

# Ligand-Enabled $\gamma$ -C(sp<sub>3</sub>)-H Olefination of Free Carboxylic Acids

Kiron Kumar Ghosh, Alexander Uttry, Francesca Ghiringhelli, **Arup Mondal, Manuel van Gemmeren**

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We report the ligand enabled C(sp<sub>3</sub>)-H activation/olefination of free carboxylic acids in the  $\gamma$ -position. Through an intramolecular Michael-addition,  $\delta$ -lactones are obtained as products. Two distinct ligand classes are identified that enable the challenging palladium-catalyzed activation of free carboxylic acids in the  $\gamma$ -position. The developed protocol features a wide range of acid substrates and olefin reaction partners and is shown to be applicable on a preparatively useful scale. Insights into the underlying reaction mechanism obtained through kinetic studies are reported.

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# Ligand-Enabled $\gamma$ -C(sp<sup>3</sup>)-H Olefination of Free Carboxylic Acids

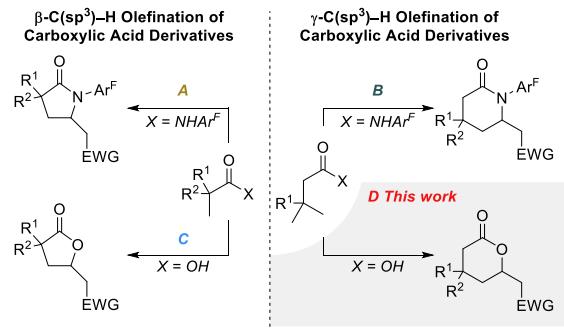
Kiron Kumar Ghosh,<sup>+</sup> Alexander Uttry,<sup>+</sup> Francesca Ghiringhelli, Arup Mondal, Manuel van Gemmeren<sup>\*</sup>

Dedication

**Abstract:** We report the ligand enabled C–H activation/olefination of free carboxylic acids in the  $\gamma$ -position. Through an intramolecular Michael-addition,  $\delta$ -lactones are obtained as products. Two distinct ligand classes are identified that enable the challenging palladium-catalyzed activation of free carboxylic acids in the  $\gamma$ -position. The developed protocol features a wide range of acid substrates and olefin reaction partners and is shown to be applicable on a preparatively useful scale. Insights into the underlying reaction mechanism obtained through kinetic studies are reported.

The synthesis of complex carboxylic acid derivatives from simple and readily available carboxylic acids is highly attractive, due to the prevalence of the carboxylic acid moiety in compounds such as pharmaceuticals, odors, flavors, etc.<sup>[1]</sup> However, despite some recent progress, the direct C–H activation and functionalization of free carboxylic acids remains highly challenging, due to the weak directing ability of the carboxylate group and competing coordination modes amongst other reasons, and thus requires the identification of suitable ligands and a careful fine-tuning of the associated reaction conditions.<sup>[2]</sup> These challenges can be circumvented through the introduction of more strongly directing exogenous directing groups, a strategy that has enabled a variety of highly useful transformations.<sup>[3]</sup> One highly attractive synthetic target in the field has been the C–H olefination of carboxylic acid derivatives. Yu and coworkers have developed conditions for the  $\beta$ -olefination of aliphatic amides bearing a perfluorinated arene substituent on the nitrogen, which delivered  $\gamma$ -lactams through a C–H-olefination followed by an intramolecular Michael addition (Scheme 1A).<sup>[4]</sup> Later, the same group developed ligands that allowed them to expand this reactivity to the C–H olefination of the substantially more challenging  $\gamma$ -position giving access to  $\delta$ -lactams (Scheme 1B).<sup>[5]</sup> In parallel to the development of methods relying on exogenous directing groups, substantial efforts by ourselves and others have recently been directed towards the use of free carboxylic acids in C–H activation processes and the identification of suitable ligands enabled several highly useful transformations.<sup>[6]</sup> Amongst these, Yu and coworkers have reported a direct synthesis of  $\gamma$ -lactones through the  $\beta$ -(Csp<sup>3</sup>)-H olefination of free carboxylic acids, followed by an intramolecular cyclization (Scheme 1C).<sup>[6i]</sup> While constituting a synthetically highly attractive approach towards the valuable  $\delta$ -lactone motif,<sup>[7]</sup>

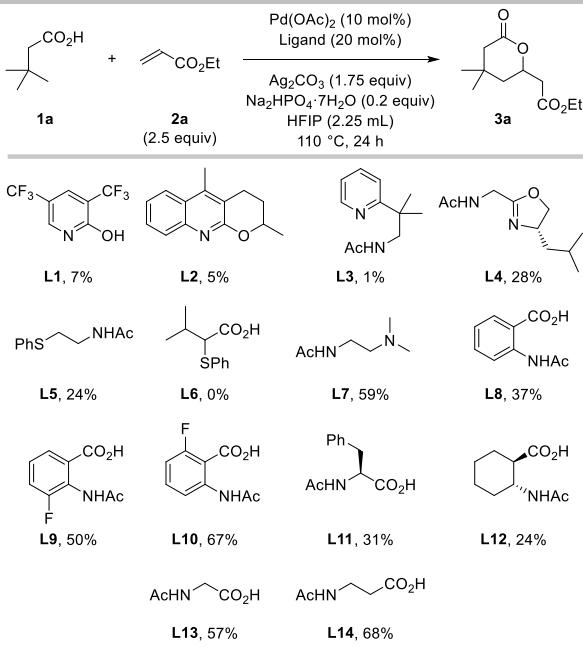
the analogous  $\gamma$ -olefination/cyclization has remained elusive to date. It should be noted that research towards the direct  $\gamma$ -C(sp<sup>3</sup>)-H activation of free carboxylic acids is still at its infancy and to the best of our knowledge only two synthetic methods relying on this type of process have been reported to date by the groups of Maiti and Shi, in both cases enabling the  $\gamma$ -arylation of free carboxylic acids through Pd(II)/Pd(IV)-catalytic cycles, albeit with complementary acid scopes.<sup>[8]</sup> We thus became interested in developing a method for the synthesis of  $\delta$ -lactones through the direct  $\gamma$ -C(sp<sup>3</sup>)-H olefination of free carboxylic acids. Herein we report the realization of this goal enabled through the identification of two suitable ligand-classes: *N*-acetyl anthranilic acid-derivatives and *N*-acetyl amino acids.



**Scheme 1.** Key advances in the C(sp<sup>3</sup>)-H olefination of carboxylic acid derivatives.

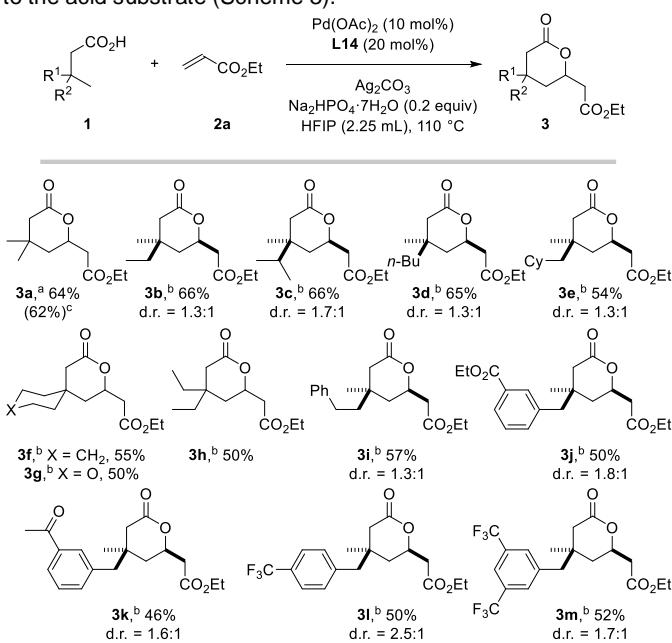
Based on our experience in the development of challenging  $\beta$ -C(sp<sup>3</sup>)-H functionalization processes for free carboxylic acids, we expected that the identification of suitable ligands would be key in order to establish the desired protocol. We thus initiated our studies using 3,3-dimethylbutyric acid (**1a**) and ethyl acrylate (**2a**) as model substrates. After an initial identification of **L10** as particularly promising ligand, we optimized the reaction conditions using this ligand (for details see the Supporting Information). After identifying the otherwise best reaction conditions, we re-evaluated representatives of common ligand classes in the C(sp<sup>3</sup>)-H activation (Scheme 1). We found that the anthranilic acid derivative **L10** continues to deliver superior results compared to pyridone **L1**,<sup>[9]</sup> pyridine **L2**,<sup>[6g, 10]</sup> and the bidentate ligands **L3**–**L7**.<sup>[6g, 6j–l, 11]</sup> Structural variants of the anthranilic acid motif **L8** and **L9** gave no further improvements. Finally, a re-investigation of amino acid-derived ligands **L11**–**L14**<sup>[6h, 6i, 8]</sup> showed that *N*-Ac- $\beta$ -alanine **L14** gave equally good results as **L10**. Notably this ligand performed substantially worse than **L10** in an initial comparison under non-optimized conditions. Having identified two suitable ligands for the  $\gamma$ -olefination of free carboxylic acids, we chose to investigate the scope of this transformation using **L14**, simply based on the broader availability of this ligand.

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Supporting information for this article is given via a link at the end of the document.



**Scheme 2.** Identification of suitable ligands for the  $\gamma$ -C(sp<sup>3</sup>)-H olefination of free carboxylic acids. Reactions were conducted on a 0.2 mmol scale. Yields were determined by <sup>1</sup>H-NMR analysis of the crude reaction mixture with 1,3,5-trimethoxy benzene as internal standard.

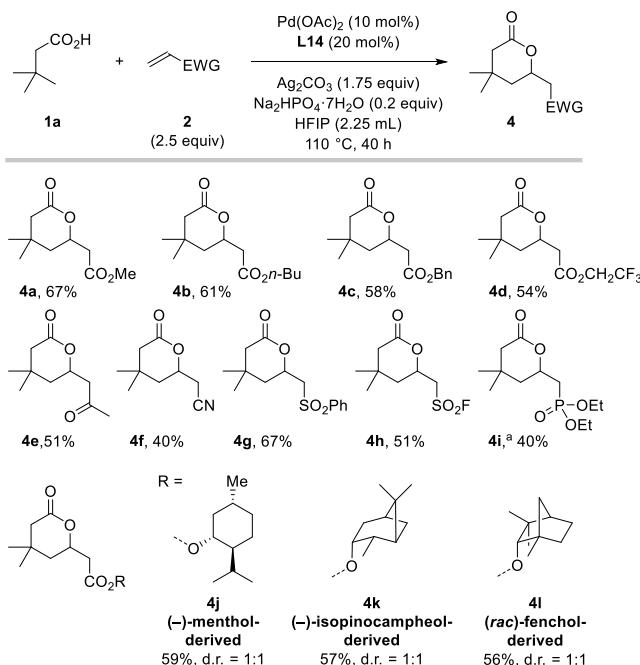
It should be noted however, that the discovery of anthranilic acid ligand **L10**, which has not previously been used in C–H activation to the best of our knowledge may prove helpful in future related studies. We began by studying the substrate scope with respect to the acid substrate (Scheme 3).



**Scheme 3.** Acid scope of the ligand-enabled  $\gamma$ -C(sp<sup>3</sup>)-H olefination of free carboxylic acids. Reactions were conducted on a 0.2 mmol scale. a. **2a** (2.5 equiv) and  $\text{Ag}_2\text{CO}_3$  (1.75 equiv) were used with 40 h reaction time. b. **2a** (7 equiv) and  $\text{Ag}_2\text{CO}_3$  (2.5 equiv) were used with 72 h reaction time. c. The yield in parentheses was obtained on a 5 mmol scale.

As expected based on our optimization studies, the model product **3a** could be obtained in good yield (64%). This example was also used to probe the scalability of our protocol. Importantly, a virtually identical yield of 62% was obtained on a 5 mmol scale. For structurally more complex acid substrates we found that an increased reaction time and acrylate loading were required to obtain optimal yields and used these conditions for the remainder of the acid scope. The alkyl substituted products **3b–e** were obtained in good yields and with moderate diastereoselectivities in favor of the cis-configured isomer. The spirocyclic products **3f** and **3g**, as well as **3h**, bearing two non-methyl substituents were all obtained in synthetically useful yields. Finally, products **3i–m**, containing aromatic substituents were again obtained in good yields and moderate to good diastereoselectivities.

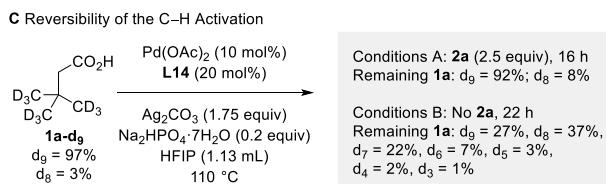
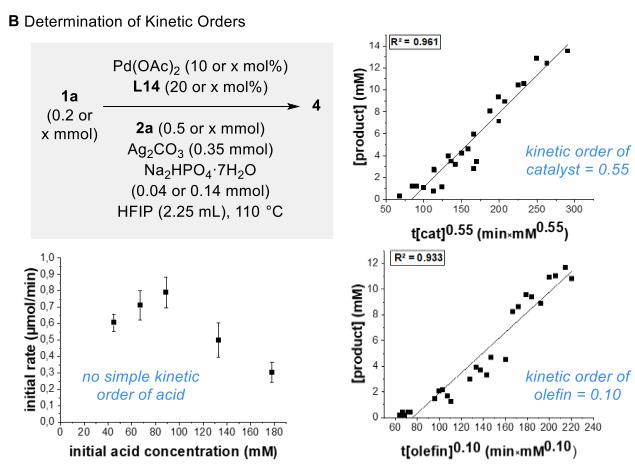
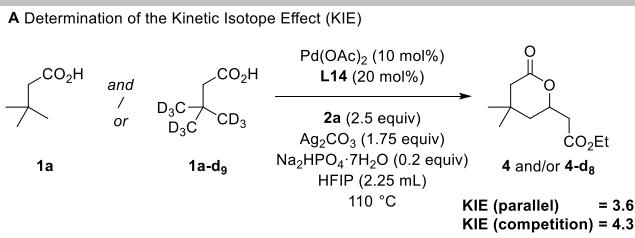
We proceeded to study the scope of this transformation with respect to the olefinic reaction partner (Scheme 4).



**Scheme 4.** Olefin scope of the ligand-enabled  $\gamma$ -C(sp<sup>3</sup>)-H olefination of free carboxylic acids. Reactions were conducted on a 0.2 mmol scale. a. Diethyl vinylphosphosphate (7 equiv) was used with 72 h reaction time.

Various acrylates were found to react smoothly, giving products **4a–d** in good yields. Olefins bearing other electron withdrawing groups, such as methyl vinyl ketone (**4e**), acrylonitrile (**4f**), phenyl vinyl sulfone (**4g**), ethenesulfonyl fluoride (**4h**), diethyl vinylphosphonate (**4i**) could all be used as reaction partners. Finally, olefins containing structurally more complex subunits were also successfully employed in the reaction, giving product **4j–l** in good yields.

Having studied the scope of this transformation, we became interested in obtaining basic insights into the underlying reaction mechanism. We began by evaluating whether the C–H activation contributes to the overall rate of the transformation (Scheme 5A). The clear primary kinetic isotope effect observed both in a competition experiment and in parallel experiments indicates that the C–H activation is indeed rate-determining.<sup>[12]</sup>

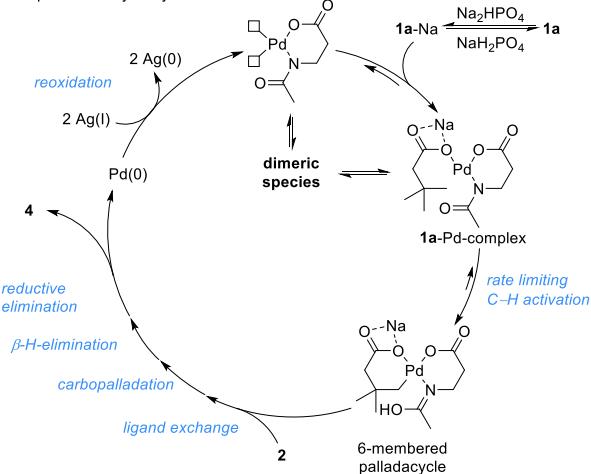


**Scheme 5.** Preliminary mechanistic studies. Experiments in Scheme 5A and B were conducted on a 0.2 mmol scale. The reversibility experiments were conducted on a 0.1 mmol scale.

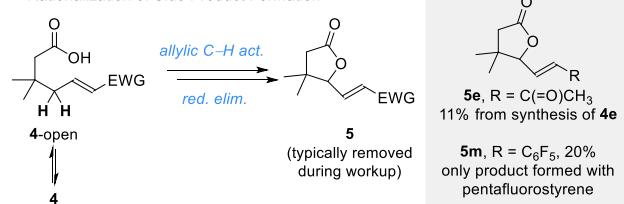
To obtain further knowledge about this step, we proceeded to determine the kinetic orders in both reaction partners and the catalyst (Scheme 5B). We began by determining the initial rates of the reaction varying one of the starting concentrations. The results were then analyzed using the method described by Burés.<sup>[13]</sup> The analysis revealed an order of 0.55 in catalyst, which is indicative of monomer-dimer-equilibria in which the monomer is the active species.<sup>[13–14]</sup> The existence of such equilibria is well documented for palladium catalysts with amino acid-derived ligands and both the monomers and the dimers have been shown to be the active species depending on the system at hand.<sup>[15]</sup> When we attempted to determine the order with respect to the acid component, we found that both an increase and a decrease in acid concentration were detrimental to the reaction outcome. Having already discovered that the catalyst exists in an equilibrium between active and inactive states, this result can easily be rationalized: The rate of product formation is influenced by the amount of substrate-palladium pre-reactive complex formed, which in turn depends more on the acid-base balance of the reaction mixture than on the actual substrate concentration. Since we optimized the acid and base amounts during our optimization studies, deviations in both directions are detrimental. Finally, we found a small, but non-zero (0.1) order in the olefin reaction partner. This result was unexpected, due to the previous identification of the C–H activation as rate-determining step, which implies a zero order in the olefin that enters the catalytic

cycle after this step. We hypothesized that this result can be explained by a reversibility of the C–H activation step, together with a lower, but comparable barrier for a subsequent step involving the olefin. In such a scenario, the C–H activation step would determine the overall rate of product formation, but a small fraction of the palladacycle formed could statistically revert to the starting material, when the subsequent reaction with the olefin does not occur fast enough. In order to probe this hypothesis, we conducted two reversibility experiments (Scheme 5C), one during the product forming reaction with **1a-d<sub>8</sub>** as substrate and one in the absence of the olefin reaction partner. In both cases the deuteration of the remaining starting material was analyzed. When no olefin is available, a strong de-deuteration was observed, showing that the C–H activation is in principle reversible under the reaction conditions. However, the result in the presence of olefin clearly demonstrates that when product formation is possible, it mostly outcompetes the retro-C–H activation, while a small but measurable backwards reaction occurs. These results are in good agreement with the observed 0.1 order in olefin. Overall, we propose the mechanism shown in Scheme 6A, which takes into account the observations discussed above.

**A Proposed Catalytic Cycle**



**B Rationalization of Side Product Formation**



**Scheme 6.** Proposed catalytic cycle and mechanism for side product formation.

Accordingly, the reaction would proceed through a (mostly) rate-determining C–H activation by a mononuclear Pd(II)-catalyst. Next, a sequence of ligand exchange, carbopalladation, β-H-elimination and reductive elimination would result in the formation of the product, concomitantly giving a Pd(0)-species, which would then be re-oxidized by the silver salt employed as terminal oxidant. A final mechanistic feature of our protocol concerns a side product observed in small quantities throughout these studies (**5**, Scheme 6B). We could isolate and characterize this side product in two cases, **5e** and **5m**. Since the formation of these compounds requires a second oxidation event, we hypothesize that they are formed through a carboxylate directed

C–H activation/oxidation starting from the open form of the primary product.

In summary, we have developed a protocol for the palladium-catalyzed  $\gamma$ -C(sp<sup>3</sup>)–H olefination of free carboxylic acids. Through an *in situ* Michael addition  $\delta$ -lactones are obtained without the need to install/remove exogenous directing groups. Our protocol features a broad scope of both reaction partners. Mechanistic experiments support a Pd(II)/Pd(0)-catalytic cycle, which renders this study the first report on a direct  $\gamma$ -C(sp<sup>3</sup>)–H activation/functionalization of free carboxylic acids through this redox manifold. We expect that these results will serve as a proof of principle and inspire research towards further transformations of this kind.

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**Keywords:**  $\gamma$ -C(sp<sup>3</sup>)–H activation • Carboxylic Acids •  $\delta$ -Lactones • Ligand-Enabled Catalysis • Palladium

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# Supporting Information for: Ligand-Enabled $\gamma$ -C(sp<sup>3</sup>)–H Olefination of Free Carboxylic Acids

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# General Information

## Solvents, Reagents and Techniques

Unless otherwise noted, all reactions were conducted in glassware previously dried in an oven at 120°C. Reaction temperatures are reported as the temperature of the oil bath or the metal block surrounding the reaction vessel. The following solvents were dried by fractional distillation: pentane, ethyl acetate, CH<sub>2</sub>Cl<sub>2</sub>. Additional anhydrous solvents (<50 ppm water) were purchased from Acros Organics, Sigma-Aldrich, or Carl Roth and stored over molecular sieves under an argon atmosphere. Commercially available chemicals were obtained from ABCR, Acros Organics, Aldrich Chemical Co., Alfa Aesar, Combi-Blocks, Fluorochem, and TCI Europe and used as received unless otherwise stated.

## Chromatography

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Merck). The compounds were visualized by the exposure to ultraviolet light (254 nm and 366 nm) and/or by staining. For staining the TLC plates were dipped into a solution of KMnO<sub>4</sub> (1 g KMnO<sub>4</sub>, 6 g K<sub>2</sub>CO<sub>3</sub> and 0.1 g KOH in 100 mL H<sub>2</sub>O) or bromocresol green (40 mg bromocresol green in 100 mL EtOH; addition of 0.1Maq. NaOH until the blue colors appears in the solution) and developed with a heat gun if necessary. Flash column chromatography was performed on silica gel (35–70µm mesh, 60 Å, Acros) with a positive argon overpressure.

## Nuclear Magnetic Resonance (NMR) Spectroscopy

<sup>1</sup>H-, <sup>13</sup>C-, and <sup>19</sup>F-NMR spectra were measured at r.t. on a Bruker Avance II 300 MHz, Avance II 400 MHz, or Agilent DD2 600 MHz spectrometer. Chemical shifts ( $\delta$ ) of <sup>1</sup>H-and <sup>13</sup>C-NMR spectra are given in ppm relative to tetramethyl silane (TMS) using the residual solvent peaks for calibration (CDCl<sub>3</sub>:  $\delta$  H= 7.26 ppm,  $\delta$  C= 77.16 ppm). <sup>19</sup>F-NMR spectra are not externally calibrated and chemical shifts is given relative to CCl<sub>3</sub>F as received from the automatic data processing. Chemical shifts are reported with two (<sup>1</sup>H) or one (all other nuclei) digits after the decimal point. Exceptions are done when requivuired to annotate clearly distinguishable signals observed in very close proximity to one another. NMR-data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad], coupling constants (J, Hz) and integration). All spectra were processed using the MestReNova 12.0.4 program. For the spectra of diastereomeric mixtures signals clearly assigned to a particular diastereomer are labelled with a superscript at the integration. The number of protons in such cases refers to the number of protons of the respective isomer. The <sup>13</sup>C-NMR spectra of mixtures are reported as observed. Due to the low signal intensity and potentially an overlap of signals, the number of signals can deviate from the hypothetical value, however, the signals of the major component are clearly recognizable in all cases.

### **Gas Chromatography with Flame Ionization Detection (GC-FID)**

GC-FID analysis was done on an Agilent Technologies 6890A equipped with an HP-5 column (0.32 mm x 30 m, film: 0.25  $\mu$ m) using flame ionization detection.

### **Mass Spectrometry (MS)**

High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicroTof or on a Thermo-Fisher Scientific Orbitrap LTQ XL spectrometer using electron spray ionization (ESI).

### **Infrared Spectroscopy (IR)**

Infrared spectra were recorded neat on a Shimadzu FTIR 8400S or a Varian Associates FTIR 3100 Excalibur spectrometer. The wave numbers ( $\nu$ ) of recorded IR-signals are quoted in  $\text{cm}^{-1}$ .

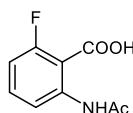
# Preparation of Ligands

## General Procedure A: Synthesis of N-acetylated Anthranilic Acid Ligands

The N-acetylation of anthranilic acids was done via a modified procedure of Roberts *et al.*<sup>1</sup>

Anthranilic acid was dissolved in dry THF (0.25 M), acetyl chloride (1.0 equiv) was added slowly and the reaction mixture was cooled to 0 °C. Et<sub>3</sub>N (1.5 equiv) was added dropwise and the reaction mixture was allowed to slowly warm up to r.t.. The reaction mixture was stirred for 16 h and THF was removed under reduced pressure. The reaction mixture was cooled to 0 °C and aq. HCl (1.0 M) was added until the pH was between 1 and 5. All volatiles were removed under reduced pressure and the crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 99:1 to 90:10).

### 2-Acetamido-6-fluorobenzoic acid (L10):



**L10** Following the general procedure A on a 32.2 mmol scale the target compound **L10** was obtained as colorless solid (5.09 g, 25.8 mmol, 80%).

<sup>1</sup>H-<sup>{19}</sup>F-NMR (500 MHz, DMSO-d<sub>6</sub>): δ = 10.12 (s, 1H), 7.63 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.48 (t, *J* = 8.3 Hz, 1H), 7.03 (dd, *J* = 8.3, 1.0 Hz, 1H), 2.05 (s, 3H) ppm.

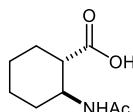
<sup>13</sup>C-<sup>{19}</sup>F-NMR (126 MHz, DMSO-d<sub>6</sub>): δ = 168.5, 165.5, 160.2, 138.6, 132.4, 118.8, 113.6, 111.4, 23.9 ppm.

<sup>19</sup>F-<sup>{1}</sup>H-NMR (470 MHz, DMSO-d<sub>6</sub>): δ = -110.9 ppm.

HRMS (ESIpos) m/z: Calcd for C<sub>9</sub>H<sub>8</sub>FNNaO<sub>3</sub><sup>+</sup> 220.0380, Found 220.0381.

IR (cm<sup>-1</sup>): 2922, 2253, 1686, 1653, 1472, 1375, 903, 723.

### trans-2-Acetamidocyclohexane-1-carboxylic acid (L12):



**L12** *trans*-2-Aminocyclohexane-1-carboxylic acid (300 mg, 2.10 mmol) was dissolved in water (5 mL), acetic anhydride (396 μL, 428 mg, 2.0 equiv) was added slowly and the mixture was stirred for 6 h. All volatiles were removed under reduced pressure and the crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 90:10). The product **L12** was obtained as a colorless solid (174 mg, 0.942 mmol, 49 %).

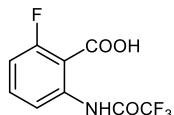
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 11.59 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 3.74 (tdd, *J* = 10.8, 8.7, 4.1 Hz, 1H), 2.25 – 2.11 (m, 1H), 1.89 – 1.54 (m, 7H), 1.45 – 0.99 (m, 4H) ppm.

<sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>): δ = 175.3, 168.0, 48.7, 48.3, 32.0, 28.6, 24.3, 24.2, 22.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_9H_{15}NNaO_3^+$  208.0944, Found 208.0956.

**IR (cm<sup>-1</sup>):** 2949, 2920, 1721, 1375, 1254, 1184, 997.

**2-Fluoro-6-(2,2,2-trifluoroacetamido)benzoic acid (L15):**



**L15** 6-fluoroanthranilic acid (155 mg, 1 mmol) was dissolved in dry THF (0.33 M), trifluoroacetic anhydride (970  $\mu$ L, 7.00 mmol) was added slowly at 0 °C. Then the reaction mixture was allowed to warm up to r.t. and was stirred for 16 h. The reaction mixture was cooled to 0 °C and aq. HCl (1.0M) was added until the pH was between 1 and 5. All volatiles were removed under reduced pressure and the crude product was purified by column chromatography ( $CH_2Cl_2:MeOH$  = 99:1 to 90:10) to obtain the target compound **L15** as colorless solid (122 mg, 0.486 mmol, 49%).

**<sup>1</sup>H-<sup>{19}F</sup>-NMR (500 MHz, DMSO-d<sub>6</sub>):**  $\delta$  = 13.76 (s, 1H), 11.71 (s, 1H), 7.62 (t,  $J$  = 8.3 Hz, 1H), 7.53 (dd,  $J$  = 8.3, 1.1 Hz, 1H), 7.27 (dd,  $J$  = 8.3, 1.1 Hz, 1H) ppm.

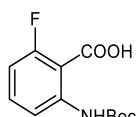
**<sup>13</sup>C-<sup>{19}F</sup>-NMR (126 MHz, DMSO-d<sub>6</sub>):**  $\delta$  = 165.0, 160.2, 155.0, 135.5, 133.0, 120.8, 115.9, 115.8, 114.6 ppm.

**<sup>19</sup>F-<sup>{1}</sup>H-NMR (470 MHz, DMSO-d<sub>6</sub>):**  $\delta$  = -74.7, -110.1 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_{13}H_{22}NaO_4^+$  265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 1732, 1707, 1616, 1580, 1449, 1246, 1157, 957.

**2-((tert-Butoxycarbonyl)atranso)-6-fluorobenzoic acid (L16):**



**L16** 6-fluoroanthranilic acid (155 mg, 1 mmol) was dissolved in dry THF (0.33 M),  $Boc_2O$  (240 mg, 1.1 mmol) was added slowly and the reaction mixture was cooled to 0 °C.  $Et_3N$  (2.0 equiv) was added dropwise and the reaction mixture was allowed to slowly warm up to r.t.. The reaction mixture was stirred for 16 h and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography ( $CH_2Cl_2:MeOH$  = 99:1 to 90:10) to obtain the target compound **L16** as colorless solid (102 mg, 0.400 mmol, 40%).

**<sup>1</sup>H-<sup>{19}F</sup>-NMR (500 MHz, CDCl<sub>3</sub>):**  $\delta$  = 9.75 (s, 1H), 8.23 (d,  $J$  = 8.5 Hz, 1H), 7.48 (t,  $J$  = 8.5 Hz, 1H), 6.79 (d,  $J$  = 8.5 Hz, 1H), 1.53 (s, 9H) ppm.

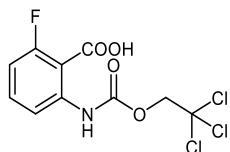
**<sup>13</sup>C-<sup>{19}F</sup>NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  = 170.0, 163.0, 152.8, 143.4, 135.5, 115.3, 109.7, 81.5, 28.4 ppm.

**<sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>):**  $\delta$  = -104.7 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_{12}H_{13}FNNaO_4^+$  278.0799, Found 278.0812.

**IR (cm<sup>-1</sup>):** 2984, 1726, 1670, 1580, 1472, 1250, 1153, 966, 887.

### 2-Fluoro-6-(((2,2,2-trichloroethoxy)carbonyl)atranso)benzoic acid (L17):



**L17** 6-fluoroanthranilic acid (155 mg, 1 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (0.33 M), 2,2,2-trichloroethoxycarbonyl chloride (150  $\mu\text{L}$ , 1.10 mmol) was added slowly and the reaction mixture was cooled to 0 °C. Pyridine (160  $\mu\text{L}$ , 2.00 mmol) was added dropwise and the reaction mixture was allowed to slowly warm up to r.t.. The reaction mixture was stirred for 16 h and  $\text{CH}_2\text{Cl}_2$  was removed under reduced pressure and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography ( $\text{CH}_2\text{Cl}_2:\text{MeOH}$  = 99:1 to 90:10) to obtain the target compound **L17** as colorless solid (137 mg, 0.414 mmol, 41%).

**$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 7.72 (td,  $J$  = 8.2 Hz,  $J_{\text{H-F}}$  = 5.6 Hz, 1H), 7.27 (dt,  $J$  = 8.1, 1.0 Hz, 1H), 7.10 (ddd,  $J$  = 8.3, 1.0 Hz,  $J_{\text{H-F}}$  = 9.5 Hz, 1H), 5.08 (s, 2H) ppm.

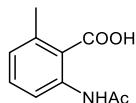
**$^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 162.6 (d,  $J_{\text{C-F}}$  = 269.1 Hz), 154.4, 154.1 (d,  $J_{\text{C-F}}$  = 5.3 Hz), 149.0, 138.0 (d,  $J_{\text{C-F}}$  = 10.7 Hz), 121.5 (d,  $J_{\text{C-F}}$  = 4.0 Hz), 113.9 (d,  $J_{\text{C-F}}$  = 20.2 Hz), 104.4 (d,  $J_{\text{C-F}}$  = 8.3 Hz), 93.7, 78.1 ppm.

**$^{19}\text{F-NMR}$  (376 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -106.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $\text{C}_{13}\text{H}_{22}\text{NaO}_4^+$  265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 2959, 2253, 1784, 1645, 1622, 1578, 1483, 1377, 1327, 1302, 1252, 905, 725.

### 2-Fluoro-6-formamidobenzoic acid (L18):



**L18** Following the general procedure **A** on a 1.50 mmol scale the target compound **L18** was obtained as colorless solid (197 mg, 1.02 mmol, 68%).

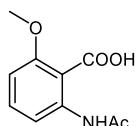
**$^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):**  $\delta$  = 9.63 (s, 1H), 7.42 (d,  $J$  = 7.7 Hz, 1H), 7.28 (t,  $J$  = 7.7 Hz, 1H), 7.05 (d,  $J$  = 7.7 Hz, 1H), 2.34 (s, 3H), 2.00 (s, 3H) ppm.

**$^{13}\text{C-NMR}$  (101 MHz,  $\text{DMSO-d}_6$ ):**  $\delta$  = 168.9, 168.4, 136.0, 135.7, 129.6, 129.5, 127.8, 126.7, 122.1, 23.6, 20.4 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $\text{C}_{10}\text{H}_{11}\text{NNaO}_3^+$  216.0631, Found 216.0641.

**IR (cm<sup>-1</sup>):** 2926, 2857, 1730, 1684, 1466, 1371, 1250, 1103, 907, 729.

### 2-Acetamido-6-methoxybenzoic acid (L19):



**L19** Following the general procedure **A** on a 1.50 mmol scale the target compound **L19** was obtained as colorless solid (151 mg, 0.722 mmol, 48%).

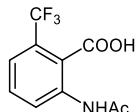
**<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>):** δ = 12.92 (s, 1H), 9.50 (s, 1H), 7.34 (t, J = 8.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 3.77 (s, 3H), 1.99 (s, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>):** δ = 168.5, 167.1, 156.7, 136.2, 130.3, 118.0, 116.8, 107.9, 55.9, 26.1 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 2934, 1730, 1692, 1645, 1609, 1470, 1375, 1267, 1090, 907, 729.

### 2-Acetamido-6-(trifluoromethyl)benzoic acid (L20):



**L20** Following the general procedure **A** on a 488 μmol scale the target compound **L20** was obtained as colorless solid (47.1 mg, 190 μmol, 39%).

**<sup>1</sup>H-<sup>{19}</sup>F-NMR (599 MHz, DMSO-d<sub>6</sub>):** δ = 10.03 (s, 1H), 8.12 – 7.99 (m, 1H), 7.52 – 7.39 (m, 2H), 2.04 (s, 3H) ppm.

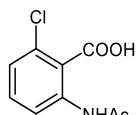
**<sup>13</sup>C-<sup>{19}</sup>F-NMR (151 MHz, DMSO-d<sub>6</sub>):** δ = 168.5, 167.0, 135.8, 128.3, 127.0, 126.1, 123.9, 121.5, 23.9 ppm.

**<sup>19</sup>F-<sup>{1}</sup>H-NMR (564 MHz, DMSO-d<sub>6</sub>):** δ = 57.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 2944, 1705, 1684, 1472, 1321, 1271, 1140, 1111, 1024.

### 2-Acetamido-6-chlorobenzoic acid (L21):



**L21** Following the general procedure **A** on a 1.10 mmol scale the target compound **L21** was obtained as colorless solid (0.15 g, 0.70 mmol, 70%).

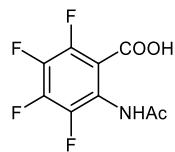
**<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>):** δ = 13.56 (s, 1H), 9.68 (s, 1H), 7.58 – 7.24 (m, 3H), 2.01 (s, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, DMSO-d<sub>6</sub>):** δ = 168.8, 166.1, 136.3, 130.4, 129.9, 125.9, 124.5, 23.2 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 3750, 3217, 3055, 2986, 2778, 2631, 2477, 1950, 1682, 1543, 1451, 1373, 1296, 1188, 1150, 1127, 1057, 1019, 980, 903, 802, 756, 710, 671, 610.

**2-Acetamido-3,4,5,6-tetrafluorobenzoic acid (L22):**



**L22** Following the general procedure **A** on a 2.10 mmol scale the target compound **L22** was obtained as colorless solid (326 mg, 1.30 mmol, 62%).

**<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>):** δ = 13.91 (s, 1H), 10.01 (s, 1H), 2.03 (s, 3H) ppm.

**<sup>13</sup>C-{19F}-NMR (151 MHz, DMSO-d<sub>6</sub>):** δ 168.7, 161.9, 144.3, 142.4, 141.1, 138.0, 120.9, 116.8, 22.5 ppm.

**<sup>19</sup>F-NMR (470 MHz, DMSO-d<sub>6</sub>):** δ -141.4 (ddd, *J* = 23.9, 10.0, 3.5 Hz), -144.4 (dd, *J* = 23.0, 10.0 Hz), -153.9 (t, *J* = 22.4 Hz), -158.7 (t, *J* = 22.8 Hz) ppm.

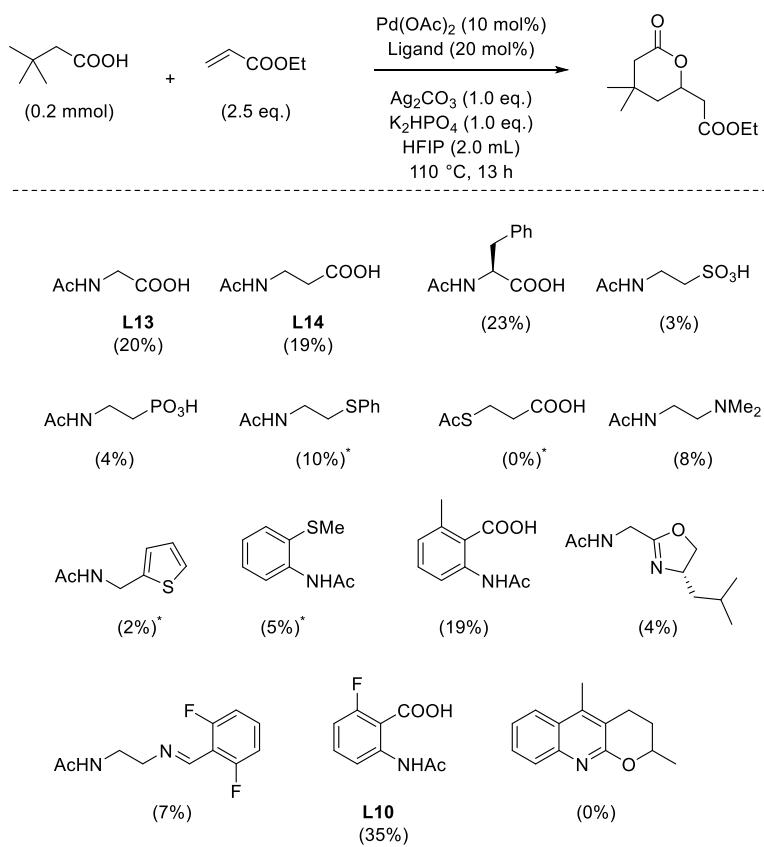
**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 2951, 2918, 1707, 1458, 1375, 1103, 905, 727.

# Optimization of the Reaction Conditions

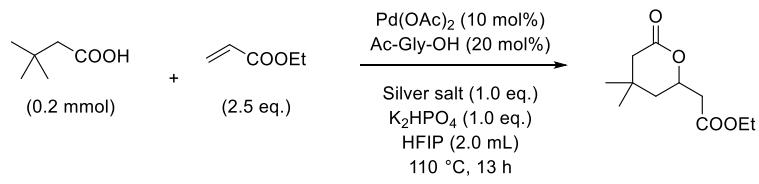
## General Procedure for the optimization reactions:

An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$ , Ac- $\beta$ -Ala-OH, silver salt, base, 3,3-dimethylbutyric acid or 3,3-dimethylpentanoic acid, acrylate and HFIP. The reaction mixture was stirred in a preheated aluminum block. After the indicated time the reaction was allowed to cool to r.t.. The reaction mixture was filtered over a pad of Celite®, the residue was washed with  $\text{CH}_2\text{Cl}_2$  (30 mL) to complete elution and all volatiles were removed under reduced pressure. 1,3,5-trimethoxybenzene (33.6 mg, 0.200 mmol) and  $\text{CDCl}_3$  (0.8 mL) were added. All yields during the optimization study were determined via  $^1\text{H-NMR}$  of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.



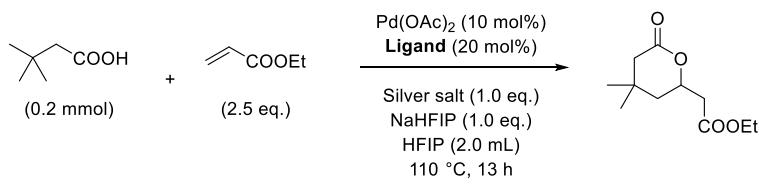
\* 10% ligands were used.

**Scheme S1:** Screening of ligands.



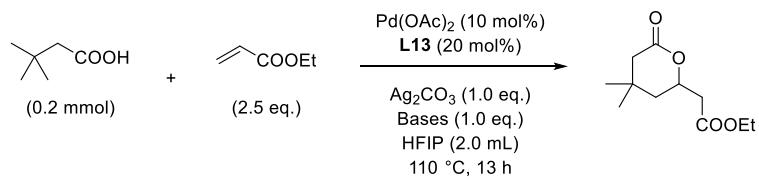
| Entry | Silver salt                     | Yield (%) |
|-------|---------------------------------|-----------|
| 1     | Ag <sub>2</sub> CO <sub>3</sub> | 21        |
| 2     | Ag <sub>2</sub> O               | 28        |
| 3     | AgOAc                           | 17        |

**Scheme S2:** Screening of silver salts.



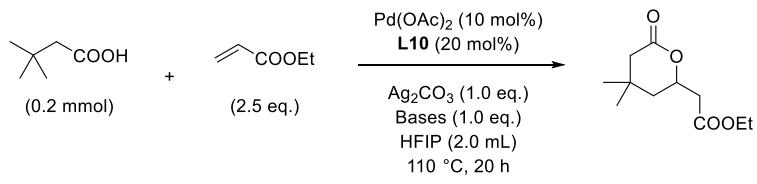
| Entry | Ligand | Silver salt                     | Yield (%) |
|-------|--------|---------------------------------|-----------|
| 1     | L10    | Ag <sub>2</sub> O               | 23        |
| 2     | L13    | Ag <sub>2</sub> O               | 8         |
| 3     | L13    | Ag <sub>2</sub> CO <sub>3</sub> | 39        |
| 4     | L10    | Ag <sub>2</sub> CO <sub>3</sub> | 54        |

**Scheme S3:** Compatibility of ligands with silver salts.



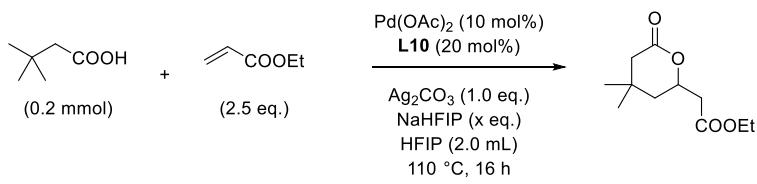
| Entry | Bases  | Yield (%) |
|-------|--------|-----------|
| 1     | LiHFIP | 8         |
| 2     | NaHFIP | 37        |
| 3     | KHFIP  | 22        |

**Scheme S4:** Screening of bases with varied counter-cations.



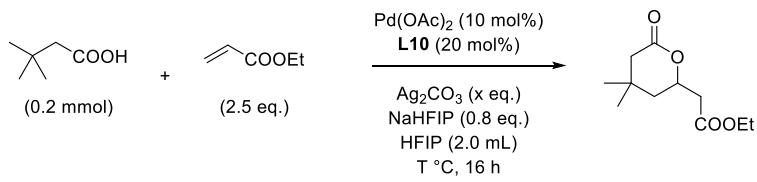
| Entry | Bases              | Yield (%) |
|-------|--------------------|-----------|
| 1     | NaHFIP             | 54        |
| 2     | NaHCO <sub>3</sub> | 28        |
| 3     | NaOAc              | 37        |
| 4     | NaOMe              | 40        |

**Scheme S5:** Screening of bases.



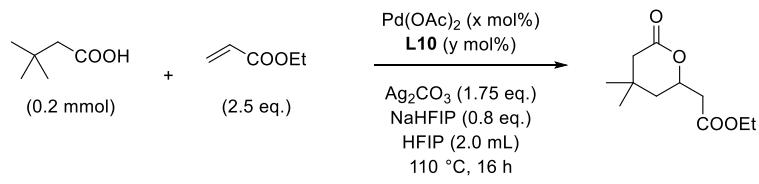
| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 0.20    | 25        |
| 2     | 0.40    | 50        |
| 3     | 0.60    | 56        |
| 4     | 0.80    | 58        |
| 5     | 1.00    | 53        |
| 6     | 1.25    | 39        |
| 7     | 1.50    | 31        |
| 8     | 1.75    | 25        |
| 9     | 2.00    | 24        |

**Scheme S6:** Screening of the amount of NaHFIP.



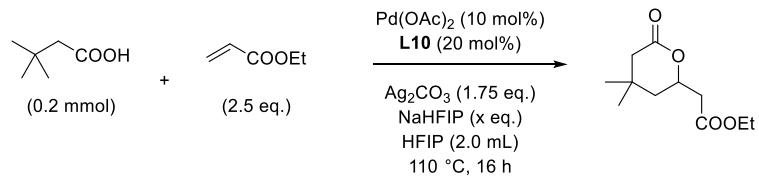
| Entry | x (eq.) | T (°C) | Yield (%) |
|-------|---------|--------|-----------|
| 1     | 0.50    | 110    | 33        |
| 2     | 0.75    | 110    | 47        |
| 3     | 1.00    | 110    | 56        |
| 4     | 1.25    | 110    | 59        |
| 5     | 1.50    | 110    | 59        |
| 6     | 1.75    | 110    | 63        |
| 7     | 2.00    | 110    | 63        |
| 8     | 1.00    | 100    | 58*       |
| 9     | 1.00    | 90     | 43        |
| 10    | 1.00    | 80     | 30        |
| 11    | 1.00    | 70     | 17        |
| 12    | 1.00    | 120    | 54        |

**Scheme S7:** Screening of the amount of Ag<sub>2</sub>CO<sub>3</sub> and temperature. \* In contrast to this result, better/more reproducible results were obtained with 110 °C, such that 110°C were used further.



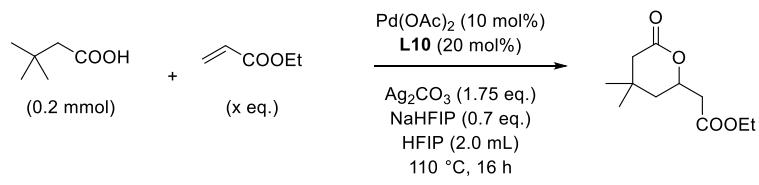
| Entry | x (mol%) | y (mol%) | Yield (%) |
|-------|----------|----------|-----------|
| 1     | 10       | 10       | 53        |
| 2     | 10       | 12       | 53        |
| 3     | 10       | 15       | 59        |
| 4     | 10       | 20       | 61        |
| 5     | 10       | 30       | 56        |
| 6     | 5        | 10       | 47        |
| 7     | 5        | 10       | 46*       |
| 8     | 2.5      | 5.0      | 40        |

**Scheme S8:** Screening of the amount of catalyst. \*reaction time = 72 h



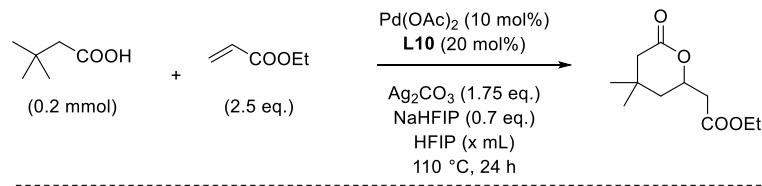
| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 0.4     | 44        |
| 2     | 0.5     | 52        |
| 3     | 0.6     | 61        |
| 4     | 0.7     | 62        |
| 5     | 0.8     | 58        |
| 6     | 0.9     | 57        |
| 7     | 1.0     | 53        |
| 8     | 1.5     | 43        |

**Scheme S9:** Screening of the amount of NaHFIP.



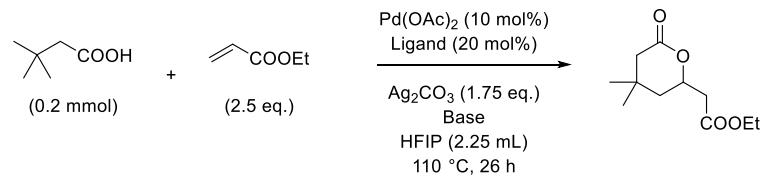
| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 1.0     | 48        |
| 2     | 1.0     | 51        |
| 3     | 1.4     | 56        |
| 4     | 1.6     | 61        |
| 5     | 1.8     | 60        |
| 6     | 2.0     | 61        |
| 7     | 2.5     | 66        |
| 8     | 3.0     | 65        |

**Scheme S10:** Screening of the amount of ethyl acrylate.



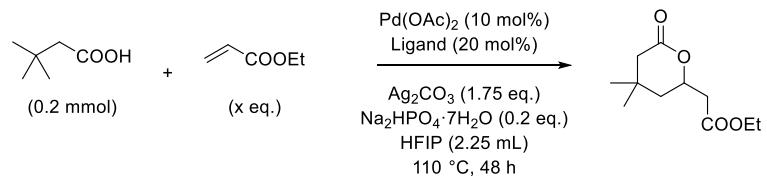
| Entry | x (mL) | Yield (%) |
|-------|--------|-----------|
| 1     | 0.50   | 36        |
| 2     | 1.00   | 59        |
| 3     | 1.25   | 59        |
| 4     | 1.50   | 61        |
| 5     | 1.75   | 61        |
| 6     | 2.00   | 62        |
| 7     | 2.25   | 63        |
| 8     | 2.50   | 62        |
| 9     | 2.75   | 61        |
| 10    | 3.00   | 61        |
| 11    | 4.00   | 61        |

**Scheme S11:** Screening of the amount of solvent.



| Bases                   | L10 | L14 |
|-------------------------|-----|-----|
| NaHFIP (0.70 eq.)       | 58% | 47% |
| Na2HPO4·7H2O (0.70 eq.) | 53% | 66% |
| Na2HPO4·7H2O (0.30 eq.) | 66% | 67% |
| Na2HPO4·7H2O (0.25 eq.) | 66% | 66% |
| Na2HPO4·7H2O (0.20 eq.) | 65% | 67% |
| Na2HPO4·7H2O (0.15 eq.) | 53% | 60% |
| Na2HPO4·7H2O (0.10 eq.) | 38% | 60% |
| Na2HPO4·7H2O (0 eq.)    | 2%  | 9%  |

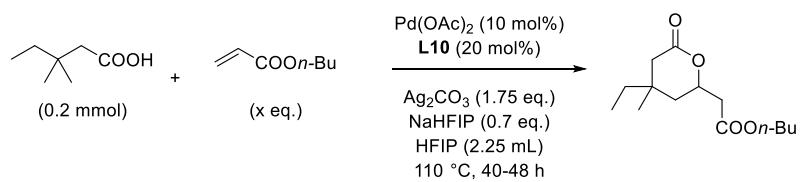
**Scheme S12:** Screening of the amount and type of base with different ligands.



| x (eq.) | L10 | L14 |
|---------|-----|-----|
| 2.5     | 68% | 67% |
| 2.0     | 67% | 63% |
| 1.6     | 61% | 63% |

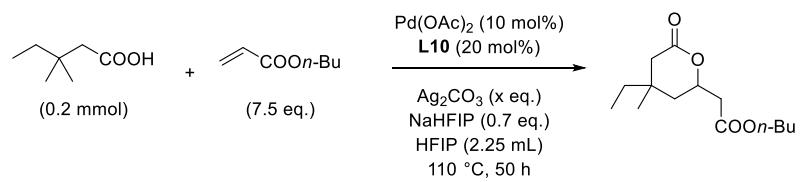
**Scheme S13:** Screening of the amount of acrylate.

#### Further optimization for substituted 3,3-dimethylbutyric acid derivatives



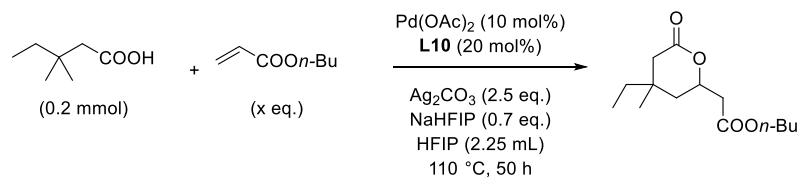
| Entry | x (eq.) | T (°C) | Yield (%) |
|-------|---------|--------|-----------|
| 1     | 1.5     | 110    | 24        |
| 2     | 2.5     | 110    | 29        |
| 3     | 3.5     | 110    | 39        |
| 4     | 4.5     | 110    | 47        |
| 5     | 7.5     | 110    | 60        |
| 6     | 9.0     | 110    | 53        |
| 7     | 4.5     | 100    | 47        |
| 8     | 4.5     | 90     | 31        |
| 9     | 4.5     | 120    | 46        |

**Scheme S14:** Screening of the amount of butyl acrylate and temperature.



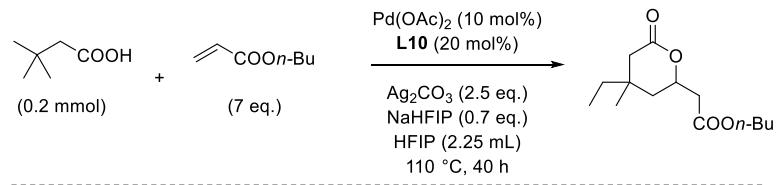
| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 1.50    | 54        |
| 2     | 1.75    | 56        |
| 3     | 2.00    | 56        |
| 4     | 2.50    | 60        |
| 5     | 3.00    | 60        |
| 6     | 3.50    | 60        |
| 7     | 4.00    | 60        |

**Scheme S15:** Screening of the amount of  $\text{Ag}_2\text{CO}_3$ .



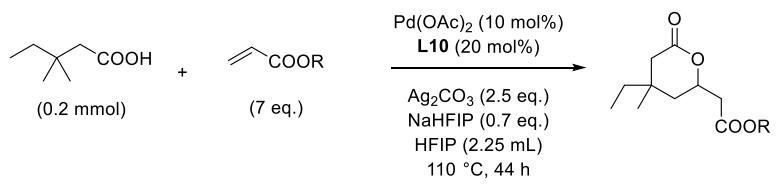
| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 4.5     | 46        |
| 2     | 5.5     | 52        |
| 3     | 6.0     | 52        |
| 4     | 6.5     | 58        |
| 5     | 7.0     | 59        |
| 6     | 7.5     | 59        |
| 7     | 8.0     | 59        |

**Scheme S16:** Screening of the amount of n-butyl acrylate.



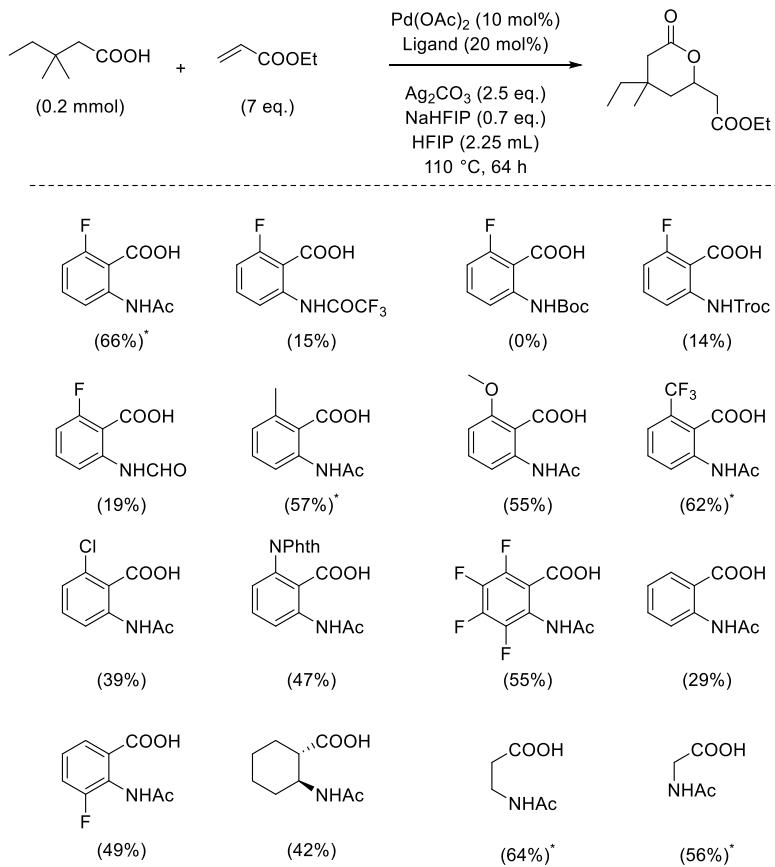
| Entry | Atmosphere | Yield (%) |
|-------|------------|-----------|
| 1     | air        | 56        |
| 2     | argon      | 56        |
| 3     | oxygen     | 48        |

**Scheme S17:** Screening of the different atmospheres.



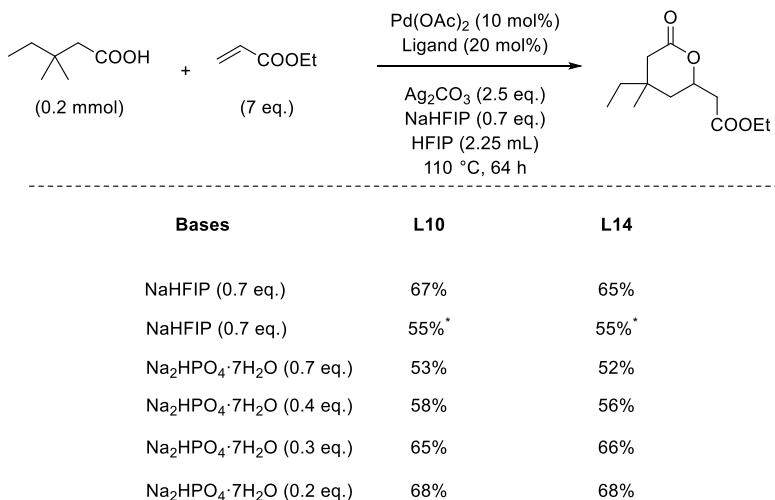
| Entry | R    | Yield (%) |
|-------|------|-----------|
| 1     | Me   | 59        |
| 2     | Et   | 59        |
| 3     | Bn   | 49        |
| 4     | n-Bu | 59        |

**Scheme S18:** Screening of the different acrylates.

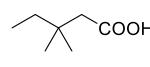
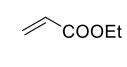
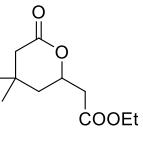


\*Average yields are calculated (with respect to light, dark, longer time)

**Scheme S19:** Screening of Ligands.



**Scheme S20:** Screening of the amount of bases. \*Reaction time = 46 h

|   |         |   |  |   |
|---|---------|---|--|---|
|  | +       |  | Pd(OAc) <sub>2</sub> (10 mol%)<br>Ligand (20 mol%)<br>Ag <sub>2</sub> CO <sub>3</sub> (2.5 eq.)<br>Na <sub>2</sub> HPO <sub>4</sub> ·7H <sub>2</sub> O (0.2 eq.)<br>HFIP (2.25 mL)<br>110 °C, 72 h |  |
|   | x (eq.) | L10   | L14  |   |
| 7   | 66%     | 69%   |  |   |
| 6   | 65%     | 67%   |  |   |
| 5   | 51%     | 61%   |  |   |
| 4   | 45%     | 57%   |  |   |
| 3   | 41%     | 48%   |  |   |

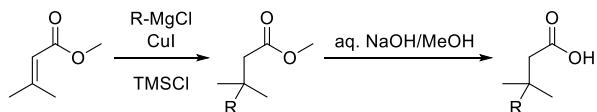
**Scheme S21:** Screening of the amount of ethyl acrylate.

# Preparation of Substrates

## General procedure B: $\gamma$ -Arylation of 3,3-dimethylbutyric acid (1a)

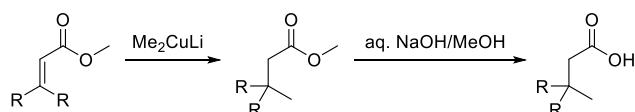
An oven dried 150 mL Schlenk tube was charged with with  $\text{Pd}(\text{OAc})_2$  (112 mg, 0.500 mmol, 10 mol%), Ac-D-Phe-OH (207 mg, 1.00 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (1.38 g, 5.00 mmol, 1.0 equiv),  $\text{K}_2\text{HPO}_4$  (871 mg, 5.00 mmol, 1.00 equiv), 3,3-dimethylbutyric acid (**1a**) (2.32 mg, 20.0 mmol, 4.0 equiv), aryl iodide (5.0 mmol, 1.0 equiv) and HFIP (50 mL). The reaction mixture was stirred for 24 h at 100 °C. The reaction was allowed to cool to room temperature and filtered over a pad of Celite®, the residue was washed with  $\text{CH}_2\text{Cl}_2$  (30 mL) to complete elution and all volatiles were removed under reduced pressure. The crude product was dissolved in water (30 mL) and the aqueous solution was washed with  $\text{CH}_2\text{Cl}_2$  (2 × 40 mL). The aqueous phase was acidified with HCl (10 wt%) until the pH was between 1 and 4 and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 40 mL). The combined organic phases were dried over  $\text{MgSO}_4 \cdot \text{H}_2\text{O}$  and all volatiles were removed under reduced pressure. The crude product was purified by silica column chromatography using  $\text{CH}_2\text{Cl}_2:\text{AcOH}$  (99.5:0.5).

## General procedure C: Synthesis of $\beta$ -quaternary carboxylic acids via 1,4 addition of Normann cuprates<sup>2</sup>



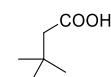
Methyl 3-methylbut-2-enoate (1.0 equiv) was dissolved in THF (0.5M), CuI (0.1 equiv) was added and the mixture was cooled to –20 °C. TMSCl (1.2 equiv) was added slowly and the Grignard reagent (1.2 equiv) was added over 90 minutes via a syringe pump. The mixture was slowly allowed to warm up to r.t. and was stirred for 16 h. The reaction was quenched by the addition of sat. aq.  $\text{NH}_4\text{Cl}$  solution (30 mL) and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 × 50 mL). The combined organic phases were washed with brine and dried over  $\text{MgSO}_4 \cdot \text{H}_2\text{O}$ . All volatiles were removed and the residue was transferred with MeOH (10 mL) to a Schlenk tube and aq. NaOH (10 wt%, 10 mL) was added. The reaction mixture was heated to 60°C and stirred for 16h. The mixture was allowed to cool down to r.t. and was concentrated under reduced pressure. Water (20 mL) was added and the aqueous solution was washed with  $\text{CH}_2\text{Cl}_2$  (2 × 40 mL). The aqueous phase was acidified with HCl (10 wt%) until the pH was between 1 and 4 and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 40 mL). The combined organic phases were dried over  $\text{MgSO}_4 \cdot \text{H}_2\text{O}$  and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using  $\text{CH}_2\text{Cl}_2:\text{AcOH}$  (99.7:0.3).

**General procedure D: Synthesis of  $\beta$ -quarternary carboxylic acids via 1,4 addition with Gilman reagent<sup>3</sup>**



In a dry argon filled schlenk tube CuI (2.0 equiv) and Et<sub>2</sub>O (30 mL) were added and the suspension was cooled to 0 °C. MeLi (1.6 M in Et<sub>2</sub>O, 4.0 equiv) was added dropwise and the mixture was stirred for 10 minutes. The solvent was removed at 0 °C under reduced pressure and CH<sub>2</sub>Cl<sub>2</sub> (15mL) was added. The mixture was stirred for 5 minutes and CH<sub>2</sub>Cl<sub>2</sub> was removed at 0 °C under reduced pressure. CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added and the reaction mixture was cooled to -78 °C. TMSCl (2.0 equiv) and the  $\alpha,\beta$ -unsaturated carbonyl compound (1.0 equiv) were added dropwise and the mixture was stirred for 1 h. The reaction mixture was allowed to slowly warm up to r.t. and stirred for 16 h. The reaction was quenched by the addition of sat. aq. NH<sub>4</sub>Cl solution (30 mL) and conc. aq. ammonia (30 mL) was added. The aqueous phase was extracted with Et<sub>2</sub>O (3 x 50 mL) and the combined organic phases were washed with brine and dried over MgSO<sub>4</sub>·H<sub>2</sub>O. All volatiles were removed and the residue was transferred with MeOH (10 mL) to a Schlenk tube and aq. NaOH (10 wt%, 10 mL) was added. The reaction mixture was heated to 60°C and stirred for 16h. The mixture was allowed to cooldown to r.t. and was concentrated under reduced pressure. Water (20 mL) was added and the aqueous solution was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 40 mL). The aqueous phase was acidified with HCl (10 wt%) until the pH was between 1 and 4. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 40 mL). The combined organic phases were dried over MgSO<sub>4</sub>·H<sub>2</sub>O and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>:AcOH (99.7:0.3).

**3,3-dimethylpentanoic acid (1b):**



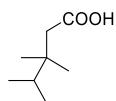
<sup>1b</sup> Following the general procedure **C** in 25.0 mmol scale and using ethylmagnesium chloride (2.0 M in THF, 15 mL, 30 mmol), the target compound **1b** was obtained as a colorless oil (1.99 g, 15.2 mmol, 61%).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  = 11.58 (s, 1H), 2.21 (s, 2H), 1.37 (q, *J* = 7.5 Hz, 2H), 1.00 (s, 6H), 0.86 (t, *J* = 7.5 Hz, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  = 179.6, 45.7, 34.7, 33.5, 26.8, 8.6 ppm.

The data are in good agreement with those reported in the literature.<sup>4</sup>

**3,3,4-trimethylpentanoic acid (1c):**



**1c** Following the general procedure **C** in 8.00 mmol scale and using isopropylmagnesium chloride (2.0 M in THF, 4.80 mL, 9.60 mmol) the target compound **1c** was obtained as a colorless oil (482 mg, 3.34 mmol, 42%).

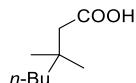
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 11.63 (s, 1H), 2.25 (s, 2H), 1.63 (hept, *J* = 6.8 Hz, 1H), 0.99 (s, 6H), 0.87 (d, *J* = 6.8 Hz, 6H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 179.6, 44.4, 36.5, 35.9, 24.3, 17.6 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>8</sub>H<sub>16</sub>NaO<sub>2</sub><sup>+</sup> 167.1043, Found 167.1039.

**IR (cm<sup>-1</sup>):** 2967, 1701, 1468, 1410, 1310, 1250, 905, 727.

**3,3-dimethylheptanoic acid (1d):**



**1d** Following the general procedure **C** in 8.00 mmol scale and using *n*-butylmagnesium bromide (1.0 M in THF, 11.2 mL, 11.2 mmol) the target compound **1d** was obtained as a colorless oil (291 mg, 1.84 mmol, 23%).

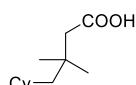
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 11.38 (s, 1H), 2.22 (s, 2H), 1.39 – 1.20 (m, 6H), 1.01 (s, 6H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 179.5, 46.1, 42.2, 33.3, 27.4, 26.4, 23.5, 14.2 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>9</sub>H<sub>18</sub>NaO<sub>2</sub><sup>+</sup> 181.1199, Found 181.1198.

**IR (cm<sup>-1</sup>):** 2932, 1793, 1470, 1408, 1369, 1252, 1177, 905, 727.

**4-cyclohexyl-3,3-dimethylbutanoic acid (1e):**



**1e** Following the general procedure **B** and using iodobenzene (1.02 g, 5.00 mmol) the intermediate 3,3-dimethyl-4-phenylbutanoic acid was obtained as a colorless oil (129 mg, 0.670 mmol, 13%). A hydrogenation vial was charged with 3,3-dimethyl-4-phenylbutanoic acid (91 mg, 0.47 mmol, 1 equiv), Rh/Al<sub>2</sub>O<sub>3</sub> (5 mol%) and acetic acid (1 mL). The reaction mixture stirred at r.t. under a H<sub>2</sub> pressure of 10 bar at r.t. for 16 h. The catalyst was removed by filtration over Celite and the filtrate was concentrated by evaporation. The crude product was purified by silica gel column chromatography using (pentane:EtOAc = 90:10). The target compound was obtained as a colorless solid (93 mg, 0.47 mmol, 99%).

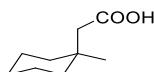
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 11.00 (s, 1H), 2.24 (s, 2H), 1.76 – 1.54 (m, 5H), 1.39 – 0.89 (m, 14H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 178.26, 50.03, 46.55, 35.99, 34.05, 33.95, 27.66, 26.74, 26.36 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>12</sub>H<sub>22</sub>NaO<sub>2</sub><sup>+</sup> 221.1512, Found 221.1511.

**IR (cm<sup>-1</sup>):** 2924, 1703, 1449, 1369, 907, 731.

**2-(1-methylcyclohexyl)acetic acid (1f):**



**1f** Following the general procedure **D** in 8.32 mmol scale and using ethyl 2-cyclohexylideneacetate (1.40 g, 8.32 mmol) the target compound **1f** was obtained as a colorless oil (944 mg, 6.04 mmol, 73%).

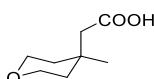
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 11.59 (s, 1H), 2.26 (s, 2H), 1.56–1.20 (m, 10H), 1.05 (s, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 179.6, 45.9, 37.9, 33.4, 26.2, 25.5, 22.1 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>9</sub>H<sub>16</sub>NaO<sub>2</sub><sup>+</sup> 179.1043, Found 179.1034.

**IR (cm<sup>-1</sup>):** 2928, 1703, 1447, 1408, 1235, 907, 731.

**2-(4-methyltetrahydro-2H-pyran-4-yl)acetic acid (1g):**



**1g** Following the general procedure **D** in 5.88 mmol scale and using ethyl 2-(tetrahydro-4H-pyran-4-ylidene)acetate (1.00 g, 5.88 mmol) the target compound **1g** was obtained as a colorless oil (562 mg, 3.55 mmol, 60%).

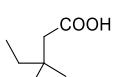
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 10.37 (s, 1H), 3.77–3.61 (m, 4H), 2.33 (s, 2H), 1.71–1.59 (m, 2H), 1.53–1.42 (m, 2H), 1.15 (s, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 177.7, 63.8, 45.9, 37.5, 31.0, 24.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>8</sub>H<sub>14</sub>NaO<sub>3</sub><sup>+</sup> 181.0835, Found 181.0840.

**IR (cm<sup>-1</sup>):** 2932, 1705, 1227, 1105, 920, 839.

**3-ethyl-3-methylpentanoic acid (1h):**



**1h** Following the general procedure **D** in 0.998 mmol scale and using ethyl 3-ethylpent-2-enoate (380 mg, 0.998 mmol) the target compound **1h** was obtained as a colorless oil (48.1 mg, 0.308 mmol, 31%).

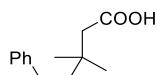
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 2.22 (s, 2H), 1.38 (q, *J* = 7.5 Hz, 4H), 0.96 (s, 2H), 0.83 (t, *J* = 7.5 Hz, 6H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 179.1, 43.1, 36.1, 31.4, 24.1, 8.1 ppm.

**HRMS (ESIneg) m/z:** Calcd for C<sub>8</sub>H<sub>15</sub>O<sub>2</sub><sup>-</sup> 143.1067, Found 143.1070.

**IR (cm<sup>-1</sup>):** 2967, 1703, 1458, 1265, 1232.

**3,3-dimethyl-5-phenylpentanoic acid (1i):**



**1i** Following the general procedure **C** in 8.00 mmol scale and using phenylethylmagnesium bromide (1.0 M in THF, 11.2 mL, 11.2 mmol) the target compound **1i** was obtained as a colorless oil (121 mg, 0.587 mmol, 7%).

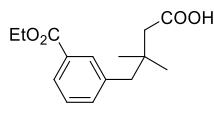
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 10.59 (s, 1H), 7.41–7.29 (m, 2H), 7.29–7.19 (m, 3H), 2.74–2.61 (m, 2H), 2.39 (s, 2H), 1.81–1.67 (m, 2H), 1.18 (s, 6H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 179.0, 142.9, 128.5, 128.5, 125.8, 45.9, 44.5, 33.5, 30.9, 27.5 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>18</sub>NaO<sub>2</sub><sup>+</sup> 229.1199, Found 229.1199.

**IR (cm<sup>-1</sup>):** 2961, 1703, 1469, 1250, 1074, 905, 727.

**4-(3-(ethoxycarbonyl)phenyl)-3,3-dimethylbutanoic acid (1j):**



**1j** Following the general procedure **B** and using ethyl 3-iodobenzoate (1.38 g, 5.00 mmol) the target compound **1j** was obtained as a colorless oil (230 mg, 0.870 mmol, 17%).

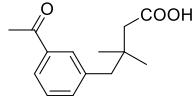
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 11.08 (s, 1H), 7.95–7.87 (m, 1H), 7.86 (s, 1H), 7.42–7.32 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.75 (s, 2H), 2.24 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 6H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 178.1, 167.0, 138.7, 135.3, 131.8, 130.3, 128.0, 127.6, 61.1, 47.6, 45.3, 34.4, 27.3, 14.5 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>15</sub>H<sub>20</sub>NaO<sub>4</sub><sup>+</sup> 287.1254, Found 287.1260.

**IR (cm<sup>-1</sup>):** 2932, 1705, 1468, 1369, 1283, 1200, 1107, 1026.

**4-(3-acetylphenyl)-3,3-dimethylbutanoic acid (1k):**



**1k** Following the general procedure **B** and using 1-(3-iodophenyl)ethan-1-one (1.23 g, 5.00 mmol) the target compound **1k** was obtained as a colorless oil (296 mg, 1.26 mmol, 25%).

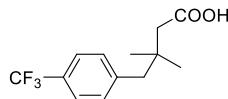
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 7.84 – 7.80 (dt, *J* = 6.8, 1.9 Hz, 1H), 7.79 (s, 1H), 7.43 – 7.35 (m, 2H), 2.77 (s, 2H), 2.60 (s, 3H), 2.24 (s, 2H), 1.06 (s, 6H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 198.6, 178.2, 139.0, 137.0, 135.6, 130.5, 128.3, 126.6, 47.5, 45.2, 34.4, 27.3, 26.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>14</sub>H<sub>18</sub>NaO<sub>3</sub><sup>+</sup> 257.1148, Found 257.1151.

**IR (cm<sup>-1</sup>):** 2961, 2255, 1705, 1684, 1437, 1275, 905, 727.

**3,3-dimethyl-4-(4-(trifluoromethyl)phenyl)butanoic acid (1l):**



Following the general procedure **B** and using 1-iodo-4-(trifluoromethyl)benzene (1.36 g, 5.00 mmol) the target compound **1l** was obtained as a colorless oil (141 mg, 0.542 mmol, 11%).

**<sup>1</sup>H-NMR (599 MHz, CDCl<sub>3</sub>):** δ = 7.54 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.77 (s, 2H), 2.24 (s, 2H), 1.06 (s, 6H) ppm.

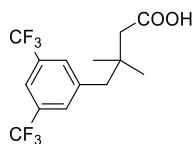
**<sup>13</sup>C-<sup>{19}</sup>F-NMR (151 MHz, CDCl<sub>3</sub>):** δ = 178.0, 142.6, 131.1, 128.8, 124.9, 124.5, 47.4, 45.1, 34.4, 27.4 ppm.

**<sup>19</sup>F-<sup>{1}</sup>H-NMR (564 MHz, CDCl<sub>3</sub>):** δ = -62.4 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>15</sub>F<sub>3</sub>NaO<sub>2</sub><sup>+</sup> 283.0916, Found 283.0910.

**IR (cm<sup>-1</sup>):** 2965, 1703, 1620, 1323, 1165, 1123, 1069, 1020, 853.

**4-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethylbutanoic acid (1m):**



Following the general procedure **B** and using 1-iodo-3,5-bis(trifluoromethyl)benzene (1.70 g, 5.00 mmol) the target compound **1m** was obtained as a colorless oil (152 mg, 0.463 mmol, 9%).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 11.34 (s, 1H), 7.77 (s, 1H), 7.68 (s, 2H), 2.87 (s, 2H), 2.25 (s, 2H), 1.08 (s, 6H) ppm.

**<sup>13</sup>C-<sup>{19}</sup>F-NMR (126 MHz, CDCl<sub>3</sub>):** δ = 178.9, 141.0, 131.4, 130.8, 123.6, 120.6, 46.9, 45.2, 34.4, 27.3 ppm.

**<sup>19</sup>F-<sup>{1}</sup>H-NMR (470 MHz, CDCl<sub>3</sub>):** δ = -63.0 ppm.

The data are in good agreement with those reported in the literature.<sup>5</sup>

## Acid Scope

### General procedure E:

An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 0.020 mmol, 10 mol%),  $\text{Ac-}\beta\text{-Ala-OH}$  (5.3 mg, 0.040 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (96.5 mg, 0.350 mmol, 1.75 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7 \text{H}_2\text{O}$  (10.7 mg, 0.04 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (**1a**) (23.2 mg, 0.2 mmol), acrylate (0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred for 24 h at 110 °C. The mixture was filtered through a pad of Celite® using  $\text{CH}_2\text{Cl}_2$  (30mL) to complete the elution and all volatiles were removed under reduced pressure.  $\text{KMnO}_4$  (31.6 mg, 0.200 mmol, 1.0 equiv),  $\text{Et}_3\text{BnNCl}$  (9.1 mg, 0.040 mmol, 0.2 equiv) and acetone (3 mL) were added and the mixture was stirred for 30 minutes. Concentrated aq.  $\text{Na}_2\text{SO}_3$  was added until all permanganate was quenched. The mixture was filtered over a pad of celite using  $\text{CH}_2\text{Cl}_2$  (30 mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 50:50).

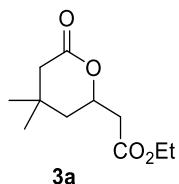
### General procedure F:

An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 0.020 mmol, 10 mol%),  $\text{Ac-}\beta\text{-Ala-OH}$  (5.3 mg, 0.040 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (96.5 mg, 0.350 mmol, 1.75 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7 \text{H}_2\text{O}$  (10.7 mg, 0.04 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (**1a**) (23.2 mg, 0.2 mmol), acrylate (0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred for 24 h at 110 °C. The mixture was filtered through a pad of Celite® using  $\text{CH}_2\text{Cl}_2$  (30 mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 50:50).

### General procedure G:

An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 0.020 mmol, 10 mol%),  $\text{Ac-}\beta\text{-Ala-OH}$  (5.3 mg, 0.040 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (138 mg, 0.500 mmol, 2.5 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7 \text{H}_2\text{O}$  (10.7 mg, 0.04 mmol, 0.2 equiv), carboxylic acid (0.2 mmol), acrylate (1.40 mmol, 7.0 equiv) and HFIP (2.25 mL). The reaction mixture was stirred for 72 h at 110 °C. The mixture was filtered through a pad of Celite® using  $\text{CH}_2\text{Cl}_2$  (30mL) to complete the elution and all volatiles were removed under reduced pressure.  $\text{KMnO}_4$  (31.6 mg, 0.2 mmol, 1.0 equiv),  $\text{Et}_3\text{BnNCl}$  (9.1 mg, 0.04 mmol, 0.2 equiv) and acetone (3 mL) were added and the mixture was stirred for 30 minutes. Concentrated aq.  $\text{Na}_2\text{SO}_3$  was added until all permanganate was quenched. The mixture was filtered over a pad of celite using  $\text{CH}_2\text{Cl}_2$  (30 mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 20:80).

**Ethyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3a):**



Following the general procedure E and using 3,3-dimethylbutyric acid (**1a**) (23.2 mg, 0.200 mmol) the target compound **3a** was obtained as a colorless oil (27.4 mg, 0.128 mmol, 64%).

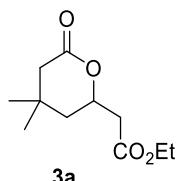
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) = 4.85-4.73 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.74 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.54 (dd, *J* = 16.1, 5.9 Hz, 1H), 2.39 (dd, *J* = 16.5, 1.6 Hz, 1H), 2.22 (d, *J* = 16.6 Hz, 1H), 1.77 (ddd, *J* = 13.9, 3.5, 1.6 Hz, 1H), 1.49 (dd, *J* = 13.9, 12.0 Hz, 1H), 1.26 (t, *J* = 7.1, 3H), 1.11 (s, 3H), 1.05 (s, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.4, 169.9, 73.8, 61.1, 43.8, 41.8, 40.7, 31.1, 30.0, 27.6, 14.2 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>11</sub>H<sub>18</sub>NaO<sub>4</sub><sup>+</sup> 237.1097, Found 237.1117.

**IR (cm<sup>-1</sup>):** 2963, 2253, 1732, 1387, 1373, 1238, 1194, 1036, 907. 792.

**Results for large scale: Ethyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3a):**



An oven dried 150 mL Schlenk tube was charged with Pd(OAc)<sub>2</sub> (104 mg, 0.500 mmol, 10 mol%), Ac-β-Ala-OH (131 mg, 1.00 mmol, 20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (2.41 g, 8.75 mmol, 1.75 equiv), Na<sub>2</sub>HPO<sub>4</sub> · 7 H<sub>2</sub>O (268 mg, 1.00 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (**1a**) (511 mg, 5.00 mmol), ethyl acrylate (1.25 g, 12.5 mmol, 2.5 equiv) and HFIP (56 mL). The reaction mixture was stirred for 24 h at 110 °C. The mixture was filtered through a pad of Celite® using CH<sub>2</sub>Cl<sub>2</sub> (100mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 70:30). To the crude product was added KMnO<sub>4</sub> (31.6 mg, 0.2 mmol, 1.0 equiv), Et<sub>3</sub>BnNCl (9.1 mg, 0.04 mmol, 0.2 equiv) and acetone (3 mL). The mixture was stirred for 30 minutes and concentrated aq. Na<sub>2</sub>SO<sub>3</sub> was added until all permanganate was quenched. The mixture was filtered over a pad of Celite® using CH<sub>2</sub>Cl<sub>2</sub> (30mL) to complete the elution and all volatiles were removed under reduced pressure. The product **3a** was obtained as a colorless oil (664 mg, 3.01 mmol, 62%).

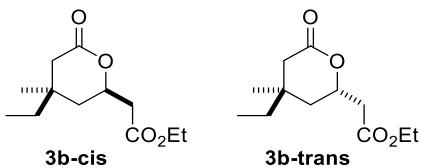
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 4.80 (dd, *J* = 12.1, 6.8, 6.0, 3.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.76 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.54 (dd, *J* = 16.1, 6.0 Hz, 1H), 2.40 (dd, *J* = 16.6, 1.6 Hz, 1H), 2.23 (d, *J* = 16.6 Hz, 1H), 1.78 (ddd, *J* = 13.9, 3.5, 1.6 Hz, 1H), 1.50 (dd, *J* = 13.9, 12.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.11 (s, 3H), 1.06 (s, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.4, 169.9, 73.8, 61.1, 43.8, 41.8, 40.7, 31.1, 30.0, 27.6, 14.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>11</sub>H<sub>18</sub>NaO<sub>4</sub><sup>+</sup> 237.1097, Found 237.1117.

**IR (cm<sup>-1</sup>):** 2963, 2253, 1732, 1387, 1373, 1238, 1194, 1036, 907, 729.

*cis*-Ethyl 2-(4-ethyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (**3b-cis**) and *trans*-ethyl 2-(4-ethyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (**3b-trans**):



Following the general procedure **G** and using 3,3-dimethylpentanoic acid (**1b**) (26 mg, 0.20 mmol) the target compound **3b** was obtained as a colorless oil (30.1 mg, 0.132 mmol, 66%, d.r. = 1.3/1.0).

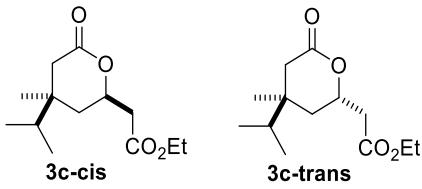
**<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):** 4.83-4.75 (m, 1H<sup>cis</sup>), 4.73-4.66 (m, 1H<sup>trans</sup>), 4.19-4.12 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.78-2.71 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.58-2.49 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.42 (dt, *J* = 16.1, 1.2 Hz, 1H<sup>trans</sup>), 2.34-2.23 (m, 2H<sup>cis</sup>+1H<sup>trans</sup>), 2.18 (dd, *J* = 16.1, 1.1 Hz, 1H<sup>trans</sup>), 1.89 (ddd, *J* = 14.2, 3.3, 1.2 Hz, 1H<sup>trans</sup>), 1.71 (ddd, *J* = 13.9, 3.2, 1.4 Hz, 1H<sup>cis</sup>), 1.59-1.31 (m, 6.9H), 1.28-1.23 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>) 1.06 (s, 3H<sup>cis</sup>), 0.99 (s, 3H<sup>trans</sup>), 0.91-0.84 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>) ppm.

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):**  $\delta$  = 172.0, 171.8, 170.0, 169.9, 73.6(3), 73.5(5), 61.1, 42.4, 42.0, 40.7, 40.5, 40.0, 39.7, 36.2, 33.1, 32.9, 32.8, 27.7, 24.9, 14.2, 8.2, 7.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>12</sub>H<sub>20</sub>NaO<sub>4</sub><sup>+</sup> 251.1254, Found 251.1269.

**IR (cm<sup>-1</sup>):** 2967, 2255, 1732, 1522, 1437, 1052, 1190, 1057, 1026, 907, 731.

*cis*-Ethyl 2-(4-isopropyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (**3c-cis**) and *trans*-ethyl 2-(4-isopropyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (**3c-trans**):



Following the general procedure **G** and using 3,3,4-trimethylpentanoic acid (**1c**) (28.8 mg, 0.200 mmol) the target compound **3c** was obtained as a colorless oil (32.1 mg, 0.132 mmol, 66%, d.r. = 1.7/1.0).

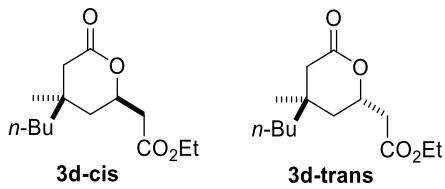
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 4.85-4.71 (m, 1H<sup>cis</sup>), 4.68-4.59 (m, 1H<sup>trans</sup>), 4.20-4.08 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.80-2.69 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.60-2.46 (m, 1H<sup>cis</sup>+2H<sup>trans</sup>), 2.35-2.24 (m, 2H<sup>cis</sup>), 2.15 (dd, *J* = 15.3, 1.1 Hz, 1H<sup>trans</sup>), 2.03 (dd, *J* = 14.4, 3.3 Hz, 1H<sup>trans</sup>), 1.73-1.58 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 1.52-1.52 (m, 2H<sup>cis</sup>), 1.34-1.21 (m, 3H<sup>cis</sup>+4H<sup>trans</sup>), 1.01 (s, 3H<sup>cis</sup>), 0.93 (s, 3H<sup>trans</sup>), 0.89 (d, *J* = 6.8 Hz, 6H<sup>trans</sup>), 0.85 (d, *J* = 6.9 Hz, 6H<sup>cis</sup>) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):**  $\delta$  = 172.8, 172.2, 169.9(8), 169.9(6), 73.6, 73.4, 61.1, 41.0, 40.7, 40.5, 40.3, 39.4, 38.3, 38.0, 35.7(0), 35.6(5), 35.5, 24.9, 22.3, 17.3, 17.1, 17.0, 16.9, 14.2 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1424.

**IR (cm<sup>-1</sup>):** 3055, 2986, 1734, 1422, 1265, 1192, 1063, 729, 704.

*cis*-Ethyl 2-(4-butyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (**3d-cis**) and *trans*-ethyl 2-(4-butyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (**3d-trans**):



Following the general procedure **G** and using 3,3-dimethylheptanoic acid (**1d**) (31.6 mg, 0.200 mmol) the target compound **3d** was obtained as a colorless oil (33.5 mg, 0.131 mmol, 65%, d.r. = 1.3/1.0).

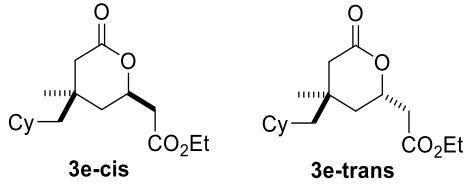
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 4.78 (dddd, *J* = 12.3, 7.0, 5.9, 3.2 Hz, 1H<sup>cis</sup>), 4.74–4.65 (m, 1H<sup>trans</sup>), 4.20–4.12 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.78–2.70 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.58–2.48 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.43 (dd, *J* = 16.1, 1.3 Hz, 1H<sup>trans</sup>), 2.33 (dd, *J* = 16.6, 1.4 Hz, 1H<sup>cis</sup>), 2.26 (d, *J* = 16.6 Hz, 1H<sup>cis</sup>), 2.18 (d, *J* = 16.1 Hz, 1H<sup>trans</sup>), 1.89 (ddd, *J* = 14.2, 3.3, 1.3 Hz, 1H<sup>trans</sup>), 1.72 (ddd, *J* = 13.9, 3.2, 1.4 Hz, 1H<sup>cis</sup>), 1.52–1.21 (m, 10H<sup>cis</sup>+10H<sup>trans</sup>), 1.07 (s, 3H<sup>cis</sup>), 1.00 (s, 3H<sup>trans</sup>), 0.93–0.84 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 172.1, 171.9, 170.0(3), 170.0(0), 73.7, 73.6, 61.1, 43.6, 42.8, 42.4, 40.7, 40.5, 40.4, 40.3, 40.1, 32.6(9), 32.6(5), 28.2, 26.0, 25.6, 25.4, 23.2(9), 23.2(7), 14.2, 14.1(1), 14.0(9) ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>14</sub>H<sub>24</sub>NaO<sub>4</sub><sup>+</sup> 279.1567, Found 279.1587.

**IR (cm<sup>-1</sup>):** 2961, 2932, 2874, 2862, 2255, 1730, 1468, 1381, 1314, 1217, 1188, 1063, 1026, 907, 725.

*cis*-Ethyl 2-(4-(cyclohexylmethyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate ) (**3e-cis**) and *trans*-ethyl 2-(4-(cyclohexylmethyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate ) (**3e-trans**):



Following the general procedure **G** and using 4-cyclohexyl-3,3-dimethylbutanoic acid (**1e**) (39.7 mg, 0.200 mmol) the target compound **3e** was obtained as a colorless oil (32.2 mg, 0.109 mmol, 54%, d.r. = 1.3/1.0).

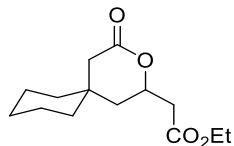
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 4.85 – 4.69 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.20 – 4.10 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.79 – 2.68 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.58 – 2.48 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.43 (dd, *J* = 16.0, 1.2 Hz, 1H<sup>trans</sup>), 2.35 (dd, *J* = 16.6, 1.6 Hz, 1H<sup>cis</sup>), 2.27 (d, *J* = 16.7 Hz, 1H<sup>cis</sup>), 2.19 (d, *J* = 16.0 Hz, 1H<sup>trans</sup>), 1.90 (ddd, *J* = 14.1, 3.5, 1.2 Hz, 1H<sup>trans</sup>), 1.75 (ddd, *J* = 13.9, 3.3, 1.6 Hz, 1H<sup>cis</sup>), 1.71 – 1.56 (m, 5H, 5H<sup>cis</sup>+5H<sup>trans</sup>), 1.54 – 1.35 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 1.34 – 0.92 (m, 14H<sup>cis</sup>+14H<sup>trans</sup>) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 172.0, 171.8, 170.0(2), 169.9(6), 73.6(2), 73.5(9), 61.1, 51.4, 48.1, 43.38, 42.4, 41.0, 40.8, 40.7, 40.6, 35.9, 35.8, 35.7(7), 35.7(5), 34.0, 33.5, 33.3(7), 33.3(6), 28.7, 26.5(3), 26.5(0), 26.4(9), 26.1, 25.5, 14.2 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>17</sub>H<sub>28</sub>NaO<sub>4</sub><sup>+</sup> 319.1880, Found 319.1894.

**IR (cm<sup>-1</sup>):** 2924, 2853, 1732, 1449, 1250, 1190, 1026.

**Ethyl 2-(4-oxo-3-oxaspiro[5.5]undecan-2-yl)acetate (3f):**



**3f** Following the general procedure **G** and using 3-cyclohexyl-3-methylbutanoic acid (**1f**) (31.2 mg, 0.200 mmol) the target compound **3f** was obtained as a colorless oil (27.8 mg, 0.109 mmol, 55%).

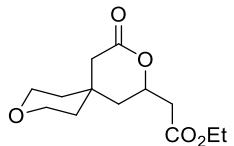
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 4.75 (dd, *J* = 12.1, 6.8, 6.0, 3.2 Hz, 1H), 4.23–4.08 (m, Hz, 2H), 2.75 (dd, *J* = 16.2, 6.8 Hz, 1H), 2.54 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.45 (dd, *J* = 16.2, 1.2 Hz, 1H), 2.26 (d, *J* = 16.2 Hz, 1H), 1.95 (ddd, *J* = 14.1, 3.2, 1.2 Hz, 1H), 1.54–1.30 (m, 11H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 171.8, 170.0, 73.1, 61.1, 40.6, 39.8, 36.4, 33.0, 25.7, 21.8, 21.6, 14.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>14</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 277.1410, Found 277.1422.

**IR (cm<sup>-1</sup>):** 2930, 2859, 2255, 1730, 1454, 1445, 1387, 1369, 1314, 1252, 1204, 1186, 1026, 907, 725.

**Ethyl 2-(4-oxo-3,9-dioxaspiro[5.5]undecan-2-yl)acetate (3g):**



**3g** Following the general procedure **G** and using 3-methyl-3-(tetrahydro-2H-pyran-4-yl)butanoic acid (**1g**) (31.6 mg, 0.200 mmol) the target compound **3g** was obtained as a colorless oil (25.6 mg, 0.100 mmol, 50%).

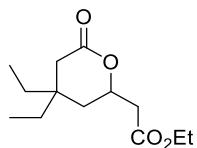
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ = 4.82–4.75 (m, 1H), 4.20–4.13 (m, 2H), 3.73–3.59 (m, 4H), 2.78 (dd, *J* = 16.2, 6.7 Hz, 1H), 2.62–2.54 (m, 2H), 2.35 (d, *J* = 16.3 Hz, 1H), 2.03 (ddd, *J* = 14.1, 3.2, 1.2 Hz, 1H), 1.64–1.60 (m, 2H), 1.56–1.46 (m, 3H), 1.29–1.25 (m, 3H) ppm.

**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ = 170.8, 169.8, 72.8, 63.5, 63.4, 61.2, 41.4, 40.4, 39.6, 39.4, 36.4, 30.9, 14.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>20</sub>NaO<sub>5</sub><sup>+</sup> 279.1203, Found 279.1207.

**IR (cm<sup>-1</sup>):** 3053, 2988, 2305, 1730, 1422, 1105, 1020, 908, 729, 704.

**Ethyl 2-(4,4-diethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3h):**



**3h** Following the general procedure **G** and using 3-ethyl-3-methylpentanoic acid (**1h**) (28.8 mg, 0.200 mmol) the target compound **3h** was obtained as a colorless oil (24.1 mg, 0.100 mmol, 50%).

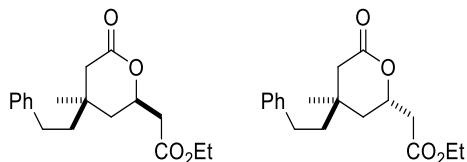
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 4.71 (dd, *J* = 12.0, 6.7, 6.3, 3.0 Hz, 1H), 4.20–4.13 (m, 2H), 2.77 (dd, *J* = 16.2, 6.7 Hz, 1H), 2.53 (dd, *J* = 16.2, 6.3 Hz, 1H), 2.37 (dd, *J* = 16.1, 1.0 Hz, 1H), 2.24 (d, *J* = 16.1 Hz, 1H), 1.81 (ddd, *J* = 14.2, 3.0, 0.9 Hz, 1H), 1.50 – 1.31 (m, 5H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.89 – 0.80 (m, 6H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 172.4, 170.0, 73.4, 61.1, 40.5, 40.3, 38.2, 35.6, 32.2, 30.0, 14.3, 7.8, 7.6 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1418.

**IR (cm<sup>-1</sup>):** 2969, 2928, 1732, 1464, 1383, 1265, 1184, 1061, 1026, 737.

**cis-Ethyl 2-(4-methyl-6-oxo-4-phenethyltetrahydro-2H-pyran-2-yl)acetate (3i-cis) and trans-ethyl 2-(4-methyl-6-oxo-4-phenethyltetrahydro-2H-pyran-2-yl)acetate (3i-trans):**



**3i-cis** **3i-trans** Following the general procedure **G** and using 3,3-dimethyl-5-phenylpentanoic acid (**1i**) (41.3 mg, 0.200 mmol) the target compound **3i** was obtained as a colorless oil (34.6 mg, mmol, 0.114 mmol, 57%, d.r. = 1.3/1.0).

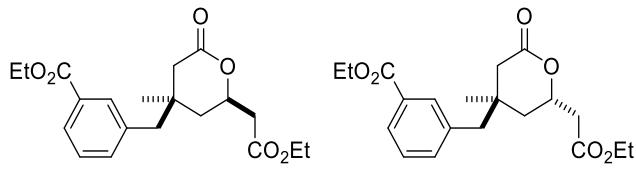
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 7.29 (ddt, *J* = 10.8, 6.3, 1.5 Hz, 2H<sup>cis</sup>+2H<sup>trans</sup>), 7.18 (tdd, *J* = 8.6, 4.3, 2.9 Hz, 3H<sup>cis</sup>+3H<sup>trans</sup>), 4.90 – 4.71 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.25 – 4.06 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.85 – 2.72 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.66 – 2.23 (m, 5H<sup>cis</sup>+5H<sup>trans</sup>), 2.00 (ddd, *J* = 14.2, 3.9, 1.6 Hz, 1H<sup>trans</sup>), 1.83 (ddd, *J* = 13.8, 3.2, 1.3 Hz, 1H<sup>cis</sup>), 1.77 – 1.42 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 1.27 (td, *J* = 7.1, 1.8 Hz, 3H<sup>cis</sup>+3H<sup>trans</sup>), 1.19 (s, 3H<sup>cis</sup>), 1.12 (s, 3H<sup>trans</sup>) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.6, 171.4, 169.9(1), 169.8(6), 141.7, 141.6, 128.7, 128.6, 128.3, 126.2, 126.1, 73.6, 73.5, 61.1, 45.9, 42.9, 42.7, 42.4, 40.6, 40.4, 40.2(4), 40.1(8), 32.9(2), 32.9(0), 30.4, 30.0, 28.2, 25.3, 14.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>18</sub>H<sub>24</sub>NaO<sub>4</sub><sup>+</sup> 327.1567, Found 327.1554.

**IR (cm<sup>-1</sup>):** 2936, 2255, 1730, 1456, 1250, 1190, 1028, 907, 725.

*cis*-Ethyl 3-((2-(2-ethoxy-2-oxoethyl)-4-methyl-6-oxotetrahydro-2H-pyran-4-yl)methyl)benzoate (3j-cis) and *trans*-ethyl 3-((2-(2-ethoxy-2-oxoethyl)-4-methyl-6-oxotetrahydro-2H-pyran-4-yl)methyl)benzoate (3j-cis):



3j-cis

## 3j-trans

**3j-cis** **3j-trans** Following the general procedure **G** and using 4-(3-(ethoxycarbonyl)phenyl)-3,3-dimethylbutanoic acid (**1j**) (52.9 mg, 0.200 mmol) the target compound **3j** was obtained as a colorless oil (36.1 mg, 0.100 mmol, 50%, d.r. = 1.8/1.0).

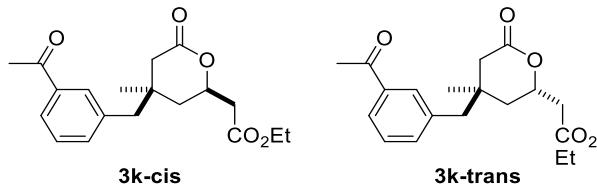
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 7.94 (dq, *J* = 7.7, 1.8 Hz, 1H<sup>cis</sup>+1H<sup>trans</sup>), 7.80 (dt, *J* = 9.8, 1.9 Hz, 1H<sup>cis</sup>+1H<sup>trans</sup>), 7.42 – 7.29 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 4.87 – 4.74 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.37 (q, *J* = 7.1 Hz, 2H<sup>cis</sup>+2H<sup>trans</sup>), 4.22 – 4.06 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.84 – 2.48 (m, 4H<sup>cis</sup>+5H<sup>trans</sup>), 2.41 – 2.26 (m, 2H<sup>cis</sup>), 2.17 (d, *J* = 15.9 Hz, 1H<sup>trans</sup>), 2.06 – 1.97 (m, 1H<sup>trans</sup>), 1.75 (ddd, *J* = 13.8, 3.6, 1.7 Hz, 1H<sup>cis</sup>), 1.58 (dd, *J* = 13.8, 11.9 Hz, 1H<sup>cis</sup>), 1.50 – 1.34 (m, 3H<sup>cis</sup>+4H<sup>trans</sup>), 1.25 (t, *J* = 7.0 Hz, 3H<sup>cis</sup>+3H<sup>trans</sup>), 1.10 (s, 3H<sup>cis</sup>), 1.02 (s, 3H<sup>trans</sup>) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 171.5, 170.8, 169.8(0), 169.7(6), 166.5(9), 166.5(6), 137.1, 136.7, 135.0, 134.9, 131.5(4), 131.5(1), 130.8, 130.7, 128.5, 128.4, 128.1(9), 128.1(7), 73.6, 73.4, 61.2, 61.1(2), 61.0(9), 49.2, 46.4, 42.0, 41.8, 40.7, 40.4, 40.0, 39.8, 34.0, 33.9, 28.8, 24.0, 14.5, 14.3(0), 14.2(7), 14.2 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_{20}H_{26}NaO_6^+$  385.1622, Found 385.1626.

**IR ( $\text{cm}^{-1}$ ):** 2986, 2255, 1719, 1447, 1369, 1283, 1200, 1026, 905, 723.

*cis*-Ethyl 2-(4-(3-acetylbenzyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3k-cis) and *trans*-ethyl 2-(4-(3-acetylbenzyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3k-trans):



**3k-cis** **3k-trans** Following the general procedure **G** using 4-(3-acetylphenyl)-3,3-dimethylbutanoic acid (**1k**) (46.9 mg, 0.200 mmol) the target compound **3k** was obtained as a colorless oil (30.6 mg, 0.092 mmol, 46%, d.r. = 1.6/1.0).

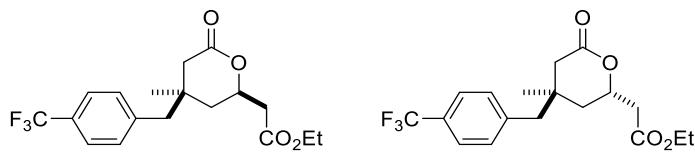
**<sup>1</sup>H-NMR (599 MHz, CDCl<sub>3</sub>):** δ = 7.85 (ddt, *J* = 7.8, 6.4, 1.5 Hz, 1H<sup>cis</sup>+1H<sup>trans</sup>), 7.73 (dt, *J* = 14.9, 1.9 Hz, 1H<sup>cis</sup>+1H<sup>trans</sup>), 7.42 (td, *J* = 7.6, 3.8 Hz, 1H<sup>cis</sup>+1H<sup>trans</sup>), 7.34 (tt, *J* = 7.6, 1.5 Hz, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.84 – 4.75 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.20 – 4.12 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.81 – 2.63 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 2.63 – 2.59 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 2.59 – 2.49 (m, 1H<sup>cis</sup>+2H<sup>trans</sup>), 2.39 – 2.28 (m, 2H<sup>cis</sup>), 2.19 (d, *J* = 16.0 Hz, 1H<sup>trans</sup>), 2.04 (dd, *J* = 14.2, 3.5 Hz, 1H<sup>trans</sup>), 1.77 (ddd, *J* = 13.8, 3.6, 1.7 Hz, 1H<sup>cis</sup>), 1.59 (dd, *J* = 13.8, 12.1 Hz, 1H<sup>cis</sup>), 1.45 (dd, *J* = 14.3, 11.9 Hz, 1H<sup>trans</sup>), 1.28 – 1.25 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 1.11 (s, 3H<sup>cis</sup>), 1.02 (s, 3H<sup>trans</sup>) ppm.

**$^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 198.1(8), 198.1(5), 171.4, 170.8, 169.8(2), 169.8(0), 137.4(0), 137.3(8), 137.3, 137.0, 135.3, 135.2, 130.2(4), 130.1(6), 128.7(4), 128.6(7), 127.2, 127.1, 73.6, 73.4, 61.2, 61.1, 49.3, 46.4, 42.1, 41.7, 40.7, 40.4, 40.1, 40.0, 34.0, 33.9, 28.7, 26.8(1), 26.8(0), 25.1, 14.2(8), 14.2(5) ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_{19}H_{24}NaO_5^+$  355.1516, Found 355.1521.

**IR ( $\text{cm}^{-1}$ ):** 3055, 2984, 2963, 2932, 1728, 1684, 1265, 1179, 1026, 733.

*cis*-Ethyl 2-(4-methyl-6-oxo-4-(trifluoromethyl)benzyl)tetrahydro-2H-pyran-2-yl)acetate (3*l*-*cis*) and *trans*-ethyl 2-(4-methyl-6-oxo-4-(trifluoromethyl)benzyl)tetrahydro-2H-pyran-2-yl)acetate (3*l*-*trans*):



**3I-cis** **3I-trans** Following the general procedure **G** and using 3,3-dimethyl-4-(4-(trifluoromethyl)phenyl)butanoic acid (**1I**) (52 mg, 0.20 mmol) the target compound **3I** was obtained as a colorless oil (35.1 mg, 0.100 mmol, 50%, d.r. = 2.5/1.0).

**<sup>1</sup>H-NMR (599 MHz, CDCl<sub>3</sub>):** δ = 7.61 – 7.53 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 7.29 – 7.21 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 4.85 – 4.77 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.23 – 4.11 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.82 – 2.63 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 2.59 – 2.49 (m, 1H<sup>cis</sup>+2H<sup>trans</sup>), 2.38 – 2.29 (m, 2H<sup>cis</sup>), 2.19 (dd, *J* = 16.1, 1.2 Hz, 1H<sup>trans</sup>), 2.05 – 2.00 (m, 1H<sup>trans</sup>), 1.77 (ddt, *J* = 13.8, 3.4, 1.3 Hz, 1H<sup>cis</sup>), 1.59 (dd, *J* = 13.8, 12.0 Hz, 1H<sup>cis</sup>), 1.49 – 1.43 (m, 1H<sup>trans</sup>), 1.27 – 1.23 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 1.10 (s, 3H<sup>cis</sup>), 1.01 (s, 3H<sup>trans</sup>) ppm.

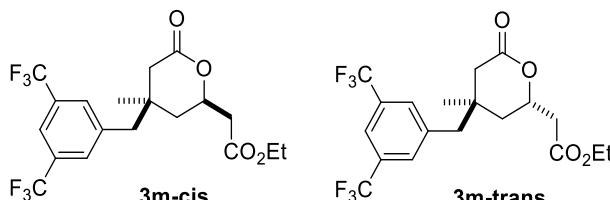
**$^{13}\text{C}$ -{ $^{19}\text{F}$ }-NMR (151 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 171.1, 170.7, 169.8(1), 169.7(7), 140.9, 140.5, 131.0, 130.9, 129.4, 125.4, 125.3, 124.3, 73.5, 73.4, 61.2, 61.1, 49.2, 46.1, 42.1, 41.7, 40.6, 40.5, 40.1, 40.0, 34.0, 33.9, 28.6, 25.1, 14.3, 14.2 ppm.

<sup>19</sup>F-<sup>{1}H</sup>-NMR (564 MHz, CDCl<sub>3</sub>): δ = -62.5 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_{18}H_{21}F_3NaO_4^+$  381.1284, Found 381.1280.

**IR (cm<sup>-1</sup>):** 2986, 2259, 1728, 1325, 1167, 1126, 1069, 1020, 907, 852, 727.

*cis*-Ethyl 2-(4-(3,5-bis(trifluoromethyl)benzyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3m-cis) and *trans*-ethyl 2-(4-(3,5-bis(trifluoromethyl)benzyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3m-trans):



Following the general procedure **G** and using 4-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethylbutanoic acid (**1m**) (65.6 mg, 0.200 mmol) the target compound **3m** was obtained as a colorless oil (44.5 mg, 0.104 mmol, 52%, d.r. = 1.7/1.0).

**$^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 7.81-7.79 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 7.62 (s, 1H<sup>cis</sup>), 7.60-7.55 (m, 1H<sup>cis</sup>+2H<sup>trans</sup>), 4.85-4.77 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 4.20-4.13 (m, 2H<sup>cis</sup>+2H<sup>trans</sup>), 2.87-2.71 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 2.61-2.53 (m, 1H<sup>cis</sup>+1H<sup>trans</sup>), 2.51 (d,  $J$  = 15.9 Hz, 1H<sup>trans</sup>), 2.38-2.32 (m, 2H<sup>cis</sup>), 2.24 (d,  $J$  = 15.8 Hz, 1H<sup>trans</sup>), 2.02 (dd,  $J$  = 14.4, 3.5 Hz, 1H<sup>trans</sup>), 1.77 (dd,  $J$  = 13.9, 3.4 Hz, 1H<sup>cis</sup>), 1.61 (dd,  $J$  = 13.7, 12.0 Hz, 1H<sup>cis</sup>), 1.45 (dd,  $J$  = 14.4, 11.9 Hz, 1H<sup>trans</sup>), 1.28-1.24 (m, 3H<sup>cis</sup>+3H<sup>trans</sup>), 1.11 (s, 3H<sup>cis</sup>), 1.03 (s, 3H<sup>trans</sup>) ppm.

**$^{13}\text{C}$ -{ $^{19}\text{F}$ }-NMR (151 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 170.9, 170.2, 169.8, 169.7, 139.3, 138.9, 131.9, 131.8, 130.5(9), 130.5(6), 123.3(3), 123.3(2), 121.1(8), 121.1(7), 73.5, 73.2, 61.2(3), 61.2(0), 49.0, 46.2, 42.2, 41.8, 40.5, 40.1, 39.9, 39.8, 34.0(3), 33.9(5), 28.4, 24.7, 14.2(3), 14.2(2) ppm.

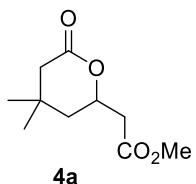
**<sup>19</sup>F-NMR (564 MHz, CDCl<sub>3</sub>):** δ = -62.9 ppm.

**HRMS (ESIpos) m/z:** Calcd for  $C_{19}H_{20}F_6NaO_4^+$  449.1158, Found 449.1162.

**IR (cm<sup>-1</sup>):** 2984, 2963, 2930, 2259, 1732, 1377, 1279, 1177, 1138, 1028, 907, 729.

## Acrylate Scope

### Methyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4a):



Following the general procedure **E** and using methyl acrylate (43 mg, 0.50 mmol) the target compound **4a** was obtained as a colorless oil (26.8 mg, 0.134 mmol, 67%).

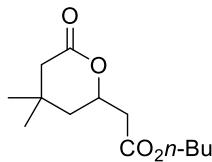
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 4.79 (dddd, *J* = 12.0, 7.0, 5.8, 3.5 Hz, 1H), 3.69 (s, 3H), 2.75 (dd, *J* = 16.1, 7.0 Hz, 1H), 2.55 (dd, *J* = 16.1, 5.8 Hz, 1H), 2.38 (dd, *J* = 16.6, 1.7 Hz, 1H), 2.22 (d, *J* = 16.6 Hz, 1H), 1.77 (ddd, *J* = 13.9, 3.5, 1.7 Hz, 1H), 1.49 (dd, *J* = 13.9, 12.0 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.3, 170.3, 73.8, 52.1, 43.8, 41.8, 40.5, 31.1, 30.0, 27.5 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>10</sub>H<sub>16</sub>NaO<sub>4</sub><sup>+</sup> 223.0941, Found 233.0962.

**IR (cm<sup>-1</sup>):** 3053, 2988, 2305, 1736, 1439, 1421, 1317, 1265, 1200, 1175, 1036, 859, 733, 704.

### Butyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4b):



Following the general procedure **E** and using *n*-butyl acrylate (64.1 mg, 0.500 mmol) the target compound **4b** was obtained as a colorless oil (29.6 mg, 0.122 mmol, 61%).

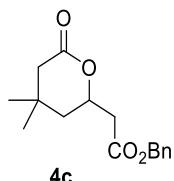
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 4.79 (dddd, *J* = 12.1, 6.8, 6.0, 3.5 Hz, 1H), 4.10 (t, *J* = 6.7 Hz, 2H), 2.75 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.54 (dd, *J* = 16.1, 6.0 Hz, 1H), 2.39 (d, *J* = 16.6, 1H), 2.22 (dd, *J* = 16.6, 1.6 Hz, 1H), 1.77 (ddd, *J* = 13.9, 3.5, 1.6 Hz, 1H), 1.67–1.44 (m, 3H), 1.43–1.30 (m, 2H), 1.11 (s, 3H), 1.06 (s, 3H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.4, 170.0, 73.8, 65.0, 43.8, 41.8, 40.7, 31.1, 30.6, 30.0, 27.6, 19.2, 13.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub><sup>+</sup> 265.1410, Found 265.1423.

**IR (cm<sup>-1</sup>):** 2963, 2936, 2257, 1732, 1466, 1315, 1240, 1059, 1036, 908, 729.

**Benzyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4c):**



Following the general procedure **E** and using benzyl acrylate (81.1 mg, 0.500 mmol) the target compound **4c** was obtained as a colorless oil (32.1 mg, 0.116 mmol, 58%).

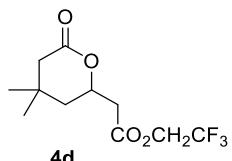
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 7.40–7.30 (m, 5H), 5.15 (s, 2H), 4.81 (dd, *J* = 12.1, 6.8, 6.0, 3.5 Hz, 1H), 2.81 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.61 (dd, *J* = 16.1, 6.0 Hz, 1H), 2.38 (dd, *J* = 16.6, 1.7 Hz, 1H), 2.21 (d, *J* = 16.6 Hz, 1H), 1.75 (ddd, *J* = 13.9, 3.5, 1.7 Hz, 1H), 1.49 (dd, *J* = 13.9, 12.1 Hz, 1H), 1.09 (s, 3H), 1.05 (s, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 171.3, 169.7, 135.6, 128.7, 128.5, 128.5, 73.7, 66.9, 43.8, 41.7, 40.6, 31.1, 30.0, 27.6 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>16</sub>H<sub>20</sub>NaO<sub>4</sub><sup>+</sup> 299.1254, Found 299.1270.

**IR (cm<sup>-1</sup>):** 2355, 2324, 1734, 1719, 1541, 1302, 1250, 1175, 1036.

**2,2,2-Trifluoroethyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4d):**



Following the general procedure **E** and using 2,2,2-trifluoroethyl acrylate (77 mg, 0.50 mmol) the target compound **4d** was obtained as a colorless oil (28.9 mg, 0.108 mmol, 54%).

**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):** δ = 4.81 (dd, *J* = 12.2, 7.0, 5.6, 3.5 Hz, 1H), 4.60–4.37 (m, 2H), 2.86 (dd, *J* = 16.4, 7.0 Hz, 1H), 2.69 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.40 (dd, *J* = 16.7, 1.7 Hz, 1H), 2.25 (d, *J* = 16.7 Hz, 1H), 1.77 (ddd, *J* = 13.9, 3.5, 1.7 Hz, 1H), 1.53 (dd, *J* = 13.9, 12.2 Hz, 1H), 1.12 (s, 3H), 1.08 (s, 3H) ppm.

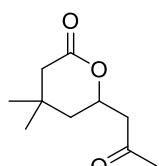
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>):** δ = 171.0, 168.3, 122.9 (q, *J*<sub>C-F</sub> = 277.2 Hz), 73.3, 60.7 (q, *J*<sub>C-F</sub> = 36.8 Hz), 43.8, 41.6, 40.1, 31.1, 30.0, 27.5 ppm.

**<sup>19</sup>F-NMR (470 MHz, CDCl<sub>3</sub>):** δ = -73.8 (t, *J*<sub>F-H</sub> = 8.3 Hz) ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>11</sub>H<sub>15</sub>F<sub>3</sub>NaO<sub>4</sub><sup>+</sup> 291.0815, Found 291.0835.

**IR (cm<sup>-1</sup>):** 2963, 2259, 1740, 1449, 1373, 1301, 1244, 1150, 1086, 912, 725.

**4,4-dimethyl-6-(2-oxopropyl)tetrahydro-2H-pyran-2-one (4e):**



Following the general procedure **F** and using but-3-en-2-one (35 mg, 0.50 mmol) the target compound **4e** was obtained as a colorless oil (18.7 mg, 0.101 mmol, 51%).

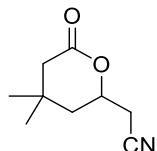
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 4.83 (dddd, *J* = 12.1, 6.5, 5.8, 3.4 Hz, 1H), 2.93 (dd, *J* = 17.0, 6.5 Hz, 1H), 2.60 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.39 (dd, *J* = 16.5, 1.6 Hz, 1H), 2.33–2.11 (m, 4H), 1.77 (ddd, *J* = 13.9, 3.4, 1.6 Hz, 1H), 1.42 (dd, *J* = 13.9, 12.1 Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 205.2, 171.6, 73.5, 49.0, 43.9, 42.1, 31.2, 31.2, 30.0, 27.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>10</sub>H<sub>16</sub>NaO<sub>3</sub><sup>+</sup> 207.0992, Found 207.1006.

**IR (cm<sup>-1</sup>):** 2963, 1740, 1449, 1310, 1242, 1151, 1084, 1042, 1032.

**2-(4,4-Dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetonitrile (4f):**



**4f** Following the general procedure E and using acrylonitrile (11.8 mg, 0.500 mmol) the target compound **4f** was obtained as a colorless oil (13.3 mg, 0.079 mmol, 40%).

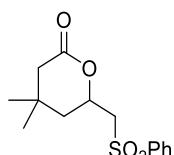
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 4.63 (dddd, *J* = 12.1, 5.9, 5.0, 3.7 Hz, 1H), 2.83–2.69 (m, 2H), 2.42 (dd, *J* = 16.9, 1.9 Hz, 1H), 2.29 (d, *J* = 16.9 Hz, 1H), 1.84 (ddd, *J* = 13.9, 3.7, 1.9 Hz, 1H), 1.66 (dd, *J* = 13.9, 12.1 Hz, 1H), 1.12 (s, 6H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 169.9, 115.7, 72.2, 43.6, 41.0, 30.9, 30.1, 27.0, 24.9 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>9</sub>H<sub>13</sub>NNaO<sub>2</sub><sup>+</sup> 190.0838, Found 190.0853.

**IR (cm<sup>-1</sup>):** 2963, 2932, 2255, 1738, 1472, 1387, 1375, 1242, 1223, 1053, 1038, 947, 725.

**4,4-Dimethyl-6-((phenylsulfonyl)methyl)tetrahydro-2H-pyran-2-one (4g):**



**4g** Following the general procedure E and using (vinylsulfonyl)benzene (84.1 mg, 0.500 mmol) the target compound **4g** was obtained as a colorless oil (37.7 mg, 0.133 mmol, 67%).

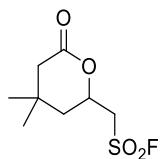
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 7.96–7.89 (m, 2H), 7.72–7.64 (m, 1H), 7.62–7.54 (m, 2H), 4.85 (dtd, *J* = 12.1, 5.9, 3.5 Hz, 1H), 3.55 (dd, *J* = 14.5, 5.9 Hz, 1H), 3.31 (dd, *J* = 14.5, 5.9 Hz, 1H), 2.36 (dd, *J* = 16.6, 1.6 Hz, 1H), 2.19 (d, *J* = 16.6 Hz, 1H), 1.97 (ddd, *J* = 14.1, 3.5, 1.6 Hz, 1H), 1.56 (dd, *J* = 14.1, 12.1 Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 170.1, 139.6, 134.3, 129.5, 128.2, 71.8, 61.1, 43.7, 41.9, 31.0, 30.1, 27.5 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>14</sub>H<sub>18</sub>NaO<sub>4</sub>S<sup>+</sup> 305.0818, Found 305.0836.

**IR (cm<sup>-1</sup>):** 2961, 2947, 2257, 1744, 1449, 1373, 1310, 1244, 1151, 1086, 903, 723.

**(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)methanesulfonyl fluoride (4h):**



**4h** Following the general procedure **F** and using ethenesulfonyl fluoride (55 mg, 0.50 mmol) the target compound **4h** was obtained as a colorless oil (22.9 mg, 0.102 mmol, 51%).

**<sup>1</sup>H-NMR (599 MHz, CDCl<sub>3</sub>):**  $\delta$  = 4.92 (dddd,  $J$  = 12.1, 6.5, 5.4, 3.6 Hz, 1H), 3.81 (ddd,  $J_{H-H}$  = 15.0, 6.5  $J_{H-F}$  = 2.0 Hz, 1H), 3.60 (ddd,  $J_{H-H}$  = 15.0, 5.4 Hz,  $J_{H-F}$  = 6.6 Hz, 1H), 2.45 (dd,  $J$  = 16.8, 1.8 Hz, 1H), 2.30 (d,  $J$  = 16.8 Hz, 1H), 1.93 (ddd,  $J$  = 13.9, 3.6, 1.8 Hz, 1H), 1.65 (dd,  $J$  = 13.9, 12.1 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H) ppm.

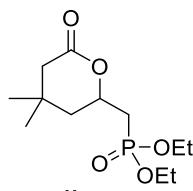
**<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):**  $\delta$  = 169.3, 71.3, 55.7, 55.6, 43.6, 41.1, 41.1, 31.0, 30.2, 27.2 ppm.

**<sup>19</sup>F-NMR (564 MHz, CDCl<sub>3</sub>):**  $\delta$  = 61.4 (dd,  $J_{F-H}$  = 6.6, 1.9 Hz) ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>8</sub>H<sub>13</sub>FNaO<sub>4</sub>S<sup>+</sup>: 247.0411, Found 247.0422.

**IR (cm<sup>-1</sup>):** 2961, 2934, 1746, 1412, 1314, 1265, 1238, 1196, 1146, 1086, 1032, 833, 789.

**diethyl ((4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)methyl)phosphonate (4i):**



**4i** Following the general procedure **E** and using diethyl vinylphosphonate (284 mg, 3.50 mmol) the target compound **4i** was obtained as a colorless oil (22.2 mg, 0.080 mmol, 40%).

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 4.77–4.62 (m, 1H), 4.24–4.02 (m, 4H), 2.38 (dd,  $J$  = 16.6, 1.6 Hz, 1H), 2.35–2.25 (m, 1H), 2.22 (d,  $J$  = 16.7 Hz, 1H), 2.11–2.00 (m, 1H), 1.94 (ddd,  $J$  = 14.2, 3.4, 1.6 Hz, 1H), 1.53 (dd,  $J$  = 14.1, 12.0 Hz, 1H), 1.36–1.30 (m, 6H), 1.09 (s, 3H), 1.06 (s, 3H) ppm.

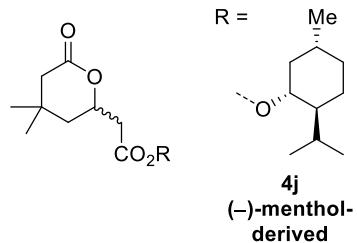
**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):**  $\delta$  = 171.21, 72.95, 62.38 (d,  $J_{C-P}$  = 6.4 Hz), 62.01 (d,  $J_{C-P}$  = 6.5 Hz), 43.81, 43.11 (d,  $J_{C-P}$  = 6.4 Hz), 33.10 (d,  $J_{C-P}$  = 140.7 Hz), 31.14, 30.06, 27.63, 16.54 (d,  $J_{C-P}$  = 6.0 Hz), 16.51 (d,  $J_{C-P}$  = 6.1 Hz) ppm.

**<sup>31</sup>P-<sup>{1}</sup>H-NMR (162 MHz, CDCl<sub>3</sub>):**  $\delta$  = 25.6 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>12</sub>H<sub>23</sub>NaO<sub>5</sub>P<sup>+</sup> 301.1175, Found 301.1191.

**IR (cm<sup>-1</sup>):** 2984, 2961, 2928, 1738, 1466, 1265, 1240, 1026, 966, 733.

**(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(4,4-dimethyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetate (4j):**



Following the general procedure **E** and using (*1S,2R,5S*)-2-isopropyl-5-methylcyclohexyl acrylate (105 mg, 0.500 mmol) the target compound **4j** was obtained as a colorless oil (38.2 mg, 0.118 mmol, 59%, d.r. = 1.0/1.0).

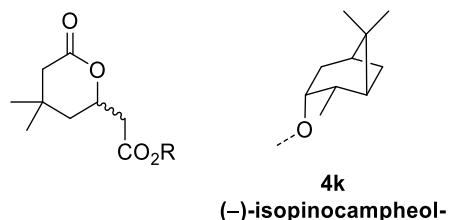
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 4.86–4.63 (m, 2H<sup>iso1</sup>+2H<sup>iso2</sup>), 2.82–2.69 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.60–2.47 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.44–2.34 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.27–2.18 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.04–1.92 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.90–1.63 (m, 4H<sup>iso1</sup>+4H<sup>iso2</sup>), 1.54–1.30 (m, 3H<sup>iso1</sup>+3H<sup>iso2</sup>), 1.10 (s, 3H<sup>iso1</sup>or3H<sup>iso2</sup>), 1.06 (s, 3H<sup>iso2</sup>), 1.04–0.85 (m, 9H<sup>iso1</sup>), 0.75 (s, 3H<sup>iso1</sup>), 0.73 (s, 3H<sup>iso2</sup>) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.4, 171.4, 169.5(4), 169.5(2), 75.2, 75.1, 73.9, 47.0, 43.9, 43.81, 41.9, 41.8, 41.0, 40.9, 40., 3.26, 31.5, 31.2, 30.0, 27.70, 27.6, 26.4, 26.3, 23.5, 23.4, 22.1, 20.9, 20.8, 16.4, 16.3 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>19</sub>H<sub>32</sub>NaO<sub>4</sub><sup>+</sup> 347.2193, Found 347.2199.

**IR (cm<sup>-1</sup>):** 2961, 2928, 2255, 1728, 1456, 1389, 1373, 1420, 1036, 905, 725.

**(2*S*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl 2-(4,4-dimethyl-6-oxotetrahydro-2*H*-pyran-2-yl)acetate (4k):**



Following the general procedure **E** and using (*1R,2S,5S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl acrylate (104 mg, 0.500 mmol) the target compound **4k** was obtained as a colorless oil (37.9 mg, 0.117 mmol, 57%, d.r. = 1.0/1.0).

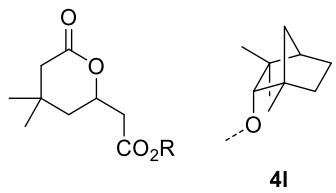
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 5.12–5.02 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 4.86–4.73 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.83–2.71 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.62–2.49 (m, 2H<sup>iso1</sup>+2H<sup>iso2</sup>), 2.43–2.30 (m, 2H<sup>iso1</sup>+2H<sup>iso2</sup>), 2.23 (m, 1H<sup>iso1</sup>), 2.16–2.04 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.96–1.87 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.85–1.74 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.72–1.61 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.56–1.44 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.21 (s, 3H<sup>iso1</sup>+3H<sup>iso2</sup>), 1.13–1.00 (m, 10H<sup>iso1</sup>+10H<sup>iso2</sup>), 0.94 (s, 3H<sup>iso1</sup>+3H<sup>iso2</sup>) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.4, 169.9, 169.8, 75.1, 75.0, 73.9(3), 73.8(9), 47.5, 43.8, 43.7, 41.9, 41.3, 40.9(3), 40.9(1), 38.3, 35.9, 33.6, 31.2, 30.0, 27.7, 27.5, 23.9, 20.6 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>19</sub>H<sub>30</sub>NaO<sub>4</sub><sup>+</sup> 345.2036, Found 345.2043.

**IR (cm<sup>-1</sup>):** 2958, 2930, 2255, 1724, 1506, 1472, 1437, 1420, 1315, 1196, 1034, 905.

**1,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4l):**



Following the general procedure E and using 1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl acrylate (104 mg, 0.500 mmol) the target compound 4l was obtained as a colorless oil (36.2 mg, 0.112 mmol, 56%, d.r. = 1.0/1.0).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 4.86-4.73(m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 4.44-4.35 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.89-2.75 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.65-2.53 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.45-2.34 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 2.28-2.18 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.86-1.76 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.75-1.39 (m, 6H<sup>iso1</sup>+6H<sup>iso2</sup>), 1.21-1.15 (m, 1H<sup>iso1</sup>+1H<sup>iso2</sup>), 1.15-1.02 (m, 13H<sup>iso1</sup>+13H<sup>iso2</sup>), 0.78 (s, 3H<sup>iso1</sup>), 0.76 (s, 3H<sup>iso2</sup>) ppm.

**<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):** δ = 171.4(4), 171.4(2), 170.4, 170.3, 87.2, 87.1, 73.9, 73.8, 48.4, 43.9, 41.9(2), 41.8(9), 41.4, 40.8, 40.7, 39.6, 39.5, 31.2, 30.0, 29.8, 27.7(0), 27.6(9), 26.7, 25.9, 20.4, 20.3, 19.5(4), 19.5(0) ppm.

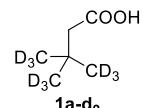
**HRMS (ESIpos) m/z:** Calcd for C<sub>19</sub>H<sub>30</sub>NaO<sub>4</sub><sup>+</sup> 345.2036, Found 345.2048.

**IR (cm<sup>-1</sup>):** 2961, 2934, 1734, 1317, 1248, 1238, 1057, 1032.

# Mechanistic Experiments

## Kinetic Isotope Experiments

### 3,3-Bis(methyl-d<sub>3</sub>)butanoic-4,4,4-d<sub>3</sub> acid (1a-d<sub>9</sub>):



Ethyl 3-(methyl-d<sub>3</sub>)but-2-enoate-4,4,4-d<sub>3</sub> and (methyl-d<sub>3</sub>)lithium had were synthesized via literature known procedures.<sup>3,6</sup>

Following the general procedure **D** in 5.40 mmol scale using ethyl 3-(methyl-d<sub>3</sub>)but-2-enoate-4,4,4-d<sub>3</sub> (725 mg, 5.40 mmol) and (methyl-d<sub>3</sub>)lithium (21.6 mmol, 4.0 equiv) the target compound **1a-d<sub>9</sub>** was obtained as a colorless oil (360 mg, 2.88 mmol, 53%).

**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):** δ = 2.23 (s, 2H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 179.5, 47.8, 30.1, 28.8 (dt, *J*<sub>C-D</sub> = 18.9 Hz) ppm.

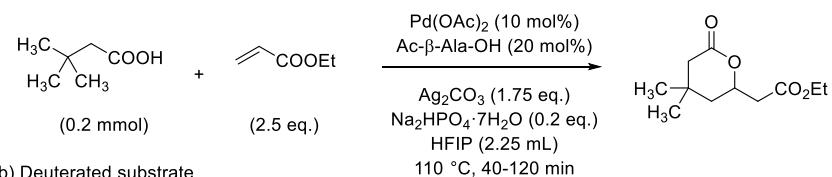
**HRMS (ESIneg) m/z:** Calcd for C<sub>6</sub>H<sub>2</sub>D<sub>9</sub>O<sub>2</sub><sup>-</sup> 124.13294, Found 124.13297.

**IR (cm<sup>-1</sup>):** 1701.

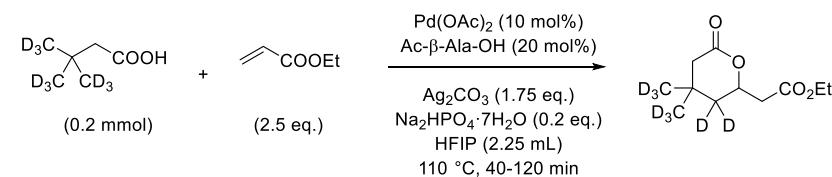
### Determination of the parallel KIE:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)<sub>2</sub> (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (96.5 mg, 0.350 mmol, 1.75 equiv), Na<sub>2</sub>HPO<sub>4</sub> · 7 H<sub>2</sub>O (10.7 mg, 0.04 mmol, 0.2 equiv), acid (0.2 mmol), ethyl acrylate (50.1 mg, 0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C. After the indicated time the reaction was cooled to -78 °C. After letting the reaction warm up to room temperature a stock solution of 1,3,5-trimethoxybenzene (1.00 mL, 20.0 μM, 3.36 mg, 20.0 μmol, 0.1 equiv) was added. The reaction mixture was filtered over a pad of silica (bottom layer) and aluminum oxide (top layer), the residue was washed with EtOAc (30 mL) to complete elution and all volatiles were removed under reduced pressure. EtOAc (1.5 mL) was added and the yield was determined via GC-FID of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

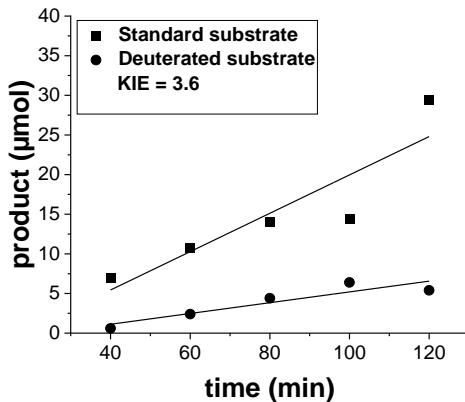
a) Standard substrate



b) Deuterated substrate

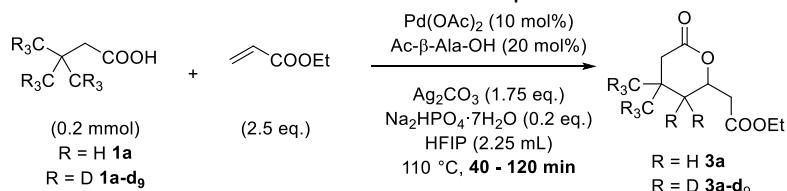


**Scheme S22:** Reaction conditions for the determination of the kinetic isotope experiments.



**Figure 1:** Determination of the KIE in parallel experiments.  $k_H/k_D$  Determination.

**Table 1:** Parallel Kinetic isotope effect.

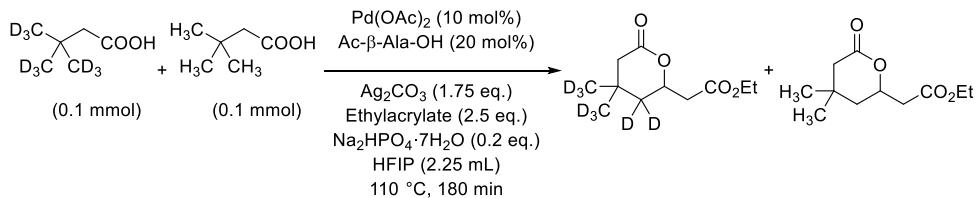


| Entry | substrate  | Reaction time (min) | Product (μmol) |
|-------|--|---------------------|----------------|
| 1     | 3,3-dimethylbutanoic acid ( <b>1a</b> )  | 40                  | 7              |
| 2     | 3,3-dimethylbutanoic acid ( <b>1a</b> )  | 60                  | 10.8           |
| 3     | 3,3-dimethylbutanoic acid ( <b>1a</b> )  | 80                  | 14             |
| 4     | 3,3-dimethylbutanoic acid ( <b>1a</b> )  | 100                 | 14.4           |
| 5     | 3,3-dimethylbutanoic acid ( <b>1a</b> )  | 120                 | 29.4           |
| 6     | 3,3-bis(methyl-d <sub>3</sub> )butanoic-4,4,4-d <sub>3</sub> acid ( <b>1a-d</b> <sub>9</sub> ) | 40                  | 0.6            |
| 7     | 3,3-bis(methyl-d <sub>3</sub> )butanoic-4,4,4-d <sub>3</sub> acid ( <b>1a-d</b> <sub>9</sub> ) | 60                  | 2.4            |
| 8     | 3,3-bis(methyl-d <sub>3</sub> )butanoic-4,4,4-d <sub>3</sub> acid ( <b>1a-d</b> <sub>9</sub> ) | 80                  | 4.4            |
| 9     | 3,3-bis(methyl-d <sub>3</sub> )butanoic-4,4,4-d <sub>3</sub> acid ( <b>1a-d</b> <sub>9</sub> ) | 100                 | 6.4            |
| 10    | 3,3-bis(methyl-d <sub>3</sub> )butanoic-4,4,4-d <sub>3</sub> acid ( <b>1a-d</b> <sub>9</sub> ) | 120                 | 5.4            |

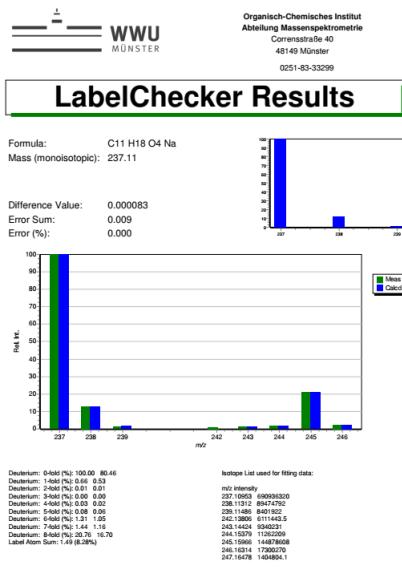
$$KIE = \frac{k_H}{k_D} = \frac{0.242}{0.068} = 3.559$$

### Competition experiment

An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 0.020 mmol, 10 mol%),  $\text{Ac-}\beta\text{-Ala-OH}$  (5.3 mg, 0.040 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (96.5 mg, 0.350 mmol, 1.75 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$  (10.7 mg, 0.04 mmol, 0.2 equiv),  $d_9$ -3,3-dimethylbutyric acid (**1a-d**<sub>9</sub>) (12.5 mg, 0.1 mmol), 3,3-dimethylbutyric acid (**1a**) (11.6 mg, 0.1 mmol), ethyl acrylate (50.1 mg, 0.50 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C for 180 min. The reaction was cooled to -78 °C. The reaction mixture was allowed to warm up to room temperature and an aliquot of the reaction was filtered over a piece of Whatman ® filter paper. The parallel KIE was determined by ESI-MS analysis of the crude reaction mixture.



$$KIE = \frac{81.00}{18.99} = 4.265$$



**Scheme S23:** Competition experiment.

## Determination of Reaction Order in Olefin, Catalyst and Substrate

For the determination of the reaction order in olefin and catalyst the variable time normalization analysis developed by Burés was used.<sup>7,8</sup>

### General Procedure H:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)<sub>2</sub> (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (96.5 mg, 0.350 mmol, 1.75 equiv), Na<sub>2</sub>HPO<sub>4</sub> · 7 H<sub>2</sub>O (10.7 mg, 0.04 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (**1a**) (23.2 mg, 0.2 mmol), ethyl acrylate (50.1 mg, 0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C. After the indicated time the reaction was cooled to -78 °C- After letting the reaction warm up to room temperature a stock solution of 1,3,5-trimethoxybenzene (1.00 mL, 20.0 μM, 3.36 mg, 20.0 μmol, 0.1 equiv) was added. The reaction mixture was filtered over a pad of silica (bottom layer) and aluminum oxide (top layer), the residue was washed with EtOAc (30 mL) to complete elution and all volatiles were removed under reduced pressure. EtOAc (1.5 mL) was added

and the yield was determined via GC-FID of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.

### General Procedure I:

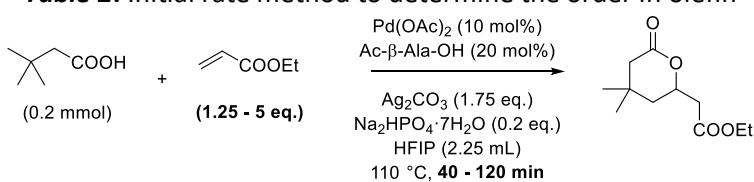
An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 0.020 mmol, 10 mol%),  $\text{Ac}-\beta\text{-Ala-OH}$  (5.3 mg, 0.040 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (96.5 mg, 0.350 mmol, 1.75 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7 \text{H}_2\text{O}$  (37.5 mg, 0.14 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (**1a**) (23.2 mg, 0.2 mmol), ethyl acrylate (50.1 mg, 0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C. After the indicated time the reaction was cooled to -78 °C. After letting the reaction warm up to room temperature a stock solution of 1,3,5-trimethoxybenzene (1.00 mL, 20.0  $\mu\text{M}$ , 3.36 mg, 20.0  $\mu\text{mol}$ , 0.1 equiv) was added. The reaction mixture was filtered over a pad of silica (bottom layer) and aluminum oxide (top layer), the residue was washed with  $\text{EtOAc}$  (30 mL) to complete elution and all volatiles were removed under reduced pressure.  $\text{EtOAc}$  (1.5 mL) was added and the yield was determined via GC-FID of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.

### Order in Olefin:

For the determination of the reaction order in olefin variable time normalization analysis was used.<sup>7</sup>

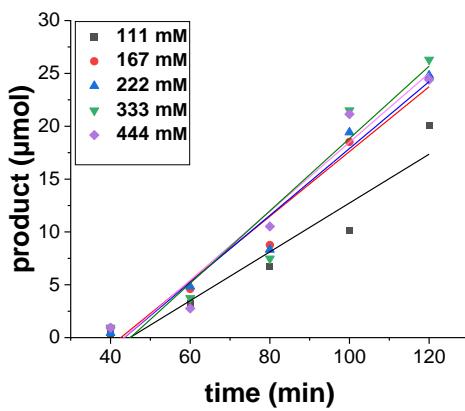
**General procedure H was utilized with the following modifications:** The amount of ethyl acrylate (27.30 – 109.1  $\mu\text{L}$ , 250 – 1000  $\mu\text{mol}$ , 1.25 – 5.00 equiv) was varied.

**Table 2:** Initial rate method to determine the order in olefin

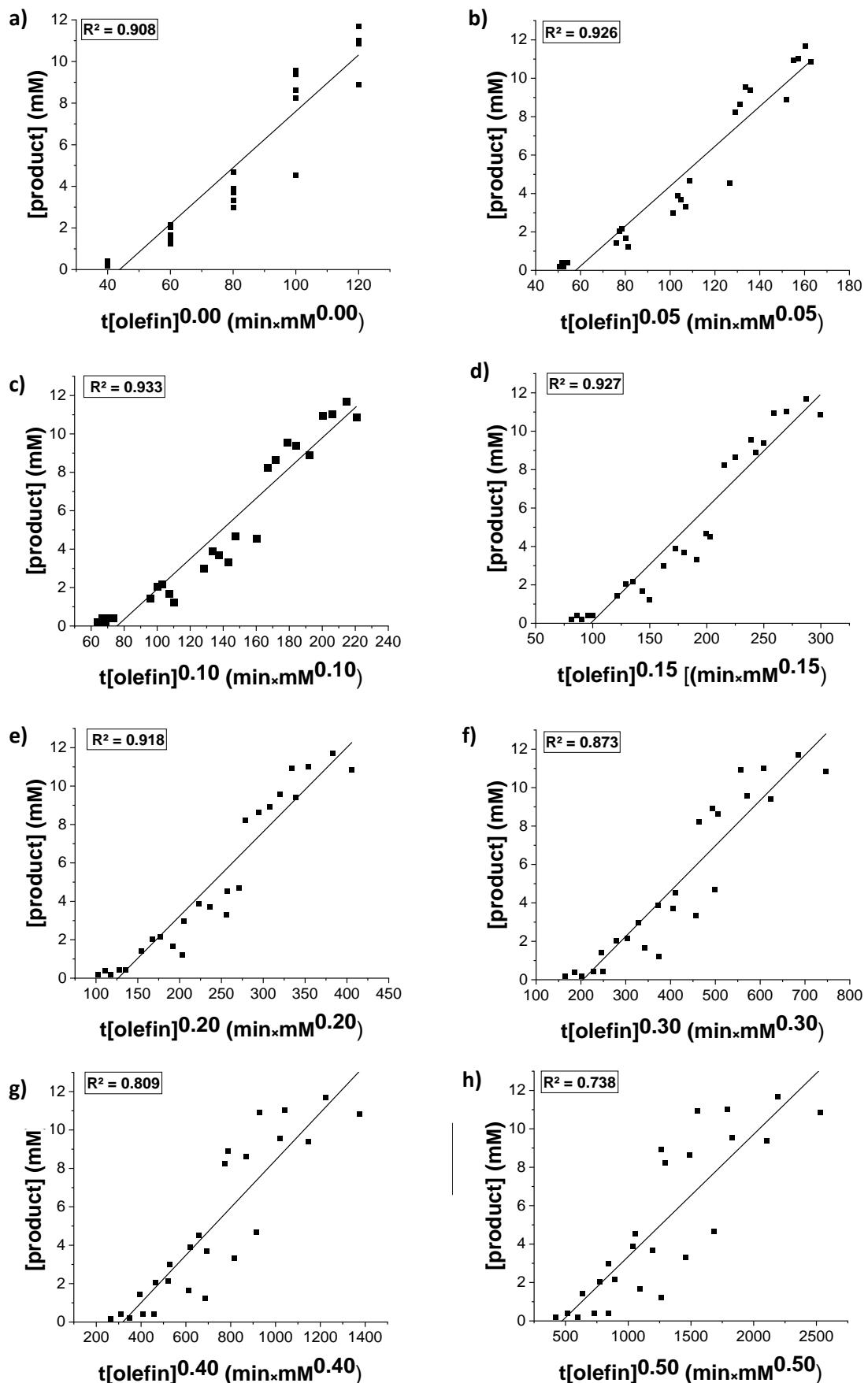


| Entry | Amount of olefin ( $\mu\text{mol}$ ) | Reaction time (min) | Product ( $\mu\text{mol}$ ) |
|-------|--------------------------------------|---------------------|-----------------------------|
| 1     | 250                                  | 40                  | 0.42                        |
| 2     | 250                                  | 60                  | 3.22                        |
| 3     | 250                                  | 80                  | 6.72                        |
| 4     | 250                                  | 100                 | 10.18                       |
| 5     | 250                                  | 120                 | 20.04                       |
| 6     | 375                                  | 40                  | 0.90                        |
| 7     | 375                                  | 60                  | 4.60                        |
| 8     | 375                                  | 80                  | 8.76                        |
| 9     | 375                                  | 100                 | 18.52                       |
| 10    | 375                                  | 120                 | 24.60                       |
| 11    | 500                                  | 40                  | 0.44                        |
| 12    | 500                                  | 60                  | 4.84                        |
| 13    | 500                                  | 80                  | 8.32                        |
| 14    | 500                                  | 100                 | 19.42                       |
| 15    | 500                                  | 120                 | 24.80                       |
| 16    | 750                                  | 40                  | 0.94                        |
| 17    | 750                                  | 60                  | 3.74                        |
| 18    | 750                                  | 80                  | 7.48                        |
| 19    | 750                                  | 100                 | 21.50                       |
| 20    | 750                                  | 120                 | 26.30                       |
| 21    | 1000                                 | 40                  | 0.94                        |
| 22    | 1000                                 | 60                  | 2.76                        |
| 23    | 1000                                 | 80                  | 10.52                       |
| 24    | 1000                                 | 100                 | 21.14                       |

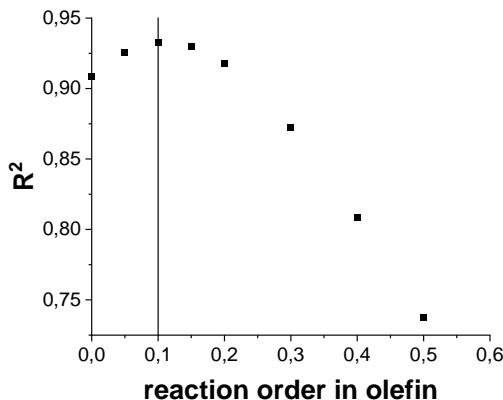
|    |      |     |       |
|----|------|-----|-------|
| 25 | 1000 | 120 | 24.40 |
|----|------|-----|-------|



**Figure 2:** Plot of product ( $\mu\text{mol}$ ) versus time (min) for various olefin concentrations with linear fits  
 $[\text{olefin}] = 111 \text{ mM}$  (black),  $167 \text{ mM}$  (red),  $222 \text{ mM}$  (blue),  $333 \text{ mM}$  (green), and  $444 \text{ mM}$  (pink).



**Figure 3-a-h:** Plot of the product concentration versus the reaction time multiplied with an exponentiation of the olefin concentration.



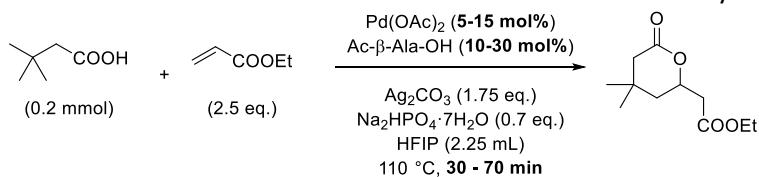
**Figure 4:** Plot of the coefficient of determination (derived from the linear regressions of the linear fits in **Figure 3-a-h**) versus the reaction order in olefin.

#### Order in catalyst:

For the determination of the reaction order in catalyst variable time normalization analysis was used.<sup>8</sup>

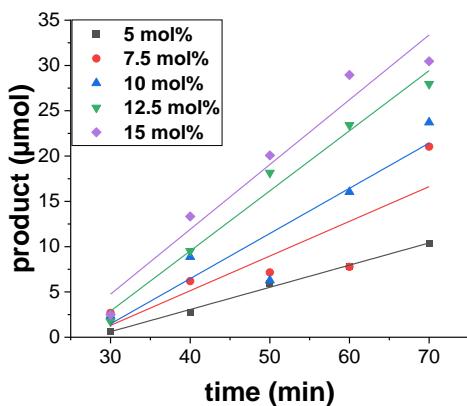
**General procedure I was utilized with the following modifications:** The amount of palladium acetate (2.25 – 6.74 mg, 10 – 30 µmol, 0.01 – 0.03 equiv) and Ac-β-Ala-OH (5.30 – 15.7 mg, 20 – 60 µmol, 0.02 – 0.06 equiv) was varied.

**Table 3:** Initial rate method to determine the order in catalyst

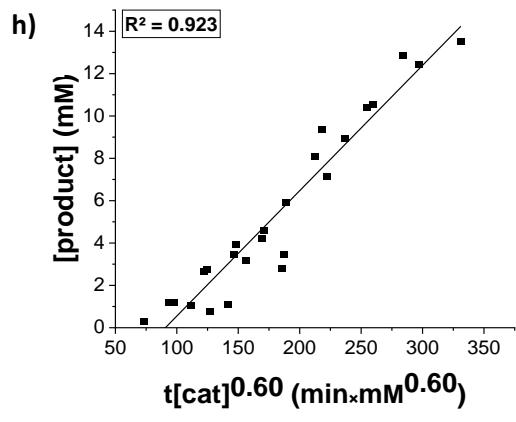
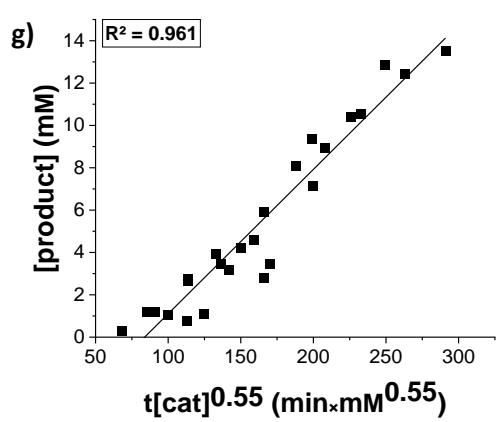
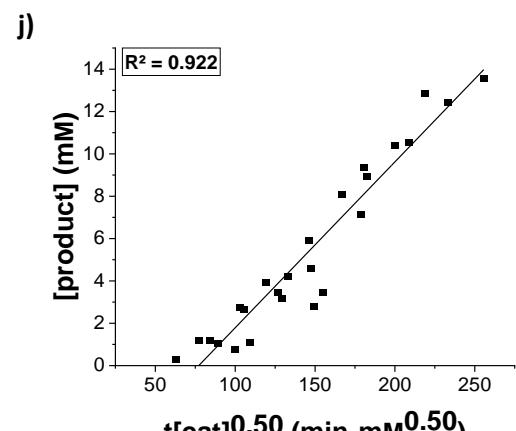
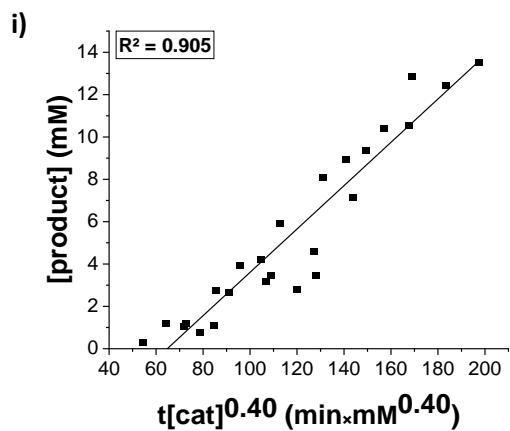
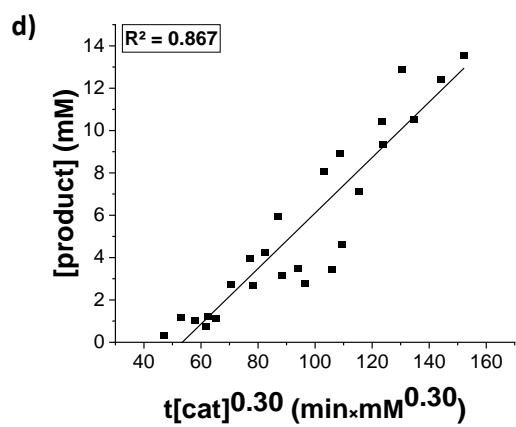
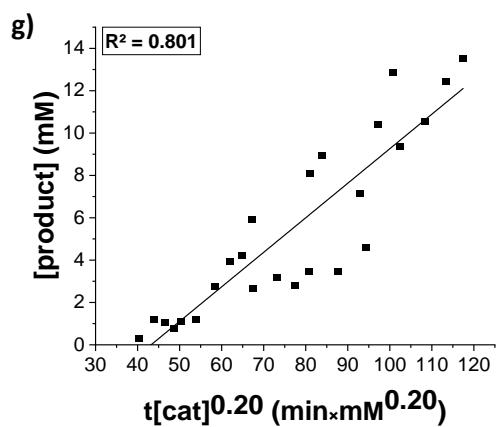
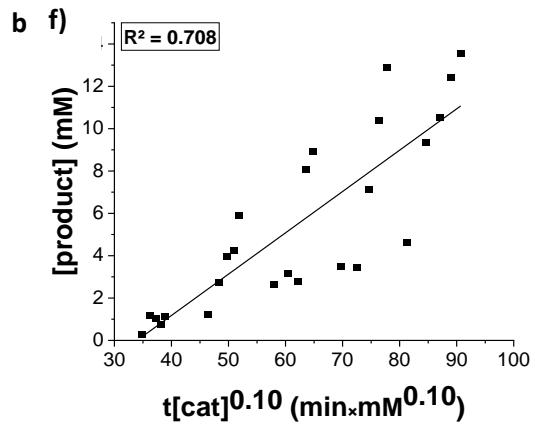
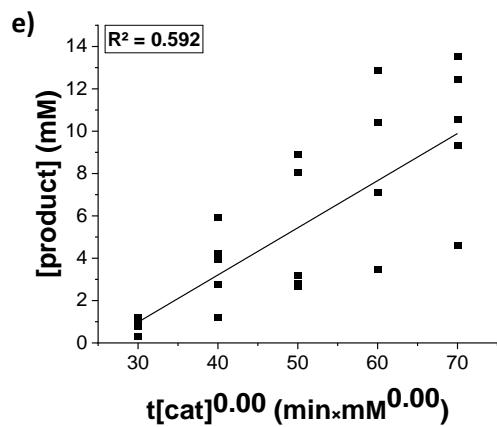


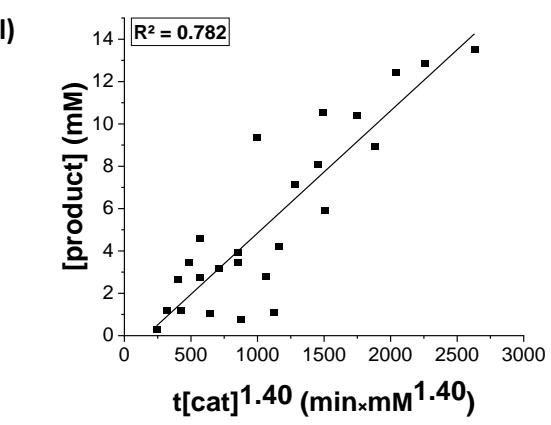
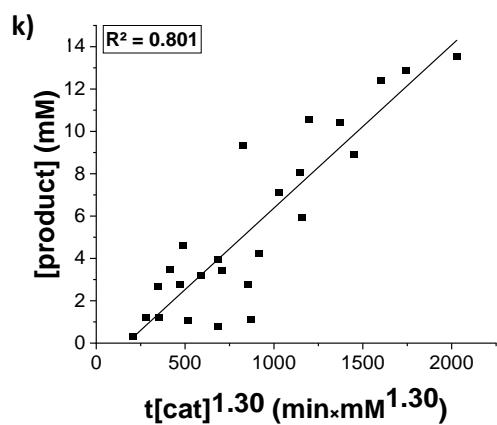
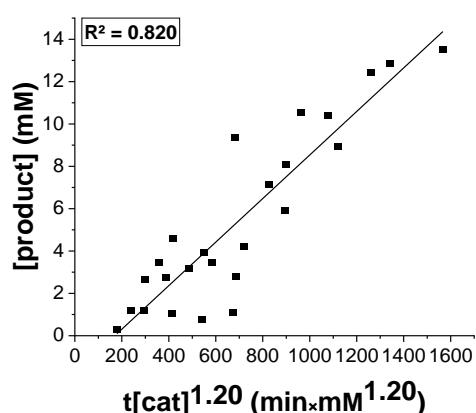
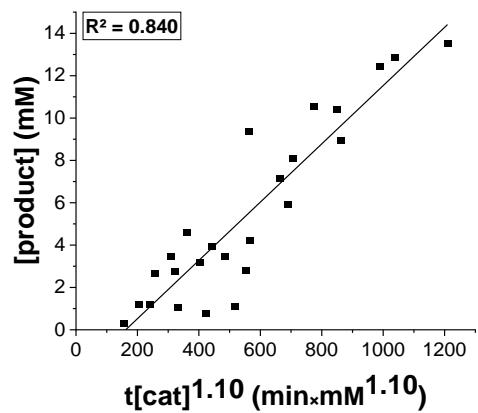
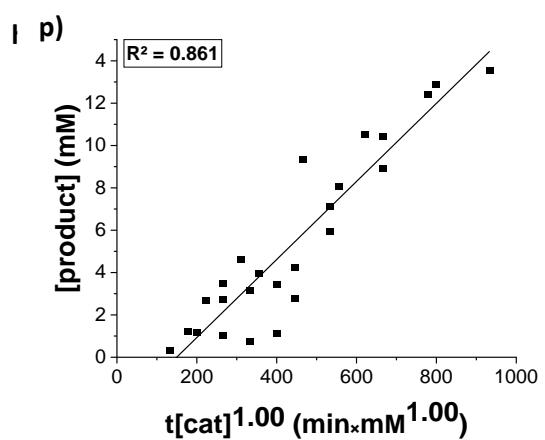
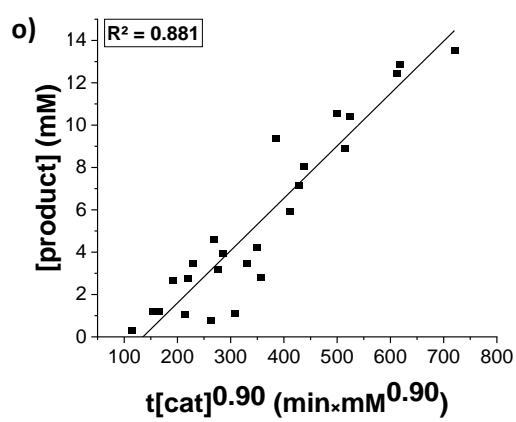
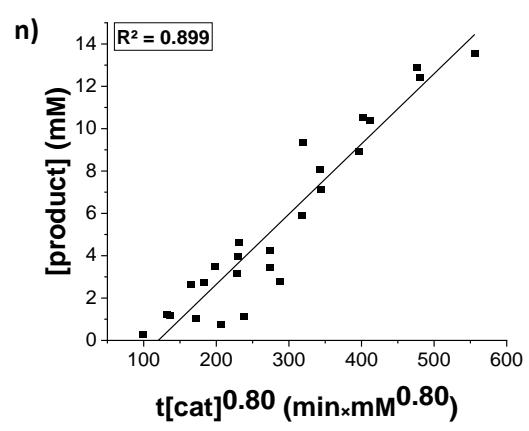
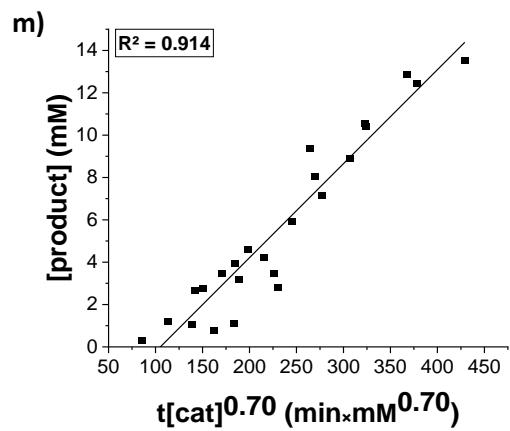
| Entry | Amount of catalyst (µmol) | Reaction time (min) | Product (µmol) |
|-------|---------------------------|---------------------|----------------|
| 1     | 10                        | 30                  | 0.68           |
| 2     | 10                        | 40                  | 2.71           |
| 3     | 10                        | 50                  | 5.99           |
| 4     | 10                        | 60                  | 7.81           |
| 5     | 10                        | 70                  | 10.37          |
| 6     | 15                        | 30                  | 2.68           |
| 7     | 15                        | 40                  | 6.19           |
| 8     | 15                        | 50                  | 7.15           |
| 9     | 15                        | 60                  | 7.77           |
| 10    | 15                        | 70                  | 21.04          |
| 11    | 20                        | 30                  | 2.37           |
| 12    | 20                        | 40                  | 8.87           |
| 13    | 20                        | 50                  | 6.27           |
| 14    | 20                        | 60                  | 16.04          |
| 15    | 20                        | 70                  | 23.72          |
| 16    | 25                        | 30                  | 1.73           |
| 17    | 25                        | 40                  | 9.52           |
| 18    | 25                        | 50                  | 18.16          |
| 19    | 25                        | 60                  | 23.42          |
| 20    | 25                        | 70                  | 27.95          |

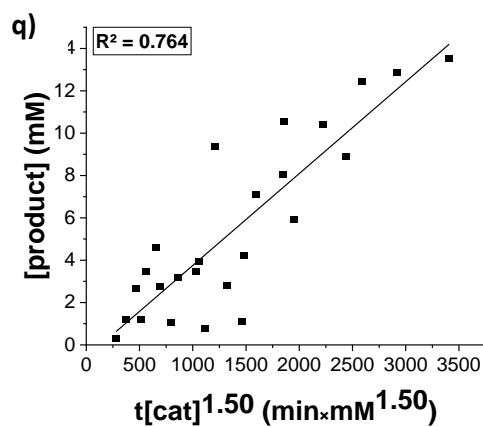
|    |    |    |       |
|----|----|----|-------|
| 21 | 30 | 30 | 2.50  |
| 22 | 30 | 40 | 13.33 |
| 23 | 30 | 50 | 20.07 |
| 24 | 30 | 60 | 28.96 |
| 25 | 30 | 70 | 30.46 |



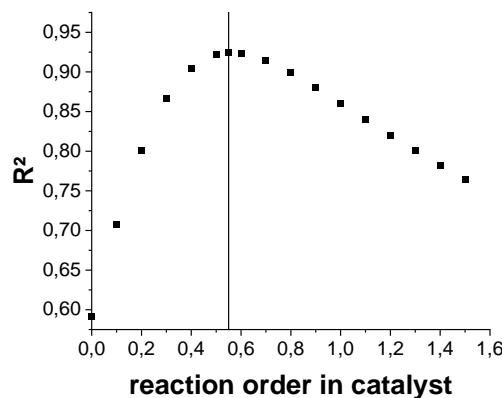
**Figure 5:** Plot of product (μmol) versus time (min) for various catalyst amounts with linear fits. [catalyst] = 10 μmol (black), 15 μmol (red), 20 μmol (blue), 25 μmol (green), and 30 μmol (pink).







**Figure 6 a-q:** Plot of the product concentration versus the reaction time multiplied with an exponentiation of the catalyst concentration.



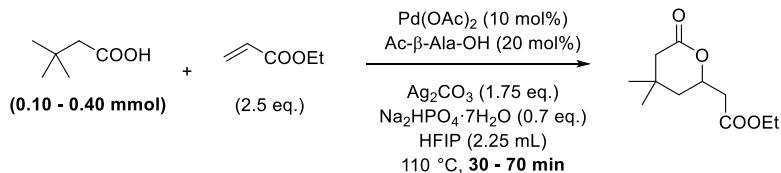
**Figure 7:** Plot of the coefficient of determination (derived from the linear fits in **Figure 6 a-q**). versus the reaction order in catalyst.

#### Order in Substrate:

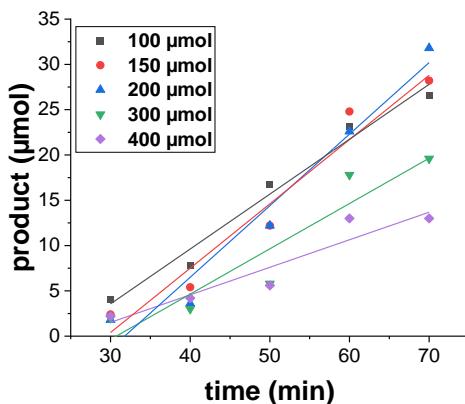
For the determination of the reaction order in substrate the initial rate method was used.

**General procedure I was utilized with the following modifications:** The amount of 3,3-dimethylbutyric acid (**1a**) (12.8 – 50.9  $\mu$ L, 0.10 – 0.40 mmol) was varied.

**Table 4:** Initial rate method to determine the order in 3,3-dimethylbutyric acid (**1a**)



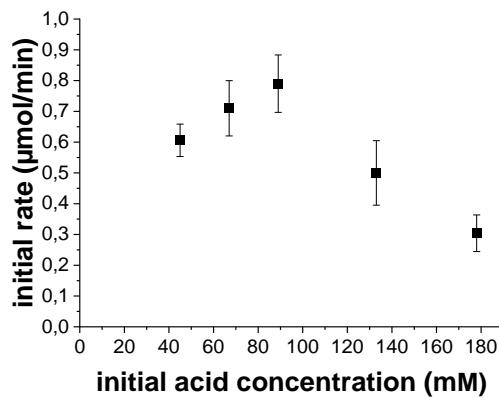
| Entry | Amount of substrate <b>1a</b> (μmol) | Reaction time (min) | Product (μmol) |
|-------|--------------------------------------|---------------------|----------------|
| 1     | 100                                  | 30                  | 4.0            |
| 2     | 100                                  | 40                  | 7.8            |
| 3     | 100                                  | 50                  | 16.8           |
| 4     | 100                                  | 60                  | 23.2           |
| 5     | 100                                  | 70                  | 26.6           |
| 6     | 150                                  | 30                  | 2.4            |
| 7     | 150                                  | 40                  | 5.4            |
| 8     | 150                                  | 50                  | 12.2           |
| 9     | 150                                  | 60                  | 24.8           |
| 10    | 150                                  | 70                  | 28.2           |
| 11    | 200                                  | 30                  | 1.8            |
| 12    | 200                                  | 40                  | 3.6            |
| 13    | 200                                  | 50                  | 12.2           |
| 14    | 200                                  | 60                  | 22.6           |
| 15    | 200                                  | 70                  | 31.8           |
| 16    | 300                                  | 30                  | 2.0            |
| 17    | 300                                  | 40                  | 3.0            |
| 18    | 300                                  | 50                  | 5.8            |
| 19    | 300                                  | 60                  | 17.8           |
| 20    | 300                                  | 70                  | 19.6           |
| 21    | 400                                  | 30                  | 2.2            |
| 22    | 400                                  | 40                  | 4.2            |
| 23    | 400                                  | 50                  | 5.6            |
| 24    | 400                                  | 60                  | 13.0           |
| 25    | 400                                  | 70                  | 13.0           |



**Figure 8 :** Plot of product ( $\mu\text{mol}$ ) versus time (min) for various concentrations of substrate **1a**.  
[substrate] = 100  $\mu\text{mol}$  (black), 150  $\mu\text{mol}$  (red), 200  $\mu\text{mol}$  (blue), 300  $\mu\text{mol}$  (green), and 400  $\mu\text{mol}$  (pink).

**Table 5:** Initial rate for various amounts of substrate **1a**:

| Conc. of the substrate<br>( $\mu\text{mol/mL}$ ) | Initial rate ( $\mu\text{mol/min}$ ) |
|--|--------------------------------------|
| 45   | 0.61                                 |
| 67   | 0.71                                 |
| 89   | 0.79                                 |
| 133  | 0.50                                 |
| 178  | 0.30                                 |



**Figure 9:** Initial rate verus the initial substrate concentration.

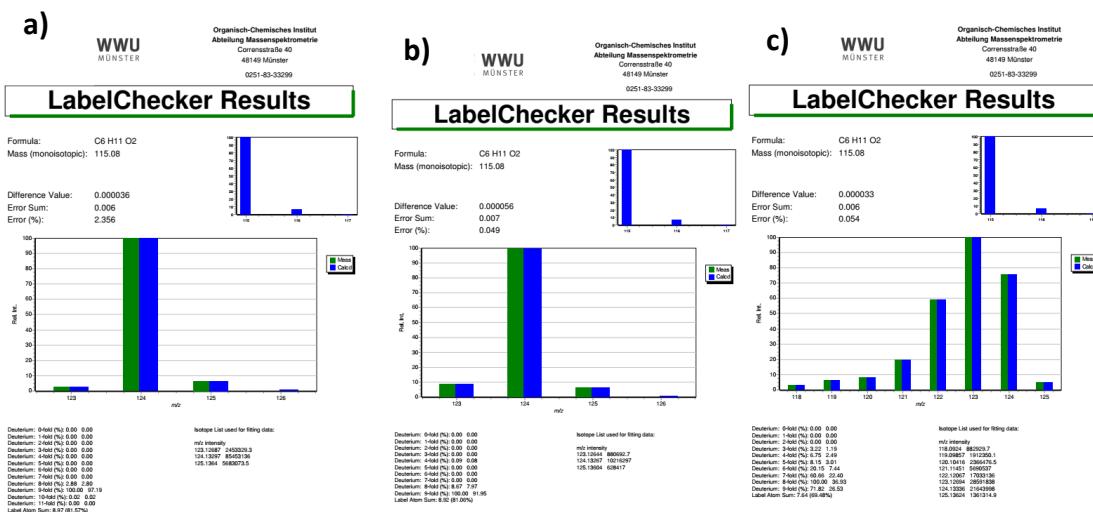
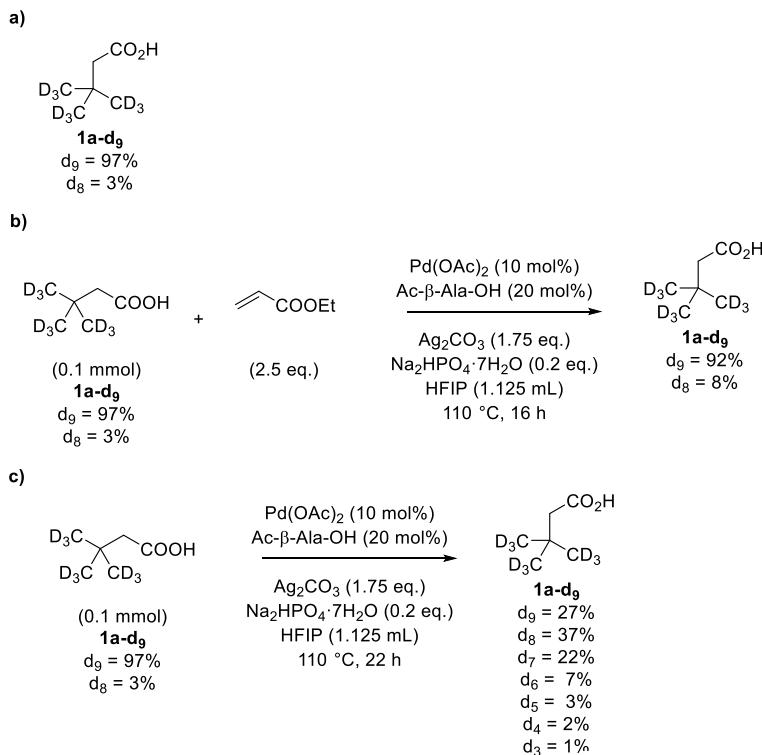
## Reversibility of the C–H Activation

### Reversibility Experiment in the presence of ethyl acrylate

An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (2.25 mg, 0.0100 mmol, 10 mol%), Ac- $\beta$ -Ala-OH (2.6 mg, 0.020 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (48.3 mg, 0.175 mmol, 1.75 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7 \text{H}_2\text{O}$  (5.4 mg, 0.02 mmol, 0.2 equiv),  $d_9$ -3,3-dimethylbutyric acid (**1a-d<sub>9</sub>**)(12.5 mg, 0.1 mmol) and ethyl acrylate (25.0 mg, 0.25 mmol, 2.5 equiv) and HFIP (1.125 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C for 16 h. The reaction was cooled to -78 °C. An aliquot of the reaction was filtered over a piece of Whatman ® filter paper and the deuterium incorporation in the leftover starting material was determined by HRMS-ESI-MS.

### Reversibility Experiment in the absence of ethyl acrylate

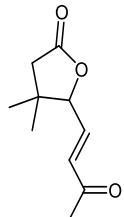
An oven dried 10 mL Schlenk tube was charged with  $\text{Pd}(\text{OAc})_2$  (2.25 mg, 0.0100 mmol, 10 mol%), Ac- $\beta$ -Ala-OH (2.6 mg, 0.020 mmol, 20 mol%),  $\text{Ag}_2\text{CO}_3$  (48.3 mg, 0.175 mmol, 1.75 equiv),  $\text{Na}_2\text{HPO}_4 \cdot 7 \text{H}_2\text{O}$  (5.4 mg, 0.02 mmol, 0.2 equiv),  $d_9$ -3,3-dimethylbutyric acid (**1a-d<sub>9</sub>**)(12.5 mg, 0.100 mmol) and HFIP (1.125 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C for 22h. The reaction was cooled to -78 °C. The reaction was allowed to warm up to room temperature and an aliquot of the reaction was filtered over a piece of Whatman ® filter paper and the deuterium incorporation of the starting material was determined by HRMS-ESI-MS.



**Scheme S24:** Reversibility experiment.

## Characterization of the Side Product

### (E)-4,4-dimethyl-5-(3-oxobut-1-en-1-yl)dihydrofuran-2(3H)-one (5e):



**5e** The compound **5e** was obtained as side product from the synthesis of **4e** in form of a colorless oil (4.1 mg, 0.022 mmol, 11%).

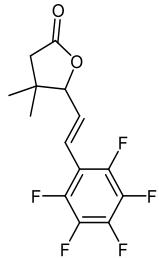
**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):** δ = 6.69 (dd, *J* = 15.9, 5.0 Hz, 1H), 6.41 (dd, *J* = 15.9, 1.7 Hz, 1H), 4.70 (dd, *J* = 5.0, 1.7 Hz, 1H), 2.48 (d, *J* = 16.9 Hz, 1H), 2.39 (d, *J* = 16.9 Hz, 1H), 2.30 (s, 3H), 1.26 (s, 3H), 1.01 (s, 3H) ppm.

**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>):** δ = 197.1, 175.2, 138.4, 131.2, 86.5, 44.1, 40.8, 28.6, 25.4, 22.6 ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>10</sub>H<sub>14</sub>NaO<sub>3</sub><sup>+</sup> 205.0835, Found 205.0841.

**IR (cm<sup>-1</sup>):** 2961, 2949, 2932, 1726, 1373, 1314, 1246, 1151, 1038.

### (E)-4,4-Dimethyl-5-(2-(perfluorophenyl)vinyl)dihydrofuran-2(3H)-one (5m):



**5m** Following the general procedure **F** and using pentafluorostyrene (97.1 mg, 0.500 mmol) the target compound **5m** was obtained as a colorless oil (12.0 mg, 39.2 μmol, 20%).

**<sup>1</sup>H-NMR (599 MHz, CDCl<sub>3</sub>):** δ = 6.62 (dd, *J* = 16.4, 1.4 Hz, 1H), 6.49 (dd, *J* = 16.4, 6.1 Hz, 1H), 4.69 (dd, *J* = 6.1, 1.4 Hz, 1H), 2.49 (d, *J* = 16.9 Hz, 1H), 2.42 (d, *J* = 16.9 Hz, 1H), 1.26 (s, 3H), 1.07 (s, 3H) ppm.

**<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>):** δ = 175.4, 145.0, 140.5, 137.9, 132.1, 117.4, 111.0, 88.3, 44.1, 40.7, 25.4, 22.5 ppm.

**<sup>19</sup>F-{<sup>1</sup>H}-NMR (564 MHz, CDCl<sub>3</sub>):** δ = -141.4 – -143.4 (m), -154.8 (t, *J* = 20.8 Hz), -162.4 (td, *J* = 21.6, 8.1 Hz) ppm.

**HRMS (ESIpos) m/z:** Calcd for C<sub>14</sub>H<sub>11</sub>F<sub>5</sub>NaO<sub>2</sub><sup>+</sup> 329.0571, Found 329.0585.

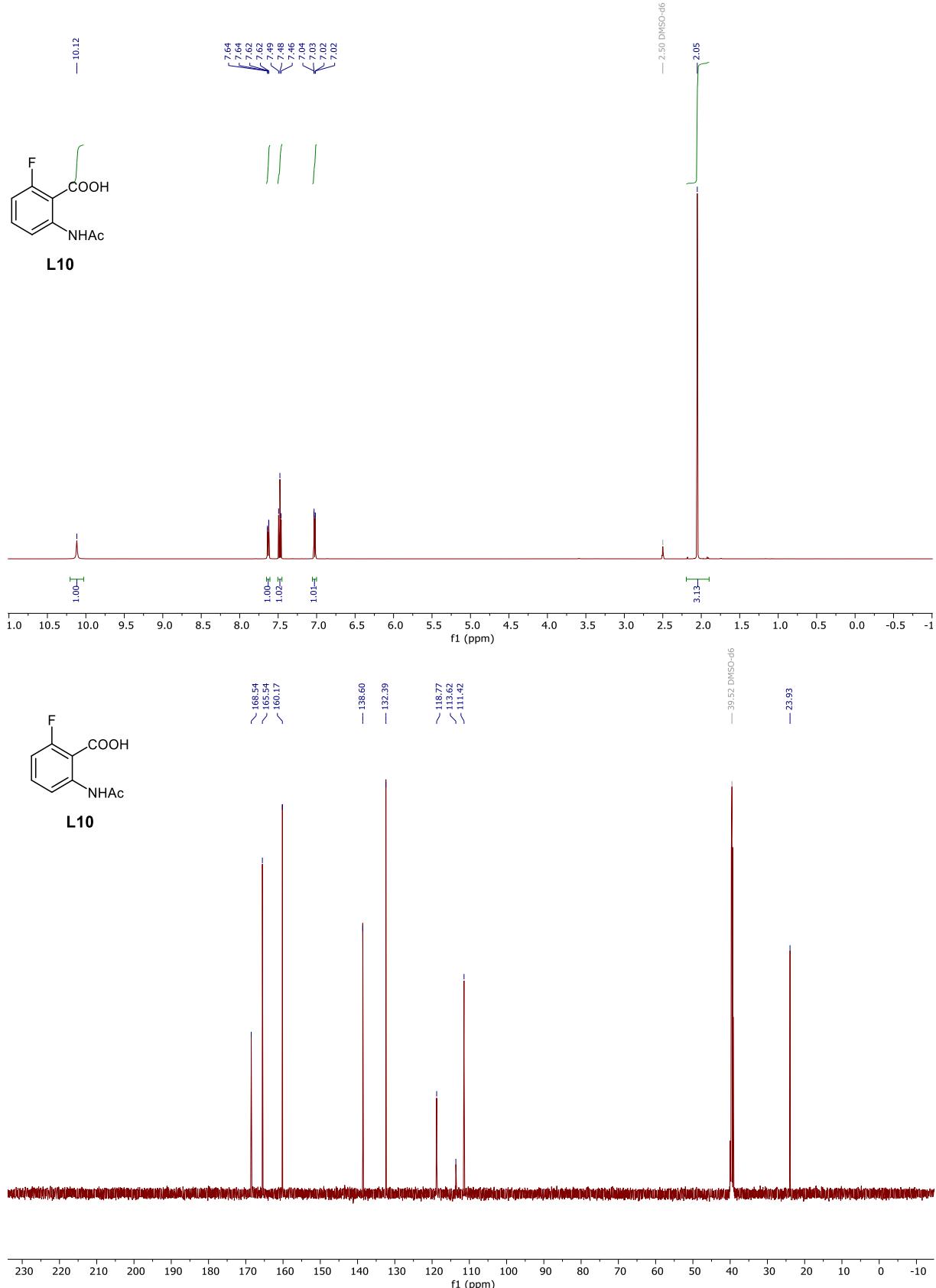
**IR (cm<sup>-1</sup>):** 2967, 2255, 1778, 1522, 1499, 993, 907, 731.

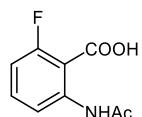
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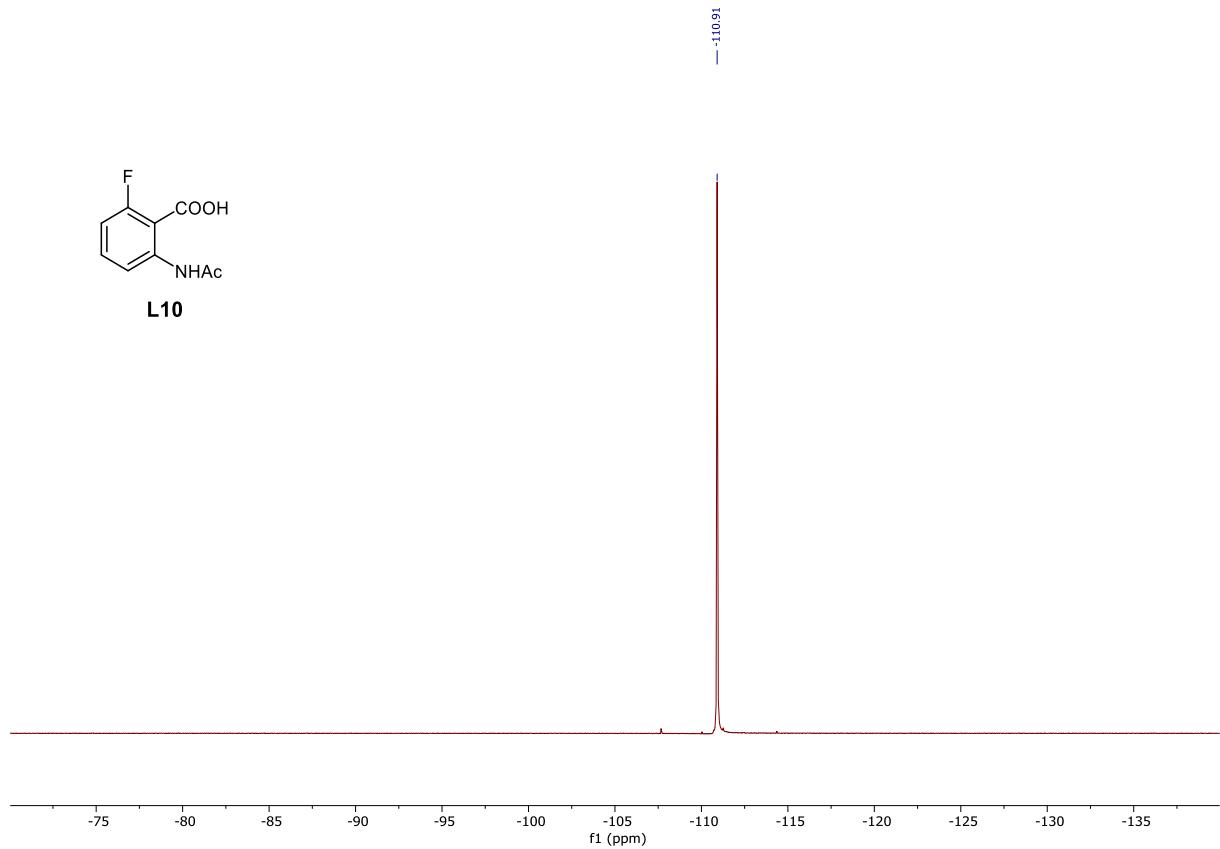
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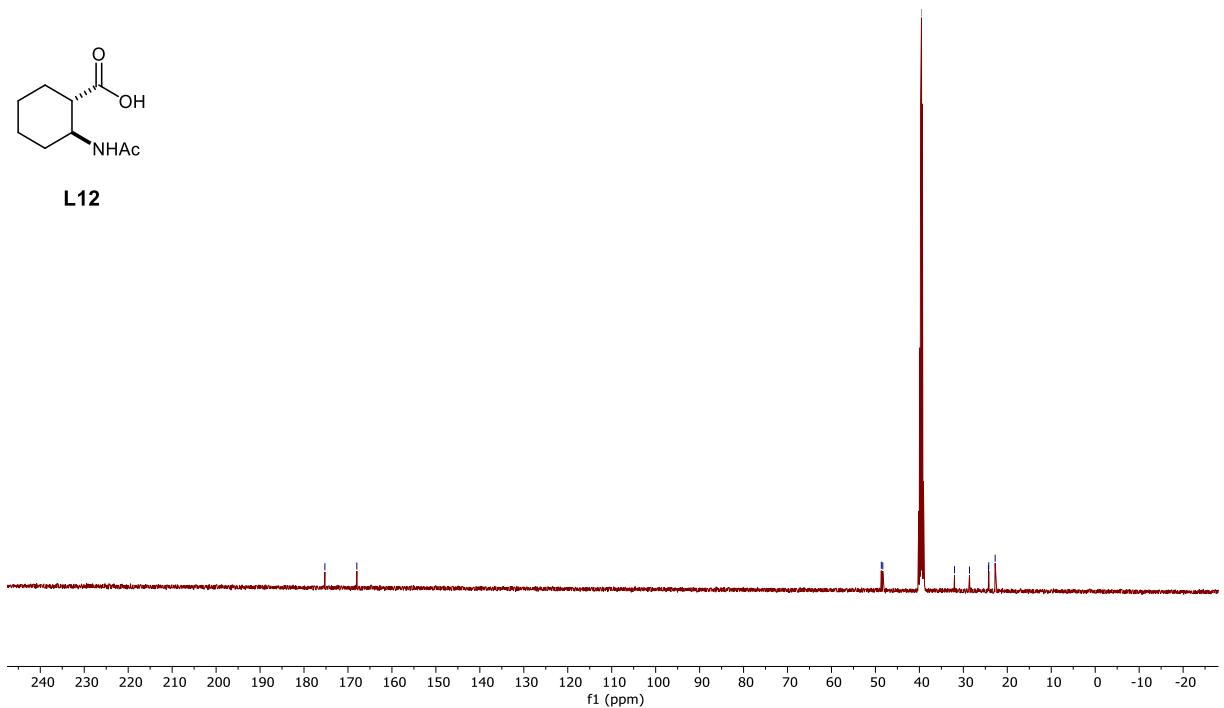
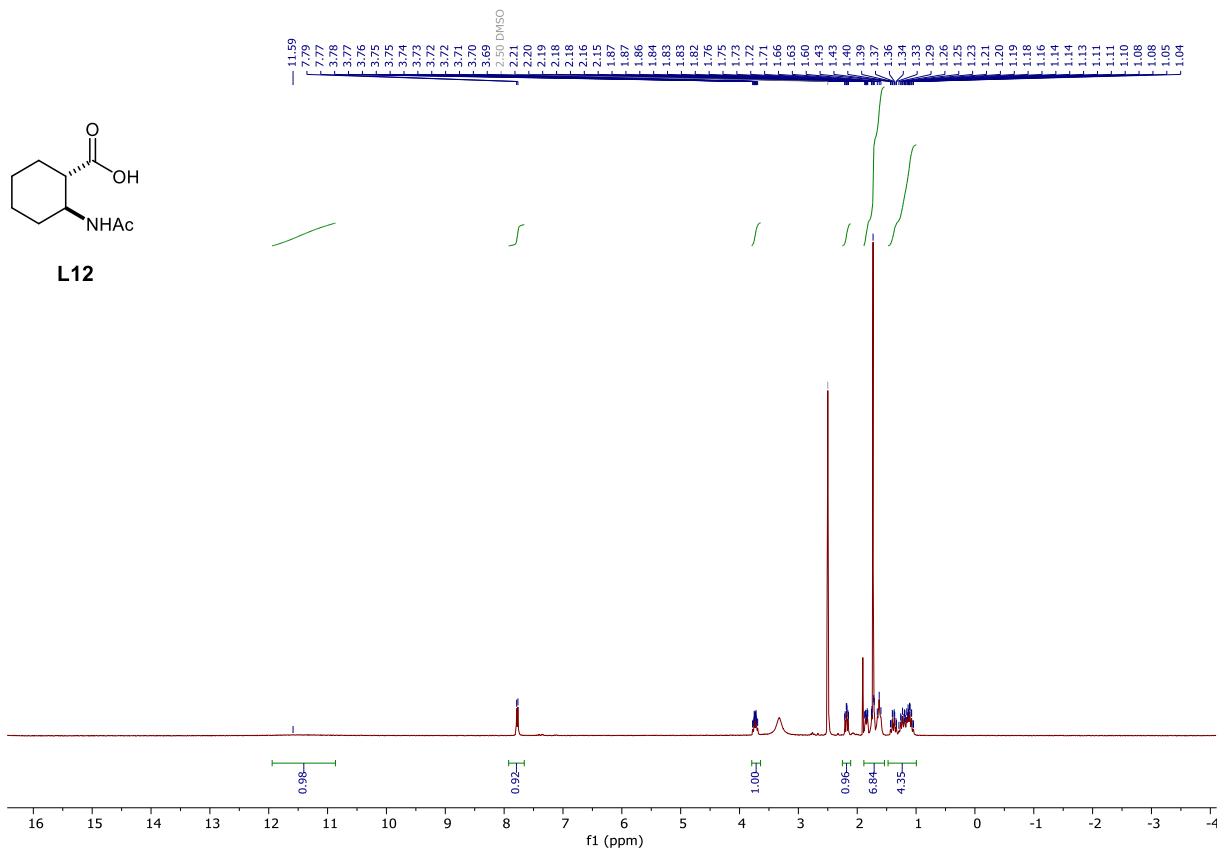
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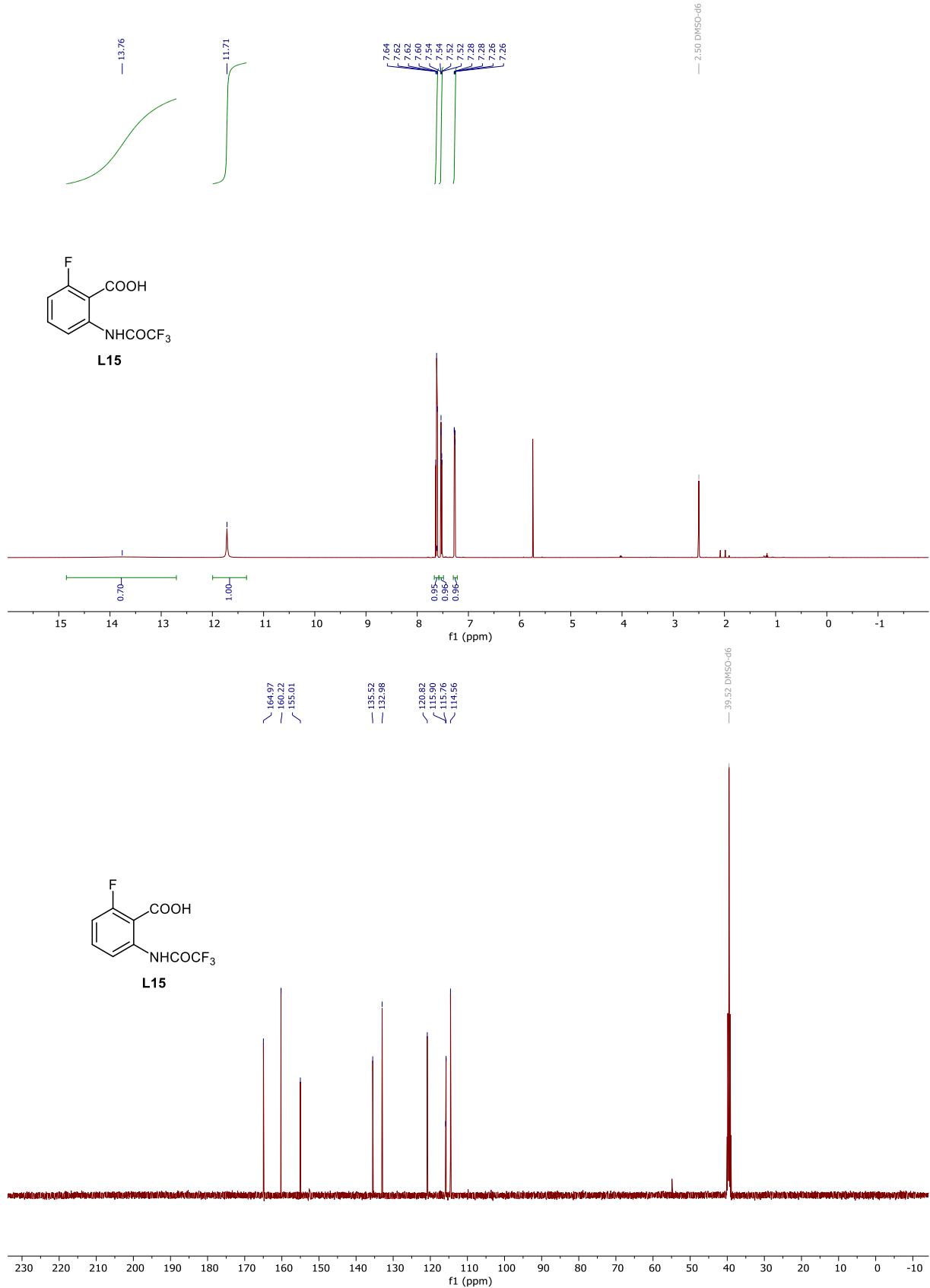




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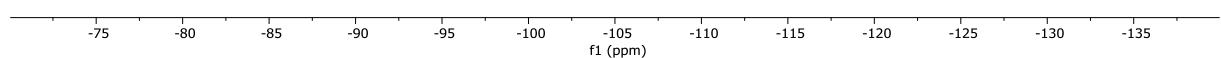
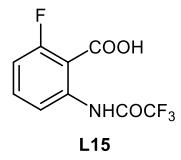


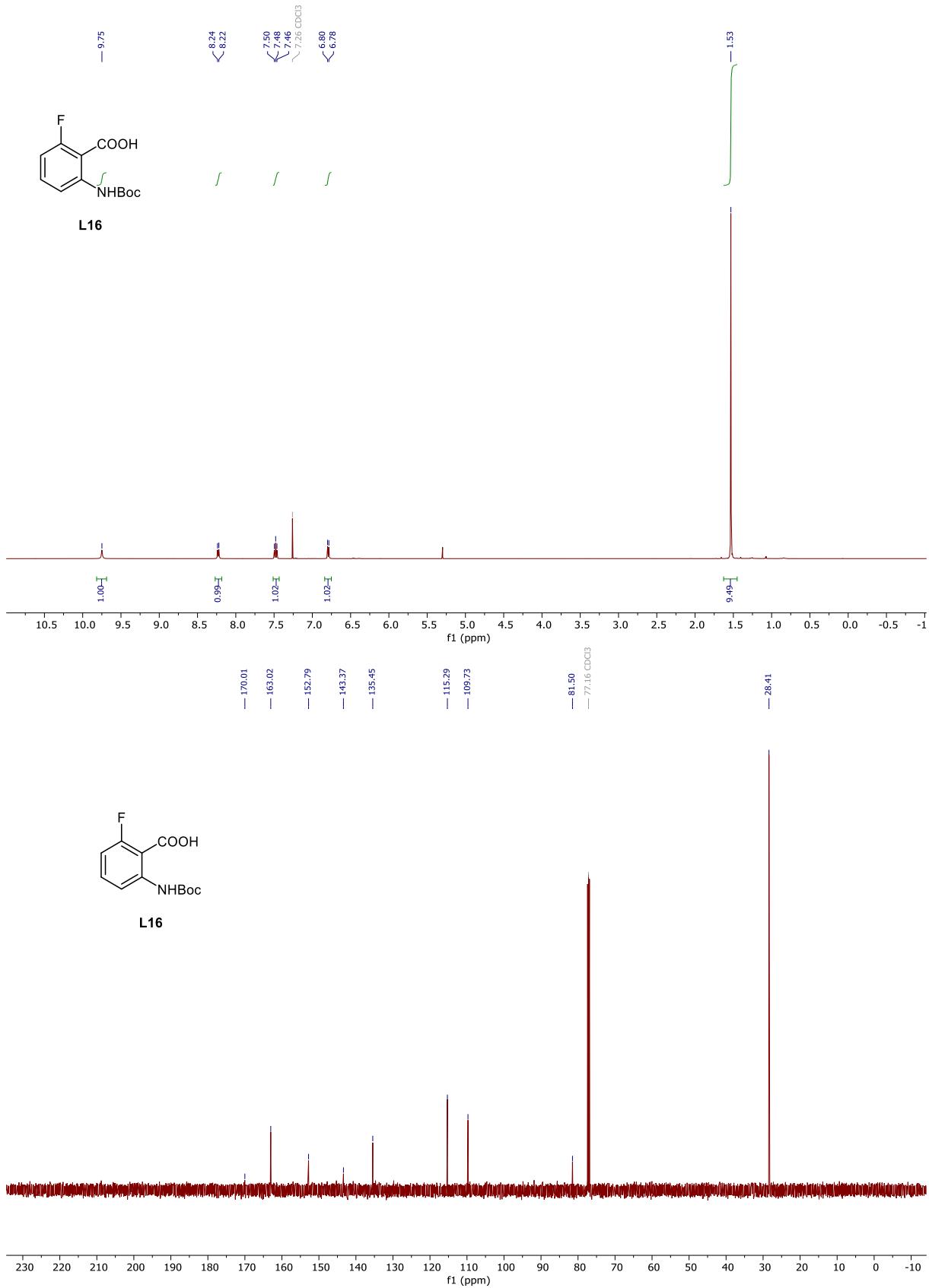


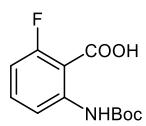


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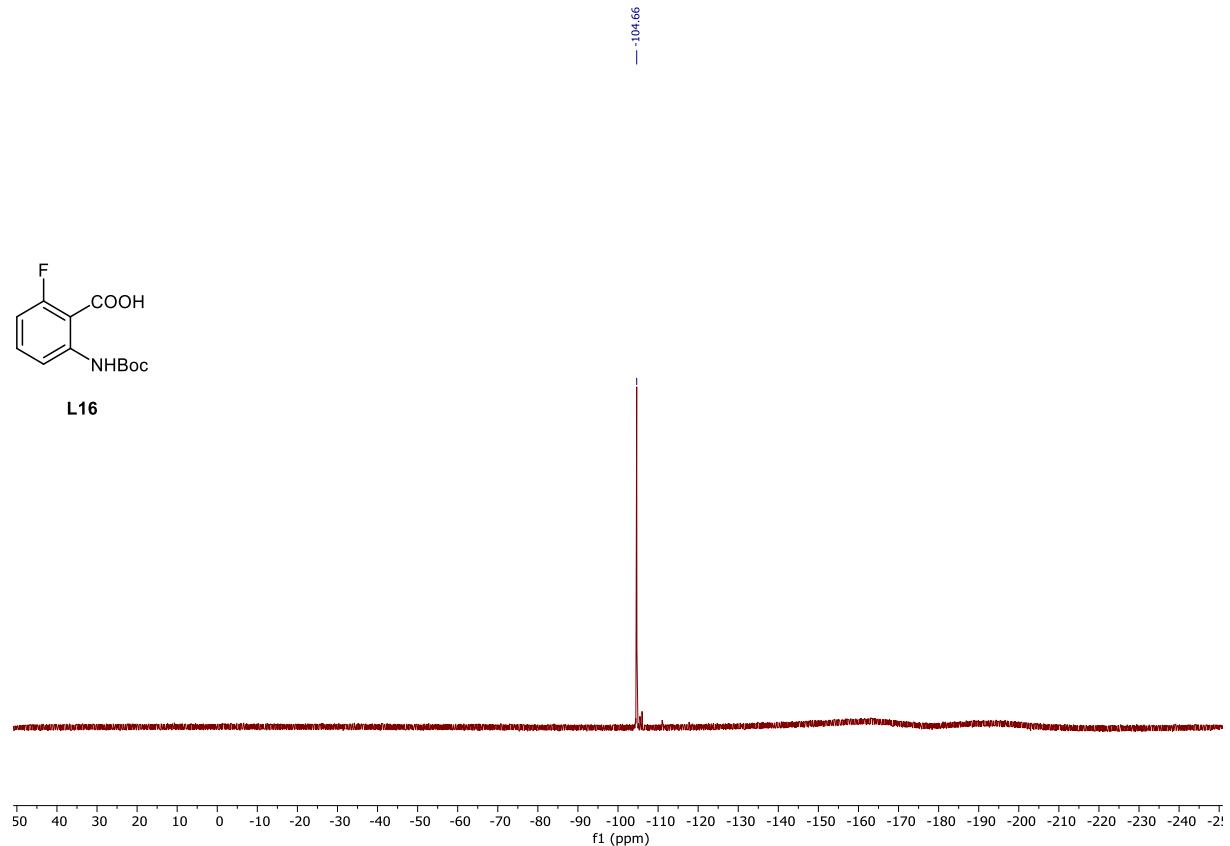
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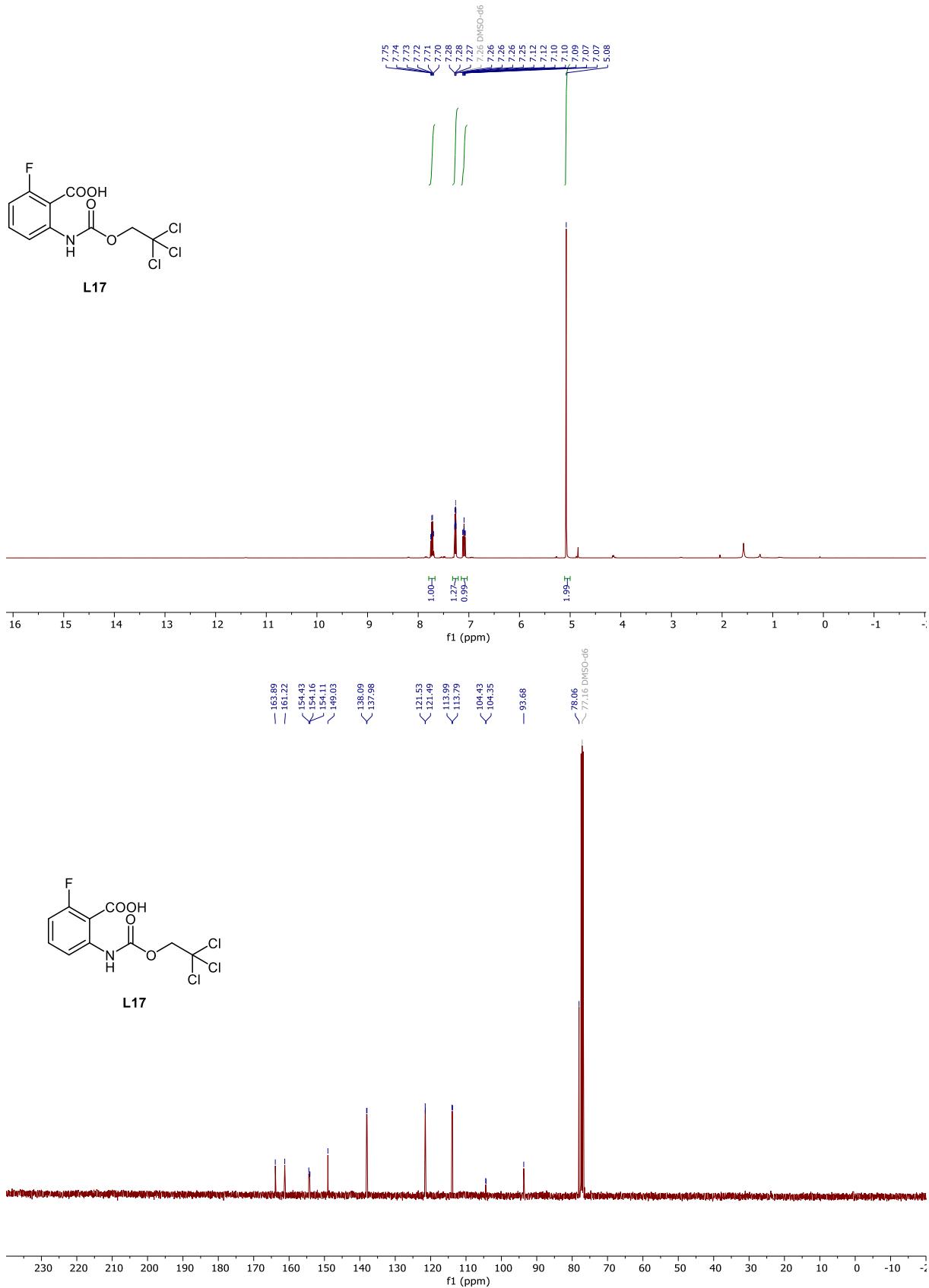




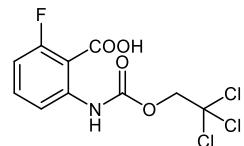


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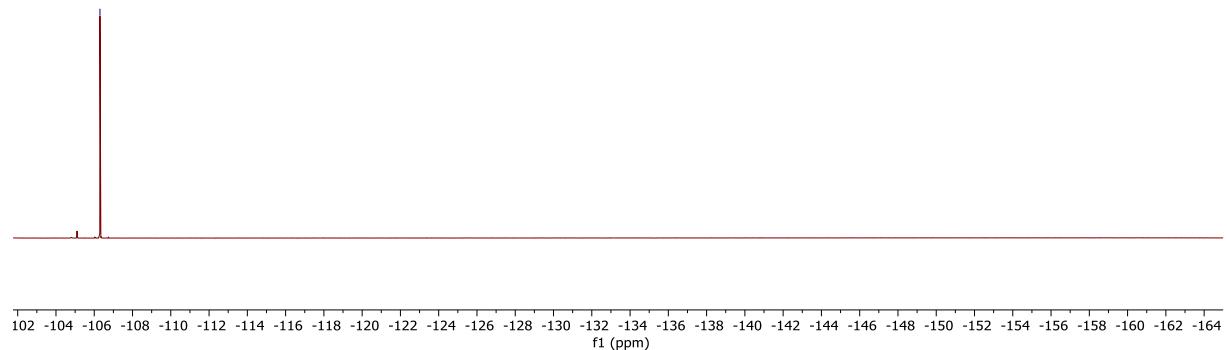


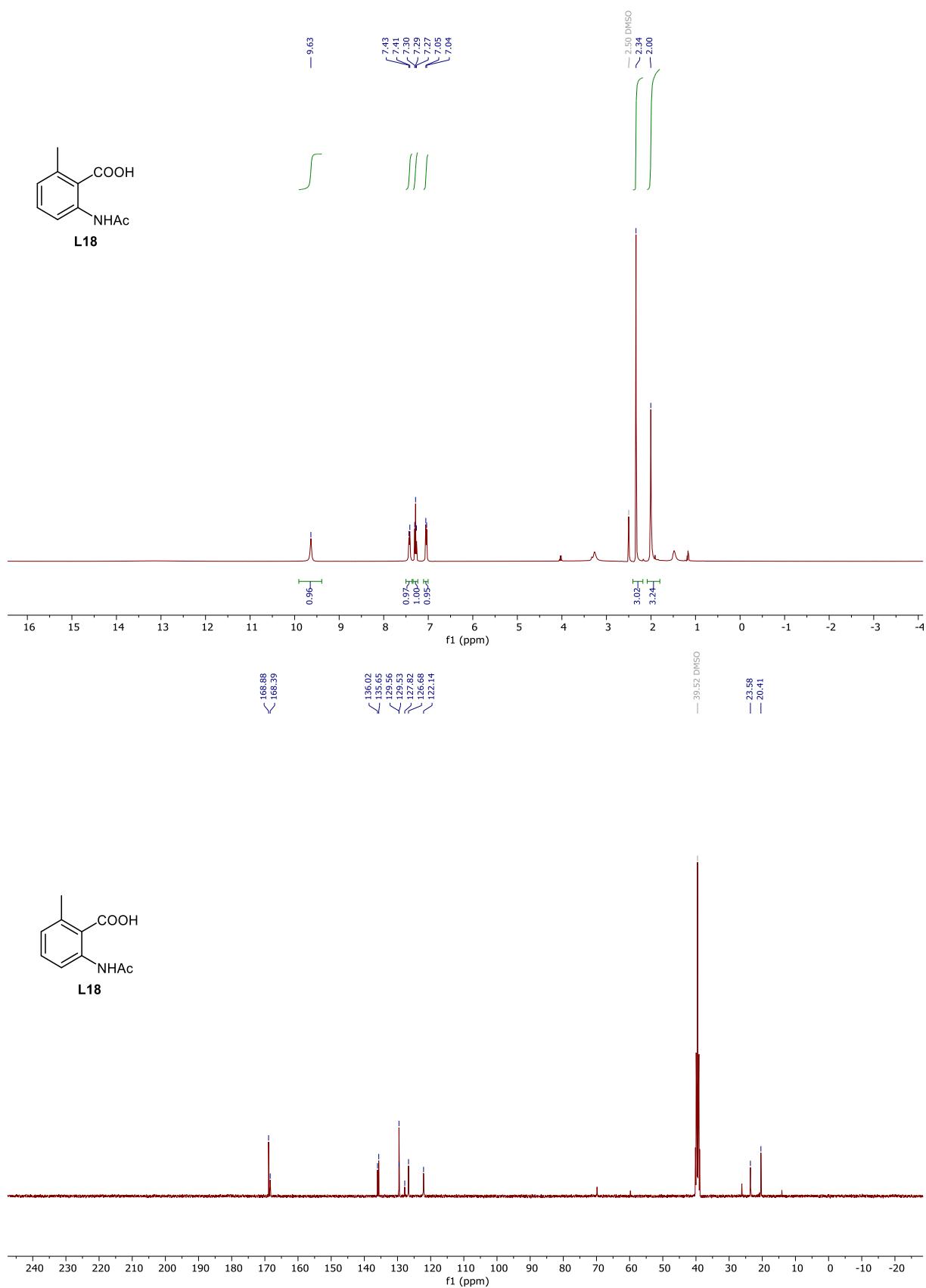


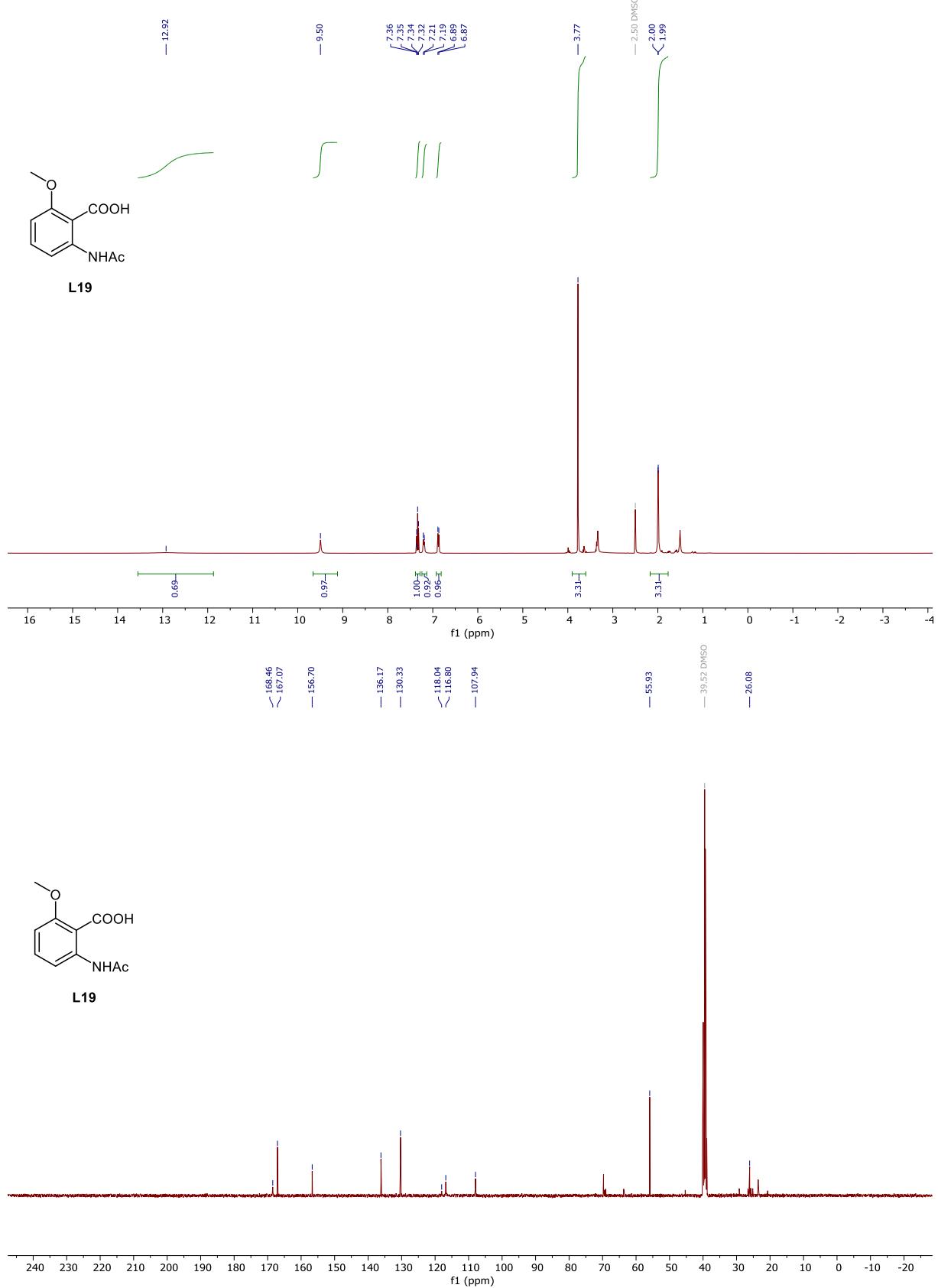
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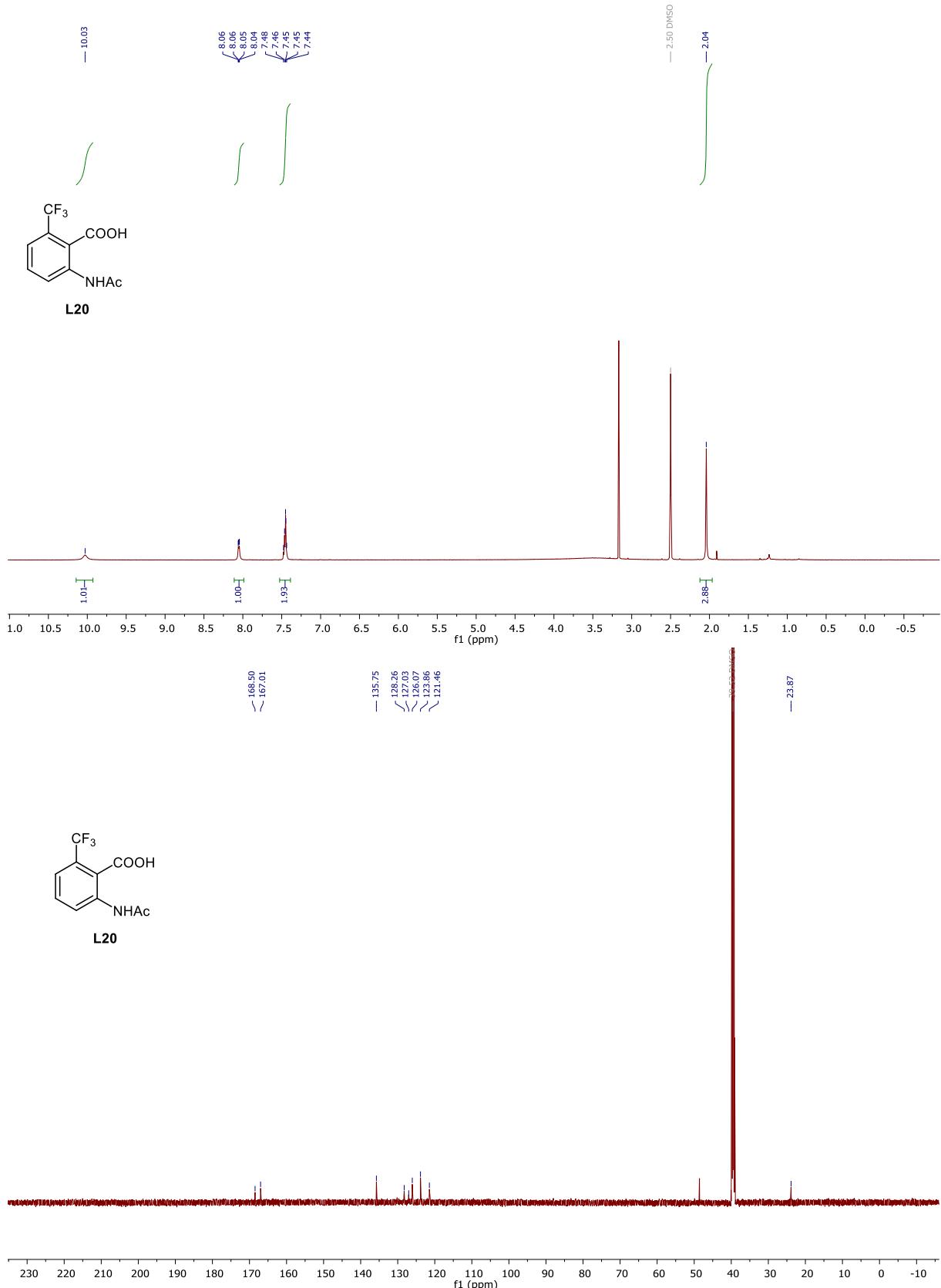


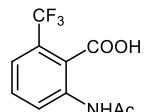
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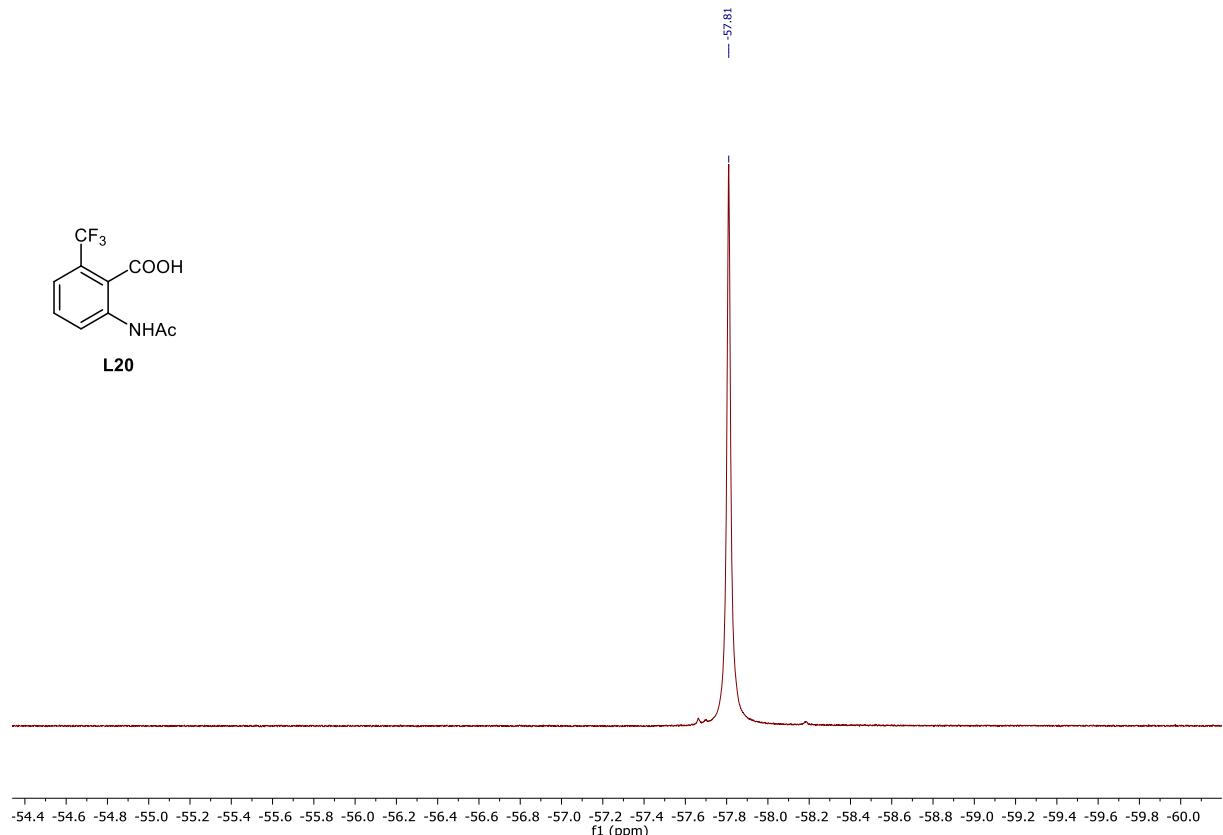


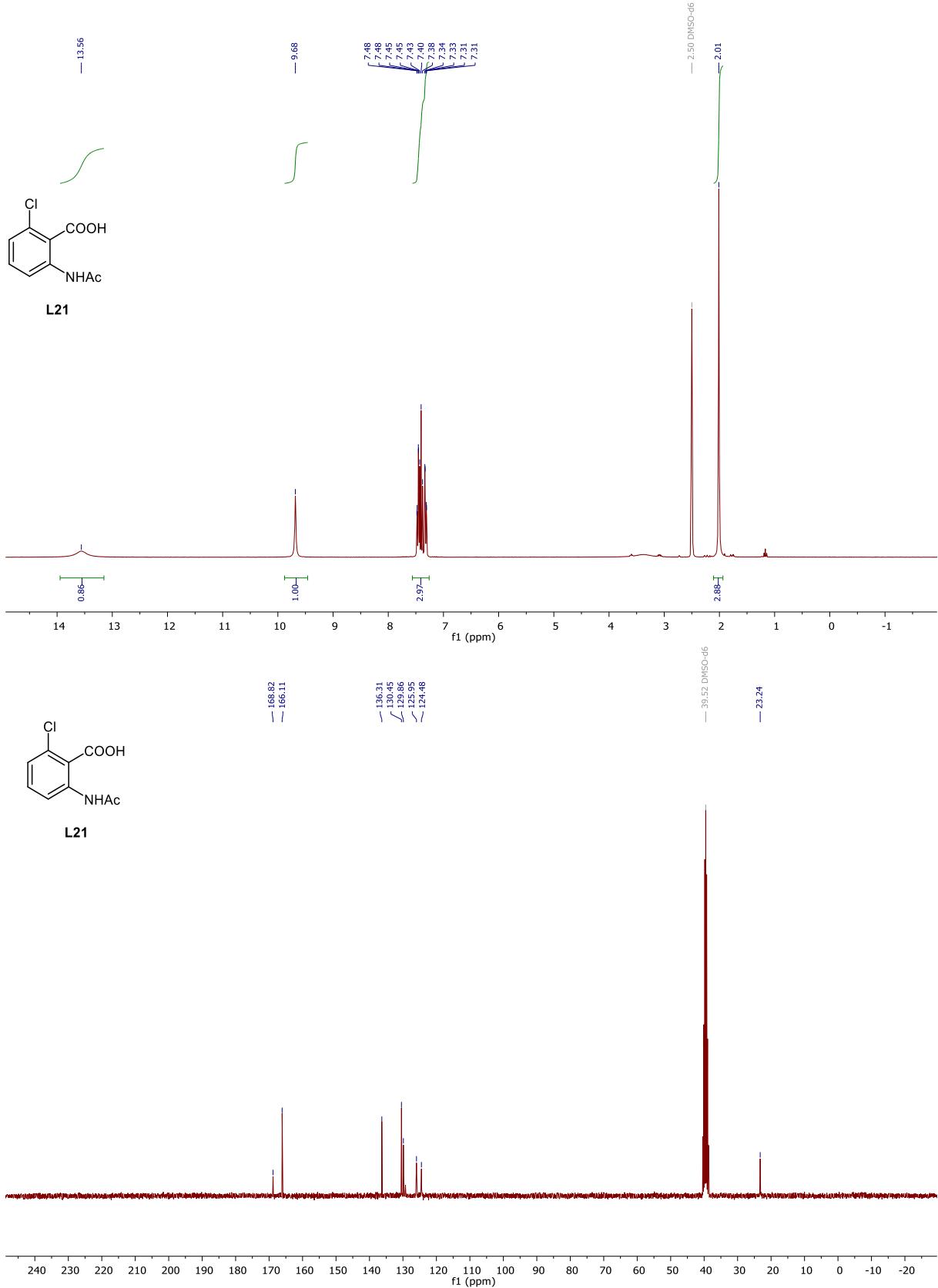


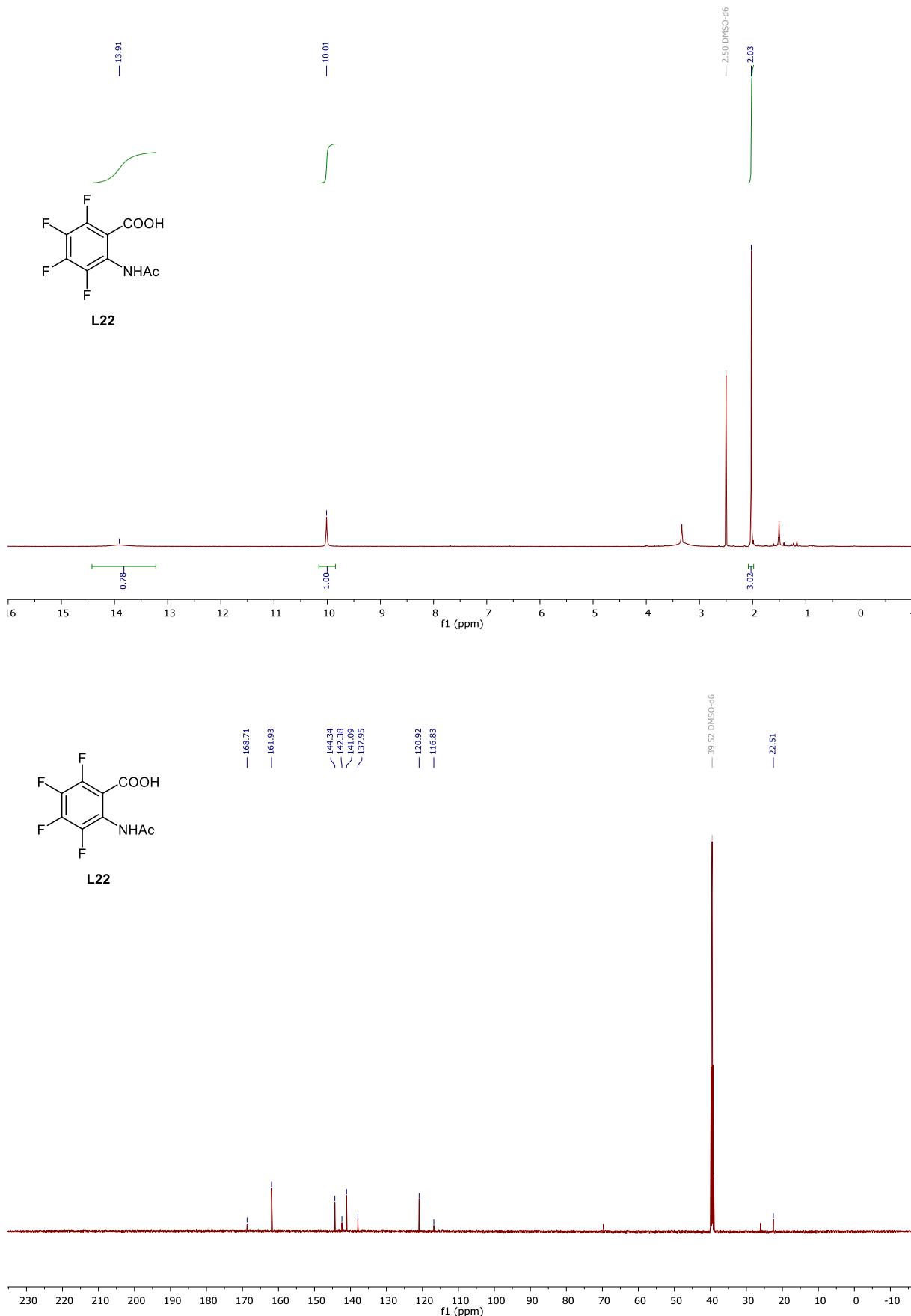


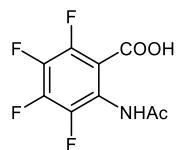


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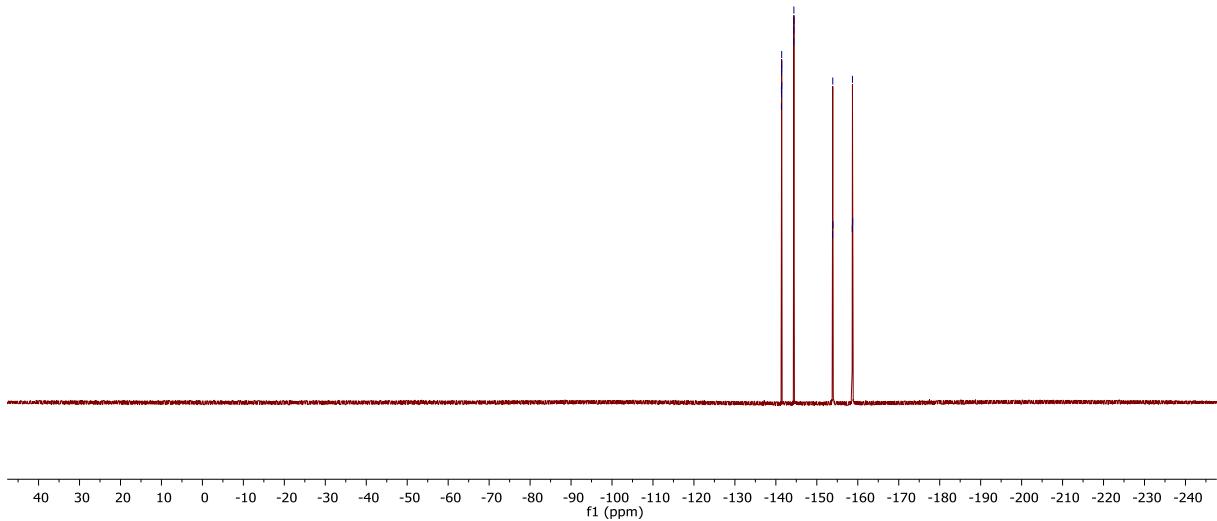




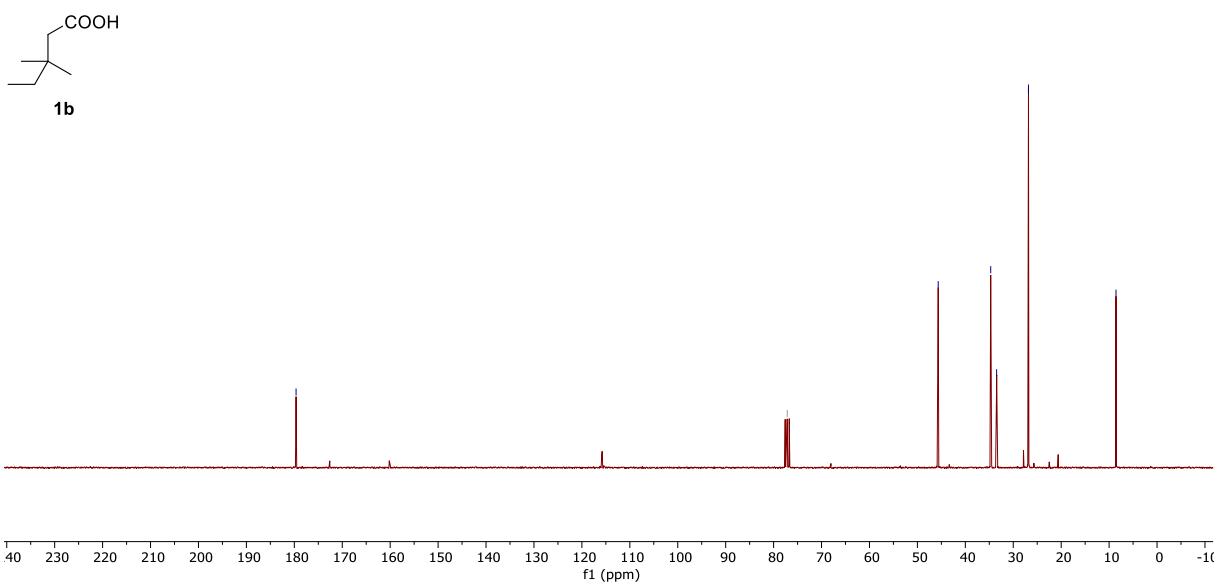
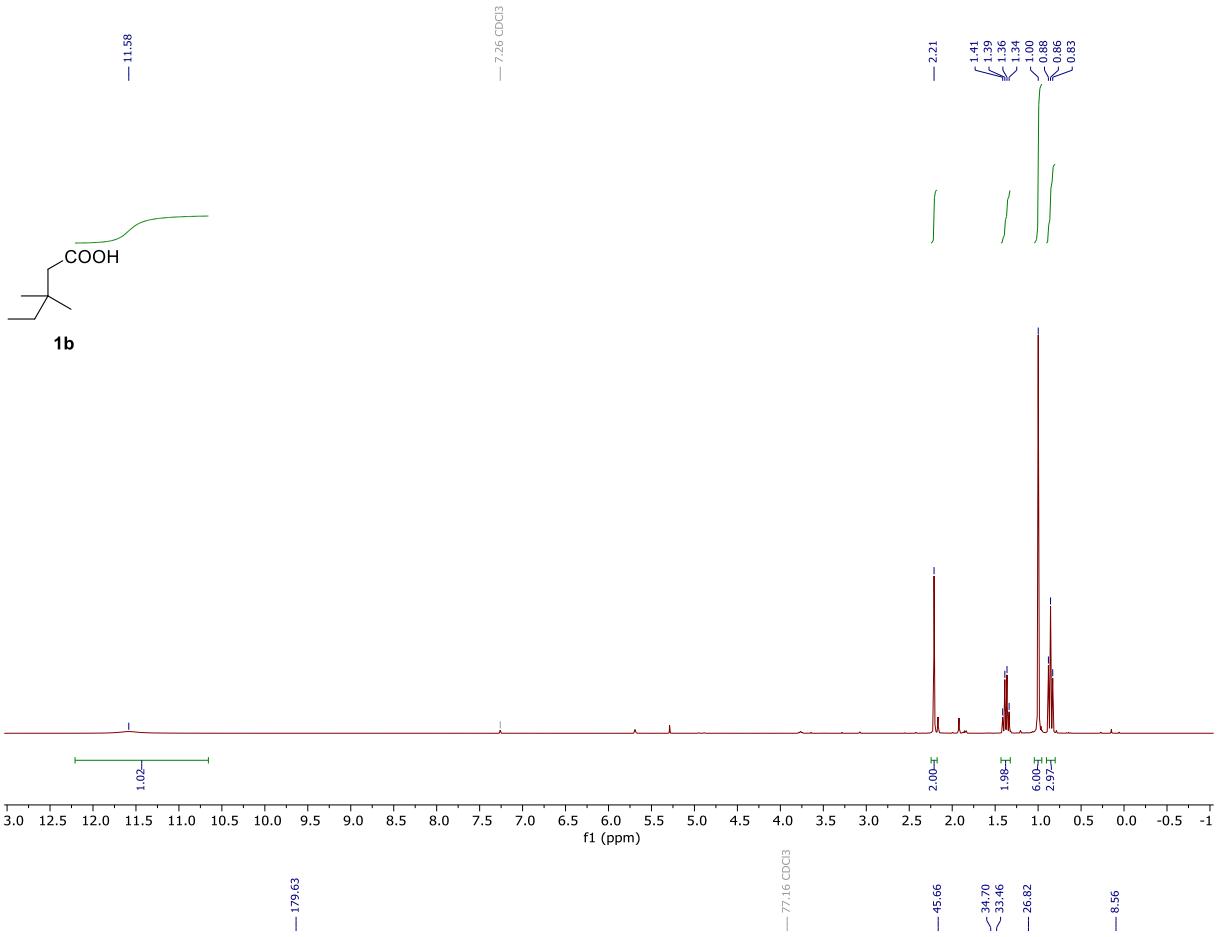


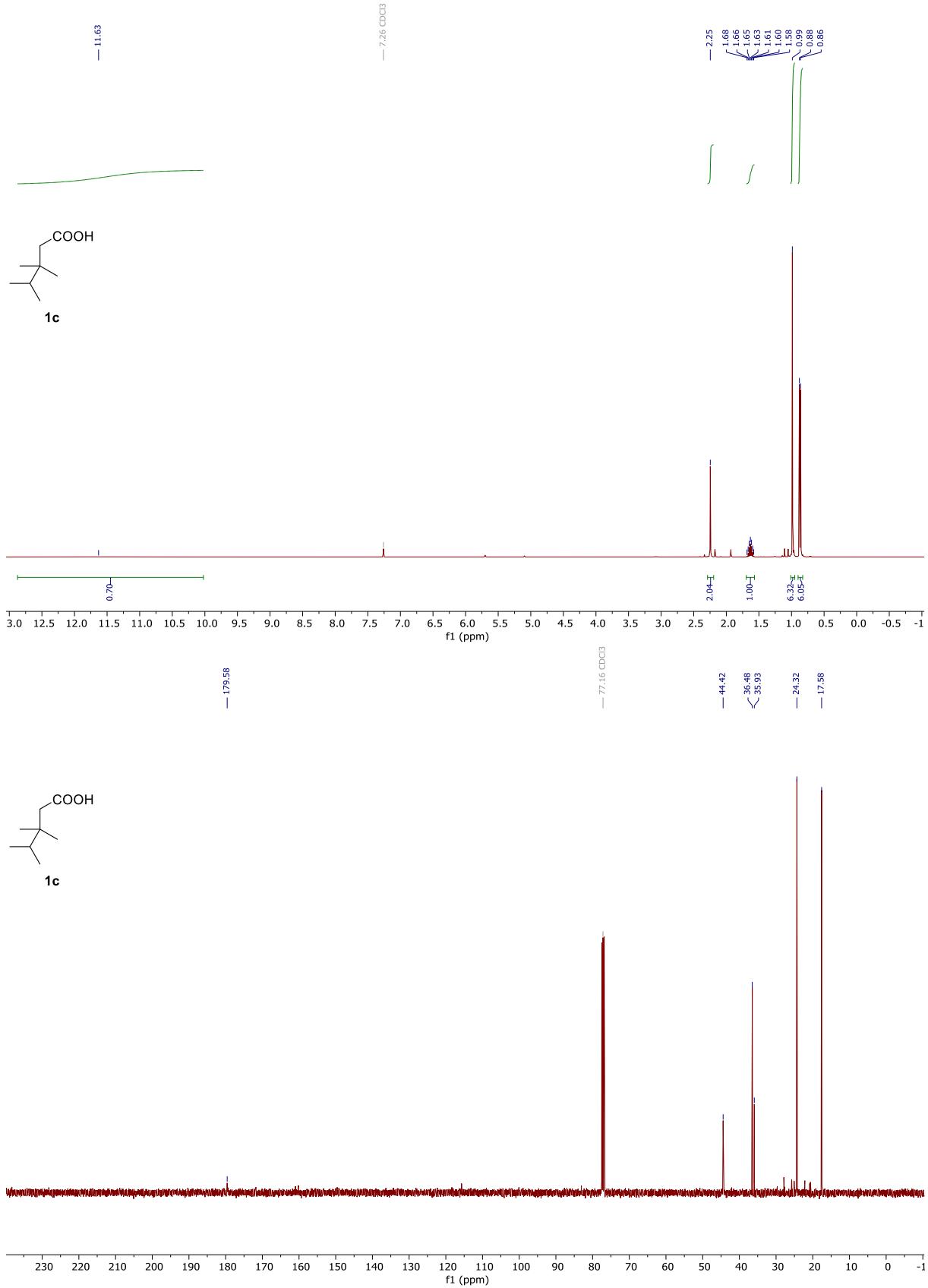


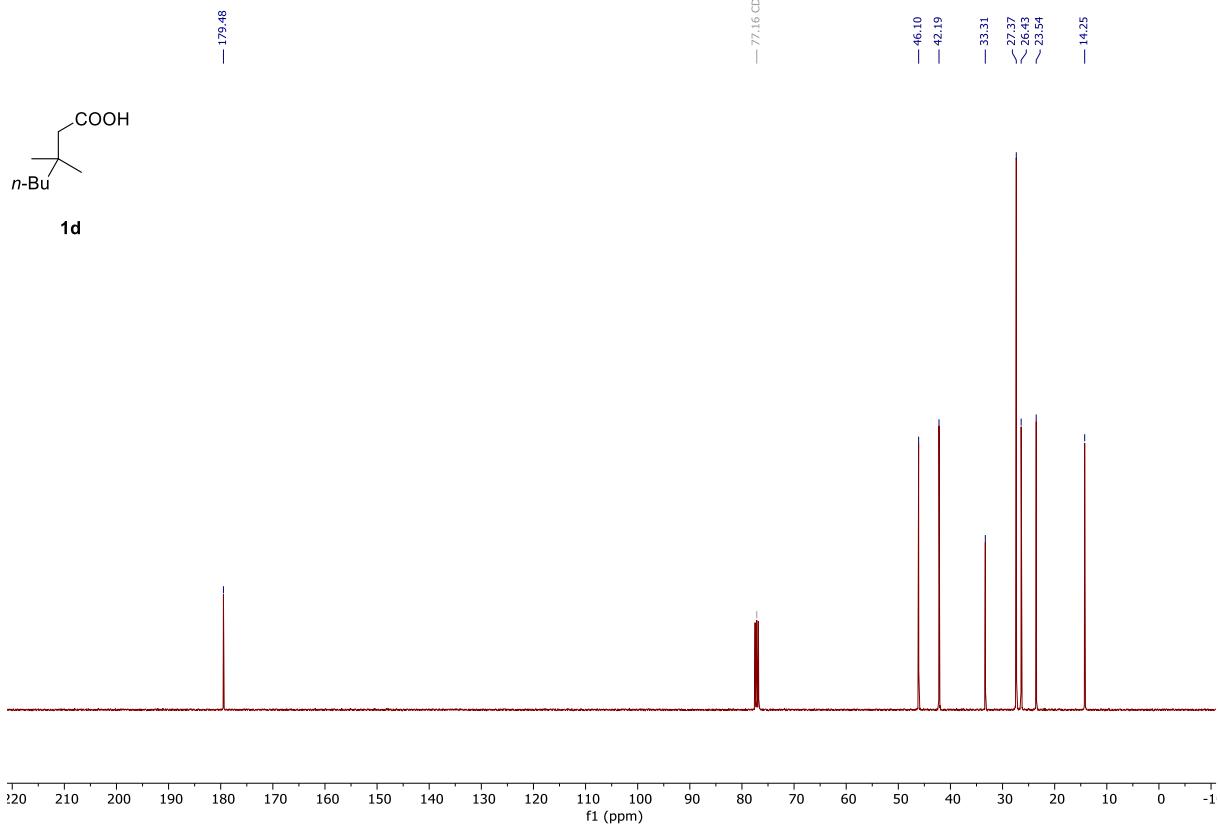
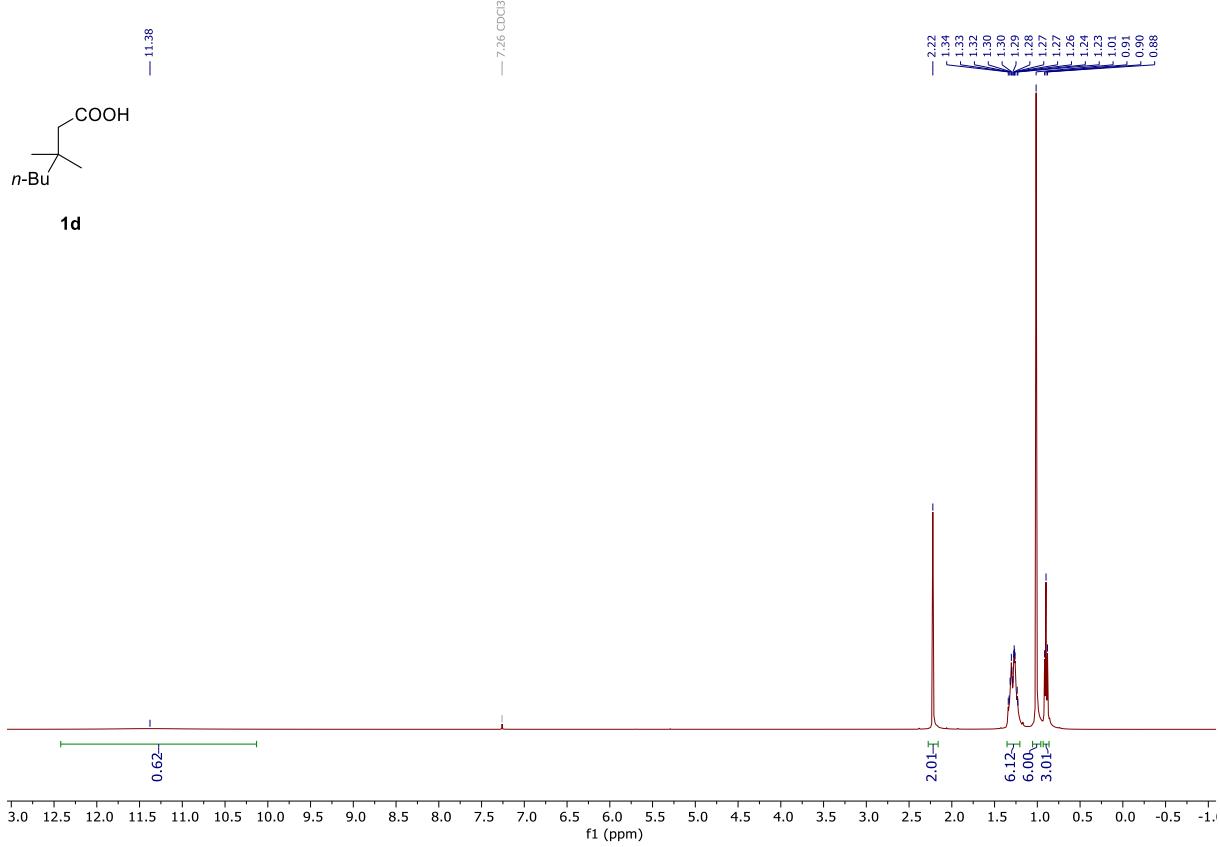
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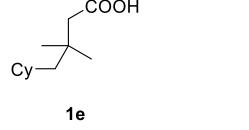


## Starting materials:

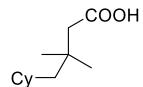
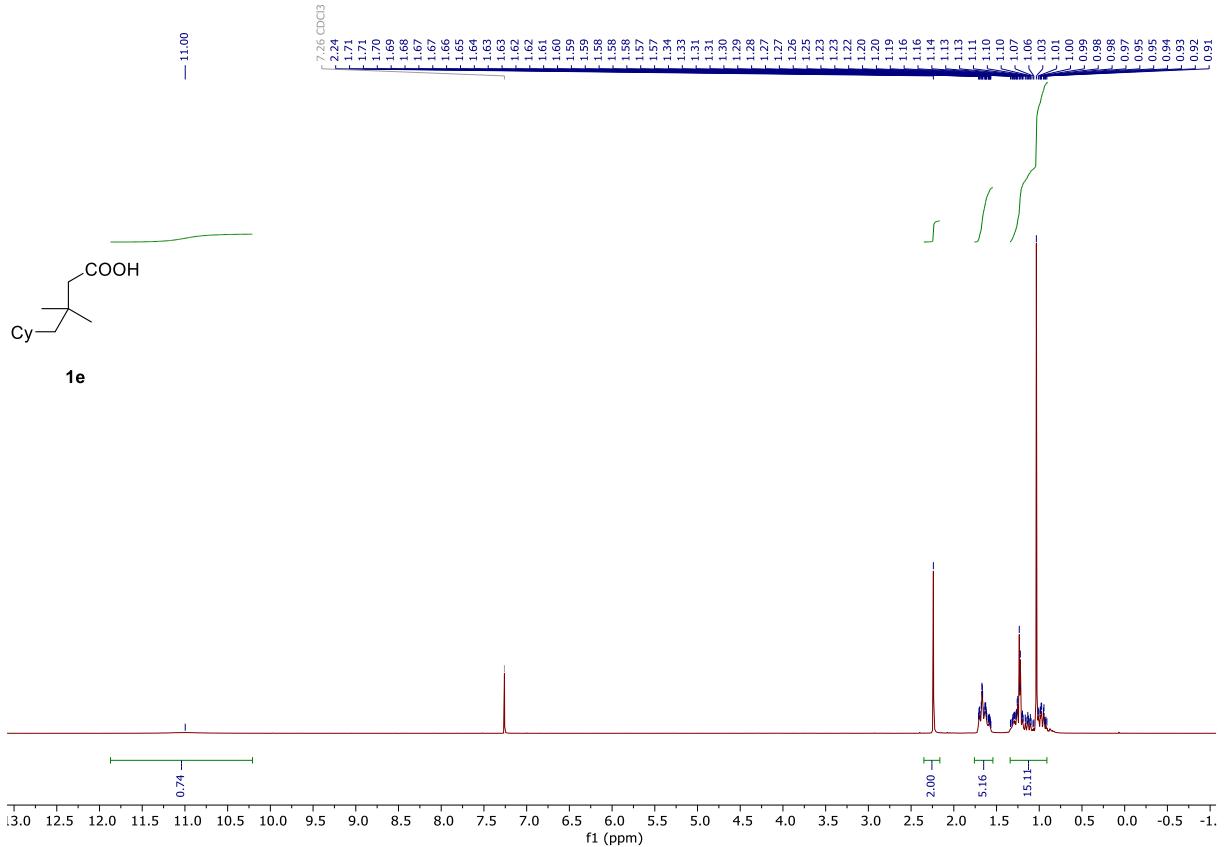




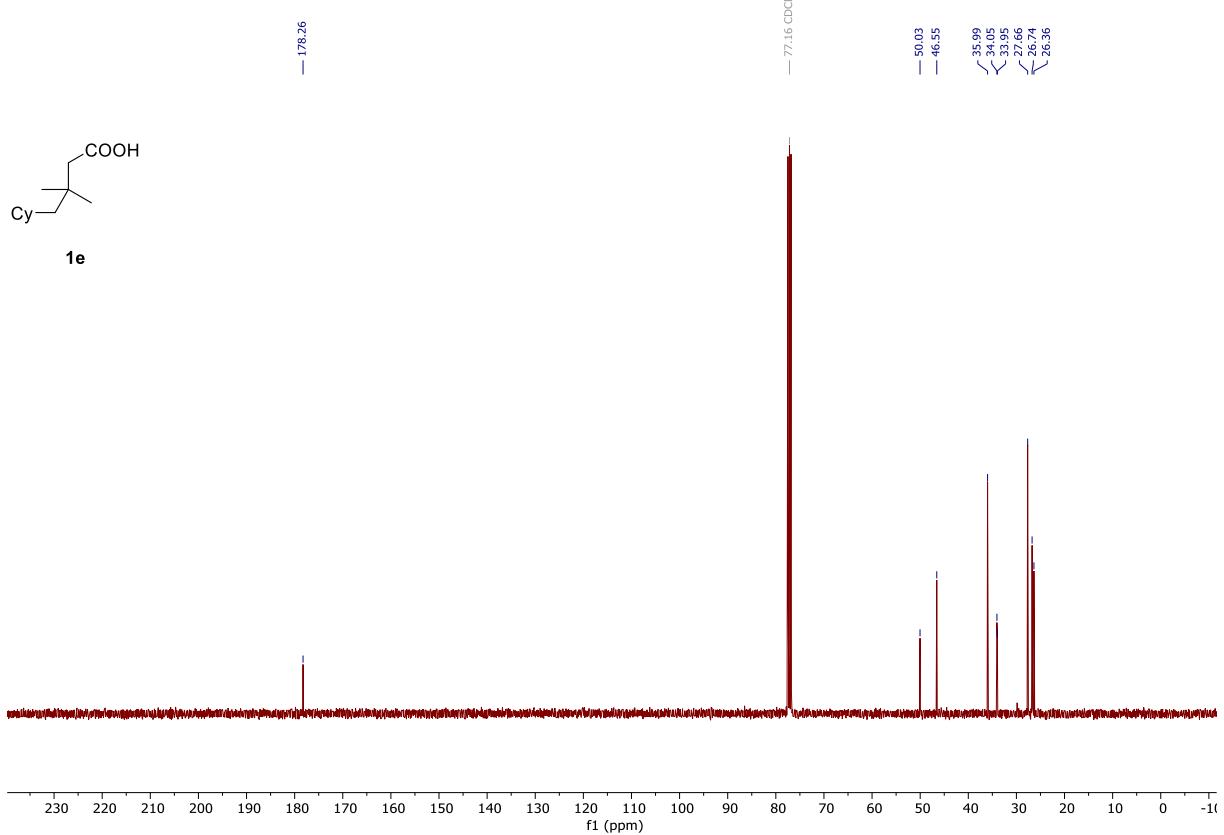


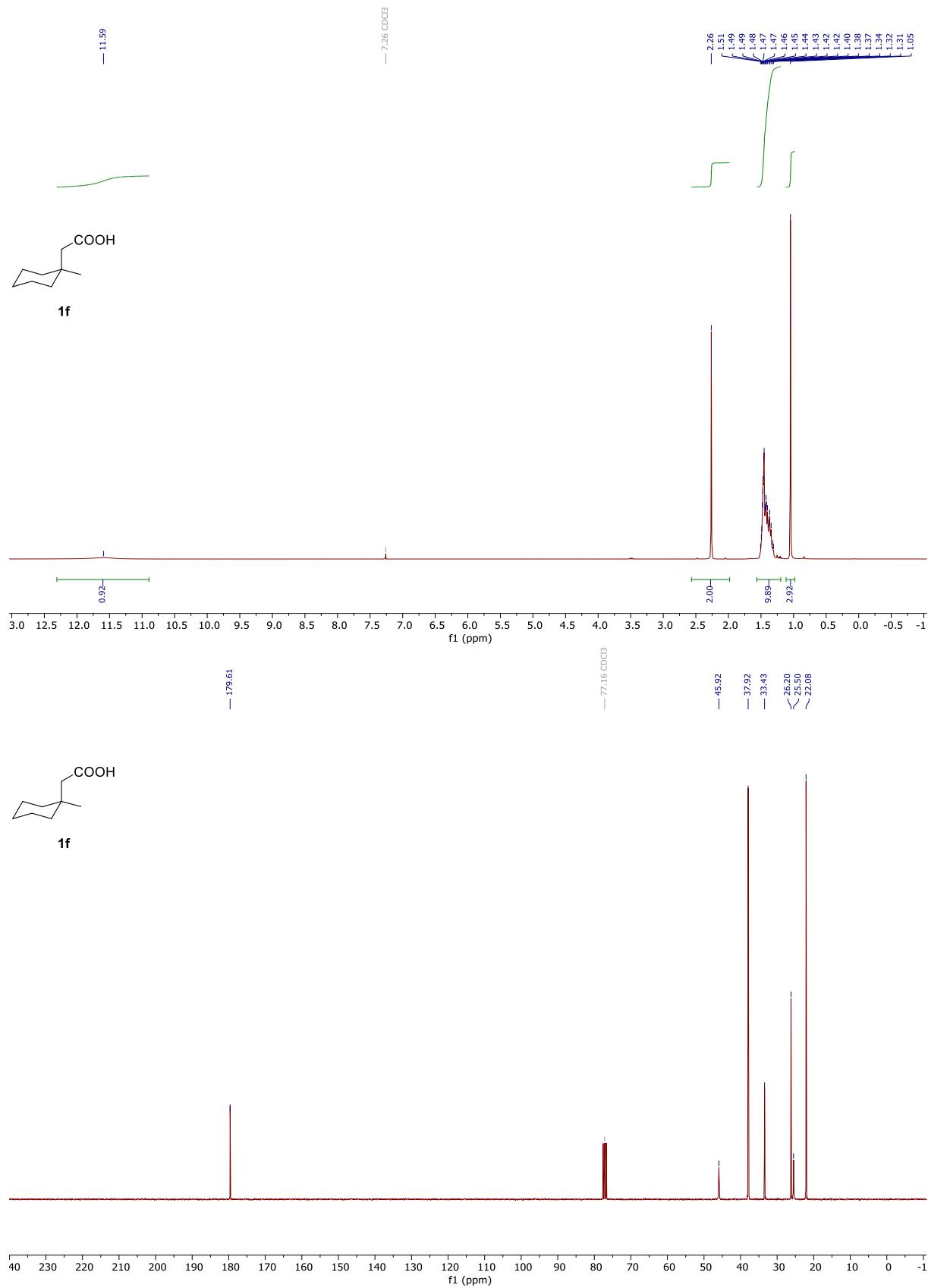


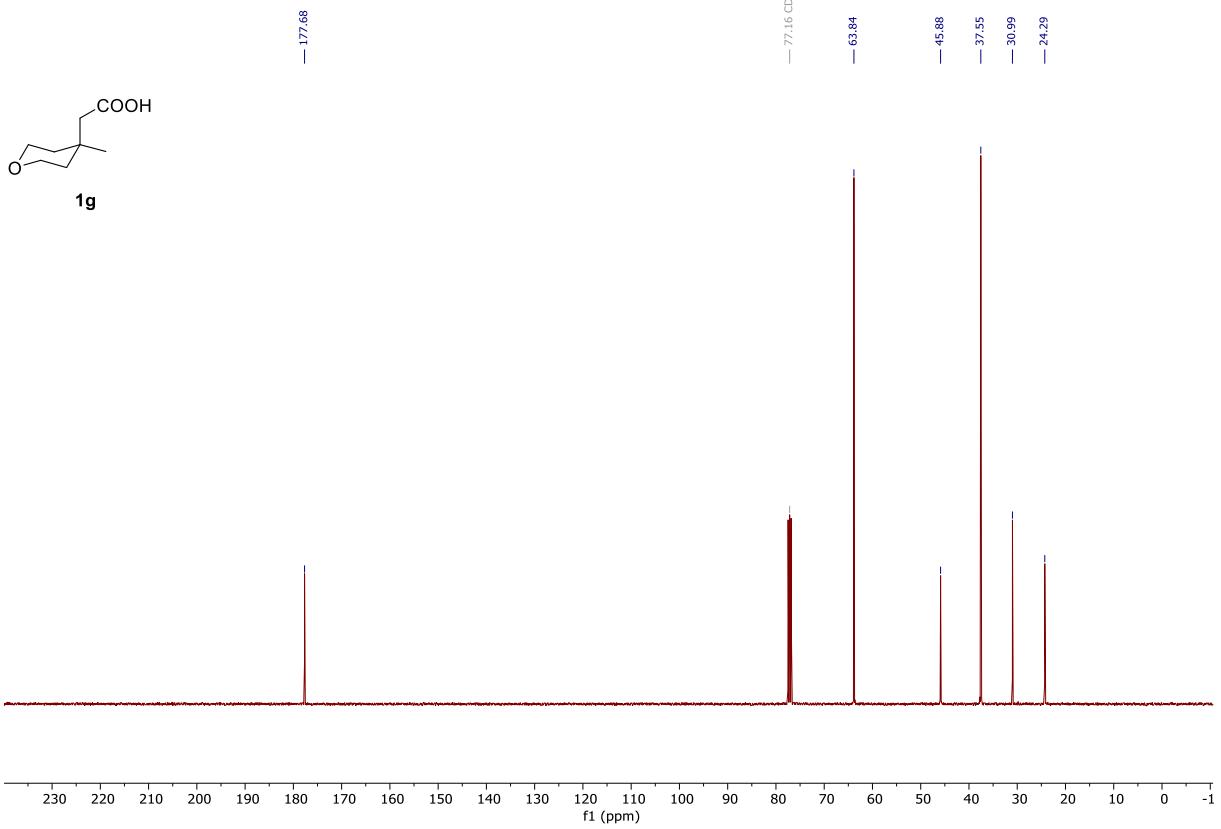
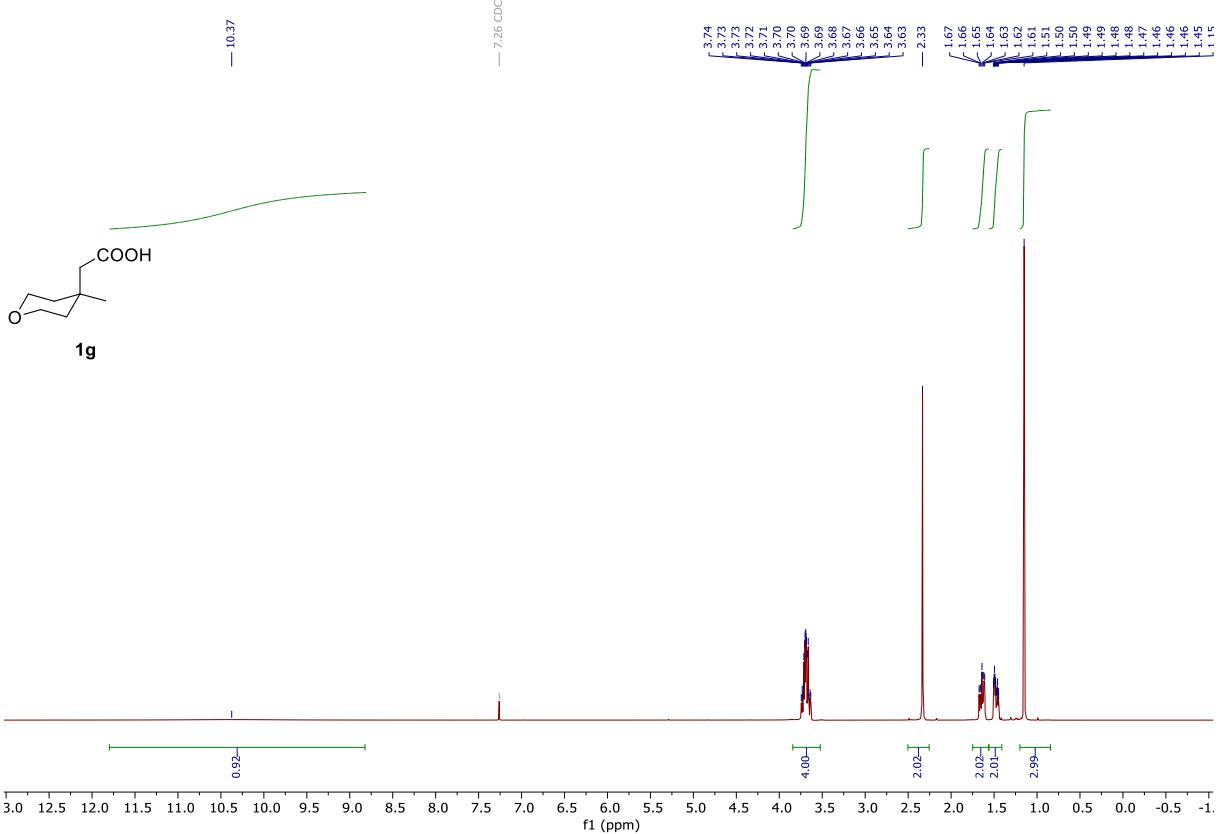
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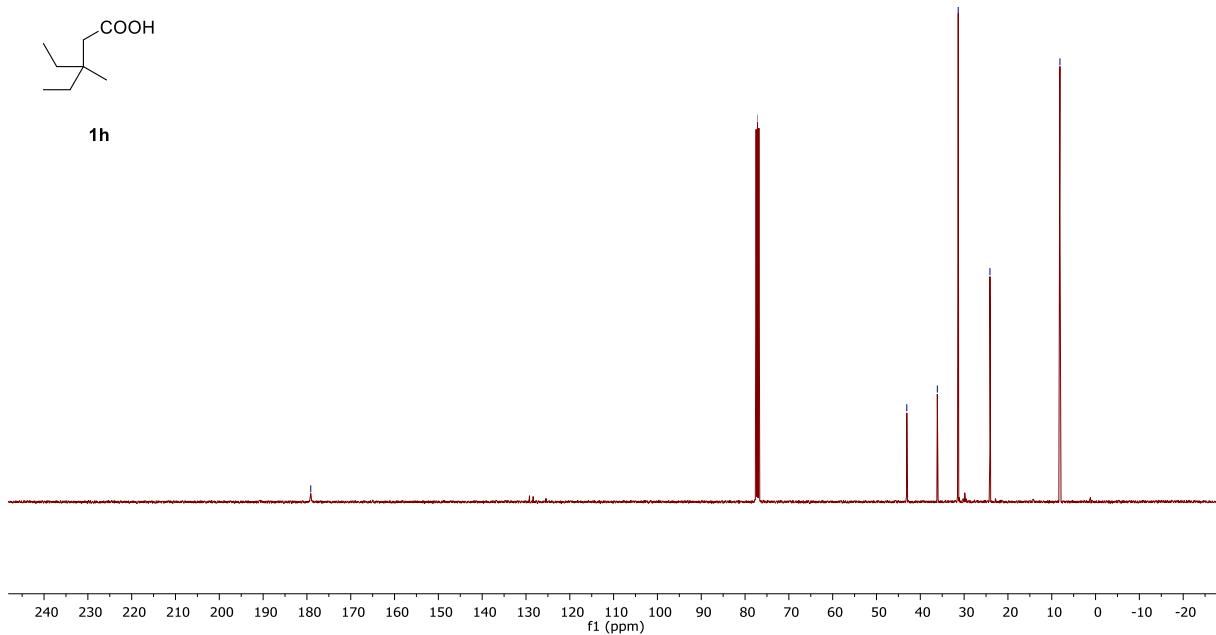
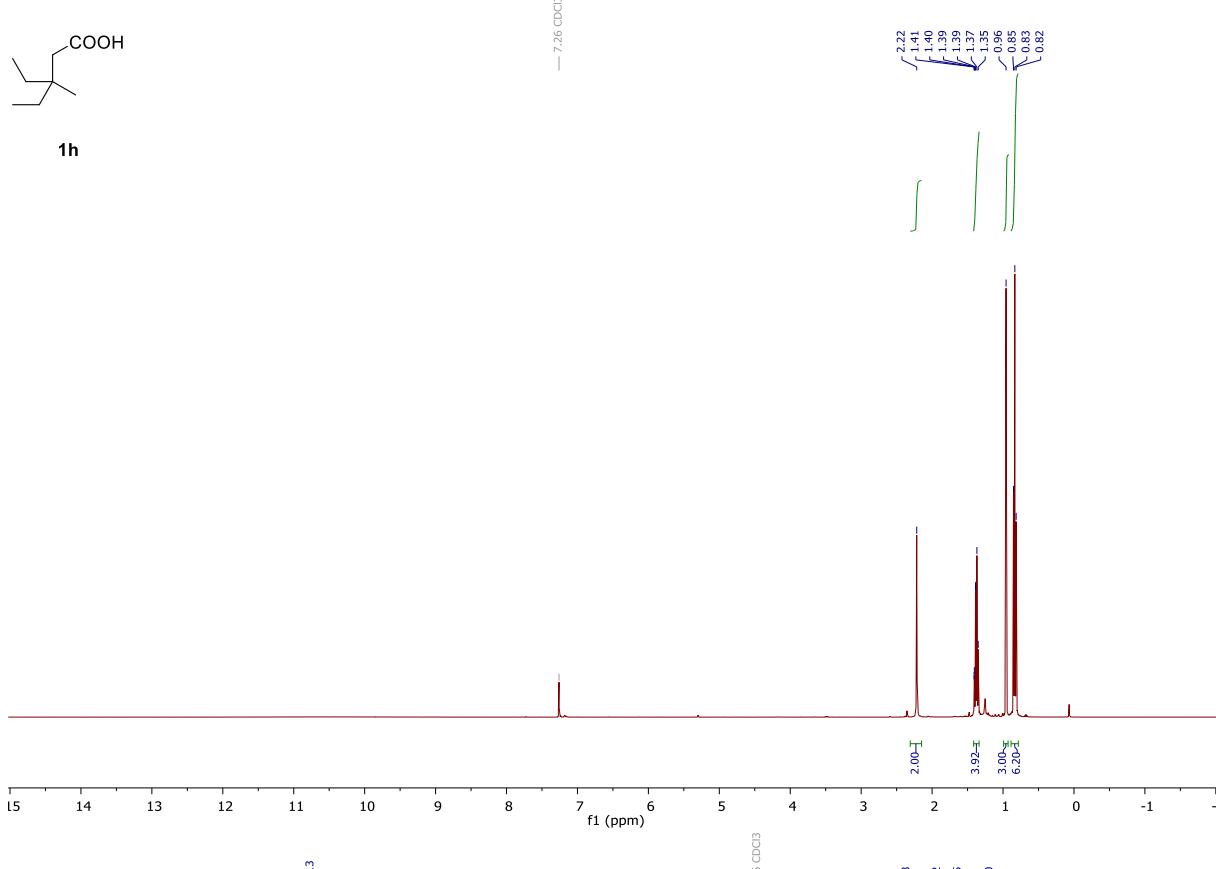


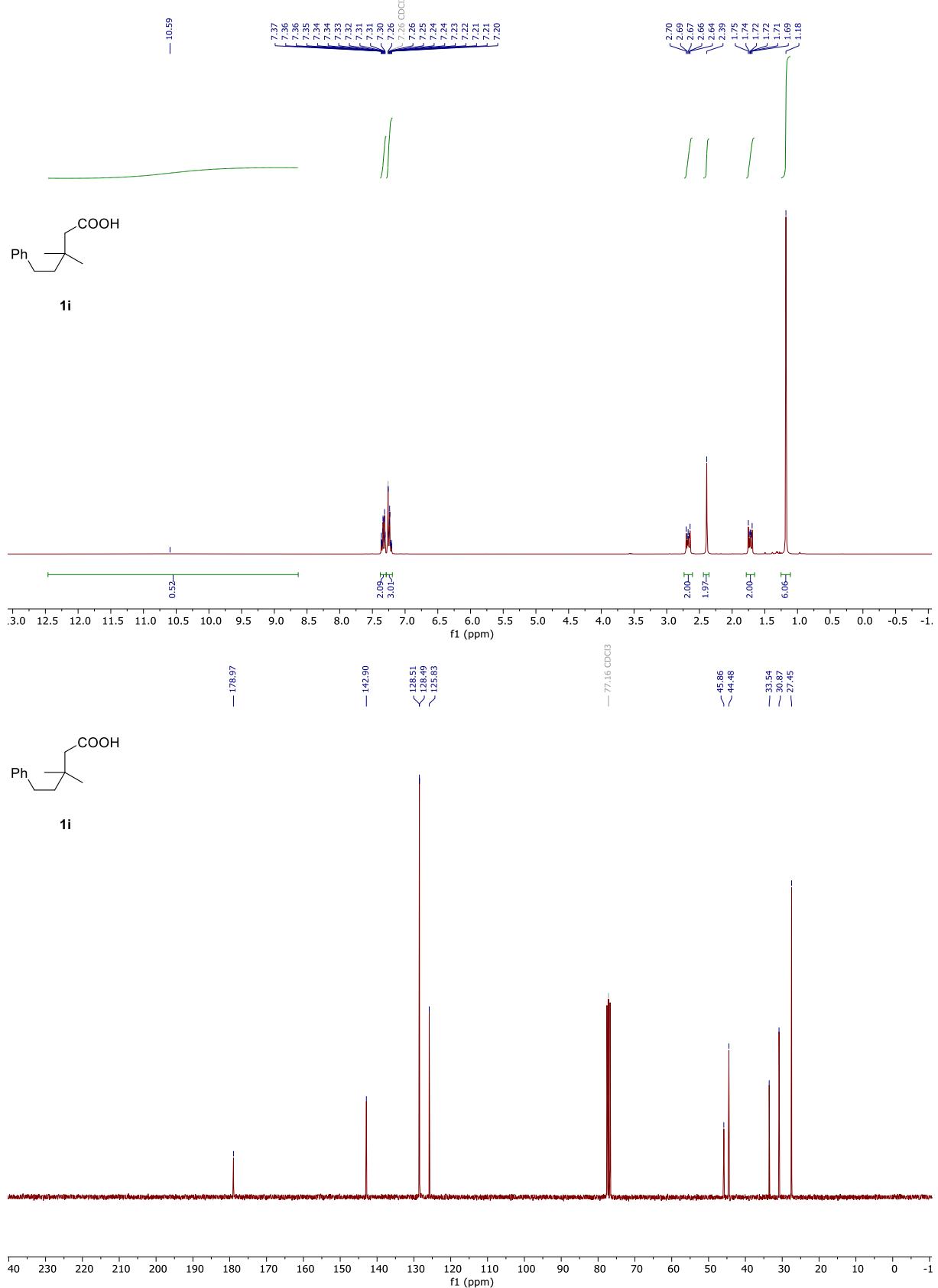
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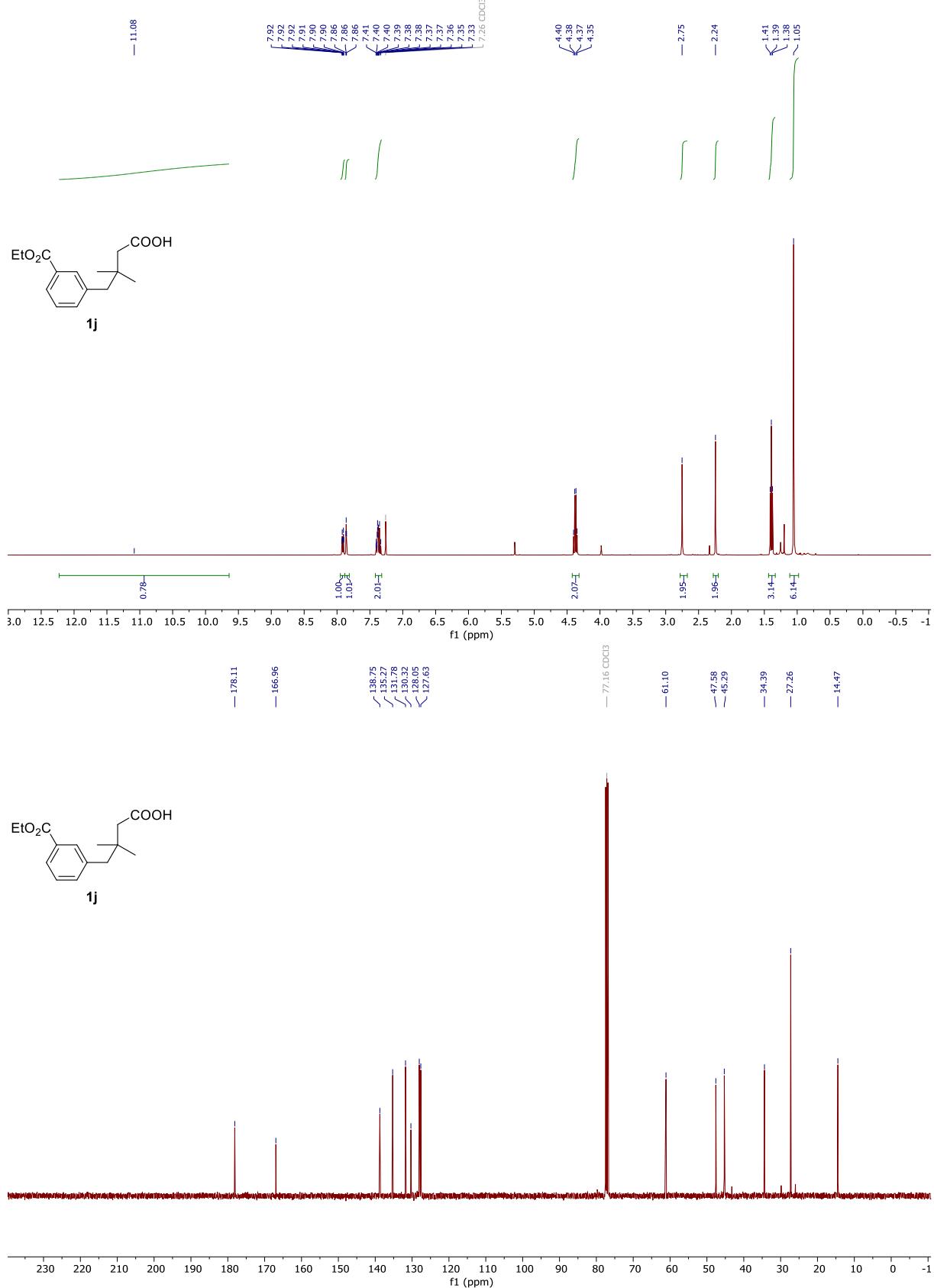


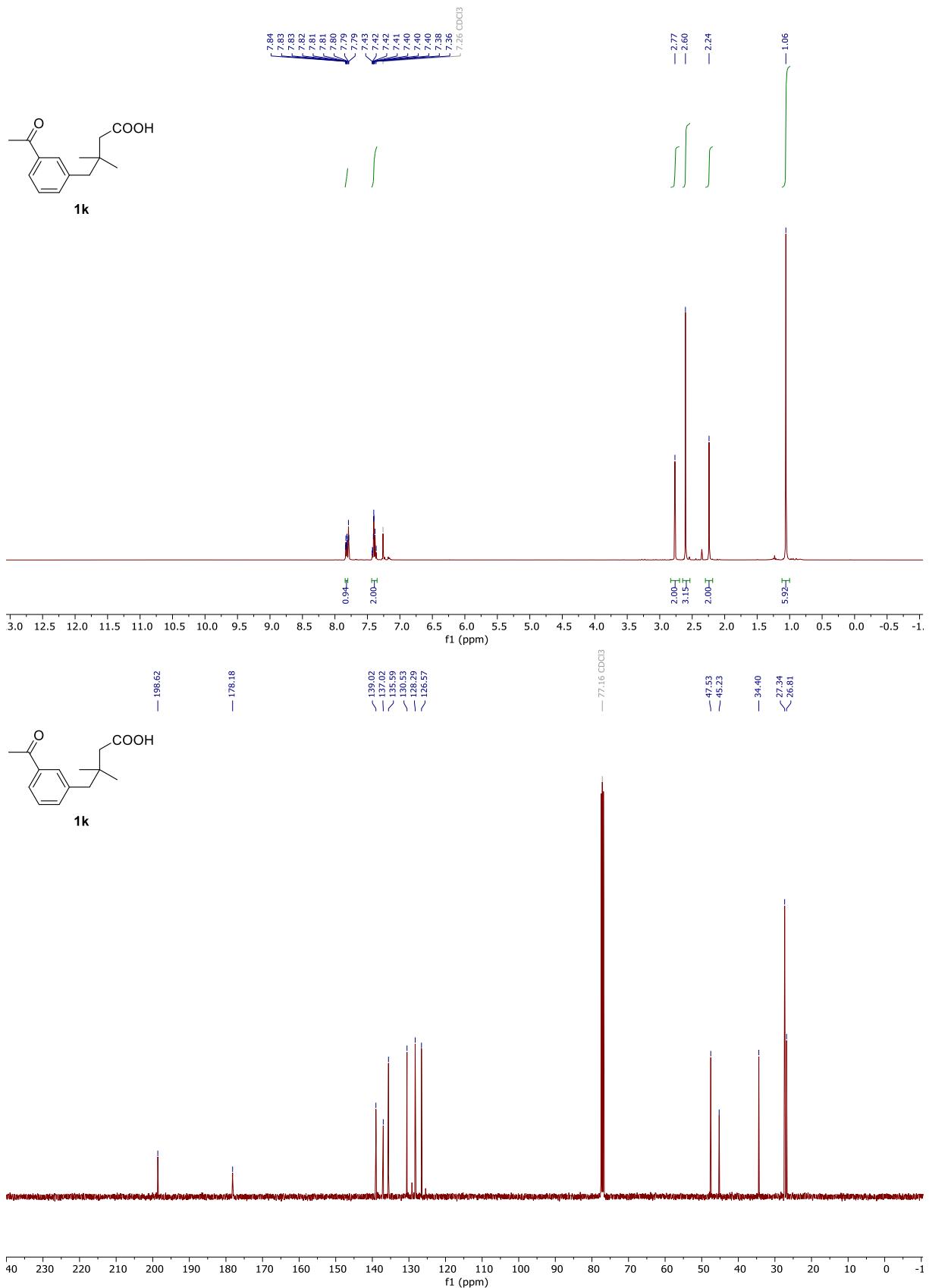


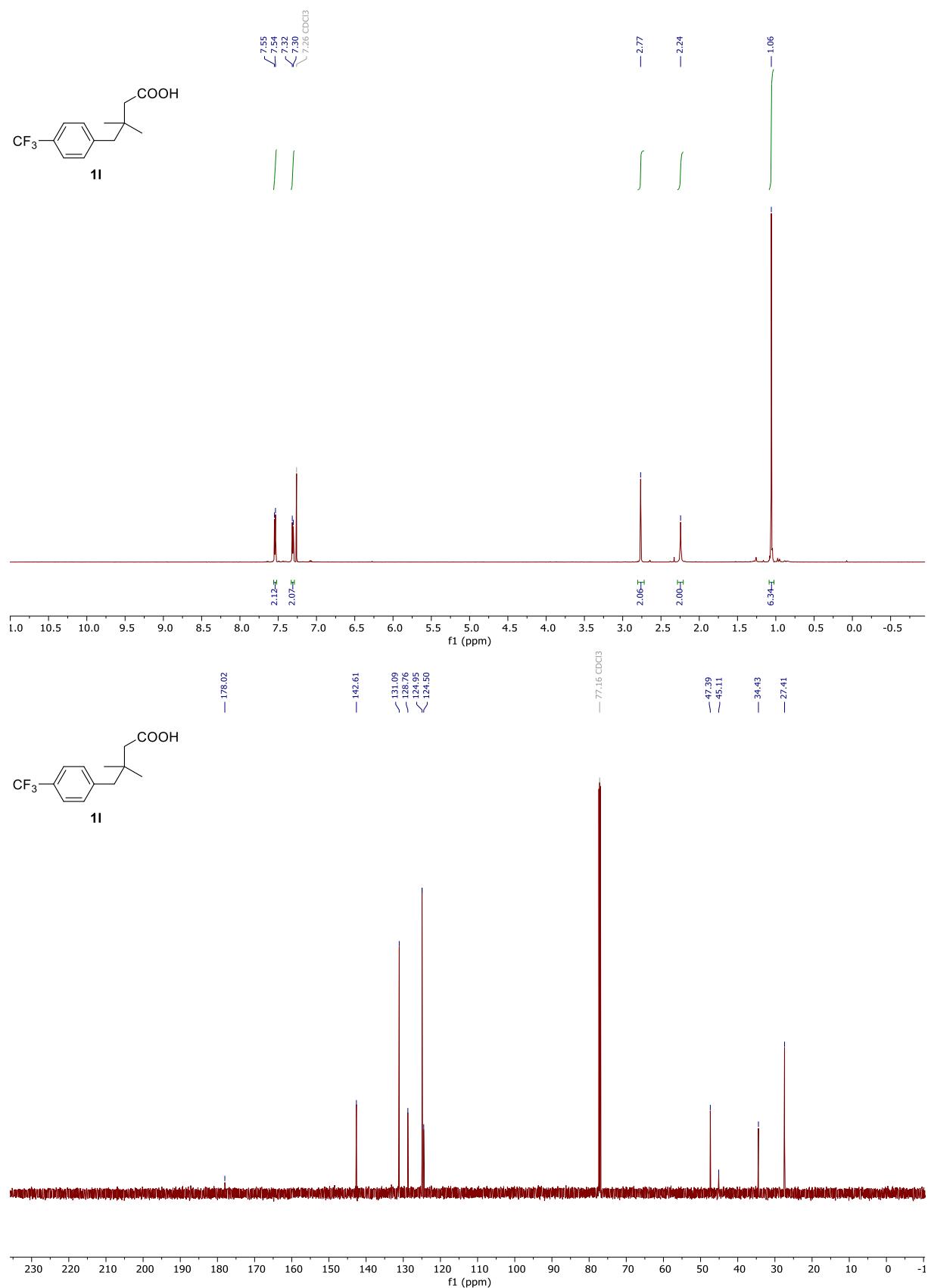


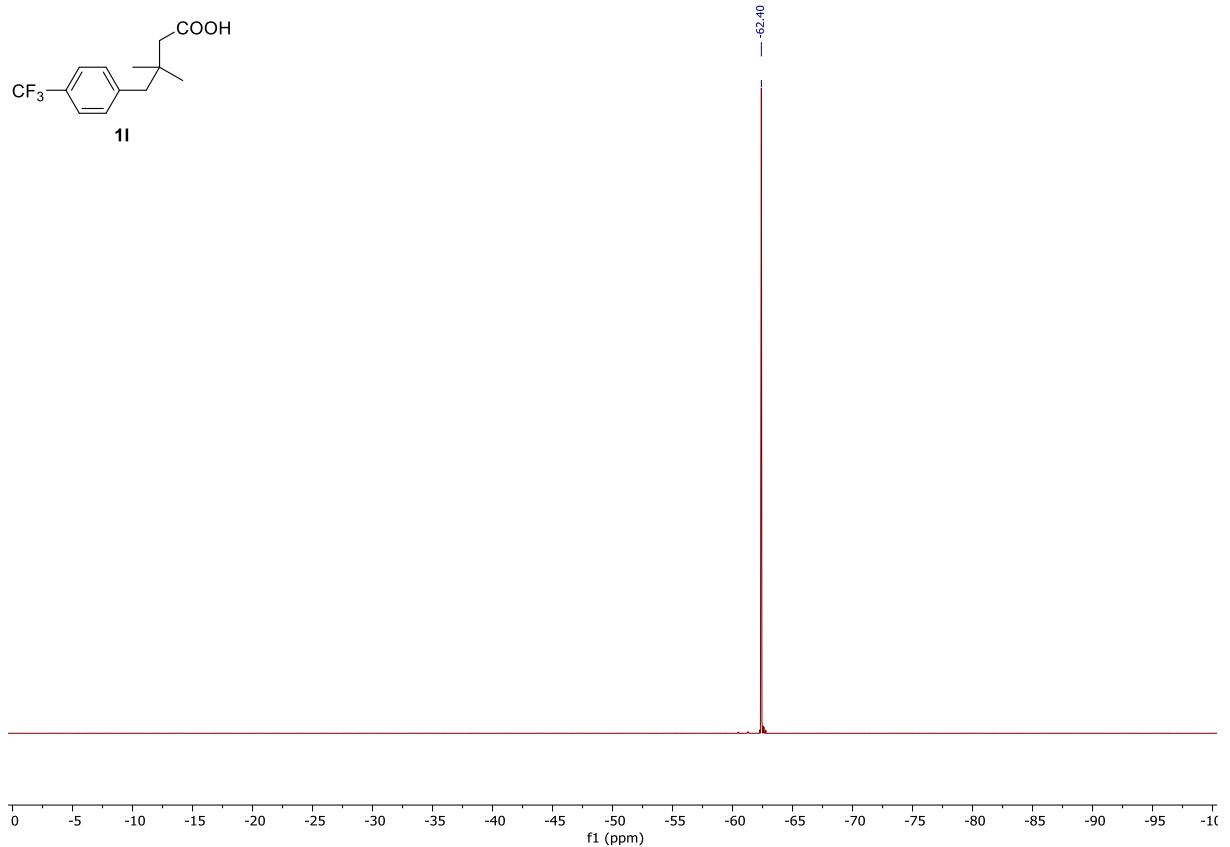
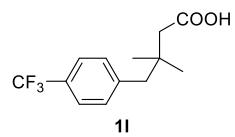


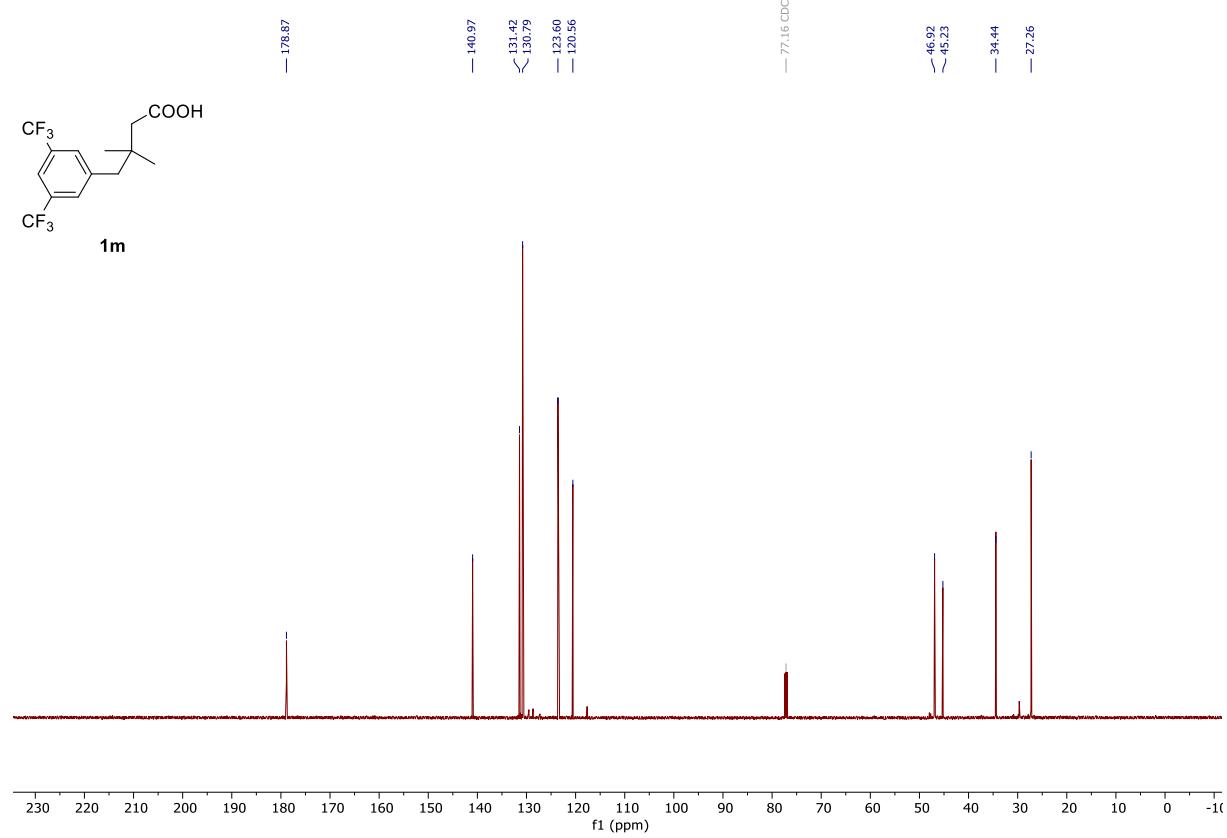
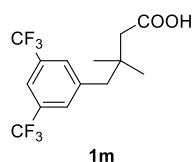
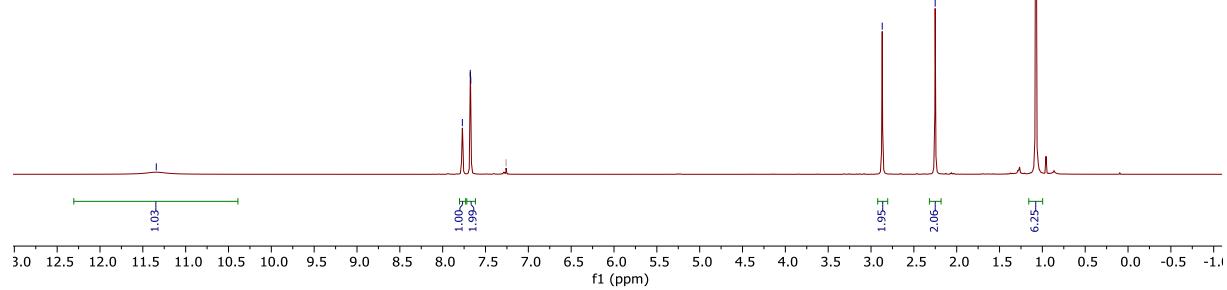
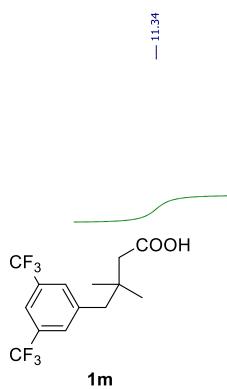


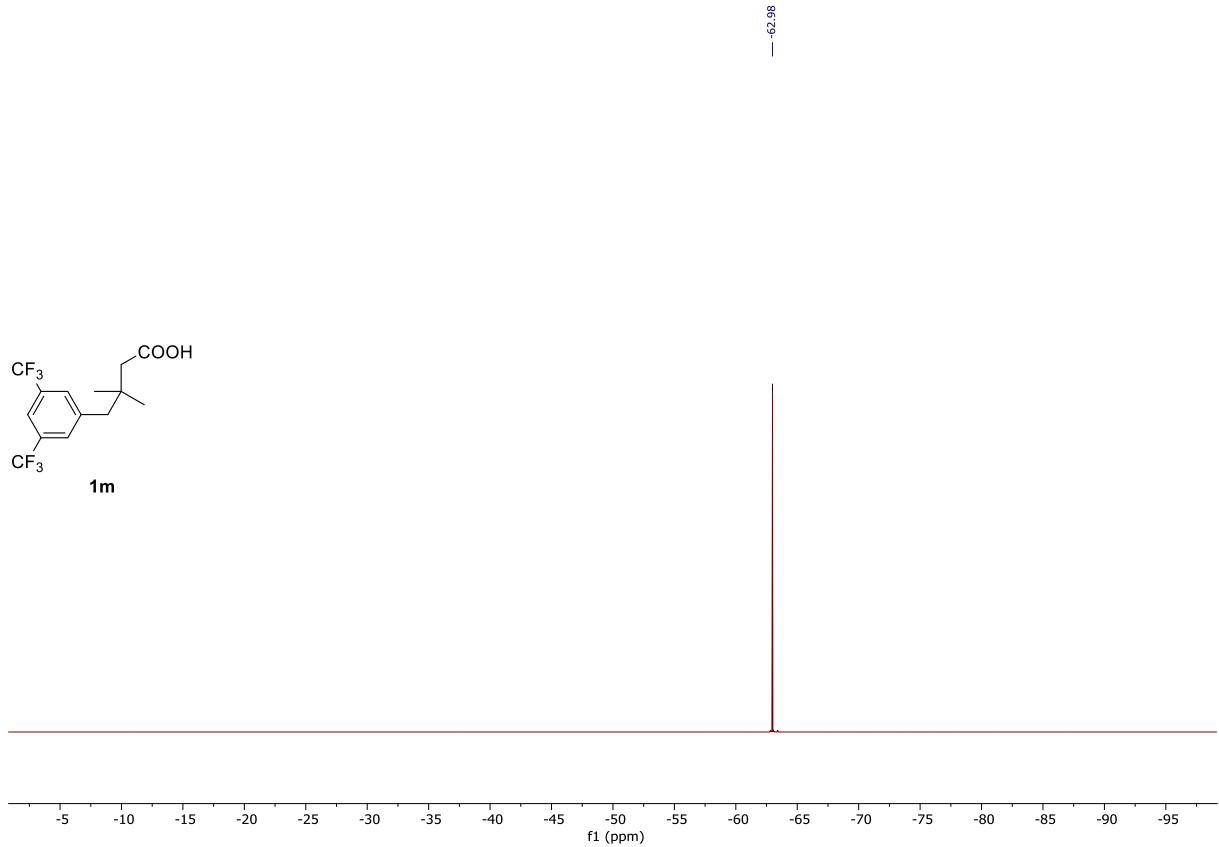
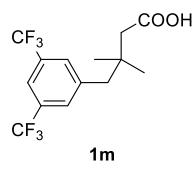




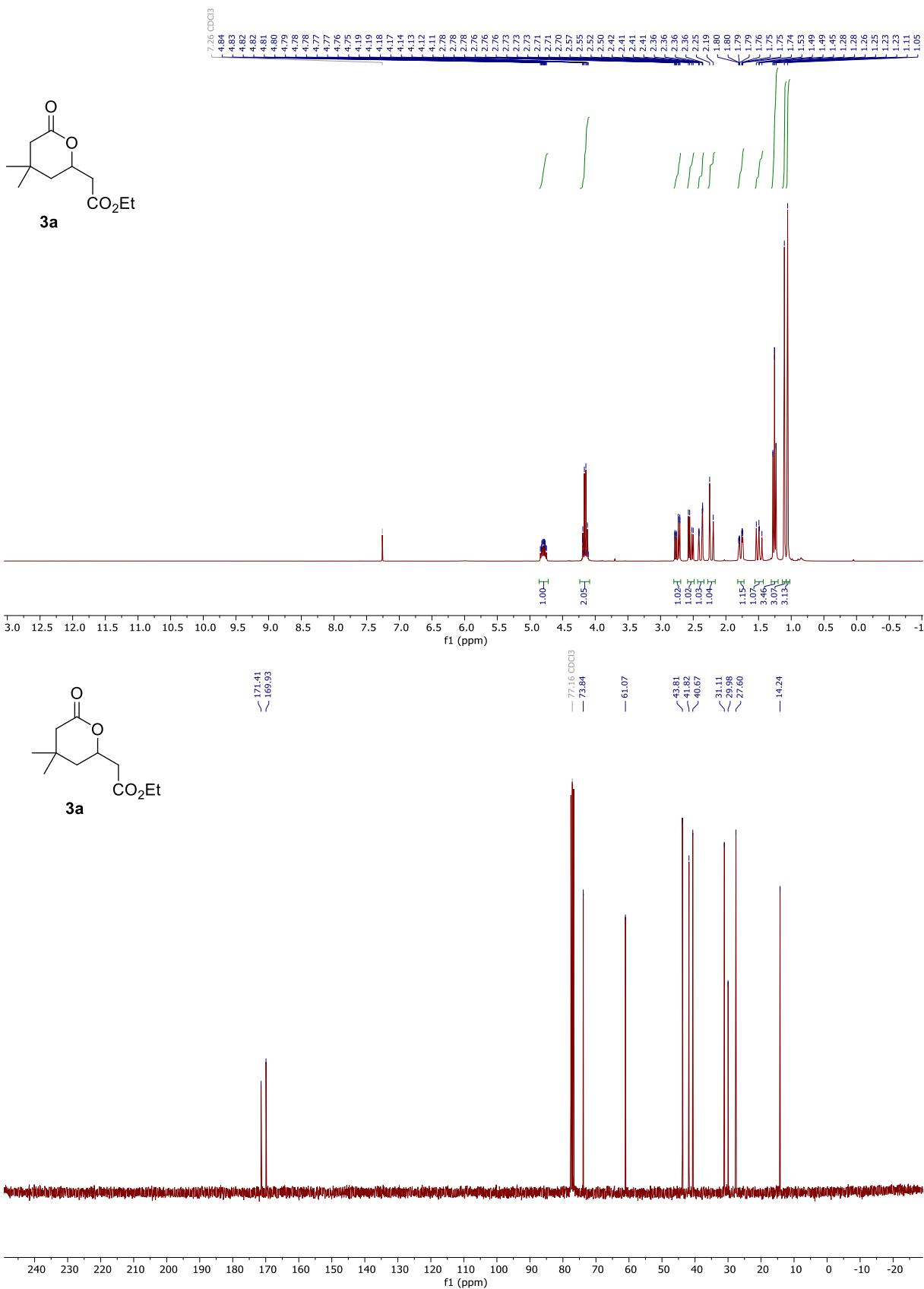


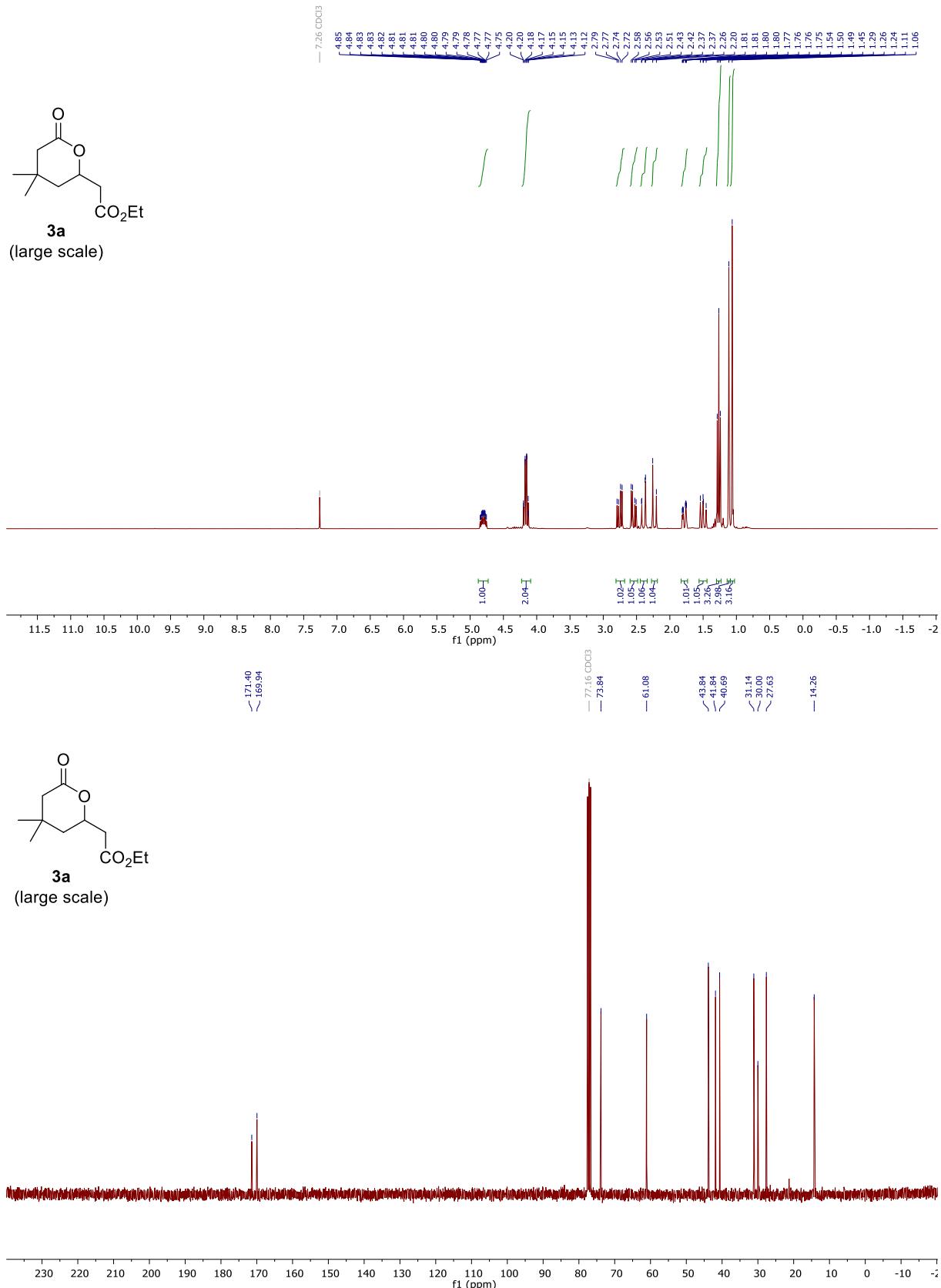


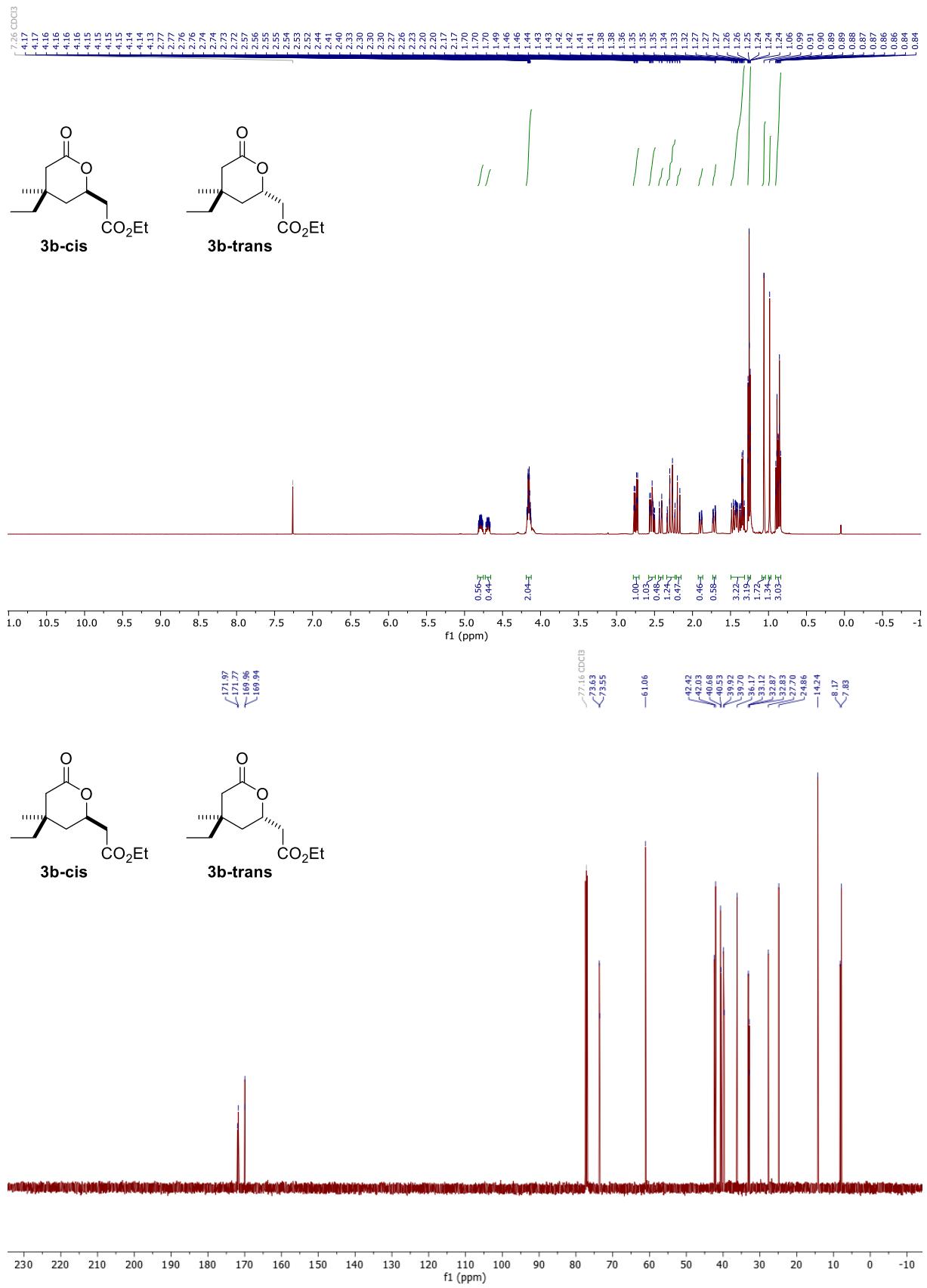


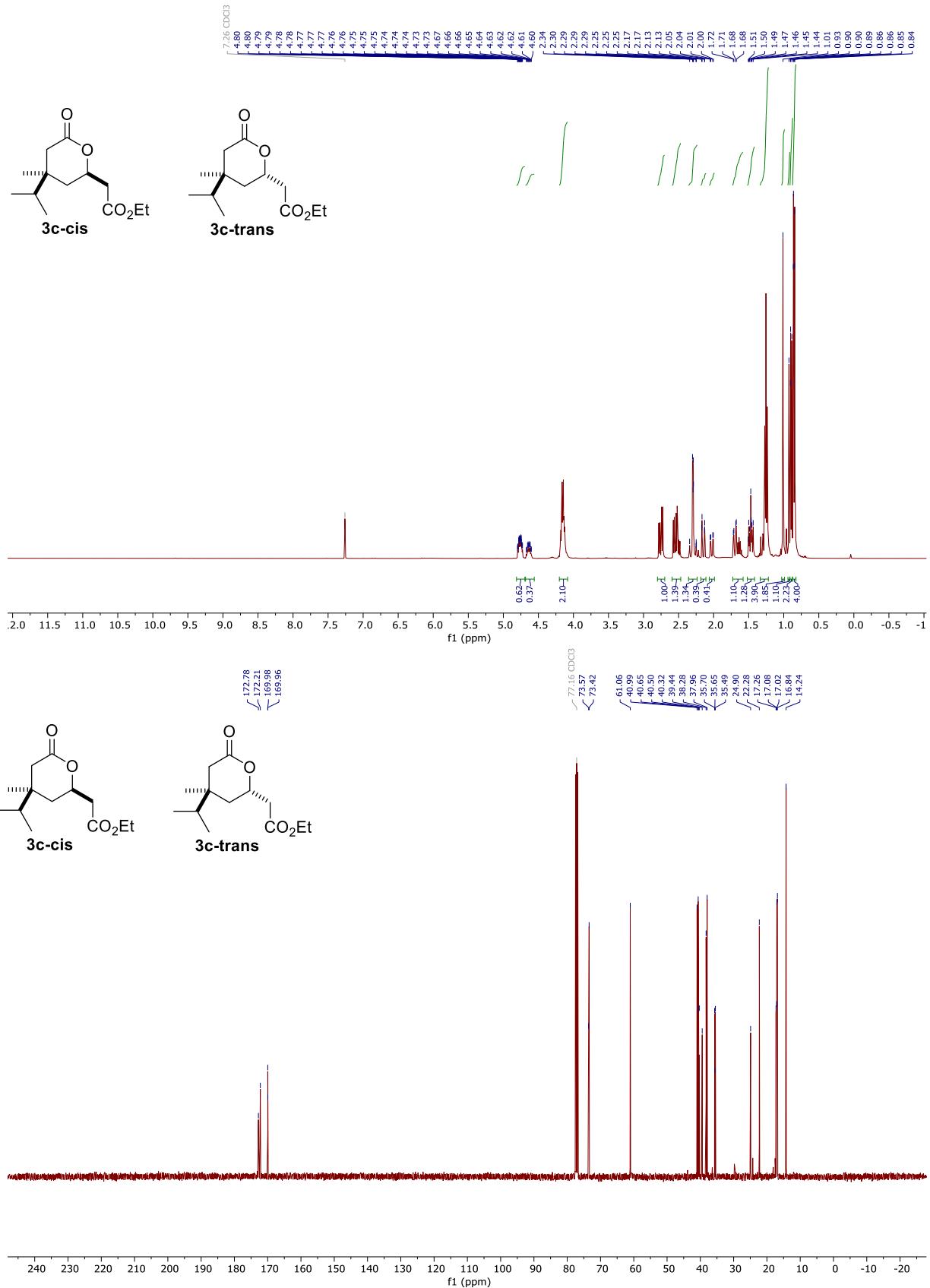


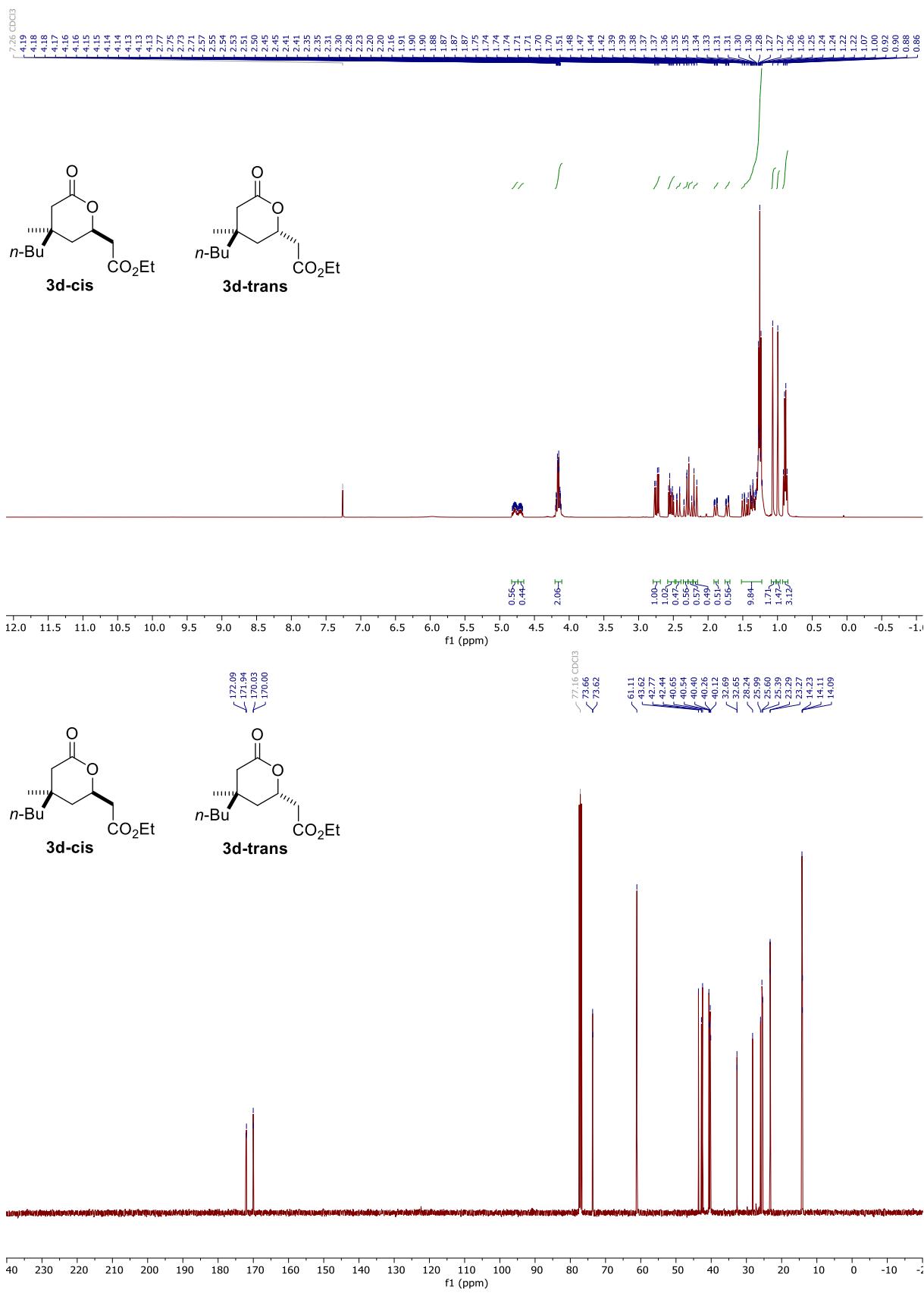
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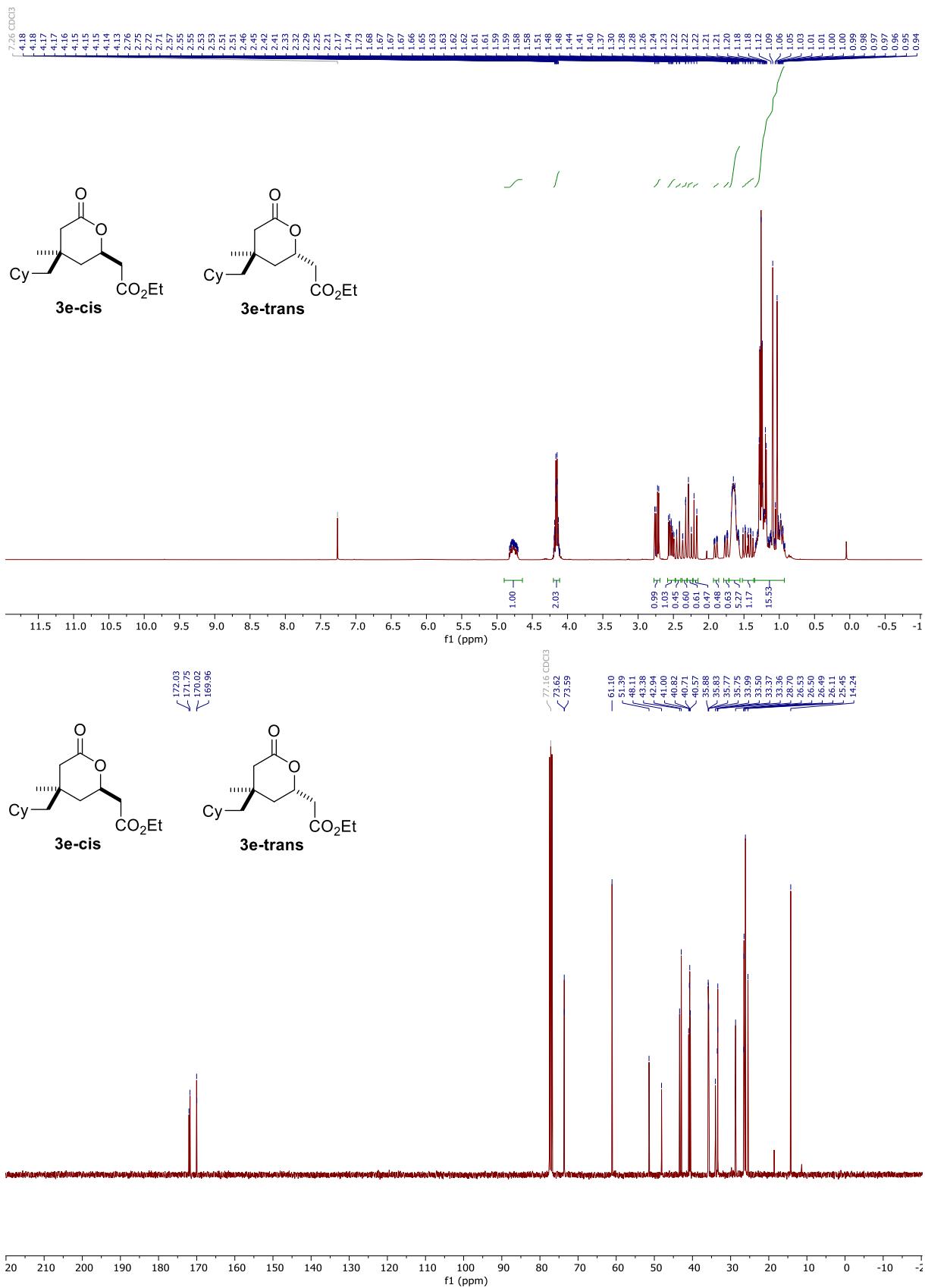


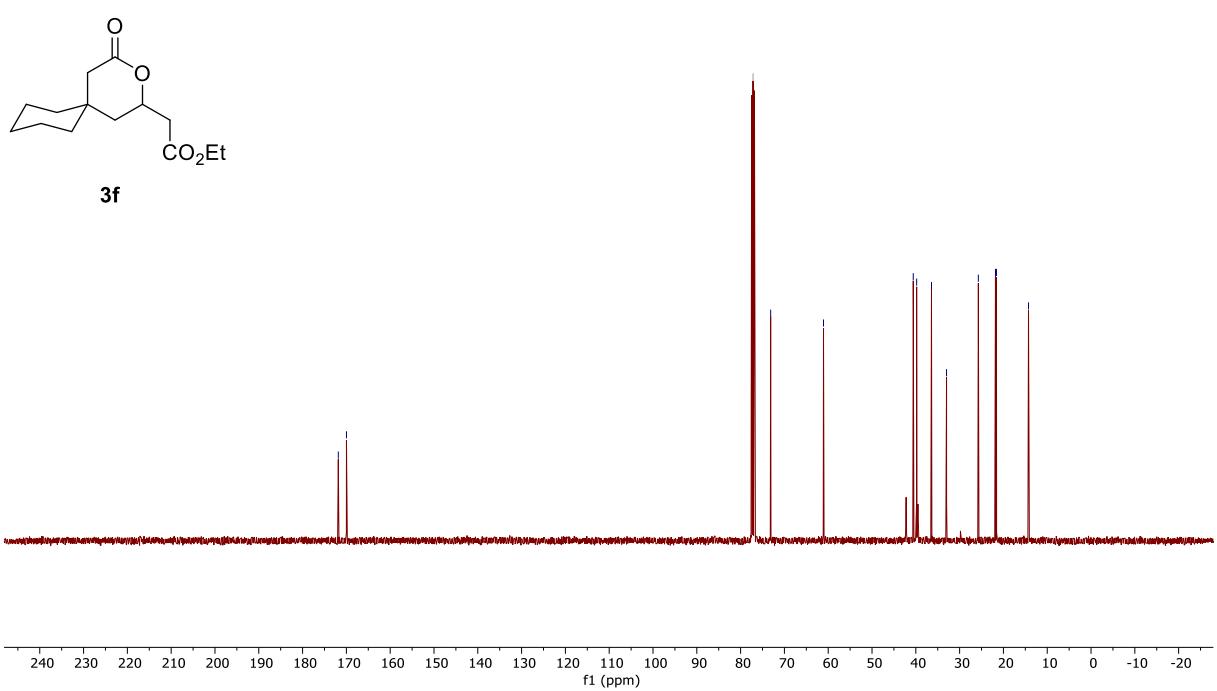
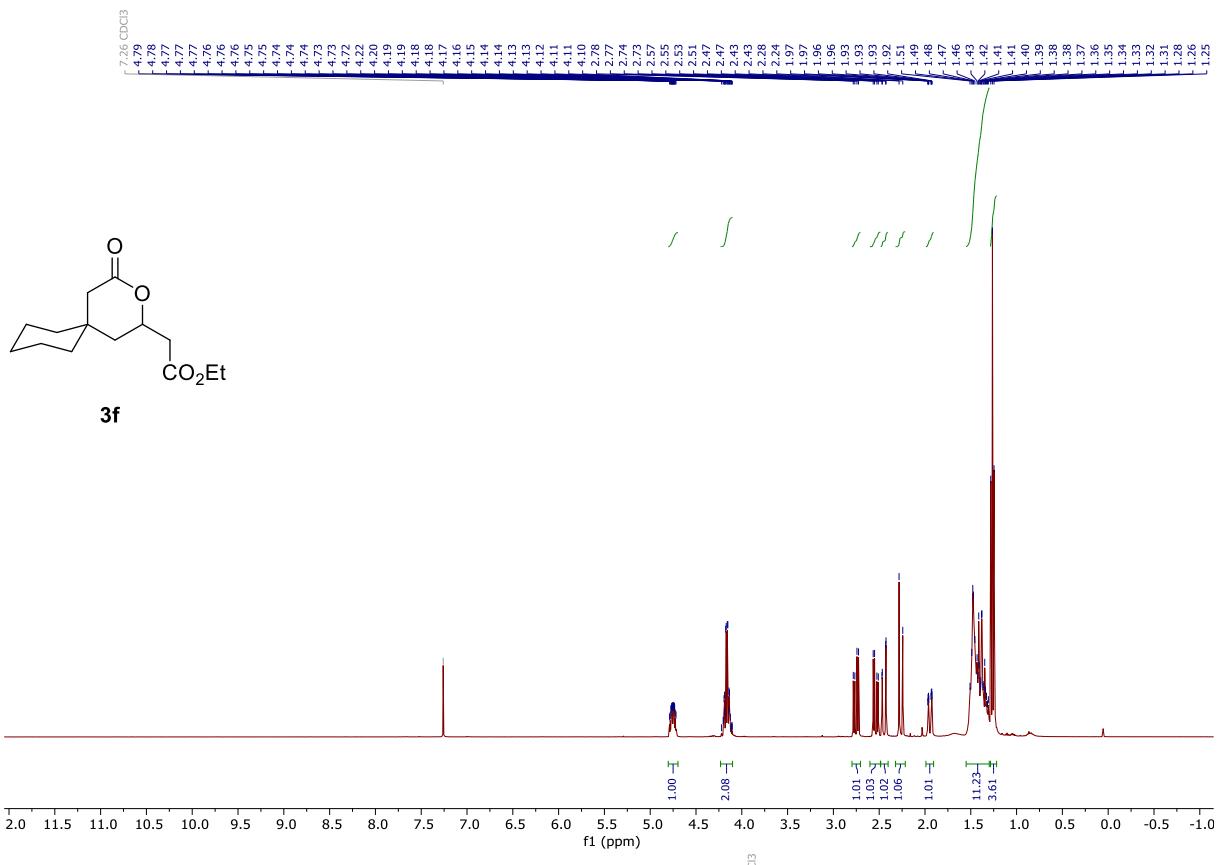


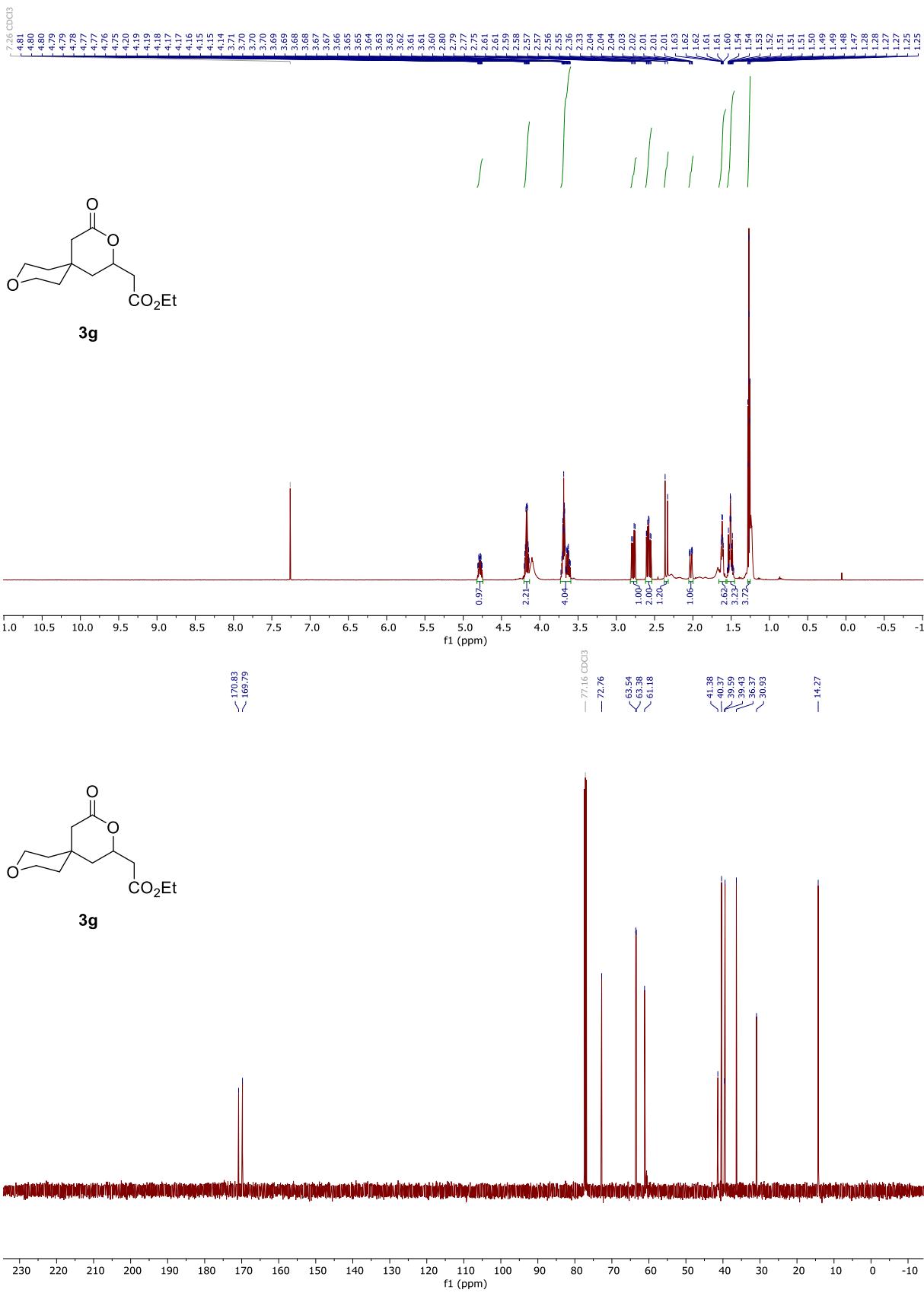


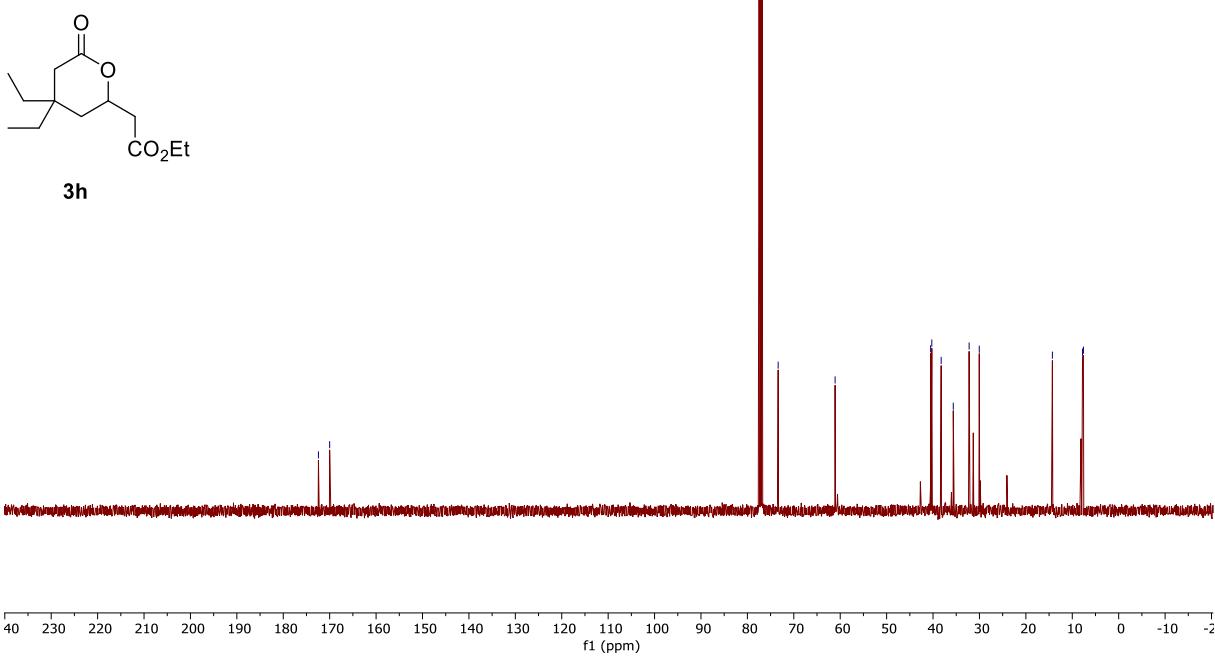
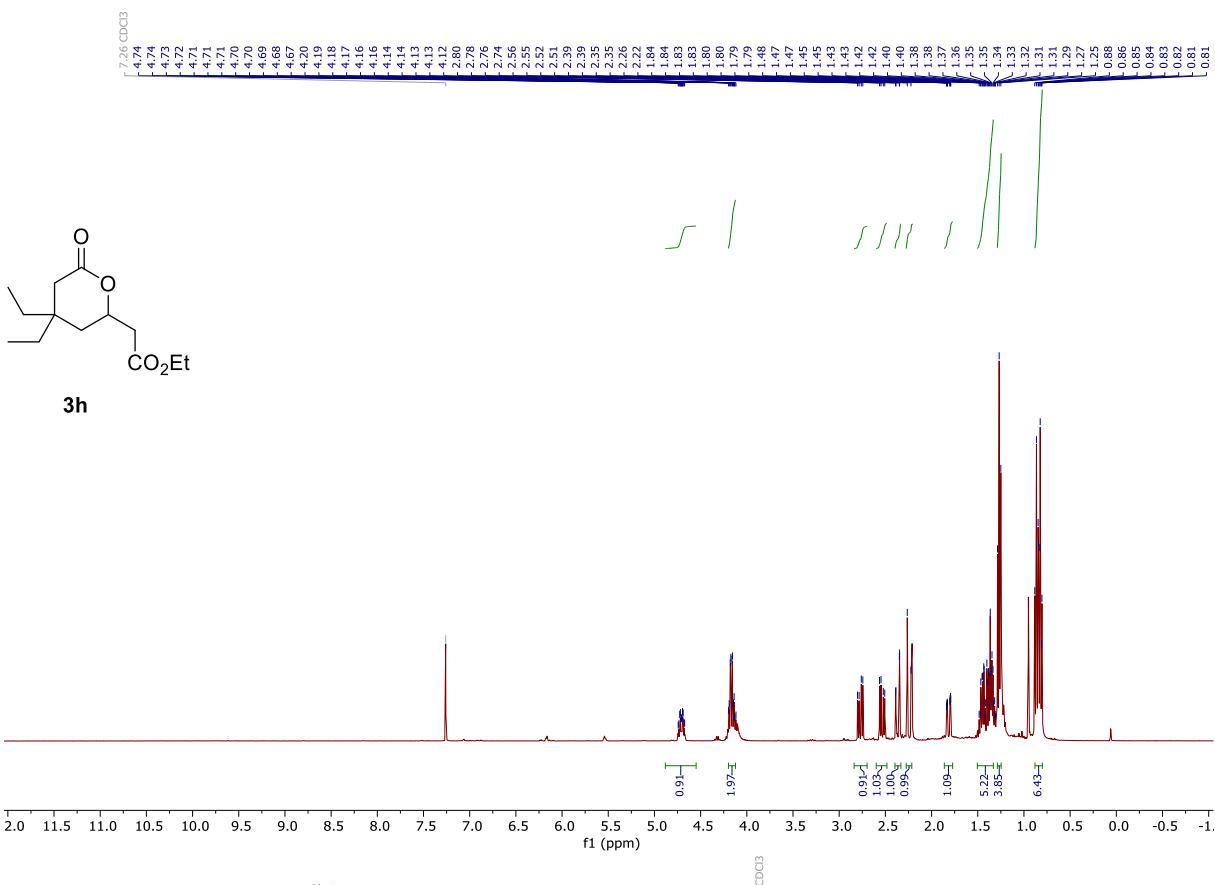


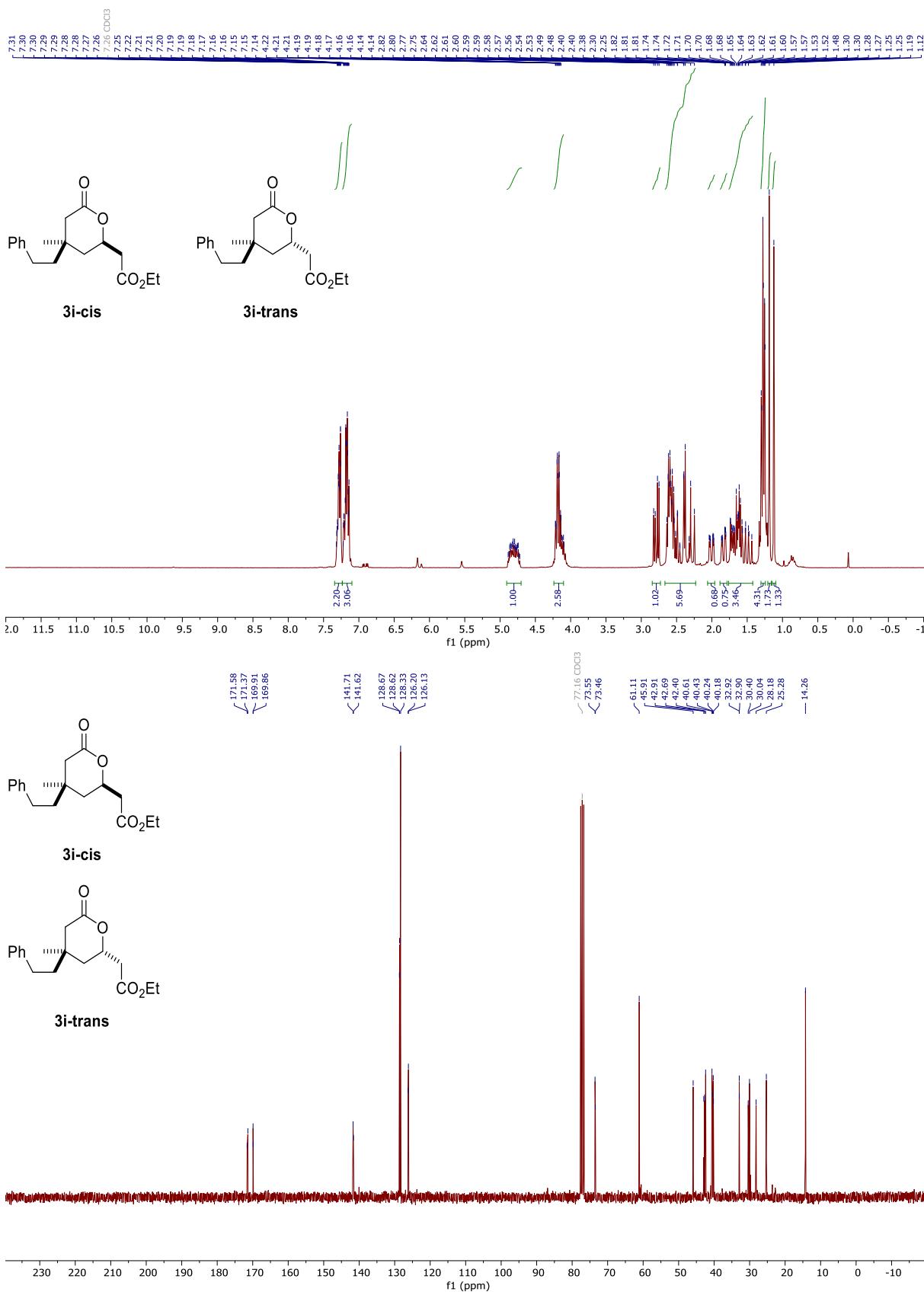


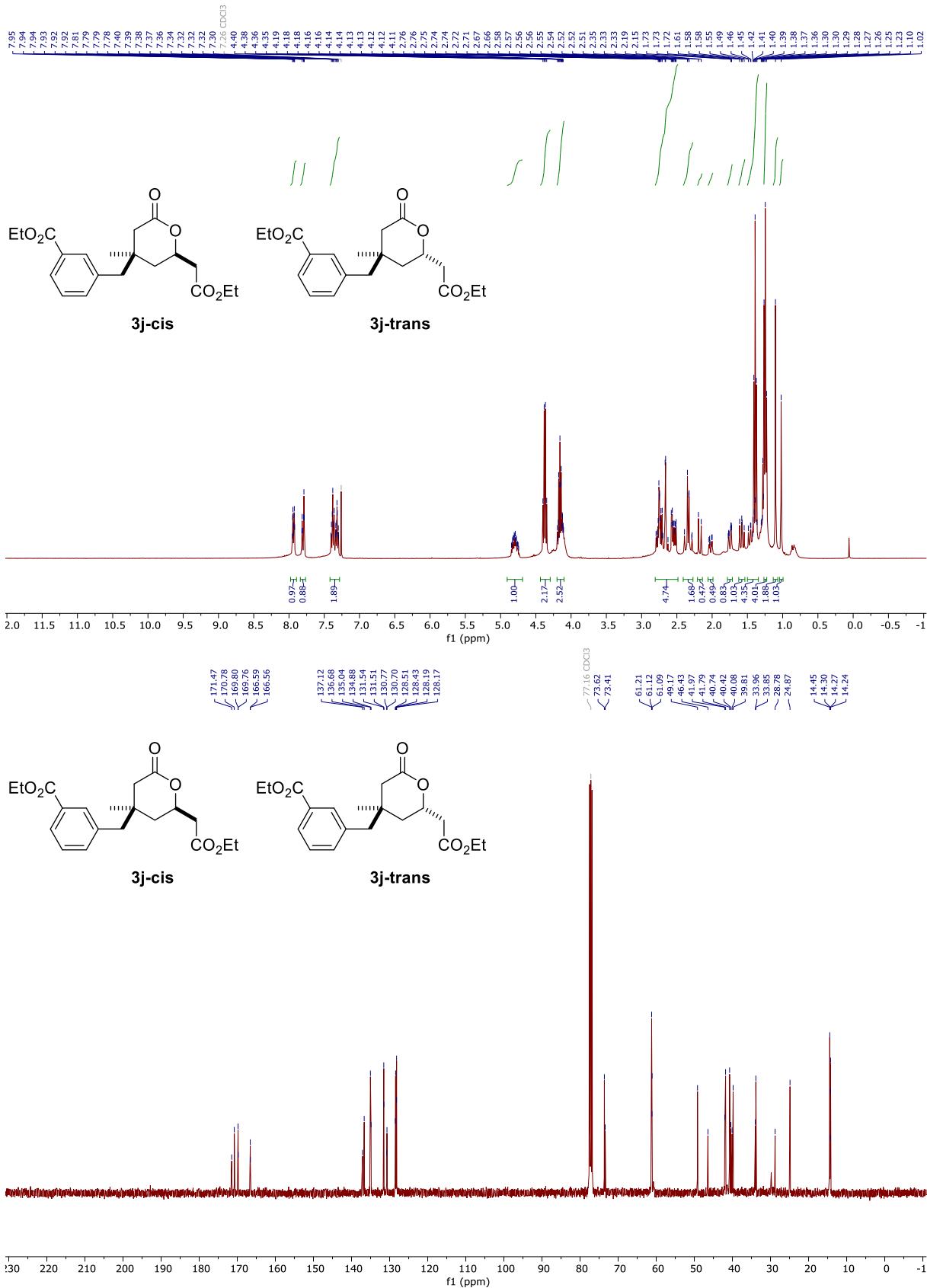


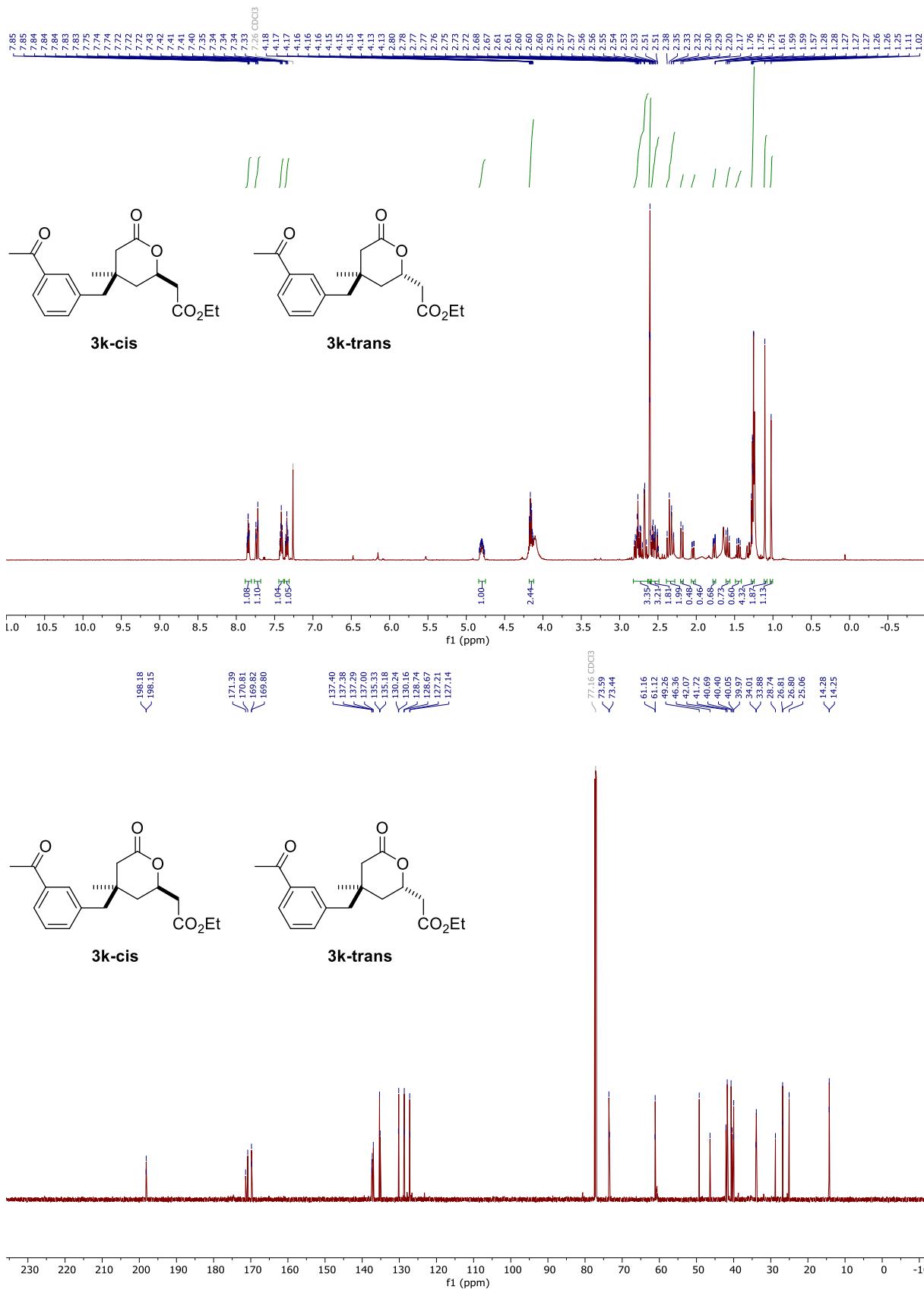


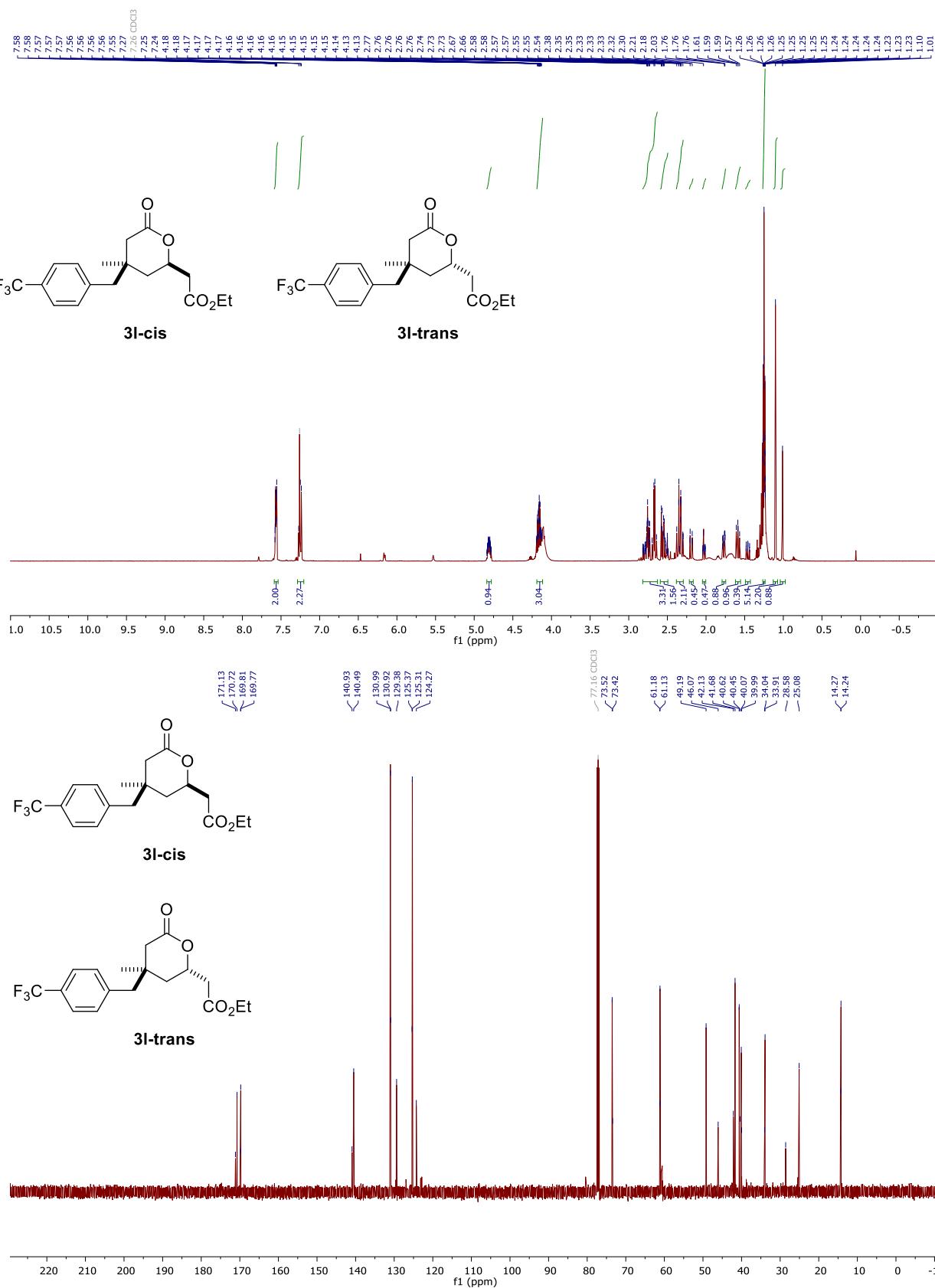


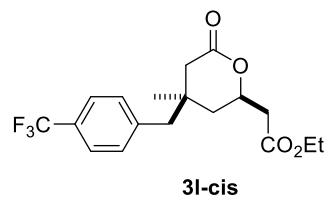




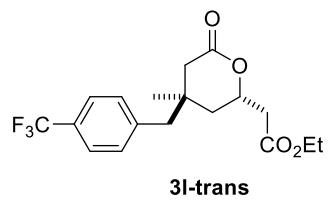






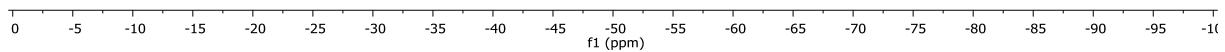


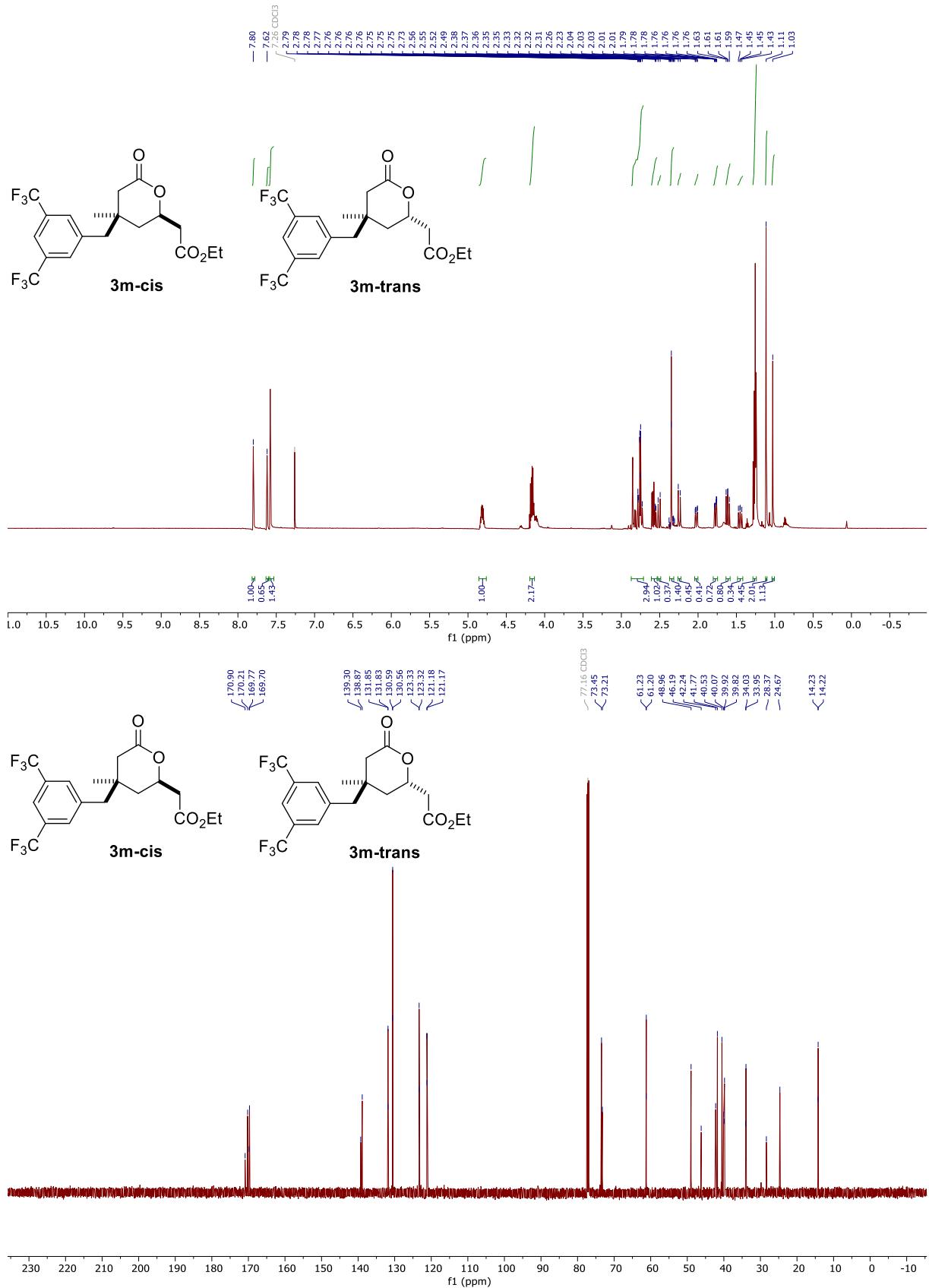
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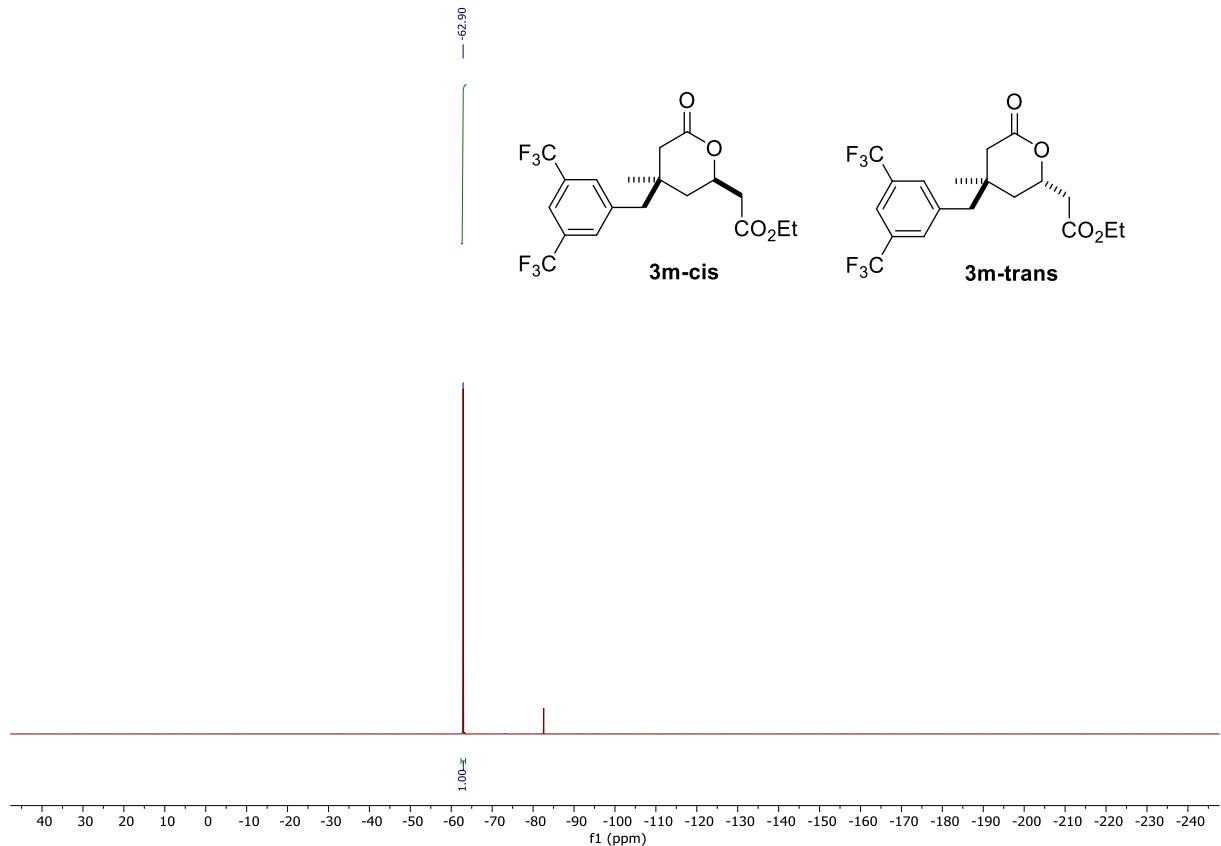


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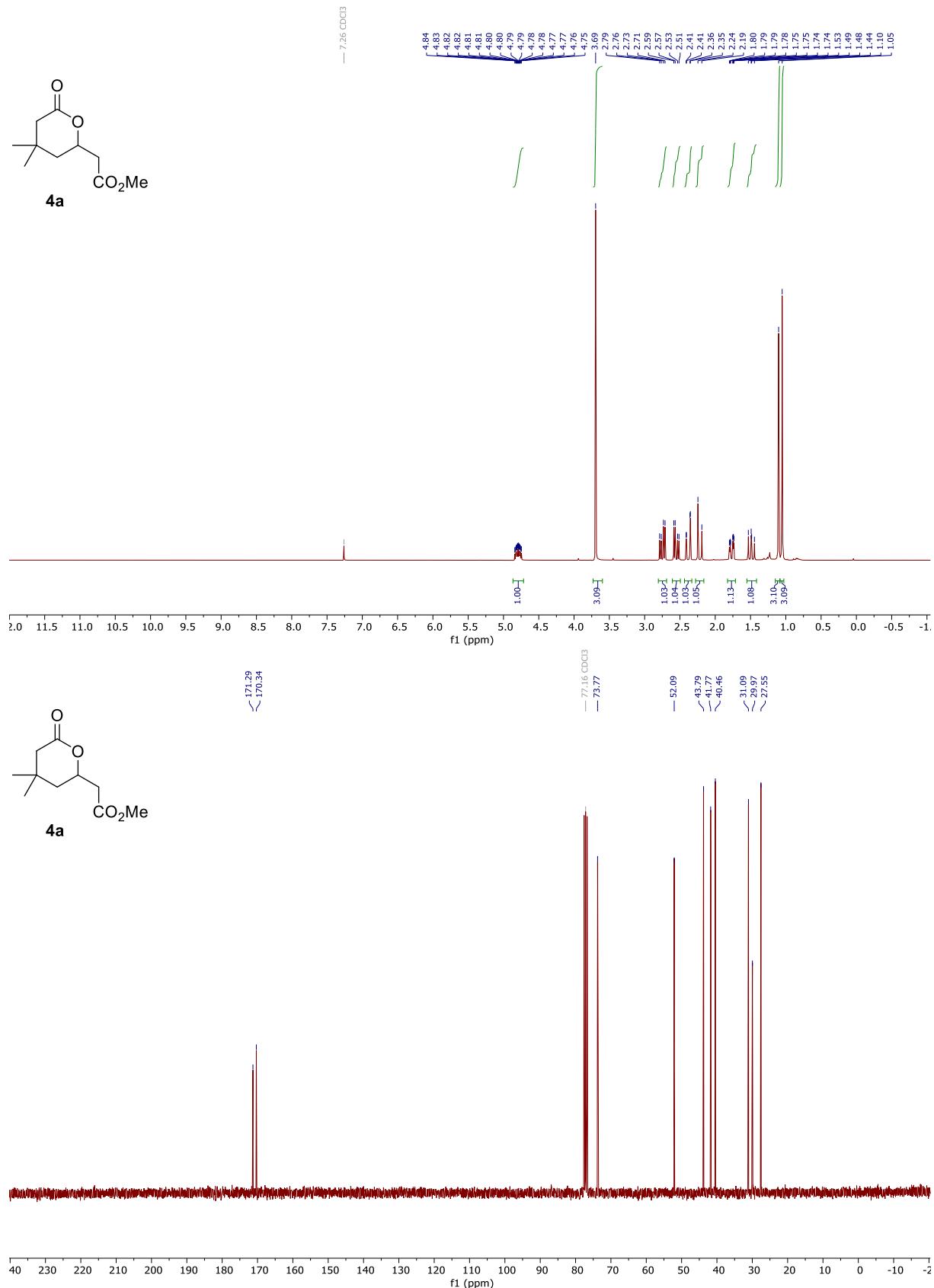
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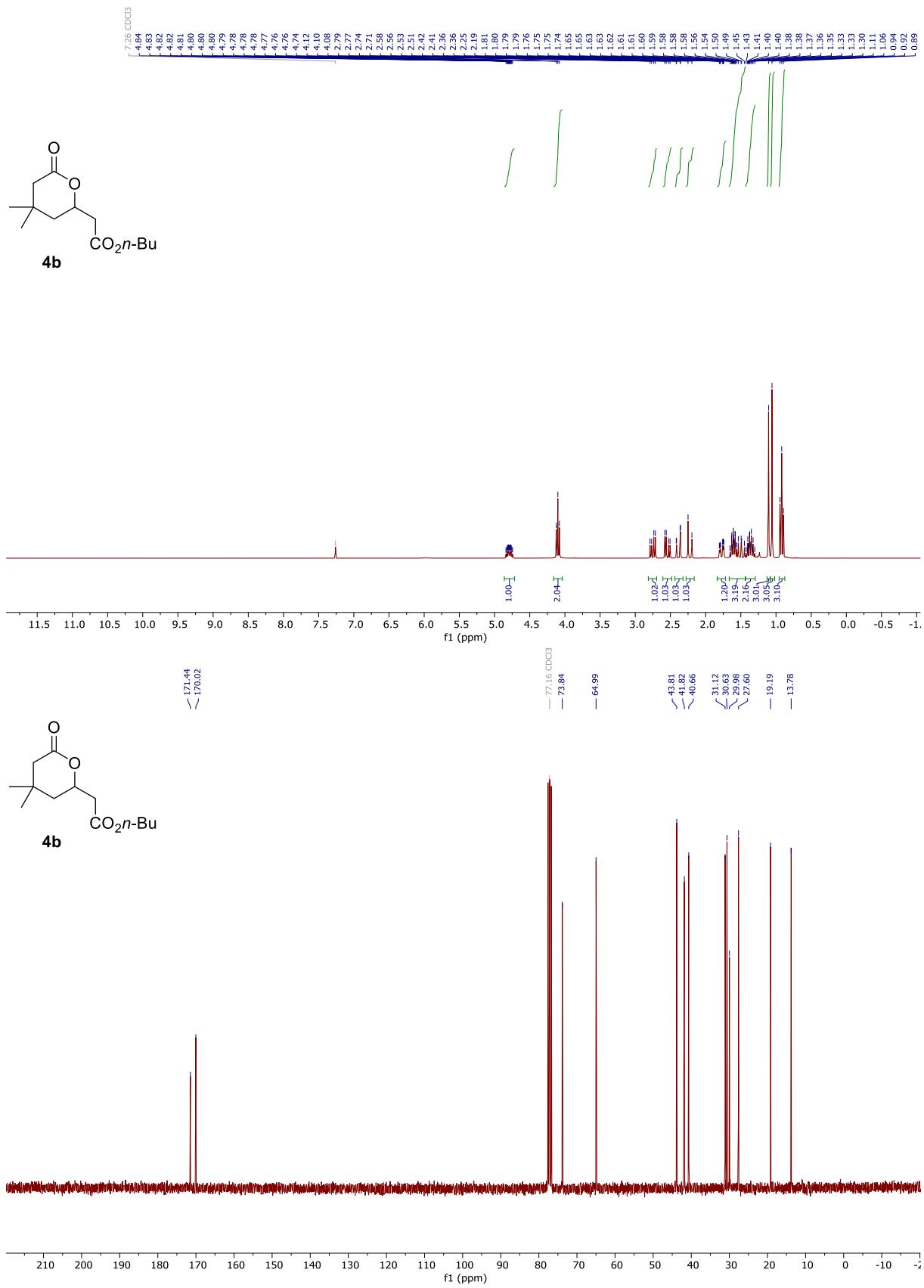


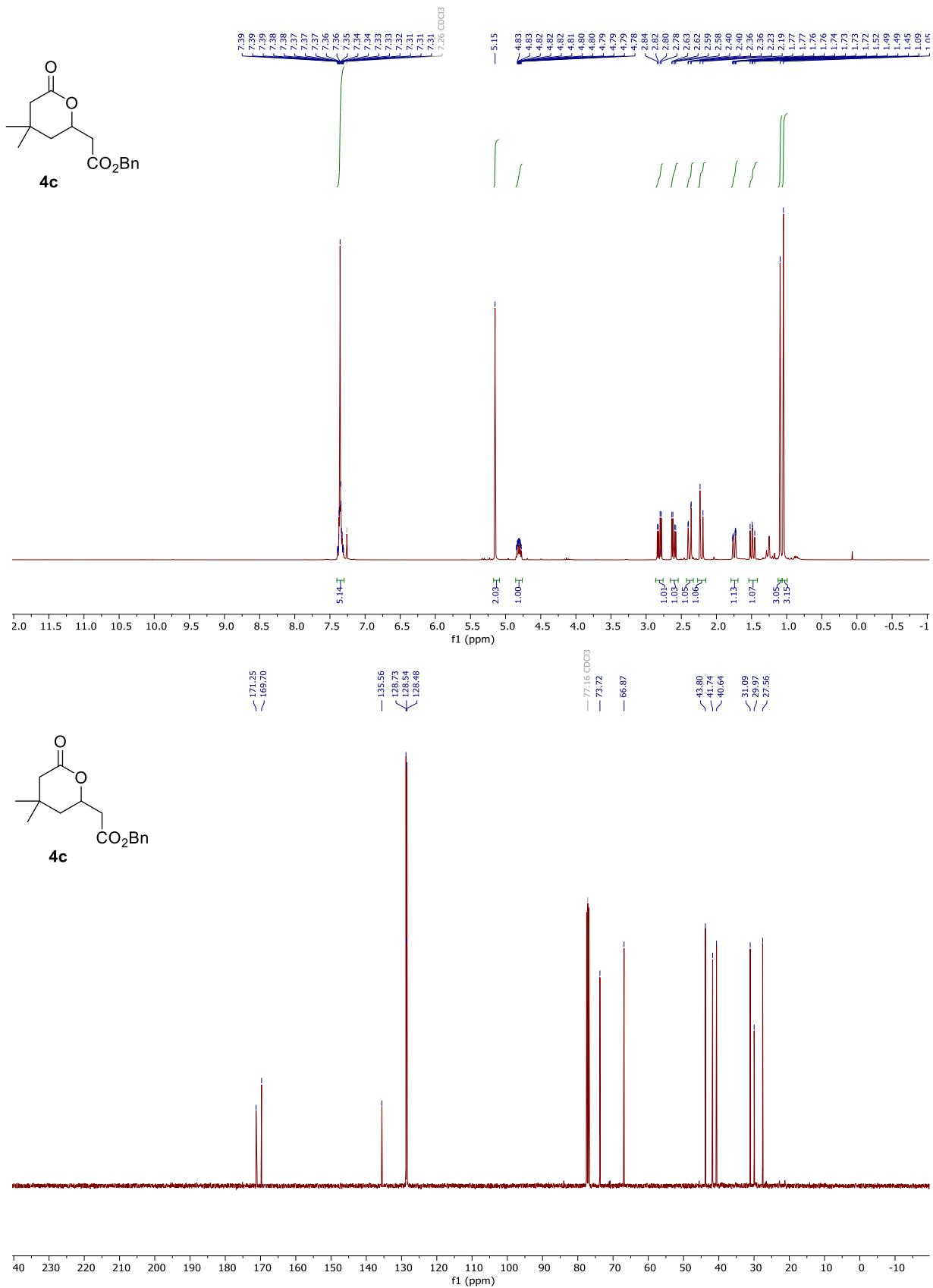


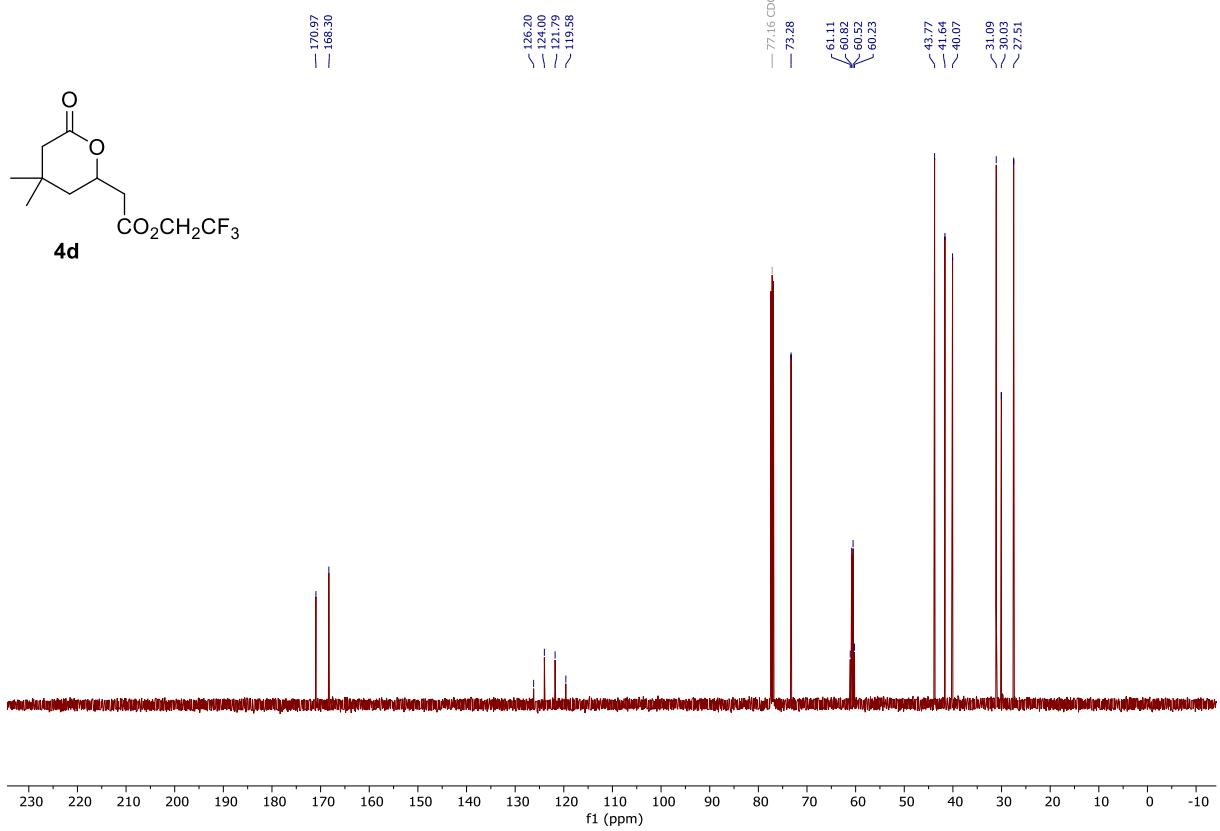
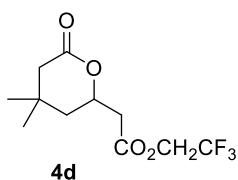
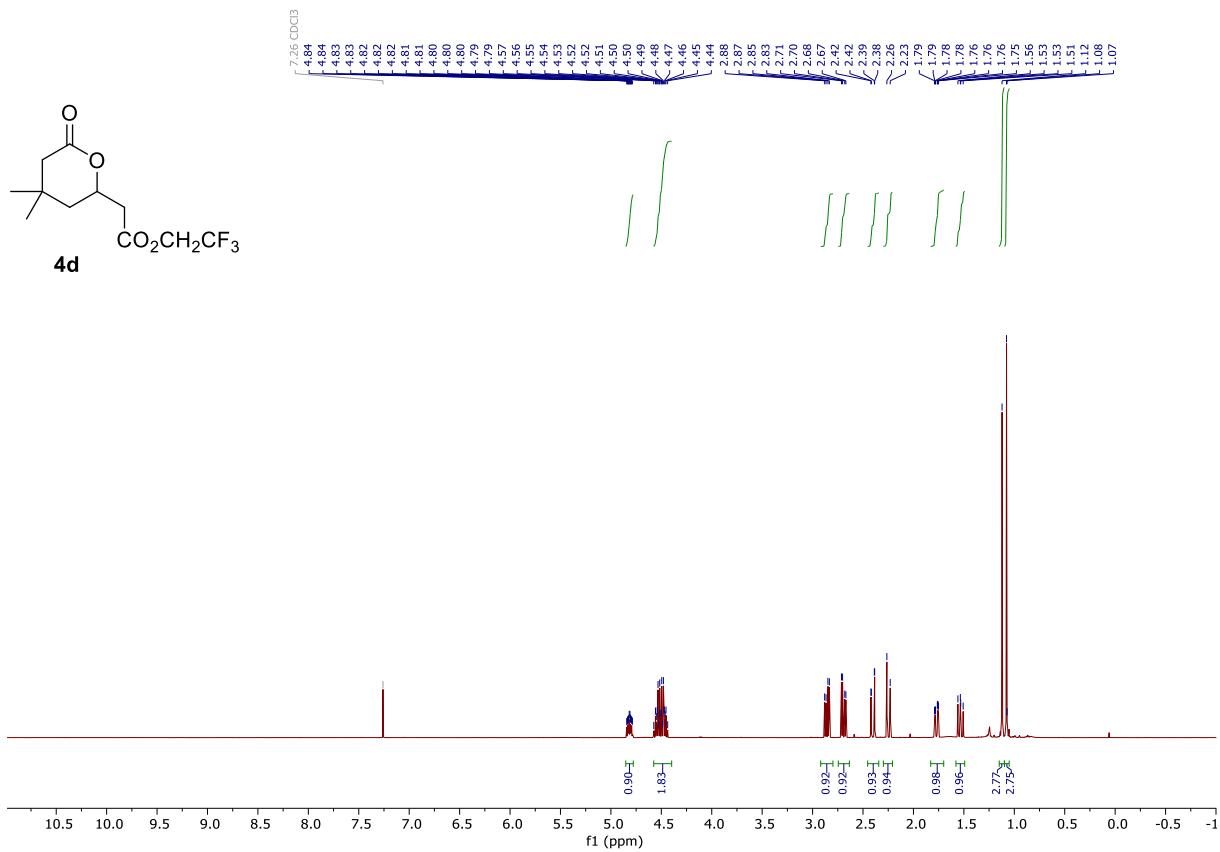
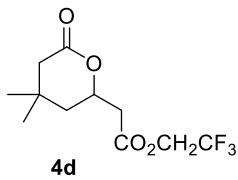


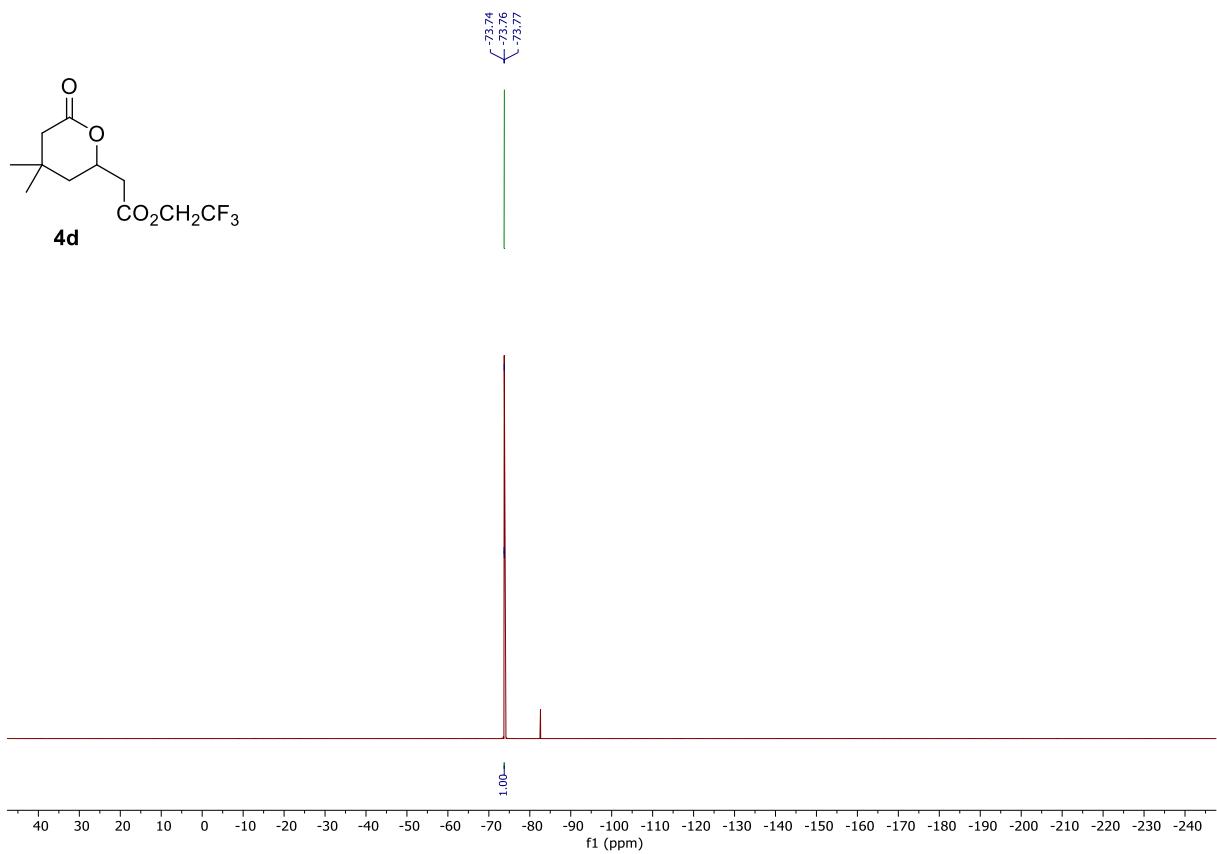
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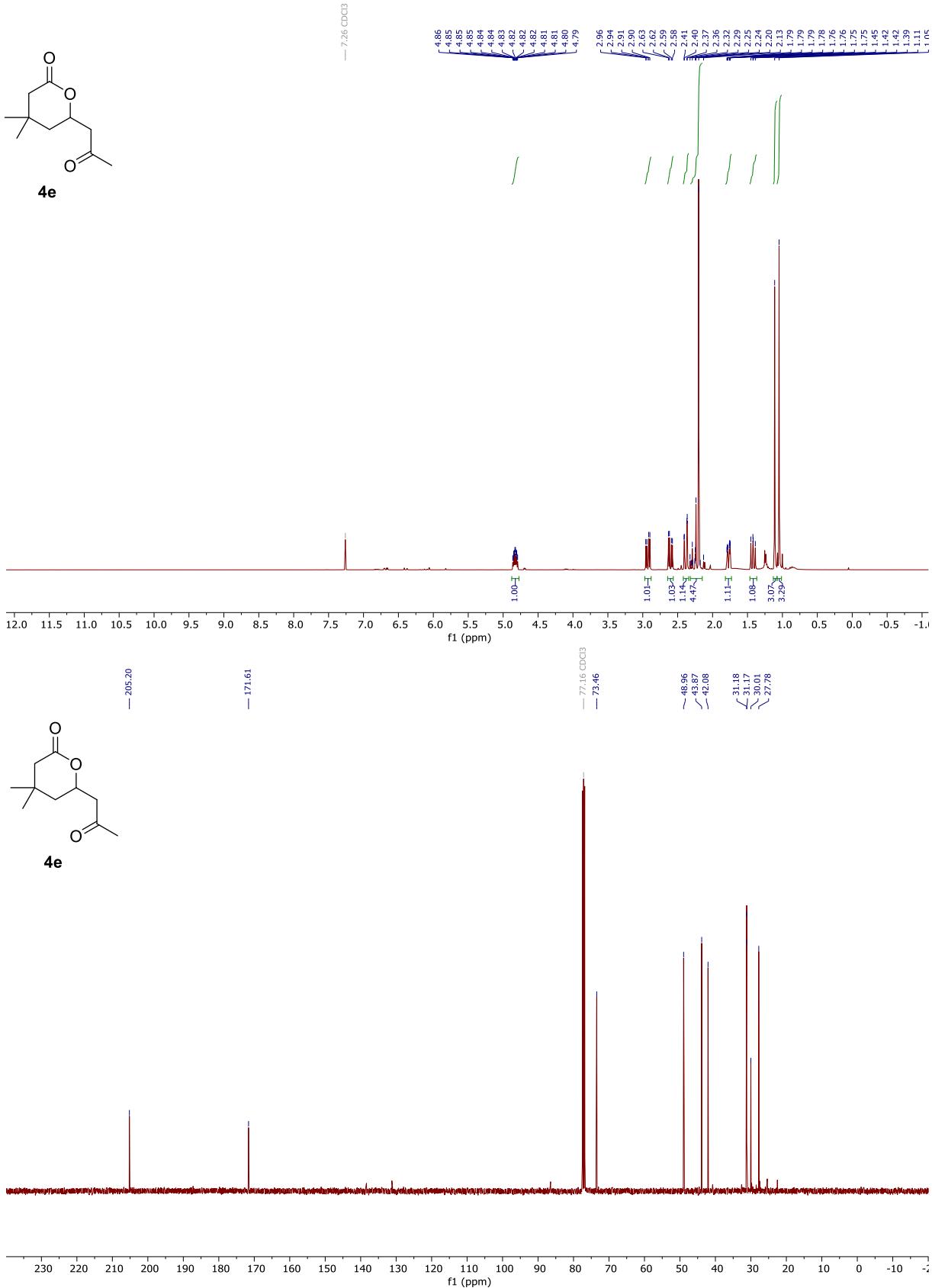


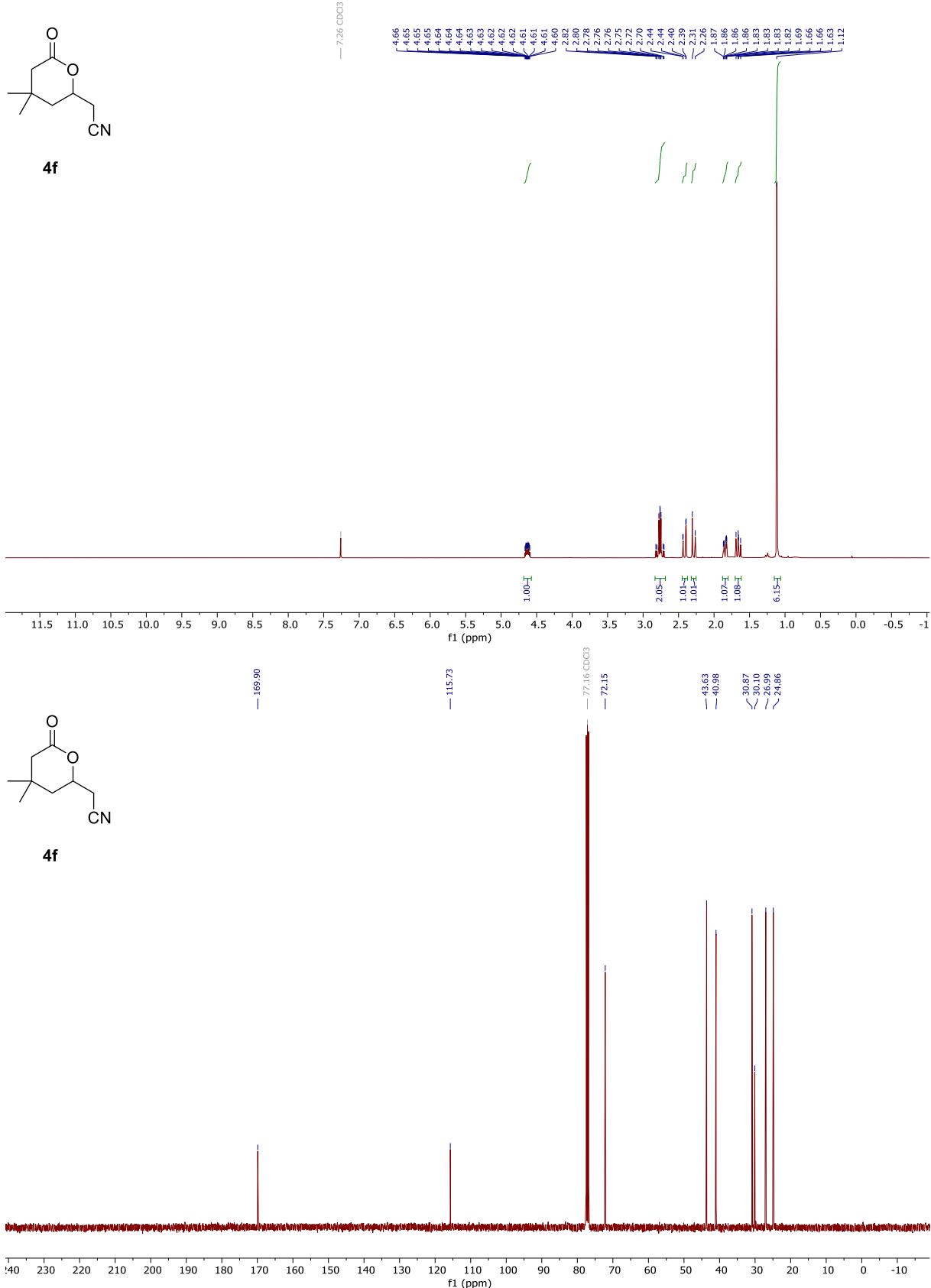


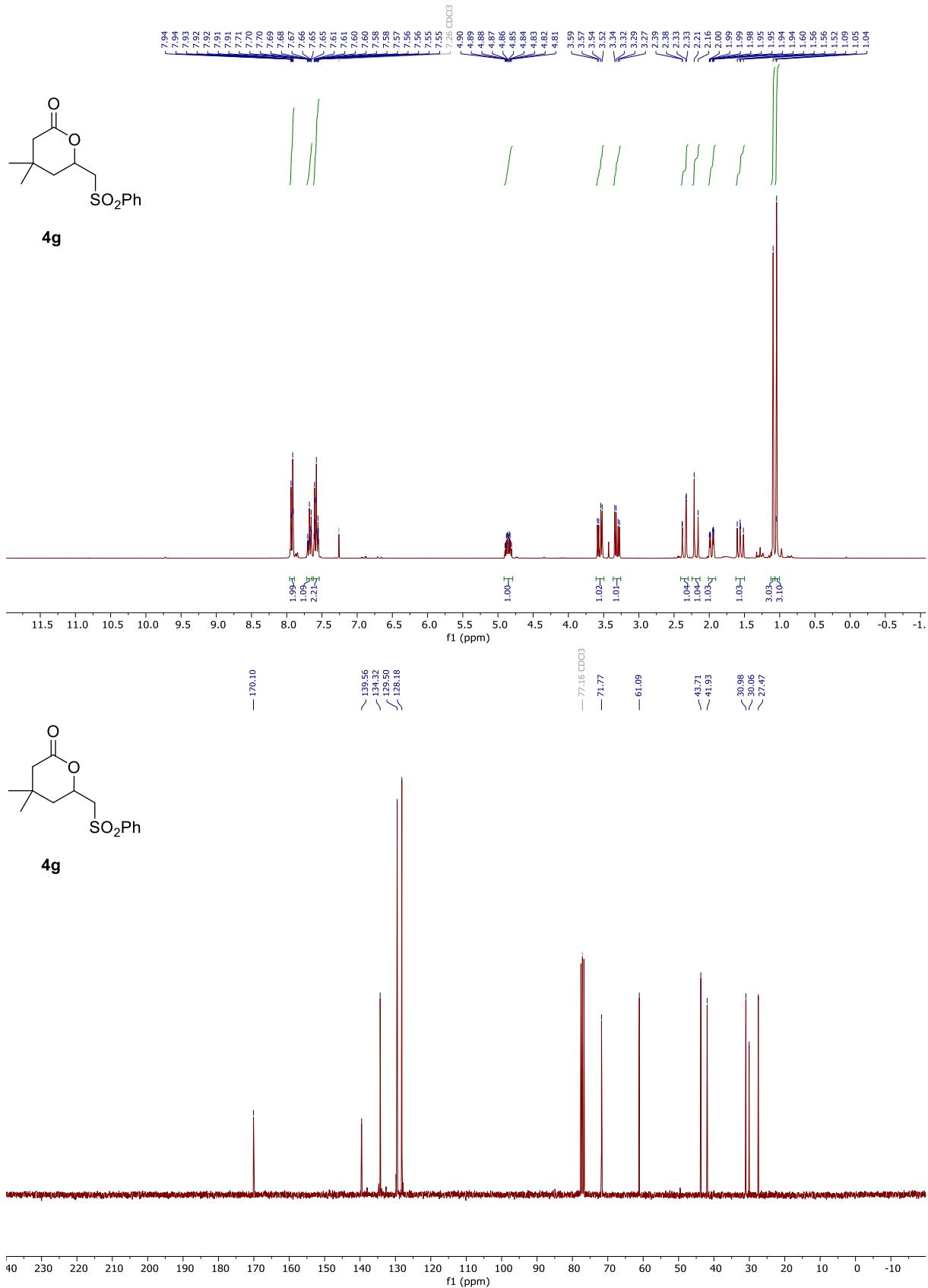


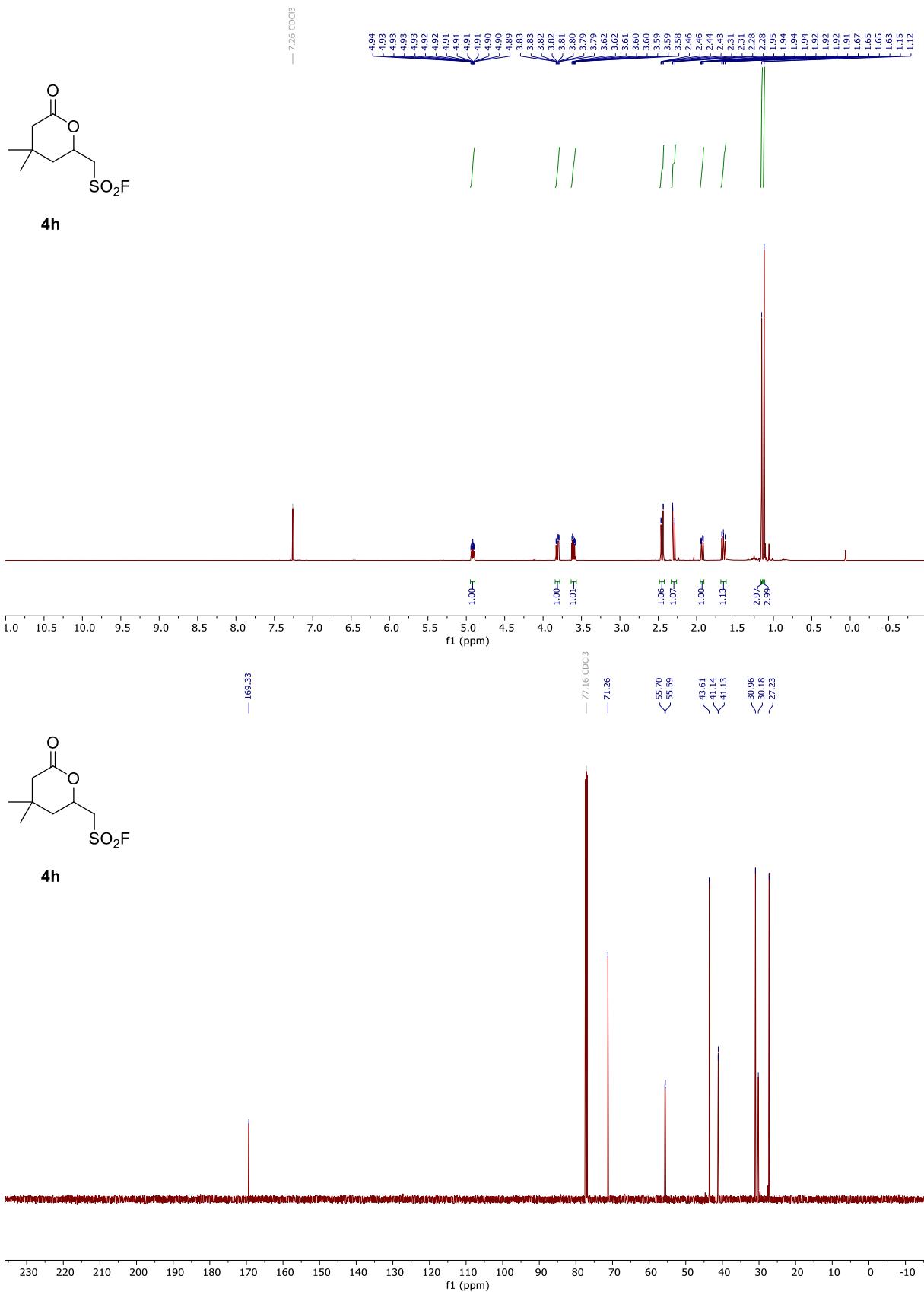


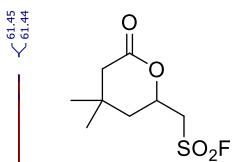




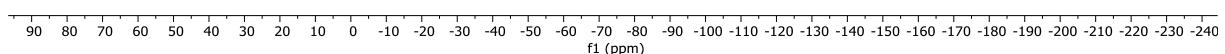


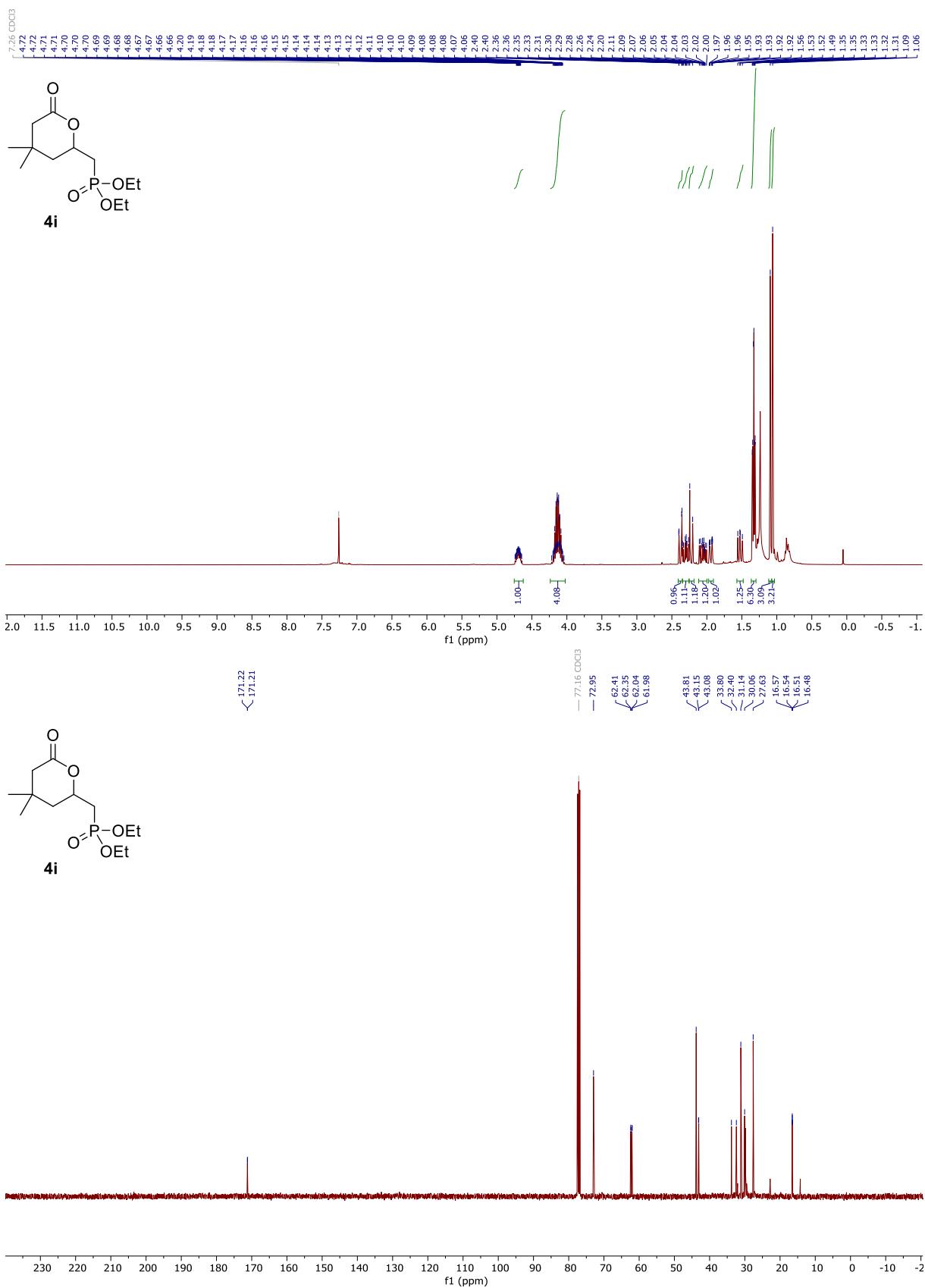


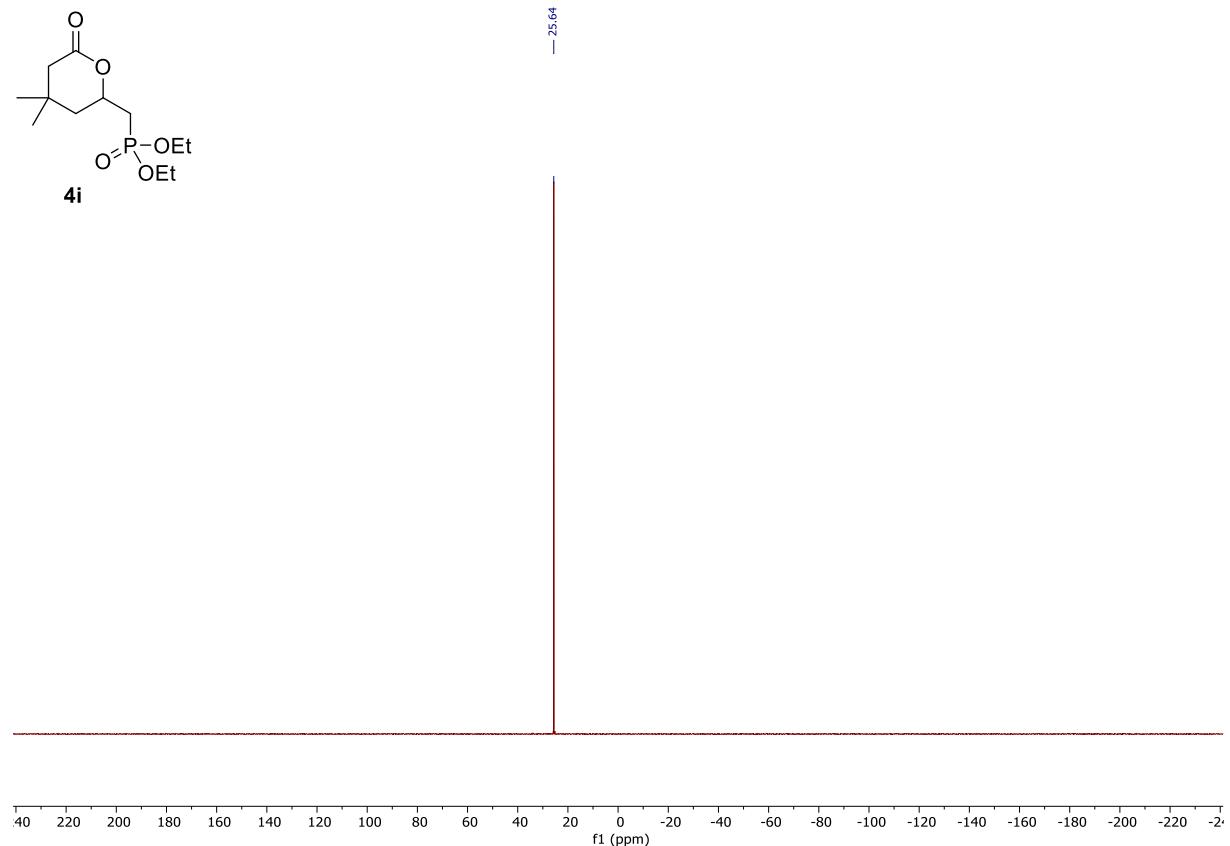
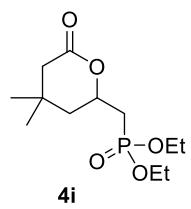


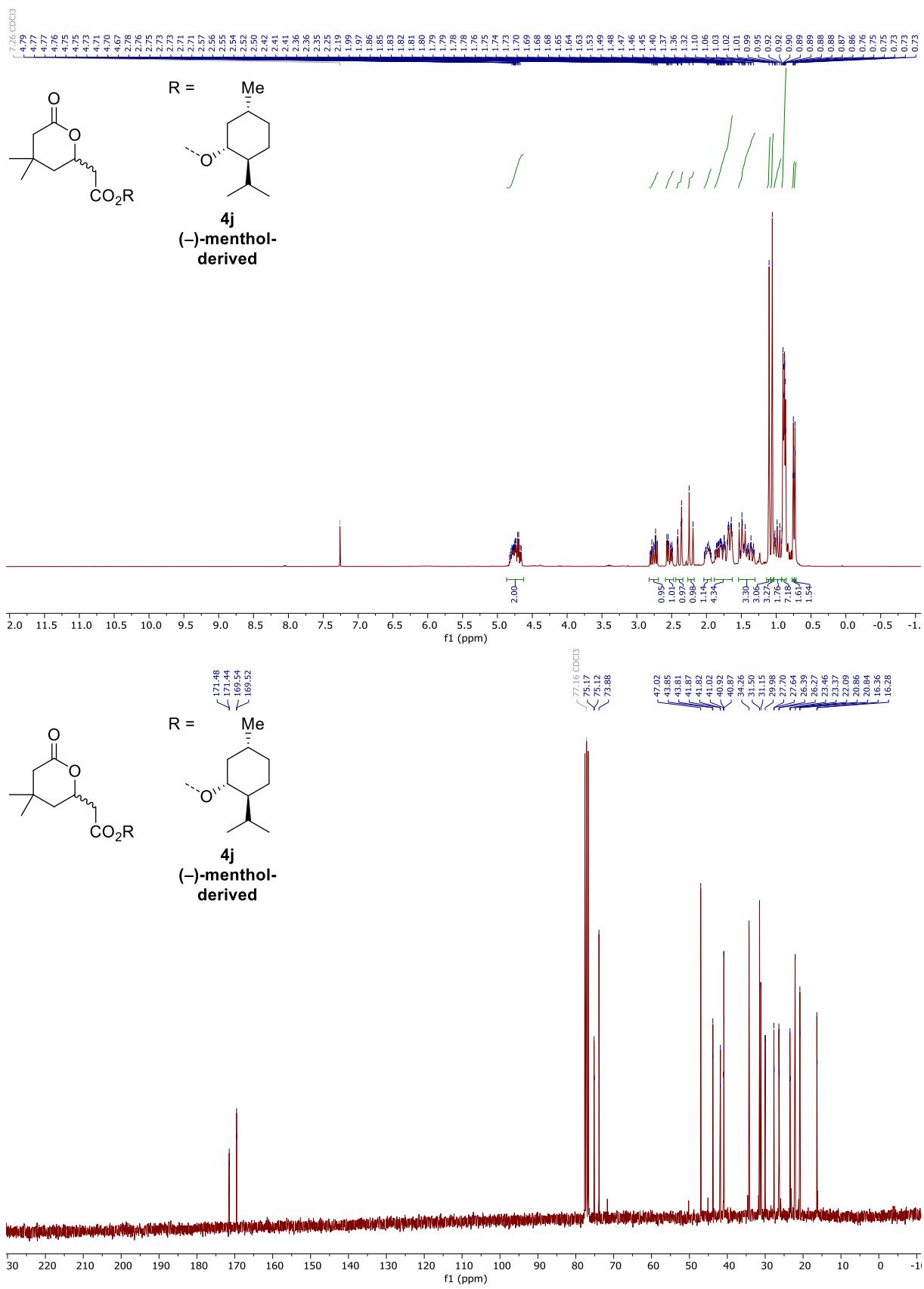


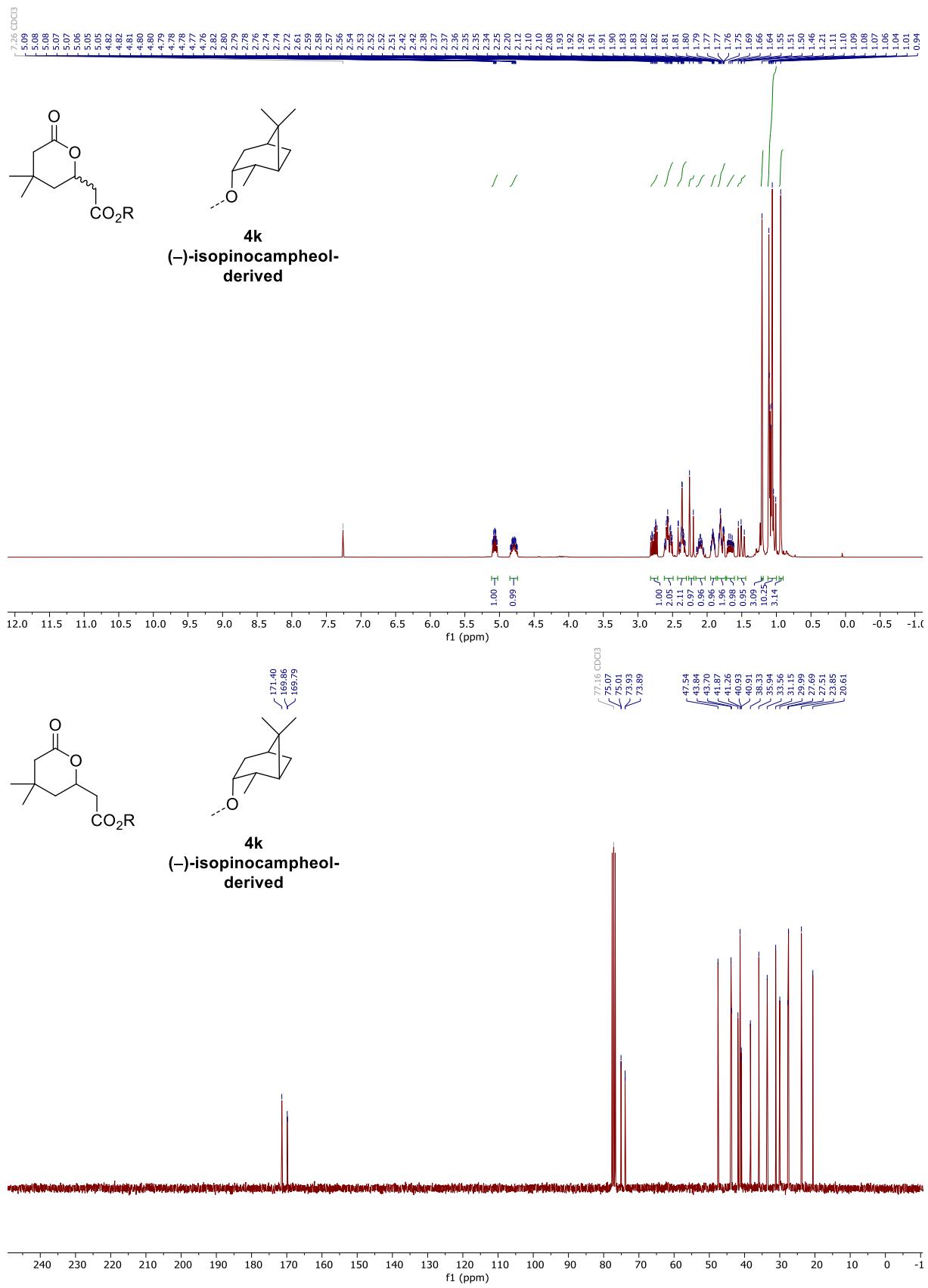
**4h**

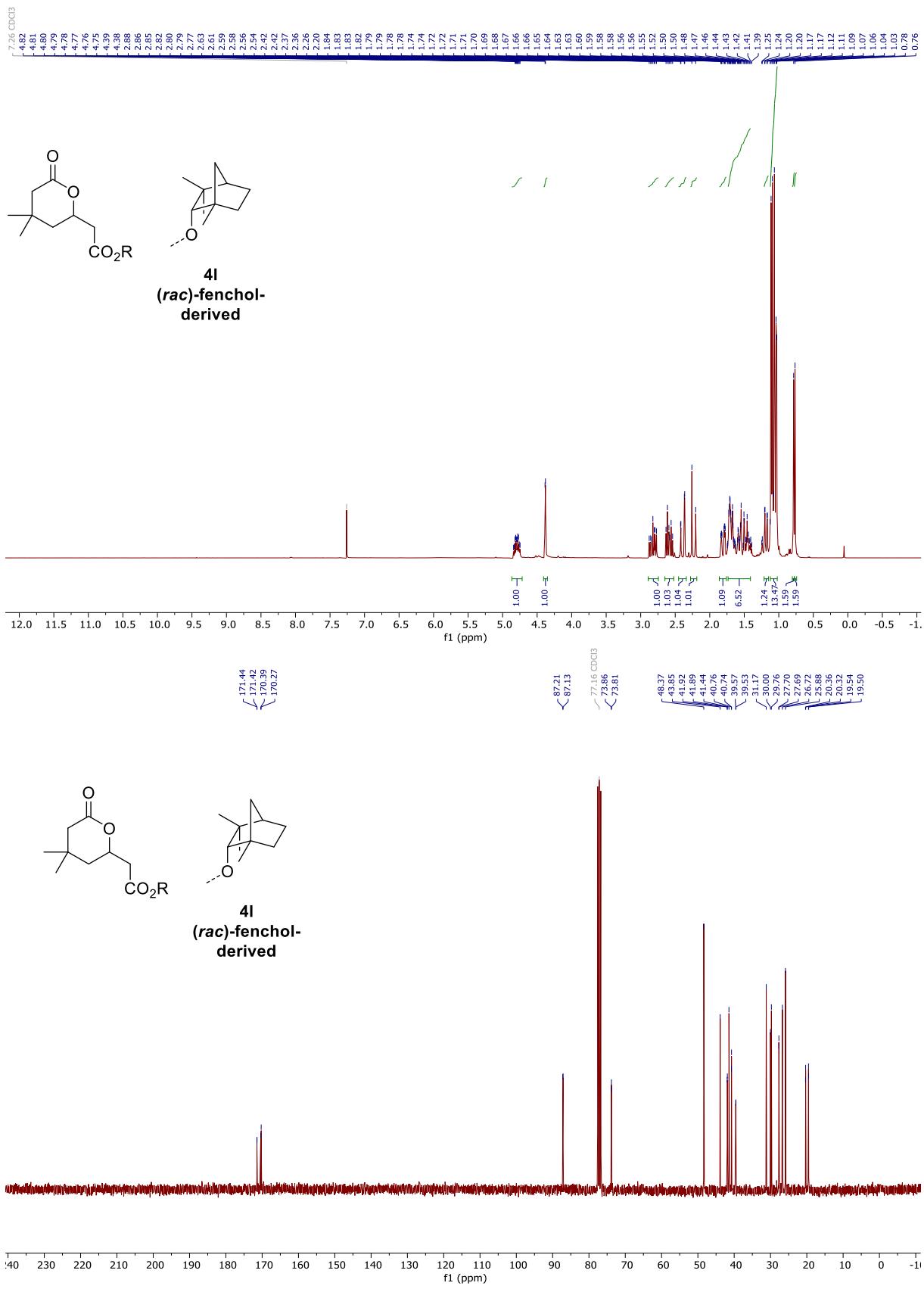












**Mechanistic Studies:**

