Enantiospecific Synthesis of both Enantiomers of the Longtailed Mealybug Pheromone and their Evaluation in a New Zealand Vineyard

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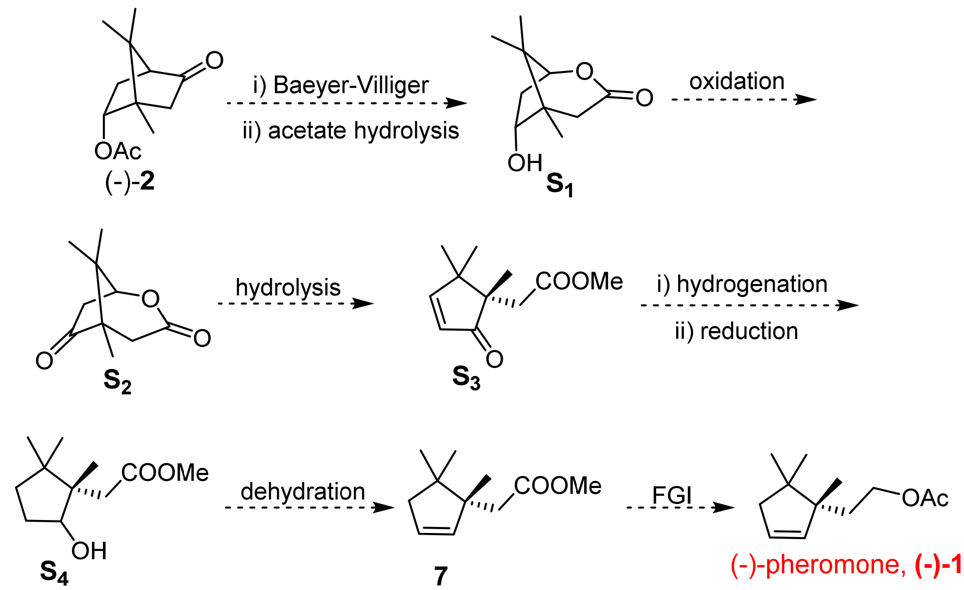
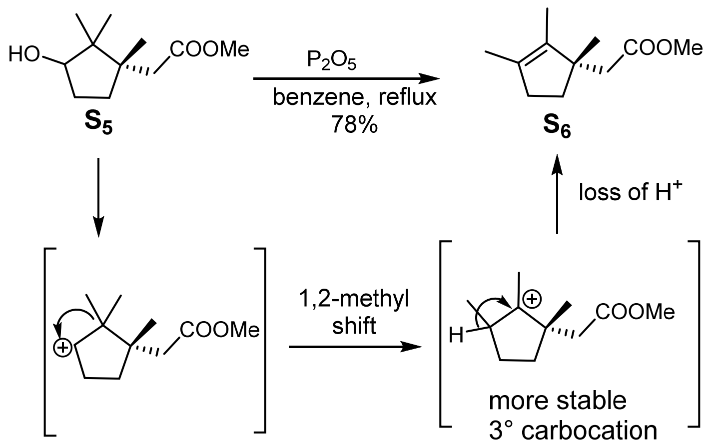
Supporting Information

Initial plan towards pheromones

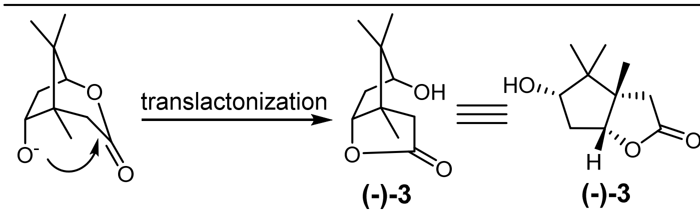


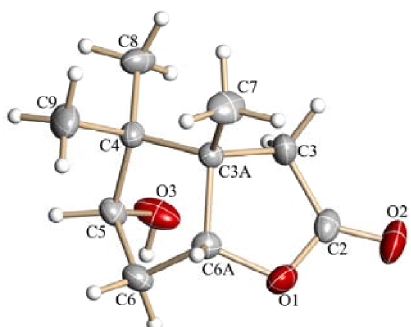
The initial synthetic plan for the target molecules is shown above. Regioselective Baeyer-Villiger oxidation of **(-)-2**[1] followed by hydrolysis and oxidation of alcohol **S_1** would give the keto-lactone **S_2**. Lactone hydrolysis with concomitant dehydration would give the cyclopentenone ester **S_3**. Hydrogenation of **S_3** followed by reduction of the ketone leads to the cyclopentanol ester **S_4**, and dehydration of the secondary alcohol present in compound **S_4** would provide the ester **7**. Compound **7** can be transformed to the target **(-)-1** by simple functional group interconversions.

However, all our attempts to prepare compound **S_1** using the standard m-CPBA reagent went in vain. We standardized the reaction using H_2O_2-H_2SO_4 conditions in acetic acid where we got the required regioisomer as the major product. Although the resulting regioisomeric acetates were inseparable, the alcohols obtained after acetate hydrolysis were cleanly separated and was oxidized to the corresponding ketone with PDC. The lactone opening was done using PTSA in methanol and the cyclopentenone ester was isolated as the sole product, along with a small amount of recovered starting material. This compound was hydrogenated and we tried several conditions to obtain the cyclopentene core.



based on formation of **S_6**, the structure of the starting material was revised to **S_5**. Subsequently, it was confirmed by the X-ray analysis of **(-)-3**.





ORTEP of (-)-3

In one of our attempts towards dehydration (P_2O_5, benzene)[2] of the saturated alcohol, we observed the formation of a cyclopentene, but with no olefinic protons. Such a product could be formed via a Wagner-Meerwein rearrangement with a 1,2-methyl shift.[3] In the ^{1}H NMR, the methyl groups were observed at 1.58 and 1.49 ppm, suggesting that they were attached to an sp^2 carbon, but the presence of an AB quartet showed that the chiral centre was still present in the molecule, indicating a possible structure **S_6**. This observation raised questions as to the veracity of the structures assigned to all the intermediates **S_1-S_4**. We thus took an X-ray crystal structure of the alcohol obtained from hydrolysis of the Baeyer-Villiger oxidation product, and found that it was in fact compound **(-)-3**. The original synthetic plan was then modified to accommodate these rearranged intermediates.

Conditions Tried for Deoxygenation of 6

Sl. No.	Conditions	Observation
1.	$NaBH_3CN$ (3 eq.), $BF_3.Et_2O$ (3 eq.), THF reflux	**7** and **7a** formed in 10:3 ratio
2.	i) Ac_2O, TEA, DCM ii) HCOOH (2 eq.), TEA (3 eq.), $Pd_2(dba)_3$ (2.5 mol%), PBu_3 (5 mol%), THF	No reaction at RT and reflux
3.	i) Ac_2O, TEA, DCM ii) TES (5 eq.), $BF_3.Et_2O$ (2 eq.), DCM	**7** and **7a** formed in 1:1 ratio
4.	$LiClO_4$ (12 eq.), TES (3 eq.), Et_2O	Compound $\mathbf{S_7}$ was formed.
5.	i) Ac_2O, TEA, DCM ii) $LiBH_4$ (5 eq.), $Pd_2(dba)_3$ (0.125 eq.), PBu_3 (0.5 eq.), DMF	**7** and **7a** formed in 5:3 ratio
6.	i) LAH, THF ii) $LiClO_4$ (10 eq.), TES (3 eq.), Et_2O	No reaction
7.	i) LAH, THF ii) $NaBH_3CN$ (3 eq.), $BF_3.Et_2O$ (3 eq.), THF reflux	(-)–**8** and **(+)–8a** formed in 1:2 ratio
8.	i) ClCOOMe, TEA, DCM ii) $LiBH_4$ (5 eq.), $Pd_2(dba)_3$ (0.125 eq.), PBu_3 (5 eq.), DME	No reaction. Methyl carbonate was recovered.
9.	$NaBH_3CN$ (3 eq.), $BF_3.Et_2O$ (3eq.), THF, RT	No reaction.
10.	$NaBH_4$ (3 eq.), $BF_3.Et_2O$ (3 eq.), THF, reflux	Complex reaction mixture
11.	$NaBH_3CN$ (3 eq.), $BF_3.Et_2O$ (3 eq.), DME, reflux	**7** and **7a** formed in 10:3 ratio
12.	i) Tf_2O, TEA, DCM ii) LAH, THF, RT	**(-)–8** and **(+)–8a** formed in 10:3 ratio

X-ray crystal structure details of (-)–3

Single crystals of the compound were obtained from chloroform. X-ray intensity data were collected on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation at room temperature 296(2) K. The X-ray generator was operated at 50 kV and 30 mA. Diffraction data were collected with a ω scan width of 0.5° and at different settings of φ and 2θ. The sample-to-detector distance was fixed at 5.00 cm. The X-ray data acquisition was monitored by APEX II program suite.[4] All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs integrated in APEX II program package. The structures were solved by direct method and refined by full matrix least squares, based on F^2, using SHELX-97.[5] ORTEP diagrams was generated using XSHELL program integrated in SHELXTL package with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii. All the H-atoms were placed in geometrically idealized position (C-H = 0.97 Å for the methylene H-atom, C-H = 0.96 Å for the methyl H-atom, C-H = 0.98 Å for the methine H-atom and O-H = 0.82 Å for the hydroxyl H-atom) and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C) for the methylene and methine group, U_{iso}(H) = 1.5 U_{eq}(C) for the methyl group and U_{iso}(H) = 1.5U_{eq}(O) for the hydroxyl group].

Crystallographic data for (-)-3. ($C_{10}H_{16}O_3$): M = 184.23, Crystal dimensions 0.64 x 0.60 x 0.20 mm^3, orthorhombic, space group P212121, a = 6.9872(7), b = 11.6575(12), c = 11.8586(12) Å, V = 965.92(17) $Å^3$, Z = 4, ρ_{calcd} = 1.267 gcm^{-3}, μ (Mo-Kα) = 0.092 mm–1, $F(000)$ = 400, $2\theta_{max}$ = 50.00°, T = 296(2) K, 5178 reflections collected, 1648 unique, 1532 observed ($I > 2\sigma(I)$) reflections, 122 refined parameters, R value 0.0329, $wR2$ = 0.0806, (all data R = 0.0356, $wR2$ = 0.0824), S = 1.091, minimum and maximum transmission 0.943 and 0.982; maximum and minimum residual electron densities +0.09 and –0.11 e $Å^{-3}$.

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **(-)-3.** *U*(eq) is defined as one third of the trace of the orthogonalized *U*ij tensor.

	x	y	z	U(eq)
O(1)	-1824(2)	6538(1)	8420(1)	51(1)
O(2)	-2325(2)	5025(1)	9510(1)	74(1)
O(3)	237(2)	4962(1)	6215(1)	67(1)
C(2)	-1245(3)	5582(2)	8940(1)	48(1)
C(3)	794(3)	5342(2)	8693(2)	49(1)
C(4)	2650(2)	6213(1)	7019(1)	36(1)
C(5)	987(2)	6093(1)	6168(1)	41(1)
C(6)	-471(3)	6972(2)	6545(1)	47(1)
C(7)	2769(3)	7096(2)	9025(2)	62(1)
C(8)	3986(2)	5177(2)	7053(2)	53(1)
C(9)	3831(3)	7265(2)	6668(2)	64(1)
C(3A)	1600(2)	6434(1)	8152(1)	33(1)
C(6A)	-249(2)	7078(1)	7820(1)	40(1)

Table 2. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (-)-**3**.

H(3)	-629	4896	5753	101
H(3A)	909	4698	8179	59
H(3B)	1481	5162	9381	59
H(5)	1432	6268	5403	49
H(6B)	-1754	6721	6354	56
H(6C)	-233	7704	6183	56
H(7A)	2066	7137	9720	93
H(7B)	3013	7857	8752	93
H(7C)	3962	6708	9152	93
H(8A)	4795	5227	7706	80
H(8B)	4763	5167	6385	80
H(8C)	3241	4486	7090	80
H(9A)	4325	7152	5921	96
H(9B)	4875	7366	7185	96
H(9C)	3032	7935	6680	96
H(6A)	-151	7888	8034	47

Table 3. Bond lengths [Å] for (-)-**3**.

O(1)-C(2)	1.337(2)
O(1)-C(6A)	1.453(2)
O(2)-C(2)	1.204(2)
O(3)-C(5)	1.419(2)
O(3)-H(3)	0.8200
C(2)-C(3)	1.482(2)
C(3)-C(3A)	1.532(2)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-C(8)	1.527(2)
C(4)-C(9)	1.535(2)
C(4)-C(5)	1.546(2)
C(4)-C(3A)	1.553(2)
C(5)-C(6)	1.512(2)
C(5)-H(5)	0.9800
C(6)-C(6A)	1.525(2)
C(6)-H(6B)	0.9700
C(6)-H(6C)	0.9700
C(7)-C(3A)	1.527(2)
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(8)-H(8A)	0.9600
C(8)-H(8B)	0.9600
C(8)-H(8C)	0.9600
C(9)-H(9A)	0.9600
C(9)-H(9B)	0.9600
C(9)-H(9C)	0.9600
C(3A)-C(6A)	1.546(2)
C(6A)-H(6A)	0.9800

Table 4. Bond angles [°] for (-)-**3**.

C(2)-O(1)-C(6A)	110.99(13)
C(5)-O(3)-H(3)	109.5
O(2)-C(2)-O(1)	121.32(18)
O(2)-C(2)-C(3)	127.76(19)
O(1)-C(2)-C(3)	110.92(15)
C(2)-C(3)-C(3A)	106.22(14)
C(2)-C(3)-H(3A)	110.5
C(3A)-C(3)-H(3A)	110.5
C(2)-C(3)-H(3B)	110.5
C(3A)-C(3)-H(3B)	110.5
H(3A)-C(3)-H(3B)	108.7
C(8)-C(4)-C(9)	108.09(14)
C(8)-C(4)-C(5)	113.89(12)
C(9)-C(4)-C(5)	107.47(13)
C(8)-C(4)-C(3A)	113.36(12)
C(9)-C(4)-C(3A)	110.86(13)
C(5)-C(4)-C(3A)	103.01(12)
O(3)-C(5)-C(6)	111.65(15)
O(3)-C(5)-C(4)	109.65(12)
C(6)-C(5)-C(4)	104.56(12)
O(3)-C(5)-H(5)	110.3
C(6)-C(5)-H(5)	110.3
C(4)-C(5)-H(5)	110.3
C(5)-C(6)-C(6A)	106.27(13)
C(5)-C(6)-H(6B)	110.5
C(6A)-C(6)-H(6B)	110.5
C(5)-C(6)-H(6C)	110.5
C(6A)-C(6)-H(6C)	110.5
H(6B)-C(6)-H(6C)	108.7
C(3A)-C(7)-H(7A)	109.5
C(3A)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(3A)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5

H(7B)-C(7)-H(7C)	109.5
C(4)-C(8)-H(8A)	109.5
C(4)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(4)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(4)-C(9)-H(9A)	109.5
C(4)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(4)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(7)-C(3A)-C(3)	109.43(14)
C(7)-C(3A)-C(6A)	111.98(14)
C(3)-C(3A)-C(6A)	101.72(12)
C(7)-C(3A)-C(4)	114.68(13)
C(3)-C(3A)-C(4)	113.48(13)
C(6A)-C(3A)-C(4)	104.73(11)
O(1)-C(6A)-C(6)	111.93(13)
O(1)-C(6A)-C(3A)	107.30(12)
C(6)-C(6A)-C(3A)	107.36(13)
O(1)-C(6A)-H(6A)	110.1
C(6)-C(6A)-H(6A)	110.1
C(3A)-C(6A)-H(6A)	110.1

Table 5. Anisotropic displacement parameters ($Å^2$ x 10^3) for (-)-**3**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	70(1)	48(1)	-5(1)	6(1)	5(1)
O(2)	67(1)	99(1)	56(1)	4(1)	22(1)	-32(1)
O(3)	76(1)	46(1)	80(1)	-10(1)	-43(1)	-1(1)
C(2)	48(1)	63(1)	31(1)	-6(1)	4(1)	-14(1)
C(3)	50(1)	53(1)	44(1)	14(1)	8(1)	3(1)
C(4)	34(1)	43(1)	31(1)	1(1)	1(1)	-1(1)
C(5)	48(1)	45(1)	30(1)	0(1)	-5(1)	3(1)
C(6)	49(1)	50(1)	42(1)	4(1)	-8(1)	8(1)
C(7)	56(1)	82(1)	48(1)	-24(1)	-12(1)	0(1)
C(8)	42(1)	71(1)	48(1)	-10(1)	-2(1)	17(1)
C(9)	53(1)	78(1)	61(1)	16(1)	2(1)	-20(1)
C(3A)	35(1)	37(1)	28(1)	-2(1)	-1(1)	0(1)
C(6A)	40(1)	37(1)	41(1)	-6(1)	-1(1)	3(1)

Table 6. Torsion angles [°] for (-)-**3**.

C(6A)-O(1)-C(2)-O(2)	177.97(15)
C(6A)-O(1)-C(2)-C(3)	-2.95(18)
O(2)-C(2)-C(3)-C(3A)	-168.10(17)
O(1)-C(2)-C(3)-C(3A)	12.90(19)
C(8)-C(4)-C(5)-O(3)	41.37(18)
C(9)-C(4)-C(5)-O(3)	161.06(15)
C(3A)-C(4)-C(5)-O(3)	-81.81(15)
C(8)-C(4)-C(5)-C(6)	161.20(14)
C(9)-C(4)-C(5)-C(6)	-79.11(16)
C(3A)-C(4)-C(5)-C(6)	38.02(15)
O(3)-C(5)-C(6)-C(6A)	88.11(16)
C(4)-C(5)-C(6)-C(6A)	-30.37(16)
C(2)-C(3)-C(3A)-C(7)	102.20(16)
C(2)-C(3)-C(3A)-C(6A)	-16.39(17)
C(2)-C(3)-C(3A)-C(4)	-128.31(14)
C(8)-C(4)-C(3A)-C(7)	82.37(17)
C(9)-C(4)-C(3A)-C(7)	-39.39(18)
C(5)-C(4)-C(3A)-C(7)	-154.09(14)
C(8)-C(4)-C(3A)-C(3)	-44.41(18)
C(9)-C(4)-C(3A)-C(3)	-166.18(14)
C(5)-C(4)-C(3A)-C(3)	79.13(15)
C(8)-C(4)-C(3A)-C(6A)	-154.48(13)
C(9)-C(4)-C(3A)-C(6A)	83.75(15)
C(5)-C(4)-C(3A)-C(6A)	-30.94(14)
C(2)-O(1)-C(6A)-C(6)	109.36(15)
C(2)-O(1)-C(6A)-C(3A)	-8.17(16)
C(5)-C(6)-C(6A)-O(1)	-106.75(15)
C(5)-C(6)-C(6A)-C(3A)	10.75(17)
C(7)-C(3A)-C(6A)-O(1)	-101.75(15)
C(3)-C(3A)-C(6A)-O(1)	15.00(15)
C(4)-C(3A)-C(6A)-O(1)	133.38(12)
C(7)-C(3A)-C(6A)-C(6)	137.78(15)
C(3)-C(3A)-C(6A)-C(6)	-105.47(14)
C(4)-C(3A)-C(6A)-C(6)	12.91(16)

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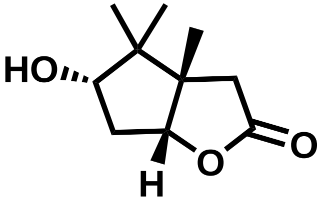
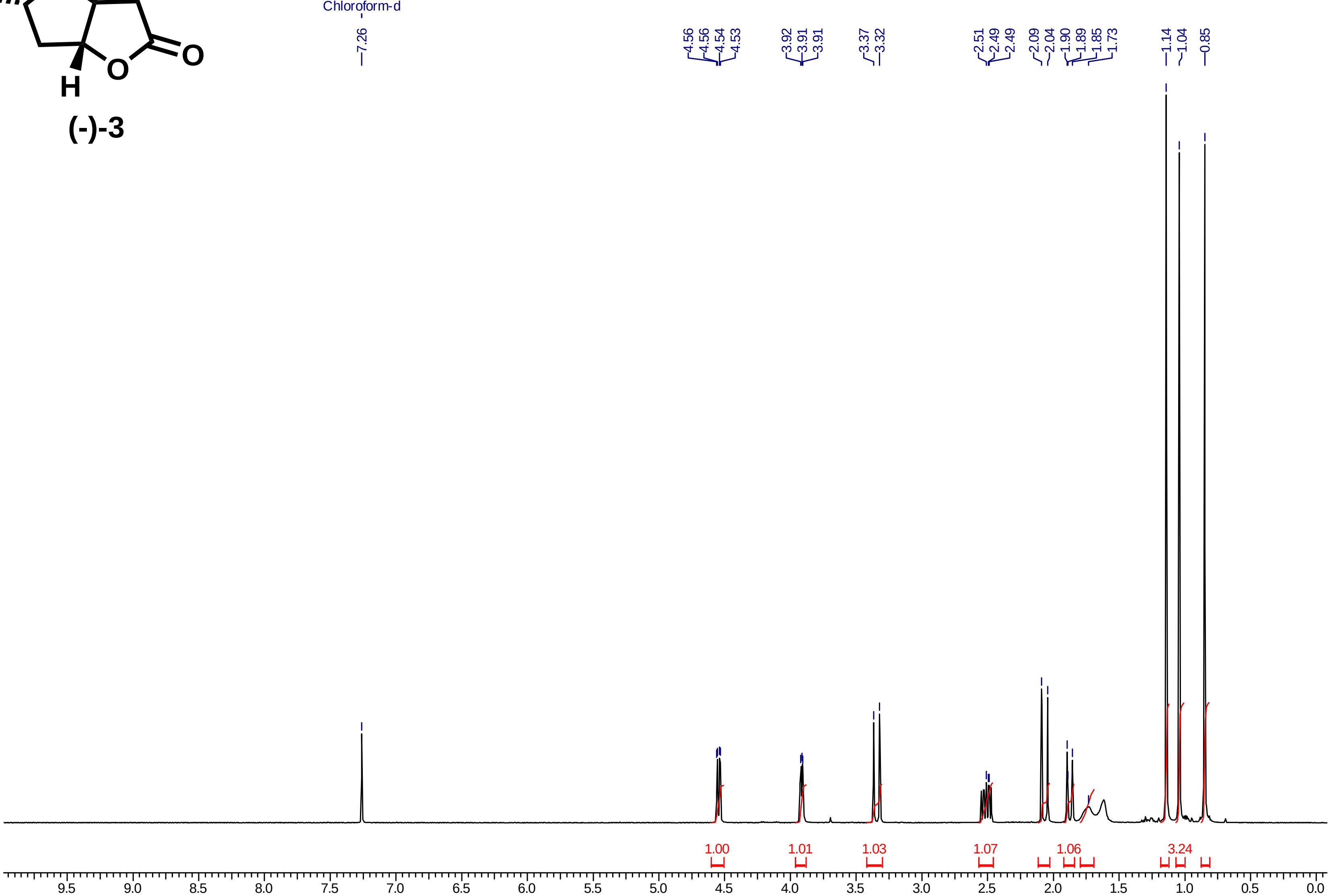
^{1}H NMR ($CDCl_3$, 400 MHz)



(-)-3



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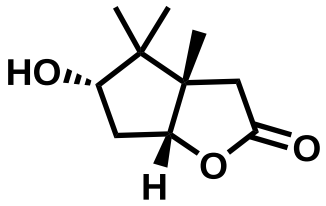
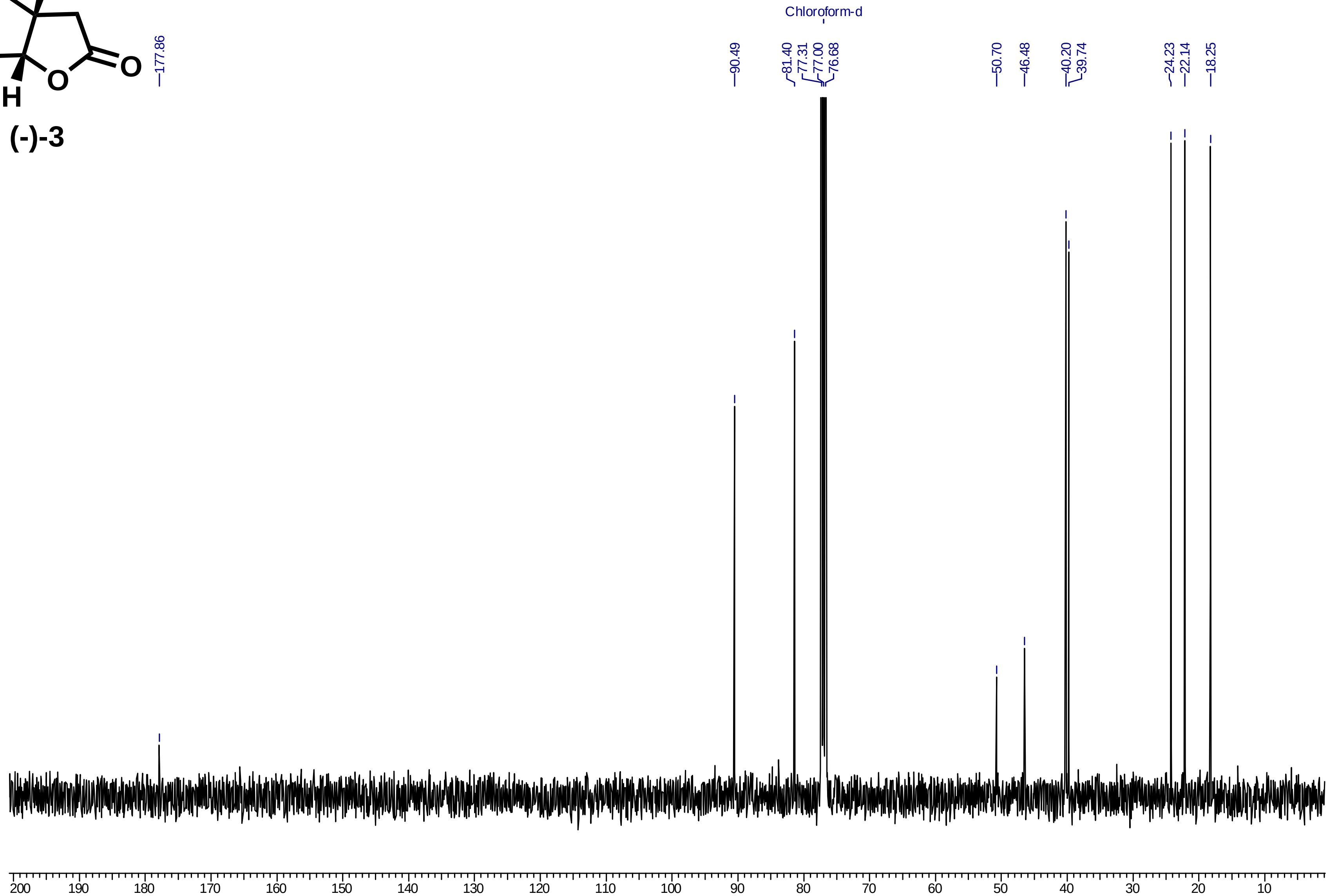


(-)-3



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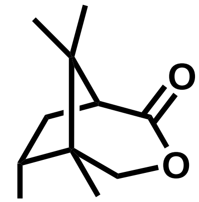
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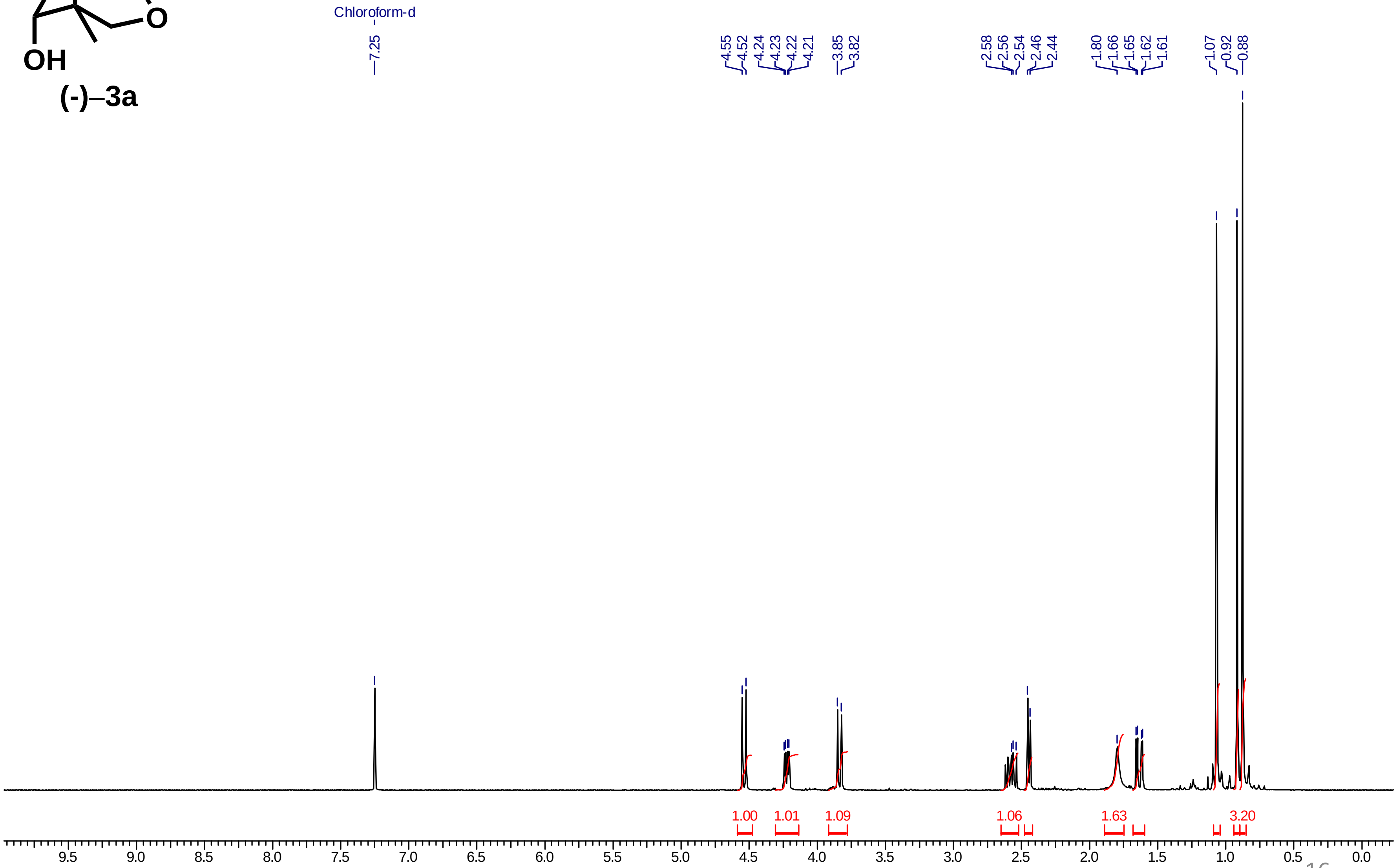
(-)–3a



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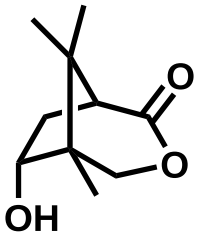

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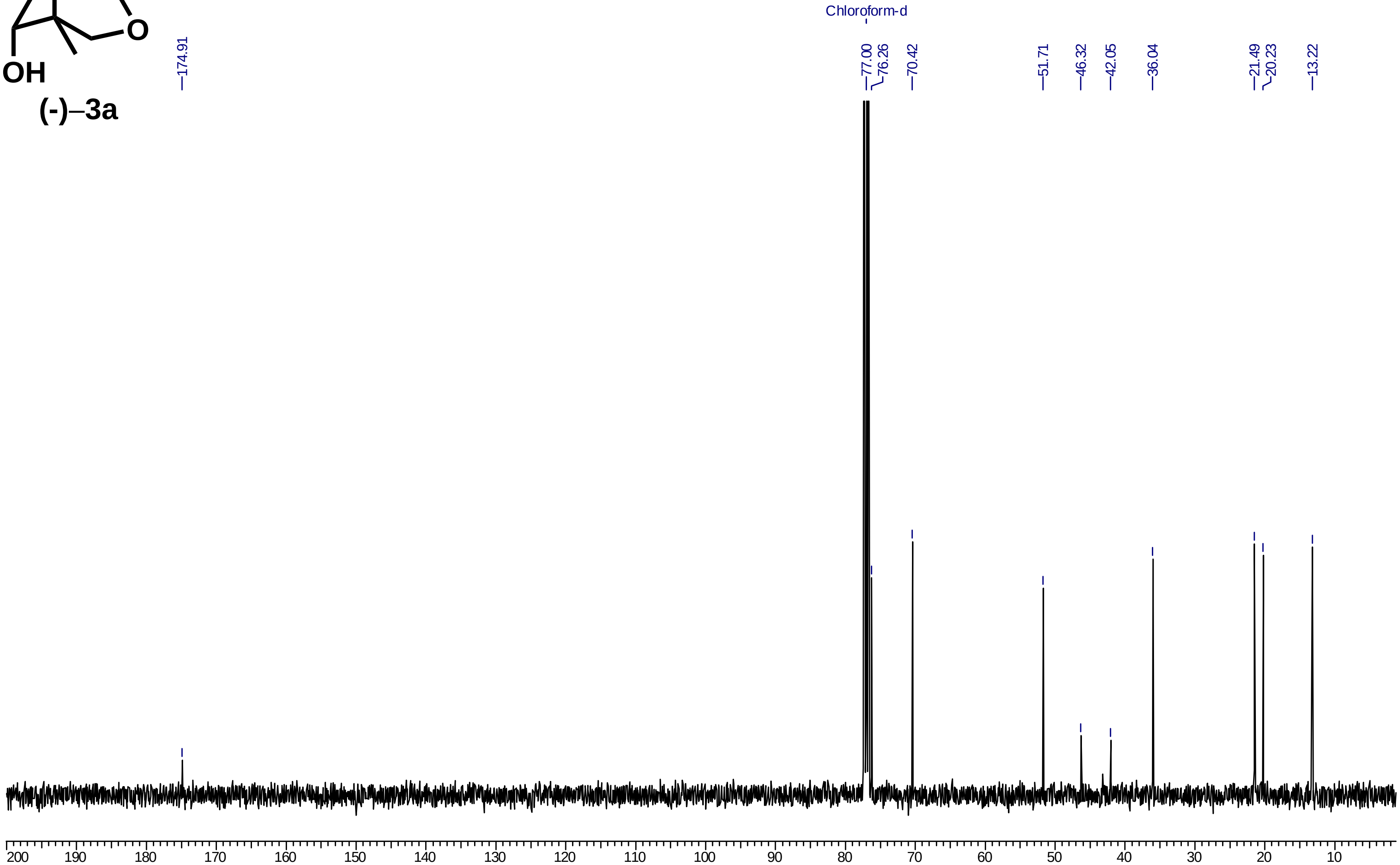

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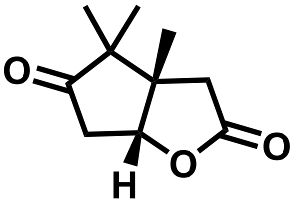
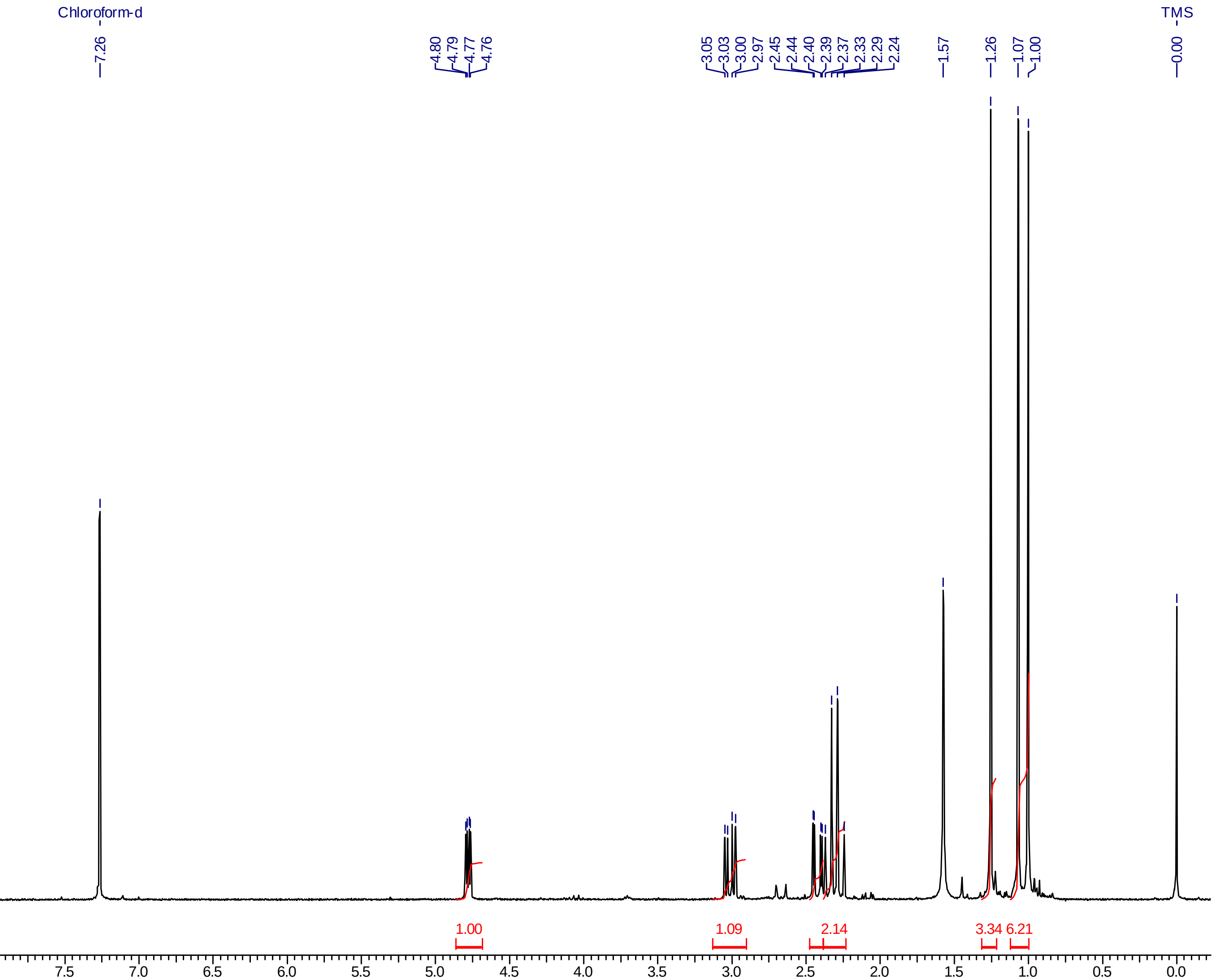


(-)-4



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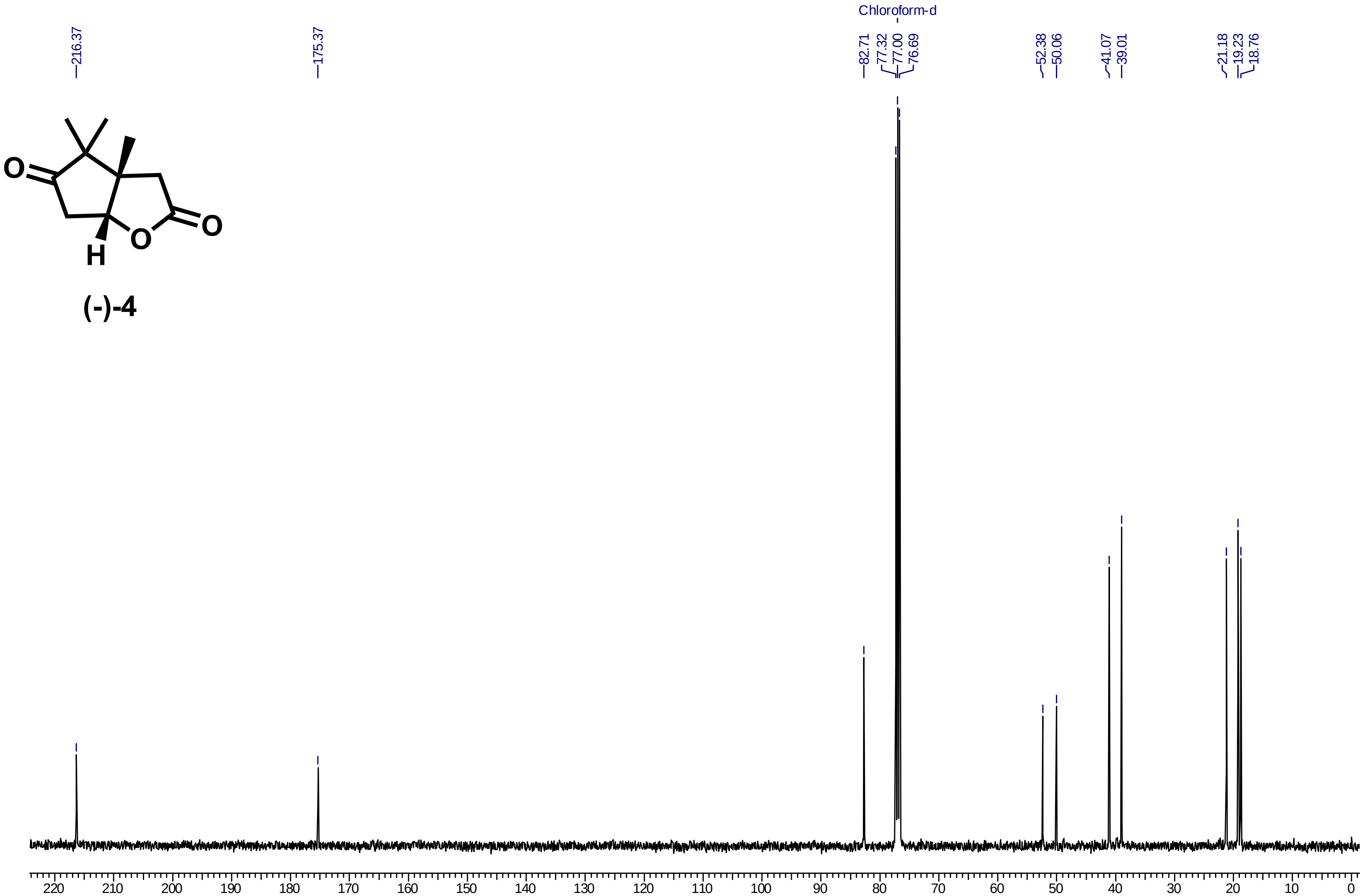
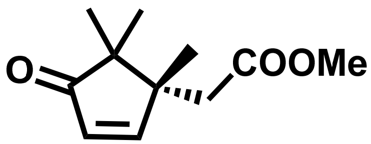
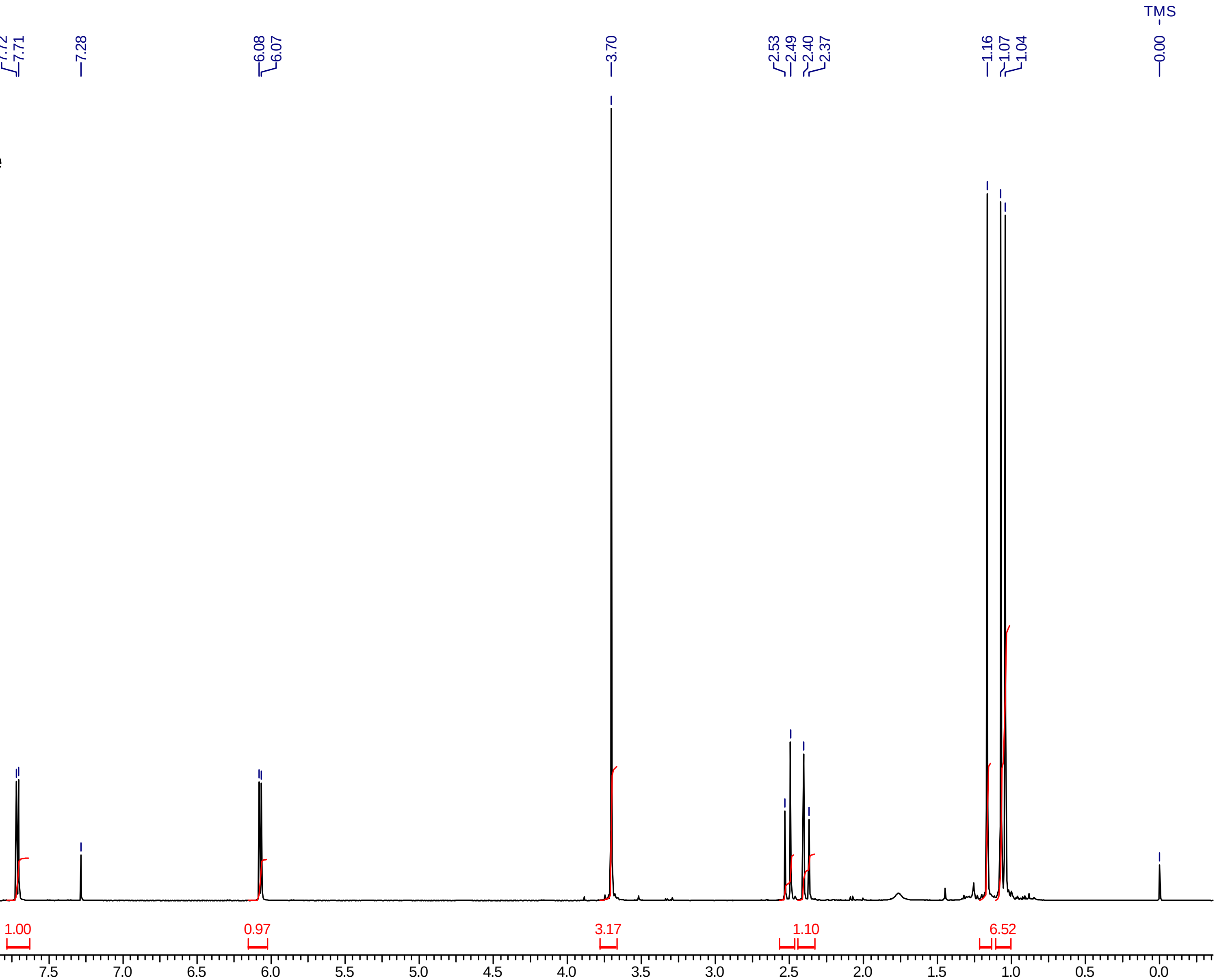


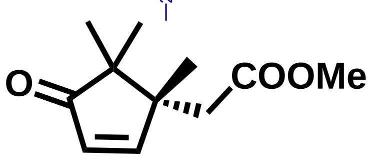
^{1}H NMR ($CDCl_3$, 500 MHz)



(-)-5



^{13}C NMR ($CDCl_3$, 125 MHz)



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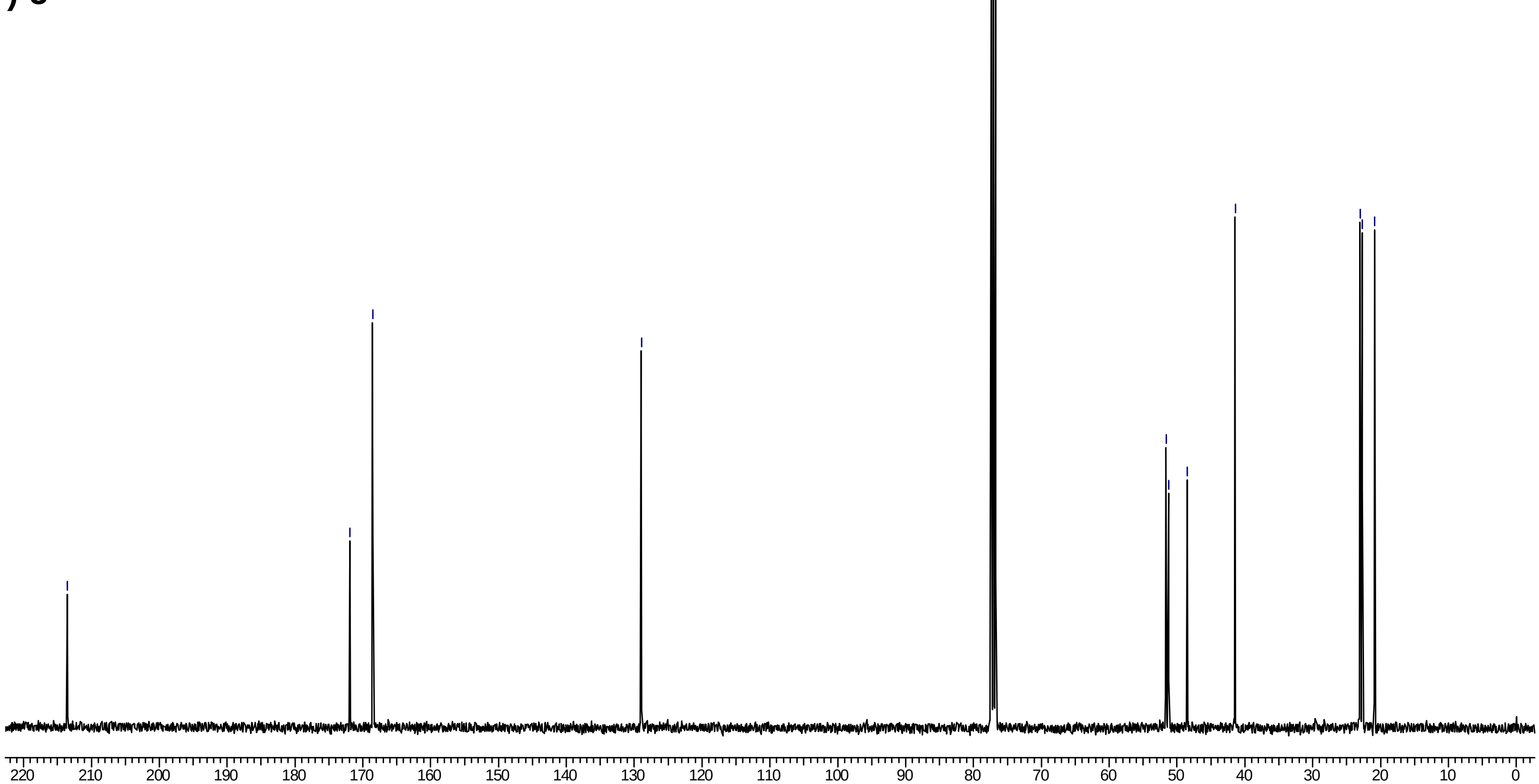
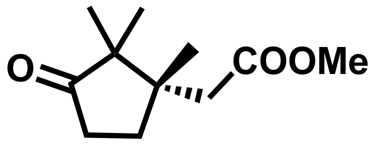
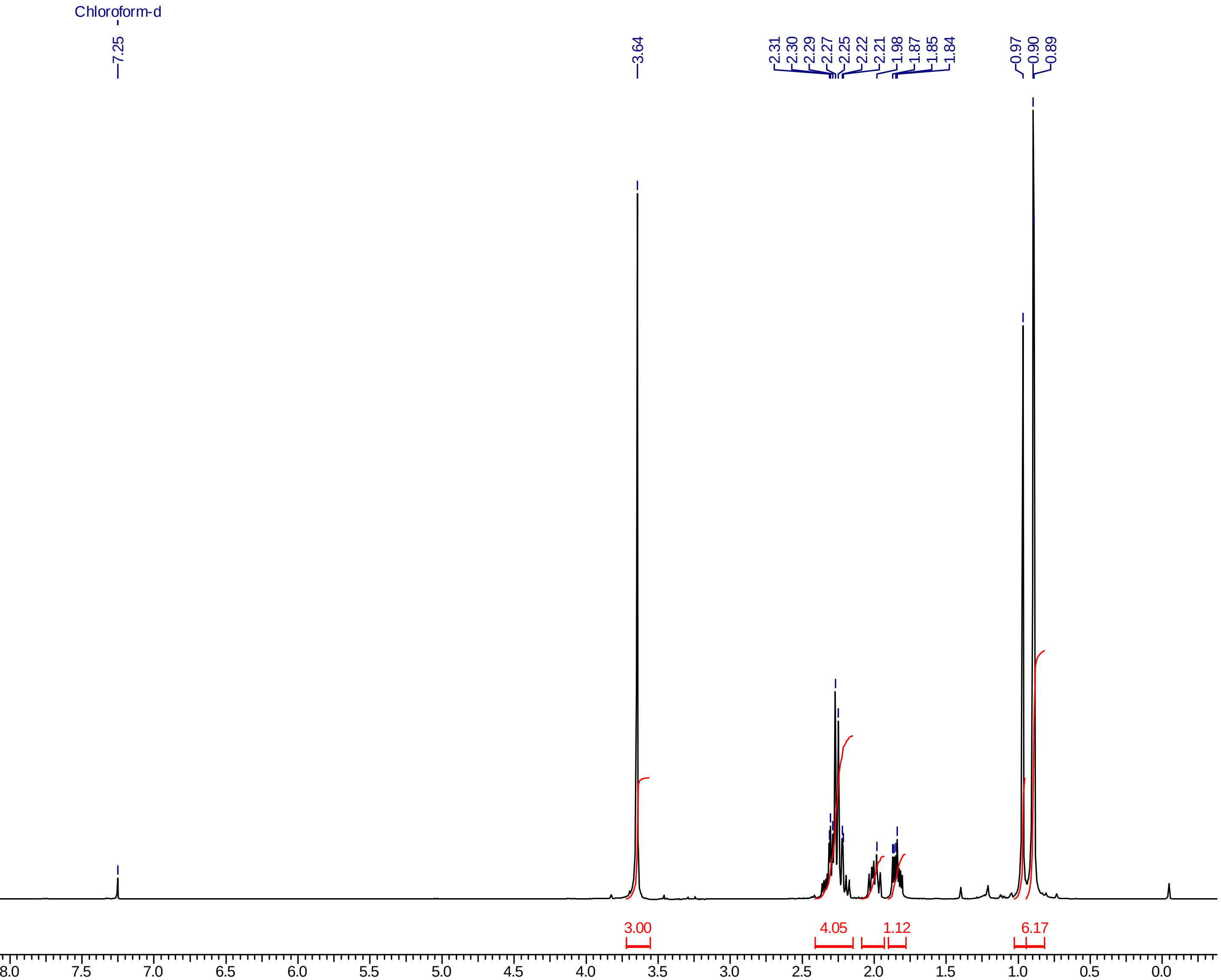
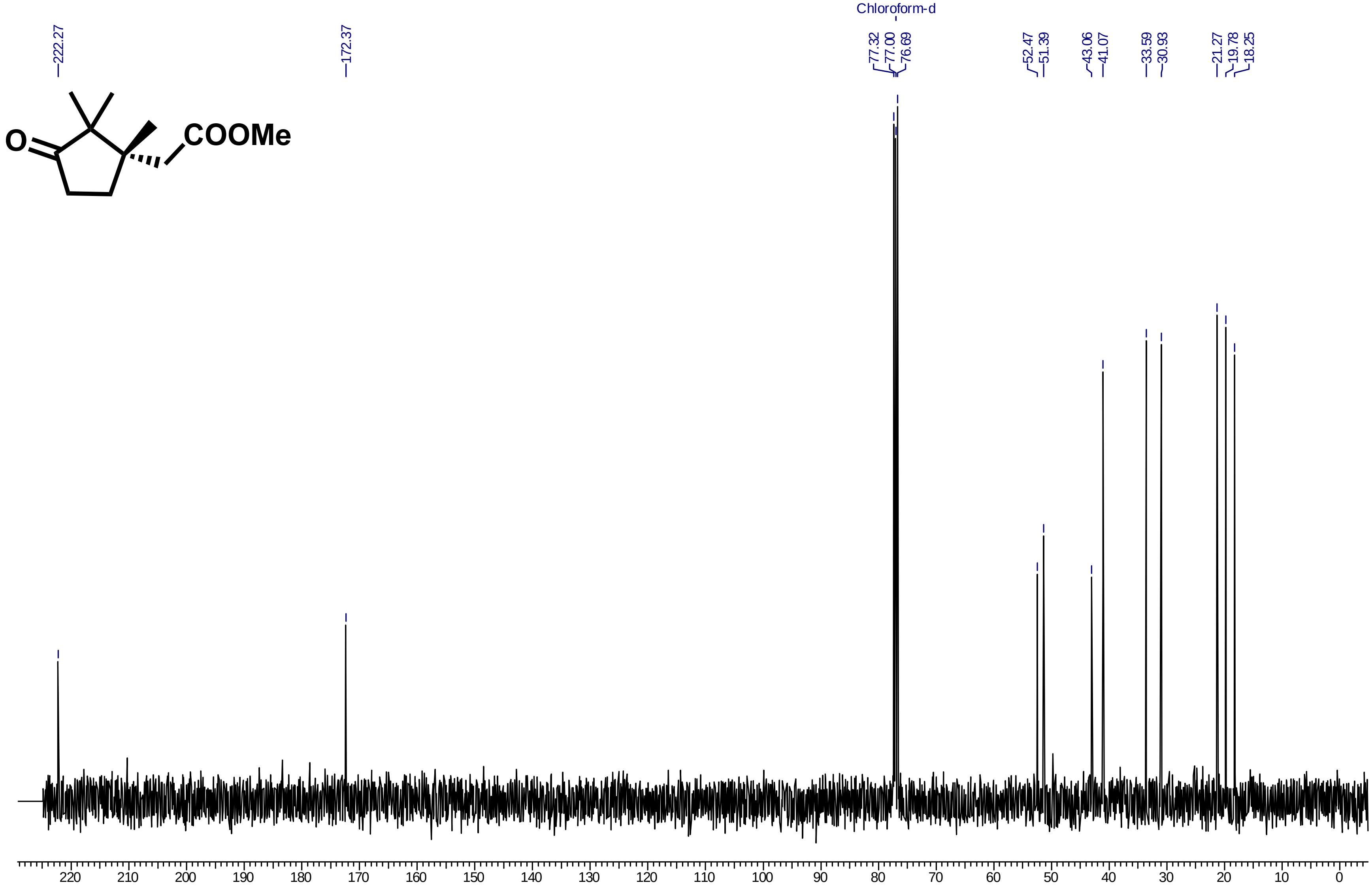


^{1}H NMR ($CDCl_3$, 400 MHz)

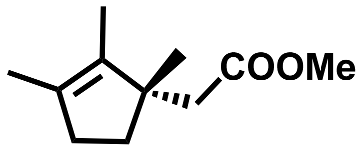




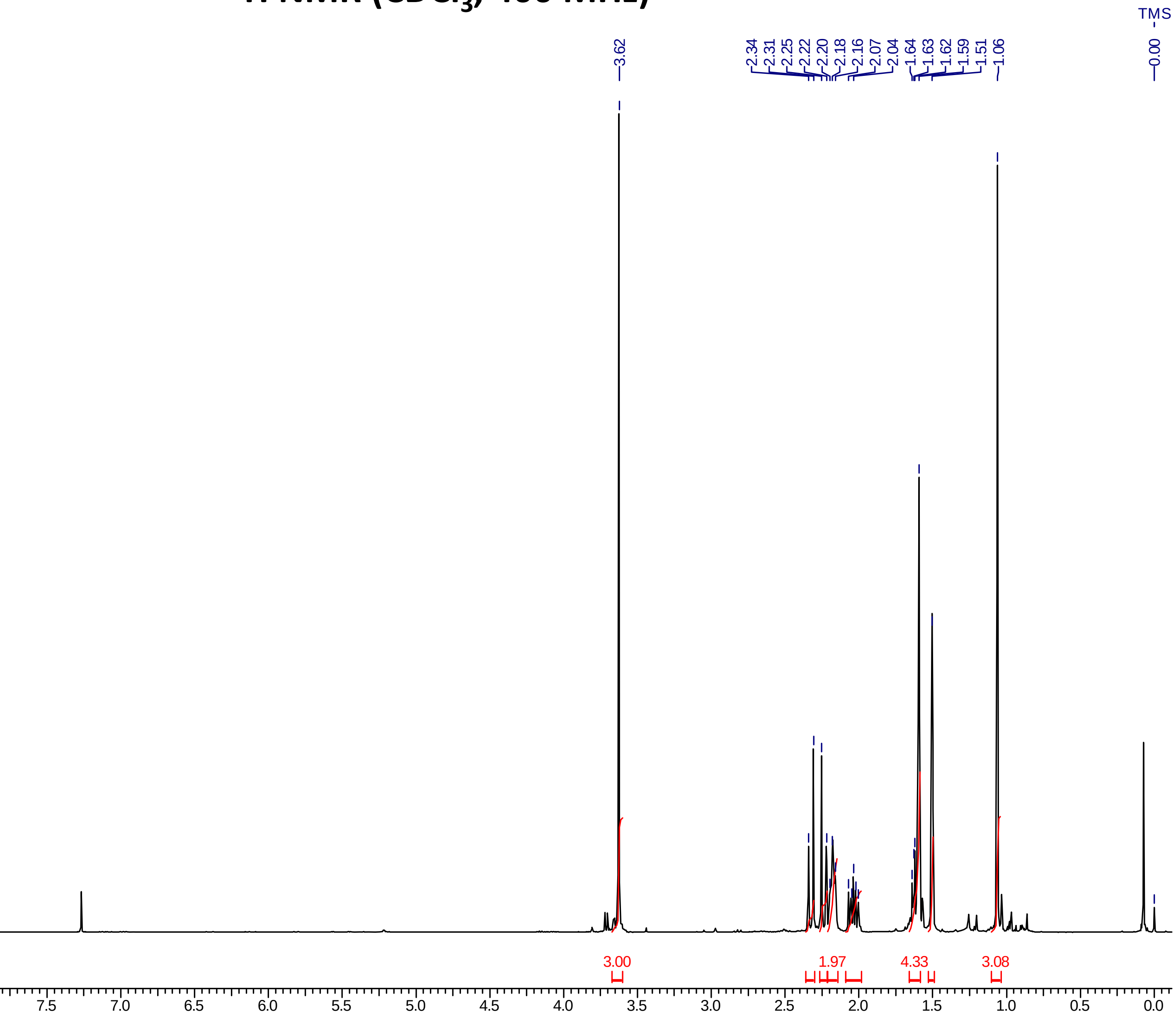
^{13}C NMR ($CDCl_3$, 100 MHz)



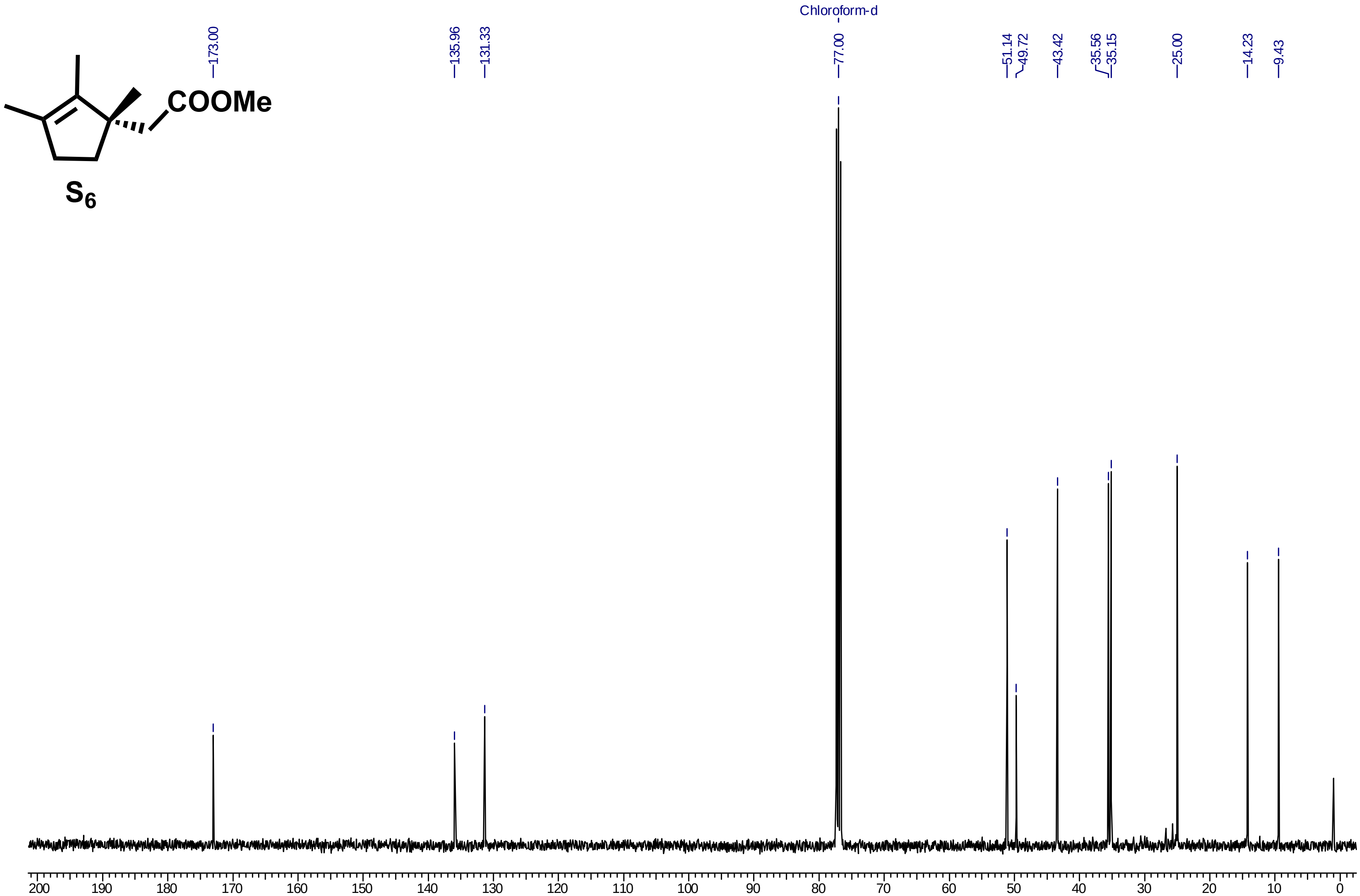
^1H NMR ($CDCl_3$, 400 MHz)



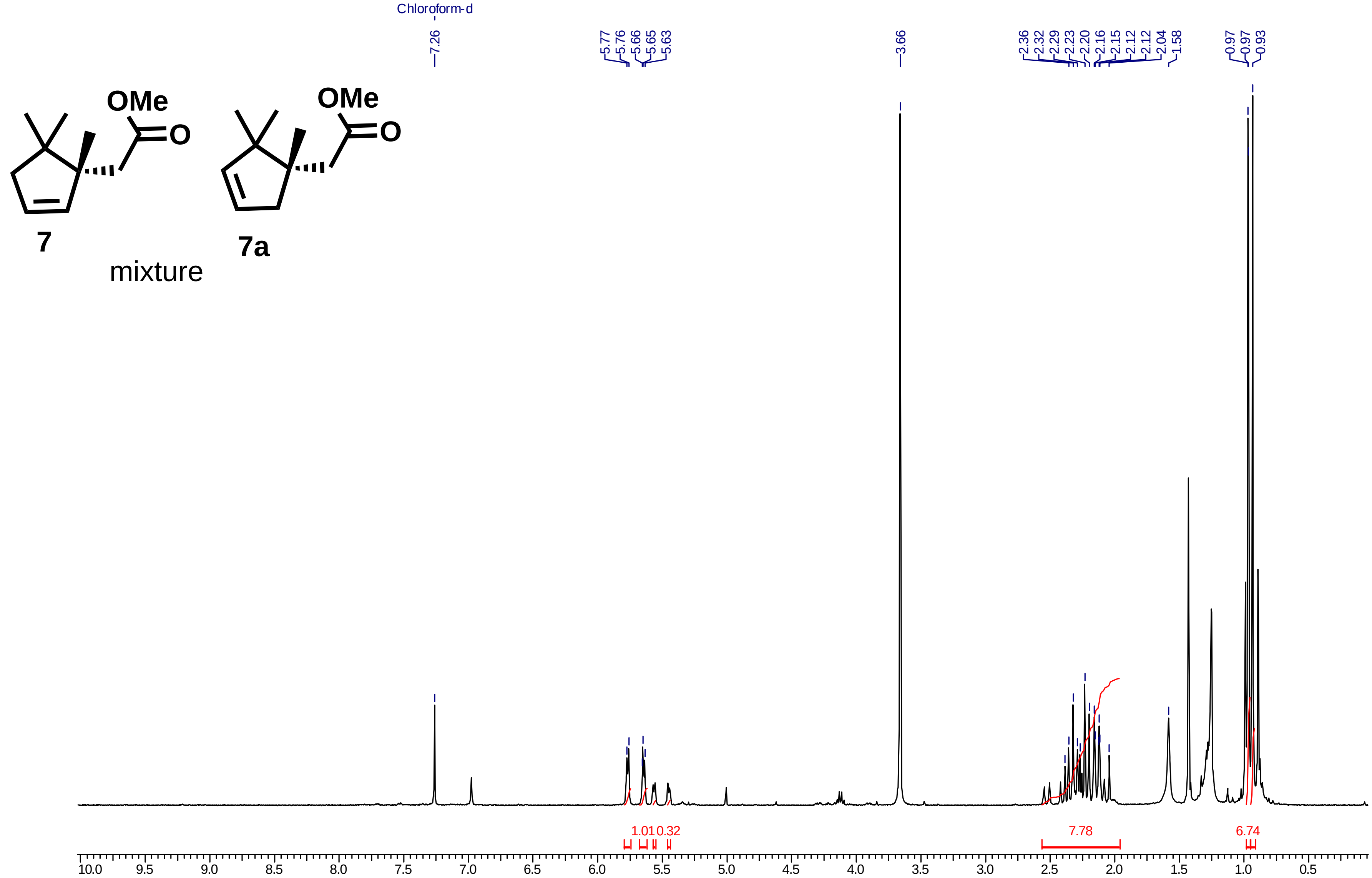
S_6



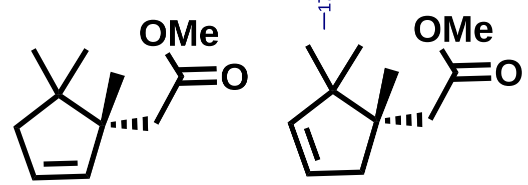
^{13}C NMR (CDCl$_3$, 100 MHz)



[1]H NMR ($CDCl_3$, 400 MHz)

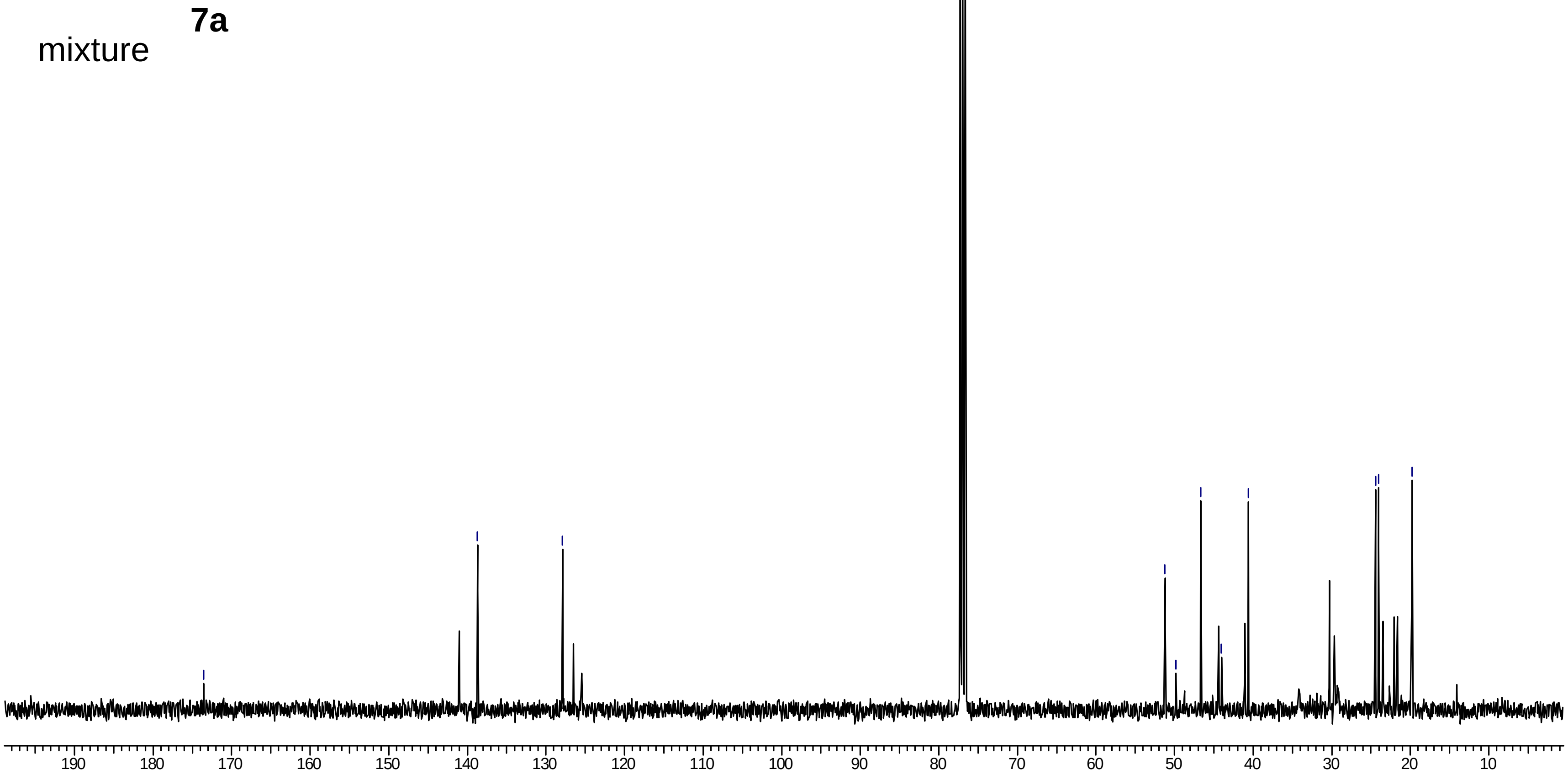


^{13}C NMR ($CDCl_3$, 100 MHz)

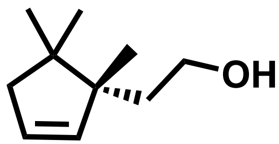


7 7a

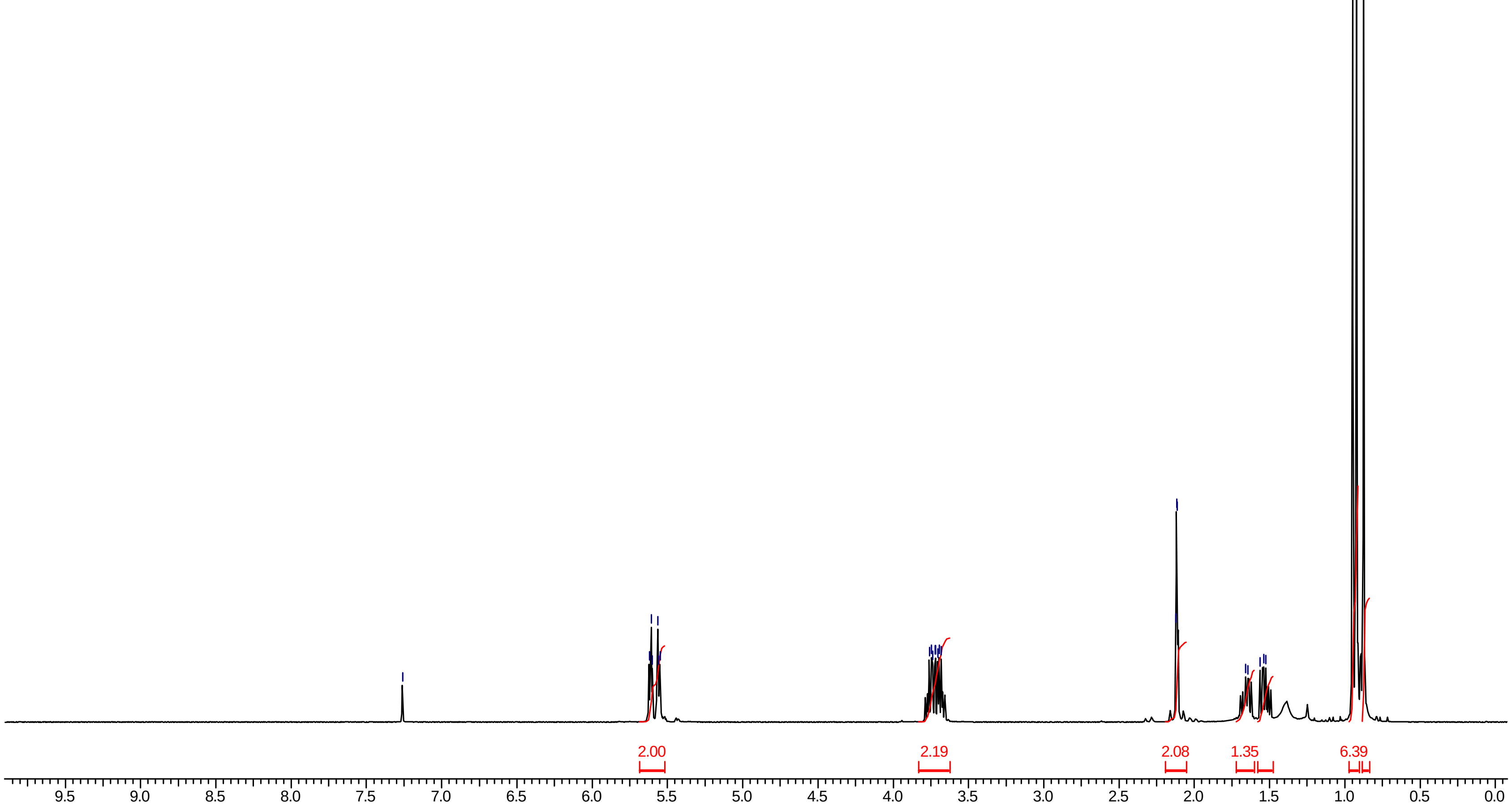
mixture



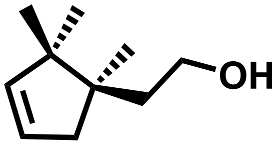
^{1}H NMR ($CDCl_3$, 400 MHz)



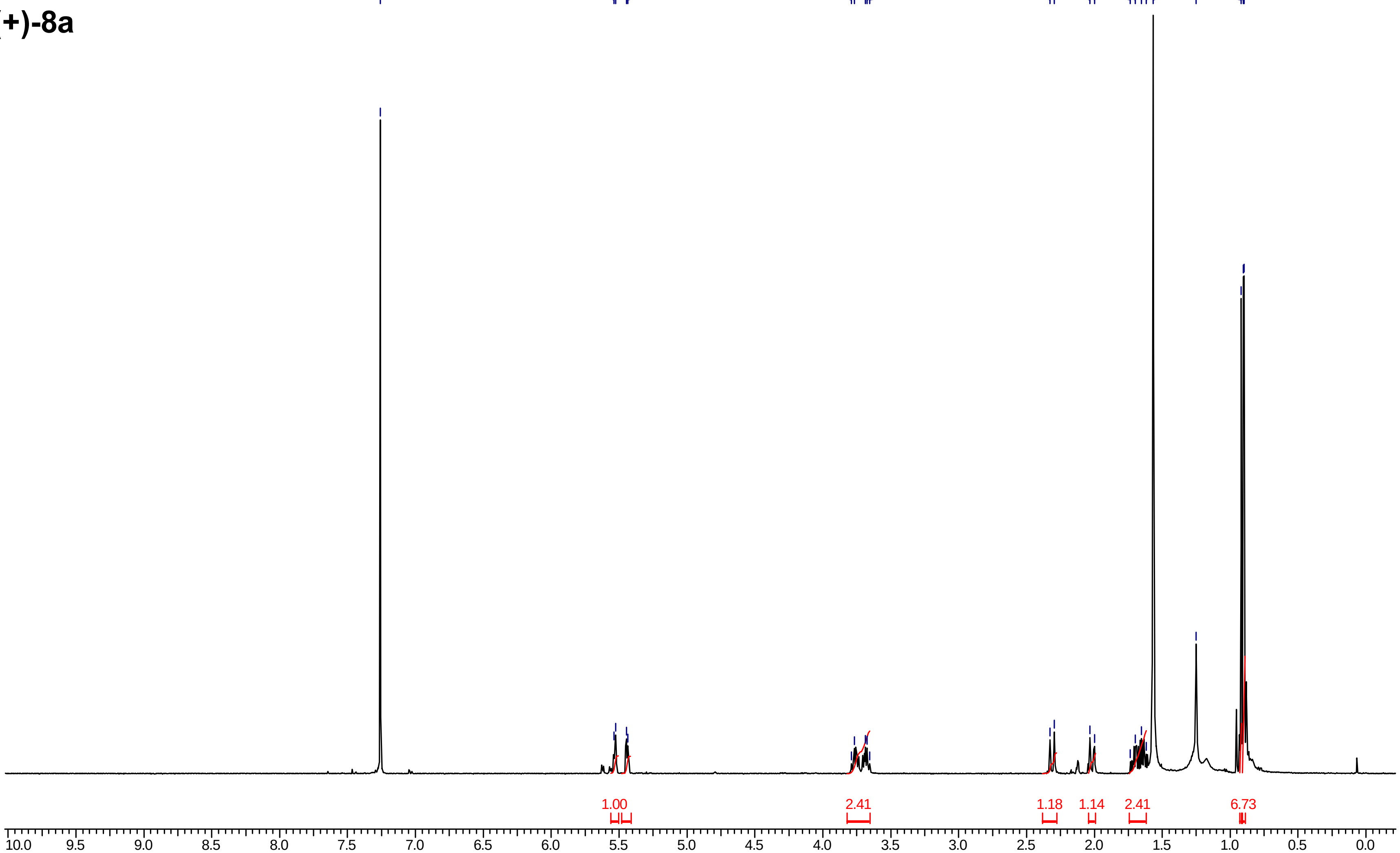
(-)-8



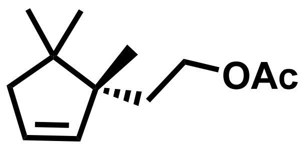
^1H NMR ($CDCl_3$, 500 MHz)



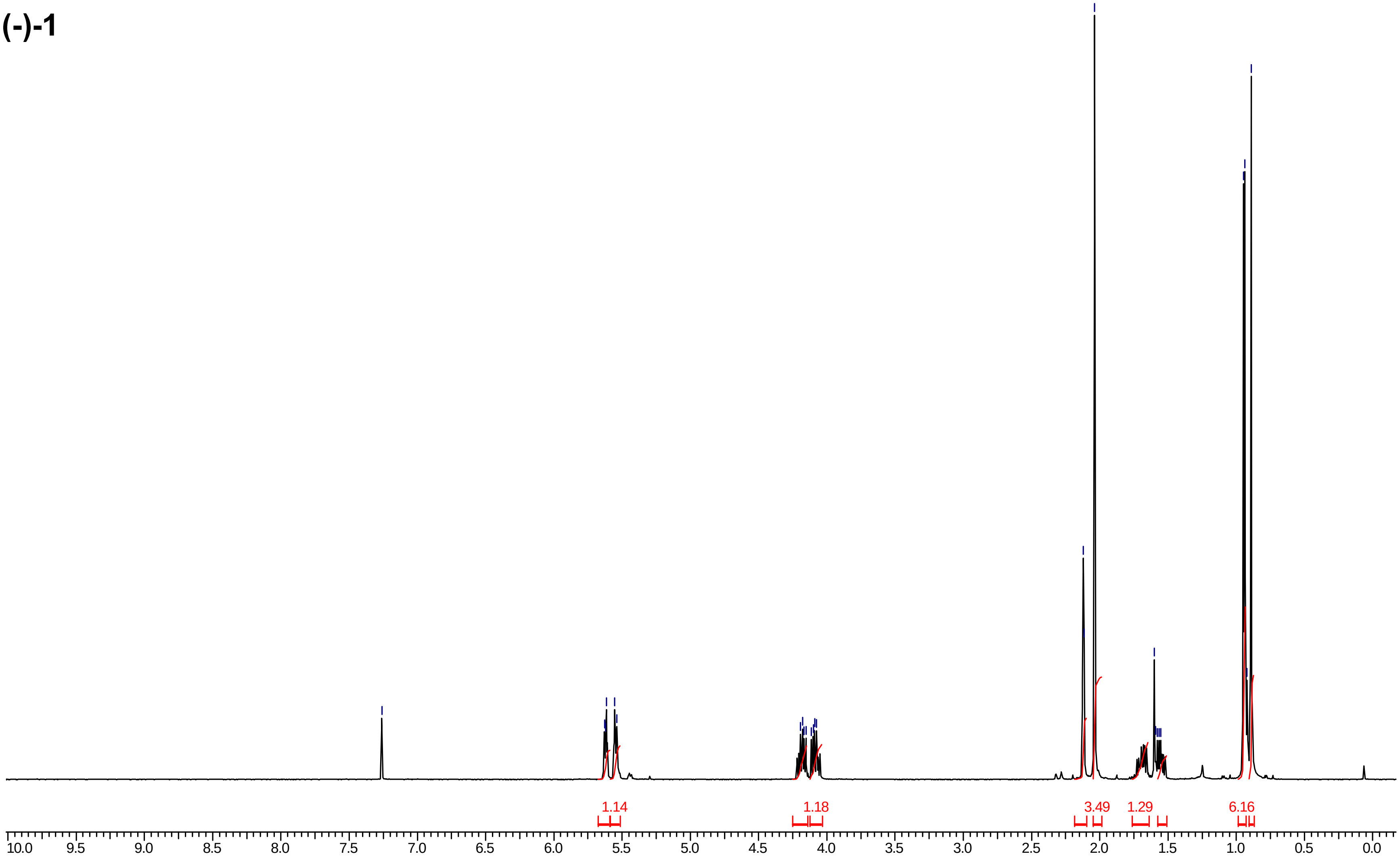
(+)-8a



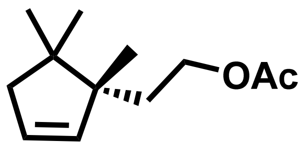
^{1}H NMR ($CDCl_3$, 400 MHz)



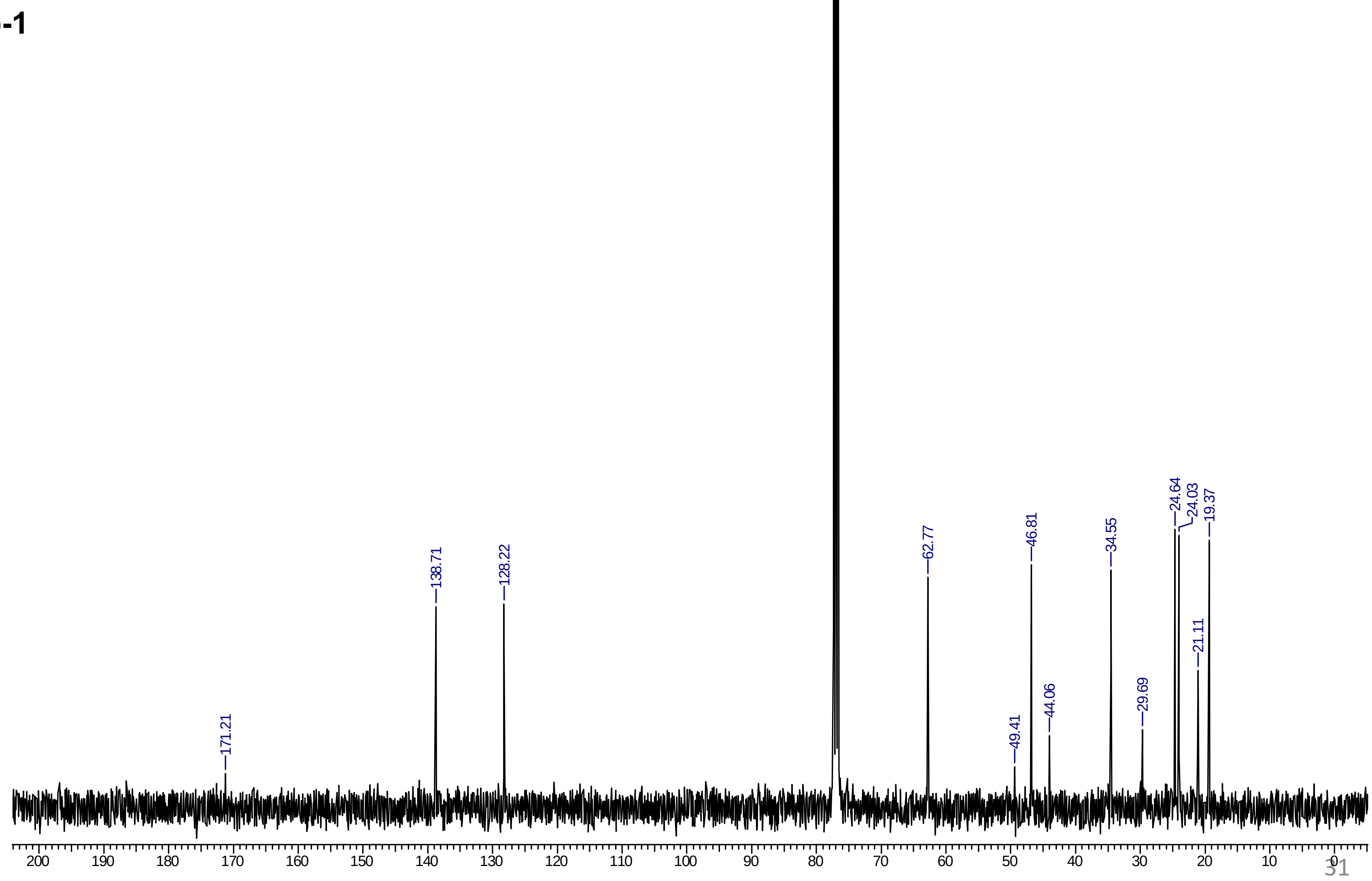
(-)-1



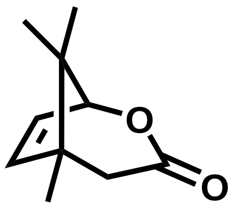
^{13}C NMR ($CDCl_3$, 100 MHz)



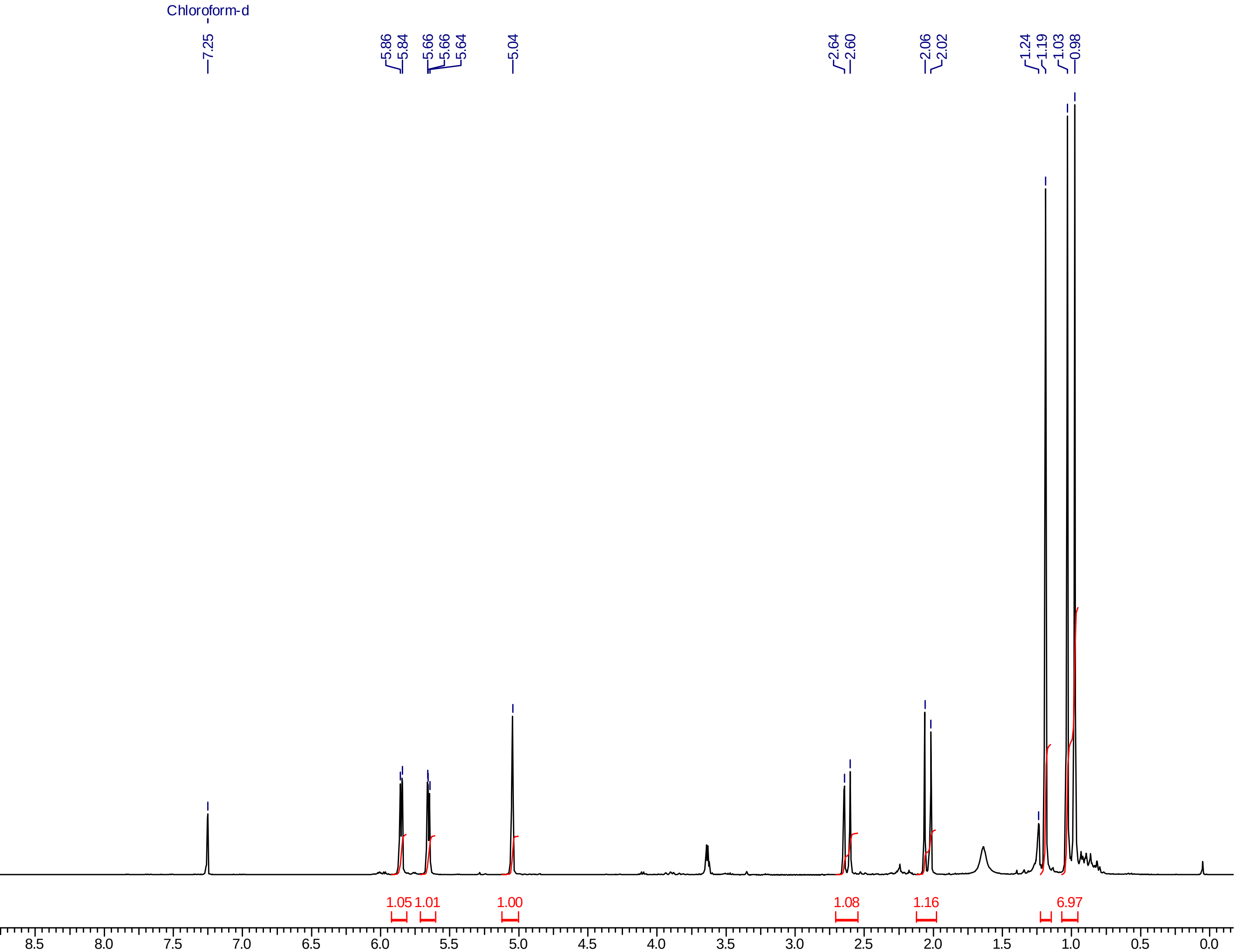
(-)-1



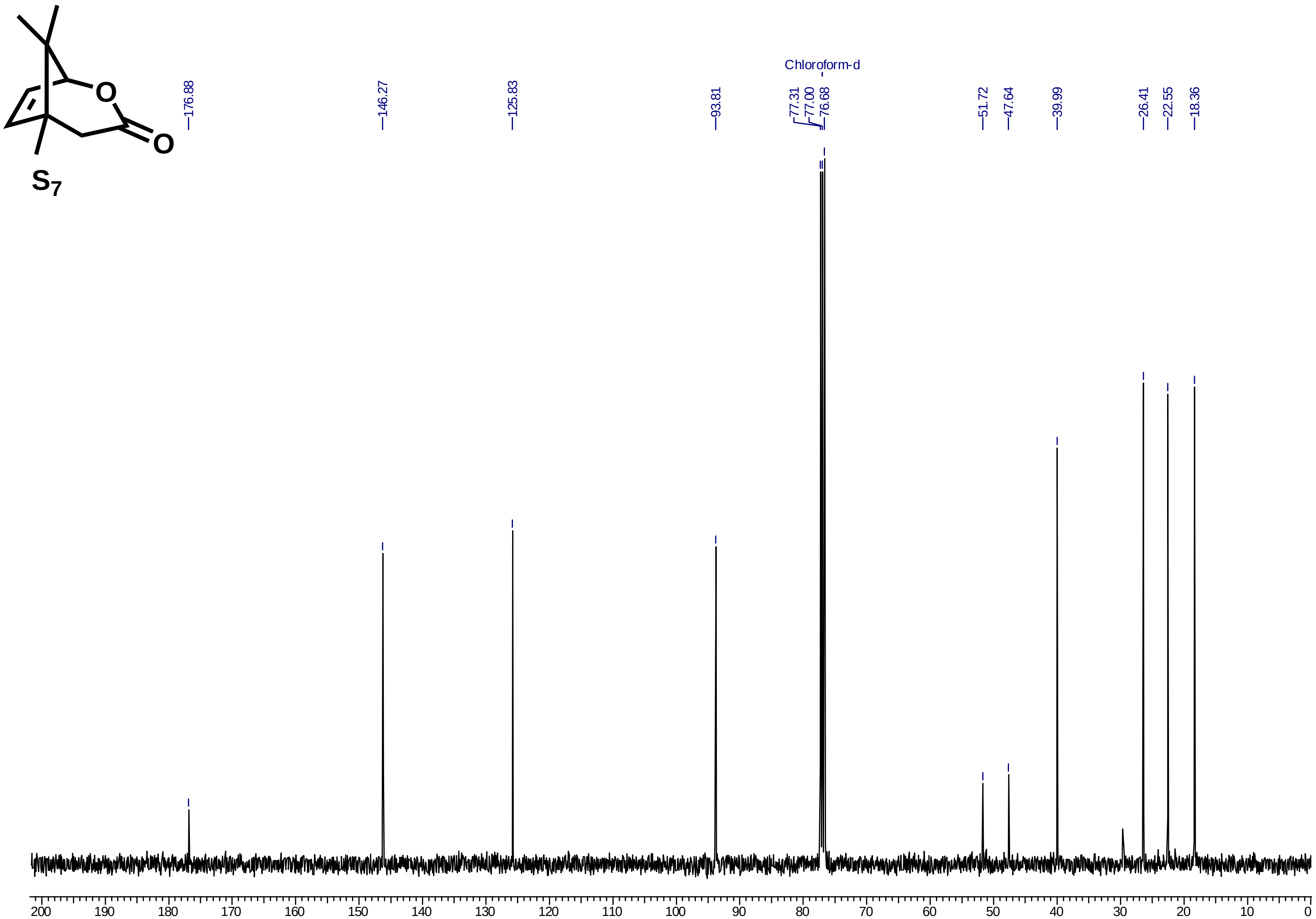
^{1}H NMR ($CDCl_3$, 400 MHz)



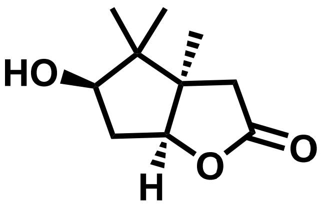
S7



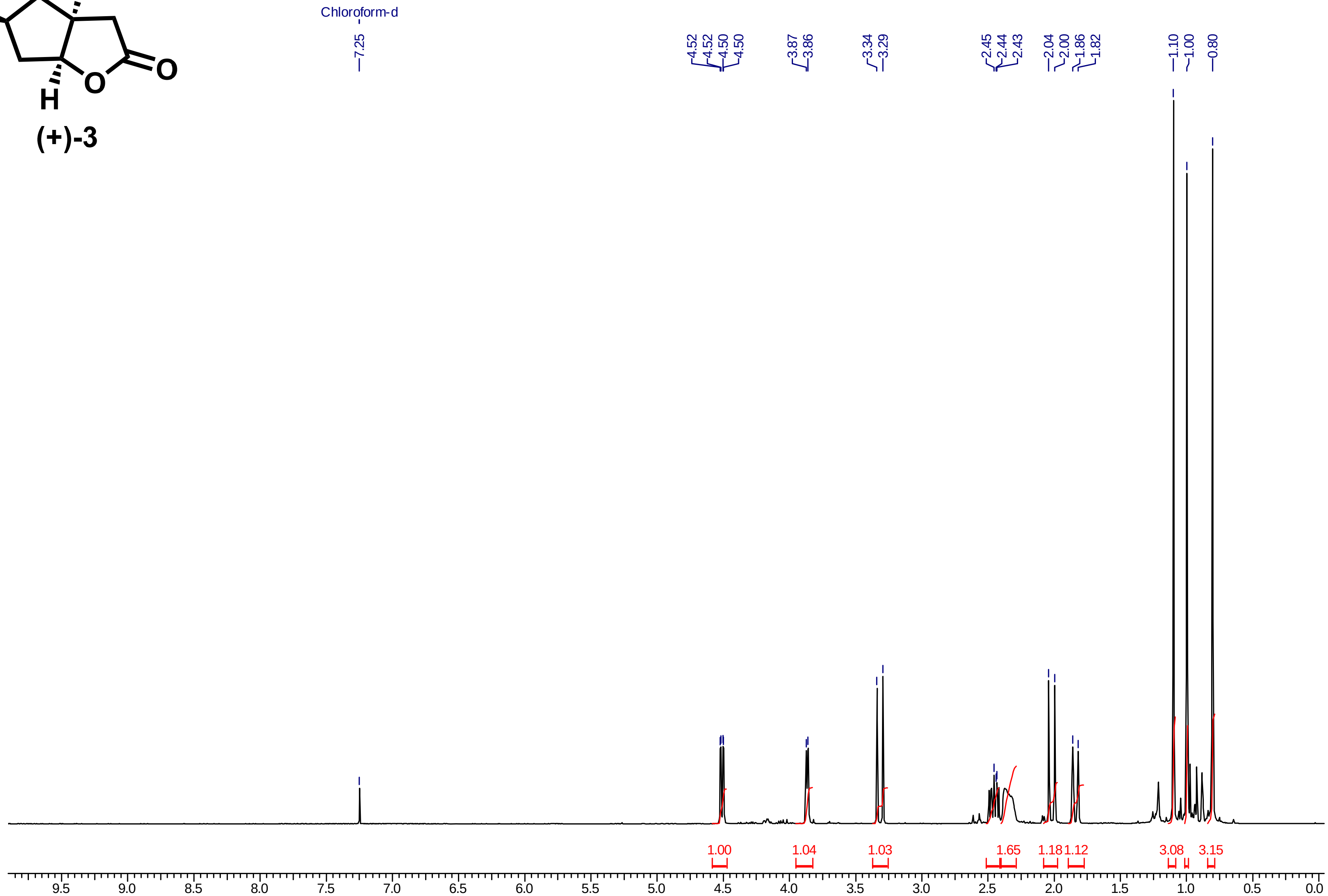
^{13}C NMR ($CDCl_3$, 100 MHz)

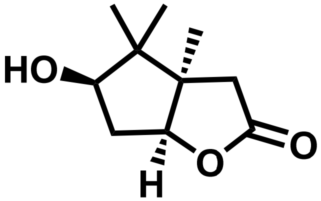


^{1}H NMR ($CDCl_3$, 400 MHz)



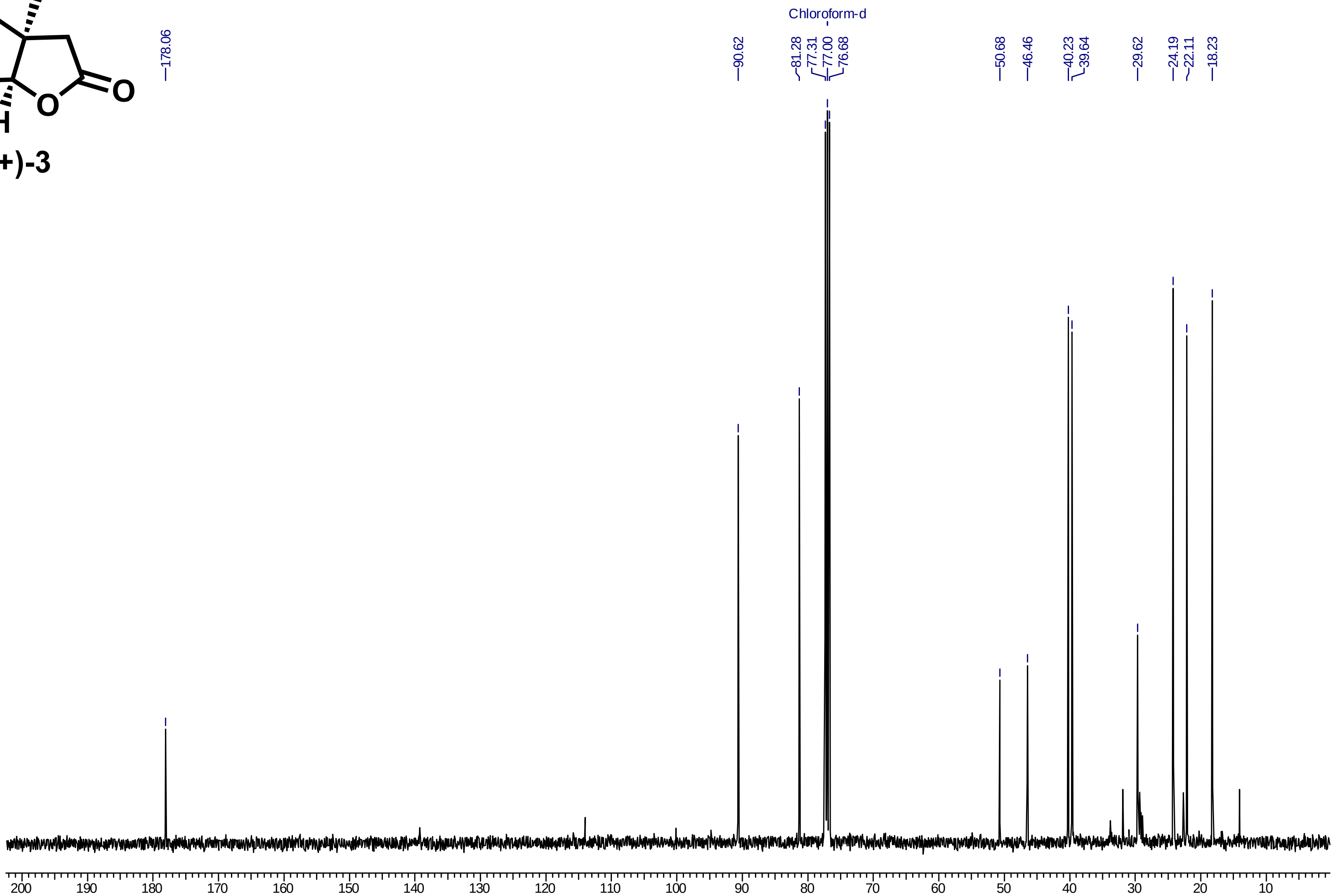
(+)-3



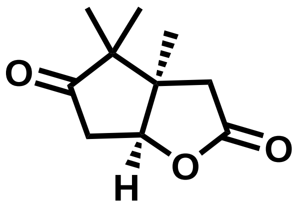


(+)-3

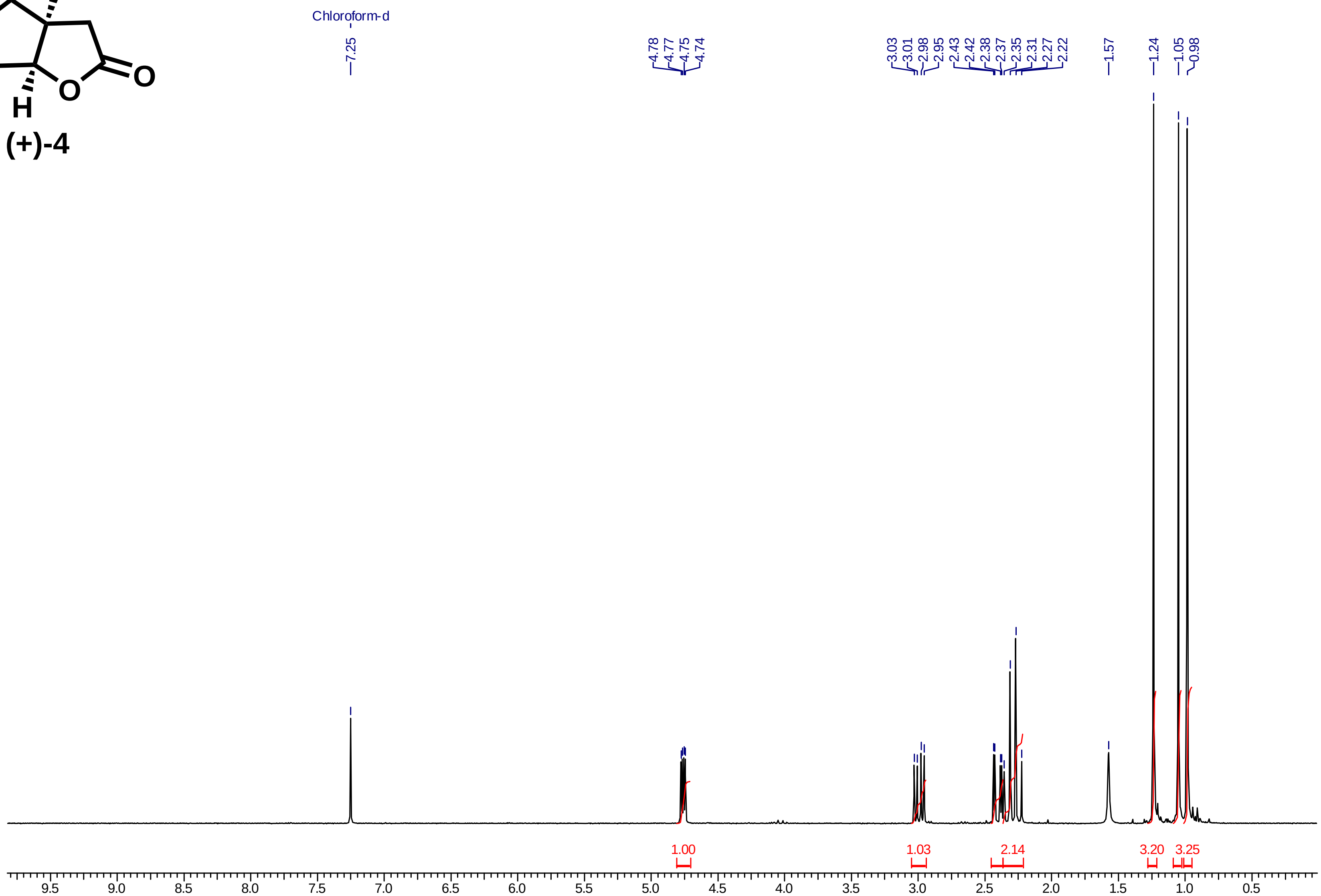
^{13}C NMR ($CDCl_3$, 100 MHz)



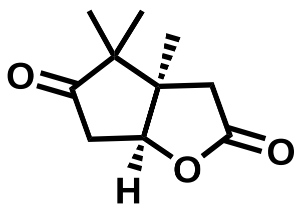
^{1}H NMR ($CDCl_3$, 400 MHz)



(+)-4



^{13}C NMR ($CDCl_3$, 100 MHz)



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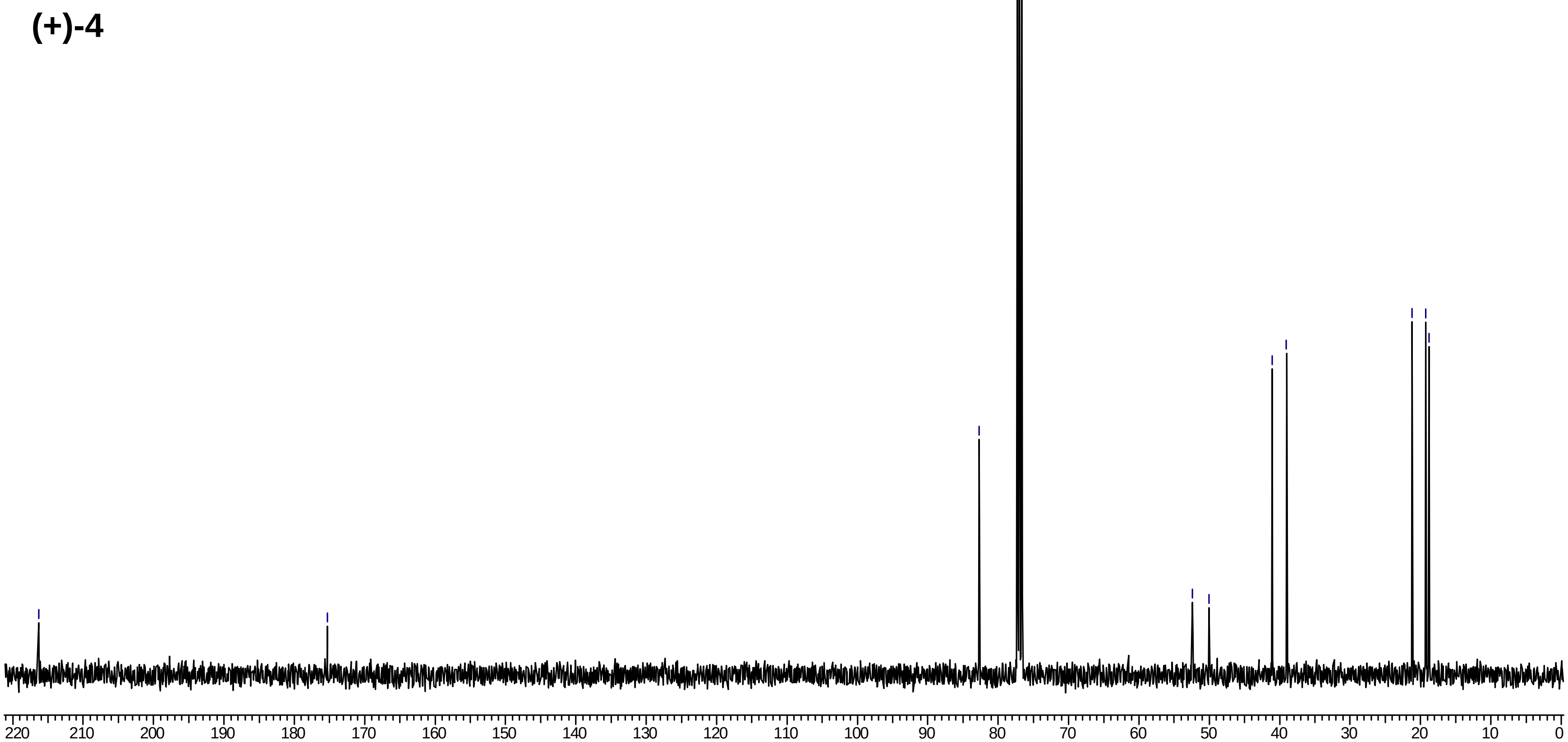
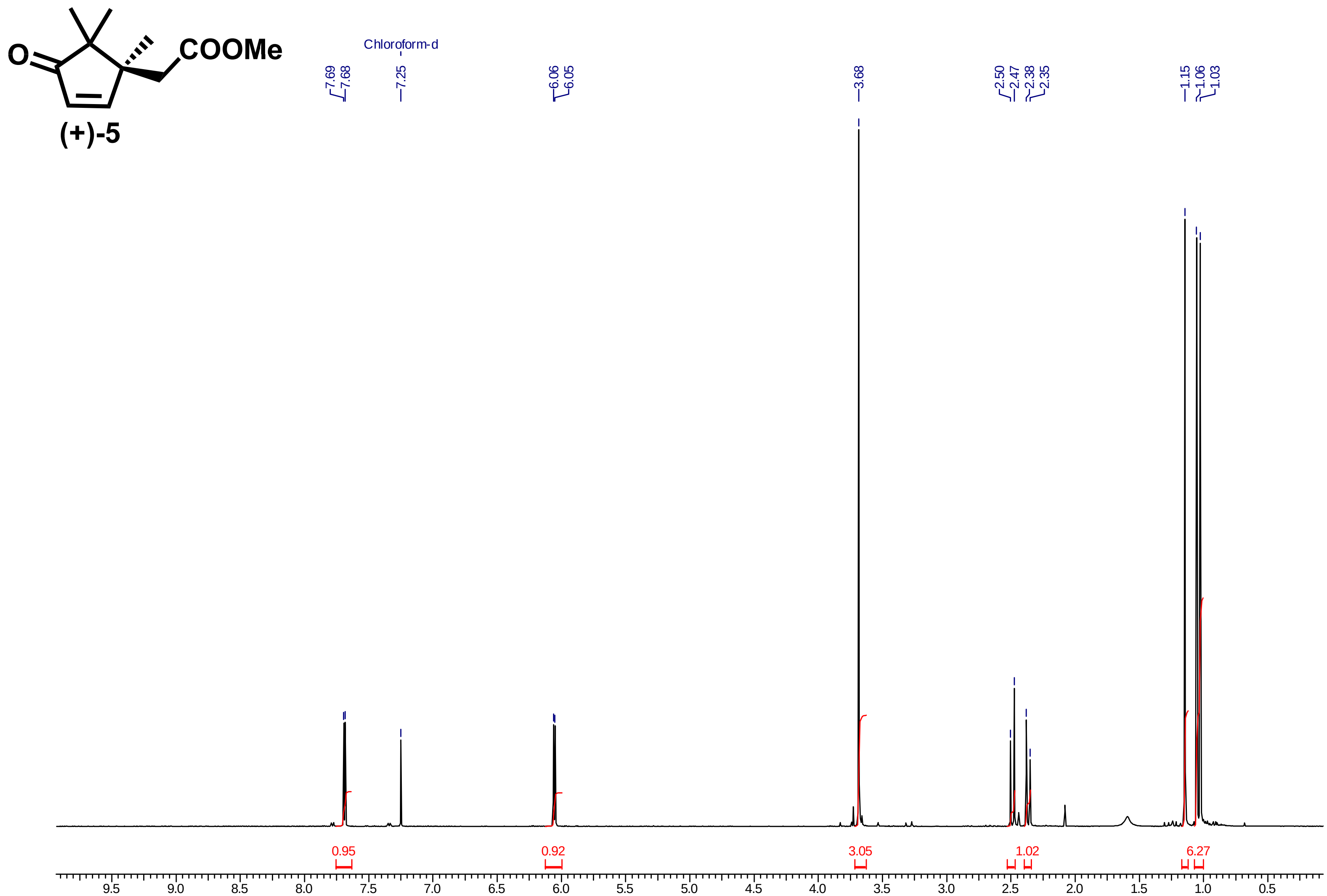
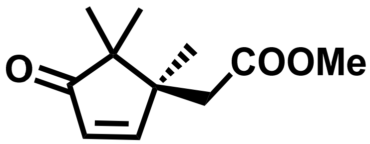


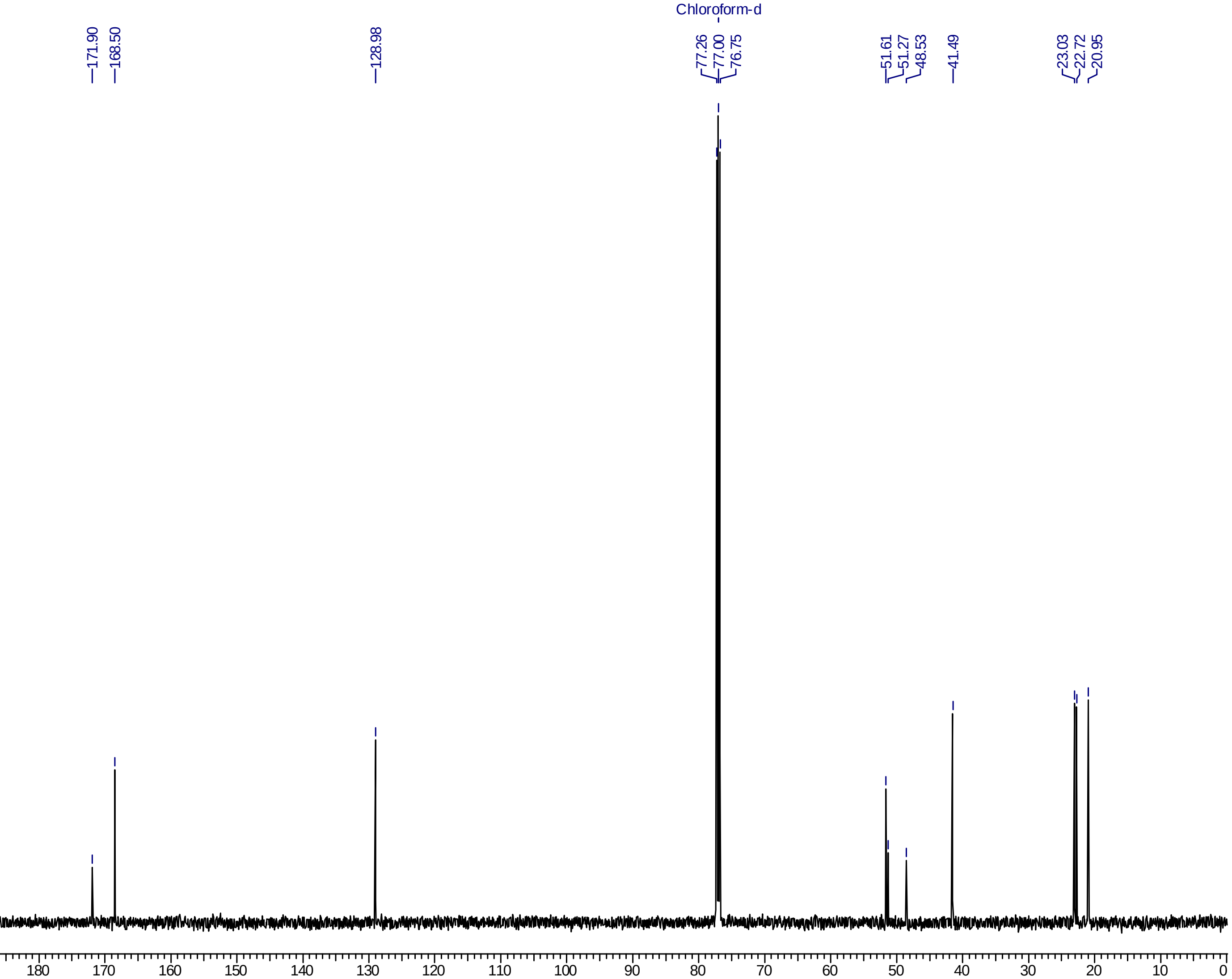
^1H NMR ($CDCl_3$, 400 MHz)



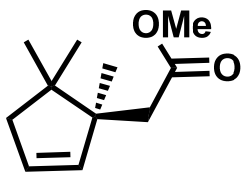
^{13}C NMR ($CDCl_3$, 100 MHz)



(+)-5



^{1}H NMR ($CDCl_3$, 400 MHz)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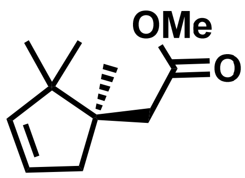
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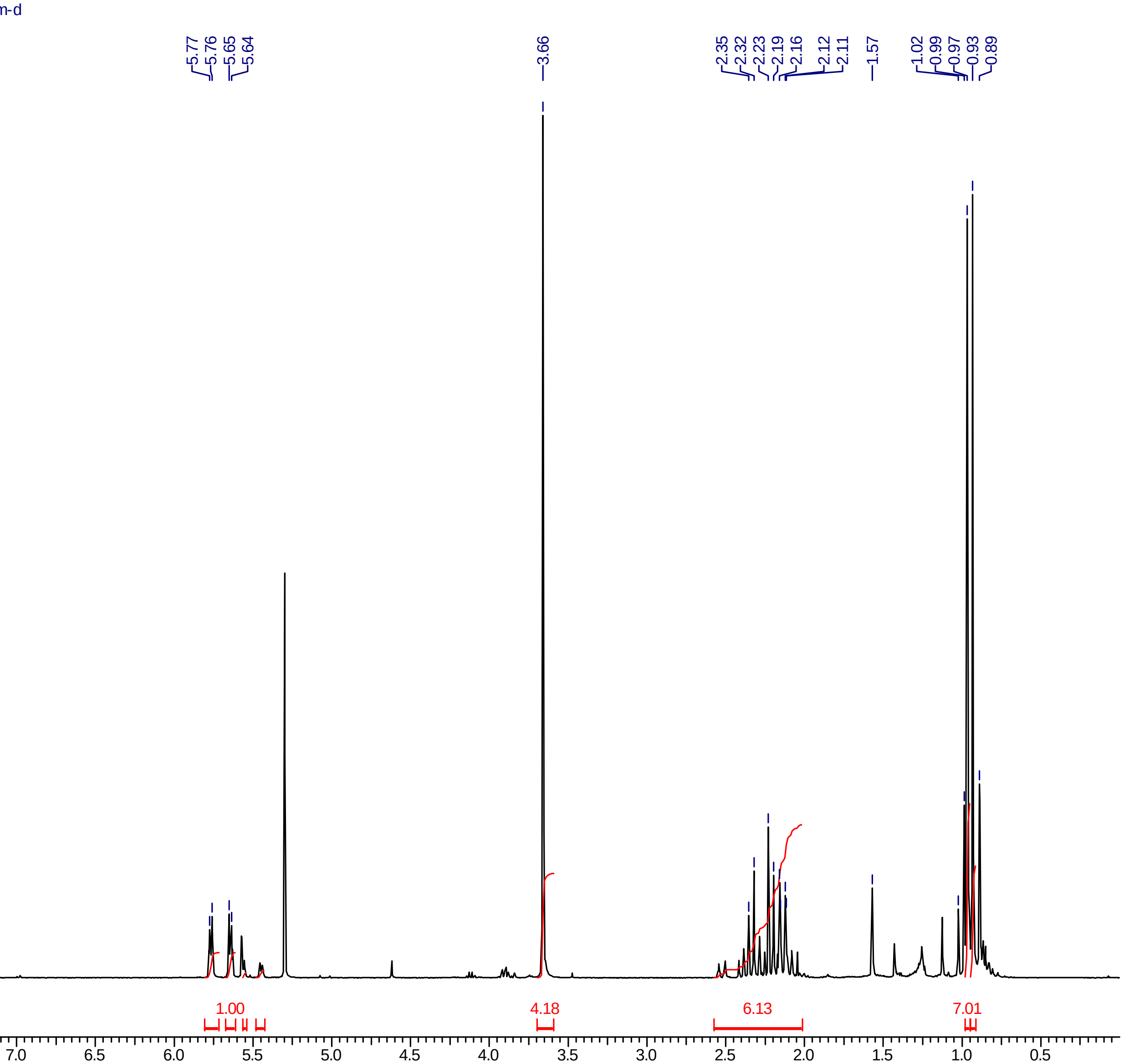
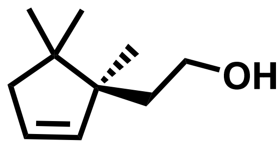


^{1}H NMR ($CDCl_3$, 400 MHz)



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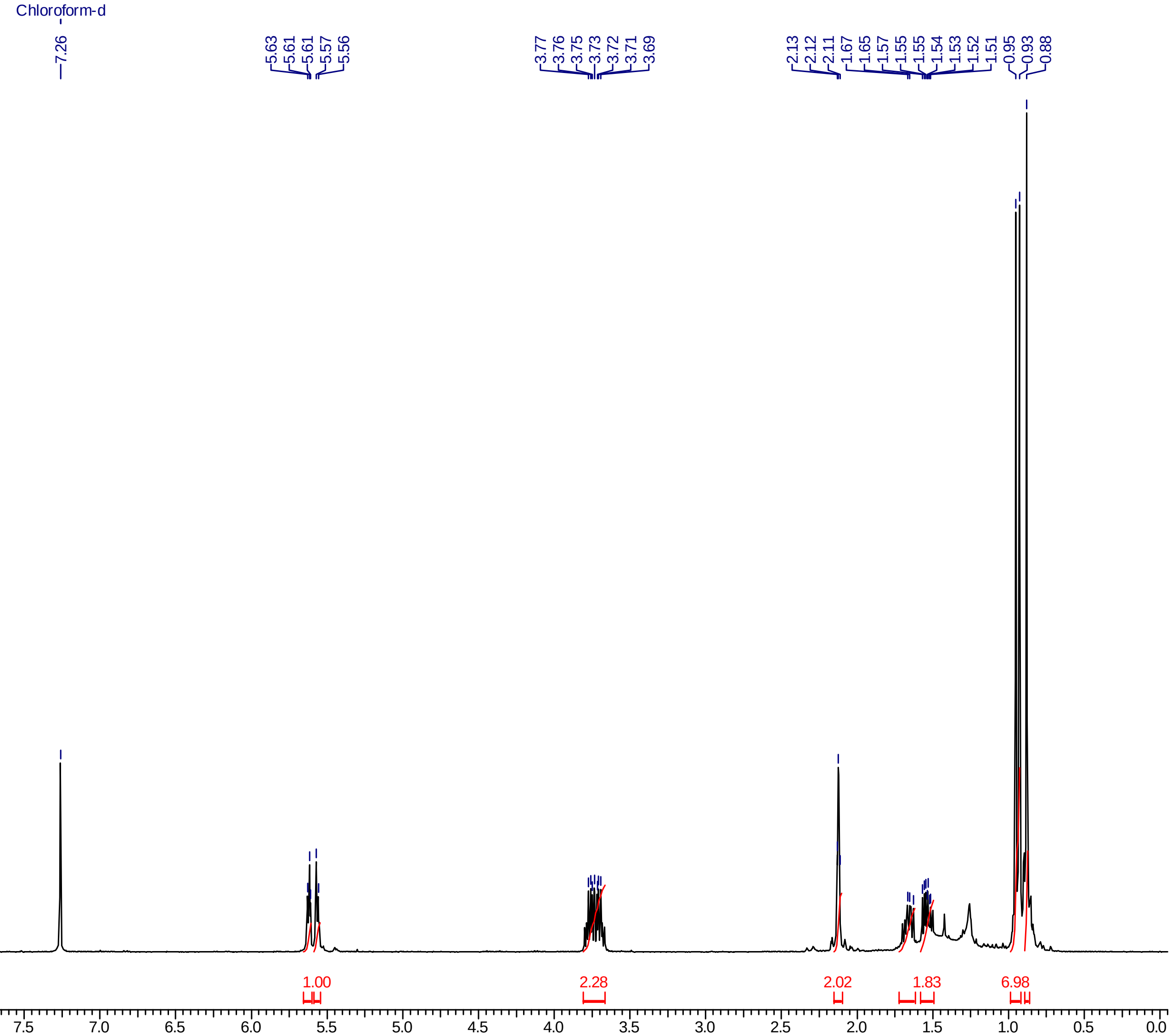
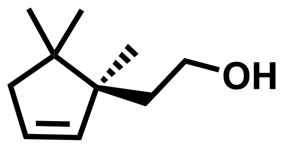


^{13}C NMR ($CDCl_3$, 100 MHz)



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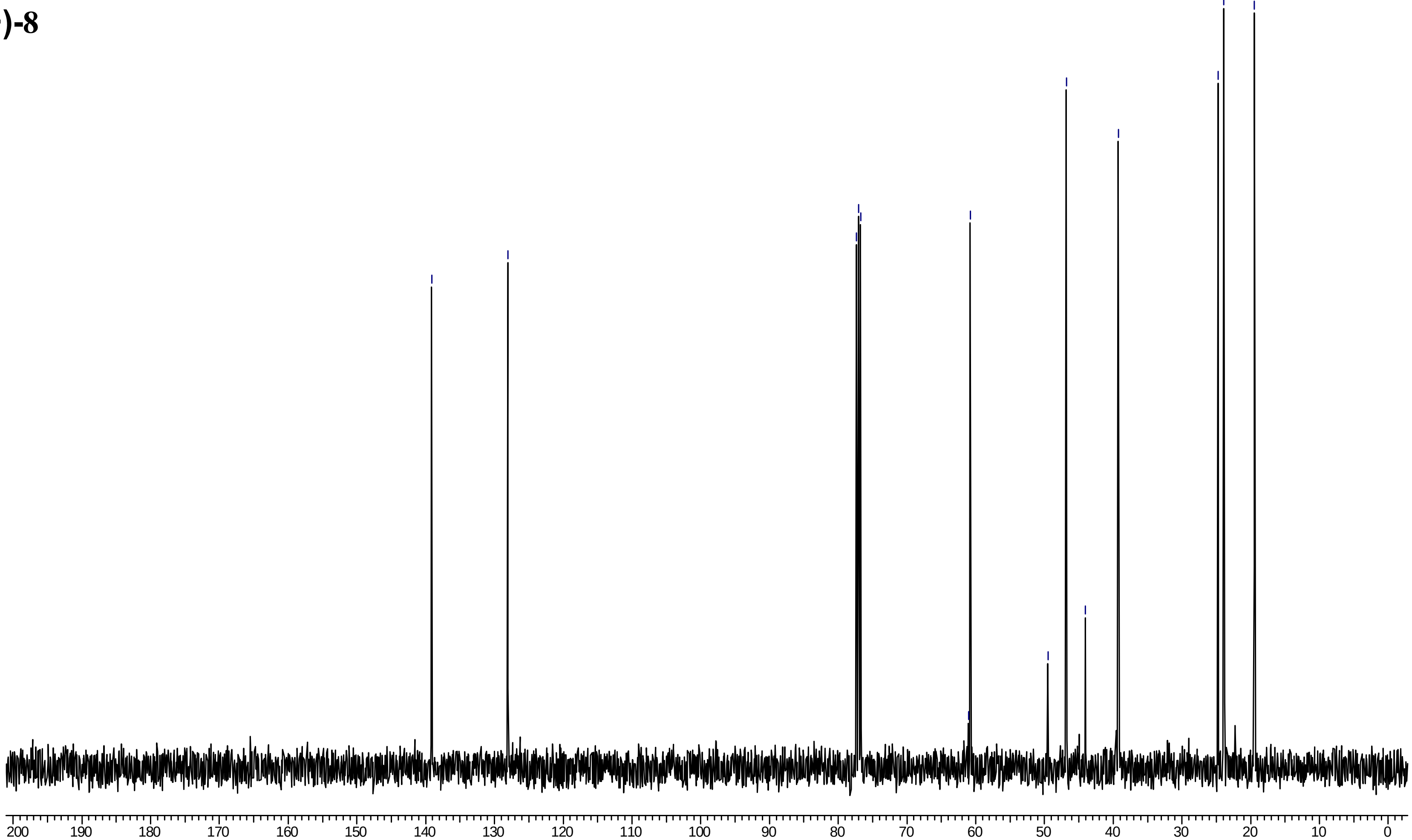
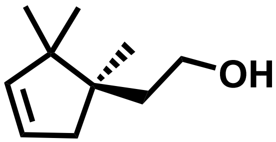
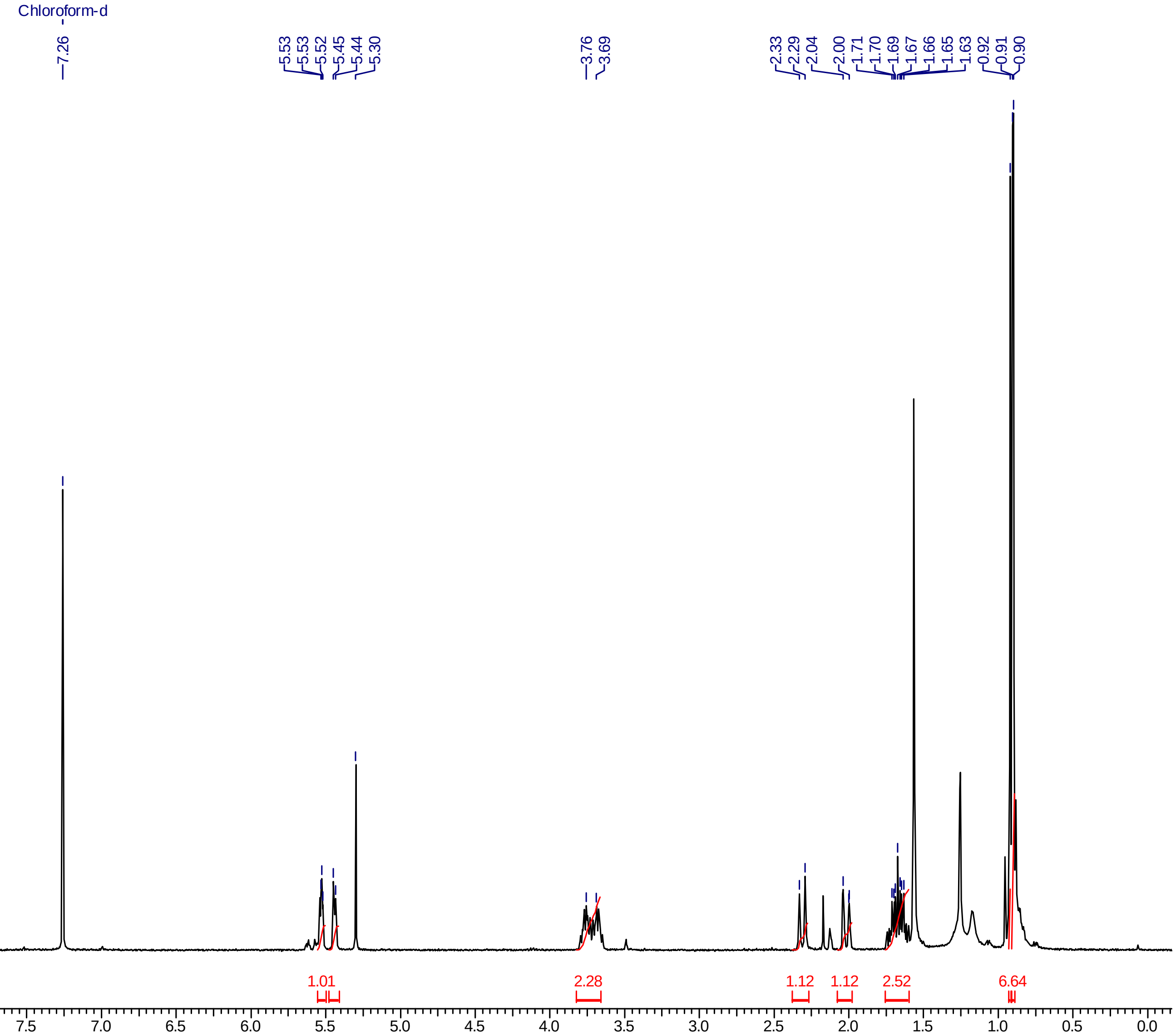


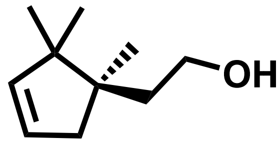
^{1}H NMR ($CDCl_3$, 400 MHz)



(-)-8a



^{13}C NMR ($CDCl_3$, 100 MHz)



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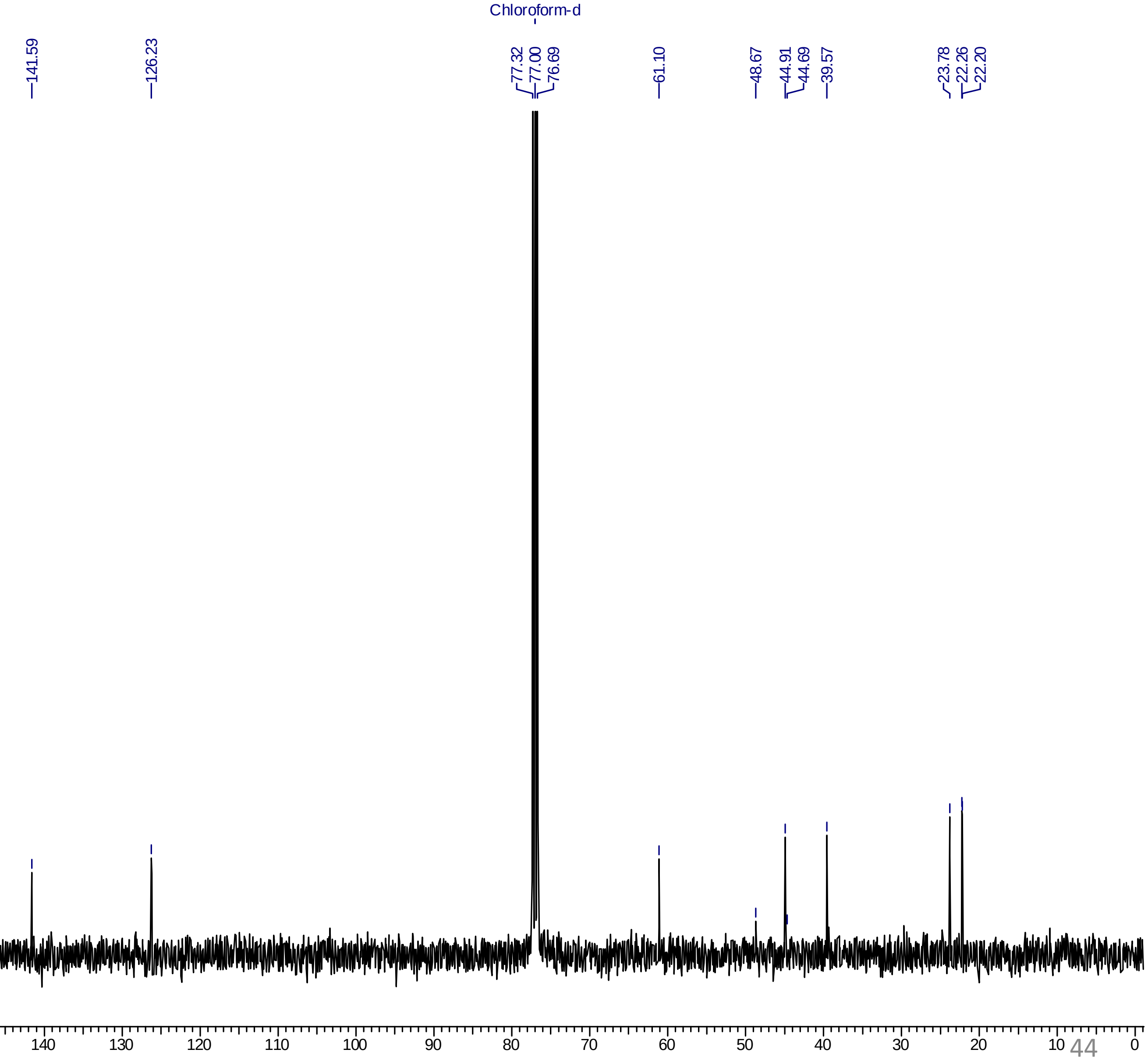
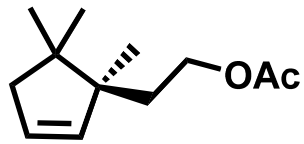


^1H NMR ($CDCl_3$, 400 MHz)



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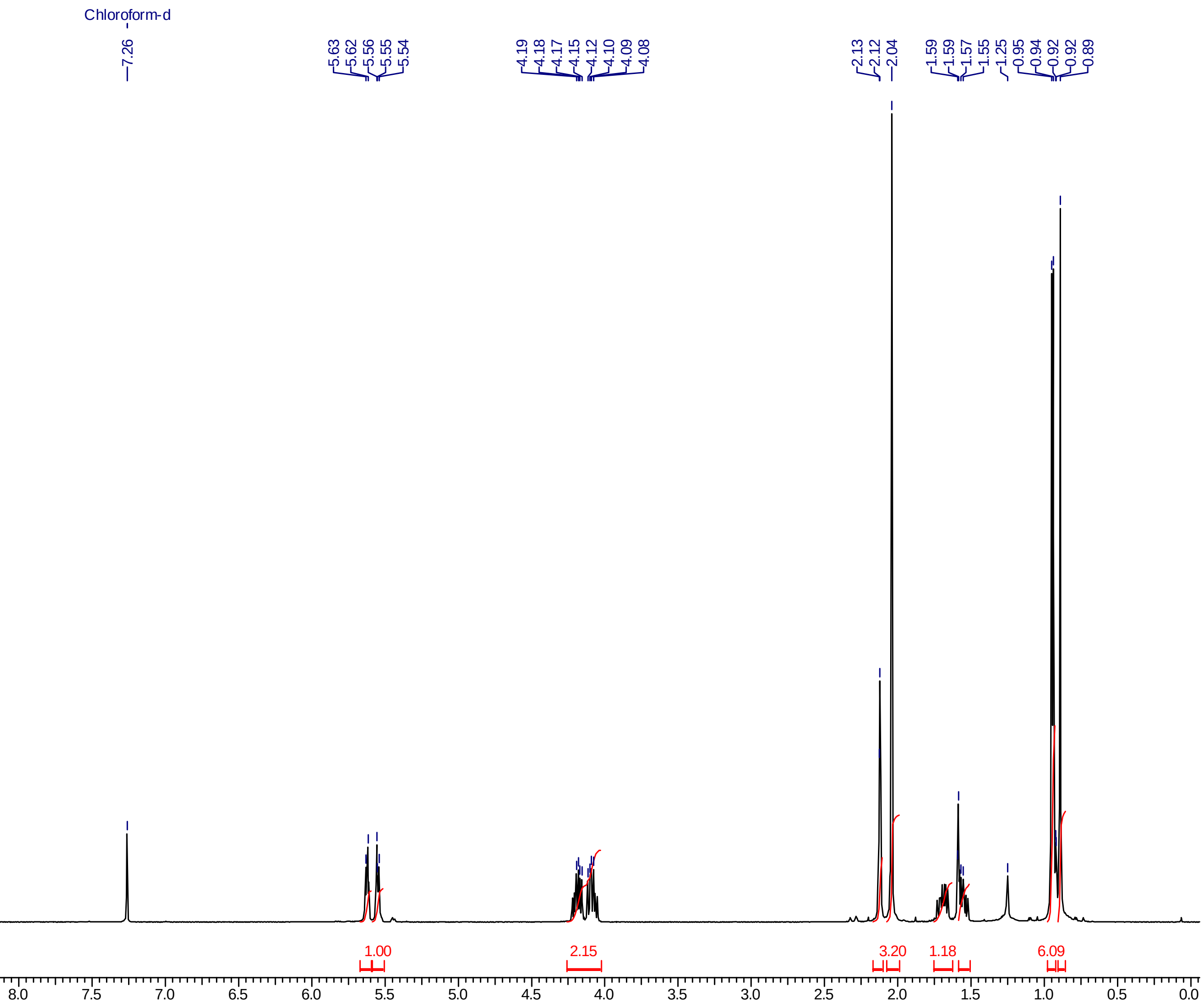
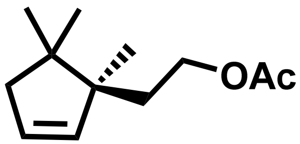


^{13}C NMR ($CDCl_3$, 100 MHz)



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