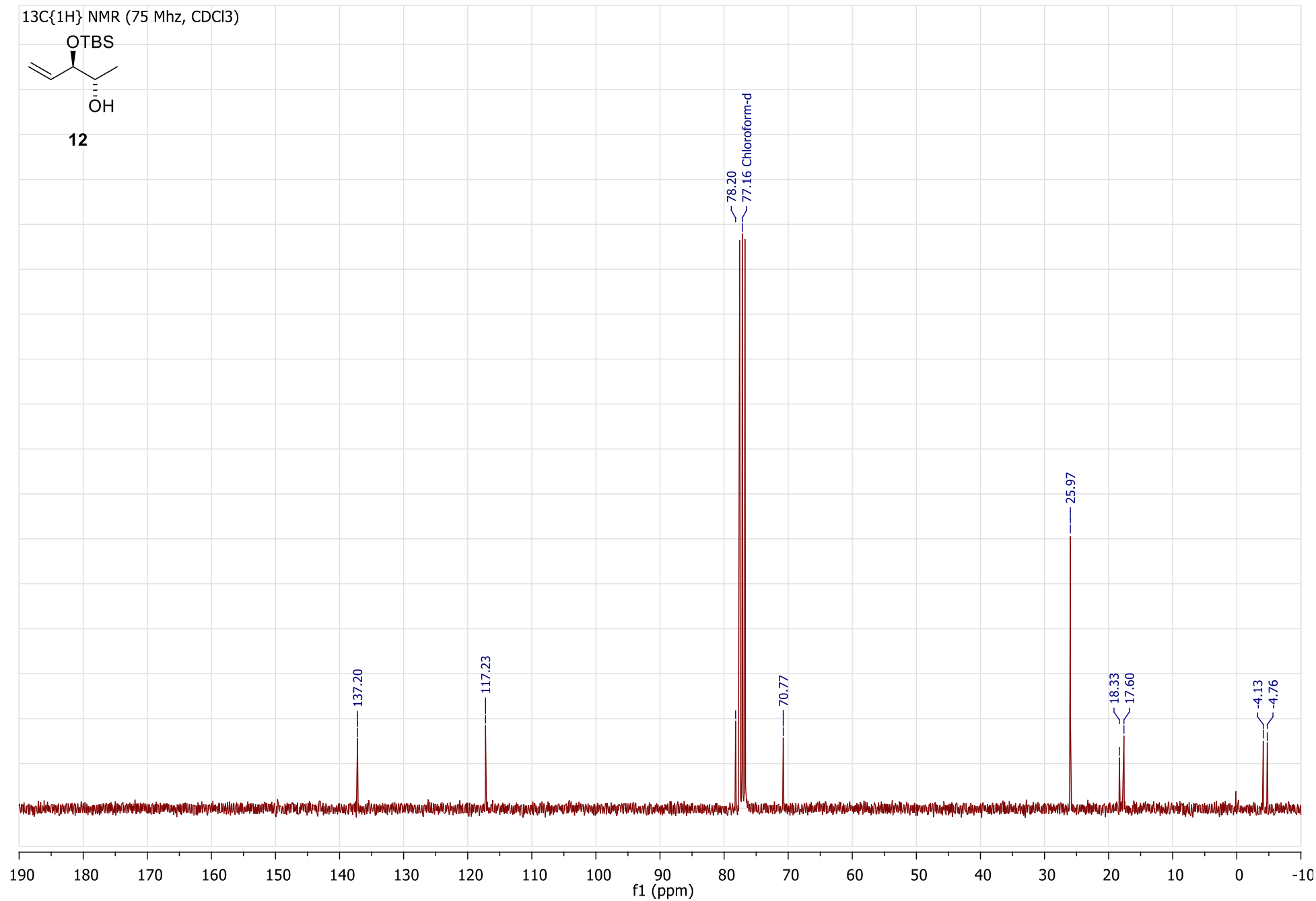


Figure S15. ^{13}C NMR spectrum of **12**.

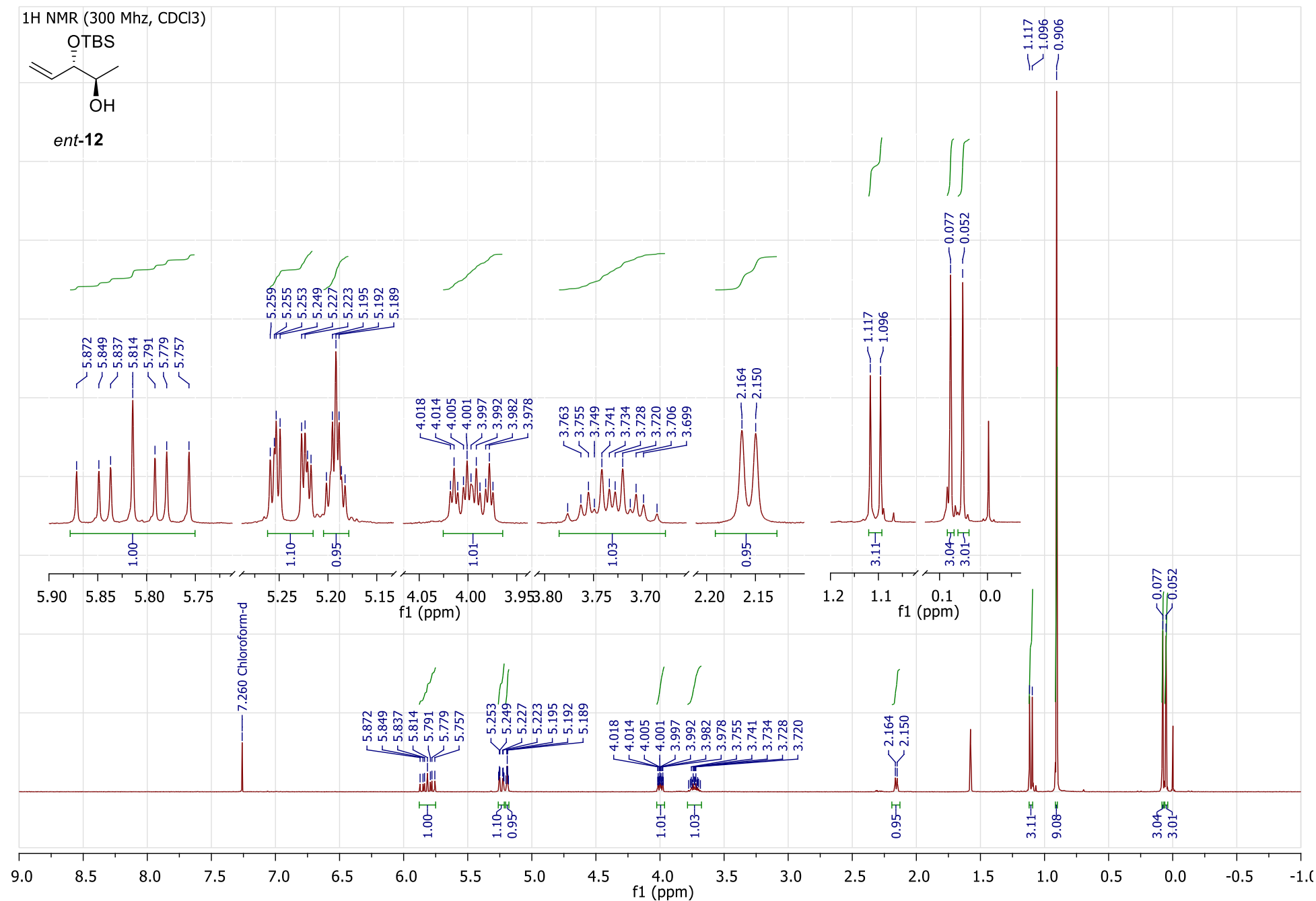


Figure S16. ¹H NMR spectrum of **ent-12**.

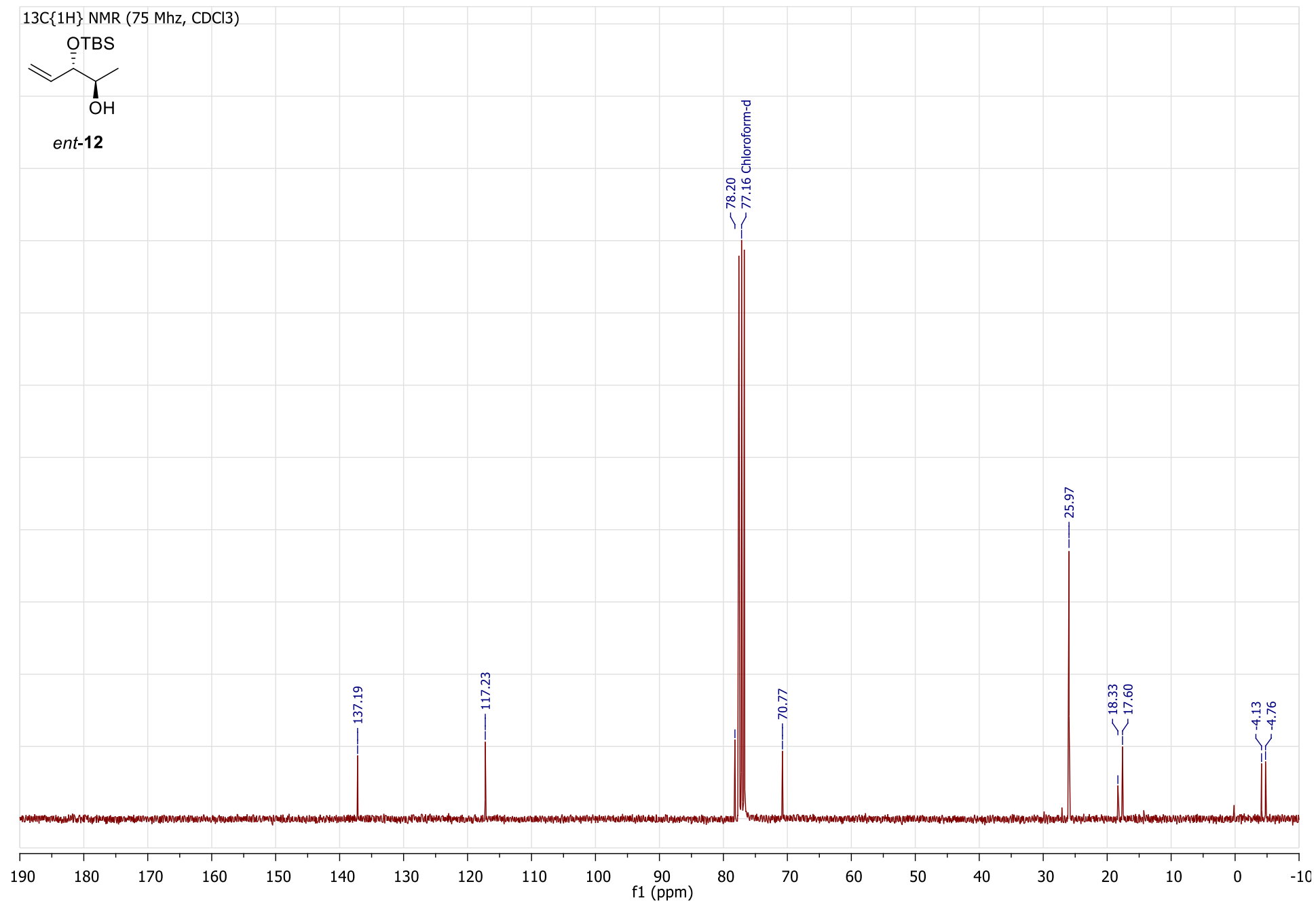



Figure S17. ^{13}C NMR spectrum of *ent*-12.


13



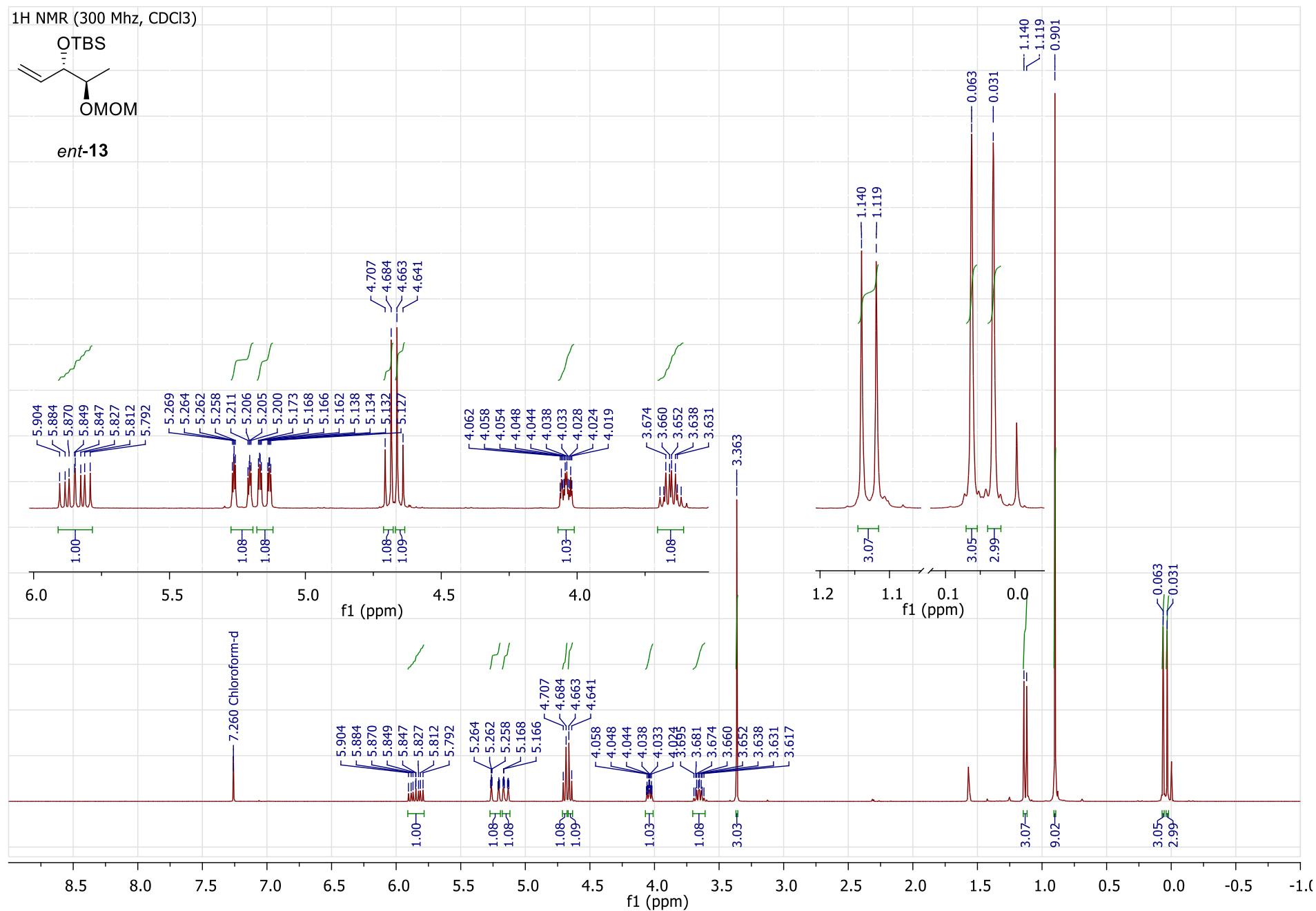


Figure S20. ¹H NMR spectrum of **ent-13**.

ent-**13**



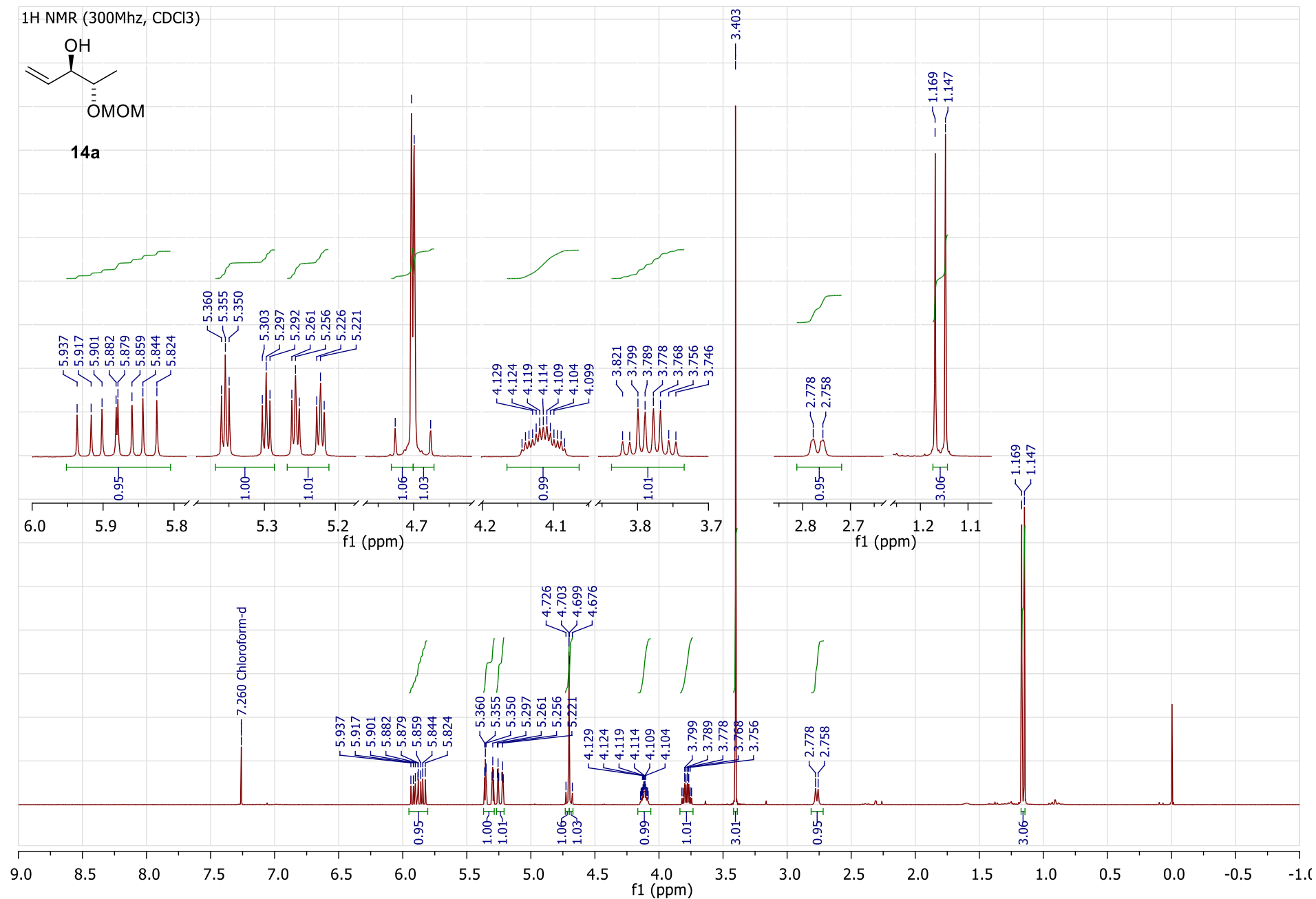


Figure S22. ¹H NMR spectrum of **14a**.

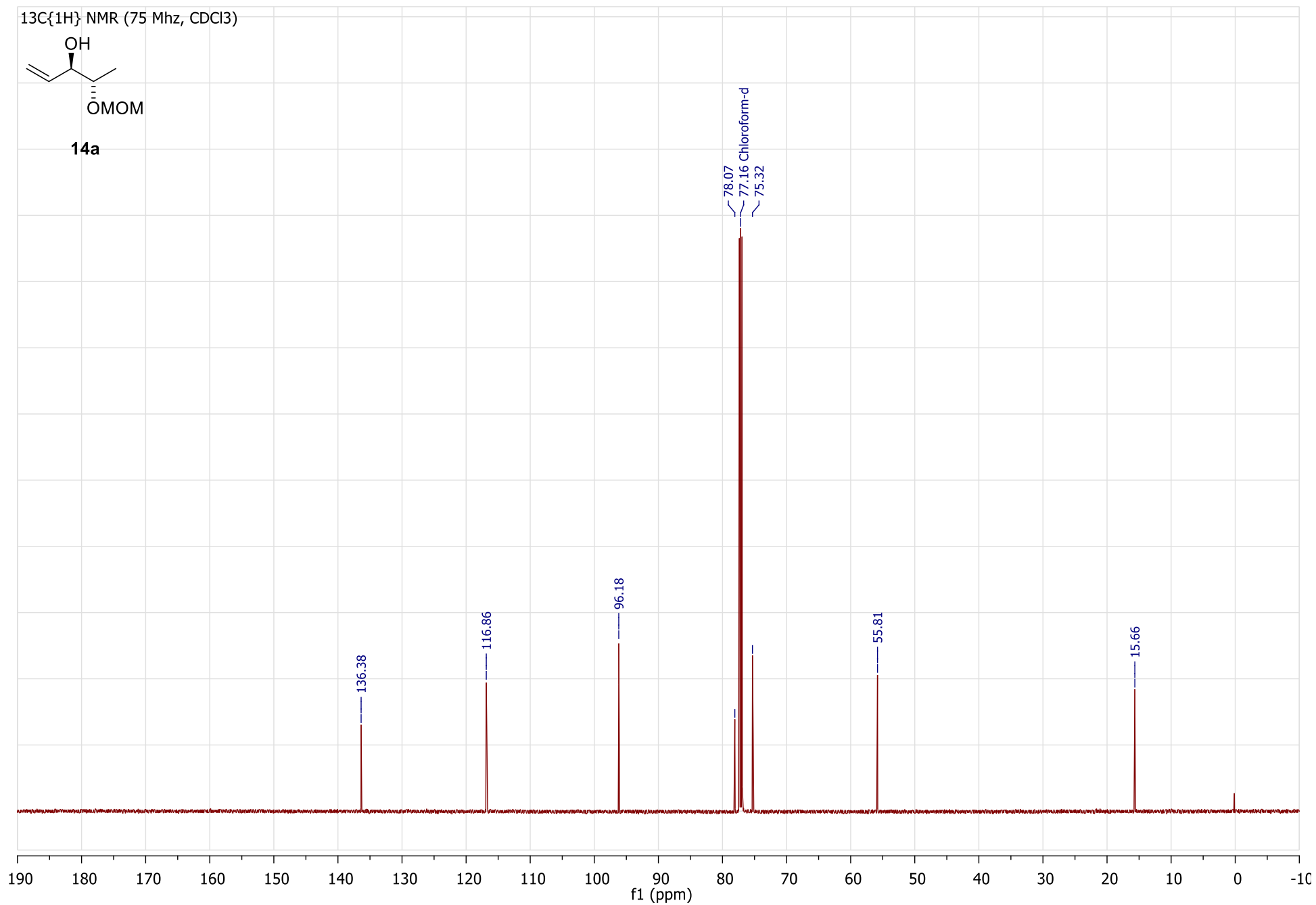


Figure S23. ¹³C NMR spectrum of **14a**.

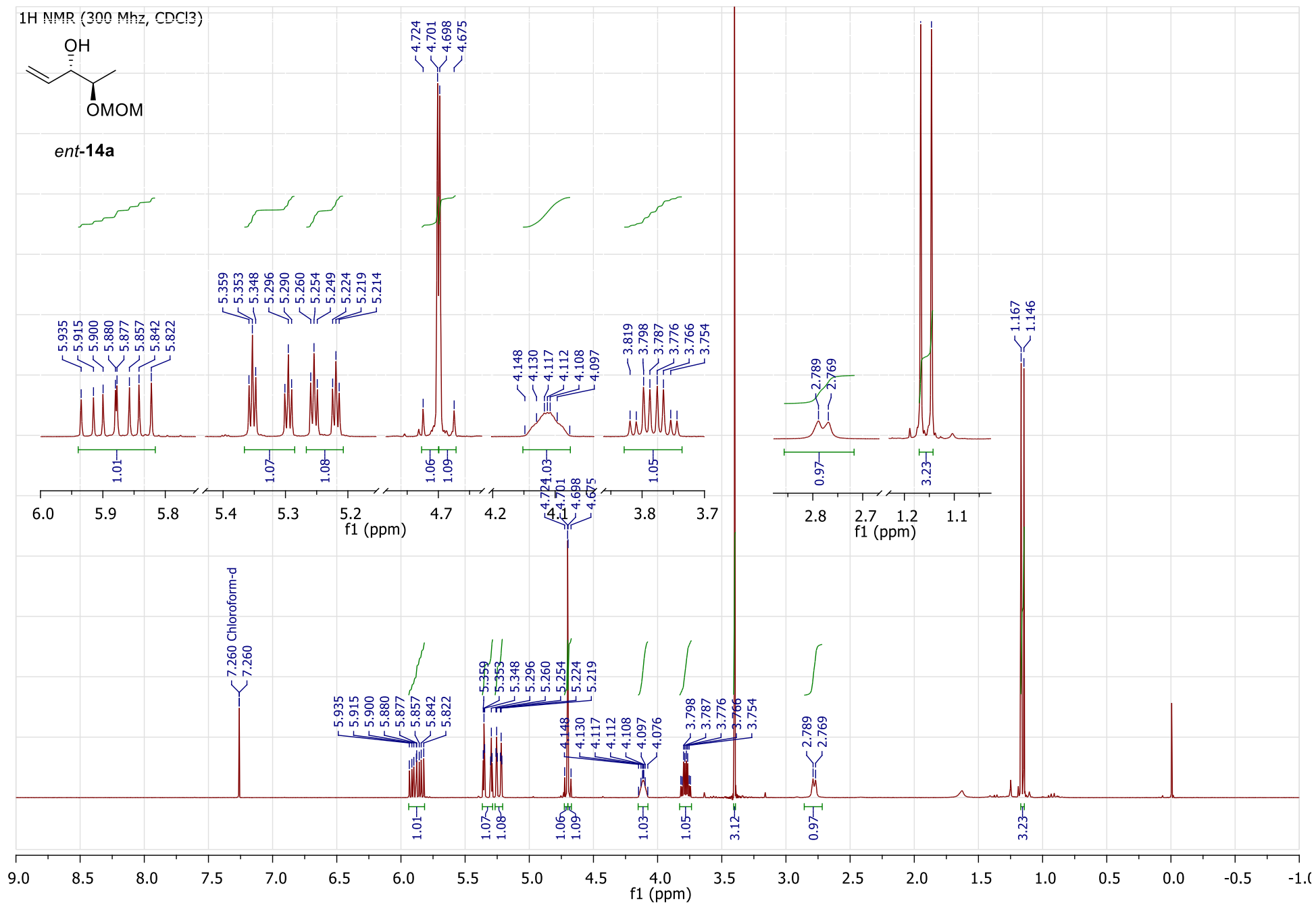
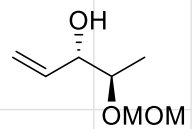


Figure S24. ¹H NMR spectrum of *ent*-14a.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)



ent-14a

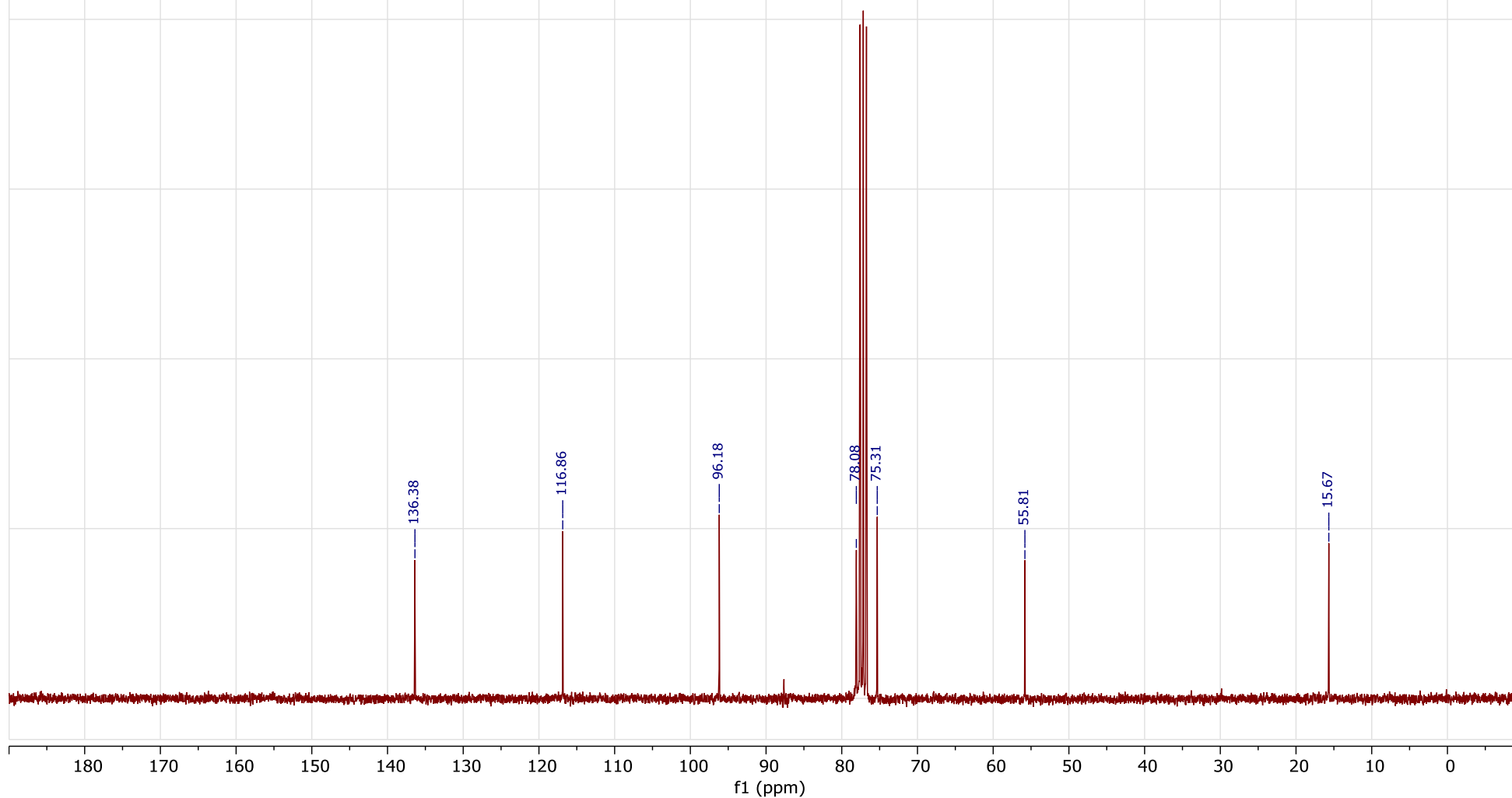


Figure S25. ^{13}C NMR spectrum of *ent*-14a.

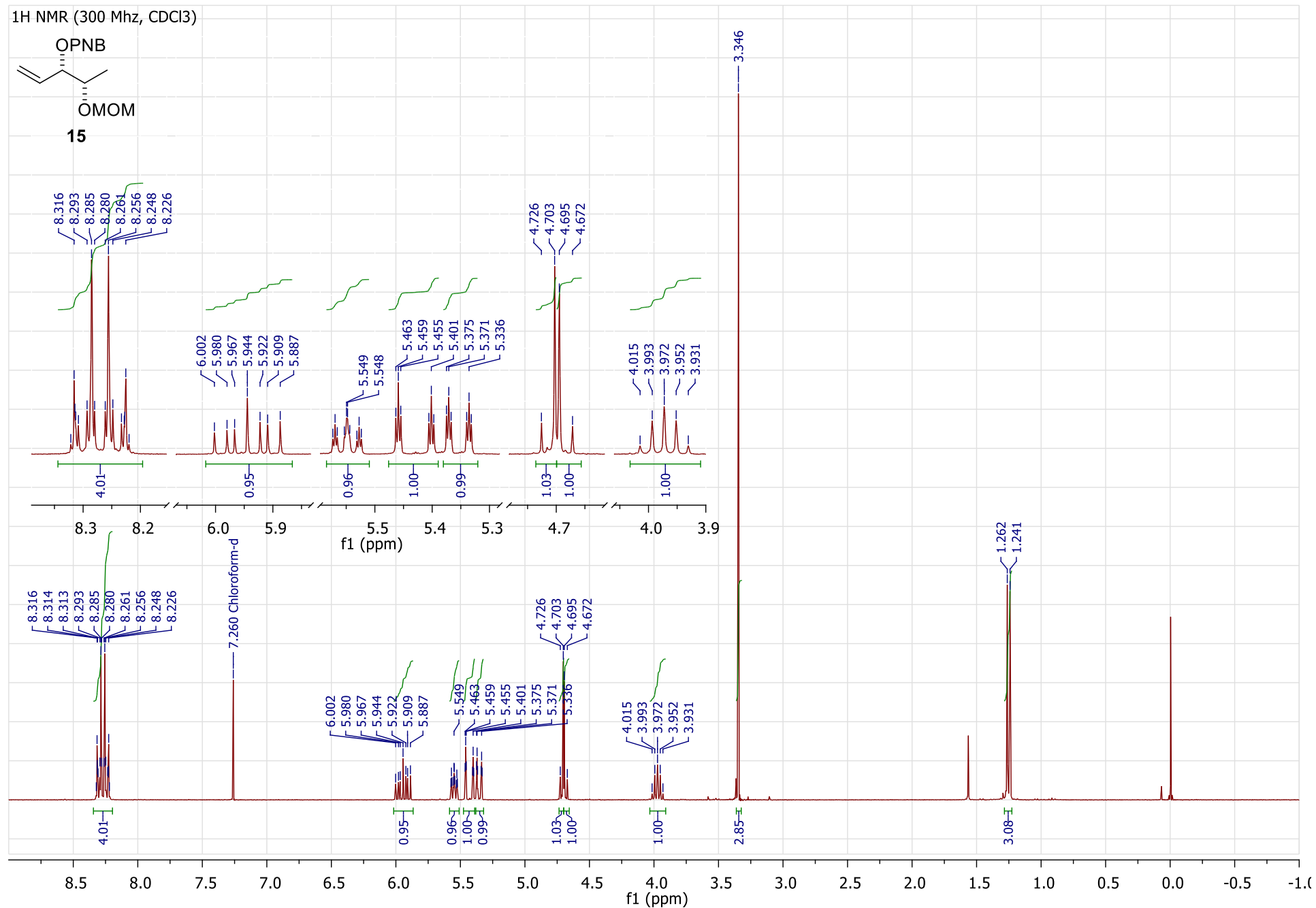


Figure S26. ¹H NMR spectrum of **15**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)

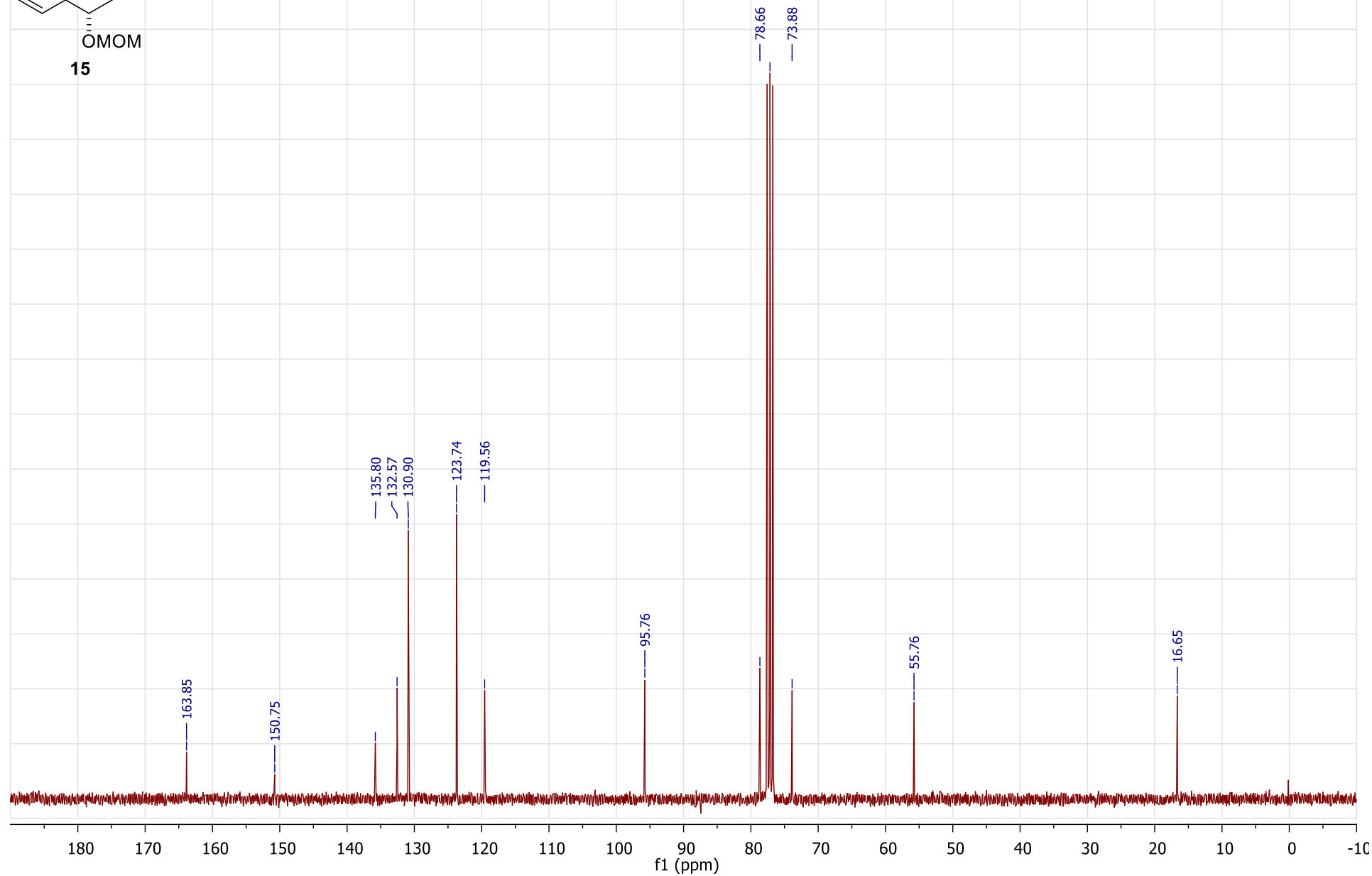
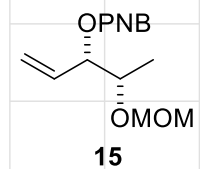


Figure S27. ^{13}C NMR spectrum of **15**.

¹H NMR (300 Mhz, CDCl₃)

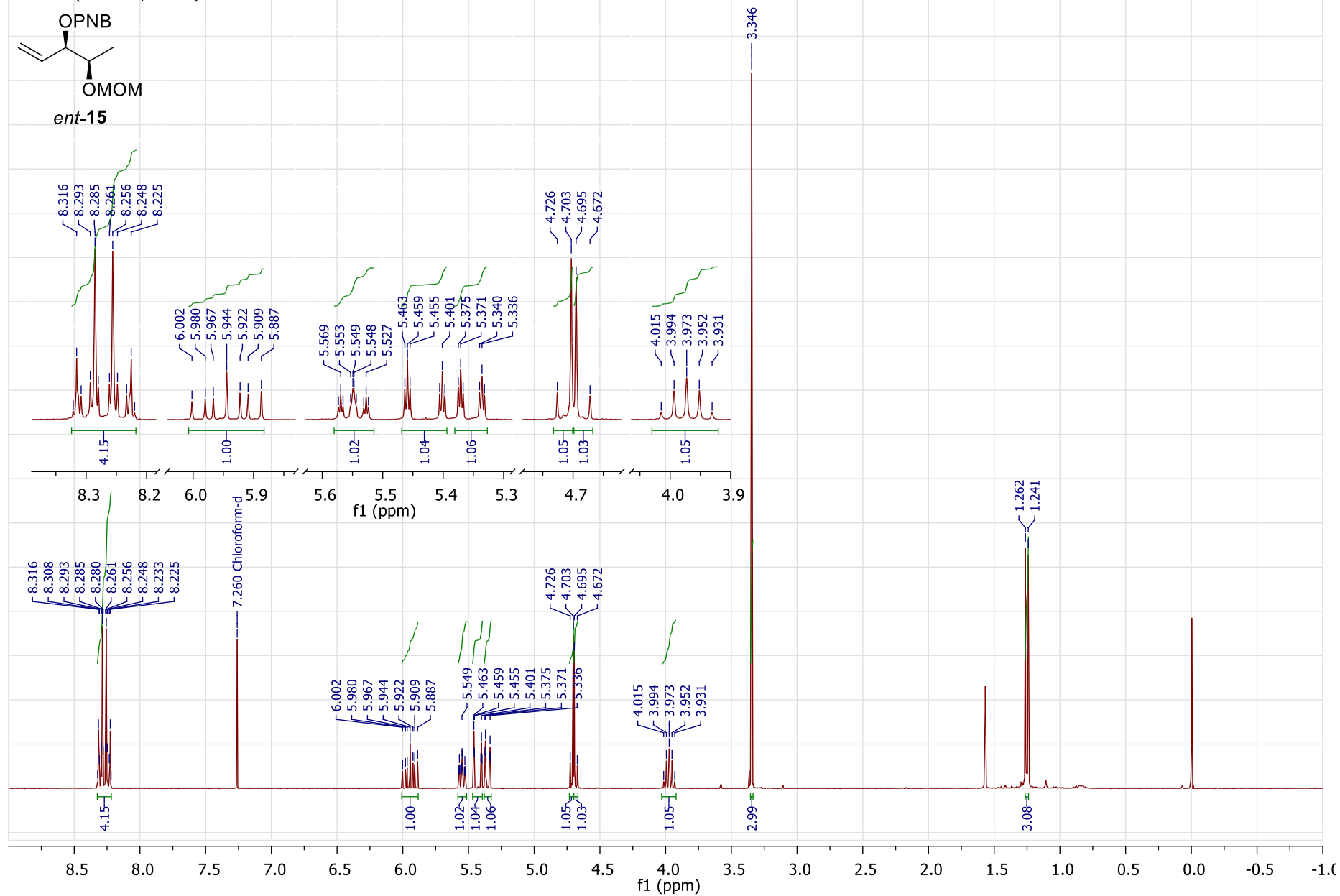
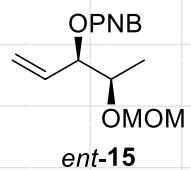


Figure S28. ¹H NMR spectrum of **ent-15**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)

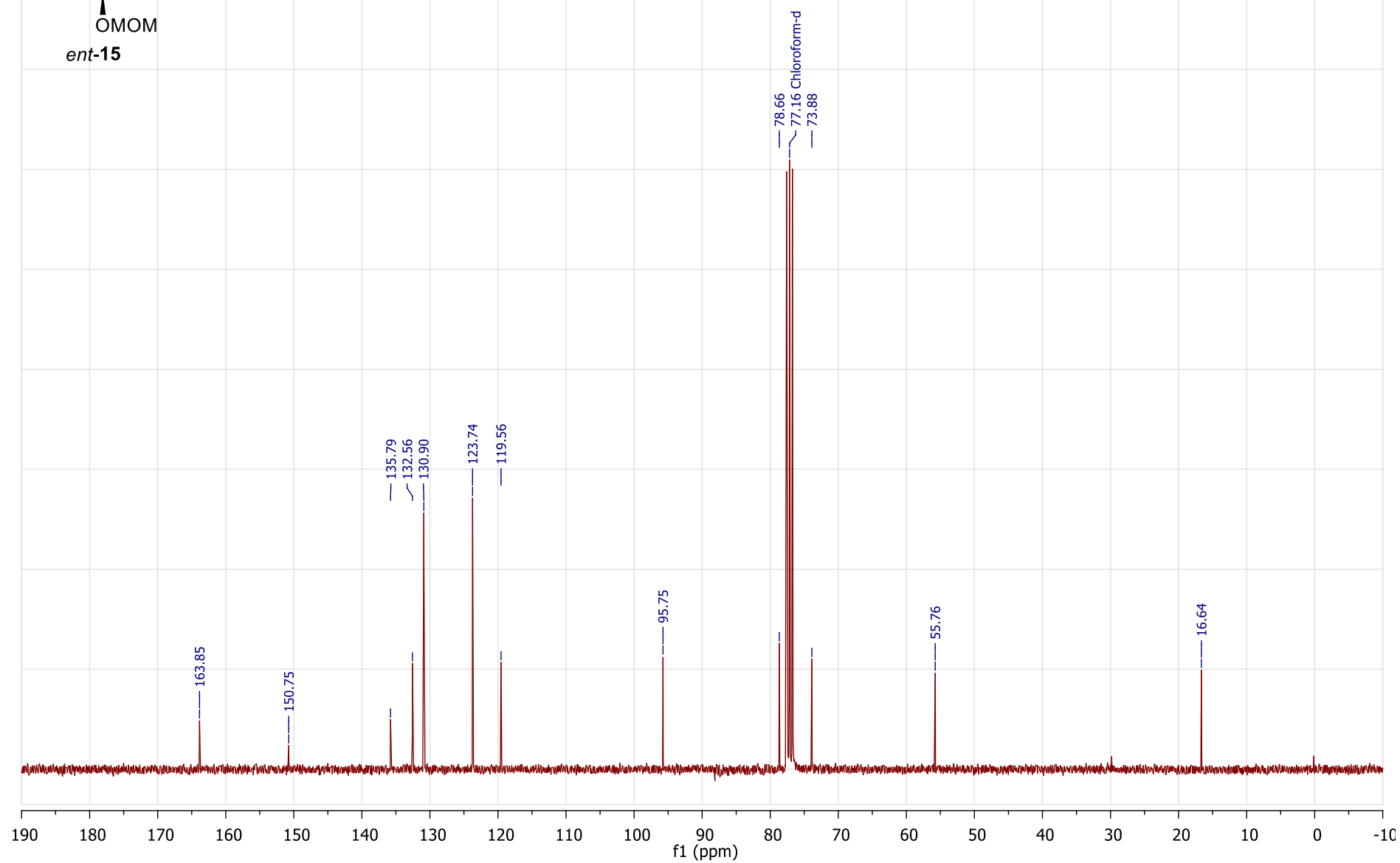
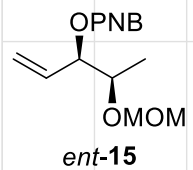


Figure S29. ^{13}C NMR spectrum of *ent-15*.

¹H NMR (300 Mhz, CDCl₃)

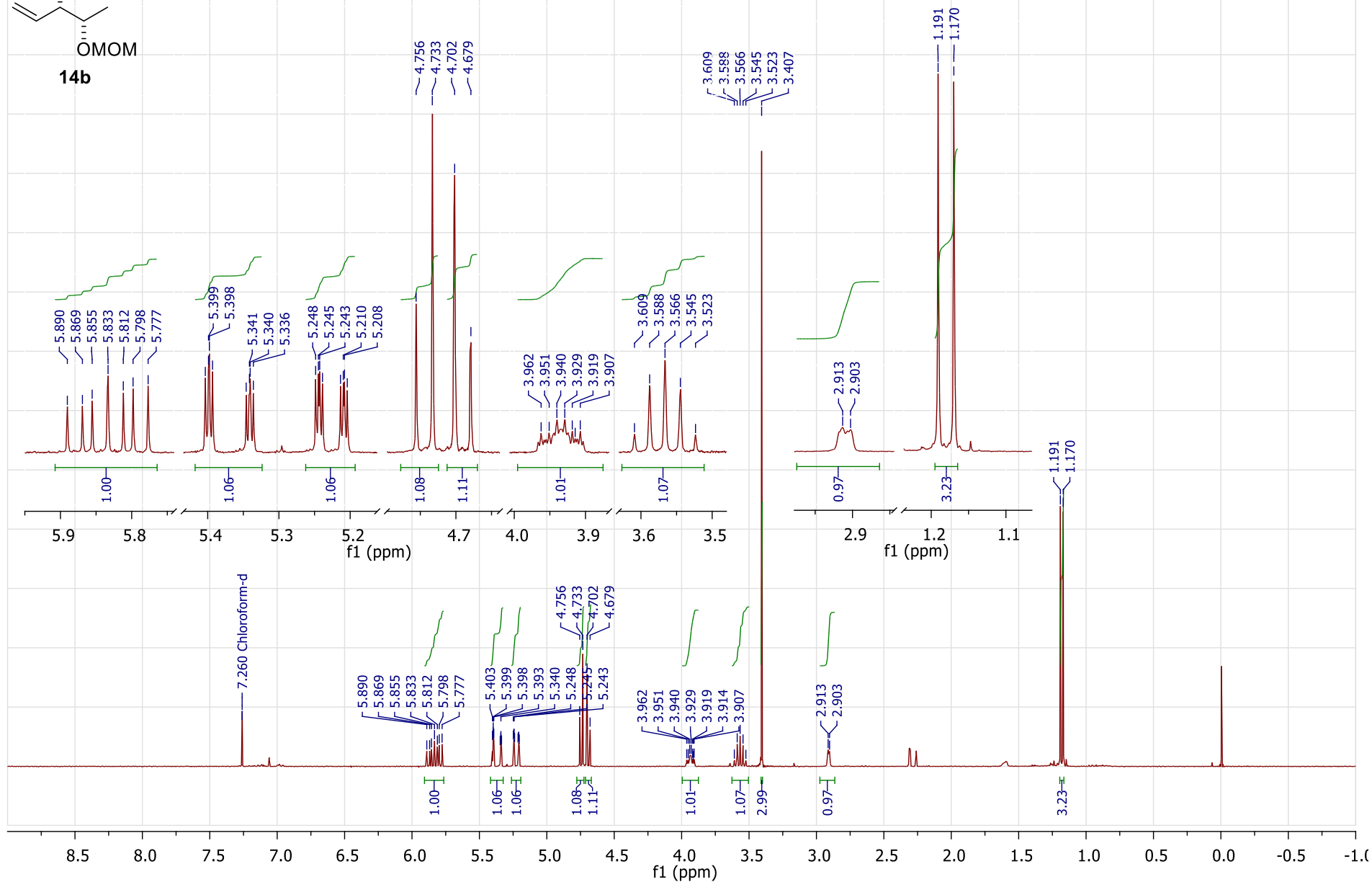
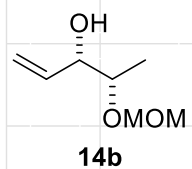


Figure S30. ¹H NMR spectrum of **14b**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)

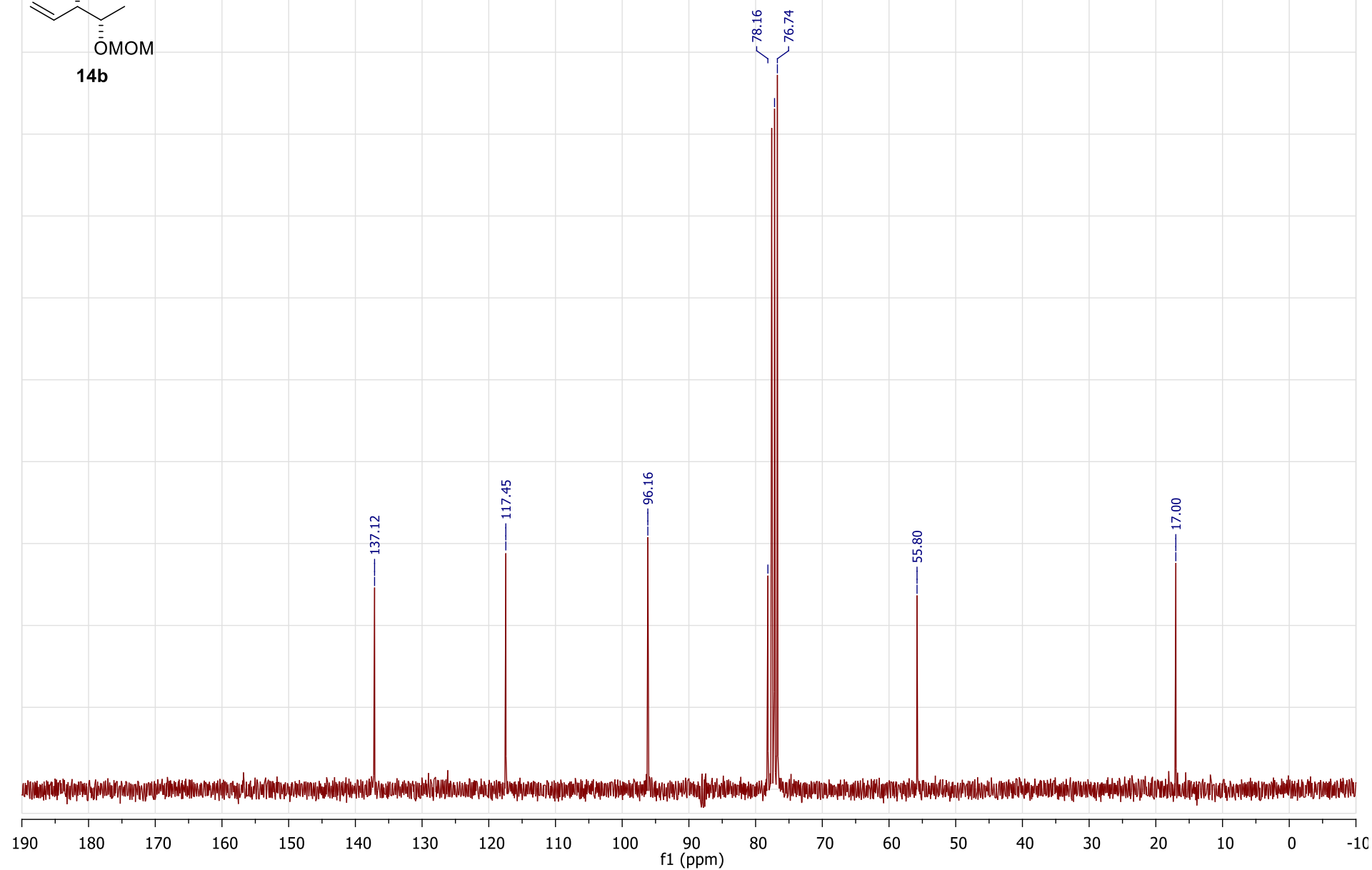
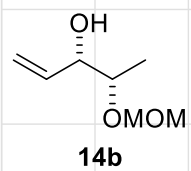


Figure S31. ^{13}C NMR spectrum of **14b**.

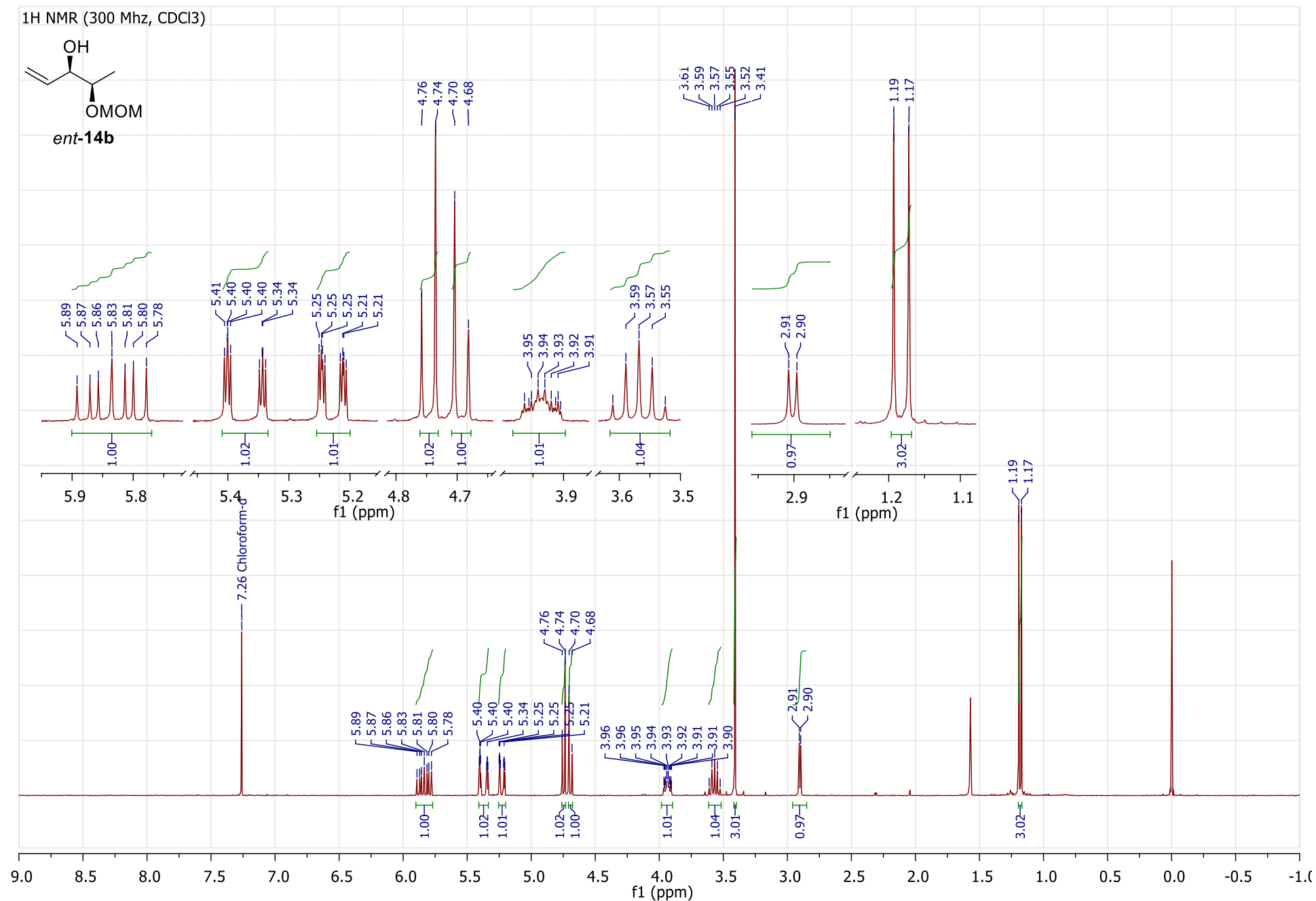


Figure S32. ¹H NMR spectrum of **ent-14b**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)

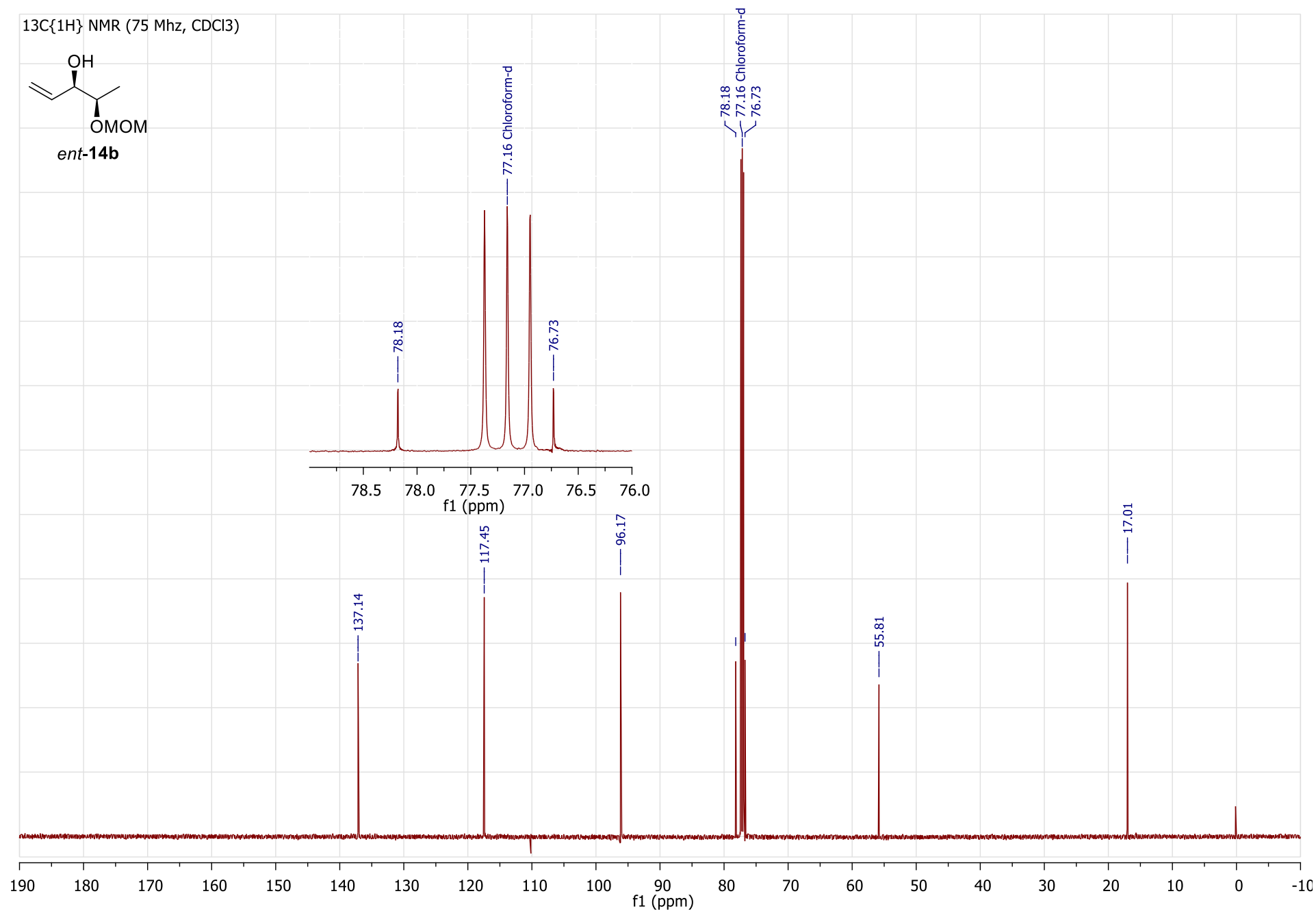
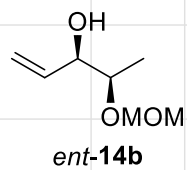


Figure S33. ^{13}C NMR spectrum of *ent*-14b.

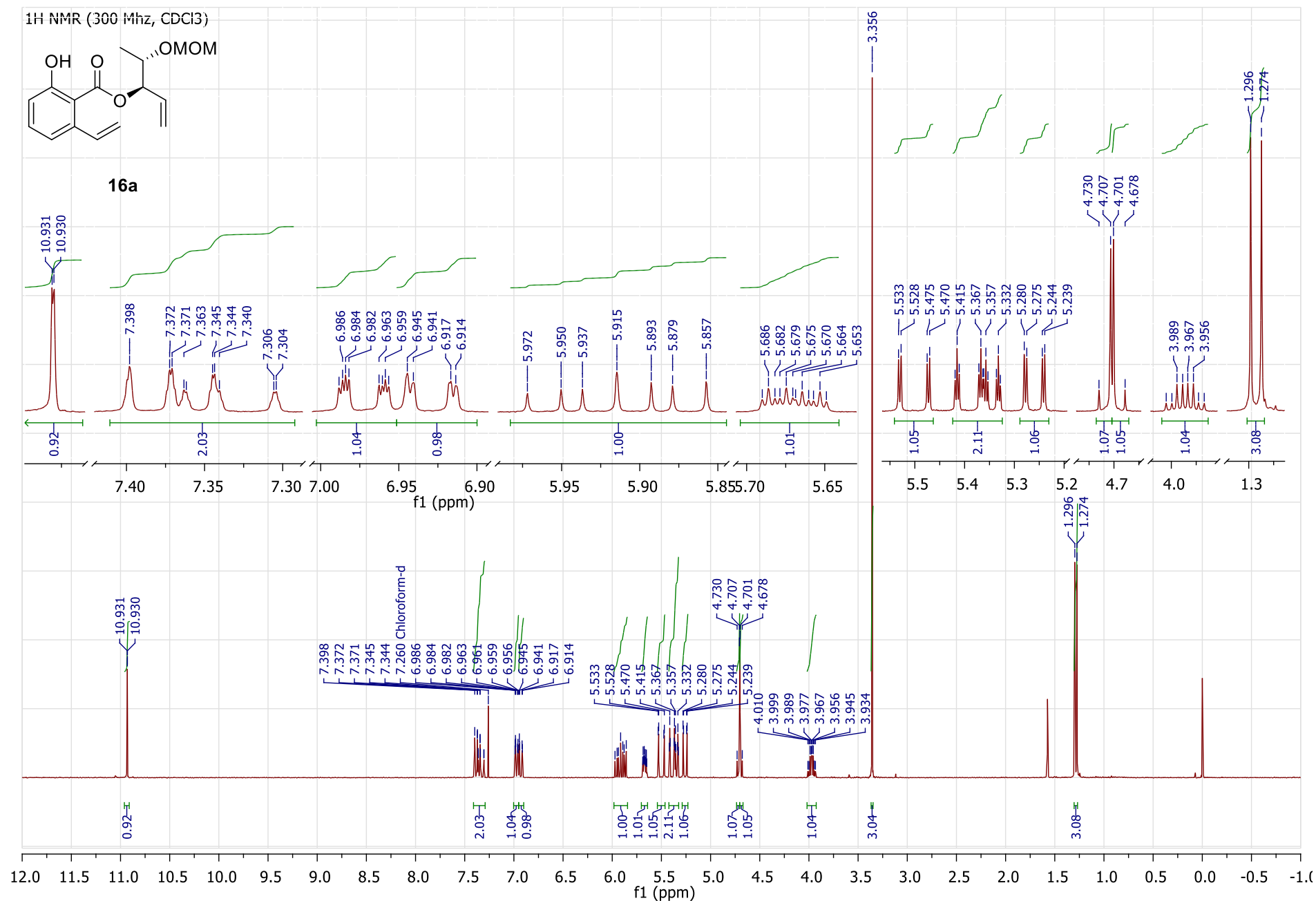
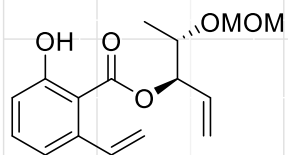


Figure S34. ¹H NMR spectrum of **16a**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 Mhz, CDCl_3)



16a

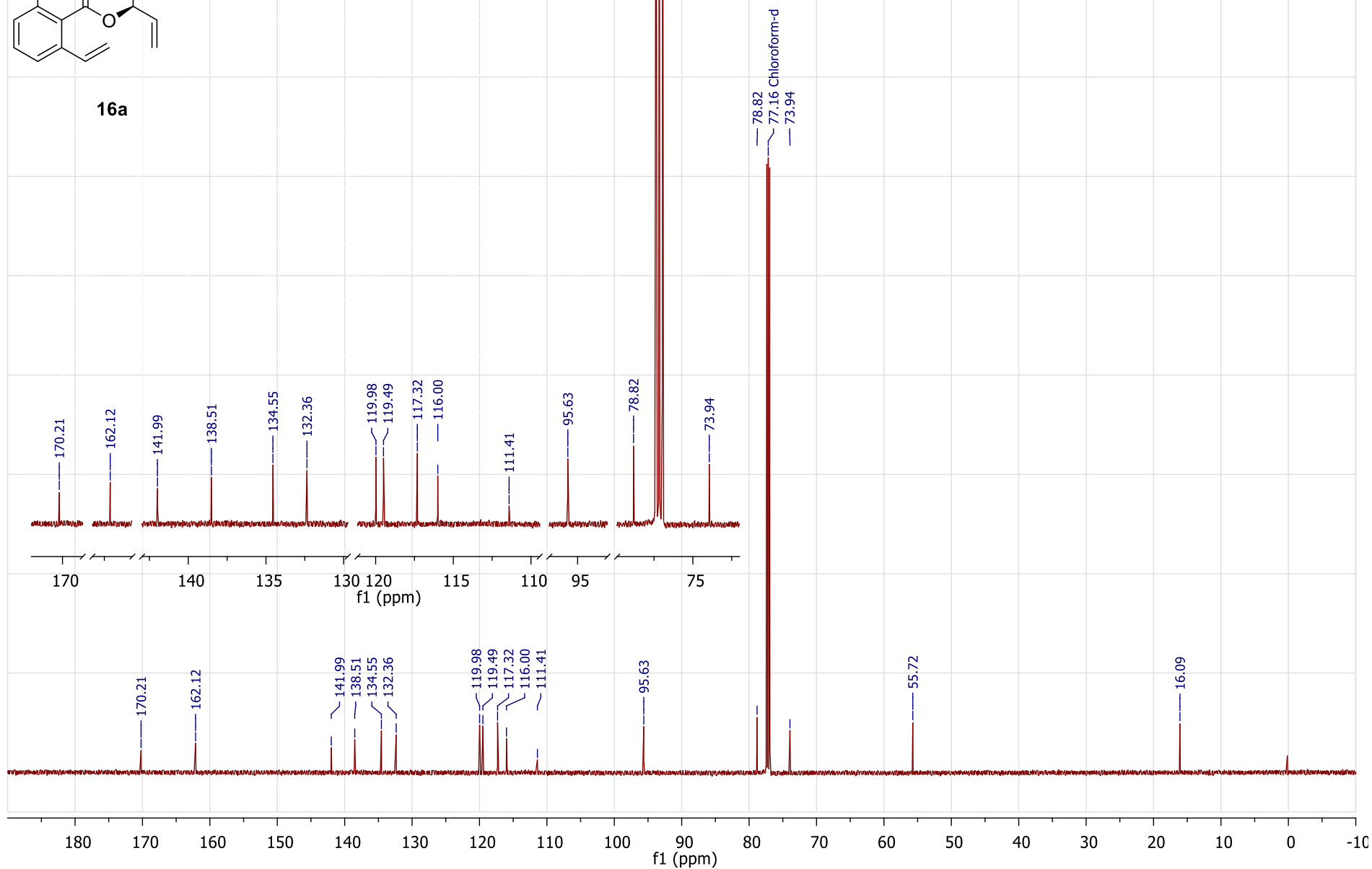


Figure S35. ^{13}C NMR spectrum of **16a**.

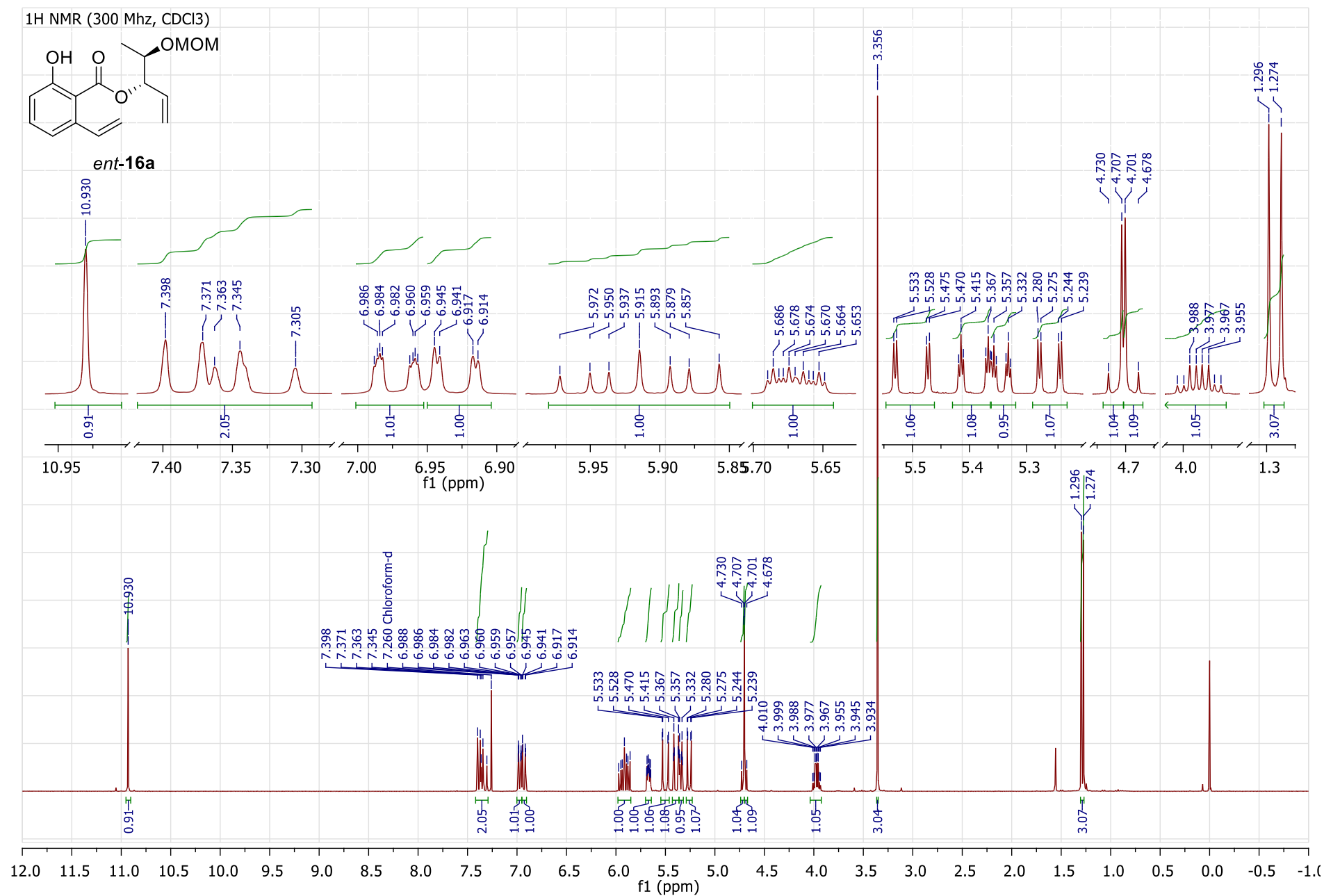


Figure S36. ¹H NMR spectrum of **ent-16a**.

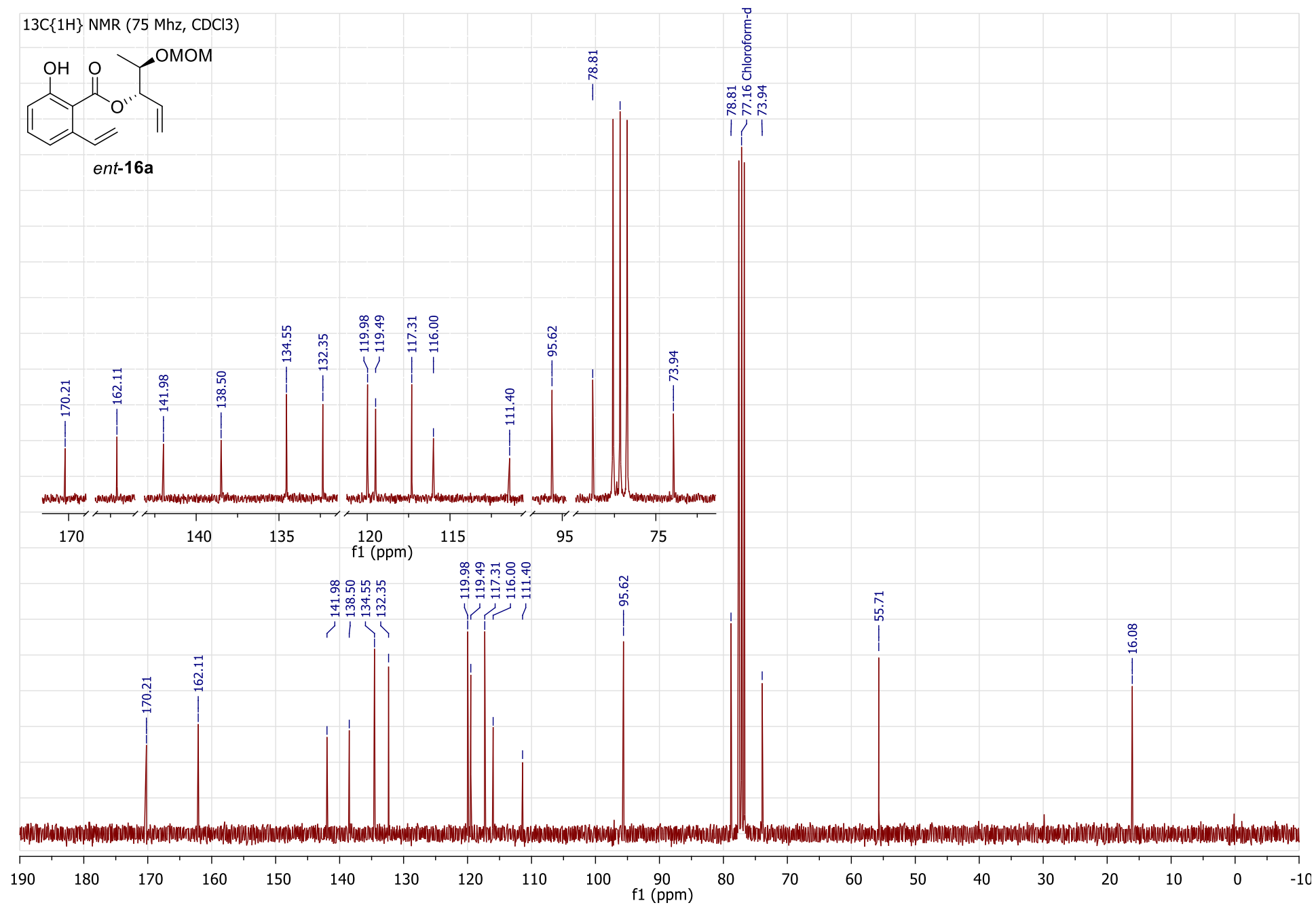


Figure S37. ^{13}C NMR spectrum of **ent-16a**.

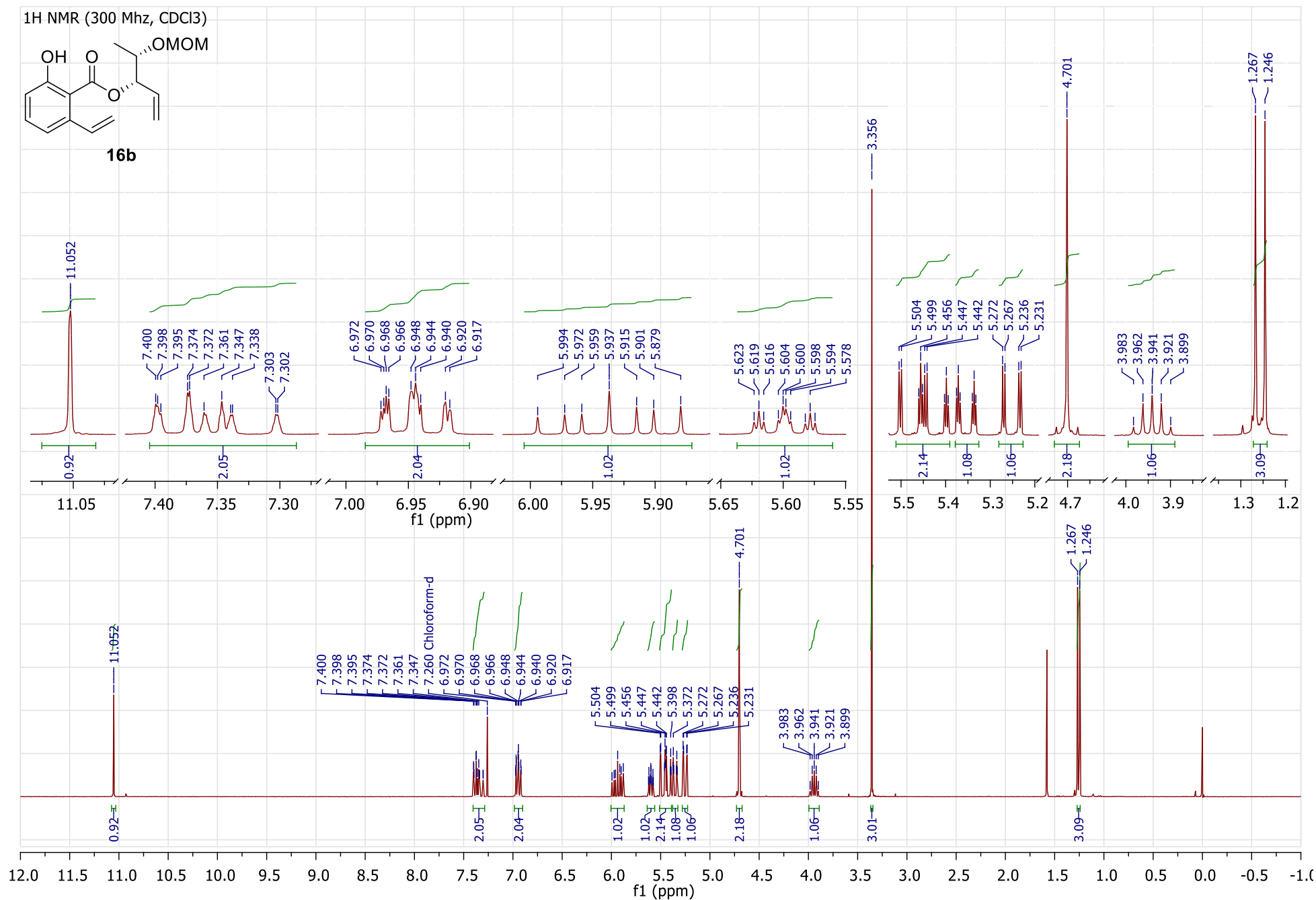


Figure S38. ¹H NMR spectrum of **16b**.

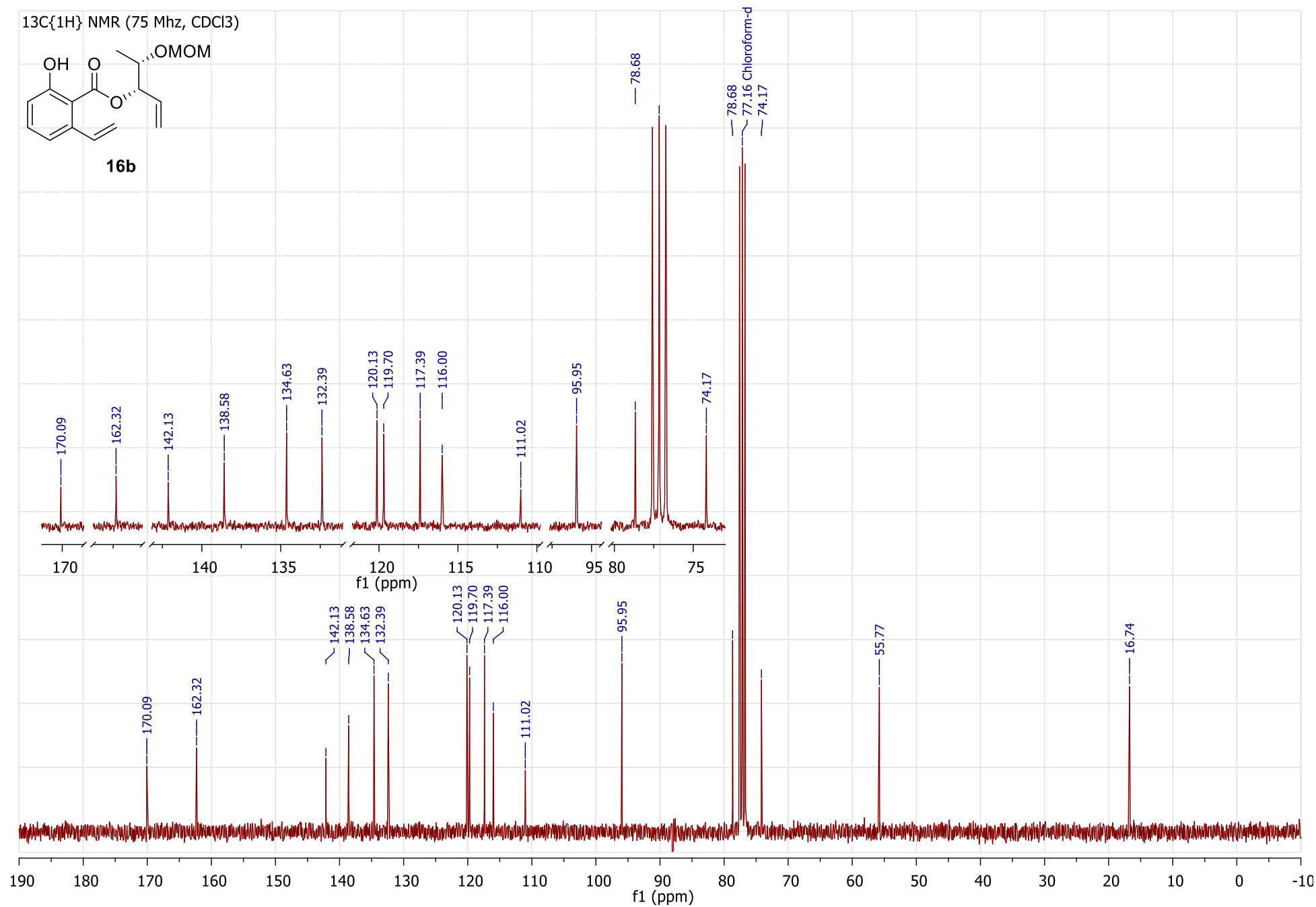


Figure S39. ¹H NMR spectrum of **16b**.

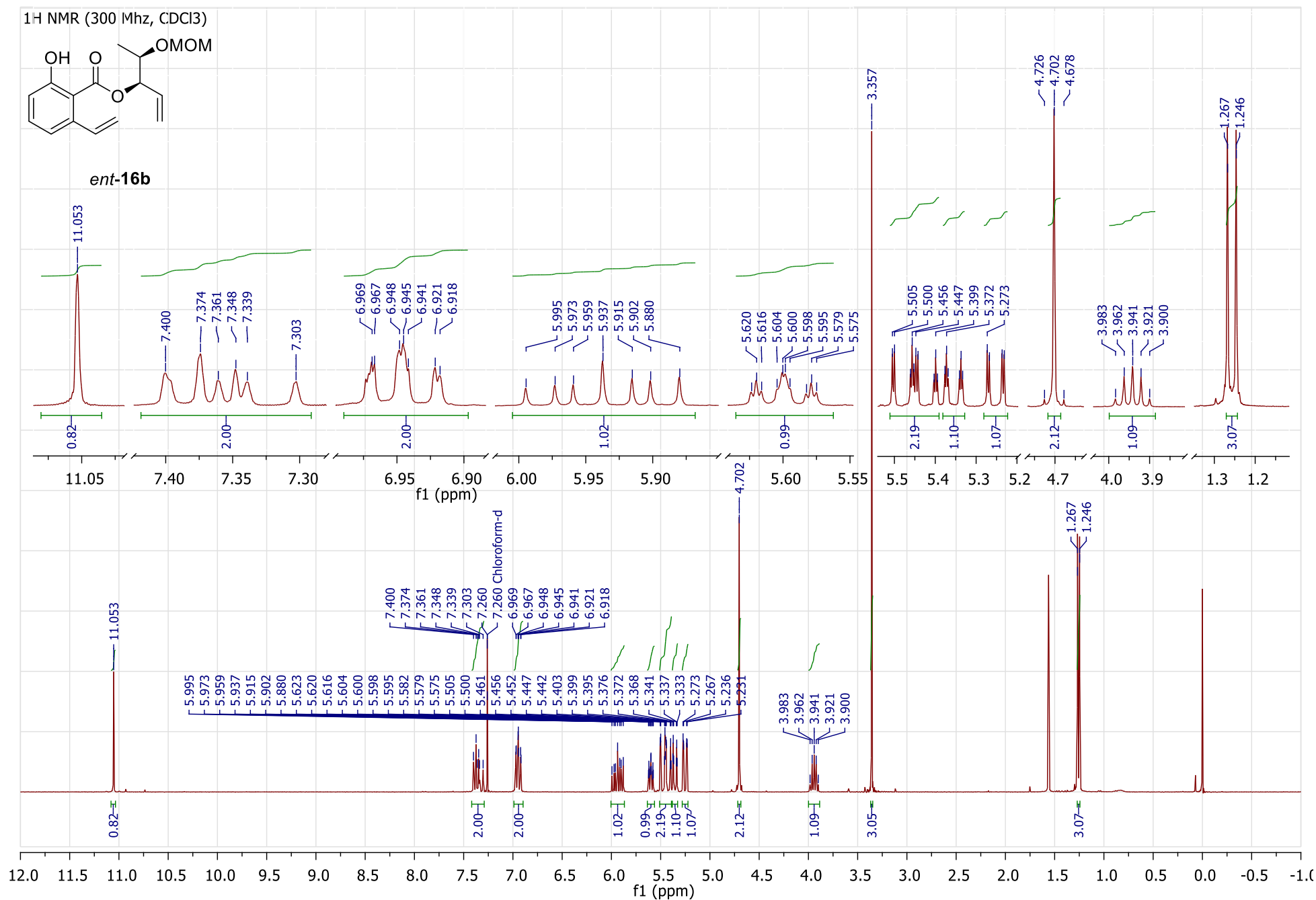


Figure S40. ¹H NMR spectrum of **ent-16b**.

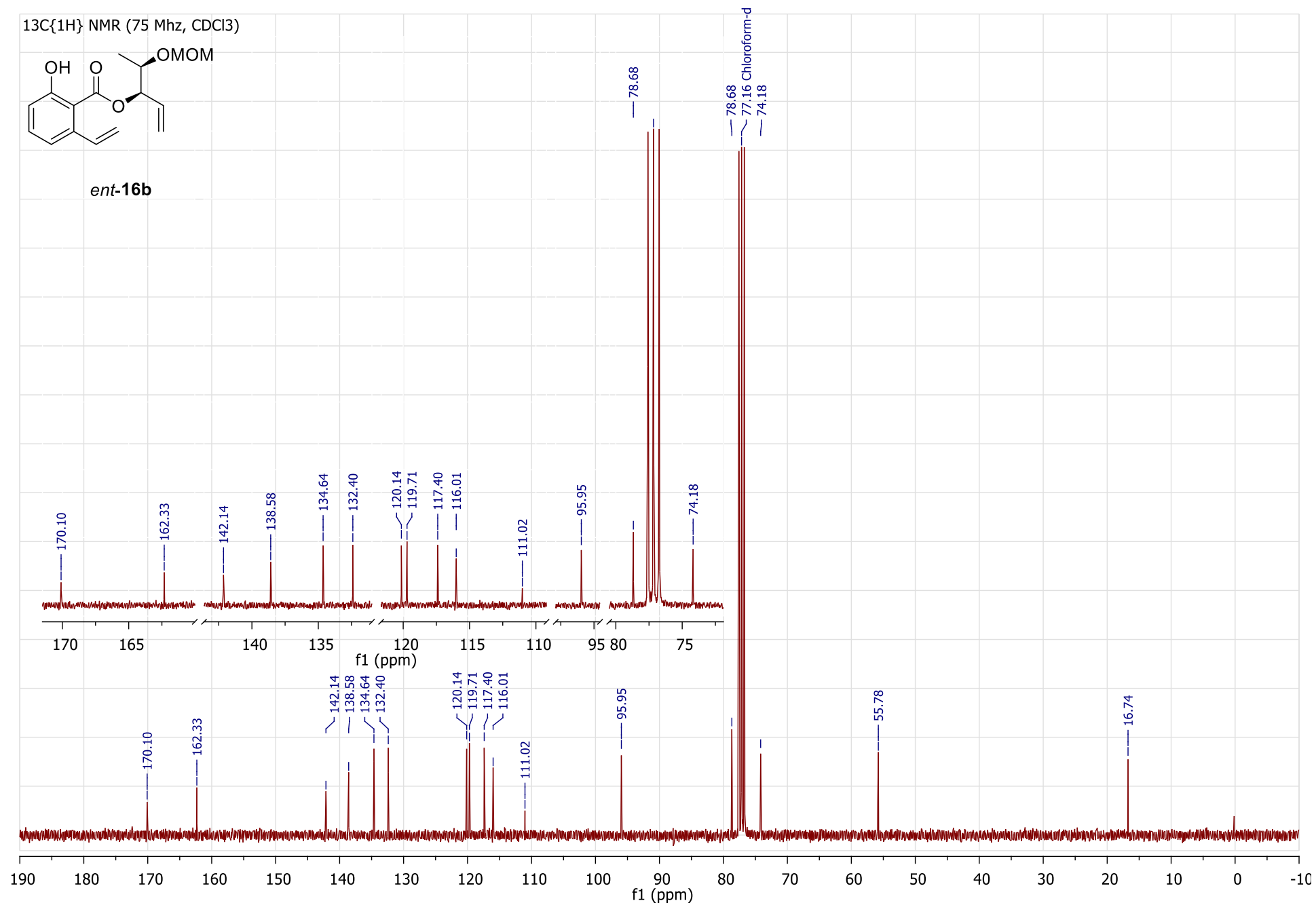


Figure S41. ¹H NMR spectrum of *ent*-**16b**.

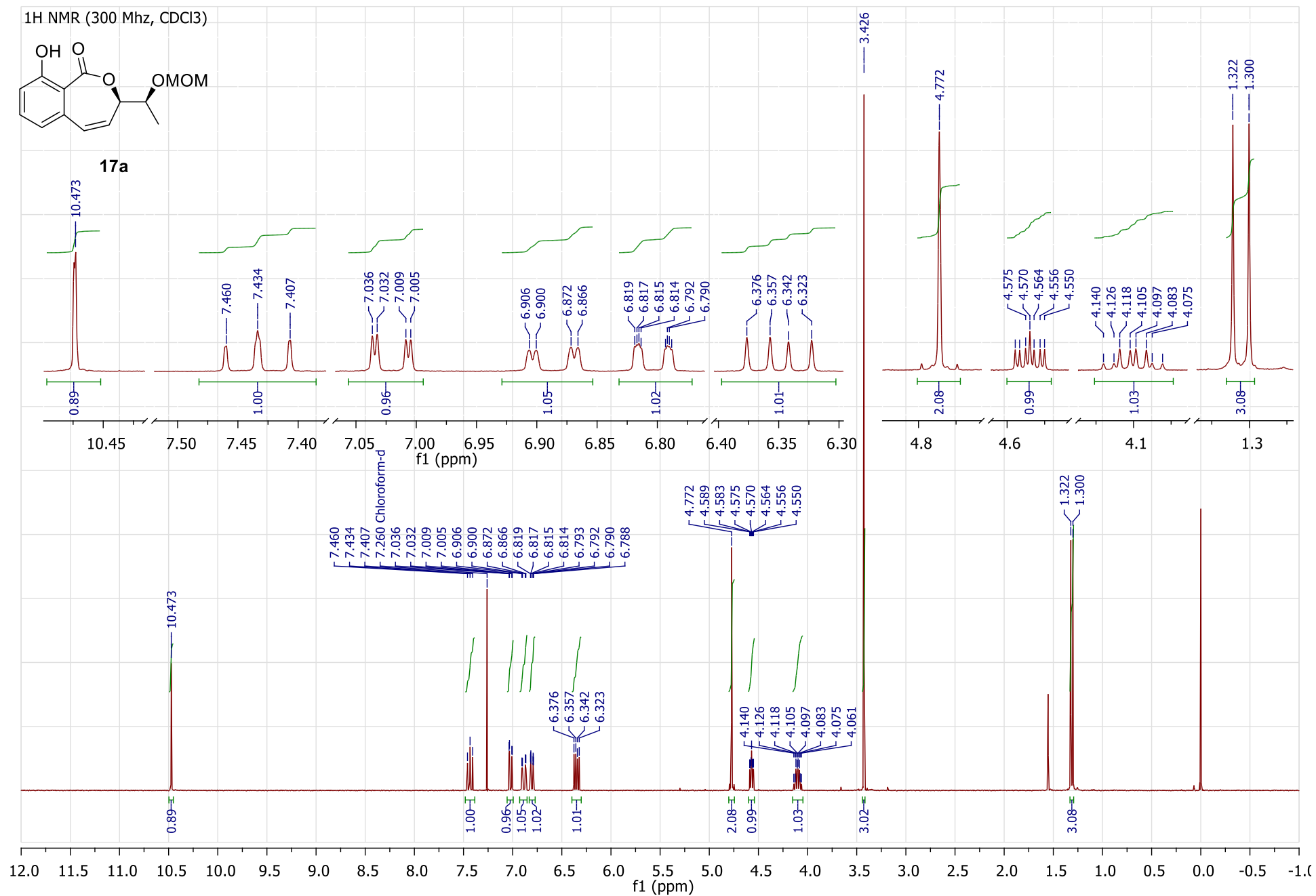
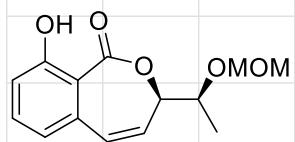


Figure S42. ¹H NMR spectrum of **17a**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)



17a

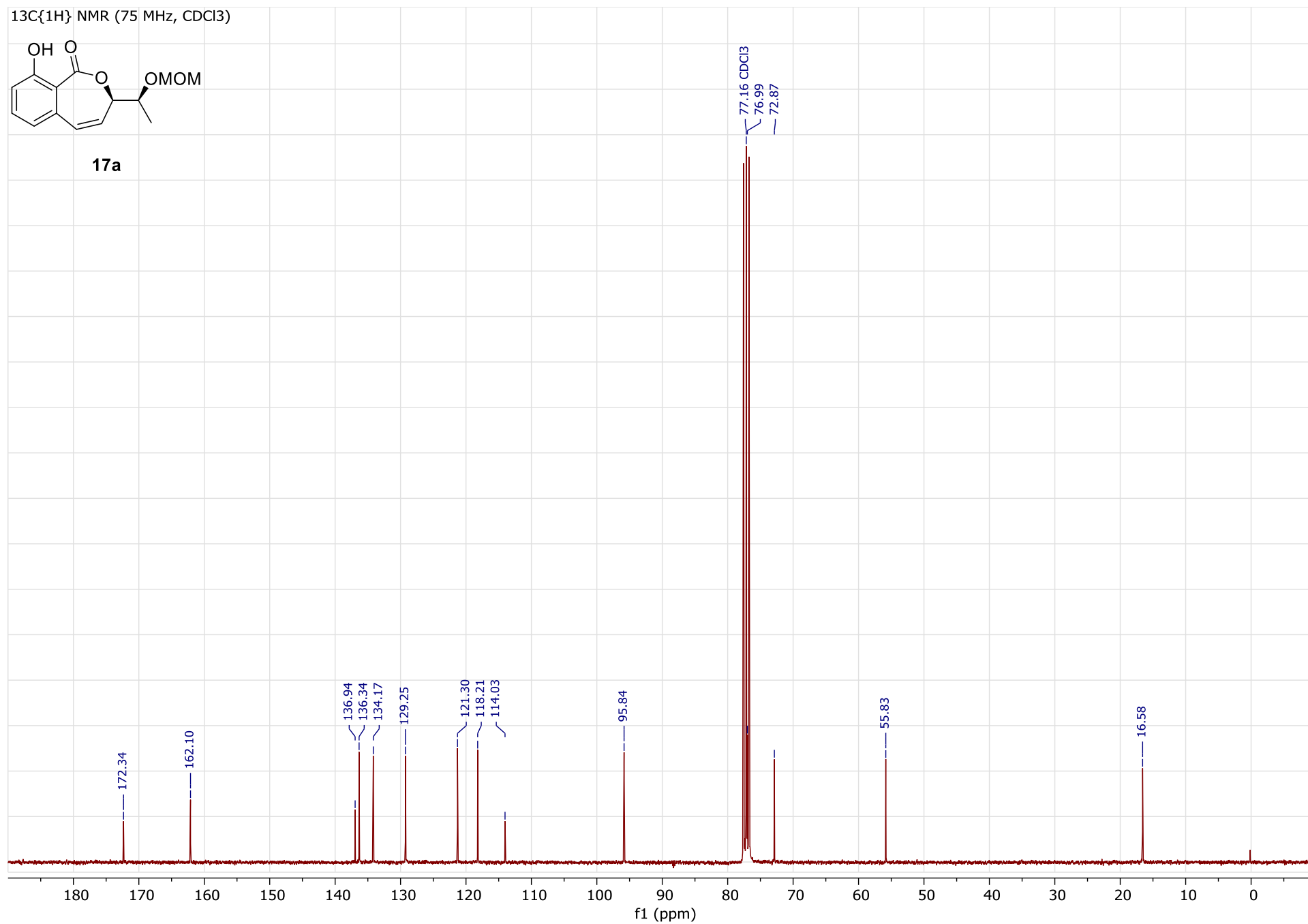


Figure S43. ^{13}C NMR spectrum of **17a**.

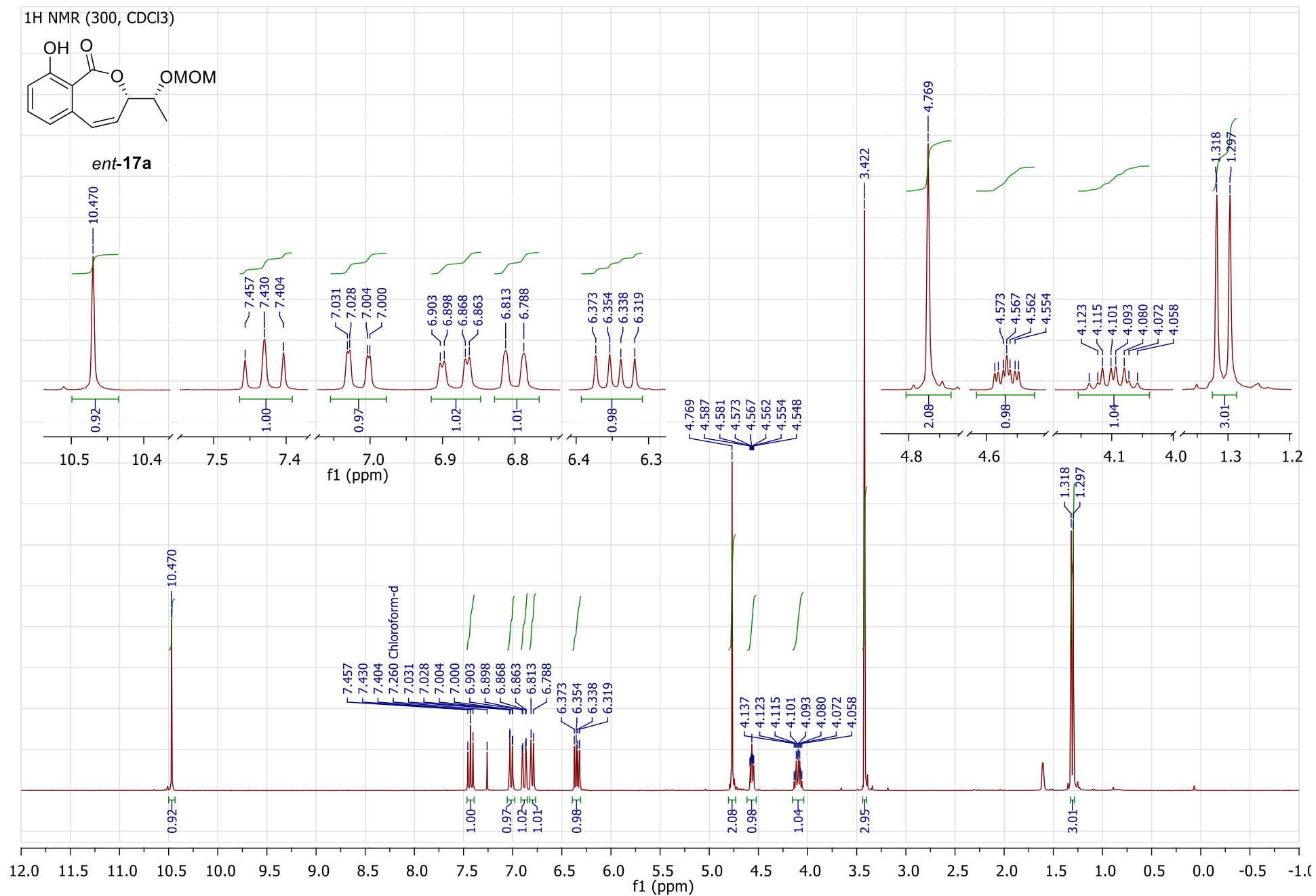


Figure S44. ¹H NMR spectrum of *ent*-17a.

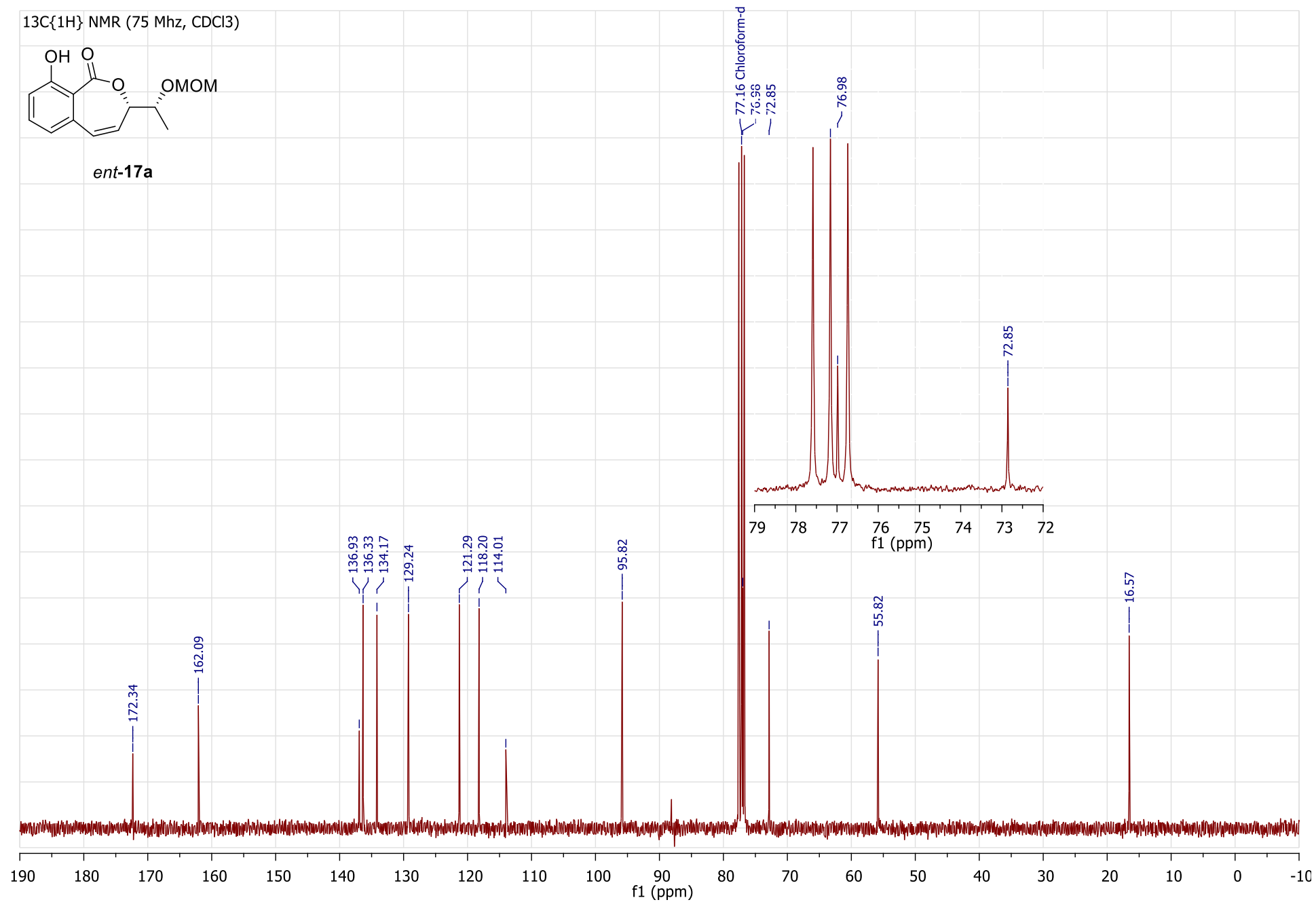


Figure S45. ^{13}C NMR spectrum of *ent-17a*.

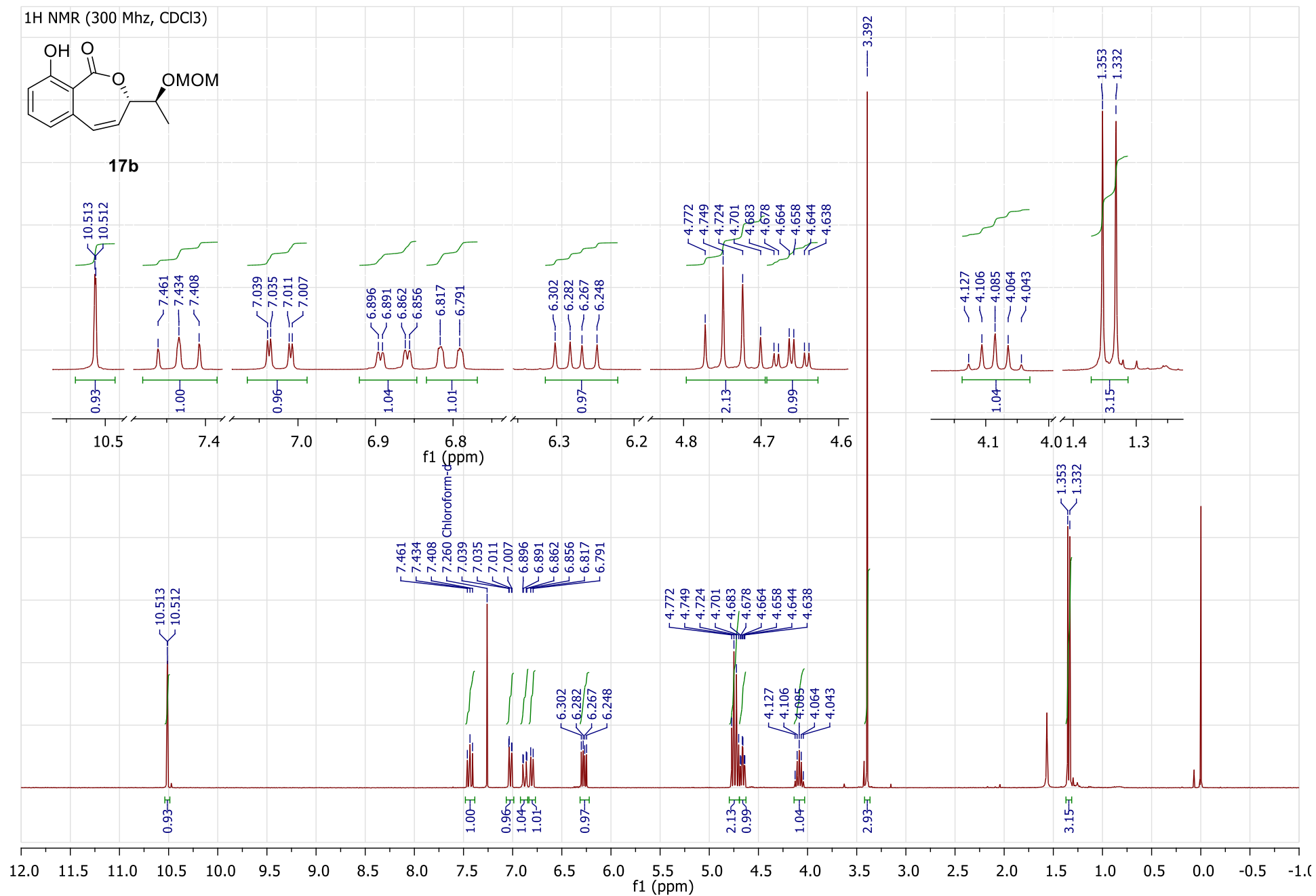


Figure S46. ¹H NMR spectrum of 17b.

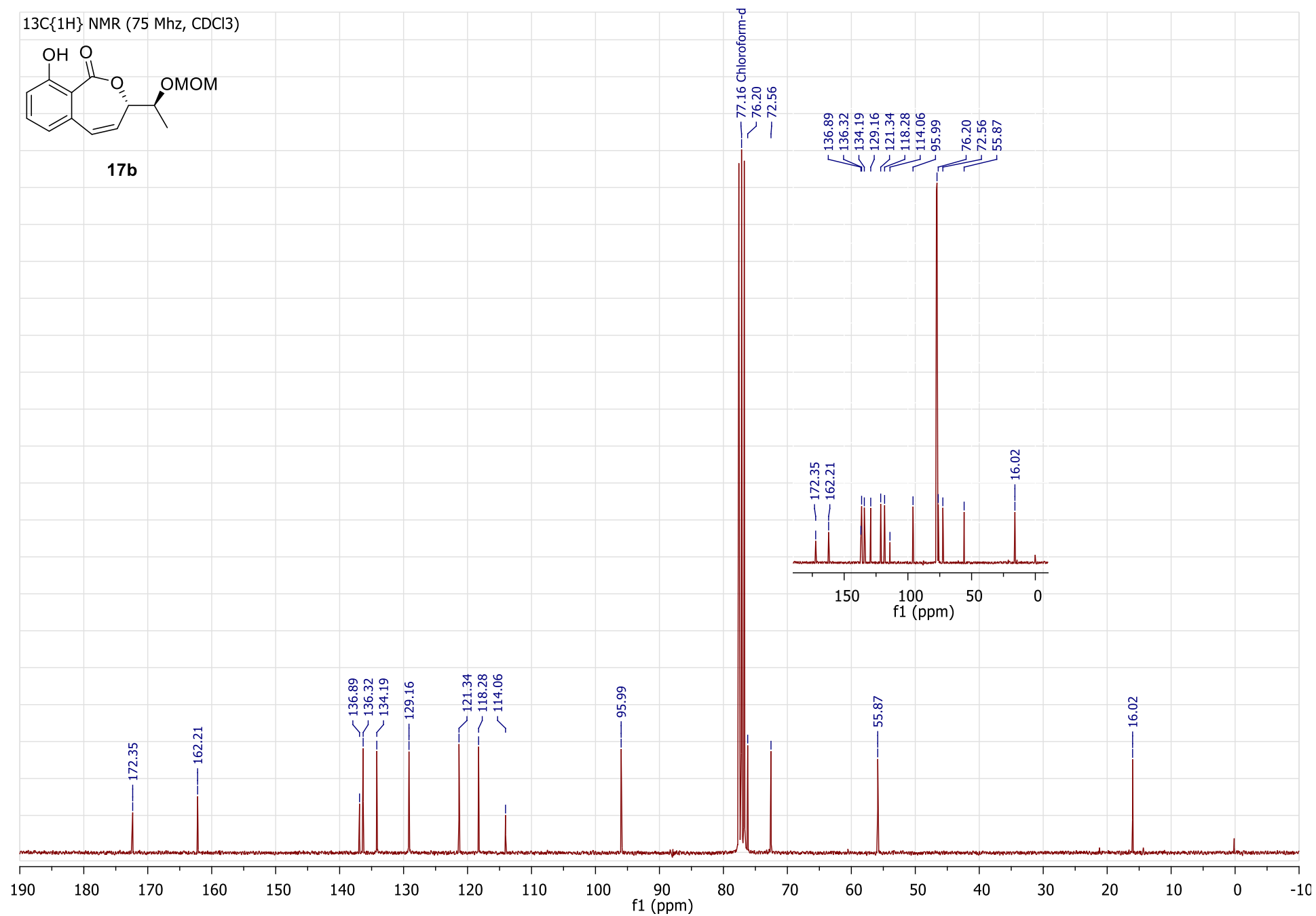


Figure S47. ^{13}C NMR spectrum of 17b.

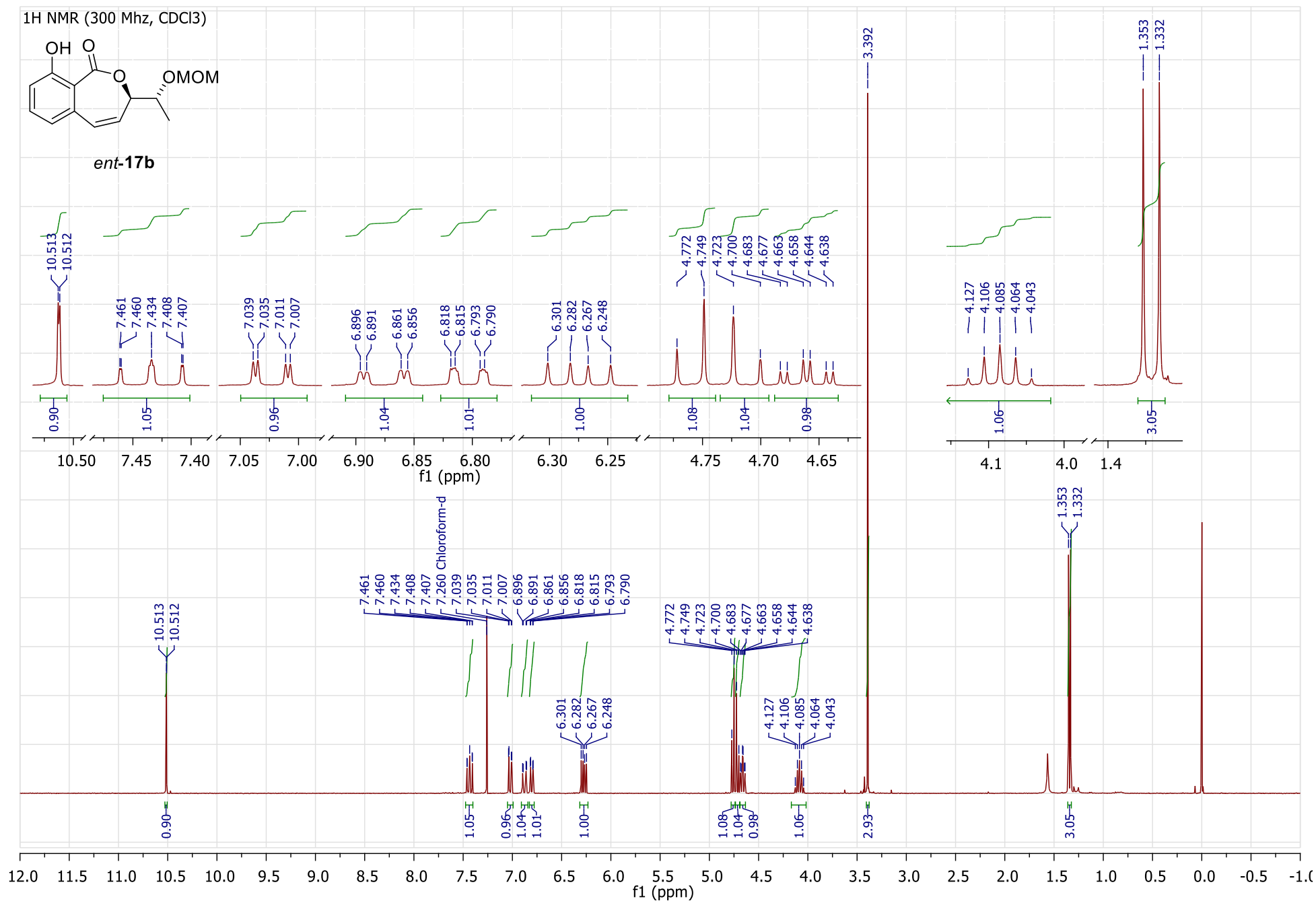


Figure S48. ¹H NMR spectrum of *ent-17b*.

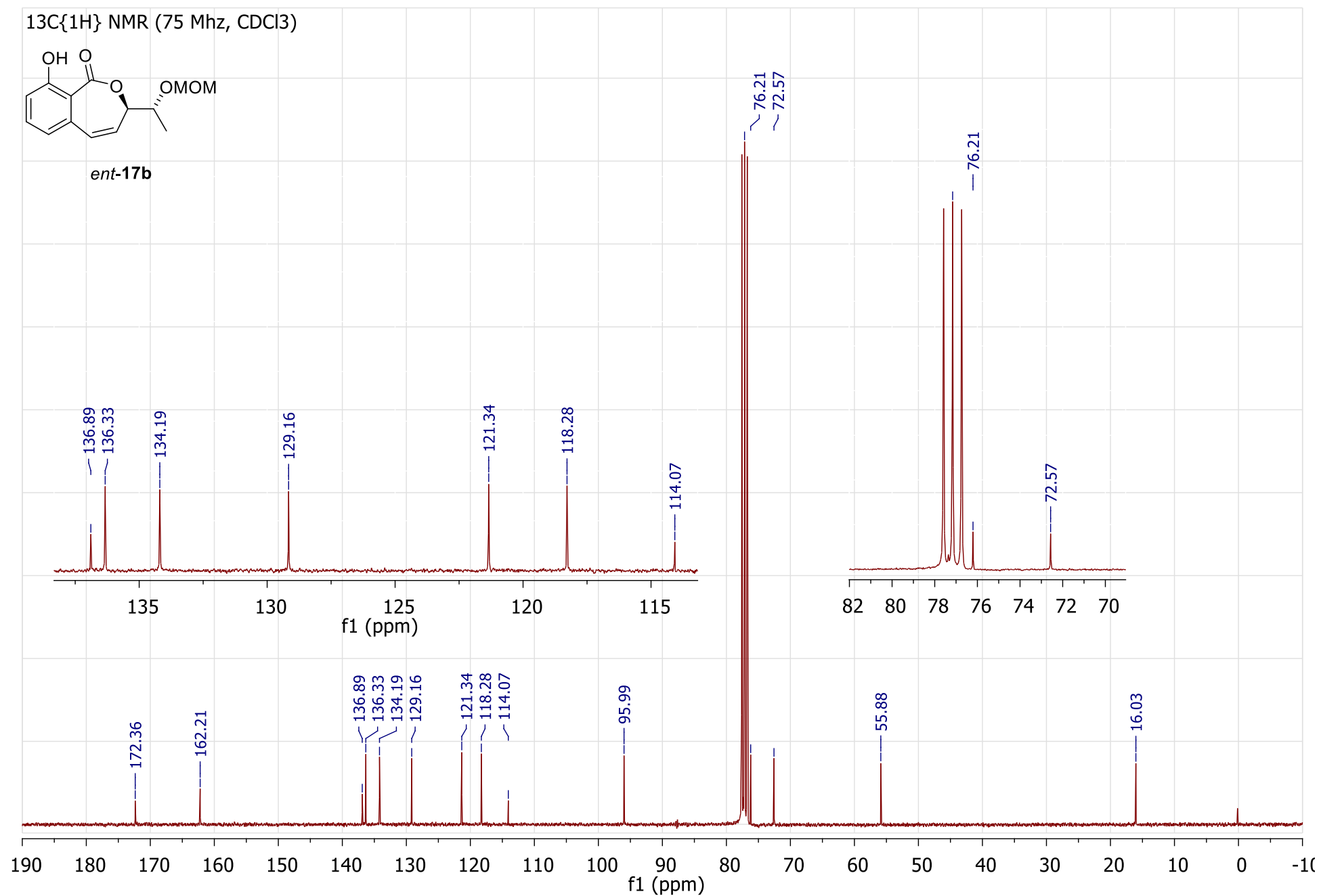


Figure S49. ^{13}C NMR spectrum of **ent-17b**.

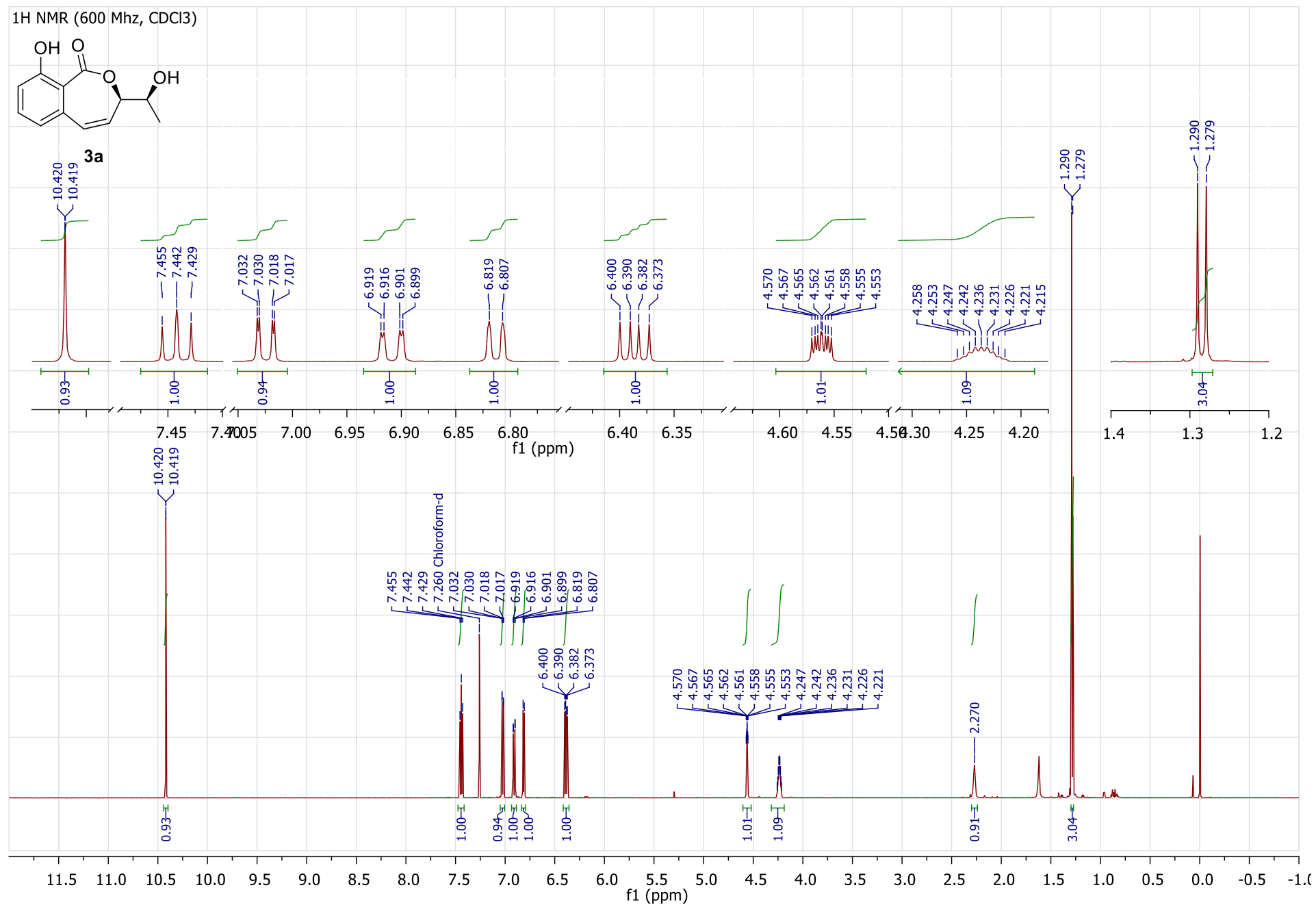


Figure S50. ¹H NMR spectrum of **3a** in CDCl₃.

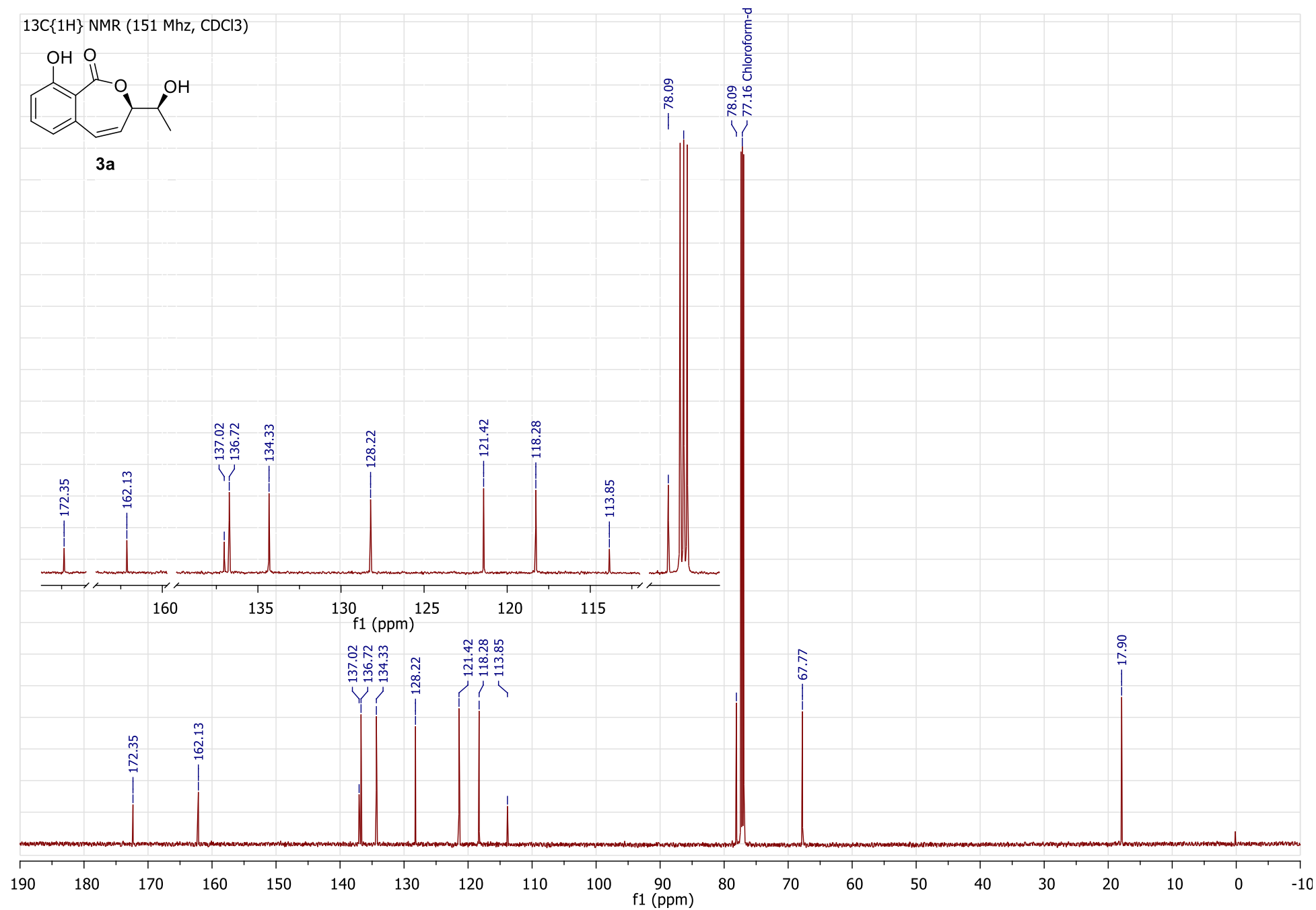


Figure S51. ^{13}C NMR spectrum of **3a** in CDCl_3 .

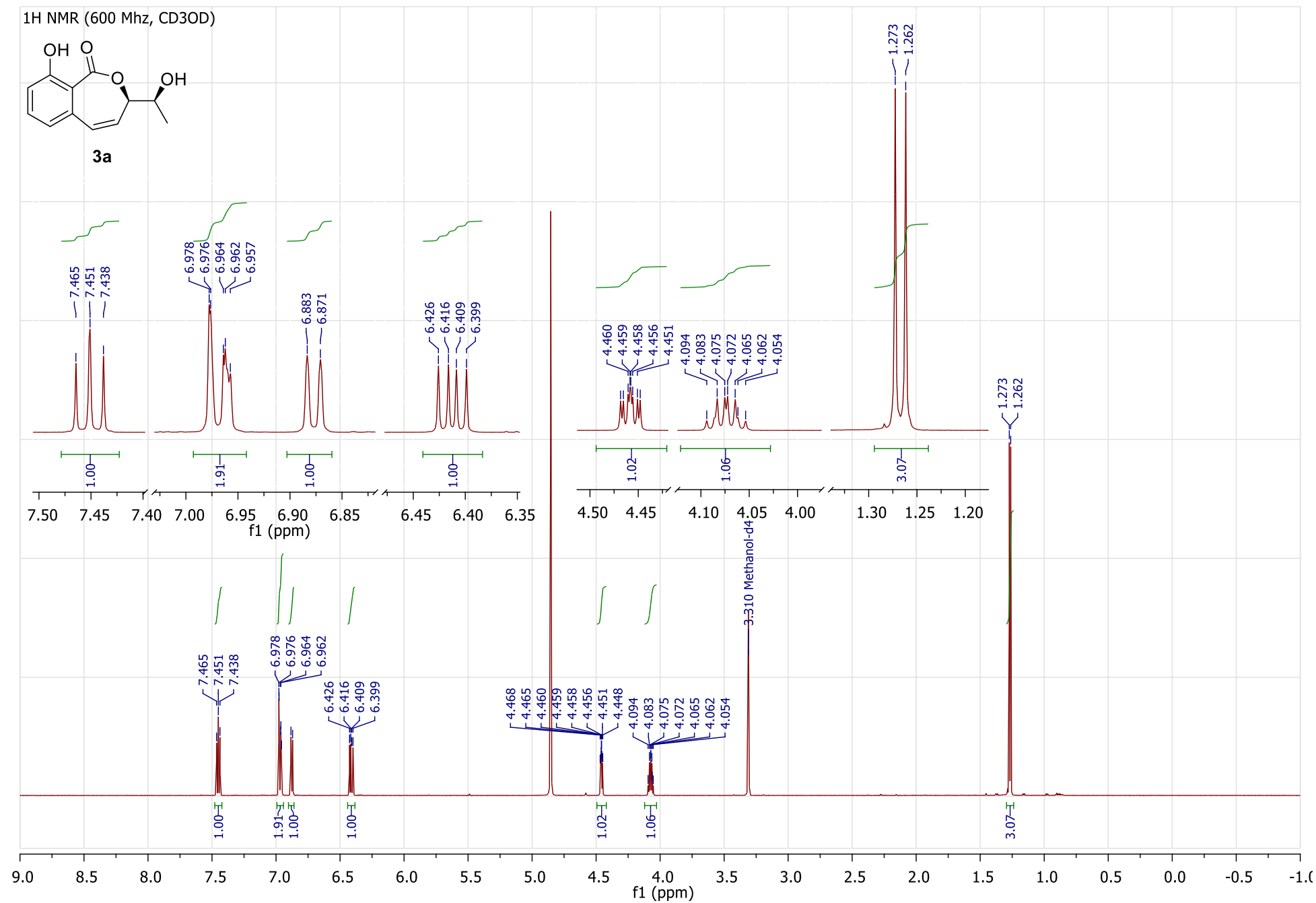


Figure S52. ¹H NMR spectrum of **3a** in CD₃OD.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 Mhz, CD_3OD)

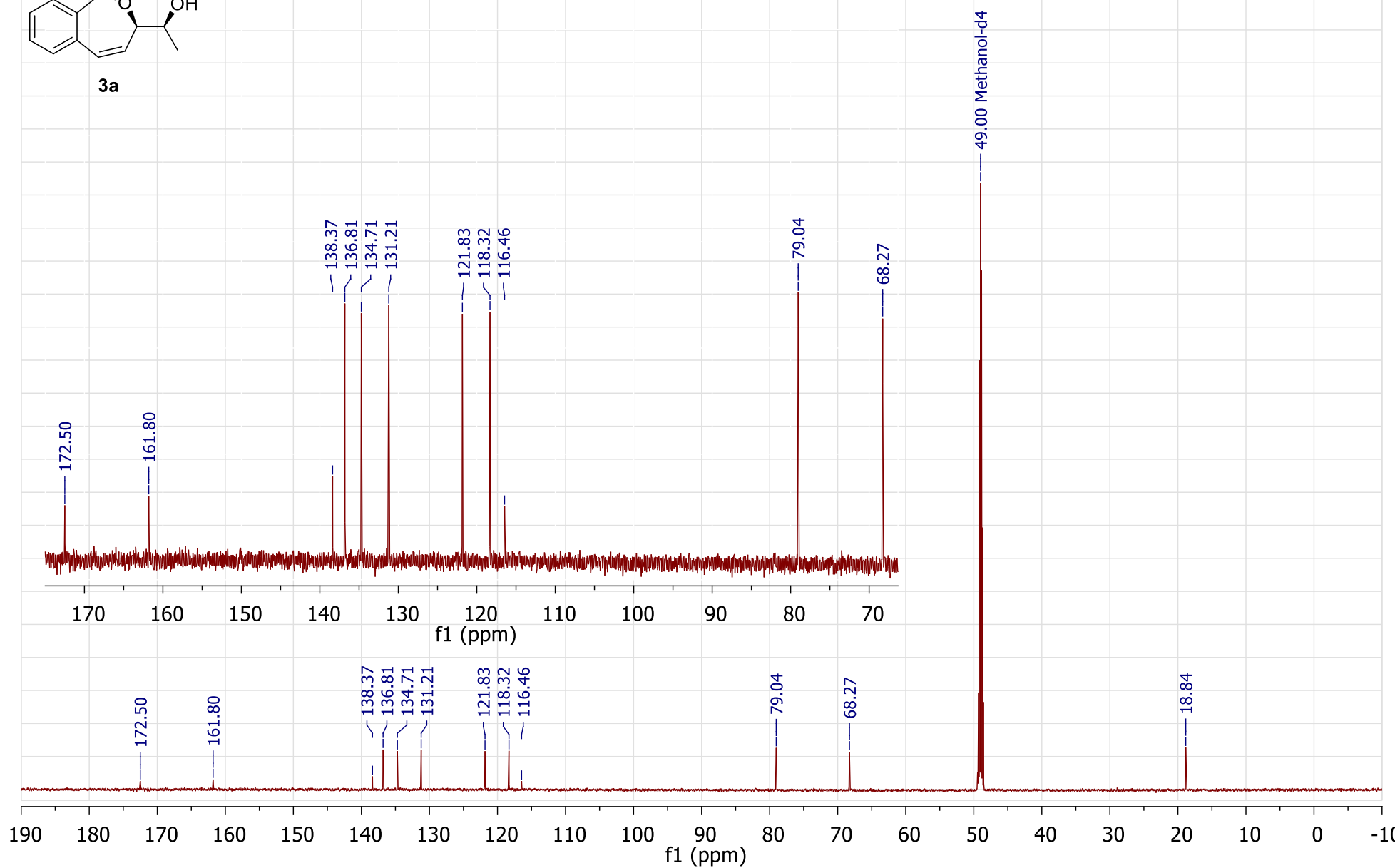
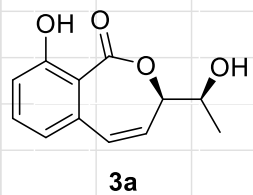


Figure S53. ^{13}C NMR spectrum of **3a** in CD_3OD .

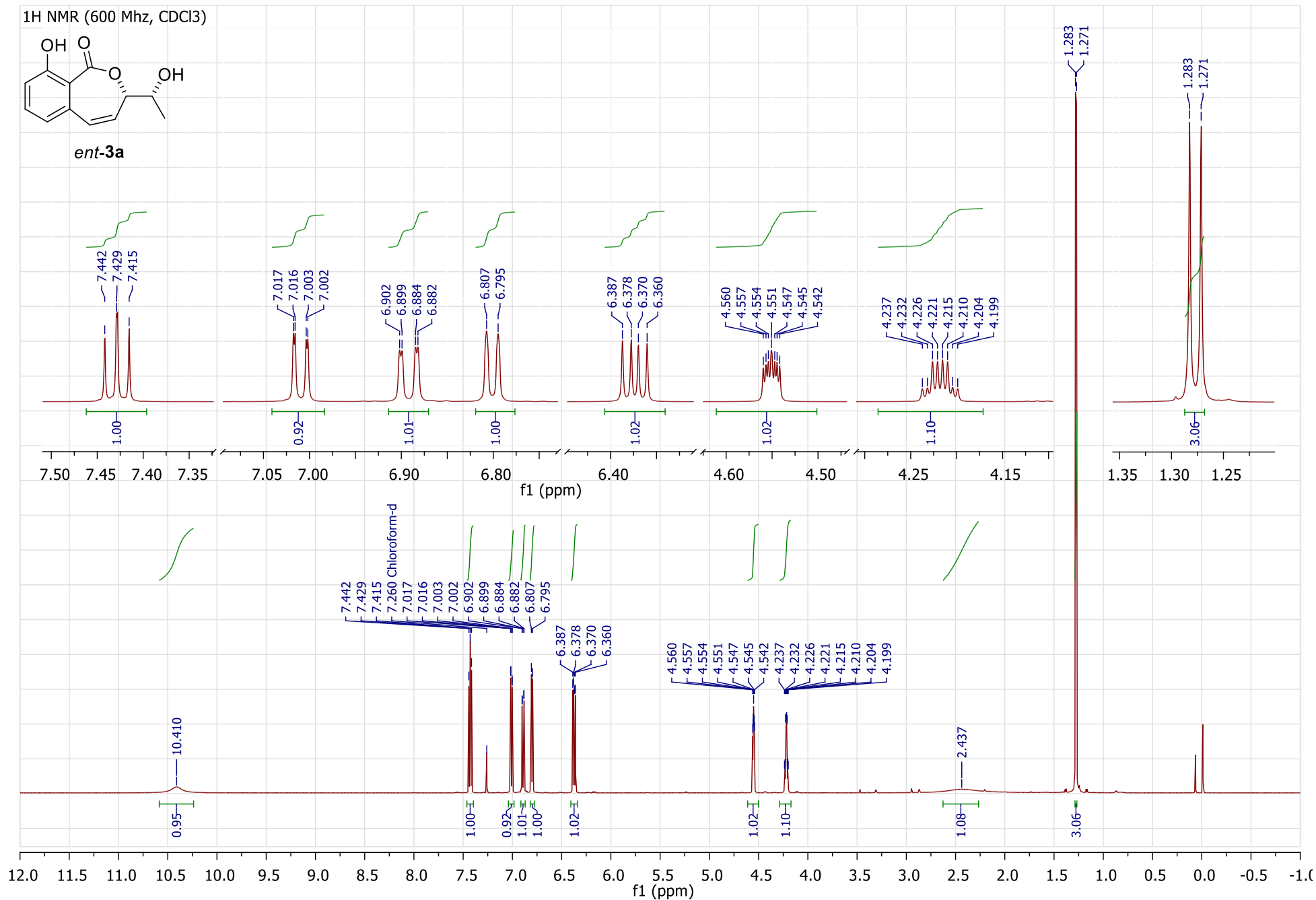


Figure S54. ¹H NMR spectrum of **ent-3a** in CDCl₃.

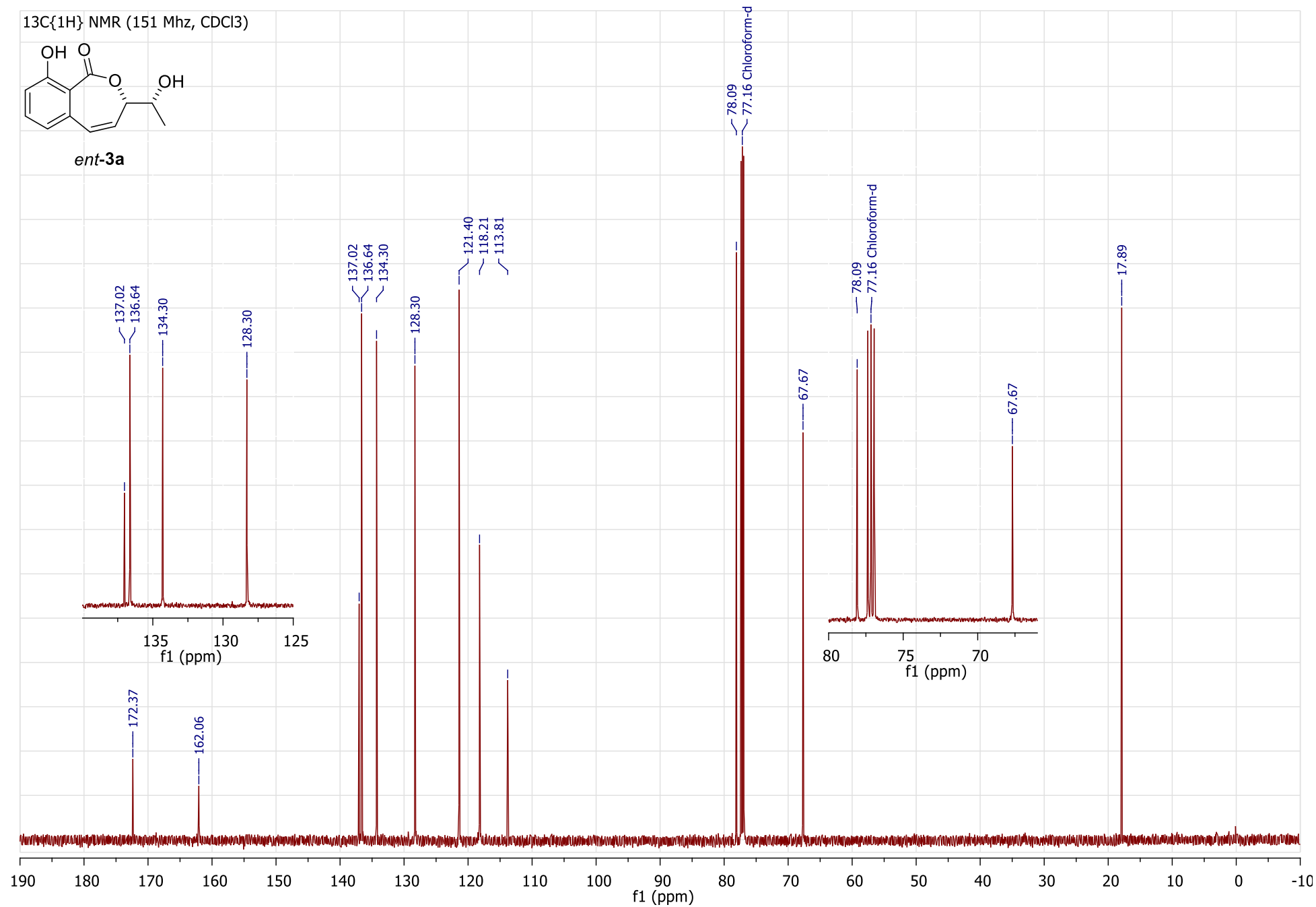
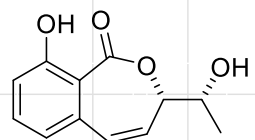


Figure S55. ^{13}C NMR spectrum of **ent-3a** in CDCl_3 .

¹H NMR (600 Mhz, CD₃OD)



ent-**3a**

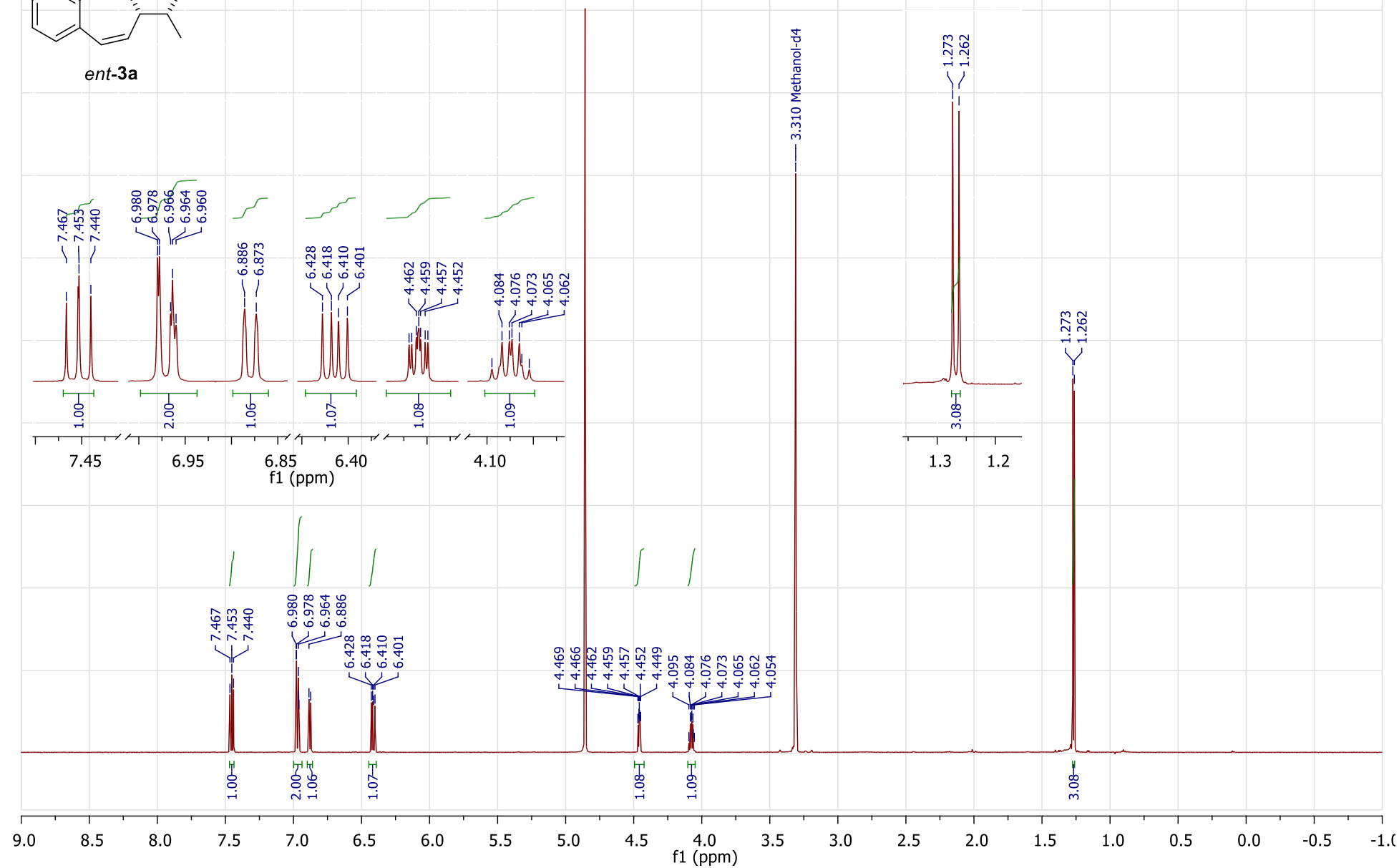


Figure S56. ¹H NMR spectrum of *ent*-**3a** in CD₃OD.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 Mhz, CD_3OD)

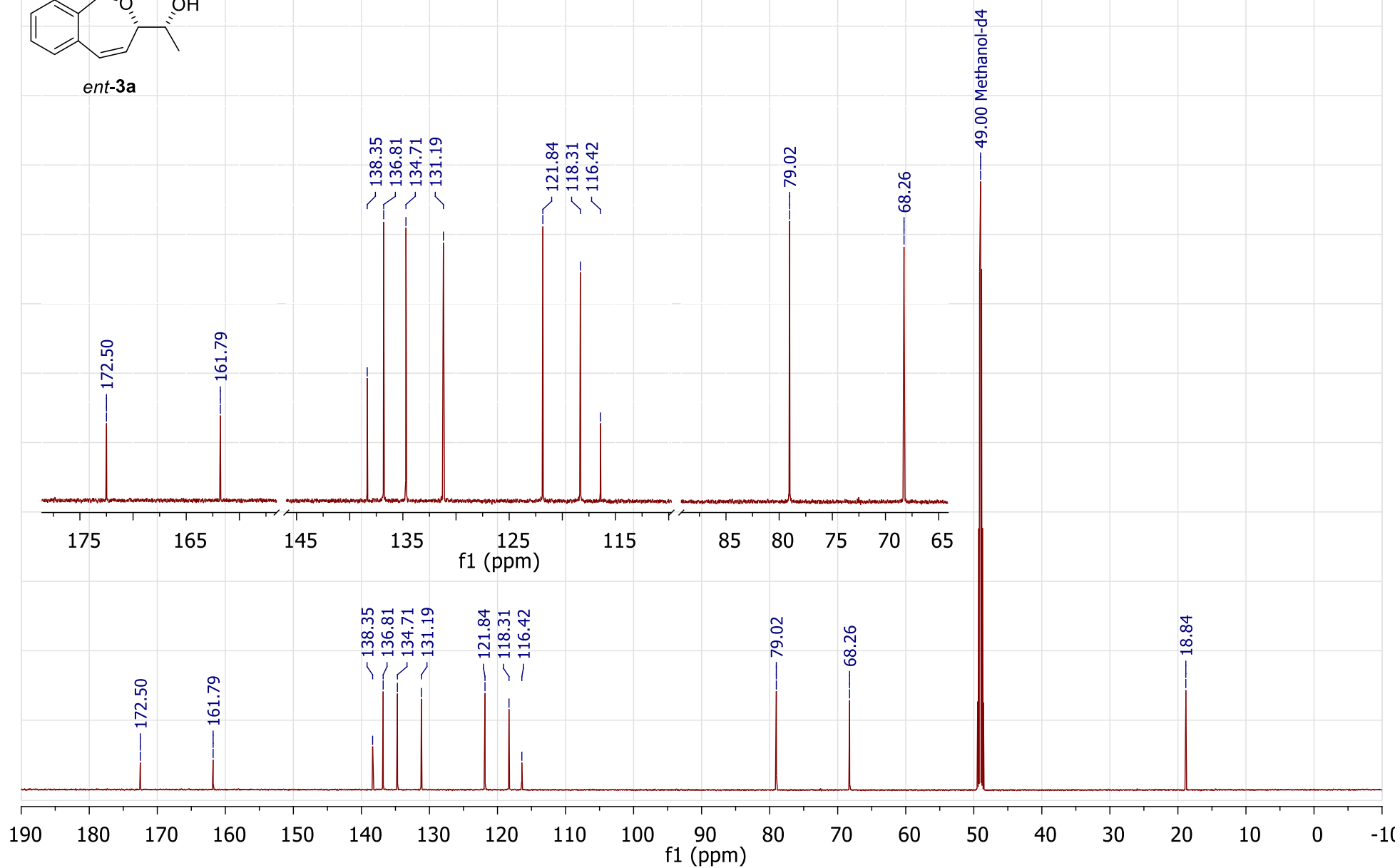
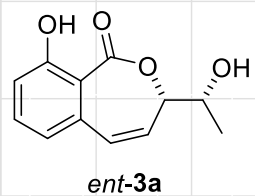


Figure S57. ^{13}C NMR spectrum of *ent-3a* in CD_3OD .

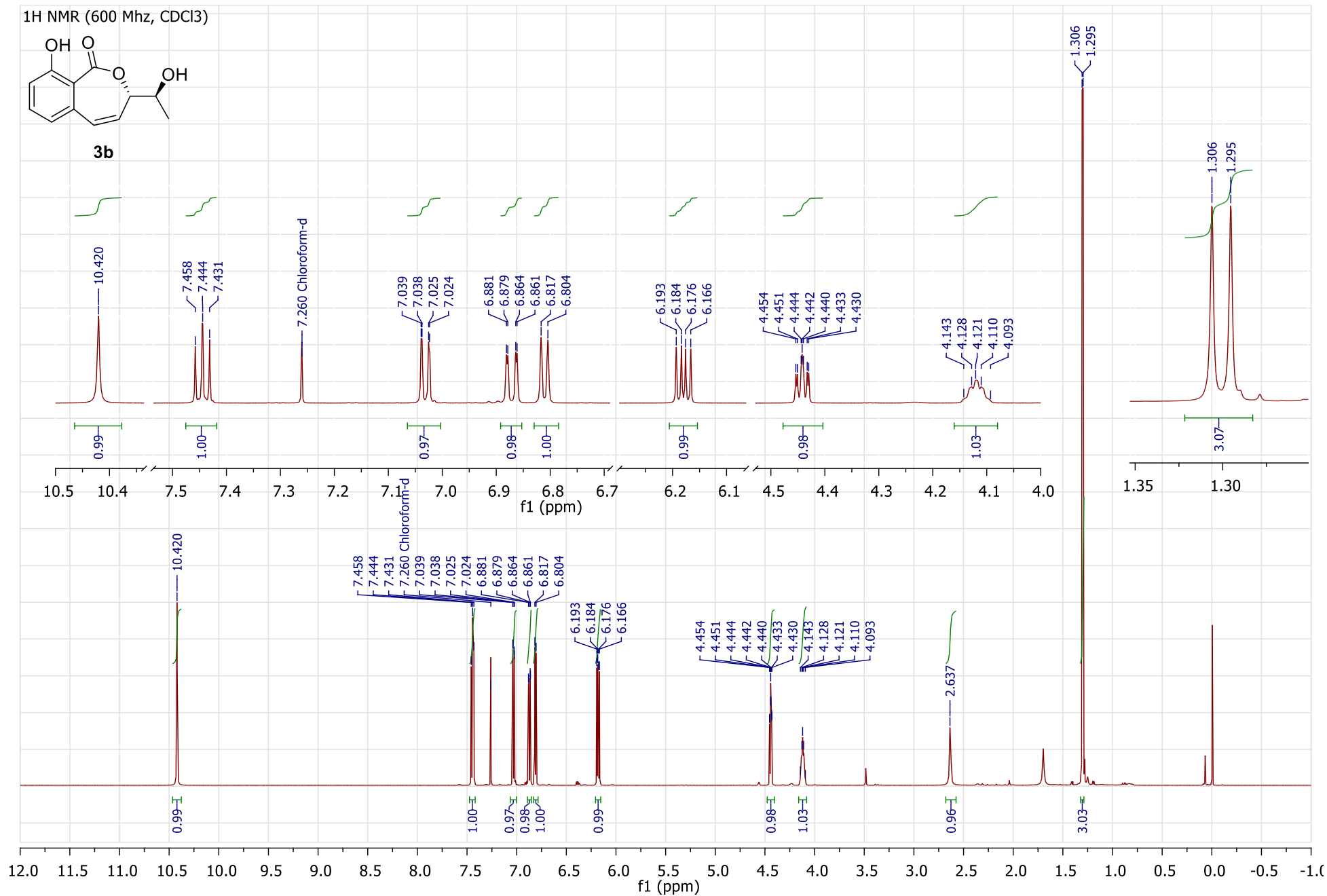
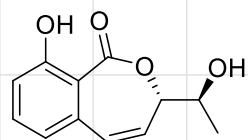


Figure S58. ¹H NMR spectrum of **3b** in CDCl₃.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 Mhz, CDCl_3)



3b

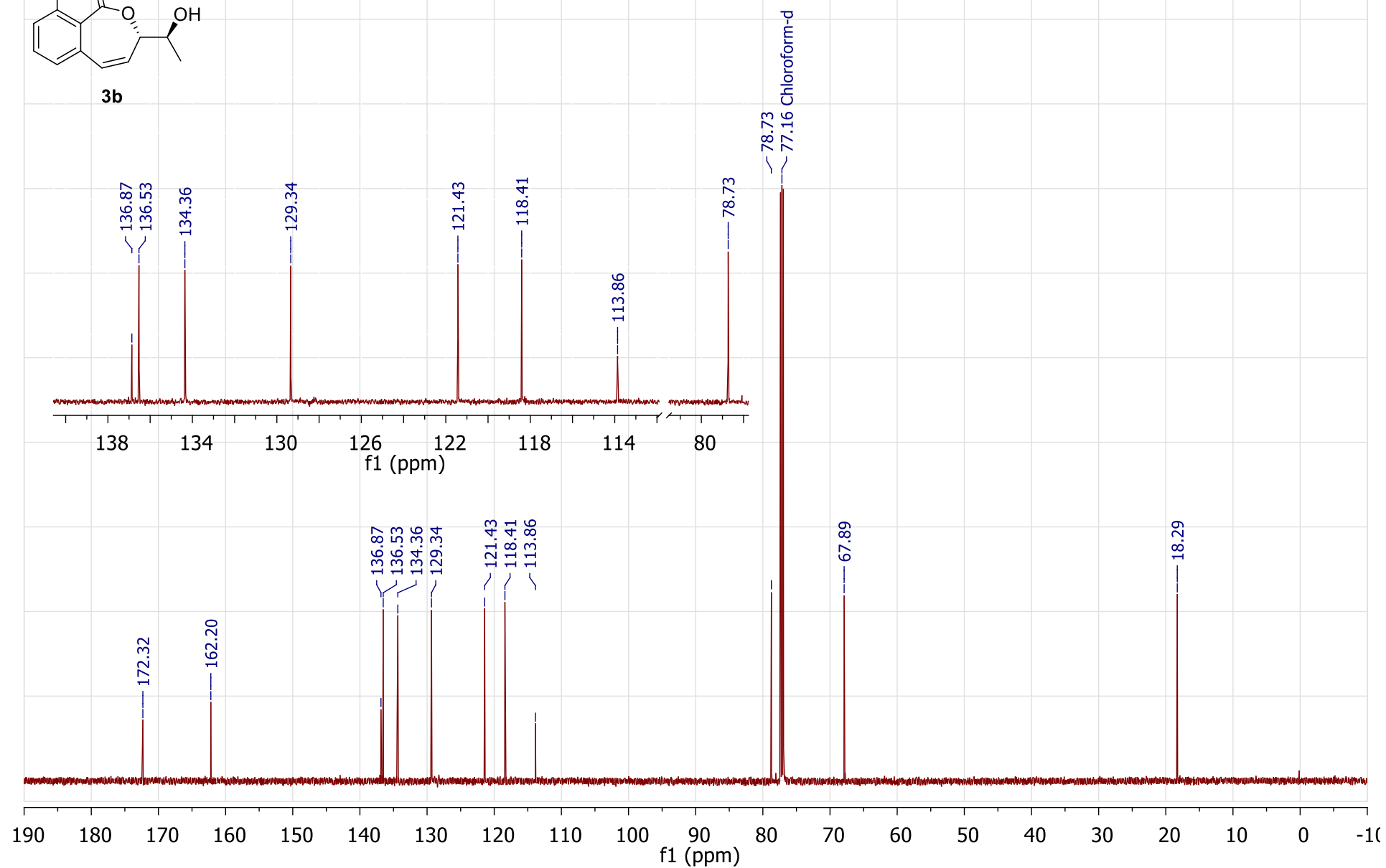


Figure S59. ^{13}C NMR spectrum of **3b** in CDCl_3 .

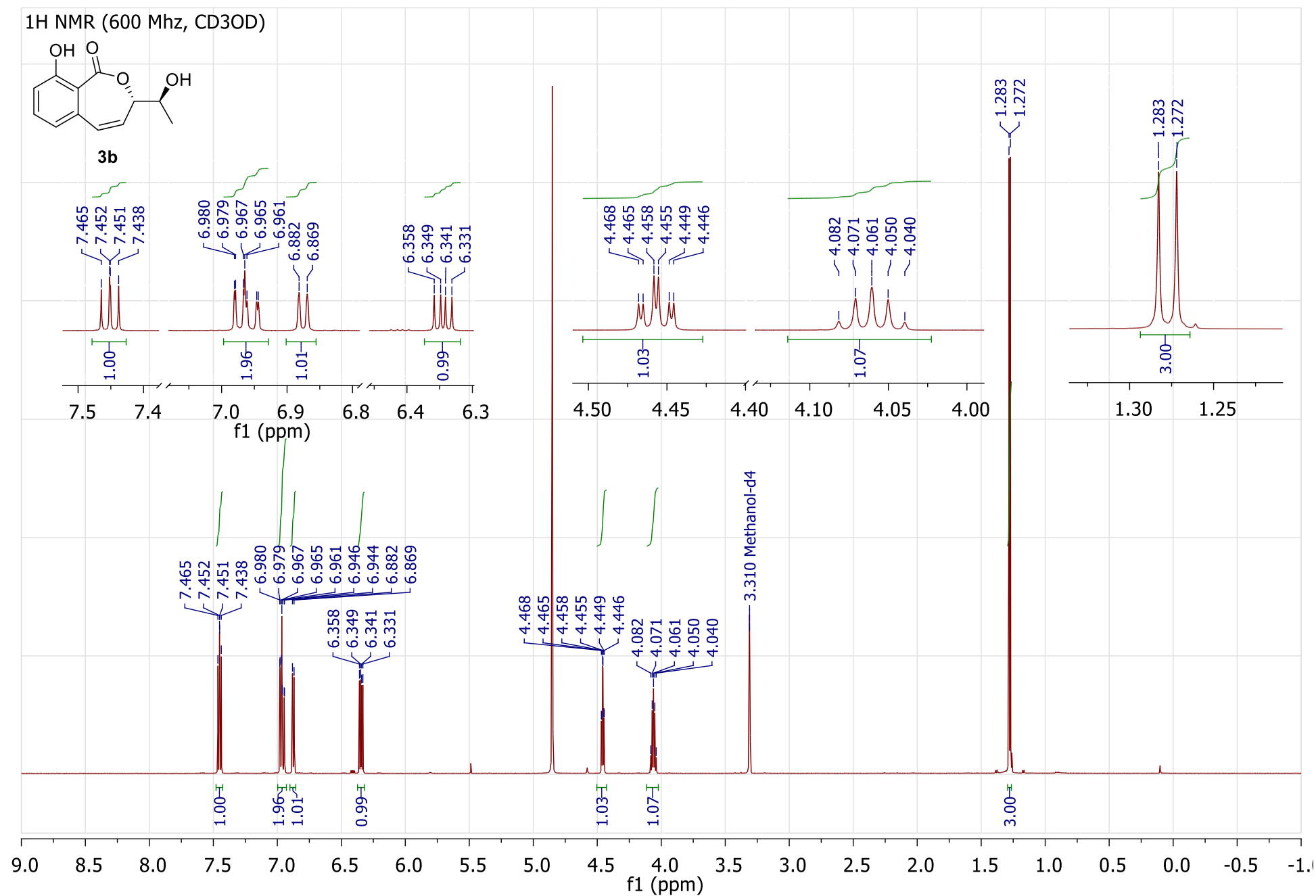
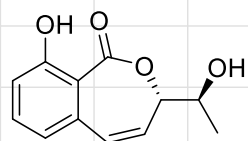


Figure S60. ¹H NMR spectrum of **3b** in CD₃OD.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 Mhz, CD_3OD)



3b

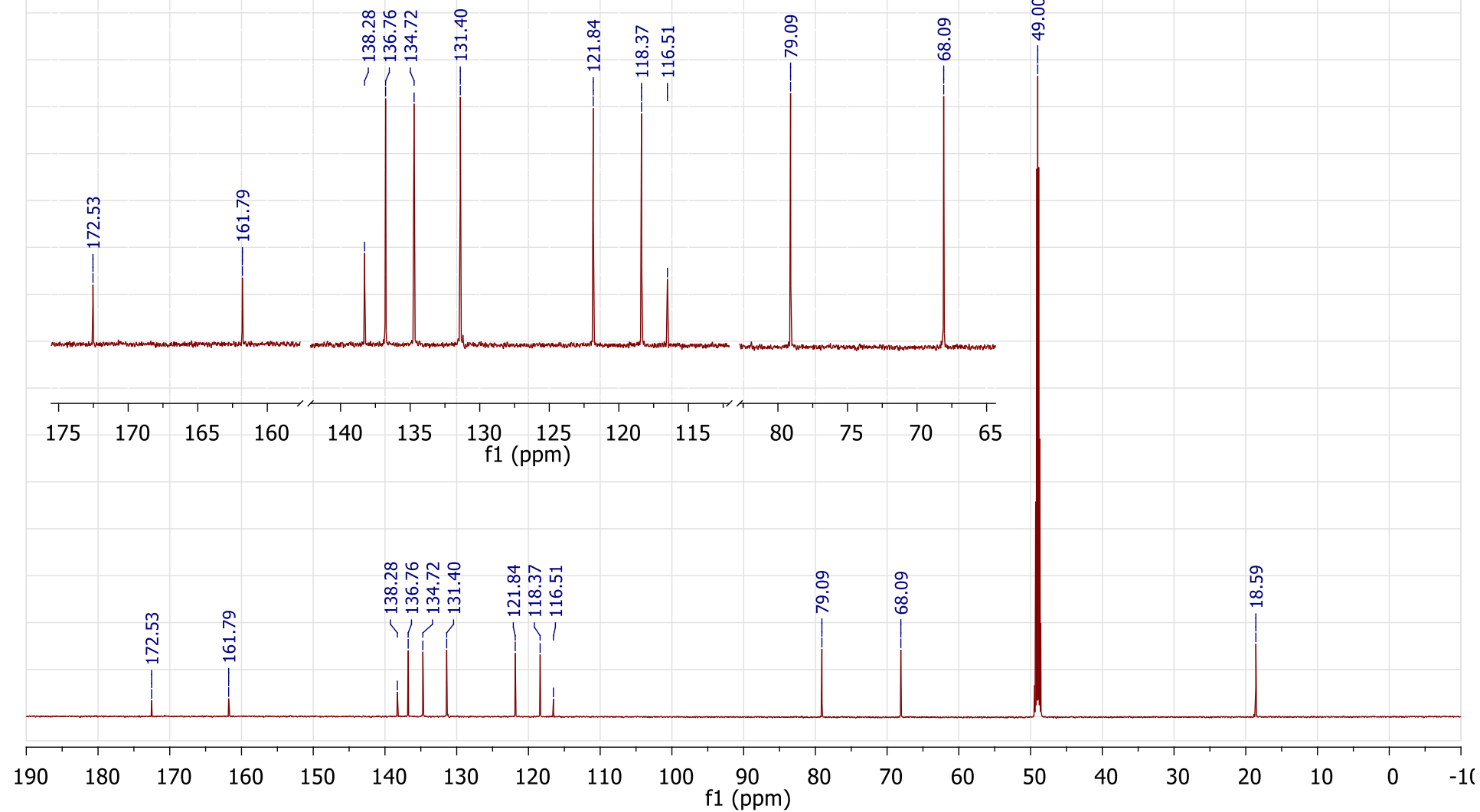


Figure S61. ^{13}C NMR spectrum of **3b** in CD_3OD .

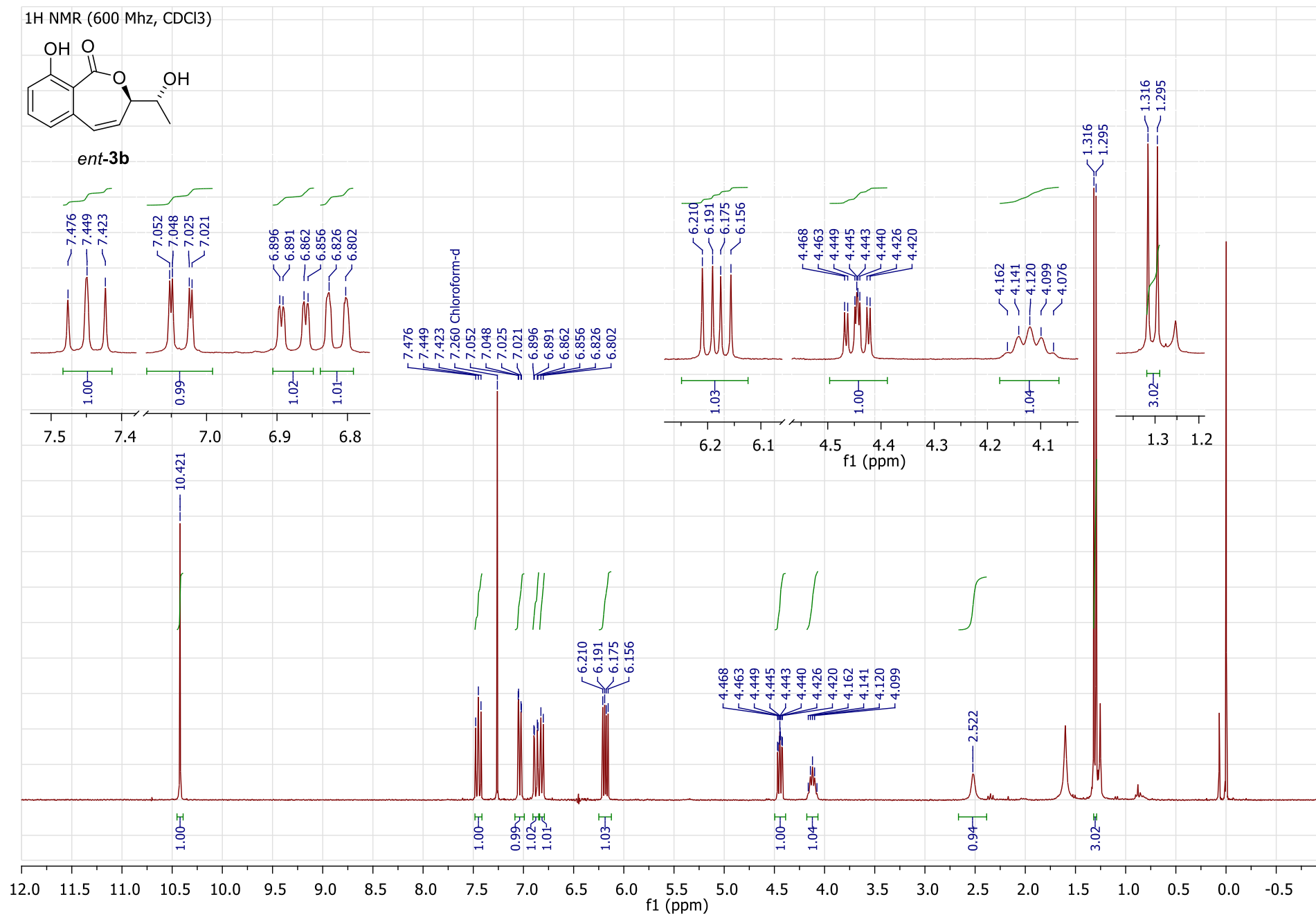
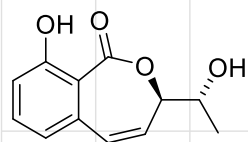


Figure S62. ¹H NMR spectrum of **ent-3b** in CDCl₃.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 Mhz, CDCl_3)



ent-**3b**

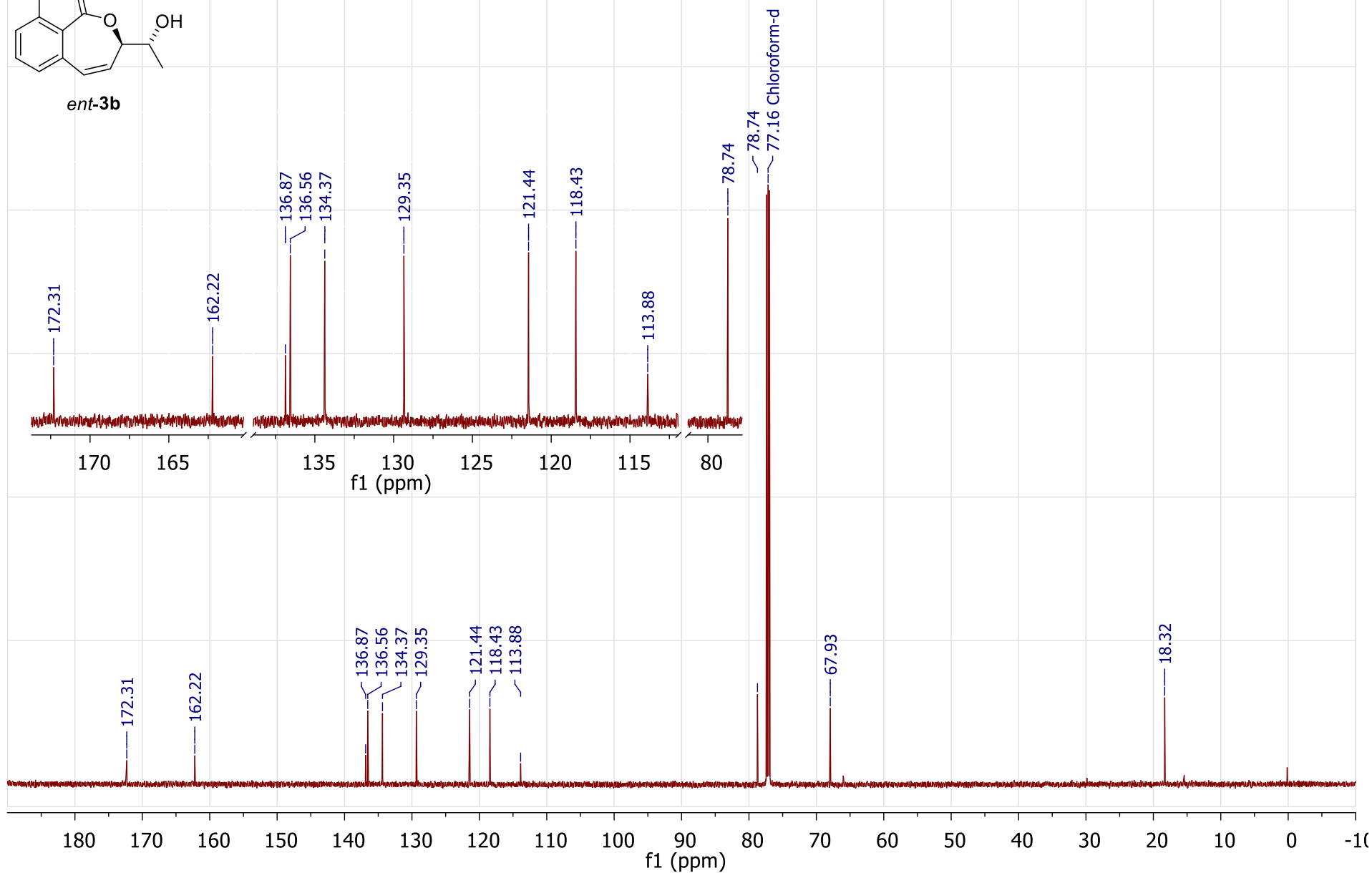


Figure S63. ^{13}C NMR spectrum of *ent*-**3b** in CDCl_3 .

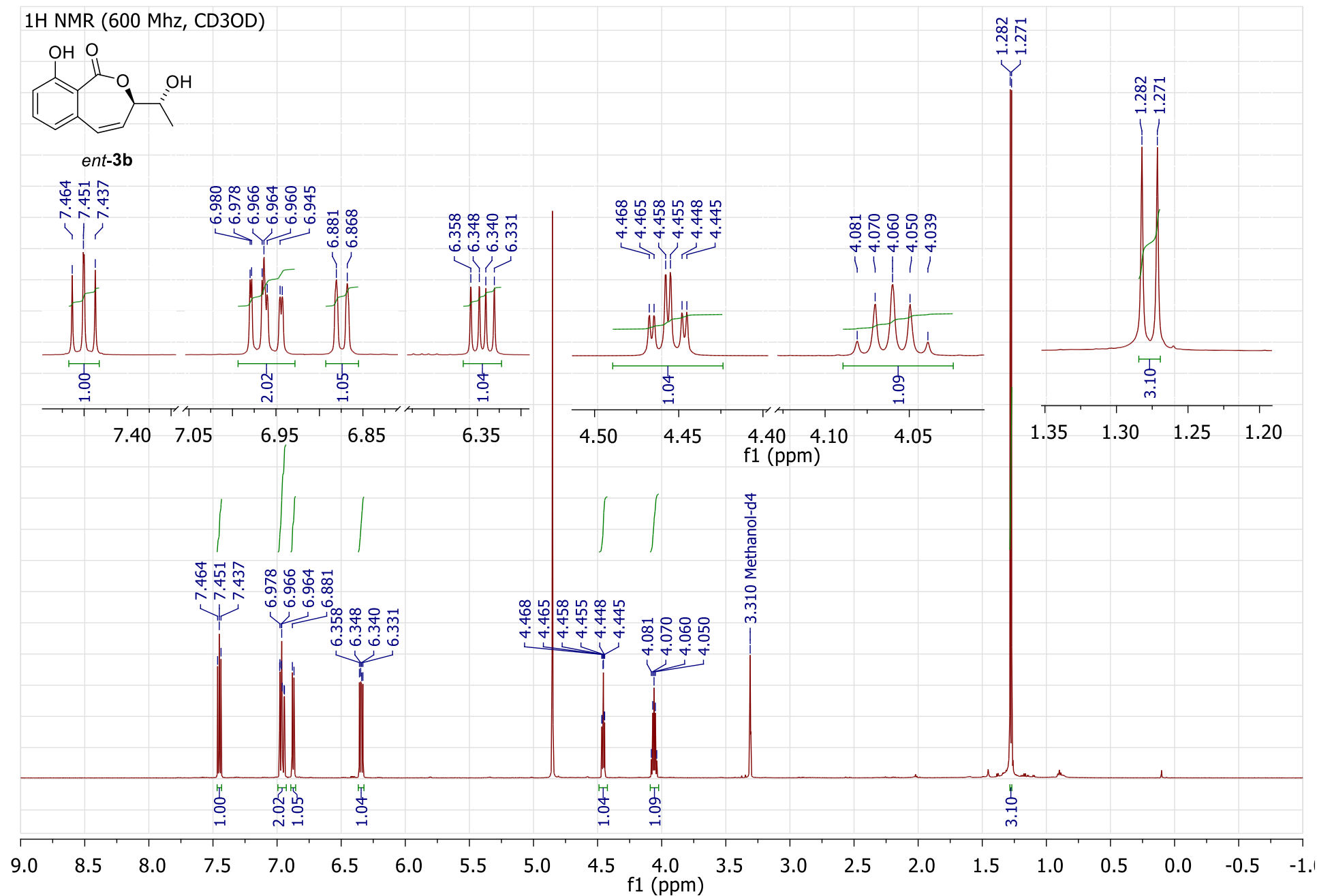


Figure S64. ¹H NMR spectrum of *ent-3b* in CD₃OD.

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 Mhz, CD_3OD)

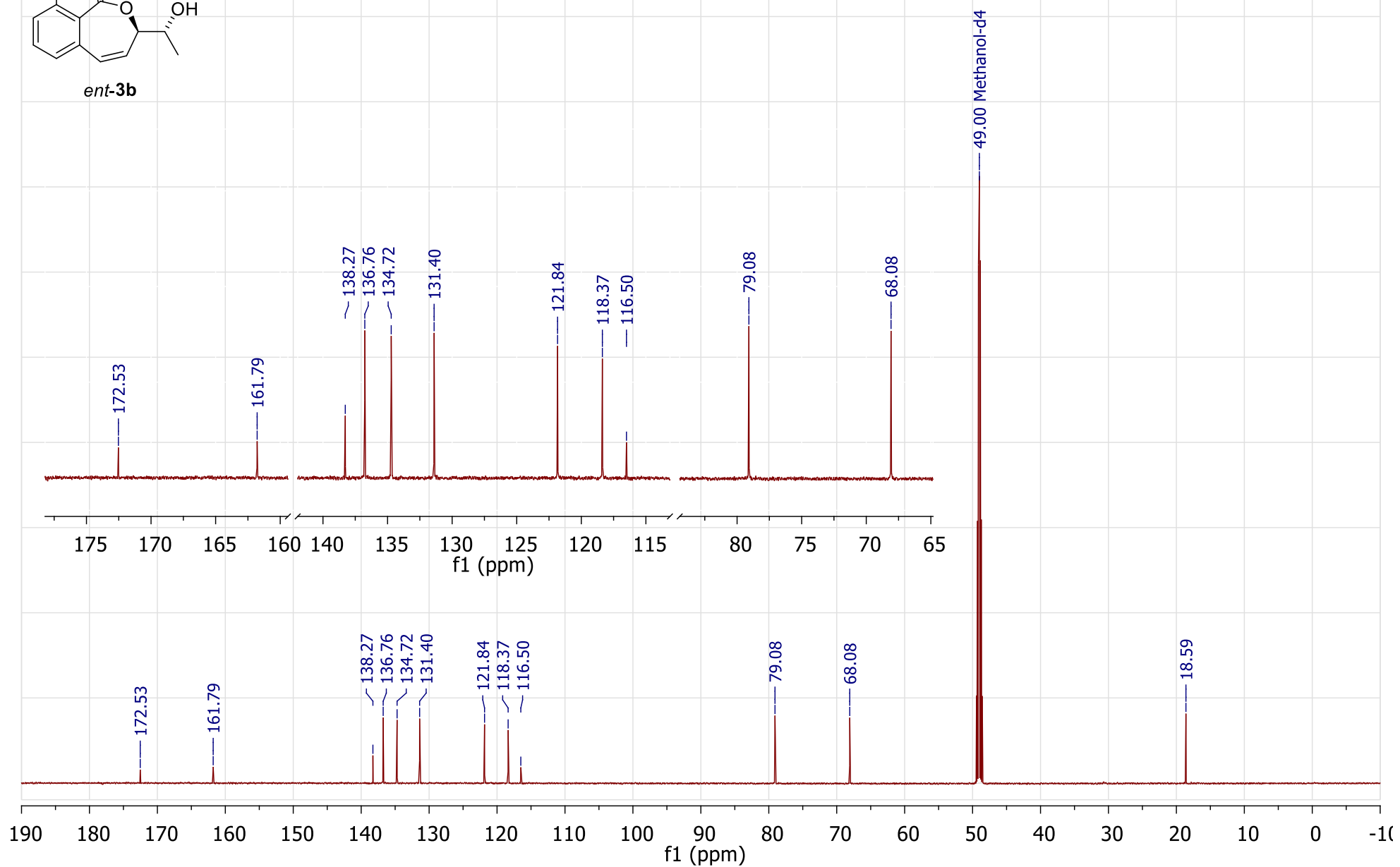
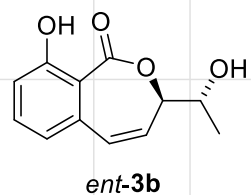


Figure S65. ^{13}C NMR spectrum of *ent-3b* in CD_3OD .

¹H NMR (400 MHz, CD₃OD)

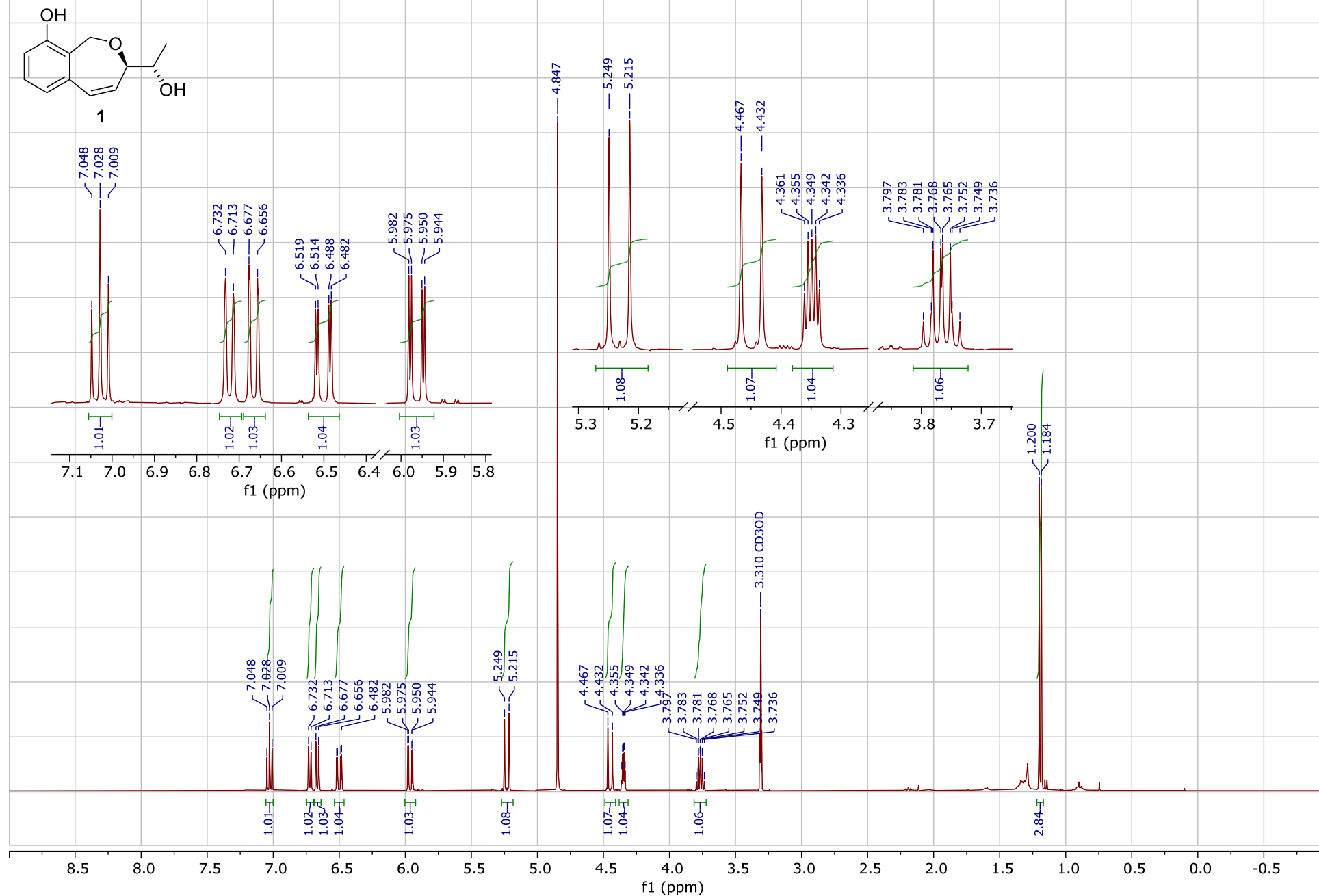


Figure S66. ¹H NMR spectrum of **1**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CD_3OD)

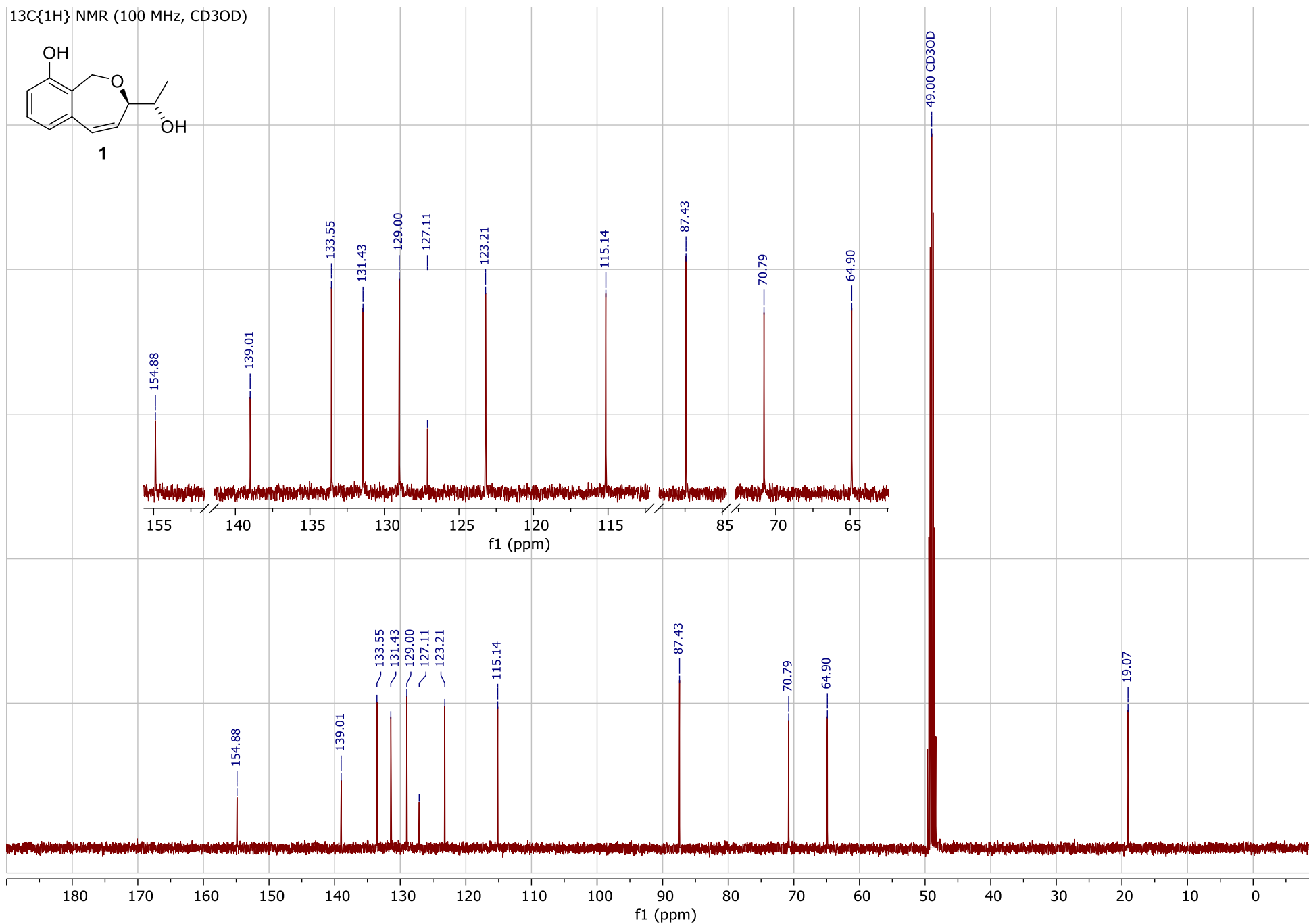
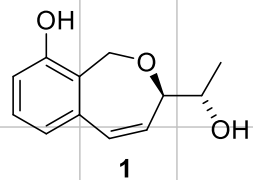


Figure S67. ^{13}C NMR spectrum of **1**.

¹H NMR (400 MHz, CD₃OD)

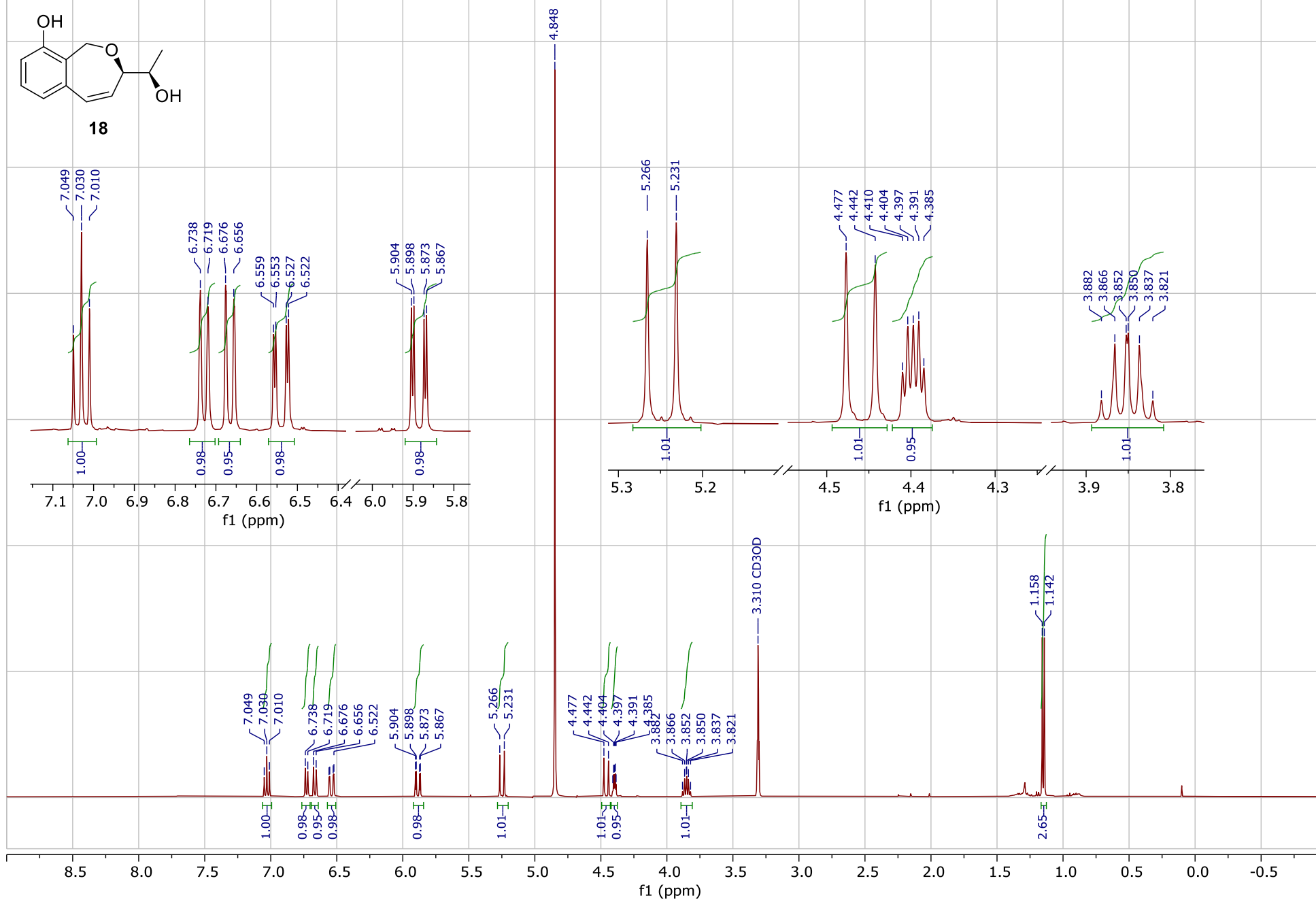
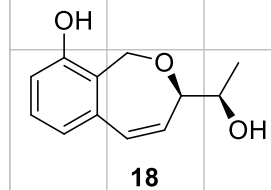
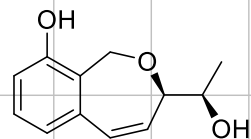


Figure S68. ¹H, NMR spectrum of **18**.

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CD_3OD)



18

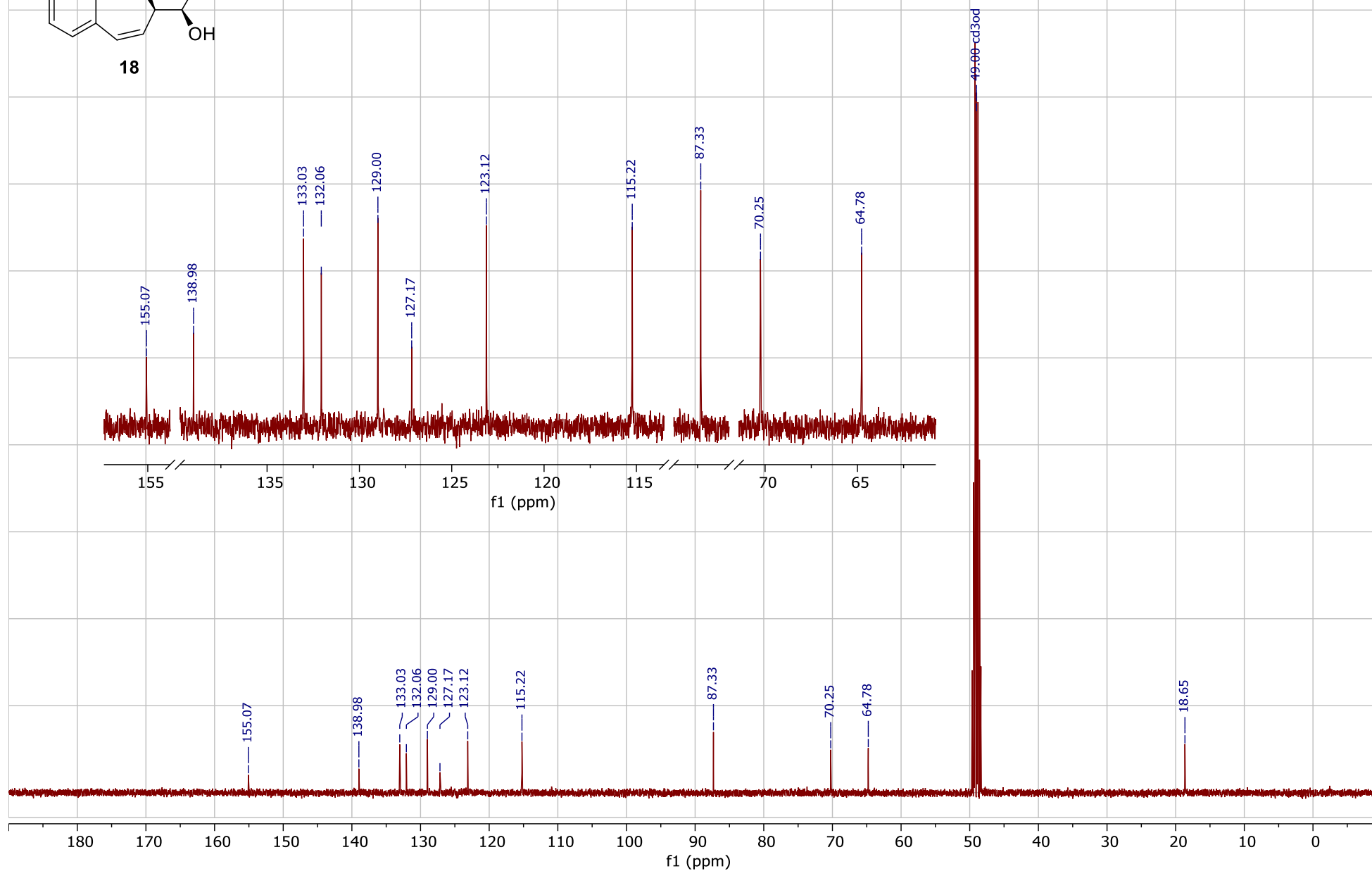


Figure S69. ^{13}C NMR spectrum of **18**.

HPLC Analytical method

Enantiomeric excesses were determined by HPLC (Agilent Technologies) using Chiralpak IC column (Daicel Chiral Technologies, dimensions 4.6 Ø x 250 mm, particle size 5 µm) using *n*-hexane/propan-2-ol (isocratic 90/10) as a mobile phase and detected by UV at 254 nm.

UV detector: 254 nm

Sample injection: 12 µL (C = 1mg/mL)

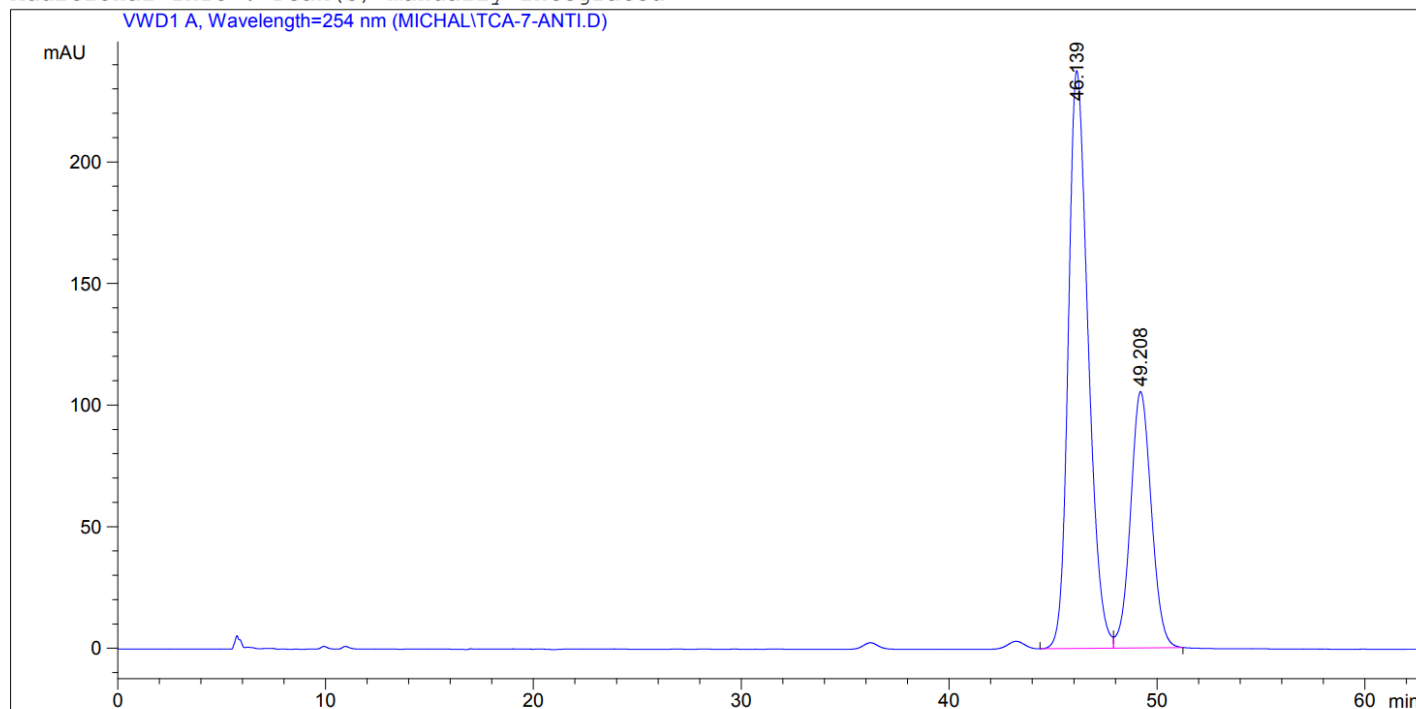
Isocratic 90/10 *n*-hexane/*i*PrOH

Flow rate: 0.6 mL/min

CHIRALPAK® IC

Retention times: **3a** 45.8 min, *ent*-**3a** 49.2 min,
 3b 42.5 min, *ent*-**3b** 35.8 min.

```
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Acq. Operator   : tomas
Acq. Instrument : Instrument 1                Location :   -
Injection Date  : 1/18/2023 2:36:19 AM
Acq. Method     : C:\CHEM32\1\METHODS\ROBO.M
Last changed    : 1/18/2023 2:23:18 AM by tomas
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\ROBO.M
Last changed    : 1/19/2023 2:16:41 AM by tomas
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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Area Percent Report
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Sorted By      :      Signal
Multiplier:    :      1.0000
Dilution:      :      1.0000
Use Multiplier & Dilution Factor with ISTDs
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Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
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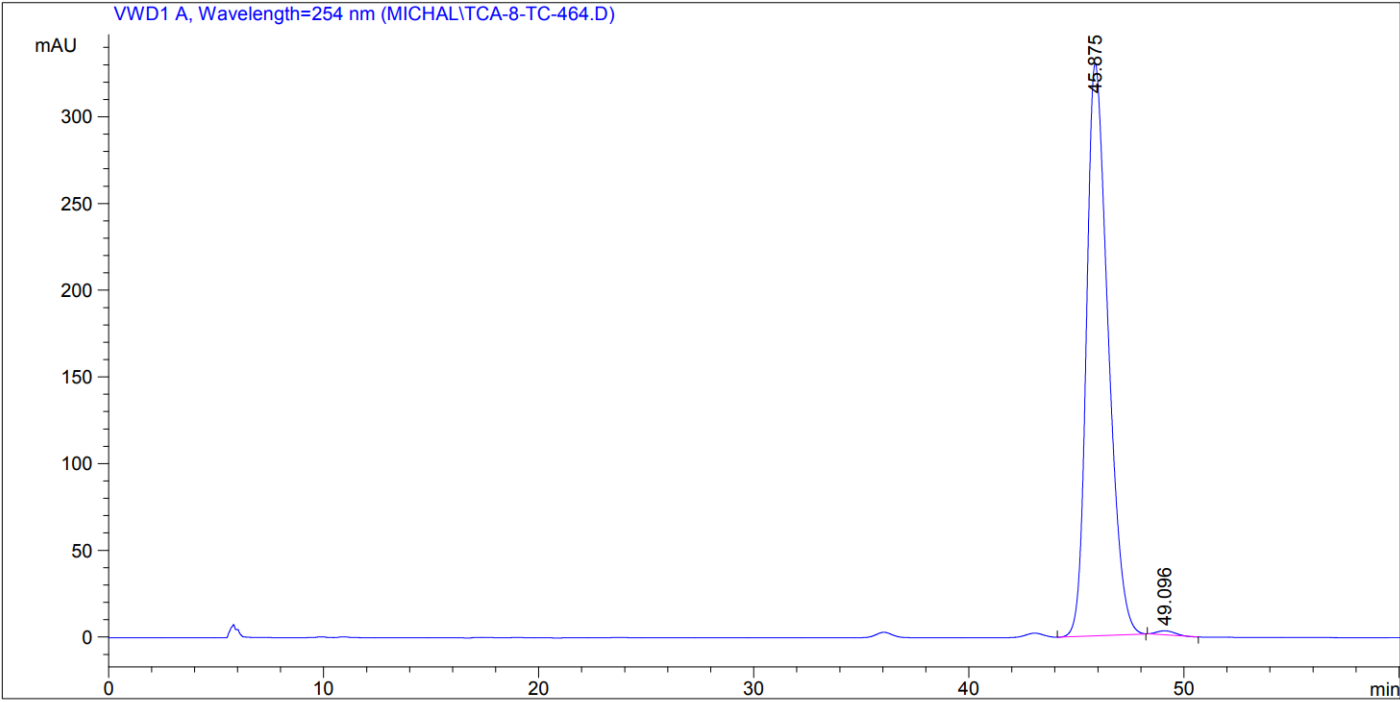
Totals : 2.31187e4 343.08157

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*** End of Report ***

Figure S70. HPLC analysis of a mixture of 3a and ent-3a.

=====

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Acq. Instrument : Instrument 1 Location : -
Injection Date : 1/18/2023 3:44:19 AM
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(modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\ROBO.M
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(modified after loading)
Additional Info : Peak(s) manually integrated



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Area Percent Report

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Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
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2	49.096	BB	0.6901	137.74297	2.38924	0.5955

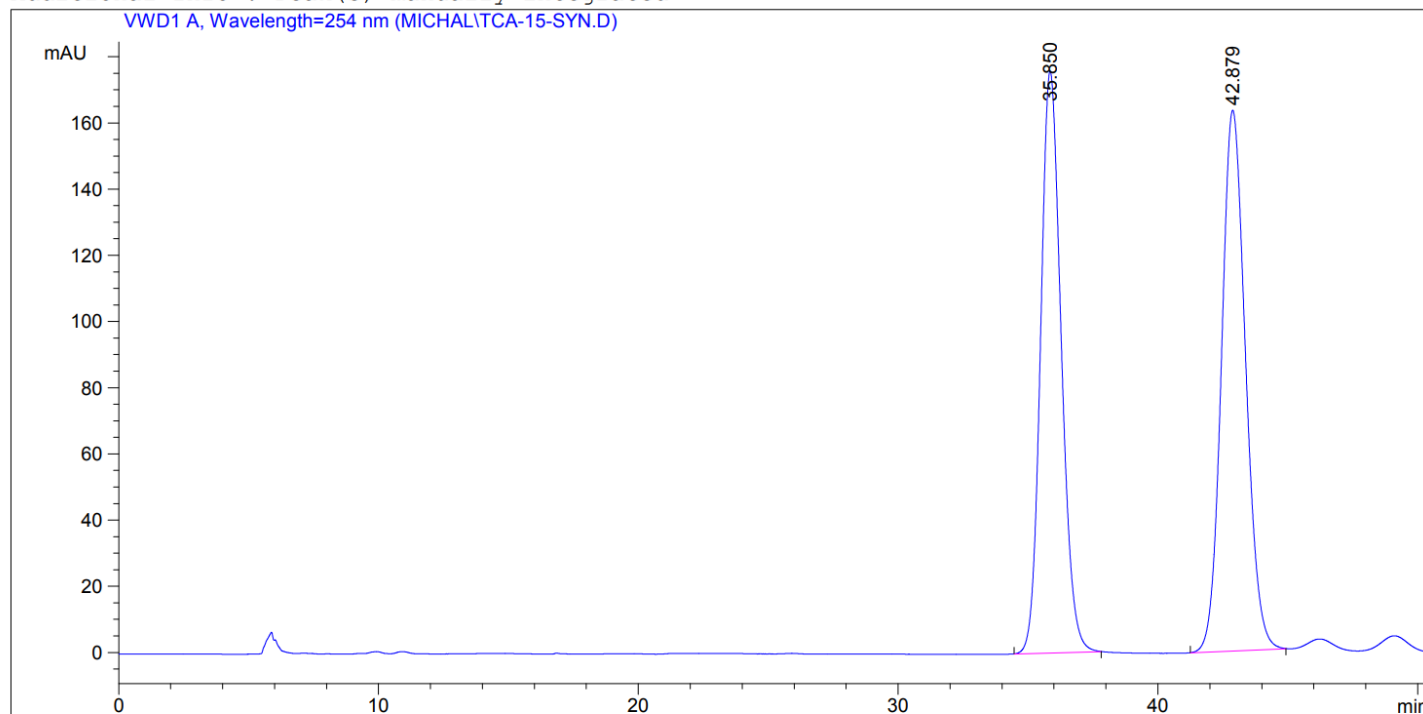
Totals : 2.31311e4 332.58474

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*** End of Report ***

Figure S71. HPLC analysis of synthetic 3a.

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Analysis Method : C:\CHEM32\1\METHODS\ROBO.M
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                  (modified after loading)
Additional Info : Peak(s) manually integrated
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                        Area Percent Report
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Dilution:            :      1.0000
Use Multiplier & Dilution Factor with ISTDs
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Signal 1: VWD1 A, Wavelength=254 nm

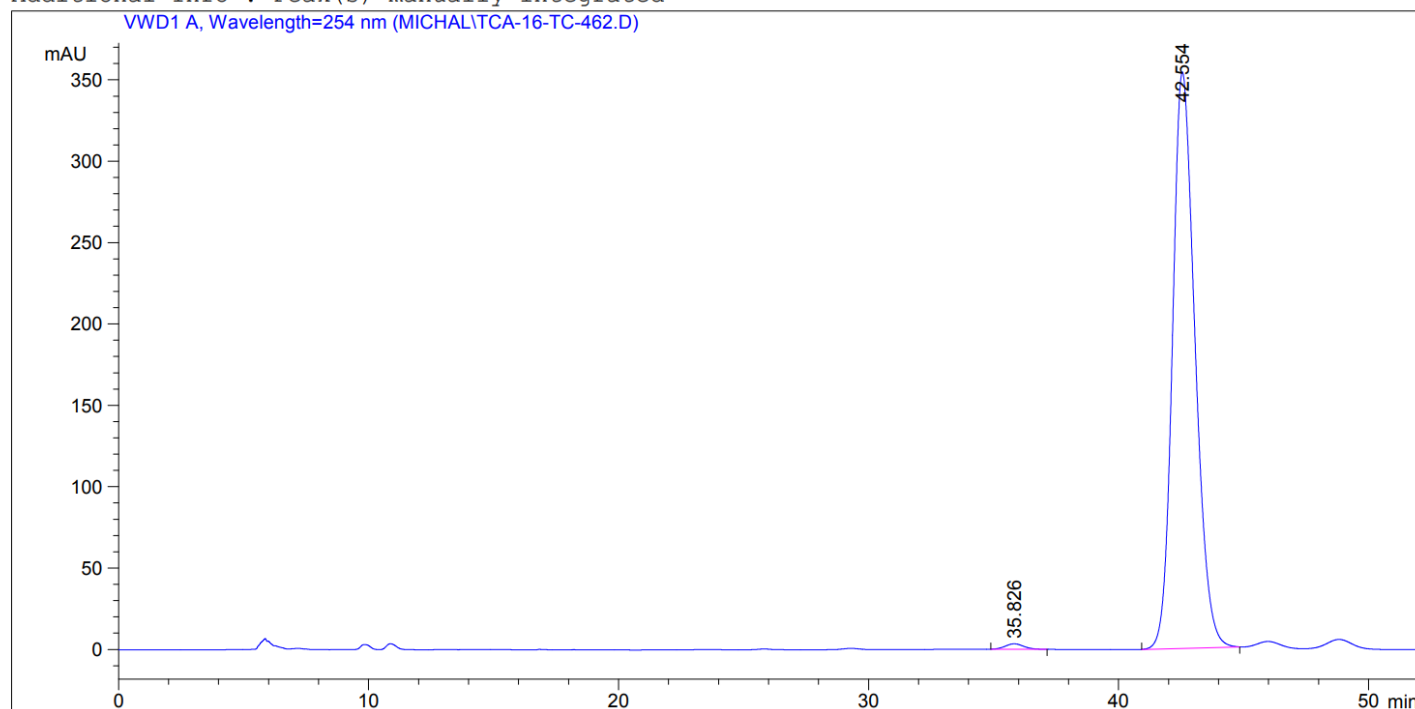
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	35.850	BB	0.8475	9680.69434	175.86061	47.9545
2	42.879	BB	0.9946	1.05066e4	163.43764	52.0455

Totals : 2.01873e4 339.29825

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                        *** End of Report ***
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Figure S72. HPLC analysis of racemic mixture of 3b and ent-3b.

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Analysis Method : C:\CHEM32\1\METHODS\ROBO.M
Last changed    : 1/19/2023 2:16:41 AM by tomas
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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=====
                        Area Percent Report
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Sorted By          :      Signal
Multiplier:         :      1.0000
Dilution:           :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	35.826	BB	0.7033	174.66859	3.36409	0.7843
2	42.554	BB	0.9578	2.20968e4	354.25656	99.2157

Totals : 2.22715e4 357.62065

```
=====
*** End of Report ***
=====
```

Figure S73. HPLC analysis of synthetic 3b.