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DISCOVERY OF THE TRIFLUOROACETATE RELEASE PROCESS AND ITS  
STRATEGIC APPLICATION TOWARD THE SYNTHESIS OF BIOLOGICALLY  
ACTIVE MOLECULES

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그 동안의 나의 노력이

학문의 지경을 넓히는

밀거름이 될 수 있기를...

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## LIST OF ABBREVIATIONS

MM	Multiple myeloma
PCs	Plasma cells
CSCs	Cancer stem cells
LSCs	Leukemic stem cells
PTH	Parthenolide
QSAR	Quantitative structure-activity relationship
PD	Parkinson's disease
PTH-Cl	13-(4-chlorophenyl)-parthenolide
IKK $\beta$	I $\kappa$ B kinase- $\beta$
3-D rBM	Three-dimensional reconstructed bone marrow
CFU	Colony-forming unit
TLC	Thin layer chromatography
CDI	Carbonyldiimidazole
MTS	3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
rac-BHFF	5,7-Bis(1,1-dimethylethyl)-3-hydroxy-3(trifluoromethyl)-2(3 <i>H</i> )-benzofuranone
HWE	Horner-Wadsworth-Emmons

GABA	Gamma-aminobutyric acid
EOM	Ethoxymethyl
TBS	<i>t</i> -Butyldimethylsilyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMP	Dess-Martin periodinane
DMF	<i>N,N</i> -Dimethylformamide
THF	Tetrahydrofuran
DIAD	Diisopropyl azodicarboxylate
DMAP	Dimethylaminopyridine
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
MsCl	Methanesulfonyl chloride
DEC	Diethylcarbamate
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
EWG	Electron-withdrawing group
EDG	Electron-donating group
LDA	Lithium diisopropylamide
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
NBS	<i>N</i> -Bromosuccinimide
TPAP	Tetrapropylammonium perruthenate
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
Boc	<i>tert</i> -Butyloxycarbonyl
LiHMDS	Lithium bis(trimethylsilyl)amide

DCE	Dichloroethene
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidinone
NMP	<i>N</i> -Methyl-2-pyrrolidone
HOMO	Highest occupied molecular orbital

## ABSTRACT

Han, Changho. Ph.D., Purdue University, May 2013. Discovery of the Trifluoroacetate Release Process and its Strategic Application toward the Synthesis of Biologically Active Molecules. Major Professor: David Colby.

The natural product parthenolide is a sesquiterpene lactone isolated from the anti-inflammatory medicinal herb, Feverfew (*Tanacetum parthenium*). Although parthenolide shows **selective cytotoxicity** toward drug-resistant multiple myeloma cancer stem cells, its low potency and poor aqueous solubility limited its potential in clinical trials. We have taken a number of approaches to **improve its potency and water solubility**.

The incorporation of fluorine into biologically active molecules is a known strategy that can be used to enhance bioavailability. Therefore, one of our approaches was to introduce fluorine into parthenolide. However, due to its structural complexity, exceedingly mild, efficient, and high-yielding reaction conditions were needed. Our efforts to incorporate fluorine atoms on parthenolide lead us to design a novel synthetic methodology to generate  **$\alpha,\alpha$ -difluoroenolates via releasing trifluoroacetate** by mimicking nature's **hydrolytic C-C bond cleavage strategy**. We have shown the synthetic utilities of our novel methodology by reacting generated  $\alpha,\alpha$ -difluoroenolates with various electrophiles. We further expanded the synthetic versatility of trifluoroacetate release process by generating other reactive intermediates, such as ***gem*-difluoro carbanions**. With the **aryl pentafluoro *gem*-diol system, the competitive path has been extensively**

investigated. The results of this study led us to apply our methodology toward the synthesis of metabolically stable anthocyanin derivatives. Among the many anthocyanins, we aimed to synthesize metabolically stable analogues of malvidin 3-glucoside because it has shown a relatively strong neuroprotective effect compared to other anthocyanins.

## CHAPTER 1. INTRODUCTION

### 1.1 Natural Products as a Potential Source for Drug Discovery

Ever since **morphine** was isolated from *Papaver somniferum* over 200 years ago, secondary metabolites of various organisms have been extensively utilized as a promising source for drug discovery.<sup>1</sup> Pharmaceutical research into natural products was accelerated during the Second World War with the development of penicillin.<sup>2</sup> Although **pharmaceutical research into natural products** has declined during the past decade due to the expansion of synthetic medicinal chemistry along with high-throughput screening, there are still more than 100 natural product-derived drugs currently in clinical trials.<sup>1</sup> The hit-rate of natural products screening is much higher than the hit-rate of high-throughput screening.<sup>3</sup> Indeed, natural products are still considered to be an important source for drug discovery. Herein, approaches to combat two challenging diseases, multiple myeloma and Parkinson's disease, with novel synthetic derivatives originated from natural products have been demonstrated.

### 1.1.1 Multiple Myeloma and the Natural Product Parthenolide

Multiple myeloma (MM) is a cancer of plasma cells (PCs) in the bone marrow.<sup>4</sup> It accounts for 10% of hematopoietic cancers, and about 10,000 patients die every year because of MM.<sup>5</sup> It has been reported that MM is more common in older people. Also, blacks are more prone to be affected by MM than whites and its frequency is almost double in this ethnicity.<sup>5</sup> Due to the presence of drug-resistant cancer stem cells (CSCs), nearly all patients with MM experience a relapse after remission.<sup>6</sup> Thus far, there is no chance of a cure with existing therapies.<sup>5</sup> The use of current chemotherapy drugs is not effective in MM patients because they are cytotoxic toward both the cancerous and normal stem cells.<sup>7-9</sup> Therefore, discovery of novel agents which can selectively kill the cancerous stem cells over normal cells is essential.

Natural products have been considered to be a good source of novel lead molecules.<sup>10,11</sup> Recently, Guzman *et al.* have demonstrated that parthenolide (**1**), a natural product isolated from Feverfew (*Tanacetum parthenium*), can kill human leukemic stem cells (LSCs) *in vitro* while sparing normal hematopoietic cells (Figure 1.1).<sup>12</sup> Due to its high degree of cell selectivity, parthenolide (**1**) has been considered to be an important candidate for MM drug discovery.

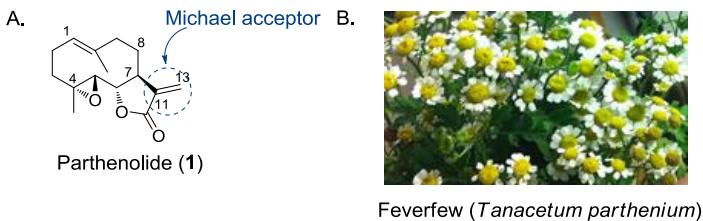


Figure 1.1 Parthenolide (**1**) and Feverfew.

- A. Structure of parthenolide (**1**)
- B. Image of feverfew

The anti-inflammatory medicinal herb Feverfew has been recognized as having various medicinal properties since ancient times. Feverfew contains various mixtures of mono- and sesquiterpenes. Among those chemical components, sesquiterpene  $\alpha$ -methylenebutyrolactones have been considered the most significant constituents present in Feverfew, and the most abundant sesquiterpene lactone is a parthenolide (**1**). The amount of parthenolide (**1**) in dry leaves can be as much as 1% of the total weight.<sup>13</sup>

Parthenolide (**1**) was first isolated from *T. parthenium* by Sorm and co-workers in 1959.<sup>13</sup> Feverfew produces parthenolide (**1**) as a defensive compound against Gram-positive bacteria, yeasts, and filamentous fungi.<sup>13</sup> It has been reported that parthenolide (**1**) can also inhibit the pro-inflammatory signaling pathway, NF- $\kappa$ B and display anti-cancer activities.<sup>14</sup>

NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a transcription factor complex present in almost all animal cells in an inactive state (Figure 1.2). In unstimulated cells, I $\kappa$ B (Inhibitor of  $\kappa$ B) sequesters NF- $\kappa$ B dimers in the cytoplasm.<sup>15</sup> The signal-induced degradation of I $\kappa$ B activates the NF- $\kappa$ B signaling pathways by releasing NF- $\kappa$ B. Freed NF- $\kappa$ B then goes into the nucleus and triggers the

expression of genes.<sup>16</sup> Because NF-κB signaling pathways regulate the DNA transcription homeostasis, misregulation of NF-κB leads to abnormal proliferation of cells and provokes diseases such as cancer.

Crews *et al.* showed the evidence with biotinylated parthenolide that parthenolide (**1**) covalently binds IKK $\beta$  with biotinylated parthenolide. Based on the fact that the C179A mutant of IKK $\beta$  lost parthenolide sensitivity, cysteine 179 is likely to be reacted with the exocyclic methylene moiety of parthenolide (**1**) (Figure 1.3).<sup>14</sup>

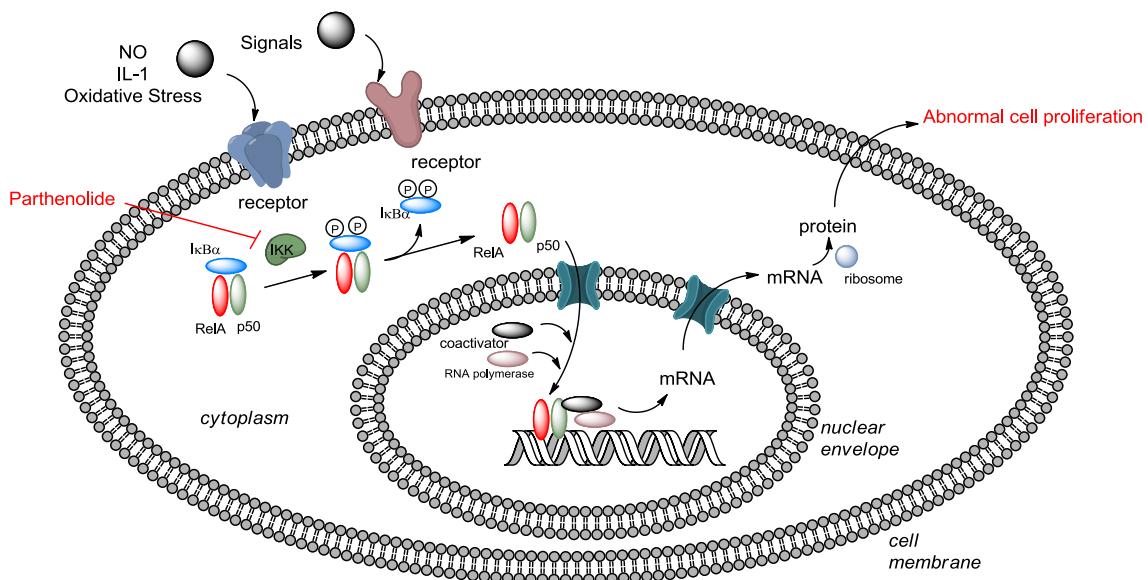


Figure 1.2 Illustration of NF-κB regulatory network.<sup>17–19</sup>

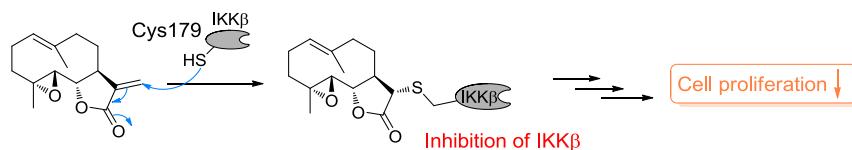


Figure 1.3 Target of parthenolide.<sup>14</sup>

Unfortunately, parthenolide (**1**) has low potency and poor water solubility<sup>12</sup>, which limit its potential in clinical trials. To address this solubility issue, Nasim *et al.*

installed several primary and secondary amines at the  $\alpha$ -methylene- $\gamma$ -butyrolactone functional group in parthenolide (**1**) (Figure 1.4 (1)).<sup>20</sup> However, even with their water-soluble parthenolide analogues, they could not improve the potency. Nearly all of their analogues have **micromolar activity** in the range of 17  $\mu\text{M}$  to 100  $\mu\text{M}$  (parthenolide (**1**),  $\text{IC}_{50} = 8 \mu\text{M}$ ).<sup>20</sup> Recently, Dell'Agli *et al.* synthesized parthenolide analogues with a modified polycyclic ring system (Figure 1.4 (2)).<sup>21</sup> Even though they found one analogue with  $\text{IC}_{50} = 2.5 \mu\text{M}$ , this improvement is modest. Previous quantitative structure-activity relationship (QSAR) studies of sesquiterpene lactone natural products<sup>22–24</sup> revealed that changes to the polycyclic ring system can lead to moderate improvement in potency, but changes to the polycyclic system may result in lower specificity.

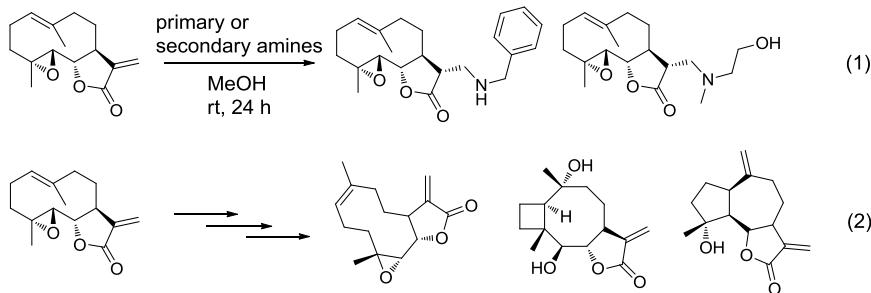


Figure 1.4 Derivatives of parthenolide (**1**).

(1) Aminoparthenolide analogues<sup>20</sup>

(2) Semisynthetic derivatives of parthenolide (**1**)<sup>21</sup>

### 1.1.2 Parkinson's Disease and Antioxidant Anthocyanins

Parkinson's disease (PD), a neurodegenerative disorder, results from the loss of dopamine neurons in the *substantia nigra*.<sup>25</sup> According to Parkinson's Disease Foundation report, about 60,000 Americans are diagnosed with PD each year and 7 to 10 million people worldwide live with PD. Nearly **\$25 billion/year** is estimated as a PD-related cost. The mitochondrial dysfunction associated with PD causes the accumulation

of neuroinflammatory agents and oxidative stress in affected neurons. Resulting oxidative stress-induced damage has been considered a main cause of the neurodegenerative disease (Figure 1.5).<sup>26</sup> Therefore, there has been growing interest in therapeutic approaches to address oxidative stress-induced damage in neurodegenerative diseases.<sup>27</sup> Recently, the importance of dietary polyphenolic antioxidants, such as anthocyanins, as neuroprotective agents has been highlighted in a number of studies.<sup>28</sup>

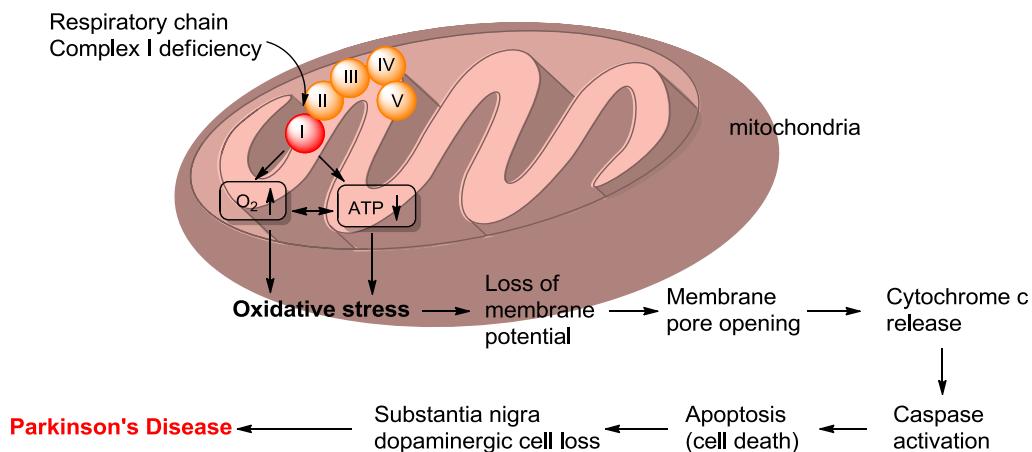


Figure 1.5 Mechanism of Parkinson's disease.

Anthocyanins, secondary metabolites (or plant pigments) isolated from various fruits, belong to a parent class of polyphenolic compounds called flavonoids. They are highly water-soluble natural products and most fruits, flower petals, and leaves contain them. Anthocyanins have various biological effects in plants, and they are mostly utilized for pollinator recruitment as well as hazardous UV protection.<sup>29</sup> Anthocyanins are classified based on their hydroxyl substituents as well as number, position, and types of sugars. Anthocyanidins are unglycosylated analogues of anthocyanins and there are six major classes of anthocyanidins: malvidin, cyanidin, pelargonidin, delphinidin, peonidin, and petunidin (Table 1.1).<sup>30</sup> Recent studies have shown that anthocyanins have

significant neuroprotective potential in neurodegenerative disorders.<sup>31,32</sup> Toscano *et al.* proposed the molecular mechanisms of natural polyphenolic compounds combatting against oxidative stress.<sup>33</sup> Dietary antioxidants can address oxidative stress via three potential working mechanisms (Figure 1.6). Polyphenolic compounds can react with free radicals and deliver a hydrogen atom to the radicals via hemolytic cleavage of the phenol. Another mechanism arises from the stabilization of radical species by single electron abstractions from the HOMO of polyphenolic rings. Last, polyphenols can be chelated to unstable transition metal ions to prevent the generation of reactive radical species. Because anthocyanins have been known to be potent antioxidants and anti-inflammatory agents, these natural products may show a strong neuroprotective effect against PD as well. To our knowledge, only a few studies have been conducted regarding the neuroprotective effects of anthocyanins against PD.<sup>34–36</sup>

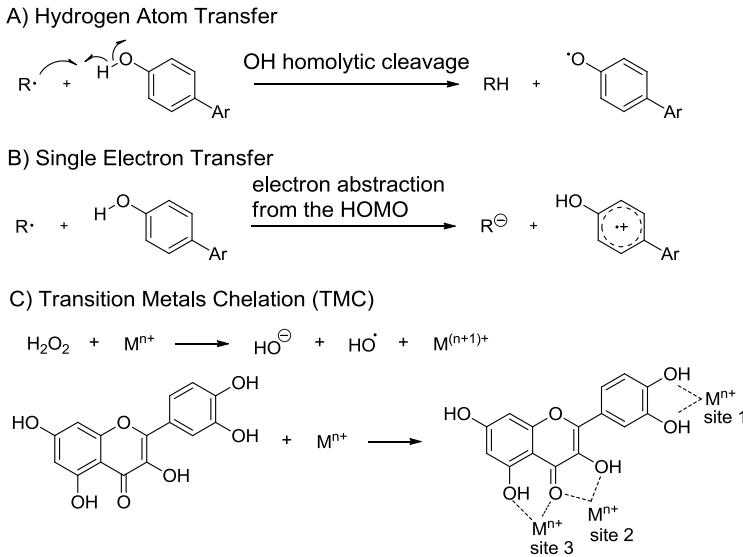


Figure 1.6 Three potential working mechanisms of dietary antioxidants<sup>33</sup>

Table 1.1 Structure of Common Anthocyanidins

Anthocyanidin	Basic Structure	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>
Malvidin		-OCH <sub>3</sub>	-OH	-OCH <sub>3</sub>	-OH	-OH	-H	-OH
Cyanidin		-OH	-OH	-H	-OH	-OH	-H	-OH
Pelargonidin		-H	-OH	-H	-OH	-OH	-H	-OH
Delphinidin		-OH	-OH	-OH	-OH	-OH	-H	-OH
Peonidin		-OCH <sub>3</sub>	-OH	-H	-OH	-OH	-H	-OH
Petunidin		-OH	-OH	-OCH <sub>3</sub>	-OH	-OH	-H	-OH

Polyphenolic molecules, such as **anthocyanins**, are prone to be metabolized in the body. In the case of anthocyanins, the sugar moieties are known to be hydrolyzed at physiological pH to make aglycones, the anthocyanidins (Figure 1.7).<sup>27</sup> Recent *in vitro* studies from the Tarozzi group have proven that not only anthocyanins but also their metabolites, such as anthocyanidin and protocatechuic acid, retain anti-oxidative properties. They even demonstrated that anthocyanins as well as their metabolites can inhibit H<sub>2</sub>O<sub>2</sub>-induced ROS formation at different cellular levels.<sup>27</sup>

Although both anthocyanins and their metabolites show antioxidant effects in *in vitro* assays, studies have shown that the **pharmacokinetic profiles between anthocyanins and metabolites are dramatically different**. Remesy and co-workers have shown that anthocyanidins were not detected in the brain tissue but were detected in the blood plasma of rats in *in vivo* studies.<sup>37</sup> Catherine and co-workers reported that anthocyanins could cross the blood brain barrier in *in vitro* models using brain endothelial cell lines and ECV304 monolayers co-cultured with C6 glioma cells.<sup>38</sup> These data indicate that **sugar moieties of anthocyanins** are critical for crossing the blood brain barrier. An acetal

linkage connecting the anthocyanidin and the sugar moiety is known to be labile in the body. Therefore, there are critical needs for the discovery of metabolically stable anthocyanins to improve their pharmacokinetic profile.

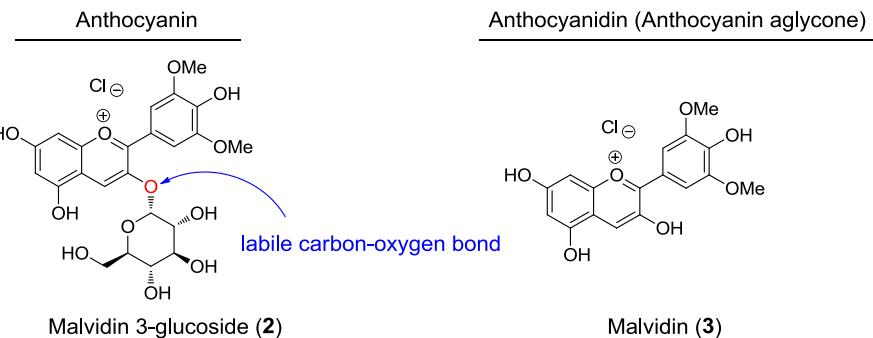


Figure 1.7 The structure of a malvidin 3-glucoside (**2**) and malvidin (**3**). Malvidin 3-glucoside is an anthocyanin and malvidin is an anthocyanidin.

## 1.2 Discovery of a Novel Synthetic Methodology Inspired by Natural Product Modification

Unlike high-throughput screening of chemical libraries, elucidating hits from natural sources is much more complicated due to the complex structure of natural products along with the labile substituents attached to them.<sup>1,39</sup> Insufficient potency or poor water solubility further limits the practical use of natural products as drug candidates. Therefore, there has been a tremendous amount of effort to modify and derivatize these natural products.<sup>40</sup> In some cases, simple modification of natural products is enough to address those issues. However, in most cases, a significant amount of time and effort are required to tune the natural products in a desired manner.

Among many strategies, bioisosteric replacement of labile substituents is well established method for improving bioavailability of natural products. Replacing an oxygen atom with a difluoromethylene unit is a typical example of bioisosteric modification. Due to the structural complexity of natural products, mild, efficient, and high-yielding reactions are critical in many synthetic strategies.

### 1.2.1 Importance of the Fluorine and *gem*-Difluoromethylene Units in Medicinal Chemistry

Fluorinated molecules play important roles in drug discovery. For example, fluorine can enhance the **bioavailability and metabolic stability of molecules**.<sup>41,42</sup> Also, fluorine can increase **lipophilicity, membrane permeability, and binding affinity** when incorporated into molecular structures.<sup>43</sup> Fluorinated compounds have been utilized as metabolic and biological probes with <sup>19</sup>F-NMR.<sup>44</sup> Moreover, the fluorine isotope has been utilized in PET imaging.<sup>45</sup>

The difluoromethylene ( $\text{CF}_2$ ) moiety is of special interest in medicinal chemistry because difluoromethylene groups are a potential bioisostere of an oxygen atom. For example, it has been shown that the metabolic stability of phosphates dramatically increased by replacing the phosphoryl ester oxygen with the difluoromethylene unit (Figure 1.8 (A)).<sup>41</sup> Also, replacing acidic  $\alpha$ -protons with fluorines can prevent enolization or  $\beta$ -elimination in metabolically unstable compounds (Figure 1.8 (B)).<sup>42</sup> Due to the decrease in bioavailability of unstable bioactive agents, there is a critical need for mild and efficient methods for installing difluoromethylene groups to replace labile oxygen linkages.<sup>43</sup>

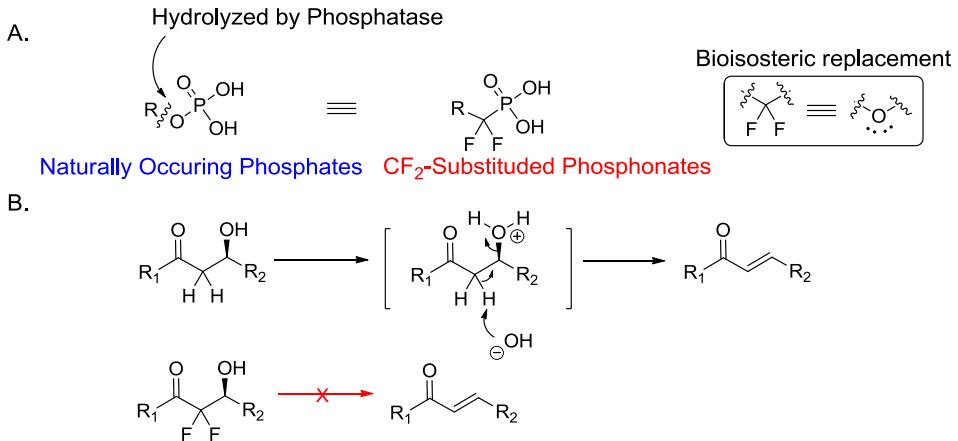


Figure 1.8 Use of the difluoromethylene ( $\text{CF}_2$ ) unit in medicinal chemistry.

- (A) Difluoromethylene ( $\text{CF}_2$ ) unit is a potential bioisostere of oxygen atom.<sup>41</sup>  
 (B)  $\beta$ -elimination prevention with difluoromethylene ( $\text{CF}_2$ ) unit.<sup>42</sup>

There are two different approaches for introducing fluorine atom(s) into large molecules: a direct fluorination method and a building-block method. Building-block methods are preferred in medicinal chemistry over direct fluorination methods because experimental procedures allow easy control of regio-, stereo- and chemoselectivities. One way of installing the difluoromethylene moiety is by using trifluoromethyl phenyl sulfone or sulfoxide as a synthon (Figure 1.9).<sup>46</sup> However, the synthon-based installation method usually limits the scope of starting materials.

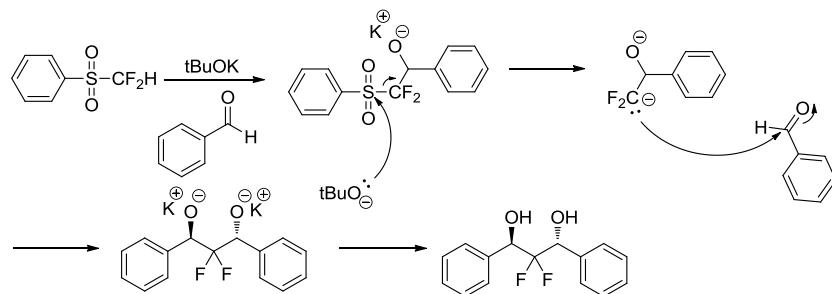
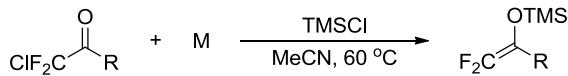


Figure 1.9 Synthon-based installation of difluoromethylene.<sup>46</sup>

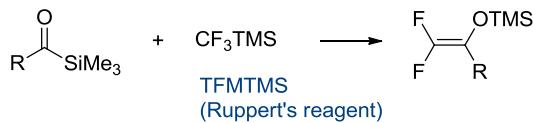
Another way of installing the difluoromethylene moiety is by generating  $\alpha,\alpha$ -difluoroenolates. So far, there are three methods of generating  $\alpha,\alpha$ -difluoroenolates or their synthetic equivalent, difluoroenoxy silanes (Figure 1.10). One method to generate difluoroenoxy silanes is by utilizing a Reformatsky-type reaction with highly halogenated methyl ketones (Figure 1.10 (A)).<sup>47–50</sup> Another method to make difluoroenoxy silanes is by using acyl silanes and Ruppert's reagent (Figure 1.10 (B)).<sup>51</sup> Lastly, difluoroenolates can be generated from trifluoroethanol along with a strong base such as LDA (Figure 1.10 (C)).<sup>52,53</sup> However, harsh reaction conditions and low product yields limit the scope of these methods. In summary, there are no versatile methods for generation of  $\alpha,\alpha$ -difluoroenolates without harsh conditions.

A. Reformatsky-type reaction



M = Zn(0), Ni(CO<sub>4</sub>), Zn-cat, CuCl, TiCl<sub>4</sub>-Zn, In

B. CF<sub>3</sub>TMS-mediated method



C. Trifluoroethanol-based approach

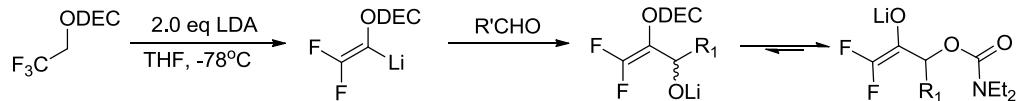


Figure 1.10 Methods for generating difluoroenolates or difluoroenolate precursors.

### 1.2.2 Synthetic Utilities of Trifluoroacetate in Synthetic Organic Chemistry

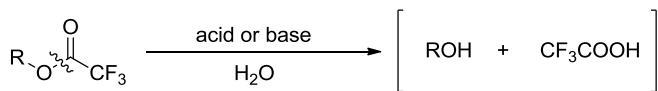
Trifluoroacetate, a widely used counter-ion, plays a key role in organic reactions.

Depending on the reaction type and the reaction conditions, trifluoroacetate can have three distinctive roles; a protecting group, a leaving group, and a ligand. Recently, our

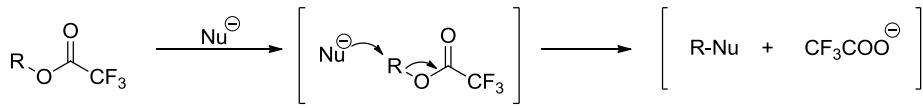
research group reported a novel method for generating reactive intermediates by releasing trifluoroacetate.<sup>54</sup> To our knowledge, this type of trifluoroacetate releasing pattern has not been examined or utilized in organic synthesis. There are various cases of trifluoroacetate-mediated reactions, and they can be separated in key categories by the type of reaction in which they participate.

Trifluoroacetate releasing patterns can be categorized into four categories; hydrolysis, substitution, elimination and fragmentation (Figure 1.11). Hydrolysis and substitution reactions that involve trifluoroacetate are well known. Hydrolysis is typically a traditional ester hydrolysis. Also, in many cases, substitution occurs by a traditional S<sub>N</sub>1 or S<sub>N</sub>2 type of substitution mechanism. In general, trifluoroacetate acts as either a protecting group or a leaving group in these cases. More interestingly, many unique reactions occur during an elimination of trifluoroacetate. Traditional E1 or E2 eliminations of trifluoroacetate and corresponding reactions have been widely reported. In addition to that, our research group has recently reported a different type of trifluoroacetate release, a fragmentation.

A. Trifluoroacetate release via hydrolysis

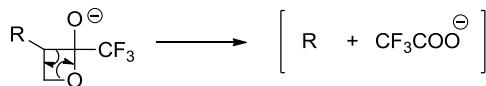


B. Trifluoroacetate release via substitution



Nu: Nucleophile

C. Trifluoroacetate release via elimination



D. Trifluoroacetate release via fragmentation

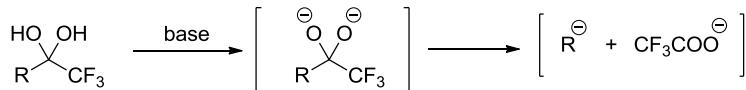
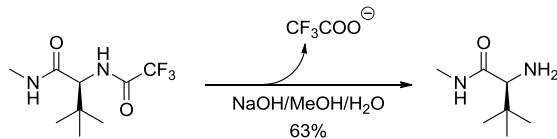
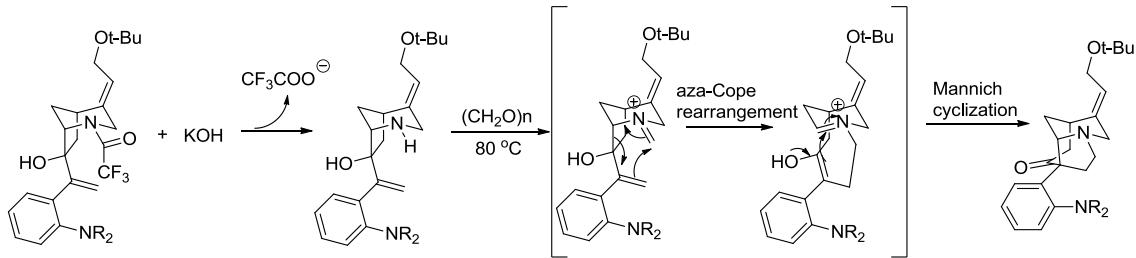


Figure 1.11 Types of trifluoroacetate release.

Trifluoroacetate can be released by simple hydrolysis. The trifluoroacetyl moiety usually acts as a protecting group in this case (Scheme 1.1).<sup>55</sup> Thanks to activation by the trifluoromethyl group, the hydrolysis of trifluoromethyl amide does not require harsh conditions. Thus, trifluoroacetate is widely used for amine protection. Overman and co-workers utilized the trifluoroacetate protecting group for an azatricyclic ketone (Scheme 1.2).<sup>56,57</sup> After hydrolyzing the trifluoroacetyl moiety with KOH, an aza-Cope rearrangement-Mannich cyclization reaction was performed to get the desired azatricyclic ketone.

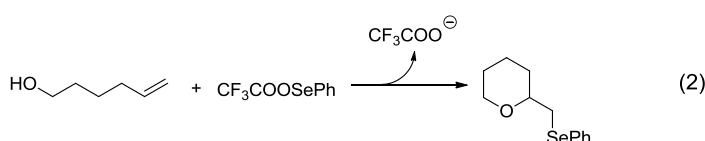
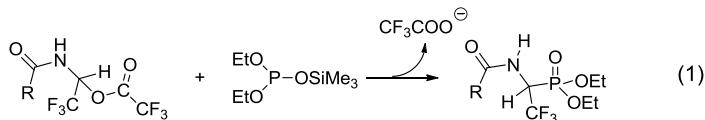


Scheme 1.1 Deprotection of Trifluoroacetate by Hydrolysis<sup>55</sup>



Scheme 1.2 Synthesis of Azatricyclic Ketone<sup>56,57</sup>

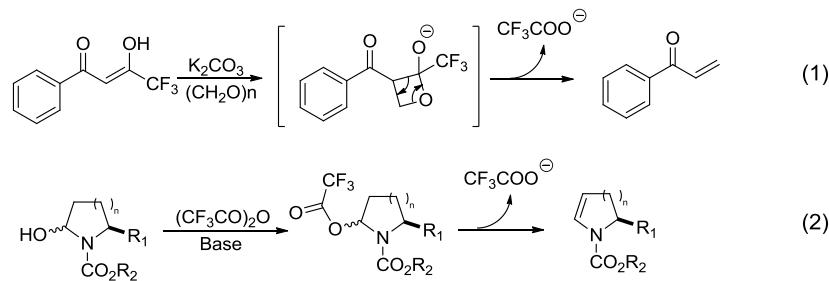
Because trifluoroacetate is such a good leaving group, many nucleophiles can displace trifluoroacetate during the reaction. The carbon-trifluoroacetate bond can be substituted by another bond, such as a carbon-phosphorus bond (Scheme 1.3 (1)).<sup>58</sup> Kutateladze and co-workers reported cyclization of enol by using an organoselenium reagent (Scheme 1.3 (2)).<sup>59,60</sup> In this case, insertion and consecutive displacement of trifluoroacetate by a terminal alcohol generates the tetrahydropyran ring.



Scheme 1.3 Substitution of Trifluoroacetate by Nucleophiles

The good leaving group character of trifluoroacetate allows for E1 and E2 elimination of trifluoroacetate when reaction conditions are suitable. In this case, release of trifluoroacetate can generate corresponding cationic intermediates and these cationic intermediates can undergo various reaction paths. Thus, elimination type of trifluoroacetate release can contribute to four different types of reactions; bond-formation reactions, bond-cleavage reactions, rearrangement reactions, and heteroatom-reduction reactions.

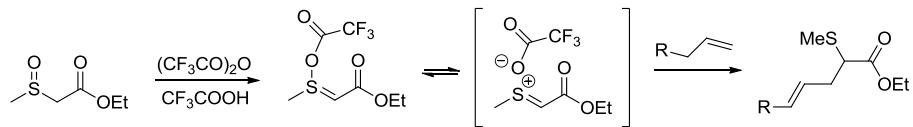
*Bond formation reaction.* More frequently, trifluoroacetate elimination causes formation or cleavage of a bond. In the case of bond formations, both intra- and intermolecular modes of bond formation have been reported.  $\alpha$ -Methylenation via the facile release of trifluoroacetate, reported by Colby and co-workers, is a good example of intra molecular C-C double bond formation (Scheme 1.5 (1)).<sup>61</sup> In addition,  $\beta$ -elimination type trifluoroacetate release also can cause C-C double bond formation (Scheme 1.5 (2)).<sup>62–65</sup>



Scheme 1.4 C-C Bond Formation Via Trifluoroacetate Release

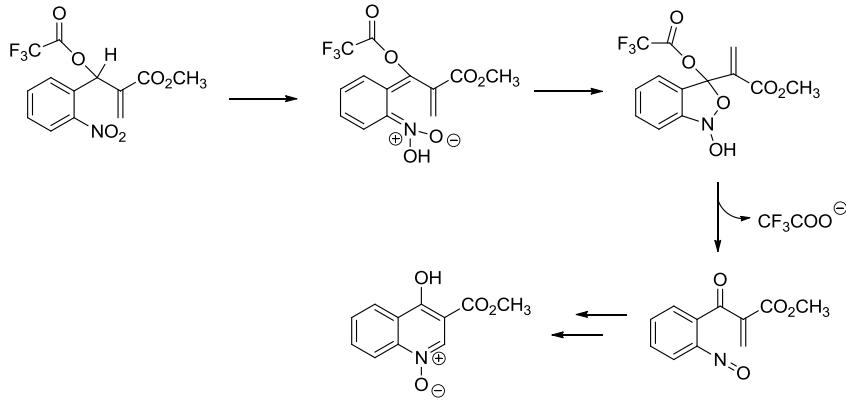
Bond formation can occur in an intermolecular manner. In this case, the generated cationic intermediates after trifluoroacetate release act as electrophiles. Ikeda and co-

workers generated sulfonium ion intermediates by releasing trifluoroacetate and subsequently reacting them with alkenes (Scheme 1.6).<sup>66</sup>



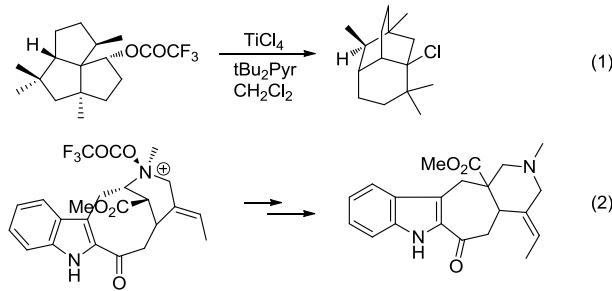
Scheme 1.5 Intramolecular Bond Formation Via Trifluoroacetate Release<sup>66</sup>

*Bond-cleavage reaction* In addition to bond formation, trifluoroacetate release can cause bond cleavage. Eberlin and co-workers assembled *N*-oxide hydroxyquinolines from an *o*-nitrophenyl Baylis-Hillman adduct (Scheme 1.7).<sup>67</sup> In this case, the result of the release of trifluoroacetate was N-O bond cleavage.



Scheme 1.6 Cleavage of an N-O Bond Via Trifluoroacetate Release<sup>67</sup>

*Rearrangement reaction.* The release of trifluoroacetate can generate carbocation intermediates for rearrangements. Zhu and co-workers reported  $TiCl_4$ -mediated rearrangement of silphin-1 $\alpha$ -yl trifluoroacetate (Scheme 1.9 (1)).<sup>68</sup> Trifluoroacetate-release mediated rearrangement has been reported in alkaloid synthesis as well. The unusual ervatamin structure had been generated from vobasin and its derivatives via the trifluoroacetate-release mediated rearrangement (Scheme 1.9 (2)).<sup>69</sup>

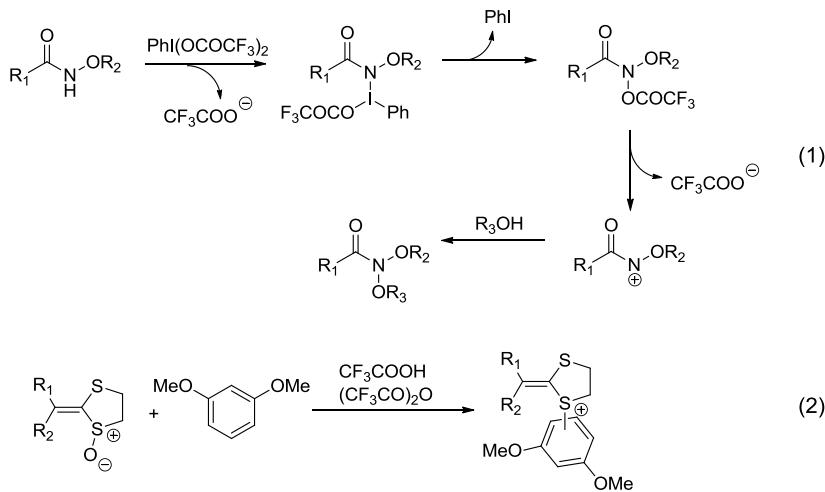


Scheme 1.7 Trifluoroacetate-release mediated rearrangement.

(1)  $\text{TiCl}_4$ -mediated rearrangement of silphin-1 $\alpha$ -yl trifluoroacetate.<sup>68</sup>

(2) Trifluoroacetate release mediated vobasin rearrangement.<sup>69</sup>

*Heteroatom oxidation/reduction reaction.* Trifluoroacetate release can be used as a heteroatom oxidation/reduction method. Rosser and co-workers recently reported the synthesis of *N,N*-dialkoxyamides from hydroxamic esters (Scheme 1.10 (1)).<sup>70</sup> During the reaction, the release of trifluoroacetate from the *N*-trifluoroacetoxy compound oxidized the nitrogen atom. In some cases, trifluoroacetate can be reductively eliminated from molecules (Scheme 1.10 (2)).<sup>71</sup>



Scheme 1.8 Reductive Elimination of Trifluoroacetate from *N*-Oxide or Sulfoxide.

(1) Trifluoroacetate oxidized nitrogen<sup>70</sup>

(2) Trifluoroacetate reduced sulfoxide<sup>71</sup>

### 1.2.3 Potential of C-C Bond Cleavage in Synthetic Chemistry

Although natural products have long been used as an important source for drug discovery, modifying natural products is still very challenging due to their complex structure and the presence of sensitive functional groups. Therefore, total synthesis of natural products has been considered an essential prerequisite to synthesize derivatives of natural products. As a consequence, many efficient methods for formation of C-C bonds have been developed. However, nature utilizes not only C-C bond formation but also C-C bond fragmentation during metabolism to assemble complex metabolites. A way of selectively cleaving C-C bonds for assembling derivatives of complex natural product would be a substantial advance in organic synthesis.

C-C cleavage has a tremendous amount of potential but is a rather under explored area in synthetic and organometallic chemistry.<sup>72-76</sup> There have been three different approaches to conduct and utilize C-C bond cleavage; C-C activation with transition metals,<sup>77-80</sup> rearrangement,<sup>68</sup> and fragmentation.<sup>54,81</sup> Although there has been a tremendous amount of effort, the selective cleavage of C-C bonds is still challenging even with the use of transition metals. There are only a few examples showing selective activation of the C-C bond adjacent to a carbonyl group by using rhodium.<sup>82-89</sup> On the other hand, nature has an ability to selectively cleave C-C bonds next to a carbonyl group efficiently without using transition metals.<sup>90-92</sup> By mimicking the strategy of these enzymes,<sup>93</sup> organic chemists can potentially cleave C-C bonds efficiently even without using transition metals.

Nature routinely uses C-C bond cleavage to degrade aromatic compounds in soil. Bacterial C-C hydrolases, which are components of bacterial meta-cleavage pathways,

play an important role in the degradation of aromatic compounds in soil by catalyzing the hydrolytic C-C bond cleavage.<sup>91</sup> 2-Hydroxy-6-ketonona-2,4-diene-1,9-dioic acid 5,6-hydrolase (MhpC) from *Escherichia coli* and 2-hydroxy-6-keto-6-phenylhexa-2,4-dienoic acid hydrolase (BphD) from *Burkholderia xenovorans* LB400 are well known example of bacterial C-C hydrolases.<sup>94</sup> Amino acid sequence alignments reveal that these enzymes contains conserved serine, histidine and aspartate catalytic triad residues.<sup>95</sup> Although the general mechanistic paradigm of serine proteases is nucleophilic catalysis, extensive mechanistic studies reveal that the **role of the serine residue in the catalytic triad of C-C hydrolases is fundamentally different from general serine hydrolases.** These proteases undergo a general base mechanism for C-C hydrolytic cleavage, rather than the nucleophilic mechanism (Figure 1.12).<sup>96</sup>

**C-C bond cleavage is essential in nature for carbon recycling.** Selective cleavage of C-C bonds also has an important synthetic utility in organic chemistry. The C-C bond cleavage strategy has been used in synthetic chemistry to construct or remodel complex molecules.<sup>97–99</sup> Recent studies show that the C-C bond cleaving processes also have extensive synthetic utility.<sup>98,100–103</sup>

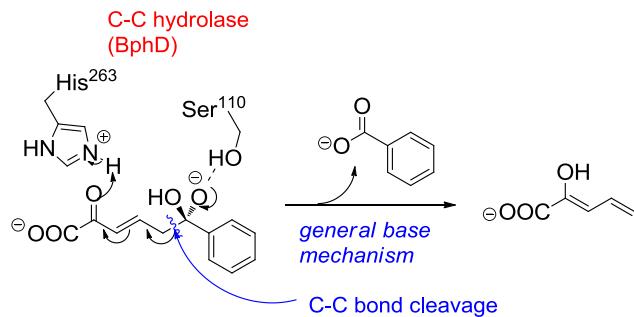


Figure 1.12 Mechanism of C-C hydrolases in the  $\alpha/\beta$ -hydrolase family.<sup>96</sup>

## CHAPTER 2. SYNTHESIS OF ARYLATED PARTHENOLIDE DERIVATIVES FOR STRUCTURE-ACTIVITY INVESTIGATIONS

### 2.1 Introduction

Parthenolide (**1**) is known to induce apoptosis in human acute myelogenous leukemia and multiple myeloma cells without affecting normal hematopoietic cells.<sup>104,105</sup> Bork *et al.* demonstrated the importance of the  $\alpha$ -methylene- $\gamma$ -butyrolactone moiety of parthenolide (**1**) for inhibiting IKK $\beta$ , which is a key kinase in the NF- $\kappa$ B pathway (Figure 1.2).<sup>106</sup> Specifically, the exomethylene group of the  $\alpha$ -methylene- $\gamma$ -butyrolactone moiety of parthenolide (**1**) is the electrophilic target for Cys179 of IKK $\beta$  (Figure 1.3).<sup>14</sup> Therefore, changes to the  $\alpha$ -methylene- $\gamma$ -butyrolactone moiety of parthenolide (**1**) have been explored to increase the potency.

### 2.2 Chemistry

Our first approach was to change the electron density of C11-C13 exomethylene unit. We hypothesized that the Michael acceptor reactivity of parthenolide (**1**) could be affected by the electron density of C13, an electrophilic site (Figure 2.1). An arylation approach to the exomethylene was elected because the electron density of C13 was expected to be tuned easily by changing substituents on the ring (Figure 2.1).

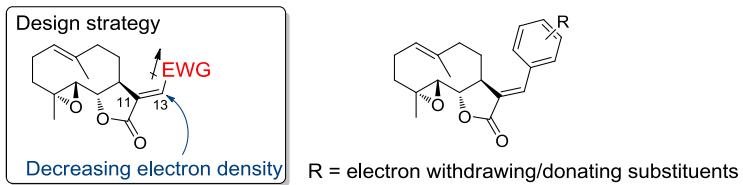


Figure 2.1 Illustration of design strategy.

Table 2.1 Heck Coupling with Parthenolide (**1**) and Aryl Iodides<sup>107</sup>

	parthenolide ( <b>1</b> )	+	Arl	Pd(OAc) <sub>2</sub> , Et <sub>3</sub> N DMF, 80°C	product	yield	
entry	Arl	product	yield	entry	Arl	product	yield
1			57%	8			58%
2			77%	9			57%
3			36%	10			72%
4			90%	11			40%
5			85%	12			26%
6			80%	13			24%
7			61%				

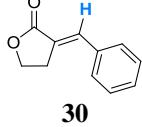
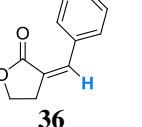
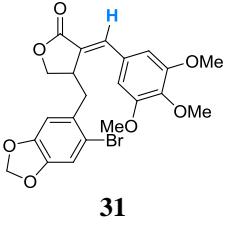
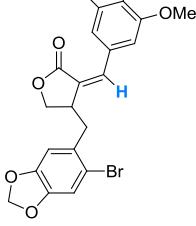
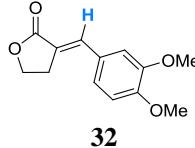
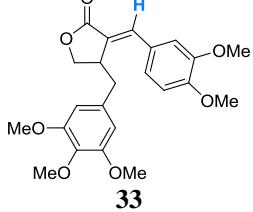
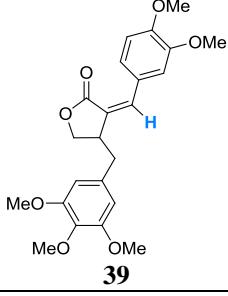
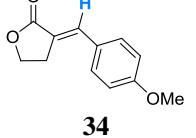
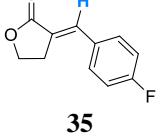
Several different aryl groups, containing various electron-withdrawing and donating groups, have been installed to the C13 site of parthenolide (**1**) (Figure 2.1). Thirteen arylated parthenolide derivatives were synthesized using a Heck coupling method (Table 2.1).<sup>107</sup>

Previously, Arcadi *et al.*<sup>108</sup> had reported that the Heck coupling between  $\alpha$ -methylene- $\gamma$ -butyrolactone and aryl halides produced coupled products having *Z*-olefin geometry. However, our assignment of olefin geometries was *E*-olefin instead of *Z*-olefin geometry. Our assignment had been further proved by X-ray crystal structures of analogues **22** and **24** (Figure 2.2). From NMR studies, we discovered the diagnostic chemical shift indicator for the olefin geometry assignment, the chemical shift of C13 vinyl proton of arylated compound (Table 2.2). The olefin geometries for the rest of compounds were assigned based on the chemical shift of the C13 proton.



Figure 2.2 X-ray structures of parthenolide (**1**) and parthenolide derivatives (A) parthenolide (**1**), (B) analogue **22**, and (C) analogue **24**.<sup>107</sup>

Table 2.2 Diagnostic Vinyl Protons in  $\alpha$ -Methylene- $\gamma$ -butyrolactone<sup>107</sup>

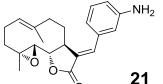
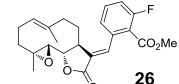
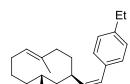
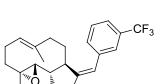
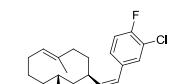
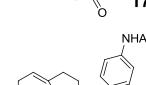
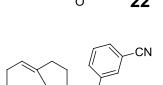
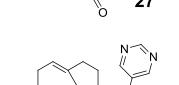
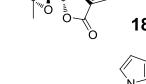
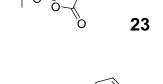
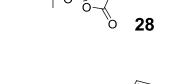
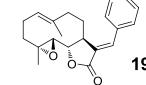
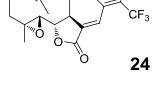
E-olefin Structure	Chemical Shift of Vinyl Proton	Z-olefin Structure	Chemical Shift of Vinyl Proton
	7.52 ppm <sup>109</sup> 7.60 ppm <sup>110</sup>		6.99 ppm <sup>110</sup>
	7.51 ppm <sup>111</sup>		6.63 ppm <sup>111</sup>
	8.13 ppm <sup>112</sup>		6.90 ppm <sup>112</sup>
	7.55 ppm <sup>112</sup>		6.53 ppm <sup>112</sup>
	7.45 ppm <sup>109</sup>		
	7.44–7.38 ppm <sup>109</sup>		

<sup>a</sup> All chemical shifts were obtained from the literature.

### 2.3 Biological Evaluation

Initial antiproliferative assays with these compounds were conducted in the HeLa (cervical cancer) cell line (Table 2.3).<sup>107</sup> Among 13 parthenolide analogues, (*E*)-13-(3-trifluoromethylphenyl)-parthenolide **22** showed the best activity ( $IC_{50}$  of  $15.2 \pm 1.5 \mu\text{M}$ ). The X-ray crystal structures of analogues **22** and **24** reveal that palladium-catalyzed arylation did not change the bicyclic ring of parthenolide (**1**) (Figure 3). This is important because changing the polycyclic system geometry of parthenolide (**1**) might negatively affect its specificity to the target.

Table 2.3 Antiproliferative Assay Data of Parthenolide Analogue in HeLa Cells<sup>107</sup>

Entry	Compound	$IC_{50}, \mu\text{M}$	Entry	Compound	$IC_{50}, \mu\text{M}$	Entry	Compound	$IC_{50}, \mu\text{M}$
1		$7.8 \pm 1.3$	6		>250	11		>250
2		$32.7 \pm 1.5$	7		$15.2 \pm 1.5$	12		- <sup>a</sup>
3		>250	8		$214 \pm 1.4$	13		- <sup>a</sup>
4		>250	9		>250	14		- <sup>a</sup>
5		>250	10		>250			

a. not tested.

Notably, parthenolide (**1**) has been reported to induce apoptosis in human acute myelogenous leukemia cells as well as in multiple myeloma cells without damaging

normal hematopoietic cells.<sup>104,105</sup> The mechanism of action of parthenolide (**1**) to initiate apoptosis in leukemic cancer stem cells was suggested to be a combination of the inhibition of transcription factor NF-κB and induction of oxidative stress.<sup>104,113,114</sup> Therefore, further studies of parthenolide (**1**) and its arylated derivatives on drug-resistant multiple myeloma cancer stem cells (MM-CSCs) were conducted by the Prof. Julia Kirshner's group in the Department of Biological Sciences.<sup>115</sup>

MM is a cancer arising through the expansion of malignant plasma cells in the bone marrow. The extremely high rate of relapse due to drug-resistant MM-CSCs emphasizes the need for new therapeutic regimens.<sup>116</sup> The interaction of cells with the surrounding extracellular matrix produces high drug resistance in MM-CSCs. This factor cannot be considered in standard culture systems. Therefore, the cellular compartments and extracellular matrix were recapitulated *in vitro* by using a three-dimensional reconstructed bone marrow (3-D rBM) culture system.<sup>117</sup>

With 3-D rBM culture system, the antiproliferative potentials of compounds against MM-CSCs have been investigated in the context of adhesion-mediated drug resistance (Table 2.4). Two different MM cell lines, RPMI-8226 and U226, were used and each cell line contains a different frequency of CSCs, 2.62% and 1.86%, respectively. The cytotoxic effect of compounds against non-tumorigenic cells was measured with 3-D rBM assay. To measure the effect on MM-CSCs, colony forming unit (CFU) assays were performed additionally; specifically designed formulation only allows MM-CSCs to form colonies in CFU assays.

Under physiological conditions reconstructed by the 3-D rBM model, parthenolide (**1**) and analogue **22** showed dose-dependent anti-MM activity. Moreover,

both compounds exhibited higher cytotoxicity toward MM-CSCs than non-tumorigenic cells. On the other hand, 13-(4-chlorophenyl)-parthenolide (PTH-Cl) exhibited a complete loss of selectivity for the MM-CSCs even though it had higher cytotoxicity toward non-tumorigenic cells than compound **22**. Unfortunately, the structural analogues of parthenolide were not as potent as parent natural product. Further studies to improve the potency of parthenolide (**1**) as well as to improve its solubility profile need to be pursued in due course.

Table 2.4 LC<sub>50</sub> Values for Anti-tumor and Anti-cancer Stem Cell Activity of Parthenolide (**1**) and Its Arylated Derivatives.<sup>115</sup>

Cell type	Culture Method	Parthenolide ( <b>1</b> )	PTH-CF <sub>3</sub> ( <b>22</b> )	PTH-Cl
RPMI-8226	3-D rBM	10 μM	60 μM	25 μM
RPMI-8226	CFU rBM	1.6 μM	13.5 μM	60 μM
U266	3-D rBM	7 μM	57.5 μM	22 μM
U266	CFU rBM	2.3 μM	25 μM	50 μM

#### 2.4 Conclusion and Future Directions

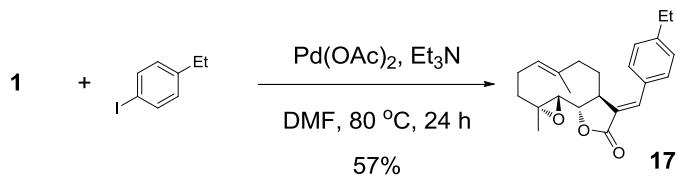
Our goal was to increase the electrophilicity of the exomethylene group of parthenolide (**1**) by decreasing electron density of C13 in exomethylene group. We expected that the electron density of C13 would be changed by installing functionalized phenyl rings. Our work shows that some parthenolide analogues with electron-withdrawing substituents on phenyl ring retain biological activities, yet without significant improvements. The most potent arylated parthenolide analogue was compound **22**, which had an IC<sub>50</sub> value of 15.2 ± 1.5 μM in an antiproliferative assay of HeLa cells. Parthenolide (**1**) showed moderate anti-MM-CSCs activity in a 3-D rBM assay (LC<sub>50</sub> = 10 μM). Unfortunately, its arylated derivative **22** was not as potent as

parthenolide itself. We believe that the steric encumbrance generated by the phenyl ring may negatively affect and interrupt the potency enhancement. However, both compounds retained selective cytotoxicity toward MM-CSCs versus non-tumorigenic cells. This selectivity can be lost by subtle structural changes (Table 2.4). Additional synthetic modification should be explored to further enhance the potency and bioavailability of parthenolide (**1**).

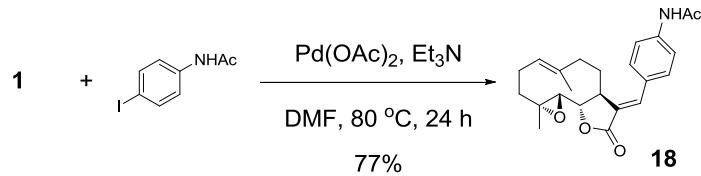
## 2.5 Experimental Details

### **Representative Reaction Procedure for Palladium-catalyzed Arylation of The**

**$\alpha$ -Methylene- $\gamma$ -lactone of Parthenolide.** A mixture of parthenolide (10.0 mg, 0.04 mmol), triethylamine (34.0  $\mu$ L, 0.24 mmol), and 4-iodoacetanilide (21.0 mg, 0.08 mmol) in DMF (200  $\mu$ L) was treated with palladium (II) acetate (0.5 mg, 0.002 mmol) and then heated at 80 °C under air. After 24 h, the reaction mixture was allowed to cool to rt, water (2 mL) was added, and the resultant mixture was extracted with EtOAc (2 mL  $\times$  5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash chromatography (19:1–7:3 hexanes/EtOAc) afforded the (*E*)-13-(4-acetamidylphenyl)-parthenolide product as a solid in 77% yield (11.8 mg).

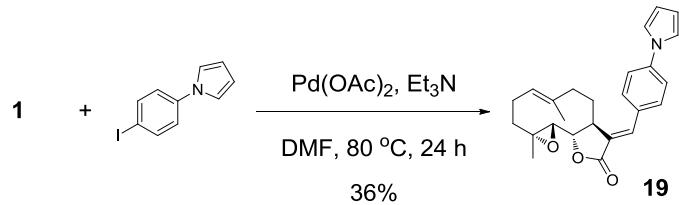


**(E)-13-(4-Ethylphenyl)-parthenolide 17.**<sup>107</sup> See representative reaction procedure. Triethylamine (6 equiv.) and 1-ethyl-4-iodobenzene (2 equiv.) were used. SiO<sub>2</sub> flash chromatography (6:2:2 hexanes/Et<sub>2</sub>O/EtOAc) afforded the title compound as a solid in 57% yield: mp 160–163 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 3.4 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.30 (dd, *J* = 12.0, 2.1 Hz, 1H), 3.96 (dd, *J* = 8.7, 6.7 Hz, 1H), 3.33–3.29 (m, 1H), 2.86 (d, *J* = 8.8 Hz, 1H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.48–2.40 (m, 1H), 2.25–2.17 (m, 5H), 1.68 (s, 3H), 1.46–1.38 (m, 1H), 1.31 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.21 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.1, 146.4, 138.3, 134.8, 130.8, 130.1 (2), 128.1 (2), 127.8, 125.1, 82.9, 66.5, 61.6, 46.8, 41.9, 36.1, 30.0, 28.8, 24.3, 17.5, 17.4, 15.2; IR (film) ν<sub>max</sub> 2963, 2930, 1750, 1643, 1193 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>23</sub>H<sub>28</sub>O<sub>3</sub> (M+H)<sup>+</sup> 353.2117, found 353.2115; [α]<sup>22</sup><sub>D</sub> +99 (*c* 0.67, CHCl<sub>3</sub>).

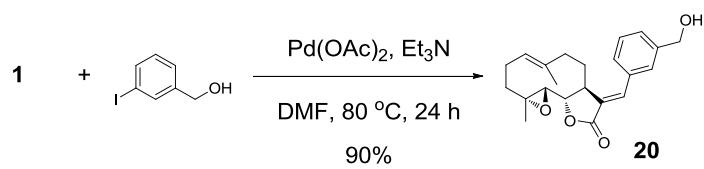


**(E)-13-(4-Acetamidylphenyl)-parthenolide 18.** See representative reaction procedure. Triethylamine (34.0 μL, 0.24 mmol) and *N*-(4-iodophenyl)acetamide (21.0 mg, 0.081 mmol) were used. SiO<sub>2</sub> flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 77% yield (11.8 mg). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 3.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 5.30 (dd, *J* = 11.5, 0.5 Hz, 1H), 3.96 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.29 (m, 1H), 2.85 (d, *J* = 8.5 Hz, 1H), 2.44 (m, 1H), 2.21 (s, 3H), 2.19 (m, 6H), 1.68 (s, 3H), 1.43 (m, 1H), 1.31 (s, 3H), 1.29 (m, 1H);

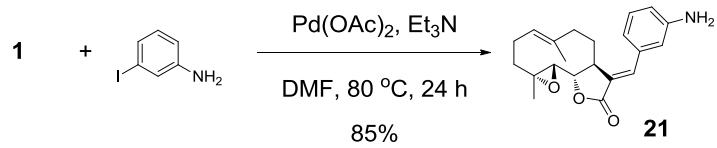
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.0, 168.3, 139.2, 137.5, 134.5, 130.8, 128.6, 127.3, 124.9, 118.9, 82.7, 66.3, 61.5, 46.6, 41.6, 35.8, 29.7, 24.5, 24.0, 17.2, 17.1; IR (film) ν<sub>max</sub> 3319, 2931, 1744, 1593, 1527, 1515, 1195 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>27</sub>NO<sub>4</sub> (M+H)<sup>+</sup> 382.2018, found 382.2023; [α]<sup>23</sup><sub>D</sub> +134 (*c* 0.98, CHCl<sub>3</sub>).



**(E)-13-(4-Pyrrolyphenyl)-parthenolide 19.** See representative reaction procedure. Triethylamine (23.0 μL, 0.16 mmol) and 1-(4-iodophenyl)-1H-pyrrole (12.0 mg, 0.044 mmol) were used. SiO<sub>2</sub> flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 36% yield (5.7 mg). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.67 (d, *J* = 3.5 Hz, 1H), 7.50–7.45 (m, 4H), 7.15 (t, *J* = 2.0 Hz, 2H), 6.40 (t, *J* = 2.0 Hz, 2H), 5.31 (dd, *J* = 11.5, 1.5 Hz, 1H), 3.98 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.33–3.30 (m, 1H), 2.86 (d, *J* = 8.5 Hz, 1H), 2.49–2.40 (m, 1H), 2.26–2.17 (m, 5H), 1.70 (s, 3H), 1.52–1.43 (m, 1H), 1.32 (s, 3H), 1.30–1.27 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 170.6, 141.0, 136.9, 134.4, 131.1 (2), 130.2, 128.4, 124.9, 119.5 (2), 118.7 (2), 111.1 (2), 82.7, 66.3, 61.4, 46.6, 41.7, 35.8, 29.8, 24.1, 17.2, 17.1; IR (film) ν<sub>max</sub> 2926, 1748, 1642, 1606, 1187 cm<sup>-1</sup>; [α]<sup>23</sup><sub>D</sub> +118 (*c* 0.48, CHCl<sub>3</sub>).

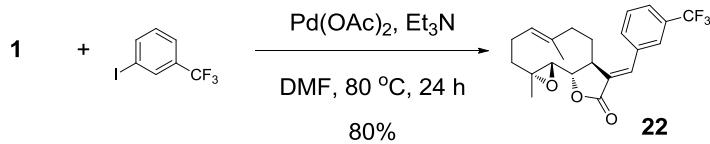


**(E)-13-(*m*-Benzyl alcohol)-parthenolide 20.** See representative reaction procedure. Triethylamine (34.0  $\mu$ L, 0.24 mmol) and 3-iodobenzyl alcohol (9.0  $\mu$ L, 0.060 mmol) were used.  $\text{SiO}_2$  flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 90% yield (12.9 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J$  = 3.5 Hz, 1H), 7.46 (s, 1H), 7.42 (t,  $J$  = 7.5 Hz, 1H), 7.38 (d,  $J$  = 7.5 Hz, 1H), 7.34 (d,  $J$  = 7.5 Hz, 1H), 7.30 (dd,  $J$  = 12.5, 2.5 Hz, 1H), 4.76 (d,  $J$  = 4.5 Hz, 1H), 3.94 (dd,  $J$  = 9.0, 7.0 Hz, 1H), 3.33–3.30 (m, 1H), 2.84 (d,  $J$  = 9.0 Hz, 1H), 2.46–2.37 (m, 1H), 2.26–2.09 (m, 5H), 2.04 (br s, 1H), 1.66 (s, 3H), 1.45–1.37 (m, 1H), 1.30 (s, 3H), 1.28 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 141.1, 137.8, 134.5, 133.5, 129.0, 128.9, 128.4, 127.8, 127.7, 124.8, 82.7, 66.2, 64.4, 61.5, 46.5, 41.5, 35.8, 29.8, 24.0, 17.2, 17.1; IR (film)  $\nu_{\text{max}}$  3437, 2930, 1749, 1643, 1202  $\text{cm}^{-1}$ ;  $[\alpha]^{24}_{\text{D}} +82$  ( $c$  1.08,  $\text{CHCl}_3$ ).

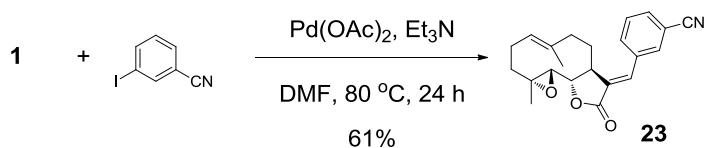


**(E)-13-(3-Aminophenyl)-parthenolide 21.<sup>107</sup>** See representative reaction procedure. Triethylamine (6 equiv.) and 3-iodoaniline (2 equiv.) were used.  $\text{SiO}_2$  flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 85% yield: mp 95–98 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J$  = 3.5 Hz, 1H), 7.20 (t,  $J$  = 7.6 Hz, 1H), 6.81 (d,  $J$  = 7.6 Hz, 1H), 6.70 (s, 1H), 6.69 (m, 1H), 5.27 (d,  $J$  = 12.2 Hz, 1H), 3.91 (dd,  $J$  = 8.7, 6.9 Hz, 1H), 3.78 (br s, 2H), 3.27 (m, 1H), 2.83 (d,  $J$  = 8.9 Hz, 1H), 2.42 (m, 1H), 2.25–2.15 (m, 5H), 1.68 (s, 3H), 1.40 (m, 1H), 1.31 (s, 3H), 1.27 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 146.5, 138.6, 134.9, 134.5, 129.3, 128.8, 124.9, 119.8, 116.3,

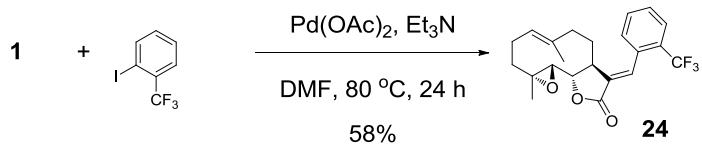
116.1, 83.0, 66.6, 61.6, 46.8, 41.9, 36.1, 30.2, 24.3, 17.5, 17.4; IR (film)  $\nu_{\text{max}}$  3460, 3368, 2928, 1743, 1640, 1208  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{25}\text{NO}_3$  ( $\text{M}^+$ ) 339.1834, found 339.1836;  $[\alpha]^{22}_{\text{D}} +87$  ( $c$  0.99,  $\text{CHCl}_3$ ).



**(E)-13-(3-Trifluoromethylphenyl)-parthenolide** **22.**<sup>107</sup> See representative reaction procedure. Triethylamine (6 equiv.) and 3-iodobenzotrifluoride (2 equiv.) were used.  $\text{SiO}_2$  flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 80% yield. Recrystallization from hexanes/chloroform provided a crystalline solid suitable for X-ray structure analysis: mp 118–123  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68–7.56 (m, 5H), 5.30 (dd,  $J = 12.1, 2.2$  Hz, 1H), 3.98 (dd,  $J = 8.9, 6.7$  Hz, 1H), 3.33 (m, 1H), 2.85 (d,  $J = 8.9$  Hz, 1H), 2.43 (m, 1H), 2.25–2.12 (m, 4H), 2.03 (m, 1H), 1.67 (s, 3H), 1.45 (m, 1H), 1.32 (s, 3H), 1.29 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 136.2, 134.5, 134.3, 133.3, 131.2, 131.1 (q,  $^2J_{\text{CF}} = 33$  Hz, 1C), 129.3, 126.1 (q,  $^3J_{\text{CF}} = 4$  Hz, 1C), 125.8 (q,  $^3J_{\text{CF}} = 4$  Hz, 1C), 125.2, 123.7 (q,  $^1J_{\text{CF}} = 271$  Hz, 1C), 83.1, 66.4, 61.7, 46.7, 41.6, 36.1, 30.0, 24.2, 17.4, 17.3;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.7; IR (film)  $\nu_{\text{max}}$  2933, 1755, 1651, 1329, 1193  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{23}\text{F}_3\text{O}_3$  ( $\text{M}+\text{H}^+$ ) 393.1678, found 393.1680;  $[\alpha]^{25}_{\text{D}} +18$  ( $c$  1.10,  $\text{CHCl}_3$ ).

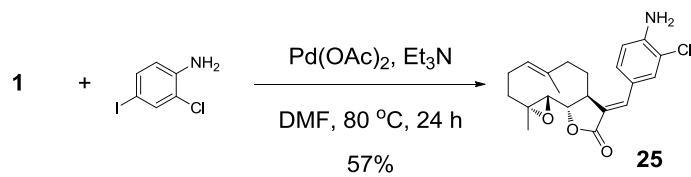


**(E)-13-(3-Cyanophenyl)-parthenolide 23.** See representative reaction procedure. Triethylamine (23.0  $\mu$ L, 0.16 mmol) and 3-iodobenzonitrile (10.0 mg, 0.044 mmol) were used.  $\text{SiO}_2$  flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 61% yield (8.6 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70–7.56 (m, 5H), 5.30 (dd,  $J$  = 11.5, 1.0 Hz, 1H), 3.98 (dd,  $J$  = 8.5, 7.0 Hz, 1H), 3.30 (m, 1H), 2.84 (d,  $J$  = 9.0 Hz, 1H), 2.43 (m, 1H), 2.26–2.16 (m, 4H), 1.98 (d,  $J$  = 15.0 Hz, 1H), 1.68 (s, 3H), 1.48 (m, 1H), 1.31 (s, 3H), 1.30 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 135.2, 135.0, 134.4, 133.8, 132.8, 132.7, 132.2, 129.7, 125.4, 118.0, 113.2, 83.2, 66.4, 61.8, 46.7, 41.7, 36.1, 30.2, 24.3, 17.5, 17.4; IR (film)  $\nu_{\text{max}}$  2928, 2231, 1754, 1649, 1201  $\text{cm}^{-1}$ ;  $[\alpha]^{22}_{\text{D}} +21$  ( $c$  1.17,  $\text{CHCl}_3$ ).

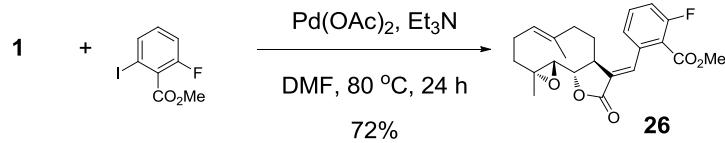


**(E)-13-(2-Trifluoromethylphenyl)-parthenolide 24.<sup>107</sup>** See representative reaction procedure. Triethylamine (6 equiv.) and 2-iodobenzotrifluoride (2 equiv.) were used.  $\text{SiO}_2$  flash chromatography (7:3 hexanes/THF) afforded the title compound as a solid in 58% yield. Recrystallization from  $\text{CDCl}_3$  provided a crystalline solid suitable for X-ray structure analysis: mp 229–232  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (s, 1H), 7.75 (d,  $J$  = 7.8 Hz, 1H), 7.61 (t,  $J$  = 7.3 Hz, 1H), 7.52–7.45 (m, 2H), 5.21 (d,  $J$  = 10.4 Hz, 1H), 3.95 (dd,  $J$  = 9.0, 7.1 Hz, 1H), 3.25–3.21 (m, 1H), 2.80 (d,  $J$  = 6.7 Hz, 1H), 2.43–2.35 (m, 1H), 2.25–2.15 (m, 2H), 1.90–1.84 (m, 2H), 1.73 (m, 1H), 1.61 (s, 3H), 1.39–1.33 (m, 1H), 1.28 (s, 3H), 1.26 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.7, 134.8,

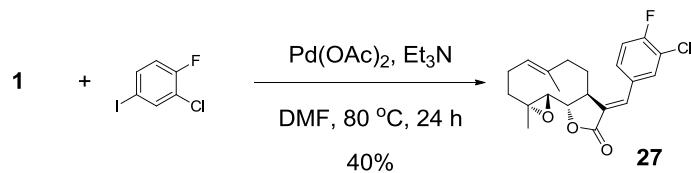
134.4, 133.1, 132.9, 131.6, 129.1, 129.0, 128.7 (q,  $^2J_{\text{CF}} = 44$  Hz, 1C), 126.3 (q,  $^3J_{\text{CF}} = 5$  Hz, 1C), 124.7, 123.6 (q,  $^1J_{\text{CF}} = 272$  Hz, 1C), 83.0, 66.6, 61.5, 46.4, 41.3, 36.2, 30.0, 24.1, 17.3(2);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -60.7; IR (film)  $\nu_{\text{max}}$  2930, 1759, 1655, 1316, 1163  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{23}\text{F}_3\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$  393.1678, found 393.1685;  $[\alpha]^{25}_{\text{D}} +43$  ( $c$  0.77,  $\text{CHCl}_3$ ).



**(E)-13-(4-Amino-3-chlorophenyl)-parthenolide 25.** See representative reaction procedure. Triethylamine (34.0  $\mu\text{L}$ , 0.24 mmol) and 2-chloro-4-iodoaniline (20.4 mg, 0.081 mmol) were used.  $\text{SiO}_2$  flash chromatography (6:2:2 hexanes/EtOAc/Et<sub>2</sub>O) afforded the title compound as a solid in 57% yield (8.5 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (d,  $J = 3.5$  Hz, 1H), 7.35 (d,  $J = 2.0$  Hz, 1H), 7.15 (dd,  $J = 8.5, 2.0$  Hz, 1H), 6.78 (d,  $J = 8.5$  Hz, 1H), 5.32 (dd,  $J = 12.0, 2.0$  Hz, 1H), 4.40 (br s, 2H), 3.96 (dd,  $J = 8.5, 6.5$  Hz, 1H), 3.26–3.23 (m, 1H), 2.84 (d,  $J = 8.5$  Hz, 1H), 2.48–2.39 (m, 1H), 2.26–2.15 (m, 5H), 1.70 (s, 3H), 1.47–1.41 (m, 1H), 1.44 (s, 3H), 1.29 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 144.0, 136.9, 134.5, 130.8, 130.3, 125.3, 124.9, 123.8, 118.5, 114.8, 82.6, 66.3, 61.4, 46.6, 41.6, 35.8, 29.7, 24.1, 17.2, 17.1; IR (film)  $\nu_{\text{max}}$  3469, 3360, 2930, 1740, 1617, 1190  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{24}\text{ClNO}_3$  ( $\text{M}$ ) $^+$  373.1445, found 373.1445;  $[\alpha]^{22}_{\text{D}} +54$  ( $c$  0.71,  $\text{CHCl}_3$ ).

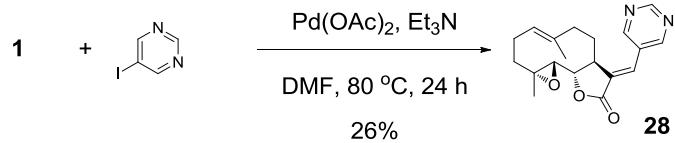


**(E)-13-(3-Fluoro-2-methoxycarbonyl)-parthenolide 26.**<sup>107</sup> See representative reaction procedure. Triethylamine (6 equiv.) and methyl 2-fluoro-6-iodobenzoate (2 equiv.) were used. SiO<sub>2</sub> flash chromatography (7:3 hexanes/THF) afforded the title compound as a solid in 72% yield: mp 180–183 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.71 (d, *J* = 3.8 Hz, 1H), 7.49 (td, *J* = 8.1, 5.4 Hz, 1H), 7.20–7.15 (m, 2H), 5.20 (dd, *J* = 12.1, 2.2 Hz, 1H), 3.94 (s, 3H), 3.96–3.92 (m, 1H), 3.22–3.19 (m, 1H), 2.79 (d, *J* = 9.0 Hz, 1H), 2.44–2.35 (m, 1H), 2.22–2.14 (m, 2H), 1.93–1.89 (m, 2H), 1.84–1.80 (m, 1H), 1.62 (s, 3H), 1.44–1.37 (m, 1H), 1.28 (s, 3H), 1.32–1.23 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 169.8, 164.6, 160.5 (d, <sup>1</sup>J<sub>CF</sub> = 254 Hz, 1C), 135.9, 135.1, 134.8, 132.5, 131.9 (d, <sup>3</sup>J<sub>CF</sub> = 9 Hz, 1C), 124.7, 124.0, 121.0 (d, <sup>2</sup>J<sub>CF</sub> = 15 Hz, 1C), 117.0 (d, <sup>2</sup>J<sub>CF</sub> = 22 Hz, 1C), 83.0, 66.6, 61.6, 52.9, 46.4, 41.3, 36.2, 30.4, 24.1, 17.3 (2); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -111.1; IR (film) ν<sub>max</sub> 2952, 2931, 1756, 1731, 1657, 1469, 1204 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>25</sub>FO<sub>5</sub> (M+Na)<sup>+</sup> 423.1584, found 423.1580; [α]<sup>26</sup><sub>D</sub> +42 (*c* 0.97, CHCl<sub>3</sub>).



**(E)-13-(3-Chloro-4-fluorophenyl)-parthenolide 27.** See representative reaction procedure. Triethylamine (34.0 μL, 0.24 mmol) and 2-chloro-1-fluoro-4-iodobenzene (15.0 μL, 0.081 mmol) were used. SiO<sub>2</sub> flash chromatography (6:2:2

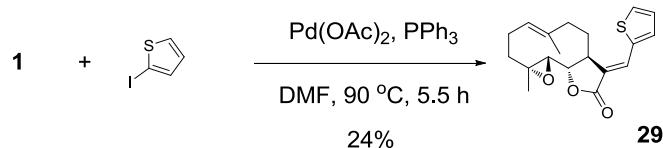
hexanes/EtOAc/Et<sub>2</sub>O) afforded the title compound as a solid in 40% yield (6.1 mg). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.57 (d, *J* = 3.5 Hz, 1H), 7.49 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.33–7.30 (m, 1H), 7.22 (t, *J* = 8.5 Hz, 1H), 5.29 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.96 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.27 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.85 (d, *J* = 9.1 Hz, 1H), 2.49–2.46 (m, 1H), 2.27–2.16 (m, 4H), 2.07 (m, 1H), 1.70 (s, 3H), 1.50–1.43 (m, 1H), 1.32 (s, 3H), 1.29 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 170.1, 159.2 (d, <sup>1</sup>*J*<sub>CF</sub> = 253.0 Hz, 1C), 135.2, 134.3, 131.3, 130.5 (d, <sup>3</sup>*J*<sub>CF</sub> = 4.1 Hz, 1C), 130.1, 129.8 (d, <sup>3</sup>*J*<sub>CF</sub> = 7.4 Hz, 1C), 125.0, 121.4 (d, <sup>2</sup>*J*<sub>CF</sub> = 18.1 Hz, 1C), 116.8 (d, <sup>2</sup>*J*<sub>CF</sub> = 21.5 Hz, 1C), 82.9, 66.2, 61.4, 46.4, 41.5, 35.8, 29.8, 24.0, 17.2, 17.1; IR (film) ν<sub>max</sub> 2931, 1754, 1650, 1499, 1192 cm<sup>-1</sup>; [α]<sub>D</sub><sup>25</sup> +94 (*c* 0.51, CHCl<sub>3</sub>).



**(E)-13-(5-Pyrimidine)-parthenolide 28.** See representative reaction procedure.

Triethylamine (34.0 μL, 0.24 mmol), 5-iodopyrimidine (12.8 mg, 0.081 mmol), triphenylphosphine (15.8 mg, 0.06 mmol) were used. SiO<sub>2</sub> flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 26% yield (3.4 mg). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 8.82 (s, 2H), 7.57 (d, *J* = 4.0 Hz, 1H), 5.29 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.00 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.34–3.31 (m, 1H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.44 (dq, *J* = 13.5, 5.5 Hz, 1H), 2.27–2.17 (m, 4H), 2.03–1.98 (m, 1H), 1.60–1.52 (m, 1H), 1.57 (s, 3H), 1.32 (s, 3H), 1.32–1.24 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 169.9, 159.0, 157.4 (2), 134.7, 134.5, 130.7, 128.4, 126.0, 83.5, 66.7, 62.2, 47.2, 42.1,

36.4, 30.6, 24.7, 17.9, 17.8; IR (film)  $\nu_{\text{max}}$  3034, 2972, 2936, 1751, 1652, 1213, 1186  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ) 326.1630, found 326.1633;  $[\alpha]^{24}_D +56$  ( $c$  0.28,  $\text{CHCl}_3$ ).



**(E)-13-(2-Thiophene)-parthenolide 29.** A mixture of parthenolide (10.0 mg, 0.04 mmol), triphenylphosphine (5.3 mg, 0.02 mmol), and potassium carbonate (16.7 mg, 0.12 mmol), and 2-iodothiophene (9.0  $\mu\text{L}$ , 0.08 mmol) in DMF (200  $\mu\text{L}$ ) was treated with palladium (II) acetate (0.50 mg, 0.002 mmol) and then heated at 90  $^\circ\text{C}$  under air. After 24 h, the reaction mixture was allowed to cool to rt, water (2 mL) was added, and the resultant mixture was extracted with EtOAc (2 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 24% yield (3.2 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (d,  $J = 3.0$  Hz, 1H), 7.59 (d,  $J = 5.0$  Hz, 1H), 7.33 (d,  $J = 3.5$  Hz, 1H), 7.16 (dd,  $J = 5.0, 4.0$  Hz, 1H), 5.33 (dd,  $J = 12.5, 3.0$  Hz, 1H), 4.02 (dd,  $J = 8.5, 6.0$  Hz, 1H), 3.14–3.10 (m, 1H), 2.83 (d,  $J = 8.5$  Hz, 1H), 2.50–2.41 (m, 3H), 2.33 (dd,  $J = 13.0, 6.0$  Hz, 1H), 2.27–2.25 (m, 1H), 2.21–2.15 (m, 1H), 1.74 (s, 3H), 1.68–1.60 (m, 1H), 1.34 (s, 3H), 1.33–1.25 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4, 137.3, 135.0, 133.7, 131.2, 131.0, 128.5, 126.5, 126.0, 83.2, 66.7, 62.1, 47.3, 42.7, 36.3, 31.6, 24.8, 18.0, 17.9; IR (film)  $\nu_{\text{max}}$  2926, 2858, 1747, 1632, 1189  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{O}_3\text{S}$  ( $\text{M}+\text{H}^+$ ) 331.2097, found 331.1368;  $[\alpha]^{24}_D +66$  ( $c$  0.24,  $\text{CHCl}_3$ ).

**CHAPTER 3. GENERATION OF ALPHA,ALPHA-DIFLUOROENOLATES VIA  
TRIFLUOROACETATE RELEASE PROCESS FOR ALDOL REACTIONS**

### 3.1 Introduction

Our next approach for the modification of parthenolide (**1**) was to change the lactone moiety of parthenolide (**1**) to an  $\alpha,\alpha$ -difluoro ketone (**42**) (Figure 3.1 (1)). We attempted a Reformatsky reaction<sup>118</sup> to open the lactone ring. However, with Reformatsky reaction conditions, three unexpected products (compounds **44**, **45**, and **46**) were isolated (Figure 3.1 (2)). The by-products were generated via rearrangement of the macrocyclic ring moiety of parthenolide (**1**). Although natural products have long been used as a source for drug discovery, modifying natural products is usually very challenging because of their complex and sensitive structure. Therefore, we decided to develop a novel reaction methodology to generate fluorinated reactive nucleophiles, such as  $\alpha,\alpha$ -difluoroenolates, under extremely mild conditions.

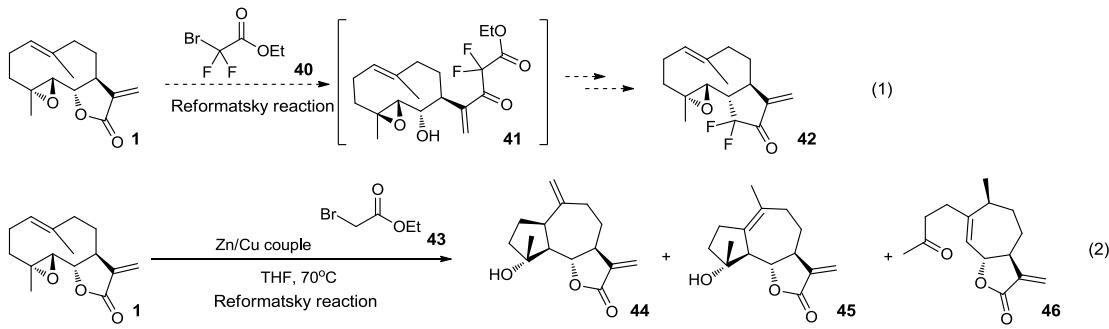
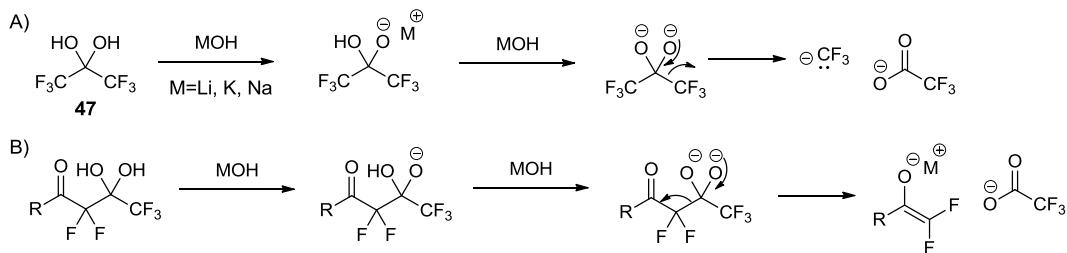


Figure 3.1 Fluorine incorporation strategy to parthenolide (**1**) utilizing the Reformatsky reaction.

### 3.2 Chemistry

Our strategy to generate  $\alpha,\alpha$ -difluoroenolates is based on the decomposition of hexafluoroacetone hydrate (**47**) reported by Prager and co-workers.<sup>119</sup> When hexafluoroacetone hydrate (**47**) was treated with one equivalent of base, it formed a stable metal complex. Then, when one additional equivalent of base was added, the stable metal complex rapidly fragmented into trifluoroacetate and trifluoromethyl anion (Scheme 3.1(A)). This result leads us to the hypothesis that an  $\alpha,\alpha$ -difluoroenolate may be generated by an analogous process when one fluorine of hexafluoroacetone hydrate is replaced with a carbonyl group (Scheme 3.1(B)).



Scheme 3.1 Trifluoroacetate Release Processes

(A) Release of trifluoroacetate from hexafluoroacetone hydrate.<sup>119</sup> (B) Release of trifluoroacetate from highly  $\alpha$ -fluorinated *gem*-diols and generation of  $\alpha,\alpha$ -difluoroenolates.<sup>54</sup>

To test our hypothesis, we needed to prepare highly  $\alpha$ -fluorinated *gem*-diols. After stirring Selectfluor<sup>TM</sup> with numerous 1,1,1-trifluoro-2,4-diones **48–52** for 24 h at room temperature, highly  $\alpha$ -fluorinated products **53–57** were prepared with excellent yields (88–99%) (Table 3.1).<sup>54</sup> The formation of highly  $\alpha$ -fluorinated *gem*-diols can also be achieved from commercially available methyl ketones (Table 3.2).<sup>54</sup> 1,1,1-Trifluoro-2,4-dione intermediates derived from methyl ketones need not be purified to react with

Selectfluor<sup>TM</sup>. Therefore, some of *gem*-diols were prepared over two steps with a single purification. In order to verify the structure and confirm the presence of the *gem*-diol, we obtained an X-ray crystal structure of compound **57**. The *gem*-diol was clearly present on this structure (Table 3.1).

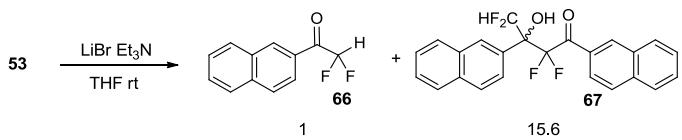
Table 3.1 Formation of Highly  $\alpha$ -Fluorinated *gem*-Diols from Commercially Available 1,1,1-Trifluoro-2,4-diones<sup>54</sup>

entry	R <sub>1</sub>	product	yield	entry	R <sub>1</sub>	product	yield
1			99%	4			91%
2			97%	5			93%
3			88%				X-ray

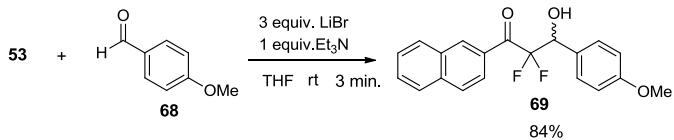
Table 3.2 Formation of Highly  $\alpha$ -Fluorinated *gem*-Diols from Commercially Available Methyl Ketones<sup>54</sup>

entry	R <sub>1</sub>	product	yield
1			99%
2			88% (2 step yield)
3			61% (2 step yield)
4			83%

With those *gem*-diols **53–57** in hand, a series of different basic reaction conditions were investigated to initiate trifluoroacetate release. With *gem*-diol **53**, trifluoroacetate release occurred instantaneously and difluoromethyl ketone **66** was formed as a product along with the dimer **67** (Scheme 3.2). Unlike other bases, when Et<sub>3</sub>N was used as a base, fragmentation occurred extremely slowly; it took overnight to completely fragment the *gem*-diols even with 20 equiv. of Et<sub>3</sub>N. Interestingly, the fragmentation process occurred instantaneously when both LiBr and Et<sub>3</sub>N were used. Moreover, a self-condensed product **67** was formed as a major product under these reaction conditions (Scheme 3.2). This result indicates that a generated difluoroenolate acted as nucleophile under LiBr/Et<sub>3</sub>N reaction conditions. We assumed that an aldol reaction can be achieved by using an aldehyde as an electrophile. We investigated and optimized an aldol process using the aldehyde **68**. Under the optimized reaction conditions, the aldol adduct was obtained in high yield in three minutes (Scheme 3.3). This aldol reaction is extremely versatile and various aldehydes **70–75** readily participated (Table 3.3).



Scheme 3.2 Base-Promoted Release of Trifluoroacetate<sup>54</sup>  
The ratio between **66** and **67** was measured by <sup>1</sup>H NMR integration.



Scheme 3.3 Trifluoroacetate-Release Followed by Aldol Reaction<sup>54</sup>

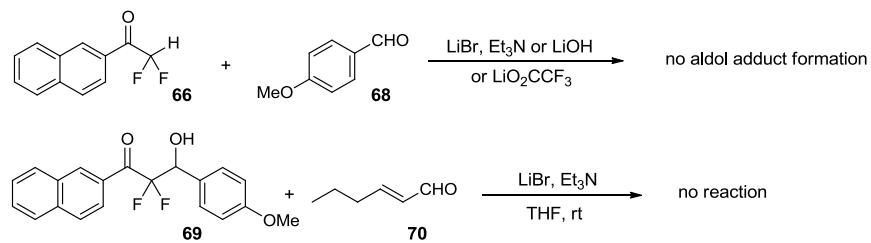
Table 3.3 Aldol Reactions with  $\alpha,\alpha$ -Difluoroenolates<sup>54</sup>

entry	R <sub>1</sub>	R <sub>2</sub> CHO	product	yield
1				84%
2				85%
3				89%
4				74%
5				79%
6				63%
7				55%
8				78%
9				89%
10				64%
11				89%
12				89%

The reaction was compatible with various functional groups. In general, all reactions gave moderate to good yields. Highly  $\alpha$ -fluorinated compounds containing aromatic (**53**), substituted aromatic (**54**), and aromatic bicyclic (**55**) substituents were tested. Also, unsaturated (**62**), saturated (**56**), saturated bulky (**57**, **63**), and a  $\alpha$ -

stereocenter-containing substituent (**64**) were tested. The reaction conditions for generating  $\alpha,\alpha$ -difluoroenolates were very mild and fully compatible with all of these substrates. Importantly, only a minimal amount of  $\alpha$ -epimerization was observed. (Table 3.3 entries 7 and 11). When unsaturated aldehydes were used, 1,2-addition products were generated exclusively (Table 3.3 entry 2, 5, and 10). This reactivity was maintained with the more sensitive  $\alpha,\beta,\gamma,\delta$ -unsaturated dienal **24** as well (Table 3.3 entries 3, 8, and 9). Also, no  $\beta$ -elimination occurred during the reaction (Table 3.3 entry 7).

A series of control experiments have been conducted to probe that the free difluoromethyl ketones are not involved in the aldol reaction (Scheme 3.4). The fact that the  $\alpha,\alpha$ -difluoromethyl ketone did not react with aldehyde using LiBr/Et<sub>3</sub>N or other basic reaction conditions indicated that the reactive species originated from the highly  $\alpha$ -fluorinated *gem*-diol starting materials. A retro-aldol process has not been observed using LiBr and Et<sub>3</sub>N with the aldol product **69** (Scheme 3.4). The results of control experiments further supports that our reaction conditions provide a powerful yet mild process for generating reactive  $\alpha,\alpha$ -difluoroenolates.



Scheme 3.4 Control Experiments<sup>54</sup>

### 3.3 Biological Evaluation

The assembled aldol adducts have a unique pharmacophoric moiety;  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones. In aqueous environments, electron-deficient difluoromethyl ketones of the aldol adduct will form a hydrate. Moreover, one of the hydroxyl groups of the *gem*-diol is expected to be ionized at biological pH. Based on these speculations, we envisioned that  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones could serve as surrogates for the  $\gamma$ -aminobutyric acid moiety of baclofen; the fluorinated ketone as an alternative to the carboxylate of baclofen and the hydroxyl group of the aldol adduct as an alternative to amine of baclofen (Figure 3.2). Therefore, the aldol adducts were tested as non-GABA-based agonists of the GABA<sub>B</sub> receptor.<sup>120</sup>

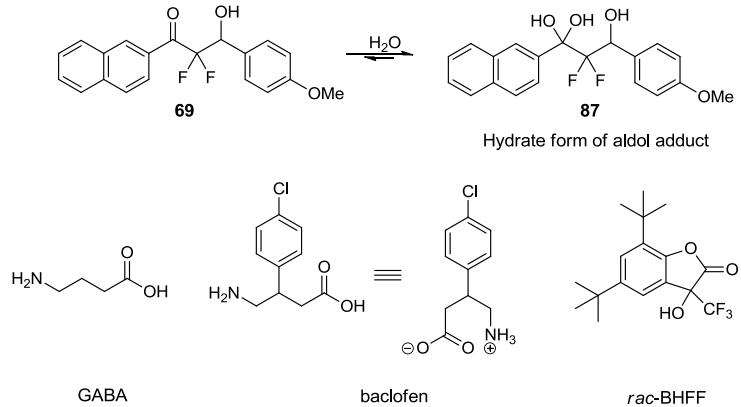


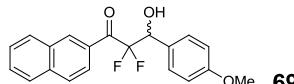
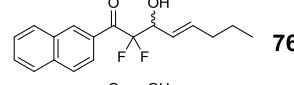
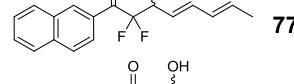
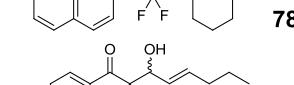
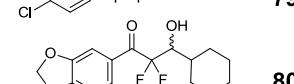
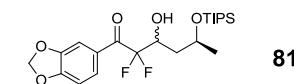
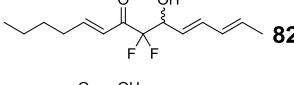
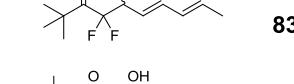
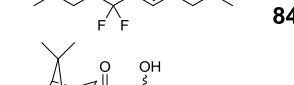
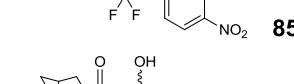
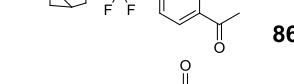
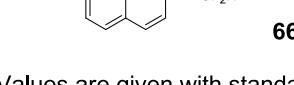
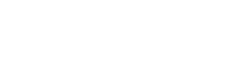
Figure 3.2 Rationale for biological investigation of  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones.<sup>120</sup>

$\gamma$ -Aminobutyric acid (GABA) is one of the most important neurotransmitters in the central nervous system and it regulates the signal transduction of neurons. There are two types of GABA receptors, ionotropic GABA<sub>A</sub> receptor and metabotropic GABA<sub>B</sub> receptor. Because the GABA<sub>B</sub> receptor is a G protein-coupled receptor, it is involved in

slow synaptic inhibition. Depending on the type of G protein, GABA<sub>B</sub> receptors can modulate Ca<sup>2+</sup> ion influx, K<sup>+</sup> ion influx, and cAMP formation; G $\beta\gamma$  represses Ca<sup>2+</sup> ion influx in presynaptic neurons and triggers K<sup>+</sup> ion influx in postsynaptic neurons. G<sub>i</sub> $\alpha$  and G<sub>o</sub> $\alpha$  inhibit the formation of cAMP. The CRE-Luc system is a well-established method for monitoring cellular level of cAMP. Therefore, GABA<sub>B</sub> receptor activity was measured by a luciferase assay. On the other hand, the GABA<sub>A</sub> receptor is involved in fast synaptic inhibition and is a ligand-gated Cl<sup>-</sup> ion channel. Therefore, GABA<sub>A</sub> receptor activity was measured by whole-cell voltage-clamp experiments. GABA, baclofen, and *rac*-BHFF were selected for positive controls; *rac*-BHFF is known allosteric modulator of the GABA<sub>B</sub> receptor. These cell-based pharmacology studies were performed by Prof. Gregory H. Hockerman's group in the Medicinal Chemistry and Molecular Pharmacology department.

Interestingly,  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones showed selective agonistic activity on GABA<sub>B</sub> receptors (Table 3.4). The naphthyl aldol adducts **69–78** displayed moderate activity and the adamantly analogue **86** showed the best agonistic activity (EC<sub>50</sub> = 22.6  $\mu$ M) in the GABA<sub>B</sub> assay. Inactive analogues **79–85** highlight the importance of the substituents neighboring the  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketone moiety for the activity. Simple difluoroketone **66** was also inactive, which proves the importance of the  $\beta$ -hydroxy moiety for the activity. Further expansion of the scope of aldol adducts will lead us to find a better lead compound in due course.

Table 3.4 GABA<sub>B</sub> and GABA<sub>A</sub> Assay Data for  $\beta$ -Hydroxy- $\alpha,\alpha$ -Difluoromethyl Ketones<sup>120</sup>

compd	GABA <sub>B</sub> EC <sub>50</sub> ( $\mu$ M) <sup>a</sup>	GABA <sub>A</sub> EC <sub>50</sub> ( $\mu$ M) <sup>a</sup>
baclofen	1.7 ± 0.10	>100
rac-BHFF	1.7 ± 0.10	>100
GABA	0.53 ± 0.33	2.30 ± 0.59
 69	61.8 ± 3.01	>100
 76	66.9 ± 1.19	>100
 77	99.3 ± 3.78	>100
 78	53.5 ± 1.76	>100
 79	>100	>100
 80	nd	nd
 81	>100	nd
 82	>100	nd
 83	>100	nd
 84	nd	nd
 85	nd	nd
 86	22.6 ± 1.69	>100
 66	>100	nd

<sup>a</sup> Values are given with standard error. nd is not determined.

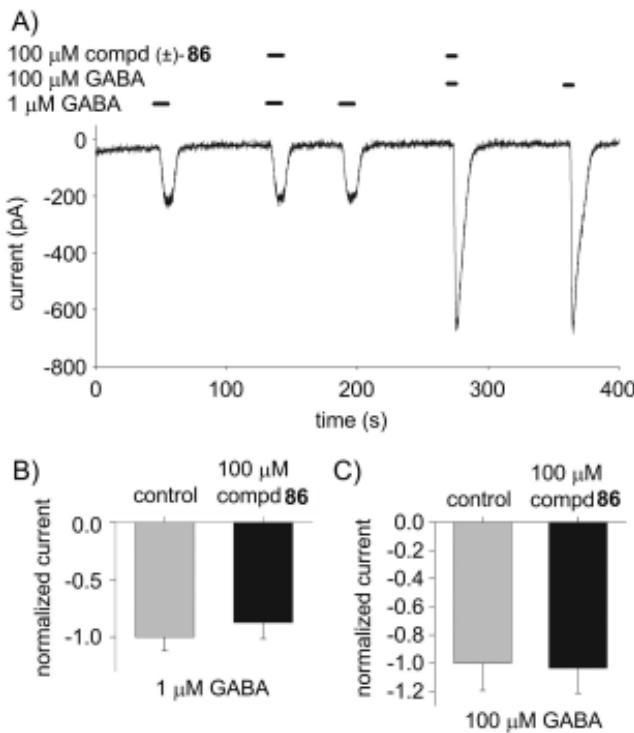


Figure 3.3 No potentiating or antagonizing effect of  $(\pm)$ -86 was observed at the GABA<sub>A</sub> receptor in presence of the natural ligand GABA<sup>120</sup>

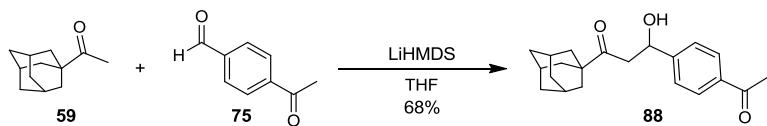
(A) The current trace was recorded from a cell transfected with the GABA<sub>A</sub> receptor subunits. Solid bars represent application of the indicated compounds to the cell.

(B) Normalized current amplitude (mean  $\pm$  SE; N = 5) which is stimulated by 1  $\mu$ M GABA.

(C) Normalized current amplitude (mean  $\pm$  SE; N = 5) which is stimulated by 100  $\mu$ M GABA.

The receptor subtype specific activity of  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones was further confirmed by whole-cell voltage-clamp experiments on cells expressing GABA<sub>A</sub> receptors. 1  $\mu$ M or 100  $\mu$ M GABA was applied along with or without 100  $\mu$ M  $(\pm)$ -86 to measure the amplitude of stimulation of Cl<sup>-</sup> current. In any case, the Cl<sup>-</sup> current was not affected by  $(\pm)$ -86 (Figure 3.3). These results further support the hypothesis that  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones have selective activity only against GABA<sub>B</sub> receptors.

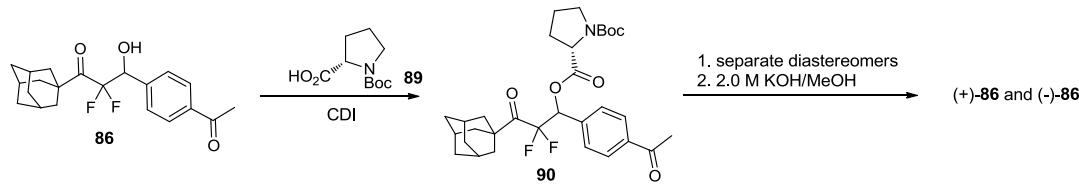
To prove the importance of the difluoroketone as a key pharmacophore, a non-fluorinated derivative of aldol adduct **86** had been synthesized by the aldol reaction of 1-adamantyl methyl ketone with 4-acetylbenzaldehyde (Scheme 3.5). As expected, the compound **86** without the two fluorines did not show the agonistic activity toward GABA<sub>B</sub> receptors. Moreover, this result indicates that  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones are novel non-GABA-based agonists of the GABA<sub>B</sub> receptor. Unlike GABA<sub>A</sub> receptors, selective modulators of the GABA<sub>B</sub> receptor are rare. Our studies of  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones against GABA<sub>B</sub> receptors will extend the structure-activity data for GABA<sub>B</sub> agonists beyond baclofen based GABA<sub>B</sub> agonists.



Scheme 3.5 Synthesis of Non-fluorinated Analogue **88**<sup>120</sup>

The most active hit from the biological assay, aldol adduct **86**, was further investigated. Because racemic mixtures were formed during the trifluoroacetate-release aldol process, we decided to isolate each enantiomer (Scheme 3.6). The racemic mixture of compound **86** was esterified with (*S*)-Boc-proline using CDI and each diastereomer was separated by prep. TLC. Upon saponification of each diastereomer, (+)-**86** ( $[\alpha]^{23}_D$  +36.0 (c 0.667, CHCl<sub>3</sub>)) and (-)-**86** ( $[\alpha]^{23}_D$  -35.8 (c 0.558, CHCl<sub>3</sub>)) were isolated and tested for pharmacological activity. The dose-response curves of the individual enantiomers along with racemic mixture were obtained (Figure 3.4). (+)-Enantiomer **86** ( $EC_{50} = 15.9 \pm 1.84 \mu M$ ) was more potent than the (-)-enantiomer **86** ( $EC_{50} = 37.8 \pm 0.78 \mu M$ ) and its potency is within 10-fold of (-)-baclofen ( $EC_{50} = 1.0 \pm 0.40 \mu M$ ). Moreover,

both enantiomers did not show cytotoxicity in an MTS cell viability assay. Therefore, we chose aldol adduct **86** as a key lead for additional development.



Scheme 3.6 Separation of Enantiomers of Compound **86**<sup>120</sup>

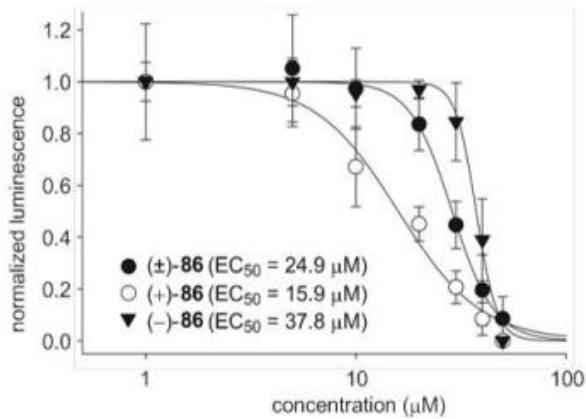


Figure 3.4 Dose-response curves for (+)-**86**, (-)-**86**, and (±)-**86** against the GABA<sub>B</sub> receptor.<sup>120</sup>

Rodent startle models, including plain acoustic startle and fear-potentiated startle, were used to predict the validity of the identified potential drug candidate, compound **86**, for treating clinical anxiety disorders. These behavioral pharmacology studies were performed by the Prof. Julia A. Chester group in the Department of Psychological Sciences. The high-alcohol preference mice (HAP2) were used to test (±)-**86** (Figure 3.5). (±)-Baclofen was selected as a reference and the known GABA<sub>B</sub> allosteric activator, *rac-BHFF*, was also used as a positive control. In experiment 1, mice were pretreated by

either vehicle or ( $\pm$ )-baclofen (7.5 mg/kg i.p.) 25 min. before the test session. As expected, ( $\pm$ )-baclofen significantly reduced the startle response (Figure 3.5(A)). In experiment 2, mice were pretreated by vehicle, *rac*-BHFF (12.5 mg/kg i.p.), or ( $\pm$ )-**86** (36 mg/kg i.p.) 25 min. before the test session. Both *rac*-BHFF and ( $\pm$ )-**86** reduced the startle response on both noise-alone and light + noise trials (Figure 3.5(B)). These results suggest anxiolytic-type effects of ( $\pm$ )-**86**. It should be noted that these reductions might be the result of the muscle-relaxant effects of these drugs and further studies are needed to validate our preliminary results.

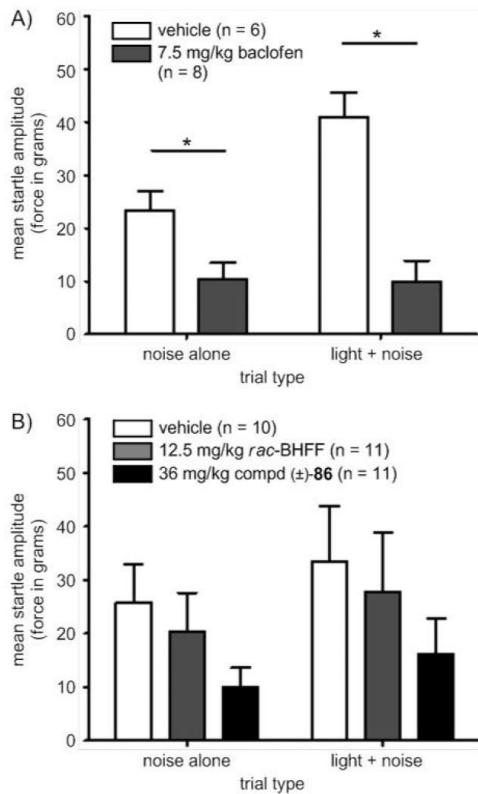
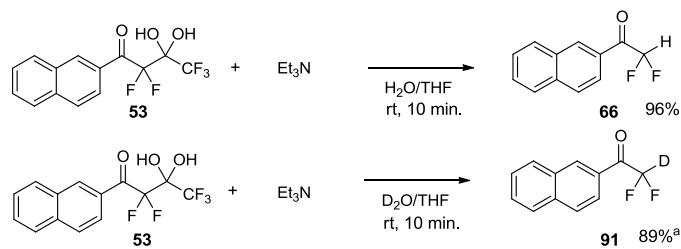


Figure 3.5 Mean ( $\pm$  sem) startle amplitude measured as force in grams in HAP2 mice.<sup>120</sup> Effects of drug treatment on startle response amplitude were measured. (A) Vehicle or ( $\pm$ )-baclofen (7.5 mg/kg i.p.) treatment effect on HAP2 mice were measured on both the noise-alone and light + noise trials. (B) Vehicle, *rac*-BHFF (12.5 mg/kg i.p.), or ( $\pm$ )-10 (36 mg/kg i.p.) treatment effect on HAP2 mice were measured on both the noise-alone and light + noise trials. \* indicates  $p < 0.05$ .

### 3.4 Further Studies

Studies to apply our trifluoroacetate-release process to prepare other classes of molecules are currently underway. After monitoring the formation of  $\alpha,\alpha$ -difluoromethyl ketone **66**, we hypothesized that a variety of  $\alpha,\alpha$ -difluoromethyl ketones can be assembled via the trifluoroacetate-release process. To test the hypothesis, new reaction conditions for the trifluoroacetate-release process were designed. Water was used as a solvent and a proton source, and LiBr was removed from the reaction, because LiBr can activate the carbonyl moiety of **53** and generate the self-condensed product **67**. These novel reaction conditions gave us the desired product **66** in excellent yield (Scheme 3.7). Deuterium incorporation is another key interest in medicinal and analytical chemistry. Therefore, we also tried to make  $\alpha,\alpha$ -difluoromethyl- $\alpha$ -deutero ketone **91** by replacing H<sub>2</sub>O to D<sub>2</sub>O. This novel method produced the  $\alpha,\alpha$ -difluoro- $\alpha$ -deutero product **91** with quantitative conversion as expected (Scheme 3.7).

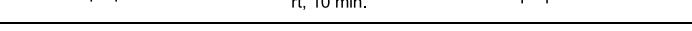
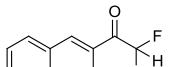
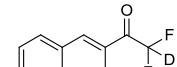
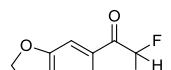
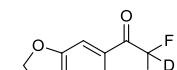
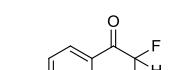
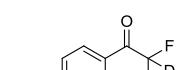
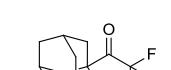
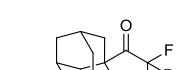
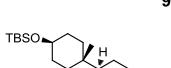
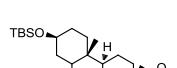


Scheme 3.7 Mild and efficient method for selectively forming  $\alpha,\alpha$ -difluoromethyl ketone and  $\alpha,\alpha$ -difluoromethyl- $\alpha$ -deutero ketone.

Previously,  $\alpha,\alpha$ -difluoromethyl ketones have been assembled via difluoroenol silyl ethers.<sup>121</sup> Although the preparation of difluoroenol silyl ethers with Mg or Zn is

relatively easy with simple molecules, strongly acidic or basic conditions were reported to hydrolyze the silyl enol ether. However, with our novel synthetic method, a variety of  $\alpha,\alpha$ -difluoromethyl ketones and  $\alpha$ -deutero- $\alpha,\alpha$ -difluoromethyl ketones can be readily accessed without the need of strong acid or base (Table 3.5). This method is compatible with a wide range of molecules such as steroids **95** and **99**. In the case of deuteration reactions, the deuterium incorporation ratios were obtained by  $^{19}\text{F}$  NMR integration. Small differences in the  $^{19}\text{F}$  NMR chemical shift between  $\alpha,\alpha$ -difluoromethyl ketones and  $\alpha$ -deutero- $\alpha,\alpha$ -difluoromethyl ketones allow us to measure integrations of each peak (Figure 3.6).

Table 3.5 A Mild and Efficient Method for Selectively Forming  $\alpha,\alpha$ -Difluoromethyl Ketones and  $\alpha$ -Deutero- $\alpha,\alpha$ -difluoromethyl Ketones.

					
entry	$\alpha,\alpha$ -difluoromethyl ketone	yield <sup>a</sup>	entry	$\alpha$ -deutero- $\alpha,\alpha$ -difluoromethyl ketone	yield <sup>a</sup>
1		96%	6		89%
2		88%	7		86%
3		71%	8		47% <sup>b</sup>
4		96%	9		90%
5		94%	10		81%

a. About 2–3% of  $\alpha,\alpha$ -difluoromethyl ketone was monitored as well. b. The yield was low because of product volatility.

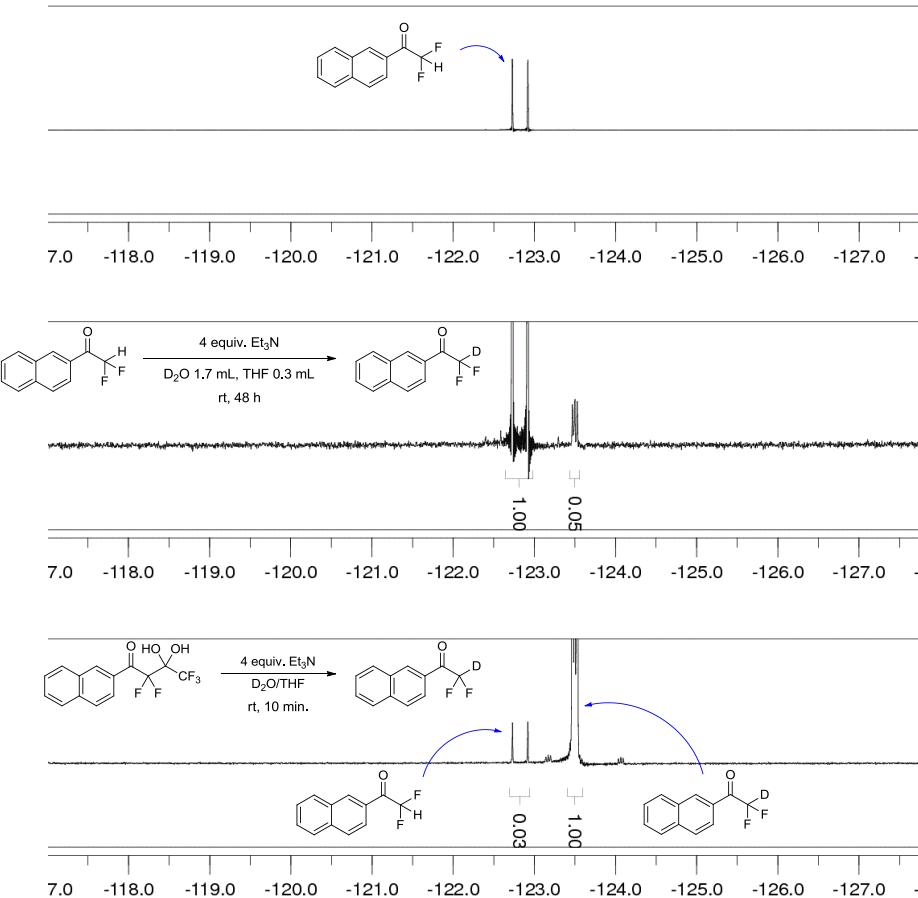
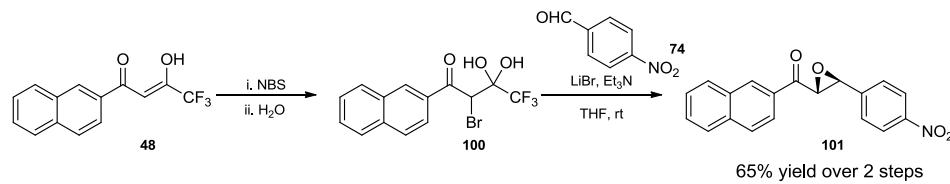


Figure 3.6  $^{19}\text{F}$  NMR peaks of  $\alpha,\alpha$ -difluoromethyl ketone and  $\alpha$ -deutero- $\alpha,\alpha$ -difluoromethyl ketone.

To show the synthetic utility of our methodology, we demonstrated that trifluoroacetate can be released from compounds other than highly  $\alpha$ -fluorinated *gem*-diols. A Darzens product has been achieved via release of trifluoroacetate from mono-brominated *gem*-diol (Scheme 3.8). Mono-bromination was conducted with 1 equiv. of NBS along with 1,1,1-trifluoro-2,4-dione **48**. In this case, the ketone between bromine

and the trifluoromethyl moiety is not activated as much as the pentafluorinated ketone. Therefore, the mono-brominated intermediate was stirred with H<sub>2</sub>O to form *gem*-diol **100**. Under the trifluoroacetate release conditions (LiBr/Et<sub>3</sub>N), the trifluoroacetate released and generated a bromoenolate which reacted with an aldehyde to form the Darzens product **101** in good yield (65% over two steps). The implication of this example is that our methodology is not limited to the generation of  $\alpha,\alpha$ -difluoroenolates.

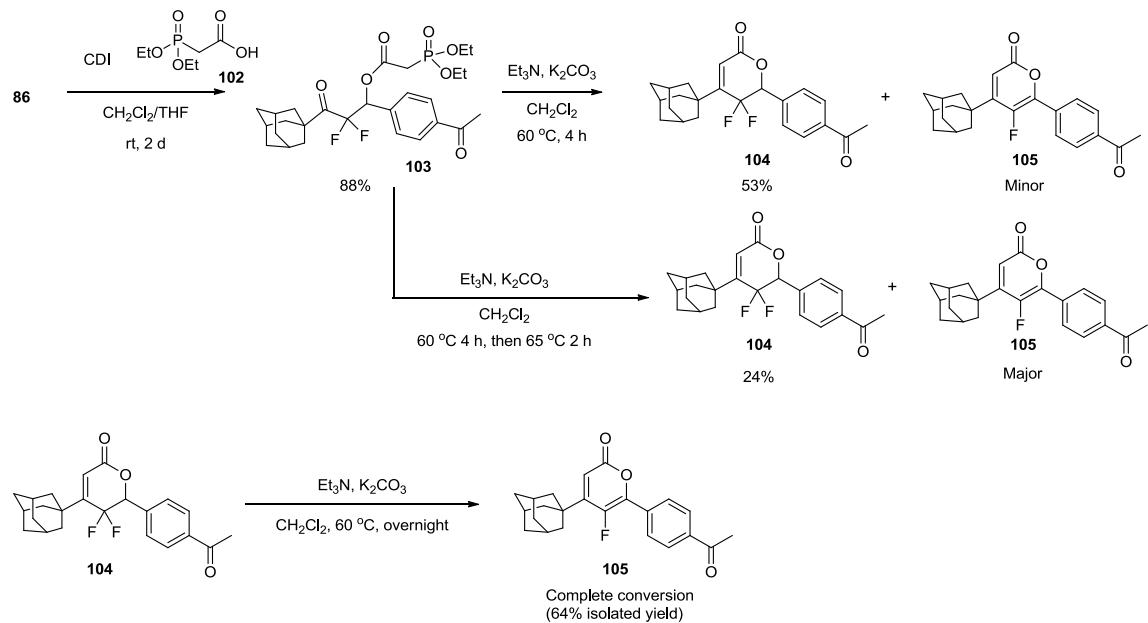


Scheme 3.8 Darzen's Product Formation via Trifluoroacetate-release<sup>54</sup>

Utilization of the trifluoroacetate release-aldol process in a multistep synthesis further proves the synthetic versatility of our methodology. To show the potential synthetic utility of our methodology, fluorinated heterocycles were assembled using the trifluoroacetate release-aldol process.

Esterification between  $\beta$ -ketophosphonate **102** and aldol product **86** generated a synthetic intermediate which can undergo an intramolecular Horner-Wadsworth-Emmons olefination (HWE olefination) reaction to form 5,5-difluoro-5,6-dihydro-2*H*-pyran-2-one **104**. (Scheme 3.9) Interestingly, 5-fluoro-2*H*-pyran-2-one **105** had been isolated along with dihydro-pyran-one **104**. The yield of 5-fluoro-2*H*-pyran-2-one **105** was improved upon after increasing the reaction temperature and reaction time. This result indicated that the beta-elimination of fluoride occurred under basic reaction conditions and this reaction path was further validated by using 5,5-difluoro-5,6-dihydro-2*H*-pyran-2-one

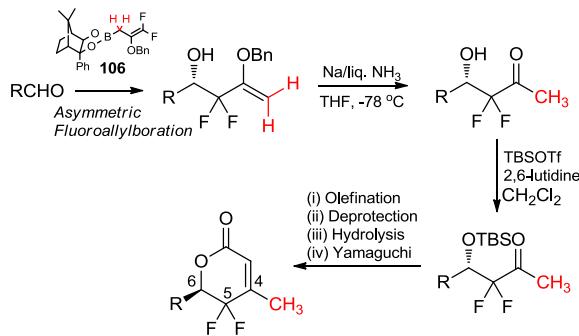
**104** as a starting material. Although defluorinative aromatization strategy has been recently utilized for the synthesis of 3-fluorothiophene derivatives,<sup>122</sup> it is noteworthy that the synthetic method directed the 5-fluoro-2*H*-pyran-2-one has not been reported.



Scheme 3.9 Efficient Formation of 5,5-Difluoro-5,6-dihydro-2*H*-pyran-2-one and 5-Fluoro-2*H*-pyran-2-one Starting from  $\beta$ -Hydroxy- $\alpha,\alpha$ -difluoromethyl Ketones

On the other hand, the asymmetric synthesis of 5,5-difluoro-4-methyl-5,6-dihydro-2*H*-pyran-2-ones starting from commercially available aldehydes has been reported recently by Ramachandran *et al.*<sup>123,124</sup> Chiral organoborane synthons **106** had been utilized to incorporate fluorines as well as a methyl substituent on the C4 position (Scheme 3.10). Further studies on the trifluoroacetate release-asymmetric aldol process will allow us to form chiral 5,5-difluoro-5,6-dihydro-2*H*-pyran-2-ones in 3 steps. Moreover, various substituents can be installed on the C4 position by changing starting materials.

Further optimization of these novel reaction conditions will allow us to synthesize one product in favor of the other; dihydro-pyran-one is expected to be the major product with decreased reaction time and temperature and pyran-one is expected to be major product with increased reaction time and temperature.



Scheme 3.10 Asymmetric synthesis of 5,5-difluoro-4-methyl-5,6-dihydro-2*H*-pyran-2-ones<sup>123,124</sup>

### 3.5 Conclusion and Future Directions

Formation of carbon-carbon bonds is a key element in organic synthesis. Breaking carbon-hydrogen bonds, carbon-halogen bonds, or carbon-metal bonds can be used to generate carbon-carbon bonds. The trifluoroacetate-release process is distinct because it breaks carbon-carbon bonds to generate different carbon-carbon bonds.  $\alpha,\alpha$ -Difluoroenolates have been generated under exceedingly mild reaction conditions by mimicking the fragmentation of hexafluoroacetone hydrate.

Some major advances have been achieved in this project. First, a mild and high yielding method for synthesizing highly  $\alpha$ -fluorinated *gem*-diols has been developed. Second, exceedingly mild reaction to release trifluoroacetate from synthesized highly  $\alpha$ -

fluorinated *gem*-diols have been discovered. Third, reactive intermediates, such as difluoroenolates and bromoenolates, were able to react with electrophiles, such as aldehyde, proton, and deuterium.

Some of the assembled  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones showed a selective agonist effects on GABA<sub>B</sub> receptors. Enantiomeric resolution of racemic **86** reveals that (+)-**86** has an EC<sub>50</sub> value of 15.9 ± 1.84  $\mu\text{M}$ , which is within 10-fold of the pharmaceutical agent, (-)-baclofen. The value of the trifluoroacetate-release process has been reemphasized with highly efficient formation of 5,5-difluoro-5,6-dihydro-2*H*-pyran-2-one and 5-fluoro-2*H*-pyran-2-one starting from  $\beta$ -hydroxy- $\alpha,\alpha$ -difluoromethyl ketones assembled via the trifluoroacetate-release aldol process. Enthusiastic exploration for the trifluoroacetate-release process on different electrophiles and starting materials should be conducted in due course (Figure 3.7). Biological evaluation of assembled fluorinated compounds may lead us to discover novel pharmacophoric moieties.

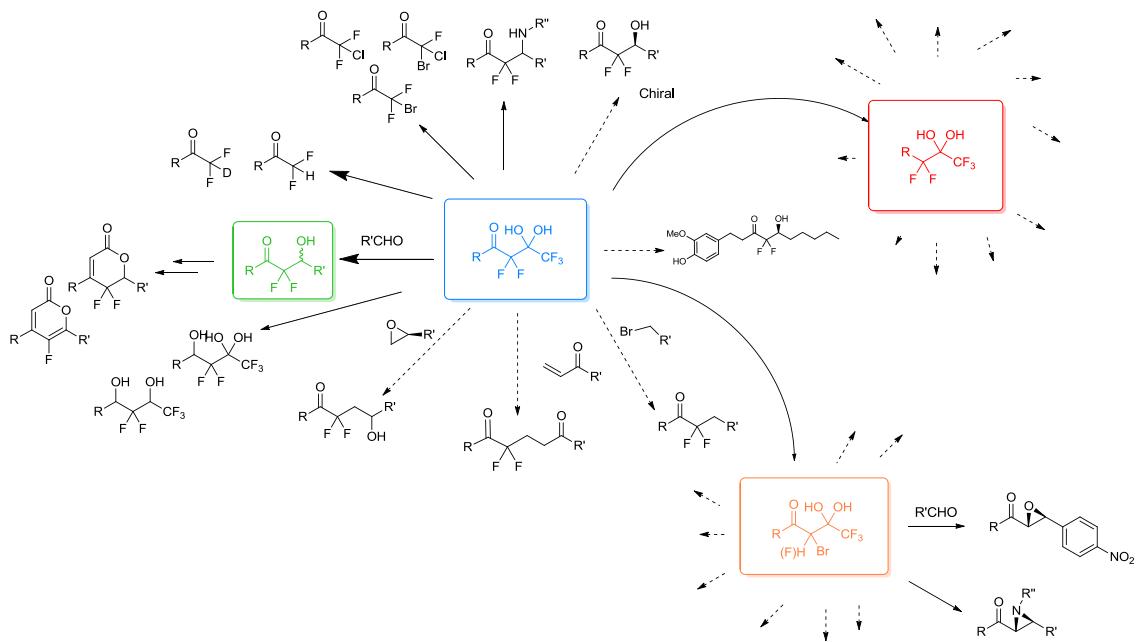
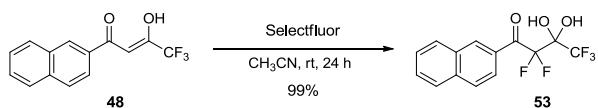


Figure 3.7 Schematic diagram of future directions.

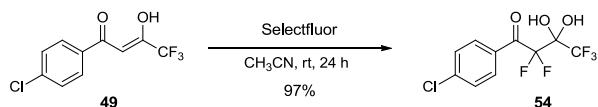
### 3.6 Experimental Details

#### Representative Reaction Procedure for Preparation of Fluorinated *gem*-Diols.

A solution of 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione **48** (216 mg, 0.811 mmol) in CH<sub>3</sub>CN (5 mL) was treated with Selectfluor® (719 mg, 2.03 mmol) at rt. After 24 h, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The residue was concentrated *in vacuo*, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and washed with water (20 ml). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The combined organics were dried over with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give the product **53** (256 mg) as a solid in 99% yield.

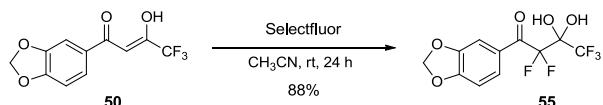


**2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one 53.** See representative reaction procedure: mp 79–81 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) δ 8.74 (s, 1H), 8.05 (d,  $J$  = 8.7 Hz, 1H), 8.01 (d,  $J$  = 8.2 Hz, 1H), 7.94 (d,  $J$  = 8.8 Hz, 1H), 7.91 (d,  $J$  = 8.2 Hz, 1H), 7.70 (ddd,  $J$  = 8.2, 7.0, 1.2 Hz, 1H), 7.62 (ddd,  $J$  = 8.2, 7.0, 1.1 Hz, 1H), 4.70 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) δ 191.3 (t,  $J_{\text{CF}}$  = 28.5 Hz, 1C), 136.5, 134.1 (t,  $J_{\text{CF}}$  = 4.9 Hz, 1C), 132.1, 130.4, 130.2, 128.9 (2C), 127.9, 127.4, 124.5, 120.9 (q,  $J_{\text{CF}}$  = 312 Hz, 1C), 111.4 (t,  $J_{\text{CF}}$  = 268 Hz, 1C), 92.9 (qt,  $J_{\text{CF}}$  = 26.8, 6.1 Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ) δ –80.4 (t,  $J$  = 11.3 Hz, 3F), –110.7 (q,  $J$  = 11.3 Hz, 2F); IR (film)  $\nu_{\text{max}}$  3435, 1683, 1626, 1597, 1470, 1204  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_9\text{F}_5\text{O}_3$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 343.0370, found 343.0368. All spectral and characterization data matched the reported data.<sup>125</sup>



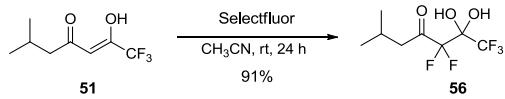
**1-(4-Chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one** **54.** See representative reaction procedure. A solution of 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione **49** (200 mg, 0.8 mmol) in CH<sub>3</sub>CN (6 mL) was treated with Selectfluor® (707 mg, 2.00 mmol). The title compound was isolated as a solid in 97% yield: mp 55–58 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.01 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 4.92 (br s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 190.1 (t, *J*<sub>CF</sub> = 28.8 Hz, 1C), 142.6, 132.0 (t, *J*<sub>CF</sub> =

3.5 Hz, 2C), 130.0, 129.3 (2), 122.0 (q,  $J_{\text{CF}} = 286$  Hz, 1C), 111.6 (t,  $J_{\text{CF}} = 267$  Hz, 1C), 92.7 (qt,  $J_{\text{CF}} = 27.1$ , 5.5 Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -80.5 (t,  $J = 11.0$  Hz, 3F), -111.5 (q,  $J = 11.0$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3435, 1695, 1627, 1590, 1491, 1207, 751  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{10}\text{H}_6\text{ClF}_5\text{O}_3$  ( $\text{M} + \text{H} - \text{H}_2\text{O}$ ) $^+$  286.9898, found 286.9901.



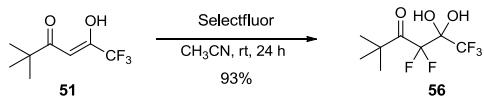
### 1-(Benzo[d][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one

**55.** See representative reaction procedure. A solution of 1-(benzo[*d*][1,3]dioxol-5-yl)-4,4,4-trifluorobutane-1,3-dione **50** (400 mg, 1.54 mmol) in CH<sub>3</sub>CN (9 mL) was treated with Selectfluor® (1.36 g, 3.84 mmol). The title compound was isolated as a solid in 88% yield: mp 58–61 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (d, *J* = 1.5 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H), 4.76 (br s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 189.0 (t, *J*<sub>CF</sub> = 28.6 Hz, 1C), 154.2, 148.4, 128.6 (t, *J*<sub>CF</sub> = 4.8 Hz, 1C), 125.9 (t, *J*<sub>CF</sub> = 2.4 Hz, 1C), 122.0 (q, *J*<sub>CF</sub> = 287 Hz, 1C), 111.2 (t, *J*<sub>CF</sub> = 268 Hz, 1C), 109.7 (t, *J*<sub>CF</sub> = 2.9 Hz, 1C), 108.5, 102.5, 93.0 (qt, *J*<sub>CF</sub> = 32.8, 6.1 Hz, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -80.5 (t, *J* = 11.3 Hz, 3F), -110.5 (q, *J* = 11.3 Hz, 2F); IR (film) ν<sub>max</sub> 3435, 2917, 1679, 1605, 1207 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>11</sub>H<sub>7</sub>F<sub>5</sub>O<sub>5</sub> (M+Na)<sup>+</sup> 337.0111, found 337.0114.



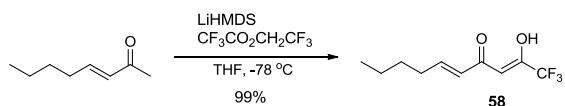
**1,1,1,3,3-Pentafluoro-2,2-dihydroxy-6-methylheptan-4-one** **56.** See

representative reaction procedure. A solution of 1,1,1-trifluoro-6-methylheptane-2,4-dione **51** (177  $\mu$ L, 1.02 mmol), CH<sub>3</sub>CN (6 mL) was treated with Selectfluor® (903 mg, 2.55 mmol). The title compound was isolated as an oil in 91% yield: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.71 (br s, 2H), 2.69 (d, *J* = 6.9 Hz, 2H), 2.20 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  203.4 (t, *J*<sub>CF</sub> = 28.4 Hz, 1C), 120.8 (q, *J*<sub>CF</sub> = 290 Hz, 1C), 109.3 (t, *J*<sub>CF</sub> = 268 Hz, 1C), 92.5 (qt, *J*<sub>CF</sub> = 27.5, 5.9 Hz, 1C), 46.5, 23.4, 22.1 (2); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -80.9 (t, *J* = 10.4 Hz, 3F), -119.5 (q, *J* = 10.4 Hz, 2F); IR (film)  $\nu$ <sub>max</sub> 3445, 2967, 2940, 2879, 2918, 1743, 1627, 1471, 1208 cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>8</sub>H<sub>11</sub>F<sub>5</sub>O<sub>3</sub> (M+H)<sup>+</sup> 251.0707, found 251.0710.

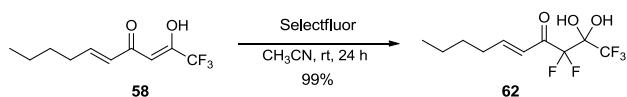


**4,4,6,6,6-Pentafluoro-5,5-dihydroxy-2,2-dimethylhexan-3-one** **57.** See

representative reaction procedure. A solution of 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione **52** (177  $\mu$ L, 1.02 mmol) in CH<sub>3</sub>CN (6 mL) was treated with Selectfluor® (903 mg, 2.55 mmol). The title compound was isolated as solid in 93% yield. Recrystallization from chloroform (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: mp 44–46 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.75 (br s, 2H), 1.31 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  208.9 (t, *J*<sub>CF</sub> = 26.8 Hz, 1C), 120.8 (q, *J*<sub>CF</sub> = 291 Hz, 1C), 110.8 (t, *J*<sub>CF</sub> = 272 Hz, 1C), 92.8 (qt, *J*<sub>CF</sub> = 27.5, 5.7 Hz, 1C), 44.8 (t, *J*<sub>CF</sub> = 1.9 Hz, 1C), 25.4 (s, 3C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -80.5 (t, *J* = 11.3 Hz, 3F), -113.2 (q, *J* = 11.0 Hz, 2F); IR (film)  $\nu$ <sub>max</sub> 3435, 2982, 2944, 2918, 2883, 1715, 1624, 1484, 1207 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>8</sub>H<sub>11</sub>F<sub>5</sub>O<sub>3</sub> (M+H-H<sub>2</sub>O)<sup>+</sup> 233.0601, found 233.0606.

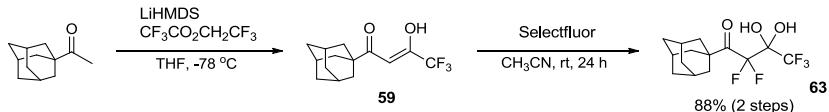


**(E)-1,1,1-Trifluorodec-5-ene-2,4-dione 58.** To a  $-78$  °C solution of *n*-BuLi (1.8 mL, 2.09 M in hexanes) in THF (15 mL) was added hexamethyldisilazane (807  $\mu$ L, 3.80 mmol). The mixture was stirred for 20 min at  $-78$  °C, and then *trans*-3-octen-2-one (467  $\mu$ L, 3.17 mmol) was added dropwise. After an additional 45 min at  $-78$  °C, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (637  $\mu$ L, 4.75 mmol) was added dropwise and the mixture was stirred for 15 min at the same temperature. The reaction mixture was quenched with 1 M H<sub>2</sub>SO<sub>4</sub> (10 mL) and stirred for 1 h. The resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL  $\times$  3). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the product **58** in 99% yield (695 mg) as an oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.07 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.96 (d, *J* = 15.6 Hz, 1H), 5.87 (s, 1H), 2.28 (q, *J* = 6.9 Hz, 2H), 1.52–1.29 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  182.1, 180.0 (q, *J*<sub>CF</sub> = 35.6 Hz, 1C), 149.8, 124.7, 118.6 (q, *J*<sub>CF</sub> = 283 Hz, 1C), 94.4, 32.7, 30.1, 22.2, 13.7; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -76.5 (s, 3F); IR (film)  $\nu$ <sub>max</sub> 2962, 2934, 1652, 1619, 1584, 1467, 1456, 1272, 1202, 1154, 1108 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>10</sub>H<sub>13</sub>F<sub>3</sub>O<sub>2</sub> (M)<sup>+</sup> 222.0868, found 222.0865.



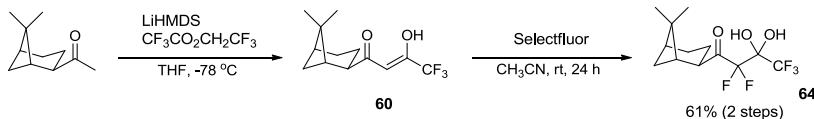
**1,1,1,3,3-Pentafluoro-2,2-dihydroxydec-5-en-4-one** **62.** See representative reaction procedure. A solution of (*E*)-1,1,1-trifluorodec-5-ene-2,4-dione **58** (583 mg, 2.62

mmol) in CH<sub>3</sub>CN (15 mL) was treated with Selectfluor® (2.32 g, 6.56 mmol). The title compound was isolated and purified by SiO<sub>2</sub> flash chromatography (10:1 hexanes/EtOAc) to give an oil in 99% yield: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.38 (dt, *J* = 15.4, 7.0 Hz, 1H), 6.70–6.64 (m, 1H), 4.47 (br s, 2H), 2.35 (ddd, *J* = 14.9, 7.2, 1.5 Hz, 2H), 1.50 (ddd, *J* = 12.8, 8.9, 6.3 Hz, 2H), 1.42–1.31 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 190.1 (t, *J*<sub>CF</sub> = 27.8 Hz, 1C), 157.8, 121.6, 121.0 (q, *J*<sub>CF</sub> = 286 Hz, 1C), 110.1 (t, *J*<sub>CF</sub> = 264 Hz, 1C), 92.5 (qt, *J*<sub>CF</sub> = 32.8, 6.0 Hz, 1C), 33.0, 29.6, 22.3, 13.7; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -80.80 (t, *J* = 10.4 Hz, 3F), -119.25 (q, *J* = 10.4 Hz, 2F); IR (film)  $\nu_{\text{max}}$  3416, 2963, 2936, 2877, 1708, 1620, 1207, 1176, 1072 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>10</sub>H<sub>13</sub>F<sub>5</sub>O<sub>3</sub> (M)<sup>+</sup> 276.0785, found 276.0782.



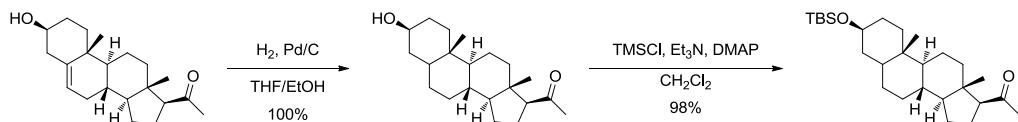
**1-(Adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 63.** To a -78 °C solution of *n*-BuLi (1.6 mL, 2.09 M in hexanes) in THF (8.5 mL) was added hexamethyldisilazane (715 μL, 3.43 mmol). The mixture was stirred for 20 min at -78 °C, and then 1-adamantyl methyl ketone (500 mg, 2.80 mmol) was added dropwise. After an additional 45 min at -78 °C, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (563 μL, 4.21 mmol) was added dropwise and the mixture was stirred for 15 min at the same temperature. The reaction mixture was quenched with 1 M H<sub>2</sub>SO<sub>4</sub> (10 mL) and stirred for 1 h. The resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 3). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford 1-(adamantan-1-yl)-4,4,4-trifluorobutane-1,3-dione **59** as an oil (760 mg). All spectral and

characterization data matched the reported data.<sup>2</sup> The intermediate **59** was immediately used in the next step. See representative reaction procedure. A solution of 1-(adamantan-1-yl)-4,4,4-trifluorobutane-1,3-dione **59** (462 mg, 1.68 mmol) in CH<sub>3</sub>CN (12 mL) was treated with Selectfluor® (1.49 g, 4.21 mmol). The title compound was isolated and purified by SiO<sub>2</sub> flash chromatography (10:1 hexanes/EtOAc) to give a solid in 88% yield (two steps from 1-adamantyl methyl ketone): mp 98–101 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.98 (br s, 2H), 2.08 (m, 3H), 1.98 (m, 6H), 1.75 (m, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 208.0 (t, *J*<sub>CF</sub> = 26.0 Hz, 1C), 122.8 (q, *J*<sub>CF</sub> = 286 Hz, 1C), 111.1 (t, *J*<sub>CF</sub> = 268 Hz, 1C), 93.0 (qt, *J*<sub>CF</sub> = 32.6, 5.6 Hz, 1C), 47.8 (t, *J*<sub>CF</sub> = 2.2 Hz, 1C), 36.4 (3C), 36.1 (3C), 27.4 (3C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ –80.5 (t, *J* = 11.0 Hz, 3F), –113.7 (q, *J* = 11.0 Hz, 2F); IR (film)  $\nu_{\text{max}}$  3452, 3360, 2909, 1718, 1701, 1204, 1073 cm<sup>–1</sup>; HRMS (EI) *m/z* calcd for C<sub>14</sub>H<sub>17</sub>F<sub>5</sub>O<sub>3</sub> (M+H–H<sub>2</sub>O)<sup>+</sup> 311.1071, found 311.1073.

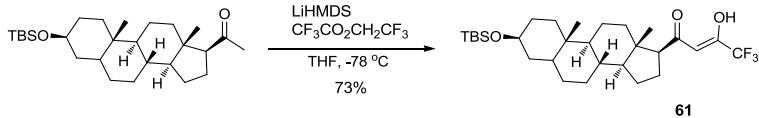


**1-((1*S*,2*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **64**.** To a –78 °C solution of *n*-BuLi (1.0 mL, 2.50 M in hexanes) in THF (12 mL) was added hexamethyldisilazane (535 µL, 2.52 mmol). The mixture was stirred for 20 min at –78 °C, and then 1-((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-ethanone<sup>3</sup> (350 mg, 2.10 mmol) was added dropwise. After an additional 45 min at –78 °C, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (417 µL, 3.12 mmol) was added dropwise and the mixture was stirred for 15 min at the same temperature. The reaction mixture was quenched with 1 M H<sub>2</sub>SO<sub>4</sub> (10 mL) and stirred for

1 h. The resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 3). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford 1-((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4,4,4-trifluorobutane-1,3-dione **60** as an oil. The intermediate **60** was immediately used in the next step. See representative reaction procedure. A solution of intermediate **60** in CH<sub>3</sub>CN (15 mL) was treated with Selectfluor® (1.86 g, 5.25 mmol). The product **64** was isolated and purified by SiO<sub>2</sub> flash chromatography (10:1 hexanes/EtOAc) to give a solid in 61% yield (two steps from 1-((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-ethanone): mp 40–42 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.54–3.47 (m, 1H), 2.52 (t, *J* = 5.5 Hz, 1H), 2.48–2.41 (m, 1H), 2.35–2.26 (m, 1H), 2.08–1.90 (m, 4H), 1.21 (s, 3H), 1.19 (d, *J* = 10.1 Hz, 1H), 0.80 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 206.5 (t, *J*<sub>CF</sub> = 26.6 Hz, 1C), 120.8 (q, *J*<sub>CF</sub> = 287 Hz, 1C), 109.6 (t, *J*<sub>CF</sub> = 267 Hz, 1C), 92.6 (qt, *J*<sub>CF</sub> = 28.8, 5.8 Hz, 1C), 49.3, 41.9, 40.3, 38.8, 31.0, 27.1, 24.9, 22.2, 13.4; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ –81.3 (t, *J* = 10.7 Hz, 3F), –116.2 (dq, *J* = 286, 10.7 Hz, 1F); –118.7 (dq, *J* = 286, 10.7 Hz, 1F); IR (film) ν<sub>max</sub> 3430, 2925, 1720, 1210, 1169, 1071 cm<sup>–1</sup>; HRMS (ESI) *m/z* calcd for C<sub>13</sub>H<sub>17</sub>F<sub>5</sub>O<sub>3</sub> (M)<sup>+</sup> 316.1098, found 316.1094; [α]<sup>21</sup><sub>D</sub> –12.0° (*c* 1.14, CHCl<sub>3</sub>).



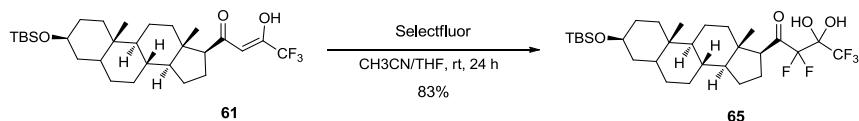
**1-((3*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-((tert-Butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)ethanone.** All spectral and characterization data matched the reported data.<sup>126</sup>



**(Z)-1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-butyldimethylsilyl)oxy)-10,13-**

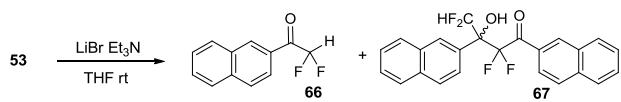
**Dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-4,4,4-trifluoro-3-hydroxybut-2-en-1-one (61).** n-butyl lithium (120 mg, 1.88 mmol) was added into THF (6.00 mL) at -78 °C dropwise. Then, hexamethyldisilazane (303 mg, 1.88 mmol) was added and stirred for 20 min at the same temperature. Then, 1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethanone (678 mg, 1.57 mmol) was slowly added into preformed LiHMDS solution and stirred for 45 min at -78 °C. Then, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (461 mg, 2.35 mmol) was added dropwise and stirred for 15 min at the same temperature. The reaction mixture was quenched with 1M aqueous H<sub>2</sub>SO<sub>4</sub> (10 mL) and stirred for 10 min. The resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 3). The organics were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure afforded the desired product 73% yield (609.7 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.9 (s, 1H), 3.5 (m, 1H), 2.4 (t, *J* = 9.0 Hz, 1H), 2.2–2.1 (m, 1H), 1.9 (m, 1H), 1.8–1.6 (m, 6H), 1.5–1.2 (m, 9H), 1.2–1.1 (m, 1H), 1.1–1.0 (m, 1H), 1.0–0.8 (m, 12H), 0.8 (s, 3H), 0.6 (s, 3H), 0.0 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 198.6, 174.8 (*q*, *J*<sub>CF</sub> = 36.0 Hz, 1C), 118.3 (*q*, *J*<sub>CF</sub> = 218.3 Hz, 1C), 96.4, 72.0, 59.3, 56.7, 54.3, 46.5, 45.0, 38.6, 38.5, 37.1, 35.7, 35.6, 32.1, 31.9, 28.6, 26.0 (3), 24.4, 22.8, 21.1, 18.3, 13.4, 12.4, -4.6 (2); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -75.8 (s, 3F); IR (film) ν<sub>max</sub> 2930, 2855, 1593, 1200, 1157, 1107, 1090, 836 cm<sup>-1</sup>; HRMS (ESI) m/z calcd

for  $C_{29}H_{47}F_3O_3Si$  ( $M+Na$ )<sup>+</sup> 551.3144, found 551.3149; mp 96–98 °C;  $[\alpha]^{23}_D + 70$  (c 1.03, CHCl<sub>3</sub>).



**1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-Butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2,2,4,4,4-pentafluoro-**

**3,3-dihydroxybutan-1-one (65).** See representative reaction procedure. Compound **61** (277 mg, 0.524 mmol), acetonitrile (2.00 ml), THF (2.00 ml), and Selectfluor (464 mg, 1.31 mmol) were used. After 24 h, additional Selectfluor (300 mg, 0.98 mmol) were added and stirred for another 24 h.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.7 (br s, 2H), 3.5 (m, 1H), 3.2 (t,  $J = 8.5$  Hz, 1H), 2.1 (m, 1H), 1.9 (d,  $J = 12.0$  Hz, 1H), 1.8–1.6 (m, 5H), 1.6–1.5 (m, 1H), 1.5–1.2 (m, 10H), 1.1 (m, 1H), 1.0–0.8 (m, 11H), 0.8 (s, 3H), 0.7 (s, 3H), 0.7–0.6 (m, 1H), 0.0 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  207.0 (t,  $J_{\text{CF}} = 28.6$  Hz, 1C), 121.9 (q,  $J_{\text{CF}} = 283.3$  Hz, 1C), 108.5 (t,  $J_{\text{CF}} = 265.9$  Hz, 1C), 93.0 (qt,  $J_{\text{CF}} = 29.8$ , 1.0 Hz, 1C), 72.1, 57.3 (2), 54.0, 48.3, 44.9, 38.5, 38.3, 37.1, 35.8, 35.5, 32.1, 31.8, 28.6 (3), 25.9, 24.6, 24.4, 21.2, 18.3, 13.7, 12.3, -4.6 (2);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -80.8 (t,  $J = 10.4$  Hz, 3F), -119.1 (dq,  $J = 35.0$ , 9.9 Hz, 2F); IR (film)  $\nu_{\text{max}}$  3436, 2931, 2858, 1717, 1386, 1209, 1087, 837, 775  $\text{cm}^{-1}$ ; HRMS (ESI) m/z calcd for  $\text{C}_{29}\text{H}_{47}\text{F}_5\text{O}_4\text{Si}$  ( $\text{M}-\text{H}-\text{H}_2\text{O}$ )<sup>+</sup> 563.2980, found 563.2973; mp 108–111 °C;  $[\alpha]^{26}_{\text{D}} + 83$  (c 2.08,  $\text{CHCl}_3$ ).



**Trifluoroacetate release from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one 66.** To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one **53** (50.0 mg, 0.156 mmol) and LiBr (40.7 mg, 0.468 mmol) in THF (1.0 mL), was added Et<sub>3</sub>N (28 µL, 0.20 mmol) dropwise. After 3 min, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL) and the resultant mixture was extracted with EtOAc (2 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash chromatography (17:3–9:1 hexanes/EtOAc) afforded the 2,2-difluoro-1-(naphthalen-2-yl)-ethanone **66** in 5.4% yield (1.7 mg, solid) and the self-adduct **67** in 78% yield (25.2 mg, solid).

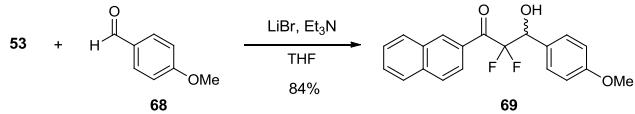
**For 2,2-difluoro-1-(naphthalen-2-yl)-ethanone 66:** mp 46–47 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.65 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.68–7.65 (m, 1H), 7.61–7.58 (m, 1H), 6.41 (*t*, *J*<sub>HF</sub> = 53.5 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 187.5 (*t*, *J*<sub>CF</sub> = 25.4 Hz, 1C), 136.3, 132.5 (*t*, *J*<sub>CF</sub> = 3.0 Hz, 1C), 132.3, 130.0, 129.6, 129.0, 128.7, 127.9, 127.2, 124.1, 111.4 (*t*, *J*<sub>CF</sub> = 253 Hz, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ –120.6 (d, *J*<sub>HF</sub> = 53.5 Hz, 2F); IR (film) ν<sub>max</sub> 1706, 1623, 1056 cm<sup>–1</sup>; HRMS (EI) *m/z* calcd for C<sub>12</sub>H<sub>8</sub>F<sub>2</sub>O (M)<sup>+</sup> 206.0543, found 206.0547. All spectral and characterization data matched the reported data.

**For self-adduct 67:** mp 111–113 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.55 (s, 1H), 8.18 (s, 1H), 7.94–7.76 (m, 8H), 7.66–7.61 (m, 1H), 7.57–7.47 (m, 3H), 6.52 (*t*, *J*<sub>HF</sub> = 54.5 Hz, 1H), 4.43 (br s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 190.1 (*t*, *J*<sub>CF</sub> = 29.4 Hz, 1C), 136.1, 133.4 (2C), 132.8, 132.0, 130.2, 129.9, 129.7, 129.6, 128.6, 128.5, 128.2, 127.7, 127.5, 127.1 (2C), 127.0, 126.5, 124.6, 123.7, 115.3 (*t*, *J*<sub>CF</sub> = 265 Hz, 1C), 114.0 (*t*, *J*<sub>CF</sub> = 250 Hz, 1C), 78.3 (*t*, *J*<sub>CF</sub> = 23.6 Hz, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ –103.5 (dt, *J*<sub>FF</sub> =

294, 8.1 Hz, 1F), -105.1 (dt,  $J_{\text{FF}} = 294$ , 9.0 Hz, 1F), -127.5 (ddt,  $J_{\text{FF}} = 289$ , 9.0 Hz,  $J_{\text{HF}} = 54.1$  Hz, 1F) -129.6 (dddd,  $J_{\text{FF}} = 289$ , 9.0, 8.1 Hz,  $J_{\text{HF}} = 54.1$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3469, 3061, 1688, 1626, 1093, 752  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{16}\text{F}_4\text{O}_2$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 435.0984, found 435.0977.

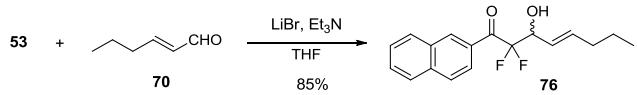
### Representative Reaction Procedure for Trifluoroacetate Release/Aldol

**Reaction.** To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one **53** (30.0 mg, 0.094 mmol), *p*-anisaldehyde (23  $\mu\text{L}$ , 0.19 mmol), and LiBr (24.4 mg, 0.28 mmol) in THF (600  $\mu\text{L}$ ), was added Et<sub>3</sub>N (13  $\mu\text{L}$ , 0.094 mmol) dropwise. After 3 min, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL), and the resultant mixture was extracted with EtOAc (2 mL  $\times$  5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **69** as a solid in 84% yield (27.0 mg).

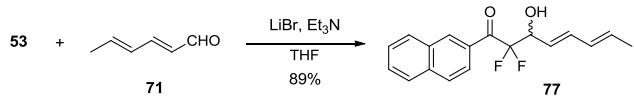


**2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)-propan-1-one **69**.** See representative reaction procedure: mp 102–104 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.62 (s, 1H), 8.04 (d,  $J = 8.5$  Hz, 1H), 7.94 (d,  $J = 8.0$  Hz, 1H), 7.90–7.86 (m, 2H), 7.66–7.62 (m, 1H), 7.56–7.55 (m, 1H), 7.46 (d,  $J = 8.5$  Hz, 2H), 6.94–6.91 (m, 2H), 5.41–5.34 (m, 1H), 3.81 (s, 3H), 3.05 (d,  $J = 4.5$  Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  190.8 (t,  $J_{\text{CF}} = 29.3$  Hz, 1C), 160.1, 136.1, 133.3 (t,  $J_{\text{CF}} = 5.0$  Hz, 1C), 132.2, 130.2, 129.6, 129.5, 129.4, 128.5, 127.7, 127.0 (2), 126.7, 124.7, 116.0 (dd,  $J_{\text{CF}} = 263, 255$  Hz, 1C)

113.8 (2), 73.1 (dd,  $J_{\text{CF}} = 28.3, 22.9$  Hz, 1C), 55.3;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta -103.3$  (dd,  $J_{\text{FF}} = 290$ ,  $J_{\text{HF}} = 5.9$  Hz, 1F),  $-114.6$  (dd,  $J_{\text{FF}} = 290$ ,  $J_{\text{HF}} = 18.3$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3468, 2934, 1690, 1626, 1612, 1465, 1177  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{16}\text{F}_2\text{O}_3$  ( $\text{M}$ ) $^+$  342.1068, found 342.1070.

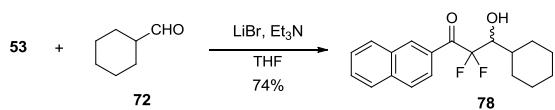


**(E)-2,2-Difluoro-3-hydroxy-1-(naphthalen-2-yl)-oct-4-en-1-one 76.** See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one **53** (30.0 mg, 0.094 mmol), LiBr (29.5 mg, 0.340 mmol), and (*E*)-hex-2-enal (22  $\mu\text{L}$ , 0.19 mmol) in THF (600  $\mu\text{L}$ ) was treated with  $\text{Et}_3\text{N}$  (13  $\mu\text{L}$ , 0.09 mmol).  $\text{SiO}_2$  flash chromatography (9:1 hexanes/EtOAc) afforded the product **76** in 85% yield (24.2 mg) as a colorless oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (s, 1H), 8.09 (dd,  $J = 8.5, 1.5$  Hz, 1H), 8.00 (d,  $J = 8.0$  Hz, 1H), 7.92 (d,  $J = 8.5$  Hz, 1H), 7.89 (d,  $J = 8.0$  Hz, 1H), 7.67–7.64 (m, 1H), 7.60–7.56 (m, 1H), 5.96 (dtd,  $J = 15.5, 6.8, 1.0$  Hz, 1H), 5.67 (dd,  $J = 15.5, 7.0$  Hz, 1H), 4.78 (dq,  $J = 15.0, 6.5$  Hz, 1H), 2.66 (d,  $J = 5.5$  Hz, 1H), 2.10 (q,  $J = 7.5$  Hz, 2H), 1.44 (sextet,  $J = 7.5$  Hz, 2H), 0.90 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  190.3 (t,  $J_{\text{CF}} = 30.8$  Hz, 1C), 138.2, 136.1, 133.1 (t,  $J_{\text{CF}} = 4.8$  Hz, 1C), 132.2, 130.1, 129.6 (t,  $J_{\text{CF}} = 2.6$  Hz, 1C), 129.5, 128.5, 127.7, 127.0, 124.7, 123.0, 116.2 (dd,  $J_{\text{CF}} = 260, 256$  Hz, 1C), 72.9 (dd,  $J_{\text{CF}} = 27.9, 24.5$  Hz, 1C), 34.4, 21.9, 13.6;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta -105.3$  (dd,  $J_{\text{FF}} = 290$ ,  $J_{\text{HF}} = 7.3$  Hz, 1F),  $-113.4$  (dd,  $J_{\text{FF}} = 290$ ,  $J_{\text{HF}} = 15.8$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3468, 3063, 2961, 2930, 2874, 1694, 1683, 1627, 1466  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{18}\text{F}_2\text{O}_2$  ( $\text{M}$ ) $^+$  304.1275, found 304.1278.



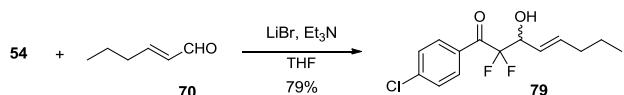
**(4E,6E)-2,2-Difluoro-3-hydroxy-1-(naphthalen-2-yl)-octa-4,6-dien-1-one 77.**

See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one **53** (30.0 mg, 0.094 mmol), LiBr (29.5 mg, 0.340 mmol), and (2*E*,4*E*)-hexa-2,4-dienal (20  $\mu$ L, 0.19 mmol) in THF (600  $\mu$ L) was treated with Et<sub>3</sub>N (13  $\mu$ L, 0.09 mmol). SiO<sub>2</sub> flash chromatography (9:1 hexanes/EtOAc) afforded the product **77** in 89% yield (26.7 mg) as a solid: mp 64–66 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.71 (s, 1H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.65 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 6.45 (dd, *J* = 15.0, 10.5 Hz, 1H), 6.12 (ddd, *J* = 15.0, 10.5, 1.5 Hz, 1H), 5.82 (dq, *J* = 14.0, 7.0 Hz, 1H), 5.71 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.85 (m, 1H), 2.60 (d, *J* = 6.0 Hz, 1H), 1.8 (dd, *J* = 6.5, 1.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  190.2 (dd, *J*<sub>CF</sub> = 30.9, 29.3 Hz, 1C), 136.1 (2), 133.2 (t, *J*<sub>CF</sub> = 4.6 Hz, 1C), 132.4, 132.2, 130.3, 130.2, 129.5, 128.6 (dd, *J*<sub>CF</sub> = 273, 207 Hz, 1C), 128.5, 127.8, 127.0, 124.7, 122.4, 116.1 (dd, *J*<sub>CF</sub> = 261, 256 Hz, 1C), 72.6 (dd, *J*<sub>CF</sub> = 28.0, 24.6 Hz, 1C), 18.2; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -105.2 (dd, *J*<sub>FF</sub> = 289, *J*<sub>HF</sub> = 7.1 Hz, 1F), -113.7 (dd, *J*<sub>FF</sub> = 289, *J*<sub>HF</sub> = 15.8 Hz, 1F); IR (film)  $\nu$ <sub>max</sub> 3468, 1693, 1626, 1467, 1100, 1072, 990 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>18</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub> (M)<sup>+</sup> 302.1118, found 302.1122.



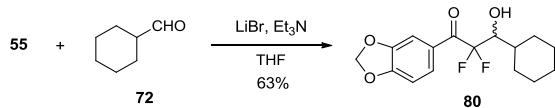
**3-Cyclohexyl-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)-propan-1-one 78.**

See representative reaction procedure. A  $-78^{\circ}\text{C}$  solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one **53** (20.0 mg, 0.062 mmol), LiBr (19.7 mg, 0.226 mmol), and cyclohexanecarbaldehyde **72** (15  $\mu\text{L}$ , 0.13 mmol) in THF (300  $\mu\text{L}$ ) was treated with  $\text{Et}_3\text{N}$  (35  $\mu\text{L}$ , 0.25 mmol). The mixture was stirred for 30 min at  $-78^{\circ}\text{C}$  and then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) at the same temperature.  $\text{SiO}_2$  flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **78** in 74% yield (14.6 mg) as a colorless oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (s, 1H), 8.09 (dd,  $J = 9.0, 1.5$  Hz, 1H), 8.01 (dd,  $J = 8.5, 1.0$  Hz, 1H), 7.93 (d,  $J = 9.0$  Hz, 1H), 7.90 (dd,  $J = 8.0, 0.5$  Hz, 1H), 7.67–7.64 (m, 1H), 7.60–7.57 (m, 1H), 4.17–4.09 (m, 1H), 2.42 (d,  $J = 7.0$  Hz, 1H), 2.03–2.00 (m, 1H), 1.92–1.86 (m, 1H), 1.82–1.76 (m, 2H), 1.69–1.67 (m, 1H), 1.43–1.14 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  190.6 (t,  $J_{\text{CF}} = 29.3$  Hz, 1C), 136.0, 132.9 (t,  $J_{\text{CF}} = 4.6$  Hz, 1C), 132.2, 130.1, 129.6 (t,  $J_{\text{CF}} = 2.5$  Hz, 1C), 129.4, 128.5, 127.8, 127.0, 124.8, 117.9 (dd,  $J_{\text{CF}} = 261, 256$  Hz, 1C), 74.9 (dd,  $J_{\text{CF}} = 26.3, 22.6$  Hz, 1C), 38.1, 30.2, 29.7, 27.3, 26.3, 26.1, 25.9;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –103.4 (dd,  $J_{\text{FF}} = 290, J_{\text{HF}} = 6.8$  Hz, 1F), –112.6 (dd,  $J_{\text{FF}} = 290, J_{\text{HF}} = 19.7$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3469, 2924, 2851, 1693, 1627, 1465  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{20}\text{F}_2\text{O}_2$  ( $\text{M}^+$ ) 318.1431, found 318.1438.

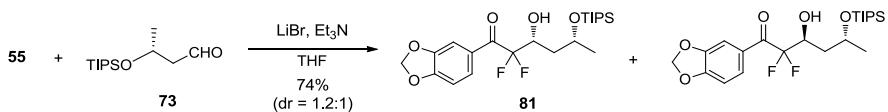


**(E)-1-(4-Chlorophenyl)-2,2-difluoro-3-hydroxyoct-4-en-1-one 79.** See representative reaction procedure. A solution of 1-(4-chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **54** (30.0 mg, 0.098 mmol), LiBr (25.7 mg, 0.295

mmol), and (*E*)-hex-2-enal **70** (23  $\mu$ L, 0.20 mmol) in THF (600  $\mu$ L) was treated with Et<sub>3</sub>N (35  $\mu$ L, 0.25 mmol). SiO<sub>2</sub> flash chromatography (12:2 pentane/dioxane) afforded the product **79** in 79% yield (22.5 mg) as a colorless oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.04 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 5.94 (ddt, *J* = 15.5, 6.5, 1.0 Hz, 1H), 5.60 (ddt, *J* = 15.5, 7.1, 1.5 Hz, 1H), 4.70 (m, 1H), 2.43 (d, *J* = 6.0 Hz, 1H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.42 (sextet, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  189.4 (dd, *J*<sub>CF</sub> = 31.1, 29.3 Hz, 1C), 141.3, 138.4, 131.6 (t, *J*<sub>CF</sub> = 3.5 Hz, 1C), 130.8, 129.1 (3), 122.8, 116.0 (dd, *J*<sub>CF</sub> = 260, 255 Hz, 1C), 72.8 (dd, *J*<sub>CF</sub> = 27.9, 24.4 Hz, 1C), 34.4, 21.9, 13.6; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -106.9 (dd, *J*<sub>FF</sub> = 290, *J*<sub>HF</sub> = 7.1 Hz, 1F), -115.5 (dd, *J*<sub>FF</sub> = 290, *J*<sub>HF</sub> = 15.8 Hz, 1F); IR (film)  $\nu$ <sub>max</sub> 3436, 2961, 2931, 2874, 1698, 1589, 1093 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>14</sub>H<sub>15</sub>ClF<sub>2</sub>O<sub>2</sub> (M)<sup>+</sup> 288.0729, found 288.0732.



**1-(Benzo[d][1,3]dioxol-5-yl)-3-cyclohexyl-2,2-difluoro-3-hydroxypropan-1-one **80**.** See representative reaction procedure. A solution of 1-(benzo[*d*][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **55** (30.0 mg, 0.095 mmol), LiBr (58.1 mg, 0.668 mmol), and cyclohexanecarbaldehyde (23  $\mu$ L, 0.191 mmol) in THF (600  $\mu$ L) was treated with Et<sub>3</sub>N (53  $\mu$ L, 0.382 mmol). The mixture was stirred for 5 min at -78 °C and the quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL) at the same temperature. SiO<sub>2</sub> flash chromatography (4:1 hexanes/EtOAc) afforded the product **80** in 63% yield (18.9 mg) as an oil.

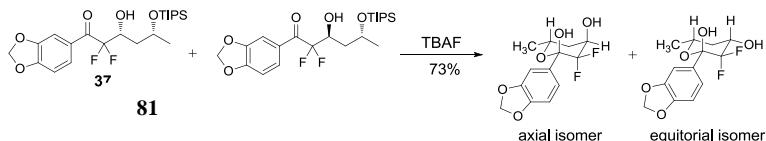


**(3*R*,5*R*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-3-hydroxy-5-((triisopropylsilyl)oxy)-hexan-1-one 81.**

**See representative reaction procedure.** A solution of 1-(benzo[*d*][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **55** (20.0 mg, 0.064 mmol), LiBr (16.6 mg, 0.191 mmol), and (*R*)-3-((triisopropylsilyl)oxy)butanal (35  $\mu$ L, 0.127 mmol) in THF (500  $\mu$ L) was treated with *i*-Pr<sub>2</sub>NEt (21  $\mu$ L, 0.15 mmol). The ratio of diastereomers was determined from <sup>19</sup>F NMR analysis of the crude reaction mixture. SiO<sub>2</sub> flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **81** and (3*S*,5*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-3-hydroxy-5-((triisopropylsilyl)oxy)-hexan-1-one as an inseparable mixture of diastereomers (dr = 1.2:1, 19.8 mg) in 74% yield: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.80 (d, *J* = 8.3 Hz, 1H), 7.56 (s, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.07 (s, 2H), 4.63\* (m, 1H), 4.43 (m, 1H), 4.31 (m, 1H), 3.90\* (d, *J* = 2.9 Hz, 1H), 3.48 (d, *J* = 3.1 Hz, 1H), 2.01–1.75 (m, 2H), 1.34\* (d, *J* = 6.3 Hz, 3H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.07 (s, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  188.6 (dd, *J*<sub>CF</sub> = 30.0, 28.8 Hz, 1C), 152.9, 148.0, 127.6 (t, *J*<sub>CF</sub> = 4.1 Hz, 1C), 127.3 (t, *J*<sub>CF</sub> = 2.1 Hz, 1C), 127.2\* (t, *J*<sub>CF</sub> = 2.3 Hz, 1C), 117.2\* (dd, *J*<sub>CF</sub> = 260, 253 Hz, 1C), 116.8 (dd, *J*<sub>CF</sub> = 260, 254 Hz, 1C), 109.8, 108.1, 102.1, 70.6 (dd, *J*<sub>CF</sub> = 28.1, 24.5 Hz, 1C), 68.9\* (dd, *J*<sub>CF</sub> = 28.3, 23.9 Hz, 1C), 68.3, 66.9\*, 38.1, 36.2\*, 24.1, 22.8\*, 18.1 (3C), 18.0 (3C), 12.7(3C), 12.3\* (3C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -106.9 (dd, *J*<sub>FF</sub> = 282, *J*<sub>HF</sub> = 6.8 Hz, 1F), -107.4\* (dd, *J*<sub>FF</sub> = 279, *J*<sub>HF</sub> = 6.2 Hz, 1F), -116.0 (dd, *J*<sub>FF</sub> = 282, *J*<sub>HF</sub> = 16.6 Hz, 1F), -116.7\* (dd, *J*<sub>FF</sub> = 279, *J*<sub>HF</sub> = 17.5 Hz, 1F); IR (film)  $\nu$ <sub>max</sub> 3468,

2944, 1683, 1607, 1447, 1267  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{34}\text{F}_2\text{O}_5\text{Si}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 445.2222, found 445.2227. \* denotes minor diastereomer.

### Determination of Absolute Stereochemical Configuration of **81**:

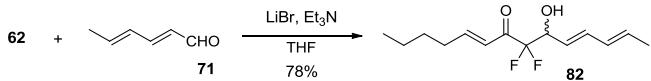


**Desilylation/cyclisation.** A solution of (*3R,5R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-3-hydroxy-5-((triisopropylsilyl)oxy)-hexan-1-one **81** and (*3S,5R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-3-hydroxy-5-((triisopropylsilyl)oxy)-hexan-1-one (19.8 mg, 0.044 mmol) in THF (0.5 mL) was treated with a solution of TBAF (0.5 mL, 1.0 M in THF). After 20 min at rt, the reaction was quenched with  $\text{H}_2\text{O}$  (5 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  2). The combined organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash chromatography (6:2:2 hexanes/EtOAc/Et<sub>2</sub>O) afforded the axial isomer (5.0 mg, 39% yield) as an oil and the equatorial isomer (4.4 mg, 34% yield) as an oil.

**For the axial isomer:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (dd,  $J = 8.2, 1.6$  Hz, 1H), 7.18 (s, 1H), 6.81 (d,  $J = 8.2$  Hz, 1H), 5.97 (dd,  $J = 3.5, 1.5$  Hz, 2H), 4.80 (br s, 1H), 4.55 (m, 1H), 4.23 (m, 1H), 3.31 (br s, 1H), 2.06–1.94 (m, 2H), 1.35 (d,  $J = 6.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  148.2, 147.2, 130.8 (d,  $J_{\text{CF}} = 1.7$  Hz, 1C), 121.5, 113.4 (dd,  $J_{\text{CF}} = 258, 247$  Hz, 1C), 108.5, 107.5, 101.2, 97.2 (dd,  $J_{\text{CF}} = 28.8, 26.2$  Hz), 68.9 (dd,  $J_{\text{CF}} = 34.0, 22.4$  Hz), 61.0, 37.5 (d,  $J_{\text{CF}} = 5.0$  Hz), 20.6;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –

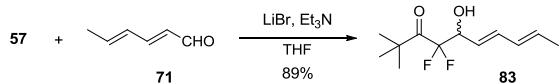
116.18 (dd,  $J_{\text{FF}} = 258$ ,  $J_{\text{HF}} = 3.2$  Hz, 1F), -127.0 (ddd,  $J_{\text{FF}} = 258$ ,  $J_{\text{HF}} = 5.6$ , 2.0 Hz, 1F); IR (film)  $\nu_{\text{max}}$  3401, 2978, 2931, 1440, 1251, 1088, 1039 cm<sup>-1</sup>; HRMS (EI)  $m/z$  calcd for C<sub>13</sub>H<sub>14</sub>F<sub>2</sub>O<sub>5</sub> (M)<sup>+</sup> 288.0809, found 288.0806;  $[\alpha]^{23}_{\text{D}} +34^\circ$  ( $c$  0.42, CHCl<sub>3</sub>).

**For the equatorial isomer:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.19–7.15 (m, 2H), 6.82 (d,  $J = 8.1$  Hz, 1H), 5.98 (dd,  $J = 3.3$ , 1.5 Hz, 2H), 4.48–4.34 (m, 2H), 2.13 (dddd,  $J = 12.9$ , 5.5, 3.3, 2.5 Hz, 1H), 1.73 (td,  $J = 12.9$ , 12.0, 1.6 Hz, 1H), 1.33 (d,  $J = 6.3$  Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  148.5, 147.4, 131.4 (d,  $J_{\text{CF}} = 1.5$  Hz), 121.2, 116.8 (dd,  $J_{\text{CF}} = 256$ , 244 Hz), 108.3, 107.6, 101.3, 96.6 (dd,  $J_{\text{CF}} = 31.3$ , 24.2 Hz), 66.7 (t,  $J_{\text{CF}} = 21.3$  Hz), 64.9, 39.1 (d,  $J_{\text{CF}} = 5.8$  Hz), 20.7; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -128.1 (dt,  $J_{\text{FF}} = 242$ ,  $J_{\text{HF}} = 3.7$  Hz, 1F), -130.1 (dd,  $J_{\text{FF}} = 242$ ,  $J_{\text{HF}} = 19.7$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3401, 2976, 2932, 1489, 1506, 1440, 1255, 1093, 1073, 1039 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>13</sub>H<sub>14</sub>F<sub>2</sub>O<sub>5</sub> (M)<sup>+</sup> 288.0809, found 288.0807;  $[\alpha]^{24}_{\text{D}} +29^\circ$  ( $c$  0.37, CHCl<sub>3</sub>).



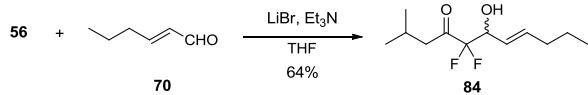
**(5E,10E,12E)-8,8-Difluoro-9-hydroxytetradeca-5,10,12-trien-7-one 82.** See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-2,2-dihydroxydec-5-en-4-one **62** (30.0 mg, 0.109 mmol), LiBr (28.3 mg, 0.326 mmol), and dienal **71\*** (23  $\mu\text{L}$ , 0.22 mmol, 95:5 (2E,4E)-isomer/(2E,4Z)-isomer mixture\*) in THF (700  $\mu\text{L}$ ) was treated with Et<sub>3</sub>N (17  $\mu\text{L}$ , 0.12 mmol). SiO<sub>2</sub> flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **82** in 78% yield (21.9 mg, 95:5 mixture of isomers\*) as a colorless oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.22 (dt,  $J = 15.5$ , 7.0 Hz, 1H), 6.54 (dt,  $J = 15.5$ , 1.4 Hz, 1H), 6.37 (ddd,  $J = 15.5$ , 10.5 Hz, 1H), 6.08 (ddd,  $J = 14.5$ ,

10.5, 1.7 Hz, 1H), 5.80 (dq,  $J = 15.1, 6.8$  Hz, 1H), 5.57 (dd,  $J = 15.0, 6.5$  Hz, 1H), 4.59 (m, 1H), 2.30 (m, 2H), 1.77 (dd,  $J = 6.5, 1.0$  Hz, 3H), 1.66 (br s, 1H), 1.48 (m, 2H), 1.35 (m, 2H), 0.92 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  189.5 (t,  $J_{\text{CF}} = 29.1$  Hz, 1C), 154.2, 136.0, 132.5, 130.2, 122.7, 122.3, 115.1 (dd,  $J_{\text{CF}} = 259, 255$  Hz, 1C), 72.3 (dd,  $J_{\text{CF}} = 27.3, 25.9$  Hz, 1C), 32.7, 29.8, 22.3, 18.2, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –114.4 (dd,  $J_{\text{FF}} = 275, J_{\text{HF}} = 7.9$  Hz, 1F), –122.1 (dd,  $J_{\text{FF}} = 275, J_{\text{HF}} = 14.4$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3436, 2960, 2932, 2874, 1708, 1624, 1134, 1088, 989  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{20}\text{F}_2\text{O}_2$  ( $\text{M}^+$ ) 258.1431, found 258.1429.

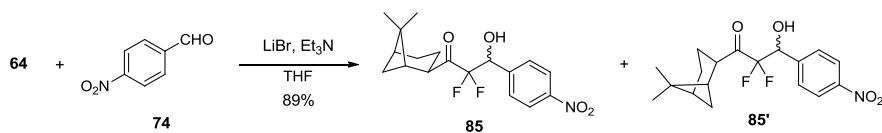


**(6E,8E)-4,4-Difluoro-5-hydroxy-2,2-dimethyldeca-6,8-dien-3-one 83.** See representative reaction procedure. A solution of 4,4,6,6,6-pentafluoro-5,5-dihydroxy-2,2-dimethylhexan-3-one **57** (30.0 mg, 0.120 mmol), LiBr (37.7 mg, 0.360 mmol), and dienal **71\*** (26  $\mu\text{L}$ , 0.24 mmol, 95:5 ( $2E,4E$ )-isomer/( $2E,4Z$ )-isomer mixture\*) in THF (750  $\mu\text{L}$ ) was treated with  $\text{Et}_3\text{N}$  (17  $\mu\text{L}$ , 0.12 mmol).  $\text{SiO}_2$  flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **83** in 89% yield (24.9 mg, 95:5 mixture of isomers\*) as a colorless oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.35 (dd,  $J = 15.5, 10.5$  Hz, 1H), 6.07 (ddd,  $J = 15.1, 10.5, 1.7$  Hz, 1H), 5.80 (dq,  $J = 15.1, 6.8$  Hz, 1H), 5.54 (dd,  $J = 15.5, 7.0$  Hz, 1H), 4.67 (m, 1H), 2.28 (d,  $J = 6.5$  Hz, 1H), 1.77 (dd,  $J = 6.8, 1.5$  Hz, 3H), 1.26 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  206.1 (dd,  $J_{\text{CF}} = 29.5, 25.9$  Hz, 1C), 136.0, 132.4, 130.2, 122.6 (dd,  $J_{\text{CF}} = 3.7, 1.9$  Hz, 1C), 166.4 (dd,  $J_{\text{CF}} = 264, 257$  Hz, 1C), 72.2 (dd,  $J_{\text{CF}} = 27.8, 24.1$  Hz, 1C), 43.8, 25.7 (3), 18.2;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –106.6

(dd,  $J_{\text{FF}} = 284$ ,  $J_{\text{HF}} = 7.3$  Hz, 1F),  $-117.3$  (dd,  $J_{\text{FF}} = 284$ ,  $J_{\text{HF}} = 16.1$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3435, 2975, 2937, 2916, 2879, 1722, 1482, 1369, 1071, 990 cm<sup>-1</sup>; HRMS (EI)  $m/z$  calcd for C<sub>12</sub>H<sub>18</sub>F<sub>2</sub>O<sub>2</sub> (M)<sup>+</sup> 232.1275, found 232.1273.

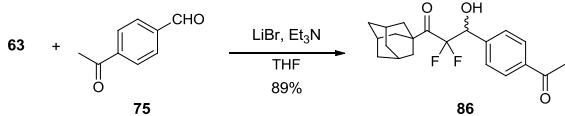


**(E)-5,5-Difluoro-6-hydroxy-2-methylundec-7-en-4-one 84.** See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-2,2-dihydroxy-6-methylheptan-4-one **56** (30.0 mg, 0.120 mmol), LiBr (31.2 mg, 0.360 mmol), and (E)-hex-2-enal **70** (24  $\mu$ L, 0.12 mmol) in THF (750  $\mu$ L) was treated with Et<sub>3</sub>N (17  $\mu$ L, 0.12 mmol). SiO<sub>2</sub> flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **84** in 64% yield (18.1 mg) as a colorless oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.89 (dtd,  $J = 15.5, 6.5, 1.0$  Hz, 1H), 5.52 (dtd,  $J = 15.5, 7.0, 1.5$  Hz, 1H), 4.49 (qu,  $J = 7.5$  Hz, 1H), 2.57 (d,  $J = 7.0$  Hz, 2H), 2.20 (m, 2H), 2.06 (q,  $J = 7.0$  Hz, 2H), 1.41 (sextet,  $J = 7.5$  Hz, 2H), 0.95 (dd,  $J = 6.5, 2.0$  Hz, 6H), 0.89 (t,  $J = 7.5$  Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  201.7 (dd,  $J_{\text{CF}} = 30.3$ , 27.8 Hz, 1C), 138.3, 122.9, 114.7 (dd,  $J_{\text{CF}} = 259, 255$  Hz, 1C), 72.3 (dd,  $J_{\text{CF}} = 27.9, 24.7$  Hz, 1C), 46.6, 34.4, 23.4, 22.4 (2), 21.9, 13.5; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$   $-114.1$  (dd,  $J_{\text{FF}} = 272$ ,  $J_{\text{HF}} = 8.2$  Hz, 1F),  $-122.5$  (dd,  $J_{\text{FF}} = 271$ ,  $J_{\text{HF}} = 14.9$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3461, 2962, 2933, 2875, 1740, 1468, 1101, 1066, 972 cm<sup>-1</sup>; HRMS (EI)  $m/z$  calcd for C<sub>12</sub>H<sub>20</sub>F<sub>2</sub>O<sub>2</sub> (M+H-H<sub>2</sub>O)<sup>+</sup> 217.1404, found 217.1407.



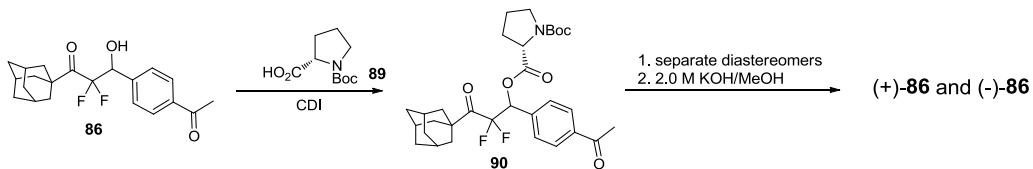
**1-((1*S*,2*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-2,2-difluoro-3-hydroxy-**

**3-(4-nitrophenyl)-propan-1-one 85.** See representative reaction procedure. A solution of 1-((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **64** (27.6 mg, 0.087 mmol), LiBr (22.7 mg, 0.262 mmol), and 4-nitrobenzaldehyde **74** (30.3 mg, 0.201 mmol) in THF (600  $\mu$ L) was treated with Et<sub>3</sub>N (21  $\mu$ L, 0.15 mmol). The ratio of diastereomers was determined from <sup>19</sup>F NMR analysis of the crude reaction mixture. SiO<sub>2</sub> flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **85** (dr = 6.8:5.6) and product **85'** (dr = 1.1:1.0) as an inseparable mixture (27.4 mg) in 89% combined yield: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.24 (dd, *J* = 8.9, 2.1 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 5.40 (dt, *J* = 19.2, 4.8 Hz, 1H), 5.35\* (dt, *J* = 18.5, 5.5 Hz, 1H), 3.43–3.31 (m, 1H), 3.05\* (d, *J* = 4.6 Hz, 1H), 2.90 (d, *J* = 5.2 Hz, 1H), 2.50 (m, 1H), 2.42–2.20 (m, 2H), 2.04–1.85 (m, 4H), 1.22\* (d, *J* = 11.3 Hz, 1H), 1.20 (s, 3H), 1.16\* (s, 3H), 1.14 (d, *J* = 10.1 Hz, 1H), 0.79 (s, 3H), 0.77\* (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  203.8 (t, *J*<sub>CF</sub> = 31.5 Hz), 148.3, 141.9, 129.0, 128.9, 123.3 (2C), 114.4 (dd, *J*<sub>CF</sub> = 266, 256 Hz), 72.1\* (dd, *J*<sub>CF</sub> = 28.3, 23.6 Hz), 71.8 (dd, *J*<sub>CF</sub> = 28.8, 23.0 Hz), 49.2\*, 49.1, 42.0, 41.9\*, 40.4, 40.3\*, 38.8\*, 38.7, 30.8, 30.7\*, 27.1, 24.9, 24.8\*, 22.3, 22.1\*, 13.7, 13.3\*; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -106.2 (dd, *J*<sub>FF</sub> = 285, 1F), -109.9\* (dd, *J*<sub>FF</sub> = 284, *J*<sub>HF</sub> = 5.4 Hz, 1F), -121.9\* (dd, *J*<sub>FF</sub> = 284, *J*<sub>HF</sub> = 18.0 Hz, 1F), -125.5 (dd, *J*<sub>FF</sub> = 285, *J*<sub>HF</sub> = 19.2 Hz, 1F); IR (film)  $\nu$ <sub>max</sub> 3513, 2918, 1733, 1606, 1517, 1346, 1074 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>4</sub> (M+Na)<sup>+</sup> 376.1336, found 376.1340. \* denotes minor diastereomer.



**3-(4-Acetylphenyl)-1-(adamantan-1-yl)-2,2-difluoro-3-hydroxypropan-1-one**

**86.** See representative reaction procedure. A solution of 1-(adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **63** (30.0 mg, 0.091 mmol), LiBr (23.8 mg, 0.274 mmol), and 4-acetylbenzaldehyde **75** (31.1 mg, 0.210 mmol) in THF (650  $\mu\text{L}$ ) was treated with  $\text{Et}_3\text{N}$  (23  $\mu\text{L}$ , 0.17 mmol).  $\text{SiO}_2$  flash chromatography (8.5:1.5–9:1 hexanes/EtOAc) afforded the product **86** in 89% yield (29.6 mg) as a solid: mp 98–101  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (td,  $J = 8.5, 2.0$  Hz, 2H), 7.54 (d,  $J = 8.0$  Hz, 2H), 5.32 (dt,  $J = 18.0, 5.5$  Hz, 1H), 2.96 (d,  $J = 5.0$  Hz, 1H), 2.61 (s, 3H), 2.03 (br s, 3H), 1.90 (br s, 6H), 1.71 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  205.4 (dd,  $J_{\text{CF}} = 29.3, 25.9$  Hz, 1C), 197.8, 140.1, 137.3, 128.3 (2), 128.1 (2), 116.1 (dd,  $J_{\text{CF}} = 267, 259$  Hz, 1C), 72.6 (dd,  $J_{\text{CF}} = 27.9, 23.4$  Hz, 1C), 46.8 (t,  $J_{\text{CF}} = 2.3$  Hz, 1C), 36.8 (3), 36.3 (3), 27.5 (3), 26.7;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –105.5 (dd,  $J_{\text{FF}} = 291, J_{\text{HF}} = 4.8$  Hz, 1F), –118.2 (dd,  $J_{\text{FF}} = 291, J_{\text{HF}} = 17.8$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  3435, 2908, 2853, 1715, 1674, 1270, 1064  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{24}\text{F}_2\text{O}_3$  ( $\text{M}+\text{H}$ )<sup>+</sup> 363.1772, found 363.1778.

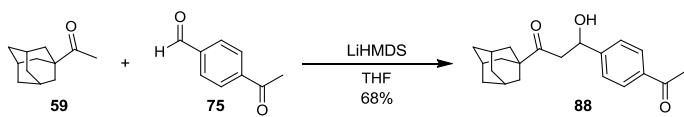


**Separation of Compounds (–)-86 and (+)-86.** To a solution of (*S*)-Boc-proline (231 mg, 1.08 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL), CDI (174 mg, 1.08 mmol) was added and stirred for 5 min at rt. Then, the reaction mixture was transferred to another vial containing 3-(4-

acetylphenyl)-1-(adamantan-1-yl)-2,2-difluoro-3-hydroxypropan-1-one **86** (78 mg, 0.22 mmol) and stirred at 70 °C overnight. Next, the reaction mixture was cooled to rt and quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL) at the same temperature, and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (6 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Preparatory TLC (SiO<sub>2</sub>, 4:2:2:1.5 hexanes:pentanes:petroleum ether:EtOAc) afforded the two pure diastereomers that were individually treated with a solution of 2 M KOH (1 mL) in MeOH (2 mL). After stirring for 2 h at rt, the reaction mixtures were quenched with saturated aqueous NH<sub>4</sub>Cl (6 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (6 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash chromatography (3:7 EtOAc:hexanes) afforded (+)-**86** in 14% yield (10.9 mg) as a solid. SiO<sub>2</sub> flash chromatography (3:7 EtOAc:hexanes) afforded (-)-**86** in 14% yield (10.5 mg) as a solid.

**(+)-3-(4-Acetylphenyl)-1-(adamantan-1-yl)-2,2-difluoro-3-hydroxypropan-1-one (86).** [α]<sup>23</sup><sub>D</sub> +36.0 (*c* 0.667, CHCl<sub>3</sub>); Anal. Calcd for C<sub>21</sub>H<sub>24</sub>F<sub>2</sub>O<sub>3</sub>: C, 69.60; H, 6.67. Found: C, 66.45; H, 6.51. Other characterization data is identical to the data reported for compound **86**.

**(-)-3-(4-Acetylphenyl)-1-(adamantan-1-yl)-2,2-difluoro-3-hydroxypropan-1-one (86).** [α]<sup>23</sup><sub>D</sub> -35.8 (*c* 0.558, CHCl<sub>3</sub>). Other characterization data is identical to the data reported for compound **10**.

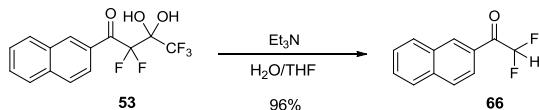


**3-(4-Acetylphenyl)-1-(adamantan-1-yl)-3-hydroxypropan-1-one (88).** To a -78 °C solution of *n*-BuLi (0.14 mL, 2.5 M in hexanes) in THF (3 mL) was added hexamethyldisilazane (71 µL, 0.337 mmol). After 20 min at -78 °C, a solution of 1-adamantyl methyl ketone (50.0 mg, 0.280 mmol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred for 40 min at -78 °C. Next, a solution of 4-acetylbenzaldehyde (50.0 mg, 0.337 mmol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred for 20 min at -78 °C. Then, the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) at -78 °C. The mixture was warmed to rt and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentration under reduced pressure. SiO<sub>2</sub> flash chromatography (8:2 hexanes/EtOAc) afforded the product **88** as a colorless oil in 68% yield (62.5 mg): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 5.16 (dt, *J* = 8.6, 2.7 Hz, 1H), 3.78 (d, *J* = 3.0 Hz, 1H), 2.86 (dd, *J* = 18.0, 3.3 Hz, 1H), 2.80 (dd, *J* = 18.0, 8.8 Hz, 1H), 2.59 (s, 3H), 2.03 (br s, 3H), 1.78–1.70 (m, 9H), 1.67–1.64 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 216.4, 197.8, 148.4, 136.3, 128.6 (2), 125.7 (2), 69.5, 46.6, 44.7, 37.9 (3), 36.3 (3), 27.7 (3), 26.6; IR (film) ν<sub>max</sub> 3468, 2905, 2850, 1682, 1268 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>21</sub>H<sub>26</sub>O<sub>3</sub> (M)<sup>+</sup> 326.1882, found 326.1876.

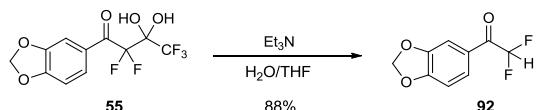
**Representative Reaction Procedure for *a,a*-Difluoromethyl Ketones A**

solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **53** (73.0 mg, 0.23 mmol) in H<sub>2</sub>O/THF (2 mL/0.5mL) was treated with Et<sub>3</sub>N (130 µL, 0.91 mmol) and stirred for 10 min. at rt. The organics was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL x 3). Then, the organic layer was dried over with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure.

$\text{SiO}_2$  flash chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **66** in 96% yield (45.1 mg, solid).

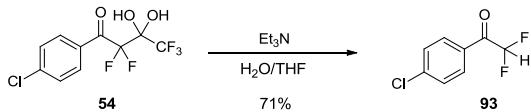


**2,2-Difluoro-1-(naphthalen-2-yl)ethanone 66.** See representative reaction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.65 (s, 1H), 8.08 (d,  $J = 8.5$  Hz, 1H), 8.02 (d,  $J = 8.5$  Hz, 1H), 7.96 (d,  $J = 8.5$  Hz, 1H), 7.91 (d,  $J = 8.5$  Hz, 1H), 7.68–7.65 (m, 1H), 7.61–7.58 (m, 1H), 6.41 (t,  $J = 53.5$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  187.3 (t,  $J_{\text{CF}} = 25.4$  Hz, 1C), 136.0, 132.2 (t,  $J_{\text{CF}} = 3.0$  Hz, 1C), 132.0, 129.8, 129.4, 128.7, 128.5, 127.6, 127.0, 123.8, 111.1 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -120.6 (d,  $J_{\text{HF}} = 53.6$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  1706, 1623, 1056  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_9\text{F}_5\text{O}_3$  ( $\text{M}^+$ ) 206.0543, found 206.0547; mp 47 °C. All spectral and characterization data matched the reported data.<sup>54,127</sup>

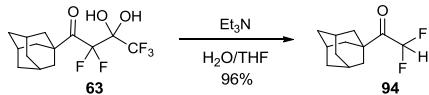


**1-(Benzo[d][1,3]dioxol-5-yl)-2,2-difluoroethanone 92.** See representative reaction procedure. 1-(benzo[d][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **55** (80.0 mg, 0.26 mmol),  $\text{Et}_3\text{N}$  (140  $\mu\text{L}$ , 0.73 mmol),  $\text{H}_2\text{O/THF}$  (2 ml/0.5 ml) were used. The reaction mixture was stirred for 10 min. at rt.  $\text{SiO}_2$  flash chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **92** in 88% yield (45.1 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (m, 1H), 7.49 (m, 1H), 6.90 (d,  $J = 8.4$  Hz,

1H), 6.24 (t,  $J = 53.6$  Hz, 1H), 6.08 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  185.6 (t,  $J_{\text{CF}} = 25.1$  Hz, 1C), 153.4, 148.5, 126.8, 126.0, 111.3 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 108.8, 108.4, 102.2;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -122.1 (d,  $J_{\text{HF}} = 53.3$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  1694, 1451, 1259, 1036  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_9\text{H}_6\text{F}_2\text{O}_3$  ( $\text{M}^+$ ) 200.0285, found 200.0286; mp 61–62 °C.

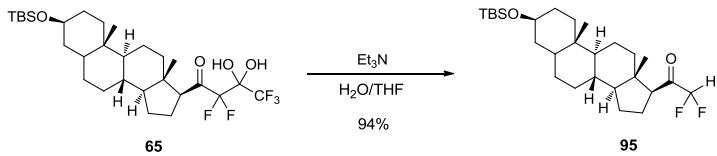


**1-(4-Chlorophenyl)-2,2-difluoroethanone 93.** See representative reaction procedure. 1-(4-chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **54** (100 mg, 0.33 mmol),  $\text{Et}_3\text{N}$  (185  $\mu\text{L}$ , 1.31 mmol),  $\text{H}_2\text{O/THF}$  (2 ml/0.5 ml) were used. The reaction mixture was stirred for 10 min. at rt.  $\text{SiO}_2$  flash chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **93** in 71% yield (44.5 mg, oil).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (m, 1H), 7.50 (m, 1H), 6.24 (t,  $J = 53.4$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  186.6 (t,  $J_{\text{CF}} = 25.9$  Hz, 1C), 141.7, 131.0 (2), 129.7, 129.4 (2), 112.3 (t,  $J_{\text{CF}} = 252.6$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -122.6 (d,  $J_{\text{HF}} = 53.3$  Hz, 2F). All spectral and characterization data matched the reported data.<sup>121</sup>



**1-(Adamantan-1-yl)-2,2-difluoroethanone 94** See representative reaction procedure. 1-(adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **63** (47.0 mg, 0.14 mmol),  $\text{Et}_3\text{N}$  (80.0  $\mu\text{L}$ , 0.57 mmol),  $\text{H}_2\text{O/THF}$  (2 ml/0.5 ml) were used. The reaction mixture was stirred for 1 h at rt.  $\text{SiO}_2$  flash chromatography (100%  $\text{CHCl}_3$ )

afforded the desired product **94** in 96% yield (29.6 mg, oil).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.97 (t,  $J = 53.3$  Hz, 1H), 2.07 (m, 3H), 1.93 (m, 6H), 1.73 (m, 6H). All spectral and characterization data matched the reported data.<sup>127</sup>



**1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-Butyldimethylsilyl)oxy)-10,13-**

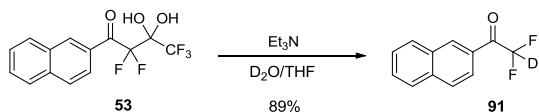
**dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2,2-difluoroethanone**

**95** See representative reaction procedure. 1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **65** (30.0 mg, 0.05 mmol),  $\text{Et}_3\text{N}$  (29.0  $\mu\text{L}$ , 0.21 mmol),  $\text{H}_2\text{O}/\text{THF}$  (500  $\mu\text{L}/100 \mu\text{L}$ ) were used. The reaction mixture was stirred for 1 h at rt.  $\text{SiO}_2$  flash chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **95** in 94% yield (22.8 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.63 (t,  $J = 54.2$  Hz, 1H), 3.55 (ddd,  $J = 15.7, 10.8, 4.8$  Hz, 1H), 2.94 (t,  $J = 8.9$  Hz, 1H), 2.17 (m, 1H), 1.88 (d,  $J = 12.7$  Hz, 1H), 1.80 – 1.63 (m, 5H), 1.62 – 1.56 (dq,  $J = 13.6, 3.9$  Hz, 1H), 1.49 – 1.17 (m, 11H), 1.13 – 1.02 (m, 1H), 0.99 – 0.90 (ddd,  $J = 15.9, 8.2, 4.2$  Hz, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.67 (s, 3H), 0.05 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  201.3 ( $t, J_{\text{CF}} = 24.9$  Hz, 1C), 109.9 ( $t, J_{\text{CF}} = 251.3$  Hz, 1C), 72.1, 57.0, 56.9, 54.2, 46.4, 45.0, 38.6 (3), 37.2, 35.7, 35.5, 32.1, 31.9, 28.6, 26.0, 24.6, 23.6, 21.2, 18.3, 13.9, 12.3, -4.6 (2);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -128.4 (d,  $J_{\text{HF}} = 54.1$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  2931, 1732, 1252, 1091  $\text{cm}^{-1}$ ;

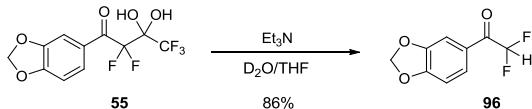
HRMS (EI)  $m/z$  calcd for  $C_{27}H_{46}F_2O_2Si$  ( $M-CH_3$ )<sup>+</sup> 453.3000, found 453.2994; mp 116–118 °C.

## **Representative Reaction Procedure for $\alpha$ -Deutro- $\alpha,a$ -Difluoromethyl**

**Ketones.** A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **53** (100 mg, 0.31 mmol) in D<sub>2</sub>O/THF (2 ml/0.5ml) was treated with Et<sub>3</sub>N (175 µL, 1.25 mmol) and stirred for 15 min. at rt. The organics was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL x 3). Then, the organic layer was dried over with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash chromatography (100% CHCl<sub>3</sub>) afforded the desired product as a major product **91** in 89% yield (58.1 mg, solid, 98% D).

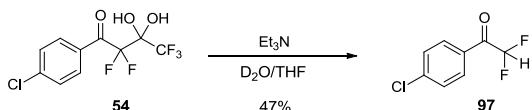


**2-Deutero-2,2-difluoro-1-(naphthalen-2-yl)ethanone** **91.** See representative reaction procedure.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.63 (s, 1H), 8.09–8.03 (m, 1H), 8.02–7.96 (m, 1H), 7.96–7.86 (m, 2H), 7.70–7.55 (m, 2H), \*6.42 (t,  $J = 54.0$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  187.5 (t,  $J = 24.8$  Hz, 1C), 136.2, 132.4, 132.2, 130.0, 129.6, 128.9, 128.7, 127.8, 127.2, 124.0, 111.4 (tt,  $J = 250.5, 29.3$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  \*-122.3 (d,  $J_{\text{HF}} = 53.6$  Hz, 2F), -123.1 (t,  $J_{\text{DF}} = 8.2$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  1707, 1108, 801  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_7\text{DF}_2\text{O} (\text{M}+\text{H})^+$  208.0684, found 208.0681; mp 58–60 °C. \* indicates minor protonated product.



**1-(Benzo[d][1,3]dioxol-5-yl)-2-deutro-2,2-difluoroethanone** **96.** See

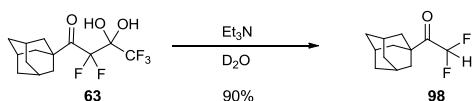
representative reaction procedure. 1-(benzo[d][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **55** (79 mg, 0.25 mmol), Et<sub>3</sub>N (140 μL, 1.01 mmol), D<sub>2</sub>O/THF (2 ml/0.5 ml) were used. The reaction mixture was stirred for 10 min. at rt. SiO<sub>2</sub> flash chromatography (100% CHCl<sub>3</sub>) afforded the desired product as a major product **96** in 86% yield (43.4 mg, solid, 98% D). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.71 (ddt, *J* = 8.3, 1.7, 1.1 Hz, 1H), 7.53–7.46 (m, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.09 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 185.6 (t, *J*<sub>CF</sub> = 25.4 Hz, 1C), 153.4, 148.5, 126.9, 126.0, 111.0 (tt, *J* = 250.0, 28.8 Hz, 1C), 108.8, 108.4, 102.2; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ \* -122.1 (d, *J*<sub>HF</sub> = 53.3 Hz, 2F), -122.8(t, *J*<sub>DF</sub> = 8.2 Hz, 2F); IR (film) ν<sub>max</sub> 1694, 1447, 1239, 1095, 1035 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>9</sub>H<sub>5</sub>DF<sub>2</sub>O<sub>3</sub> (M)<sup>+</sup> 201.0348, found 201.0345; mp 61–63 °C. \* indicates minor protonated product.



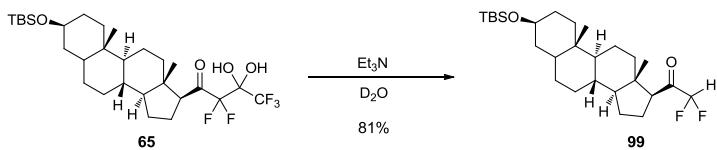
**1-(4-Chlorophenyl)-2-deutero-2,2-difluoroethanone** **97** See representative

reaction procedure. 1-(4-chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **54** (68.5 mg, 0.23 mmol), Et<sub>3</sub>N (125 μL, 0.90 mmol), D<sub>2</sub>O/THF (2 ml/0.5 ml) were used. The reaction mixture was stirred for 10 min. at rt. SiO<sub>2</sub> flash chromatography (100% CHCl<sub>3</sub>) afforded the desired product as a major product **97** in 47% yield (20.3 mg, oil, 96% D). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (m, 2H), 7.51 (m, 2H), \*6.24 (t, *J*<sub>HF</sub> = 31.0 Hz);

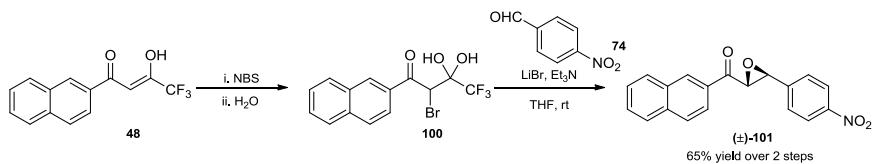
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 186.6 (t, *J* = 56.4 Hz, 1C), 141.7, 131.0 (2), 129.6, 129.4 (2), 111.0 (tt, *J* = 566.8, 64.9 Hz, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ \*-122.5 (d, *J*<sub>HF</sub> = 53.6 Hz, 2F), -123.2 (t, *J*<sub>DF</sub> = 8.2 Hz, 2F); IR (film) ν<sub>max</sub> 1711, 1591, 1172, 1094 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>8</sub>H<sub>4</sub>DClF<sub>2</sub>O (M)<sup>+</sup> 191.0060, found 191.056. \* indicates minor protonated product.



**1-(Adamantan-1-yl)-2-deutero-2,2-difluoroethanone** **98** See representative reaction procedure. 1-(adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **63** (30.0 mg, 0.09 mmol), Et<sub>3</sub>N (100 μL, 0.73 mmol), D<sub>2</sub>O (600 μL) were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash chromatography (100% CHCl<sub>3</sub>) afforded the desired product as a major product **98** in 90% yield (17.8 mg, oil, 98% D). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ \*5.97 (t, J<sub>HF</sub> = 55.0 Hz, 1H), 2.08 (s, 3H), 1.94 (d, J = 2.7 Hz, 6H), 1.83–1.69 (m, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 201.9 (t, J = 21.8 Hz, 1C), 109.1 (tt, J = 566.8, 62.0 Hz, 1C), 45.2, 37.1 (3), 36.2 (3), 27.5 (3); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -125.7 (d, J<sub>HF</sub> = 53.6 Hz, 2F), -126.4 (t, J<sub>DF</sub> = 8.5 Hz, 2F); IR (film) ν<sub>max</sub> 2910, 1732, 1454, 1109 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd for C<sub>12</sub>H<sub>15</sub>DF<sub>2</sub>O (M+H)<sup>+</sup> 216.1301, found 216.1312. \* indicates minor protonated product.

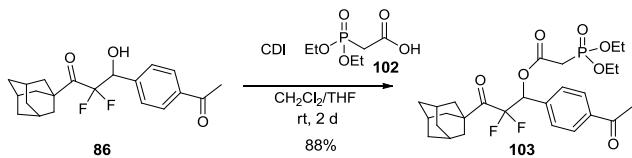


**1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-Butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-deutro-2,2-difluoroethanone 99** See representative reaction procedure. 1-((3S,8R,9S,10S,13S,14S,17S)-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **65** (30 mg, 0.05 mmol), Et<sub>3</sub>N (58.0 μL, 0.41 mmol), D<sub>2</sub>O (400 μL) were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash chromatography (100% CHCl<sub>3</sub>) afforded the desired product as a major product **99** in 81% yield (19.7 mg, solid, 99% D). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.54 (ddd, *J* = 15.7, 10.8, 4.8 Hz, 1H), 2.95 (t, *J* = 8.9 Hz, 1H), 2.15 (m, 1H), 1.91–1.84 (m, 1H), 1.80–1.63 (m, 5H), 1.61–1.55 (m, 1H), 1.48–1.17 (m, 11H), 1.11–1.02 (m, 1H), 0.98–0.89 (m, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.66 (s, 3H), 0.04 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 201.3 (dt, *J* = 24.8, 9.5 Hz, 1C), 109.5 (tt, *J* = 250.9, 28.9 Hz, 1C), 72.0, 57.0, 54.1, 46.4 (2), 44.9, 38.6, 37.1, 35.6, 35.5, 32.1, 31.9, 28.6, 25.9 (3), 24.6, 23.6, 23.5, 21.1, 18.3, 13.9, 12.3, -4.6 (2); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -129.0–129.1 (m, 2F); IR (film) ν<sub>max</sub> 2931, 1730, 1252 cm<sup>-1</sup>; mp 130–131 °C.



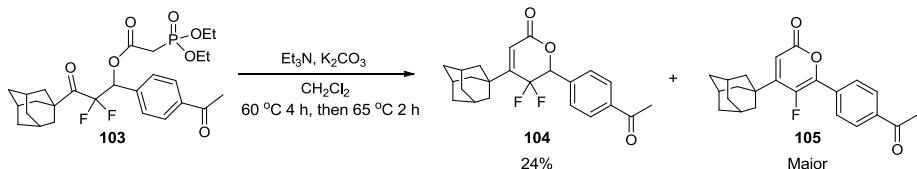
**2,3-Epoxy-1-(naphthalen-2-yl)-3-(4-nitrophenyl)-propan-1-one 101.** To a solution of 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione **48** (200 mg, 0.8 mmol) in CH<sub>3</sub>CN (3 mL) was added NBS (134 mg, 0.751 mmol). The mixture was stirred

overnight at rt, H<sub>2</sub>O (3 mL) was added, and then, the mixture was stirred overnight at rt. Next, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (6 mL × 2) and the organics were concentrated under reduced pressure to give a solid (294 mg). This intermediate product (i.e., crude product and succinimide) was carried to the next step without any purification. To a solution of the intermediate product (32 mg), 4-nitrobenzaldehyde (21.0 mg, 0.138 mmol), and LiBr (18.0 mg, 0.21 mmol) in THF (600 μL), was added Et<sub>3</sub>N (17 μL, 0.12 mmol) dropwise. After 10 min at rt, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL), and the resultant mixture was extracted with EtOAc (2 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. PTLC (SiO<sub>2</sub>, chloroform) afforded the product **101** (17.0 mg) as a solid in 65% yield (from **48**): All spectral and characterization data matched the reported data.<sup>128</sup> Stereochemical assignment was determined from prior literature precedent.<sup>129</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.56 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 2H), 8.05 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.95 (t, *J* = 7.8 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.65 (m, 1H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.59 (m, 1H), 4.42 (d, *J* = 2.0 Hz, 1H), 4.28 (d, *J* = 2.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 191.9, 148.3, 142.8, 136.0, 132.6, 132.3, 130.6, 129.7, 129.3, 129.1, 127.9, 127.3, 126.7(2), 124.1 (2), 123.5, 60.9, 58.1.



**1-(4-Acetylphenyl)-3-((3r,5r,7r)-adamantan-1-yl)-2,2-difluoro-3-oxopropyl 2-(diethoxyphosphoryl)acetate **103**.** To a solution of 2-(diethoxyphosphoryl) acetic acid

(611 mg, 3.12 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 ml), CDI (505 mg, 3.12 mmol) was added and stirred for 10 min. at rt. Then, compound **86** (113 mg, 0.31 mmol) was dissolved in THF and added to the reaction mixture. Then, the reaction mixture was stirred at rt. After 2 days, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (1:1 hexanes/EtOAc) afforded the desired product in 88% yield (148.7 mg, oil).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95 (dd,  $J = 6.7, 1.8$  Hz, 2H), 7.55 (d,  $J = 8.3$  Hz, 2H), 6.39 (dd,  $J = 15.4, 9.8$  Hz, 1H), 4.12 (m, 4H), 3.03 (m, 2H), 2.60 (s, 3H), 2.02 (br s, 3H), 1.85 (d,  $J = 2.5$  Hz, 6H), 1.76 – 1.62 (dd,  $J = 32.3, 12.1$  Hz, 6H), 1.25 (td,  $J = 7.1, 4.7$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  202.5 (t,  $J_{\text{CF}} = 26.3$  Hz, 1C), 197.5, 163.6 (d,  $J_{\text{CF}} = 6.4$  Hz, 1C), 137.6, 136.7, 128.9 (2), 128.2 (2), 115.8 (dd,  $J_{\text{CF}} = 266.5, 258.4$  Hz, 1C), 73.4 (dd,  $J_{\text{CF}} = 28.3, 22.0$  Hz, 1C), 62.8 (t,  $J_{\text{CF}} = 7.3$  Hz, 1C), 46.6, 36.6 (3), 36.2 (3), 34.6, 33.5, 27.5 (3), 26.7, 16.2(2);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  – 109.6 (dd,  $J = 287.6, 9.9$  Hz, 1F), -113.7 (dd,  $J = 287.4, 15.2$  Hz, 1F); IR (film)  $\nu_{\text{max}}$  2909, 1756, 1718, 1687, 1266, 1024  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{27}\text{H}_{35}\text{F}_2\text{O}_7\text{P}$  ( $\text{M}+\text{H}$ ) $^+$ , 541.2167; found, 541.2186.



**6-(4-Acetylphenyl)-4-((3r,5r,7r)-adamantan-1-yl)-5,5-difluoro-5,6-dihydro-2H-pyran-2-one **104**.** To a solution of compound **103** (113 mg, 0.21 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.5 ml),  $\text{Et}_3\text{N}$  (987  $\mu\text{L}$ , 7.08 mmol) and  $\text{K}_2\text{CO}_3$  (288 mg, 2.08 mmol) were added. After

stirring for 4 h at 60 °C, the reaction temperature was increased to 65 °C and stirred for 2 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (3 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (5:2:13 CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/hexanes) afforded the desired product in 24% yield (19.7 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.01 (m, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 6.13 (d, *J* = 3.3 Hz, 1H), 5.52 (dd, *J* = 19.9, 3.9 Hz, 1H), 2.63 (s, 3H), 2.07 (br s, 3H), 1.95 (d, *J* = 13.2 Hz, 3H), 1.83 (d, *J* = 12.2 Hz, 3H), 1.76 (m 3H), 1.70 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 197.5, 161.7, 159.8 (dd, *J* = 24.8, 19.5 Hz, 1C), 138.0, 135.3, 128.6 (2), 128.2 (2), 120.0 (t, *J* = 7.7 Hz, 1C), 115.0 (dd, *J* = 251.4, 243.5 Hz, 1C), 79.9 (dd, *J* = 33.9, 27.1 Hz, 1C), 40.0 (3), 38.4, 36.2 (3), 28.0 (3), 26.7; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ – 102.7 (dd, *J* = 285.7, 19.7 Hz, 1F), -114.3 (d, *J* = 285.7 Hz, 1F); IR (film) ν<sub>max</sub> 2908, 1740, 1687, 1268, 1247, 1067 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd. for C<sub>23</sub>H<sub>24</sub>F<sub>2</sub>O<sub>3</sub> (M)<sup>+</sup>, 386.1688; found, 386.1686.

**6-(4-Acetylphenyl)-4-((3r,5r,7r)-adamantan-1-yl)-5-fluoro-2H-pyran-2-one**

**105.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.01 (td, *J* = 8.8, 6.5 Hz, 4H), 6.14 (d, *J* = 6.0 Hz, 1H), 2.65 (s, 3H), 2.14 (br s, 3H), 1.99 (m, 6H), 1.78 (m, 6H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ – 149.0 (d, *J*<sub>HF</sub> = 5.1 Hz, 1F); HRMS (EI) *m/z* calcd. for C<sub>23</sub>H<sub>23</sub>FO<sub>3</sub> (M)<sup>+</sup>, 366.1626; found, 366.1621.

## CHAPTER 4. C-C BOND CLEAVAGE STUDIES ON HIGHLY ALPHA-FLUORINATED ARYL *GEM*-DIOLS

### 4.1 Introduction

Previously, base-promoted fragmentation studies of highly  $\alpha$ -fluorinated *gem*-diols, including hexafluoroacetone hydrate, have been reported.<sup>119,130</sup> In these cases, fragmentation leads to the release of trifluoroacetate from the parent *gem*-diols (Scheme 4.1(A)). Interestingly, the synthetic methodology toward synthesis of 2,2-difluoro-3-hydroxyacids, reported by Guerrero *et al.*, also follows a deprotonation and subsequent C-C bond fragmentation reaction sequence.<sup>130</sup> However, the fragmentation patterns of  $\beta$ -hydroxy pentafluoro *gem*-diols were different from  $\alpha$ -keto pentafluoro *gem*-diols;  $\beta$ -hydroxy pentafluoro *gem*-diols released fluoroform instead of trifluoroacetate (Scheme 4.1(B)).

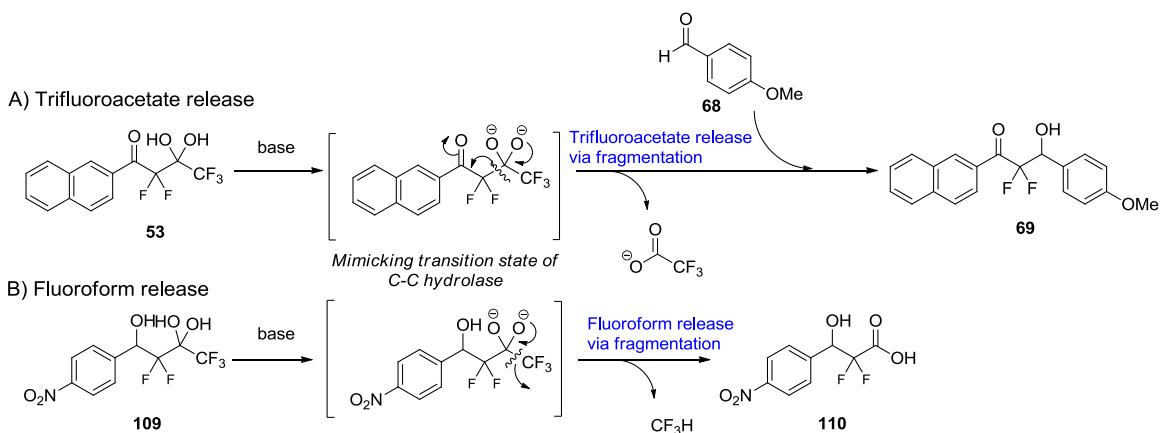


Figure 4.1 Comparison between the trifluoroacetate release and the fluoriform release (A) Generation of  $\alpha,\alpha$ -difluoroenolates via a mild trifluoroacetate release process<sup>54</sup>, (B) Fragmentation of  $\beta$ -hydroxy pentafluoro *gem*-diols.<sup>130</sup>

Because only a small difference in bond strength between the CO-CF<sub>3</sub> bond and the CO-CF<sub>2</sub>R bond is expected, we questioned what factors mainly contribute to the cleavage patterns. We also questioned whether these results were two extremes of a gradient fragmentation patterns between trifluoroacetate release and fluoriform release. A class of preliminary fragmentation studies was performed with ketone-, ester-, and a phenyl group attached to a pentafluoro *gem*-diol (Table 4.1). *gem*-Diols **53** and **57** were exposed to NaH to promote fragmentation. Then, crude reaction mixtures were analyzed by <sup>19</sup>F NMR. In the case of compounds **111** and **112**, transiently formed pentafluoro *gem*-diols were not isolated. Using on excess NaH promoted fragmentation directly and the fragmentation patterns were determined by a <sup>19</sup>F NMR of the crude product. In the cases of a ketone adjacent to the pentafluoro *gem*-diols, only trifluoroacetate release was observed (Table 4.1, entry 1, 2). However, in phenyl substrate **112**, only fluoriform was released (Table 4.1, entry 4). Interestingly, we were able to observe both trifluoroacetate release and fluoriform release from the ester **111** (Table 4.1, entry 3). This result shows

that the rates of trifluoroacetate release and fluoroform release are very similar. Based on these results, we concluded that the fragmentation patterns between trifluoroacetate release and fluoroform release were dependent upon the nature of the group adjacent to the pentafluoro *gem*-diol.

Table 4.1 Fragmentation Studies with Various Pentafluoro *gem*-Diols

	Base: NaH Solvent: THF	Trifluoroacetate release	Fluoroform reaction
entry	R <sub>1</sub>		
1		100 <sup>b</sup> (1 : 1.2)	---
2		100	---
3		91.8 <sup>c</sup>	8.2 <sup>c</sup>
4		---	100

R = naphthyl or t-butyl

a. Not detected by <sup>19</sup>F NMR.

b. Both protonated compound and self-adduct were monitored. (ratio = protonated : self-adduct).

Ratio was determined by <sup>1</sup>H NMR and <sup>19</sup>F NMR integration.

c. After 12 h at rt, the ratio between compounds was not changed.

To better understand the fragmentation patterns of highly  $\alpha$ -fluorinated *gem*-diols, the  $\alpha$ -aryl pentafluoro *gem*-diols were selected as model systems. We envisioned that various substituents on the phenyl ring might reveal a wide spectrum of cleavage patterns (Figure 4.2). Fragmentation studies will give us further insight into controlling the cleavage competition.

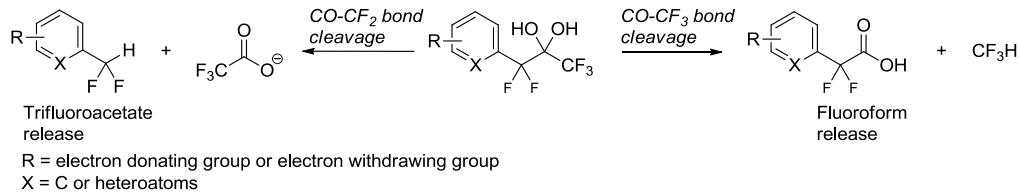


Figure 4.2 Base-promoted fragmentation of  $\alpha$ -aryl pentafluoro *gem*-diols.

## 4.2 Chemistry

Because phenyl pentafluoro *gem*-diol **112** releases fluoroform during fragmentation, we wanted to make some derivatives containing electron-withdrawing substituents to see whether changes in the cleavage pattern might be observed. The synthesis of  $\alpha$ -aryl pentafluoro *gem*-diols has not been reported; therefore two discrete synthetic plans were proposed based on retrosynthetic analysis of  $\alpha$ -aryl pentafluoro *gem*-diols (Figure 4.3). First,  $\alpha$ -aryl pentafluoro *gem*-diols have been disconnected to trifluoromethyl ketones and they are further disconnected to carboxylic acids (Figure 4.3(A)). Second,  $\alpha$ -aryl pentafluoro *gem*-diols have been disconnected to difluoroethyl acetates and they are further disconnected to aryl iodides and bromo-difluoro ethyl acetate (Figure 4.3(B)). Both retrosynthetic approaches were examined.

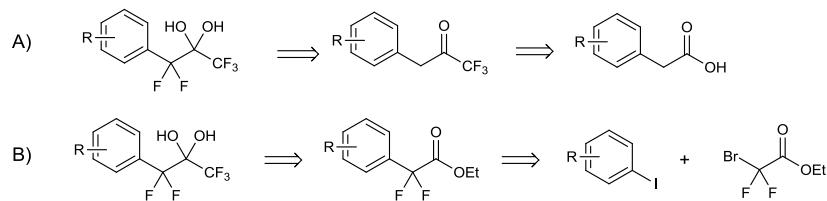
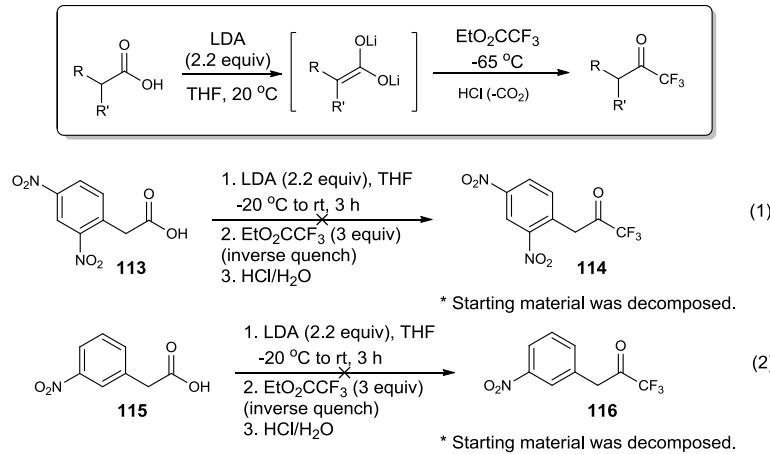
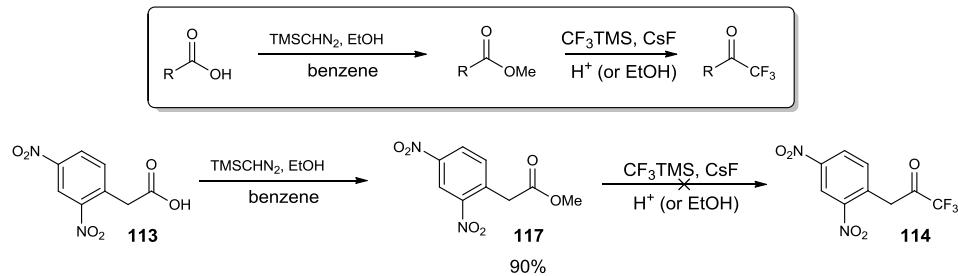


Figure 4.3 Two different retrosynthetic analyses of  $\alpha$ -aryl pentafluoro *gem*-diols.

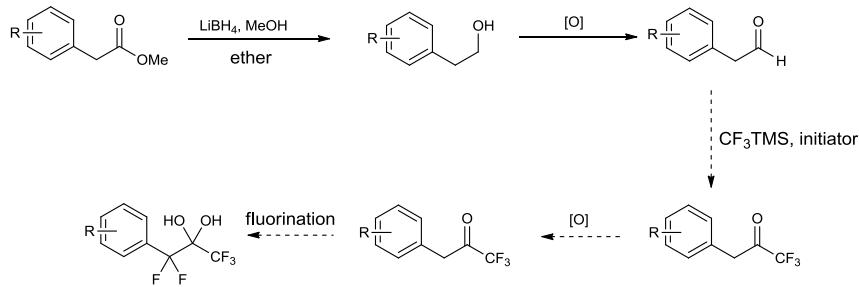
First, the implementation of the first plan required converting carboxylic acids into trifluoromethyl ketones. Reeves *et al.* reported a one-pot protocol to convert carboxylic acids into trifluoromethyl ketones.<sup>101</sup> Double deprotonation with strong bases, such as LDA, followed by trifluoroacetylation and decarboxylation converts carboxylic acids into trifluoromethyl ketones in one pot. This methodology has been applied for the synthesis of electron-deficient phenyl acetic acids into trifluoromethyl ketones. However, the use of strong base led to the decomposition of the electron-deficient starting materials (Scheme 4.1 eq. 1 and 2). Therefore, an alternative strategy was proposed. Carboxylic acids can be converted into methyl esters with TMSCHN<sub>2</sub>. Then, the corresponding methyl esters can be converted to trifluoromethyl ketones by using Ruppert's reagent. However, this alternative approach also failed in the second step; because starting materials decomposed (Scheme 4.2). Modifications of this synthetic route could have been pursued but adding more steps was not desirable (Figure 4.4). Therefore, we decided to develop a novel methodology for converting carboxylic acids into trifluoromethyl ketones.



Scheme 4.1 One-step Transformation of Carboxylic Acids into Trifluoromethyl Ketones<sup>101</sup>



Scheme 4.2 Two-step Transformation of Carboxylic Acid into Trifluoromethyl Ketone



Scheme 4.3 Multistep Transformation of Carboxylic Acid into trifluoromethyl ketone.

A novel protocol was devised based on a two-step approach (Figure 4.5). Instead of forming methyl esters with  $\text{TMSCHN}_2$ , imidazolyl ketone intermediates were formed

by using CDI. The imidazolyl ketones then could be treated with Ruppert's reagent and catalytic initiator to install a trifluoromethyl moiety. Tetrahedral intermediates were expected to be trapped by a the trimethyl silyl (TMS) group and then break down during work up and flash column chromatography because protonation of imidazole makes it better leaving group.

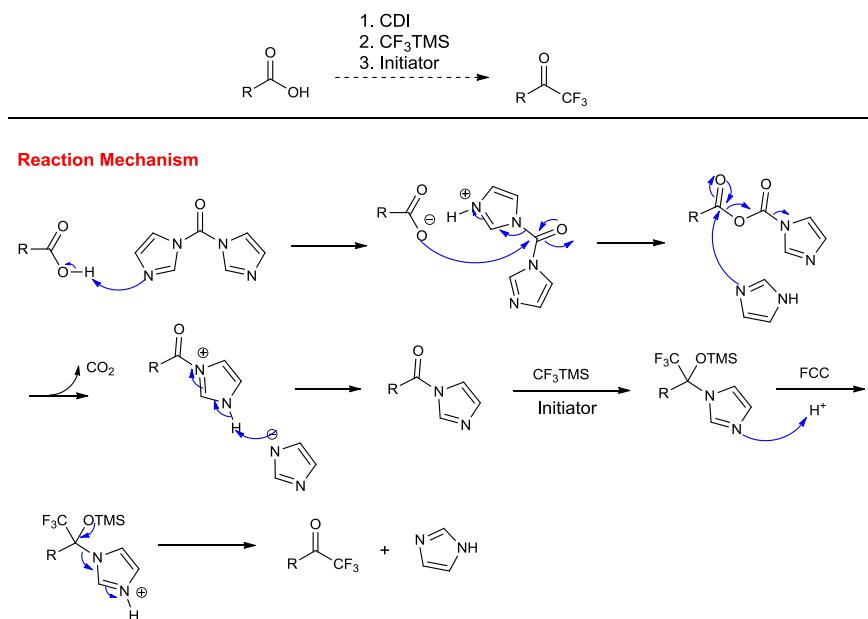
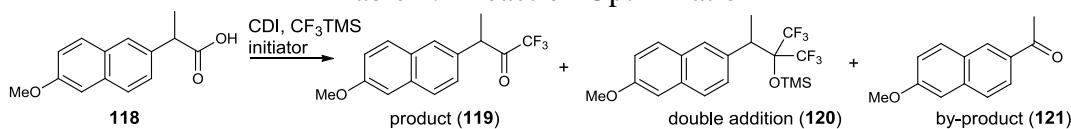


Figure 4.4 Proposed reaction mechanism.

Table 4.2 Reaction Optimization



entry	CDI equiv.	initiator equiv.	CF <sub>3</sub> TMS equiv.	time	product	double addition	by-product	additives	
1	1.0	CsF	1.0	2.5	overnight	21%	not detected	28%	-
2	1.0	KF	30.0	2.5	overnight	23%	not detected	15%	DMAP
3	1.0	KF	2.5	2.5	2 days	not detected	not detected	35%	18-crown-6
4	1.0	KF	2.5	5.0	1 h	20%	not isolated	not isolated	18-crown-6
5	1.0	K <sub>2</sub> CO <sub>3</sub>	10.0	5.0	overnight	53%	19%	not isolated	-
6	1.0	K <sub>2</sub> CO <sub>3</sub>	0.5	5.0	2 days	65%	8%	12%	-
7	1.0	K <sub>2</sub> CO <sub>3</sub>	2.5	5.0	overnight	60%	16%	15%	-

A series of reaction conditions were examined and three different products were isolated: desired product, double-addition byproduct, and ketone that originating from starting material via decarboxylation (Table 4.2). Indeed, TMS-trapped tetrahedral intermediates observed by TLC released imidazole and formed the desired product during flash column chromatography. An un-optimized yield of 65% was obtained from these studies (Table 4.2 entry 6). Further optimization of the reaction will lead us to discover a novel method to convert carboxylic acids into trifluoromethyl ketones. While the first plan (Figure 4.3(A)) was investigated, the second plan was explored as well (Figure 4.3(B)).

Unlike the first plan, the second plan was much more promising. Cu-mediated coupling has been conducted between aryl iodides and  $\alpha,\alpha,\alpha$ -bromodifluoroethyl acetates (Table 4.3) followed by addition of Ruppert's reagent (Table 4.4) to synthesize our desired starting materials,  $\alpha$ -aryl pentafluoro *gem*-diols. Cu-mediated coupling gave us the desired aryl difluoro ethyl acetate in good to excellent yield (71%–quantitative). Although crude yields were higher, the isolated yields of desired products were only

28%–89% due to the loss of product during purification by flash column chromatography.

To prove the structure of the desired starting materials, X-ray crystal structures of *gem*-diols **136** and **140** have been obtained. To our knowledge, these are the first X-ray crystal structures of  $\alpha$ -aryl pentafluoro *gem*-diols. Indeed, the attachment of the two OH groups to the same carbon distinguished between *gem*-diols and ketone hydrates. There were no significant differences in bond length between the CO-CF<sub>3</sub> and CO-CF<sub>2</sub>R bonds in both cases. The pyridine *N*-oxide **139** was obtained by *m*-CPBA oxidation from precursor pyridine **138**.

Table 4.3 Cu-Mediated Coupling between Allyl Iodides and  $\alpha,\alpha,\alpha$ -Bromodifluoroethyl Acetates

entry	product	yield	entry	product	yield
1		86%	7		99%
2		71%	8		85%
3		92%	9		quantitative
4		quantitative	10		quantitative
5		99%	11		quantitative
6		80%	12		94%

Table 4.4 Synthesis of  $\alpha$ -Aryl Pentafluoro *gem*-Diols with Ruppert's Reagent

entry	product	yield	entry	product	yield
1		31%	4		68% 
2		46%	5		99%
3		73% 	6		
8		71%	12		36%
9		46%	13		26%
10		23%	14		77%
			14		58%
			15		28%

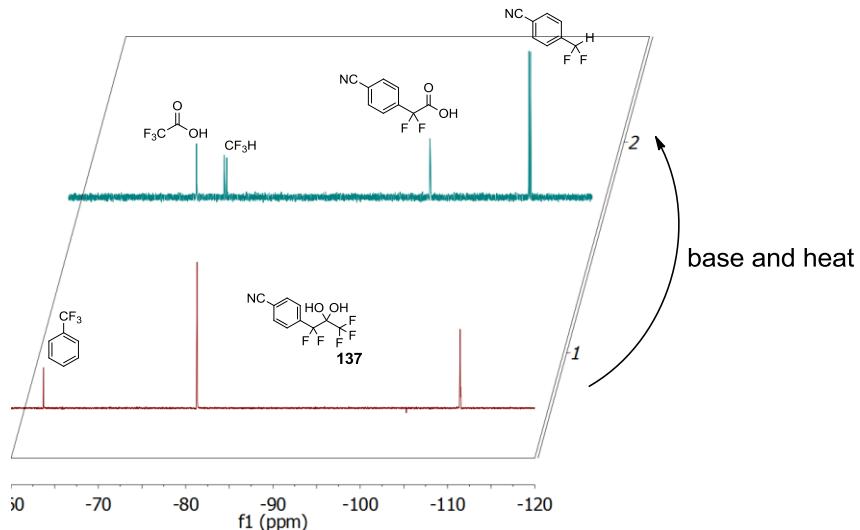


Figure 4.5 Fragmentation studies of  $\alpha$ -aryl pentafluoro *gem*-diol **137** with  $\text{K}_2\text{CO}_3$ .

With a variety of  $\alpha$ -aryl pentafluoro *gem*-diols in hand, fragmentation studies were conducted. Among many different bases,  $\text{K}_2\text{CO}_3$  was selected because the basicity of amine bases was not sufficient to doubly deprotonate the  $\alpha$ -aryl pentafluoro *gem*-diols. Hydroxides were also not suitable because of their nucleophilic character.  $\text{CO}-\text{CF}_2\text{R}$  and  $\text{CO}-\text{CF}_3$  bond cleavage percentages were determined by  $^{19}\text{F}$ -NMR integration (Figure 4.6). Due to the small difference in bond energy, cleavages of the  $\text{CO}-\text{CF}_2\text{R}$  and  $\text{CO}-\text{CF}_3$  bonds were highly affected by substituents on the aromatic ring (Table 4.5). Electron-withdrawing substituents, such as *p*-nitro, promoted the release of trifluoroacetate while electron-donating substituents, such as *p*-methoxy, promoted fluoroform release. Interestingly, *p*-trifluoromethyl phenyl and 2-pyridyl substituted compounds, **141** and **138**, released only 4% and 14% of trifluoroacetate, respectively. The compound **144** which is the *p*-trifluoromethyl pyridyl derivative exclusively released trifluoroacetate

during fragmentation. These data suggest that there is a synergistic electron-withdrawing effect between the 5-trifluoromethyl substituent and the 2-pyridyl ring (Table 4.5 entry 3).

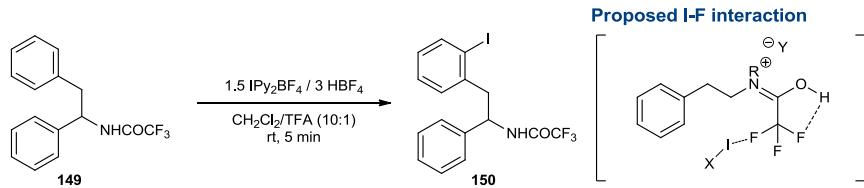
Table 4.5 Cleavage Studies of Substituted  $\alpha$ -Aryl Pentafluoro *gem*-Diols with  $K_2CO_3$

entry	 139	% TFAR <sup>a</sup>	% FR <sup>a</sup>			entry	 145	% TFAR <sup>a</sup>	% FR <sup>a</sup>	entry	 140	% TFAR <sup>a</sup>	% FR <sup>a</sup>
				TFAR	FR								
1	 139	100	— <sup>b</sup>			5	 145	94.4	5.6	10	 140	— <sup>b</sup>	100
2	 143	100	— <sup>b</sup>			6	 137	54	46	11	 142	— <sup>b</sup>	100
3	 144	100	— <sup>b</sup>			7	 146	27	73	12	 134	— <sup>b</sup>	100
4	 136	100	— <sup>b</sup>			8	 138	14	86	13	 135	— <sup>b</sup>	100
						9	 141	4	96				

TFAR: trifluoroacetate release, FR: fluoroform release.

a. % is calculated by  $^{19}F$  NMR integration. b. not monitored by  $^{19}F$  NMR.

Fluorine is a highly electronegative small atom. Therefore, in terms of the hard-soft interaction concept presented by Pearson, covalently bonded fluorine can be considered as a hard donor for metal ions.<sup>131</sup> Previous studies in coordination chemistry reveal that covalently bonded fluorine can form cation-dipole interactions with alkali and alkaline earth metals.<sup>132</sup> The relatively strong interaction between C-F and M<sup>+</sup> has been strategically utilized in stereoselective synthesis.<sup>131,133,134</sup> In addition to alkali and alkaline earth metals, recent studies have shown that iodonium ions may form close contact with fluorine and this interaction contributes to the regioselectivity of the iodination reaction (Scheme 4.3).<sup>135</sup>



Scheme 4.4 Chemo- and Regioselective Iodination<sup>135</sup>

Pentafluoro *gem*-diols have three  $\alpha$ -fluorines and two  $\alpha'$ -fluorines adjacent to *gem*-diol group. We hypothesized that by using cation-dipole interactions, one extra fluorine in the  $\alpha$  position can possibly be used as a handle to control fragmentation patterns of pentafluoro *gem*-diols. This will potentially lead us toward the controlled cleavage of one C-C bond over the other.

To test our hypothesis, the easily accessible *gem*-diol **136** along with different carbonate bases were used to observe C-C bond cleavage (Table 4.6). Different fragmentation patterns have been observed during carbonate screening. No fragmentation was seen in the case of dicationic salts, such as  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$  because dicationic salts can

presumably stabilize dianion and prevent the fragmentation process (Table 4.6, entry 5, 6). In the case of  $\text{Ag}_2\text{CO}_3$ , the fragmentation did not occur because of the poor solubility of the base.

Table 4.6 Cleavage Studies of **136** with Different Kinds of Carbonates

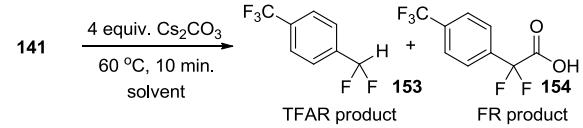
entry	base	% TFAR	% FR	solvent
1	$\text{K}_2\text{CO}_3$	100	0	DMSO
2	$\text{Cs}_2\text{CO}_3$	79.4	20.6	DMSO
3	$\text{Cs}_2\text{CO}_3$	87.8	12.2	DMF
4	$\text{Ag}_2\text{CO}_3$	No fragmentation		DMF
5	$\text{CaCO}_3$	No fragmentation		DMF
6	$\text{BaCO}_3$	No fragmentation		DMF
7	$\text{Rb}_2\text{CO}_3$	96.3	3.7	DMF

When  $\text{Cs}_2\text{CO}_3$  was used as a base in DMSO, the product resulting from fluoroform release was observed in 20.6% yield by  $^{19}\text{F}$  NMR along with 79.4% of trifluoroacetate release (Table 4.6, entry 2). This result was very surprising because the former product has never been monitored in our prior work with  $\text{K}_2\text{CO}_3$  using DMSO as a solvent (Table 4.6, entry 1). This result indicates that  $\text{Cs}^+$  ions interacted with the starting material and deactivated the CO-CF<sub>2</sub>R bond and activated the CO-CF<sub>3</sub> bond during fragmentation. Moreover, when we changed the reaction solvent from DMSO to DMF, a small decrease in the product formation was observed (Table 4.6, entry 3). Based on the fact that the cleavage patterns of *gem*-diol **136** using DMSO and DMF were different, we hypothesized that selective control can be maximized by using different solvent systems. Compound **136** and compound **141** have been screened under various

solvent systems (Table 4.7 and Table 4.8). In general, polar solvent systems were more suitable for trifluoroacetate release and nonpolar solvent systems were more suitable for fluoroform release. These results support the hypothesis that cation-dipole interactions play an important role during the fragmentation process. In the case of *gem*-diol **141**, up to 16.6% of the trifluoroacetate release product was observed when using DMSO and Cs<sub>2</sub>CO<sub>3</sub>, a 4-fold increase over the use of K<sub>2</sub>CO<sub>3</sub> (Table 4.8 entry 1). Also, in the case of *gem*-diol **136**, up to 82% of the fluoroform release product was observed when using trifluorotoluene and Cs<sub>2</sub>CO<sub>3</sub>. This is in contrast to 0% observed fluoroform release product, when DMSO and K<sub>2</sub>CO<sub>3</sub> were used (Table 4.7 entry 15).

Table 4.7 Cleavage Studies of *gem*-diol **136** with Cs<sub>2</sub>CO<sub>3</sub> and Different Solvents

entry	solvent	% TFAR	% FR
1	DMPU	95.3	4.7
2	NMP	90.7	9.2
3	DMF	87.8	12.2
4	acetone	83.3	16.7
5	DMSO	79.4	20.6
6	ethyl acetate	49.5	50.5
7	CH <sub>3</sub> CN	45.1	54.9
8	dioxane	44.4	55.6
9	toluene	41.5	58.5
10	THF	34.2	65.8
12	DCE	33.8	66.2
13	allyl bromide	31	69
14	monofluorobenzene	25.4	74.6
15	trifluorotoluene	18	82
17	nitromethane		No fragmentation
18	ethyl 3,3,3-trifluoropyruvate		No fragmentation

Table 4.8 Cleavage Studies of *gem*-diol **141** with Cs<sub>2</sub>CO<sub>3</sub> and Different Solvent

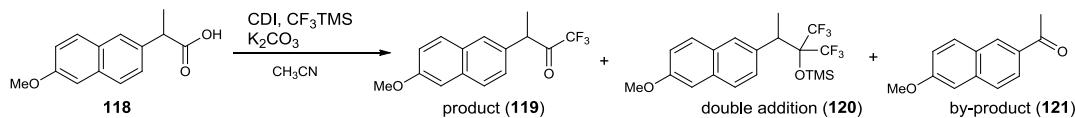
entry	solvent	% TFAR	% FR
1	DMSO	16.6	83.4
2	DMPU	13.7	86.3
3	NMP	9.1	90.9
4	DMF	5.7	94.3
5	THF	2	98
6	CH <sub>3</sub> CN	2	98
7	allyl bromide	-	100
8	DCE	-	100
9	toluene	-	100
10	trifluorotoluene	-	100
11	monofluorobenzene	-	100

#### 4.3 Conclusion and Future Directions

In this study, strategic activation and cleavage of the C-C bond adjacent to the carbonyl group without using transition metals has been demonstrated by utilizing the trifluoroacetate-release process. Our methodology is based on the deprotonation and subsequent C-C bond fragmentation of highly  $\alpha$ -fluorinated *gem*-diols, which resembles the fragmentation of hexafluoroacetone hydrate. A series of fragmentation studies of  $\alpha$ -aryl pentafluoro *gem*-diols have shown electronic difference between  $\alpha,\alpha$ -difluorotoluene derivatives closely correlated with the fragmentation patterns. We also have demonstrated that controlled cleavage of one C-C bond over the other can be achieved by using fluorine as a handle. Relatively strong cation-dipole interaction between covalently bound fluorine and Cs<sup>+</sup> metal promotes fluoroform release in nonpolar solvents over

trifluoroacetate release. To our knowledge, this is the first example of the reagent/reaction condition-based control of the cleavage of the C-C bonds. Further studies on the cleavage patterns may allow us to fully control the cleavage of the C-C bond in highly  $\alpha$ -fluorinated *gem*-diols.

#### 4.4 Experimental Details



**1,1,1-Trifluoro-3-(6-methoxynaphthalen-2-yl)butan-2-one 119.** To a solution of compound **118** (15.0 mg, 0.065 mmol) in  $\text{CH}_3\text{CN}$  (0.5 ml), CDI (11.0 mg, 0.066 mmol) was added and stirred for 10 min. at rt. Then,  $\text{CF}_3\text{TMS}$  (49.0  $\mu\text{L}$ , 0.326 mmol) was added and stirred for 5 min. at the same temperature. Then,  $\text{K}_2\text{CO}_3$  (23.0 mg, 0.163 mmol) was added and stirred for overnight at rt. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (3 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (1:1 EtOAc/hexanes) afforded the desired product in 59% yield (31 mg).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78–7.67 (t,  $J$  = 7.9 Hz, 2H), 7.61 (d,  $J$  = 1.9 Hz, 1H), 7.31–7.27 (dd,  $J$  = 8.5, 1.9 Hz, 1H), 7.21–7.10 (m, 2H), 4.32 (q,  $J$  = 7.0 Hz, 1H), 3.92 (s, 3H), 1.59 (d,  $J$  = 6.9 Hz, 3H)

**Trimethyl((1,1,1-trifluoro-3-(6-methoxynaphthalen-2-yl)-2-(trifluoromethyl)butan-2-yl)oxy)silane 120.**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76–7.58

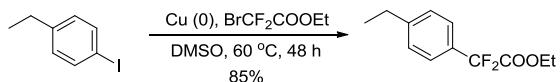
(m, 3H), 7.38 (dd,  $J = 8.6, 1.8$  Hz, 1H), 7.16–7.09 (m, 2H), 3.92 (s, 3H), 3.50 (q,  $J = 6.9$  Hz, 1H), 1.55–1.51 (m, 1H), 0.18 (s, 9H)

**1-(6-Methoxynaphthalen-2-yl)ethanone 121.**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

$\delta$  8.40 (s, 1H), 8.01 (dd,  $J = 8.6, 1.8$  Hz, 1H), 7.86 (d,  $J = 8.9$  Hz, 1H), 7.77 (d,  $J = 8.6$  Hz, 1H), 7.25–7.13 (m, 2H), 3.95 (s, 3H), 2.70 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  197.9, 159.7, 137.3, 132.6, 131.1, 130.1, 127.8, 127.1, 124.7, 119.7, 105.7, 55.4, 26.6. All spectral and characterization data matched the reported data.<sup>136</sup>

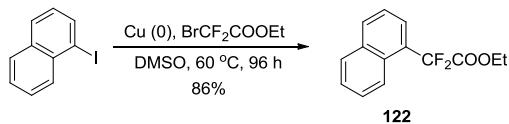
**Representative Reaction Procedure for Ethyl Phenyl-2,2-difluoroacetate Compounds.**<sup>137</sup>

To a solution of 1-ethyl-4-iodobenzene (314  $\mu\text{L}$ , 2.16 mmol) in DMSO (5.4 mL), Cu (548 mg, 8.62 mmol) was added and stirred for 10 sec. Then,  $\text{BrCF}_2\text{COOEt}$  (330  $\mu\text{L}$ , 2.59 mmol) was added and the temperature was warmed to 60 °C. After 48 h, the reaction mixture was cooled down to rt and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (6 mL) at the same temperature and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (6 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash chromatography ( $\text{CHCl}_3$ ) afforded the desired product in 85% yield (417.8 mg, oil).

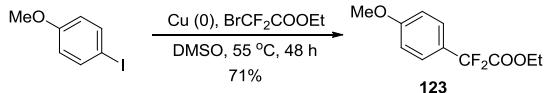


**Ethyl 2-(4-ethylphenyl)-2,2-difluoroacetate.** See representative reaction procedure.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (d,  $J = 8.4$  Hz, 2H), 7.28 (d,  $J = 8.1$  Hz,

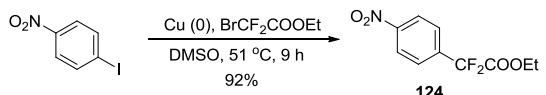
2H), 4.30 (q,  $J = 7.2$  Hz, 2H), 2.69 (q,  $J = 7.8$  Hz, 2H), 1.31 (t,  $J = 6.9$  Hz, 3H), 1.25 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.4 (t,  $J_{\text{CF}} = 35.4$  Hz, 1C), 147.4, 130.1 (t,  $J_{\text{CF}} = 25.5$  Hz, 1C), 128.1 (2), 125.4 (t,  $J_{\text{CF}} = 5.9$  Hz, 2C), 113.5 (t,  $J_{\text{CF}} = 250.0$  Hz, 1C), 63.0, 28.7, 15.3, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -104.35 (2); IR (film)  $\nu_{\text{max}}$  1766, 1269, 1103, 835  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}\text{F}_2\text{O}_2$  ( $\text{M}^+$ ) 228.0962, found 228.0965.



**Ethyl 2,2-difluoro-2-(naphthalen-1-yl)acetate 122.** See representative reaction procedure. 1-Iodonaphthalene (500 mg, 1.97 mmol), DMSO (4.9 ml), copper (500 mg, 7.87 mmol), and ethyl 2-bromo-2,2-difluoroacetate (300  $\mu\text{L}$ , 2.36 mmol) were used. The reaction temperature was 60  $^\circ\text{C}$  and the reaction time was 96 h.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **122** in 86% yield (421.3 mg, oil)  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (d,  $J = 8.6$  Hz, 1H), 7.98 (d,  $J = 8.2$  Hz, 1H), 7.90 (t,  $J = 7.8$  Hz, 2H), 7.64–7.49 (m, 3H), 4.29 (q,  $J = 7.2$  Hz, 2H), 1.24 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  164.4 (t,  $J_{\text{CF}} = 34.6$  Hz, 1C), 133.8, 131.9, 129.3 (d,  $J_{\text{CF}} = 2.2$  Hz, 1C), 128.8, 128.4, 127.3, 126.3, 124.9 (t,  $J_{\text{CF}} = 9.4$  Hz, 1C), 124.5, 124.2 (t,  $J_{\text{CF}} = 3.0$  Hz, 1C), 114.3 (t,  $J_{\text{CF}} = 250.1$  Hz, 1C), 63.2, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -101.1 (s, 2F); IR (film)  $\nu_{\text{max}}$  1765, 1281, 1130, 1089, 777  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{12}\text{F}_2\text{O}_2$  ( $\text{M}^+$ ), 250.0805; found, 250.0807. All spectral and characterization data matched the reported data.

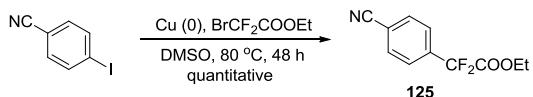


**Ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate **123**.** See representative reaction procedure. 4-iodoanisole (300 mg, 1.28 mmol), DMSO (3.2 ml), copper (326 mg, 5.13 mmol), and ethyl 2-bromo-2,2-difluoroacetate (200  $\mu$ L, 1.54 mmol) were used. The reaction temperature was 55 °C and the reaction time was 48 h. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub>) afforded the desired product **123** in 71% yield (210.8 mg, oil). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 (dd, *J* = 6.9, 2.2 Hz, 2H), 6.95 (dd, *J* = 6.9, 2.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  164.4 (t, *J*<sub>CF</sub> = 35.7 Hz, 1C), 161.5, 127.0 (t, *J*<sub>CF</sub> = 6.0 Hz, 1C), 124.9 (t, *J*<sub>CF</sub> = 26.0 Hz, 1C), 113.9, 113.5 (t, *J*<sub>CF</sub> = 250.0 Hz, 1C), 63.0, 55.4, 13.9; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -103.6 (2); IR (film)  $\nu$ <sub>max</sub> 1764, 1615, 1517, 1255, 1101 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd. for C<sub>11</sub>H<sub>12</sub>F<sub>2</sub>O<sub>3</sub> (M)<sup>+</sup>, 230.0755; found, 230.0759. All spectral and characterization data matched the reported data.<sup>137</sup>

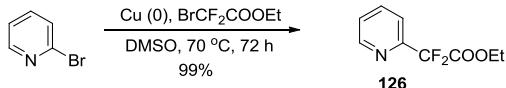


**Ethyl 2,2-difluoro-2-(4-nitrophenyl)acetate **124**.** See representative reaction procedure. 1-iodo-4-nitrobenzene (500 mg, 2.01 mmol), DMSO (5.0 ml), copper (510 mg, 8.03 mmol), and ethyl 2-bromo-2,2-difluoroacetate (309  $\mu$ L, 2.41 mmol) were used. The reaction temperature was 51 °C and the reaction time was 9 h. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub>) afforded the desired product **124** in 92% yield (455.2 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.32 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H),

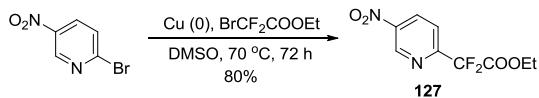
4.32 (q,  $J = 7.1$  Hz, 2H), 1.31 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.1 (t,  $J_{\text{CF}} = 33.8$  Hz, 1C), 149.6, 138.8 (t,  $J_{\text{CF}} = 26.3$  Hz, 1C), 127.0 (t,  $J_{\text{CF}} = 6.3$  Hz, 2C), 123.9 (2), 112.4 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 63.7, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -105.4 (s, 2F); IR (film)  $\nu_{\text{max}}$  1761, 1531, 1311, 1263, 1103  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_9\text{F}_2\text{NO}_4$  ( $\text{M}^+$ ), 245.0500; found, 245.0503; mp 34–36 °C.



**Ethyl 2-(4-cyanophenyl)-2,2-difluoroacetate 125.** See representative reaction procedure. 4-iodobenzonitrile (500 mg, 2.18 mmol), DMSO (5.0 ml), copper (555 mg, 8.73 mmol), and ethyl 2-bromo-2,2-difluoroacetate (336  $\mu\text{L}$ , 2.62 mmol) were used. The reaction temperature was 80 °C and the reaction time was 48 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **125** in quantitative yield (492.0 mg, oil).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75–7.67 (m, 4H), 4.26 (q,  $J = 7.1$  Hz, 2H), 1.25 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.1 (t,  $J_{\text{CF}} = 34.4$  Hz, 1C), 137.1 (t,  $J_{\text{CF}} = 26.0$  Hz, 1C), 132.4, 126.4 (t,  $J_{\text{CF}} = 6.3$  Hz, 1C), 117.7, 115.1, 112.3 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 63.6, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -105.9 (2); IR (film)  $\nu_{\text{max}}$  2235, 1770, 1265, 1110  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_9\text{F}_2\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 226.0680; found, 226.0677.

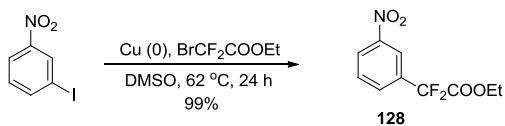


**Ethyl 2,2-difluoro-2-(pyridin-2-yl)acetate 126.** See representative reaction procedure. 2-bromopyridine (500 mg, 3.16 mmol), DMSO (5.0 ml), copper (804 mg, 12.7 mmol), and ethyl 2-bromo-2,2-difluoroacetate (487  $\mu$ L, 3.80 mmol) were used. The reaction temperature was 70  $^\circ$ C and the reaction time was 72 h. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub>) afforded the desired product **126** in 99% yield (627.8 mg, oil). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.62 (d,  $J$  = 4.8 Hz, 1H), 7.84 (td,  $J$  = 7.8, 1.8 Hz, 1H), 7.71 (d,  $J$  = 7.8 Hz, 1H), 7.40 (dd,  $J$  = 7.5, 4.8 Hz, 1H), 4.35 (q,  $J$  = 7.2 Hz, 2H), 1.29 (q,  $J$  = 7.2 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  163.3 (t,  $J_{\text{CF}} = 32.7$  Hz, 1C), 151.6 (t,  $J_{\text{CF}} = 28.0$  Hz, 1C), 149.5, 137.3, 125.6, 120.3, 112.1 (t,  $J_{\text{CF}} = 251.7$  Hz, 1C), 63.1, 13.8. All spectral and characterization data matched the reported data.<sup>138</sup>

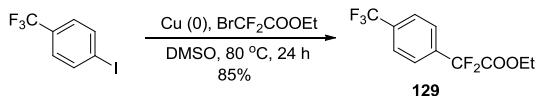


**Ethyl 2,2-difluoro-2-(5-nitropyridin-2-yl)acetate 127.** See representative reaction procedure. 2-bromo-5-nitropyridine (500 mg, 2.46 mmol), DMSO (5.0 ml), copper (626 mg, 9.85 mmol), and ethyl 2-bromo-2,2-difluoroacetate (379  $\mu$ L, 2.96 mmol) were used. The reaction temperature was 70  $^\circ$ C and the reaction time was 72 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL  $\times$  5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub>) afforded the desired product **127** in 80% yield (485.5 mg, oil). <sup>1</sup>H NMR (500 MHz,

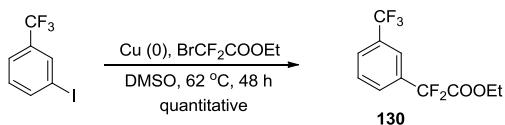
$\text{CDCl}_3$ )  $\delta$  9.44 (d,  $J = 2.3$  Hz, 1H), 8.67 (dd,  $J = 8.5, 2.3$  Hz, 1H), 7.98 (d,  $J = 8.5$  Hz, 1H), 4.38 (q,  $J = 7.2$  Hz, 2H), 1.32 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2 (t,  $J_{\text{CF}} = 32.5$  Hz, 1C), 156.5 (t,  $J_{\text{CF}} = 28.6$  Hz, 1C), 144.9, 132.8, 121.2, 111.1 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 109.3, 63.7, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -106.5 (2); IR (film)  $\nu_{\text{max}}$  1775, 1535, 1359, 1135, 1107, 859  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_9\text{H}_8\text{F}_2\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ , 247.0530; found, 247.0535.



**Ethyl 2,2-difluoro-2-(3-nitrophenyl)acetate 128.** See representative reaction procedure. 1-iodo-3-nitrobenzene (500 mg, 2.01 mmol), DMSO (5.00 ml), copper (510 mg, 8.03 mmol), and ethyl 2-bromo-2,2-difluoroacetate (309  $\mu\text{L}$ , 2.41 mmol) were used. The reaction temperature was 62  $^\circ\text{C}$  and the reaction time was 24 h.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **128** in 99% yield (485.5 mg, oil).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (s, 1H), 8.38 (d,  $J = 8.2$  Hz, 1H), 7.96 (d,  $J = 7.4$  Hz, 1C), 7.69 (t,  $J = 8.0$  Hz, 1H), 4.33 (q,  $J = 7.1$  Hz, 2H), 1.33 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.1 (t,  $J_{\text{CF}} = 34.2$  Hz, 1C), 148.2, 134.8 (t,  $J_{\text{CF}} = 26.3$  Hz, 1C), 131.5 (t,  $J_{\text{CF}} = 5.8$  Hz, 1C), 130.0, 125.9, 121.1 (t,  $J_{\text{CF}} = 6.4$  Hz, 1C), 112.1 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 63.7, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -104.9 (2); IR (film)  $\nu_{\text{max}}$  1769, 1539, 1353, 1096, 717  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_9\text{F}_2\text{NO}_4$  ( $\text{M}+\text{H}$ ) $^+$ , 246.0578; found, 246.0576.

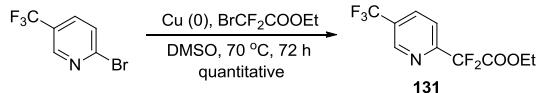


**Ethyl 2,2-difluoro-2-(4-(trifluoromethyl)phenyl)acetate 129.** See representative reaction procedure. 1-iodo-4-(trifluoromethyl)benzene (500 mg, 1.84 mmol), DMSO (5.00 ml), copper (467 mg, 7.35 mmol), and ethyl 2-bromo-2,2-difluoroacetate (285  $\mu$ L, 2.21 mmol) were used. The reaction temperature was 80  $^{\circ}$ C and the reaction time was 24 h.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product in 85% yield (421.2 mg, oil).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87–7.63 (m, 4H), 4.31 (q,  $J = 7.1$  Hz, 2H), 1.31 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.5 (t,  $J_{\text{CF}} = 34.3$  Hz, 1C), 136.4 (t,  $J_{\text{CF}} = 25.6$  Hz, 1C), 133.1 (q,  $J_{\text{CF}} = 32.2$  Hz, 1C), 126.2 (t,  $J_{\text{CF}} = 6.0$  Hz, 2C), 125.7 (d,  $J_{\text{CF}} = 3.4$  Hz, 2C), 123.5 (q,  $J_{\text{CF}} = 270.4$  Hz, 1C), 112.7 (t,  $J_{\text{CF}} = 251.0$  Hz, 1C), 63.5, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -64.1 (s, 3F), -105.5 (s, 2F); IR (film)  $\nu_{\text{max}}$  1771, 1328, 1134, 1104, 1070  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_9\text{F}_5\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$ , 269.0601; found, 269.0603.



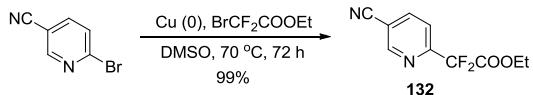
**Ethyl 2,2-difluoro-2-(3-(trifluoromethyl)phenyl)acetate 130.** See representative reaction procedure. 1-iodo-3-(trifluoromethyl)benzene (500 mg, 1.84 mmol), DMSO (4.6 ml), copper (467 mg, 7.35 mmol), and ethyl 2-bromo-2,2-difluoroacetate (285  $\mu$ L, 2.21 mmol) were used. The reaction temperature was 62  $^{\circ}$ C and the reaction time was 48 h.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **130** in quantitative yield (493.0 mg, oil).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (s, 1H), 7.85–7.73

(m, 2H), 7.60 (t,  $J = 7.9$  Hz, 1H), 4.32 (q,  $J = 7.2$  Hz, 2H), 1.30 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  163.5 (t,  $J_{\text{CF}} = 34.8$  Hz, 1C), 133.9 (t,  $J_{\text{CF}} = 26.1$  Hz, 1C), 131.3 (q,  $J_{\text{CF}} = 33.4$  Hz, 1C), 129.4, 129.0 (t,  $J_{\text{CF}} = 6.0$  Hz, 1C), 127.9 (d,  $J_{\text{CF}} = 3.1$  Hz, 1C), 123.5 (q,  $J_{\text{CF}} = 270.7$  Hz, 1C), 122.6 (dh,  $J_{\text{CF}} = 6.9, 3.5$  Hz, 1C), 112.6 (t,  $J_{\text{CF}} = 251.4$  Hz, 1C), 63.5, 13.7;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.9 (s, 3F), -105.2 (s, 2F); IR (film)  $\nu_{\text{max}}$  1771, 1338, 1245, 1134, 1026  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_9\text{F}_5\text{O}_2$  ( $\text{M}+\text{H})^+$ , 269.0601; found, 269.0598.

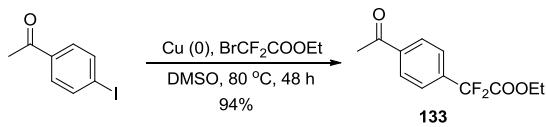


**Ethyl 2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)acetate 131.** See representative reaction procedure. 2-bromo-5-(trifluoromethyl)pyridine (500 mg, 2.21 mmol), DMSO (5.0 ml), copper (562 mg, 8.85 mmol), and ethyl 2-bromo-2,2-difluoroacetate (340  $\mu\text{L}$ , 2.65 mmol) were used. The reaction temperature was 70 °C and the reaction time was 72 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **131** in quantitative yield (596.0 mg, oil).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.90 (s, 1H), 8.12 (dd,  $J = 8.3, 2.1$  Hz, 1H), 7.89 (d,  $J = 8.3$  Hz, 1H), 4.37 (q,  $J = 7.2$  Hz, 2H), 1.32 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.7 (t,  $J_{\text{CF}} = 32.1$  Hz, 1C), 155.0 (t,  $J_{\text{CF}} = 28.2$  Hz, 1C), 146.5, 134.9, 128.5 (q,  $J_{\text{CF}} = 33.2$  Hz, 1C), 122.8 (q,  $J_{\text{CF}} = 270.6$  Hz, 1C), 120.5, 111.5 (t,  $J_{\text{CF}} = 250.8$  Hz, 1C), 63.5, 13.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.7 (3), -106.7 (2); IR (film)

$\nu_{\text{max}}$  1779, 1332, 1138, 1017  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_8\text{F}_5\text{NO}_2$  ( $\text{M}+\text{H}$ ) $^+$ , 270.0554; found, 270.0551.



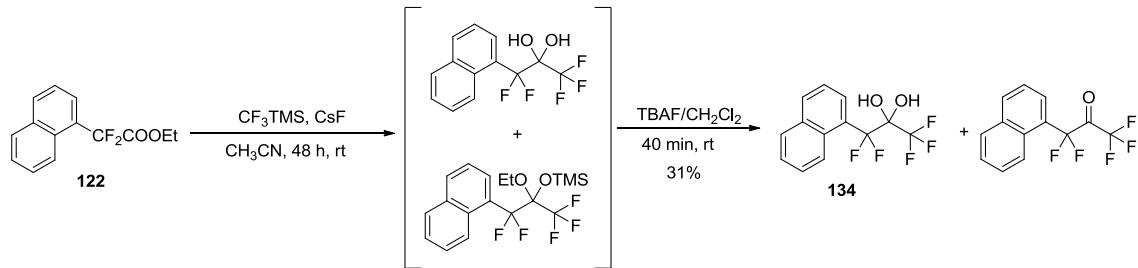
**Ethyl 2-(5-cyanopyridin-2-yl)-2,2-difluoroacetate 132.** See representative reaction procedure. 6-bromonicotinonitrile (500 mg, 2.73 mmol), DMSO (6.0 ml), copper (694 mg, 10.9 mmol), and ethyl 2-bromo-2,2-difluoroacetate (420  $\mu\text{L}$ , 3.28 mmol) were used. The reaction temperature was 70  $^{\circ}\text{C}$  and the reaction time was 72 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$ ) afforded the desired product **132** in 99% yield (609.1 mg, oil).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.92 (S, 1H), 8.17 (dd,  $J$  = 8.2, 1.8 Hz, 1H), 7.89 (dd,  $J$  = 8.1, 0.9 Hz, 1H), 4.38 (q,  $J$  = 7.1 Hz, 2H), 1.33 (t,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3 (t,  $J_{\text{CF}} = 31.5$  Hz, 1C), 154.6 (t,  $J_{\text{CF}} = 28.7$  Hz, 1C), 151.9, 141.0, 120.6 (t,  $J_{\text{CF}} = 3.6$  Hz, 1C), 115.5, 112.0, 111.1 (t,  $J_{\text{CF}} = 252.0$  Hz, 1C), 63.6, 13.7;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  –107.0 (2); IR (film)  $\nu_{\text{max}}$  2239, 1774, 1294, 1120, 1019  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_8\text{F}_2\text{N}_2\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$ , 227.0632; found, 227.0639.



**Ethyl 2-(4-acetylphenyl)-2,2-difluoroacetate 133.** See representative reaction procedure. 1-(4-iodophenyl)ethanone (500 mg, 2.03 mmol), DMSO (5.0 ml), copper (517 mg, 8.13 mmol), and ethyl 2-bromo-2,2-difluoroacetate (313  $\mu$ L, 2.44 mmol) were used. The reaction temperature was 80 °C and the reaction time was 48 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL  $\times$  5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub>) afforded the desired product in 94% yield (462 mg, oil). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.03 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  197.2, 163.6 (t, *J*<sub>CF</sub> = 34.5 Hz, 1C), 139.0, 137.0 (t, *J*<sub>CF</sub> = 25.4 Hz, 1C), 128.5, 125.9 (t, *J*<sub>CF</sub> = 6.1 Hz, 1C), 112.9 (t, *J*<sub>CF</sub> = 252.5 Hz, 1C), 63.4, 26.8, 13.8; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)  $\delta$  -105.6 (2); IR (film)  $\nu$ <sub>max</sub> 1768, 1693, 1267, 1106 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd. for C<sub>12</sub>H<sub>12</sub>F<sub>2</sub>O<sub>3</sub> (M)<sup>+</sup>, 242.0755; found, 242.0758.

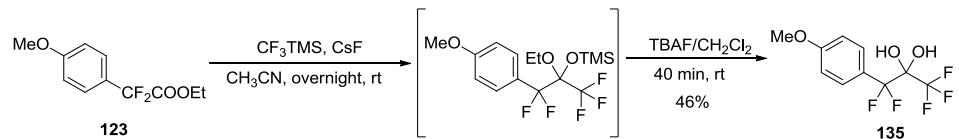
**Representative Reaction Procedure for Preparation of Pentafluoro *gem*-Diols.<sup>139</sup>** To a solution of ethyl 2,2-difluoro-2-(naphthalen-1-yl)acetate **122** (200 mg, 0.80 mmol) and CH<sub>3</sub>CN (2.0 mL) in a reaction vial, CF<sub>3</sub>TMS (598  $\mu$ L, 4.00 mmol) was added and stirred for 3 min. Then, CsF (364 mg, 2.40 mmol) was added and stirred 48 h at rt. Then, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL  $\times$  5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude reaction mixture was exposed to TBAF/CH<sub>2</sub>Cl<sub>2</sub> (1 mL/2 mL) and stirred for 40 min. at rt. Then, the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL) and the resultant mixture was extracted

with  $\text{CH}_2\text{Cl}_2$  ( $5 \text{ mL} \times 5$ ). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$  to 8:2 hexanes/EtOAc) afforded the desired product **134** in 31% (73.6 mg, oil).

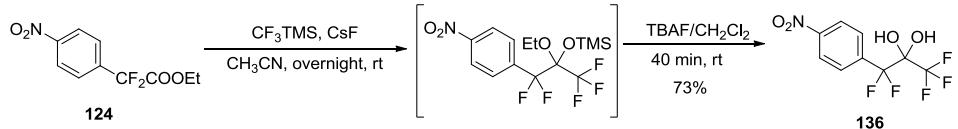


**1,1,1,3,3-Pentafluoro-3-(naphthalen-1-yl)propane-2,2-diol** **134.** See

representative reaction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45 (m, 1H), 8.06\* (m, 1H), 8.03 (m, 1H), 7.94\*(m, 1H), 7.91 (dd,  $J = 8.4, 1.2 \text{ Hz}$ , 1H), 7.83 (dd,  $J = 7.4, 1.2 \text{ Hz}$ , 1H), 7.58 (m, 3H), 3.34 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  180.3\* (q,  $J_{\text{CF}} = 36.6 \text{ Hz}$ , 1C), 134.2, 133.9\*, 133.3\*, 132.7, 130.5\*, 129.2, 128.8, 128.1(t,  $J_{\text{CF}} = 11.4 \text{ Hz}$ , 1C), 127.2, 126.7, 126.3, 126.2\* (m, 1C), 124.6, 124.3, 123.6\*, 121.7\* (q,  $J_{\text{CF}} = 286.6 \text{ Hz}$ , 1C), 121.2 (q,  $J_{\text{CF}} = 255.6 \text{ Hz}$ , 1C), 116.8\* (t,  $J_{\text{CF}} = 289.9 \text{ Hz}$ , 1C), 115.8 (t,  $J_{\text{CF}} = 254.5 \text{ Hz}$ , 1C), 93.1 (q,  $J_{\text{CF}} = 32.3 \text{ Hz}$ , 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -73.8\* (t,  $J_{\text{FF}} = 7.6 \text{ Hz}$ , 3F), -81.1 (t,  $J_{\text{FF}} = 11.2 \text{ Hz}$ , 3F), -102.5\* (q,  $J_{\text{FF}} = 7.3 \text{ Hz}$ , 2F), -104.4 (q,  $J_{\text{FF}} = 11.1 \text{ Hz}$ , 2F); IR (film)  $\nu_{\text{max}}$  3519, 1202, 1049, 796  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_9\text{F}_5\text{O}_2$  ( $\text{M}-\text{H}_2\text{O}$ ) $^+$ , 274.0417; found, 274.0424.\* denotes ketone form of the product.

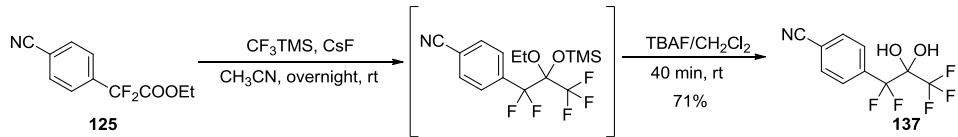


**1,1,1,3,3-Pentafluoro-3-(4-methoxyphenyl)propane-2,2-diol 135.** See representative reaction procedure. Ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate **123** (203 mg, 0.88 mmol), CF<sub>3</sub>TMS (660 μL, 4.40 mmol), CsF (560 mg, 3.69 mmol) and no solvent were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub> to 8:2 hexanes/EtOAc) afforded the desired product **135** in 46% yield (112.2 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.55 (dd, *J* = 6.9, 2.0 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 161.7, 128.7 (t, *J*<sub>CF</sub> = 6.4 Hz, 2C), 122.7 (t, *J*<sub>CF</sub> = 25.0 Hz, 1C), 121.5 (q, *J*<sub>CF</sub> = 286.3 Hz, 1C), 118.20 (t, *J*<sub>CF</sub> = 252.5 Hz, 1C), 113.7 (2), 92.5 (sextet, *J*<sub>CF</sub> = 31.3 Hz, 1C), 55.4; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -81.2 (t, *J*<sub>FF</sub> = 10.2 Hz, 3F), -109.8 (q, *J*<sub>FF</sub> = 10.8 Hz, 2F); IR (film) ν<sub>max</sub> 3368, 1195, 1057, 831 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd. for C<sub>10</sub>H<sub>9</sub>F<sub>5</sub>O<sub>3</sub> (M-H<sub>2</sub>O)<sup>+</sup>, 254.0366; found, 254.0372; mp 85–87 °C.



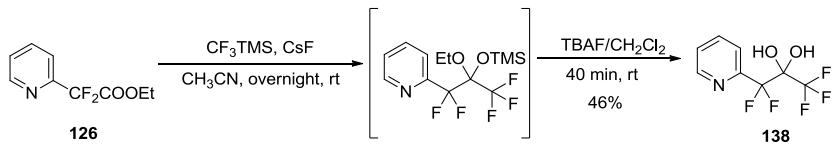
**1,1,1,3,3-Pentafluoro-3-(4-nitrophenyl)propane-2,2-diol 136.** See representative reaction procedure. Ethyl 2,2-difluoro-2-(4-nitrophenyl)acetate **124** (96.0 mg, 0.39 mmol), CF<sub>3</sub>TMS (88.0 μL, 0.59 mmol), CsF (30.0 mg, 0.20 mmol) and CH<sub>3</sub>CN (2.0 mL) were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub> to 8:2 hexanes/EtOAc) afforded the desired product **136** in 73% yield (82.1 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.30 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 8.9 Hz, 2H), 3.77 (br s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 149.4,

137.6 (t,  $J_{\text{CF}} = 25.0$  Hz, 1C), 128.6 (t,  $J_{\text{CF}} = 6.3$  Hz, 2C), 123.2 (2), 121.2 (q,  $J_{\text{CF}} = 286.3$  Hz, 1C), 117.1 (t,  $J_{\text{CF}} = 253.8$  Hz, 1C), 92.6 (sextet,  $J_{\text{CF}} = 32.5$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.2 (t,  $J_{\text{FF}} = 9.6$  Hz, 3F), -110.9 (q,  $J_{\text{FF}} = 9.3$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3391, 1531, 1192, 1177, 1064  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_9\text{H}_6\text{F}_5\text{NO}_4$  ( $\text{M}+\text{H}-\text{H}_2\text{O}$ ) $^+$ , 270.0190; found, 270.0193; mp 86–88 °C.

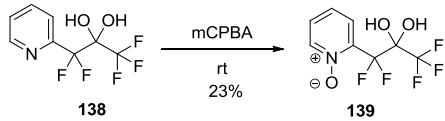


**4-(1,1,3,3,3-Pentafluoro-2,2-dihydroxypropyl)benzonitrile 137.** See

representative reaction procedure. Ethyl 2-(4-cyanophenyl)-2,2-difluoroacetate **125** (120 mg, 0.53 mmol),  $\text{CF}_3\text{TMS}$  (120  $\mu\text{L}$ , 0.80 mmol),  $\text{CsF}$  (40.5 mg, 0.27 mmol) and  $\text{CH}_3\text{CN}$  (2.0 mL) were used. The reaction mixture was stirred for overnight at rt.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$  to 1:1 hexanes/EtOAc) afforded the desired product **137** in 71% yield (101.1 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (s, 4H), 3.73 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  135.9 (t,  $J_{\text{CF}} = 25.0$  Hz, 1C), 131.9 (2), 128.1 (t,  $J_{\text{CF}} = 7.5$  Hz, 2C), 121.2 (q,  $J_{\text{CF}} = 286.3$  Hz, 1C), 117.8, 117.1 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 115.0, 92.7;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.7 (t,  $J_{\text{FF}} = 9.3$  Hz, 3F), -111.5 (q,  $J_{\text{FF}} = 9.6$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3272, 2249, 1278, 1195, 1071  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_6\text{F}_5\text{NO}_2$  ( $\text{M}+\text{H}-\text{H}_2\text{O}$ ) $^+$ , 250.0291; found, 250.0295; mp 98–100 °C.

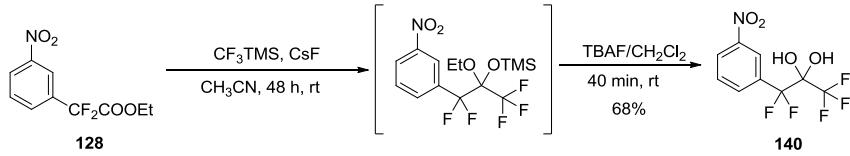


**1,1,1,3,3-Pentafluoro-3-(pyridin-2-yl)propane-2,2-diol 138.** See representative reaction procedure. Ethyl 2,2-difluoro-2-(pyridin-2-yl)acetate **126** (238 mg, 1.19 mmol), CF<sub>3</sub>TMS (266 µL, 1.78 mmol), CsF (90.0 mg, 0.59 mmol) and CH<sub>3</sub>CN (3.0 mL) were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub> to 7:3 hexanes/EtOAc) afforded the desired product **138** in 46% yield (134 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.60 (ddd, *J* = 4.9, 1.6, 0.8 Hz, 1H), 7.99 (td, *J* = 7.8, 1.7 Hz, 1H), 7.85 (dt, *J* = 6.0, 3.0 Hz, 1H), 7.55 (ddd, *J* = 7.7, 4.9, 1.0 Hz, 1H), 5.97 (br s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 152.3 (t, *J*<sub>CF</sub> = 28.8 Hz, 1C), 147.8 (d, *J*<sub>CF</sub> = 31.6 Hz, 1C), 138.8, 126.1 (d, *J*<sub>CF</sub> = 22.9 Hz, 1C), 121.4 (q, *J*<sub>CF</sub> = 286.3 Hz, 1C), 121.2, 112.5 (t, *J*<sub>CF</sub> = 252.5 Hz, 1C), 93.5 (m, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -82.1 (t, *J*<sub>FF</sub> = 10.9 Hz, 3F), -113.2 (q, *J*<sub>FF</sub> = 10.8 Hz, 2F); IR (film) ν<sub>max</sub> 3351, 1203, 1169, 1081 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd. for C<sub>8</sub>H<sub>6</sub>F<sub>5</sub>NO<sub>2</sub> (M-H<sub>2</sub>O)<sup>+</sup>, 225.0213; found, 225.0219; mp 47–48 °C.



**2-(1,1,1,3,3-Pentafluoro-2,2-dihydroxypropyl)pyridine 1-oxide 139.** To a solution of 1,1,1,3,3-pentafluoro-3-(pyridin-2-yl)propane-2,2-diol **138** (173 mg, 0.713 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL), 77% *m*CPBA (1231 mg, 7.13 mmol) was added and stirred for overnight at rt. Then, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (5 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash pipette chromatography (100% CHCl<sub>3</sub> to 100% EtOAc) afforded the desired product **139** in 23%

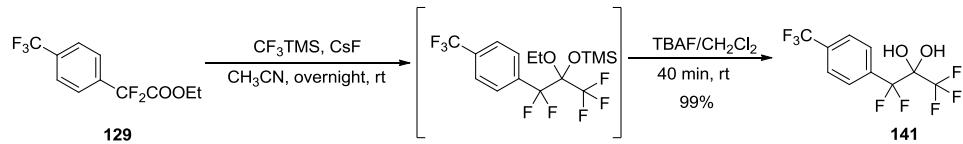
(43.1 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (d,  $J = 6.5$  Hz, 1H), 8.24\* (d,  $J = 5.0$  Hz, 1H), 7.86 (dd,  $J = 8.1, 1.9$  Hz, 1H), 7.83\* (dd,  $J = 8.0, 2.0$  Hz, 1H), 7.66 (td,  $J = 8.0, 1.0$  Hz, 1H), 7.61\* (td,  $J = 7.5, 1.0$  Hz, 1H), 7.57 (td,  $J = 6.5, 2.0$  Hz, 1H), 7.39 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1 (t,  $J_{\text{CF}} = 27.5$  Hz, 1C), 140.8, 129.9, 128.1, 126.3 (t,  $J_{\text{CF}} = 7.9$  Hz, 1C), 121.6 (q,  $J_{\text{CF}} = 286.3$  Hz, 1C), 116.2 (t,  $J_{\text{CF}} = 258.8$  Hz, 1C), 95.5 (m, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -75.6\* (t,  $J_{\text{FF}} = 8.5$  Hz, 3F), -82.5 (t,  $J_{\text{FF}} = 11.3$  Hz, 3F), -109.6\* (q,  $J_{\text{FF}} = 5.6$  Hz, 2F), -112.8 (q,  $J_{\text{FF}} = 11.3$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3306, 1438, 1304, 1165  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd. for  $\text{C}_8\text{H}_6\text{F}_5\text{NO}_3$  ( $\text{M}+\text{H})^+$ , 260.0346; found, 260.0350; mp 90–92 °C. \* denotes ketone form of the product.



**1,1,1,3,3-Pentafluoro-3-(3-nitrophenyl)propane-2,2-diol** **140.** See

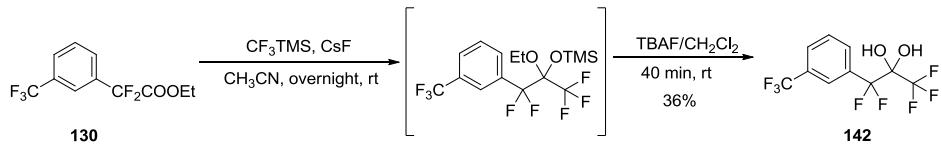
representative reaction procedure. Ethyl 2,2-difluoro-2-(3-nitrophenyl)acetate **128** (117 mg, 0.48 mmol),  $\text{CF}_3\text{TMS}$  (107  $\mu\text{L}$ , 0.72 mmol),  $\text{CsF}$  (36.0 mg, 0.24 mmol), and  $\text{CH}_3\text{CN}$  (2.4 mL) were used. The reaction mixture was stirred for 48 h at rt.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$  to 8:2 hexanes/EtOAc) afforded the desired product **140** in 68% (94.0 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (t,  $J = 2.0$  Hz, 1H), 8.40 (dd,  $J = 8.0, 1.5$  Hz, 1H), 7.97 (d,  $J = 8.0$  Hz, 1H), 7.68 (t,  $J = 8.0$  Hz, 1H), 3.56 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  147.9, 133.3 (t,  $J_{\text{CF}} = 26.0$  Hz, 1C), 133.1 (t,  $J_{\text{CF}} = 6.3$  Hz, 1C), 129.4, 125.9, 122.7 (t,  $J_{\text{CF}} = 7.1$  Hz, 1C), 121.2 (q,  $J_{\text{CF}} = 286.4$  Hz, 1C), 116.9 (t,  $J_{\text{CF}} = 253.5$  Hz, 1C), 92.6 (sextet,  $J_{\text{CF}} = 32.3$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.32

(t,  $J_{\text{FF}} = 9.6$  Hz, 3F), -110.62 (q,  $J_{\text{FF}} = 9.6$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3367, 1534, 1356, 1197, 715 cm<sup>-1</sup>; HRMS (EI)  $m/z$  calcd. for C<sub>9</sub>H<sub>6</sub>F<sub>5</sub>NO<sub>4</sub> (M+H-H<sub>2</sub>O)<sup>+</sup>, 270.0190; found, 270.0193.

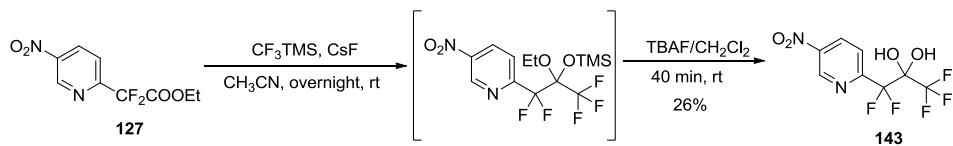


**1,1,1,3,3-Pentafluoro-3-(4-(trifluoromethyl)phenyl)propane-2,2-diol 141.** See representative reaction procedure. Ethyl 2,2-difluoro-2-(3-(trifluoromethyl)phenyl)acetate **129** (358 mg, 1.34 mmol), CF<sub>3</sub>TMS (600 μL, 4.01 mmol), CsF (609 mg, 4.01 mmol) and no solvent were used. The reaction mixture was stirred for overnight at rt. Then, the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 5). The crude reaction mixture was exposed to TBAF/CH<sub>2</sub>Cl<sub>2</sub> (1 mL/2 mL) and stirred for 30 min. at rt. Then, the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub> to 1:1 hexanes/EtOAc) afforded the desired product **141** in 99% yield (137.4 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.89–7.60 (m, 4H), 3.74 (br s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 134.7 (t,  $J_{\text{CF}} = 25.4$  Hz, 1C), 133.1 (q,  $J_{\text{CF}} = 34.0$  Hz, 1C), 127.8 (t,  $J_{\text{CF}} = 6.5$  Hz, 2C), 125.2 (q,  $J_{\text{CF}} = 4.0$  Hz, 2C), 123.5 (q,  $J_{\text{CF}} = 271.3$  Hz, 1C), 121.3 (q,  $J_{\text{CF}} = 286.4$  Hz, 1C), 117.3 (t,  $J_{\text{CF}} = 253.1$  Hz, 1C), 92.6 (sextet,  $J_{\text{CF}} = 32.0$  Hz, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -64.1 (3), -81.3 (t,  $J_{\text{FF}} = 9.6$  Hz, 3F), -110.0 (q,  $J_{\text{FF}} = 9.6$  Hz, 2F); IR (film)

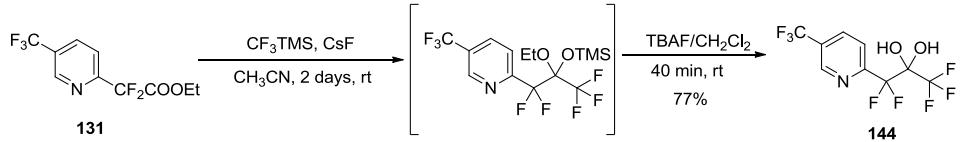
$\nu_{\text{max}}$  3435, 1416, 1329, 1138, 1071  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_6\text{F}_8\text{O}_2$  ( $\text{M}-\text{F}$ ) $^+$ , 291.0256; found, 291.0251; mp 56–58 °C.



**1,1,1,3,3-Pentafluoro-3-(3-(trifluoromethyl)phenyl)propane-2,2-diol 142.** See representative reaction procedure. Ethyl 2,2-difluoro-2-(3-(trifluoromethyl)phenyl)acetate **130** (358 mg, 1.34 mmol),  $\text{CF}_3\text{TMS}$  (600  $\mu\text{L}$ , 4.01 mmol),  $\text{CsF}$  (609 mg, 4.01 mmol) and no solvent were used. The reaction mixture was stirred for overnight at rt.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$  to 1:1 hexanes/EtOAc) afforded the desired product **142** in 36% yield (150.6 mg, oil).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (s, 1H), 7.81 (t,  $J = 8.3$  Hz, 2H), 7.61 (t,  $J = 7.9$  Hz, 1H), 3.44 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  132.2 (t,  $J_{\text{CF}} = 26.3$  Hz, 1C), 130.9 (q,  $J_{\text{CF}} = 32.5$  Hz, 1C), 130.5 (t,  $J_{\text{CF}} = 6.3$  Hz, 1C), 128.8, 127.9 (m, 1C), 124.3 (m, 1C), 123.5 (q,  $J_{\text{CF}} = 271.3$  Hz, 1C), 121.4 (q,  $J_{\text{CF}} = 286.3$  Hz, 1C), 117.3 (t,  $J_{\text{CF}} = 252.5$  Hz, 1C), 92.5 (sextet,  $J_{\text{CF}} = 32.5$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.2 (t,  $J_{\text{FF}} = 9.7$  Hz, 3F), -110.7 (q,  $J_{\text{FF}} = 9.7$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3446, 1339, 1259, 1135  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_6\text{F}_8\text{O}_2$  ( $\text{M}+\text{H}-\text{H}_2\text{O}$ ) $^+$ , 293.0213; found, 293.0219.



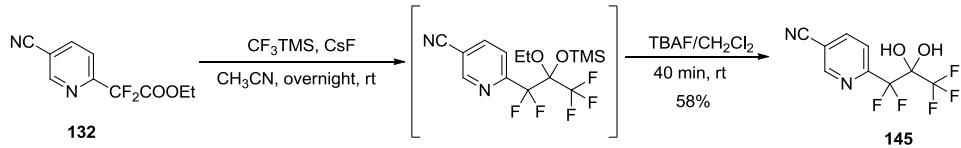
**1,1,1,3,3-Pentafluoro-3-(5-nitropyridin-2-yl)propane-2,2-diol 143.** See representative reaction procedure. Ethyl 2,2-difluoro-2-(5-nitropyridin-2-yl)acetate **127** (200 mg, 0.81 mmol), CF<sub>3</sub>TMS (243 μL, 1.63 mmol), CsF (62.0 mg, 0.41 mmol) and CH<sub>3</sub>CN (3.5 mL) were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub> to 2:1:1 CH<sub>2</sub>Cl<sub>2</sub>/hexanes/EtOAc) afforded the desired product **143** in 26% yield (61.7 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.46 (m, 1H), 8.78 (dd, *J* = 8.6, 2.5 Hz, 1H), 8.08 (dd, *J* = 8.6, 7.0 Hz, 1H), 5.58 (br s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 157.1 (t, *J*<sub>CF</sub> = 28.4 Hz, 1C), 145.2, 143.9, 133.9, 122.2 (t, *J*<sub>CF</sub> = 3.8 Hz, 1C), 121.1 (q, *J*<sub>CF</sub> = 287.5 Hz, 1C), 112.6 (t, *J*<sub>CF</sub> = 255.0 Hz, 1C), 93.3 (dtd, *J*<sub>CF</sub> = 61.4, 33.1, 29.1 Hz, 1C); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -81.9 (t, *J*<sub>FF</sub> = 10.9 Hz, 3F), -113.2 (q, *J*<sub>FF</sub> = 10.8 Hz, 2F); IR (film) ν<sub>max</sub> 3218, 1614, 1539, 1361, 1201 cm<sup>-1</sup>; HRMS (EI) *m/z* calcd. for C<sub>8</sub>H<sub>5</sub>F<sub>5</sub>N<sub>2</sub>O<sub>4</sub> (M-H<sub>2</sub>O)<sup>+</sup>, 270.0064; found, 270.0060; mp 66–68 °C.



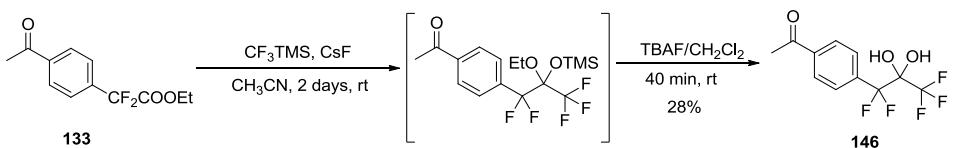
**1,1,1,3,3-Pentafluoro-3-(5-(trifluoromethyl)pyridin-2-yl)propane-2,2-diol 144.**

See representative reaction procedure. Ethyl 2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)acetate **131** (200 mg, 0.74 mmol), CF<sub>3</sub>TMS (222 μL, 1.49 mmol), CsF (56.4 mg, 0.37 mmol) and CH<sub>3</sub>CN (3.5 mL) were used. The reaction mixture was stirred for overnight at rt. SiO<sub>2</sub> flash column chromatography (100% CHCl<sub>3</sub> to 1:1 hexanes/EtOAc) afforded the desired product **144** in 77% yield (177.9 mg, solid). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.91

(s, 1H), 8.24 (dd,  $J = 8.3, 1.9$  Hz, 1H), 8.00 (d,  $J = 8.3$  Hz, 1H), 5.74 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  155.6 (t,  $J_{\text{CF}} = 29.0$  Hz, 1C), 145.3 (q,  $J_{\text{CF}} = 4.0$  Hz, 1C), 136.2 (q,  $J_{\text{CF}} = 3.6$  Hz, 1C), 129.1 (q,  $J_{\text{CF}} = 33.1$  Hz, 1C), 122.5 (q,  $J_{\text{CF}} = 139.3$  Hz, 1C), 121.4 (t,  $J_{\text{CF}} = 4.9$  Hz, 1C), 121.2 (q,  $J_{\text{CF}} = 286.4$  Hz, 1C), 112.5 (t,  $J_{\text{CF}} = 254.1$  Hz, 1C), 93.2 (m, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -63.7 (3), -82.0 (t,  $J_{\text{FF}} = 11.1$  Hz, 3F), -113.4 (q,  $J_{\text{FF}} = 11.0$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3392, 1615, 1204, 1083  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_9\text{H}_5\text{F}_8\text{NO}_2$  ( $\text{M}+\text{H}-\text{H}_2\text{O}$ ) $^+$ , 294.0165; found, 294.0168; mp 79–81 °C.



**6-(1,1,3,3,3-Pentafluoro-2,2-dihydroxypropyl)nicotinonitrile 145.** See representative reaction procedure. Ethyl 2-(5-cyanopyridin-2-yl)-2,2-difluoroacetate **132** (232 mg, 1.03 mmol),  $\text{CF}_3\text{TMS}$  (308  $\mu\text{L}$ , 2.06 mmol),  $\text{CsF}$  (78.0 mg, 0.51 mmol) and  $\text{CH}_3\text{CN}$  (3.5 mL) were used. The reaction mixture was stirred for overnight at rt.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$  to 1:1 hexanes/EtOAc) afforded the desired product **145** in 58% yield (160.5 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.90 (s, 1H), 8.27 (dd,  $J = 8.2, 2.0$  Hz, 1H), 7.99 (dd,  $J = 8.0, 1.0$  Hz, 1H), 5.6 (br s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  155.4 (t,  $J_{\text{CF}} = 28.4$  Hz, 1C), 150.7, 142.2, 121.6 (t,  $J_{\text{CF}} = 3.8$  Hz, 1C), 121.1 (q,  $J_{\text{CF}} = 286.3$  Hz, 1C), 114.9, 112.6, 112.5 (t,  $J_{\text{CF}} = 253.8$  Hz, 1C), 93.3 (m, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -82.0 (t,  $J_{\text{FF}} = 11.0$  Hz, 3F), -113.7 (q,  $J_{\text{FF}} = 11.0$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3368, 2239, 1203, 1118  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_9\text{H}_5\text{F}_5\text{N}_2\text{O}_2$  ( $\text{M}-\text{H}_2\text{O}$ ) $^+$ , 250.0166; found, 250.0164; mp 90–92 °C.



**1-(4-(1,1,3,3,3-Pentafluoro-2,2-dihydroxypropyl)phenyl)ethanone 146.** See representative reaction procedure. Ethyl 2-(4-acetylphenyl)-2,2-difluoroacetate **133** (50.0 mg, 0.21 mmol),  $\text{CF}_3\text{TMS}$  (46.0  $\mu\text{L}$ , 0.31 mmol),  $\text{CsF}$  (15.7 mg, 0.10 mmol) and  $\text{CH}_3\text{CN}$  (1.0 mL) were used. The reaction mixture was stirred for overnight at rt.  $\text{SiO}_2$  flash column chromatography (100%  $\text{CHCl}_3$  to 1:1 hexanes/EtOAc) afforded the desired product **146** in 28% yield (16.7 mg, solid).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01 (d,  $J = 8.4$  Hz, 2H), 7.73 (d,  $J = 8.7$  Hz, 2H), 3.73 (br s, 2H), 2.63 (br s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  197.4, 139.0, 135.4 (t,  $J_{\text{CF}} = 25.0$  Hz, 1C), 128.0 (2), 127.6 (t,  $J_{\text{CF}} = 6.3$  Hz, 2C), 122.3 (q,  $J_{\text{CF}} = 286.3$  Hz, 1C), 117.5 (t,  $J_{\text{CF}} = 253.8$  Hz, 1C), 92.6 (sextet,  $J_{\text{CF}} = 31.3$  Hz, 1C), 26.8;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.3 (t,  $J_{\text{FF}} = 9.6$  Hz, 3F), -111.1 (q,  $J_{\text{FF}} = 9.3$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3391, 1679, 1277, 1198  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_9\text{F}_5\text{O}_3$  ( $\text{M}+\text{H}-\text{H}_2\text{O}$ ) $^+$ , 267.0445; found, 267.0448; mp 106–108 °C.

## CHAPTER 5. SYNTHESIS OF METABOLICALLY STABLE MALVIDIN 3-GLUCOSIDE DERIVATIVES

### 5.1 Introduction

Although the sugar moiety of anthocyanin is critical for a better pharmacokinetic profile, anthocyanins are prone to metabolism in the body which form anthocyanin aglycones or anthocyanidins.<sup>37</sup> Using our novel synthetic methodology, we wanted to replace the labile acetal linkage between the sugar and anthocyanidin to improve its pharmacokinetic profile (Figure 5.1). This bioisosteric replacement strategy successfully prevented the hydrolysis of phosphate from phosphatases.<sup>140</sup> Therefore, we strongly believe that fluorinated anthocyanin derivatives will show improved pharmacokinetic profiles.

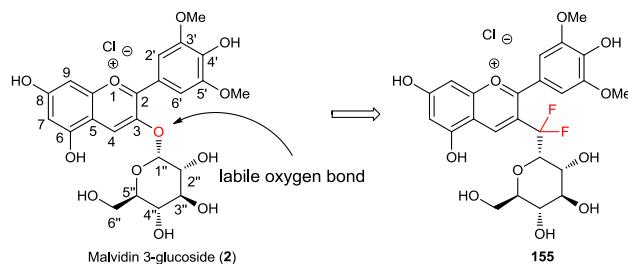


Figure 5.1 Illustration of bioisosteric replacement of oxygen linkage with a difluoromethylene unit.

## 5.2 Chemistry

Among many anthocyanins, malvidin 3-glucoside has been selected as a key target molecule because malvidin 3-glucoside showed relatively strong neuroprotective potency compared to other anthocyanins in biological studies conducted by Prof. Jean-Christophe Rochet's group in the Medicinal Chemistry and Molecular Pharmacology department. A series of metabolically stable malvidin 3-glucoside derivatives have been designed for pharmacokinetic studies (Figure 5.2) and two different bond disconnection strategies were designed to efficiently assemble target molecules (Figure 5.3). The first synthetic route is based on bond disconnection between C3 and glucose linkage. For the sugar part, protected streptol was chosen as a key synthetic intermediate to access fluorinated and non-fluorinated sugar derivatives. Also, the 3-bromoflavone scaffold was selected as a key synthetic intermediate to assemble the polyphenolic ring part. This key intermediate can also be utilized in a second synthetic route. This second synthetic route is based on a bond disconnection between the glucosidic linkage and C1'' (Figure 5.3). In this synthetic route, a pentafluoro *gem*-diol was selected as a key intermediate.

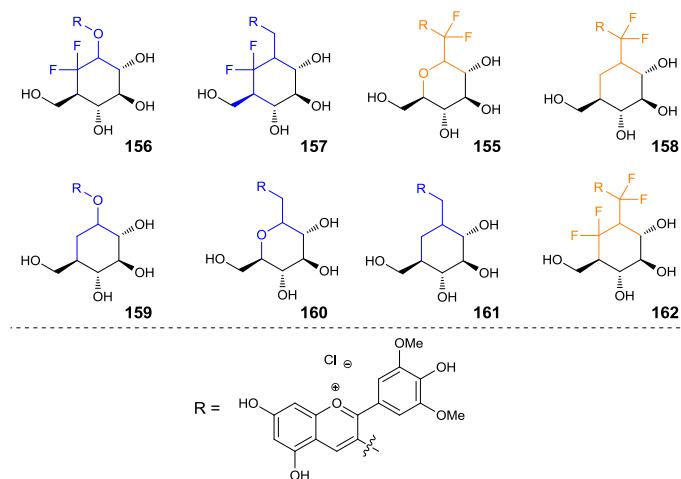


Figure 5.2 Designed metabolically stable anthocyanin derivatives.

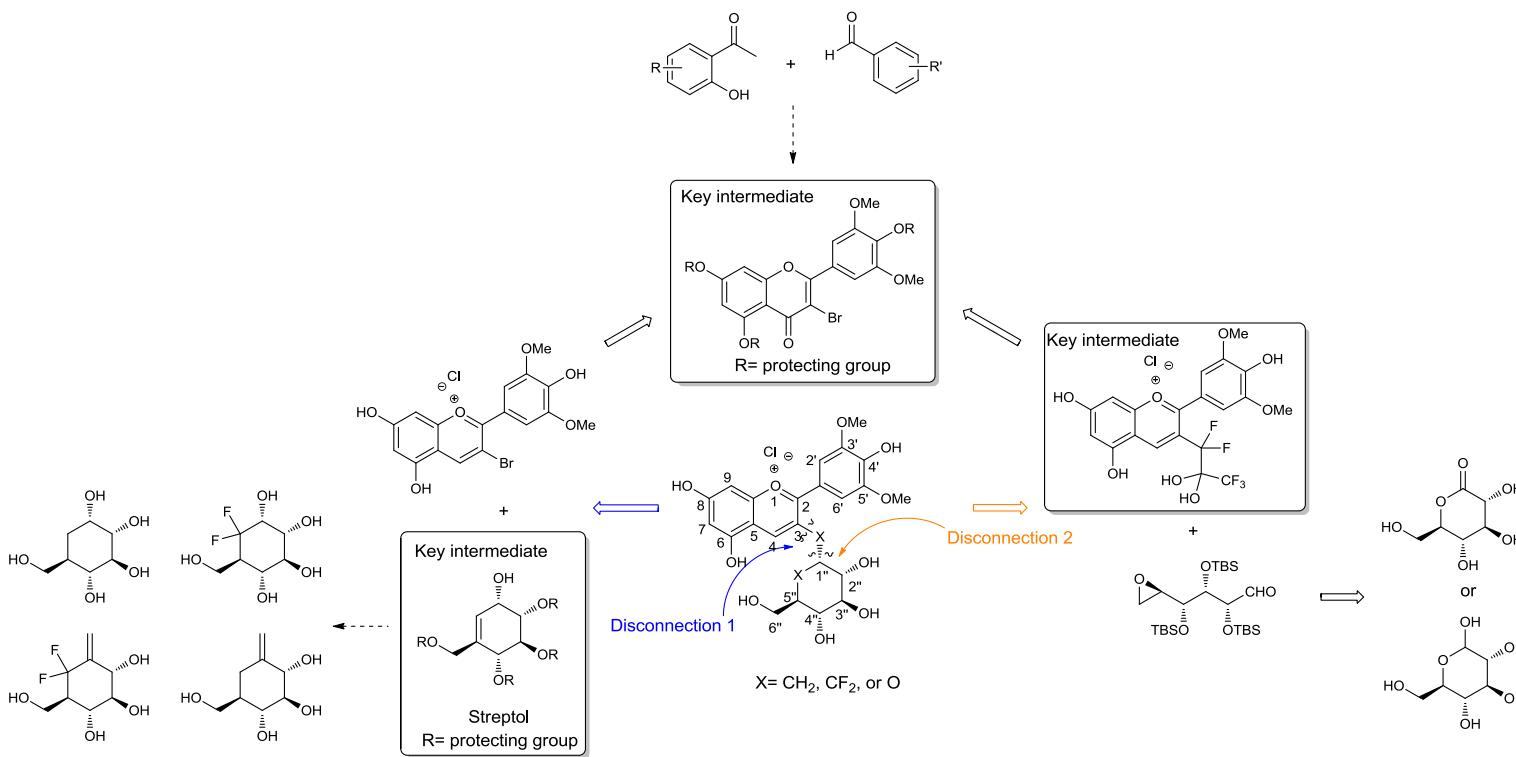
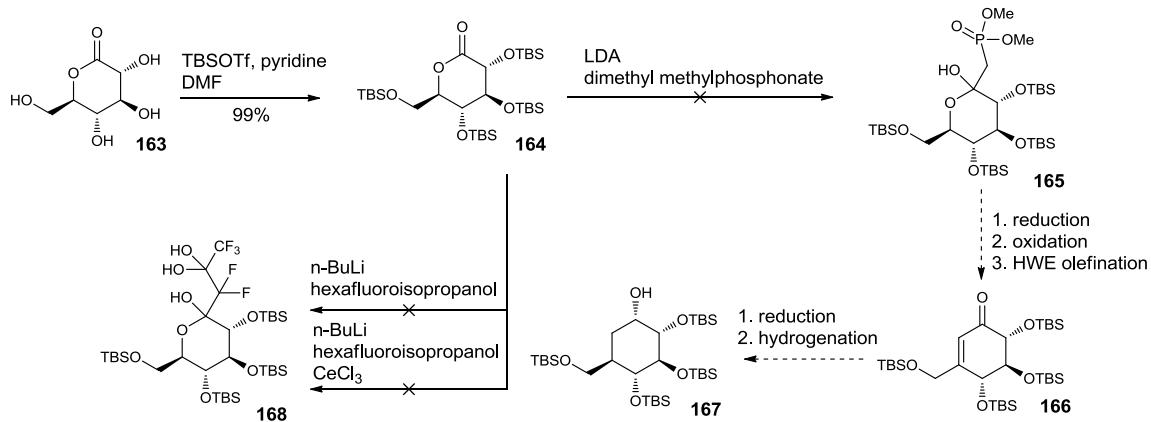


Figure 5.3 Synthetic strategies to assemble designed target molecules.

### 5.2.1 Synthesis of Streptol

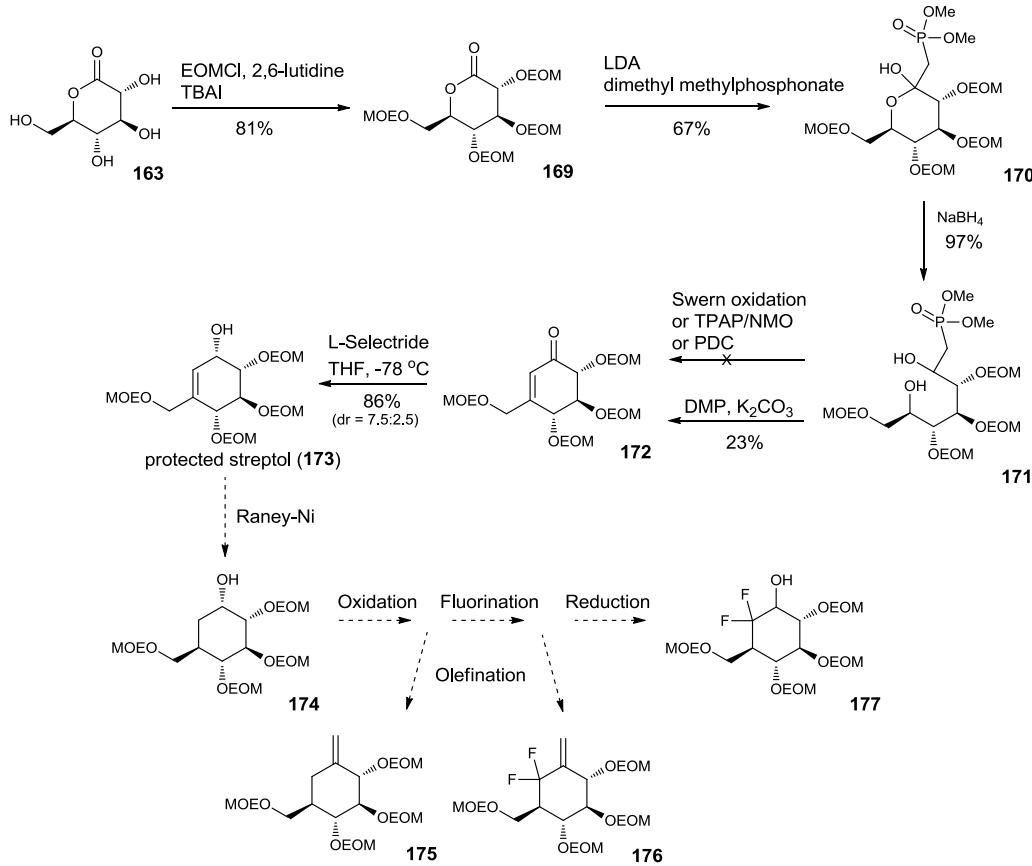
D-(+)-Gluconic acid  $\delta$ -lactone **163** was utilized as a starting material for the synthesis of streptol (Scheme 5.1). After TBS protection, dimethyl methylphosphonate was reacted with protected  $\delta$ -lactone **164** to assemble the HWE olefination intermediate **165**. However, this reaction failed, probably because steric congestion generated by the bulky TBS protecting group prevented the reaction of the  $\delta$ -lactone with other nucleophiles such as a perfluoro enolate. Only MeLi was small enough to react with the sterically hindered  $\delta$ -lactone.



Scheme 5.1 Synthetic Approach Toward Carba- $\alpha$ -D-glucose

To resolve the issue generated by steric hindrance by the protecting group, the EOM protecting group was selected (Scheme 5.2). After the global protection with EOMCl, dimethyl methylphosphonate reacted with the  $\delta$ -lactone and formed the HWE intermediate **170**. After NaBH<sub>4</sub>-mediated reduction of hemiacetal **171**, the previously reported TFAA-mediated Swern oxidation was performed to obtain enone **172**.<sup>141</sup> However, the result was not promising; only a trace amount of enone **172** was formed.

Therefore, a number of oxidation conditions were explored to increase the yield. None of them provided any improvement except DMP/K<sub>2</sub>CO<sub>3</sub>; enone **172** was successfully formed using the Dess-Martin oxidation followed by K<sub>2</sub>CO<sub>3</sub>-mediated HWE olefination. Then, the reduction of enone **172** yielded the protected streptol **173**. Using L-selectride at -78 °C, the desired protected streptol (**173**) was formed as a major diastereomer (dr = 7.5:2.5). A number of glucose-based coupling partners, **174**, **175**, **176**, and **177**, can be made in due course (Scheme 5.2). With these coupling partners in hand, coupling reactions with 3-bromoflavone derivatives will be pursued to synthesize the target molecules.



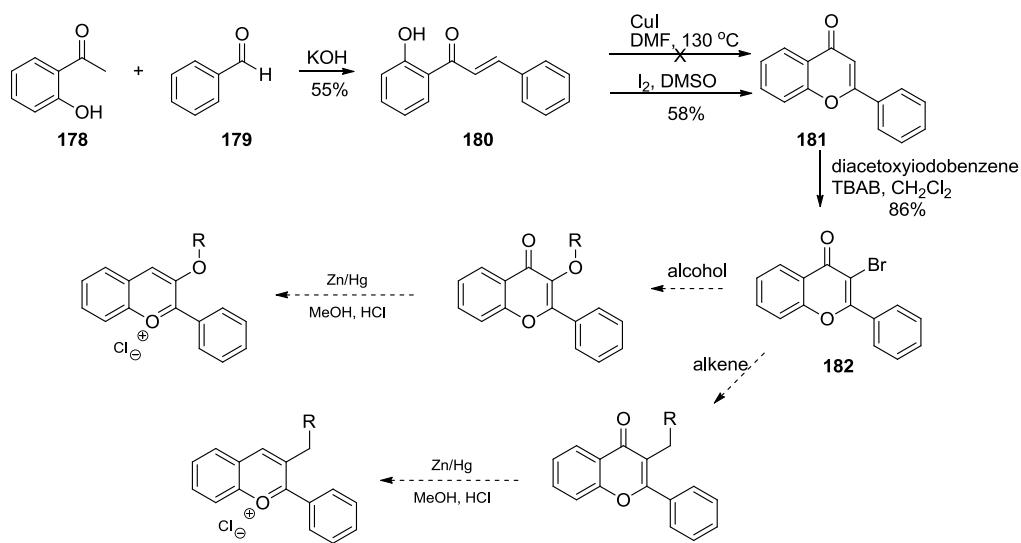
Scheme 5.2 Alternative Synthetic Approach Toward Streptol

### 5.2.2 Synthesis of the 3-Bromoflavone Scaffold

Malvidin 3-glucoside has an electron-deficient 2-phenylchromenylium ring and this moiety can be obtained by reduction of its precursor, flavone.<sup>142</sup> We have selected 3-bromoflavone **182** as a model system to explore the coupling reaction conditions between substituted 3-bromoflavone **182** and glucose-derived coupling partners (Scheme 5.3). Commercially available 1-(2-hydroxyphenyl)ethanone **178** and bezaldehyde **179** were coupled via KOH-mediated aldol condensation.<sup>143</sup> CuI-mediated cyclization was unsuccessful.<sup>144</sup> On the other hand, I<sub>2</sub>-mediated intramolecular cyclization formed the flavone (**181**) in a reasonably good yield of 58%.<sup>145,146</sup> Subsequent

diacetoxyiodobenzene-mediated bromination reaction provided the 3-bromoflavone **182** in 86% yield.<sup>147</sup>

The synthesized 3-bromoflavone **182** will be used as a model for coupling studies with glucose-derived coupling partners. The coupling methods can be diverse based on the respective partners. Both organometallic and nucleophilic coupling approach will be explored. A test experiment with 3-aminopropan-1-ol was conducted and complete conversion to the product was observed. This result may give us some useful insight for using a nucleophilic coupling approach. Slight modifications of the synthetic path to flavone will allow us to make the key intermediate, a precursor of 3-bromomalvidine.



Scheme 5.3 Synthesis of 3-Bromoflavone Scaffold

### 5.2.3 Model Studies with Aryl Pentafluoro *gem*-Diols; Investigation of Difluorocarbanion Reactivity

We have recently efficiently generated difluoroenolates via a mild trifluoroacetate release process. Our methodology has been extended toward the generation of difluorocarbanions with  $\alpha$ -aryl pentafluoro *gem*-diols. Due to the highly electron-deficient

chromenylium ring moiety in the polyphenolic side of anthocyanin, predominant trifluoroacetate release under the basic reaction condition was expected from previous cleavage study results with highly fluorinated aryl *gem*-diols (Figure 5.4).

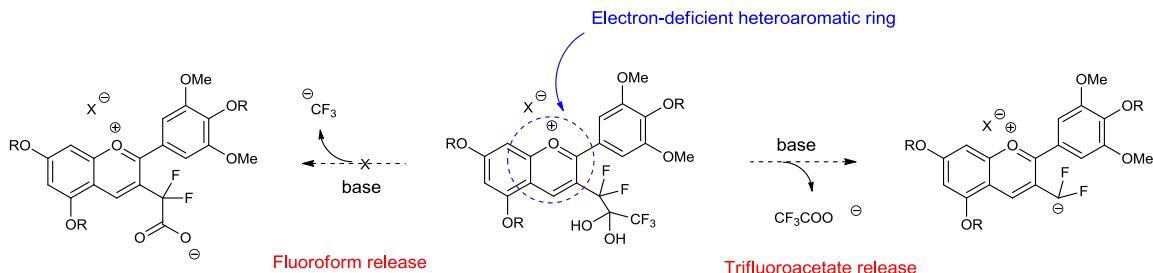
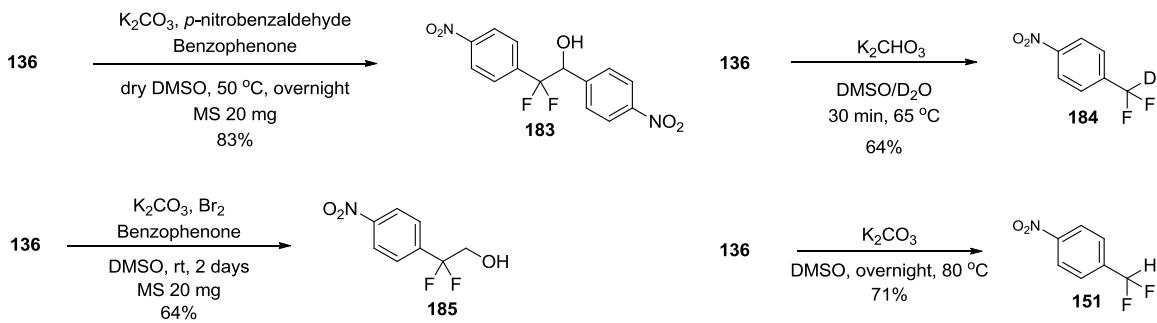


Figure 5.4 Expected cleavage path of a key *gem*-diol intermediate.

Electrophile coupling reactions with  $\alpha,\alpha$ -difluoroaryl carbanions will distinguish which bond disconnection strategy is going to be feasible or not. Easily accessible *gem*-diol **136** was selected as a model compound.  $\alpha,\alpha$ -Difluoroaryl carbanions generated via the trifluoroacetate-release process reacted not only with readily available electrophiles, such as D<sub>2</sub>O and *p*-nitrobenzaldehyde, but also with *in situ* generated DMSO-bromonium type electrophiles (Scheme 5.4).



Scheme 5.4 Reactions between  $\alpha,\alpha$ -Difluoroaryl Carbanion and Electrophiles

The proposed mechanism of hydroxyl methylation is presented in Figure 5.5. The reaction between DMSO and bromine generates activated DMSO<sup>148</sup> and subsequent

deprotonation by  $\text{K}_2\text{CO}_3$  generates DMSO-bromonium type electrophiles. Then, nucleophilic addition of the generated  $\alpha,\alpha$ -difluoroaryl carbanions causes subsequent Pummerer rearrangement which led to formation of hydroxymethylated product.

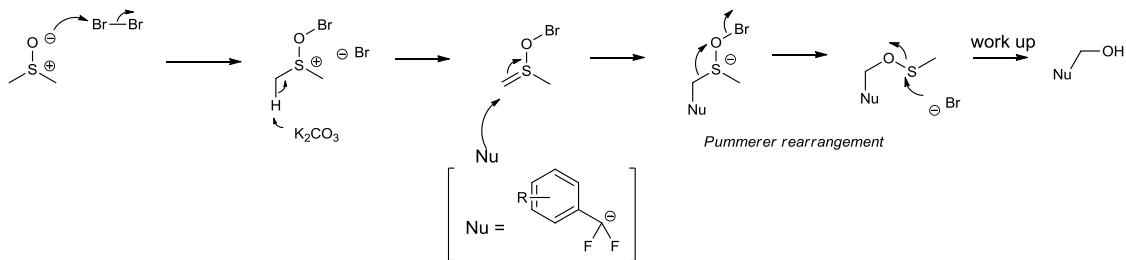
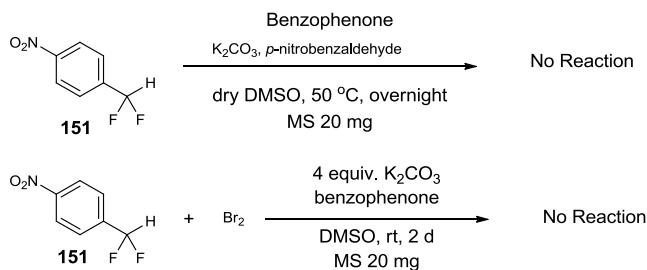


Figure 5.5 Proposed mechanism of hydroxymethylation reaction

Test reactions have been performed to verify that the electrophile coupling reaction is not a stepwise process (Scheme 5.5). Indeed, 1-(difluoromethyl)-4-nitrobenzene **151** did not react with aldehyde or the DMSO-bromonium type species using the trifluoroacetate release conditions. By trapping the reactive difluorocarbanions with an epoxy aldehyde **186** originating from glucose, the key framework of the target molecule will be directly assembled (Figure 5.6).



Scheme 5.5 Test Reactions with 1-(Difluoromethyl)-4-nitrobenzene

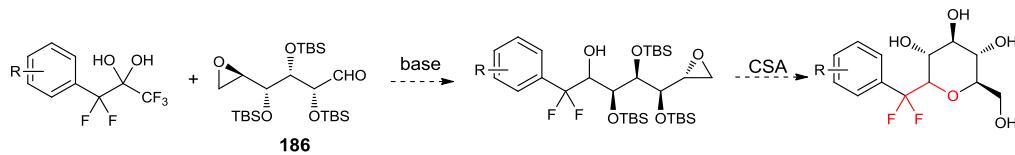
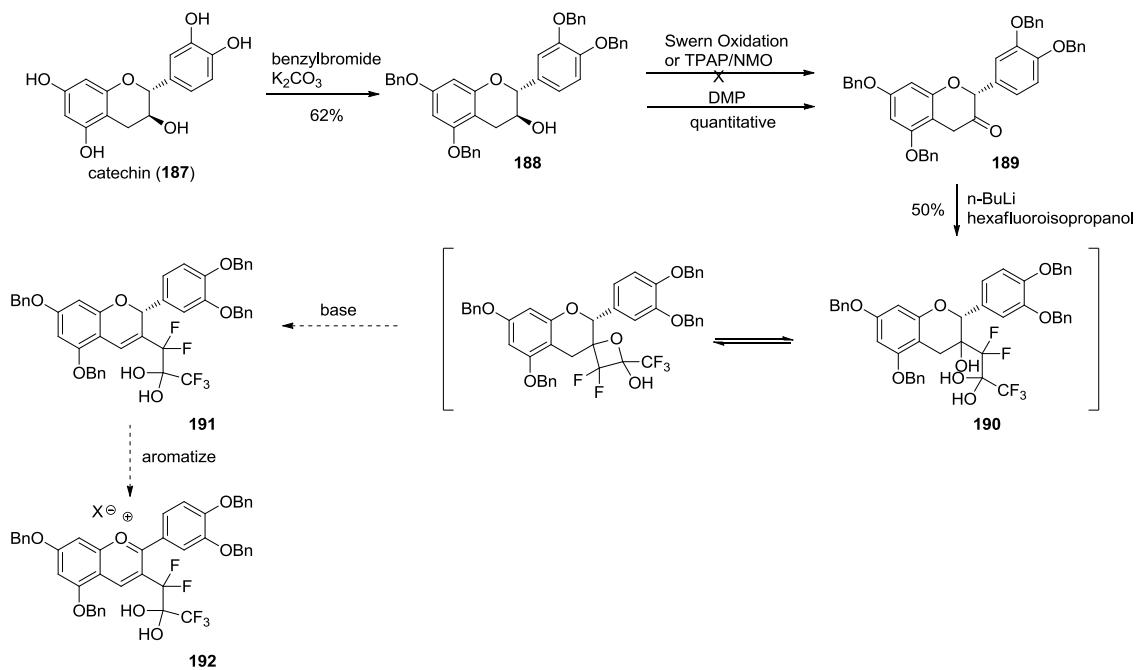


Figure 5.6 Application of trifluoroacetate release process toward the assembly of the key framework of fluorinated anthocyanin derivative.

#### 5.2.4 Semisynthesis of Cyanidin Derived Pentafluoro *gem*-Diol as a Model System

Recently, Kondo, T. *et al.* reported an efficient synthesis of cyanidin 3-glucoside from (+)-catechin.<sup>149</sup> The starting material, (+)-catechin hydrate, is more readily available than malvidin. Moreover, its structure is very similar to malvidin. Therefore, we decided to make cyanidin-derived pentafluoro *gem*-diols as a model system (Scheme 5.6). The selective protection of phenols in the presence of secondary alcohols was performed with benzyl bromide and  $K_2CO_3$ . Exploitation of the  $pK_a$  difference between phenols and secondary alcohols allowed for the selectivity. Then, the oxidation of the secondary alcohol was attempted. Both Swern and TPAP/NMO oxidations failed to give us our desired product. However, the alcohol was successfully converted into a ketone under the Dess-Martin oxidation. Then the pentafluoro *gem*-diol moiety was installed via reaction between the ketone **189** and perfluoroenolate generated from hexafluoroisopropanol. Subsequent steps will lead us to form the cyanidin derived pentafluoro *gem*-diol and this compound will be used as a model system for the aldehyde coupling reaction.



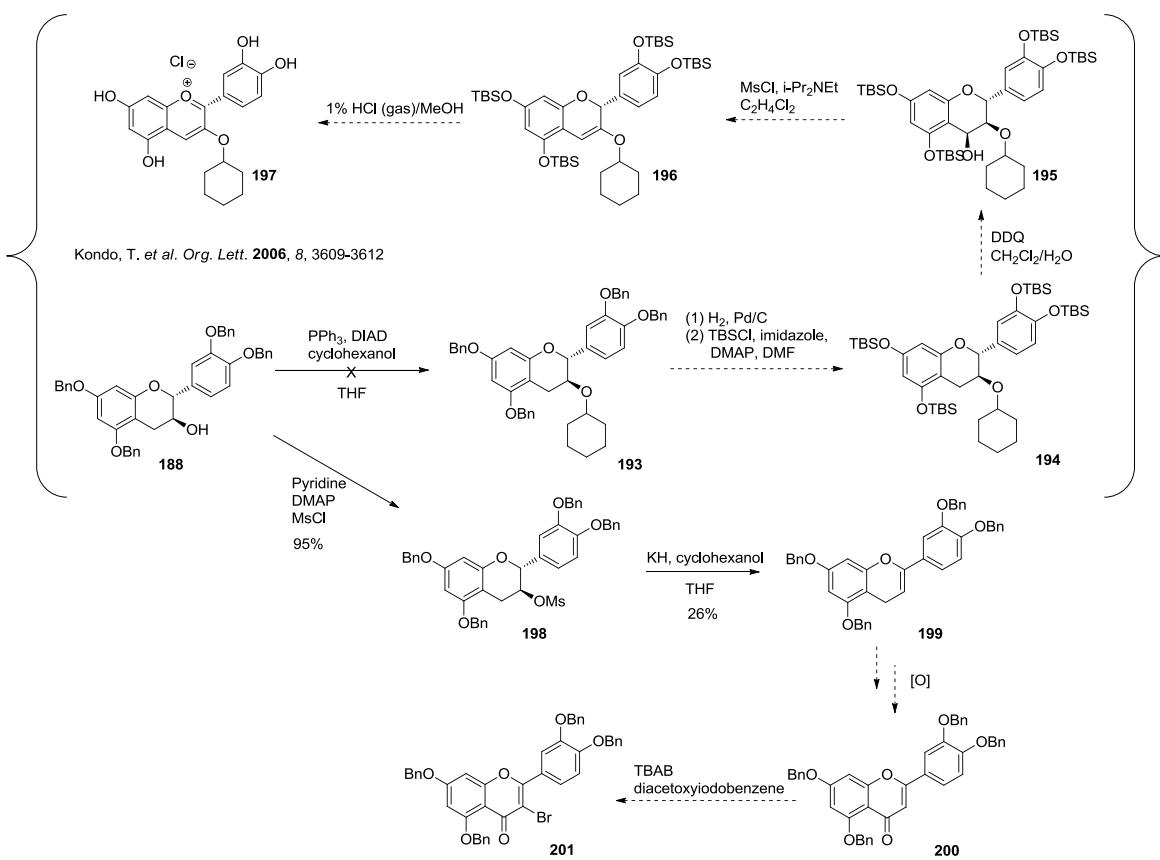
Scheme 5.6 Synthetic Route for Cyanidin-Derived Pentafluoro *gem*-Diols

### 5.2.5 Alternative Approaches: Synthesis of Metabolically Stable Cyanidin 3-Glucoside Derivatives

Cyanidin is a pigment found in various berries and it is a kind of anthocyanidin. Like malvidin, cyanidin also shows antioxidant effects due to the radical-scavenging effects of its polyphenolic ring structure. Synthesizing metabolically stable cyanidin 3-glucoside derivatives will extend the structure-activity data for the neuroprotective effects against neurodegenerative diseases. Kondo, T. *et al.* synthesized cyanidin 3-glucoside with chemically glycosylated (+)-catechin. Because we wanted to make non-hydrolyzable derivatives, we planned to follow their synthetic route with cyclohexylated catechin derivative **193**. (Scheme 5.7) We envisioned that the cyclohexylation reaction condition

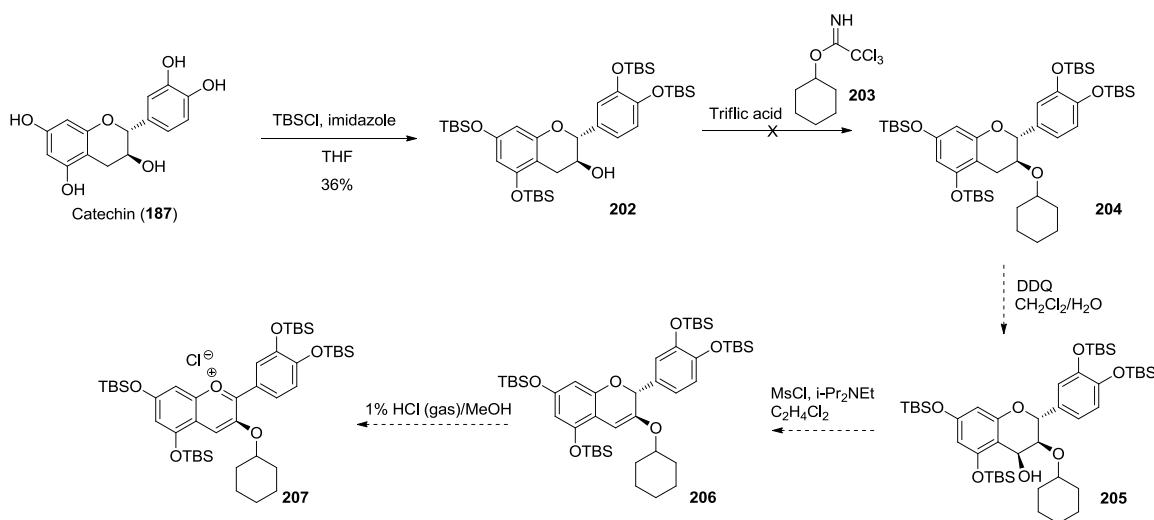
could be applied for the coupling of non-hydrolysable glucose derivatives such as compound **174** and **177**.

Efficient reaction conditions for cyclohexylation of (+)-catechin is being actively pursued. Unfortunately, conditions to install a cyclohexyl group have not been found so far. Trials with a Mitsunobu coupling with cyclohexanol were unsuccessful. Because the hydrogen on C2 was too acidic, nucleophilic displacement of mesylate also did not succeed; beta-elimination occurred instead. Although appending a cyclohexyl group was not successful, the beta-elimination product **199** may be used for the synthesis of 3-bromoflavone derivatives in the future. A trichloroacetimidate-mediated cyclohexylation reaction was also examined (Scheme 5.8). However, the desired product has not been observed so far.



Scheme 5.7 The Synthesis of Metabolically Stable Cyanidin Derivatives

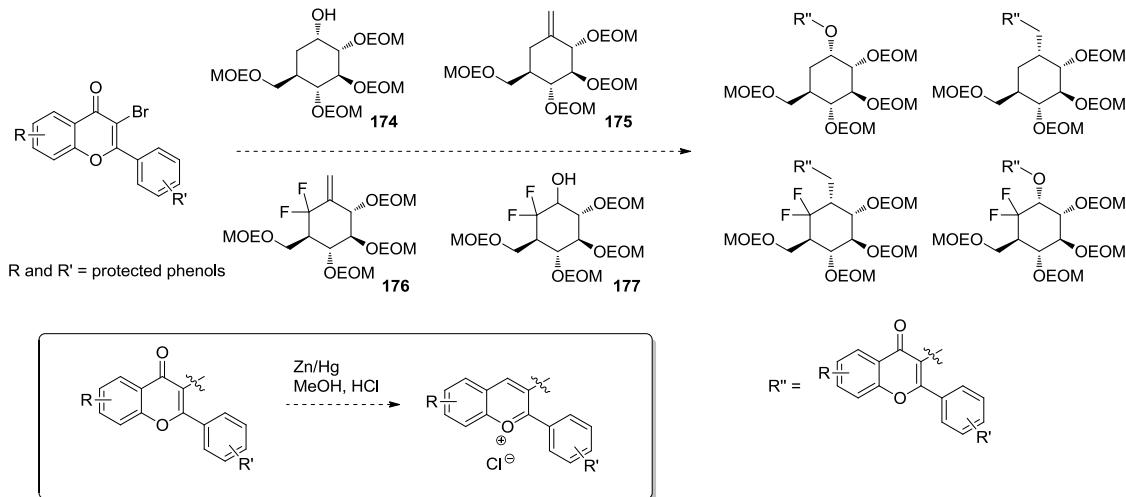
The reported synthetic route for cyanidin 3-glucoside requires two extra steps for switching the protecting group from benzyl to TBS (Scheme 5.7). This early-stage protection group swap is essential because catalytic hydrogenation is not compatible with later steps. Nevertheless, the benzyl protection is presumably used due to difficulties in chemoselective protection with TBSCl. Efficient TBS protection conditions can shorten the synthetic steps. Therefore, a series of TBS protection conditions have been explored and an unoptimized yield of 36% was obtained (Scheme 5.8). Further studies on TBS protection will lead us to assemble the target molecule in a more efficient manner.



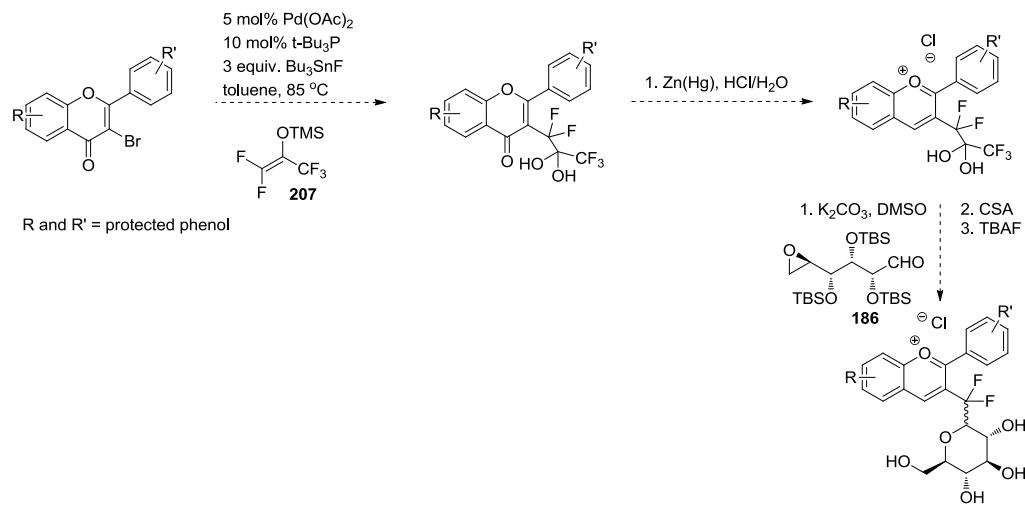
Scheme 5.8 TBS Protection of Catechin (**187**)

### 5.3 Conclusion and Future Directions

The synthesis of the metabolically stable fluorinated malvidin 3-gluoside derivatives is currently underway. Various synthetic approaches have been explored. Synthetic modification of D-(+)-gluconic acid  $\delta$ -lactone **163** forms a key intermediate, protected streptol (**173**). A number of glucose-derived coupling partners are expected to be made by modification of streptol. With these compounds in hand, we will perform coupling reaction with 3-bromo-flavone derivatives (Scheme 5.9). In addition, further studies to install pentafluoro *gem*-diol moieties in anthocyanidins, cyanidin and malvidin, will be pursued in due course (Scheme 5.10). The reaction between a difluoro-carbanion and a glucose-derived aldehyde **186** will allow the formation of the target molecules in a highly efficient manner.

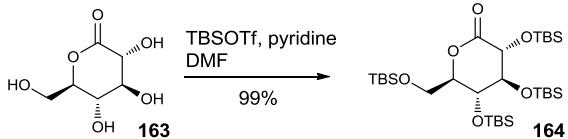


Scheme 5.9 Future Directions for Disconnection Path 1

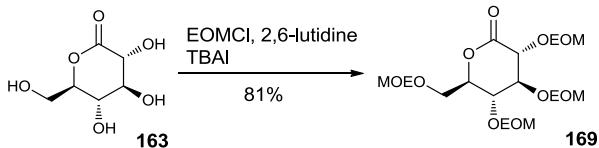


Scheme 5.10 Future Directions for Disconnection Path 2

#### 5.4 Experimental Details

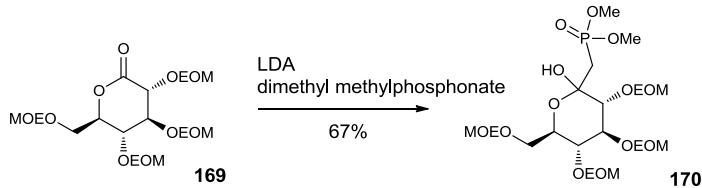


**TBS protected D-(+)-Gluconic acid  $\delta$ -lactone 164.** To a solution of compound **163** (50.0 mg, 0.28 mmol) in DMF (2.0 ml), pyridine (0.36 ml, 4.49 mmol) and TBSOTf (0.52 ml, 2.25 mmol) were added and stirred at rt for overnight. Then, the reaction mixture was purified by  $\text{SiO}_2$  flash column chromatography (1:1 EtOAc/hexanes) without work-up process. The desired product was obtained after purification in 99% yield (176.3 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.62–4.54 (m, 1H), 4.15–4.08 (m, 2H), 3.93–3.75 (m, 3H), 0.92–0.82 (m, 36H), 0.16–0.05 (m, 24H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 80.7, 76.7, 73.5, 70.6, 61.2, 25.8 (3), 25.7 (3), 25.6 (3), 25.5 (3), 18.2, 18.0, 17.8 (2), –3.0, –4.1, –4.4, –4.7, –5.1 (2), –5.2, –5.4

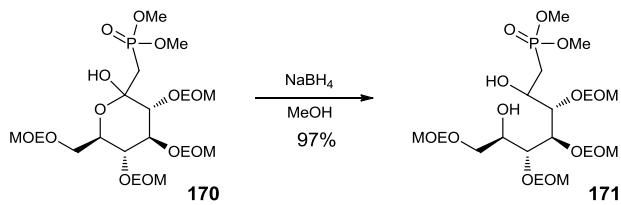


**EOM protected D-(+)-Gluconic acid  $\delta$ -lactone 169.** To a solution of compound **163** (100 mg, 0.561 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 ml), Molecular Sieves (200 mg),  $\text{Bu}_4\text{NI}$  (21.0 mg, 0.056 mmol), EOMCl (530 mg, 5.61 mmol), and 2,6-lutidine (0.65 ml, 5.61 mmol) were added sequentially. The reaction mixture was stirred at rt for overnight under  $\text{N}_2$ . Then, the reaction mixture was diluted with EtOAc (3.0 ml) and filtered through a pad of silica gel.  $\text{SiO}_2$  flash column chromatography (1:1 EtOAc/hexanes) afforded the desired

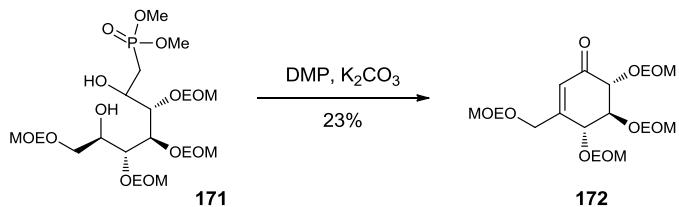
product in 81% yield (186.7 mg). All spectral and characterization data matched the reported data.<sup>141</sup>



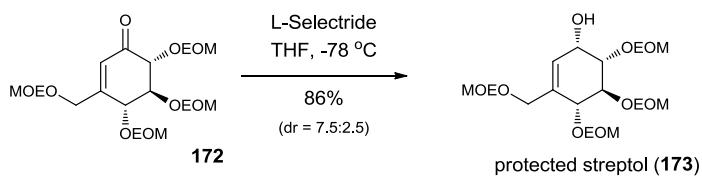
**Hemiacetal 170.** To a solution of diisopropylamine (1.4 ml, 9.74 mmol) in dry THF (20.0 ml) was added dropwise n-butyllithium (5.2 ml, 9.74 mmol) at -78 °C under N<sub>2</sub>. The reaction mixture was stirred for 30 min. at -78 °C and dimethyl methylphosphonate (0.52 ml, 4.87 mmol) was then added. The reaction mixture was stirred for additional 30 min. at -78 °C and was added slowly to a solution of lactone **169** (1.0 g, 2.44 mmol) in THF (20.0 ml) at -78 °C. Stirring was continued for an additional 15 min. at the same temperature. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (20.0 mL) at -78 °C and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (100% EtOAc) afforded the desired product in 67% yield (875.2 mg). All spectral and characterization data matched the reported data.<sup>141</sup>



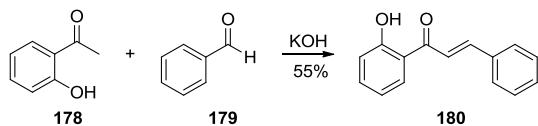
**Diol 171.** To a solution of hemiacetal **170** (373.7 mg, 0.70 mmol) in MeOH (10.0 ml), NaBH<sub>4</sub> (185 mg, 4.89 mmol) was added and stirred for 30 min. at rt. Then, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10.0 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (1:9 MeOH/EtOAc) afforded the desired product in 97% yield (364.5 mg). All spectral and characterization data matched the reported data.<sup>141</sup>



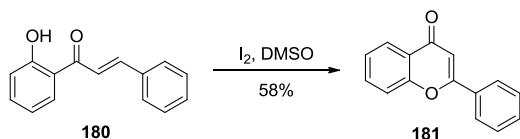
**Enone 172.** To a solution of diol **171** (132.7 mg, 0.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL), Dess-Martin periodinane (262 mg, 0.62 mmol) was added and stirred at rt for overnight. Then, K<sub>2</sub>CO<sub>3</sub> (513 mg, 3.71 mmol) was added and stirred at rt for 2 days. Then, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (3.0 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (3:7 EtOAc/hexanes) afforded the desired product in 23% yield (23.1 mg). All spectral and characterization data matched the reported data.<sup>141</sup>



**Protected Streptol 173.** To a solution of enone **172** (30.5 mg, 0.075 mmol) in THF (1.0 ml), L-selectride (184 mg, 0.97 mmol) was added at -78 °C and stirred for 1 h. Then, excess hydride was quenched with MeOH. The organics were concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (1:1 EtOAc/hexanes) afforded the desired product in 86% yield (26.4 mg, dr = 7.5:2.5). All spectral and characterization data matched the reported data.<sup>141</sup>

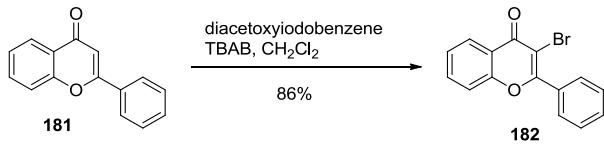


**(E)-1-(2-Hydroxyphenyl)-3-phenylprop-2-en-1-one** **180.** 1-(2-hydroxyphenyl)ethanone **178** (0.62 ml, 5.14 mmol) and benzaldehyde **179** (0.52 ml, 5.14 mmol) were dissolved in EtOH (10.0 ml). Then, 50% aqueous KOH (10.0 ml) was added and stirred at 30 °C for 1.5 h. Then, the reaction mixture was quenched with 1N H<sub>2</sub>SO<sub>4</sub> (10.0 ml). Recrystallization with MeOH afforded the desired product in 55% yield (637.3 mg). All spectral and characterization data matched the reported data.<sup>143</sup>

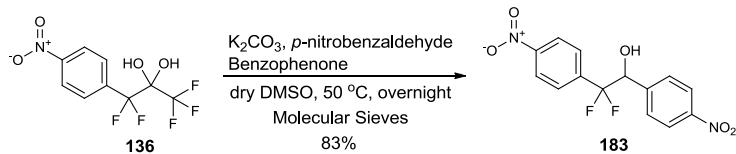


**Flavone 181.** To a solution of compound **180** (100 mg, 0.45 mmol) in DMSO (1.5 ml), I<sub>2</sub> (113 mg, 0.45 mmol) was added and stirred at 130 °C for 1 h. Then, the reaction mixture was quenched with 20% sodium thiosulfate solution (3.0 ml) and extracted with CHCl<sub>3</sub> (5.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under

reduced pressure.  $\text{SiO}_2$  flash column chromatography (1:4 EtOAc/hexanes) afforded the desired product in 55% yield (58.2 mg). All spectral and characterization data matched the reported data.<sup>144,146</sup>

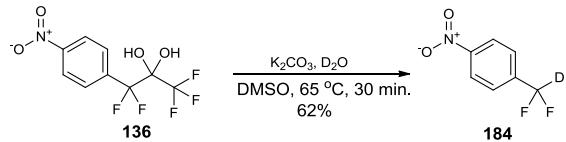


**3-Bromo-flavone 182.**  $\text{PhI(OAc)}_2$  (29 mg, 0.09 mmol) was suspended in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.15 ml) under  $\text{N}_2$  at rt.  $\text{Bu}_4\text{NBr}$  (29.2 mg, 0.09 mmol) was added and stirred at rt for 30 min. Then, flavone **181** (6.7 mg, 0.03 mmol) in 0.1 ml of  $\text{CH}_2\text{Cl}_2$  was added and stirred at rt for overnight. Then, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5.0 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5.0 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (1:4 EtOAc/hexanes) afforded the desired product in 86% yield (7.8 mg). All spectral and characterization data matched the reported data.<sup>147</sup>



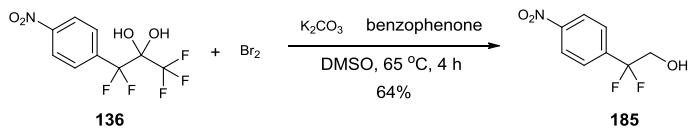
**2,2-Difluoro-1,2-bis(4-nitrophenyl)ethanol 183.** 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol **136** (15.0 mg, 0.052 mmol) was dissolved in DMSO (2.0 ml). Then, benzophenone (38.0 mg, 0.209 mmol), 4-nitrobenzaldehyde (31.6 mg, 0.209 mmol), and 4 $\text{\AA}$  molecular sieves (20.0 mg) were added and stirred for 3 min. Then,

$\text{K}_2\text{CO}_3$  (144.0 mg, 1.045 mmol) was added and the reaction vial was flushed with nitrogen. Then, the temperature was increased to 50 °C and stirred overnight. Then, the temperature was decreased to rt and the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL × 5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (8:2 hexanes/EtOAc) afforded the desired product **183** in 83% (14.2 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) δ 8.20 (d,  $J$  = 8.6 Hz, 2H), 8.16 (m, 2H), 7.45 (d,  $J$  = 8.7 Hz, 2H), 7.42 (d,  $J$  = 8.5 Hz, 2H), 5.30 (t,  $J$  = 8.5 Hz, 1H), 2.81 (br s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) δ 149.1, 148.3, 141.9, 138.9 (t,  $J_{\text{CF}}$  = 26.1 Hz, 1C), 128.5 (2), 127.7 (t,  $J_{\text{CF}}$  = 6.0 Hz, 2C), 123.3 (2), 123.2 (2), 119.8 (t,  $J_{\text{CF}}$  = 248.6 Hz, 1C), 75.5 (t,  $J_{\text{CF}}$  = 31.3 Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ) δ -104.5 (dd,  $J$  = 253.8, 8.2 Hz, 1F), -108.6 (dd,  $J$  = 253.8, 9.0 Hz, 1F); IR (film)  $\nu_{\text{max}}$  3497, 1519, 1347, 1080  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{10}\text{F}_2\text{N}_2\text{O}_5$  ( $\text{M}+\text{H}$ )<sup>+</sup>, 325.0636; found, 325.0634; mp 188–190 °C.



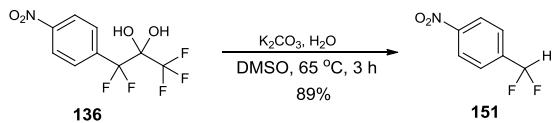
**1-Deutro-1-(difluoromethyl)-4-nitrobenzene 184.** 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol **136** (100 mg, 0.348 mmol) was dissolved in DMSO (2.0 mL). Then,  $\text{H}_2\text{O}$  (19  $\mu\text{L}$ , 1.055 mmol) was added and stirred for 3 min. Then,  $\text{K}_2\text{CO}_3$  (194.0 mg, 1.406 mmol) was added and the temperature was increased to 65 °C. After 30 min., the temperature was decreased to rt. Then, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL × 5).

The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (8:2 hexanes/EtOAc) afforded the desired product **184** in 62% (37.8 mg, oil).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (m, 2H), 7.72 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  149.3, 140.1 (t,  $J_{\text{CF}} = 22.7$  Hz, 1C), 126.8 (t,  $J_{\text{CF}} = 5.9$  Hz, 1C), 124.0, 112.6 (tt,  $J_{\text{CF}} = 238.8, 28.4$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.7 (t,  $J_{\text{DF}} = 8.5$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  1529, 1351, 1277, 1080  $\text{cm}^{-1}$ ; HRMS (CI)  $m/z$  calcd. for  $\text{C}_7\text{H}_4\text{DF}_2\text{NO}_2$  ( $\text{M}^+$ ), 174.0351; found, 174.0353.

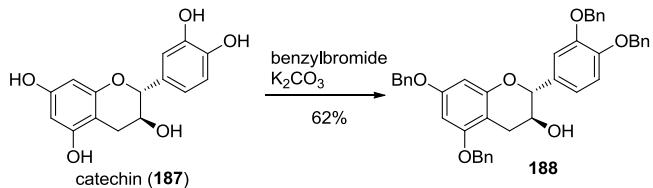


**2,2-Difluoro-2-(4-nitrophenyl)ethanol** **185.** 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol **136** (15.0 mg, 0.052 mmol) was dissolved in DMSO (0.3 ml). Then, benzophenone (38.1 mg, 0.209 mmol) and  $\text{Br}_2$  (10.7  $\mu\text{L}$ , 0.209 mmol) were added and stirred for 5 min. at rt. Then,  $\text{K}_2\text{CO}_3$  (144.0 mg, 1.045 mmol) was added and the reaction vial was flushed with nitrogen. The reaction mixture was stirred for 2 h at rt. After 2 h, additional  $\text{K}_2\text{CO}_3$  (72.0 mg, 0.523 mmol) was added and the reaction vial was flushed with nitrogen. After stirring 4 h at 65  $^\circ\text{C}$ , the temperature was decreased to rt and the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (8:2 hexanes/EtOAc to 1:1 hexanes/EtOAc) afforded the desired product **185** in 64% (6.8 mg, solid).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d,  $J = 8.4$  Hz, 2H), 7.74 (d,  $J = 8.5$  Hz, 2H),

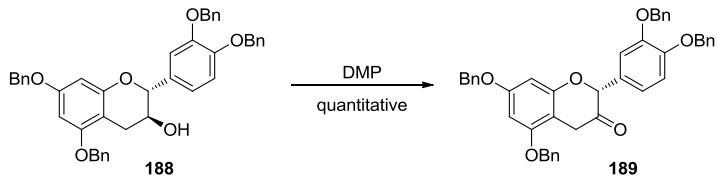
4.03 (td,  $J = 12.7, 6.5$  Hz, 2H), 2.01 (t,  $J = 6.7$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  149.1, 140.7 (t,  $J_{\text{CF}} = 25.8$  Hz, 1C), 127.0 (t,  $J_{\text{CF}} = 6.0$  Hz, 2C), 123.7 (2), 120.6 (t,  $J_{\text{CF}} = 243.4$  Hz, 1C), 65.6 (t,  $J_{\text{CF}} = 32.6$  Hz, 1C);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -108.2 (t,  $J_{\text{HF}} = 12.7$  Hz, 2F); IR (film)  $\nu_{\text{max}}$  3519, 1519, 1352, 1314, 1078  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd. for  $\text{C}_8\text{H}_7\text{F}_2\text{NO}_3$  ( $\text{M}^+$ ), 203.0394; found, 203.0392; mp 86–89 °C.



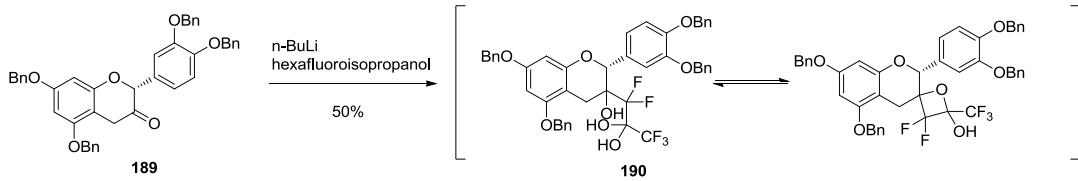
**1-(Difluoromethyl)-4-nitrobenzene** **151.** **1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol** **136** (100 mg, 0.348 mmol) was dissolved in DMSO (2.0 mL). Then,  $\text{H}_2\text{O}$  (19.0  $\mu\text{L}$ , 1.055 mmol) and  $\text{K}_2\text{CO}_3$  (194.0 mg, 1.406 mmol) were added. Then, the temperature was increased to 65 °C and stirred for 3 h. After 3 h, the temperature was decreased to rt. Then, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) and the resultant mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL  $\times$  5). The organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.  $\text{SiO}_2$  flash column chromatography (8:2 hexanes/EtOAc) afforded the desired product **151** in 89% (54.1 mg, oil).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (d,  $J = 8.9$  Hz, 2H), 7.72 (d,  $J = 8.6$  Hz, 2H), 6.75 (t,  $J = 55.7$  Hz, 1H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.0 (d,  $J_{\text{HF}} = 55.7$  Hz, 2F); All spectral and characterization data matched the reported data.<sup>150</sup>



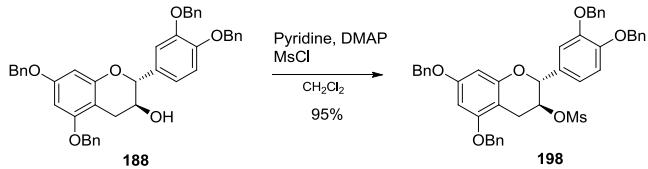
**Benzyl protected catechin 188.** To a solution of catechin **187** (1000 mg, 3.45 mmol) in DMF (5.0 ml), benzylbromide (1.64 ml, 13.78 mmol) and K<sub>2</sub>CO<sub>3</sub> (2857 mg, 20.67 mmol) was added and stirred at rt. After 2 days, the reaction mixture was diluted with EtOAc and washed with H<sub>2</sub>O. The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (100% CH<sub>2</sub>Cl<sub>2</sub>) afforded the desired product in 62% yield (1392.7 mg). All spectral and characterization data matched the reported data.<sup>151,152</sup>



**Ketone 189.** To a solution of compound **188** (24.5 mg, 0.038 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.3 ml), Dess-Martin periodinane (21.0 mg, 0.049 mmol) was added and stirred at rt for overnight. Then, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (3.0 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (1:4 EtOAc/hexanes) afforded the desired product in quantitative yield (24.4 mg). All spectral and characterization data matched the reported data.<sup>152</sup>

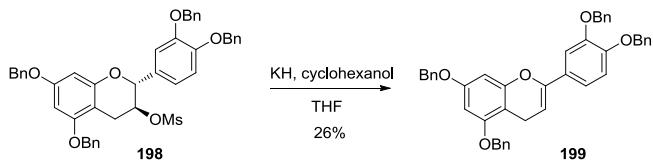


**Pentafluoro *gem*-diol 190.** To a solution of hexafluoroisopropanol (0.2 ml, 0.19 mmol) in THF (5.0 ml) at -78 °C, n-BuLi (0.15 ml, 0.38 mmol) was added and stirred for 10 min. at -78 °C. Then, the reaction mixture was warmed to 0 °C and stirred for 1 h at 0 °C. Compound **189** (32.0 mg, 0.19 mmol) in 0.3 ml THF was slowly added to a solution of preformed enolate and stirred at 0 °C for 1 h. Then, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (6.0 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (1:1 EtOAc/hexanes) afforded the desired product in 50% yield (15.4 mg).

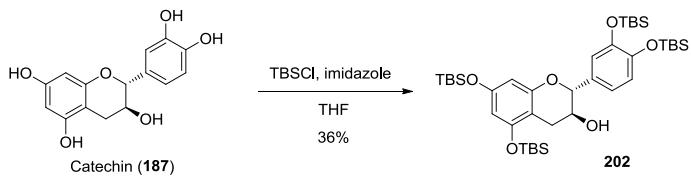


**Mesylate 198.** To a solution of benzyl protected catechin **192** (50.0 mg, 0.077 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 ml) at 0 °C, pyridine (0.16 ml, 1.921 mmol), MsCl (89.0 μL, 1.153 mmol), and DMAP (23.0 mg, 0.192 mmol) were added. The reaction mixture was stirred for 1.5 h and the reaction temperature was allowed to increase to rt. Then, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 ml) and quenched by addition of saturated aqueous NH<sub>4</sub>Cl (5.0 ml). The resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column

chromatography (100% CH<sub>2</sub>Cl<sub>2</sub>) afforded the desired product in 95% yield (53.3 mg, solid).



**5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)-4H-chromene 199.** To a solution of cyclohexanol (40  $\mu$ L, 0.384 mmol) in THF (1.5 ml), 50% KH (30mg, 0.384 mmol) was added and stirred at rt for 5 min. Then, mesylate **198** (56.0 mg, 0.077 mmol) was added and stirred for 1 h at rt. Then, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (3.0 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL  $\times$  5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (100% CH<sub>2</sub>Cl<sub>2</sub>) afforded the desired product in 26% yield (12.7 mg).



**TBS protected catechin 202.** To a solution of catechin **187** (500 mg, 1.72 mmol) in THF (2.0 ml), imidazole (1035 mg, 15.2 mmol) was added and stirred until completely dissolved. Then, the reaction mixture was cooled to 0 °C in ice bath. TBSCl (1145 mg, 7.60 mmol) in 1.0 ml THF was added dropwise with stirring the solution. Then, CH<sub>2</sub>Cl<sub>2</sub> (1.0 ml) was added and stirred for 18 h at rt. Then, the reaction was quenched with

saturated aqueous NH<sub>4</sub>Cl (10.0 mL) and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL × 5). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. SiO<sub>2</sub> flash column chromatography (1:4 EtOAc/hexanes) afforded the desired product in 36% yield (467.6 mg). All spectral and characterization data matched the reported data.<sup>153</sup>

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## LIST OF REFERENCES

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## APPENDIX

## APPENDIX

- NMR Spectra Order of CHAPTER 2

Compound 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29

- NMR Spectra Order of CHAPTER 3

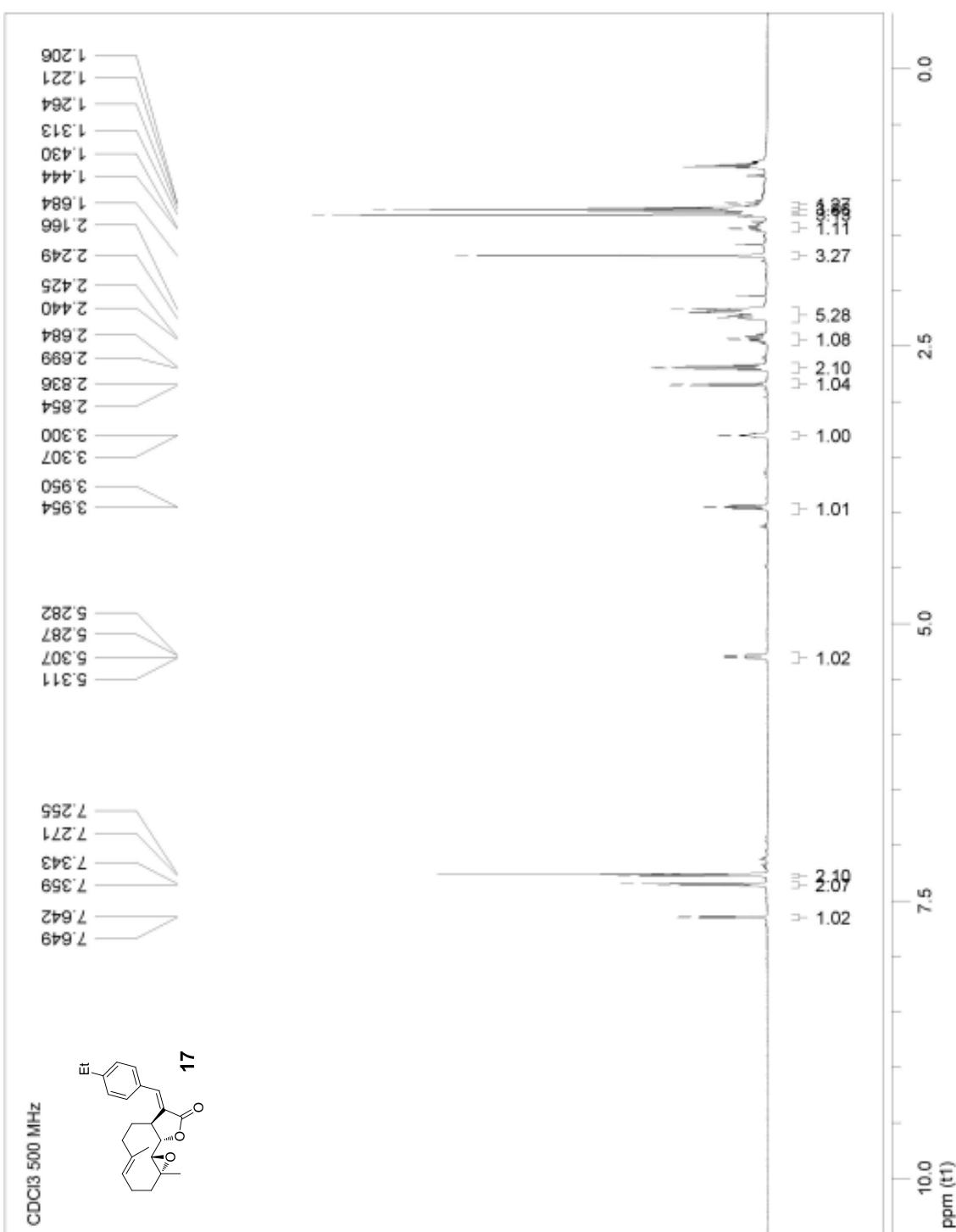
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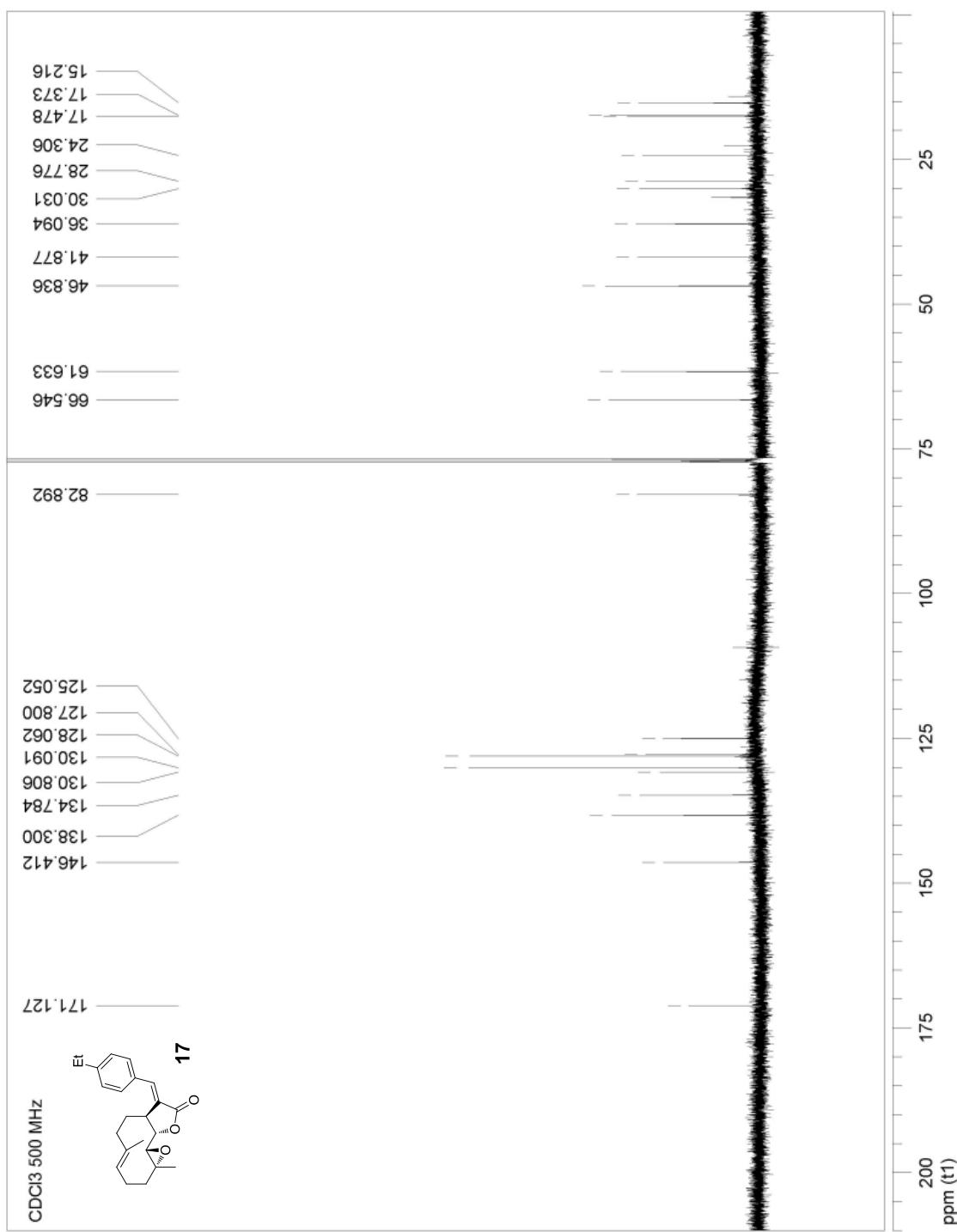
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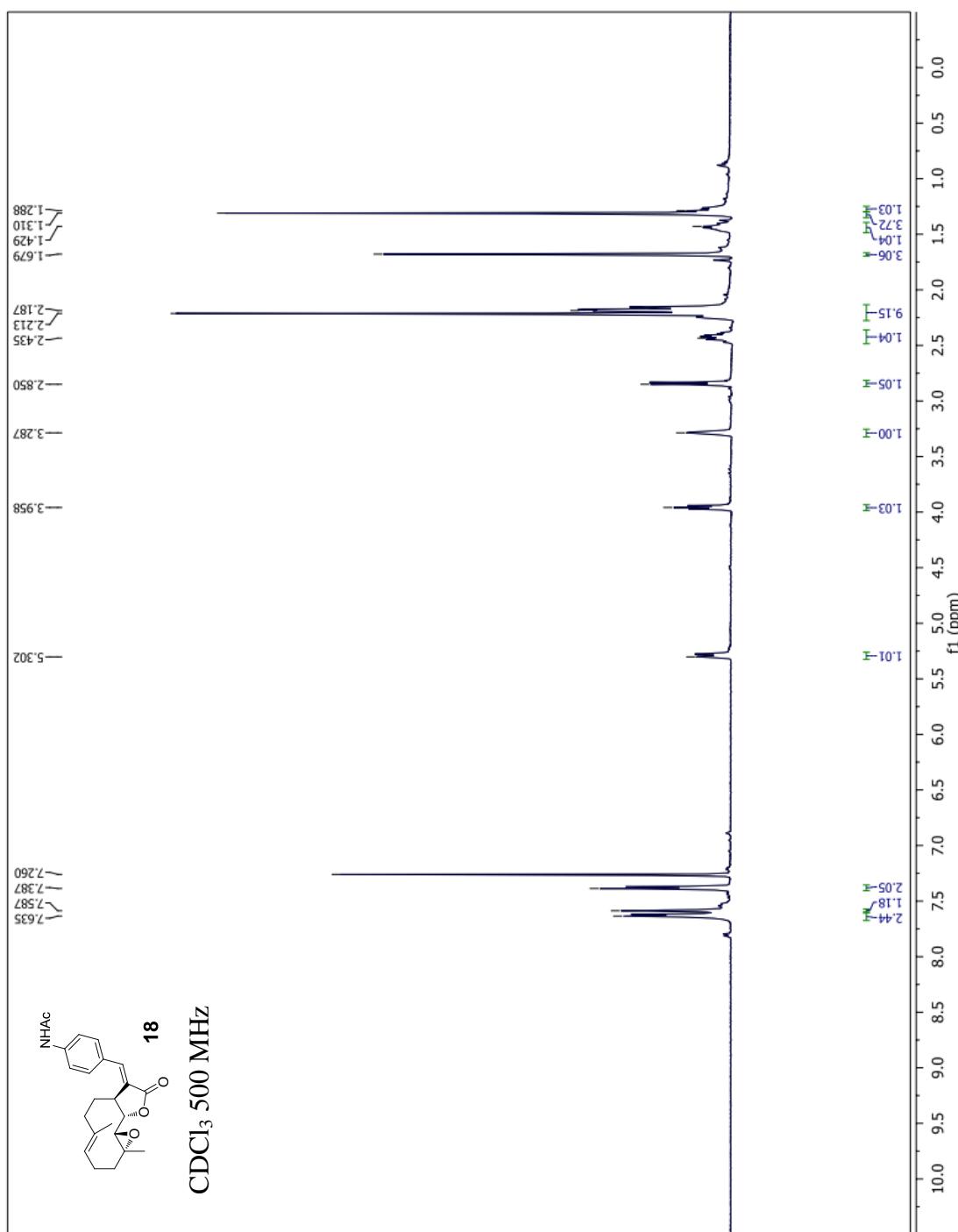
Compound 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133,  
134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146

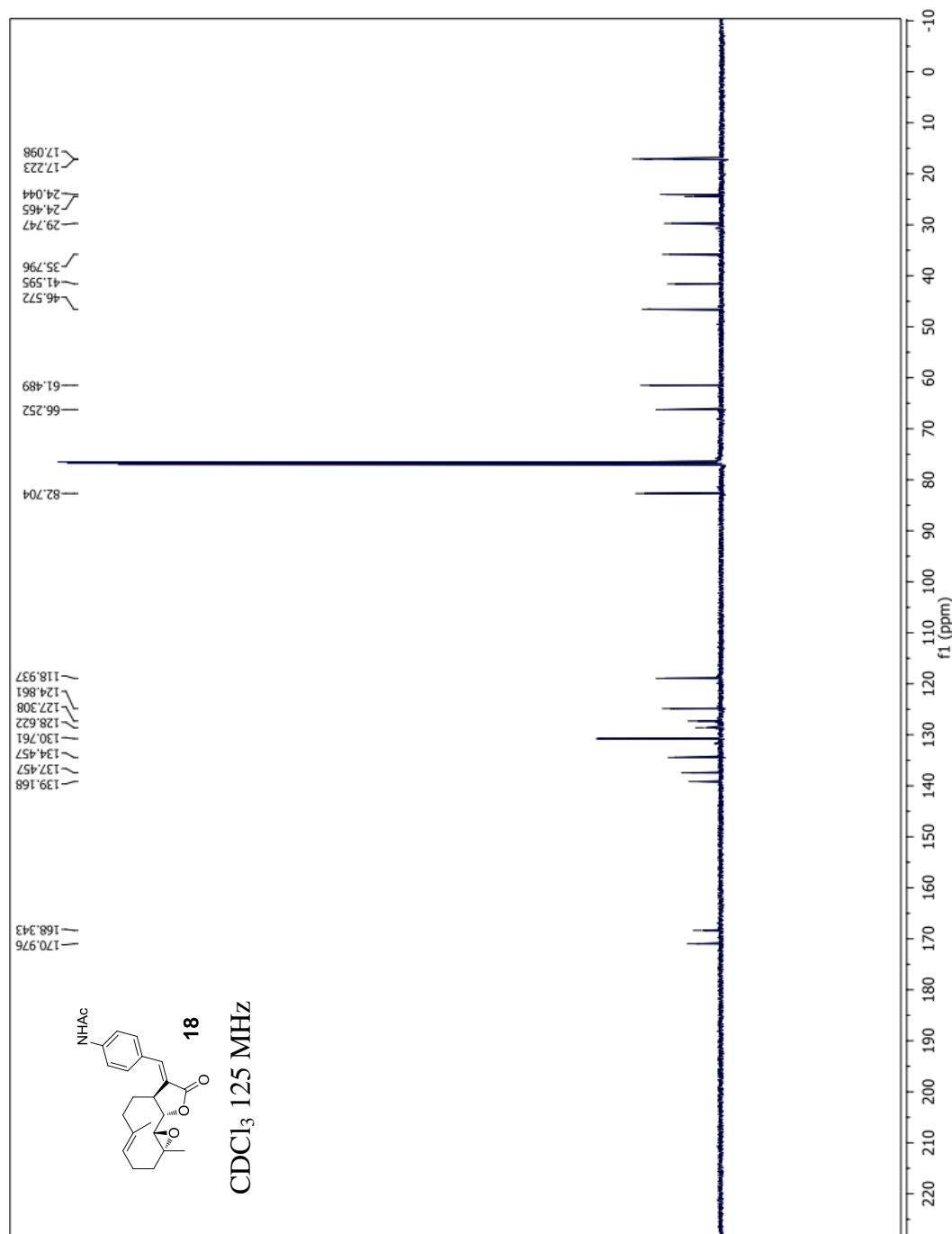
- NMR Spectra Order of CHAPTER 5

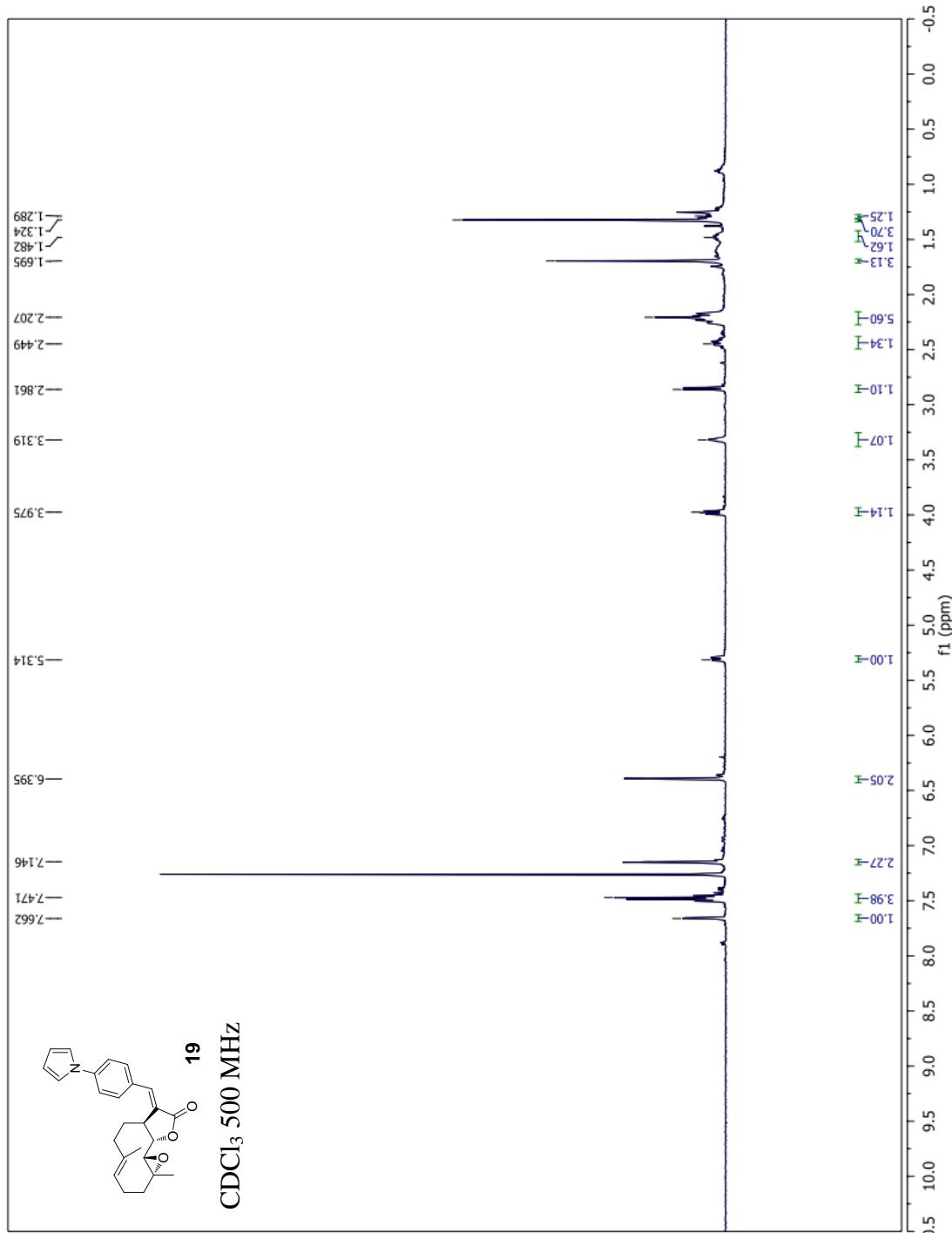
Compound 151, 164, 187, 188, 189

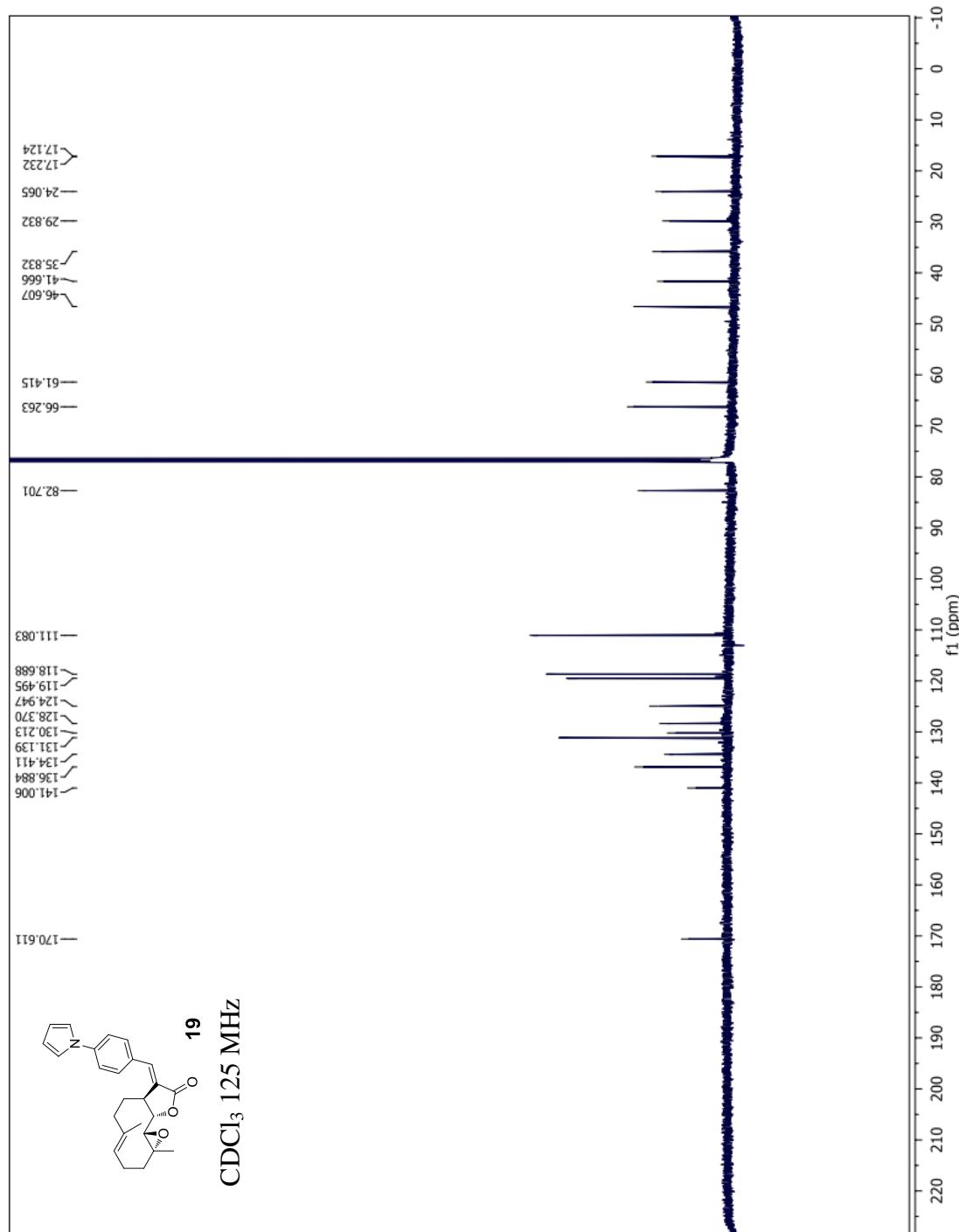


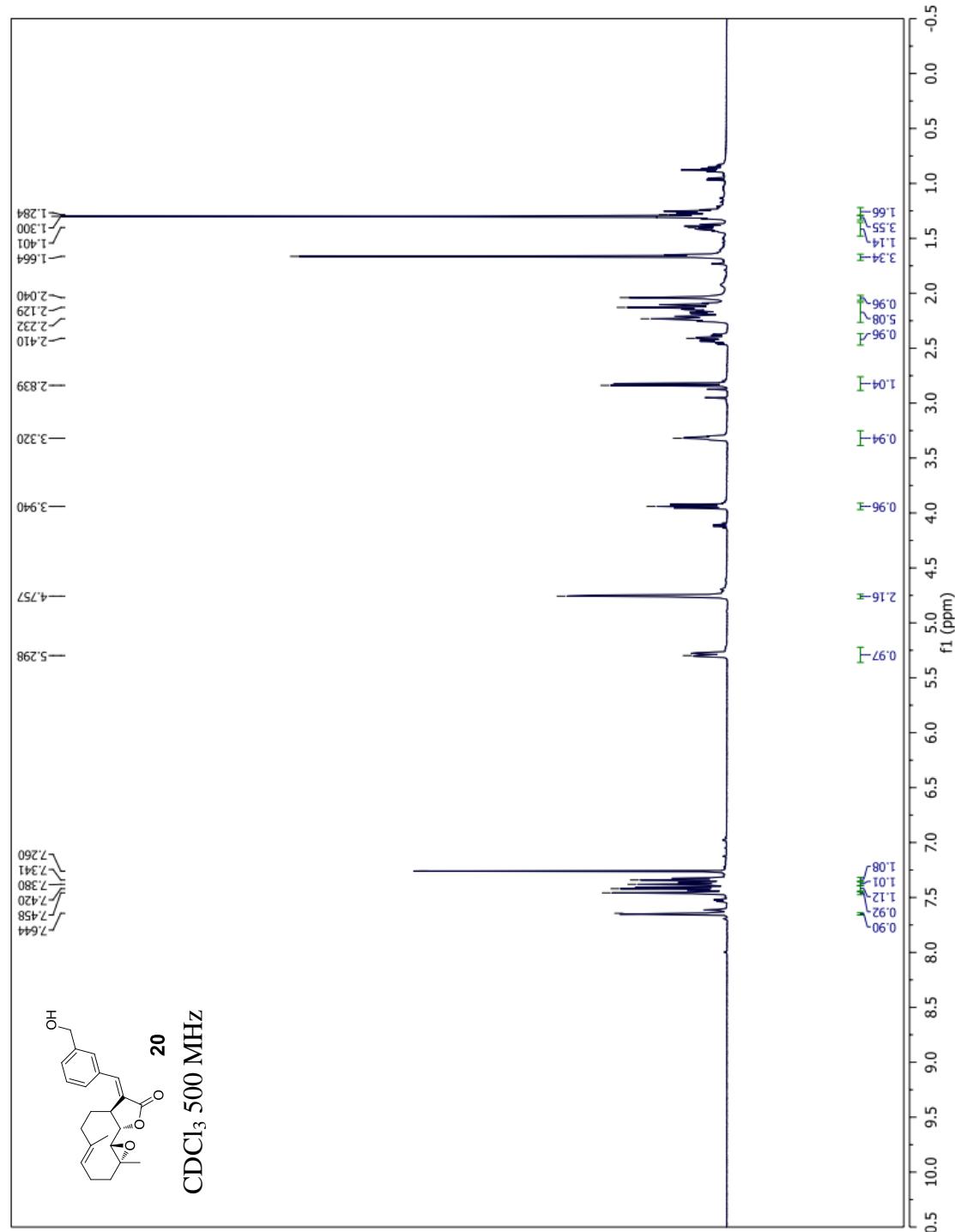


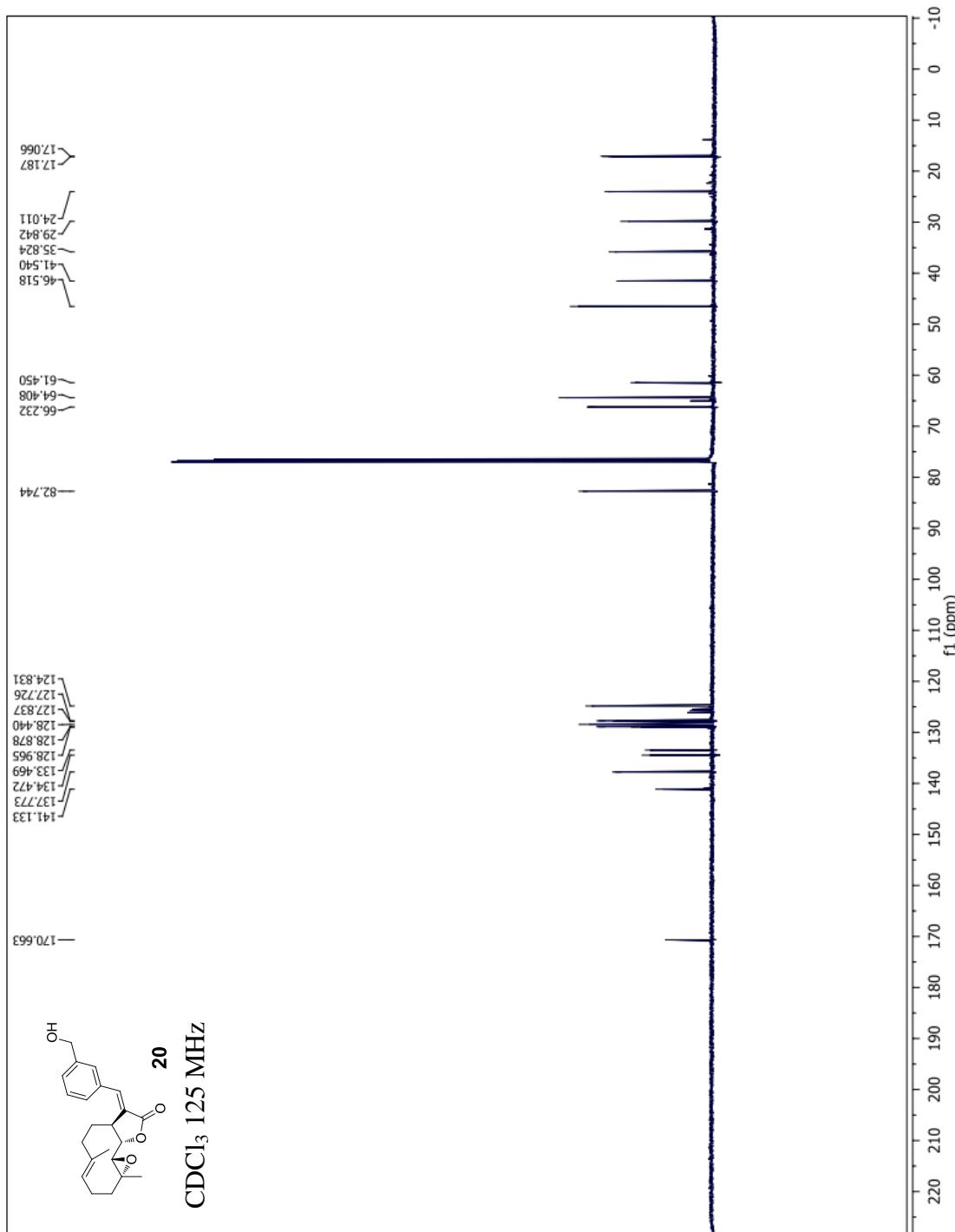


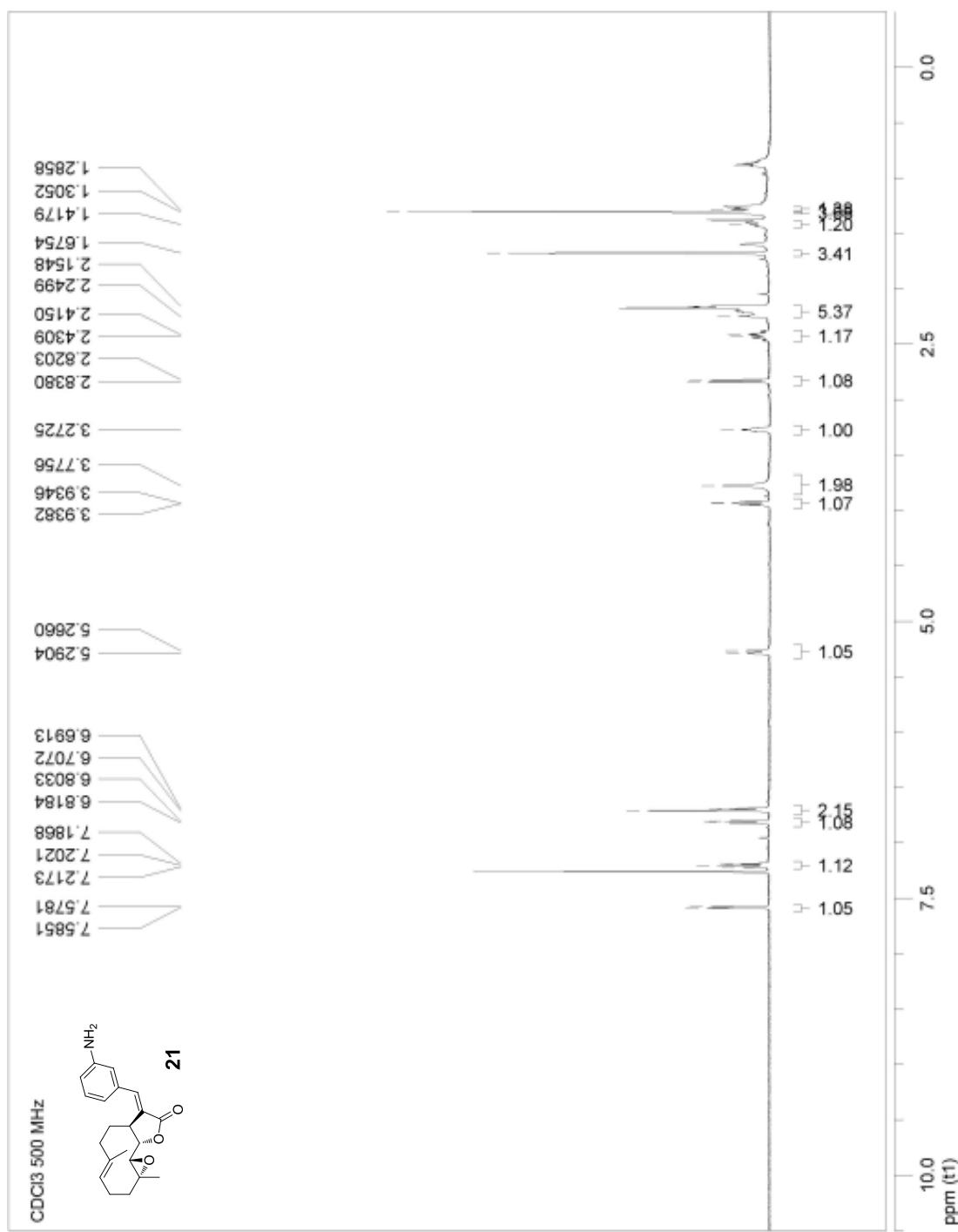


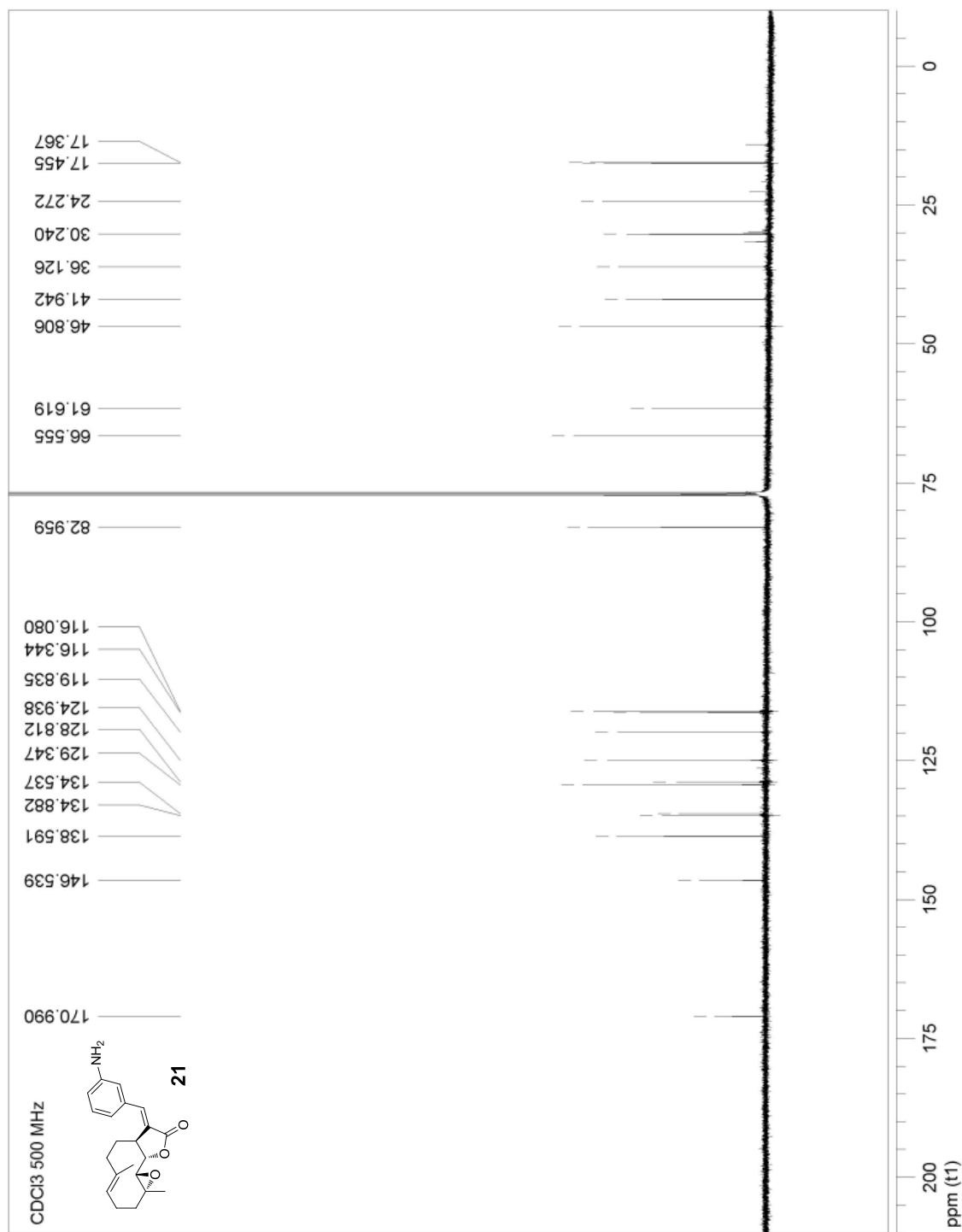


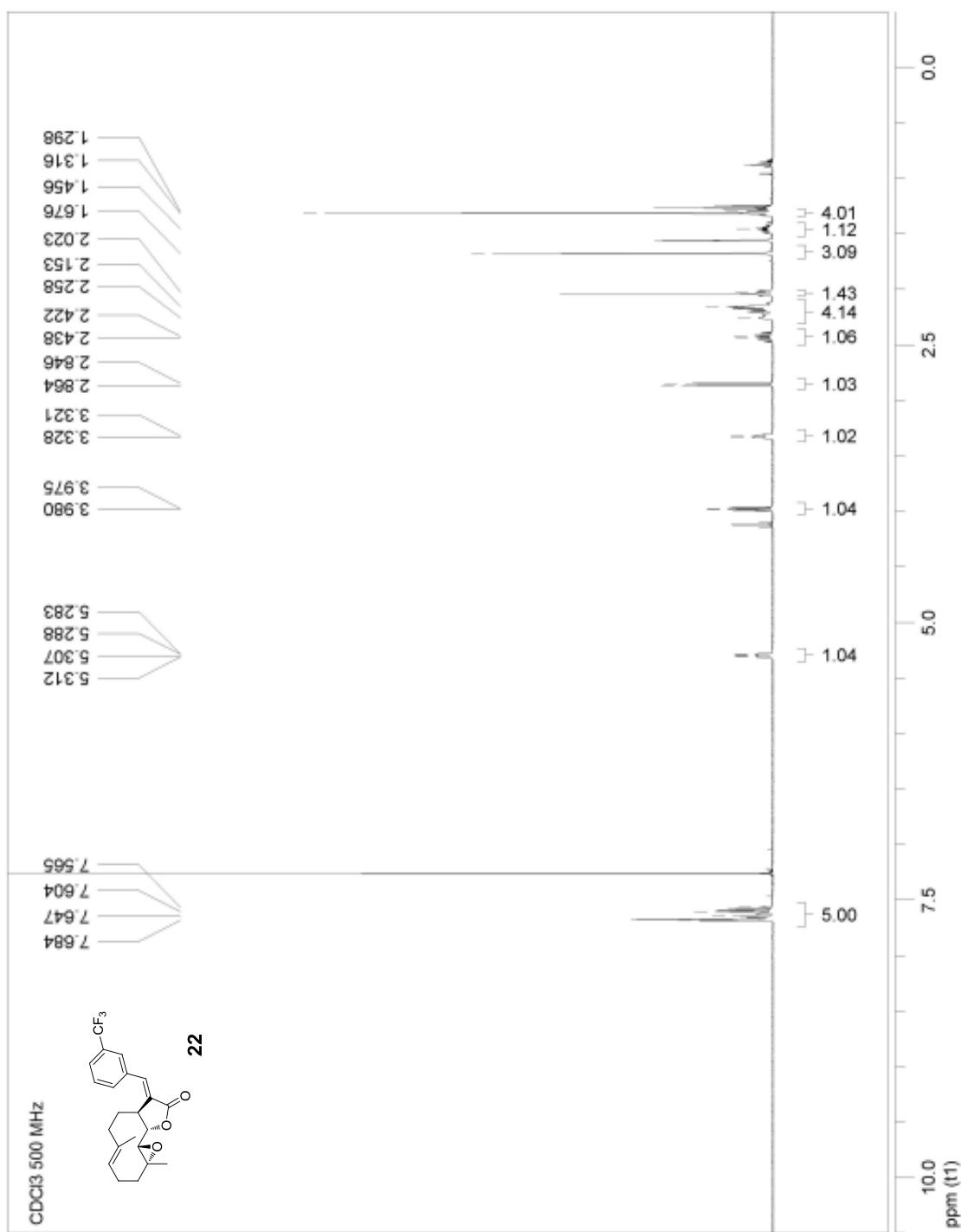


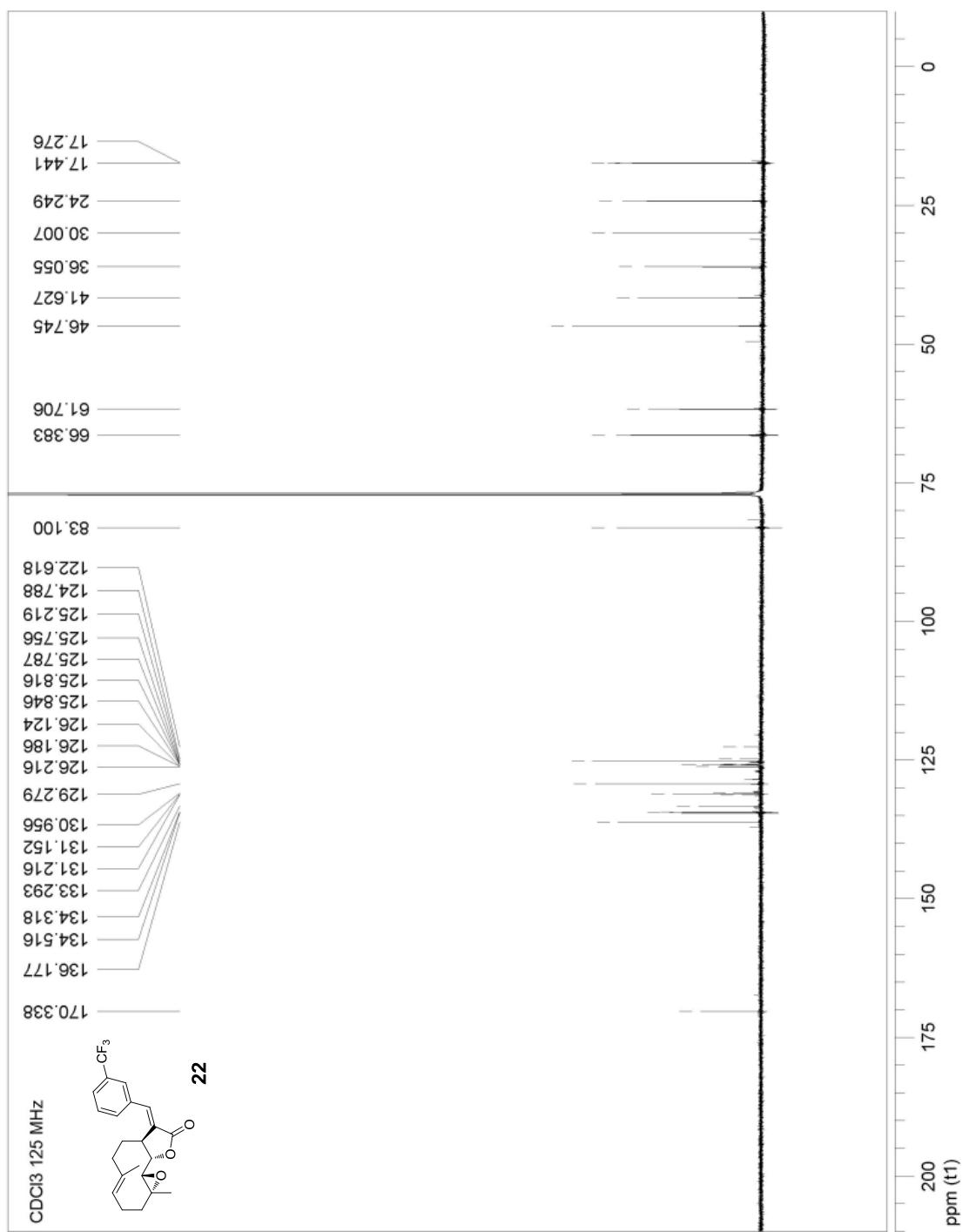


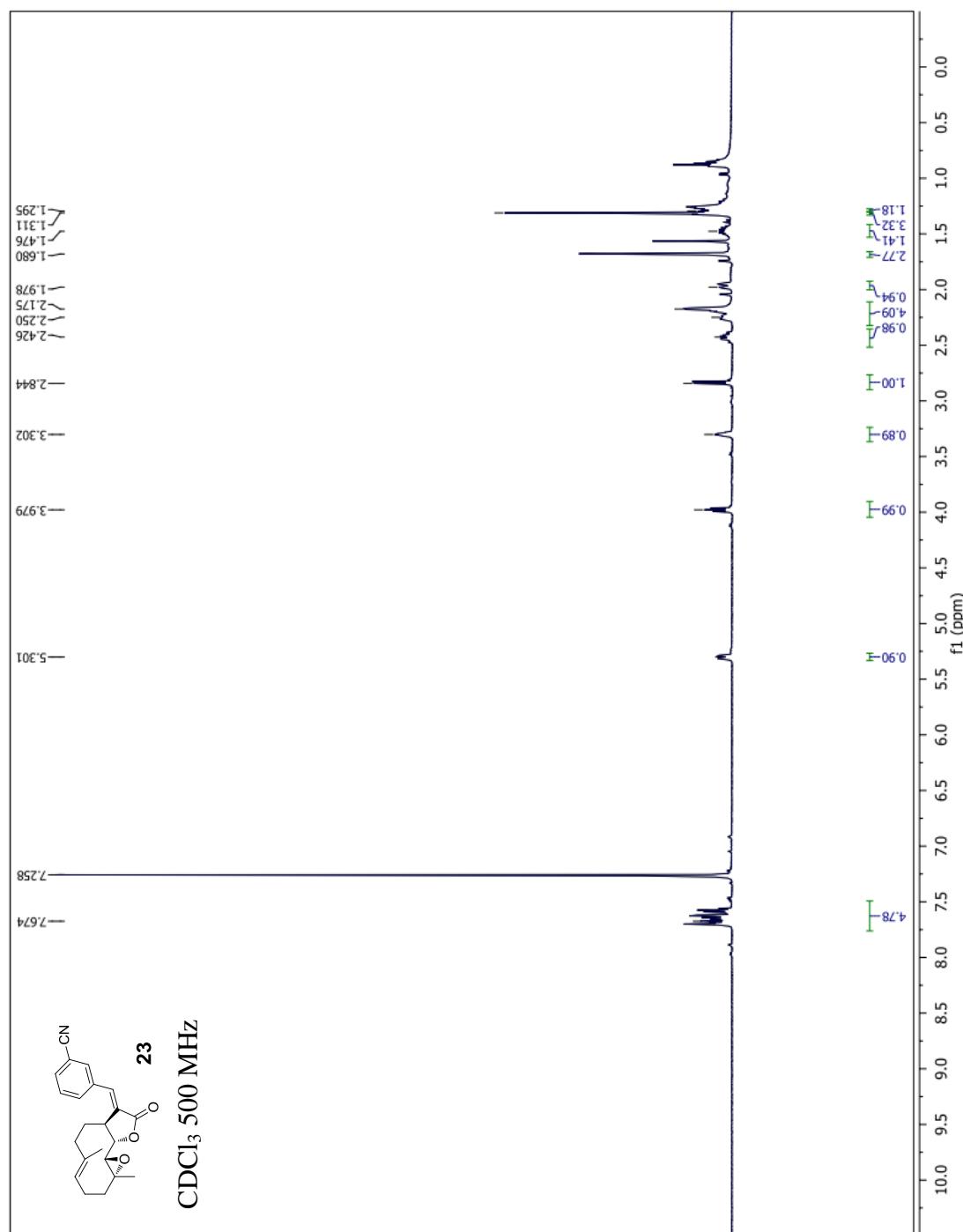


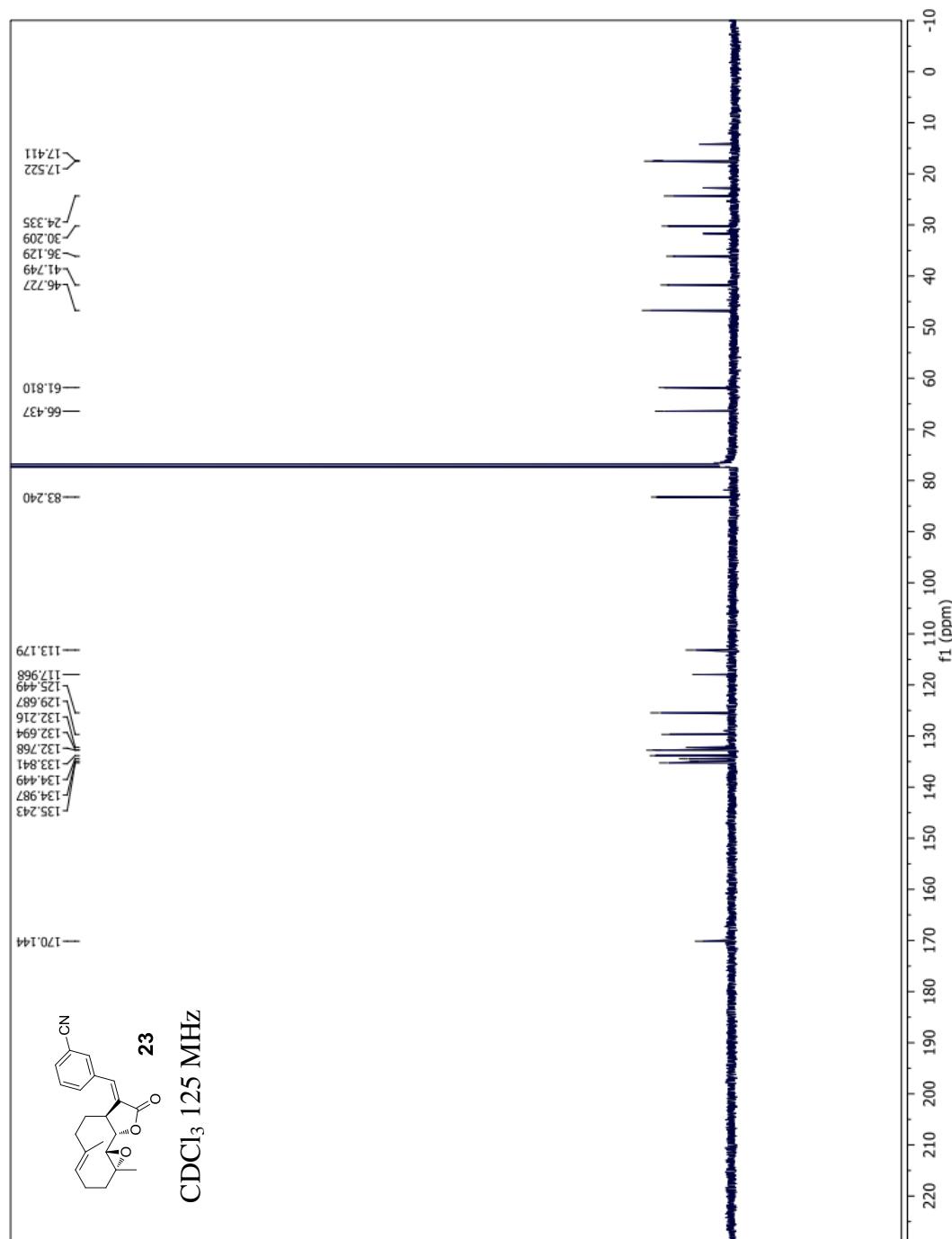


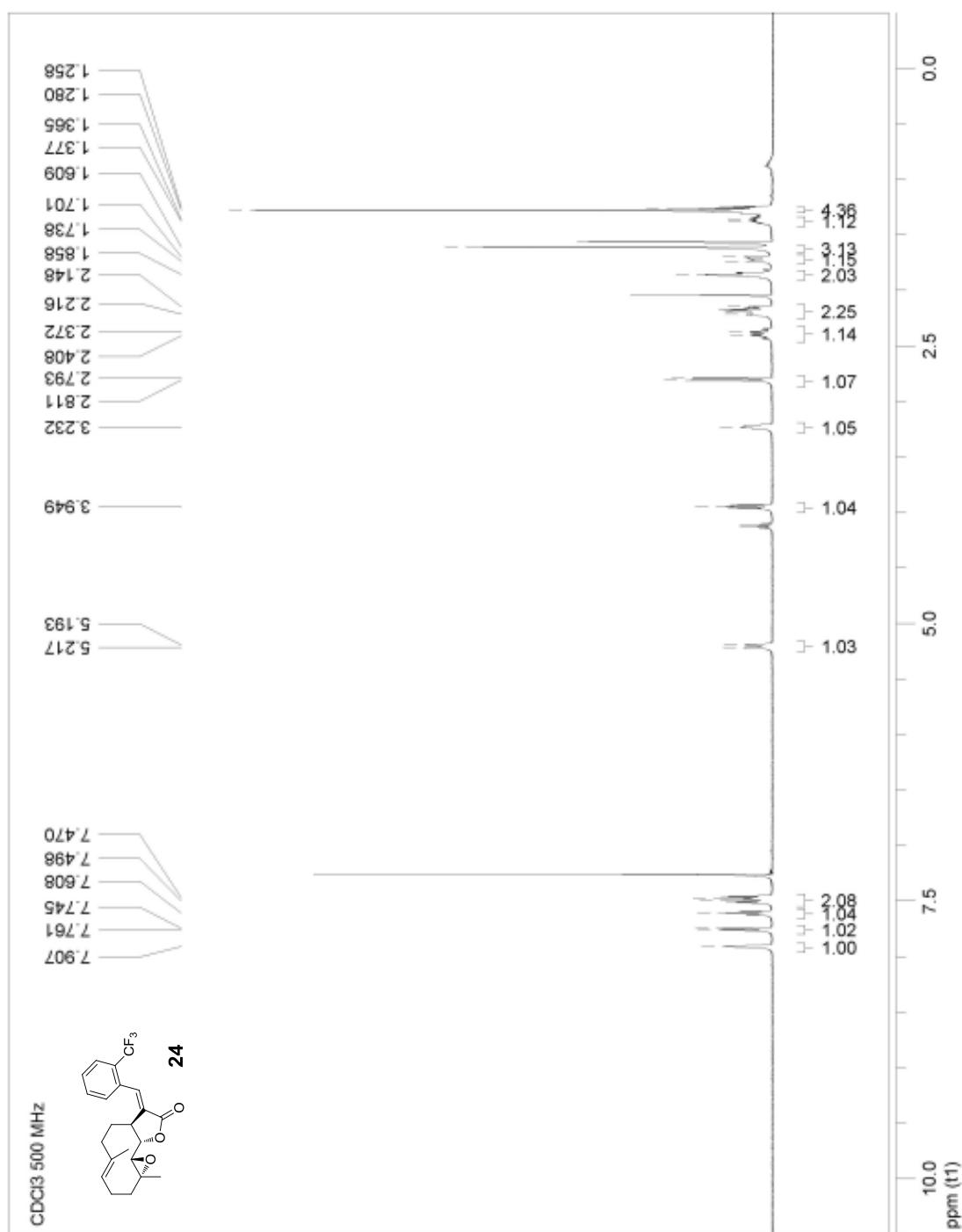


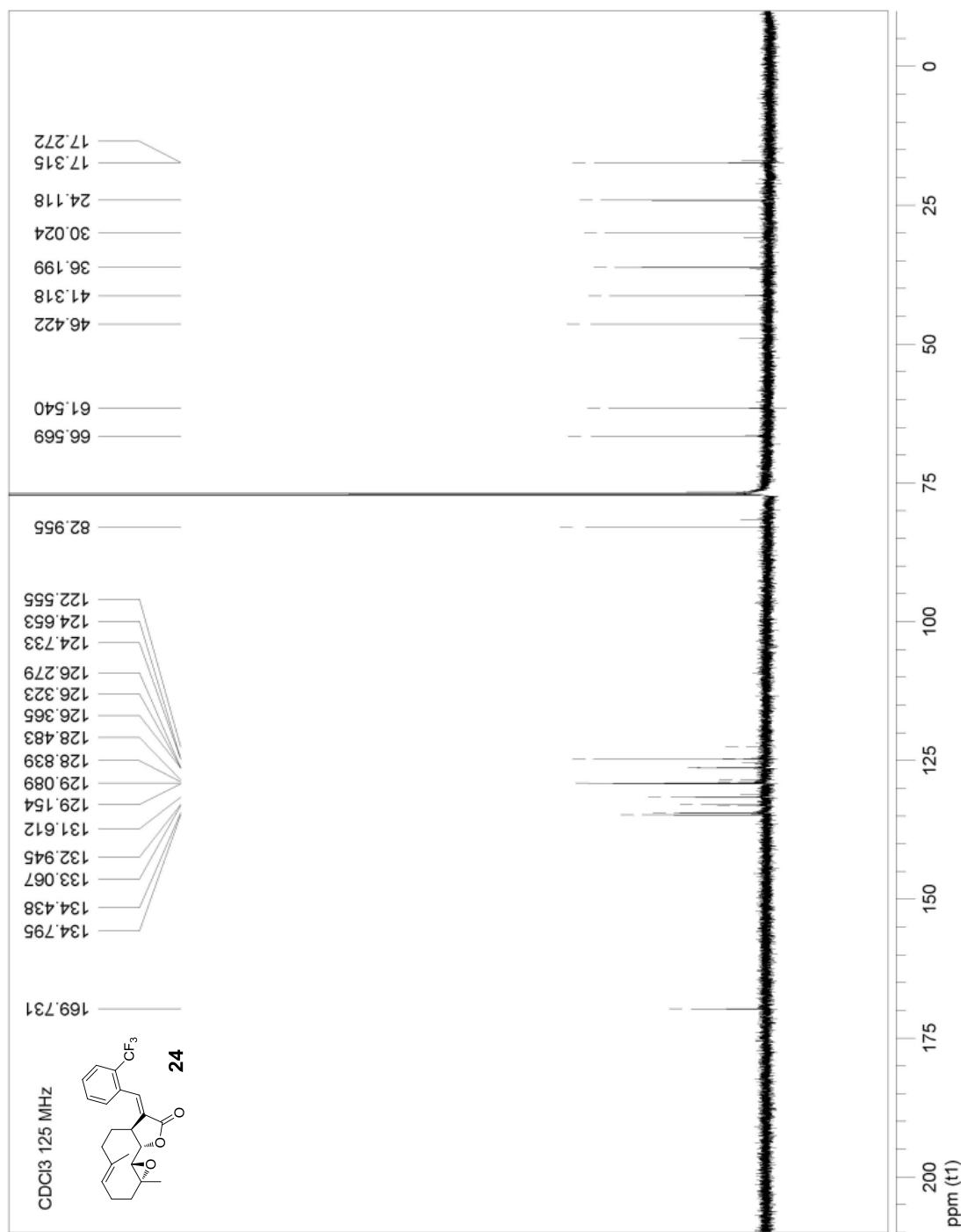


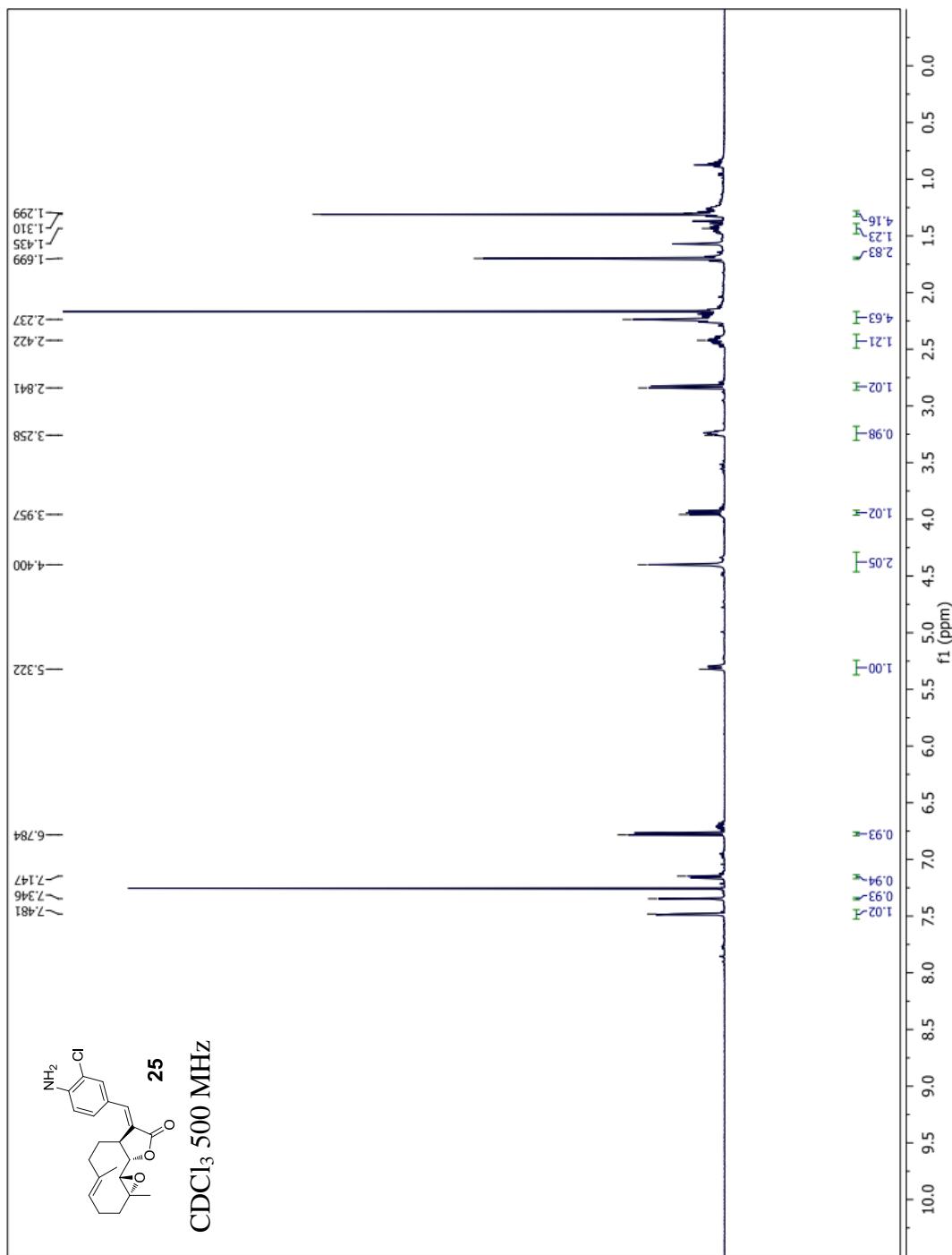


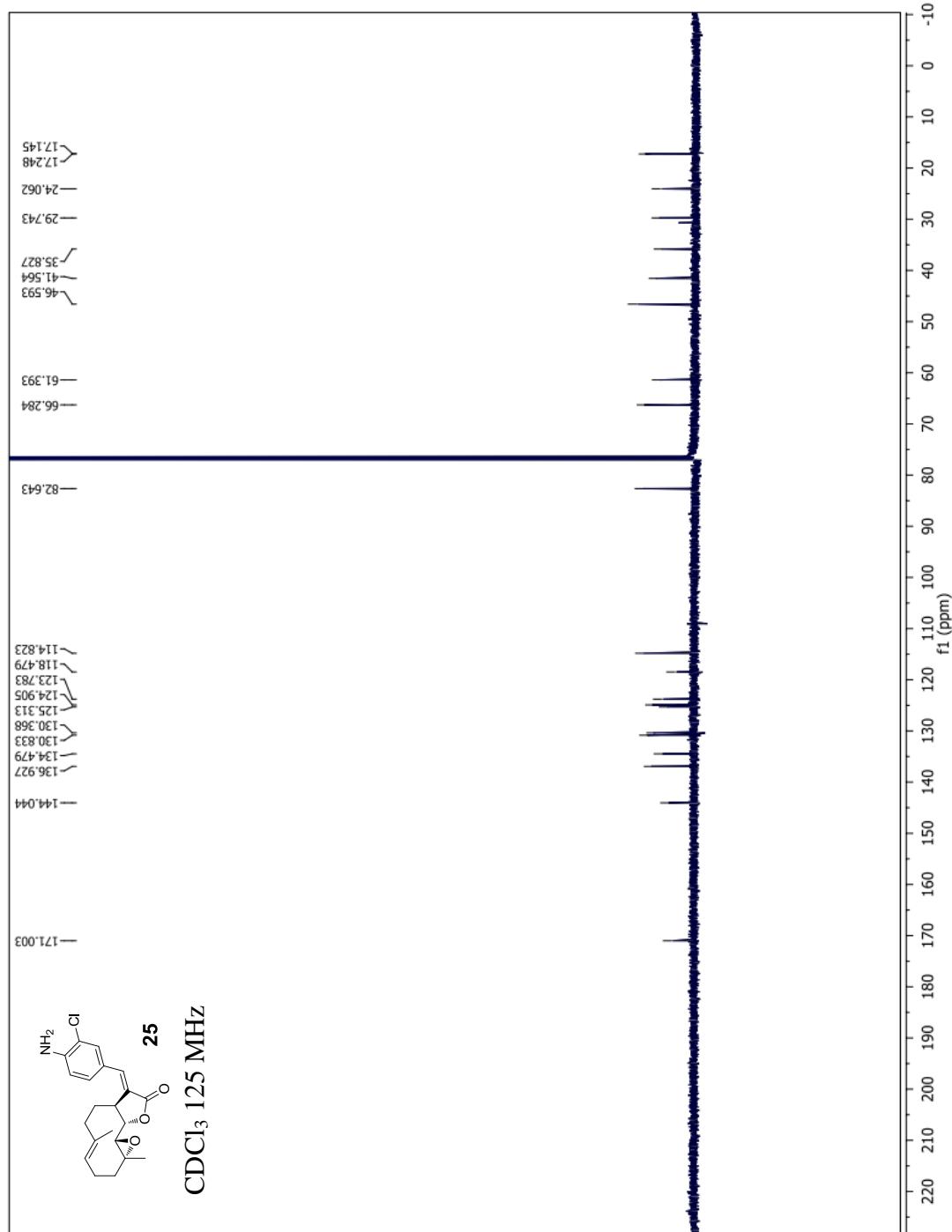


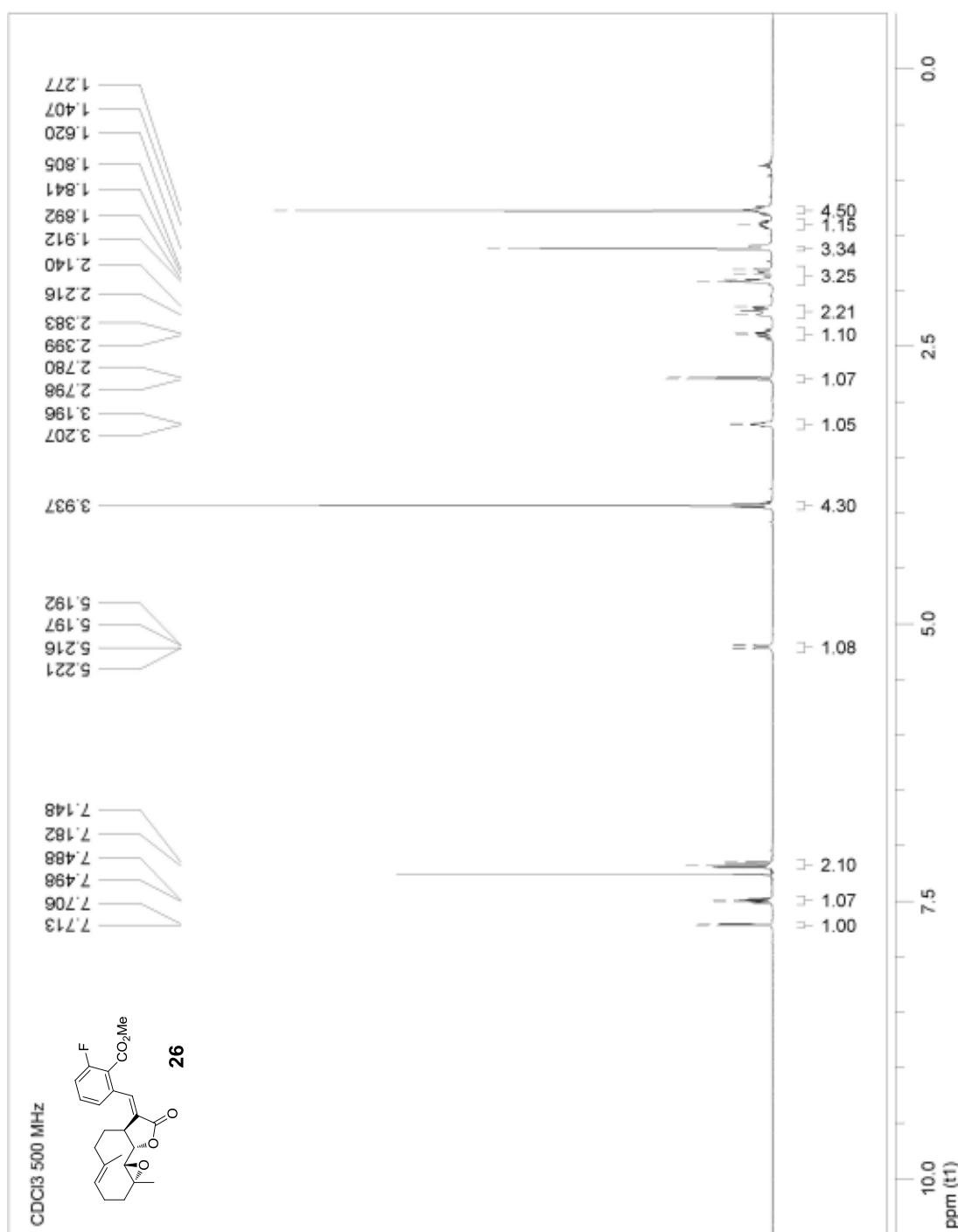


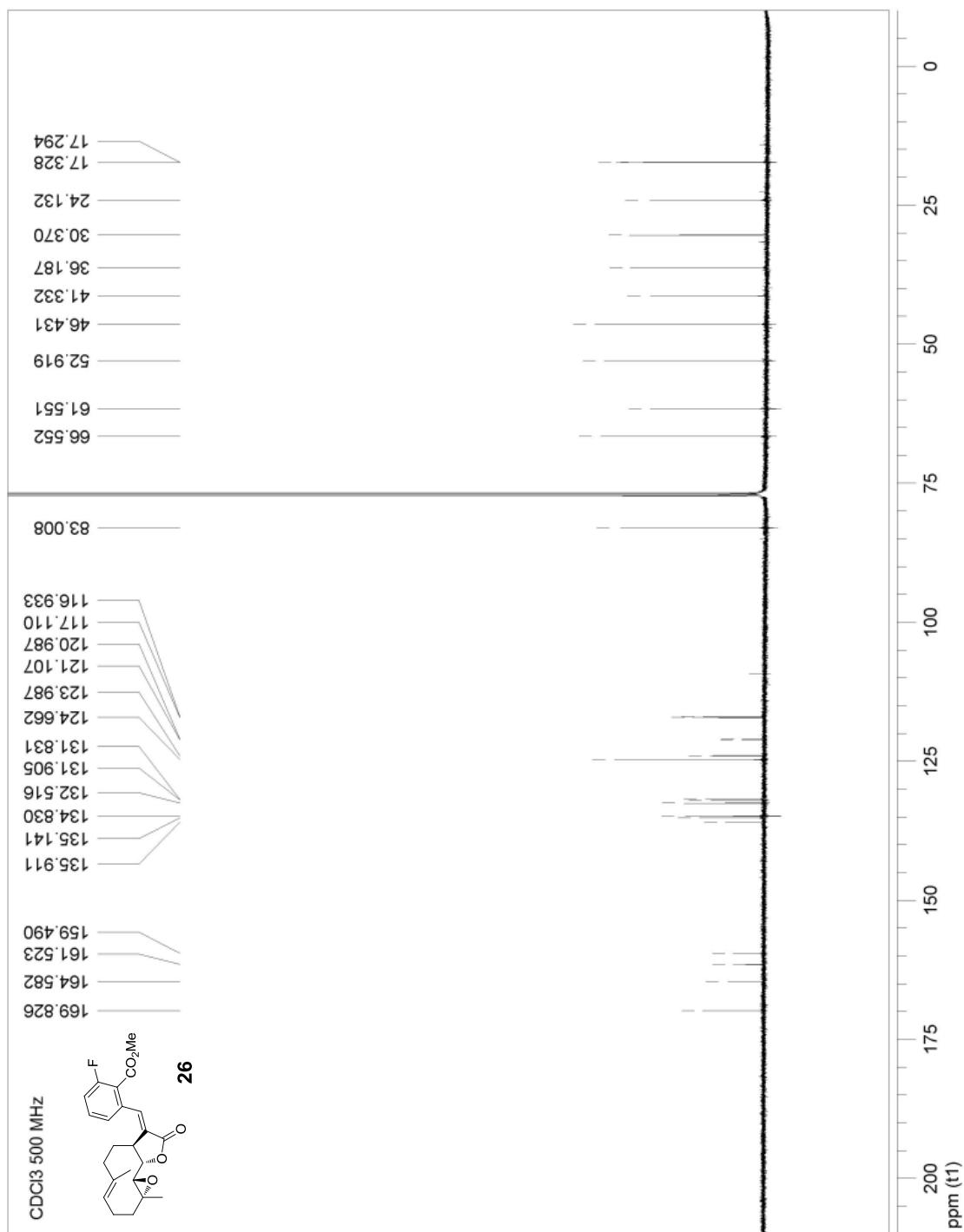


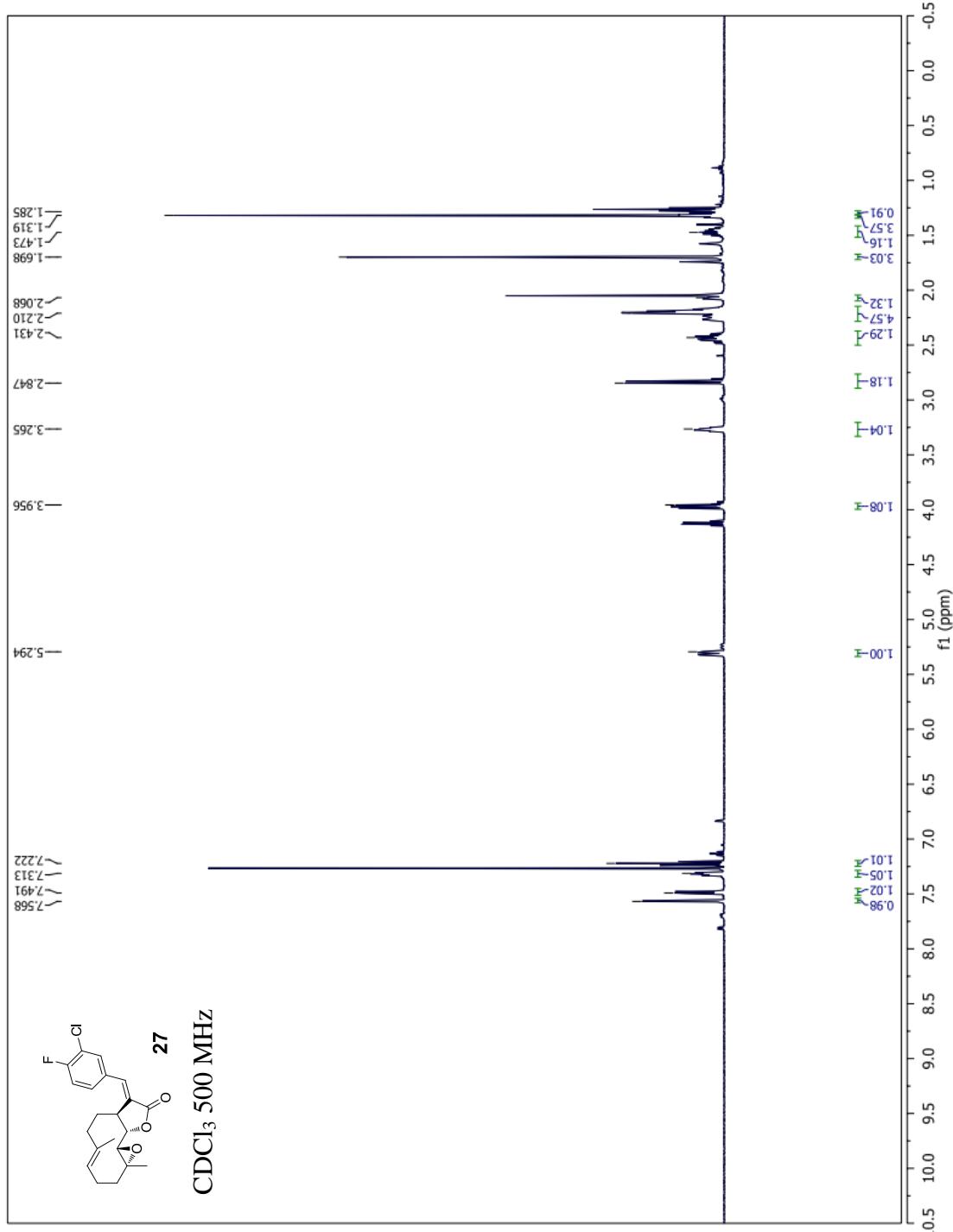


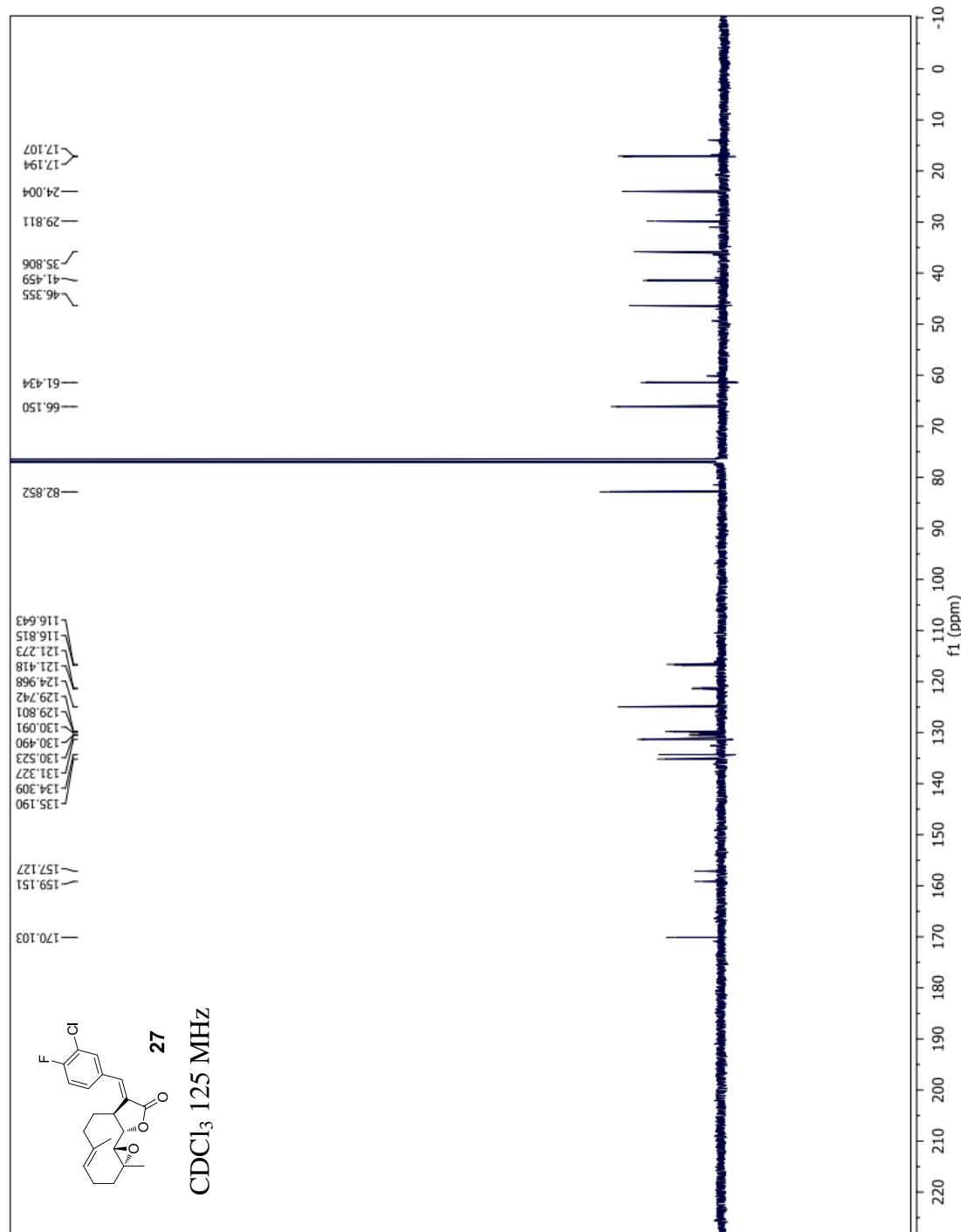


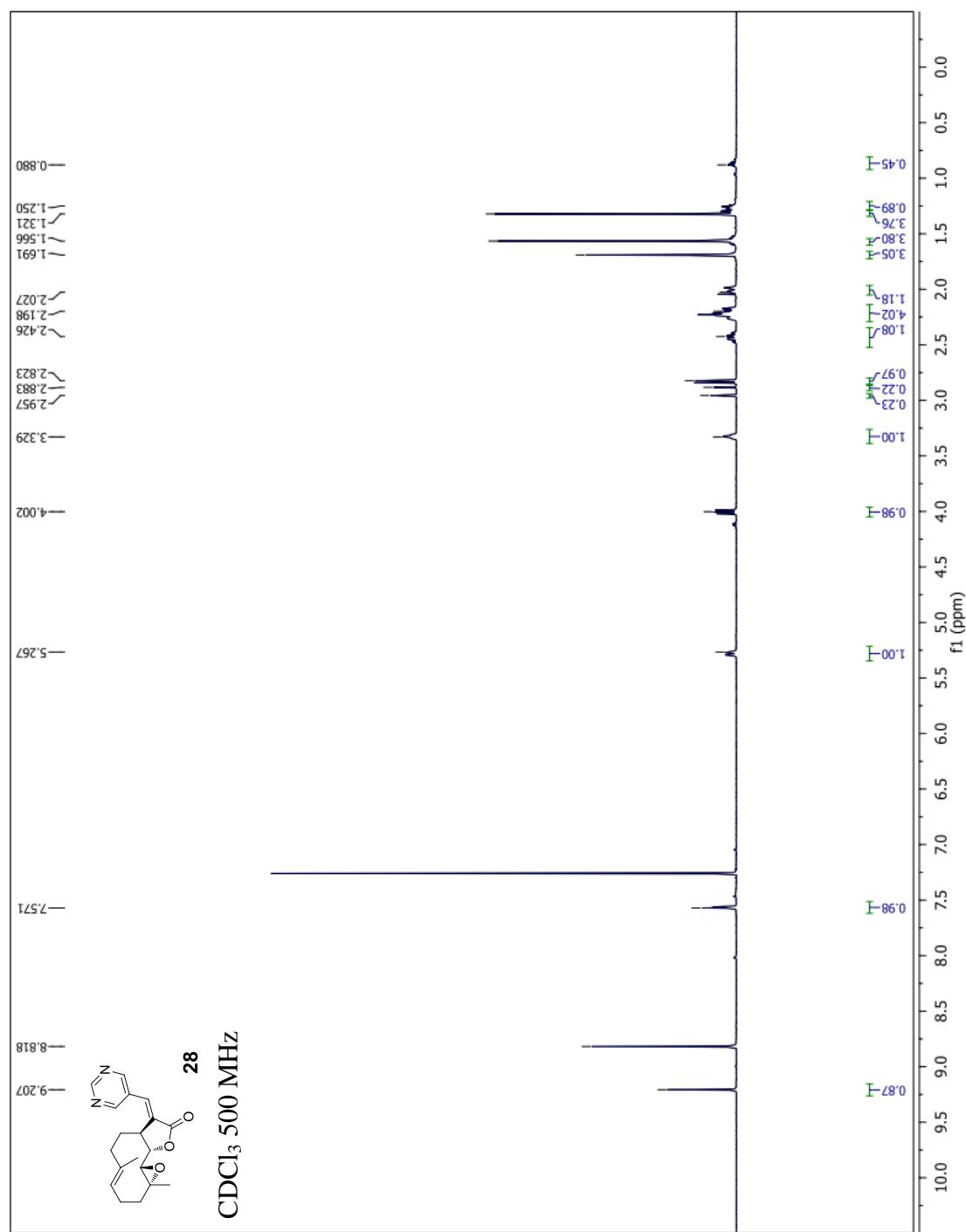


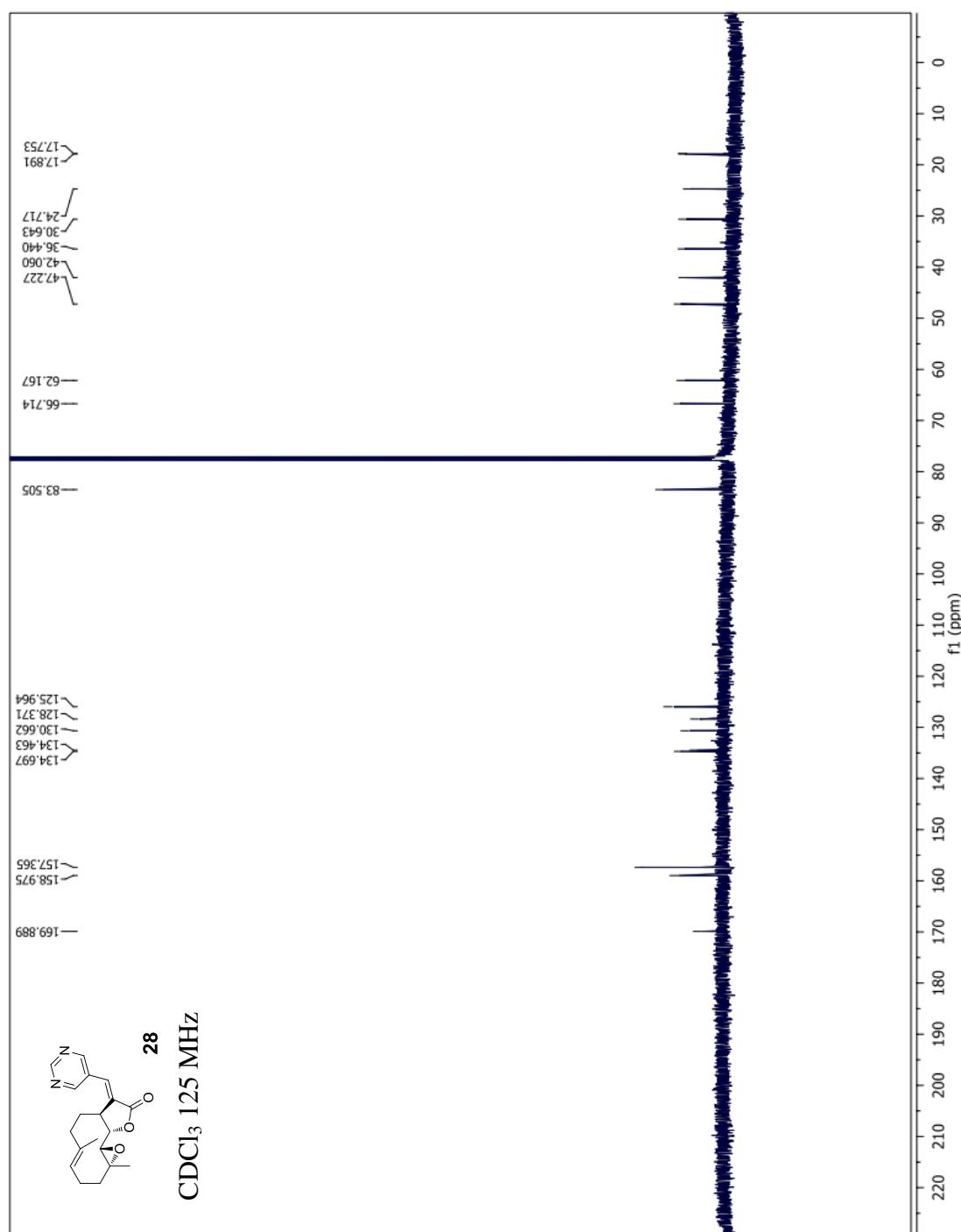


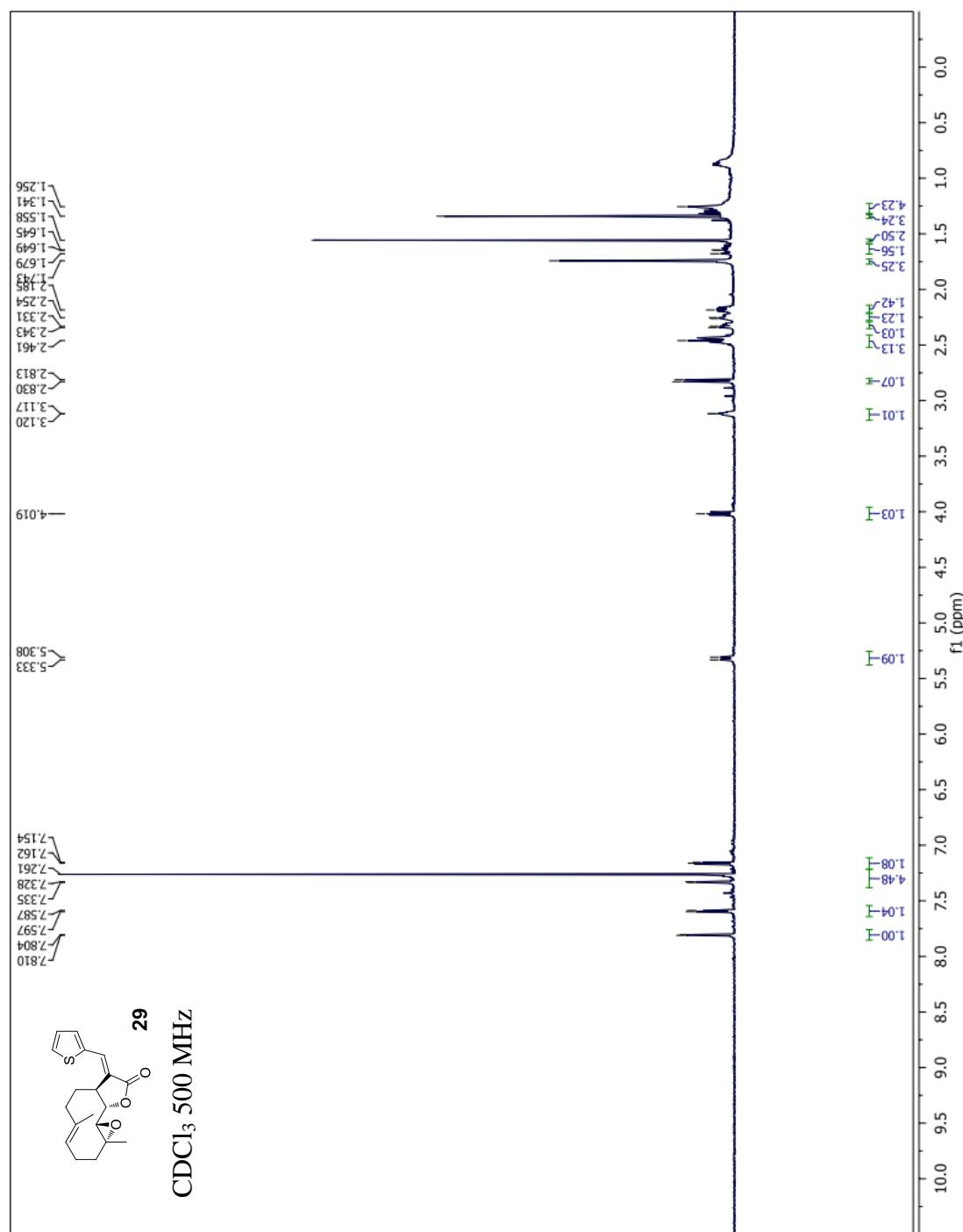


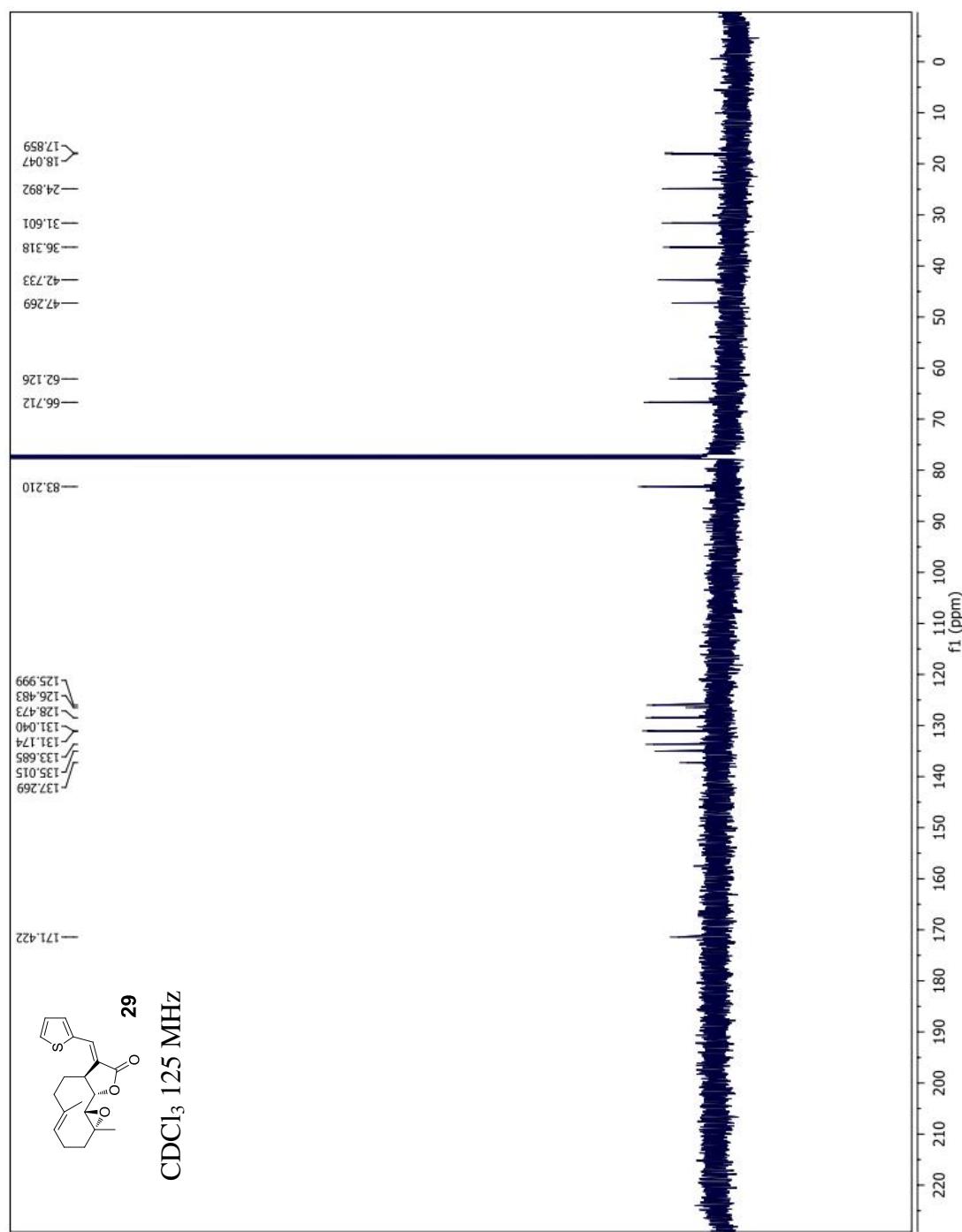


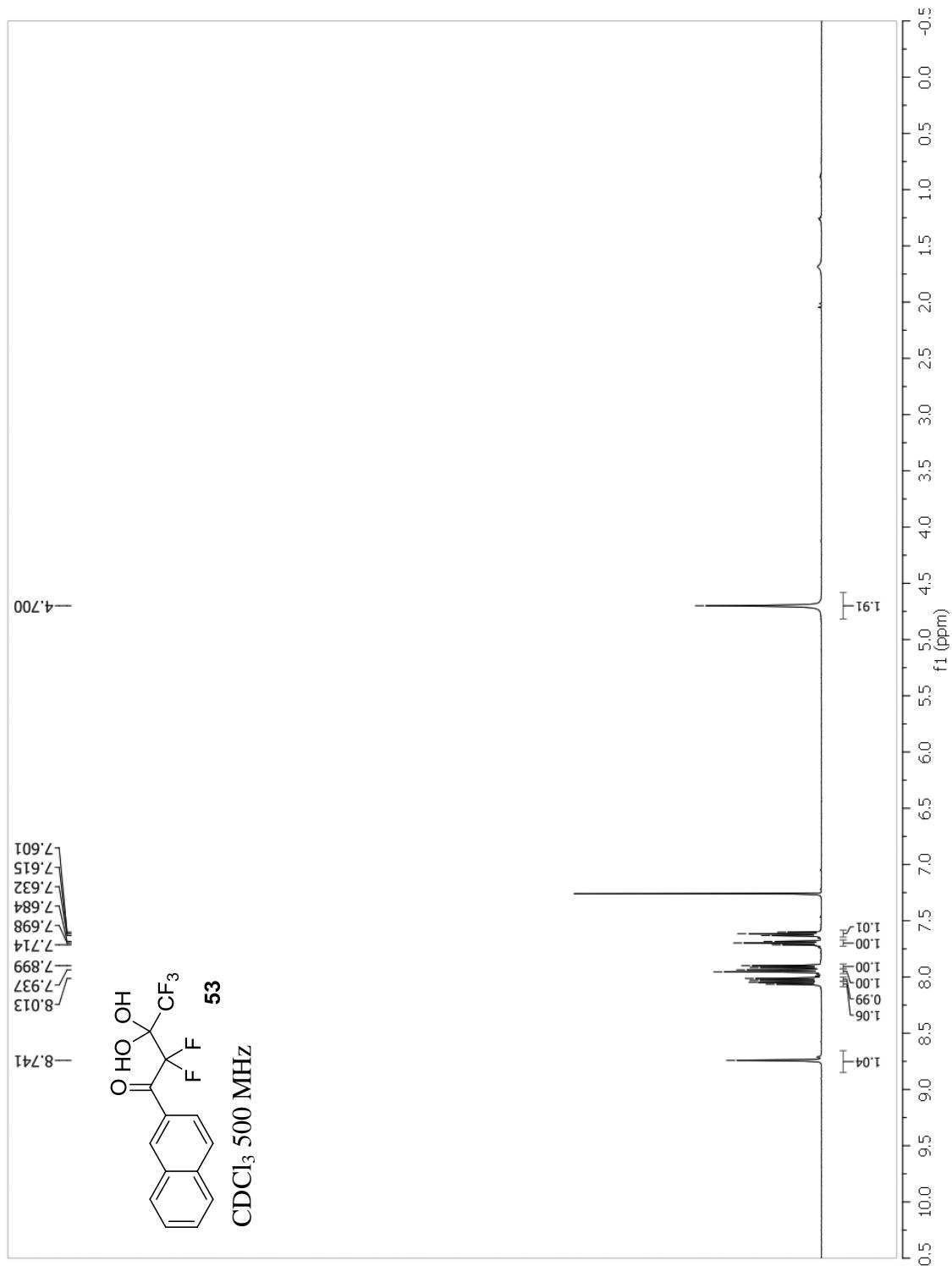


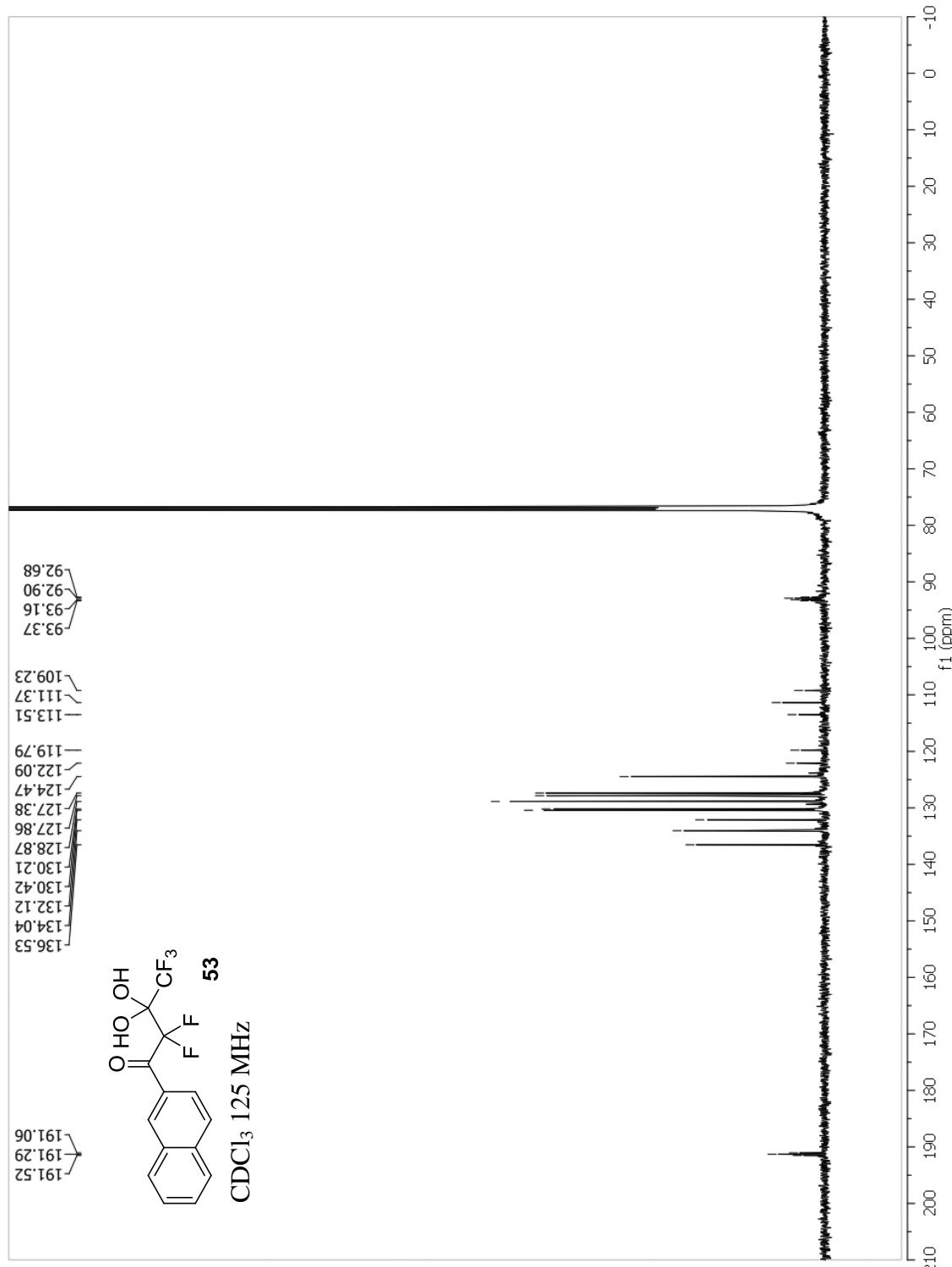


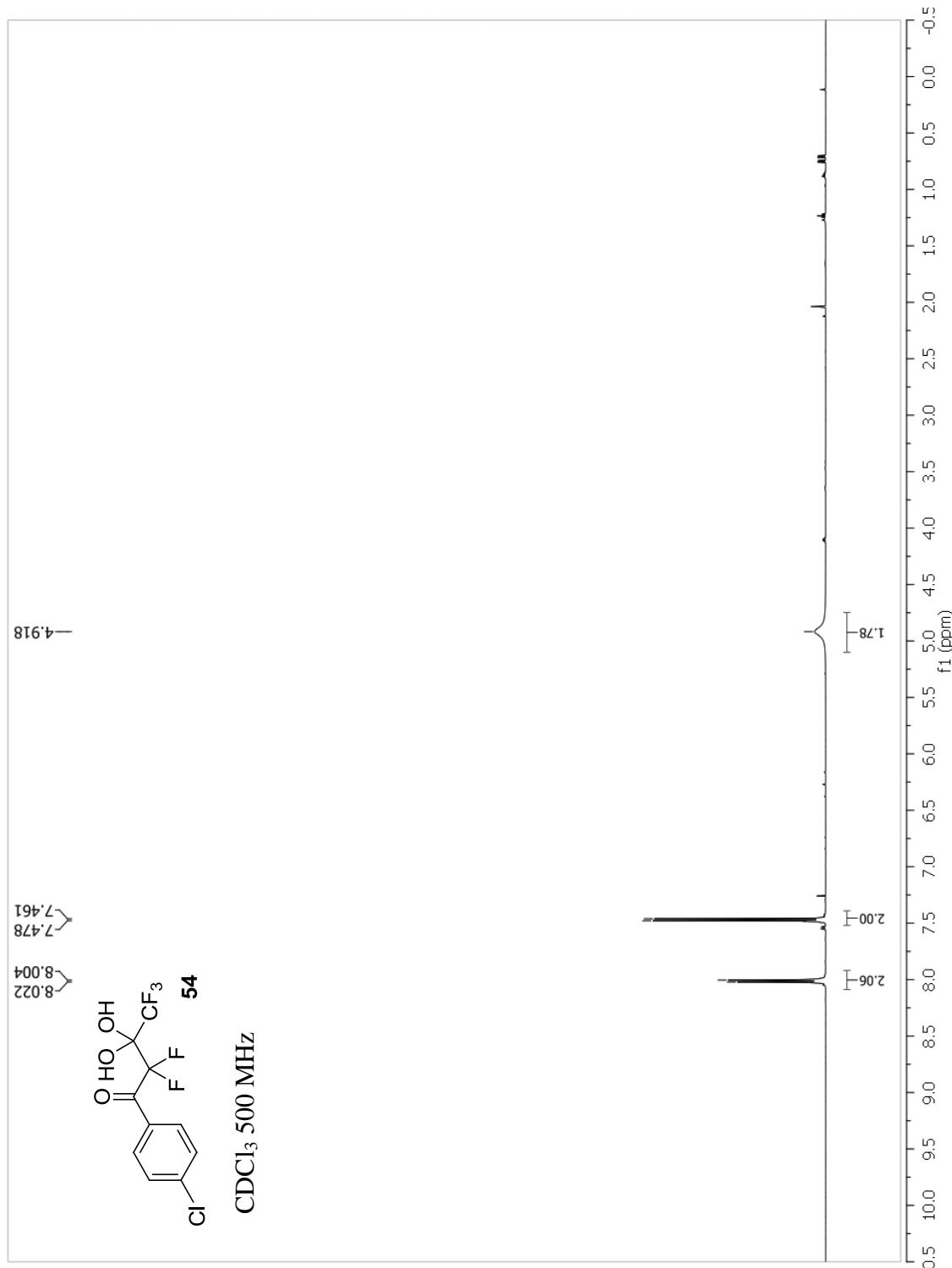


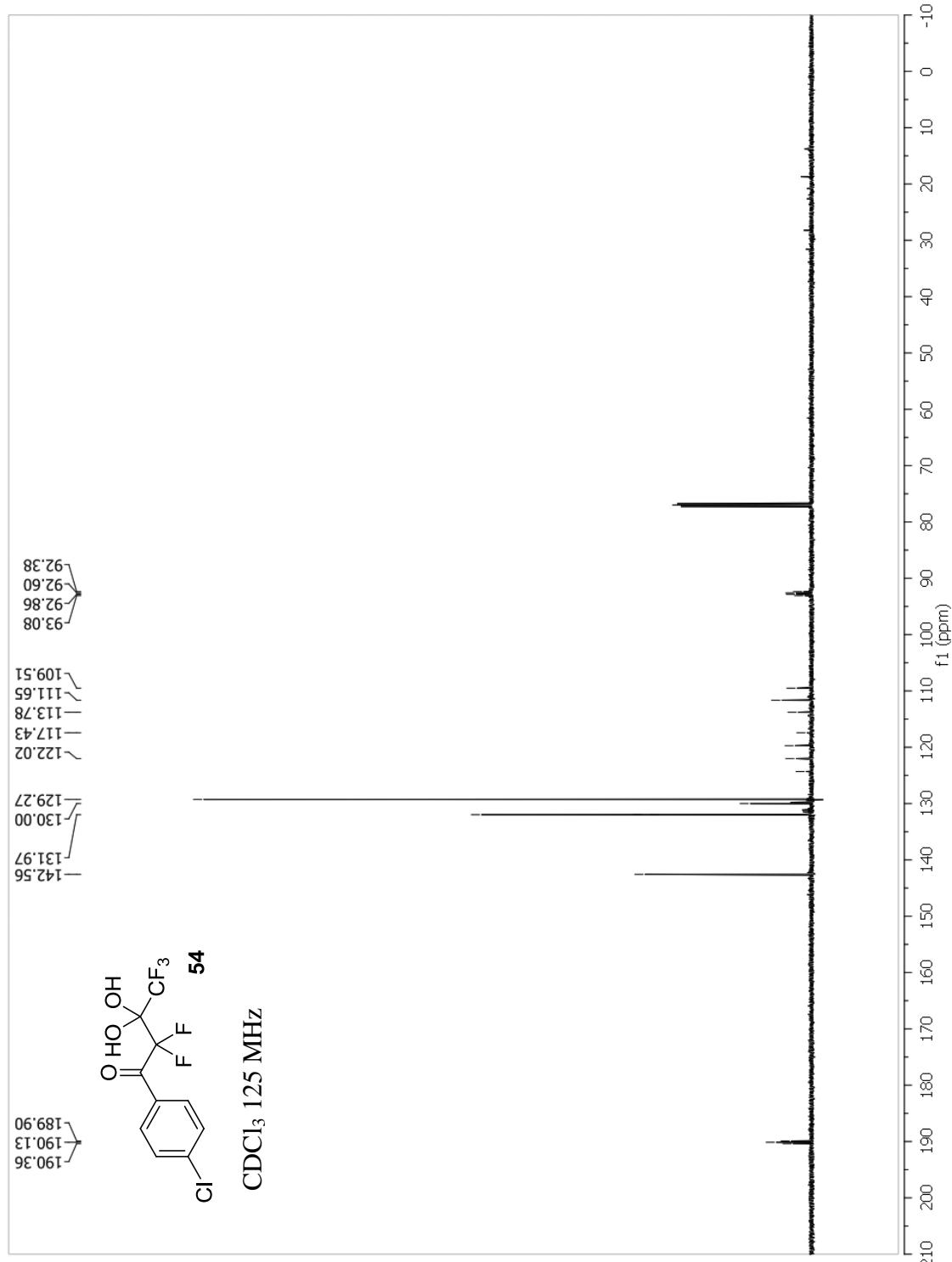


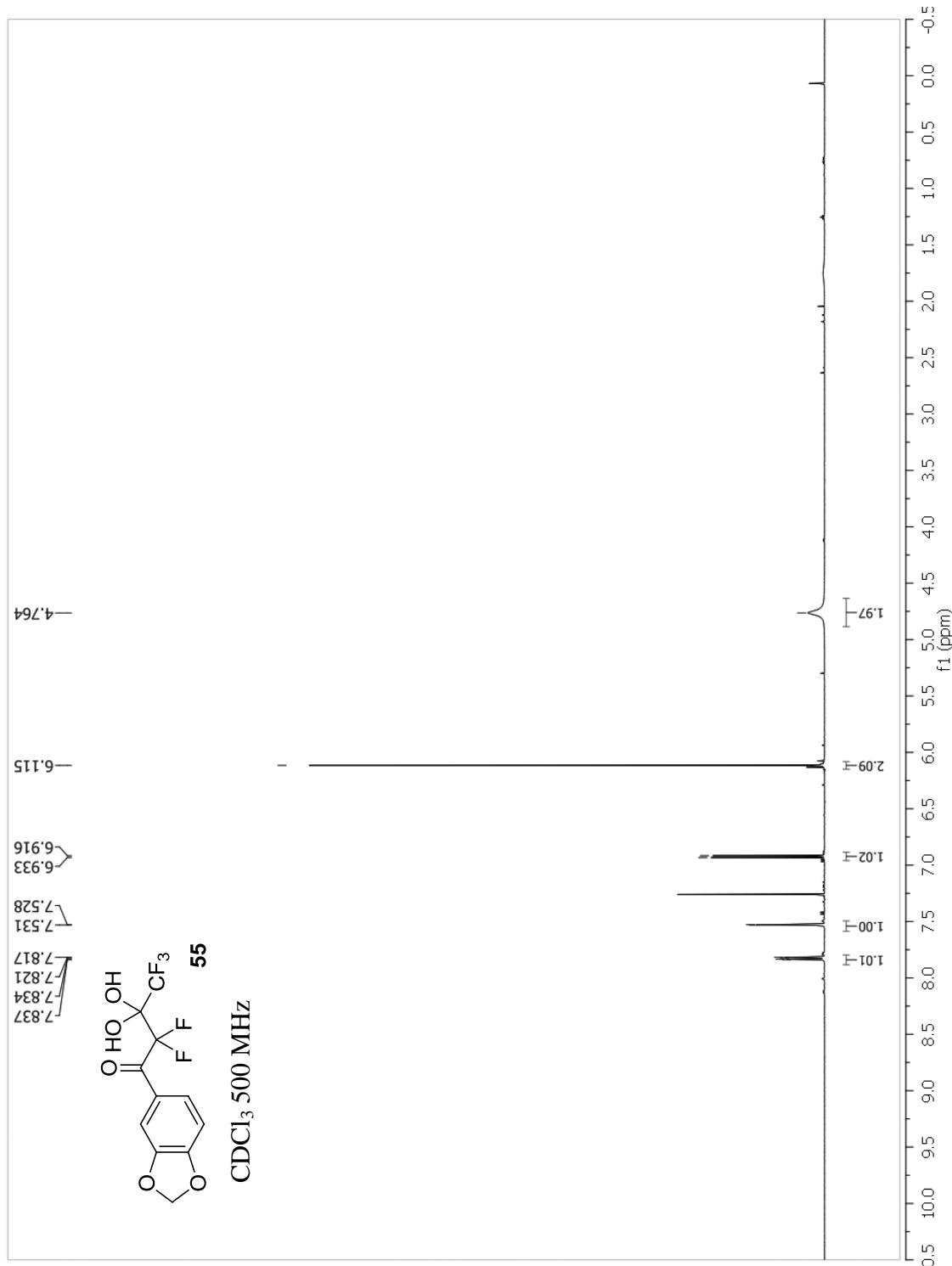


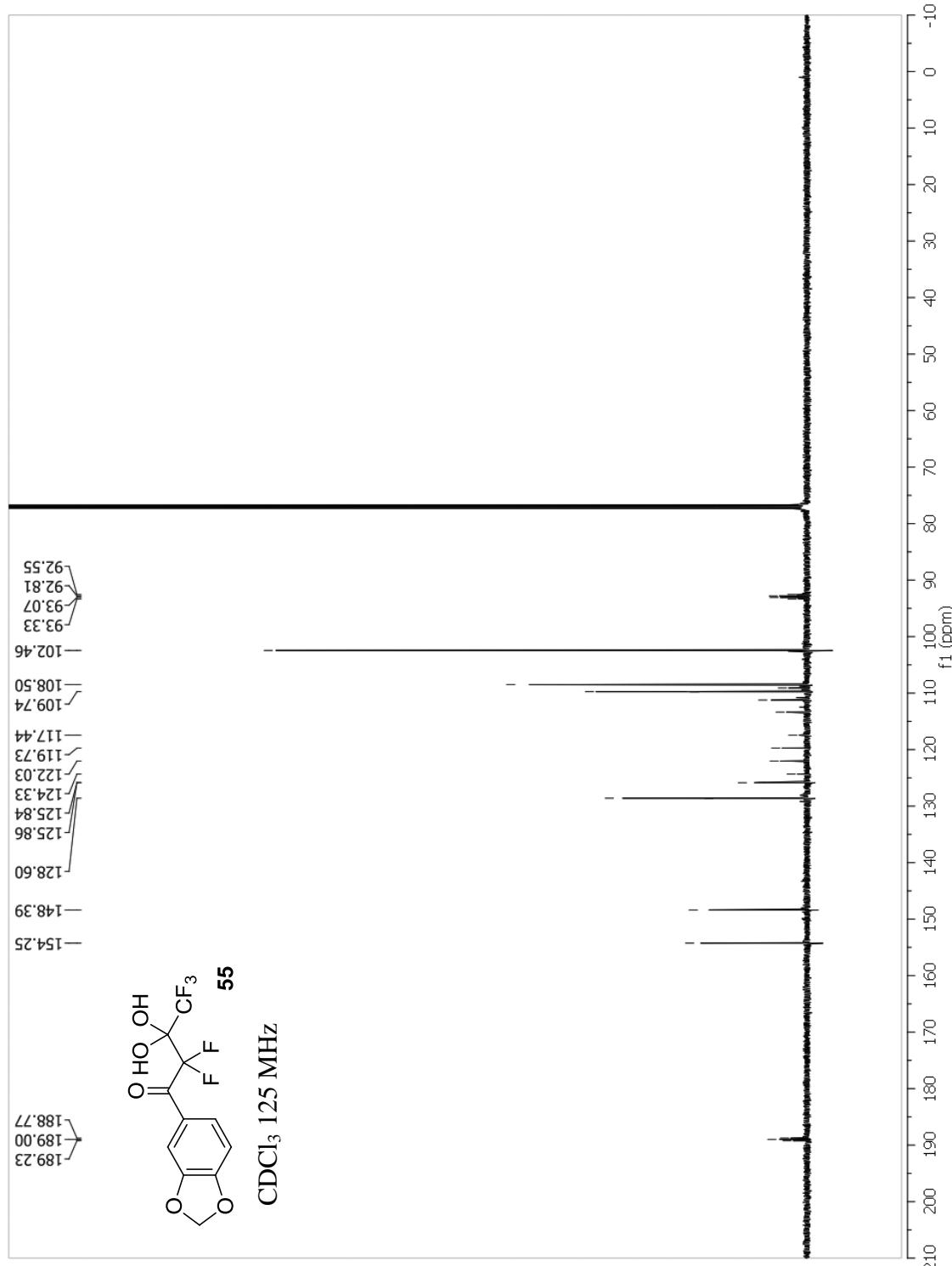


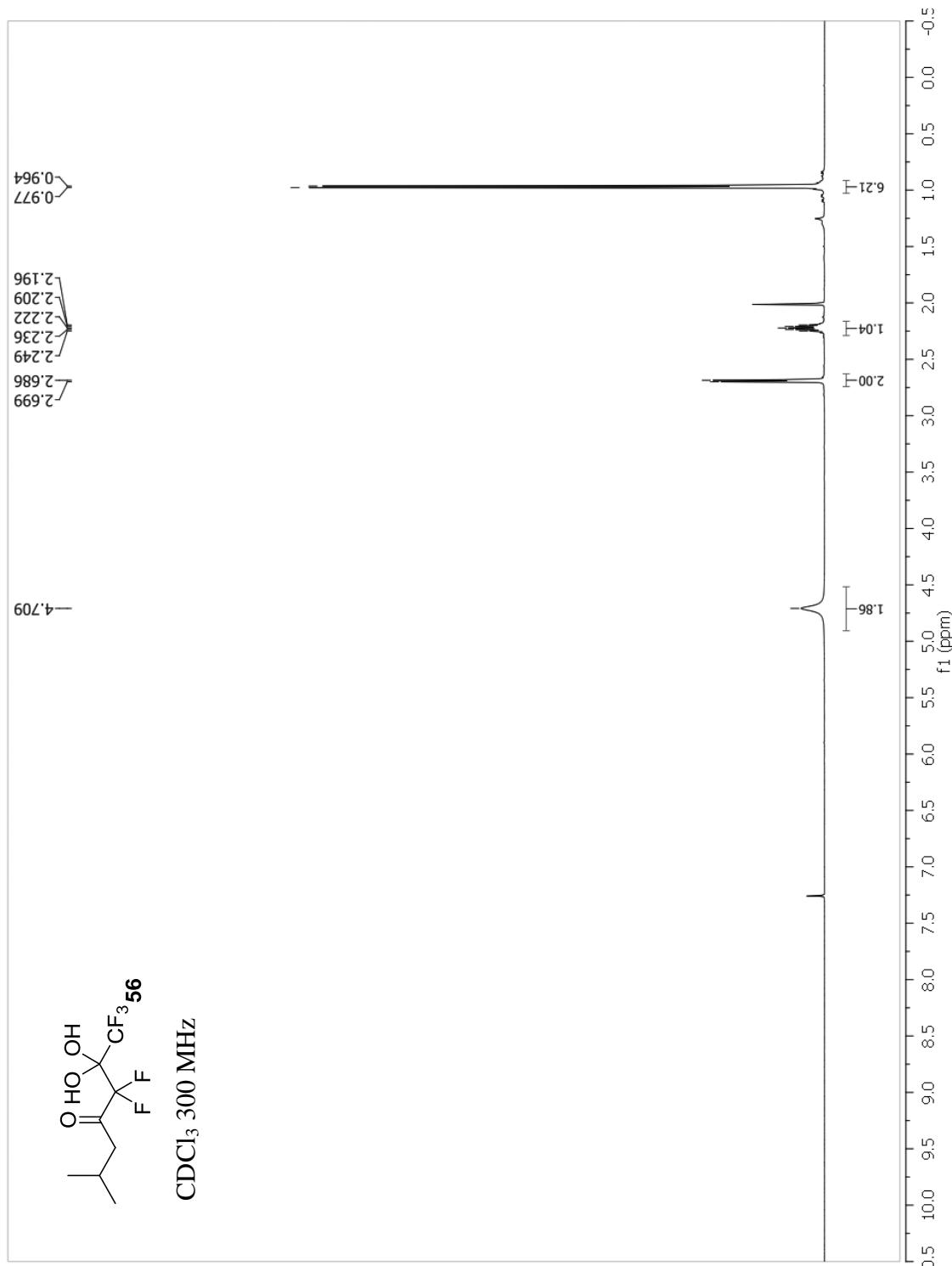


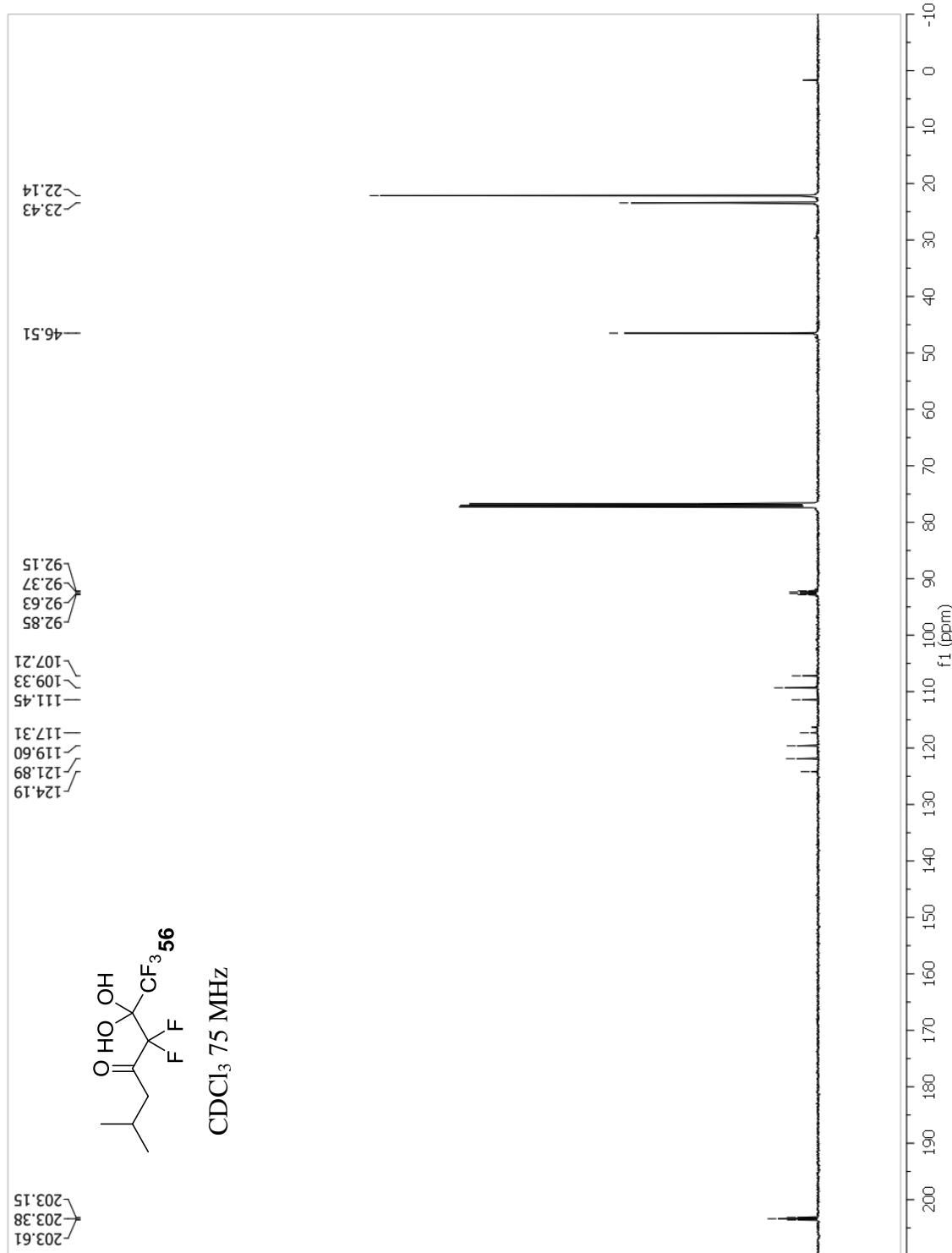


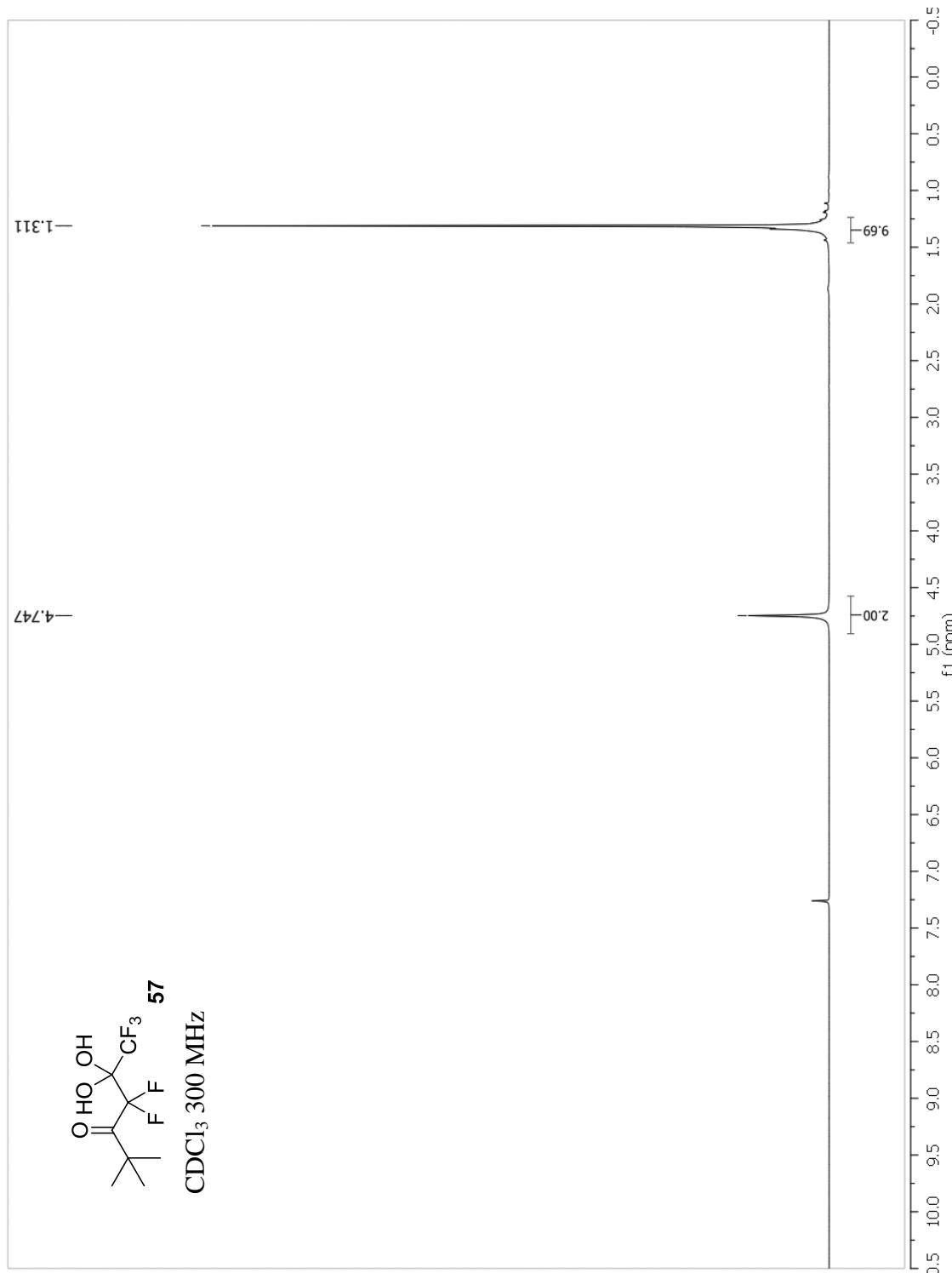


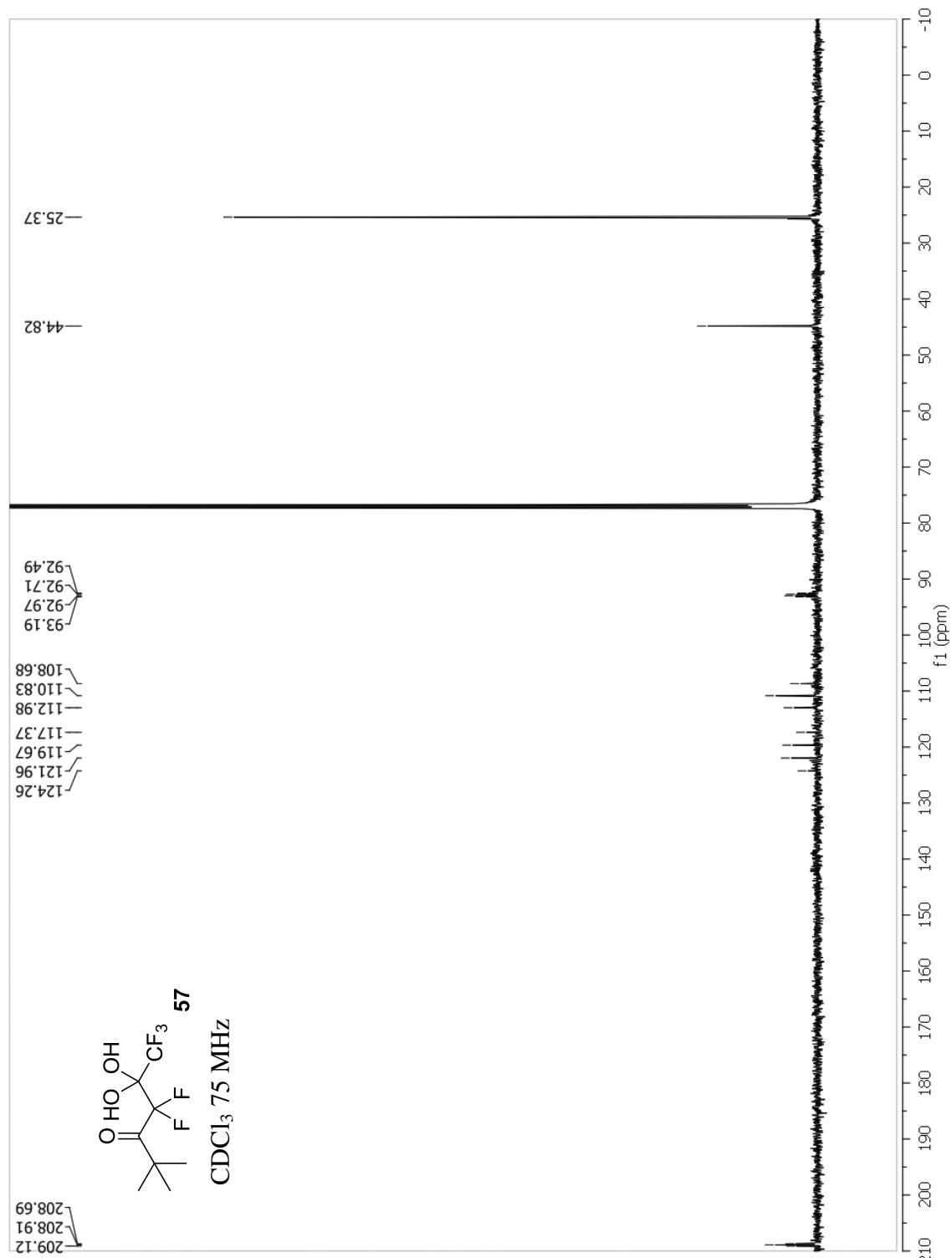


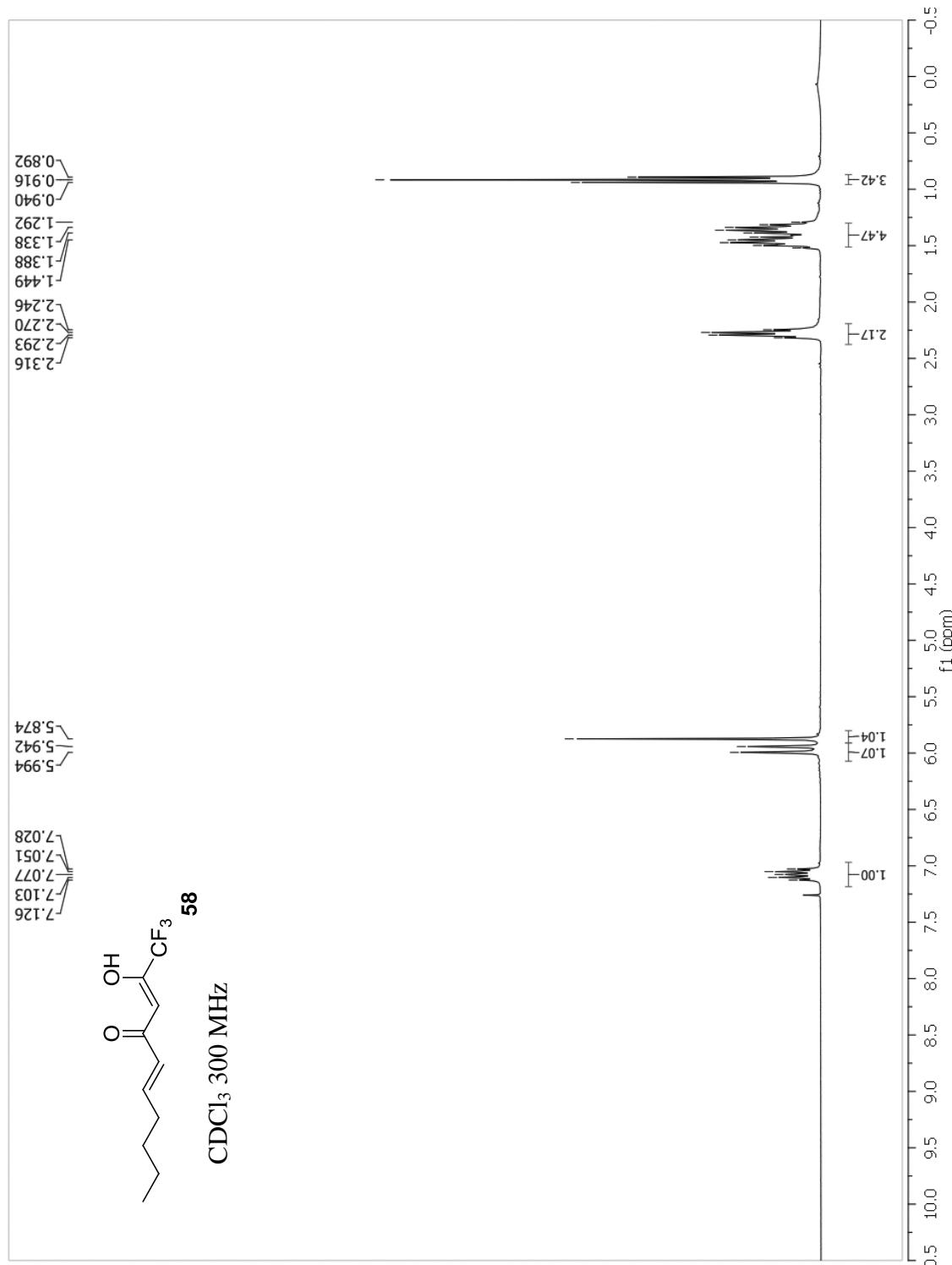


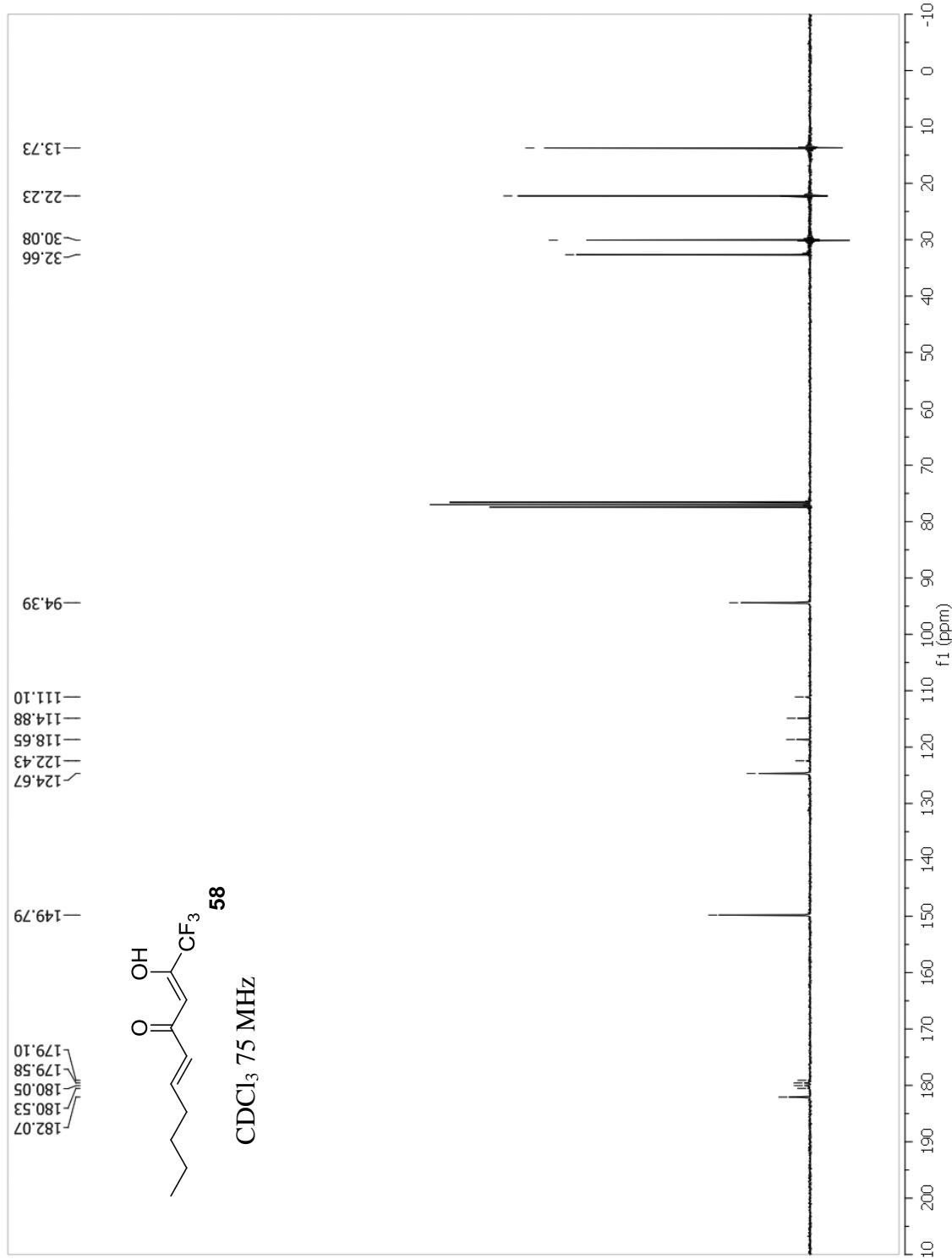


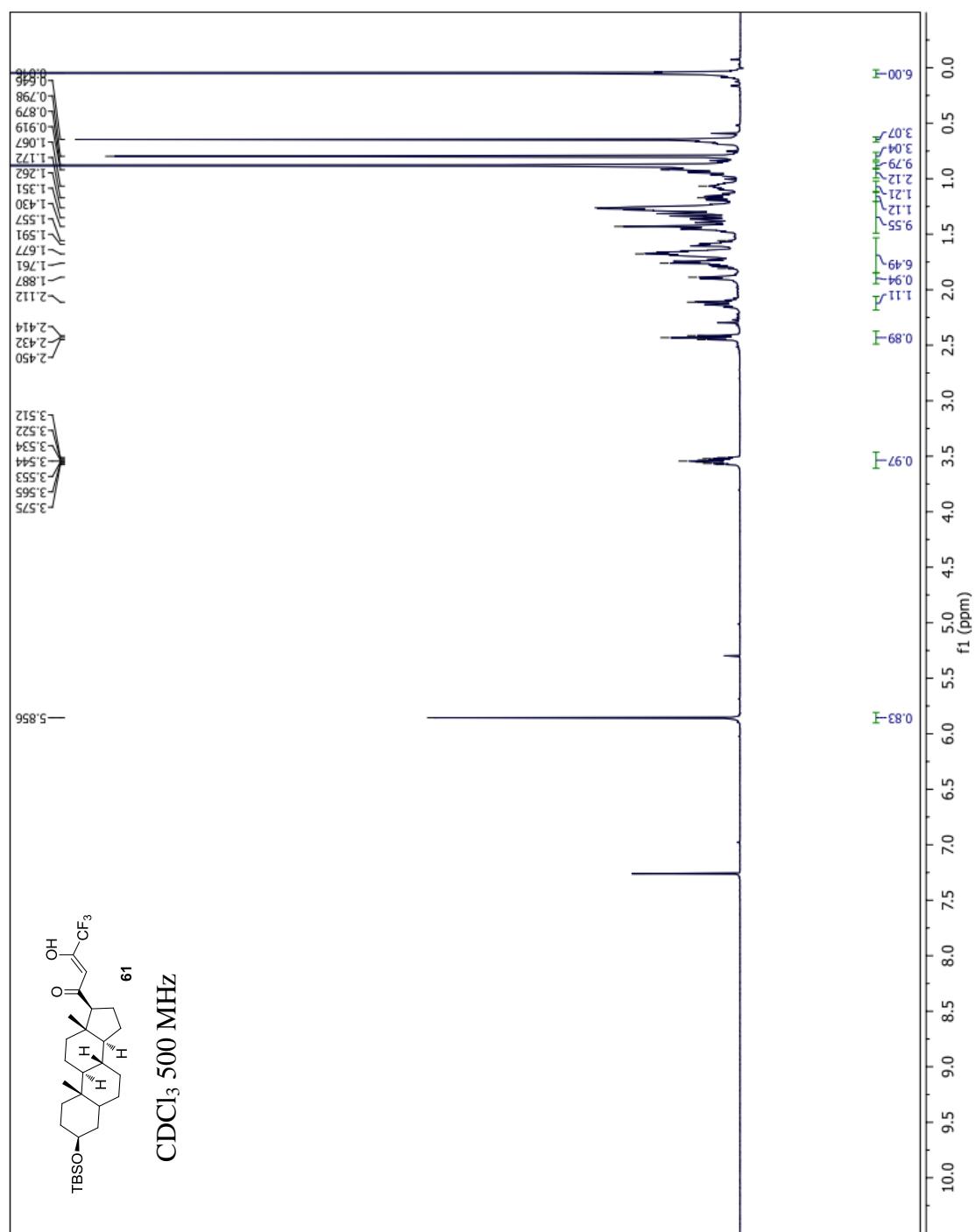


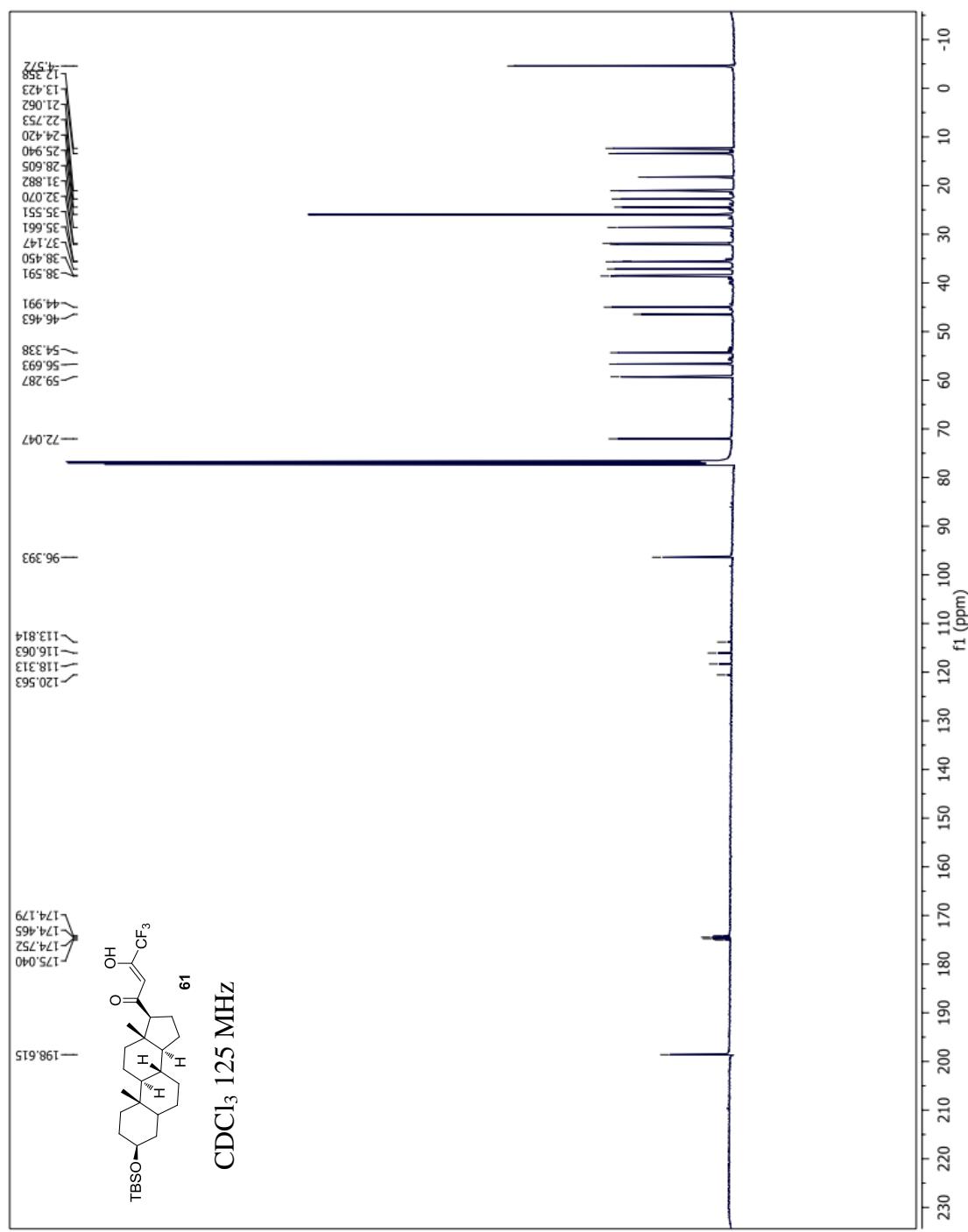


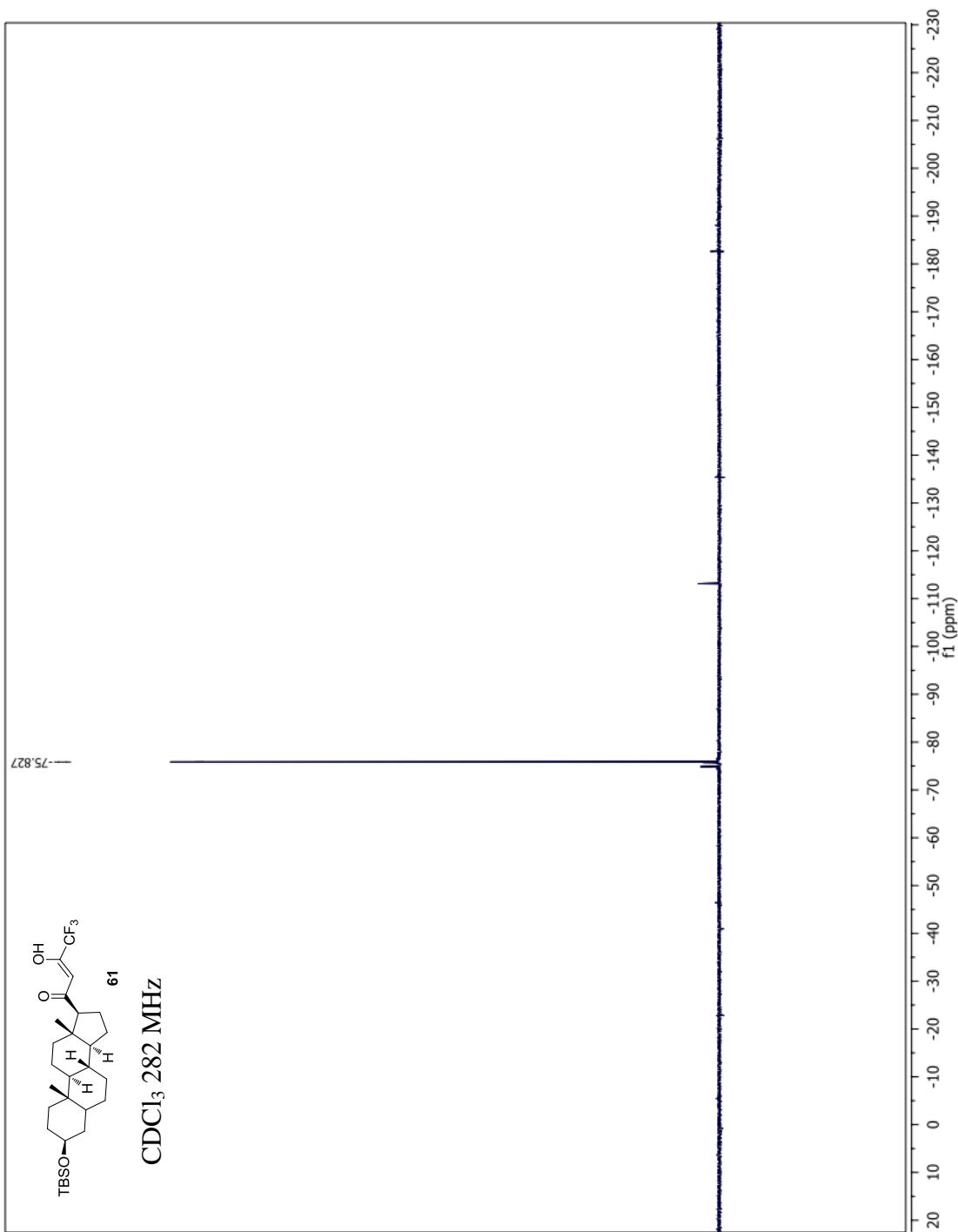


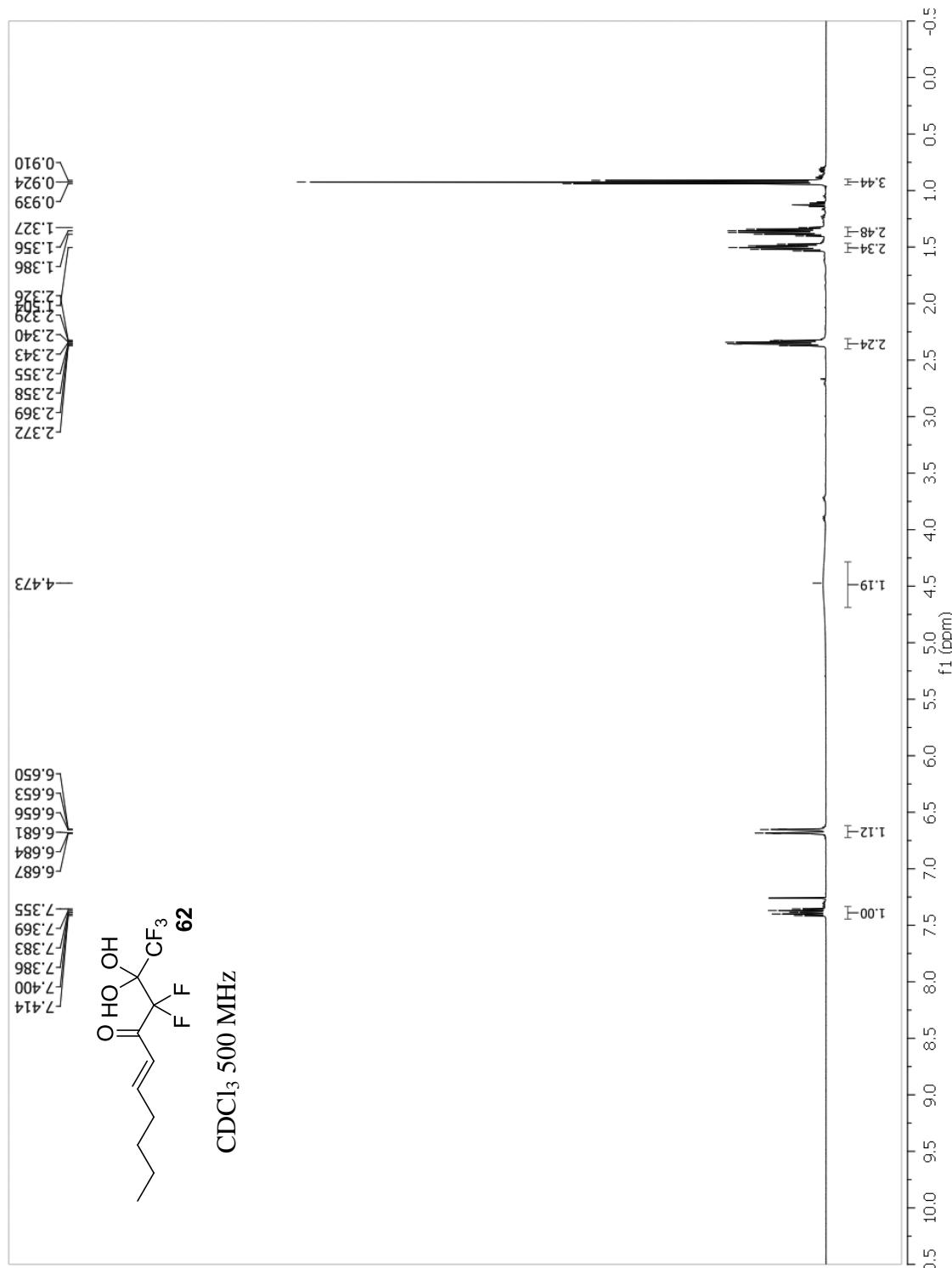


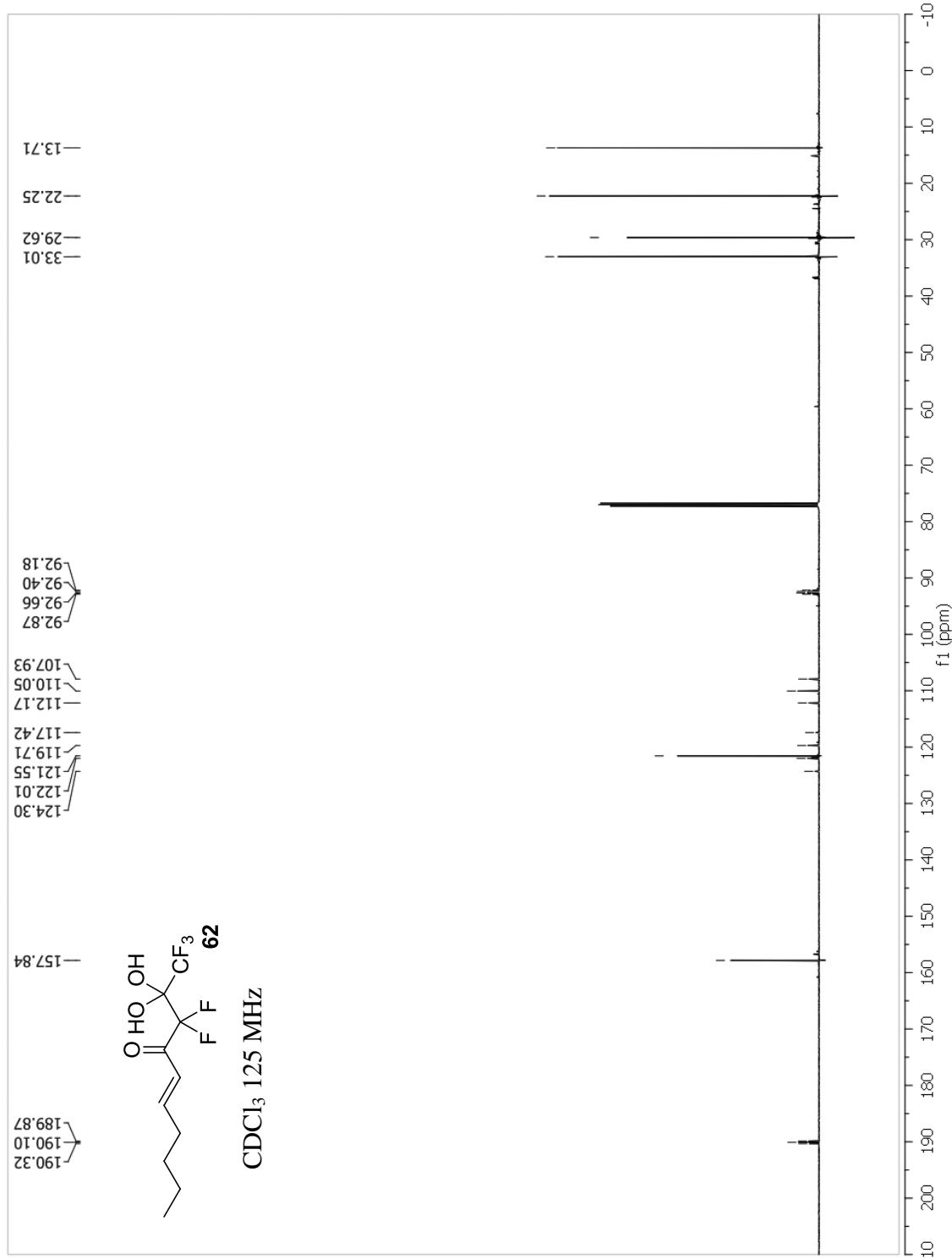


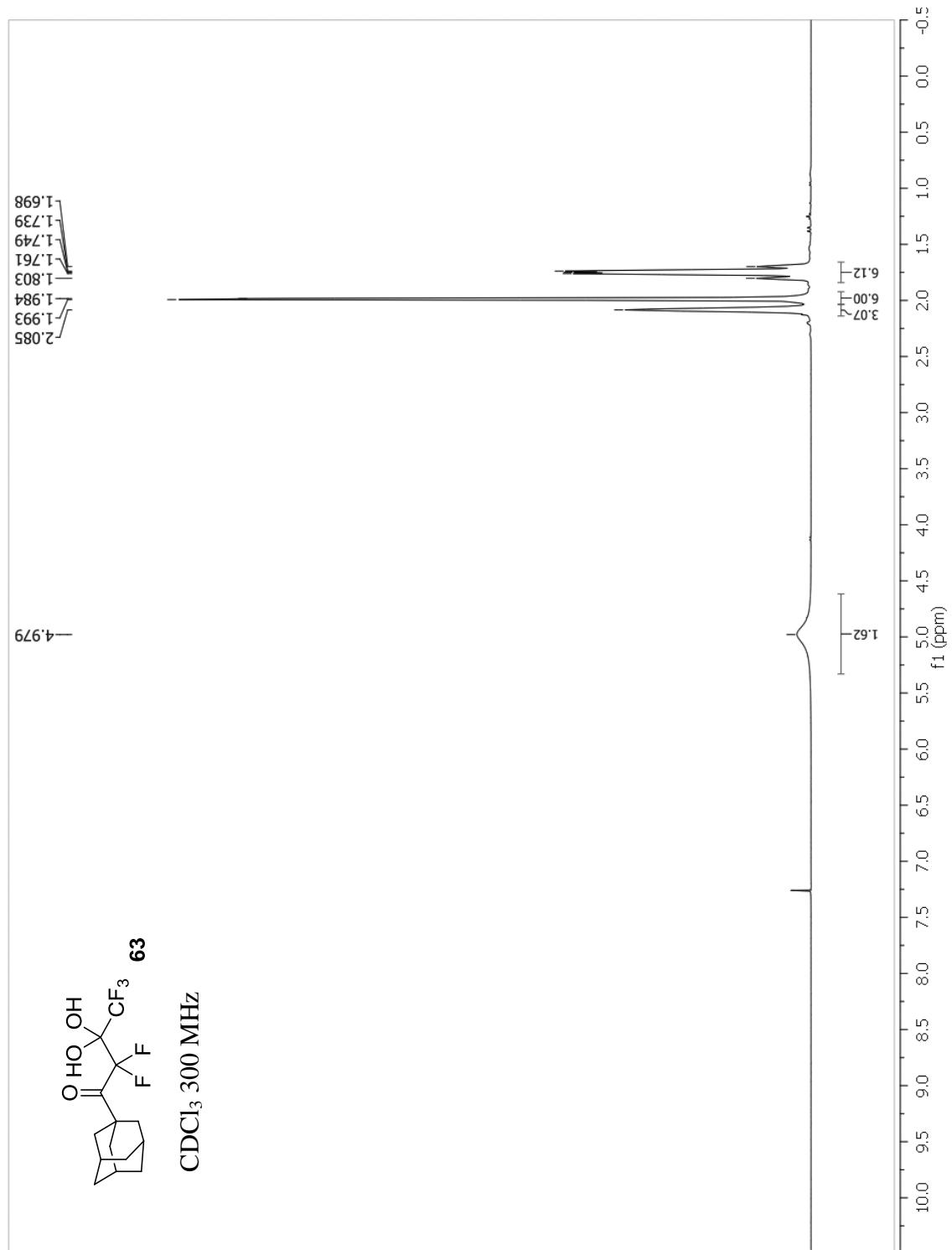


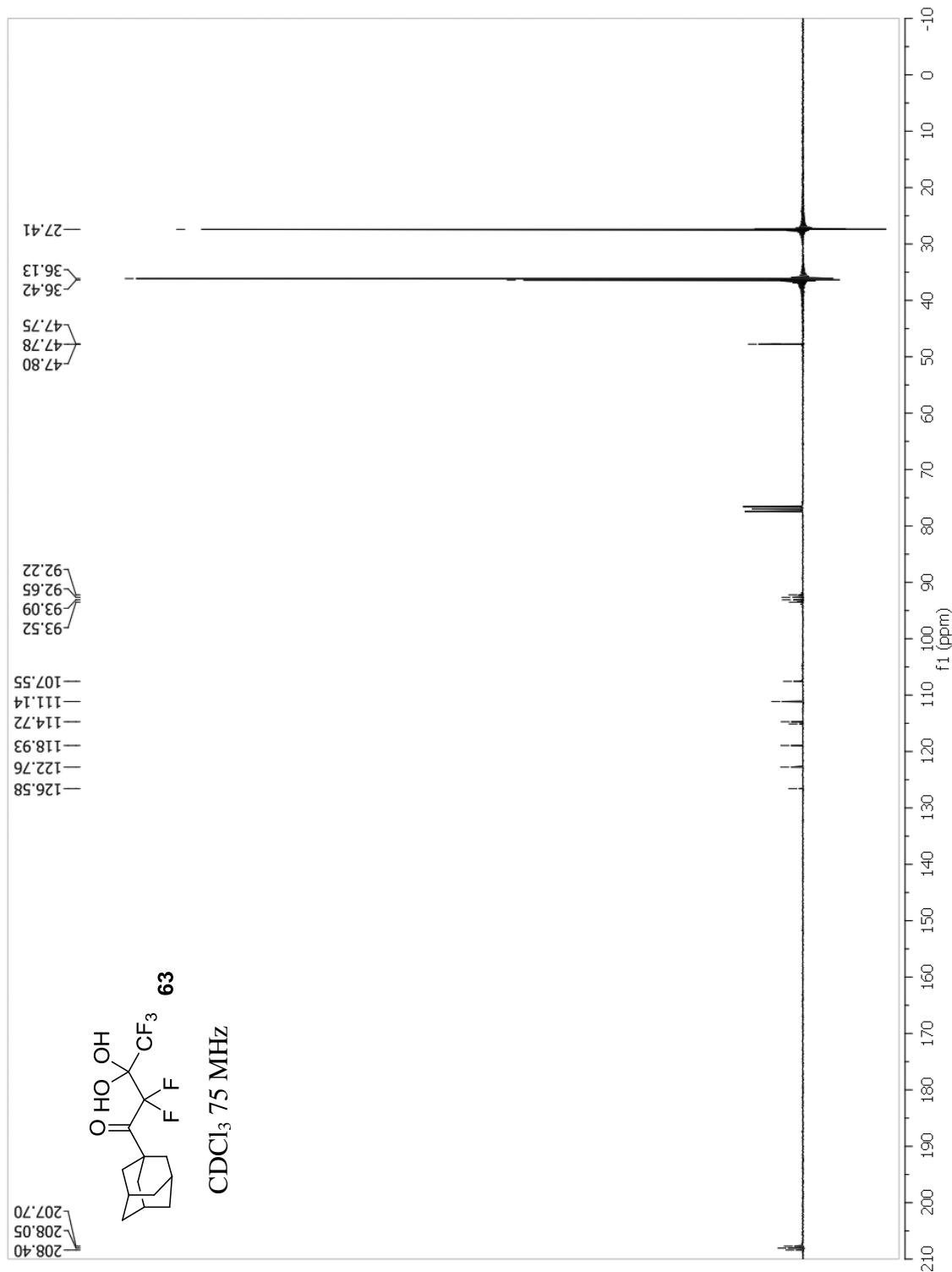


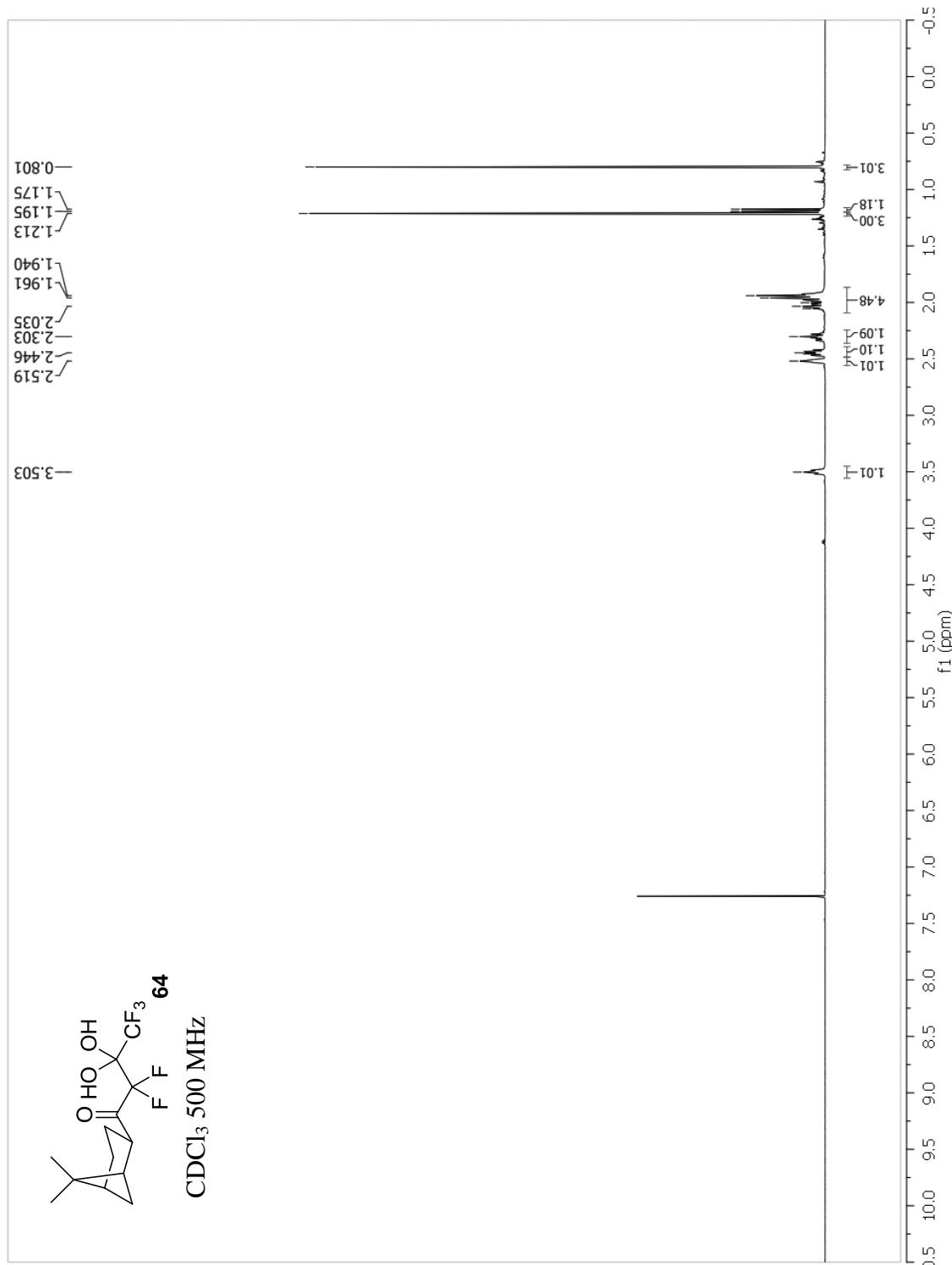


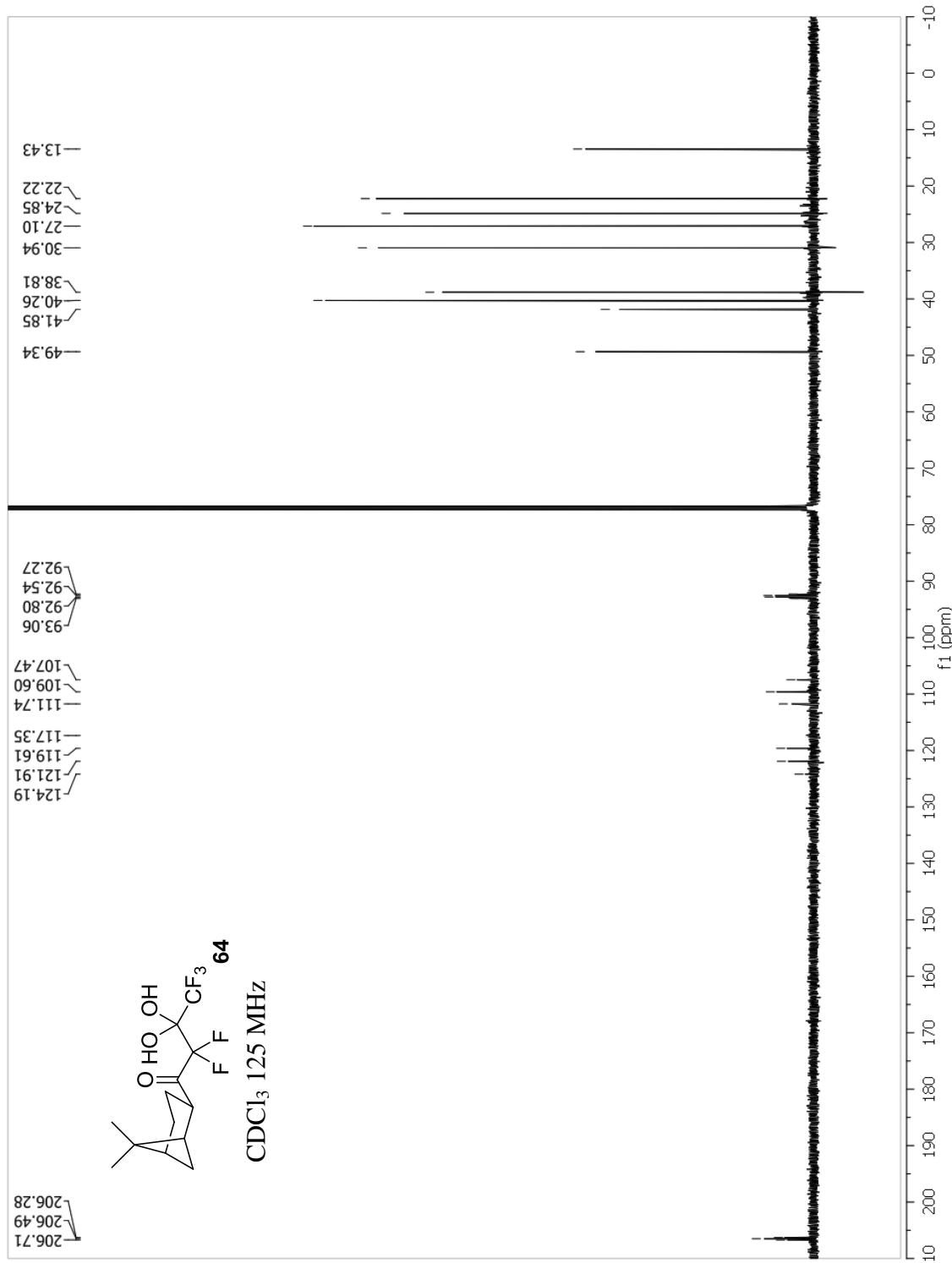


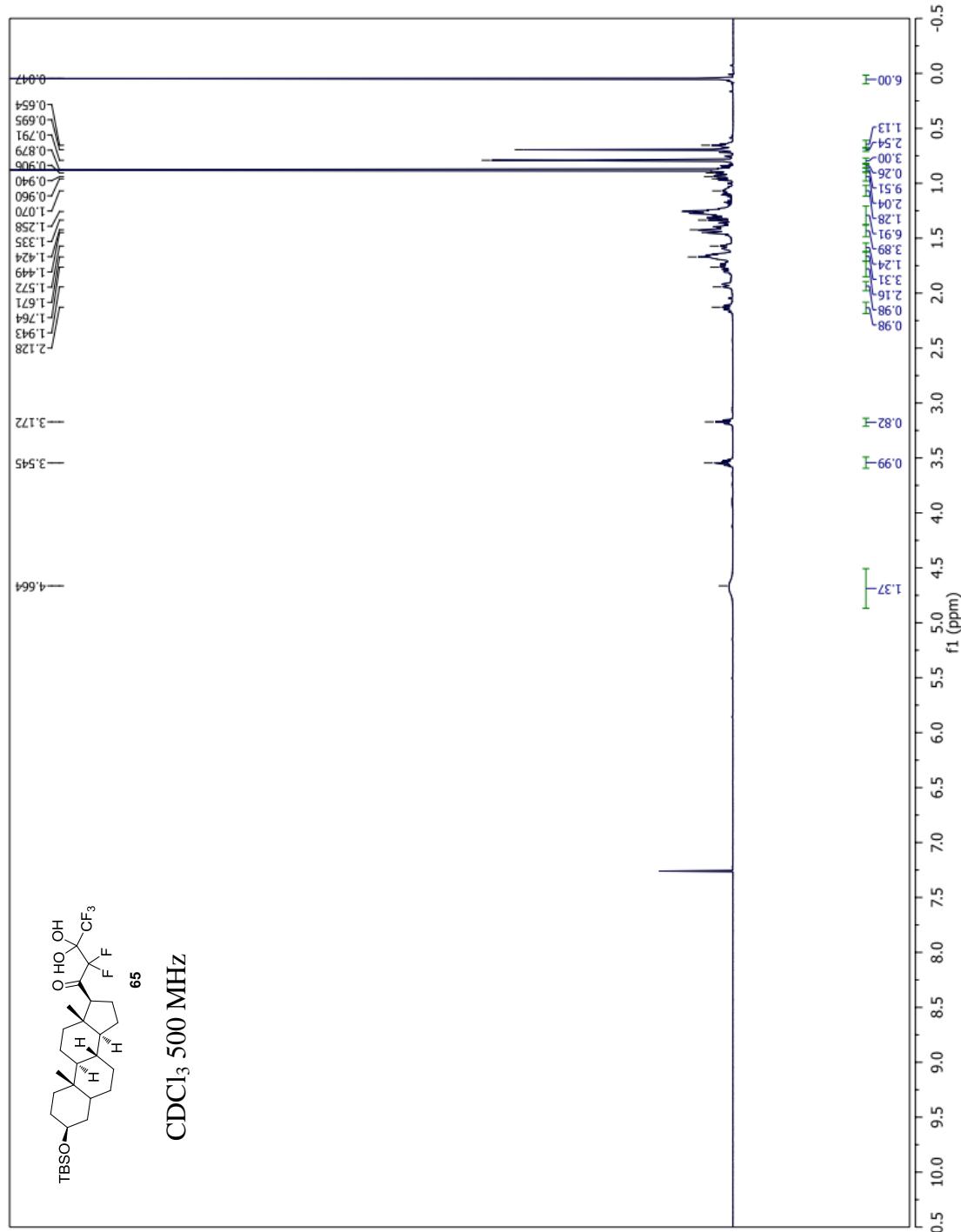


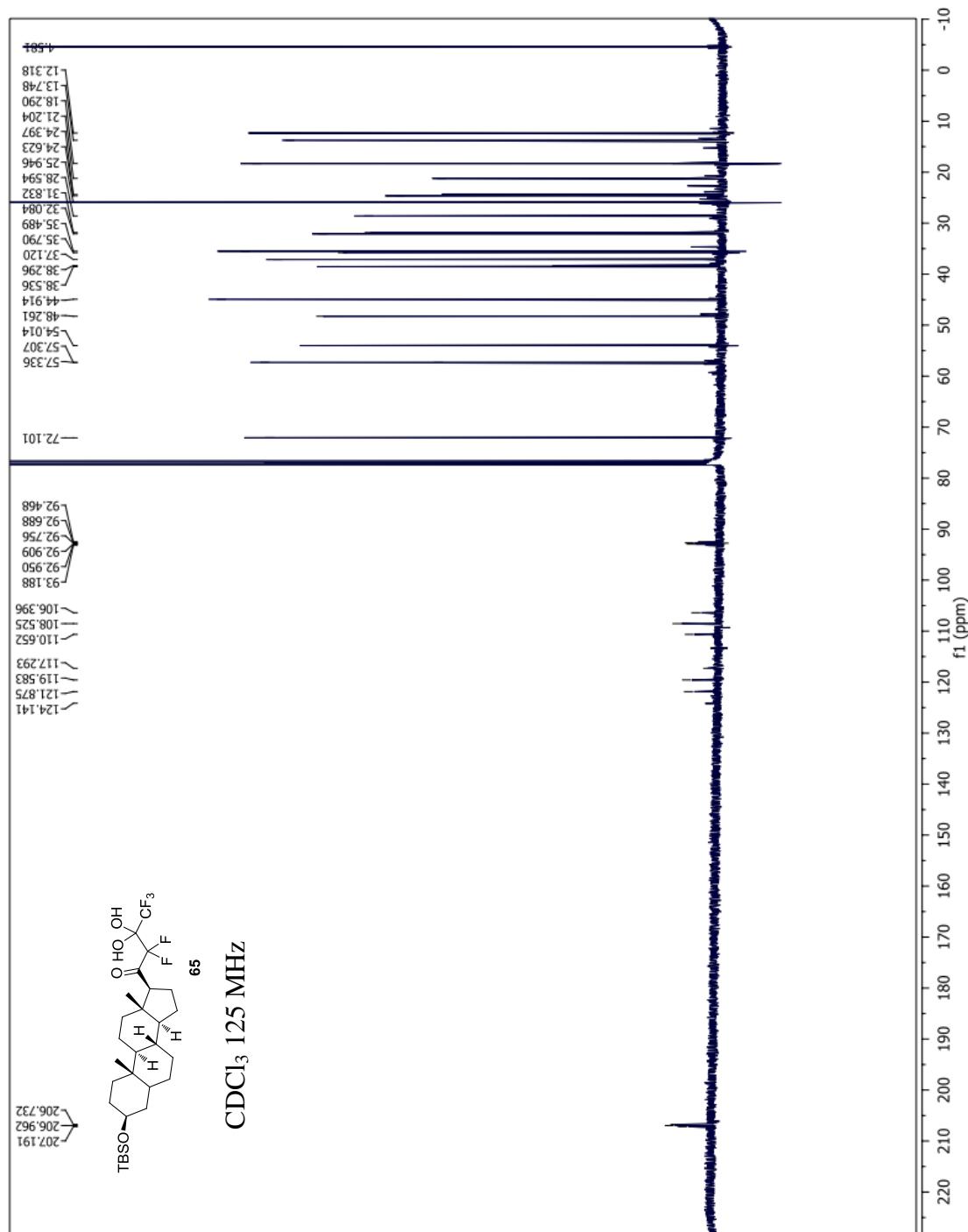


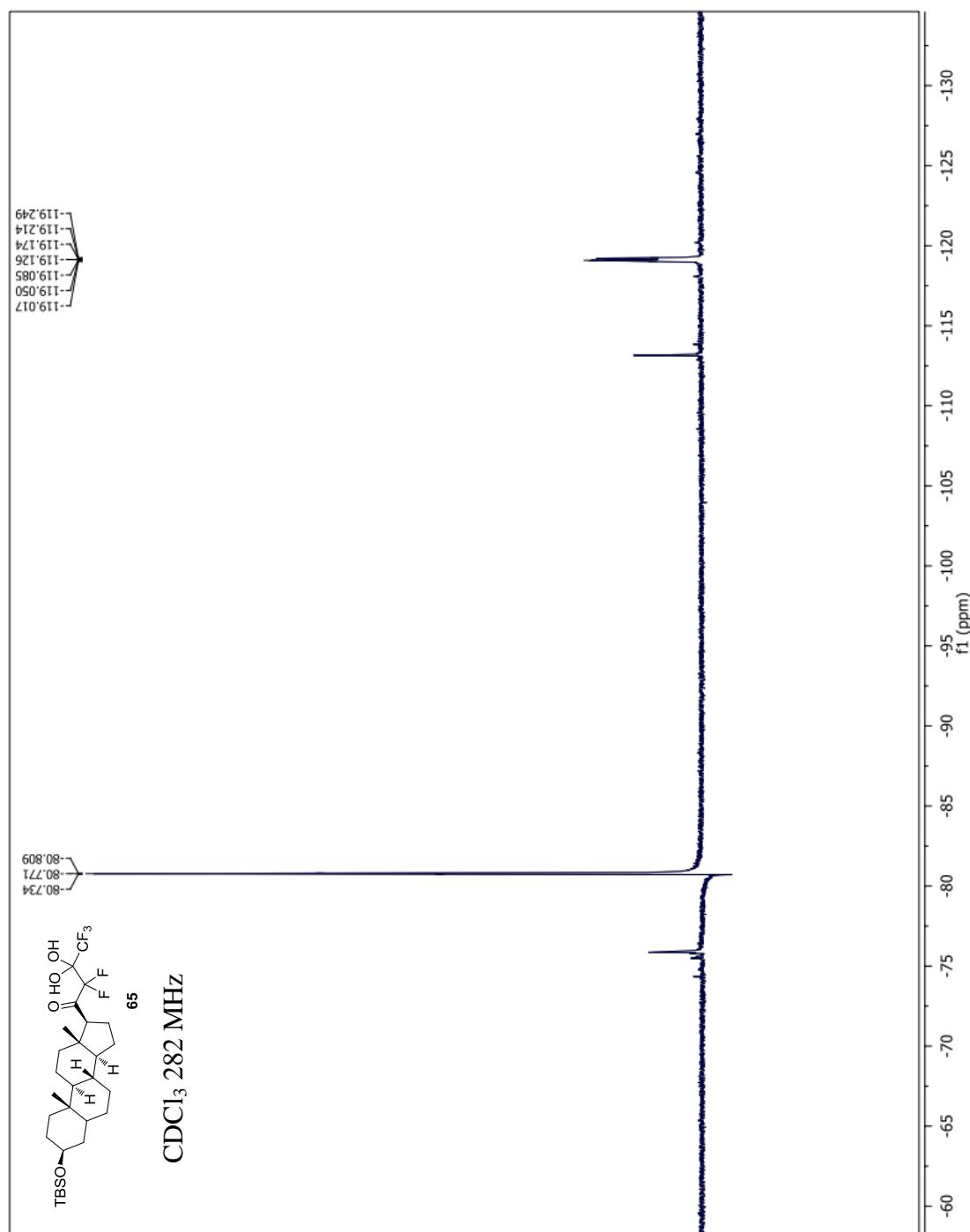


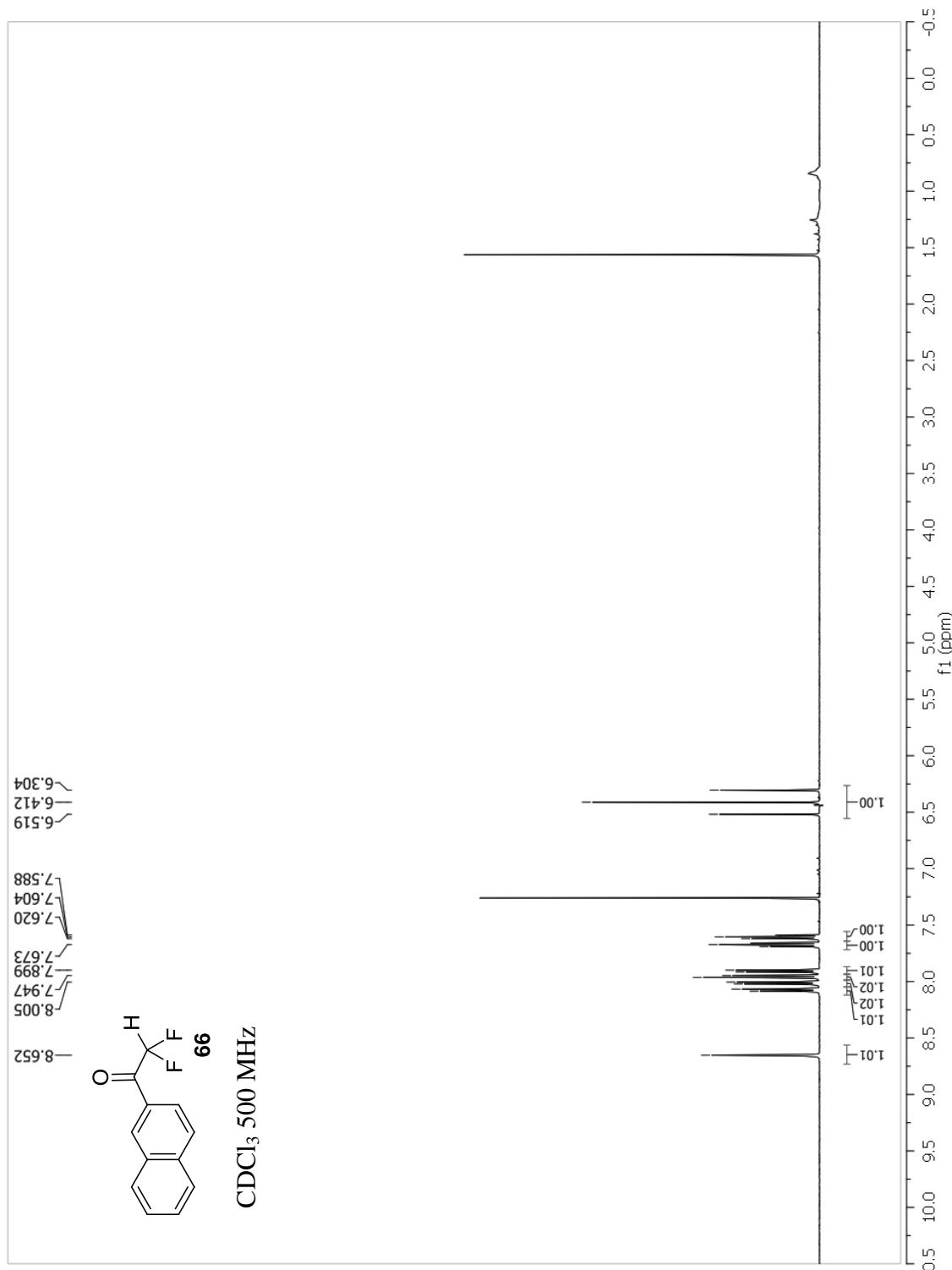


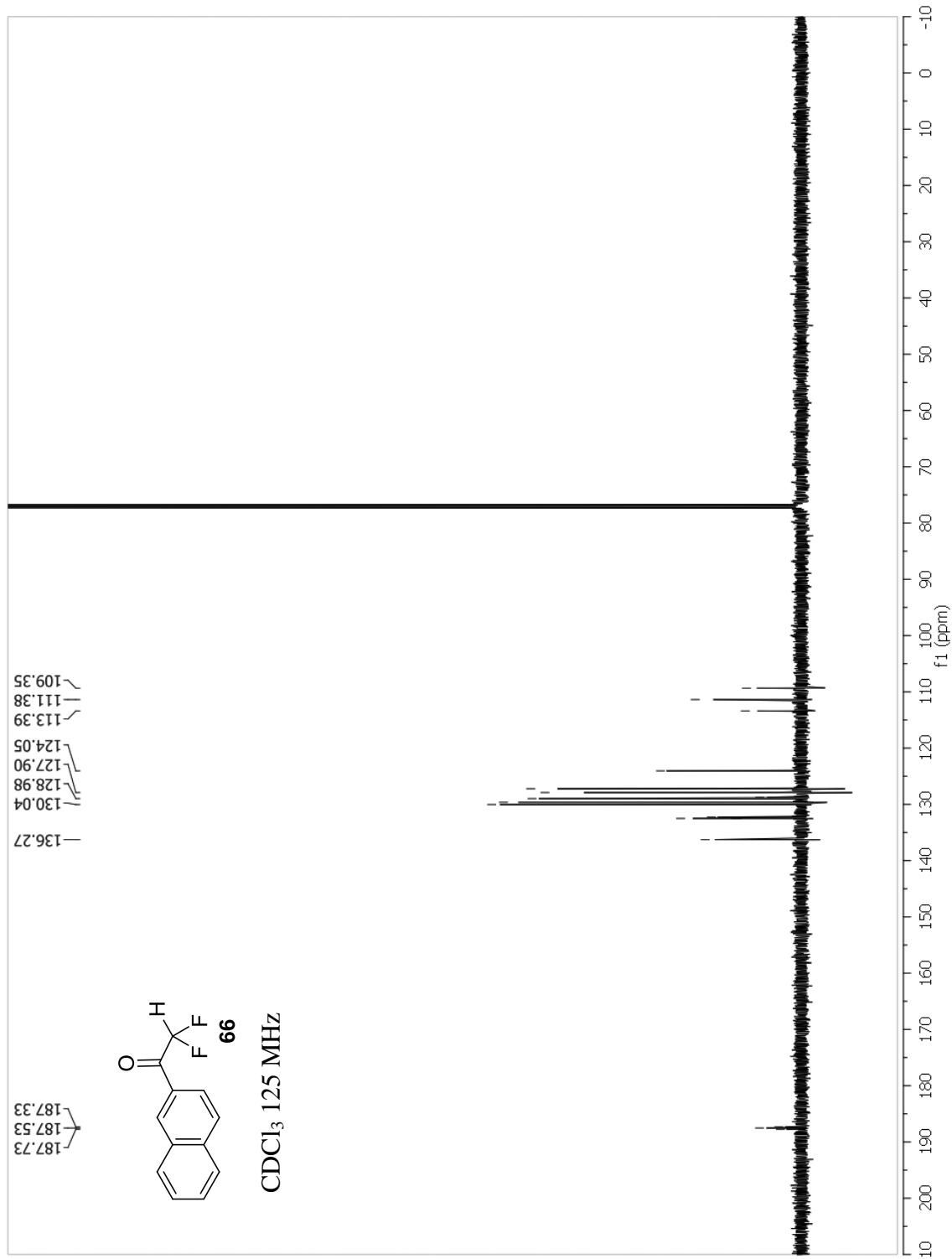


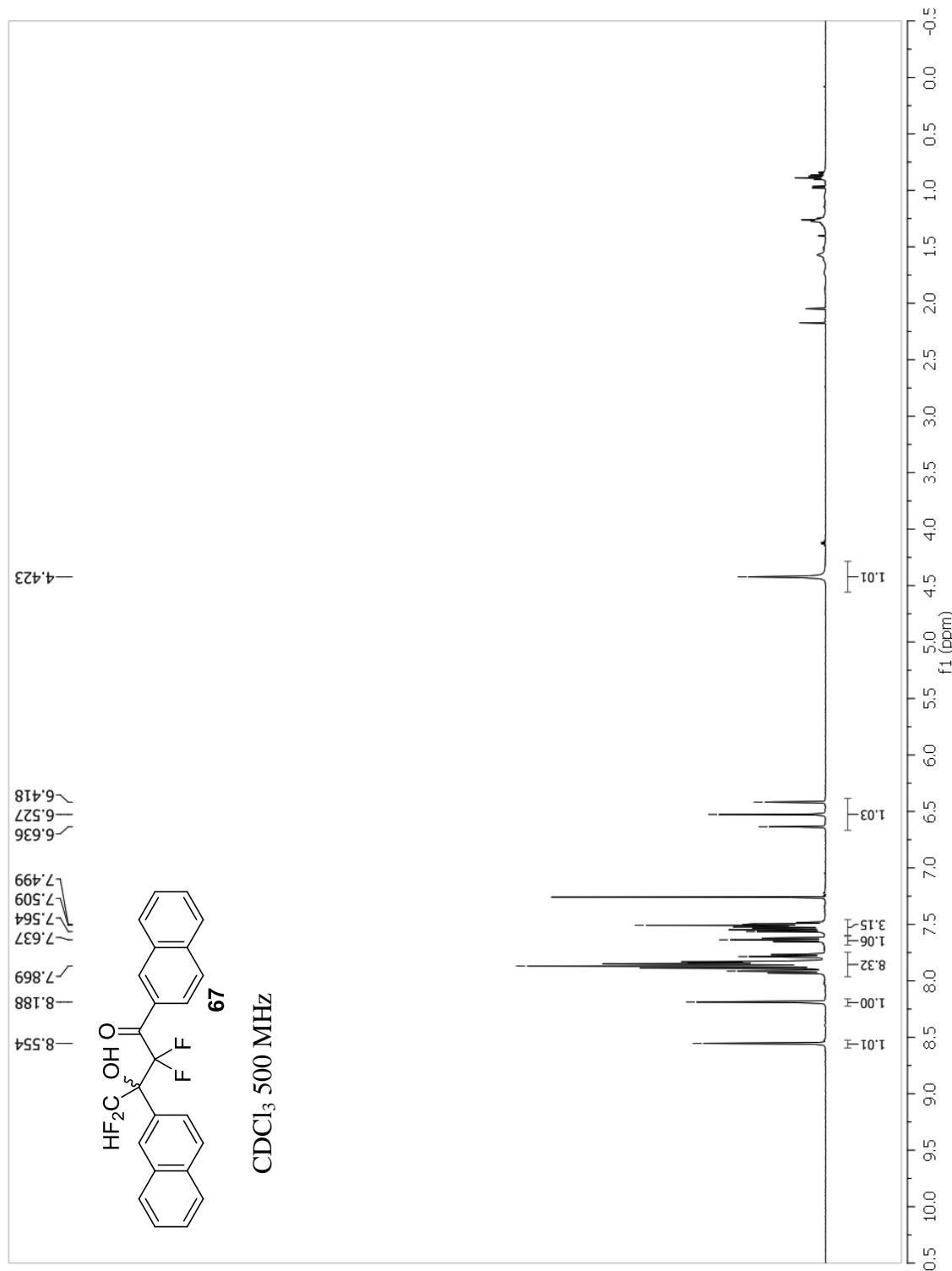


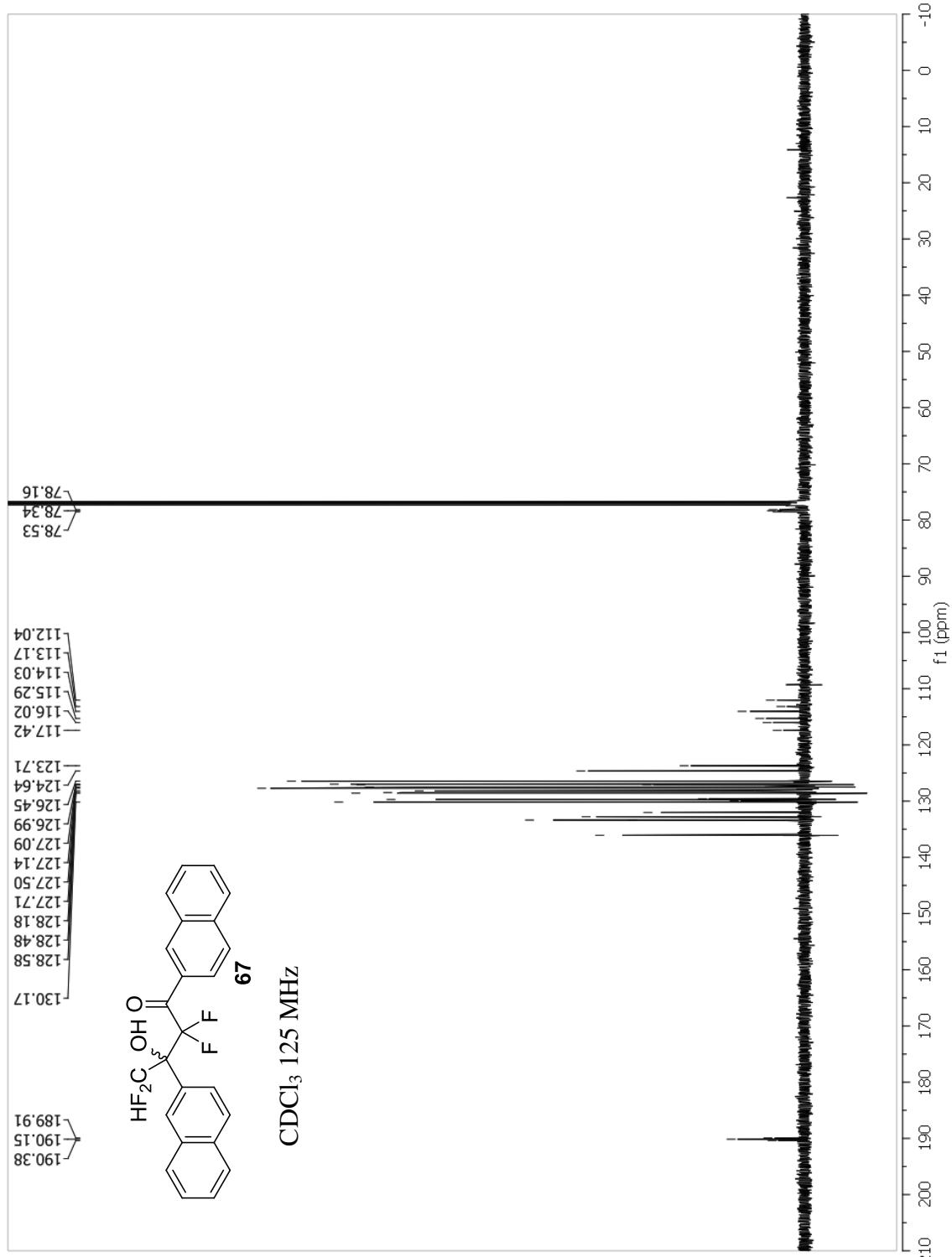


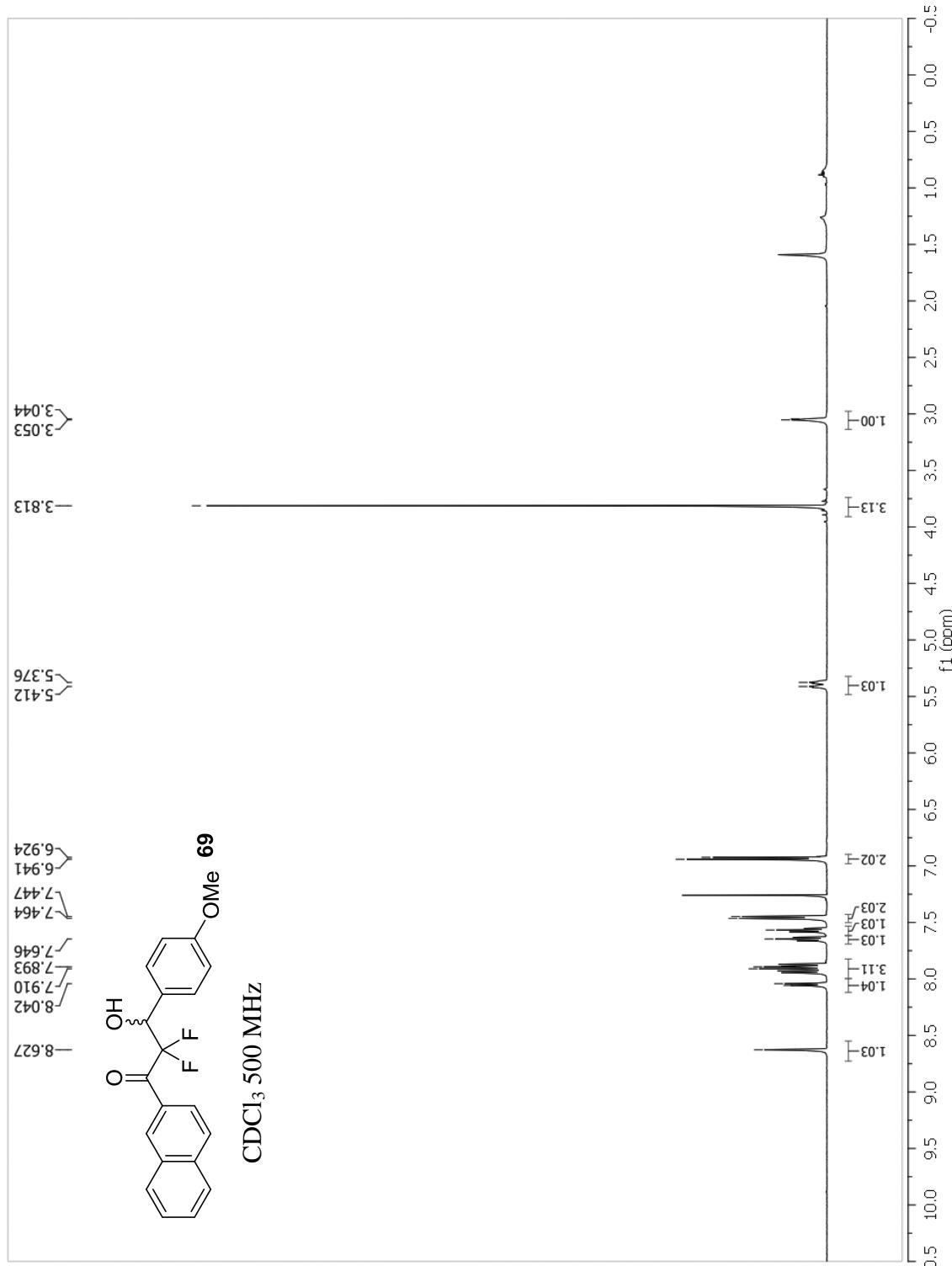


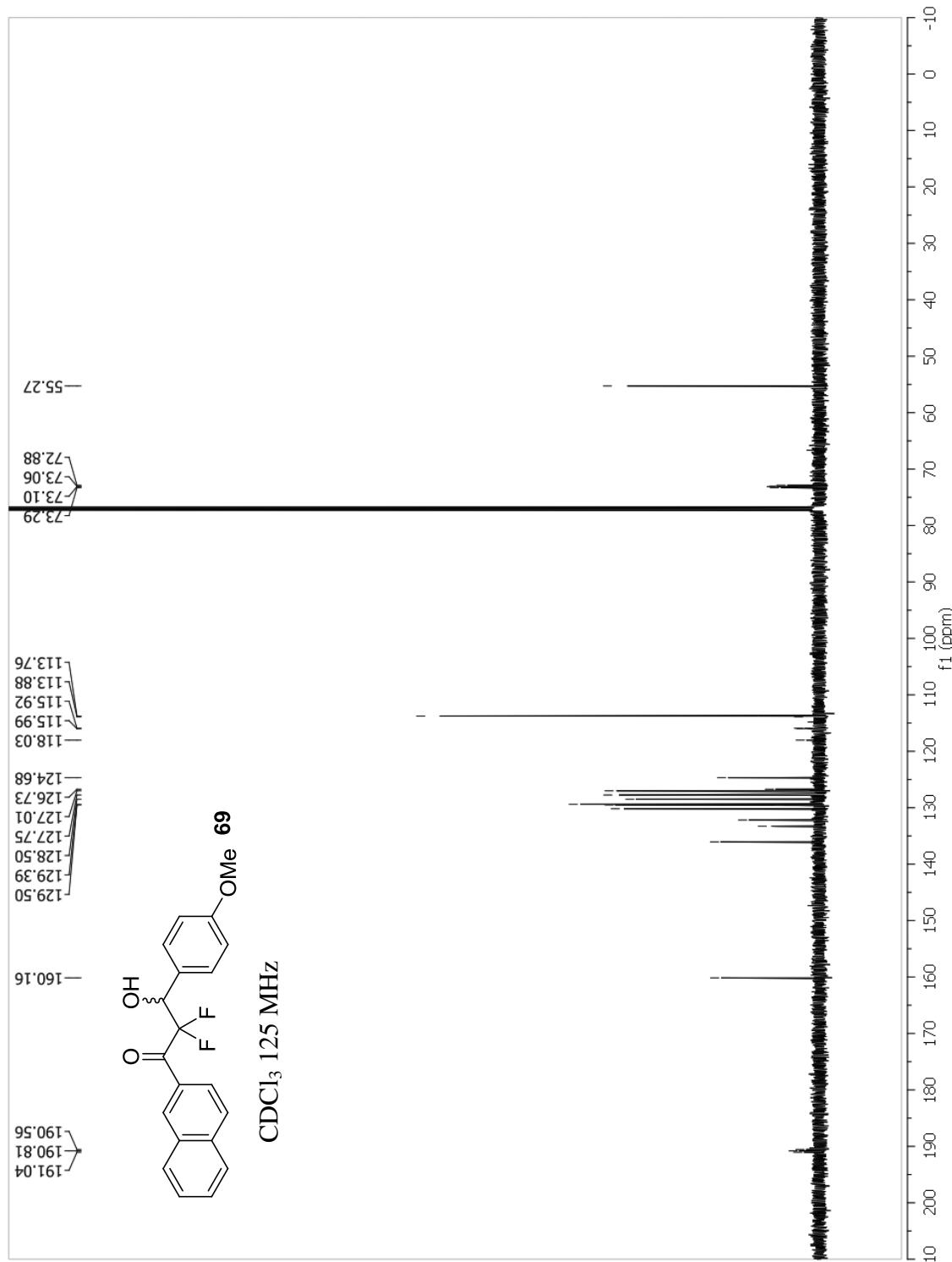


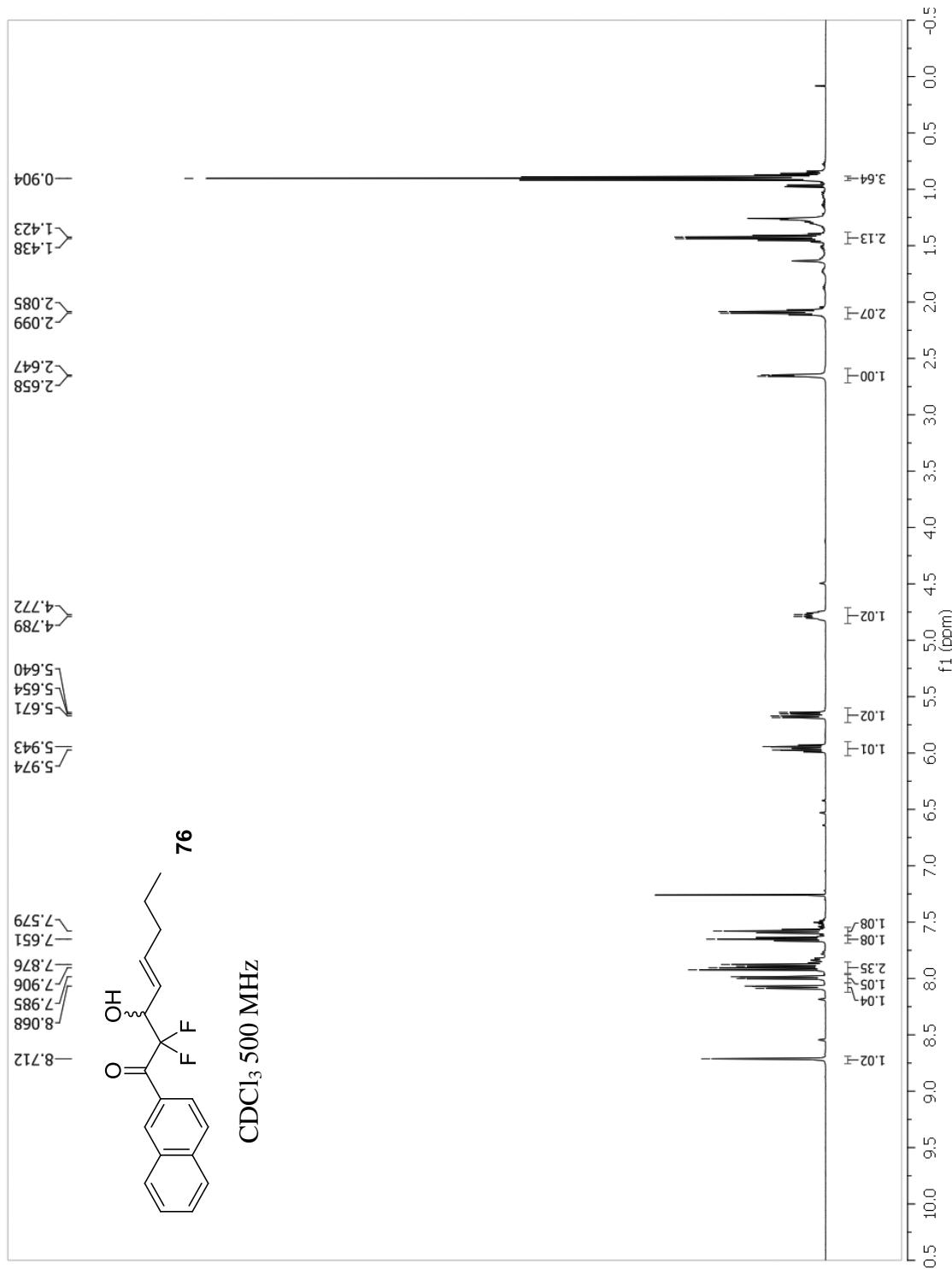


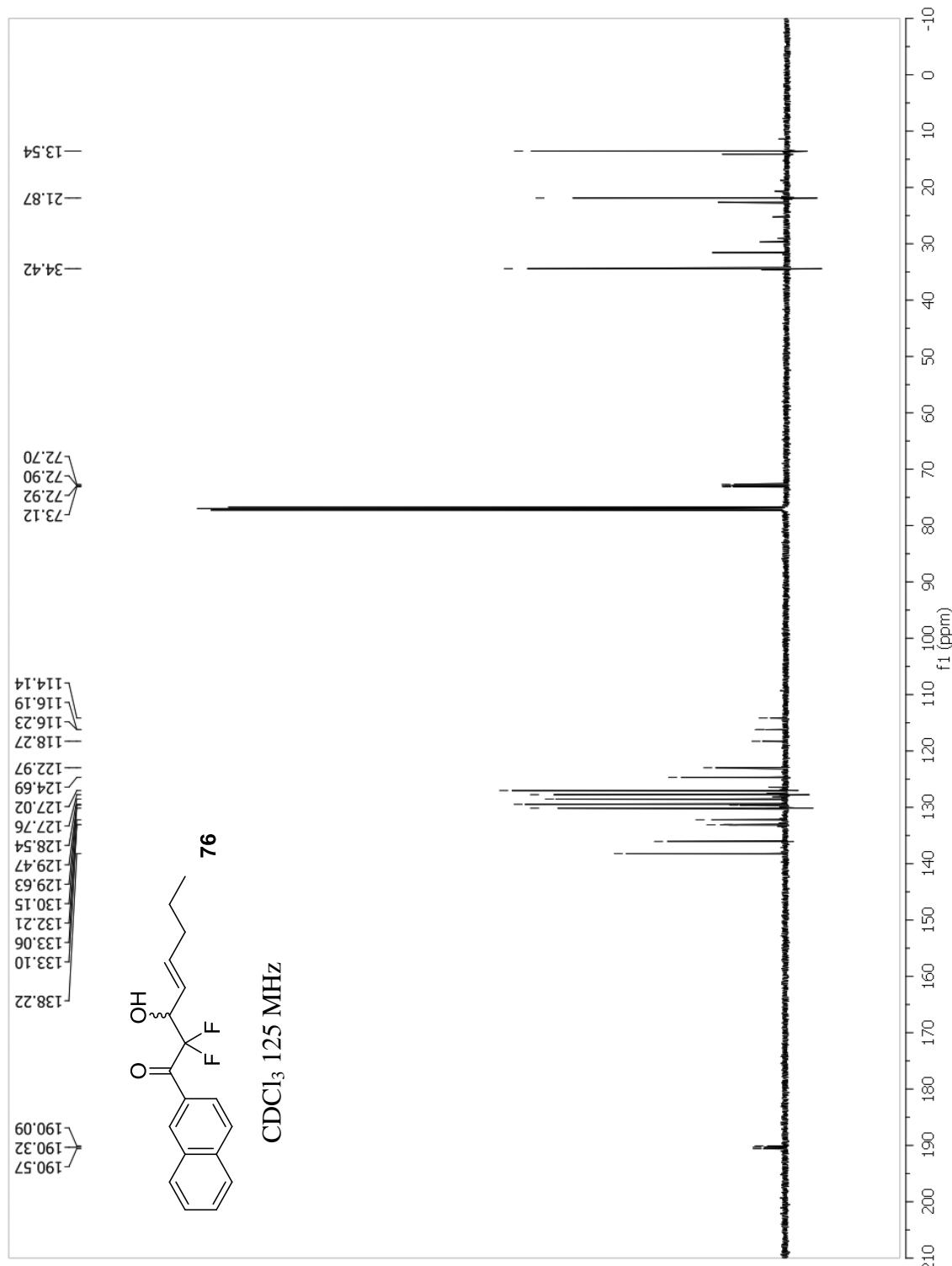


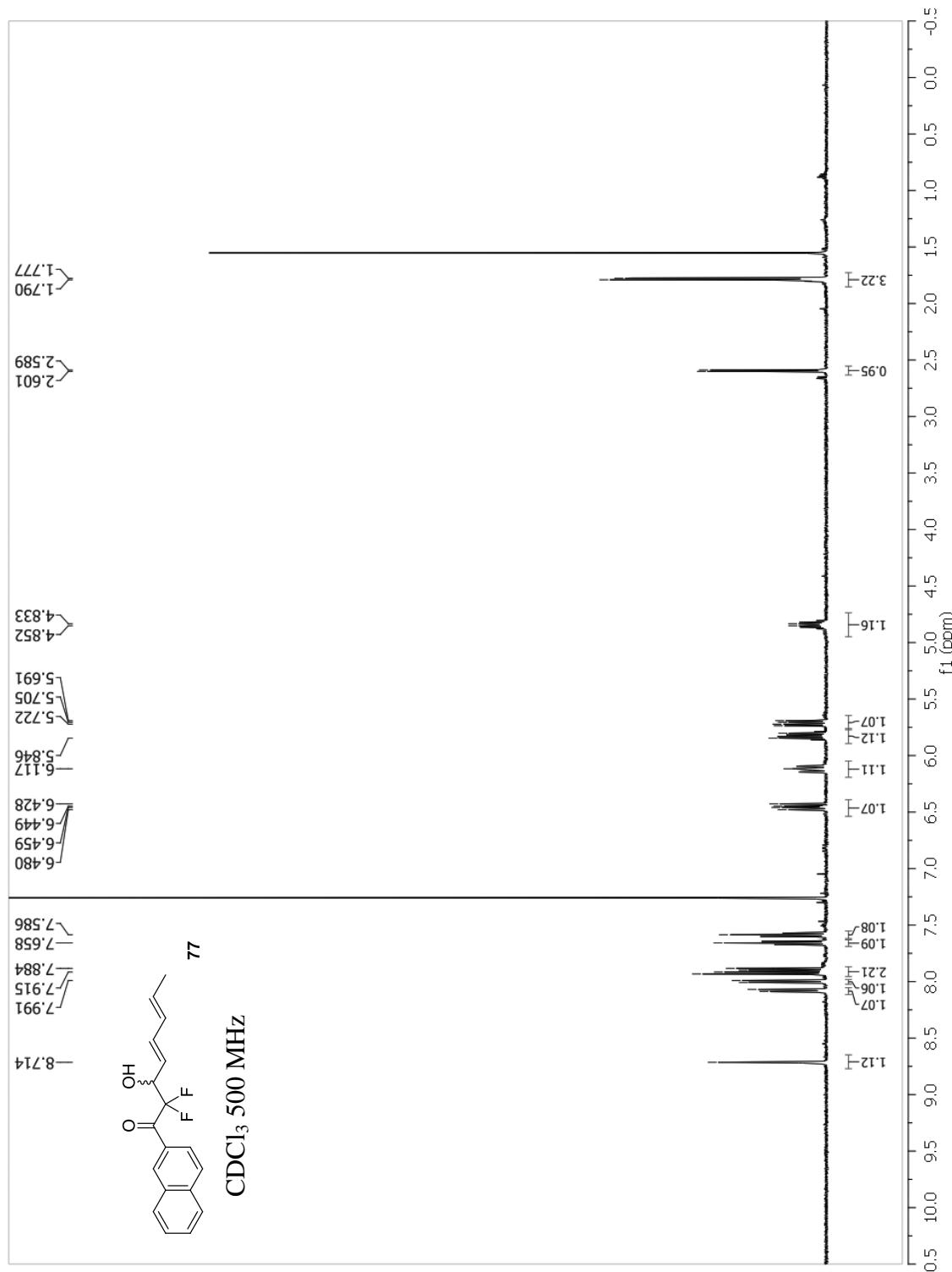


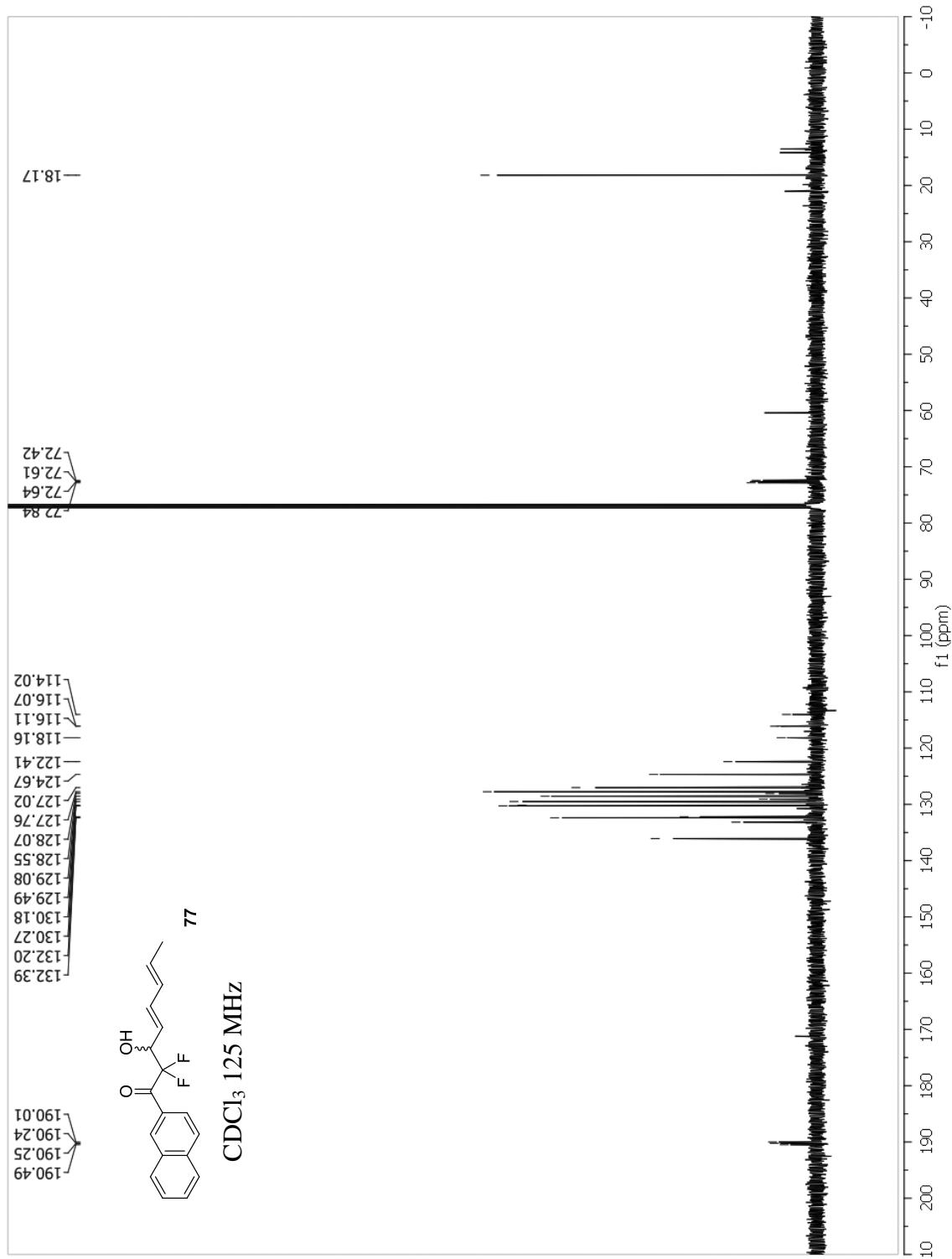


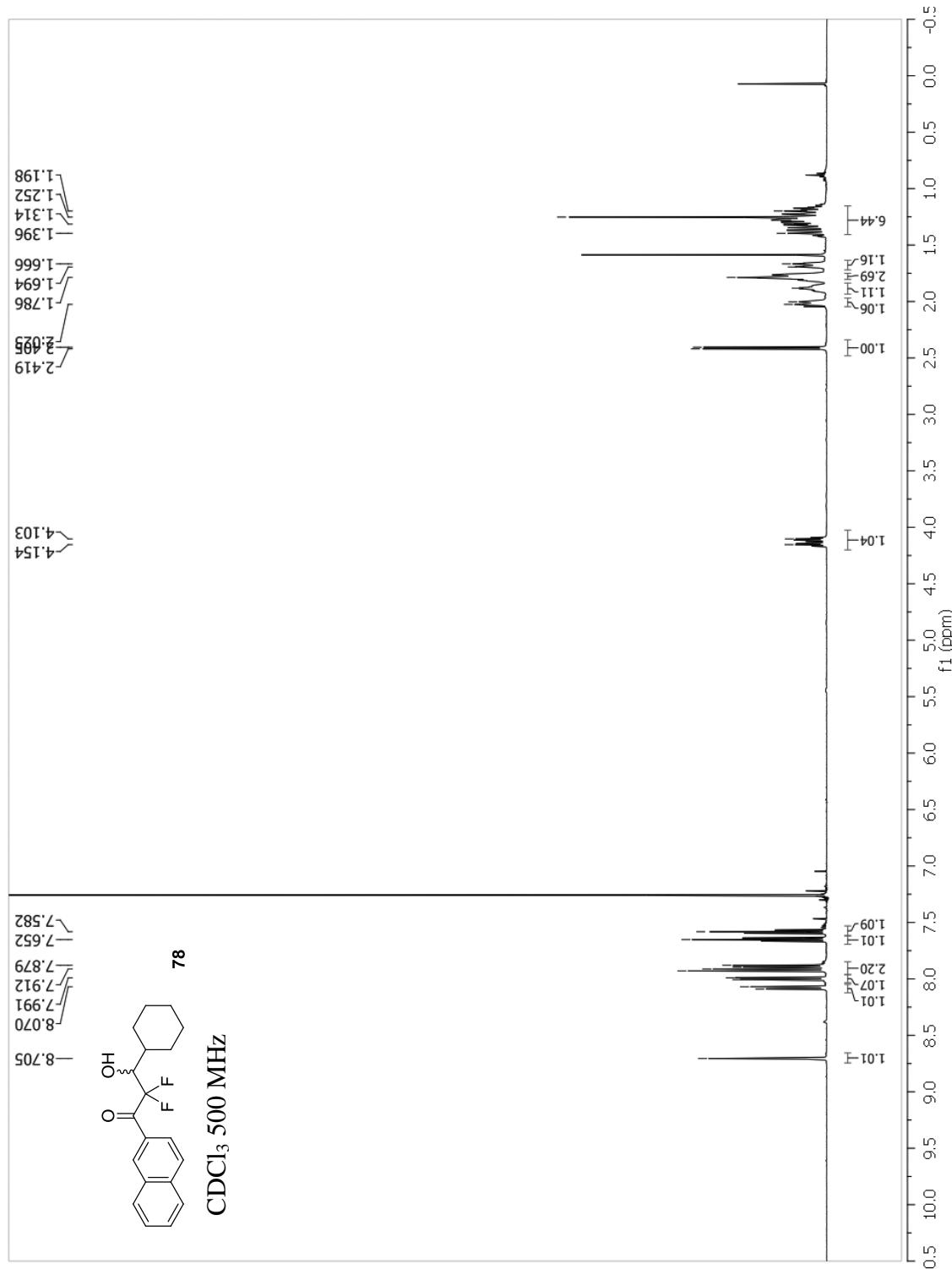


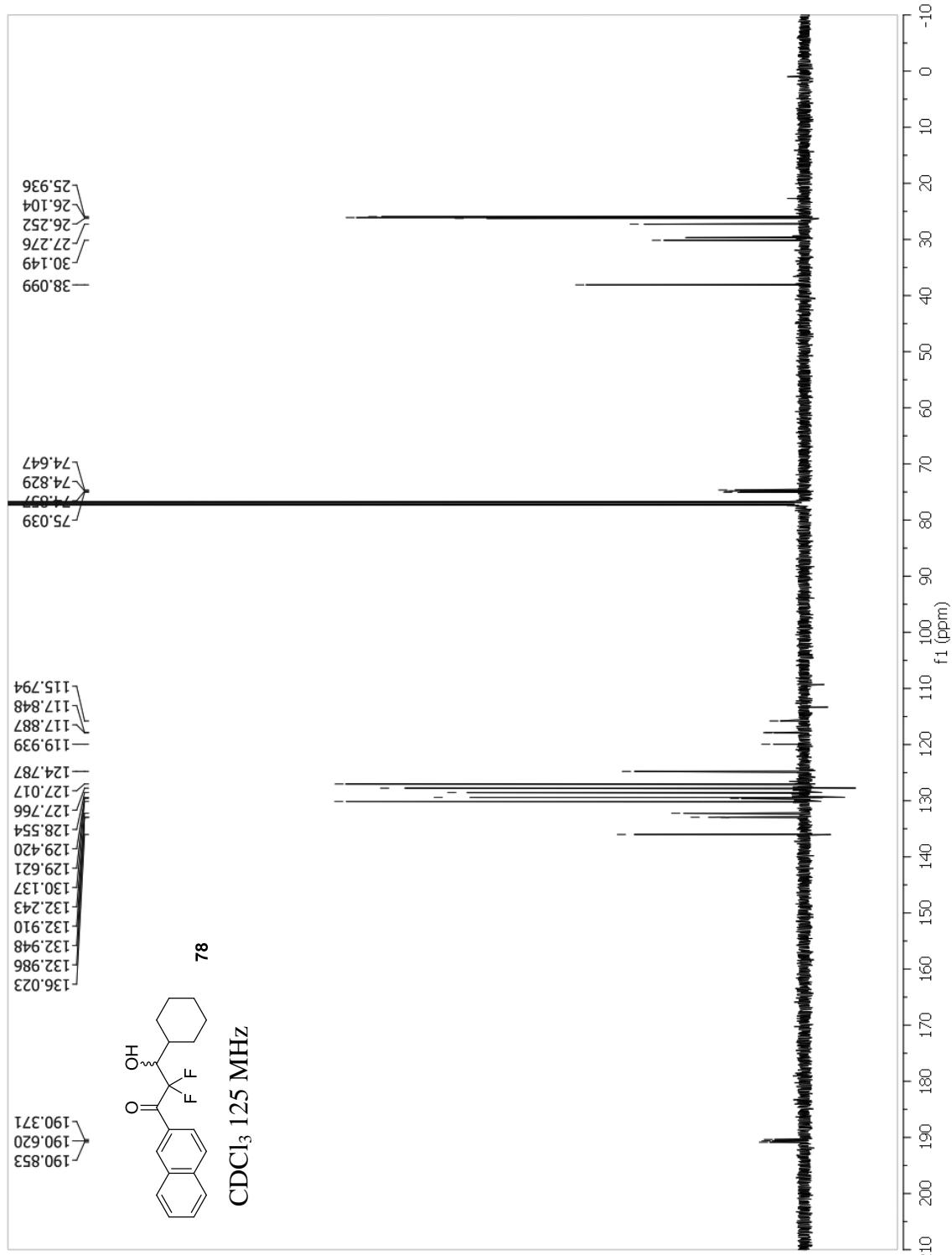


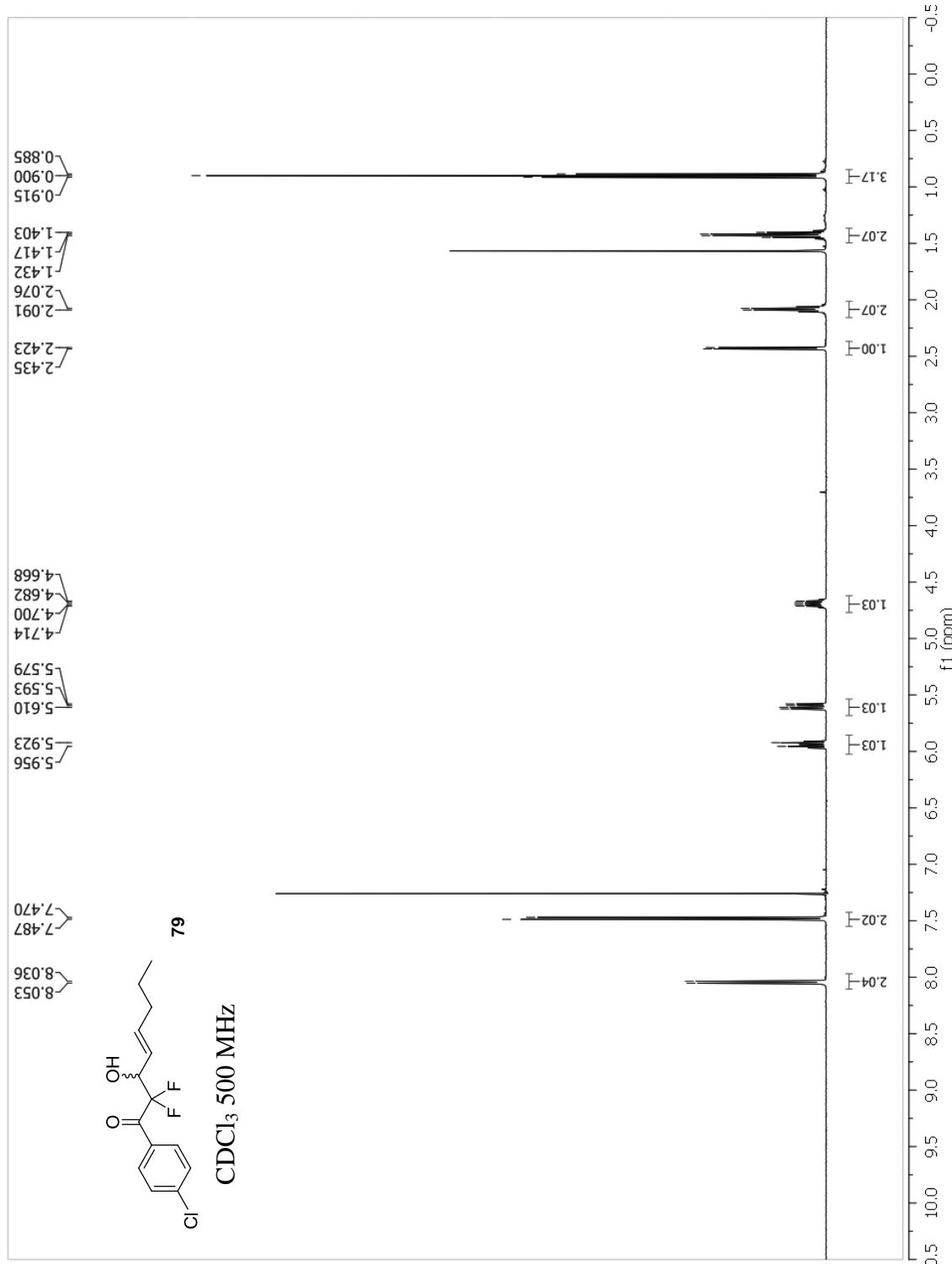


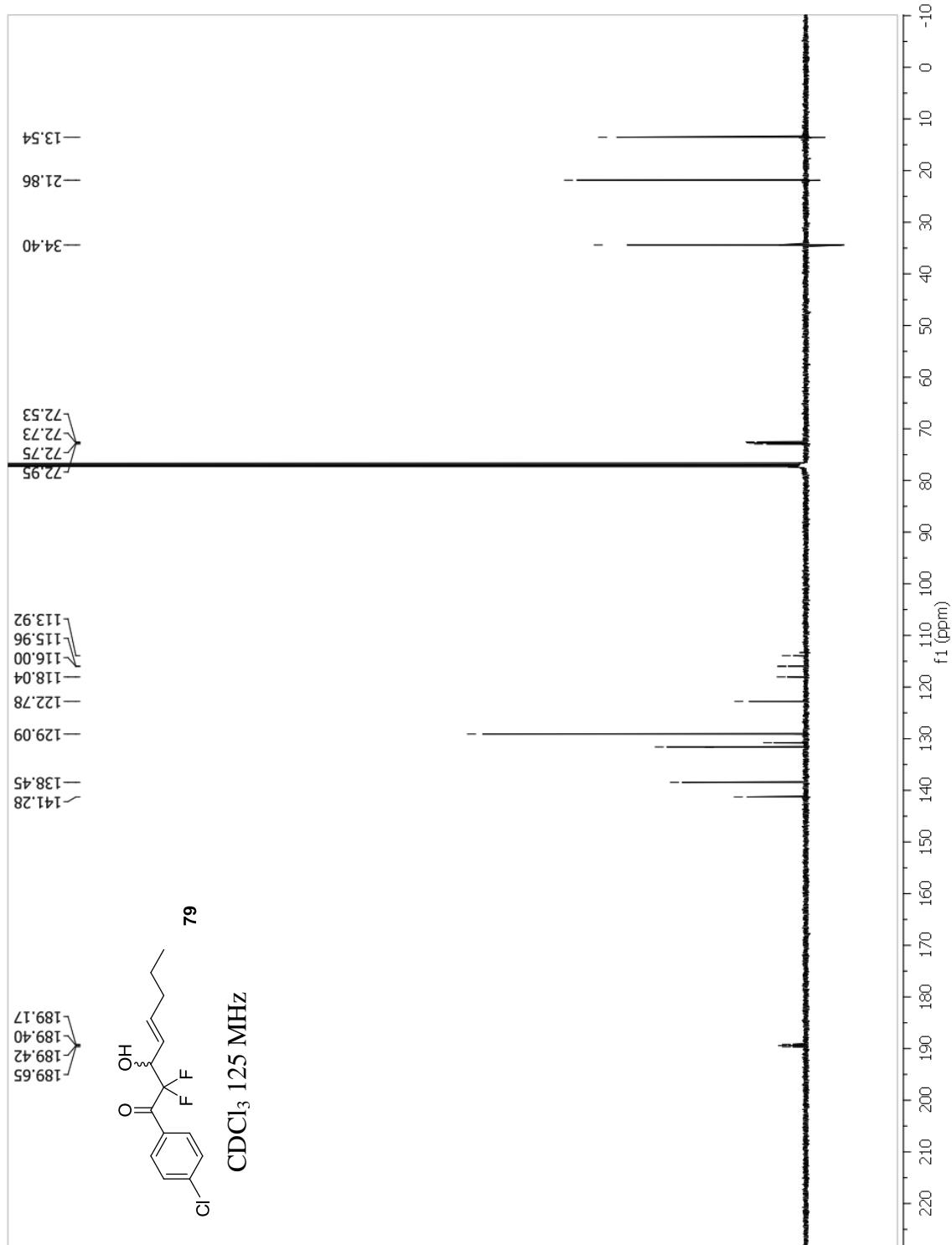


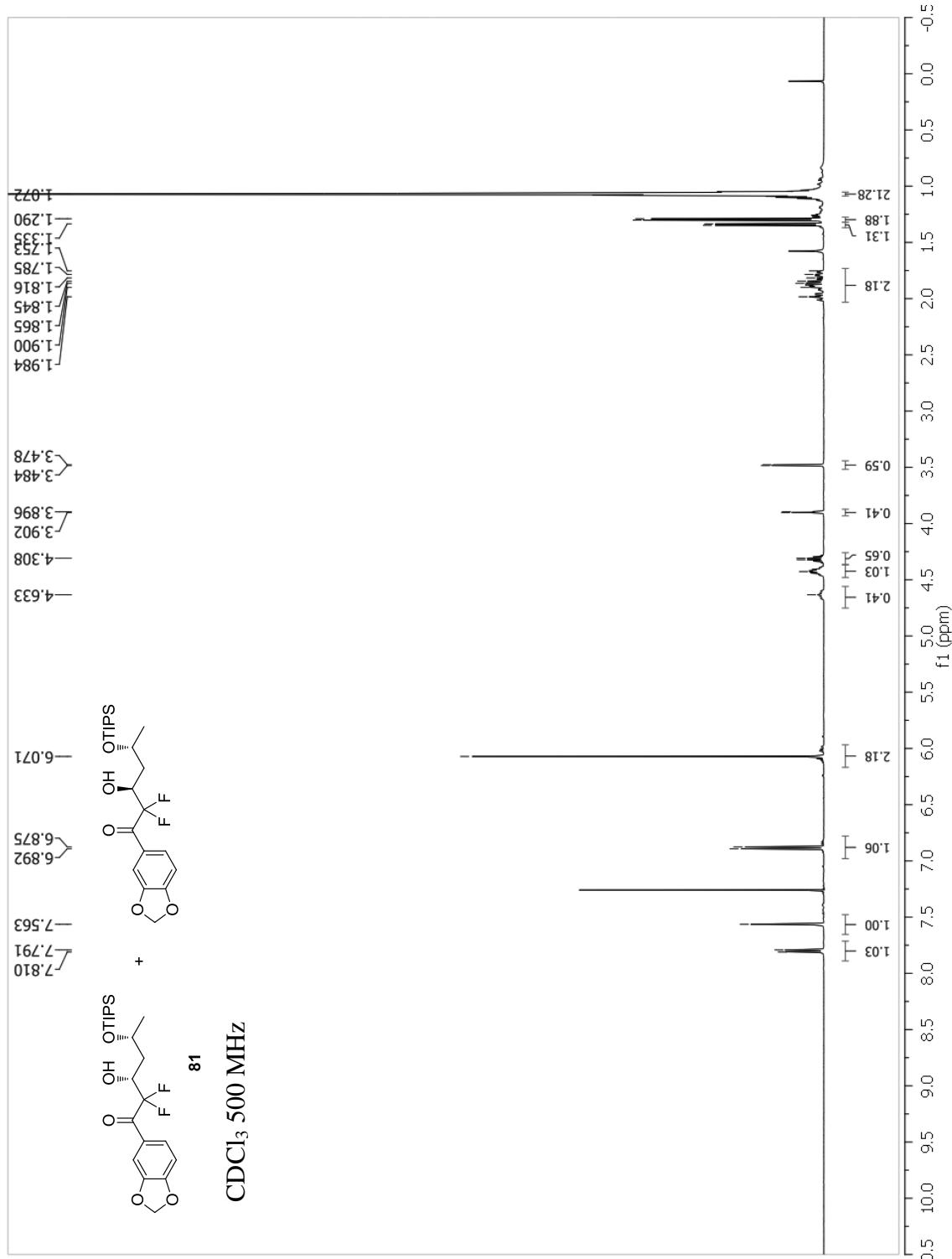


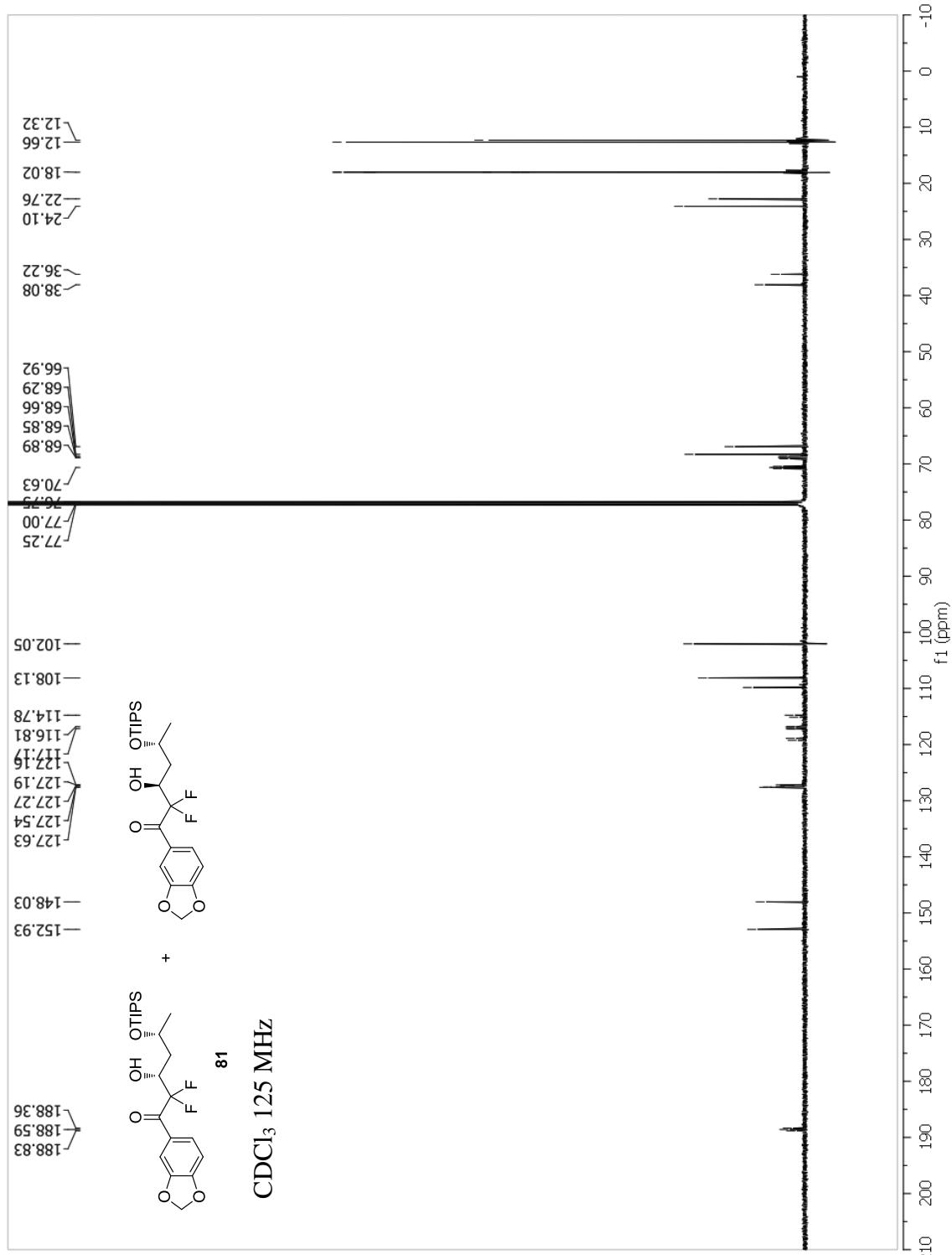


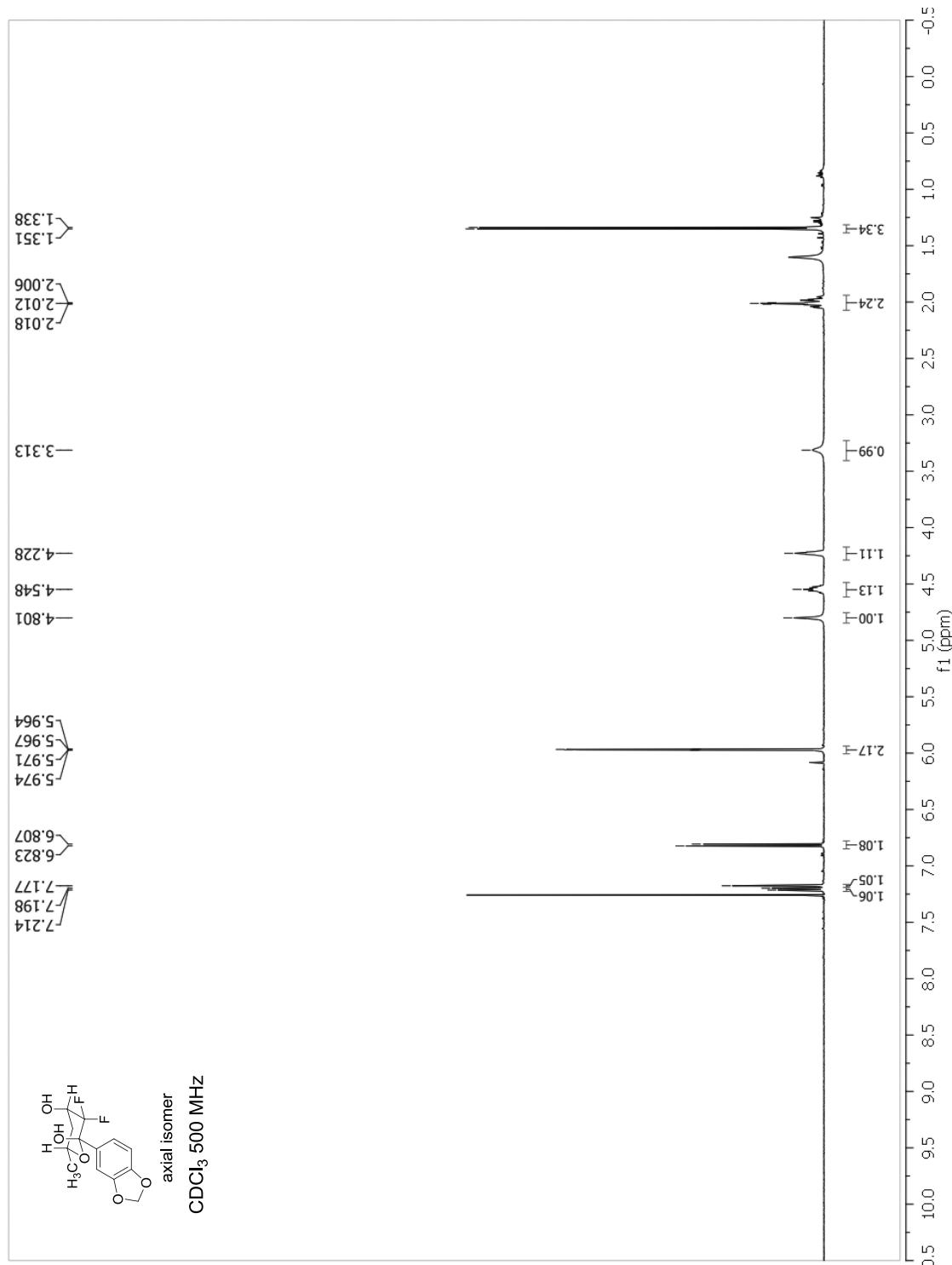


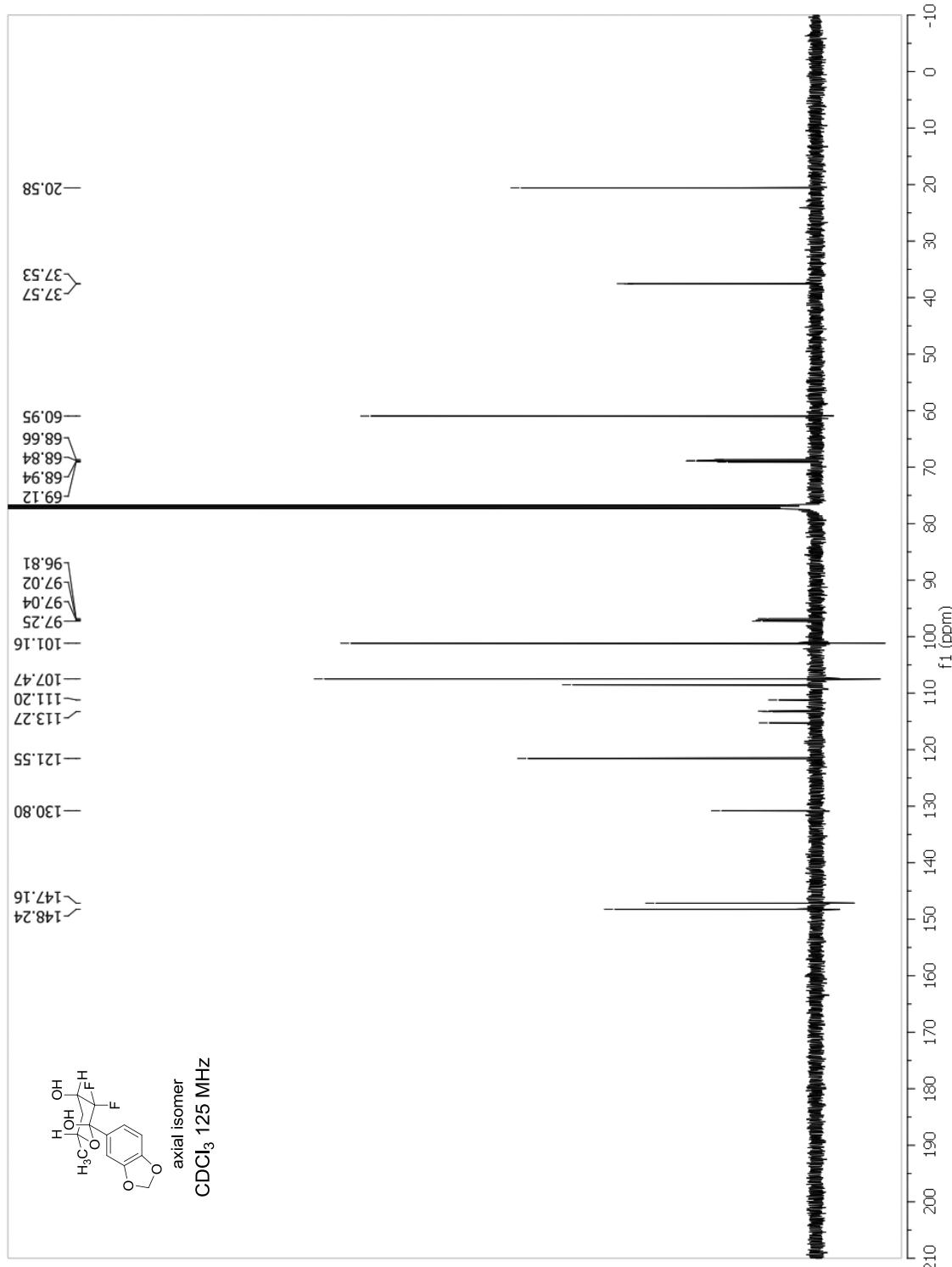


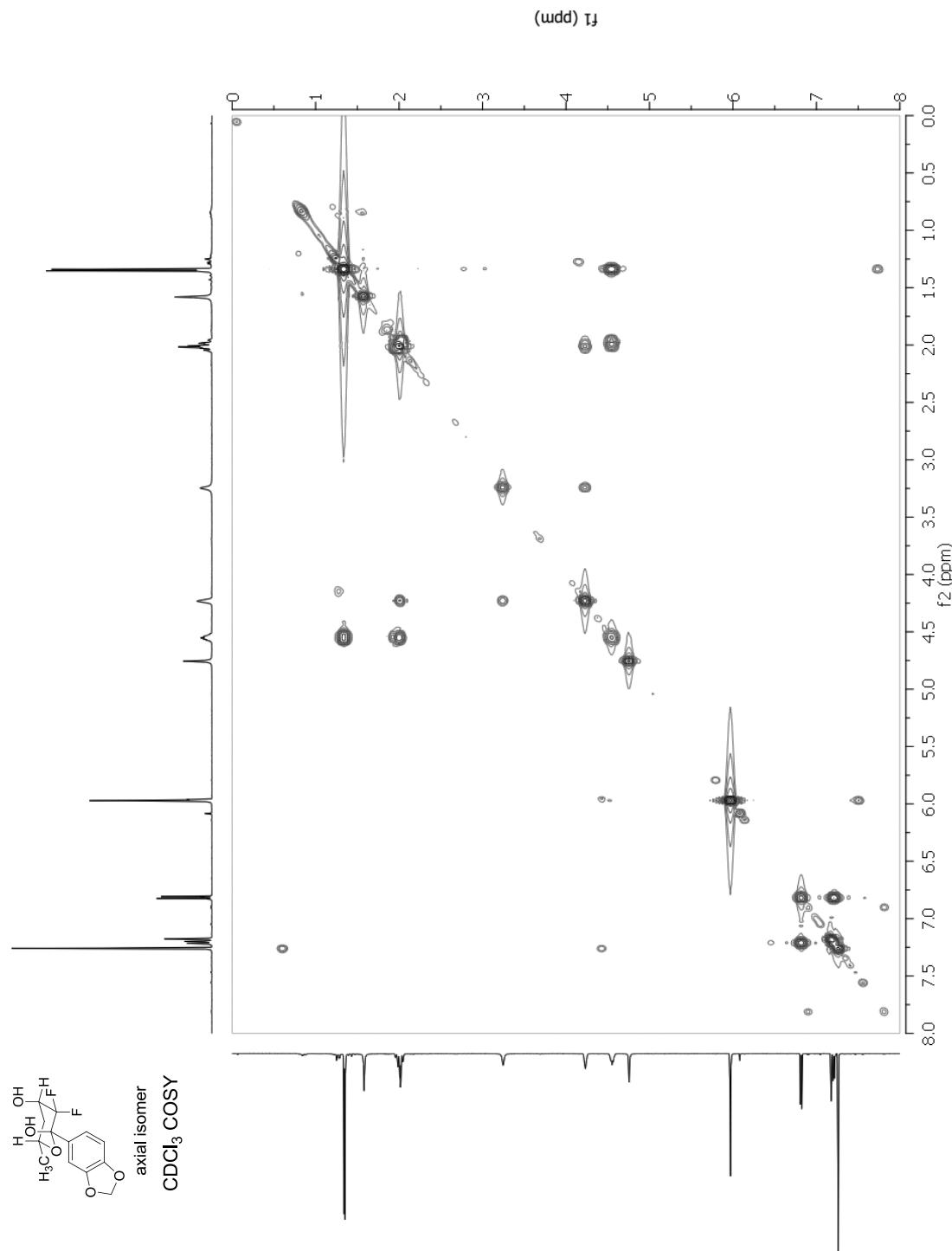


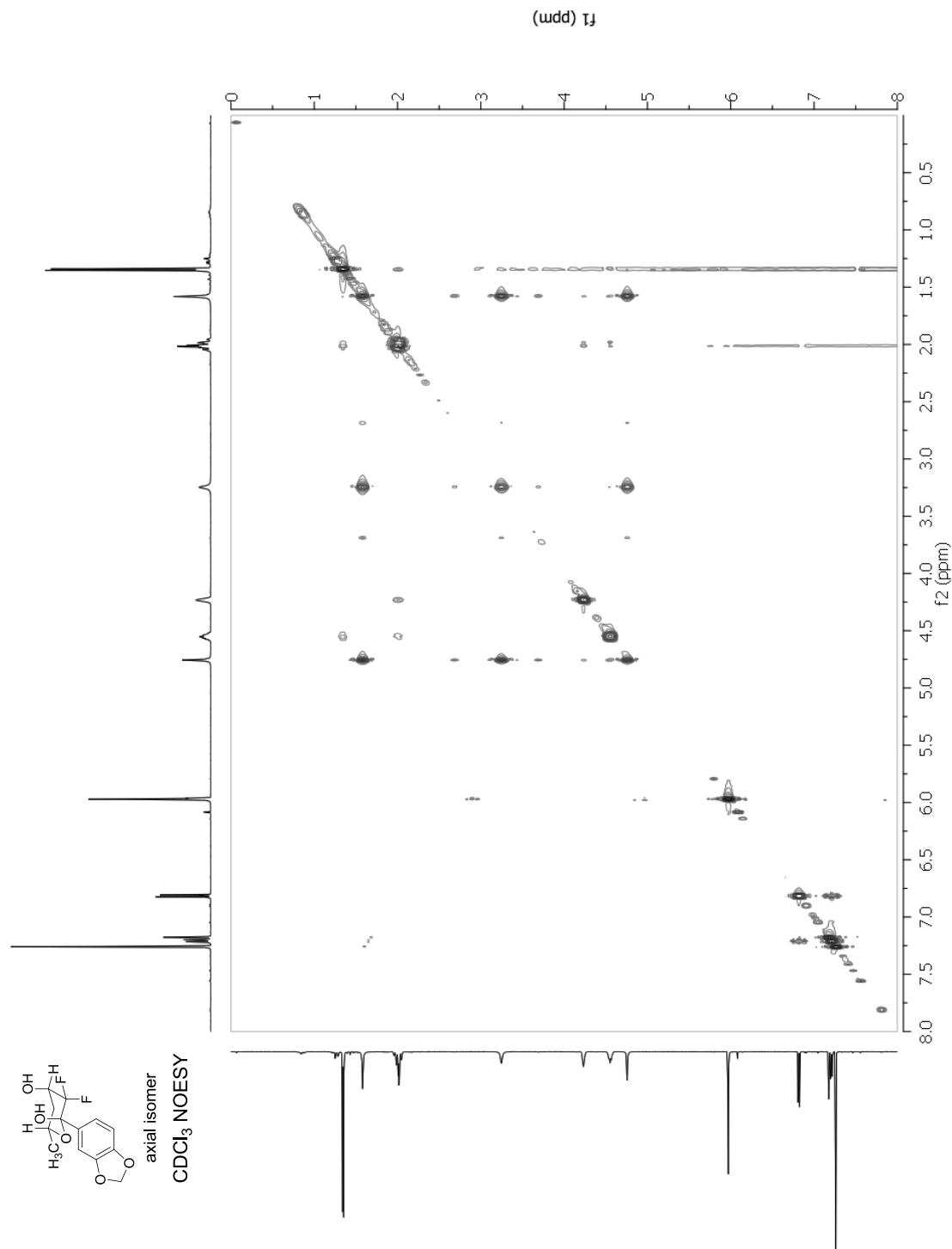


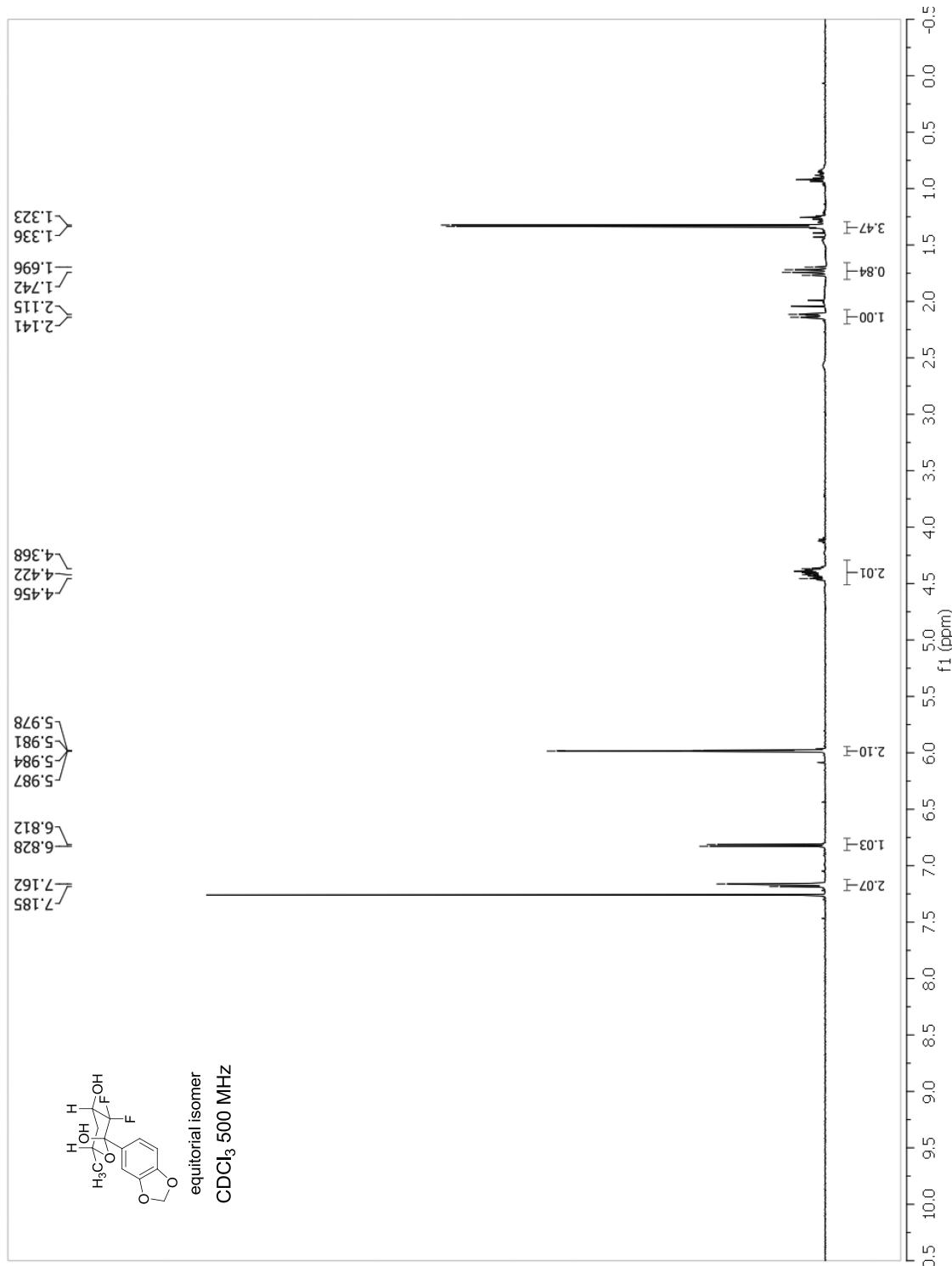


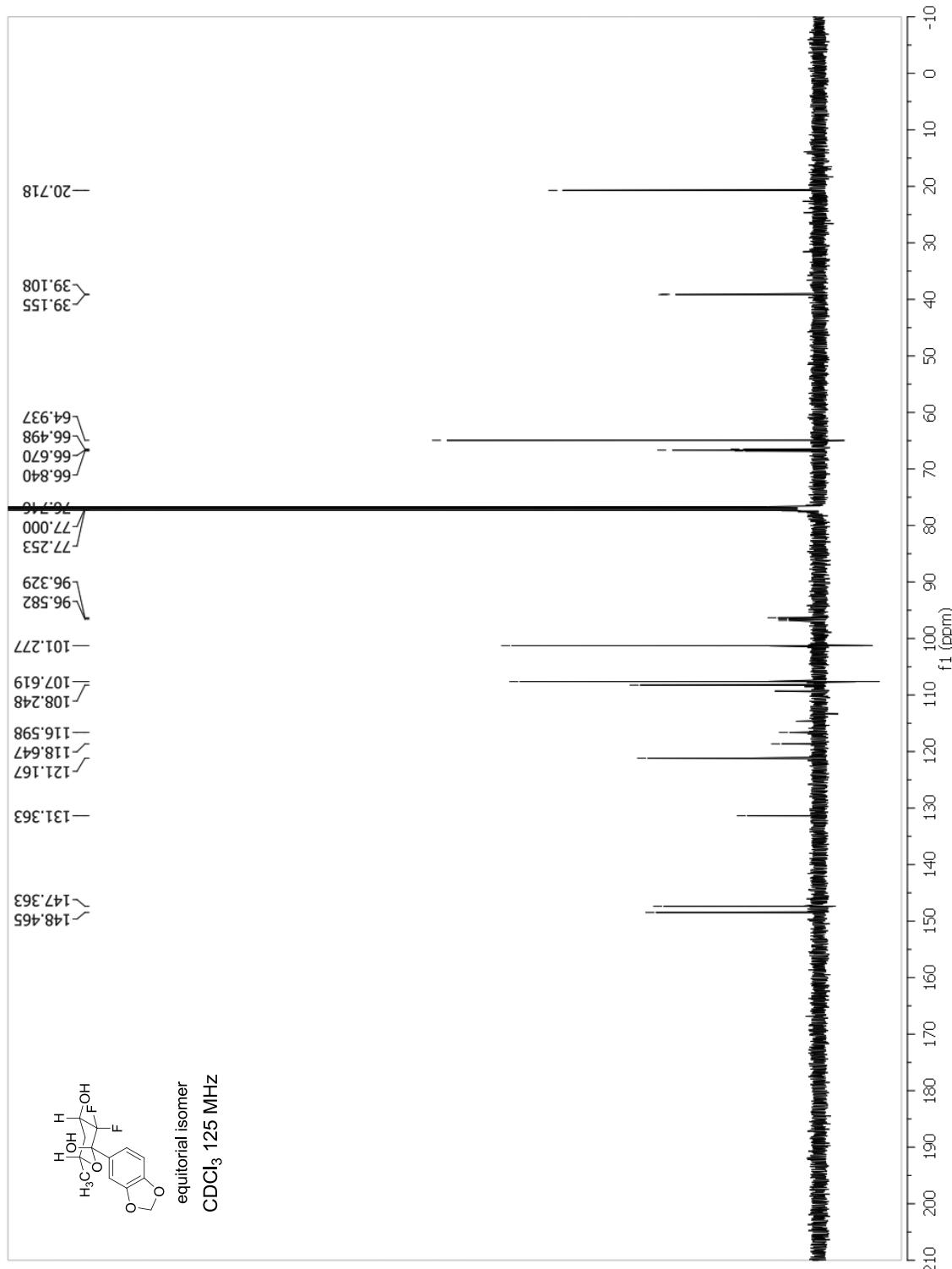


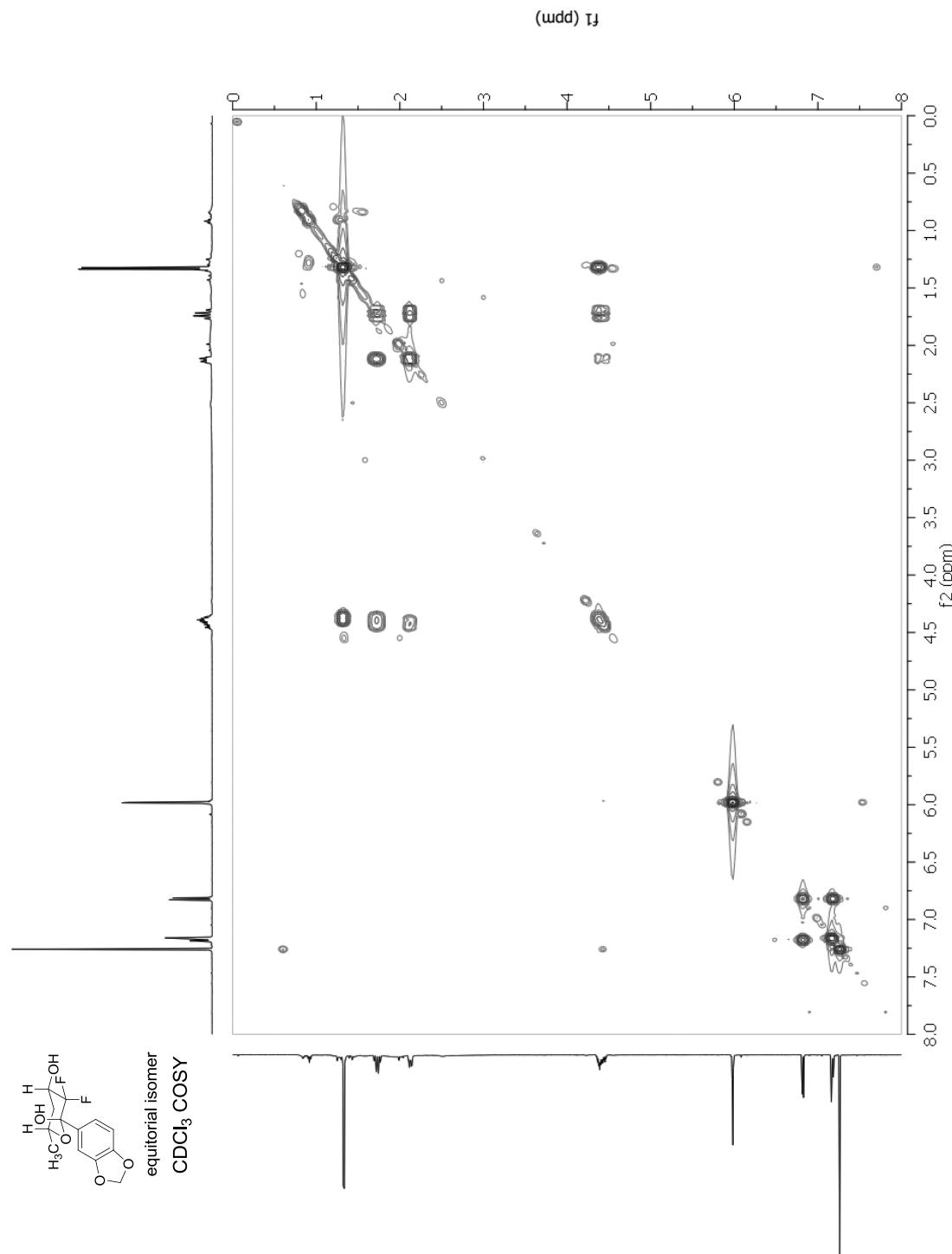


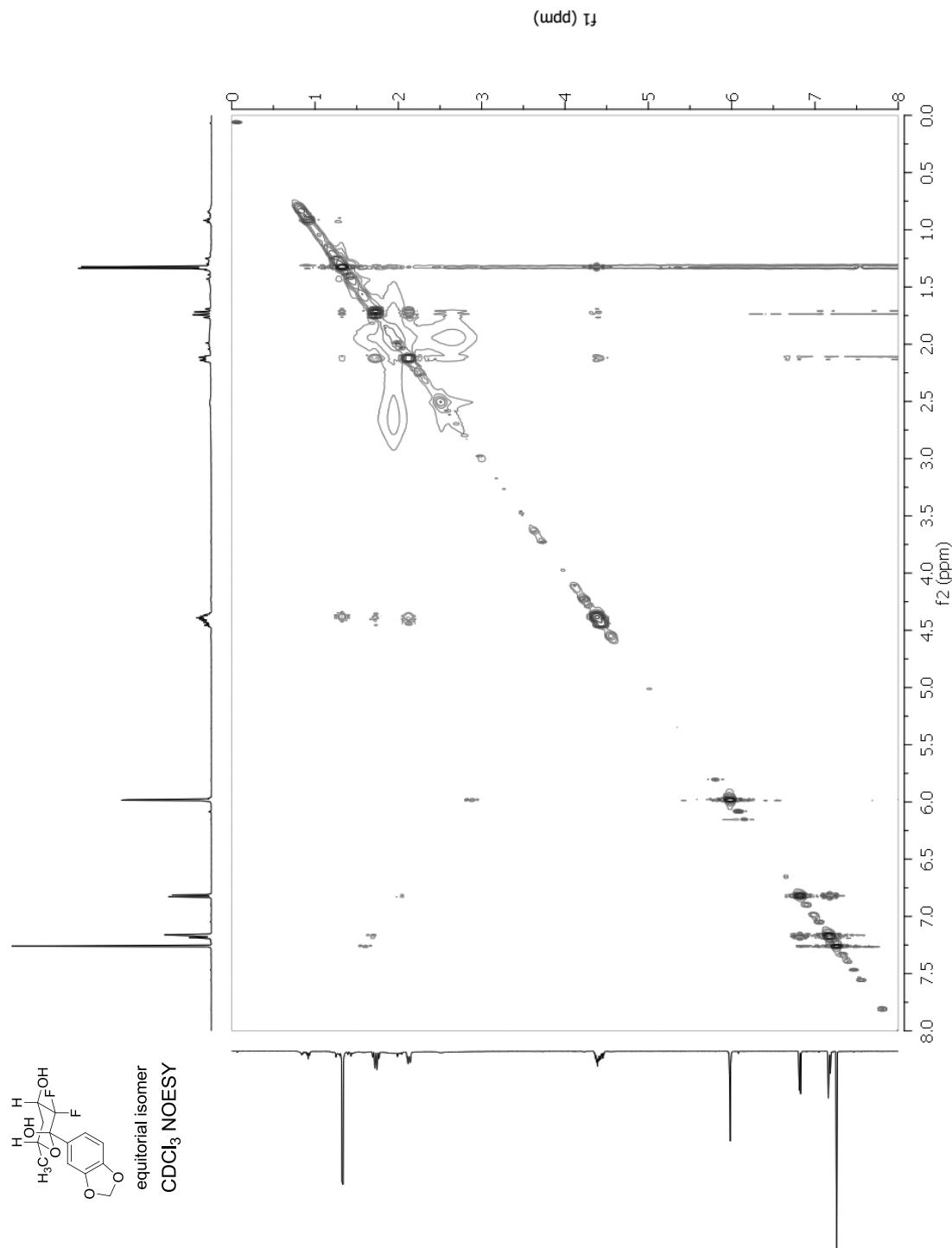


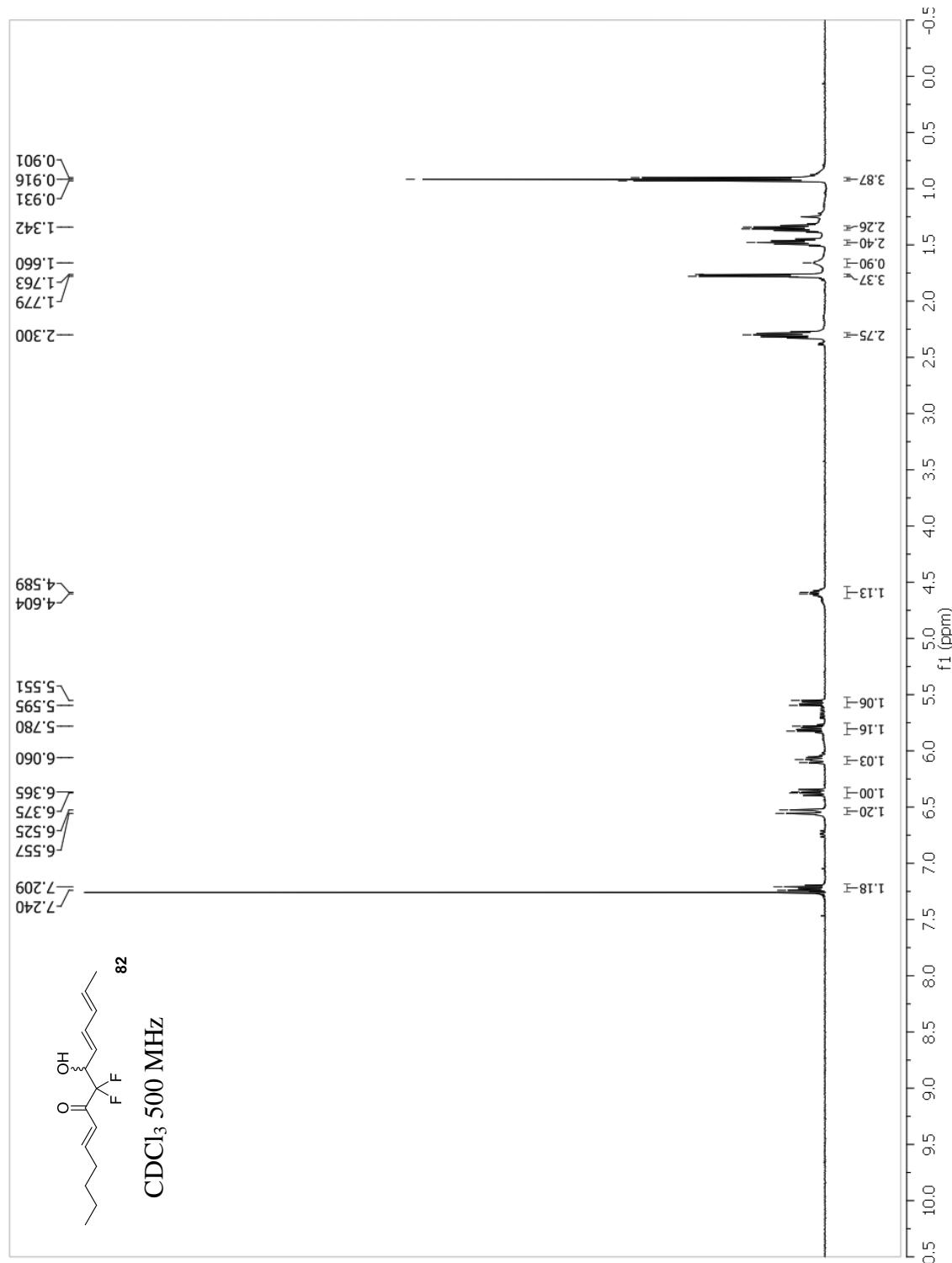


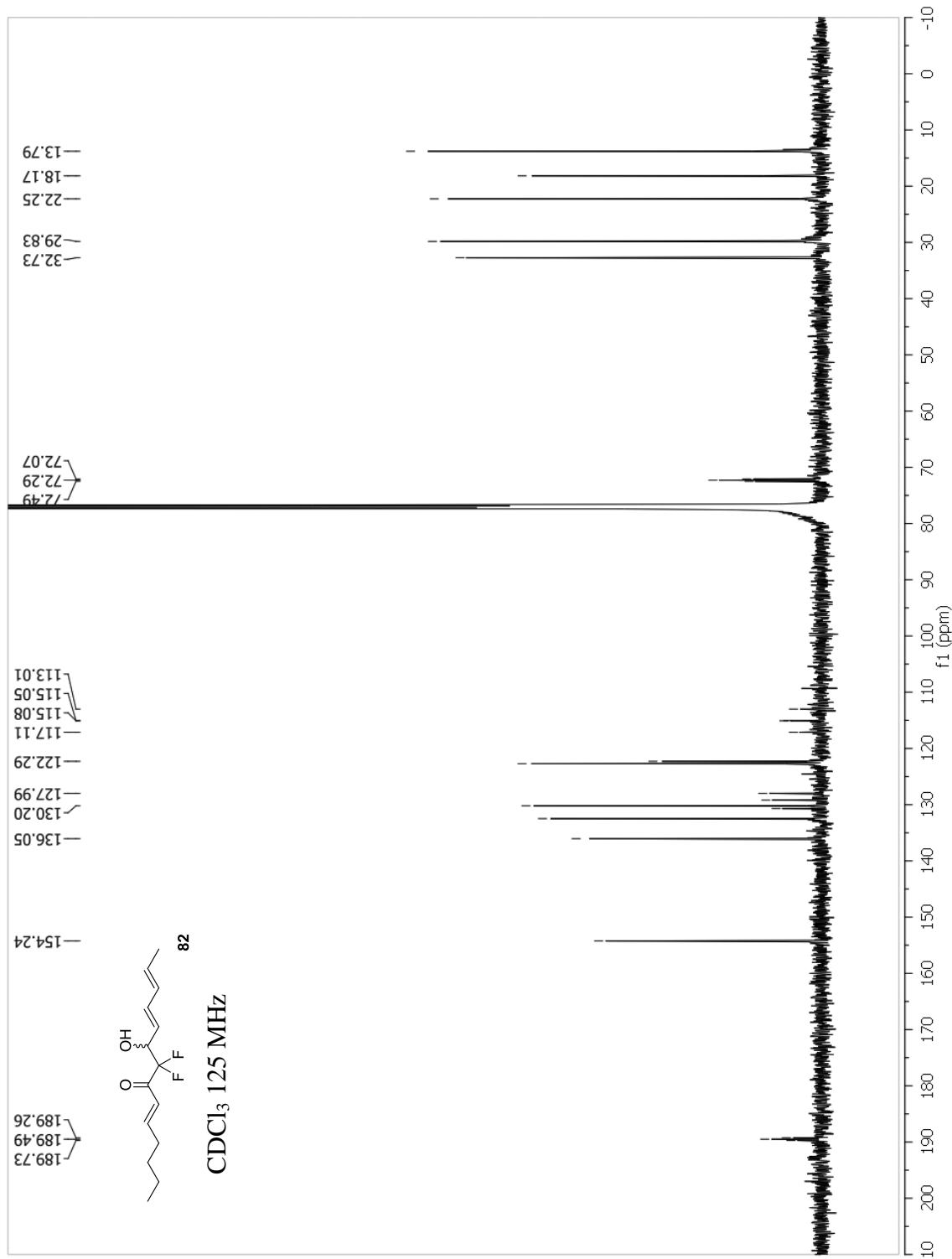


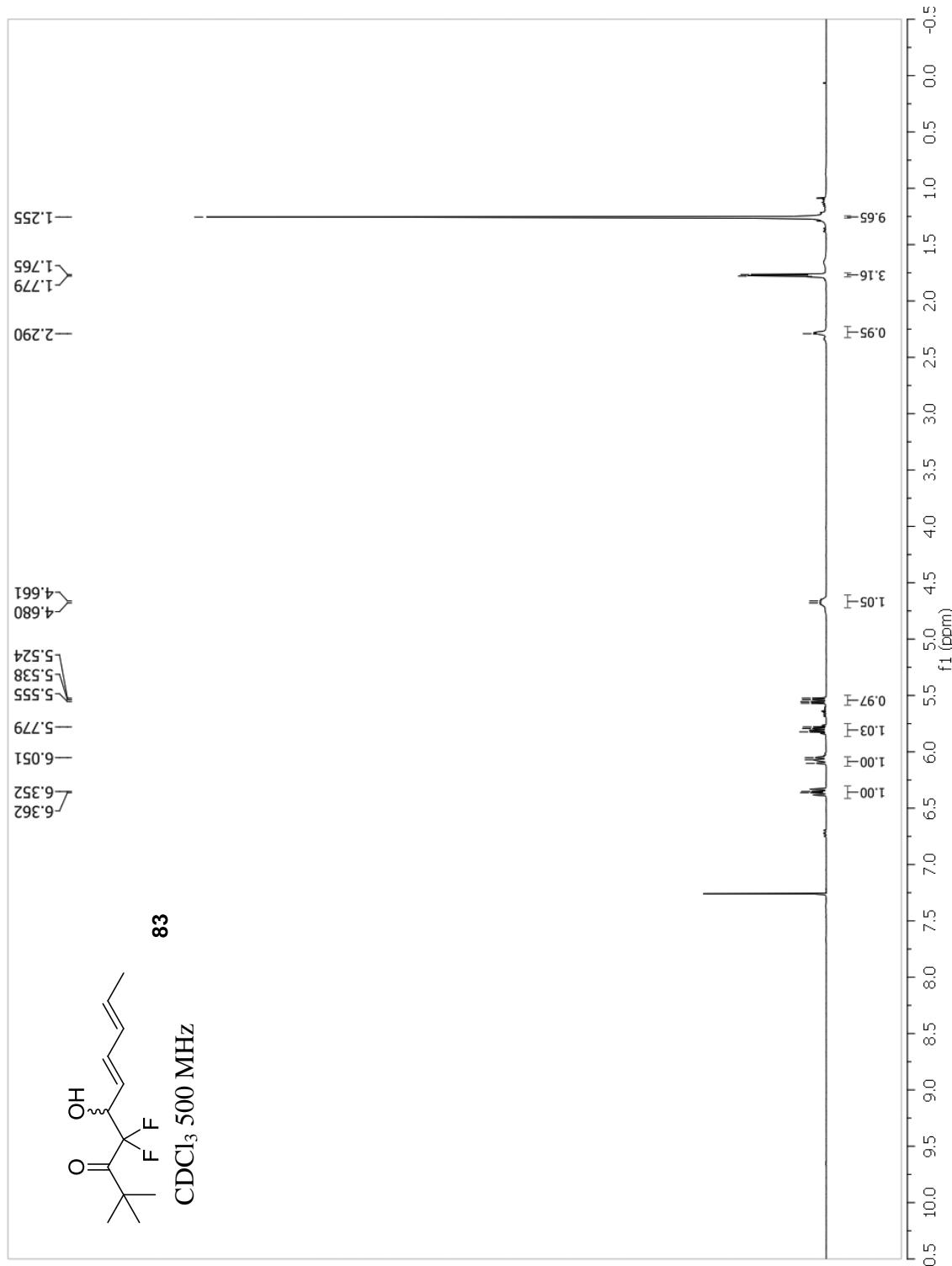


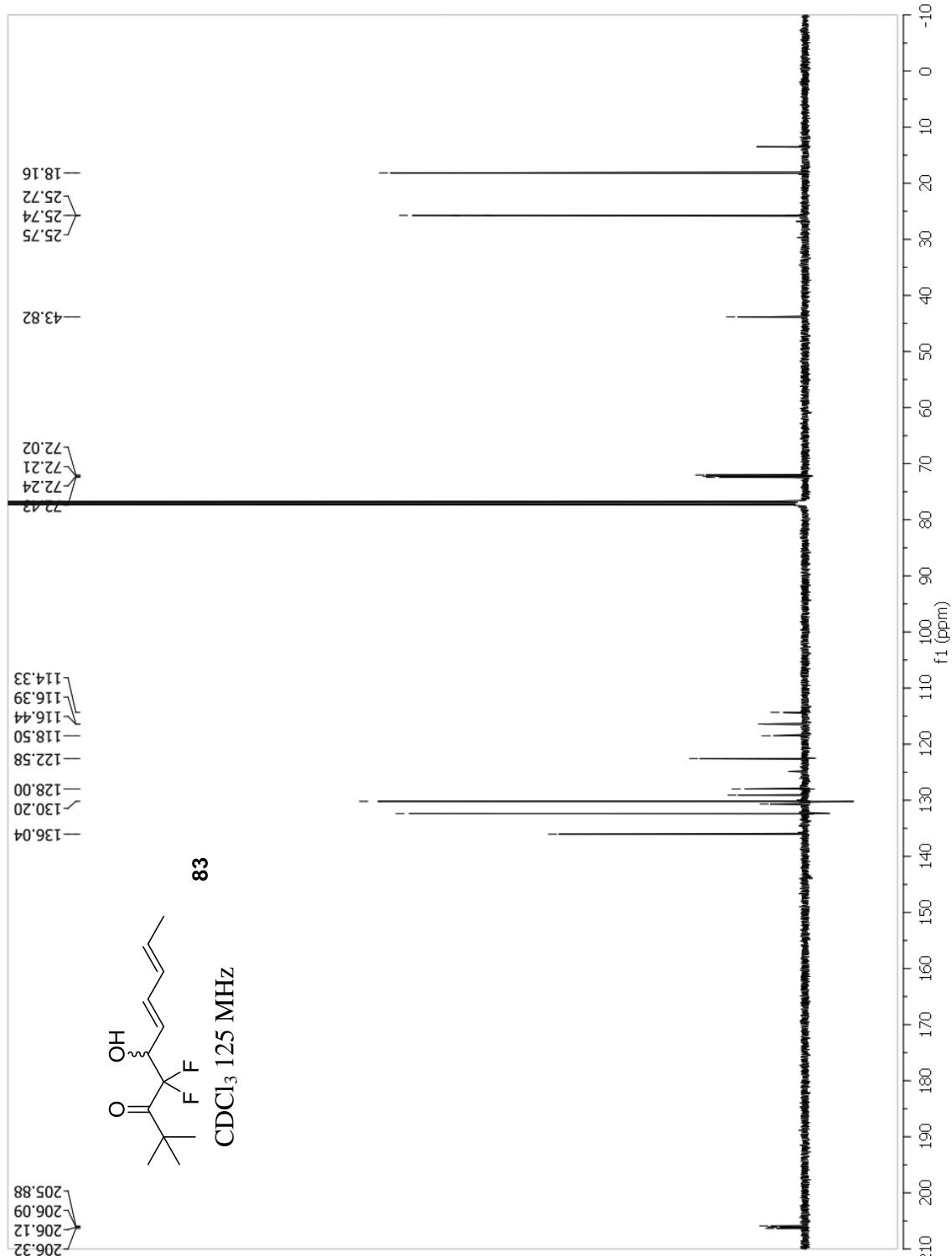


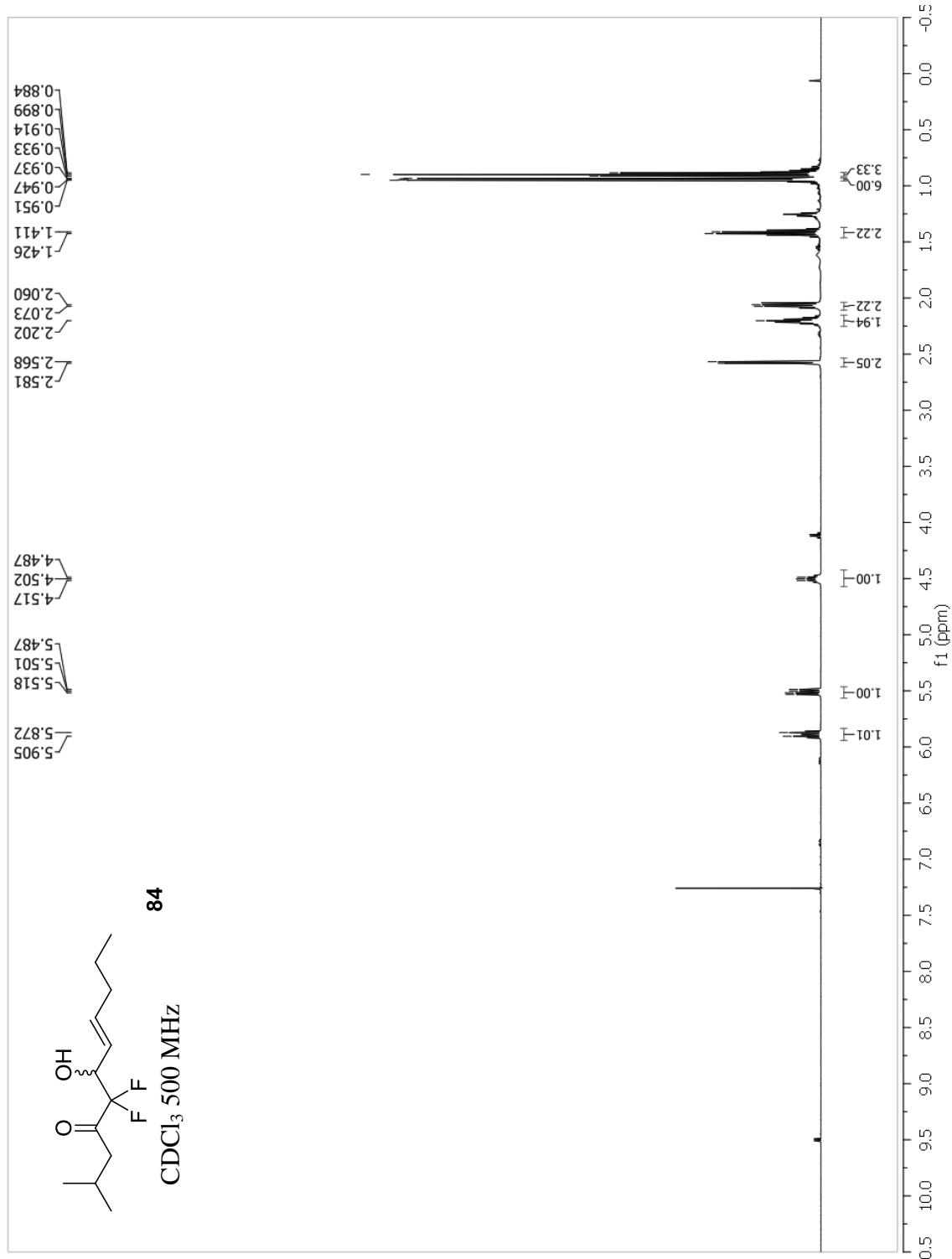


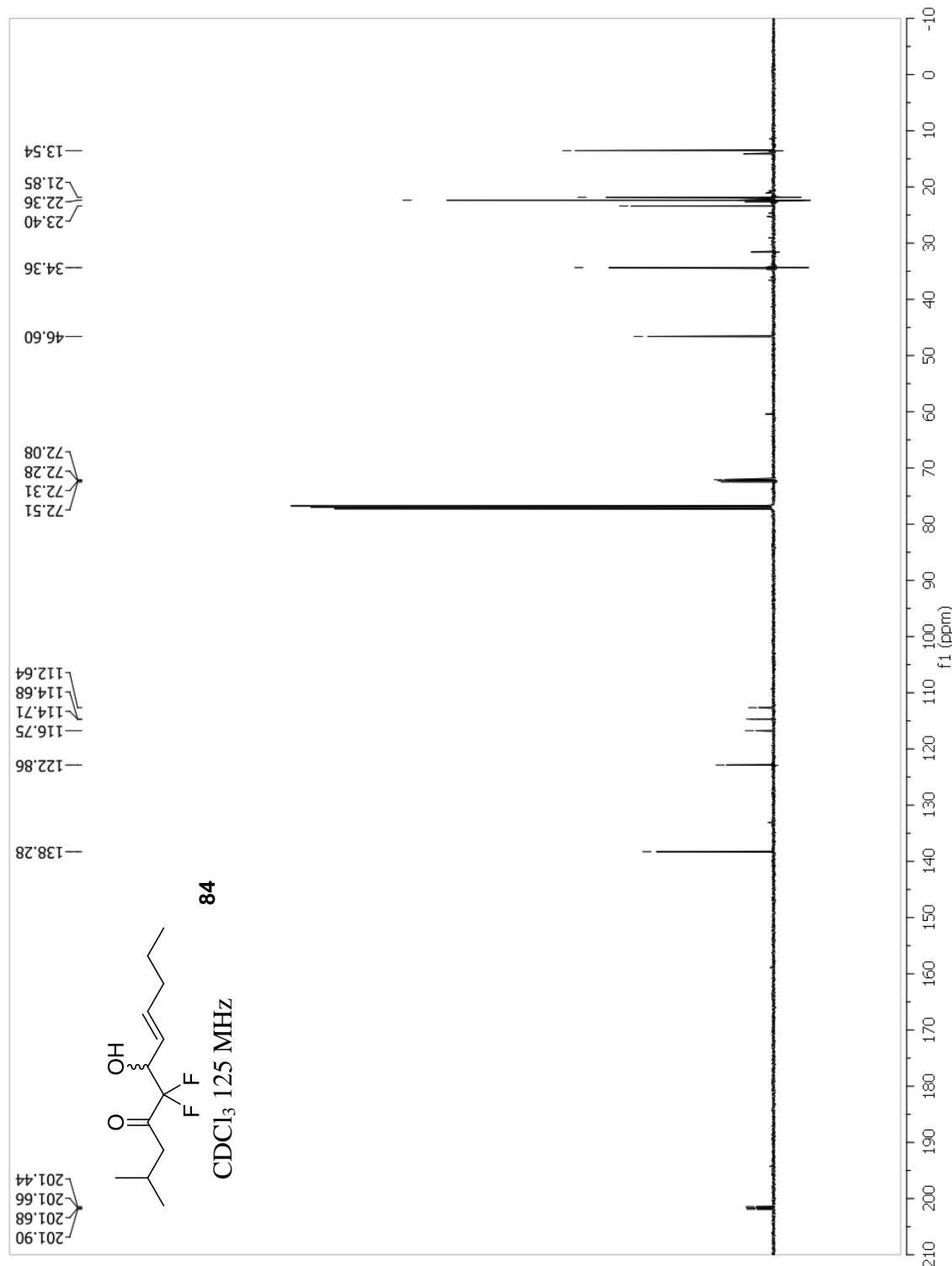


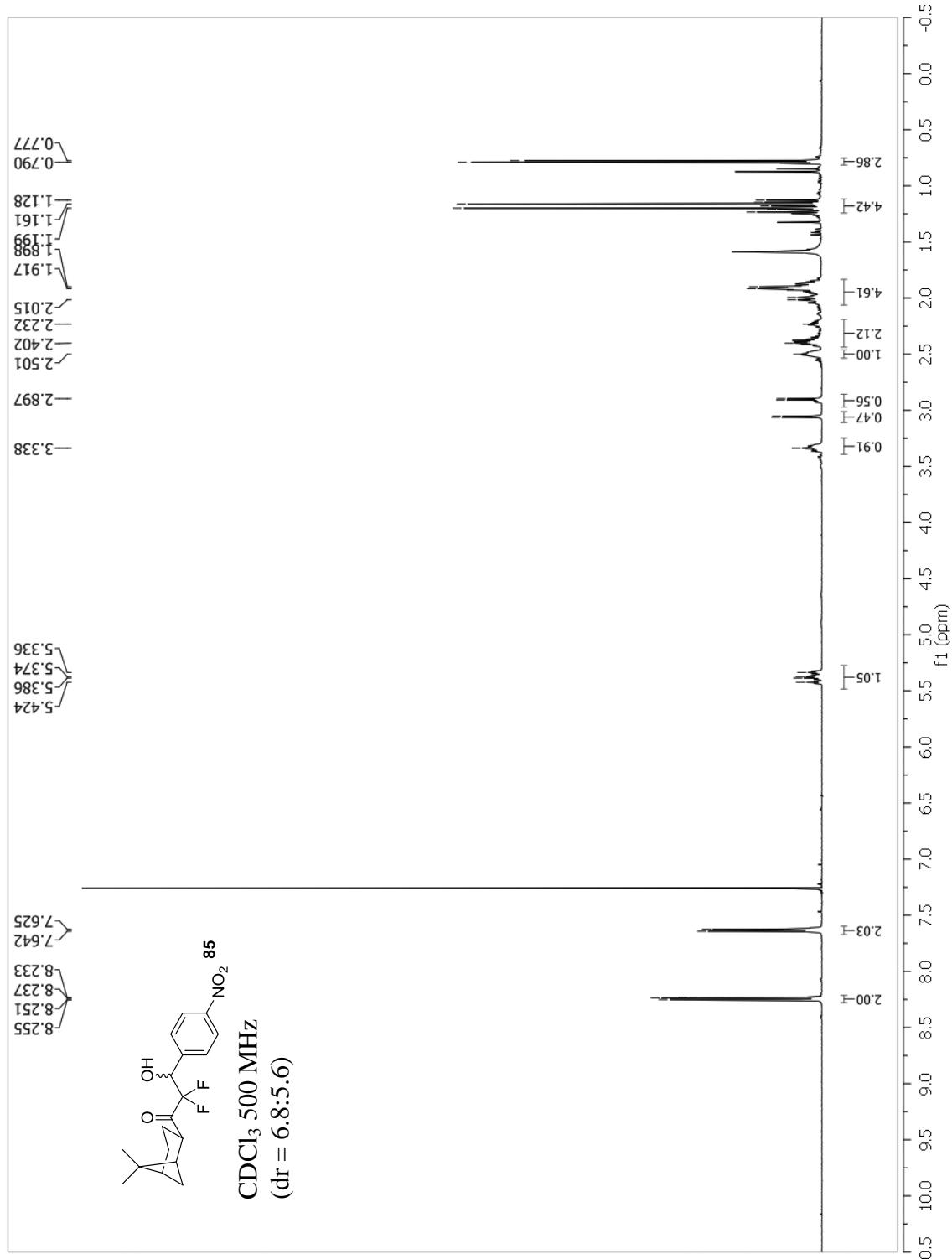


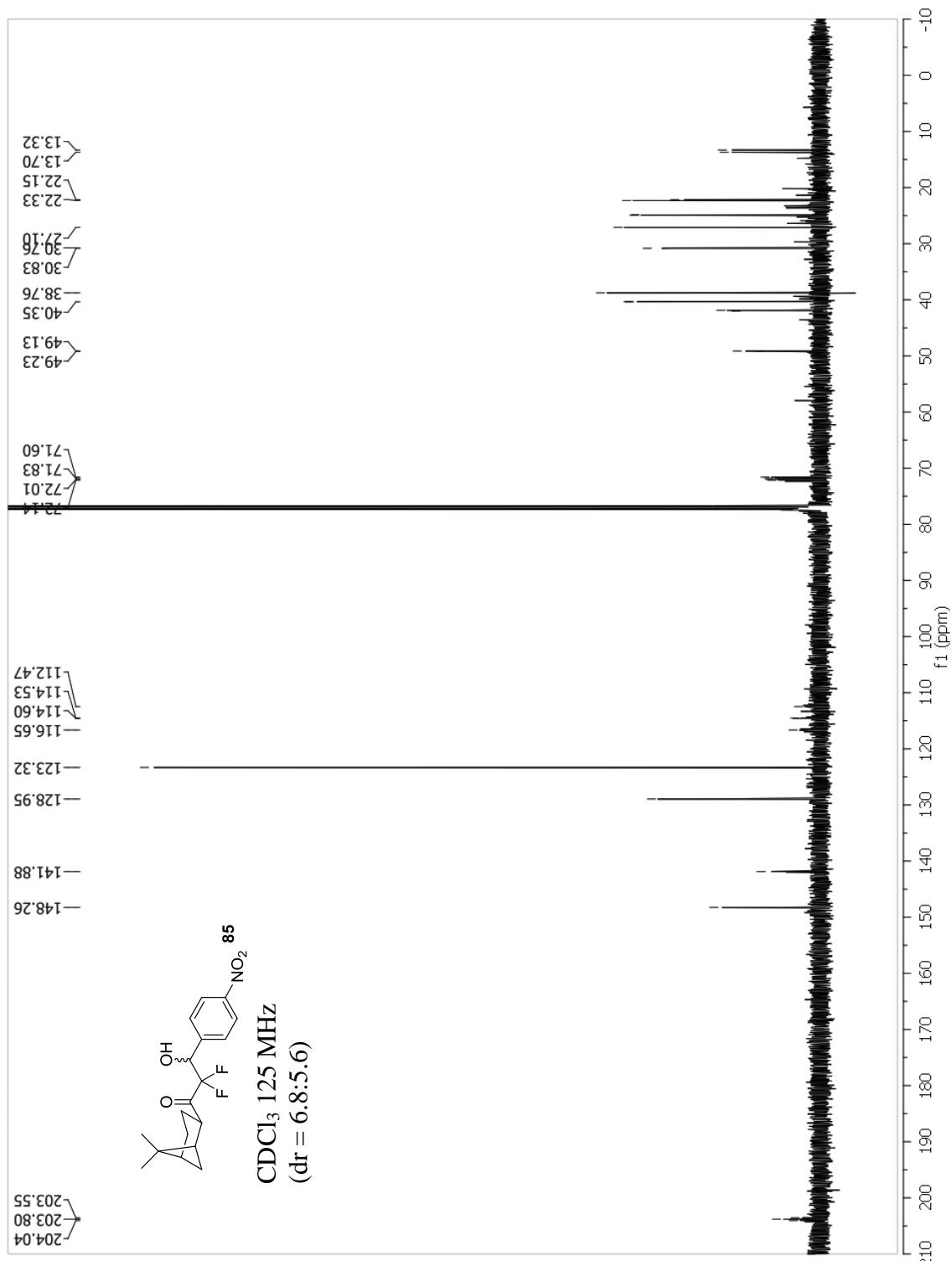


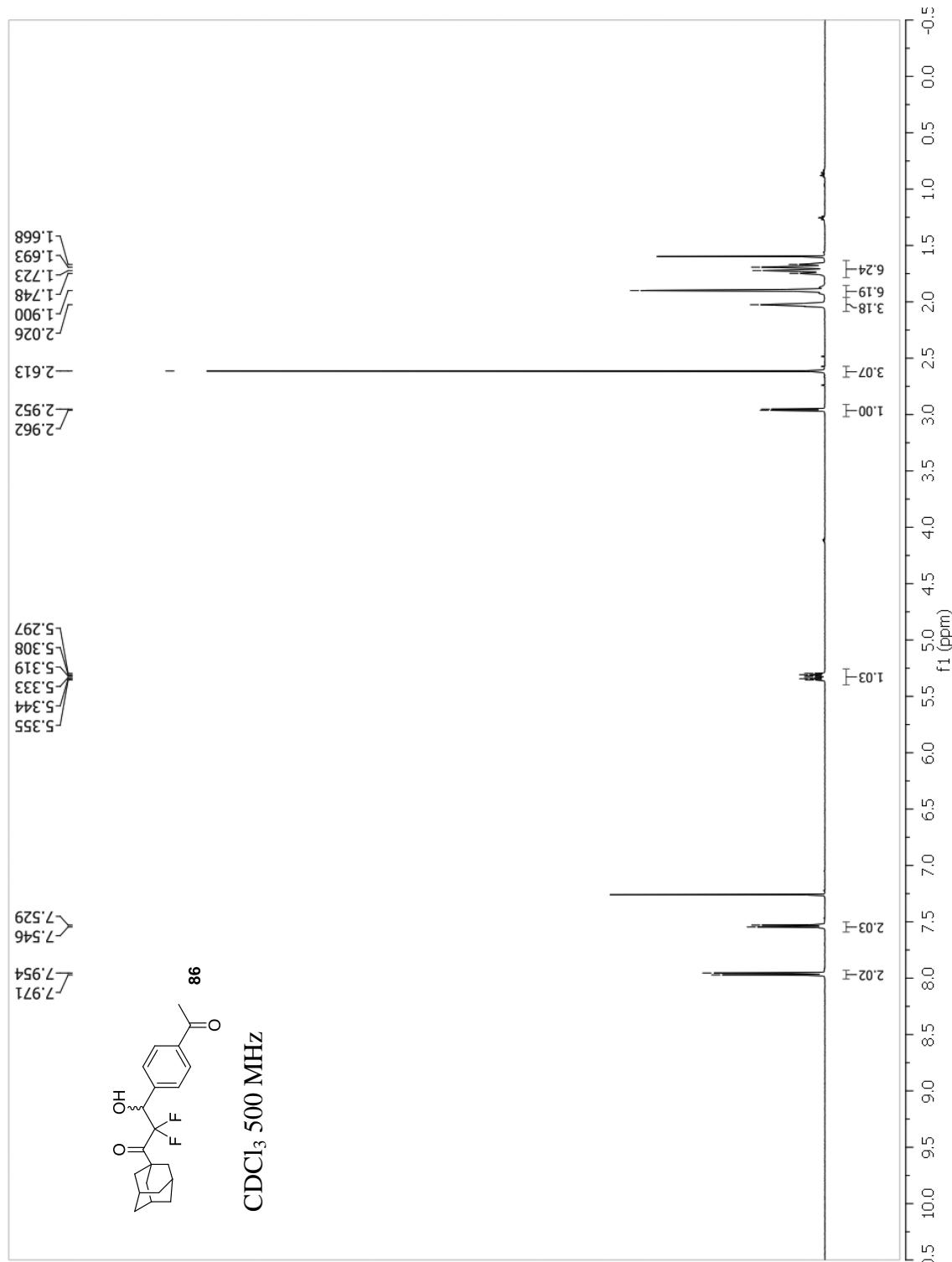


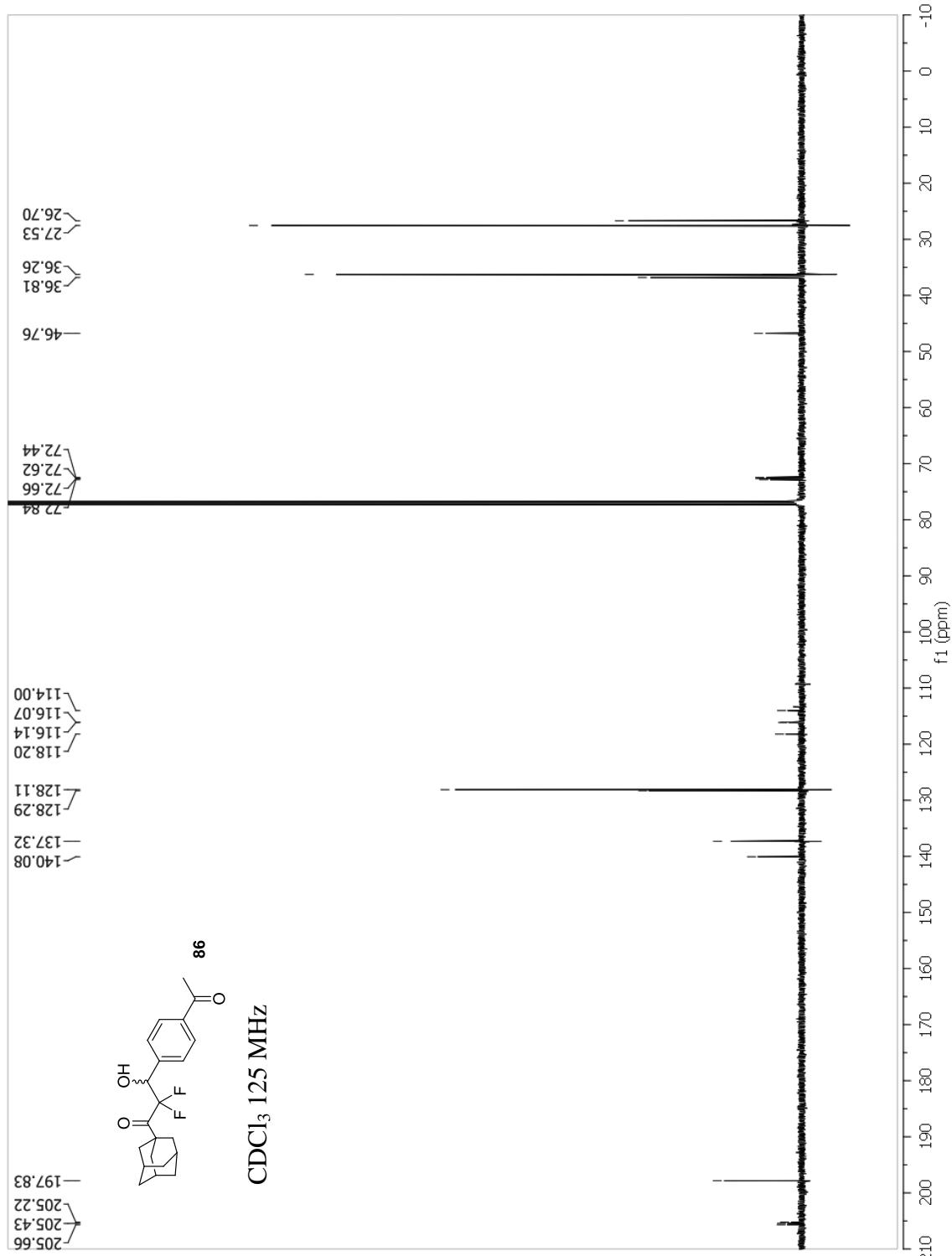


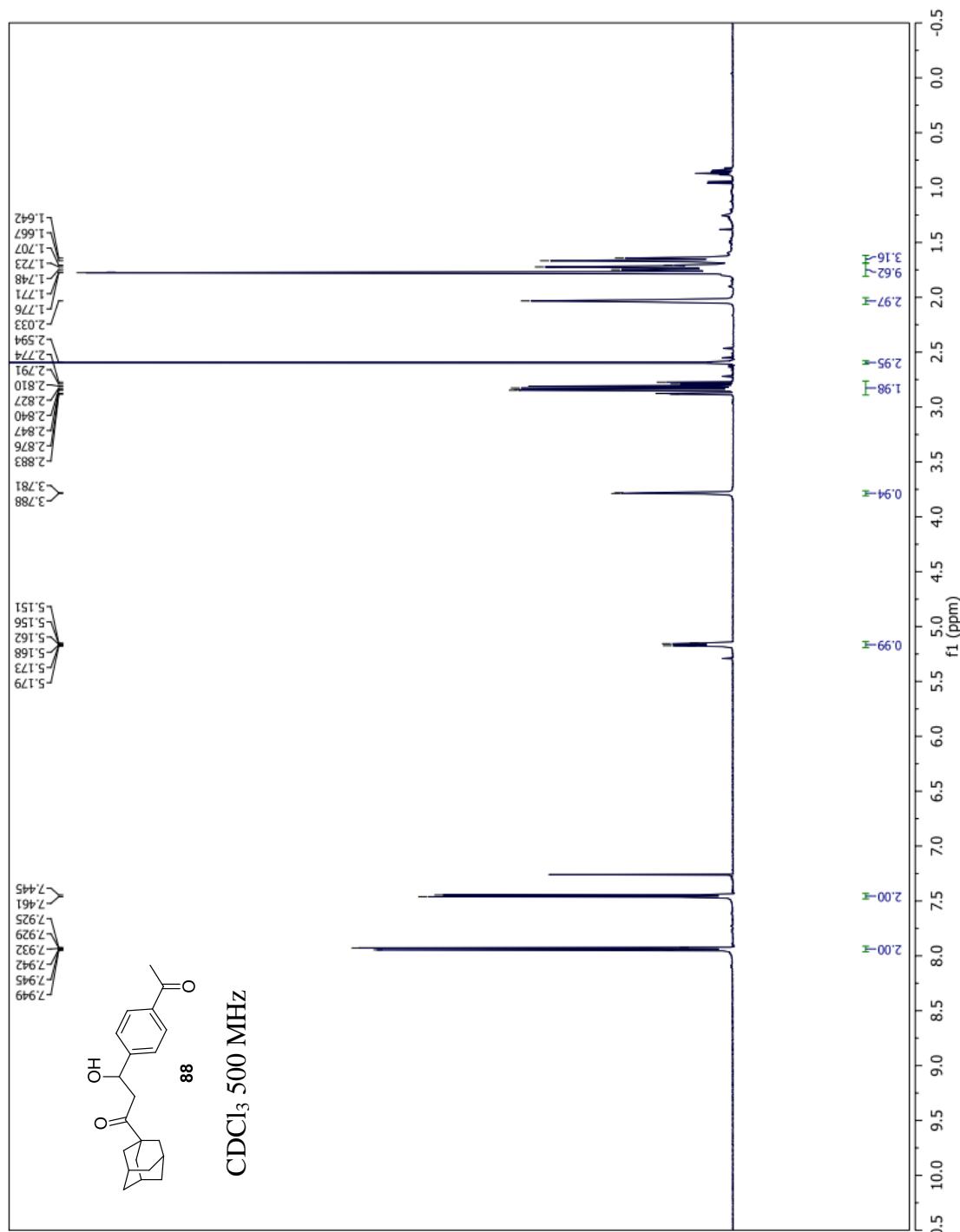


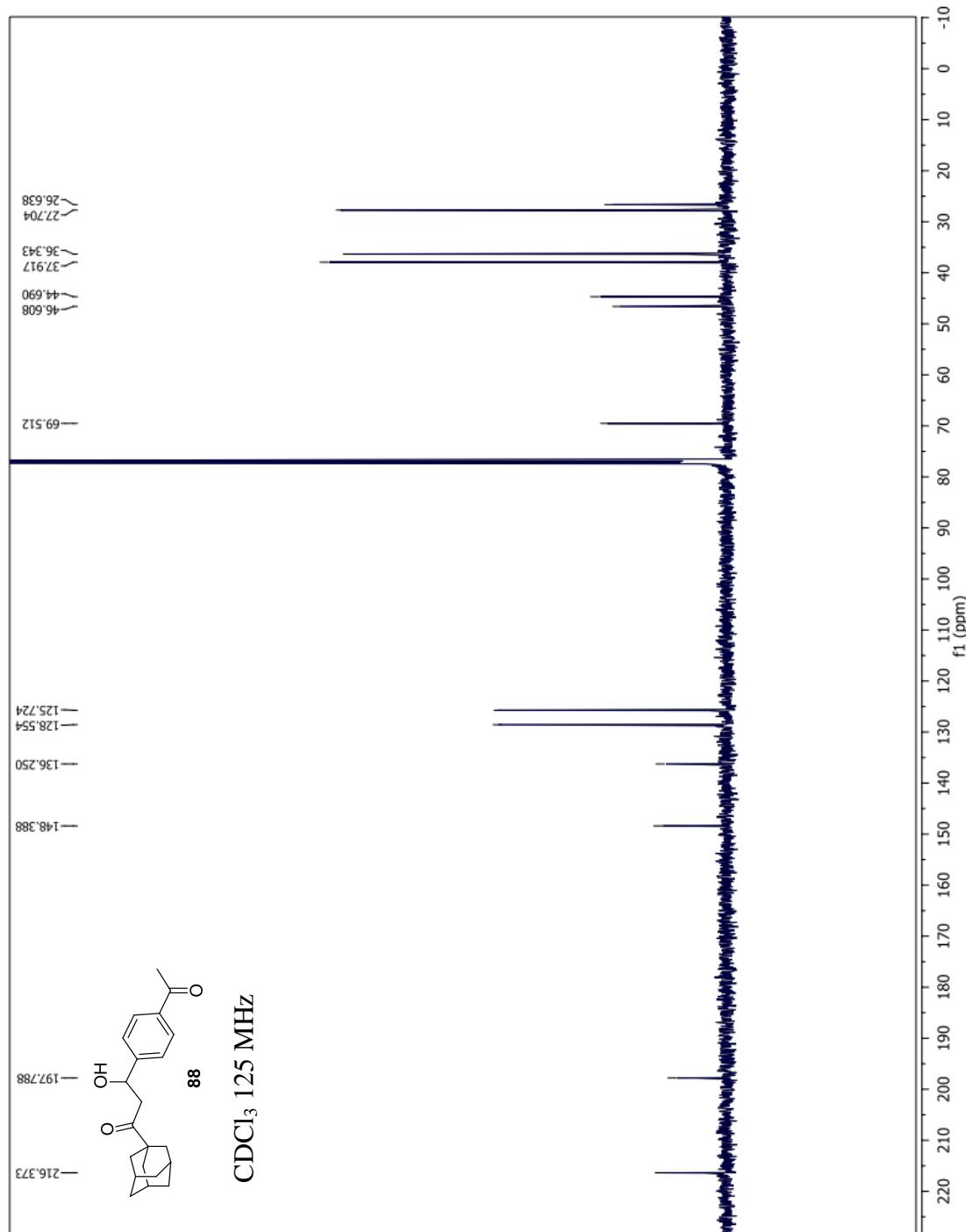


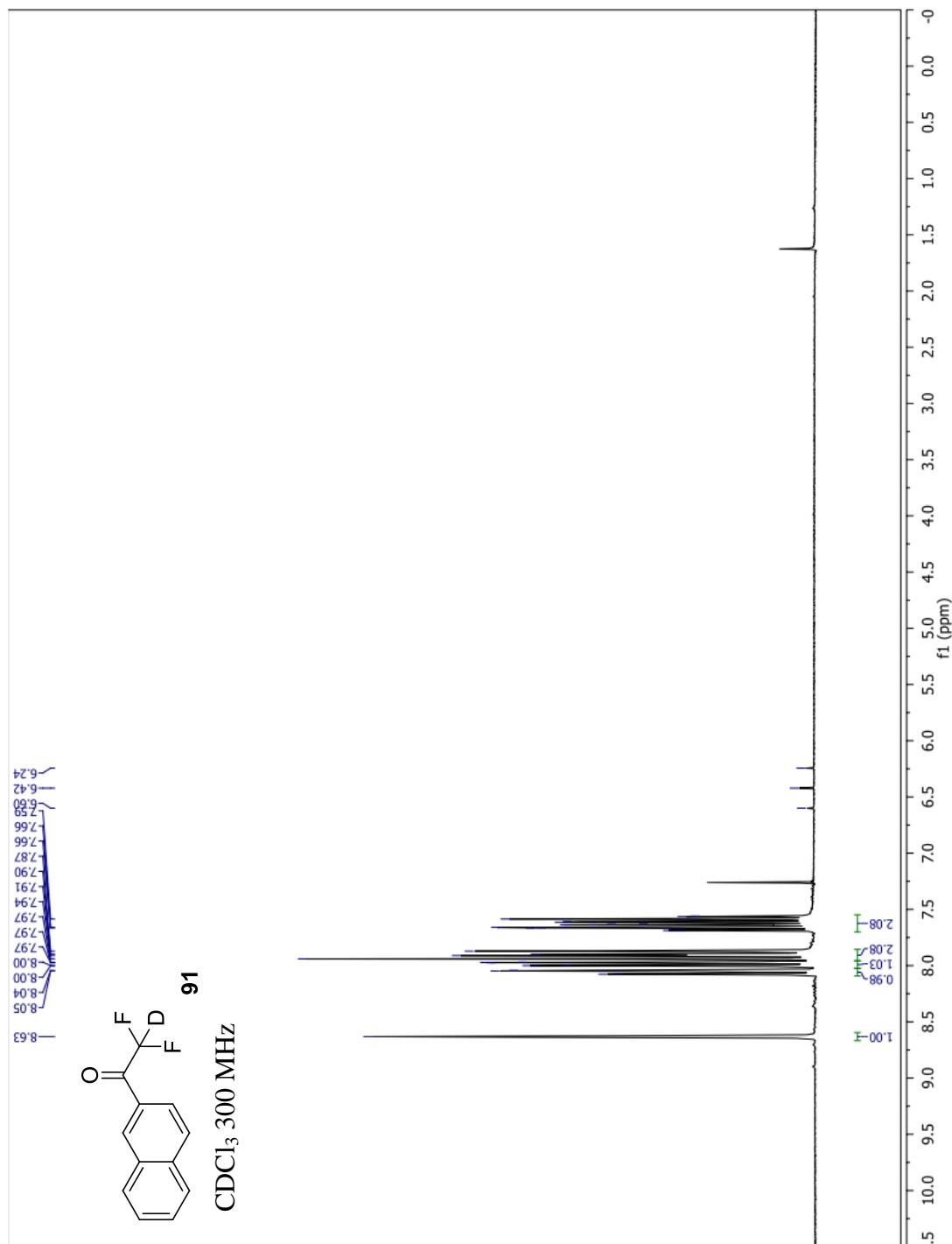


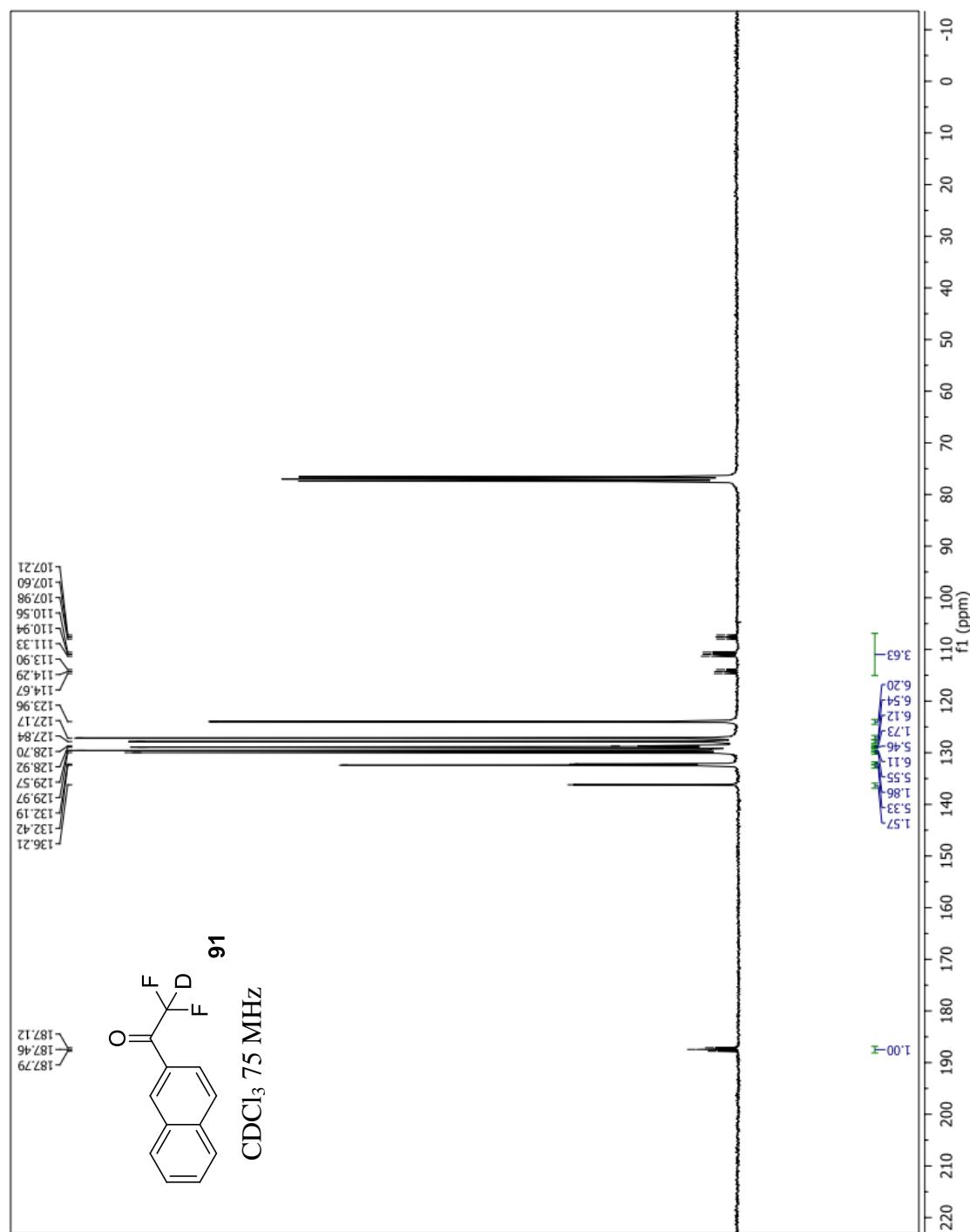


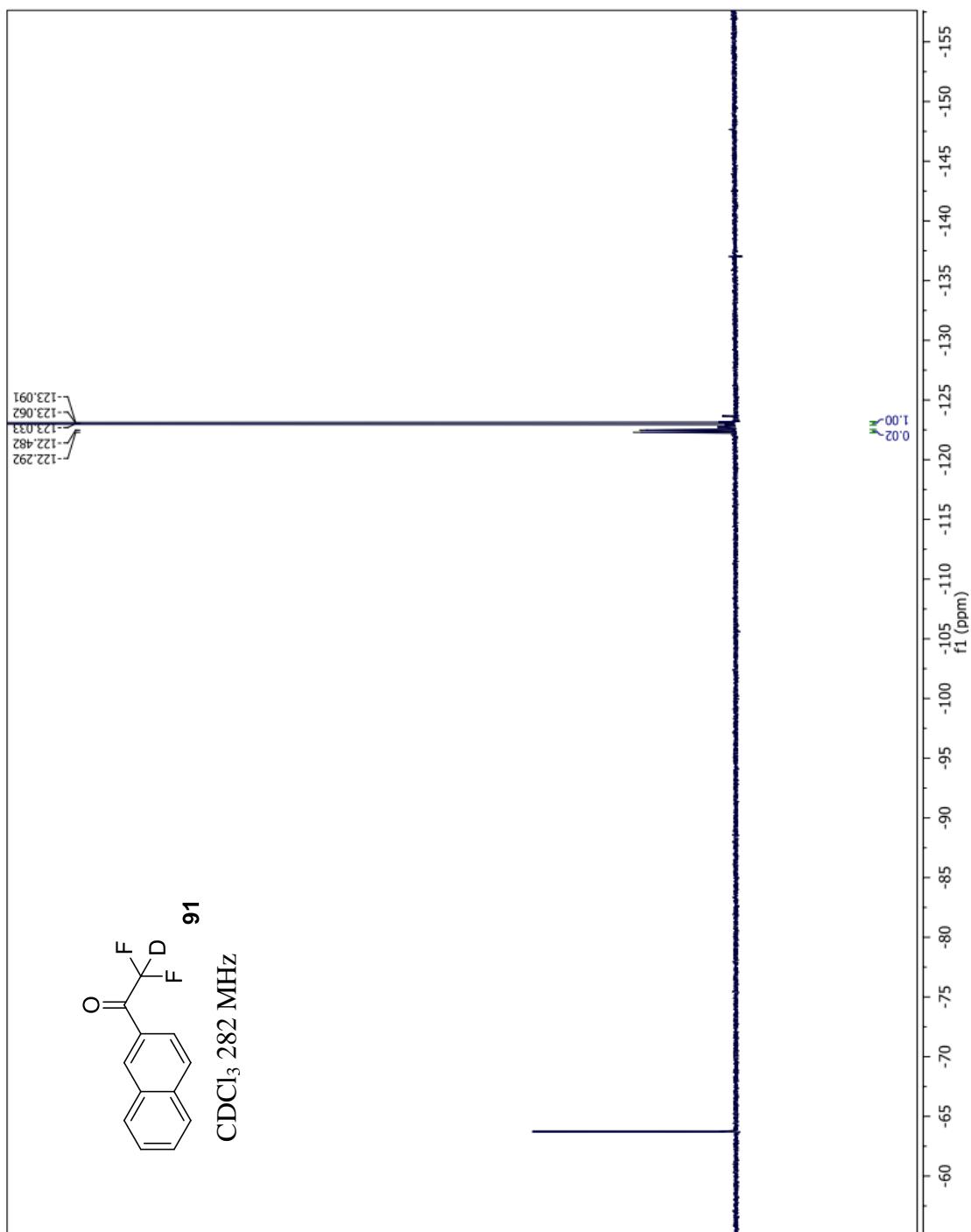


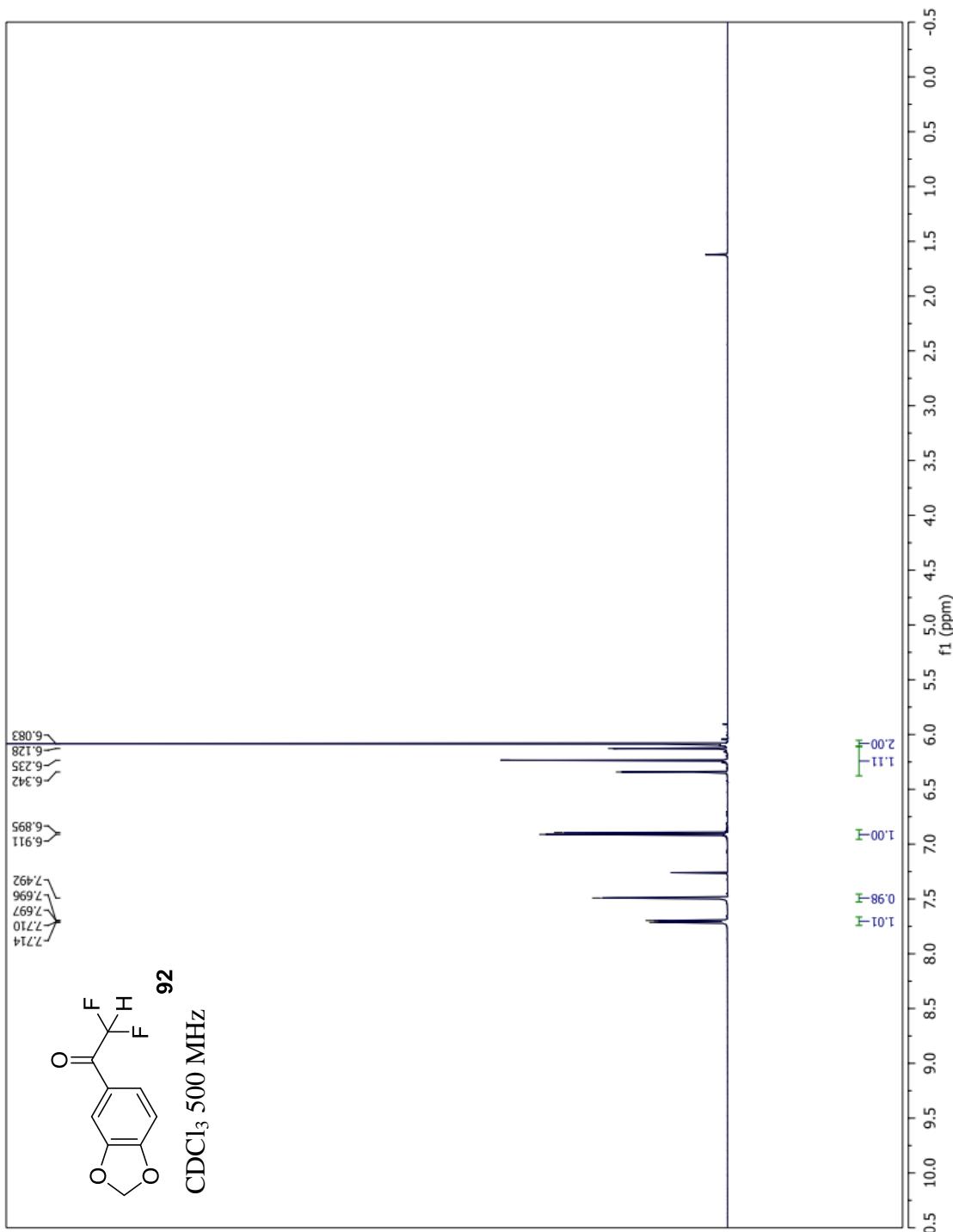


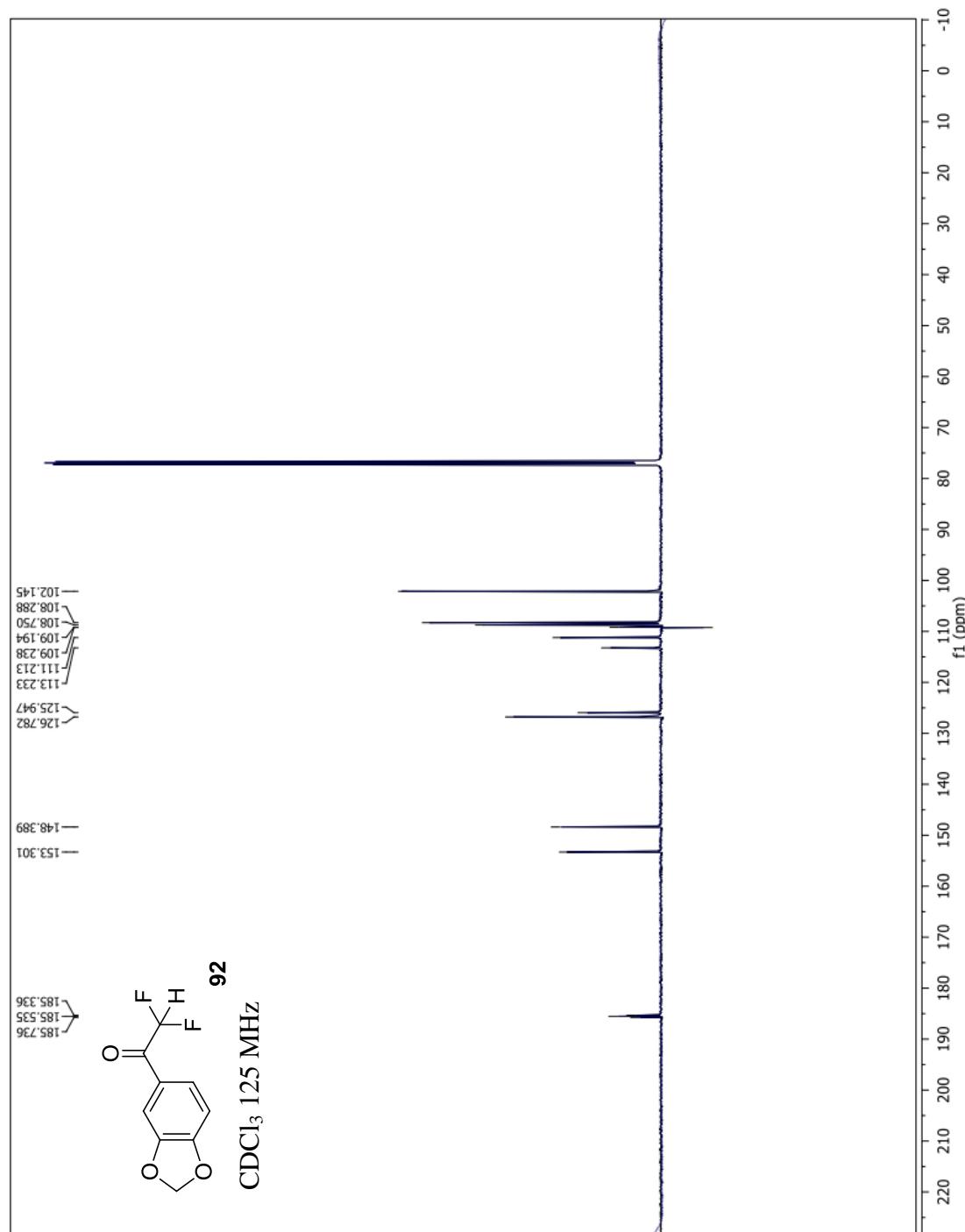


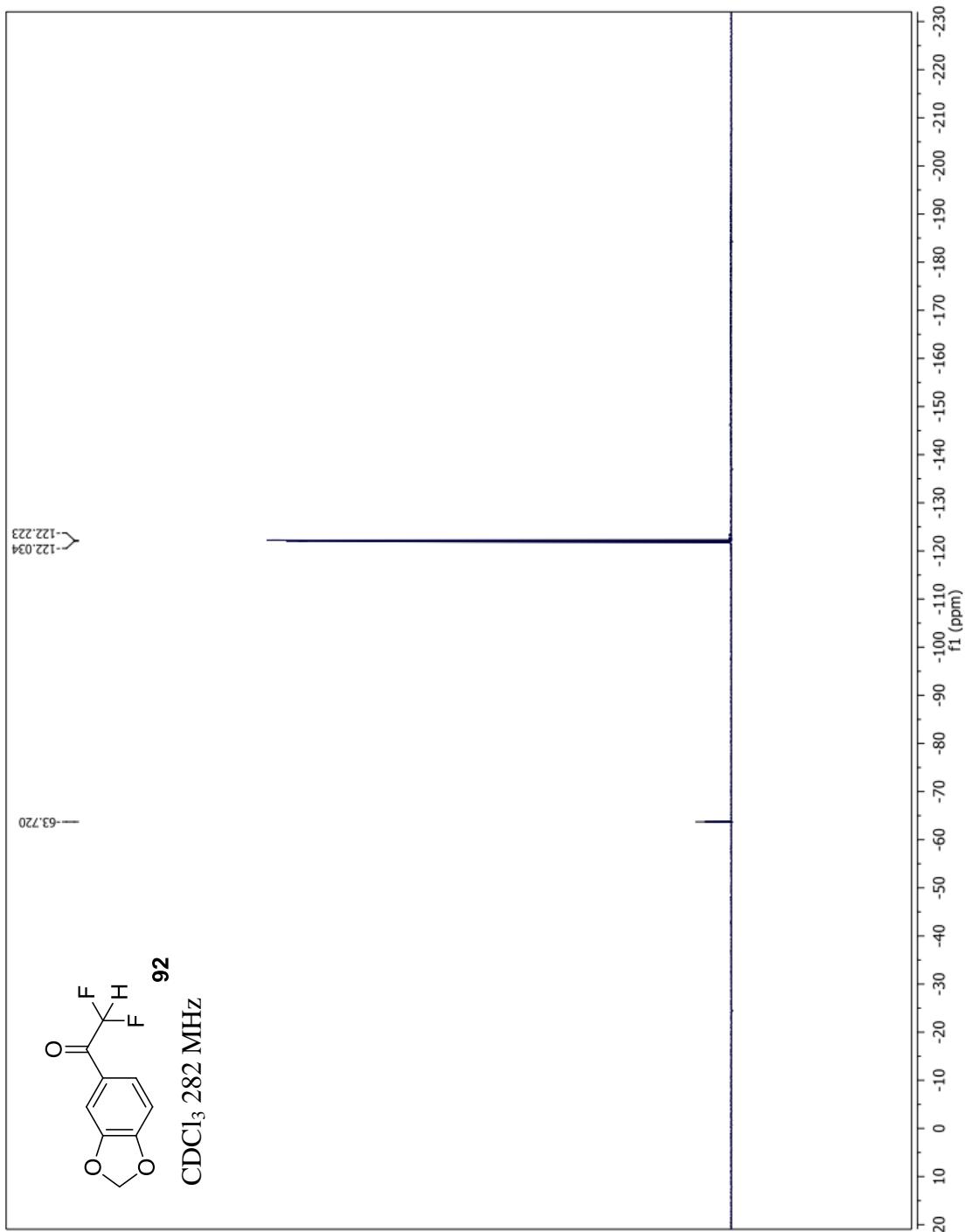


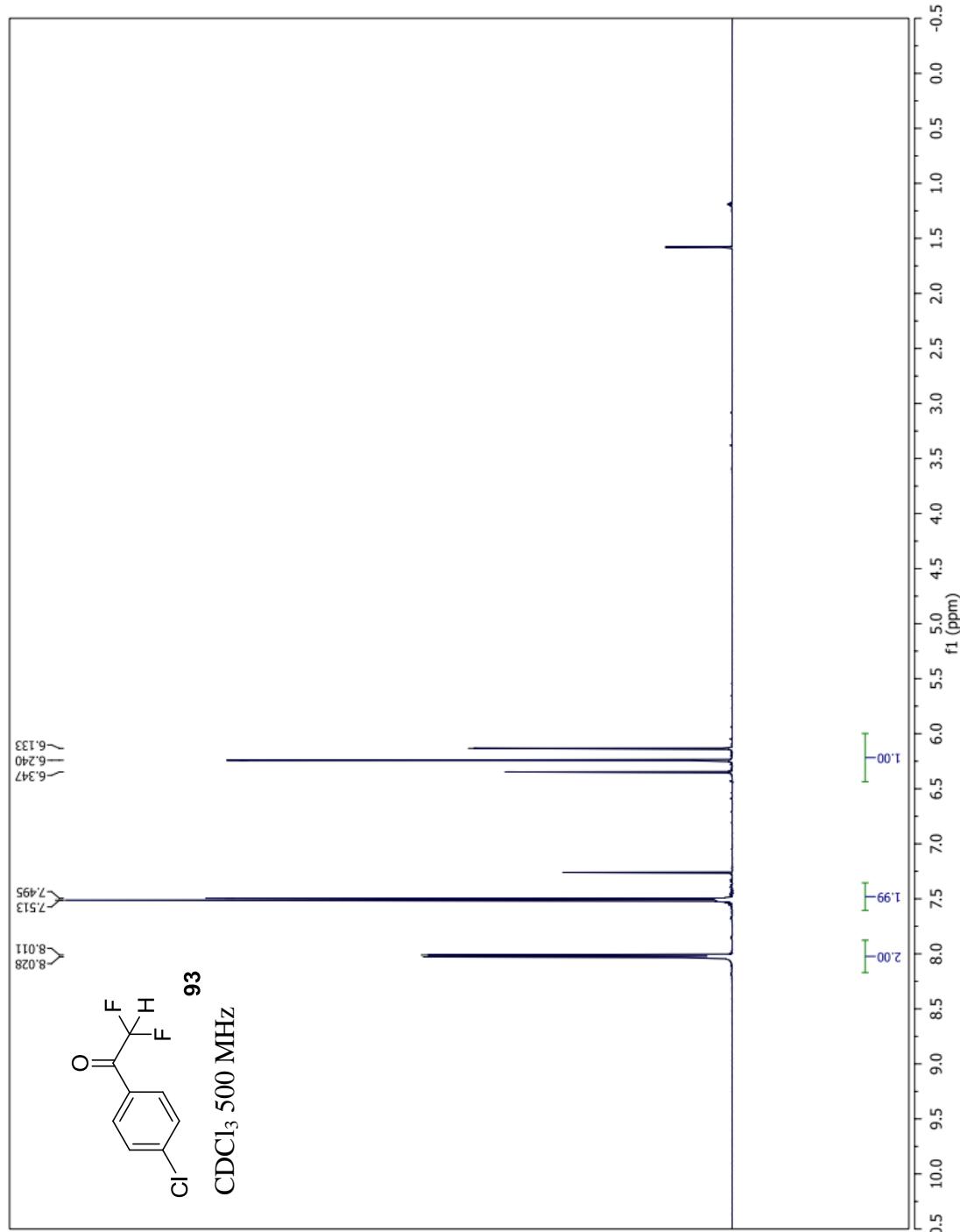


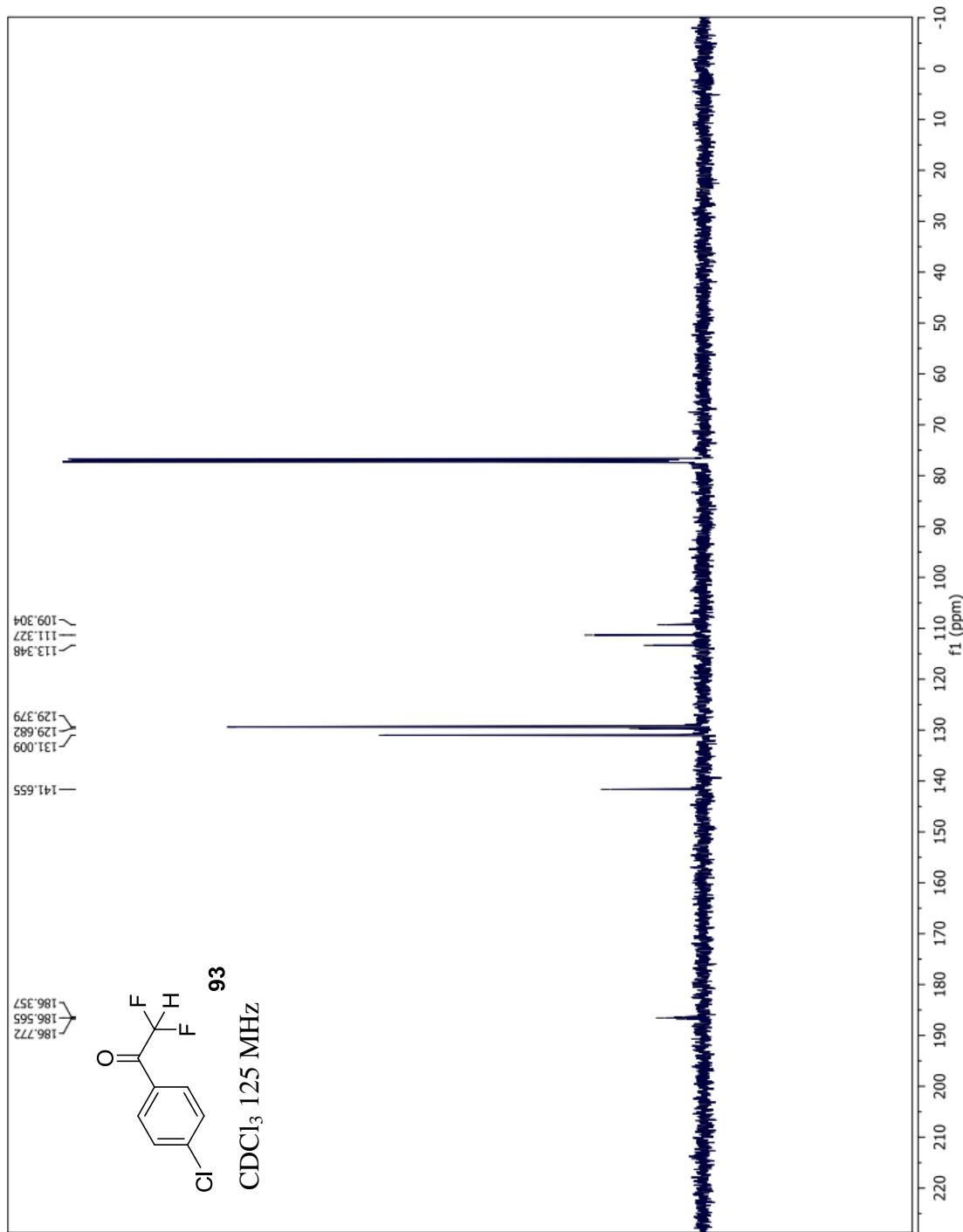


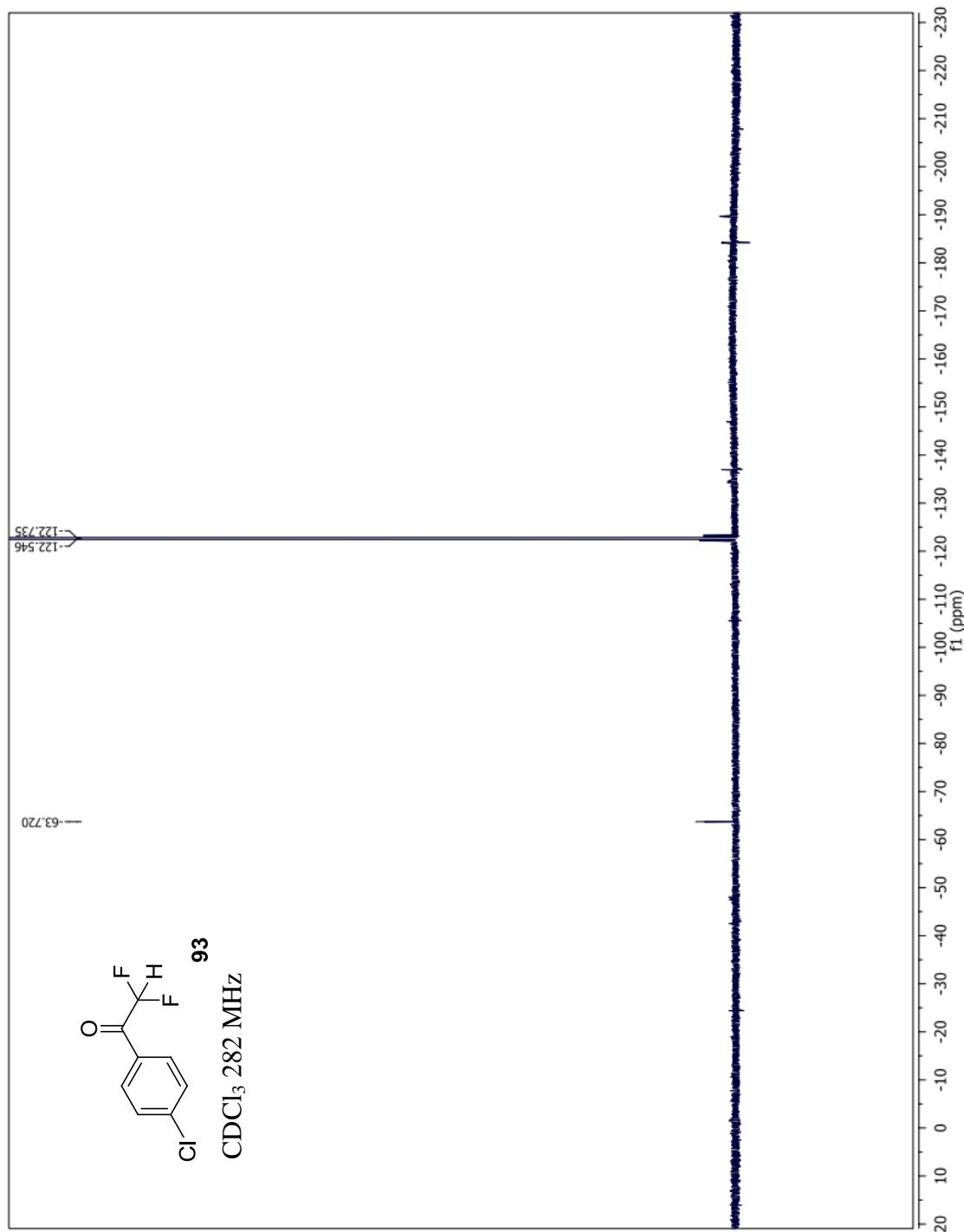


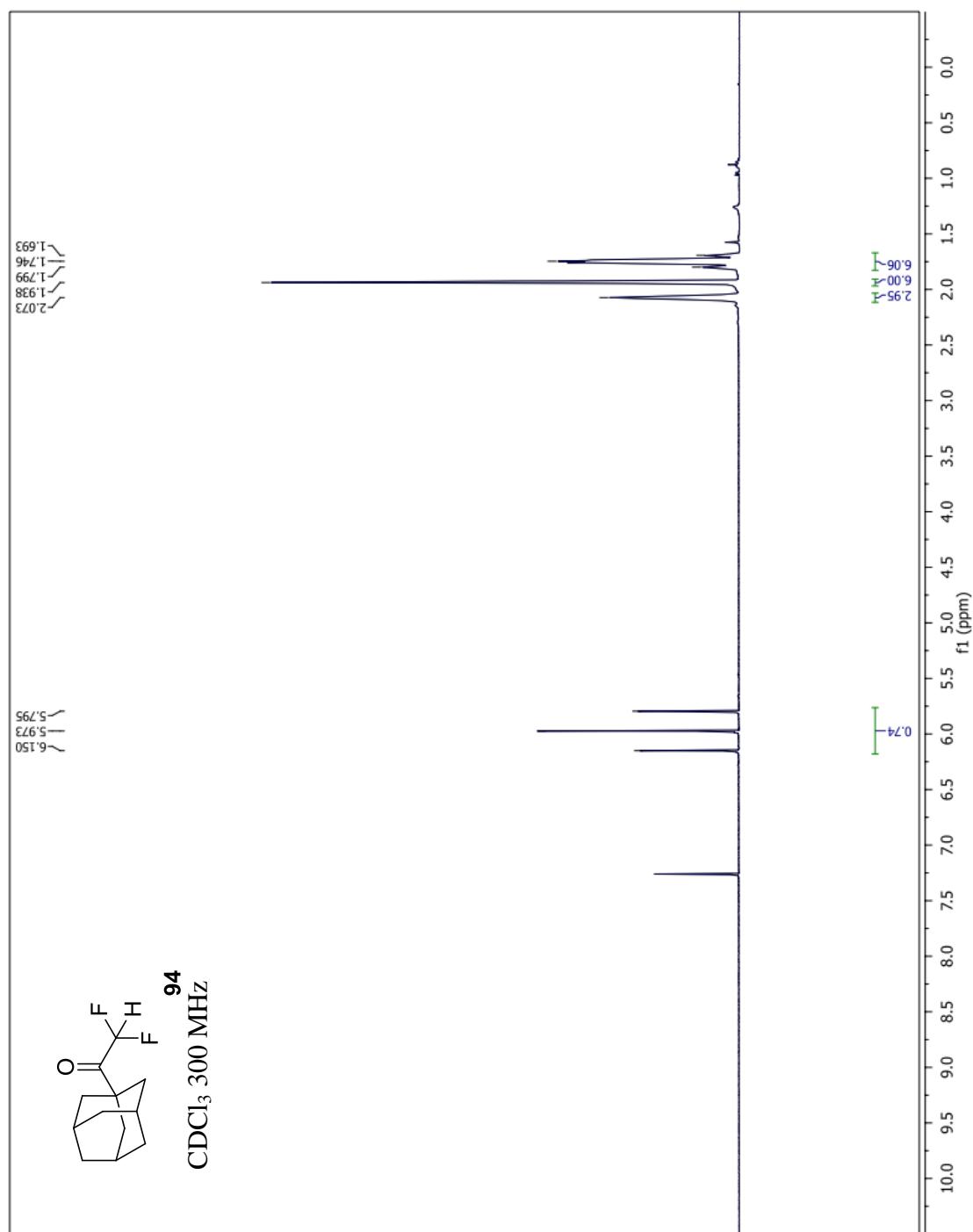


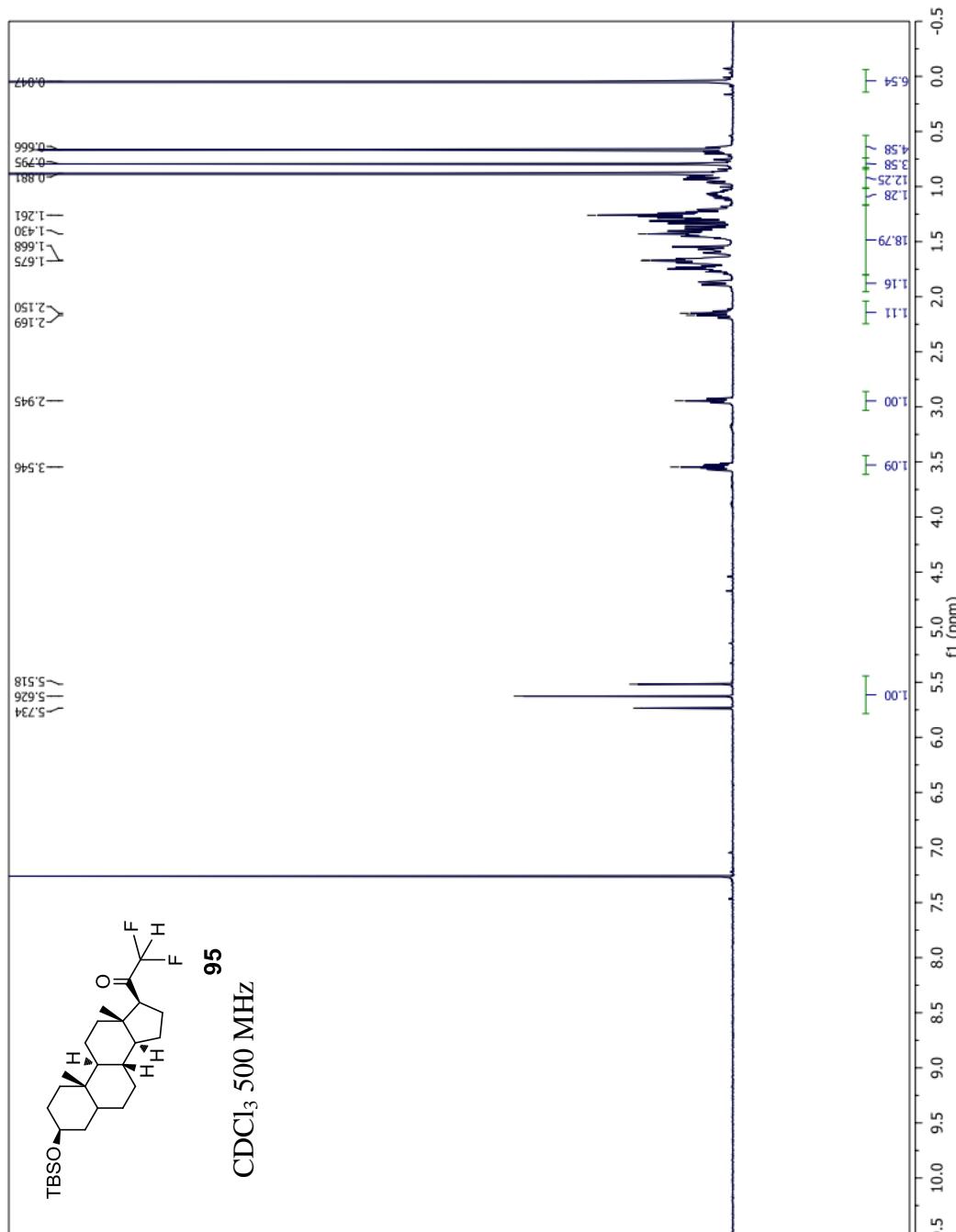


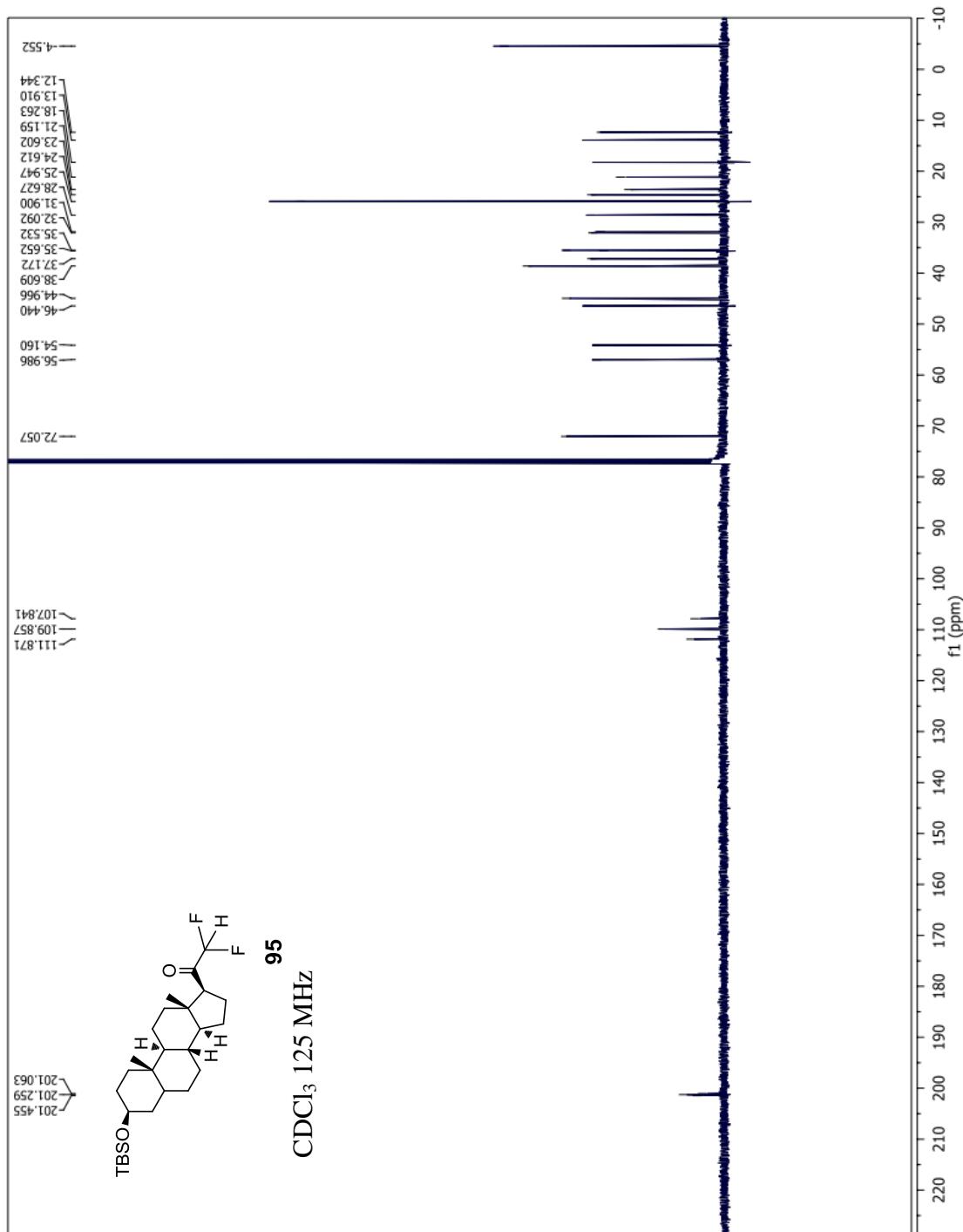


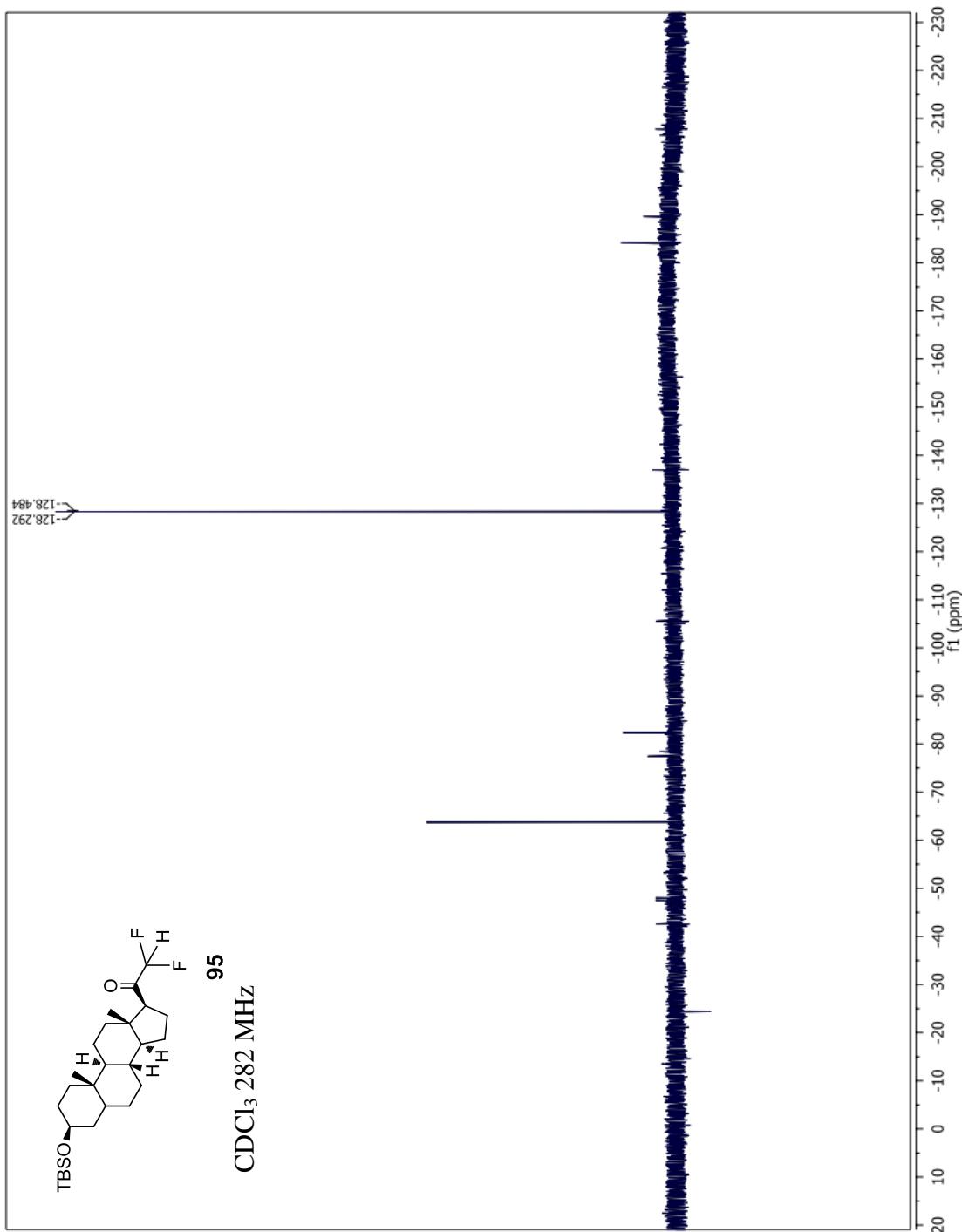


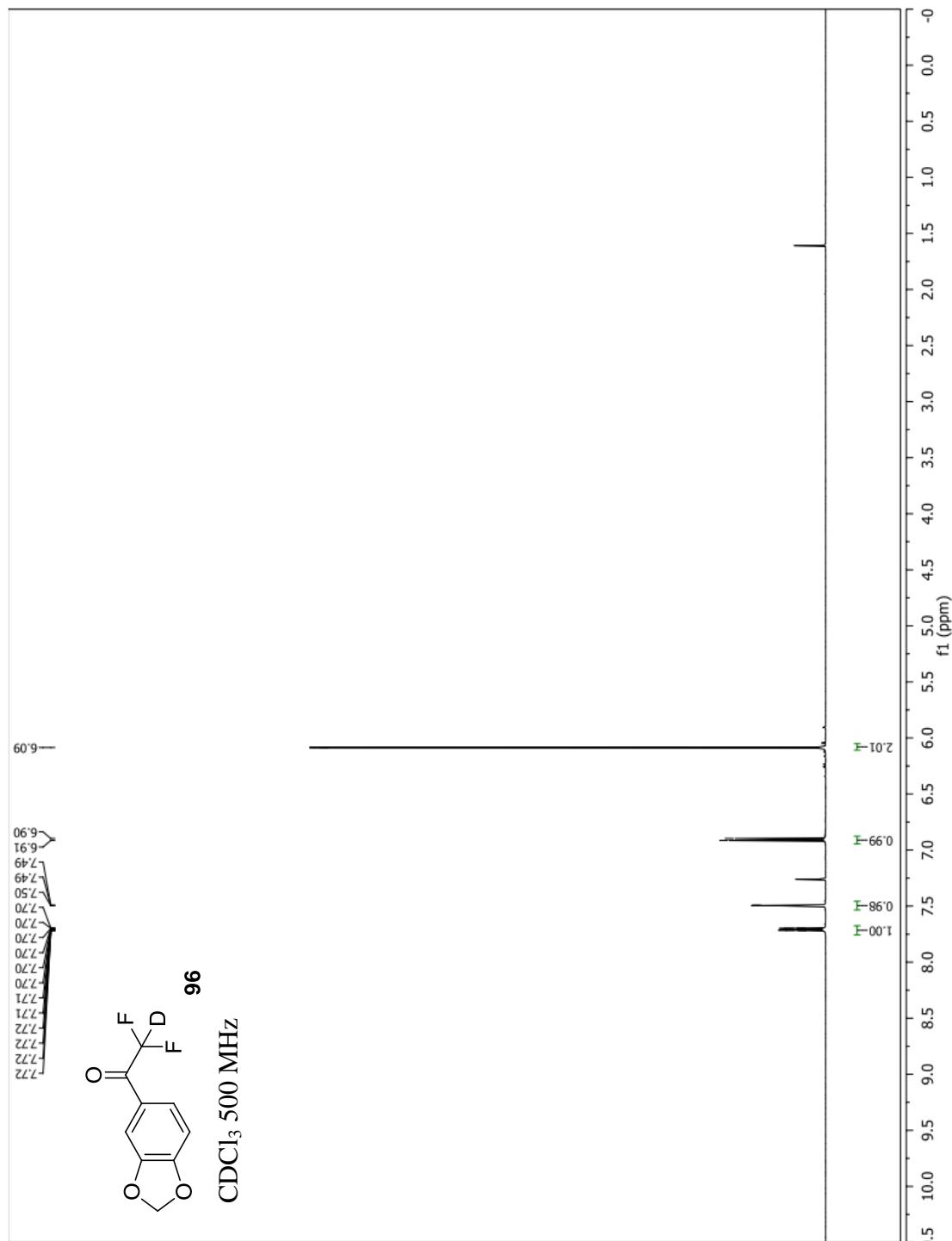


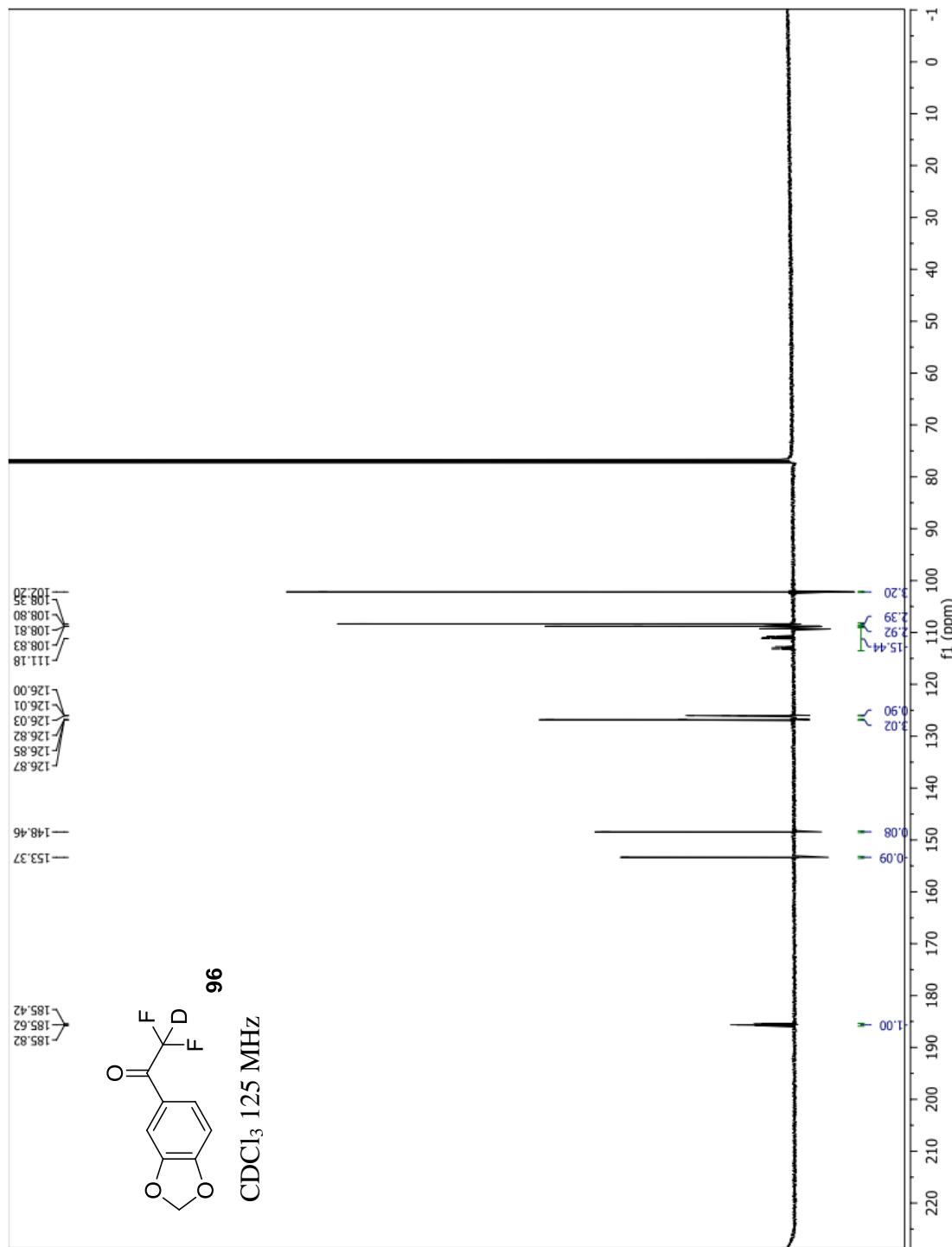


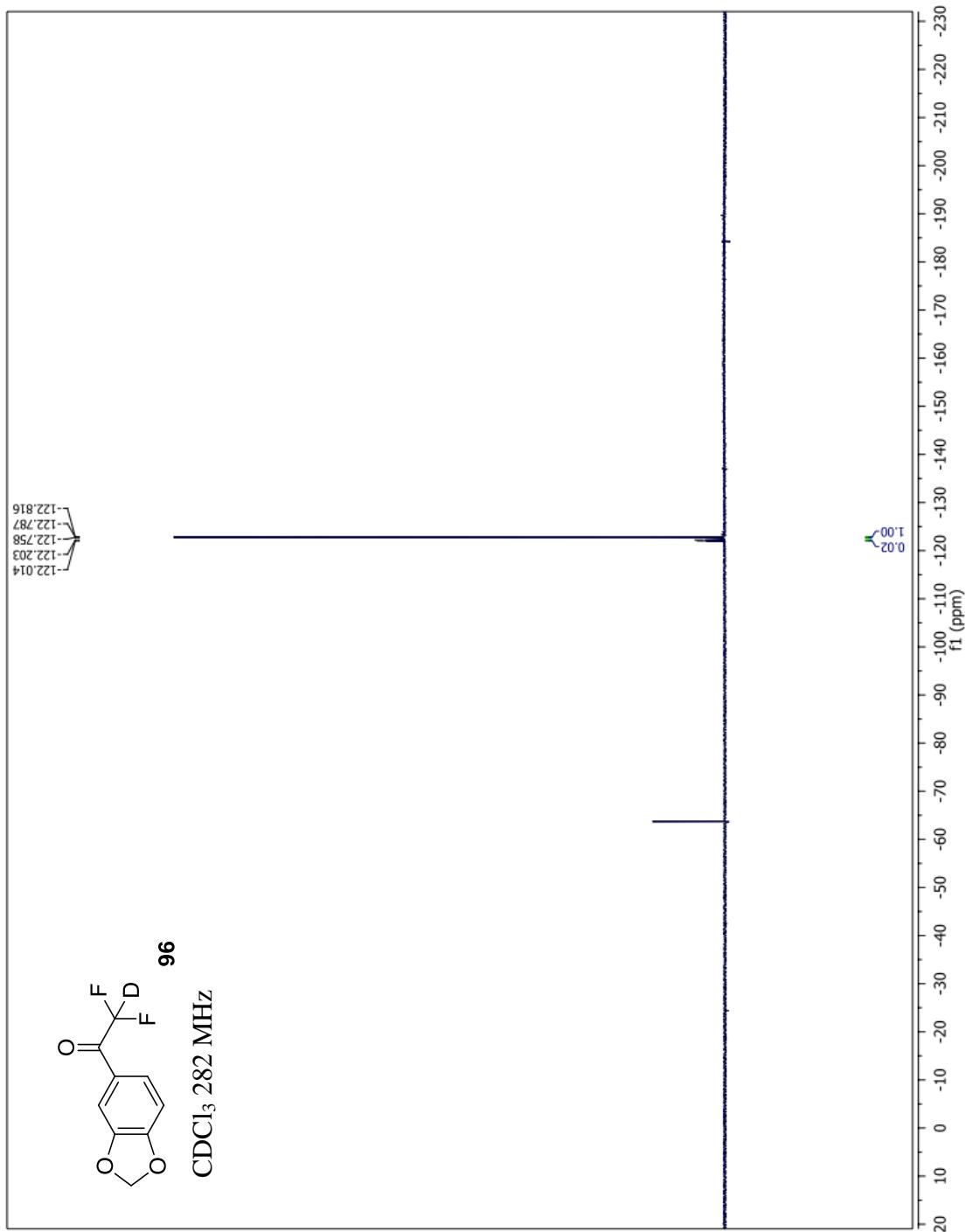


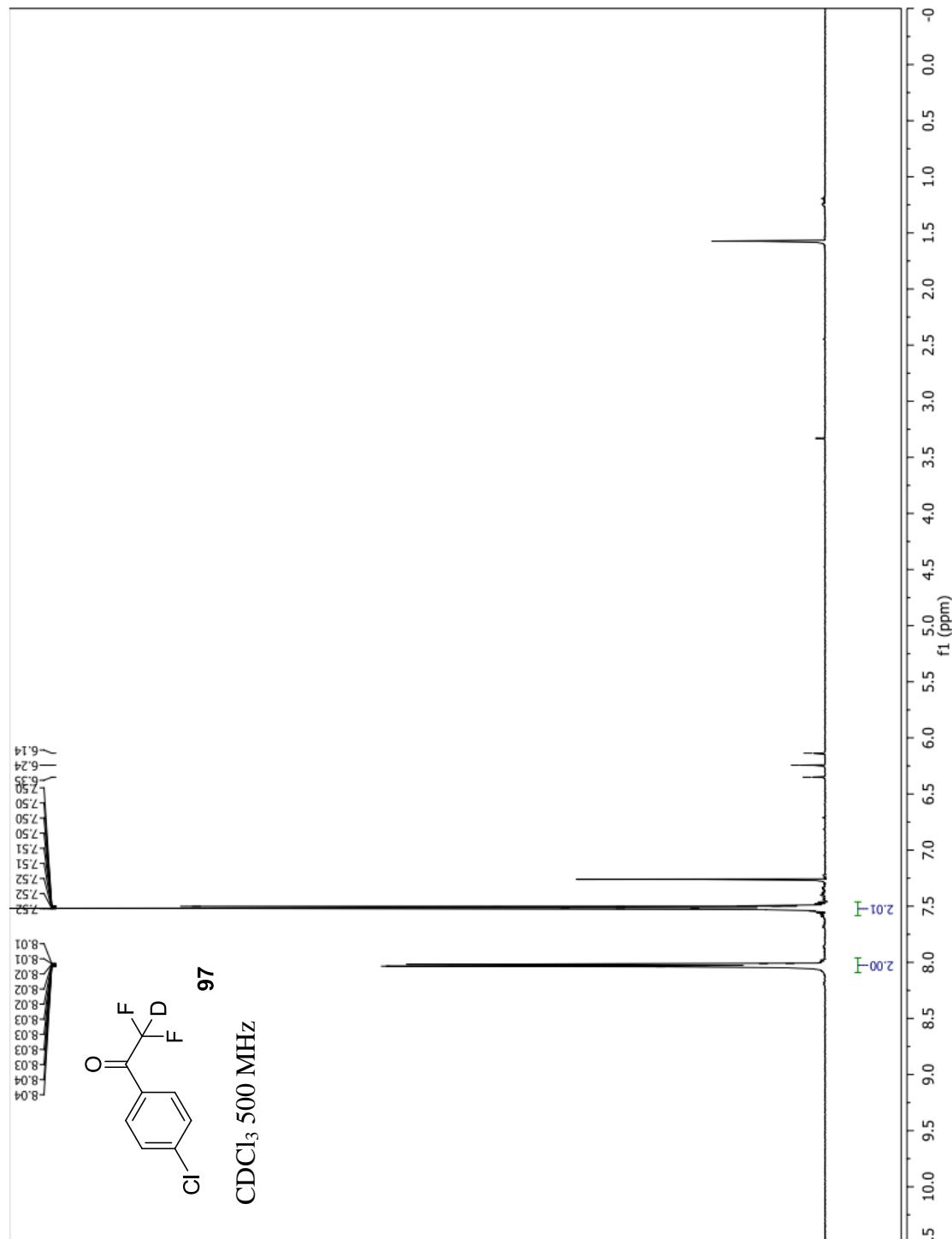


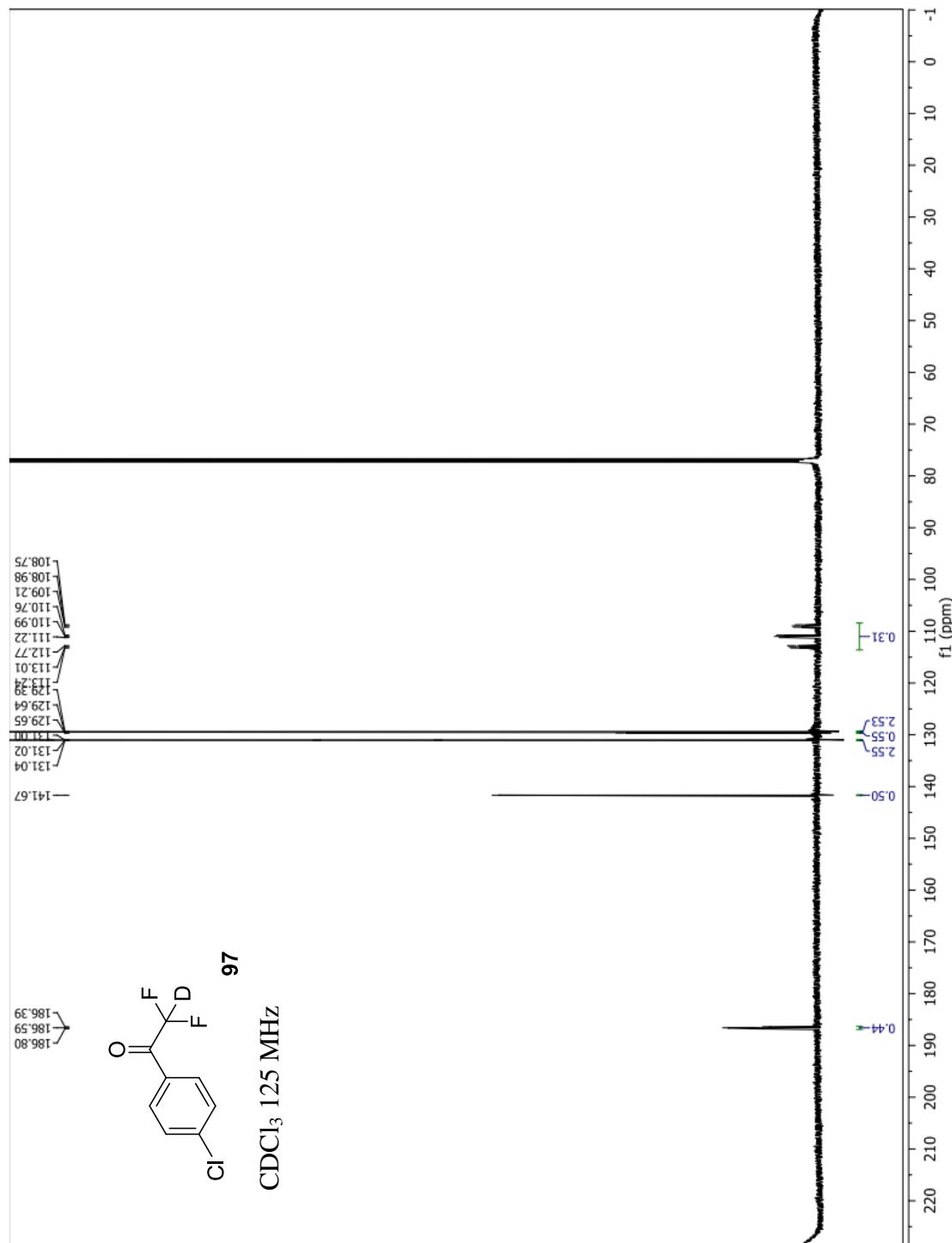


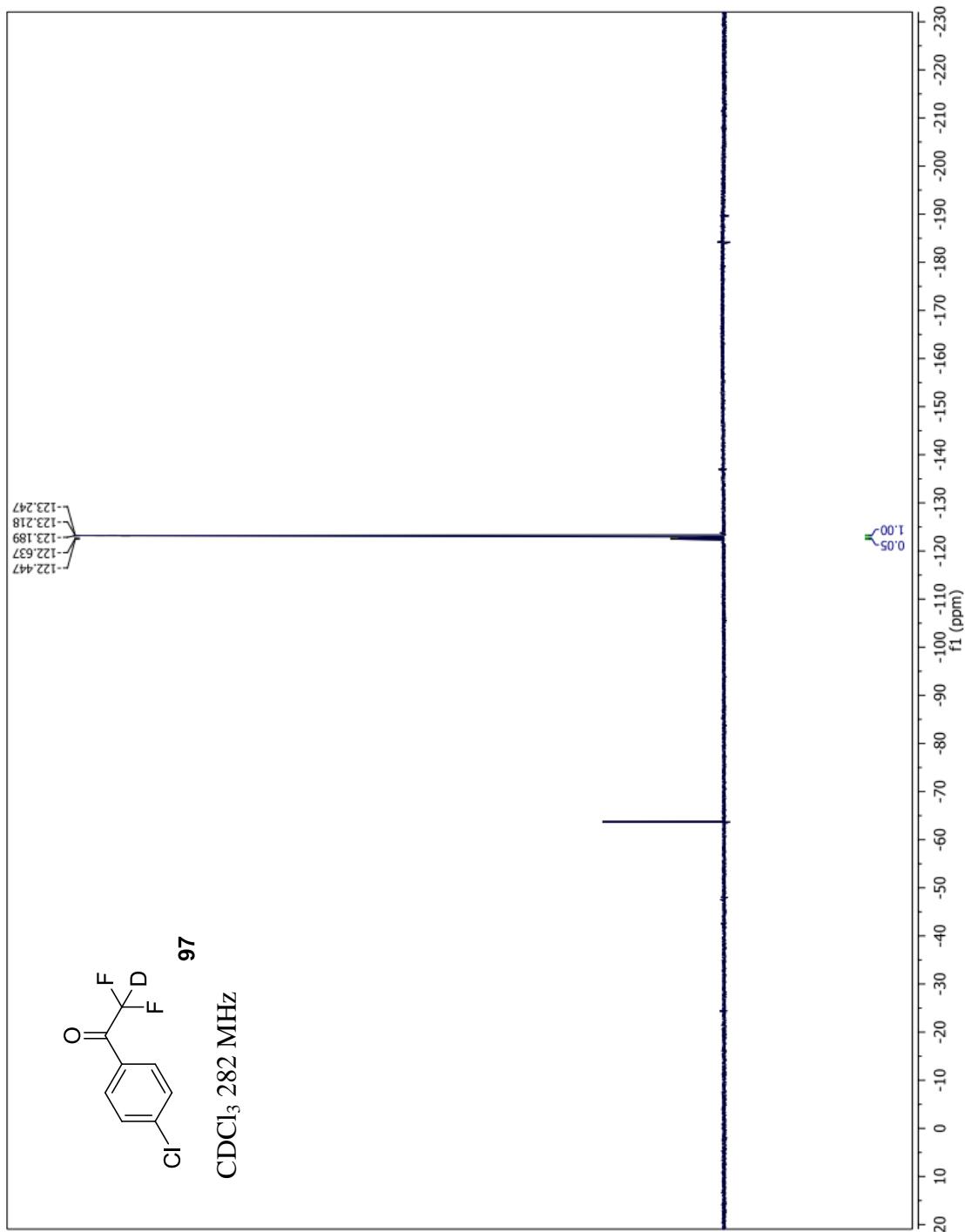


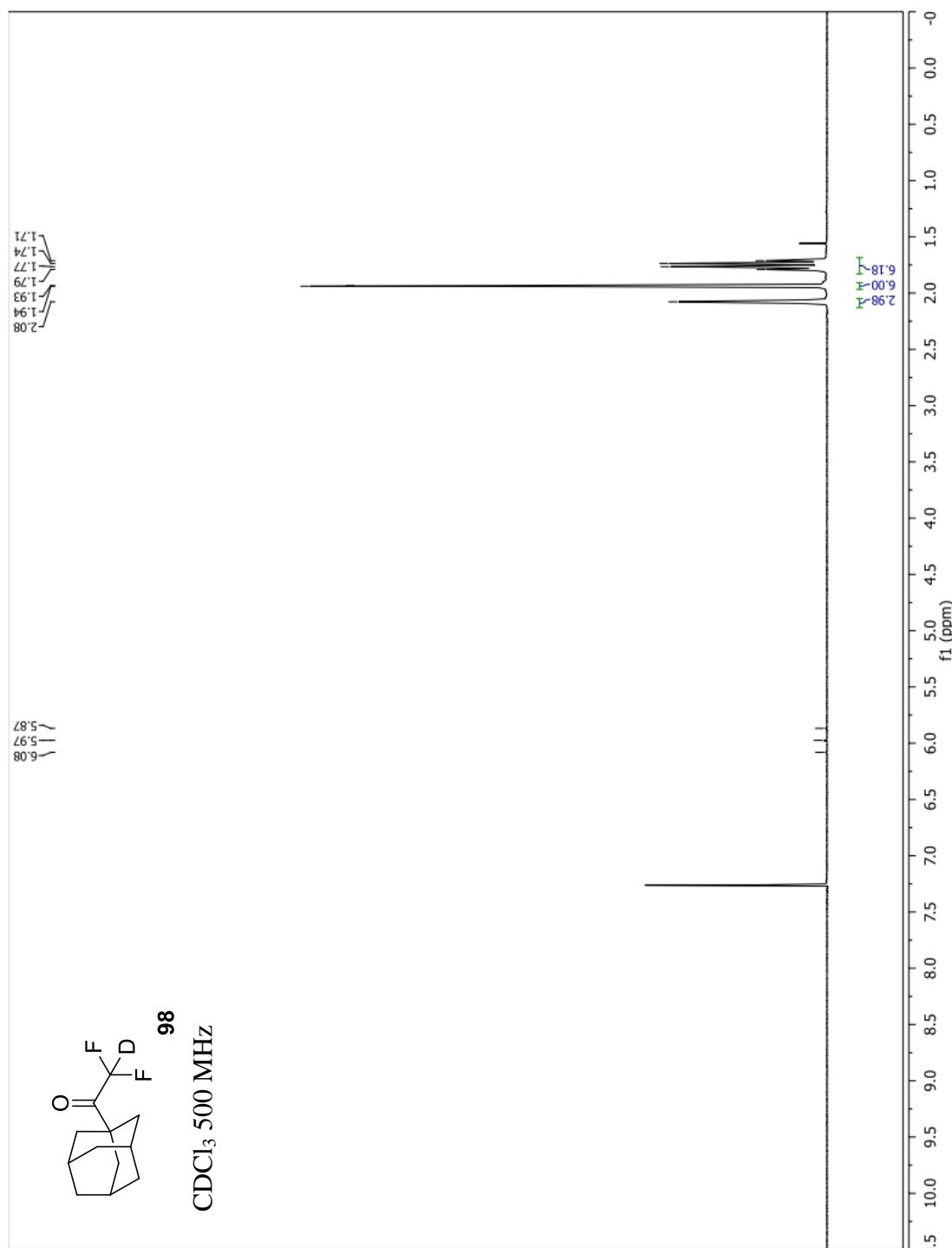


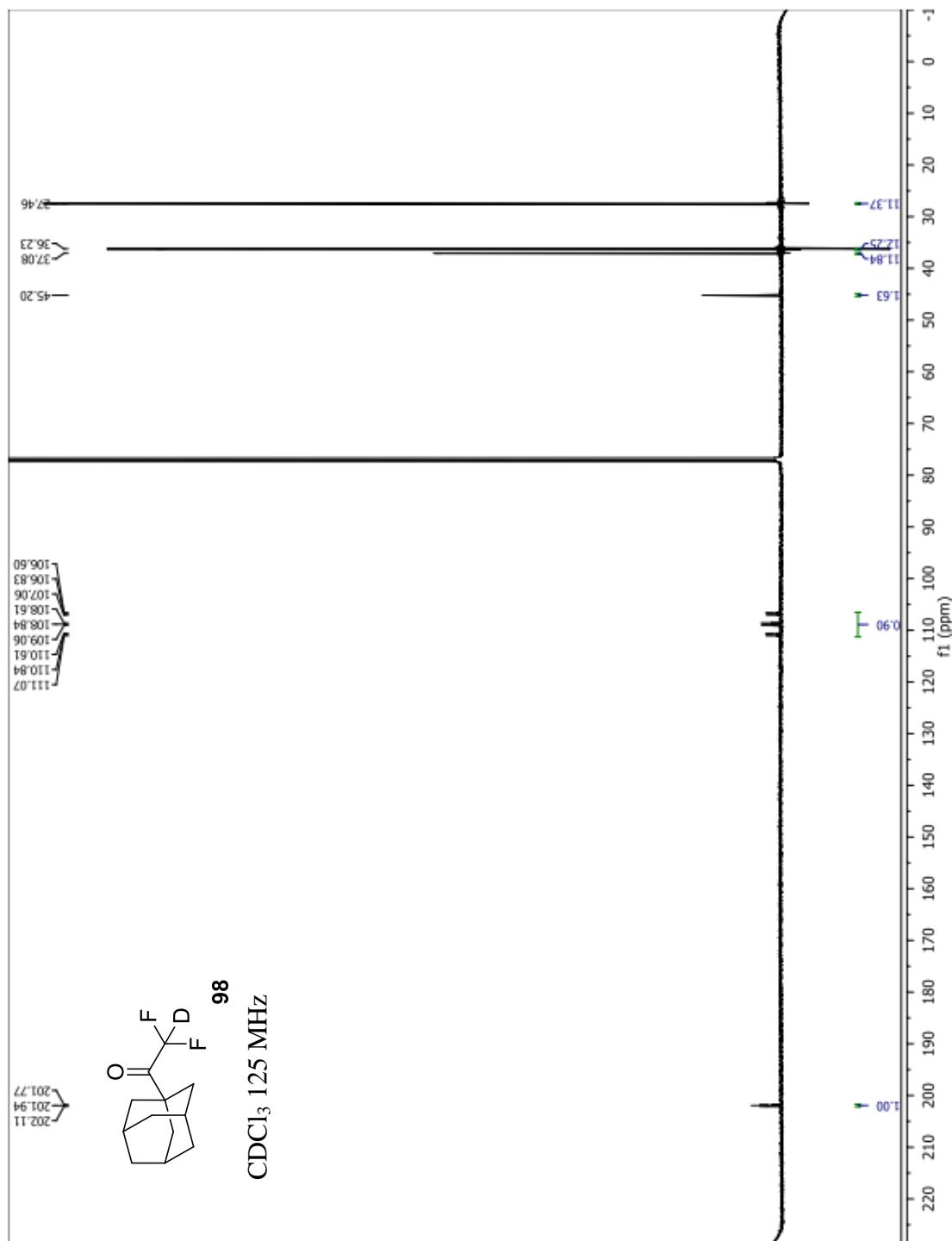


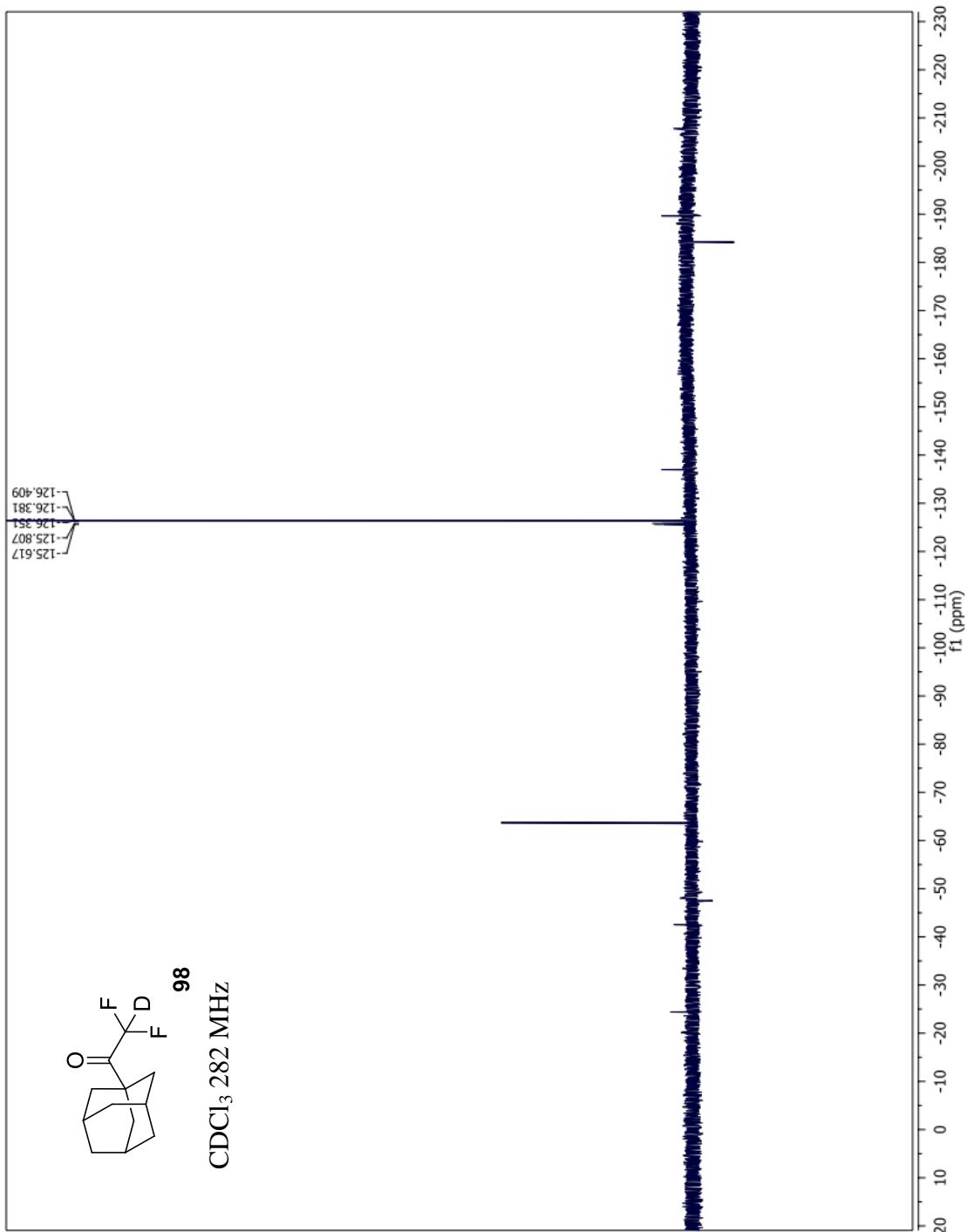


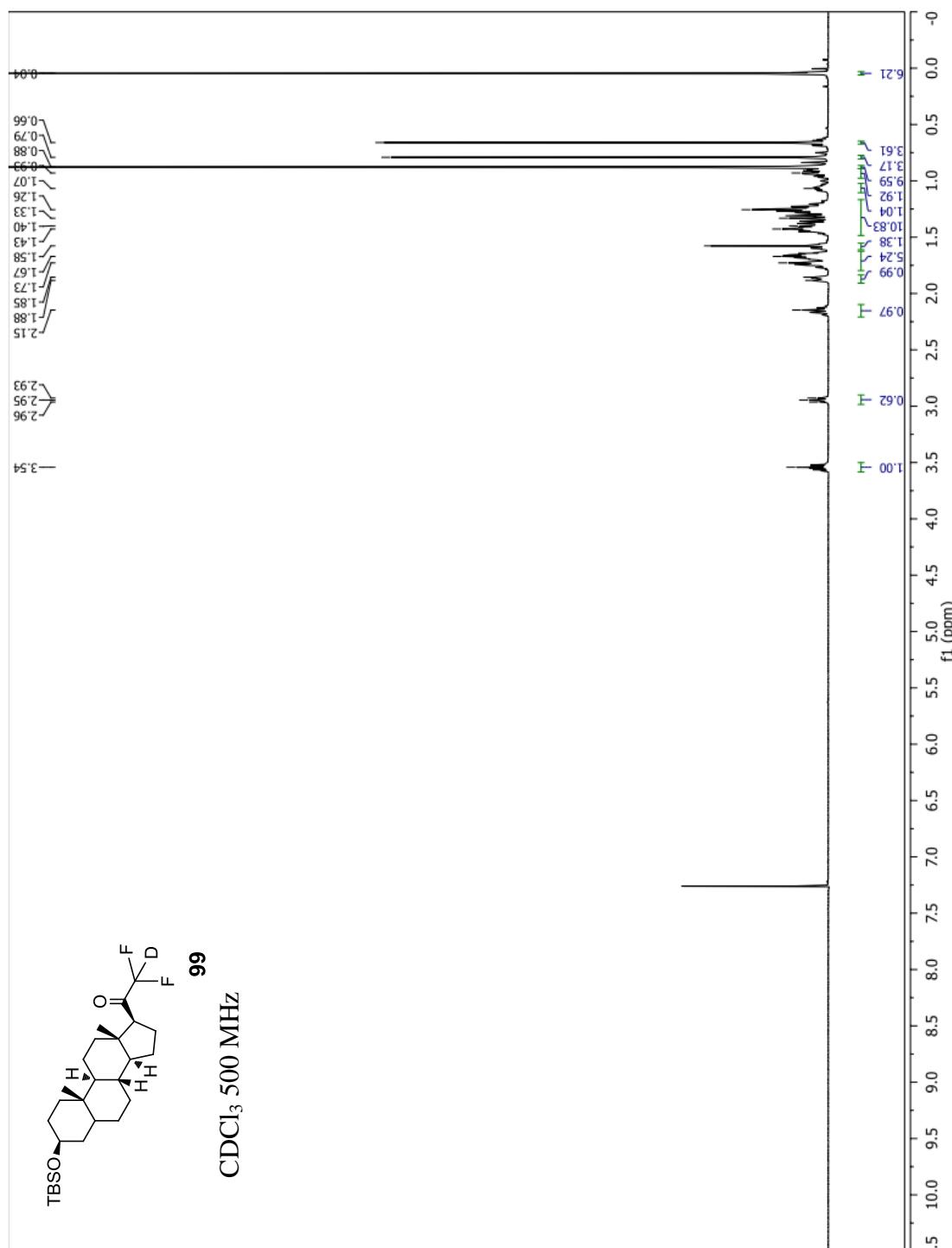


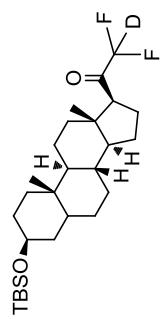
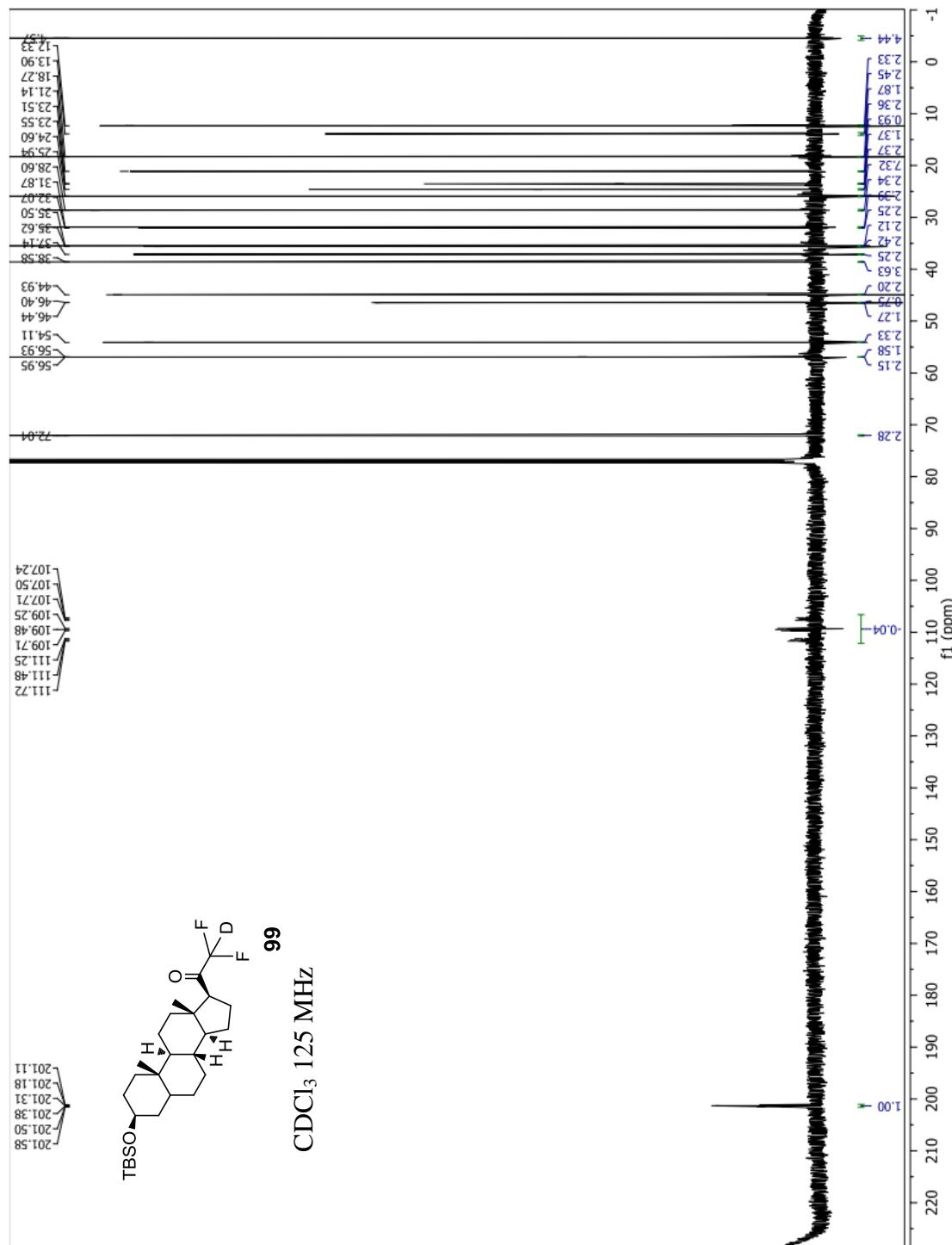


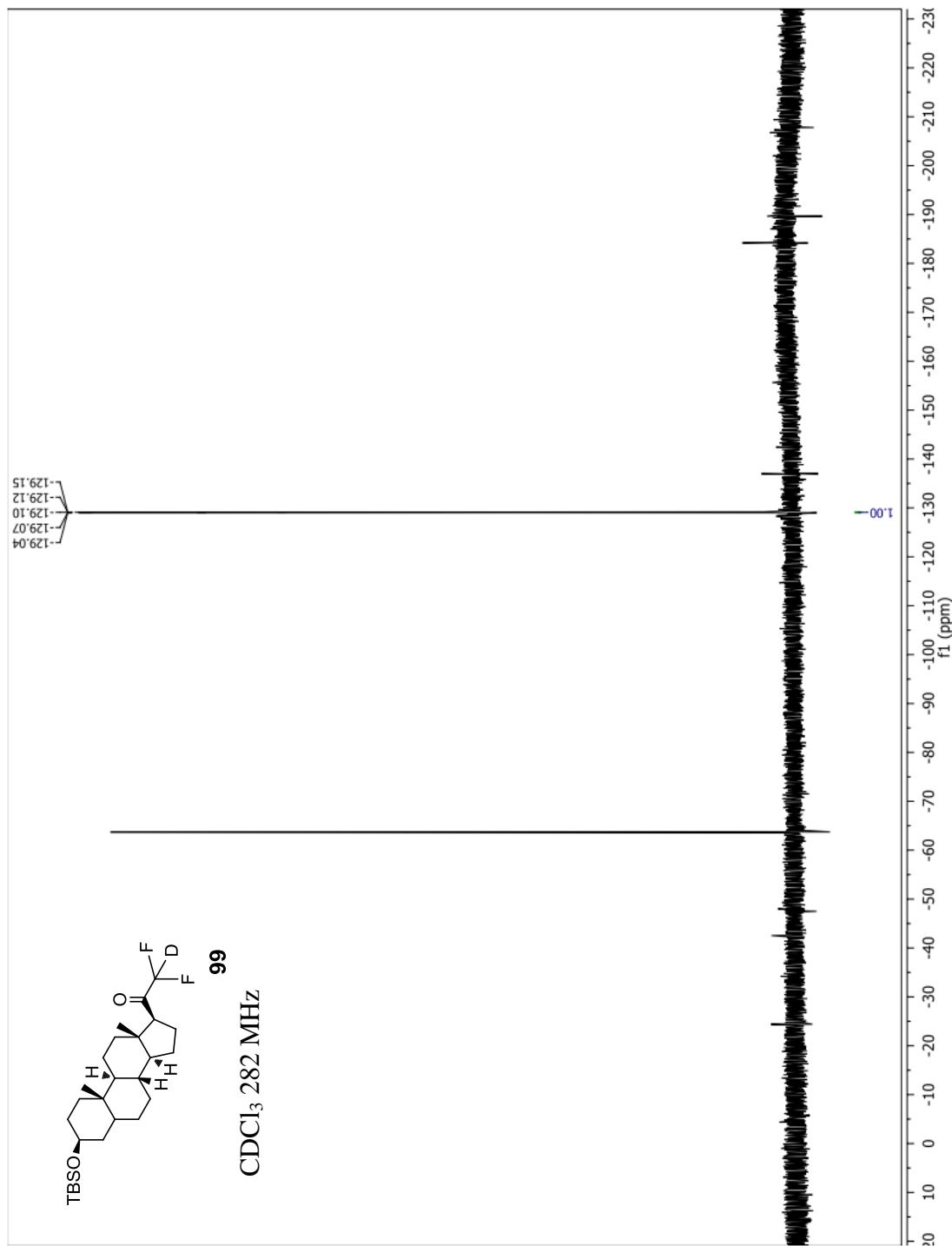


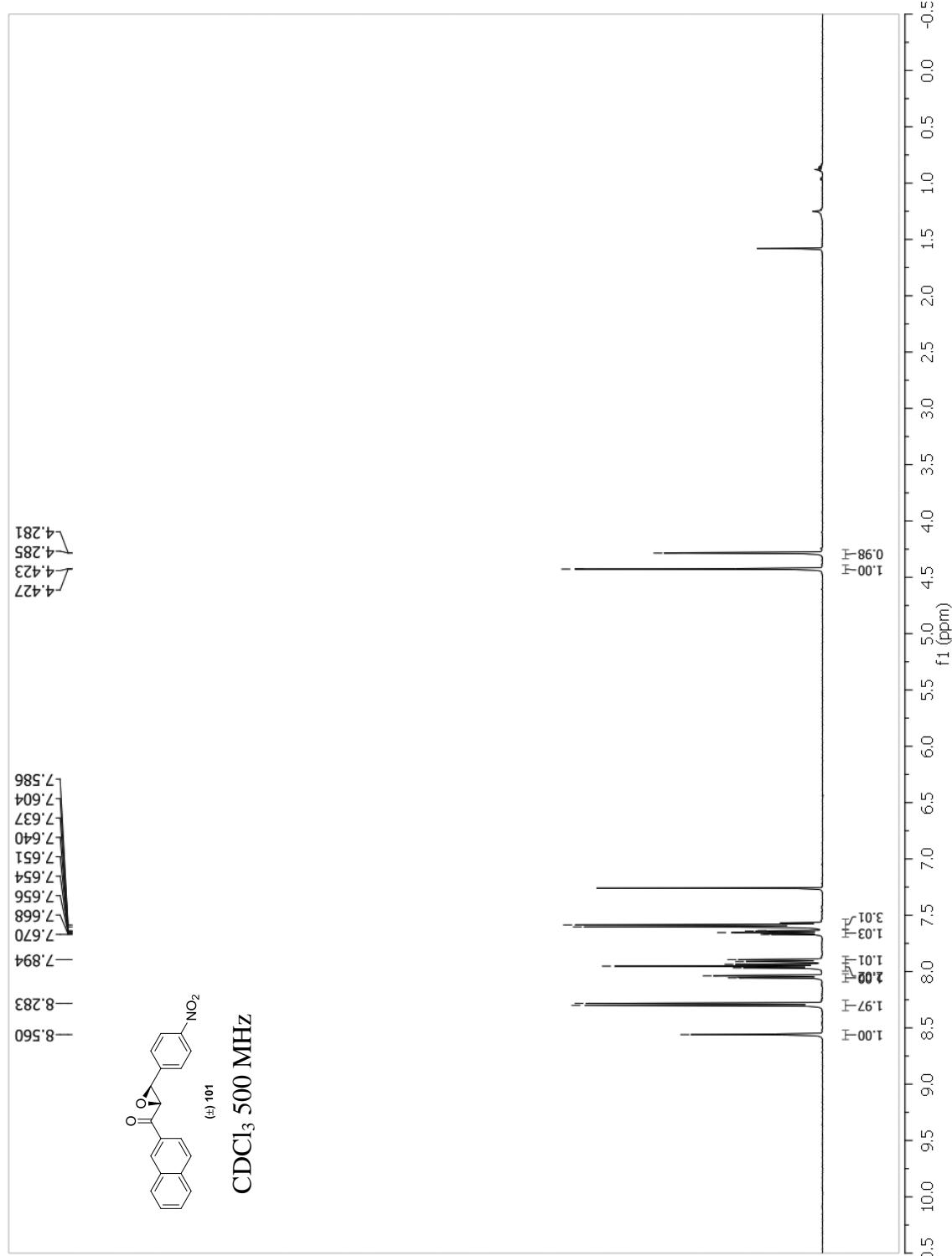


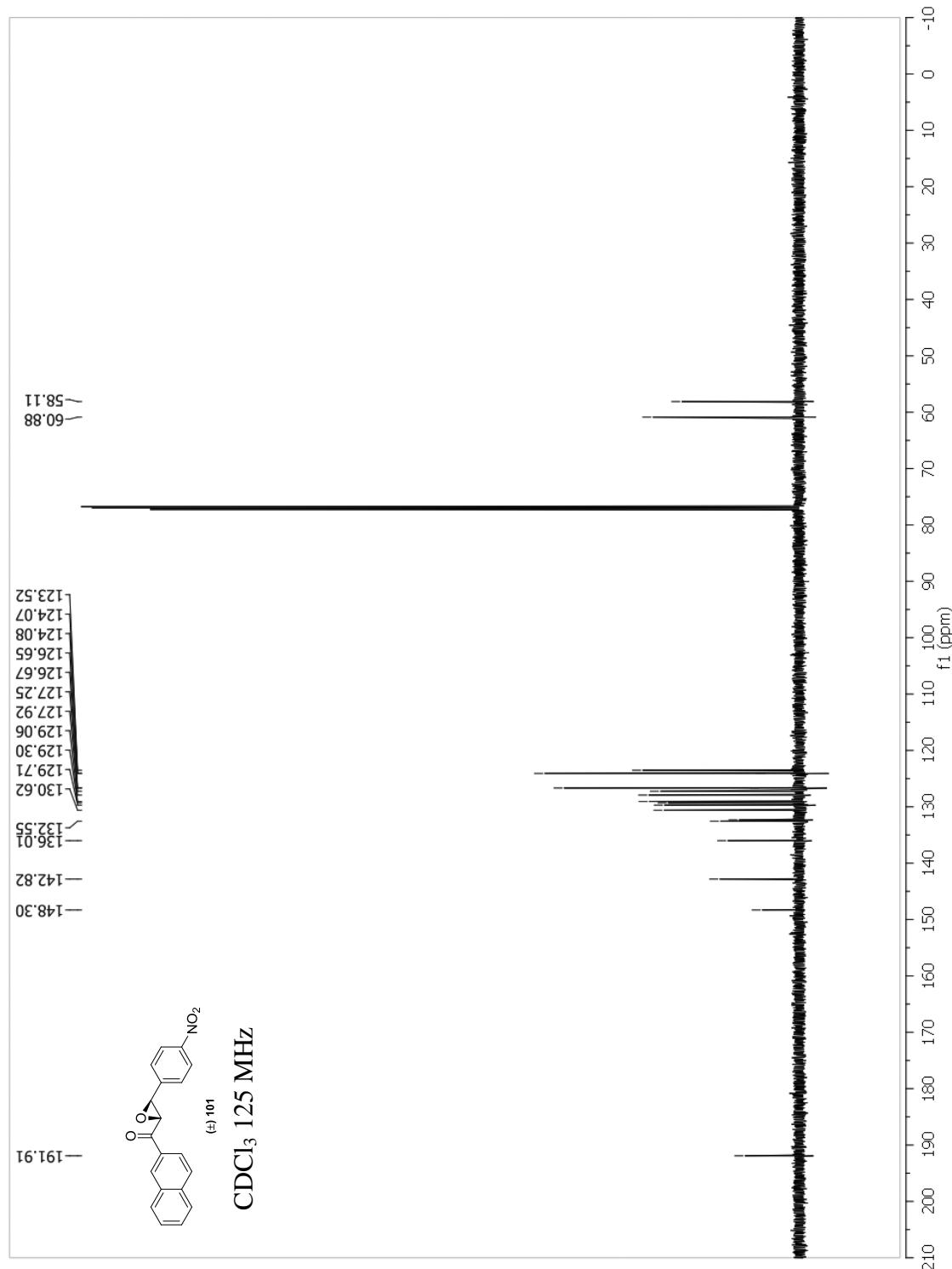


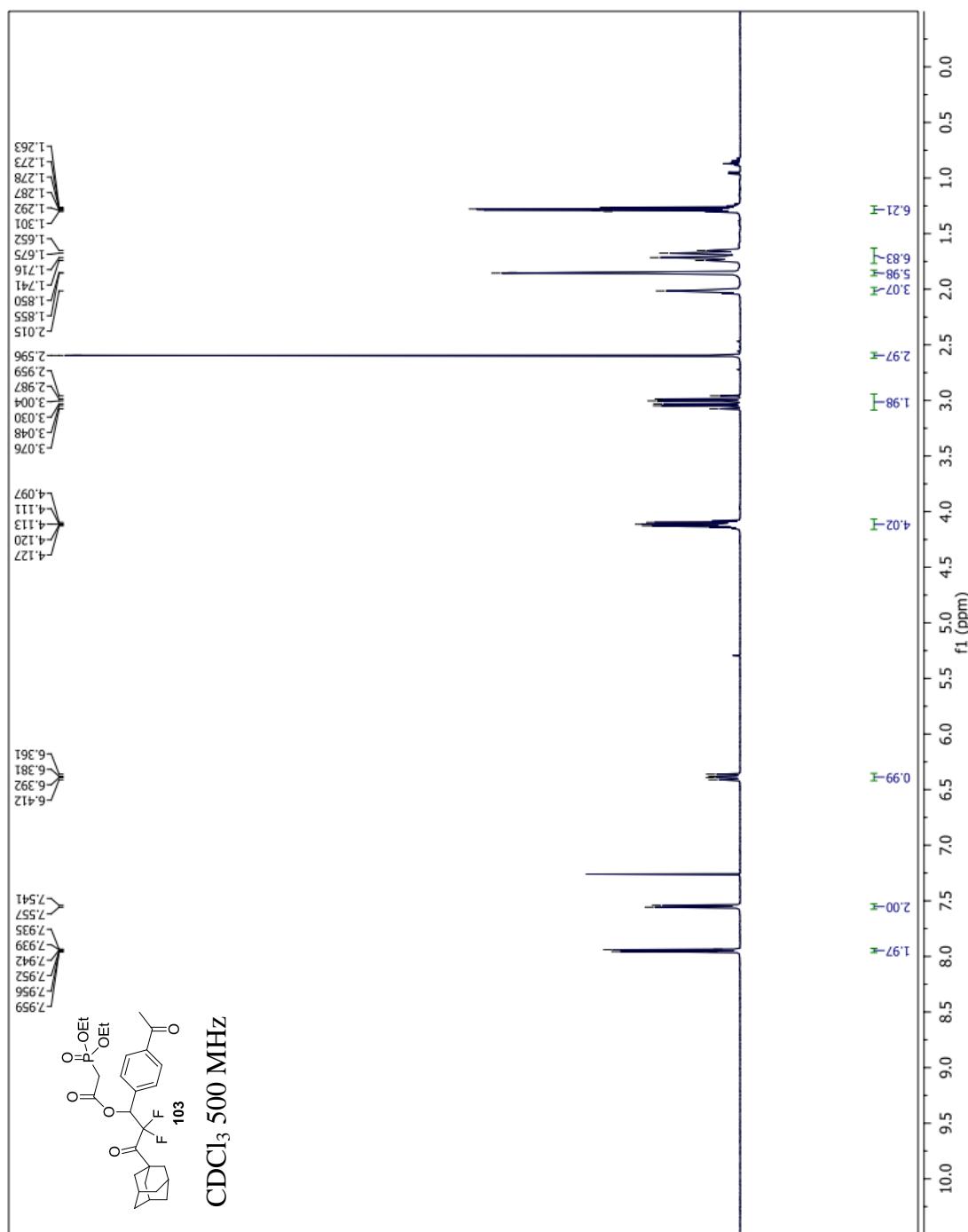


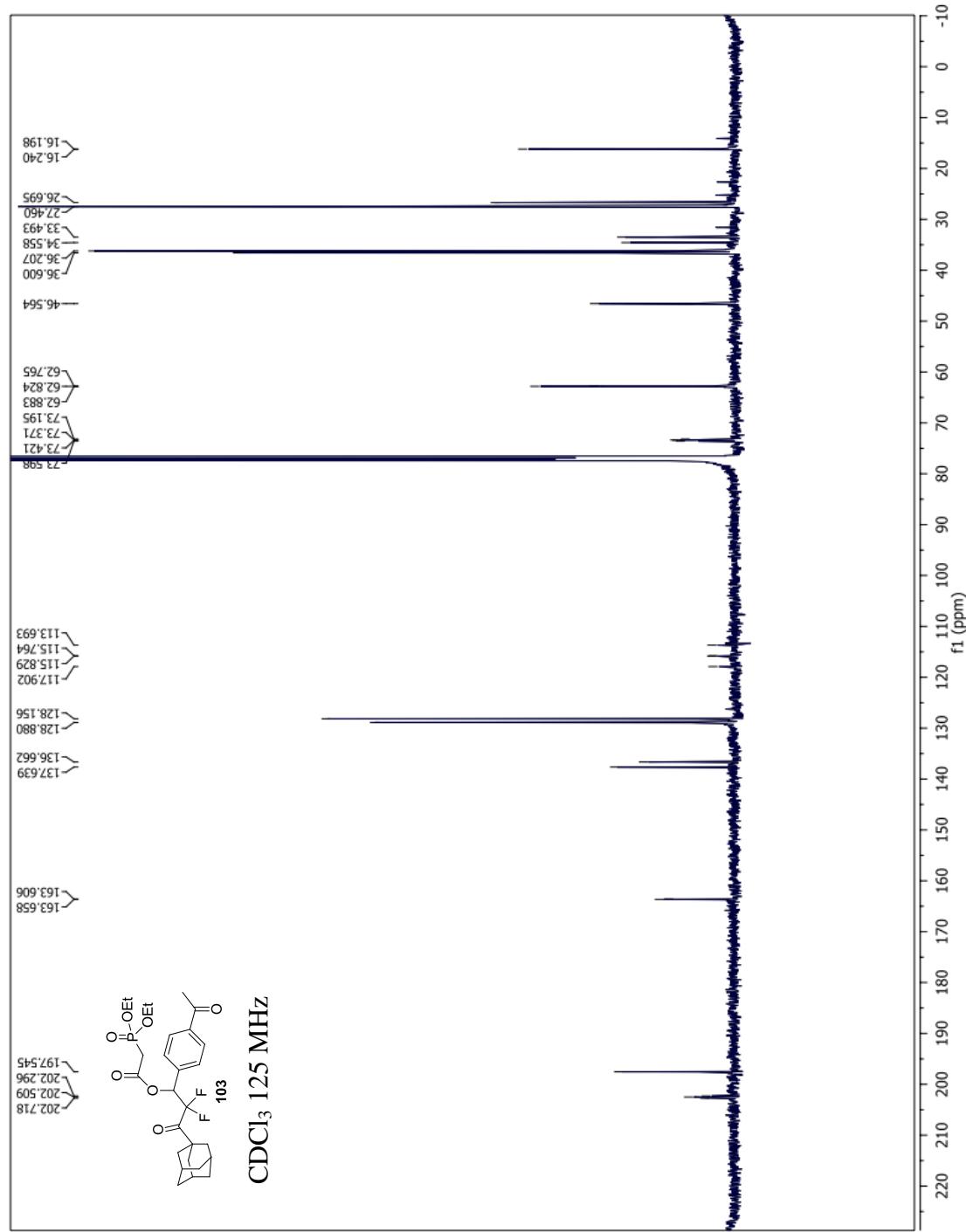


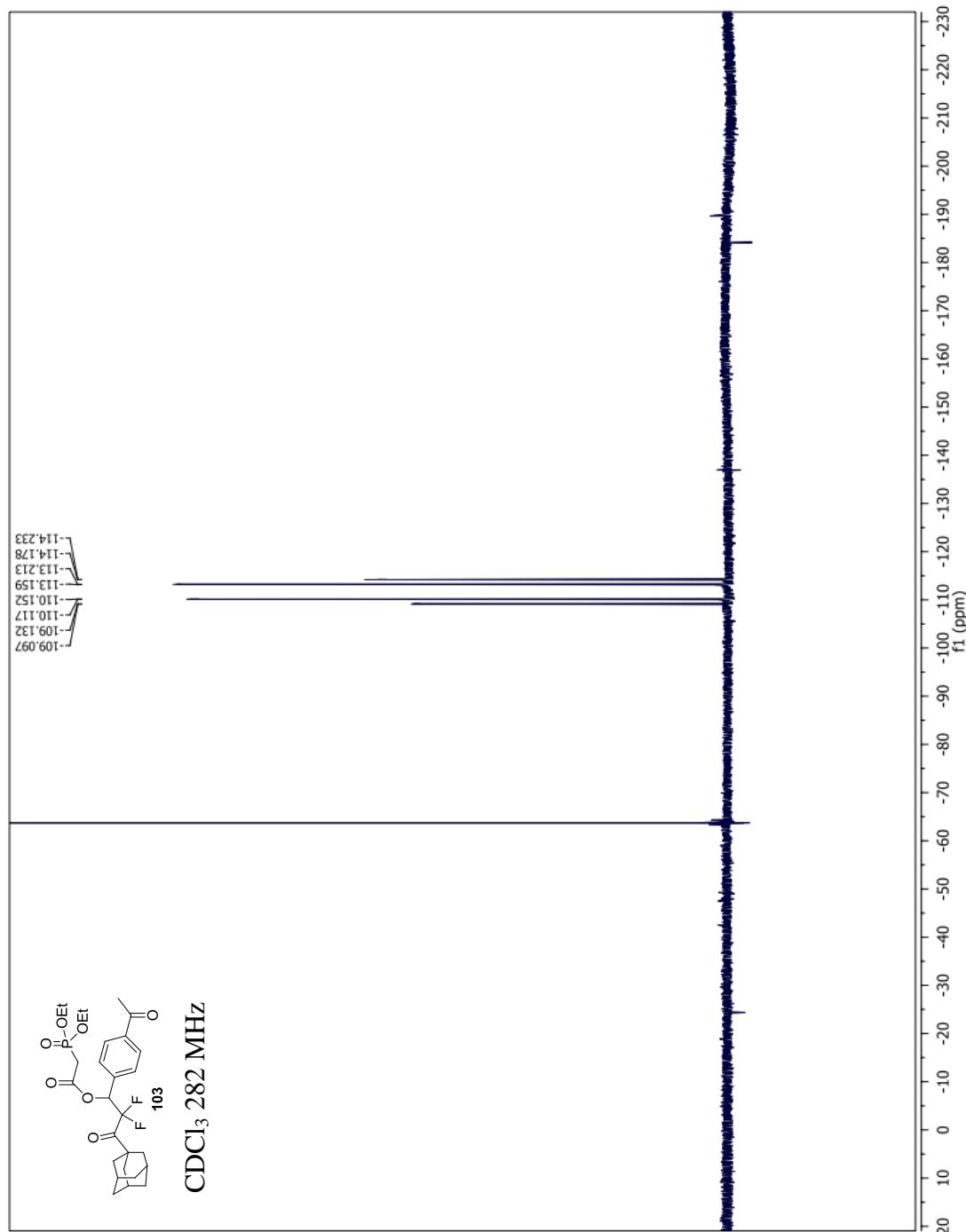


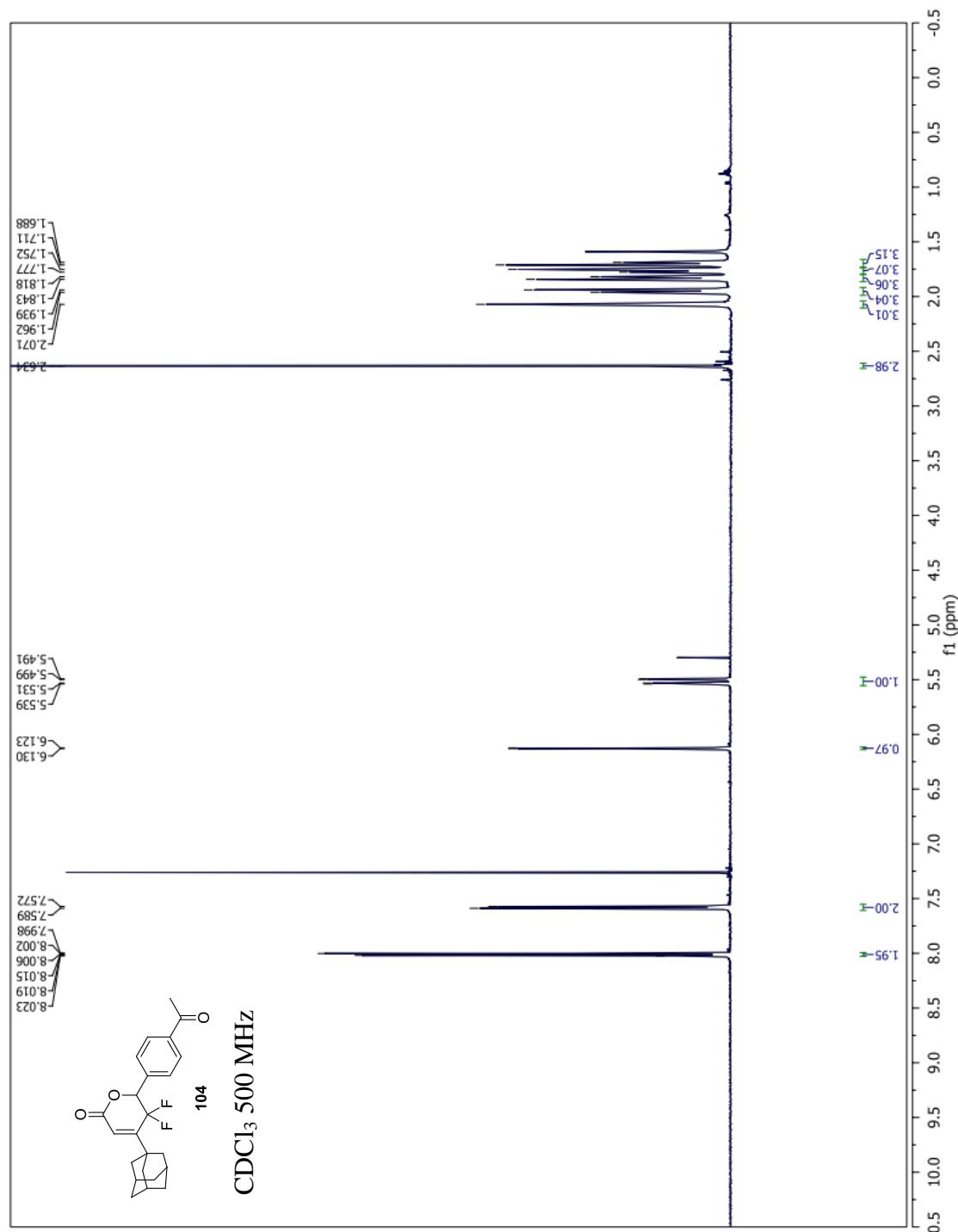


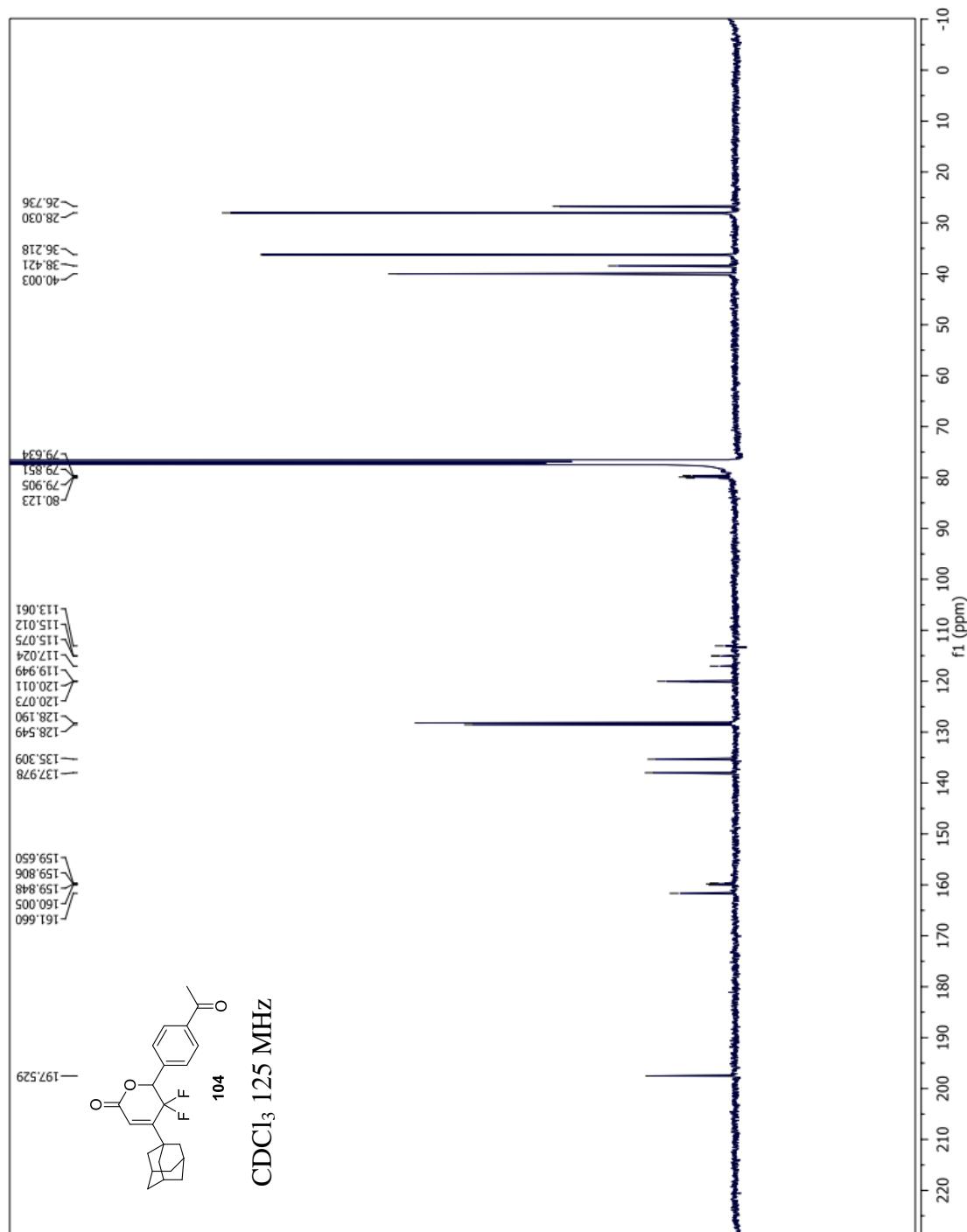


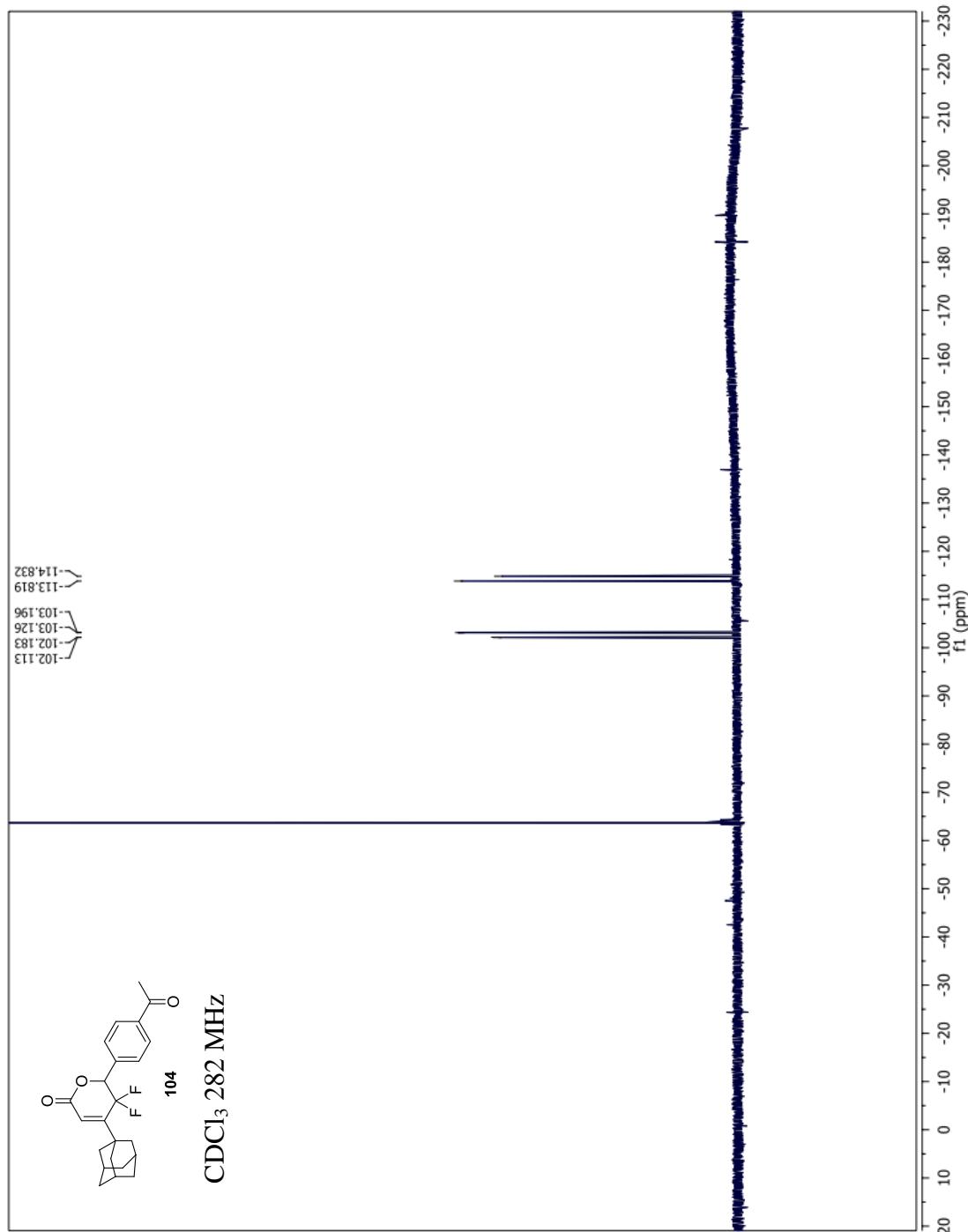


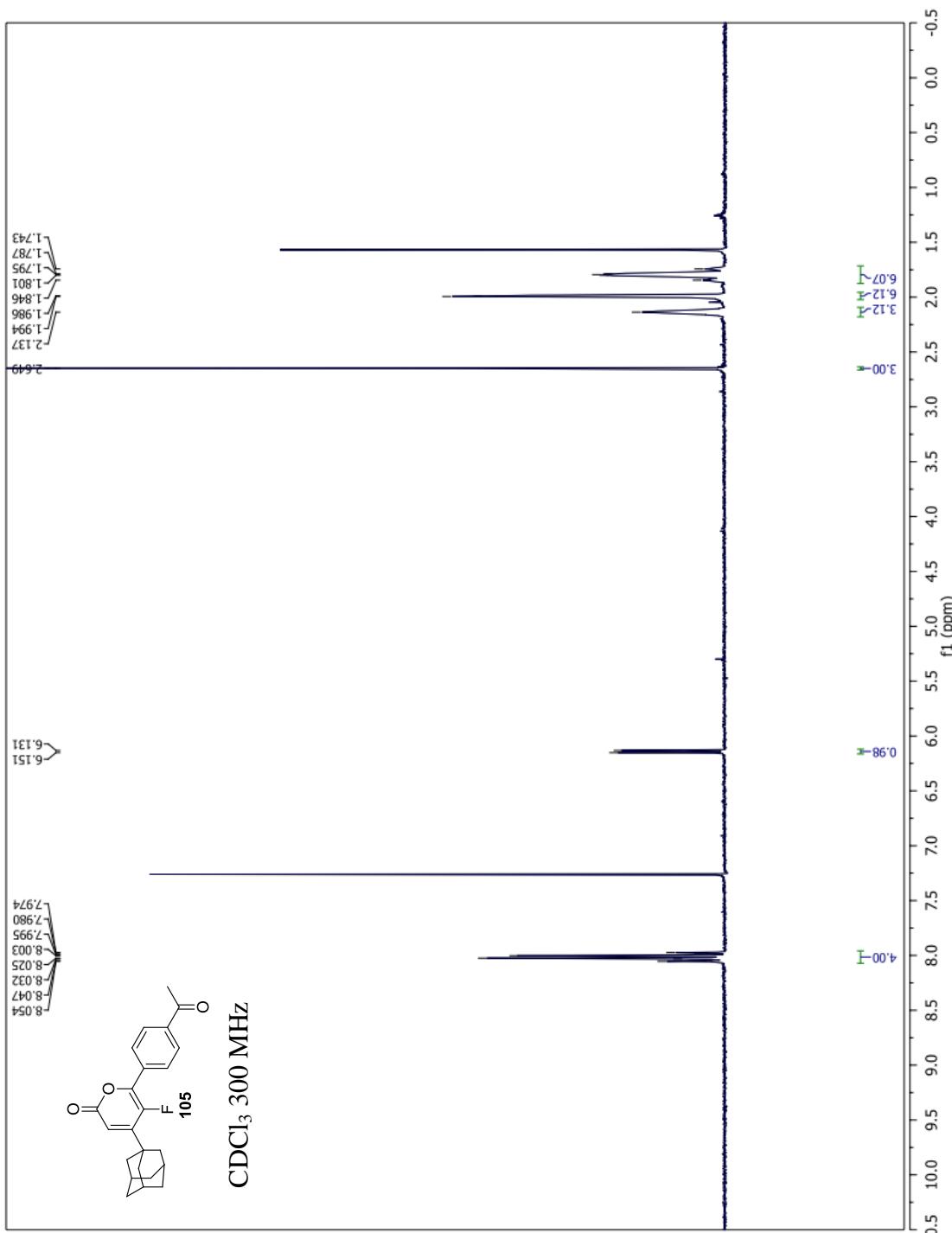


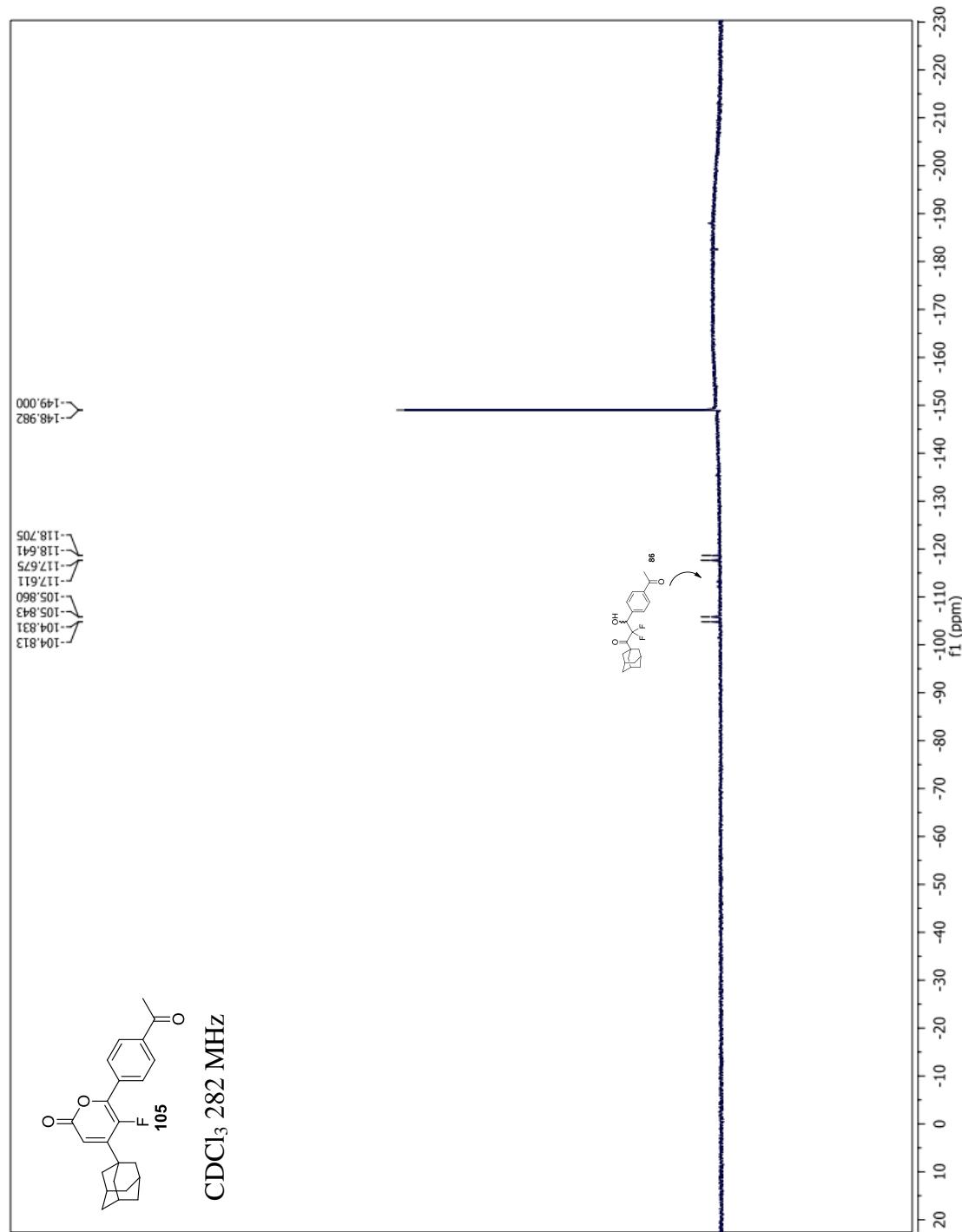


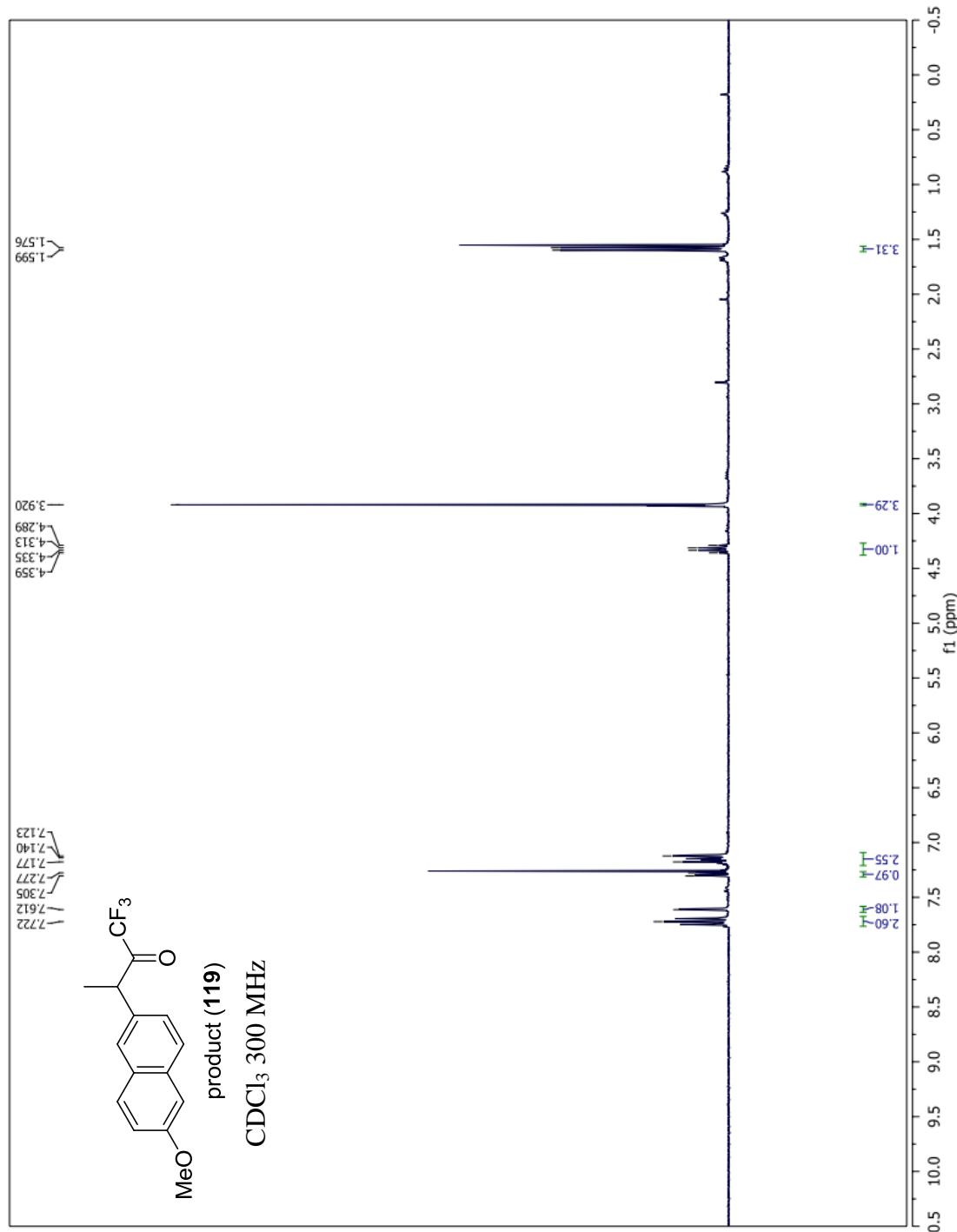


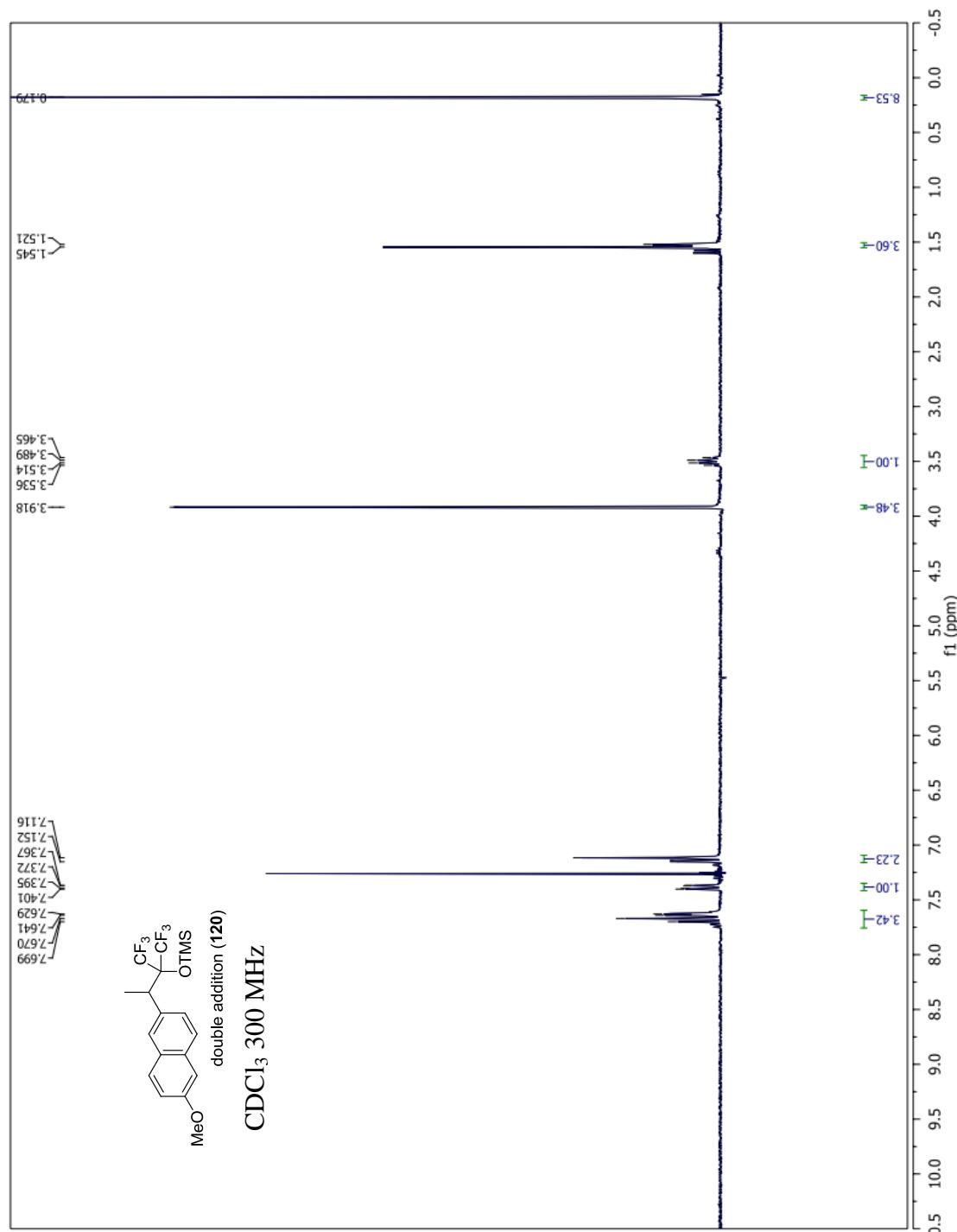


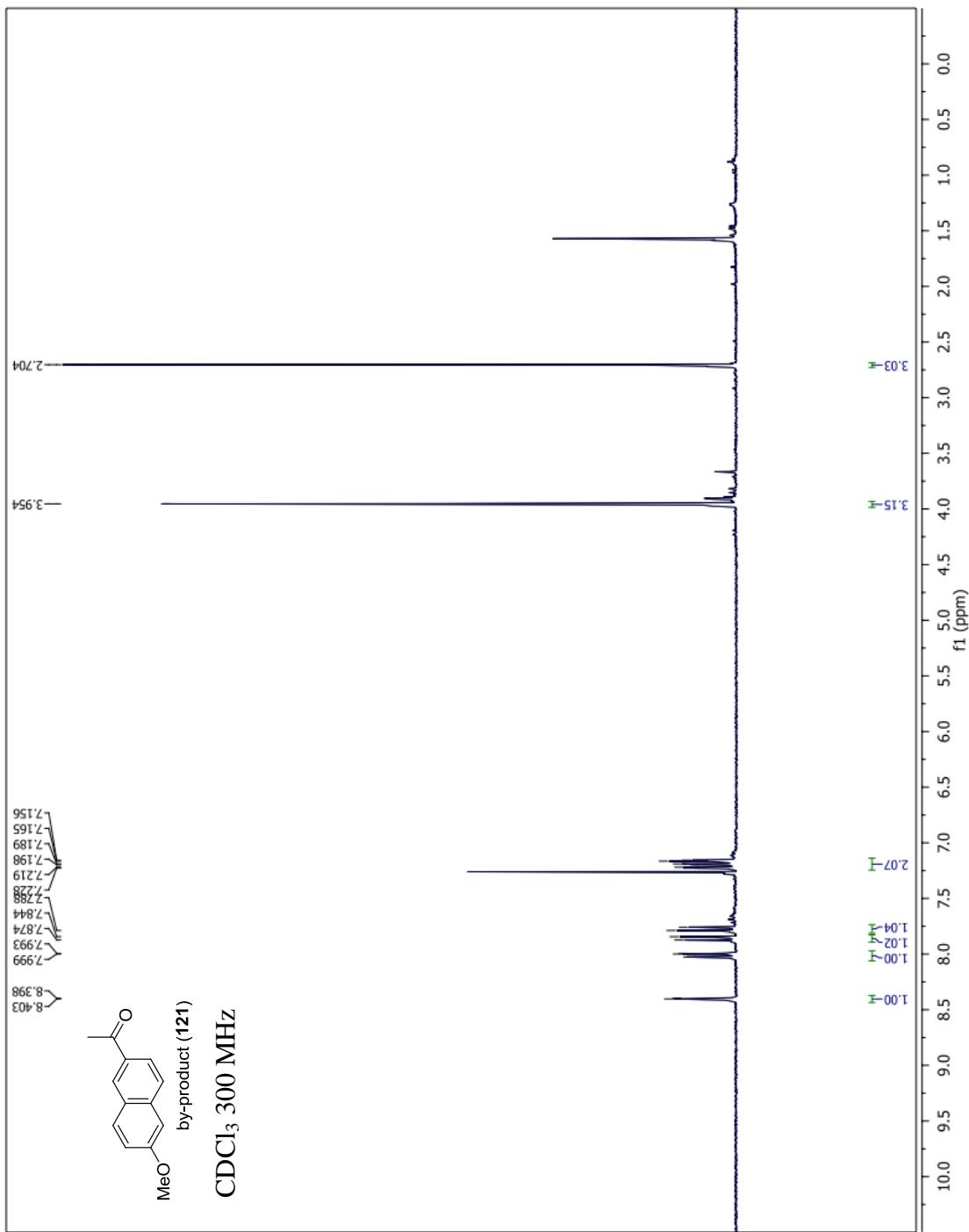


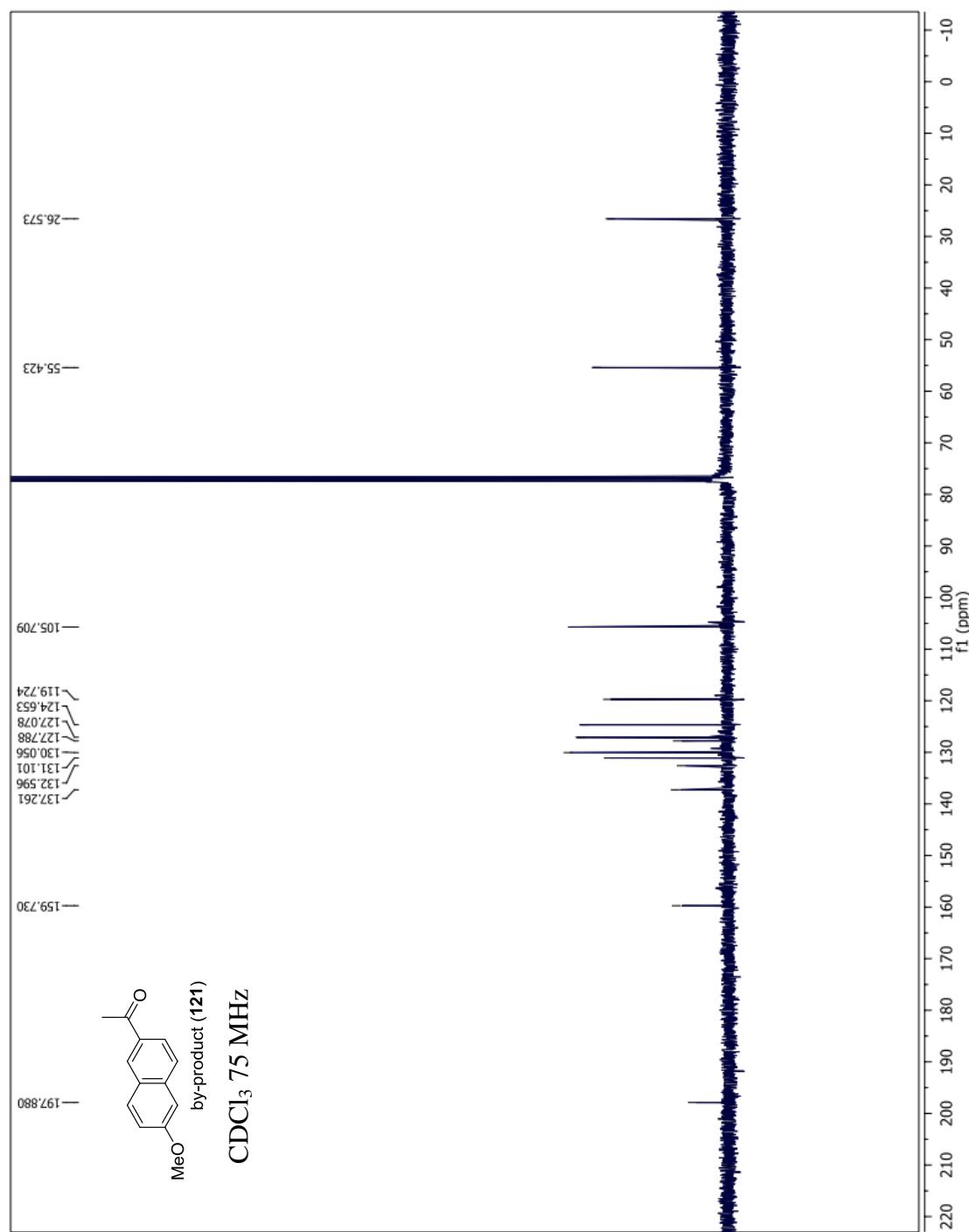


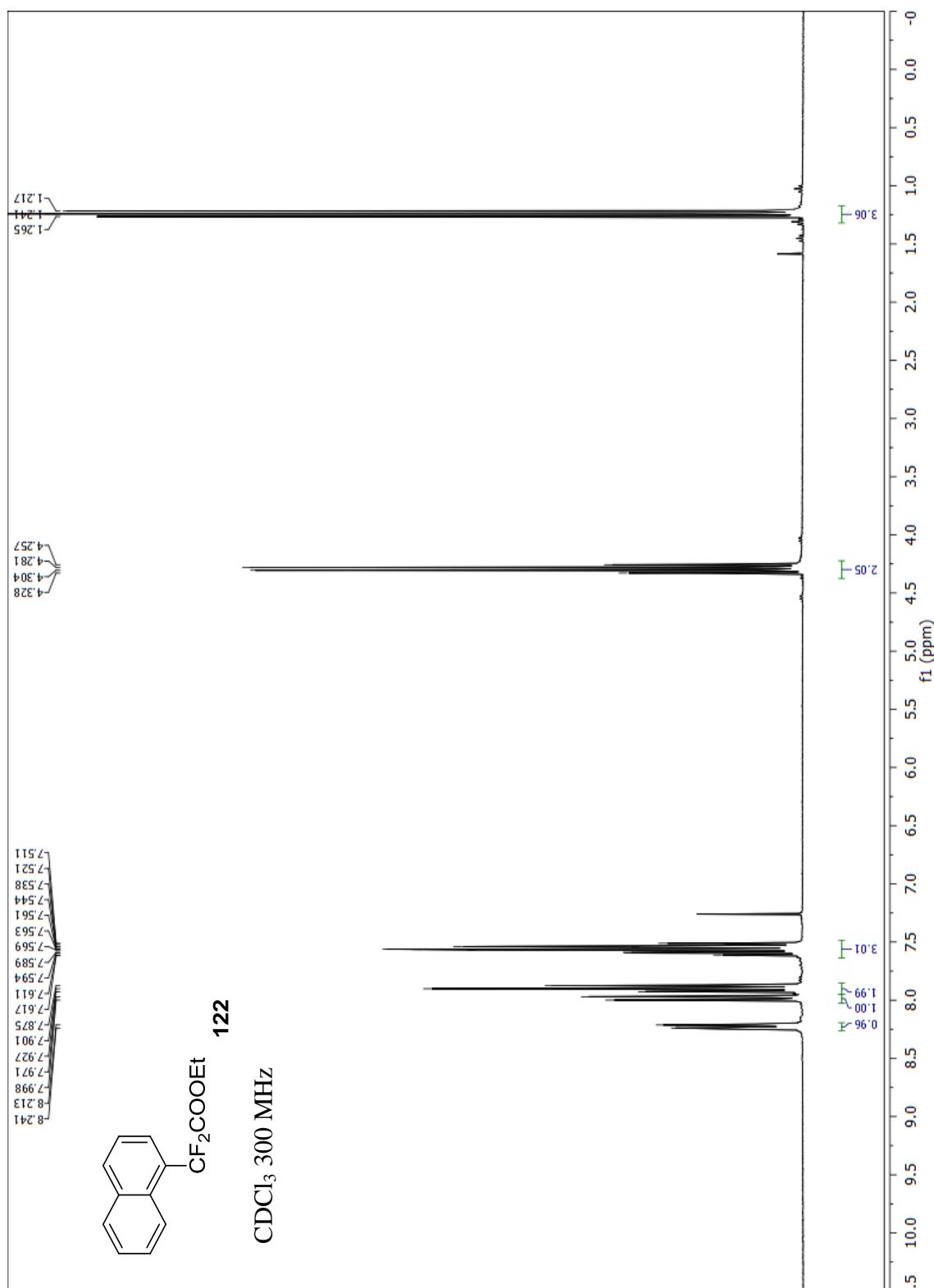


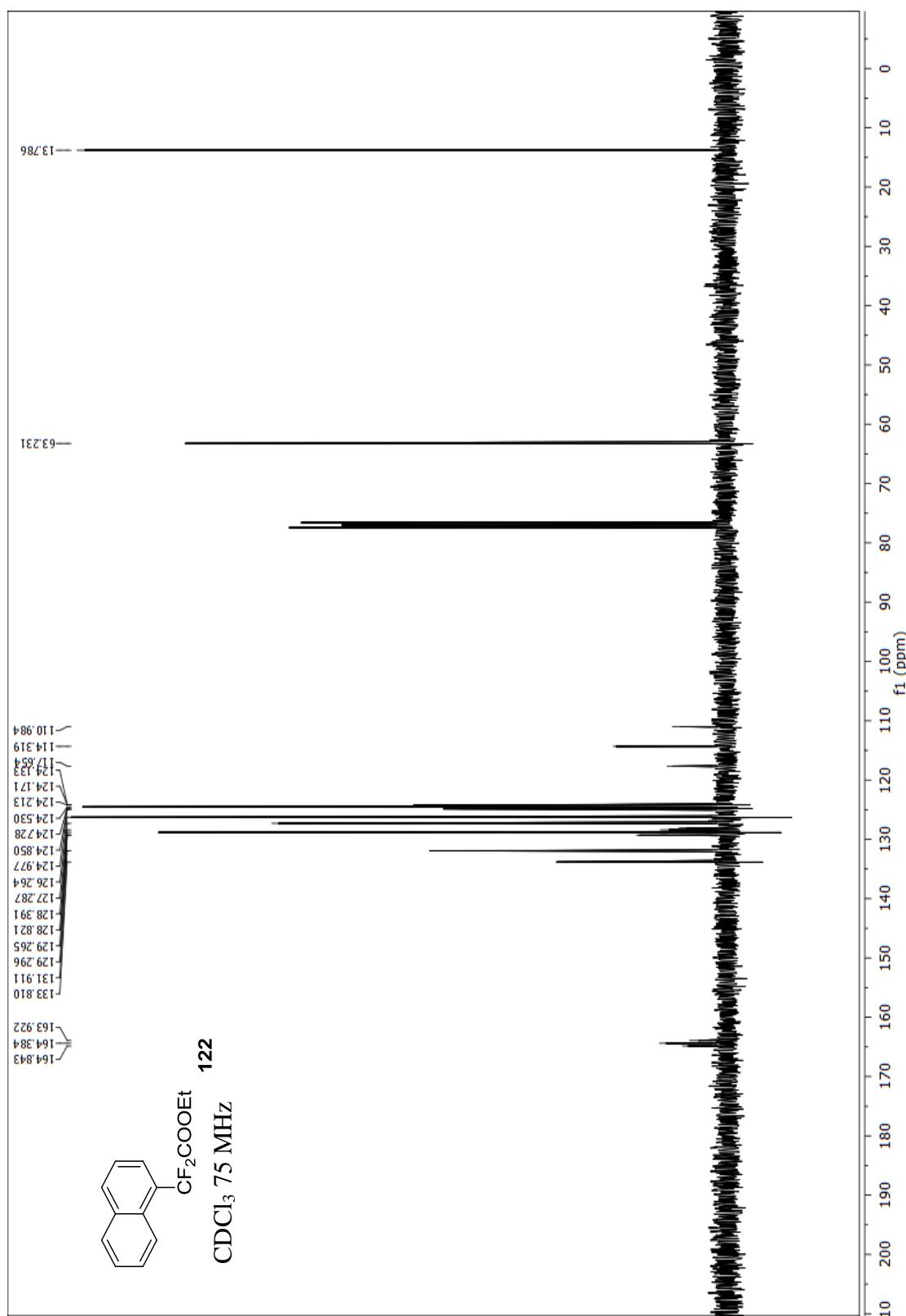


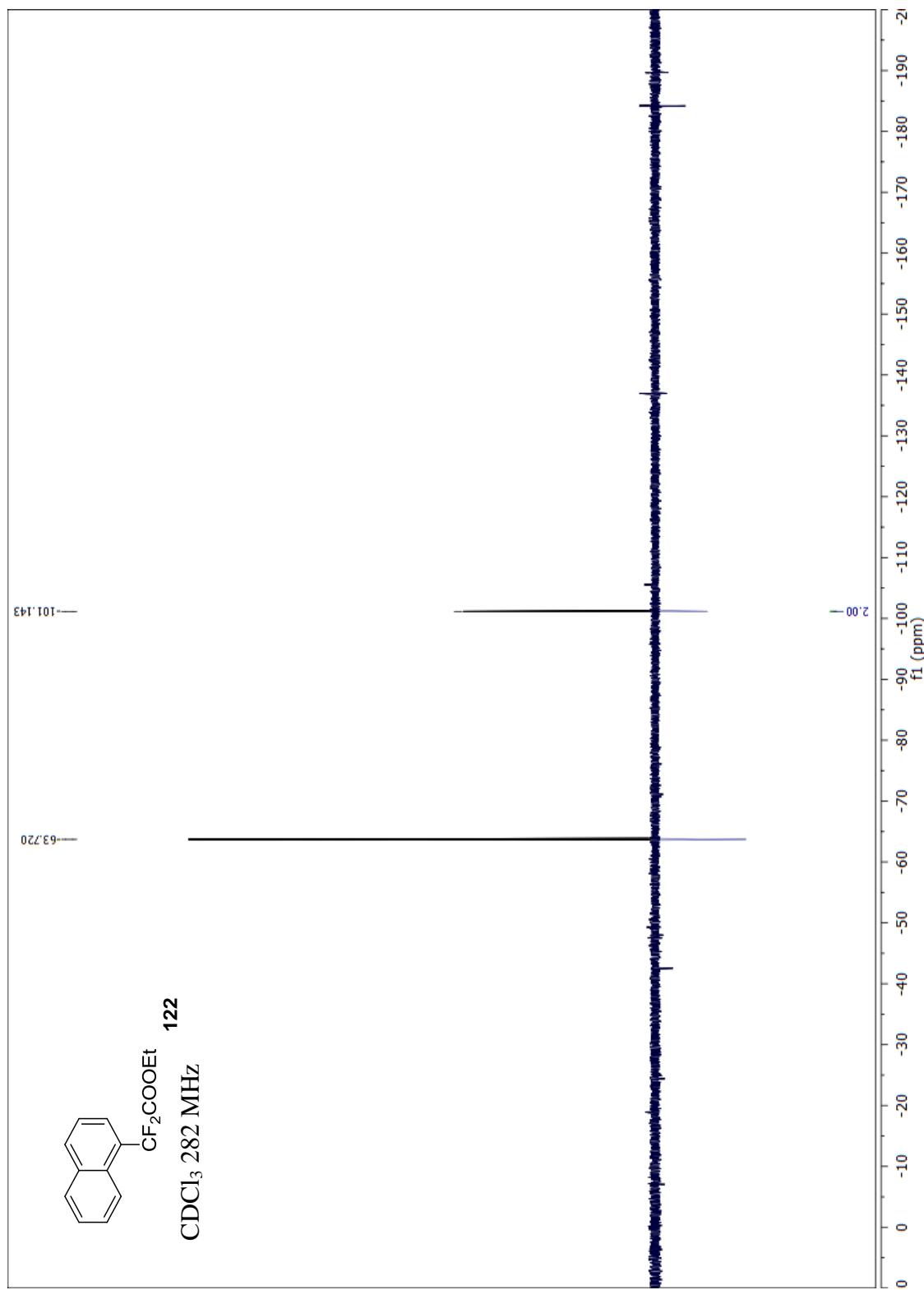


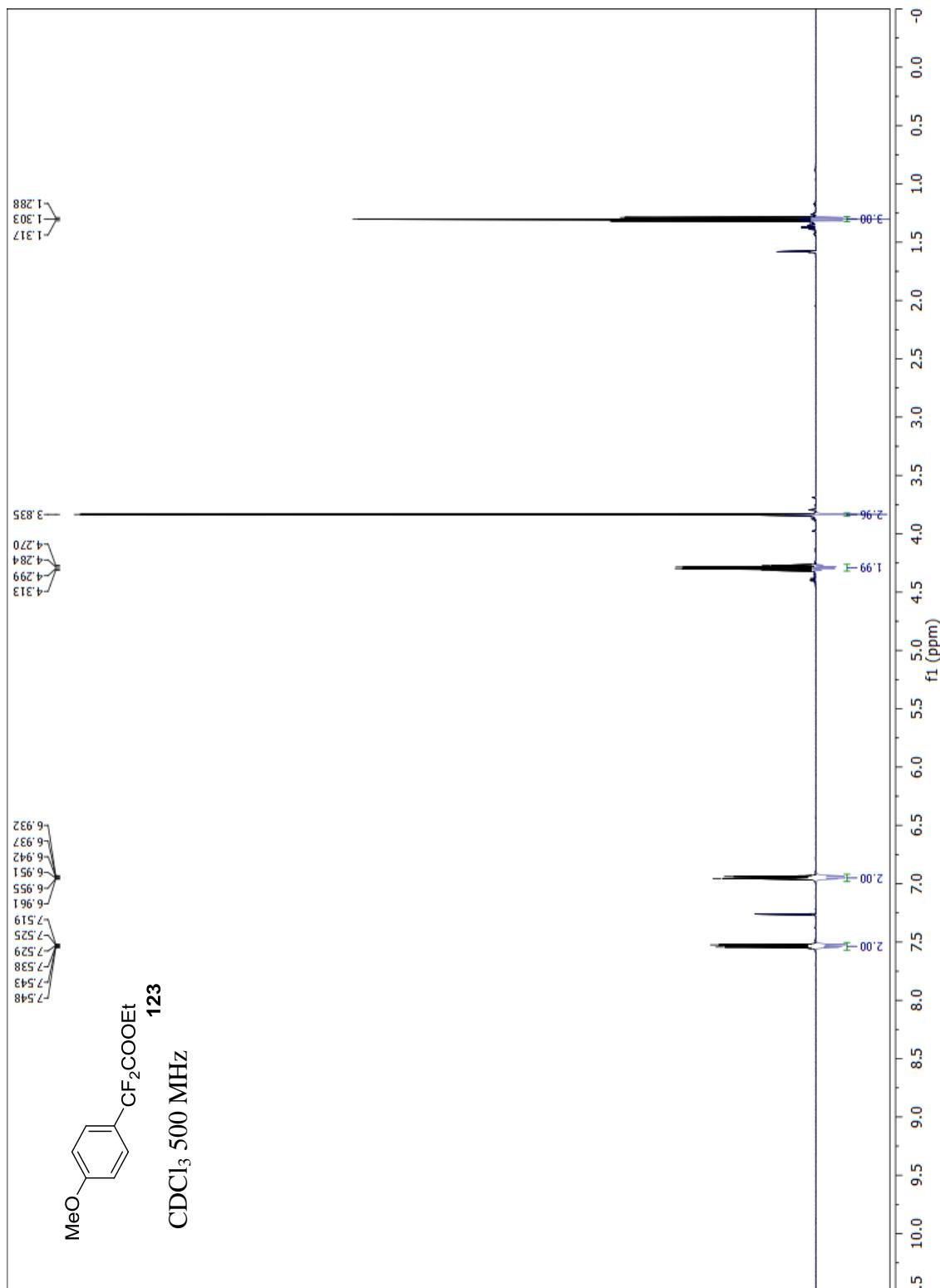


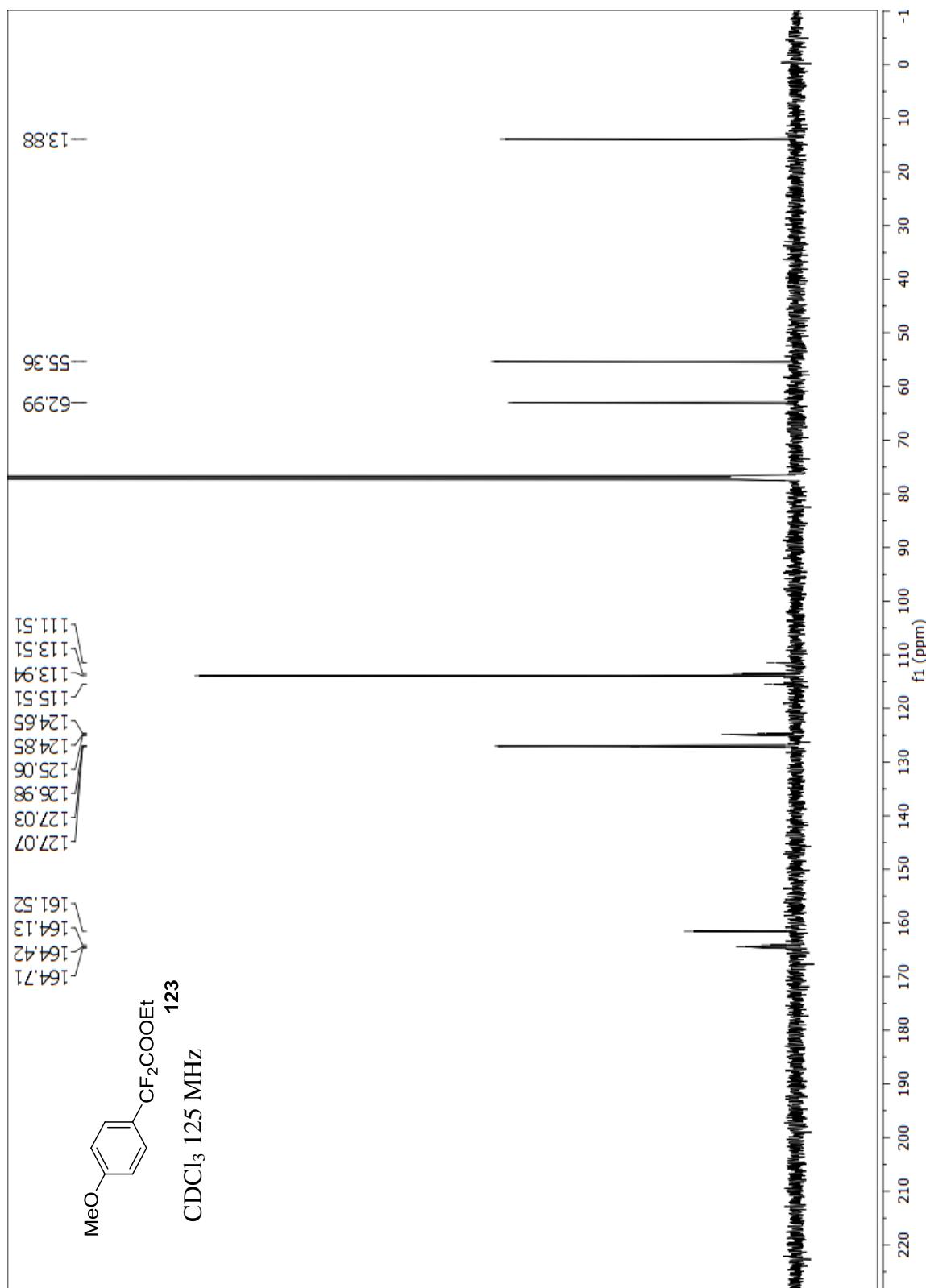


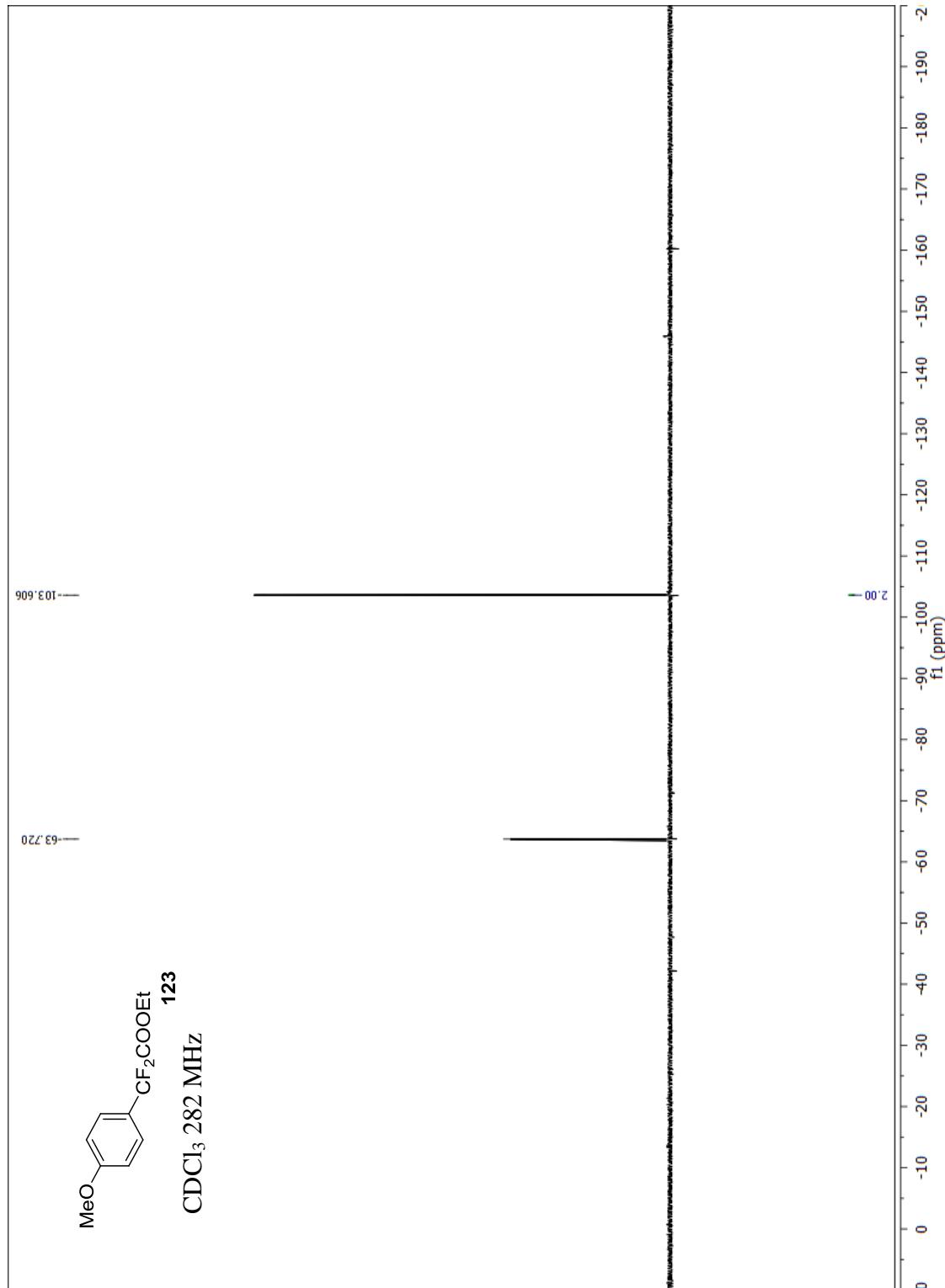


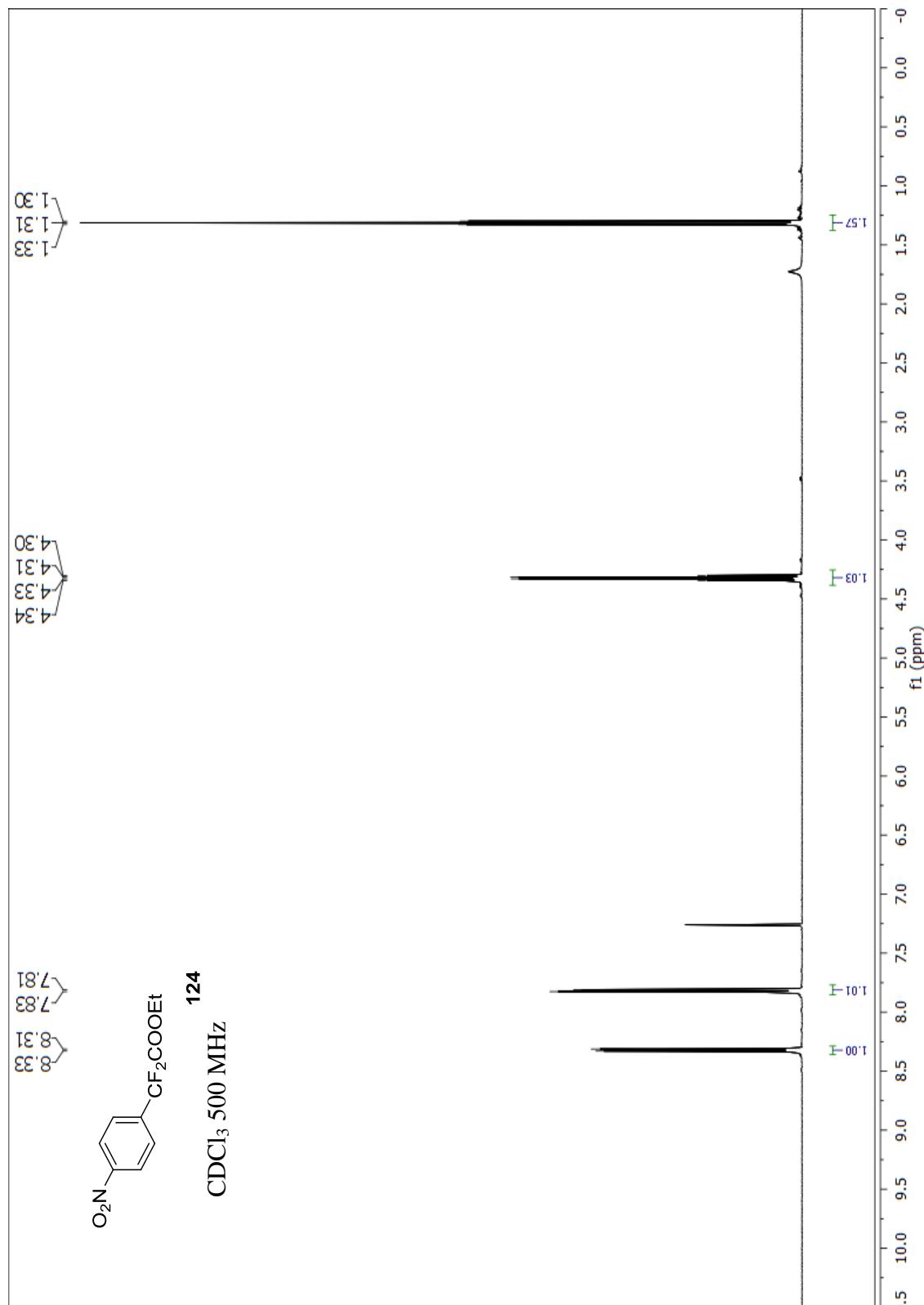


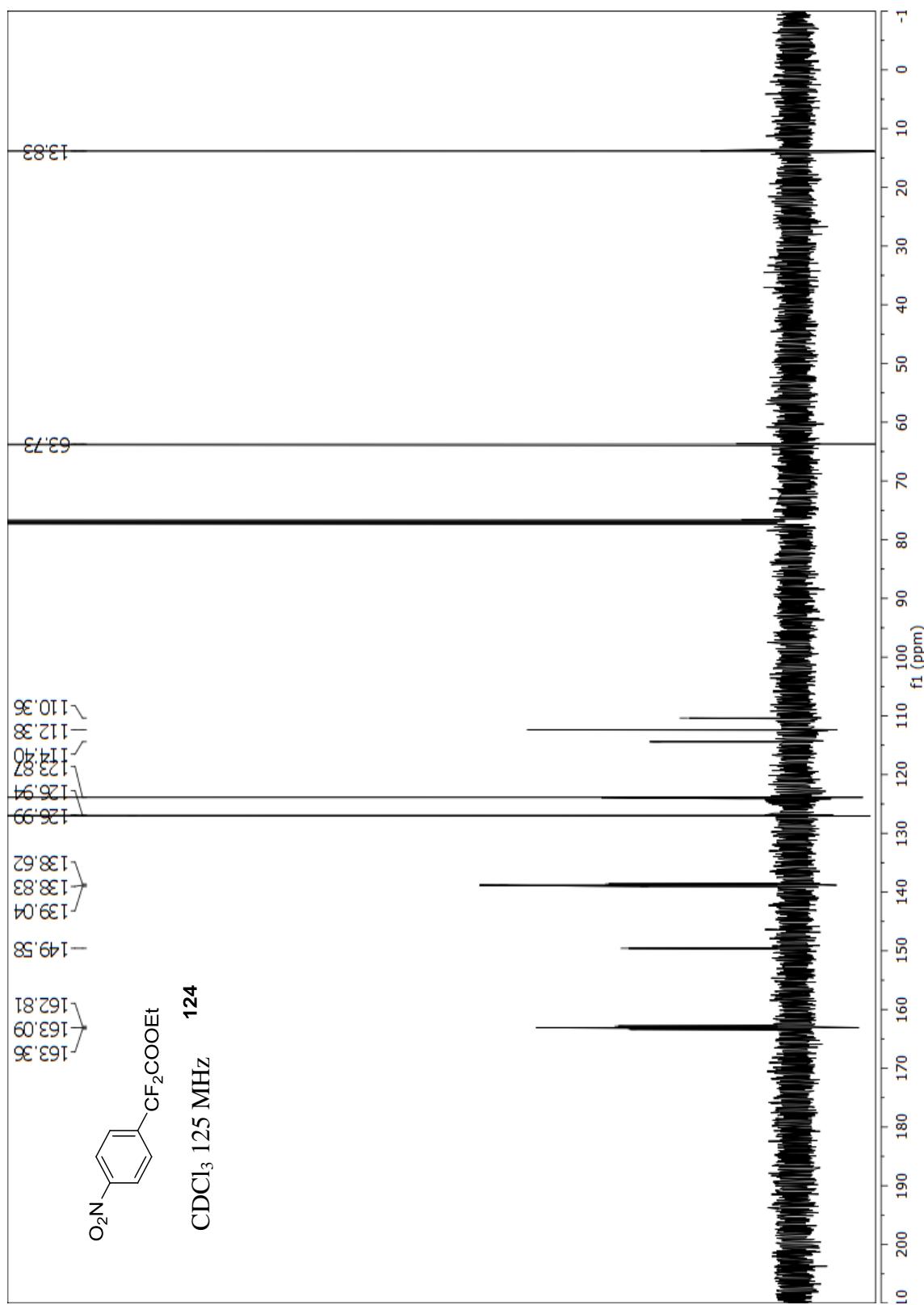


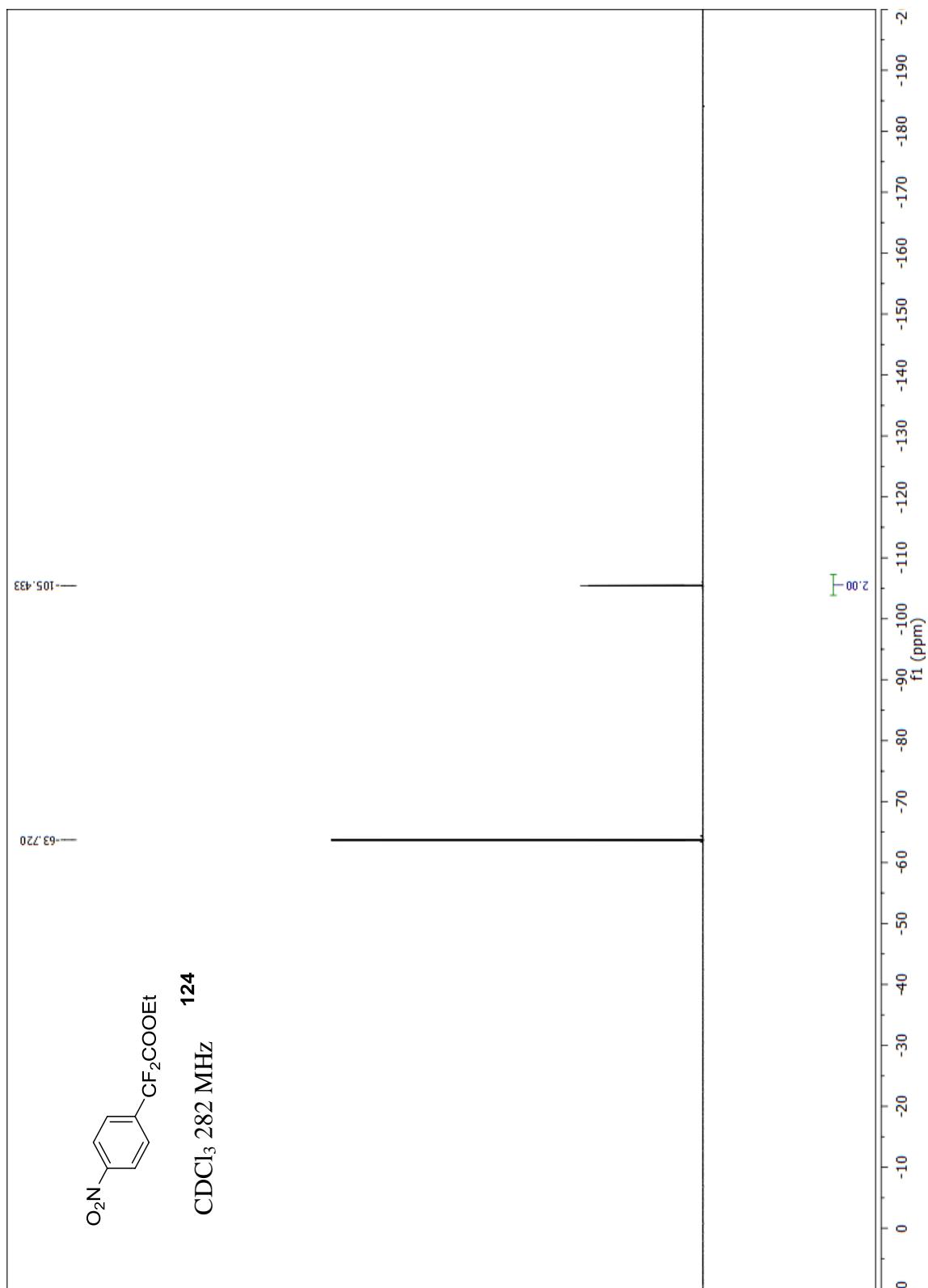


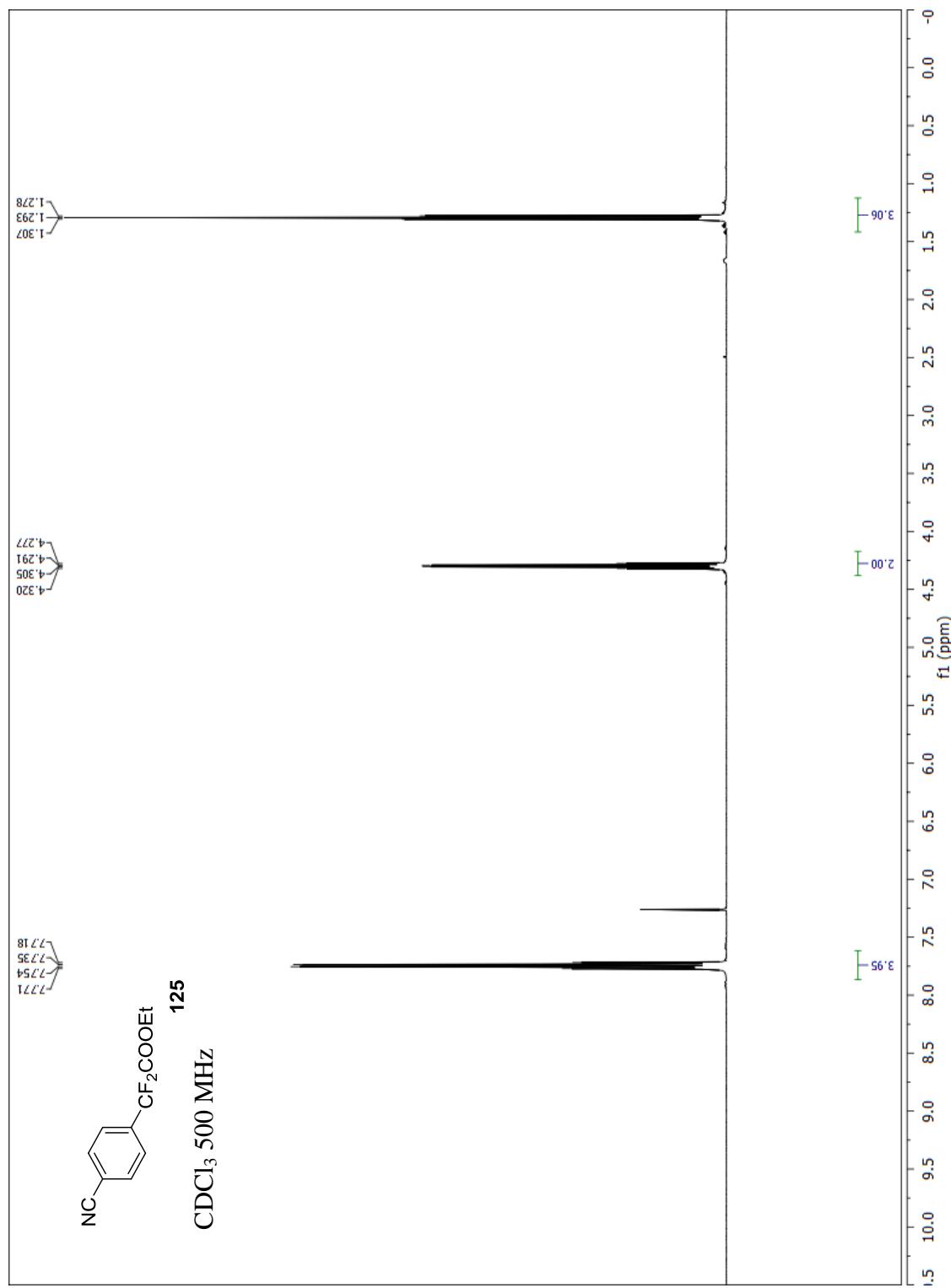


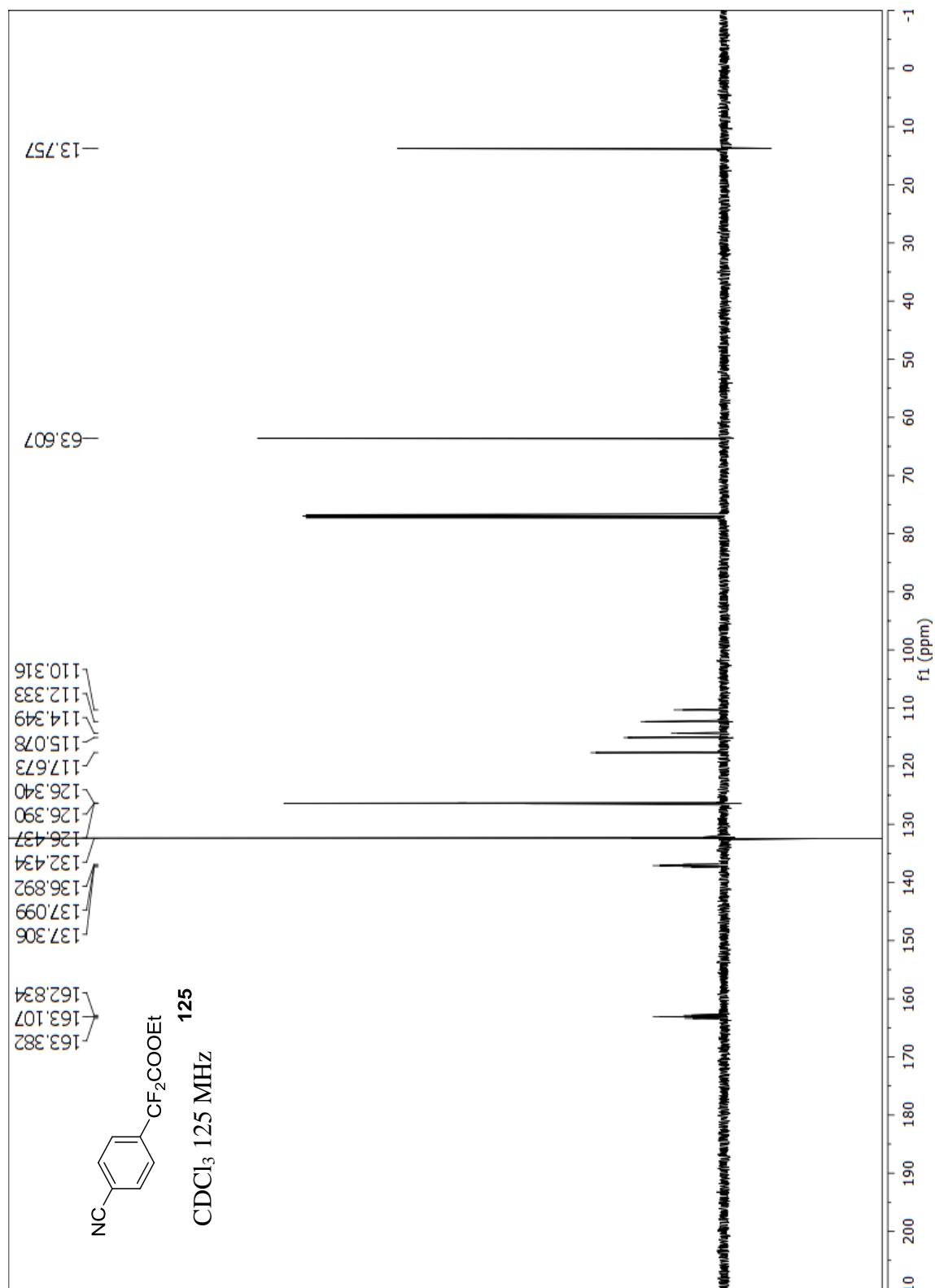


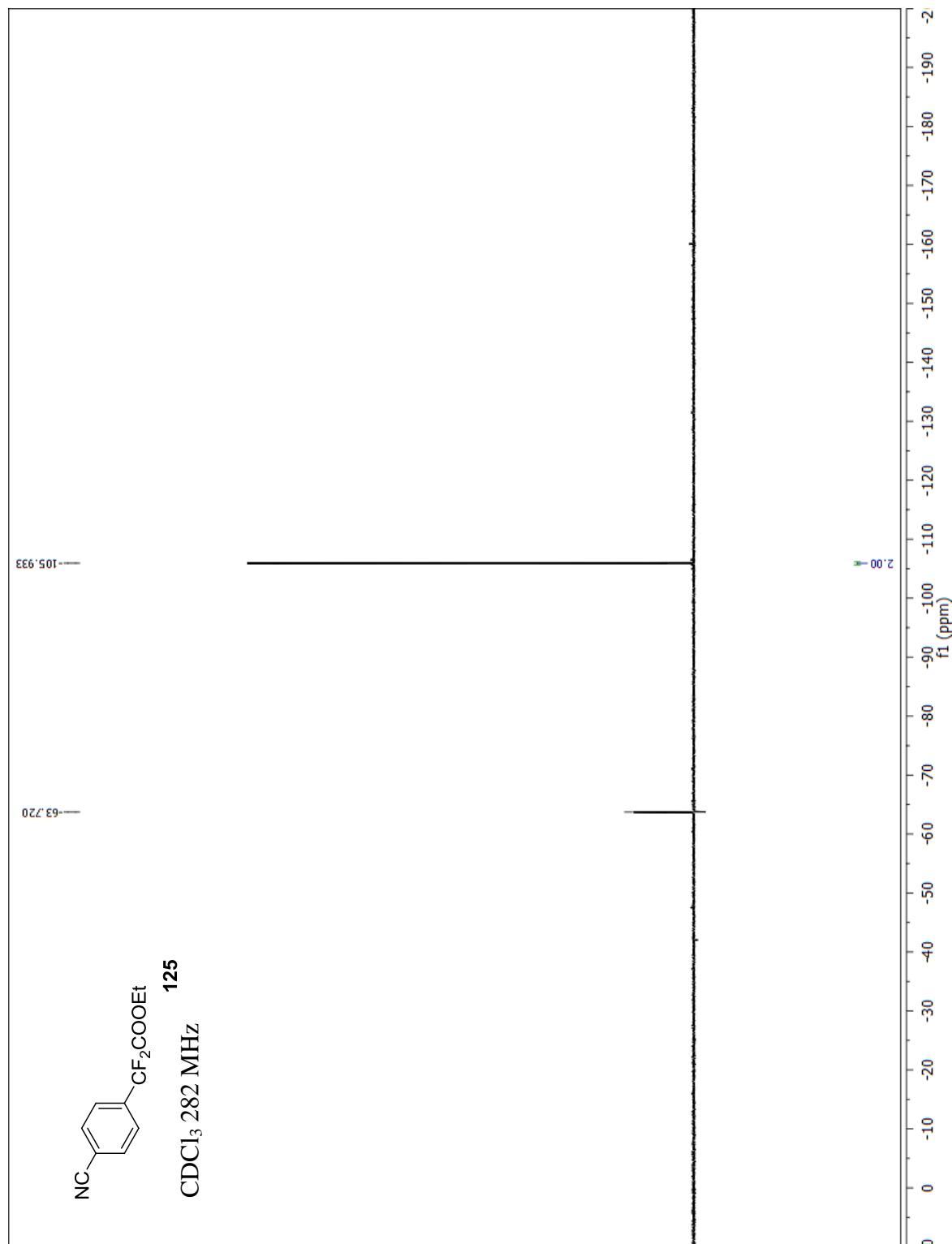


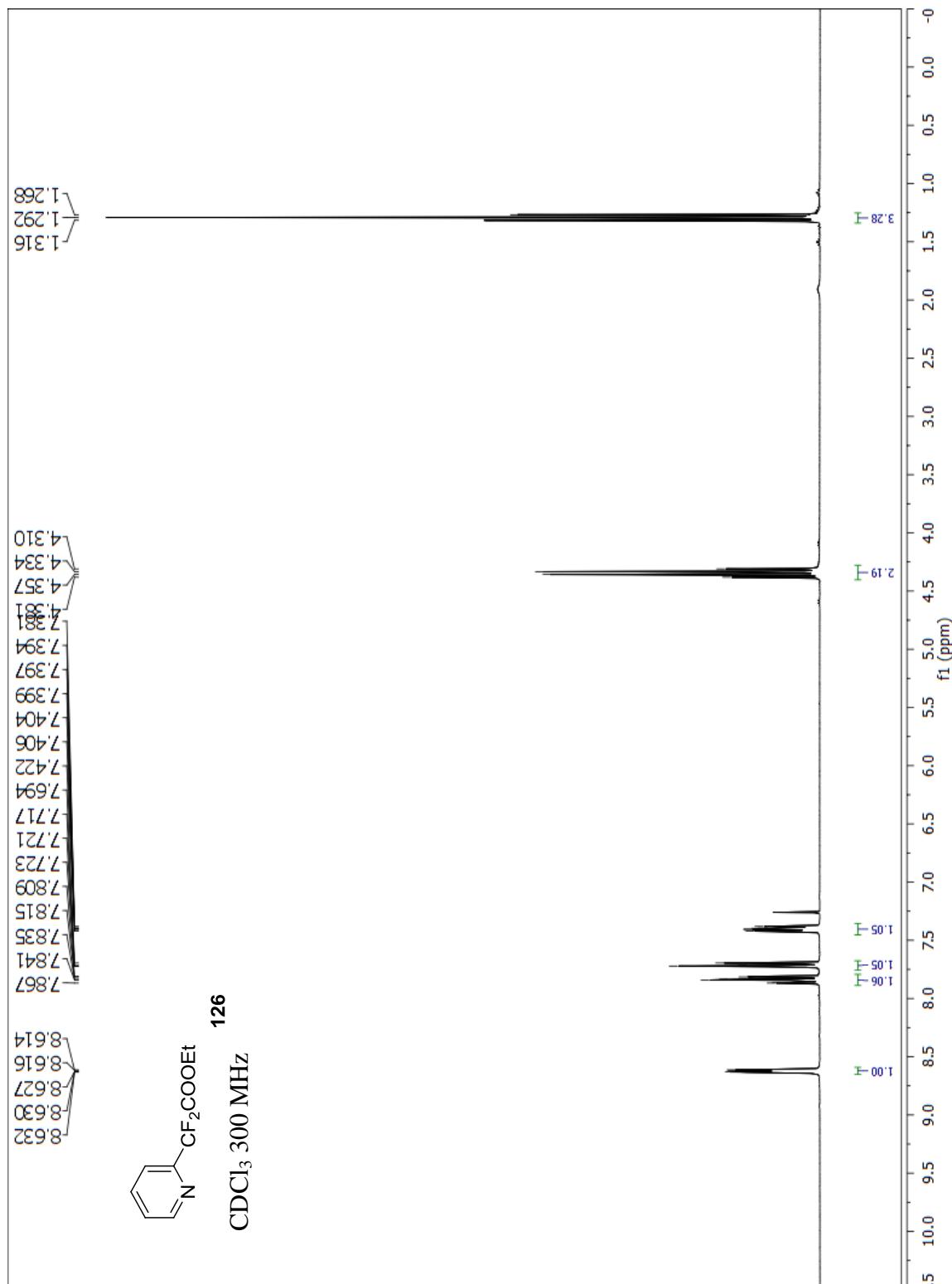


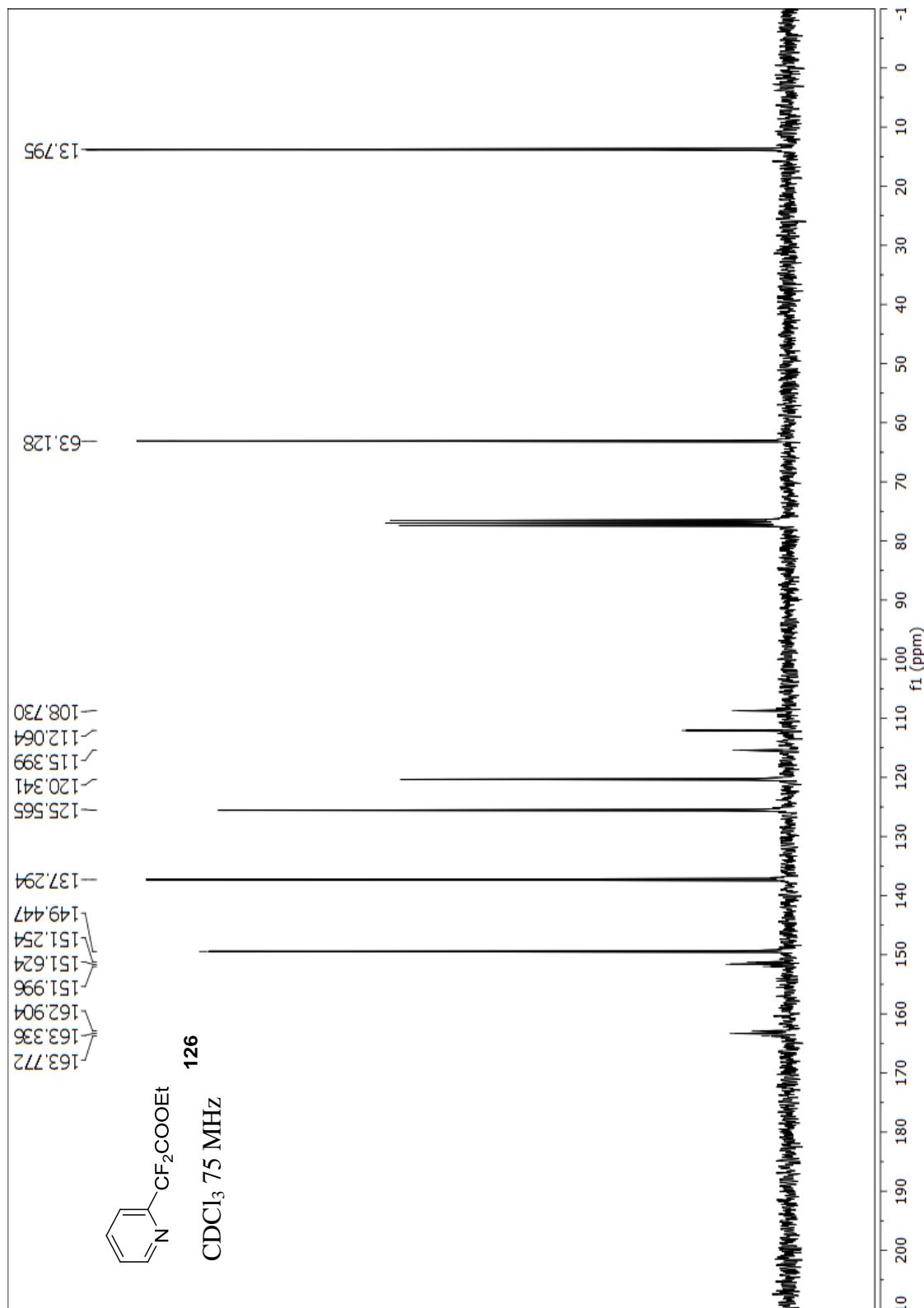


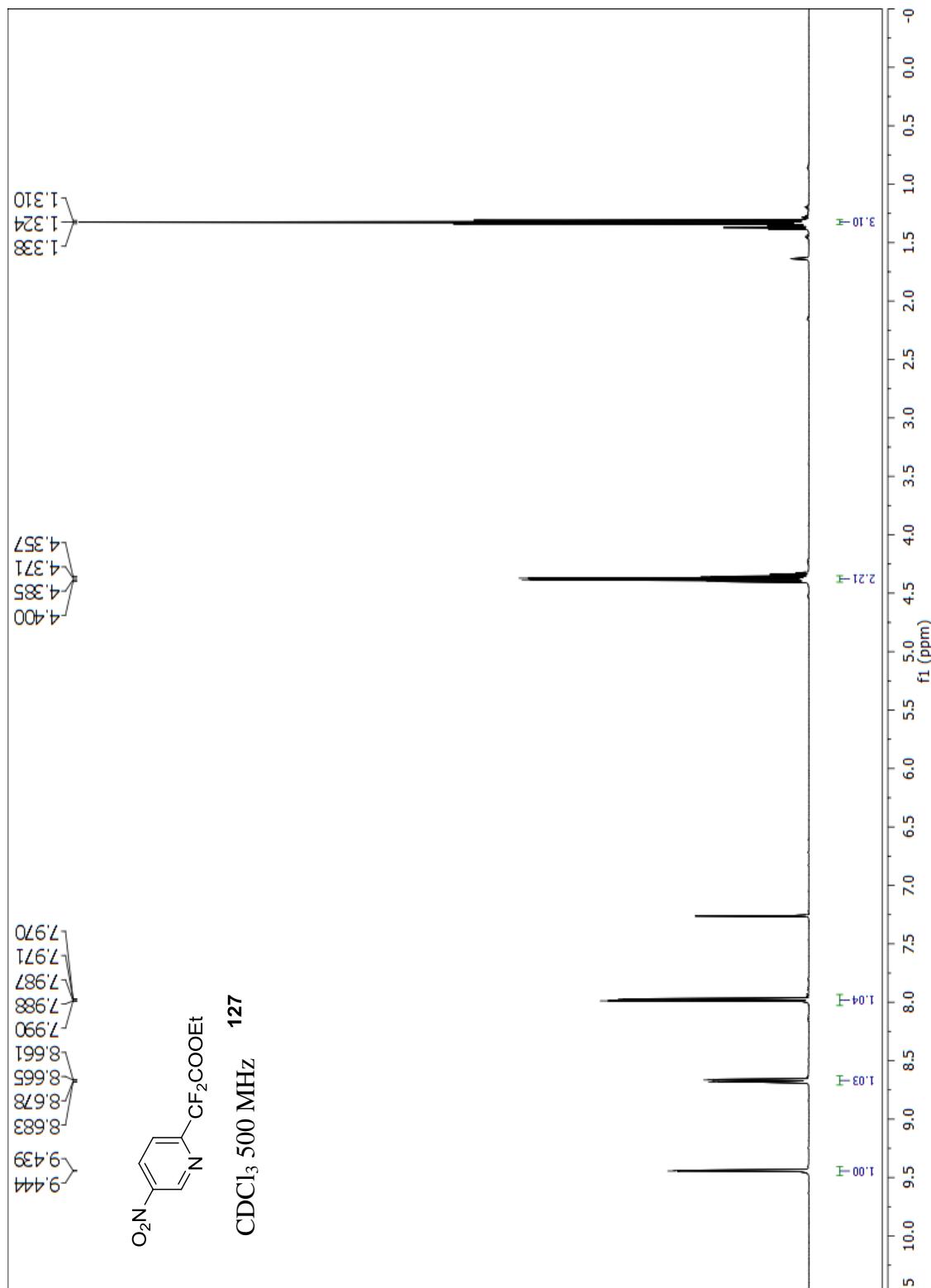


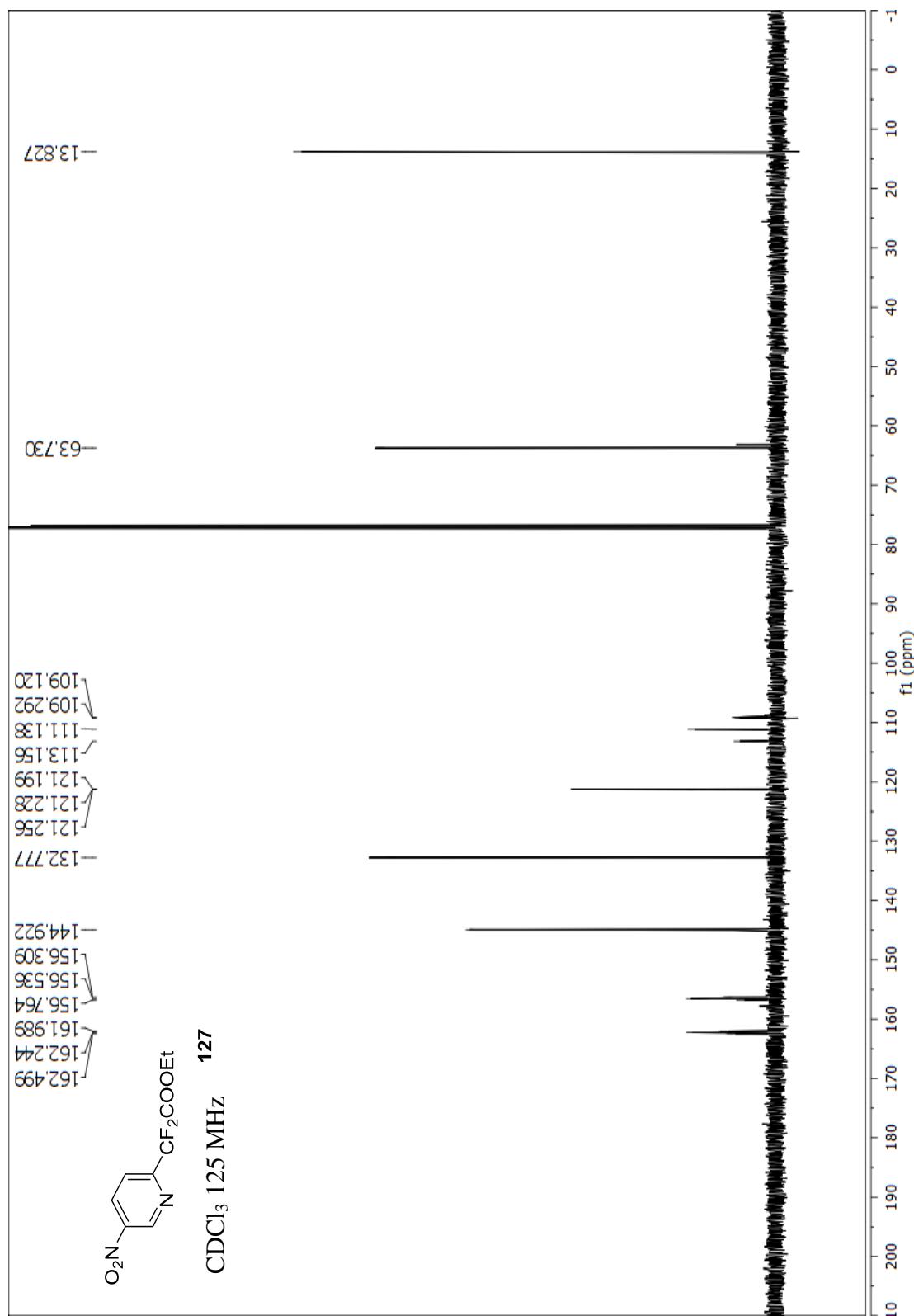


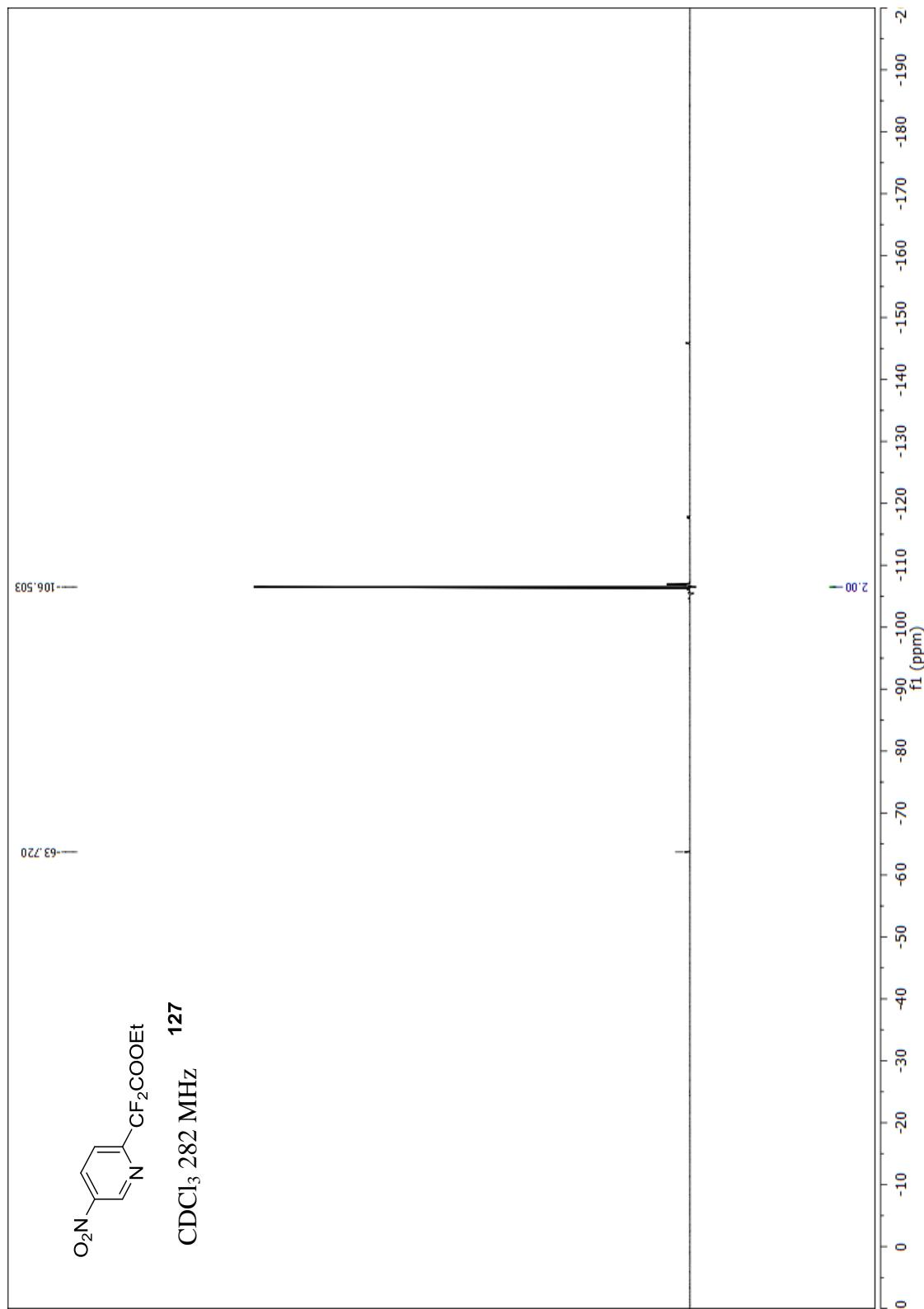


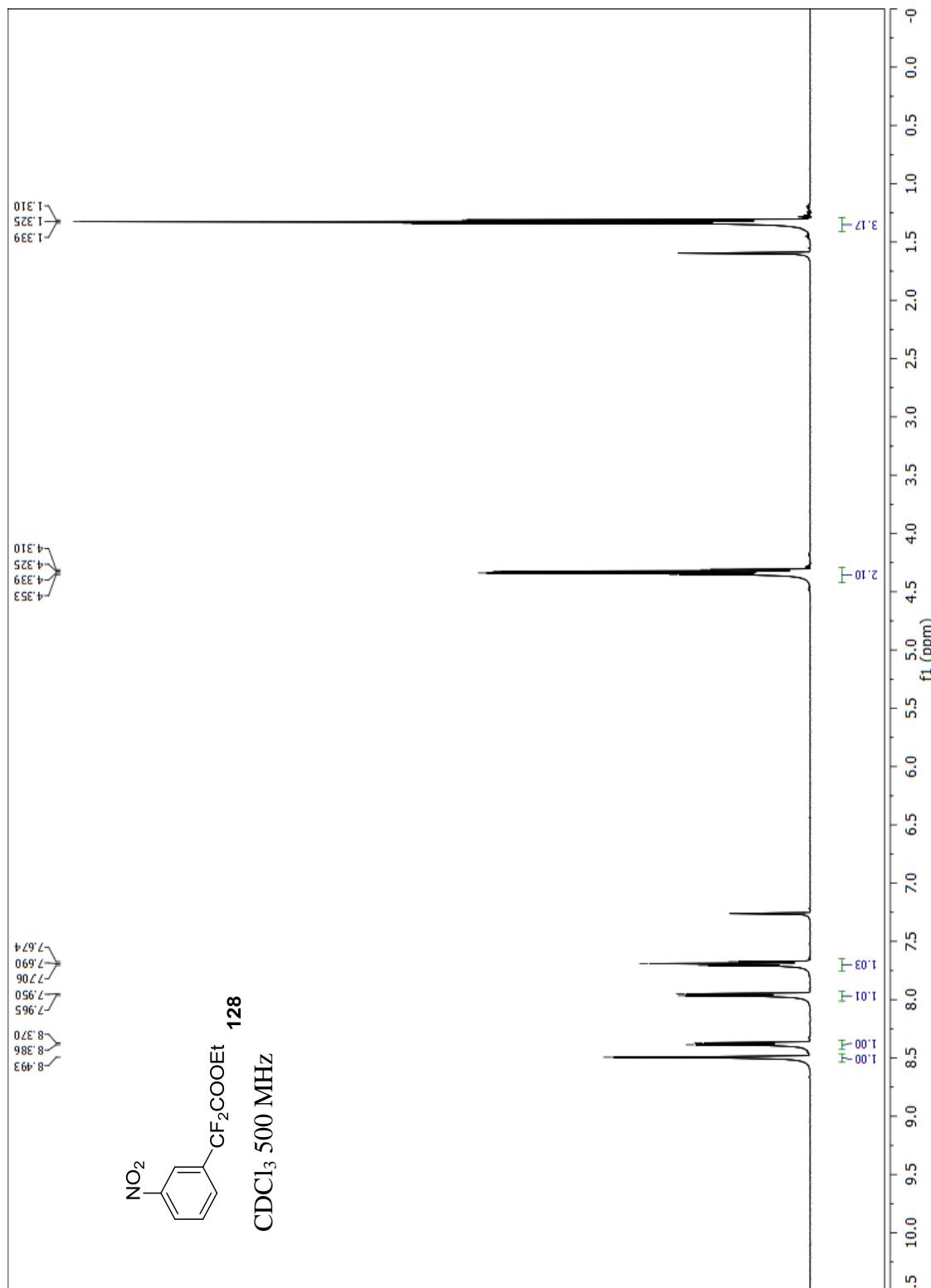


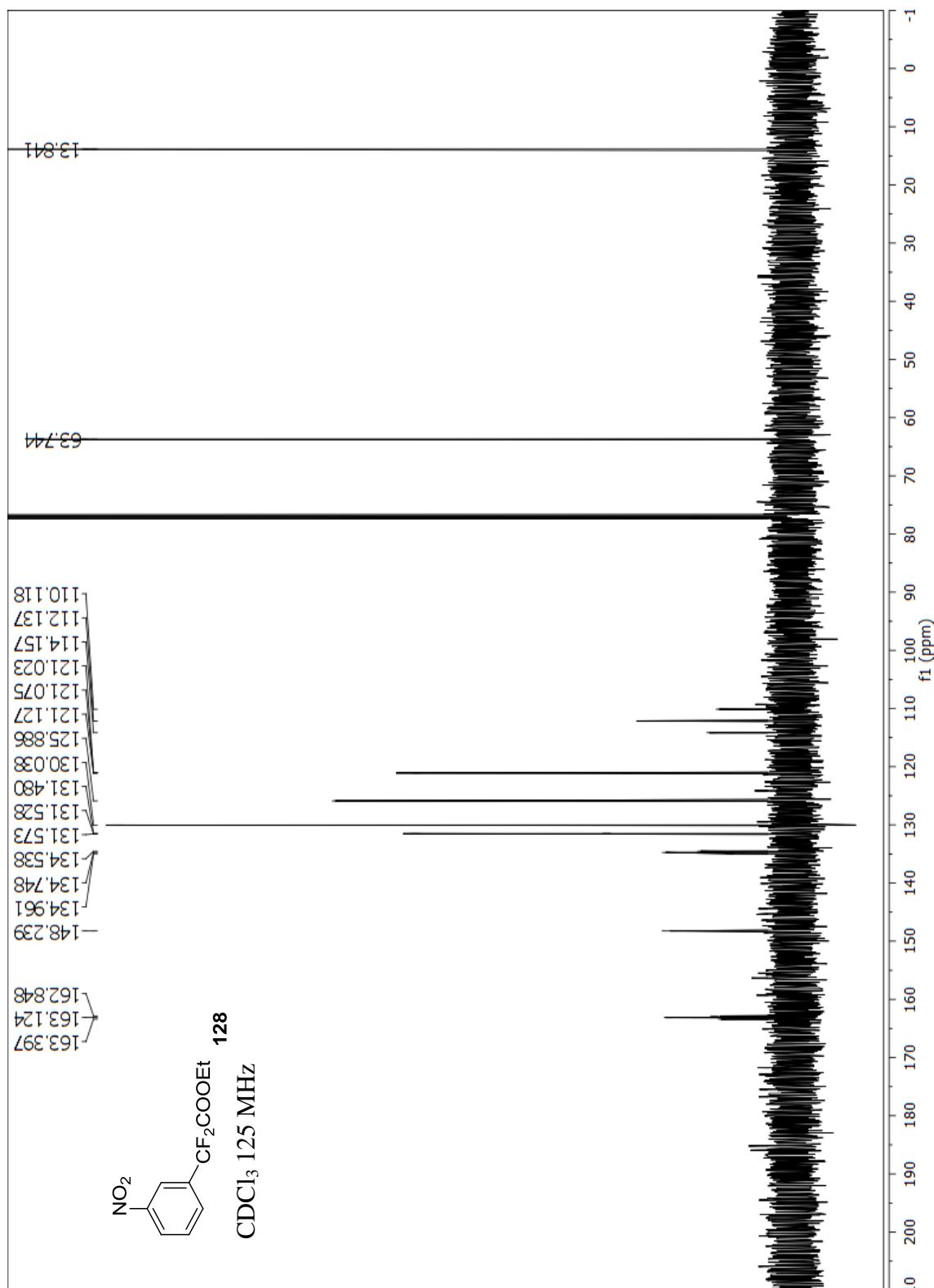


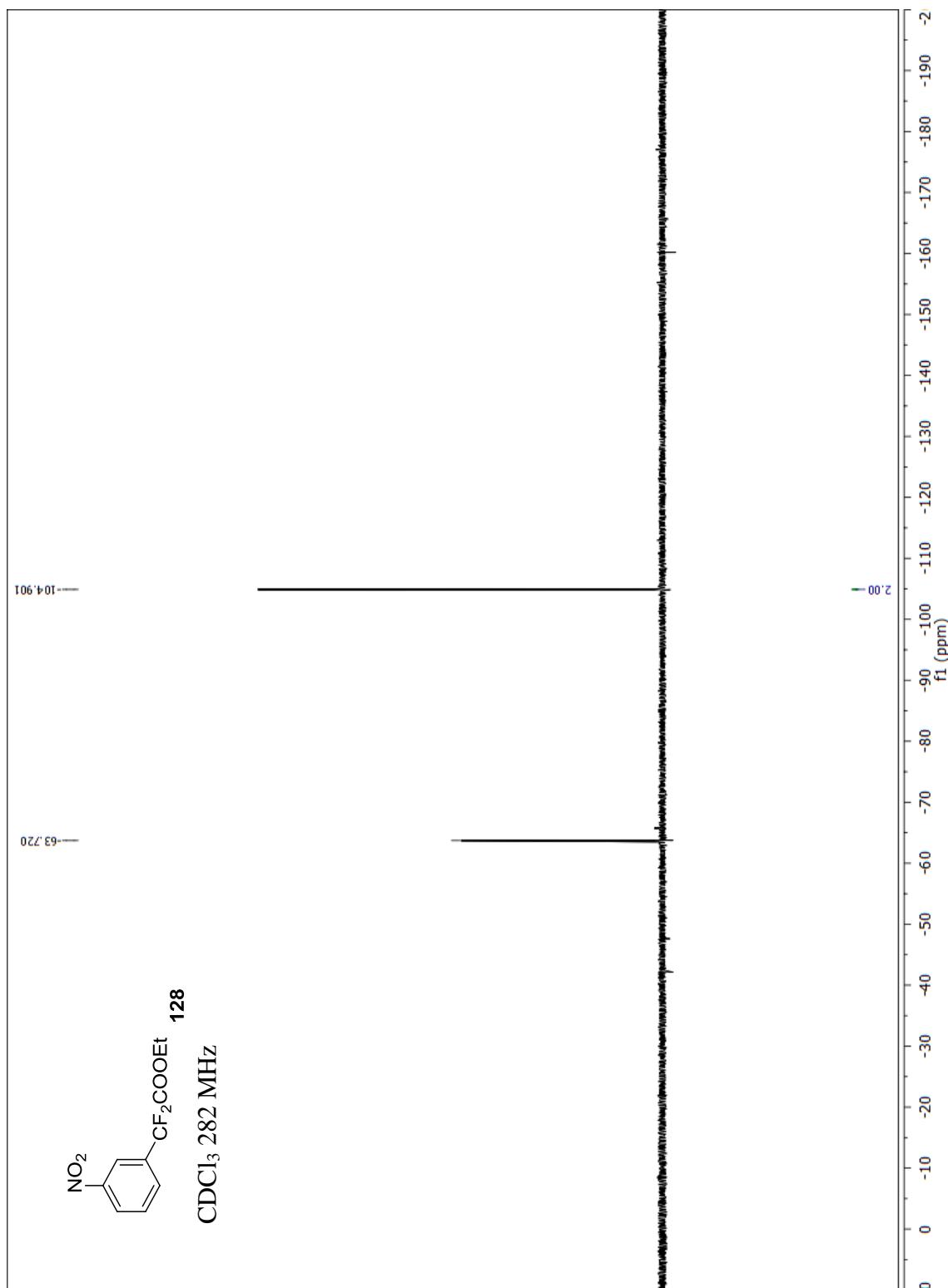


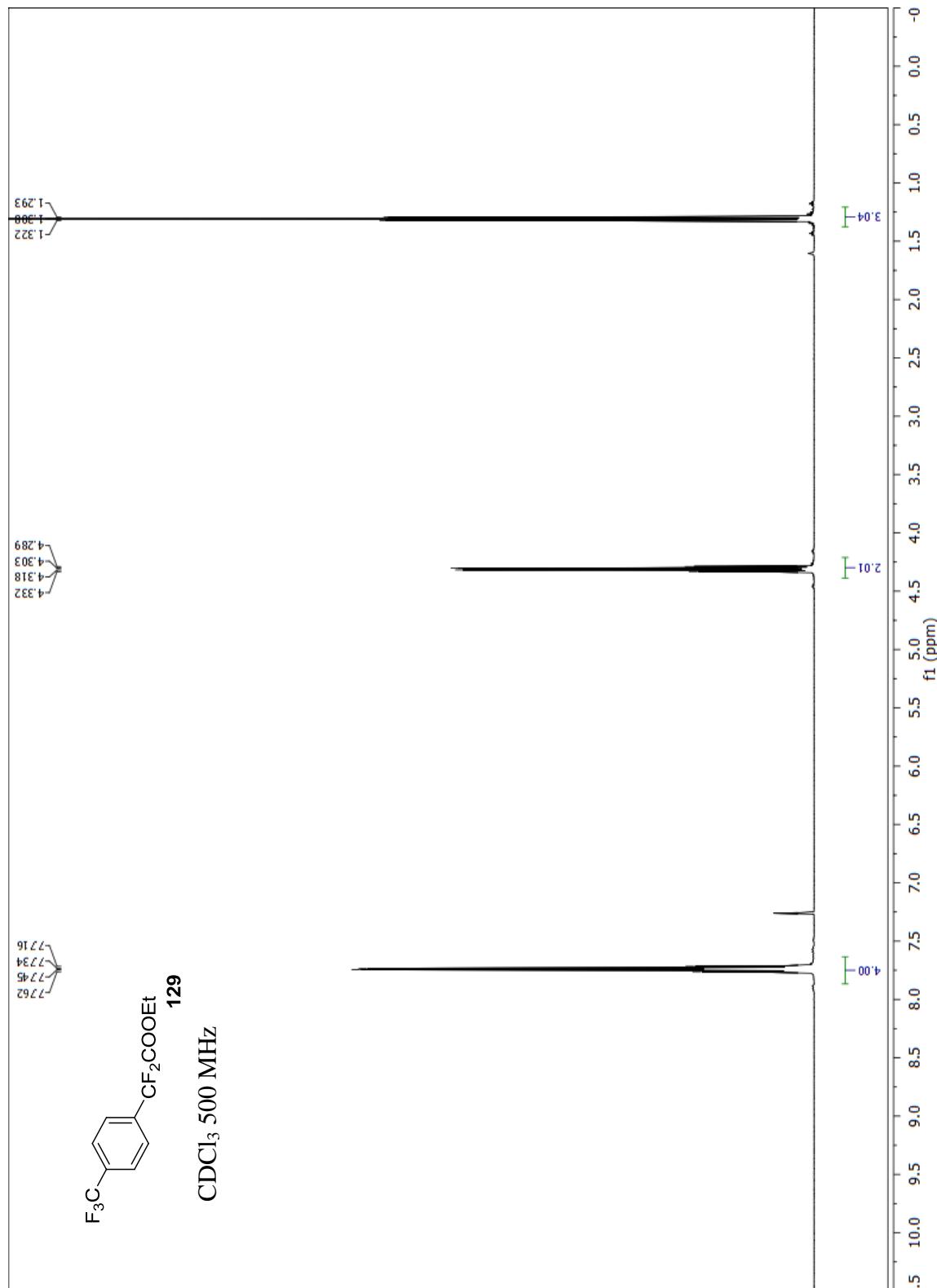


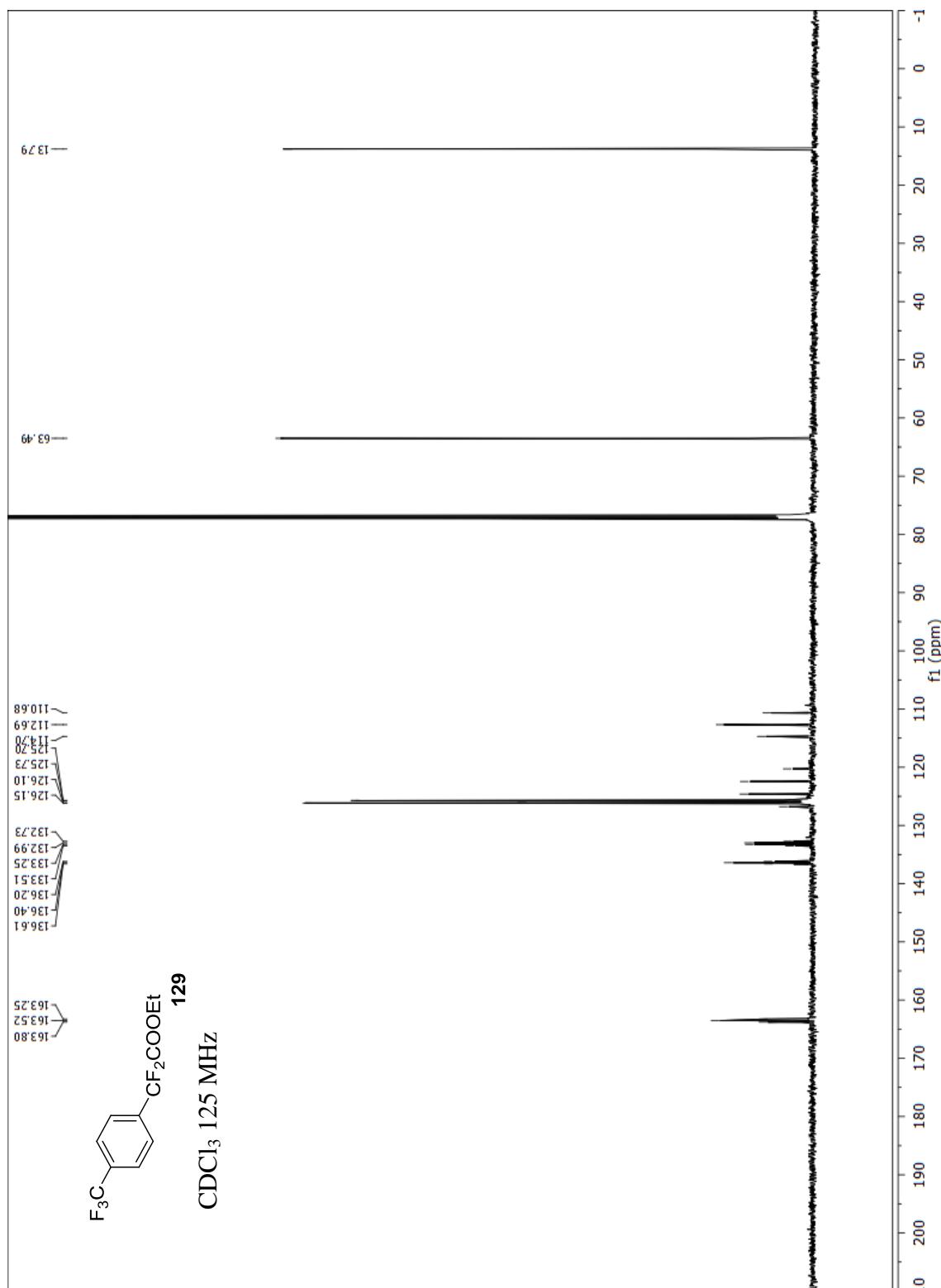


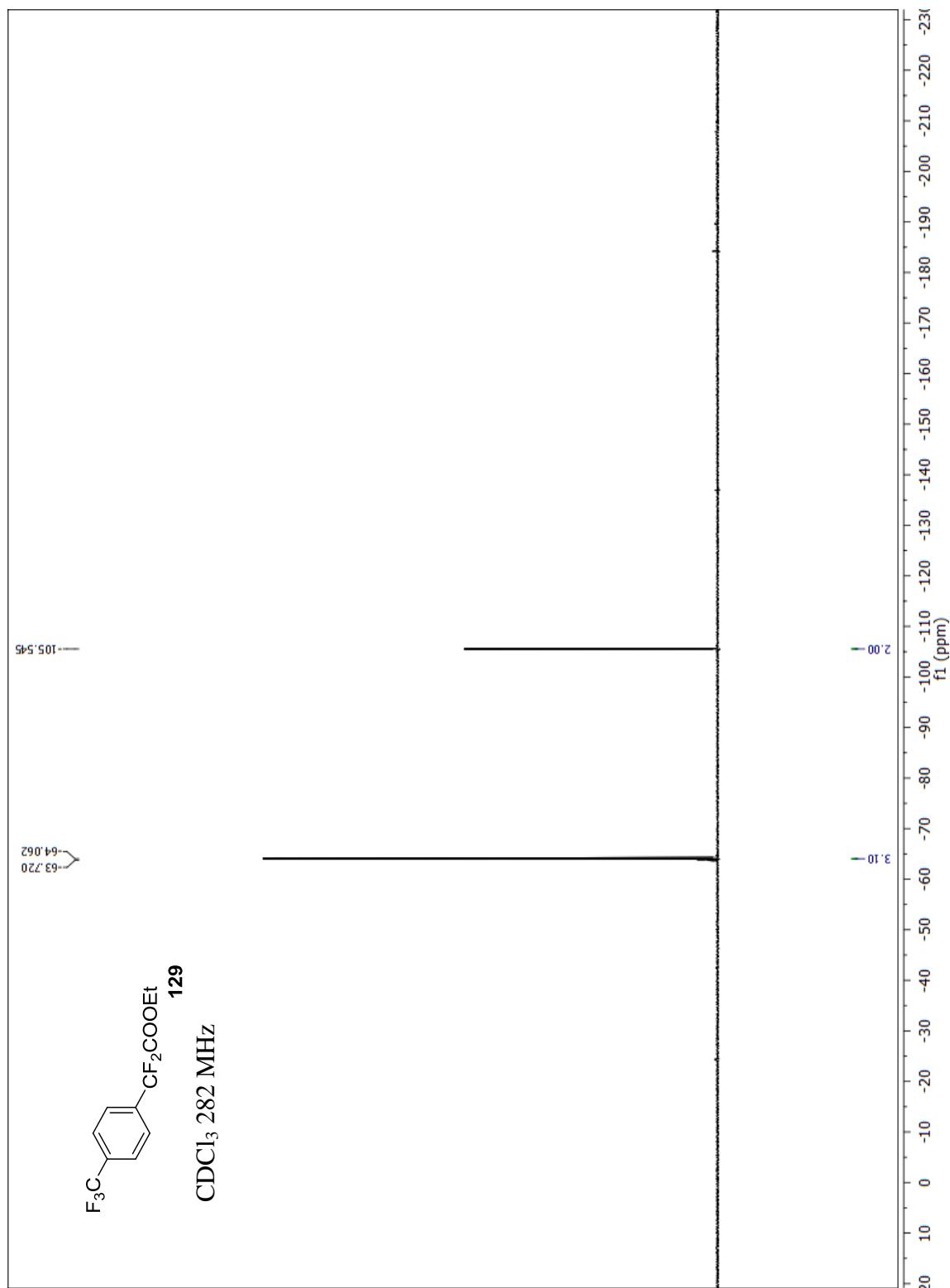


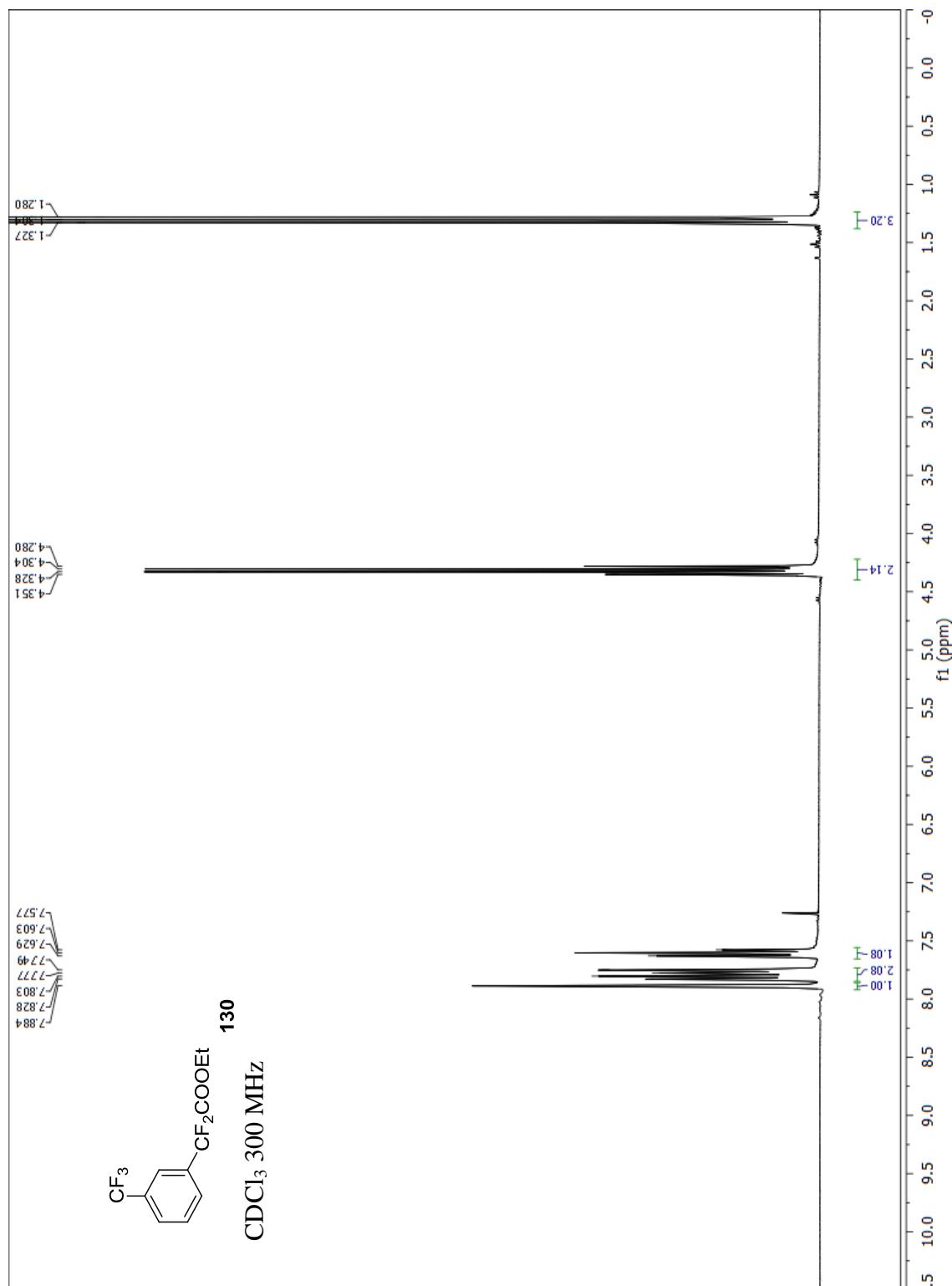


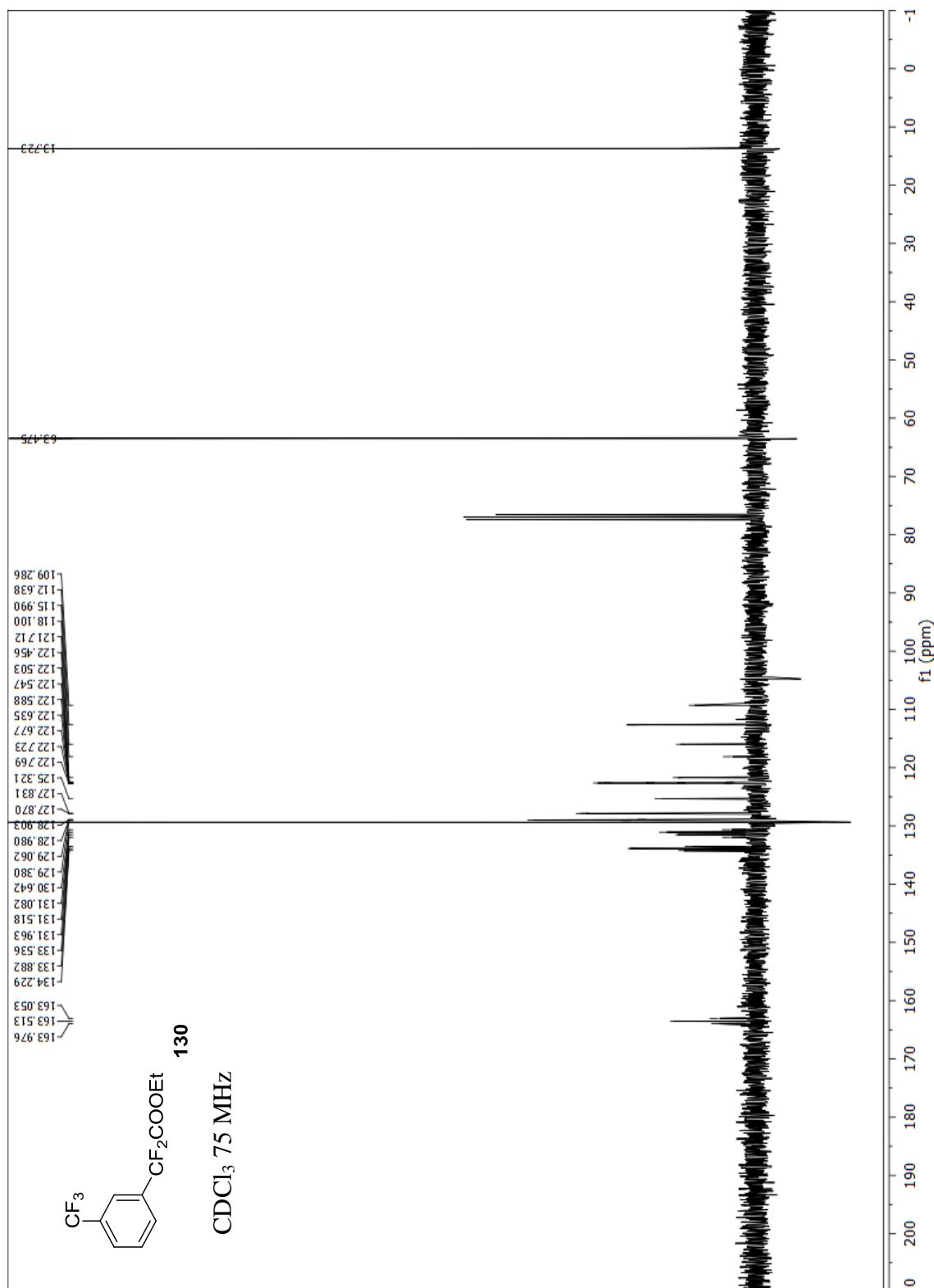


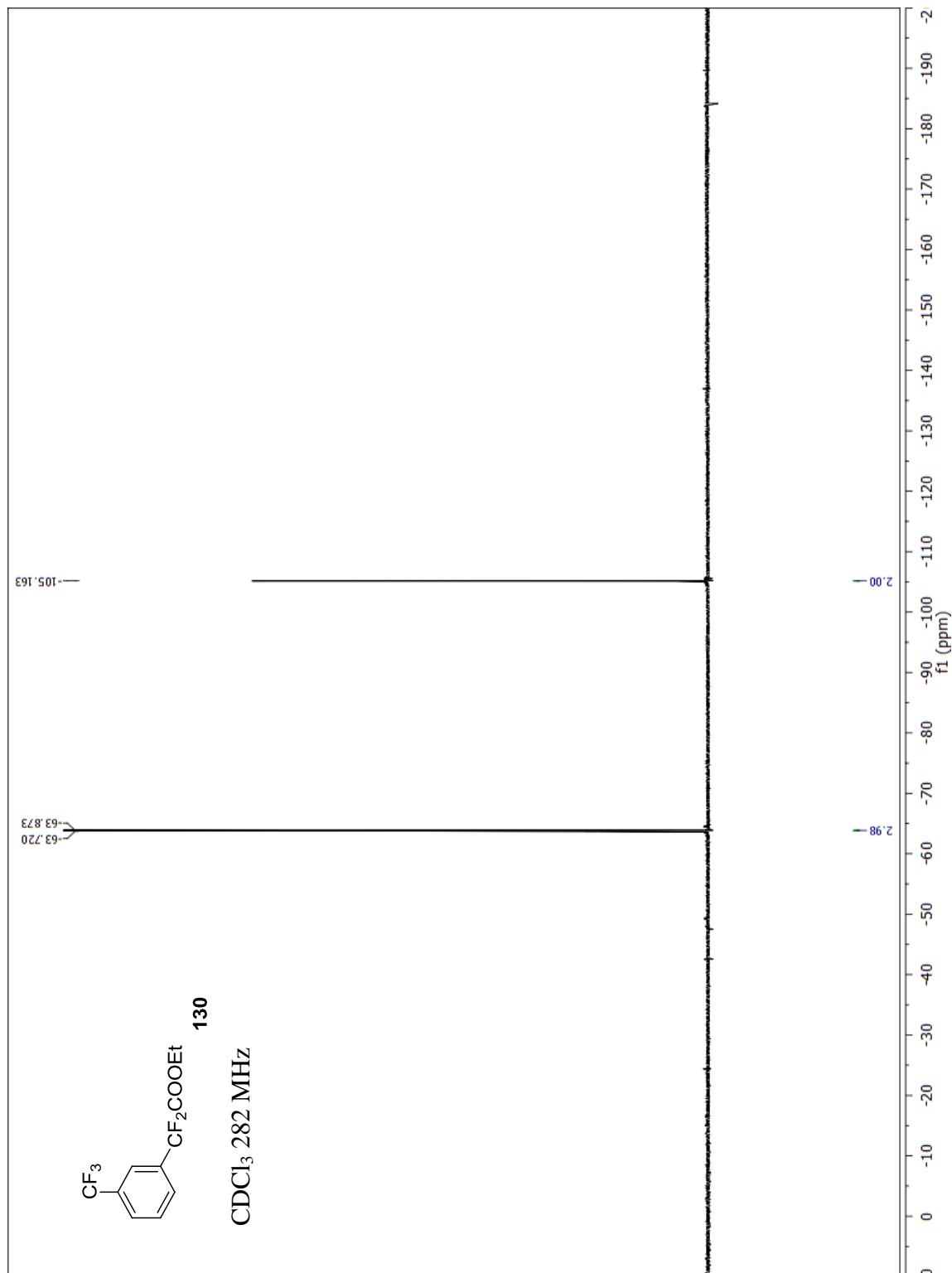


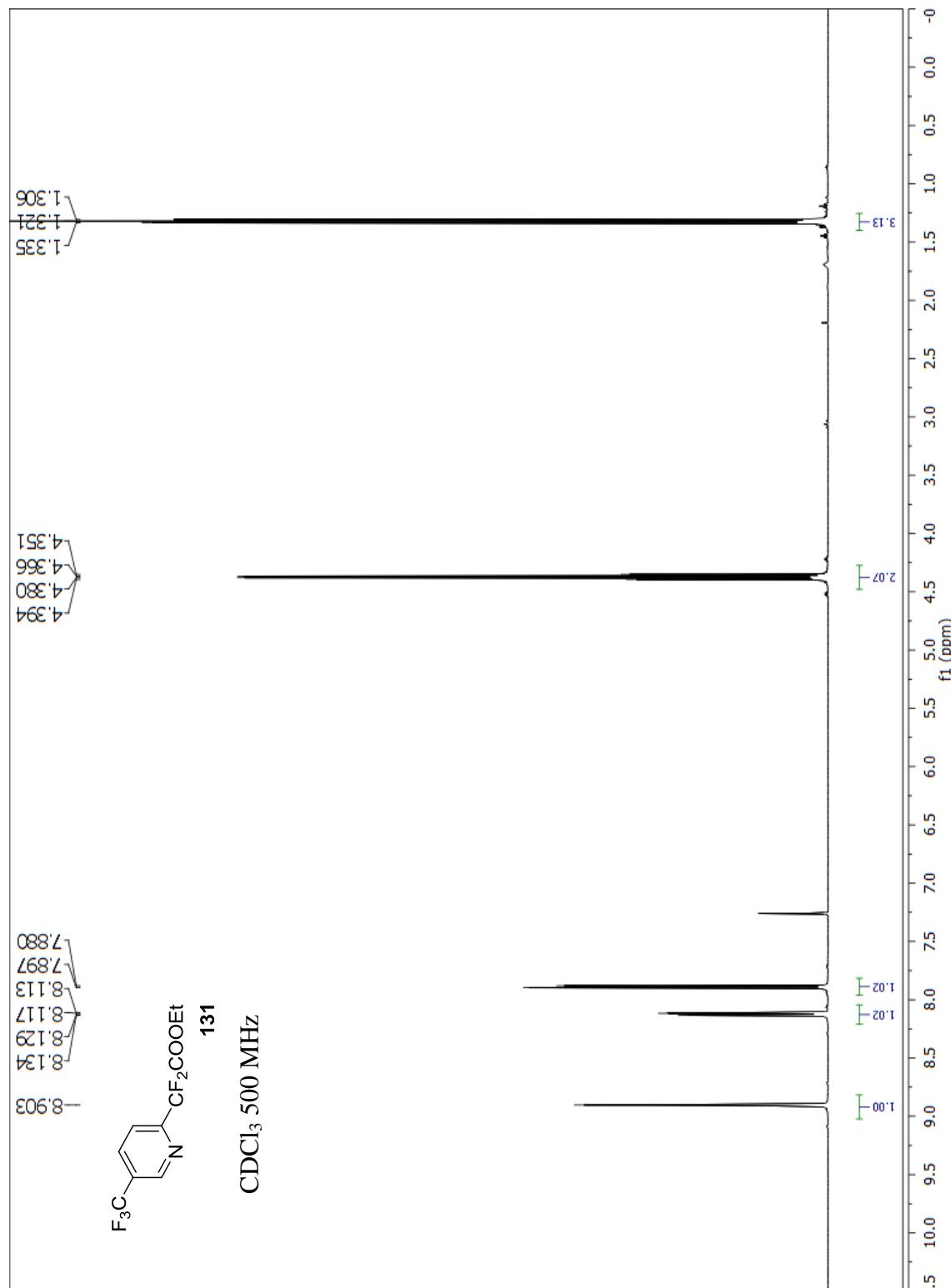


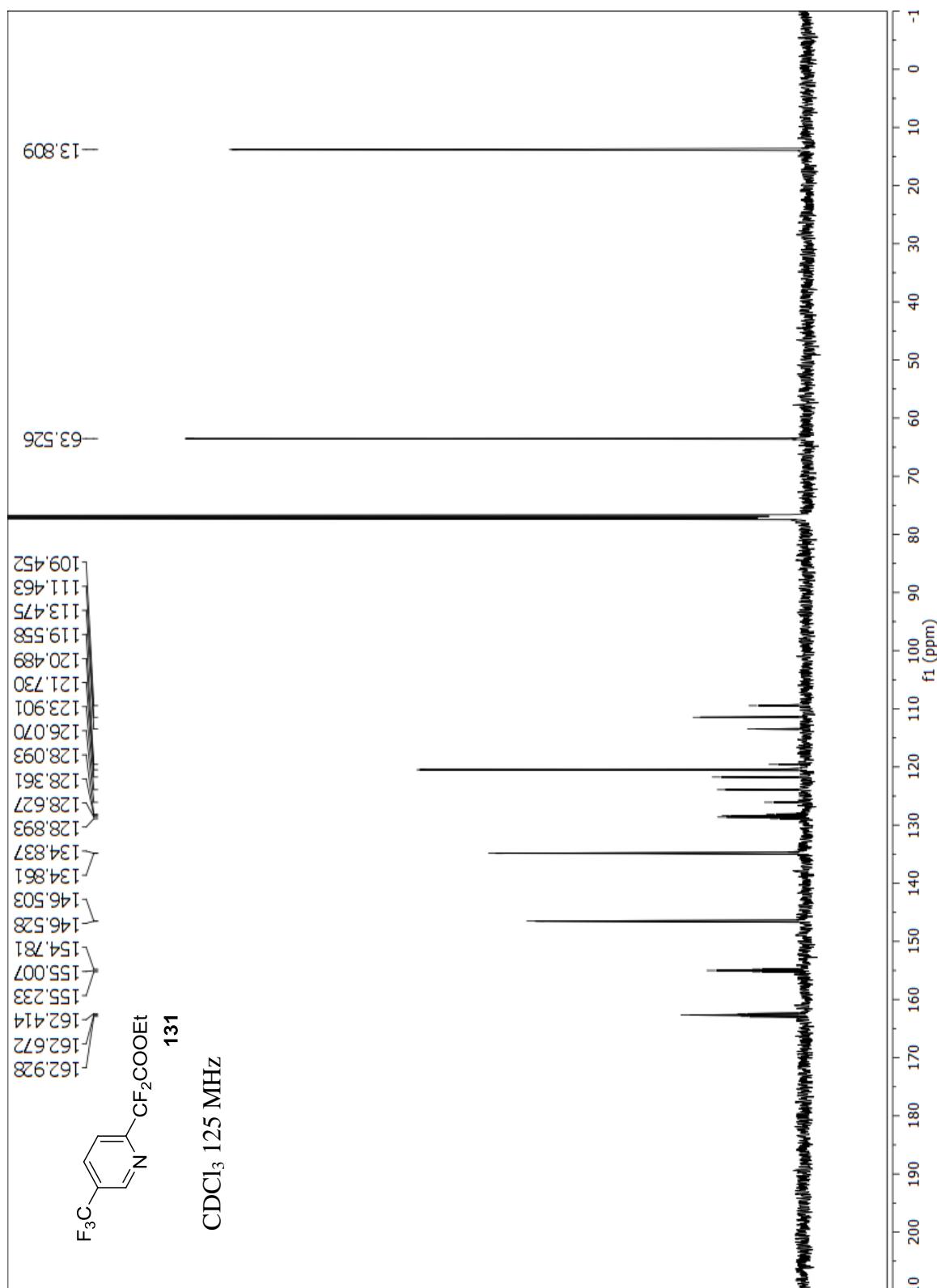


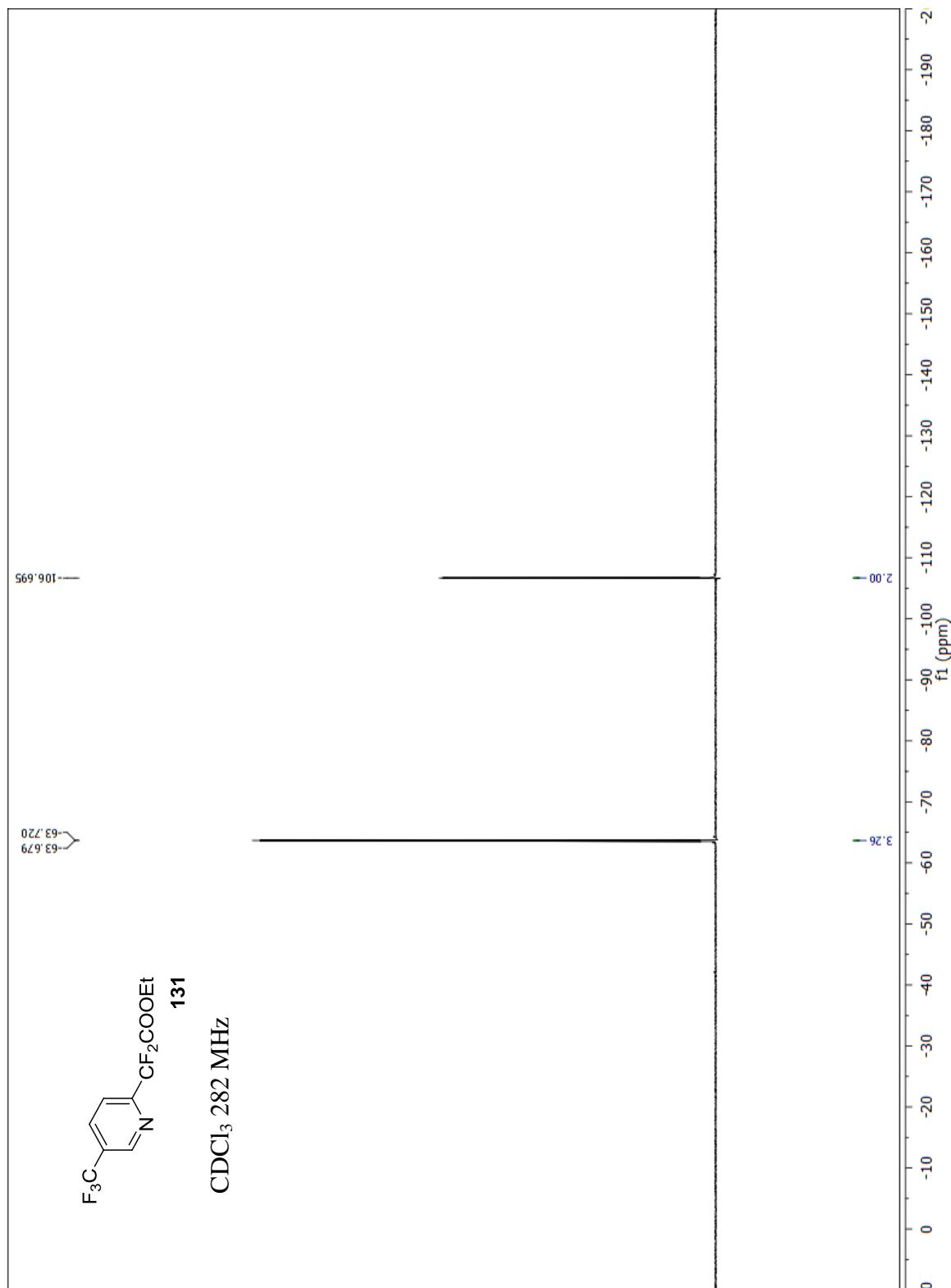


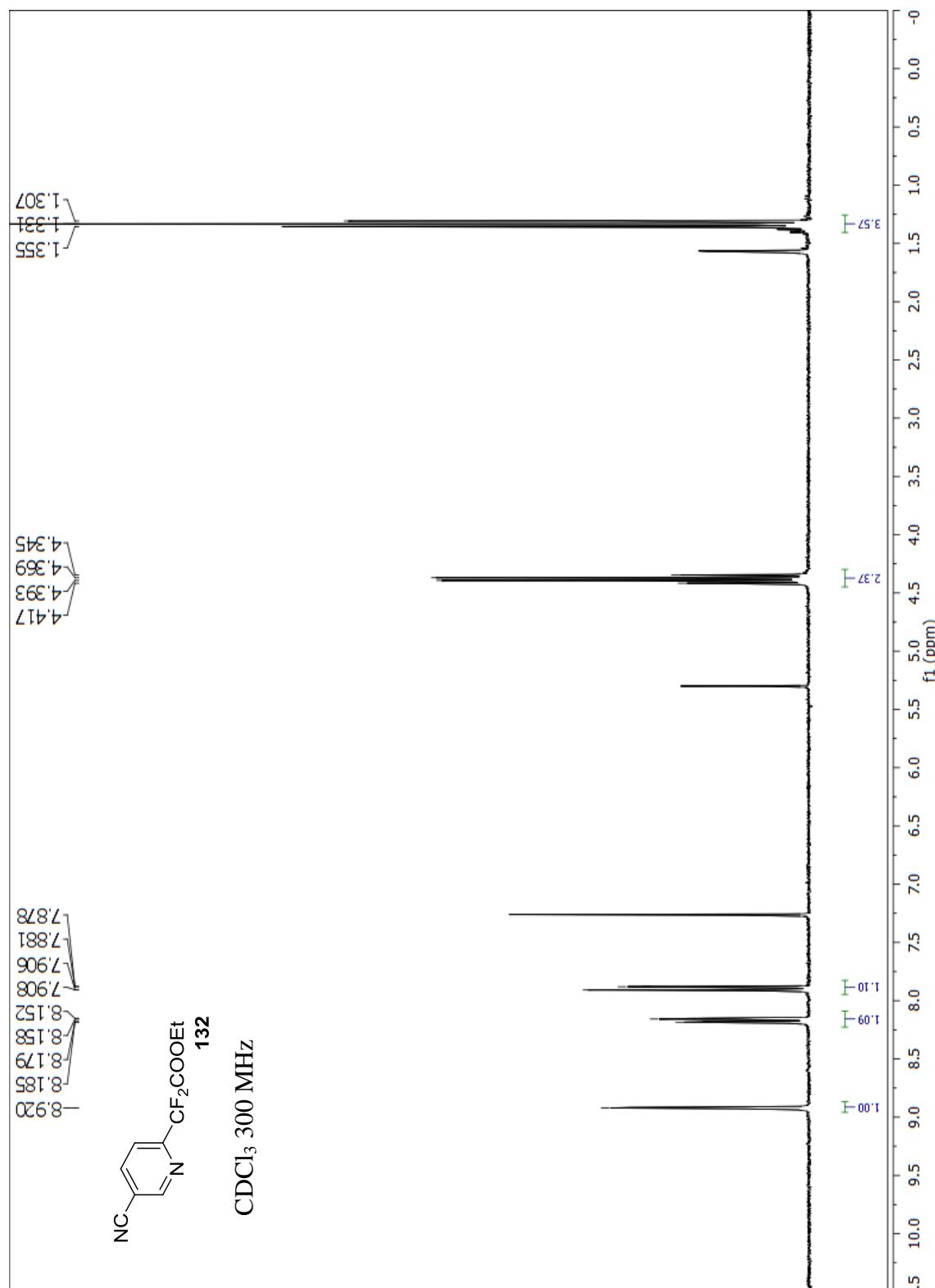


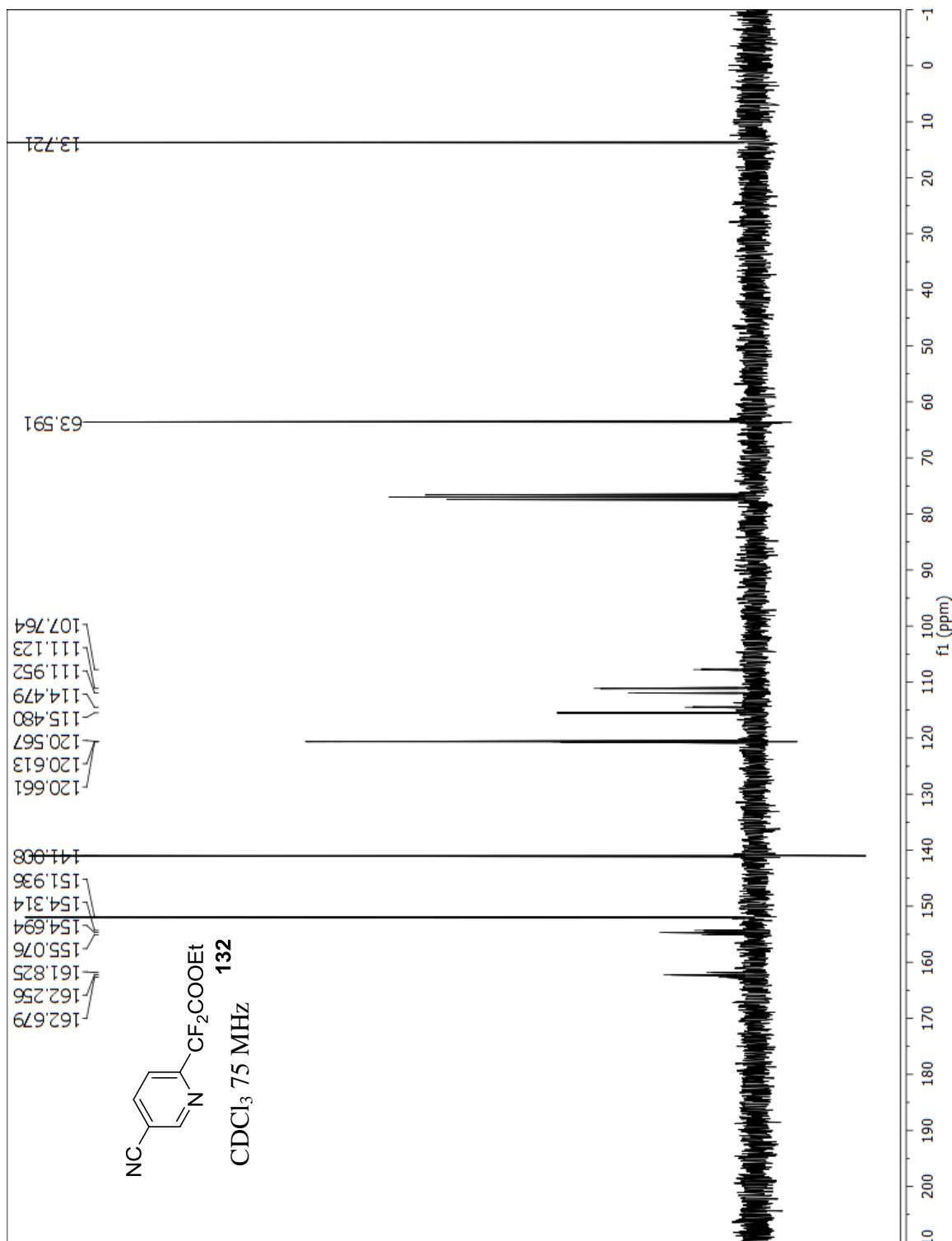


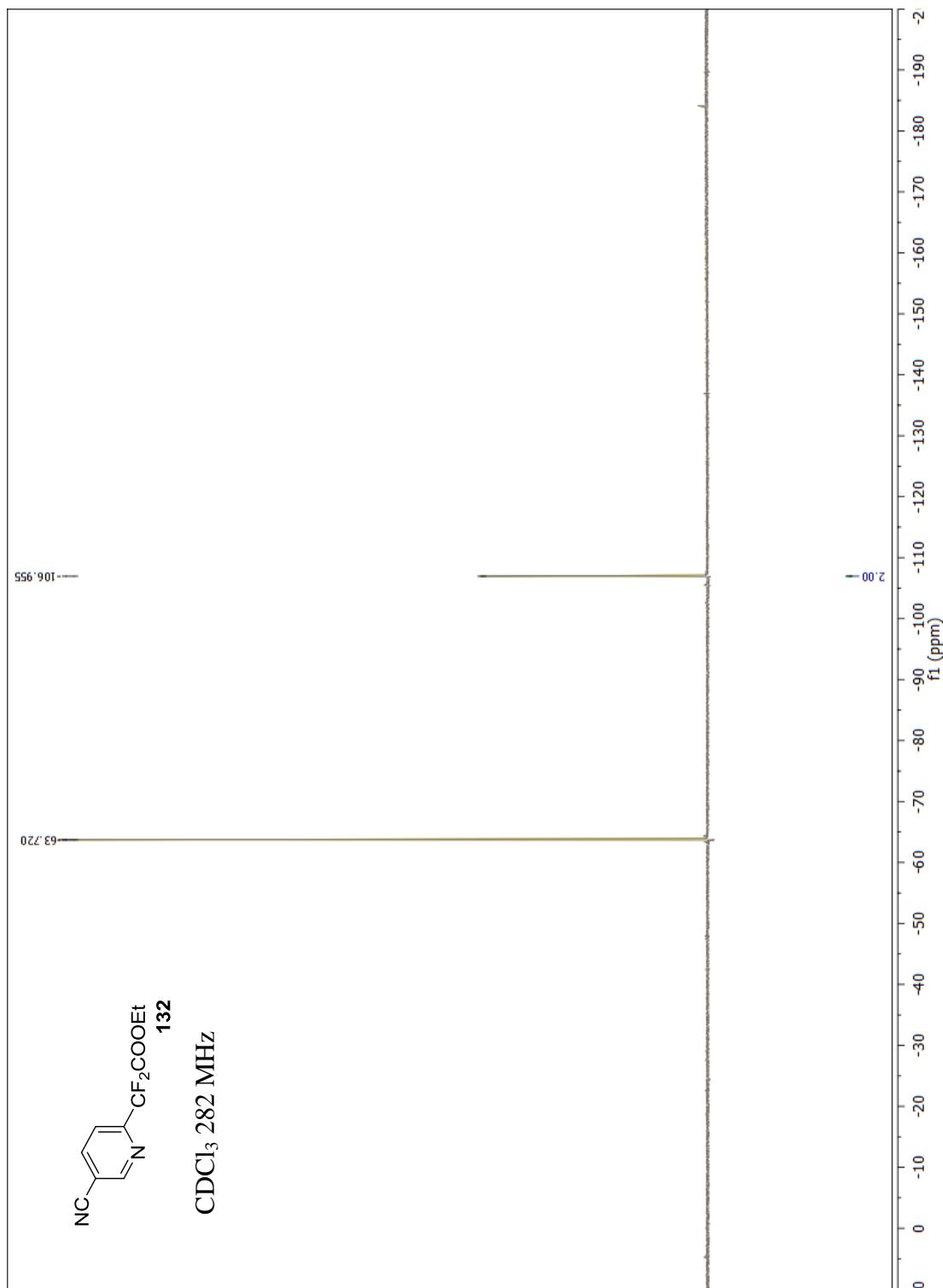


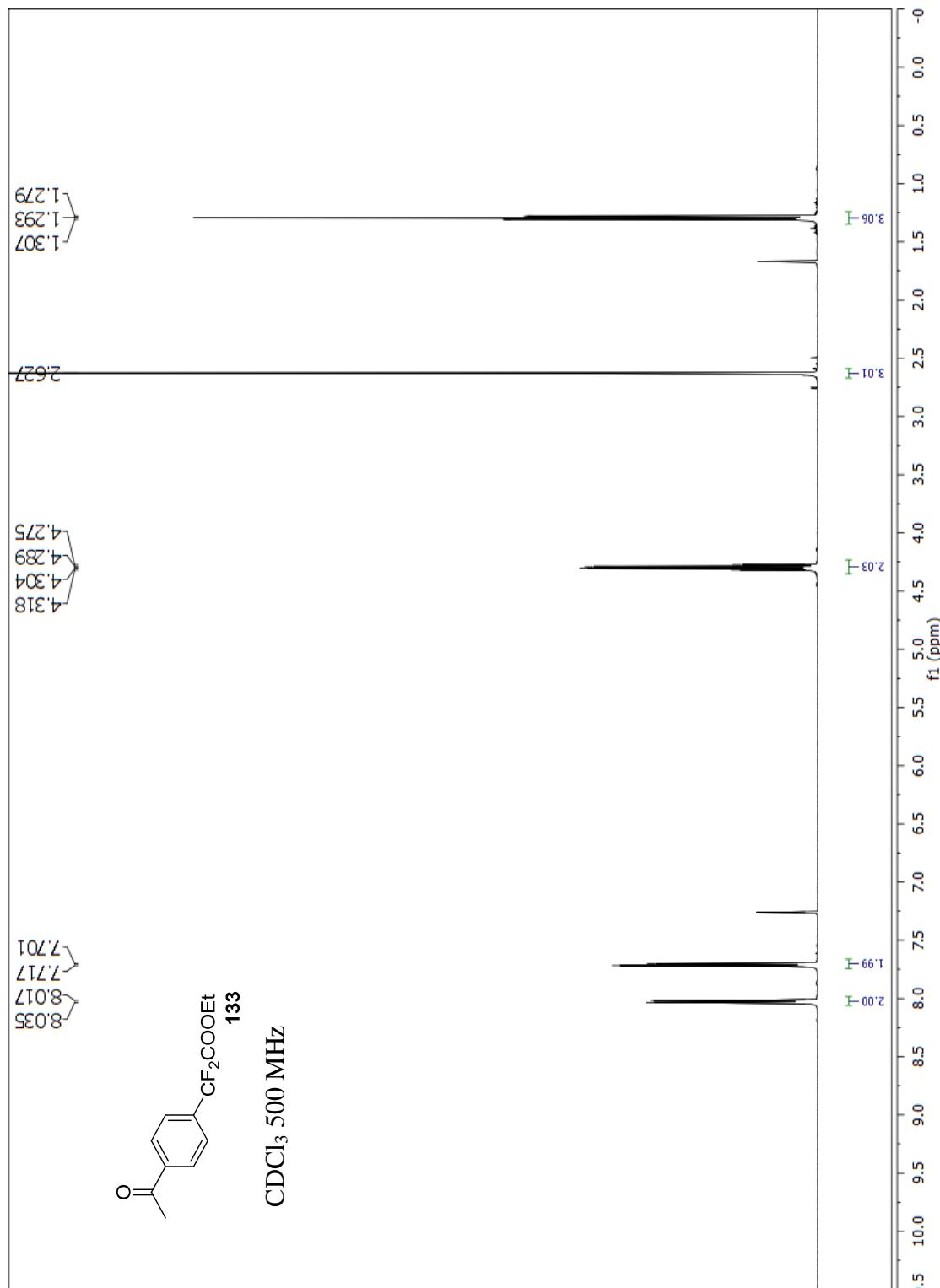


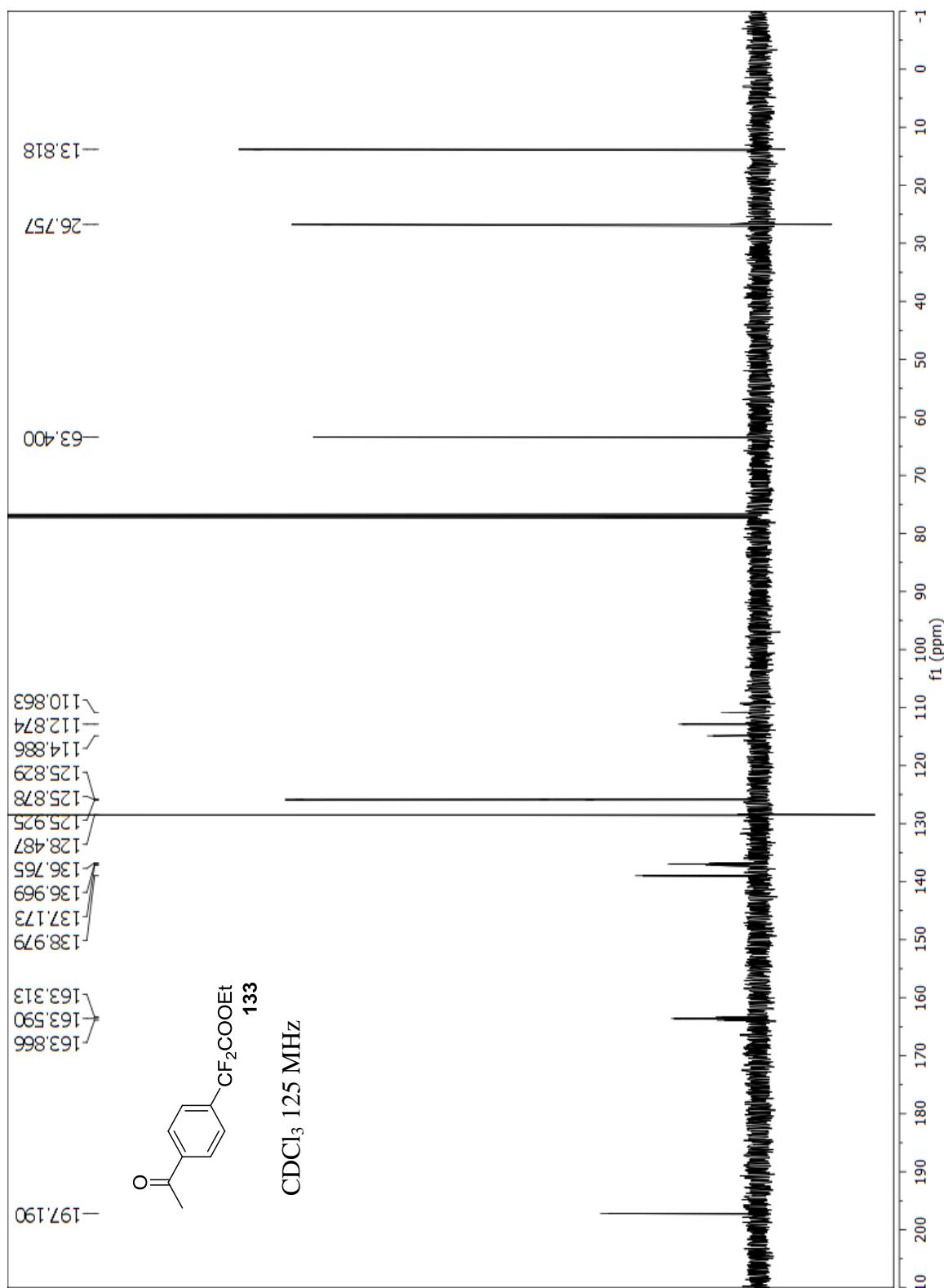


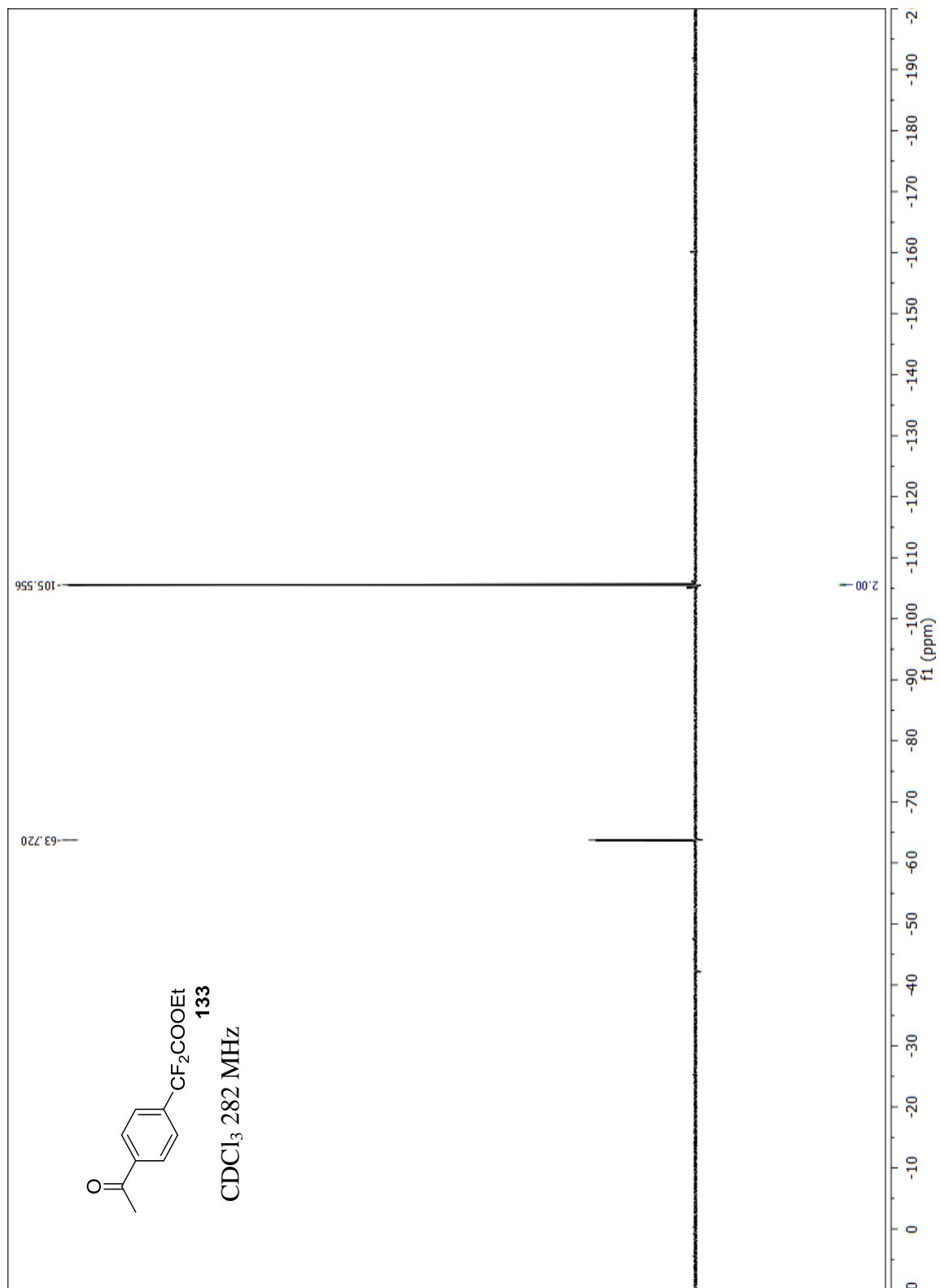


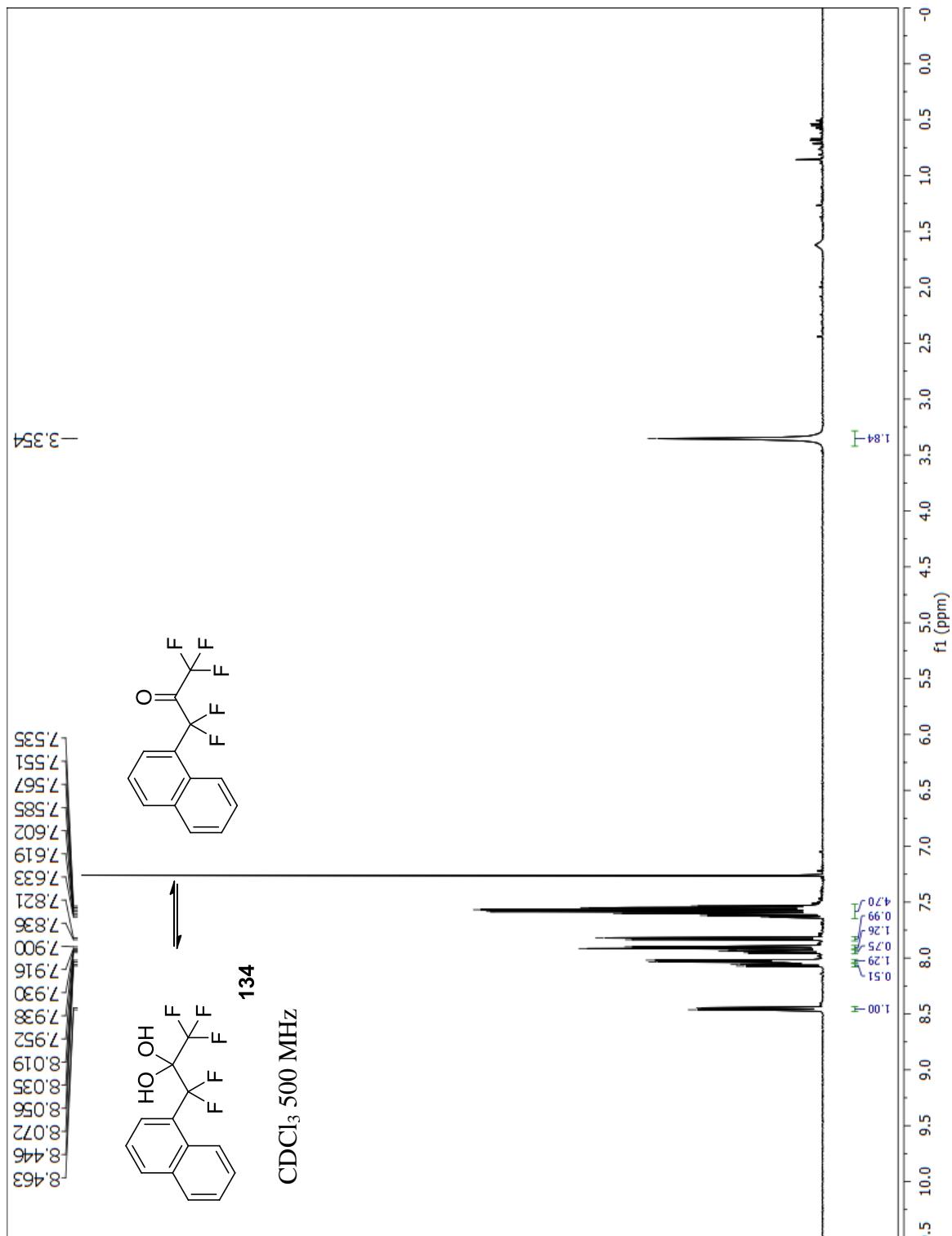


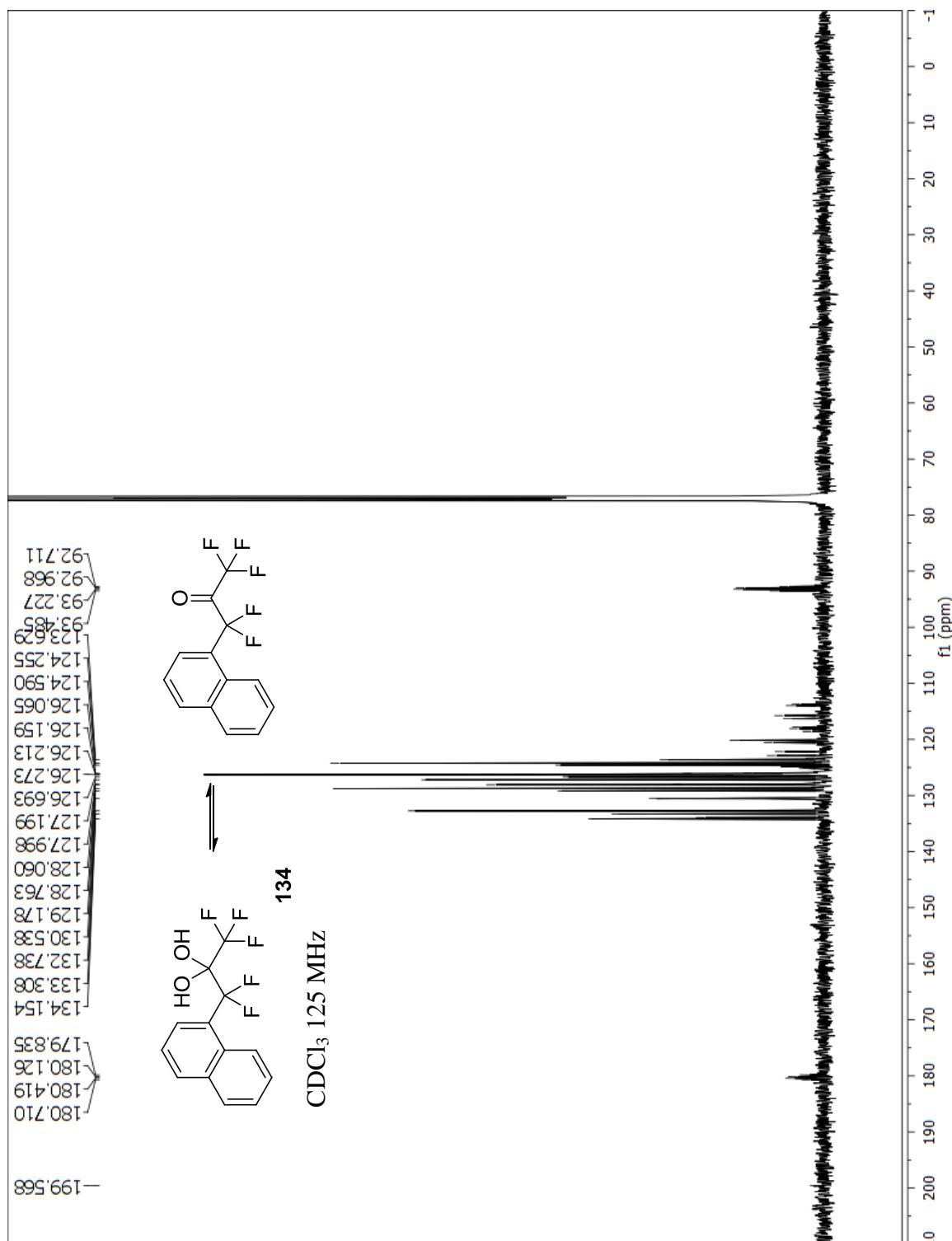


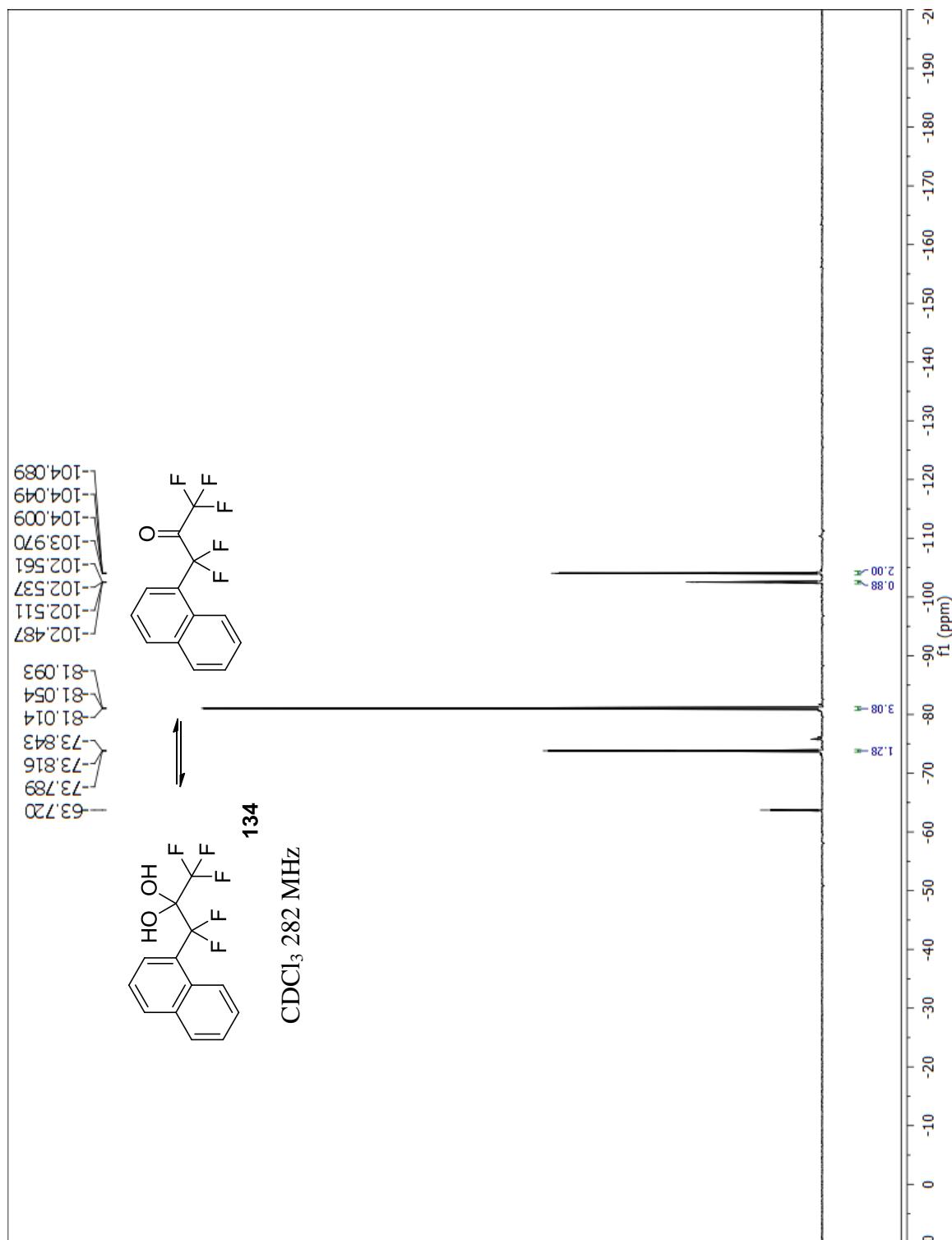


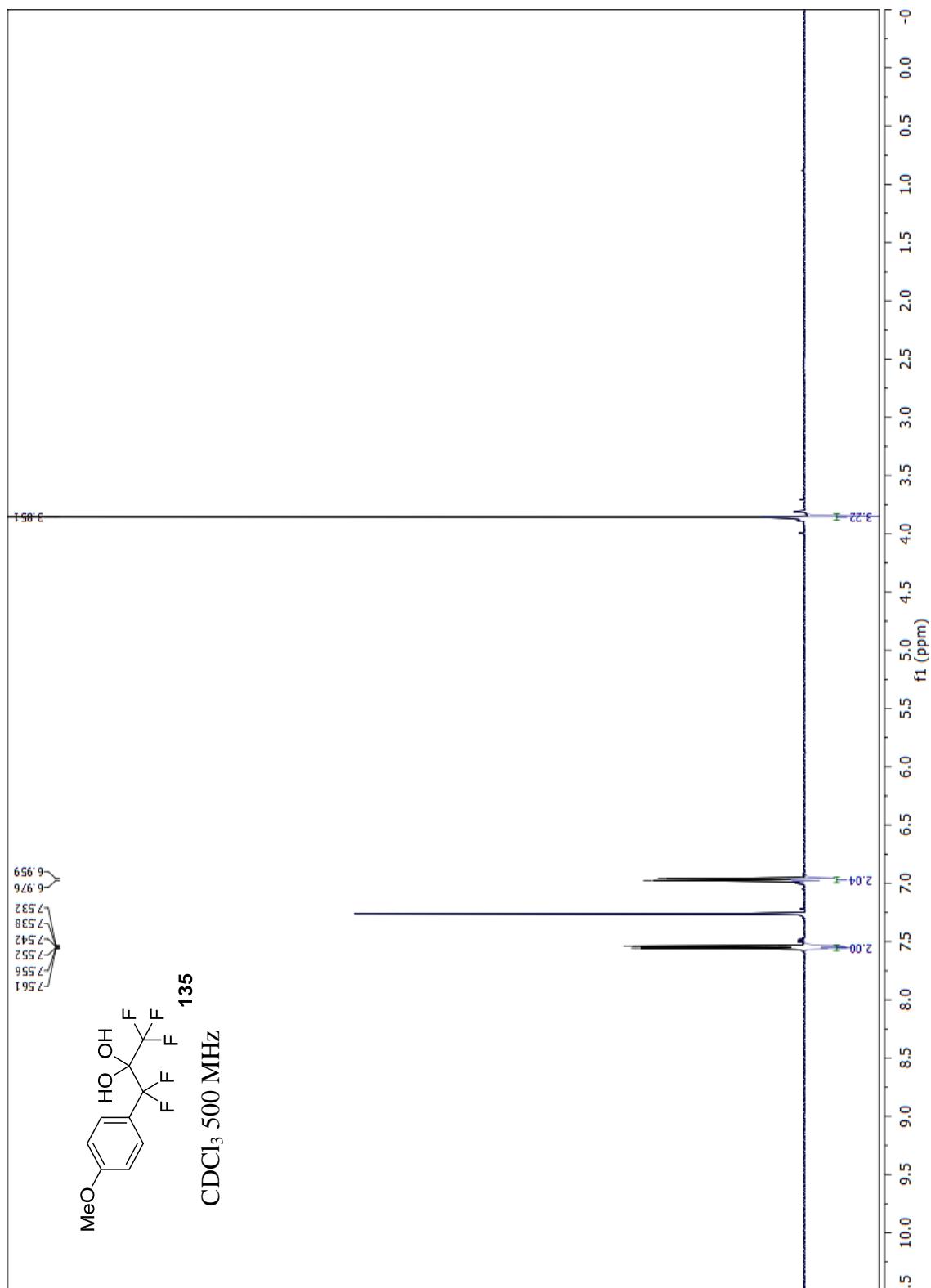


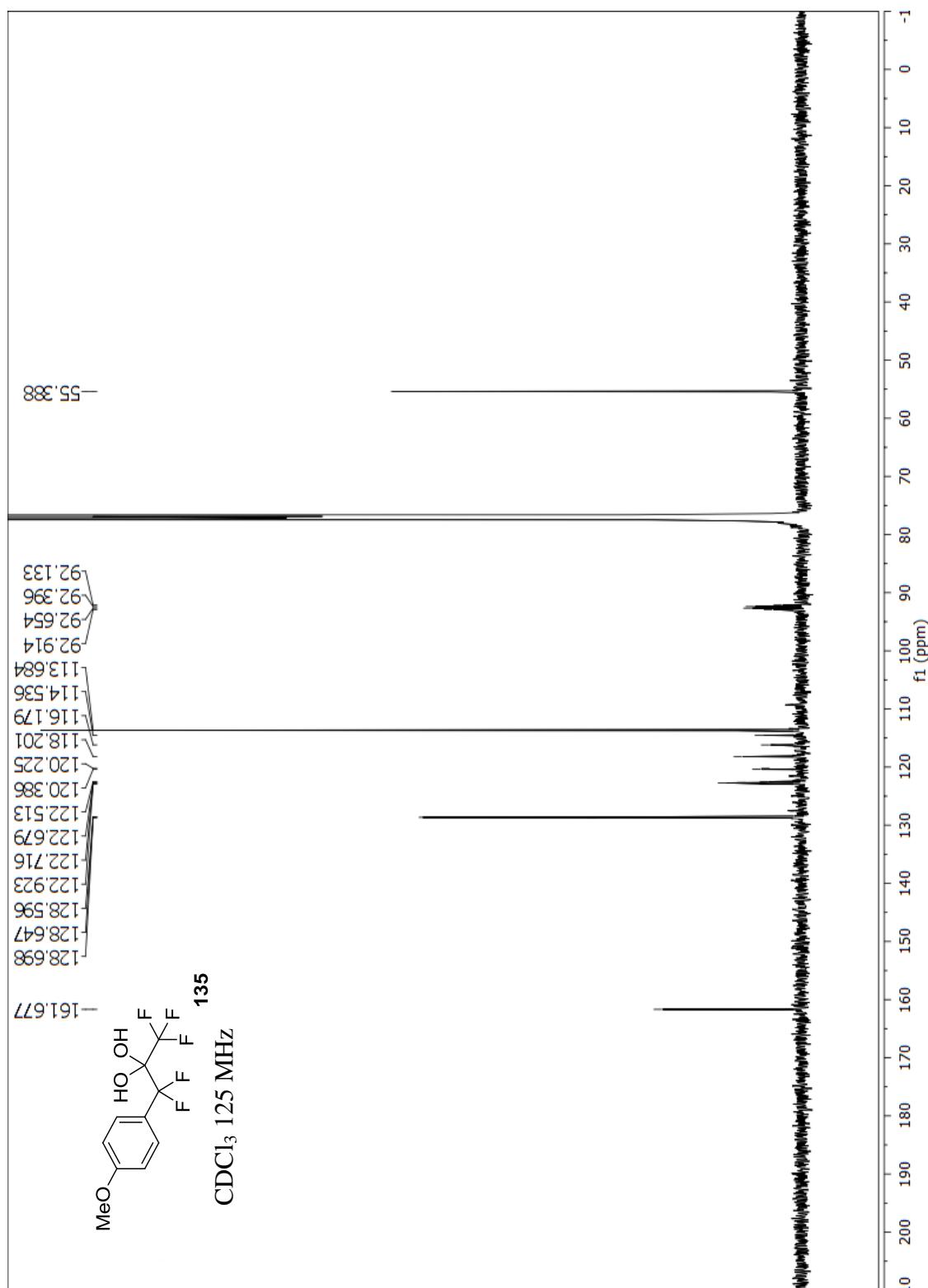


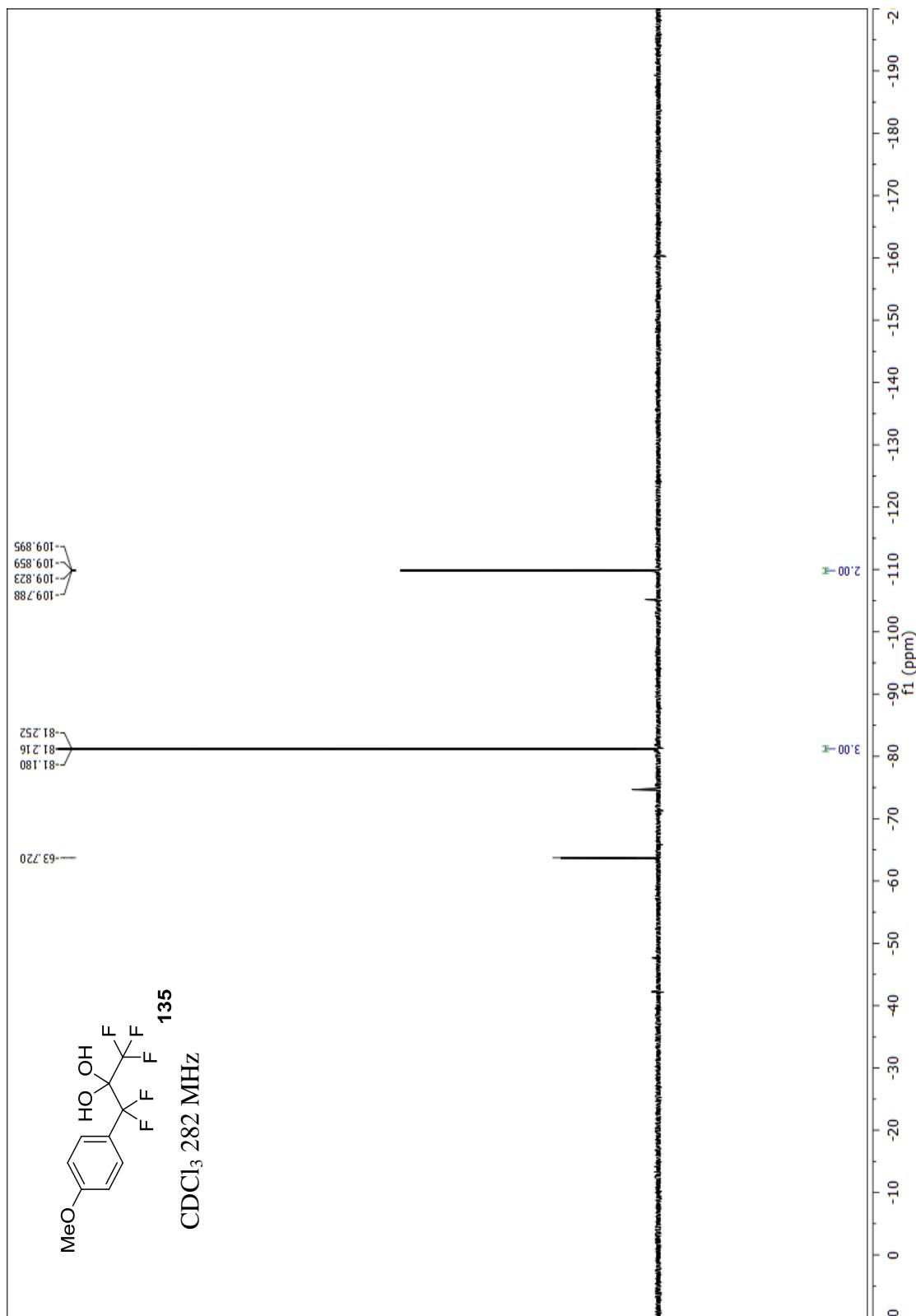


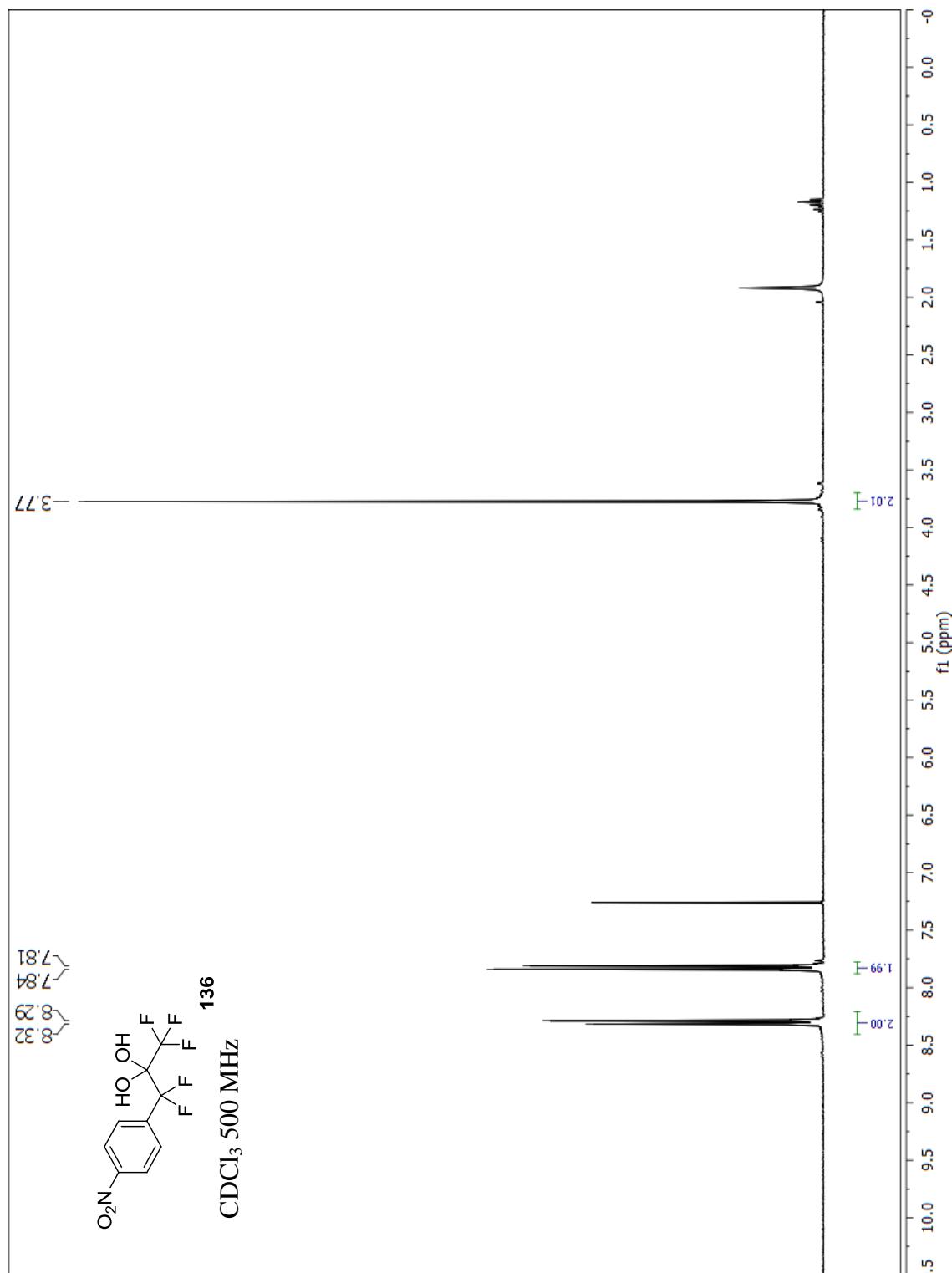


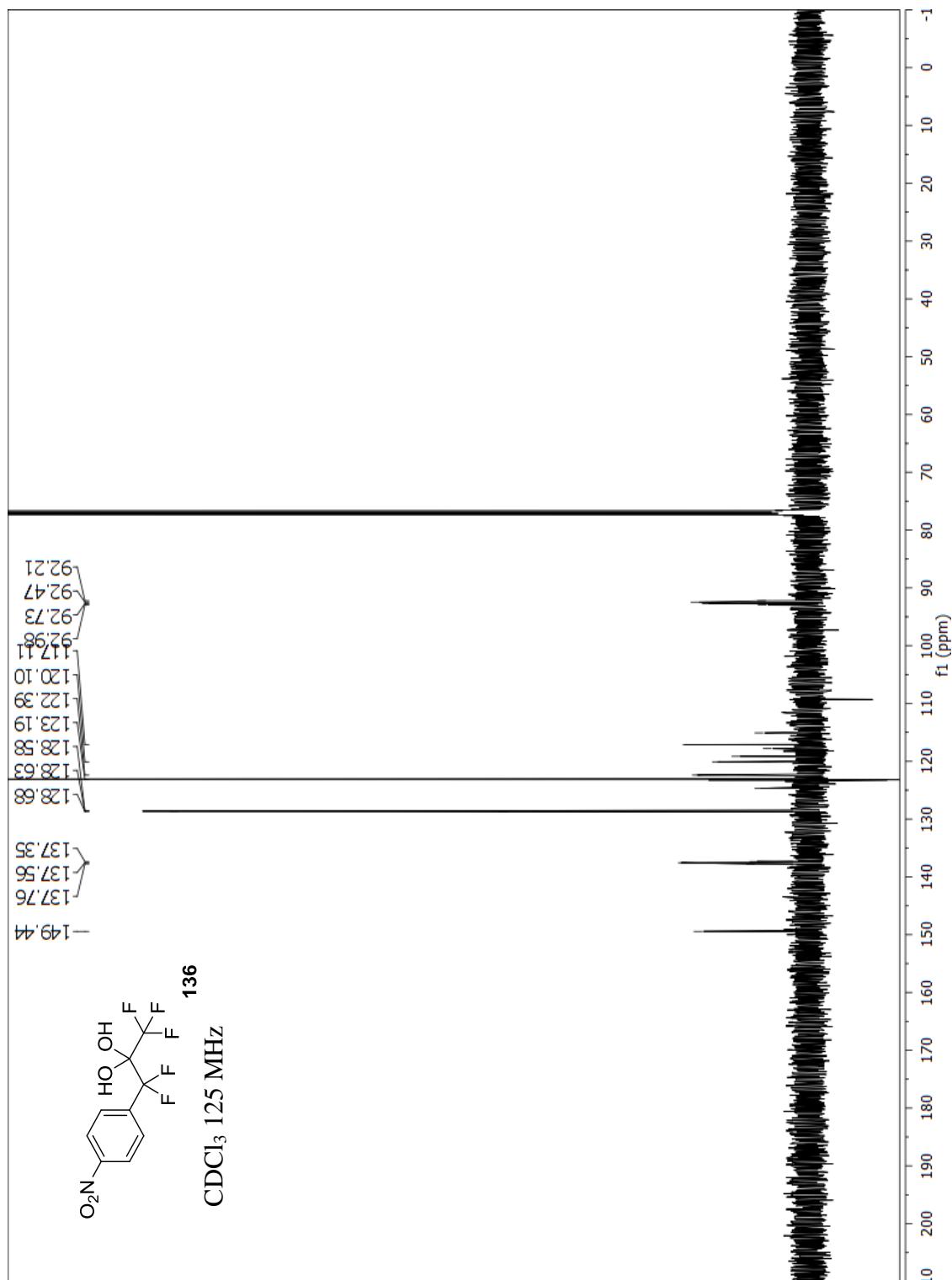


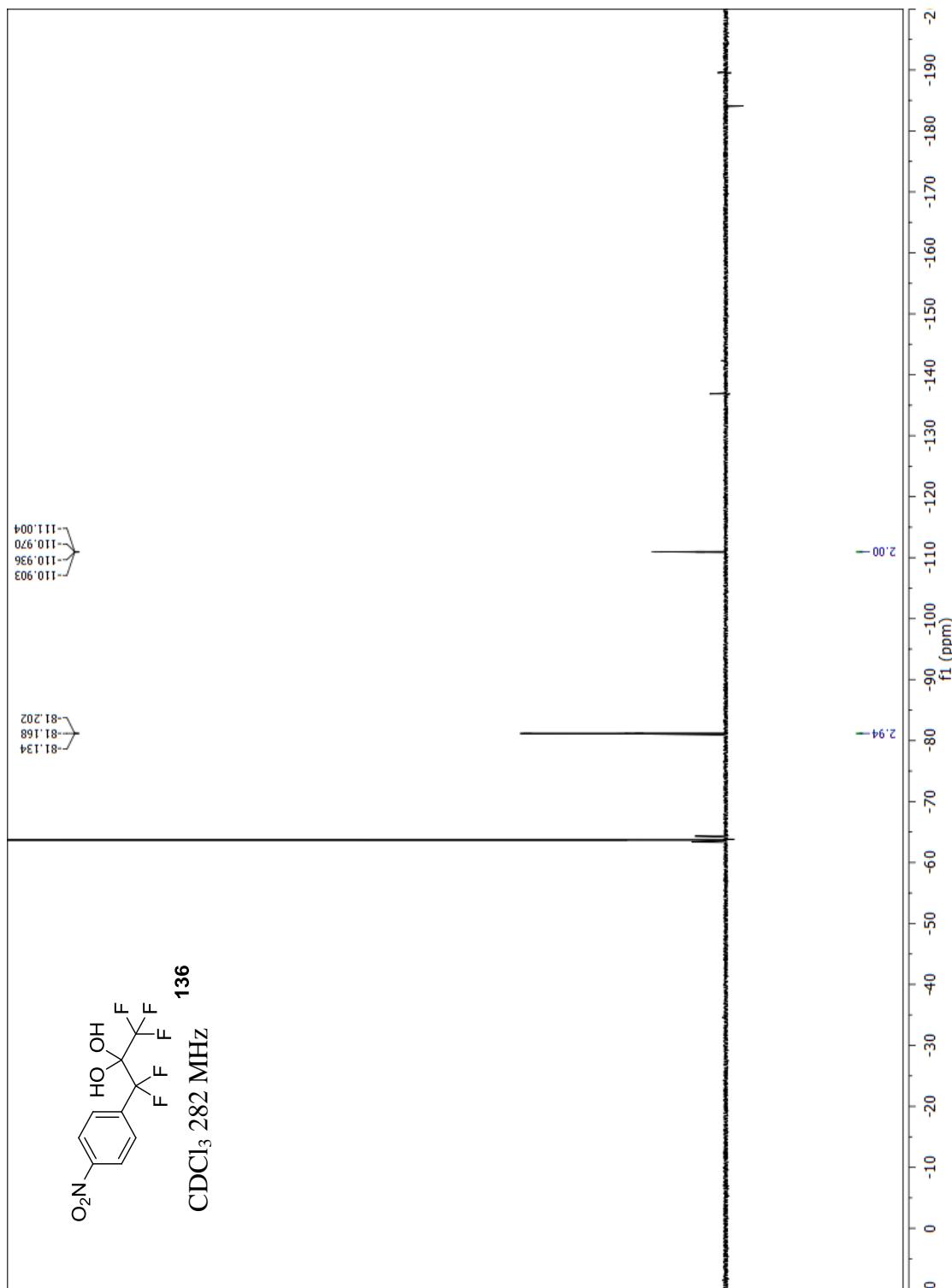


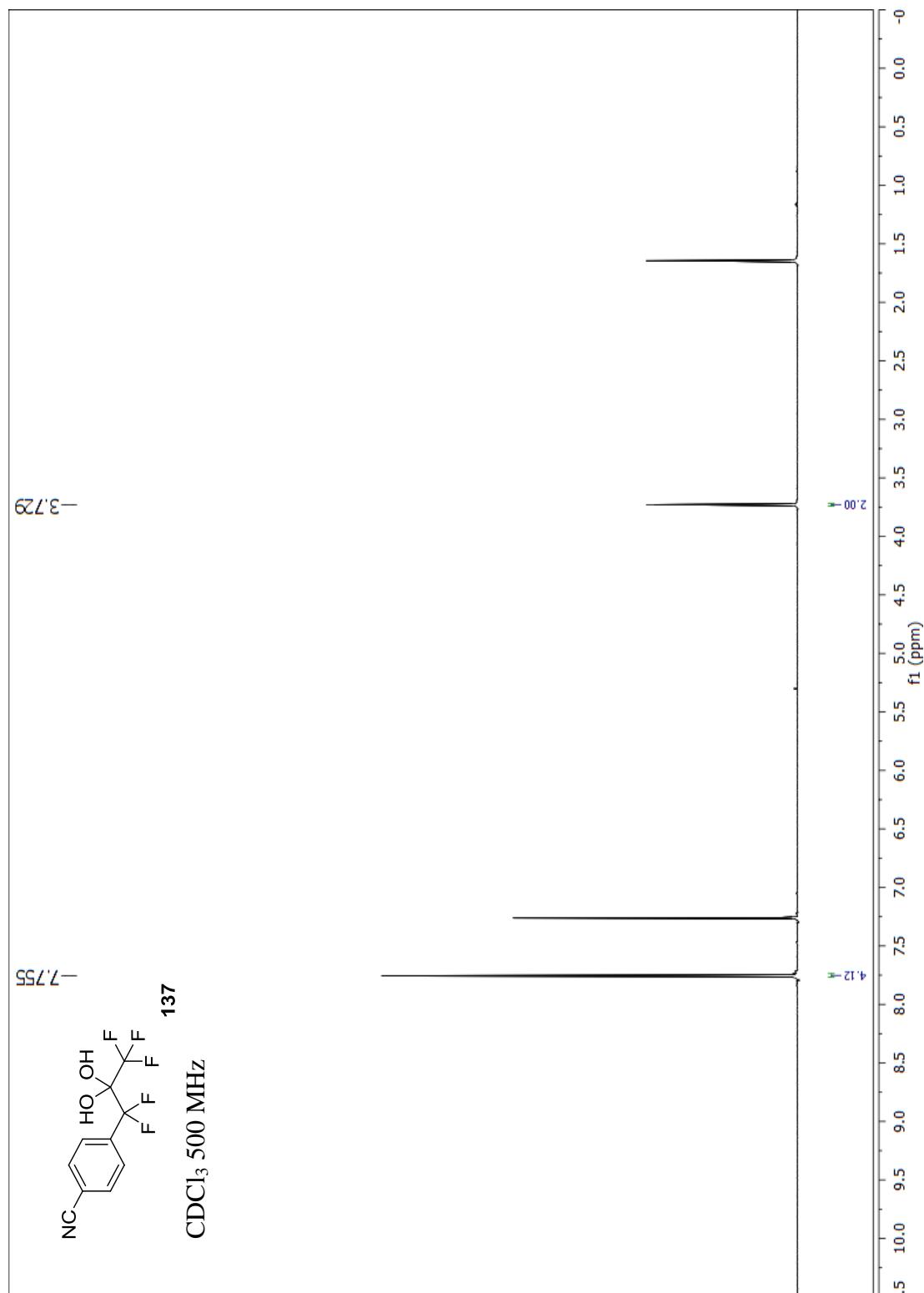


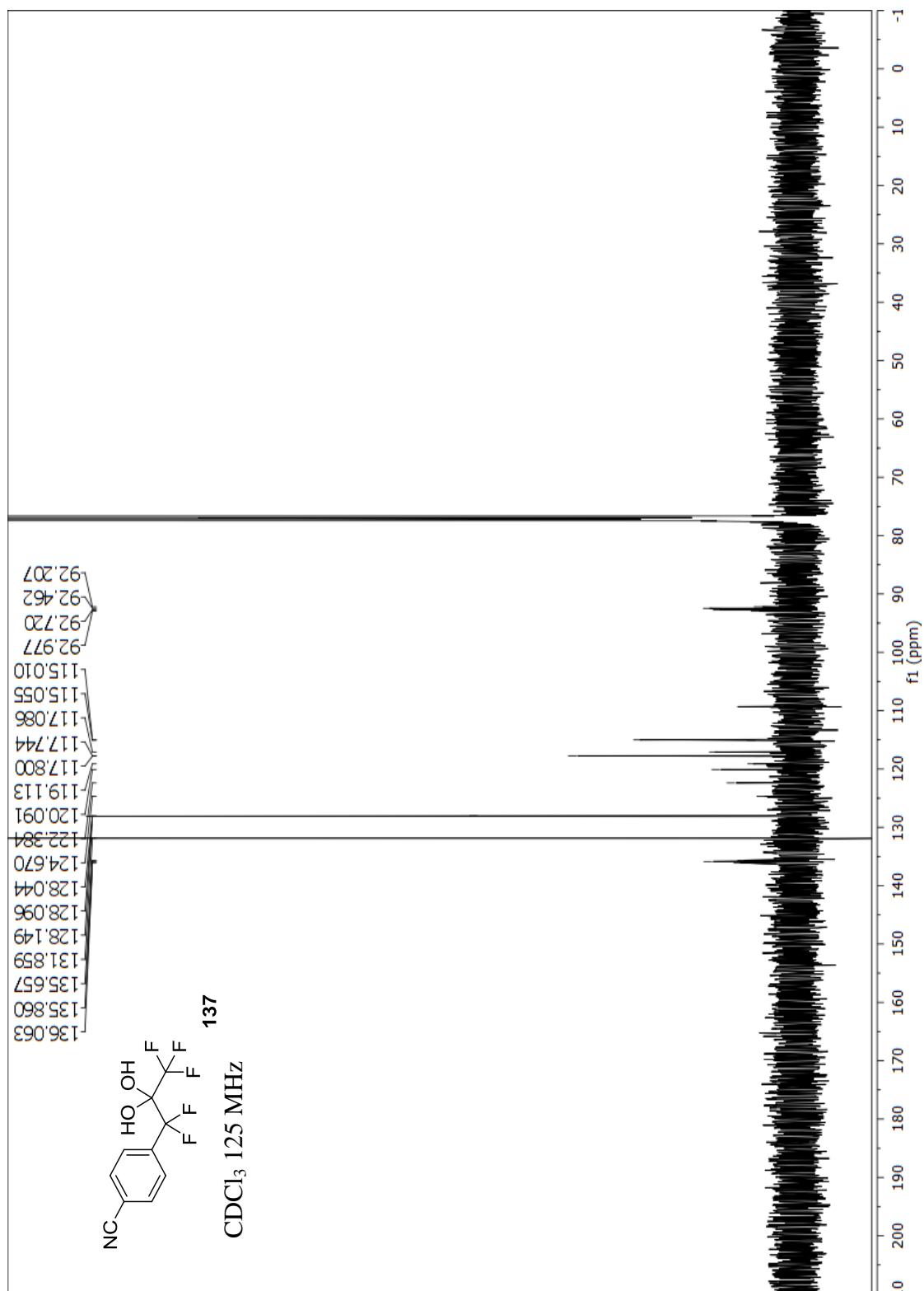


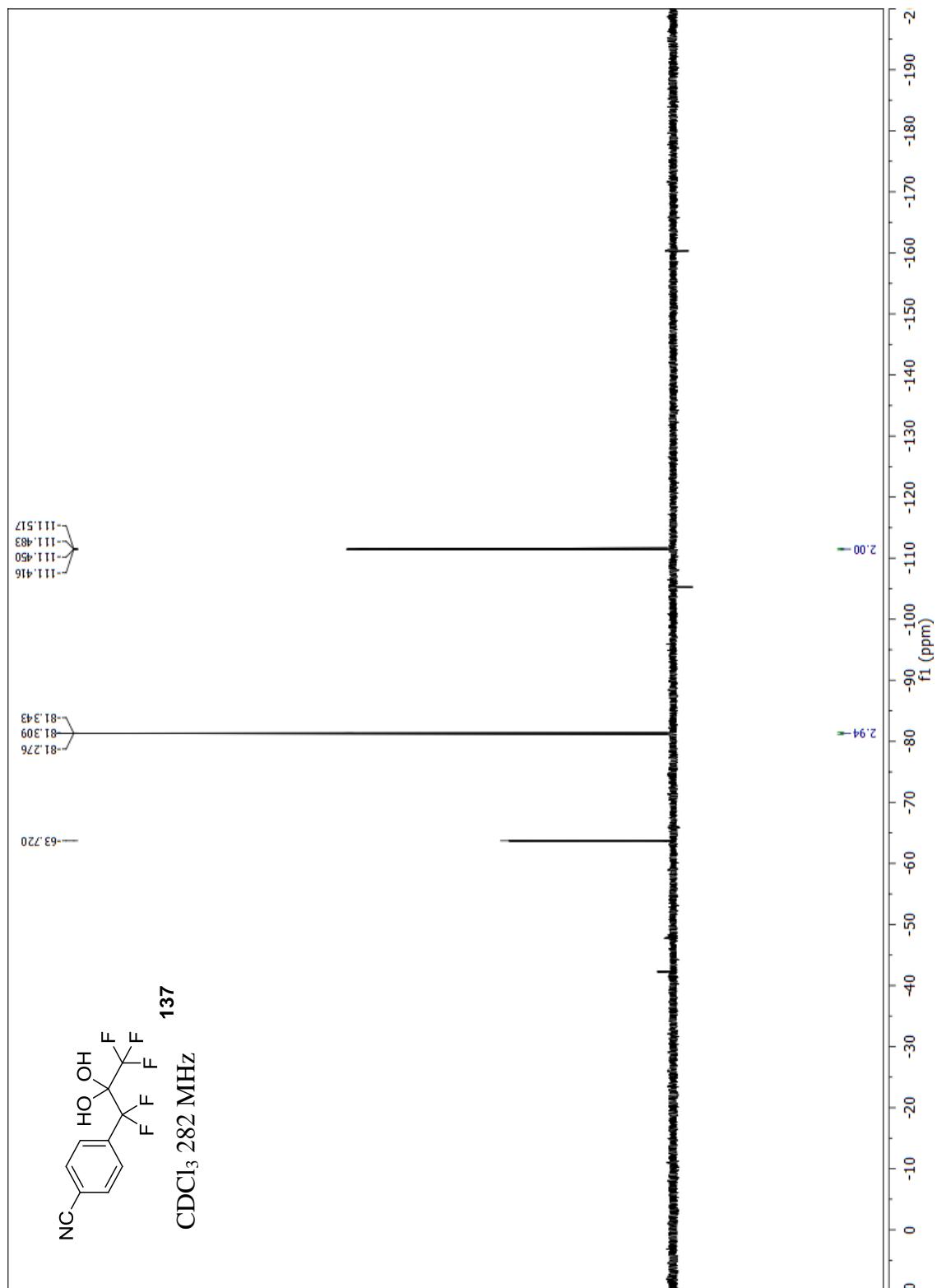


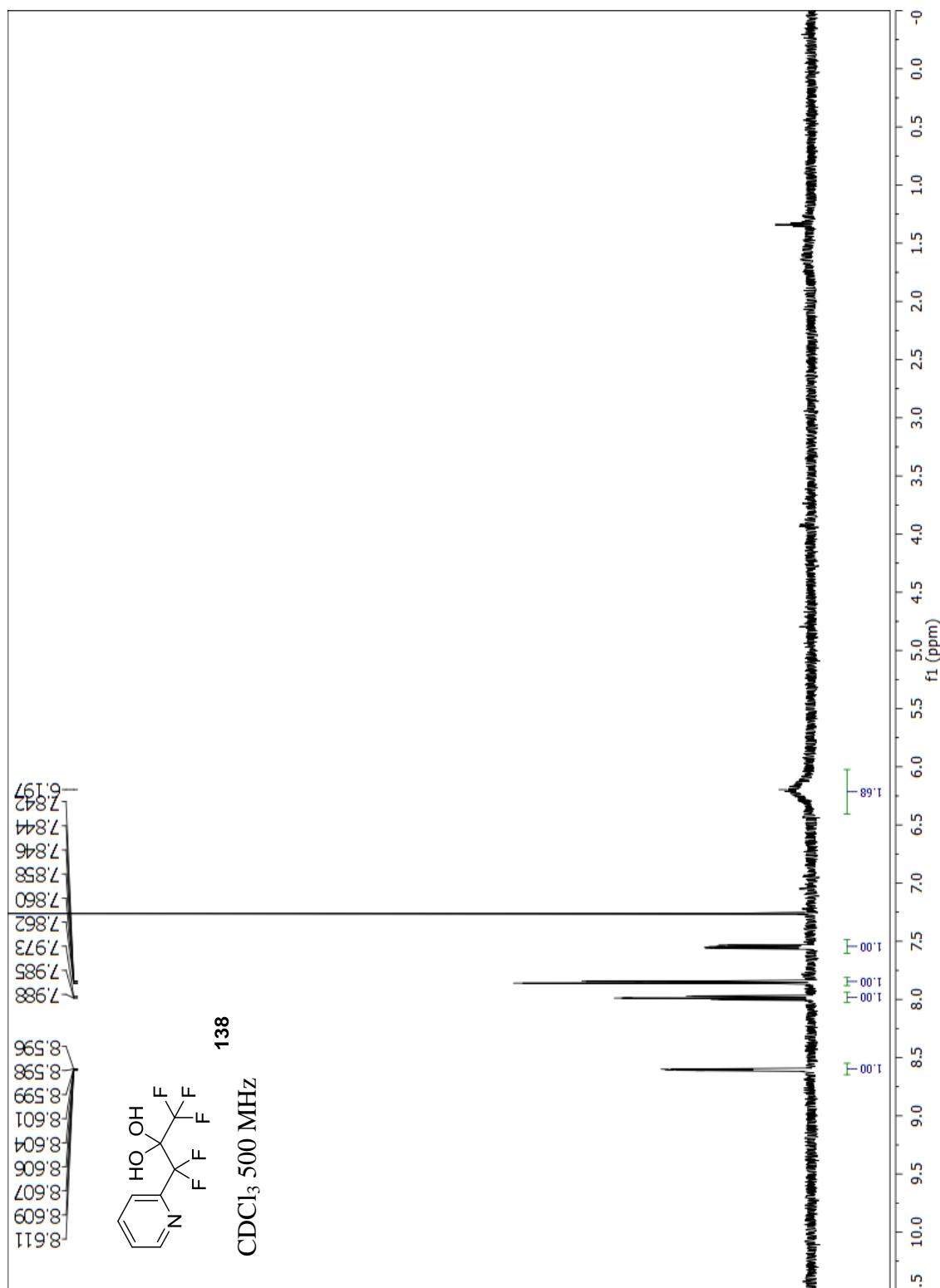


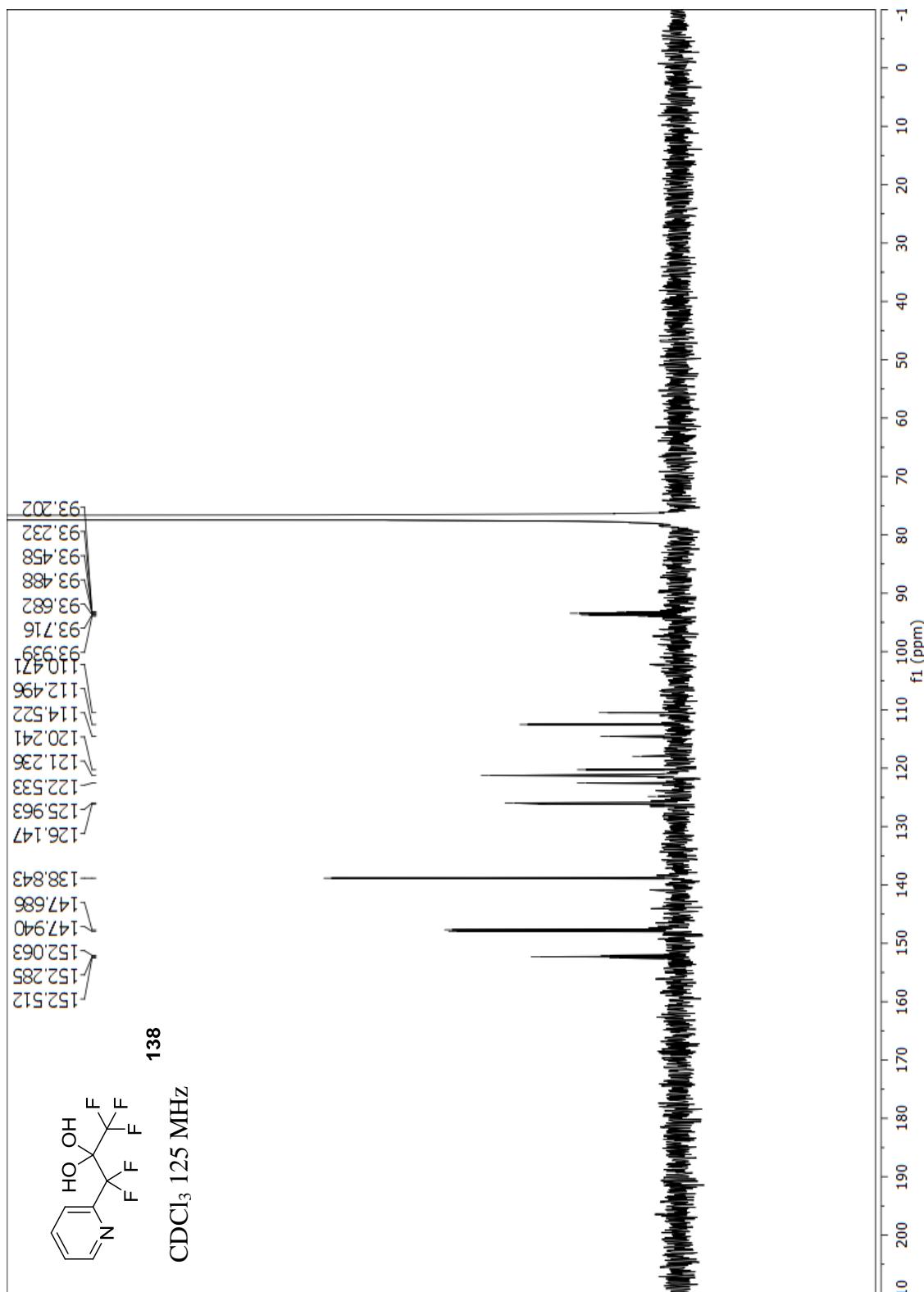


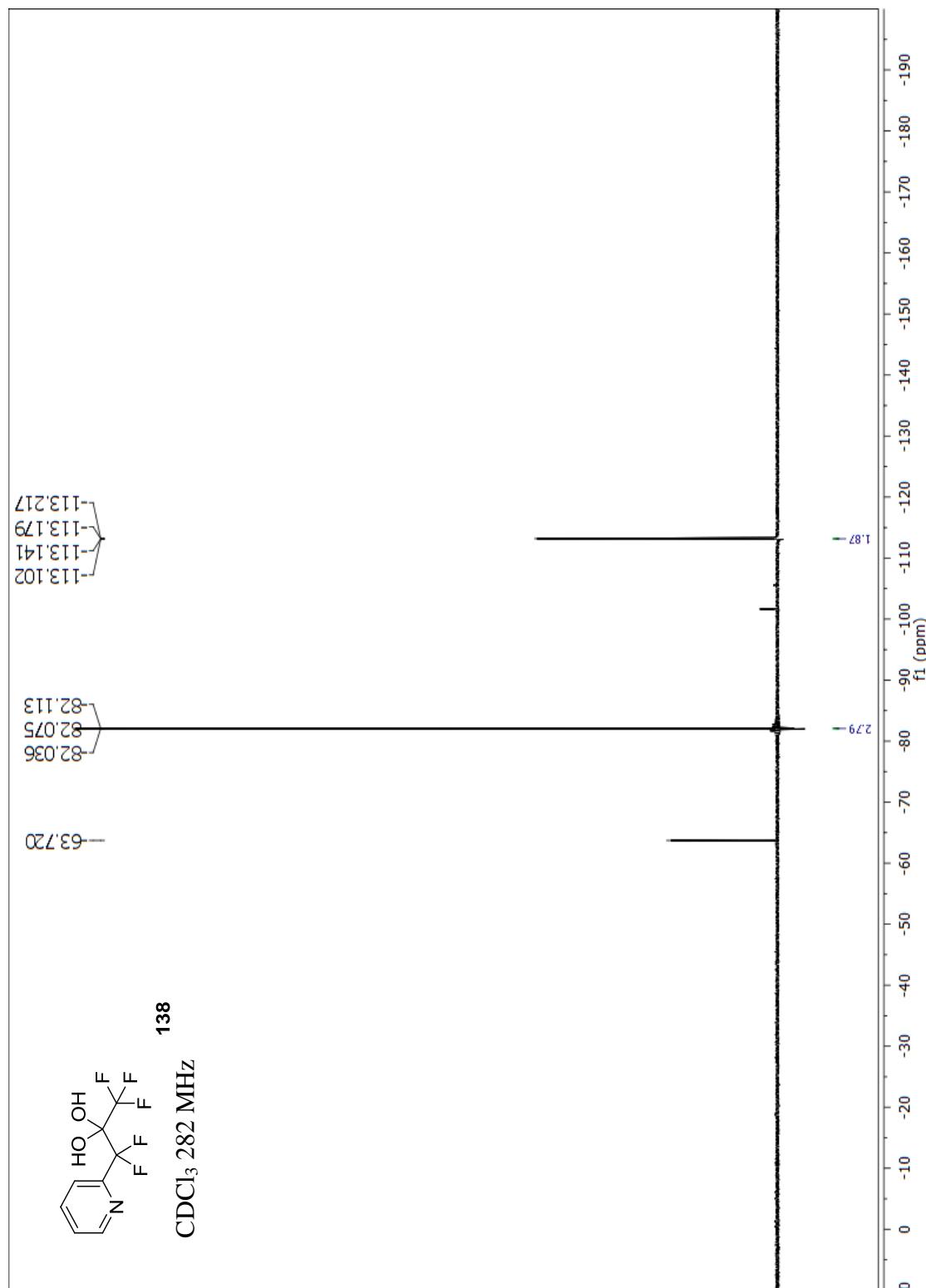


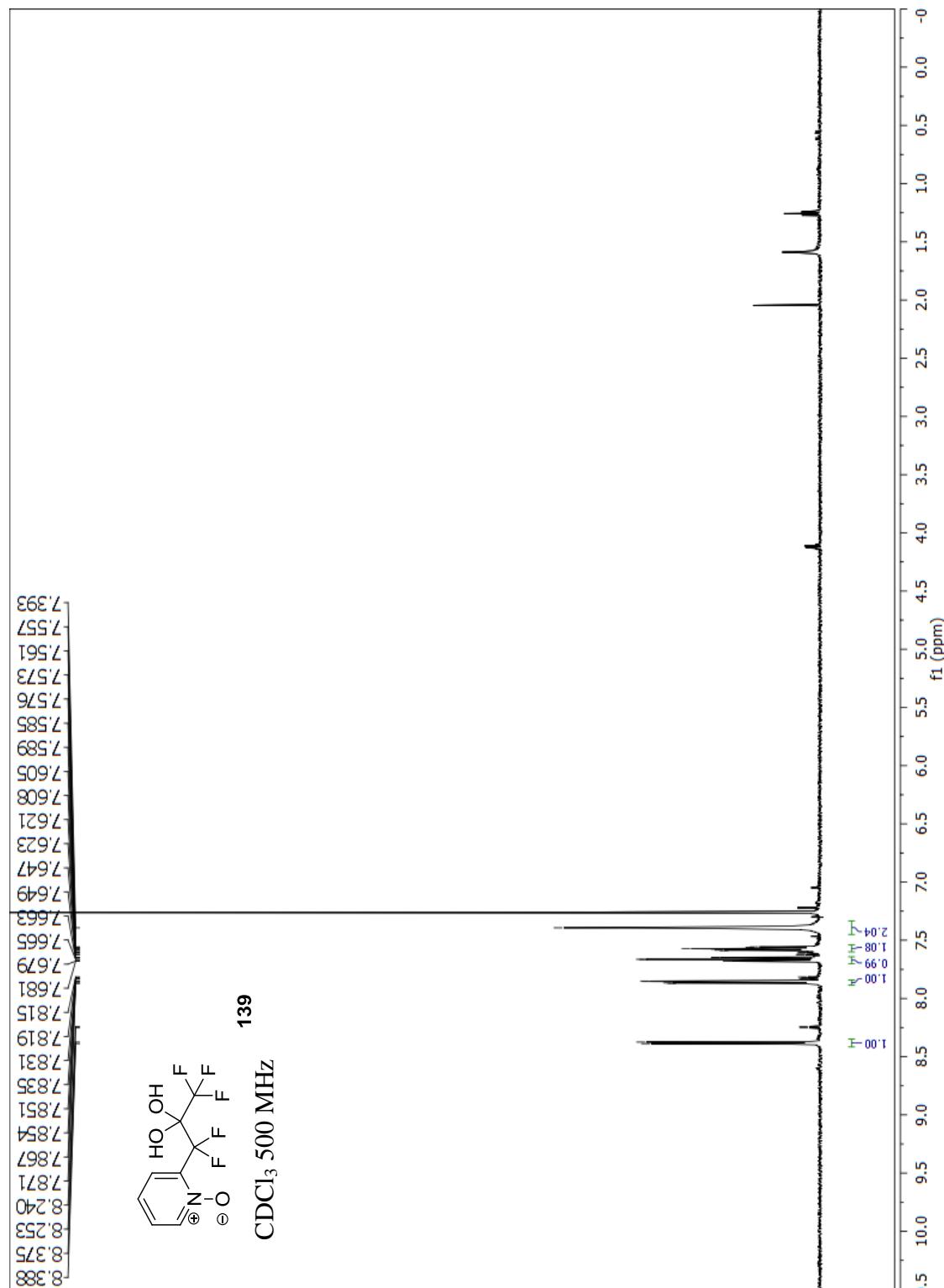


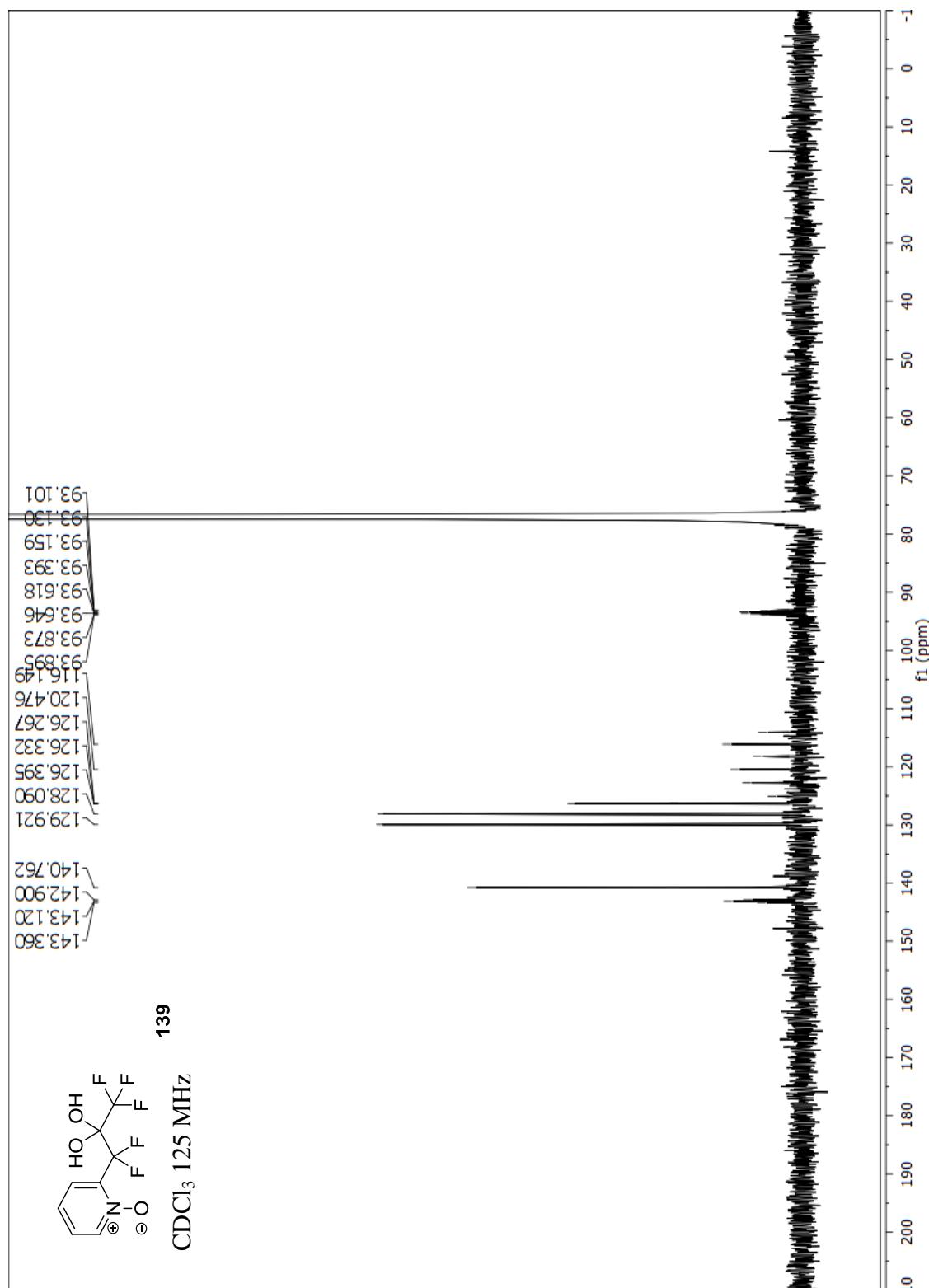


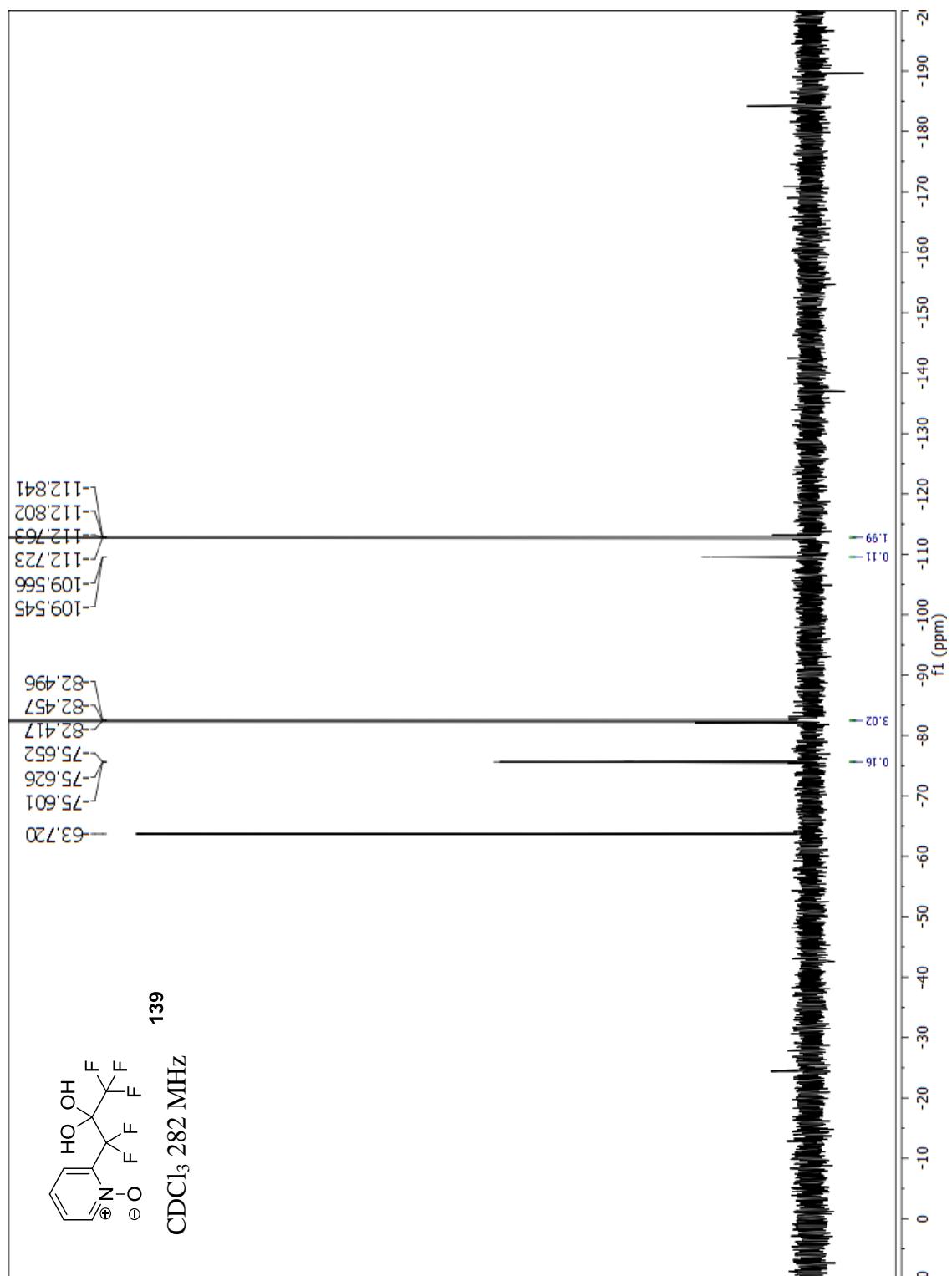


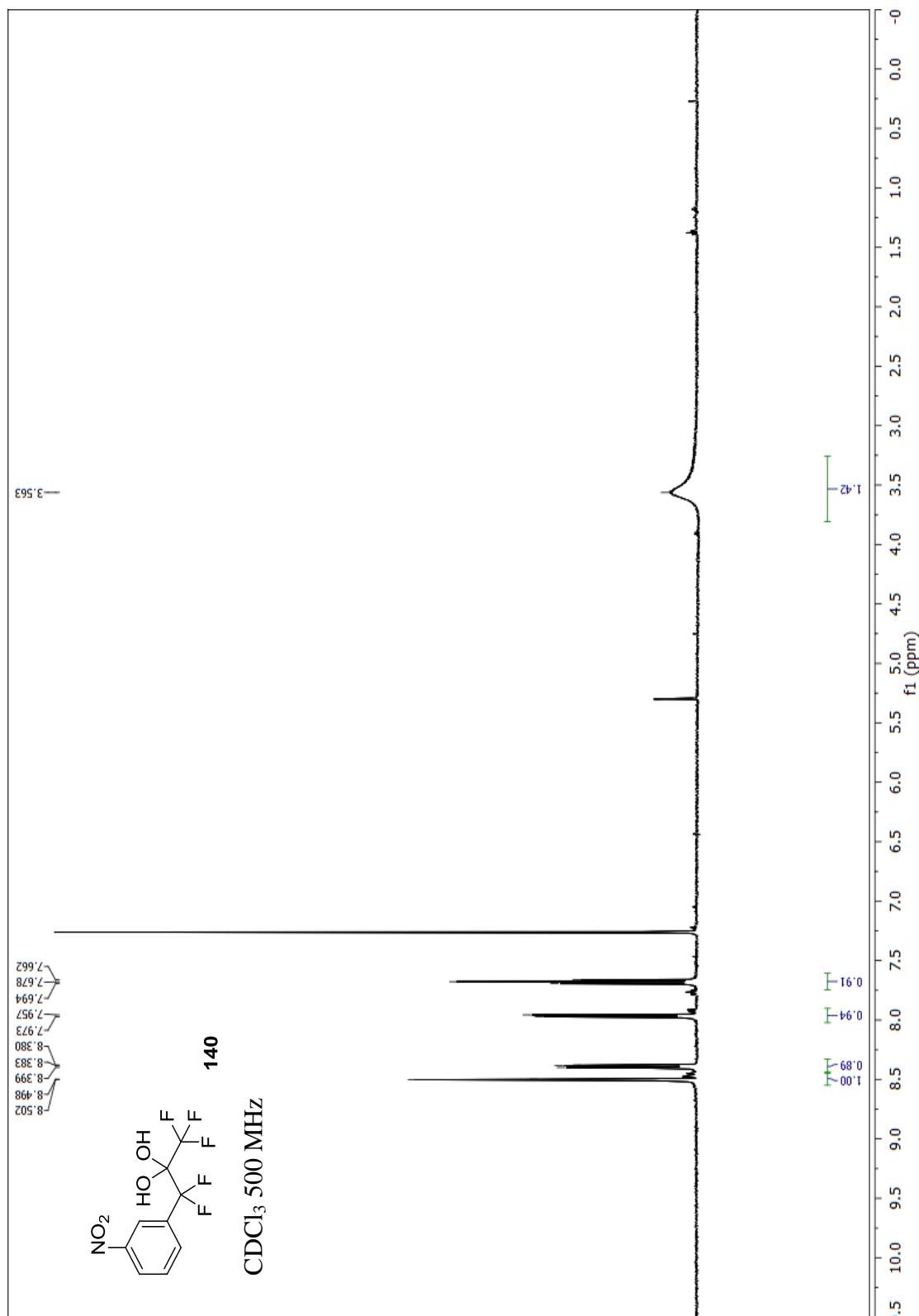


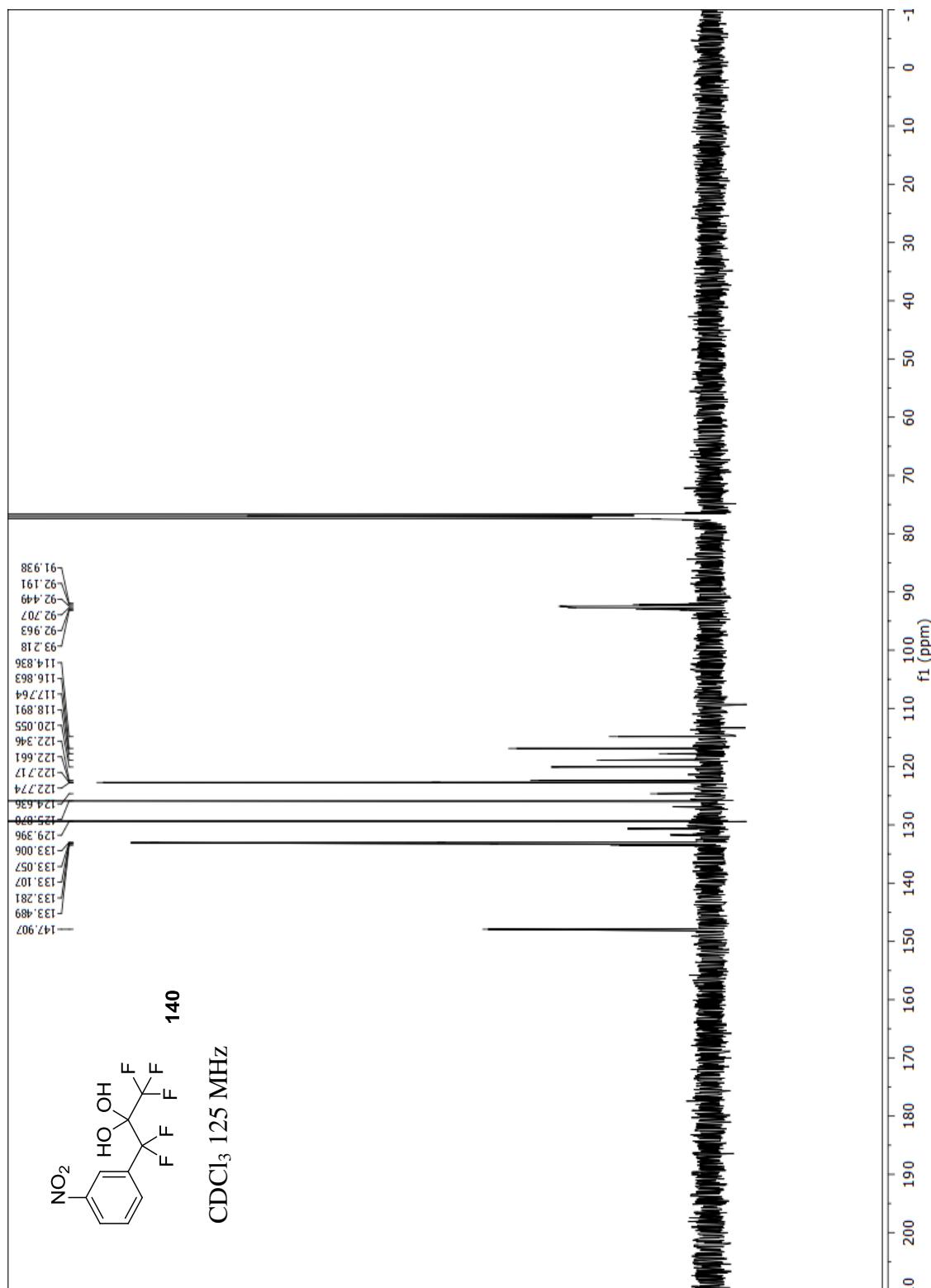


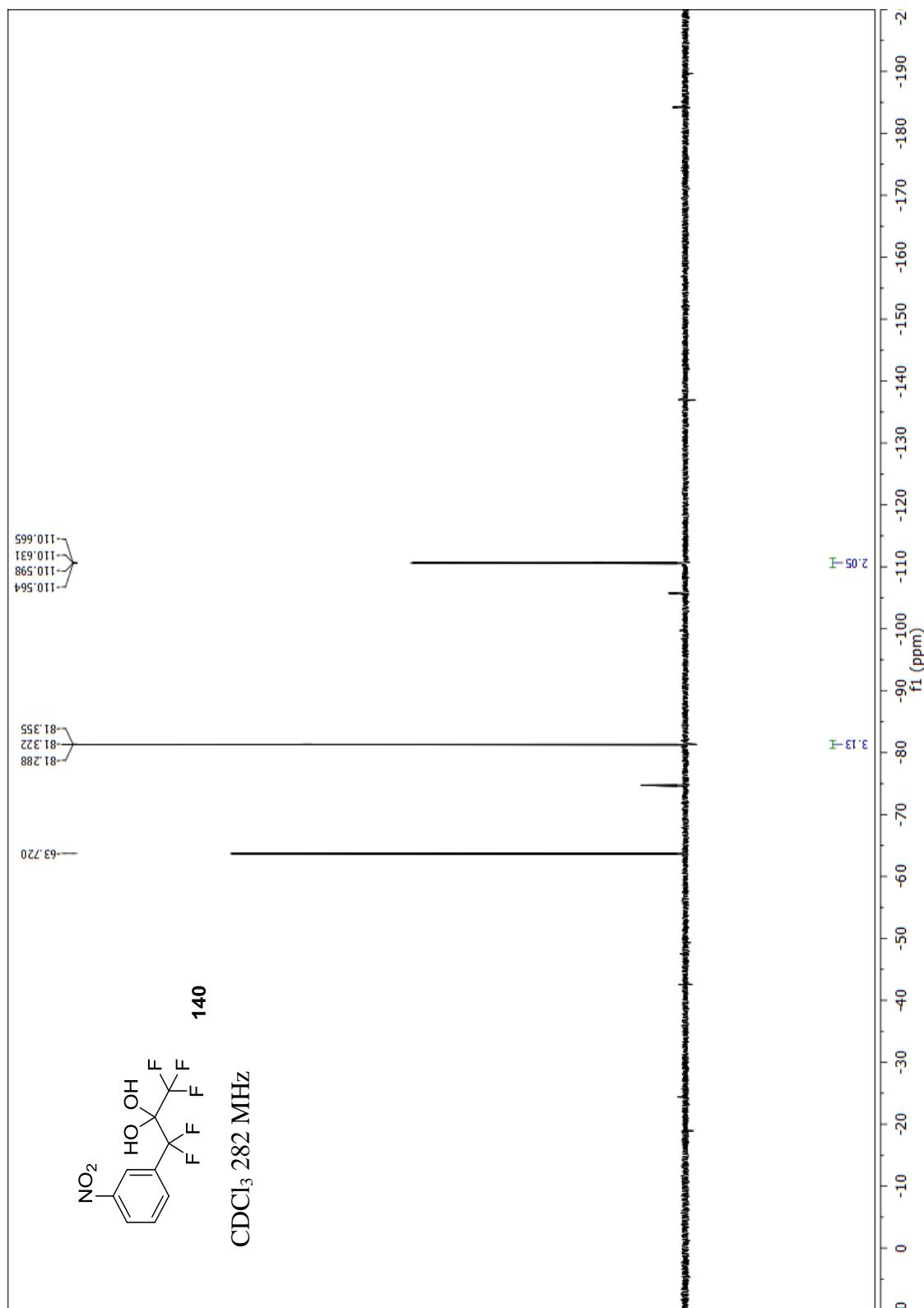


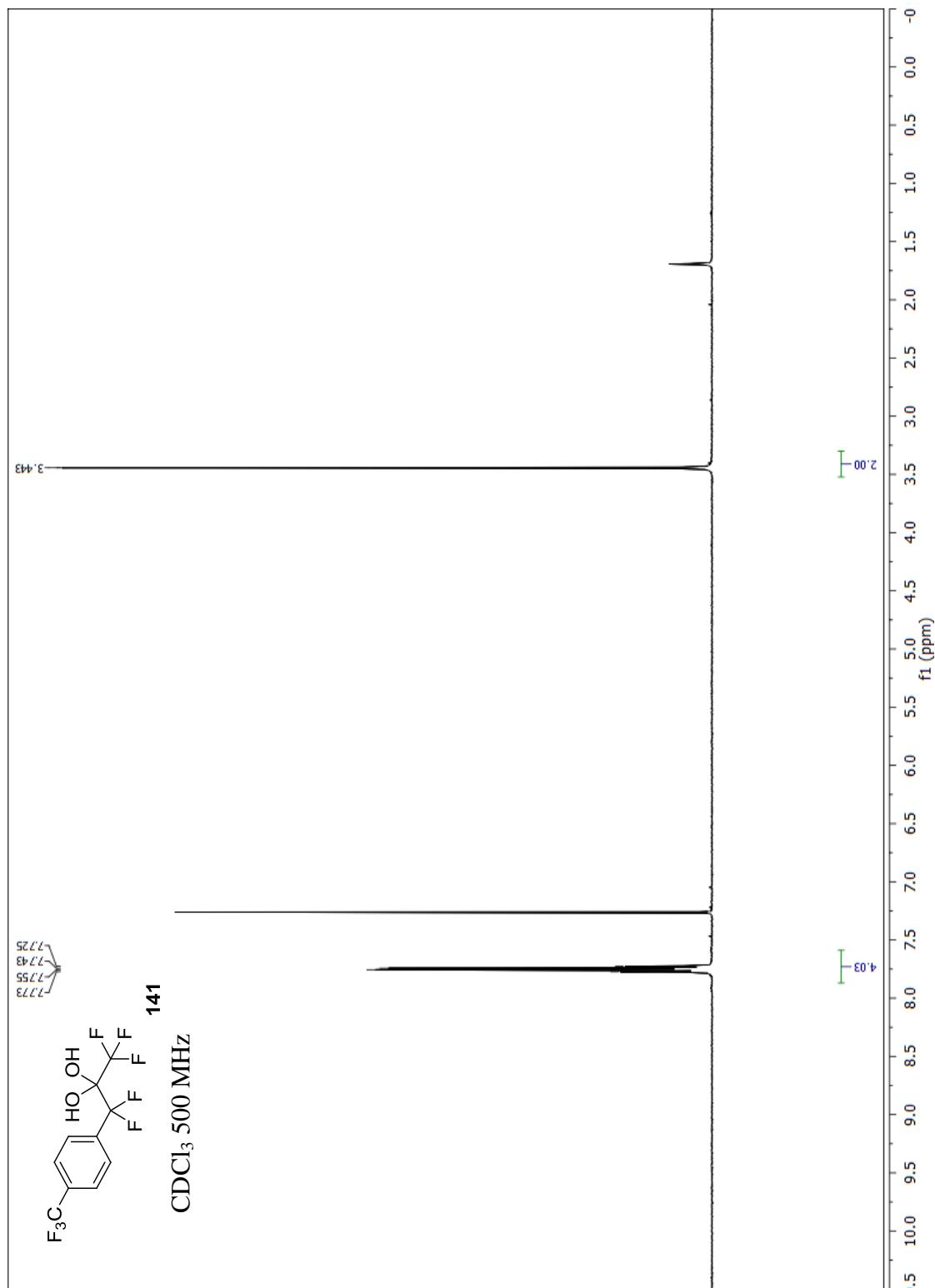


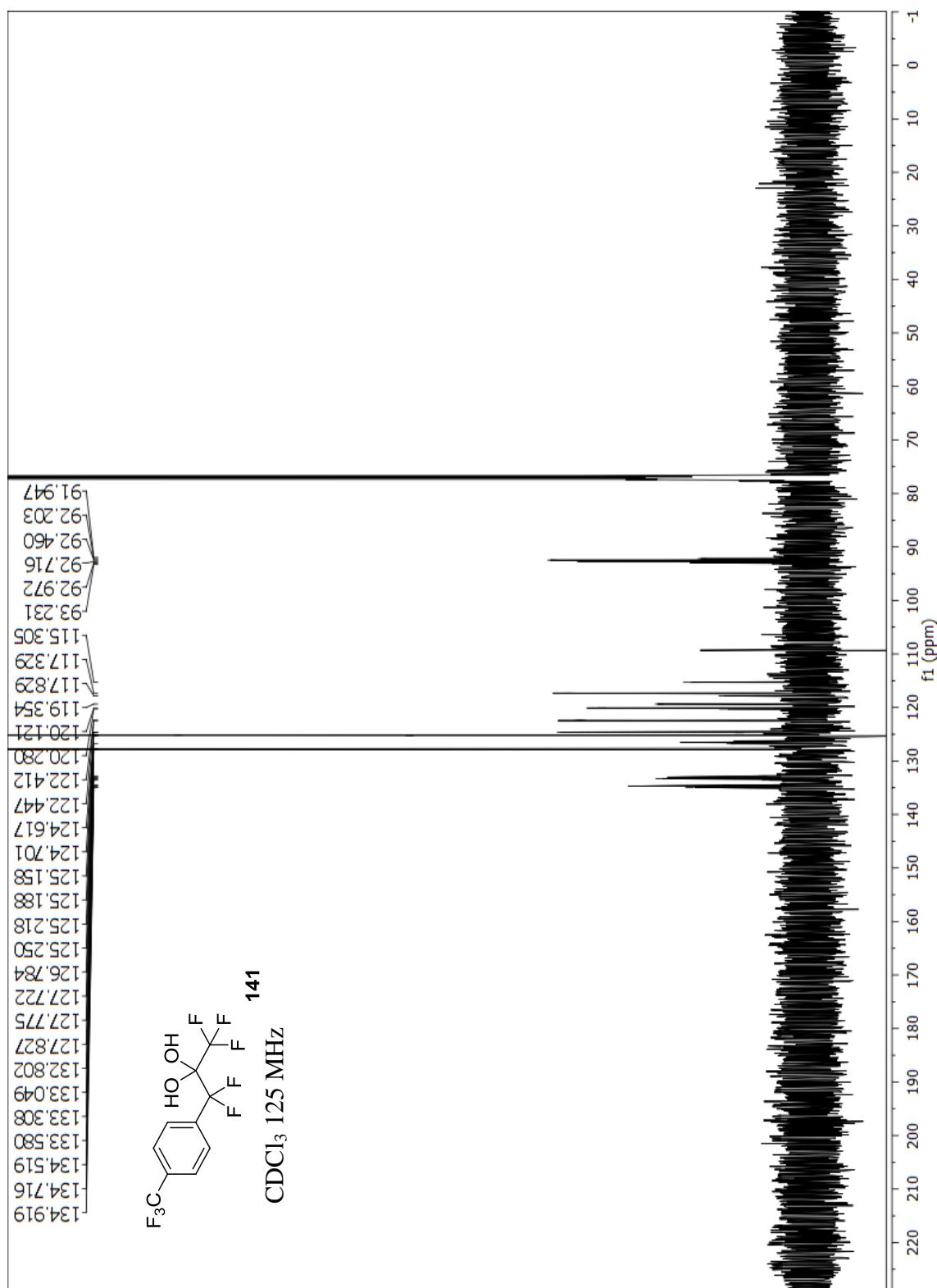


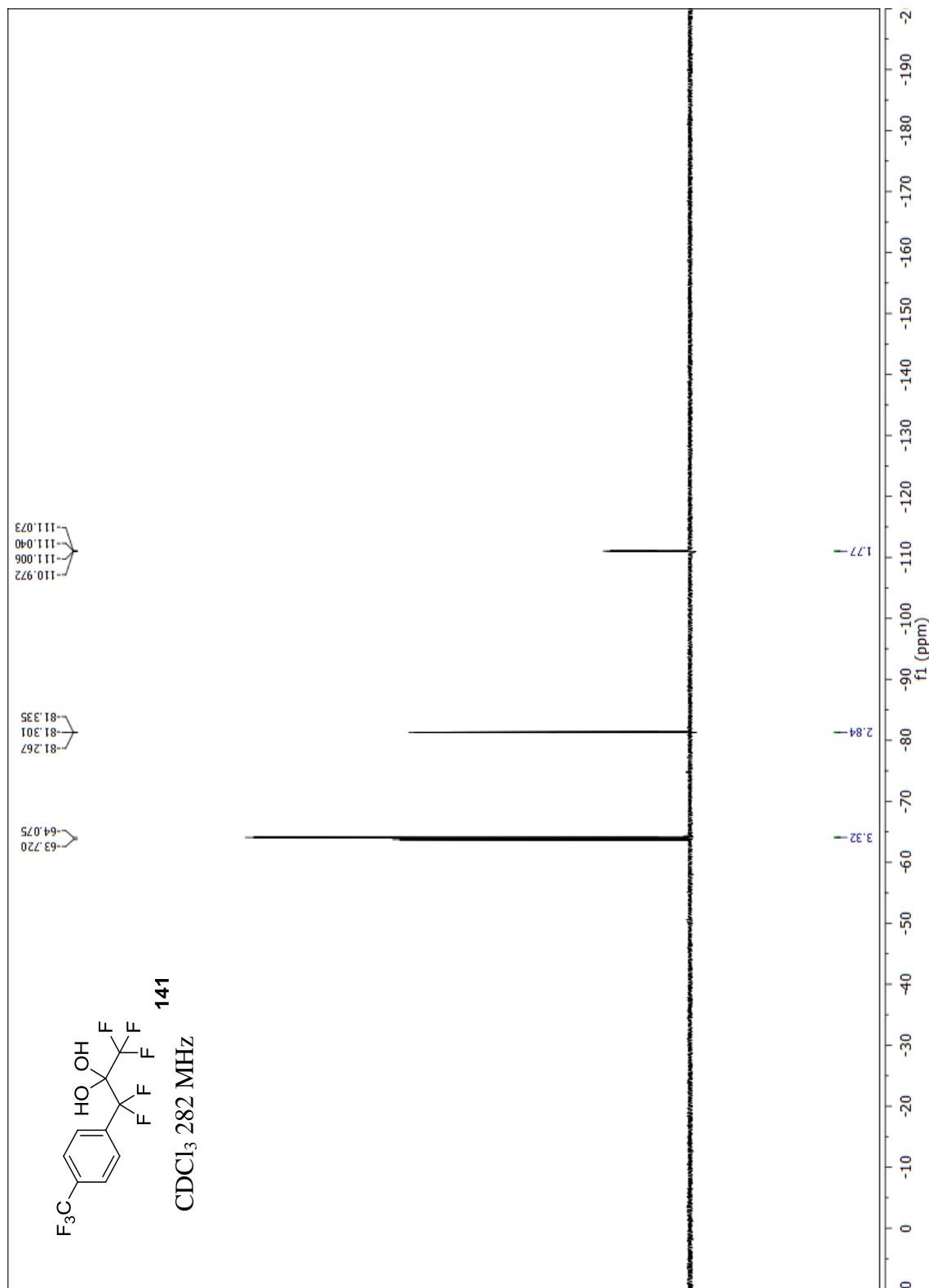


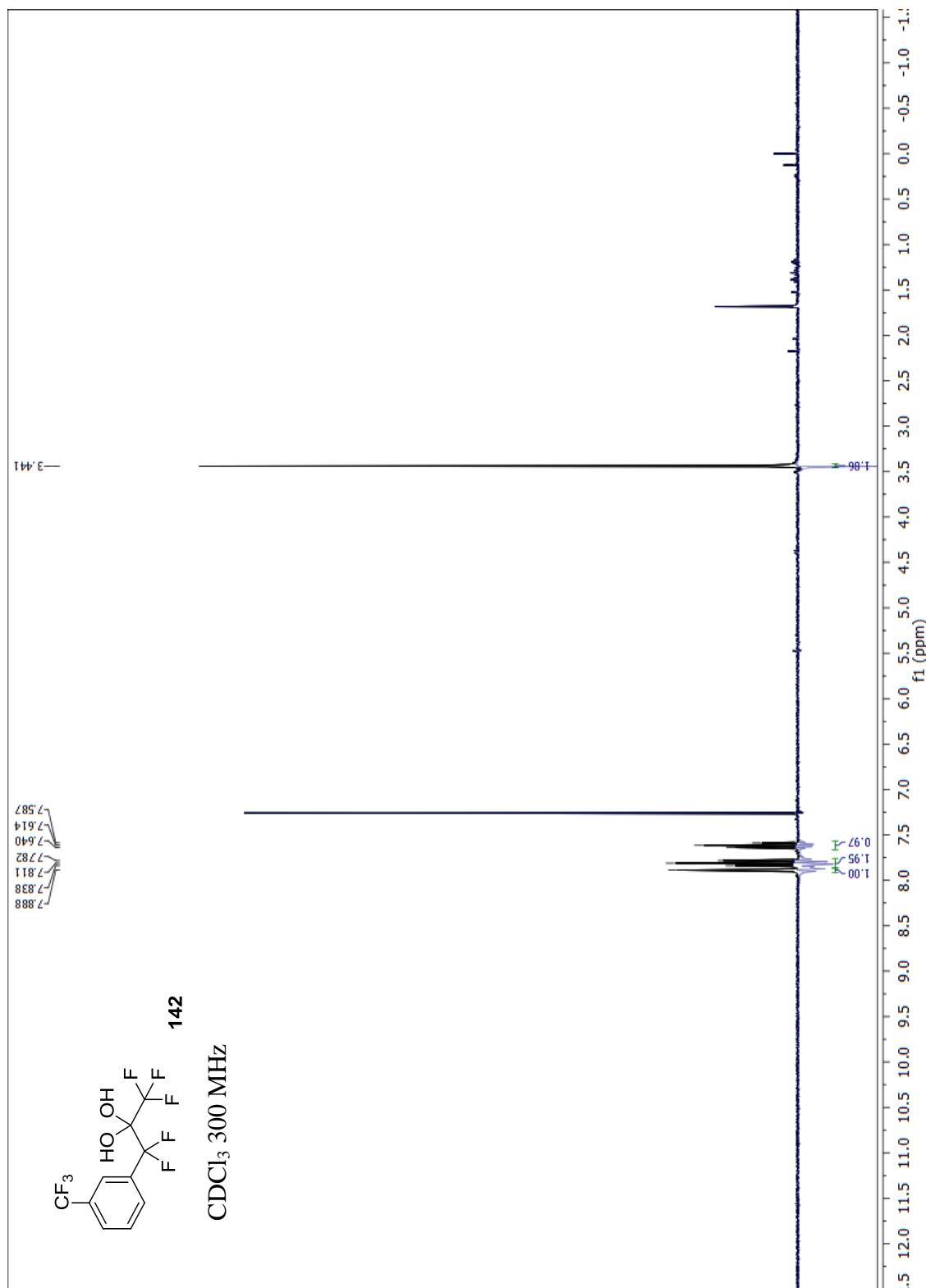


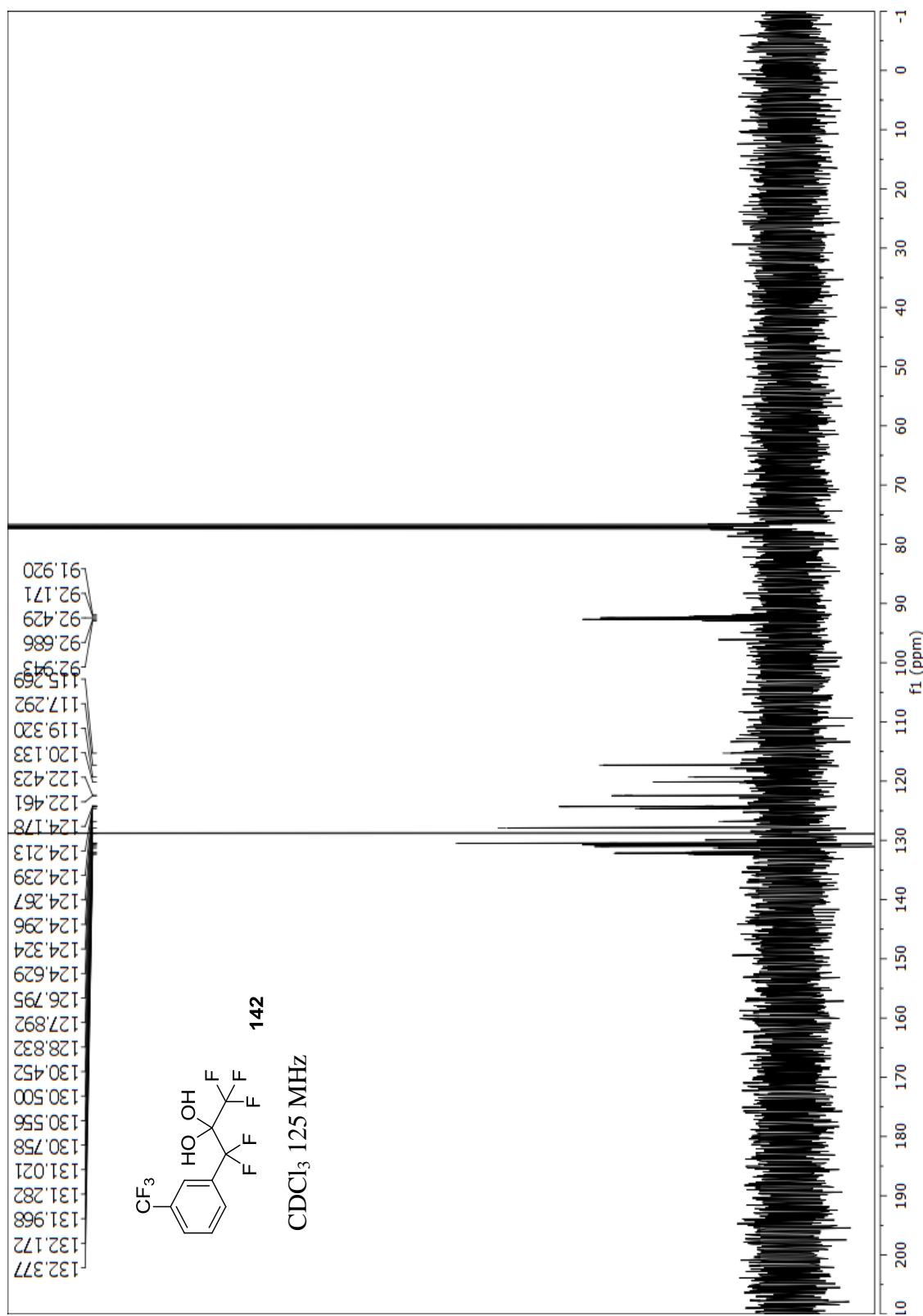


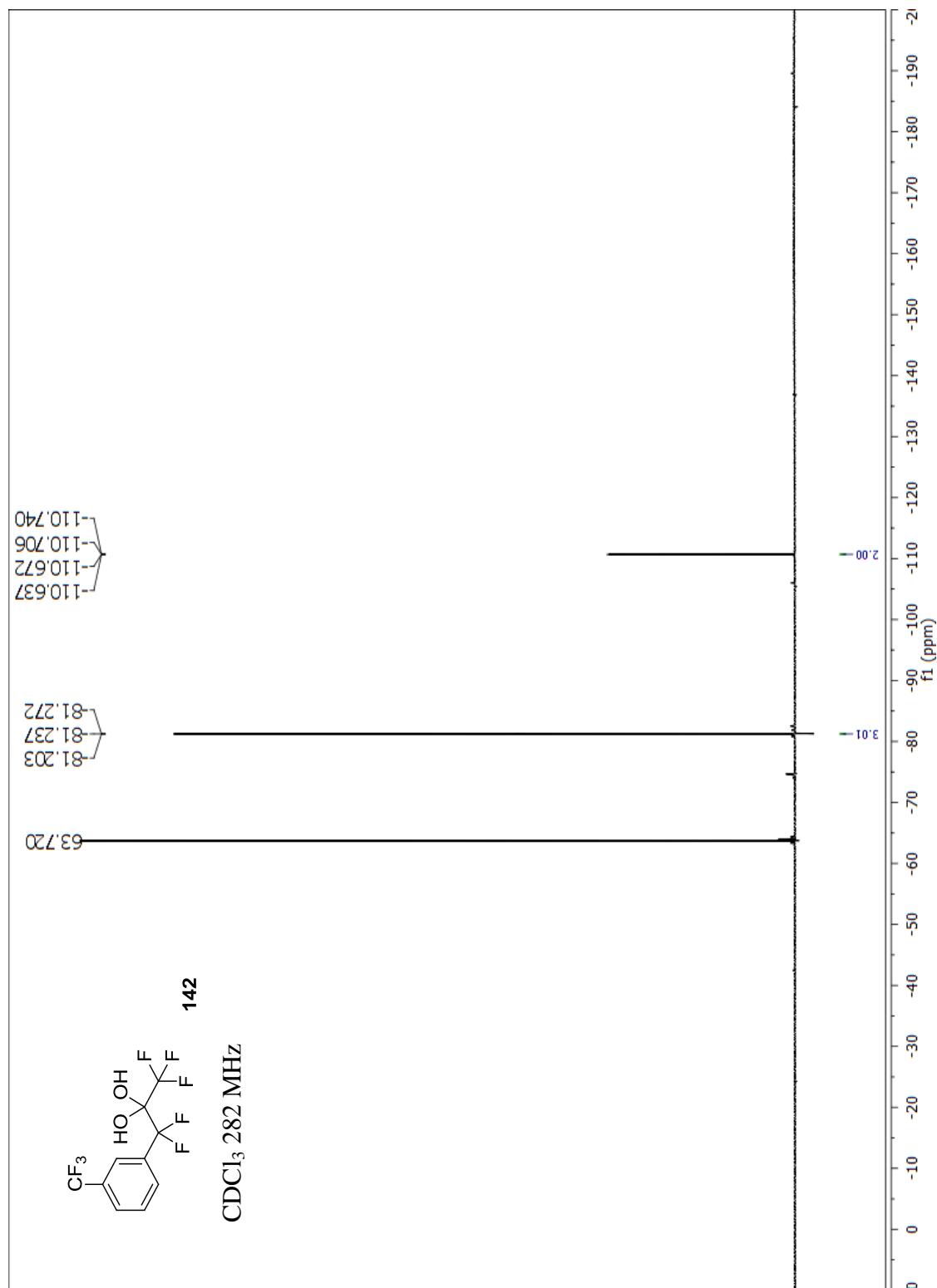


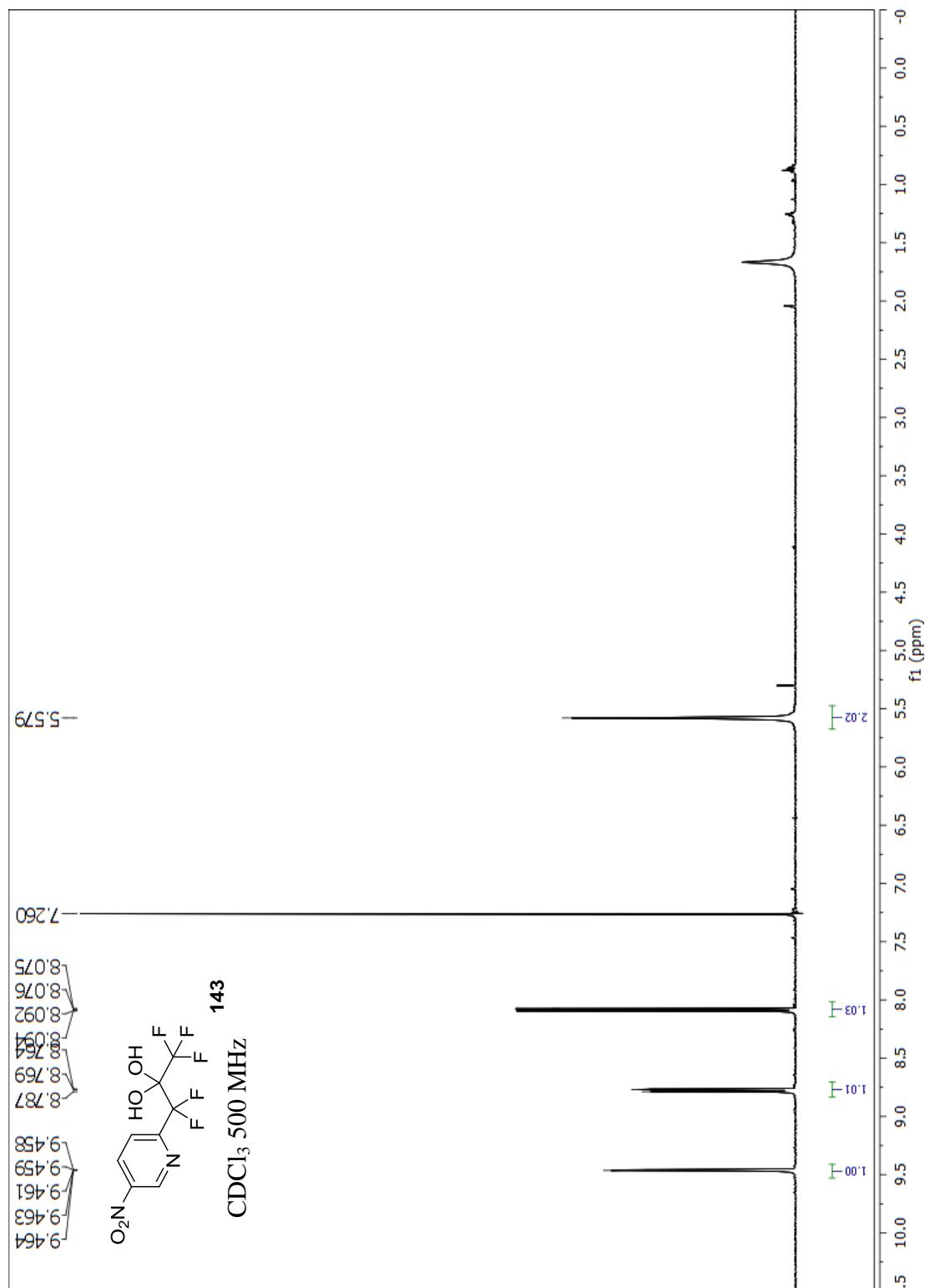


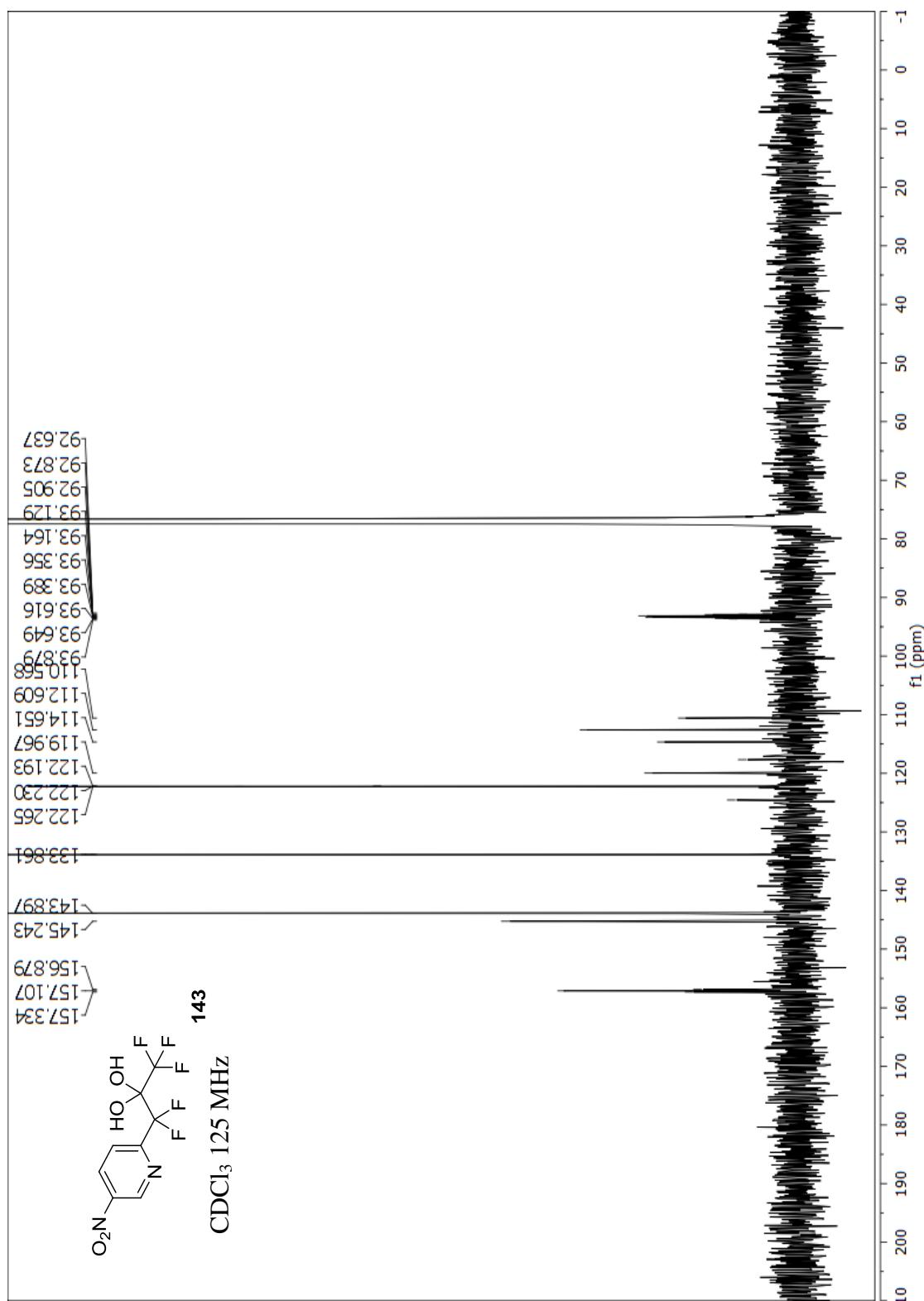


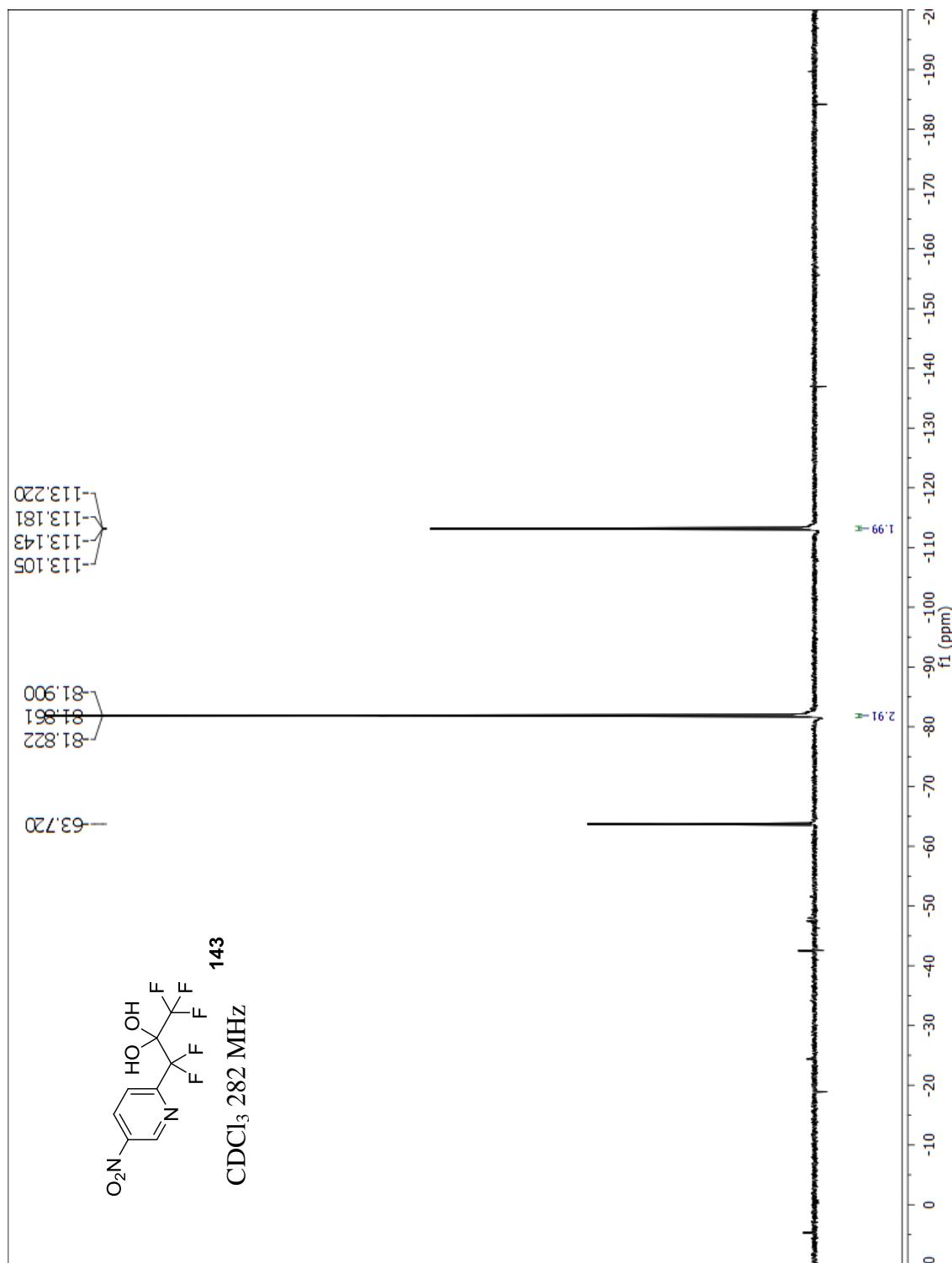


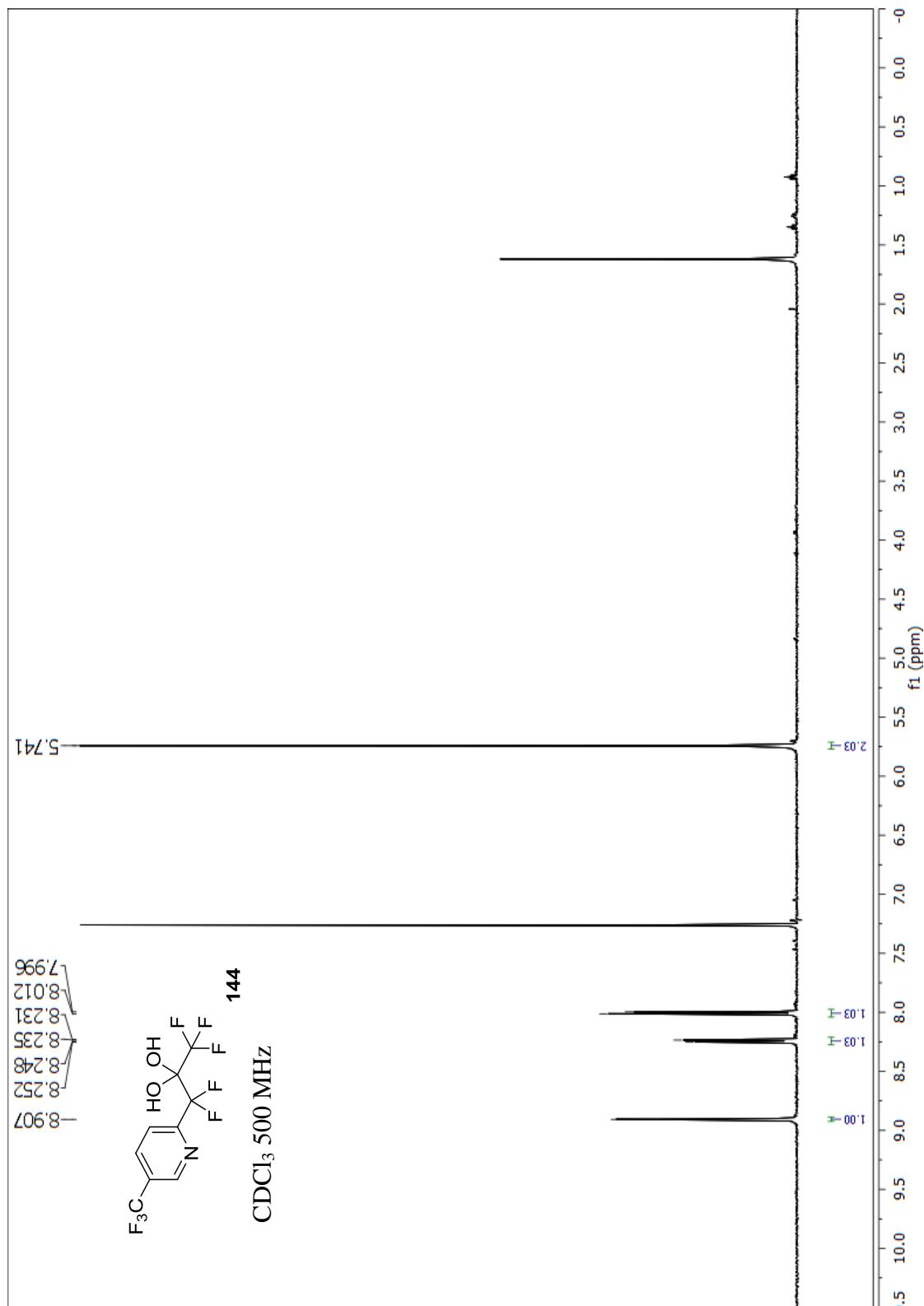


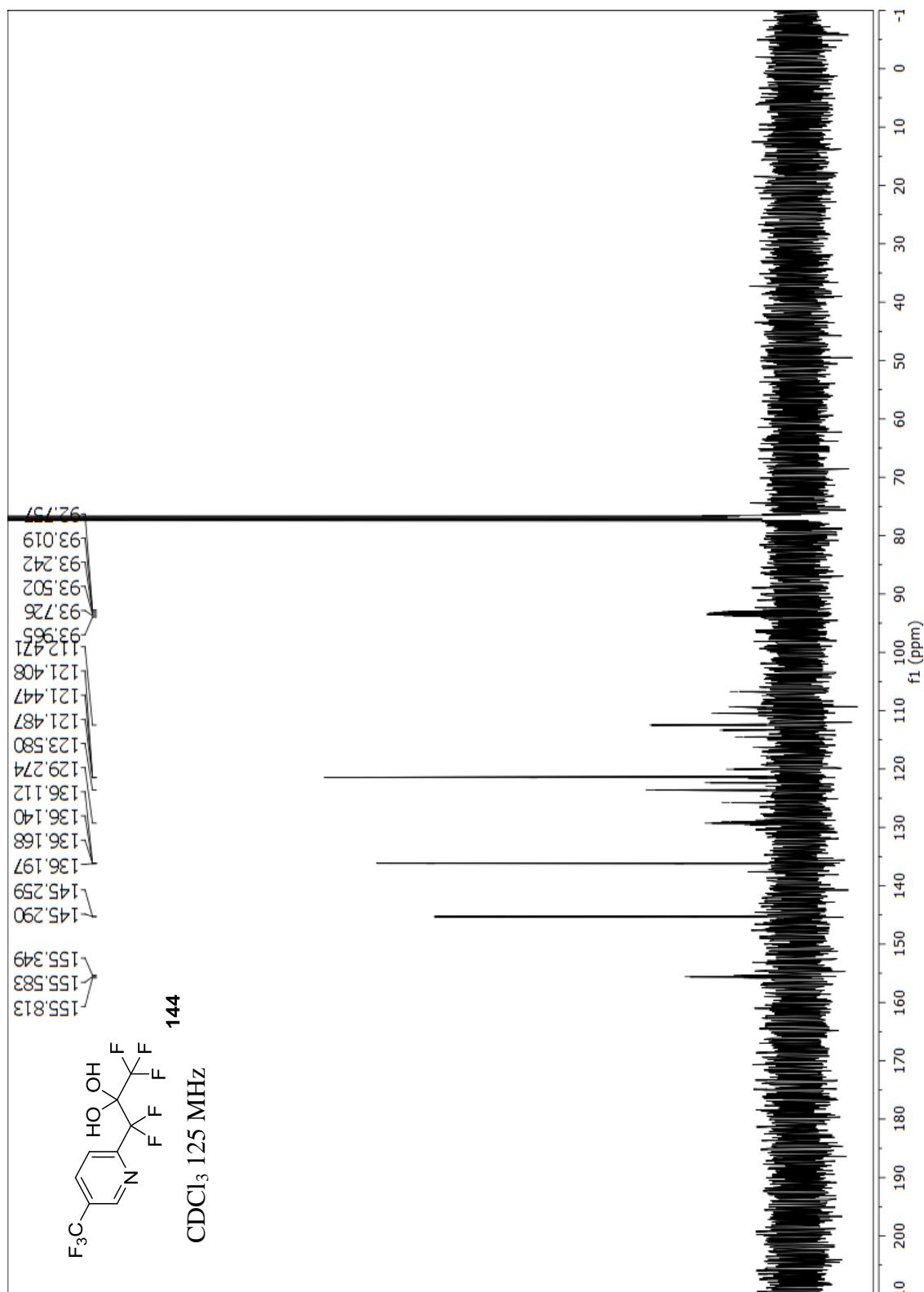


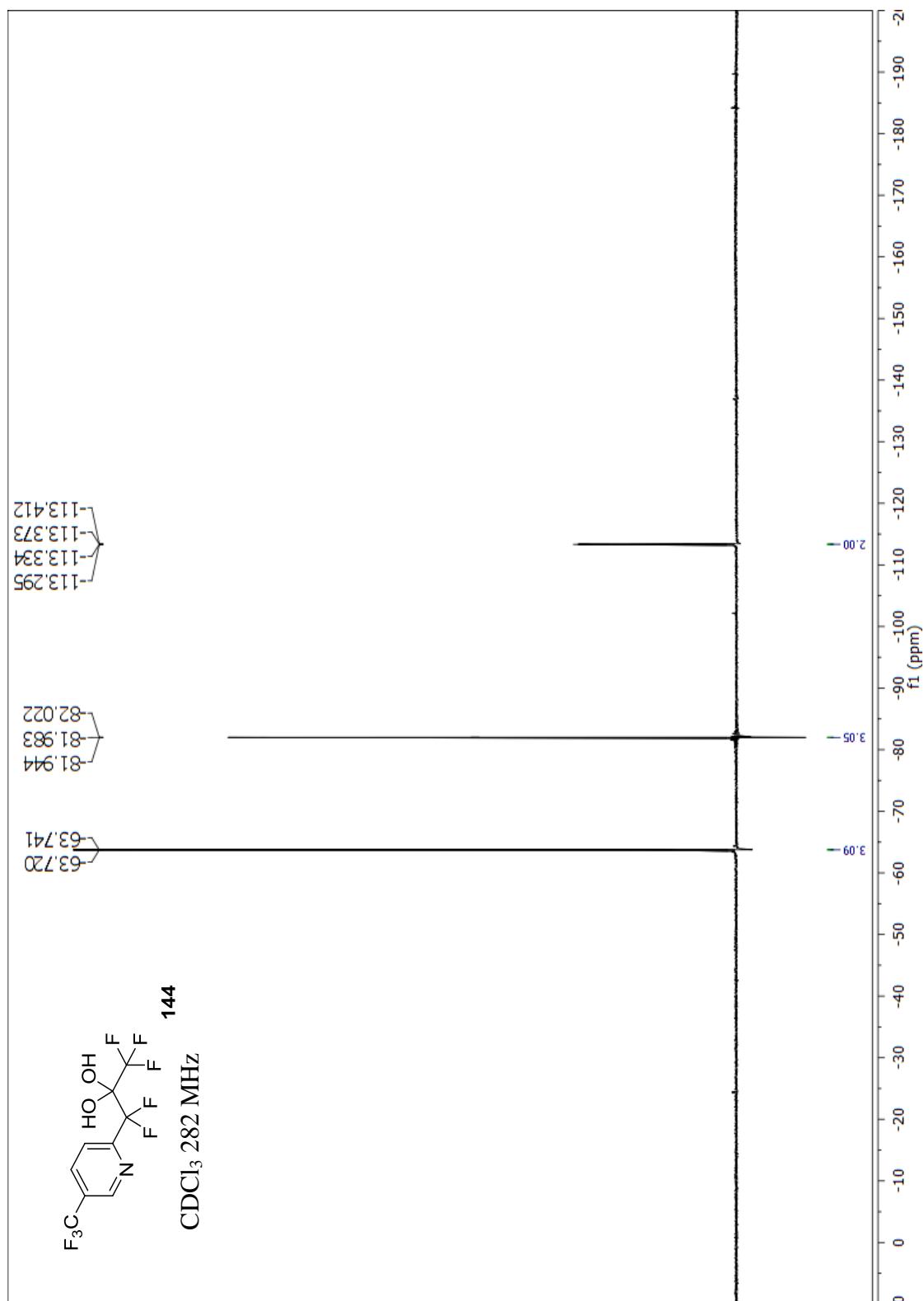


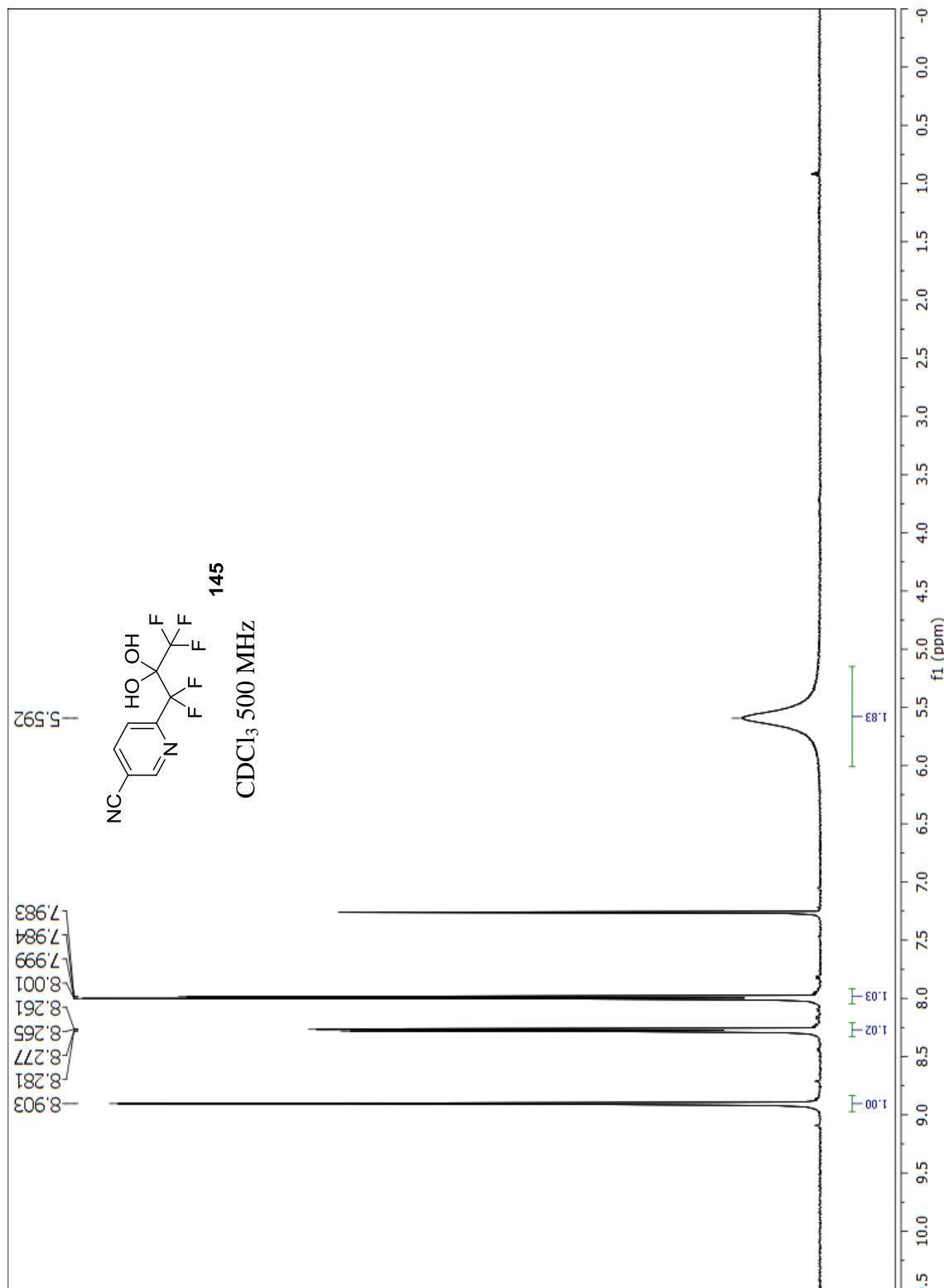


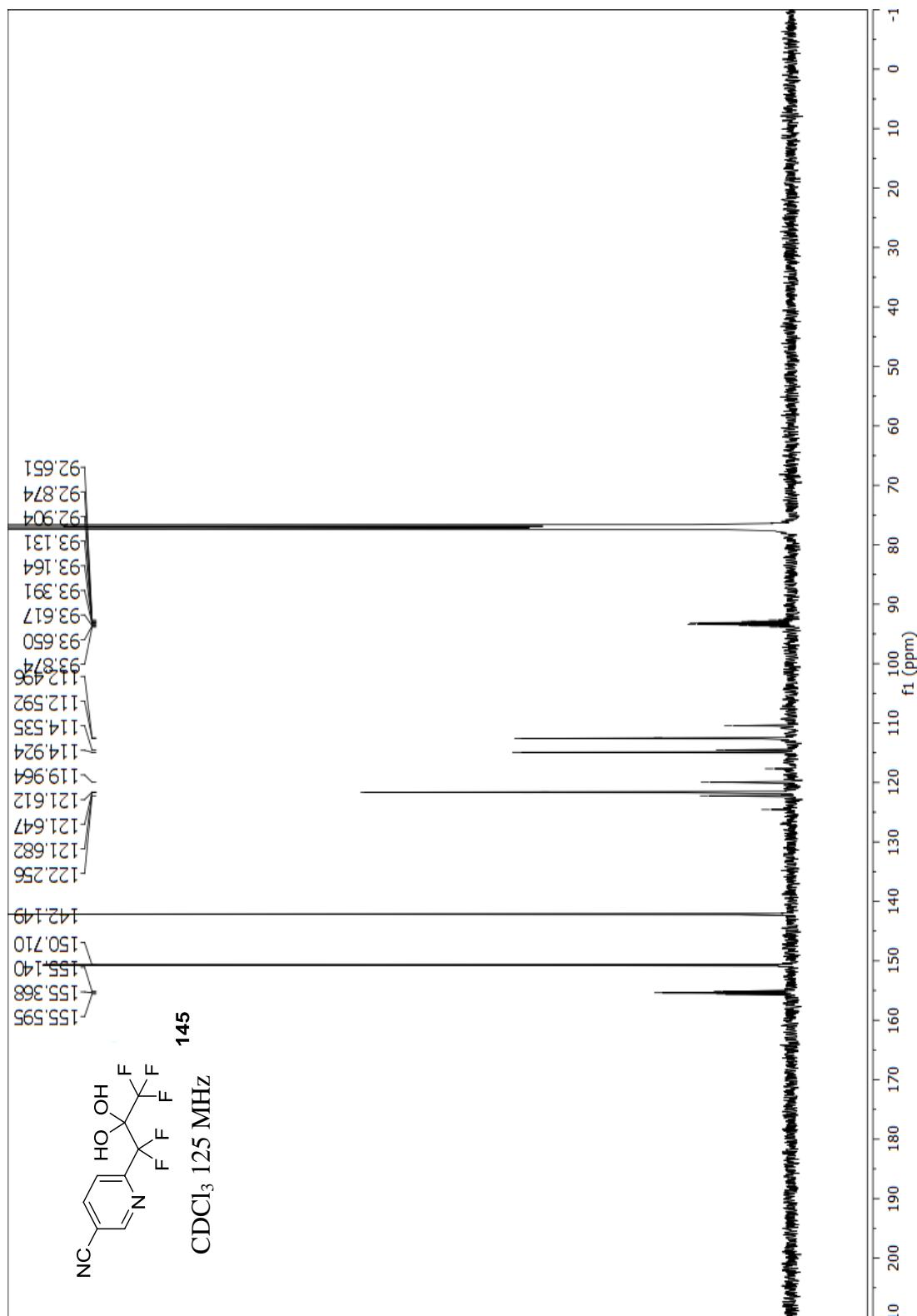


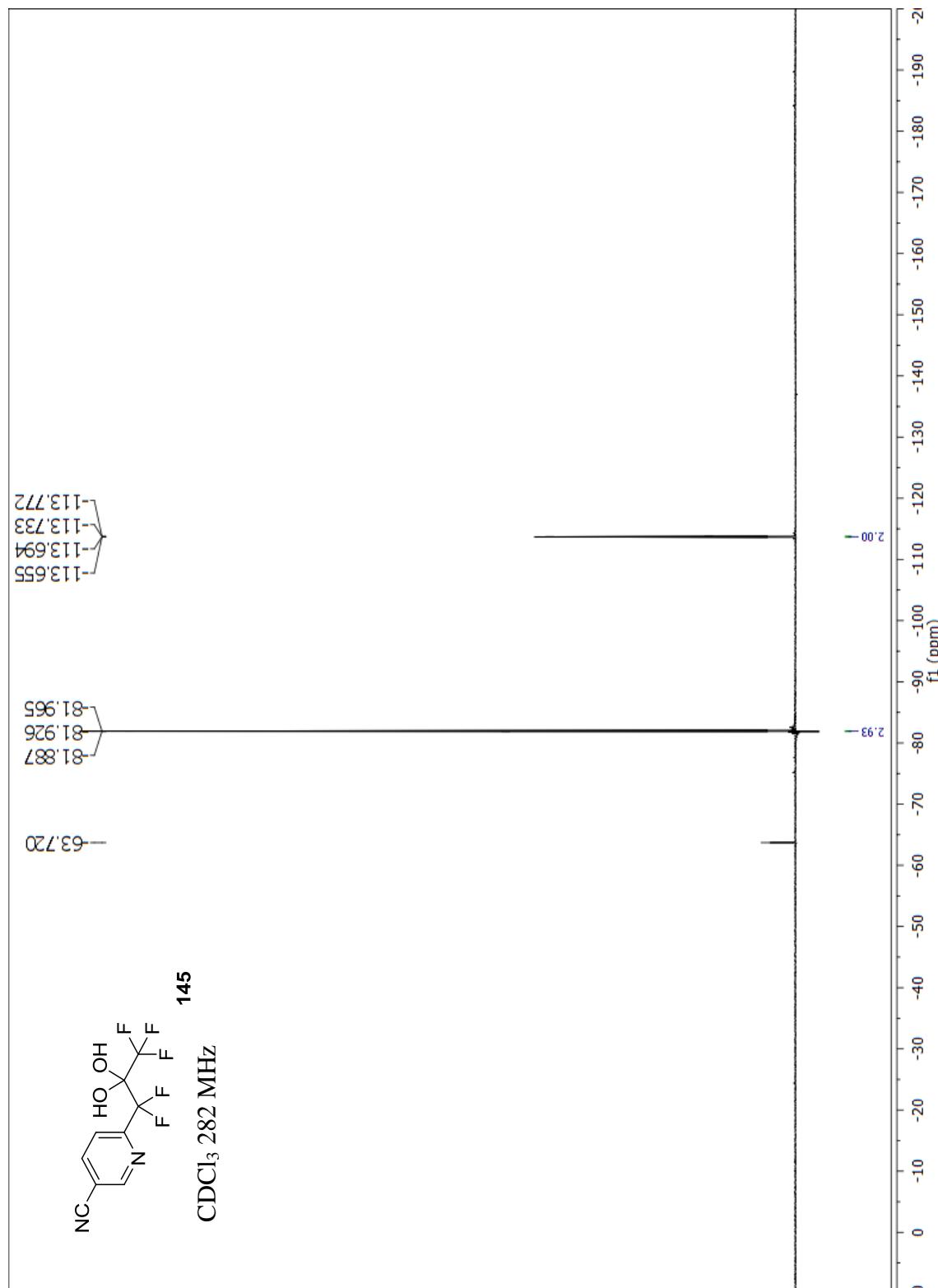


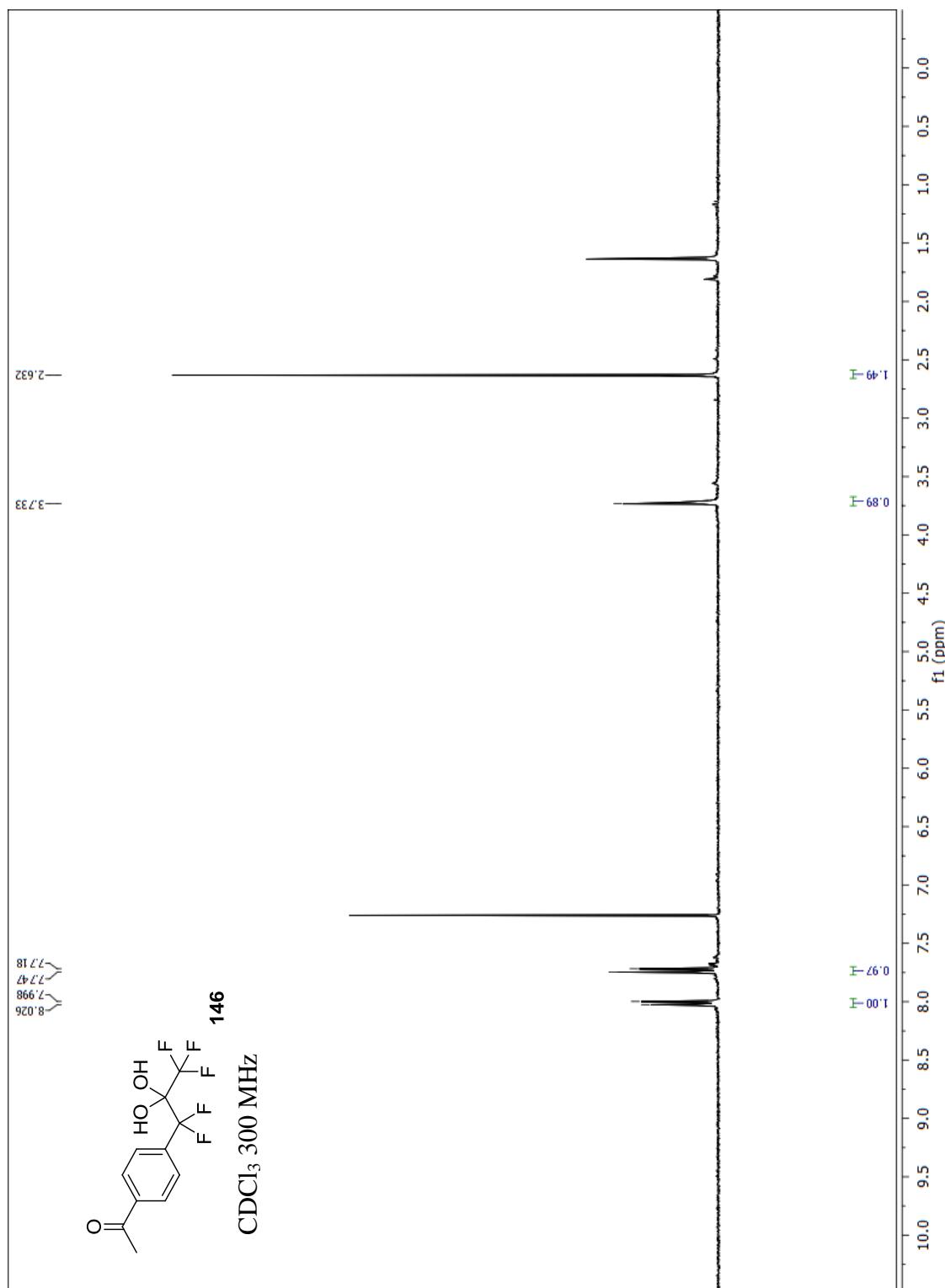


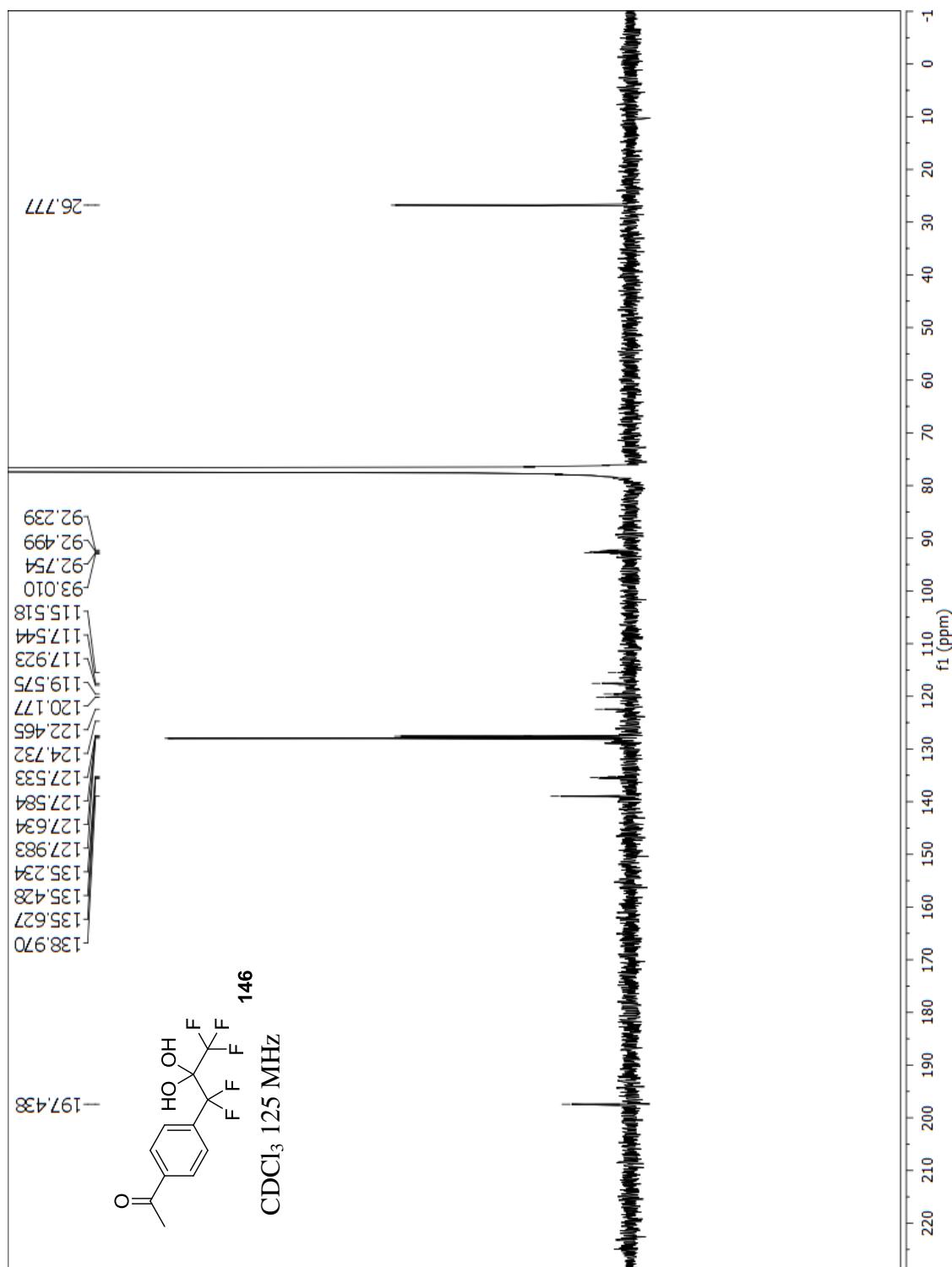


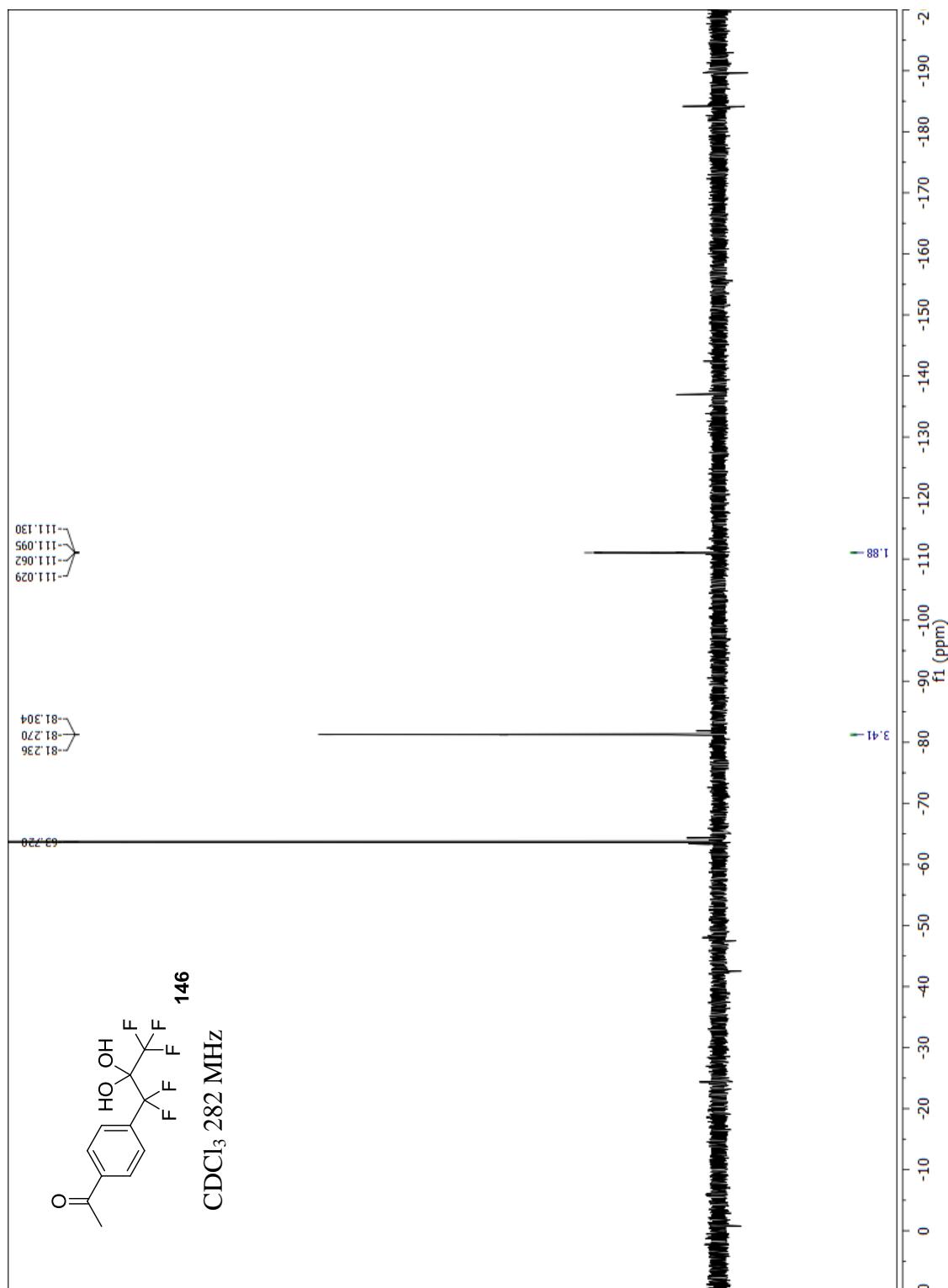


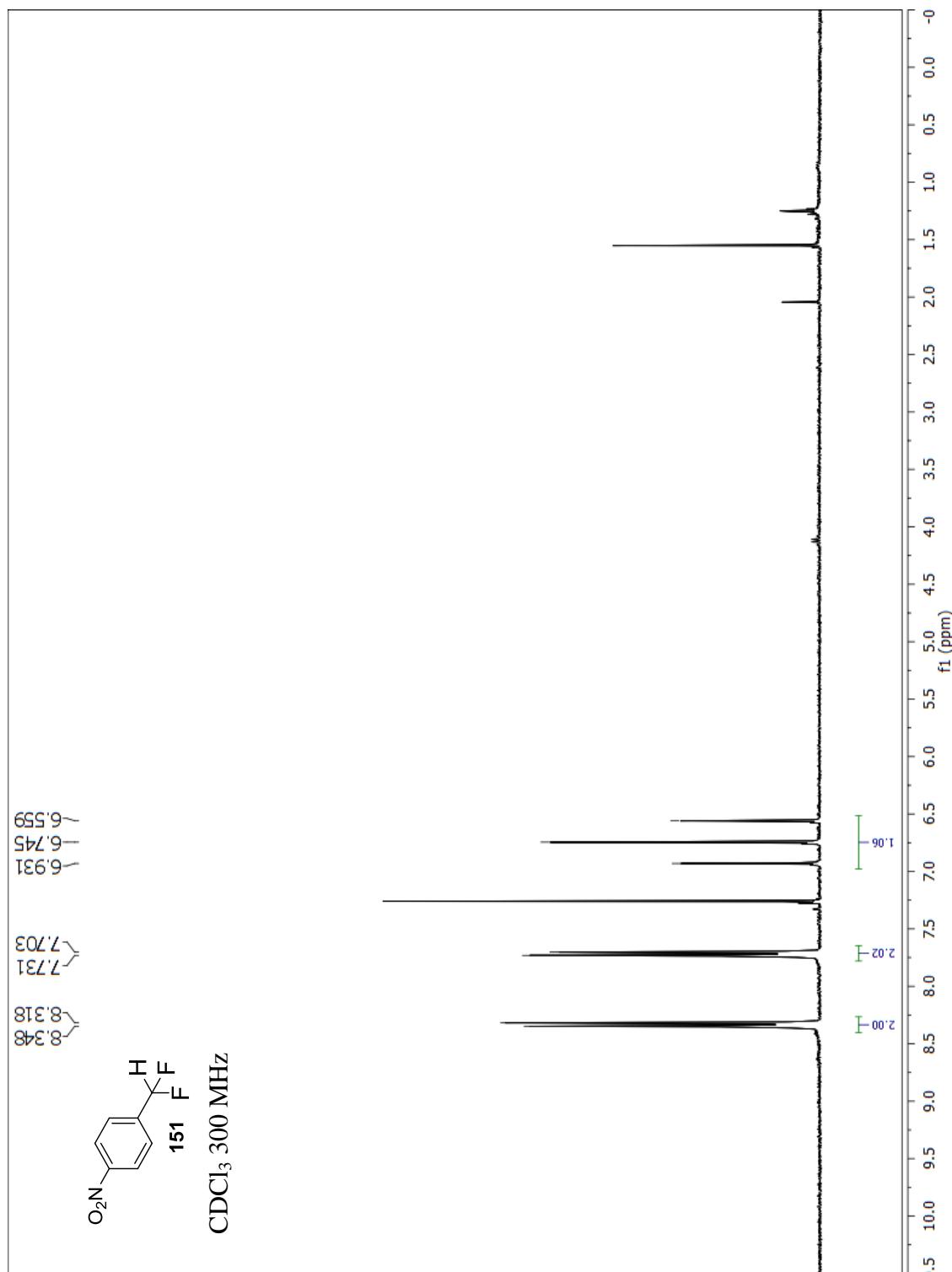


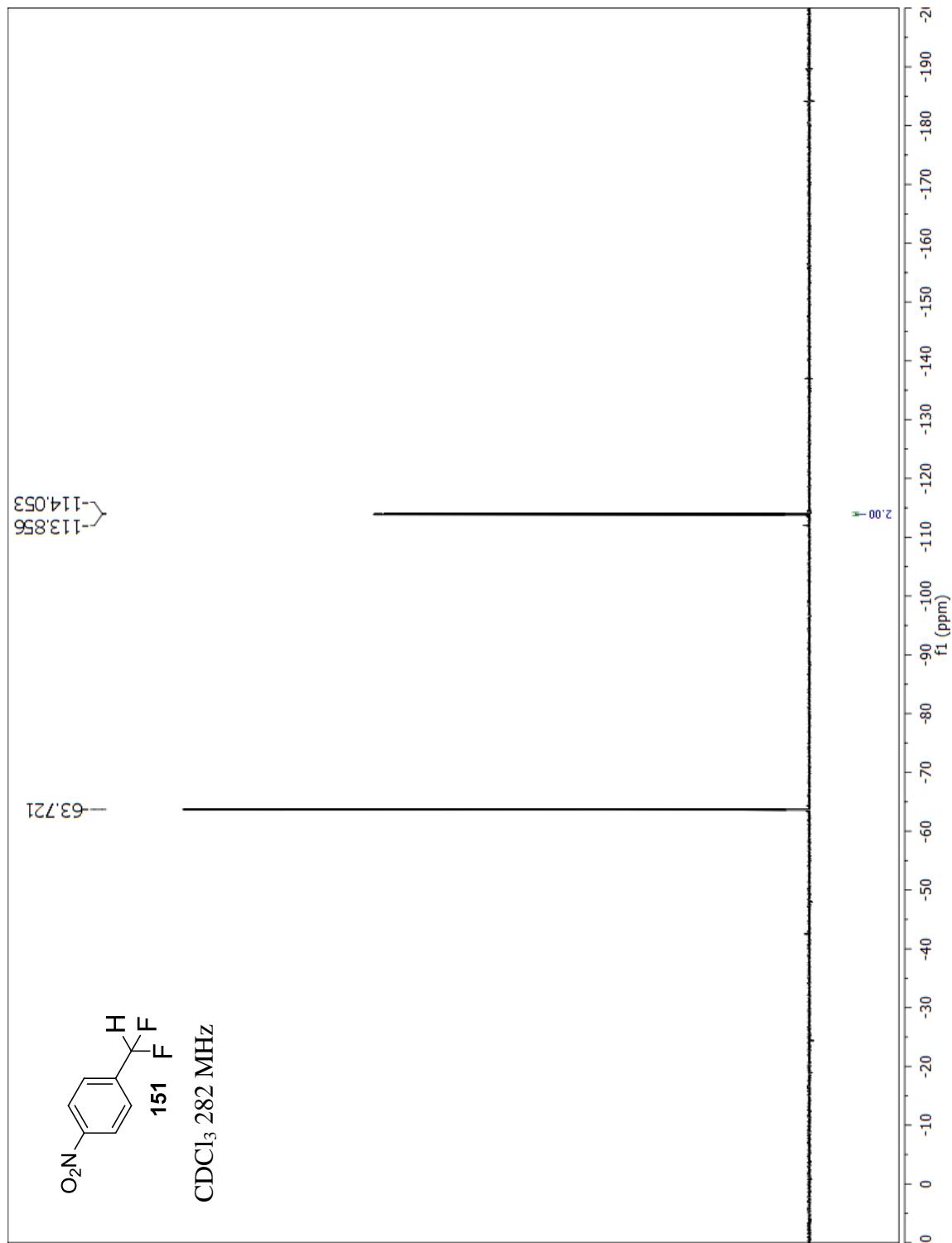


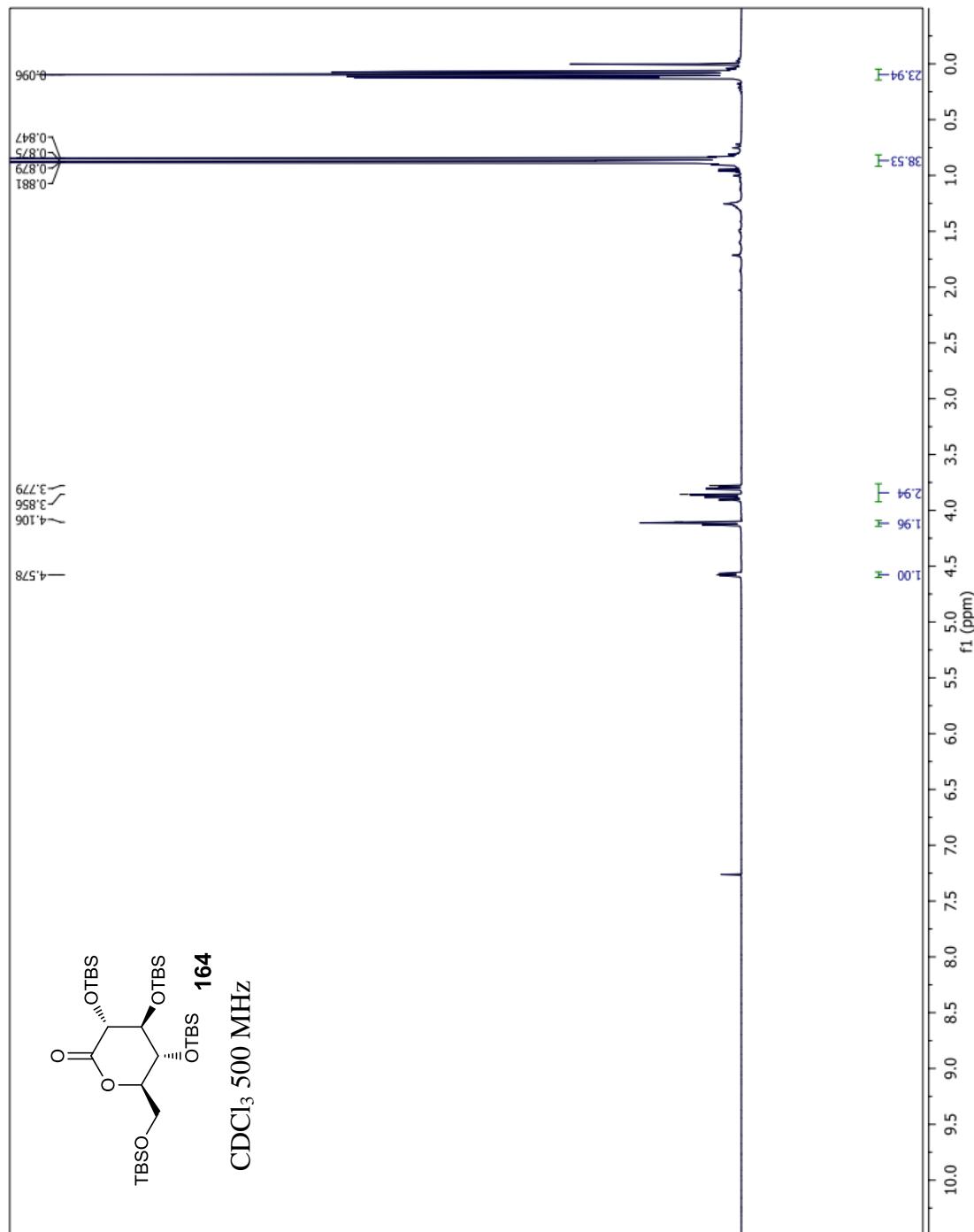


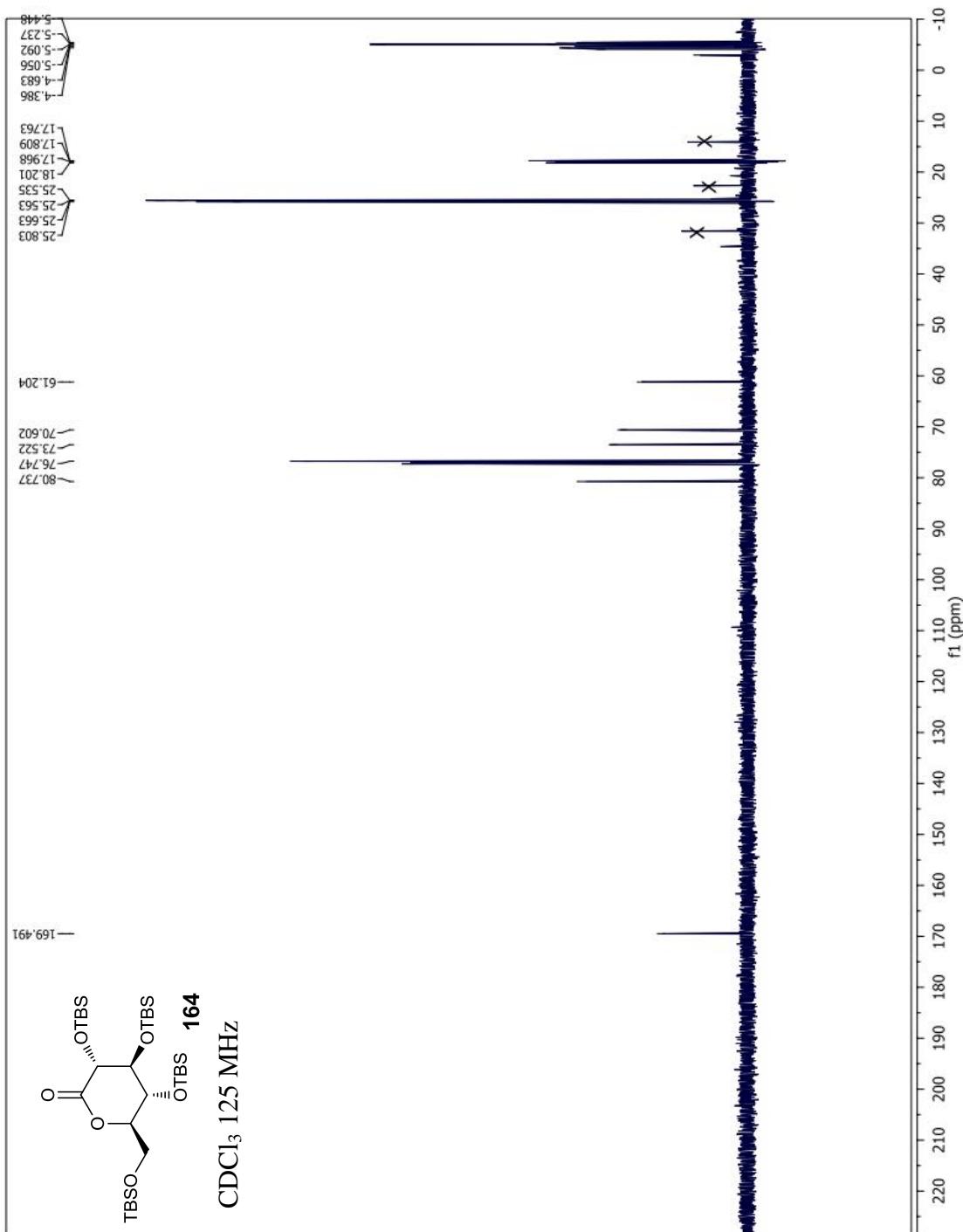


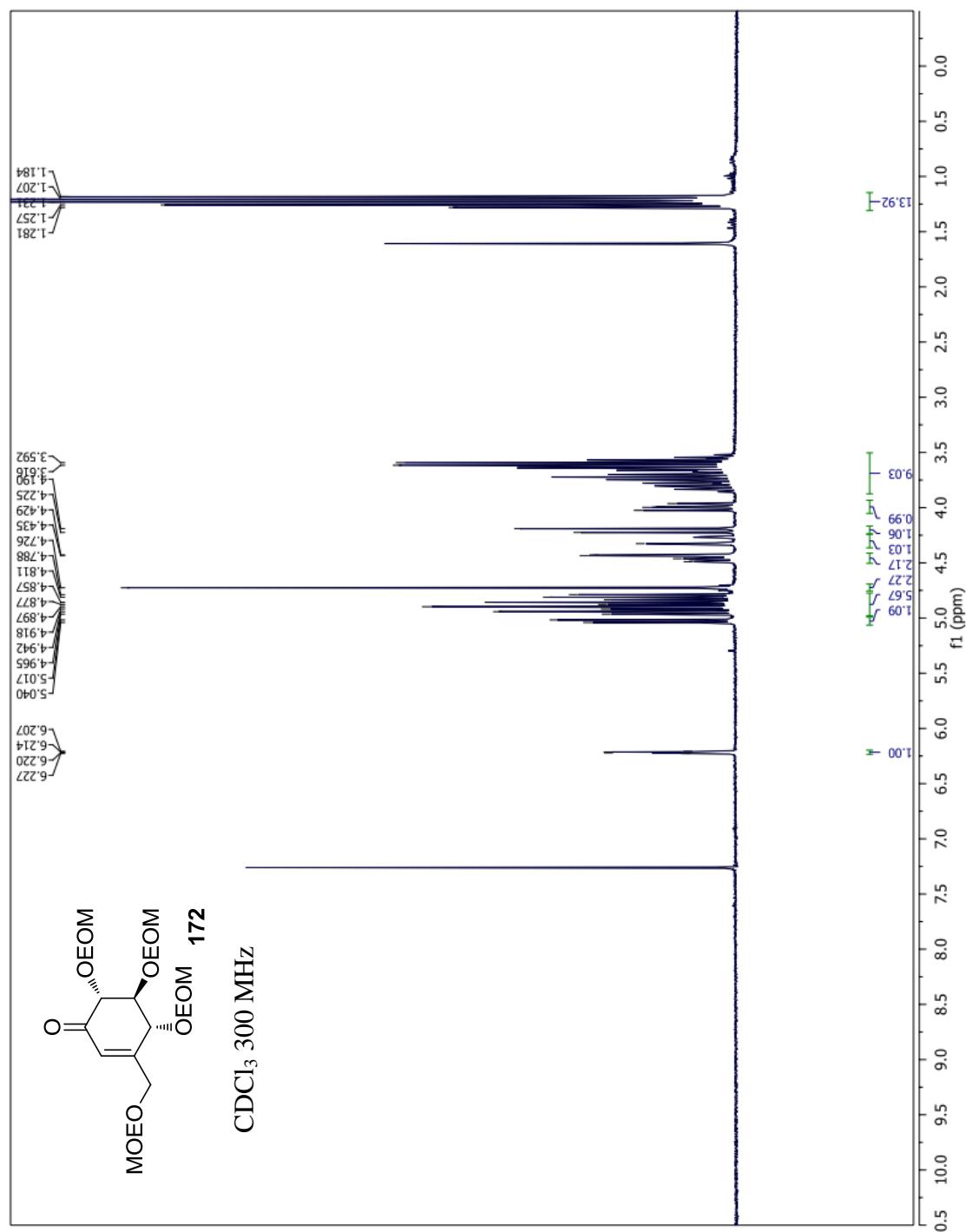


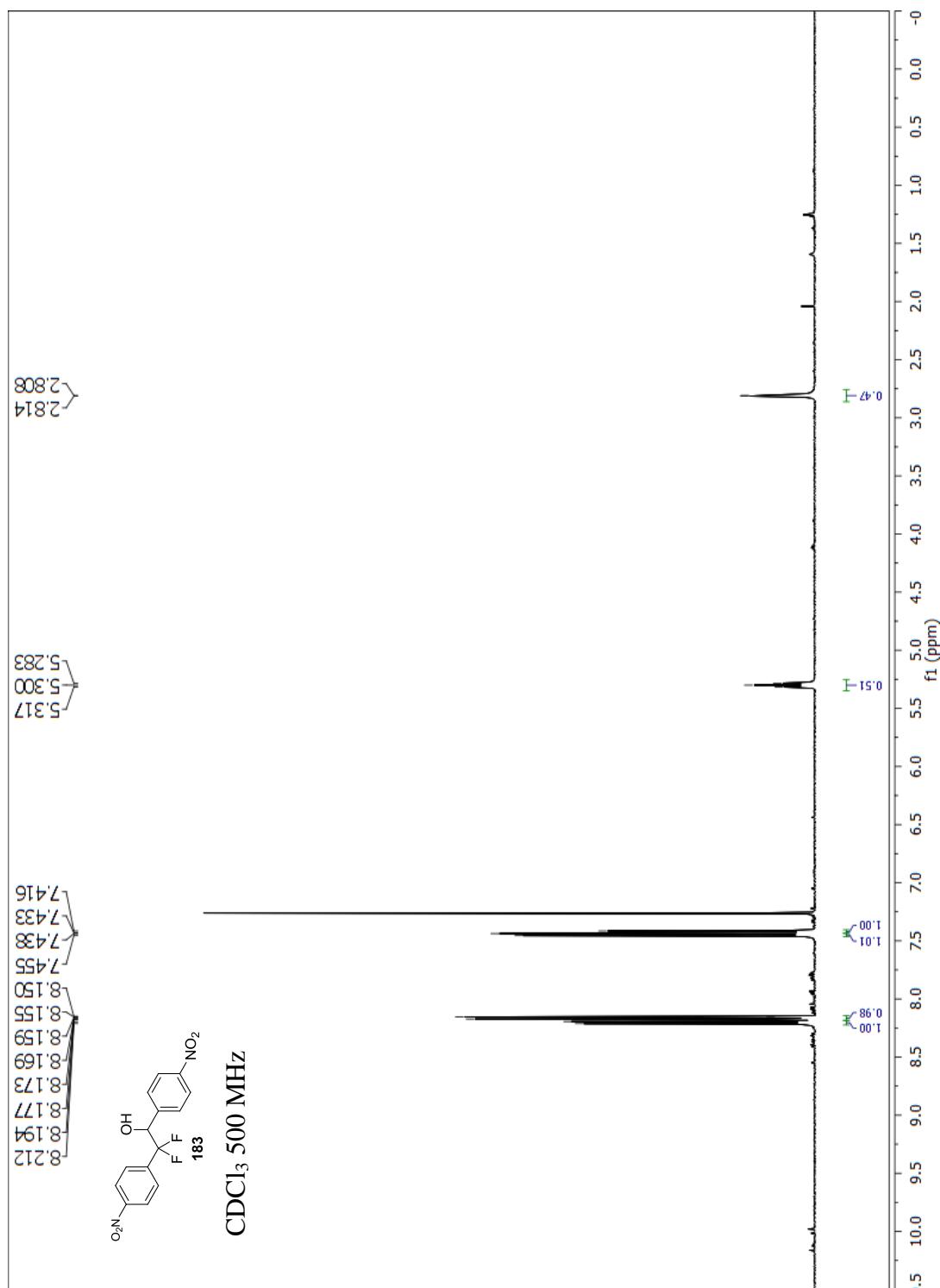


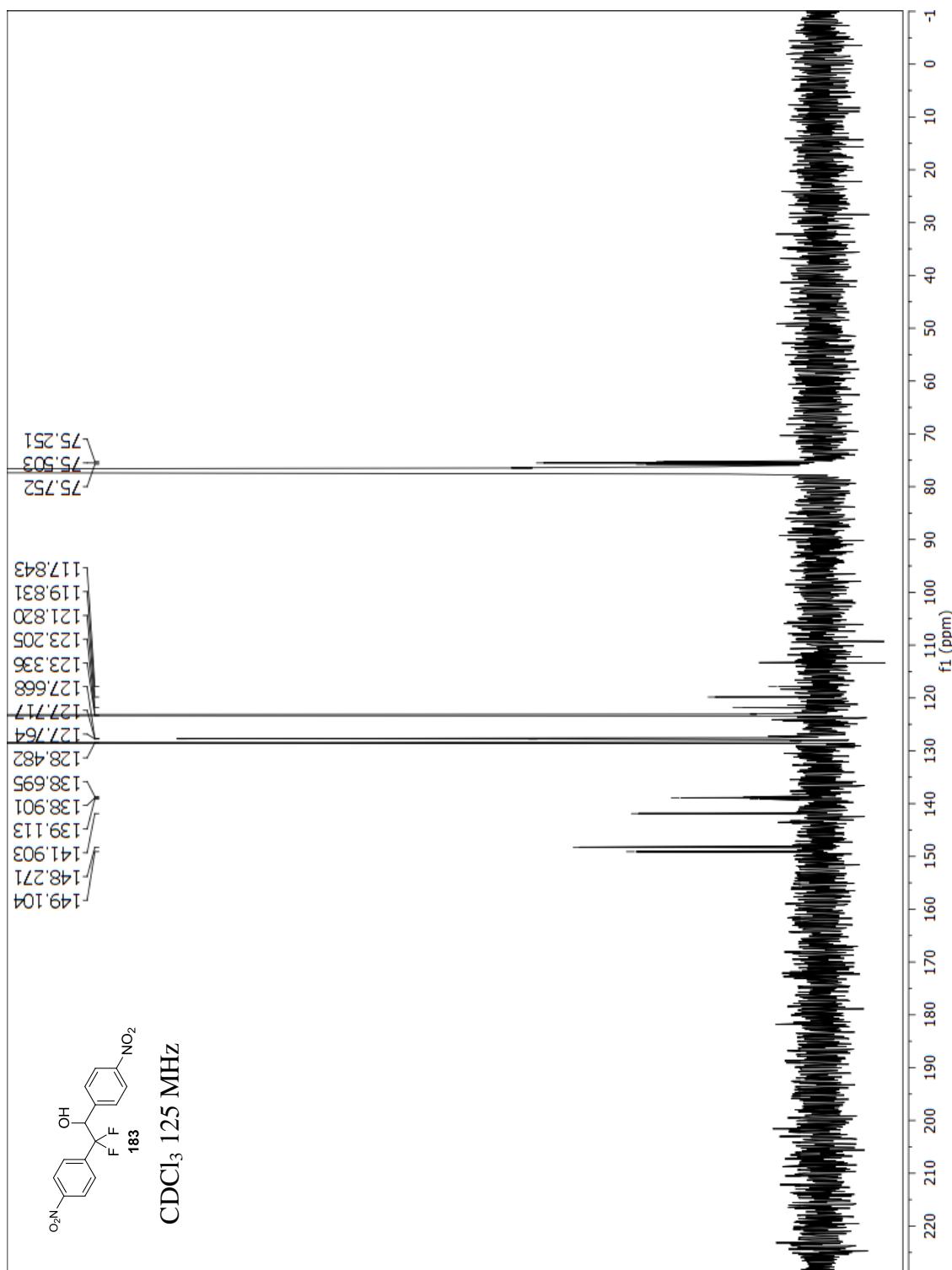


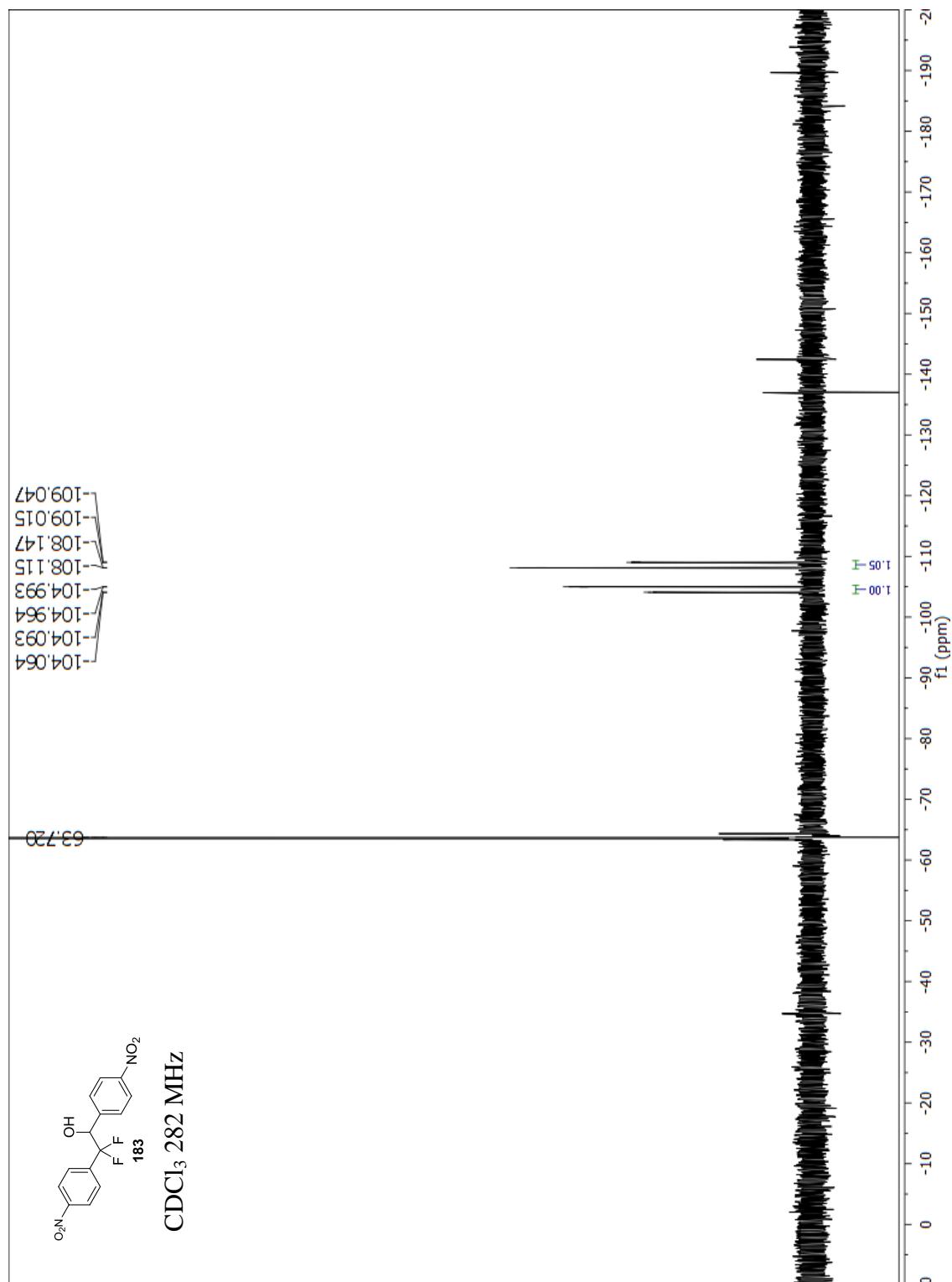


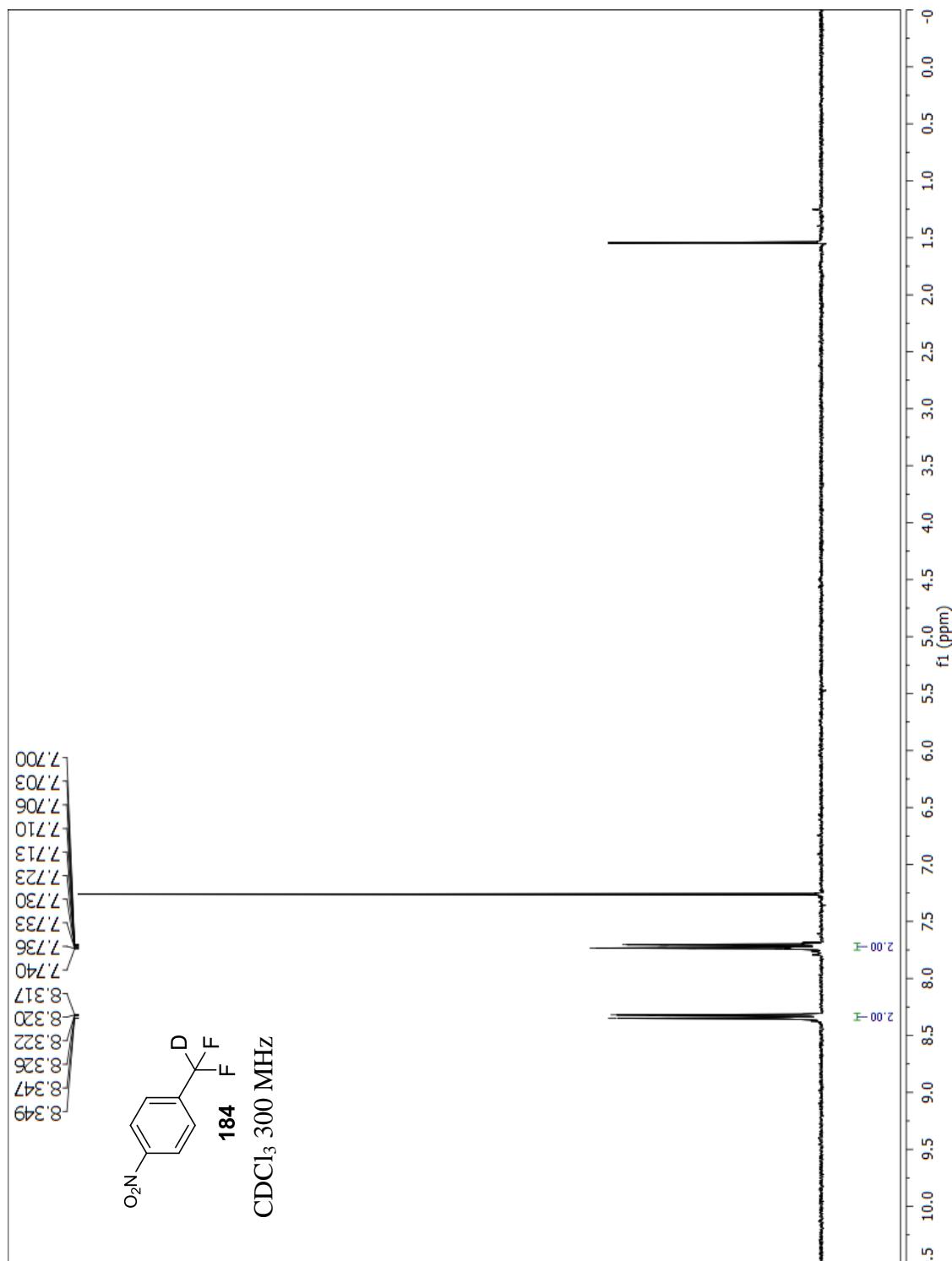


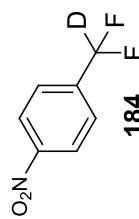
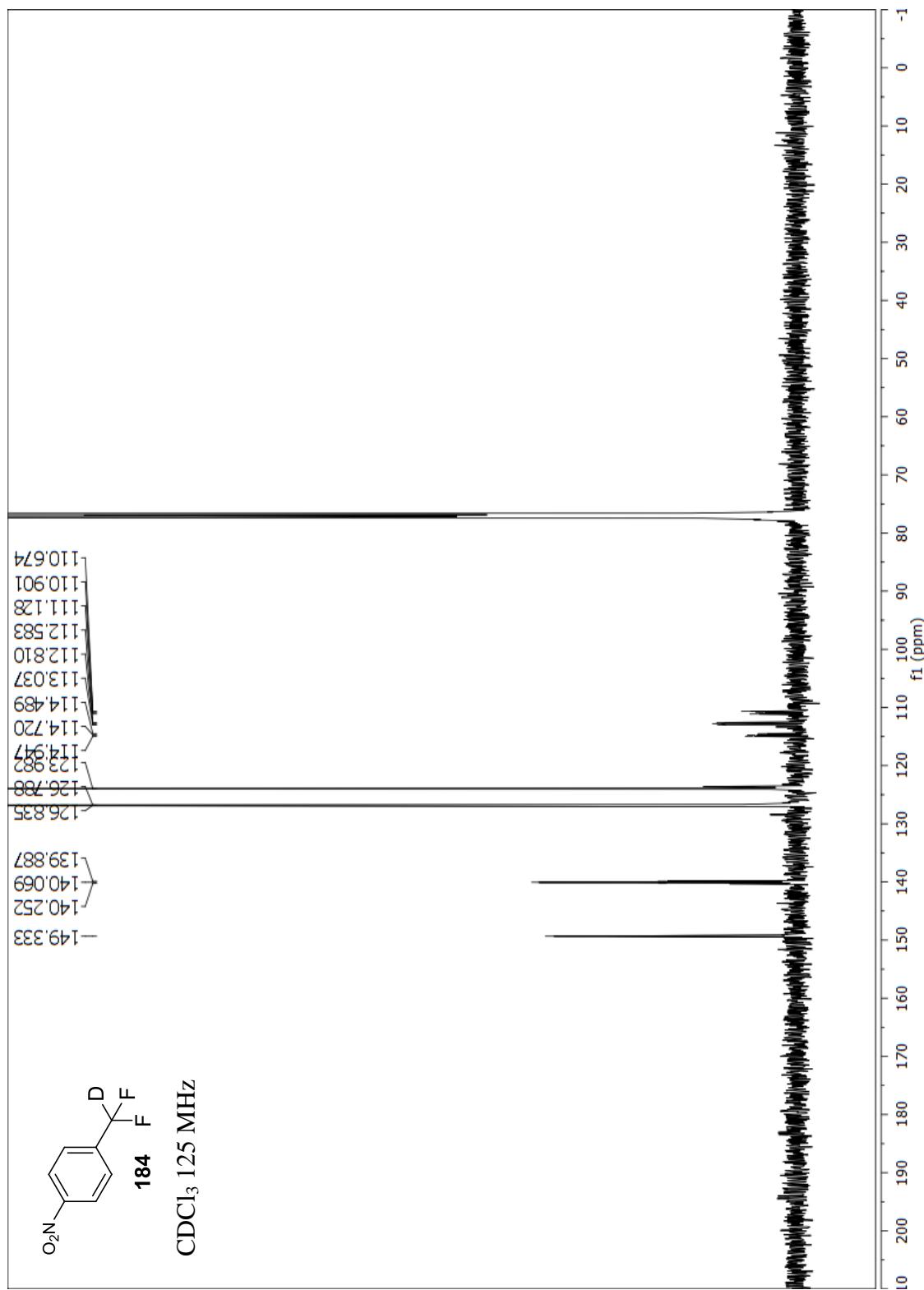




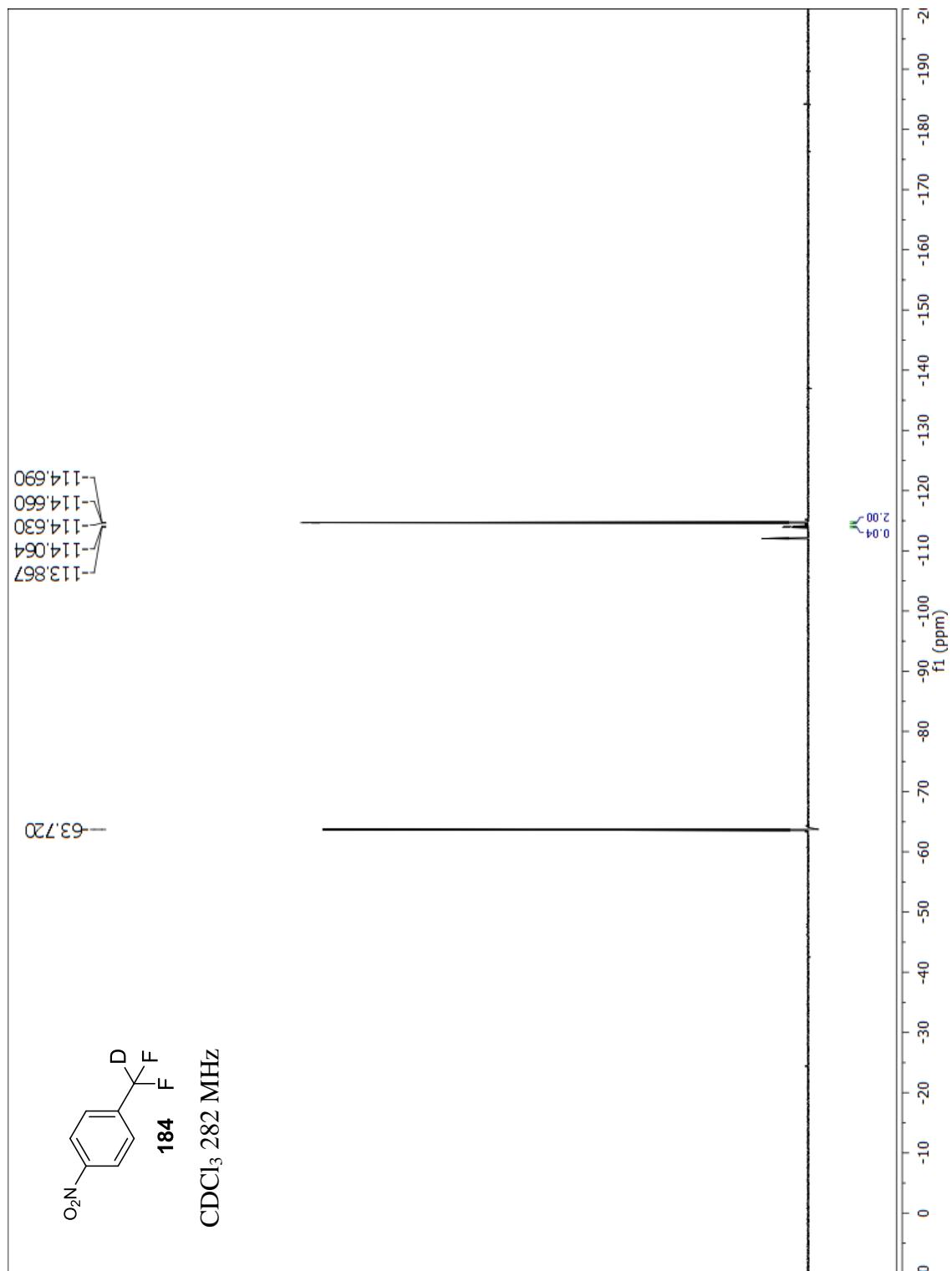


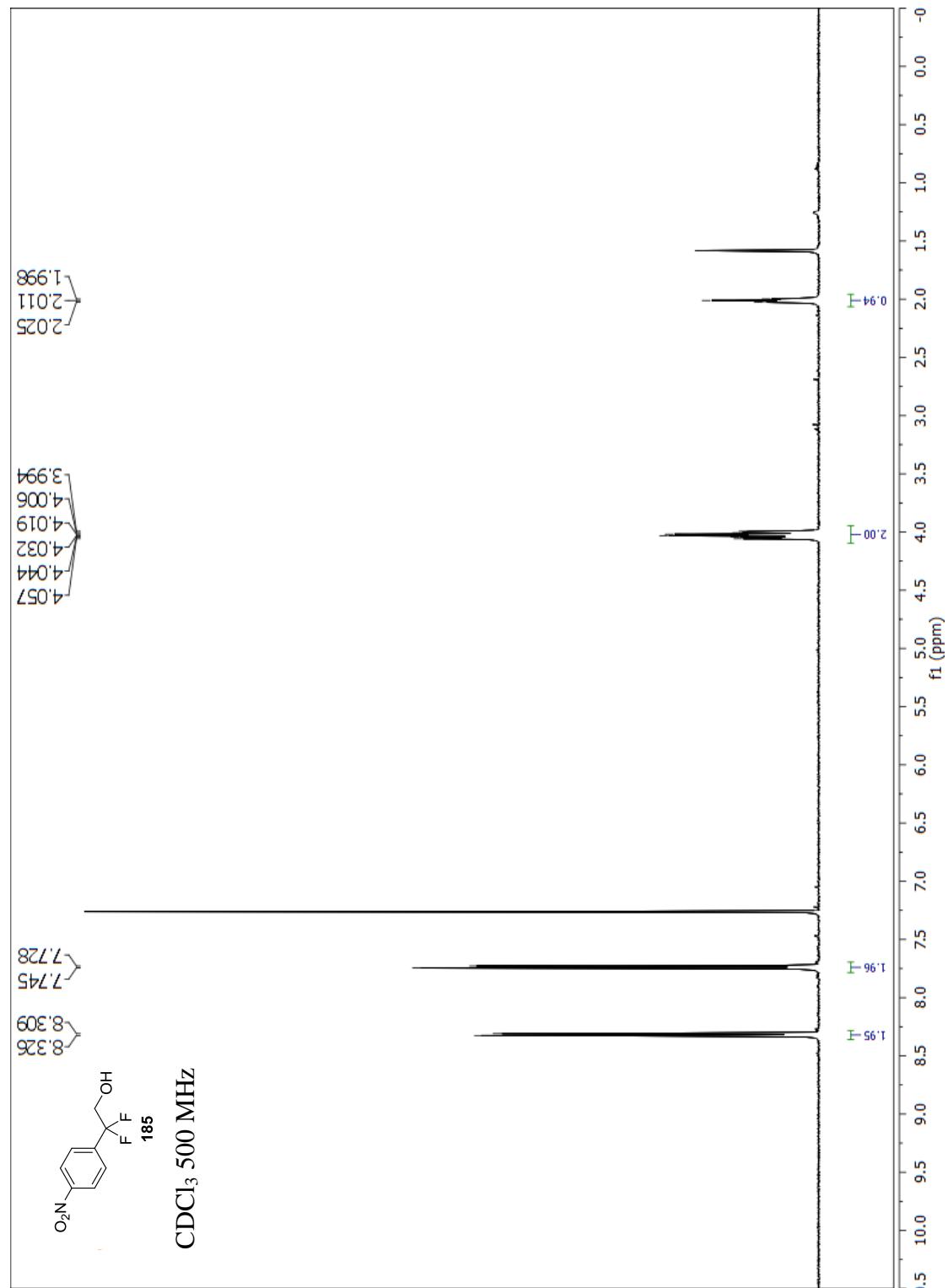


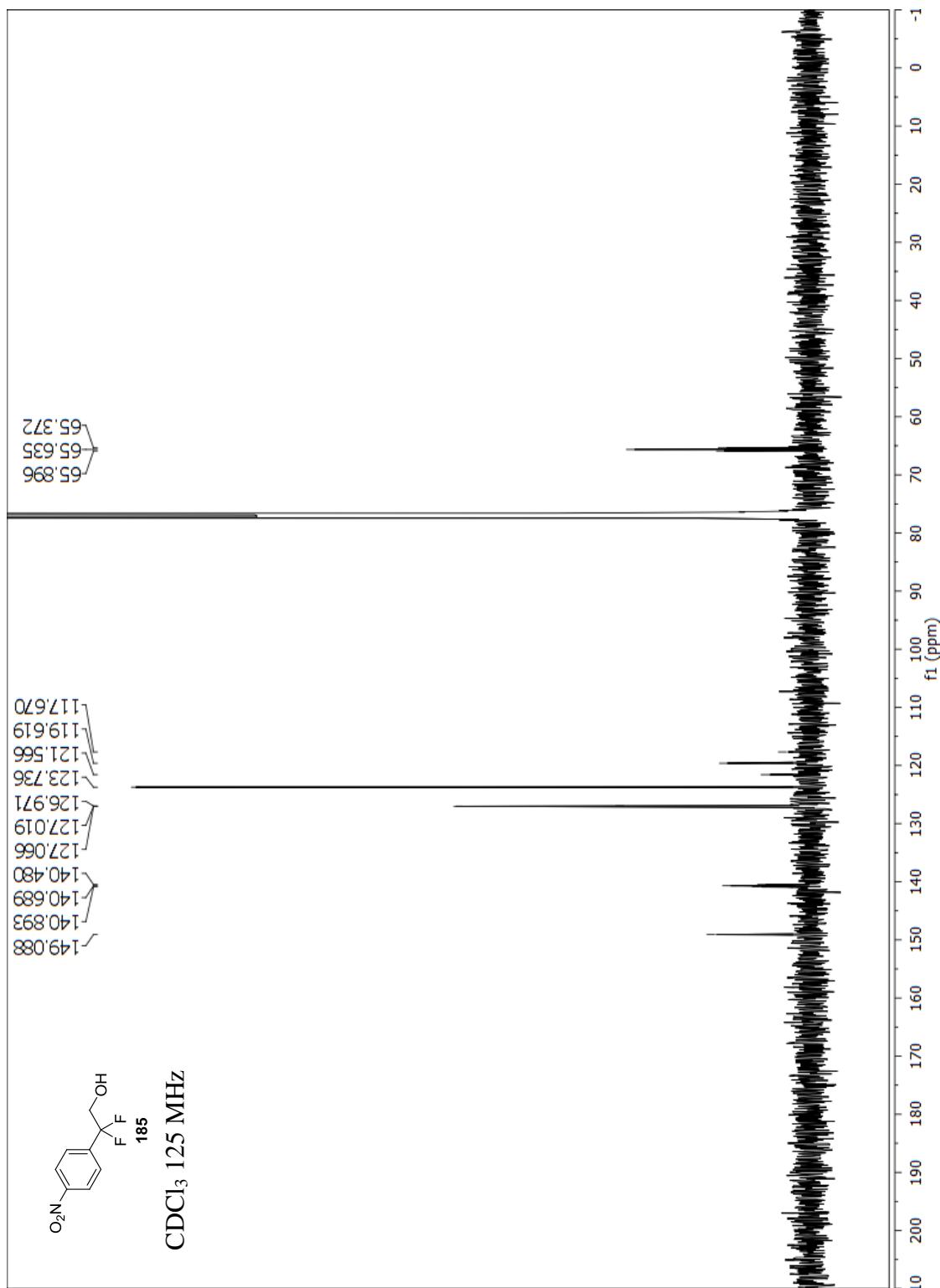


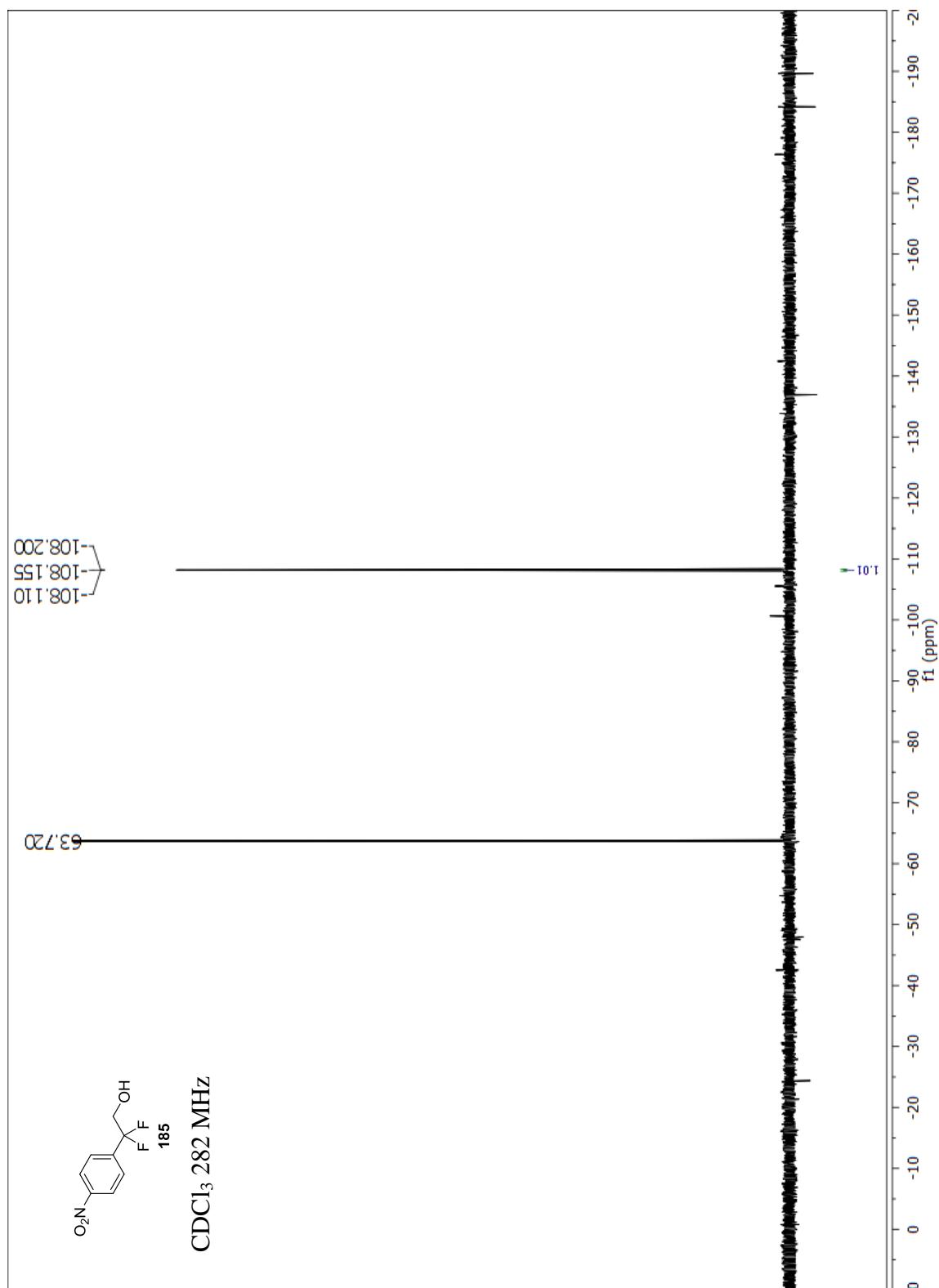


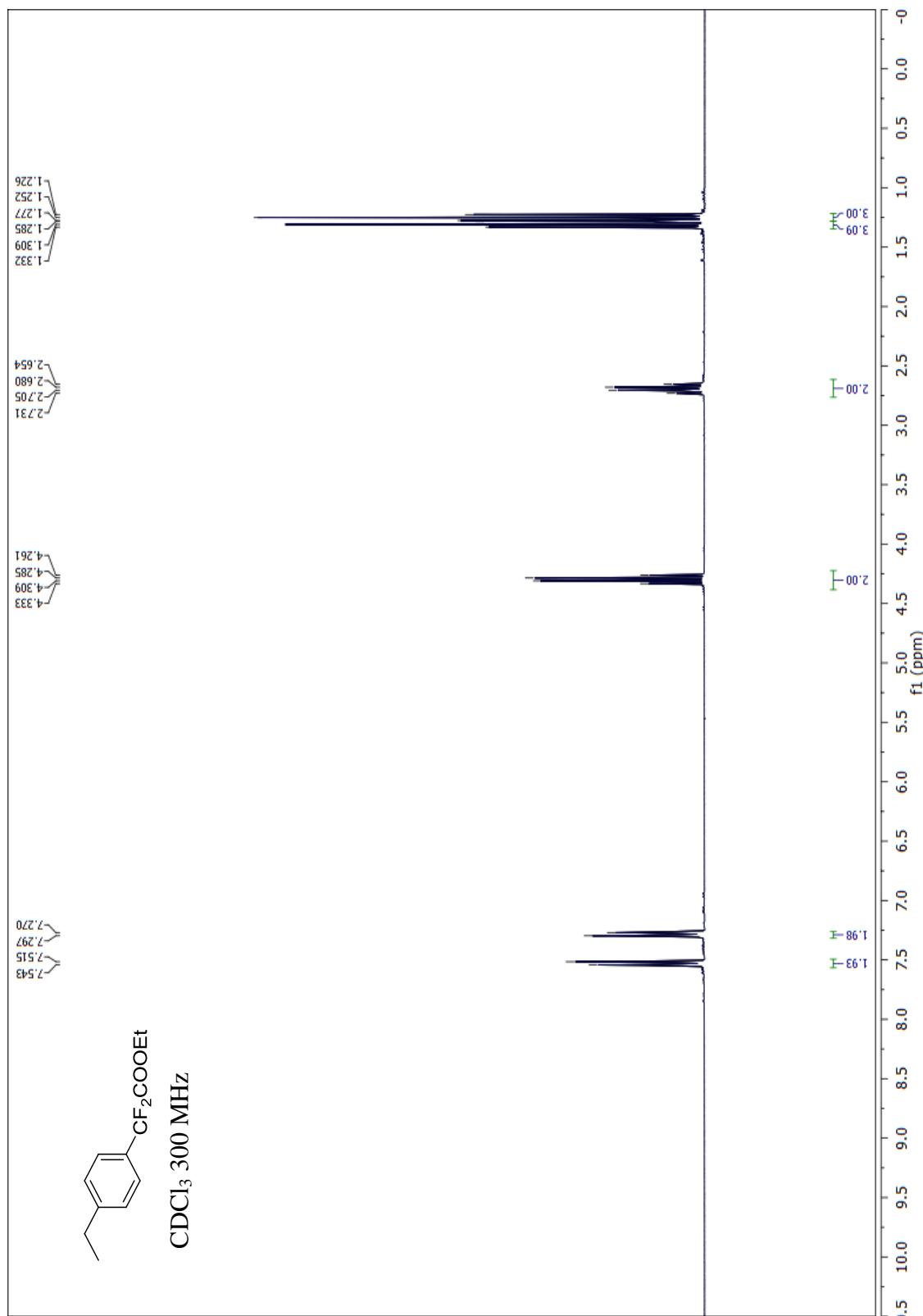
$\text{CDCl}_3$  125 MHz

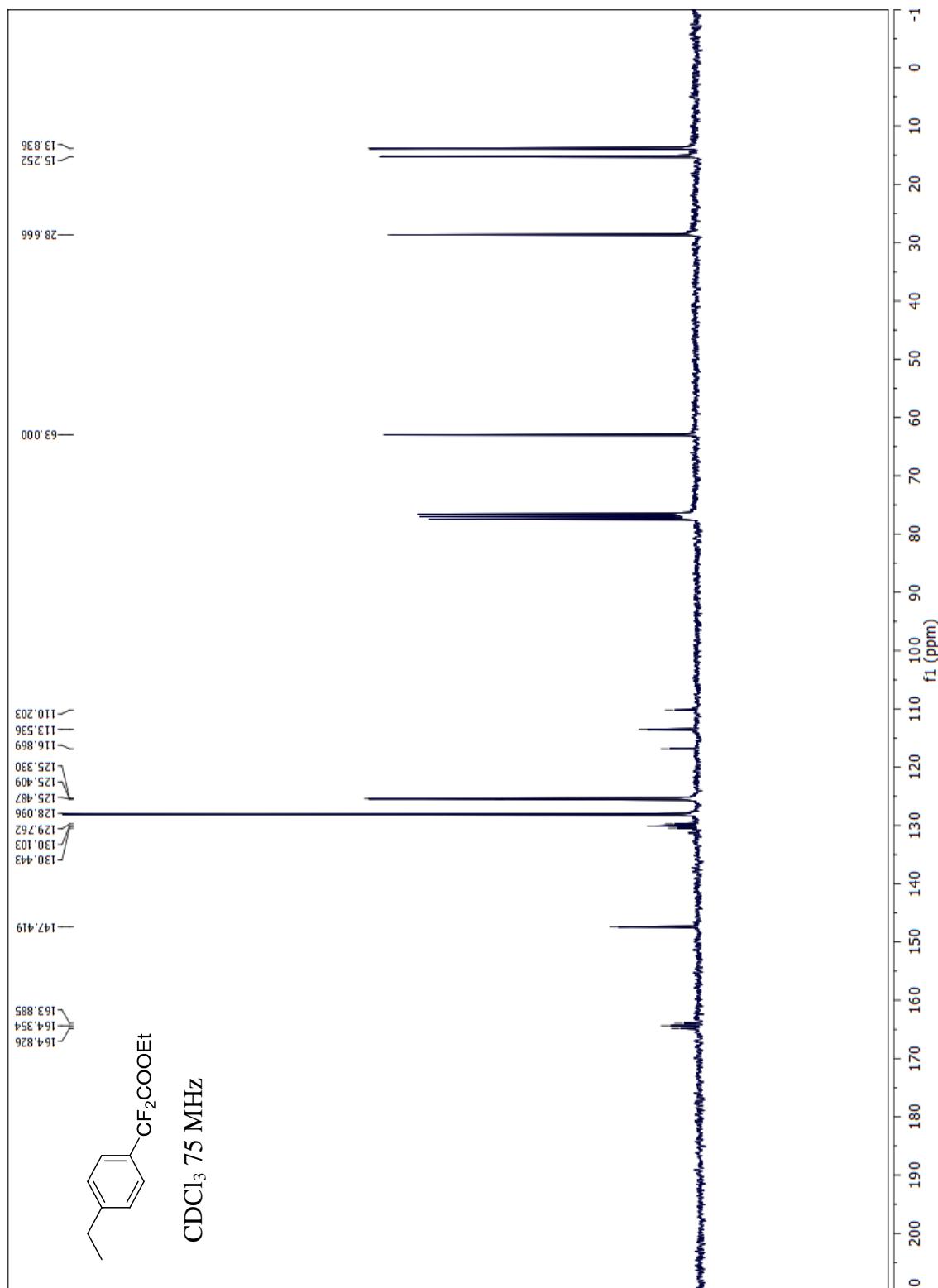


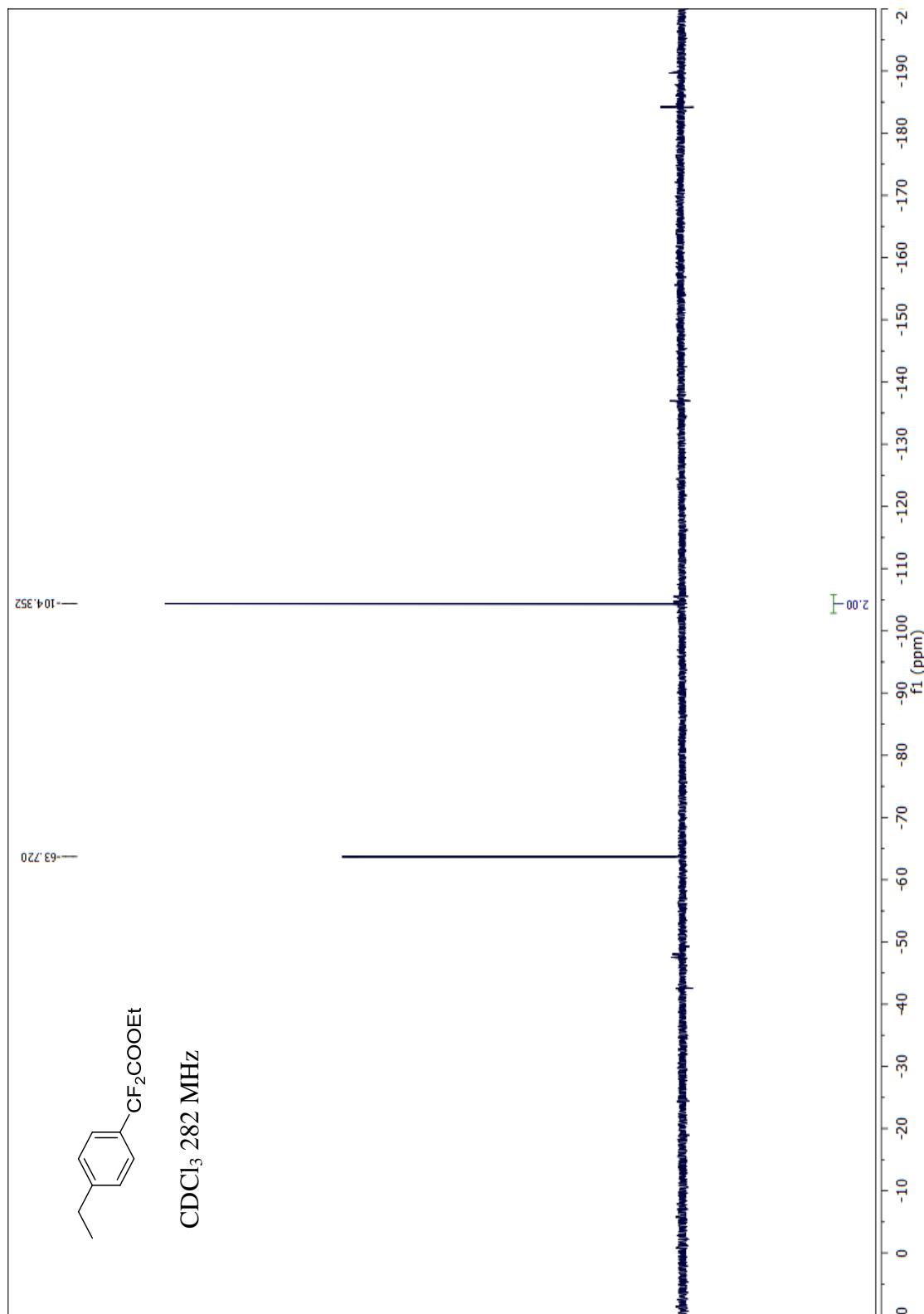












VITA

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Graduate School, Purdue University

Changho Han was born in Changwon, South Korea. He received a B.S. in chemistry, a B.S. in life science, and a B.E. in integrated biotechnology from Sogang University in Seoul, South Korea in 2008. He then joined the Department of Medicinal Chemistry and Molecular Pharmacology at Purdue University in West Lafayette, Indiana. He chose to pursue his Doctoral studies under the excellent mentorship of Professor David A. Colby.

## PUBLICATIONS

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**Peer-reviewed Papers:**

1. Han, C.; Barrios, F. J.; Riofski, M. V; Colby, D. A., “Semisynthetic Derivatives of Sesquiterpene Lactones by Palladium-Catalyzed Arylation of the  $\alpha$ -Methylene- $\gamma$ -lactone Substructure”, *J. Org. Chem.* **2009**, 74, 7176–7179.
2. Gunn, E. J.; Williams, J. T.; Huynh, D. T.; Iannotti, M. J.; Han, C.; Barrios, F. J.; Kendall, S.; Glackin, C. A.; Colby, D. A.; Kirshner, J. “The Natural Products, Parthenolide and Andrographolide, Exhibit Anti-Cancer Stem Cell Activity in Multiple Myeloma”, *Leuk. Lymphoma*, **2011**, 52, 1085–1097.
3. Han, C.; Kim, E. H.; Colby D. A., “Cleavage of Carbon-Carbon Bonds through the Mild Release of Trifluoroacetate: Generation of  $\alpha,\alpha$ -Difluoroenolates for Aldol Reactions”, *J. Am. Chem. Soc.* **2011**, 133, 5802–5805.
  - Featured as a SynStory in *SynForm* **2011**, 7, A62–A63.
  - Featured as a SynPact in *Synlett* **2012**, 23, 1559–1563.
4. Han, C.; Kim, E. H.; Colby, D. A. “Cleaving Carbon-Carbon Bonds by the Release of Trifluoroacetate to Remodel Molecules and Assemble Fluorinated Structures”, *Synlett*, **2012**, 23, 1559–1563.

5. Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A., “Evaluation of Difluoromethyl Ketone as Agonists of the  $\gamma$ -Aminobutyric Acid Type B (GABA<sub>B</sub>) Receptor”, *J. Med. Chem.* **2013**, *56*, 2456–2465.

**Patents:**

1. “Processes for Preparing Fluoro-containing Compounds” by David A. Colby, Changho Han, and James R. Woods, US Provisional Patent Application No. 61/316,076, filed March 22, **2010**.
2. “The Release of Trifluoroacetate and Application to Synthesis” by David A. Colby, Mark V. Riofski, and Changho Han. US Patent Application No. PCT/US12/30089, filed March 22, **2012**.
3. “Fluorinated Compounds as GABA-B Receptor Agonists” by David A. Colby, Changho Han, Gregory H. Hockerman, Amy Salyer, and Julia Chester. US provisional Patent Application No. 61/693,698 filed August 27, **2012**.