

## Supplemental Information

### ***Photoenzymatic Generation of Unstabilized Alkyl Radicals: An Asymmetric Reductive Cyclization***

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## **Experimental Procedures**

**General.** Unless otherwise noted, all chemicals and reagents for chemical reactions were obtained from commercial suppliers and used as received (Sigma-Aldrich, Oakwood Chemical, Combi-Blocks, Chem-Impex, VWR, and Acros Chemicals). GDH-105 was purchased from Codexis as cell free lysate and used as received. Silica gel chromatography purifications were carried out using AMD Silica Gel 60. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker UltraShield 500 Plus instrument (500 and 126 MHz, respectively), and are internally referenced to residual proton signals in CDCl<sub>3</sub> (7.26 ppm). <sup>19</sup>F-NMR spectra were recorded on a Bruker 400 instrument (367 MHz). Data for <sup>1</sup>H-NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet), coupling constant (Hz), and integration. Data for <sup>13</sup>C-NMR are reported in terms of chemical shift relative to CDCl<sub>3</sub> (77.16 ppm). High-resolution mass spectra were obtained on an Agilent 6220 LC/MS with an electrospray ionization time-of-flight (ESI-TOF) detector. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm<sup>-1</sup>).

**LED Lamps.** The cyan LEDs lamps were constructed in house from Chanzon High Power 50W Cyan LED Chips (497nm / 1500mA / DC30-34V / 50W) (Amazon 1DGL-JC-50W-490) powered by Mean Well HLG-320H-C1750A power supplies (320W / 183V / 1750 mA) by wiring four LED Chips in series. Each LED chip was secured to a Nagulagu cooling aluminum LED heatsink equipped with a 12V fan (Amazon B01K1Z6VP6).

**Chromatography.** Analytical chiral gas chromatography (GC) was carried out using an Agilent 6850 Network GC System. CHIRALDEX B-DM (50 m x 0.25 mm x 0.12 μm) and γ-DEX-225 (30 m x 0.25 mm x 0.25 μm) were used to separate enantiomers. Analytical high-performance liquid chromatography (HPLC) was carried out using an Agilent 1260 Infinity LCMS System. Chiral HPLC was conducted using an Agilent 1260 Infinity Chiral HPLC system with isopropanol and hexanes as the mobile phase. Chiral AS, ID, and OJ-H columns were used to separate enantiomers (4.6 x 250 mm, 5 μm).

**Cloning.** pET22b(+) was used as a cloning and expression vector for all enzymes described in this study. Genes for all 'ene'-reductases were purchased as gBlocks from IDT and cloned using the Gibson cloning method.<sup>1</sup> All C-terminal 6xHis tagged constructs were cloned directly between the NdeI and XhoI restriction sites. N-terminal 6xHis tagged constructs were created by introduction of an N-terminal 6xHis sequence directly after the NdeI site and replacement of the C-terminal 6xHis tag with an XhoI cut site. Cloning for each construct was carried out using DH5α E. coli.

**Site Directed Mutagenesis.** Site directed mutagenesis primers were designed using the PCR protocol from Acevedo.<sup>2</sup> The PCR products were digested with DpnI, repaired using Gibson Mix<sup>TM</sup>, and were directly transformed into E. coli strain BL21(DE3). Primers used for mutagenesis are listed along with gene sequences for each protein.

**Protein Expression.** Enzymes were produced in BL21(DE3) E. coli transformed with plasmids encoding each of the 'ene'-reductase variants. Point mutants were expressed identically to *wild-type*. Transformed glycerol stocks were used to initiate a 10 mL overnight culture in LB media with 100 μg/mL ampicillin (37 °C, 250 rpm). Expression cultures (500 mL of the appropriate media in a 2 L baffled shake flask) were inoculated with 1 mL of the overnight culture, then grown according to the specifications of

each enzyme. After expression cells were harvested by centrifugation (4000 x g, 20 min, 4 °C) and frozen at -20 °C for later purification.

**Protein Purification.** Frozen cells were thawed on ice and resuspended in buffer A (see individual purification procedures for buffer components) to a final concentration of 2 mL/g of cells. The resuspended cells were supplemented with lysozyme (1mg/mL), FMN (1mg/mL), DNase (0.1 mg/mL), PMSF (1mM) and allowed to shake for 1 hour at 25 °C. The cells were further disrupted by sonication (2 x 4 min, output control 5, 35% duty cycle; Sonicator QSonica Q500 Ultra Sonicator). To pellet insoluble material, lysates were centrifuged (20,000 x g, 1.5 hours, 4 °C). Proteins were purified using a nickel-NTA column (5 mL HisTrap HP, GE Healthcare, Piscataway, NJ) using an AKTASart purifier FPLC system (GE Healthcare). Enzymes were eluted with 100 % buffer B (see individual purification procedures for buffer components) over five column volumes. Yellow fractions containing 'ene'-reductase enzymes were pooled, concentrated, and subjected to three buffer exchanges into an imidazole free storage buffer. Concentrated enzymes (1-4 mM) were aliquoted, flash frozen in liquid nitrogen, and stored at -20 °C until later use. Protein purity was assessed with SDS-PAGE.

**Determination of Protein Concentrations.** Concentrations were determined using the extinction coefficient ( $12.2 \times 10^{-3} \text{ m}^{-1}\text{cm}^{-1}$  @ 446 nm) for free FMN released after protein denaturation.<sup>3</sup>

**Recipe for Auto Inducing Media.** For autoinducing cultures Turbo Broth™ media was supplemented with a sterile filtered solution of 1.25% glucose, 5% lactose, and 15% glycerol. (40 mL/L media).

**GluER Expression and Purification.** Auto-Inducing Turbo Broth™ media (500 mL in 2 L flask) containing 100 µg/mL ampicillin was inoculated with 1 mL of the overnight culture and grown for 24 hours (30 °C, 250 rpm). After growth and expression, the cells were harvested, and the enzyme purified as described above. Buffer A: 50 mM TEOA pH 7, 25 mM imidazole. Buffer B: 50 mM TEOA pH 7, 250 mM imidazole. Storage buffer 50 mM TEOA pH 7.

**YqjM Expression and Purification.** Turbo Broth™ media (500 mL in 2 L flask) containing 100 µg/mL ampicillin was inoculated with 1 mL of the overnight culture and grown until the cells reached an OD<sub>600</sub> of 0.6-0.8 (37 °C, 250 rpm). Flasks were chilled on ice and protein expression was induced with 0.1 mM IPTG (4 hours, 30 °C, 250 rpm). The cells were harvested, and the enzyme purified as described above. Buffer A: 50 mM Tris pH 7, 25 mM imidazole. Buffer B: 50 mM Tris pH 7, 250 mM imidazole. Storage buffer: 50 mM Tris pH 7.

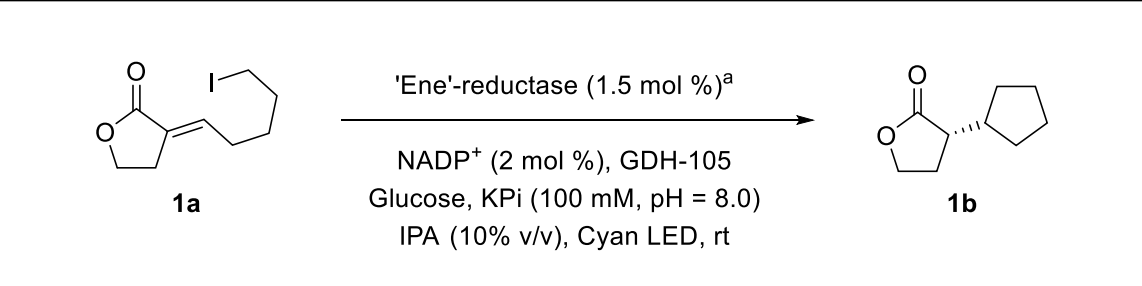
**PETNr Expression and Purification.** Auto-Inducing Turbo Broth™ media (500 mL in 2 L flask) containing 100 µg/mL ampicillin was inoculated with 1 mL of the overnight culture and grown for 24 hours (30 °C, 250 rpm). After growth and expression, the cells were harvested, and the enzyme purified as described above. Buffer A: 50 mM KPi pH 8, 300mM NaCl, 25 mM imidazole. Buffer B: 50 mM KPi pH 8, 300mM NaCl, 250 mM imidazole. Storage buffer: 50 mM KPi pH 8, 300mM NaCl.

**OPR1, NCR, OYE3, TOYE, and PAMO Expression and Purification.** Turbo Broth™ media (500 mL in 2 L flask) containing 100 µg/mL ampicillin was inoculated with 1 mL of the overnight culture and grown until the cells reached an OD<sub>600</sub> of 0.6-0.8 (37 °C, 250 rpm). Flasks were chilled on ice and protein expression was induced with 0.1 mM IPTG (24 hours, 18 °C, 250 rpm). The cells were harvested, and the enzyme purified as described above Buffer A: 20 mM KPi pH 7, 300mM NaCl, 25 mM imidazole. Buffer B: 20 mM KPi pH 7, 300mM NaCl, 250 mM imidazole. Storage buffer: 20 mM KPi pH 7, 300mM NaCl.

**OYE2 Expression and Purification.** Turbo Broth™ media (500 mL in 2 L flask) containing 100 µg/mL ampicillin was inoculated with 1 mL of the overnight culture and grown until the cells reached an OD<sub>600</sub> of 0.6-0.8 (37 °C, 250 rpm). Protein expression was induced with 0.1 mM IPTG (5 hours, 37 °C, 250 rpm). The cells were harvested, and the enzyme purified as described above. Buffer A: 20 mM KPi pH 7, 300mM NaCl, 25 mM imidazole. Buffer B: 20 mM KPi pH 7, 300mM NaCl, 250 mM imidazole. Storage buffer: 20 mM KPi pH 7, 300mM NaCl.

**MorB Expression and Purification.** Auto-Inducing Turbo Broth™ media (500 mL in 2 L flask) containing 100 µg/mL ampicillin was inoculated with 1 mL of the overnight culture and grown for 24 hours (30 °C, 250 rpm). After growth and expression, the cells were harvested, and the enzyme purified as described above. Buffer A: 20 mM KPi pH 7, 300mM NaCl, 25 mM imidazole. Buffer B: 20 mM KPi pH 7, 300mM NaCl, 250 mM imidazole. Storage buffer: 20 mM KPi pH 7, 300mM NaCl.

## Enzyme Screen

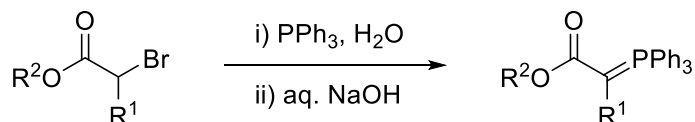
			
entry	'ene'-reductase	yield (%)	enantiomeric ratio (er)
1	GluER-Y177F	56	92:8
2	YqjM-Y169F	9	73:27
3	PETNr-Y187F	14	72:28
4	OPR1-Y192F	5	54:46
5	NCR-Y177F	25	56:44
6	OYE2-Y197F	41	14:86
7	OYE3-Y197F	15	24:76
8	TOYE-Y168F	<5	n.d.
9	MorB	79	48:52
10	PAMO	8	47:53

<sup>a</sup> **1a** (10  $\mu$ mol), 'ene'-reductase (0.15  $\mu$ mol), NADP<sup>+</sup> (0.2  $\mu$ mol) GDH-105 (1 mg/rxn), glucose (60  $\mu$ mol), KPi (100 mM, pH = 8.0, 900  $\mu$ L), iPrOH (100  $\mu$ L), 48 h, rt, anaerobic.

**Supplemental Figure 1.** 'Ene'-reductase screen of alkyl iodide reductive cyclization under ambient conditions.

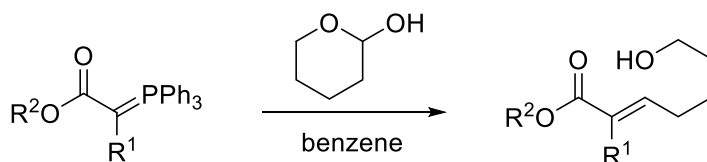
## General Synthetic Procedures

### Synthesis of stabilized Wittig reagents (General Procedure A)



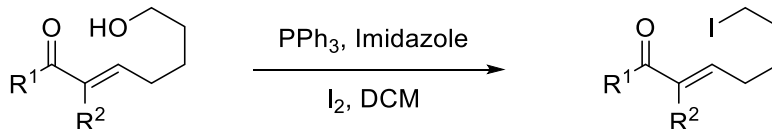
Triphenylphosphine (1 equiv.) was suspended in H<sub>2</sub>O (0.5 M) then  $\alpha$ -bromoester (1 equiv.) added dropwise. The reaction was heated to 70 °C overnight or until the solution turned homogeneous. The reaction was cooled to 0 °C. 10% NaOH solution (2 equiv.) was added dropwise, with DCM added as needed to dissolve the solid ylide product. The organic phase was separated, and the aqueous phase extracted twice more with DCM. The combined organic extracts were washed with brine and dried with Na<sub>2</sub>SO<sub>4</sub>. Excess solvent was removed *in vacuo* and hexanes added, resulting in precipitation of ylide product, which was collected by filtration, washed with additional hexanes, then dried under high vacuum.

### Wittig Reaction (General Procedure B)



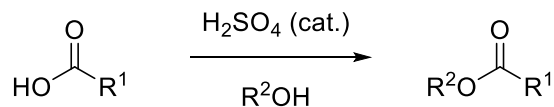
Stabilized Wittig reagent (1 equiv.) was suspended in benzene (0.25 M) and lactol (1 equiv.) was added. The reaction was stirred overnight, during which the suspension turned homogeneous. Upon completion of the reaction, solvent was removed *in vacuo*, the residue redissolved in minimal DCM, and crude product purified by flash chromatography.

### Appel Reaction (General Procedure C)



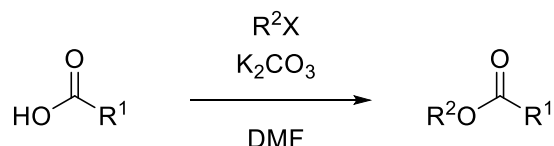
Alcohol (1 equiv.) was dissolved in DCM (0.25 M), triphenylphosphine (1.1 equiv.) and imidazole (3 equiv.) added, and the reaction cooled to 0 °C. Iodine (1.1 equiv.) was added in portions, allowing for the complete disappearance of color between each addition. After complete addition, the reaction was allowed to warm to room temperature and stirred until disappearance of starting material by TLC (approx. 3 hours). Solvent volume was minimized *in vacuo* and the residue purified directly by flash chromatography.

### Fisher Esterification (General Procedure D)



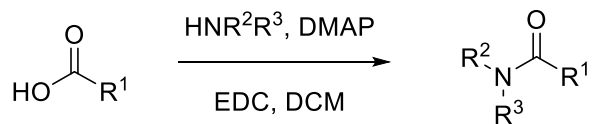
Carboxylic acid (1 equiv.) was dissolved in alcohol (0.2 M) and a couple drops conc. H<sub>2</sub>SO<sub>4</sub> added. The reaction was refluxed overnight then cooled to room temperature. The reaction was quenched with sat. NaHCO<sub>3</sub>, extracted with Et<sub>2</sub>O, washed with additional sat. NaHCO<sub>3</sub>, then brine, then dried with Na<sub>2</sub>SO<sub>4</sub>. Crude product was passed through a plug of silica, eluting with DCM, to obtain pure product.

### Basic Esterification (General Procedure E)



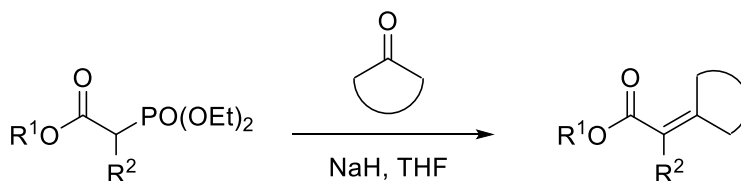
Carboxylic acid (1 equiv.) was dissolved in DMF (0.5 M), potassium carbonate added (2 equiv.), and the reaction cooled to 0 °C. Alkyl iodide or allyl bromide was then added dropwise, and the reaction stirred overnight. The reaction was quenched with water, extracted with Et<sub>2</sub>O, washed with sat. NaHCO<sub>3</sub>, brine, then dried with Na<sub>2</sub>SO<sub>4</sub> to obtain crude product. Unless noted otherwise, crude product was passed through a plug of silica, eluting with DCM, to obtain pure product.

### Amide Coupling (General Procedure F)



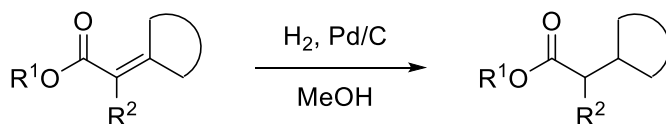
Carboxylic acid (1 equiv.), amine (see specific procedure), and 4-dimethylaminopyridine (0.1 equiv.) were dissolved in DCM (0.25M). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.3 equiv.) was added and the reaction stirred overnight. The reaction was diluted with DCM, washed twice with 1 M HCl, once with sat. NaHCO<sub>3</sub>, then brine, then dried with Na<sub>2</sub>SO<sub>4</sub>. Solvent removed *in vacuo* to obtain crude product which was used directly in the next step unless noted otherwise.

### Horner-Wadsworth-Emmons Reaction (General Procedure G)



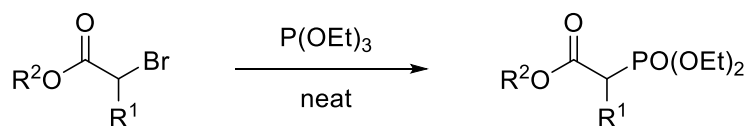
See specific procedure for reactant equivalents. Sodium hydride was suspended in THF (0.25 M) and cooled to 0 °C. Phosphonate ester was added dropwise to prevent rapid hydrogen evolution. The reaction was warmed to room temperature and stirred until hydrogen evolution ceased (approx. 30 min.). The reaction was recooled to 0 °C, ketone added, and the reaction stirred overnight. Solvent was removed in vacuo and the residue purified by flash chromatography.

#### Hydrogenation (General Procedure H)



Alkene (1 equiv.) was dissolved in MeOH (0.2 M) and 10 wt% palladium on carbon (10 wt% relative to mass of alkene; e.g. 10 mg of Pd/C to reduce 100 mg of alkene) was added. The reaction was sparged with hydrogen from a balloon and then vigorously stirred under hydrogen atmosphere until disappearance of alkene by TLC (KMnO<sub>4</sub> stain to confirm presence of saturated product). The reaction was then filtered through Celite® and crude product purified through a short plug of silica.

#### Arbuzov Reaction (General Procedure I)

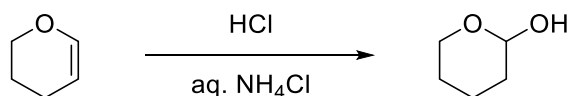


Bromoester (1 equiv.) was dissolved in triethylphosphite (1.3 equiv.) and heated to 130 °C overnight. After cooling to room temperature, the reaction was purified by flash chromatography to obtain pure phosphonate ester.

## Synthesis and Characterization of Alkyl Iodide Substrates

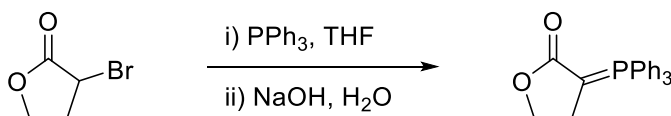
**General comments:** Olefin geometries were obtained primarily as the single isomer indicated with less than 5% of the opposite isomer. Therefore, for the majority of substrates, NMRs are reported for only this major isomer. However, the characteristic  $\beta$ -CH and  $\gamma$ -CH<sub>2</sub> peaks are sometimes still observed as trace peaks in the NMR. In cases where greater than 5% of the opposite olefin isomer is present, these peaks are reported as well, indicated as subscripts in the hydrogen count. Additionally, some amide and phosphonium ylide materials exist in solution as a mixture of interconverting rotamers, and as such, display distinct peaks for each rotamer. These peaks are also reported separately. E.g. 2H<sub>major</sub> and 2H<sub>minor</sub>, which would correspond to the same methylene on the major and minor rotamers and integrate to a total of two.

### 5-exo-substrates



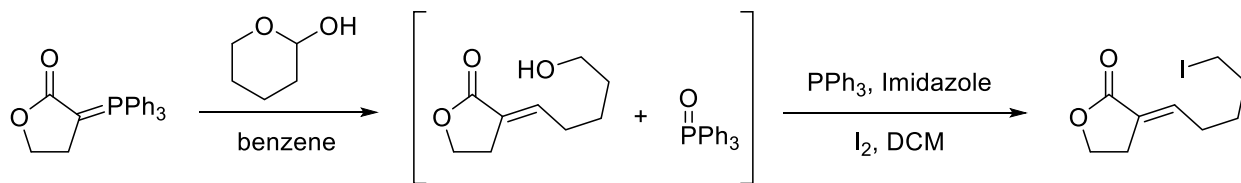
**tetrahydro-2H-pyran-2-ol:** To a rigorously stirred saturated aqueous NH<sub>4</sub>Cl solution (200 mL) was added 0.01M HCl (8 mL) followed by 3,4-dihydro-2H-pyran (18.17 mL, 200 mmol, 1 equiv.). Additional 0.01M HCl (6 mL) was added over the next hour, then the reaction was stirred overnight. The reaction was extracted with DCM, the combined organic extracts washed with brine, then dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was concentrated *in vacuo* and used without further purification (17.1 g, 84% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>):  $\delta$  4.89 (dd,  $J$  = 6.6, 3.3 Hz, 1H), 4.01 (ddt,  $J$  = 11.3, 4.1, 2.2 Hz, 1H), 3.53 (dt,  $J$  = 11.5, 5.7 Hz, 1H), 3.34 (s, 1H), 1.92-1.73 (m, 2H), 1.58-1.45 (m, 4H).



**3-(triphenylphosphoranylidene)dihydrofuran-2(3H)-one:** Triphenylphosphine (15.9 g, 60.6 mmol, 1 equiv.) was dissolved in 60 mL THF, bromolactone (10 g, 60.6 mmol, 1 equiv.) added dropwise, and the reaction heated to reflux overnight. After cooling to room temperature, water was added, followed by 500 ml of 10% NaOH solution. CHCl<sub>3</sub> was added as needed to dissolve the solid ylide product. The organic phase was separated, and the aqueous phase extracted with CHCl<sub>3</sub>. The combined organic extracts were washed with brine and dried with MgSO<sub>4</sub>. Excess solvent was removed *in vacuo* and hexanes added resulting in precipitation of ylide product, which was collected by filtration, washed with additional hexanes, then dried under high vacuum overnight. Product obtained as a reddish brown powdery solid (16.4 g, 78% yield)

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.67 – 7.56 (m, 9H), 7.53 – 7.46 (m, 6H), 4.32 (t,  $J$  = 7.8 Hz, 2H), 2.64 (t,  $J$  = 7.8 Hz, 2H).



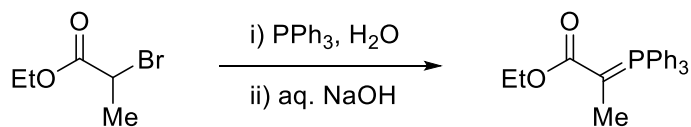
**(E)-3-(5-iodopentylidene)dihydrofuran-2(3H)-one (1a)**: 3-(triphenylphosphoranylidene)dihydrofuran-2(3H)-one (1.39 g, 4 mmol, 1 equiv.) was suspended in benzene (0.25 M) and tetrahydro-2H-pyran-2-ol (409 mg, 4 mmol, 1 equiv.) added. Reaction was heated to reflux for 2 hrs. After cooling to room temperature, solvent was removed *in vacuo*, the residue redissolved in minimal DCM, and purified by flash chromatography. Alcohol product and triphenylphosphine oxide coeluted. This mixture was taken forward assuming complete conversion. The alcohol/phosphine oxide mixture was redissolved in DCM (0.25 M), triphenylphosphine (1.15g, 4.4 mmol, 1.1 equiv.) and imidazole (1.09g, 16 mmol, 4 equiv.) added, and the reaction cooled to 0 °C. Iodine (1.11g, 4.4 mmol, 1.1 equiv.) was added in portions, allowing for the complete disappearance of color between each addition. The reaction was then allowed to warm to room temperature and stirred until disappearance of starting material by TLC (approx. 3 hours). Solvent volume was minimized *in vacuo* and the residue purified directly by flash chromatography to obtain product as a clear oil which turned solid white upon cooling (820 mg, 73% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.73 (tt,  $J$  = 7.6, 2.9 Hz, 1H), 4.39 (t,  $J$  = 7.5 Hz, 2H), 3.19 (t,  $J$  = 6.9 Hz, 2H), 2.87 (dddd,  $J$  = 9.2, 7.2, 3.3, 1.8 Hz, 2H), 2.22 (qt,  $J$  = 7.5, 1.8 Hz, 2H), 1.86 (p,  $J$  = 7.0 Hz, 2H), 1.67 – 1.57 (m, 2H).

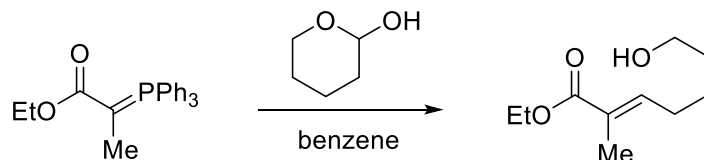
$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  171.2, 139.8, 126.0, 65.5, 32.9, 29.2, 29.1, 25.2, 6.1.

$\text{IR}(\text{cm}^{-1})$ : 2980.5, 2924.5, 2856.1, 1746.0, 1677.2, 1195.3, 1023.7, 960.0, 715.1.

$\text{HRMS}$ : Calc'd for  $[(\text{C}_9\text{H}_{13}\text{IO}_2)+\text{H}]^+$ : 281.00330, found 281.0035

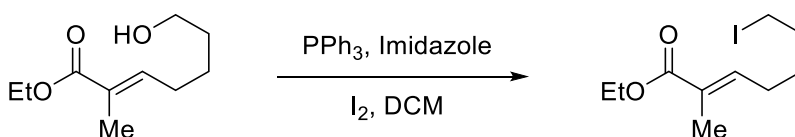


**ethyl 2-(triphenylphosphoranylidene)propanoate**: Synthesized from ethyl 2-bromopropanoate (35 mmol) according to general procedure A. Product obtained as powdery, light yellow crystals (11.2 g, 88% yield).  $^1\text{H NMR}$  data was consistent with the literature.<sup>4</sup>



**ethyl (E)-7-hydroxy-2-methylhept-2-enoate:** Synthesized from ethyl 2-(triphenylphosphoranylidene)propanoate (12 mmol) according to general procedure B. Product obtained as a clear oil (1.87g, 84% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.75 (tq,  $J = 7.5, 1.5$  Hz, 1H), 4.18 (q,  $J = 7.1$  Hz, 2H), 3.66 (t,  $J = 6.3$  Hz, 2H), 2.25 – 2.17 (m, 2H), 1.83 (q,  $J = 1.1$  Hz, 3H), 1.65 – 1.47 (m, 4H), 1.29 (t,  $J = 7.1$  Hz, 3H).



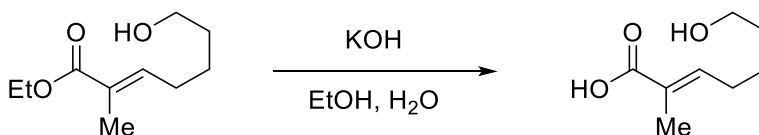
**ethyl (E)-7-iodo-2-methylhept-2-enoate (2a):** Synthesized from ethyl (E)-7-hydroxy-2-methylhept-2-enoate (2 mmol) according to general procedure C. Product obtained as a clear oil (566 mg, 96% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.73 (tq,  $J = 7.5, 1.5$  Hz, 1H), 4.19 (q,  $J = 7.1$  Hz, 2H), 3.19 (t,  $J = 6.9$  Hz, 2H), 2.27 – 2.13 (m, 2H), 1.94 – 1.77 (m, 5H), 1.59 – 1.50 (m, 2H), 1.30 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  168.3, 141.2, 128.6, 60.6, 33.1, 29.6, 27.7, 14.4, 12.6, 6.5.

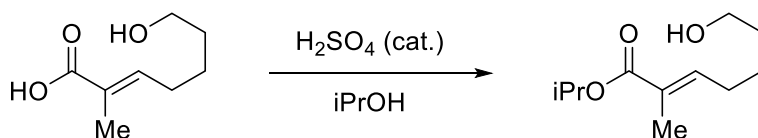
IR ( $\text{cm}^{-1}$ ): 2978.3, 2931.0, 2859.2, 1703.4, 1648.7, 1260.9, 1099.7, 743.7

HRMS: Calc'd for  $[(\text{C}_{10}\text{H}_{18}\text{IO}_2)+\text{H}]^+$ : 297.03460, found 297.0343



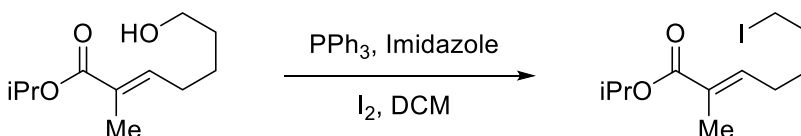
**(E)-7-hydroxy-2-methylhept-2-enoic acid:** Ethyl (E)-7-hydroxy-2-methylhept-2-enoate (1.12g, 6 mmol, 1 equiv.) was dissolved in 30 mL EtOH. KOH (1.35g, 24 mmol, 4 equiv.) dissolved in 30 mL  $\text{H}_2\text{O}$  was added and the mixture heated to 80 °C overnight. After cooling to room temperature, EtOH was removed *in vacuo*, and the resulting aqueous solution acidified with 2 M HCl. The mixture was extracted with  $\text{Et}_2\text{O}$ , the combined organic extracts washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Crude product was purified by flash chromatography to give pure acid as a viscous clear oil which crystallized upon cooling (920 mg, 97% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.90 (tq,  $J = 7.6, 1.5$  Hz, 1H), 3.67 (t,  $J = 6.3$  Hz, 2H), 2.25 (q,  $J = 7.2$  Hz, 2H), 1.84 (s, 3H), 1.66 – 1.50 (m, 4H).



**isopropyl (E)-7-hydroxy-2-methylhept-2-enoate:** Synthesized from (E)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol) following general procedure D. Product obtained as a clear oil (305 mg, 76% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.72 (tq, *J* = 7.5, 1.6 Hz, 1H), 5.05 (hept, *J* = 6.3 Hz, 1H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.20 (q, *J* = 7.3 Hz, 2H), 1.82 (s, 3H), 1.66 – 1.48 (m, 4H), 1.26 (d, *J* = 6.3 Hz, 6H).



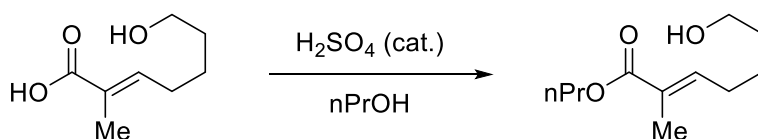
**isopropyl (E)-7-iodo-2-methylhept-2-enoate (3a):** Synthesized from isopropyl (E)-7-hydroxy-2-methylhept-2-enoate (240 mg, 1.2 mmol) according to general procedure C. Product obtained as a clear oil (372 mg, 77% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.70 (tq, *J* = 7.5, 1.5 Hz, 1H), 5.05 (hept, *J* = 6.3 Hz, 1H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.24 – 2.14 (m, 2H), 1.91 – 1.79 (m, 5H), 1.59 – 1.54 (m, 2H), 1.27 (d, *J* = 6.2 Hz, 6H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 167.8, 140.9, 128.9, 77.4, 77.2, 76.9, 67.8, 33.2, 29.6, 27.7, 22.1, 12.6, 6.6.

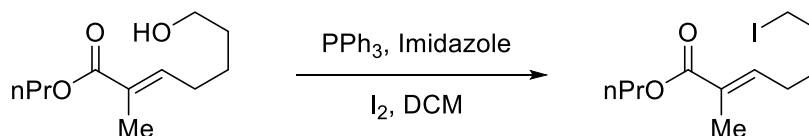
IR (cm<sup>-1</sup>): 2977.5, 2932.6, 2860.1, 1701.4, 1262.1, 1099.5, 744.2

HRMS: Calc'd for ([C<sub>11</sub>H<sub>19</sub>I O<sub>2</sub>]+H)<sup>+</sup>: 311.05025, found 311.0496



**propyl (E)-7-hydroxy-2-methylhept-2-enoate:** Synthesized from (E)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol) following general procedure D. Product obtained as a clear oil (300 mg, 75% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.75 (tq, *J* = 7.6, 1.5 Hz, 1H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.21 (q, *J* = 7.4 Hz, 2H), 1.83 (s, 3H), 1.69 (h, *J* = 7.2 Hz, 2H), 1.64 – 1.48 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H).



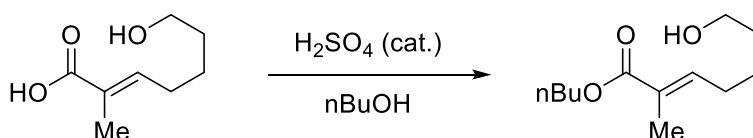
**propyl (E)-7-iodo-2-methylhept-2-enoate (4a)**: Synthesized from propyl (E)-7-hydroxy-2-methylhept-2-enoate (225 mg, 1.12 mmol) according to general procedure C. Product obtained as a clear oil (297 mg, 85% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.73 (tq,  $J = 7.4, 1.5$  Hz, 1H), 4.09 (t,  $J = 6.7$  Hz, 2H), 3.19 (t,  $J = 6.9$  Hz, 2H), 2.20 (q,  $J = 7.5$  Hz, 2H), 1.93 – 1.80 (m, 5H), 1.69 (h,  $J = 7.2$  Hz, 2H), 1.62 – 1.50 (m, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  168.3, 141.2, 128.6, 66.3, 33.2, 29.6, 27.7, 22.2, 12.6, 10.7, 6.5.

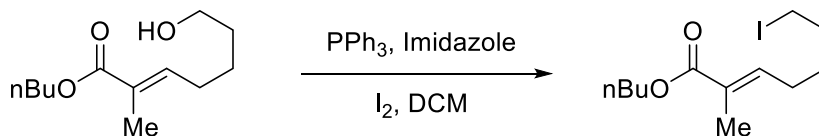
$\text{IR}$  ( $\text{cm}^{-1}$ ): 2963.4, 2933.8, 2877.1, 1704.8, 1648.7, 1456.0, 1261.3, 1101.6, 742.9

$\text{HRMS}$ : Calc'd for  $([\text{C}_{11}\text{H}_{19}\text{O}_2+\text{H}]^+)$ : 311.05025, found 311.0495



**butyl (E)-7-hydroxy-2-methylhept-2-enoate**: Synthesized from (E)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol) following general procedure D. Product obtained as a clear oil (236 mg, 55% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.75 (t,  $J = 7.7$  Hz, 1H), 4.13 (t,  $J = 6.7$  Hz, 2H), 3.66 (t,  $J = 6.4$  Hz, 2H), 2.21 (q,  $J = 7.4$  Hz, 2H), 1.83 (s, 2H), 1.64 – 1.52 (m, 7H), 1.41 (h,  $J = 7.6$  Hz, 2H), 0.95 (t,  $J = 7.5$  Hz, 3H).



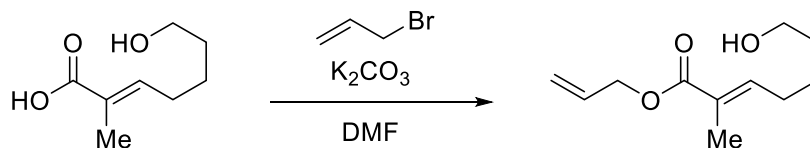
**butyl (E)-7-iodo-2-methylhept-2-enoate (5a)**: Synthesized from butyl (E)-7-hydroxy-2-methylhept-2-enoate (200 mg, 0.93 mmol) according to general procedure C. Product obtained as a clear oil (256 mg, 85% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.72 (td,  $J = 7.3, 1.6$  Hz, 1H), 4.13 (t,  $J = 6.6$  Hz, 2H), 3.19 (t,  $J = 6.9$  Hz, 2H), 2.20 (q,  $J = 7.5$  Hz, 2H), 1.92 – 1.81 (m, 5H), 1.70 – 1.60 (m, 2H), 1.62 – 1.53 (m, 2H), 1.47 – 1.35 (m, 2H), 0.95 (t,  $J = 7.3$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  168.3, 141.2, 128.6, 64.6, 33.1, 30.9, 29.6, 27.7, 19.4, 13.9, 12.6, 6.6.

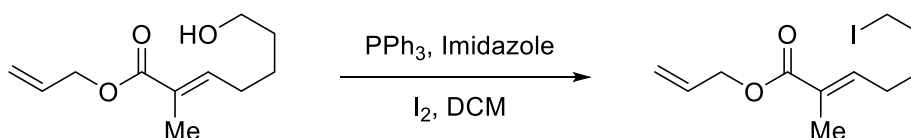
$\text{IR}$  ( $\text{cm}^{-1}$ ): 2956.0, 2930.9, 2870.6, 1705.0, 1260.0, 1102.0, 742.4

$\text{HRMS}$ : Calc'd for  $([\text{C}_{12}\text{H}_{22}\text{O}_2+\text{H}]^+)$ : 325.06590, found 325.0653



**allyl (E)-7-hydroxy-2-methylhept-2-enoate:** Synthesized from (E)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol) according to general procedure E. Product obtained as a clear oil (311 mg, 78% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.80 (ddt, *J* = 7.5, 6.0, 1.5 Hz, 1H), 6.02 – 5.90 (m, 1H), 5.33 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.64 (dt, *J* = 5.4, 1.5 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.22 (q, *J* = 7.3 Hz, 2H), 1.85 (s, 3H), 1.66 – 1.56 (m, 2H), 1.60 – 1.48 (m, 2H).



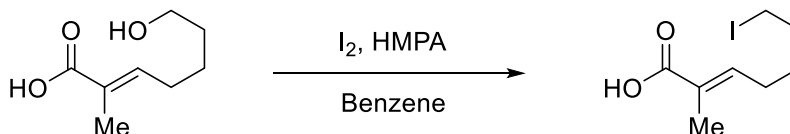
**allyl (E)-7-iodo-2-methylhept-2-enoate (6a):** Synthesized from allyl (E)-7-hydroxy-2-methylhept-2-enoate (250 mg, 1.26 mmol) according to general procedure C. Product obtained as a clear oil (357 mg, 92% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.77 (tq, *J* = 7.4, 1.5 Hz, 1H), 5.96 (ddt, *J* = 17.4, 10.9, 5.6 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.64 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.19 (t, *J* = 6.9 Hz, 2H), 2.25 – 2.16 (m, 2H), 1.94 – 1.80 (m, 5H), 1.58 (dt, *J* = 10.2, 6.6 Hz, 2H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 167.8, 141.8, 132.7, 128.3, 118.0, 65.3, 33.1, 29.6, 27.7, 12.6, 6.4.

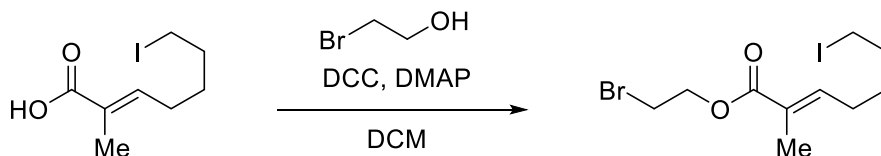
IR (cm<sup>-1</sup>): 2930.0, 2858.8, 1706.7, 1647.3, 1260.0, 1207.7, 1103.0, 988.7, 927.4, 742.3.

HRMS: Calc'd for ([C<sub>11</sub>H<sub>17</sub>I<sub>2</sub>O<sub>2</sub>]+H)<sup>+</sup>: 309.03460, found 309.0344



**(E)-7-iodo-2-methylhept-2-enoic acid:** Procedure adapted from (reference). Triphenylphosphine (629 mg, 2.4 mmol, 1.2 equiv.) and hexamethylphosphoramide (835 μL, 4.8 mmol, 2.4 equiv.) were dissolved in 8 mL benzene and cooled to 0 °C. Iodine (609 mg, 2.4 mmol, 1.2 equiv.) was added in four portions and stirred for 30 min. (E)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol, 1 equiv.) in 1 mL benzene was added dropwise and the reaction stirred overnight. Solvent was removed and the residue purified by flash chromatography to obtain pure product (333 mg, 62% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.89 (tq, *J* = 7.4, 1.5 Hz, 1H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.24 (q, *J* = 7.4 Hz, 2H), 1.96 – 1.78 (m, 5H), 1.64 – 1.48 (m, 2H).



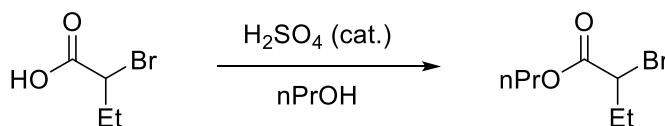
**2-bromoethyl (E)-7-iodo-2-methylhept-2-enoate (7a):** (E)-7-iodo-2-methylhept-2-enoic acid (100 mg, 0.37 mmol, 1 equiv.), 2-bromoethanol (29  $\mu$ L, 0.41 mmol, 1.1 equiv.), and 4-dimethylaminopyridine (5 mg, 0.04 mmol, 0.1 equiv.) were dissolved in 2 mL dichloromethane. N,N'-Dicyclohexylcarbodiimide (93 mg, 0.45 mmol, 1.2 equiv.) was added and the reaction stirred overnight. Precipitated urea biproduct was filtered off and crude product purified by flash chromatography. Product obtained as a pale-yellow oil (120 mg, 86% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.80 (tq,  $J = 7.6, 1.5$  Hz, 1H), 4.44 (t,  $J = 6.2$  Hz, 2H), 3.56 (t,  $J = 6.1$  Hz, 2H), 3.20 (t,  $J = 6.9$  Hz, 2H), 2.26 – 2.18 (m, 2H), 1.95 – 1.81 (m, 5H), 1.63 – 1.53 (m, 2H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  167.6, 142.6, 127.9, 64.0, 33.1, 29.5, 29.1, 27.8, 12.5, 6.4.

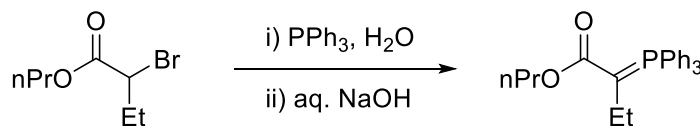
IR ( $\text{cm}^{-1}$ ): 2928.7, 2856.9, 1707.8, 1647.1, 1425.5, 1376.1, 1258.8, 1207.0, 1101.3, 740.6.

HRMS: Calc'd for  $([\text{C}_{10}\text{H}_{17}\text{BrIO}_2] + \text{H})^+$ : 374.94511, found 374.9442



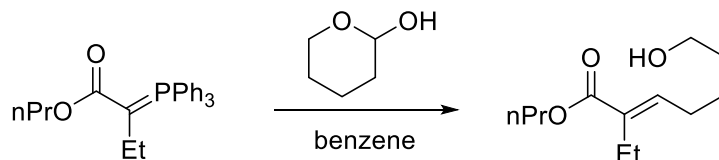
**propyl 2-bromobutanoate:** Synthesized from 2-bromobutanoic acid (3.34g, 20 mmol) following general procedure D. Product obtained as a clear oil (3.11 g, 74% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.25 – 4.06 (m, 3H), 2.06 (ddq,  $J = 44.2, 14.5, 7.3$  Hz, 2H), 1.70 (p,  $J = 7.1$  Hz, 2H), 1.03 (t,  $J = 7.3$  Hz, 3H), 0.97 (t,  $J = 7.4$  Hz, 3H).



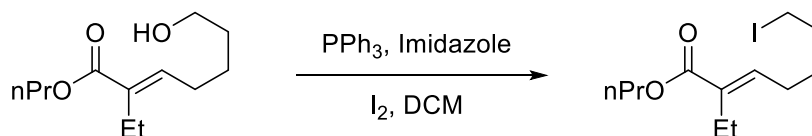
**propyl 2-(triphenylphosphoranylidene)butanoate:** Synthesized from propyl 2-bromobutanoate (1.05 g, 5 mmol) according to general procedure A. Product obtained as powdery, light yellow crystals (1.6 g, 82% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.66 – 7.58 (m, 6H), 7.56 – 7.49 (m, 3H), 7.48 – 7.40 (m, 6H), 3.96 (t,  $J = 6.6$  Hz, 2H<sub>minor</sub>), 3.61 (t,  $J = 6.6$  Hz, 2H<sub>major</sub>), 1.95 (ddq,  $J = 26.4, 19.7, 7.0$  Hz, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H<sub>minor</sub>), 0.90 – 0.75 (m, 5H), 0.29 (t,  $J = 7.4$  Hz, 3H<sub>major</sub>).



**propyl (E)-2-ethyl-7-hydroxyhept-2-enoate:** Synthesized from propyl 2-(triphenylphosphoranylidene)butanoate (1.6 g, 4.1 mmol) according to general procedure B. Product obtained as a clear oil (518 mg, 59% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 6.71 (t, *J* = 7.5 Hz, 1H), 4.09 (t, *J* = 6.7 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 2.22 (q, *J* = 7.4 Hz, 2H), 1.69 (h, *J* = 7.4 Hz, 2H), 1.64 – 1.57 (m, 2H), 1.57 – 1.49 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).



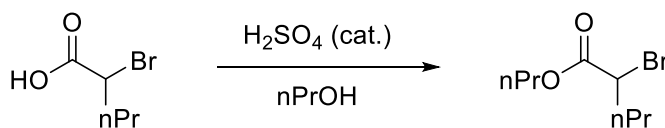
**propyl (E)-2-ethyl-7-iodohept-2-enoate (8a):** Synthesized from propyl (E)-2-ethyl-7-hydroxyhept-2-enoate (415 mg, 1.9 mmol) according to general procedure C. Product obtained as a clear oil (567 mg, 90% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 6.68 (t, *J* = 7.5 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* = 6.7 Hz, 2H), 2.31 (q, *J* = 7.4 Hz, 2H), 2.21 (q, *J* = 7.4 Hz, 2H), 1.86 (p, *J* = 6.9 Hz, 2H), 1.69 (h, *J* = 7.1, 6.7 Hz, 2H), 1.57 (q, *J* = 8.0, 7.5 Hz, 2H), 0.99 (dt, *J* = 18.3, 7.4 Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 168.0, 140.8, 134.8, 66.2, 33.2, 29.9, 27.3, 22.2, 20.2, 14.1, 10.7, 6.5.

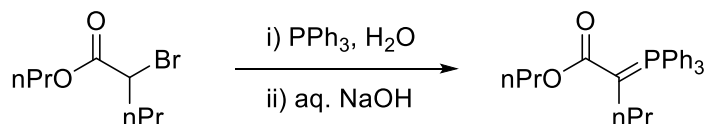
**IR** (cm<sup>-1</sup>): 2964.3, 2933.8, 2975.3, 1704.3, 1644.4, 1456.5, 1288.6, 1234.3, 1207.6, 1107.6, 755.5.

**HRMS:** Calc'd for ([C<sub>12</sub>H<sub>21</sub>I O<sub>2</sub>]+H)<sup>+</sup>: 325.06590, found 325.0654



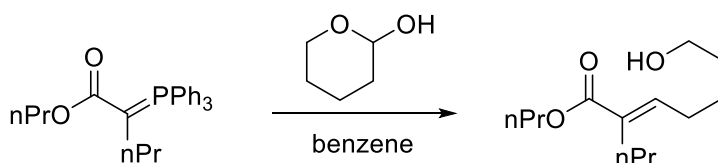
**propyl 2-bromopentanoate:** Synthesized from 2-bromopentanoic acid (3.62g, 20 mmol) following general procedure D. Product obtained as a clear oil (3.88 g, 87% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.23 (dd, *J* = 7.9, 6.9 Hz, 1H), 4.19 – 4.07 (m, 2H), 2.10 – 1.91 (m, 2H), 1.69 (dtd, *J* = 14.1, 7.4, 6.6 Hz, 2H), 1.57 – 1.32 (m, 2H), 0.96 (dt, *J* = 8.9, 7.4 Hz, 6H).



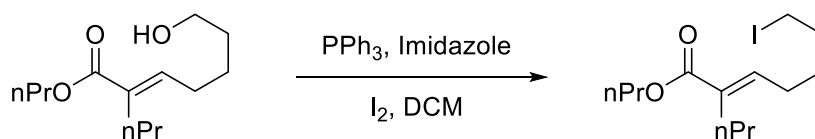
**propyl 2-(triphenylphosphoranylidene)pentanoate:** Synthesized from propyl 2-bromopentanoate (2.23 g, 10 mmol) according to general procedure A. Product obtained as powdery, light yellow crystals (3.07 g, 76% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.65 – 7.58 (m, 6H), 7.56 – 7.49 (m, 3H), 7.48 – 7.41 (m, 6H), 3.95 (t, *J* = 6.7 Hz, 2H<sub>minor</sub>), 3.60 (t, *J* = 6.6 Hz, 2H<sub>major</sub>), 1.92 – 1.79 (m, 2H), 1.32 – 1.21 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H<sub>minor</sub>), 0.79 (h, *J* = 7.0 Hz, 2H), 0.64 (td, *J* = 7.3, 2.3 Hz, 3H), 0.29 (t, *J* = 7.4 Hz, 3H<sub>major</sub>).



**propyl (E)-2-propyl-7-hydroxyhept-2-enoate:** Synthesized from propyl 2-(triphenylphosphoranylidene)pentanoate (1.12 g, 3 mmol) according to general procedure B with modification that the reaction was refluxed. Product obtained as a clear oil (490 mg, 71% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.74 (t, *J* = 7.5 Hz, 1H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.30 – 2.17 (m, 4H), 1.74 – 1.64 (m, 2H), 1.64 – 1.57 (m, 2H), 1.57 – 1.48 (m, 2H), 1.47 – 1.36 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).



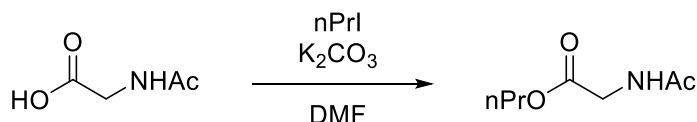
**propyl (E)-2-propyl-7-iodohept-2-enoate (9a):** Synthesized from propyl (E)-2-propyl-7-hydroxyhept-2-enoate (200 mg, 0.88 mmol) according to general procedure C. Product obtained as a clear oil (221 mg, 75% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.72 (t, *J* = 7.5 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.30 – 2.23 (m, 2H), 2.21 (q, *J* = 7.5 Hz, 2H), 1.86 (dt, *J* = 14.7, 7.1 Hz, 2H), 1.69 (hept, *J* = 6.9 Hz, 2H), 1.60 – 1.50 (m, 2H), 1.47 – 1.36 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 168.2, 141.4, 133.2, 66.2, 33.2, 29.9, 28.9, 27.6, 22.7, 22.2, 14.2, 10.7, 6.5.

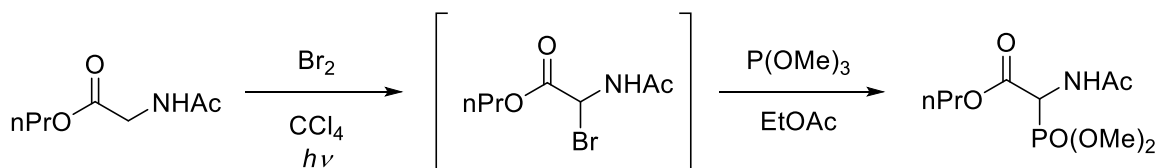
IR (cm<sup>-1</sup>): 2958.9, 2931.2, 2870.9, 1705.0, 1643.3, 1456.2, 1269.5, 1207.2, 1111.8, 746.1.

HRMS: Calc'd for ([C<sub>13</sub>H<sub>23</sub>I<sub>2</sub>O<sub>2</sub>]+H)<sup>+</sup>: 339.08155, found 339.0811



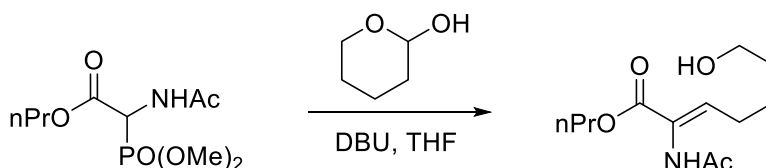
**propyl acetylglycinate:** Synthesized from *N*-acetylglycine (20 mmol) according to general procedure E. Product obtained as a clear viscous oil (2.83 g, 89% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.02 (s, 1H), 4.12 (t,  $J = 6.7$  Hz, 2H), 4.04 (d,  $J = 5.0$  Hz, 2H), 2.05 (s, 3H), 1.67 (q,  $J = 7.3$  Hz, 2H), 0.94 (t,  $J = 7.4$  Hz, 3H).



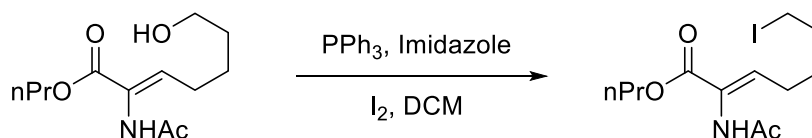
**propyl 2-acetamido-2-(dimethoxyphosphoryl)acetate:** Propyl acetylglycinate (1.91 g, 12 mmol, 1 equiv.) was dissolved in 24 mL carbon tetrachloride and the solution sparged with nitrogen. Bromine (0.62 mL, 12 mmol, 1 equiv.) was added, and the reaction irradiated with a 390 nm Kessil LED for 6 hours. Solvent was removed to obtain crude propyl 2-acetamido-2-bromoacetate which was redissolved in 24 mL ethyl acetate, trimethyl phosphite (1.42 mL, 12 mmol, 1 equiv.) added, and stirred overnight. Solvent was removed and the residue purified by flash chromatography to obtain pure product (1.2 g, 37% yield)

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.39 (d,  $J = 9.1$  Hz, 1H), 5.34 – 5.13 (m, 1H), 4.26 – 4.13 (m, 2H), 3.82 (dd,  $J = 11.1, 8.9$  Hz, 6H), 2.08 (d,  $J = 0.9$  Hz, 3H), 1.71 (h,  $J = 7.2$  Hz, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H).



**propyl (Z)-2-acetamido-7-hydroxyhept-2-enoate:** Propyl 2-acetamido-2-(dimethoxyphosphoryl)acetate (600 mg, 2.25 mmol, 1 equiv.) was dissolved in 9 mL THF and the solution cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.34 mL, 2.25 mmol, 1 equiv.) was added, then lactol (252 mg, 2.47 mmol, 1.1 equiv.), and the reaction stirred overnight. The reaction was quenched with sat.  $\text{NH}_4\text{Cl}$ , extracted with DCM, and dried with  $\text{Na}_2\text{SO}_4$ . Crude product was purified by flash chromatography to obtain pure product (350 mg, 64% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.98 (s, 1H), 6.66 (t,  $J = 7.4$  Hz, 1H), 4.12 (t,  $J = 6.6$  Hz, 2H), 3.66 (t,  $J = 6.0$  Hz, 2H), 2.19 (q,  $J = 7.3$  Hz, 2H), 2.12 (s, 3H), 1.76 – 1.51 (m, 6H), 0.96 (t,  $J = 7.4$  Hz, 3H).



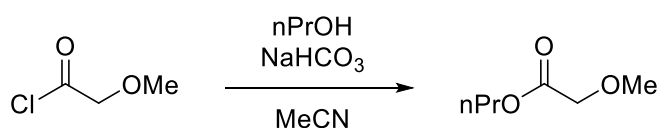
**propyl (Z)-2-acetamido-7-iodohept-2-enoate (10a):** Synthesized from propyl (Z)-2-acetamido-7-hydroxyhept-2-enoate (243 mg, 1 mmol) according to general procedure C. Product obtained as a clear oil (285 mg, 81% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.86 (s, 1H), 6.65 (t,  $J = 7.2$  Hz, 1H), 4.13 (t,  $J = 6.7$  Hz, 2H), 3.19 (t,  $J = 6.9$  Hz, 2H), 2.18 (q,  $J = 7.4$  Hz, 2H), 2.13 (s, 3H), 1.85 (p,  $J = 7.0$  Hz, 2H), 1.70 (h,  $J = 7.2$  Hz, 2H), 1.59 (dd,  $J = 8.8, 6.1$  Hz, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  168.2, 164.7, 137.1, 125.1, 67.2, 33.1, 29.1, 28.1, 23.7, 22.0, 10.5, 6.5.

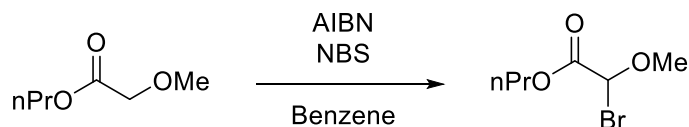
$\text{IR}$  ( $\text{cm}^{-1}$ ): 3260.2, 2966.5, 2934.4, 1714.0, 1651.7, 1516.4, 1234.2, 1160.3, 696.4, 590.2.

$\text{HRMS}$ : Calc'd for  $([\text{C}_{12}\text{H}_{20}\text{INO}_3 + \text{H}]^+)$ : 354.05606, found 354.0557



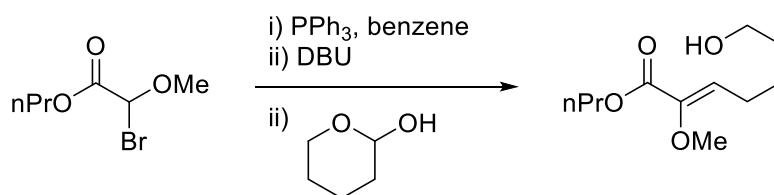
**propyl 2-methoxyacetate:** Sodium bicarbonate (1.68 g, 20 mmol, 2 equiv.) was suspended in 20 mL acetonitrile, propanol (748  $\mu\text{L}$ , 10 mmol, 1 equiv.) added, and the reaction cooled to 0  $^\circ\text{C}$ . 2-Methoxyacetyl chloride (912  $\mu\text{L}$ , 10 mmol, 1 equiv.) was added dropwise and the reaction stirred overnight. The reaction was quenched with water, extracted with  $\text{Et}_2\text{O}$ , washed with sat.  $\text{NaHCO}_3$ , brine, then dried with  $\text{Na}_2\text{SO}_4$  to obtain crude product which was used directly in the next step (1.23 g, 93% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.13 (t,  $J = 6.8$  Hz, 2H), 4.04 (s, 2H), 3.45 (s, 3H), 1.68 (h,  $J = 7.2$  Hz, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H).



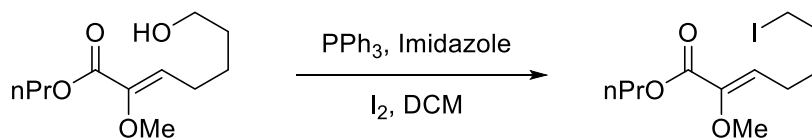
**propyl 2-bromo-2-methoxyacetate:** Propyl 2-methoxyacetate (1.23 g, 9.31 mmol, 1 equiv.), *N*-bromosuccinimide (1.66 g, 9.31 mmol, 1 equiv.), and azobisisobutyronitrile (8 mg, 47  $\mu\text{mol}$ , 0.005 equiv.) were dissolved in 12 mL nitrogen-sparged benzene and refluxed for 2.5 hours. The reaction was cooled to 0  $^\circ\text{C}$  and hexanes added to fully precipitate succinimide byproduct which was filtered off. Solvent was removed *in vacuo* to obtain crude product which was used directly.

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.01 (s, 1H), 4.22 (td,  $J = 6.7, 1.8$  Hz, 2H), 3.59 (s, 3H), 1.74 (h,  $J = 7.4$  Hz, 2H), 0.98 (t,  $J = 7.4$  Hz, 3H).



**propyl (Z)-7-hydroxy-2-methoxyhept-2-enoate:** Triphenylphosphine (1.05 g, 4 mmol, 1 equiv.) was dissolved in 12 mL benzene and cooled to 0 °C. Propyl 2-bromo-2-methoxyacetate (844 mg, 4 mmol, 1 equiv.) in 4 mL benzene was added dropwise over 1 hour resulting in the formation of a white precipitate. Stirring was continued overnight as the reaction warmed to room temperature. The reaction was and recooled to 0 °C and diazabicyclo[5.4.0]undec-7-ene (597  $\mu$ L, 4 mmol, 1 equiv.) added dropwise. The reaction was warmed to room temperature and stirred for 1 hour then lactol (408 mg, 4 mmol, 1 equiv.) was added and the reaction stirred for 1 day. Excess solvent was removed *in vacuo*, the residue taken up in DCM, and crude product purified by flash chromatography (330 mg, 38% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.24 (t,  $J = 7.7$  Hz, 1H), 4.13 (t,  $J = 6.7$  Hz, 2H), 3.69 – 3.63 (m, 5H), 2.27 (q,  $J = 7.5$  Hz, 2H), 1.71 (h,  $J = 7.3$  Hz, 2H), 1.57 – 1.45 (m, 4H), 0.97 (t,  $J = 7.4$  Hz, 3H).



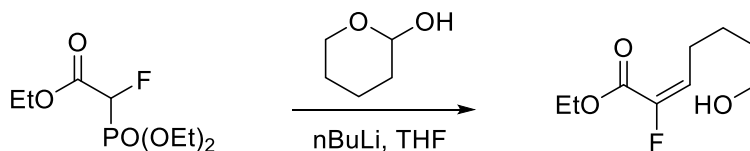
**propyl (Z)-7-iodo-2-methoxyhept-2-enoate (11a):** Synthesized from propyl (Z)-7-hydroxy-2-methoxyhept-2-enoate (330 mg, 1.53 mmol) according to general procedure C. Product obtained as a clear oil (326 mg, 63% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.21 (t,  $J = 7.7$  Hz, 1H), 4.14 (t,  $J = 6.7$  Hz, 2H), 3.66 (s, 3H), 3.20 (t,  $J = 6.9$  Hz, 2H), 2.26 (q,  $J = 7.6$  Hz, 2H), 1.85 (p,  $J = 7.1$  Hz, 2H), 1.72 (h,  $J = 7.2$  Hz, 2H), 1.60 – 1.51 (m, 2H), 0.98 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  163.9, 146.9, 127.7, 66.6, 60.2, 33.1, 29.7, 24.5, 22.2, 10.6, 6.6.

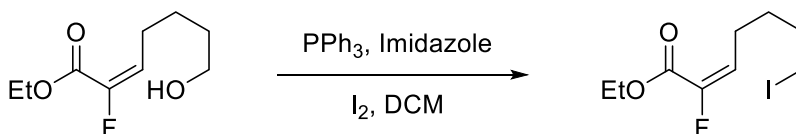
IR ( $\text{cm}^{-1}$ ): 2964.2, 2932.7, 1716.4, 1649.3, 1453.5, 1262.2, 1207.7, 1098.9, 777.2.

HRMS: Calc'd for  $([\text{C}_{11}\text{H}_{19}\text{IO}_3 + \text{H}]^+)$ : 327.04516, found 327.0450



**ethyl (E)-2-fluoro-7-hydroxyhept-2-enoate:** Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (560  $\mu$ L, 2.75 mmol, 1.1 equiv.) was dissolved in 8 mL THF and cooled to 0  $^{\circ}$ C. *n*-butyllithium solution (2.5 M, 1.1 mL, 2.75 mmol, 1.1 equiv.) was added dropwise and the reaction stirred for 30 minutes. Lactol (255 mg, 2.5 mmol, 1 equiv.) was added in 2 mL THF and the reaction stirred for 2 hours. The reaction was quenched with sat.  $\text{NH}_4\text{Cl}$ , extracted with  $\text{Et}_2\text{O}$ , washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and solvent removed *in vacuo* to obtain crude product which was purified by flash chromatography yielding pure product (340 mg, 72% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.01 – 5.83 (m, 1H), 4.29 (q,  $J = 7.1$  Hz, 2H), 3.67 (t,  $J = 6.3$  Hz, 2H), 2.61 – 2.50 (m, 2H), 1.64 – 1.47 (m, 5H), 1.35 (t,  $J = 7.1$  Hz, 3H).



**ethyl (E)-2-fluoro-7-iodohept-2-enoate (12a):** Synthesized from ethyl (E)-2-fluoro-7-hydroxyhept-2-enoate (340 mg, 1.79 mmol) according to general procedure C. Product obtained as a clear oil (313 mg, 58% yield, E:Z = 91:9).

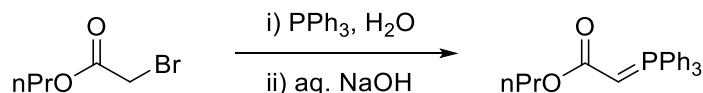
$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.10 (dt,  $J = 21.3, 8.3$  Hz, 1 $\text{H}_{\text{Z-isomer}}$ ), 5.90 (dt,  $J = 21.3, 8.3$  Hz, 1 $\text{H}_{\text{E-isomer}}$ ), 4.30 (q,  $J = 7.1$  Hz, 2H), 3.20 (t,  $J = 6.9$  Hz, 2H), 2.55 (qd,  $J = 7.7, 1.7$  Hz, 2 $\text{H}_{\text{E-isomer}}$ ), 2.28 (qd,  $J = 7.7, 1.7$  Hz, 2 $\text{H}_{\text{Z-isomer}}$ ), 1.86 (p,  $J = 7.0$  Hz, 2H), 1.60 – 1.53 (m, 2H), 1.35 (t,  $J = 7.2$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  161.1 (d,  $J = 35.6$  Hz), 147.5 (d,  $J = 252.4$  Hz), 122.8 (d,  $J = 18.3$  Hz), 61.6, 32.9, 30.1 (d,  $J = 2.3$  Hz), 24.5 (d,  $J = 5.2$  Hz), 14.3, 6.3.

$^{19}\text{F NMR}$  (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -121.65 (d,  $J = 21.3$  Hz, E-isomer), -129.93 (d,  $J = 32.8$  Hz, Z-isomer).

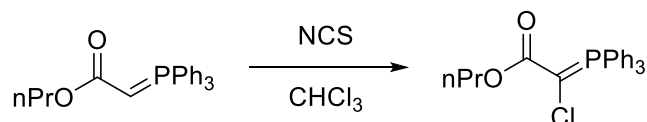
IR ( $\text{cm}^{-1}$ ): 2933.4, 1720.8, 1374.3, 1208.3, 1102.3, 1024.0, 775.8.

HRMS: Calc'd for  $([\text{C}_9\text{H}_{14}\text{FIO}_2] - [\text{C}_2\text{H}_4] + \text{H})^+$ : 272.97823, found 272.9780



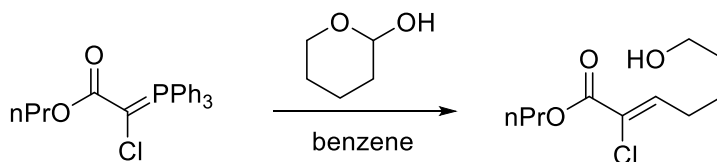
**propyl 2-(triphenylphosphoranylidene)acetate:** Synthesized from propyl 2-bromoacetate (9.05 g, 50 mmol) according to general procedure A. Product obtained as powdery, white crystals (14.2 g, 78% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.70 – 7.60 (m, 6H), 7.57 – 7.51 (m, 3H), 7.45 (td,  $J = 7.6, 2.8$  Hz, 6H), 3.94 (t,  $J = 6.9$  Hz, 2 $\text{H}_{\text{minor}}$ ), 3.75 (t,  $J = 6.9$  Hz, 2 $\text{H}_{\text{major}}$ ), 2.94 (d,  $J = 21.6$  Hz, 2 $\text{H}_{\text{major}}$ ), 2.72 (d,  $J = 21.6$  Hz, 2 $\text{H}_{\text{minor}}$ ), 1.64 (q,  $J = 7.1$  Hz, 2 $\text{H}_{\text{major}}$ ), 1.08 (q,  $J = 7.1$  Hz, 2 $\text{H}_{\text{minor}}$ ), 0.94 (t,  $J = 7.6$  Hz, 3 $\text{H}_{\text{minor}}$ ), 0.44 (t,  $J = 7.6$  Hz, 3 $\text{H}_{\text{minor}}$ ).



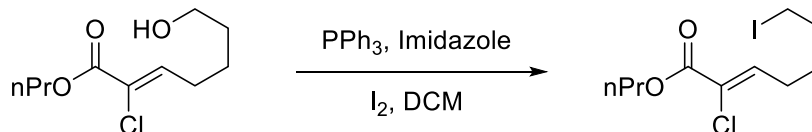
**propyl 2-chloro-2-(triphenylphosphoranylidene)acetate:** Propyl 2-(triphenylphosphoranylidene)acetate (1.45 g, 4 mmol, 1 equiv.) was dissolved in 16 mL chloroform and cooled to 0 °C. *N*-chlorosuccinimide (588 mg, 4.4 mmol, 1.1 equiv.) was added in portions and the reaction stirred overnight. The reaction was quenched with sat. NaHCO<sub>3</sub>, extracted with DCM, washed with water then brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and solvent removed in *vacuo*. Crude product was recrystallized from acetone/hexanes to obtain product as orange powdery crystals (950 mg, 60% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.71 – 7.63 (m, 6H), 7.58 (d, *J* = 7.3 Hz, 3H), 7.49 (td, *J* = 7.7, 3.0 Hz, 6H), 4.03 (t, *J* = 5.7 Hz, 2H<sub>minor</sub>), 3.69 (t, *J* = 5.7 Hz, 2H<sub>major</sub>), 1.74–1.64 (m, 2H<sub>minor</sub>), 0.95 (t, *J* = 8.5 Hz, 3H<sub>minor</sub>), 0.90 – 0.81 (m, 2H<sub>major</sub>), 0.36 (t, *J* = 8.5 Hz, 3H<sub>major</sub>).



**propyl (Z)-2-chloro-7-hydroxyhept-2-enoate:** Synthesized from propyl 2-chloro-2-(triphenylphosphoranylidene)acetate (800 mg, 2.02 mmol) according to general procedure B. Product obtained as a yellow oil (325 mg, 73% yield, Z:E = 77:23).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.07 (t, *J* = 7.3 Hz, 1H<sub>Z-isomer</sub>), 6.45 (t, *J* = 7.3 Hz, 1H<sub>E-isomer</sub>), 4.17 (td, *J* = 6.7, 1.9 Hz, 2H), 3.68 (q, *J* = 5.5 Hz, 2H), 2.59 (q, *J* = 7.6 Hz, 2H<sub>E-isomer</sub>), 2.40 (q, *J* = 7.1 Hz, 2H<sub>Z-isomer</sub>), 1.73 (qd, *J* = 7.1, 4.3 Hz, 2H), 1.66 – 1.52 (m, 4H), 0.98 (td, *J* = 7.4, 5.2 Hz, 3H).



**propyl (Z)-2-chloro-7-iodohept-2-enoate (13a):** Synthesized from propyl (Z)-2-chloro-7-hydroxyhept-2-enoate (300 mg, 1.39 mmol) according to general procedure C. Product obtained as a yellow oil (351 mg, 77% yield, Z:E = 77:23).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.05 (t, *J* = 7.3 Hz, 1H<sub>Z-isomer</sub>), 6.42 (t, *J* = 7.9 Hz, 1H<sub>E-isomer</sub>), 4.18 (t, *J* = 6.7 Hz, 2H), 3.20 (td, *J* = 6.9, 5.2 Hz, 2H), 2.59 (q, *J* = 7.7 Hz, 2H<sub>E-isomer</sub>), 2.39 (q, *J* = 7.4 Hz, 2H<sub>Z-isomer</sub>), 1.92 – 1.82 (m, 2H), 1.79 – 1.67 (m, 2H), 1.66 – 1.58 (m, 2H), 0.99 (td, *J* = 7.4, 4.4 Hz, 3H).

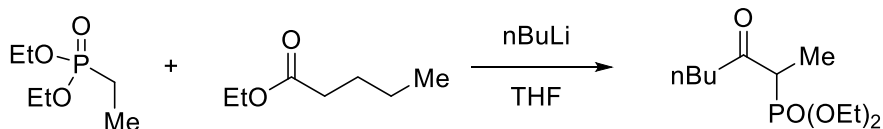
<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>):

Z-isomer: δ 162.6, 141.2, 125.6, 67.9, 33.0, 28.7, 28.4, 22.1, 10.5, 6.2.

E-isomer: δ 162.8, 143.9, 123.0, 67.7, 32.9, 29.9, 28.9, 22.0, 10.6, 6.3.

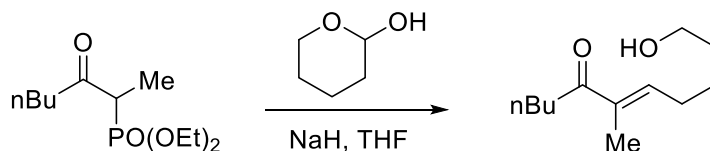
IR (cm<sup>-1</sup>): 2964.9, 2934.4, 1716.1, 1629.3, 1456.5, 1258.1, 1207.8, 1059.5, 747.9.

HRMS: Calc'd for [(C<sub>10</sub>H<sub>16</sub>ClIO<sub>2</sub>)+H]<sup>+</sup>: 330.99563, found 330.9951



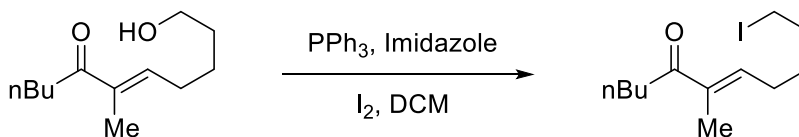
**diethyl (3-oxoheptan-2-yl)phosphonate:** Procedure adapted from the literature.<sup>5</sup> Diethyl ethylphosphonate (1.63 mL, 10 mmol, 1 equiv.) was dissolved in 20 mL THF and cooled to -78 °C. *n*-butyllithium solution (2.5 M, 4.2 mL, 10.5 mmol, 1.05 equiv.) was added dropwise and the reaction stirred for 2 hours at -78 °C. Ethyl pentanoate (1.64 mL, 11 mmol, 1.1 equiv.) was added dropwise and the reaction stirred overnight while warming to room temperature. The reaction was quenched with sat. NH<sub>4</sub>Cl, extracted with Et<sub>2</sub>O, and dried with MgSO<sub>4</sub>. Crude product was purified by flash chromatography to obtain product as a clear oil (1.5 g, 60% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 4.18 – 4.05 (m, 4H), 3.22 (dq, *J* = 25.0, 7.1 Hz, 1H), 2.79 (dt, *J* = 17.5, 7.4 Hz, 1H), 2.54 (dt, *J* = 17.5, 7.3 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.39 – 1.26 (m, 11H), 0.90 (t, *J* = 7.3 Hz, 3H).



**(*E*)-11-hydroxy-6-methylundec-6-en-5-one:** Sodium hydride (60% in mineral oil, 80 mg, 2 mmol, 1 equiv.) was suspended in 6 mL THF and cooled to 0 °C. Diethyl (3-oxoheptan-2-yl)phosphonate (600 mg, 2.4 mmol, 1.2 equiv.) was added dropwise and the reaction warmed to room temperature and stirred until hydrogen evolution ceased, approximately 30 minutes. The reaction was recooled to 0 °C, lactol (204 mg, 2 mmol, 1 equiv.) added, and the reaction stirred overnight. The reaction was quenched with sat. NaHCO<sub>3</sub>, extracted with brine, and dried with Na<sub>2</sub>SO<sub>4</sub>. Crude product purified by flash chromatography (350 mg, 88% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.61 (td, *J* = 7.3, 1.5 Hz, 1H), 3.68 (q, *J* = 5.7 Hz, 2H), 2.69 – 2.58 (m, 2H), 2.28 (q, *J* = 7.0 Hz, 2H), 1.77 (s, 3H), 1.71 – 1.47 (m, 6H), 1.42 – 1.22 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).



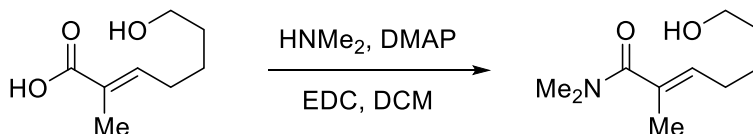
**(*E*)-11-iodo-6-methylundec-6-en-5-one (14a):** Synthesized from (*E*)-11-hydroxy-6-methylundec-6-en-5-one (200 mg, 1.01 mmol) according to general procedure C. Product obtained as a clear oil (300 mg, 97% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 6.59 (td, *J* = 7.3, 1.5 Hz, 1H), 3.21 (t, *J* = 6.8 Hz, 2H), 2.68 – 2.61 (m, 2H), 2.26 (q, *J* = 7.4 Hz, 2H), 1.87 (dt, *J* = 14.5, 7.0 Hz, 2H), 1.77 (s, 3H), 1.59 (dd, *J* = 15.2, 7.5 Hz, 4H), 1.33 (h, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 202.3, 141.1, 137.8, 37.2, 33.2, 29.6, 28.1, 27.3, 22.7, 14.1, 11.6, 6.6.

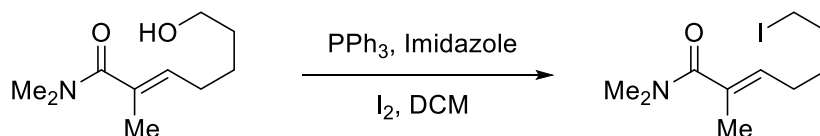
**IR** (cm<sup>-1</sup>): 2954.6, 2928.8, 2860.6, 1663.3, 1453.1, 1367.2, 1205.4, 1046.0, 728.1.

**HRMS**: Calc'd for ([C<sub>12</sub>H<sub>21</sub>O<sub>2</sub>]+H)<sup>+</sup>: 309.07098, found 309.0717



**(E)-7-hydroxy-N,N,2-trimethylhept-2-enamide**: Synthesized from (E)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol, 1 equiv.) and dimethylamine (2M, 1.3 mL, 2.6 mmol, 1.3 equiv.) according to general procedure F. Product obtained as a clear oil (280 mg, 76% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 5.58 – 5.50 (m, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.98 (s, 6H), 2.14 (q, *J* = 7.3 Hz, 2H), 1.83 (s, 3H), 1.65 – 1.55 (m, 2H), 1.50 (q, *J* = 7.9 Hz, 2H).



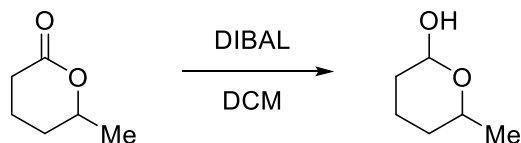
**(E)-7-iodo-N,N,2-trimethylhept-2-enamide (15a)**: Synthesized from (E)-7-hydroxy-N,N,2-trimethylhept-2-enamide (220 mg, 1.19 mmol) according to general procedure C. Product obtained as a pale-yellow oil (275 mg, 78% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 5.52 (ddt, *J* = 7.3, 5.6, 1.6 Hz, 1H), 3.19 (t, *J* = 6.9 Hz, 2H), 2.98 (s, 6H), 2.13 (q, *J* = 7.4 Hz, 2H), 1.90 – 1.81 (m, 5H), 1.53 (p, *J* = 7.5 Hz, 2H).

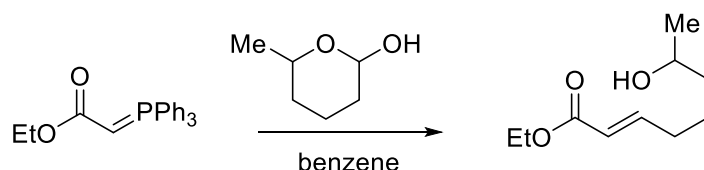
**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 173.7, 132.2, 130.4, 38.9, 34.9, 33.1, 29.8, 26.6, 14.3, 6.7.

**IR** (cm<sup>-1</sup>): 3461.8 (br), 2926.4, 2856.2, 2360.9, 2340.4, 1609.3, 1391.1, 1087.4, 739.2.

**HRMS**: Calc'd for ([C<sub>10</sub>H<sub>18</sub>INO]+H)<sup>+</sup>: 296.05058, found 296.0507

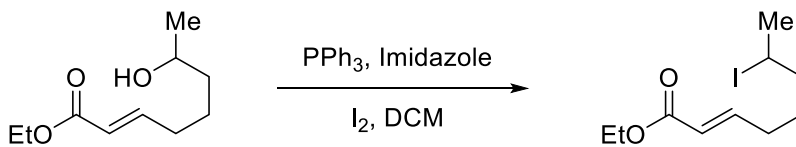


**6-methyltetrahydro-2H-pyran-2-ol:** 6-methyltetrahydro-2H-pyran-2-one (1.14 g, 10 mmol, 1 equiv.) was dissolved in 15 mL DCM and cooled to  $-78\text{ }^{\circ}\text{C}$ . DIBAL (1 M in hexanes, 12 mL, 12 mmol, 1.2 equiv.) was added dropwise and the reaction stirred for 2 hours. The reaction was quenched with MeOH then sat. Rochelle salt solution and stirred overnight. The reaction was extracted with DCM, washed twice with water, then brine, dried with  $\text{MgSO}_4$  and solvent removed. Crude product (900 mg, 78% yield) was used without purification and was not characterized.



**ethyl (E)-7-hydroxyoct-2-enoate:** Synthesized from ethyl 2-(triphenylphosphoranylidene)acetate (4 mmol) according to general procedure B. Product obtained as a clear oil (660 mg, 88% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.95 (dt,  $J = 15.6, 6.9$  Hz, 1H), 5.82 (dt,  $J = 15.6, 1.6$  Hz, 1H), 4.18 (q,  $J = 7.2$  Hz, 2H), 3.80 (hept,  $J = 6.0$  Hz, 1H), 2.28 – 2.18 (m, 2H), 1.63 – 1.42 (m, 4H), 1.28 (t,  $J = 7.2$  Hz, 3H), 1.19 (d,  $J = 6.2$  Hz, 3H).



**ethyl (E)-7-iodooct-2-enoate (16a):** Synthesized from ethyl (E)-7-hydroxyoct-2-enoate (2.15 mmol) according to general procedure C. Product obtained as a clear oil (334 mg, 53% yield).

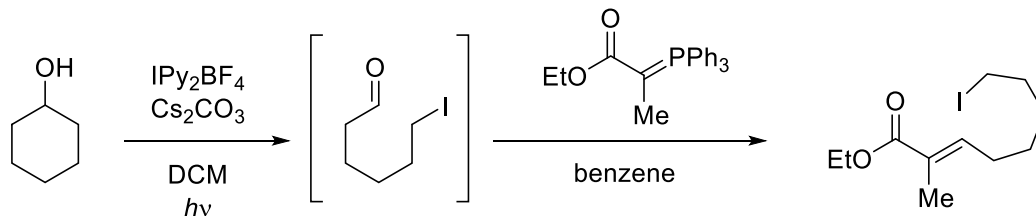
$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.94 (dt,  $J = 15.6, 6.9$  Hz, 1H), 5.83 (dt,  $J = 15.6, 1.6$  Hz, 1H), 4.23 – 4.11 (m, 3H), 2.23 (dddd,  $J = 14.9, 13.4, 8.4, 6.8$  Hz, 2H), 1.92 (d,  $J = 6.8$  Hz, 3H), 1.89 – 1.78 (m, 1H), 1.76 – 1.50 (m, 3H), 1.29 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  166.7, 148.4, 122.0, 60.4, 42.2, 31.3, 29.7, 29.1, 28.4, 14.4.

**IR** ( $\text{cm}^{-1}$ ): 2979.5, 2933.0, 2660.8 1714.4, 1652.8, 1444.3, 1174.9, 1037.2, 977.1, 865.0.

**HRMS:** Calc'd for  $([\text{C}_{10}\text{H}_{17}\text{IO}_2] + \text{H})^+$ : 297.03460, found 297.0340

## 6-exo-substrates



**ethyl (E)-8-iodo-2-methyloct-2-enoate (17a):** The first oxidative step was adapted from the literature.<sup>6</sup> Cyclohexanol (100 mg, 1 mmol, 1 equiv.), cesium carbonate (3.26 g, 10 mmol, 10 equiv.), and bis(pyridine)iodonium tetrafluoroborate (IPy<sub>2</sub>BF<sub>4</sub>) (929 mg, 2.5 mmol, 2.5 equiv.) were suspended in 50 mL dry DCM and irradiated with a 100W CFL overnight. The reaction was then cooled to 0 °C and quenched with 1 M H<sub>2</sub>SO<sub>4</sub> (50 mL). The reaction was extracted with DCM, washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, water, and brine, then dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and solvent removed *in vacuo*. The residue was then taken up in 4 mL benzene, added to a suspension of ethyl 2-(triphenylphosphoranylidene)propanoate (362 mg, 1 mmol, 1 equiv.) in 4 mL benzene, and stirred overnight. Solvent was removed and the residue purified by flash chromatography to obtain pure product as a clear oil (140 mg, 45% yield, E:Z = 89:11).

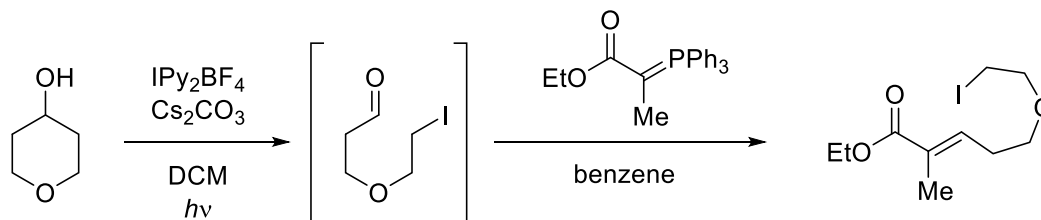
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.73 (tq, *J* = 7.4, 1.5 Hz, 1H<sub>E-isomer</sub>), 5.90 (tq, *J* = 7.5, 1.5 Hz, 1H<sub>Z-isomer</sub>), 4.19 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.19 (t, *J* = 7.0 Hz, 2H), 2.55 – 2.39 (m, 2H<sub>Z-isomer</sub>), 2.25 – 2.12 (m, 2H<sub>E-isomer</sub>), 1.88 – 1.80 (m, 5H), 1.51 – 1.40 (m, 4H), 1.30 (td, *J* = 7.1, 4.7 Hz, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 168.4, 141.8, 128.2, 60.6, 33.4, 30.4, 28.6, 27.7, 14.5, 12.6, 6.9.

Note: The minor Z-isomer peaks can also be observed in the <sup>13</sup>C NMR but are not reported.

IR (cm<sup>-1</sup>): 2978.5, 2929.0, 2856.2, 1704.2, 1647.8, 1253.2, 1100.5, 743.7.

HRMS: Calc'd for ([C<sub>11</sub>H<sub>19</sub>I O<sub>2</sub>]+H)<sup>+</sup>: 311.05025, found 311.0505



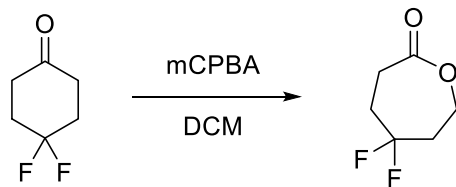
**ethyl (E)-5-(2-iodoethoxy)-2-methylpent-2-enoate (18a):** Synthesized in an identical procedure as ethyl (E)-8-iodo-2-methyloct-2-enoate starting from tetrahydro-2H-pyran-4-ol (102 mg, 1 mmol). Product obtained as a clear oil (56 mg, 18% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.77 (tt, *J* = 7.3, 1.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.71 (t, *J* = 6.7 Hz, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 2.47 (q, *J* = 6.9 Hz, 2H), 1.85 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 168.1, 138.0, 129.8, 71.7, 69.4, 60.7, 29.5, 14.5, 12.7, 3.0.

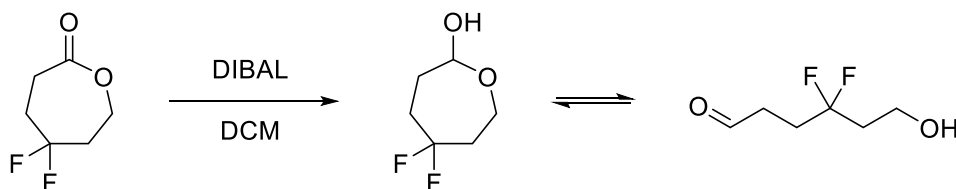
IR (cm<sup>-1</sup>): 2978.1, 2866.7, 1703.9, 1651.5, 1365.9, 1241.7, 1084.6, 744.1.

HRMS: Calc'd for ([C<sub>10</sub>H<sub>17</sub>O<sub>3</sub>]+H)<sup>+</sup>: 313.02951, found 313.02998

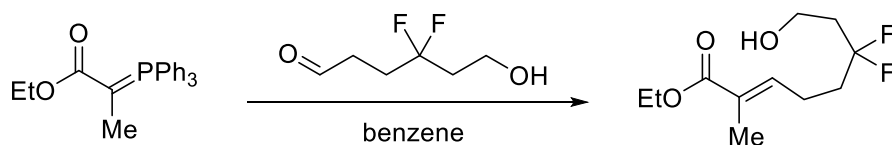


**5,5-difluorooxepan-2-one:** 4,4-difluorocyclohexan-1-one (1.34 g, 10 mmol, 1 equiv.) was dissolved in 15 mL DCM and cooled to 0 °C. *meta*-Chloroperbenzoic acid (2.59 g, 15 mmol, 1.5 equiv) was added in portions then the reaction stirred at room temperature for 2 days. Solid benzoic acid biproducts were filtered off and the filtrate washed twice with 1:1 sat. NaHCO<sub>3</sub> and sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, water, brine, then dried with MgSO<sub>4</sub> and solvent removed to obtain crude product (1.13 g, 75% yield) which was used without purification.

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 4.34 – 4.27 (m, 2H), 2.77 – 2.69 (m, 2H), 2.40 – 2.14 (m, 4H).

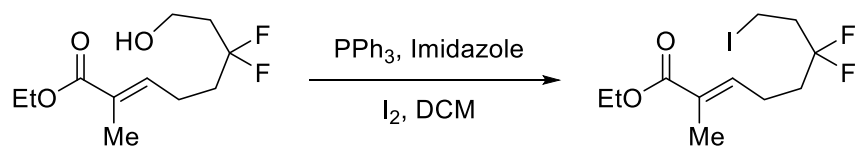


**4,4-difluoro-6-hydroxyhexanal:** 5,5-difluorooxepan-2-one (1.13 g, 7.5 mmol, 1 equiv.) was dissolved in 8 mL DCM and cooled to -78 °C. DIBAL (1 M in hexanes, 9 mL, 9 mmol, 1.2 equiv.) was added dropwise and the reaction stirred for 2 hours. The reaction was quenched with MeOH then sat. Rochelle salt solution and stirred overnight. The reaction was extracted with DCM, washed twice with water, then brine, dried with MgSO<sub>4</sub> and solvent removed. Crude product (260 mg, 23% yield) was used without purification and was not characterized.



**ethyl (E)-6,6-difluoro-8-hydroxy-2-methyloct-2-enoate:** Synthesized from ethyl 2-(triphenylphosphoranylidene)propanoate (310 mg, 0.85 mmol) and 4,4-difluoro-6-hydroxyhexanal (130 mg, 0.85 mmol) according to general procedure B. Product obtained as a clear oil (94 mg, 47% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.71 (t, *J* = 7.5 Hz, 1H), 4.19 (qd, *J* = 7.1, 1.2 Hz, 2H), 3.95 – 3.84 (m, 2H), 2.39 (q, *J* = 7.7 Hz, 2H), 2.23 – 1.92 (m, 4H), 1.93 – 1.78 (m, 5H), 1.29 (td, *J* = 7.1, 1.1 Hz, 3H).



**ethyl (E)-6,6-difluoro-8-iodo-2-methyloct-2-enoate (19a)**: Synthesized from ethyl (E)-6,6-difluoro-8-hydroxy-2-methyloct-2-enoate (94 mg, 0.4 mmol) according to general procedure C. Product obtained as clear oil (95 mg, 67% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.72 – 6.65 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.25 – 3.18 (m, 2H), 2.48 (tdd, *J* = 16.2, 9.3, 7.4 Hz, 2H), 2.38 (q, *J* = 7.7 Hz, 2H), 2.04 – 1.89 (m, 2H), 1.85 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

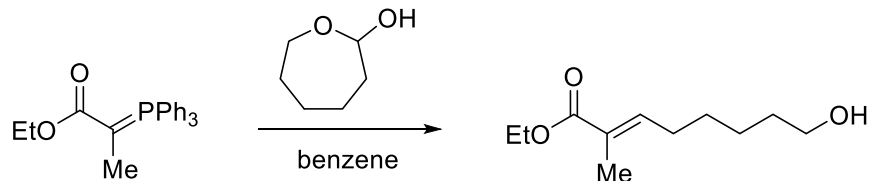
<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 168.0, 139.2, 129.4, 123.7 (t, *J* = 242.9 Hz), 60.8, 42.0 (t, *J* = 25.7 Hz), 35.4 (t, *J* = 25.0 Hz), 21.5 (t, *J* = 5.0 Hz), 14.4, 12.5, -7.2 (t, *J* = 5.6 Hz).

<sup>19</sup>F NMR (376 MHz; CDCl<sub>3</sub>): δ -100.75 (p, *J* = 16.4 Hz).

IR (cm<sup>-1</sup>): 2979.2, 1704.7, 1651.2, 1442.0, 1254.8, 896.9, 743.4, 528.3.

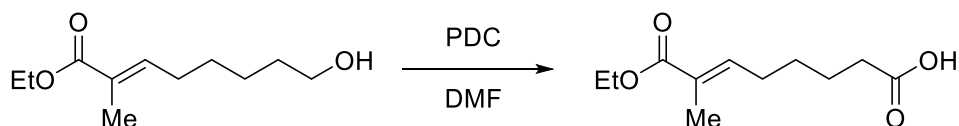
HRMS: Calc'd for ([C<sub>11</sub>H<sub>17</sub>F<sub>2</sub>IO<sub>2</sub>]+H)<sup>+</sup>: 347.03141, found 347.0309

## NHPI ester and tandem cyclization substrates



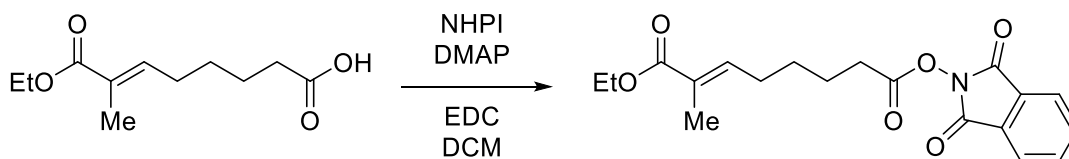
**ethyl (E)-8-hydroxy-2-methyloct-2-enoate:** Synthesized from ethyl 2-(triphenylphosphoranylidene)propanoate (1.45 g, 4 mmol) according to general procedure B. Lactol was prepared as previously reported.<sup>7</sup> Product obtained as a clear oil (400 mg, 50% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.75 (tq, *J* = 7.6, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.26 – 2.10 (m, 2H), 1.82 (q, *J* = 1.1 Hz, 3H), 1.62 – 1.54 (m, 2H), 1.52 – 1.45 (m, 2H), 1.44 – 1.36 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).



**(E)-8-ethoxy-7-methyl-8-oxooct-6-enoic acid:** Ethyl (E)-8-hydroxy-2-methyloct-2-enoate (400 mg, 2 mmol) was dissolved in 6 mL DMF, pyridinium dichromate (3.01 g, 8 mmol, 4 equiv.) was added in portions, then the reaction stirred overnight. The reaction was quenched with water, extracted with Et<sub>2</sub>O, washed twice with 1 M HCl, water, then brine, and dried with Na<sub>2</sub>SO<sub>4</sub>. Crude product was purified by flash chromatography (233 mg, 54% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.73 (tq, *J* = 7.5, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.20 (q, *J* = 7.5 Hz, 2H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.67 (p, *J* = 7.5 Hz, 2H), 1.51 (p, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).



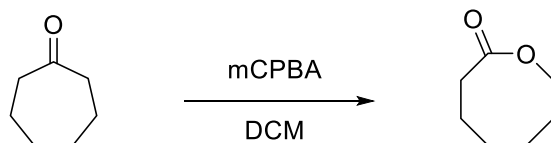
**8-(1,3-dioxisoindolin-2-yl) 1-ethyl (E)-2-methyloct-2-enedioate (20):** Synthesized from (E)-8-ethoxy-7-methyl-8-oxooct-6-enoic acid (100 mg, 0.47 mmol, 1 equiv.) and *N*-hydroxyphthalimide (84 mg, 0.51 mmol, 1.1 equiv.) according to general procedure F with the following modification. Instead of the aqueous work up, the reaction solvent volume was minimized *in vacuo* and the reaction purified directly by flash chromatography. Product obtained as off-white crystals (130 mg, 78% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.93 – 7.85 (m, 2H), 7.83 – 7.75 (m, 2H), 6.75 (tq, *J* = 7.6, 1.5 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.29 – 2.20 (m, 2H), 1.89 – 1.76 (m, 5H), 1.66 – 1.53 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 169.5, 168.3, 162.1, 141.1, 134.9, 129.1, 128.7, 124.1, 60.6, 31.0, 28.3, 27.9, 24.5, 14.4, 12.6.

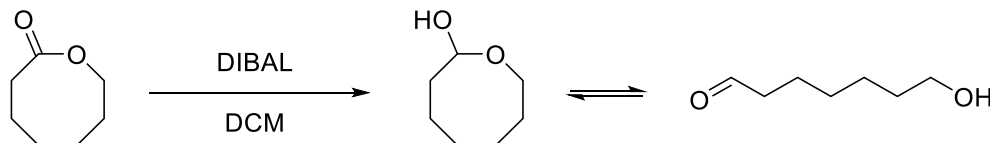
IR (cm<sup>-1</sup>): 2981.1, 2947.6, 2870.8, 1740.9, 1704.3, 1272.2, 1080.1, 875.6, 692.0, 516.8.

HRMS: Calc'd for ([C<sub>19</sub>H<sub>21</sub>NO<sub>6</sub>]+H)<sup>+</sup>: 360.14416, found 360.1441

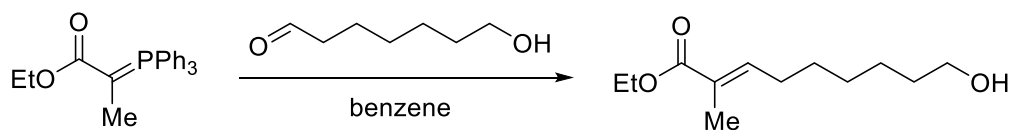


**2-oxocanone:** Cycloheptanone (2.36 mL, 20 mmol, 1 equiv.) was dissolved in 30 mL DCM and cooled to 0 °C. *meta*-Chloroperbenzoic acid (5.18 g, 30 mmol, 1.5 equiv.) was added in portions and the reaction stirred for 2 days. Precipitated benzoic acid was removed by filtration and the filtrate quenched with sat. NaHCO<sub>3</sub> and sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The reaction was extracted with DCM, the combined extracts washed with sat. NaHCO<sub>3</sub>, water, and brine, then dried with Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed *in vacuo* to obtain crude product (1.75 g, 68% yield) was used directly in the next step.

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 4.34 (t, *J* = 5.7 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 1.85 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.79 (q, *J* = 5.8 Hz, 2H), 1.74 – 1.52 (m, 7H).

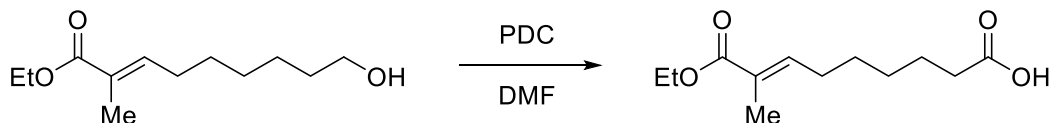


**7-hydroxyheptanal:** 2-oxocanone (1.75 g, 13.7 mmol, 1 equiv.) was dissolved in 14 mL DCM and cooled to -78 °C. Diisobutylaluminium hydride (1 M in hexanes, 16.4 mL, 16.4 mmol, 1.2 equiv.) was added dropwise and the reaction stirred for 2 hours. The reaction was quenched with MeOH then sat. Rochelle salt and stirred overnight. The mixture was extracted with DCM, the combined organic extracts washed twice with water then brine then dried with MgSO<sub>4</sub>. Solvent was removed *in vacuo* to obtain crude product (1.13 g, 63% yield) which was used directly in the next step without characterization.



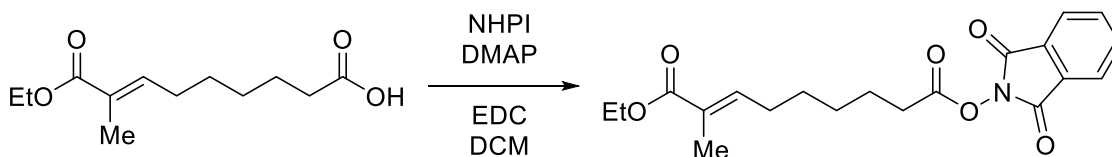
**ethyl (E)-9-hydroxy-2-methylnon-2-enoate:** Synthesized from ethyl 2-(triphenylphosphoranylidene)propanoate (1.45 g, 4 mmol) and 7-hydroxyheptanal (520 mg, 4 mmol) according to general procedure B. Product obtained as a clear oil (457 mg, 53% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.75 (tq, *J* = 7.5, 1.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.22 – 2.12 (m, 2H), 1.82 (q, *J* = 1.1 Hz, 3H), 1.61 – 1.53 (m, 2H), 1.51 – 1.33 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 3H).



**(E)-9-ethoxy-8-methyl-9-oxonon-7-enoic acid:** Ethyl (E)-9-hydroxy-2-methylnon-2-enoate (428 mg, 2 mmol, 1 equiv.) was dissolved in 6 mL DMF, pyridinium dichromate (3.01 g, 8 mmol, 4 equiv.) was added in portions, then the reaction stirred overnight. The reaction was quenched with water, extracted with Et<sub>2</sub>O, washed twice with 1 M HCl, water, then brine, and dried with Na<sub>2</sub>SO<sub>4</sub>. Crude product was purified by flash chromatography (260 mg, 57% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 6.74 (tq, *J* = 7.4, 1.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.18 (q, *J* = 7.2 Hz, 2H), 1.82 (t, *J* = 1.2 Hz, 2H), 1.66 (p, *J* = 7.5 Hz, 2H), 1.56 – 1.33 (m, 5H), 1.29 (t, *J* = 7.1 Hz, 3H).



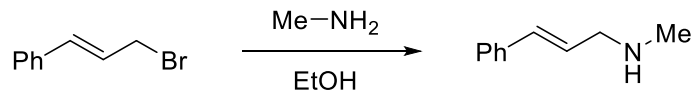
**9-(1,3-dioxoisindolin-2-yl) 1-ethyl (E)-2-methylnon-2-enedioate (21):** Synthesized from (E)-9-ethoxy-8-methyl-9-oxonon-7-enoic acid (125 mg, 0.55 mmol, 1 equiv.) and *N*-hydroxyphthalimide (98 mg, 0.6 mmol, 1.1 equiv.) according to general procedure F with the following modification. Instead of the aqueous work up, the reaction solvent volume was minimized *in vacuo* and the reaction purified directly by flash chromatography. Product obtained as a semi-transparent oil (160 mg, 78% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.88 (dt, *J* = 7.8, 3.8 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.75 (t, *J* = 7.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.21 (q, *J* = 7.0 Hz, 2H), 1.85 – 1.76 (m, 5H), 1.53 – 1.44 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 169.6, 168.4, 162.1, 141.8, 134.9, 129.1, 128.2, 124.1, 60.6, 31.0, 28.7, 28.5, 28.3, 24.7, 14.4, 12.5.

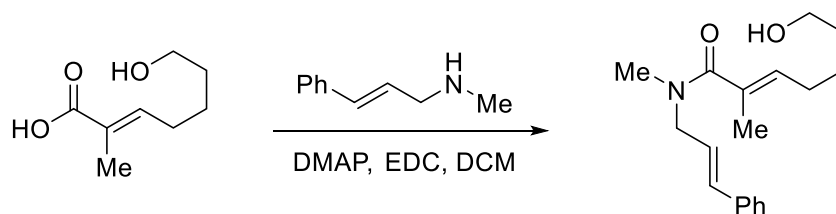
IR (cm<sup>-1</sup>): 2932.0, 2860.2, 1739.9, 1701.6, 1364.9, 1257.0, 876.6, 694.9, 517.4.

HRMS: Calc'd for ([C<sub>20</sub>H<sub>23</sub>NO<sub>6</sub>]+H)<sup>+</sup>: 374.15981, found 374.1596



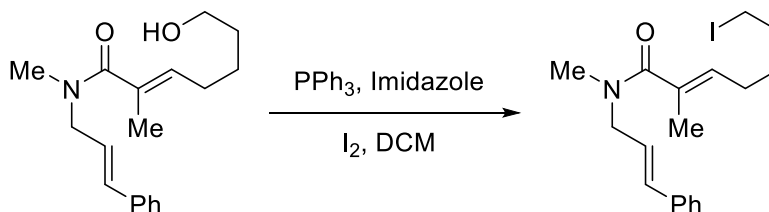
***N*-methyl-3-phenylprop-2-en-1-amine:** Procedure adapted from the literature.<sup>8</sup> Methylamine in ethanol (33 wt%, 10 mL, 80 mmol, 10 equiv.) was cooled to 0 °C. Cinnamyl bromide (1.58 g, 8 mmol, 1 equiv.) was added in one portion with rapid stirring. The reaction was stirred for 1 hour at 0 °C then warmed to room temperature for 2 hours. The reaction was quenched with 1 M sodium hydroxide, extracted with Et<sub>2</sub>O, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and solvent removed *in vacuo* to obtain crude product which was used directly (1.18 g, 100% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.44 – 7.36 (m, 2H), 7.31 (td, *J* = 7.6, 3.0 Hz, 2H), 7.22 (ddq, *J* = 8.6, 5.0, 1.8, 1.4 Hz, 1H), 6.54 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.39 – 6.18 (m, 1H), 3.38 (dd, *J* = 6.3, 1.6 Hz, 2H<sub>major</sub>), 3.22 (dd, *J* = 6.7, 1.3 Hz, 2H<sub>minor</sub>), 2.48 (s, 3H<sub>major</sub>), 2.31 (s, 3H<sub>minor</sub>).



***(E)*-N-cinnamyl-7-hydroxy-N,2-dimethylhept-2-enamide:** Synthesized from (*E*)-7-hydroxy-2-methylhept-2-enoic acid (316 mg, 2 mmol, 1 equiv.) and *N*-methyl-3-phenylprop-2-en-1-amine (353 mg, 2.4 mmol, 1.2 equiv.) according to general procedure F. Product obtained as a clear oil (490 mg, 85% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.42 – 7.29 (m, 4H), 7.25 (d, *J* = 13.9 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.26 – 5.98 (m, 1H), 5.60 (t, *J* = 7.2 Hz, 1H), 4.12 (q, *J* = 7.4 Hz, 2H), 3.62 (dt, *J* = 16.6, 6.4 Hz, 2H), 2.97 (s, 3H), 2.14 (q, *J* = 7.4 Hz, 2H), 1.86 (s, 3H), 1.66 – 1.41 (m, 4H).



***(E)*-N-cinnamyl-7-iodo-N,2-dimethylhept-2-enamide (22a):** Synthesized from propyl (*E*)-*N*-cinnamyl-7-hydroxy-*N*,2-dimethylhept-2-enamide (490 mg, 1.7 mmol) according to general procedure C. Product obtained as a clear oil (490 mg, 72% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.42 – 7.21 (m, 5H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.14 (s, 1H), 5.58 (td, *J* = 7.3, 1.7 Hz, 1H), 4.12 (d, *J* = 6.0 Hz, 2H), 3.17 (t, *J* = 6.9 Hz, 2H), 2.97 (s, 3H), 2.14 (q, *J* = 7.5 Hz, 2H), 1.90 – 1.78 (m, 5H), 1.52 (p, *J* = 7.5 Hz, 2H).

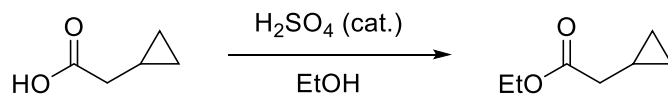
**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 173.7 (d, *J* = 83.7 Hz), 136.4, 132.9 (d, *J* = 58.8 Hz), 132.2, 130.2 (d, *J* = 74.3 Hz), 128.7, 127.9, 126.5, 124.6, 51.1 (d, *J* = 507.7 Hz), 34.4 (d, *J* = 456.6 Hz), 33.1, 29.8, 26.6, 14.6, 6.7.

Note: While distinct rotamer peaks were not observed in the <sup>1</sup>H NMR, they were observable in the <sup>13</sup>C NMR. These peaks are reported as doublets.

**IR** (cm<sup>-1</sup>): 2921.1, 2854.3, 1615.7, 1394.1, 1072.7, 965.2, 728.1, 691.1

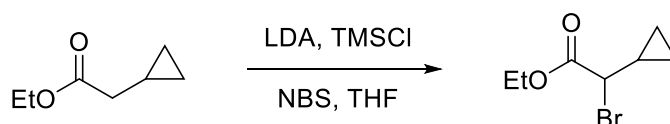
**HRMS**: Calc'd for ([C<sub>18</sub>H<sub>24</sub>INO]<sup>+</sup>H)<sup>+</sup>: 398.09753, found 398.0973

## Radical clock substrate



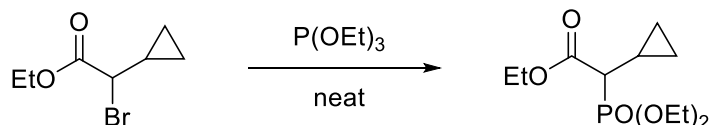
**ethyl 2-cyclopropylacetate:** Synthesized from 2-cyclopropylacetic acid (2.0 g, 20 mmol) following general procedure D. Product obtained as a clear oil (1.93 g, 75% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.14 (q, *J* = 7.1 Hz, 2H), 2.20 (d, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.10 – 0.98 (m, 1H), 0.59 – 0.49 (m, 2H), 0.15 (dt, *J* = 6.0, 4.7 Hz, 2H).



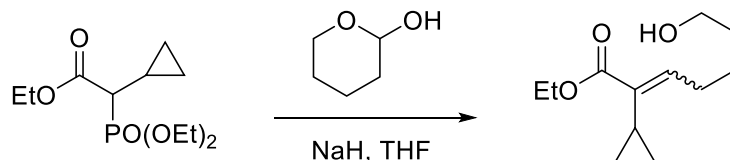
**ethyl 2-bromo-2-cyclopropylacetate:** Diisopropylamine (2.33 mL, 16.5 mmol, 1.1 equiv.) was dissolved in 15 mL THF and cooled to 0 °C. *n*-Butyllithium (2.5 M, 6.3 mL, 15.75 mmol, 1.05 equiv.) was added dropwise and the reaction stirred for 30 minutes. The reaction was then cooled to -78 °C and ethyl 2-cyclopropylacetate (1.92 g, 15 mmol, 1 equiv.) in 15 mL THF added dropwise. The reaction was stirred for 1 hour then trimethylsilyl chloride (1.9 mL, 15 mmol, 1 equiv.) added dropwise and the reaction stirred for 3 hours as it warmed to room temperature. The reaction was recooled to -78 °C and *N*-bromosuccinimide (2.94 g, 16.5 mmol, 1.1 equiv.) in 15 mL THF added dropwise. The reaction was then stirred for 2 hours and allowed to warm to room temperature. The reaction was quenched with sat. NH<sub>4</sub>Cl, extracted with hexanes, washed with brine, and dried with Na<sub>2</sub>SO<sub>4</sub>. Crude product filtered through a silica plug to obtain semipurified product which was used directly. (3.08 g, 99% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.25 (qd, *J* = 7.2, 0.9 Hz, 2H), 3.57 (d, *J* = 10.4 Hz, 1H), 1.64 – 1.53 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.90 – 0.78 (m, 2H), 0.58 – 0.48 (m, 1H), 0.48 – 0.38 (m, 1H).



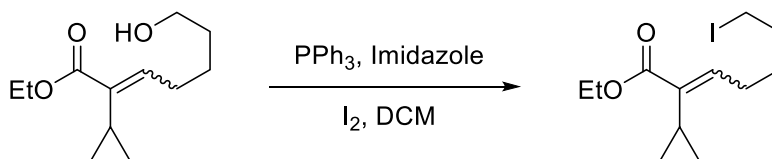
**ethyl 2-cyclopropyl-2-(diethoxyphosphoryl)acetate:** Synthesized from ethyl 2-bromo-2-cyclopropylacetate (1.66 g, 8 mmol) according to general procedure I. Product obtained as a light-yellow oil (1.69 g, 80% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.26 – 4.13 (m, 6H), 2.19 (dd, *J* = 22.0, 10.6 Hz, 1H), 1.38 – 1.31 (m, 7H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.72 (dddd, *J* = 9.3, 8.2, 6.0, 5.0 Hz, 1H), 0.61 (dddd, *J* = 9.2, 7.9, 6.1, 4.8, 2.9 Hz, 1H), 0.43 (ddt, *J* = 9.7, 6.0, 5.0 Hz, 1H), 0.25 (ddtd, *J* = 9.5, 6.2, 4.7, 1.4 Hz, 1H).



**ethyl 2-cyclopropyl-7-hydroxyhept-2-enoate:** Ethyl 2-cyclopropyl-2-(diethoxyphosphoryl)acetate (793 mg, 3 mmol, 1 equiv.) dissolved in 3 mL THF was added dropwise to sodium hydride (120 mg, 3 mmol, 1 equiv.) suspended in 6 mL THF. The reaction was allowed to stir until hydrogen evolution ceased (several hours) then lactol (337 mg, 3.3 mmol, 1.1 equiv.) in 3 mL THF was added dropwise and the reaction allowed to stir for 6 hours. Solvent was removed and the residue purified by flash chromatography to obtain product as a clear oil (420 mg, 66% yield, E/Z = 46:54).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 6.70 (td, *J* = 7.5, 1.7 Hz, 1H<sub>E-isomer</sub>), 5.73 (td, *J* = 7.6, 1.3 Hz, 1H<sub>Z-isomer</sub>), 4.22 (q, *J* = 7.1 Hz, 2H<sub>Z-isomer</sub>), 4.16 (q, *J* = 7.1 Hz, 2H<sub>E-isomer</sub>), 3.65 (dt, *J* = 12.7, 6.4 Hz, 2H), 2.37 (qdd, *J* = 7.6, 2.7, 1.1 Hz, 2H), 1.66 – 1.40 (m, 5H), 1.33 – 1.25 (m, 3H), 0.80 – 0.75 (m, 2H<sub>E-isomer</sub>), 0.67 (dtd, *J* = 8.2, 6.3, 2.0 Hz, 2H<sub>Z-isomer</sub>), 0.58 – 0.54 (m, 2H<sub>E-isomer</sub>), 0.45 – 0.40 (m, 2H<sub>Z-isomer</sub>).



**ethyl (E)-2-cyclopropyl-7-iodohept-2-enoate (S1a):** Synthesized from ethyl 2-cyclopropyl-7-hydroxyhept-2-enoate (300 mg, 1.4 mmol) according to general procedure C. Product obtained as clear oil (385 mg, 85% yield, E/Z = 46:54).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 6.67 (td, *J* = 7.5, 1.6 Hz, 1H<sub>E-isomer</sub>), 5.69 (t, *J* = 7.5 Hz, 1H<sub>Z-isomer</sub>), 4.22 (q, *J* = 7.1 Hz, 2H<sub>Z-isomer</sub>), 4.16 (q, *J* = 7.1 Hz, 2H<sub>E-isomer</sub>), 3.19 (dt, *J* = 10.4, 6.9 Hz, 2H), 2.44 – 2.32 (m, 2H), 1.84 (dp, *J* = 25.8, 7.1 Hz, 2H), 1.65 – 1.40 (m, 3H), 1.30 (dt, *J* = 14.3, 7.1 Hz, 3H), 0.82 – 0.76 (m, 2H<sub>E-isomer</sub>), 0.71 – 0.65 (m, 2H<sub>Z-isomer</sub>), 0.57 (m, 2H<sub>E-isomer</sub>), 0.46 – 0.41 (m, 2H<sub>Z-isomer</sub>).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>):

Z-isomer: δ 168.5, 137.1, 134.4, 60.40, 33.1, 30.3, 27.5, 14.49, 14.32, 7.0, 6.58, 6.1.

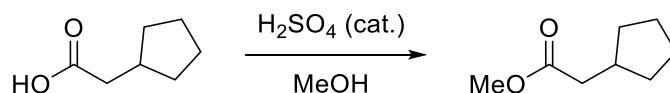
E-isomer: δ 168.1, 143.4, 133.6, 60.44, 33.2, 29.7, 28.2, 14.42, 9.1, 6.59, 6.58, 6.1.

**IR** (cm<sup>-1</sup>): 2978.7, 2930.8, 1707.8, 1639.6, 1190.3, 1031.0, 754.5, 595.4.

**HRMS:** Calc'd for ([C<sub>12</sub>H<sub>19</sub>IO<sub>2</sub>]+H)<sup>+</sup>: 323.05025, found 323.0502

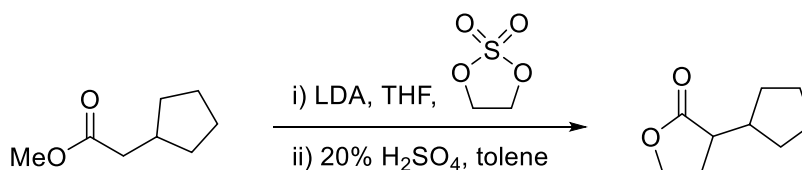
## Synthesis and Characterization of Product Standards

### 5-exo products



**methyl 2-cyclopentylacetate:** Synthesized from 2-cyclopentylacetic acid (2.05 g, 16 mmol) following general procedure D. Product obtained as a clear oil (1.39. 61% yield). Note: product is fairly volatile and loss of some product upon concentration at reduced pressure accounts for low yield.

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  3.66 (s, 3H), 2.32 (d,  $J = 7.4$  Hz, 2H), 2.22 (tdd,  $J = 15.4, 8.2, 7.1$  Hz, 1H), 1.87 – 1.77 (m, 2H), 1.68 – 1.59 (m, 2H), 1.58 – 1.49 (m, 2H), 1.15 (ddt,  $J = 11.9, 9.3, 7.3$  Hz, 2H).



**3-cyclopentylidihydrofuran-2(3H)-one (rac-1b):** Based on a procedure from the literature.<sup>9</sup>

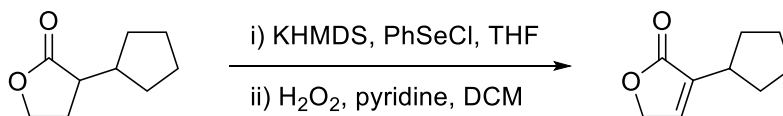
Diisopropylamine (1.05 mL, 7.38 mmol, 1.05 equiv.) was dissolved in 7 mL dry THF and cooled to 0 °C. *n*-butyllithium (2.5 M, 2.81 mL, 7.03 mmol, 1 equiv.) was added dropwise and the reaction stirred for 30 minutes. The reaction was cooled to -78 °C, methyl 2-cyclopentylacetate (1 g, 7.03 mmol, 1 equiv.) in 7 mL THF added dropwise, and the reaction stirred for 30 minutes. 1,3,2-Dioxathiolane 2,2-dioxide (916 mg, 7.38 mmol, 1.05 equiv.) in 7 mL THF was added dropwise, the reaction warmed to room temperature, and stirred for 5 hours. The reaction was concentrated *in vacuo*, the residue redissolved in 14 mL 20%  $\text{H}_2\text{SO}_4$  and 14 mL toluene, and the reaction refluxed overnight. After cooling to room temperature, the reaction was extracted with EtOAc, washed with sat.  $\text{NaHCO}_3$ , then brine, then dried with  $\text{Na}_2\text{SO}_4$ . Crude product purified by flash chromatography to obtain product as a clear oil which solidified upon cooling (856 mg, 79% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.32 (td,  $J = 8.7, 3.7$  Hz, 1H), 4.19 (td,  $J = 8.9, 7.0$  Hz, 1H), 2.54 (td,  $J = 9.2, 7.4$  Hz, 1H), 2.32 (dddd,  $J = 12.6, 8.8, 7.0, 3.6$  Hz, 1H), 2.16 (ddt,  $J = 16.7, 9.2, 7.4$  Hz, 1H), 2.09 – 1.94 (m, 2H), 1.77 (ddd,  $J = 11.6, 7.7, 4.0$  Hz, 1H), 1.72 – 1.51 (m, 4H), 1.41 – 1.21 (m, 2H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  179.1, 66.6, 43.4, 40.4, 30.7, 30.0, 27.0, 25.4, 25.1.

IR ( $\text{cm}^{-1}$ ): 2948.3, 2867.6, 1759.2, 1452.4, 1374.1, 1177.4, 1139.9, 1022.4, 954.7.

HRMS: Calc'd for  $([\text{C}_9\text{H}_{14}\text{O}_2] + \text{H})^+$ : 155.10666, found 155.1065



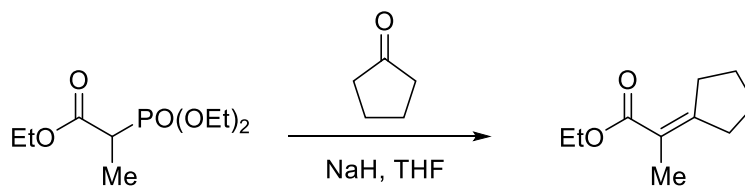
**3-cyclopentylfuran-2(5H)-one (1c):** Potassium hexamethyldisilylamide (1 M, 2.4 mL, 2.4 mmol, 1.2 equiv.) was added to 15 mL THF and cooled to  $-78^{\circ}\text{C}$ . 3-Cyclopentyl-2,5-dihydrofuran-2-one (308 mg, 2 mmol, 1 equiv.) in 4.5 mL THF was added dropwise and the reaction stirred for 1 hour. Phenylselenenyl chloride (460 mg, 2.4 mmol, 1.2 equiv.) in 2 mL THF was added and the reaction stirred for 30 min. The reaction was then warmed to room temperature and quenched with sat.  $\text{NH}_4\text{Cl}$ . The mixture was extracted with  $\text{Et}_2\text{O}$  and washed with brine. The organic extracts were dried with  $\text{MgSO}_4$  and solvent removed *in vacuo*. The resulting residue was redissolved in 20 mL DCM and cooled to  $0^{\circ}\text{C}$ . 1 mL of pyridine and 1.5 mL of 30% hydrogen peroxide were added and the reaction warmed to room temperature over 20 minutes. The reaction was diluted with  $\text{Et}_2\text{O}$ , washed with sat.  $\text{NaHSO}_4$ , 5% HCl, sat.  $\text{NaHCO}_3$ , and brine, then dried with  $\text{Na}_2\text{SO}_4$ . Crude product was purified by flash chromatography.

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.05 (q,  $J = 1.7$  Hz, 1H), 4.76 (t,  $J = 1.8$  Hz, 2H), 2.77 (ttd,  $J = 9.0, 7.4, 1.8$  Hz, 1H), 2.01 (dddd,  $J = 11.3, 9.4, 7.4, 3.6$  Hz, 2H), 1.77 – 1.61 (m, 4H), 1.55 – 1.45 (m, 2H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  174.2, 142.4, 138.4, 70.1, 36.7, 31.6, 25.1.

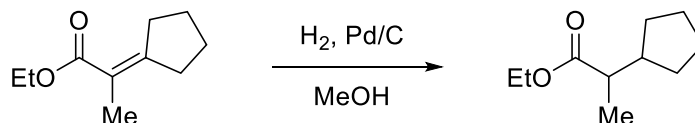
IR ( $\text{cm}^{-1}$ ): 2950.5, 2869.2, 1740.0, 1450.2, 1344.7, 1207.4, 1063.7, 1043.0, 826.4.

HRMS: Calc'd for  $[(\text{C}_9\text{H}_{12}\text{O}_2)+\text{H}]^+$ : 153.09155, found 153.0911



**ethyl 2-cyclopentylidenepropanoate:** Synthesized from ethyl 2-(diethoxyphosphoryl)propanoate (2.79 mL, 13 mmol, 1.3 equiv.), cyclopentanone (886  $\mu\text{L}$ , 10 mmol, 1 equiv.) and sodium hydride (440 mg, 11 mmol, 1.1 equiv.) according to general procedure G. Product obtained as a clear oil (1.5 g, 89% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.17 (q,  $J = 7.1$  Hz, 2H), 2.72 (dd,  $J = 9.0, 4.1$  Hz, 2H), 2.36 (t,  $J = 6.7$  Hz, 2H), 1.85 (s, 3H), 1.69 (ddt,  $J = 14.8, 11.7, 5.6$  Hz, 4H), 1.29 (t,  $J = 7.2$  Hz, 3H).



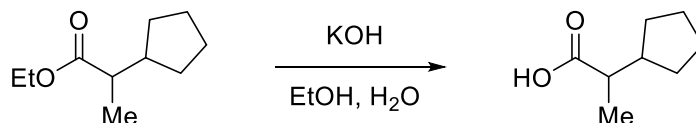
**ethyl 2-cyclopentylpropanoate (rac-2b):** Synthesized from ethyl 2-cyclopentylidenepropanoate (1.35 g, 8 mmol) according to general procedure H. Product obtained as a clear oil (1.26 g, 93% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.12 (qd, *J* = 7.1, 2.9 Hz, 2H), 2.22 (dq, *J* = 9.3, 6.9 Hz, 1H), 1.97 (qt, *J* = 9.3, 7.4 Hz, 1H), 1.79 (dddd, *J* = 13.8, 7.2, 3.6, 1.5 Hz, 1H), 1.71 (tdd, *J* = 11.4, 5.1, 2.3 Hz, 1H), 1.65 – 1.57 (m, 2H), 1.55 – 1.48 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22 – 1.08 (m, 5H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 176.9, 60.1, 45.3, 43.6, 31.0, 30.4, 25.3, 25.2, 16.3, 14.4.

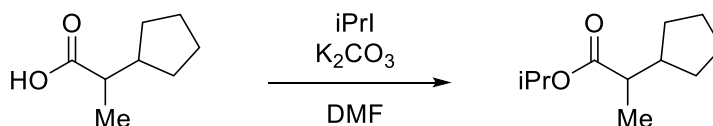
**IR** (cm<sup>-1</sup>): 2952.2, 2870.0, 1730.7, 1455.1, 1372.8, 1252.3, 1151.2, 1046.9.

**HRMS**: Calc'd for ([C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>]+H)<sup>+</sup>: 171.13796, found 171.1382



**2-cyclopentylpropanoic acid**: Ethyl 2-cyclopentylpropanoate (1.02 g, 6 mmol, 1 equiv.) was dissolved in 30 mL ethanol. KOH (1.35g, 24 mmol, 4 equiv.) dissolved in 30 mL H<sub>2</sub>O was added and the mixture heated to 70 °C overnight. After cooling to room temperature, EtOH was removed *in vacuo*, and the resulting aqueous solution extracted twice with hexanes. These extracts were discarded. The aqueous solution was then acidified with 2 M HCl, extracted with Et<sub>2</sub>O, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Crude product was used directly (807 mg, 95% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 11.32 (bs, 1H), 2.32 – 2.22 (m, 1H), 1.99 (dtd, *J* = 16.9, 9.3, 7.5 Hz, 1H), 1.80 (dq, *J* = 18.3, 7.2, 3.1 Hz, 2H), 1.68 – 1.49 (m, 4H), 1.29 – 1.10 (m, 5H).



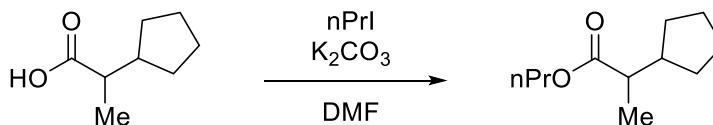
**isopropyl 2-cyclopentylpropanoate (rac-3b)**: Synthesized from 2-cyclopentylpropanoic acid (142 mg, 1 mmol) according to general procedure E. Product obtained as a clear oil (150 mg, 81% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 5.00 (hept, *J* = 6.2 Hz, 1H), 2.18 (dq, *J* = 9.5, 6.9 Hz, 1H), 1.97 (dtd, *J* = 16.9, 9.3, 7.5 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.75 – 1.67 (m, 1H), 1.60 (ddt, *J* = 11.5, 8.3, 3.7 Hz, 2H), 1.55 – 1.46 (m, 2H), 1.26 – 1.10 (m, 11H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 176.5, 67.2, 45.5, 43.6, 30.9, 30.5, 25.4, 25.3, 22.0, 22.0, 16.4.

**IR** (cm<sup>-1</sup>): 2976.6, 2952.2, 2870.2, 1726.3, 1454.8, 1737.2, 1260.9, 1161.6, 1107.9, 922.5.

**HRMS**: Calc'd for ([C<sub>11</sub>H<sub>20</sub>O<sub>2</sub>]-[C<sub>3</sub>H<sub>6</sub>]+H)<sup>+</sup>: 143.10666, found 143.1067



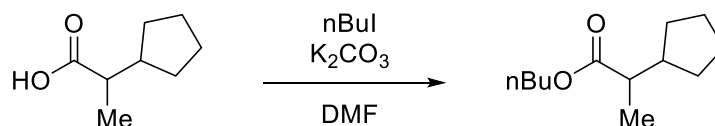
**propyl 2-cyclopentylpropanoate (rac-4b):** Synthesized from 2-cyclopentylpropanoic acid (213 mg, 1.5 mmol) according to general procedure E. Product obtained as a clear oil (218 mg, 79% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.10 – 3.96 (m, 2H), 2.29 – 2.15 (m, 1H), 1.97 (dtd, *J* = 16.8, 9.3, 7.4 Hz, 1H), 1.79 (dddd, *J* = 13.6, 7.4, 3.6, 1.5 Hz, 1H), 1.76 – 1.47 (m, 7H), 1.28 – 1.08 (m, 5H), 0.94 (t, *J* = 7.4 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 177.0, 65.8, 45.4, 43.6, 31.1, 30.4, 25.3, 25.3, 22.2, 16.4, 10.6.

**IR** (cm<sup>-1</sup>): 2952.6, 2871.9, 1730.9, 1456.0, 1245.8, 1150.6, 1060.6.

**HRMS:** Calc'd for ([C<sub>11</sub>H<sub>20</sub>O<sub>2</sub>]-[C<sub>3</sub>H<sub>6</sub>]+H)<sup>+</sup>: 143.10666, found 143.1067



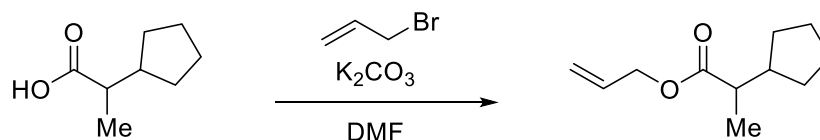
**butyl 2-cyclopentylpropanoate (rac-5b):** Synthesized from 2-cyclopentylpropanoic acid (142 mg, 1 mmol) according to general procedure E. Product obtained as a clear oil (166 mg, 84% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.07 (tt, *J* = 6.7, 3.6 Hz, 2H), 2.23 (dq, *J* = 9.4, 6.9 Hz, 1H), 1.97 (dtd, *J* = 16.7, 9.3, 7.4 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.71 (dddd, *J* = 14.2, 7.0, 3.6, 1.6 Hz, 1H), 1.64 – 1.49 (m, 6H), 1.45 – 1.32 (m, 2H), 1.26 – 1.07 (m, 5H), 0.93 (t, *J* = 7.4 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 177.0, 64.1, 45.4, 43.6, 31.0, 30.9, 30.4, 25.3, 25.3, 19.3, 16.4, 13.9.

**IR** (cm<sup>-1</sup>): 2954.5, 2870.6, 1730.9, 1455.3, 1249.3, 1152.1, 1062.3.

**HRMS:** Calc'd for ([C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>]+H)<sup>+</sup>: 199.16926, found 199.1692



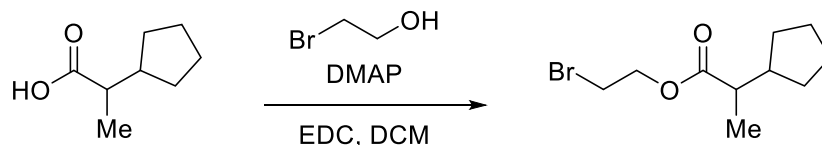
**allyl 2-cyclopentylpropanoate (rac-6b):** Synthesized from 2-cyclopentylpropanoic acid (142 mg, 1 mmol) according to general procedure E. Product obtained as a clear oil (156 mg, 86% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 5.92 (ddt, *J* = 16.3, 10.9, 5.7 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.22 (dt, *J* = 10.2, 1.5 Hz, 1H), 4.64 – 4.48 (m, 2H), 2.28 (dq, *J* = 9.7, 6.9 Hz, 1H), 2.05 – 1.92 (m, 1H), 1.84 – 1.76 (m, 1H), 1.76 – 1.67 (m, 1H), 1.66 – 1.47 (m, 4H), 1.25 – 1.07 (m, 5H).

**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 176.5, 132.6, 118.1, 64.9, 45.2, 43.6, 31.1, 30.4, 25.3, 25.2, 16.3.

**IR** (cm<sup>-1</sup>): 2951.1, 2869.9, 1731.8, 1455.4, 1241.8, 1147.0, 983.6, 928.1.

**HRMS:** Calc'd for ([C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>]+H)<sup>+</sup>: 183.13796, found 183.1382



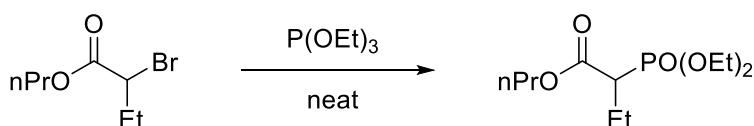
**2-bromoethyl 2-cyclopentylpropanoate (rac-7b):** Synthesized from 2-cyclopentylpropanoic acid (100 mg, 0.7 mmol, 1 equiv.) according to general procedure F using 2-bromoethanol (97 mg, 0.77 mmol, 1.1 equiv.) in place of amine. Product obtained as a clear oil (120 mg, 69% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.38 (t,  $J = 6.1$  Hz, 2H), 3.51 (t,  $J = 6.1$  Hz, 2H), 2.30 (dq,  $J = 9.3, 6.9$  Hz, 1H), 2.10 – 1.91 (m, 1H), 1.88 – 1.67 (m, 2H), 1.67 – 1.45 (m, 4H), 1.34 – 1.07 (m, 5H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  176.4, 63.6, 45.1, 43.5, 31.1, 30.4, 29.0, 25.3, 25.2, 16.3.

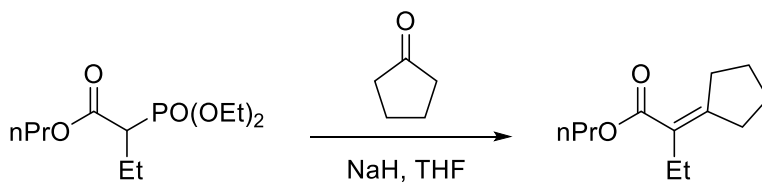
IR ( $\text{cm}^{-1}$ ): 2951.1, 2868.4, 1732.2, 1453.6, 1245.5, 1143.7, 571.0.

HRMS: Calc'd for  $([\text{C}_{10}\text{H}_{17}\text{BrO}_2] + \text{H})^+$ : 249.04847, found 249.0486



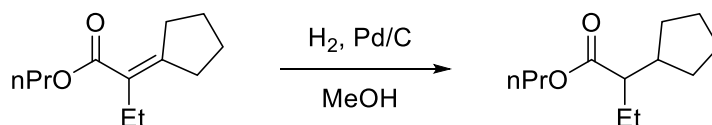
**propyl 2-(diethoxyphosphoryl)butanoate:** Synthesized from propyl 2-bromobutanoate (836 mg, 4 mmol) according to general procedure I. Product obtained as a clear oil (580 mg, 54% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.14 (dq,  $J = 16.9, 7.0, 6.0$  Hz, 6H), 2.86 (ddd,  $J = 22.4, 10.9, 3.9$  Hz, 1H), 2.09 – 1.83 (m, 2H), 1.68 (h,  $J = 7.2$  Hz, 2H), 1.33 (td,  $J = 7.1, 2.9$  Hz, 6H), 1.05 – 0.89 (m, 6H).



**propyl 2-cyclopentylidenebutanoate:** Synthesized from propyl 2-(diethoxyphosphoryl)butanoate (266 mg, 1 mmol, 1 equiv.), cyclopentanone (98  $\mu\text{L}$ , 1.1 mmol, 1.1 equiv.) and sodium hydride (40 mg, 1 mmol, 1 equiv.) according to general procedure G. Product obtained as a clear oil (100 mg, 51% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.09 (t,  $J = 6.6$  Hz, 2H), 2.70 (t,  $J = 6.9$  Hz, 2H), 2.40 (t,  $J = 6.9$  Hz, 2H), 2.30 (q,  $J = 7.5$  Hz, 2H), 1.75 – 1.63 (m, 6H), 0.99 (dt,  $J = 13.6, 7.4$  Hz, 6H).



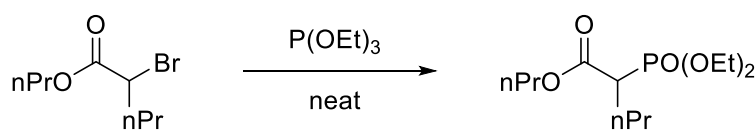
**propyl 2-cyclopentylbutanoate (rac-8b)**: Synthesized from propyl 2-cyclopentylidenebutanoate (90 mg, 0.46 mmol) according to general procedure H. Product obtained as a clear oil (75 mg, 82% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.04 (t,  $J = 6.7$  Hz, 2H), 2.07 (ddd,  $J = 9.7, 8.3, 5.9$  Hz, 1H), 2.03 – 1.91 (m, 1H), 1.86 – 1.76 (m, 1H), 1.72 – 1.45 (m, 9H), 1.29 – 1.06 (m, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H), 0.88 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  176.4, 65.7, 53.6, 42.8, 31.0, 30.9, 25.2, 25.1, 24.9, 22.2, 12.2, 10.6.

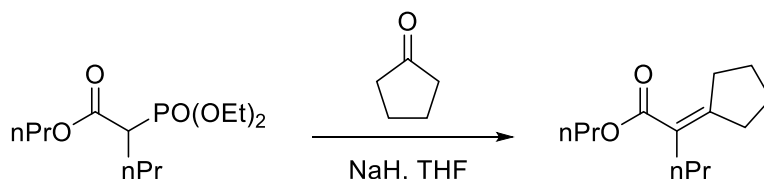
$\text{IR}$  ( $\text{cm}^{-1}$ ): 2957.3, 2874.2, 1729.8, 1458.6, 1265.2, 1226.8, 1183.2, 1148.3, 964.8.

$\text{HRMS}$ : Calc'd for  $[(\text{C}_{12}\text{H}_{22}\text{O}_2)+\text{H}]^+$ : 199.16926, found 199.1691



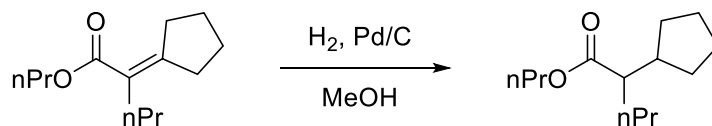
**propyl 2-(diethoxyphosphoryl)pentanoate**: Synthesized from propyl 2-bromopentanoate (1.12 g, 5 mmol) according to general procedure I. Product obtained as a clear oil (678 mg, 48% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.14 (dt,  $J = 17.2, 9.9, 4.0$  Hz, 6H), 2.95 (ddd,  $J = 22.7, 11.2, 4.3$  Hz, 1H), 1.98 (ddh,  $J = 14.8, 10.0, 5.8, 4.9$  Hz, 1H), 1.81 (dh,  $J = 16.0, 5.6, 4.1$  Hz, 1H), 1.68 (q,  $J = 7.8, 7.4$  Hz, 2H), 1.48 – 1.24 (m, 8H), 0.94 (dt,  $J = 14.3, 6.9$  Hz, 6H).



**propyl 2-cyclopentylidenepentanoate**: Synthesized from propyl 2-(diethoxyphosphoryl)pentanoate (280 mg, 1 mmol, 1 equiv.), cyclopentanone (98  $\mu\text{L}$ , 1.1 mmol, 1.1 equiv.) and sodium hydride (40 mg, 1 mmol, 1 equiv.) according to general procedure G. Product obtained as a clear oil (75 mg, 36% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.08 (t,  $J = 6.6$  Hz, 2H), 2.70 (t,  $J = 7.0$  Hz, 2H), 2.40 (t,  $J = 6.9$  Hz, 2H), 2.26 (m, 2H), 1.68 (tdd,  $J = 10.7, 8.2, 6.2$  Hz, 6H), 1.48 – 1.37 (m, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H), 0.91 (t,  $J = 7.4$  Hz, 3H).



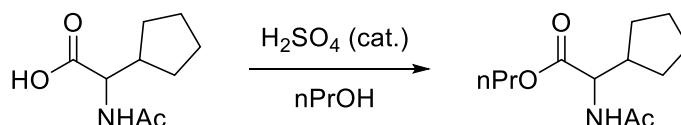
**propyl 2-cyclopentylpentanoate (rac-9b)**: Synthesized from propyl 2-cyclopentylidenepentanoate (75 mg, 0.36 mmol) according to general procedure H. Product obtained as a clear oil (55 mg, 73% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.03 (t,  $J = 6.7$  Hz, 2H), 2.15 (ddd,  $J = 10.7, 9.6, 3.8$  Hz, 1H), 1.96 (qt,  $J = 9.5, 7.3$  Hz, 1H), 1.86 – 1.78 (m, 1H), 1.71 – 1.44 (m, 9H), 1.36 – 1.07 (m, 4H), 0.94 (t,  $J = 7.4$  Hz, 3H), 0.89 (t,  $J = 7.3$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  176.6, 65.7, 51.7, 43.0, 34.0, 31.0 (2C), 25.2, 25.1, 22.2, 21.1, 14.2, 10.7.

IR ( $\text{cm}^{-1}$ ): 2954.4, 2871.6, 1730.5, 1454.8, 1177.6, 1147.8, 1061.6, 945.9.

HRMS: Calc'd for  $([\text{C}_{13}\text{H}_{24}\text{O}_2] + \text{H})^+$ : 213.18491, found 213.1850



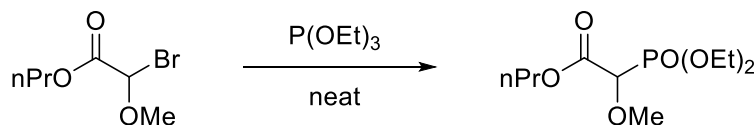
**propyl 2-acetamido-2-cyclopentylacetate (rac-10b)**: Synthesized from 2-acetamido-2-cyclopentylacetic acid (185 mg, 1 mmol) according to general procedure D. Product obtained as a clear oil (185 mg, 81% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  5.94 (d,  $J = 8.8$  Hz, 1H), 4.57 (dd,  $J = 8.8, 7.0$  Hz, 1H), 4.08 (td,  $J = 6.7, 1.0$  Hz, 2H), 2.28 – 2.17 (m, 1H), 2.03 (s, 3H), 1.75 – 1.62 (m, 6H), 1.56 – 1.48 (m, 2H), 1.40 – 1.29 (m, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  172.9, 167.0, 67.0, 55.2, 43.0, 29.1, 28.5, 25.4, 25.1, 23.5, 22.1, 10.6.

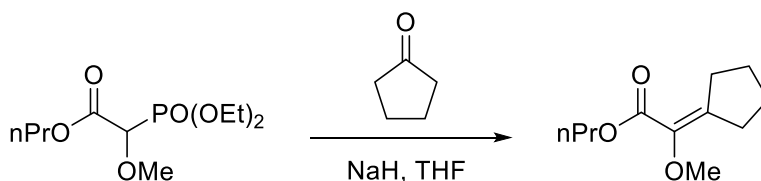
IR ( $\text{cm}^{-1}$ ): 3247.1, 3066.7, 2959.5, 2873.9, 1731.3, 1650.8, 1551.5, 1372.7, 1190.5, 1158.9, 1130.1, 938.7, 735.8, 902.9, 512.3.

HRMS: Calc'd for  $([\text{C}_{12}\text{H}_{21}\text{NO}_3] + \text{H})^+$ : 228.15942, found 228.1594



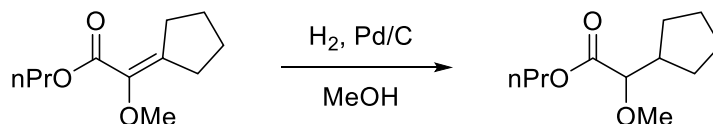
**propyl 2-(diethoxyphosphoryl)-2-methoxyacetate**: Synthesized from propyl 2-bromo-2-methoxyacetate (1.06 g, 5 mmol) according to general procedure I. Product obtained as a clear oil (1.2 g, 90% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.28 – 4.08 (m, 7H), 3.52 (s, 3H), 1.71 (q,  $J = 7.0$  Hz, 2H), 1.34 (td,  $J = 7.1, 1.7$  Hz, 6H), 0.97 (t,  $J = 7.4$  Hz, 3H).



**propyl 2-cyclopentylidene-2-methoxyacetate:** Synthesized from propyl 2-(diethoxyphosphoryl)-2-methoxyacetate (402 mg, 1.5 mmol, 1 equiv.), cyclopentanone (146  $\mu$ L, 1.1 mmol, 1.1 equiv.) and sodium hydride (60 mg, 1 mmol, 1 equiv.) according to general procedure G. Product obtained as a clear oil (107 mg, 36% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.15 (t,  $J = 6.7$  Hz, 2H), 3.60 (s, 3H), 2.68 (tt,  $J = 7.3, 1.4$  Hz, 2H), 2.51 (tt,  $J = 7.1, 1.4$  Hz, 2H), 1.78 – 1.69 (m, 4H), 1.69 – 1.61 (m, 2H), 0.99 (t,  $J = 7.4$  Hz, 3H).



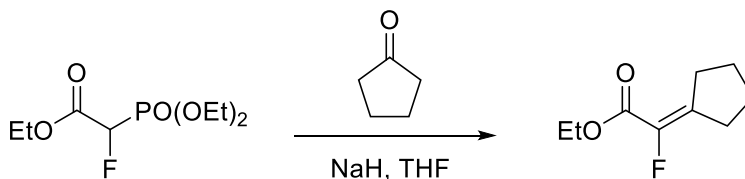
**propyl 2-cyclopentyl-2-methoxyacetate (rac-11b):** Synthesized from propyl 2-cyclopentylidene-2-methoxyacetate (107 mg, 0.54 mmol) according to general procedure H. Product obtained as a clear oil (107 mg, 99% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.13 (t,  $J = 6.7$  Hz, 2H), 3.57 (d,  $J = 7.0$  Hz, 1H), 3.37 (s, 3H), 2.30 – 2.15 (m, 1H), 1.79 – 1.58 (m, 6H), 1.56 – 1.35 (m, 4H), 0.96 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  172.9, 84.6, 66.4, 58.4, 42.7, 28.6, 28.6, 25.7, 25.6, 22.2, 10.6.

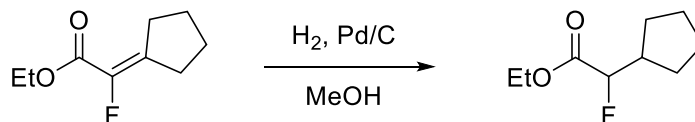
**IR** ( $\text{cm}^{-1}$ ): 2953.3, 2869.3, 1745.7, 1729.5, 1453.3, 1264.7, 1182.3, 1113.4, 1057.8, 993.4.

**HRMS:** Calc'd for  $([\text{C}_{11}\text{H}_{20}\text{O}_3] + \text{H})^+$ : 201.14852, found 201.1484



**ethyl 2-cyclopentylidene-2-fluoroacetate:** Synthesized from ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (1.16 g, 4.8 mmol, 1.2 equiv.), cyclopentanone (355  $\mu$ L, 4 mmol, 1 equiv.) and sodium hydride (176 mg, 4.4 mmol, 1.1 equiv.) according to general procedure G. Product obtained as a clear oil (511 mg, 74% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.27 (q,  $J = 7.1$  Hz, 2H), 2.76 – 2.64 (m, 2H), 2.53 (dddd,  $J = 7.2, 5.6, 4.1, 2.4$  Hz, 2H), 1.82 – 1.64 (m, 4H), 1.33 (t,  $J = 7.1$  Hz, 3H).



**ethyl 2-cyclopentyl-2-fluoroacetate (rac-12b)**: Synthesized from ethyl 2-cyclopentylidene-2-fluoroacetate (200 mg, 1.16 mmol) according to general procedure H. Product obtained as a clear oil (125 mg, 62% yield).

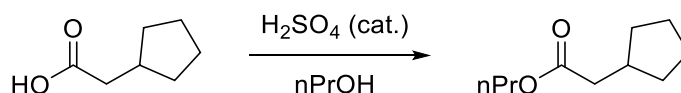
$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.78 (dd,  $J = 49.5, 5.4$  Hz, 1H), 4.25 (q,  $J = 7.1$  Hz, 2H), 2.40 (dq,  $J = 25.3, 8.2, 5.4$  Hz, 1H), 1.80 – 1.61 (m, 4H), 1.58 – 1.47 (m, 4H), 1.31 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  169.9 (d,  $J = 24.2$  Hz), 91.4 (d,  $J = 185.3$  Hz), 61.4, 41.9 (d,  $J = 20.4$  Hz), 28.2 (d,  $J = 4.6$  Hz), 27.0 (d,  $J = 3.5$  Hz), 25.8, 25.7, 14.3.

$^{19}\text{F NMR}$  (376 MHz;  $\text{CDCl}_3$ ):  $\delta$  -196.29 (dd,  $J = 49.6, 25.2$  Hz).

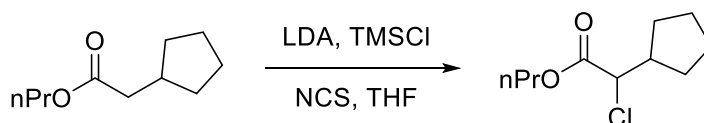
**IR** ( $\text{cm}^{-1}$ ): 2955.6, 2871.9, 1756.9, 1736.8, 1451.6, 1372.9, 1273.8, 1201.2, 1161.1, 1027.4.

**HRMS**: Calc'd for  $[(\text{C}_9\text{H}_{15}\text{FO}_2)\text{-F}]^+$ : 155.10666, found 155.1065



**propyl 2-cyclopentylacetate**: Synthesized from 2-cyclopentylacetic acid (1.03 mg, 8 mmol) according to general procedure D. Product obtained as a clear oil (990 mg, 73% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.02 (t,  $J = 6.7$  Hz, 2H), 2.31 (d,  $J = 7.8$  Hz, 2H), 2.28 – 2.17 (m, 1H), 1.87 – 1.77 (m, 2H), 1.70 – 1.59 (m, 4H), 1.54 (td,  $J = 12.1, 7.7, 3.9, 2.2$  Hz, 2H), 1.21 – 1.10 (m, 2H), 0.94 (t,  $J = 7.4$  Hz, 3H).



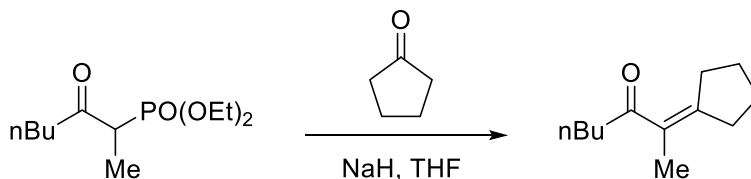
**propyl 2-chloro-2-cyclopentylacetate (rac-13b)**: Diisopropylamine (620  $\mu\text{L}$ , 4.4 mmol, 1.1 equiv.) was dissolved in 4 mL THF and cooled to 0  $^\circ\text{C}$ . n-Butyllithium (2.5 M, 1.68 mL, 4.2 mmol, 1.05 equiv.) was added dropwise and the reaction stirred for 30 minutes. The reaction was then cooled to -78  $^\circ\text{C}$  and propyl 2-cyclopentylacetate (681 mg, 4 mmol, 1 equiv.) in 2 mL THF added dropwise. The reaction was stirred for 30 minutes then trimethylsilyl chloride (533  $\mu\text{L}$ , 4.2 mmol, 1.05 equiv.) added dropwise and the reaction stirred for 2 hours as it warmed to room temperature. The reaction was recooled to -78  $^\circ\text{C}$  and N-chlorosuccinimide (801 mg, 6 mmol, 1.5 equiv.) in 4 mL THF added dropwise. The reaction was then stirred overnight and allowed to warm to room temperature. The reaction was quenched with sat.  $\text{NH}_4\text{Cl}$ , extracted with  $\text{Et}_2\text{O}$ , washed with brine, and dried with  $\text{Na}_2\text{SO}_4$ . Crude product purified by flash chromatography to obtain pure product as a clear oil. (737 mg, 90% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.19 – 4.07 (m, 3H), 2.49 (h,  $J = 8.3$  Hz, 1H), 1.93 – 1.85 (m, 1H), 1.80 – 1.55 (m, 7H), 1.48 (dq,  $J = 12.4, 7.8$  Hz, 1H), 1.34 (ddt,  $J = 14.3, 12.7, 4.6$  Hz, 1H), 0.96 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  169.9, 67.5, 62.1, 44.0, 30.0, 29.9, 25.9, 25.4, 22.0, 10.5.

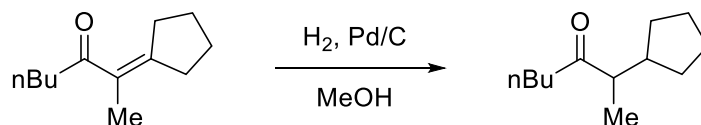
IR (cm<sup>-1</sup>): 2960.2, 2871.3, 1744.1, 1454.0, 1271.3, 1170.1, 979.7, 724.6.

HRMS: Calc'd for ([C<sub>10</sub>H<sub>17</sub>ClO<sub>2</sub>]-Cl)<sup>+</sup>: 169.12231, found 169.1225



**2-cyclopentylideneheptan-3-one:** Synthesized from diethyl (3-oxoheptan-2-yl)phosphonate (275 mg, 1.1 mmol, 1.1 equiv.), cyclopentanone (89  $\mu$ L, 1 mmol, 1 equiv.) and sodium hydride (40 mg, 1 mmol, 1 equiv.) according to general procedure G. Product obtained as a clear oil (70 mg, 39% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>):  $\delta$  2.68 – 2.59 (m, 2H), 2.53 (t,  $J$  = 7.4 Hz, 2H), 2.33 (tdd,  $J$  = 6.9, 3.0, 1.5 Hz, 2H), 1.90 (p,  $J$  = 1.7 Hz, 3H), 1.76 – 1.63 (m, 4H), 1.57 (q,  $J$  = 8.0 Hz, 2H), 1.38 – 1.28 (m, 2H), 0.91 (t,  $J$  = 7.3 Hz, 3H).



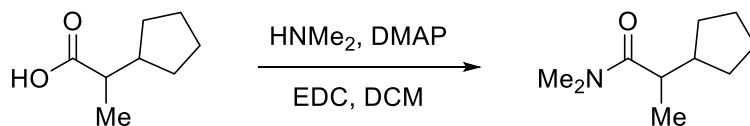
**2-cyclopentylheptan-3-one (rac-14b):** Synthesized from 2-cyclopentylideneheptan-3-one (70 mg, 0.39 mmol) according to general procedure H. Product obtained as a clear oil (59 mg, 83% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>):  $\delta$  2.49 – 2.29 (m, 3H), 1.97 (h,  $J$  = 8.7 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.71 – 1.64 (m, 1H), 1.63 – 1.47 (m, 6H), 1.31 (p,  $J$  = 7.3 Hz, 2H), 1.15 – 1.00 (m, 5H), 0.90 (t,  $J$  = 7.3 Hz, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>):  $\delta$  215.4, 52.2, 42.8, 41.4, 31.2, 30.3, 25.7, 25.3, 24.9, 22.4, 15.7, 13.9.

IR (cm<sup>-1</sup>): 2953.8, 2870.1, 1708.1, 1454.5, 1371.4, 1026.0.

HRMS: Calc'd for ([C<sub>12</sub>H<sub>22</sub>O]+H)<sup>+</sup>: 183.17489, found 183.1742



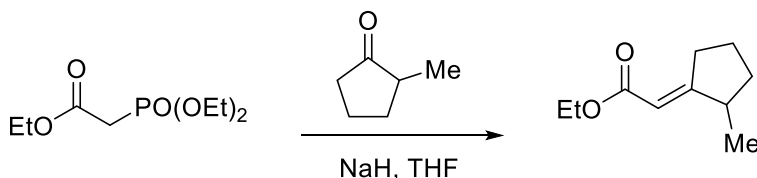
**2-cyclopentyl-N,N-dimethylpropanamide (rac-15b):** Synthesized from 2-cyclopentylpropanoic acid (113 mg, 0.8 mmol, 1 equiv.) and dimethylamine (2M, 0.6 mL, 1.2 mmol, 1.5 equiv.) according to general procedure F. Product obtained as a pale yellow oil (95 mg, 70% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>):  $\delta$  3.05 (s, 3H), 2.95 (s, 3H), 2.55 – 2.44 (m, 1H), 2.09 (hept,  $J$  = 8.9, 8.0 Hz, 1H), 1.79 (dddd,  $J$  = 31.8, 16.0, 7.0, 3.3 Hz, 2H), 1.66 – 1.46 (m, 4H), 1.18 – 1.07 (m, 4H), 1.00 (dq,  $J$  = 12.4, 8.4 Hz, 1H).

$^{13}\text{C}$  NMR (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  177.0, 77.4, 77.2, 76.9, 43.9, 41.3, 37.6, 35.7, 31.6, 30.4, 25.3, 25.2, 16.8.

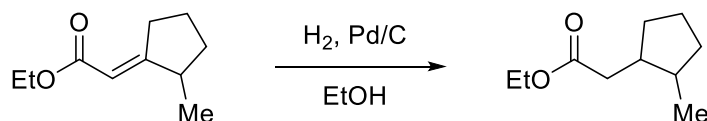
IR ( $\text{cm}^{-1}$ ): 2947.8, 2867.0, 1633.4, 1452.6, 1412.5, 1395.0, 1129.4, 730.2.

HRMS: Calc'd for  $([\text{C}_{10}\text{H}_{19}\text{NO}]+\text{H})^+$ : 170.15394, found 170.1539



**ethyl 2-(2-methylcyclopentylidene)acetate**: Synthesized from triethyl phosphonoacetate (538 mg, 2.4 mmol, 1.2 equiv.), 2-methylcyclopentanone (214  $\mu\text{L}$ , 2 mmol, 1 equiv.) and sodium hydride (80 mg, 2 mmol, 1 equiv.) according to general procedure G. Product obtained as a clear oil (256 mg, 76% yield, E:Z = 86:14).

$^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  5.69 (q,  $J$  = 2.5 Hz, 1H), 4.15 (q,  $J$  = 7.1 Hz, 2H), 2.98 – 2.87 (m, 1H), 2.73 (dtt,  $J$  = 20.0, 8.8, 2.6 Hz, 1H), 2.51 (dtt,  $J$  = 9.3, 6.9, 2.3 Hz, 1H), 1.97 – 1.78 (m, 2H), 1.67 – 1.48 (m, 1H), 1.31 – 1.19 (m, 4H), 1.12 (d,  $J$  = 6.8 Hz, 3H).



**ethyl 2-(2-methylcyclopentyl)acetate (rac-16b)**: Synthesized from ethyl 2-(2-methylcyclopentylidene)acetate (100 mg, 0.59 mmol) according to general procedure H. Product obtained as a clear oil (90 mg, 89% yield, trans/cis = 70:30). Diastereomers were assigned based on the literature for this compound.<sup>10</sup>

$^1\text{H}$  NMR (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.12 (qd,  $J$  = 7.2, 1.9 Hz, 2H), 2.50 – 2.03 (m, 3H), 1.95 – 1.41 (m, 6H), 1.25 (t,  $J$  = 7.1 Hz, 4H), 0.97 (d,  $J$  = 6.6 Hz, 3H<sub>trans-isomer</sub>), 0.81 (d,  $J$  = 7.0 Hz, 3H<sub>cis-isomer</sub>).

$^{13}\text{C}$  NMR (126 MHz;  $\text{CDCl}_3$ ):

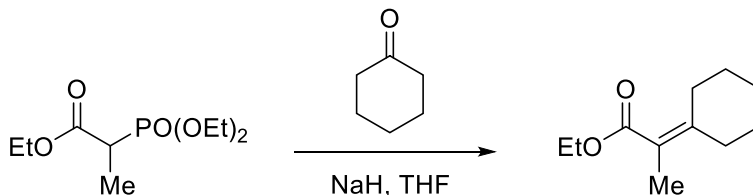
*trans*-isomer:  $\delta$  173.8, 60.3, 44.2, 40.6, 39.5, 34.5, 32.5, 23.3, 19.1, 14.43.

*cis*-isomer:  $\delta$  174.0, 60.3, 39.8, 36.2, 35.8, 33.3, 30.2, 22.7, 15.3, 14.42.

IR ( $\text{cm}^{-1}$ ): 2951.9, 2869.5, 1732.5, 1249.0, 1182.6, 1132.0, 1030.9.

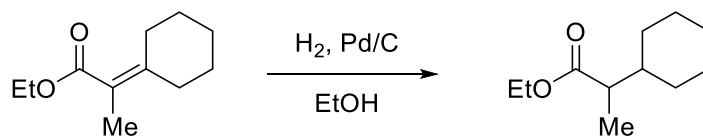
HRMS: Calc'd for  $([\text{C}_{10}\text{H}_{18}\text{O}_2]+\text{H})^+$ : 171.13796, found 171.1378

## 6-exo products



**ethyl 2-cyclohexylidenepropanoate:** Synthesized from triethyl 2-phosphonopropionate (310 mg, 1.3 mmol, 1.3 equiv.), cyclohexanone (103  $\mu$ L, 1 mmol, 1 equiv.) and sodium hydride (42 mg, 1.1 mmol, 1.1 equiv.) according to general procedure G. Product obtained as a clear oil (134 mg, 74% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.18 (q,  $J = 7.1$  Hz, 2H), 2.41 (d,  $J = 5.4$  Hz, 2H), 2.21 (t,  $J = 5.4$  Hz, 2H), 1.85 (s, 3H), 1.63 – 1.54 (m, 6H), 1.29 (t,  $J = 7.1$  Hz, 3H).



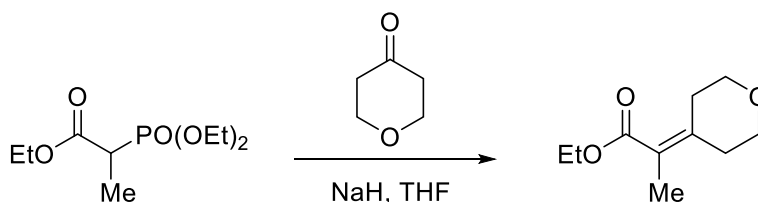
**ethyl 2-cyclohexylpropanoate (rac-17b):** Synthesized from ethyl 2-cyclohexylidenepropanoate (134 mg, 0.74 mmol) according to general procedure H. Product obtained as a clear oil (128 mg, 94% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.15 (qd,  $J = 7.1, 3.9$  Hz, 2H), 2.24 (p,  $J = 7.1$  Hz, 1H), 1.79 – 1.50 (m, 6H), 1.32 – 1.20 (m, 5H), 1.20 – 0.88 (m, 6H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  176.8, 60.1, 45.7, 40.9, 31.3, 29.8, 26.5, 26.5, 26.4, 14.5, 14.2.

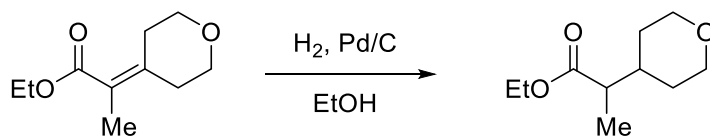
IR ( $\text{cm}^{-1}$ ): 2979.7, 2923.6, 2852.3, 1730.6, 1448.2, 1170.5, 1145.2, 1057.4, 892.4.

HRMS: Calc'd for  $[\text{C}_{11}\text{H}_{20}\text{O}_2 + \text{H}]^+$ : 185.15361, found 185.1537



**ethyl 2-(tetrahydro-4H-pyran-4-ylidene)propanoate:** Synthesized from triethyl 2-phosphonopropionate (357 mg, 1.5 mmol, 1.2 equiv.), tetrahydro-4H-pyran-4-one (125 mg, 1.25 mmol, 1 equiv.) and sodium hydride (55 mg, 1.38 mmol, 1.1 equiv.) according to general procedure G. Product obtained as a clear oil (163 mg, 71% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.19 (q,  $J = 7.1$  Hz, 2H), 3.75 – 3.72 (m, 2H), 3.70 (t,  $J = 5.6$  Hz, 2H), 2.67 (tt,  $J = 6.2, 1.1$  Hz, 2H), 2.41 – 2.33 (m, 2H), 1.88 (s, 3H), 1.30 (t,  $J = 7.1$  Hz, 3H).



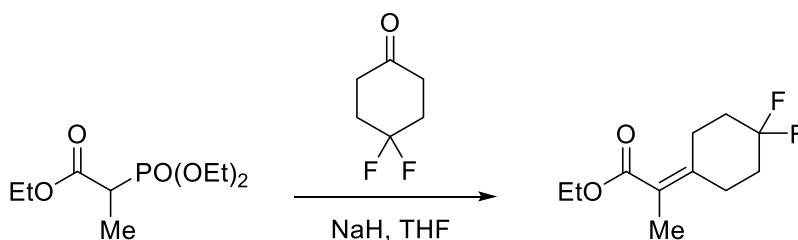
**ethyl 2-(tetrahydro-2H-pyran-4-yl)propanoate (rac-18b):** Synthesized from ethyl 2-(tetrahydro-4H-pyran-4-ylidene)propanoate (163 mg, 0.88 mmol) according to general procedure H. Product obtained as a clear oil (153 mg, 93% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.96 (ddd, *J* = 17.4, 11.5, 4.3 Hz, 2H), 3.36 (tdd, *J* = 11.9, 4.6, 2.3 Hz, 2H), 2.25 (p, *J* = 7.2 Hz, 1H), 1.77 (m, 1H), 1.66 – 1.57 (m, 1H), 1.54 – 1.45 (m, 1H), 1.45 – 1.29 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H)

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 176.0, 68.1, 68.0, 60.3, 45.3, 38.2, 31.2, 29.9, 14.5, 14.1.

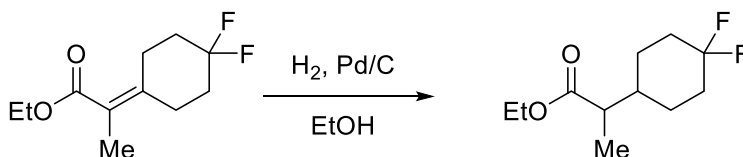
IR (cm<sup>-1</sup>): 2938.1, 2840.2, 1727.8, 1371.9, 1240.7, 1173.6, 1136.3, 1091.1, 1055.3, 1015.7, 856.7.

HRMS: Calc'd for ([C<sub>10</sub>H<sub>18</sub>O<sub>3</sub>]+H)<sup>+</sup>: 187.13287, found 187.1328



**ethyl 2-(4,4-difluorocyclohexylidene)propanoate:** Synthesized from triethyl 2-phosphonopropionate (357 mg, 1.5 mmol, 1.2 equiv.), 4,4-difluorocyclohexan-1-one (167 mg, 1.25 mmol, 1 equiv.) and sodium hydride (55 mg, 1.38 mmol, 1.1 equiv.) according to general procedure G. Product obtained as a clear oil (189 mg, 69% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 4.21 (q, *J* = 7.1 Hz, 2H), 2.69 – 2.57 (m, 2H), 2.41 (dd, *J* = 7.9, 5.5 Hz, 2H), 2.07 – 1.93 (m, 4H), 1.90 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).



**ethyl 2-(4,4-difluorocyclohexyl)propanoate (rac-19b):** Synthesized from ethyl 2-(4,4-difluorocyclohexylidene)propanoate (189 mg, 0.87 mmol) according to general procedure H. Product obtained as a clear oil (176 mg, 92% yield).

**<sup>1</sup>H NMR** (500 MHz; CDCl<sub>3</sub>): δ 4.14 (qt, *J* = 7.3, 3.3 Hz, 2H), 2.30 (p, *J* = 7.2 Hz, 1H), 2.09 (dq, *J* = 13.7, 6.8, 3.3 Hz, 2H), 1.84 – 1.59 (m, 5H), 1.46 – 1.29 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H).

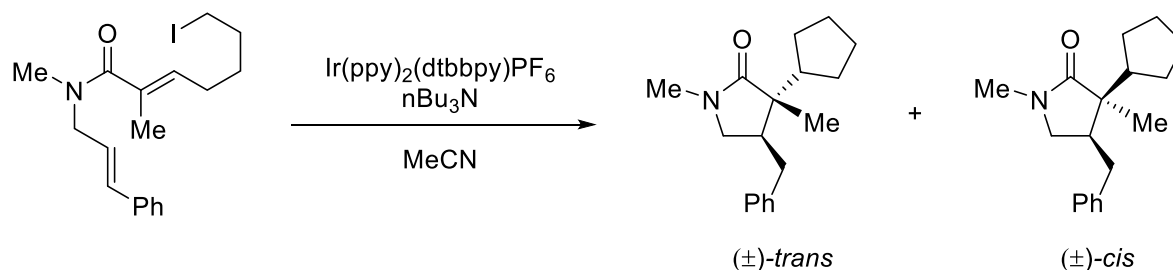
**<sup>13</sup>C NMR** (126 MHz; CDCl<sub>3</sub>): δ 176.0, 123.4 (dd, *J* = 242.2, 239.4 Hz), 60.4, 44.3 (d, *J* = 2.5 Hz), 38.8 (d, *J* = 1.5 Hz), 33.6 (ddd, *J* = 25.7, 22.7, 3.3 Hz), 27.2 (d, *J* = 9.7 Hz), 25.7 (d, *J* = 9.8 Hz), 14.5 (d, *J* = 7.4 Hz).

**<sup>19</sup>F NMR** (376 MHz; CDCl<sub>3</sub>): δ -91.92 (d, *J* = 235.5 Hz), -102.48 (dt, *J* = 235.3, 34.5 Hz).

**IR** (cm<sup>-1</sup>): 2941.0, 1727.9, 1448.3, 1095.0, 955.4, 742.7, 497.7.

**HRMS**: Calc'd for ([C<sub>11</sub>H<sub>18</sub>F<sub>2</sub>O<sub>2</sub>]+Na)<sup>+</sup>: 243.11671, found 243.1168

## Tandem cyclization product



**4-benzyl-3-cyclopentyl-1,3-dimethylpyrrolidin-2-one (rac-22b):** (E)-N-cinnamyl-7-iodo-N,2-dimethylhept-2-enamide (119 mg, 0.3 mmol, 1 equiv.), Ir(ppy)<sub>2</sub>(dtbbpy)PF<sub>6</sub> (5.5 mg, 6 μmol, 0.02 equiv.), and tributylamine (143 μL, 0.6 mmol, 2 equiv.) were dissolved in 10 mL acetonitrile and sparged with nitrogen for 20 minutes. The reaction was then irradiated with a blue Kessil LED lamp overnight. <sup>1</sup>H-NMR analysis of the crude mixture indicated a 3:2 mixture of diastereomers. Solvent was removed and the residue purified by flash chromatography. The overall yield was not determined but fractions of each diastereomer were obtained in sufficient purity to characterize individually. The less polar (first to elute) isomer was the more prevalent isomer which we tentatively assign as *trans*.

### Major isomer

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 3.01 (t, *J* = 9.9 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.78 (s, 3H), 2.58 (dd, *J* = 13.3, 11.7 Hz, 1H), 2.31 (dddd, *J* = 12.0, 9.9, 8.1, 4.2 Hz, 1H), 1.93 (tt, *J* = 10.7, 7.2 Hz, 1H), 1.85 – 1.40 (m, 7H), 1.24 (s, 3H), 1.17 – 1.03 (m, 1H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 178.0, 140.1, 128.7, 128.7, 126.5, 52.5, 48.0, 47.9, 44.9, 34.5, 29.5, 28.7, 28.3, 25.4, 23.8, 23.0.

IR (cm<sup>-1</sup>): 2952.6, 2868.1, 1687.7, 1495.2, 1453.7, 1268.1, 701.5.

HRMS: Calc'd for ([C<sub>18</sub>H<sub>25</sub>NO]+H)<sup>+</sup>: 272.20089, found 272.2008

### Minor isomer

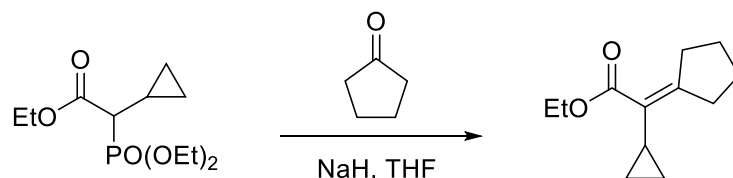
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>): δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 3.08 – 3.00 (m, 1H), 2.93 (t, *J* = 8.8 Hz, 2H), 2.76 (s, 3H), 2.50 – 2.41 (m, 2H), 2.13 (ddd, *J* = 14.9, 9.9, 7.6 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.73 – 1.51 (m, 6H), 1.36 – 1.29 (m, 1H), 1.14 (s, 3H).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 179.1, 140.1, 128.8, 128.7, 126.5, 52.4, 48.0, 47.0, 40.4, 36.4, 29.7, 27.9, 27.2, 25.6, 25.5, 17.6.

IR (cm<sup>-1</sup>): 2944.5, 2865.8, 1681.6, 1494.4, 1452.4, 1400.0, 1269.5, 701.6.

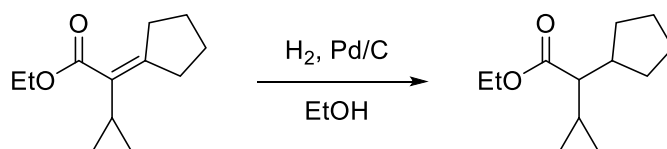
HRMS: Calc'd for ([C<sub>18</sub>H<sub>25</sub>NO]+H)<sup>+</sup>: 272.20089, found 272.2006

## Radical clock products



**ethyl 2-cyclopentylidene-2-cyclopropylacetate:** Synthesized from ethyl 2-cyclopropyl-2-(diethoxyphosphoryl)acetate (357 mg, 1.35 mmol, 1 equiv.), cyclopentanone (120  $\mu$ L, 1.35 mmol, 1 equiv.) and sodium hydride (54 mg, 1.35 mmol, 1 equiv.) according to general procedure G, with exception that the reaction was refluxed for 6 hours after addition of cyclopentanone. Product obtained as a clear oil (100 mg, 38% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.18 (q,  $J = 7.1$  Hz, 2H), 2.58 (tq,  $J = 5.1, 2.3$  Hz, 2H), 2.50 (dddt,  $J = 7.3, 5.7, 2.7, 1.5$  Hz, 2H), 1.72 – 1.64 (m, 4H), 1.49 – 1.41 (m, 1H), 1.29 (t,  $J = 7.2$  Hz, 3H), 0.79 – 0.71 (m, 2H), 0.48 – 0.42 (m, 2H).



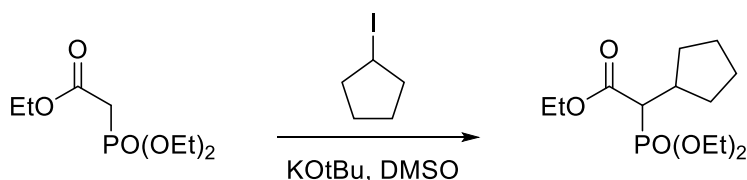
**ethyl 2-cyclopentyl-2-cyclopropylacetate (*rac*-S1b):** Synthesized from ethyl 2-cyclopentylidene-2-cyclopropylacetate (50 mg, 0.26 mmol) according to general procedure H. Product obtained as a clear oil (20 mg, 40% yield).

$^1\text{H NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  4.20 – 4.09 (m, 2H), 2.16 (qt,  $J = 9.8, 7.2$  Hz, 1H), 1.99 – 1.89 (m, 1H), 1.72 – 1.51 (m, 6H), 1.31 – 1.23 (m, 5H), 0.99 – 0.84 (m, 1H), 0.62 – 0.54 (m, 1H), 0.46 – 0.35 (m, 1H), 0.26 – 0.14 (m, 2H).

$^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  175.9, 60.1, 56.0, 43.8, 31.0, 30.9, 25.1, 24.7, 14.5, 13.3, 5.8, 2.2.

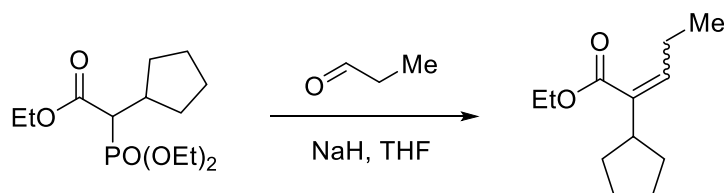
**IR** ( $\text{cm}^{-1}$ ): 2952.7, 2869.3, 1729.9, 1451.8, 1242.3, 1145.4, 1032.3, 1020.6, 823.9.

**HRMS:** Calc'd for  $([\text{C}_{12}\text{H}_{20}\text{O}_2] + \text{H})^+$ : 197.15361, found 197.1533



**ethyl 2-cyclopentyl-2-(diethoxyphosphoryl)acetate:** Potassium *tert*-butoxide (494 mg, 4.4 mmol, 1.1 equiv.) was suspended in 4 mL DMSO, triethyl phosphonoacetate (794  $\mu$ L, 4 mmol, 1 equiv.) was added dropwise, and the reaction stirred for 30 min. Cyclopentyl iodide (509  $\mu$ L, 4 mmol, 1 equiv.) was added dropwise then the reaction heated to 75  $^{\circ}$ C for 3 hours. After cooling to room temperature, the reaction was quenched with water, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> added to quench iodine formed during the reaction, the mixture extracted with Et<sub>2</sub>O, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and solvent removed in vacuo to obtain crude product which was used directly (930 mg, 79% yield).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>):  $\delta$  4.22 – 4.09 (m, 6H), 2.79 (dd,  $J$  = 20.0, 10.6 Hz, 1H), 2.49 – 2.36 (m, 1H), 1.99 (dp,  $J$  = 13.6, 3.6 Hz, 1H), 1.81 (tdd,  $J$  = 11.3, 7.6, 2.3 Hz, 1H), 1.71 – 1.50 (m, 4H), 1.38 – 1.16 (m, 11H).



**ethyl 2-cyclopentylpent-2-enoate (S1c):** Synthesized from ethyl 2-cyclopentyl-2-(diethoxyphosphoryl)acetate (584 mg, 2 mmol, 1 equiv.), propanal (143  $\mu$ L, 2 mmol, 1 equiv.) and sodium hydride (80 mg, 2 mmol, 1 equiv.) according to general procedure G. Product obtained as a clear oil (310 mg, 79% yield, E/Z = 29:71).

<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>):  $\delta$  6.62 (t,  $J$  = 7.5 Hz, 1H<sub>E-isomer</sub>), 5.69 (td,  $J$  = 7.4, 1.4 Hz, 1H<sub>Z-isomer</sub>), 4.19 (dq,  $J$  = 21.7, 7.1 Hz, 2H), 2.95 (q,  $J$  = 9.0 Hz, 1H<sub>E-isomer</sub>), 2.76 – 2.65 (m, 1H<sub>Z-isomer</sub>), 2.28 (pd,  $J$  = 7.5, 1.1 Hz, 2H<sub>Z-isomer</sub>), 2.21 (p,  $J$  = 7.6 Hz, 2H<sub>E-isomer</sub>), 1.86 – 1.51 (m, 7H), 1.43 – 1.35 (m, 1H), 1.29 (q,  $J$  = 7.1 Hz, 3H), 1.04 (t,  $J$  = 7.6 Hz, 3H<sub>E-isomer</sub>), 1.00 (t,  $J$  = 7.5 Hz, 3H<sub>Z-isomer</sub>).

<sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>):

Z-isomer:  $\delta$  169.4, 137.1, 135.9, 60.17, 43.7, 31.7, 26.8, 25.0, 14.47, 14.2.

E-isomer:  $\delta$  168.1, 143.4, 135.2, 60.11, 38.1, 31.5, 23.0, 21.7, 14.41, 13.8.

IR (cm<sup>-1</sup>): 2956.5, 2870.6, 1709.8, 1223.8, 1172.2, 1132.6, 1031.8.

HRMS: Calc'd for ([C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>]+H)<sup>+</sup>: 197.15361, found 197.1535

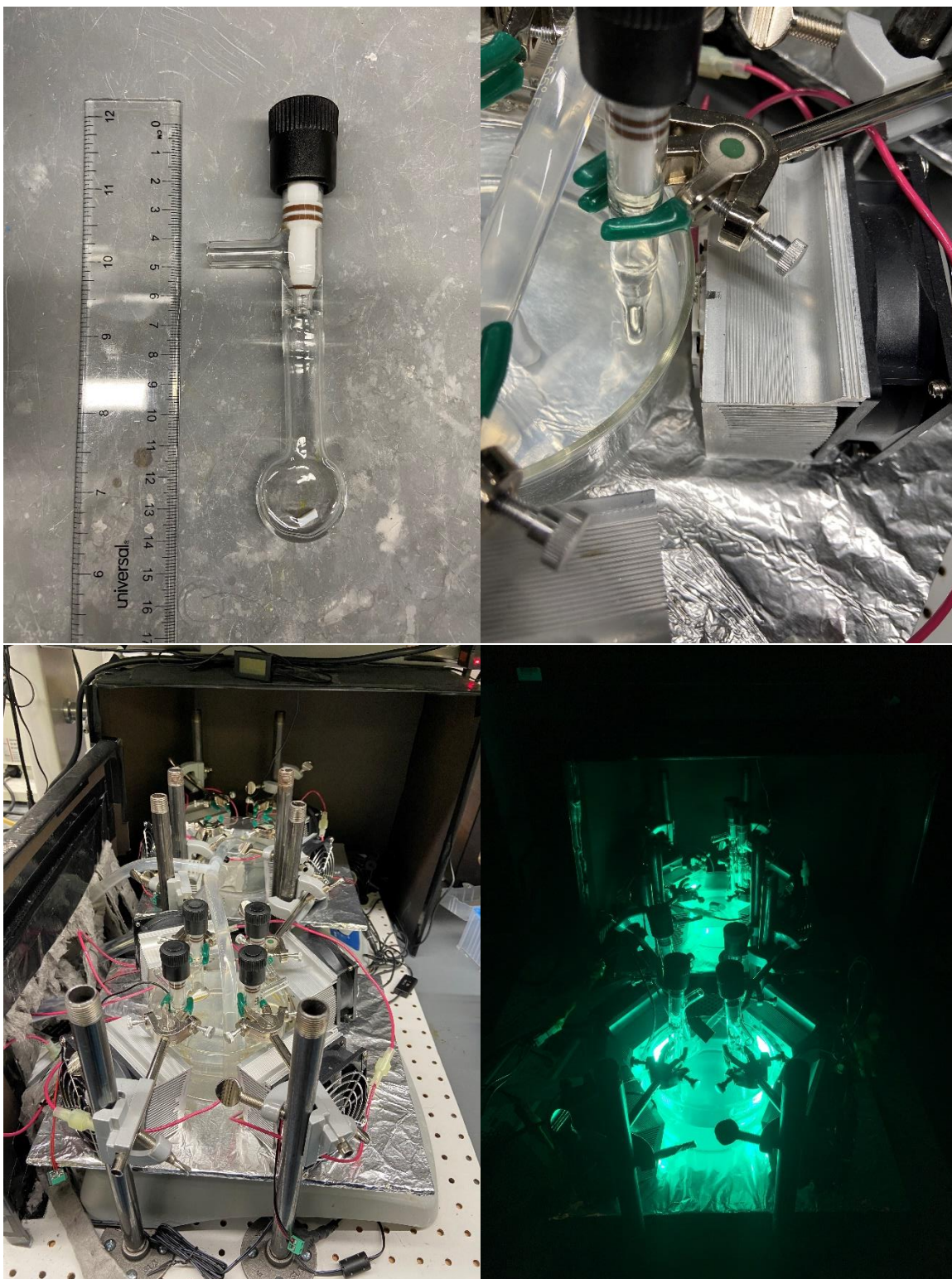
## **General Biocatalytic Procedures**

**General Comments.** Each substrate was tested in triplicate. Reactions were run in custom blown Schlenk vials (approximately 3 mL bulb volume) containing a small flea stir bar (pictured below). Stock solutions were prepared by weighting dry reagents into separate 4 mL dram vials, transferring these into an anaerobic chamber, then diluting to the desired concentrations with degassed buffer or solvent. Reactions were then assembled by addition of these stock solutions, purified enzyme aliquot, and additional buffer to the Schlenk tube, which was sealed and removed from the anaerobic chamber. The reaction was then further degassed by the freeze-pump-thaw procedure below. After the final round of thawing, the reaction was placed in a water-cooled reaction setup and irradiated with cyan LEDs (Supplemental Figure 2).

**Freeze-Pump-Thaw Procedure.** The closed Schlenk tube containing the complete reaction mixture was connected to a high-vacuum pump and the lines placed under vacuum. The reaction was frozen by submerging the Schlenk tube in a dry ice/IPA bath to solvent level. After freezing, the Schlenk tube was opened to vacuum and pumped down for 3 minutes. The Schlenk tube was then closed, transferred to a lukewarm water bath, and allowed to thaw until gas evolution ceased. The reaction was then refrozen, and this cycle completed for a total of 4 times. After the fourth thaw, the reaction is ready to be irradiated.

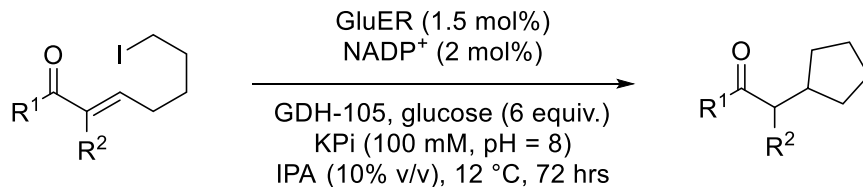
**Water-cooled setup.** A Thermo Fisher Digital One water chiller was used to maintain an approximately 12 °C water bath. An aquarium pump was used to pump chilled water from the bath into the large glass crystallization dishes pictured in the setup below. A barbed hose adapted was fitted to the glass dishes by Princeton's glass blower which allowed water to overflow through tubing back to the water chiller.

**Preparation of Standard Curves.** Standard curves were prepared by extraction from mock reactions containing various concentrations of product standard. Mock reactions were set up identical to the general procedures below with the following exceptions: an equal mass of bovine serum albumin was used in place of purified ERED, a solution containing independently synthesized and fully characterized product standard was used in place of substrate solution, and the mock reactions were not set up in an anaerobic chamber. Otherwise, GDH-105, NADP<sup>+</sup>, and glucose concentrations remained the same, as did organic cosolvent concentration. These mock reactions were extracted following the yield and enantiomer determination procedures below and analyzed by chiral GC. Standard curves were prepared by summing the areas for each product enantiomer and normalizing to naphthalene standard. Linear regressions were calculated in Microsoft Excel.



**Supplemental Figure 2.** Reaction setup. Custom Schlenk tube (top left). Tube positioning with respect to LED (top right). Complete setup before irradiation (bottom left) and during (bottom right).

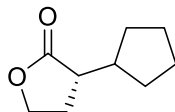
## 5-Exo Enantioselective Hydroalkylation



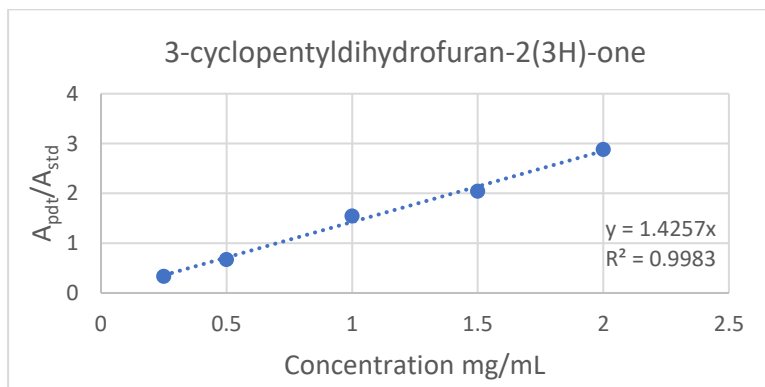
**General Procedure:** In a Coy® anaerobic chamber (<20 ppm O<sub>2</sub>), stock solutions of GDH-105 (5 mg/mL), NADP<sup>+</sup> (7.8 mg/mL), and glucose (108 mg/mL) in degassed KPi (100 mM, pH 8), and of substrate (0.1 mmol/mL) in isopropanol were prepared. To the reaction vessel was then added sequentially 20 μL NADP<sup>+</sup> solution, 100 μL glucose solution, 530 μL KPi, 100 μL substrate solution, 200 μL GDH-105 solution, and 50 μL GluER-Y177F (3 mM). The reaction vessel was sealed, removed from the chamber, and freeze-pump-thawed before being irradiated with water cooling for 72 hours.

Note: enzyme solutions varied in concentration from 1 mM to 4 mM. Therefore, KPi volume and enzyme volume were scaled accordingly such that the desired enzyme loading was achieved while the total reaction volume remained 1 mL.

**Yield and Enantiomeric Ratio Determination.** For lactone, ester, and ketone products, 3 mL of ethyl acetate containing 1 mM naphthalene standard were added to the reaction vessel, the biphasic mixture vortexed for 1 minute, and the layers allowed to separate completely (approximately 15 minutes). 2 mL of the organic phase was removed and filtered through a small plug of sodium sulfate and cotton then analyzed by chiral GC. For amide products, 3 mL acetonitrile containing 0.5 mM tribromobenzene were added to the reaction mixture resulting in the precipitation of enzymatic reaction components. After complete precipitation (approx. 3 hours), 1.5 mL was removed and analyzed by LCMS. The remaining solvent was removed in vacuo, the residue redissolved in hexanes/IPA (1:1) and analyzed by chiral HPLC. Yields were determined by comparison to a standard curve of independently synthesized product. The yields reported are an average of triplicate reactions.



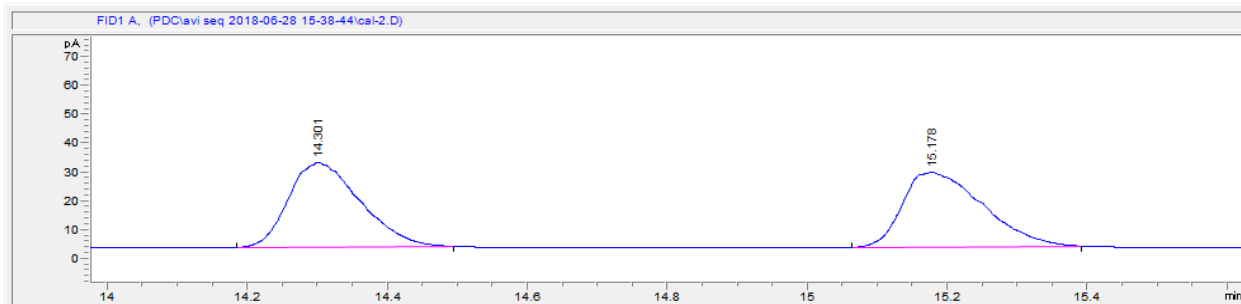
**(S)-3-cyclopentylidihydrofuran-2(3H)-one (1b):** Synthesized from (E)-3-(5-iodopentylidene)dihydrofuran-2(3H)-one (**1a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



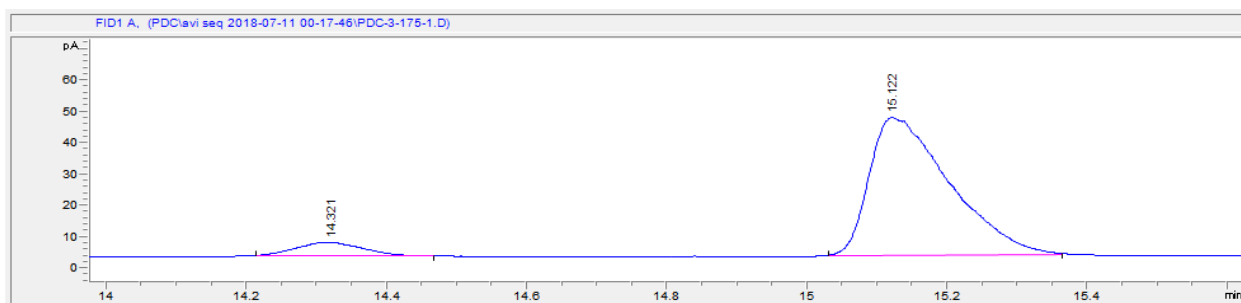
Standard Curve:

**Yield:** 92%

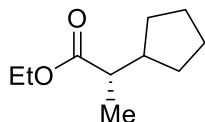
**Enantioselectivity:** 92:8 (Supelco  $\gamma$ -DEX™ 225, 15.2 psi, isothermal 160 °C)



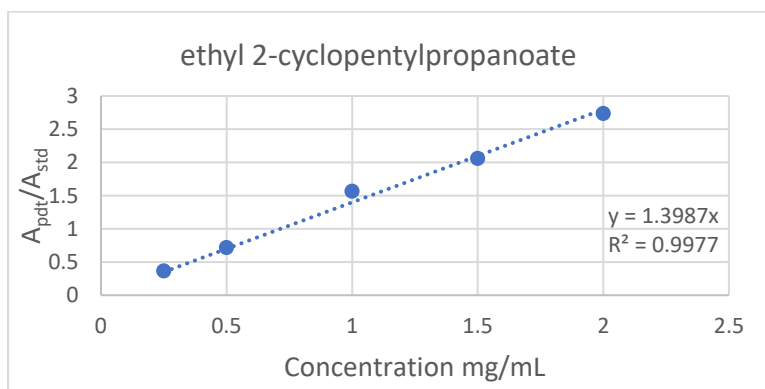
#	Time	Area	Height	Width	Area%	Symmetry
1	14.301	211.1	29.4	0.0938	50.234	0.674
2	15.178	209.1	26.2	0.0961	49.766	0.556



#	Time	Area	Height	Width	Area%	Symmetry
1	14.321	28.9	4.3	0.0853	7.614	1.03
2	15.122	351.1	44	0.106	92.386	0.392



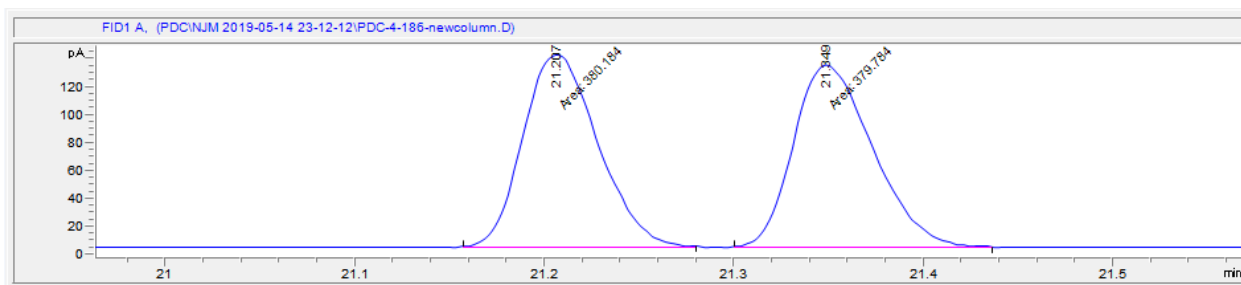
**ethyl (S)-2-cyclopentylpropanoate (2b):** Synthesized from ethyl (E)-7-iodo-2-methylhept-2-enoate (**2a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



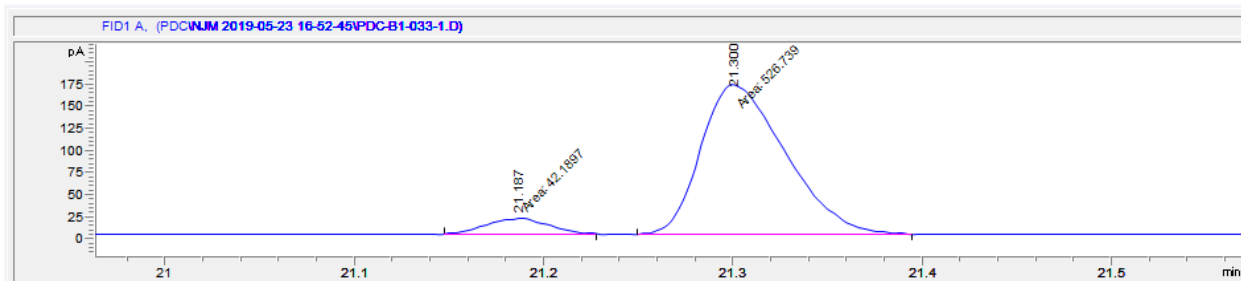
Standard Curve:

**Yield:** 85%

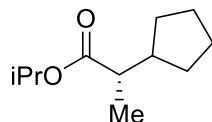
**Enantioselectivity:** 93:7 er (Astec® CHIRALDEX B-DM, 10.4 psi, 50 °C, 5 min., ramp to 200 °C by 5 °C/min.)



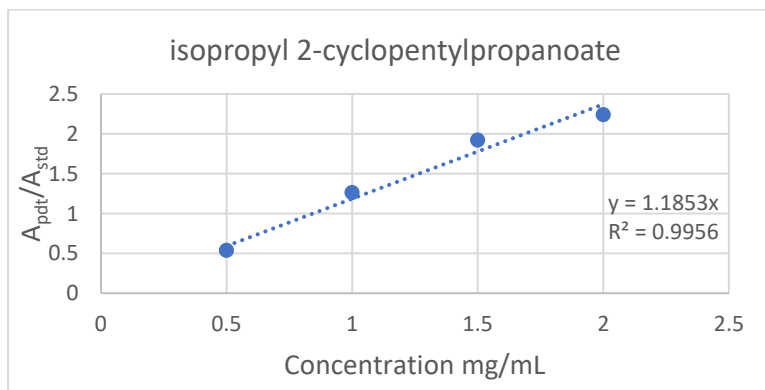
#	Time	Area	Height	Width	Area%	Symmetry
1	21.207	380.2	138.2	0.0459	50.026	0.796
2	21.349	379.8	130.2	0.0486	49.974	0.697



#	Time	Area	Height	Width	Area%	Symmetry
1	21.187	42.2	17.7	0.0398	7.416	0
2	21.3	526.7	169.3	0.0518	92.584	0.615



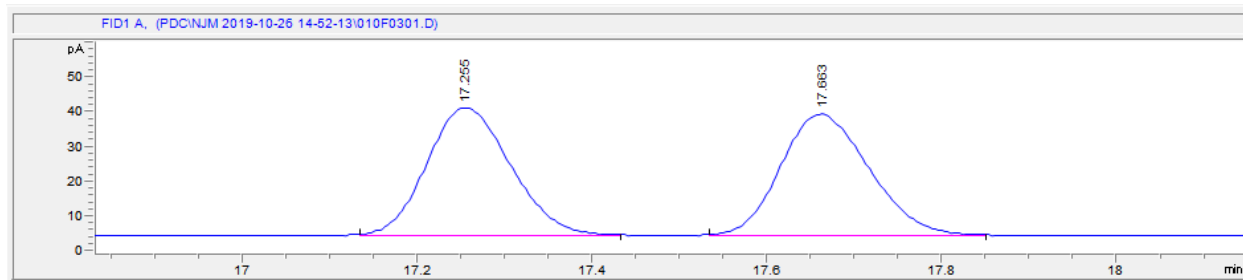
**isopropyl (S)-2-cyclopentylpropanoate (3b):** Synthesized from isopropyl (E)-7-iodo-2-methylhept-2-enoate (**3a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



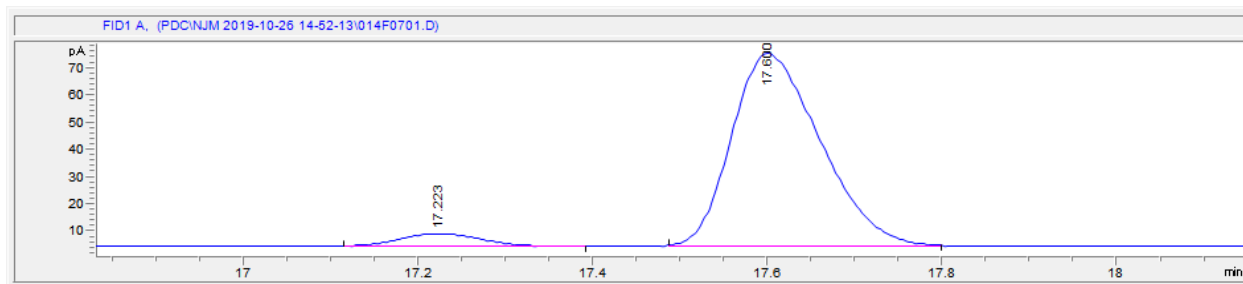
Standard Curve:

**Yield:** 93% yield

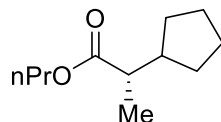
**Enantioselectivity:** 94:6 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 100 °C)



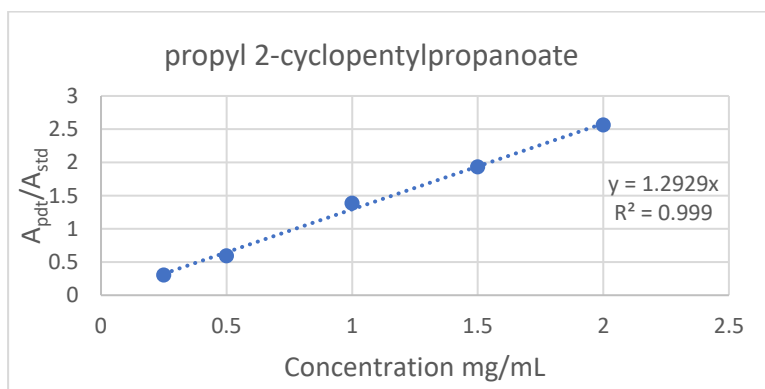
#	Time	Area	Height	Width	Area%	Symmetry
1	17.255	245.2	36.7	0.1009	50.052	0.81
2	17.663	244.7	34.9	0.1077	49.948	0.832



#	Time	Area	Height	Width	Area%	Symmetry
1	17.223	30	4.7	0.1	5.653	0.872
2	17.6	500.5	71	0.1052	94.347	0.652



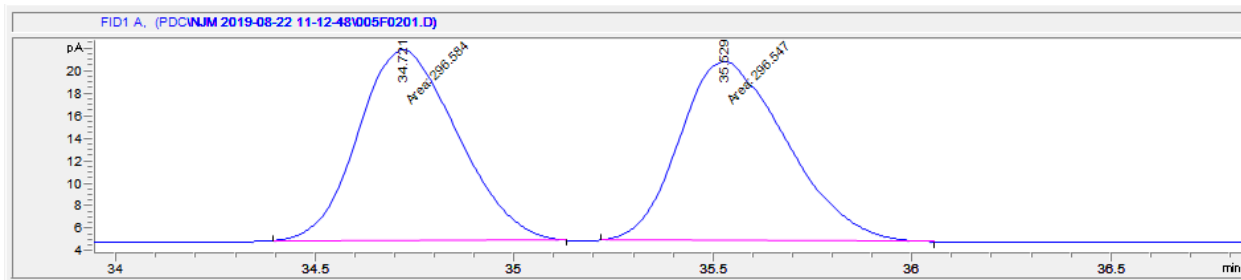
**propyl (S)-2-cyclopentylpropanoate (4b):** Synthesized from propyl (E)-7-iodo-2-methylhept-2-enoate (4a) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



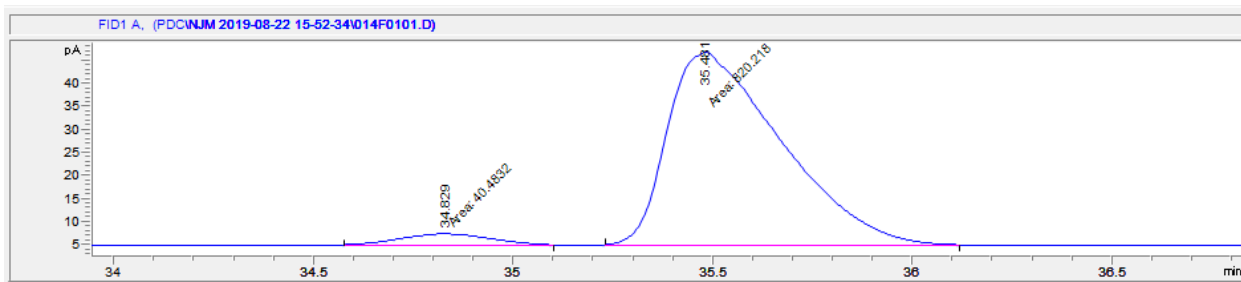
Standard Curve:

**Yield:** 95%

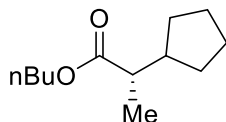
**Enantioselectivity:** 95:5 er (Astec® CHIRALDEX B-DM, 12.2 psi, isothermal 90 °C)



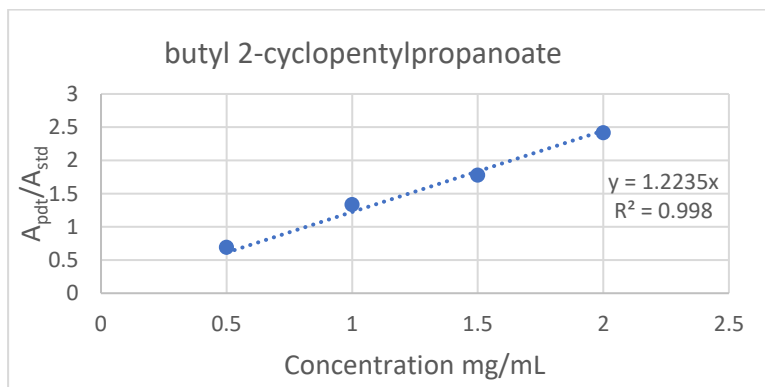
#	Time	Area	Height	Width	Area%	Symmetry
1	34.721	296.6	17	0.2906	50.003	0.813
2	35.529	296.5	15.9	0.3106	49.997	0.708



#	Time	Area	Height	Width	Area%	Symmetry
1	34.829	40.5	2.5	0.2693	4.704	0.862
2	35.481	820.2	41.9	0.3265	95.296	0.477



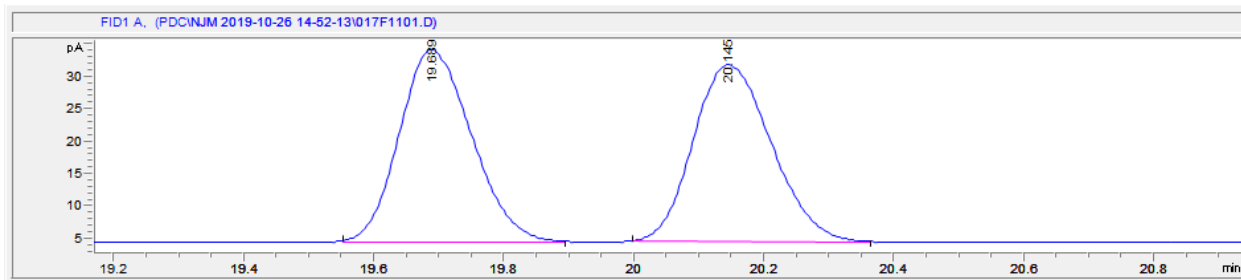
**butyl (S)-2-cyclopentylpropanoate (5b):** Synthesized from butyl (E)-7-iodo-2-methylhept-2-enoate (**5a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



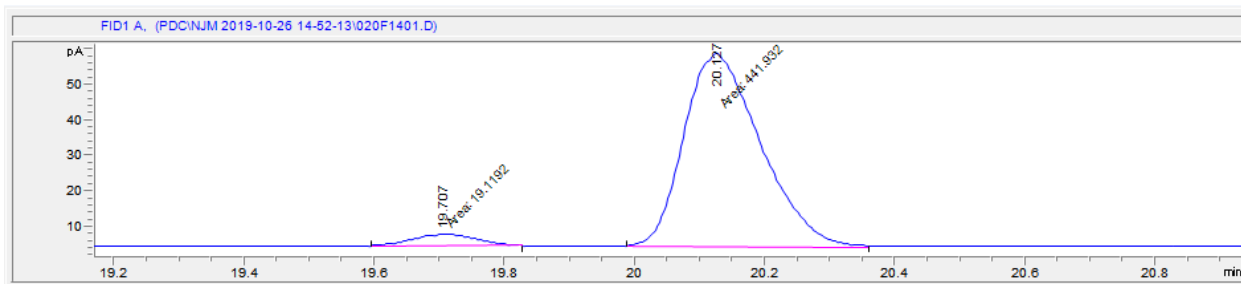
Standard Curve:

**Yield:** 52%

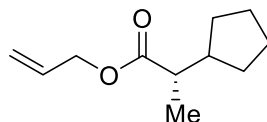
**Enantioselectivity:** 96:4 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 120 °C)



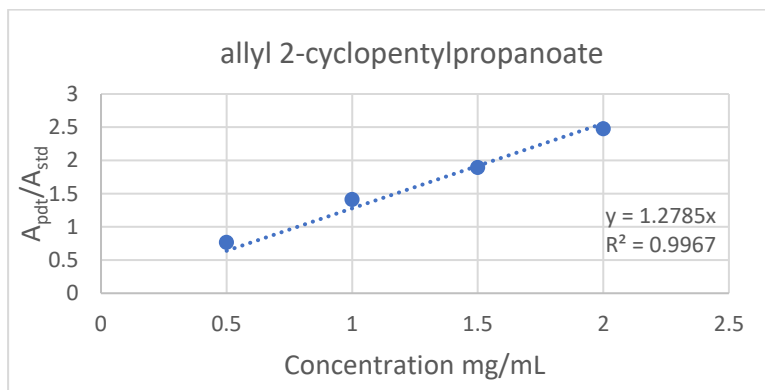
#	Time	Area	Height	Width	Area%	Symmetry
1	19.689	230.5	29.7	0.1054	50.133	0.78
2	20.145	229.3	27.4	0.1206	49.867	0.782



#	Time	Area	Height	Width	Area%	Symmetry
1	19.707	19.1	3	0.1064	4.147	1.012
2	20.127	441.9	54.3	0.1356	95.853	0.723



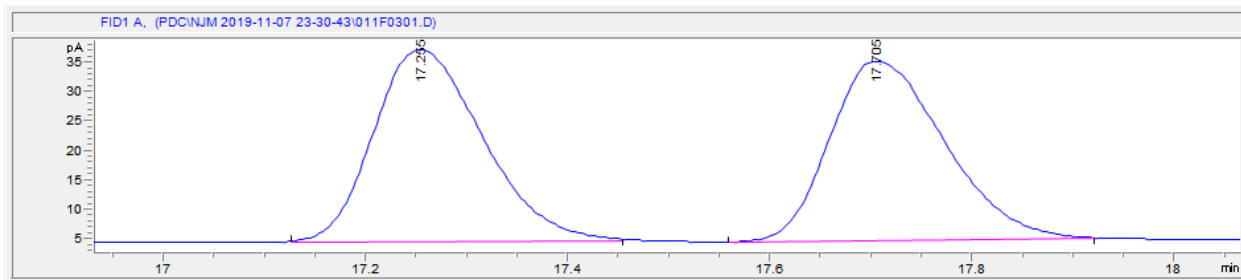
**allyl (S)-2-cyclopentylpropanoate (6b):** Synthesized from allyl (E)-7-iodo-2-methylhept-2-enoate (**6a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



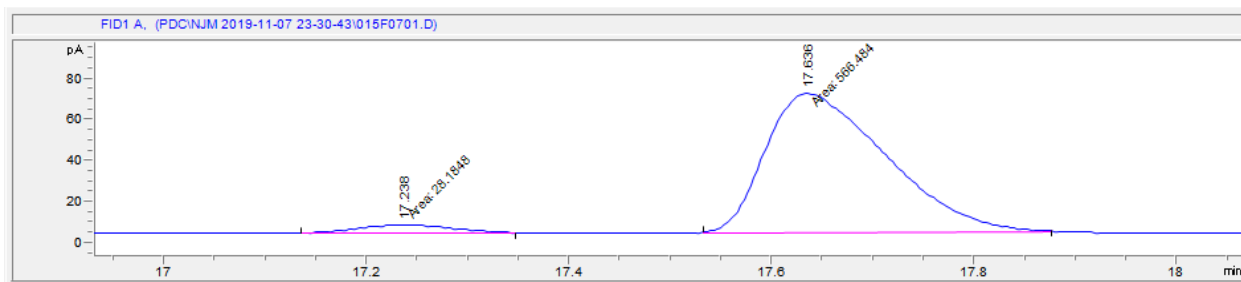
Standard Curve:

**Yield:** 97%

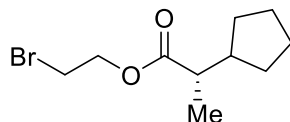
**Enantioselectivity:** 95:5 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 110 °C)



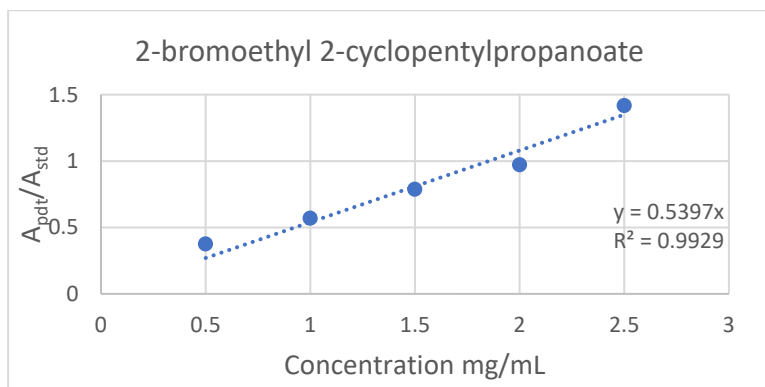
#	Time	Area	Height	Width	Area%	Symmetry
1	17.255	244.7	32.6	0.1116	50.297	0.727
2	17.705	241.8	30.5	0.1195	49.703	0.665



#	Time	Area	Height	Width	Area%	Symmetry
1	17.238	28.2	4.3	0.1103	4.740	0
2	17.636	566.5	68	0.1389	95.260	0.526



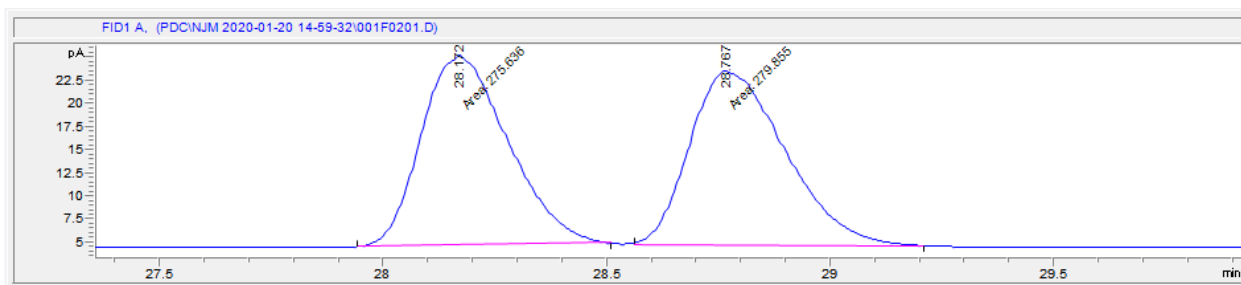
**2-bromoethyl (S)-2-cyclopentylpropanoate (7b):** Synthesized from 2-bromoethyl (E)-7-iodo-2-methylhept-2-enoate (**7a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



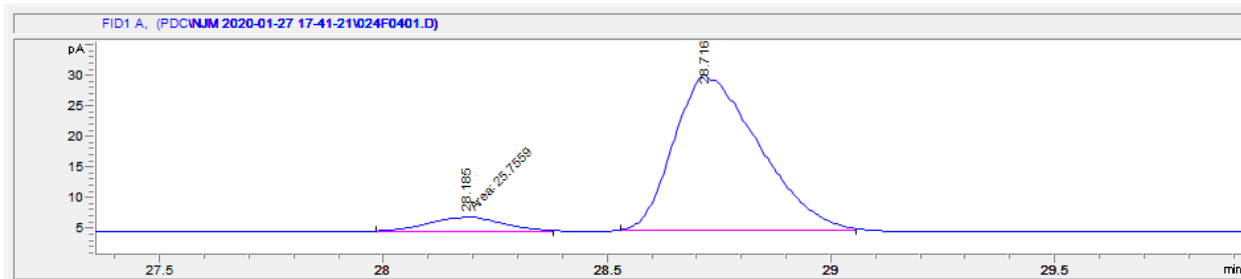
Standard Curve:

**Yield:** 62%

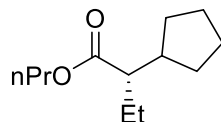
**Enantioselectivity:** 93:7 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 130 °C)



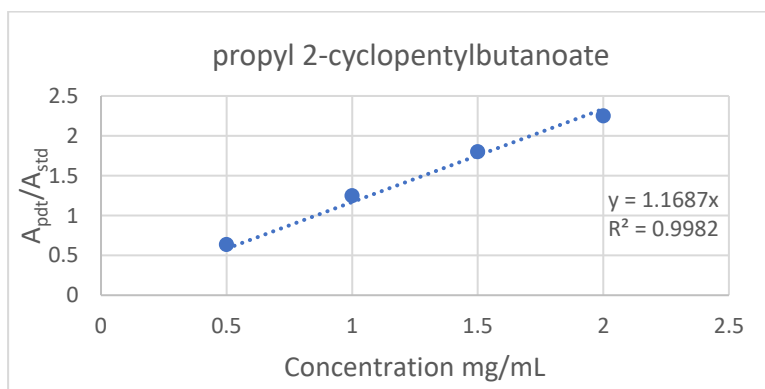
#	Time	Area	Height	Width	Area%	Symmetry
1	28.172	275.6	20.6	0.2231	49.620	0.772
2	28.767	279.9	18.8	0.2485	50.380	0.603



#	Time	Area	Height	Width	Area%	Symmetry
1	28.185	25.8	2.2	0.1917	7.135	0.991
2	28.716	335.2	25.4	0.1629	92.865	0.535



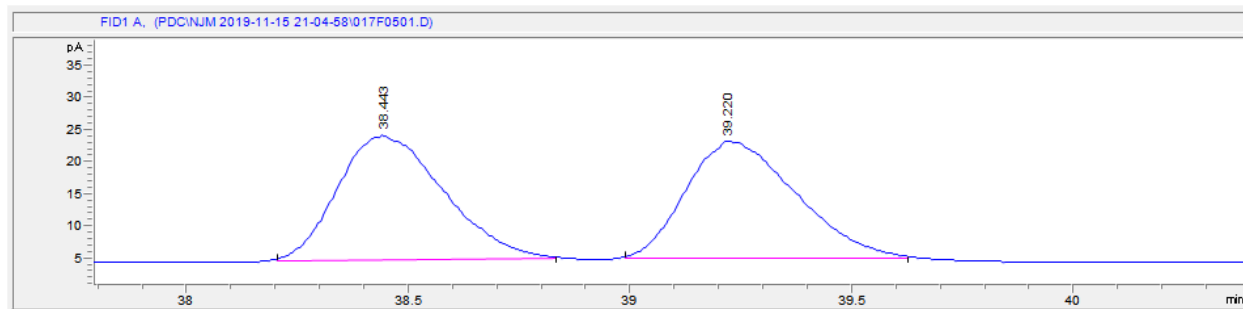
**propyl (S)-2-cyclopentylidenebutanoate (8b):** Synthesized from propyl (E)-2-ethyl-7-iodohept-2-enoate (**8a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



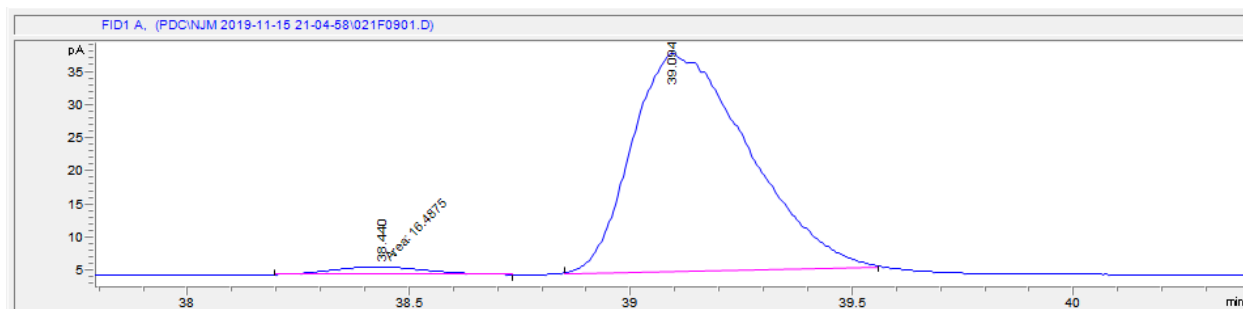
Standard Curve:

**Yield:** 65%

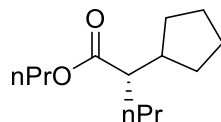
**Enantioselectivity:** 97:3 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 100 °C)



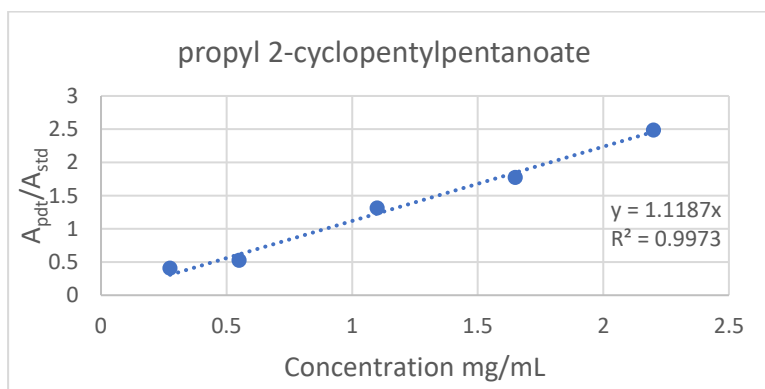
#	Time	Area	Height	Width	Area%	Symmetry
1	38.443	321.2	19.4	0.2005	50.738	0.734
2	39.22	311.8	18.2	0.2079	49.262	0.606



#	Time	Area	Height	Width	Area%	Symmetry
1	38.44	16.5	1.1	0.2432	2.661	1.065
2	39.094	603.1	32.9	0.221	97.339	0.515



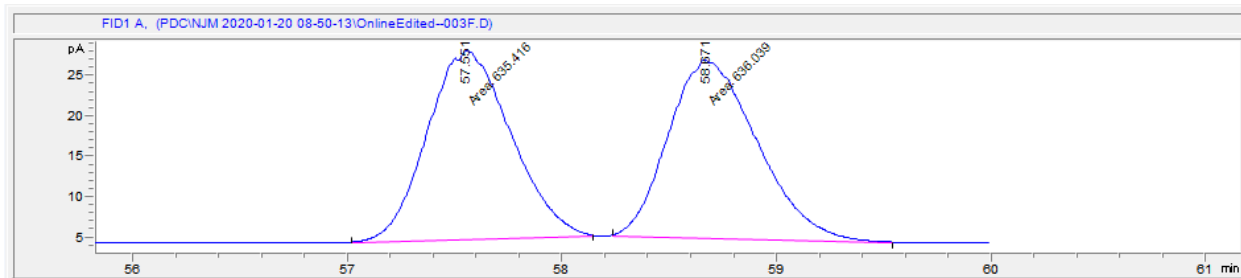
**propyl (S)-2-cyclopentylpentanoate (9b):** Synthesized from propyl (E)-2-propyl-7-iodohept-2-enoate (**9a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



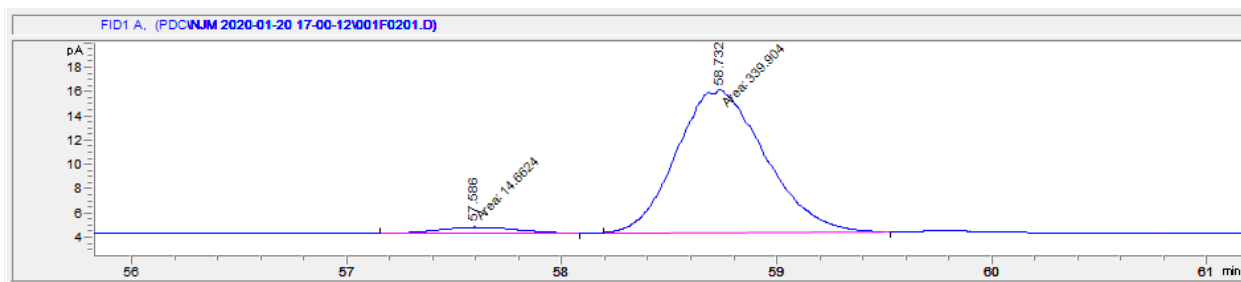
Standard Curve:

**Yield:** 36%

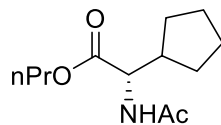
**Enantioselectivity:** 96:4 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 100 °C)



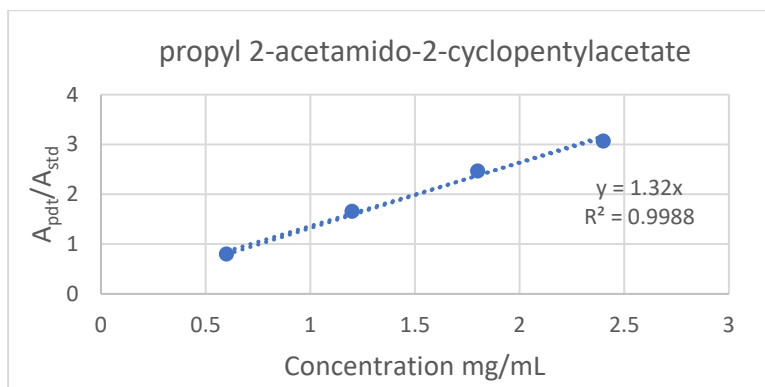
#	Time	Area	Height	Width	Area%	Symmetry
1	57.551	635.4	23.4	0.4534	49.976	0.831
2	58.671	636	22.1	0.4804	50.024	0.72



#	Time	Area	Height	Width	Area%	Symmetry
1	57.586	14.7	5.4E-1	0.4553	4.135	0.745
2	58.732	339.9	11.8	0.4802	95.865	0.892



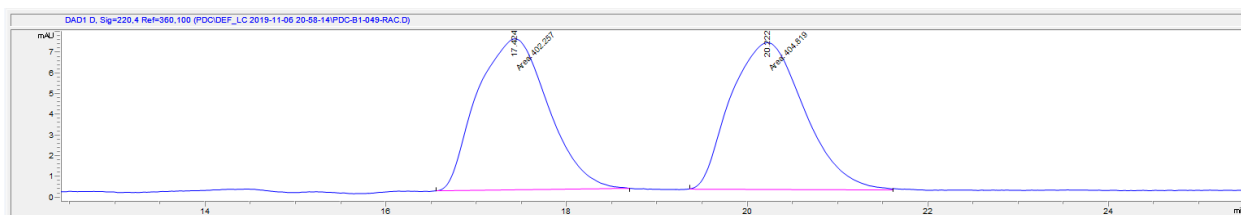
**propyl (S)-2-acetamido-2-cyclopentylacetate (10b):** Synthesized from propyl (Z)-2-acetamido-7-iodohept-2-enoate (**10a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



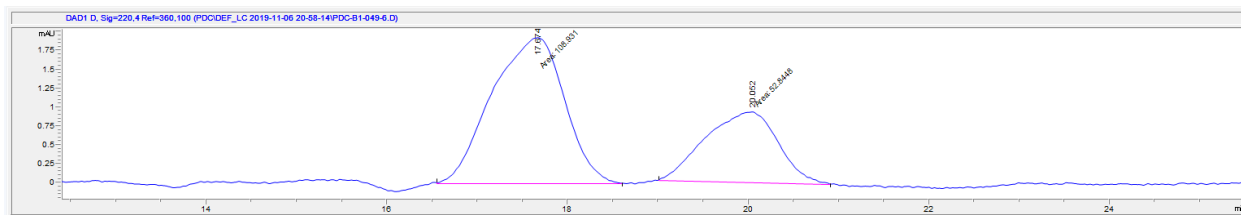
Standard Curve:

**Yield:** 90%

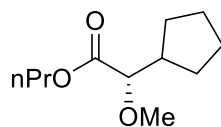
**Enantioselectivity:** 67:33 er (ChiralCel® OJ-H, 2% IPA/Hexanes, 1 mL/min)



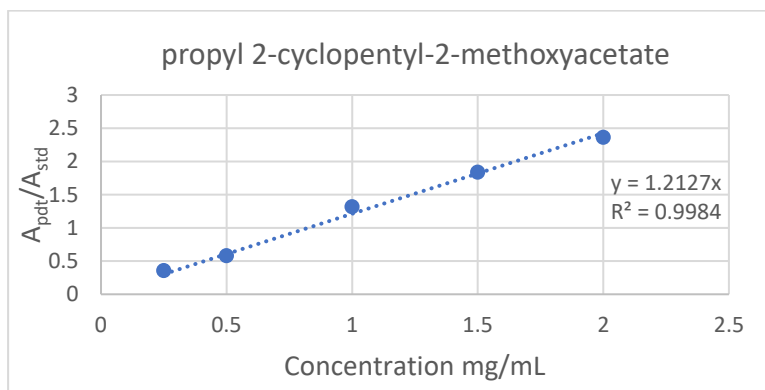
#	Time	Area	Height	Width	Area%	Symmetry
1	17.424	402.3	7.3	0.9166	49.841	1.049
2	20.222	404.8	7.1	0.9498	50.159	0.93



#	Time	Area	Height	Width	Area%	Symmetry
1	17.674	108.9	1.9	0.935	67.335	1.62
2	20.052	52.8	9.4E-1	0.9355	32.665	1.719



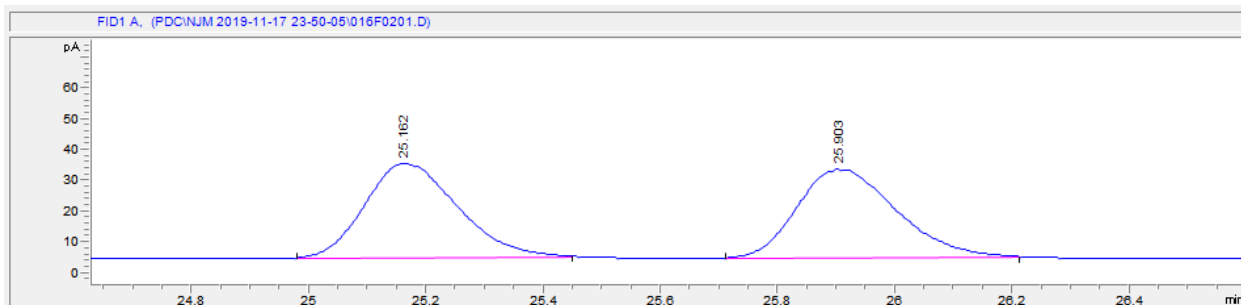
**propyl (S)-2-cyclopentyl-2-methoxyacetate (11b):** Synthesized from propyl (Z)-7-iodo-2-methoxyhept-2-enoate according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



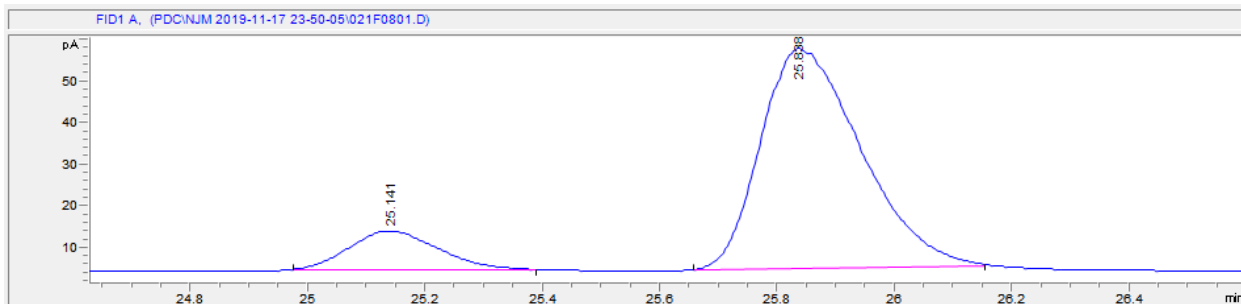
Standard Curve:

**Yield:** 86%

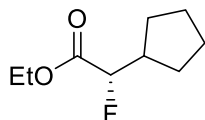
**Enantioselectivity:** 86:14 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 110 °C)



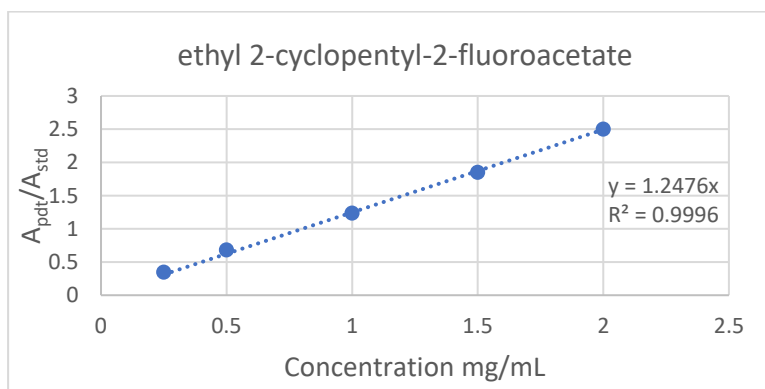
#	Time	Area	Height	Width	Area%	Symmetry
1	25.162	339.3	30.8	0.1324	50.038	0.715
2	25.903	338.8	28.7	0.1415	49.962	0.686



#	Time	Area	Height	Width	Area%	Symmetry
1	25.141	100.8	9.4	0.1416	13.793	0.823
2	25.838	630.2	53	0.1486	86.207	0.589



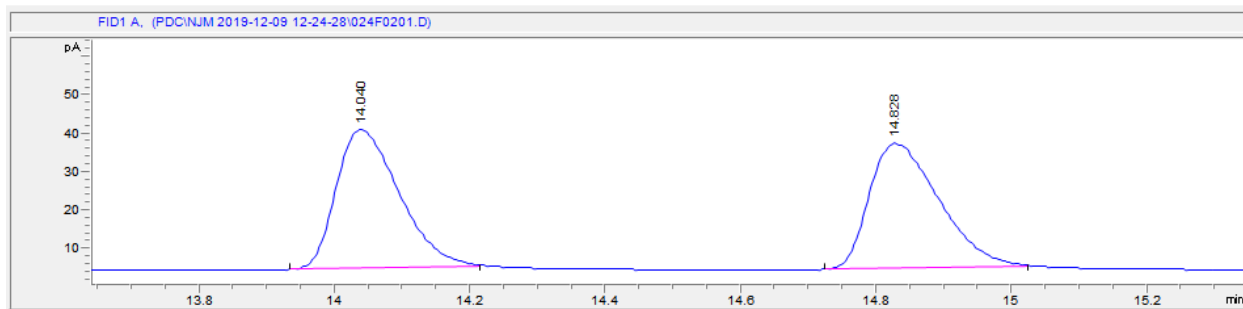
**ethyl (S)-2-cyclopentyl-2-fluoroacetate (12b):** Synthesized from ethyl (E)-2-fluoro-7-iodohept-2-enoate (12a) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



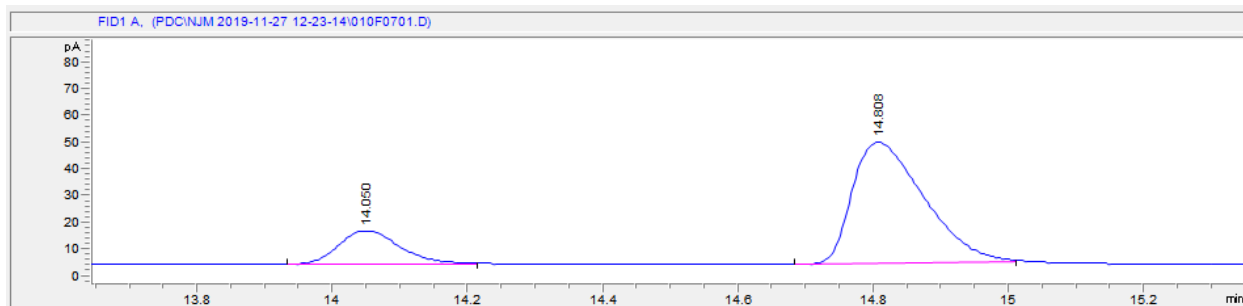
Standard Curve:

**Yield:** 73%

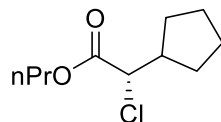
**Enantioselectivity:** 81:19 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 105 °C)



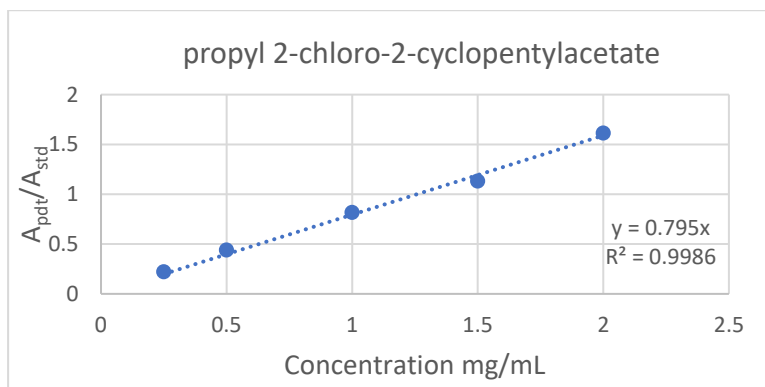
#	Time	Area	Height	Width	Area%	Symmetry
1	14.04	234	36.2	0.0994	50.007	0.612
2	14.828	233.9	32.6	0.0978	49.993	0.546



#	Time	Area	Height	Width	Area%	Symmetry
1	14.05	77.9	12.4	0.0962	18.908	0.764
2	14.808	333.9	45.4	0.1108	81.092	0.536



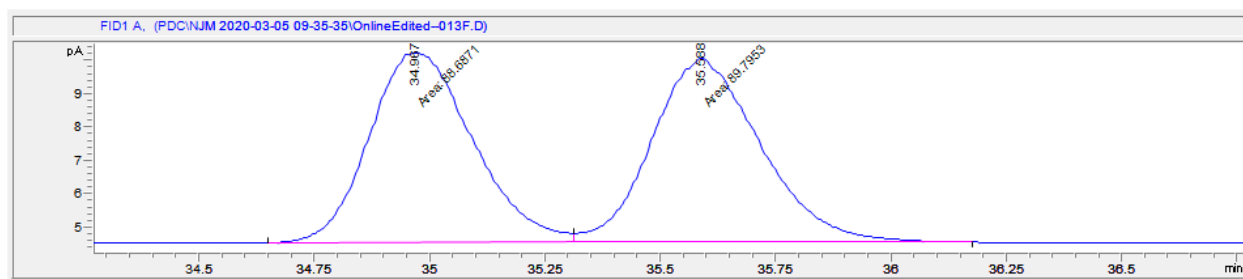
**propyl (S)-2-chloro-2-cyclopentylacetate (13b):** Synthesized from propyl (Z)-2-chloro-7-iodohept-2-enoate (**13a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



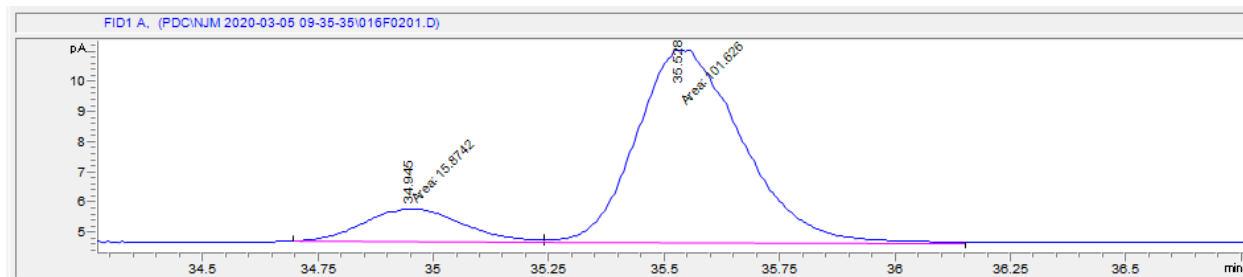
Standard Curve:

**Yield:** 20%

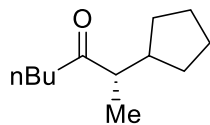
**Enantioselectivity:** 86:14 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 110 °C)



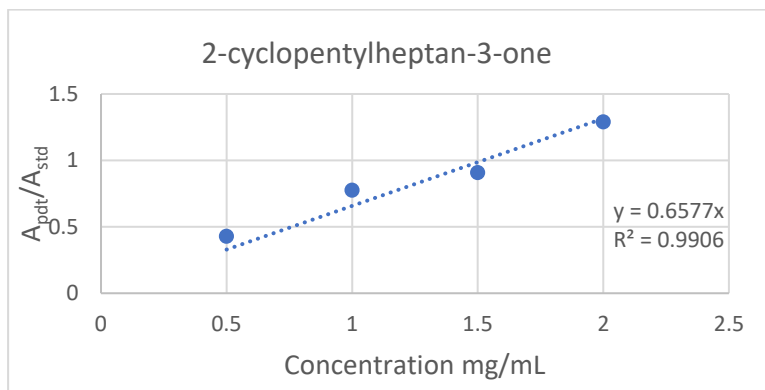
#	Time	Area	Height	Width	Area%	Symmetry
1	34.967	88.7	5.7	0.2601	49.690	0
2	35.588	89.8	5.5	0.2711	50.310	0.803



#	Time	Area	Height	Width	Area%	Symmetry
1	34.945	15.9	1.1	0.2438	13.510	0
2	35.528	101.6	6.4	0.2657	86.490	0.623



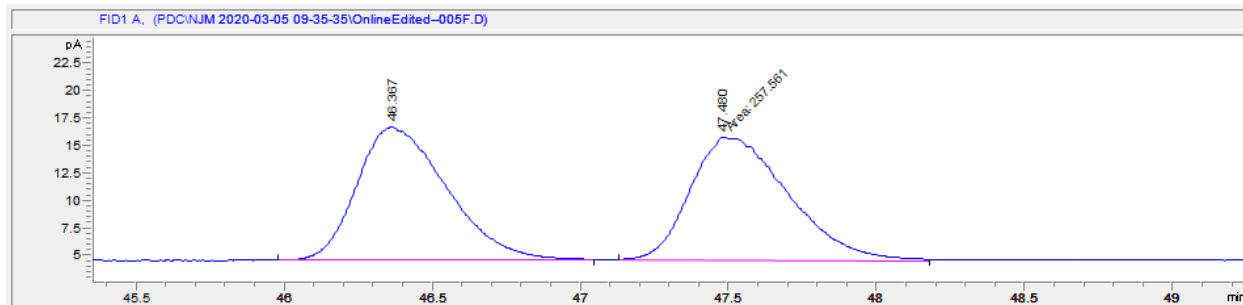
**(S)-2-cyclopentylheptan-3-one (14b):** Synthesized from (E)-11-iodo-6-methylundec-6-en-5-one (**14a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



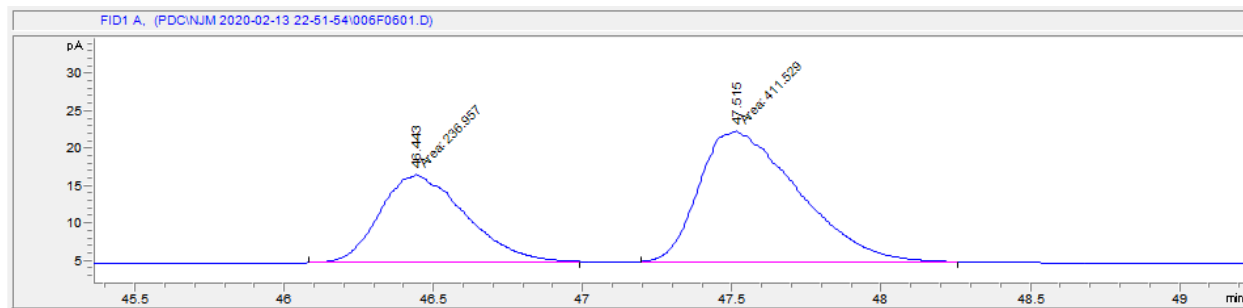
Standard Curve:

**Yield:** 62%

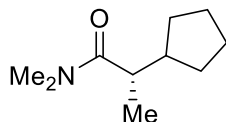
**Enantioselectivity:** 63:37 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 100 °C)



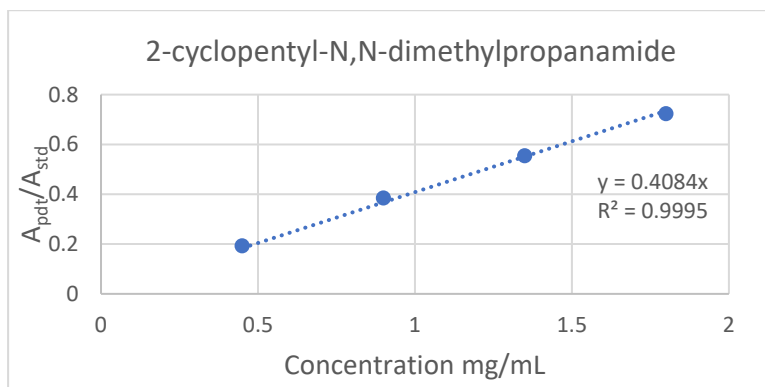
#	Time	Area	Height	Width	Area%	Symmetry
1	46.367	255.3	12.1	0.2513	49.782	0.658
2	47.48	257.6	11.2	0.3838	50.218	0.491



#	Time	Area	Height	Width	Area%	Symmetry
1	46.443	237	11.8	0.3346	36.540	0.71
2	47.515	411.5	17.6	0.3896	63.460	0.582



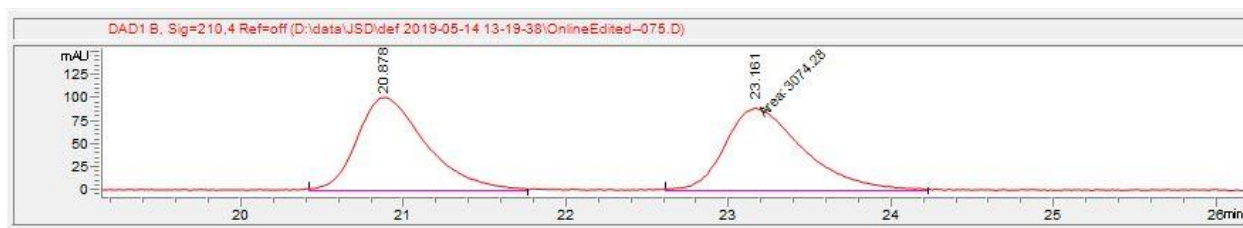
**(S)-2-cyclopentyl-N,N-dimethylpropanamide (15b):** Synthesized from (E)-7-iodo-N,N,2-trimethylhept-2-enamide (**15a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



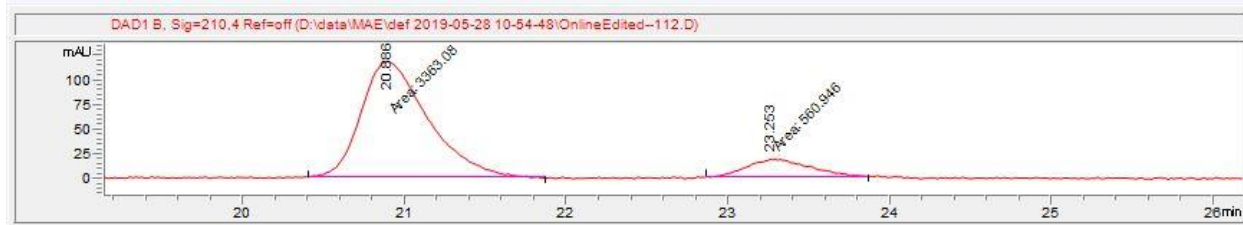
Standard Curve:

**Yield:** 88%

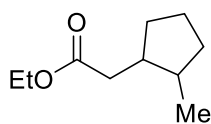
**Enantioselectivity:** 86:14 er (ChiralCel® ID, 2% IPA/Hexanes, 1 mL/min)



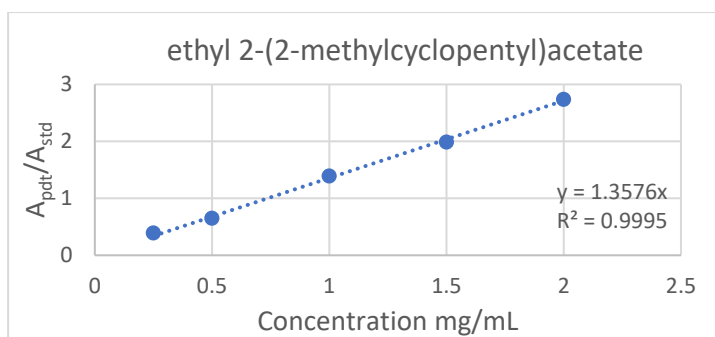
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.878	VV	3058.2	102.7	0.3623	49.869	0.657
2	23.161	MM	3074.3	91.1	0.5626	50.131	0.631



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.886	MM	3363.1	116.9	0.4796	85.705	0.615
2	23.253	MM	560.9	19.2	0.4882	14.295	0.59



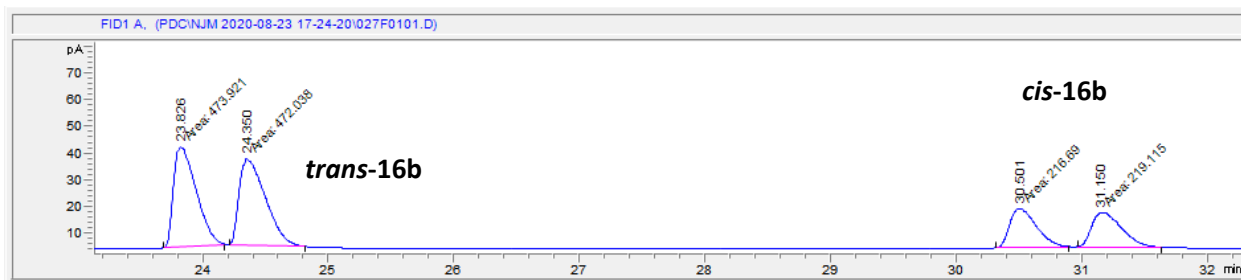
**ethyl 2-(2-methylcyclopentyl)acetate (16b):** Synthesized from ethyl (E)-7-iodooct-2-enoate (**16a**) according to the general procedure for a biocatalytic 5-exo enantioselective hydroalkylation.



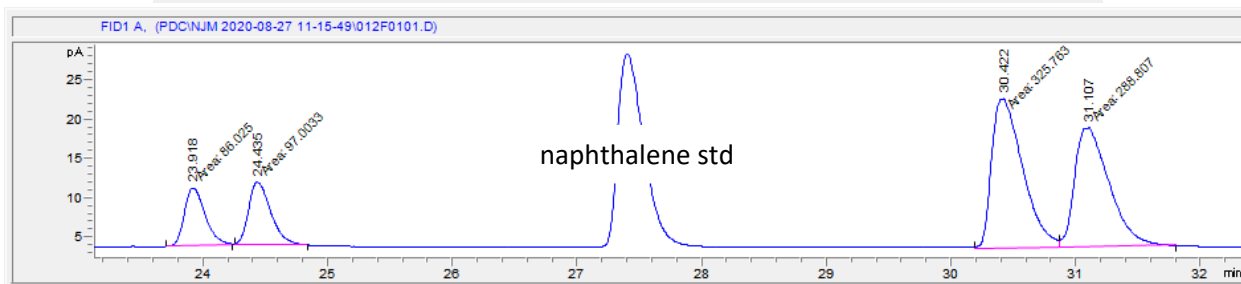
Standard Curve:

**Yield:** 91%

**Enantioselectivity:** 77:23 dr (cis:trans); 53:47 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 90 °C)

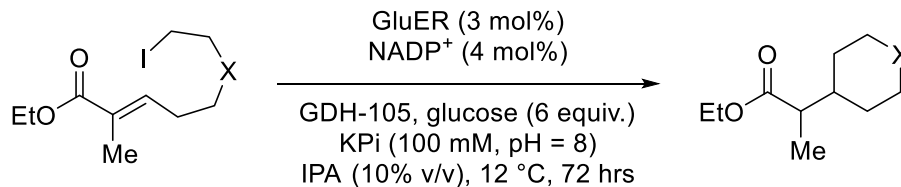


#	Time	Area	Height	Width	Area%	Symmetry
1	23.826	473.9	37.4	0.211	34.298	0.453
2	24.35	472	32.6	0.2417	34.162	0.388
3	30.501	216.7	14.7	0.2465	15.682	0.548
4	31.15	219.1	13	0.2803	15.858	0.44



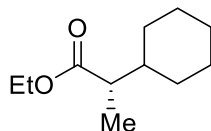
#	Time	Area	Height	Width	Area%	Symmetry
1	23.918	86	7.4	0.1946	10.786	0.646
2	24.435	97	7.9	0.2035	12.162	0.605
3	30.422	325.8	18.9	0.287	40.843	0
4	31.107	288.8	15.1	0.3198	36.210	0.677

## 6-Exo Enantioselective Hydroalkylation

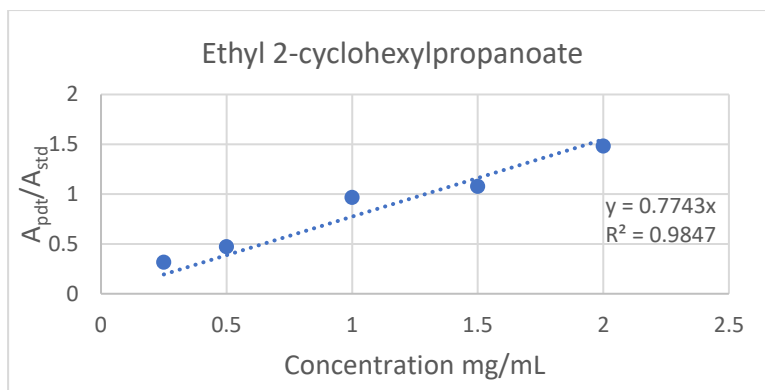


**General Procedure:** In a Coy<sup>®</sup> anaerobic chamber (<20 ppm O<sub>2</sub>), stock solutions of GDH-105 (5 mg/mL), NADP<sup>+</sup> (7.8 mg/mL), and glucose (108 mg/mL) in degassed KPi (100 mM, pH 8), and of substrate (0.1 mmol/mL) in isopropanol were prepared. To the reaction vessel was then added sequentially 40 μL NADP<sup>+</sup> solution, 100 μL glucose solution, 460 μL KPi, 100 μL substrate solution, 200 μL GDH-105 solution, and 100 μL GluER-Y177F (3 mM). The reaction vessel was sealed, removed from the chamber, and freeze-pump-thawed before being irradiated with water cooling for 72 hours.

**Yield and Enantiomeric Ratio Determination.** 3 mL of ethyl acetate containing 1 mM naphthalene standard were added to the reaction vessel, the biphasic mixture vortexed for 1 minute, and the layers allowed to separate completely (approximately 15 minutes). 2 mL of the organic phase was removed and filtered through a small plug of sodium sulfate and cotton then analyzed by chiral GC. Yields were determined by comparison to a standard curve of independently synthesized product. The yields reported are an average of triplicate reactions. The enantioselectivity of the gem-difluoro product was determined by chiral HPLC.



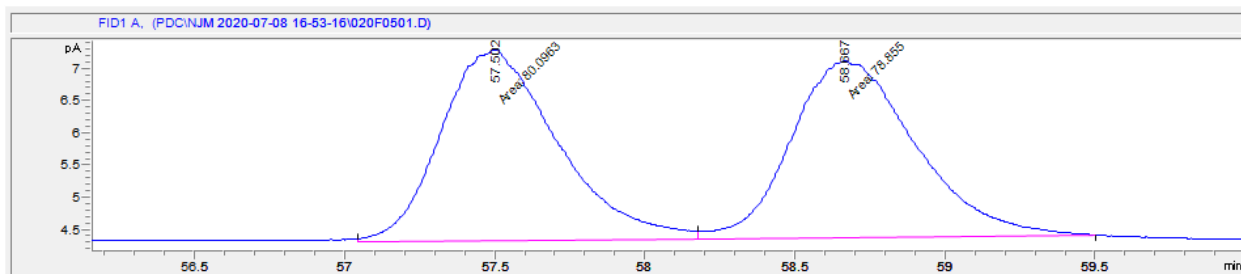
**ethyl (S)-2-cyclohexylpropanoate (17b):** Synthesized from ethyl (E)-8-iodo-2-methyloct-2-enoate (**17a**) according to the general procedure for a biocatalytic 6-exo enantioselective hydroalkylation.



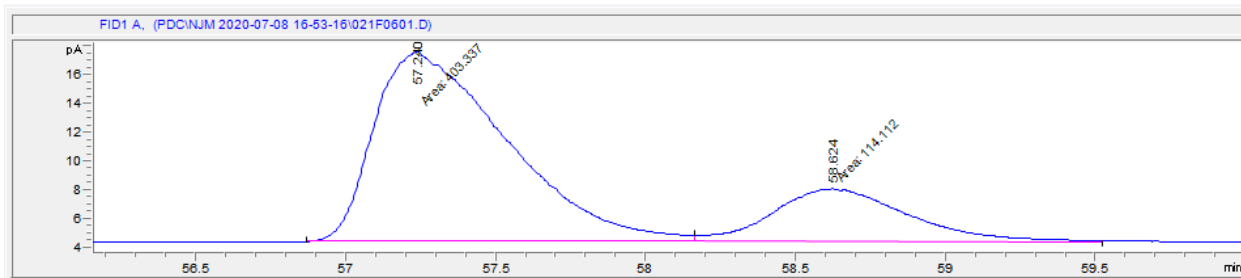
Standard Curve:

**Yield:** 79%

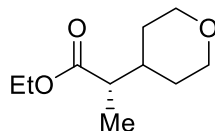
**Enantioselectivity:** 78:22 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 85 °C)



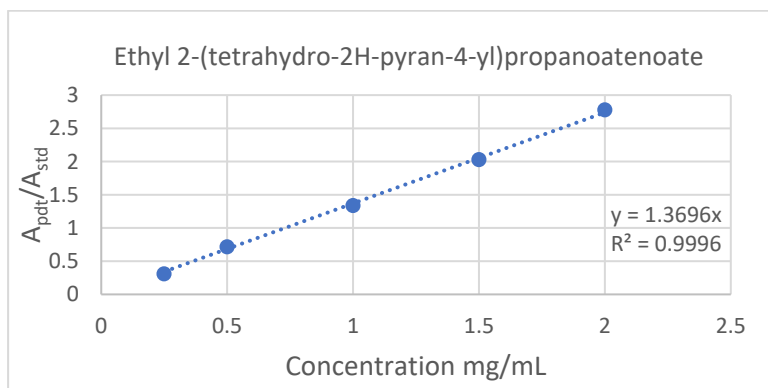
#	Time	Area	Height	Width	Area%	Symmetry
1	57.502	80.1	3	0.4508	50.390	0
2	58.667	78.9	2.7	0.4789	49.610	0.754



#	Time	Area	Height	Width	Area%	Symmetry
1	57.24	403.3	13.2	0.5112	77.947	0
2	58.624	114.1	3.7	0.5204	22.053	0.775



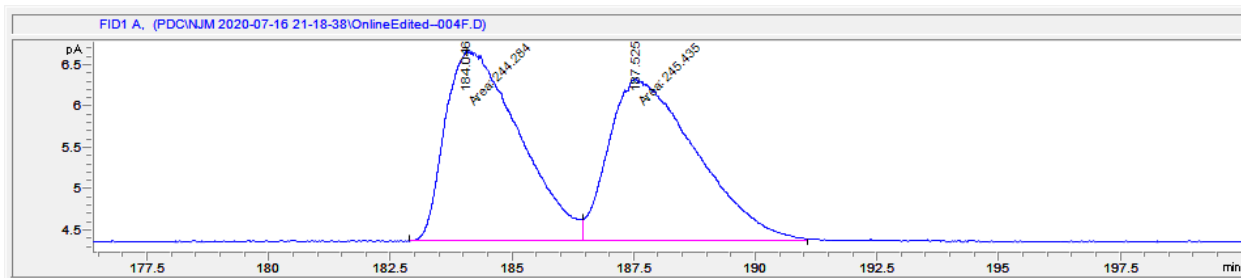
**ethyl (S)-2-(tetrahydro-2H-pyran-4-yl)propanoate (18b):** Synthesized from ethyl (E)-5-(2-iodoethoxy)-2-methylpent-2-enoate (**18a**) according to the general procedure for a biocatalytic 6-exo enantioselective hydroalkylation.



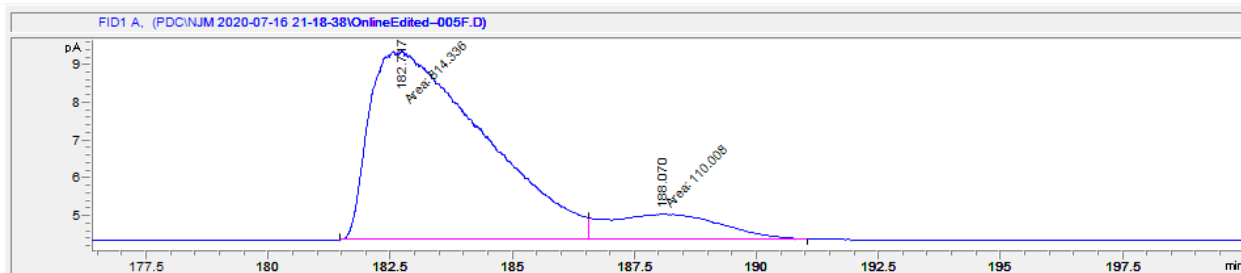
Standard Curve:

**Yield:** 95%

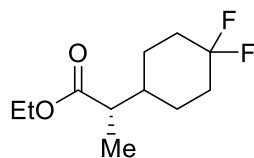
**Enantioselectivity:** 88:12 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 75 °C)



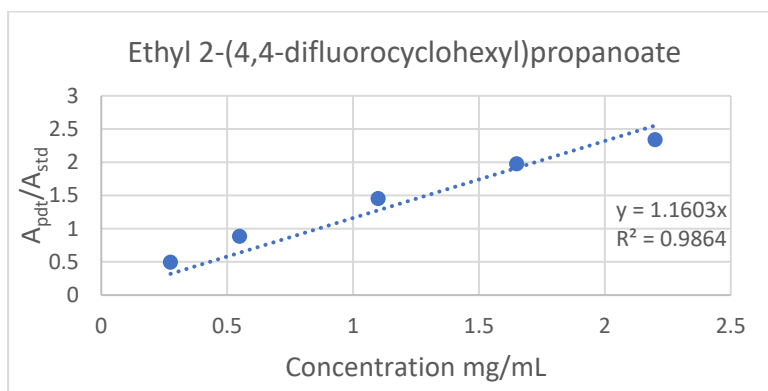
#	Time	Area	Height	Width	Area%	Symmetry
1	184.046	244.3	2.3	1.7743	49.882	0
2	187.525	245.4	2	2.0862	50.118	0.438



#	Time	Area	Height	Width	Area%	Symmetry
1	182.717	814.3	5	2.6934	88.099	0
2	188.07	110	6.8E-1	2.6795	11.901	0.905



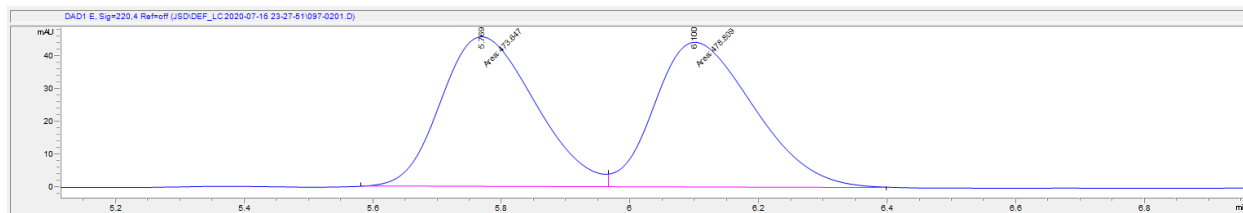
**ethyl (S)-2-(4,4-difluorocyclohexyl)propanoate (19b):** Synthesized from ethyl (E)-6,6-difluoro-8-iodo-2-methyloct-2-enoate (**19a**) according to the general procedure for a biocatalytic 6-exo enantioselective hydroalkylation.



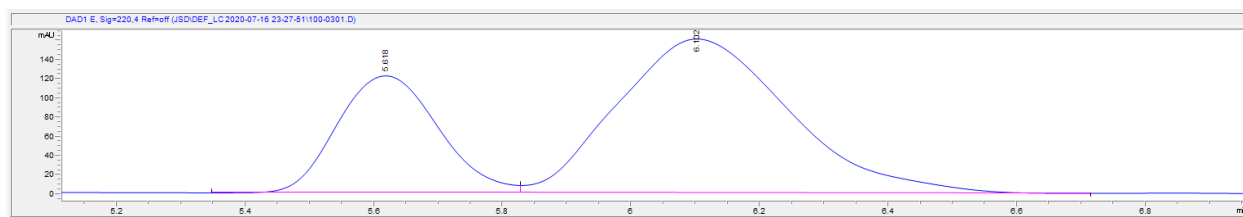
Standard Curve:

**Yield:** 86%

**Enantioselectivity:** 69:31 er (ChiralCel® OJ-H, 1% IPA/Hexanes, 1 mL/min)

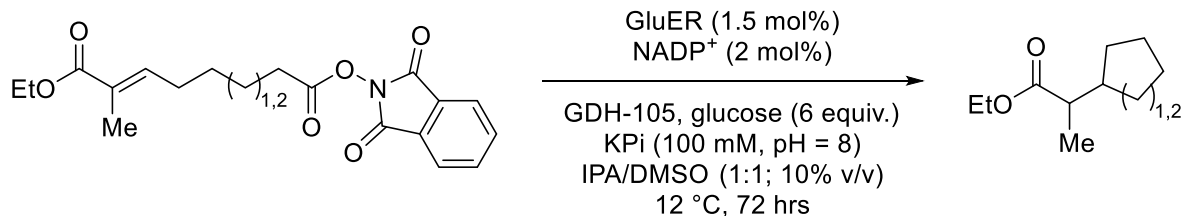


#	Time	Area	Height	Width	Area%	Symmetry
1	5.769	473.6	46.3	0.1707	49.729	0.742
2	6.1	478.8	44.7	0.1787	50.271	0.666



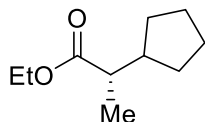
#	Time	Area	Height	Width	Area%	Symmetry
1	5.618	1340.1	122.4	0.1737	30.950	0.875
2	6.102	2989.8	161.1	0.2785	69.050	0.813

## NHPI Ester Cyclization

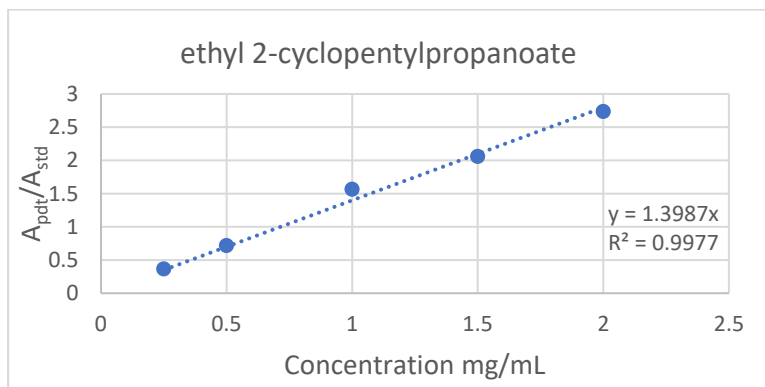


**General Procedure:** In a Coy<sup>®</sup> anaerobic chamber (<20 ppm O<sub>2</sub>), stock solutions of GDH-105 (5 mg/mL), NADP<sup>+</sup> (7.8 mg/mL), and glucose (108 mg/mL) in degassed KPi (100 mM, pH 8), and of substrate (0.1 mmol/mL) in isopropanol/DMSO (1:1) were prepared. To the reaction vessel was then added sequentially 20 μL NADP<sup>+</sup> solution, 100 μL glucose solution, 530 μL KPi, 100 μL substrate solution, 200 μL GDH-105 solution, and 50 μL GluER-Y177F (3 mM). The reaction vessel was sealed, removed from the chamber, and freeze-pump-thawed before being irradiated with water cooling for 72 hours.

**Yield and Enantiomeric Ratio Determination.** 3 mL of ethyl acetate containing 1 mM naphthalene standard were added to the reaction vessel, the biphasic mixture vortexed for 1 minute, and the layers allowed to separate completely (approximately 15 minutes). 2 mL of the organic phase was removed and filtered through a small plug of sodium sulfate and cotton then analyzed by chiral GC. Standard curves were identical to those used for the corresponding iodide.



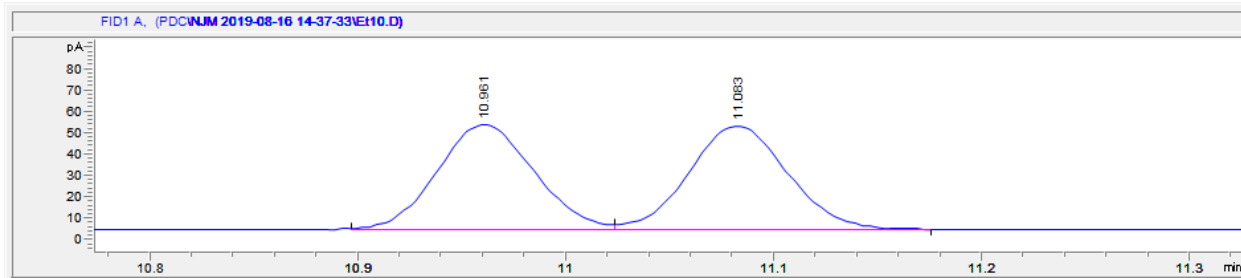
**ethyl (S)-2-cyclopentylpropanoate (2b):** Synthesized from 8-(1,3-dioxoisindolin-2-yl) 1-ethyl (E)-2-methyloct-2-enedioate (**20**) according to the general procedure.



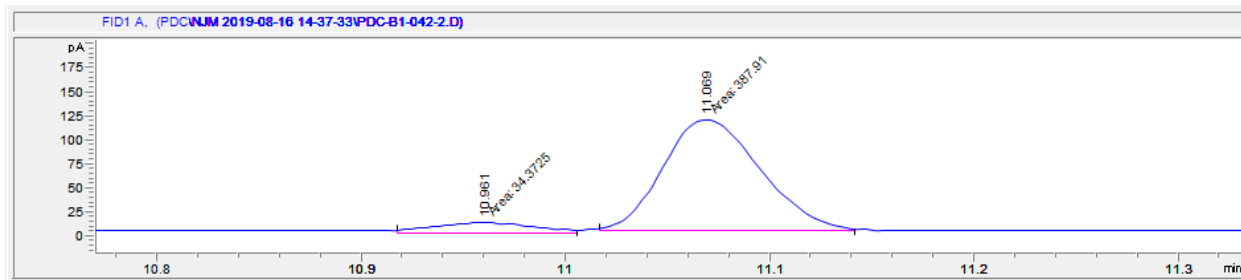
Standard Curve:

**Yield:** 93%

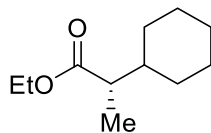
**Enantioselectivity:** 92:8 er (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 100 °C)



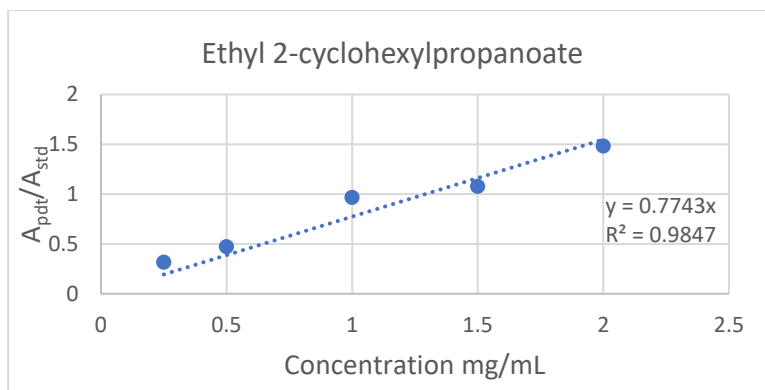
#	Time	Area	Height	Width	Area%	Symmetry
1	10.961	158.6	48.8	0.0519	49.876	0.899
2	11.083	159.3	48.1	0.0497	50.124	0.931



#	Time	Area	Height	Width	Area%	Symmetry
1	10.961	34.4	10.2	0.0562	8.140	0.99
2	11.069	387.9	116	0.0557	91.860	0.787



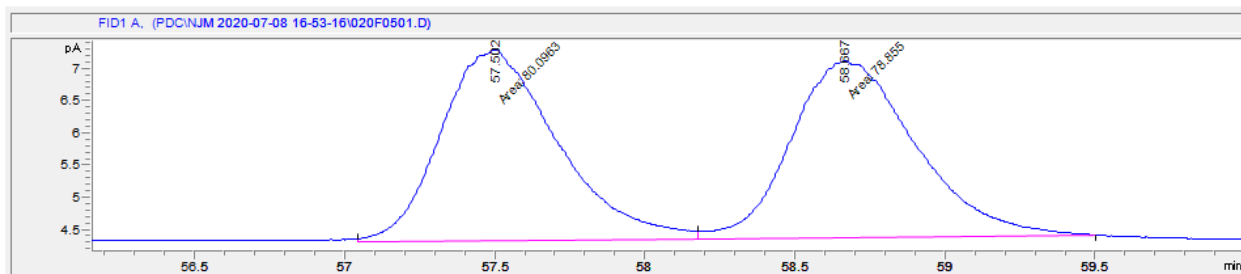
**ethyl (S)-2-cyclohexylpropanoate (16b):** Synthesized from 9-(1,3-dioxoisindolin-2-yl) 1-ethyl (E)-2-methylnon-2-enedioate (**21**) according to the general procedure.



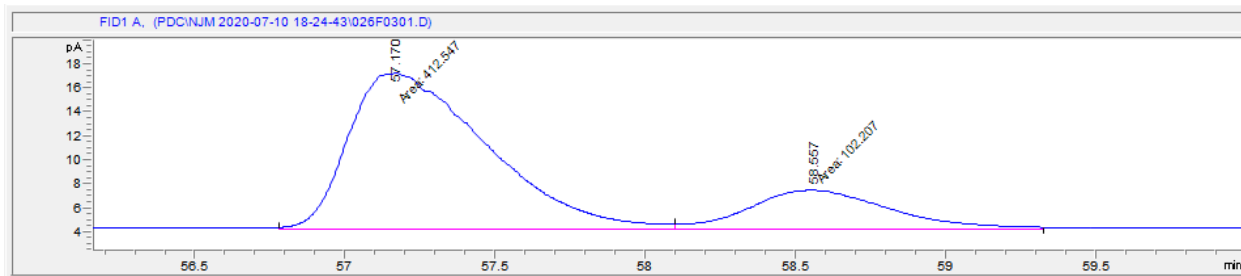
Standard Curve:

**Yield:** 73%

**Enantioselectivity:** 80:20 (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 85 °C)

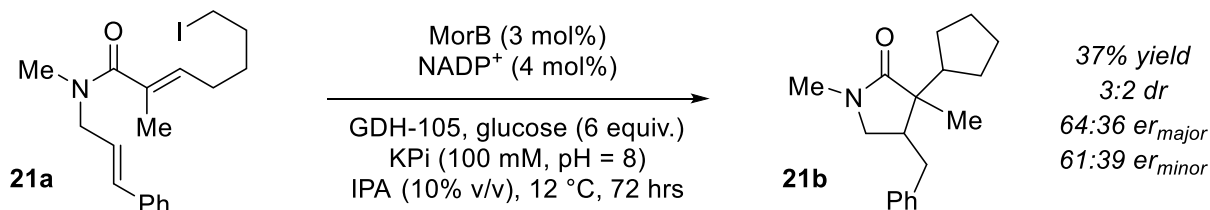


#	Time	Area	Height	Width	Area%	Symmetry
1	57.502	80.1	3	0.4508	50.390	0
2	58.667	78.9	2.7	0.4789	49.610	0.754



#	Time	Area	Height	Width	Area%	Symmetry
1	57.17	412.5	13	0.5279	80.144	0.51
2	58.557	102.2	3.2	0.5252	19.856	0.817

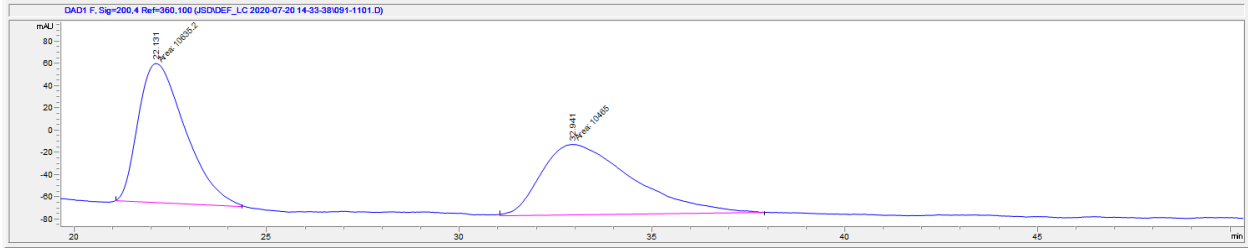
## Tandem Cyclization



**Procedure:** In a Coy<sup>®</sup> anaerobic chamber (<20 ppm O<sub>2</sub>), stock solutions of GDH-105 (5 mg/mL), NADP<sup>+</sup> (7.8 mg/mL), and glucose (108 mg/mL) in degassed KPi (100 mM, pH 8), and of (E)-N-cinnamyl-7-iodo-N,2-dimethylhept-2-enamide (**21a**) (0.1 mmol/mL) in isopropanol were prepared. To the reaction vessel was then added sequentially 40  $\mu$ L NADP<sup>+</sup> solution, 100  $\mu$ L glucose solution, 460  $\mu$ L KPi, 100  $\mu$ L substrate solution, 200  $\mu$ L GDH-105 solution, and 100  $\mu$ L MorB (3 mM). The reaction vessel was sealed, removed from the chamber, and freeze-pump-thawed before being irradiated with water cooling for 72 hours.

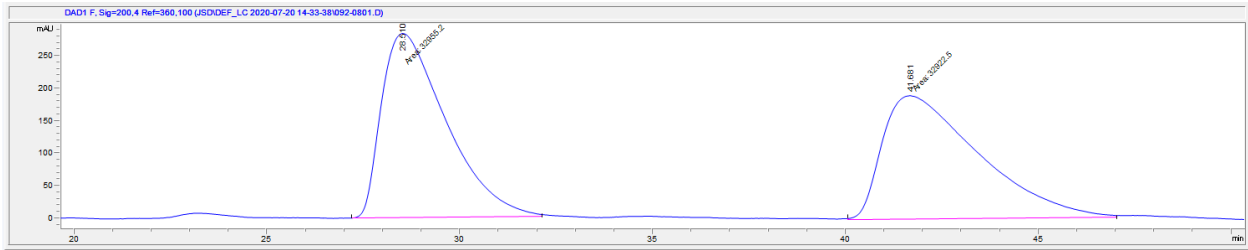
**Yield and Enantiomeric Ratio Determination.** The reaction mixture was transferred to a dram vial, 1 mL of ethyl acetate containing 3 mM 1,3,5-tribromobenzene was added, and the mixture vortexed for 1 minute. The mixture was centrifuged (4000 g x 10 min.) and the organic layer pipetted off. This extraction was repeated twice more with pure ethyl acetate. The combined organic extracts were concentrated and analyzed by NMR. Yields were determined by comparison to tribromobenzene standard. Diastereomers were distinguished by their characteristic N-methyl peaks. Enantioselectivity was determined by chiral HPLC (ChiralPaK<sup>®</sup> AS, 0.5% IPA/Hexanes, 1 mL/min).

**Major diastereomer**



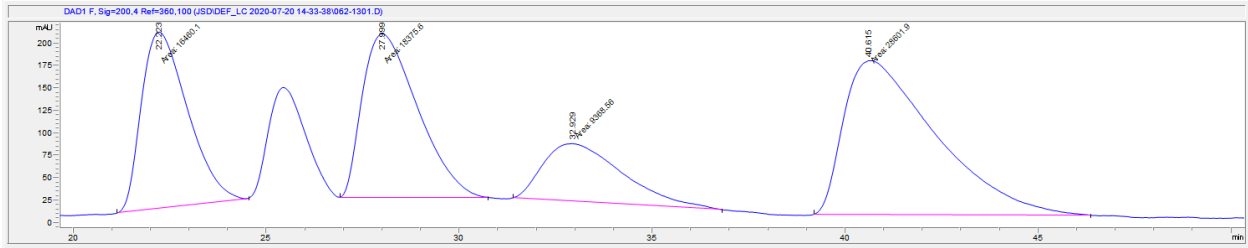
#	Time	Area	Height	Width	Area%	Symmetry
1	22.131	10635.2	125.1	1.4172	50.403	0.599
2	32.941	10465	63.3	2.7539	49.597	0.516

**Minor diastereomer**



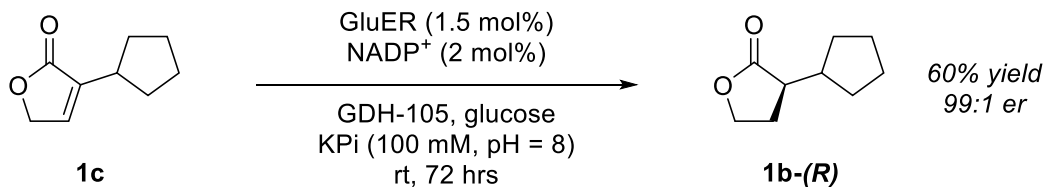
#	Time	Area	Height	Width	Area%	Symmetry
1	28.51	32955.2	283	1.9407	50.025	0.464
2	41.681	32922.5	189.7	2.8928	49.975	0.397

**Biocatalytic**

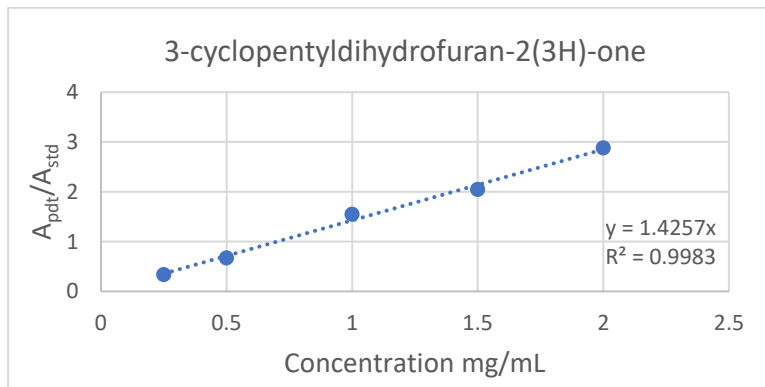


#	Time	Area	Height	Width	Area%	Symmetry
1	22.223	16460.1	196.7	1.3945	22.608	0.531
2	27.999	18375.6	183	1.6734	25.239	0.545
3	32.929	9368.6	64.8	2.4114	12.868	0.436
4	40.615	28601.9	171.2	2.7838	39.285	0.365

## Enone Reduction



**Procedure.** In a Coy<sup>®</sup> anaerobic chamber (<20 ppm O<sub>2</sub>), stock solutions of GDH-105 (5 mg/mL), NADP<sup>+</sup> (7.8 mg/mL), and glucose (108 mg/mL) in degassed KPi (100 mM, pH 8), and of 3-cyclopentylfuran-2(5H)-one (**1c**) (0.1 mmol/mL) in isopropanol were prepared. To the reaction vessel was then added sequentially 20  $\mu$ L NADP<sup>+</sup> solution, 100  $\mu$ L glucose solution, 530  $\mu$ L KPi, 100  $\mu$ L substrate solution, 200  $\mu$ L GDH-105 solution, and 50  $\mu$ L GluER (3 mM). The reaction vessel was sealed, removed from the chamber, and stirred for 72 hours. The reaction work-up and analysis were identically to that of the 5-exo hydroalkylation.



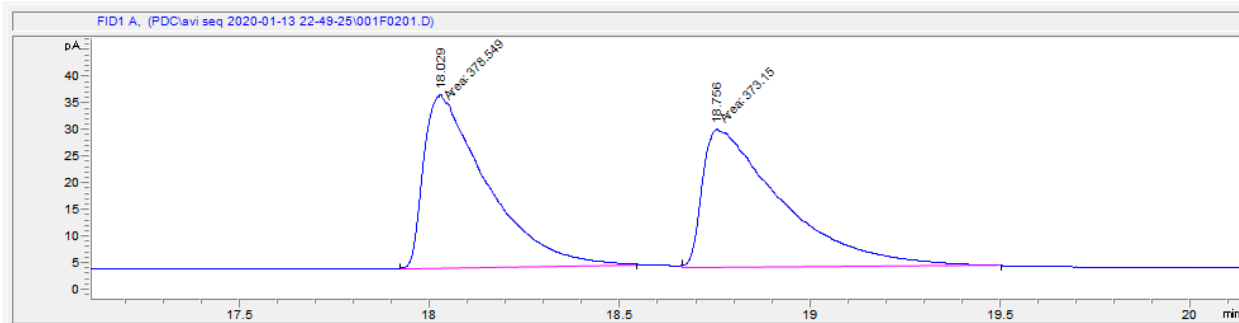
Standard Curve:

**Yield:** 60%

**Enantioselectivity:** >99:1 (Supelco  $\gamma$ -DEX<sup>™</sup> 225, 15.2 psi, isothermal 150 °C)

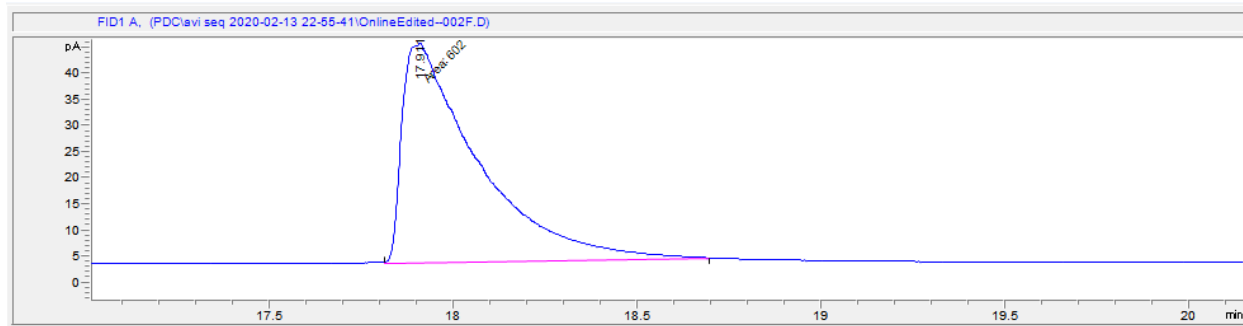
Note: over time the column degraded, requiring a lower temperature to achieve good separation in comparison to the results reported above for the corresponding alkyl iodide substrate. The enantioselectivity of the scaled reductive cyclization which was carried out around the same time and separated under these conditions is provided below for comparison.

### Racemate



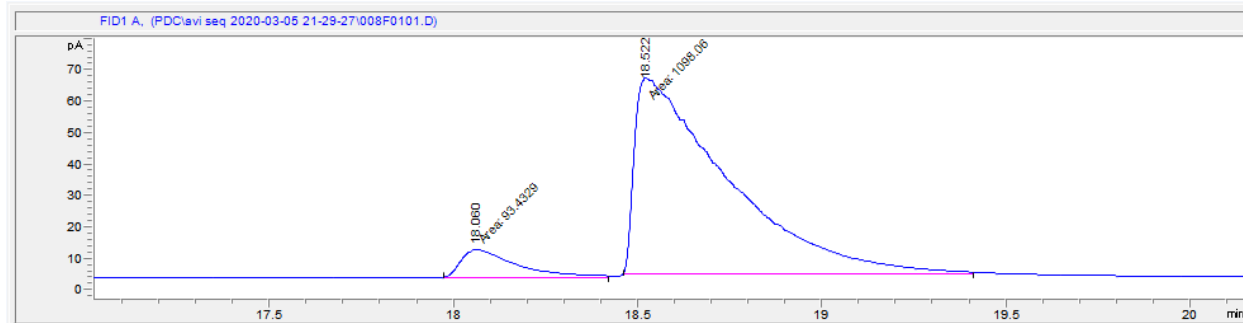
#	Time	Area	Height	Width	Area%	Symmetry
1	18.029	378.5	32.7	0.1927	50.359	0.341
2	18.756	373.1	25.8	0.2411	49.641	0.225

### Enone reduction



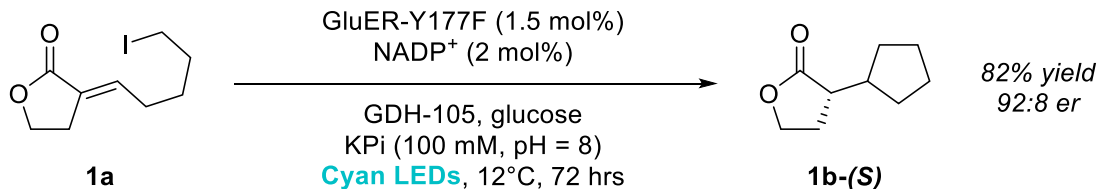
#	Time	Area	Height	Width	Area%	Symmetry
1	17.911	602	41.9	0.2395	100.000	0.276

### Scaled Reductive Cyclization



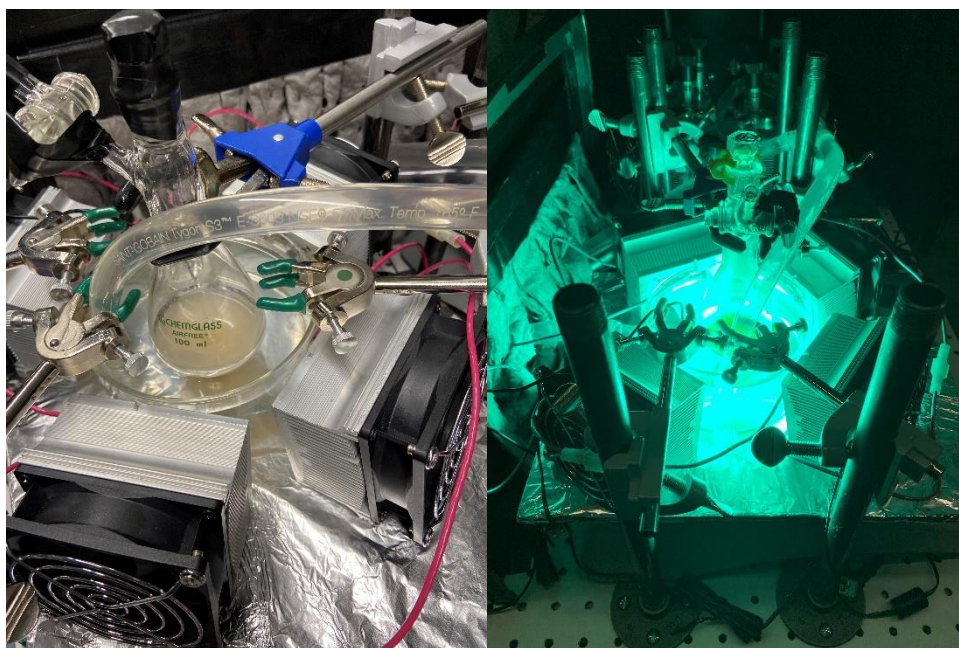
#	Time	Area	Height	Width	Area%	Symmetry
1	18.06	93.4	9	0.1723	7.842	0.341
2	18.522	1098.1	62.5	0.2926	92.158	0.124

## Scaled Enantioselective Hydroalkylation



**Procedure:** GluER-Y177F aliquots were taken into an MBraun<sup>®</sup> anaerobic chamber (<0.1 ppm O<sub>2</sub>) and stored open at 4 °C overnight to allow for passive oxygen degassing. GDH-105 (35 mg), NADP<sup>+</sup> (5.6 mg, 7.1 μmol, 0.02 equiv.), and glucose (386 mg, 2.14 mmol, 6 equiv.) were weighed into a 100 mL Schlenk flask containing a stir bar and the flask imported into the chamber. 30 mL KPi (100 mM, pH 8), previously degassed by freeze-pump-thaw, were added to the flask and the mixture stirred to completely dissolved dry components. (E)-3-(5-iodopentylidene)dihydrofuran-2(3H)-one (**1a**) (100 mg, 0.357 mmol, 1 equiv.) in 3.5 mL IPA was added followed by GluER-Y177F aliquots (1.67 mL, 3.2 mM, 5.4 μmol, 0.015 equiv.). The flask was sealed with a glass stopper, further secured with electric tape, and removed from the chamber. The flask was placed in the center of the water-cooled light setup and irradiated for 72 hours while a water bath temperature of approximately 12 °C was maintained.

The reaction was quenched with 5 mL of 1 M HCl, 30 mL of DCM was added, and the mixture stirred for 1 hour. The biphasic mixture was filtered through a plug of Celite to remove precipitated proteins and then transferred to a separatory funnel. The organic phase was collected and the aqueous phase reextracted with DCM (4 x 30 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and solvent removed in vacuo. Crude product was purified by flash chromatography (45 mg, 82% yield, 92:8 er).

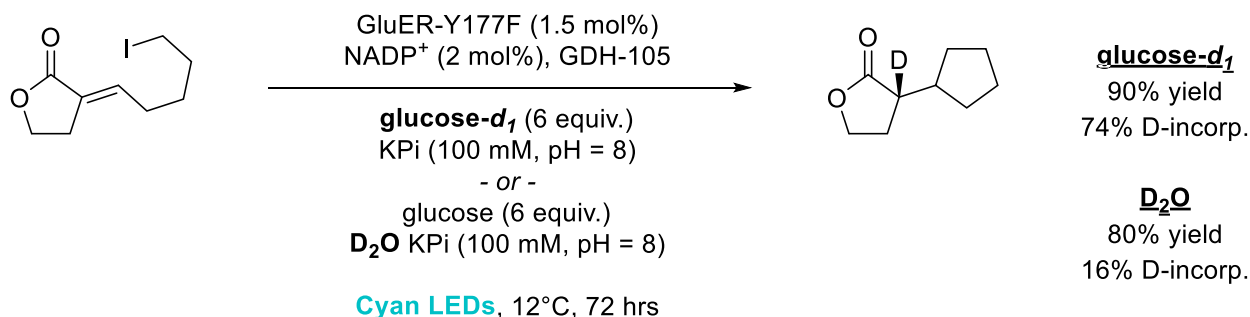


**Supplemental Figure 3.** Alkyl iodide cyclization on a 100 mg scale. Reaction flask before irradiation (left) and during (right).

## Deuterium Incorporation Experiments

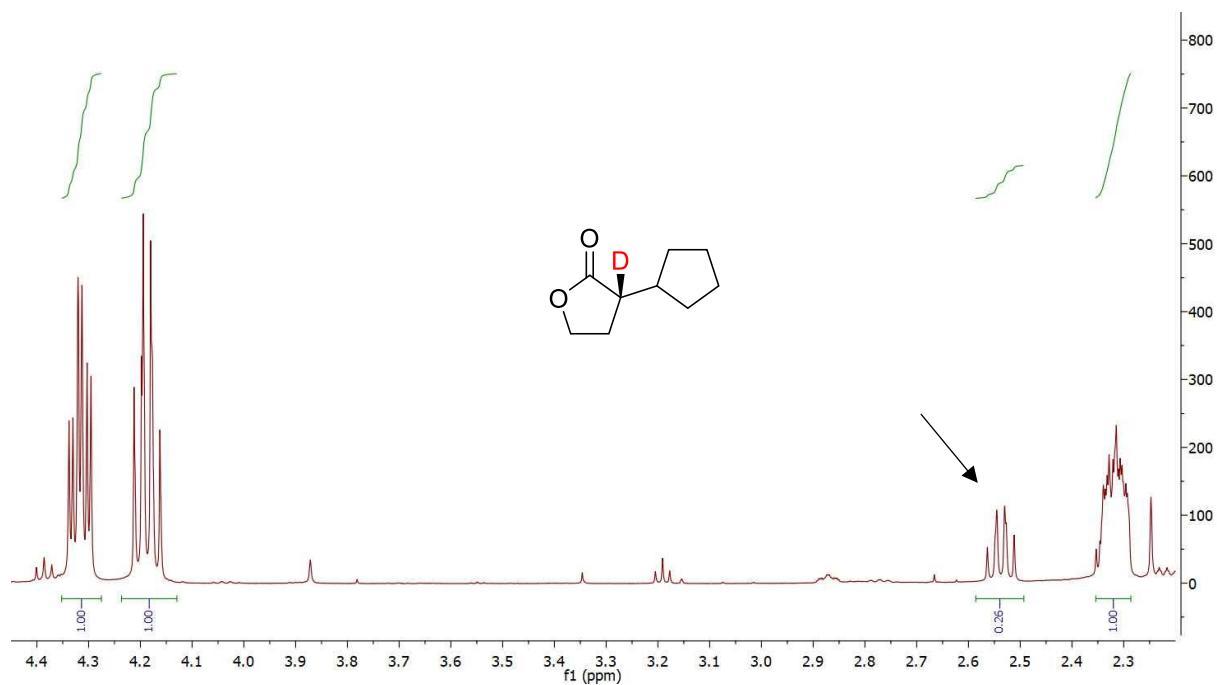
**General Procedure.** The biocatalytic procedure corresponding to the respective substrate was followed but using either D-glucose-1- $d_1$  or buffer prepared from  $D_2O$ . Reactions were run in quadruplicate for each substrate and condition (glucose- $d_1$  or  $D_2O$ ). After completion, the quadruplicate reactions were combined in a 14 mL conical tube and extracted with hexanes (5 x 5 mL). Centrifuging at 5000 rpm for 10 minutes was required to separate the phases in between each extraction. The combined organic extracts were concentrated *in vacuo*. The residue was dissolved in 700  $\mu$ L of  $CDCl_3$  containing 10 mM 1,3,5-tribromobenzene as standard for yield determination. The reaction was analyzed by quantitative  $^1H$  and  $^{13}C$  NMR.

The extent of deuterium incorporation in each reaction can be calculated using integrations of the corresponding C-H and C-D peaks in the quantitative  $^{13}C$  NMR spectrum for either the  $\alpha$ -carbon bearing the deuterium or the adjacent  $\beta$ -carbons. MestReNova's (version 11.0.4) "fit region" tool was used to get accurate peak integrations, with the standard settings. The average of the three values is reported in the main text.

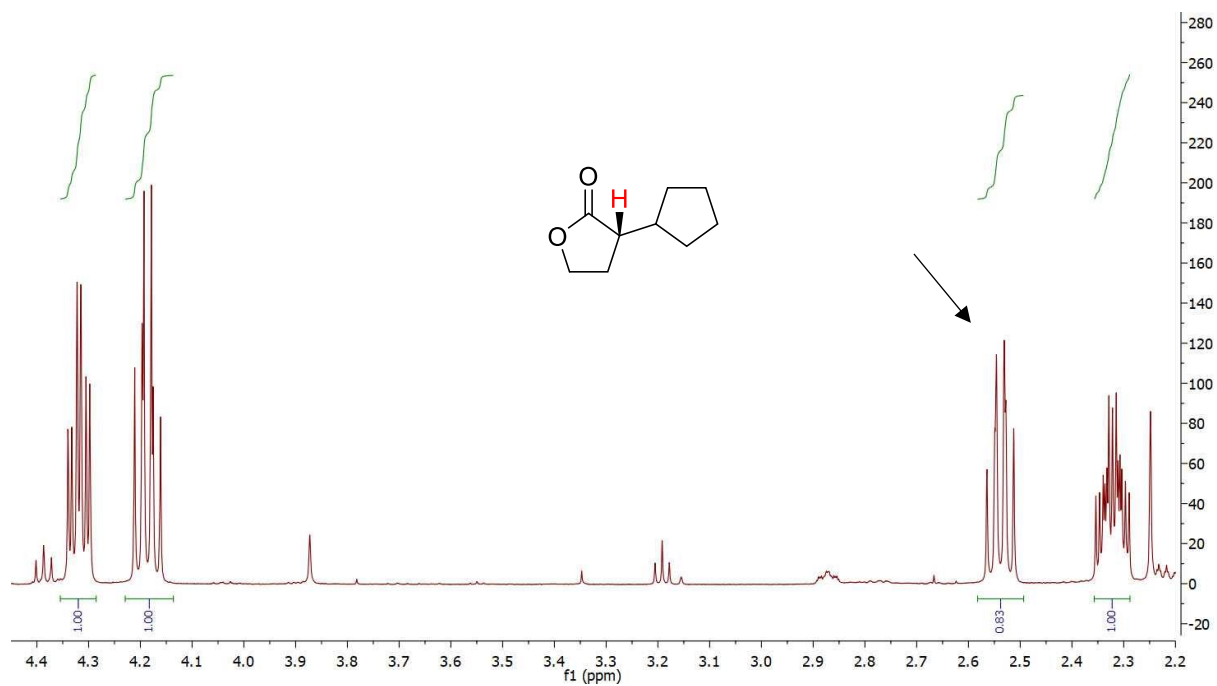


Discussion:

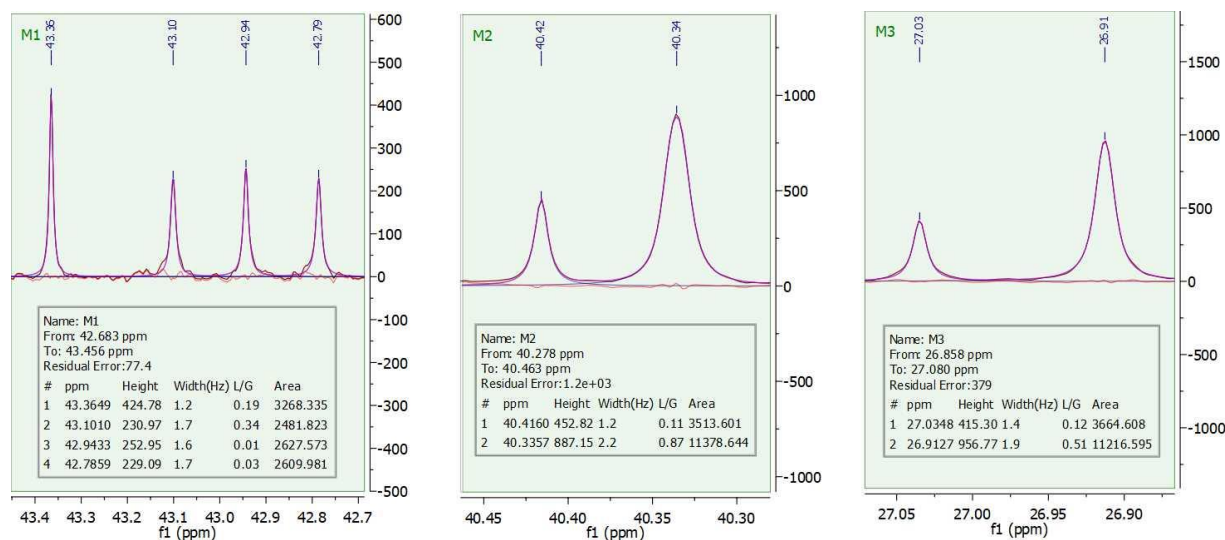
$^1H$  and  $^{13}C$  NMR data both support the conclusion that termination of the  $\alpha$ -acyl radical following cyclization occurs via a hydrogen atom transfer pathway, not reduction followed by protonation, and that flavin is the dominant source of the hydrogen atom. Examination of the  $^1H$  NMR spectrum of the reaction run with glucose- $d_1$  shows that the majority of the  $\alpha$ -proton peak is suppressed (Supplemental Figure 4), indicating a high level of deuterium incorporation at that position. Conversely, the  $^1H$  NMR spectrum of the reaction run in deuterated buffer shows minimal suppression of the  $\alpha$ -proton peak (Supplemental Figure 5). Additional evidence of deuterium incorporation can be found in the  $^{13}C$  NMR spectra, where new upfield peaks can be seen for the  $\alpha$ - and  $\beta$ -carbons (Supplemental Figures 6 and 7). The new  $\alpha$ -carbon peak is a triplet, indicating direct attachment of a deuterium to that position, while the  $\beta$ -carbon peaks are singlets, consistent with their position adjacent to a deuterium bound carbon. In the reaction with glucose- $d_1$ , the new peaks are the major peaks, while in the reaction run in deuterated buffer, the major peaks are identical to those that we find in the independently synthesized, non-deuterated product standard. Integration of these peaks was the basis for quantification of deuterium incorporation.



**Supplemental Figure 4.**  $^1\text{H}$  NMR of product obtained from reaction with glucose- $d_1$ .



**Supplemental Figure 5.**  $^1\text{H}$  NMR of product obtained from reaction in  $\text{D}_2\text{O}$  buffer.

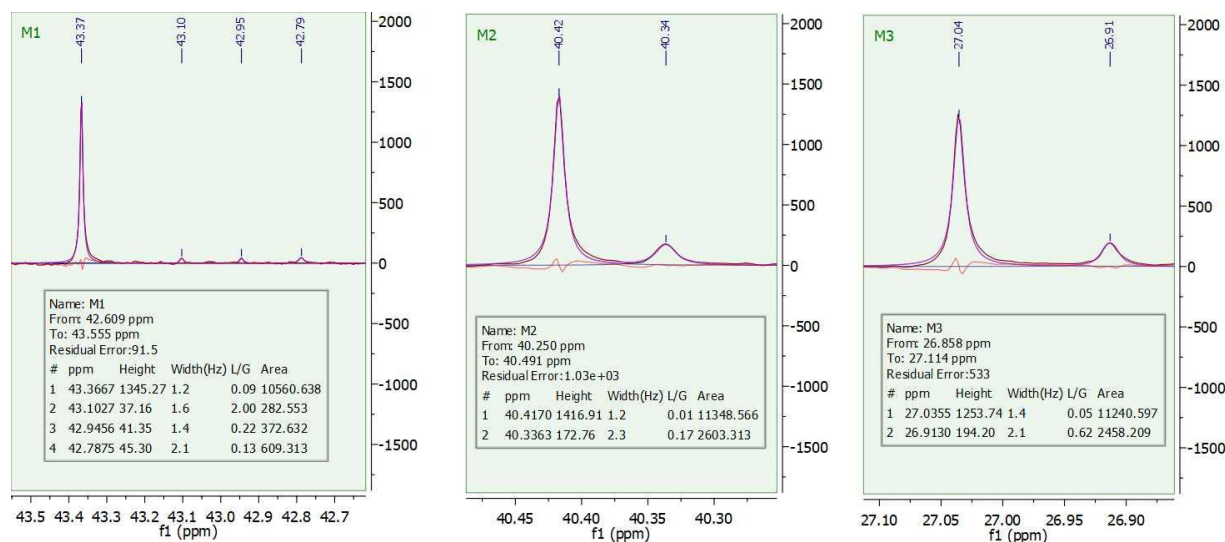


$$\%D_{\alpha} = \frac{\sum_{n=2}^4 A_n}{\sum_{n=1}^4 A_n} \times 100 = 70.3\%$$

$$\%D_{\beta 1} = \frac{A_2}{A_1 + A_2} \times 100 = 76.4\%$$

$$\%D_{\beta 2} = \frac{A_2}{A_1 + A_2} \times 100 = 75.4\%$$

**Supplemental Figure 6.**  $^{13}\text{C}$  NMR integrations of  $\alpha$ - and  $\beta$ -carbon peaks for product obtained from reactions with glucose- $d_1$ . Average deuterium incorporation was 74%.

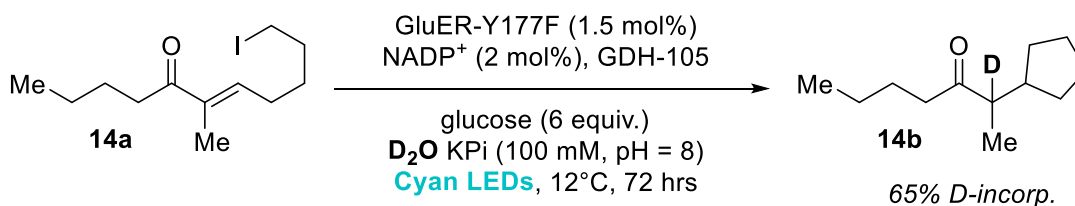


$$\%D_{\alpha} = \frac{\sum_{n=2}^4 A_n}{\sum_{n=1}^4 A_n} \times 100 = 10.7\%$$

$$\%D_{\beta 1} = \frac{A_2}{A_1 + A_2} \times 100 = 18.7\%$$

$$\%D_{\beta 2} = \frac{A_2}{A_1 + A_2} \times 100 = 17.9\%$$

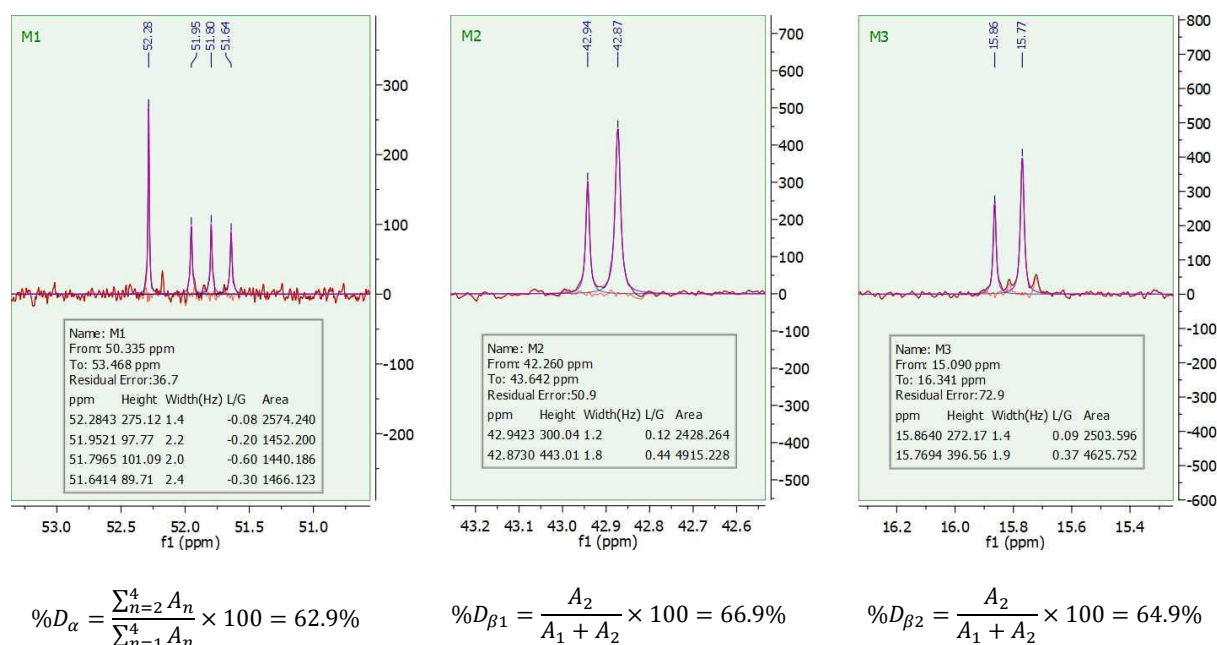
**Supplemental Figure 7.**  $^{13}\text{C}$  NMR integrations of  $\alpha$ - and  $\beta$ -carbon peaks for product obtained from reactions in  $\text{D}_2\text{O}$  buffer. Average deuterium incorporation was 16%.



**Supplemental Figure 8.** Deuterium incorporation in the reductive cyclization of ketone **14a**.

**Discussion.** As noted in the main text, termination of the  $\alpha$ -acyl radical could potentially occur through either HAT or reduction to the corresponding enolate followed by protonation. The low levels of enantioselectivity observed in ketone product **14b** and more facile reduction of  $\alpha$ -keto radicals<sup>11</sup> led us to question if the latter mechanism was operative in this example, with protonation occurring unselectively. Indeed, when the reaction with ketone **14a** was run in  $D_2O$ , ketone product **14b** is obtained with relatively high levels of deuterium incorporation. This stands in contrast to the results obtained for lactone **1b**, consistent with a change in the primary mechanism of  $\alpha$ -acyl radical termination from HAT to reduction/protonation.

Note: no deuterium incorporation is observed stirring product standard in deuterated buffer, indicating that the product is configurationally stable at pH 8, and that the deuterium incorporation observed during the course of the radical cyclization is due to reduction of the  $\alpha$ -acyl radical to the enolate.



**Supplemental Figure 9.**  $^{13}C$  NMR integrations of  $\alpha$ - and  $\beta$ -carbon peaks for product obtained from reactions in  $D_2O$  buffer. Average deuterium incorporation was 65%.

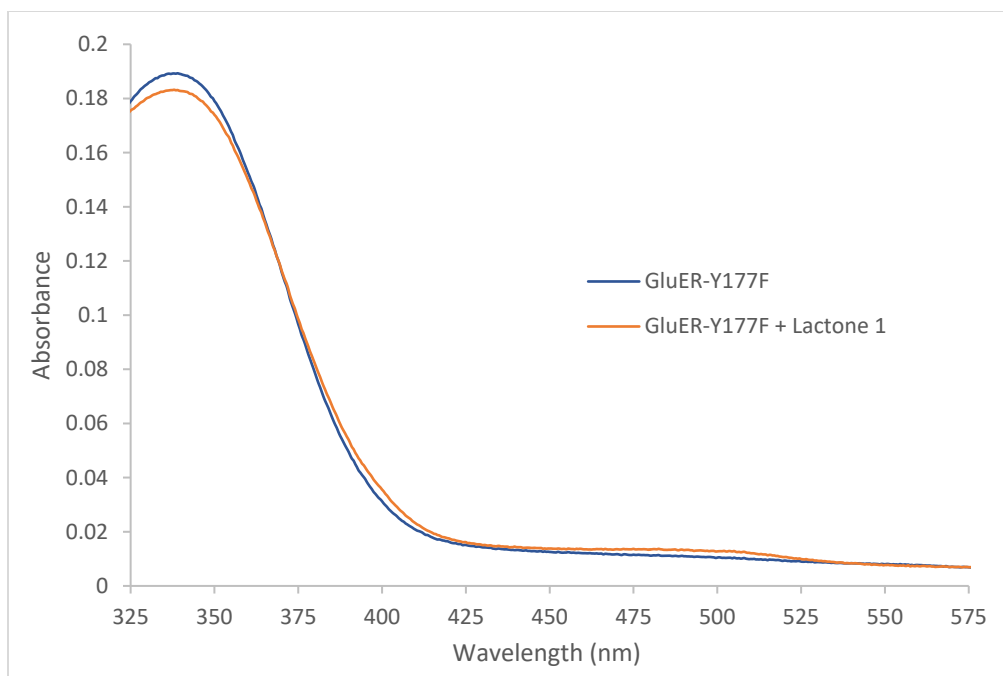
## **Spectroscopic Studies**

**General Comments.** All Samples were prepared in an MBraun® glovebox (<0.1 ppm O<sub>2</sub>). Cuvette used was custom designed quartz with a 1 mm pathlength and a JY valve. All samples were identical to substrate scope reactions in volume (1 mL) and reactant/reagent equivalents. However, due to the heterogeneous nature of these reactions caused by substrate insolubility, solutions were prepared differently to allow for consistent filtration. Filtration of the dilute substrate mixture also had to occur prior to combination with reduced enzyme otherwise enzyme was removed with precipitated substrate upon filtration.

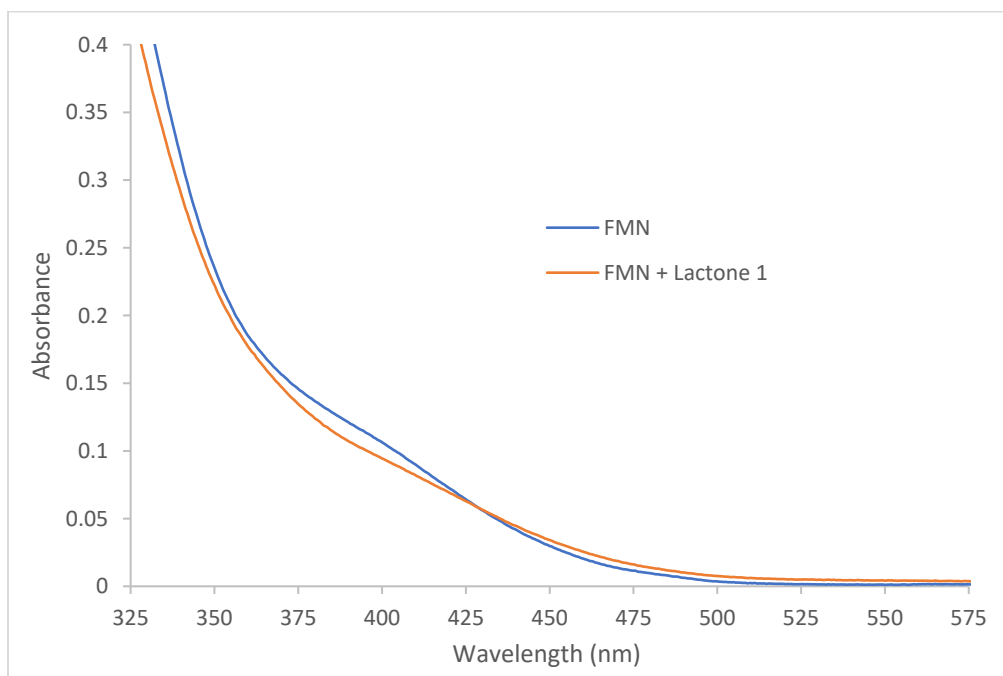
**Procedure.** Stock solutions of GDH-105 (20 mg/mL), NADP<sup>+</sup> (7.8 mg/mL), and glucose (216 mg/mL) in degassed KPi (100 mM, pH 8), and of substrate (0.1 mmol/mL) in isopropanol were prepared. A blank was prepared from 20 μL NADP<sup>+</sup> solution, 50 μL glucose solution, 780 μL KPi, 100 μL IPA, and 50 μL GDH-105 solution. This solution was filtered through a syringe filter (hydrophilic PTFE, 0.2 μm) and used to zero the spectrometer. A concentrated solution of reduced enzyme was prepared from 60 μL NADP<sup>+</sup> solution, 150 μL glucose solution, 90 μL KPi, 150 μL GDH-105 solution, and 150 μL GluER-Y177F (3 mM). Separately, 100 μL IPA was added to 700 μL KPi and filtered through a syringe filter. To obtain a spectrum of reduced enzyme without substrate, 200 μL of reduced enzyme solution was added and the combined solution analyzed. To obtain a spectrum of reduced enzyme with substrate, 100 μL substrate solution was added to 700 μL KPi and the opaque mixture filtered to obtain a homogeneous solution. This was combined with 200 μL of reduced enzyme solution and analyzed. The overlaid spectra are shown in the main text and Supplemental Figure X.

Stock solutions of FMN (3.4 mg/mL) and NaBH<sub>4</sub> (3.8 mg/mL) in KPi were prepared. 20 μL of each was added to 860 μL KPi and the solution stirred for 30 min to allow for complete reduction (note: in contrast to enzymatic conditions, solutions must be dilute for chemical reduction of free FMN to occur). 100 μL of IPA was added, the solution filtered, and a spectrum of reduced free FMN obtained. This process was repeated but with 100 μL of substrate solution. The overlaid spectra are shown in Supplemental Figure X.

**Discussion.** Analysis of the UV-Vis spectra of reduced GluER-Y177F in the presence of alkyl iodide substrate shows the appearance of a new peak ( $\lambda_{\text{max}} = 485 \text{ nm}$ ) that is not present in the absence of substrate (see main text for an expanded view). Furthermore, substrate causes a decrease in absorbance of the hydroquinone peak ( $\lambda_{\text{max}} = 338 \text{ nm}$ ) and a bathochromic shift of that peak shoulder. Taken together, these spectroscopic features strongly suggest a charge transfer complex is formed between enzyme-bound flavin hydroquinone and alkyl iodide substrate. Analogous comparison of the UV-Vis spectra of reduced FMN shows some perturbation in the presence of substrate but no distinct features are formed that would suggest a solution phase charge transfer complex. This is consistent with the lack of reactivity with free FMN in solution.

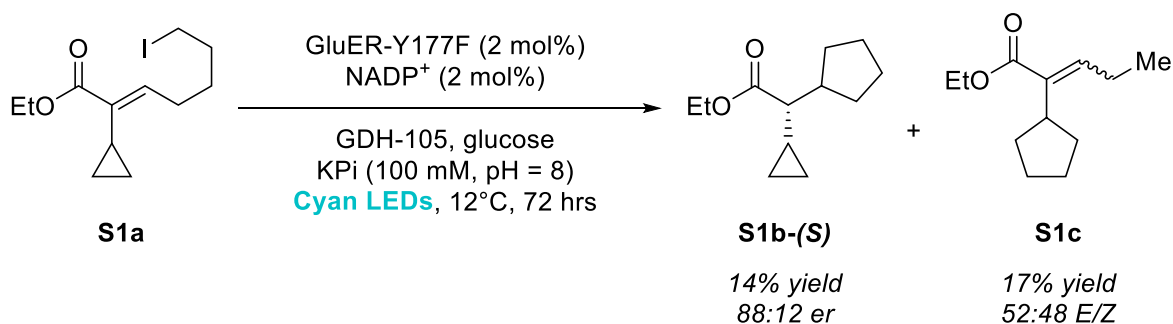


**Supplemental Figure 10.** UV-Vis absorption traces showing GluER-Y177F bound flavin hydroquinone in the absence of substrate (blue), and the CT complex formed in the presence of lactone alkyl iodide **1a** (orange).



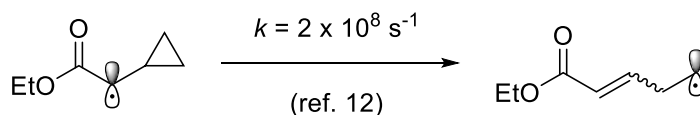
**Supplemental Figure 11.** UV-Vis absorption traces showing free FMN hydroquinone in the absence of substrate (blue) and in the presence of lactone alkyl iodide **1a** (orange).

## Radical Clock Experiment



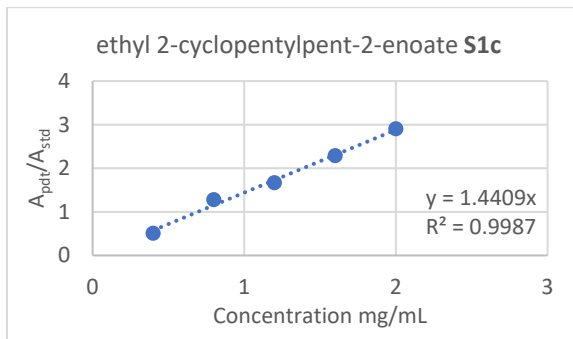
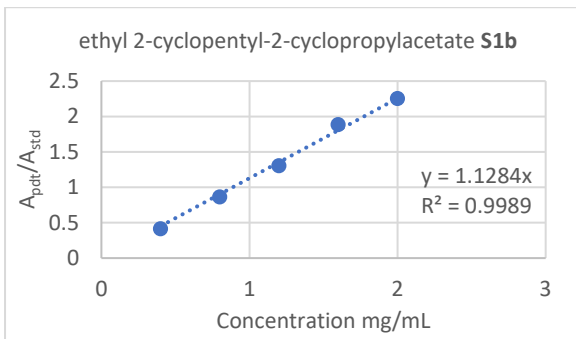
**Supplemental Figure 12.** Outcome of an  $\alpha$ -cyclopropyl radical clock substrate.

**Discussion.** In order to investigate the rate of HAT in our system, we examined a substrate with a cyclopropane at the  $\alpha$ -position.  $\alpha$ -Acyl radicals adjacent to a cyclopropane, such as the kind that would be obtained after the initial 5-*exo* cyclization, are known to open rapidly (see below).<sup>12</sup> The presence of ring-opened product supports our proposed radical mechanism. Furthermore, a close to equal mixture of ring-opened and ring-closed products indicates that HAT occurs at a rate competitive with ring opening. As such, we hypothesize that in our system HAT from FMN is also occurring at a rate upwards of  $10^8 \text{ s}^{-1}$ .

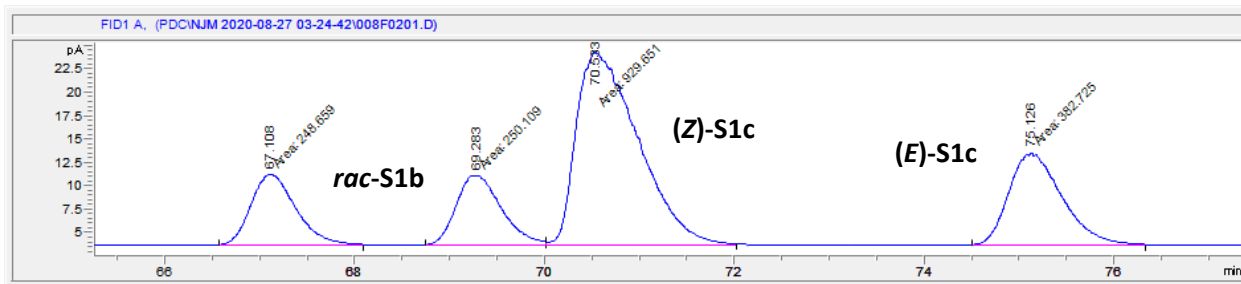


**Procedure:** Substrate **S1a** was subject to the exact reaction conditions used for all 5-exo enantioselective hydroalkylations with exception that the GluER-Y177F loading was increased from 1.5 mol % to 2 mol %.

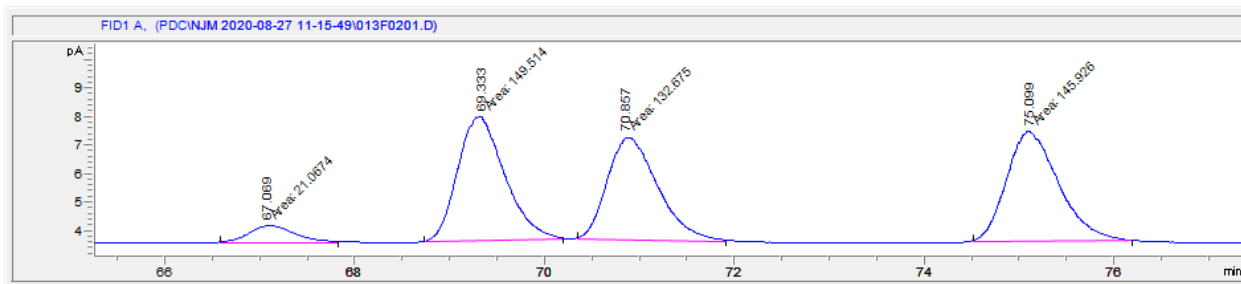
Standard Curves:



Selectivity (Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 90 °C):



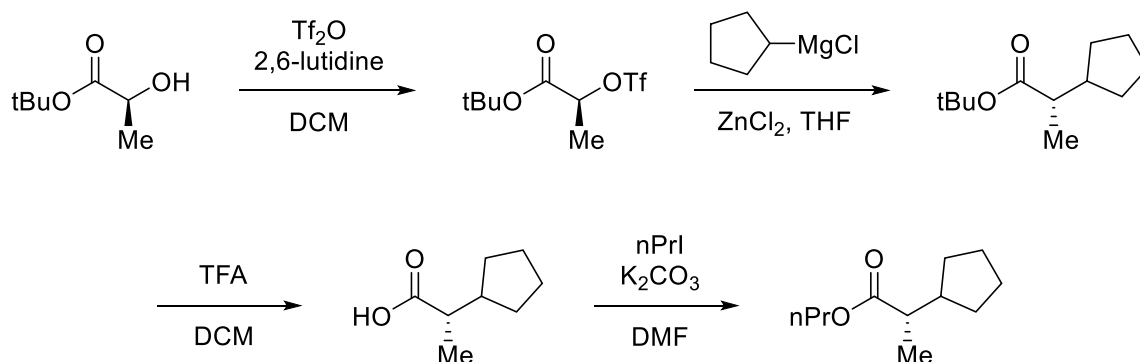
#	Time	Area	Height	Width	Area%	Symmetry
1	67.108	248.7	7.6	0.5471	13.729	0.736
2	69.283	250.1	7.5	0.5562	13.809	0
3	70.533	929.7	20.6	0.7509	51.329	0.453
4	75.126	382.7	9.9	0.6449	21.132	0.711



#	Time	Area	Height	Width	Area%	Symmetry
1	67.069	21.1	6.1E-1	0.5714	4.690	0.65
2	69.333	149.5	4.3	0.5752	33.286	0.986
3	70.857	132.7	3.6	0.6155	29.537	0.606
4	75.099	145.9	3.9	0.6285	32.487	0.746

## Determination of Absolute Stereochemistry

**Discussion:** Enantiopure propyl (S)-2-cyclopentylpropanoate standard was prepared from chiral pool (S)-lactic acid via an enantiospecific procedure from the literature.<sup>13</sup> Starting from enantiopure tert-butyl lactate, enantiopure product standard was obtained with inversion of stereochemistry. Comparison of elution times and spiking experiments confirmed that our synthetically prepared propyl (S)-2-cyclopentylpropanoate matched the major enantiomer from the enzymatic reaction.



**tert-butyl (S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate:** Commercially available tert-butyl (S)-2-hydroxypropanoate (1.46 g, 10 mmol, 1 equiv.), was dissolved in 40 mL DCM and cooled to 0 °C. 2,6-Lutidine (1.74 mL, 15 mmol, 1.5 equiv.) was added, followed by the dropwise addition of triflic anhydride (2.36 mL, 14 mmol, 1.4 equiv.). After stirring for 1 hour, the reaction was quenched with 1M HCl, extracted with  $\text{Et}_2\text{O}$ , washed with brine, and dried with  $\text{MgSO}_4$ . Crude product purified by flash chromatography (2.26 g, 81% yield). NMR spectra were consistent with those previously reported.<sup>13</sup>

**tert-butyl (S)-2-cyclopentylpropanoate:** Zinc chloride (41 mg, 0.3 mmol, 0.1 equiv.) was dissolved in 10 mL dry THF and cooled to 0 °C. Tert-butyl (S)-2-(((trifluoromethyl)sulfonyl)oxy)propanoate (835 mg, 3 mmol, 1 equiv.) was added, followed by cyclopentyl magnesium bromide (2 M, 2.1 mL, 4.2 mmol, 1.4 equiv.), and the reaction stirred for 3 hours. The reaction was then quenched with sat.  $\text{NH}_4\text{Cl}$ , extracted with  $\text{Et}_2\text{O}$ , and dried with  $\text{Na}_2\text{SO}_4$ . Crude product was purified by flash chromatography (335 mg, 56% yield).

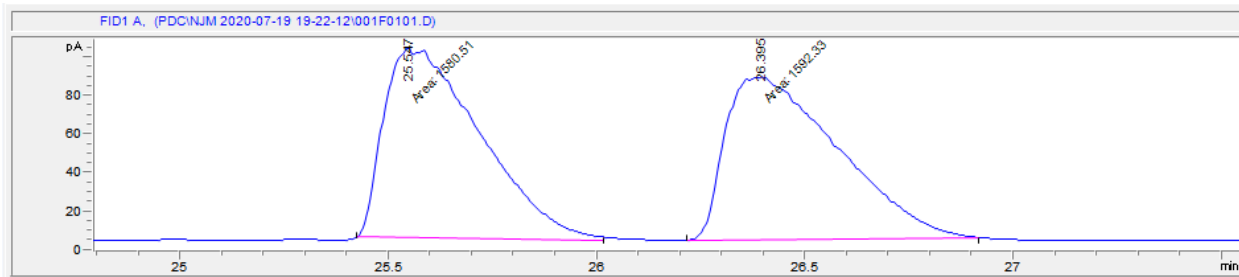
**$^1\text{H}$  NMR** (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.11 (dq,  $J = 9.4, 6.9$  Hz, 1H), 1.93 (dtd,  $J = 16.8, 9.4, 7.5$  Hz, 1H), 1.82 – 1.69 (m, 2H), 1.67 – 1.47 (m, 4H), 1.44 (s, 9H), 1.21 (dq,  $J = 12.4, 9.5, 8.5$  Hz, 1H), 1.15 – 1.07 (d,  $J = 6.9$  Hz, 4H).

**(S)-2-cyclopentylpropanoic acid:** tert-butyl (S)-2-cyclopentylpropanoate (198 mg, 1 mmol, 1 equiv.) was dissolved 10 mL DCM, cooled to 0 °C, trifluoroacetic acid (760  $\mu\text{L}$ , 10 mmol, 10 equiv.) added dropwise, and the reaction stirred overnight. Solvent was removed by nitrogen flowing nitrogen over the reaction and crude product purified by flash chromatography (140 mg, 98% yield). NMR spectra were consistent with the racemic compound.

**propyl (S)-2-cyclopentylpropanoate:** Synthesized from (S)-2-cyclopentylpropanoic acid (140 mg, 0.98 mmol) according to general procedure E. Product obtained as a clear oil (155 mg, 85% yield). NMR spectra were consistent with the racemic compound.

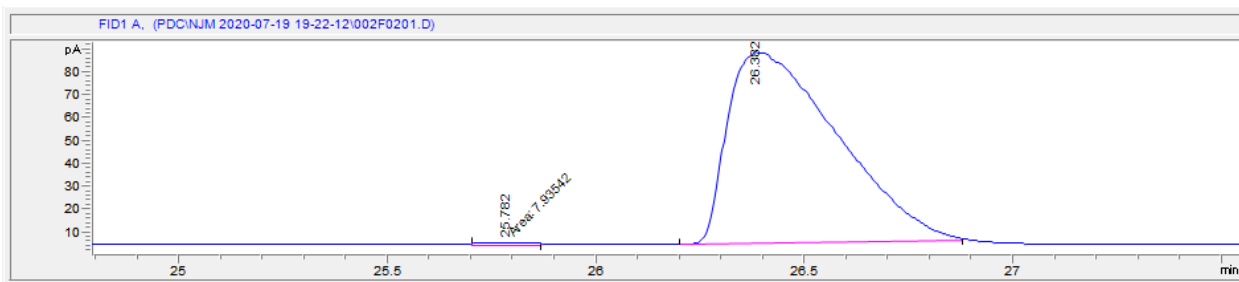
Note: Astec® CHIRALDEX B-DM, 33.2 psi, isothermal 100 °C. Superior separation was achieved under these conditions and with a longer column in order to unambiguously confirm the matching stereochemistry.

### Racemate



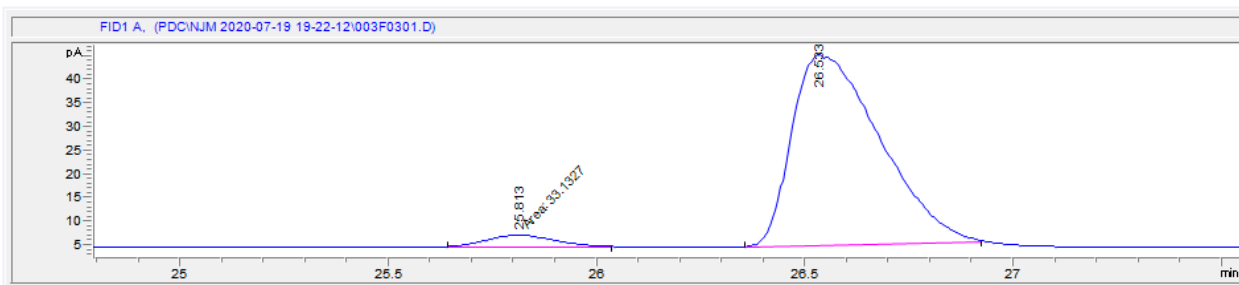
#	Time	Area	Height	Width	Area%	Symmetry
1	25.547	1580.5	98.3	0.268	49.814	0.331
2	26.395	1592.3	84.4	0.3143	50.186	0.446

### Synthesized from Chiral Pool



#	Time	Area	Height	Width	Area%	Symmetry
1	25.782	7.9	9.5E-1	0.139	0.517	0.861
2	26.382	1525.5	84	0.215	99.483	0.329

### Reductive Cyclization

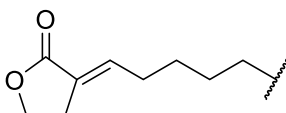


#	Time	Area	Height	Width	Area%	Symmetry
1	25.813	33.1	2.7	0.206	5.286	0.845
2	26.533	593.7	40.4	0.1863	94.714	0.412

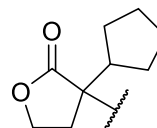
## LC-MS/MS Analysis

**Procedure.** Following a standard reaction with alkyl iodide **1a**, a small aliquot was subject to a trypsin digest followed by LC-MS/MS analysis of the resulting peptide fragments on a Thermo Fusion LUMOS MS instrument connected to a Thermo Easy nLC 1200 UPLC system.

**Results and Discussion:** Several of the peptides resulting from the trypsin digest were found to have a modification of +152 MW. This nicely corresponds with alkylation by substrate. Alignment of these peptides with the protein sequence allowed for determination of their positions in the overall protein scaffold. The peptide sequences, residues modified (in bold), and locations of those residues in the protein sequence, are showed in Supplemental Table 1 below. Alkylation could foreseeably occur through addition of the alkyl radical formed after the initial dehalogenation, addition of the  $\alpha$ -acyl radical formed after cyclization, or  $S_N2$  displacement of the starting alkyl iodide. However, the observed alkylations occurred only on nucleophilic residues, suggesting that the primary mechanism of alkylation is nucleophilic displacement. We hypothesize that alkylation of the enzyme results in catalyst deactivation. Given the known effects of temperature on the rate of nucleophilic alkylation, the improved reaction outcome at lower temperature can reasonably be attributed to a reduced rate of alkylation.



Exact Mass: 153.09



Exact Mass: 153.09

**Supplemental Table 1.** Alkylated peptide fragments of GluER-Y177F after a standard reaction

Peptide	Sequence Position
EGLGWPFAPGI <b>W</b> SDAQVEAWKPIVAGVHAK	W73
MVHSSVTGTQPVSSSATTAPGEVHTYEGK	Y130
TDE <b>Y</b> GGVPENR	Y194
TDQ <b>P</b> KLSPQIR	K276
GIALQPDDMKTWYSQGPEG <b>Y</b> TDYPSATSGPN	Y350
GIALQPDDMKTWYSQGPEG <b>Y</b> TDYPSATSGPN	Y353
GIAL <b>Q</b> PDDMKTWYSQGPEGYTDYPSATSGPN	Q335, Y343, Y353
GIALQPDDMKTWYSQGPEGYTDYPSATSGPN	K340

## **Sequence Information**

### **Gluconobacter oxydans 'ene'-reductase (GluER)<sup>14</sup>**

GenBank Accession Number: WP\_011252080.1

#### **Protein Sequence**

MHHHHHHMPTLFDPIDFGPIHAKNRIVMSPLTRGRADKEAVPTPIMA EYQAQRASAGLIITEATGISREGLGWPFAPGI  
WSDAQVEAWKPIVAGVHAKGGKIVCQLWHMGRMVHSSVTGTQPVSSSATTAPGEVHTYEGKKPFEQARAIDAADIS  
RILNDYENAARNAIRAGFDGVQIHAANGYLIDEFLRNGTNHRTDEYGGV PENRIRFLKEVTERVIAAIGADRTGVR LSPN  
GDTQGCIDSAPETVFPAAKLLQDLGVAWLELREPGNNGTFGKTDQPKLSPQIRKVFRLPLVLNQDYTFEAAQTALAE G  
KADAIAFGRKFISNPDLPERFARGIALQPDDMKTWYSQGPEGYTDYPSATSGPN

#### **DNA Sequence**

ATGCACCACCACCACCACATGCCGACCCTTTTCGACCCCATCGATTTCCGACCTATCCACGCCAAGAATCGTAT  
CGTCATGTCCCCCTGACTCGCGGTCGCGCTGACAAAGAGGCGGTTCCAACCCCATTATGGCTGAATACTACGCC  
CAACGCGCTTCGGCGGGTTAATTACTACTGAAGCGACGGGATTTACGCGAAGGCTTAGGTTGGCCGTTTGCG  
CCGGGAATTTGGTCCGATGCACAGGTTGAGGCGTGAAACCTATCGTCGCGGGTGTCCATGCAAAGGGCGGCAA  
GATCGTATGTCAGCTTTGGCATATGGGCCGTATGGTACATTCTTCAGTTACAGGGACGCAGCCCGTAAGCAGTTCC  
GCCACTACTGCTCCAGGTGAGGTTACACCTATGAGGGCAAGAAGCCCTTCGAACAAGCGCGTGCAATCGATGCT  
GCAGACATCTCCCGCATCCTTAACGATTACGAAAATGCAGCACGTAATGCAATCCGCGCGGGTTTTCGATGGAGTG  
CAGATCCACGCAGCCAATGGCTACCTTATCGATGAGTTTTTGCCTAACGGAACCAATCATCGCACCGATGAGTATG  
GGGGGGTGCCGGAGAACCGTATTCGTTTCTTGAAAGAGGTAACAGAACGCGTCATCGCGGCGATTGGCGCTGAC  
CGTACGGGTGTGCGTCTGAGTCCAAACGGTGACACACAGGGTTGTATCGACAGTGCTCCCGAAACCGTTTTTGTTC  
CTGCCGCAAAGCTTTTGCAAGATTTAGGGGTAGCGTGCTTGAGCTGCGTGAACCTGGTCCGAATGGTACGTTTG  
GAAAGACGGATCAACCAAATTATCTCCACAAATCCGTAAGGTATTCCTTCGTCCATTGGTCTTAAATCAAGACTAT  
ACTTTTGAGGCGGCACAGACGGCCCTGGCTGAGGGCAAGGCGGACGCTATTGCGTTTGGCCGTAAGTTCATTCA  
AATCCAGACTTGCTGAGCGCTTTGCCCGTGGCATCGCACTGCAACCAGACGATATGAAAACATGGTACTCCCAAG  
GCCCAGAGGGTTACACAGACTATCCATCCGCAACTTCTGGGCCGAAC

#### **GluER-Y177F**

Fwd: 5'-AGATCCACGCAGCCAATGGCTTCCTTATCGATGAGTTTTTGGC-3'

Rev: 5'-GCCATTGGCTGCGTGGATCTGCACTCCATCGAAACCCGCGC-3'

**Bacillus subtilis NADPH dehydrogenase (YqjM)<sup>15</sup>**

Genbank Accession Number: BAA12619

**Protein Sequence:**

MHHHHHHMARKLFTPITIKDMTLKNRIVMSPMCMYSSHEKDGLTPFHMAHYISRAIGQVGLIIVEASAVNPQGRITD  
QDLGIWSDEHIEGFAKLTEQVKEQGSKIGIQLAHAGRKAELEGDIFAPSAIAFDEQSATPVEMSAEKVKETVQEFKQAAA  
RAKEAGFDVIEIHAAHGYLIHEFLSPLSNHRTDEYGGSPENRYRFLREIIDEVKQVWDGPLFVRVSASDYTDKGLDIADHI  
GFAKWMKEQGVLDICSSGALVHADINVFPGYQVSFAEKIREQADMATGAVGMITDGSMAEELQNGRADLIFIGREL  
LRDPFFARTAAKQLNTEIPAPVQYERGW

**DNA Sequence:**

ATGCACCACCATCACCACCACGCCCGTAAGCTGTTACGCCCATCACCATTAAGGATATGACTTTGAAAAACCGTAT  
CGTTATGAGTCCCATGTGCATGTACAGCAGCCATGAAAAAGACGGAAAATTAECTCCGTTTCATATGGCGCATTAT  
ATCAGTCGTGCAATCGGCCAAGTTGGTCTTATTATCGTGGAGGCAAGTGCCGTAATCCCCAGGGACGTATTACG  
GATCAAGATTTGGGTATCTGGAGCGATGAACACATCGAAGGCTTCGCGAAGCTGACAGAACAGGTTAAGGAACA  
AGGGTCTAAGATCGGCATTCAACTGGCCCACGCCGACGTAAGGCTGAATTGGAGGGTGACATCTTTGCTCCATC  
TGCTATCGCGTTTGACGAGCAATCTGCGACTCCGGTCGAGATGAGCGCTGAGAAGGTGAAGGAAACAGTGCAAG  
AGTTCAAGCAGGCAGCAGCACGTGCGAAGGAAGCAGGGTTCGATGTGATTGAGATCCATGCAGCACATGGTTAT  
CTGATTCACGAGTTTCTGTCCCCTCTGTCAAACCATCGCACCGATGAGTATGGAGGAAGCCCTGAGAATCGCTATC  
GCTTCCTGCGTGAAATTATCGATGAAGTTAAACAGGTTTGGGACGGTCCGCTTTTTGTGCGCGTGTCTGCCTCAGA  
TTACACGGATAAAGGCTTGATATTGCTGACCACATCGGGTTCGAAAAGTGGATGAAGGAGCAAGGAGTGGACT  
TAATTGATTGCAGCAGCGGGGCTTAGTACACGCGGACATTAACGTATCCCGGGCTACCAAGTTTCCTTGCAGA  
AAAGATCCGCGAACAAGCGGATATGGCAACAGGTGCTGTTGGGATGATCACGGACGGTTCGATGGCCGAGGAAA  
TCCTTCAAACCGCCGTGCCGACTTGATCTTTATCGGTCGTGAATTACTTCGCGACCCTTTTTTGCTCGCACCGCA  
GCGAAACAATTAATACGGAAATTCCTGCACCAGTGCAATACGAGCGTGGTTGGTGA

**YqjM-Y169F**

Fwd: 5'-AGATCCATGCAGCACATGGTTTTCTGATTCACGAGTTTCTGTC-3'

Rev: 5'-ACCATGTGCTGCATGGATCTCAATCACATCGAACCCCTGCTT-3'

## **Pentaerythritol tetranitrate reductase (PETNr)<sup>16</sup>**

Genbank Accession Number: AAB38683

### **Protein Sequence:**

MSAEKLF TPLKVGAVTAPNRVFMAPLTRLRSIEPGDIPTPLMGEYRQRASAGLIIEATQISQAQAKGYAGAPGLHSPEQI  
AAWKKITAGVHAEDGRIAVQLWHTGRISHSSIQPGGQAPVSASALNANTRTSLRDENGNAIRVDTTTTPRALELDEIPGI  
VNDFRQAVANAREAGFDLVELHSAHYLLHQFLSPSSNQRTDQYGGSVENRARLVLEVVDVAVCNEWSADRIGIRVSP  
GTFQNV DNGPN E EADALYLIEELAKRGIAYLHMSETDLAGGKPYSEAFRQKVRERFHGVIIGAGAYTAEKAEDLIGKGLI  
DAVAFGRDYIANPDLVARLQKKAELNPQRPESEFYGG GAEGYTDYPSLHHHHHH

### **DNA Sequence**

ATGTCGGCCGAGAAGTTGTTACGCCCTTAAAGGTCGGTGCGGTGACCGCTCCTAACCGCGTATTCATGGCTCCAC  
TGACCCGCTTGCGTTCAATCGAGCCGGGCGACATCCCAACGCCGCTTATGGGTGAATACTACCGCCAACGTGCCTC  
CGCTGGATTGATTATCTCGGAAGCGACACAAATCTCTGCGCAGGCGAAAGGCTACGCCGGTGCGCCCGGTTGCA  
TTCACCCGAACAAATCGCCGCTGGAAGAAAATTACCGCAGGAGTTCATGCCGAGGACGGCCGTATTGCGGTACA  
ACTGTGGCATAACGGACGCATCTCCCATTCGAGTATTCAGCCCGGCGGTGAGGCGCCAGTAAGCGCATCGGCGCT  
TAATGCGAACACGCGCACCTCTCTGCGCGACGAGAATGGTAACGCCATCCGCGTTGATAACAACACCCCCGCGCT  
TTAGAATTAGATGAGATTCCAGGTATTGTAATGATTTTCGTGAGGCTGTGGCCAACGCCCGTGAAGCTGGTTTTG  
ACCTGGTAGAACTTCACTCGGCTCACGGCTACTTACTGCATCAGTTTTTAAGCCCTTCAAGTAATCAACGCACCGAC  
CAATACGGCGGCTCGGTGGAAAATCGTGCCCGTCTGGTTCTGGAGGTGGTCGACGCCGTTTGTAAATGAGTGGAGC  
GCGGATCGTATCGGCATCCGTGTGTCTCCCATTTGGACGTTCCAAAACGTGGACAACGGACCGAATGAAGAGGCC  
GACGCTCTTTACCTGATCGAAGAGCTGGCGAAGCGCGGTATTGCTTATCTGCACATGTCGGAAACGGACTTGGCG  
GGAGGTAAGCCATACAGTGAAGCGTTTTCGCCAAAAGTCCGTGAACGCTTTCATGGGGTAATTATCGGCGCCGGT  
GCGTACACGGCAGAAAAGGCGGAAGACTTAATCGGAAAAGTTTTGATCGATGCCGTGGCGTTTGGACGTGACTA  
TATTGCTAACCAGACCTTGTGCCCCGTTGCAAAAAGAAAGCGGAGTTGAACCCCCAGCGTCCAGAGTCCTTTTAT  
GGCGGTGGGGCGGAAGGATATACTGACTACCCAAGCTTGACCAACCATCACCACCACTGA

### **PETNr-Y187F**

Fwd: 5'-AACTTCACTCGGCTCACGGCTTCTTACTGCATCAGTTTTTAAG-3'

Rev: 5'-GCCGTGAGCCGAGTGAAGTTCTACCAGGTCAAACCAGCTT-3'

## 12-Oxophytodienoate reductase 1 (OPR1)<sup>17</sup>

Genbank Accession Number: NP\_001234781.1

### Protein Sequence

MENKVVEEKQVDKIPLMSPCKMGKFELCHRVLAPLTRQRSYGYIPQPHAILHYSQRSTNGLLIGEATVISETGIGYKD  
VPGIWTKEQVEAWKPIVDVAVHAKGGIFFCQIWHVGRVSNKDFQPNGEDPISCTDRGLTPQIRSNIDIAHFTRPRRLTT  
DEIPQIVNEFRVAARNAIEAGFDGVEIHGAHGYLIDQFMKDQVNDRSQYGGSLNRCRFALEIVEAVANEIGSDRVGI  
RISPFAYNEAGDTNPTALGLYMVESLNKYDLAYCHVVEPRMKTAWEKIECTESLVPMRKAYKGTFFIVAGGYDREDGN  
RALIEDRADLVAYGRLFISNPDLPKRFELNAPLNKYNRDFTFYSDPIVGTYDYPFLETMTLEHHHHHH

### DNA Sequence

ATGGAGAATAAAGTTGTGGAGGAGAAACAAGTCGATAAAATCCCCTTGATGTCACCGTGCAAGATGGGAAAGTTT  
GAACTTTGCCACCGTGTGTCTGCTCCGCTGACACGGCAACGCTCCTACGGGTATATACCGCAGCCCCATGCAA  
TCTTACATTACTCTCAGCGTTCAACCAACGGAGGGCTGTTGATAGGTGAAGCAACAGTCATTAGCGAAACGGGTAT  
AGGCTATAAGGACGTACCCGGCATCTGGACTAAAGAACAAGTTGAGGCATGGAAACCCATAGTAGACGCCGTAC  
ATGCAAAGGGAGGGATCTTCTTCTGCCAGATATGGCATGTGGGTAGAGTGAGTAATAAGGACTTCCAACCTAACG  
GTGAGGATCCCATTAGCTGTACCGATCGGGGATTAACGCCACAGATACGGTCAAATGGTATTGACATAGCTCATT  
TACAAGACCTAGACGTCTTACCACGGACGAGATCCCAAAATTGTCAACGAATTCCGCGTGGCGGCTAGAAATGC  
CATCGAAGCAGGATTCGACGGCGTAGAGATACACGGAGCACACGGTTATCTGATAGACCAGTTCATGAAAGACCA  
AGTTAATGACCGGTCCGATAAGTATGGAGGATCTCTGGAAAACCGGTGTCGGTTCGCCTTGGAGATTGTTGAAGC  
CGTCGCTAATGAAATCGGAAGCGACCGTGTCCGAATACGCATTAGTCCATTTCGCGCACTACAATGAGGCAGGGGA  
TACCAATCCCACTGCGCTGGGTTTATATATGGTGGAGAGCCTGAATAAATACGATTTAGCATATTGTCATGTAGTG  
GAACCTCGCATGAAAACGCTTGGGAAAAAATTGAATGCACTGAGAGTCTTGTCCGATGCGTAAAGCGTACAAG  
GGAACGTTCATAGTAGCTGGGGTTATGATCGGGAGGACGGGAACCGGGCCCTGATAGAAGACCGGGCCGACCT  
TGTCGCATACGGACGTTTGTTCATATCCAACCCAGATTTACCGAAACGTTTTGAGTTAAACGCTCCCCTGAATAAAT  
ACAATCGTGACACGTTCTATACTTCTGATCCAATCGTGGGTTATACGGACTATCCGTTTTTAGAGACGATGACGCTC  
GAGCACCACCACCACCACCACTGA

### OPR1-Y192F

Fwd: 5'-AGATACACGGAGCACACGGTTTTCTGATAGACCAGTTCATGAA-3'

Rev: 5'-ACCGTGTGCTCCGTGTATCTCTACGCCGTCGAATCCTGCT-3'

## Nicotinamide-dependent cyclohexanone reductase (NCR)<sup>18</sup>

Genbank Accession Number: AAV90509

### Protein Sequence

MPSLFDPIRFGAFTAKNRIWMAPLTRGRATRDHVPTEIMA EYQAQRASAGLI SEATGISQ EGLGWPYAPGIWSDAQV  
EAWLPITQAVHDAGGLIFAQLWHMGRMVPSNVSGMQPVAPSASQAPGLGHTYDGKKPYDVARALRLDEIPRLDDY  
EKAARHALKAGFDGVQIHAANGYLIDEFIRDSTNHRHDEYGGAVENRIRLLKDVTERVIATIGKERTAVRLSPNGEIQGT  
VDSHPEQVFIPAAKMLSDLDIAFLGMREGAVDGTGFKTDQPKLSPEIRKVKPPLVLNQDYTFETAQAALDSGVADAISF  
GRPFIGNPDLPRRFFEKAPLTKDVIETWYQTTPKGYTDYPLLGDHHHHHH

### DNA Sequence

ATGCCGTCACTGTTTCGATCCAATCCGCTTTGGGGCTTTCACTGCAAAAAATCGTATCTGGATGGCGCCGTTAACAC  
GGGGTCGGGCAACCCGTGACCATGTCCCAACAGAGATAATGGCTGAATACTATGCCCAACGCGCATCCGCGGGCT  
TGATCATCAGCGAGGCGACCGGGATCAGCCAAGAGGGCCTGGGCTGGCCCTATGCACCAGGAATCTGGAGTGAT  
GCGCAGGTCGAGGCATGGTTACCCATAACCCAAGCGGTACACGATGCCGAGGTTTGATATTTGCACA ACTGTGG  
CACATGGGGCGTATGGTGCCTTCCAACGTTTCTGGAATGCAACCTGTGCGACCTAGCGCTTCAACAAGCGCCCGGCT  
TGGGCCATACTTATGATGGCAAAAAGCCATACGATGTAGCCAGAGCATTGAGACTTGACGAGATCCCACGGCTGC  
TGGACGACTATGAAAAGGCAGCTCGGCACGCACTGAAAGCTGGGTTTCGATGGAGTTCAGATTCATGCTGCCAACG  
GATACCTGATTGACGAGTTCATCCGGGATTCAACAAATCATAGACACGACGAATACGGGGGGGCGGTTGAGAAC  
AGAATACGGTTATTGAAGGATGTCACTGAGCGGGTTATCGCAACCATCGGAAAGGAGCGCACAGCAGTGC GTTTA  
AGTCCGAATGGAGAGATAACAAGGCACAGTAGACTCGCATCCAGAACAGGTATTTATCCCGGCTGCAAAGATGTTA  
TCTGATTTAGATATCGCGTTCCTTGGGATGCGCGAGGGTGCTGTAGACGGGACATTTGGCAAACAGACCAGCCC  
AAACTTTCGCCCAGATCCGTAAAGTTTTCAAGCCACCCCTTGTTCTGAATCAAGATTACTTTTCGAGACTGCCCA  
GGCTGCGTTAGATTCGGGTGTAGCCGATGCAATCAGTTTTGGTCGTCCATTATTGGGAATCCCGACTTACCGAGA  
AGATTCTTTGAAAAGGCACCGTAACTAAGGACGTAATTGAGACTTGGTACTCAGACTCCCAAAGGTTACACCG  
ACTATCCACTGTTAGGTGATCTCGAGCACCACCATCACCACCACTGA

### NCR-Y177F

Fwd: 5'-CAGATTCATGCTGCCAACGGATACCTGATTGACGAGTTCATCCG-3'

Rev: 5'-TCCGTTGGCAGCATGAATCTGAACTCCATCGAACCCAGC-3'

## Old yellow enzyme 2 (OYE2)<sup>19</sup>

Genbank Accession Number: AAA83386

### Protein Sequence:

MPFVKDFKPQALGDTNLFKPIKIGNNELLHRAVIPPLTRMRAQHPGNIPNRDWAVEYYAQRARPGTLIITEGTFPSPQ  
SGGYDNAPGIWSEEQIKEWTKIFKAIHENKSFQWVQLWVLGWAAFDPDLARDGLRYDSASDNVYMNAEQEEKAKKA  
NPNQHSITKDEIKQYVKEYVQAANKNSIAAGADGVEIHSANGYLLNQFLDPHSNRRTDEYGGSIENRARFTLEVVDVVD  
AIGPEKVGLRLSPYGVFNSMSGGAETGIVAQYAYVLGELERRAKAGKRLAFVHLEPRVTNPFLEGEGEYNGGSNKFA  
YSIWKGPIIRAGNFALHPEVVREEVKDPRTLIGYGRFFISNPDLVDRLEKGLPLNKYDRDRTFYKMSAEGYIDYPTYEALKL  
GWDKNHHHHHH

### DNA Sequence:

ATGCCCTTCGTGAAAGACTTCAAACCTCAAGCCCTGGGCGATACTAATTTATTTAAGCCAATTAATAATTGGAACA  
ATGAGTTGTTACACCGCGCTGTAATTCACCCCTTAACCCGCATGCGCGCCCAACATCCAGGGAACATCCCTAATCG  
CGATTGGGCAGTCGAGTACTATGCTCAGCGTGCTCAGCGTCCGGGTACCCTTATCATCACGGAAGGAACGTTTCCG  
TCGCCGCAATCGGGAGGGTATGACAACGCTCCCGGTATCTGGTTCGGAAGAAGAGATTAAAGAATGGACCAAATC  
TTTAAAGCAATTCATGAGAATAAATCTTTCGCCTGGGTCCAACCTTTGGTCTGGGCTGGGCAGCCTTCCCTGACA  
CATTGGCGCGTGACGGGCTTCGTTATGATAGTGCTTCGGATAACGTGTATATGAATGCTGAACAAGAAGAAAAGG  
CAAAAAAGCAAACAATCCACAGCATTGATTACTAAAGACGAGATTAAGCAGTATGTTAAGGAATACGTACAAG  
CAGCAAAGAATTCTATTGCCGAGGGGCGGACGGGGTAGAAATCCACTCTGCTAATGGGTACTTGCTTAACCAAGT  
TCCTGGACCCGCATTCAAACAACCGCACTGATGAGTACGGAGGGTCCATCGAAAATCGTGCACGTTTTACTTTAGA  
GGTCGTAGATGCTGTAGTCGACGCGATTGGCCCTGAGAAGGTAGGTTTGCCTTAAGTCCTTATGGCGTGTTCAAT  
TCAATGTCAGGGGCGCTGAAACAGGTATCGTCGCGCAGTACGCATACGTCTTGGGAGAGCTGGAGCGTCGTGC  
TAAGGCTGGCAAGCGTTTAGCTTTTGTGCATTTAGTTGAACCGCGCGTGACAAACCCCTTCTTGACGGAAGGCGAA  
GGAGAGTATAACGGAGGATCGAATAAATTTGCGTATTCCATCTGGAAGGGCCCGATCATTGTCGCCGGTAACTTT  
GCCTTACATCCCGAAGTTGTTTCGCGAGGAAGTAAAAGACCCACGTACCTTGATCGGGTATGGCCGTTTCTTTATTT  
AAACCCCGACTTGGTGGATCGCCTTGAAAAAGGTCTTCCCTTGAATAAGTATGACCGTGATACGTTCTACAAAATG  
TCAGCCGAAGGTTACATCGACTACCCACCTACGAAGAGGCTTTGAACTTGGTTGGGACAAGAACCACCACCATC  
ACCACCACTGA

### OYE2-Y197F

Fwd: 5'-AAATCCAACCTCTGCTAATGGGTTCTTGCTTAACCAGTTCCTGGACCCGC-3'

Rev: 5'-CCCATTAGCAGAGTGGATTTCTACCCCGTCCGCCCTGC-3'

## Old yellow enzyme 3 (OYE3)<sup>20</sup>

Genbank Accession Number: AAA64522

### Protein Sequence:

MPFVKGFEPISLRDTNLFEPKIGNTQLAHRAVMPPLTRMRATHPGNIPNKEWAAVYYGQRAQRPGTMIITEGTFISPO  
AGGYDNAPGIWSDEQVAEWKNIFLAIHDCQSFQVWVQLWSLWASFPDVLARDGLRYDCASDRVYMNATLQEKAKD  
ANNLEHSLTKDDIKQYIKDYIHAAKNSIAAGADGVEIHSANGYLLNQFLDPHSNKRTDEYGGTIENRARFTLEVVDALIE  
TIGPERVGLRLSPYGTFNMSMSGGAEPGIIAQYSYVLGELEKRAKAGKRLAFVHLVEPRVTDPSLVEGEGEYSEGTNDFAYS  
IWKGPPIRAGNYALHPEVVREQVKDPRTLIGYGRFFISNPDLVYRLEEGLPLNKYDRSTFYTMSAEGYTDYPTYEEAVDLG  
WKNKHHHHHHH

### DNA Sequence:

ATGCCTTTCGTGAAGGGGTTTCGAGCCGATCTCTCTGCGCGATACAACTTGTTTCAACCTATCAAGATCGGTAATA  
CCCAATTAGCGCACCGTGCTGTAATGCCCCATTGACCCGATGCGCGCGACGCACCCCGGTAATATCCCAATAA  
AGAGTGGGCGGCGGTCTACTATGGACAACGTGCGCAACGTCTCTGGGACGATGATTATTACTGAAGGTACTTTTAT  
TTCACCCCAAGCCGGCGGGTATGATAACGCACCTGGAATCTGGAGTGATGAGCAAGTGGCTGAGTGGAAAAACA  
TCTTCCTTGAATCCATGACTGCCAATCTTTTCTTGGGTTTCTGCTGTGGAGCTTAGGATGGGCATCATTCCAGAT  
GTATTAGCCCGTGACGGTCTTCGTTATGATTGTGCTTACAGCCGCGTGTATATGAACGCAACATTACAAGAAAAAG  
CCAAAGACGCAAACAACCTTGAGCACTCGCTGACTAAAGACGACATTAAGCAATACATTAAGGACTATATTCATGC  
AGCGAAGAATAGTATCGCTGCCGGAGCCGATGGCGTGGAAATTCACAGCGCTAATGGCTACCTGCTGAACCAATT  
CTTAGACCCCCATTCTAATAAACGCACTGATGAGTACGGGGGAACGATTGAGAACCCTGCTCGTTTCACATTAGAG  
GTAGTCGATGCTTTGATTGAGACGATCGGCCGGAGCGCGTAGGCCTGCGTTTGTCCCCCTATGGGACCTTCAACA  
GTATGAGTGGAGGGGAGAGCCTGGAATCATTGCACAGTATAGCTATGTCCTGGGTGAATTGGAAAAGCGTGCA  
AAAGCGGGCAAACGTCTTGCCTTCGTTTCATCTGGTGGAGCCGCGTGTACCGACCCCTCCTTAGTTGAGGGAGAG  
GGAGAGTACAGTGAAGGTACGAATGACTTCGCCTACAGCATCTGGAAGGGGCCCATCATTGCGGCTGGCAATTAC  
GCCTTGACCCAGAAGTCGTCGCGAGCAGGTAAAGGATCCACGTACACTGATCGGCTATGGGCGCTTCTTCATTT  
CAAATCCAGACTTGGTCTACCGTCTGGAAGAGGGATTACCATTAAATAAATATGACCGCTCCACATTTTATACCATG  
TCGGCTGAGGGGTATACAGACTACCCACCTATGAGGAAGCAGTGGATCTTGGTTGGAACAAGAATCACCACCAT  
CACCACCACTGA

### OYE3-Y197F

Fwd: 5'-AAATTCACAGCGCTAATGGCTTCCTGCTGAACCAATTCTTAGACCCCC-3'

Rev: 5'-GCCATTAGCGCTGTGAATTTCCACGCCATCGGCTCCG-3'

## Thermophilic 'ene'-reductase (TOYE)<sup>21</sup>

Genbank Accession Number: WP\_012268805.1

### Protein Sequence:

MSILHMPLKIKDITIKNRIMMSPMCMYASTDGMPPNDWHIVHYATRAIGGVGLIMQEATAVESRGRITDHDLDGIWND  
EQVKELKKIVDICKANGAVMGIQLAHAGRKCNISYEDVVGPSPIKAGDRYKLPRELSVEEIKSIVKAFGEAAKLANLAGYD  
VVEIHAAHGYLIHEFLSPLSNKRKDEYGNISIENRARFLIEVIDEVRKNWPENKPIFVRVSADDYMEGGINIDMMVEYINM  
IKDKVDLIDVSSGGLLNVDINLYPGYQVKYAETIKKRCNIKTSAVGLITTQELAEIILSNERADLVALGRELLRNPYWVLHTY  
TSKEDWPKQYERAFKHHHHHHH

### DNA Sequence:

ATGTCAATCCTTCATATGCCTCTTAAAATCAAGGATATTACAATCAAAAACCGCATCATGATGTCTCCGATGTGCAT  
GTATAGCGCCTCCACAGACGGGATGCCAAACGACTGGCACATCGTGCACTATGCGACCCGCGCTATCGGGGGTGT  
CGGTTTAATTATGCAAGAAGCAACAGCTGTGCAAAGTCGTGGGCGTATTACGGATCACGACTTAGGTATCTGGAA  
CGATGAACAAGTCAAGGAGTTAAAAAATCGTCGACATCTGTAAGCGAATGGCGCGTAATGGGGATTCAAC  
TGGCCCATGCGGGACGCAAGTGAATATCAGTTATGAGGATGTTGTAGGCCATCACCTATTAAGGCAGGAGACC  
GTTATAAATTGCCCCGCGAACTTTTCAGTTGAAGAAATTAATCTATCGTAAAAGCGTTTGGTGAAGCAGCTAAACG  
TGCAAATTTGGCAGGATACGACGTTGTGGAGATCCACGCTGCCCATGGTTATCTTATTCACGAGTTTTTGAGTCCG  
TTAAGTAATAAACGCAAGGATGAGTACGGAAATTCGATCGAGAATCGTGCTCGCTCCTGATCGAAGTCATCGAT  
GAGGTACGTAAGAATTGGCCCGAAAACAAACCCATTTTCGTCCGCGTTTCAGCTGACGATTATATGGAAGGTGGG  
ATTAATATCGACATGATGGTAGAGTATATTAATATGATTAAGGATAAAGTGGATTTAATCGATGTAAGTTCAGGAG  
GATTACTTAACGTAGATATCAACTTGTACCCTGGGTACCAGGTTAAGTATGCCGAACTATCAAAAAGCGCTGCAA  
CATAAGACTTCAGCGTTGGACTTATCACGACACAGGAGCTGGCTGAAGAAATCTTTCGAACGAACGTGCAGA  
TTTAGTTGCTCTTGGTCGTGAGTACTTCGCAATCCATATTGGGTGCTGCACACATACACCAGCAAGGAAGACTGG  
CCGAAGCAATACGAGCGTGCTTTTAAAAAG

### TOYE-Y169F

Fwd: 5'-AGATCCACGCTGCCCATGGTTTTCTTATTCACGAGTTTTTGAGTCCG-3'

Rev: 5'-ACCATGGGCAGCGTGGATCTCCACAACGTCGTATCCTG-3'

## Morphinone reductase (MorB)<sup>22</sup>

Genbank Accession Number: AAC43569

### Protein Sequence

MPDTSFSNPGLFTPLQLGSLSLPNRVIMAPLTRSRTPDSVPGRLQQIYYGQRASAGLIISEATNISPTARGYVYTPGIWTD  
AQEAGWKGVVEAVHAKGGRIALQLWHVGRVSHELVQPDGQQPVAPSALKAEGAECFVEFEDGTAGLHPTSTPRALE  
TDEIPGIVEDYRQAAQRAKRAGFDMVEVHAANAQLPNQFLATGTNRRTDQYGGSIENRARFPLEVVDAVAEVFGPER  
VGIRLTPFLELFGLTDDEPEAMAFYLAGELDRRGLAYLHFNEPDWIGGDITYPEGFREQMRQRFKGLIYCGNYDAGRA  
QARLDDNTADAVAFGRPFIANPDLPERFRLGAALNE PDPSTFYGGAEVGYTDYPFLDNHGHDLGHHHHHH

### DNA Sequence

ATGCCCCGACACTTCTTTTTCGAATCCAGGACTTTTTACTCCTCTTCAGTTGGGTAGTCTGTCTCTTCCAAATCGTGTC  
ATAATGGCACCTTTAACCCGCTCACGCACGCCAGATTCTGTACCTGGACGCCTTCAACAGATATACTATGGTCAAC  
GCGCCAGCGCCGGGTTAATCATCTCCGAAGCGACAAATATCAGTCCCACCGCTCGGGGATACGTATACACGCCAG  
GCATTTGGACTGACGCTCAGGAGGCCGTTGAAAAGGTGTGGTCTGAAGCTGTCCATGCTAAAGGGGGTCTGATA  
GCGTTGCAGTTATGGCATGTCGGCCGGGTCTCTCATGAGCTGGTGCAGCCAGACGGCCAACAACCCGTGGCACCA  
TCCGCCTTAAAAGCCGAAGGGGCCGAGTGCTTTGTGCAATTCGAGGATGGGACTGCTGGCCTGCACCCTACGTCA  
ACTCCCAGAGCCCTGGAGACAGATGAGATACCCGGTATTGTTGAAGATTACAGACAGGCCGCGCAGCGTGCGAA  
GCGGGCCGGATTTCGATATGGTAGAGTCCACGCGGCAAATGCTTGTCTTCTAATCAGTTCCTGGCGACAGGAAC  
CAATCGTCGCACAGACCAGTACGGTGGATCAATTGAGAACCGGGCTAGATTCCCATTAGAGGTTGTCGATGCTGT  
AGCCGAGGTATTCGGGCCCGAAAGAGTGGGGATACGGCTGACTCCTTCTGGAGTTATTTGGATTAACGGATGA  
TGAACCCGAGGCAATGGCTTTTTACCTTTCGGGAGAATTAGACCGCGTGGTTTAGCGTATTTACACTTTAATGAA  
CCCGATTGGATAGGTGGGGACATCACGTACCCGGAAGGGTTTCGTGAGCAAATGCGTCAACGGTTCAAGGGGGG  
GCTTATATATTGTGGAAACTACGACGCAGGTCGGGCCCAAGCCGGCTTGACGACAATACAGCAGATGCAGTGGC  
GTTTGGGCGTCCATTTATTGCCAACCCCGACTTGCCAGAACGTTTCCGCTTAGGAGCAGCGCTGAACGAACCTGAC  
CCCTCTACTTTTTACGGCGGGGCAGAGGTGGGGTACACAGACTACCCGTTCTGGACAACGGTCATGACCGCCTG  
GGACTCGAGCACCACCATCACCACCACTGA

## Phenylacetone monooxygenase (PAMO-P440L)<sup>23</sup>

Parent Genbank Accession Number: WP\_011291921.1

### Protein Sequence:

MHHHHHHMAGQTTVDSRRQPPEEVDVLVVGAGFSGLYALYRLRELGRSVHVIETAGDVGGVWYWNRYPGARCDIE  
SIEYCYSFSEEVLEQEWNWTERYASQPEILRYINFVADKFDLRSGITFHHTTVTAAAFDEATNTWTVDTNHGDRIRARYLIM  
ASGQLSVPQLPNFPGLKDFAGNLYHTGNWPHEPVDVFSGQRVGVIGTGSSGIQVSPQIAKQAAELFVQRTPHFAVPAR  
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AEFIRNKIRNTVRDPEVAERLVPKGYPFGTKRILEIDYEMFNDRNVHLVDLSAPIETITPRGVRTSEREYELDSLVLATG  
FDALTGALFKIDIRGVGNVALKEKWAAGPRTYLGLSTAGFPNLFfiAGPGSLSALS NMLV SIEQHVEVWVDHAIYMFKN  
GLTRSEAVLEKEDEWVEHVNEIADETLYPMTASWYTGANVPGKPRVFMlyVGGFHRyRQICDEVAAGYEGFVLT

### DNA Sequence:

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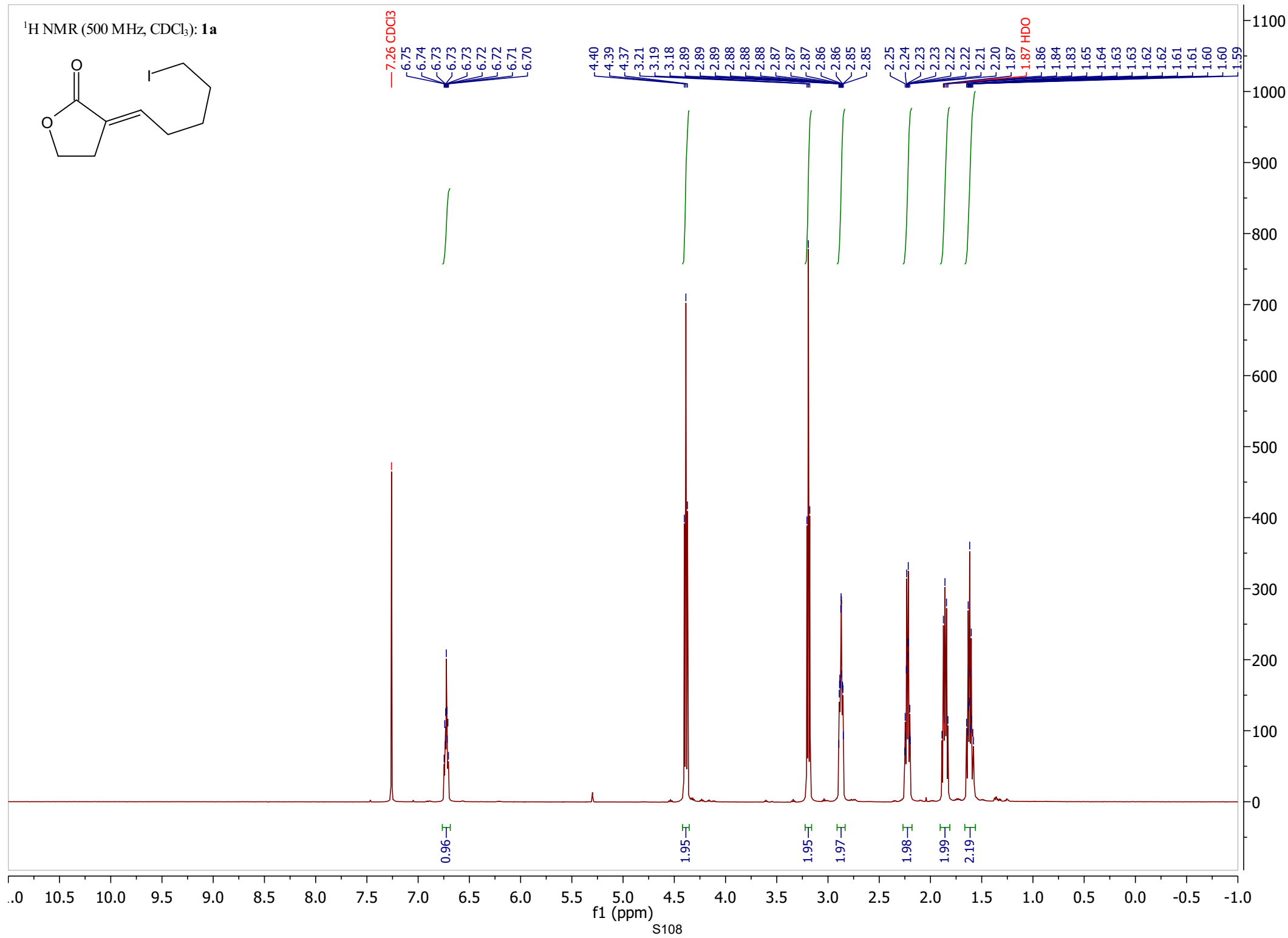
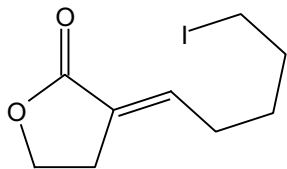
**Note:** Wild-type PAMO shows high reactivity only for acyclic compounds closely resembling its namesake, phenylacetone. However, Reetz and Wu showed that the incorporation of the P440L mutation significantly expanded PAMO's scope to include  $\alpha$ -aryl cyclohexanones and bicyclic ketones.<sup>24</sup> Therefore, our lab has utilized this more substrate permissive mutant as a starting point for screening.

## References

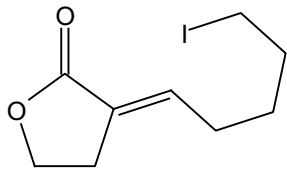
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<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **1a**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **1a**



—171.25

—139.84

—126.02

—77.16 CDCl<sub>3</sub>

—65.49

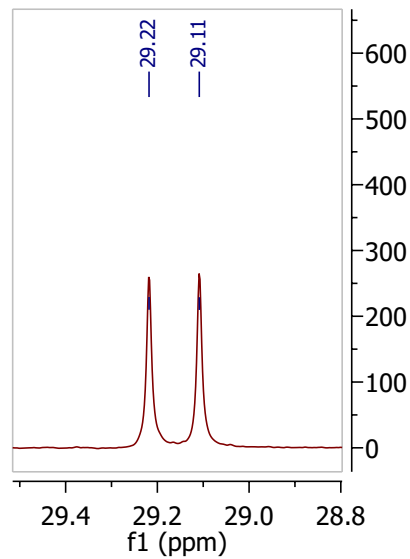
—32.93

—29.22

—29.11

—25.21

—6.08

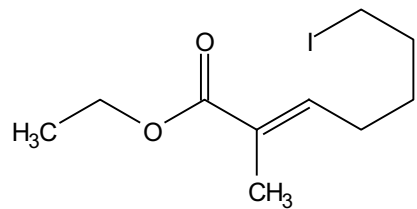


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f1 (ppm)

S109

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **2a**



7.26 CDCl<sub>3</sub>

6.74  
6.74  
6.73  
6.72  
6.71  
6.71

4.21  
4.19  
4.18  
4.17

3.21  
3.19  
3.18

2.22  
2.21  
2.19  
2.18

1.90  
1.89  
1.88

1.87  
1.86  
1.85

1.84  
1.83  
1.82

1.59 H<sub>2</sub>O  
1.58  
1.57

1.56  
1.55  
1.52  
1.51

1.31  
1.29  
1.28

1.00

2.12

2.10

1.99

5.24

2.06

3.10

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

f1 (ppm)

S110

-100

0

100

200

300

400

500

600

700

800

900

1000

1100

1200

1300

1400

1500

1600

1700

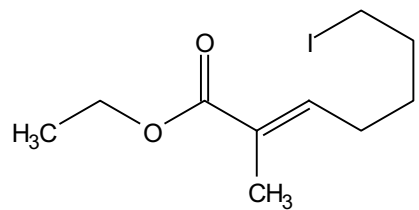
1800

1900

2000

2100

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **2a**



— 168.27

— 141.22

— 128.56

— 77.16 CDCl<sub>3</sub>

— 60.63

— 33.13

— 29.57

— 27.67

— 14.43

— 12.54

— 6.48

300

250

200

150

100

50

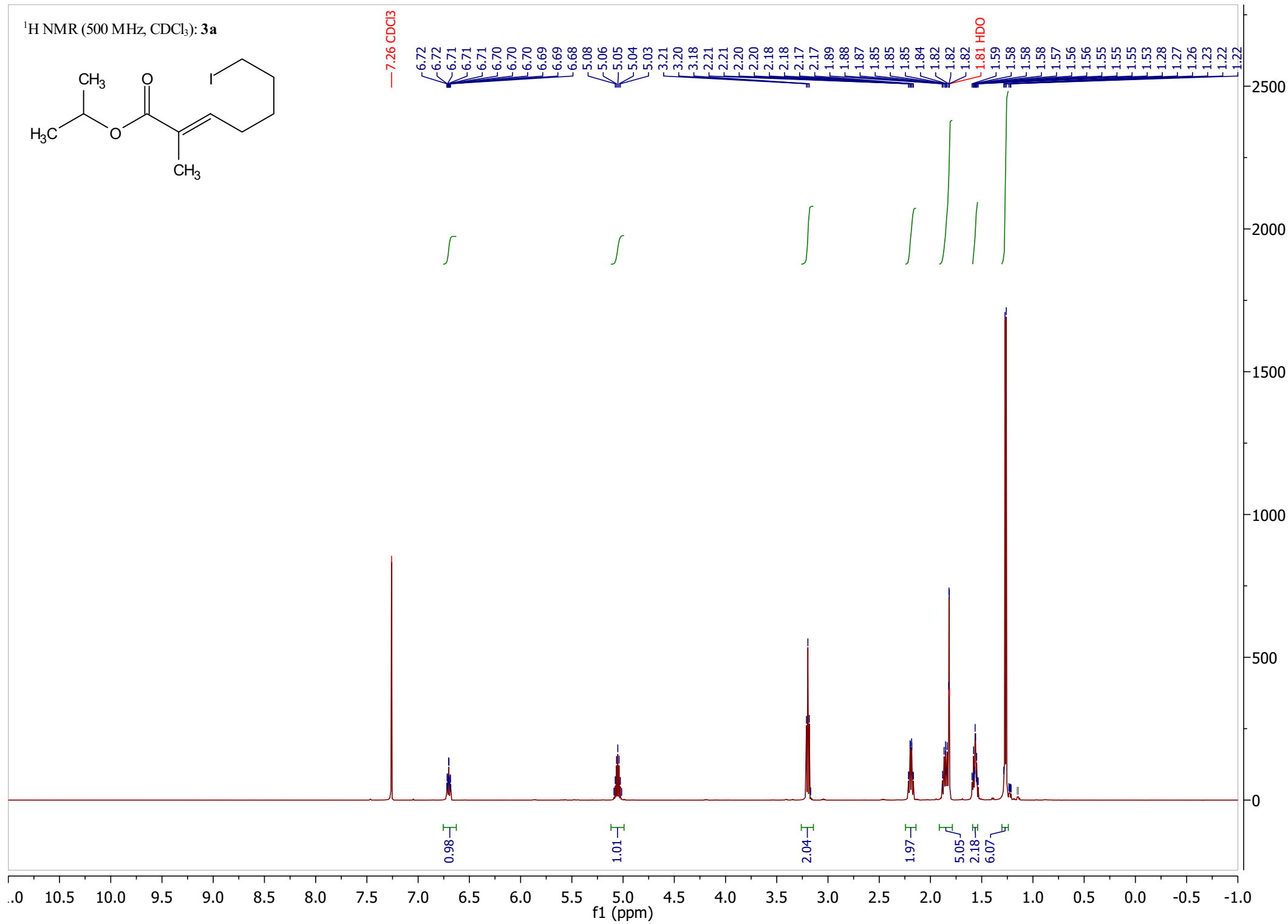
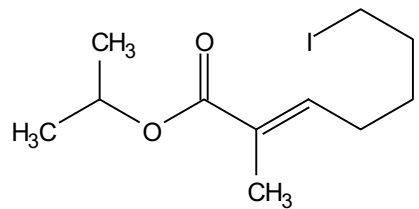
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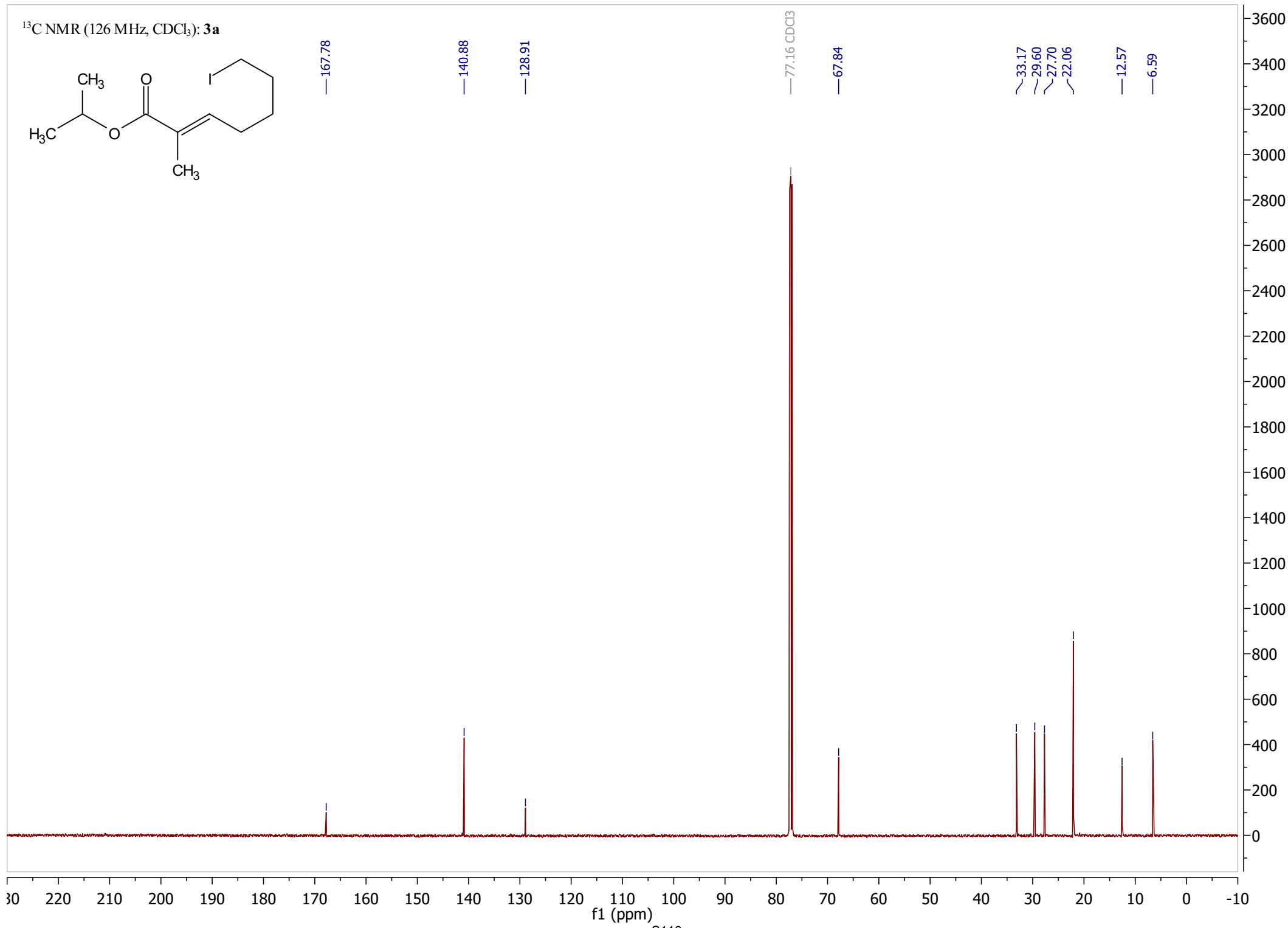
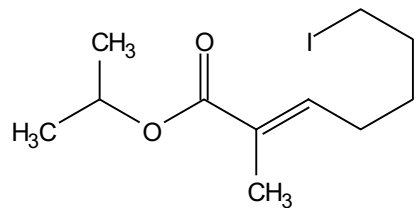
f1 (ppm)

S111

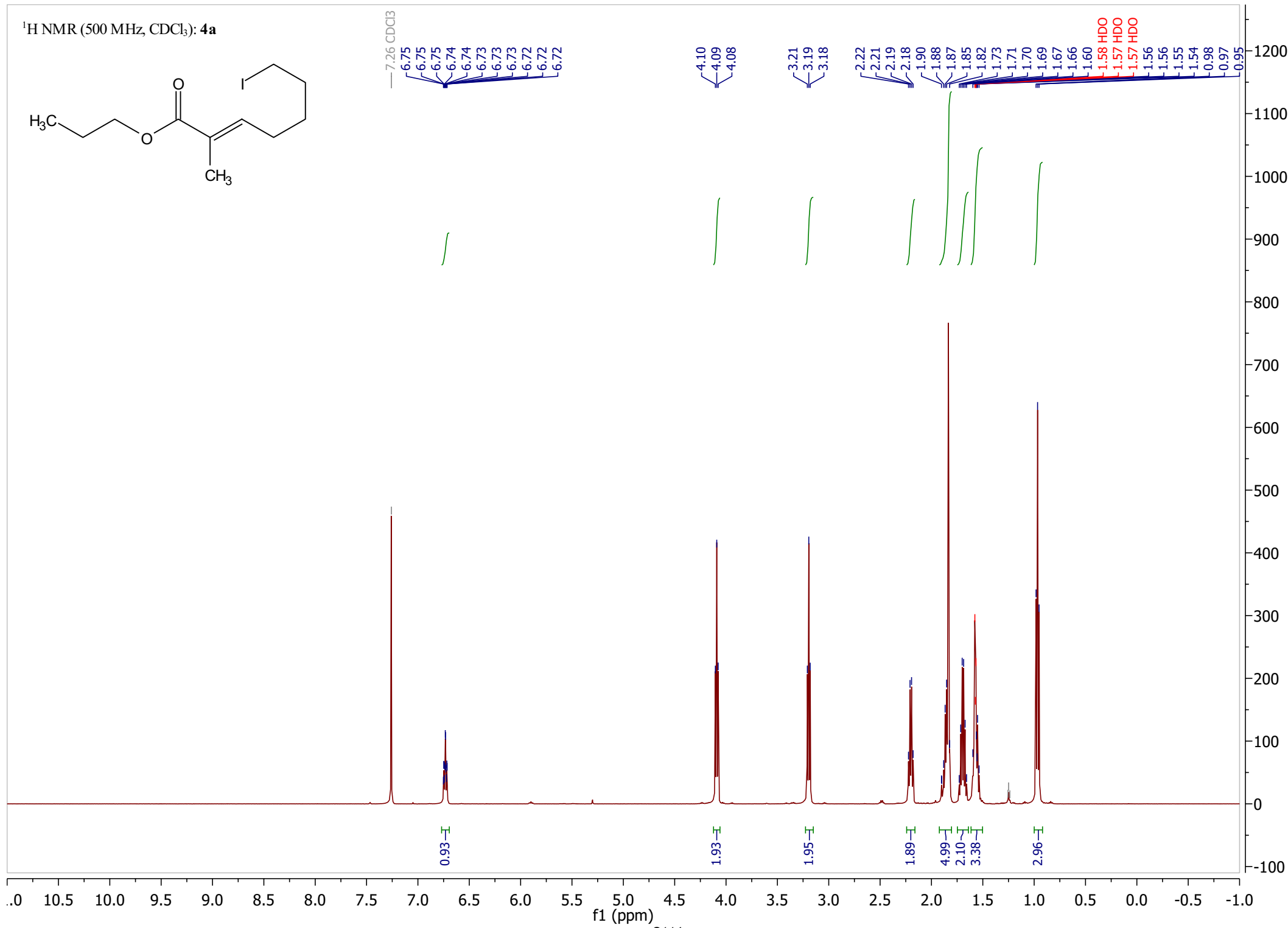
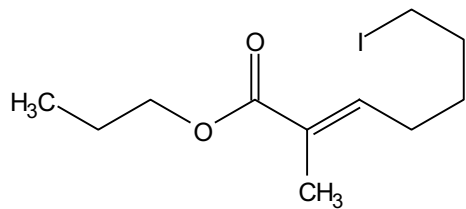
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **3a**



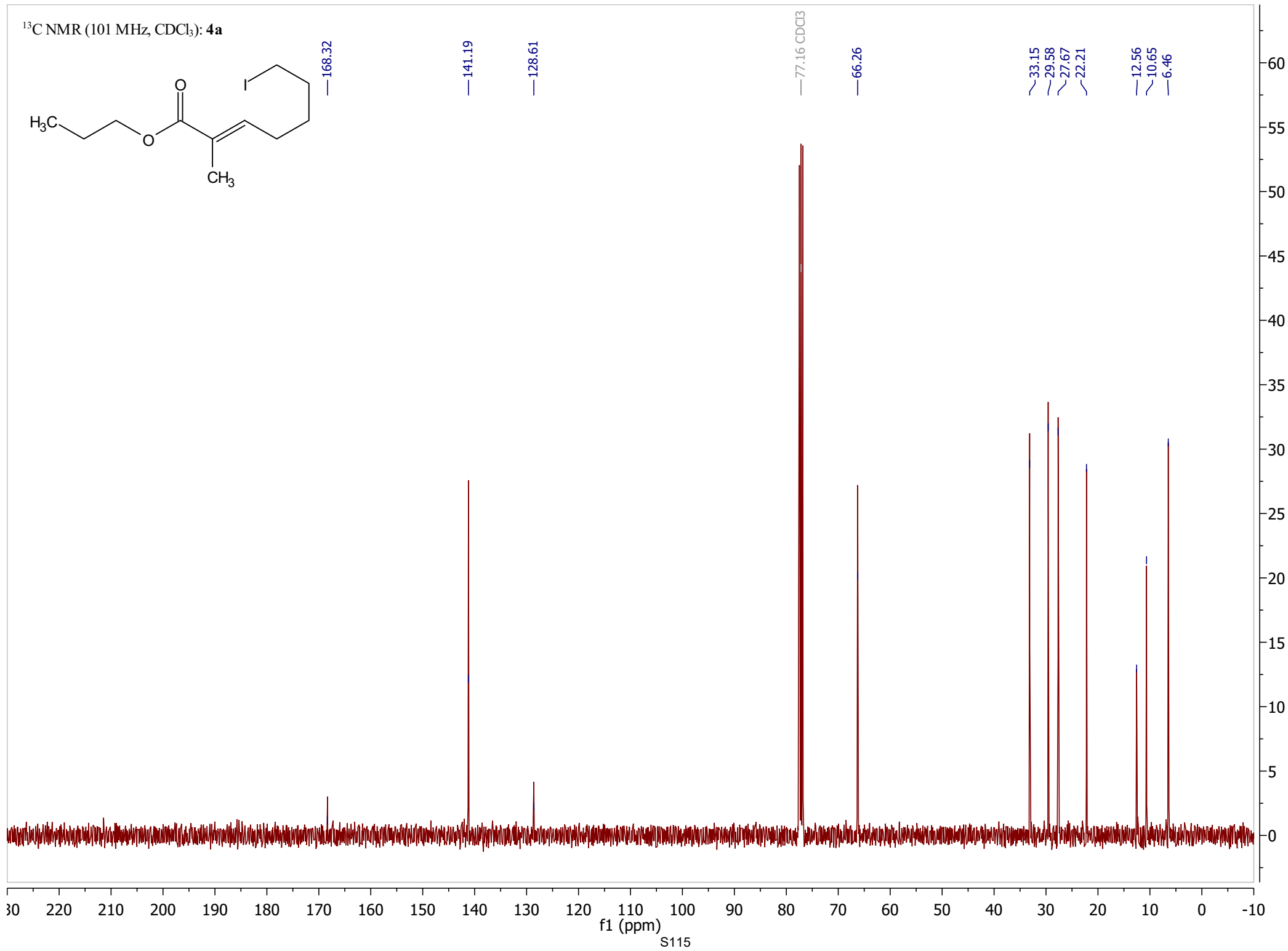
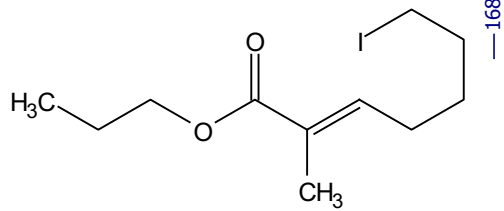
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **3a**



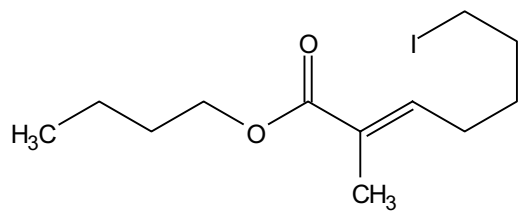
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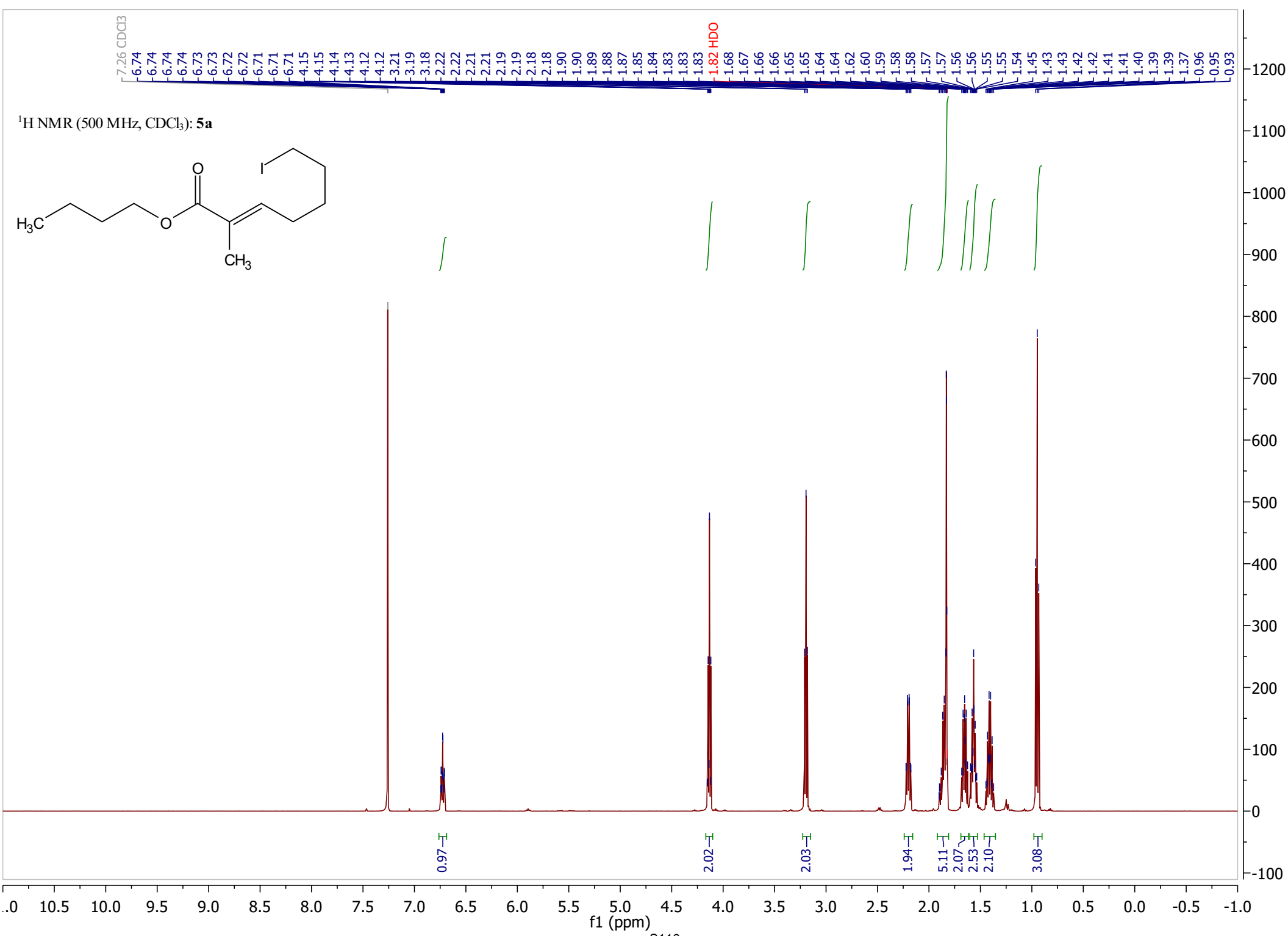
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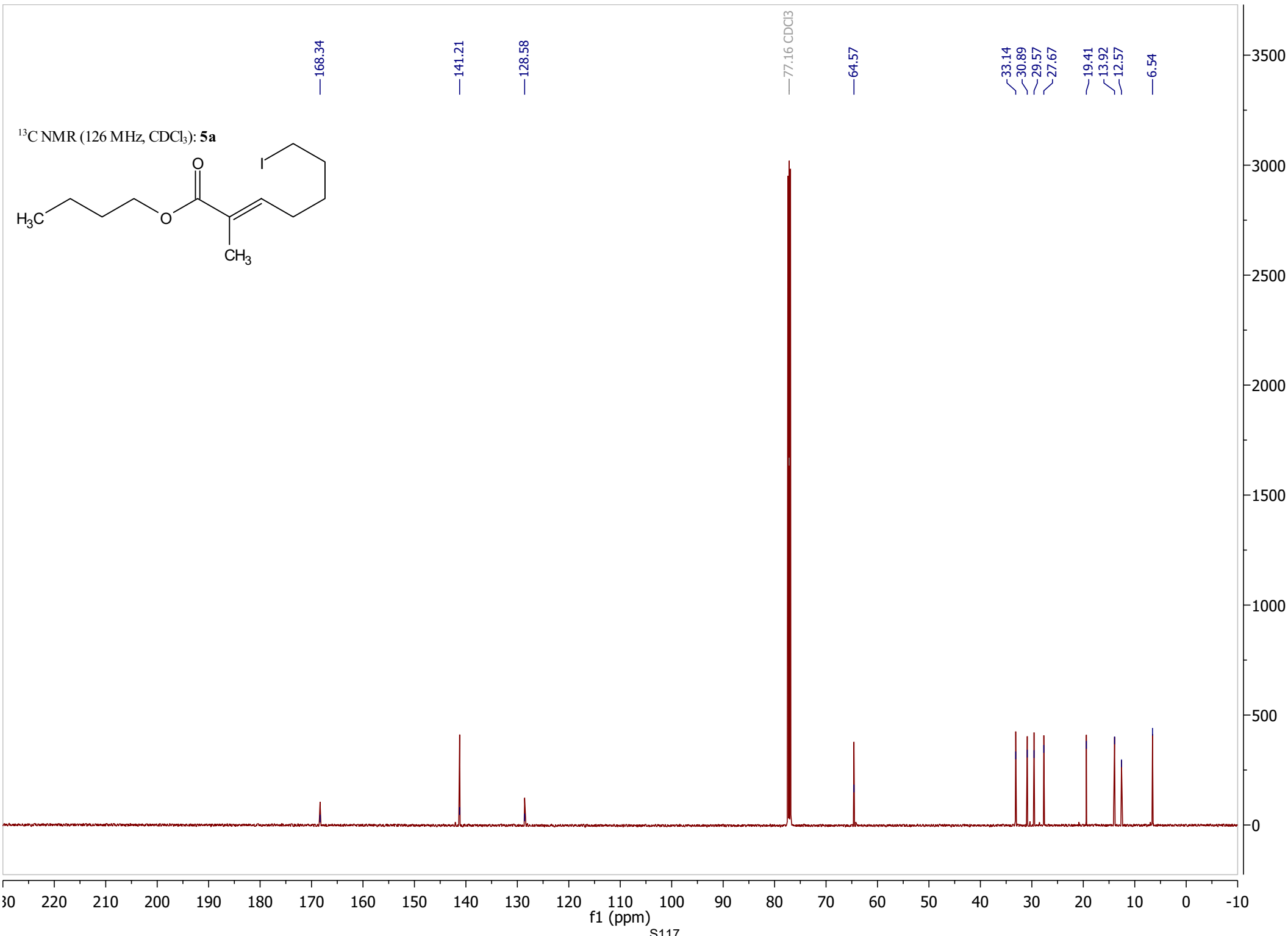


<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **5a**

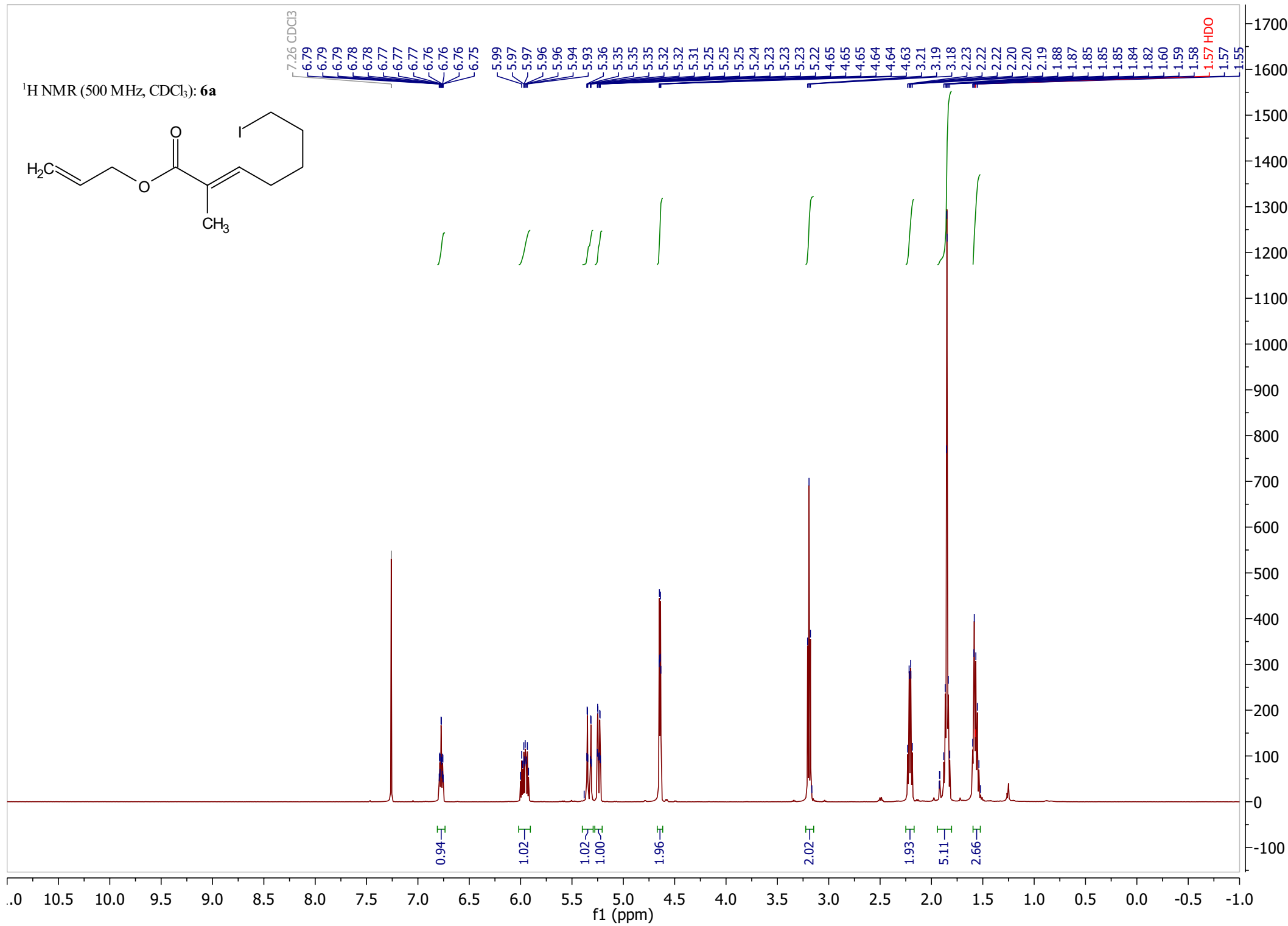
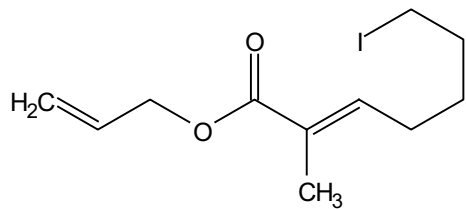


7.26 CDCl<sub>3</sub>  
-6.74  
-6.74  
-6.74  
-6.74  
-6.73  
-6.72  
-6.72  
-6.71  
-6.71  
-6.71  
-4.15  
-4.15  
-4.14  
-4.13  
-4.12  
-4.12  
-3.21  
-3.19  
-3.18  
-2.22  
-2.22  
-2.21  
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-2.19  
-2.19  
-2.18  
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-1.90  
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-1.89  
-1.88  
-1.87  
-1.85  
-1.84  
-1.83  
-1.83  
-1.83  
-1.82 HDO  
-1.68  
-1.67  
-1.66  
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-1.65  
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-1.54  
-1.45  
-1.43  
-1.43  
-1.42  
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-0.95  
0.93

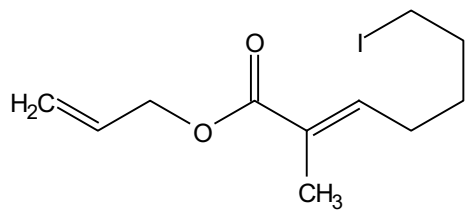




<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **6a**



<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): **6a**



— 167.83

— 141.79

— 132.65

— 128.33

— 118.00

— 77.16 CDCl<sub>3</sub>

— 65.33

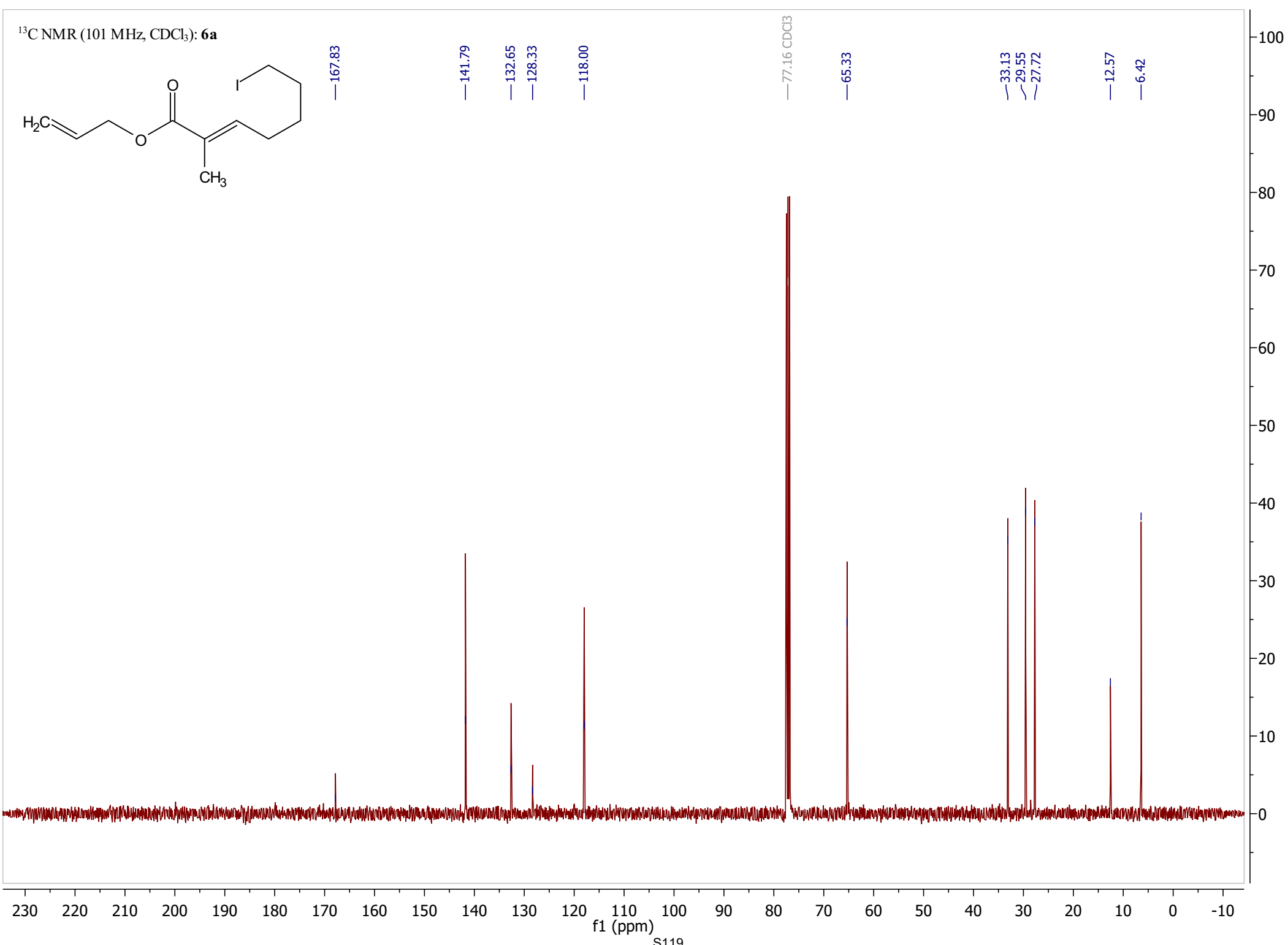
— 33.13

— 29.55

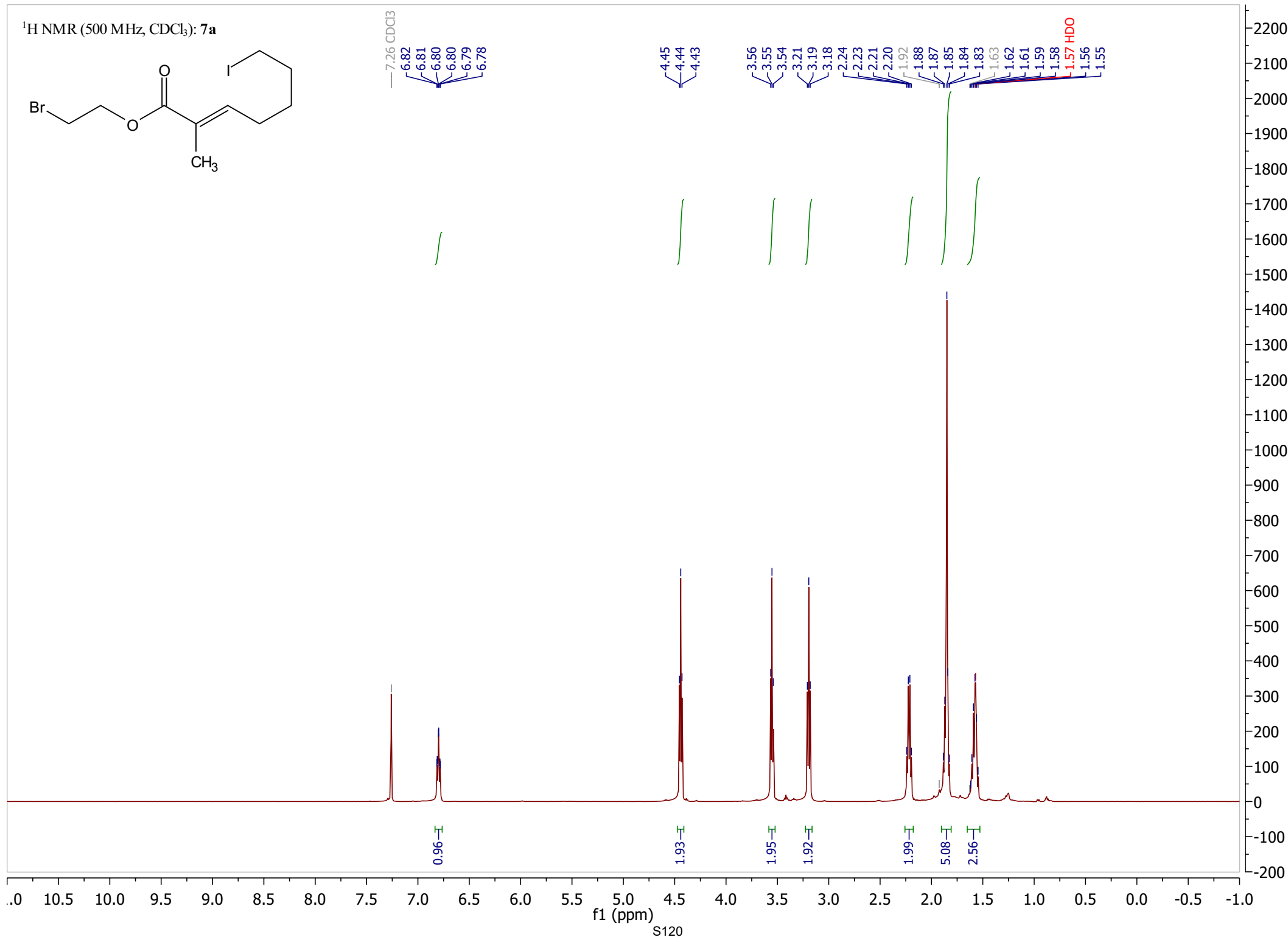
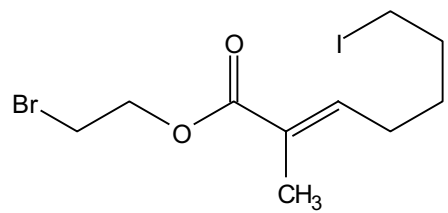
— 27.72

— 12.57

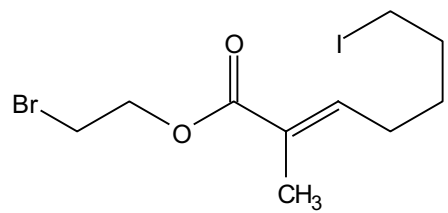
— 6.42



$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): **7a**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **7a**



— 167.55

— 142.58

— 127.90

— 77.16 CDCl<sub>3</sub>

— 63.99

— 33.10

— 29.48

— 29.10

— 27.76

— 12.52

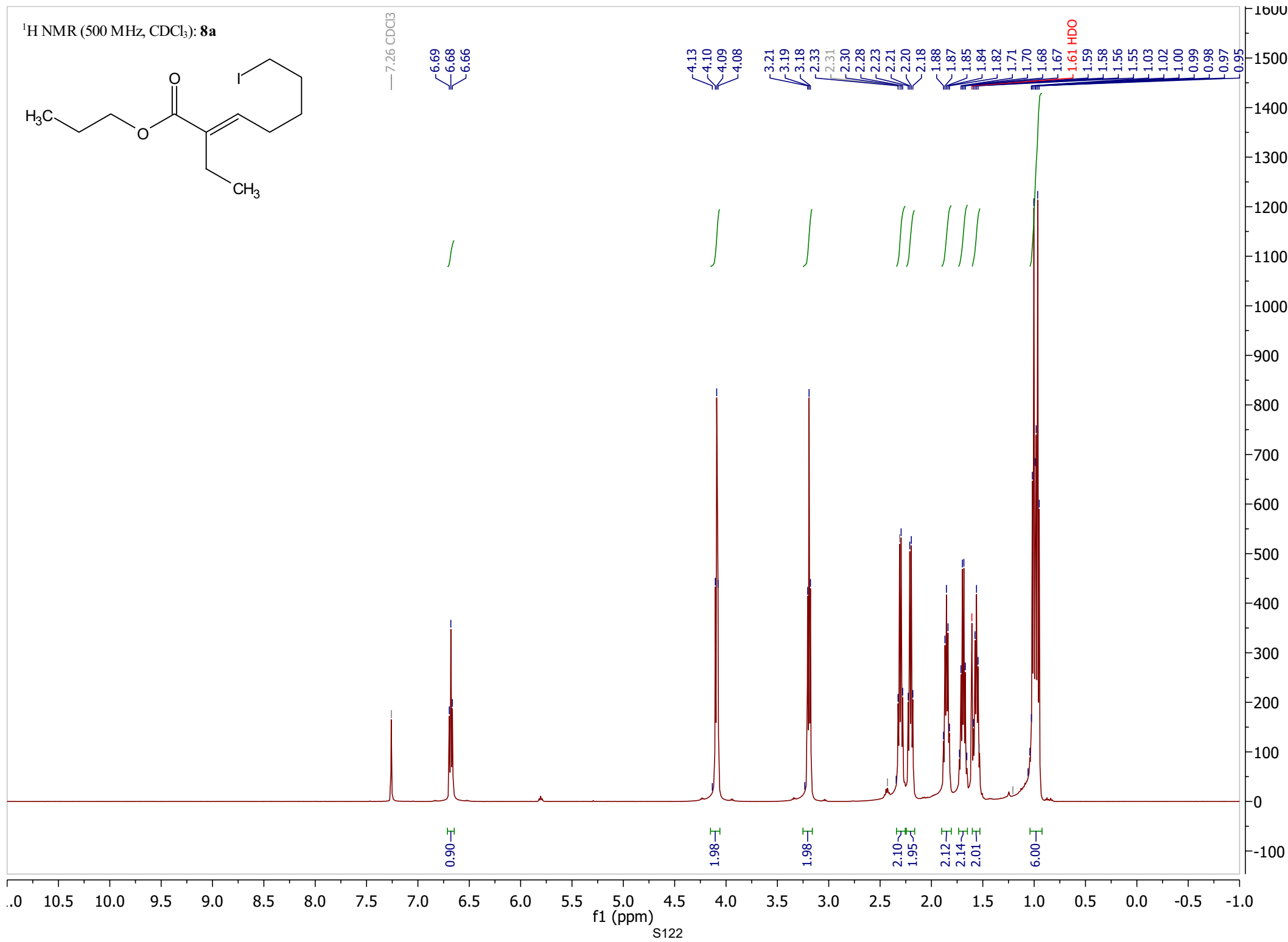
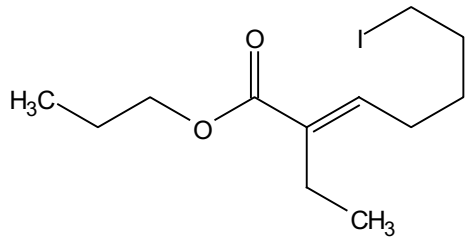
— 6.41

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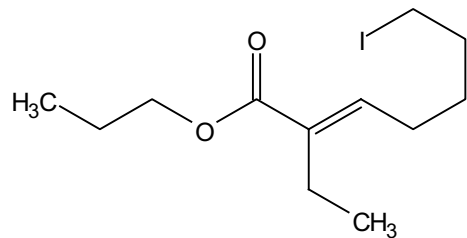
f1 (ppm)

S121

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **8a**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **8a**



—167.99

—140.84

—134.81

—77.16 CDCl<sub>3</sub>

—66.15

—33.17

—29.85

—27.33

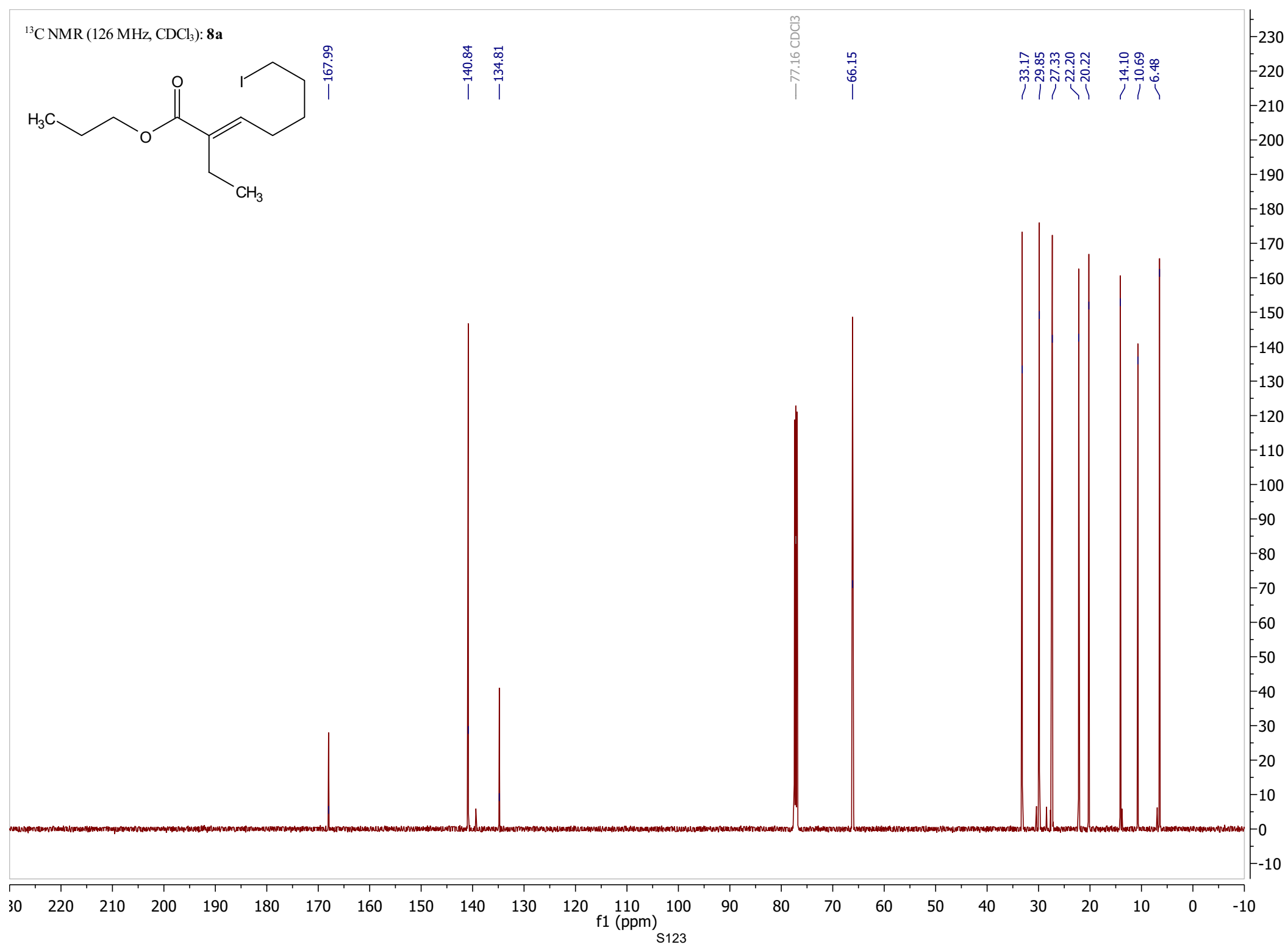
—22.20

—20.22

—14.10

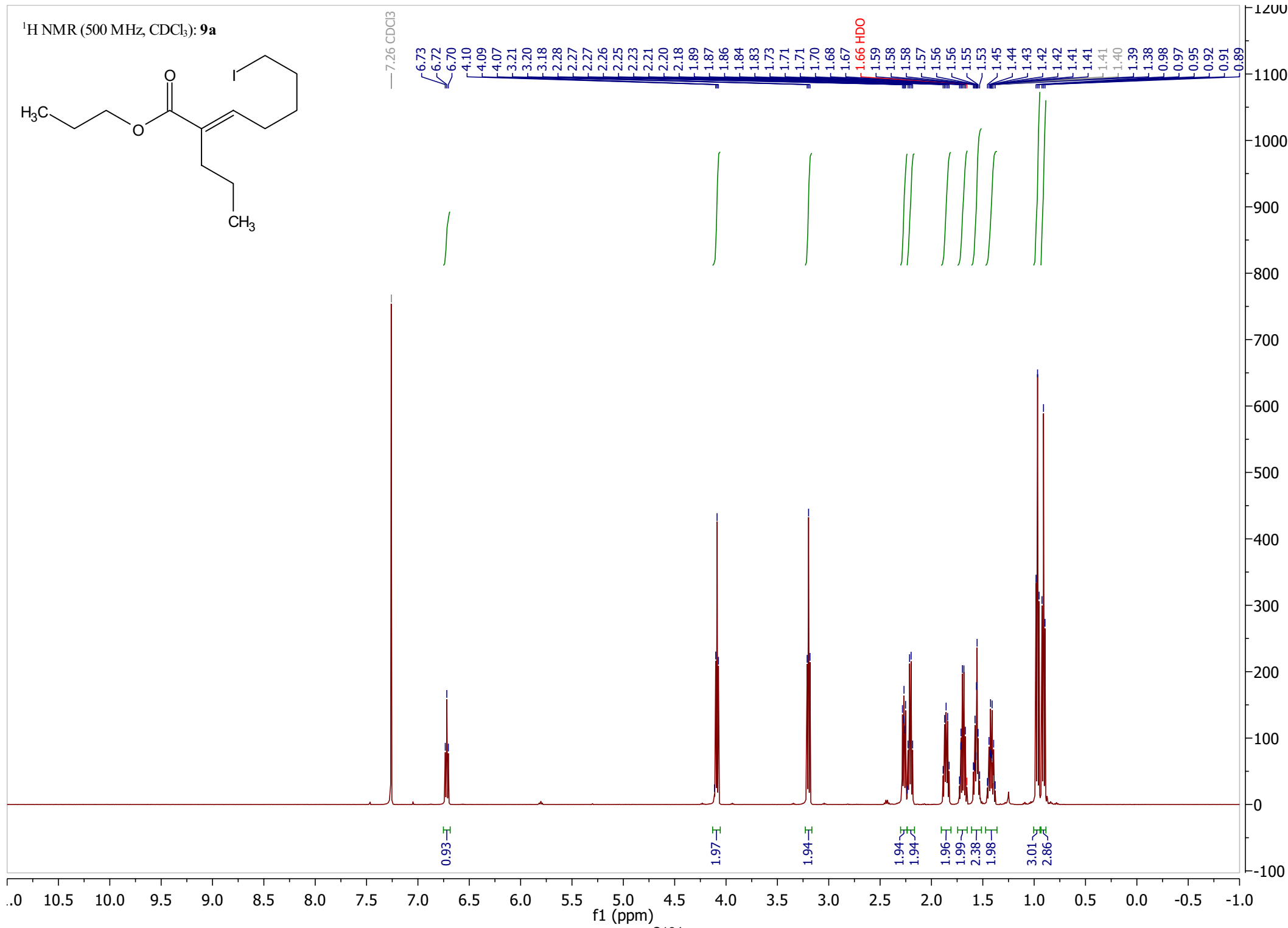
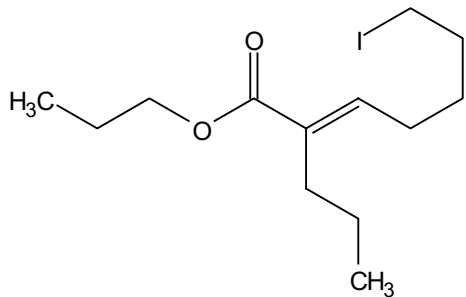
—10.69

—6.48

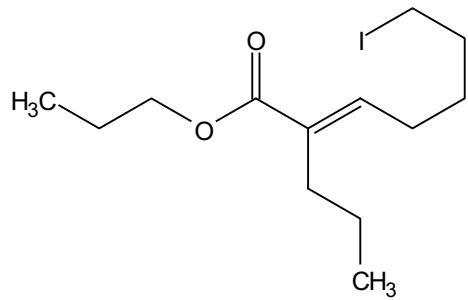


f1 (ppm)  
S123

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **9a**



<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): **9a**



—168.17

—141.42

—133.24

—77.16 CDCl<sub>3</sub>

—66.16

—33.20

—29.87

—28.92

—27.57

—22.70

—22.22

—14.16

—10.69

—6.48

100

90

80

70

60

50

40

30

20

10

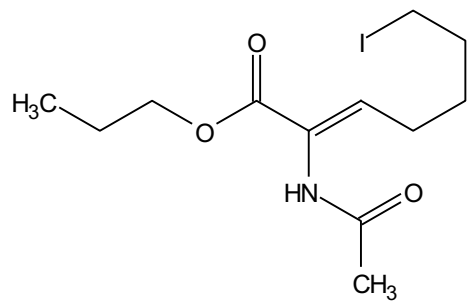
0

30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

S125

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **10a**



— 7.26 CDCl<sub>3</sub>

6.86  
6.67  
6.65  
6.64

— 6.30

4.14  
4.13  
4.11

3.21  
3.19  
3.18

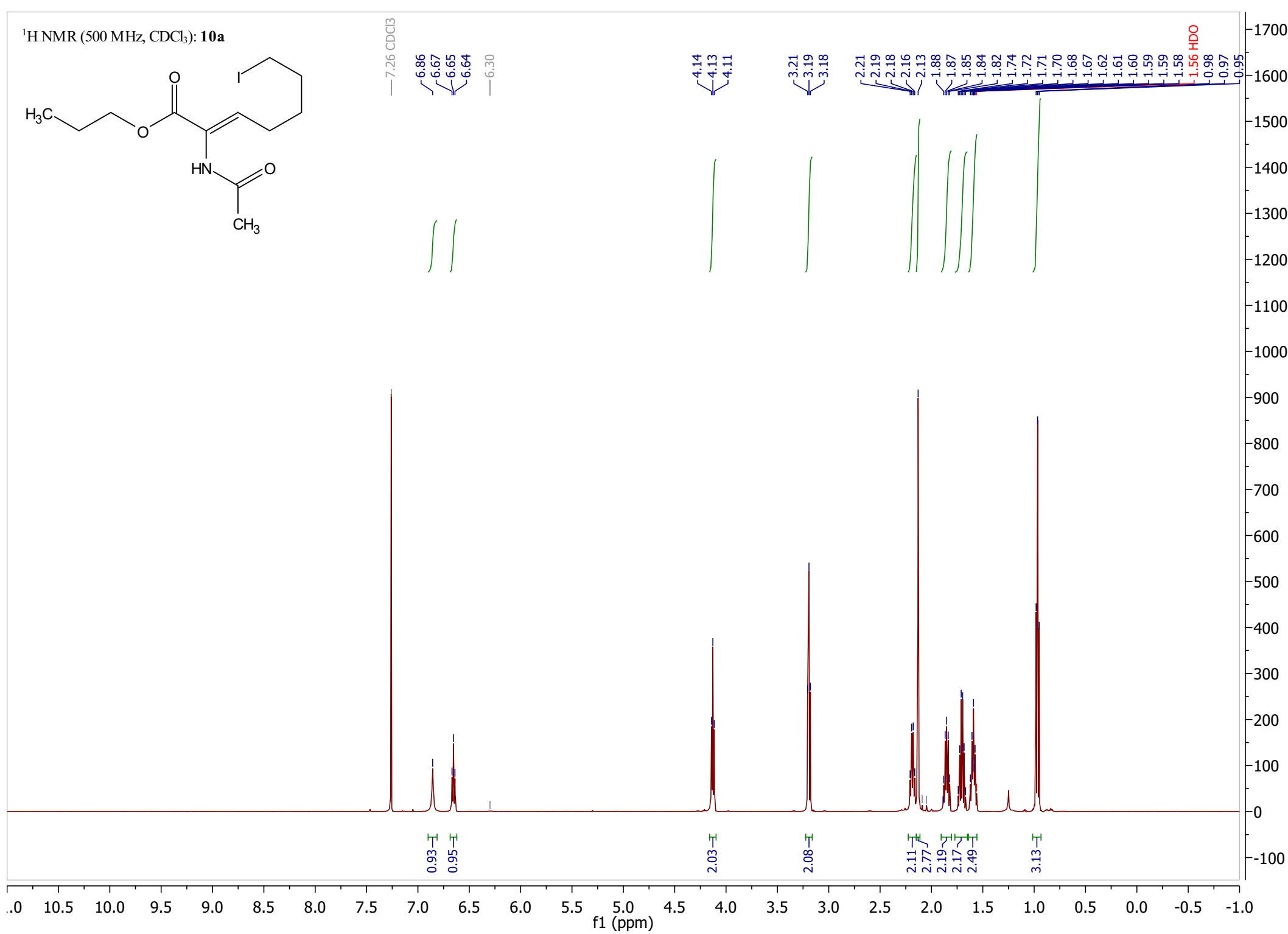
2.21  
2.19  
2.18  
2.16  
2.13

1.88  
1.87  
1.85  
1.84

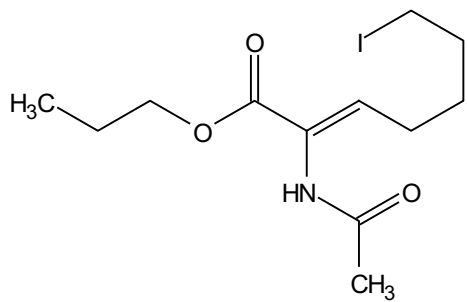
1.74  
1.72  
1.71

1.70  
1.68  
1.67  
1.62  
1.61  
1.60  
1.59  
1.58

1.56 H<sub>2</sub>O  
0.98  
0.97  
0.95



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **10a**



— 168.36

— 164.85

— 137.25

— 125.21

— 77.16 CDCl<sub>3</sub>

— 67.30

— 33.24

— 29.24

— 28.26

— 23.77

— 22.10

— 10.58

— 6.65

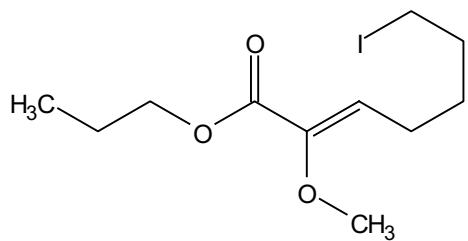
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

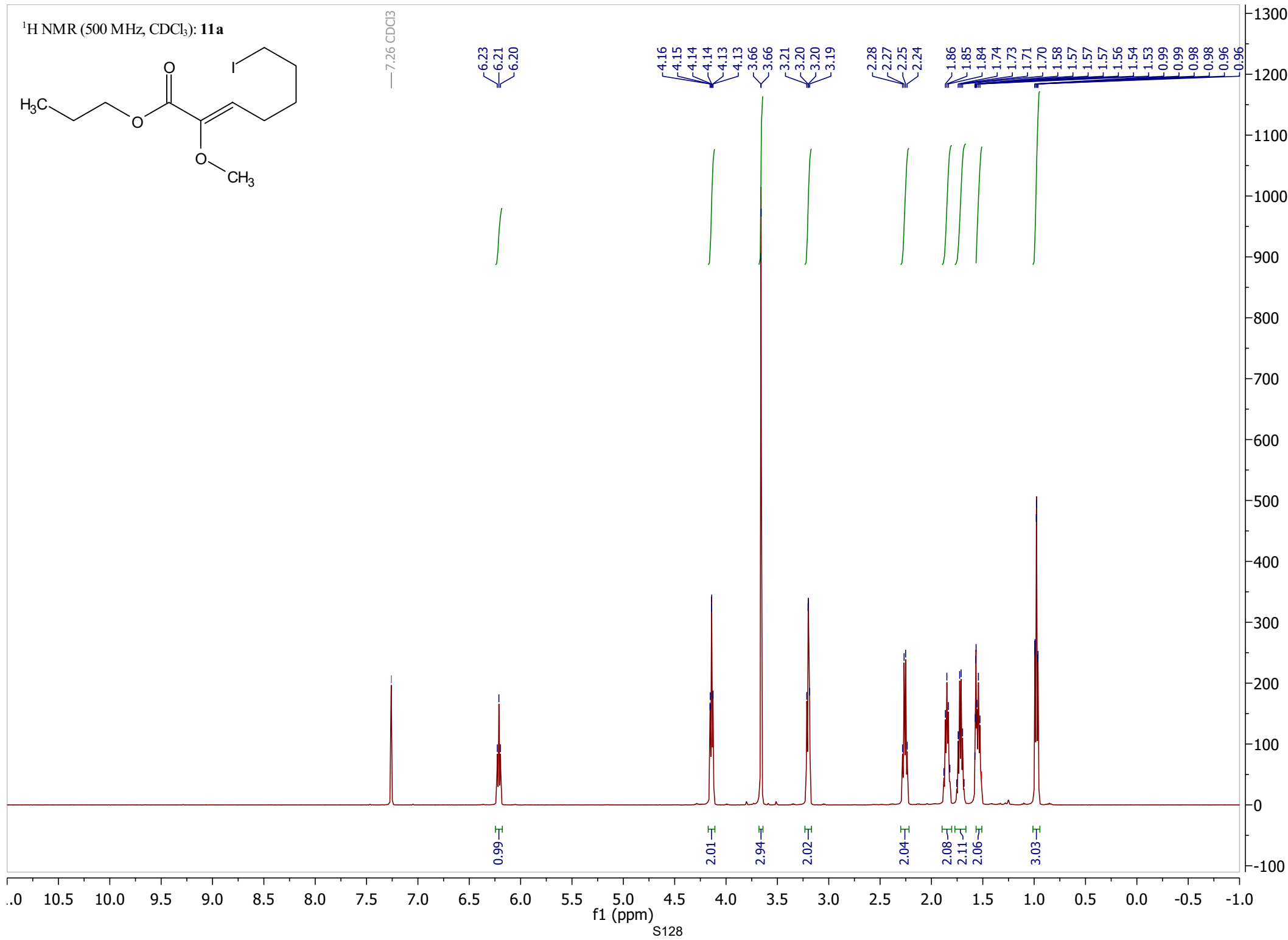
S127

1700  
1600  
1500  
1400  
1300  
1200  
1100  
1000  
900  
800  
700  
600  
500  
400  
300  
200  
100  
0

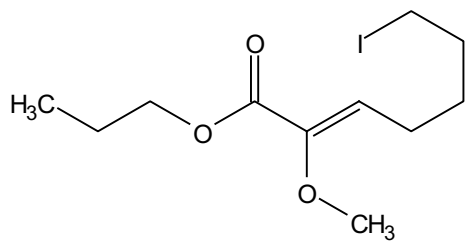
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **11a**



— 7.26 CDCl<sub>3</sub>



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **11a**



—163.95

—146.84

—127.77

—77.16 CDCl<sub>3</sub>

—66.66

—60.22

—33.07

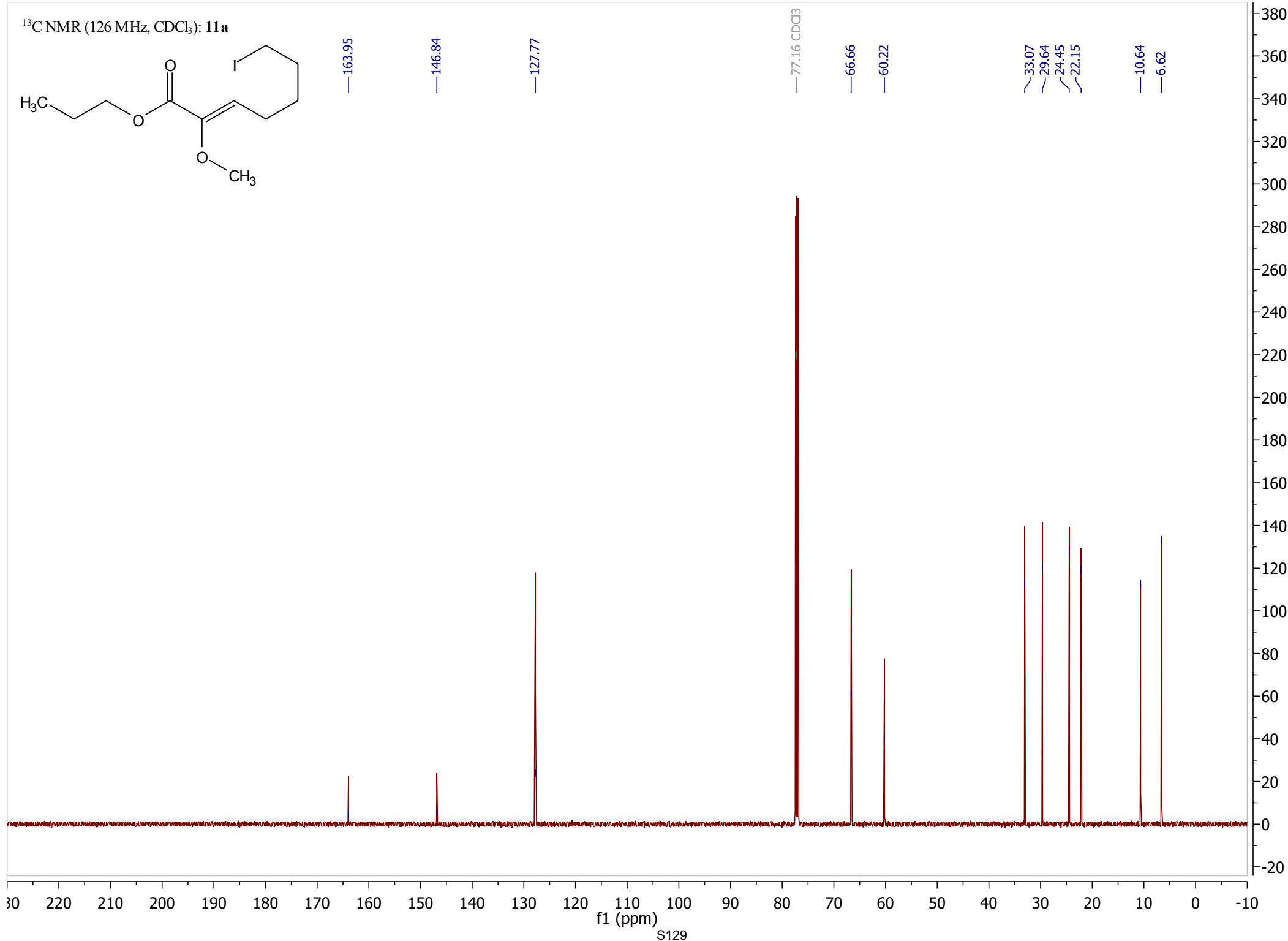
—29.64

—24.45

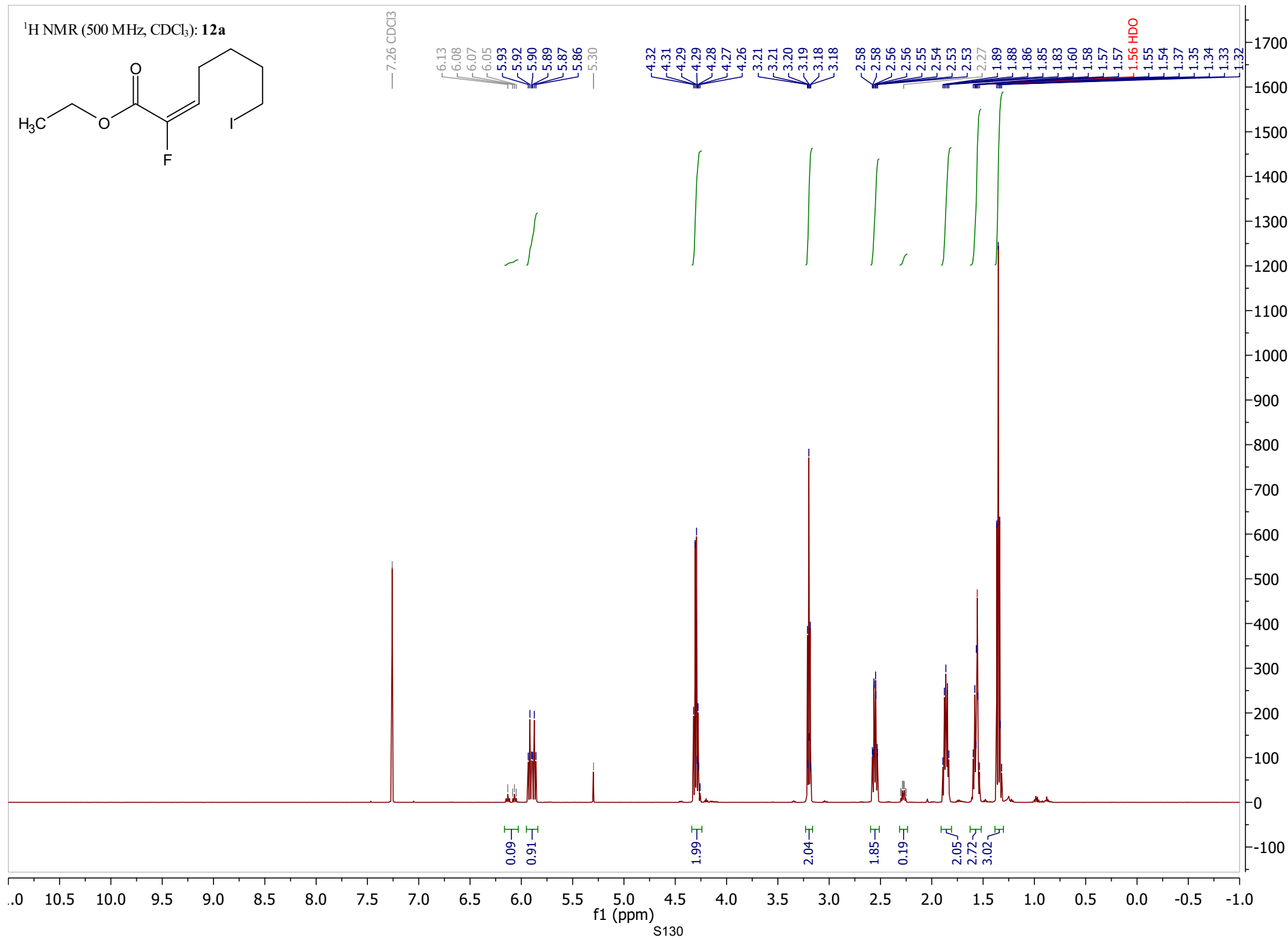
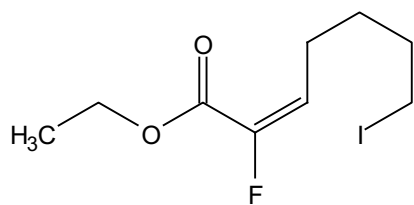
—22.15

—10.64

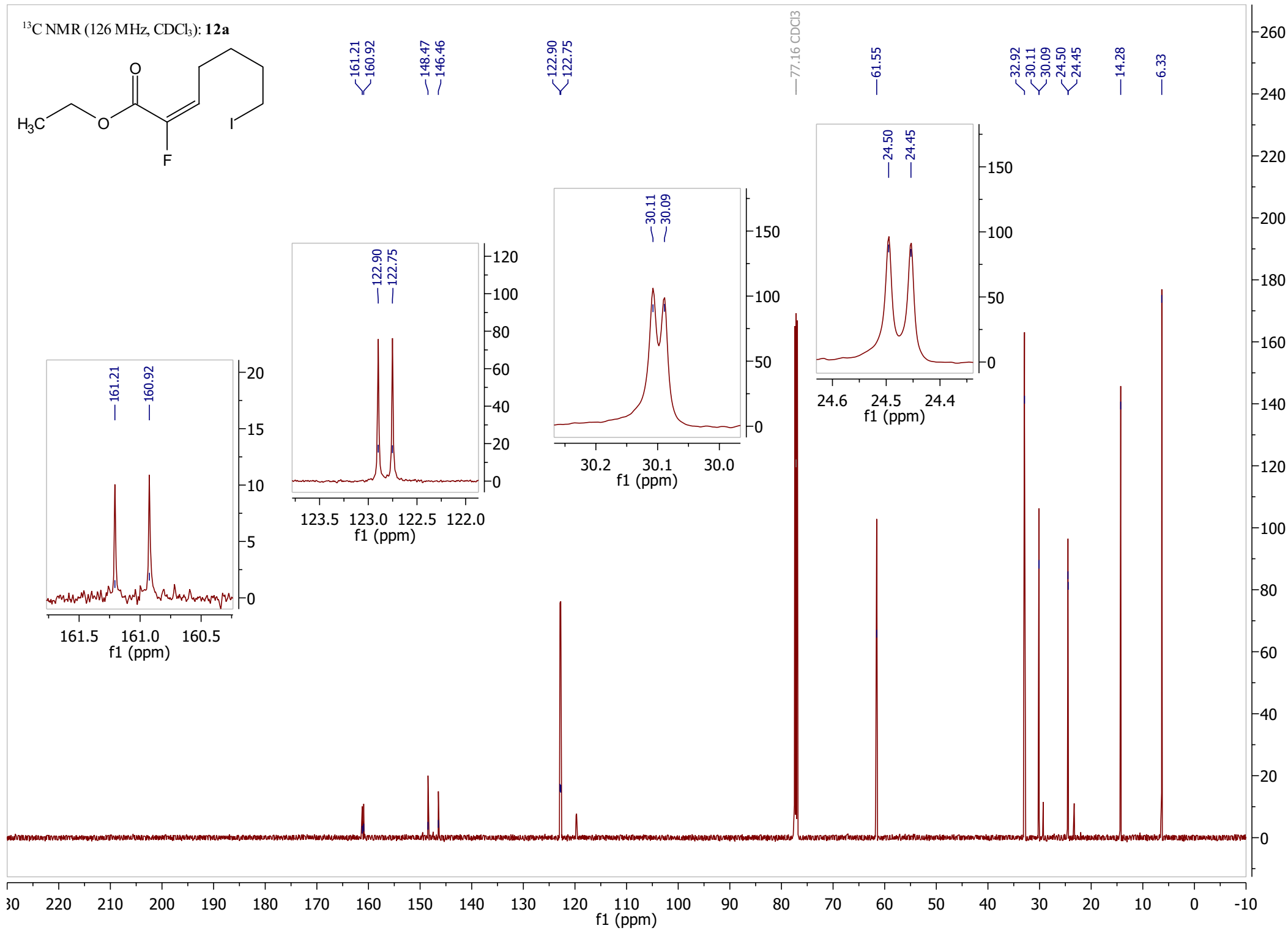
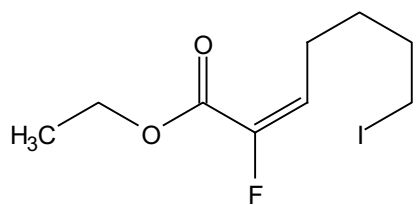
—6.62



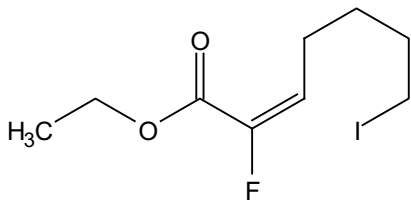
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **12a**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **12a**

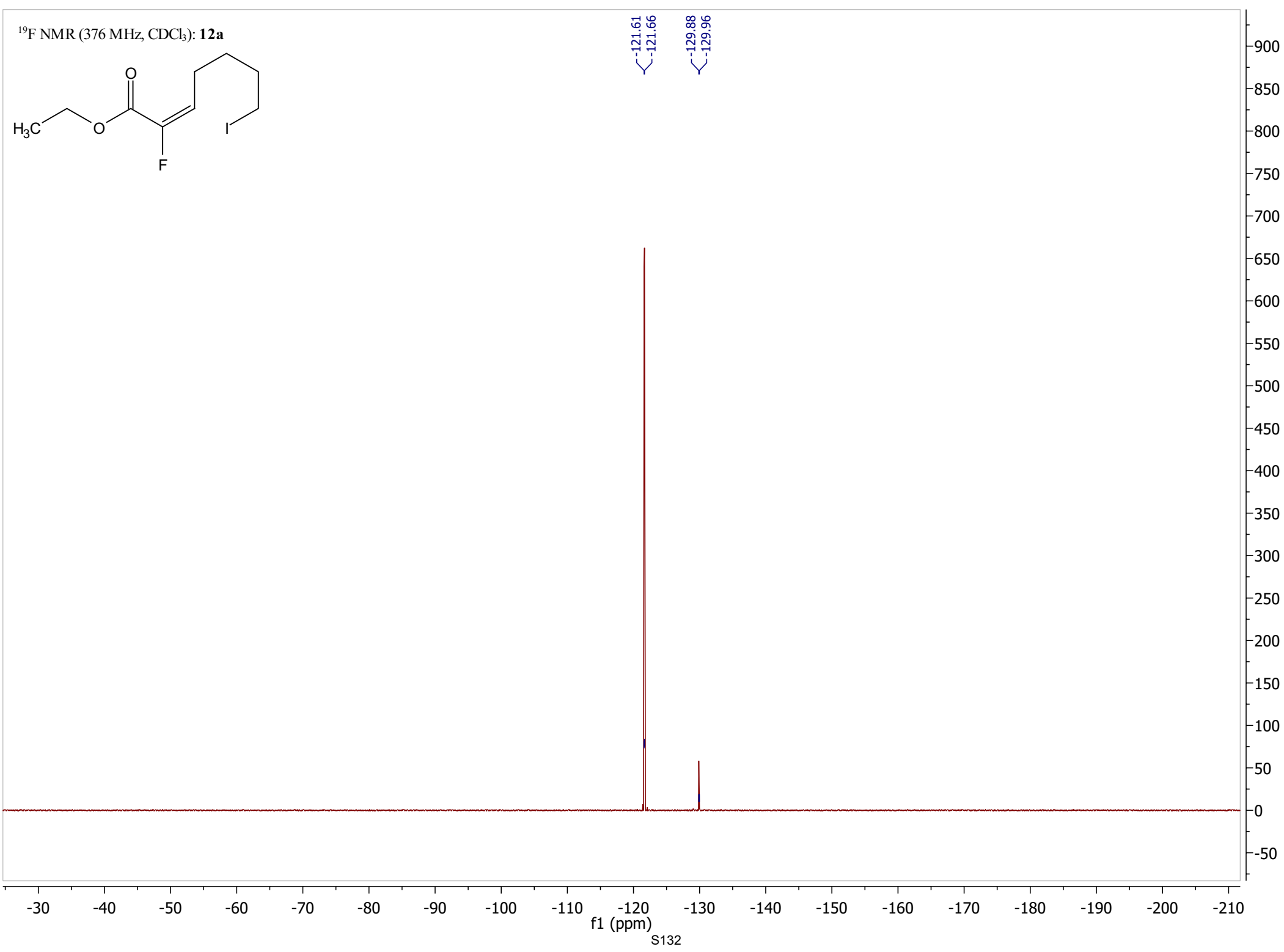


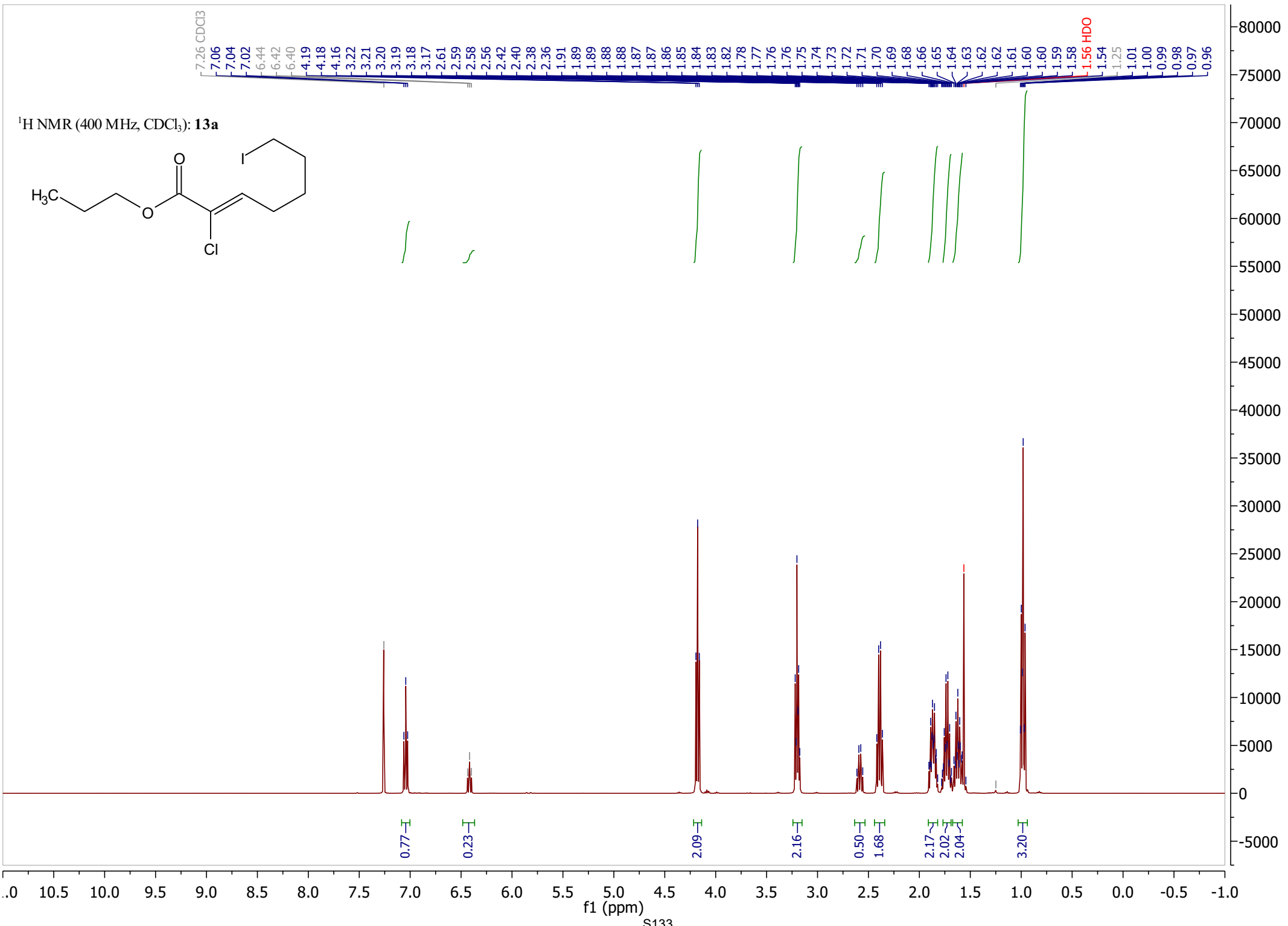
<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): **12a**



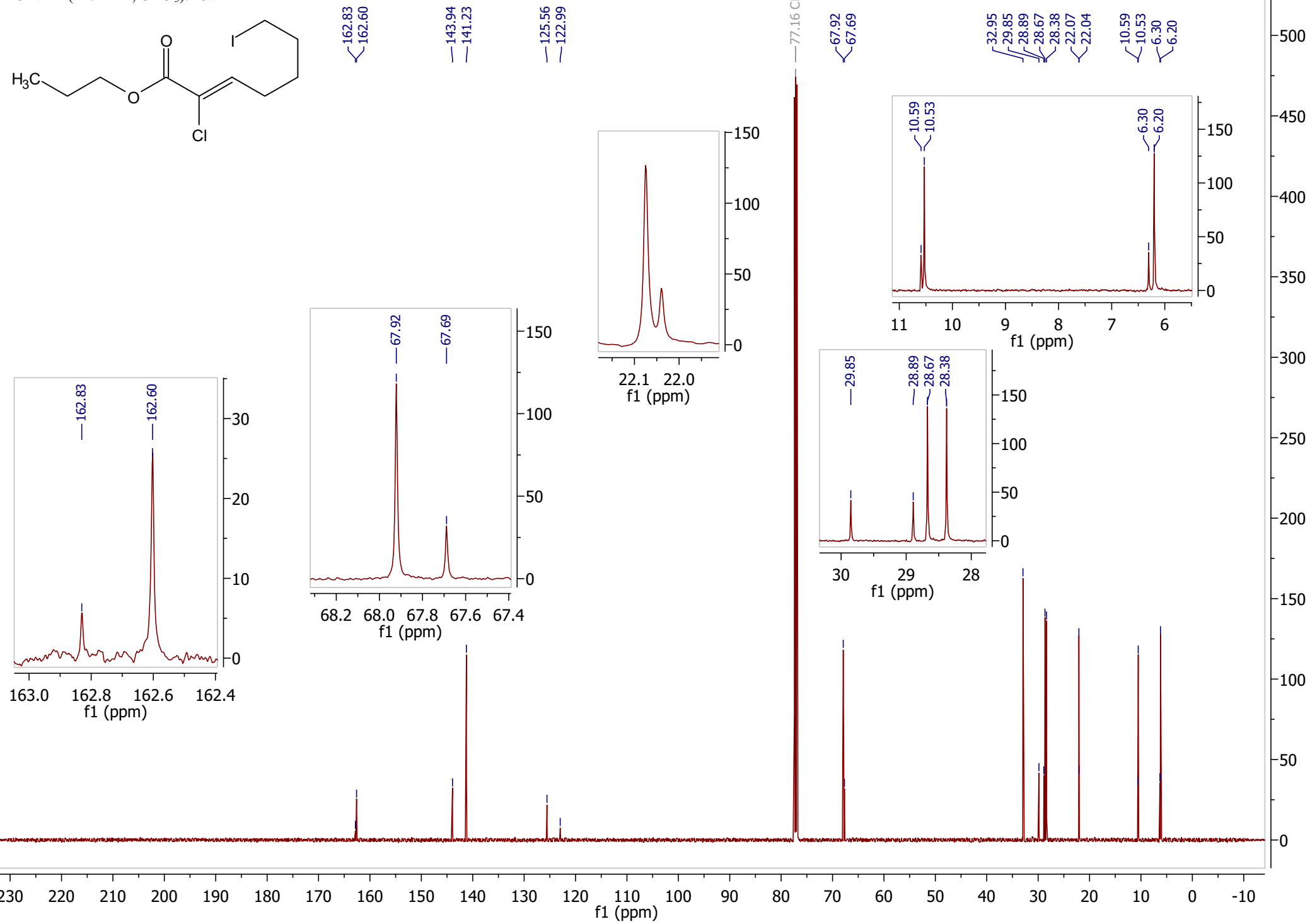
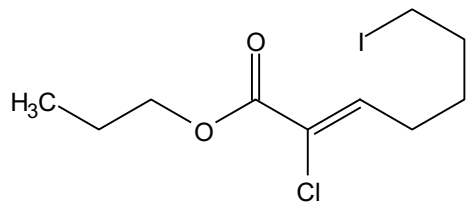
-121.61  
-121.66

-129.88  
-129.96

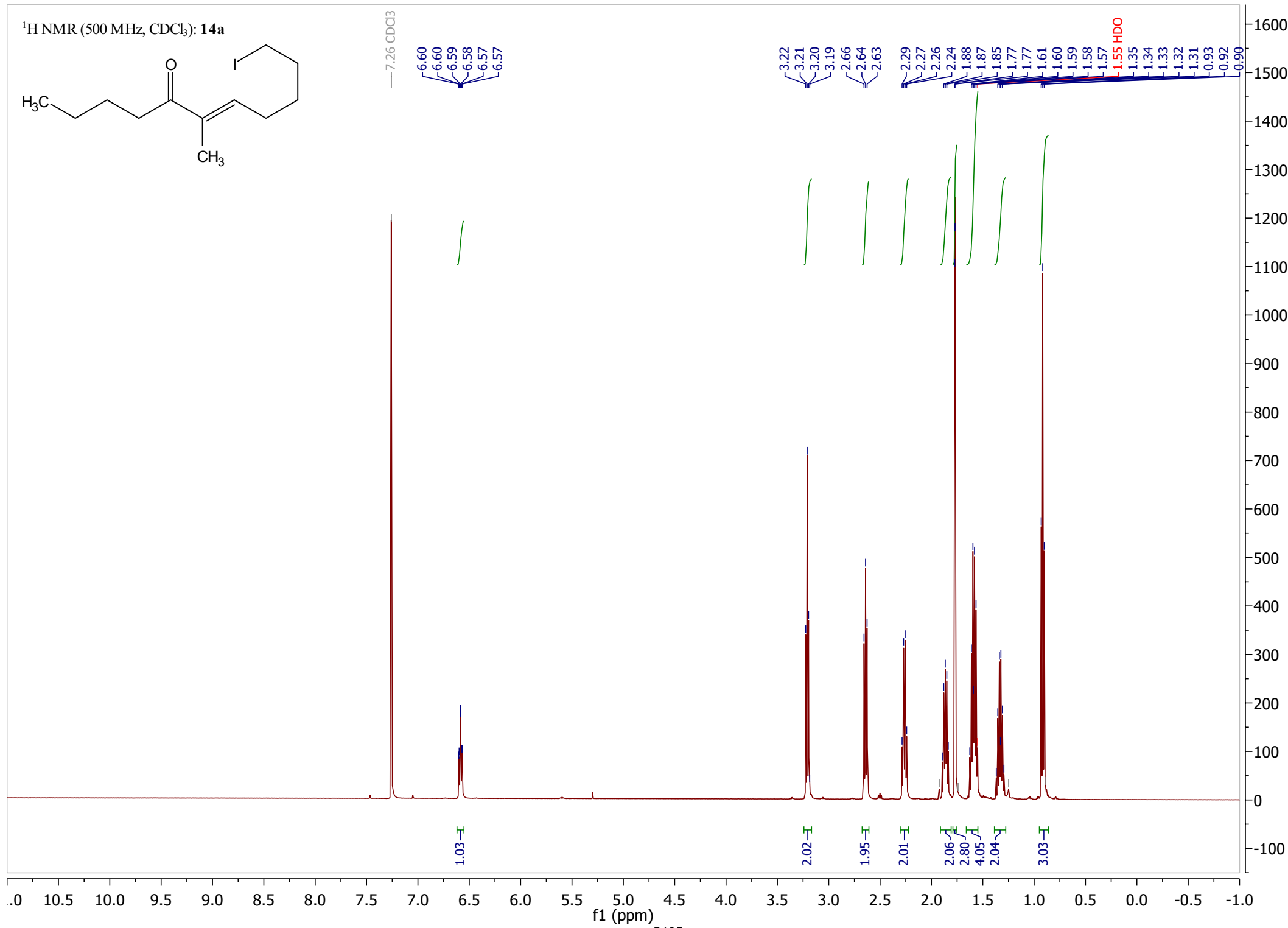
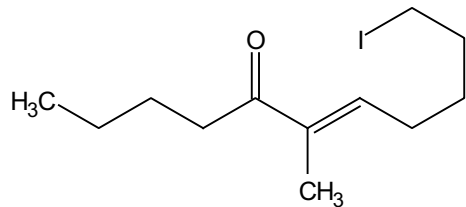




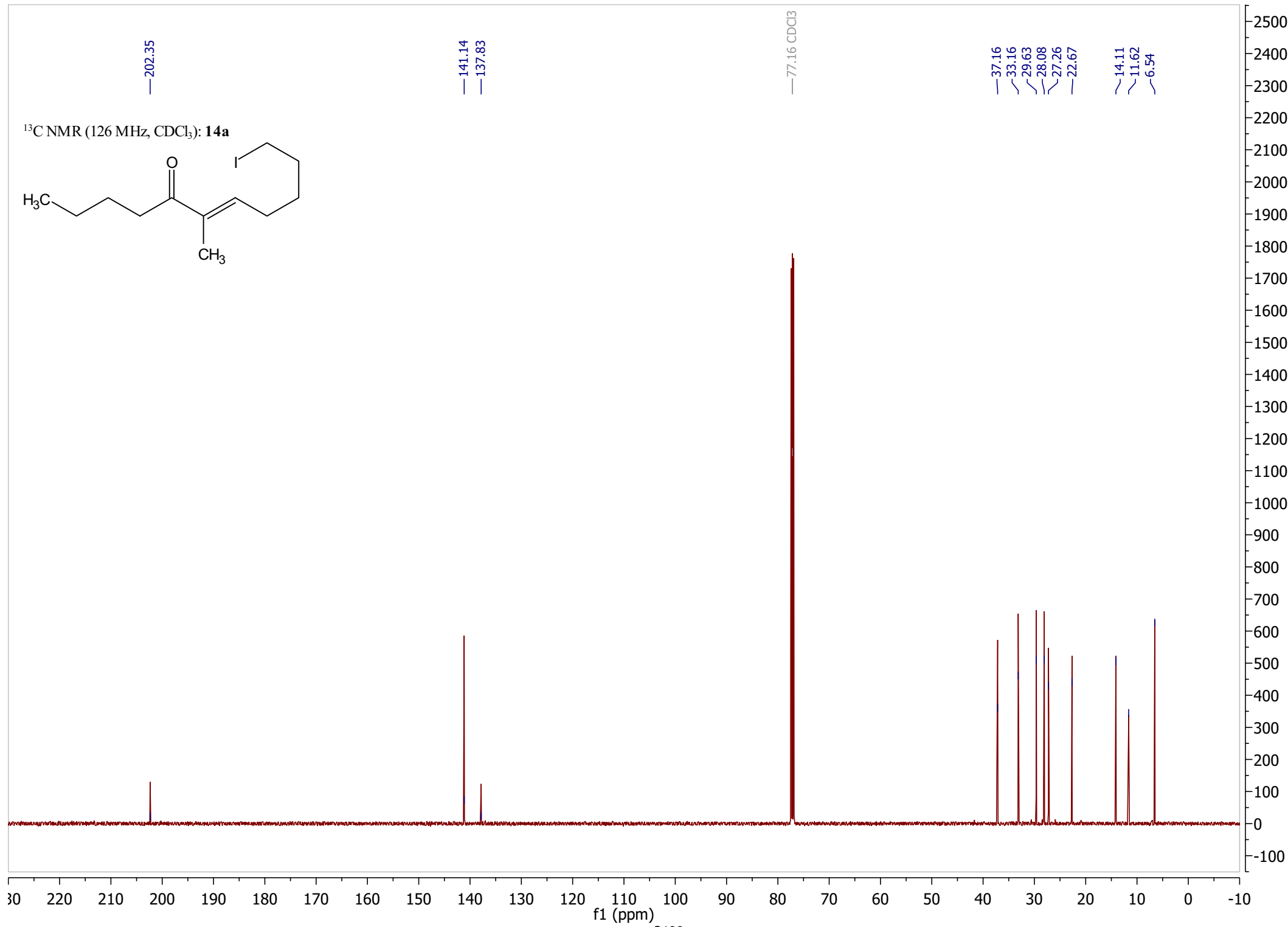
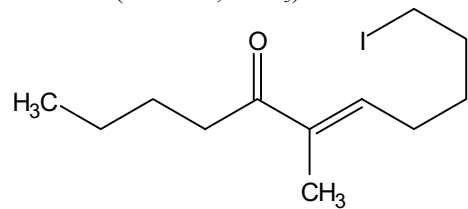
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **13a**



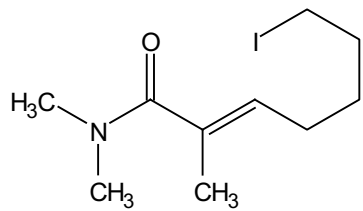
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **14a**



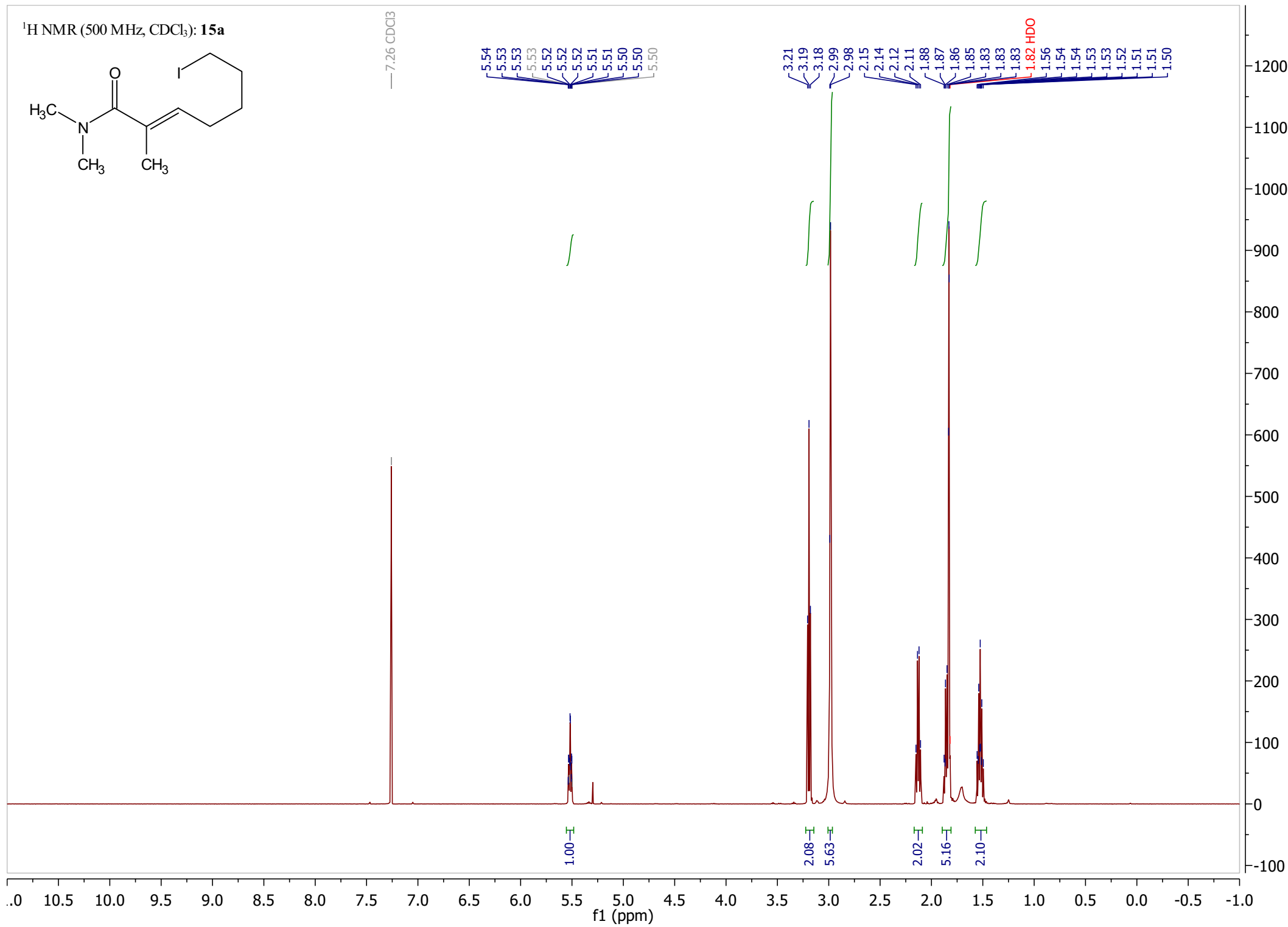
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **14a**



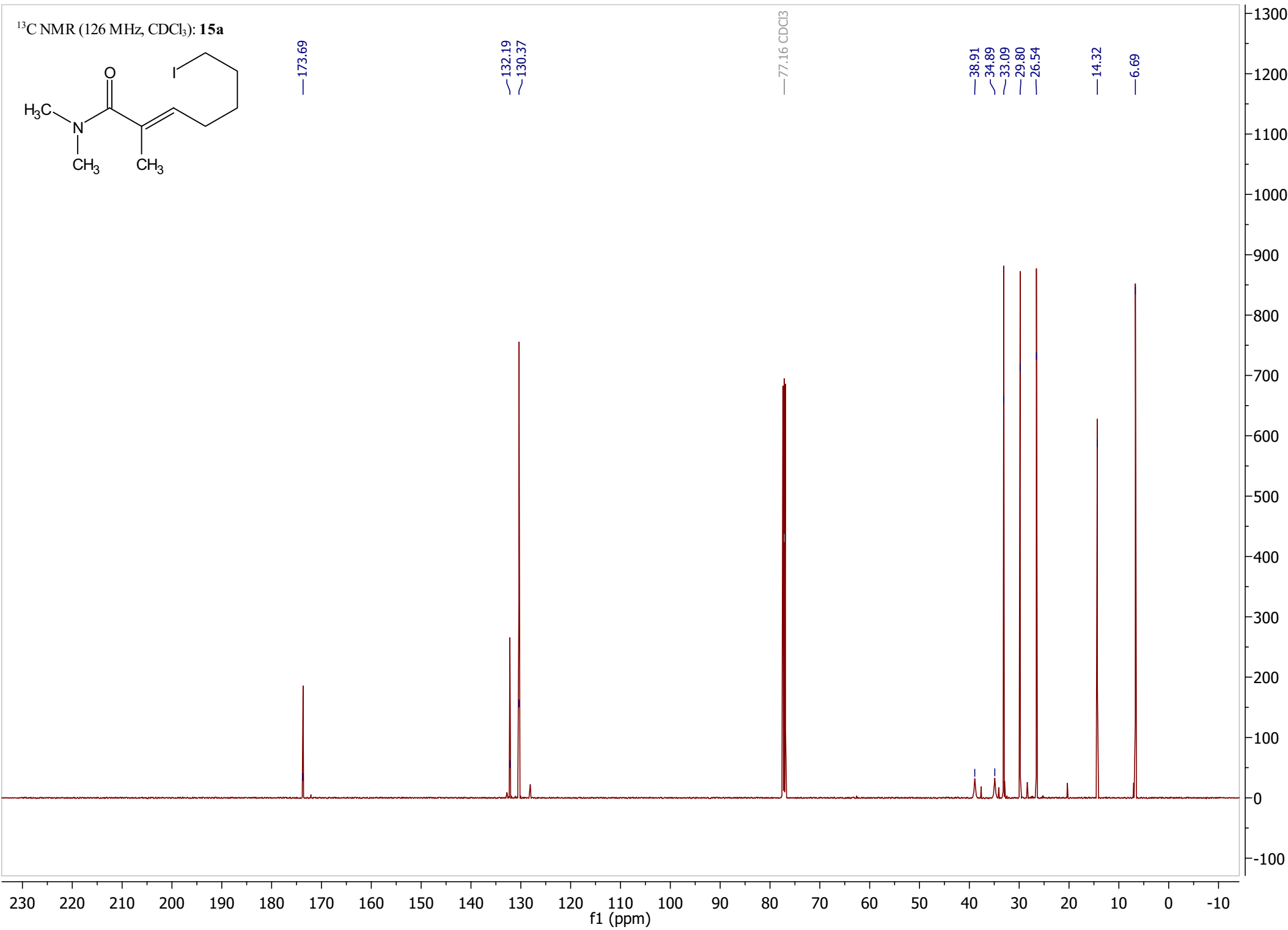
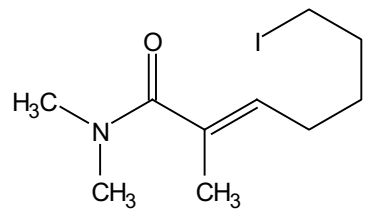
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **15a**



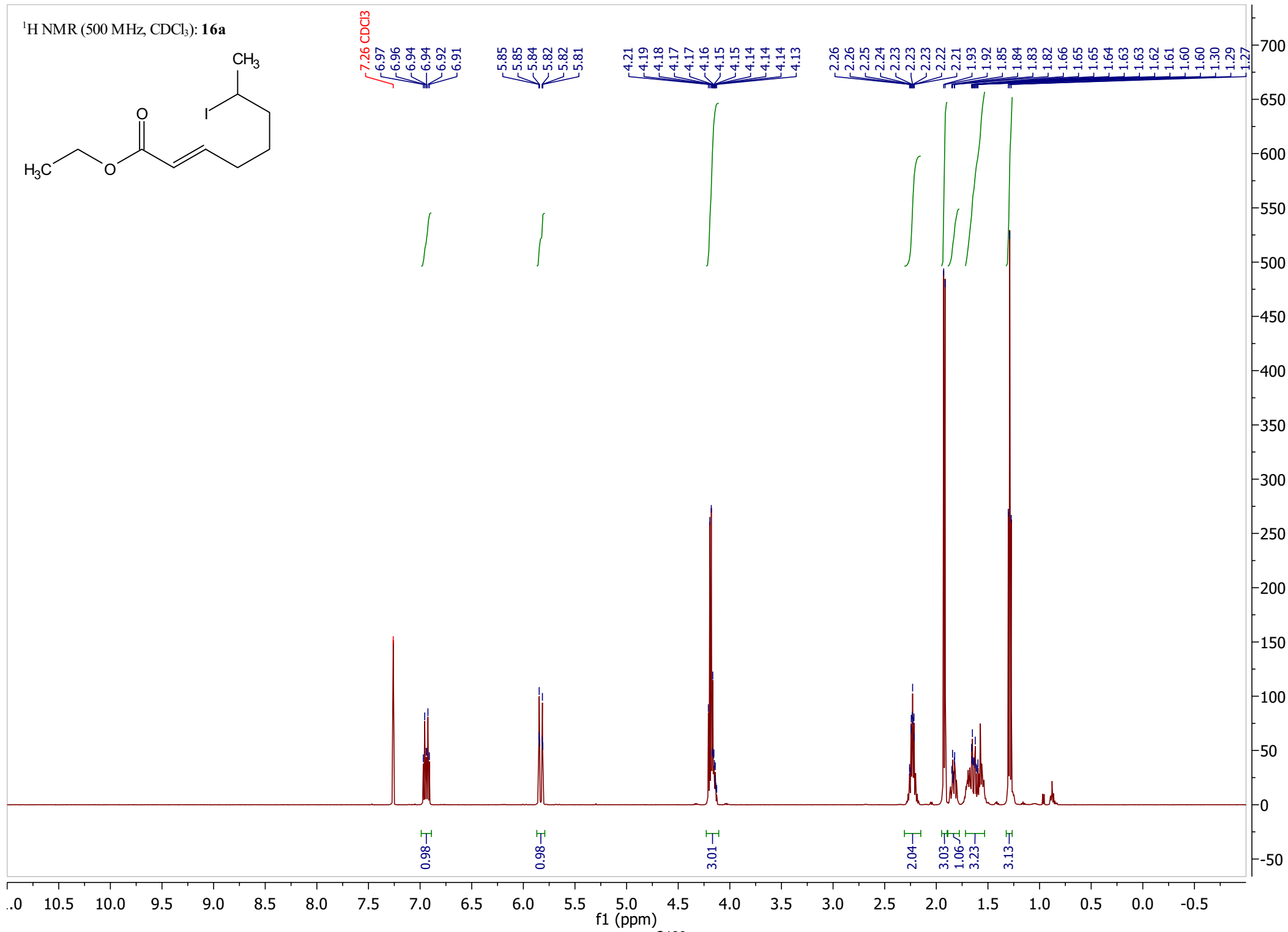
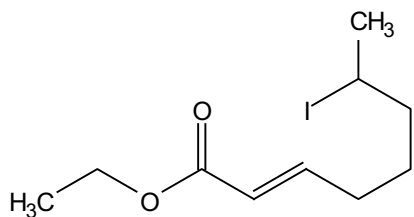
— 7.26 CDCl<sub>3</sub>



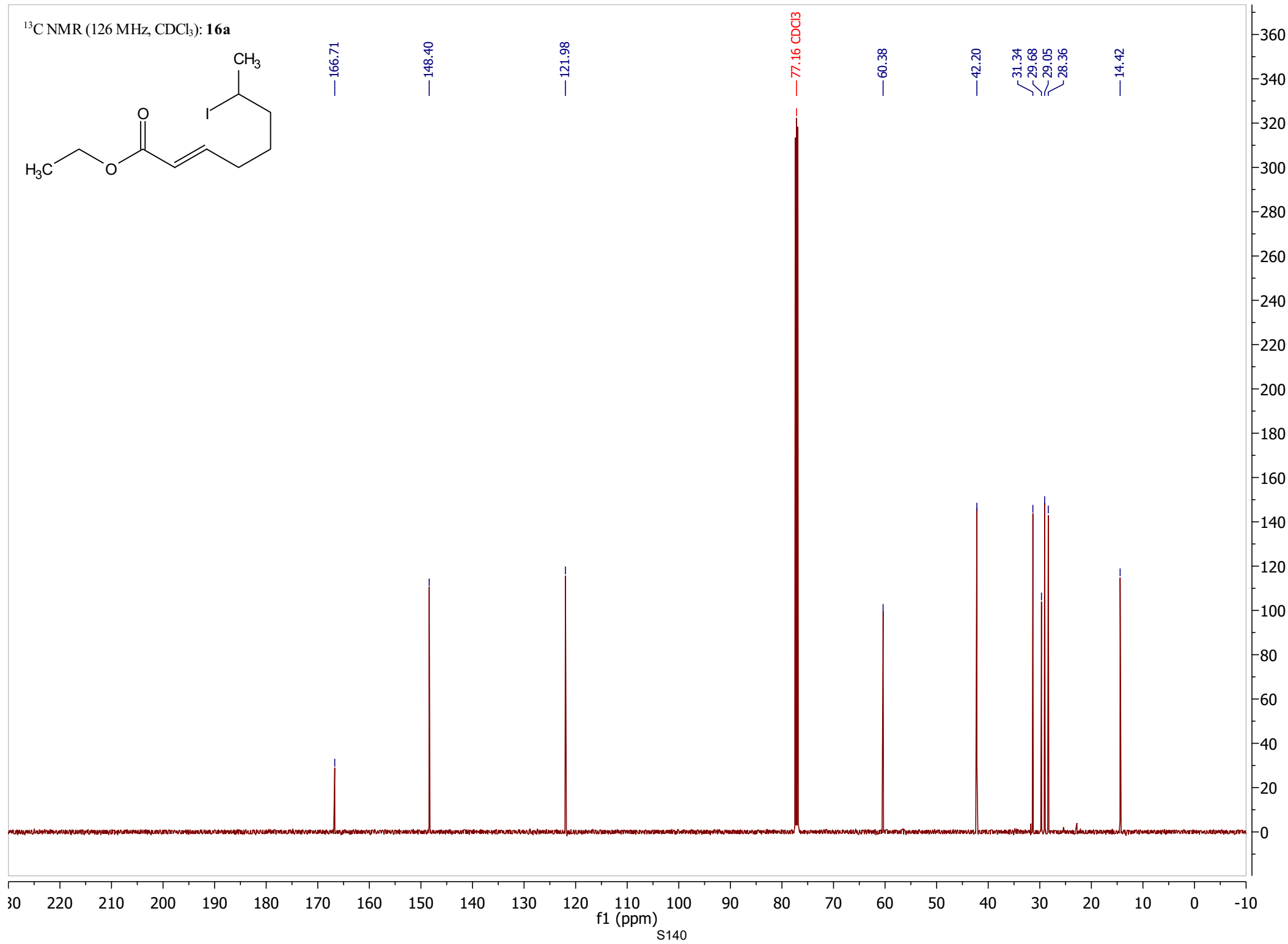
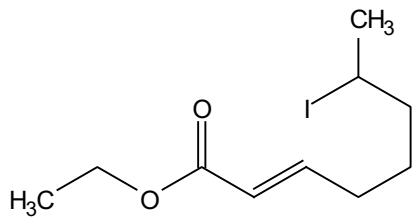
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **15a**



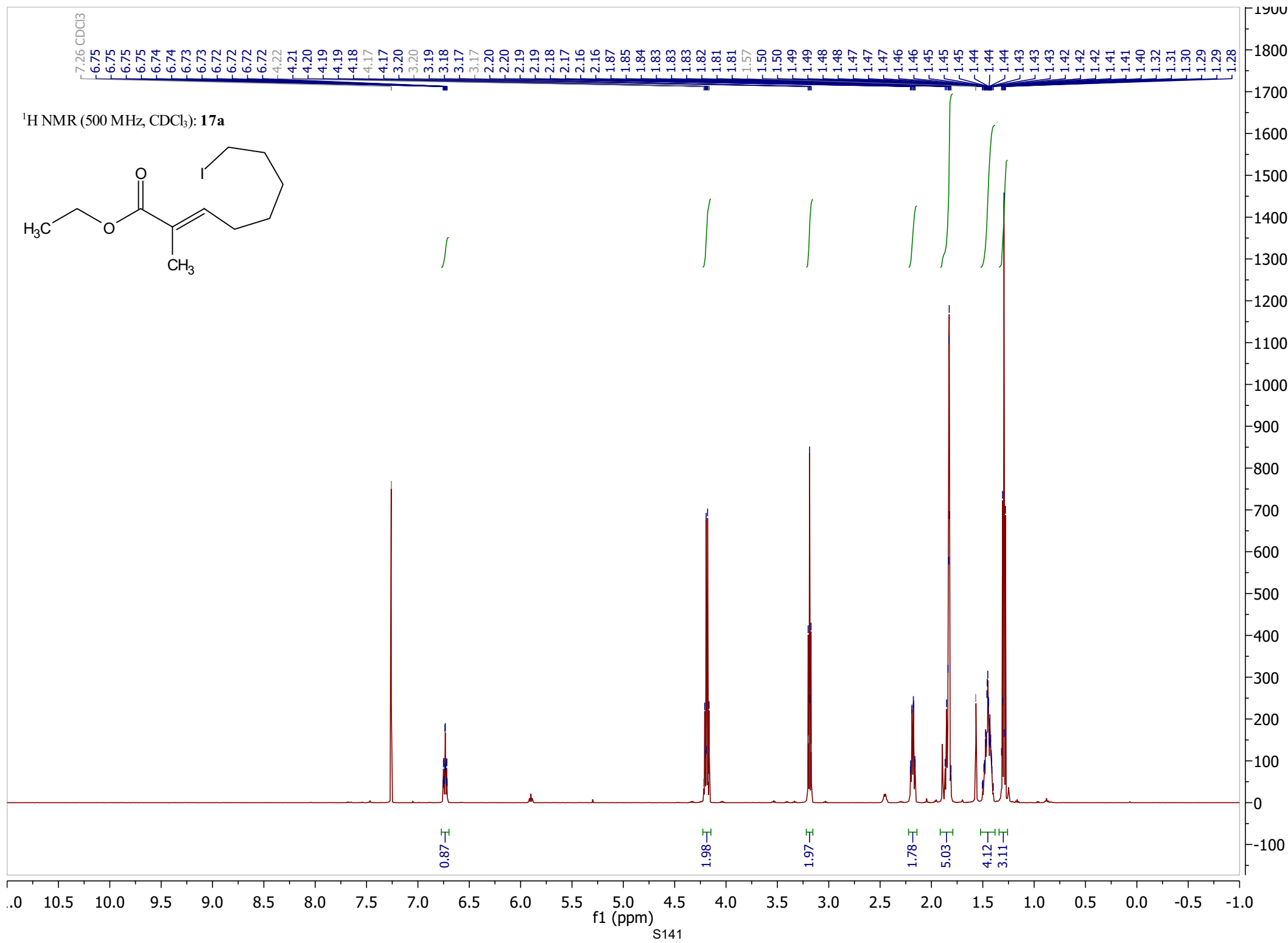
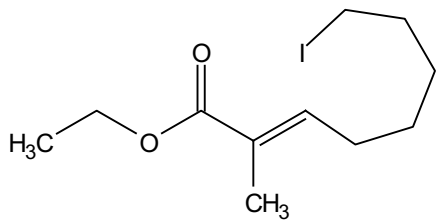
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **16a**



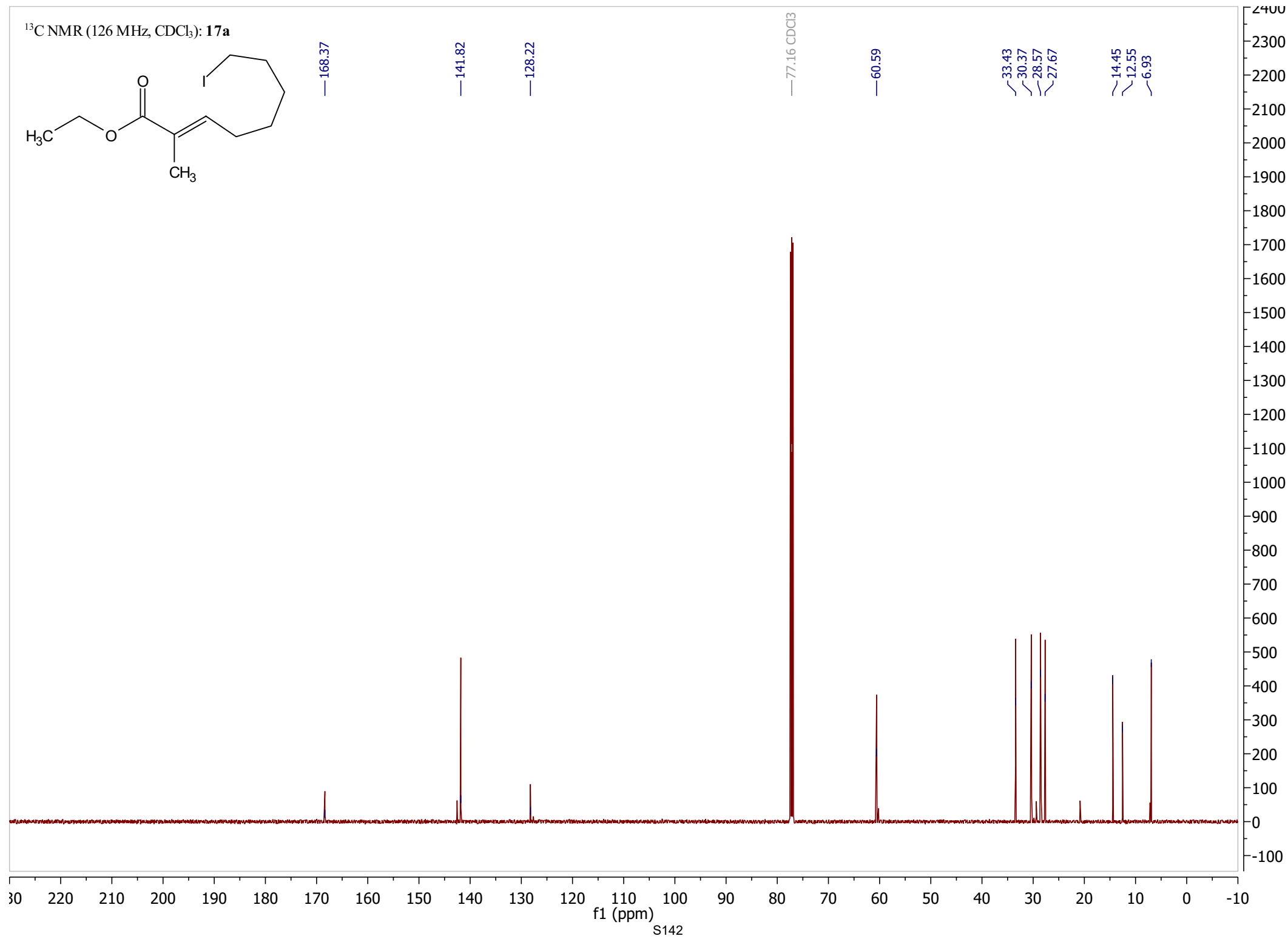
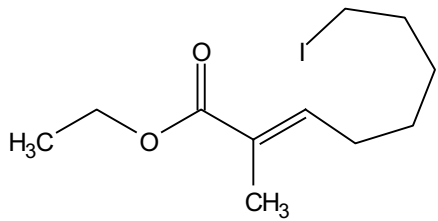
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **16a**



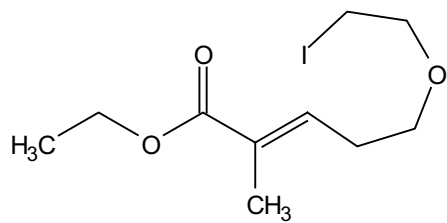
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **17a**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **17a**



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **18a**



7.26 CDCl<sub>3</sub>

6.79  
6.79  
6.78  
6.77  
6.77  
6.77  
6.76  
6.75

4.21  
4.19  
4.18  
4.17  
3.72  
3.71  
3.70  
3.60  
3.58  
3.57  
3.26  
3.25  
3.23

2.49  
2.48  
2.47  
2.45

1.85  
1.85  
1.58 H<sub>2</sub>O  
1.30  
1.29  
1.28

1.00

2.12

2.13

2.07

2.06

2.04

2.94

3.27

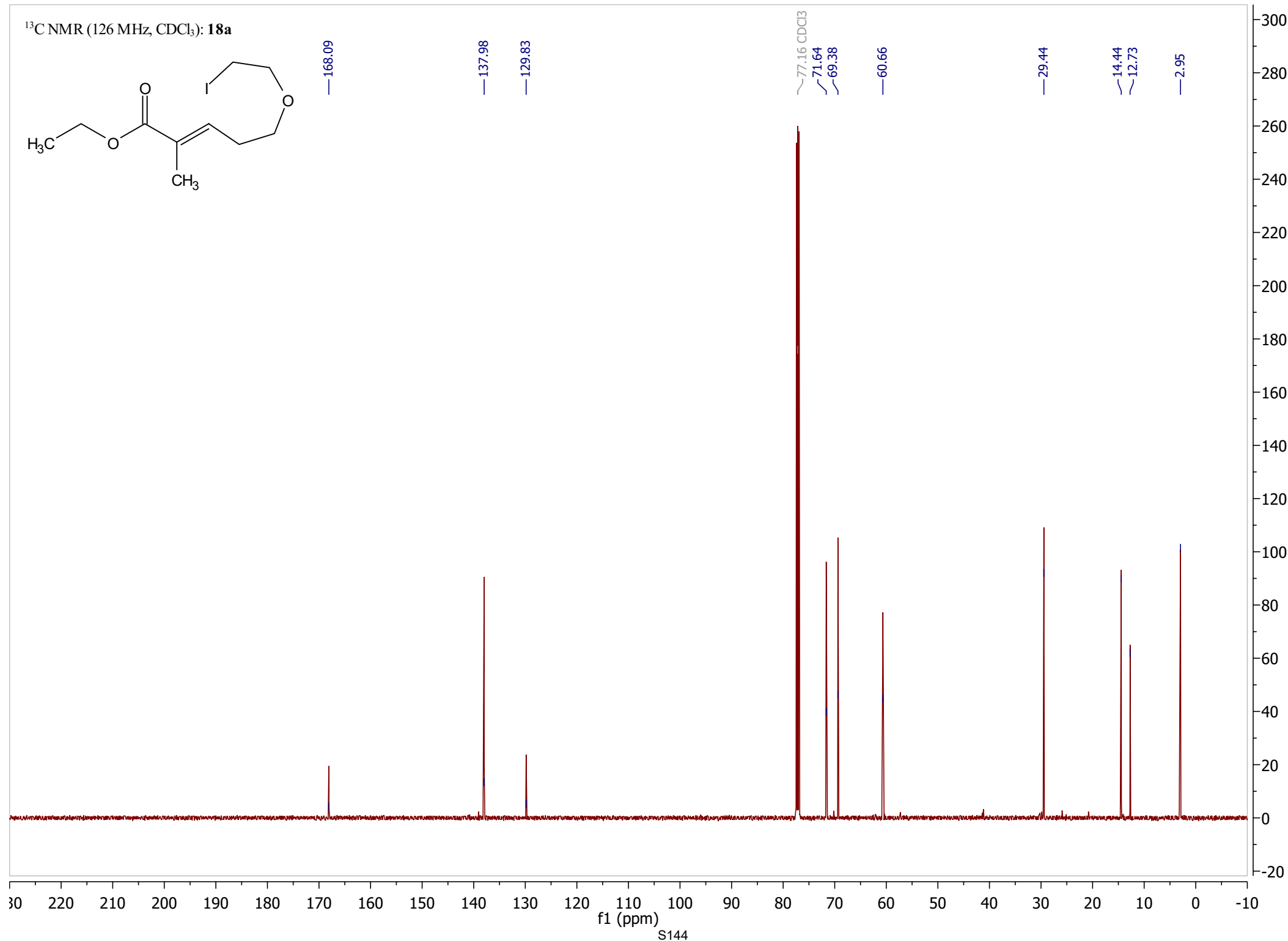
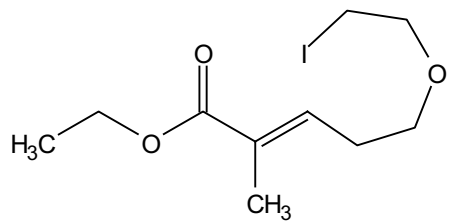
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

f1 (ppm)

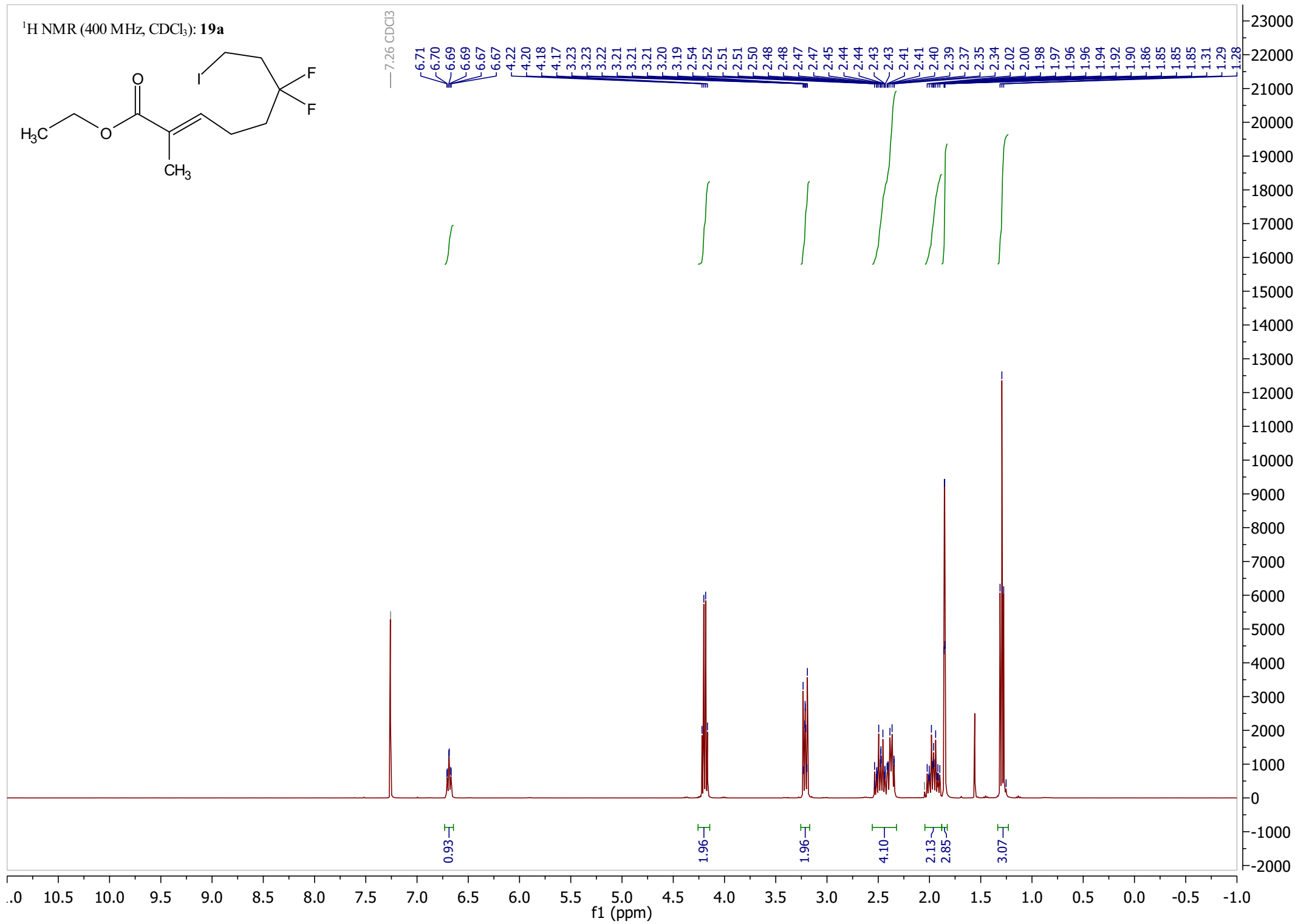
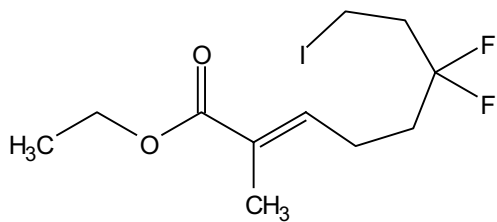
S143

1300  
1200  
1100  
1000  
900  
800  
700  
600  
500  
400  
300  
200  
100  
0  
-100

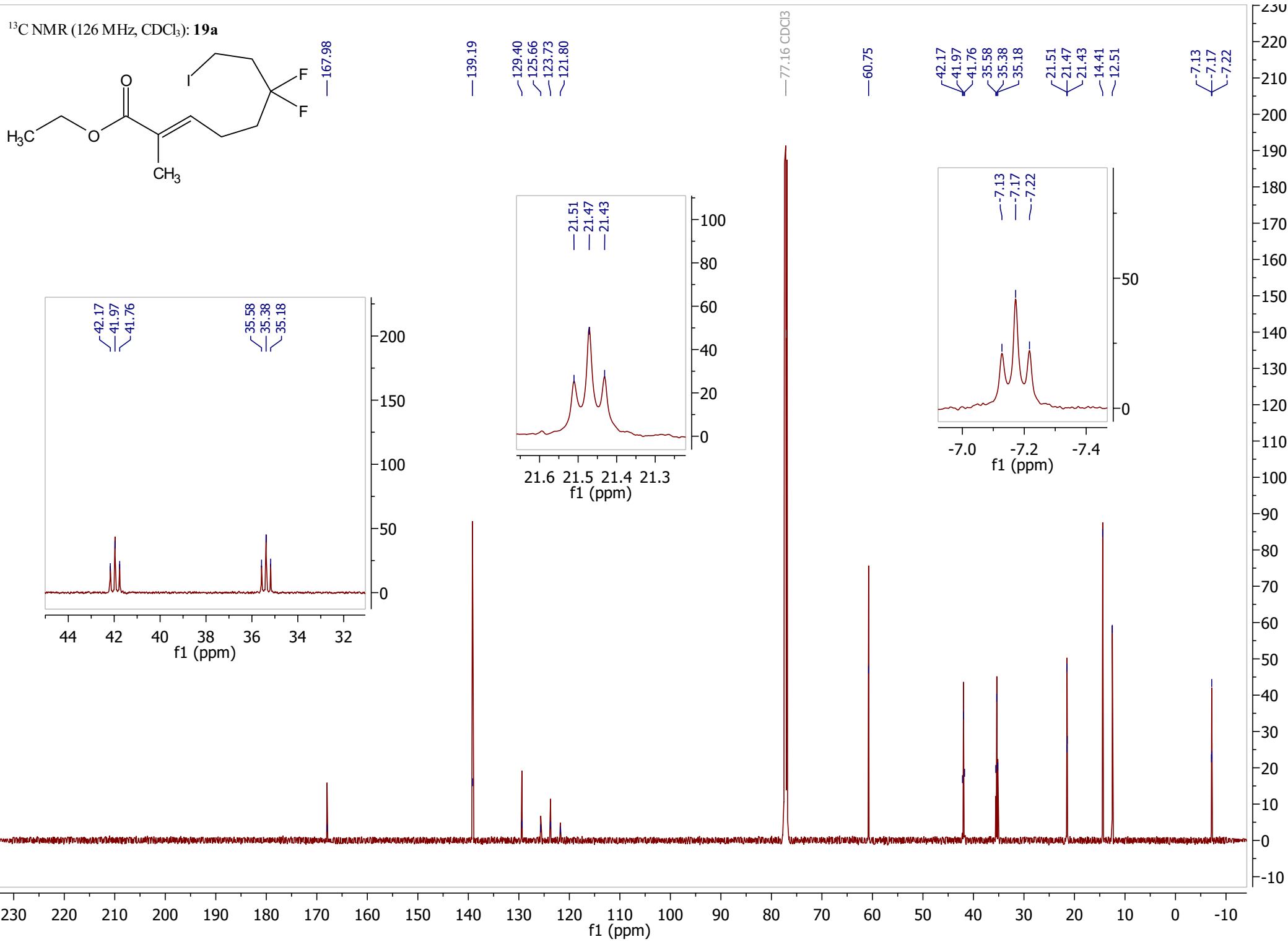
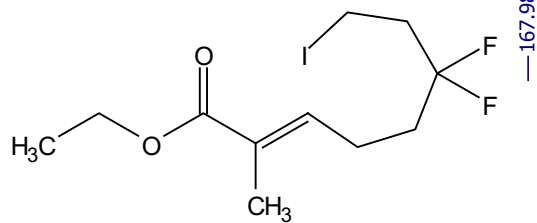
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **18a**



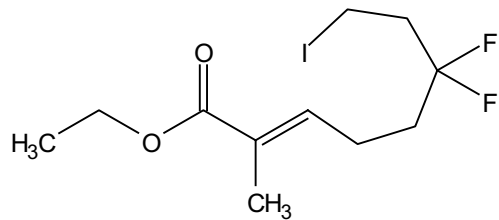
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): **19a**



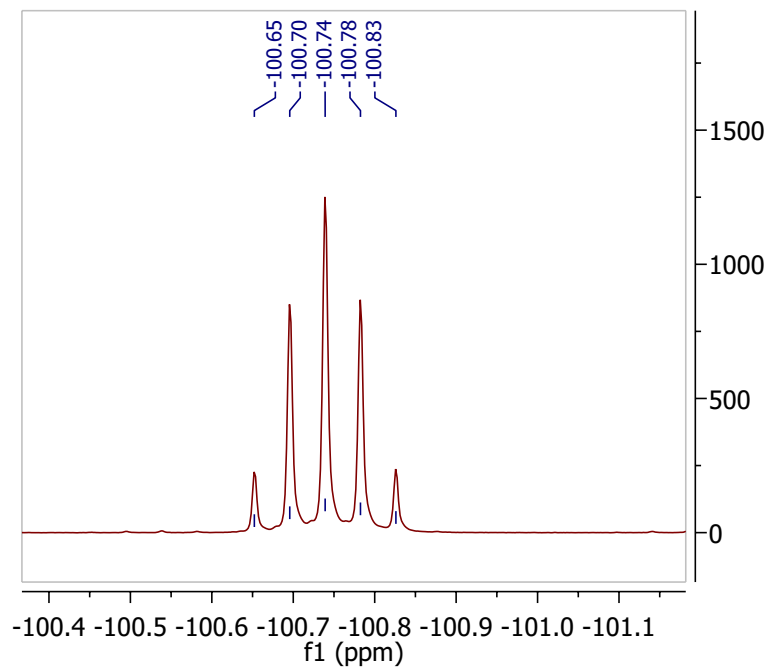
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **19a**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ): **19a**



-100.65  
-100.70  
-100.74  
-100.78  
-100.83

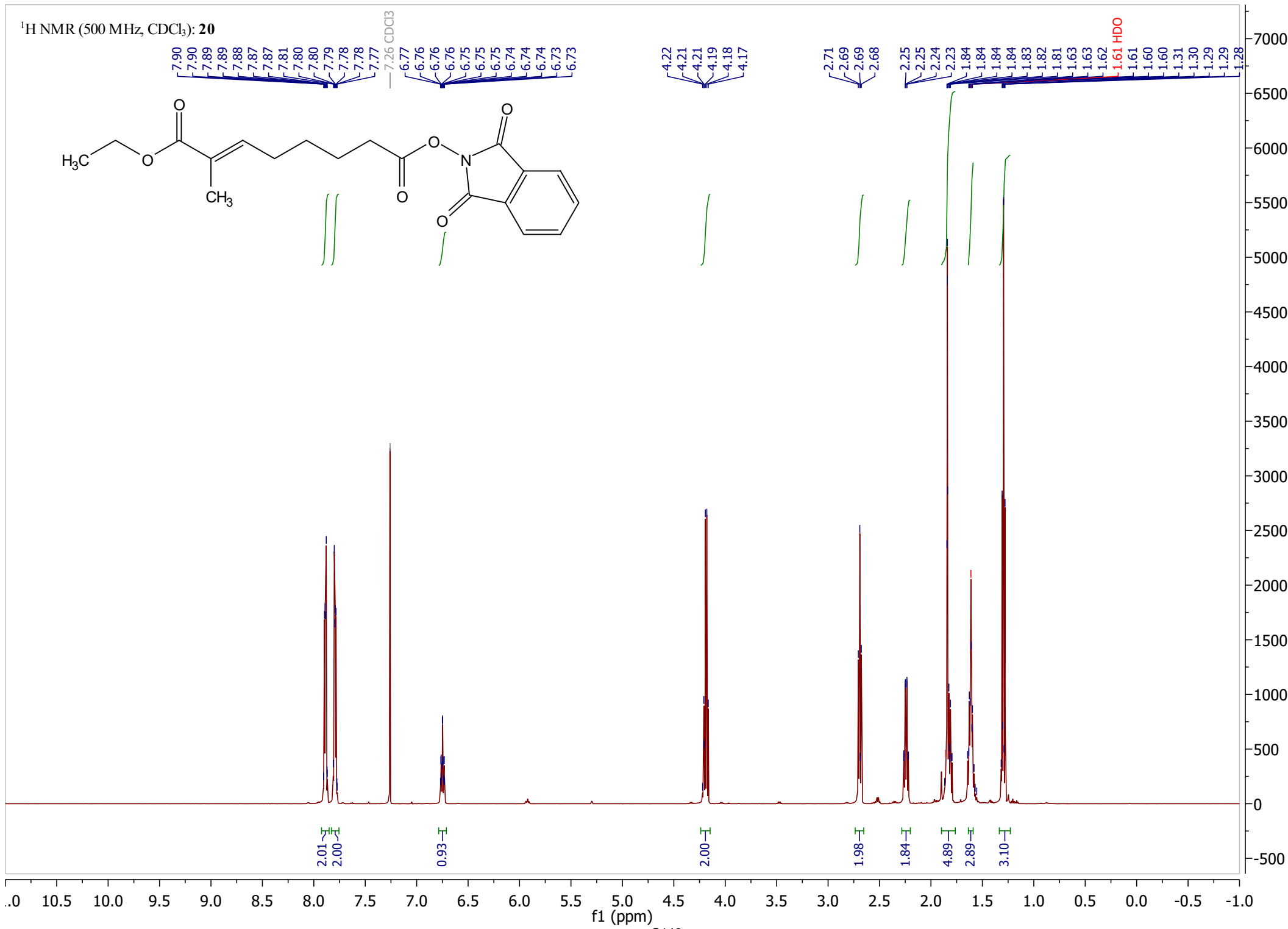
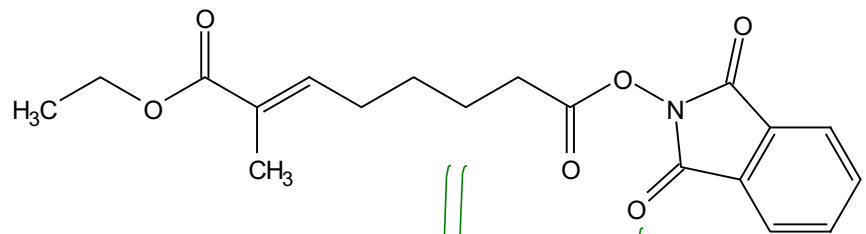


10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

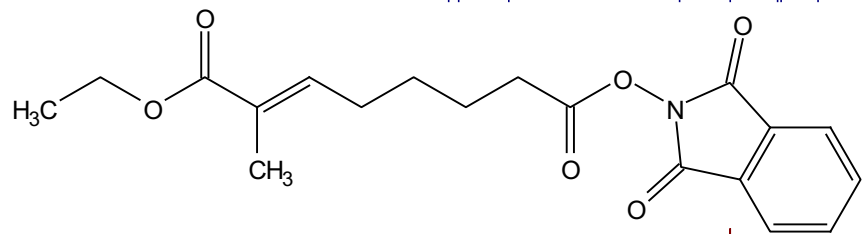
f1 (ppm)

S147

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **20**



<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): **20**



169.49  
168.26

162.10

141.13

134.91

129.09

128.66

124.12

77.16 CDCl<sub>3</sub>

60.60

30.96

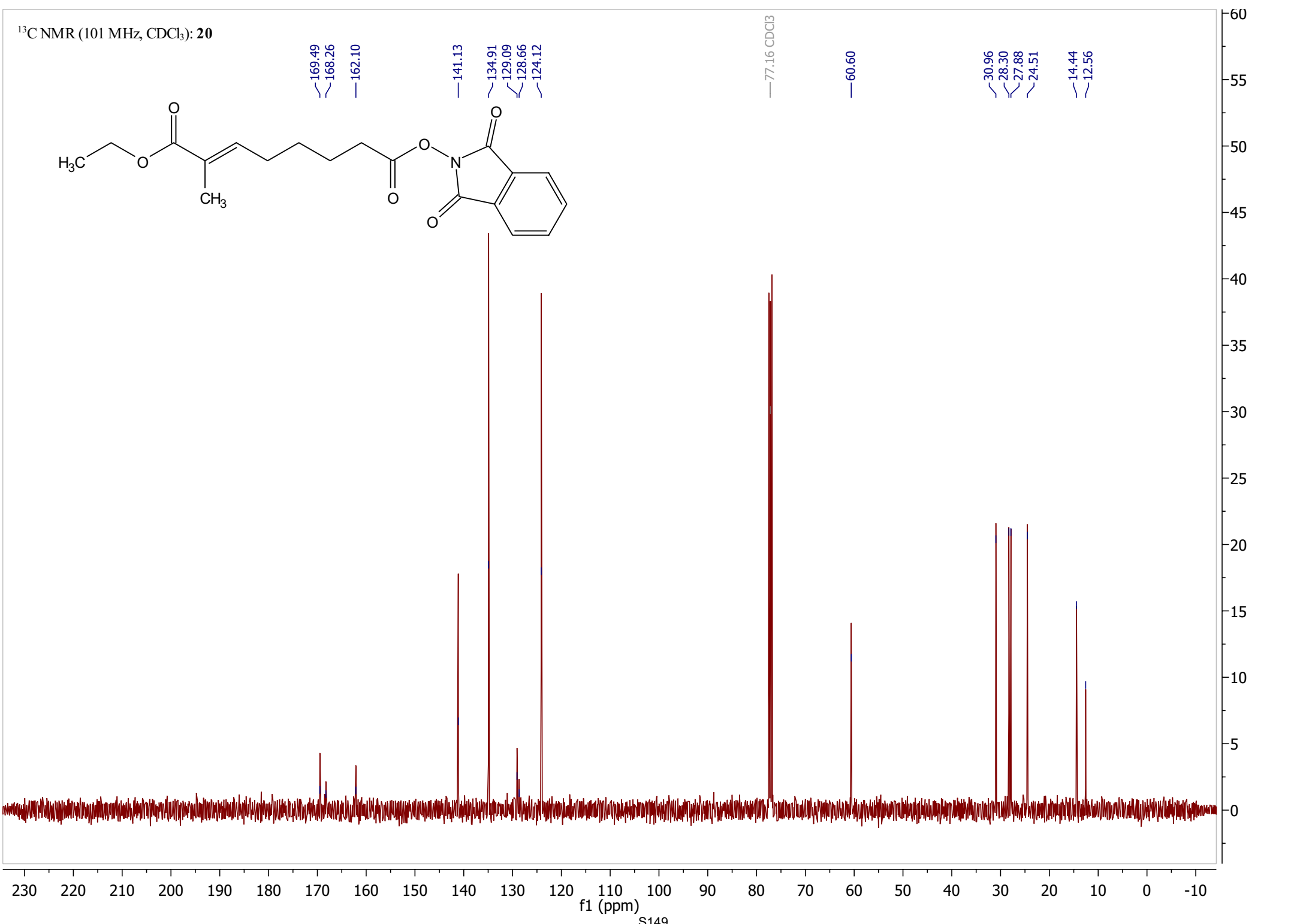
28.30

27.88

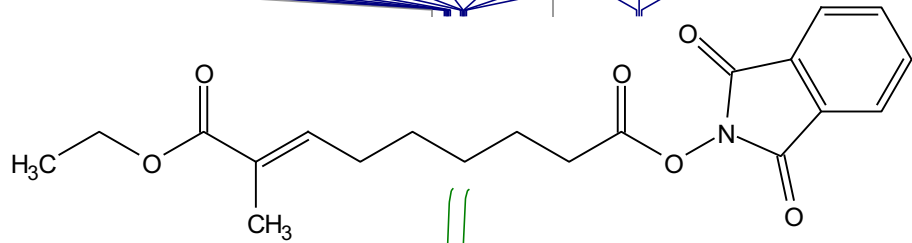
24.51

14.44

12.56



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **21**



7.97  
7.90  
7.89  
7.89  
7.88  
7.88  
7.87  
7.81  
7.80  
7.79  
7.78  
7.77

7.26 CDCl<sub>3</sub>

6.76  
6.75  
6.73

4.21  
4.19  
4.18  
4.16

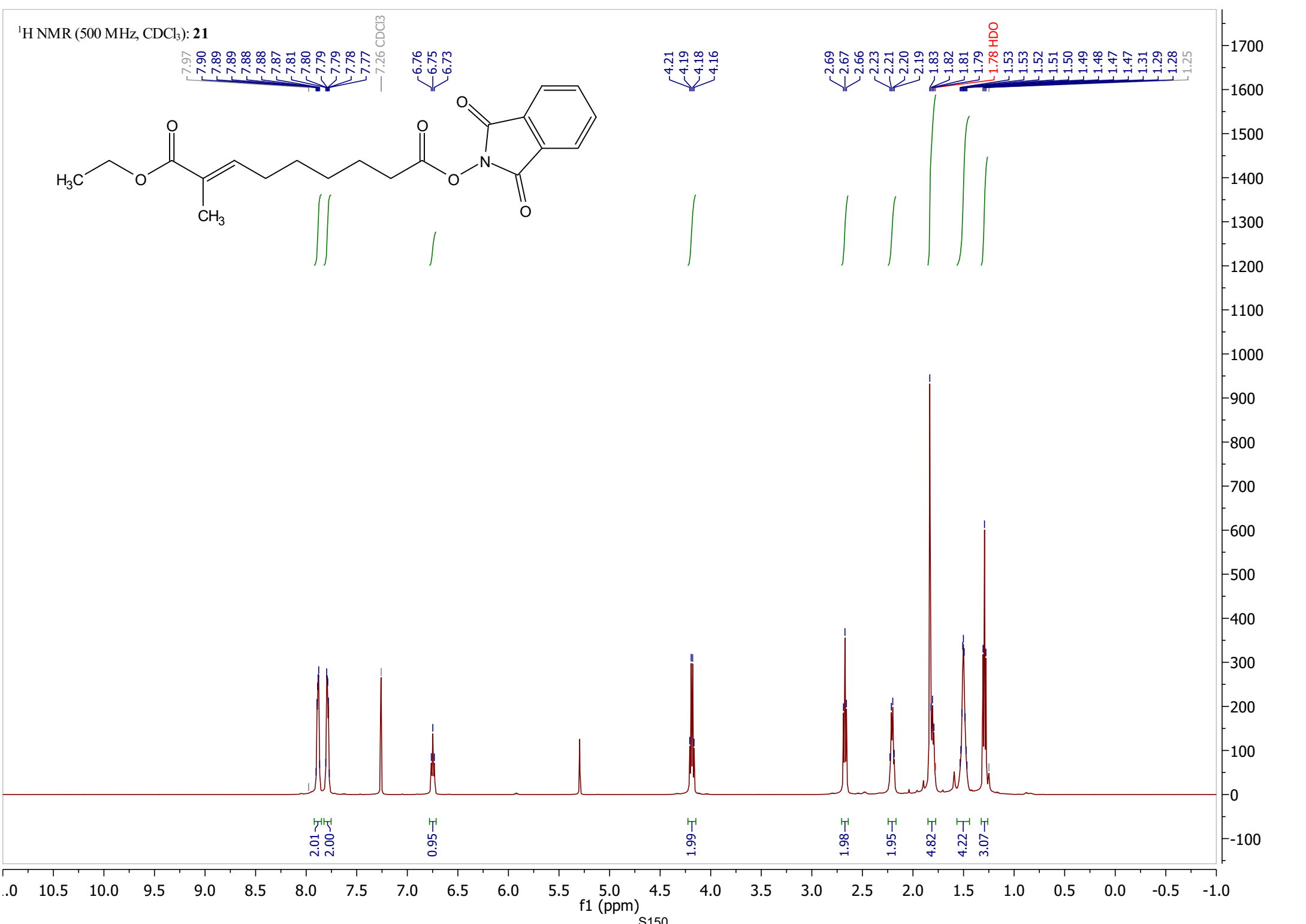
2.69  
2.66  
2.66

2.23  
2.21  
2.20  
2.19

1.83  
1.82  
1.81

1.79  
1.78 H<sub>2</sub>O

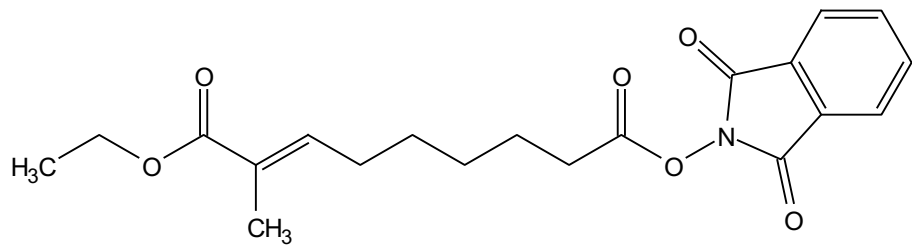
1.53  
1.52  
1.51  
1.50  
1.49  
1.48  
1.47  
1.47  
1.31  
1.29  
1.28  
1.25



f1 (ppm)

S150

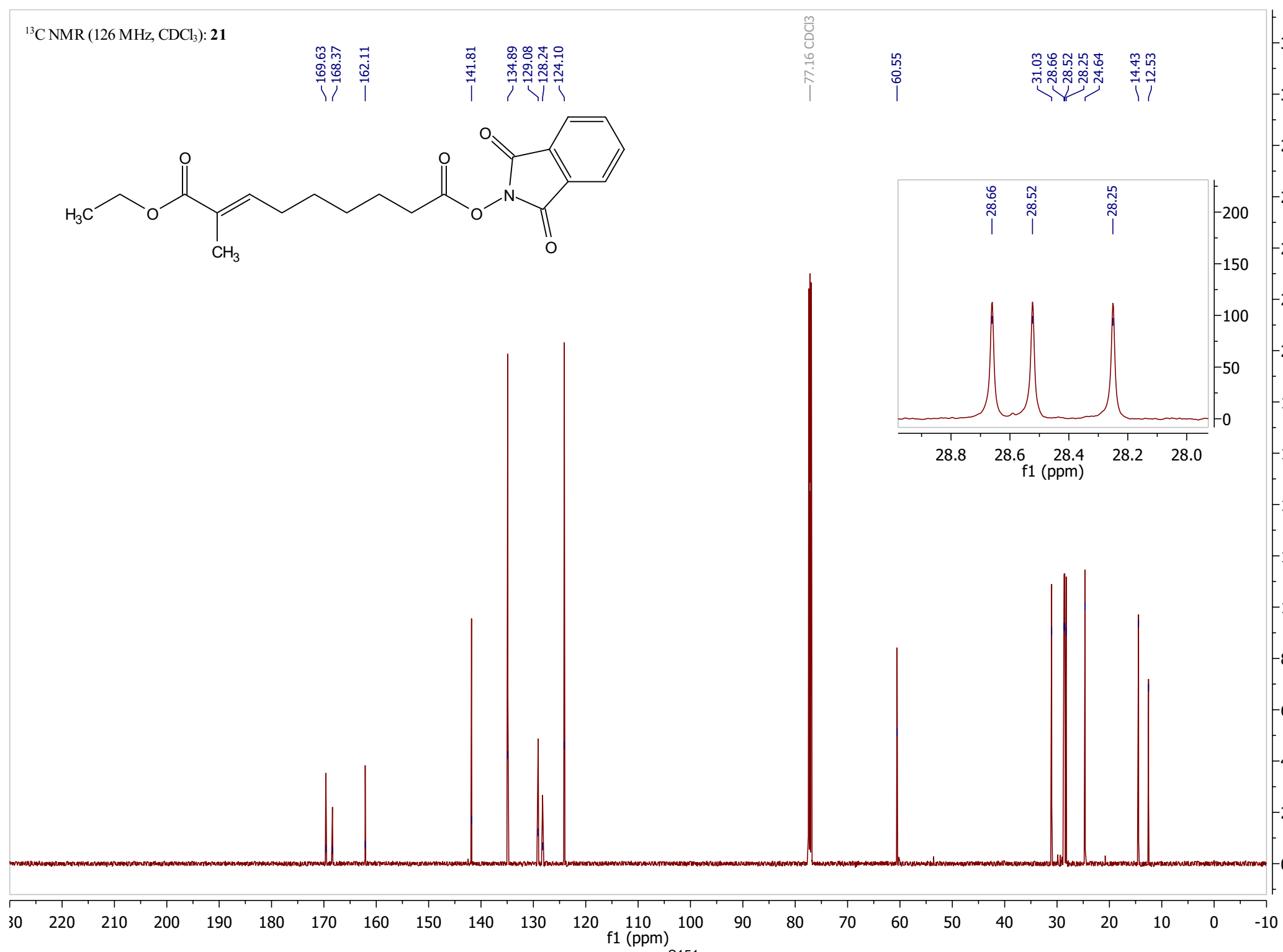
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **21**



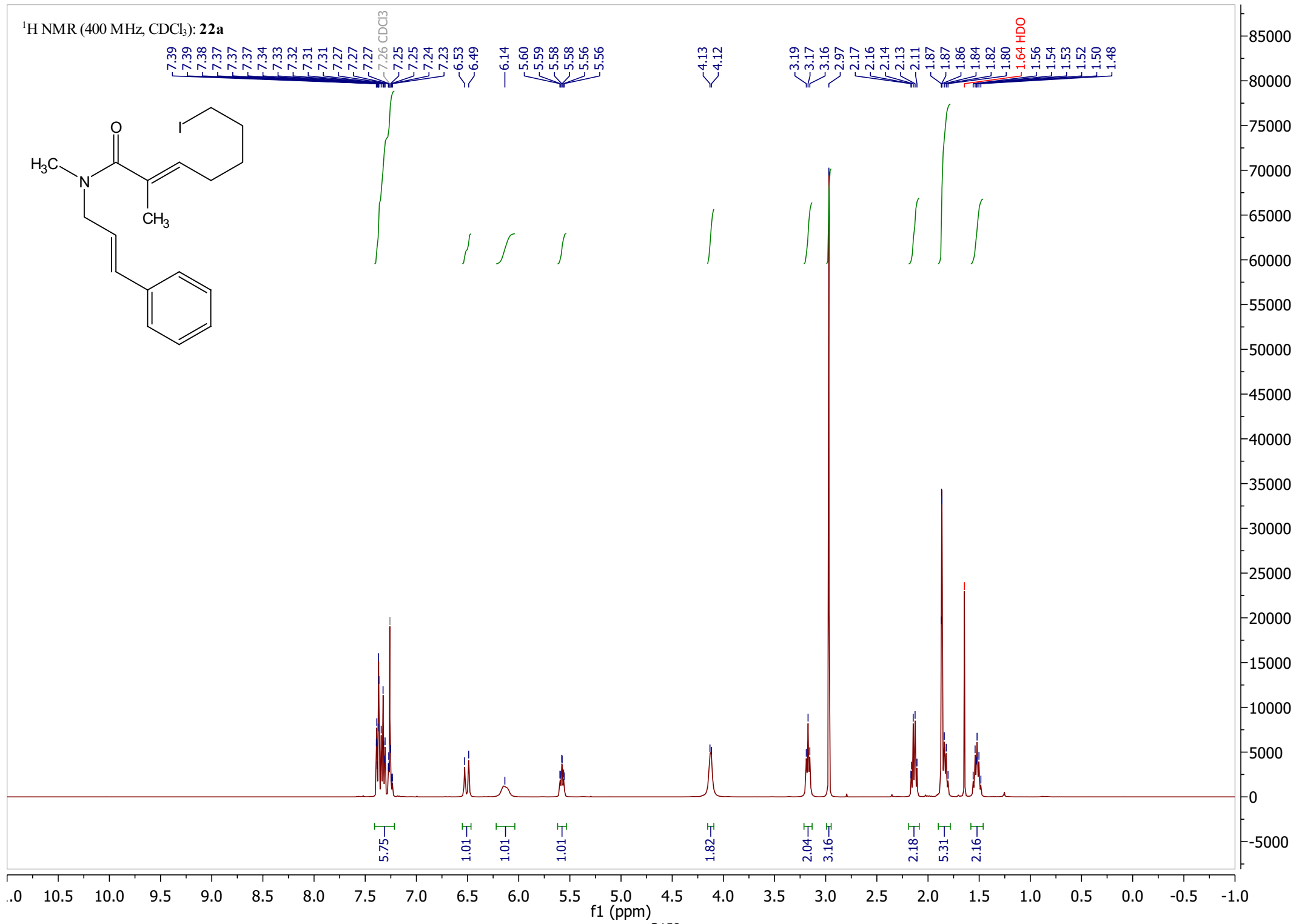
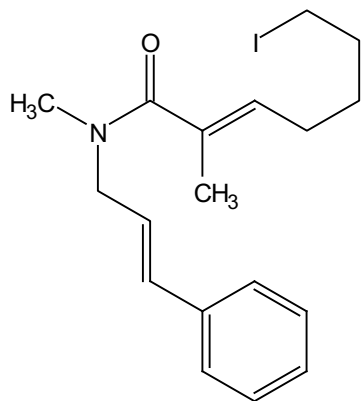
169.63  
168.37  
162.11  
141.81  
134.89  
129.08  
128.24  
124.10

77.16 CDCl<sub>3</sub>

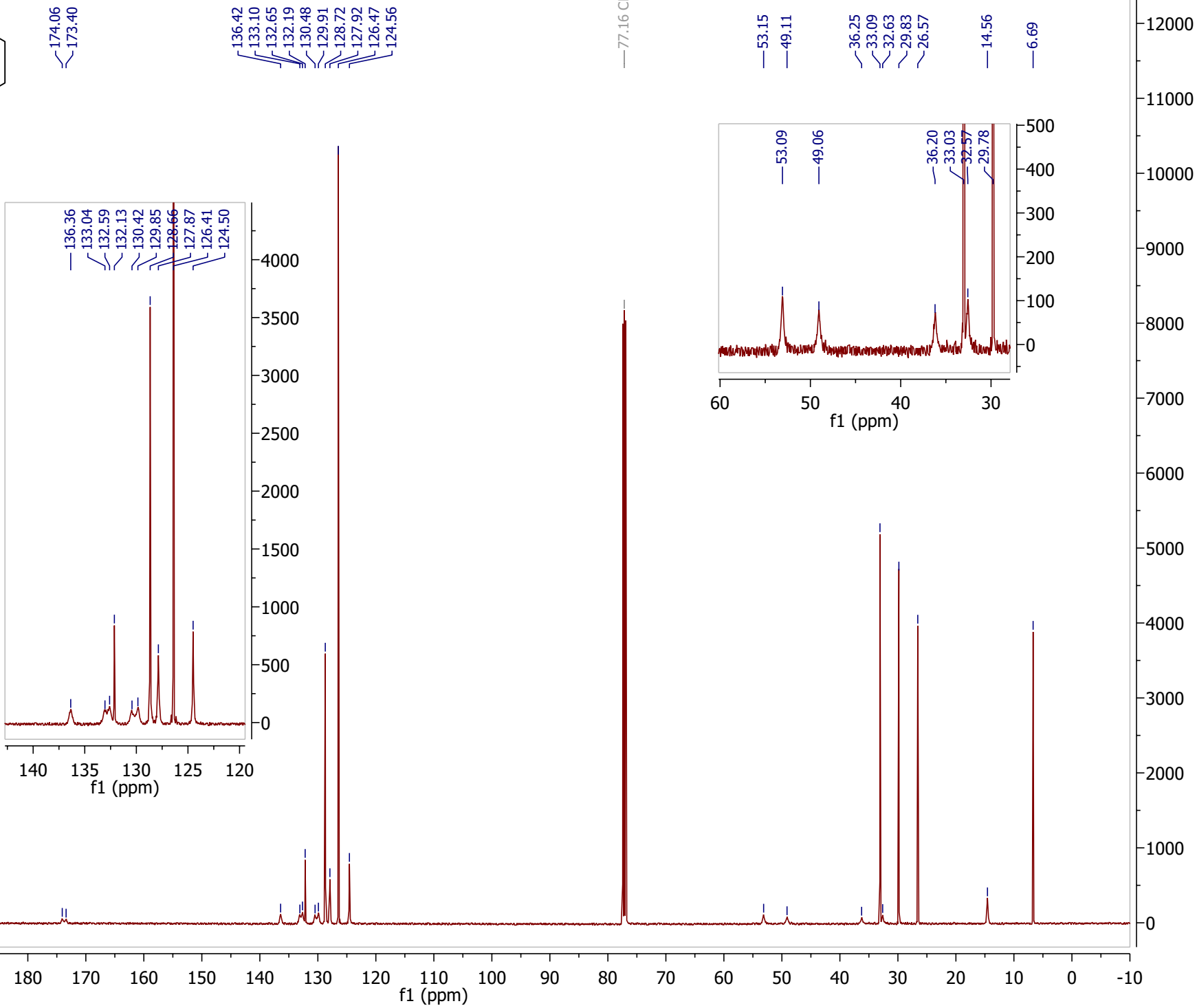
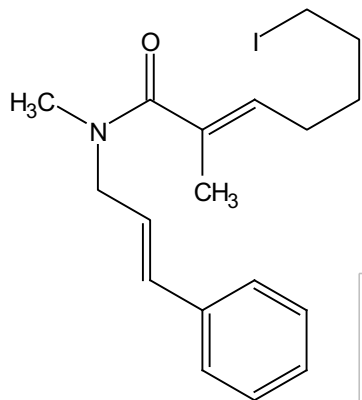
60.55  
31.03  
28.66  
28.52  
28.25  
24.64  
14.43  
12.53



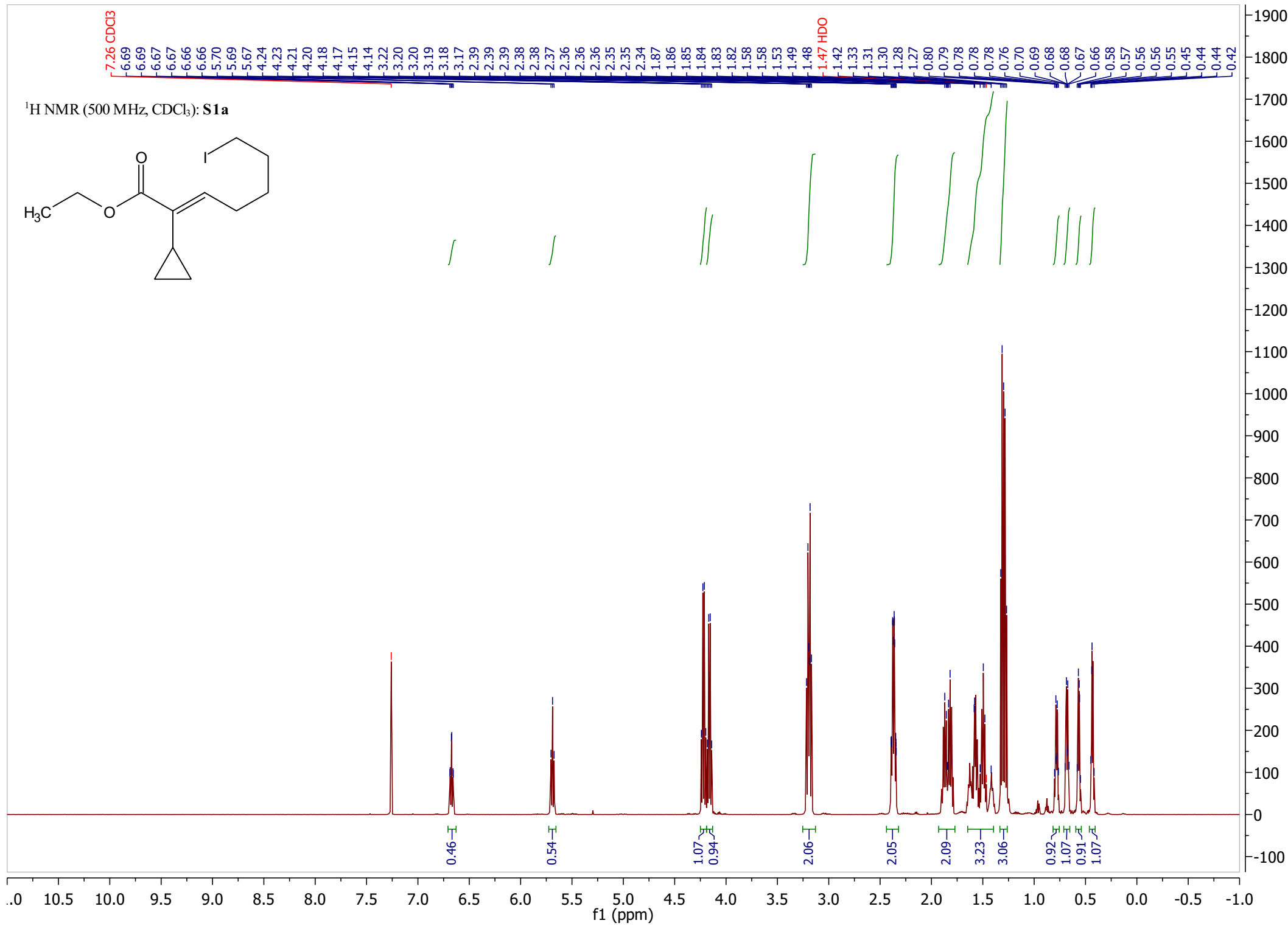
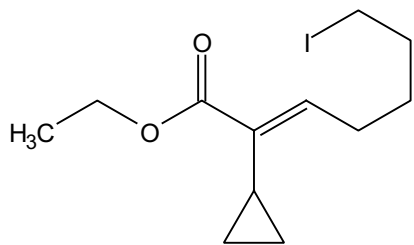
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): **22a**



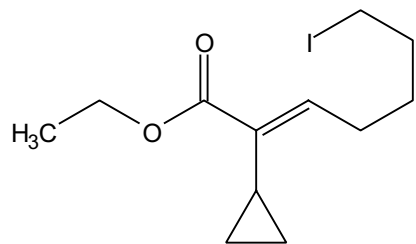
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **22a**



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): S1a



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): S1a



168.47  
168.07

143.36

137.11

134.36

133.62

77.16 CDCl<sub>3</sub>

60.44  
60.40

33.24

33.13

30.33

29.72

28.19

27.50

14.49

14.42

14.32

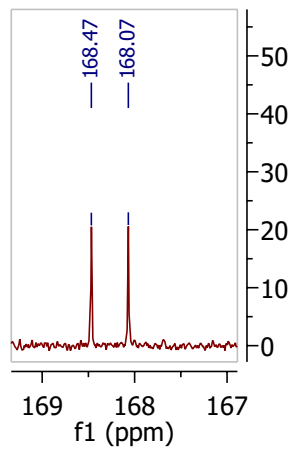
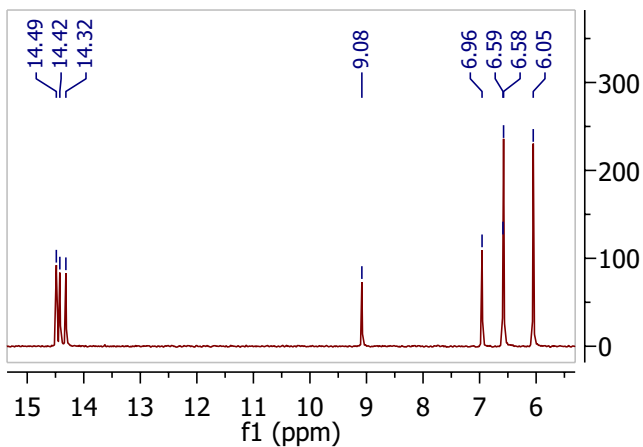
9.08

6.96

6.59

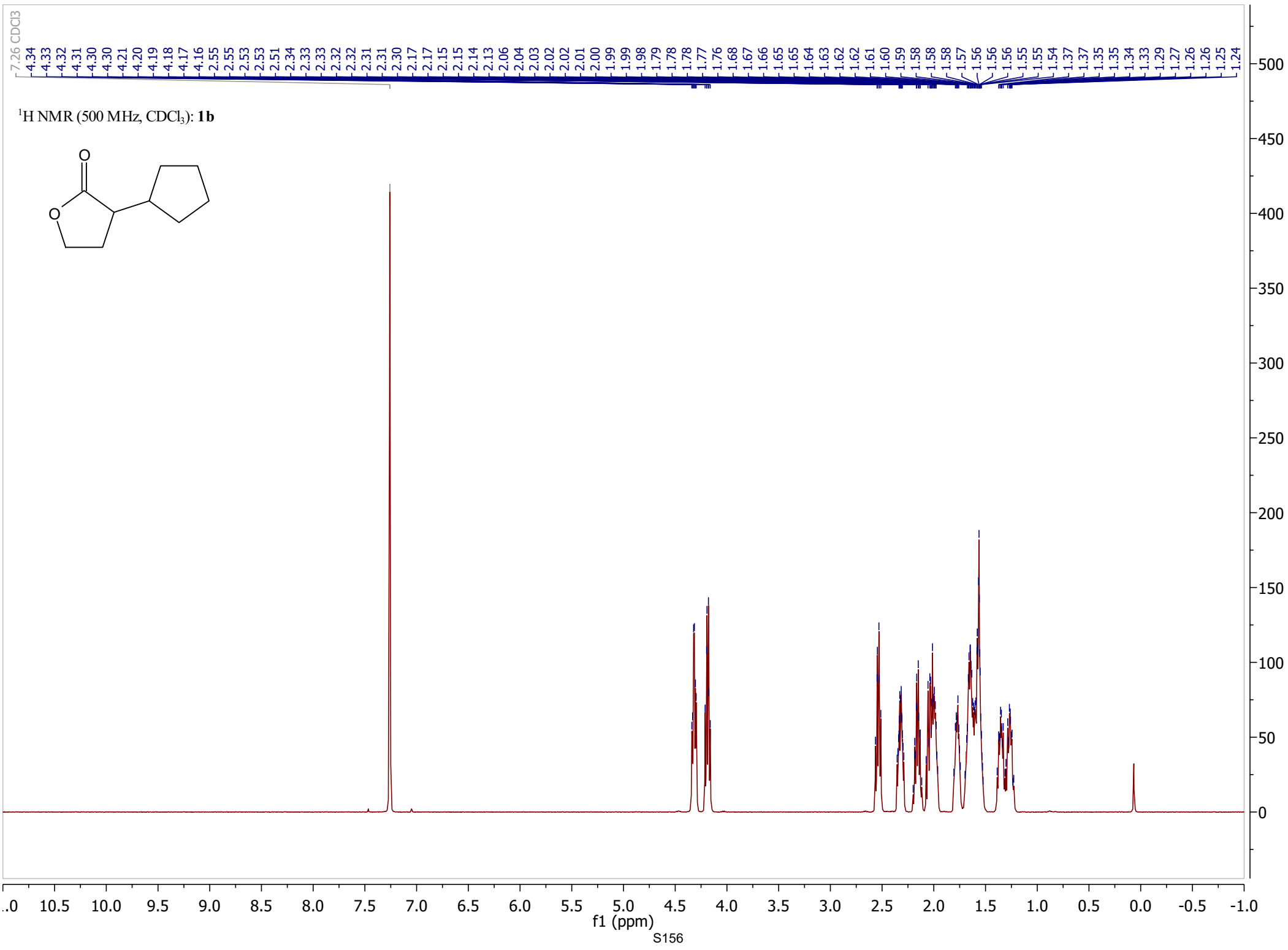
6.58

6.05

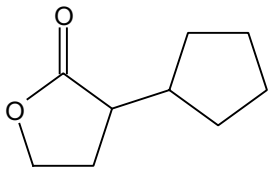


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)



$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ): **1b**



— 179.11

— 77.16  $\text{CDCl}_3$

— 66.55

— 43.37

— 40.42

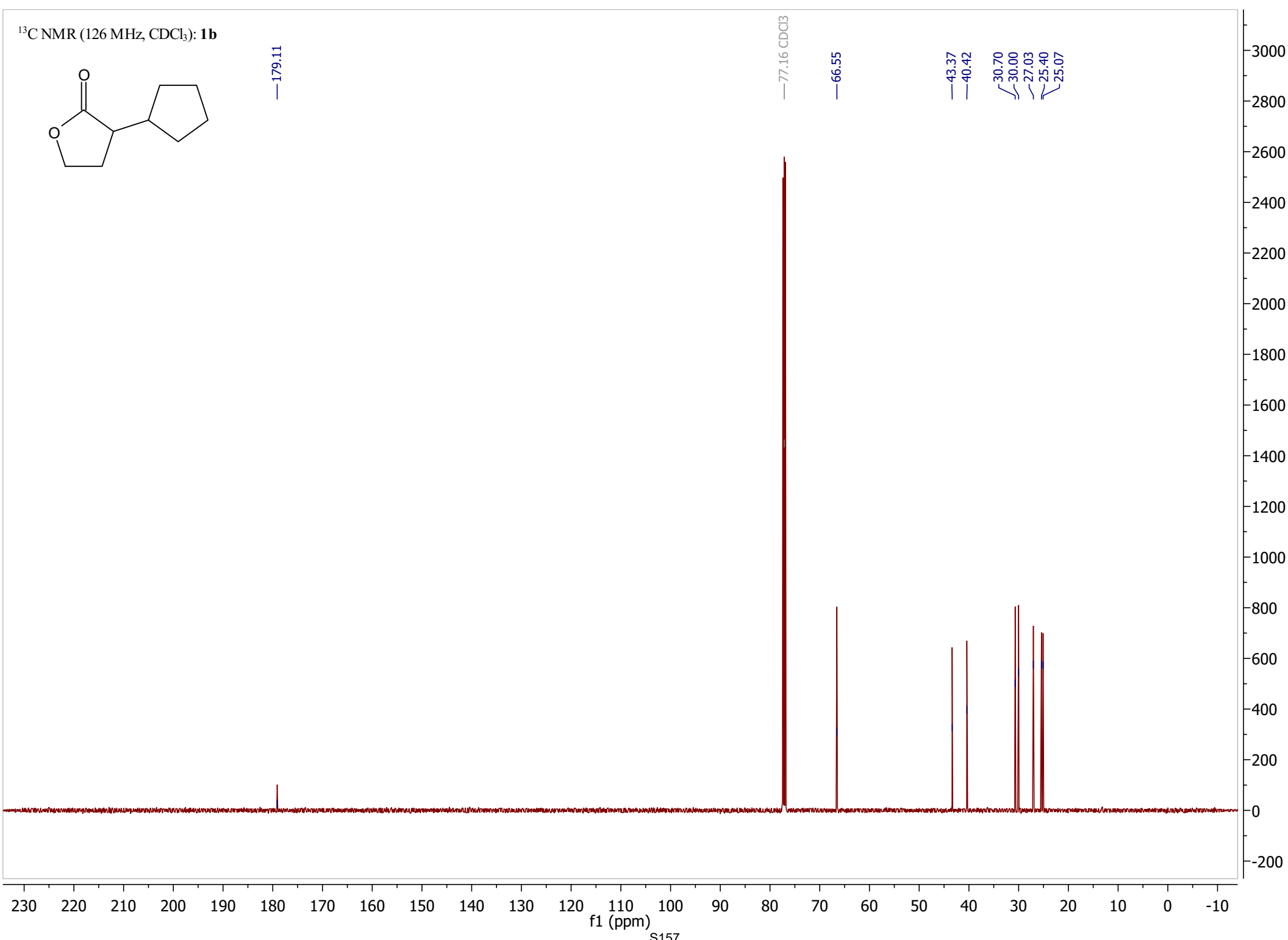
— 30.70

— 30.00

— 27.03

— 25.40

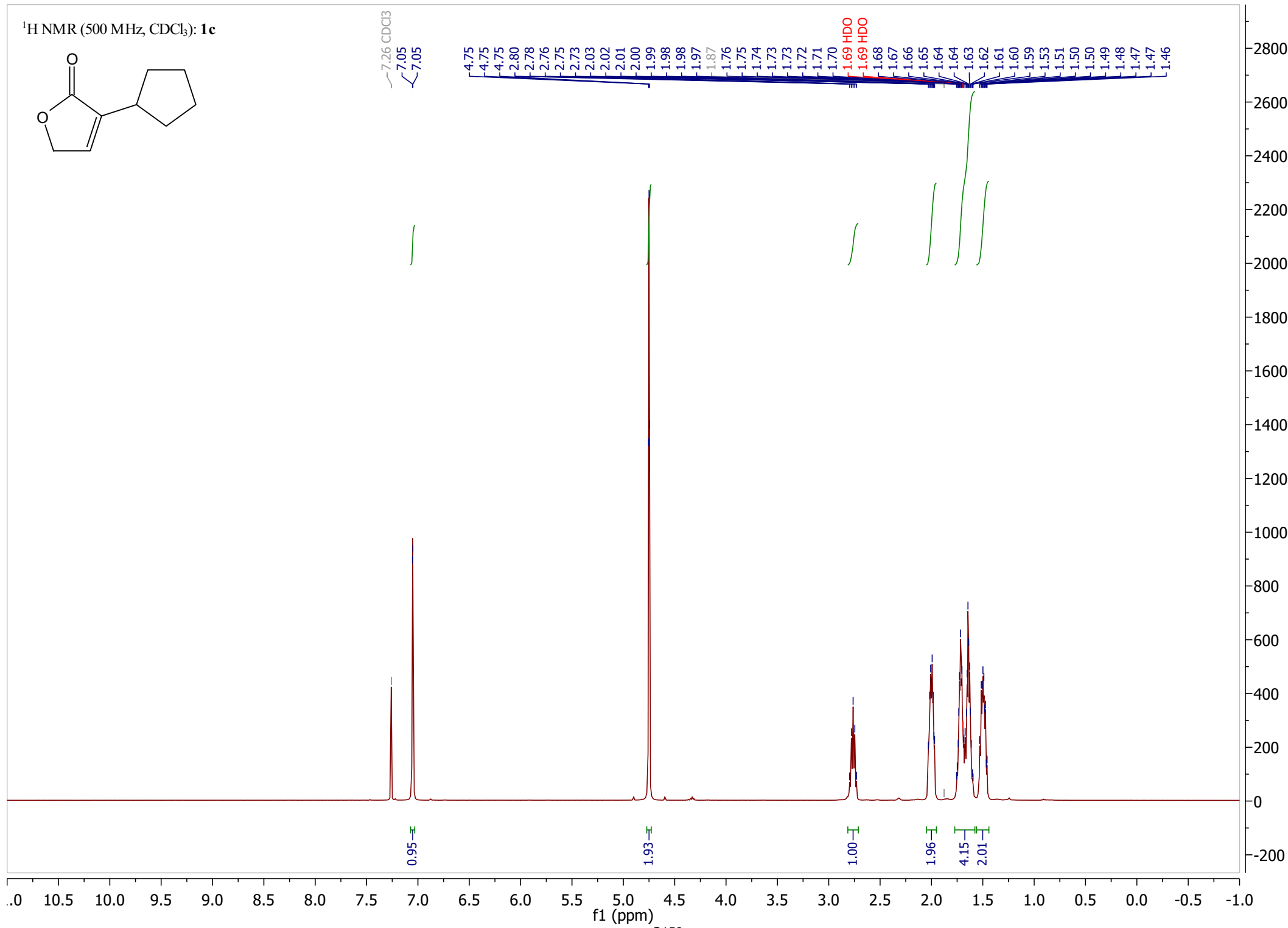
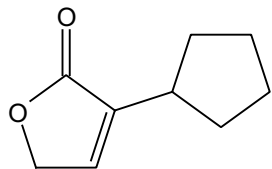
— 25.07



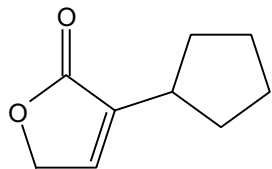
f1 (ppm)

S157

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **1c**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **1c**



—174.23

—142.42

—138.42

—77.16 CDCl<sub>3</sub>

—70.13

—36.68

—31.61

—25.12

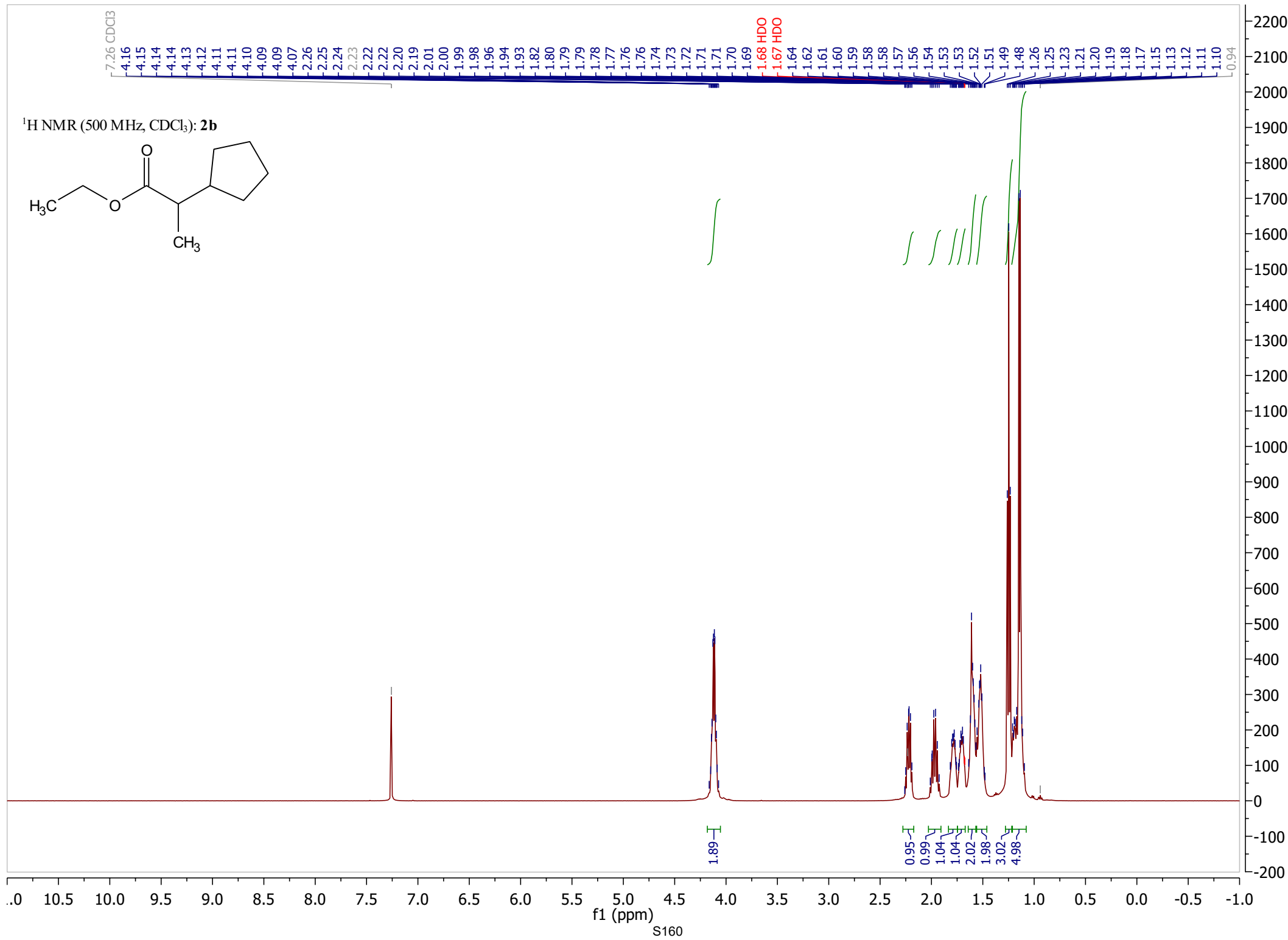
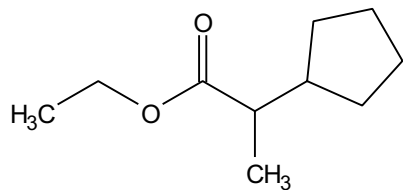
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

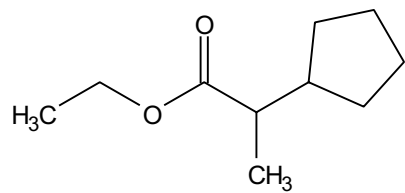
S159

450  
400  
350  
300  
250  
200  
150  
100  
50  
0

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **2b**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **2b**



—176.92

—77.16 CDCl<sub>3</sub>

—60.10

—45.26

—43.64

—30.98

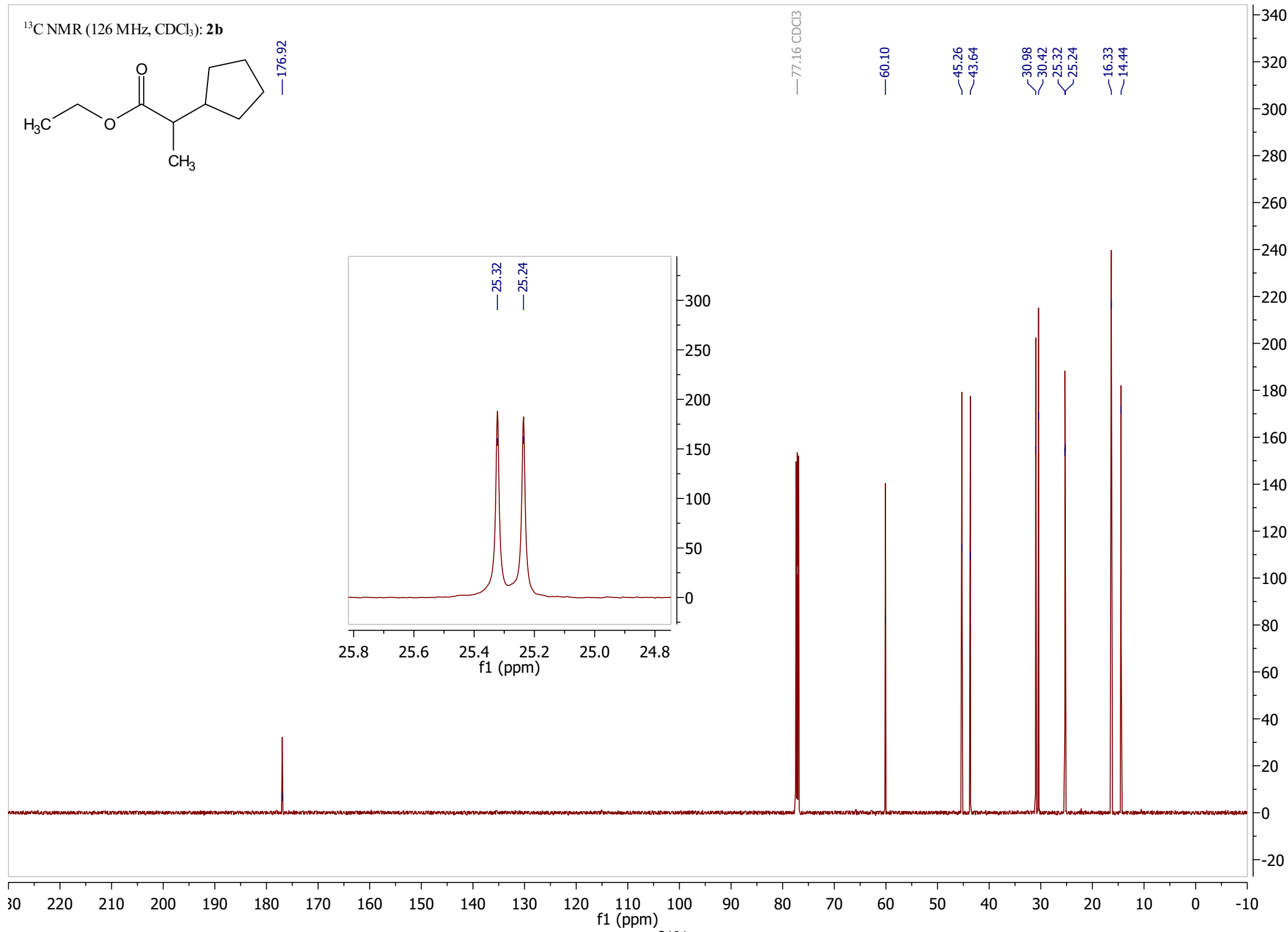
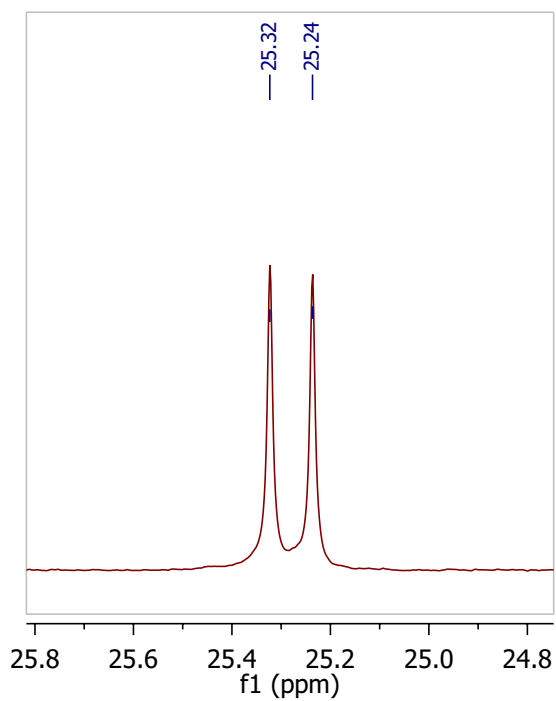
—30.42

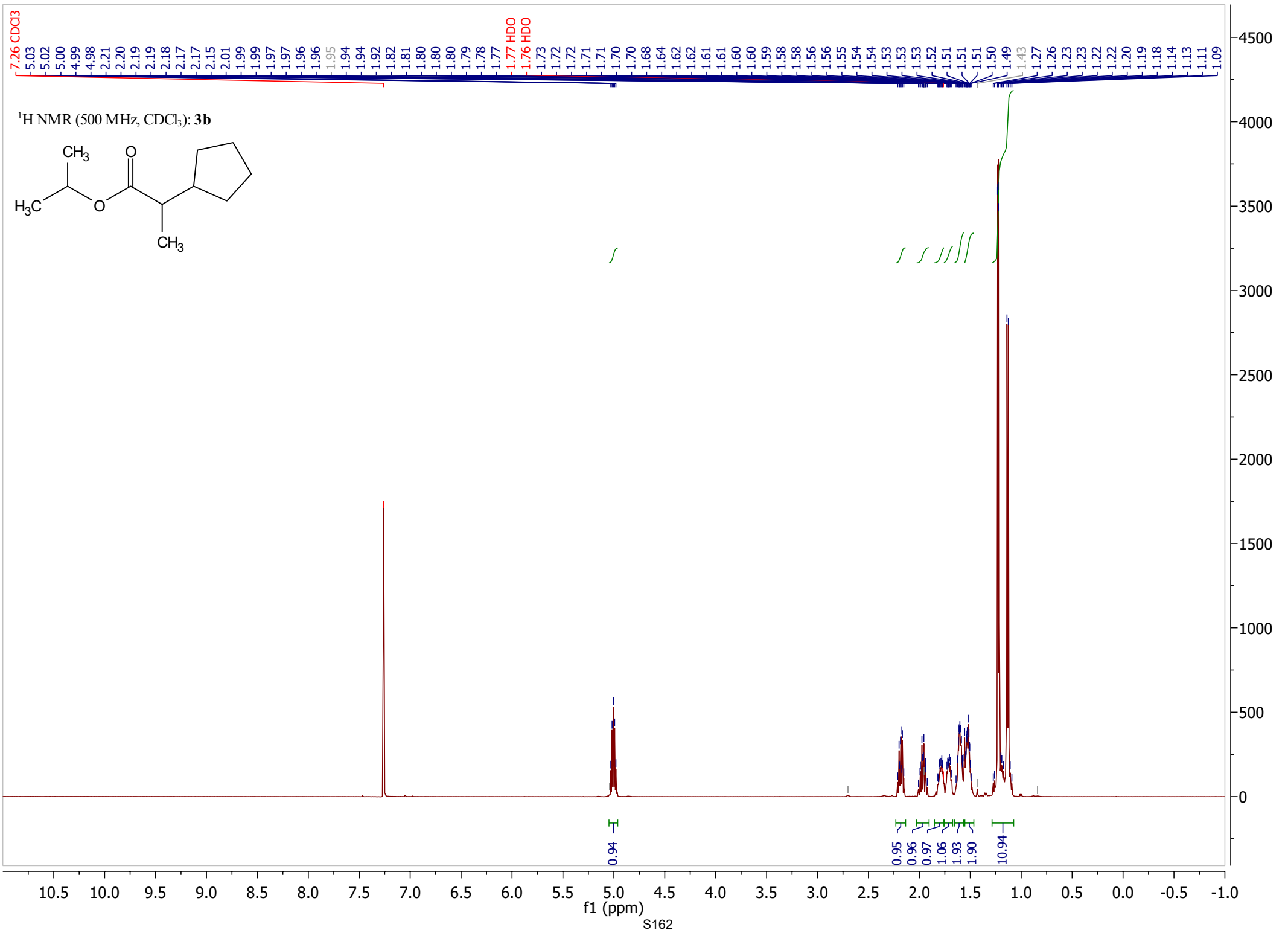
—25.32

—25.24

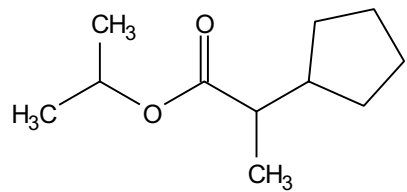
—16.33

—14.44





<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **3b**



— 176.46

— 77.16 CDCl<sub>3</sub>

— 67.20

— 45.51

— 43.64

— 30.93

— 30.46

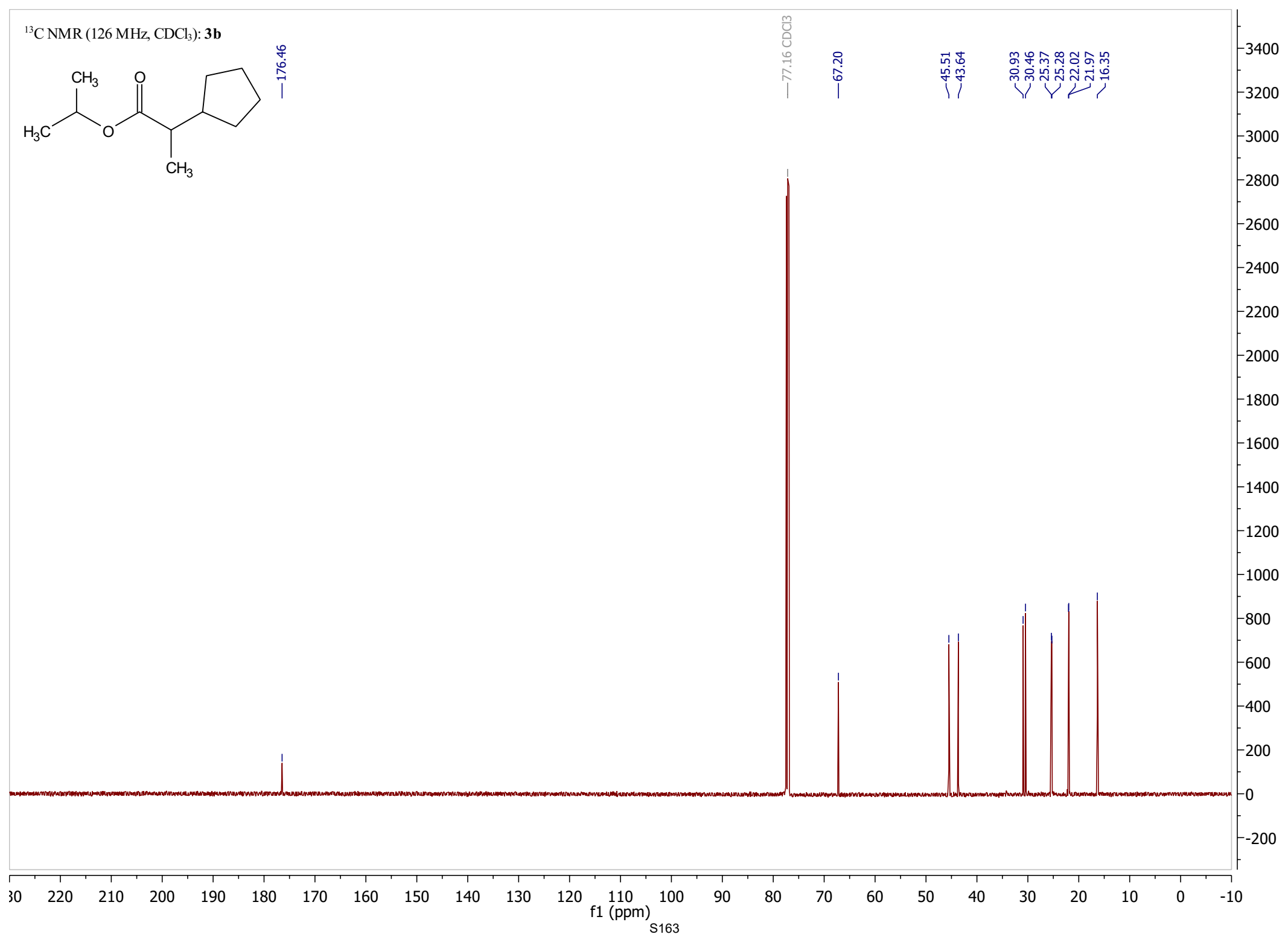
— 25.37

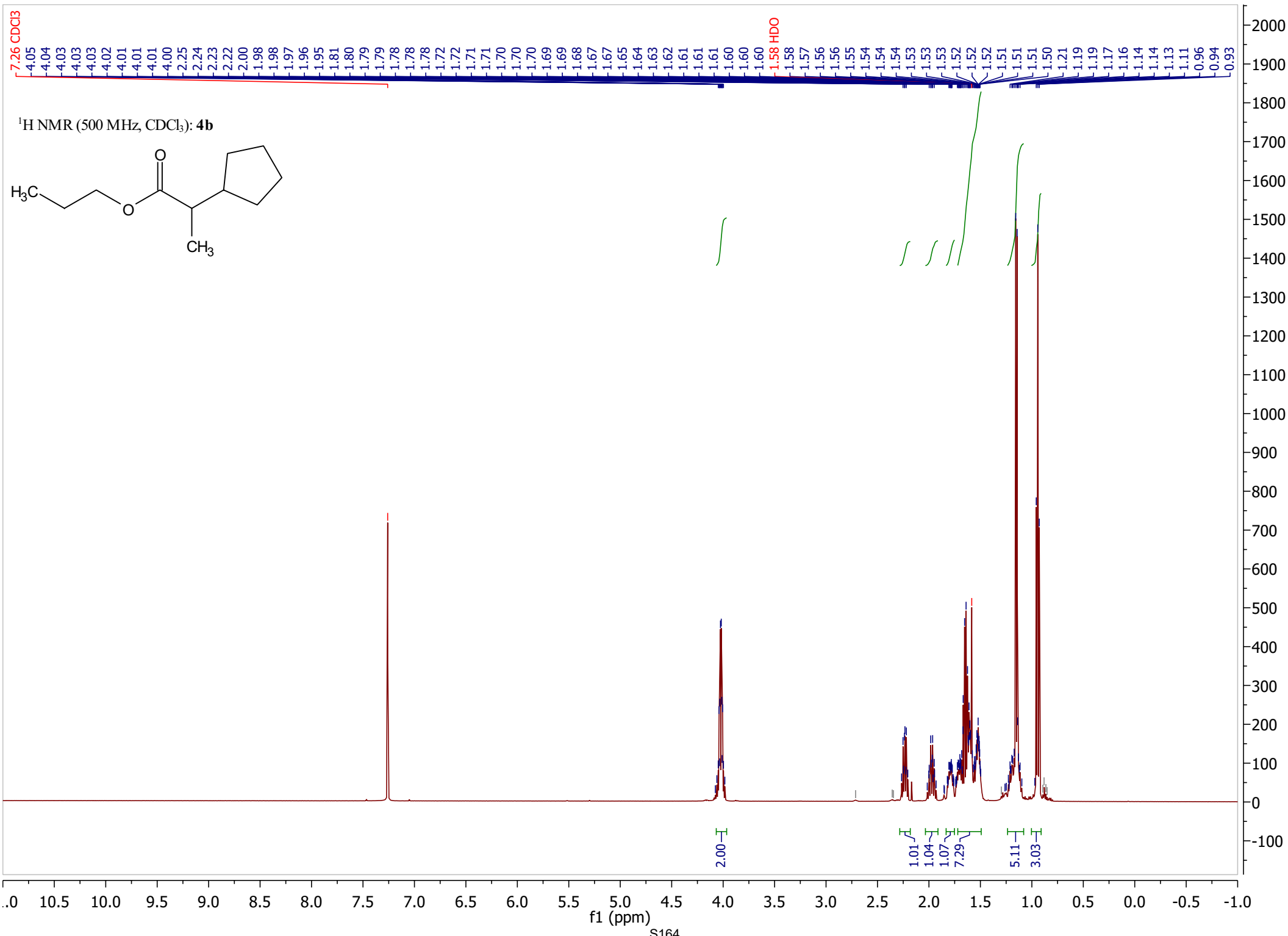
— 25.28

— 22.02

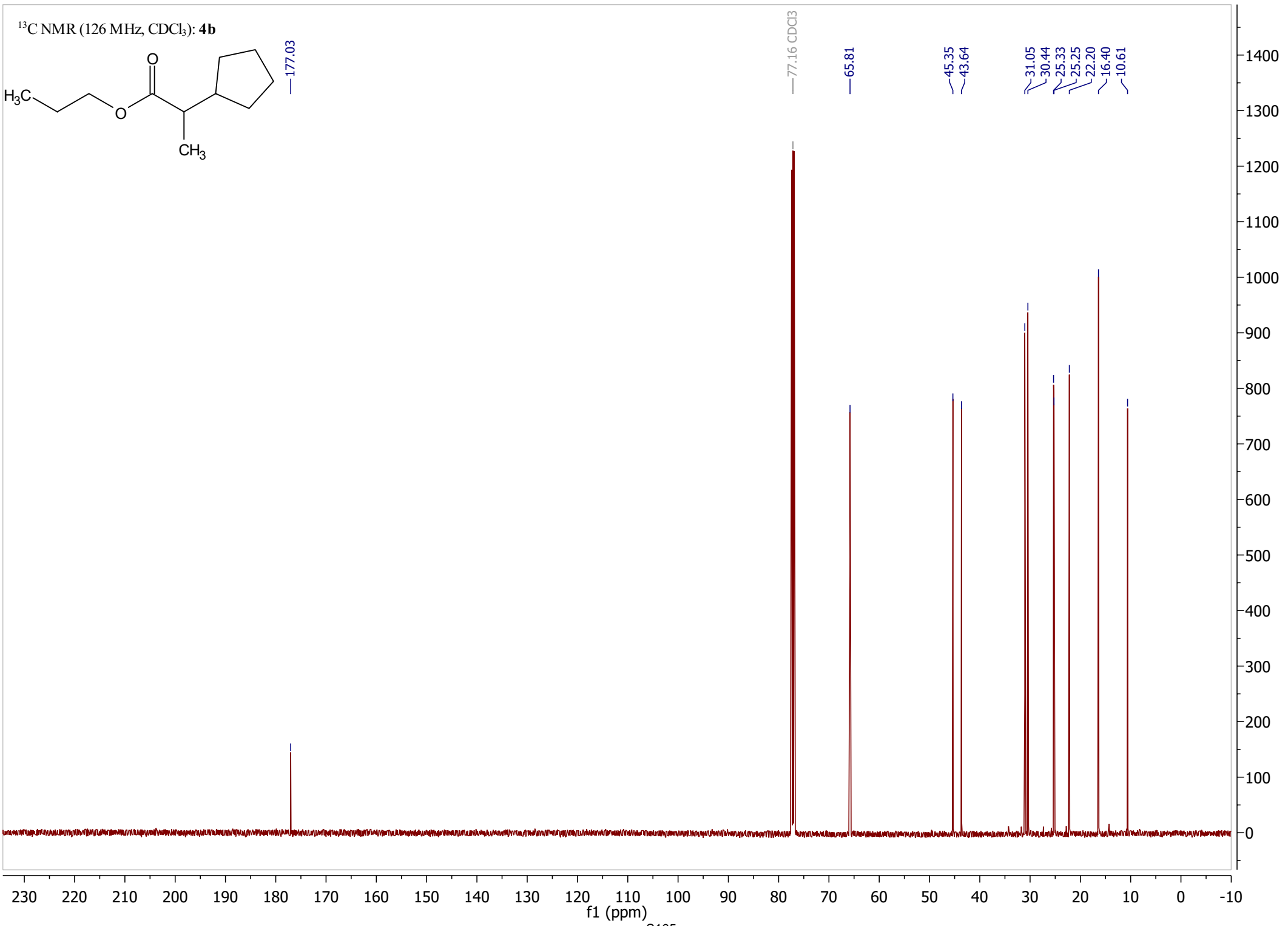
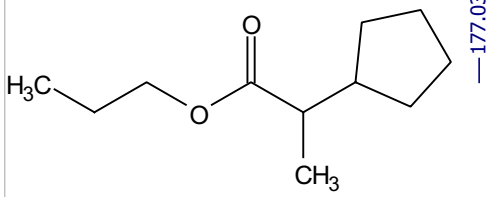
— 21.97

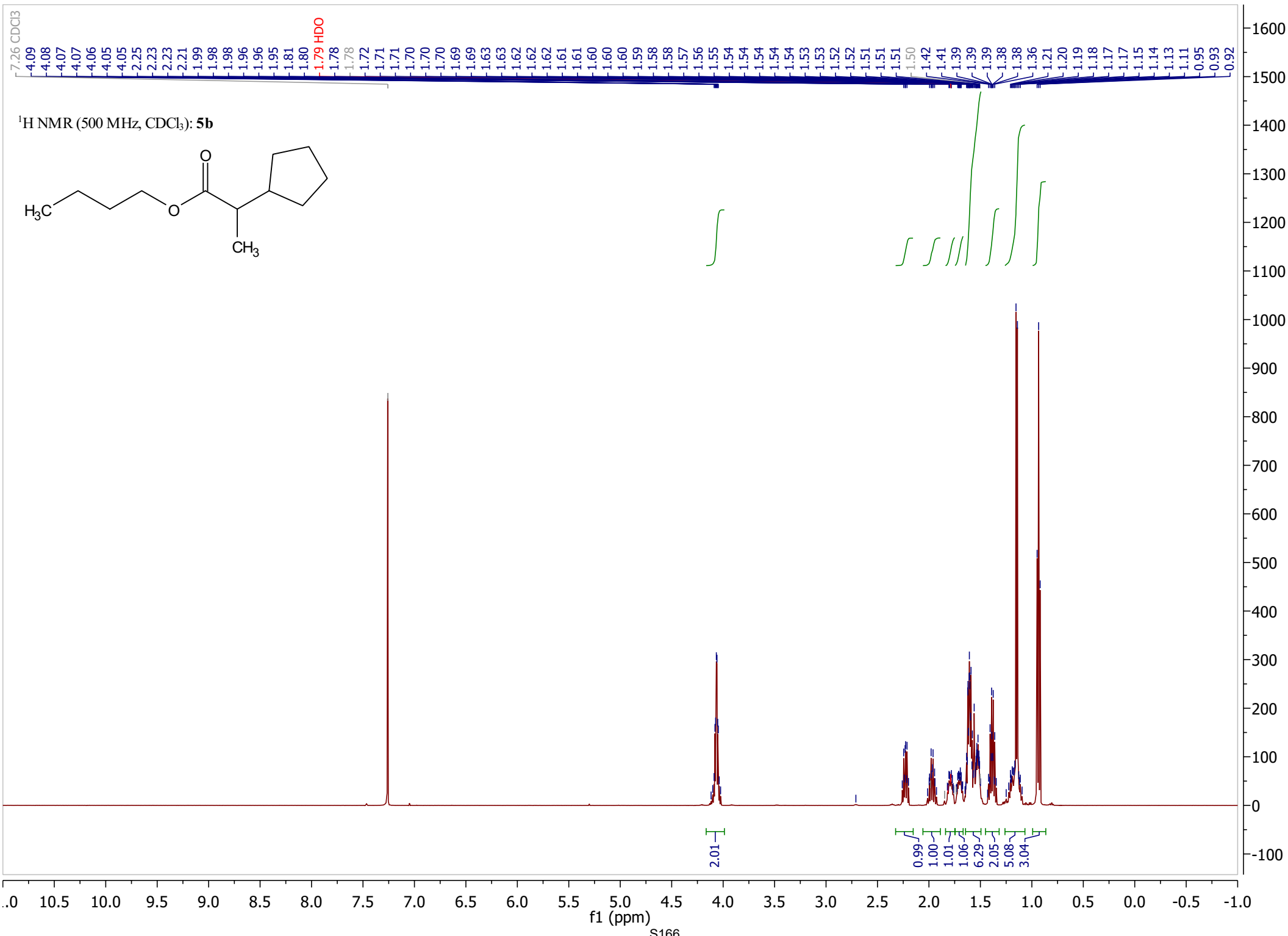
— 16.35



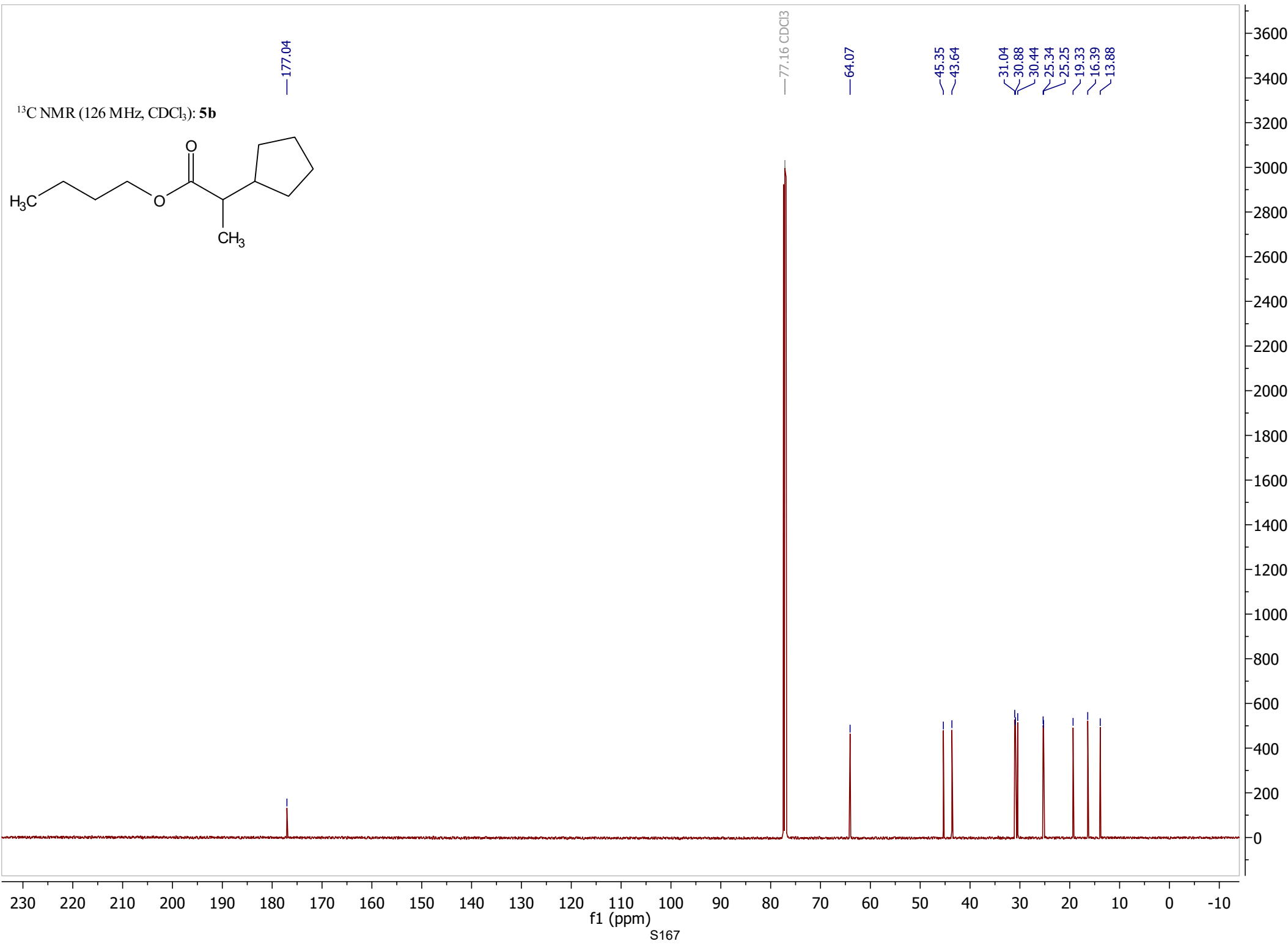
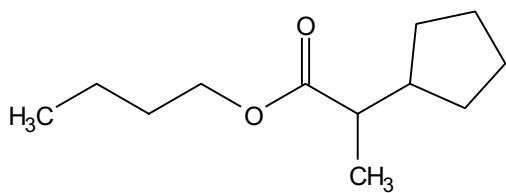


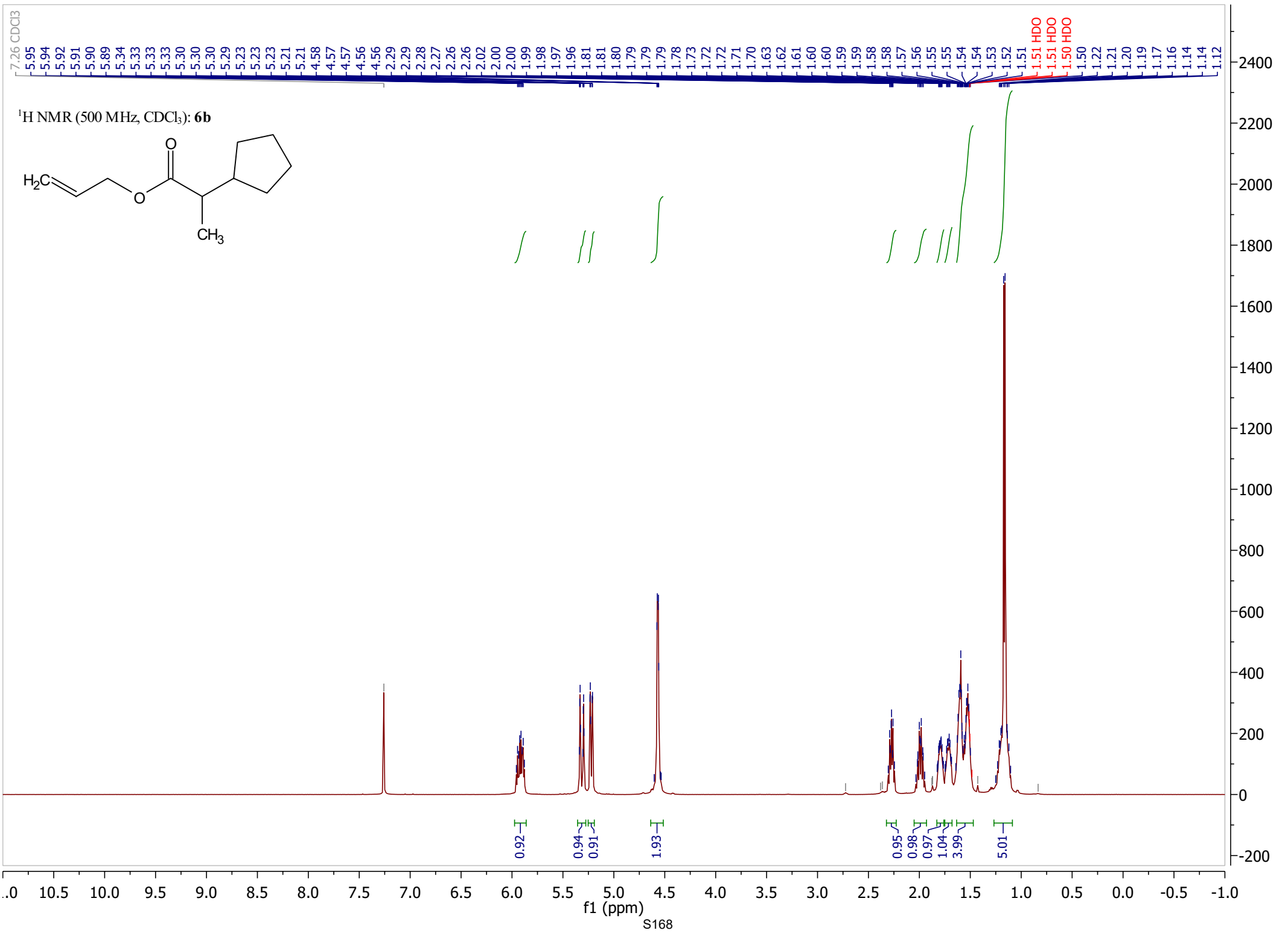
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **4b**



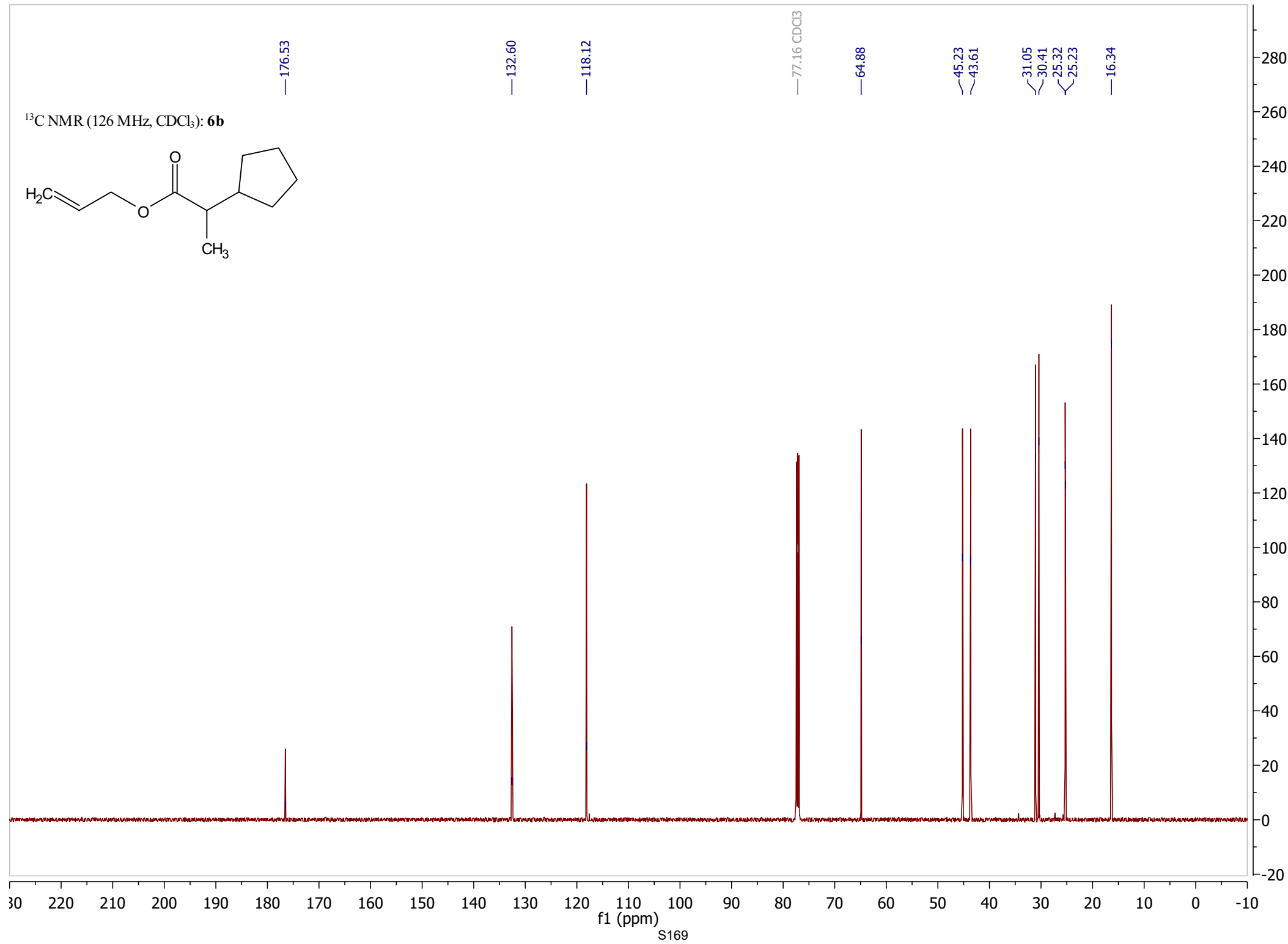
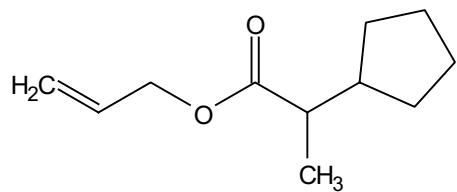


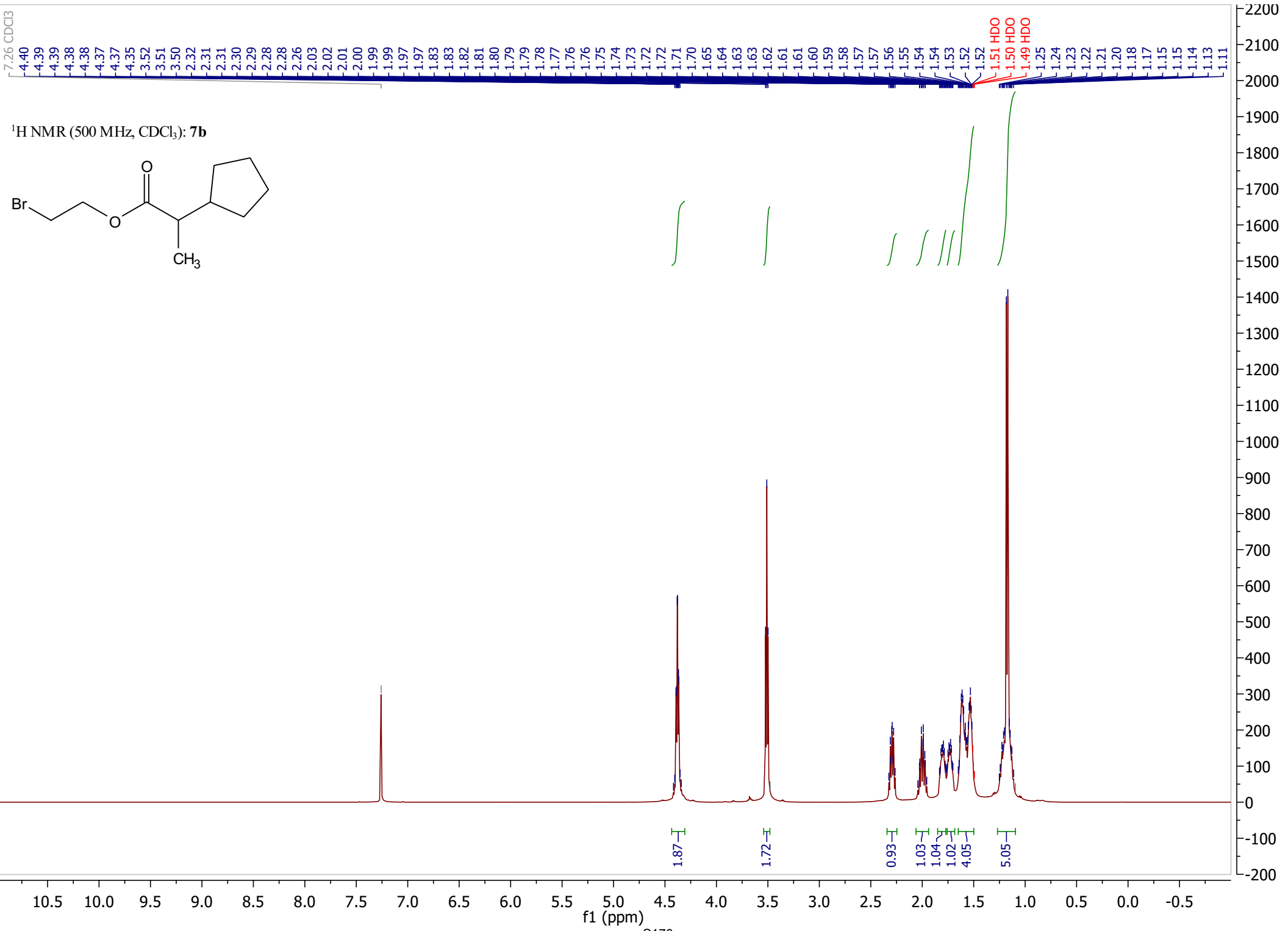
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **5b**



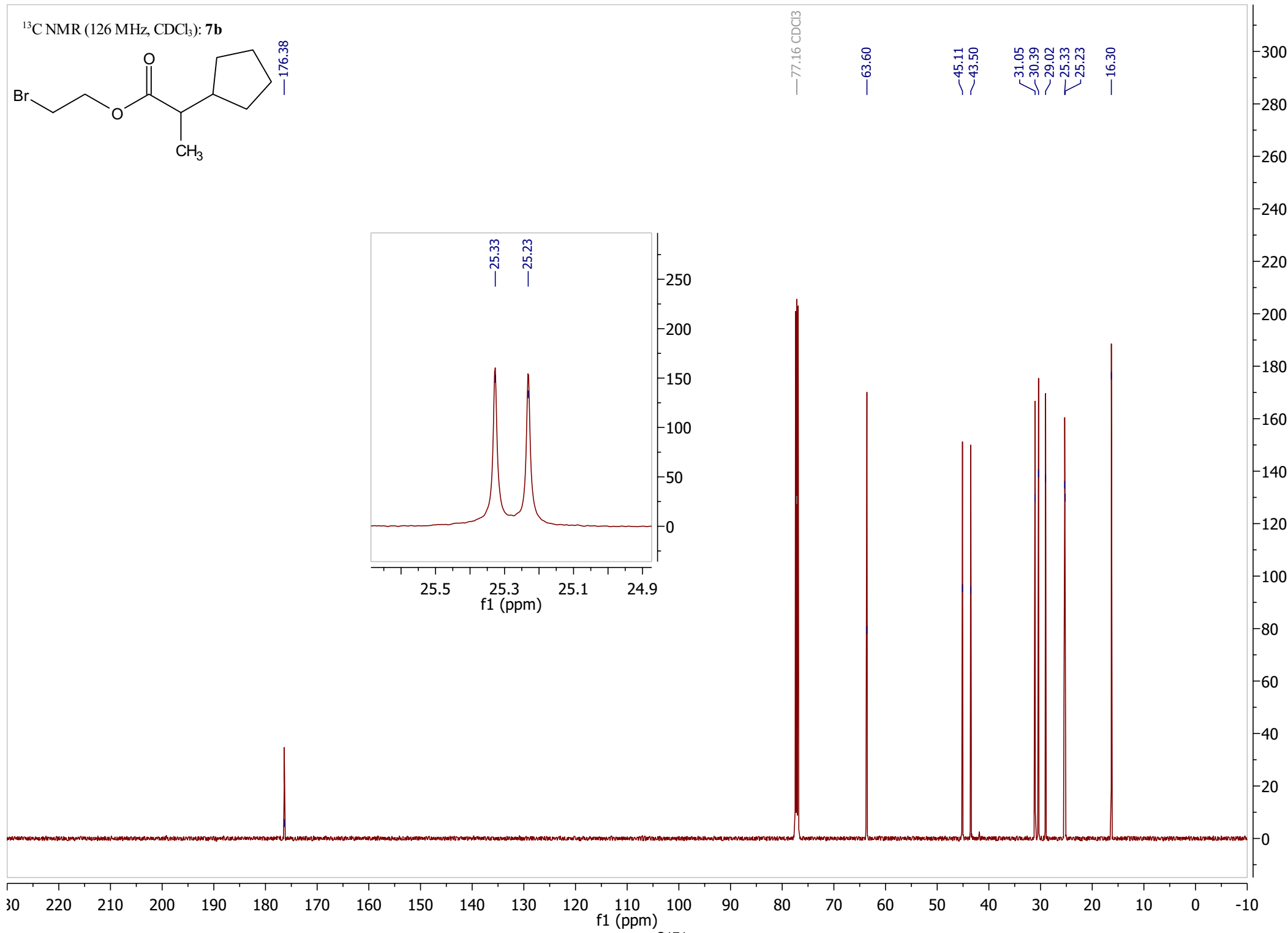
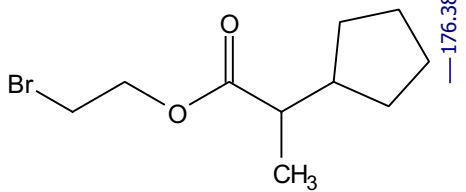


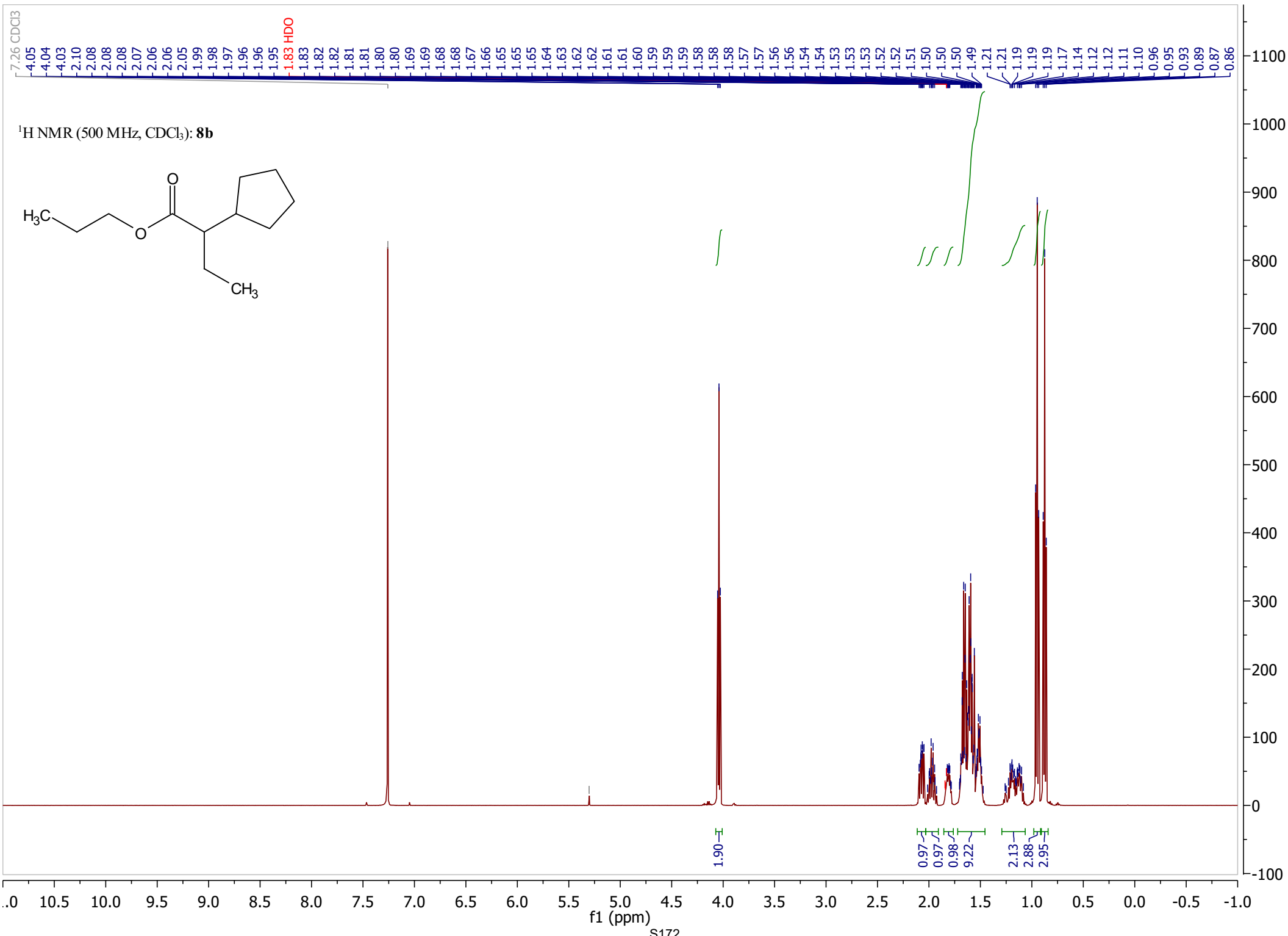
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **6b**



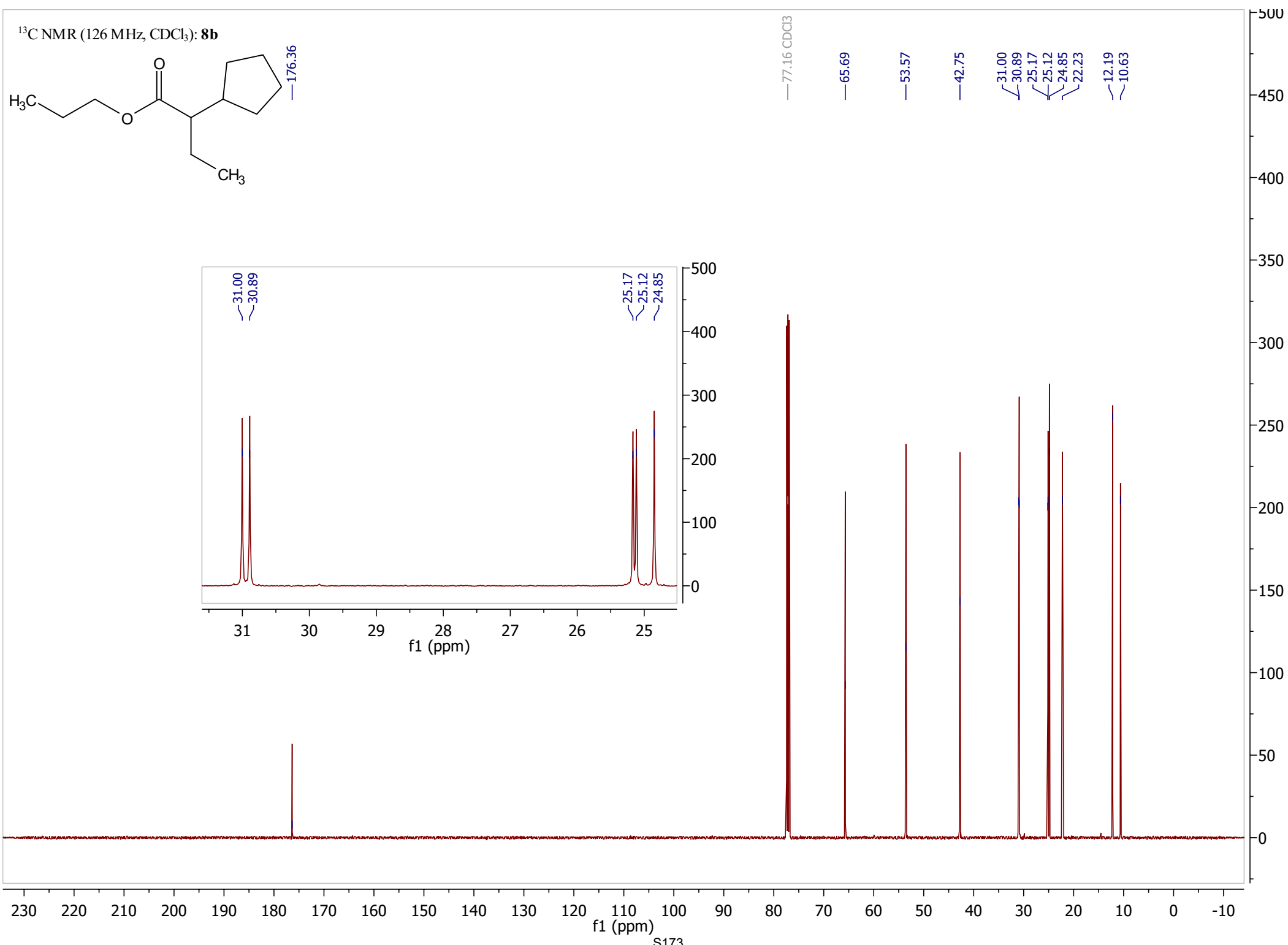
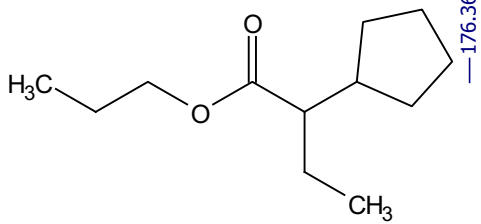


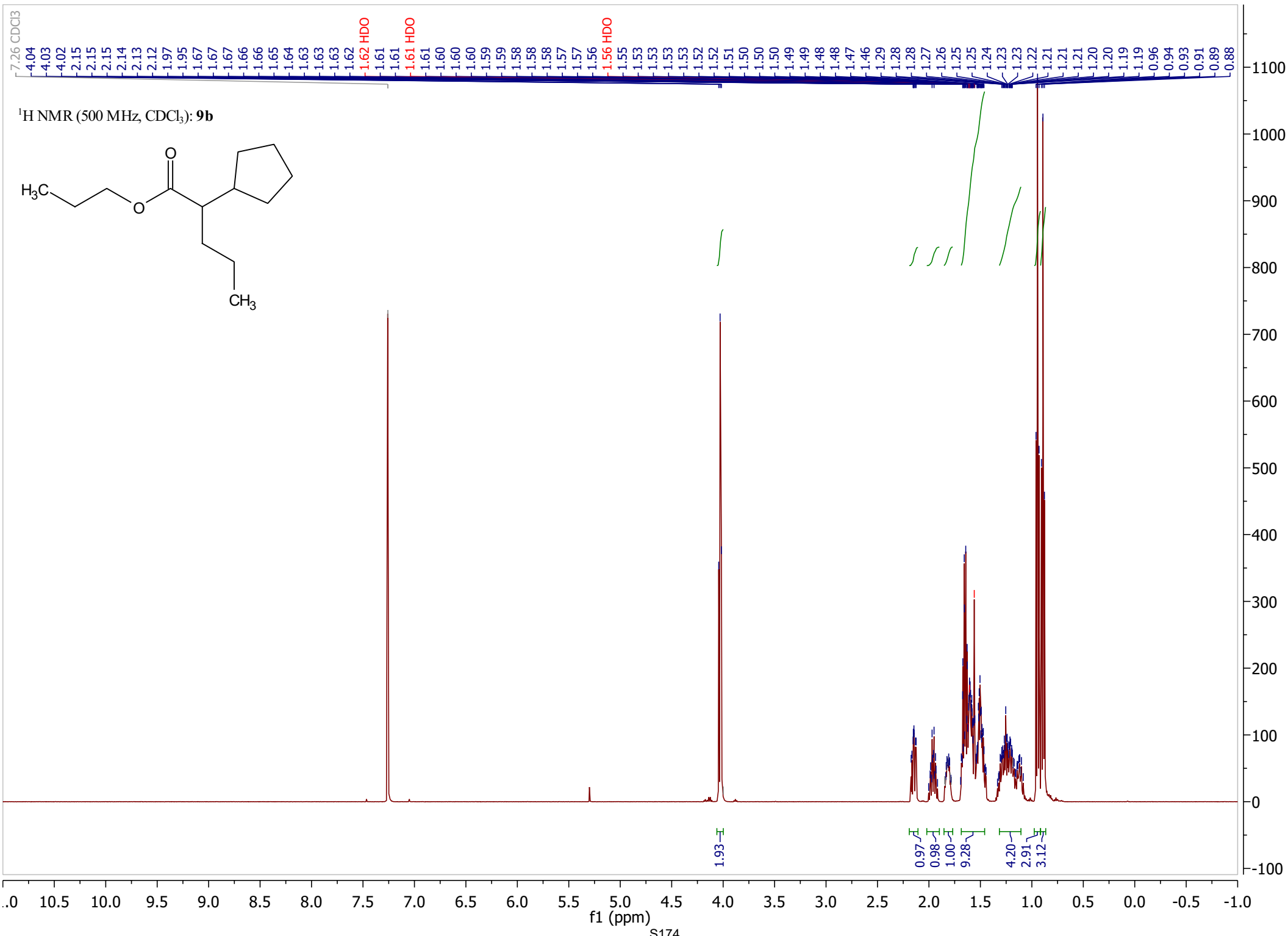
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **7b**

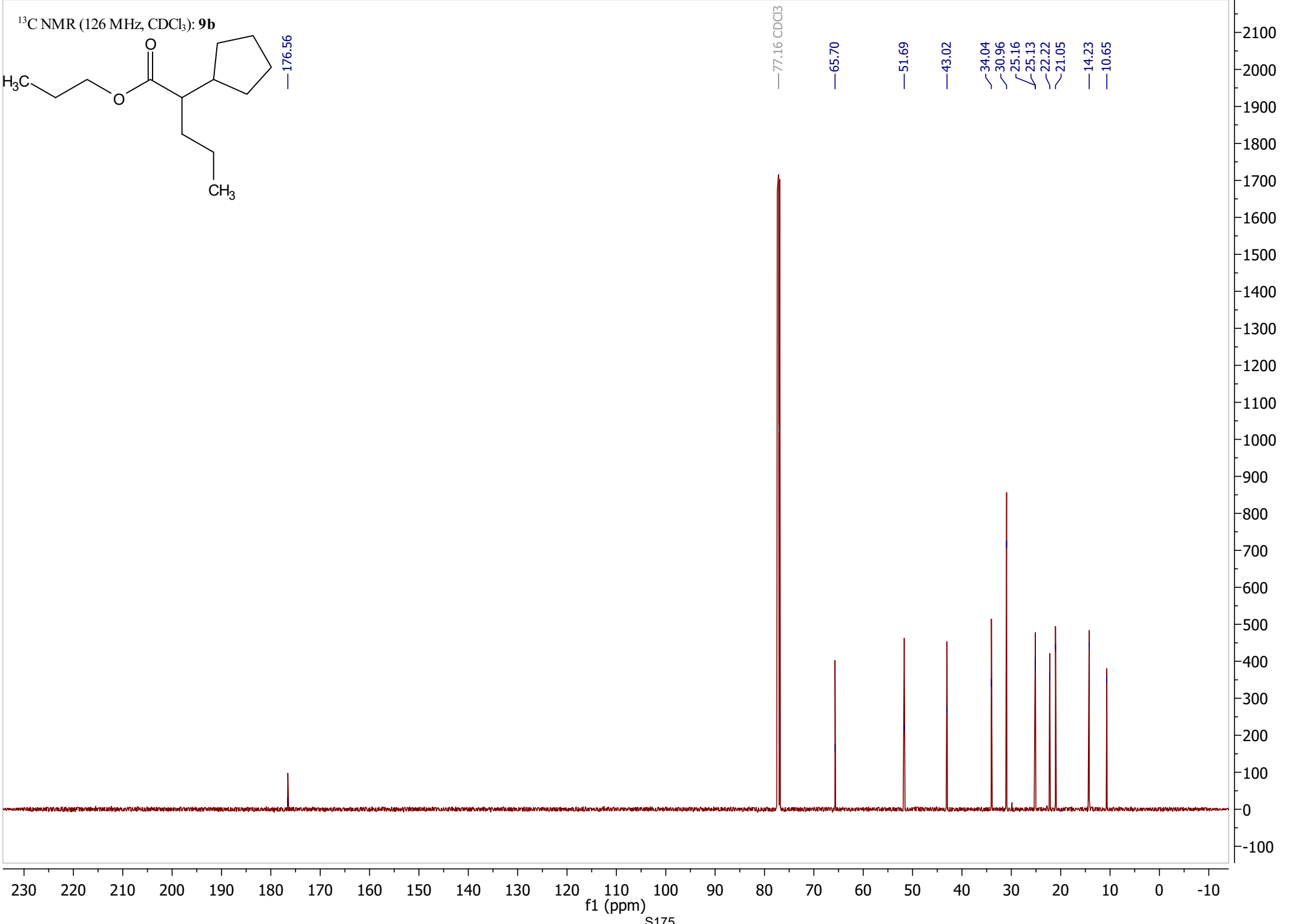




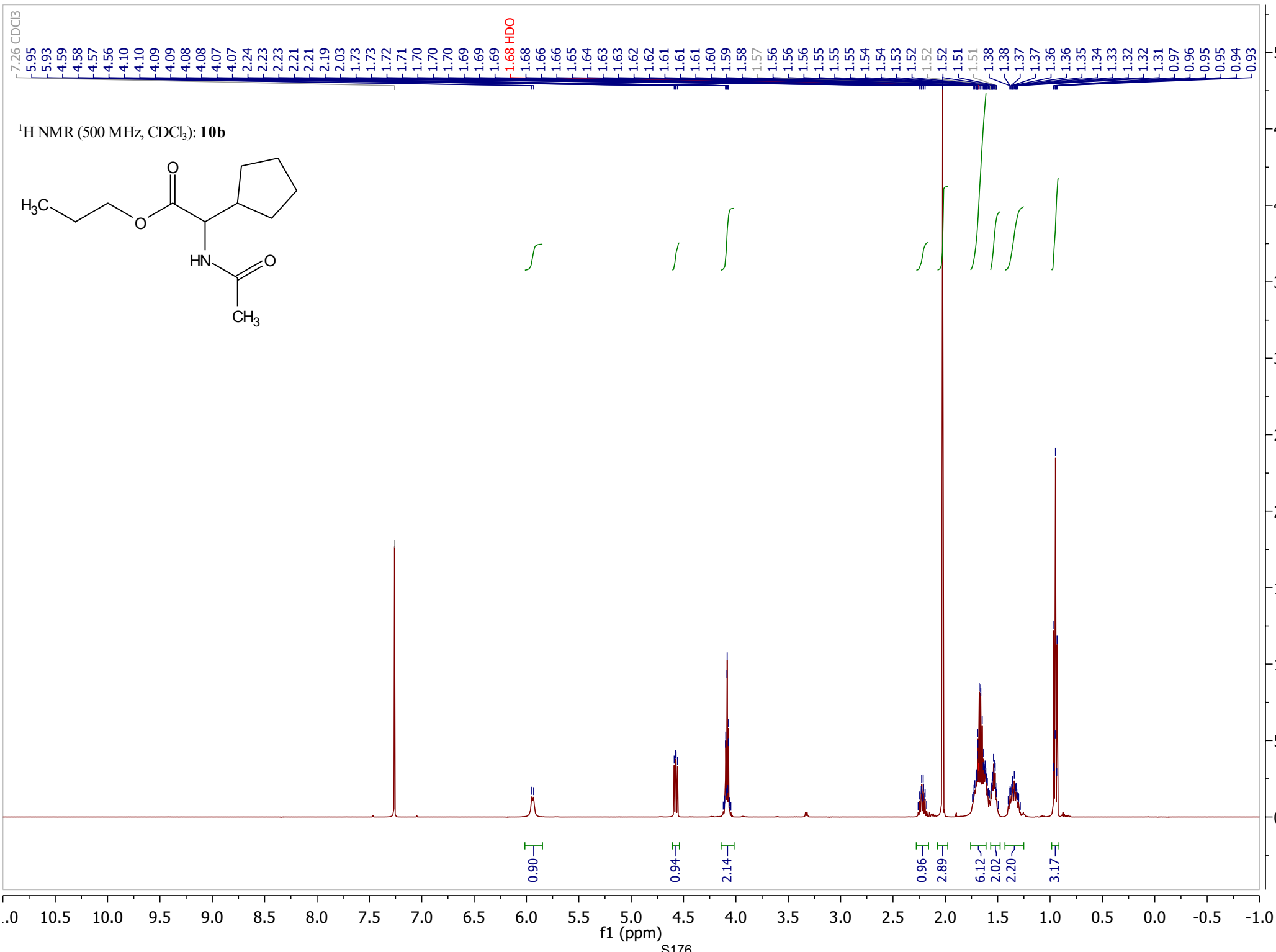
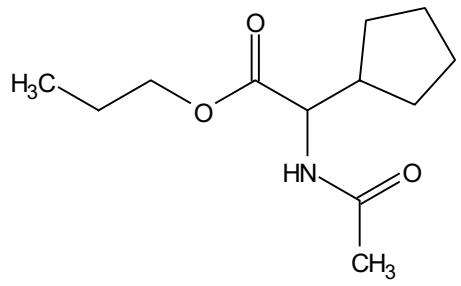
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **8b**



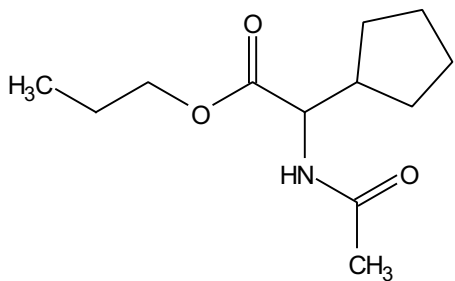




<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **10b**



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **10b**



—172.88  
—169.98

—77.16 CDCl<sub>3</sub>

—67.01

—55.22

—42.97

—29.07

—28.49

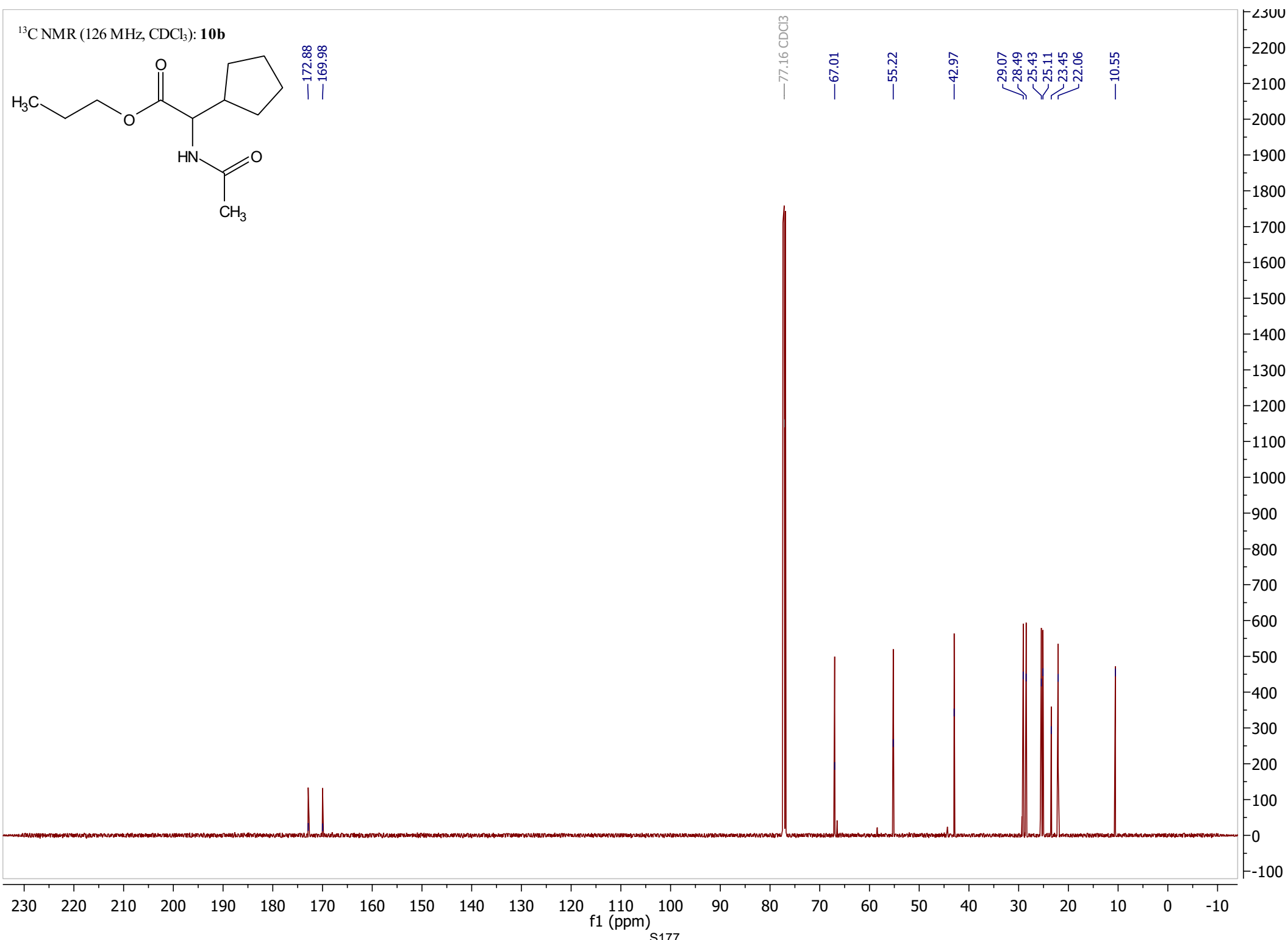
—25.43

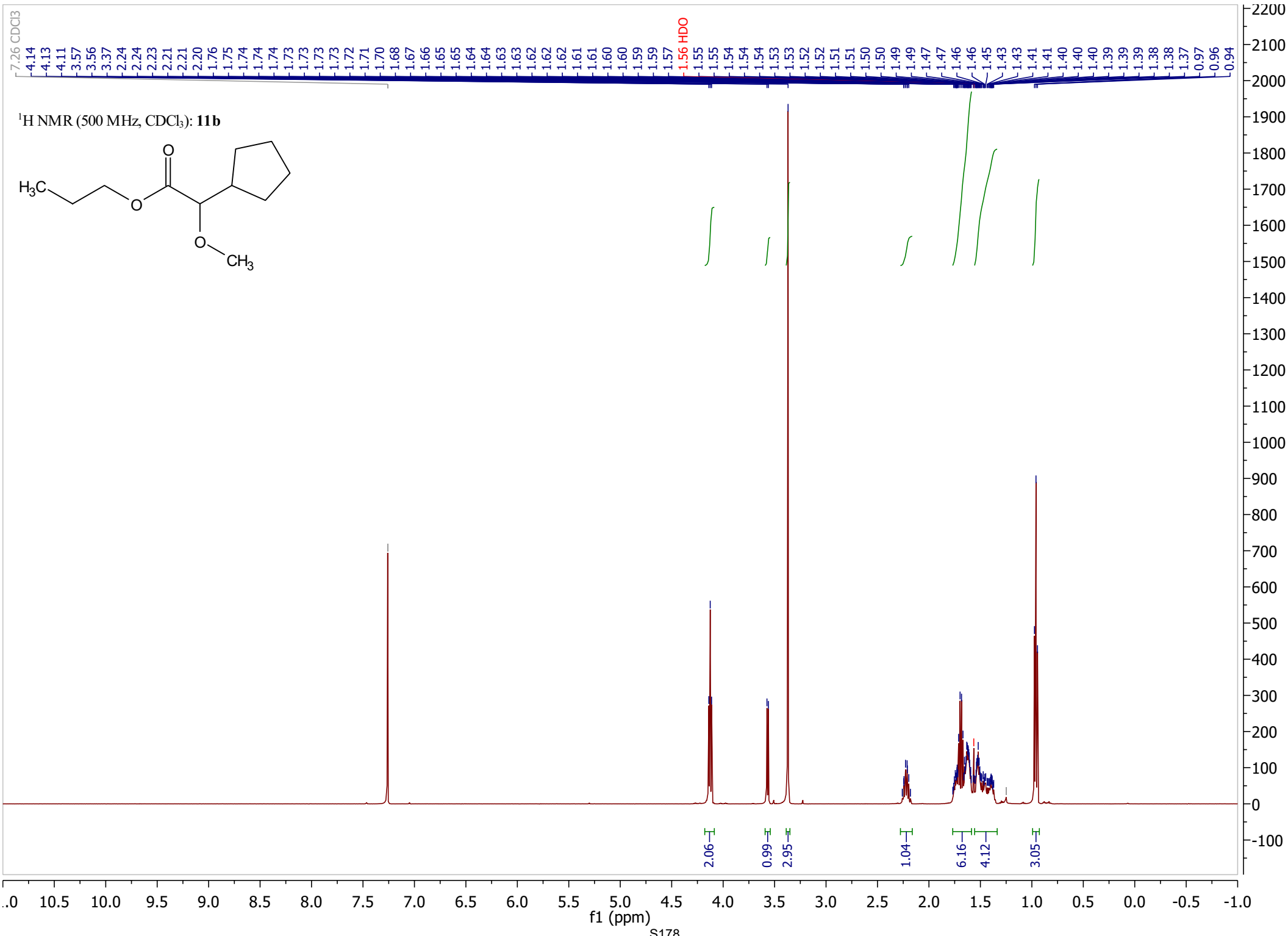
—25.11

—23.45

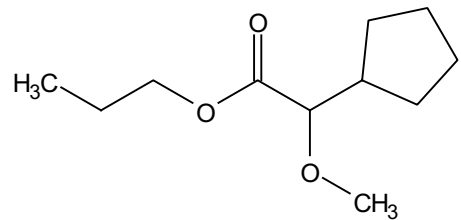
—22.06

—10.55





<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **11b**



—172.93

—84.62

—77.16 CDCl<sub>3</sub>

—66.38

—58.39

—42.67

—28.61

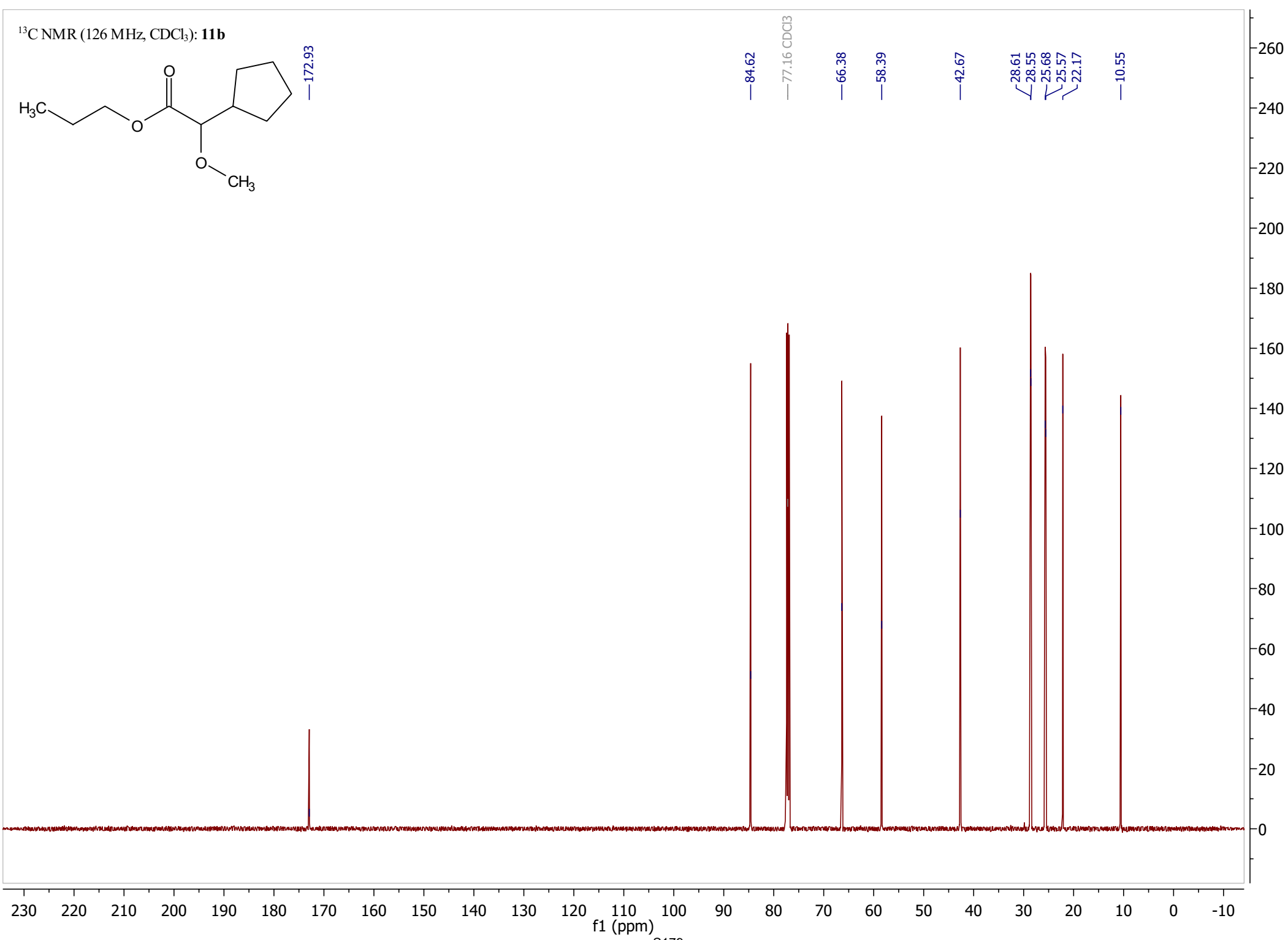
—28.55

—25.68

—25.57

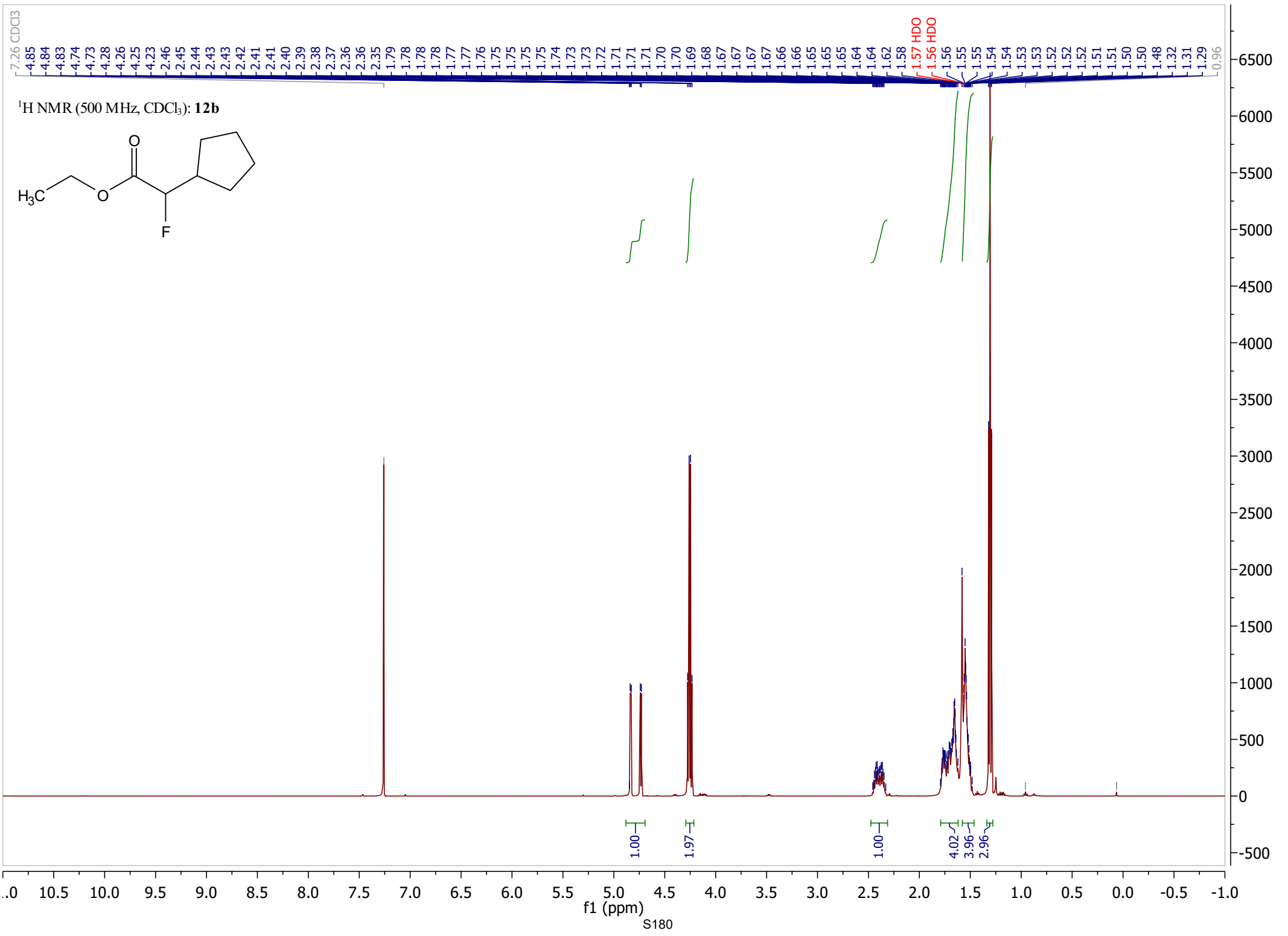
—22.17

—10.55

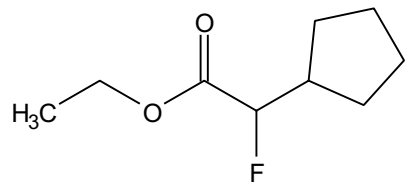


f1 (ppm)

S179



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **12b**



170.05  
169.85

92.16  
90.68

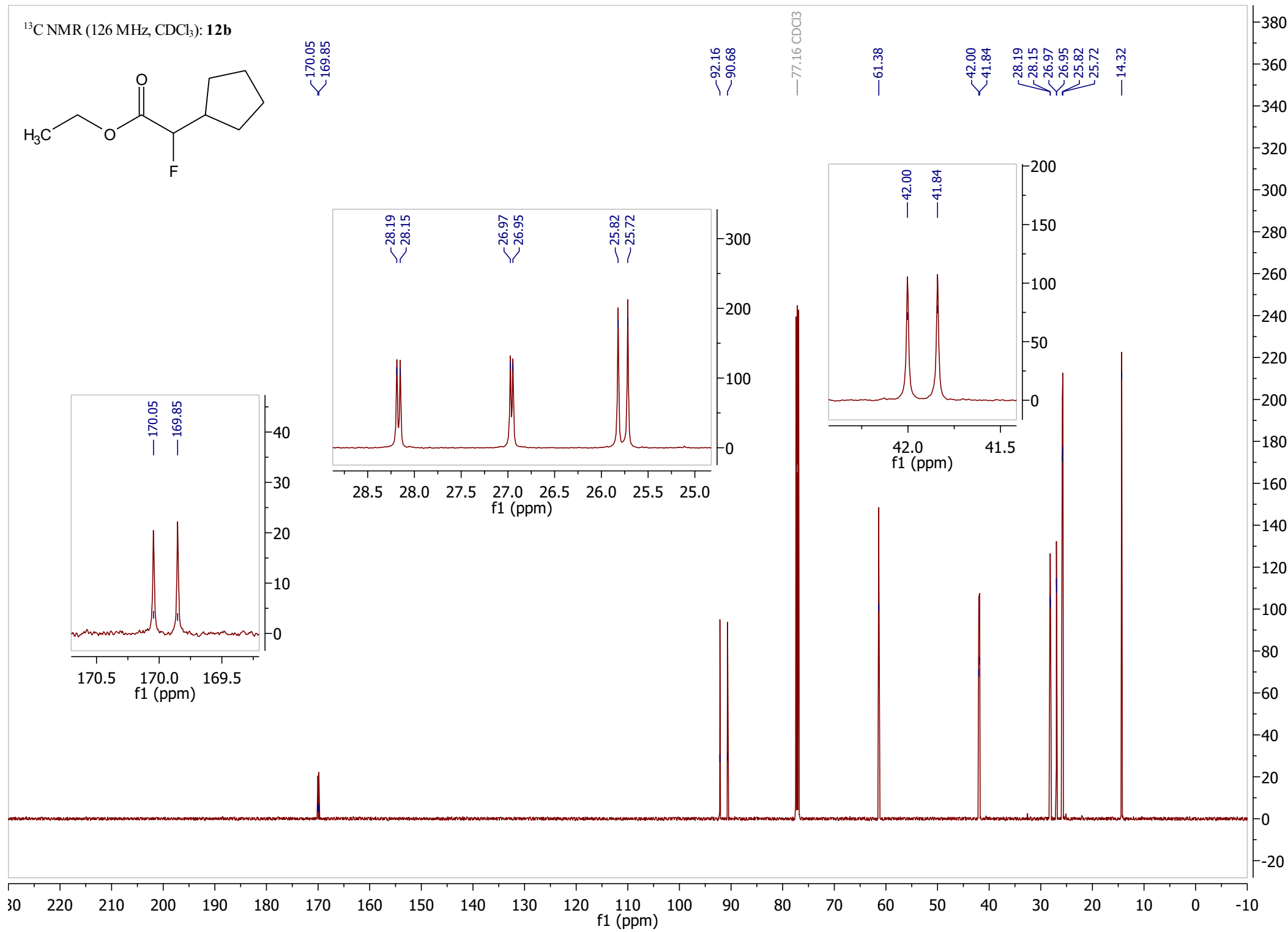
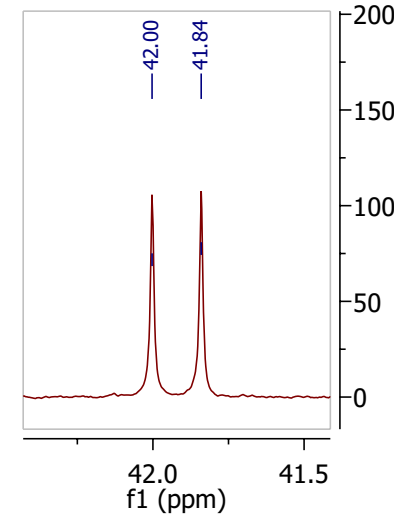
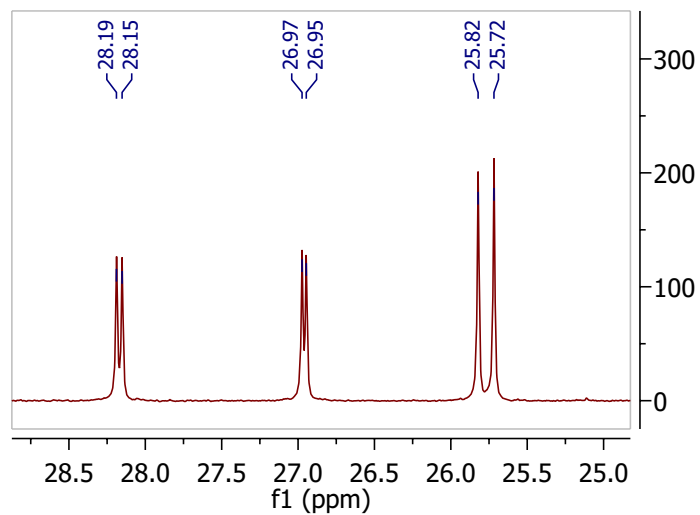
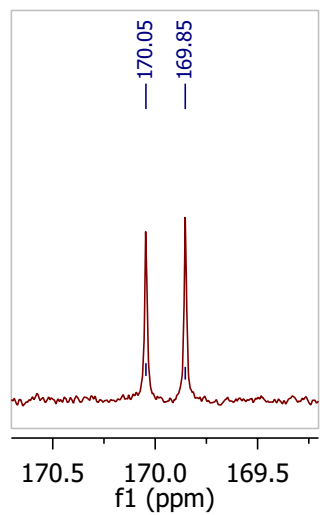
77.16 CDCl<sub>3</sub>

61.38

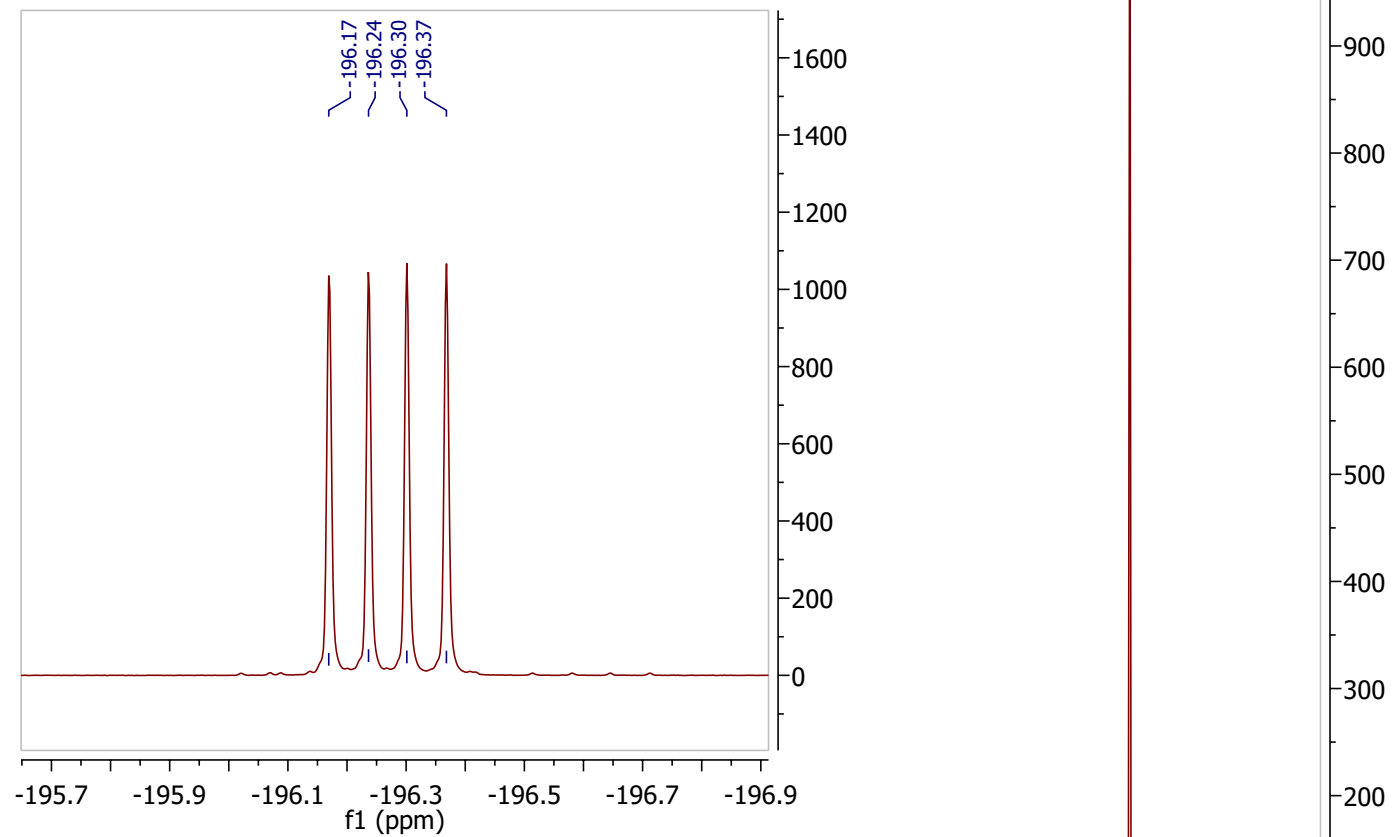
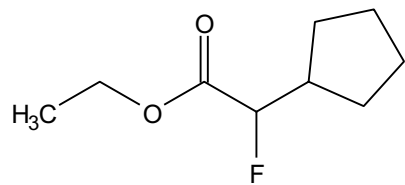
42.00  
41.84

28.19  
28.15  
26.97  
26.95  
25.82  
25.72

14.32



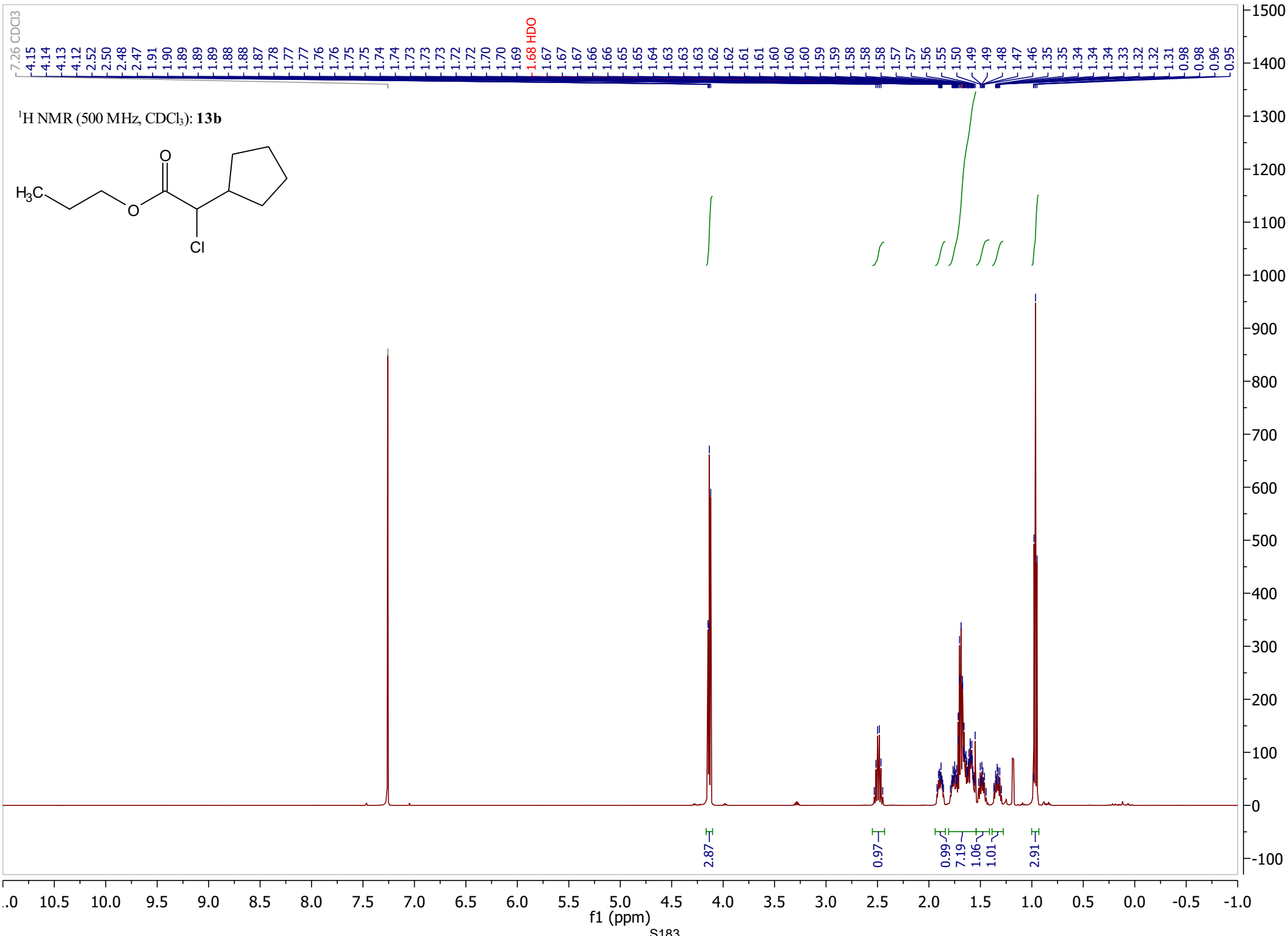
<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): **12b**



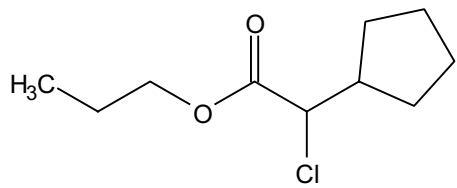
-196.17  
-196.24  
-196.30  
-196.37

-195.7 -195.9 -196.1 -196.3 -196.5 -196.7 -196.9  
f1 (ppm)

10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210  
f1 (ppm)



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **13b**



—169.90

—77.16 CDCl<sub>3</sub>

—67.46

—62.12

—44.00

—29.99

—29.85

—25.89

—25.39

—22.01

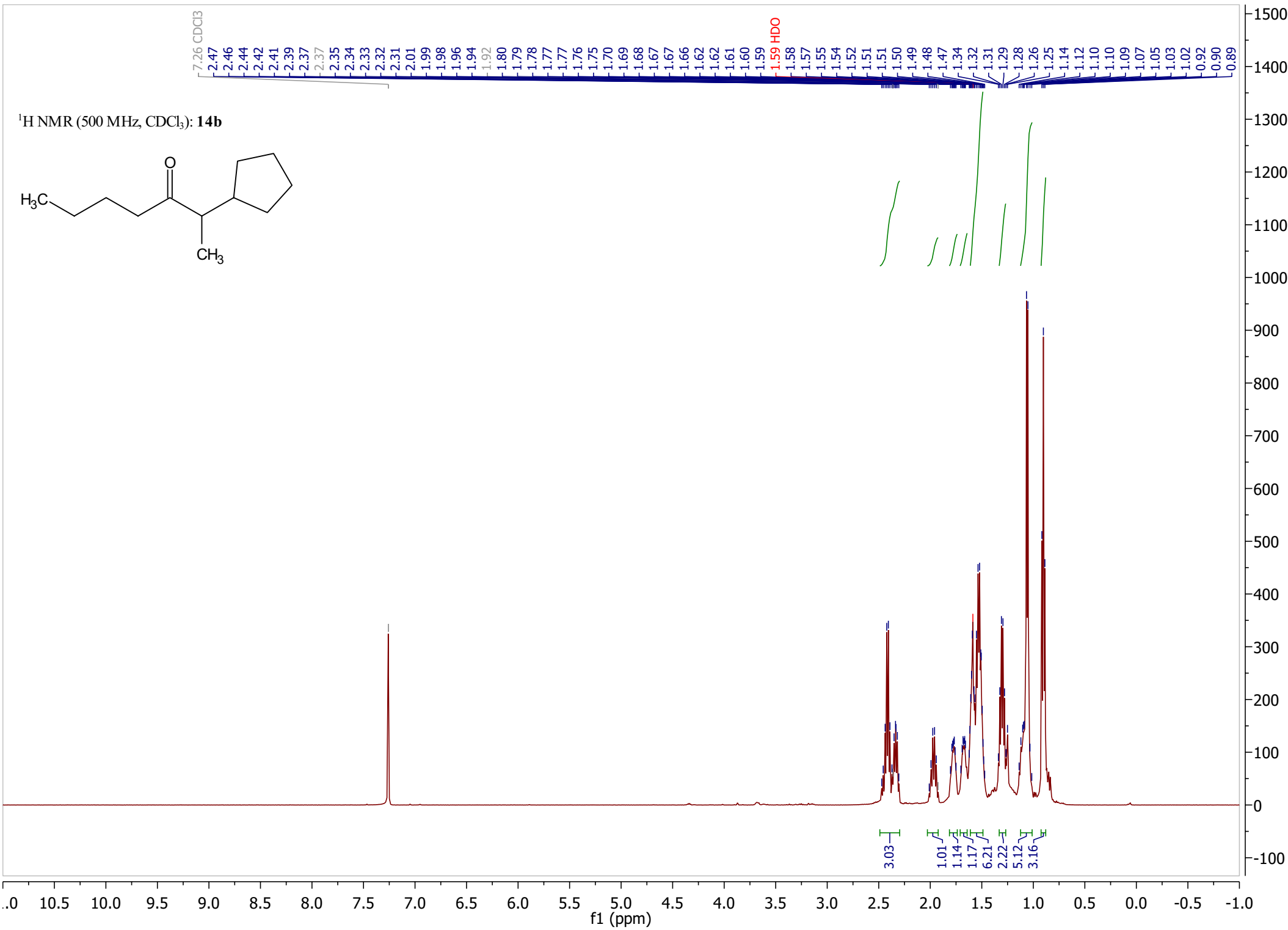
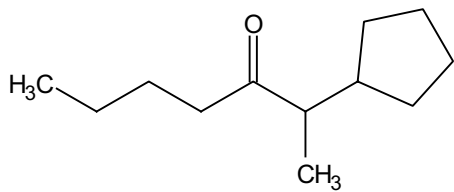
—10.45

30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

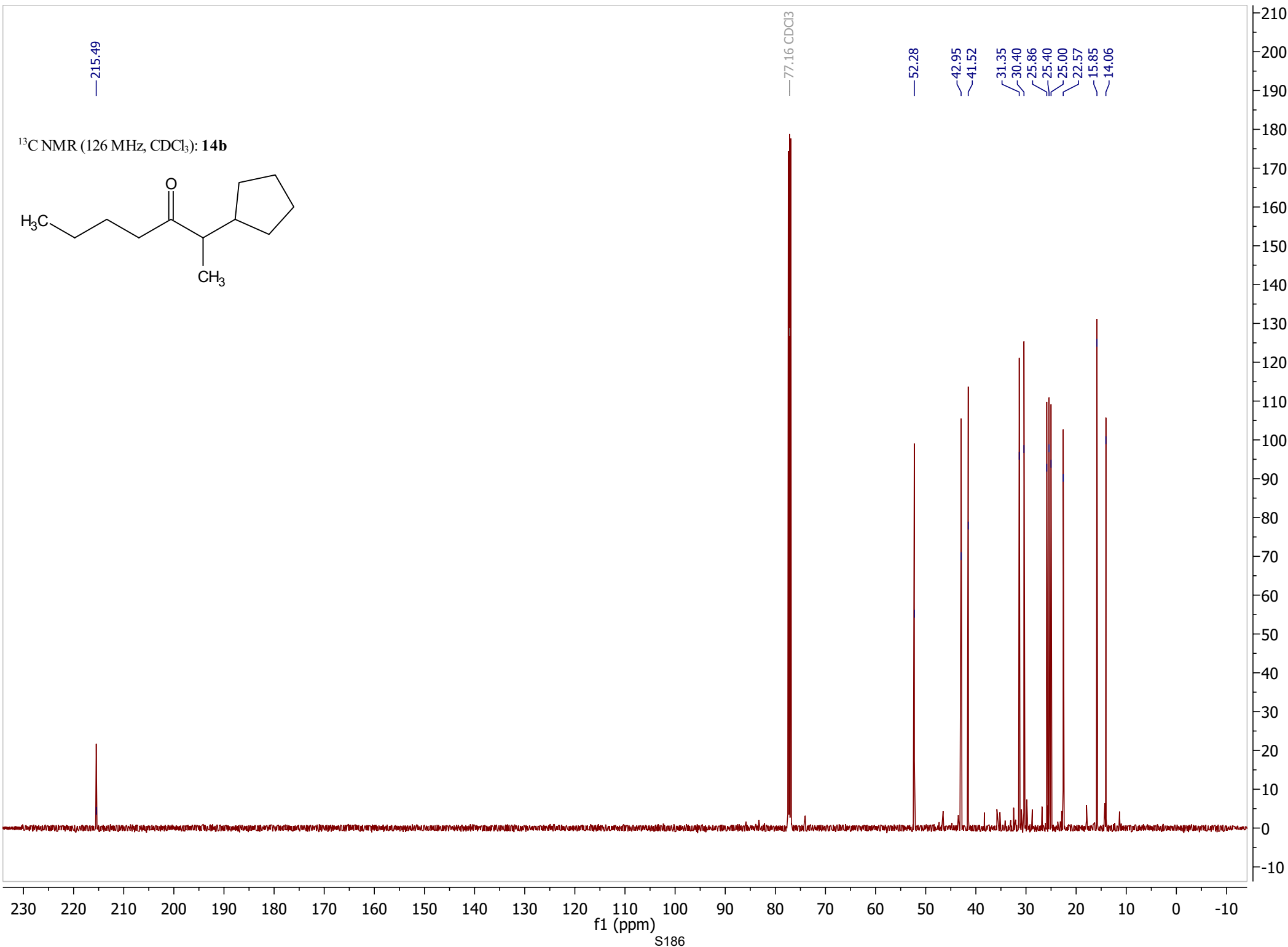
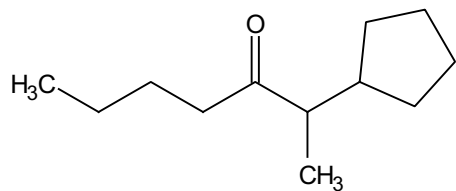
f1 (ppm)

S184

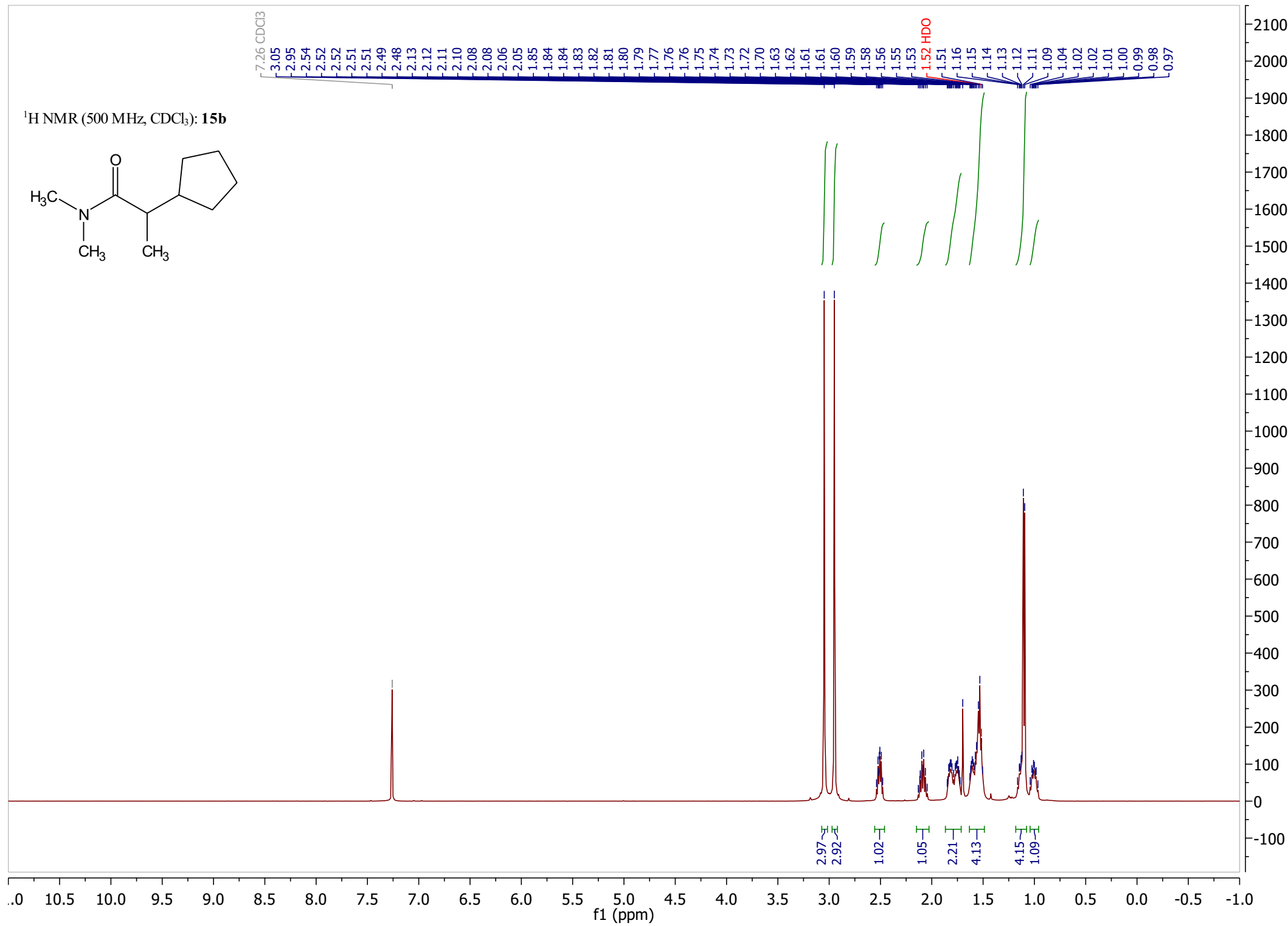
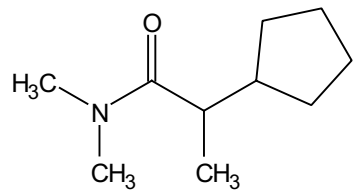
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **14b**



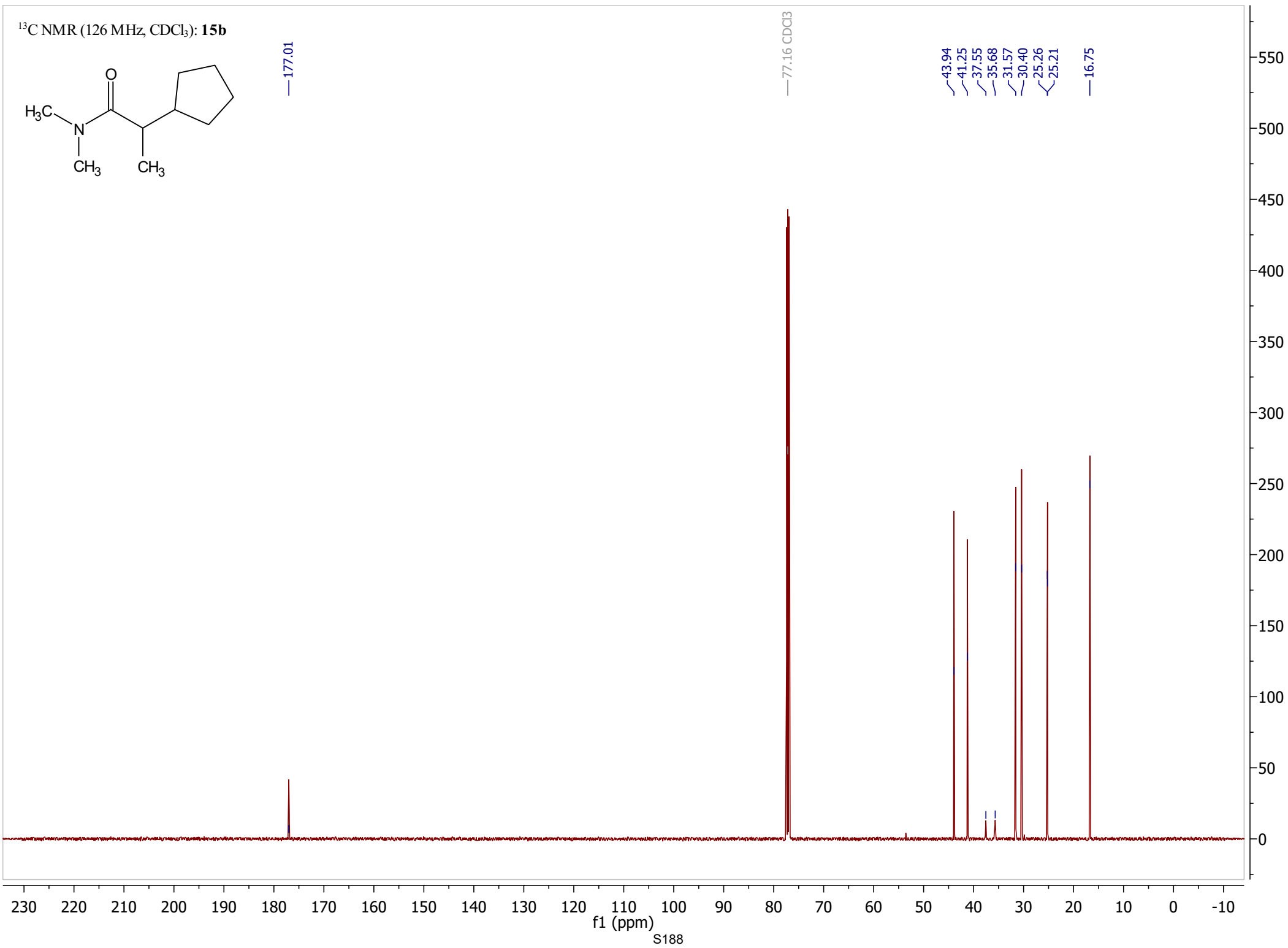
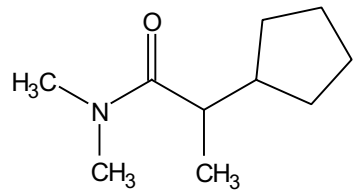
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **14b**



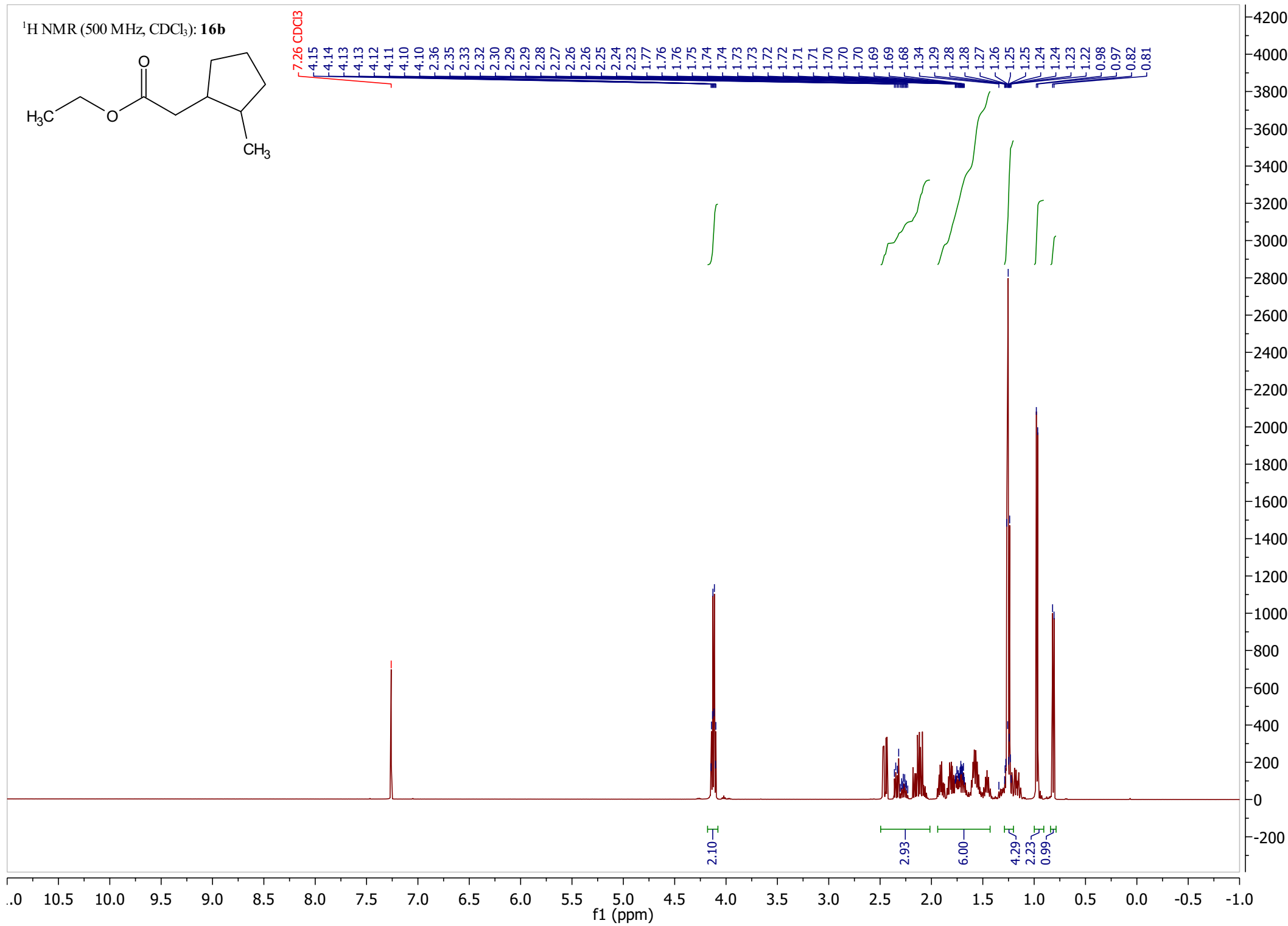
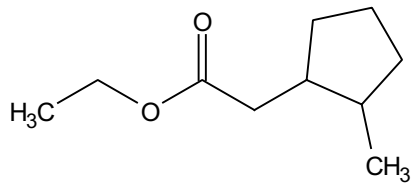
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **15b**



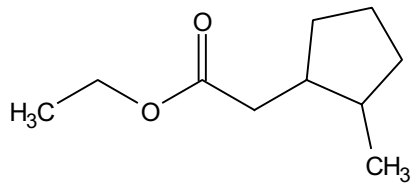
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **15b**



<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **16b**



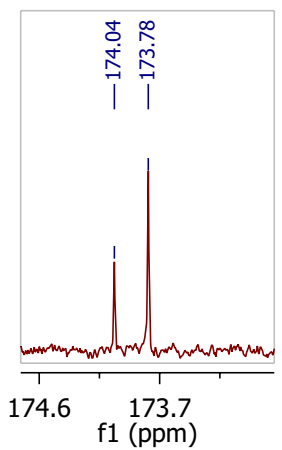
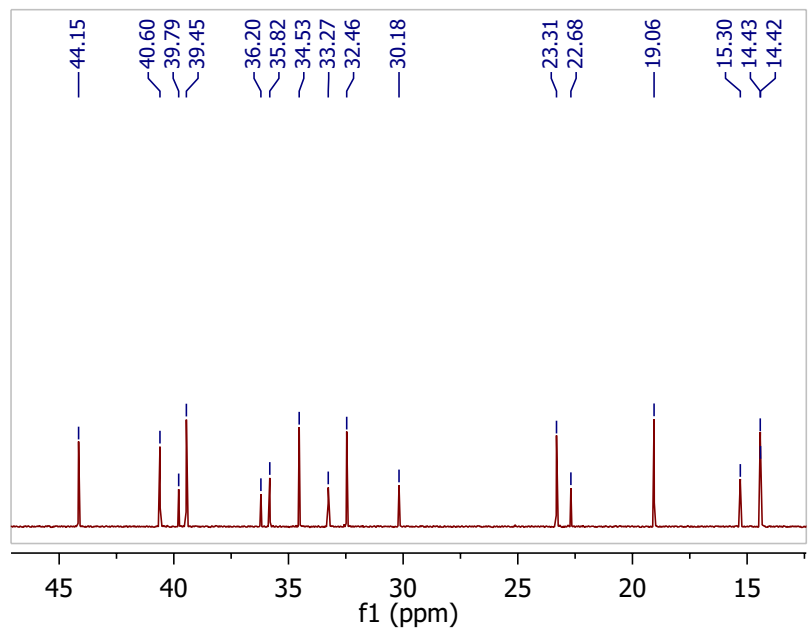
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **16b**



174.04  
173.78

77.16 CDCl<sub>3</sub>

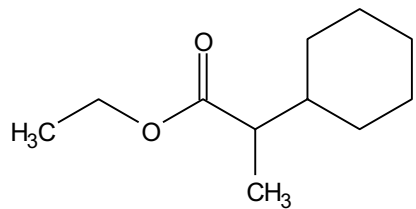
60.25  
44.15  
40.60  
39.79  
39.45  
36.20  
35.82  
34.53  
33.27  
32.46  
30.18  
23.31  
22.68  
19.06  
15.30  
14.43  
14.42



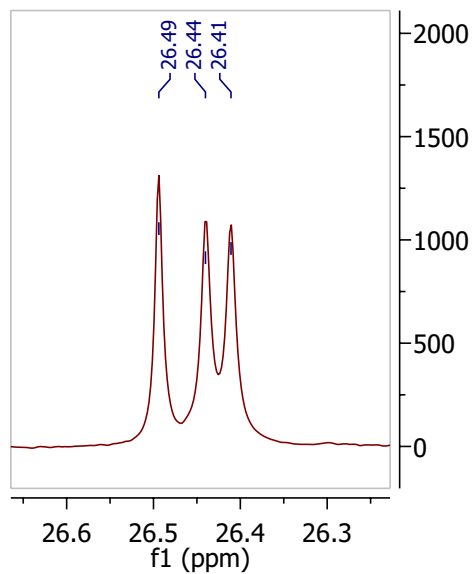
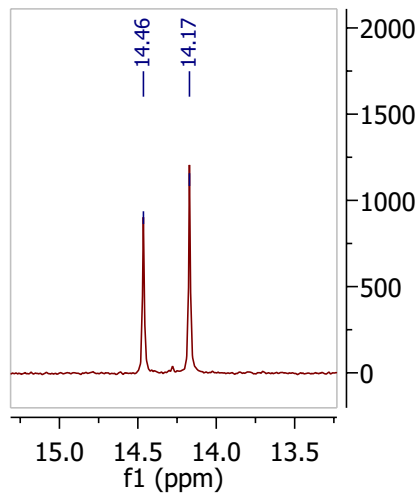
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10  
f1 (ppm)



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **17b**



— 176.76



— 77.16 CDCl<sub>3</sub>

— 60.09

— 45.65

— 40.90

31.31

29.77

26.49

26.44

26.41

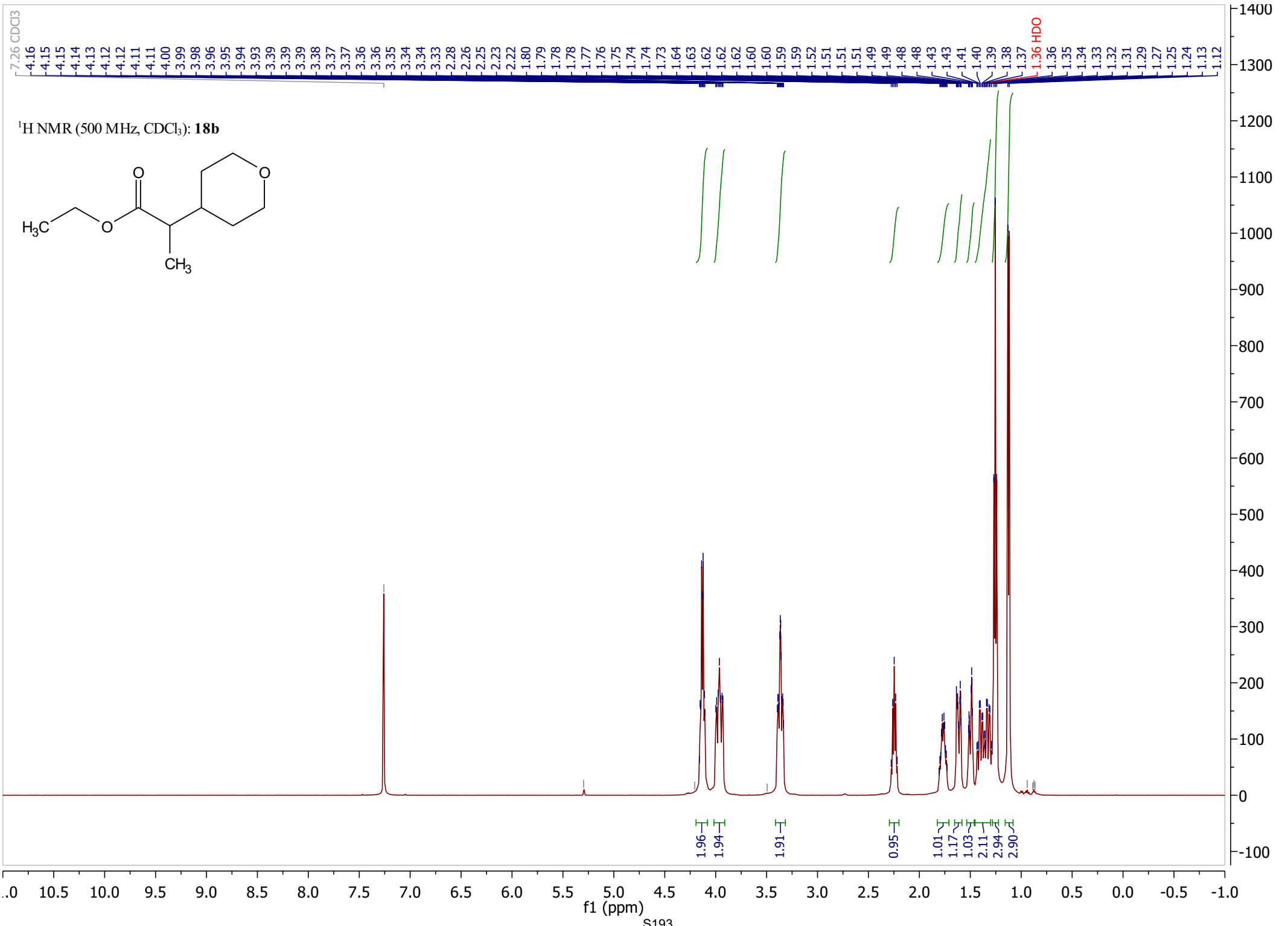
14.46

14.17

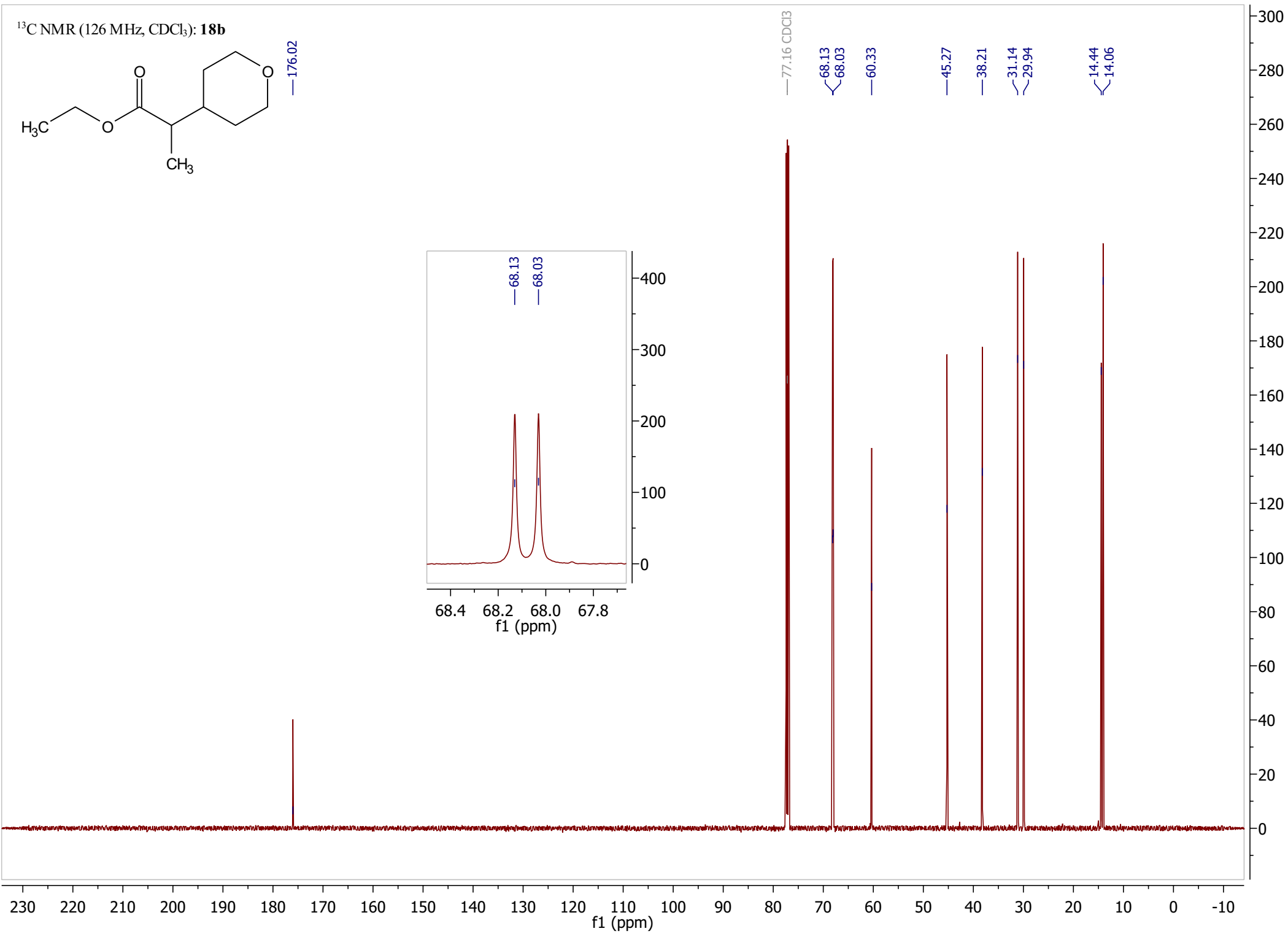
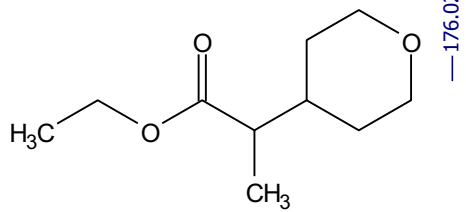
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

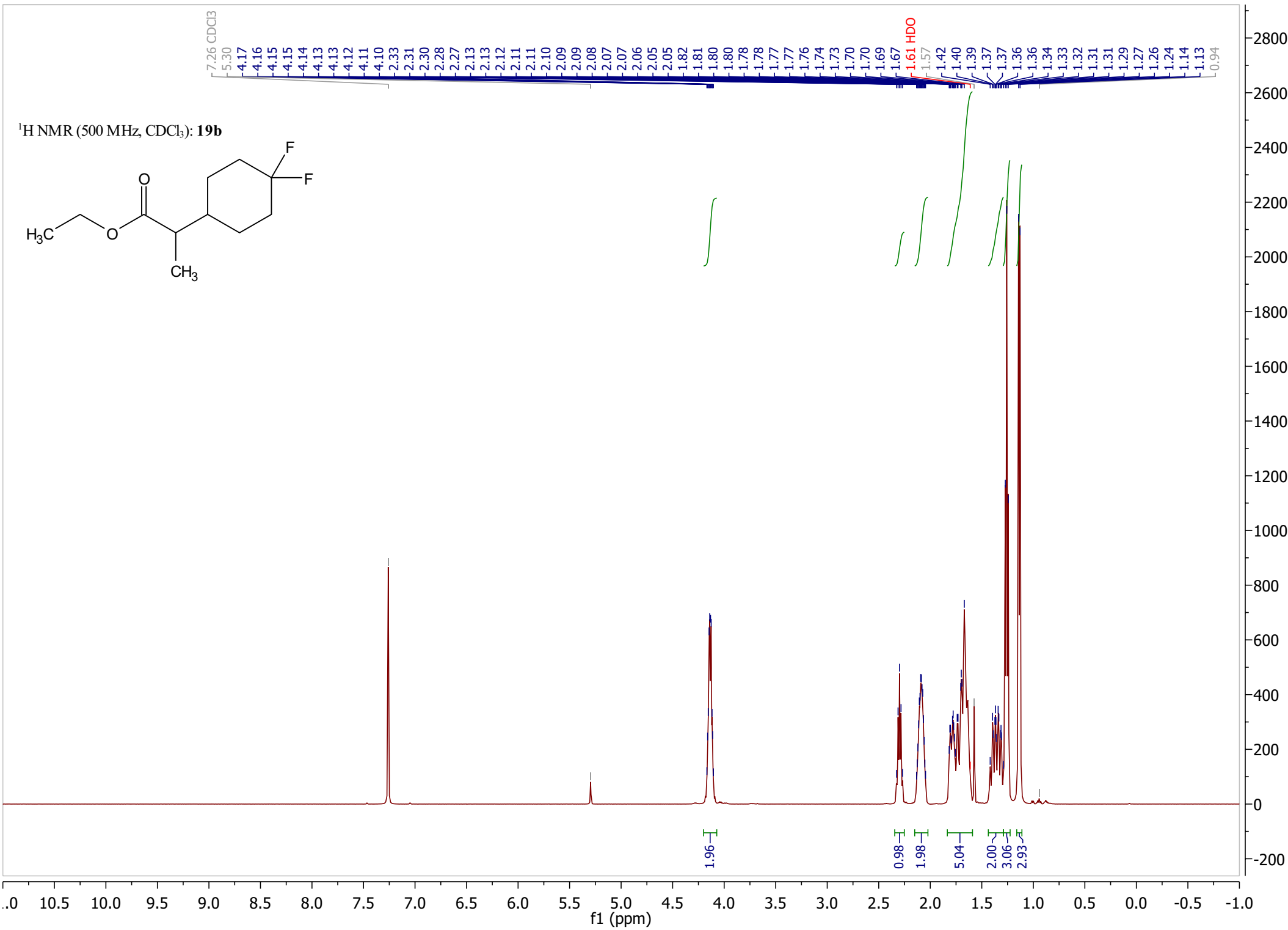
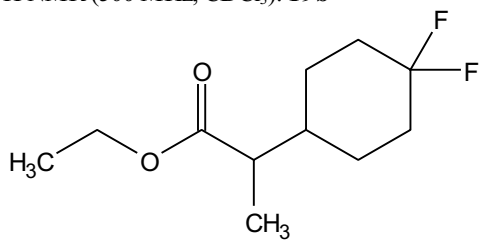
S192



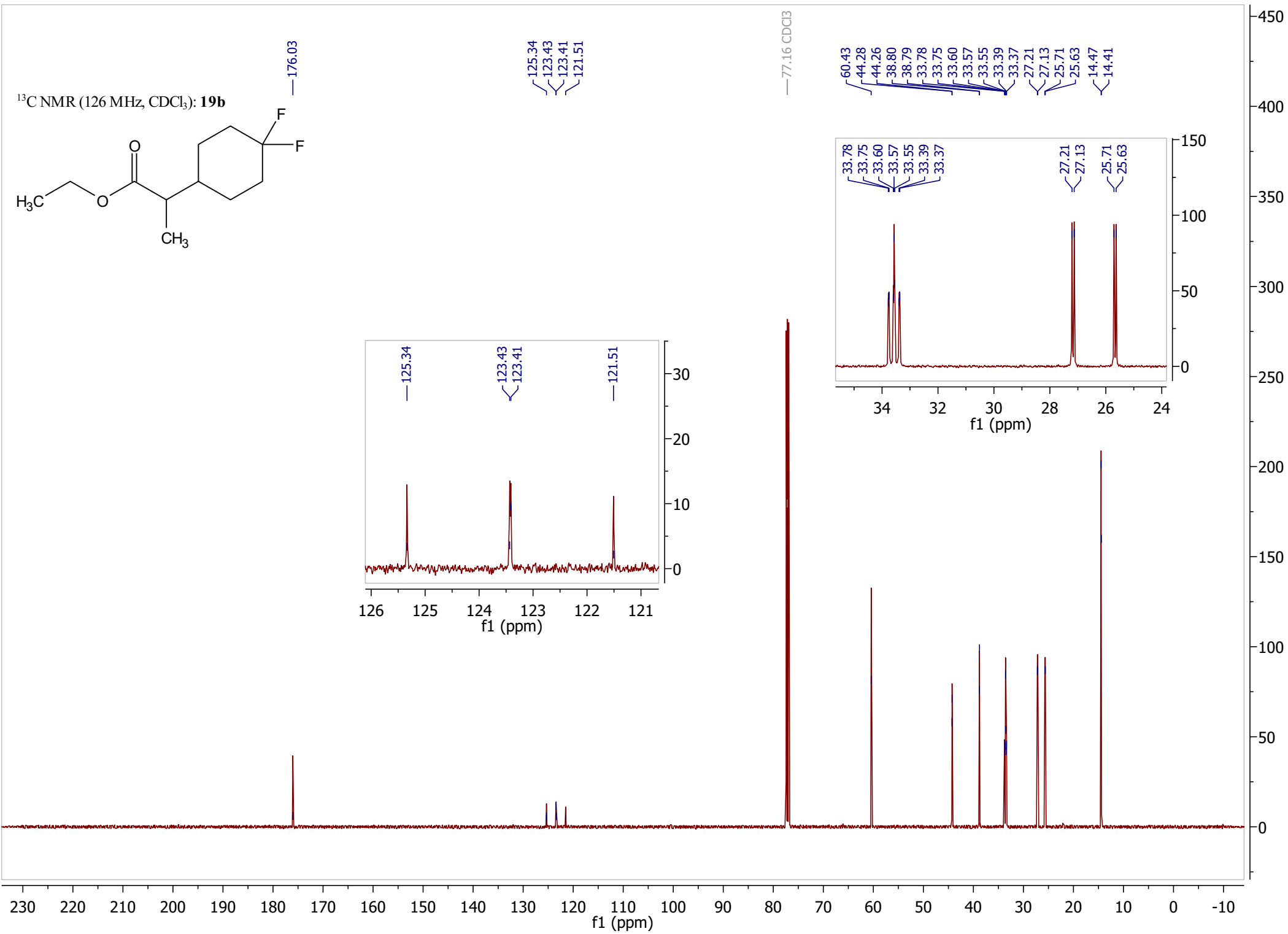
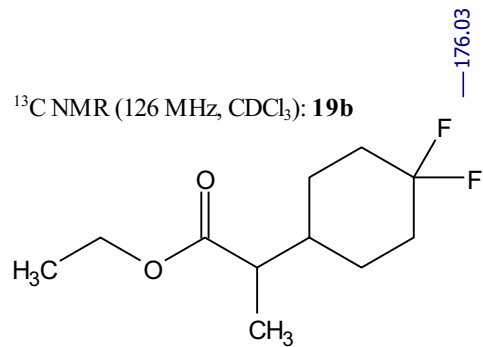
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **18b**



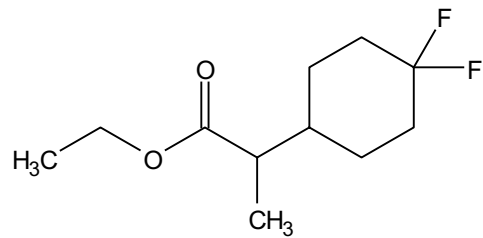
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): **19b**



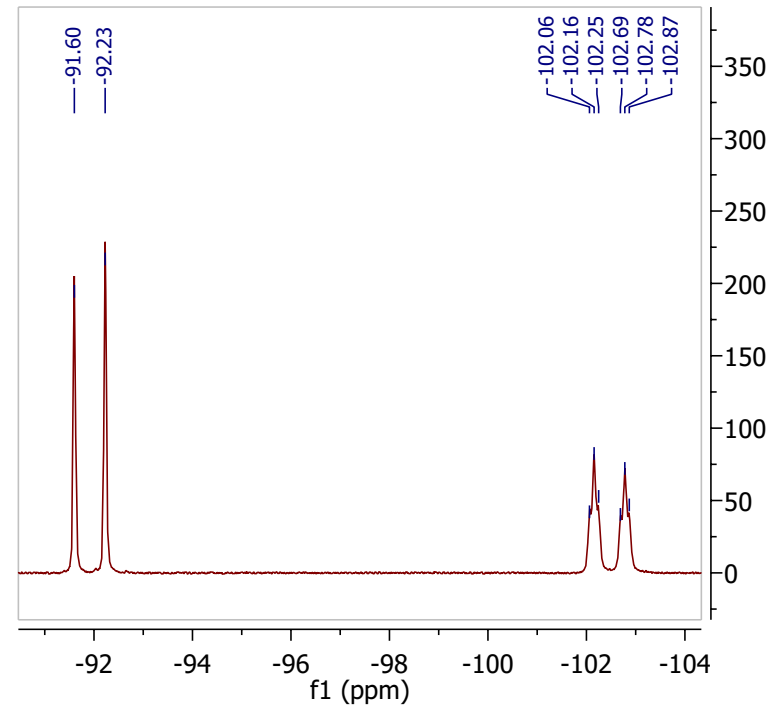
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **19b**



<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): **19b**



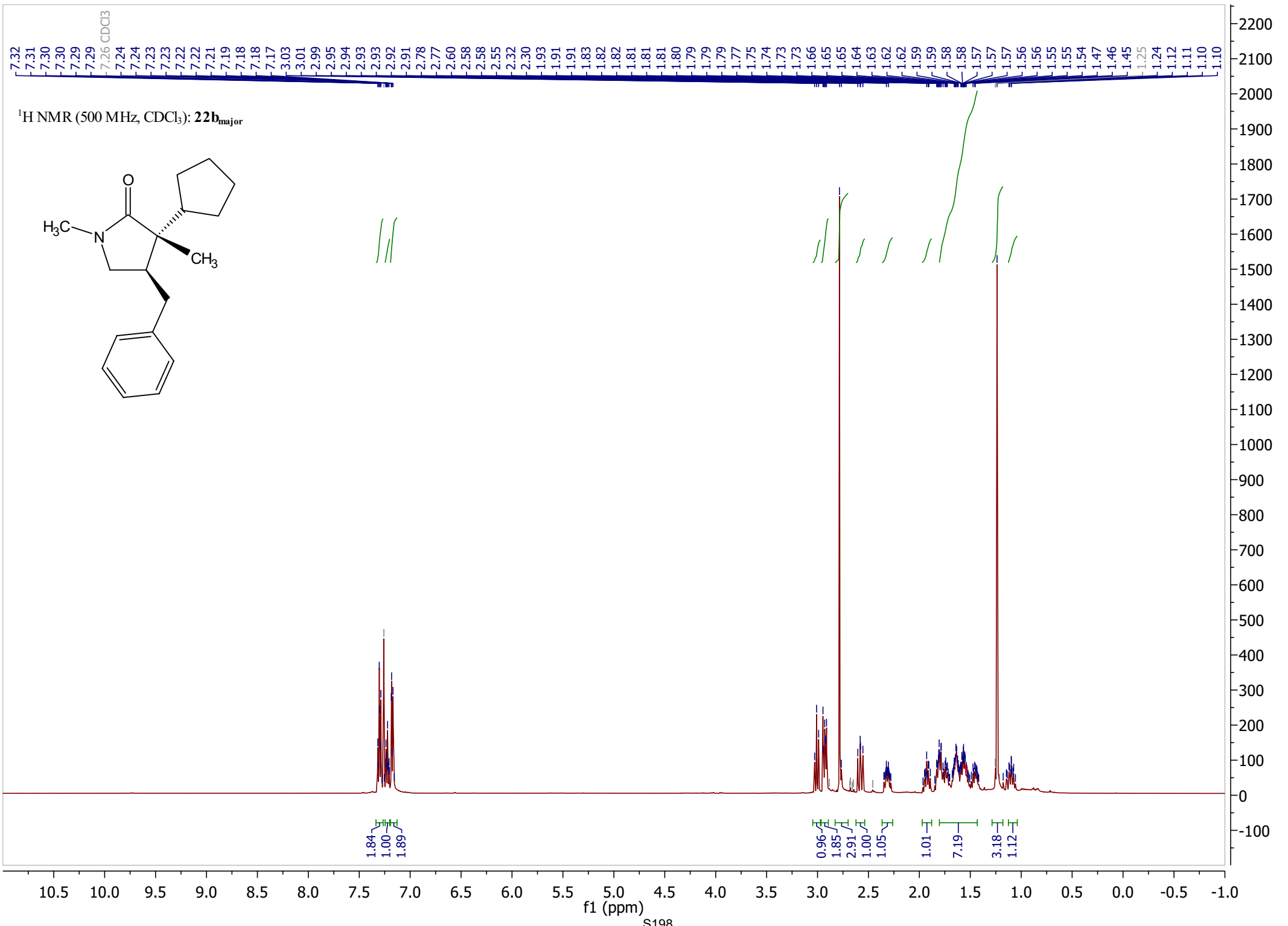
-91.60  
-92.23  
-102.06  
-102.16  
-102.25  
-102.69  
-102.78  
-102.87



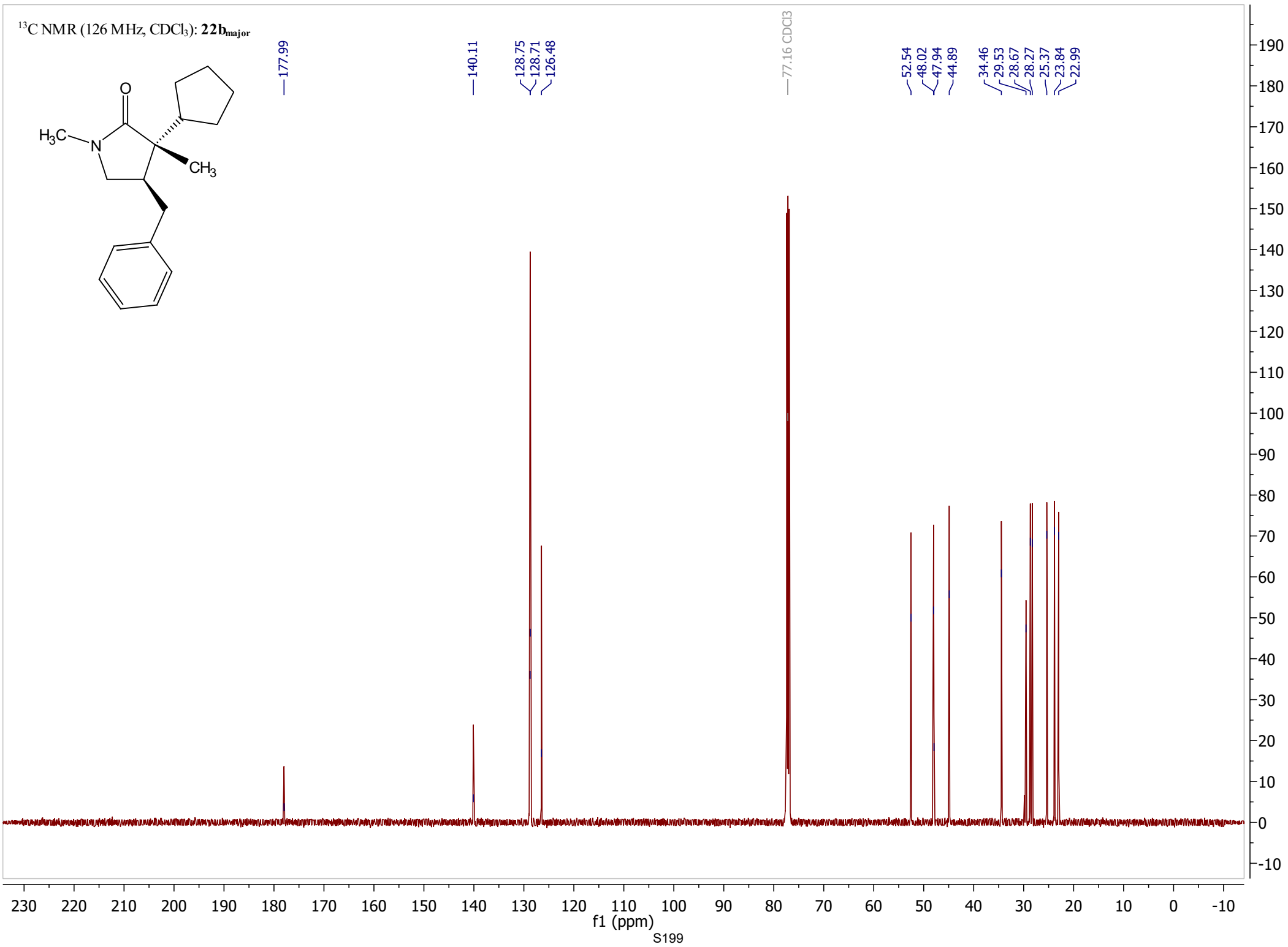
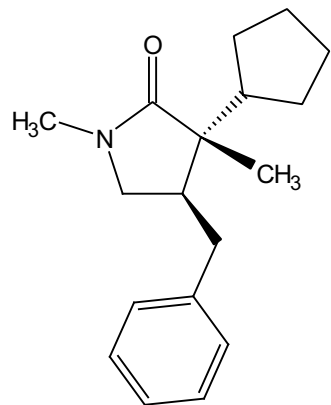
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

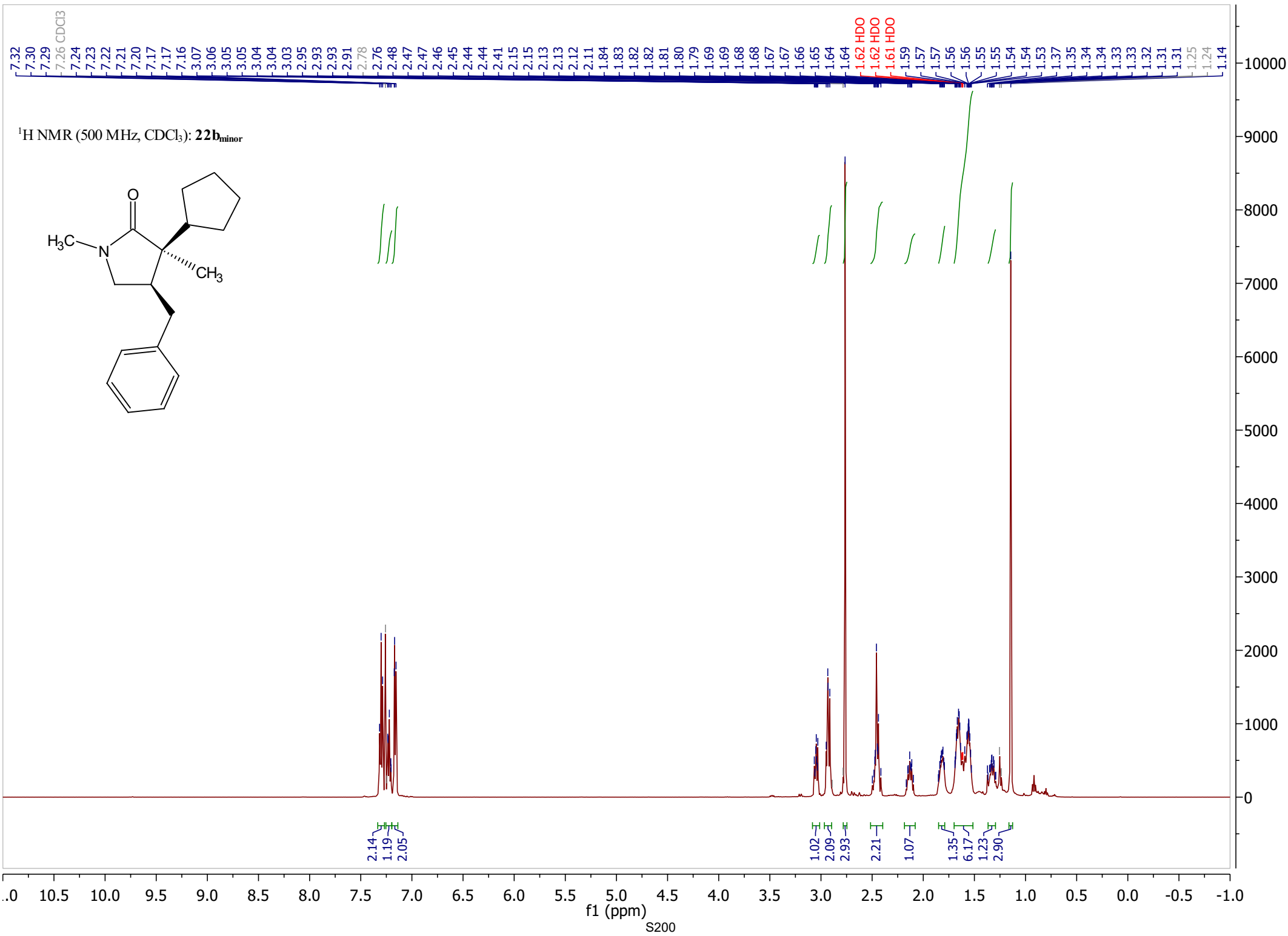
f1 (ppm)

S197

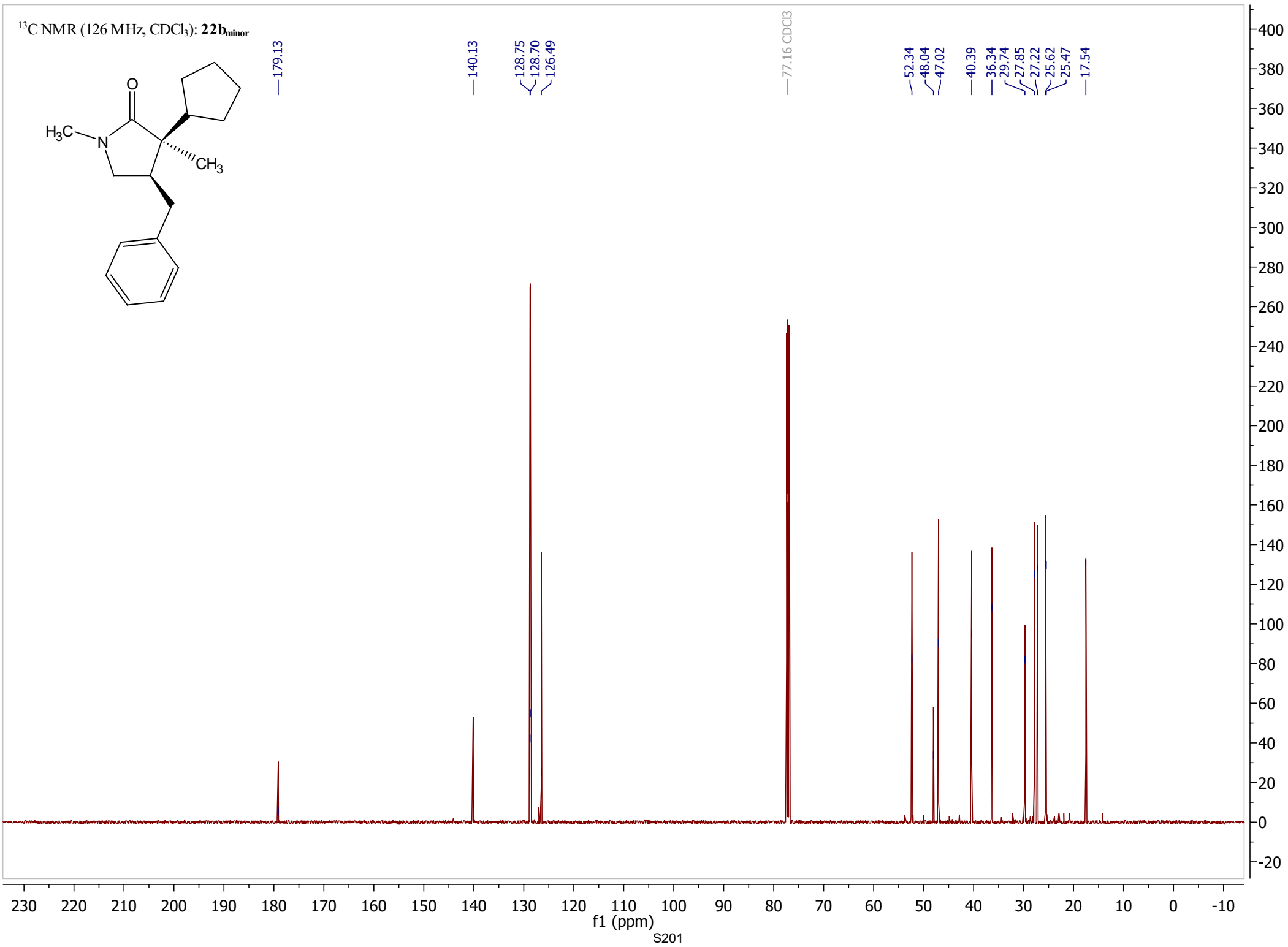
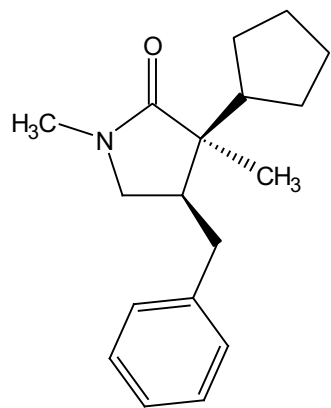


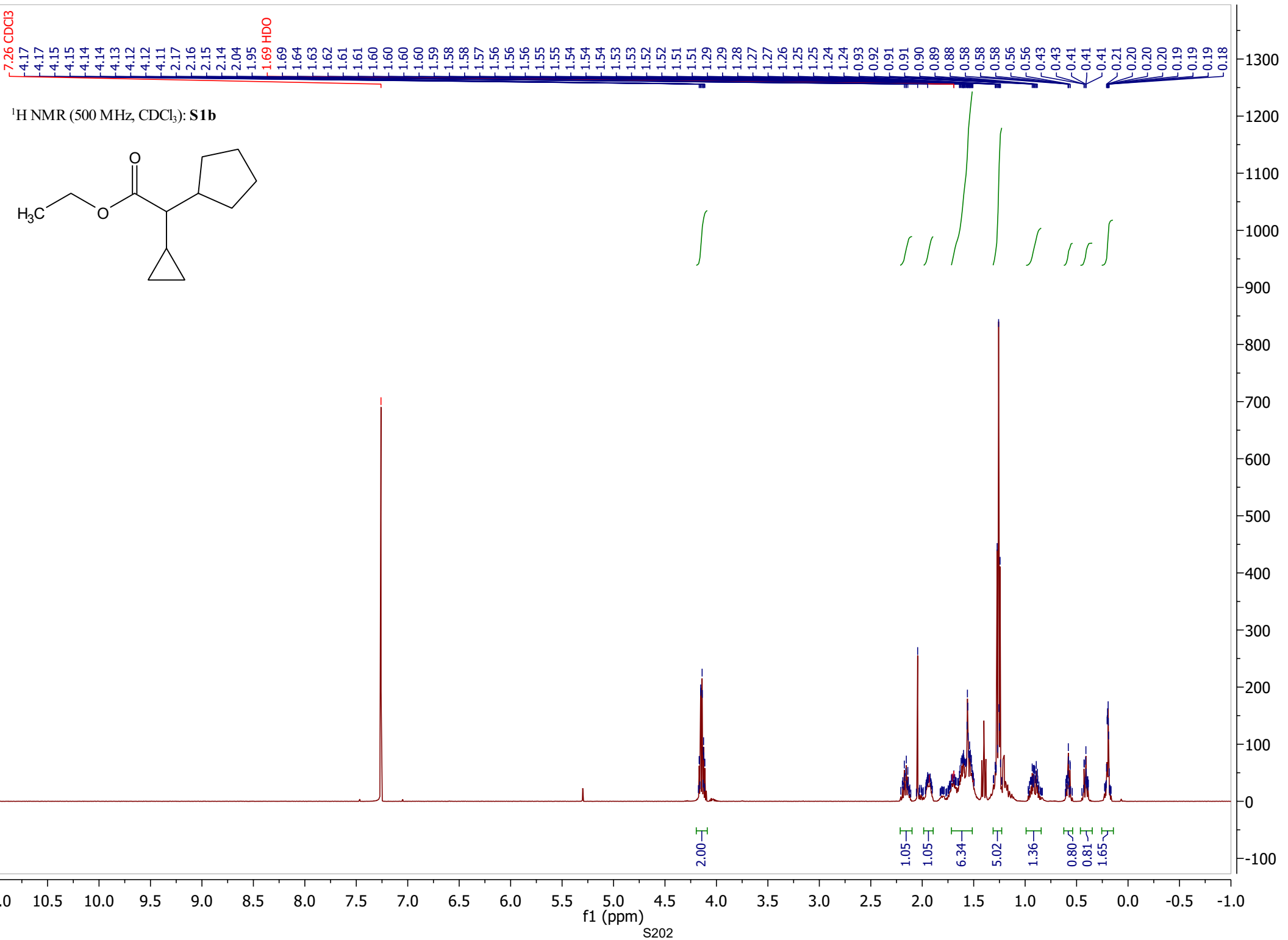
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **22b<sub>major</sub>**



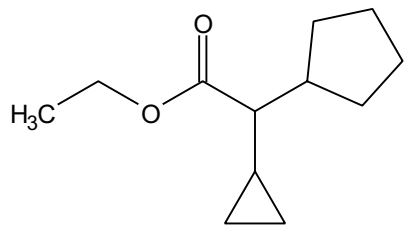


<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **22b<sub>minor</sub>**





<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **S1b**



—175.91

—60.09

—56.03

—43.81

—30.97

—30.92

—25.12

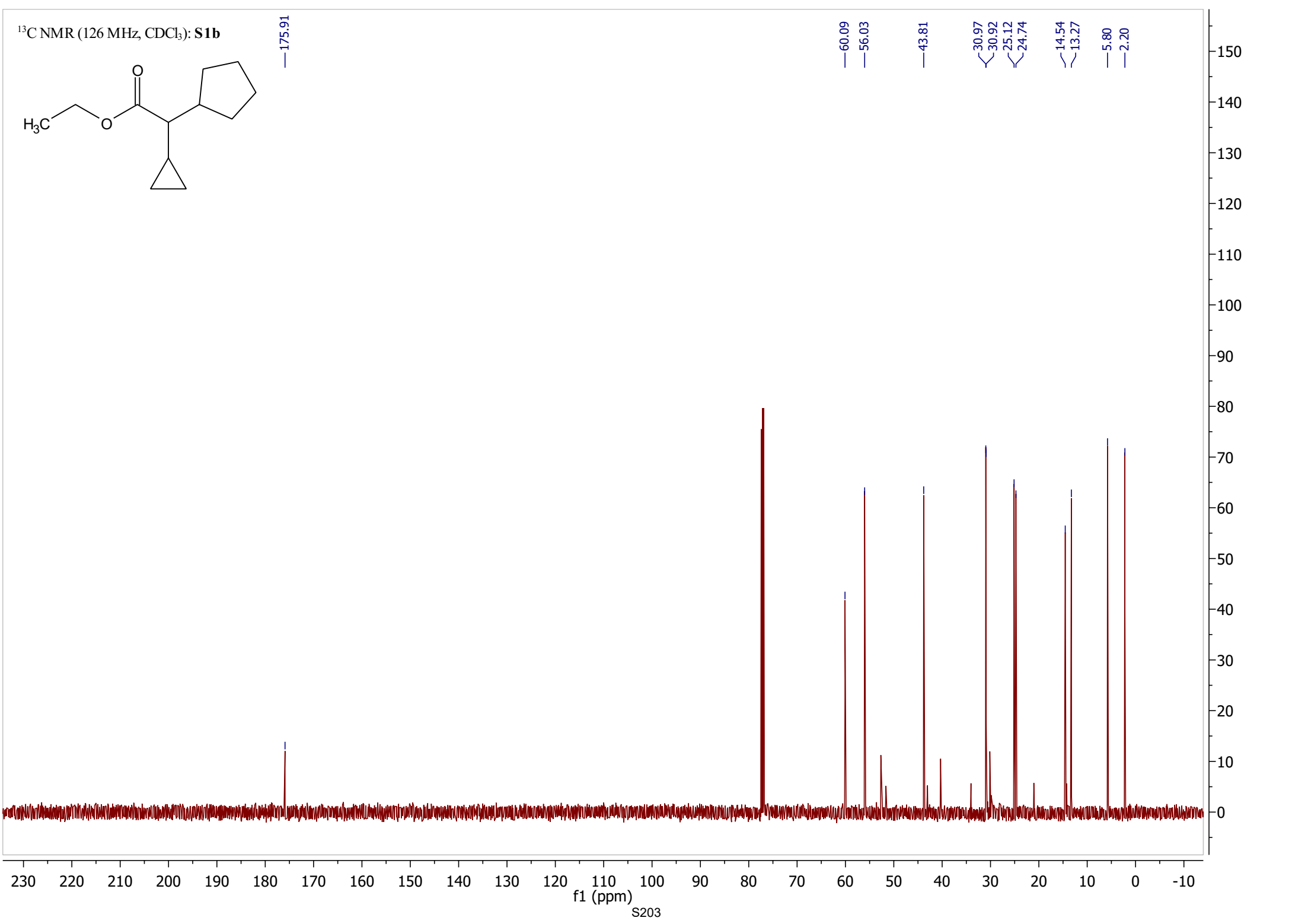
—24.74

—14.54

—13.27

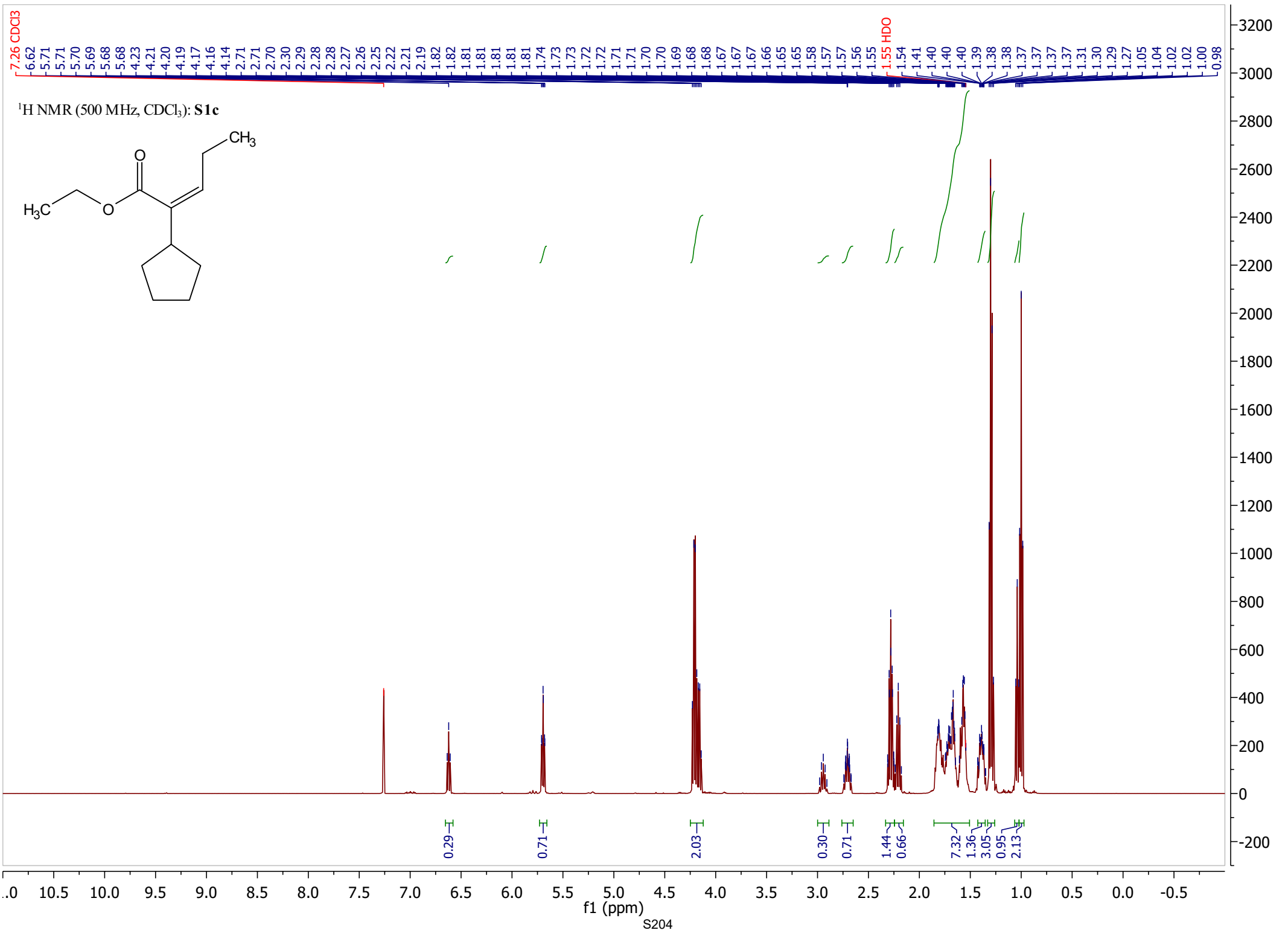
—5.80

—2.20

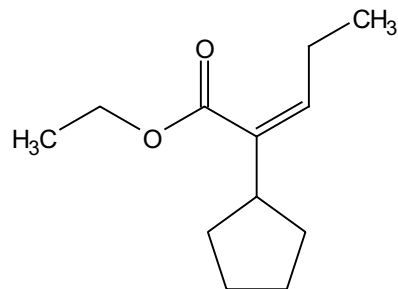


f1 (ppm)

S203



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): **S1c**



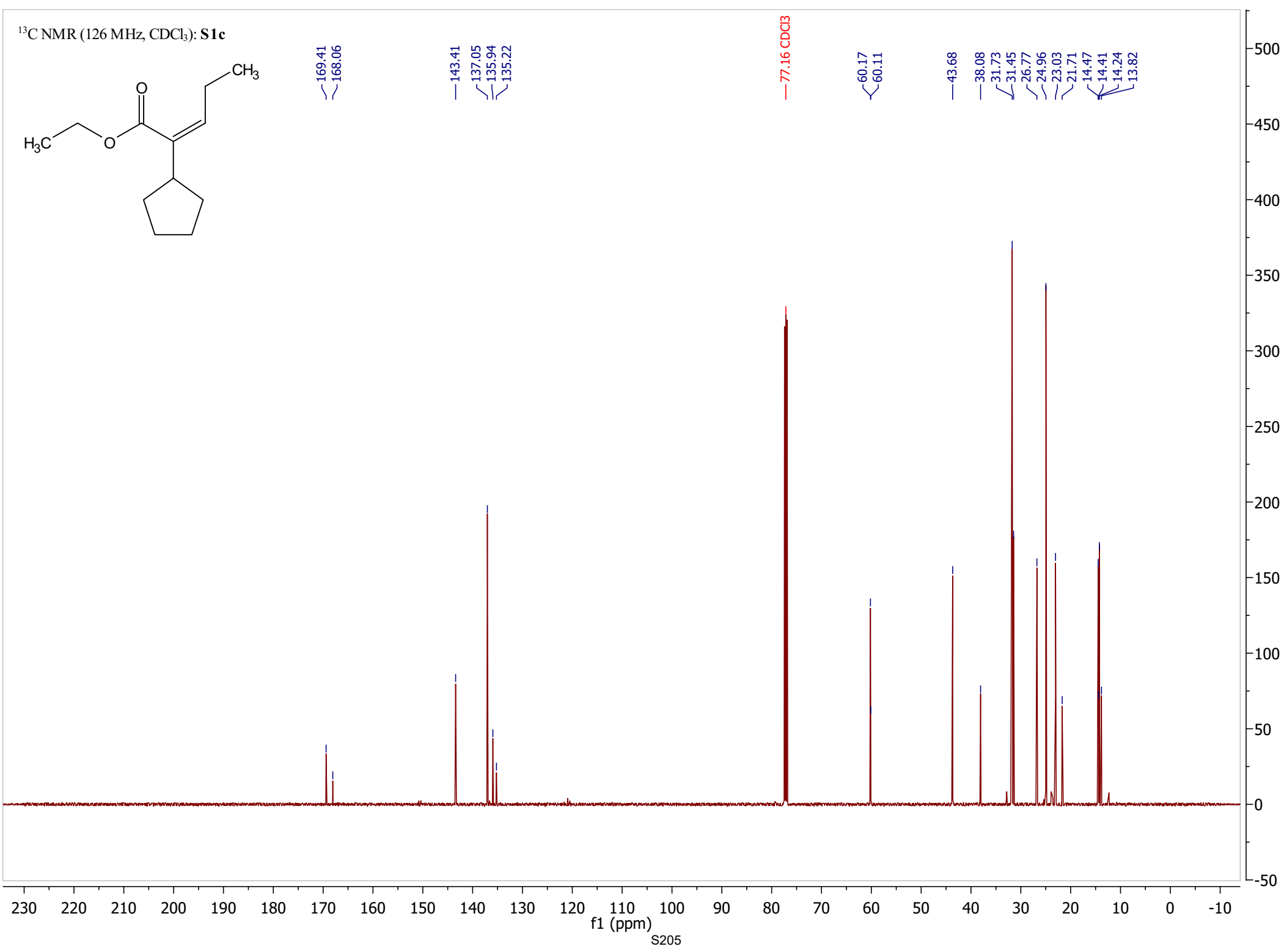
169.41  
168.06

143.41  
137.05  
135.94  
135.22

77.16 CDCl<sub>3</sub>

60.17  
60.11

43.68  
38.08  
31.73  
31.45  
26.77  
24.96  
23.03  
21.71  
14.47  
14.41  
14.24  
13.82



f1 (ppm)  
S205