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Application Of Fluorinated Reagents In Synthesis And Drug Discovery

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APPLICATION OF FLUORINATED REAGENTS IN SYNTHESIS AND DRUG DISCOVERY

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ABSTRACT

The introduction of fluorine or fluorine containing moieties in pharmaceuticals may increase metabolic stability, binding affinity, bioavailability, lipophilicity, selectivity for targets, and fluorine-labelled groups can be used as imagining probes, i.e. in positron emission tomography (PET). Within the past decade, approximately 20% of all marketed pharmaceuticals contain fluorine and in 2018 alone 36% of the top 50 selling drugs on the market contained one or more fluorine atoms. Fluorinated reagents also plays an important role in the development of methods to introduce unique groups into an organic molecule, such as fluorination and methylenation. In this work, the scope of the trifluoroacetate release reaction was expanded to generate fluorinated lactam intermediates in oder to introduce an α-methylene into a lactam for the purposes of synthesizing L-γ-methyleneglutamine and amide derivatives. A fluorinated reagent was designed to allow the synthesis of compounds containing an α-fluoro-α,β-unsaturated carbonyl group and we attempt to produce organic molecules containing heavily fluorinated methylene carbons such as fluorotrifluoromethyl groups.

Dedicated to my future children and family

Acknowledgements

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CHAPTER I

FLUORINE AND FLUORINATION

1.1 Fluorine in Medicinal Chemistry

Fluorine is the ninth atom on the periodic table and the most electronegative atom by the Pauling scale. It has the van der Waals radius of 1.47 Å, comparable to the radius of hydrogen (1.20 Å).[1,2] It is found in nature predominately in the molecular form of F_2; however, trace amounts of the free element are found in fluorspar. Fluorspar or fluorite (CaF_2) is the main fluorine-containing mineral and for centuries it was used as a flux. In 1886, the element fluorine was isolated for the first time by Hanri Moissan.[1,3] Nonetheless, the toxic properties of the pure element and the lack of safe handling protocol hindered the application of fluorine in chemistry and subsequently medicinal chemistry. After World War II, the development of organic fluorine compounds for industrial use bloomed and it continues to progress slowly. The physical and chemical properties of fluorine provide an insight into this slow progress in the development of new applications. Fluorine is a gas that is dangerous to human health but when cooled it liquifies.[1–3] Fluorine-19 is the only stable isotope of the element but the minor fluorine-18 isotope is useful in imaging techniques such as positron emission tomography (PET) imaging.[1,2,4] Furthermore, due to the high electronegativity of fluorine, heavily fluorinated compounds exhibit a different charge distribution. For example, the dipole moment in CH_3I and CF_3I is inverted,

because the charge distribution shifts from iodide to the trifluoromethylated carbon. The discovery that the presence of fluorine in pharmaceutical agents improves pharmacokinetic and physicochemical properties led to an innovation in drug development.

1.2 Fluorine in Drug Development

Fluorine is comparable hydrogen in size, and many studies have demonstrated that is a reasonable hydrogen mimetic.[2] Until the 1970s, fluorinated compounds in medicinal chemistry were rare. In fact, fludrocortisone was introduced in 1954 as the first fluorinated pharmaceutical.[6] Studies have shown that the incorporation of fluorine into a pharmaceutical can improve metabolic stability by changing the rate, route, or extent of metabolism, and this directly influences the bioavailability of the drug.[2,6,7] Furthermore, by reducing the metabolism, fluorine incorporation can also block the formation of toxic metabolites.[2] Fluorine can directly or indirectly influence the rate of a drug metabolism if it is incorporated directly on the site of metabolism or if it is substituted at an adjacent site. Fluorination introduces new resonance, inductive, conformation, or electrostatic effects. Also, fluorination may increase bioavailability by reducing the basicity of neighboring groups, such as nitrogen, because it can alter the electron distribution which affects the pKa or dipole moment. Additionally, chemical reactivity of nearby functional groups can change when fluorine is introduced which may affect membrane permeability.[2,8,9] In a similar fashion, fluorine incorporation can increase the binding affinity or selectivity of a compound to a protein binding site. Fluorine can directly interact with residues in the binding domain or affect the polarity of nearby functional groups that interact with the protein binding site.[2] A more recent application of fluorine in pharmaceutical industry is the use

of the less stable isotope, ^{18}F, as a radiolabeling atom in PET. Fluorine-18 (^{18}F) positron emission tomography is a powerful, non-invasive diagnostic and scanning technique to study living tissues or organs in humans. Also, fluorine-19 is observed by Magnetic Resonance Imaging (MRI) and Nuclear Magnetic Resonance (NMR). MRI is another powerful tool used to scan living tissues in humans, especially in oncology studies and treatment.[10] NMR is an immensely useful tool in the field of organic chemistry synthesis.[11,12] Thus, the fluorine atom is becoming increasingly important because it can be used in imaging agent with PET, MRI, of NMR spectroscopy.

1.3 Fluorinated Drugs

As of 2018, 36% of the leading 50 blockbuster drugs by sales contain fluorine and 20% of all marketed drugs are fluorinated. A survey of the marketed pharmaceuticals will reveal various fluorination strategies; however, in the majority of marketed drugs, fluorination and trifluoromethylation are placed on aromatic rings and conformationally rigid structures. Aliphatic fluorination is limited to compounds with restricted conformation and quaternary carbons to avoid epimerization that can lead to racemization of the drug *in vivo*. The introduction of fluorine in drugs that are susceptible to metabolism led to the development of various classes of drugs such as statins, steroids, and anti-virals. Crestor and Lipitor are statin drugs that are prescribed for patients with high cholesterol levels.[2,7] These drugs were developed from studies on the structure-activity relationships of the parent drug and its metabolites. The parent drugs were susceptible to metabolism via oxidation, hydroxylation, and/or demethylation. Fluorination at one of these sites of metabolism was a viable strategy to reduce metabolism and increase the

bioavailability as well. This strategy was utilized on many other top selling pharmaceuticals such as the anti-diabetic drug Januvia, the anti-viral agent Solvadi, and the oral contraceptive, 16α-fluoro-17β-estradiol.[2,7]

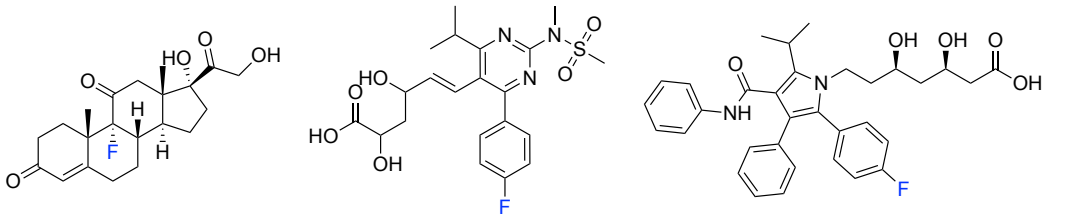


Figure 1: Examples of fluorinated pharmaceuticals

A difluoromethylene was also found to increase potency in a study of protein tyrosine phosphatases (PTP) inhibition.[13] Studies had shown PTP inhibitors, specifically PTP 1B inhibitors have a role as potential therapeutic agents for the treatment of type II diabetes.[14,15] The fluorinated derivatives, benzylic α,α-difluorophosphonates, α,α-difluorosulfonates, and α,α-fluorocarboxylates, were more potent PTP 1B inhibitors than their non-fluorinated analogues. This increased potency is attributed to a conformational change, induced by the difluoromethylene, that allows the fluorine atoms to interact with the active site.[16] An avenue of growing interest is the use of fluorinated amino acids in peptide and protein chemistry.[17] For instance, monofluorinated analogues of amino acids are used as substituents in protein biosynthesis, because studies demonstrated that fluorinated amino acids can increase the stability of polypeptides. Due to fluorine having the highest electronegativity, it can increase the hydrophobic characteristics of a peptide or residue. Also, the fluorine–carbon bond is much higher in energy than a fluorine–nitrogen bond and this difference can decrease the rate of peptide metabolism *in vivo*.[17–20] As the use of fluorinated compounds increased, the interest in innovative synthetic approaches also increased.[21,22] There are many methods to produce

fluorinated compounds but some of the existing limitations are the requirement of fluorinated starting materials, expensive catalysts, or reagents with poor reactivity.[23] Nonetheless, fluorinating reagents allow the synthesis of valuable compounds and the need for new reagents remains strong.

1.4 Aliphatic Fluorination and Trifluoromethylation: Synthetic Strategies and Challenges

Mono-fluorination can be observed in different categories of organic systems, such as aromatic, alkenes, and quaternary stereogenic centers. The introduction of fluorine into each of the systems poses a different challenge and the efforts to address these needs are continuing. However, there are numerous methods to generate fluorinated aromatics, monofluoroalkenes, and difluoroalkens.[23–25] The synthetic strategies to generate fluoroalkenes include hydrofluorination of alkynes, Julia or Julia-Kocienski-type difluoroolefination of carbonyl groups, and the Hornor-Wadsworth-Emmons-type *gem*-difluoroolefination reactions.[24,25] Other methods are Wittig-type difluoromethylenation of carbonyl compounds, Reformatsky reaction, and metal-mediated olefination reactions.[26–31] Fluorinated alkenes are valuable in studying the effects of fluorinated peptides in protein folding and stability. Also, the *gem*-difluoroalkenes opened a new avenue of C–F activation chemistry that led to functionalization fluorinated aromatics and synthesis of complex fluorinated building blocks and molecules.[25,32]

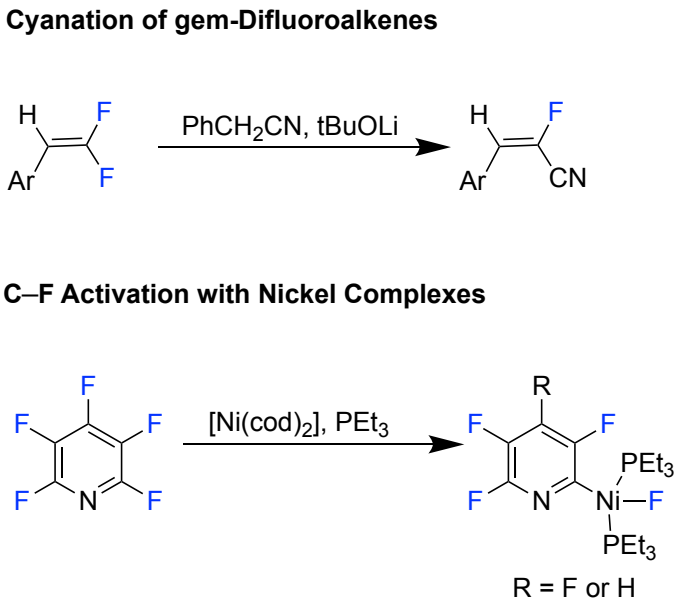
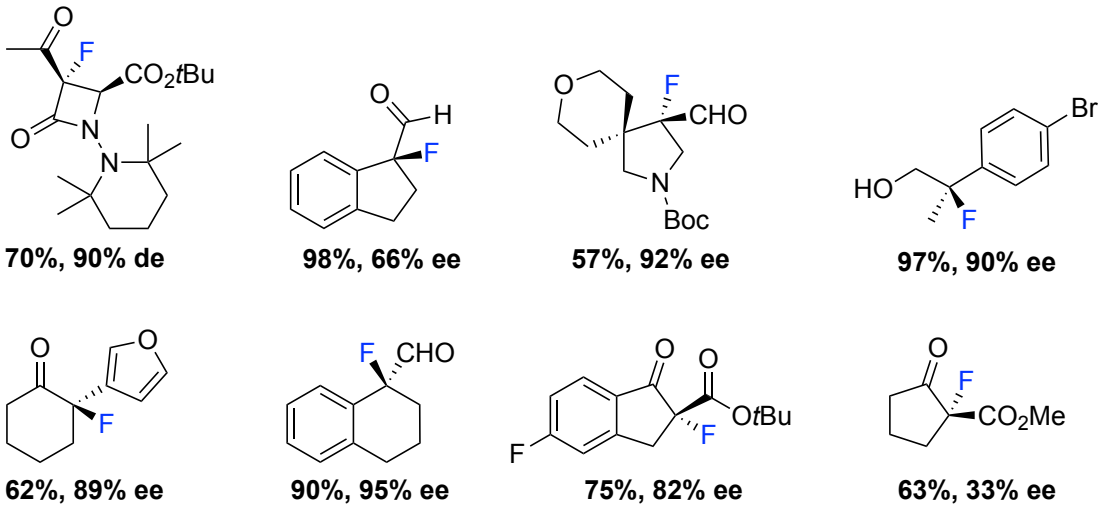


Figure 2: Examples of new bond formation via functionalization of fluorinated substrates.

Unfortunately, fluorinated quaternary stereogenic centers are the most difficult to make. However, the development of chiral *N*-fluoroammonium salts of cinchona alkaloids, Selectfluor, *N*-fluorobenzenesulfonimide (NSFI), and *N*-fluoro pyridinium salts mark significant progress in enantioselective, asymmetric fluorination.[33–37] Subsequently, asymmetric fluorination using a nucleophilic fluorinating source are under-developed compared to the electrophilic methods. The diastereoselective formation of fluorinated quaternary stereogenic centers via electrophilic fluorination mainly focuses on the α-fluorination of carbonyl compounds followed by functionalization of the carbonyl group. Furthermore, an array of chiral sulfonamide-type fluorinating reagents was developed to achieve an enantioselective fluorination, but due the multistep procedures and the requirement of toxic reagents to prepare them, these reagents are not widely used.[38–40] Nonetheless, this avenue of fluorination is of interest to researchers despite the challenges that remain.

Enantioselective, asymmetric electrophilic fluorination using NSFI



Enantioselective, asymmetric electrophilic fluorination using Selectfluor

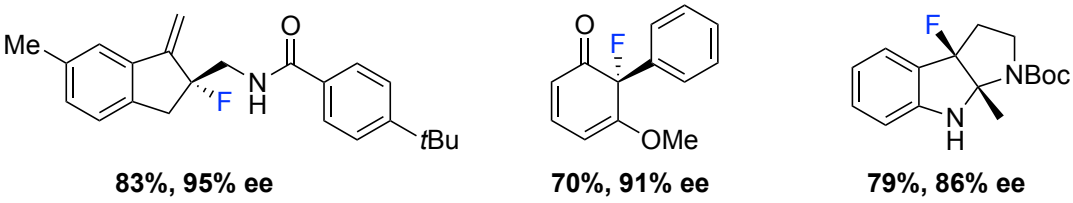


Figure 3: Enantioselective, electrophilic fluorination of compounds bearing quaternary stereogenic centers.

In fact, with the exception of fluticasone propionate, there are no active pharmaceuticals bearing a fluorinated tertiary stereogenic center because the stereogenic center may undergo epimerization which gives either a racemic or diastereomeric mixture of compounds *in vivo*.[41] Epimers are two compounds that are non-superimposable, mirror images of each other. Epimerization is a chemical process where a stereogenic center is converted to its opposite counterpart. This process can happen spontaneously in the presence of acid or base or by enzymatic catalysis.[41] Methods to stereoselectively generate fluorinated stereocenters with epimerizable protons do exists. Other important fluorination reactions in drug design are the Prins cyclization that generates fluorinated tetrahydropyran derivatives, the aza-Prins cyclization that generates 4-fluoropiperidines, and ring expansions by fluorinative semipinacol

rearrangements.[42–49] A comprehensive review of progress in this area was reported by Paquin in 2015.[50]

Trifluoromethylation is another area of fluorination that captures the interest of chemists. Many trifluoromethylation reagents are commercially available. Also, there a quite a few methods for enantioselective trifluoromethylation using electrophilic trifluoromethylating reagents such as Togni's, Umemoto's, Shreeve's, Yapoulskii's, Shibata's, Ishihara's, and Adachi's reagents.[51,52] Copper-mediated/catalyzed trifluoromethylation reactions are reported using alkynes and silyl enol ethers as substrates.[53,54] Asymmetric trifluoromethylation was investigated using $TMSCF_3$ as a nucleophilic source.[55,56] Furthermore, Ireland–Claisen rearrangement, $TiCl_4$-catalyzed Evans–Aldol, and Et_3Al-mediated Reformatsky reaction were also effective in accessing a trifluoromethylated stereogenic center.[57,58] The ability of dialkylboron reagents to control diastereoselectivity was exploited to generate trifluoromethylated compounds as reported by Ramachandran.[59] The use of dialkylboron reagents to control the stereoselectivity of a reaction was established by Brown in 1989 (Figure 4).[60] A trifluoromethyl group adjacent to a carbonyl group can create an easily epimerized stereogenic center. The quantity of stereoisomers produced from theses transformation can be measured and are reported as an enantiomeric excess or ratio of diastereomers.

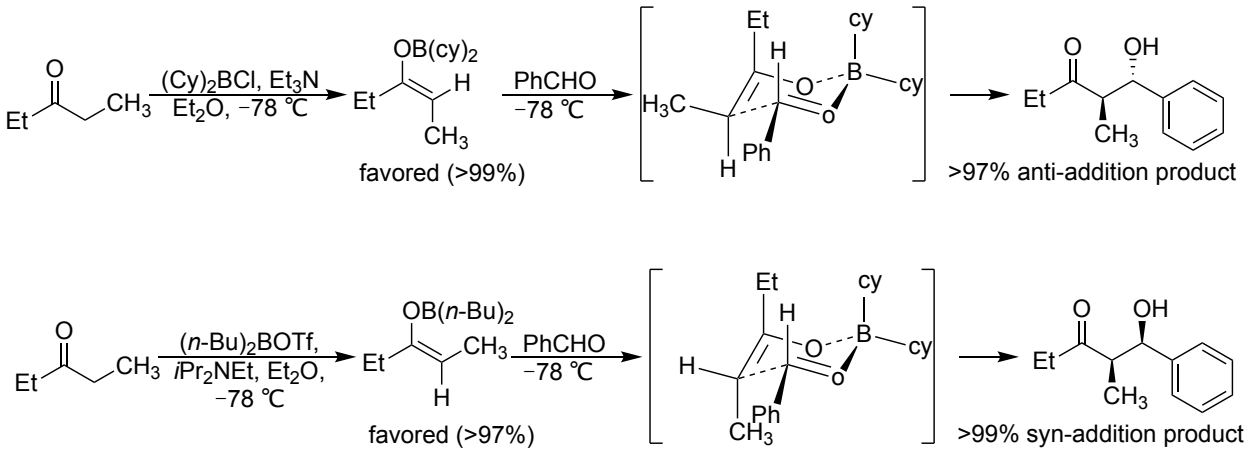


Figure 4: Controlling diastereoselectivity using dialkylboron reagent and transition states.

Enantiomeric excess is the absolute difference in the mole fraction of each enantiomer (*R* and *S*), is an important method to measure the purity of a chiral compound. It conveys the ratio of one enantiomer to the other in percentage (i.e., %*ee*). The percent of enantiomeric excess indicates the success of an asymmetric synthesis, such as during the production of a fluorinated quaternary stereogenic center. An enantiomeric excess of 95% means the sample contains 95% of one pure enantiomer (*R* or *S*) and 5% racemic mixture of *R* and *S.* Enantiomeric excess is calculated from the moles of each enantiomer as follows:

$$\%ee = \left(\left(\frac{R-S}{R+S}\right) \times 100\right) \qquad \boxed{1}$$

Or

$$\%ee = |F_R - F_S| \times 100 \qquad \boxed{2}$$

Where $F_R + F_S = 1$

The enantiomeric excess of a mixture can be measured by chiral chromatography such as chiral HPLC to separate the two enantiomers.[61,62] If the mole fractions of each enantiomer is known, equation 1 can be applied to calculate the percent enantiomeric excess, otherwise equation 2 is more suitable. The diasereomeric ration can be measured in a similar fashion. An alternative

method to measure the enantiomeric ratio is by measuring the optical activity (optical rotation) of a pure solution of each individual enantiomer.[63] The optical activity is determined by the rotation of the plane of polarization clockwise or counter-clockwise about the optical axis of a linearly polarized light as it travels through the solution of a pure enantiomer. A clockwise rotation is associated with dextro-rotation (to the right) and a counter-clockwise rotation is associated with levo-rotation (to the left). A racemic (1:1 ratio of *R* to *S*) mixture of enantiomers will give an optical rotation of 0%, but a non-racemic mixture of two enantiomers will have a net optical rotation.[64] One can also determine the optical purity of a mixture, if the specific rotation of the pure enantiomer is known using the equation below:

$$optical\ purity\ (\%) = \frac{[\alpha]_{obs}}{[\alpha]max} \times 100 \qquad \boxed{3}$$

Theoretically, the optical rotation is directly proportional to the mole fraction within the mixture and as a result the measured optical purity should be equivalent to the percent enantiomeric excess. However, the direct correlation between optical purity and enantiomeric excess is not always accurate.[65] A common method to ensure a transformation will produce the desired stereochemistry is through the use of chiral auxiliaries. These chemical reagents will dictate a favorable low-energy transition state which will determine the diastereoselectivity of the process.[66–68] The substitution pattern on the chiral auxiliaries can change the conformation of these transition states which is also influenced by the choice of reagent. The high-field ^{1}H NMR is a powerful tool that can be used to derive the enantiomeric excess. In this technique, a strong non-covalent interaction with a chiral reagent additive is needed.[69] X-ray crystallography is an experiment to determine absolute configuration by observing the diffraction pattern of a beam of incident X-rays.[70] Unlike the aforementioned techniques, this method requires the crystalline of the compound.

CHAPTER II

DETRIFLUOROACETYLATIVE α-METHYLENATION TO ACCESS A SUBSTITUTED α-METHYLENE-γ-LACTAM

2.1 Introduction

2.1.1 Importance of Fluorine and Organofluorines in Medicinal Chemistry

Fluorine is an immensely valuable atom in pharmaceuticals because it may increase metabolic stability, binding affinity, bioavailability, lipophilicity and selectivity for targets. Fluorinated organic compounds can exhibit different activities than their parent analogues.[7,20,71,72] Within the past decade, approximately 25% of all marketed pharmaceuticals contain fluorine. Many of the fluorinated drugs on the market and drug candidates contain either a fluorine atom, a difluoromethylene, a trifluoromethyl- or an aryl pentafluorosulfanyl moiety.[7] However, fluorine and fluorinated compounds are also used as reagents in chemical reactions. In this study, the trifluoroacetate-release promoted methylenation was used to install an α-methylene group at a sterically hindered position to generate an α-methylene-γ-lactam as a synthetic key intermediate.

2.1.2 Bioisosteric Motifs

Compounds isolated from natural products that display α-methylene-γ-lactones motif are important leads in drug discovery. The α-methylene- γ-lactone motif can also serve as a key synthetic intermediate for other molecules containing an α-methylene group.[72–74] Natural products with this group were shown to have potential applications as chemotherapy, such as anti-leukemic properties but they do exhibit toxic side effects. [73,42] A bioisosteric motif for the α-methylene-γ-lactones are the α-methylene-γ-lactams, which have much lower cytotoxic effects and similar antibacterial, anti-inflammatory, and anti-anaphylactic properties.[75–83] Therefore, the synthesis of α-methylene-γ-lactams received attention in the total synthesis of mimetics of natural and as bioisoteric replacements.[85–86]

There are a number of reported methods to synthesize an α-methylene-γ-lactam. The synthetic approaches include the cycloaddition reaction,[87–89] the ring expansion of β-lactams,[90–92] tandem sequence aza-Michael/intramolecular nucleophilic substitution,[84] NHC-catalyzed addition of enals to imines,[93] and cyclization of nitrogen radicals.[95] Notably, the earliest report of the synthesis of α-methylene-γ-lactams is the reaction of the organozinc derivative of ethyl α-(bromomethyl) acrylate with *N*-trimethylsilyl aldimines and was published in 1988.[95] However, most examples pertain to the α-methylenation of lactones. Notable exceptions are Zn-promoted aza-Barbier-type allylations of (*R*)-*N*-*tert*-butanesulfinyl imines with allyl bromide[86] and α-methylenation via trifluoroacetate-release.[28]

2.1.3 Synthetic Strategies for α-Methylenation

The use of bis(dimethylamino)methoxymethane (Bredereck's reagent) under basic conditions to produce an aminoalkene that undergoes reduction from DIBALH to introduce an α-methylene into a lactone of the common.[97] There are a number of reported synthesis that adopt this method to generate a methylene in a simple lactam ring.[98–99] However, due to the bulkiness of the Bredereck's reagent, it is an ineffective approach on sterically congested systems. Another shortcoming of the method is the need for excess amounts of the reagent, which is incompatible in large scale reactions.

Alternatively, the Colby group reported the use of the trifluoroacetate-release reaction to install an α-methylene group into a sterically hindered lactam to access 15-methylene-eburnamonine derivative of (–)-eburnamonine.[96] The strategic replacement of the formyl group[100,101] with a trifluoroacetyl group circumvented the difficulty of releasing a formate to access the methylene because trifluoroacetate-release is a facile elimination. The shift from deformylation to detrifluoroacetylation expanded the application of this synthetic approach and broadened the scope of the reaction to lactones, lactams, and ketones.[96] Although this method is a two-step reaction that required α-trifluoroacetylation of ketones, lactones, and lactams, the transformation is efficiently accomplished with lithium hexamethyldisilazide (LiHMDS) and 2,2,2-trifluoroethyl trifluoroacetate. Not only did this methodology demonstrate a wide scope but it also gave good yields across transformations of ketones, lactones, and lactams **1–4** (Figure 5).

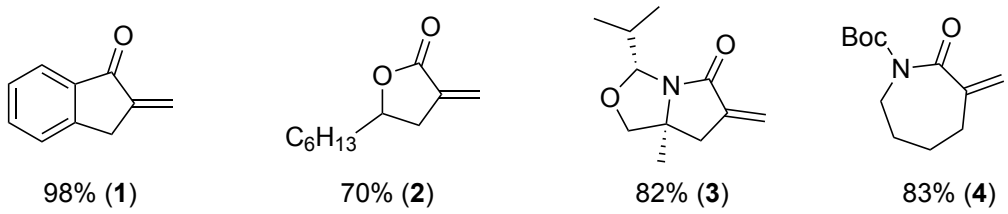


Figure 5: Examples of the ketones, lactones, and lactams synthesized using trifluoroacetate-release reaction

2.2 Synthesis and Discussion

This work was completed in the Le Laboratory to access derivatives of the naturally occurring glutamine, L-γ-methyleneglutamine, and its amide derivatives to explore potential anticancer activity. A manuscript is submitted for publication.[102] In this chapter, I will disclose my work to establish a short and efficient synthetic route to synthesize an α-methylene-γ-lactam (Figure 6). Specifically, I will highlight the synthetic strategy to install an α–methylene on a sterically hindered lactam, which was key to accessing the L-γ-methyleneglutamine and its amide derivatives. The conditions to install a methylene adjacent to a carbonyl group were developed by my predecessors in the Colby Laboratory.[96]

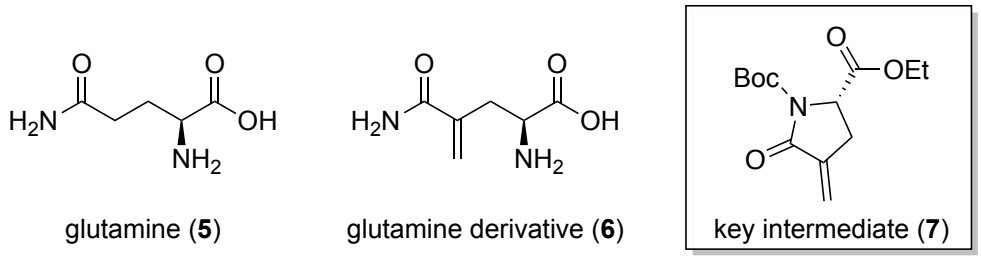


Figure 6: Structural similarity of the naturally occurring non-essential amino acid **5**, its methylene derivatives **6**, he key intermediate **7**

Initially, the plan was to start with the cyclization of glutamine **(5),** but L-pyroglutamic acid (**8**) is commercially available and inexpensive, which eliminates the need of this step. The carboxylic acid and amide groups of **8** were first protected as an ethyl ester via Fisher esterification and a Boc group under acidic conditions, respectively (Figure 7). Both protections gave excellent yields of 99% and 92%. Also, both reactions were scaled to 10 grams without any decrease in yield (i.e., quant. and 85%). Next, we envisioned the methylation via a simple deprotonation of the α-proton using a weak base.[103] We opted for this approach to avoid deprotonation of the proton in the γ-position, which epimerizes the stereogenic center adjacent to the ether ester.

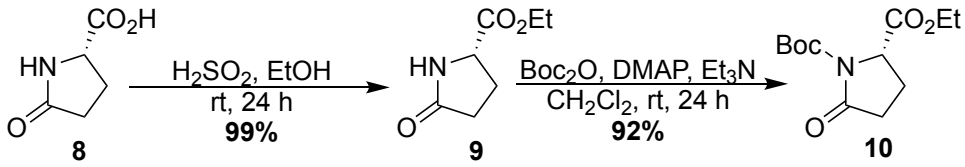


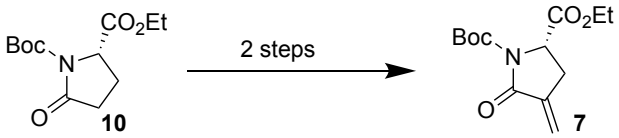
Figure 7: Protection of carboxylate and amide to give substrate **10**.

We proceeded to the *α*-methylenation using diethylamine as the base and dibromomethane as the source of the methylene.[103] However, this method was ineffective and we retrieved the starting material **10**. Next, we employed the use of a milder yet bulkier base, diisopropylammonium trifluoroacetate complex, and paraformaldehyde with acid or base catalyst,[104,105] but product was not formed. We turn to the Bredereck's reagent to accomplish selective deprotonation, which was a stronger base but also bulky. This synthetic strategy did provide the desired product, albeit in low isolated yields (i.e., 0–28%) after optimization.

An examination of the compatible substrates in the trifluoroacetate-release protocol led to the hypothesis that steric congestion of the ester will hinder a competing deprotonation at the γ-

position.[96] Upon subjecting **10** to α-trifluoroacetylation then detrifluoroacetylation we obtained **7** in 51% yield at 0.5 g-scale reaction using K_2CO_3 with paraformaldehyde in refluxing benzene. In an effort to optimize the yield, we increased the temperature (80→90 °C) and then switched the solvent to toluene at 100 °C. We isolated **7** in 58% and 38%, respectively. Increasing the temperature improved the yield, while the use of toluene instead of benzene decreased the yield. Out of five synthetic reactions, the trifluoroacetate-release reaction gave the highest yields of the methylenated intermediate (Table 1) and the Boc-protecting group was easily cleaved with TFA to give **7a**. Later studies conducted by Md. Hossian in the Le Laboratory found that the use of a bulky *tert*-butyl ester increased the yield to 66%.[102]

Table 1: Reaction conditions to access methylenated lactam



	Step 1	step 2		
Entry	Base	catalyst	Electrophile	Yield
1	Et_2NH	-	CH_2Br_2	n/o
2	*i*-Pr_2NH•TFA	TFA	(HCHO)n	n/o
3	*i*-Pr_2NH•TFA	*i*-Pr_2NH	(HCHO)n	n/o
4	*t*-BuOCH(NMe)2	K_2CO_3	(HCHO)n	28%
5	$LiN(SiMe_3)_2$	K_2CO_3	(HCHO)n	58%

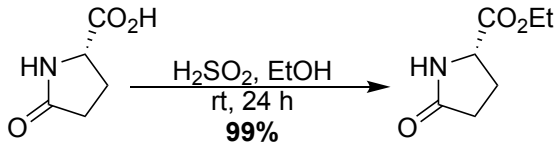
Solvents and additional reagents: 1) CH_2Cl_2, rt (Δ), 1 (1.5) h. 2) 10 mol% TFA, THF, Δ, 2 h. 3) 10 mol% *i*-Pr_2NH, THF, Δ, 6 h. 4) DME then 1N HCl, THF. 5) $F_3CCO_2CH_2CF_3$, THF, −78 °C then 18-crown-6, Benzene, 80→90 °C, 4.5 h

2.3 Conclusion

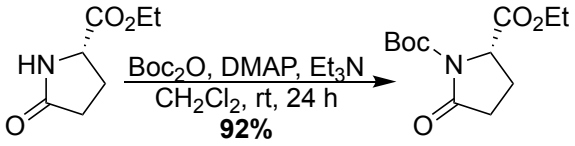
We have expanded the scope of the trifluoroacetate-release reaction to access a key intermediate in the synthesis of L-γ-methyleneglutamine. Also, we identified an improved protocol to generate this intermediate. Through this advance, the methylene group was introduced at the C4 position of glutamine via the α-methylenation. This approach was also shown to tolerate bulky esters. A manuscript with these data was submitted for publication.

2.4 Experimental and Characterization Data

All reactions were performed under inert gas with oven-dried glassware and solvents were dried over molecular sieves. Flash chromatography was conducted using SiliCycle Siliaflash silica gel P60 (40–63 μm) 60 Å. NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer. The residual solvent peaks of $CDCl_3$, CH_3OD, or DMSO-d_6 were used as an internal standard for ^1H and ^{13}C NMR spectra.

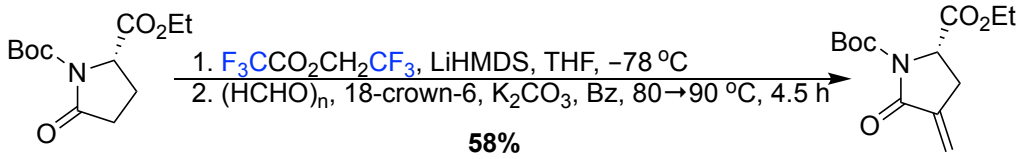


Ethyl-(*2S*)-pyroglutamate (**8**). To a solution of L-pyroglutamic acid (502 mg, 3.89 mmol) in pure EtOH (4.1 mL) was added H_2SO_4 (2 drops), and the reaction mixture was stirred at rt for 24 h. Next, Na_2SCO_3 (157 mg, 0.62 mmol) was added and the resultant mixture was stirred at rt for 1.5 h then filtered through celite and washed with EtOH (10 mL). The solvent was evaporated under reduced pressure, the excess EtOH was azeotroped with co-evaporation with CH_2Cl_2 (2 × 25 mL), and the residue was placed under high vacuum to afford **8** as a white solid (610 mg, 99%): ^1H NMR (400 MHz, CH_3OD) δ 4.30 (dd, J = 8.0, 4.0 Hz, 1H), 4.21 (q, J = 8.0 Hz, 2H), 2.48 (m, 1H), 2.39 (m, 2H), 2.34 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1, 174.0, 62.5, 57.2, 30.3, 25.9, 14.4.



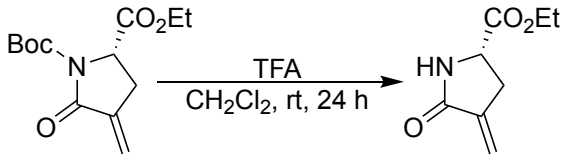
Ethyl-(*2S*)-*N*-(*tert*-butyoxycarbonyl)pyroglutamate (9). To a solution of **8** (610 mg, 3.89 mmol) in CH_2Cl_2 (4.5 mL) was added DMAP (524 mg, 4.29mmL) followed by Et_3N (0.66 mL,

4.74 mmol), and the mixture was stirred mixture for 5 min at rt. Then, di-*tert*-butyldicarbonate (937 mg, 4.29 mmol) was added and the resultant mixture was stirred for 24 h at rt. The mixture was quenched with saturated NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. SiO_2 flash chromatography (1:1 EtOAc/hexanes) gave **9** as viscous oil (913 mg, 92%): ^{1}H NMR (400 MHz, CH_3OD) δ 4.70 (dd, *J* = 8.0 Hz, 1H), 4.29 (q, *J* = 8.0, 4.0 Hz, 2H) 2.52 (m, 3H), 2.06 (m, 1H), 1.52 (s, 9H), 1.34 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, CH_3OD) δ 176.3, 173.2, 84.7, 62.8, 60.6, 32.0, 28.1, 22.3, 14.5.



1-(*tert*-Butyl) 2-ethyl (*S*)-4-methylene-5-oxopyrrolidine-1,2-dicarboxylate (7). To a –78 °C solution of LiHMDS (9.85 mL, 0.6 M in THF) was added a solution of **9** (512 mg, 1.94 mmol) in THF (11.4 mL). The reaction mixture was allowed to stir for 30 min, and then $CF_3CO_2CH_2CF_3$ was added (0.56 mL, 4.2 mmol). After an additional 1.5 h at –78 °C, saturated aqueous NH_4Cl (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 12 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. Without further purification, the crude mixture was taken up in benzene (20 mL), and K_2CO_3 (830 mg, 5.02 mmol), 18-crown-6 (135 mg, 0.51 mmol), and paraformaldehyde (200 mg, 66.5 mmol) were added. The suspension was heated to 80 °C for 1 h and then heated to reflux (oil bath = 90 °C) for 4 h. The mixture was allowed to cool to rt, saturated aqueous NH_4Cl (30 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (25→50% Et_2O in CH_2Cl_2) afforded the **7** as a pale-yellow oil (277 mg, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ

6.11 (d, J = 4.0 Hz,1H), 5.43 (d, J = 4.0 Hz, 1H), 4.52 (dd, J = 12.0, 8.0 Hz, 1H), 4.13 (q, J = 8.0 Hz, 2H), 3.02 (m, 1H), 2.97 (m, 1H) 1.41 (s, 9H), 1.18 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 165.6, 149.6, 136.6, 120.7, 83.6, 61.6, 55.7, 27.7, 14.0.



Ethyl (*S*)-4-methylene-5-oxopyrrolidine-2-carboxylate (7a). To a mixture of **7** (584 mg, 2.17 mmol) in CH_2Cl_2 (35 mL) at rt was added TFA (10 mL) dropwise, then the mixture was stirred for 24 h. The reaction mixture was concentrated under reduced pressure and SiO_2 flash chromatography in MeOH:CH_2Cl_2 (0→5%) gave **7a** (268 mg, 73%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 5.11 (s, 1H), 5.33 (d, J = 4.0 Hz, 1H), 4.25 (m, 1H), 4.13 (q, J = 8.0 Hz, 2H), 3.11 (m, 1H), 2.72 (dq or dddd, J = 20.0, 8.0, 8.0, 4.0 Hz, 1H), 1.20 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 169.0, 138.8, 114.9, 60.9, 51.6, 29.9, 14.0.

CHAPTER III

SYNTHESIS OF β-FLUORO-α,β-UNSATURATED AMIDE VIA FACILE FRAGMENTATION OF MORPHOLINE 3,3,3-TRIFLUOROPROPANAMIDE BY GRIGNARD REAGENTS

3.1 Introduction

3.1.1 Fluoroalkenes

Fluoroalkenes are an important class of Michael acceptors, and they serve as bioisoteres for peptide bonds. Also, fluoroalkenes are resistant to the proteases that hydrolyze the amide bonds in peptides.[20,71] An example of peptide bond surrogate is demonstrated by the fluorinated analogue of the antihypertensive drug enalapril (Figure 8), synthesized by Pannecoucke and coworkers.[71] Other examples of this strategy have been reported by Altman,[106] Augustyns,[107] Welch,[108] Leumann,[109] and Fujii.[110] In addition, most of these reports demonstrated the application of innovative synthetic methods to synthesize the fluoroalkene.

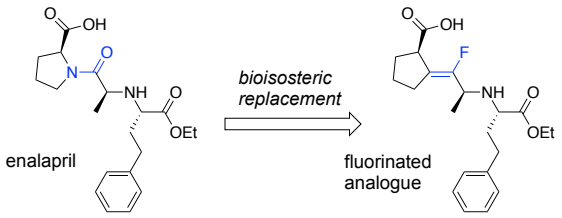


Figure 8: Enalapril and its fluorinated analogue that bioisosterically replaces the amide bond with a fluoroalkene

There are general methods to synthesize α-fluoro-α,β-unsaturated carbonyl compounds,[111,112] such as the Julia olefination,[28] the Peterson olefination,[111] the Horner-Wadsworth-Emmons reaction,[71] and a Reformatsky addition/elimination process.[27] Synthetic methods do exist for the preparation of β-fluoro-α,β-unsaturated carbonyl compounds, but most are limited by low yields and poor stereoselectivities.[114–116] Recent exceptions are the hydrofluorination of alkynes using gold catalysts that provide access to (*Z*)-β-fluoro-α,β-unsaturated carbonyl compounds,[29] the chromium-mediated reductive coupling of $CBrF_2$-containing compounds with aldehydes to give (*E*)-α-fluoro-α,β-unsaturated amides,[31] and the bisphosphine-copper catalyzed boryl substitution of difluorosubstituted *Z*-/*E*-alkenes to produce enantioselective (*Z*)- or (*E*)-γ-monofluoroallylic boronates.[117] Herein, the synthesis of (*E*)-β-fluoro-α,β-unsaturated amides in a single step was accomplished by reacting a morpholine 3,3,3-trifluoropropanamide with commercially available Grignard reagents.

3.1.2 Metal-Catalyzed/Mediated Reductive Coupling Synthetic Approach of Fluoroalkenes

Although transition metal-catalyzed/mediated cross-coupling reaction of *gem*-difluoroalkenes with organometallic reagents are a great challenge. Generally, alkenyl fluorides were considered to be uncommon coupling partners for the transition metal-catalyzed cross-

couplings due to the great strength of the C–F bond (120–129 kcal/mol for olefinic C–F bonds).[118] In 2016, Toste and co-workers investigated the coupling of *gem*-difluoroalkenes and boronic acids and discovered that 1-aryl-2,2-difluoroalkenes readily react with boronic acids in the presence of 10 mol% $Pd(TFA)_2$ and 11 mol% dtbbpy. This transformation gives (*Z*)-monofluoroastilbenes in moderate yields.[119] The proposed mechanism of this reaction was hypothesized to be through β-fluoride elimination of the palladium (II) intermediate in the catalytic process. Furthermore, Konno and colleagues reported a highly stereoselective synthesis of (*E*)- and (*Z*)-β-fluoroallylic alcohols by C–F bond cleavage of $CBrF_2$-containing compounds in the presence of chromium (II).[120] The two shortcomings of this transformation are the stoichiometric amounts of chromium (II) and the need of $CBrF_2$-containing compounds, which are difficult to access.

3.2 Synthesis and Discussion

3.2.1 Synthesis of Fluorinated Amide Substrate

Initially, our plan was to synthesize a 3,3,3-trifluoropropanamide from *N,O*-dimethylhydroxylamine in order to create a Weinreb amide. Our first attempt proceeded by converting the acid to an acetyl halide and reacting it *in situ* with *N,O*-dimethylhydroxylamine to give the Weinreb amide. However, this method was ineffective and gave a complex mixture. An alternative method to access the Weinreb amide was via reacting *N*,O-dimethylhydroxylamine •HCl and an acid in the presences of *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide•HCl (EDCI) and hydroxybenzotriazole hydrate (HOBT) to produce a Weinreb amide.[121] Unfortunately, the coupling of 3,3,3-trifluoropropanoic acid with *N,O*-dimethylhydroxylamine produced low and inconsistent yields, varying from 0 to 33%. Although Weinreb amides are

versatile synthetic intermediates, morpholine amides also participate in similar functional group transformations.[122,123]

An indirect approach to access a morpholino-analogue of Weinreb amide was through the use of unsymmetrical carbamoylimidazole. This route reacts morphline with *N,N*-carbonyldiimidazole (CDI) to generate carbamoylimidazole, which is then reacted with iodomethane to generate a carbamoylimidazolium salt. We have successfully optimized the conditions to generate the carbamoylimidazole and carbamoylimidazolium salt in quantitative yields.[124–126] However, decarboxylative coupling with the 3,3,3-trifluoropropanoic acid to generate the morpholine 3,3,3-trifluoropropanamide only gave an optimized yield of 10%. Therefore, it became necessary to develop an alternative route to access morpholine 3,3,3-trifluoropropanamide.

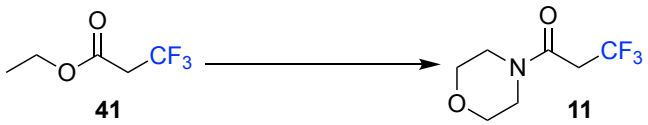
To our delight we discovered that reacting 3,3,3-trifluoropropanoic acid with morpholine, EDCI, HOBT, triethylamine, produced morpholine 3,3,3-trifluoropropanamide **11** in 59% yield. However, increasing the temperature to 65 ºC and adjusting the solvent system to THF/DMF (9:1) substantially increased the yield from 59% to quantitative amounts. This method is much improved compared to previously reported approaches because it does not require *N*-pentafluoropropyl morpholines as substrates.[127,128] Our reaction allows a simple purification via SiO_2 flash chromatography.

3.2.2 Direct Amidation of Fluorinated Ester Derivatives

Preliminary experiments to convert methyl 3,3,3-trifluoropropionate and ethyl 3,3,3-trifluoropropionate **41** into the corresponding morpholine 3,3,3-trifluoropropanamide were

conducted. To our surprise, when the ester was reacted with morpholine (neat) for 24 h, we were able to isolate the two alcohol, 3,3,3-trifluoro-1-methoxy-1-morpholinopropan-1-ol and 3,3,3-trifluoro-1-ethoxy-1-morpholinopropan-1-ol, as major products. These intermediates were treated with TFA to give the fluorinated morpholine amide **11** in 38–44% yields. We are currently investigating the direct conversion of ester derivatives to morpholine 3,3,3-trifluoropropanamide **11**. We subjected ethyl 3,3,3-trifluoropropionate **41** to a series of reagents in different solvents, and temperatures (Table 2). We found that reacting **41** with one equivalent of diethyl aluminum chloride and morpholine followed by gradual warming to reflux **11** in the highest yield of 56% (Table 2, entry 14). Optimization efforts will continue to improve the yield of this reaction.

Table 2: Attempted amidation of ethyl 3,3,3-trifluoropropionate



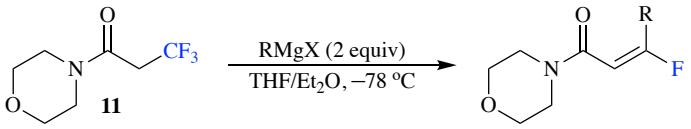
Entry	Cat. Reagent (equiv)	Morpholine (equiv)	Solvent (0.08 M)	Temp. (°C)	Atm.	Comments
1	^{t}BuOK (3.0)	1.1	THF	rt (24 h)	in air	minor
2	^{t}BuOK (3.0)	1.1	THF	rt (5 h)	Argon	minor
3	^{t}BuOK (3.0)	1.1	THF	65	Argon	46%
4	^{t}BuOK (3.0)	1.1	THF	rt (18 h)	in air	trace
5	^{t}BuOK (3.0)	1.1	neat	rt (18 h)	in air	minor
6	$AlCl_3$ (1.0)	1.0	Toluene	rt (5 h)	Argon	trace
7	$AlCl_3$ (1.0)	1.0	Toluene	70	Argon	10%
8	$AlMe_3$ (1.0)	1.0	Toluene	rt (5 h)	Argon	trace
9	$AlMe_3$ (1.0)	1.0	Toluene	70	Argon	6%
10	$FeCl_3$ (0.2)	1.0	Toluene	rt (5 h)	Argon	trace
11	$FeCl_3$ (0.2)	1.0	Toluene	70	Argon	8%
12	Et_2AlCl (1.0)	1.0	Toluene	rt (6 h)	Argon	Trace
13	Et_2AlCl (1.0)	1.0	Toluene	70	Argon	42%
14	Et_2AlCl (1.0)	1.0	THF	rt (3 h) -> 60	Argon	56%
15	Et_2AlCl (1.0)	1.0	THF	62	Argon	24%

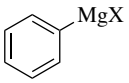
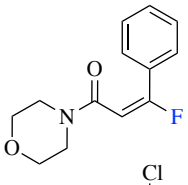
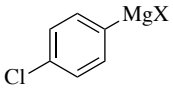
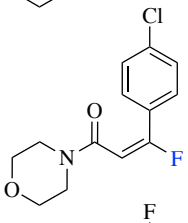
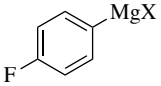
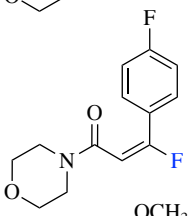
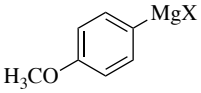
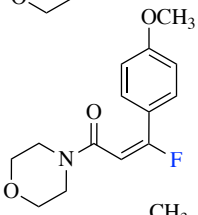
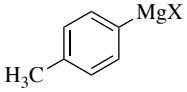
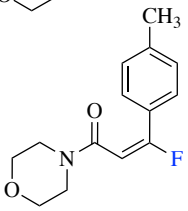
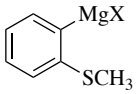
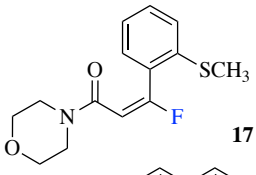
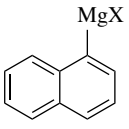
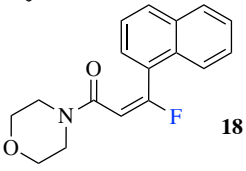
3.2.3 Synthesis of β-Fluoro-α,β-Unsaturated Amides

Amide **11** was treated with 2 equivalents of phenylmagnesium bromide in THF, CH_2Cl_2, Et_2O, and 1:1 THF/Et_2O at −78 °C, and after 4 h, the fluoroalkene product **12** was observed in all

of the reaction mixtures by ^{19}F NMR. The solvent system 1:1 THF/Et_2O was observed to have the best reactivity, and upon scale up of the reaction, the fluoroalkene **12** was obtained in 73% isolated yield. The stereochemical assignment was determined by the characteristic coupling constant between the vinyl proton and vinyl fluoride. In the case of phenyl **12**, the $J_{HF}(cis)$ is 19.3 Hz, which establishes the identity of the (*E*)-alkene. Other common aryl Grignard reagents, such as *p*-chlorophenyl, *p*-fluorophenyl, *p*-methoxyphenyl, tolyl, and naphthyl, participate in a similar fashion and give (*E*)-products **13**, **14**, **15**, **16**, and **18**, respectively, in yields of 50%−59%. Lithium salts (i.e., lithium chloride or lithium bromide) were added to the Grignard reagents to improve the isolated yields of products **14**, **15**, **16** and **18**. Knochel has previously reported the beneficial role of lithium salts in the reactivity of Grignard reagents, and an increase in yield was observed during optimization for this process.[129] The cyclohexyl, butyl, and isopropyl Grignard reagents give products **21**−**23** with the expected (*E*)-alkene as the major product in yields at 62%−71%. The 1,3-dioxan-2-ylethyl magnesium bromide affords **20** in the yield of 82% and enabled the acquisition of its X-ray structure, confirming the (*E*)-fluoroalkene. All of X-ray experiments and X-ray data analysis were conducted by Frank R. Fronczek at Louisiana State University. The *o*-methylthiophenyl and 2-thienyl Grignard reagents give products **17** and **19**, respectively. The *o*-methylthiophenyl-product **17** was isolated as an inseparable 8:2 mixture of *E/Z*-isomers. Overall, both alkyl and aryl Grignard reagents add to amide **11** to create the (*E*)-fluoroalkenes in modest to good yields (Table 3).

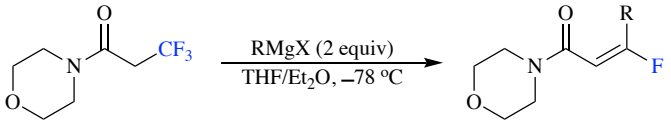
Table 3: Scope of the trifluoromethyl fragmentation reaction.

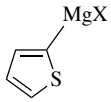
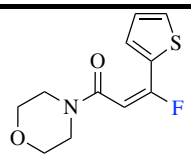
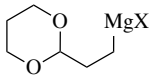
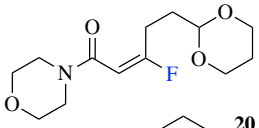
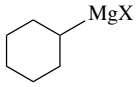
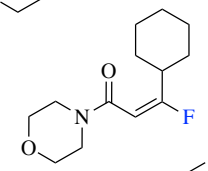
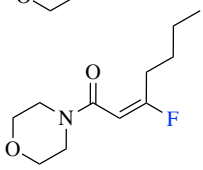
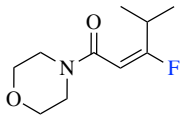


Entry	Grignard Reagent	Product	Yield
1		 **12**	73%
2		 **13**	50%
3		 **14**	57%
4		 **15**	53%
5		 **16**	59%
6		 **17**	43% (dr 8:2)
7		 **18**	58%

*X = Br or Cl

Table 3: Continued…



8		 **19**	46%
9		 **20**	82%
10		 **21**	71%
11	*n*-BuMgX[a]	 **22**	71%
12	*i*-PrMgX[a]	 **23**	62%

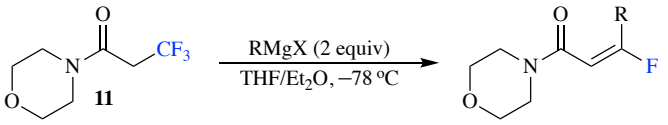
[a]X = Br or Cl

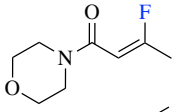
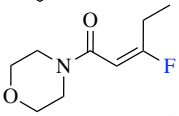
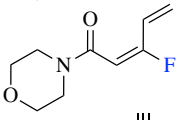
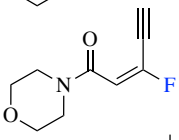
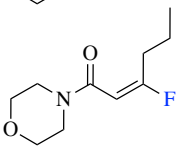
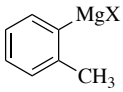
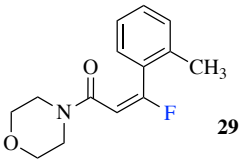
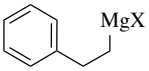
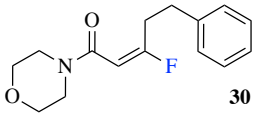
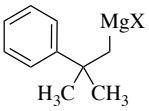
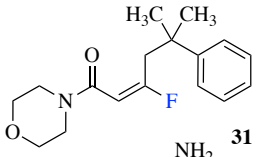
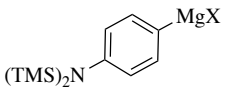
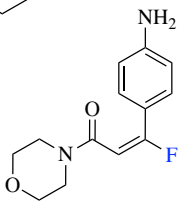
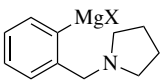
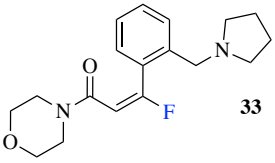
3.2.4 Limitations of the Reaction

Although methylmagnesium chloride/bromide, ethylmagnesium bromide, vinylmagnesium bromide, ethynylmagnesium bromide, *n*-propylmagnesium chloride were also added to **11**, only low yields of volatile products (i.e., 31%, 10%, 9%, and 11%, 27% respectively) were observed by ^{19}F NMR with $CF_3C_6H_5$ as internal standard (Table 4). In addition, amide **11** was also reacted with *o*-tolylmagnesium bromide, phenethylmagnesium chloride, and 2-methyl-2-phenylpropylmagnesium chloride; the observed yield of **29**, **30**, **31** by ^{19}F NMR were 59%, 58% and 65%, respectively (Table 4). However, the ^{1}H NMR showed a double addition by-product that was not possible to separate from the fluorinated product. The

reaction of **11** with 4-[bis(trimethylsilyl)amino]phenylmagnesium bromide and [2-(1-pyrrolidinylmethyl)phenyl]magnesium bromide led to complex mixtures whereas the products **32** and **33** were observed by ^{19}F NMR but the yields were low (i.e., 36% and 15% respectively).

Table 4: Limitations of the reaction condition



Entry	Grignard Reagent	Product	19F NMR Yield
13	MeMgX	 **24**	31%
14	EtMgX	 **25**	10%
15	vinylMgX	 **26**	9%
16	ethynylMgX	 **27**	11%
17	*n*-PrMgX	 **28**	27%
18		 **29**	59% (2:1)
19		 **30**	58%
20		 **31**	65%
21		 **32**	36%
22		 **33**	15%

*X = Br or Cl; best yields of multiple trials are reported here

3.2.5 Application of Amides

Morpholine amides are versatile groups that can be easily transformed to other functional groups. Usually, they provide access to ketones following the addition of a suitable nucleophile. Accordingly, reagent **11** was treated with two equivalents of phenyl lithium in the presence of TMEDA, and the double addition product **34** was produced in 75% yield (Figure 9).

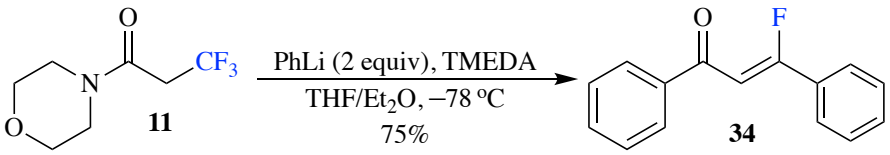


Figure 9: Reaction of morpholine 3,3,3-trifluoropropanamide with phenyllithium

The ketone **34** was isolated exclusively as the (*Z*)-fluoroalkene; TMEDA improved the selectivity and yields. The characteristic J_{HF}(trans) is 34.2 Hz, and all characterization data for **34** matched the reported values.[51] These data suggest that the transformation of the morpholine amide to a ketone occurs with inversion of the stereochemistry of the fluoroalkene. These results broaden the potential utility of reagent **11** in the stereoselective synthesis of fluoroalkenes, and we are currently investigating this avenue. Morpholine amides **12** and **18** were transformed to amine **35** and methyl ester **36**, respectively (Figure 10).

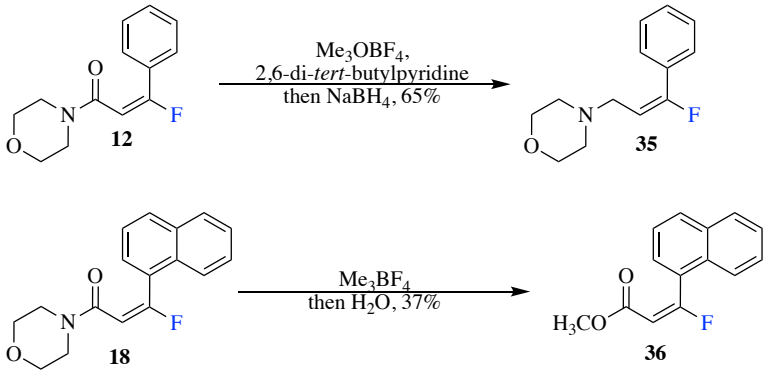
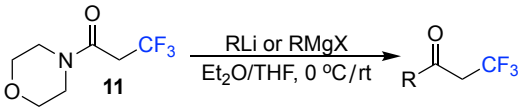


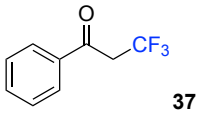
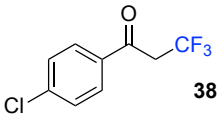
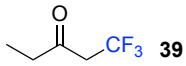
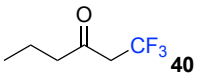
Figure 10: Reduction of amides to an amine or an ester

The conversion of morpholine amide **12** to amine **35** is accomplished by activation with trimethyloxonium tetrafluoroborate in the presence of 2,6-di-*tert*-butylpyridine, followed by the addition of $NaBH_4$, which are similar to the conditions reported by Toste and workers.[29] Morpholine amide **18** was also activated with trimethyloxonium tetrafluoroborate and then treated with water to produce the methyl ester **36**. Both of these reactions occur with complete retention of the (*E*)-fluoroalkene and demonstrate the potential uses of the products obtained from the morpholine 3,3,3-trifluoropropanamide.

We hypothesize that a competing nucleophilic substitution reaction that will replace the morpholine with a phenyl, *p*-chlorophenyl, ethyl, or propyl group. The products **37**−**40** (Table 5) of this transformation were observed when the reaction is run at 0 °C and a minor presence is observed at −78 °C. Optimization efforts of this by-product failed and efforts to isolate these structures were not successful. We theorize that the presence of the trifluoromethyl group on the compound increases the volatility of this by-product because we only observe the diagnostic triplet at –59.22 ppm in the crude reaction mixture. We noticed performing the reaction consistently at sub-zero temperatures reduced presence of the by-products.

Table 5: Observed products of competing nucleophilic reaction

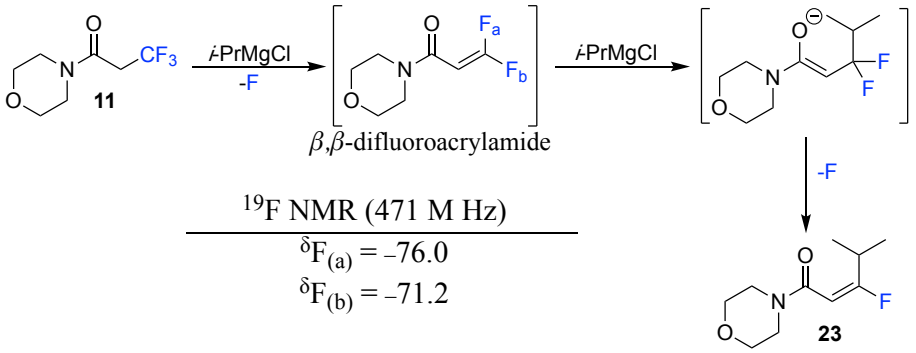


Entry	Nucleophile	Product	Yield
1	C_6H_5MgBr	 **37**	20%
2	*p*-ClC_6H_4MgCl	 **38**	25%
3	EtMgBr	 **39**	25%
4	*n*-PrMgCl	 **40**	33%

[a]Competing reaction generating these products were observed by ^{19}F NMR

3.3 Mechanistic Experiment by ^{19}F NMR

We have attempted to understand how we could obtain a mono-fluoroalkene from a trifluoromethylated compound. In the scheme below, we assumed that the first equivalent Grignard reagent acts as a base to extract a proton and produces a transiently stabilized difluoroacrylate. This transformation is accomplished by elimination of the fluoride after formation of the enolate. This intermediate then undergoes an electrophilic addition at the β-carbon by a second equivalent of Grignard reagent to form a new C–C bond and give β-fluoro-α,β-unsaturated amides.



Scheme 1: Proposed reaction mechanism and diagnostic peaks observed in the ^{19}F NMR spectrum of difluoroacrylate

Observation of the diagnostic peaks of the β,β-difluoroacrylamide by ^{19}F NMR at –71.2 and –76.0 ppm are similar to the data reported by Shimada, Konno, and Ishihara.[121] In order to study the reaction mechanism, a solution of isopropylmagnesium chloride in THF-d_8 was cooled to –78 ºC, treated with a solution of amide **11** (one equiv.) in THF-d_8, and then stirred for 18 h at rt. The mixture was analyzed by ^{19}F NMR (471 MHz, THF-d_8) at rt. Following the addition of the second equivalent of isopropyl magnesium chloride, the (*E)*-fluoroalkene **23** is observed. The enolate intermediate is not observed by ^{19}F NMR, suggesting that the elimination of fluoride to generate is instantaneous during the formation of the difluoroacrylate. The stereochemical outcome of the addition of nucleophiles to *gem*-difluoroalkenes is known in the literature to provide the (*E*)-isomer with high selectivity.[25] These results apply to this case, because the electronic repulsion of the fluorine atom controls the transition state prior to the elimination and formation of the (*E*)-fluoroalkene.

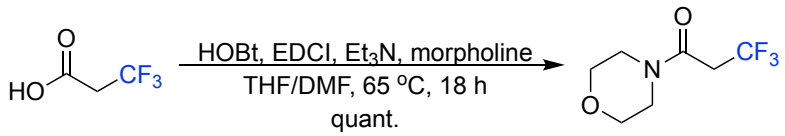
3.4 Conclusion

In summary, morpholine 3,3,3-trifluoropropanamide **11** provides access to (*E)*-β-fluoro-α,β-unsaturated amides upon the addition of two equivalents of alkyl, aryl, and heteroaryl Grignard reagents. It avoids the use of toxic metals such as chromium. This one-pot

transformation provides good yields and a high level of stereocontrol for the *E*-fluoroalkene. ^{19}F NMR experiments demonstrate the formation of the β,β-difluoroacrylamide as the likely mechanistic intermediate. Also, the addition of an organolithium reagent provides the (*Z)*-β-fluoro-α,β-unsaturated ketone. The transformation of the morpholine amides into other functional groups is demonstrated. Overall, reagent **11** offers a simple process for accessing fluoroalkenes, which have a growing utility in medicinal chemistry and drug design. This role encourages the future expansion of the scope of use for the morpholine 3,3,3-trifluoropropanamide **11** as well as methods to produce it.

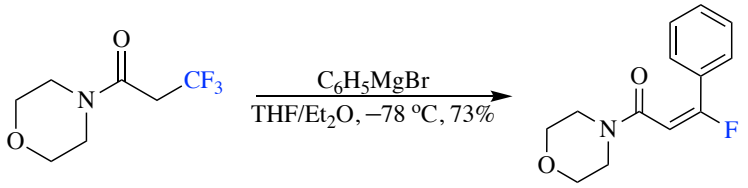
3.5 Experimental and Characterization Data

All reactions were performed under inert gass in oven-dried glassware and solvents were dried over molecular seives. Thin-layer chromatography was conducted using MilliporeSigma TLC silica gel 60 F_{254} plates. Preparative thin-layer chromatography was performed using Sorbent Technologies silica G prep TLC plates with UV254. Flash chromatography was conducted using SiliCycle Siliaflash silica gel P60 (40–63 μm) 60Å. Melting points were taken on an OptiMelt apparatus from Stanford Research Systems and are not corrected. NMR spectra were recorded on a Bruker Topspin Avance III HD 500 MHz spectrometer equipped with prodigy cryoprobe or a Bruker Avance III HD 400 MHz spectrometer. The residual solvent peaks were used as an internal standard for ^{1}H and ^{13}C NMR spectra whereas trifluorotoluene was used as an added internal standard for ^{19}F NMR spectra. Mass spectrometry were acquired by the Department of Chemistry at the University of Mississippi using SYNAPT HD Mass Spectrometer from Waters. Infrared spectra were recorded on Agilent Technologies Cary 630 FTIR.



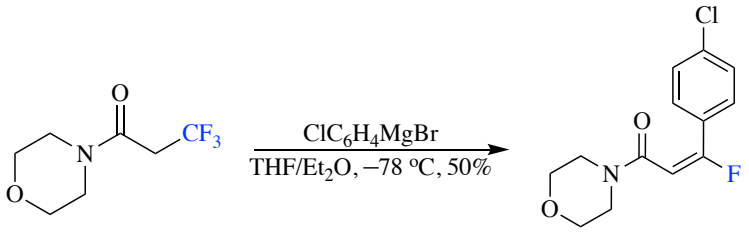
Morpholine 3,3,3-trifluoropropanamide (11). To a solution of 3,3,3-trifluoropropionic acid in THF/DMF (9:1, 150 mL) at rt was added morpholine (1.5 mL, 17 mmol), triethylamine (1.8 mL, 12 mmol), 1-hydroxybenzotriazole hydrate (1.76 g, 13.0 mmol), and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide HCl (2.5 g, 13 mmol). The reaction mixture was heated for 24 h in an oil bath at 65 °C. Next, the reaction mixture was cooled to rt, diluted with EtOAc (50 mL), quenched with a saturated aqueous NH_4Cl (30 mL), and extracted with EtOAc

(3 × 25 mL). The organics were washed with 1.0 N HCl solution (30 mL), saturated aqueous $NaHCO_3$ (30 mL), saturated aqueous NaCl (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by SiO_2 flash chromatography (10→30% EtOAc in hexanes) to yield the title compound **11** as a colorless solid (2.24 g, quant.). Recrystallization from a 1:1 solution of hexanes and cyclohexanes (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: mp 76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (m, 6H), 3.47 (t, J = 4.8 Hz, 2H), 3.23 (q, J = 10.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (q, J_{CF} = 3.3 Hz, 1C), 124.0 (q, J_{CF} = 275.3 Hz, 1C), 66.7, 66.4, 46.8, 42.3, 38.0 (q, J_{CF} = 29.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.41 (t, J_{HF} = 10.0 Hz, 3F); IR (film) ν_{max} 2862, 1653, 1439, 1094 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_7H_{10}F_3NO_2Cs$ $[M+Cs]^+$ 329.9718, found 329.9741; Anal. Calcd for $C_7H_{10}F_3NO_2 \cdot 0.2C_6H_6$: C, 46.29; H, 5.46; N, 6.58. Found: C, 46.62; H, 5.46; N, 6.79.



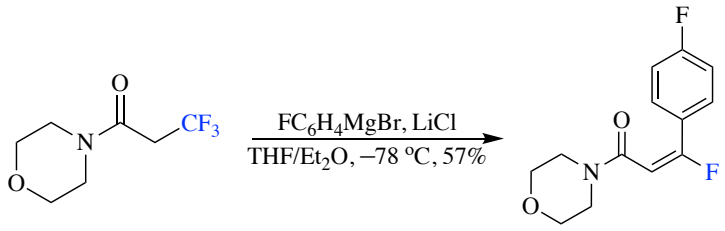
(*E*)-3-Fluoro-1-morpholino-3-phenylprop-2-en-1-one (12). A solution of **11** (100 mg, 0.51 mmol) in THF/Et_2O (1:1, 2 mL) was cooled to –78 °C, treated with a solution of phenylmagnesium bromide (1.0 mL, 1.0 M in THF), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (10→90% EtOAc in hexanes) afforded the title compound **12** as a pale yellow oil (88 mg, 73% yield): ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.56 (d, J = 6.8 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 7.40 (m, 1H), 5.86 (d, J = 19.3 Hz, 1H), 3.61 (d, J = 5.3 Hz, 4H), 3.34 (d, J = 5.2 Hz, 2H), 3.30 (d, J = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (d, J_{CF} = 18.6 Hz, 1C), 161.7 (d, J_{CF} = 257.8 Hz, 1C), 130.7, 130.4 (d, J_{CF} = 28.2 Hz, 1C), 128.5 (2C), 127.2 (d, J_{CF} = 6.0 Hz, 2C), 101.7 (d, J_{CF} = 27.9 Hz, 1C), 66.3 (2C), 46.8, 41.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –96.7 (d, J_{HF} = 19.3 Hz, 1F); IR (film) ν_{max} 2857, 1627, 1433, 1109 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{14}FNO_2Cs$ $[M+Cs]^+$ 368.0063, found 368.0076.

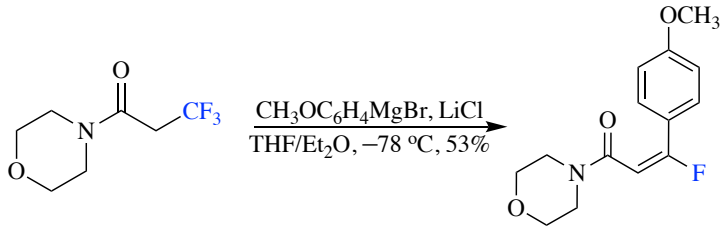


(*E*)-3-(4-Chlorophenyl)-3-fluoro-1-morpholinoprop-2-en-1-one (13). A solution of **11** (100 mg, 0.51 mmol) in THF/Et_2O (1:1, 2 mL) was cooled to –78 °C, treated with a solution of 4-chlorophenylmagnesium bromide (1.0 mL, 1.0 M in Et_2O), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography in (5→70% EtOAc in hexanes) afforded the title compound **13** as a colorless oil (69 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 5.90 (d, J = 19.9 Hz, 1H), 3.61 (m, 4H), 3.39 (app d, J = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J_{CF} = 18.5 Hz, 1C), 161.1 (d, J_{CF} = 257.0 Hz, 1C), 136.8, 128.7 (d, J_{CF} = 28.7 Hz, 1C), 128.7 (2C), 128.6 (d, J_{CF} = 6.2 Hz, 2C), 102.1 (d, J_{CF} = 28.0 Hz, 1C), 66.4 (2C), 46.7, 41.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –

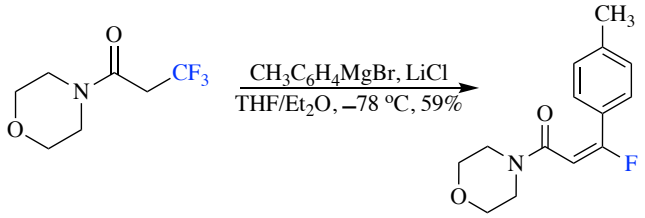
96.1 (d, J_{HF} = 19.9 Hz, 1F); IR (film) ν_{max} 2855, 1623, 1431, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{14}ClFNO_2$ $[M+H]^+$ 270.0697, found 270.0699.



(*E*)-3-Fluoro-3-(4-fluorophenyl)-1-morpholinoprop-2-en-1-one (14). A solution of **11** (100 mg, 0.51 mmol) and LiCl (43.0 mg, 1.0 mmol) in THF/Et_2O (1:1, 8 mL) was cooled to –78 °C, treated with a solution of 4-fluorophenylmagnesium bromide (0.5 mL, 2.0 M in Et_2O), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (8 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→80% EtOAc in hexanes) afforded the title compound **14** as an orange-yellow oil (74 mg, 57%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 5.87 (d, *J* = 19.8 Hz, 1H), 3.62 (m, 4H), 3.39 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1 (d, J_{CF} = 18.6 Hz, 1C), 163.9 (d, J_{CF} = 250.8 Hz, 1C), 161.2 (d, J_{CF} = 257.2 Hz, 1C), 129.6 (dd, J_{CF} = 8.7, 6.2 Hz, 2C), 126.5 (dd, J_{CF} = 28.8, 3.4 Hz, 1C), 115.7 (d, J_{CF} = 22.0 Hz, 2C), 101.5 (d, J_{CF} = 28.2 Hz, 1C), 66.4 (2C), 46.8, 41.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ –95.7 (d, J_{HF} = 19.8 Hz, 1F), –108.3 (ddd, J_{HF} = 13.6, 8.5, 5.3 Hz, 1F); IR (film) ν_{max} 2855, 1625, 1508, 1228, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{14}F_2NO_2$ $[M+H]^+$ 254.0993, found 254.0978.

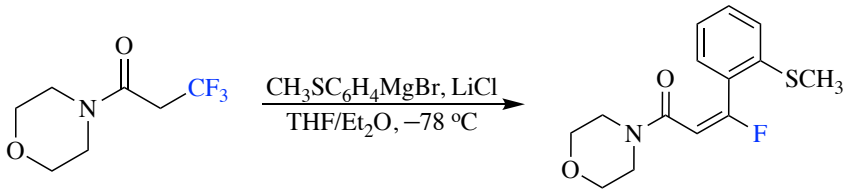


(*E*)-3-Fluoro-3-(4-methoxyphenyl)-1-morpholinoprop-2-en-1-one (15). A solution of **11** (100 mg, 0.51 mmol) and LiCl (65 mg, 1.5 mmol) in THF/Et_2O (1:1, 6 mL) was cooled to –78 °C, treated with a solution of 4-methoxyphenylmagnesium bromide (1.1 mL, 1.0 M in THF), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (6 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→80% EtOAc in hexanes) afforded the title compound **15** as a yellow oil (72 mg, 53%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.76 (d, J = 19.5 Hz, 1H), 3.82 (s, 3H), 3.61 (m, 4H), 3.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7 (d, J_{CF} = 19.0 Hz, 1C), 162.1 (d, J_{CF} = 255.1 Hz, 1C), 161.4, 128.9 (d, J_{CF} = 6.3 Hz, 2C), 122.7 (d, J_{CF} = 28.8 Hz, 1C), 113.8 (2C), 99.9 (d, J_{CF} = 29.0 Hz, 1C), 66.4 (2C), 55.3, 46.8, 41.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –96.2 (d, J_{HF} = 19.5 Hz, 1F); IR (film) ν_{max} 2853, 1604, 1429, 1237, 1111 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{14}H_{16}FNO_3Cs$ $[M+Cs]^+$ 398.0169, found 398.0168.



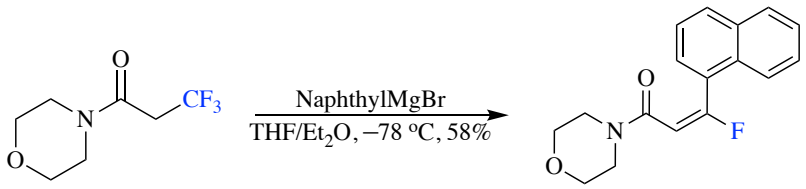
(*E*)-3-Fluoro-1-morpholino-3-(*p*-tolyl)prop-2-en-1-one (16). A solution of **11** (100 mg, 0.51 mmol) and LiCl (43.0 mg, 1.0 mmol) in THF/Et_2O (1:1, 8 mL) was cooled to –78 °C, treated with a solution of *p*-tolylmagnesium bromide (2.0 mL, 0.5 M in Et_2O), and stirred for 4 h. The

reaction mixture was quenched with 0.2 N HCl solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→80% EtOAc in hexanes) afforded the title compound **16** as a pale yellow oil (75 mg, 59%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 5.81 (d, J = 19.3 Hz, 1H), 3.62 (app d, J = 2.6 Hz, 4H), 3.34 (app d, J = 4.0 Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (d, J_{CF} = 18.7 Hz, 1C), 162.0 (d, J_{CF} = 257.5 Hz, 1C), 141.1, 129.2 (2C), 127.5 (d, J_{CF} = 28.3 Hz, 1C), 127.1 (d, J_{CF} = 5.9 Hz, 2C), 100.9 (d, J_{CF} = 28.3 Hz, 1C), 66.3 (2C), 46.8, 41.8, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –96.3 (d, J_{HF} = 19.2 Hz, 1F); IR (film) ν_{max} 2855, 1627, 1431, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{14}H_{17}FNO_2$ $[M+H]^+$ 250.1243, found 250.1273.



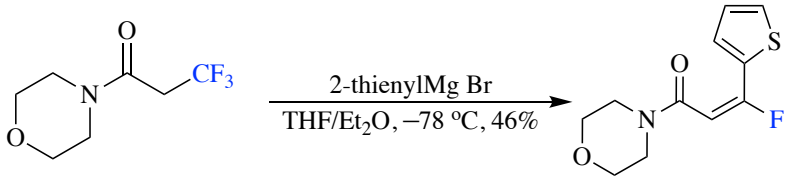
(*E*)-3-Fluoro-3-(2-(methylthio)phenyl)-1-morpholinoprop-2-en-1-one (17). A solution of 2-thioanisolemagnesium bromide (2.0 mL, 0.5 M in THF) and LiBr (88.6 mg, 1.0 mmol) in 1:1 THF/Et_2O (10 mL) was stirred at rt for 1 h, cooled to –78 °C, treated with a solution of **11** (100 mg, 0.5 mmol) in THF (7 mL), and then stirred for 8 h. The reaction mixture was quenched with 0.2 N HCl solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (5→80% EtOAc in hexanes) then preparative TLC (25% Et_2O in CH_2Cl_2) to afforded the title compound **17** as a pale yellow oil (62 mg, 43%) as a

8:1 mixture of *E*/*Z*-isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.05 (d, J = 16.5, 1H), 5.84 (d, J = 37.5 Hz, 1H)*, 3.48 (m, 4H), 3.41 (m, 2H), 3.26 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, J_{CF} = 17.4 Hz, 1C), 163.3 (d, J_{CF} = 263.3 Hz, 1C), 138.3, 131.1 (d, J_{CF} = 2.2 Hz, 1C), 130.6 (d, J_{CF} = 3.4 Hz, 1C), 129.9 (d, J_{CF} = 24.8 Hz, 1C), 126.2, 124.9, 104.5 (d, J_{CF} = 26.8 Hz, 1C), 66.5 (2C), 46.9, 41.9, 16.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.1 (d, J = 16.4 Hz), –87.8 (d, J = 37.7 Hz)*; IR (film) ν_{max} 2920, 2855, 1675, 1627, 1435, 1112 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{14}H_{17}FNO_2S$ $[M+H]^+$ 282.0964, found 282.0944. *denotes the minor (*Z*)-isomer.



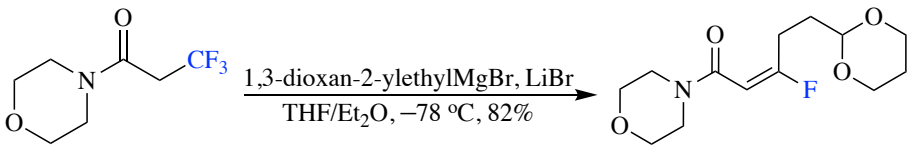
(*E*)-3-Fluoro-1-morpholino-3-(naphthalen-1-yl)prop-2-en-1-one (18). A solution of LiBr (310 mg, 3.57 mmol) in THF (24 mL) was treated with a solution of naphthylmagnesium bromide (21.4 mL, 0.5 M in MeTHF) and stirred for 1 h at rt. Next, the reaction mixture was cooled to –78 °C and a solution of **11** (352 mg, 1.79 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 4 h at –78 °C and then quenched with 1 N HCl solution (10 mL). The resultant mixture was diluted with EtOAc (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization from a solution of hexanes/EtOAc (8:2, by slow evaporation) followed by SiO_2 flash chromatography (8:2→7:3 hexanes/EtOAc) afforded the title compound **18** as a colorless solid (297 mg, 58%): mp 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.0, 2.8 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.56 (m, 2H),

7.49 (t, J = 7.7 Hz, 1H), 6.18 (d, J = 16.7 Hz, 1H), 3.42 (m, 2H), 3.33 (m, 2H), 3.23 (m, 2H), 2.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (d, J_{CF} = 17.4 Hz, 1C), 163.5 (d, J_{CF} = 263.0 Hz, 1C), 133.4 (d, J_{CF} = 1.3 Hz, 1C), 131.4 (d, J_{CF} = 2.0 Hz, 1C), 130.3 (d, J_{CF} = 1.1 Hz, 1C), 128.8 (d, J_{CF} = 4.7 Hz, 1C), 128.7, 128.0 (d, J_{CF} = 24.9 Hz, 1C), 127.3 (d, J_{CF} = 1.2 Hz, 1C), 126.5, 124.9, 124.6 (d, J_{CF} = 3.3 Hz, 1C), 104.9 (d, J_{CF} = 26.9 Hz, 1C), 66.5 (d, J_{CF} = 30.4 Hz, 1C), 66.1 (d, J_{CF} = 38.7 Hz, 1C), 46.9, 41.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ –82.9 (d, J_{HF} = 16.9 Hz, 1F); IR (film) ν_{max} 3010, 1670, 1618, 1437, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{17}H_{17}FNO_2$ $[M+H]^+$ 286.1243, found 286.1244.

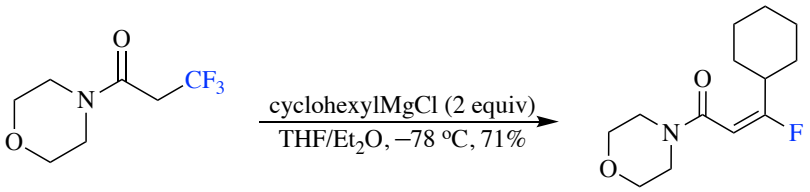


(*E*)-3-Fluoro-1-morpholino-3-(thiophen-2-yl)prop-2-en-1-one (19). A solution of **11** (100 mg, 0.51 mmol) in THF (17 mL) was cooled to –78 °C, treated with a solution of 2-thienylmagnesium bromide (1.0 mL, 1.0 M in THF), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (5→60% EtOAc in hexanes) afforded the title compound **19** as a colorless oil (57 mg, 46%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 3.8, 1.2 Hz, 1H), 7.47 (ddd, J = 5.6, 2.8, 1.4 Hz, 1H), 7.05 (ddd, J = 5.1, 3.9, 1.6 Hz, 1H), 5.84 (d, J = 21.4 Hz, 1H), 3.67 (m, 4H), 3.55 (m, 2H), 3.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 (d, J_{CF} = 19.1 Hz), 158.7 (d, J_{CF} = 249.4 Hz), 131.5 (d, J_{CF} = 33.3 Hz), 130.0, 129.9 (d, J_{CF} = 6.9 Hz), 127.0, 99.1 (d, J_{CF} = 29.8 Hz), 66.5 (2C), 46.7, 41.8; ^{19}F NMR

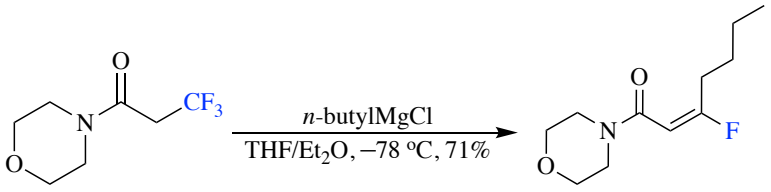
(471 MHz, $CDCl_3$) δ –92.1 (d, J = 21.0 Hz); IR (film) ν_{max} 2853, 2201, 1620, 1415, 1111 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{11}H_{13}FNO_2S$ $[M+H]^+$ 242.0651, found 242.0670.



(*E*)-5-(1,3-Dioxan-2-yl)-3-fluoro-1-morpholinopent-2-en-1-one (20). A solution of **11** (212 mg, 1.07 mmol) and LiBr (186 mg, 2.2 mmol) in THF/Et_2O (1:1, 2 mL) was cooled to –78 °C, treated with a solution of 1,3-dioxan-2-ylethylmagnesium bromide (4.0 mL, 0.5 M in THF), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→80% EtOAc in hexanes) afforded the title compound **20** as a solid (213 mg, 73%). Recrystallization from toluene (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: mp 55–56 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (d, J = 20.4 Hz, 1H), 4.58 (t, J = 5.1 Hz, 1H), 4.09 (dd, J = 10.7, 5.0 Hz, 2H), 3.74 (td, J = 12.4, 2.5 Hz, 2H), 3.69–3.60 (m, 6H), 3.50–3.44 (m, 2H), 2.81 (t, J = 8.0 Hz, 1H), 2.76 (t, J = 8.0 Hz, 1H), 2.06 (dtt, J = 13.4, 12.5, 5.0 Hz, 1H), 1.90–1.84 (m, 2H), 1.32 (dt, J = 13.5, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (d, J_{CF} = 269.4 Hz, 1C), 164.4 (d, J_{CF} = 20.7 Hz, 1C), 101.1, 100.1 (d, J_{CF} = 26.5 Hz, 1C), 66.8 (2C), 66.6 (2C), 46.5, 41.9, 31.3, 25.7, 24.7 (d, J_{CF} = 23.9 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.6 (td, J_{HF} = 24.3, 20.9 Hz, 1F); IR (film) ν_{max} 2851, 1677, 1619, 1429, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{20}FNO_4Cs$ $[M+Cs]^+$ 406.0431, found 406.0439.

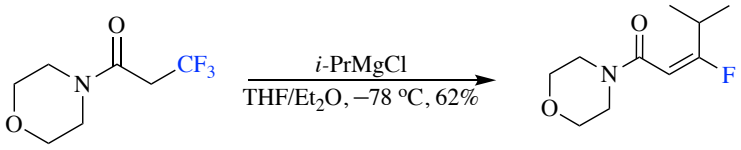


(*E*)-3-Cyclohexyl-3-fluoro-1-morpholinoprop-2-en-1-one (21). A solution of **11** (100 mg, 0.51 mmol) in THF/Et_2O (1:1, 3 mL) was cooled to –78 °C, treated with a solution of cyclohexylmagnesium chloride (0.92 mL, 1.3 M in 1:1 THF/toluene), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→80% EtOAc in hexanes) afforded the title compound **21** as a colorless oil (87 mg, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, J = 21.2 Hz, 1H), 3.77–3.55 (m, 8H), 3.20 (dt, J = 33.2, 11.9 Hz, 1H), 1.76–1.63 (m, 5H), 1.43 (q, J = 12.4 Hz, 2H), 1.31 (q, J = 12.9 Hz, 2H), 1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (d, J_{CF} = 272.0 Hz, 1C), 164.5 (d, J_{CF} = 21.7 Hz, 1C), 98.1 (d, J_{CF} = 27.9 Hz, 1C), 66.6, 66.5, 46.4, 41.7, 38.3 (d, J_{CF} = 22.0 Hz, 1C), 31.5, 28.5 (2C), 25.5 (2C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –93.4 (dd, J_{HF} = 33.0, 21.2 Hz, 1F); IR (film) ν_{max} 2928, 2853, 1631, 1433, 1114 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{20}FNO_2Cs$ $[M+Cs]^+$ 374.0533, found 374.0541.



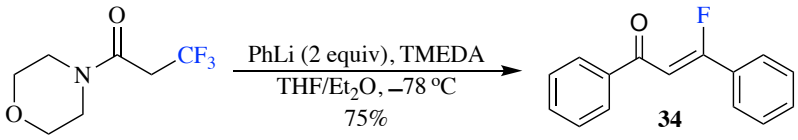
(*E*)-3-Fluoro-1-morpholinohept-2-en-1-one (22). A solution of **11** (100 mg, 0.51 mmol) in THF/Et_2O (1:1, 3 mL) was cooled to –78 °C, treated with a solution of *n*-butylmagnesium

chloride (1.0 mL, 2.0 M in Et_2O), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→80% EtOAc in hexanes) afforded the title compound **22** as a colorless oil (78 mg, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, J = 20.8 Hz, 1H), 3.68–3.45 (m, 8H), 2.68 (dt, *J* = 25.2, 7.6 Hz, 2H), 1.57 (p, *J* = 7.6 Hz, 2H), 1.38 (q, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (d, J_{CF} = 269.0 Hz, 1C), 164.6 (d, J_{CF} = 21.5 Hz, 1C), 99.7 (d, J_{CF} = 27.1 Hz, 1C), 66.8, 66.6, 46.5, 41.8, 29.5 (d, J_{CF} = 23.4 Hz, 1C), 28.0, 22.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –81.7 (td, J_{HF} = 25.2, 21.0 Hz, 1F); IR (film) ν_{max} 2859, 1675, 1619, 1426, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{11}H_{18}FNO_2Cs$ $[M+Cs]^+$ 348.0376, found 348.0348.



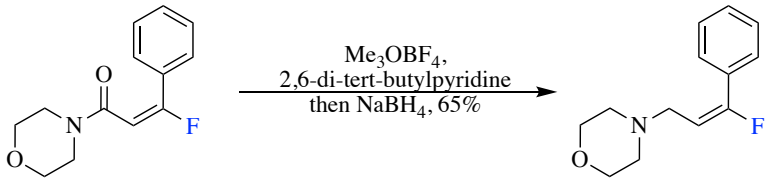
(*E*)-3-Fluoro-4-methyl-1-morpholinopent-2-en-1-one (23). A solution of isopropylmagnesium chloride (2.2 mL, 2.0 M in THF) and LiCl (184 mg, 4.34 mmol) in THF (36 mL) was stirred at rt for 1 h, cooled to −78 °C, treated with a solution of **11** (428 mg, 2.17 mmol) in THF (7 mL), and stirred for 4 h. The reaction mixture was quenched with 1.0 N HCl solution (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with saturated aqueous NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (20→60% EtOAc in hexanes) afforded the title compound **23** as a colorless oil (272.4 mg, 62%): ^{1}H NMR (500 MHz, $CDCl_3$); δ 5.67 (d, *J* = 20.9 Hz, 1H), 3.70–3.58 (m, 6H), 3.55 (m, 1H), 3.48 (m, 2H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (d,

J_{CF} = 272.9 Hz, 1C), 164.6 (d, J_{CF} = 21.5 Hz, 1C), 98.1 (d, J_{CF} = 27.5 Hz, 1C), 66.8, 66.6, 46.6, 41.9, 28.7 (d, J_{CF} = 23.1 Hz, 1C), 18.8 (2C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –98.2 (dd, J_{HF} = 34.0, 21.0 Hz, 1F); IR (film) ν_{max} 2857, 1675, 1618, 1429, 1113 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{10}H_{16}FNO_2Cs$ $[M+Cs]^+$ 334.0220, found 334.0236.

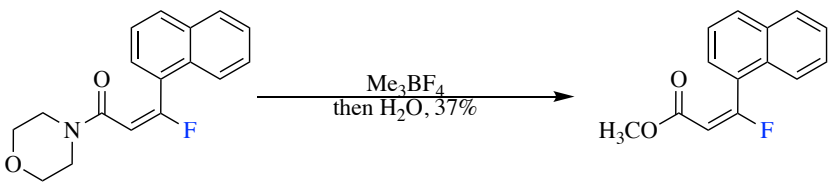


34

(*Z*)-3-Fluoro-1,3-diphenylprop-2-en-1-one (34). A solution of **11** (100 mg, 0.51 mmol) and TMEDA (0.15 mL, 1.02 mmol) in THF (2 mL) was cooled to −78 °C, treated with a solution of phenyllithium (1.0 mL, 1.9 M in dibutylether), and stirred for 4 h. The reaction mixture was quenched with 0.2 N HCl solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (5→80% EtOAc in hexanes) afforded the title compound **34** as yellow oil (105 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 6.8 Hz, 2H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.52–7.44 (m, 5H), 6.80 (d, *J* = 34.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 165.2 (d, J_{CF} = 276.5 Hz, 1C), 138.6, 132.9, 131.6, 130.9 (d, J_{CF} = 26.2 Hz, 1C), 128.9 (d, J_{CF} = 2.1 Hz, 2C), 128.6 (2C), 128.3 (2C), 125.8 (d, J_{CF} = 8.0 Hz, 2C), 101.7 (d, J_{CF} = 6.9 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –97.6 (d, J_{HF} = 34.2 Hz, 1F); IR (film) ν_{max} 3058, 1636, 1284, 1208 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{15}H_{11}FOCs$ $[M+Cs]^+$ 358.9848, found 358.9846. All data matched the reported data.[1]



(*E*)-4-(3-Fluoro-3-phenylallyl)morpholine (35). A solution of amide **12** (341 mg, 1.45 mmol) in CH_2Cl_2 (24 mL) was treated with trimethyloxonium tetrafluoroborate (578 mg, 3.91 mmol) and 2,6-di-*tert*-butylpyridine (0.94 mL, 4.22 mmol), and the reaction mixture was stirred for 24 h at rt. Next, the reaction mixture was cooled to 0 °C, diluted with methanol (15 mL), and stirred for 20 min at 0 °C. $NaBH_4$ (564 mg, 14.9 mmol) was added and the resultant mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and diluted with CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (7:3 hexanes/EtOAc with 0.5% AcOH→7:3 hexanes/EtOAc with 0.5% Et_3N) afforded the title compound **35** as colorless oil (27 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H), 7.43–7.38 (m, 3H), 5.53 (dt, J = 21.4, 7.5 Hz, 1H), 3.72 (t, J = 4.7 Hz, 4H), 3.15 (d, J = 7.5 Hz, 2H), 2.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, J_{CF} = 246.0 Hz, 1C), 131.4 (d, J_{CF} = 29.4 Hz, 1C), 129.4 (d, J_{CF} = 1.4 Hz, 1C), 128.3 (2C), 128.0 (d, J_{CF} = 4.8 Hz, 2C), 104.5 (d, J_{CF} = 26.7 Hz, 1C), 66.8 (2C), 54.4 (d, J_{CF} = 10.1 Hz, 1C), 53.3 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –95.0 (d, J_{HF} = 21.1 Hz, 1F); IR (film) ν_{max} 2959, 2918, 2853, 2808, 1677, 1115, 1060 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{17}FNO$ $[M+H]^+$ 222.1294 found 222.1296.



Methyl (*E*)-3-fluoro-3-(naphthalen-1-yl)acrylate (36). A solution of amide **18** (38 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was treated with trimethyloxonium tetrafluoroborate (97 mg, 0.66 mmol) and stirred for 24 h at rt. The resultant mixture was concentrated under reduced pressure, diluted with THF (3 mL), treated with H_2O (2 mL), and stirred for 1 h at rt. Next, the mixture was added to H_2O (4 mL) and acidified to pH 2. Then, the mixture was extracted with Et_2O (3 × 10 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (8:2 hexanes/EtOAc) afforded the title compound **36** as a colorless oil (11.1 mg, 37%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.89 (m, 3H), 7.64 (m, 1H), 7.57–7.49 (m, 3H), 6.18 (d, J = 16.8 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (d, J_{CF} = 271.0 Hz, 1C), 165.2 (d, J_{CF} = 23.5 Hz, 1C), 133.2 (d, J_{CF} = 1.7 Hz, 1C), 131.2 (d, J_{CF} = 3.0 Hz, 1C), 130.6, 128.8, 128.8, 128.5, 128.0 (d, J_{CF} = 24.0 Hz, 1C), 127.1 (d, J_{CF} = 1.2 Hz, 1C), 126.3, 124.6, 104.3 (d, J_{CF} = 32.0 Hz, 1C), 51.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.2 (d, J_{HF} = 16.8 Hz, 1F); IR (film) ν_{max} 2952, 1731, 1666, 1202, 1101 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{14}H_{10}FO_2$ $[M–H]^-$ 229.0665, found 229.0663.

CHAPTER IV

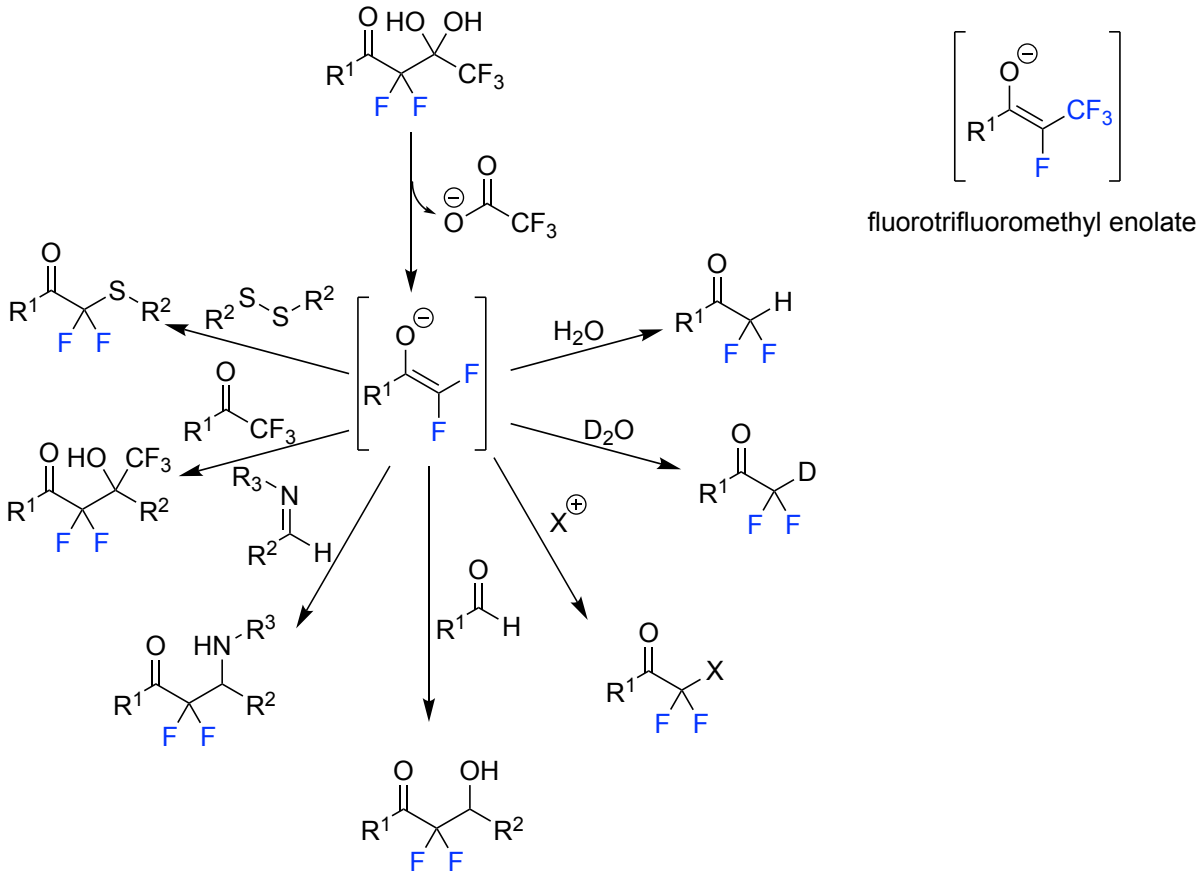
SYNTHESIS OF FLUOROTRIFLUOROMETHYLENE

4.1 Introduction

4.1.1 Heavily Fluorinated Methylene and Methodology

Fluorine has an important reputation in pharmaceutical and the drug discovery process. A survey of the top 50 small molecule pharmaceuticals by retail sales in 2018 showed that 36% of the drugs are fluorinated but only one anesthetic drug contains a highly fluorinated methylene, sevoflurane.[130] In fact, there are only a few pharmaceuticals that bear a difluoromethylene.[131,133] The strategic incorporation of fluorine can serve as a bioisostere;[133] for example, compounds bearing a fluoro-substituted quaternary carbon are isosteric with a more common tertiary substituted carbon.[117] Unfortunately, the incorporation of a heavily fluorinated methylene into an organic molecule is challenging. There are a several methods to fluorinate a carbon atom or add a trifluoromethyl group, but none exist for fluorotrifluoromethylation. [23,30,51,52,55,57,58,132] Trifluoromethylation is typically achieved through the use of trifluoromethylating reagents such as Togni and Umemoto reagents.[51] Hence, our goal is to develop efficient methodology to generate organic compounds bearing a fluorotrifluoromethylene fragment. We intended to accomplish this goal by expanding the previously developed trifluoroacetate-release reaction.[96] The Colby group was able to synthesize difluoromethylene (CF_2) containing molecules from α,α-

difluoroenolates via a unique carbon-carbon fragmentation strategy that releases trifluoroacetate and we envisioned generating fluorotrifluoromethylmethylene centers in a similar fashion (Scheme 2).



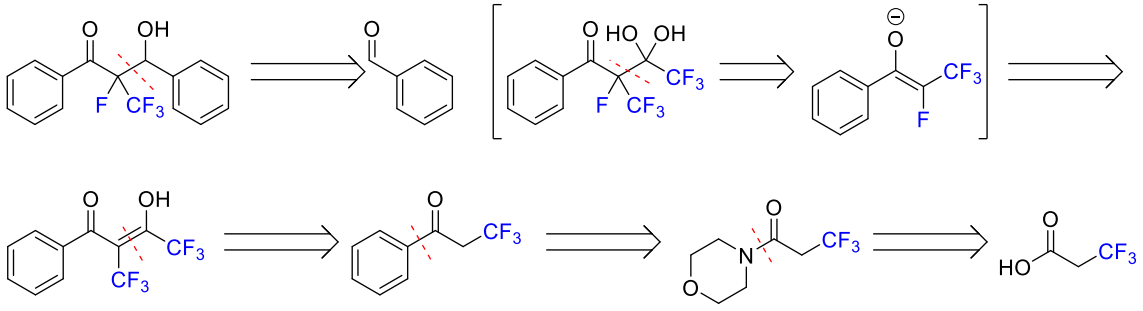
Scheme 2: Generation and reaction of difluoroenolates produced by the release of trifluoroacetate.

4.1.2 Generation of *α,α*-Difluorinated Enolates

In 2011, the Colby group introduced the highly fluorinated *gem*-diols,[96] which provide access to difluoroenolates under mild conditions. The highly fluorinated *gem*-diols release trifluoroacetate and generate a difluoroenolate *in situ* that undergoes aldol addition,[57,136]

Mannich,[132,137] halogenation[138] and sulfenylation[139] reactions. The Colby lab characterized the scope of this process and was able to trap the difluoroenolate with H_2O as difluoromethyl ketones[140] or with D_2O as deuterodifluoromethyl ketones.[141] The difluoromethylene compounds generated were tested for their activity as agonist of the γ-aminobutyric acid type B receptors and some showed promising activity.[142] In this study, we explored the potential of this method to introduce a fluorotrifluormethylmethylene into organic molecules and generate compounds containing highly fluorinated methylenes. However, the greatest challenge in this endeavor was developing methodologies to generate *α*-fluoro-*α*-trifluoromethylated *gem*-diols. Therefore, we also investigated fluorination,[135] trifluoromethylation,[51] and enolboration reactions.[55,59]

Initially, we envisioned accessing α-fluoro-α-trifluoromethylinated *gem*-diols from the monofluorination of *α*-trifluoromethyl-4,4,4-triflurомethyl-1,3-butanediones. We hypothesized that the *α*-trifluoromethyl-4,4,4-triflurомethyl-1,3-butanedione can be generated by treating 4,4,4-triflurомethyl-1,3-butanediones with trifluoromethylating reagents.[114] We imagined that the nucleophilic substitution of the morpholine 3,3,3-trifluoropropanamide, which is generated by amidation, with an organolithium[143] would give the ketone intermediates (Scheme 3).



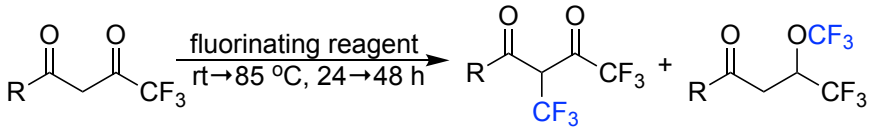
Scheme 3: Retrosynthetic strategy to molecules containing a fluortrifluoromethyl group.

4.2 Synthesis and Discussion

4.2.1 Trifluoromethylation of Dione Substrates

With ample amounts of 4,4,4-trifluoro-1,3-dione containing substrates, we began the synthesis by treating 4,4,4-trifluoro-[2-naphthyl]-1,3-butanedione **42** and 4,4,4-trifluoro-[2-furyl]-1,3-butanedione **43** with Togni I, Togni II, and Umemoto's trifluoromethylating reagents.[52] We did not observe diagnostic peaks that correspond to the product or for any potential by-product in the ^{19}F NMR. However, the Togni reagents showed four major peaks by ^{19}F NMR and we examined these conditions in more details. We realized these reagents are electrophilic and the site for the desired trifluoromethylation is not nucleophilic. We surmised that the observed reactivity was due to decomposition of our starting material and possible *o*-trifluoromethylation. Catalytic amounts were added to reactions to investigate any changes in reactivity, but despite variations in the temperature and solvent, the results were consistent with complex reactivity (Table 6). Overall, the Togni I reagent provided less reactivity than the Togni II reagent. Umemoto's reagent on the other hand was inferior to both Togni reagents. In a last effort we attempted to trifluoromethylate the diones using the Ruppert-Prakash reagent but this route also failed and was abandoned.

Table 6: Attempts at trifluoromethylation using common reagents



R = 2-naphthyl (**42**) or 2-furyl (**43**)

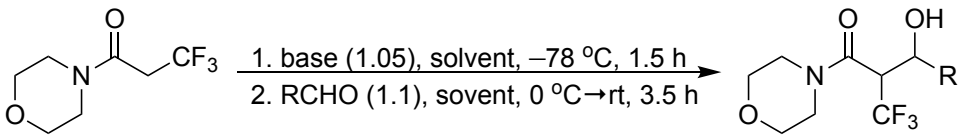
entry	fluorinating reagent	CuI (cat.)	sovlent	^{19}FNMR observation
1	Togni II	-/+	CH_3CN	complex mixture
2		-/+	CH_3CN/DMF	complex mixture
3		-/+	DMF	complex mixture
4	Togni I	-/+	CH_3CN	complex mixture
5		-/+	CH_3CN/DMF	complex mixture
6		-/+	DMF	complex mixture
7	Umemoto	-/+	CH_3CN	sm
8		-/+	CH_3CN/DMF	complex mixture
9		-/+	DMF	complex mixture

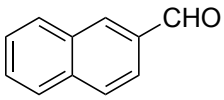
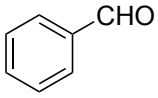
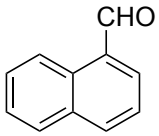
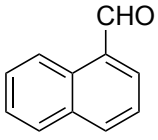
4.2.2 Aldol Reaction of Morpholine 3,3,3-Trifluoropropanamide

Next, we attempted nucleophilic substitution of the morpholine 3,3,3-trifluoropropanamide to generate a ketone but we quickly realized that β-fluoro elimination is the predominant pathway. Although we observed the generation of the ketone by ^{19}F NMR, isolation was not successful due to volatility of the compound. Next, we investigated the formation of the enolate. We explored the use of the base, LDA, to generate the enolate and make α-trifluoromethyl-β-hydroxyl amides by an aldol reaction. However, these efforts were unsuccessful despite variations in the base, aldehyde, solvent and temperature (Table 7). We consistently retrieved the unreacted morpholine 3,3,3-trifluoropropanamide and aldehyde. We

treated the morpholine 3,3,3-trifluoropropanamide with LDA and LiHMDS in an effort to promote the enolate to form we believe that the formation of the enolate is the rate-limiting step in this transformation. Unfortunately, this approach was not successful.

Table 7: Formation of the enolate and subsequent aldol reaction

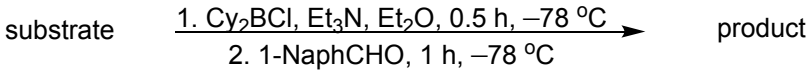


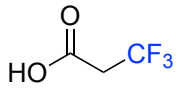
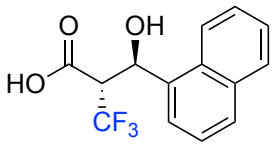
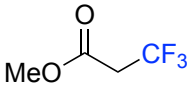
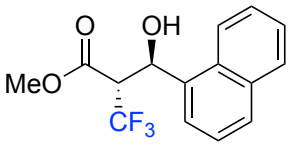
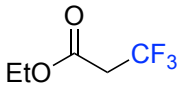
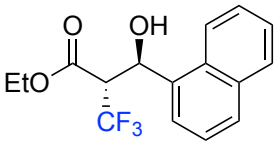
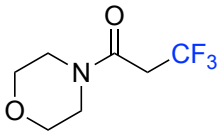
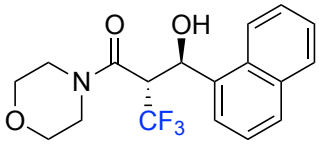
entry	base	solvent	aldehyde
1	LDA	THF	
2	LDA	Et_2O	
3	LDA	THF/Et_2O	
4	LDA	CH_2Cl_2	
5	LDA	THF	
6	LDA	Et_2O	
7	LDA	THF/Et_2O	
8	LDA	CH_2Cl_2	
9	LDA	THF	
10	LDA	Et_2O	
11	LDA	THF/Et_2O	
12	LDA	CH_2Cl_2	
13	LiHMDS	THF	
14	LiHMDS	Et_2O	
15	LiHMDS	THF/Et_2O	
16	LiHMDS	CH_2Cl_2	

4.2.3 Aldol Reactions from Enolboration and Fluorination

We turned our efforts to the enolboration of 3,3,3-trifuoropropionic acid **44** to generate anti-diastereomers of α-trifluoromethyl-β-hydroxyl carboxylic acid as reported by Ramachandran and coworkers.[59] We were able to reproduce their findings with similar yields. Also, we tested the method using methyl and ethyl ester derivatives of the 3,3,3-trifluoropropionic acid. The yield decreased when we substituted the acid with methyl or ethyl ester to 59% and 37%, respectively (Table 8). However, when the terminal carboxylic acid is replaced with a morpholine amide, only trace amounts of desired α-trifluoromethyl-β-hydroxyl amide were observed. Attempts to optimize this transformation lead to an increased yield of the ethyl acetate product **49** from 37% to 60%. Next, oxidation of the β-hydroxyl group to a ketone using Dess-Martin periodinane gave the dione. The carboxylate **45** and the acetate **47** and **49** β-hydroxyl underwent oxidation to give 57%, 81%, and 90% yields, respectively. We treated the α-trifluoromethyl-β-keto carboxylic acid with SelectFluor and NFSI at room temperature under anhydrous conditions for 24 h in an attempt to fluorinate the position adjacent to the carbonyl group but these fluorinations were not successful. We believe the carboxylic acid reduced the reactivity of SelectFluor. So, **49** was treated with SelectFluor and NFSI but the desired product was not observed by ^{19}F NMR. The methyl ester analogue was also treated with SelectFluor, and a minor product was observed based on the appearance of a new peak at –73.33 Hz (dd) in the fluorine spectrum. We will continue to explore this transformation but we are also pursuing additional routes.

Table 8: Enolboration of 3,3,3-trifuoropropionic acid, esters, and amide derivatives to generate α-trifluoromethyl-β-hydroxyl intermediates



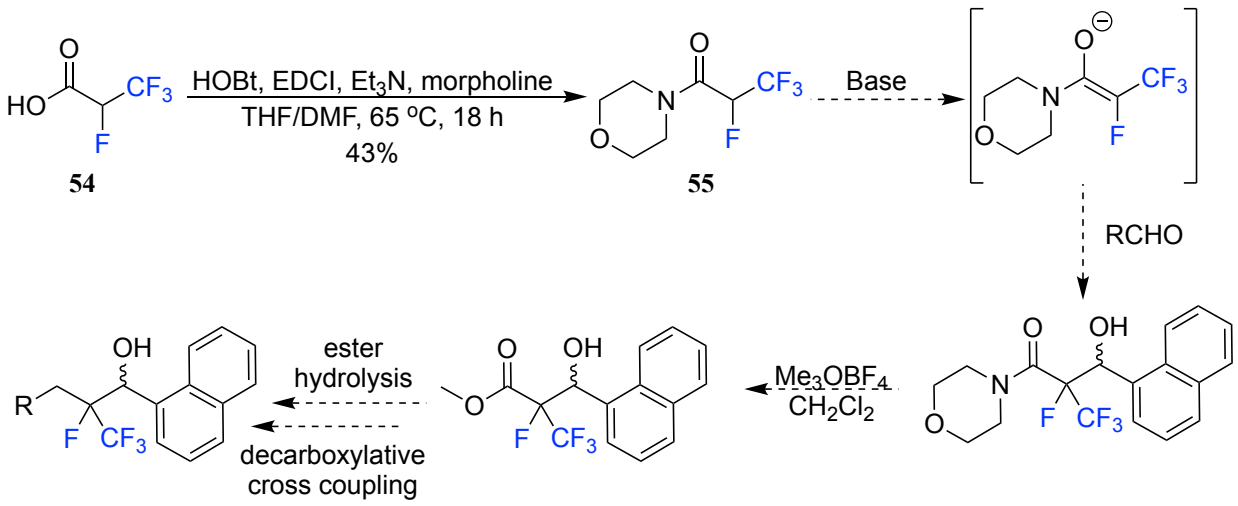
Entry	Substrate	Product	Yield
1	 **44**	 **45**	80%
2	 **46**	 **47**	59%
3	 **48**	 **49**	37%
4	 **11**	 **50**	10%[a]

[a] ^{19}F NMR yield using $CF_3C_6H_5$ as internal standard

4.2.4 Alternative Synthetic Route

We plan to exploit 2,3,3,3,-tetrafluoropropionic acid to generate morpholine 2,3,3,3-tetrafluoropropanamide, which we will using to investigate aldol type reactions to access α-fluoro-α-trifluoromethyl-β-hydroxyl intermediates (Scheme 4). These products will be esterified

to prepare for a decarboxylative coupling and give us the final fluorotrifluoromethylene-containing compounds.[144] We synthesized mopholine 2,3,3,3-tetrafluoropropanamide in 43% yield and we are working to optimize this yield and scale-up the process.

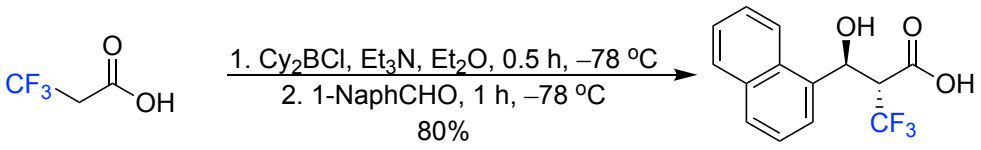


Scheme 4: Alternative route to accessing intermediates containing fluorotrifluromethylmethylene.

4.3 Conclusion

We will continue our ongoing efforts to generate a library of fluorotrifluoromethylene-containing organic compounds using morpholine 2,3,3,3-tetrafluoropropanamide as a substrate. At the same time, we will continue the efforts to fluorinate ethyl α-trifluoromethyl-β-ketocarboxylate derivatives. We aim to pursue these two approaches to create novel synthetic methods to synthesize a new fluorinated moiety. The potential value of the fluorotrifluoromethyl group has not been but this deficiency drives the need for new synthetic methods for medicinal chemistry research.

4.4 Experimental and Characterization Data



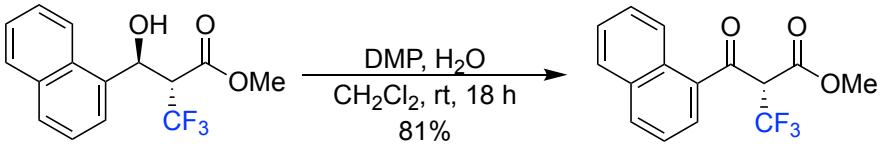
Representative Reaction Procedure for the Enolboration: To a solution of chlorodicyclohexylborane 1 M in hexanes 9 (2.7 mL, 2.7 mmol) in Et_2O (9.0 mL) at –78 °C was added Et_3N (0.40 mL, 2.7 mmol) followed by ethyl 3,3,3-trifluoropropionic acid **44** (0.1 mL, 1.1 mmol). The mixture was stirred for 30 min. 1-Naphthaldehyde (0.22 mL, 1.65 mmol) was added dropwise and the reaction mixture was stirred for 5 hours at –78 °C. The reaction was quenched with aqueous $NaHCO_3$ (2.5 mL) and the organics were separated and extracted with aqueous $NaHCO_3$ (3 × 5 mL). The aqueous layers were combined, acidified to pH 2 with 6 M HCl, then extracted with Et_2O (3 × 15 mL). The organics were combined and dried with Na_2SO_4, filtered, and concentrated under reduced pressure. SiO_2 flash chromatography in EtOAc/hexanes (5→40%, 0.1% AcOH additive) afforded the **45** in (258 mg, 80%).

(*R*)-2-(1-Naphthoyl)-3,3,3-trifluoropropanoic acid (45). See representative reaction procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 5.0 Hz, 1H), 7.91 (dd, J = 10.0, 10.0 Hz, 2H), 7.66 (d, J = 10.0 Hz, 1H), 7.54 (m, 3H), 6.05 (d, $J_{H,F}$ = 5.0 Hz, 1H), 3.91 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 170.6, 134.7, 134.1, 129.8, , 126.1, 124.9, 122,2, 68.3, 55.82 (q, $J_{C,F}$ = 26.0 Hz, 1C); ^{19}F NMR (470 MHz, $CDCl_3$) δ –66.32 (d, $J_{H,F}$ = 9.4 Hz, 3F).

Methyl (*R*)-3,3,3-trifluoro-2-((*S*)-hydroxy(naphthalen-1-yl)methyl)propanoate (47). See representative reaction procedure. The aqueous layers were combined and extracted with CH_2Cl_2 (3 × 5 mL). SiO_2 flash chromatography in EtOAc/hexanes (5→40%) afforded the **47** (195 mg, 59%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.88 (dd, J = 8.0, 8.0 Hz, 2H),

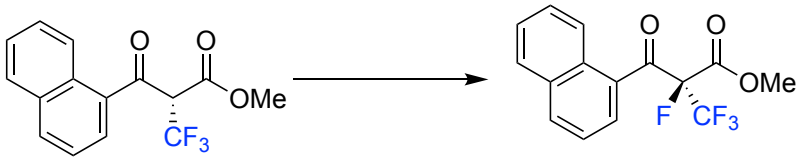
7.55 (m, 4H), 6.03 (t, $J_{H,F}$ = 8.0, 4.0 Hz, 1H), 3.86 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 134.3, 129.4, 127.0, 126.0, 125.4, 124.5, 122.3, 68.2, 55.4 (q, $J_{C,F}$ = 26.0 Hz, 1C), 53.0, 35.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.99 (d, $J_{H,F}$ = 7.5 Hz, 3F).

Ethyl (*R*)-3,3,3-trifluoro-2-((*S*)-hydroxy(naphthalen-1-yl)methyl)propanoate (49). See representative reaction procedure. SiO_2 flash chromatography in EtOAc/hexanes (5→40%) afforded the **49** (123 mg, 37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 12.0 Hz, 1H), 7.54 (m, 4H), 6.05 (d, $J_{H,F}$ = 4.0 Hz, 1H), 4.17 (q, *J* = 8.0 Hz, 2H), 3.81 (m, 1H), 3,62 (m, 1H) 1.14 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.0, 129.5, 127.0, 126.0, 125.3, 124.5, 122.1, 68.1, 62.3, 55.3 (q, $J_{C,F}$ = 26.0 Hz, 1C), 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.39 (d, $J_{H,F}$ = 7.5 Hz, 3F).



Representative Reaction Procedure for β-Hydroxyl Oxidation: To a mixture of **47** (62 mg, 0.21 mmol) in CH_2Cl_2 (4.0 mL) and H_2O (0.5 mL) was added Dess-Martin periodinane (114 mg, 0.27 mmol). The resultant mixture was stirred at rt for 5 h. The reaction mixture was quenched with a saturated aqueous of $Na_2S_2O_3$ (6.0 mL). Then the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organics were combined, washed with saturated aqueous NaCl (25 mL), dried with Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography in EtOAc/hexanes (5% isogradient) afforded the **52** (56 mg, 90%).

Methyl (*R*)-2-(1-naphthoyl)-3,3,3-trifluoropropanoate (52). See Representative reaction procedure. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR data are not available from campus due to restrictions caused by the COVID-19 epidemic.



Methyl (*S*)-2-(1-naphthoyl)-2,3,3,3-tetrafluoropropanoate (54). To a mixture of **52** (56 mg, 0.19 mmol) in MeCN (5 mL) was added SelectFluor (90 mg, 0.25 mmol). The mixture was stirred at rt for 48 h. The reaction mixture was diluted with EtOAc (5 mL) and filtered through Celite. The organics were concentrated under reduced pressure, dissolved in CH_2Cl_2 (5 mL), washed with H_2O (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Preparative TLC in 15% EtOAc:hexanes gave a mixture of **54** and **52** (24 mg, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79, (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.90 (m, 2H), 7.53 (m, 4H), 3.75 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.77 (d, J = 7.5 Hz, 3F), –73.35 (q, J = 7.5 Hz, 1F).

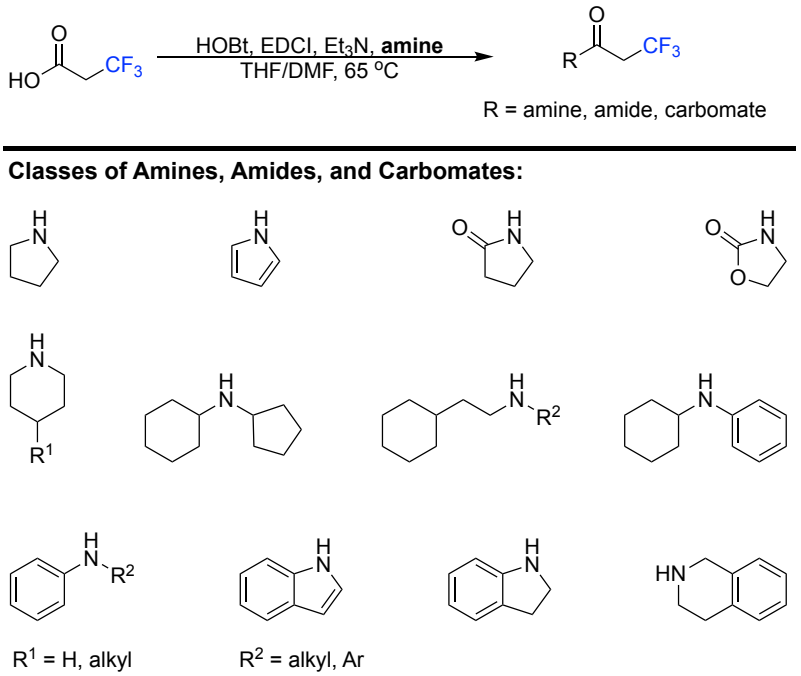
CHAPTER V

CONCLUDING REMARKS AND FUTURE DIRECTIONS

5.1 Conclusions and Future Directions

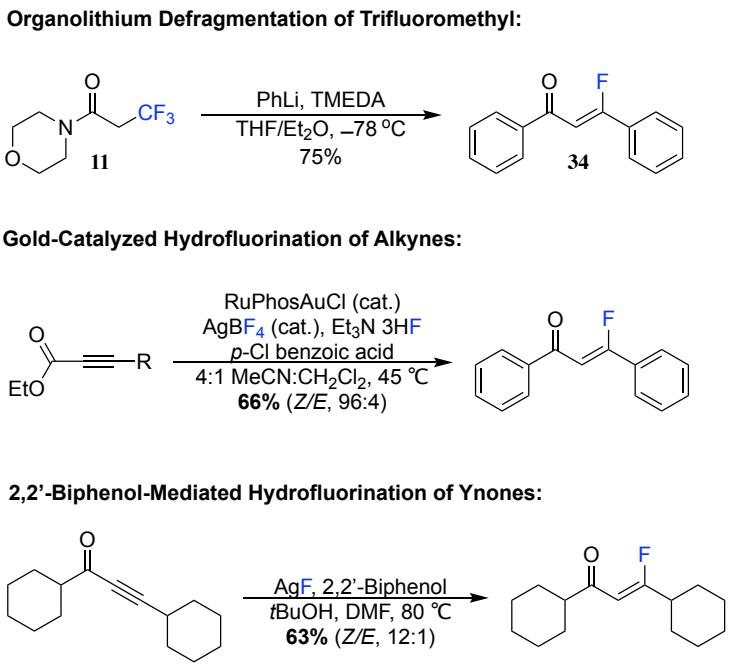
Fluorinated reagents and intermediates are valuable tools in medicinal chemistry. Within this dissertation, we exploited a fluorinated intermediate to make an α-methylene-γ-lactam that is difficult to access with other methods. We successfully applied a trifluoroacetate-release reaction that was critical to converting the fluorinated intermediate into the α-methylene-γ-lactam. The α-methylene-γ-lactam was essential for the completion of the synthesis of L-γ-methyleneglutamine. We demonstrated the versatility of the trifluoroacetate-release strategy and the tolerance of this approach to different substrates with varying degrees of substitution.[96,102]

During the course of the subsequent studies detailed in this dissertation, the morpholine 3,3,3-trifluoropropionamide **11** was invaluable in synthesizing β-fluoro-amides **12–33**. We are investigating amidation process and have identified that reacting ethyl 3,3,3-trifluoropropionate with morphline in the presence of diethyl aluminum chloride gave the best transformation with the yield of 56% (Table 2). However, we also plan to study the scope of the reaction with other amines, using EDCI, HOBT, and triethylamine as coupling reagents, to produce various fluorinated amides.



Scheme 5: Examples of amines, lactams, and oxazolidinones for the coupling reaction

In addition to exploring the possibility of producing new fluorinated amides, we will investigate the use of organolithiums to make (*Z*)-fluoroketones such as **34**. We were able to synthesize **34** using phenyllithium with comparable stereoselectivity as reported by the Toste group but we obtained an improved yield of 75%. Next, we will investigate the reactivity of organolithiums with morpholine 3,3,3-trifluoropropanamide to make β-fluoroenones.[29,135]



Scheme 6: Approaches to (*Z*)-β-fluoroenones.

The fluorotrifluoromethylene is an important class of functional group that we aimed to synthesize. In our effort towards this end, we were met with challenges that we are working to overcome. We have changed the substrate to 2,3,3,3-tetrafluoropropanoic acid, and with this substrate, we can pursue a couple of routes: 1) Amidation followed by an aldol reaction to access α-fluoro-α-trifluoromethyl-β-hydroxyl groups. 2) Enolboration of the 2,3,3,3-tetrafluoropropanoic acid to generate α-fluoro-α-trifluoromethyl-β-hydroxyl carboxylic acids. These studies provide the basis of creating the fluorotrifluoromethyl group, which will open new avenues for the use of fluorine in medicinal chemistry.

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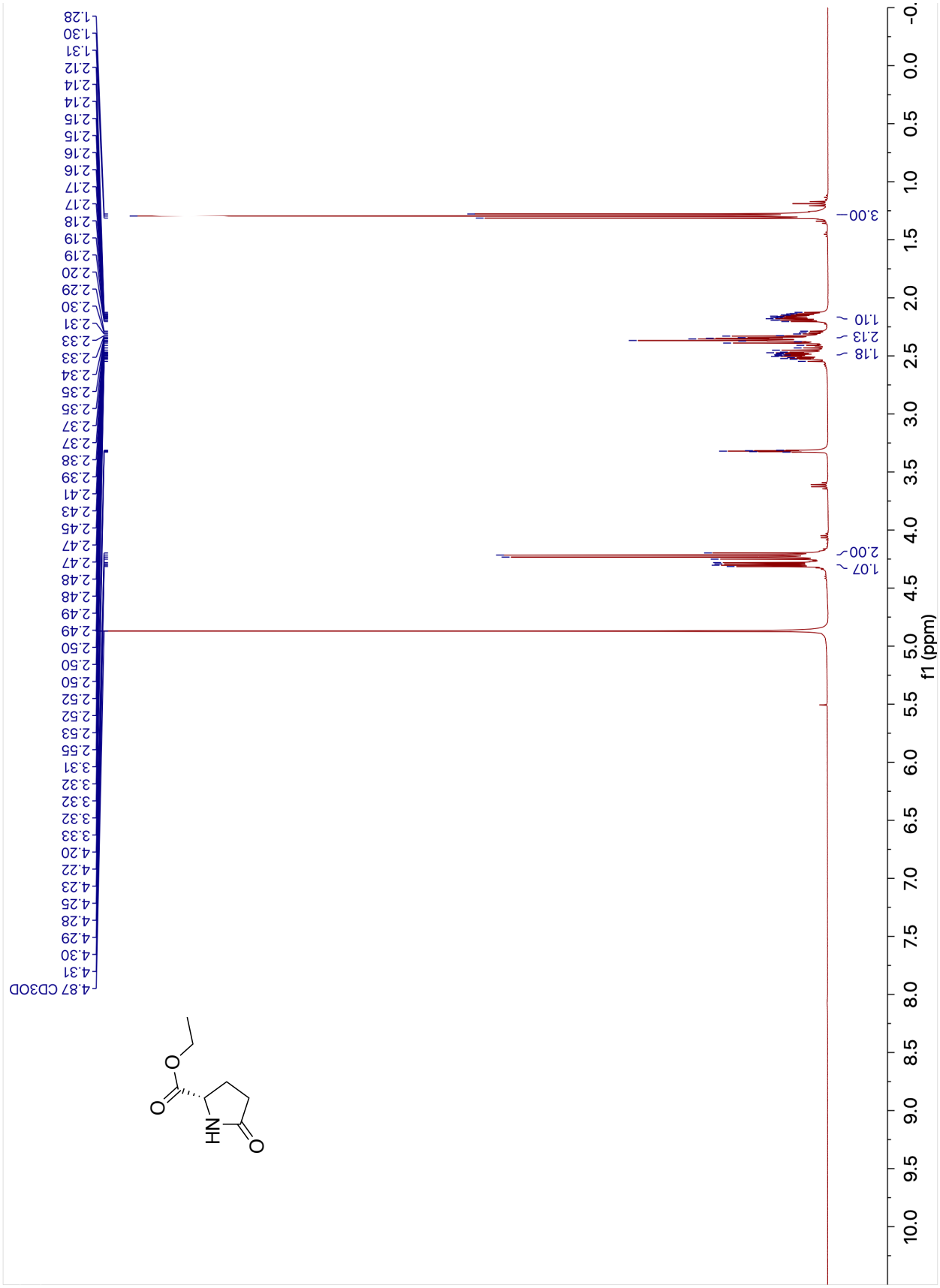
APPENDICES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4.30
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4.28
4.25
4.23
4.22
4.20
3.33
3.32
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3.32
3.31
2.55
2.53
2.52
2.52
2.50
2.50
2.50
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2.48
2.48
2.47
2.47
2.45
2.43
2.41
2.39
2.38
2.37
2.37
2.35
2.35
2.34
2.33
2.33
2.31
2.30
2.29
2.20
2.19
2.19
2.18
2.17
2.17
2.16
2.16
2.15
2.15
2.14
2.14
2.12
1.31
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f1 (ppm)
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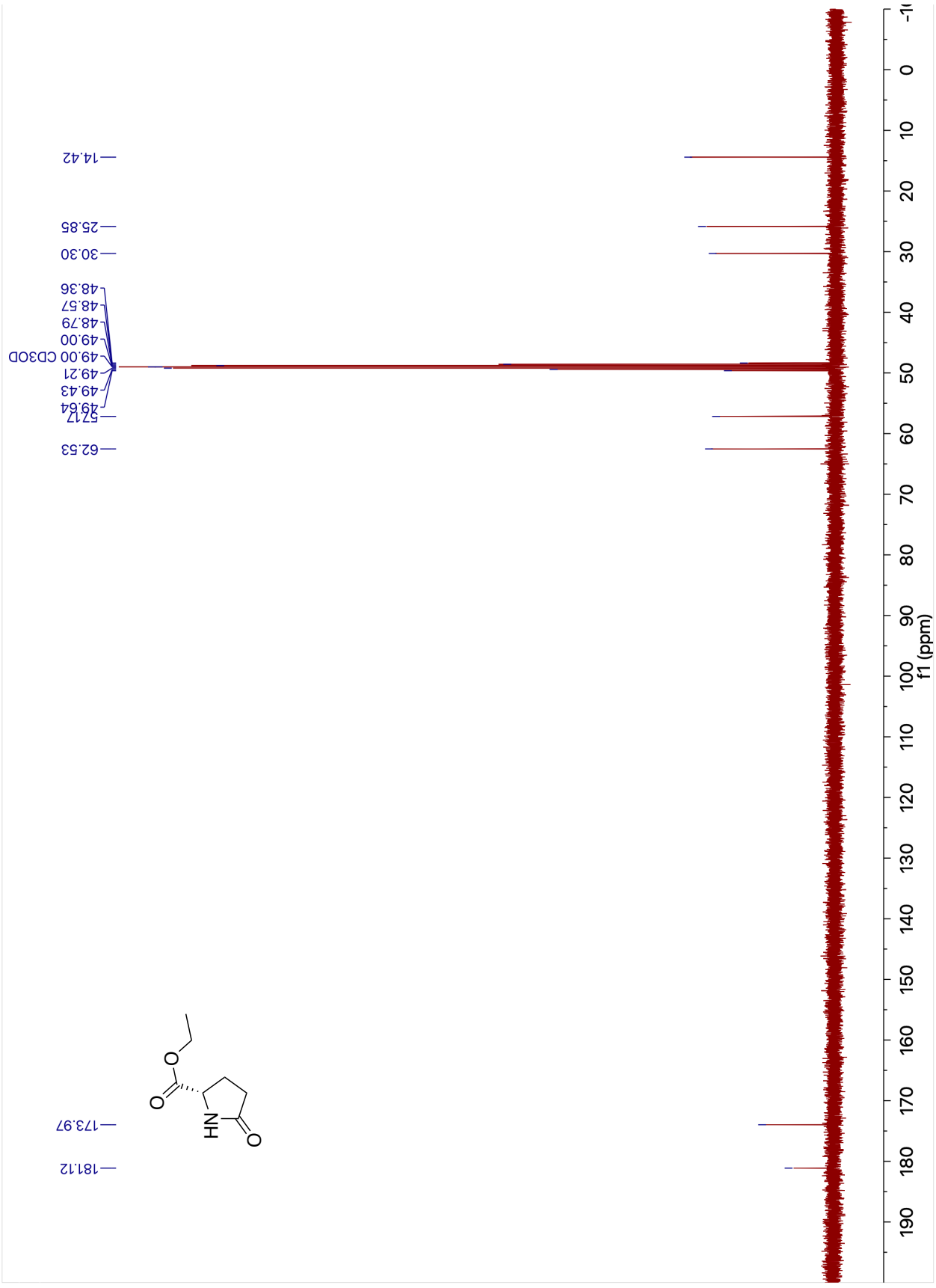
O
O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25.85
30.30
48.36
48.57
48.79
49.00
49.00 CD3OD
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49.43
49.64
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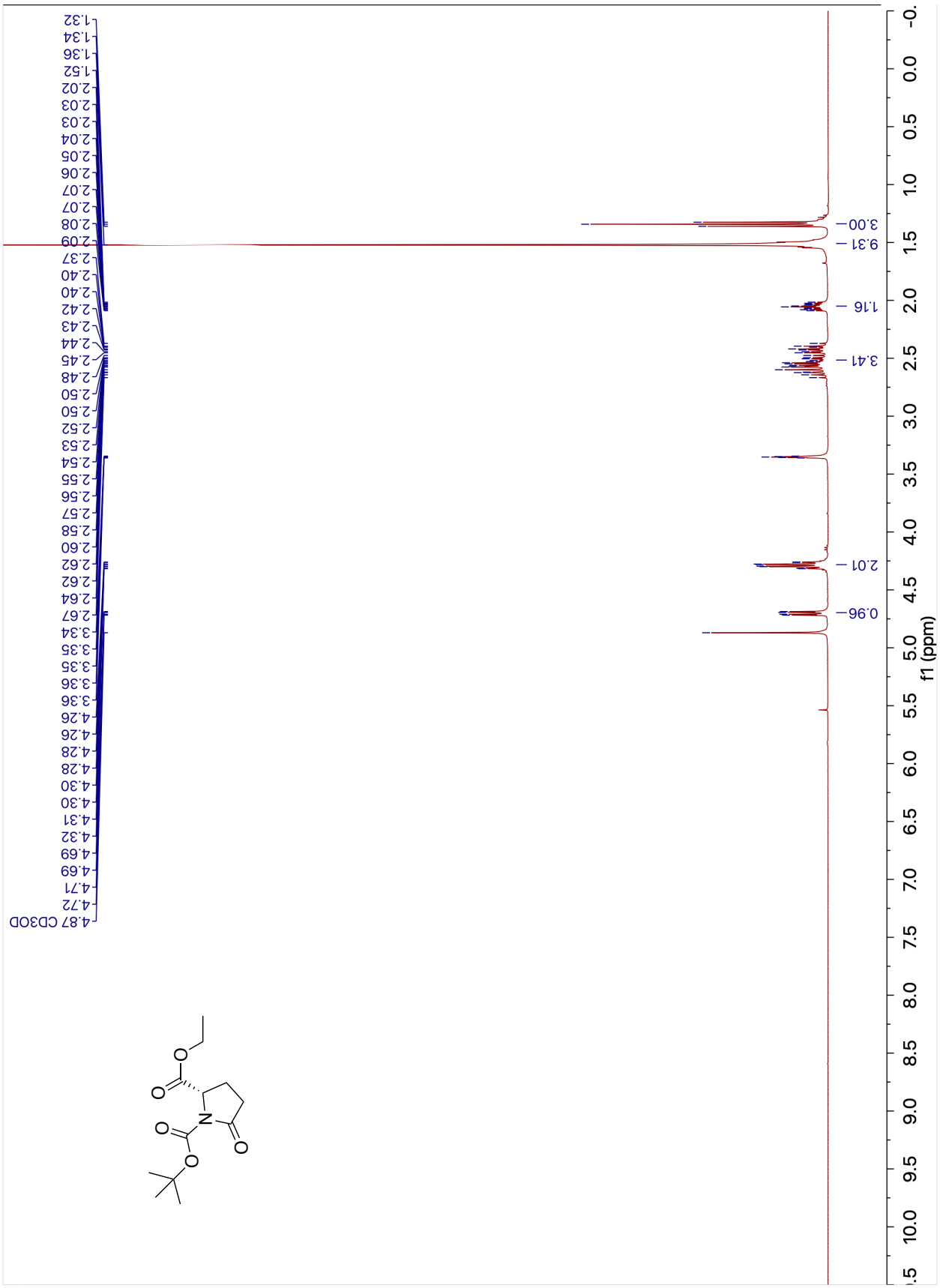
62.53
173.97
181.12
NH
O
O
O
f1 (ppm)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4.69
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4.31
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4.30
4.28
4.28
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4.26
3.36
3.36
3.35
3.35
3.34
2.67
2.64
2.62
2.62
2.60
2.58
2.57
2.56
2.55
2.54
2.53
2.52
2.50
2.50
2.48
2.45
2.44
2.43
2.42
2.40
2.40
2.37
2.09
2.08
2.07
2.07
2.06
2.06
2.05
2.04
2.03
2.03
2.02
2.02
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3.41
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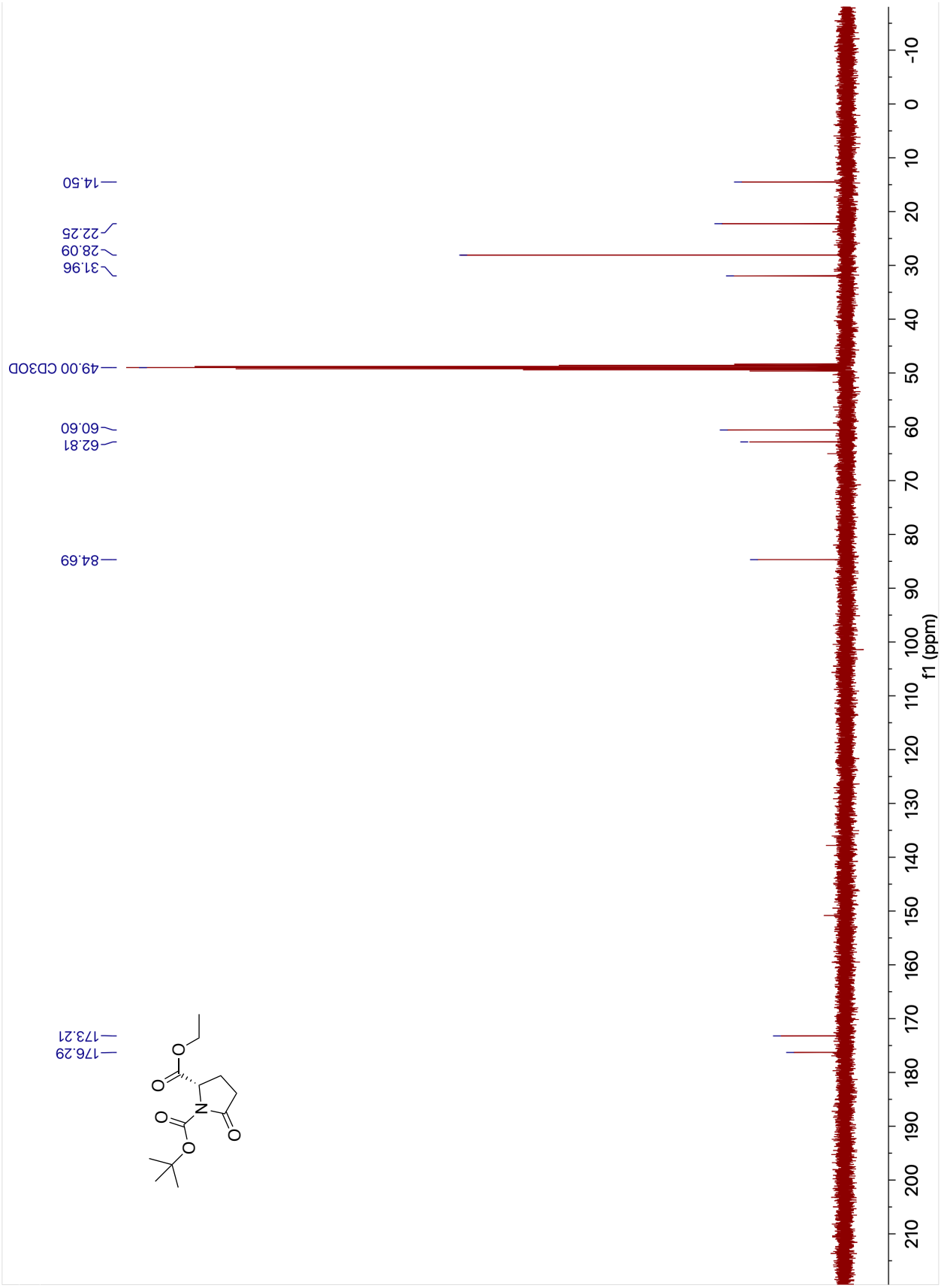
0.96
f1 (ppm)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176.29
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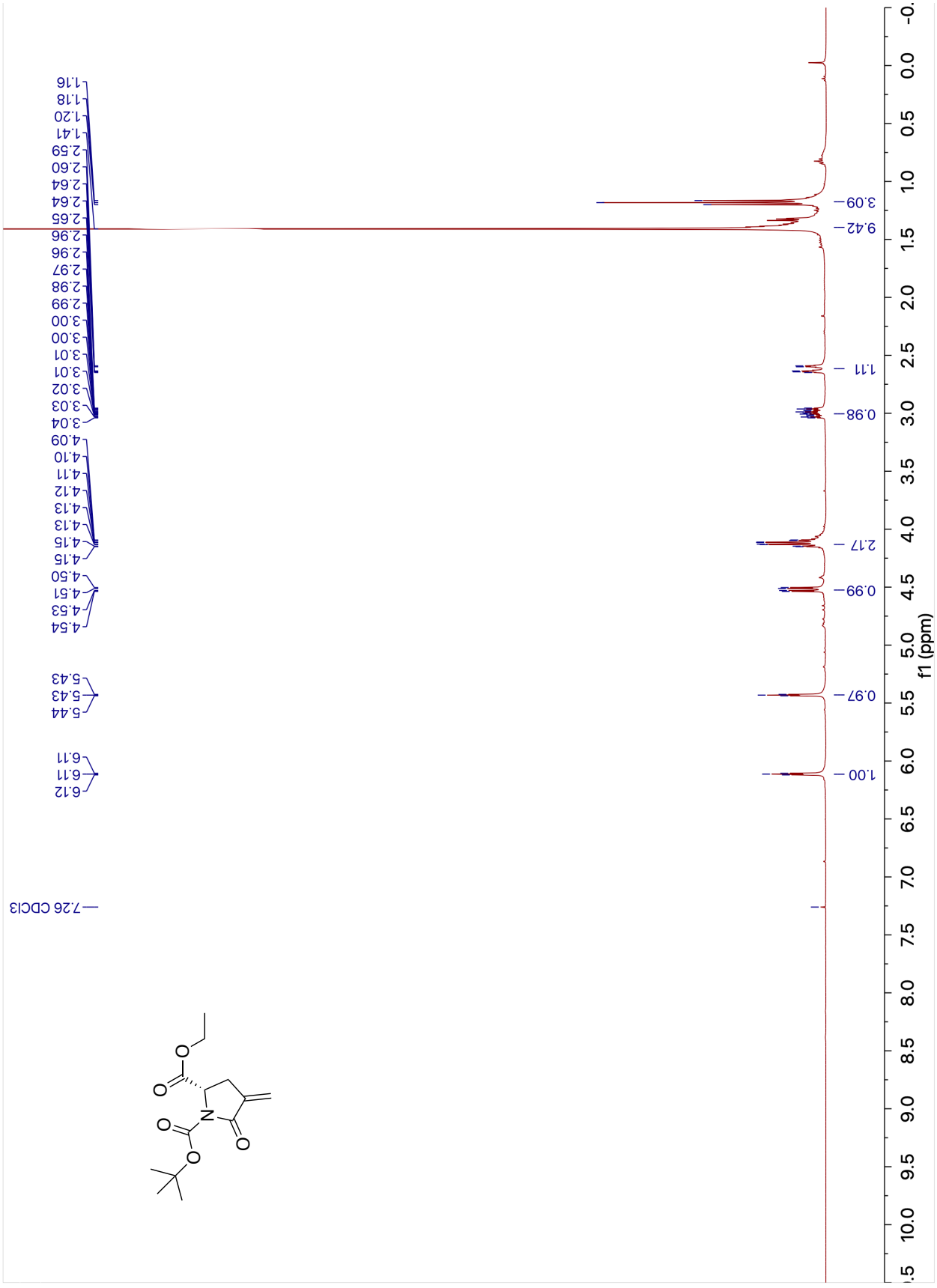
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6.11
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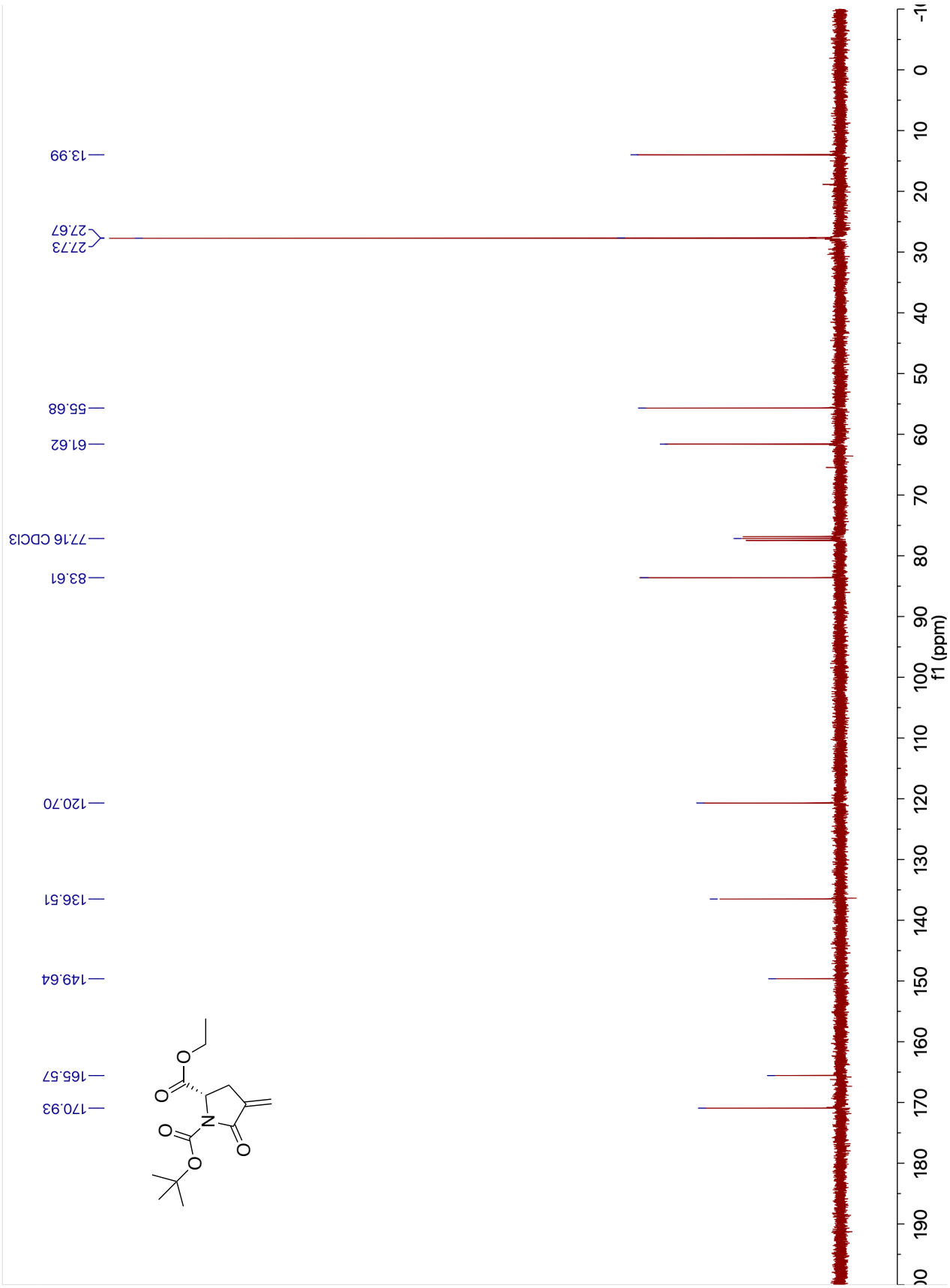
5.43
4.54
4.53
4.51
4.50
4.15
4.15
4.13
4.13
4.12
4.11
4.10
4.09
3.04
3.03
3.02
3.01
3.01
3.00
3.00
2.99
2.98
2.97
2.96
2.96
2.65
2.64
2.64
2.60
2.59
1.41
1.20
1.18
1.16
3.09
9.42
1.11
0.98
2.17
0.99
0.97
1.00
f1 (ppm)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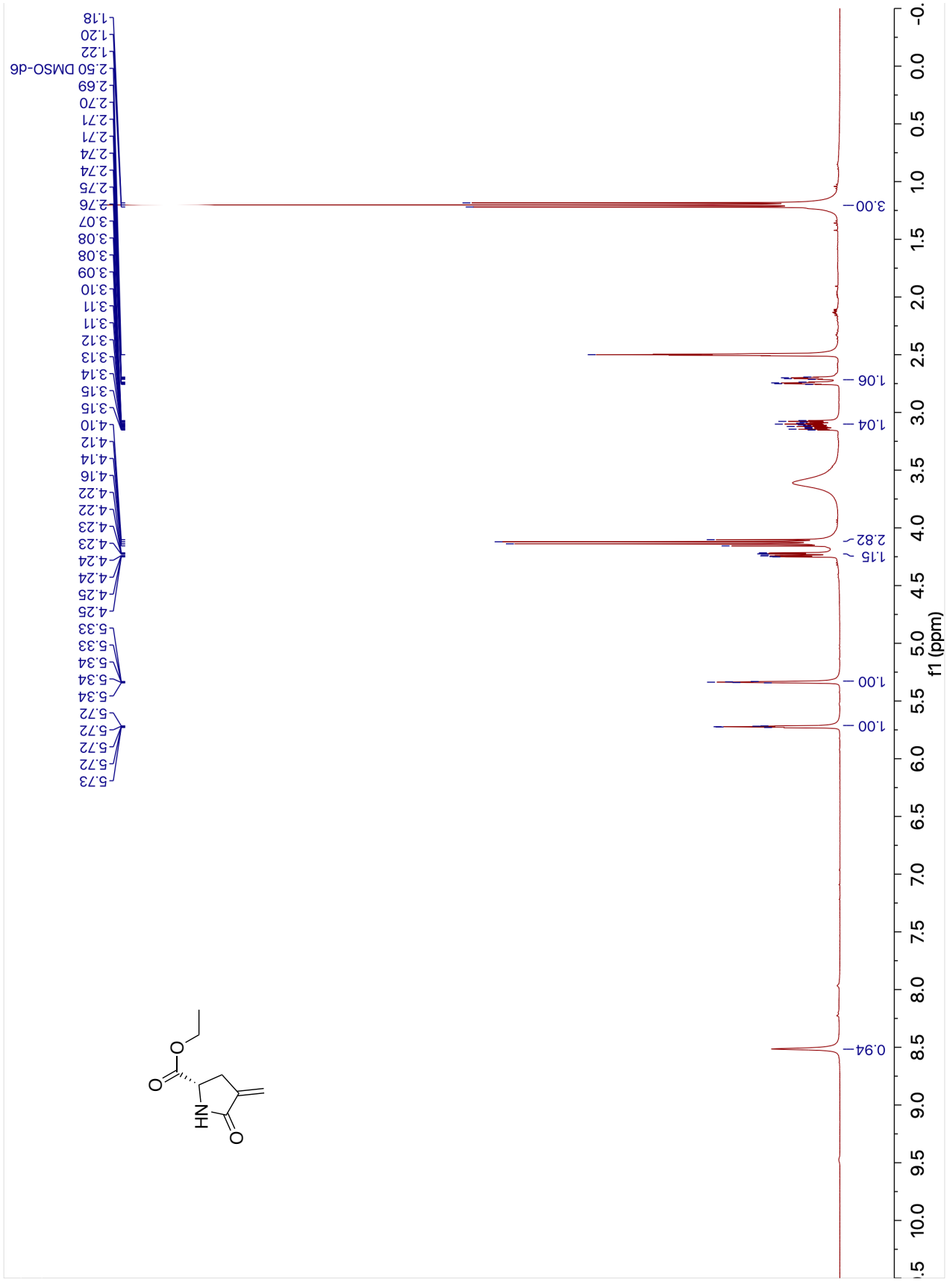
170.93
f1 (ppm)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3.07
3.08
3.08
3.09
3.10
3.11
3.11
3.12
3.13
3.14
3.15
3.15
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4.14
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4.22
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4.23
4.23
4.24
4.24
4.25
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5.33
5.33
5.34
5.34
5.34
5.72
5.72
5.72
5.72
5.73
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1.04
2.82
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1.00
0.94
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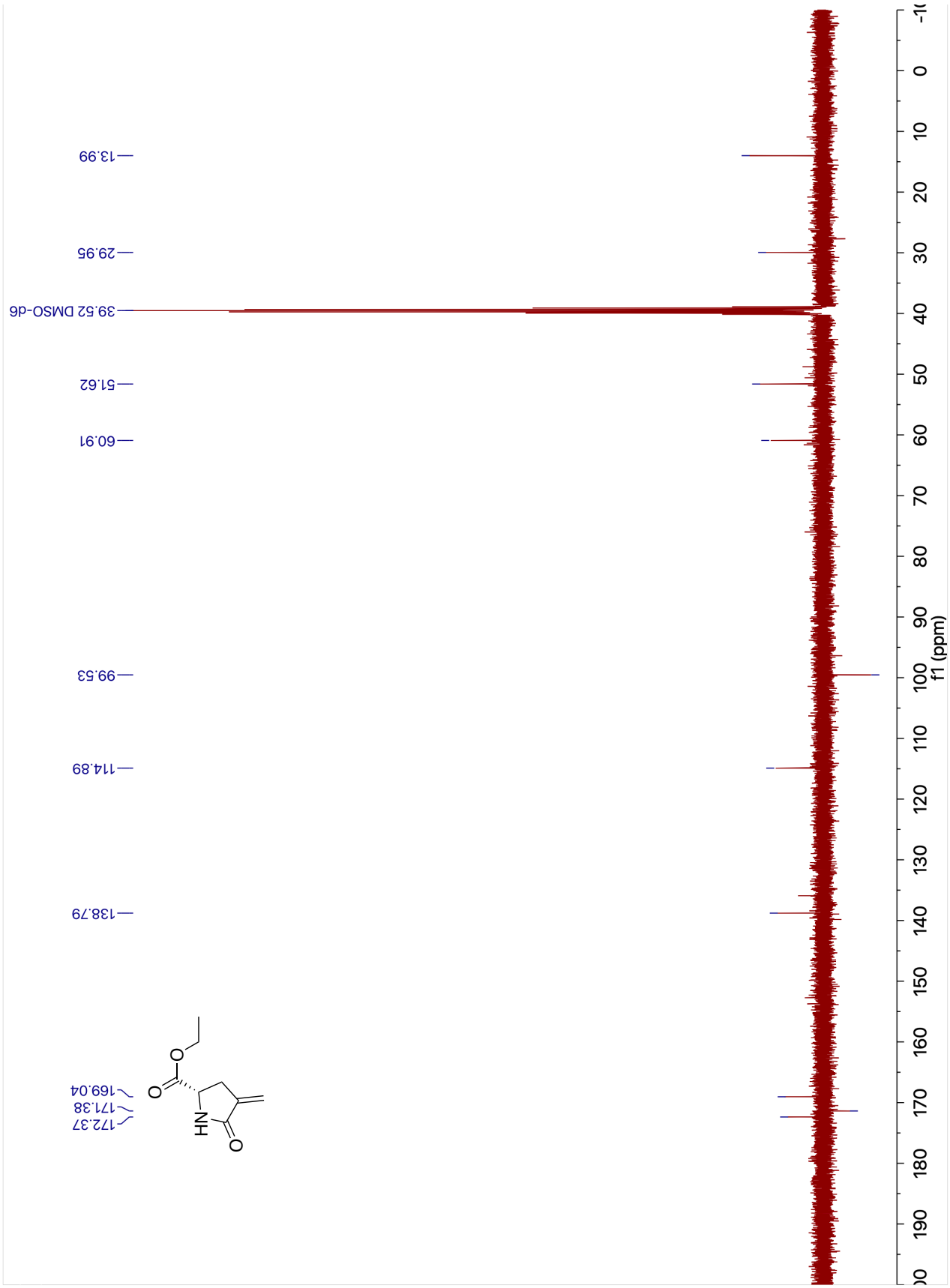
O
NH
O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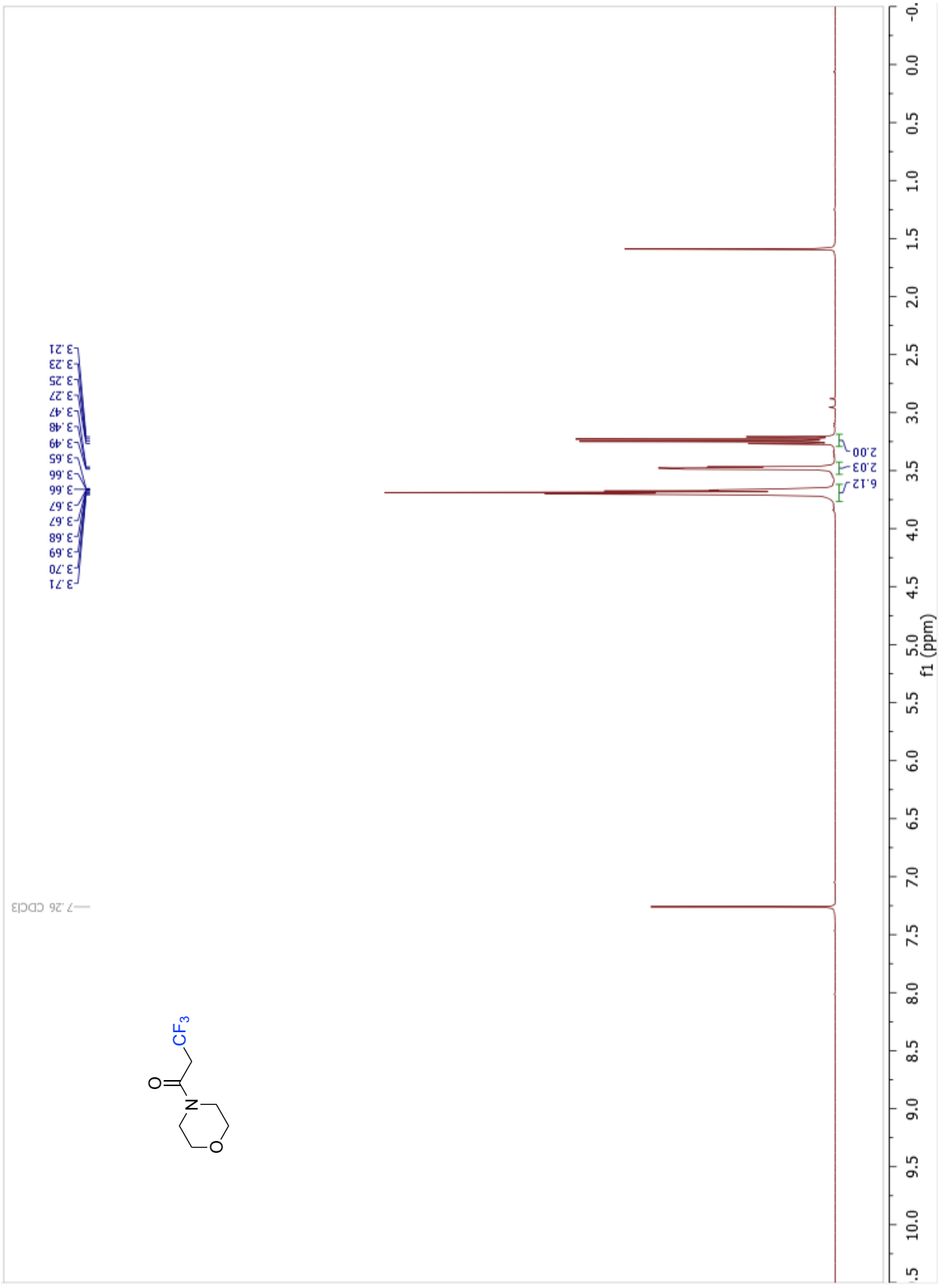
O
NH
O
f1 (ppm)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3.67
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3.66
3.65
3.49
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3.47
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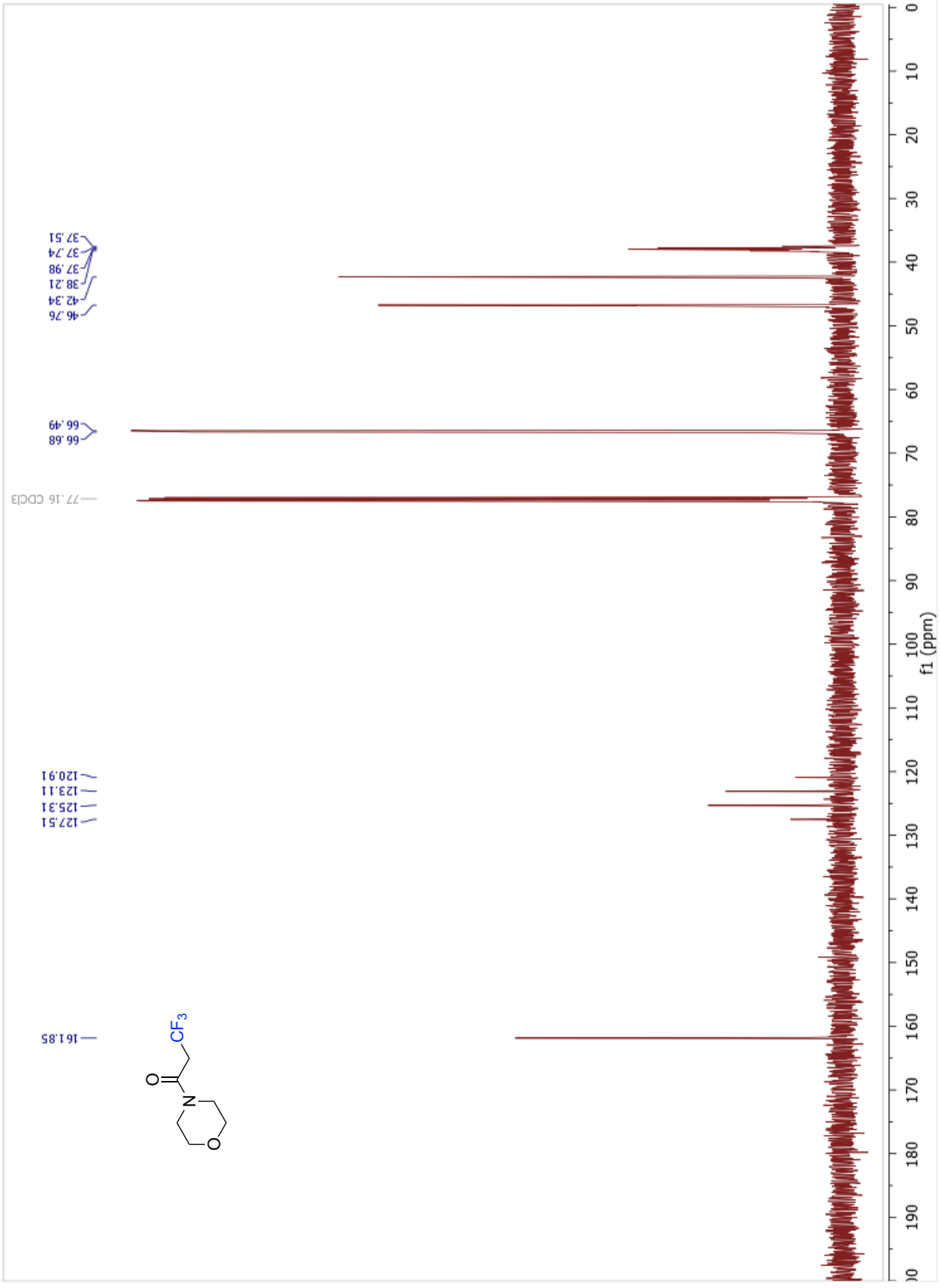
3.25
3.23
3.21
6.12
2.03
2.00
f1 (ppm)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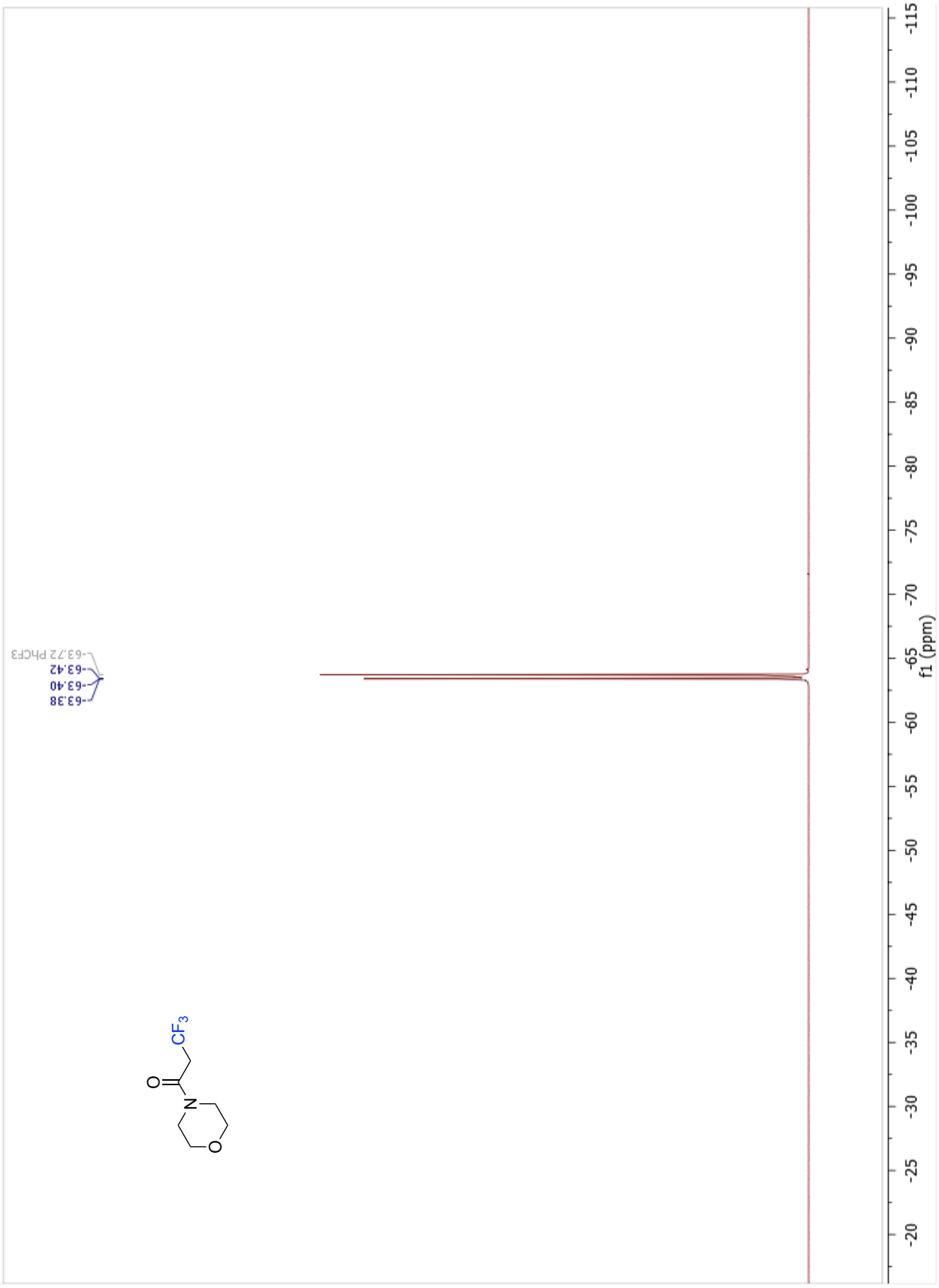
37.74
37.51
CF3
O
N
O
f1 (ppm)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-63.42
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O
N
O
CF3
-20
-25
-30
-35
-40
-45
-50
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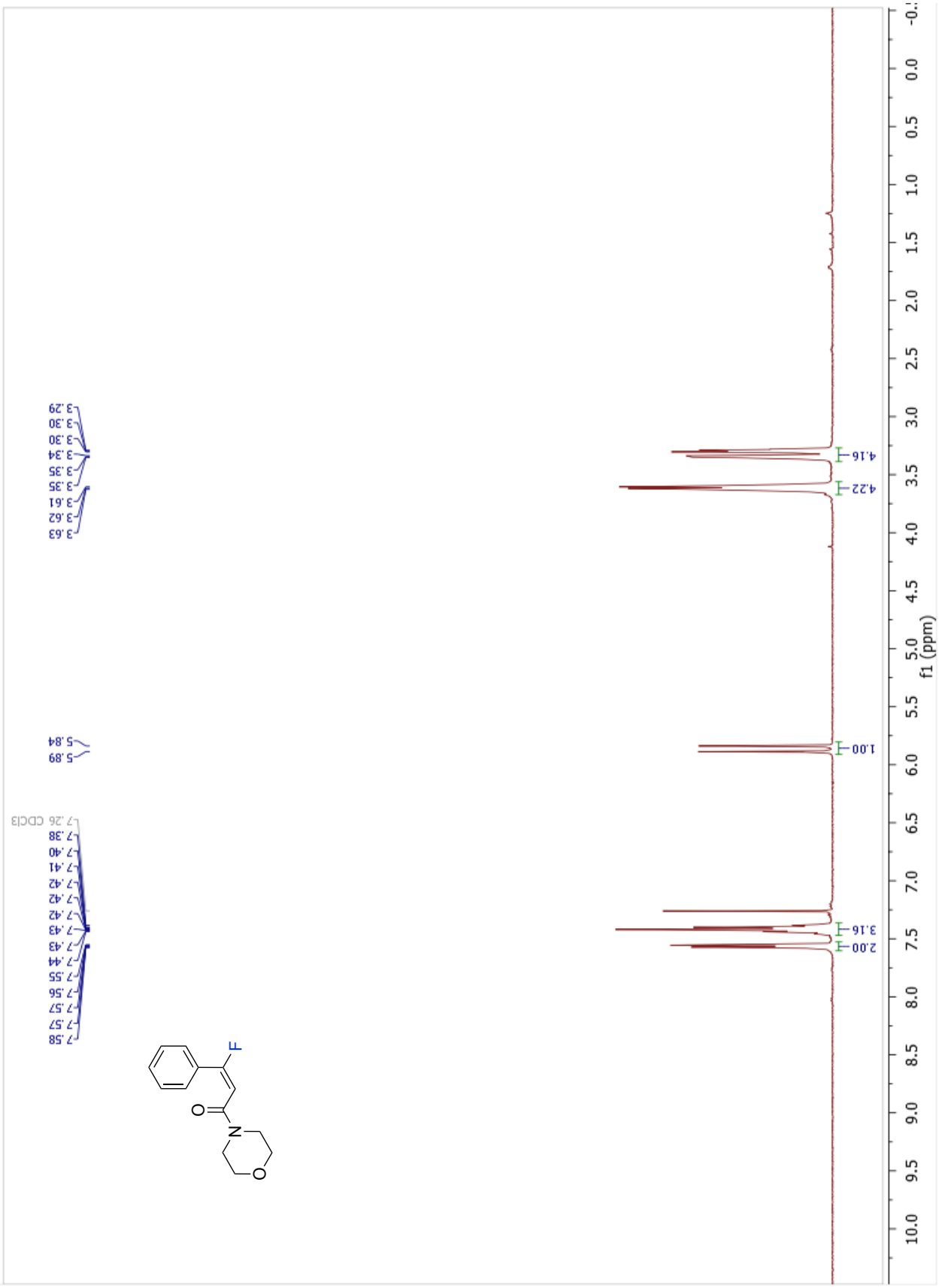
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
f1 (ppm)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7.56
7.55
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7.43
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7.42
7.42
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7.40
7.38
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3.30
3.29
F
O
N
O
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10.0
9.5
9.0
8.5
8.0
7.5
7.0
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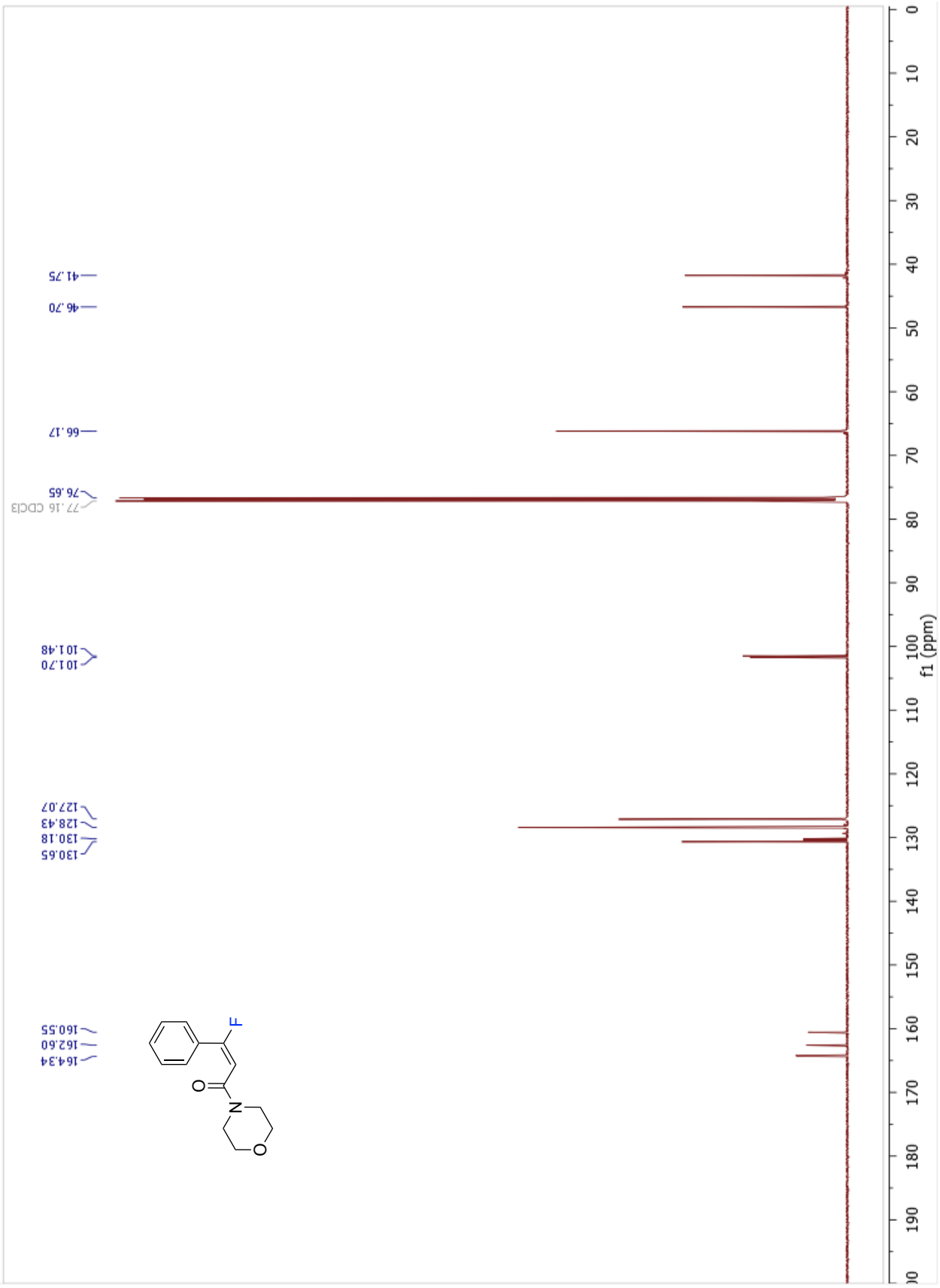
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162.60
164.34
F
O
N
O
0
10
20
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40
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60
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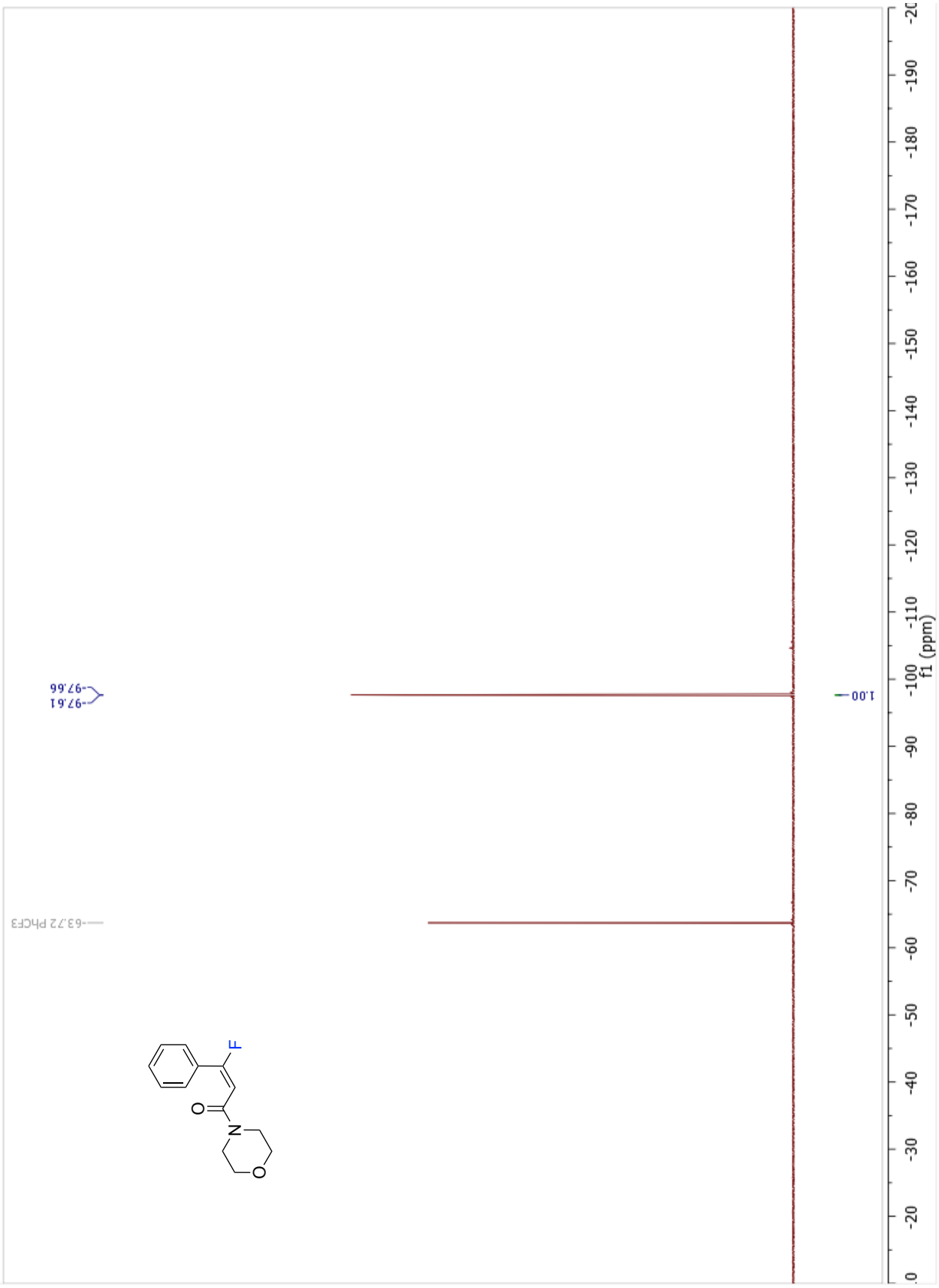
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)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N
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-40
-50
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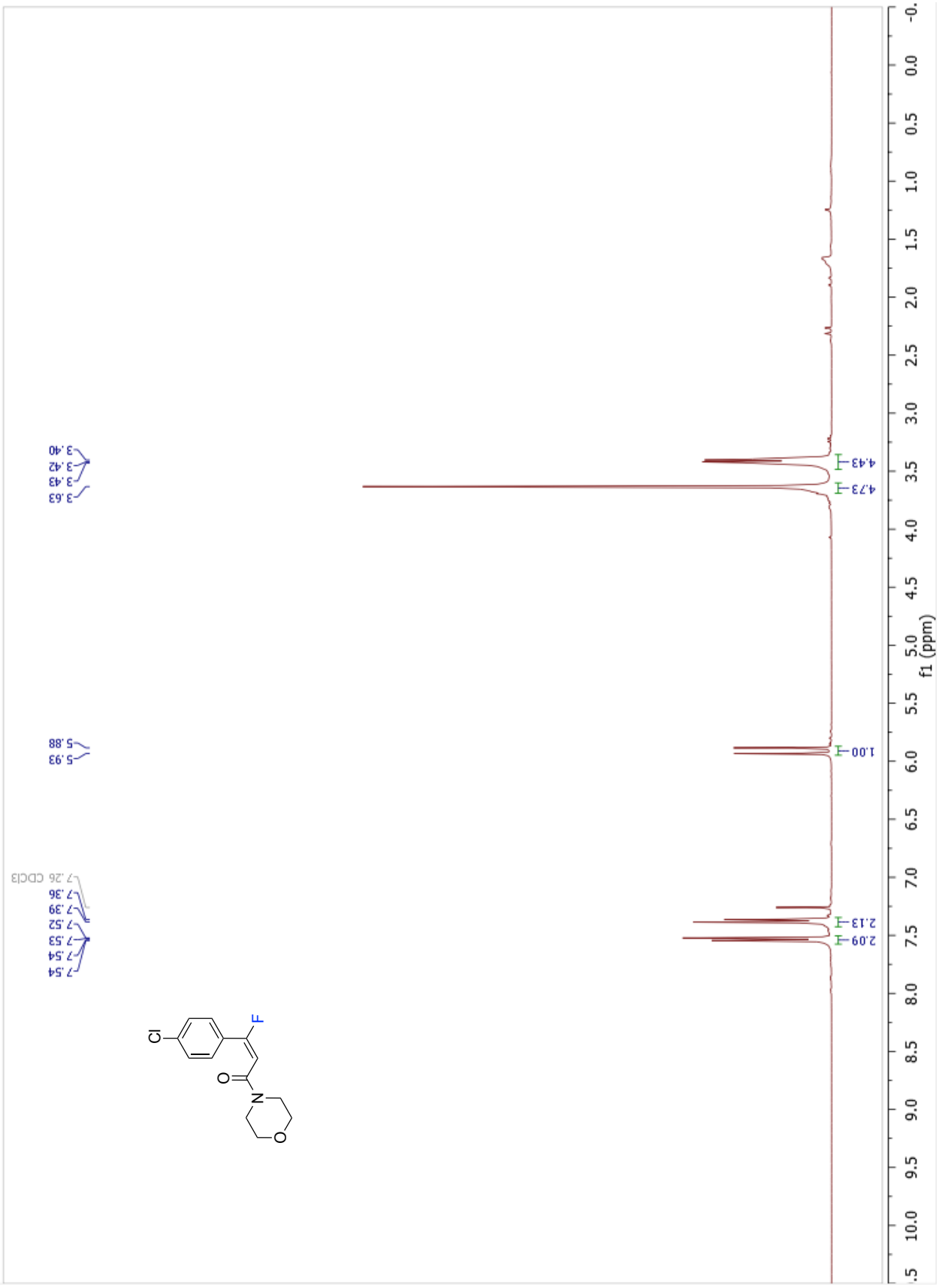
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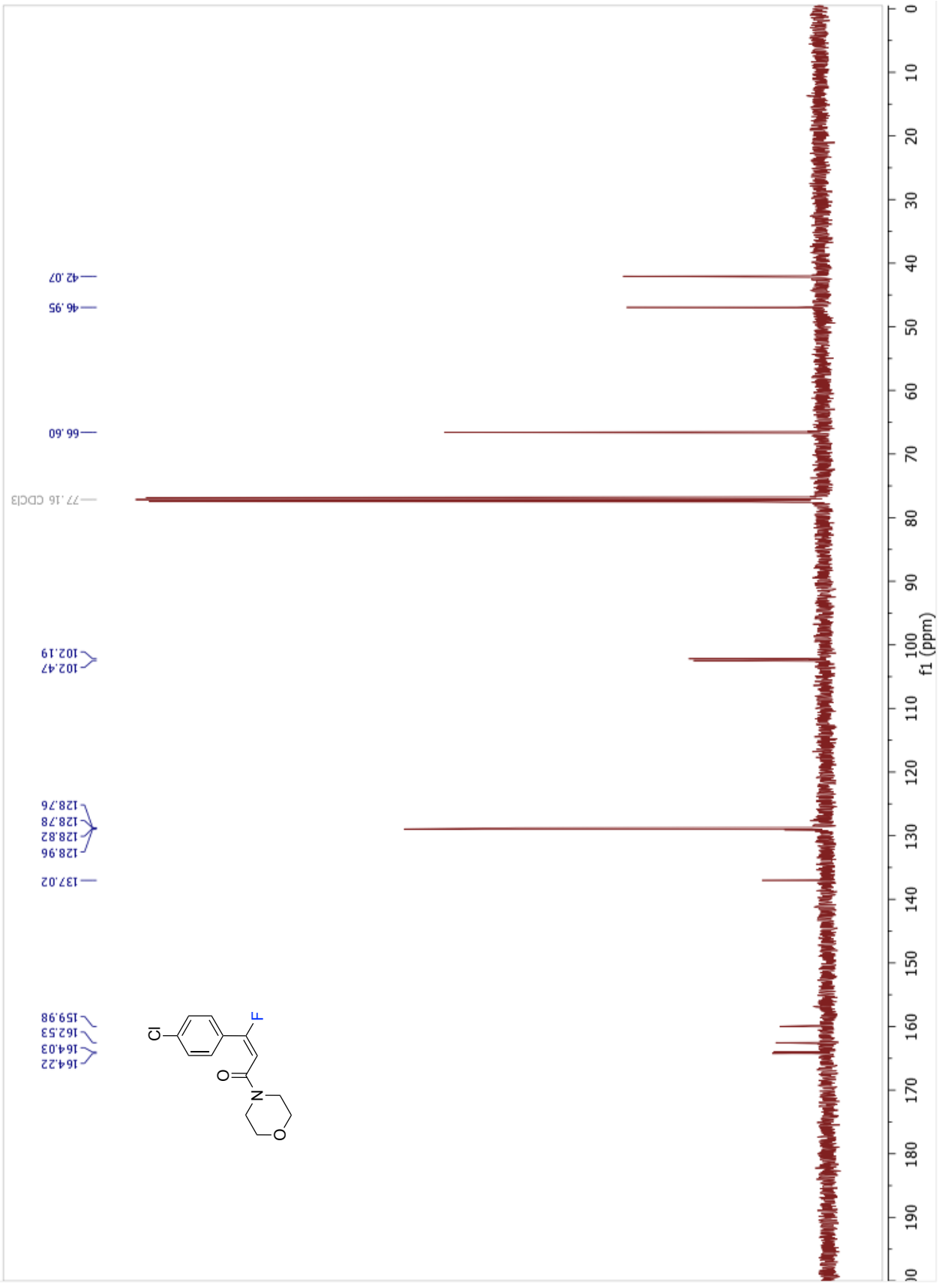
4.43
4.73
2.09
2.13
1.00
f1 (ppm)
Cl
F
O
N
O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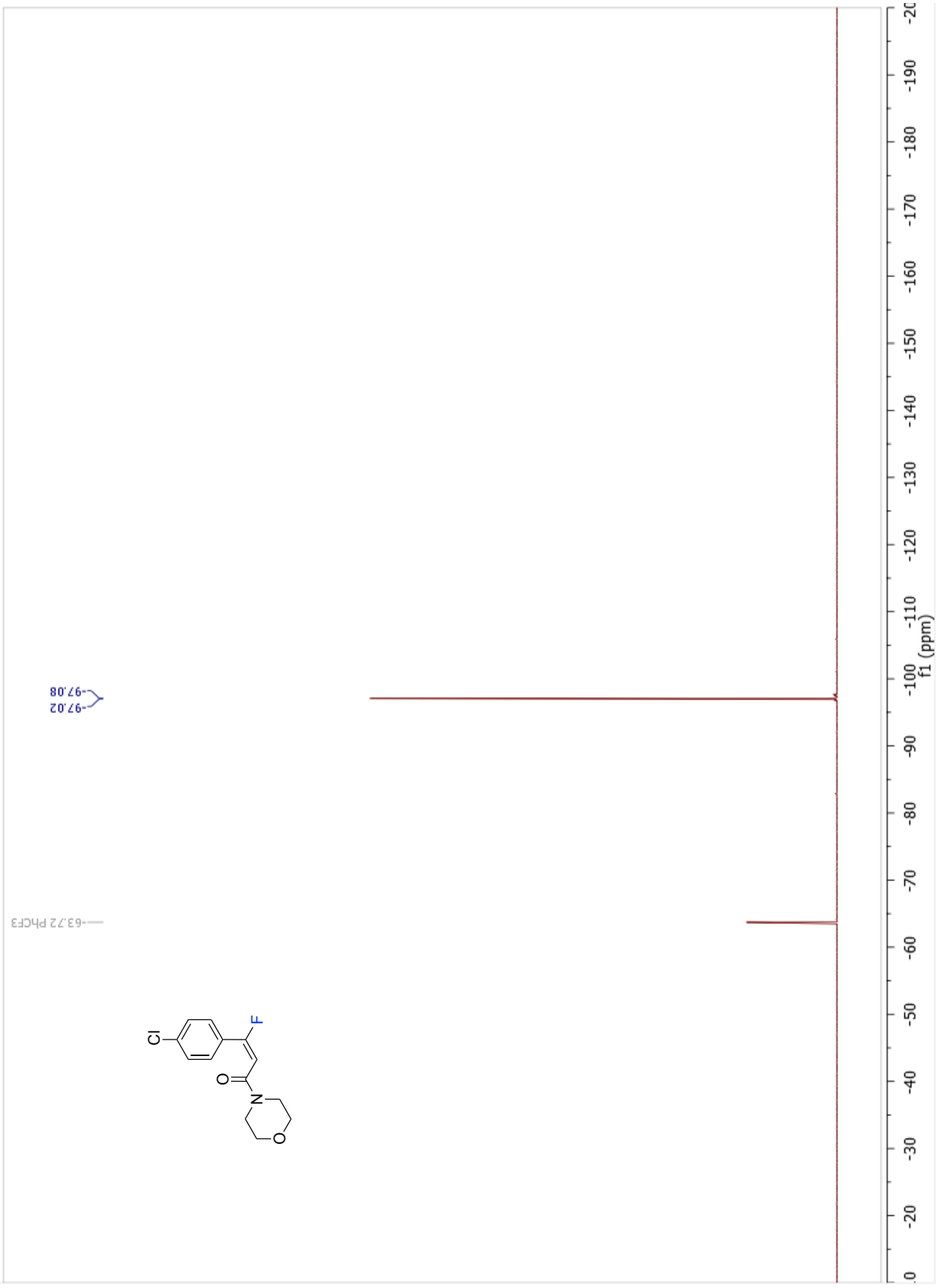
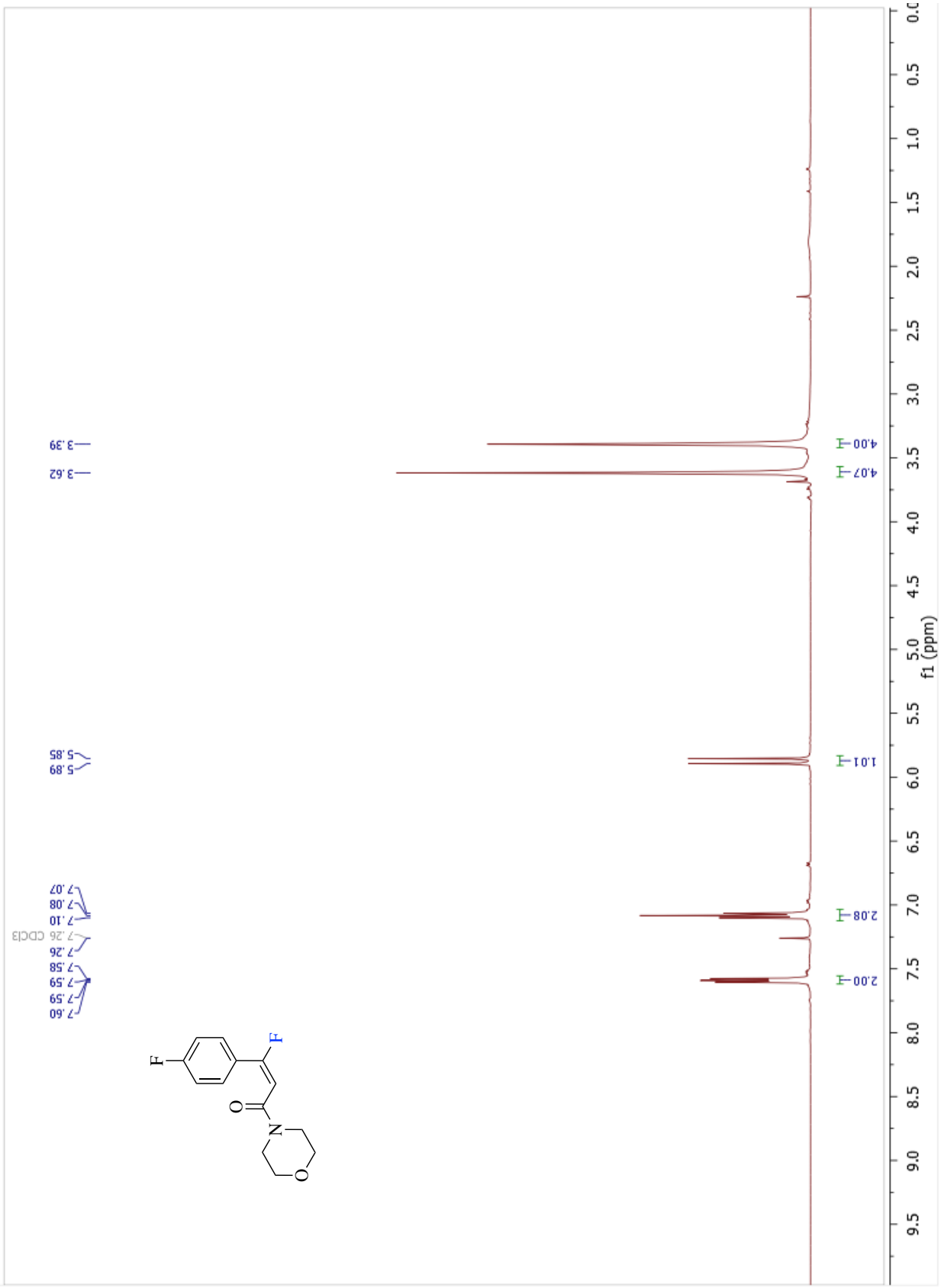
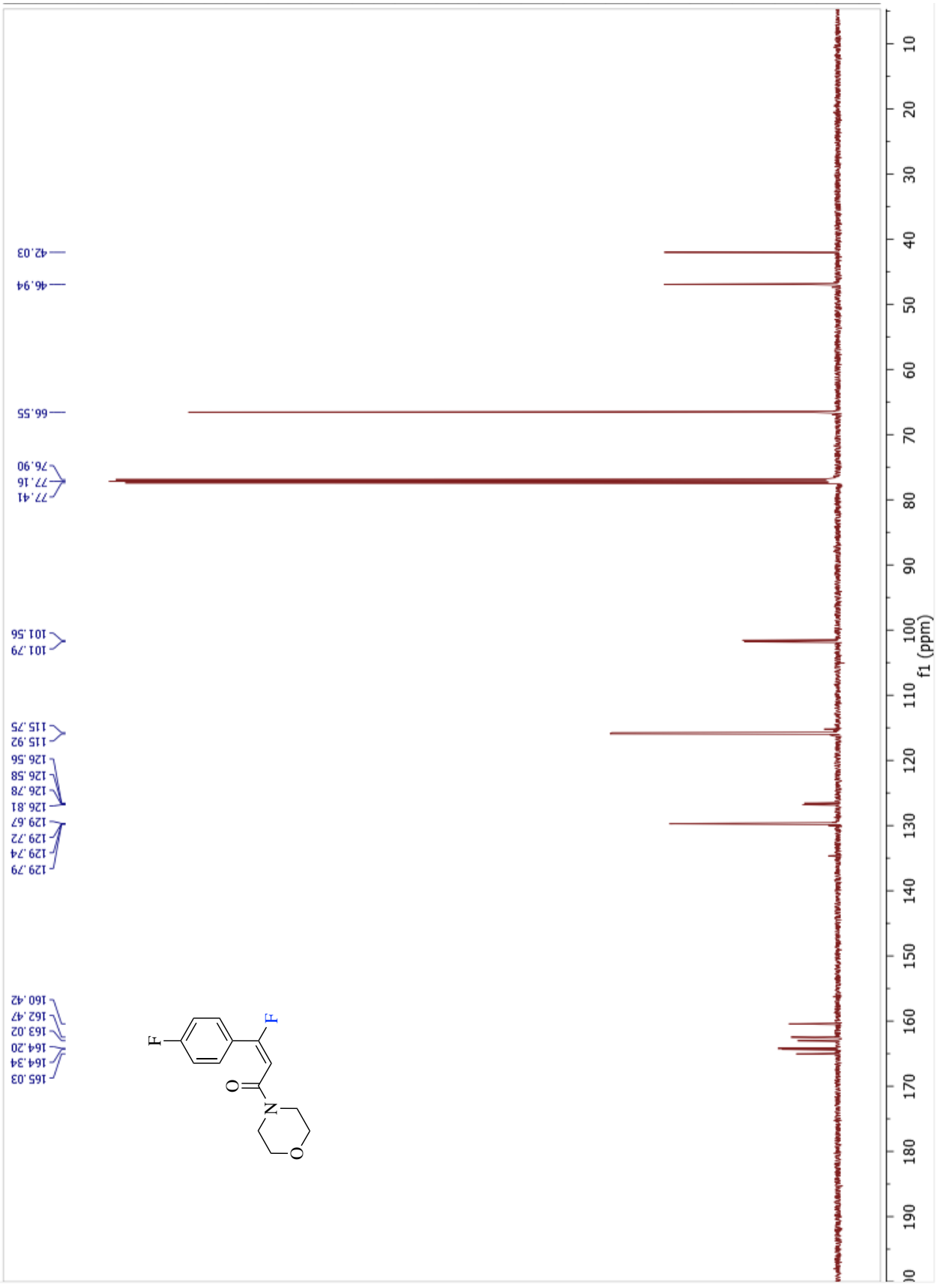
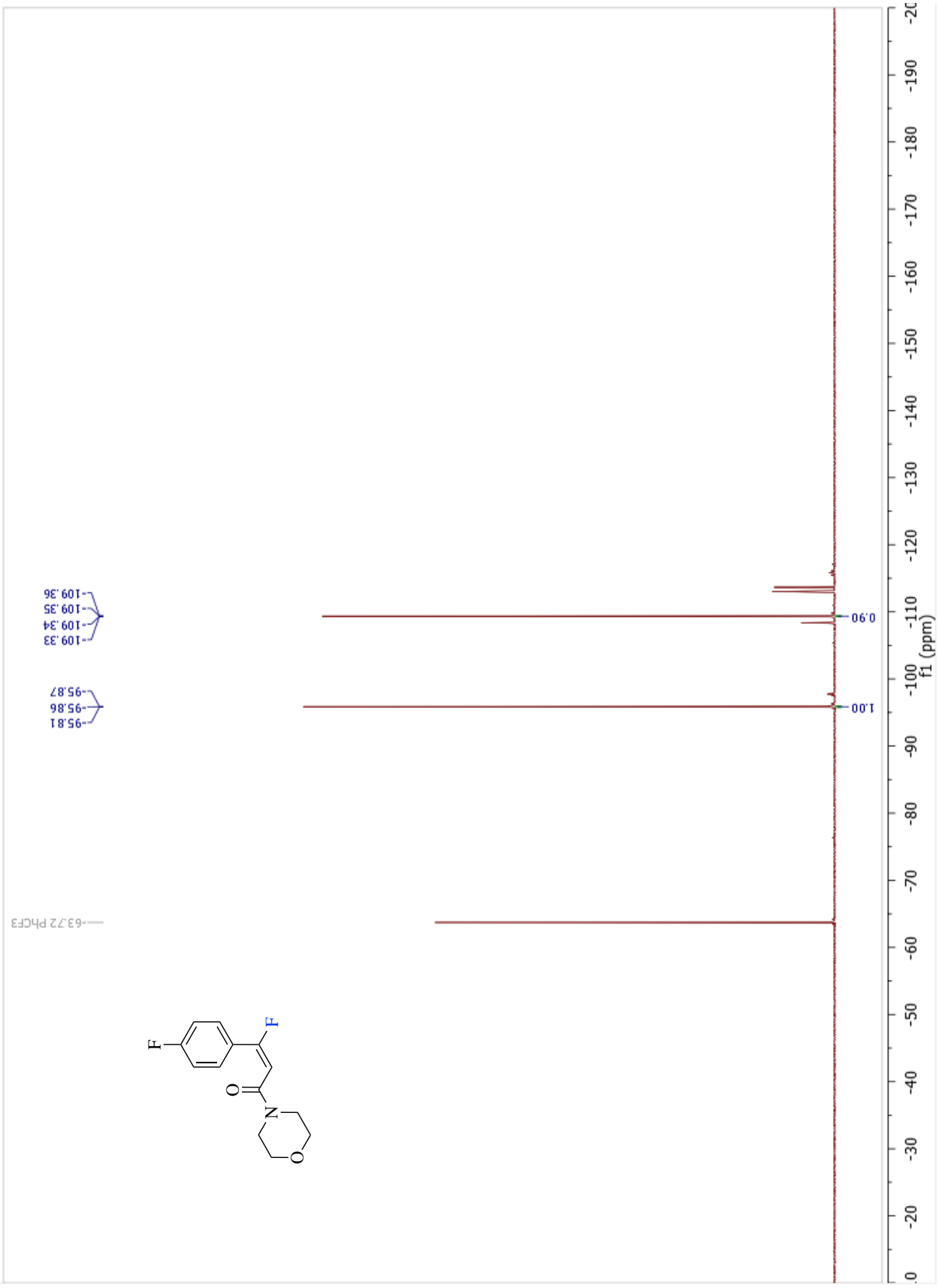
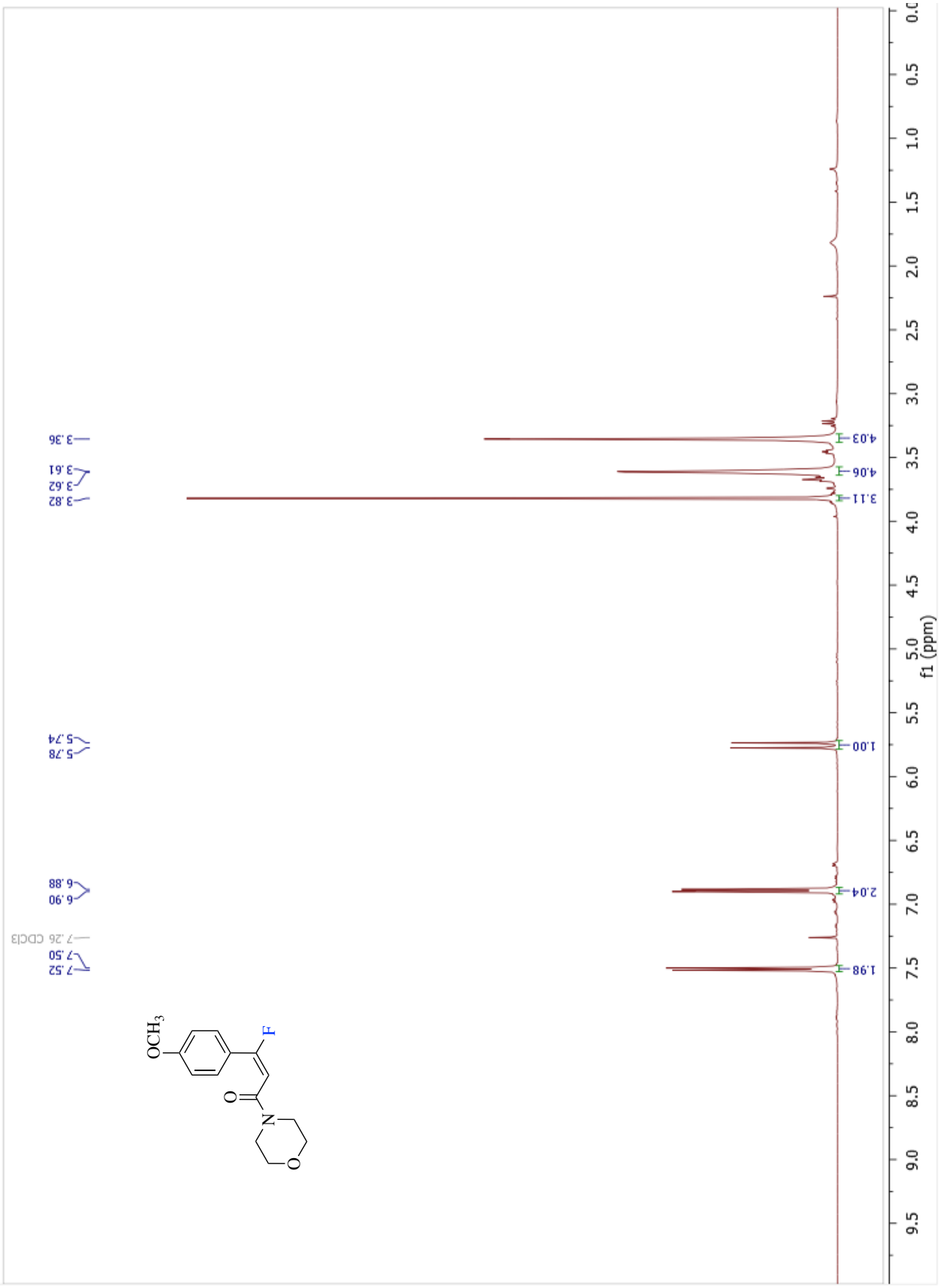
137.02
164.22
164.03
162.53
159.98
Cl
F
O
N
O
f1 (ppm)

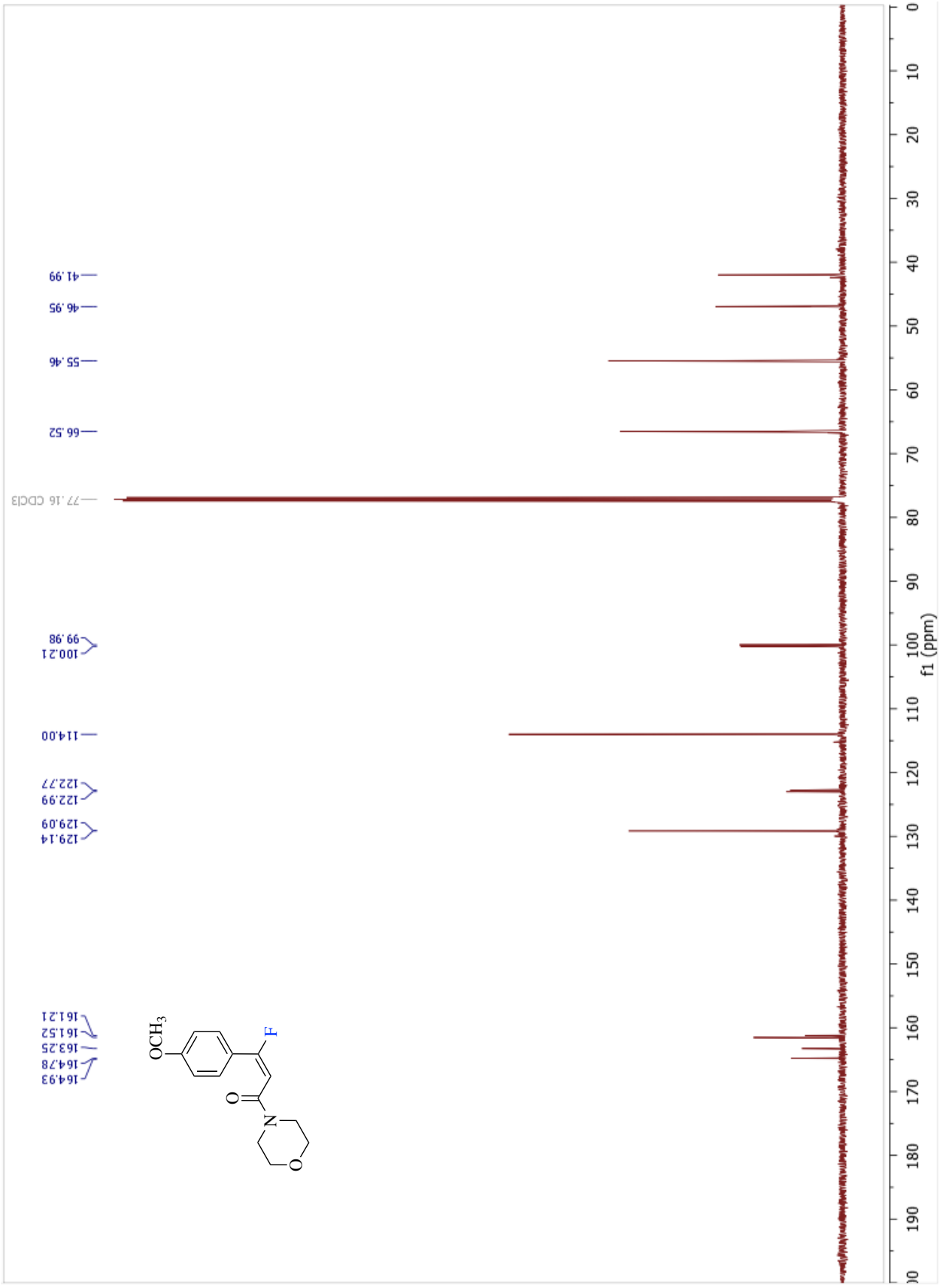

-97.02
-97.08
-63.72 PhCF3
Cl
F
O
N
O
f1 (ppm)

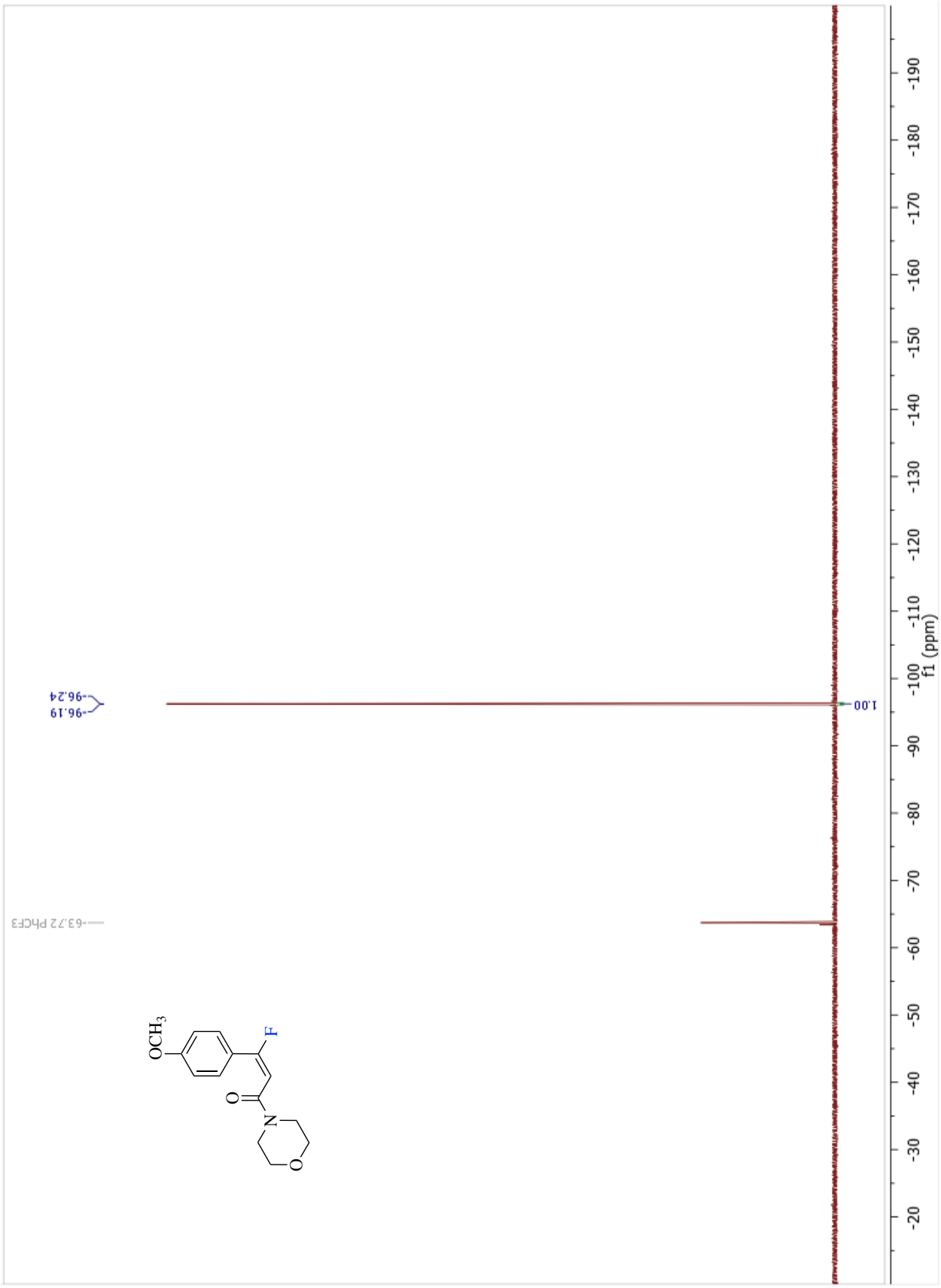

3.39
3.62
5.89
5.85
7.60
7.59
7.59
7.58
7.26
7.26 CDCl3
7.10
7.08
7.07
4.00
4.07
1.01
2.08
2.00
F
F
O
N
O
f1 (ppm)

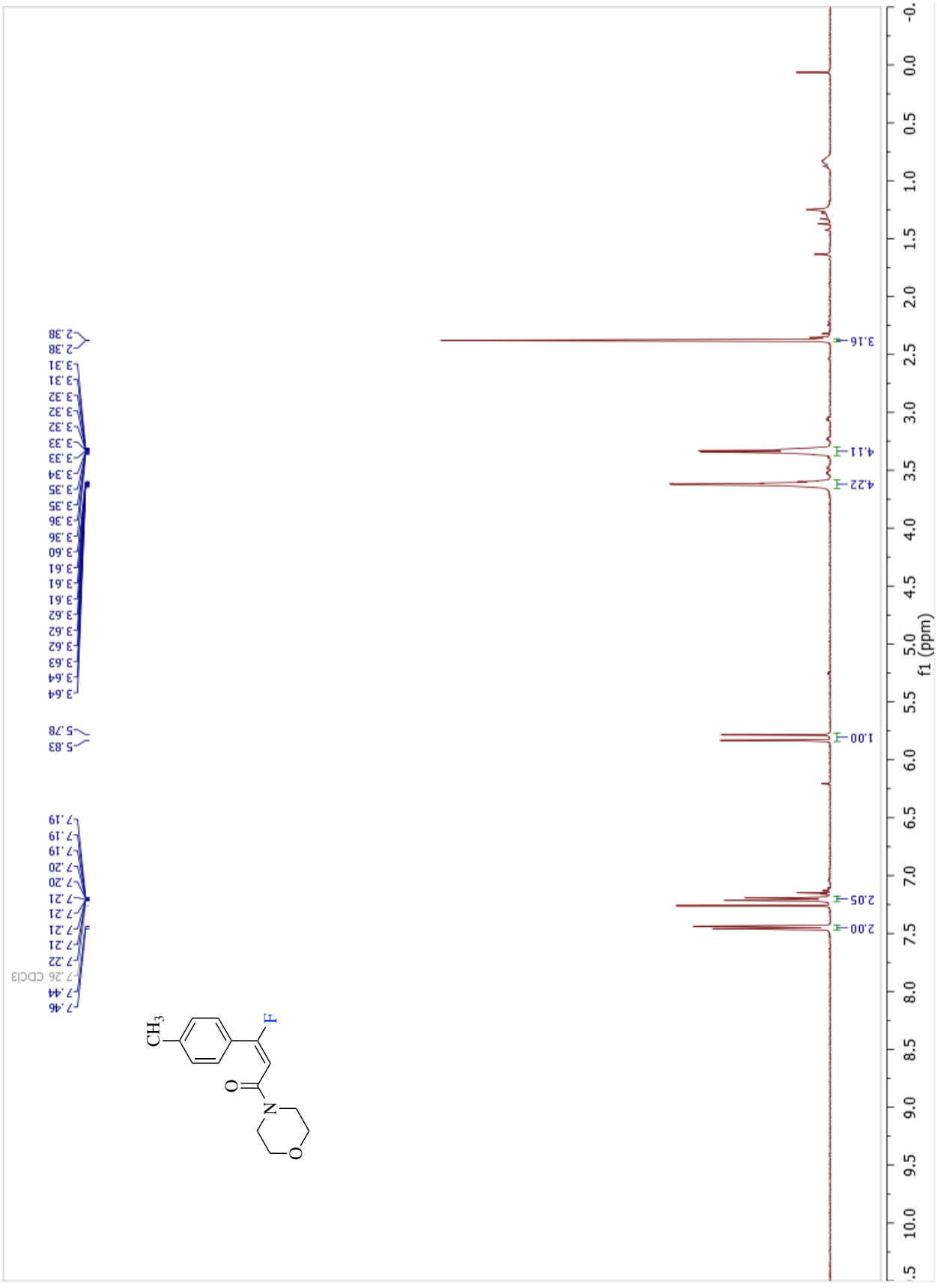

42.03
46.94
66.55
76.90
77.16
77.41
101.56
101.79
115.75
115.92
126.56
126.58
126.78
126.81
129.67
129.72
129.74
129.79
160.42
162.47
163.02
164.20
164.34
165.03
F
F
O
N
O
f1 (ppm)

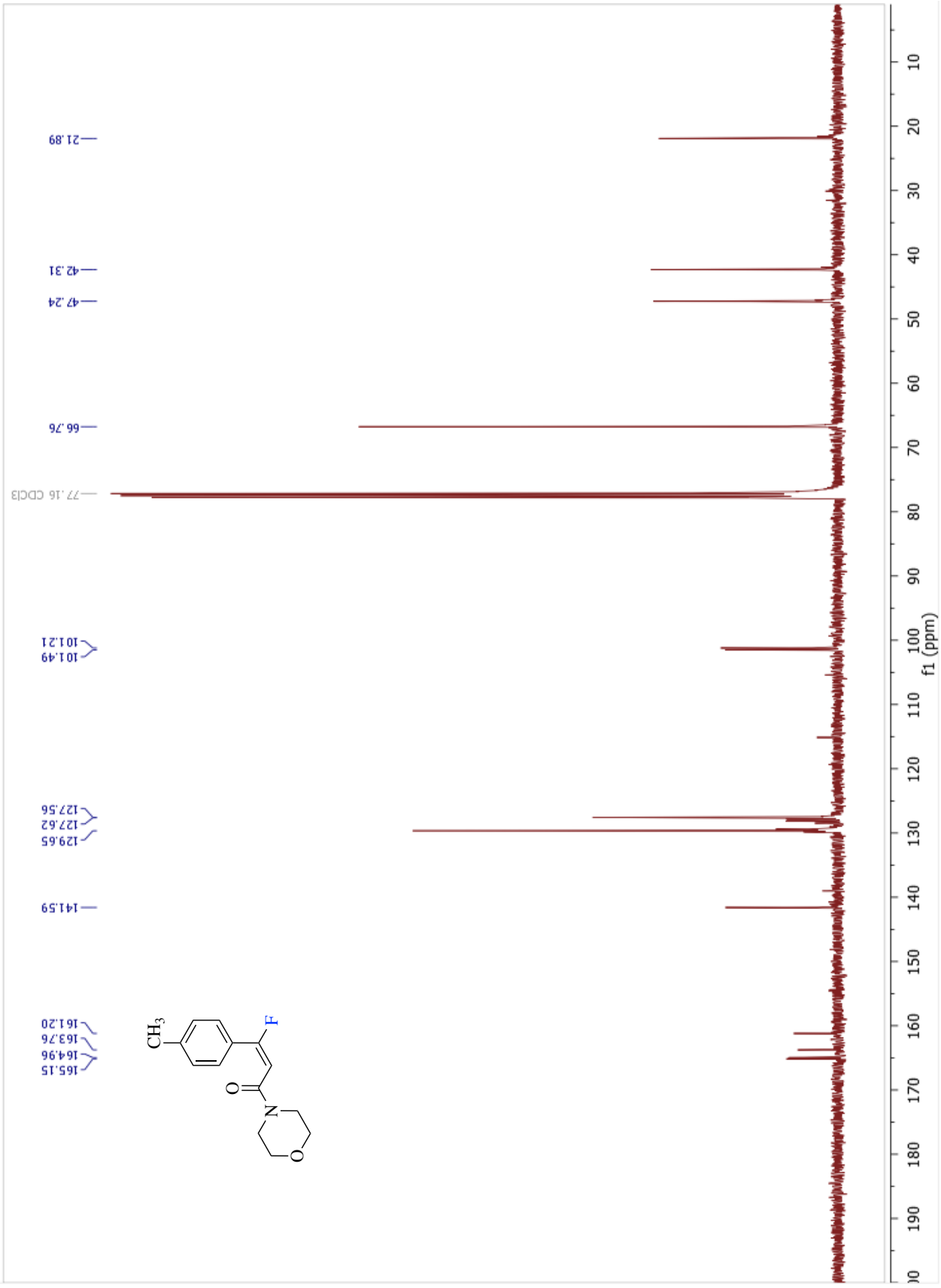

-63.72 PhCF3
-95.81
-95.86
-95.87
-109.33
-109.34
-109.35
-109.36
0.90
1.00
f1 (ppm)

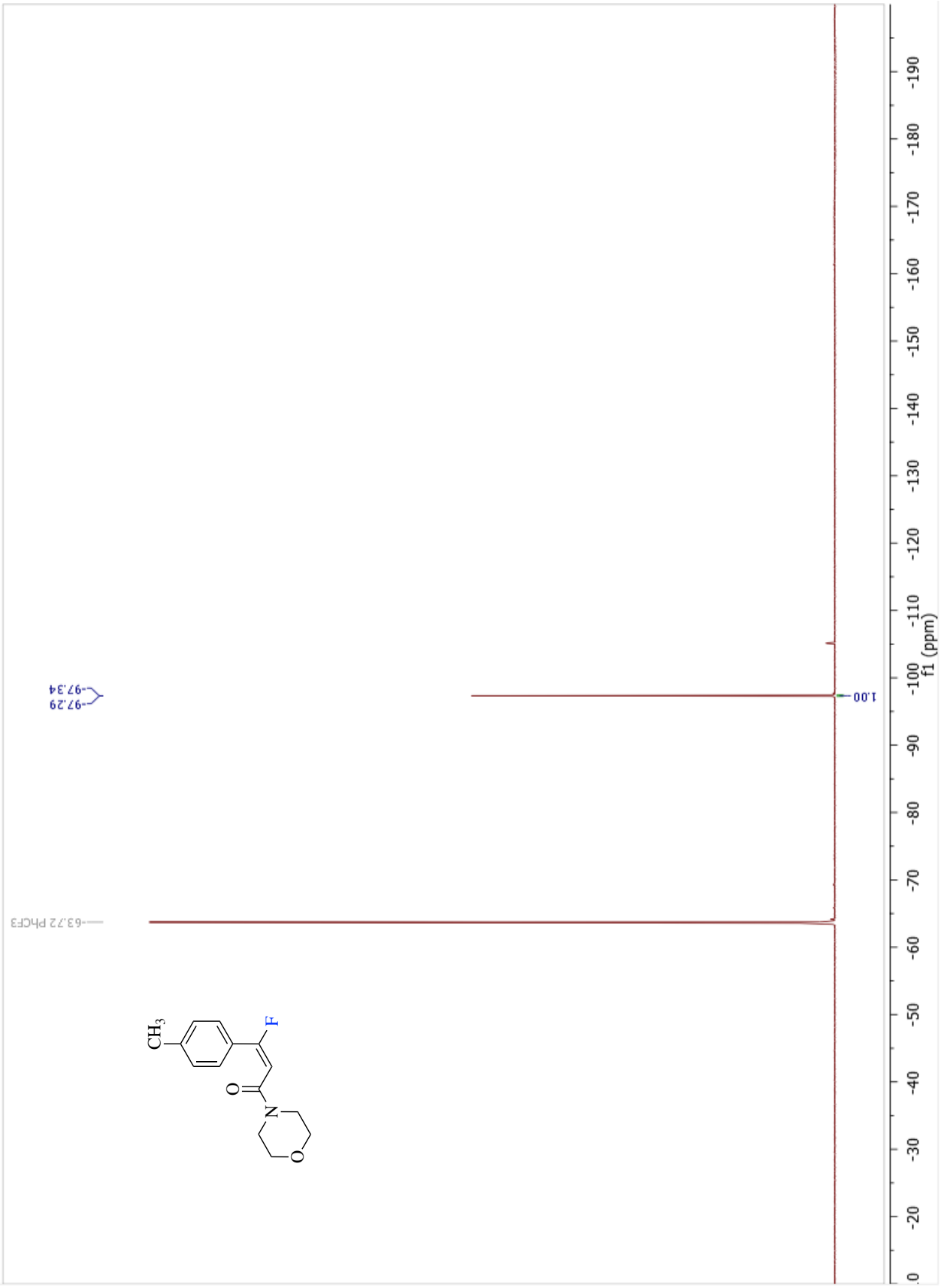

3.36
3.61
3.62
3.82
5.74
5.78
6.88
6.90
7.26 CDCl3
7.50
7.52
4.03
4.06
3.11
1.00
2.04
1.98
f1 (ppm)
OCH3
F
O
N
O

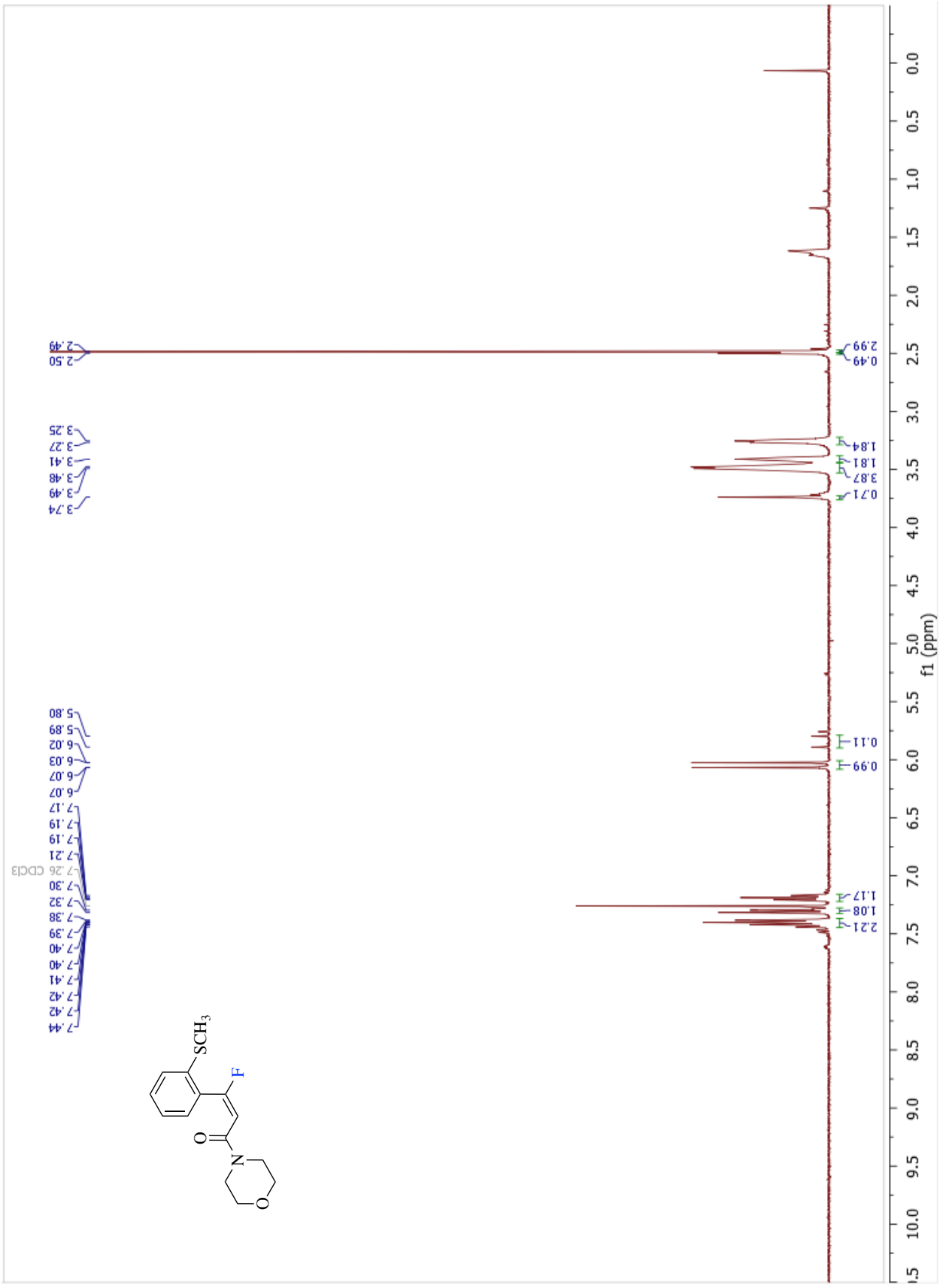

41.99
46.95
55.46
66.52
77.16 CDCl3
99.98
100.21
114.00
122.77
122.99
129.09
129.14
161.21
161.52
163.25
164.78
164.93
OCH3
F
O
N
O
f1 (ppm)

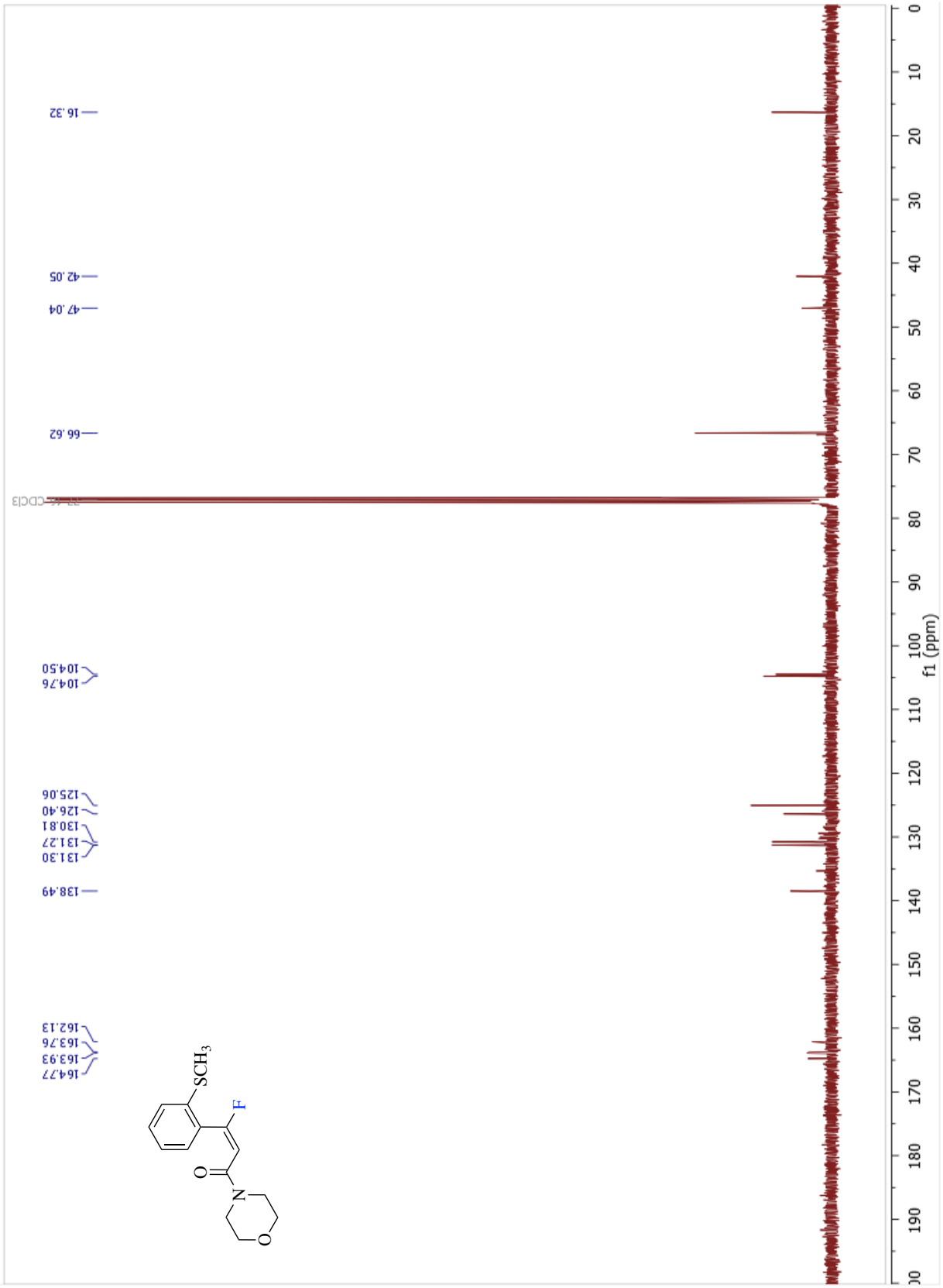

-63.72 PhCF3
-96.19
-96.24
1.00
f1 (ppm)
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
OCH3
F
O
N
O

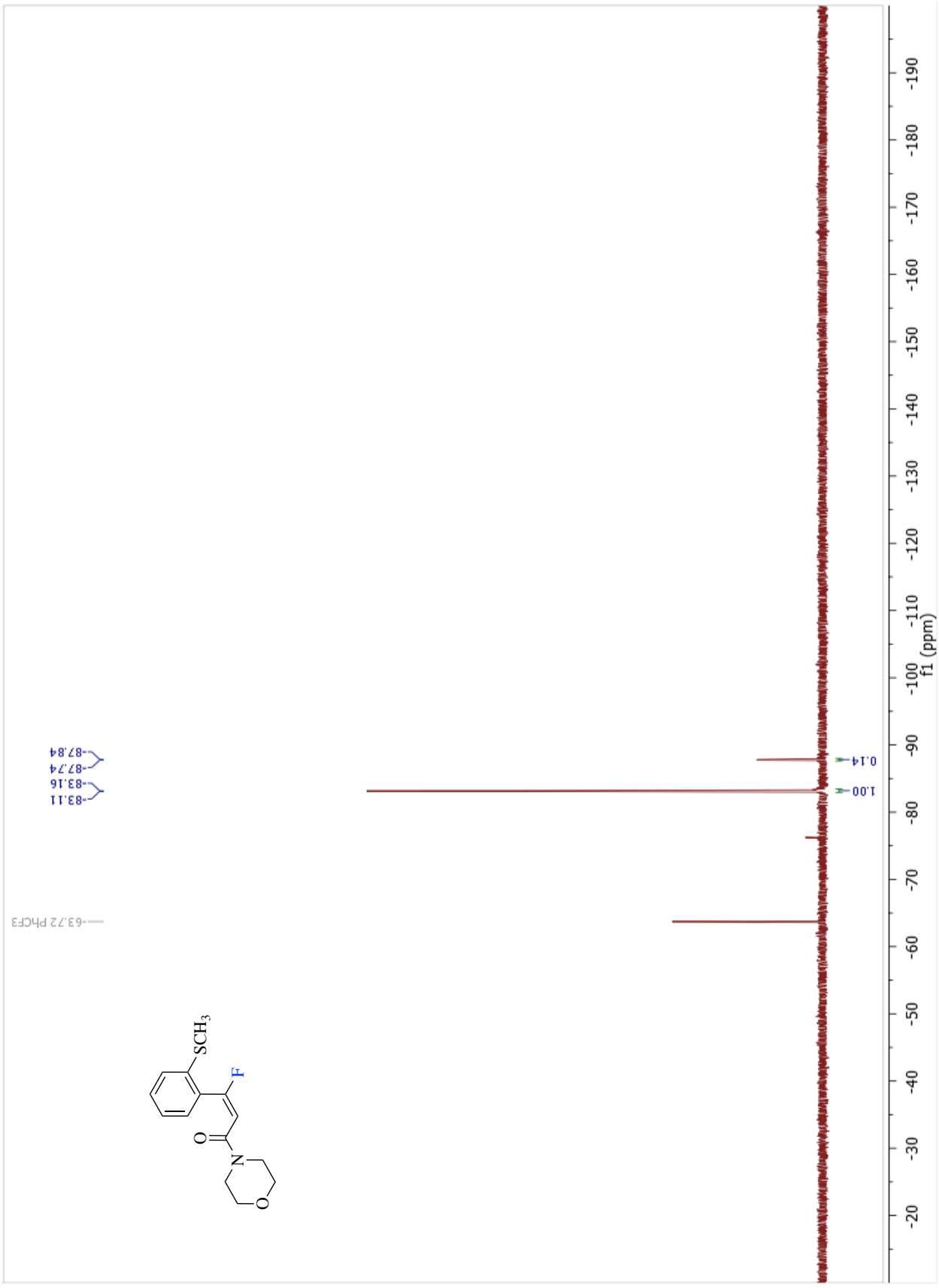

f1 (ppm)
3.16
4.11
4.22
1.00
2.05
2.00
CDCl3

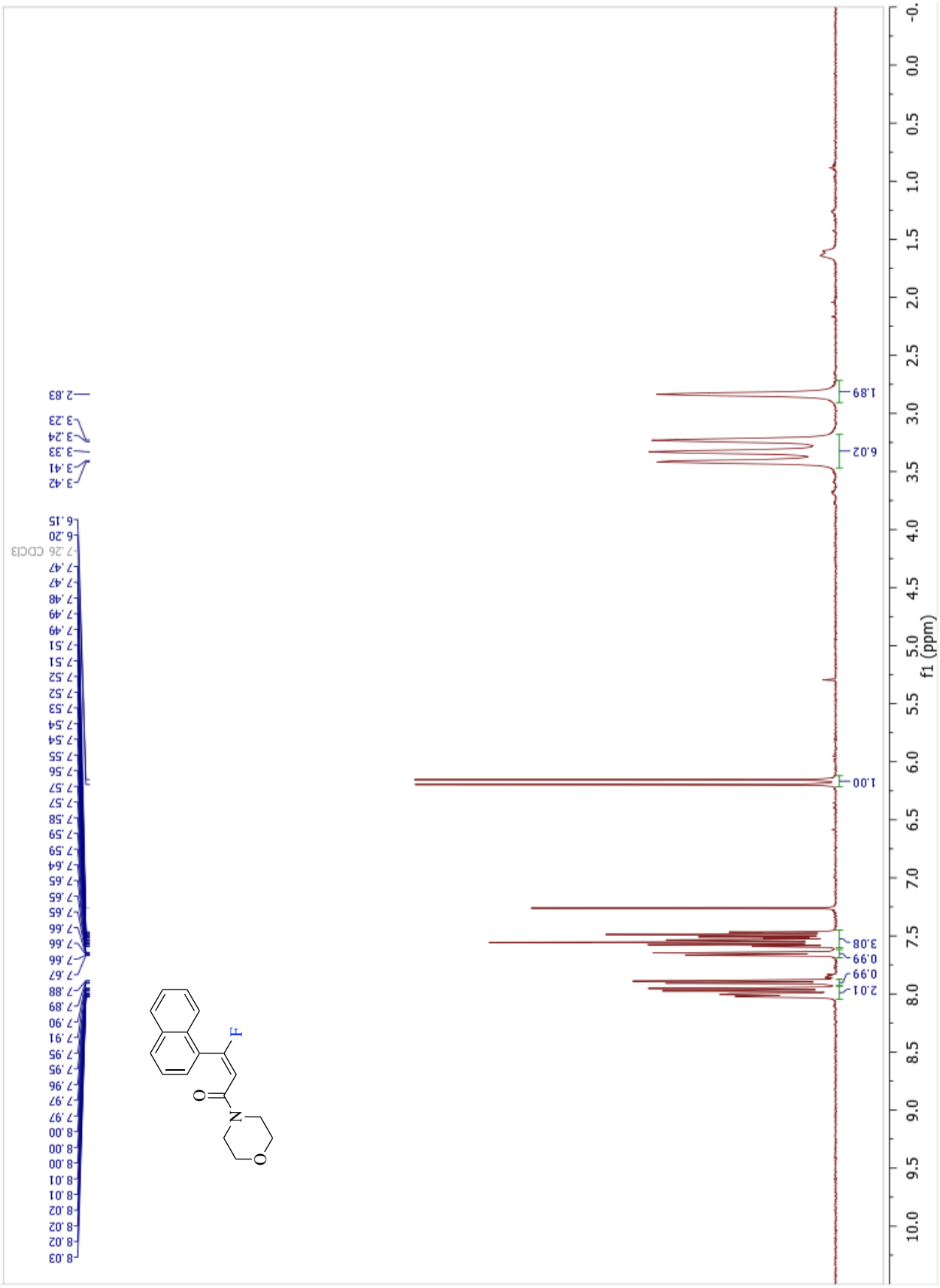

165.15
164.96
163.76
161.20
141.59
129.65
127.62
127.56
101.49
101.21
77.16 CDCl3
66.76
47.24
42.31
21.89
f1 (ppm)

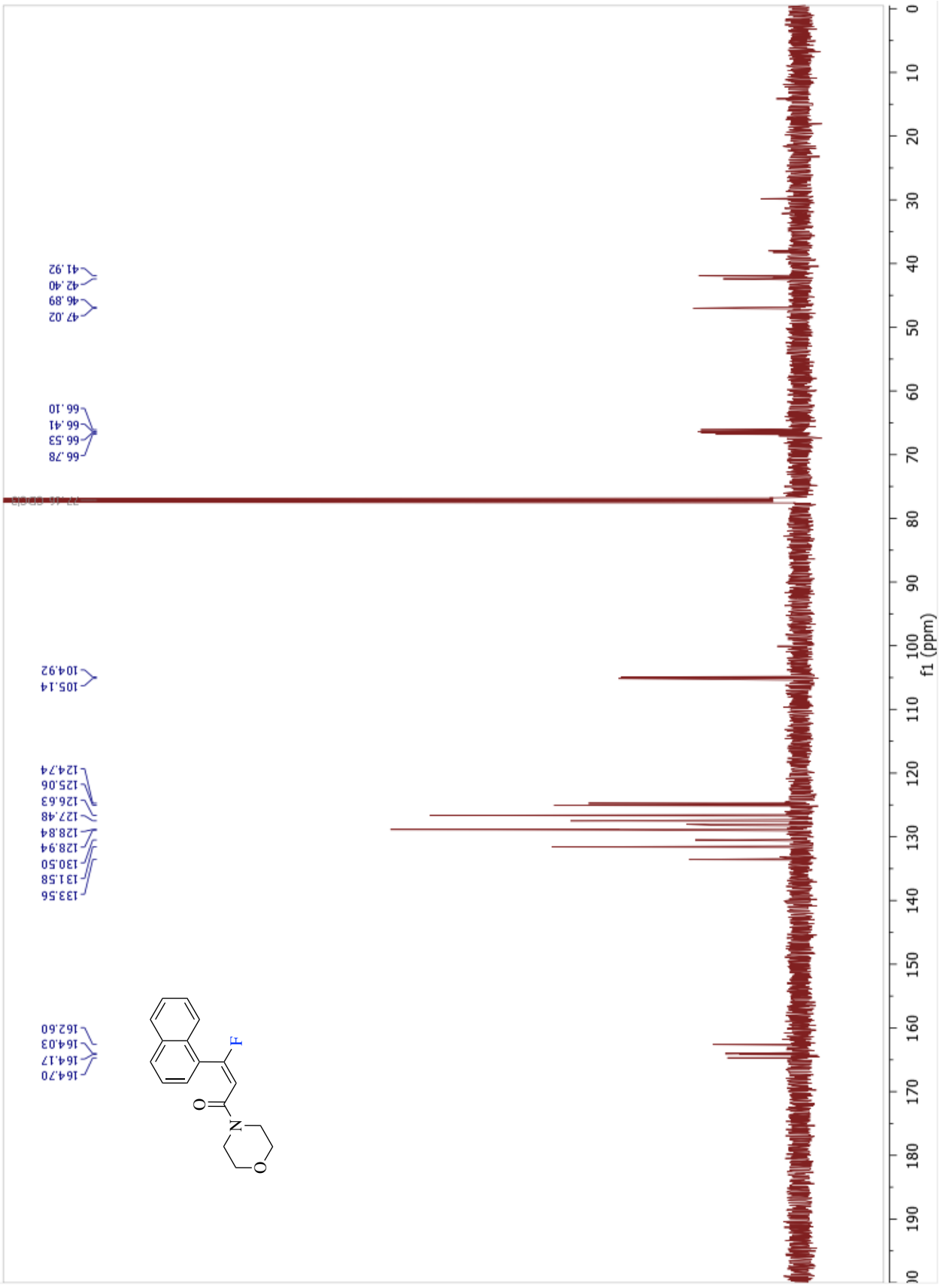

-63.72 PhCF3
-97.29
-97.34
1.00
f1 (ppm)
0
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
CH3
F
O
N
O


SCH3
F
O
N
O
f1 (ppm)

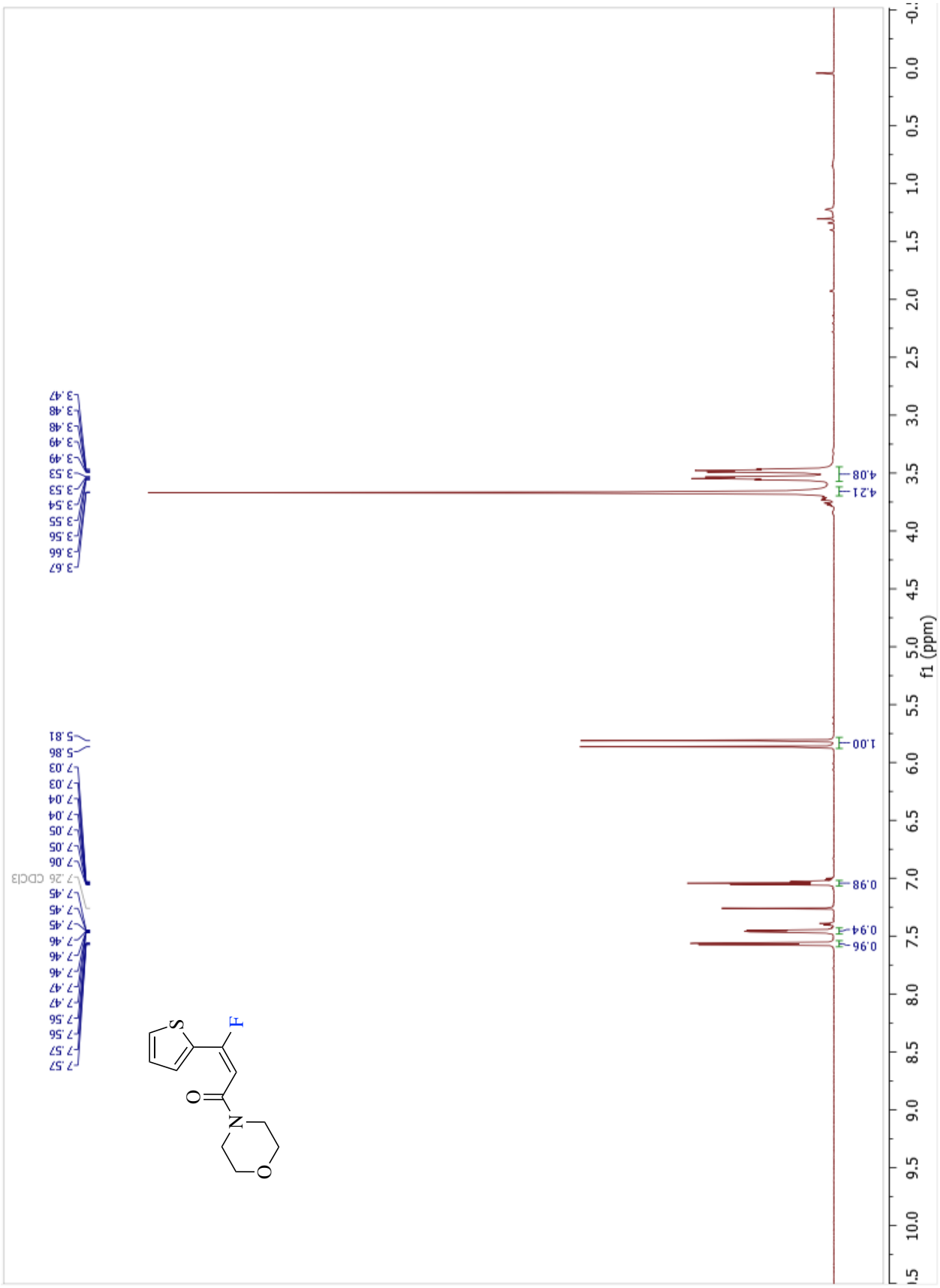

16.32
42.05
47.04
66.62
77.16 CDCl3
104.50
104.76
125.06
126.40
130.81
131.27
131.30
138.49
162.13
163.76
163.93
164.77
SCH3
F
O
N
O
f1 (ppm)

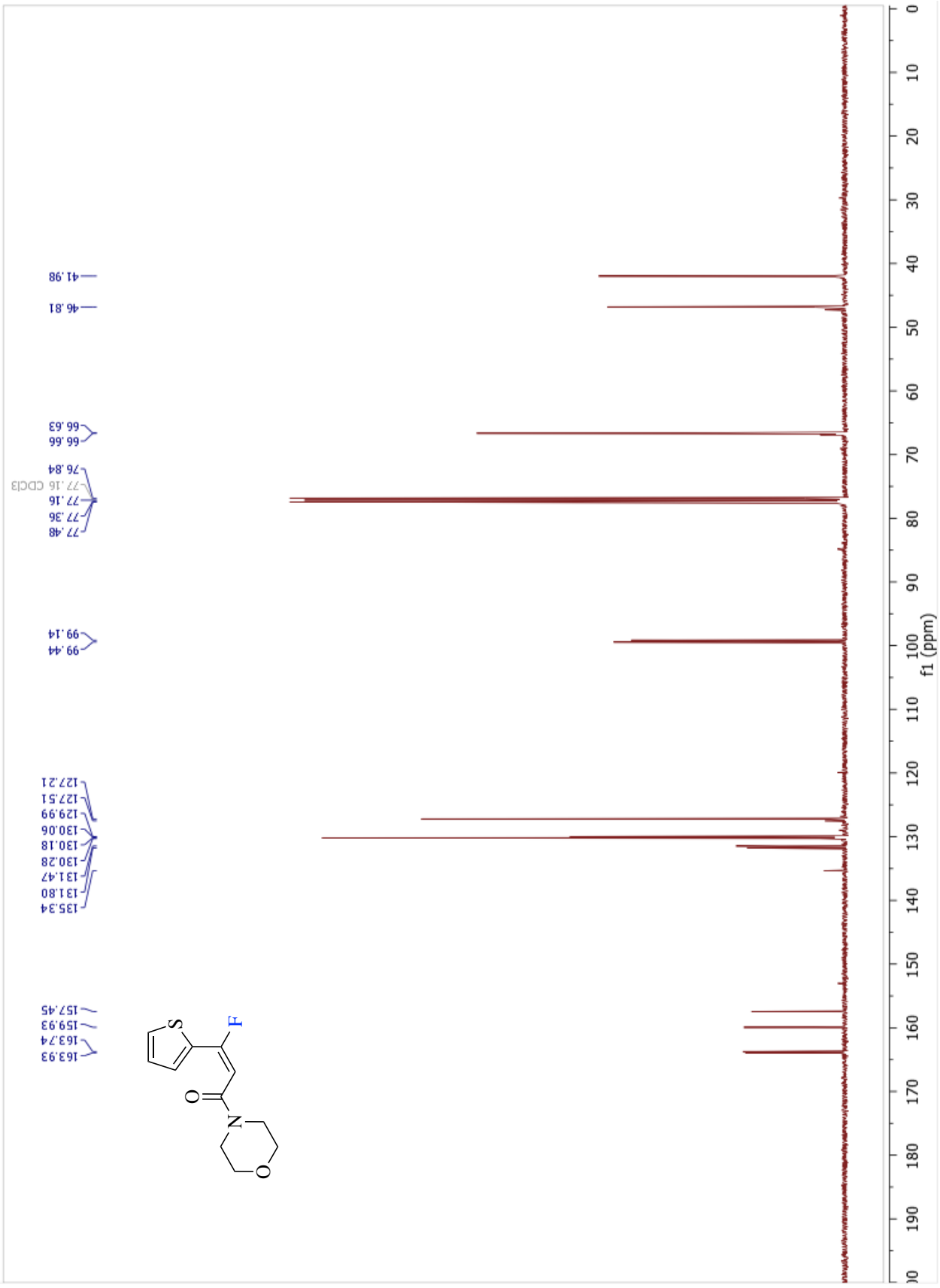

-83.11
-83.16
-87.74
-87.84
-63.72 PhCF3
0.14
1.00
f1 (ppm)
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
SCH3
F
O
N
O

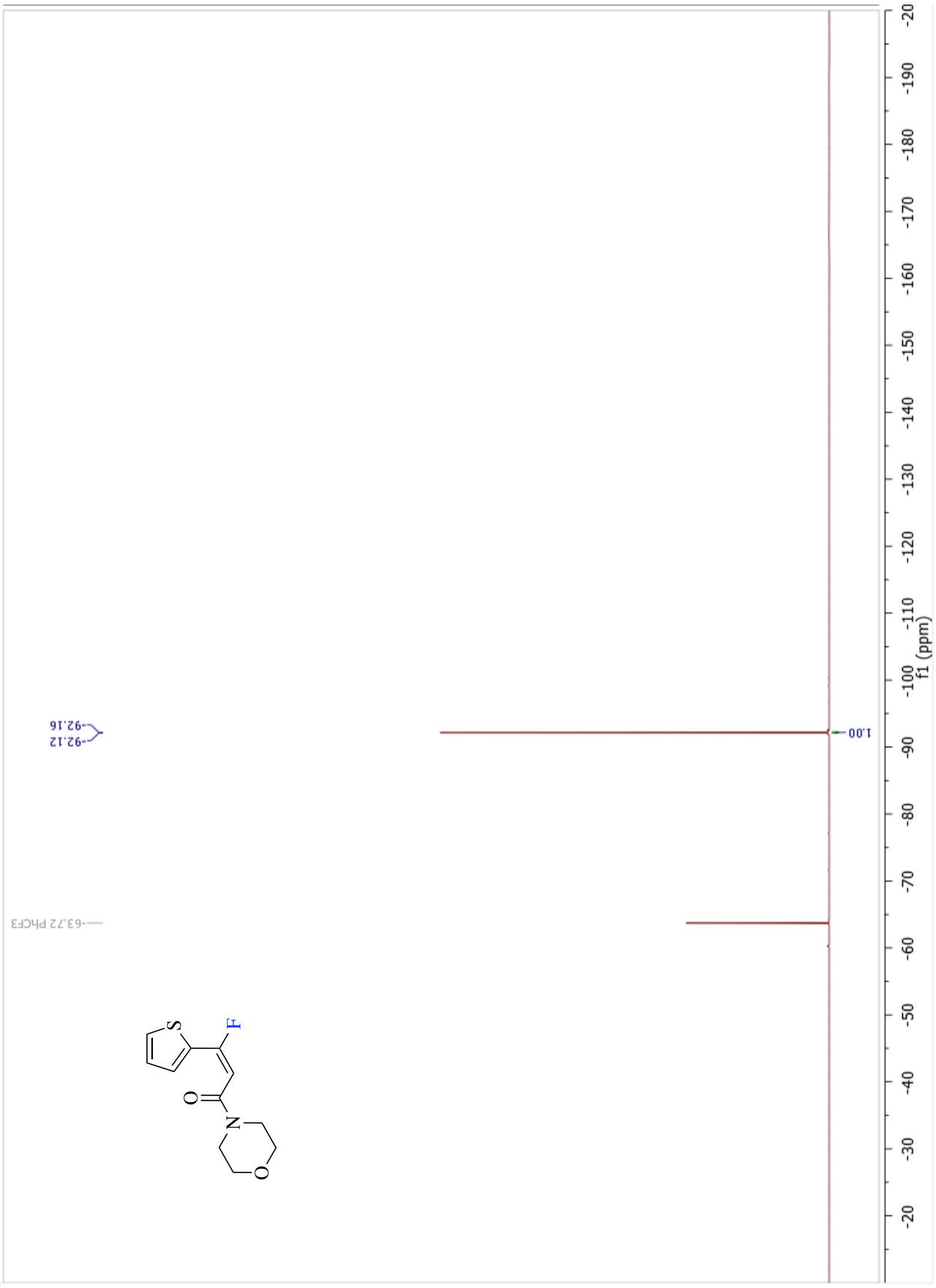

F
O
N
O
1.89
6.02
1.00
3.08
0.99
0.99
2.01
f1 (ppm)

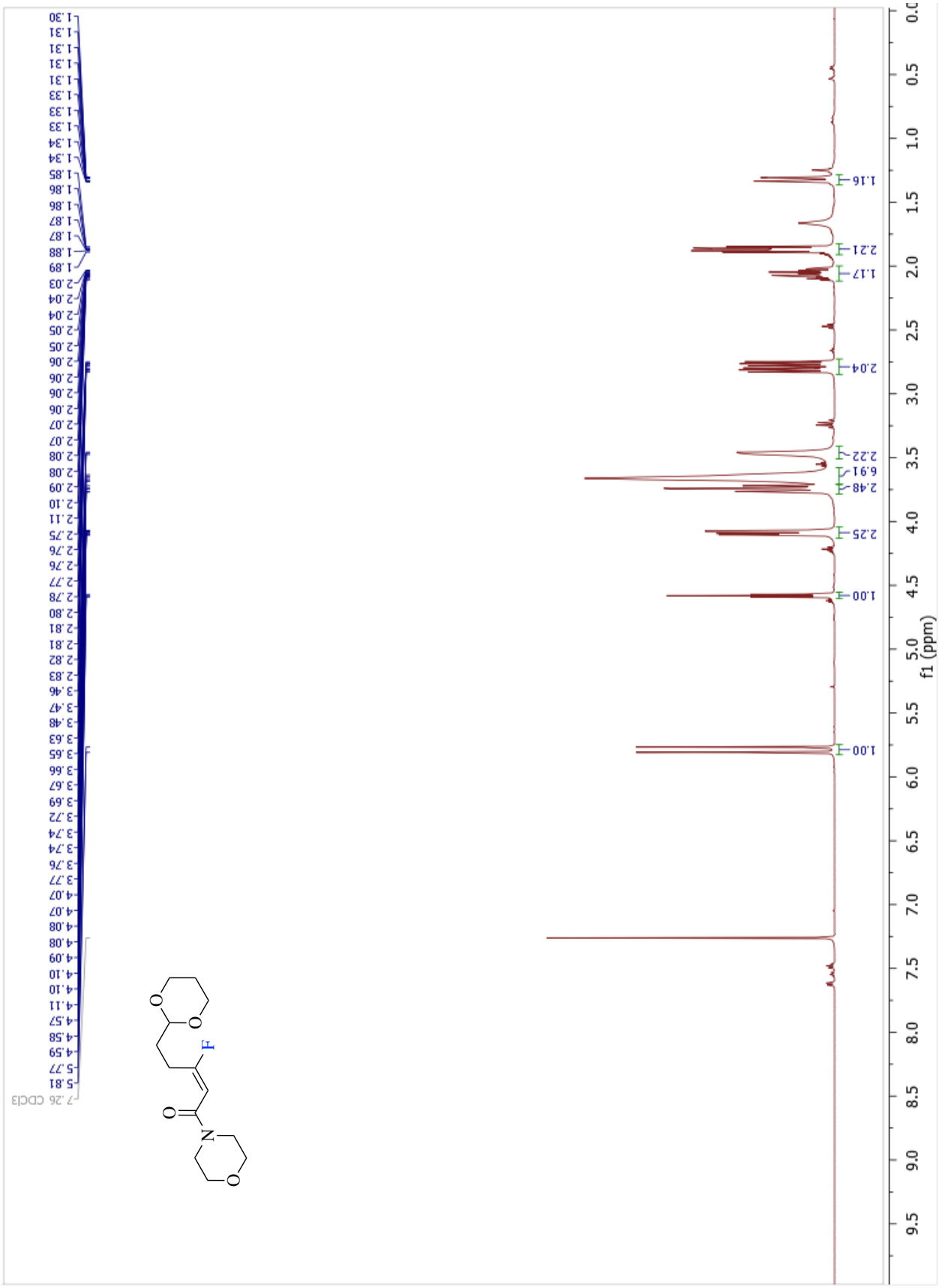

41.92
42.40
46.89
47.02
66.10
66.41
66.53
66.78
77.16 - 82.83
104.92
105.14
124.74
125.06
126.63
127.48
128.84
128.94
130.50
131.58
133.56
162.60
164.03
164.17
164.70
F
O
N
O
f1 (ppm)

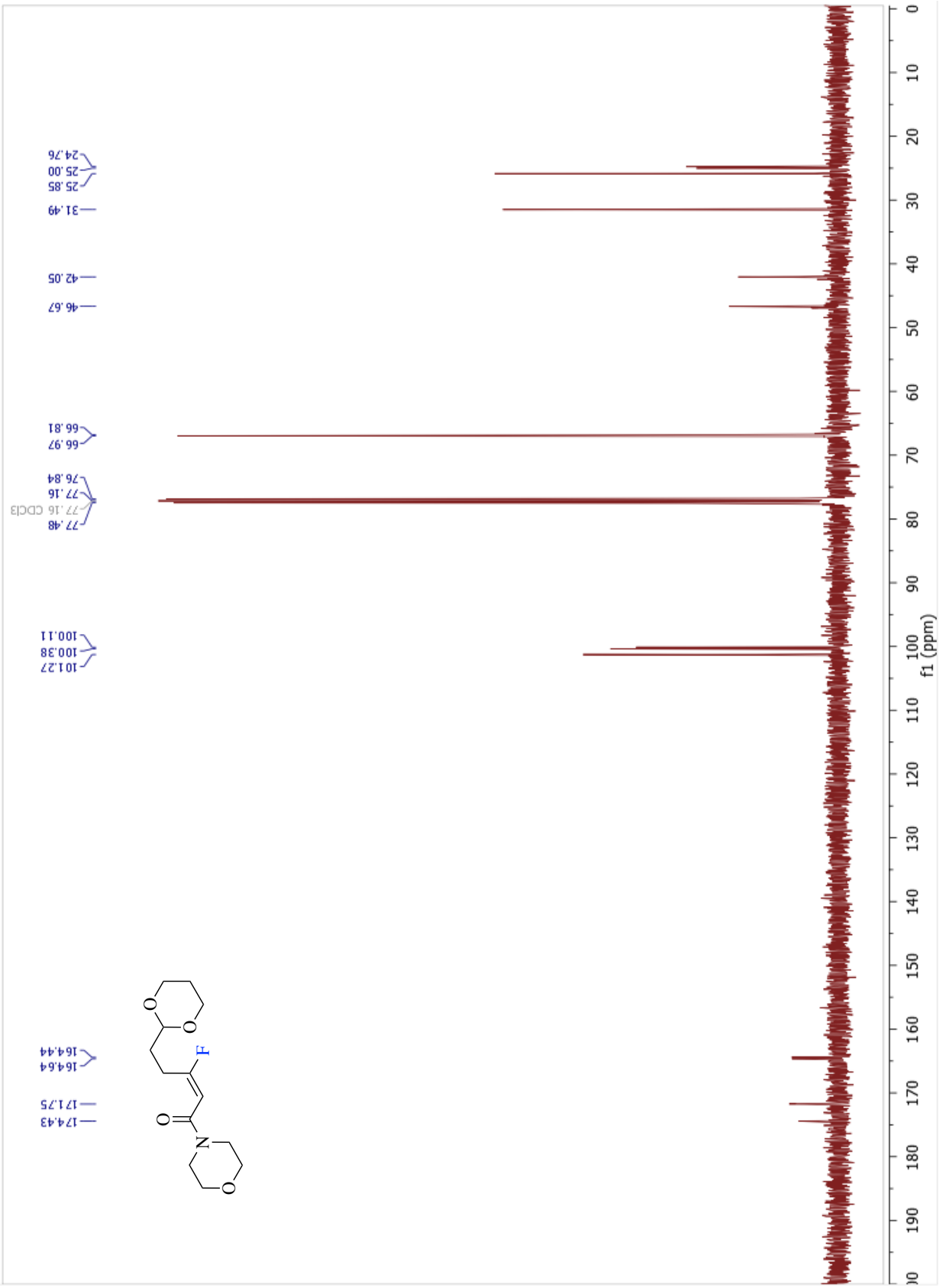

-82.91
-82.94
63.22 Ph-CF3
F
O
N
O
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-20
f1 (ppm)

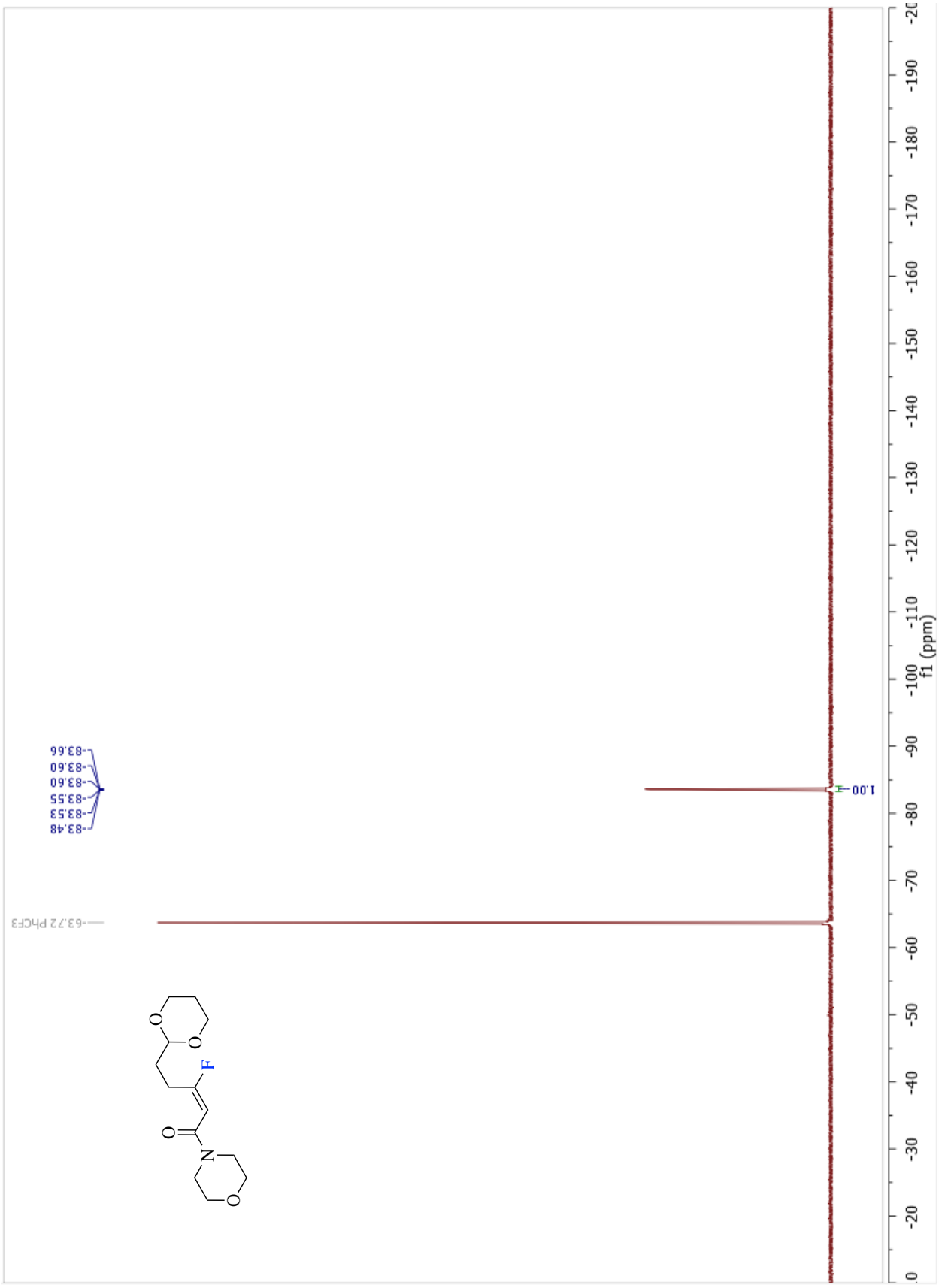

3.47
3.48
3.48
3.49
3.49
3.53
3.53
3.54
3.55
3.56
3.66
3.67
4.08
4.21
5.81
5.86
7.03
7.03
7.04
7.04
7.05
7.05
7.06
7.26 CDCl3
7.45
7.45
7.45
7.46
7.46
7.46
7.47
7.47
7.56
7.56
7.57
7.57
1.00
0.98
0.94
0.96
S
F
O
N
O
f1 (ppm)

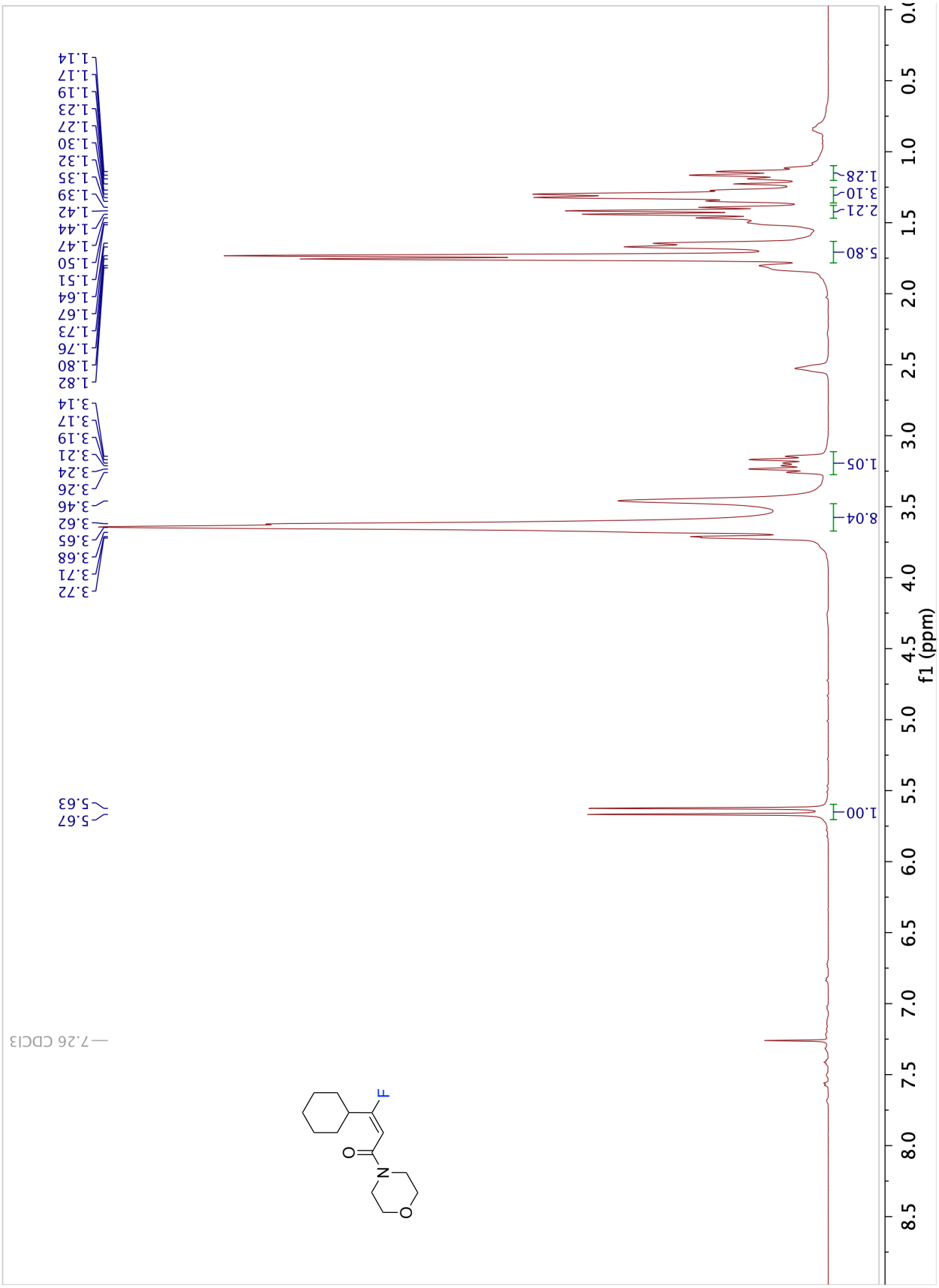

163.93
163.74
159.93
157.45
135.34
131.80
131.47
130.28
130.18
130.06
129.99
127.51
127.21
99.44
99.14
77.48
77.36
77.16
77.16 CDCl3
76.84
66.66
66.63
46.81
41.98
f1 (ppm)
F
S
O
N
O

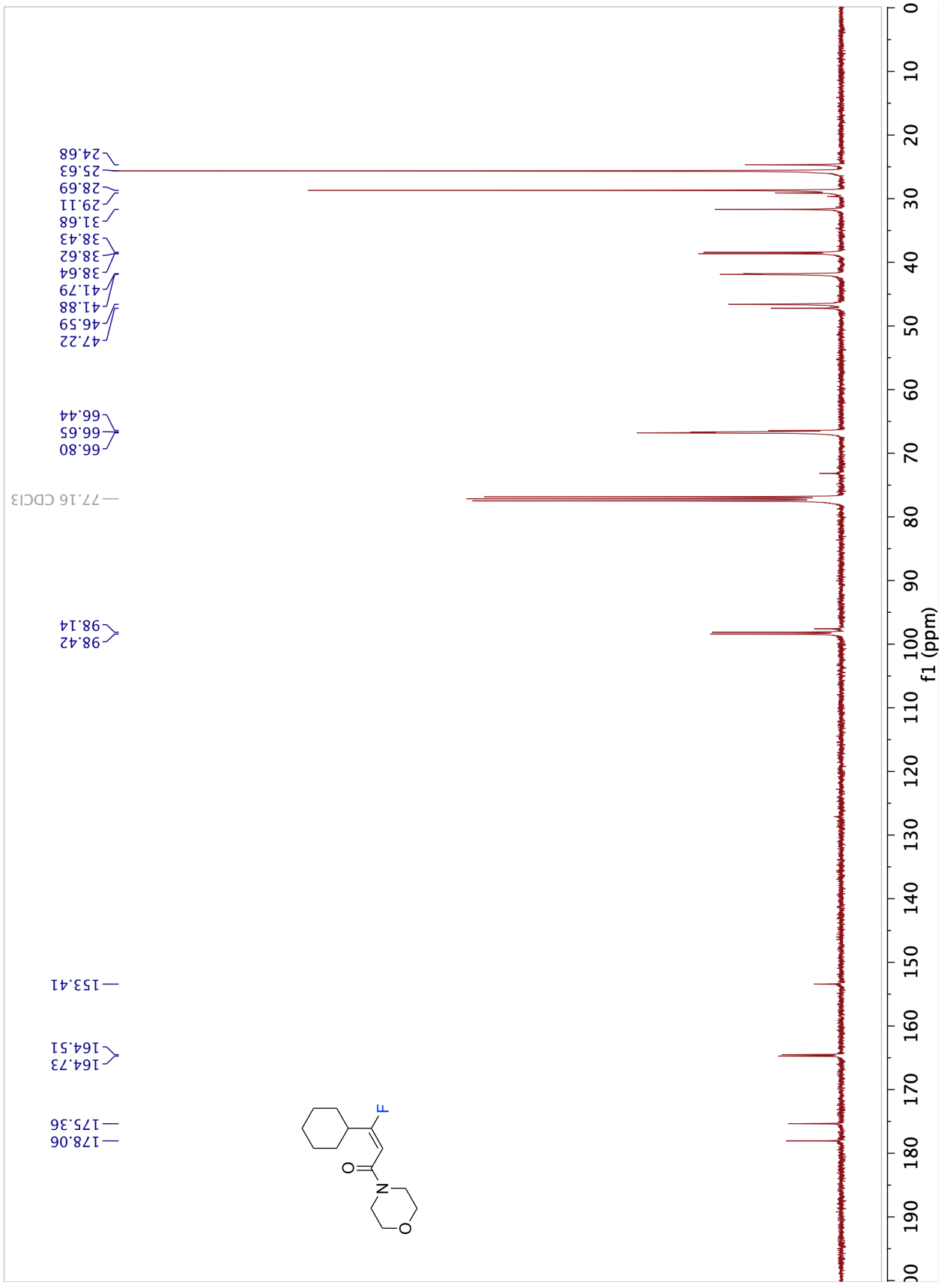

-92.12
-92.16
1.00
-63.72 PhCF3
F
S
O
N
O
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-20
f1 (ppm)

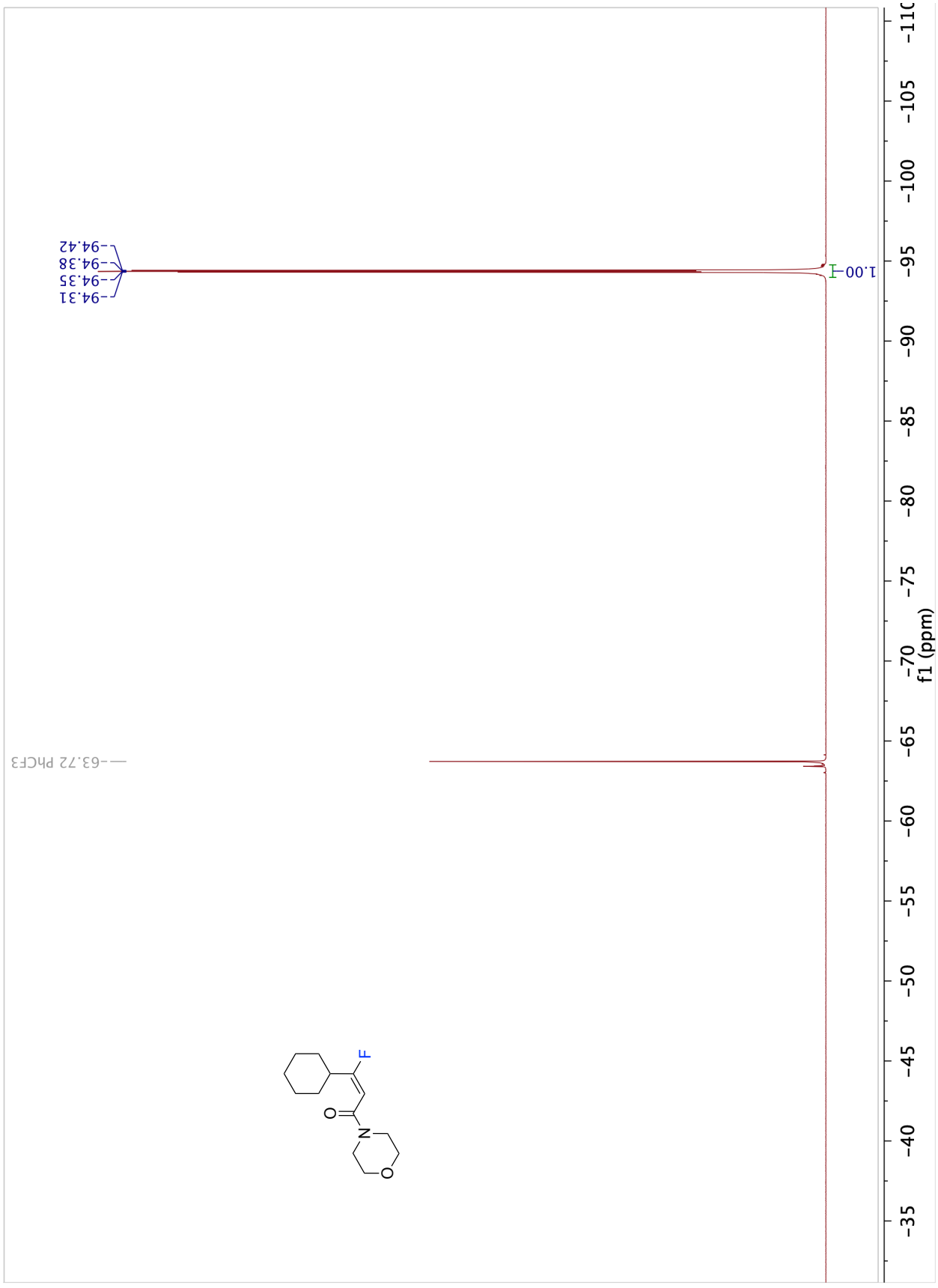

f1 (ppm)
1.16
2.21
1.17
2.04
2.22
6.91
2.48
2.25
1.00
1.00
7.26 CDCl3

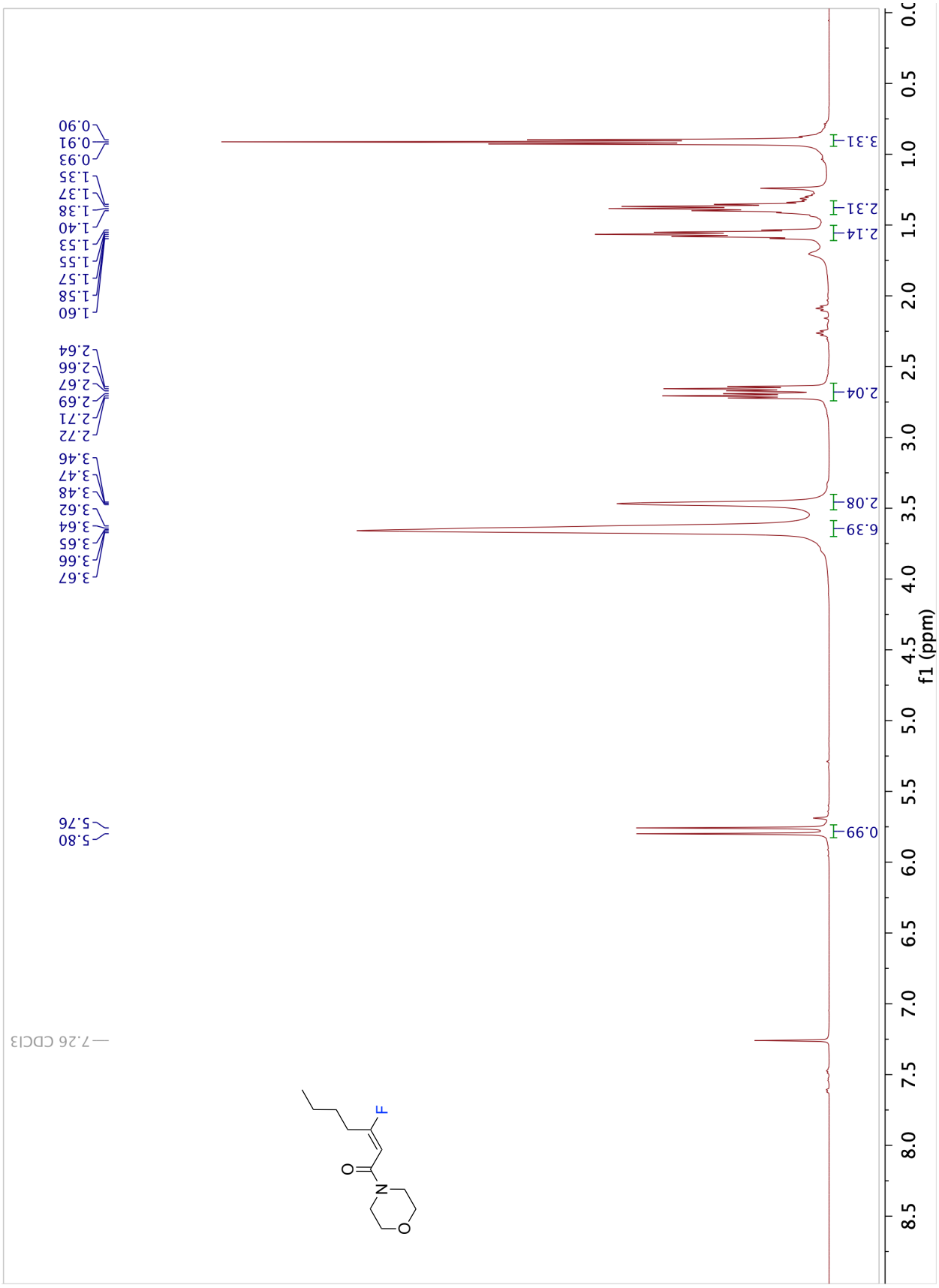

174.43
171.75
164.64
164.44
101.27
100.38
100.11
77.48
77.16 CDCl3
77.16
76.84
66.97
66.81
46.67
42.05
31.49
25.85
25.00
24.76
F
O
O
O
N
O
f1 (ppm)

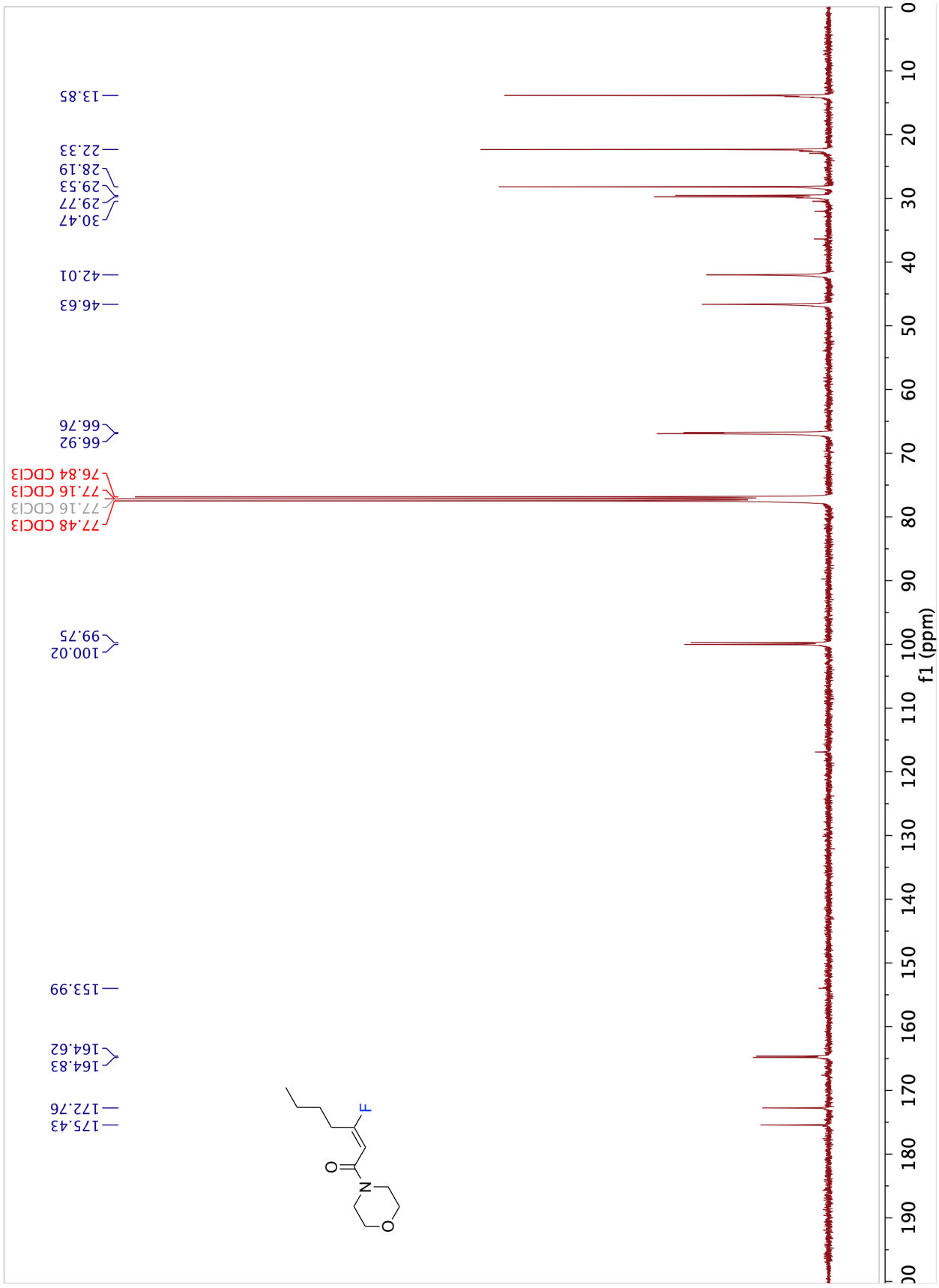

-63.72 PhCF3
-83.48
-83.53
-83.55
-83.60
-83.60
-83.66
1.00
f1 (ppm)

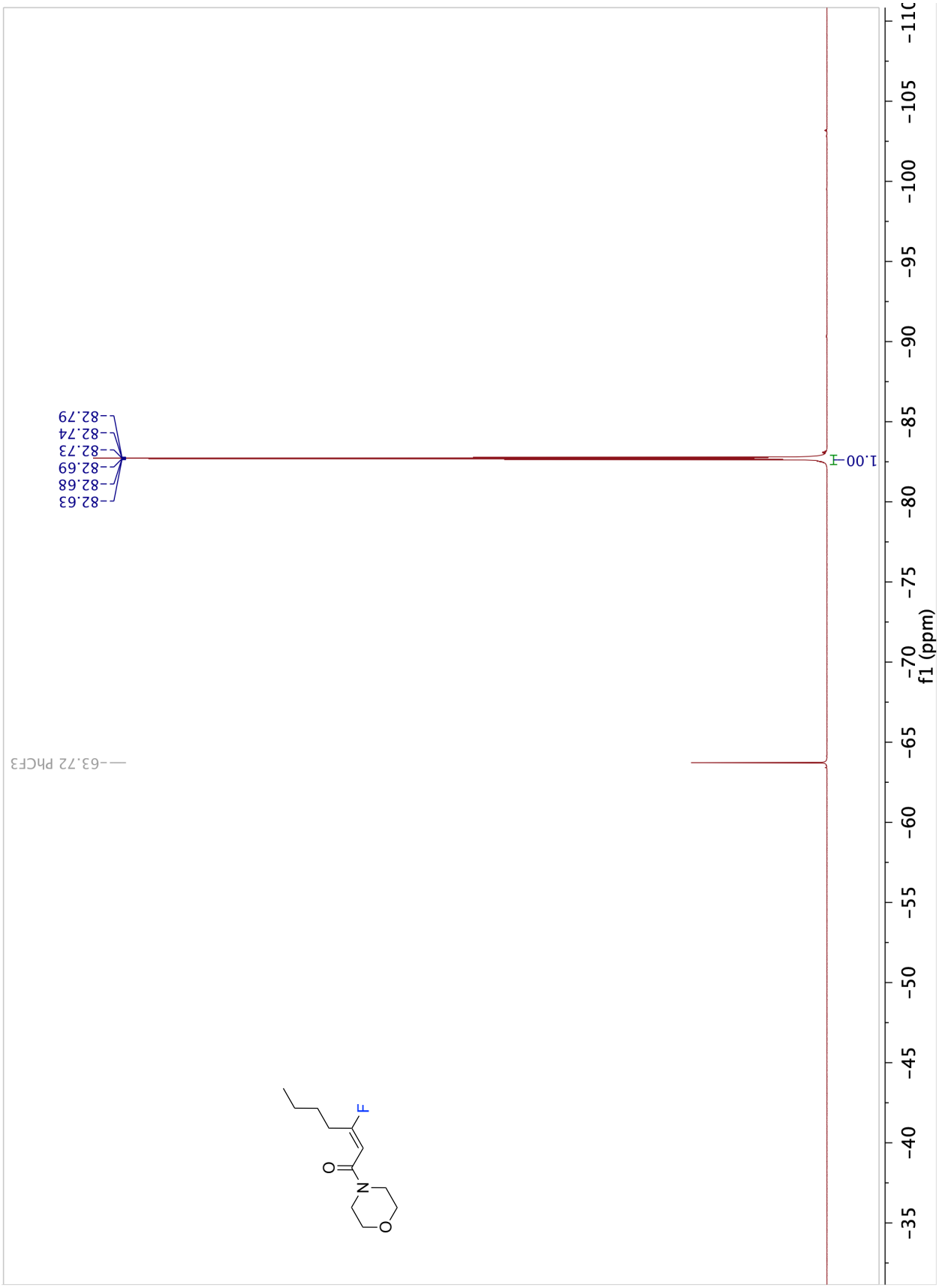

1.14
1.17
1.19
1.23
1.27
1.30
1.32
1.35
1.39
1.42
1.44
1.47
1.50
1.51
1.64
1.67
1.73
1.76
1.80
1.82
3.14
3.17
3.19
3.21
3.24
3.26
3.46
3.62
3.65
3.68
3.71
3.72
5.63
5.67
7.26 CDCl3
1.00
8.04
1.05
5.80
2.21
3.10
1.28
F
O
N
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

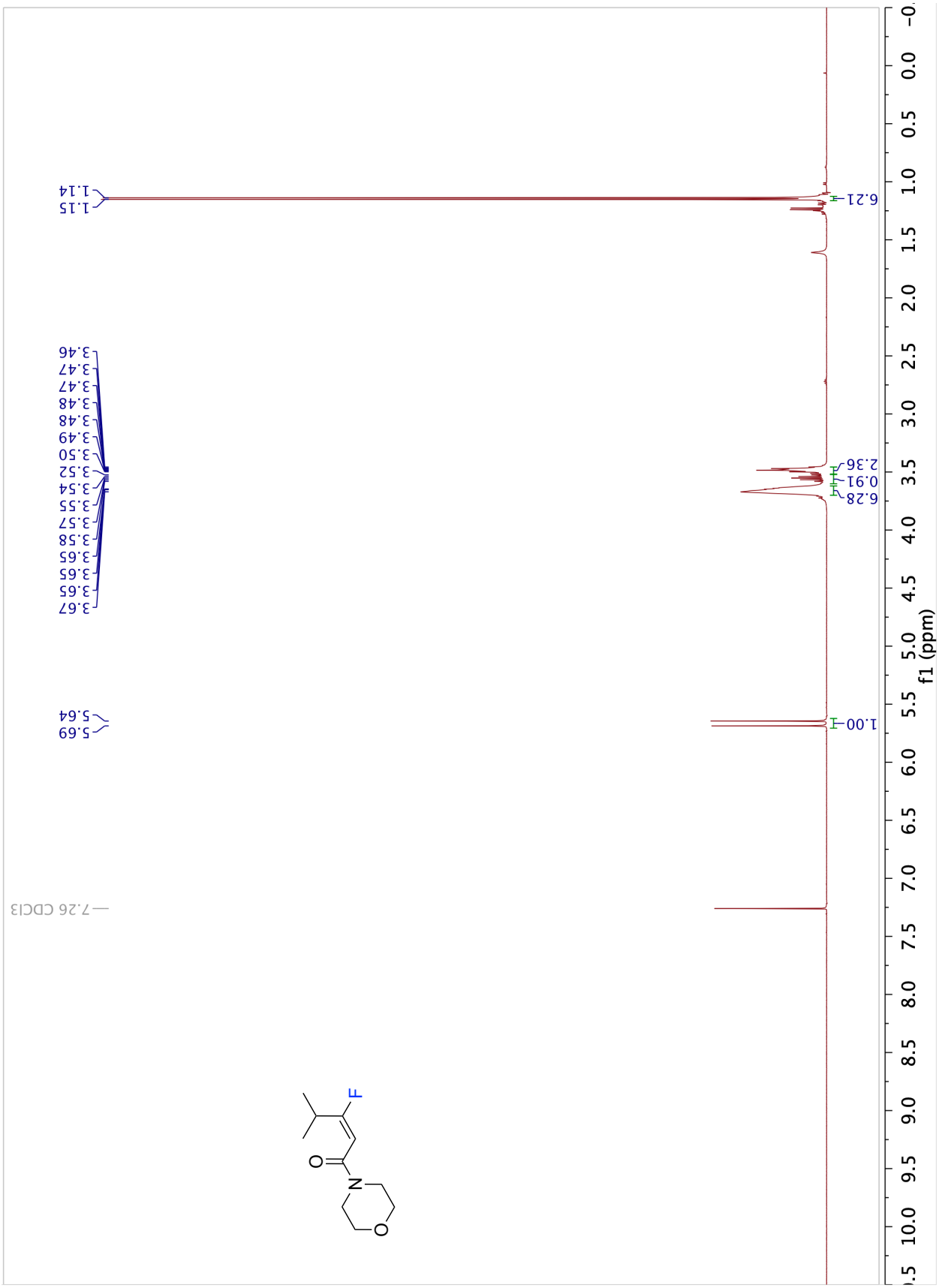

178.06
175.36
164.73
164.51
153.41
98.42
98.14
77.16 CDCl3
66.80
66.65
66.44
47.22
46.59
41.88
41.79
38.64
38.62
38.43
31.68
29.11
28.69
25.63
24.68
F
O
N
O
f1 (ppm)

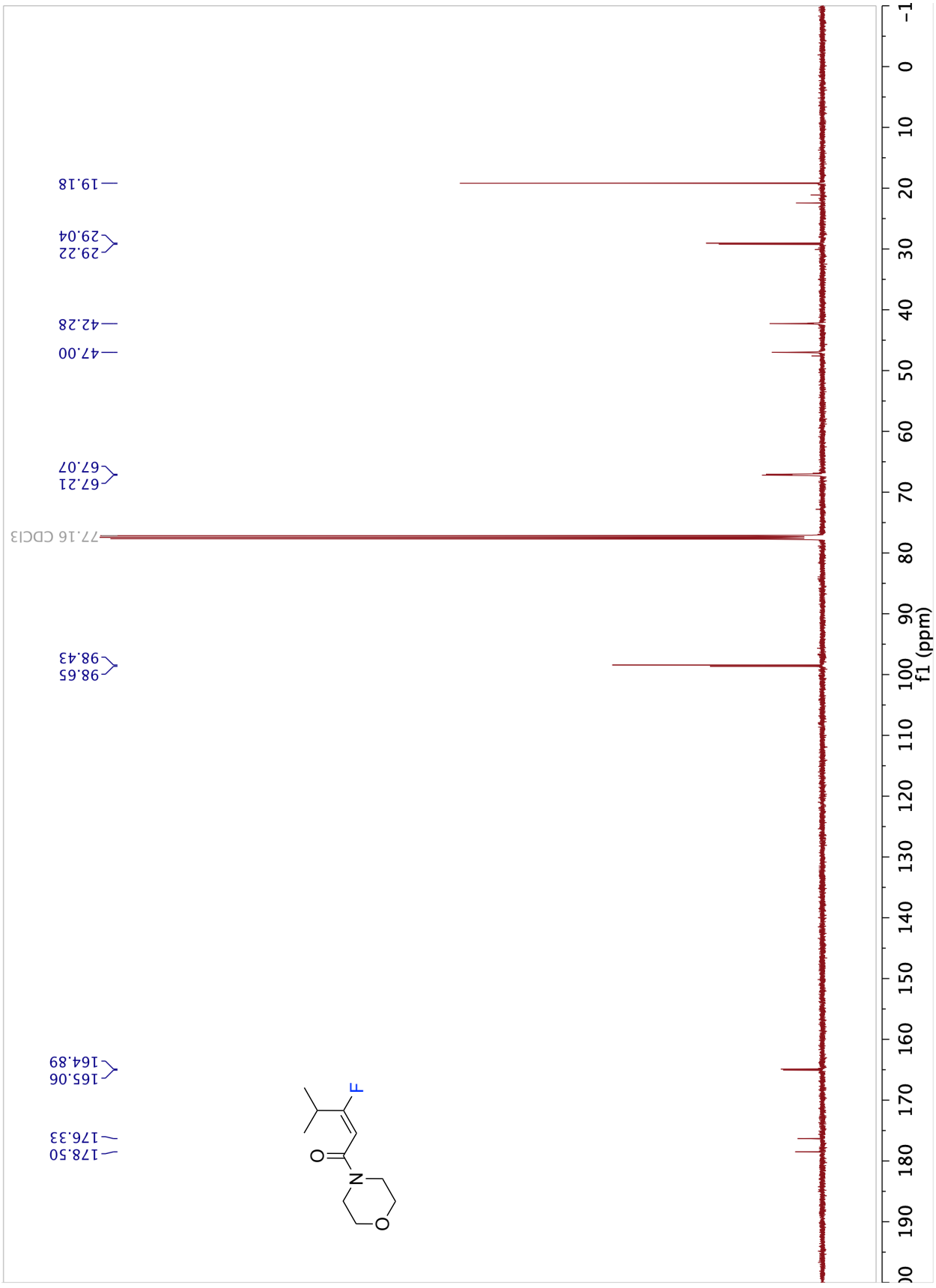

-94.42
-94.38
-94.35
-94.31
1.00
-63.72 PhCF3
F
O
N
O
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
f1 (ppm)

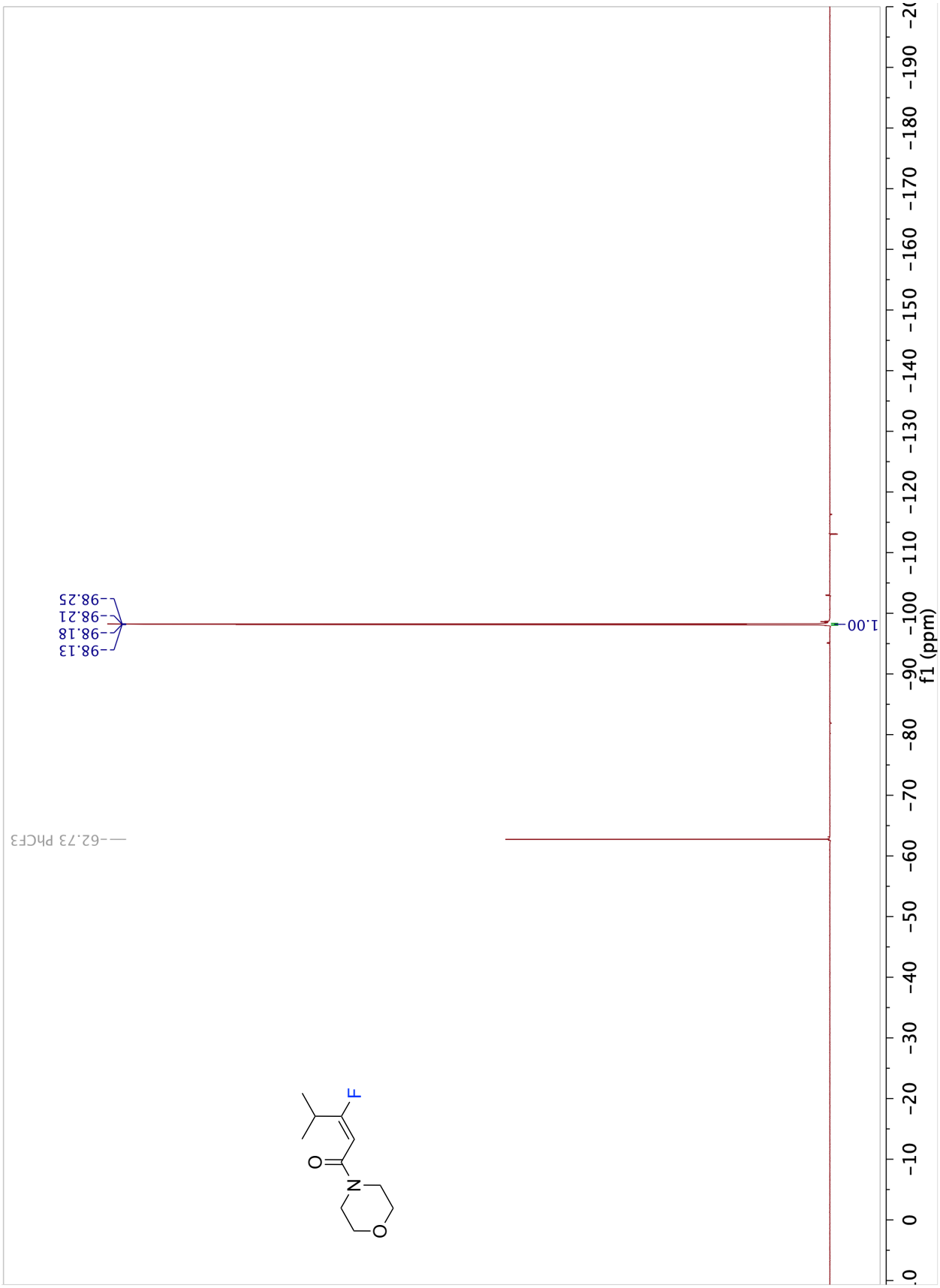

f1 (ppm)
0.90
0.91
0.93
1.35
1.37
1.38
1.40
1.53
1.55
1.57
1.58
1.60
2.64
2.66
2.67
2.69
2.71
2.72
3.46
3.47
3.48
3.62
3.64
3.65
3.66
3.67
5.76
5.80
7.26 CDCl3
3.31
2.31
2.14
2.04
2.08
6.39
0.99
F
O
N
O

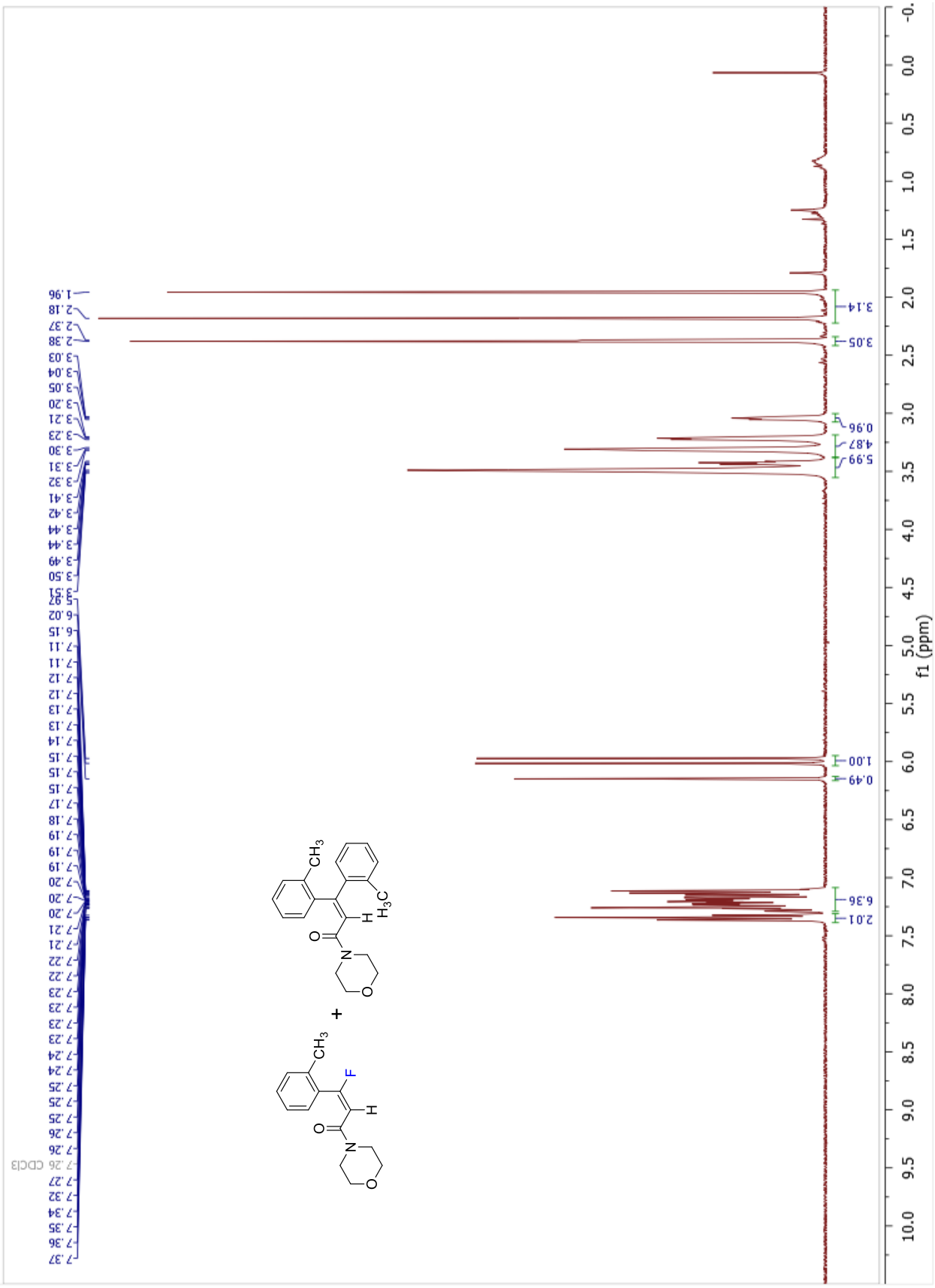

13.85
22.33
28.19
29.53
29.77
30.47
42.01
46.63
66.76
66.92
76.84 CDCl3
77.16 CDCl3
77.16 CDCl3
77.48 CDCl3
99.75
100.02
153.99
164.62
164.83
172.76
175.43
F
O
N
O
f1 (ppm)

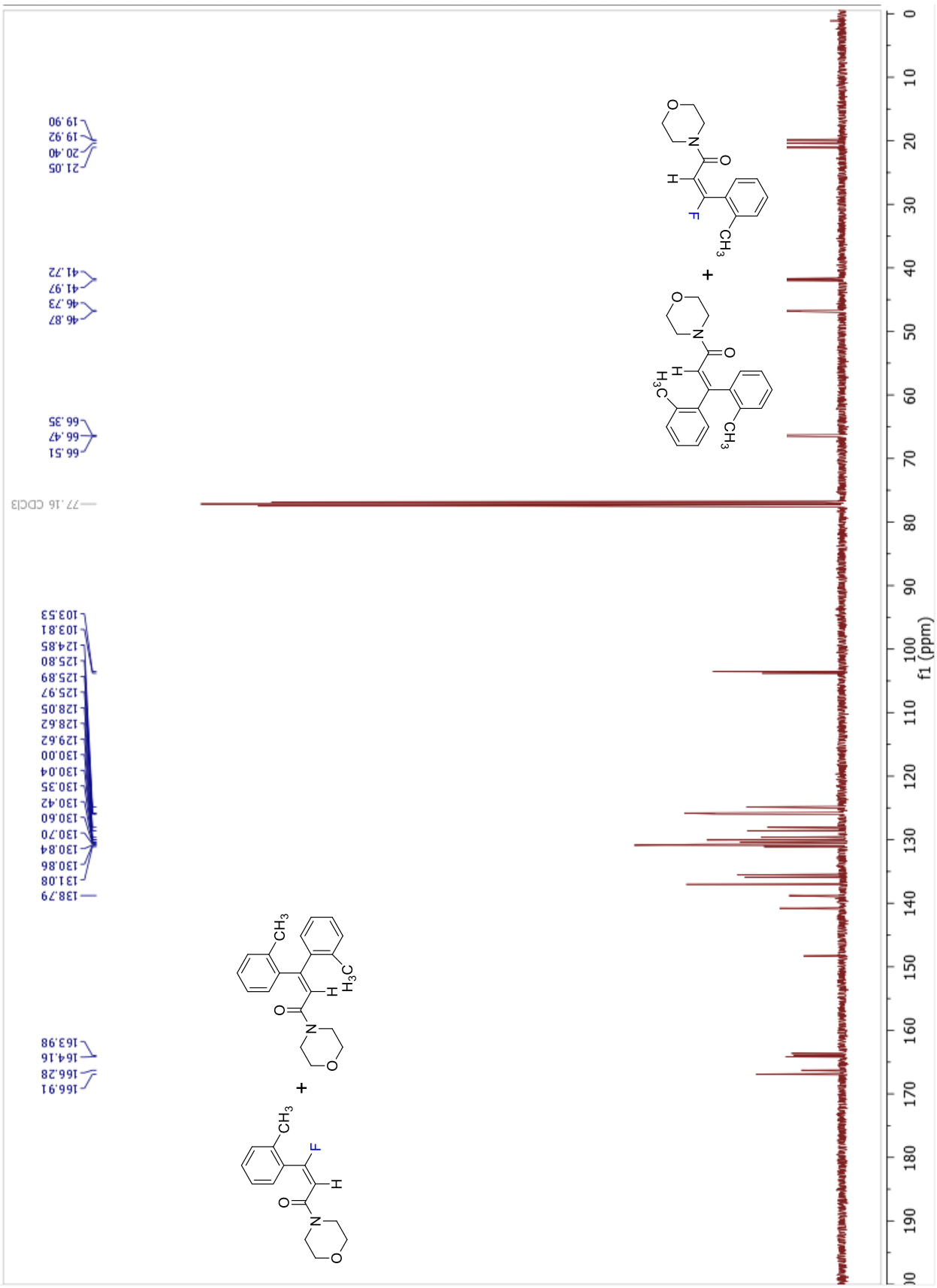

-82.63
-82.68
-82.69
-82.73
-82.74
-82.79
1.00
-63.72 PhCF3
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
f1 (ppm)
F
O
N
O

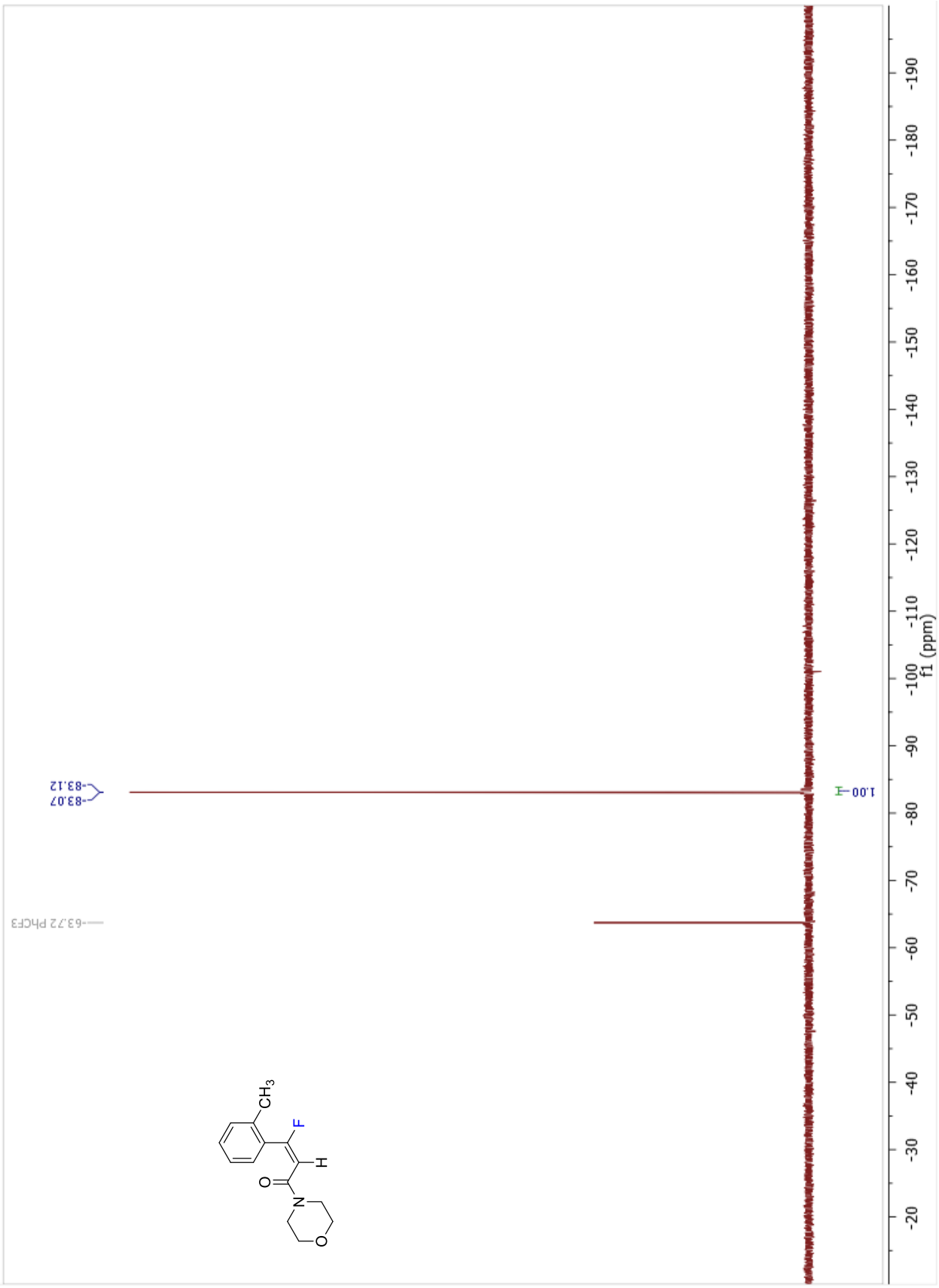

1.15
1.14
3.46
3.47
3.47
3.48
3.48
3.49
3.50
3.52
3.54
3.55
3.57
3.58
3.65
3.65
3.65
3.67
5.64
5.69
7.26 CDCl3
6.21
6.28
0.91
2.36
1.00
F
O
N
O
f1 (ppm)

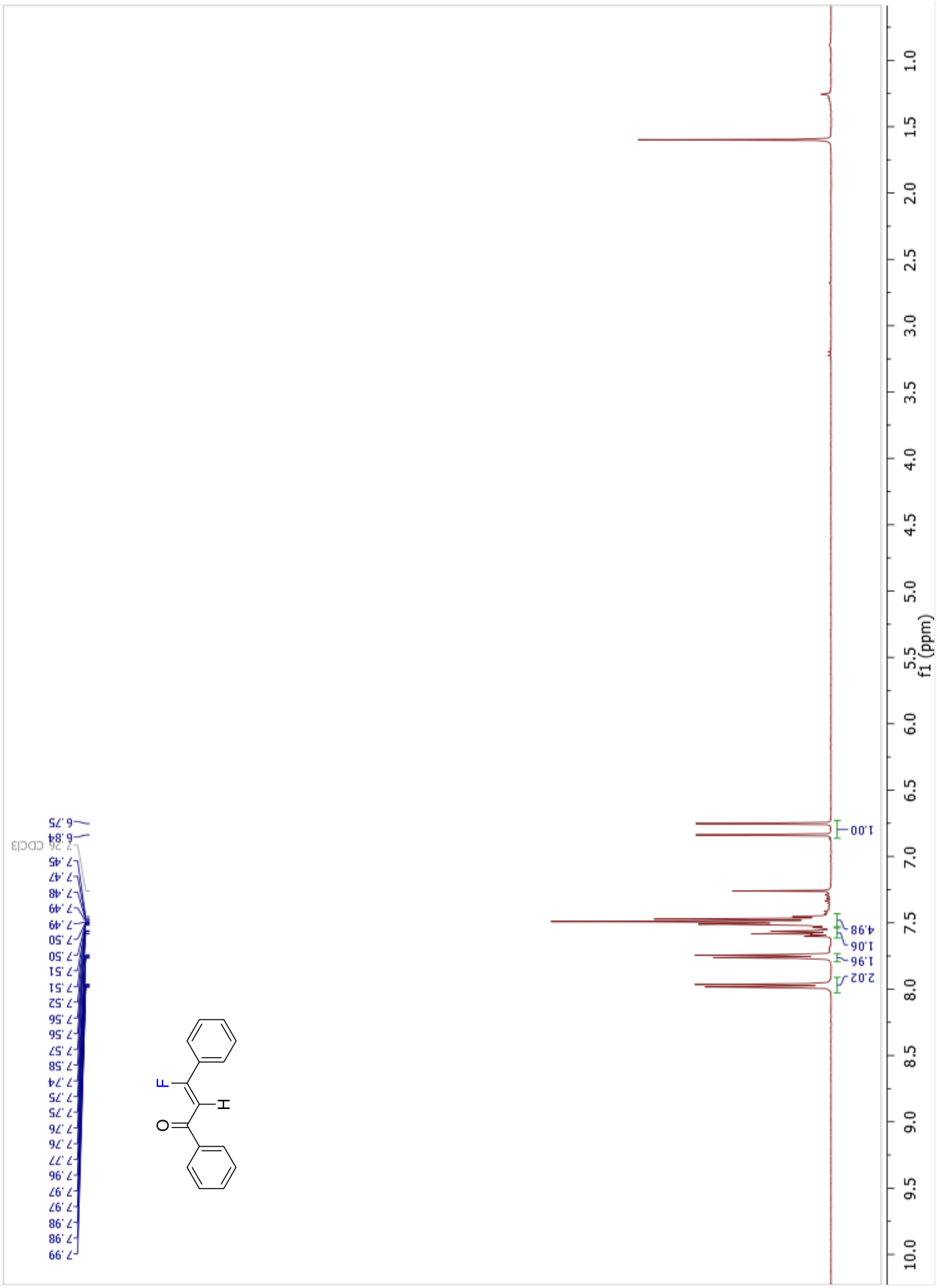

178.50
176.33
165.06
164.89
98.65
98.43
77.16 CDCl3
67.21
67.07
47.00
42.28
29.22
29.04
19.18
F
O
N
O
f1 (ppm)

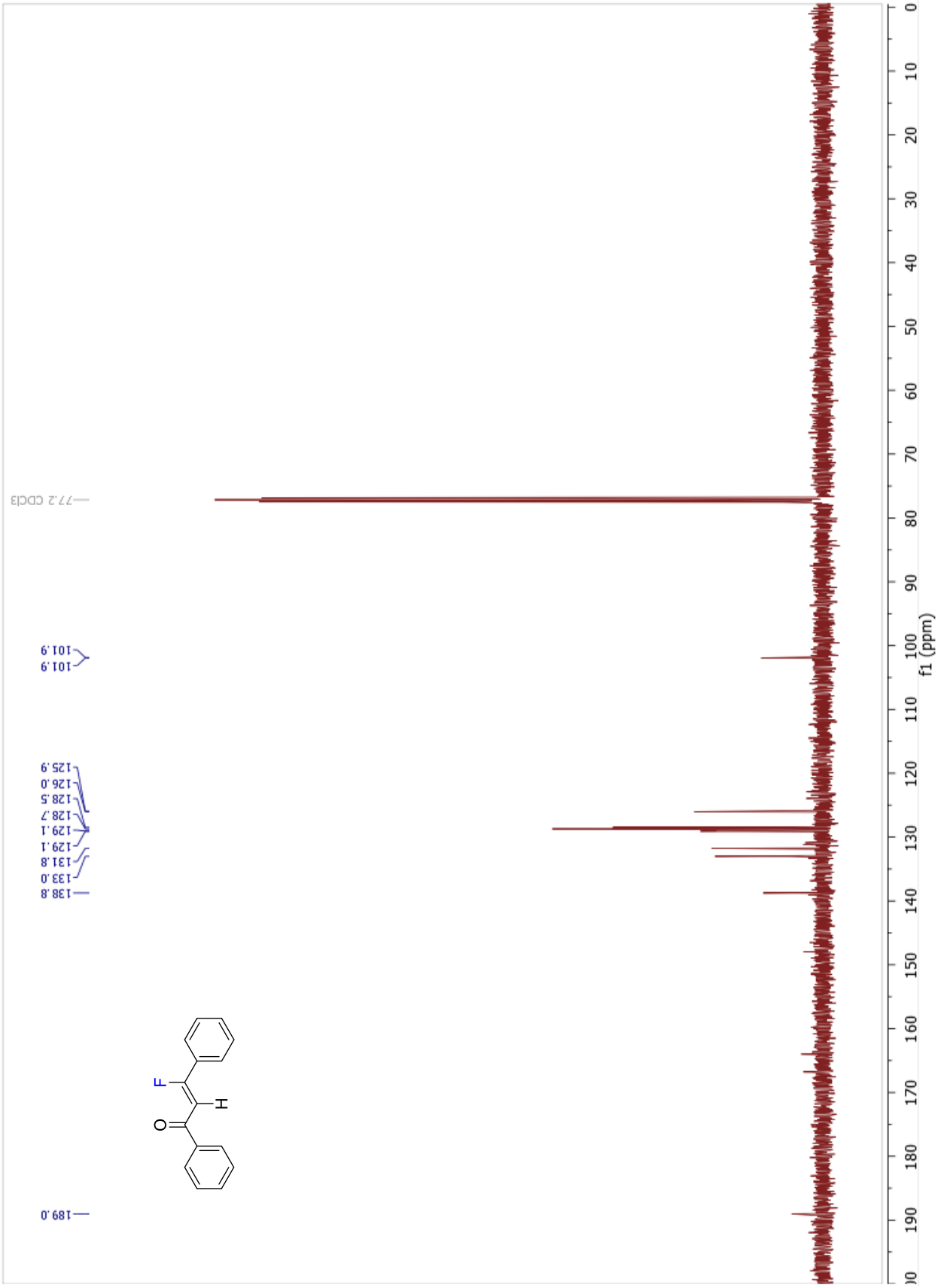

-98.25
-98.21
-98.18
-98.13
1.00
-62.73 PhCF3
f1 (ppm)
F
O
N
O

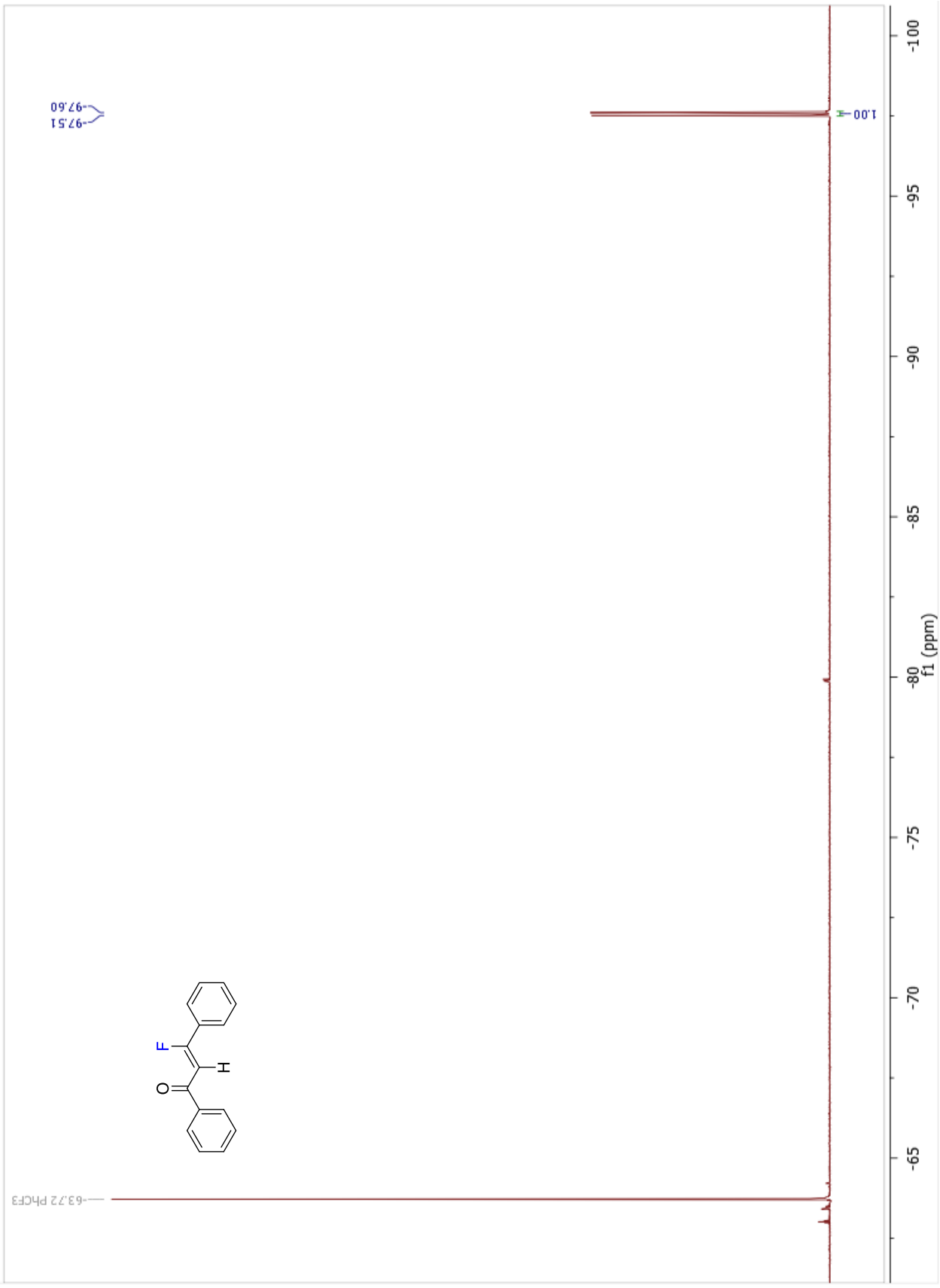

f1 (ppm)
CDCl3
CH3
H3C
F
O
N
H

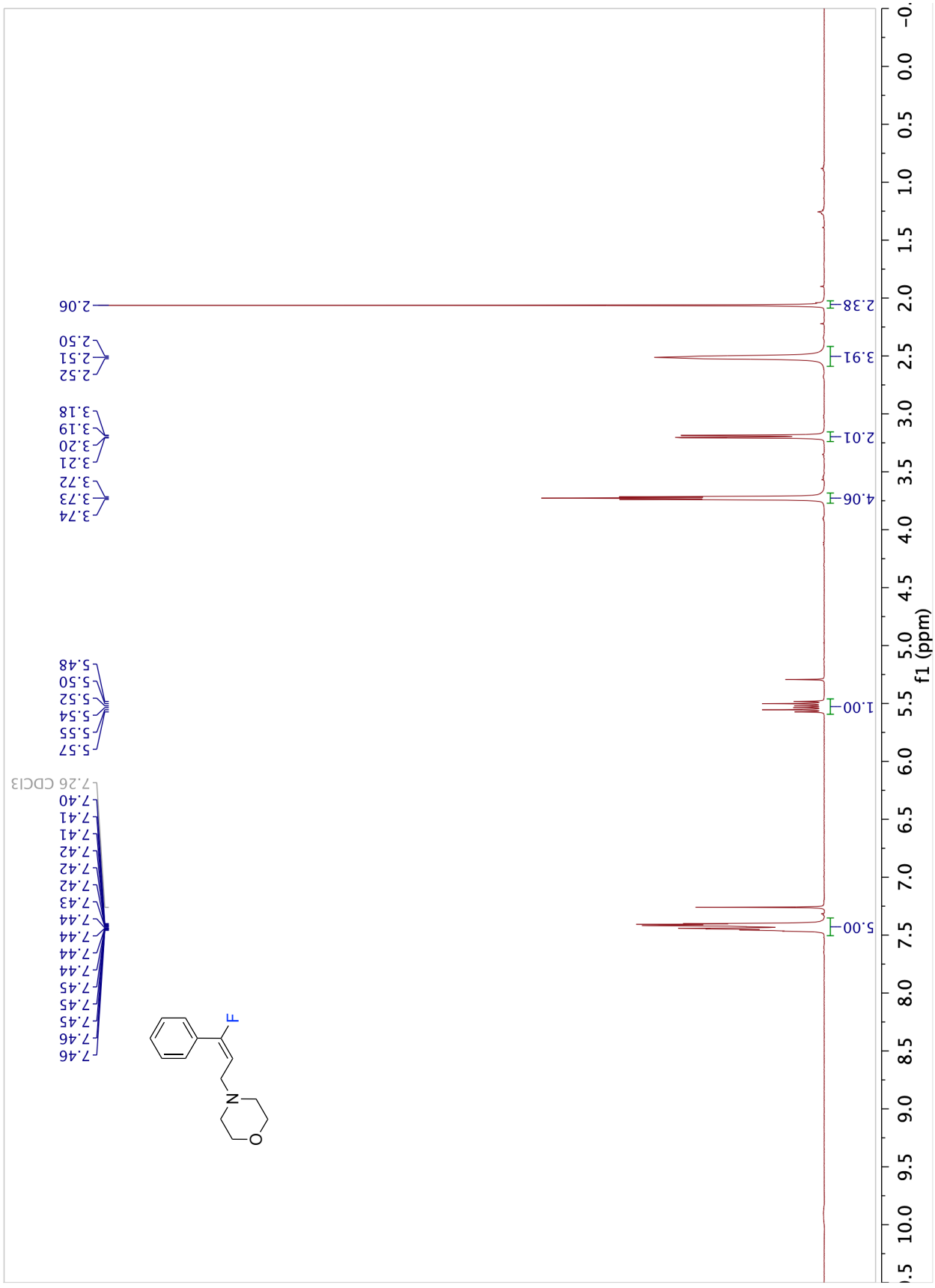

f1 (ppm)

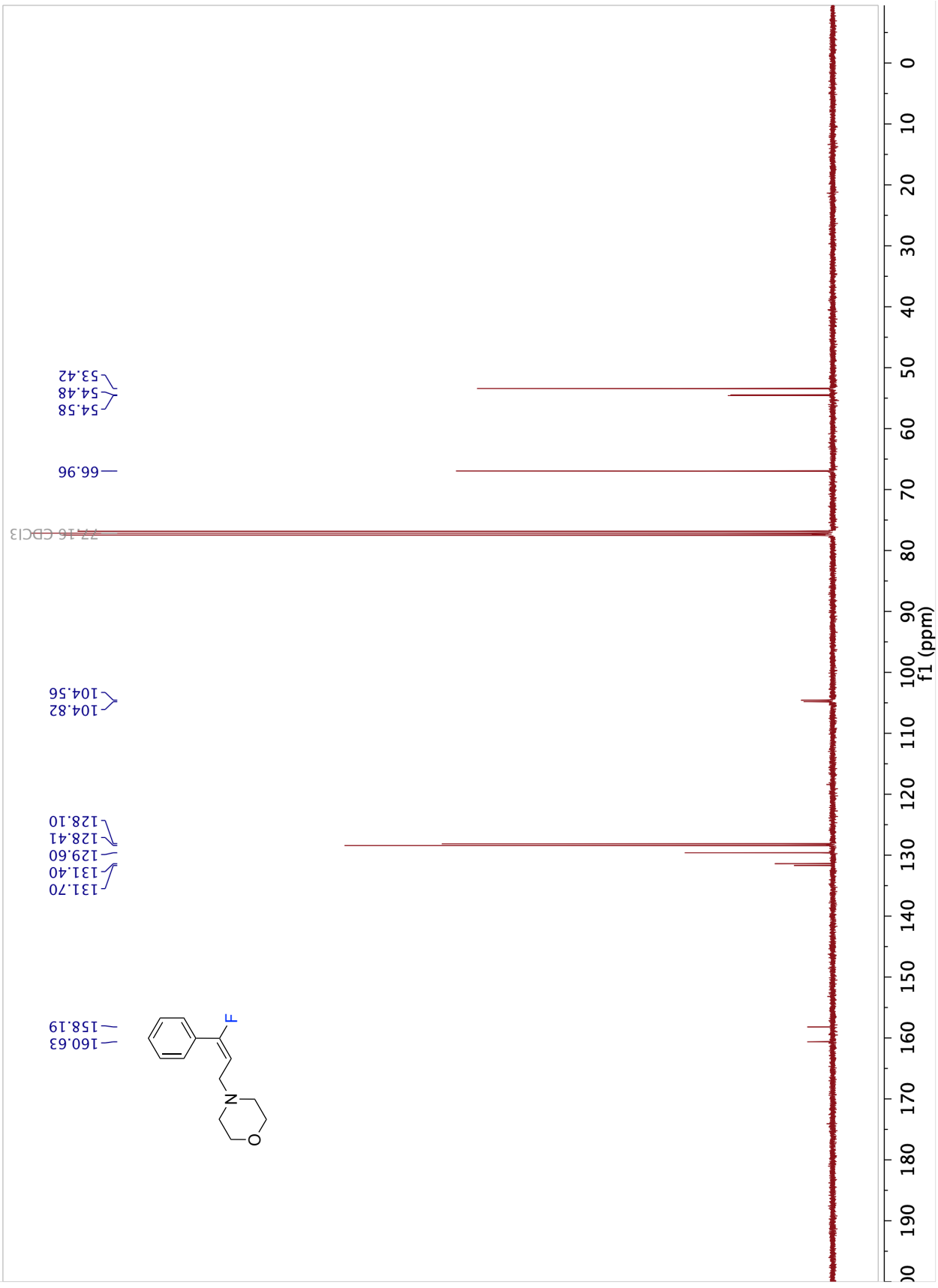

-83.07
-83.12
-63.72 PhCF3
1.00
f1 (ppm)
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
CH3
F
H
O
N
O

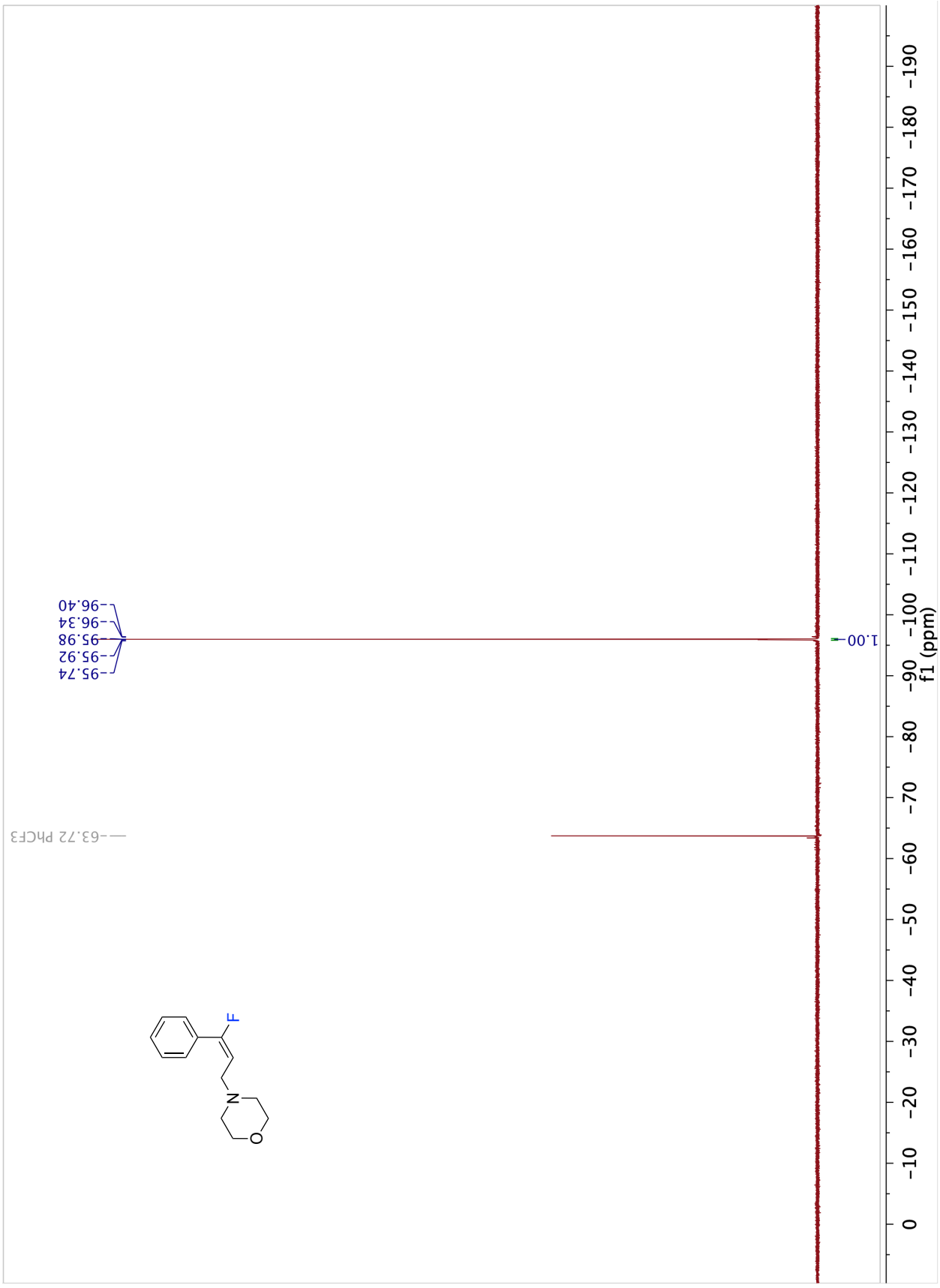

F
H
O
CDCl3
1.00
4.98
1.06
1.96
2.02
f1 (ppm)

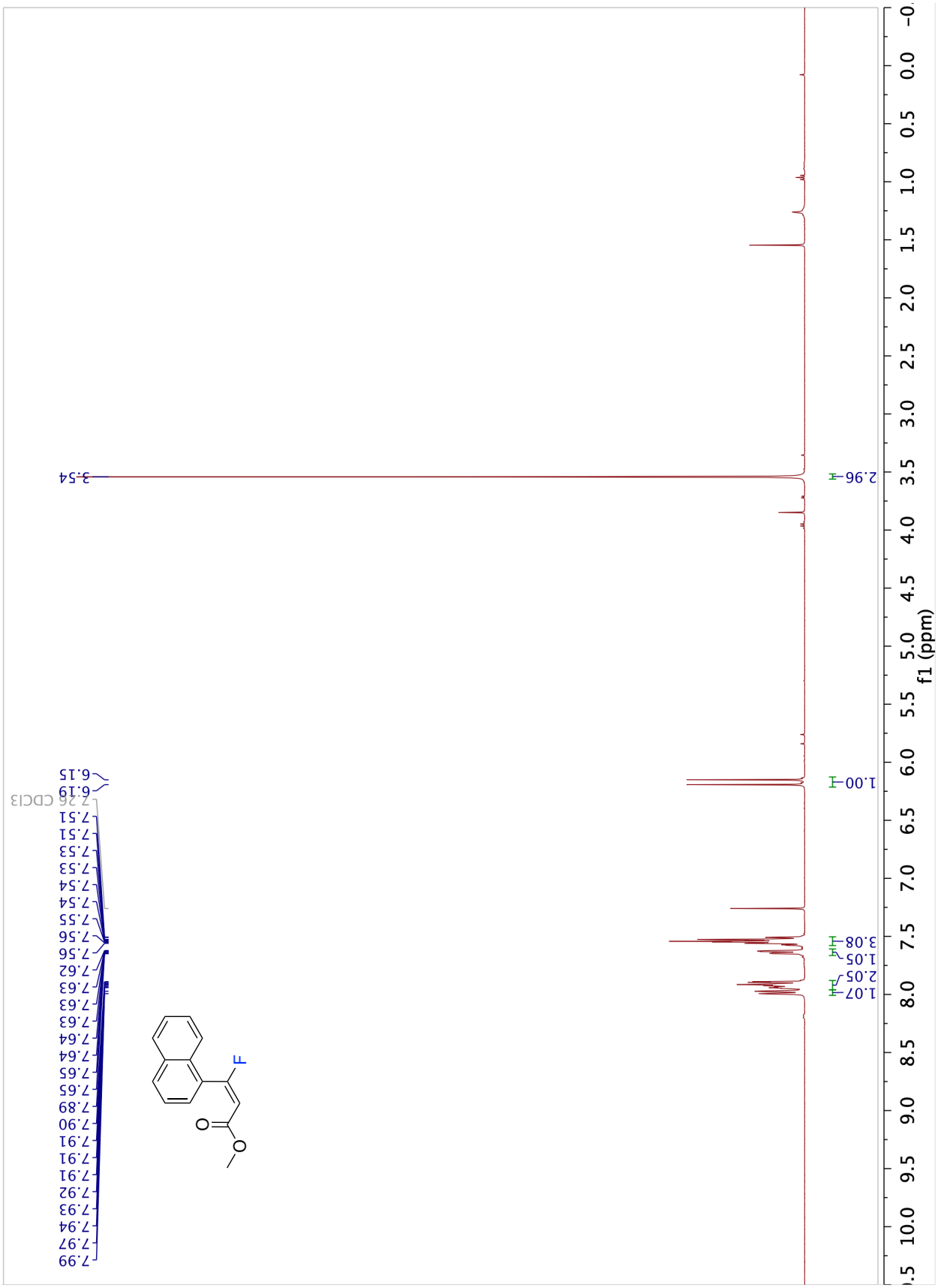

189.0
138.8
133.0
131.8
129.1
129.1
128.7
128.5
126.0
125.9
101.9
101.9
77.2 CDCl3
F
H
O
f1 (ppm)

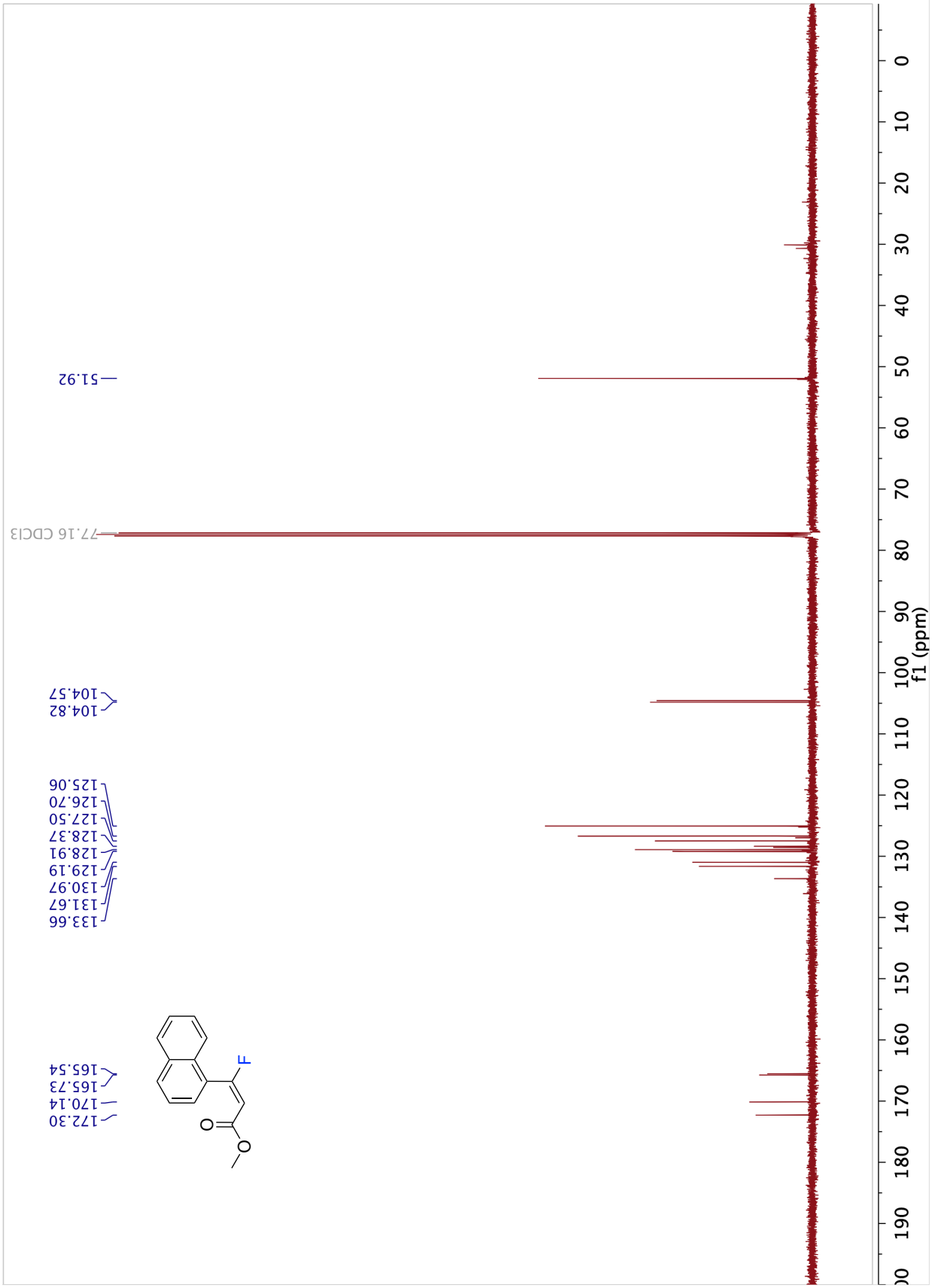

-97.60
-97.51
1.00
-63.72 PhCF3
-100
-95
-90
-85
-80
-75
-70
-65
f1 (ppm)
F
H
O

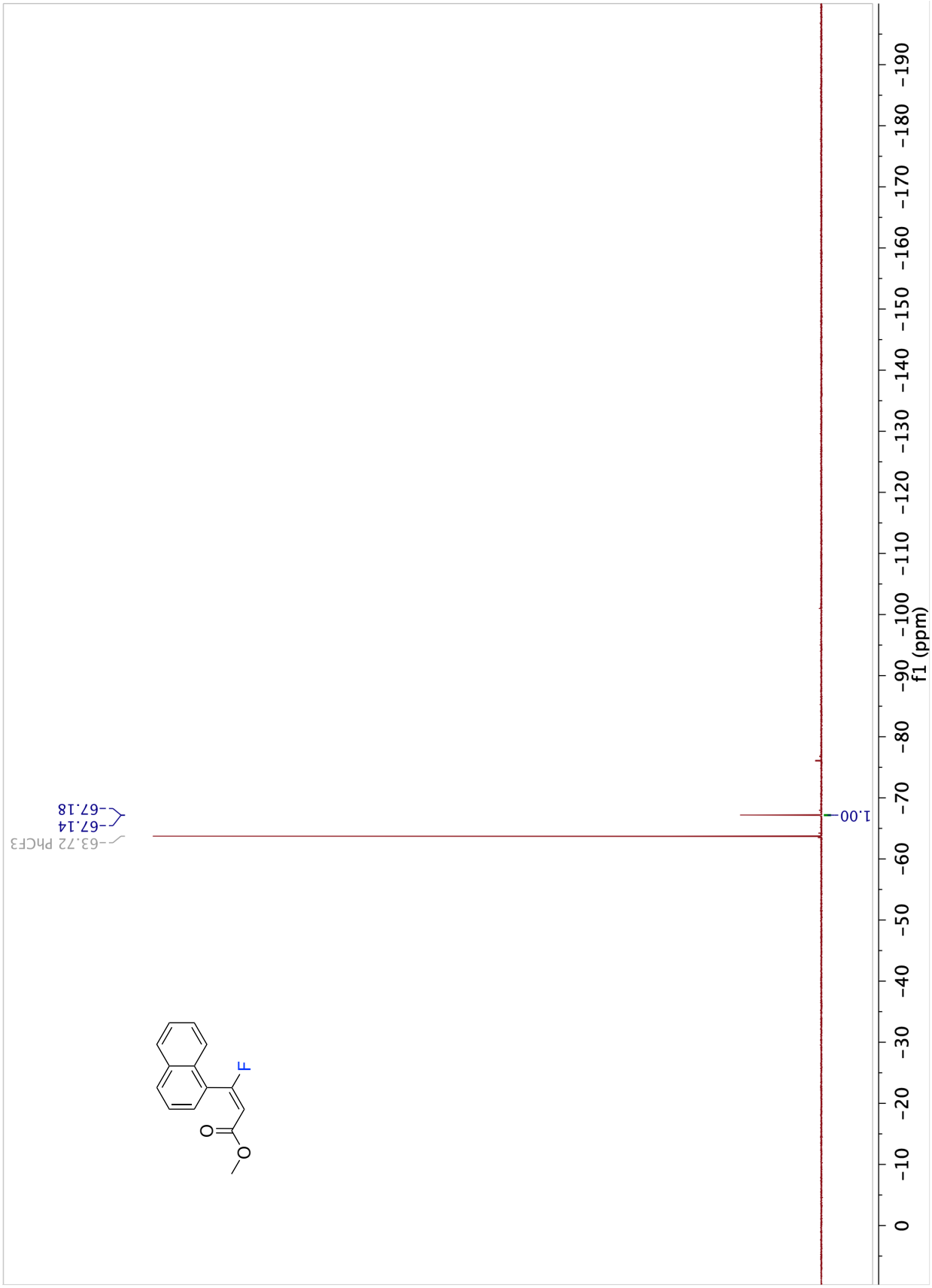

2.06
2.50
2.51
2.52
3.18
3.19
3.20
3.21
3.72
3.73
3.74
5.48
5.50
5.52
5.54
5.55
5.57
7.26 CDCl3
7.40
7.41
7.41
7.42
7.42
7.42
7.43
7.44
7.44
7.44
7.44
7.45
7.45
7.45
7.46
7.46
2.38
3.91
2.01
4.06
1.00
5.00
F
N
O
f1 (ppm)

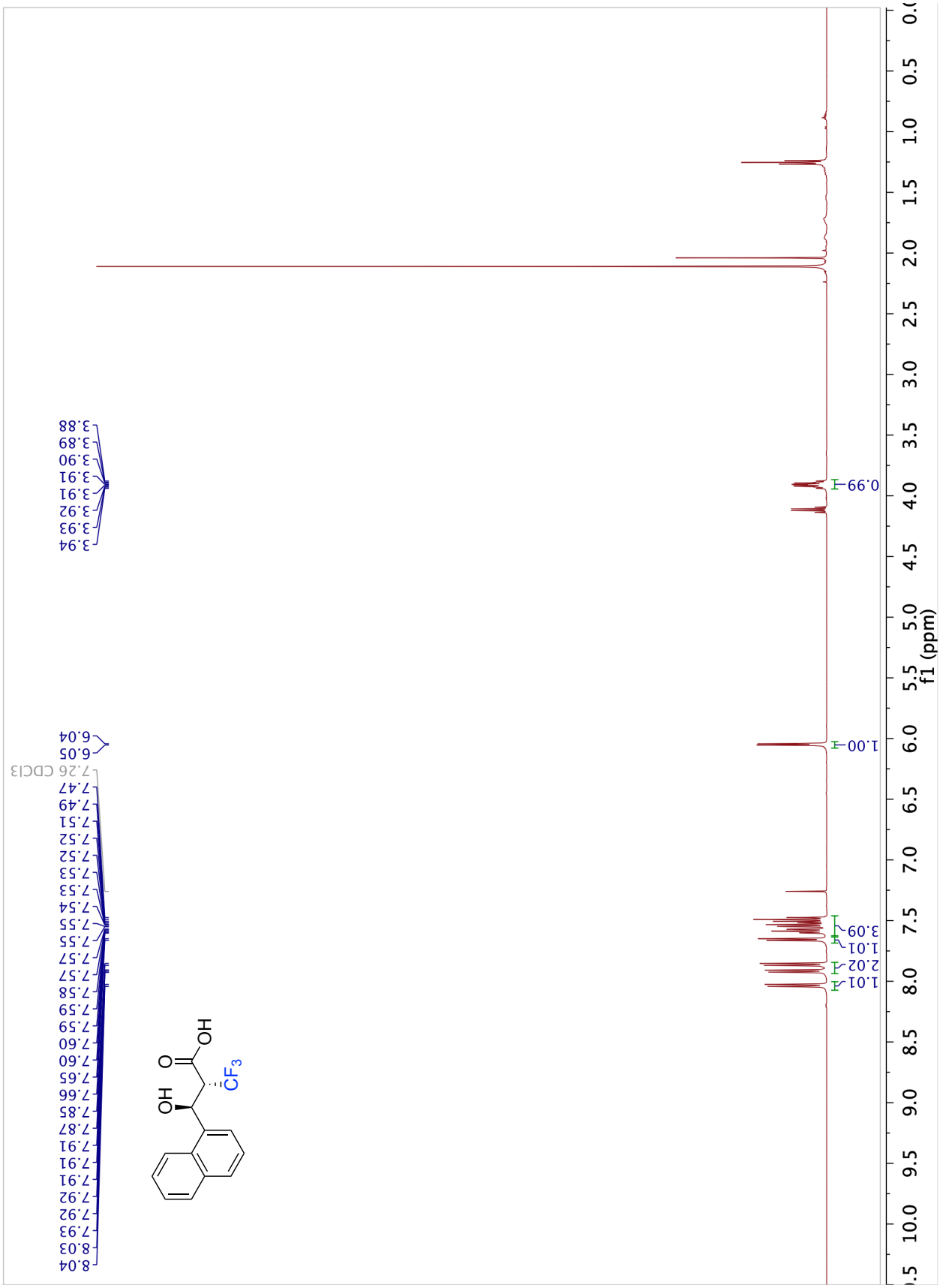

158.19
160.63
131.70
131.40
129.60
128.41
128.10
104.82
104.56
77.16 CDCl3
66.96
54.58
54.48
53.42
F
N
O
f1 (ppm)

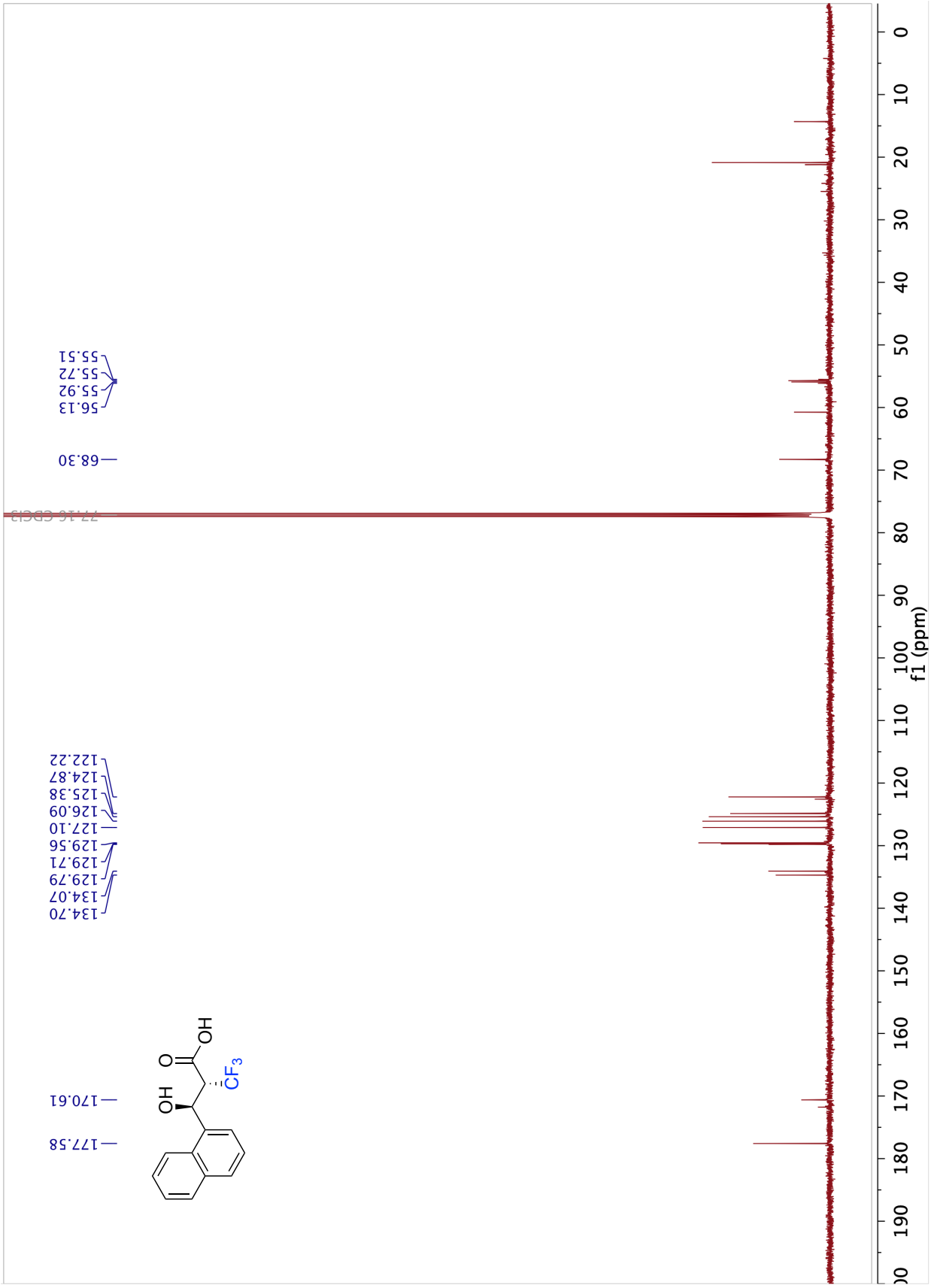

-95.74
-95.92
-95.98
-96.34
-96.40
-63.72 PhCF3
1.00
f1 (ppm)
F
N
O

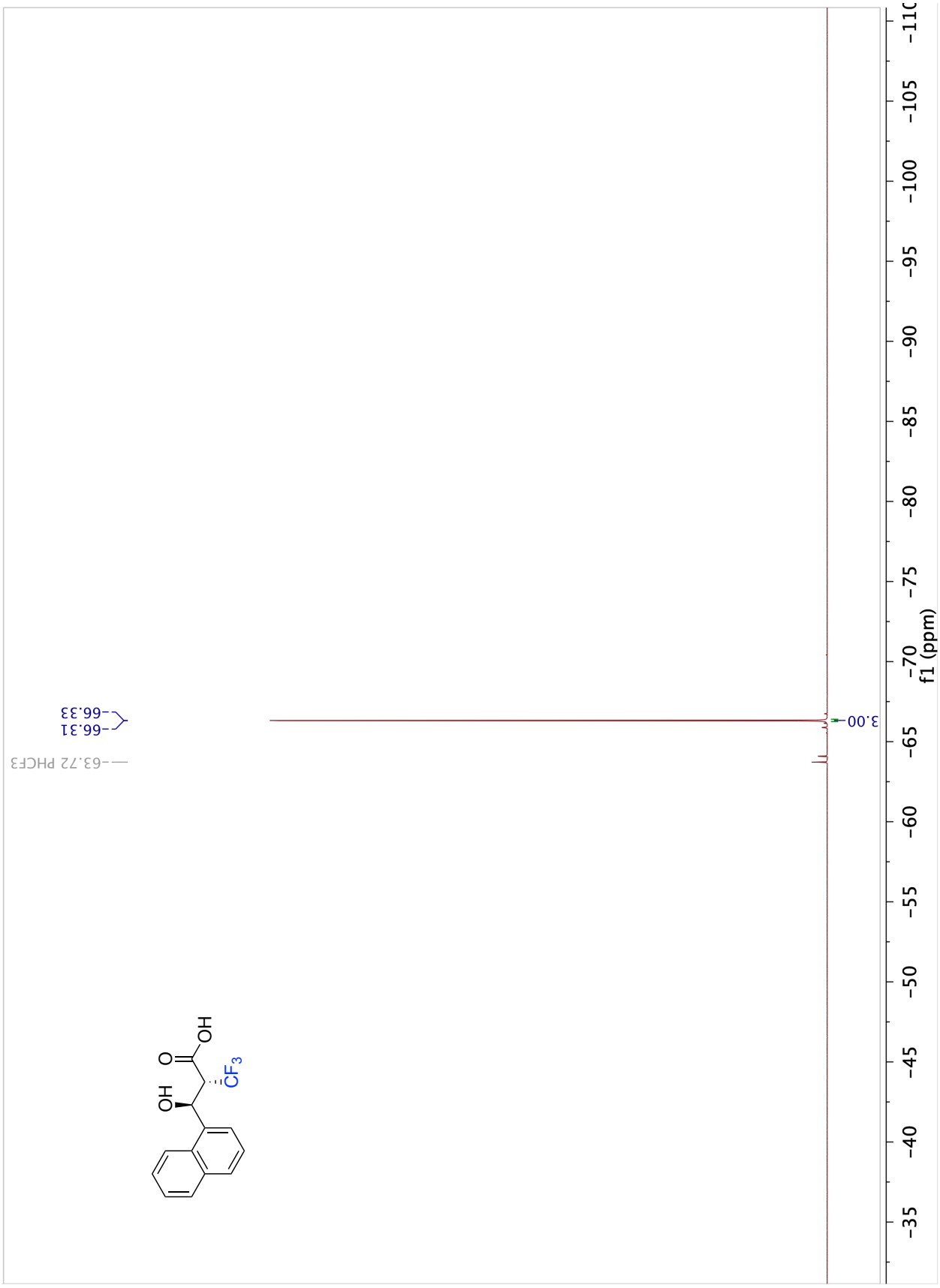

3.54
2.96
1.00
3.08
1.05
2.05
1.07
6.15
6.19
7.26 CDCl3
7.51
7.51
7.53
7.53
7.54
7.54
7.55
7.56
7.56
7.62
7.63
7.63
7.63
7.64
7.64
7.65
7.65
7.89
7.90
7.91
7.91
7.91
7.92
7.93
7.94
7.97
7.99
F
O
O
f1 (ppm)

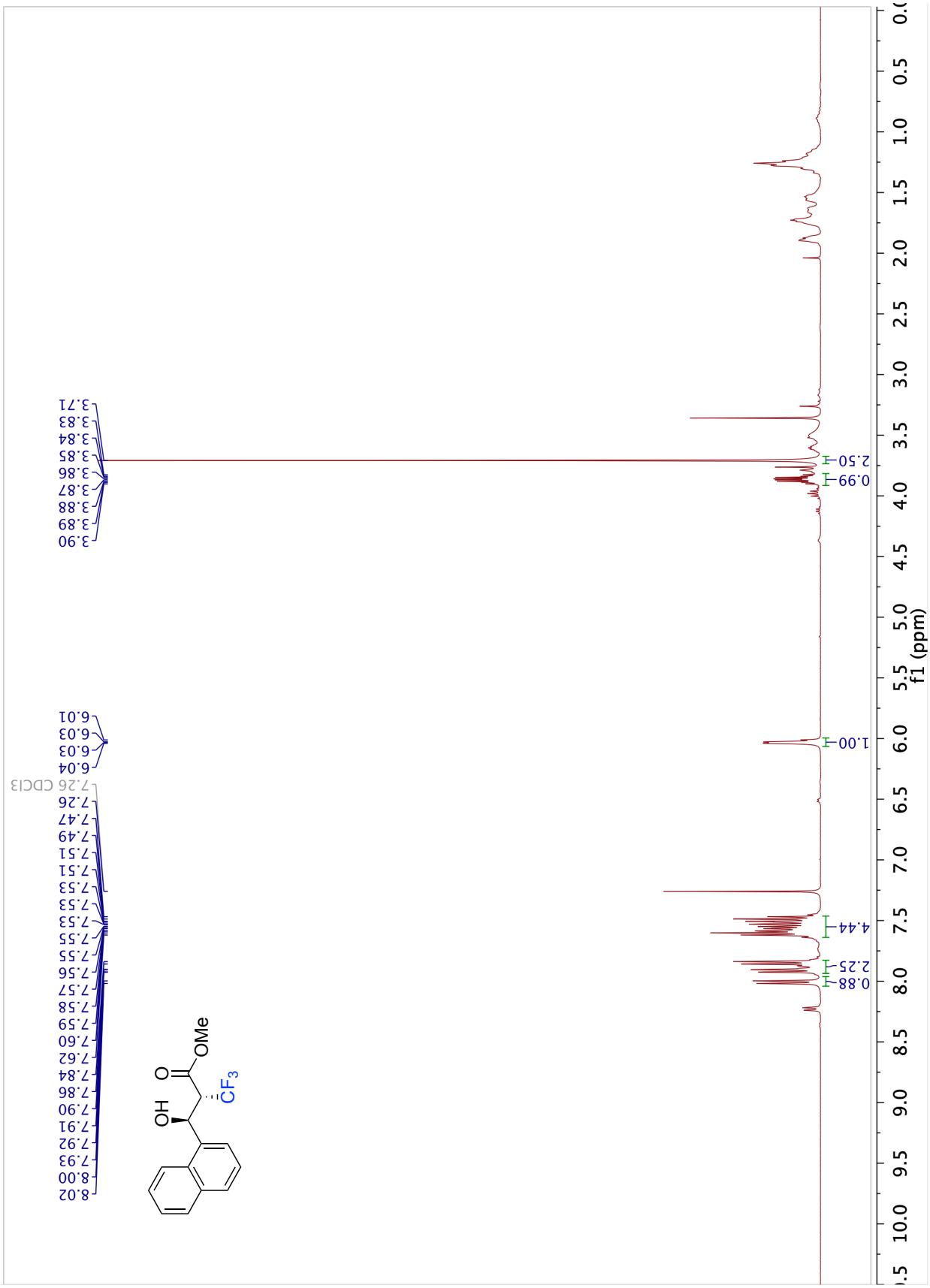

172.30
170.14
165.73
165.54
133.66
131.67
130.97
129.19
128.91
128.37
127.50
126.70
125.06
104.82
104.57
77.16 CDCl3
51.92
F
O
O
f1 (ppm)

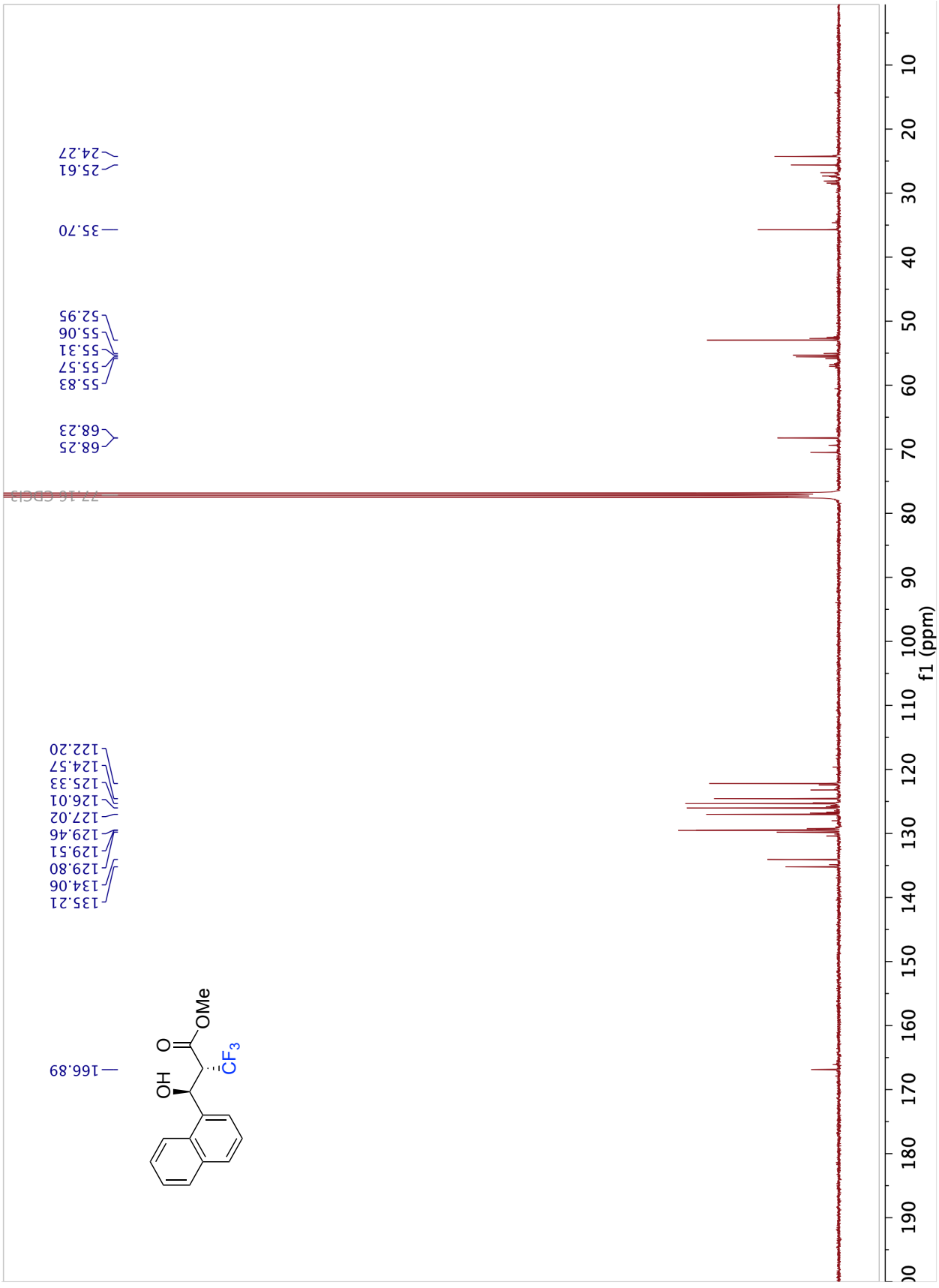

-63.72 PhCF3
-67.14
-67.18
1.00
F
O
O
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

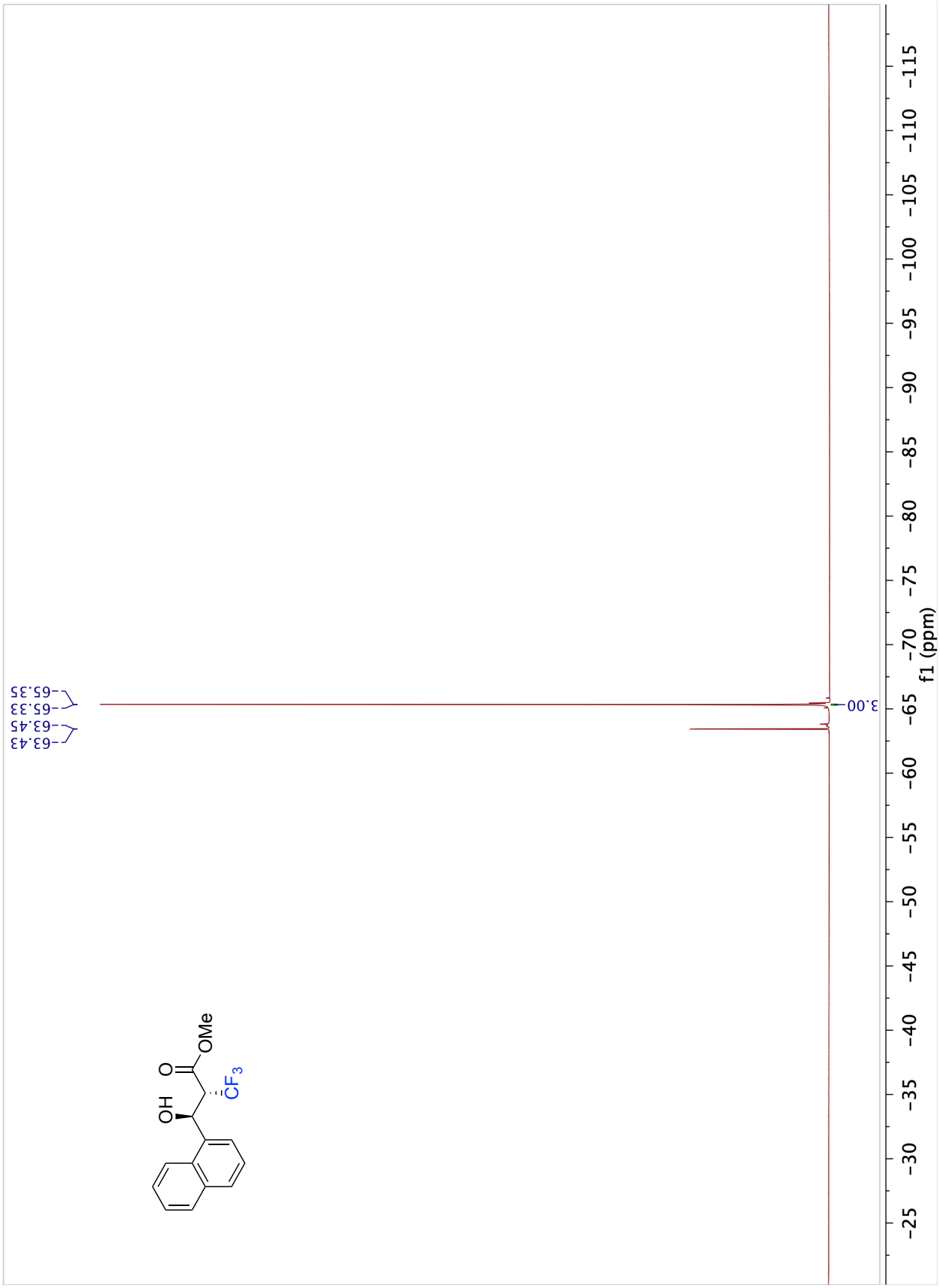

8.04
8.03
7.93
7.92
7.92
7.91
7.91
7.91
7.87
7.85
7.66
7.65
7.60
7.60
7.59
7.59
7.58
7.57
7.57
7.55
7.55
7.54
7.53
7.53
7.52
7.52
7.51
7.49
7.47
7.26 CDCl3
6.05
6.04
3.94
3.93
3.92
3.91
3.91
3.90
3.89
3.88
OH
O
OH
CF3
1.01
2.02
1.01
3.09
1.00
0.99
f1 (ppm)

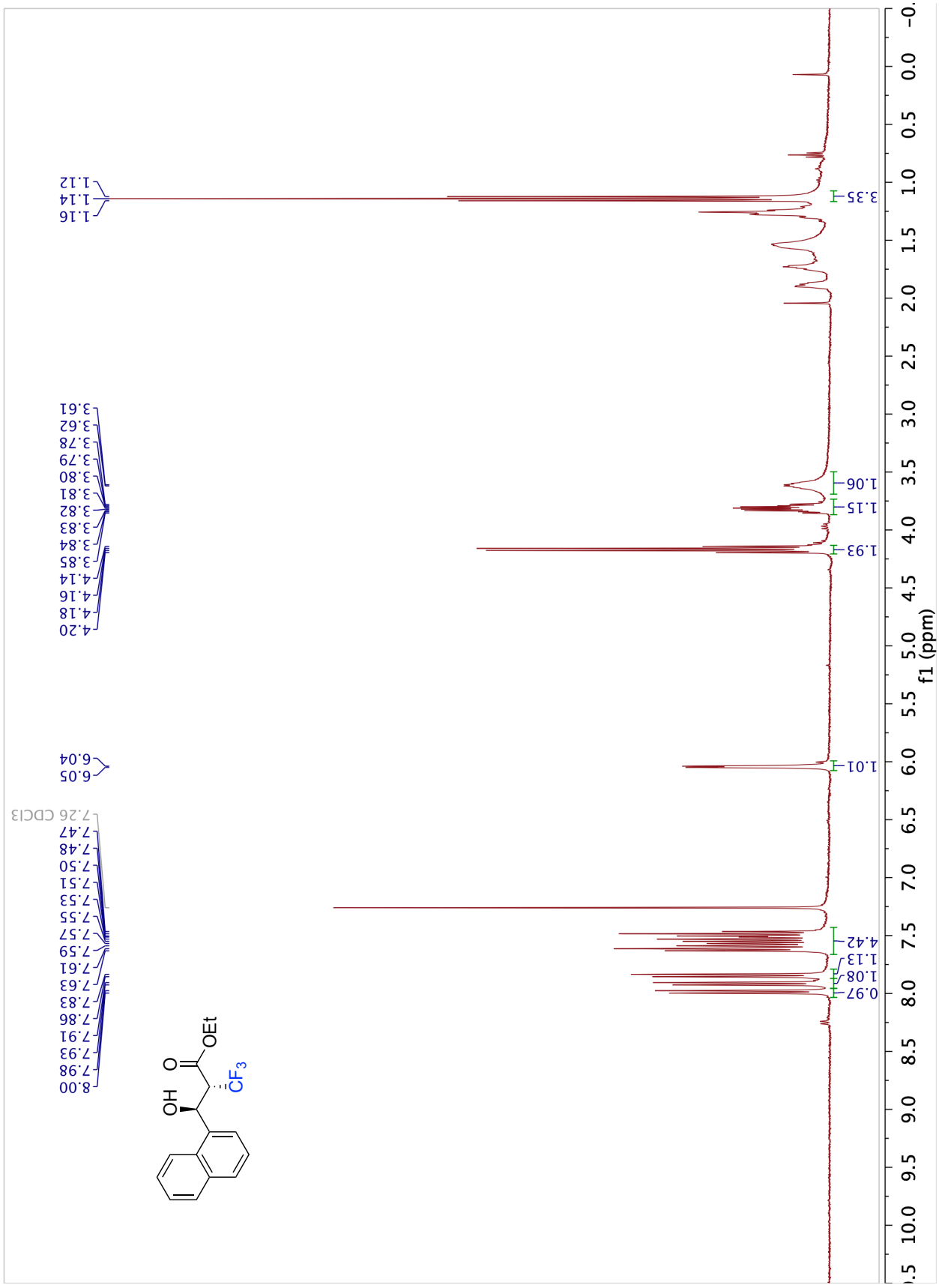

177.58
170.61
134.70
134.07
129.79
129.71
129.56
127.10
126.09
125.38
124.87
122.22
77.16 CDCl3
68.30
56.13
55.92
55.72
55.51
OH
O
OH
CF3
f1 (ppm)

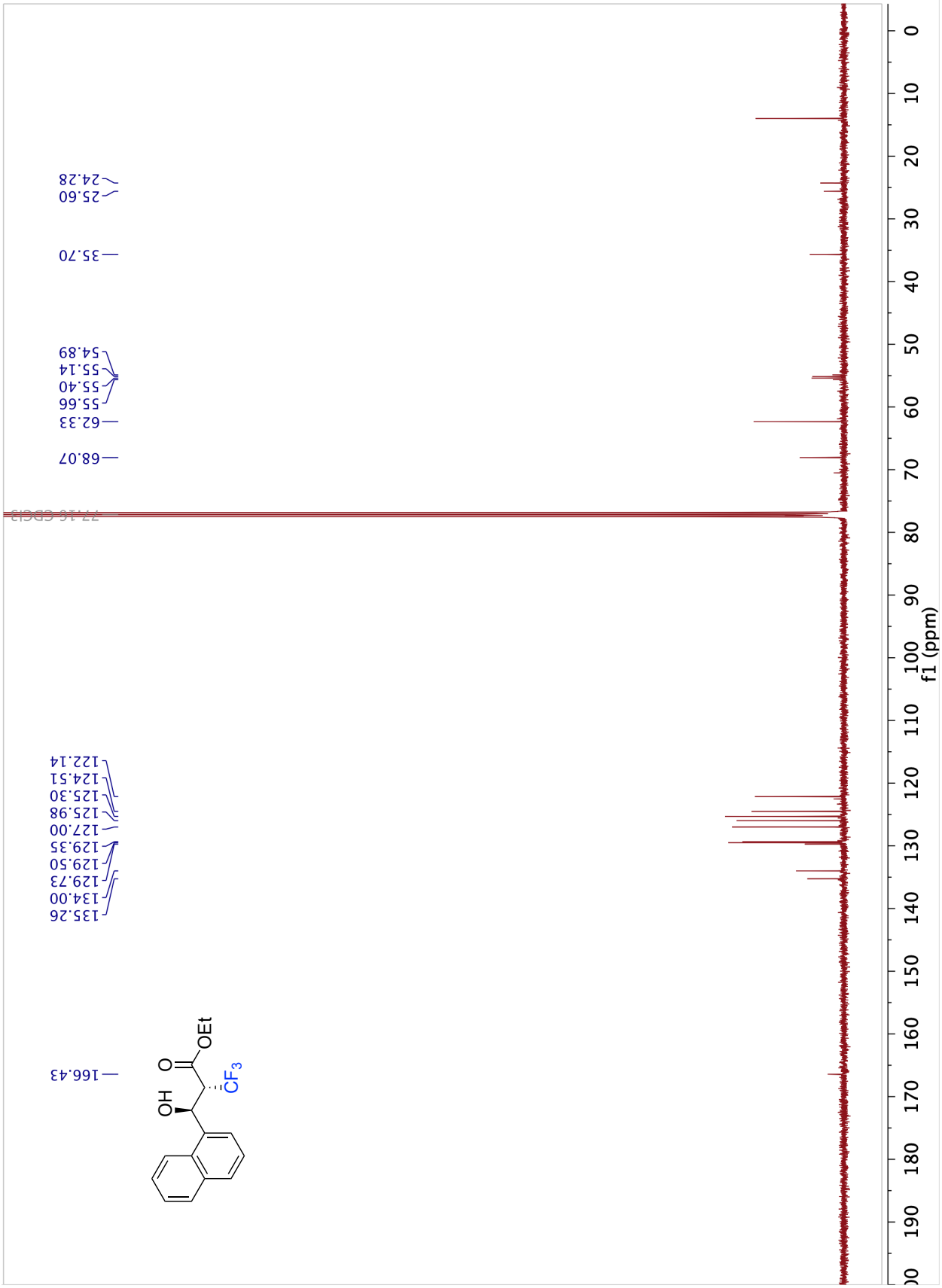

-66.31
-66.33
-63.72 pHCF3
3.00
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
f1 (ppm)
OH
O
OH
CF3

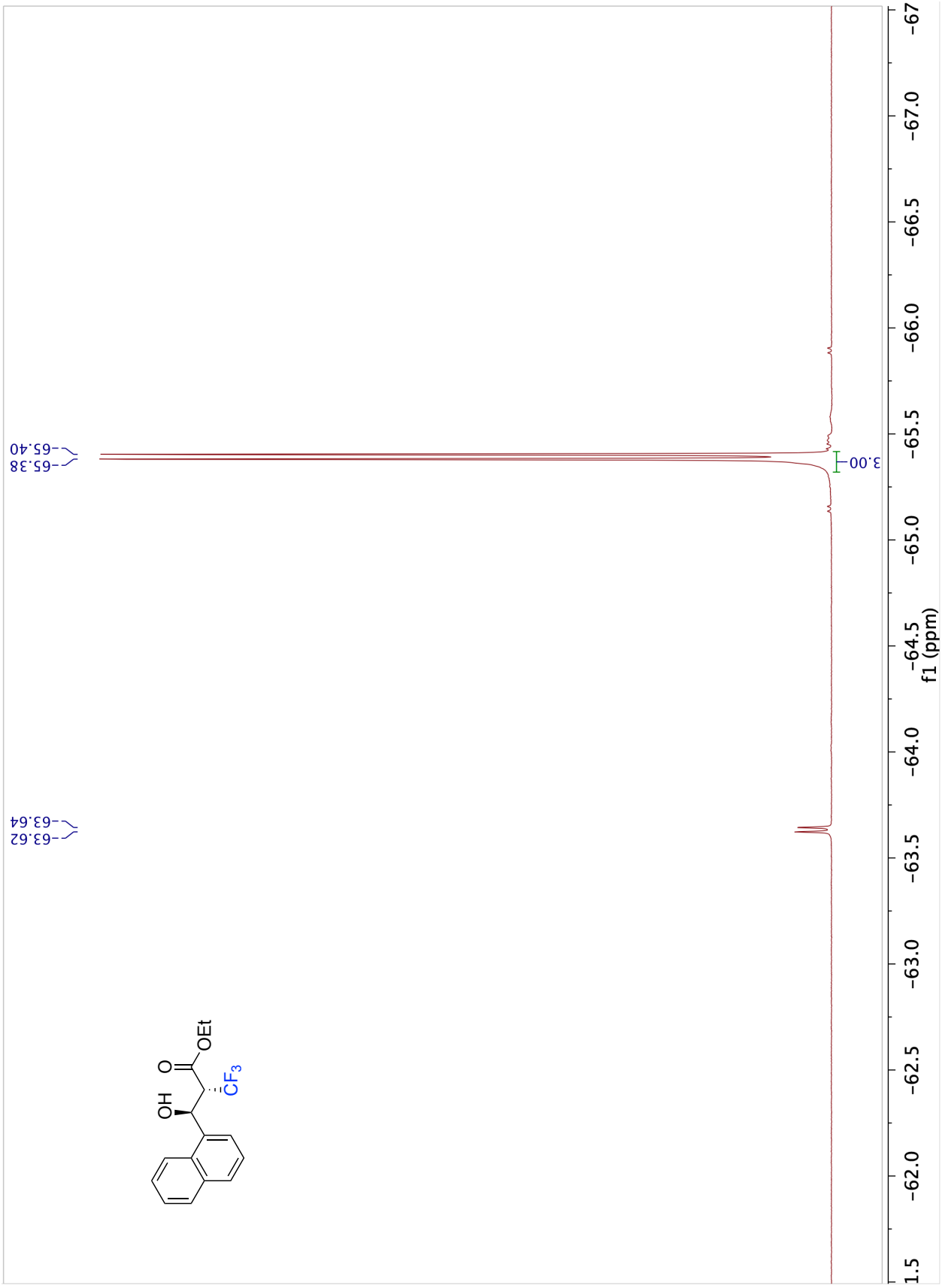

3.90
3.89
3.88
3.87
3.86
3.85
3.84
3.83
3.71
6.04
6.03
6.03
6.01
7.26 CDCl3
7.26
7.47
7.49
7.51
7.51
7.53
7.53
7.53
7.55
7.55
7.56
7.57
7.58
7.59
7.60
7.62
7.84
7.86
7.90
7.91
7.92
7.93
8.00
8.02
OH
O
OMe
CF3
2.50
0.99
1.00
4.44
2.25
0.88
f1 (ppm)

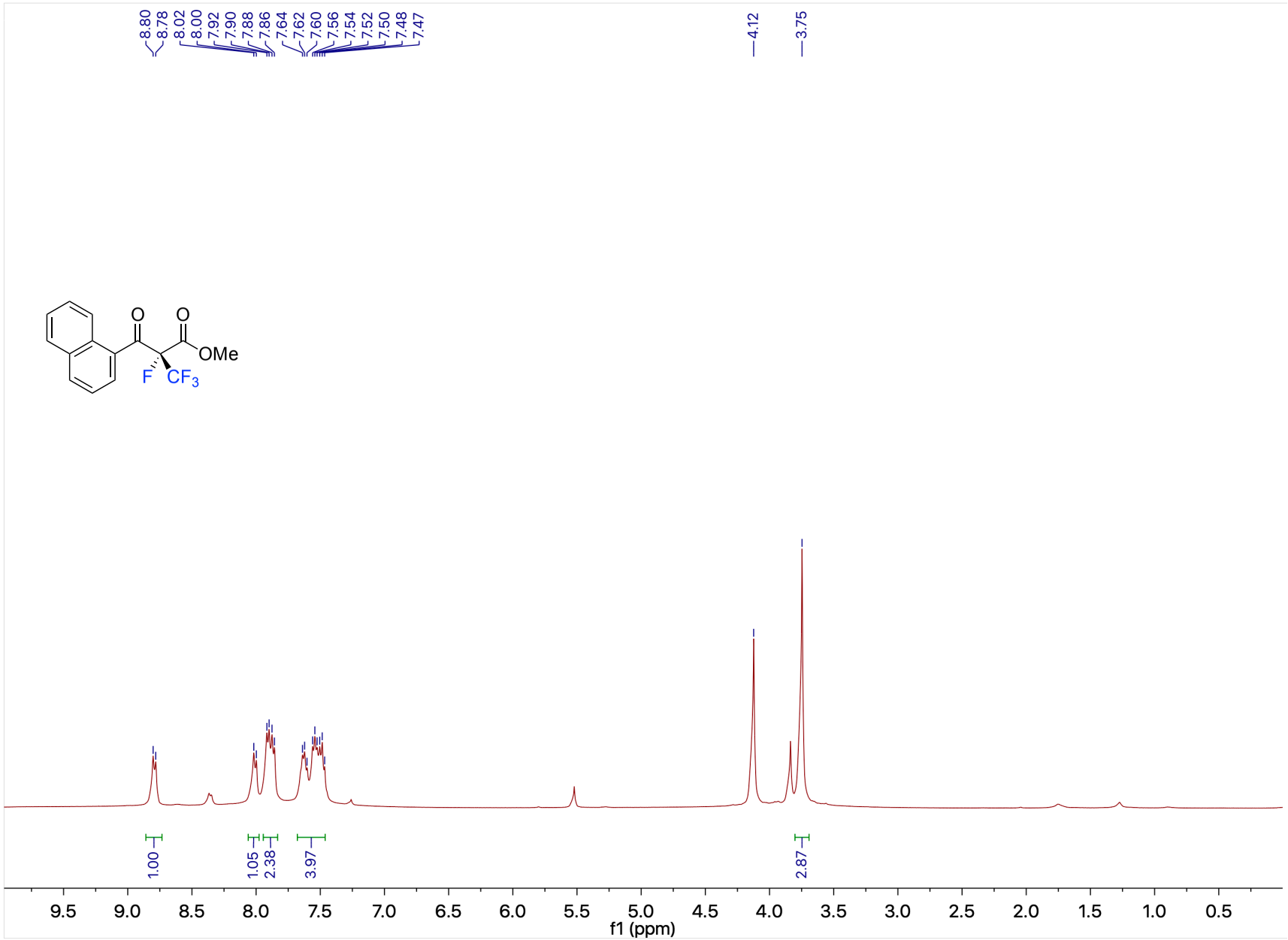

166.89
135.21
134.06
129.80
129.51
129.46
127.02
126.01
125.33
124.57
122.20
77.16 CDCl3
68.25
68.23
55.83
55.57
55.31
55.06
52.95
35.70
25.61
24.27
OH
O
OMe
CF3
f1 (ppm)

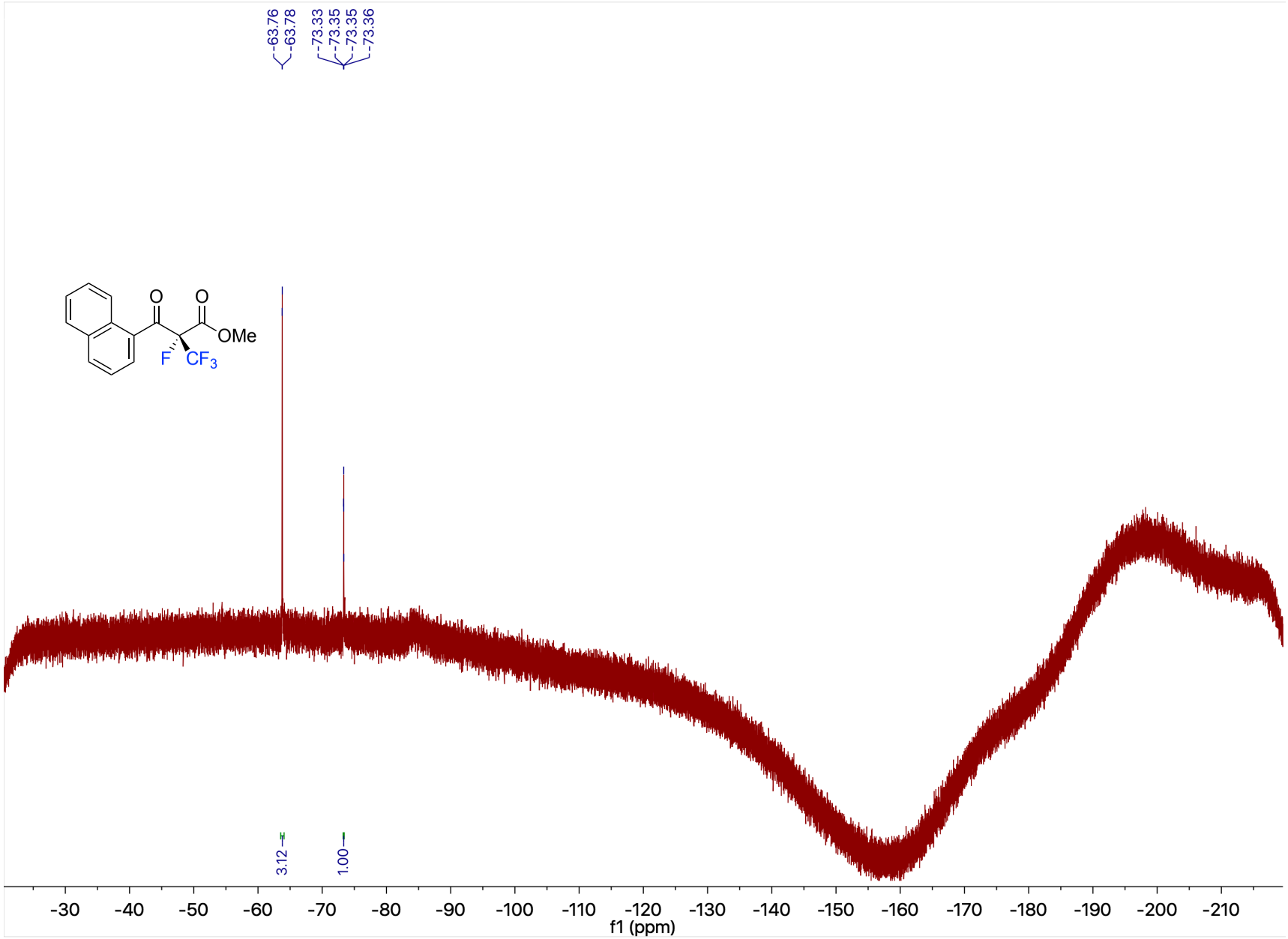

-63.43
-63.45
-65.33
-65.35
3.00
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
f1 (ppm)
OH
O
OMe
CF3


f1 (ppm)
1.16
1.14
1.12
3.35
3.61
3.62
3.78
3.79
3.80
3.81
3.82
3.83
3.84
3.85
4.14
4.16
4.18
4.20
1.06
1.15
1.93
6.04
6.05
1.01
7.26 CDCl3
7.47
7.48
7.50
7.51
7.53
7.55
7.57
7.59
7.61
7.63
7.83
7.86
7.91
7.93
7.98
8.00
4.42
1.13
1.08
0.97
OEt
O
OH
CF3


166.43
135.26
134.00
129.73
129.50
129.35
127.00
125.98
125.30
124.51
122.14
77.16 CDCl3
68.07
62.33
55.66
55.40
55.14
54.89
35.70
25.60
24.28
OEt
O
OH
CF3
f1 (ppm)


-63.62
-63.64
-65.38
-65.40
3.00
OH
O
OEt
CF3
-62.0
-62.5
-63.0
-63.5
-64.0
-64.5
-65.0
-65.5
-66.0
-66.5
-67.0
-67
f1 (ppm)


8.80
8.78
8.02
8.00
7.92
7.90
7.88
7.86
7.64
7.62
7.60
7.56
7.54
7.52
7.50
7.48
7.47
4.12
3.75
O
O
OMe
F
CF3
1.00
1.05
2.38
3.97
2.87
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


-63.76
-63.78
-73.33
-73.35
-73.35
-73.36
O
O
OMe
F
CF3
3.12
1.00
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

PUBLICATIONS AND COMMERCIALIZATION

1) Khatri, H. R.; Han, C.; Luong, E.; Pan, X.; Adam, A. T.; Alshammari, M. D.; Shao, Y.; Colby, D. A. Controlling the Cleavage of Carbon–Carbon Bonds to Generate α,α-Difluorobenzyl Carbanions for the Construction of Difluoromethylbenzenes. *J. Org. Chem.* **2019**, *84*, 11665–11675.
2) Adam, A. T.; Fronczeck, F. R.; Colby, D. A. Synthesis of β-Fluoro-α,β-Unsaturated Amides from the Fragmentation of Morpholine 3,3,3-Trifluoropropanamide by Grignard Reagents. *Org. Lett.* **2020**, *22*, 2630–2633.
3) Morpholine 3,3,3-trifluoropropanamide is now available in the MilliporeSigma Catalog (No. 911933).

VITA

Amna Trinity Adam was born in the Sudan; she and her family emigrated to San Diego, California in 2005. She earned her high school diploma 2010 and attended Montclair State University, where she earned a Bachelor's of Science in Chemistry and Molecular Biology in 2015. As an under graduate, she participated in research and has two second author publications from her undergraduate work. She joined the BioMolecular Sciences department at the University of Mississippi in August of 2015 under the mentorship of Dr. Stephen Cutler. She then joined the Colby lab in October of 2017, after a transition year in the Le Lab, where she completed her degree.