Supporting Information

for

A Continuous Flow Sulfuryl Chloride Based Reaction – Synthesis of a Key Intermediate in a New Route Toward Emtricitabine and Lamivudine

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Contents

1. Calorimetry – Adiabatic Temperature Rise (ΔT_{ad})

Step 1: For the sulfenyl chloride **4** formation ($\Delta H_{Step\ 1}$ = 242 kJ/mol), the adiabatic temperature rise ΔT_{ad} is given by:

$\Delta T_{ad} = \Delta H_{rxn} / Cp_{solvent}$

ΔT_{ad} = (242 kJ/mol ME) / (5*Cp solvent), ME = Menthol ester **3**

Considering 5 volumes of toluene used and $Cp_{toluene}$ = 1.595 J/(g ºC):

ΔT_{ad} = (242 kJ/mol/1kJ*1000 J) / (5*$Cp_{toluene}$)

ΔT_{ad} = 242,000 J/mol ME / (5*$Cp_{toluene}$)

ΔT_{ad} = 242,000/mol ME *1 mol ME / 230 g ME)/ (5*$Cp_{toluene}$)

ΔT_{ad} = 1052 J/g ME / (5*$Cp_{toluene}$)

ΔT_{ad} = 1052 J/g ME / (7.975 J/(g ºC))

ΔT_{ad} = 132.9 ºC

Menthol ester **3** comprises 1.47 volumes compared to the 5 volumes of toluene. That brings total mass up to 6.47 volumes. This would change the ΔT_{ad} to 101.9 ºC, if we assume **3** has same heat capacity as toluene. If methylene chloride (DCM) is used as solvent (Cp_{DCM} is 1.205 J/(g ºC)), the ΔT_{ad} at 5 volumes is 174 ºC, and at 6.47 volumes adjusted is 134.9 ºC.

Step 2: Values are even higher ($\Delta H_{Step\ 2}$ = 438 kJ/mol): ΔT_{ad} = 207 ºC at 5 volumes and 138 ºC at 7.54 volumes of toluene. If reaction is carried out in DCM, ΔT_{ad} = 275 ºC at 5 volumes of DCM and 182 ºC at 7.54 volumes adjusted.

Based on these calculations, we predict this translates to an adiabatic temperature rise of 102–133 ºC in toluene for the reaction of **3** with SO_2Cl_2 (Step 1) and 138–207 ºC for the reaction with vinyl acetate (**5**)/SO_2Cl_2 (Step 2).

Figure S1 shows the EasyMax reactor from Mettler Toledo used for better temperature control during reagent addition and to perform HFCal runs.

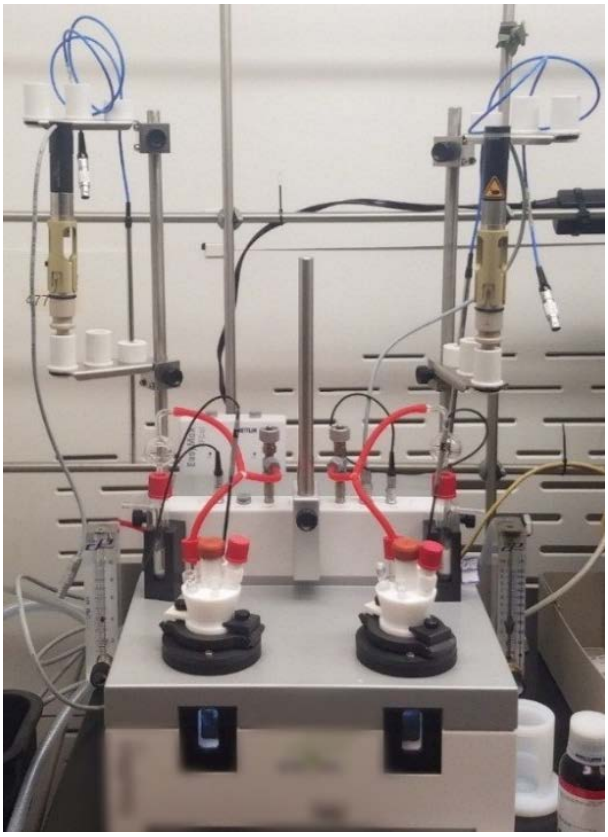
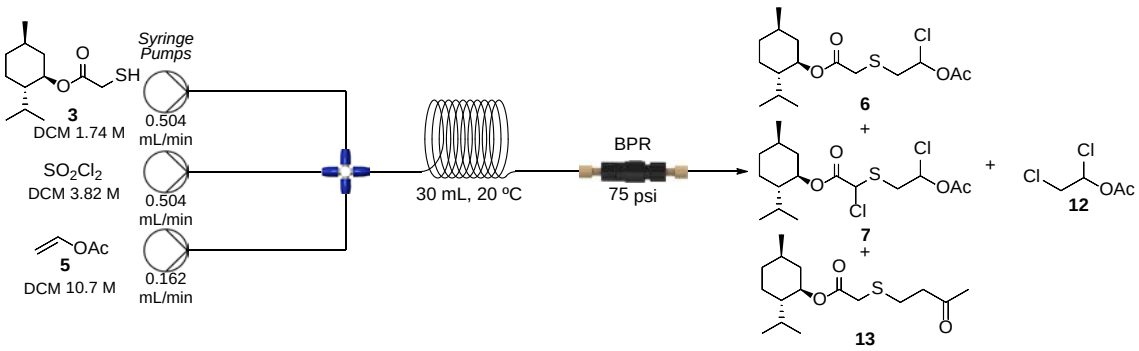


Figure S1. EasyMax 102 from Mettler Toledo used to carry out batch experiments.

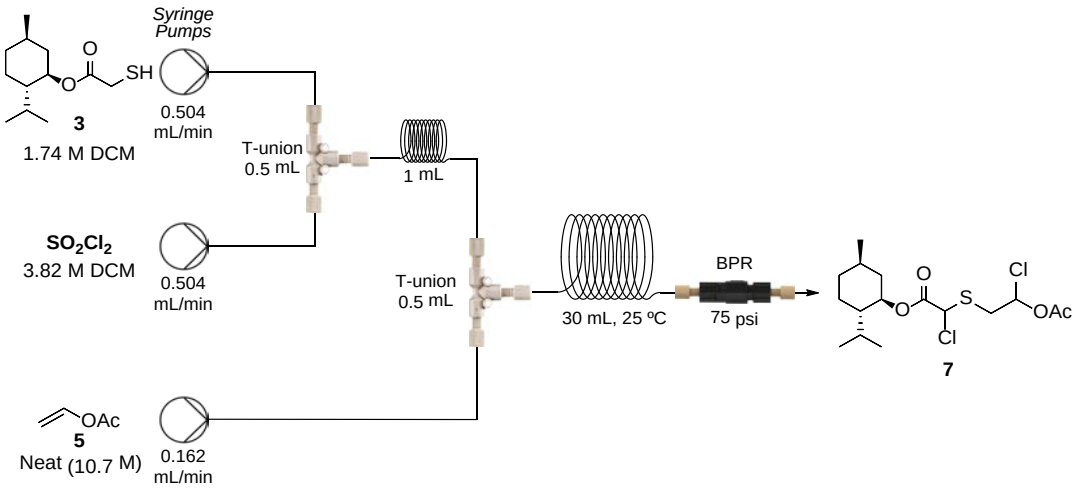
2. Continuous flow configurations to test hypothesis shown in Scheme 3

A. *The three-stream combination experiment* – All solutions were pumped using syringe pumps. Solutions of thiol **3**, SO_2Cl_2 and vinyl acetate (**5**) were mixed simultaneously using a four-way union. ^{1}H NMR analysis of the crude mixture showed considerably higher amounts of byproducts **12** and **13** than observed in previous experiments. Dichloro acetate **7** assay yield dropped from 99% to 57% and 20% of the monochlorinated intermediate **6** was recovered.



Scheme S1. The three-stream combination experiment – small scale experiment (1.0 g of thiol **3**).

B. *Premixing of thiol **3** and SO_2Cl_2 using a small loop (1 mL)* **–** All solutions were pumped using syringe pumps. Thiol **3** in DCM (1.74 M) and sulfuryl chloride in DCM (3.82 M) at 0.504 mL/min and vinyl acetate **5** neat (10.7 M) at 0.162 mL/min flow rates. Residence time (t_R) of the whole system was 26 min. Dichloro acetate **7** (95% AY) and only 5% AY of trichloro acetate **8** was formed confirming our hypothesis that intermediate **14** does not react with vinyl acetate acting as a temporary protecting group against unwanted thio-ene reaction.



Scheme S2. Premixing of thiol **3** and SO_2Cl_2 using a small loop (1 mL) – small scale experiment (1.0 g of thiol **3**).

3. System Configuration

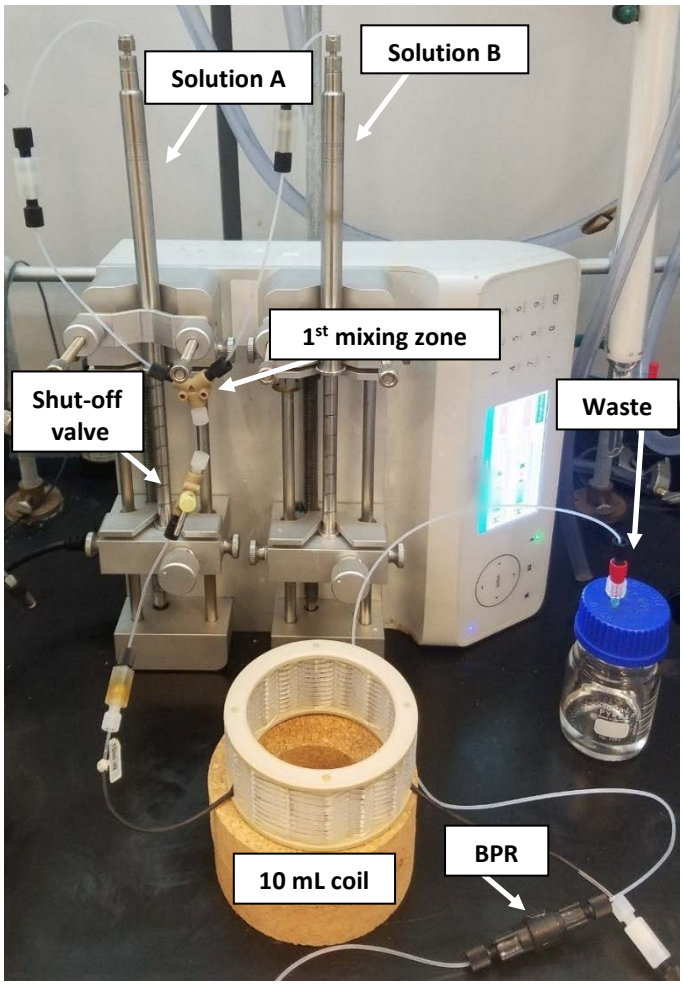


Figure S2. Initial system to study sulfenyl chloride **4** synthesis in continuous flow conditions.

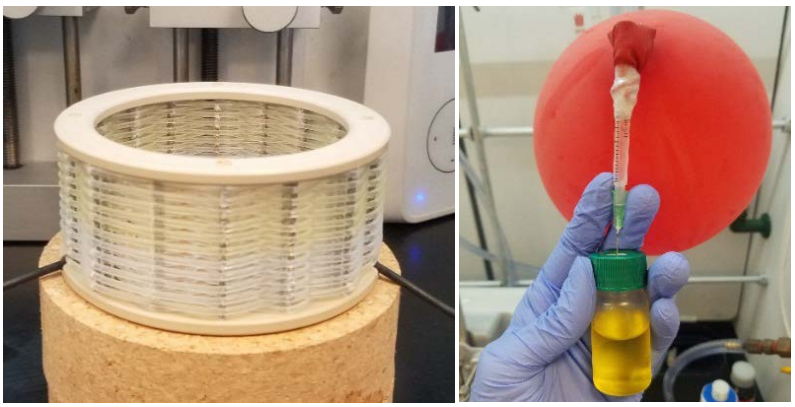


Figure S3. Change in the reaction mixture color when sulfenyl chloride **4** is formed.

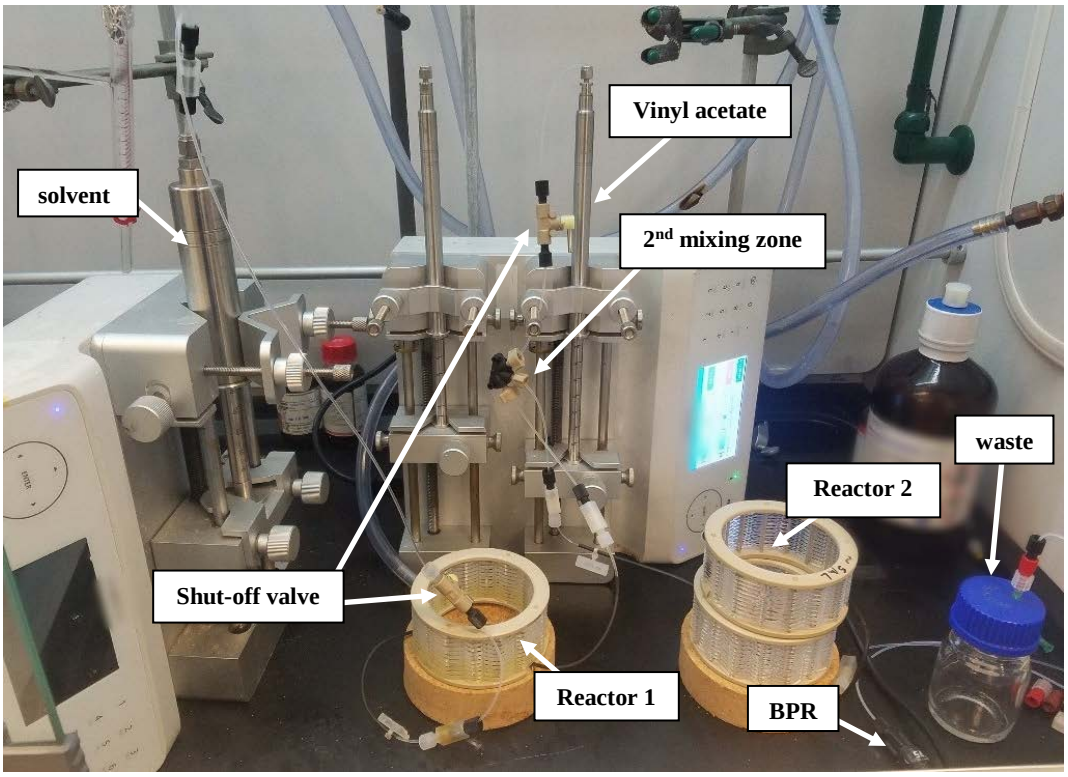


Figure S4. First two-module flow set-up for compound **7** synthesis under continuous conditions.

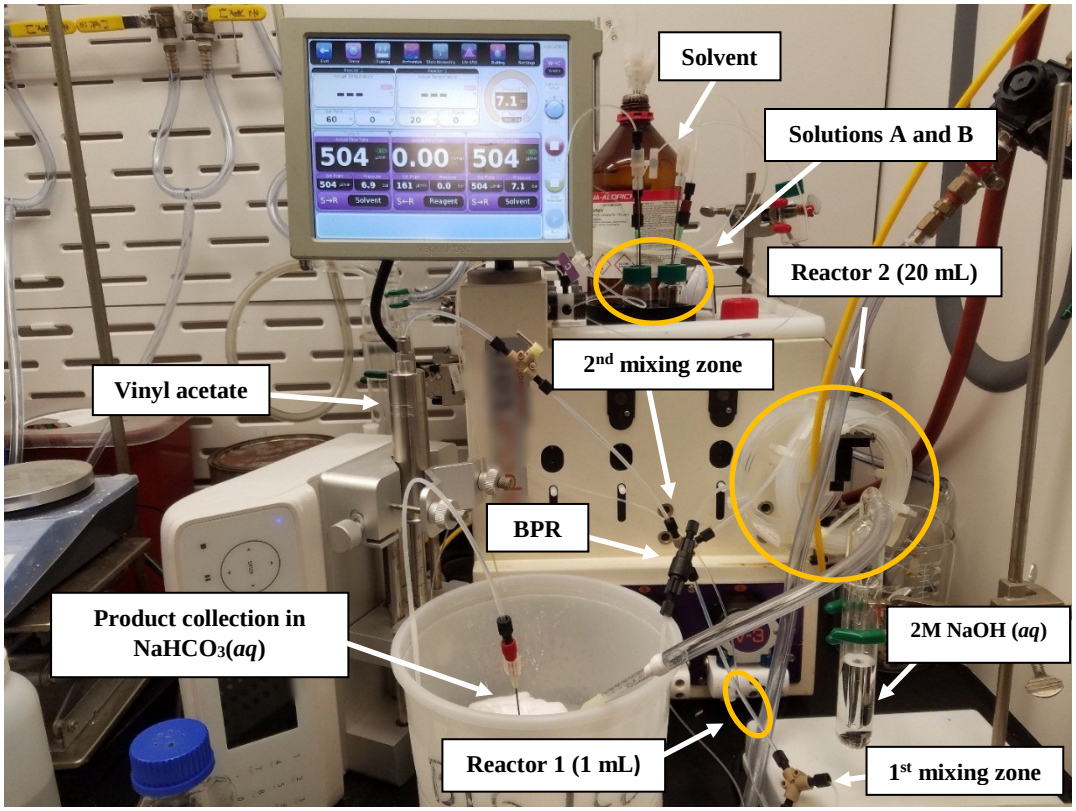


Figure S5. Continuous flow setup to determine steady state stability – Vapourtec E-Series to pump solutions A and B and Chemyx syringe pump for vinyl acetate.

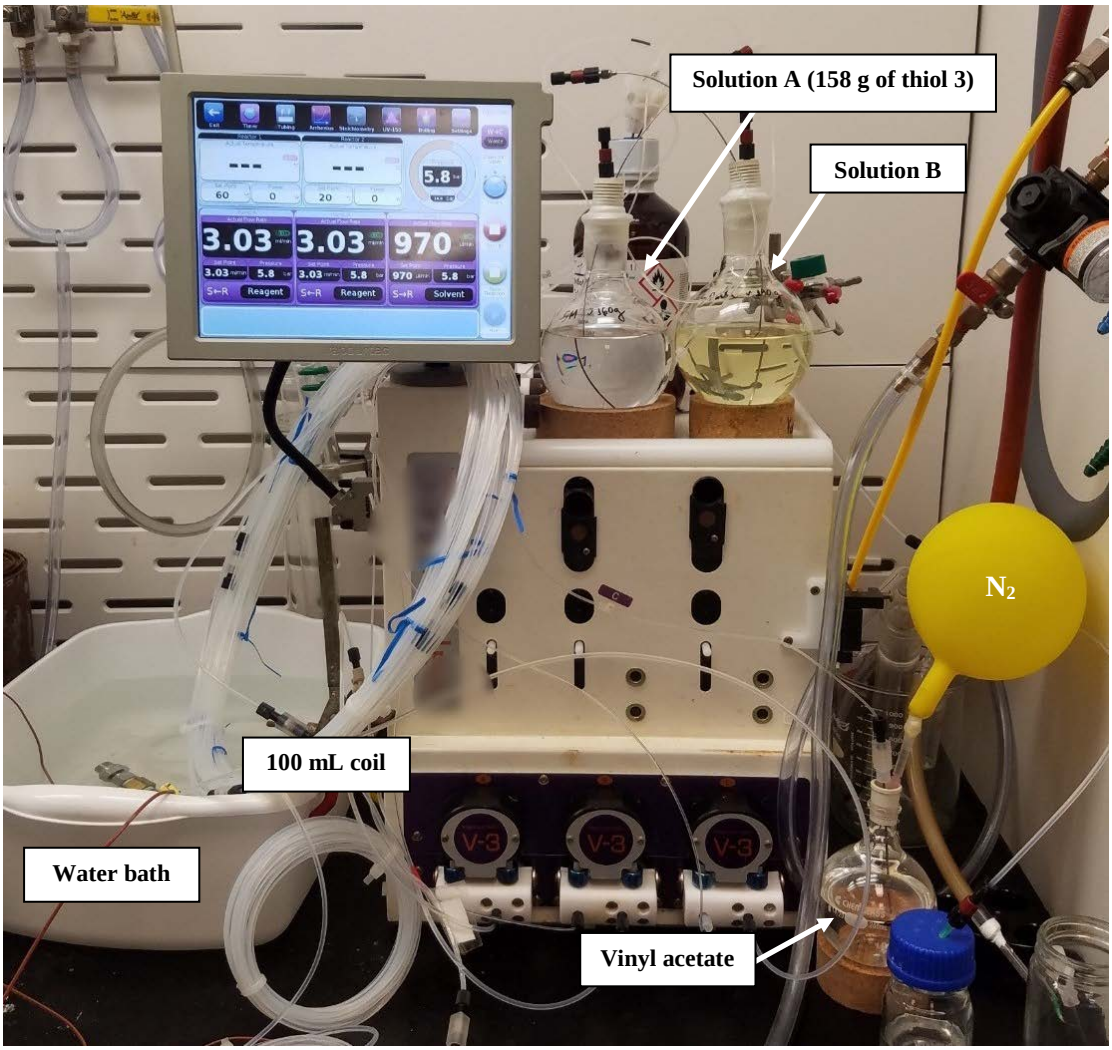


Figure S6. Final continuous flow setup used to scale-up the reaction (Table 5, Entry 3).

4. Crystallization of the compound 7

After neutralization with $NaHCO_3$ saturated solution, extraction with DCM and elimination of solvent under reduce pressure (rotatory evaporator), compound **7** was obtained as an oil. When compound **7** was left for 9 h under vacuum to remove remaining solvent and kept at -18 ºC overnight, the oil became a sticky solid (Figure S7A). Solubilization of this solid in DCM and crystallization in hexanes (Figure S7B) allow to obtain high-quality crystal for X-ray analysis (Figure S8, Cambridge Structural Database - Deposition Number: 1999799). Results indicated the crystal was only formed by one isomer (**7a**) out of four possible structures (the other three remain in the mother liquor). Thus, the crude mixture must be used to proceed in the route toward 3TC or FTC.

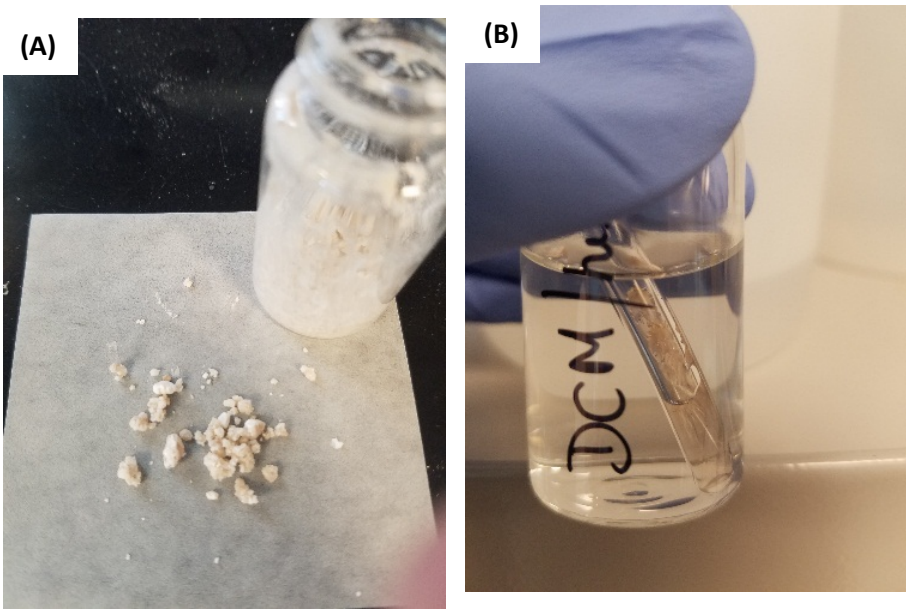
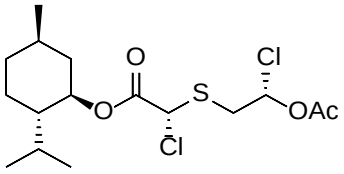
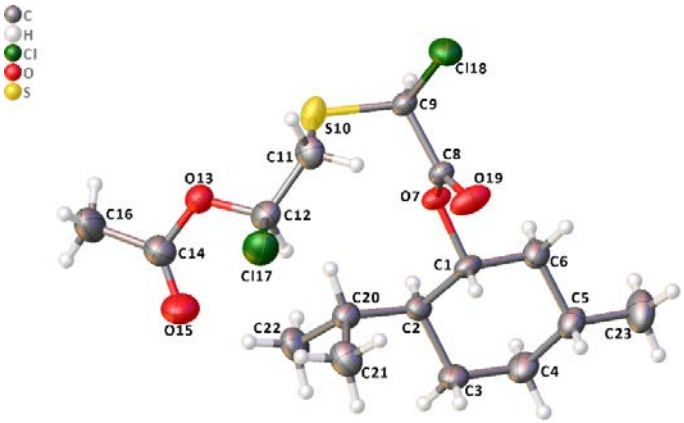


Figure S7. Compound **7**: **(A)** Sticky solid after drying and storage at low temperature. **(B)** Crystallization in DCM/hexanes.



7a



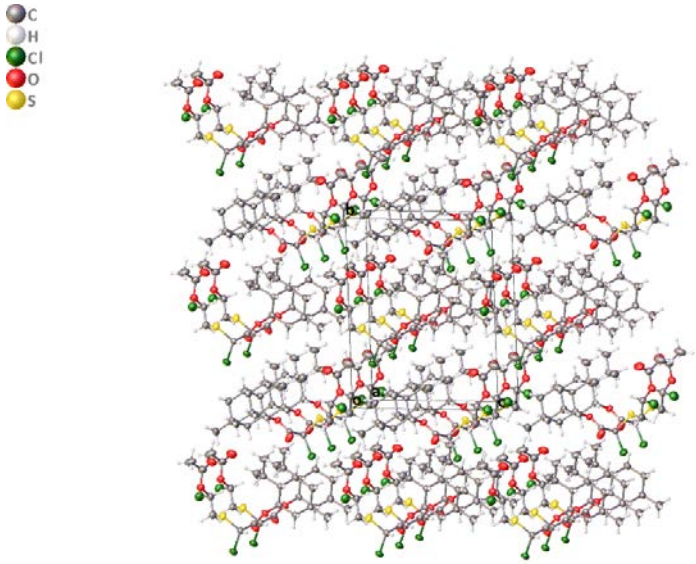


Figure S8. X-ray crystallography of the compound **7a**.

5. Reaction of vinyl acetate (5) with SO_2Cl_2

The ^{1}H NMR of the crude reaction mixture after full consumption of the monochlorinated specie **6** is showed in Figure S9C. The signals are integrated relative to mesitylene (3H, 6.8 ppm), used as an internal standard in 1:1 ratio (compound **3**: mesitylene). Byproduct **12** is highlighted in red in Figure S9B and S9C. Its signals match perfectly with the previously unidentified byproducts in the crude mixture.

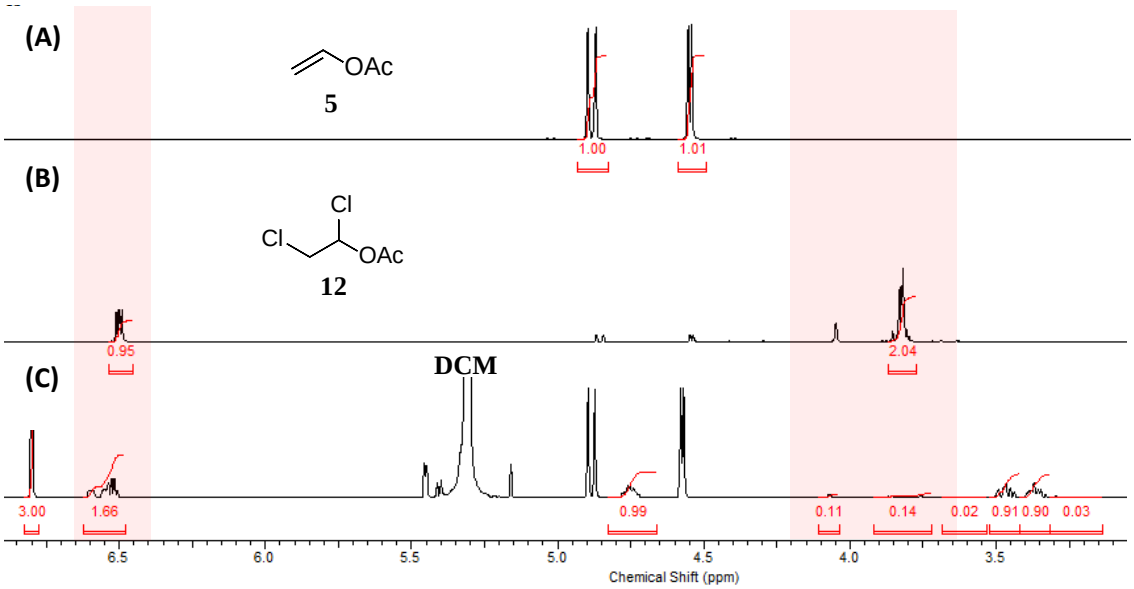


Figure S9. ^{1}H NMR of byproduct **12** in the crude reaction mixture: **(A)** Vinyl acetate (**5**). **(B)** Vinyl acetate (**5**) after reaction with SO_2Cl_2. **(C)** Crude reaction mixture in DCM.

6. 1,2,3-trichloropropane as the NMR internal standard

Many NMR standards were tested with no success. Most of them was incompatible with SO_2Cl_2, leading to the formation of unwanted chlorinated species. We sought to select not only an inert internal standard but also one with high boiling point. Gas release after the BPR is very intense and volatile standards would be easily lost during samples collection, resulting in not reliable assay yields. The ^{1}H NMR analysis of the crude mixture is displayed in Figure S10A. Dichloro acetate **7** was formed in 97% AY based on the new standard (Table 4, Entry 2). All samples collected at steady state were neutralized with $NaHCO_3$ sat. before NMR analysis, to remove SO_2Cl_2 excess and HCl. To confirm 1,2,3-trichloropropane is inert to SO_2Cl_2, one sample was not neutralized and stored overnight (Figure S10B). ^{1}H NMR analysis showed that remaining SO_2Cl_2 reacted with the residual vinyl acetate (**5**) present in the crude mixture. Furthermore, the increase

of trichloro **8** from the reaction of **7** with SO_2Cl_2 was also observed. Even after 16 h, 1,2,3-trichloropropane remains intact. The –CH– hydrogen signal (1H) in 4.23 ppm appears in a spectrum region free of signals, while the $–CH_2–$ groups in 3.85 ppm (4H) overlap with some impurities (Figure S10).

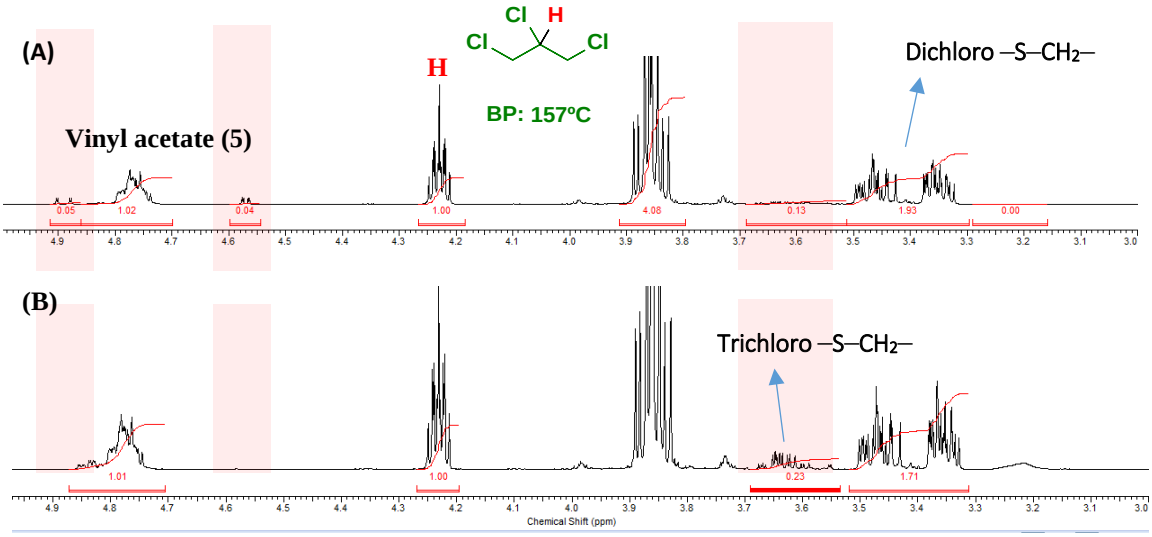
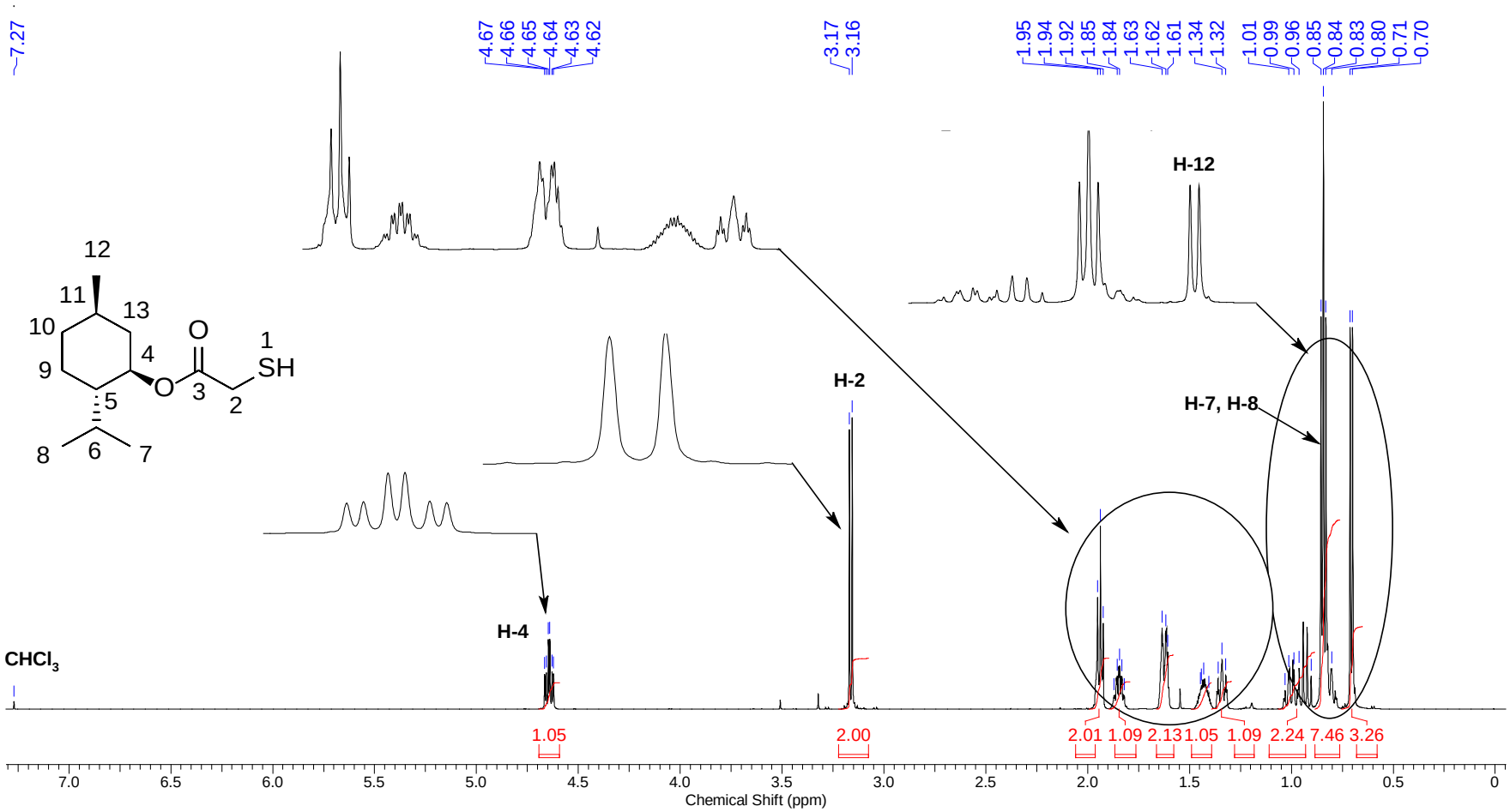


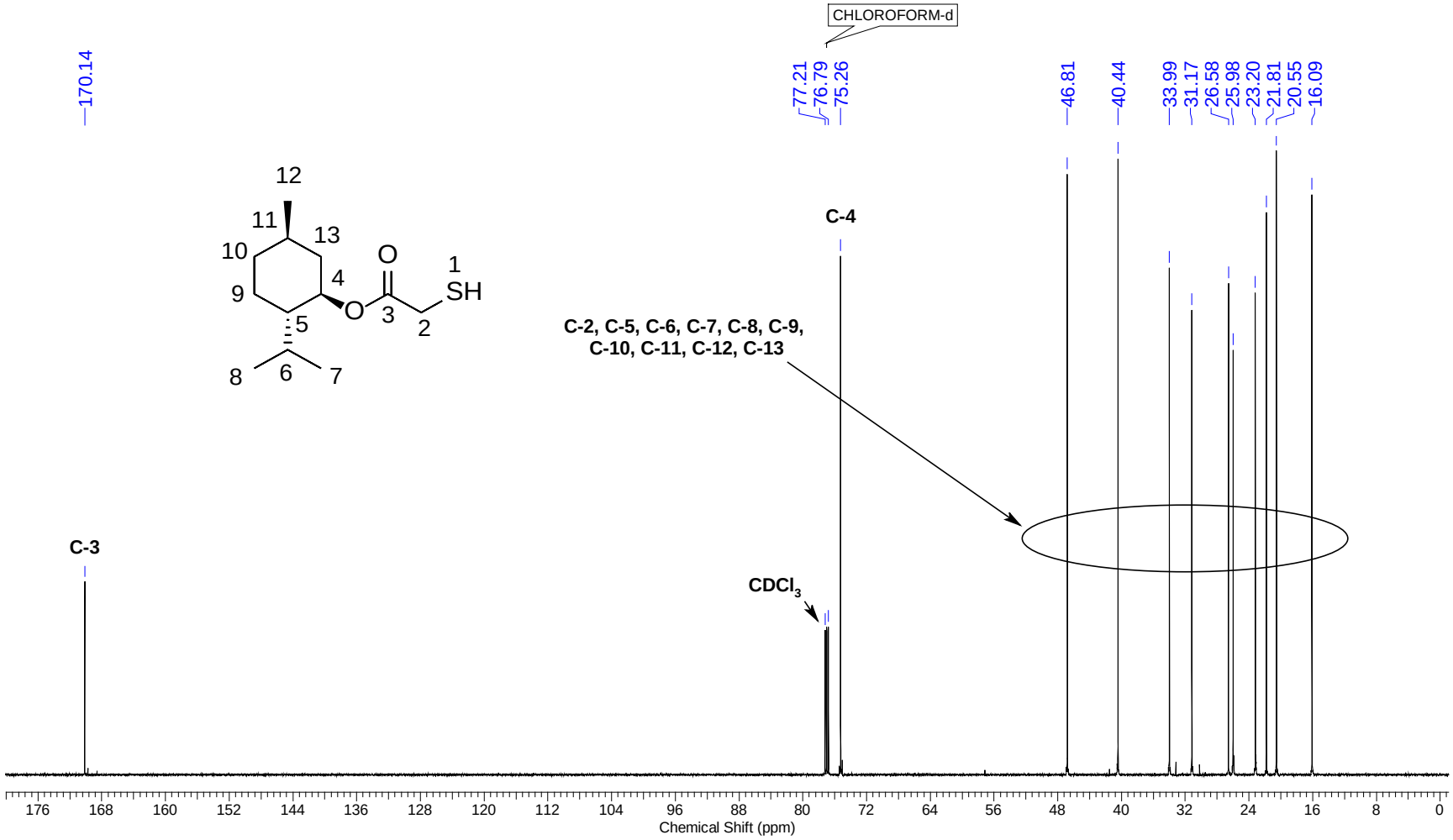
Figure S10. Use of 1,2,3-trichloropropane as NMR internal standard for the steady state stability studies. **(A)** Crude mixture at steady state + 1,2,3-trichloropropane (^{1}H NMR immediately after fraction collection). **(B)** Same sample no-neutralized with $NaHCO_3$ sat. solution (^{1}H NMR overnight).

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

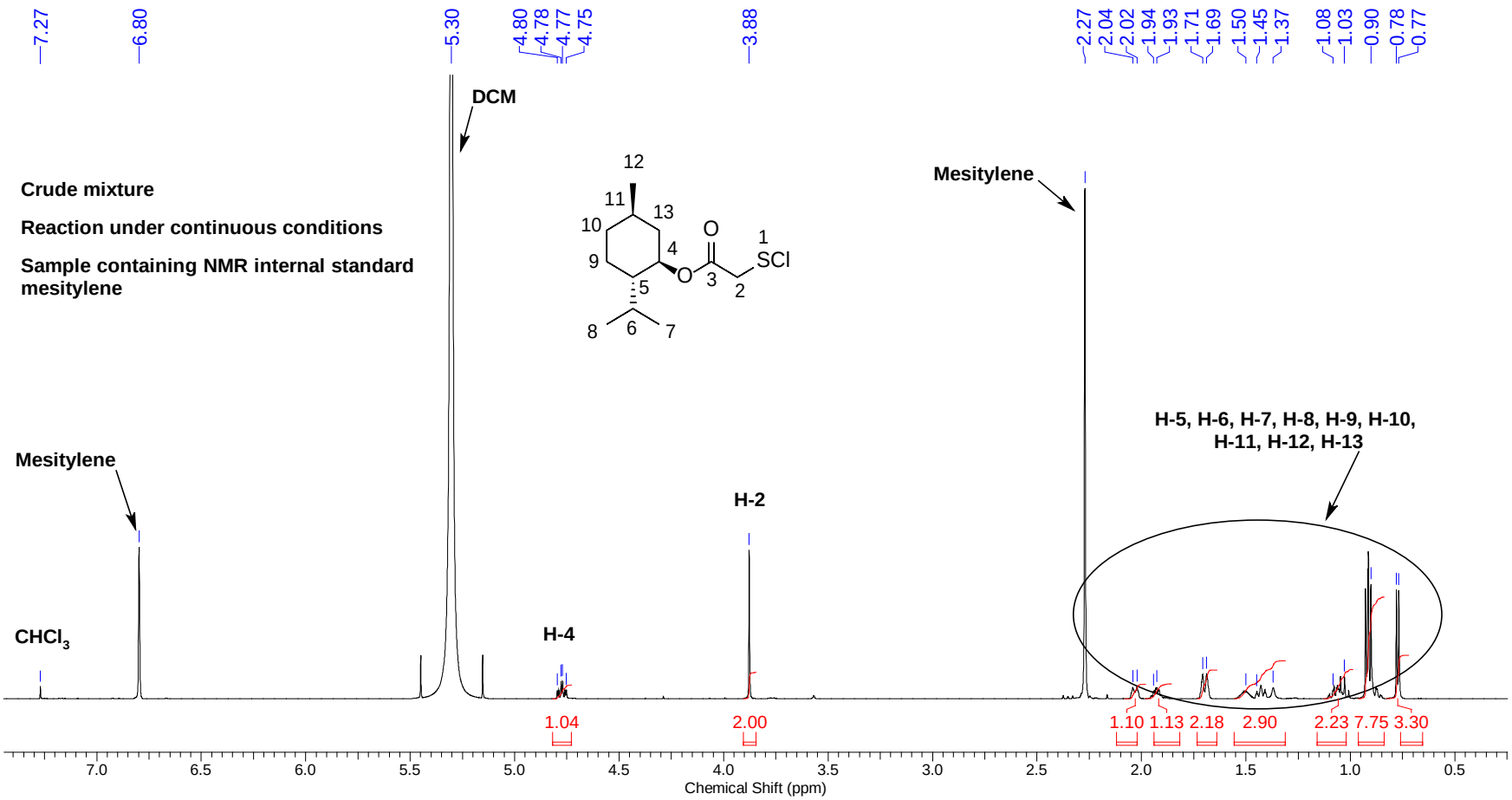
Frequency (MHz)	600.01	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	9.97	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3743.7068
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.557		



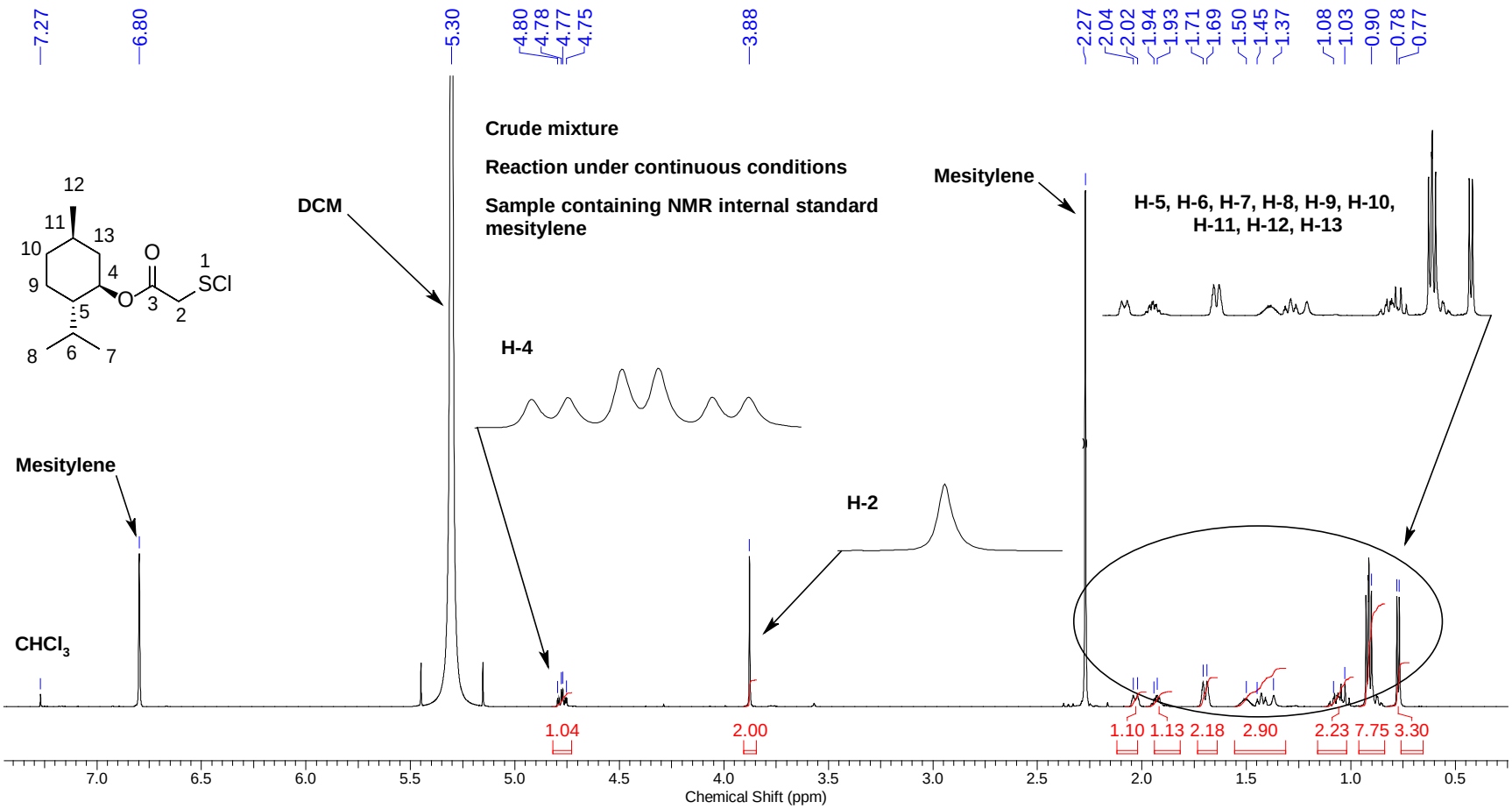
Frequency (MHz)	150.87	***Nucleus***	13C	***Number of Transients***	300	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	199.73	***SW(cyclical) (Hz)***	36231.88	***Acquisition Time (sec)***	0.9044	***Spectrum Offset (Hz)***	15075.2021
Spectrum Type	STANDARD	***Sweep Width (Hz)***	36230.78	***Temperature (degree C)***	25.319		



Frequency (MHz)	599.96	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	9.05	***SW(cyclical) (Hz)***	12019.23	***Solvent***	CDCl3	***Spectrum Offset (Hz)***	3695.2930
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	20.513	***Acquisition Time (sec)***	2.7263



Frequency (MHz)	599.96	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	9.05	***SW(cyclical) (Hz)***	12019.23	***Solvent***	CDCl3	***Spectrum Offset (Hz)***	3695.2930
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	20.513	***Acquisition Time (sec)***	2.7263



Nucleus	1H	***Number of Transients***	8	***Origin***	spect	***Original Points Count***	32768
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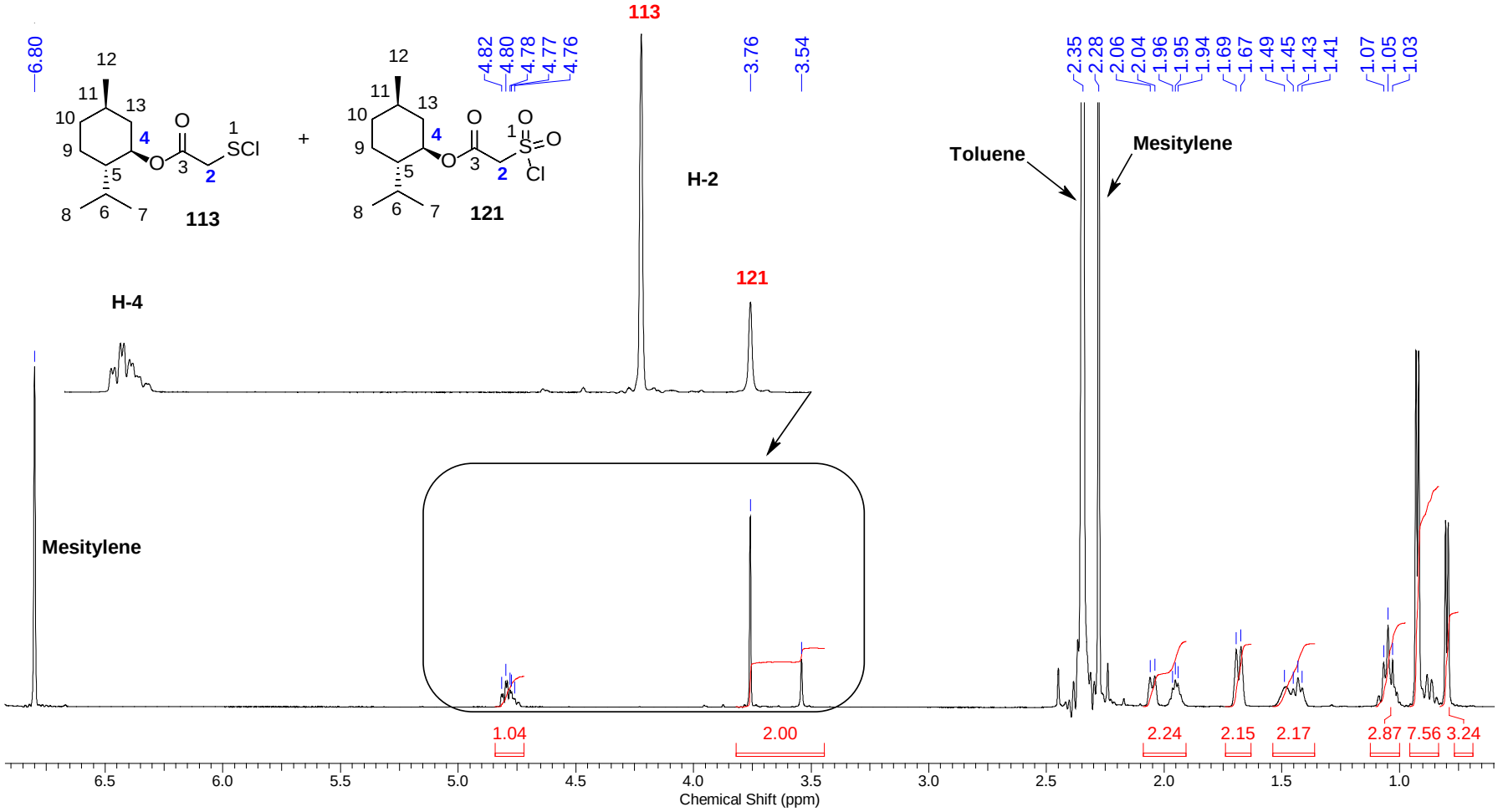

Frequency (MHz)	600.01	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
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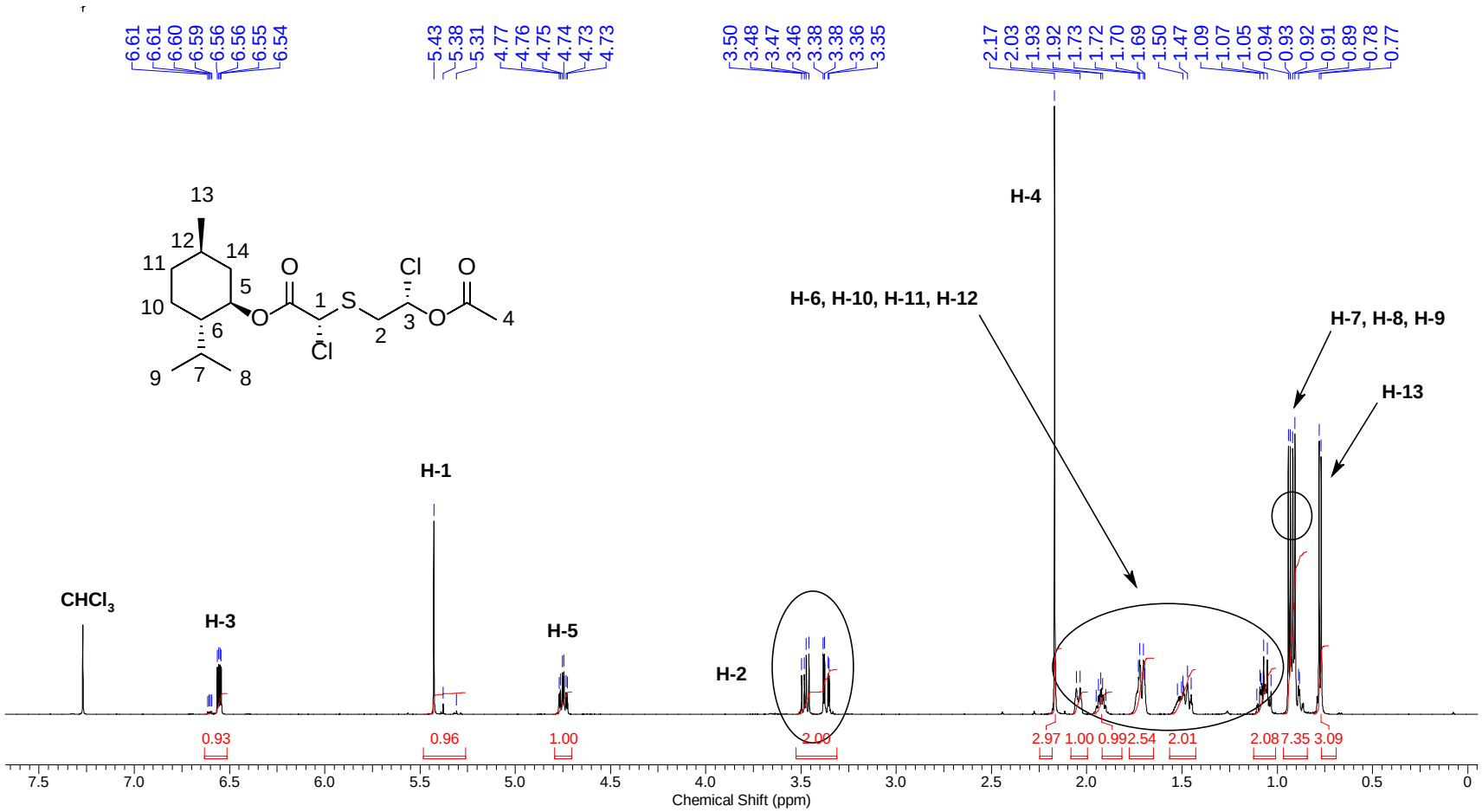
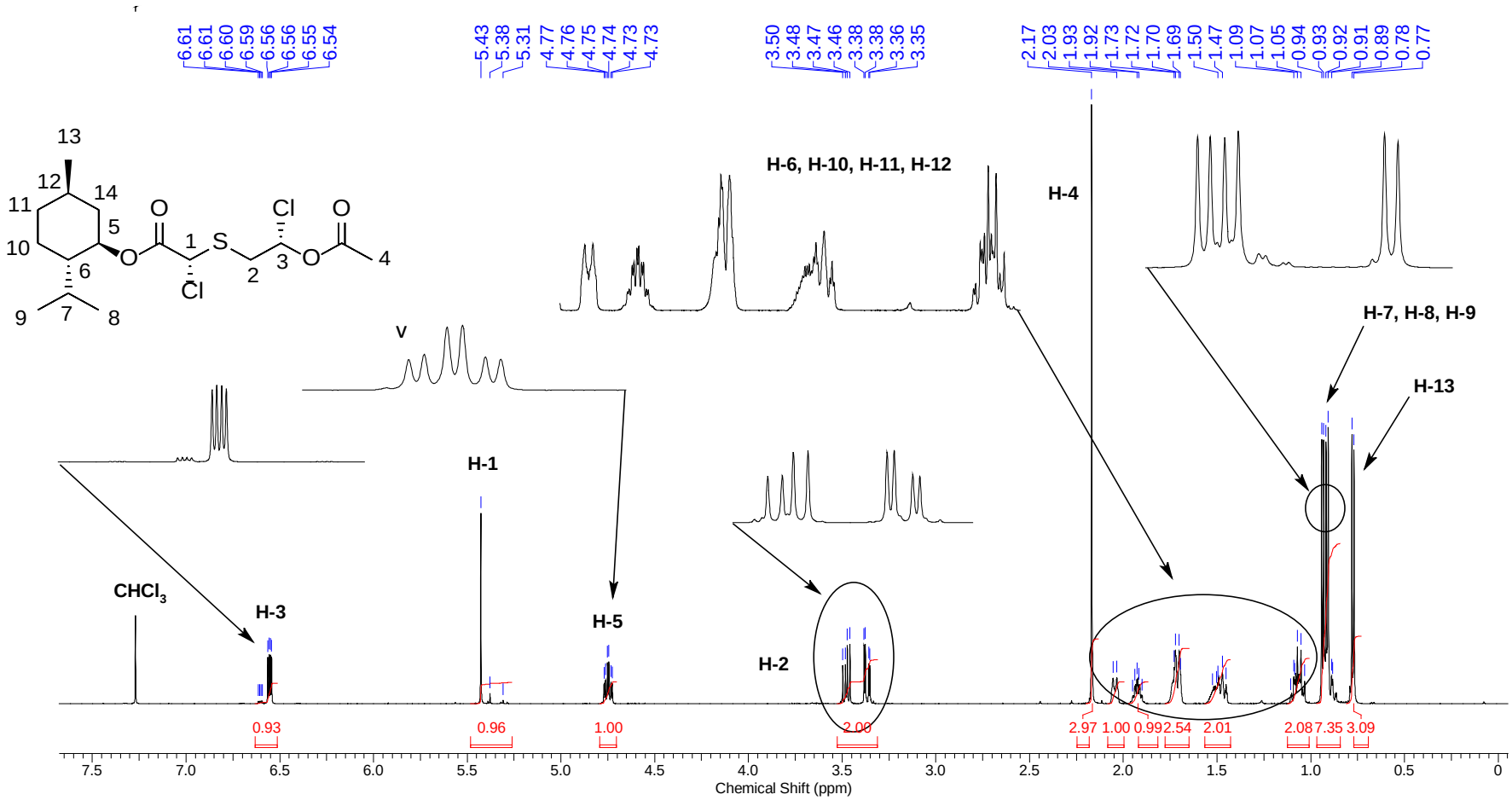
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.682		



Frequency (MHz)	600.01	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	176.24	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3743.5234
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.682		



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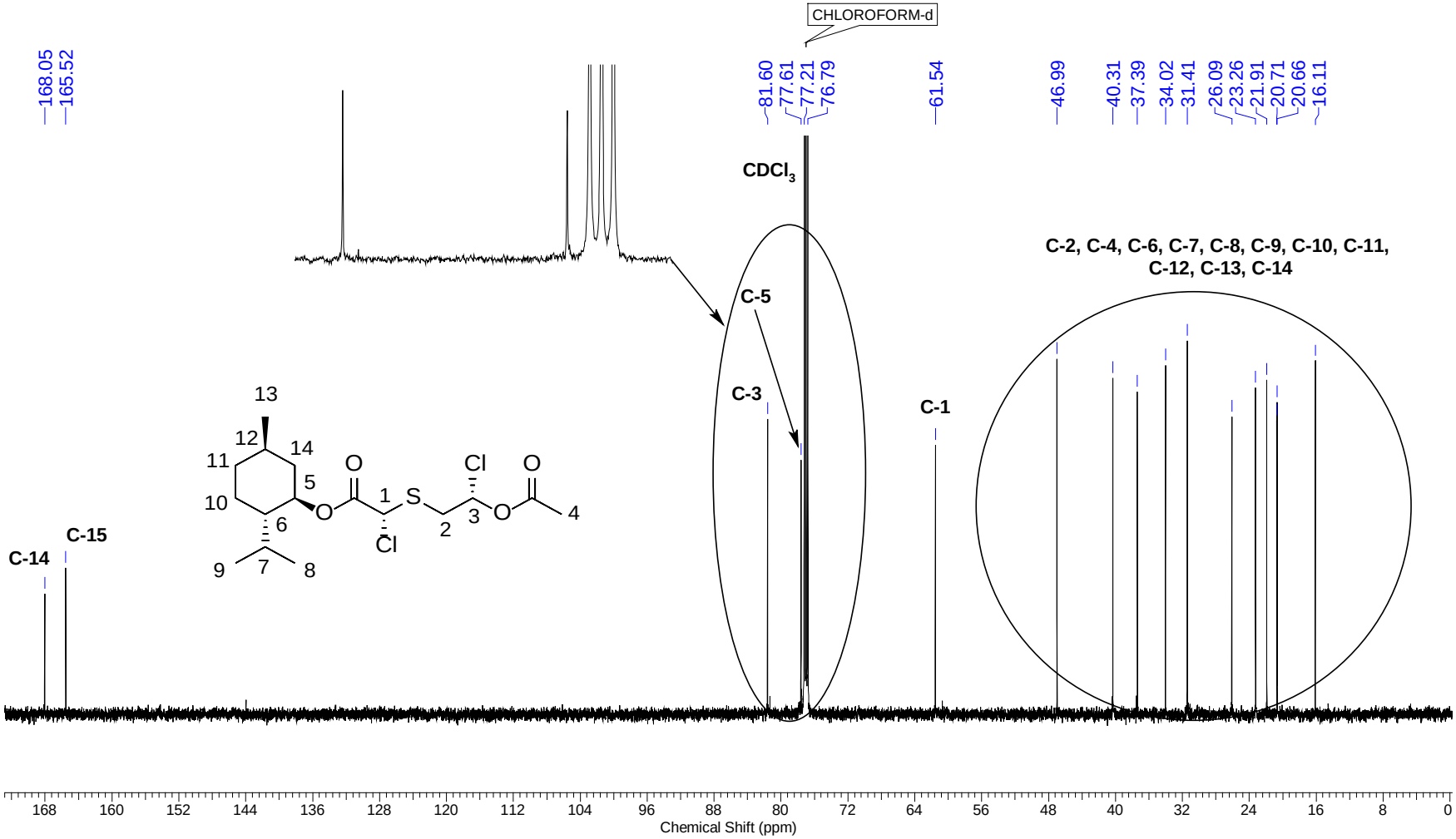

Frequency (MHz)	599.96	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
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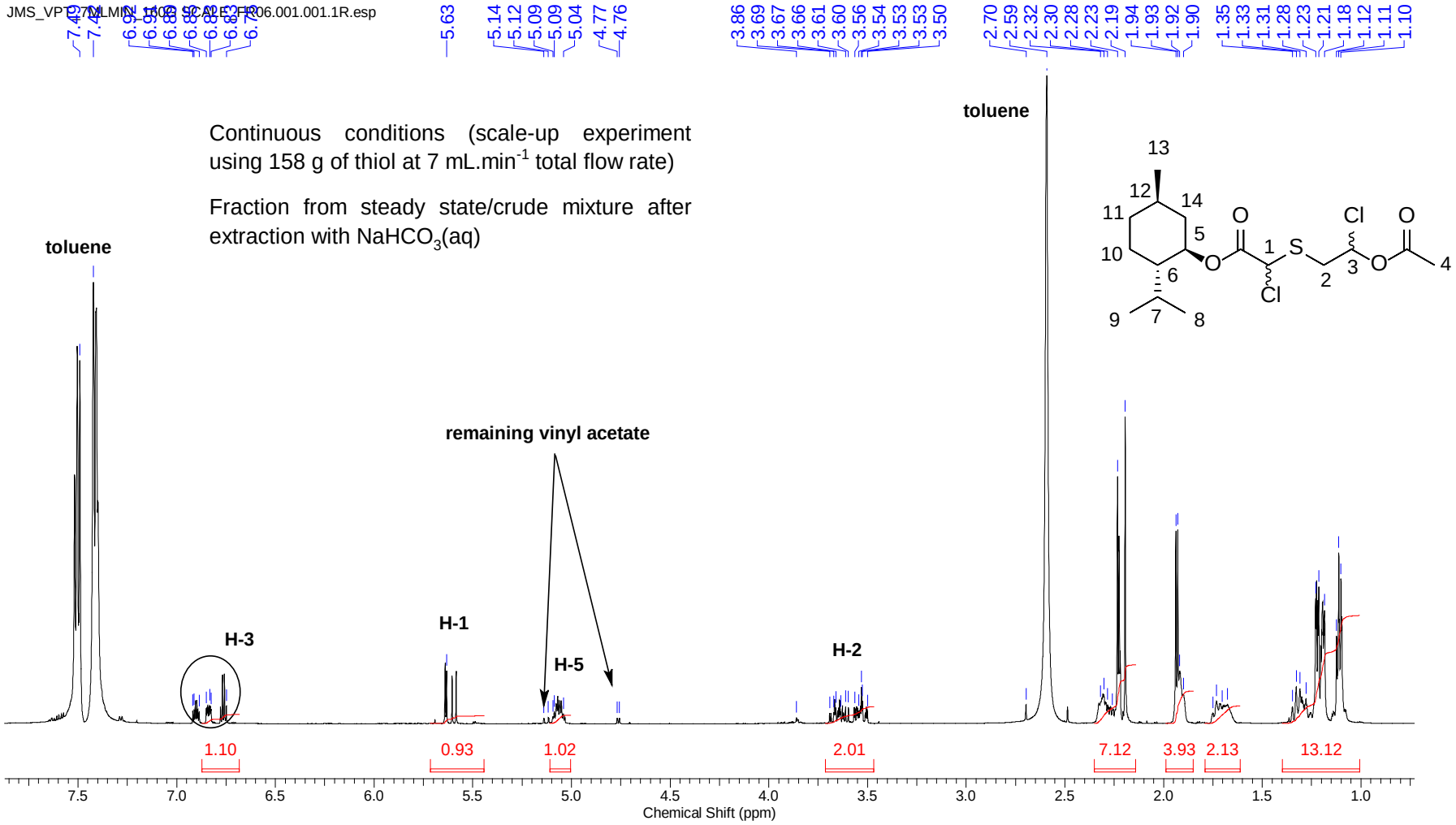
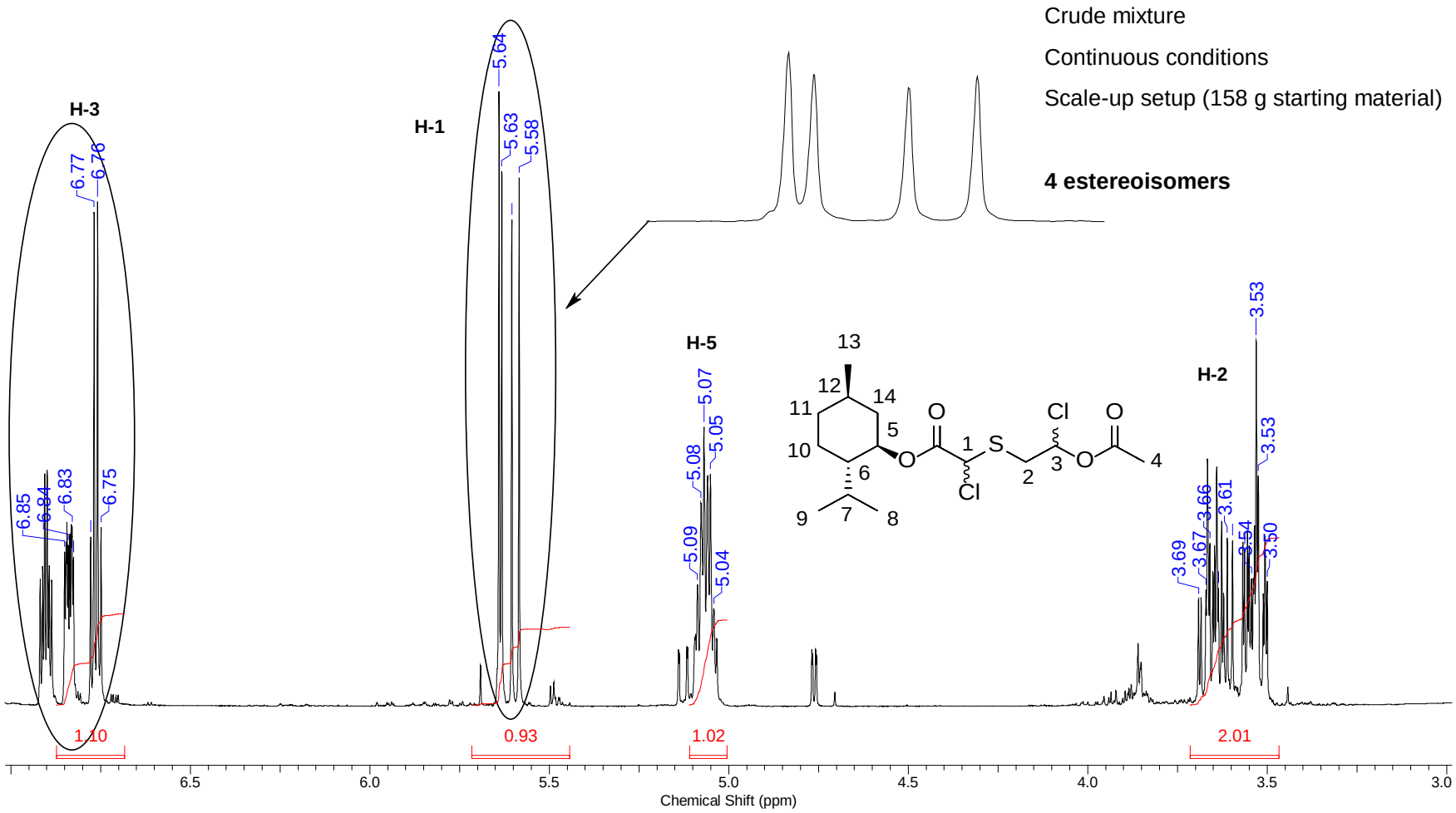
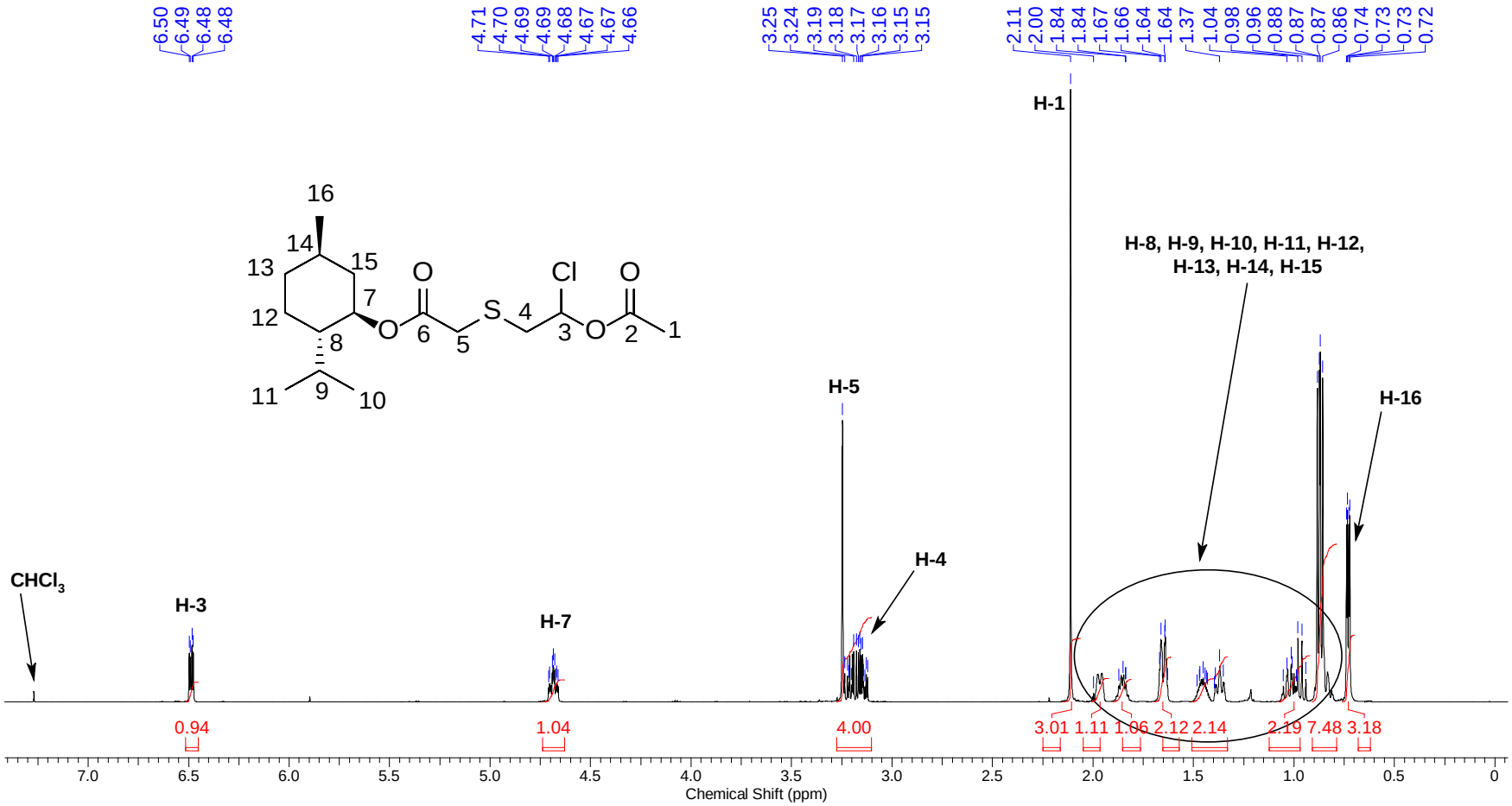


Frequency (MHz)	599.96	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	3.63	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3704.7244
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.303		



Frequency (MHz)	600.01	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	15.88	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3743.7068
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.513		



Frequency (MHz)	600.01	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
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Receiver Gain	15.88	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3743.7068
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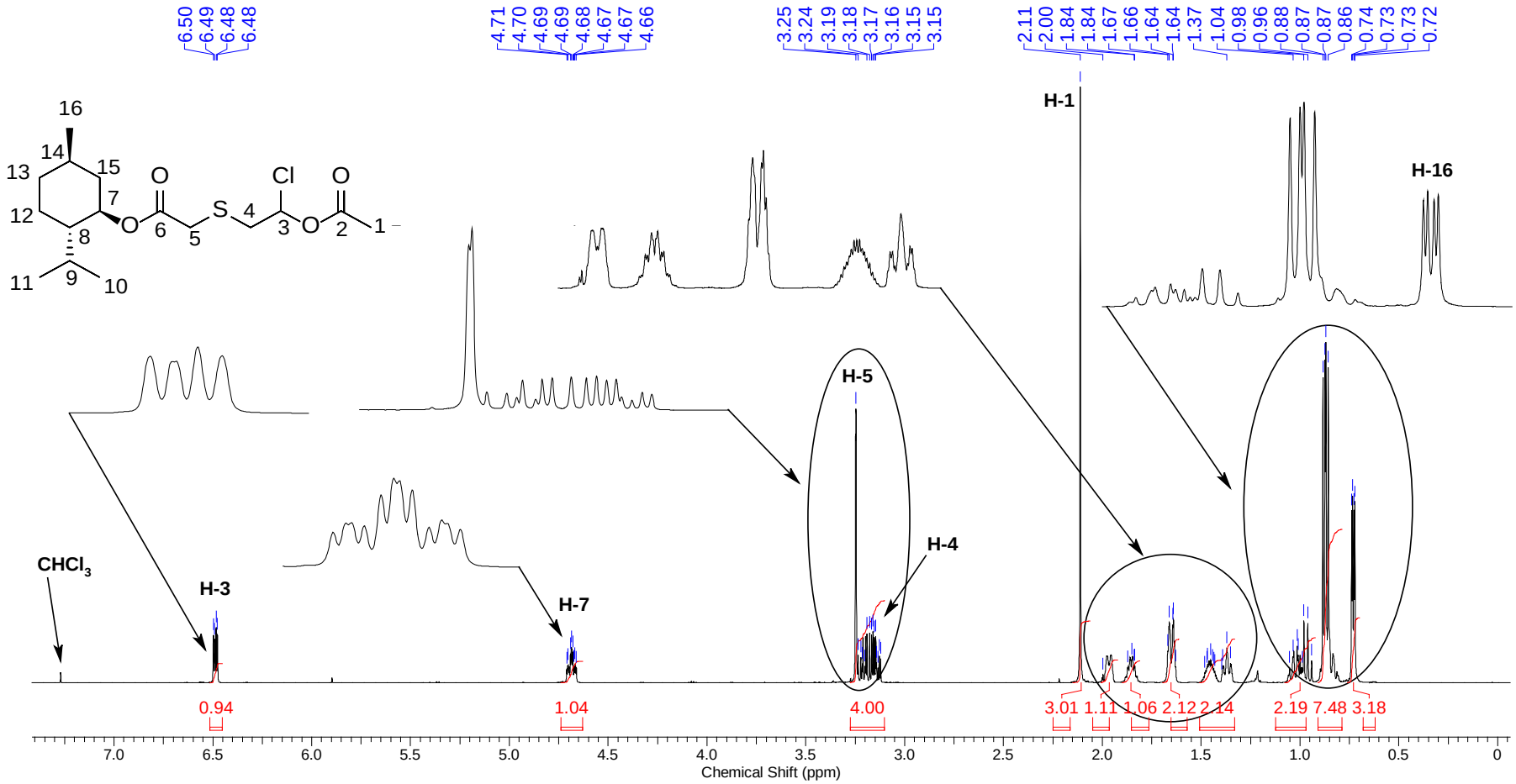

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Original Points Count	32768	***Owner***	nmrsu	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	199.73	***SW(cyclical) (Hz)***	36231.88	***Acquisition Time (sec)***	0.9044	***Spectrum Offset (Hz)***	15080.7305
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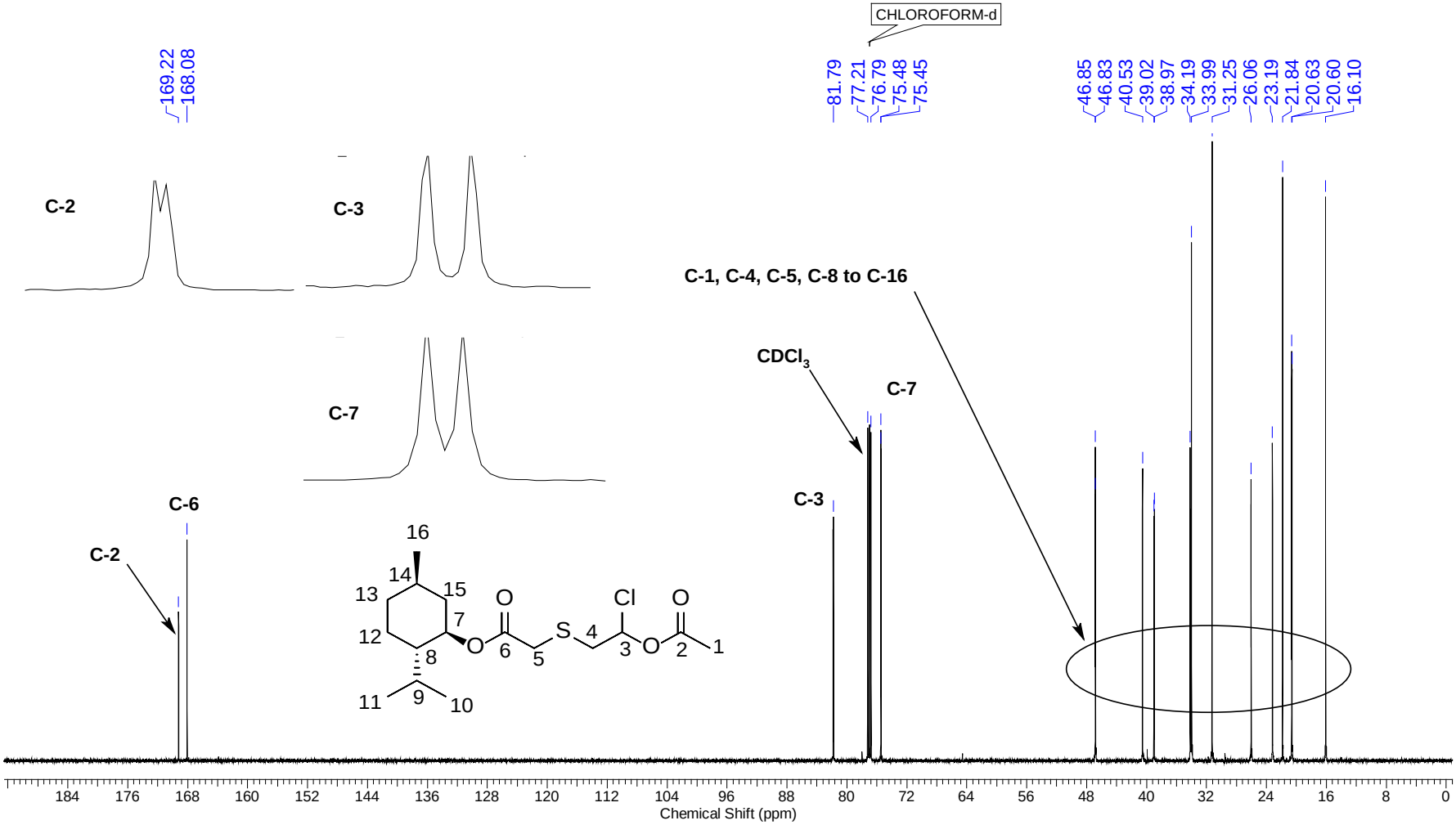

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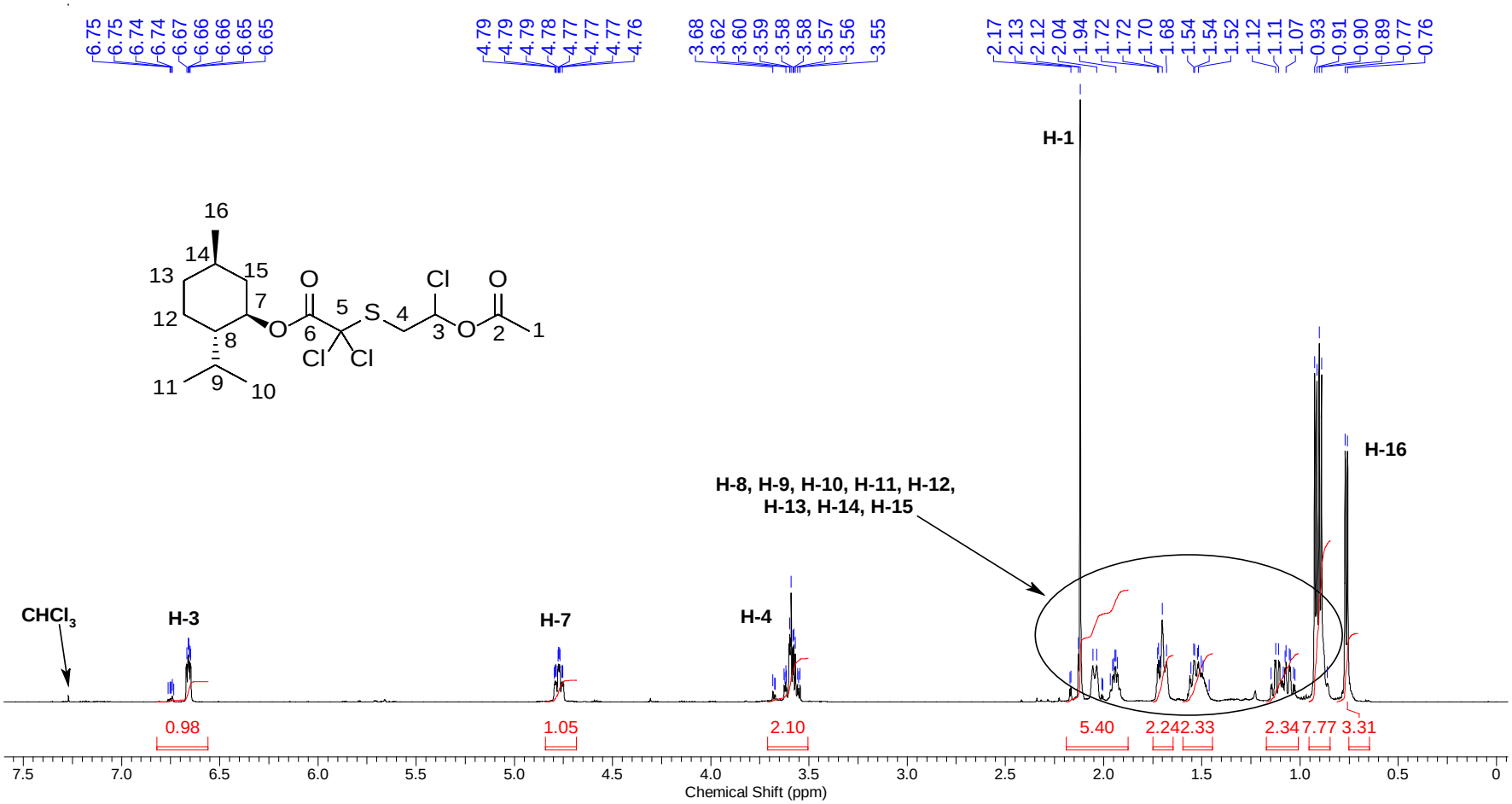
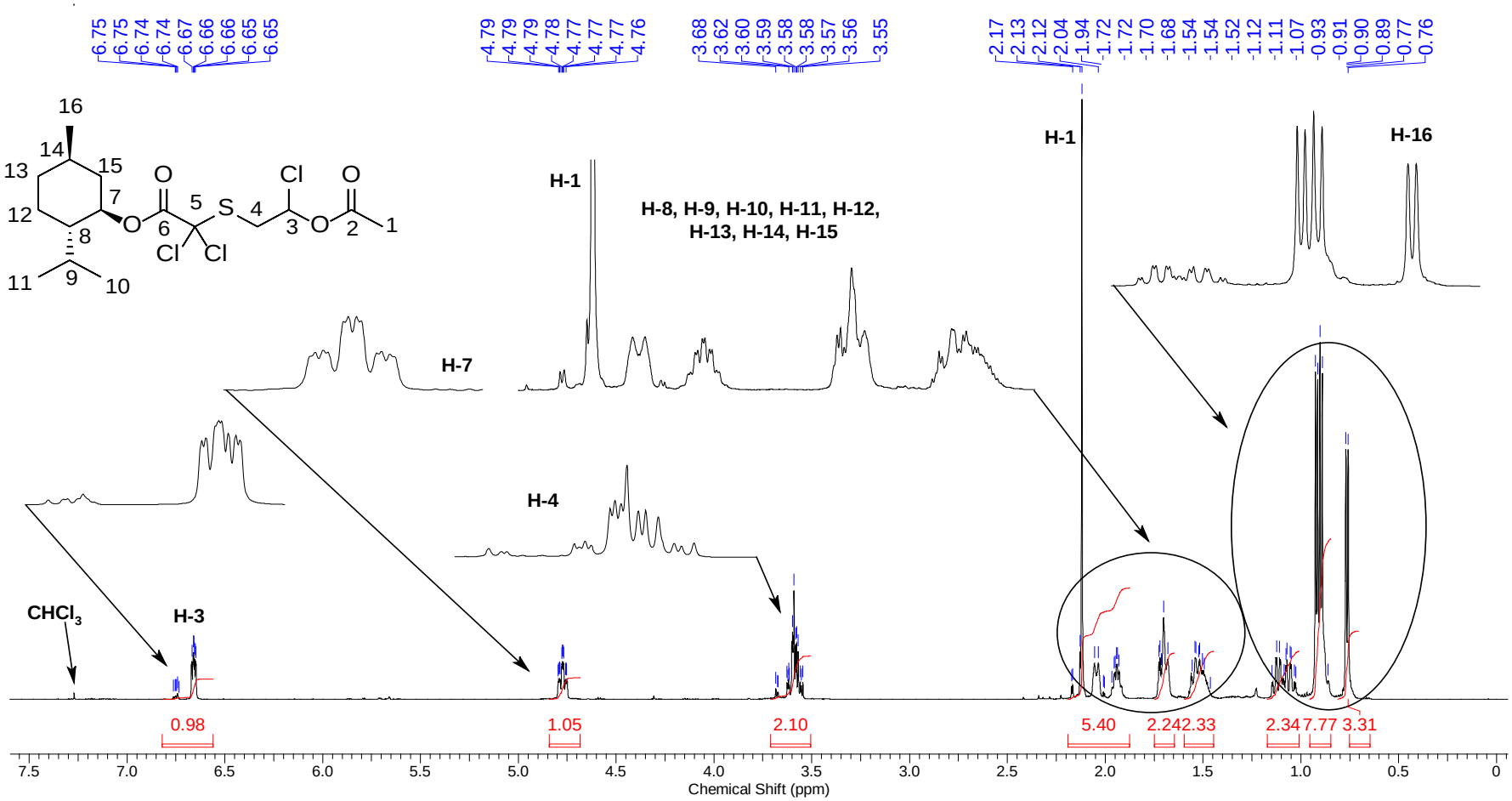
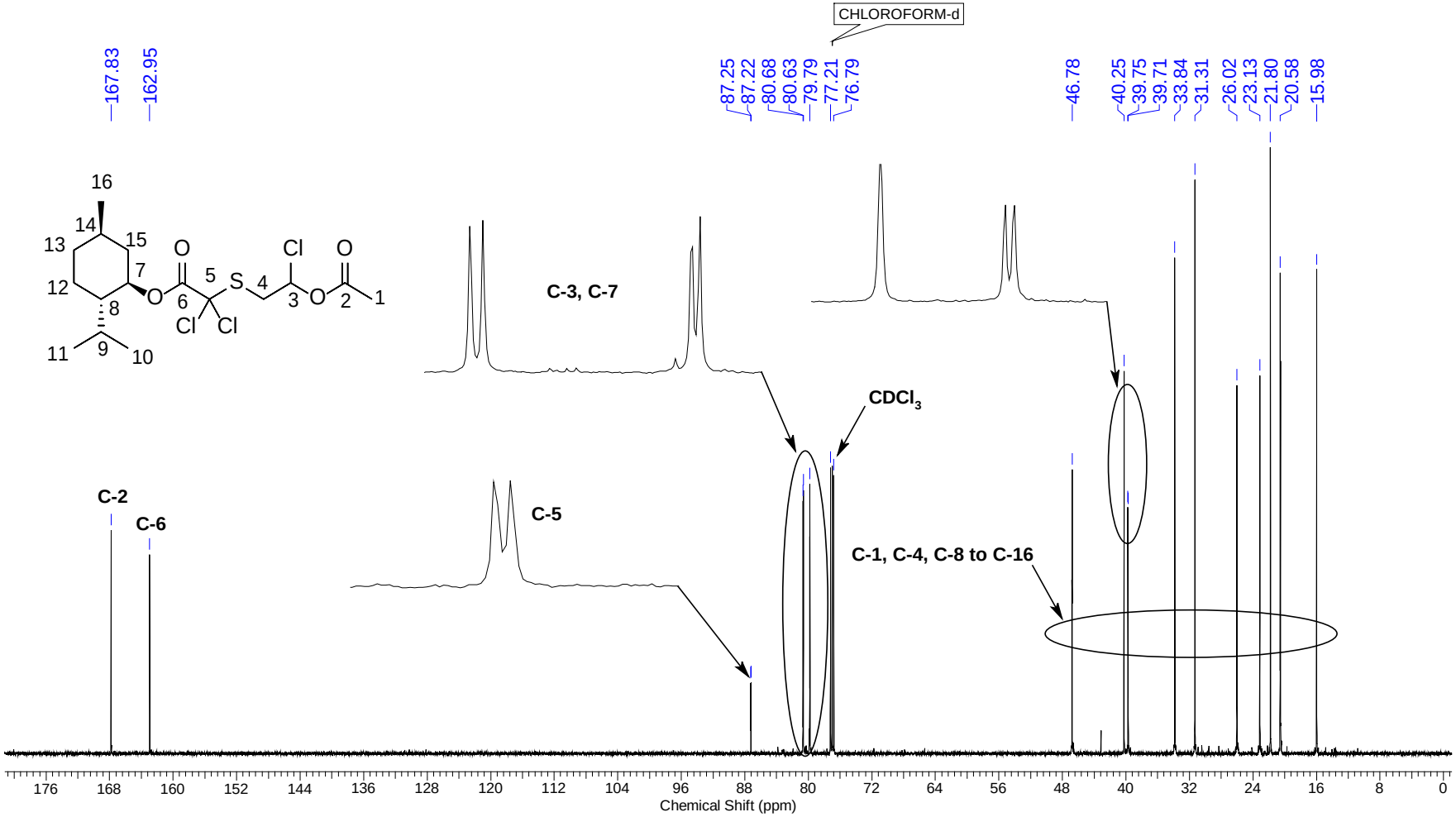


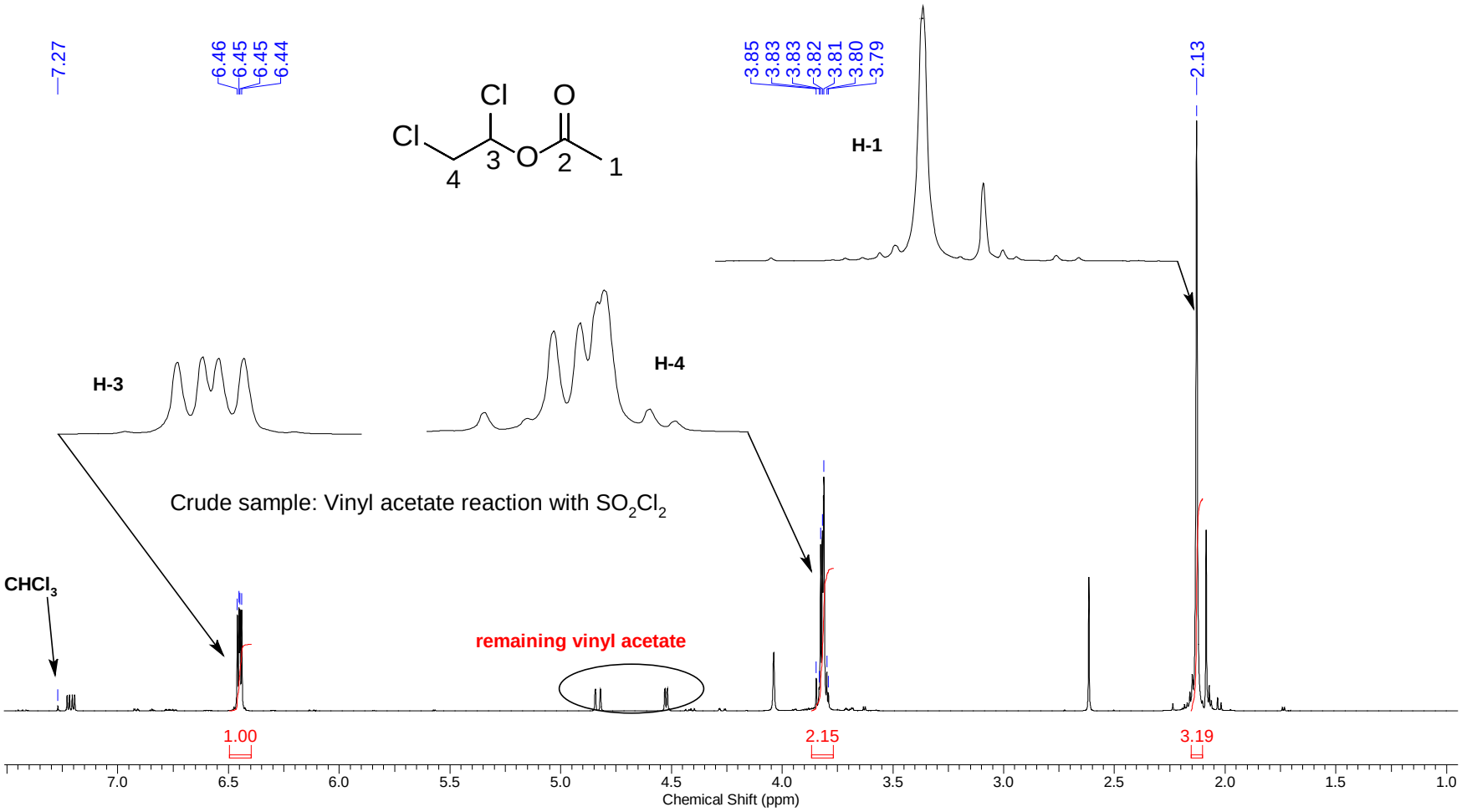
Frequency (MHz)	600.01	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	14.42	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3743.7068
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.567		



Frequency (MHz)	150.87	***Nucleus***	13C	***Number of Transients***	300	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	199.73	***SW(cyclical) (Hz)***	36231.88	***Acquisition Time (sec)***	0.9044	***Spectrum Offset (Hz)***	15081.8369
Spectrum Type	STANDARD	***Sweep Width (Hz)***	36230.78	***Temperature (degree C)***	25.253		



Frequency (MHz)	599.96	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	20.16	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3695.6599
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.091		



Frequency (MHz)	599.96	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	nmrsu	***Points Count***	65536	***Pulse Sequence***	zg30
Receiver Gain	9.89	***SW(cyclical) (Hz)***	12019.23	***Acquisition Time (sec)***	2.7263	***Spectrum Offset (Hz)***	3714.6445
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12019.05	***Temperature (degree C)***	23.228