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Fluorinated Organic Molecules for Medicinal Applications

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FLUORINATED ORGANIC MOLECULES FOR MEDICINAL APPLICATIONS

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ABSTRACT

The significant applications of fluorinated molecules in the pharmaceutical, agrochemical, and material sciences make them attractive synthetic targets. Difluoromethylation methods are of exceptional value and a limited number of techniques are available to perform that transformation. The primary method for introducing CF_2 groups is through the use of difluoroenolates. Difluoroenolates can be generated from α-keto pentafluoro *gem*-diols under mild conditions. The process involves the cleavage of carbon-carbon bond and the release of trifluoroacetate. The release of trifluoroacetate is a versatile method to generate fluorinated molecules. We explored the utility of this method in generating various fluorinated moieties including α,α-difluoroketones, α-deutero-α,α-difluoroketones, α,α-difluoromethyl sulfones, α-deutero-α,α-difluoromethyl sulfones, monofluoro β-hydroxy ketones and α,α-difluorohalohydrins.

We also endeavored to design and synthesize fluorinated molecules for biological applications. Our efforts were aimed at the use of a novel fluorinated β-hydroxy ketone scaffold developed in our lab to develop new agonists of the $GABA_B$ receptor. The value of $GABA_B$ agonists as muscle relaxants is well established, and interest in these agonists has been rekindled due to reports of new applications in managing drug and alcohol tolerance. We have developed several new analogues, characterized new structure-activity relationships of the fluorinated β-hydroxy ketone scaffold, and identified more active agents.

We are also interested in using fluorine as a tag to track anti-body drug conjugates (ADCs). The chemistry of ADC linkers has attracted a lot of interest recently. The cleavage of the linker is essential for the function of ADCs and in addition to this traditional role, linkers can provide a

handle for tagging ADCs. The incorporation of fluorine into linkers minimally affects the sterics of the linker owing to the small size of fluorine atom while at the same time provides a tractable tag. A fluorinated ADC linker has been designed and its synthesis was explored.

DEDICATION

To my mom for being my role model, my rock, and best friend.

LIST OF ABBREVIATIONS AND SYMBOLS

α	alpha
β	beta
AC	adenylyl cyclase
ADC	antibody-drug conjugate
9-BBN	9-borabicyclo(3.3.1)nonane
BOX	bis(oxazoline)
n-BuLi	*n*-butyl lithium
calcd	calculated
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
CXCR4	C-X-C chemokine receptor type 4
DAST	diethylaminosulfur trifluoride
DCC	*N,N'*-dicyclohexylcarbodiimide
DEC	diethylcarbamate
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPP-IV	dipeptidyl peptidase-IV
EEDQ	N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EtOAc	ethyl acetate
equiv	equivalents
FDA	food and drug administration
FSK	forskolin
GABA	γ-aminobutyric acid

h	hour
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HER2	receptor tyrosine-protein kinase erbB-2
Hex	hexane
HFIP	hexafluoro isopropanol
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum correlation
HOSu	*N*-hydroxysuccinimide
HRMS	high resolution mass spectrometry
KHMDS	potassium bis(trimethylsilyl)amide
LES	lower esophageal sphincter
LiHMDS	lithium bis(trimethylsilyl)amide
mc	maleimidocaproyl
MS	molecular sieves
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser spectroscopy
PABA	*p*-aminobenzyl alcohol
PEPT1	peptide transporter 1
PET	positron emission tomography
PPM	parts per million
TBS	*tert*-butyldimethylsillyl ether

TLC	thin layer chromatography
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
vc	valine-citrulline
VLA-4	very late antigen 4

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I would like to express my sincere gratitude to my advisor Prof. David Colby for his support, kindness, and guidance during my time in his group. I am indebted to him for sharing his expertise, he shaped the way I think about chemistry, science and life and for that I am extremely thankful. I would also like to thank my thesis committee members: Prof. Rimoldi, Prof. McCurdy, and Prof. Delcamp, for their insightful comments and friendly advice. I also want to express my gratitude to the Department faculty members and administrative staff for their help and support.

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CHAPTER 1

INTRODUCTION

1.1 Fluorine in Medicinal Chemistry

Fluorine is rarely found in biological systems, nonetheless it's been extensively used by medicinal and pharmaceutical chemists owing to its unique properties. Five of the ten bestselling small molecule drugs in 2016 are fluorinated molecules; namely Harvoni®, Advair®, Januvia®, Truvada®, and Crestor® (**Figure 1.1**).[1] In addition to its distinct role in pharmaceutical products, fluorine has significant applications in medical imaging,[2] material science,[3] and agrochemicals.[4] While monofluorinated and trifluorinated molecules have found widespread applications, *gem*-difluorinated molecules are not as prevalent. However, several drugs on the market are *gem*-difluorinated (**Figure 1.2**), demonstrating the significance of this group.

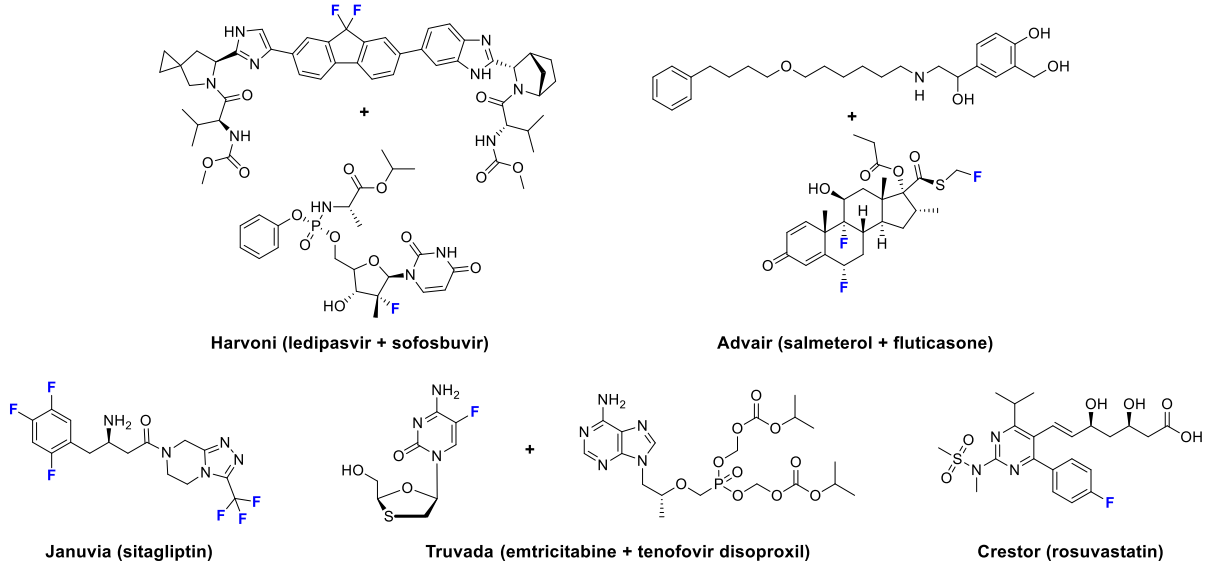


Figure 1.1. Structures of the top five fluorinated drugs: Harvoni®, Advair®, Truvada®, Januvia®, and Crestor®

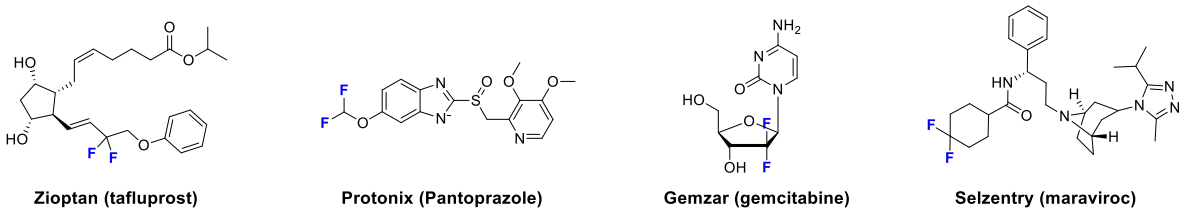


Figure 1.2. Structures of *gem*-difluorinated drugs: Zioptan, Protonix, Gemzar, and Selzentry

1.1.2. Fluorination Reagents and Fluorinated Building Blocks

The incorporation of fluorine into organic molecules remains a synthetic challenge despite the many advances in the field. The synthesis of fluorinated compounds is typically accomplished through direct fluorination or the incorporation of fluorinated building blocks. Harsh reagents like fluorine and hydrogen fluoride gases were the mainstay of the fluorination field for a long time. They remain relevant today as most of the currently used fluorinating reagents require the use of these gasses for their synthesis. Attempts to minimize the use of these reagents led to the development of more stable fluorine sources. For example, the HF complex with pyridine known as Olah's reagent is a stabilized, less volatile form of HF; nonetheless, it's still a corrosive and toxic reagent due to the presence of HF.[5] Xenon difluoride is used as a more stable alternative to F_2 gas, however it's a highly reactive reagent and intolerant to many types of substrate intolerance.[6]

The field of fluorination has seen a lot of progress with several new fluorinating reagents being commercialized; these reagents can be classified as nucleophilic or electrophilic sources of fluorine (**Figure 1.3** (a)). Nucleophilic fluorinating reagents, such DAST[7] and Deoxo-Fluor,[8] are generally aminosulfur trifluorides that deoxyfluorinate or dethiofluorinate carbonyl, hydroxyl, thiocarbonyl, or sulfide groups. On the other hand, electrophilic fluorinating reagents, such as Selectfluor[9] and NFSI,[10] are *N*–fluoro compounds that fluorinate nucleophiles like enolates, enol ethers, and electron-rich aromatic rings.

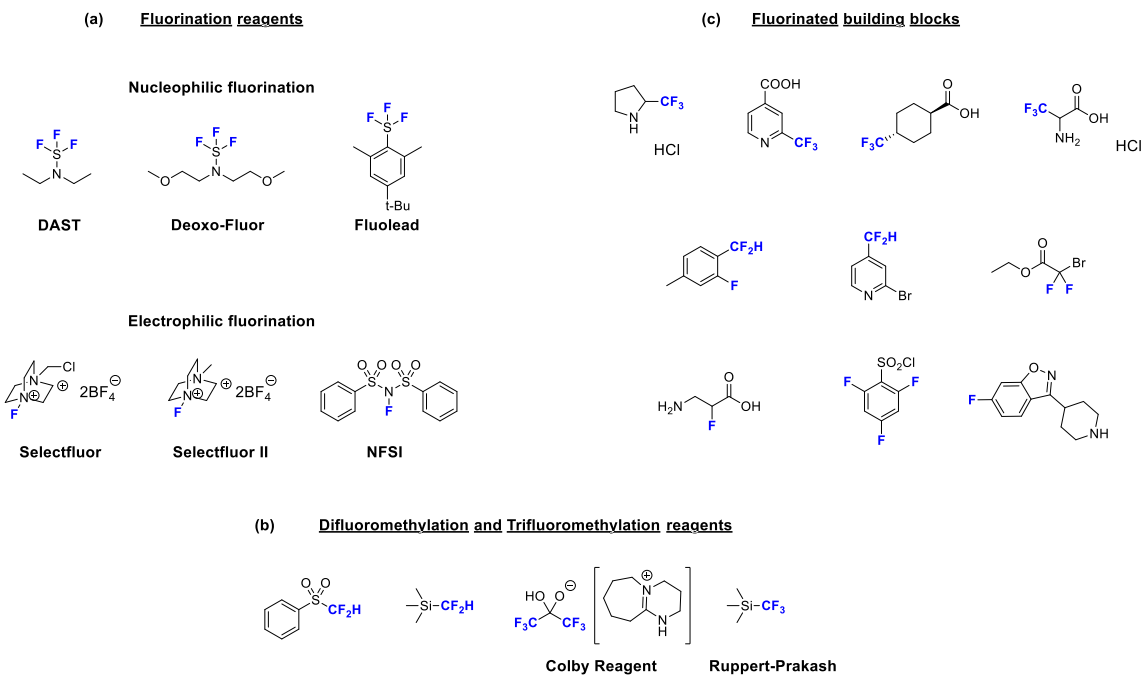


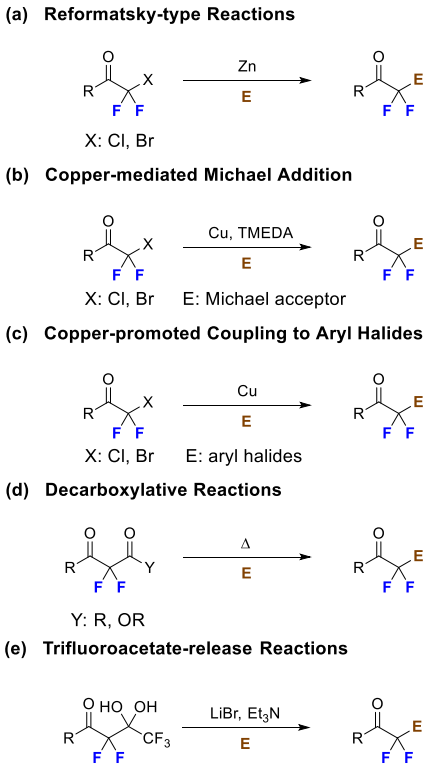
Figure 1.3. (a) Fluorination reagents, (b) difluoromethylation and trifluoromethylation reagents, (c) fluorinated building blocks

Moreover, difluoromethylating and trifluoromethylating reagents, such as the Ruppert-Prakash reagent[11] and the Colby reagent,[12] can be utilized to introduce a CF_2H or a CF_3 group directly (**Figure 1.3** (b)). These reagents help overcome issues of incompatibility with fluorinating reagents as well as improve atom economy. On the other hand, the synthesis of fluorinated organic molecules can be accomplished by utilizing fluorinated building blocks (**Figure 1.3** (c)). This approach helps address issues of over- and under-fluorination and functional group tolerance of fluorination reagents, moreover it provides a cheaper alternative to using the expensive fluorination reagents. Despite the abundance of commercially available fluorinated building blocks, they are especially limited in the context of internal fluorinated groups like the difluoromethylene group.

1.1.3. Fluoroenolates

Installing a difluoromethylene subunit is relatively more challenging than monofluoronation or trifluoromethylation. Nonetheless, compounds containing a difluoromethylene group are beneficial intermediates in the synthesis of pharmaceuticals and agrochemicals. α,α-Difluorinated ketones are privileged moieties that have shown enzymatic inhibition activity on various targets.[13-19] The preparation of these types of ketones can be accomplished mainly by one of two methods: direct fluorination or using a fluorinated synthon. The synthon method typically involves fluoroenolates. Fluoroenolates can be trapped as difluoroenoxysilanes, fluoroenol ethers, fluoroenol phosphates, or fluoroenol sulfonates then used in subsequent reactions; however, this strategy can be time consuming as well as lacking in atom economy. On the other hand, metal fluoroenolates can be generated *in situ* and used directly in the reaction without the need for trapping and isolation. A comprehensive review of fluorinated enol ethers was published in 2015.[20]

Metal fluoroenolates are generally generated through nucleophilic displacement of a leaving group at the α-position of a carbonyl group. Prominent examples of this transformation include Reformatsky-type reactions and copper-mediated coupling reactions (**Scheme 1.1** (a–c)). An alternative strategy to access metal enolates is through carbon-carbon bond cleavage in decarboxylative reactions and trifluoroacetate-release reactions (**Scheme 1.1** (d, e)).



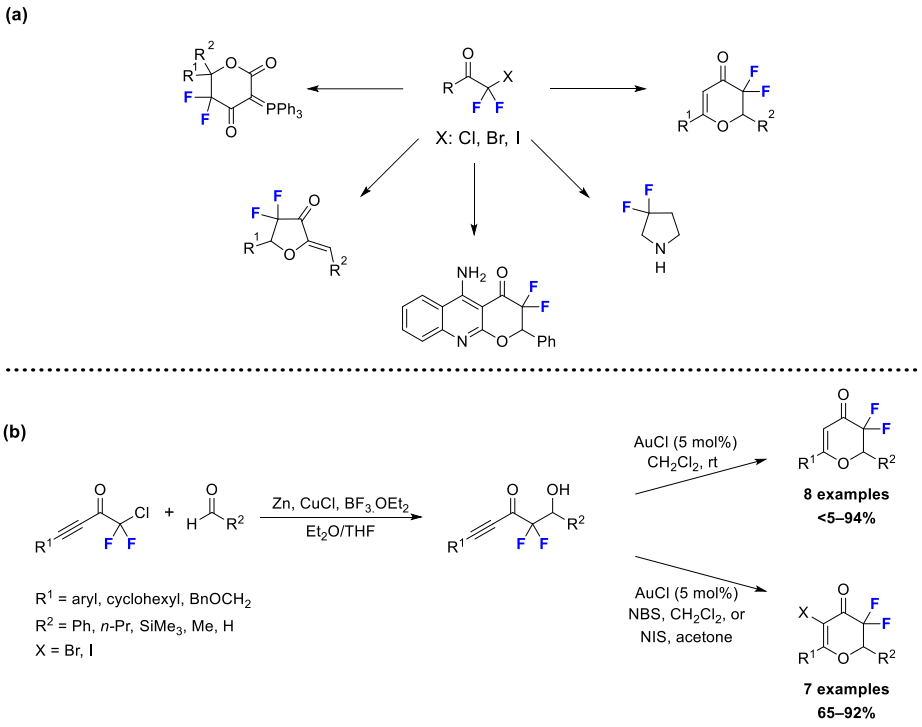
Scheme 1.1. Reactions employing transient fluoroenolates

1.2. Reformatsky-type Reactions

The Reformatsky reaction is one of the earliest examples of organometallic chemistry. It was first reported in 1887 and had been used extensively ever since as an effective C-C bond forming reaction.[21] It is one of the most popular methodologies for the formation of α-fluorinated carbonyl compounds. In this reaction, metal enolates (usually zinc) are generated from α-halocarbonyl compounds under neutral conditions. The fact that no base or acid is required for the enolate generation is one of the appeals of this technique. In addition to the versatility of the reaction due to the variety of electrophiles compatible with the reaction conditions, its applicability to inter- and intra-molecular transformations, and the low cost of the reagents used.[22] Nonetheless, the Reformatsky reaction is limited by its relatively low yields and the difficulty of development of stereoselective variants of the reaction.[23]

In 1955, McBee and co-workers were the first to apply the Reformatsky reaction to α-fluorinated substrates, namely ethyl bromofluoroacetate, using zinc dust under reflux.[24] This report prompted a cascade of developments in this field, limited at first to monofluorinated substrates and later expanded to difluorinated substrates. In 1984, Hallinan and Fried applied this reaction to ethyl α,α-bromodifluoroacetate using similar conditions to the McBee report.[25] A few years later, Kuroboshi and Ishihara used zinc and copper chloride to react bromodifluoroketones with aldehydes, whereas to effect the same reaction with ketones, zinc and silver acetate were required.[26] Many variations of the reaction have been reported; these include using different metals such indium[27-30] as a catalyst or using different solvents including water.[31] In other variants, benzotriazole substituted methyl amines can act as iminium cation precursors. In these reactions, benzotriazole serves as a leaving group and CH_2-NR_2 group is added to difluoroacetate.[32-36]

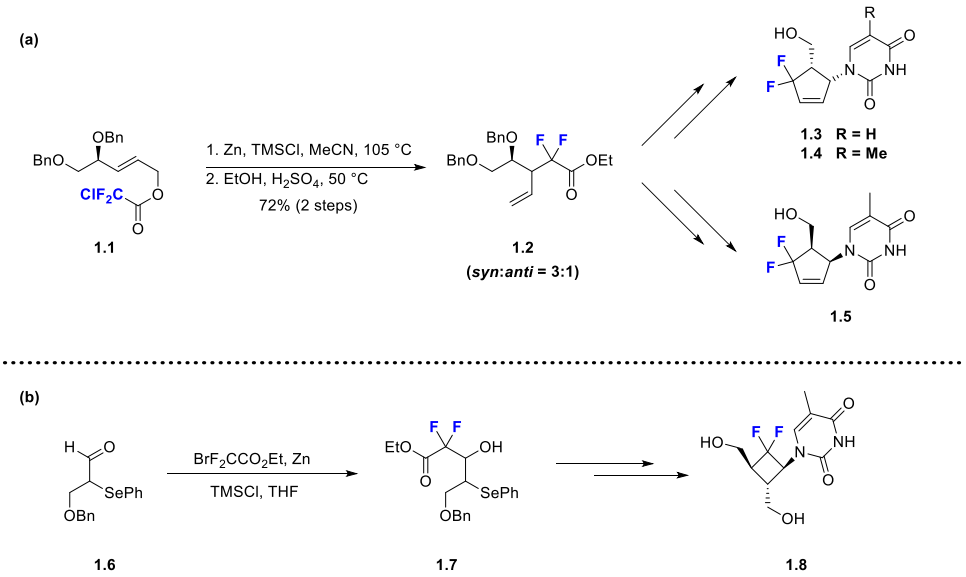
The Reformatsky reaction is used to provide *gem*-difluorocarbonyl compounds as a starting point for many synthesized routes, ranging from enzyme-catalyzed[37] and biocatalysis reactions[38] to cross-coupling[39] and rearrangement reactions.[40] Methodologies employing Reformatsky reaction were also developed to access fluorinated heterocycles (**Scheme 1.2** (a)).[41-45] An interesting example of these methodologies comes from the Gouverneur group where following a Reformatsky reaction to construct *gem*-difluorinated β-hydroxyynones, a gold-catalyzed 6-endo-dig cyclization produced difluorodihydropyranones in good yields (**Scheme 1.2** (b)).[41]



Scheme 1.2. Reformatsky reaction to access fluorinated heterocycles

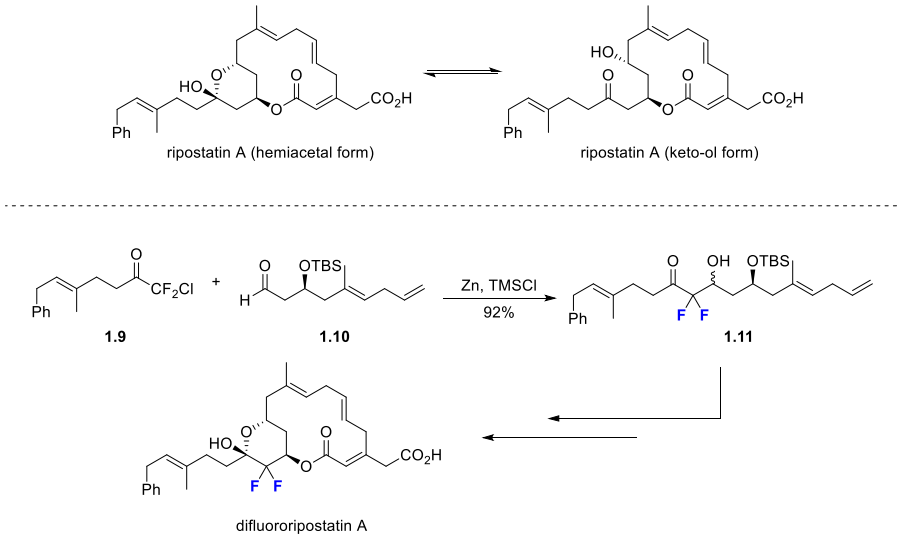
1.2.1. Biologically Relevant Applications

Being a reliable and well established difluoroacetylation method, the Reformatsky reaction has been employed extensively in the synthesis of biologically relevant molecules, varying from probes[46] to receptor modulators[47] and enzyme inhibitors.[36, 48-53] An interesting example of these applications is a report by Qing and co-workers in which the *gem*-difluorinated carbocyclic nucleosides **1.3**, **1.4**, and **1.5** are synthesized as potential highly stable antiviral and anticancer agents.[54-55] The key step in the synthesis of these carbocyclic nucleosides is a diastereoselective Reformatsky-Claisen rearrangement; a zinc-mediated [3,3]-sigmatropic rearrangement (**Scheme 1.3** (a)).[54] Similarly, Tanaka and co-workers used Reformatsky reactions to introduce fluorine in their synthetic route of *gem*-difluorocyclobutane analogue **1.8** (**Scheme 1.3** (b)).[56]



Scheme 1.3. Carbocyclic nucleoside synthesis using Reformatsky-Claisen rearrangement

The Reformatsky reaction was used in the total synthesis of difluorinated analogue of ripostatin A to gain insight into the active form of ripoostatins (**Scheme 1.4**). Ripostatin A exists as an equilibrium mixture of the bicyclic and monocyclic forms. Introducing two fluorine atoms at the α-position of the keto group effectively locks the compound in the bicyclic form. Comparing the activity of ripostatin A and its difluorinated analogue revealed that the bicyclic-trapped analogue difluororipostatin A is two orders of magnitudes less active than ripostatin A, suggesting that the monocyclic form of ripostatin A is the active form.[46]



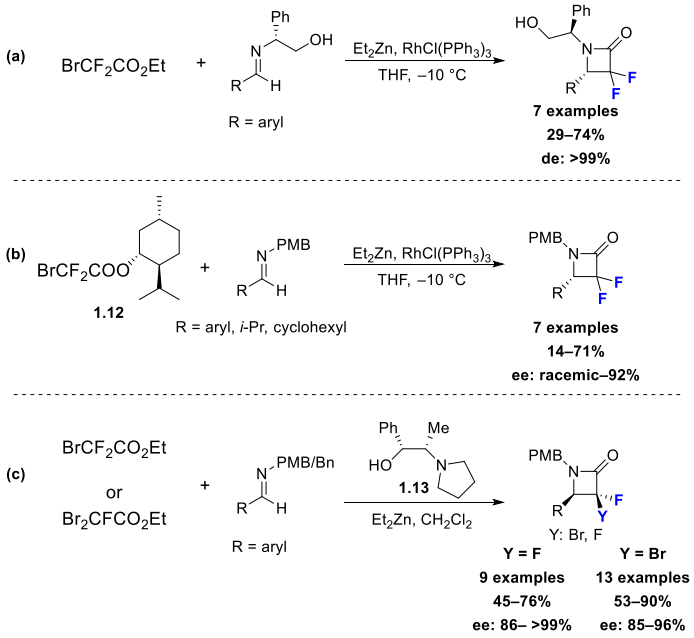
Scheme 1.4. Fluorinated analogue of ripostatin A

1.2.2. Stereoselective Reformatsky

The Honda modification of the Reformatsky reaction is a mild transition metal-catalyzed reaction in which the Wilkinson catalyst $RhCl(PPh_3)_3$ is used with Et_2Zn as the zinc source.[57] The use of Et_2Zn ensures the homogeneity of the reaction mixture which facilitates the design of stereoselective variations of the reaction. Honda applied these conditions to the synthesis of chiral β-amino esters via a three-component coupling, using the (*R*)-phenylglycinol chiral auxiliary.[58] Fuji and co-workers were the first to use the Reformatsky-Honda reaction in the diastereoselective formation of fluorinated substrates. They reported the diastereoselective synthesis of α,α-difluoro-β-amino ester from ethyl bromodifluoroacetate and chiral aldimine.[59]

Several studies used variations of the Reformatsky reaction for the stereoselective synthesis of fluoro-β-amino esters, fluoro-β-hydroxy esters and fluoro-β-lactams. In these reactions, diastereoselectivity can be achieved by using chiral imines (**Scheme 1.5** (a)),[60] chiral sulfinylimines,[61-63] or chiral fluorobromoesters (**Scheme 1.5** (b)).[64] On the other hand, amino alcohol chiral ligands (such as ligand **15**) were shown to promote enantioselective Reformatsky

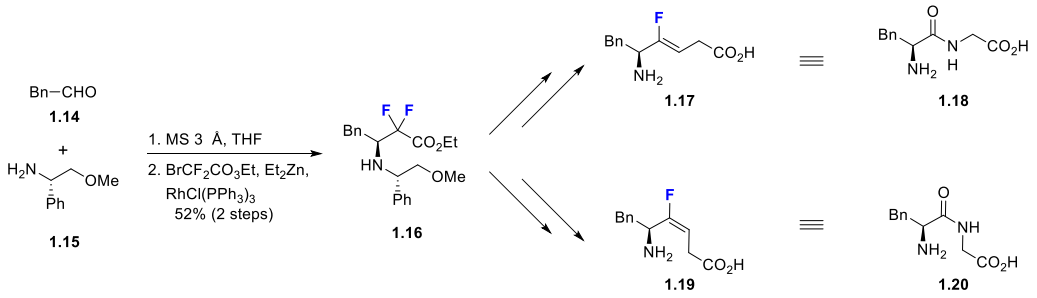
reactions with imines[65-66] and ketones[67] (**Scheme 1.5** (c)). Moreover, using ethyl dibromofluoroacetate gives access to *syn*-α-bromo-α-fluoro-β-lactams[68] which can further react with aryl Grignard reagents[69] or aryl-(9-BBN) reagents[70] to introduce an aryl group at the α-position, or with butyl lithium followed by alkyl halides or carbonyl compounds to alkylate the same position.[71]



Scheme 1.5. Stereoselective synthesis of fluoro-β-lactams via Reformatsky reaction

The diastereoselective Reformatsky-Honda reaction has found useful applications in the synthesis of fluoroalkene peptidomimetics. These compounds are structurally similar to peptides but are resistant to enzymatic action which makes them appealing peptide-based probes. Fujii and co-workers disclosed a synthetic methodology for (*Z*)- and (*E*)-fluoroalkenes in which they utilized Reformatsky-Honda reaction (**Scheme 1.6**).[72] The (*Z*)- and (*E*)-fluoroalkenes (**1.17** and **1.19**) act as *trans*- and *cis*-amide (**1.18** and **1.20**) isosteres, respectively. When the affinities of the fluoroalkenes were determined for the peptide transporter PEPT1, the (*Z*)-fluoroalkene shows

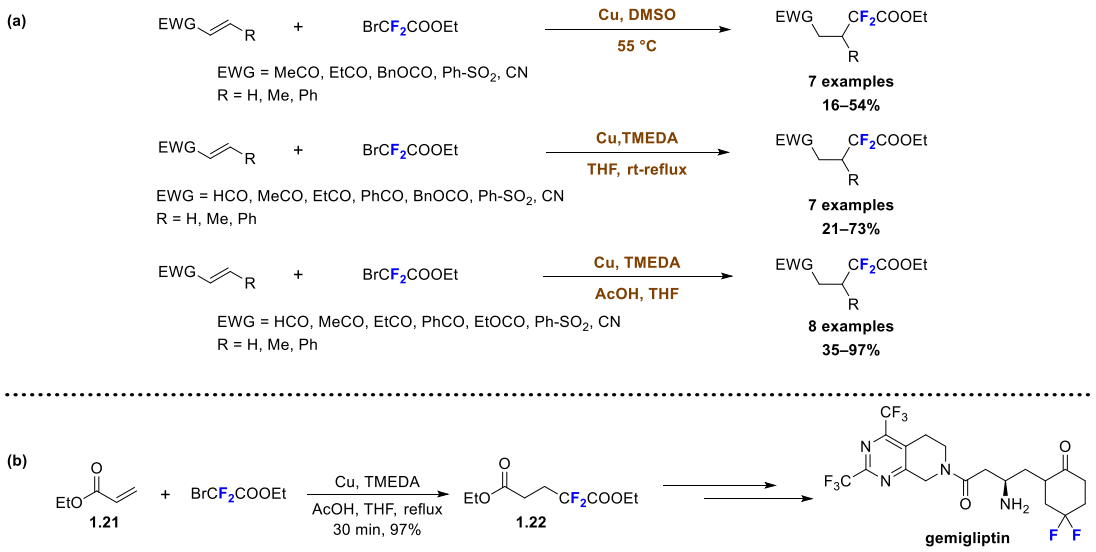
higher affinity suggesting that this transporter binds to the *trans* conformation of the peptide.[72] A similar strategy was applied in the synthesis of fluoroalkene analogues of α-helical anti-HIV peptide[73] and CXCR4 antagonistic pseudopeptide,[74] and the endogenous opioid neuropeptide, Leu-enkephalin.[75]



Scheme 1.6. Reformatsky-Honda reaction in the synthesis of fluoroalkene peptidomimetics

1.3. Copper-mediated Michael Additions

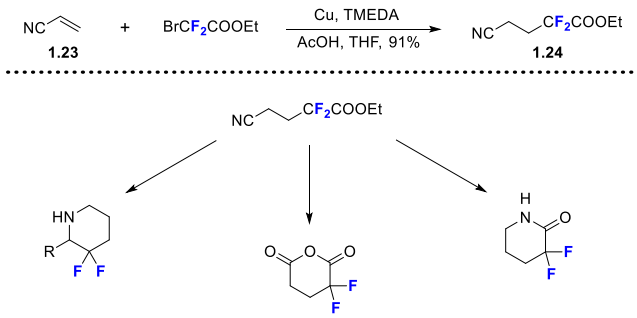
The copper-mediated Michael addition was first reported by Kumadaki and co-workers. In this work, copper powder in DMSO is used to react ethyl α,α-bromodifluoroacetate with Michael acceptors (**Scheme 1.7** (a)).[76] In a following study, Kumadaki reported an improved protocol that utilizes the bidentate ligand tetramethylethylenediamine (TMEDA) to promote the reaction using THF as a solvent, and this modification resulted in better yields and easier work up.[77] Recently, Shin and co-workers disclosed that adding a protic additive, namely acetic acid (AcOH), reduced the side products and improved the yields.[78] In addition, they applied the optimized conditions in large-scale preparation of gemigliptin, a dipeptidyl peptidase-IV (DPP-IV) inhibitor (**Scheme 1.7** (b)).[78]



Scheme 1.7. (a) Copper-mediated Michael addition conditions, (b) application in gemigliptin synthesis

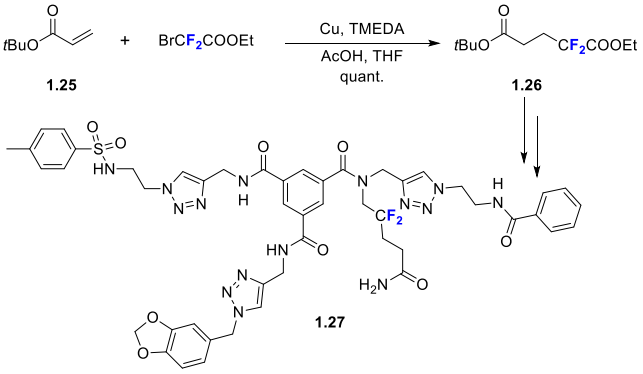
1.3.1. Application of Copper-mediated Michael additions

Applications of the copper-mediated Michael addition include the construction of heterocycles as building block in medicinal chemistry. Examples of these applications include the reaction of ethyl α,α-bromodifluoroacetate with acrylonitrile to give rise to ethyl 4-cyano-2,2-difluorobutanoate, which then can cyclize to form difluoropiperidines or difluoroglutaric anhydride (**Scheme 1.8**).[79-81] This method provides access to novel building blocks via simple protocols and readily available starting materials.



Scheme 1.8. Copper-mediated Michael addition application in the synthesis of heterocycles

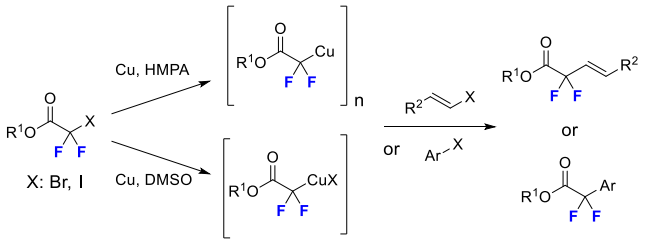
Jiracek and co-workers applied the copper-mediated Michael addition in the synthesis of a trifunctional scaffold that can be selectively functionalized for biological applications like sequential bioconjugations.[82] In this synthesis, the Michael addition reaction was used to install a difluorinated spacer (**Scheme 1.9**), which allowed the use of ^{19}F NMR to quantify the fluorine-containing compounds in the crude mixture at the end of the solid-phase synthesis. ^{19}F NMR can later be used to quantify the products of any following application of this scaffold.



Scheme 1.9. Fluorinated trifunctional scaffold

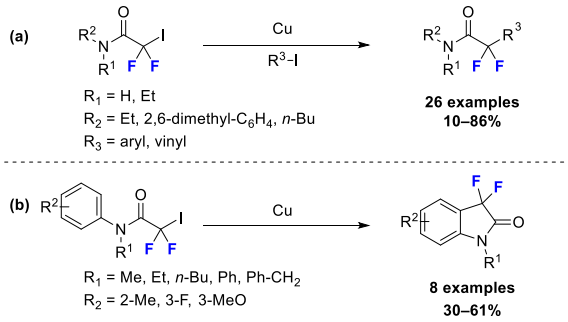
1.4. Copper-promoted Coupling to Vinyl and Aryl Halides

Kobayashi and co-workers reported the copper-promoted coupling of iododifluoroacetate to vinyl and aryl halides, in which three equivalents of iododifluoroacetate reacted with one equivalent of the alkenyl halide in DMSO.[83] In a following publication, Kobayashi further investigated the effects of solvent on the coupling reaction using ^{19}F NMR. He found that HMPA better stabilized the reaction intermediate, produced less by-products and resulted in almost quantitative conversion.[84] However, Kobayashi's attempts to apply this method to bromodifluoroacetate were unsuccessful. Over a decade later, Kumadaki and co-workers expanded this method to the cheaper bromodifluoroacetate by using activated copper in DMSO and reducing the number of bromodifluoroacetate equivalents to one equivalent. This helped reduce the formation of the double addition by-product.[85] The Kumadaki modification was incompatible with alkyl and alkynyl halides,[85] on the other hand, the Kobayashi method resulted in poor in DMSO[83] and moderate to good in HMPA.[84] Kumadaki and Kobayashi proposed different complexes as the active intermediate in this reaction, presumably the choice of solvent determines which intermediate is formed (**Scheme 1.10**). α-Silyldifluoroacetates have also been shown to participate in this reaction. In a report from Amii and co-workers, copper iodide and potassium fluoride were heated in DMF to promote the coupling of silyldifluoroacetates with aryl halides.[86] Furthermore, this reaction is not limited to fluoroacetates; fluoroamides, fluorosulfones and even fluoromethyl-benzo-1,3-oxazoles which have been shown to participate in a cross-coupling reaction.[87]



Scheme 1.10. Copper-promoted coupling to vinyl and aryl halides

Hu and co-workers investigated the selectivity of the copper-mediated coupling reaction and found that in the presence of a coupling partner, the cross-coupling adduct is the major product (**Scheme 1.11** (a)); however, in the absence of a suitable coupling partner, the homocoupling product was predominantly formed especially when one of the nitrogen substituents is a hydrogen atom.[88] For cases in which one of the substitutions on the nitrogen is an aromatic ring, a competing intramolecular cyclization takes place, especially with electron rich rings (**Scheme 1.11** (b)).

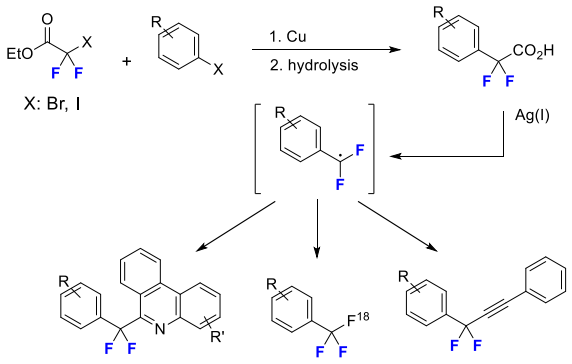


Scheme 1.11. Selectivity of copper-mediated reactions

1.4.1. Applications of Copper-promoted Coupling to Vinyl and Aryl Halides

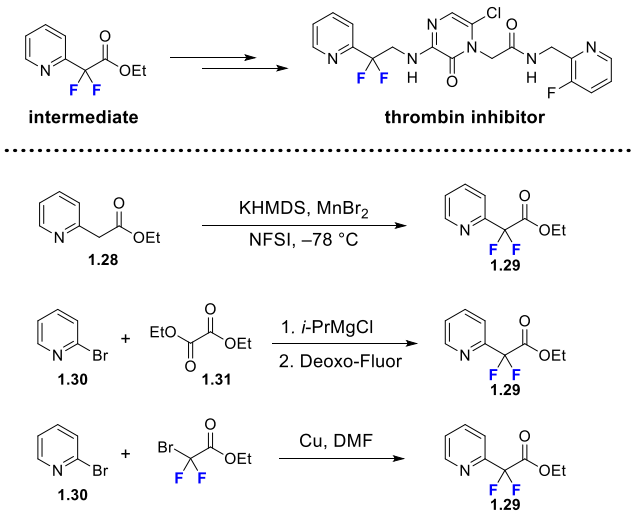
The product of this copper-mediated coupling reaction is different from most other difluoromethylation methods in that it doesn't contain an α-hydroxy group, because this group is relatively difficult to remove. Thus, this cross-coupling reaction has enabled new developments in synthetic methodologies by providing novel fluorinated starting materials.[89-92] Silver-catalyzed

decarboxylative difluoromethylenation is enabled by a copper-mediated coupling followed by hydrolysis and decarboxylation of 2,2-difluoro-2-phenylacetic acid using Ag(I) (**Scheme 1.12**). The intermediate is a radical that can be alkenylated using ethynyl-benziodoxolone reagents,[93] ^{18}F labelled,[94-95] or can add to isocyanide followed by intramolecular cyclization to form difluoromethylenated phenanthridine.[96]



Scheme 1.12. Silver-catalyzed decarboxylative difluoromethylenation

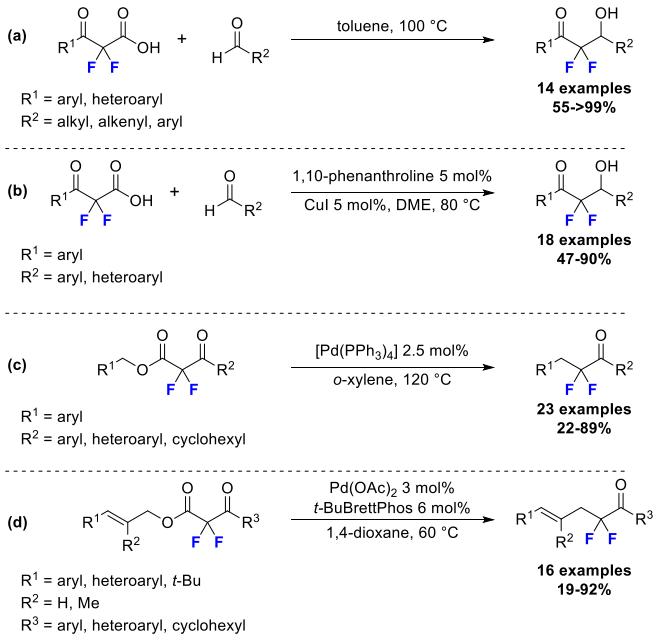
This coupling reaction has found applications in the synthesis of biologically active compounds.[97-99] For instance, Wilson and co-workers utilized it in their search of an efficient scalable protocol for the synthesis of a thrombin inhibitor.[100] In the optimization of the synthesis of a difluoroethylester intermediate, the original route used NFSI at –78 °C to fluorinate the starting material (**Scheme 1.13**). To avoid running the reaction at low temperature, a second route was developed in which Deoxo-Fluor was used to introduce the two fluorines. Nonetheless, both routes used expensive fluorinating reagents and were relatively low yielding. Hence, they explored a third route that employed the copper-mediated coupling reaction to incorporate the fluorine atoms using the bromodifluoroacetate building block which proceeded in very good yield.



Scheme 1.13. Optimizing the synthesis of a thrombin inhibitor

1.5. Decarboxylative Reactions

Decarboxylative reactions can be used to assemble fluorinated compounds. Starting with α,α-difluoro-β-keto acids or esters, heat with or without the help of a metal catalysts is employed to release CO_2 and form difluoroenolates. Although this method forms fluoroenolates under neutral conditions, it frequently requires the use of high temperatures which might limit its applications. Decarboxylative aldol reactions generate α,α-difluoro-β-hydroxyketones when heated to 100 °C,[101] or when catalyzed by copper-phenanthroline complex in addition to heating to 80 °C (**Scheme 1.14** (a) & (b)).[102] Also, palladium-catalyzed decarboxylative benzylation reactions can be used to form α-benzyl-α,α-difluoroketones when heated to 120 °C (**Scheme 1.14** (c)).[103] Similarly, α-allyl-α,α-difluoroketones can be accessed using palladium-catalyzed decarboxylative allylation reactions product (**Scheme 1.14** (d)). In this allylation reaction, the regioselectivity of the addition is dependent on the ligand. Specifically, when *t*-BuBrettPhos is used the linear product is predominantly formed, whereas when PhXPhos is used the branched form is the main product.[104]



Scheme 1.14. Decarboxylative reactions in the synthesis of difluorinated compounds

1.6. Trifluoroacetate-release Reactions

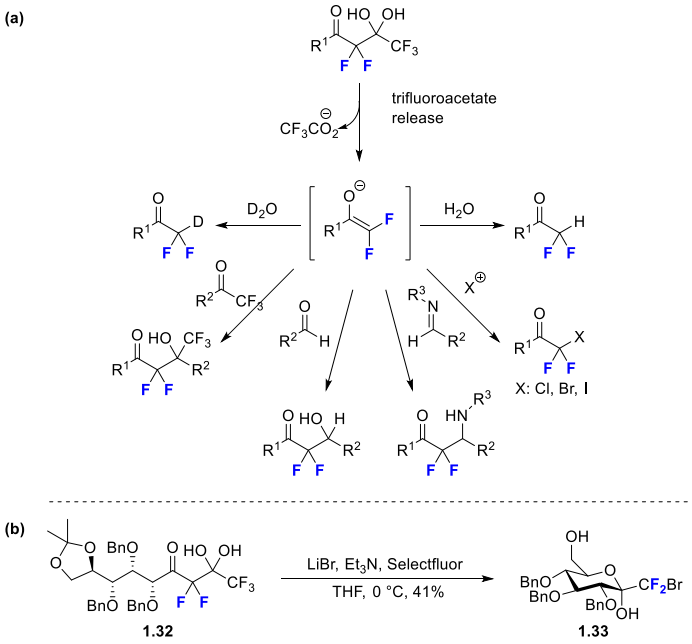
The trifluoroacetate-release method is an innovative technique that generates fluoroenolates from highly fluorinated β-keto-*gem*-diols via C-C bond scission under mild conditions.[105] In the presence of a metal salt, mild bases such as triethylamine and potassium bicarbonate are added to cleave the C-C bond, form fluoroenolates, and release trifluoroacetate over the course of a few minutes (**Scheme 15** part (a)). Stronger bases such as NaH, KHMDS and *n*-BuLi can be used as well, and under these conditions, the reaction is usually instantaneous. Salts of metals including lithium, copper, zinc and magnesium are typically added to the reaction mixture to accelerate the reaction and stabilize the fluoroenolates.[106]

1.6.1. Applications of Trifluoroacetate-release Reactions

The fluoroenolates produced via the trifluoroacetate-release approach have been shown to react with various electrophiles (**Scheme 1.15** (a)). The trifluoroacetate-release based aldol reaction with aldehydes was the first reported reaction to utilize this approach. The reaction produced α,α-difluoro-β-hydroxy ketones in good to excellent yields and with a wide substrate scope, including aromatic and aliphatic aldehydes.[105] Attempts to extend the scope of this reaction to ketones were limited to the highly activated trifluoromethyl aryl and heteroaryl ketones which requires the use of a strong base, namely LiHMDS, to effect the transformation in good yields.[107] Trifluoroacetate-release Mannich reactions have been reported with activated imines such as *N*-sulfinyl,[108] *N*-sulfonyl,[109-110] *N*-Boc,[109] and *N*-tosyl imines.[110] This method was later extended to non-activated imines by utilizing magnesium salts. The trifluoroacetate-release Mannich reaction was applied in the synthesis of difluoromethyl tetrahydroisoquinolines through the reaction of difluoroenolates with dihydroisoquinolines that are generated *in situ* by visible-light photoredox catalysis.[111]

The difluoroenolates can also be trapped with water or deuterated water to produce difluoromethyl ketones[112] and deutero-methyl ketones respectively.[113] Furthermore, difluoroenolates generated from pentafluoro-*gem*-diols react with halogenation reagents including I_2, Br_2, and NCS to generate iodo, bromo and chlorodifluoromethyl ketones. In a similar manner, 2-chloro-2,4,4,4-tetrafluoro-*gem*-diols can undergo trifluoroacetate-release followed by bromination to produce bromochlorofluoromethyl ketones respectively.[114] The iododifluoromethyl ketones formed using the trifluoroacetate-release halogenation reaction were further utilized in methodologies to access α,α-difluoro-β,γ-alkenyl ketones[115] and α,α-

difluorobenzoyl oxygen heterocycles.[116] An interesting application of the trifluoroacetate-release reaction is the synthesis of CF_2Br-glucopyranose **1.33** (**Scheme 1.15** (b)). Starting with pentafluoro-*gem*-diol **1.32**, a tandem cascade reaction ensued upon the addition of triethylamine. A series of trifluoroacetate-release, halogenation, deprotection, and finally cyclization produced **1.33** as a single diastereomer in 41% yield.[117]

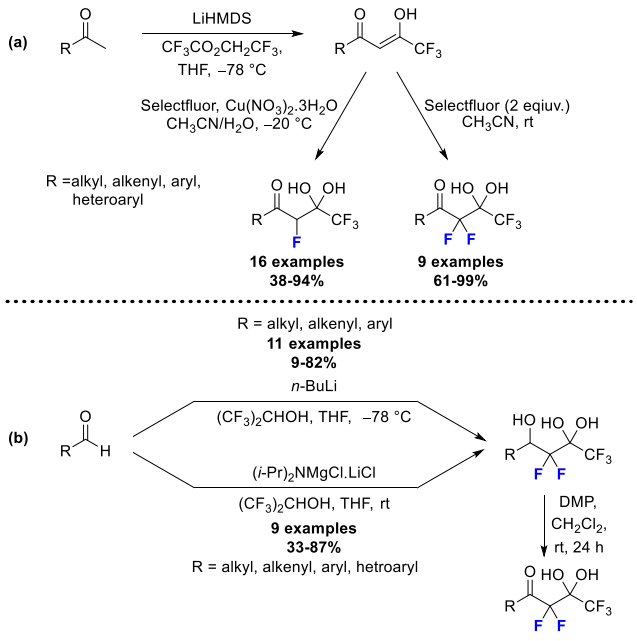


Scheme 1.15. Reactions of fluoroenolates generated via trifluoroacetate release

1.6.2. Synthesis of Highly Fluorinated *gem*-diols

Typically, highly fluorinated *gem*-diols are synthesized from ketones through trifluoroacetylation using trifluoroethyl trifluoroacetate[118] followed by fluorination using Selectfluor (**Scheme 1.16** (a)).[105] This method can be applied to ketones with two α-protons to generate pentafluoro-*gem*-diols[105] and to ketones with one α-proton to form tetrafluoro-*gem*-diols.[119] The fluorination step can be modified to produce tetrafluoro-*gem*-diols from ketones with two α-protons by limiting the number of Selectfluor equivalents to one. However, this approach results in modest yields and is complicated by the formation of the difluorinated by-product.[120] To

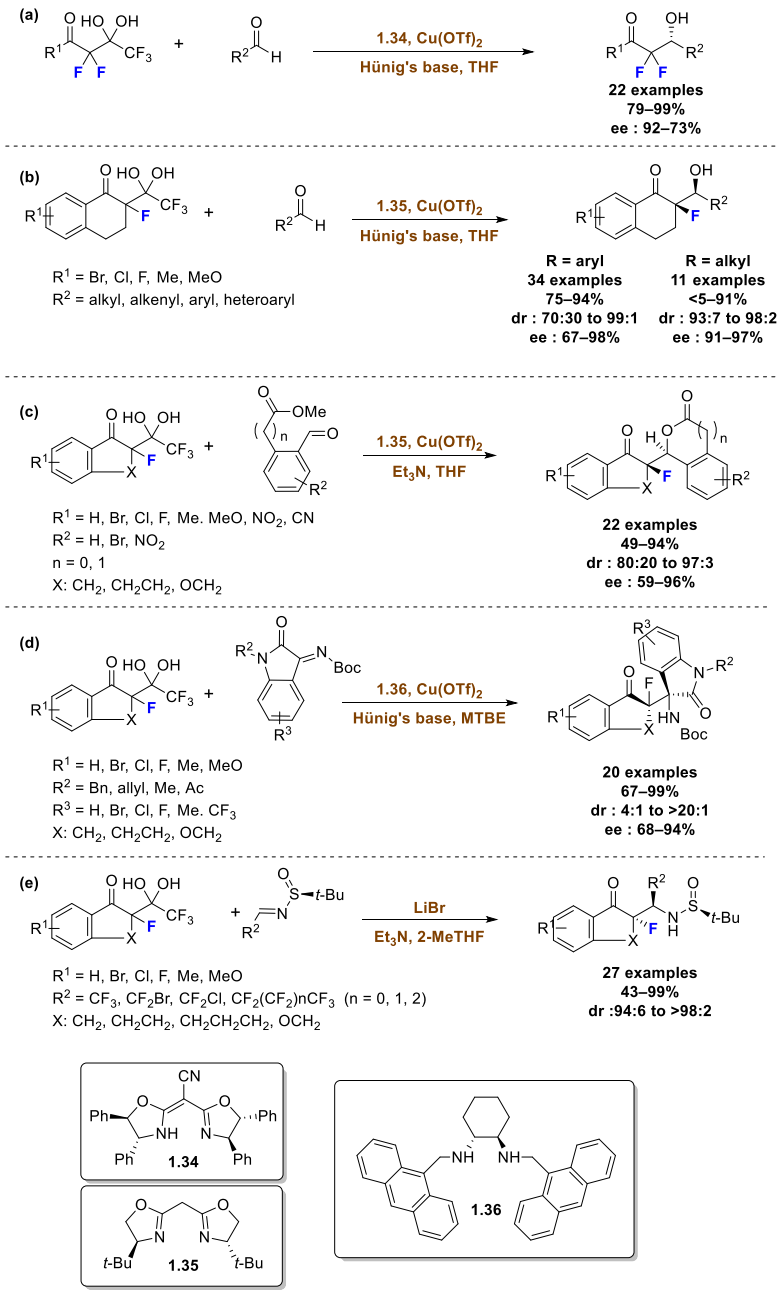
improve the efficiency of this transformation, Wu and co-workers reported using copper nitrate as a catalyst and a water/acetonitrile mixture as the reaction solvent to get tetrafluoro-*gem*-diols in high yields.[121] Alternatively, highly fluorinated *gem*-diols can be accessed from aldehydes through the addition of fluoroenolates generated from hexafluoroisopropanol followed by oxidation of the β-hydroxy group to a β-keto group (**Scheme 1.16** (b)). In this technique, lithium pentafluoropropen-2-olate can be formed by treating hexafluoroisopropanol with *n*-BuLi.[117, 122-123] however, a milder alternative employs magnesium pentafluoropropen-2-olate generated from (*i*-Pr)$_2$NMgCl·LiCl and hexafluoroisopropanol.[124]



Scheme 1.16. Synthesis of highly fluorinated *gem*-diols

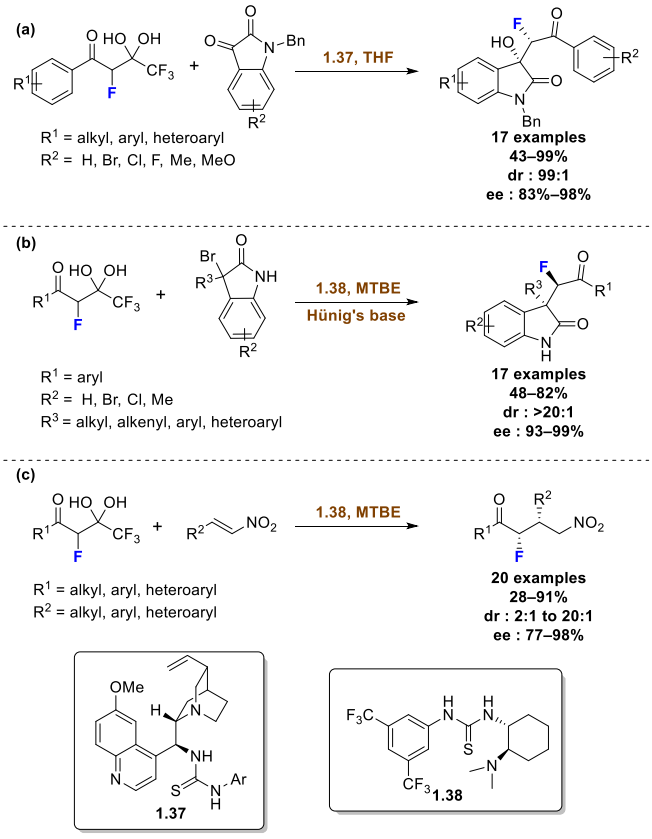
1.6.3. Stereoselective Trifluoroacetate-Release Reactions

The use of difluoroenolates in asymmetric reactions can be challenging. Even though the stereoselective Reformatsky reaction has found some success, it usually requires the use of stoichiometric amounts of chiral ligands to accomplish these transformations. On the other hand, the mild homogeneous conditions of the trifluoroacetate-release reaction lend themselves well to stereoselective control. Consequently, an array of catalytic reactions with various substrates have been reported to utilize this method for the assembly of stereogenic centers. These reactions employ different types of ligands, including bis(oxazoline) (BOX), thiourea, diamine and monophosphine ligands. Zhang and Wolf reported a catalytic enantioselective trifluoroacetate-release aldol reaction, in which α,α-difluoro-β-hydroxy ketones are synthesized using copper(II) triflate (5 mol%) and the new chiral bidentate BOX ligand **1.34** (6 mol%) (**Scheme 1.17** (a)).[106] Pan and co-workers utilized a similar method in the catalytic asymmetric synthesis of C-F quaternary stereogenic centers using the *t*-butyl-substituted BOX ligand **1.35**, first with aromatic aldehydes[119] and later with alkyl aldehydes but with less success (**Scheme 1.17** (b)).[125] In a following paper, Pan applied the same reaction in a cascade aldol–cyclization reaction to prepare 2-fluoro-isobenzofuran-1(*3H*)-one in good diastereoselectivities and enantioselectivities (**Scheme 1.17** (c)).[126] Stereoselective trifluoroacetate-release Mannich reactions have also been developed. Cyclic tetrafluoro-*gem*-diols react with isatin-derived ketimines using the diamine ligand **1.36** (**Scheme 1.17** (d))[127] and chiral *N*-sulfinylimines without the use of chiral ligands (**Scheme 1.17** (e))[128] to generate α-fluoro-β-keto-amines in high diastereoselectivities. Furthermore, catalytic enantioselective aryl coupling reactions can be accomplished using palladium complex and (*S*)-difluorphos or (*S*)-segphos ligands.[129]



Scheme 1.17. Stereoselective trifluoroacetate-release reactions to install C-F quaternary stereogenic centers

Several other methods employ trifluoroacetate-release reactions using thiourea-based ligands to introduce the monofluoroalkyl group enantioselectively. Wu and co-workers used ligand **1.37** to produce 3-hydroxy oxindoles through aldol reactions with indoline-2,3-diones (**Scheme 1.18** (a)).[121] In a similar effort, Wang and co-workers asymmetrically synthesized 3-alkyl oxindoles by utilizing ligand **1.38** and using 3-bromooxindoles as indol-2-ones precursors (**Scheme 1.18** (b)).[130] The method was also applied to Micheal addition reactions with nitroolefins using the same ligand but with lower stereocontrol (**Scheme 1.18** (c)).[131]



Scheme 1.18. Stereoselective trifluoroacetate-release reactions to install monofluoroalkyl group

CHAPTER 2

DEVELOPMENT OF FLUORINATION METHODOLOGY

2.1. Difluoromethyl Ketones

The development of fluorination methods to install the difluoromethyl (CF_2) group is of particular interest to medicinal chemists. The CF_2H group can act as a hydrogen bond donor, whereas the fluorine lone pair can partake in hydrogen bonding as an acceptor.[132] Moreover, the CF_2 group is considered a valuable bioisostere of oxygen since it has comparable size and electronic properties to oxygen, and can coordinate different metals such as Na^+, K^+, Mg^{2+}, and Ca^{2+}.[133] We are principally interested in the α,α-difluoromethyl keto group. This group has great potential as a synthetic intermediate as well as having prospective pharmaceutical applications. Difluoromethyl ketones have been used in enzyme and receptor modulators, like serine[134] and aspartyl protease inhibitors[135] (**Figure 2.1**).

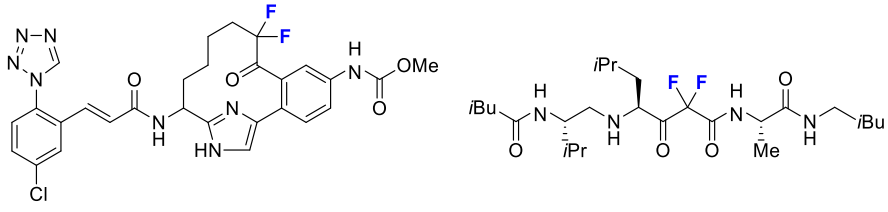


Figure 2.1. Serine and aspartyl protease inhibitors containing difluoromethyl keto group

The high electronegativity of the neighboring fluorine atoms activates the keto group to nucleophilic attacks. Also, this group exists as a mixture of the keto and diol (hydrated) forms, in

the presence of water (**Figure 2.2a**). The diol improves the water solubility of the compound, and in the context of enzyme binding, the tetrahedral shape of the hydrated form mimics a tetrahedral transition state which might result in favorable binding. Furthermore, in some structures, the increased electrophilicity of the fluorinated keto group facilitates intramolecular attacks that can lead to the formation of the corresponding hemiacetal. An example of this transformation can be seen in Lubiprostone, which exists as a mixture of the keto and hemiacetal forms (**Figure 2.2b**).[136] The bicyclic hemiacetal is the active form of this drug.

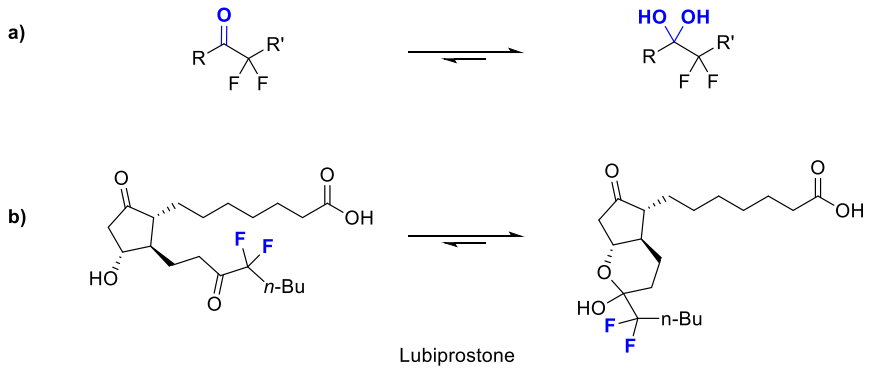
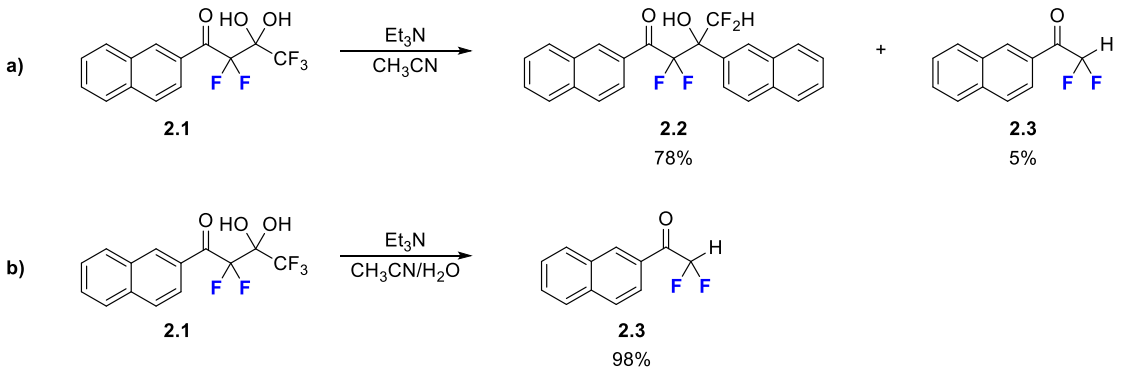


Figure 2.2. a) Keto and diol forms of difluoromethyl keto group, b) ketone and hemiacetal forms of Lubiprostone

2.2. Preparation of Difluoromethyl Ketones

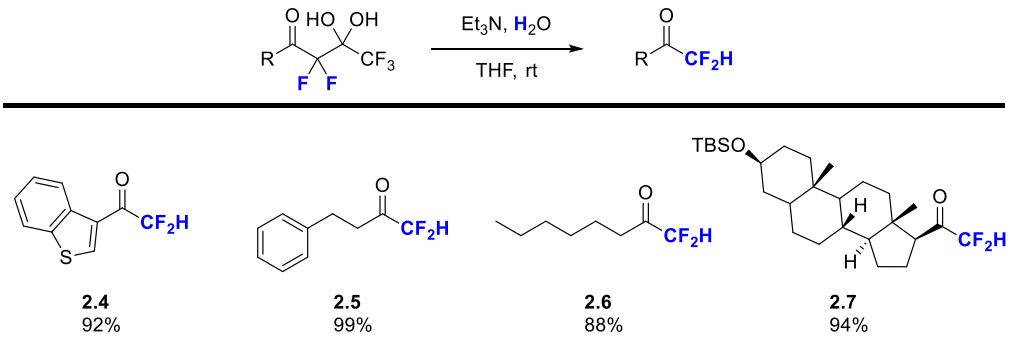
Current methods to access difluoromethyl ketones include magnesium catalyzed defluorination of trifluoromethyl ketones,[137] alkylation of ethyl difluoroacetate utilizing Grignard reagents[138] and difluoromethylation of acyl chlorides using *N*-heterocyclic carbene Ag(CF_2H) complexes.[139] These methods typically require the use of sensitive organometalics and can be low yielding. We aim to utilize the trifluoroacetate-release method to generate difluoromethyl ketones.

When difluoroenolates are generated in the absence of an electrophile and then quenched with water, the difluoromethyl ketone product can be observed only in about a 5% yield, because the self-adduct is the major product (**Scheme 2.1a**). To prevent the formation of the self-adduct product, we decided to add water to the reaction mixture before the fragmentation process begins to trap the enolate as soon as it forms. Fortunately, this procedure produced the difluoromethyl ketone as the major product (**Scheme 2.1b**).[113]



Scheme 2.1. Using water to trap difluoromethyl enolates as difluoromethyl ketones

In this method, the generation of α,α-difluoromethyl ketones can be accomplished under mild conditions through a base-mediated fragmentation of pentafluoro-*gem*-diols in the presence of water (**Scheme 2.2**). This process is compatible with aromatic, heteroaromatic and aliphatic ketones. The trifluoroacetate-release method generates difluoromethyl ketones in good yields without issues of over- or under-fluorination.[113]



Scheme 2.2. Preparation of difluoromethyl ketones

2.3. Preparation of Deuterated Difluoromethyl Ketones

The incorporation of deuterium into pharmaceuticals to block sites of metabolism is a growing field. The stronger deuterium-carbon bond is harder to break than a hydrogen-carbon bond, and this change slows the metabolism of deuterated agents. In 2017, Austedo became the first deuterium containing drug to be approved by the FDA. Austedo is the deuterated analogue of Xenazine; a drug used for the treatment of chorea associated with Huntington's disease (**Figure 2.3**). The six methoxy protons of Xenazine are replaced by deuterium atoms to produce Austedo, doubling the half-life of this drug.[140]

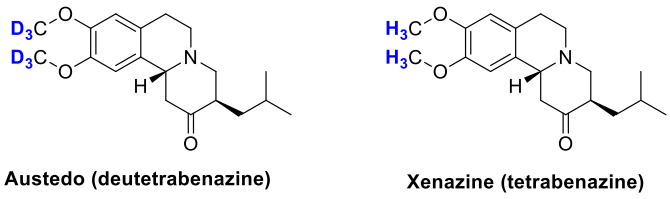
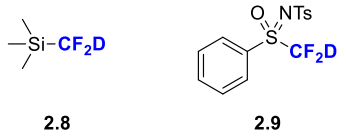


Figure 2.3. Structures of Austedo and Xenazine

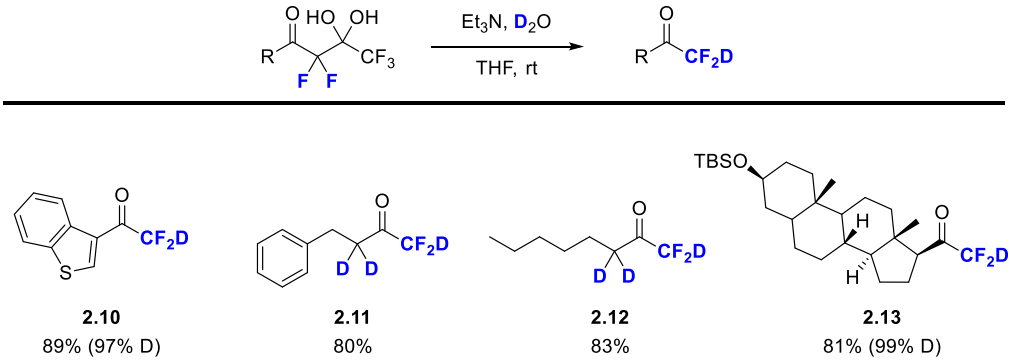
We are interested in developing a method to generate deuterated difluoromethyl compounds. The two reported CF_2D-based reagents are derived from trifluoromethylating reagents by replacing one of the fluorines with a deuterium atom (**Figure 2.4**). Reagent **2.8** derived from the Rupert-Prakash reagent has been reported to deliver a deuterium atom rather than a CF_2D group.[141] On the other hand, the sulfoximine-based reagent **2.9** successfully introduces a CF_2D group, albeit with low deuterium incorporation yields.[142]



2.8 **2.9**

Figure 2.4. Structures of CF_2D-based reagents

The trifluoroacetate-release protocol developed for the synthesis of α,α-difluoromethyl ketones can be adopted to generate α-deutero-α,α-difluoromethyl ketones by substituting D_2O for water. This process produced α-deutero-α,α-difluoromethyl ketones in very good yields. Fortunately, the deuterated ketones were generated with excellent levels of deuterium incorporation (>97%) (**Scheme 2.3**).[113]



2.10 89% (97% D)

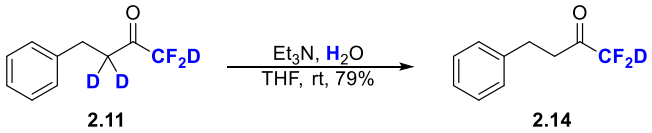
2.11 80%

2.12 83%

2.13 81% (99% D)

Scheme 2.3. Preparation of deutero difluoromethyl ketones

Over-deuteration at susceptible α-positions is observed in the presence of D_2O and base, such as in compounds **2.11** and **2.12** (**Scheme 2.3**). Fluorine substituents noticeably reduce the acidity of neighboring deuteriums; thus, the formation of CF_2 carbanion by dedeuteration of CF_2D is a slow unfavorable process. Therefore, over-deuteration can easily be addressed utilizing the differences in acidity between the deuterium atoms on the two α-carbons. Treating the over-deuterated product **2.11** with triethylamine in water replaces the deuterium atoms on the non-fluorinated α-carbon with hydrogen, whereas the deuterium on the fluorinated carbon atom is stable under these conditions and no exchange is observed (**Scheme 2.4**).

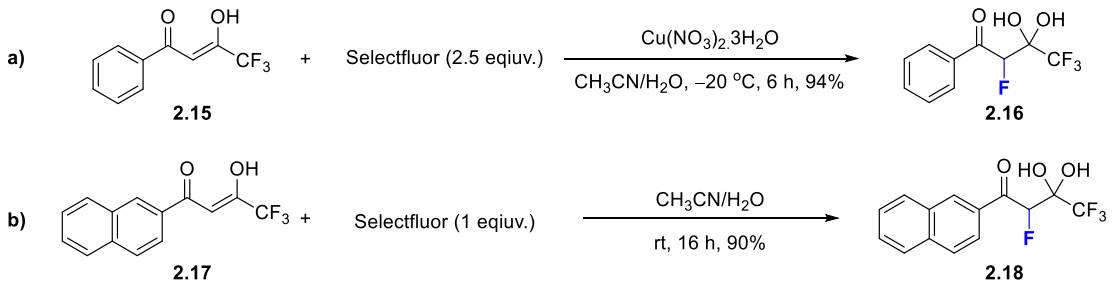


2.11 2.14

Scheme 2.4. Selective dedeuteration on the non-fluorinated α-position

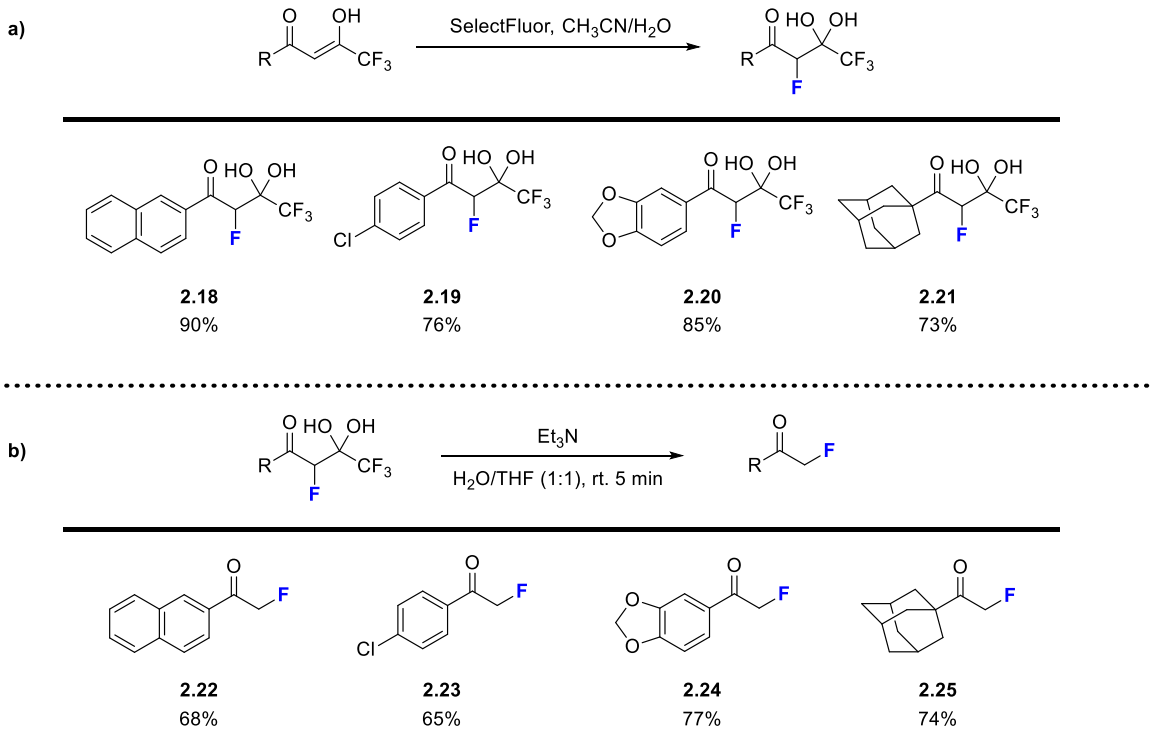
2.4. Preparation of Monofluoromethyl Ketones

Typically treating trifluoromethyl β-diketones with Selectfluor in acetonitrile results in difluorination of the α-carbon. Wu and co-workers reported that monofluorination of these diketones can be accomplished in presence of cupper nitrate as a catalyst (**Scheme 2.5a**).[121] We have found that carrying the reaction in acetonitrile and water in absence of a catalyst produced the monofluoronated product in high yields (**Scheme 2.5b**).



Scheme 2.5. Monofluorination of trifluoromethyl β-diketones

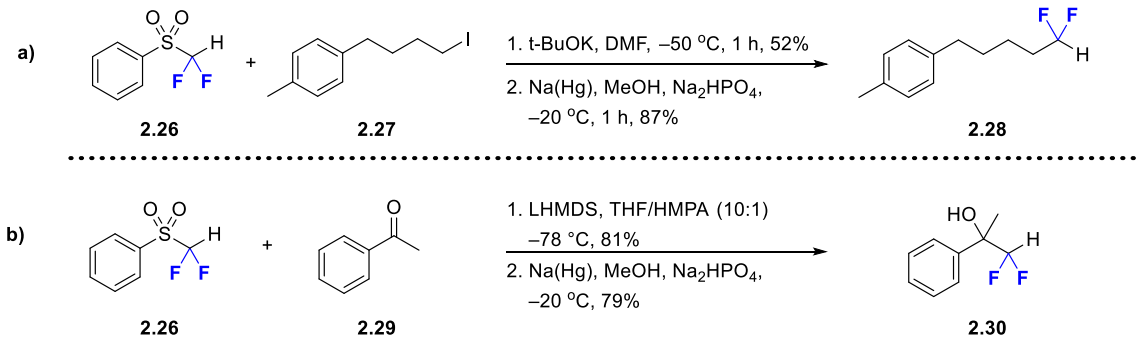
The monofluoronation of trifluoromethyl β-diketones under these conditions produced the tertafluorinated *gem*-diol products in very good yields for aromatic and aliphatic substrates (**Scheme 2.6a**). The tertafluorinated *gem*-diol product can go through trifluoroacetate release to generate a monofluoromethyl enolate. These enolates can be quenched with water to generate monofluoromethyl ketones in good yields (**Scheme 2.6b**).



Scheme 2.6. Preparation of monofluoromethyl ketones

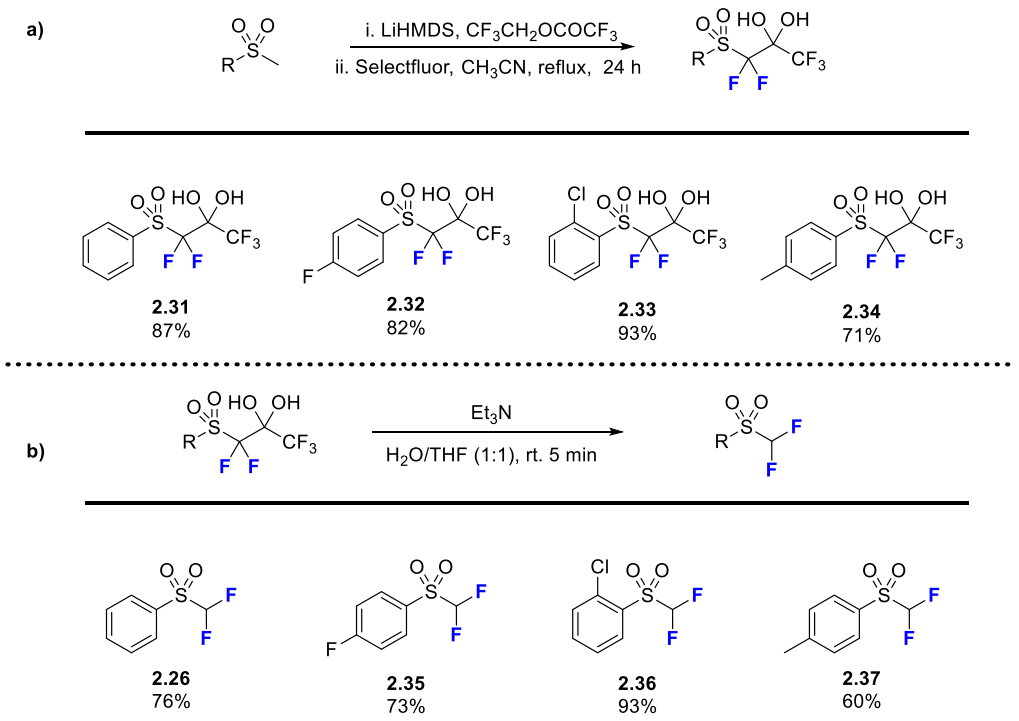
2.5. Preparation of Fluoromethyl Sulfones

Difluoromethyl sulfones are useful difluoromethylating reagents. They can be used to install a CF_2H moiety by deprotonation of the difluoromethyl group to generate a difluoromethyl sulfone carbanion that attacks an electrophile to add a difluoromethyl sulfone group, followed by desulfonation and protonation. This process has been shown to generate alkylated difluoromethylene by substituting a halide atom (**Scheme 2.7a**),[143] and α-difluoromethyl alcohols in reactions with carbonyl (**Scheme 2.7b**).[144]



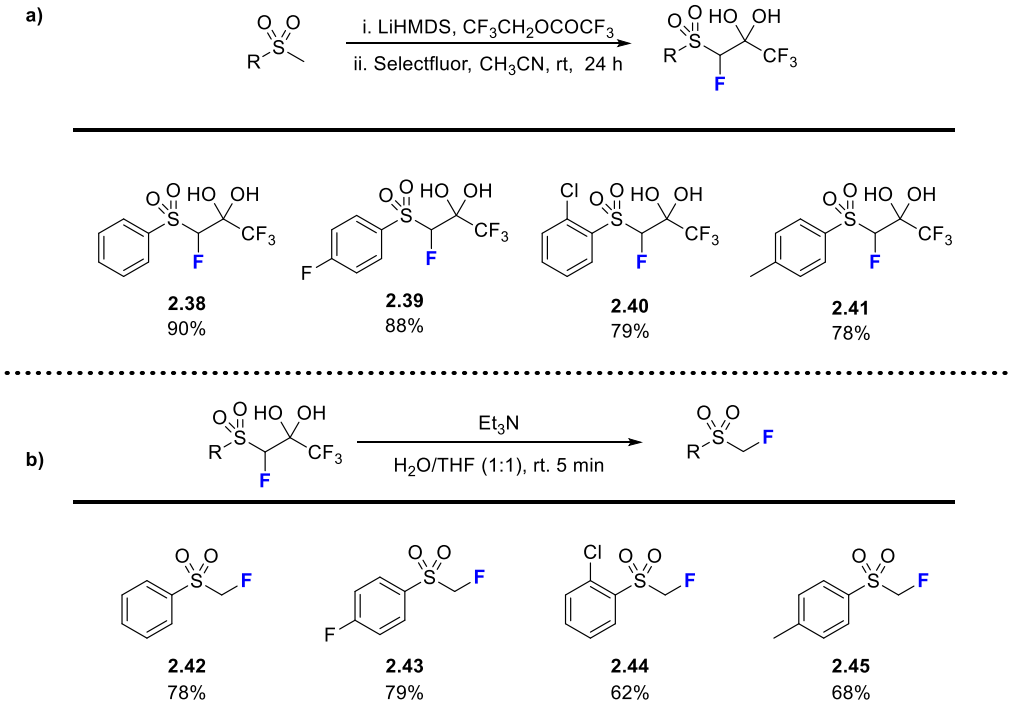
Scheme 2.7. Difluoromethyl sulfones use as difluoromethylating reagents

Difluoromethyl sulfones are usually synthesized from thiols using dangerous gases like chlorodifluoromethane and dibromodifluoromethane. We aim to develop a method to prepare fluorinated sulfones that avoids these gases. Typically, the starting material of the trifluoroacetate release process is α-keto pentafluoro *gem*-diol. The keto group stabilizes the carbanion that forms upon fragmentation. We envisioned that α-sulfonyl pentafluoro gem-diols would be capable of effecting the same fragmentation as its ketone counterpart. The synthesis of α-sulfonyl pentafluoro *gem*-diols starts with methyl sulfones that can be trifluoroacetylated using trifluoroethyl trifluoroacetate which would then be fluorinated using Selectfluor (**Scheme 2.8a**). Trifluoroacetate release from sulfonyl pentafluoro-*gem*-diols followed by protonation will generate difluoromethyl and monofluoromethyl sulfones, respectively (**Scheme 2.8b**).[113]



Scheme 2.8. Preparation of difluoromethyl sulfones

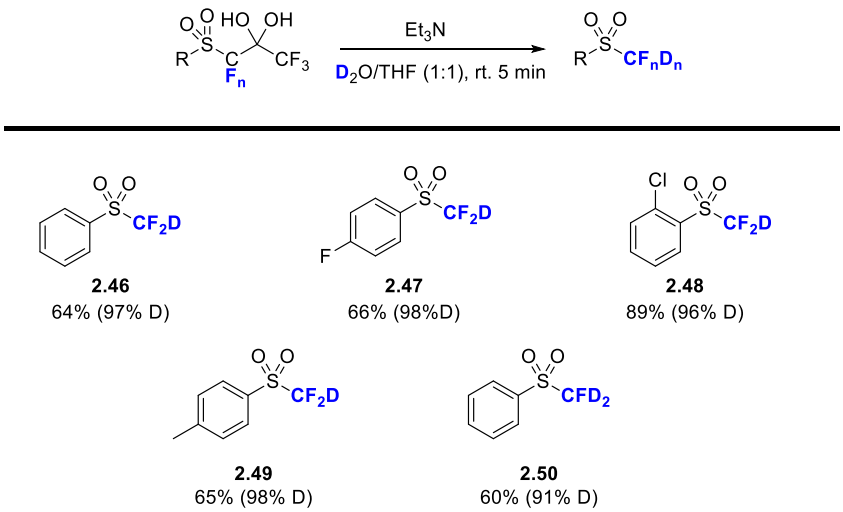
The temperature at which the fluorination reaction is carried out controls the level of fluorination; monofluorination is predominant at room temperature and heating at reflux is needed to push the reaction toward difluorination. We exploited this selectivity to prepare tetrafluoro *gem*-diols from methyl ketones at room temperature (**Scheme 2.9a**). With tetrafluoro *gem*-diols on hand, monofluorinated methyl ketones can be accessed using the trifluoroacetate release process (**Scheme 2.9b**).



Scheme 2.9. Preparation of monofluoromethyl sulfones

2.6. Preparation of Deuterated Fluoromethyl Sulfones

Extending this method to synthesize α-deutero-α,α-difluoromethyl sulfones proved easy. The substitution of H_2O with D_2O provided the deuterated analogues in good yields and with deuterium incorporation yields ≥ 96% (**Scheme 2.10**). This represents a simple method for the synthesis of novel deuterodifluoromethylating reagents that were not reviously reported. The process was less efficient in generating the α,α-dideutero-α-fluoromethyl sulfone **2.50**. In the case of this compound, a mixture of the CFH_2, CFHD, and CFD_2 analogues was retrieved with desired product **2.50** constituting 91% of this mixture.[113]

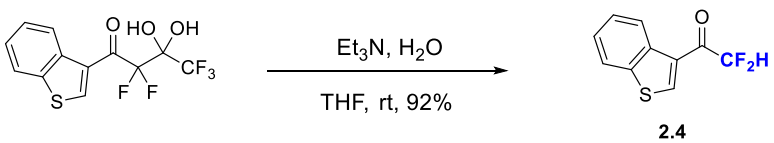


Scheme 2.10. Preparation of deuterofluoromethyl sulfones

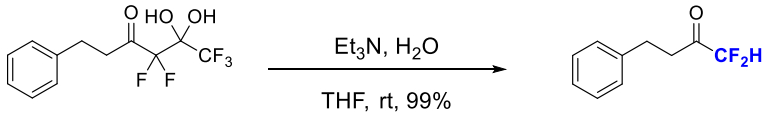
2.7 Experimental Details

All reactions were performed in oven-dried glassware. All air and moisture sensitive solvents were transferred via syringe. Column chromatography was performed using Sorbent Technologies silica gel (200–400 mesh).

Representative Reaction Procedure for Preparation of α,α-Difluoromethyl Ketones. A solution of 1-(benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one[145] (25 mg, 0.08 mmol) in H_2O/THF (2 mL/0.5 mL) was treated with Et_3N (21 µL, 0.15 mmol), and the resultant mixture was stirred for 10 min at rt. The organics were extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (17:3 hexanes/Et_2O) afforded the title compound **2.4** as a colorless oil (15 mg) in 93% yield.

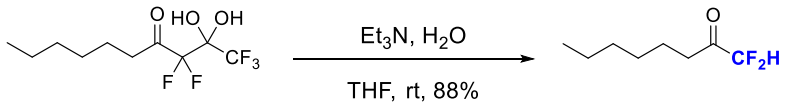


1-(Benzothiophen-3-yl)-2,2-difluoroethanone 2.4. See representative reaction procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78–8.73 (m, 1H), 8.70 (t, *J* = 1.5 Hz, 1H), 7.95–7.89 (m, 1H), 7.55 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.52–7.45 (m, 1H), 6.22 (t, *J* = 53.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4 (t, *J* = 25.4 Hz, 1C), 141.3 (t, *J* = 6.1 Hz, 1C), 139.0, 136.6, 128.6, 126.4, 126.0, 125.1, 122.2, 111.5 (t, *J* = 254.7 Hz, 1C);^{19}F NMR (282 MHz, $CDCl_3$) δ –121.1 (d, J_{HF} = 53.8 Hz, 2F); IR(film) ν_{max} 1679, 1491, 1462, 1424, 1135, 1109, 1055 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{10}H_6F_2OS$ $(M)^+$ 212.0107, found 212.0109.



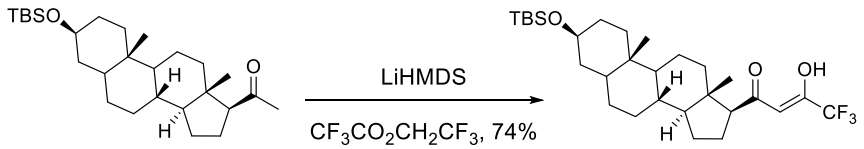
2.5

1,1-Difluoro-4-phenylbutan-2-one 2.5. See representative reaction procedure. 4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one[145] (35.7 mg, 0.120 mmol), Et_3N (67 μL, 0.48 mmol), and H_2O/THF (1.5 mL/1.5 mL) were used. The title compound **2.5** was isolated as a colorless oil in 99% yield (22 mg). All spectral and characterization data matched the reported data.[146]

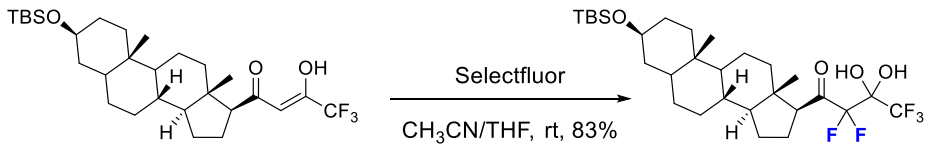


2.6

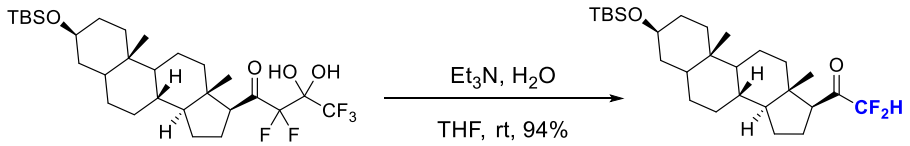
1,1-Difluorooctan-2-one 2.6. See representative reaction procedure. 1,1,1,3,3-Pentafluoro-2,2-dihydroxydecan-4-one (44.8 mg, 0.161 mmol), Et_3N (91 μL, 0.64 mmol), and H_2O/THF (1.6 mL/1.5 mL) were used. The title compound **2.6** was isolated as a colorless oil in 88% yield (23 mg). All spectral and characterization data matched the reported data.[146]



3-(*tert*-Butyldimethylsilyl)-21-(trifluoroacetyl)pregnenolone. To –78 °C solution of *n*-BuLi (120 µL, 1.56M in hexanes) in THF (6 mL) was added hexamethyldisilazane (303 mg, 1.88 mmol) dropwise. The mixture was stirred at –78 °C for 20 min, and then, 3-(*tert*-butyldimethylsilyl)pregnenolone[147] (678 mg, 1.57 mmol) was added. The resultant mixture was stirred for 45 min at –78 °C. Next, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (461 mg, 2.35 mmol) was added dropwise and the mixture was stirred for 15 min at –78 °C. The reaction mixture was quenched with 1 M aq. H_2SO_4 (10 mL) and stirred for 10 min. The resultant mixture was extracted with CH_2Cl_2 (10 mL × 3), and the organics were dried over Na_2SO_4. Concentration under reduced pressure afforded the title compound in 74% yield (610 mg) as a solid: mp 96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ5.86 (s, 1H), 3.54 (tt, *J* = 10.8, 4.7 Hz, 1H), 2.43 (t, *J* = 9.0 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.89 (dd, *J* = 8.2, 2.6 Hz, 1H), 1.82–1.72 (m, 2H), 1.71–1.63 (m, 3H), 1.62–1.56 (m, 1H), 1.49–1.41 (m, 2H), 1.38 (dt, *J* = 18.3, 4.9 Hz, 1H), 1.35–1.29 (m, 1H), 1.30–1.22 (m, 6H), 1.20–1.13 (m, 1H), 1.07 (dtd, *J* = 12.7, 8.0, 3.1 Hz, 1H), 0.98–0.91 (m, 3H), 0.88 (s, 9H), 0.80 (s, 3H), 0.65 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 174.8 (q, J_{CF} = 36.0 Hz, 1C), 118.3 (q, J_{CF} = 218.3 Hz, 1C), 96.4, 72.0, 59.3, 56.7, 54.3, 46.5, 45.0, 38.6, 38.5, 37.1, 35.7, 35.6, 32.1, 31.9, 28.6, 26.0 (3), 24.4, 22.8, 21.1, 18.3, 13.4, 12.4, –4.6 (2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.8 (s, 3F); IR (film) ν_{max} 2930, 2855, 1593, 1200, 1157, 1107, 1090, 836 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{47}F_3O_3Si$ $(M+Na)^+$ 551.3144, found 551.3149; $[\alpha]^{23}_D$ +70° (*c* 1.03, $CHCl_3$).



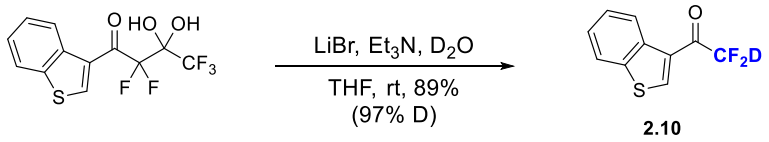
3-(*tert*-Butyldimethylsilyl)-21,21-difluoro-21-(2,2,2-trifluoro-1,1-dihydroxyethyl)-pregnenolone. A solution of 3-(*tert*-butyldimethylsilyl)-21-(trifluoroacetyl)pregnenolone (277 mg, 0.52 mmol) in CH_3CN (2 mL) and THF (2 mL) was treated with Selectfluor (464 mg, 1.31 mmol). After 24 h, Selectfluor (300 mg, 0.98 mmol) was added and the mixture was stirred for an additional 24 h. Next, the reaction was diluted with EtOAc (50 mL) and filtered through Celite. The residue was concentrated *in vacuo*, dissolved in CH_2Cl_2 (20 mL), and washed with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound in 83% yield (252 mg) as a solid: mp 108–111 °C;^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (s, 2H), 3.54 (tt, J = 10.8, 4.8 Hz, 1H), 3.17 (t, J = 8.8 Hz, 1H), 2.20–2.09 (m, 1H), 1.93 (d, J = 12.3 Hz, 1H), 1.84–1.71 (m, 2H), 1.71–1.63 (m, 4H), 1.58 (dt, J = 9.7, 3.1 Hz, 1H), 1.48–1.38 (m, 3H), 1.32 (d, J = 10.8 Hz, 1H), 1.30–1.20 (m, 6H), 1.11–1.02 (m, 1H), 0.99–0.90 (m, 3H), 0.88 (s, 9H), 0.79 (s, 3H), 0.69 (s, 3H), 0.05 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0 (t, J_{CF} = 28.6 Hz, 1C), 121.9 (q, J_{CF} = 283.3 Hz, 1C), 108.5 (t, J_{CF} = 265.9 Hz, 1C), 93.0 (qt, J_{CF} = 29.8, 1.0 Hz, 1C), 72.1, 57.3 (2), 54.0, 48.3, 44.9, 38.5, 38.3, 37.1, 35.8, 35.5, 32.1, 31.8, 28.6 (3), 25.9, 24.6, 24.4, 21.2, 18.3, 13.7, 12.3, –4.6 (2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, J_{FF} = 10.4 Hz, 3F), −119.1 (dq, J_{FF} = 35.0, 9.9 Hz, 2F); IR (film) ν_{max} 3436, 2931, 2858, 1717, 1386, 1209, 1087, 837, 775 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{47}F_5O_4Si$ $(M\text{-}H\text{-}H_2O)^+$ 563.2980, found 563.2973; $[\alpha]^{26}_D$ +83° (*c* 2.08, $CHCl_3$).



2.7

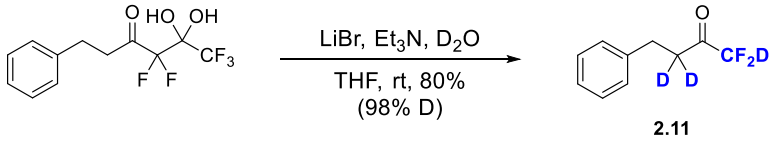
3-(*tert*-Butyldimethylsilyl)-21,21-difluoropregnenolone 2.7. See representative reaction procedure.3-(*tert*-Butyldimethylsilyl)-21,21-difluoro-21-(2,2,2-trifluoro-1,1-dihydroxyethyl)-pregnenolone (30 mg, 0.05 mmol), Et_3N (29μL, 0.21 mmol), H_2O/THF (500 μL/100 μL) were used. The reaction mixture was stirred for 1 h at rt. The title compound **2.7** was isolated as a solid in 94% yield (23 mg): mp 116–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (t, *J* = 54.2 Hz, 1H), 3.55 (ddd, *J* = 15.7, 10.8, 4.8 Hz, 1H), 2.94 (t, *J* = 8.9 Hz, 1H), 2.17 (m, 1H), 1.88 (d, *J* = 12.7 Hz, 1H), 1.80–1.63 (m, 5H), 1.62–1.56 (dq, *J* = 13.6, 3.9 Hz, 1H), 1.49–1.17 (m, 11H), 1.13–1.02 (m, 1H), 0.99–0.90 (ddd, *J* = 15.9, 8.2, 4.2 Hz, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.67 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (t, J_{CF} = 24.9 Hz, 1C), 109.9 (t, J_{CF} = 251.3 Hz, 1C), 72.1, 57.0, 56.9, 54.2, 46.4, 45.0, 38.6 (3), 37.2, 35.7, 35.5, 32.1, 31.9, 28.6, 26.0, 24.6, 23.6, 21.2, 18.3, 13.9, 12.3, –4.6 (2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −128.4 (d, J_{HF} = 54.1 Hz, 2F); IR (film) ν_{max} 2931, 1732, 1252, 1091 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{26}H_{43}F_2O_2Si$ $(M\text{-}CH_3)^+$ 453.3000, found 453.2994; $[\alpha]^{23}$D +77° (*c* 0.16, $CHCl_3$).

Representative Reaction Procedure for Preparation of α-Deutro-α,α-difluoromethyl Ketones. A solution of 1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one[145] (10 mg, 0.03 mmol) in D_2O/THF (2 mL/0.5 mL) was treated with Et_3N (9 μL, 0.06 mmol), and the resultant mixture was stirred for 10 min at rt. The organics were extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (17:3 hexanes/Et_2O) afforded the title compound **2.10** as a colorless oil (5.7 mg) in 86% yield (97% deuterium incorporation).



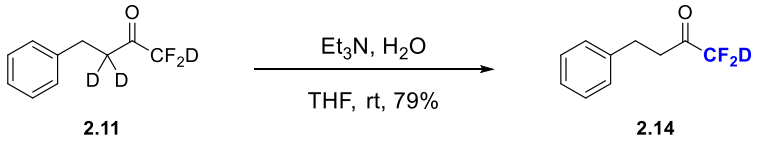
2.10

1-(Benzo[b]thiophen-3-yl)-2-deutero-2,2-difluoroethanone 2.10. See representative reaction procedure: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 8.1 Hz, 1H), 8.69 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.43 (t, *J* = 25.6 Hz, 1C), 141.42 (t, *J* = 6.1 Hz, 1C), 139.0, 136.6, 128.5, 126.4, 126.0, 125.1, 122.2, 111.2 (tt, *J* = 252.5, 28.8 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –121.72 (t, *J* = 8.1 Hz, 2F); IR(film)ν_{max} 3110, 1678, 1490, 1462, 1424, 1375, 1245, 1106 cm^{-1};HRMS (EI) m/z calcd for $C_{10}H_5DF_2OS$ $(M)^+$ 213.0170, found 213.0162.



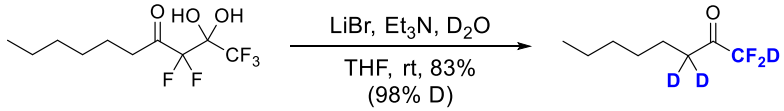
2.11

1,1-Difluoro-1,3,3-trideutero-4-phenylbutan-2-one 2.11. See representative reaction procedure. 4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one (57.0 mg, 0.191 mmol), Et_3N (107 μL, 0.765 mmol), and D_2O/THF (1.9 mL/1.9 mL) were used. The title compound **2.11** was isolated as a colorless oil (30 mg) in 80% yield (98% deuterium incorporation):^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5H), 2.96 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0 (t, *J* = 26.5 Hz, 1C), 139.8, 128.6, 128.3, 126.5, 109.5 (tt, *J* = 251.7, 29.0 Hz, 1C), 37.0 (m, 1C) 28.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –129.3 (t, *J* = 8.5 Hz, 2F); IR (film) ν_{max} 3066, 3031, 2930, 2870, 2918, 1747, 1605, 1498, 1456, 1163, 1110, 955 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_7D_3F_2O$ $(M)^+$ 187.0888, found 187.0868.



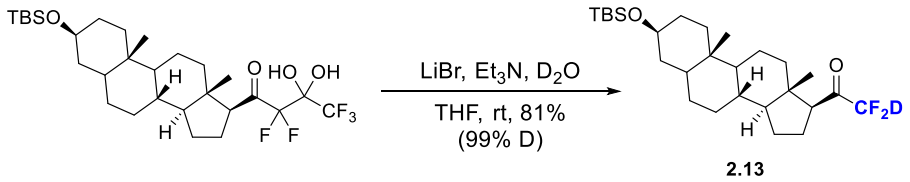
2.11 2.14

1-Deutero-1,1-difluoro-4-phenylbutan-2-one 2.14. To a solution of 1,1-difluoro-1,3,3-trideutero-4-phenylbutan-2-one (10.1 mg, 0.054 mmol) in H_2O/THF (0.5 mL/0.5 mL) was added Et_3N (20 μL, 0.22 mmol) dropwise. After 24h, the reaction was extracted with CH_2Cl_2 (3 mL × 2). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. The title compound **2.14** was isolated as a colorless oil (7.9 mg) in 79% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03–6.91 (m, 5H), 2.73–2.64 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9 (t, *J* = 26.5 Hz), 139.8, 128.6, 128.3, 126.5, 109. 5 (t, *J* = 28.8 Hz, 1C), 37.7, 28.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ –101.06 (t, *J* = 8.5 Hz, 2F); IR (film) ν_{max} 3065, 3030, 2958, 2918, 2950, 1742, 1660, 1605, 956 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_8DF_2O$ (M–H) $^-$ 184.0690, found 184.0690.



2.12

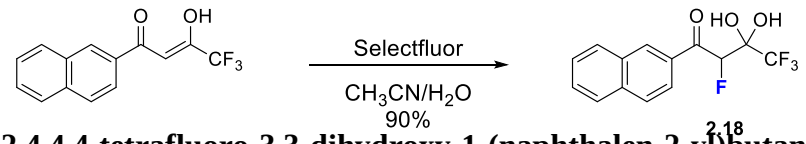
1-Deutero-1,1-difluoro-3,3-deutero-octan-2-one 2.12. 1,1,1,3,3-Pentafluoro-2,2-dihydroxydecan-4-one (59.2 mg, 0.213 mmol), Et_3N (120 μL, 0.85 mmol), and D_2O/THF (2.0 mL/0.6 mL) were used. The reaction mixture was stirred for 18 h at rt. The title compound **2.12** was isolated as a colorless oil (29 mg) in 83% yield (98% deuterium incorporation): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.36 (m, 6H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2 (dt, *J* = 26.1, 7.7 Hz, 1C), 110.0 (m, 1C), 35.2, 31.4, 28.5, 22.4, 22.2, 14.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ –129.24 (t, *J* = 11.3 Hz, 2F); IR (film) ν_{max} 2955, 2924, 1713, 1464, 1097, 805 cm^{-1}; HRMS (CI) *m/z* calcd for $C_8H_{11}D_3F_2O$ $(M+H)^+$ 168.1279, found 168.1286.



2.13

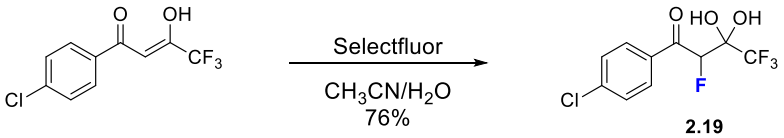
3-(*tert*-Butyldimethylsilyl)-21-deutero-21,21-difluoropregnenolone 2.13. See representative reaction procedure. 3-(*tert*-Butyldimethylsilyl)-21,21-difluoro-21-(2,2,2-trifluoro-1,1-dihydroxyethyl)-pregnenolone (30 mg, 0.05 mmol) and Et_3N (58 μL, 0.41 mmol) were used. The reaction mixture was stirred for 12 h at rt. The title compound **2.13** was isolated as a colorless solid (20 mg) in 81% yield (99% deuterium incorporation): mp 130–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54 (ddd, *J* = 15.7, 10.8, 4.8 Hz, 1H), 2.95 (t, *J* = 8.9 Hz, 1H), 2.15 (m, 1H), 1.91–1.84 (m, 1H), 1.80–1.63 (m, 5H), 1.61–1.55 (m, 1H), 1.48–1.17 (m, 11H), 1.11–1.02 (m, 1H), 0.98–0.89 (m, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.66 (s, 3H), 0.04 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (dt, *J* = 24.8, 9.5 Hz, 1C), 109.5 (tt, *J* = 250.9, 28.9 Hz, 1C), 72.0, 57.0, 54.1, 46.4 (2), 44.9, 38.6, 37.1, 35.6, 35.5, 32.1, 31.9, 28.6, 25.9 (3), 24.6, 23.6, 23.5, 21.1, 18.3, 13.9, 12.3, -4.6 (2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −129.0–129.1 (m, 2F); IR (film) ν_{max} 2931, 1730, 1252 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{45}DF_2O_2Si$ (M+H) 470.3371, found 470.3372; $[\alpha]_D^{25}$ +59° (*c* 0.18, $CHCl_3$).

Representative Reaction Procedure for Preparation of Fluorinated *gem*-Diols. A solution of 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (200 mg, 0.751 mmol) in CH_3CN (2 mL) and H_2O (2 mL) was treated with Selectfluor® (266 mg, 0.751 mmol) at rt. After 18 h, the reaction was diluted with CH_2Cl_2 (10 ml) and washed with water (10 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to give the product **2.18** (204 mg) as a solid in 90% yield.



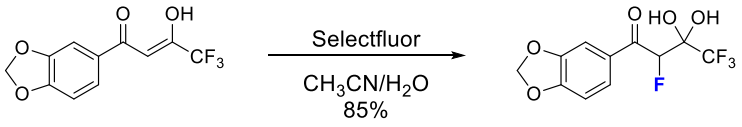
2.18

2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one 2.18. See representative reaction procedure**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.06–8.02 (m, 2H), 7.96–7.88 (m, 2H), 7.69 (t, *J* = 6.9 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 47.8 Hz, 1H), 5.05 (s, 1H), 4.75 (s, 1H).



2.19

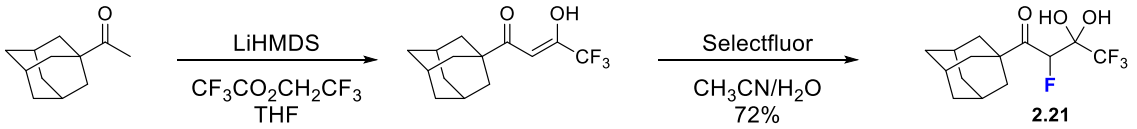
1-(4-chlorophenyl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one 2.19. See representative reaction procedure**.** A solution of 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (60 mg, 0.24 mmol) in CH_3CN (1 mL) and H_2O (1 mL) was treated with Selectfluor® (85 mg, 0.24 mmol). The title compound **2.19** was isolated as a colorless solid (52 mg) in 76% yield. All spectral and characterization data matched the reported data.[121]



2.20

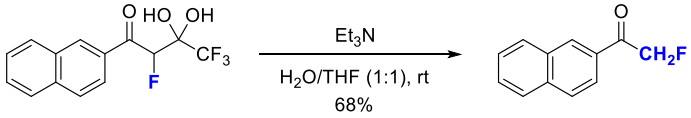
1-(benzo[d][1,3]dioxol-5-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one 2.20. See representative reaction procedure**.** A solution of 1-(benzo[d][1,3]dioxol-5-yl)-4,4,4-trifluorobutane-1,3-dione (200 mg, 0.769 mmol) in CH_3CN (2 mL) and H_2O (2 mL) was treated with Selectfluor® (273 mg, 0.769 mmol). The title compound **2.20** was isolated as a colorless solid (194 mg) in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.46 (d, *J* = 1.2 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.09 (s, 2H), 5.66 (d, *J* = 47.8 Hz, 1H), 5.21 (bs, 1H), 4.80

(bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0 (d, *J* = 18.9 Hz), 154.0, 148.6, 129.4, 127.5 (d, *J* = 4.9 Hz), 121.8 (q, *J* = 288.3 Hz), 109.0 (d, *J* = 3.2 Hz), 108.5, 102.5, 93.1 (dd, *J* = 35.2, 23.0 Hz), 85.1 (d, *J* = 193.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.7 (d, *J* = 11.2 Hz, 3F), –195.3 (dq, *J* = 47.7, 11.2 Hz, 1F).



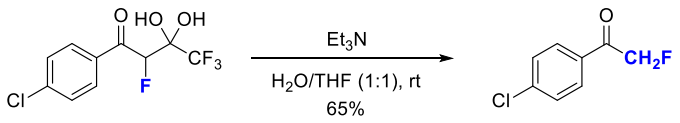
1-((3r,5r,7r)-adamantan-1-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one 2.21. To –78 °C solution of *n*-BuLi (600 µL, 2.25 M in hexanes) in THF (6 mL) was added hexamethyldisilazane (283 mg, 1.34 mmol) dropwise. The mixture was stirred at –78 °C for 20 min, and then 1-(adamantan-1-yl)ethan-1-one (200 mg, 1.12 mmol) was added. The resultant mixture was stirred for 45 min at –78 °C. Next, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (226 mg, 1.68 mmol) was added dropwise and the mixture was stirred for 15 min at –78 °C. The reaction mixture was quenched with 1 M aq. H_2SO_4 (10 mL) and stirred for 10 min. The resultant mixture was extracted with CH_2Cl_2 (10 mL × 3), and the organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in CH_3CN (2 mL) and H_2O (2 mL), then treated with Selectfluor® (398 mg, 1.12 mmol). The title compound **2.21** was isolated as a colorless solid (348 mg) in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.26 (d, *J* = 47.4 Hz, 1H), 4.69 (d, *J* = 2.6 Hz, 1H), 2.08 (s, 3H), 1.94–1.83 (m, 6H), 1.74 (q, *J* = 12.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4 (d, *J* = 15.6 Hz, 1C), 121.7 (q, *J* = 287.1 Hz, 1C), 93.8–92.9 (m, 1C), 82.3 (d, *J* = 192.6 Hz, 1C), 47.9 (d, *J* = 1.1 Hz, 1C), 36.6 (d, *J* = 1.3 Hz, 3C), 36.3 (3C), 27.5 (3C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –85.0 (d, *J* = 11.0 Hz, 3F), –196.6 (dq, *J* = 47.6, 11.5 Hz, 1F).

Representative Reaction Procedure for Preparation of α,α-Difluoromethyl Ketones. A solution of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (30 mg, 0.10 mmol) in H_2O/THF (0.2 mL/0.2 mL) was treated with Et_3N (55 µL, 0.40 mmol), and the resultant mixture was stirred for 10 min at rt. The organics were extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (17:3 hexanes/Et_2O) afforded the title compound **2.22** in 68% yield (12.6 mg).



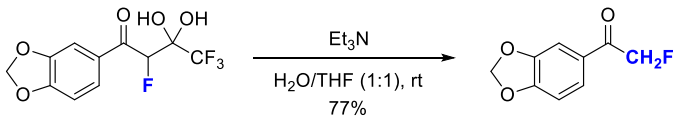
2.22

2-fluoro-1-(naphthalen-2-yl)ethan-1-one 2.22. See representative reaction procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.02–7.94 (m, 3H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.1 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 5.68 (d, *J* = 46.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5 (d, J_{CF} = 15.6 Hz), 136.1, 132.5, 131.2, 130.0 (d, J_{CF} = 3.2 Hz), 129.8, 129.2, 129.1, 128.1, 127.3, 123.4 (d, J_{CF} = 1.9 Hz), 83.8 (d, J_{CF} = 182.7 Hz).



2.23

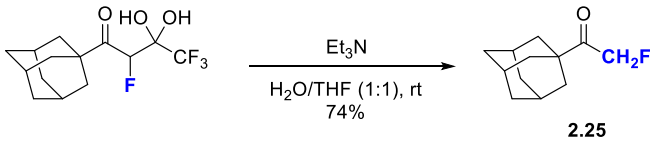
1-(4-chlorophenyl)-2-fluoroethan-1-one 2.23. 1-(4-chlorophenyl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one (10 mg, 0.04 mmol), Et_3N (24 µL, 0.17 mmol), and H_2O/THF (0.1 mL/0.1 mL) were used. The title compound **2.23** was isolated in 65% yield (4 mg). All spectral and characterization data matched the reported data.[148]



2.24

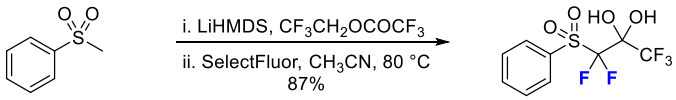
1-(benzo[d][1,3]dioxol-5-yl)-2-fluoroethan-1-one 2.24. See representative reaction procedure. 1-(benzo[d][1,3]dioxol-5-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one (30 mg, 0.10 mmol),

Et_3N (57 µL, 0.41 mmol), and H_2O/THF (0.2 mL/0.2 mL) were used. The title compound **2.24** was isolated in 77% yield (14 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.1 Hz, 1H), 7.40 (s, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.07 (s, 2H), 5.44 (d, J = 47.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6 (d, J_{CF} = 15.5 Hz, 1C), 152.7, 148.6, 128.6, 124.5 (d, J_{CF} = 3.2 Hz, 1C), 108.4, 107.8 (d, J_{CF} = 2.8 Hz, 1C), 102.2, 83.6 (d, J_{CF} = 182.3 Hz, 1C);



2.25

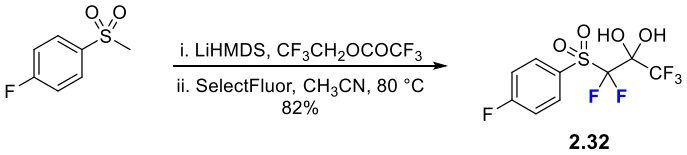
1-(adamantan-1-yl)-2-fluoroethan-1-one 2.25. See representative reaction procedure. 1-(adamantan-1-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one (30 mg, 0.10 mmol), Et_3N (54 µL, 0.39 mmol), and H_2O/THF (0.2 mL/0.2 mL) were used. The title compound **2.25** was isolated in 74% yield (14 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (d, J = 47.2 Hz, 2H), 2.04 (s, 3H), 1.84 (s, 6H), 1.83–1.67 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6 (d, J_{CF} = 12.1 Hz), 208.6, 82.2 (d, J_{CF} = 182.9 Hz), 45.2, 37.8, 36.5, 27.7.



2.31

1,1,1,3,3-pentafluoro-3-(phenylsulfonyl)propane-2,2-diol 2.31. To a –78 °C solution of n-BuLi (452 µL, 1.7 M in hexanes) in THF (3 mL) was added hexamethyldisilazane (161 µL, 0.768 mmol). After stirring the reaction for 20 min at –78 °C, a solution of methyl phenyl sulfone (100 mg, 0.640 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (129 µL, 0.960 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted

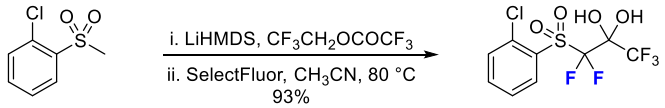
with CH_2Cl_2 (5 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (1.13 g, 3.20 mmol). After 24 h of stirring at 80 °C, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **2.31** in 87% yield (170 mg) as a colorless solid: mp 84–86 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 2H), 5.17 (bs, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.6, 132.7, 131.2, 129.9, 121.5 (q, J_{CF} = 289.2 Hz), 115.0 (t, J_{CF} = 303.3 Hz), 94.2–93.1 (m); ^{19}F NMR (564 MHz, Chloroform-*d*) δ –82.5 (t, *J* = 10.8 Hz, 3F), –111.2 (q, *J* = 10.8 Hz, 2F); IR (film) ν_{max} 3442, 2925, 2853, 1336, 1177, 1151, 1072 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_9H_7ClF_5O_4S$ $(M+Cl)^-$ 340.9674, found 340.9645.



2.32

1,1,1,3,3-pentafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol 2.32. To a –78 °C solution of n-BuLi (680 µL, 2 M in hexanes) in THF (5 mL) was added hexamethyldisilazane (288 µL, 1.38 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 4-fluorophenyl methyl sulfone (200 mg, 1.15 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (231 µL, 1.72 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (5 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (15 mL) and treated with Selectfluor® (2.03 mg, 5.74 mmol). After 24 h of stirring at 80 °C, the reaction was

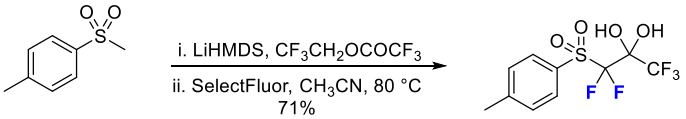
diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **2.32** in 82% yield (306 mg) as a colorless solid: mp 74–75 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 8.7, 4.9 Hz, 2H), 7.25 (appt, *J* = 8.5 Hz, 2H), 5.07 (s, 2H).; ^{13}C NMR (100 MHz, Chloroform-*d*) δ 167.5 (d, J_{CF} = 260.3 Hz), 134.1 (d, J_{CF} = 10.3 Hz), 128.5 (d, J_{CF} = 3.1 Hz), 120.9 (q, J_{CF} = 286.8 Hz), 117.0 (t, J_{CF} = 301.0 Hz), 117.1 (d, J_{CF} = 23.1 Hz), 94.0 – 92.8 (m); ^{19}F NMR (376 MHz, Chloroform-*d*) δ –82.5 (t, *J* = 10.9 Hz, 3F), –99.1 (tt, *J* = 8.2, 5.0 Hz, 1F), –111.0 (q, *J* = 10.9 Hz, 2F); IR (film) ν_{max} 3445, 3110, 1342, 1177, 1154, 1075 cm^{-1}; HRMS (EI) *m/z* calcd for $C_7H_5F_3O_2S$ (M+H–TFA)$^+$ 209.9962, found 209.9951.



2.33

1-((2-chlorophenyl)sulfonyl)-1,1,3,3,3-pentafluoropropane-2,2-diol 2.33. To a –78 °C solution of n-BuLi (370 µL, 1.7 M in hexanes) in THF (4 mL) was added hexamethyldisilazane (132 µL, 0.629 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 2-chlorophenyl methyl sulfone (100 mg, 0.525 mmol) in THF (1 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (106 µL, 0.788 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (930 mg, 263 mmol). After 24 h of stirring at 80 °C, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **2.33** in 93% yield (166 mg) as a colorless solid: mp 118–

120 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 4.16 (bs, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.2, 135.3, 133.8, 132.1, 130.1, 126.8, 115.9 (t, J_{CF} = 306.1 Hz), 119.5 (q, J_{CF} = 289.9 Hz), 92.8 – 91.7 (m); ^{19}F NMR (376 MHz, Chloroform-*d*) δ –82.4 (t, *J* = 10.9 Hz, 3F), –109.0 (q, *J* = 10.9 Hz, 2F); IR (film) ν_{max} 3470, 3099, 1345, 1208, 1180, 1076 cm^{-1}; HRMS (EI) *m/z* calcd for $C_9H_4ClF_5O_3S$ $(M–H_2O)^-$ 321.9490, found 321.9493.

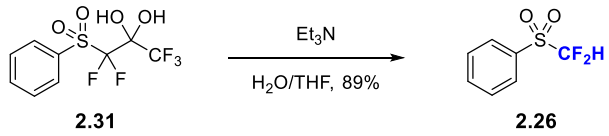


2.34

1,1,1,3,3-pentafluoro-3-tosylpropane-2,2-diol 2.34. To a –78 °C solution of n-BuLi (420 µL, 1.7 M in hexanes) in THF (4 mL) was added hexamethyldisilazane (149 µL, 0.708 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 4-(methylsulfonyl)toluene (100 mg, 0.590 mmol) in THF (1 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (119 µL, 0.855 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (1.05 mg, 2.95 mmol). After 24 h of stirring at 80 °C, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **43** in 71% yield (134 mg) as a colorless solid: mp 73–74 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 5.20 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 148.1 , 131.0 , 130.3 , 129.4 , 122.1 (q, J_{CF} = 287.1 Hz), 116.4

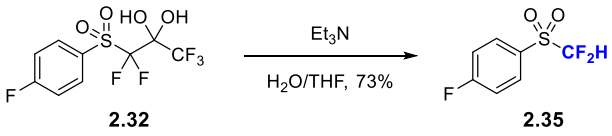
(t, J_{CF} = 301.1 Hz), 96.4–91.1 (m), 21.9; ^{19}F NMR (564 MHz, Chloroform-*d*) δ –82.49 (t, *J* = 10.8 Hz), –111.55 (q, *J* = 10.9 Hz); IR (film) ν_{max} 3433, 3073, 2930, 1338, 1177, 1153, 1074 cm^{-1}; HRMS (ESI) *m/z* calcd for C10H9F5NaO4S $(M+Na)^+$ 343.0034, found 343.0012.

Representative reaction procedure for α,α-difluoromethyl sulfone compounds. A solution of 1,1,1,3,3-pentafluoro-3-(phenylsulfonyl)propane-2,2-diol **2.31** (30 mg, 0.10 mmol) in H_2O/THF (0.3 mL/0.3 mL) was treated with Et_3N (55 μL, 0.39 mmol) and stirred for 30 min at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) then extracted with CH_2Cl_2 (5 mL x 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the desired product **2.26** as a solid in 89% yield (17 mg).



2.31 **2.26**

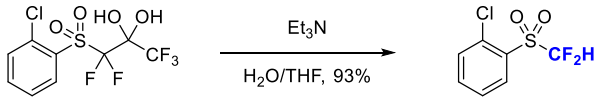
((difluoromethyl)sulfonyl)benzene 2.26. See representative reaction procedure. All spectral and characterization data matched the reported data.[149]



2.32 **2.35**

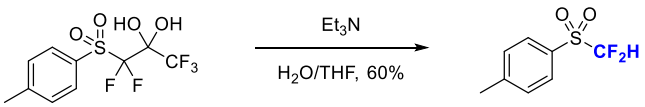
1-((difluoromethyl)sulfonyl)-4-fluorobenzene 2.35. See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol **2.32** (50 mg, 0.15 mmol) in H_2O/THF (0.3 mL/0.3 mL) was treated with Et_3N (107 μL, 0.771 mmol). The desired product **2.35** was isolated as a solid in 89% yield (28 mg): mp 51–52 °C; ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 8.01 (dp, *J* = 8.0, 5.0 Hz, 2H), 7.32 (appt, *J* = 8.3 Hz, 2H), 6.21 (t, *J* = 53.4 Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 167.5 (d, J_{CF} = 260.0 Hz), 133.9 (d, J_{CF} = 10.2 Hz), 127.8 (d, J_{CF} = 3.1 Hz), 117.3 (d, J_{CF} = 22.9 Hz), 114.7 (t, J_{CF} = 285.6 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ –98.8 – –101.2 (m, 1F), –122.4 (d, *J* = 53.4 Hz, 2F); IR (film) ν_{max} 2921, 2849, 1347, 1156, 1108, 1077 cm^{-1}; HRMS (EI) *m/z* calcd for $C_7H_5F_3O_2S$ $(M)^+$ 209.9962, found 209.9975.



2.33 **2.36**

1-chloro-2-((difluoromethyl)sulfonyl)benzene 2.36. See representative reaction procedure. A solution of 1-((2-chlorophenyl)sulfonyl)-1,1,3,3,3-pentafluoropropane-2,2-diol **2.33** (30 mg, 0.088 mmol) in H_2O/THF (0.5 mL/0.5 mL) was treated with Et_3N (49 μL, 0.35 mmol). The desired product **2.36** was isolated as a solid in 98% yield (19.5 mg): mp 47–49 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.69 (td, *J* = 7.9, 1.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.2 Hz, 1H), 6.52 (t, *J* = 53.8 Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.8, 134.5, 134.0, 132.5, 131.5, 128.0, 114.5 (t, J_{CF} = 287.1 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ –122.9 (d, *J* = 53.8 Hz, 2F); IR (film) ν_{max} 3087, 2924, 1349, 1172, 1096, 1039 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_7H_5ClF_2NaO_2S$ $(M+Na)^+$ 248.9559, found 248.9540.



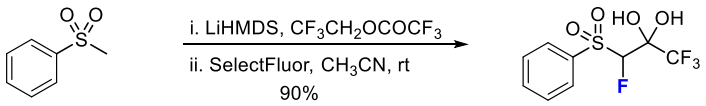
2.34 **2.37**

1-((difluoromethyl)sulfonyl)-4-methylbenzene 2.37. See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-3-tosylpropane-2,2-diol **2.34** (40 mg, 0.13 mmol) in H_2O/THF

(0.3 mL/0.3 mL) was treated with Et_3N (70 μL, 0.50 mmol). The desired product **2.37** was isolated as a solid in 85% yield (22 mg): mp 68–69 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 6.16 (t, *J* = 53.5 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.5, 130.8, 130.4, 128.8, 114.8 (t, J_{CF} = 285.4 Hz), 22.0; ^{19}F NMR (376 MHz, Chloroform-*d*) δ –122.7 (d, *J* = 53.6 Hz, 2F); IR (film) ν_{max} 2924, 2854, 1343, 1167, 1159, 1077 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_8F_2NaO_2S$ $(M+Na)^+$ 229.0103, found 229.0104.

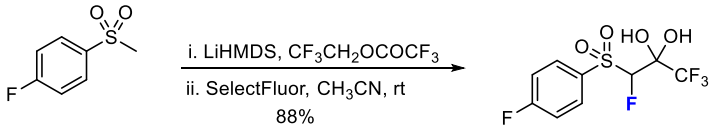
Representative Reaction Procedure for Synthesis of tetrafluorosulfone-based gem-diols.

To a –78 °C solution of n-BuLi (452 μL, 1.7 M in hexanes) in THF (3 mL) was added hexamethyldisilazane (161 μL, 0.768 mmol). After stirring the reaction for 20 min at –78 °C, a solution of methyl phenyl sulfone (100 mg, 0.640 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (129 μL, 0.960 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (454 mg, 1.28 mmol). After 24 h of stirring at room temperature, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **2.38** in 90% yield (166 mg) as a colorless solid.



2.38

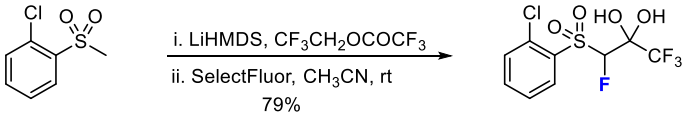
1,1,1,3-tetrafluoro-3-(phenylsulfonyl)propane-2,2-diol 2.38. See representative reaction procedure: mp 75–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H), 5.35 (d, *J* = 46.5 Hz, 1H), 5.20 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.9, 135.5, 131.1, 130.1, 129.8, 121.4 (q, J_{CF} = 289.9 Hz, 1C), 96.9 (d, J_{CF} = 232.9 Hz, 1C), 93.8–92.5 (m, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.9 (d, *J* = 11.2 Hz, 3F), –185.6 (dq, *J* = 46.4, 11.1 Hz, 1F).



2.39

1,1,1,3-tetrafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol 2.39. To a –78 °C solution of n-BuLi (400 µL, 1.7 M in hexanes) in THF (3 mL) was added hexamethyldisilazane (143 µL, 0.684 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 4-fluorophenyl methyl sulfone **14** (100 mg, 0.570 mmol) in THF (2 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (115 µL, 0.855 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (404 mg, 1.14 mmol). After 24 h of stirring at room temperature, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was

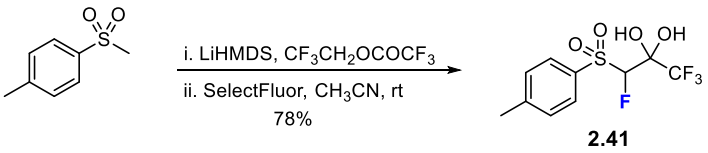
concentrated under reduced pressure to afford the product **2.39** in 88% yield (154 mg) as a colorless solid: mp 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.8, 4.9 Hz, 2H), 7.29 (t, *J* = 8.4 Hz, 2H), 5.35 (d, *J* = 46.3 Hz, 1H), 4.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (d, J_{CF} = 259.7 Hz, 1C), 133.5 (d, J_{CF} = 10.7 Hz, 2C), 131.4 (d, J_{CF} = 3.0 Hz, 1C), 121.4 (dq, J_{CF} = 288.7, 1.5 Hz, 1C), 117.3 (d, J_{CF} = 23.0 Hz, 2C), 97.1 (d, J_{CF} = 232.9 Hz, 1C), 93.8–92.3 (m, 1C); ^{19}F NMR (564 MHz, $CDCl_3$) δ –84.9 (d, *J* = 11.1 Hz, 3F), –100.4 (s, 1F) , –185.3 (dq, *J* = 33.4, 11.1 Hz, 1F).



2.40

3-((2-chlorophenyl)sulfonyl)-1,1,1,3-tetrafluoropropane-2,2-diol 2.40. To a –78 °C solution of n-BuLi (370 µL, 1.7 M in hexanes) in THF (4 mL) was added hexamethyldisilazane (132 µL, 0.629 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 2-chlorophenyl methyl sulfone **15** (100 mg, 0.525 mmol) in THF (1 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (106 µL, 0.788 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (372 mg, 1.05 mmol). After 24 h of stirring at room temperature, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **41** in 79% yield (134 mg) as a colorless solid: mp 105–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 5.82 (d, *J* = 46.9 Hz, 1H), 4.45 (bs, 2H);

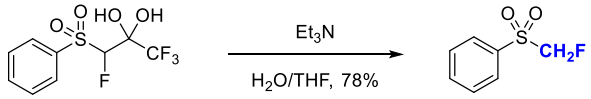
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.0, 133.7, 133.3, 132.6, 128.1, 121.3 (q, J_{CF} = 287.0 Hz, 1C), 95.2 (d, J_{CF} = 233.0 Hz, 1C), 94.3–92.9 (m, 1C); ^{19}F NMR (564 MHz, $CDCl_3$) δ –85.0 (d, J = 10.5 Hz, 3F), –185.8 (dq, J = 46.2, 9.6 Hz, 1F).



2.41

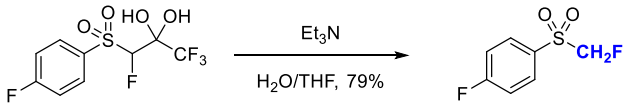
1,1,1,3-tetrafluoro-3-tosylpropane-2,2-diol 2.41. To a –78 °C solution of n-BuLi (420 μL, 1.7 M in hexanes) in THF (4 mL) was added hexamethyldisilazane (149 μL, 0.708 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 4-(methylsulfonyl)toluene **39** (100 mg, 0.590 mmol) in THF (1 ml) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (119 μL, 0.855 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature the reaction was warmed to room temperature and quenched with 1 M H_2SO_4 (3 mL) and stirred for 60 min. The resultant mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (10 mL) and treated with Selectfluor® (418 mg, 1.18 mmol). After 24 h of stirring at room temperature, the reaction was diluted with EtOAc (50 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure to afford the product **2.41** in 78% yield (137 mg) as a colorless solid: mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 3H), 5.31 (d, J = 46.6 Hz, 1H), 4.90 (bs, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 132.3, 130.5 (2C), 130.3 (2C), 121.3 (q, J_{CF} = 288.2 Hz, 1C), 96.5 (d, J_{CF} = 232.8 Hz, 1C), 93.9–92.4 (m, 1C), 22.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ –84.90 (d, J = 11.1 Hz, 3F), –185.60 (dq, J = 46.6, 11.1 Hz, 1F).

Representative reaction procedure for α,α-difluoromethyl sulfone compounds. A solution of 1,1,1,3-tetrafluoro-3-(phenylsulfonyl)propane-2,2-diol **2.38** (40 mg, 0.13 mmol) in H_2O/THF (0.3 mL/0.3 mL) was treated with Et_3N (73 μL, 0.52 mmol) and stirred for 30 min at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) then extracted with CH_2Cl_2 (5 mL x 3). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the desired product **2.42** as a solid in 78% yield (18 mg).



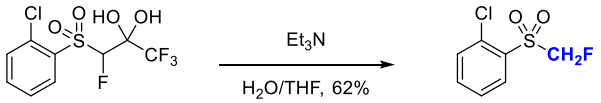
2.38 **2.42**

((fluoromethyl)sulfonyl)benzene 2.38. See representative reaction procedure. All spectral and characterization data matched the reported data.[150]



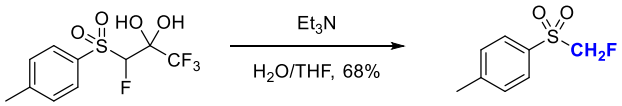
2.39 **2.43**

1-fluoro-4-((fluoromethyl)sulfonyl)benzene 2.43. See representative reaction procedure. A solution of 1,1,1,3-tetrafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol **2.39** (30 mg, 0.098 mmol) in H_2O/THF (0.5 mL/0.5 mL) was treated with Et_3N (55 μL, 0.39 mmol). The desired product **2.43** was isolated as an oil in 79% yield (15 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.8 Hz, 1H), 7.69–7.64 (m, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 5.46 (d, J = 47.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (d, J_{CF} = 258.2 Hz, 1C), 132.2 (d, J_{CF} = 9.9 Hz, 2C), 132.0 (d, J_{CF} = 3.1 Hz, 1C), 117.1 (d, J_{CF} = 22.8 Hz, 2C), 92.1 (d, J_{CF} = 219.9 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –102.3 (ddt, J = 13.0, 8.3, 4.9 Hz, 1F), –211.5 (t, J = 47.1 Hz, 1F).



2.40 **2.44**

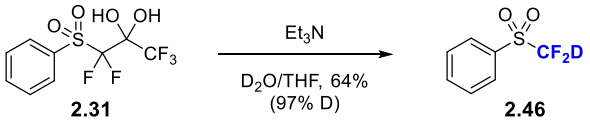
1-chloro-2-((fluoromethyl)sulfonyl)benzene 2.44. See representative reaction procedure. A solution of 3-((2-chlorophenyl)sulfonyl)-1,1,1,3-tetrafluoropropane-2,2-diol **2.40** (30 mg, 0.093 mmol) in H_2O/THF (0.5 mL/0.5 mL) was treated with Et_3N (52 μL, 0.37 mmol). The desired product **2.44** was isolated as a solid in 62% yield (12 mg): mp 48–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.15 (m, 1H), 7.73–7.5 (m, 2H), 7.56–7.50 (m, 1H), 5.47 (d, J = 48.1 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –211.90 (p, J = 7.2 Hz, 1F).



2.41 **2.45**

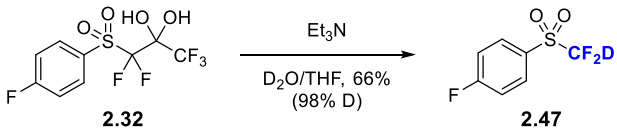
1-((fluoromethyl)sulfonyl)-4-methylbenzene 2.45. See representative reaction procedure. A solution of 1,1,1,3-tetrafluoro-3-tosylpropane-2,2-diol **2.41** (30 mg, 0.099 mmol) in H_2O/THF (0.3 mL/0.3 mL) was treated with Et_3N (55 μL, 0.39 mmol). The desired product **2.45** was isolated as an oil in 68% yield (13 mg). All spectral and characterization data matched the reported data.[151]

Representative reaction procedure for α-deutero-α,α-difluoromethyl sulfone compounds. A solution of 1,1,1,3,3-pentafluoro-3-(phenylsulfonyl)propane-2,2-diol **2.31** (85 mg, 0.28 mmol) in D_2O/THF (0.5 mL/0.5 mL) was treated with Et_3N (155 μL, 1.11 mmol) and stirred for overnight at rt. The reaction mixture was extracted with CH_2Cl_2 (5 mL x 3). Then, the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the desired product **2.46** as a colorless oil in 74% yield (54 mg).



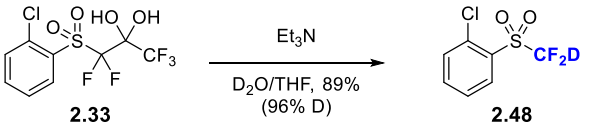
2.31 2.46

((difluoromethyl-d)sulfonyl)benzene 2.46. See representative reaction procedure. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 135.9, 131.8, 130.6, 129.7, 114.7 (tt, J_{CF} = 284.2, J_{CD} = 30.8 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ –123.5 (t, *J* = 8.1 Hz, 2F); IR (film) ν_{max} 2992, 2916, 1327, 1167, 1121, 1073 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_7H_5DF_2NaO_2S$ $(M+Na)^+$ 216.0012, found 216.0038.



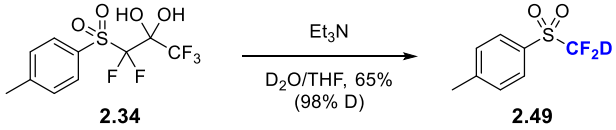
2.32 2.47

1-((difluoromethyl-d)sulfonyl)-4-fluorobenzene 2.47. See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol **2.32** (50 mg, 0.15 mmol) in H_2O/THF (0.3 mL/0.3 mL) was treated with Et_3N (107 μL, 0.771 mmol). The desired product **2.47** was isolated as a solid in 80% yield (26 mg): mp 50–51 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (dd, *J* = 8.8, 5.0 Hz, 1H), 7.32 (appt, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 167.5 (d, J_{CF} = 259.9 Hz), 133.9, 127.7, 117.2, 112.9 (tt, J_{CF} = 284.3, J_{CD} = 31.1 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ –100.2 – –100.3 (m, 1F), –123.0 (t, *J* = 7.9 Hz, 2F); IR (film) ν_{max} 2922, 2853, 1345, 1191, 1125, 1075 cm^{-1}; HRMS (EI) *m/z* calcd for $C_7H_4DF_3O_2S$ $(M)^+$ 211.0025, found 211.0035.



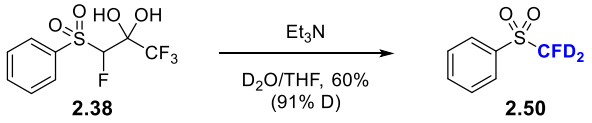
2.33 **2.48**

1-chloro-2-((difluoromethyl-d)sulfonyl)benzene 2.48. See representative reaction procedure. A solution of 1-((2-chlorophenyl)sulfonyl)-1,1,3,3,3-pentafluoropropane-2,2-diol **2.33** (40 mg, 0.12 mmol) in H_2O/THF (0.5 mL/0.5 mL) was treated with Et_3N (65 μL, 0.47 mmol). The desired product **2.48** was isolated as a solid in 96% yield (20 mg): mp 49–50 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 136.6, 134.4, 133.9, 132.4, 131.5, 127.8, 114.0 (t, J_{CF} = 284.4, J_{CD} = 31.5 Hz), ^{19}F NMR (376 MHz, Chloroform-*d*) δ –123.6 (t, *J* = 8.4 Hz, 2F); IR (film) ν_{max} 2921, 2851, 1346, 1191, 1124, 1093 cm^{-1}; HRMS (EI) *m/z* calcd for $C_7H_4DClF_2O_2S$ $(M)^+$ 226.9730, found 226.9738.



2.34 **2.49**

1-((difluoromethyl-d)sulfonyl)-4-methylbenzene 51. See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-3-tosylpropane-2,2-diol **43** (50 mg, 0.16 mmol) in H_2O/THF (0.3 mL/0.3 mL) was treated with Et_3N (109 μL, 0.781 mmol). The desired product was isolated as a solid in 91% yield (29 mg): mp 70–71 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.5, 130.7, 130.4, 128.8, 114.4 (tt, J_{CF} = 282.4, J_{CD} = 30.2 Hz), 21.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ –123.6 (t, *J* = 8.4 Hz, 2F); IR (film) ν_{max} 2924, 2849, 1339, 1180, 1123, 1075 cm^{-1}; HRMS (EI) *m/z* calcd for $C_8H_7DF_2O_2S$ $(M)^+$ 207.0276, found 207.0242.



2.38 **2.50**

((fluoromethyl-d2)sulfonyl)benzene 25. A solution of 1,1,1,3-tetrafluoro-3-(phenylsulfonyl)propane-2,2-diol **13** (35 mg, 0.12 mmol) in D_2O/THF (0.5 mL/0.5 mL) was treated with Et_3N (65 μL, 0.46 mmol) and stirred for 16 h at rt. The reaction mixture was extracted with CH_2Cl_2 (5 mL x 3). Then, the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the desired product **25** as a colorless oil in 75% yield (15 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –213.3 (p, *J* = 6.8 Hz, 1F).

CHAPTER 3

DEVELOPMENT OF $GABA_B$ AGONISTS

3.1. $GABA_B$ Receptor

GABA is the major inhibitory neurotransmitter in the central nervous system (**Figure 3.1**). Stimulation of the $GABA_B$ receptor, a G-protein coupled receptor, inhibits cyclic-AMP production.[152] The two major types of GABA receptors are $GABA_A$ and $GABA_B$ and both are validated targets for drug discovery.[153] The $GABA_A$ receptors are ion channels and can be controlled by three classes of pharmaceuticals, the barbiturates, the benzodiazepines, and the newer non-benzodiazepine sedatives, such as zaleplon and zopiclone.[154] Baclofen, the only FDA approved $GABA_B$ agonist, is indicated for the treatment of spasticity associated with spinal cord injury, cerebral palsy and multiple sclerosis (**Figure 3.1**). Baclofen has been reported to inhibit transient lower esophageal sphincter (LES) relaxations which indicates that it could help manage gastroesophageal reflux disease.[155] Baclofen exerts a dose-dependent antinociceptive effect, increases pain threshold[156] and enhances morphine analgesia.[157] $GABA_B$ agonists have been reported to reduce dopamine levels in the ventral striatum and thereby reduce self-administration of cocaine,[158] alcohol,[159] and cigarettes.[160] The various potential applications of $GABA_B$ agonists are not matched with an increased number of agonists in the market and in clinical trials.

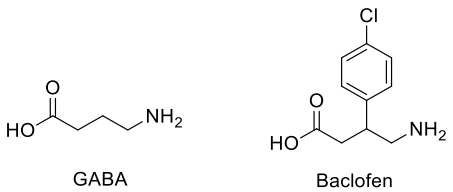


Figure 3.1. Structures of GABA and Baclofen

3.2. Fluorinated $GABA_B$ Receptor Agonists

A novel series of fluorinated $GABA_B$ agonists were reported by our group.[16] The most potent compound in the series is compound **3.1** with an EC_{50} of 24.9 μM compared to an EC_{50} of 2.8 μM for baclofen (**Figure 3.2**). The core structure of these new agonists is a difluoromethyl β-hydroxy ketone which is distinct from all other known $GABA_B$ ligands which display the GABA core structure. This scaffold presents a distinct opportunity to identify new structure-activity relationships for agonist activity for the $GABA_B$ receptor.

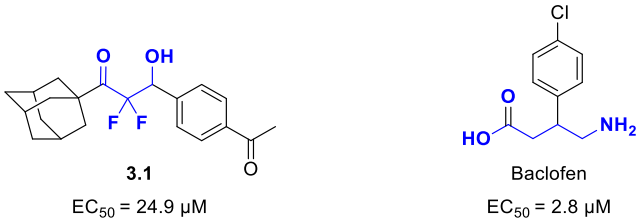


Figure 3.2. EC_{50} of the lead compound and Baclofen

Most known $GABA_B$ agonists have a carboxylic acid group or one of its bioisosteres. In compounds with the difluoromethyl β-hydroxy ketone, the presence of the difluoromethyl group stabilizes the hydrated form of the keto group which can act as a carboxylic acid bioisostere (**Figure 3.3**). Figure 3.4 shows the lead compound **3.1** docked in the active site of $GABA_B$ receptor as the hydrated form. The docking studies show that the diol group of this compound overlaps with baclofen's carboxylic acid group inside the active site. This theory provides an insight on the role fluorination plays in the activity of these compounds.

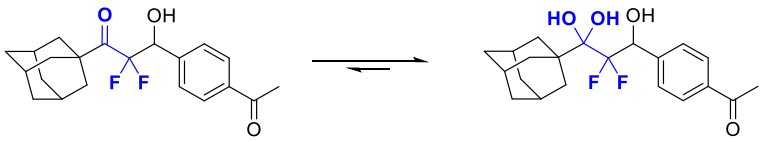


Figure 3.3. The equilibrium between the ketone and the hydrated forms of compound **1**

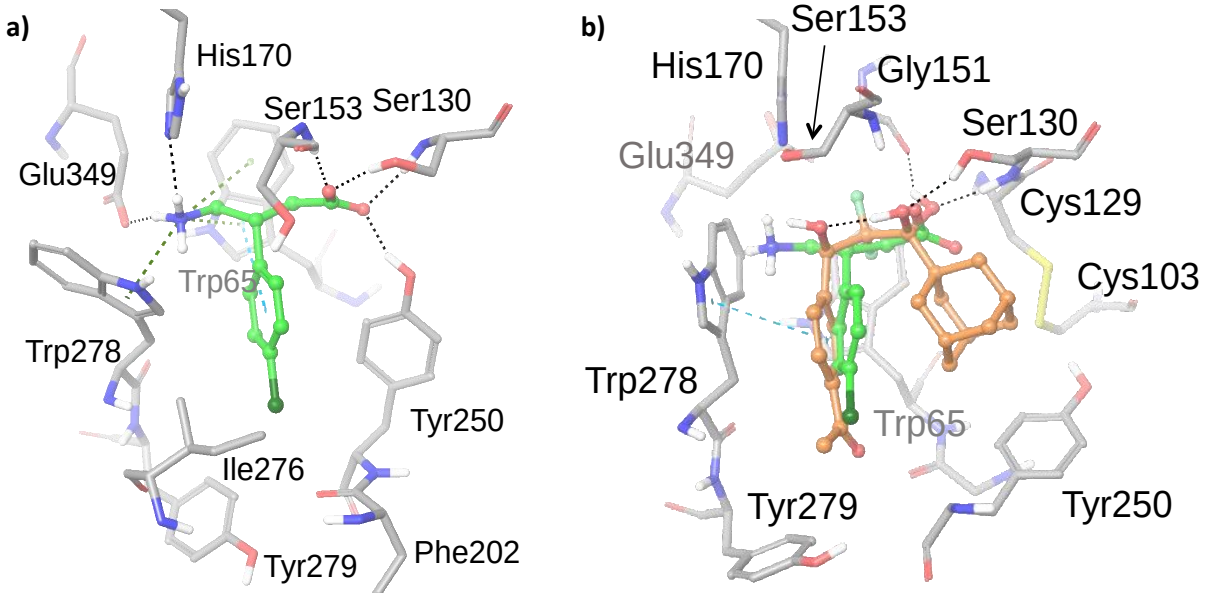


Figure 3.4. a) Crystal structure of Baclofen inside the binding pocket of $GABA_B$ receptor, b) compound **3.1** docked in the binding pocket of $GABA_B$ receptor

3.3. Lead Compound Binding Profile

The lead compound was screened on a range of neurotransmitter receptors (**Table 3.1**) to determine its receptor binding profile (data was provided by the National Institute of Mental Health's Psychoactive Drug Screening Program). Compound **3.1** proved selective for $GABA_B$ over $GABA_A$ (EC_{50} >100 µM). The compound also yielded inhibition of binding of 30% or less against at all of the tested receptor, suggesting that compound **3.1** is a selective $GABA_B$ receptor agonist.

Table 3.1. Primary radioligand binding assays.

Serotonin receptors	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7
Biogenic amine transporters	SERT, NET
Adrenoceptors	α_{1A}, α_{1B}, α_{1D}, β_1, β_3
Cannabinoid	CB_1, CB_2
Opioid receptors	MOR, KOR, DOR
Dopamine receptors	D_1, D_2, D_3, D_5
Histamine receptors	H_1, H_2, H_3, H_4
Sigma receptors	$Sigma_1$, $Sigma_2$
Muscarinic receptors	M_1, M_2, M_3, M_4, M_5

3.4. Analogues at the *para* Position on the Phenyl Ring

To evaluate the tolerance for variations at the *para* position on the phenyl ring, the *p*-acetyl group was removed **3.2**, replaced with a chlorine atom **3.3** or an ethyl group **3.4** (**Figure 3.5**). The target compounds **3.2–3.4** were synthesized using trifluoroacetate-release aldol reaction of pentafluoro-*gem*-diol **3.5** with benzaldehyde, *p*-chlorobenzaldehyde, and *p*-ethyl benzaldehyde (**Scheme 3.1**). With these analogues on hand, a cell line that expresses human $GABA_B$ receptor was used to measure $GABA_B$ agonist activity. Activation of $GABA_B$ receptors leads to inhibition of cAMP production. Forskolin (FSK) is used to activate adenylyl cyclase (AC) to produce cAMP. The addition of a $GABA_B$ agonist suppresses this activation of cAMP production and so the assay measures % block of FSK activation of AC.[16] All three compounds were inactive even at 100 µM concentration. This suggests that the acetyl group in essential for binding.

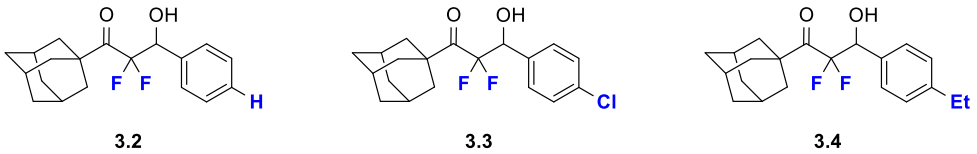
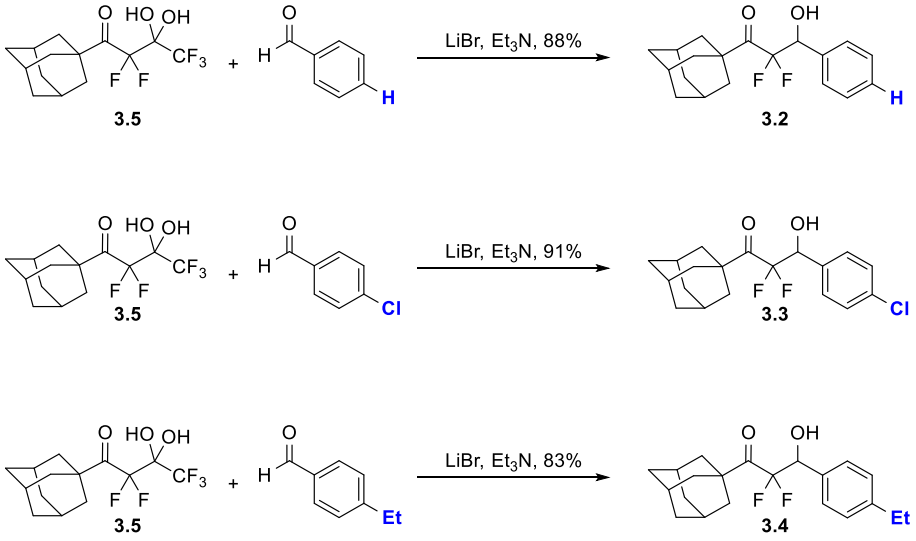


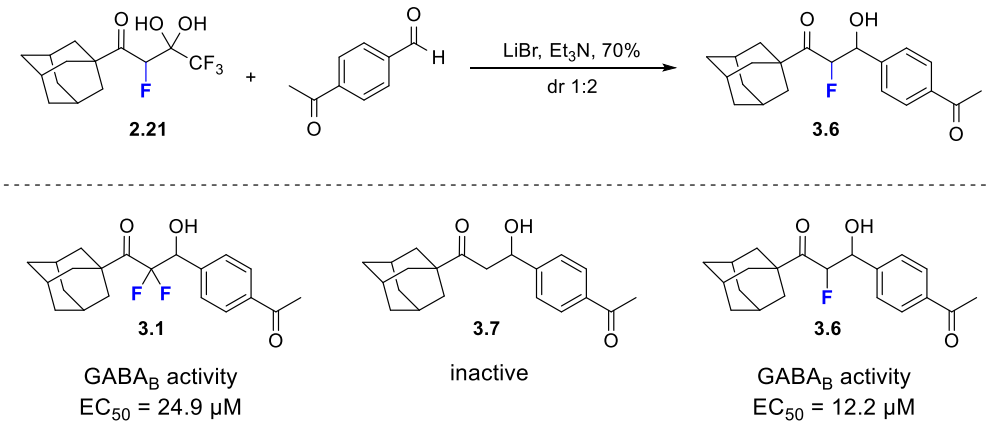
Figure 3.5. Analogues at the *para* position on the phenyl ring



Scheme 3.1. Synthesis of compounds **3.2–3.4**

3.5. Monofluorinated Analogues

Compound **3.6** was prepared to understand if a monofluoromethyl group could replace the difluoromethyl group (**Scheme 3.2**). It is already known that the non-fluorinated analogue **3.7** is inactive as a $GABA_B$ agonist, presumably because this compound predominantly exists in the keto form. The tertafluorinated *gem*-diol **2.21** (see section 2.4) was reacted with *p*-acetylbenzaldehyde to generate analogue **3.6**. When evaluated in the $GABA_B$ assay, compound **3.6** exhibits an EC_{50} of 12.2 µM, thus being twice as active as the difluorinated analogue **3.1**. The enhanced activity of compound **3.6** could be a result of it exhibiting better physicochemical properties, as the removal of one fluorine makes the compound less lipophilic.



Scheme 3.2. Synthesis and $GABA_B$ activity of monofluorinated analogues

The monofluorinated analogue **3.6** was tested as a mixture of enantiomers. In an attempt to better understand the structure activity relationship, the *syn*- and *anti*-diastereomers were purified using preparative TLC and will be tested for $GABA_B$ activity separately. The crystal structure of the *syn*-diastereomer **3.8** was obtained to confirm the structure (**Figure 3.6**).

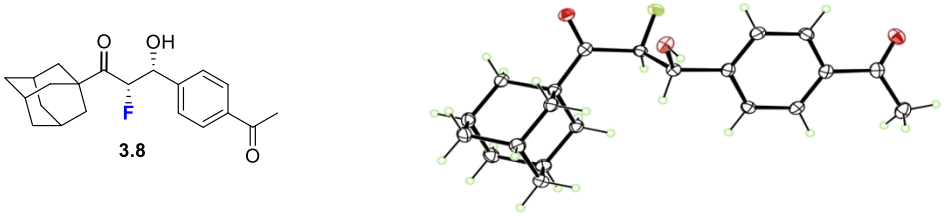


Figure 3.6. Crystal structure of the syn-monofluoro analogue

To further investigate if the monofluorinated compounds are more active than teir difluorinated counterparts, other monofluorinated analogues were designed and synthesized (**Figure 3.7**). The adamantly group was retained because a lipophilic group at this position is required. On the other hand, on the alcohol side it's more flexible, so a styrene **3.9**, a *p*-methoxy-phenyl **3.10**, and a hexenyl analogue **3.11** were prepared. The analogues will be tested for their $GABA_B$ activity to identify additional structure-activity relationship at this position.

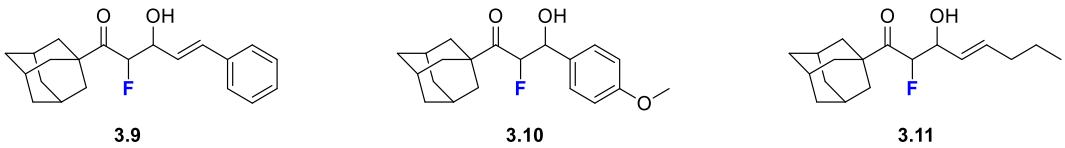


Figure 3.7. Monofluorinated analogues **3.9–3.11**

3.6. Analogues at the β-Position

Next, we are interested in exploring analogues with various groups on the β-position. We aim to add a methyl group at the β-position or exchange the hydroxy group with an amine methyl, oxirane, or oxazoline group. To accomplish these replacements, halohydrins were proposed as intermediates that can be utilized to access the analogues of interest (**Figure 3.8**). Halohydrins can be debrominated to synthesize the tertiary methyl alcohol analogue and can be cyclized to the epoxide and oxazoline analogues.

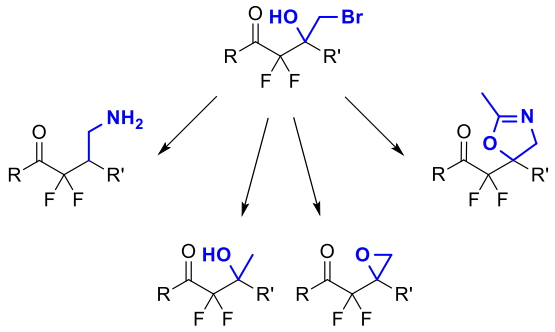
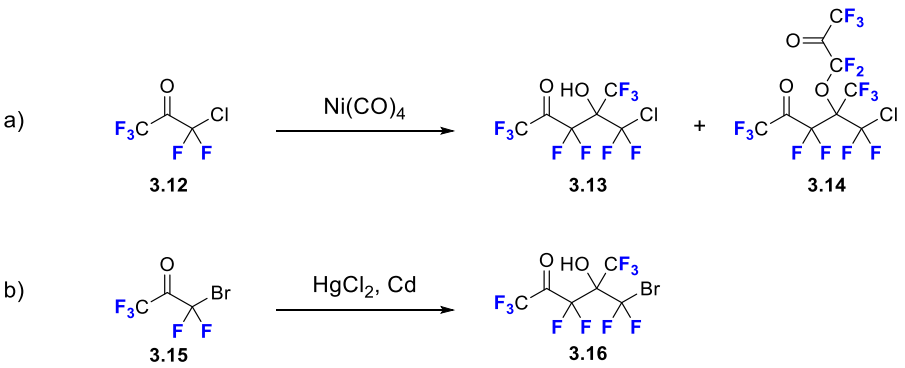


Figure 3.8. Analogues at the β-position

3.7. Synthesis of Fluorinated Halohydrins

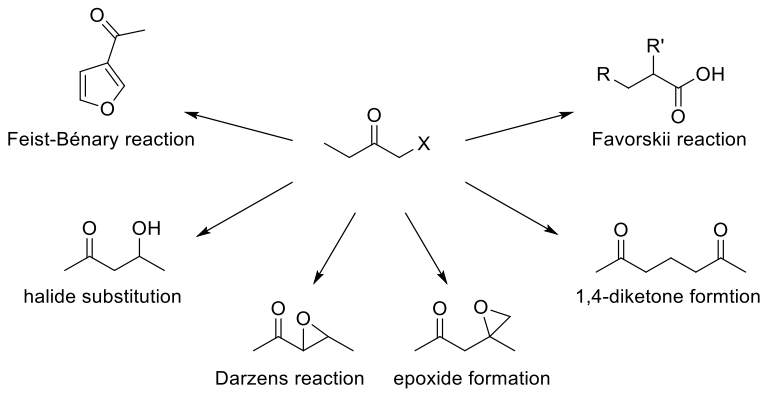
Halohydrins are versatile building blocks with applications in the synthesis of pharmaceuticals, agrochemicals, plasticizers, dyes intermediates and others. Fluorinated halohydrins are underexplored despite their potential. Very few reports of α,α-difluoro-halohydrin can be found in literature and are limited to polyfluorinated compounds.[161-164] To our knowledge the only reports of synthesis of α,α-difluoro-β-keto bromohydrin and chlorohydrins were by Zeifman *et al.* and Krespan (**Scheme 3.3**).[165-166] Both methods are limited by their narrow scope

of application since they are reports of self-condensation of polyfluorinated haloketones. Furthermore, the use of toxic reagents like nickel tetracarbonyl, cadmium and mercury chloride renders these methods impractical.

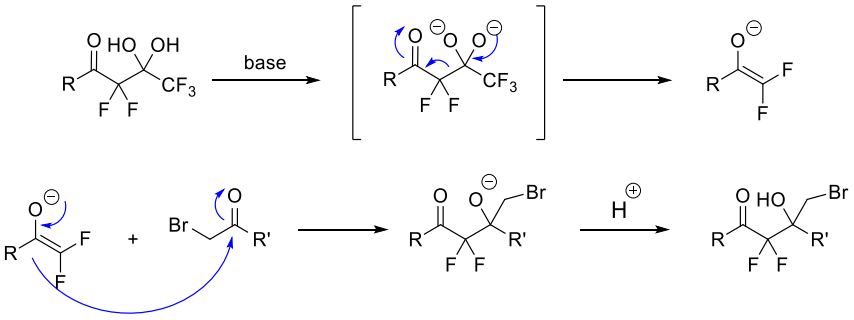


Scheme 3.3. Synthetic approaches to (a) α,α-difluoro-β-keto bromohydrin and (b) chlorohydrins

The α,α-difluoroenolates generated during the release of trifluoroacetate can react with aldehydes to produce α,α-difluoro-β-hydroxy ketones,[107] and with α-trifluoromethyl ketones to provide α,α-difluoro-β-hydroxy-β-trifluoromethyl ketones.[105] Accordingly, we hypothesized that this method will be compatible with α-haloketones and will go through aldol reaction to generate the versatile fluorinated halohydrins. However, relatively few examples of halohydrin synthesis through aldol-type reactions are reported in literature.[167-168] This fact is probably due to competing reactions of α-haloketones; including nucleophilic replacement of the halide,[169] terminal epoxide formation[170] or internal epoxide formation through Darzens reaction,[171] as well as rearrangement reactions like Favorskii reaction,[172] Feist–Benary reaction,[173] and 1,4-diketone formation (**Scheme 3.4**).[174] Thus, chemoselectivity is essential for the success of our synthetic plan. Fortunately, due to the mildness of the conditions of trifluoroacetate-release, α,α-difluoroenolates add selectively to the carbonyl generating α,α-difluoro-β-keto halohydrins (**Scheme 3.5**).



Scheme 3.4. Aldol-type reactions of α-Haloketones

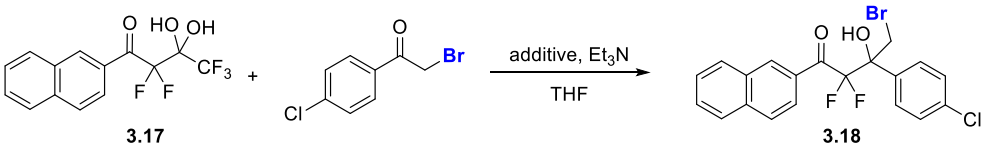


Scheme 3.5. Aldol reactions of α-haloketones with α,α-difluoroenolates from trifluoroacetate release

3.8. Fluorinated Halohydrins Via Trifluoroacetate-Release Reaction

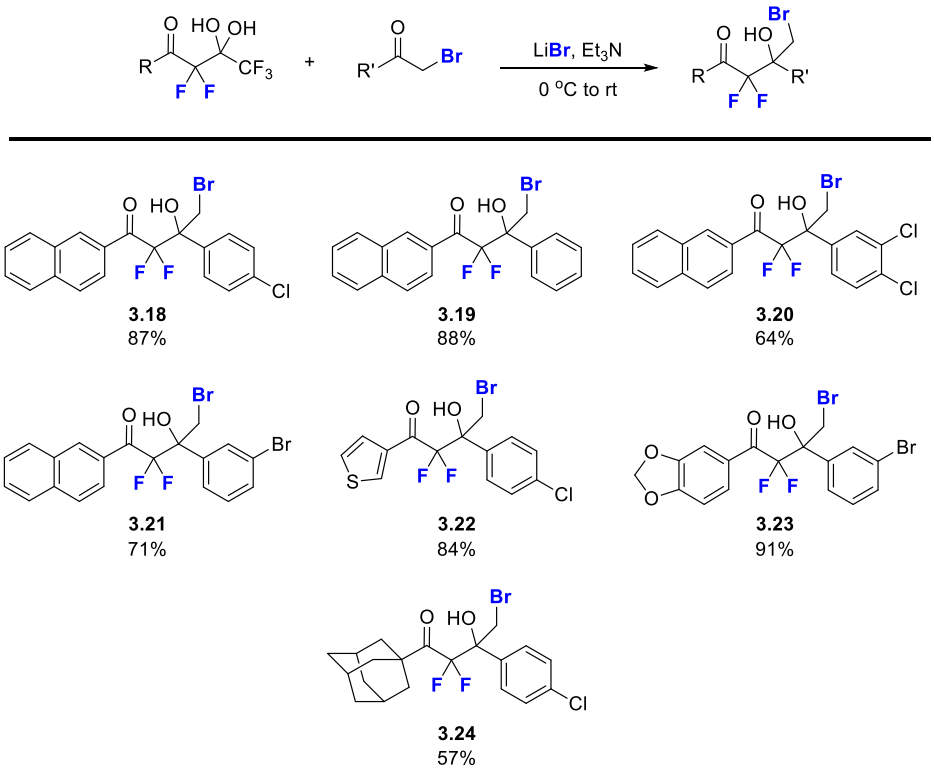
Our efforts to explore the optimum conditions for this transformation revealed that the use of LiBr is essential to drive the reaction, nonetheless, the protonated enolate remained a major by-product. Fortunately, using an extra equivalent of the ketone and increasing the reaction concentration to 0.5 M eliminated this by-product and a quantitative transformation was achieved (**Table 3.2**). On the other hand, increasing the equivalents of triethylamine was detrimental to the yield, partially due to epoxide formation and promoting the formation of the α-haloketone self-adduct. Interestingly, applying the optimized reaction conditions to unhalogenated ketones, including acetophenone and acetone, resulted in poor yields; presumably because they lacked the activation of the carbonyl group by the halogen on the α-position.

Table 3.2. Optimization of the aldol reactions of α-haloketones with α,α-difluoroenolates



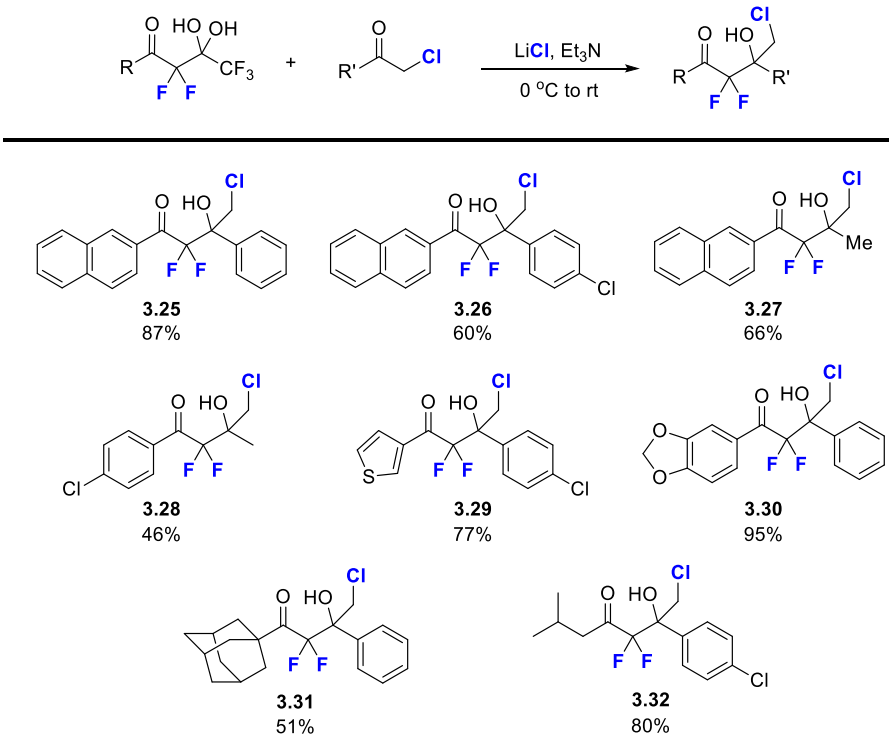
entry	equiv. of ketone	equiv. of Et_3N	equiv. of LiBr	conc. (M)	^{19}F NMR yeild
1	1	1.2	-	0.1	0%
2	1	1.2	5	0.1	54%
3	2	1.2	5	0.1	77%
4	2	1.2	5	0.5	quant.
5	2	3	5	0.5	65%

We sought to explore the scope of this reaction to various α-bromoketones and α-chloroketones. During this investigation, we found that it is essential to match the lithium salt counterion to the α-haloketone halogen to achieve satisfactory yields. This observation is probably due to halogen exchange; as the by-products expected from this side reaction were observed by mass spectroscopy. Hence, LiBr was used with α-bromoketones and LiCl was used with α-chloroketones. Aromatic, heteroaromatic and aliphatic pentafluoro-*gem*-diols reacted with α-bromoketones to produce α-bromohydrins **3.18**-**3.24** in good to excellent yields (**Scheme 3.6**). In case of compound **3.24**, the halohydrin was isolated in 57% yield, most likely due to the steric encumbrance of the adamantly group.



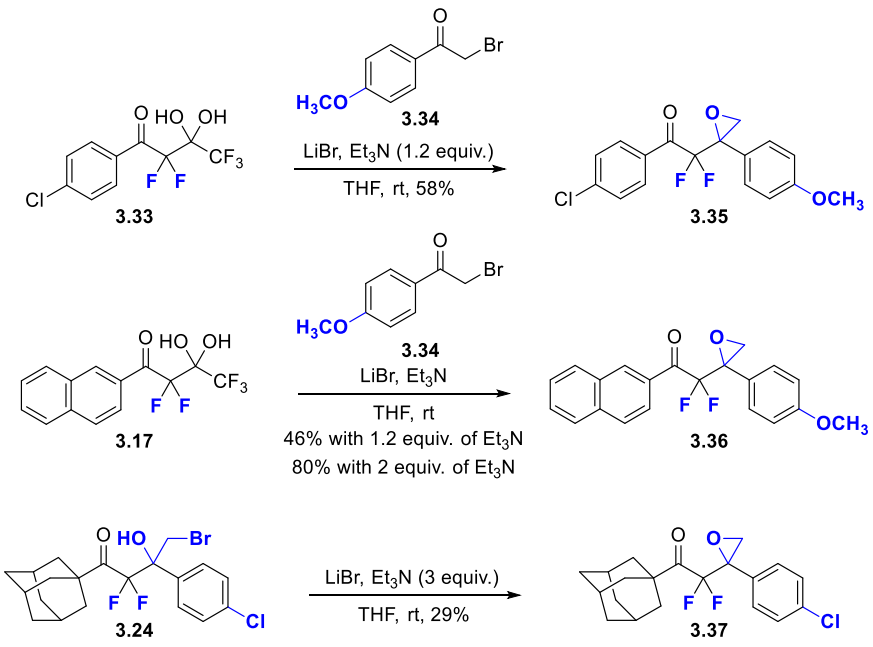
Scheme 3.6. Aldol reactions of α-bromoketones

Next, we treated mixtures of pentafluoro-*gem*-diols and α-chloroketones in THF with LiCl and Et_3N and generated the α-chlorohydrins **3.25-3.32** (**Scheme 3.7**). As with α-bromoketones, a wide range of substituted pentafluoro-*gem*-diols were found to be compatible with this process. Phenyl and substituted phenyl α-chloroketones reacted under these conditions in good yields. On the other hand, chloroacetone, an aliphatic α-chloroketone, reacted to give compounds **3.27** and **3.28** in slightly lower yields than the aromatic α-chloroketones.



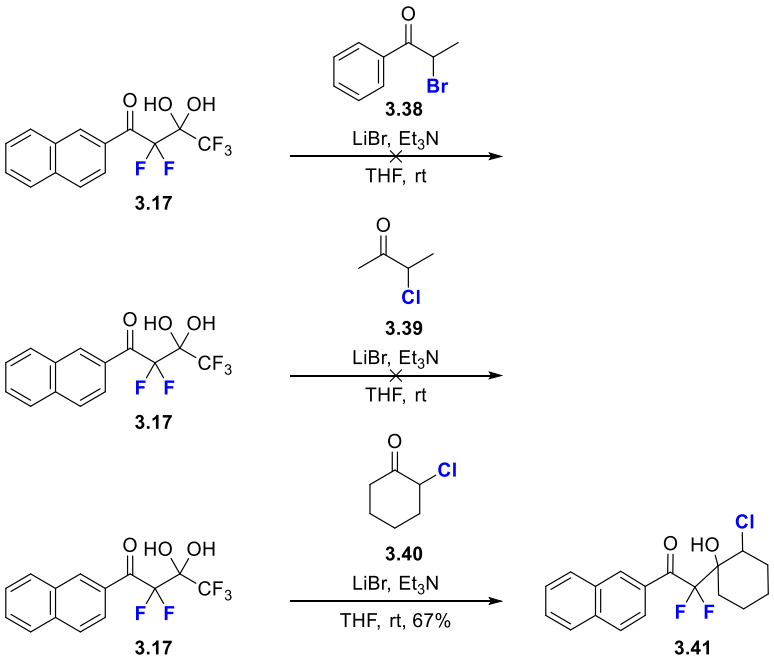
Scheme 3.7. Aldol reactions of α-chloroketones

Despite being compatible with various α-halohydrins, this method didn't give the expected product in the case of the electron rich α-bromoketone **3.34**. The addition of compound **3.34** to pentafluoro-*gem*-diols **3.33** and **3.17** led to the formation of the epoxides **3.35** and **3.36** (**Scheme 3.8**). Moreover, increasing the amount of triethylamine used from 1.2 to 2 equivalents almost doubled the yield of epoxide **3.36** formation. On the other hand, electron deficient α-haloketones produce predominantly halohydrins when reacted with pentafluoro-*gem*-diols. Furthermore, when the resulting electron poor bromohydrins were further treated with triethylamine, they mostly remained unreacted and epoxides were isolated in poor yields. Accordingly, when compound **3.24** was treated with 3 equivalents of triethylamine for 24 hours, it resulted in the formation of the epoxide **3.27** in 29% yield.



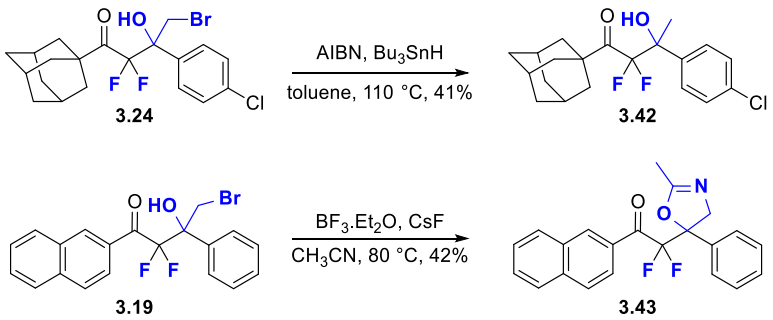
Scheme 3.8. Epoxide formation with electron rich α-bromoketone

When the same conditions were attempted with α-haloketones in which the halogenated α-carbon is a secondary carbon, namely 2-bromopropiophenone (**3.38**) and 3-chloro-2-butanone (**3.39**), no halohydrin formation was observed (**Scheme 3.9**). Instead the fluoroenolates remained unreacted until they were quenched to form the α,α-difluoromethyl ketones as the major products. However, chlorocyclohexanone (**3.40**) reacted under these conditions to produce chlorohydrin **3.41** in a good yield. The reactivity of **25** is probably driven by the release of the ring strain.



Scheme 3.9. Reactions of α-haloketones with a secondary halogenated α-carbon

The trifluoroacetate-release aldol reaction with α-haloketones has substantial potential in accessing fluorinated halohydrin compounds. The products of this reaction can be further modified to access other interesting functionalities. Debromination of bromohydrins creates tertiary methyl alcohols, a group of compounds that was previously inaccessible using this approach due to the lack of reactivity of methyl ketones under these reaction conditions. Under radical debromination conditions compound **3.42** was formed in a fair yield (**Scheme 3.10**). Furthermore, halohydrins are known intermediates in the synthesis of heterocycles like epoxides and oxazolines. Examples of epoxide synthesis can be found in scheme 4. Moreover, halohydrin **3.19** was found to react with acetonitrile in the presence of $BF_3 \cdot Et_2O$ and CsF and oxazoline **3.43** was retrieved in 42% yield (**Scheme 6**).



Scheme 3.10. Reactions of α-bomoketones

3.9. Biological Evaluation of Fluorinated Halohydrins and Their Derivatives

We are interested to find if the halohydrin analogues would display activity at $GABA_B$ receptors. Whereas halohydrins are generally not considered ideal for biological applications, they have been used as probes in structure-activity relationship studies.[175-176] Hence, halohydrins **3.18-3.33** were tested for agonist activity at the $GABA_B$ receptor according to the previously reported procedures (**Table 3.3**).[16] Several compounds demonstrated activity at the $GABA_B$ receptor that ranged from 30% to 90% at 100 µL. Bromohydrins are known to revert to their epoxide counterparts in physiological conditions;[175] thus the activity demonstrated by bromohydrins are potentially precipitated by the epoxides formed *in situ*. When comparing the activity of bromohydrin **3.24** to its epoxide analogue **3.27**, we found that the epoxide was the more active form (**Figure 3.9**). On the other hand, the correspondent noncyclic compound **3.42** is more active than the cyclic agent **3.27**, suggesting that a hydrogen bond donor is beneficial for the activity. However, the methyl group is essential to preserve the activity as demonstrated by the lack of activity of the non-methylated alcohol **3.44**. The trifluoroacetate-release aldol reaction provides access to this interesting class of biologically active compounds; and future studies will target the investigation of the activity of fluorinated tertiary methyl alcohols as $GABA_B$ agonists.

Table 3.3. Agonist activity of halohydrins at $GABA_B$ receptor

Compound	$GABA_B$ agonist activity
3.18	50%
3.19	nd
3.20	nd
3.21	nd
3.22	30%
3.23	80%
3.24	nd
3.25	nd
3.26	nd
3.27	50%
3.28	90%
3.29	90%
3.30	40%
3.31	nd
3.32	nd
3.33	40%

nd is not determined

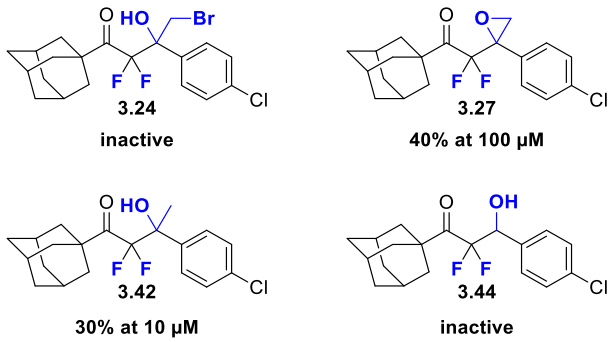
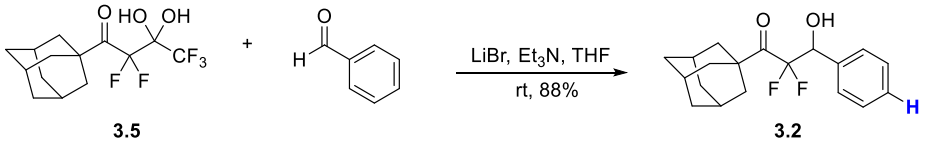


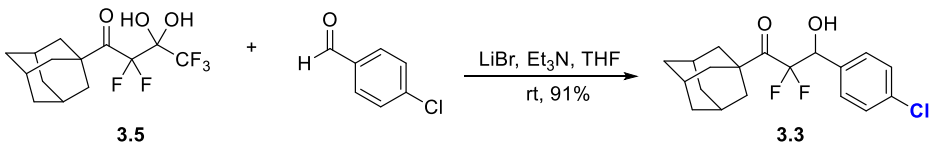
Figure 3.9. $GABA_B$ agonist activity of halohydrin **3.24** and its derivatives

3.10. Experimental Details

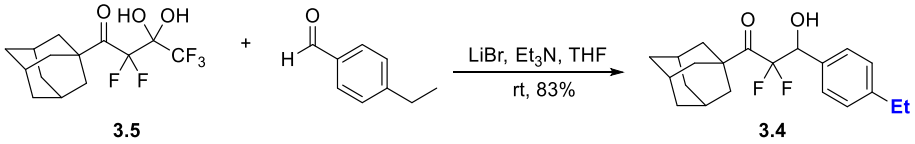
Representative Reaction Procedure for Trifluoroacetate Release/Aldol Reaction. To a solution of 1-adamantan-1-yl-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **3.5** (50 mg, 0.15 mmol), benzaldehyde (31 μL, 0.30 mmol), and LiBr (40 mg, 0.46 mmol) in THF (500 μL), was added Et_3N (32 μL, 0.23 mmol) dropwise. The mixture was stirred for 30 minutes at room temperature, then quenched with saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (5 mL × 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.2** in 88% yield (43 mg) as a colorless solid.



1-(adamantan-1-yl)-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one 3.2. See representative reaction procedure: mp 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H), 7.39–7.33 (m, 3H), 5.25 (ddd, J = 17.4, 7.1, 5.1 Hz, 1H), 2.85 (d, J = 5.1 Hz, 1H), 2.01 (s, 3H), 1.87 (d, J = 2.4 Hz, 6H), 1.70 (q, J = 12.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9 (dd, J_{CF} = 29.0, 26.1 Hz, 1C), 135.1 (d, J_{CF} = 2.2 Hz, 1C), 129.0, 128.4 (2C), 128.2 (2C), 116.6 (dd, J_{CF} = 266.6, 259.5 Hz, 1C), 73.3 (dd, J_{CF} = 27.6, 23.4 Hz, 1C), 46.9 (t, J_{CF} = 2.4 Hz, 1C), 36.9 (3C), 36.5 (3C), 27.7 (3C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –108.2 (dd, J = 284.5, 6.9 Hz, 1F), –119.0 (dd, J = 284.5, 17.4 Hz, 1F); IR (film) ν_{max} 3511, 2906, 2852, 1712, 1454, 1056 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}F_2O_2Cs$ $(M+Cs)^+$ 453.0642, found 453.0631.

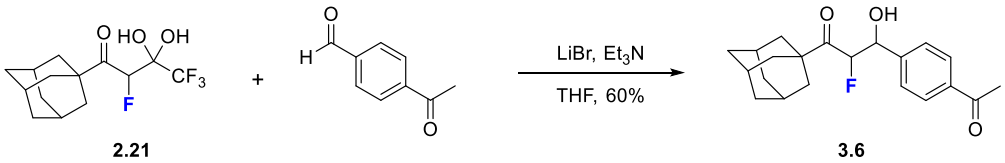


1-(adamantan-1-yl)-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxypropan-1-one 3.3. See representative reaction procedure. To a solution of 1-adamantan-1-yl-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **3.5** (100 mg, 0.304 mmol), 4-chlorobenzaldehyde (87 mg, 0.61 mmol), and LiBr (132 mg, 1.52 mmol) in THF (500 μL), was added Et_3N (51 μL, 0.37 mmol) dropwise. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.3** as a colorless solid (98 mg, 91% yield): mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 4H), 5.23 (ddd, J = 17.7, 6.6, 4.9 Hz, 1H), 2.95 (d, J = 5.0 Hz, 1H), 2.03 (s, 3H), 1.89 (d, J = 2.2 Hz, 6H), 1.71 (q, J = 12.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7 (dd, J_{CF} = 29.3, 26.1 Hz, 1C), 134.9, 133.6 (d, J_{CF} = 2.1 Hz, 1C), 129.6 (2C), 128.5 (2C), 116.3 (dd, J_{CF} = 267.5, 259.4 Hz, 1C), 72.6 (dd, J_{CF} = 28.0, 23.4 Hz, 1C), 46.9 (dd, J_{CF} = 3.1, 1.9 Hz, 1C), 36.9 (dd, J_{CF} = 2.5, 1.5 Hz, 3C), 36.4 (3C), 27.7 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.4 (dd, J = 288.8, 6.0 Hz, 1F), –119.9 (dd, J = 288.8, 17.8 Hz, 1F); IR (film) ν_{max} 3494, 2910, 2856, 1712, 1494, 1063, 800 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}Cl_2F_2O_2$ $(M+Cl)^-$ 389.0887, found 389.0861.



1-(adamantan-1-yl)-3-(4-ethylphenyl)-2,2-difluoro-3-hydroxypropan-1-one 3.4. See representative reaction procedure. To a solution of 1-adamantan-1-yl-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **3.5** (50 mg, 0.15 mmol), 4-ethylbenzaldehyde (42 μL, 0.30 mmol), and LiBr (40 mg, 0.46 mmol) in THF (500 μL), was added Et_3N (32 μL, 0.23 mmol) dropwise. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.4** as a colorless solid

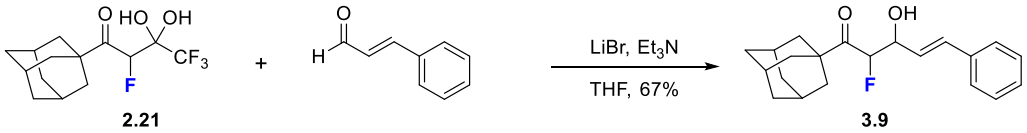
(44 mg, 83% yield): mp 102–103 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.21 (ddd, *J* = 17.7, 7.1, 4.6 Hz, 1H), 2.77 (d, *J* = 5.0 Hz, 1H), 2.66 (q, *J* = 7.7 Hz, 2H), 2.01 (s, 3H), 1.88 (s, 6H), 1.70 (q, *J* = 12.3 Hz, 6H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9 (dd, J_{CF} = 29.3, 25.8 Hz, 1C), 145.2, 132.4 (d, J_{CF} = 1.9 Hz, 1C), 128.2 (2C), 127.9 (2C), 116.7 (dd, J_{CF} = 266.6, 258.9 Hz, 1C), 73.2 (dd, J_{CF} = 27.8, 23.4 Hz, 1C), 46.9 (t, J_{CF} = 1.9 Hz, 1C), 36.9 (3C), 36.5 (3C), 28.8, 27.8 (3C), 15.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –108.00 (d, *J* = 284.0 Hz, 1F), –119.26 (dd, *J* = 285.1, 18.0 Hz, 1F); IR (film) ν_{max} 3502, 2909, 2851, 1712, 1453, 1273, 1052 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}F_2O_2Cs$ $(M+Cs)^+$ 481.0955, found 481.0947.



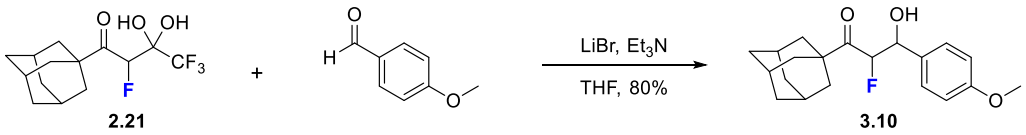
3-(4-acetylphenyl)-1-(adamantan-1-yl)-2-fluoro-3-hydroxypropan-1-one 3.6. See representative reaction procedure. To a solution of 1-(adamantan-1-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one **2.21** (100 mg, 0.322 mmol), *p*-acetylbenzaldehyde (95 mg, 0.65 mmol), and LiBr (140 mg, 1.61 mmol) in THF (2 ml), was added Et_3N (54 μL, 0.39 mmol) dropwise. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.6** in 60% yield (67 mg).

Syn-diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 5.26 (dd, *J* = 21.2, 4.0 Hz, 1H), 5.15 (dd, *J* = 47.3, 4.0 Hz, 1H), 2.61 (s, 3H), 2.00 (s, 3H), 1.75 (s, 6H), 1.74–1.53 (m, 6H); ^{19}F NMR (471 MHz, $CDCl_3$) δ –196.6 (dd, *J* = 47.4, 21.2 Hz, 1F).

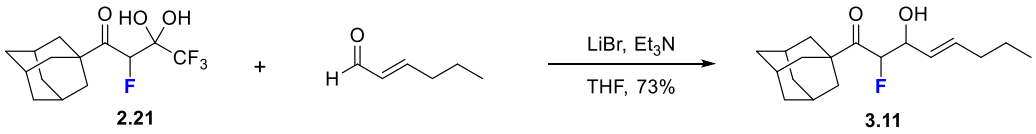
Anti-diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 5.16 (d, *J* = 7.2 Hz, 1H), 5.09–4.94 (m, 1H), 2.61 (s, 3H), 2.03 (s, 3H), 1.83 (q, *J* = 13.0 Hz, 6H), 1.78–1.65 (m, 6H); ^{19}F NMR (471 MHz, $CDCl_3$) δ –190.4 (dd, *J* = 46.8, 9.5 Hz, 1F).



(E)-1-(adamantan-1-yl)-2-fluoro-3-hydroxy-5-phenylpent-4-en-1-one 3.9. See representative reaction procedure. To a solution of 1-(adamantan-1-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one **2.21** (100 mg, 0.322 mmol), cinnamaldehyde (81 μL, 0.65 mmol), and LiBr (140 mg, 1.61 mmol) in THF (2 ml), was added Et_3N (54 μL, 0.0.39 mmol) dropwise. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.9** in 67% yield (71 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (m, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.31–7.25 (m, 1H), 6.74 (dd, *J* = 15.9, 4.9 Hz, 1H), 6.26 (ddd, *J* = 22.6, 16.0, 6.4 Hz, 1H), 5.09 (ddd, *J* = 47.5, 18.9, 4.9 Hz, 1H), 4.85–4.70 (m, 1H), 2.65 (d, *J* = 26.1 Hz, 1H), 2.08 (s, 3H), 1.93 (s, 6H), 1.75 (q, *J* = 11.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2 (d, J_{CF} = 17.9 Hz, 1C), 210.9 (d, J_{CF} = 17.8 Hz, 1C)*, 136.3, 136.2*, 133.4, 133.3*, 128.8 (2C), 128.7(2C)*, 128.2, 128.2*, 126.8 (2C), 126.8 (2C)*, 125.8 (d, J_{CF} = 3.9 Hz), 125.7 (d, J_{CF} = 4.6 Hz)*, 94.1 (d, J_{CF} = 161.8 Hz), 92.6 (d, J_{CF} = 159.0 Hz)*, 72.6 (d, J_{CF} = 20.9 Hz), 72.1 (d, J_{CF} = 22.8 Hz)*, 37.2 (d, J_{CF} = 2.4 Hz, 3C), 37.1 (d, J_{CF} = 2.6 Hz, 3C)*, 36.5 (3C), 29.8, 27.8 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –195.4 (dd, *J* = 47.6, 13.6 Hz, 1F), –199.2 (dd, *J* = 47.8, 19.1 Hz, 1F).



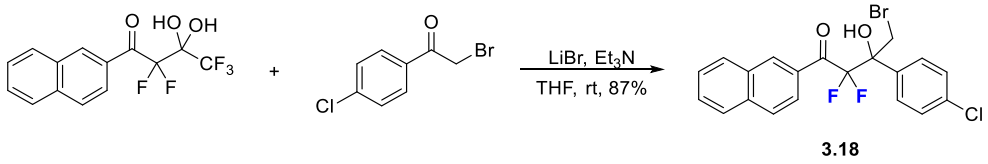
1-(adamantan-1-yl)-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)propan-1-one 3.10. See representative reaction procedure. To a solution of 1-(adamantan-1-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one **2.21** (100 mg, 0.322 mmol), *p*-methoxybenzaldehyde (88 mg, 0.65 mmol), and LiBr (140 mg, 1.61 mmol) in THF (2 ml), was added Et_3N (54 μL, 0.0.39 mmol) dropwise. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.10** in 80% yield (86 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 9.2 Hz, 2H), 6.88 (t, *J* = 7.9 Hz, 2H), 5.20 – 5.08 (m, 1H), 5.07–4.96 (m, 1H), 3.80 (d, *J* = 2.9 Hz, 3H), 3.03 (d, *J* = 64.9 Hz, 1H), 2.00 (d, *J* = 13.0 Hz, 3H), 1.86–1.60 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (d, J_{CF} = 17.3 Hz, 1C), 210.2 (d, J_{CF} = 16.9 Hz, 1C)*, 159.7, 159.7*, 131.1 (d, J_{CF} = 1.4 Hz, 1C), 130.1 (d, J_{CF} = 4.4 Hz, 1C)*, 128.4 (d, J_{CF} = 1.4 Hz, 2C), 128.4 (d, J_{CF} = 1.0 Hz, 2C)*, 114.0 (2C), 113.9 (2C)*, 93.3 (d, J_{CF} = 134.0 Hz, 1C), 91.5 (d, J_{CF} = 131.6 Hz, 1C)*, 73.2 (d, J_{CF} = 20.2 Hz, 1C), 72.7 (d, J_{CF} = 23.6 Hz, 1C)*, 55.4, 55.4*, 36.9 (d, J_{CF} = 2.2 Hz, 3c), 36.7 (d, J_{CF} = 1.9 Hz, 3C)*, 36.5 (3C), 36.4 (3C)*, 29.8, 27.7 (3C), 27.6 (3C)*.



(E)-1-(adamantan-1-yl)-2-fluoro-3-hydroxyoct-4-en-1-one 3.11. See representative reaction procedure. To a solution of 1-(adamantan-1-yl)-2,4,4,4-tetrafluoro-3,3-dihydroxybutan-1-one **2.21** (10 mg, 0.322 mmol), (E)-hex-2-enal (75 μL, 0.65 mmol), and LiBr (140 mg, 1.61 mmol) in THF (2 ml), was added Et_3N (54 μL, 0.0.39 mmol) dropwise. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded the title compound **3.11** in 73% yield (69 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (dq, *J* = 14.9, 7.2 Hz, 1H), 5.48 (td, *J* = 15.2, 6.9 Hz, 1H), 4.96 (dd, *J* = 47.9, 4.5

Hz, 1H), 4.51 (ddt, J = 24.3, 13.7, 6.1 Hz, 1H), 2.47 (s, 1H), 2.04 (s, 3H), 1.88 (s, 6H), 1.72 (q, J = 12.0 Hz, 6H), 1.39 (h, J = 7.3 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1 (d, J_{CF} = 17.3 Hz. 1C), 210.7 (d, J_{CF} = 17.9 Hz, 1C)*, 135.8, 135.4*, 126.6 (d, J_{CF} = 3.9 Hz, 1C), 126.5 (d, J_{CF} = 4.8 Hz, 1C)*, 72.6 (d, J_{CF} = 20.7 Hz, 1C), 72.3 (d, J_{CF} = 22.7 Hz, 1C)*, 37.2 (d, J_{CF} = 2.4 Hz, 3C), 37.1 (d, J_{CF} = 2.5 Hz, 3C)*, 36.6 (3C), 36.5 (3C)*, 34.5, 34.5*, 27.8 (3C), 22.2, 13.8, 13.8*; ^{19}F NMR (376 MHz, $CDCl_3$) δ –196.3 (dd, J = 47.7, 14.6 Hz, 1F), –199.2 (dd, J = 47.8, 20.9 Hz, 1F).

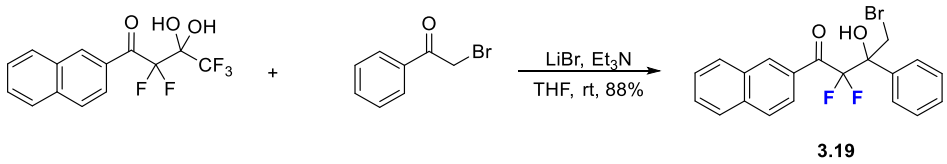
Representative Reaction Procedure for Trifluoroacetate-release/Aldol Reaction with α-Haloketones. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (300 mg, 0.937 mmol), 2-Bromo-4'-chloroacetophenone (438 mg, 1.87 mmol), and LiBr (244 mg, 2.81 mmol) in THF (2 mL) was added Et_3N (157 μL, 1.12 mmol) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 30 minutes. The mixture was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 × 5 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.18** in 87% yield (358 mg) as a colorless solid.



3.18

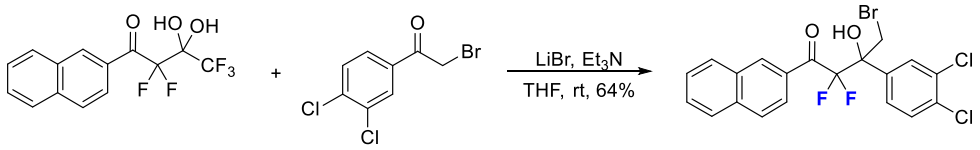
4-bromo-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)butan-1-one 3.18. See representative reaction procedure: mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.97 (dd, J = 13.9, 8.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 2H), 7.65 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.57 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.42–7.36 (m, 2H), 4.22 (q, J = 11.2 Hz, 2H), 3.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (dd, J_{CF} = 29.9, 27.8 Hz, 1C), 136.2, 135.3, 135.2, 133.8 (dd, J_{CF} = 5.7, 4.1 Hz, 1C), 132.2, 130.4 (2C), 129.7, 128.8 (2C), 128.5 (2C),

128.4, 127.9, 127.2, 125.1 (t, J_{CF} = 2.0 Hz, 1C), 116.2 (dd, J_{CF} = 266.3, 264.2 Hz, 1C), 78.1 (t, J_{CF} = 24.8 Hz, 1C), 37.7 (t, J_{CF} = 3.5 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.7 (d, J_{FF} = 274.5 Hz, 1F), –107.2 (d, J_{FF} = 274.4 Hz, 1F); IR (film) ν_{max} 3518, 3061, 2961, 2925, 1686, 1626, 1493, 1094, 755 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{14}BrClF_2O_2$ $(M+Na)^+$ 460.9726, found 460.9740.



3.19

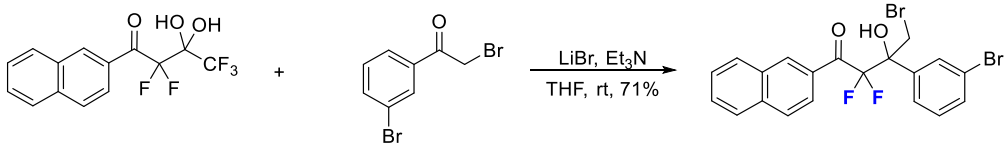
4-bromo-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)-3-phenylbutan-1-one 3.19. See representative reaction procedure. **.** To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)- butan-1-one (100 mg, 0.312 mmol), 2-bromoacetophenone (124 mg, 0.624 mmol), and LiBr (135 mg, 1.56 mmol) in THF (500 μL), was added Et_3N (53 μL, 0.37 mmol) dropwise. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.19** in 88% yield (98 mg) as a solid: mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.95 (dd, *J* = 14.2, 8.5 Hz, 2H), 7.85 (dd, *J* = 8.4, 4.6 Hz, 2H), 7.63 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.61–7.53 (m, 4H), 7.46–7.33 (m, 2H), 4.26 (s, 2H), 3.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (dd, J_{CF} = 29.9, 27.7 Hz, 1C), 136.5, 136.0, 133.7 (dd, J_{CF} = 5.9, 4.0 Hz, 1C), 132.2, 130.6, 130.3, 129.5, 129.0, 128.5 (2C), 128.2, 127.8, 127.0 (2C), 127.0, 125.2–125.1 (m, 1C), 116.5 (dd, J_{CF} = 266.3, 264.2 Hz, 1C), 78.2 (t, J_{CF} = 24.8 Hz, 1C), 38.0 (t, J_{CF} = 3.6 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.0 (d, J_{FF} = 270.6 Hz, 1F), –107.4 (d, J_{FF} = 270.7 Hz, 1F); IR (film) ν_{max} 3519, 3061, 2925, 1688, 1626, 1450, 1108 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}BrF_2O_2$ $(M+H)^+$ 405.0296, found 405.0306.



3.20

4-bromo-3-(3,4-dichlorophenyl)-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)butan-1-one

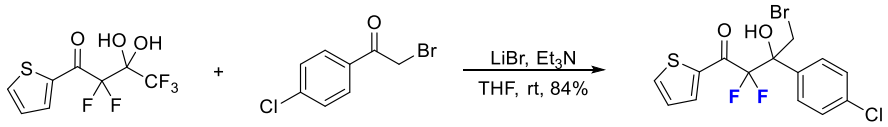
3.20. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (100 mg, 0.312 mmol), 2-bromo-3′,4′-dichloroacetophenone (167 mg, 0.624 mmol), and LiBr (135 mg, 1.56 mmol) in THF (500 μL) was treated with Et_3N (53 μL, 0.37 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.20** in 64% yield (94 mg) as a pale yellow solid: mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.98 (dd, *J* = 12.0, 8.4 Hz, 2H), 7.88 (d, *J* = 9.3 Hz, 2H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.40 (dd, *J* = 8.5, 1.1 Hz, 1H), 4.18 (dd, *J* = 38, 11.3 Hz, 2H), 3.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0 (dd, J_{CF} = 29.9, 27.7 Hz, 1C), 136.9, 136.1, 133.6 (dd, J_{CF} = 5.8, 4.0 Hz, 1C), 133.4, 132.9, 132.1, 130.3, 130.2, 130.1, 129.7, 129.3, 128.4, 127.7, 127.1, 126.2, 124.9 (t, J_{CF} = 2.1 Hz, 1C), 115.8 (dd, J_{CF} = 65.6, 62.4 Hz, 1C), 77.7 (t, J_{CF} = 25.0 Hz, 1C), 37.1 (t, J_{CF} = 3.3 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.3 (d, J_{FF} = 277.6 Hz, 1F), –106.9 (d, J_{FF} = 277.7 Hz, 1F); IR (film) ν_{max} 3519, 3061, 2924, 1685, 1626, 1471, 1107, 749 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{13}BrCl_2F_2O_2$ $(M+H)^+$ 472.9517, found 472.9539.



3.21

4-bromo-3-(3-bromophenyl)-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)butan-1-one 3.21. See representative reaction procedure. . A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-

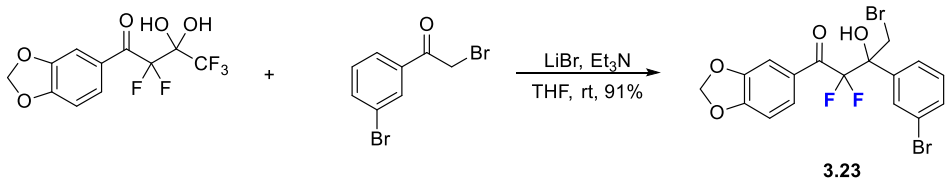
(naphthalen-2-yl)-butan-1-one (100 mg, 0.312 mmol),), 2,3′-dibromoacetophenone (260 mg, 0.936 mmol), and LiBr (135 mg, 1.56 mmol) in THF (500 μL) was treated with Et_3N (53 μL, 0.37 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.21** in 71% yield (128 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.99 (dd, *J* = 11.8, 8.4 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.79 (s, 1H), 7.66 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.55–7.49 (m, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), (dd, *J* = 26.5, 11.2 Hz , 2H), 3.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (dd, J_{CF} = 30.2, 27.5 Hz, 1C), 139.0, 136.1, 133.7 (dd, J_{CF} = 6.1, 3.7 Hz, 1C), 132.2, 132.2, 130.4, 130.3, 130.0, 129.7, 128.4, 127.9, 127.2, 125.6, 125.1, 122.9, 116.1 (dd, J_{CF} = 267.2, 263.9 Hz, 1C), 78.0 (t, J_{CF} = 25.0 Hz, 1C), 37.6 (t, J_{CF} = 3.6 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.6 (d, J_{FF} = 274.7 Hz, 1F), –107.0 (d, J_{FF} = 274.7 Hz, 1F); IR (film) ν_{max} 3512, 3062, 2925, 1682, 1625, 1076 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{14}Br_2F_2O_2$ $(M+H)^+$ 482.9401, found 482.9433



3.22

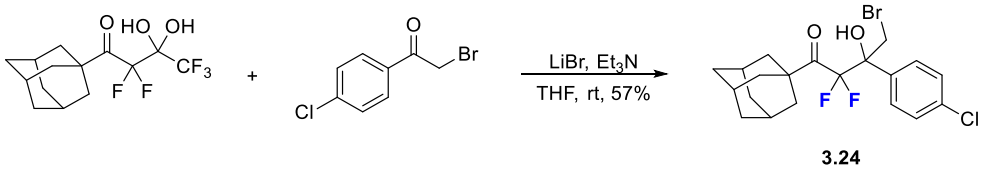
4-bromo-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-1-(thiophen-2-yl)butan-1-one 3.22. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(thiophen-2-yl)butan-1-one (100 mg, 0.363 mmol), 2-bromo-4′-chloroacetophenone (170 mg, 0.727 mmol), and LiBr (156 mg, 1.82 mmol) in THF (500 μL) was treated with Et_3N (61 μL, 0.44 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.22** in 84% yield (121 mg) as colorless solid: mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 3.3, 1.5 Hz, 1H), 7.79 (d, *J* = 4.9 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.41–7.32 (m, 2H), 7.14 (t, *J* = 4.5 Hz, 1H), 4.16 (dd, *J* = 14.5, 11.3 Hz, 2H), 3.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5 (dd, J_{CF} = 30.9, 28.9 Hz, 1C), 139.1 (dd, J_{CF} = 2.7, 0.8 Hz, 1C), 137.3, 137.0 (dd, J_{CF} = 7.0, 4.5 Hz, 1C), 135.1, 134.8,

128.8, 128.6 (2C), 128.4 (2C), 115.5 (q, J_{CF} = 266.5, 263.6 Hz, 1C), 77.7 (t, J_{CF} = 24.9 Hz, 1C), 37.2 (t, J_{CF} = 3.2 Hz, 1C);^{19}F NMR (376 MHz, $CDCl_3$) δ –108.6 (d, J_{FF} = 266.7 Hz, 1F), –109.7 (d, J_{FF} = 266.6 Hz, 1F); IR (film) ν_{max} 3501, 3108, 1659, 1409, 1058, 728 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{10}BrCl_2F_2O_2S$ $(M+Cl)^-$ 428.8930, found 428.8904.



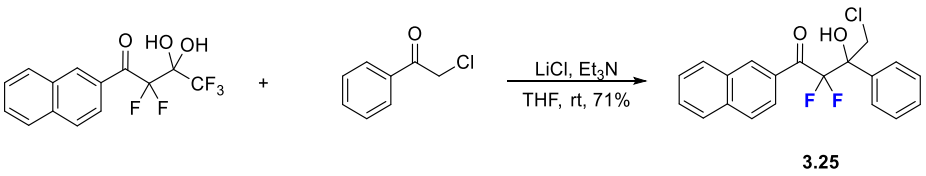
3.23

1-(benzo[d][1,3]dioxol-5-yl)-4-bromo-3-(3-bromophenyl)-2,2-difluoro-3-hydroxybutan-1-one 3.23. See representative reaction procedure. A solution of 1-(benzo[d][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (100 mg, 0.318 mmol), 2,3′-dibromoacetophenone (177 mg, 0.637 mmol), and LiBr (138 mg, 1.59 mmol) in THF (500 μL) was treated with Et_3N (53 μL, 0.38 mmol). SiO_2 flash chromatography (9:1 hexanes/EtOAc) afforded the product **3.23** in 91% yield (139 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.67 (m, 2H), 7.51 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H), 7.49–7.44 (m, 2H), 7.28 (t, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.07 (s, 2H), 4.18–4.08 (m, 2H), 3.62 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2 (dd, J_{CF} = 30.3, 27.6 Hz, 1C), 153.4, 148.1, 139.0, 132.1, 130.3, 129.9, 128.3 (dd, J_{CF} = 5.7, 3.6 Hz, 1C), 127.5–127.4 (m, 1C), 125.6, 122.8, 115.9 (dd, J_{CF} = 267.5, 263.5 Hz, 1C), 110.2 (dd, J_{CF} = 4.3, 2.5 Hz, 1C), 108.2, 102.3, 77.9 (t, J_{CF} = 25.5, 24.4 Hz, 1C), 37.5 (t, J_{CF} = 3.5 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.2 (d, J_{FF} = 275.8 Hz, 1F), –106.7 (d, J_{FF} = 275.9 Hz, 1F); IR (film) ν_{max} 3507, 3079, 2910, 1680, 1605, 1445, 1268, 1089, 797 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}ClBr_2F_2O_4$ $(M+Cl)^-$ 510.8759, found 510.8751.



3.24

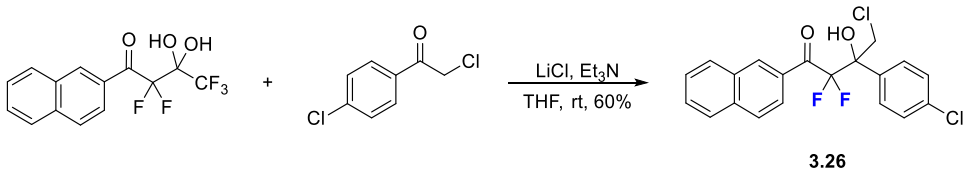
1-((3r,5r,7r)-adamantan-1-yl)-4-bromo-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxybutan-1-one 3.24. See representative reaction procedure. A solution of 1-((3r,5r,7r)-adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (300 mg, 0.914 mmol), 2-bromo-4′-chloroacetophenone (427 mg, 1.83 mmol), and LiBr (397 mg, 4.57 mmol) in THF (2 mL) was treated with Et_3N (153 μL, 1.10 mmol). SiO_2 flash chromatography (19:2:1 hexanes/dichloromethane/EtOAc) afforded the product **3.24** in 57% yield (236 mg) as a colorless solid: mp 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 4.16–3.99 (m, 3H), 2.00 (s, 3H), 1.79 (t, J = 20.7, 13.5 Hz, 6H), 1.68 (dd, J = 34.4, 13.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3 (dd, J_{CF} = 30.0, 25.3 Hz, 1C), 135.6, 135.0, 128.6 (2C), 128.5 (2C), 115.4 (dd, J_{CF} = 271.4, 267.1 Hz, 1C), 78.4 (t, J_{CF} = 23.9 Hz), 47.6 (d, J_{CF} = 2.1 Hz), 37.1 (d, J_{CF} = 3.8 Hz, 1C), 36.8 (d, J_{CF} = 2.3 Hz, 3C), 36.3 (3C), 27.7 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.3 (d, J_{FF} = 284.2 Hz, 1F), –110.4 (d, J_{FF} = 284.2 Hz, 1F); IR (film) ν_{max} 3520, 2912, 2856, 1714, 1495, 1093 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}BrCl_2F_2O_2$ $(M+Cl)^-$ 481.0148, found 481.0116.



3.25

4-chloro-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)-3-phenylbutan-1-one 3.25. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (100 mg, 0.312 mmol), 2-chloroacetophenone (97 mg, 0.62 mmol), and LiCl (66 mg, 1.6 mmol) in THF (500 μL) was treated with Et_3N (53 μL, 0.37 mmol). SiO_2

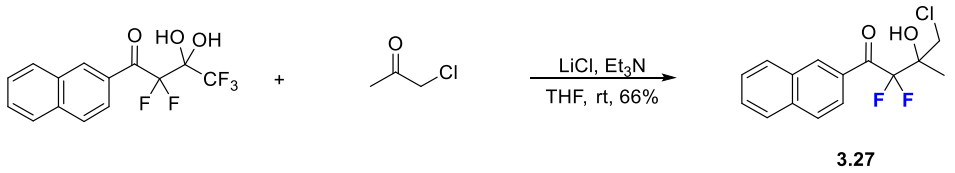
flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.25** in 71% yield (80 mg) as a colorless film: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.95 (dd, *J* = 14.3, 8.2 Hz, 2H), 7.85 (dd, *J* = 8.4, 4.5 Hz, 2H), 7.67–7.53 (m, 4H), 7.44–7.36 (m, 3H), 4.38 (s, 2H), 3.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.59 (dd, J_{CF} = 30.0, 27.8 Hz, 1C), 136.06, 135.99, 133.67 (dd, J_{CF} = 5.5, 4.1 Hz, 1C), 132.24, 130.66, 130.36, 129.58, 129.10, 128.58, 128.30, 127.83, 127.08, 127.06, 125.17, 118.25 (dd, J_{CF} = 220.7 Hz, 265.9 Hz, 1C), 78.64 (t, J_{CF} = 24.8 Hz, 1C), 48.31 (t, J_{CF} = 3.9 Hz, 1C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –106.6 (d, J_{FF} = 271.8 Hz, 1F), –107. 8 (d, J_{FF} = 271.8 Hz, 1F); IR (film) ν_{max} 3529, 3061, 2925, 1685, 1625, 1450, 1091, 1072, 701 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{16}ClF_2O_2$ $(M+H)^+$ 361.0801, found 361.0782.



3.26

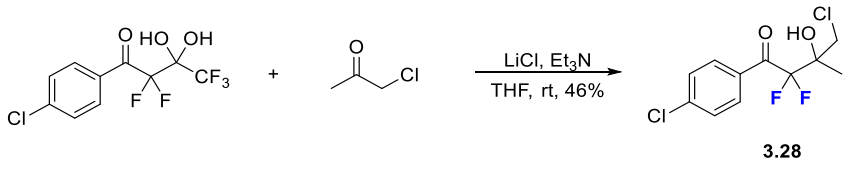
4-chloro-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)butan-1-one 3.26. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (30 mg, 0.094 mmol), 2,4'-dichloroacetophenone (35 mg, 0.19 mmol), and LiCl (26 mg, 0.61 mmol) in THF (500 μL) was treated with Et_3N (26 μL, 0.189 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.26** in 60% yield (22 mg) as a colorless solid: mp 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.97 (dd, *J* = 15.3, 8.4 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.69 – 7.61 (m, 1H), 7.58 (d, *J* = 7.1 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 4.37 (dd, *J* = 11.9, 11.9 Hz, 2H), 3.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.20 (t, J_{CF} = 27.9 Hz, 1C), 136.00, 135.12, 134.49, 133.60 (dd, J_{CF} = 4.2, 4.2 Hz, 1C), 132.10, 130.31, 130.22, 129.58, 128.62, 128.49, 128.28, 127.72, 127.03, 124.95 (t, J_{CF} = 2.1 Hz, 1C), 116.8 (dd, J_{CF} = 204.4, 201.7 Hz, 1C), 78.36 (t, J_{CF} = 24.8 Hz, 1C), 47.95 (t, J_{CF} = 3.8 Hz, 1C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –106.3 (d, J_{FF} = 275.8 Hz, 1F), –107.7 (d, J_{FF} =

275.6 Hz, 1F); IR (film) ν_{max} 3513, 3060, 2925, 1682, 1671, 1624, 1495, 1089, 1009, 735 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{14}Cl_2F_2NaO_2$ $(M+Na)^+$ 417.0231, found 417.0242.



3.27

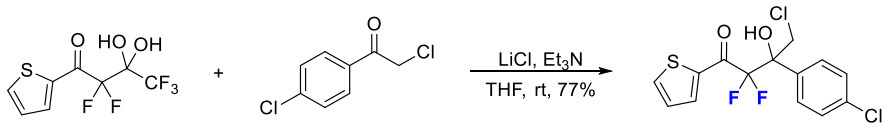
4-chloro-2,2-difluoro-3-hydroxy-3-methyl-1-(naphthalen-2-yl)butan-1-one 3.27. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)-butan-1-one (100 mg, 0.312 mmol), chloroacetone (125 µL, 1.56 mmol), and LiCl (66 mg, 1.6 mmol) in THF (500 µL) was treated with Et_3N (53 µL, 0.37 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.27** in 66% yield (68 mg) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.09 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 3.91 (dd, J = 85.3, 11.7 Hz, 2H), 3.09 (s, 1H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (t, J_{CF} = 29.8 Hz, 1C), 136.1, 133.8 (t, J_{CF} = 4.9 Hz, 1C), 132.3, 130.3, 129.6, 128.4, 127.8, 127.1, 125.1, 117.2 (t, J_{CF} = 263.3 Hz, 1C), 75.2 (t, J_{CF} = 24.4 Hz, 1C), 48.7– 48.5 (m, 1C), 19.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –108.9 (d, J_{FF} = 284.0 Hz, 1F), –110.6 (d, J_{FF} = 284.0 Hz 1F); IR (film) ν_{max} 3361, 2924, 2853, 1686, 1662, 1625, 1494, 1109, 762, 747 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}ClF_2O_2$ $(M+H)^+$ 299.0645, found 299.0623.



3.28

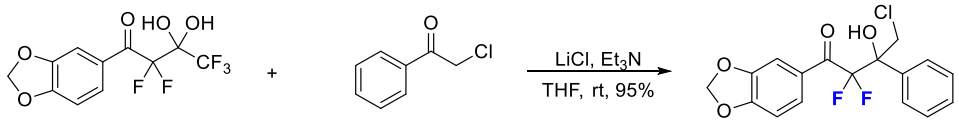
4-chloro-1-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-3-methylbutan-1-one 3.28. See representative reaction procedure. A solution of 1-(4-chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (65 mg, 0.21 mmol), chloroacetone (85 µL, 1.1 mmol), and LiCl (45 mg,

1.1 mmol) in THF (500 μL) was treated with Et_3N (36 μL, 0.26 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.28** in 46% yield (30 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 3.85 (dd, *J* = 83.4, 11.7 Hz, 2H), 2.92 (s, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (t, J_{CF} = 30.3 Hz, 1C), 140.5, 131.2 (t, J_{CF} = 3.7 Hz, 2C), 130.5 (t, J_{CF} = 2.0 Hz, 1C), 128.1 (2C), 122.6–112.1 (m, 1C), 74.1 (t, J_{CF} = 24.7 Hz, 1C), 47.6 (dd, J_{CF} = 4.6, 3.2 Hz, 1C), 18.8 (dd, J_{CF} = 3.8, 2.3 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –109.7 (d, J_{FF} = 281.0 Hz, 1F), –111.4 (d, J_{FF} = 281.1 Hz, 1F); IR (film) ν_{max} 3509, 2929, 2860, 1695, 1589, 1090 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}Cl_2F_2O_2$ $(M+H)^+$ 283.0099, found 283.0095.



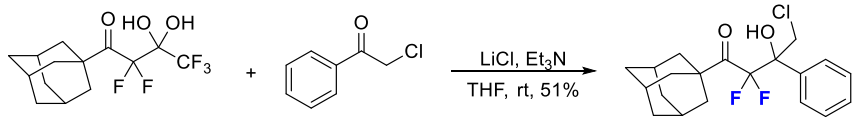
3.29

4-chloro-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-1-(thiophen-2-yl)butan-1-one 3.29. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(thiophen-2-yl)butan-1-one (55 mg, 0.20 mmol), 2,4'-dichloroacetophenone (76 mg, 0.04 mmol), and LiCl (42 mg, 1.0 mmol) in THF (500 μL) was treated with Et_3N (33 μL, 0.24 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.29** in 77% yield (54 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.91 (m, 1H), 7.79 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.39–7.35 (m, 2H), 7.15 (dd, *J* = 4.8, 4.1 Hz, 1H), 4.33–4.24 (m, 2H), 3.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7 (t, J_{CF} = 29.9 Hz, 1C), 139.3, 137.4, 137.1 (dd, J_{CF} = 6.6, 5.2 Hz, 1C), 135.3, 134.4, 128.9, 128.8 (2C), 128.6 (2C), 116.1 (t, J_{CF} = 267.5 Hz, 1C), 78.3 (t, J_{CF} = 24.7 Hz, 1C), 47.9 (t, J_{CF} = 3.6 Hz, 1C);^{19}F NMR (376 MHz, $CDCl_3$) δ –109.0 (d, J_{FF} = 268.6 Hz, 1F), –110.0 (d, J_{FF} = 268.6 Hz, 1F); IR (film) ν_{max} 3493, 3115, 2926, 1666, 1414, 1095, 733 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}Cl_2F_2O_2S$ $(M+H)^+$ 350.9819, found 350.9849.



3.30

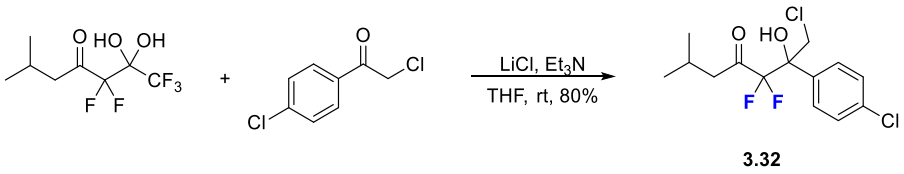
1-(benzo[d][1,3]dioxol-5-yl)-4-chloro-2,2-difluoro-3-hydroxy-3-phenylbutan-1-one 3.30. See representative reaction procedure. A solution of 1-(benzo[d][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (100 mg, 0.318 mmol), 2-chloroacetophenone (98 mg, 0.64 mmol), and LiCl (67 mg, 1.6 mmol) in THF (500 μL) was treated with Et_3N (53 μL, 0.38 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.30** in 95% yield (107 mg) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.1 Hz, 2H), 7.45 (s, 1H), 7.44–7.35 (m, 3H), 6.82 (d, J = 8.4 Hz, 1H), 6.05 (s, 2H), 4.31 (dd, J = 16.6, 11.6 Hz, 2H), 3.63 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.5 (dd, J_{CF} = 29.5, 27.3 Hz, 1C), 153.1, 148.0, 136.0, 129.0, 128.5 (2C), 128.2 (dd, J_{CF} = 5.4, 3.7 Hz, 1C), 127.7, 127.0 (2C), 116.7 (dd, J_{CF} = 265.9, 263.2 Hz, 1C), 110.2 (dd, J_{CF} = 4.1, 2.8 Hz, 1C), 108.1, 102.2, 78.5 (t, J_{CF} = 24.8 Hz, 1C), 48.2 (t, J_{CF} = 4.1 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.3 (d, J_{FF} = 272.1 Hz, 1F), –107.6 (d, J_{FF} = 272.1 Hz, 1F); IR (film) ν_{max} 3504, 2911, 1680, 1604, 1444, 1268, 1034, 701 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}Cl_2F_2O_4$ $(M+Cl)^-$ 389.0159, found 389.0162.



3.31

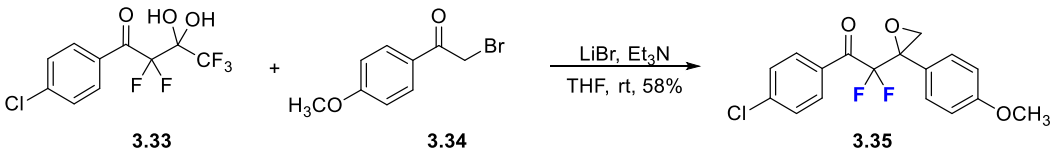
1-((3r,5r,7r)-adamantan-1-yl)-4-chloro-2,2-difluoro-3-hydroxy-3-phenylbutan-1-one 3.21. See representative reaction procedure. A solution of 1-((3r,5r,7r)-adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (100 mg, 0.304 mmol), 2-chloroacetophenone (94 mg, 0.61 mmol), and LiCl (65 mg, 1.5 mmol) in THF (500 μL) was treated with Et_3N (51 μL, 0.37 mmol).

SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.21** in 51% yield (57 mg) as a colorless solid: 102–103 mp °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.43–7.33 (m, 3H), 4.24 (dd, *J* = 28.4, 11.7 Hz, 2H), 4.08 (s, 1H), 1.98 (s, 3H), 1.83–1.74 (m, 6H), 1.73–1.58 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5 (dd, J_{CF} = 29.2, 24.3 Hz, 1C), 136.3, 128.9, 128.5 (2C), 127.1 (2C), 119.1–113.1 (m, 1C), 77.0 (t, J_{CF} = 23.7 Hz, 1C), 48.0 (t, J_{CF} = 4.1 Hz, 1C), 36.7 (d, J_{CF} = 2.2 Hz, 3C), 36.4 (3C), 27.7 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.7 (d, J_{FF} = 282.3 Hz, 1F), –111.2 (d, J_{FF} = 282.0 Hz, 1F); IR (film) ν_{max} 3506, 2912, 2856, 1716, 1452, 1075, 773 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}ClF_2NaO_2$ $(M+Na)^+$ 391.1252, found 391.1230.



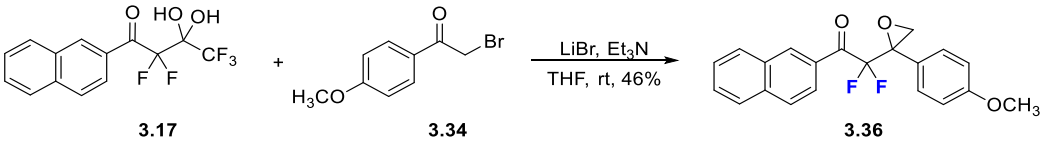
3.32

1-chloro-2-(4-chlorophenyl)-3,3-difluoro-2-hydroxy-6-methylheptan-4-one 3.22. See representative reaction procedure. A solution of 1,1,1,3,3-pentafluoro-2,2-dihydroxy-6-methylheptan-4-one (75 mg, 0.30 mmol), 2,4'-dichloroacetophenone (108 mg, 0.598 mmol), and LiCl (63 mg, 1.5 mmol) in THF (500 μL) was treated with Et_3N (50 μL, 0.36 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.22** in 80% yield (70 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 4.17 (dd, *J* = 34.2, 12.0 Hz, 2H), 3.14 (s, 1H), 2.58–2.41 (m, 2H), 2.18–2.03 (m, 1H), 0.87 (dd, *J* = 6.4, 2.6 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1 (t, J_{CF} = 29.1, 28.0 Hz, 1C), 135.3, 134.3, 128.8 (2C), 128.3 (2C), 114.7 (t, J_{CF} = 264.1 Hz, 1C), 78.1 (t, J_{CF} = 24.9 Hz, 1C), 48.0 (t, J_{CF} = 3.8 Hz, 1C), 47.7, 23.5, 22.4, 22.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1 (d, J_{FF} = 263.0 Hz, 1F), –115.9 (d, J_{FF} = 262.6 Hz, 1F); IR (film) ν_{max} 3514, 2965, 2930, 1741, 1496, 1097, 372 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}Cl_3F_2O_2$ $(M+Cl)^-$ 359.0184, found 359.0205.



3.33 3.34 3.35

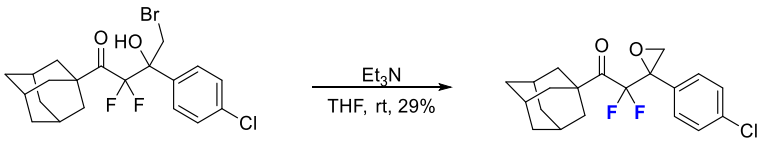
1-(4-chlorophenyl)-2,2-difluoro-2-(2-(4-methoxyphenyl)oxiran-2-yl)ethan-1-one 3.35. See representative reaction procedure. A solution of 1-(4-chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (75 mg, 0.25 mmol), 2-bromo-4′-methoxyacetophenone (65 mg, 0.49 mmol), and LiBr (107 mg, 1.23 mmol) in THF (500 μL) was treated with Et_3N (41 μL, 0.30 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.35** in 58% yield (48 mg) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.79 (s, 2H), 3.42 (d, J = 5.2 Hz, 1H), 2.93 (d, J = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5 (t, J_{CF} = 28.9 Hz, 1C), 160.3, 141.2, 131.8 (t, J_{CF} = 3.1 Hz, 2C), 131.1, 129.3 (2C), 129.1 (2C), 124.1, 116.6 (dd, J_{CF} = 261.0, 257.6 Hz, 1C), 114.0 (2C), 59.1 (dd, J_{CF} = 32.0, 28.9 Hz, 1C), 55.4, 51.2 (dd, J_{CF} = 3.9, 2.6 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –104.88 (d, J_{FF} = 270.8 Hz, 1F), –107.50 (d, J_{FF} = 270.8 Hz, 1F); IR (film) ν_{max} 3418, 2965, 2844, 1675, 1601, 1256, 1093 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}ClF_2O_3$ $(M+H)^+$ 339.0594, found 339.0603.



3.17 3.34 3.36

2,2-difluoro-2-(2-(4-methoxyphenyl)oxiran-2-yl)-1-(naphthalen-2-yl)ethan-1-one 3.36. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **3.17** (200 mg, 0.624 mmol), 2-bromo-4′-methoxyacetophenone **3.34** (347 mg, 1.25 mmol), and LiBr (270 mg, 3.12 mmol) in THF (500 μL) was treated with Et_3N (104 μL, 0.749 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.36** in

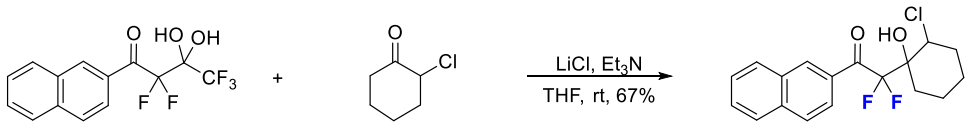
46% yield (101 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.00 (t, *J* = 9.2 Hz, 2H), 7.91–7.83 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 8.6, 1.6 Hz, 2H), 6.87 (dd, *J* = 8.9, 2.1 Hz, 2H), 3.78 (d, *J* = 2.2 Hz, 2H), 3.52 (dd, *J* = 5.3, 2.1 Hz, 1H), 3.00–2.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (t, J_{CF} = 28.6 Hz, 1C), 160.3, 136.1, 133.3 (t, J_{CF} = 4.0 Hz, 1C), 132.3, 130.3, 130.0, 129.5, 129.4 (2C), 128.5, 127.8, 127.1, 124.9, 124.4, 116.8 (dd, J_{CF} = 260.7, 256.9 Hz, 1C), 113.9 (2C), 59.3 (dd, J_{CF} = 32.0, 28.6 Hz, 1C), 55.4, 51.3 (dd, J_{CF} = 3.9, 2.6 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –104.61 (d, J_{FF} = 270.4 Hz, 1F), –107.18 (d, J_{FF} = 270.3 Hz, 1F); IR (film) ν_{max} 3062, 2934, 1697, 1516, 1250, 1120 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}F_2O_3$ $(M+H)^+$ 355.1140, found 355.1147.



3.24 **3.37**

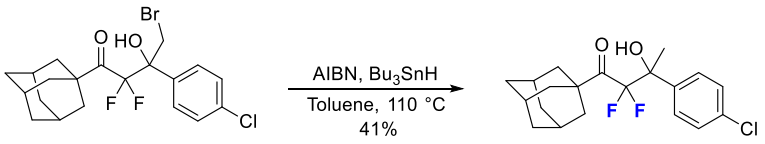
1-((3r,5r,7r)-adamantan-1-yl)-3-(4-chlorophenyl)-2,2-difluoro-3-hydroxybutan-1-one 3.37. To a solution of bromohydrin **3.24** (25 mg, 0.056 mmol) in THF (1 ml), Et_3N (23 µL, 0.17 mmol) was added dropwise. The reaction was stirred for 24 hours at rt. The mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (4:1 hexanes/ CH_2Cl_2) afforded the product **3.37** in 29% yield (6 mg) as a solid: mp 88-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 3.32 (d, *J* = 5.2 Hz, 1H), 2.82 (dt, *J* = 4.4, 1.7 Hz, 1H), 2.01 (s, 1H), 1.95–1.76 (m, 6H), 1.69 (q, *J* = 12.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0 (t, J_{CF} = 26.6 Hz, 1C), 135.2, 131.5, 129.6 (2C), 128.7 (2C), 116.8 (t,

J_{CF} = 261.8 Hz, 1C), 59.2 (t, J_{CF} = 29.7 Hz, 1C), 50.7 (t, J_{CF} = 3.7 Hz, 1C), 46.7 (t, J_{CF} = 2.1 Hz, 1C), 36.9 (3C), 36.4 (3C), 27.7 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.0 (s, 2F); IR (film) ν_{max} 3501, 2912, 2856, 1706, 1454, 1093 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}Cl_2F_2O_2$ $(M+Cl)^-$ 403.1043, found 403.1070.



3.17 **3.40** **3.41**

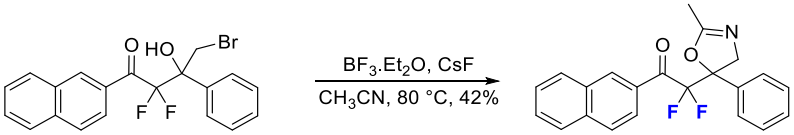
2-(2-chloro-1-hydroxycyclohexyl)-2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one 3.41. See representative reaction procedure. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **3.17** (100 mg, 0.312 mmol), chlorocyclohexanone **3.40** (178 µL, 1.56 mmol), and LiCl (66 mg, 1.6 mmol) in THF (500 µL) was treated with Et_3N (53 µL, 0.37 mmol). SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.41** in 67% yield (106 mg) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.07 (d, *J* = 8.9 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.89 (t, *J* = 8.4 Hz, 2H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 4.45 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.60 (d, *J* = 2.1 Hz, 1H), 2.14 (d, *J* = 13.9 Hz, 1H), 2.10– 1.98 (m, 2H), 1.76 (t, *J* = 15.4 Hz, 2H), 1.70–1.59 (m, 2H), 1.41 (d, *J* = 16.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6 (dd, J_{CF} = 30.7, 28.7 Hz, 1C), 136.0, 133.4 (dd, J_{CF} = 6.3, 4.0 Hz, 1C), 132.4, 131.1, 130.3, 129.5, 128.5, 127.9, 127.1, 125.5–125.4 (m, 1C), 117.0 (dd, J_{CF} = 264.8, 261.9 Hz, 1C), 76.7 (t, J_{CF} = 23.6 Hz, 1C), 33.1, 31.3 (dd, J_{CF} = 2.8, 2.9 Hz, 1C), 29.9–29.8 (m, 1C), 19.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ –108.7 (d, J_{FF} = 279.0 Hz, 1F), –110.5 (d, J_{FF} = 278.8 Hz, 1F); IR (film) ν_{max} 2474, 2944, 2867, 1720, 1626, 1449, 1114, 758 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}Cl_2NaO_2$ $(M+Na)^+$ 361.0777, found 361.0764.



3.24 3.42

1-((3r,5r,7r)-adamantan-1-yl)-2-(2-(4-chlorophenyl)oxiran-2-yl)-2,2-difluoroethan-1-one

3.42. A solution of bromohydrin **3.24** (50 mg, 0.11 mmol) and Bu_3SnH (36 µL, 0.134 mmol) in toluene (5 ml) was heated to 110 °C, then AIBN (1 mg, 0.06 mmol) was added and the reaction was stirred for 16 hours. The mixture was concentrated under reduced pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.42** in 41% yield (17 mg) as a solid: mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.7 Hz, 1H), 4.34 (s, 1H), 1.99 (s, 3H), 1.86–1.68 (m, 9H), 1.67–1.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8 (dd, J_{CF} = 30.7, 27.5 Hz, 1C), 139.1 (d, J_{CF} = 2.6 Hz, 1C), 134.0, 128.2 (2C), 127.9 (2C), 115.5 (t, J_{CF} = 267.4 Hz, 1C), 76.5 (t, J_{CF} = 24.2 Hz, 1C), 36.7 (3C), 36.2 (3C), 29.7, 27.5 (3C), 23.5 (dd, J_{CF} = 3.7, 2.4 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –108.79 (d, J_{FF} = 293.6 Hz, 1F), –112.87 (d, J_{FF} = 294.5 Hz, 1F); IR (film) ν_{max} 2912, 2853, 1720, 1498, 1092 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}ClF_2NaO_2$ $(M+Na)^+$ 389.1096, found 389.1090.



3.19 3.43

2,2-difluoro-2-(2-methyl-5-phenyl-4,5-dihydrooxazol-5-yl)-1-(naphthalen-2-yl)ethan-1-one

28. To a solution of bromohydrin **3.19** (140 mg, 0.388 mmol) and CsF (314 mg, 1.94 mmol) in CH_3CN (5 ml), $BF_3.Et_2O$ (239 µL, 1.94 mmol) was added dropwise. The reaction was stirred for 16 hours at 80 °C. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organics were dried over Na_2SO_4 and concentrated under reduced

pressure. SiO_2 flash chromatography (19:1 hexanes/EtOAc) afforded the product **3.43** in 42% yield (60 mg) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.96–7.76 (m, 4H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.0 Hz, 3H), 7.37–7.27 (m, 3H), 5.24 (d, *J* = 9.3 Hz, 1H), 4.57 (d, *J* = 9.3 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3 (t, J_{CF} = 29.1 Hz, 1C), 168.0, 139.1, 135.9, 133.6 (t, J_{CF} = 4.9 Hz, 1C), 132.2, 130.9, 130.3, 129.3, 128.6, 128.5 (2C), 128.1, 128.0 (2C), 127.8, 126.9, 125.3, 117.9 (t, J_{CF} = 262.8 Hz, 1C), 80.4 (t, J_{CF} = 23.0 Hz, 1C), 74.7 (t, J_{CF} = 3.6 Hz, 1C), 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.27 (d, J_{FF} = 264.4 Hz, 1F), –109.16 (d, J_{FF} = 264.8 Hz, 1F); IR (film) ν_{max} 3318, 2924, 1663, 1275, 1112, 749 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{26}F_2NaO_2$ $(M+Na)^+$ 383.1793, found 383.1796.

CHAPTER 4

FLUORINATED BIOLOGICAL TAGS

4.1. Fluorinated Antibody-Drug Conjugates

Despite the large strides in cancer research, treating cancer remains one of the major challenges facing mankind. Cancer is among the leading causes of death worldwide; it's responsible for 1 in 6 deaths globally.[177] Approximately 40% of people will be diagnosed with cancer during their lifetime. Efforts to treat cancer are often limited by the high toxicity of the small molecules used in chemotherapy. One approach to address this issue is through the use of antibody-drug conjugates (ADCs). These conjugates are comprised of a highly cytotoxic agent linked to an antibody that preferentially target cancer cells. ADCs utilize the targetability of antibodies in delivering the anticancer drug selectively to the cancerous cells; thus, reducing the dose-limiting toxicities while at the same time increasing the therapeutic effect. The concept of ADCs can also be employed in other diseases.

In 2000, Mylotarg was granted expedited approval by the FDA to become the first ADC to enter the market.[179] It was marketed for the treatment of acute myeloid leukemia and remained the only ADC on the market until 2010 when it was voluntarily withdrawn due to concerns about safety and clinical benefits. In 2017, Mylotarg was reapproved by the FDA for the same indication but with a new dosing regimen.

The second and third ADCs to be approved by the FDA were Adcetris in 2011 and Kadcyla in 2013. Adcetris is used to treat Hodgkin lymphoma and systemic anaplastic large cell lymphoma, and Kadcyla for the treatment of HER2-positive breast cancer.[179] The latest addition to the list of marketed ADCs came in 2017, when Besponsa was approved for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

Linkers are an important part of the ADC structure, they connect the drug to the carrier antibody (**Figure 4.1**). ADC linkers can be cleavable or non-cleavable under physiological conditions. ADCs containing non-cleavable linkers release the drug through the degradation of the antibody following its internalization into the cancer cell. These linkers provide higher stability in plasma, but their efficacy might be restricted by the limitations of the "bystander" effect.[182] On the other hand, cleavable linkers release the drug by chemical or enzymatic degradation of the linker.[183] The chemically labile linkers usually contain a hydrazone functional group or a disulfide group. The hydrazine group is hydrolyzed at the acidic pH found in the lysosomal and endosomal compartments of the tumor tissue while being stable in the slightly basic plasma and cytosol, and the disulfide-based linkers release the drug upon reduction by glutathione. On the other hand, the enzymatically cleavable linkers contain a dipeptide moiety, typically a valine-citrulline dipeptide, that is susceptible to hydrolysis by proteases in the tumor cells.[184]

Figure 4.1. Antibody-drug conjugates structure

ADCs realize Paul Ehrlich's theory of the “magic bullet” drug. They deliver the drug with high specificity to the site of action, reducing the possible side effects of highly toxic therapeutic agents in many anticancer treatments. With several ADCs on the market and over 60 ADCs in clinical trials, means to monitor their efficiency, strength and quality become necessary. This is especially important since most ADCs are generated through non-specific conjugation between the drug and the antibody. This non-specific conjugation results in heterogeneous mixtures where one antibody can carry a variable number of drug molecules. The different ADC species in this heterogeneous mixture have different physico-chemical properties, and as a result, different efficacies.

The chemistry of ADC linkers has been gaining a lot of interest recently. The successful and selective cleavage of the linker is essential for the function of ADCs. In addition to their traditional role, linkers can provide a handle for tagging ADCs. The incorporation of fluorine into linkers minimally affect the sterics of the linker owing to the small size of fluorine atom, while at the same time providing an observable tag. Fluorinated ADC linkers provide a means to validate the stability of the ADC in circulation *in vivo* and the effective degradation at the site of action. Fluorinated linkers allow the facile evaluation of the stability of ADCs in formulation as well as the rate of release of the drug from the conjugate. Methods like ^{19}F NMR and PET scans can be integrated in this approach.

^{19}F nucleus occurs at 100% natural abundance; which accounts for the high sensitivity of ^{19}F NMR. ^{19}F NMR spectra are well resolved with a chemical shift range that is 100-fold larger than that of ^{1}H. Due to the great sensitivity of the chemical shifts in ^{19}F NMR to the local electrostatic field, minor changes in the structure of the molecule can be easily detected in the ^{19}F NMR spectra. These characteristics distinguish ^{19}F NMR as a valuable analytical tool. ^{19}F NMR

is ideal for studying fluorinated molecules *in vitro* and *in vivo* without any interfering background signal, since ^{19}F does not occur naturally in biological systems.[185] We aim to monitor drug release from ADC using ^{19}F NMR. As the linker is being hydrolyzed, the peak for the ADC bound linker will start to disappear and that of the free linker will start to be observed. By using the integration of the peaks in reference to the integration of the internal standard (trifluorotoluene) we can quantitatively measure the release of the drug over time.

4.1.1. Design and Synthesis of Fluorinated Antibody-Drug Conjugates

This linker is comprised of a maleimidocaproyl (mc) group linking the antibody to the enzymatically cleavable valine-citrulline (vc) moiety, which in turn is linked to the drug through a *p*-aminobenzyl alcohol (PABA) spacer (**Figure 4.2-a**). The linker is modified to contain fluorine at both sides of the linker; at the antibody side and the drug side. Two fluorine atoms are introduced on the mc group to monitor the release of the antibody and a trifluoromethyl (CF_3) group is introduced on the PABA group to monitor the release of the drug (**Figure 4.2-b**). Furthermore, for the initial studies we opted to use 5-fluorouracil, a fluorinated chemotherapeutic agent, to allow tracking of the drug itself using ^{19}F NMR.

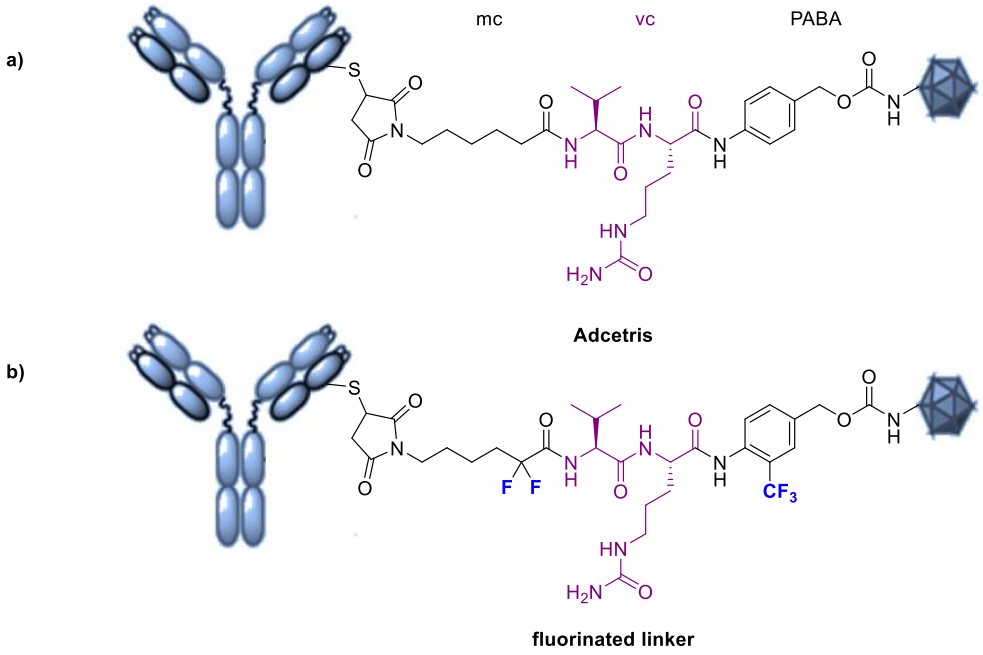
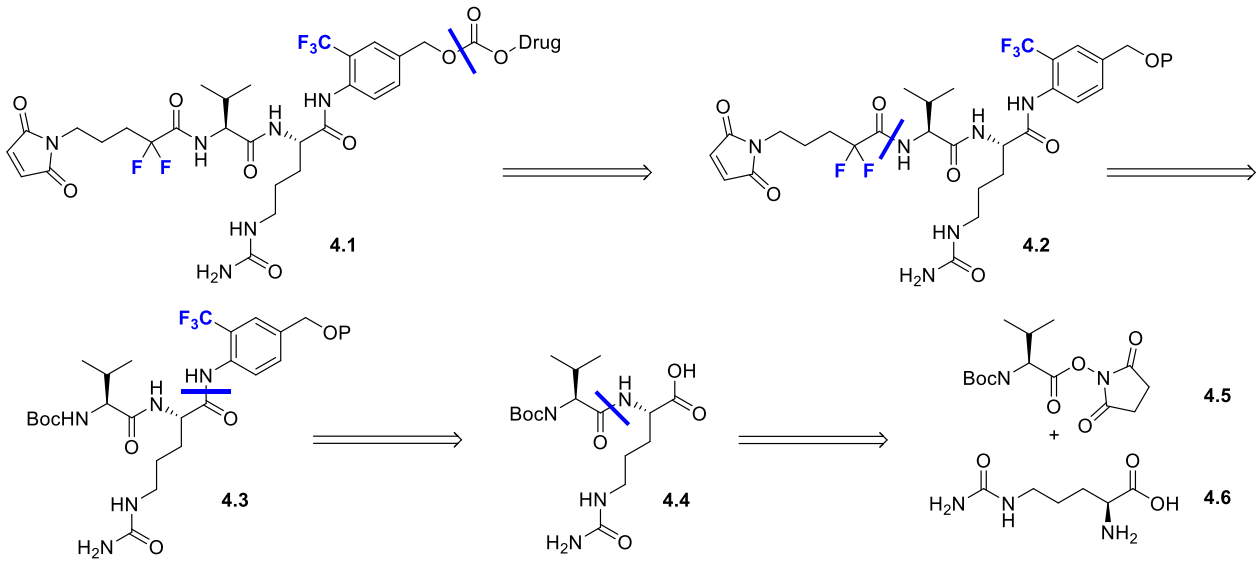


Figure 4.2. The structures of: a) the Adcetris linker and, b) its fluorinated analogue

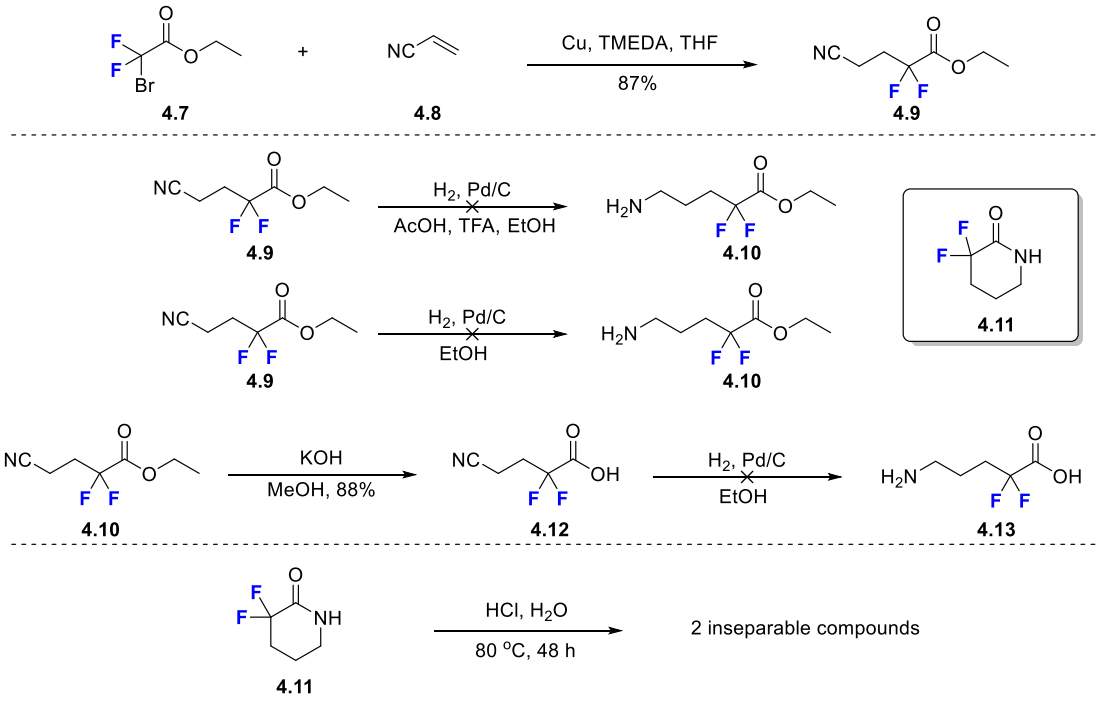
4.1.2. First Approach Towards Synthesis of Fluorinated Antibody-Drug Conjugates

Our retrosynthetic analysis started with disconnecting the drug from the linker. This was followed by disconnecting the mc group, then the PABA group. Finally, the dipeptide was disconnected to the commercially available amino acids (**Scheme 4.1**).



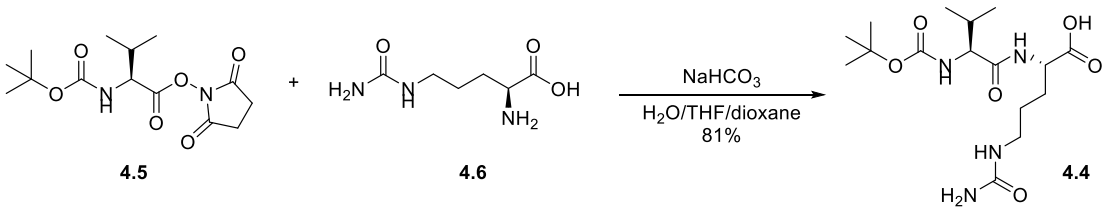
Scheme 4.1. Retrosynthetic analysis of the fluorinated linker

The synthesis of the linker commenced with the construction of the mc group. A copper-mediated coupling reaction between ethyl bromodifluoroacetate (**4.7**) and acrylonitrile (**4.8**) afforded compound **4.9** in 87% yield (**Scheme 4.2**).[186] Next, we attempted to reduce the nitrile group to the corresponding amine (**4.10**). Using palladium catalyzed hydrogenation under acidic conditions successfully reduced the nitrile but unfortunately the product proceeded to cyclize to give rise to the lactam (**4.11**). Carrying the same transformation under neutral conditions resulted in cyclization as well. To reduce the unwanted cyclization, we reduced the ester in compound **4.10** to the corresponding carboxylic acid **4.12** then attempted the hydrogenation reaction, but yet again the major product was the lactam **4.11**. Since we haven't been able to avoid the formation of compound **4.11**, we tried next to hydrolyze it to the uncyclized form, but this resulted in a mixture of 2 inseparable products. In view of the difficulty we faced in accessing the amine, we decided to move forward with compound **4.12**.

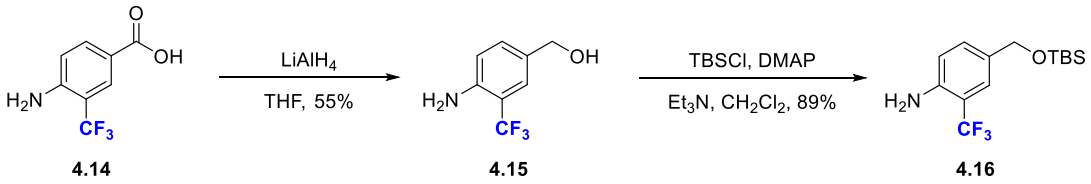


Scheme 4.2. Synthesis of the mc group

Next, we proceeded to couple the boc-protected valine **4.5** with citrulline (**4.6**) to make the vc dipeptide **4.4** (**Scheme 4.3**). this reaction proceeded in 81% yield, and no epimerization was observed. On the other hand, the fluorinated PABA group was synthesized by reducing 4-amino-3-(trifluoromethyl)benzoic acid (**4.14**) to the alcohol **4.15**, which was then protected with a *tert*-butyldimethylsilyl group to give rise to compound **4.16** (**Scheme 4.4**).

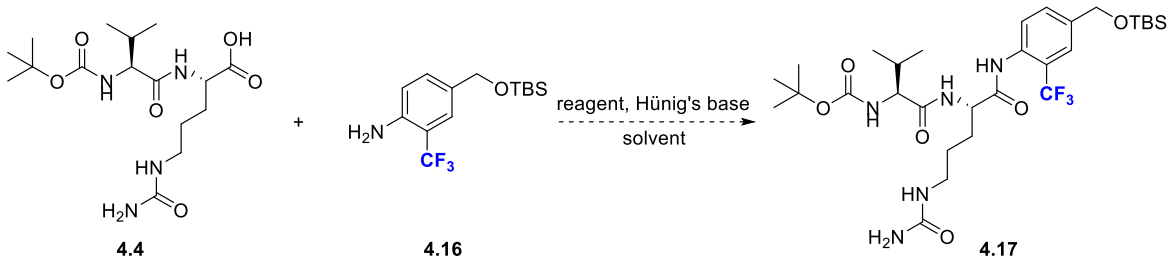


Scheme 4.3. Synthesis of the vc dipeptide



Scheme 4.4. Synthesis of the protected trifluoromethylated PABA group

Once we had compounds **4.4** and **4.16** on hand we attempted amide coupling reaction to access compound **4.17** (**Scheme 4.5**). We first attempted to use *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EDQQ) as a coupling reagent and Hünig's base in CH_2Cl_2/MeOH for 24 h, these conditions failed to produce the desired product. Next, we tried HATU as a coupling reagent but again we were not successful in generating compound **4.17**. Increasing reaction time to 72 as well as using DMF as solvent didn't help. Next, we screened other coupling reagents, including DCC/HOBt, EDC/HOBt and DIC/HOBt but none of them provided the desired product.

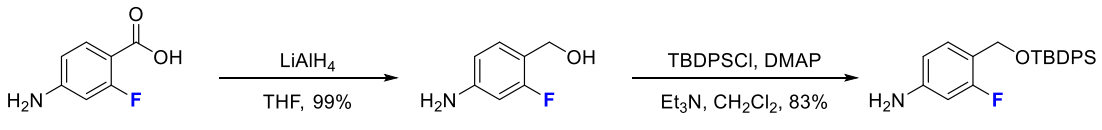


4.4 4.16 4.17

entry	reagent	solvent	time
1	EEDQ	CH_2Cl_2/MeOH	24 h
2	HATU	CH_2Cl_2	24 h
3	EEDQ	CH_2Cl_2/MeOH	72 h
4	HATU	CH_2Cl_2	72 h
5	HATU	DMF	72 h
6	DCC, HOBt	DMF	72 h
7	EDC, HOBt	DMF	72 h
8	DIC, HOBt	DMF	72 h

Scheme 4.5. Attempted coupling of trifluoromethylated PABA to the vc dipeptide

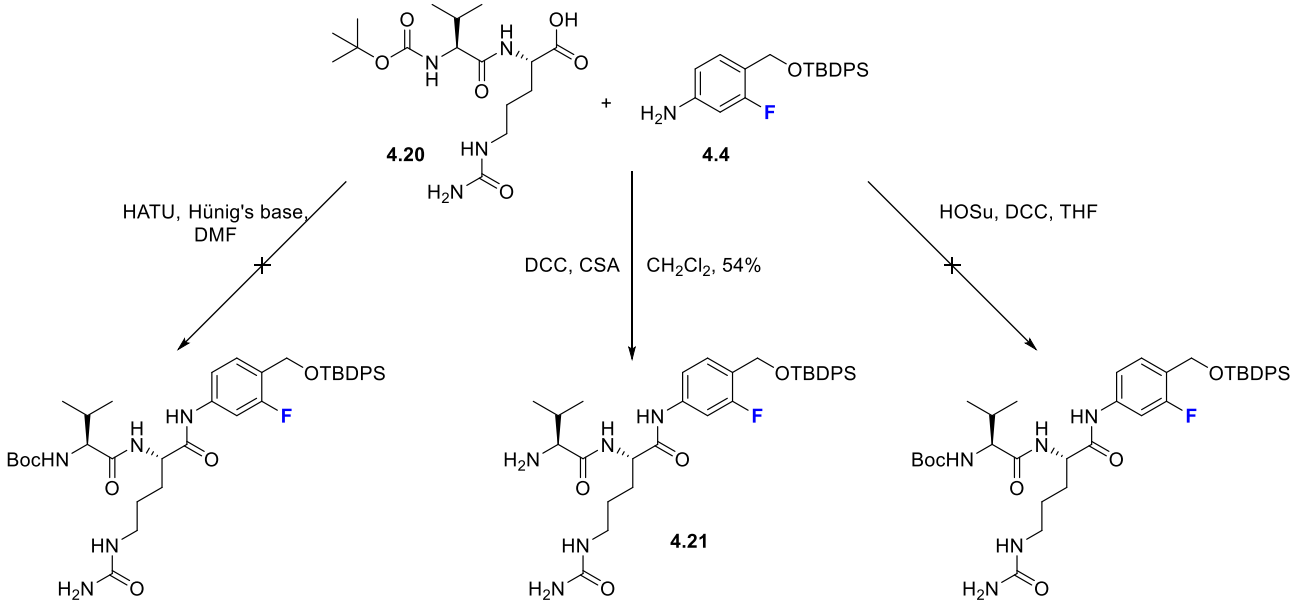
We believed that the steric hindrance of the CF_3 group and its proximity to the reaction site could have prevented the successful coupling of PABA to the vc peptide. To address this issue, we decided to use one fluorine atom instead of the CF_3 group and to place it at the meta position. The reduction of 4-amino-2-fluorobenzoic acid (**4.18**) using $LiAlH_4$ followed by protection of the alcohol using TBDPSCl afforded the protected monofluorinated PABA (**4.20**) (**Scheme 4.6**).



4.18 4.19 4.20

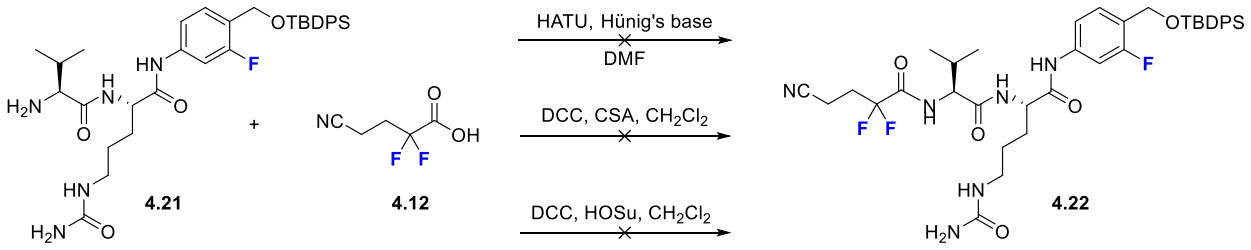
Scheme 4.6. Synthesis of the protected monofluorinated PABA group

Once we had compound **4.20**, we tried to couple it to the vc dipeptide **4.4**. Neither using HATU coupling reagent nor using *N*-hydroxysuccinimide (HOSu) provided the desired coupling product (**Scheme 4.7**). Fortunately, using DCC under acidic conditions provided the coupled product but at the same time removed the Boc protecting group. This transformation accomplished two steps in one pot, and with compound **4.21** in hand we could move forward with the synthesis.



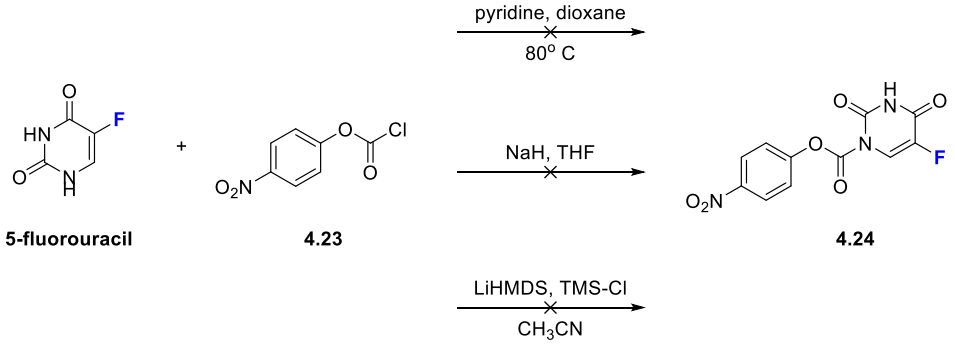
Scheme 4.7. Coupling of monofluorinated PABA to the vc dipeptide

The next step in the synthesis is to couple compound **4.21** to the fluorinated mc analogue **4.12** (**Scheme 4.8**). The conditions screened for this step were, HATU with Hünig's base, DCC under acidic conditions, and DCC with HOSu. None of these conditions resulted in the desired coupling.



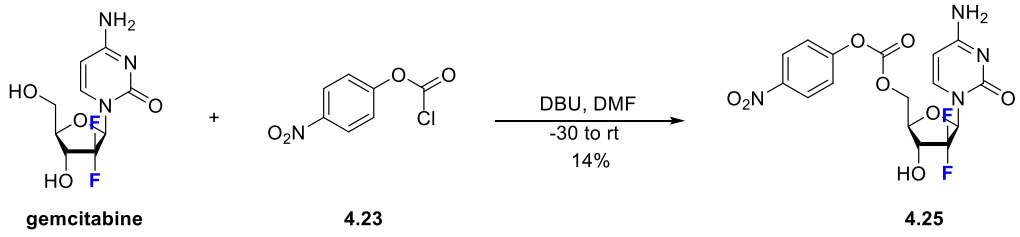
Scheme 4.8. Coupling of mc fluorinated analogue to the vc-PABA fragment

The last fragment of the synthesis is the addition of the chemotherapeutic agent 5-fluorouracil.This agent needs to be activated to be able to couple to the linker. To activate it, we attempted to couple it to 4-nitrophenyl chloroformate (**4.23**) using various bases but in all cases only starting material was recovered (**Scheme 4.9**). The relative low reactivity of 5-fluorouracil coupled with the instability of the chloroformate **4.23** are the possible reasons behind the failure of this reaction.



Scheme 4.9. Coupling of 4-nitrophenyl chloroformate to 5-fluorouracil

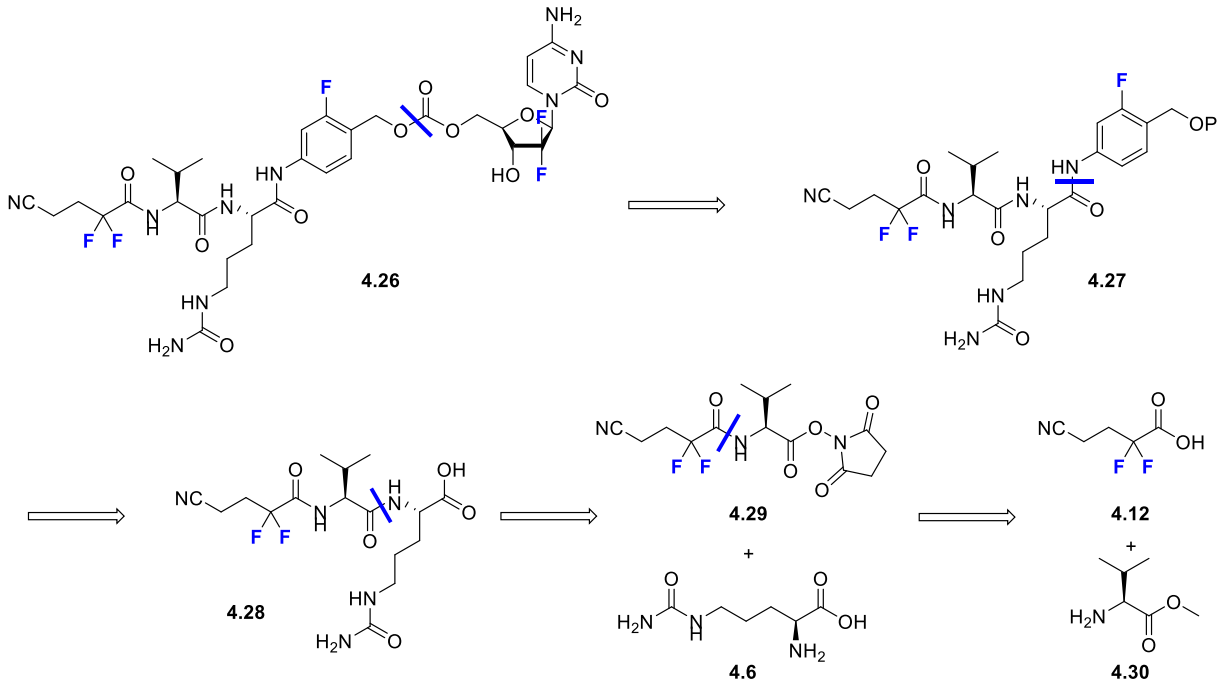
Since 5-fluorouracil wasn't ideal for our synthetic route, we decided to use another fluorinated chemotherapeutic agent, gemcitabine. The coupling of gemcitabine with the chloroformate **4.23** proceeded in low yields of compound **4.25** (Scheme **4.10**)). In this reaction, satisfactory conversion was observed by TLC but when purification by chromatography was attempted low yields resulted, possibly due to instability of the product on silica. Hence, for the purposes of our synthesis the crude mixture of this reaction will be carried forward to the next step.



Scheme 4.10. Coupling of 4-nitrophenyl chloroformate to gemcitabine

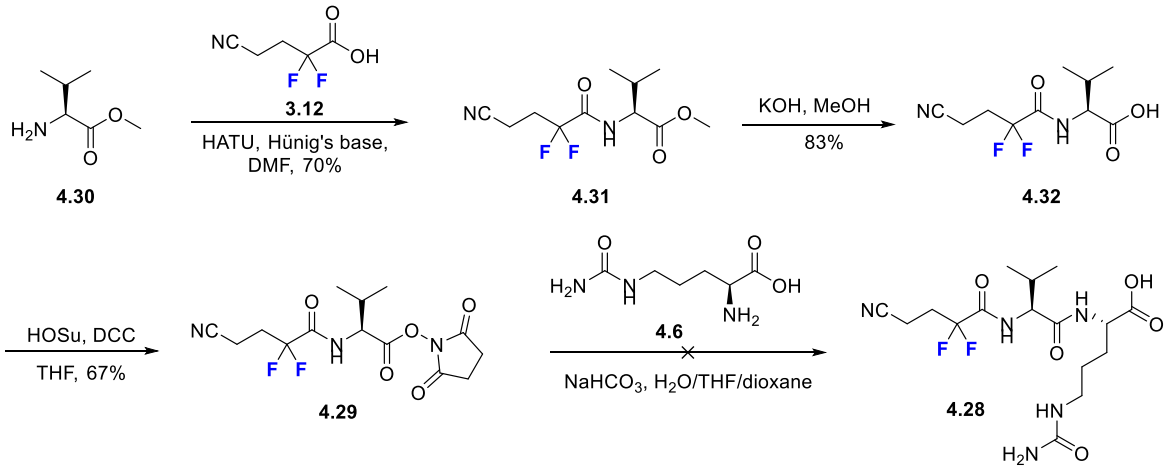
4.1.3. Second Approach Towards Synthesis of Fluorinated Antibody-Drug Conjugates

To address the issue with coupling the fluorinated mc analogue **4.12** to the rest of the linker we decided to modify our synthetic route to carry this step early in the synthesis. For this alternative approach, we disconnect gemcitabine from the linker first, next we disconnect the monofluorinated PABA group (**Scheme 4.11**). The next disconnection is of the citrulline amino acid and lastly valine is disconnected from the mc analogue **4.12**.



Scheme 4.11. Second approach towards synthesis of fluorinated linker

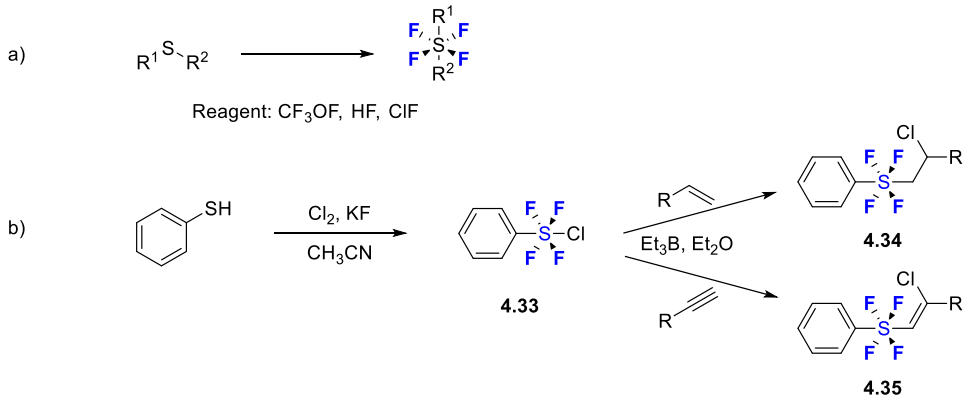
The synthesis started with a coupling reaction of the mc analogue **4.12** with valine methyl ester (**4.30**), which proceeded in 35% yield (**Scheme 4.12**). The methyl ester was next saponified to the give the carboxylic acid **4.32** in 82% yield. The carboxylic acid was activated by coupling it to HOSu to produce **4.29** in 67% yield. The attempt to couple the activated carboxylic acid **4.29** to citrulline was unsuccessful.



Scheme 4.12. Synthesis of fluorine tagged vc dipeptide

4.2. Tetrafluorosulfanyl Group

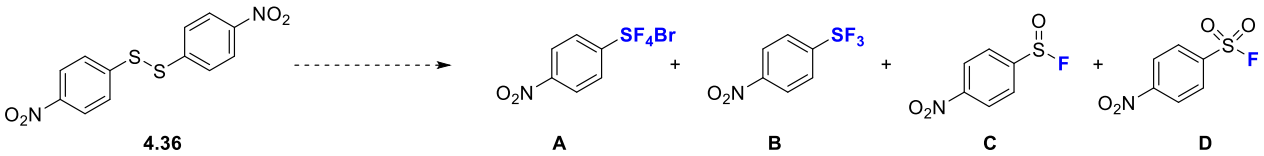
The tetrafluorosulfanyl (SF_4) group is a novel, highly fluorinated group with potential applications in medicinal chemistry and as fluorinated probes. Typically, this group is synthesized through fluorination of sulfides using hydrofluoric acid or other similar fluorine sources (**Scheme 4.13a**).[187] These conditions usually results in over-fluorination due to the use of harsh fluorinating reagents. A recent advance in the synthesis of SF_4-containing compounds was reported by Umemoto et al. in which thiols or disulfides form chlorotetrafluorosulfanyl (R-SF_4Cl) compounds when treated with chlorine gas and potassium fluoride.[188] The SF_4Cl group can then react with fluoride salts to form the pentafluorosulfanyl (SF_5) group,[188] or with alkenes or alkynes under radical conditions to form internal SF_4 group (**Scheme 4.13b**).[189-190]



Scheme 4.13. Known synthetic methods of tetrafluorosulfanyl containing compounds

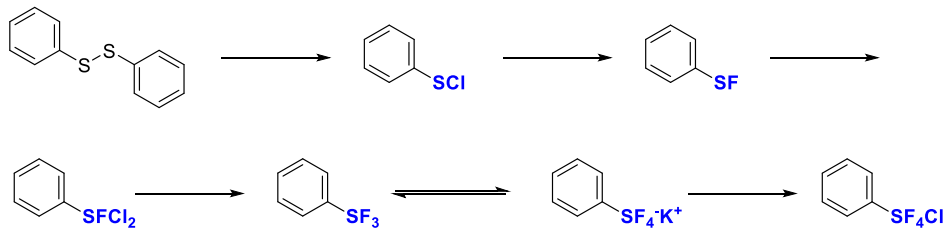
The bromotetrafluorosulfanyl (SF_4Br) group is not known. In an attempt to access this group, we tried using bromine with fluoride salts in an analogous manner to the reported synthesis of the SF_4Cl group. Various attempts with different solvents, sources of fluorine and bromine, different temperatures, use of crown ethers and molecular sieves failed to afford the desired product (**Table 4.1**). In most cases, the major product was the sulfinyl fluoride or the sulfonyl fluoride.

Table 4.1. Conditions used to access the SF_4Br group

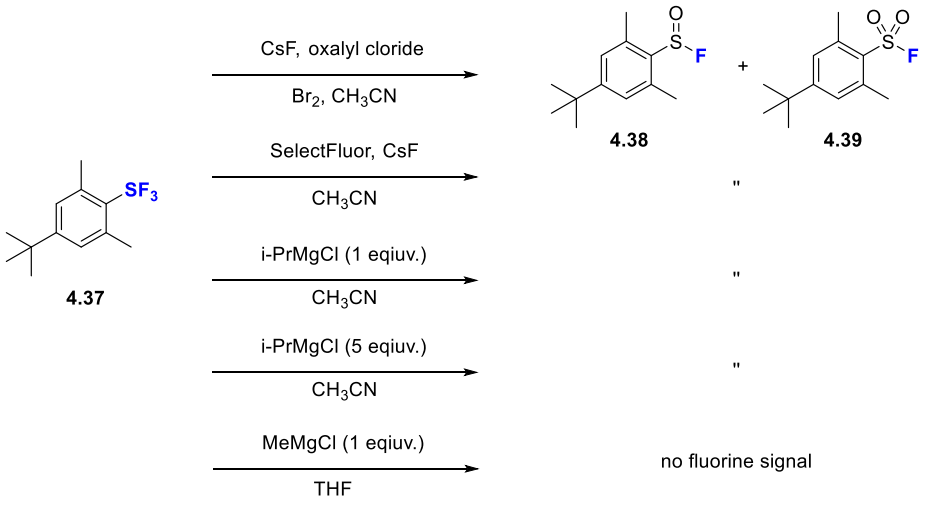


reagent	salt	drying of salt	solvent	product
Br_2	KF	130 °C overnight	CH_3CN	D
Br_2	CsF	130 °C 2 h	CH_3CN	B, C, D
Br_2	CsF	130 °C overnight	CH_3CN	B, C
Br_2	CsF	130 °C overnight,/molecular sieves	CH_3CN	D
Br_2	CsF	130 °C overnight	THF	D
Br_2	CsF	130 °C overnight	dioxane	D
Br_2	CsF	130 °C overnight	CH_2Cl_2	C
Br_2/selecfluor	CsF	130 °C overnight	CH_3CN	C
Selectfluor	CsF	130 °C overnight	CH_3CN	C
Deoxo-Fluor	CsF	130 °C overnight	CH_3CN	C
NFSI	CsF	130 °C overnight	CH_3CN	C
Br_2/crown ether	CsF	130 °C overnight	CH_2Cl_2	C
NBS	CsF	130 °C overnight	CH_2Cl_2	C

Trifluorosulfanyl (SF_3) containing compounds are intermediates in the proposed mechanism of SF_4Cl synthesis (**Scheme 4.14**). Thus, SF_3 compounds provide a good starting point for SF_4Br synthesis. Attempts to further fluorinate these compounds using CsF/oxalyl chloride or CsF/Selectfluor failed. Alternatively, we tried alkylation strategies using Grignard or methyl lithium reagents, these reactions were also unsuccessful (**Scheme 4.15**).

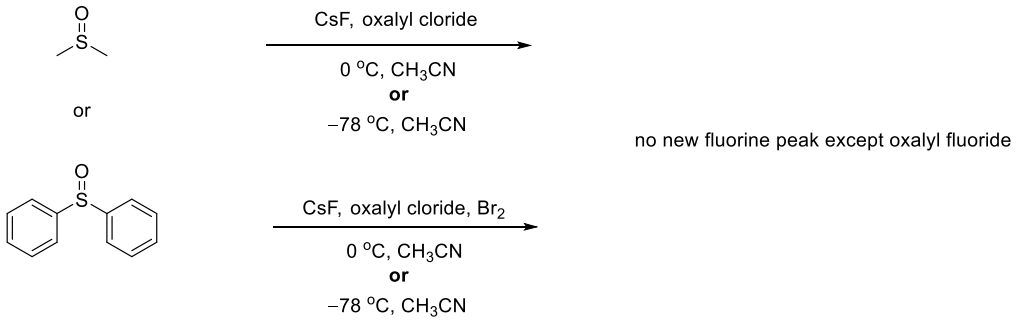


Scheme 4.14. Mechanism of SF_4Cl formation



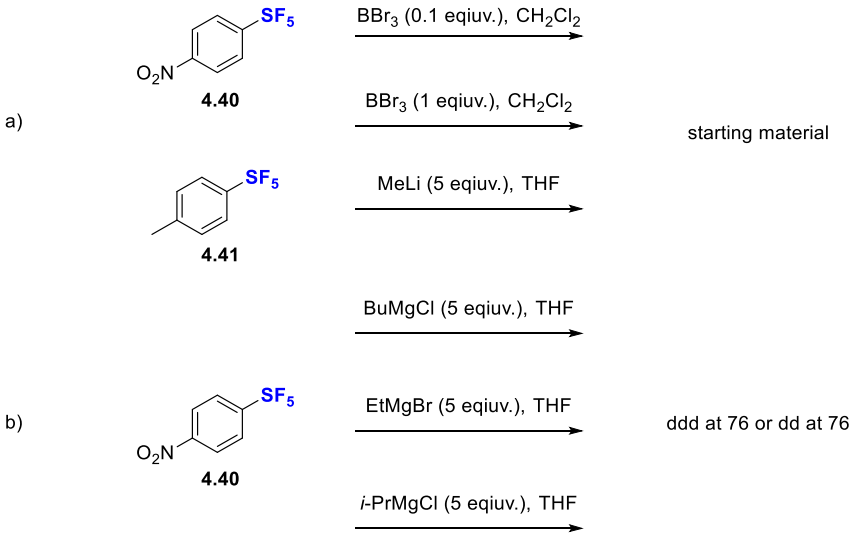
Scheme 4.15. Attempts to fluorinate/alkylate trifluorosulfanyl compounds

Since oxidized sulfurs were the main product in our previous attempts, we endeavored to fluorinate sulfoxides using cesium fluoride and oxalyl chloride in an attempt to replicate the active species observed during sworn oxidation reactions. We tried dimethylsulfoxide and diphenyl sulfoxide in the presence and absence of bromine both at 0 ^{o}C and –78 ^{o}C (**Scheme 4.16**). But in all cases no major fluorinated product was observed.



Scheme 4.16. Attempts to fluorinate sulfoxides

Next, we turned to the pentafluorosulfanyl group and ventured to defluorinate it. Since BBr_3 has been reported to convert CF_3 compounds to CF_2Br compounds,[191] we were curious to see if a similar reaction would take place with SF_5 compounds. Unfortunately, the only observed fluorine signal was that of the starting material (**Scheme 4.17a**). We also tried methyl lithium, but no reaction was observed. Lastly, several Grignard reagents were used, and they resulted in alkylation of the ring of *p*-nitropentafluorosulfanyl benzene but the SF_5 group remained intact (**Scheme 4.17b**). The alkylation of the ring in *p*-nitropentafluorosulfanyl benzene using Grignard reagents has been reported by Beier and Vida.[192]



Scheme 4.17. Attempts to defluorinate pentafluorosulfanyl compounds

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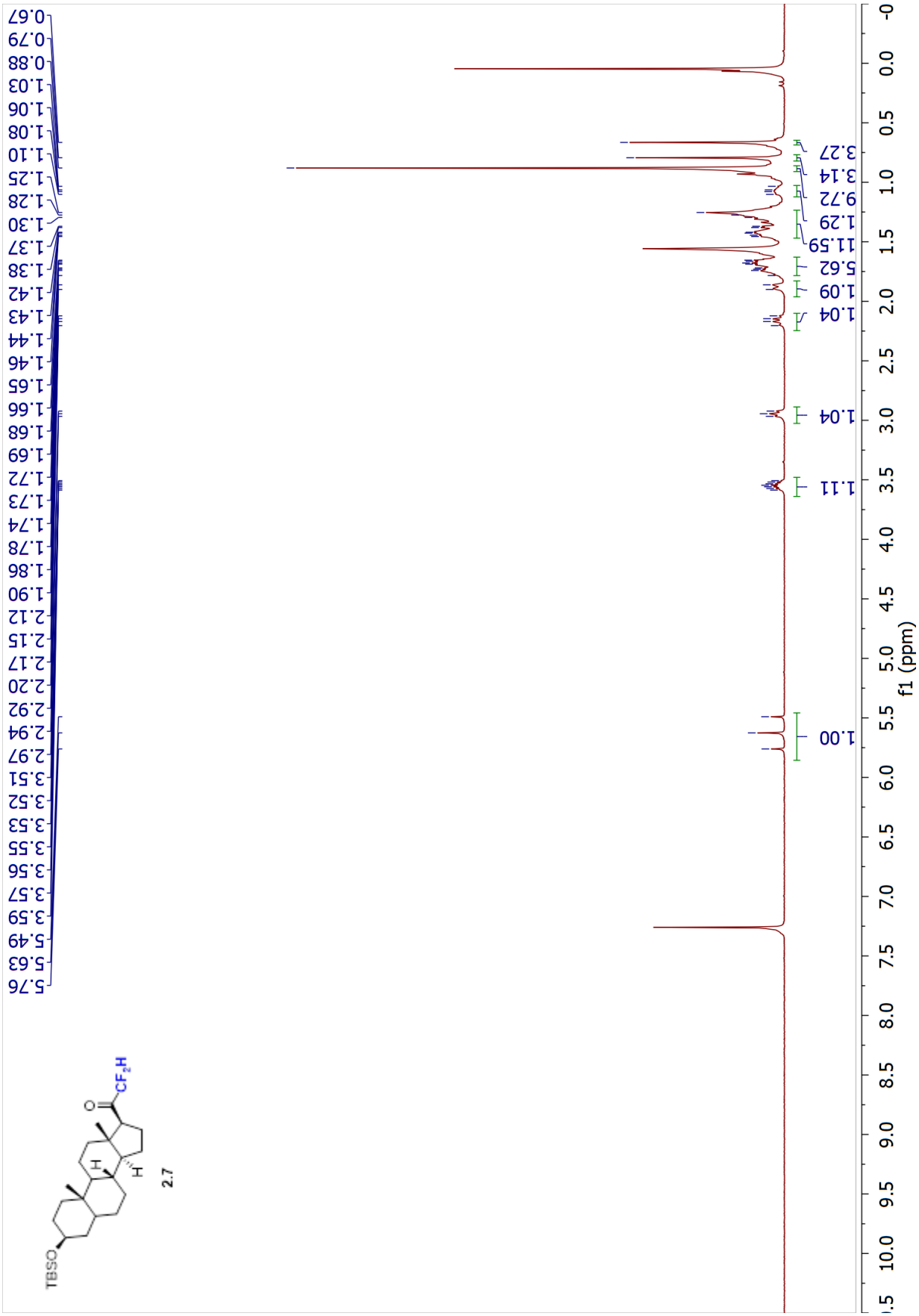
APPENDIX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CF2H
O
H
H
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f1 (ppm)
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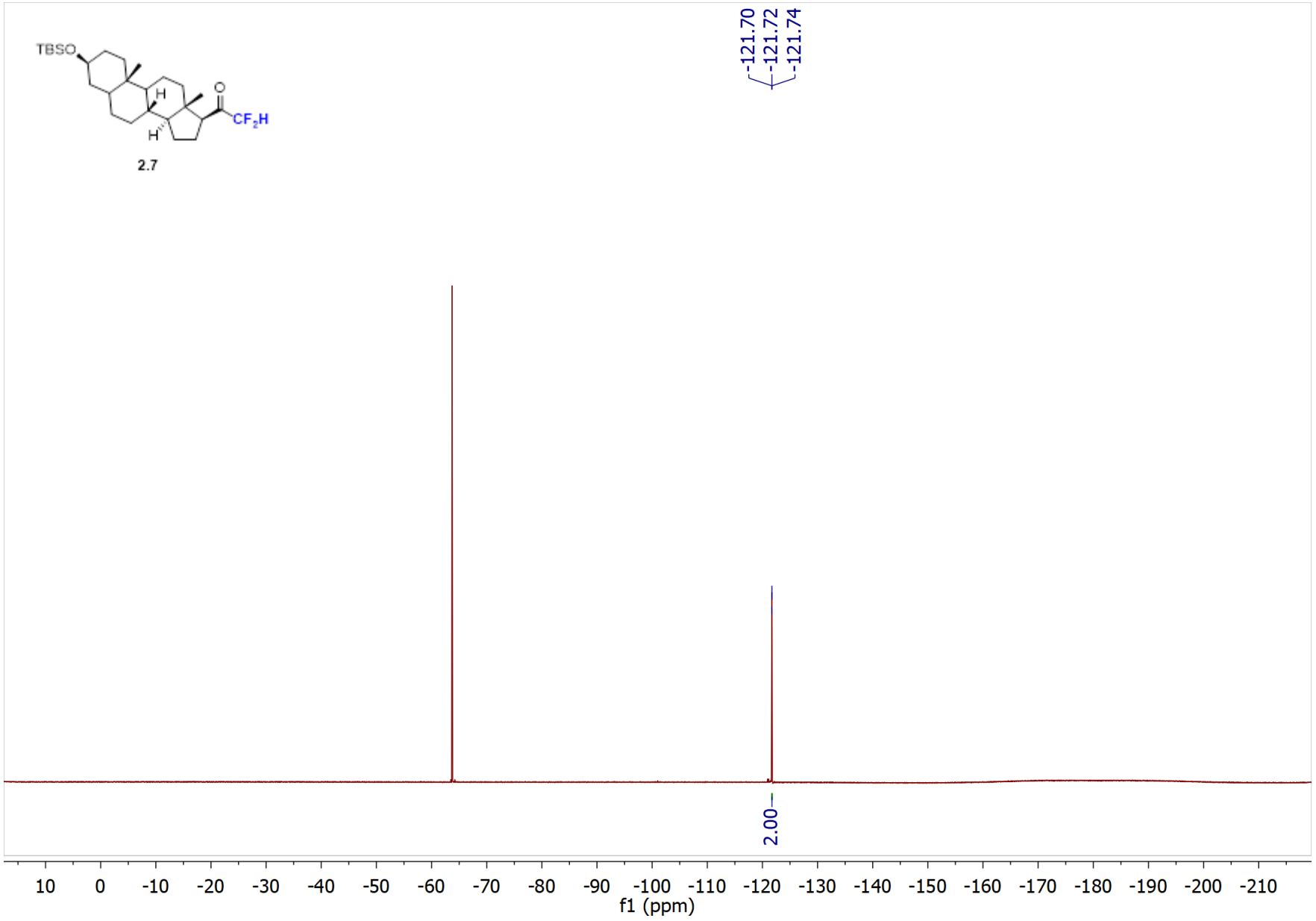
1.11
1.04
1.04
1.09
5.62
11.59
1.29
9.72
3.14
3.27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H
H
O
CF2H
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-121.70
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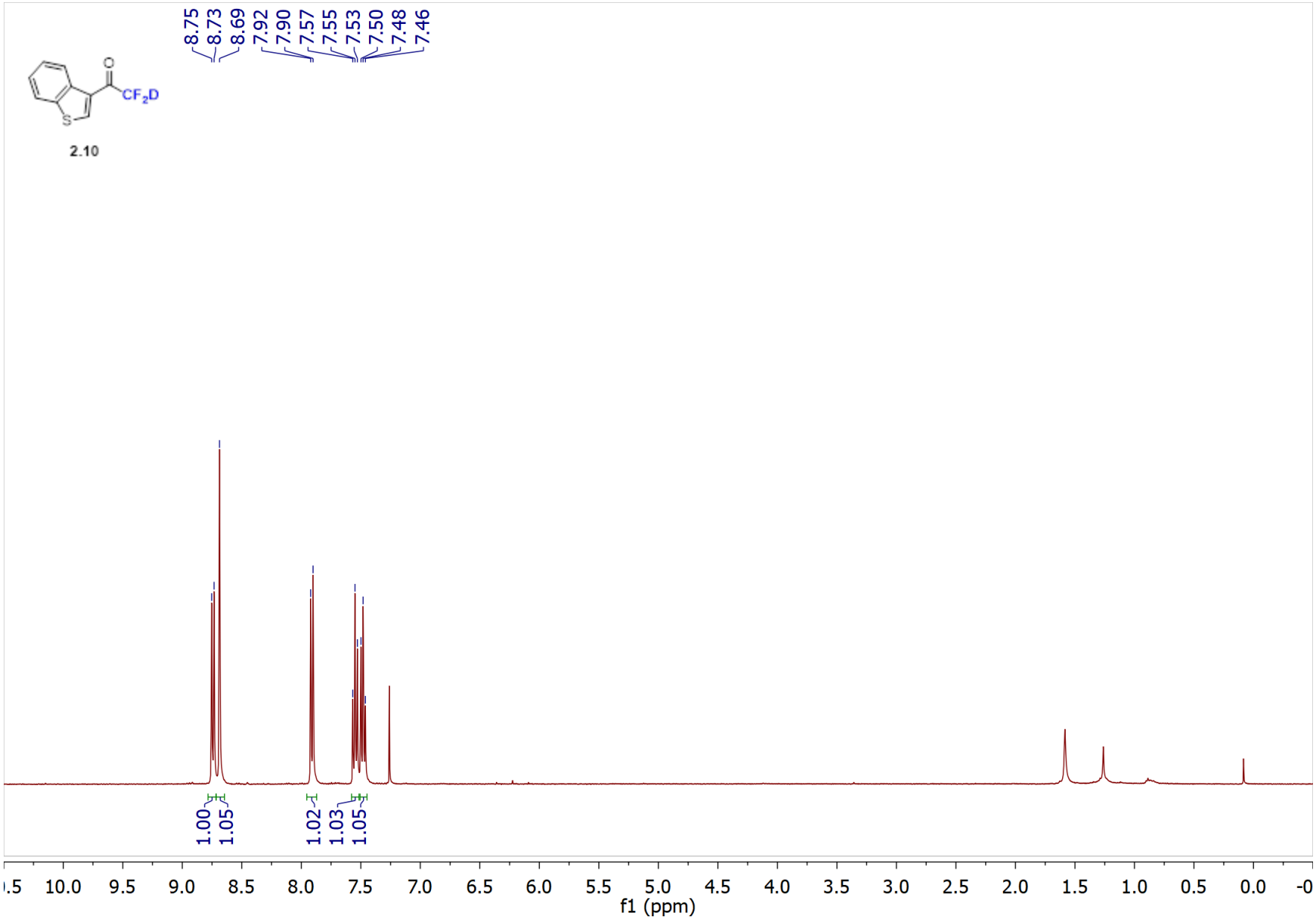
2.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


8.75
8.73
8.69
7.92
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7.57
7.55
7.53
7.50
7.48
7.46
O
CF2D
S
2.10
1.00
1.05
1.02
1.03
1.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
2.5
2.0
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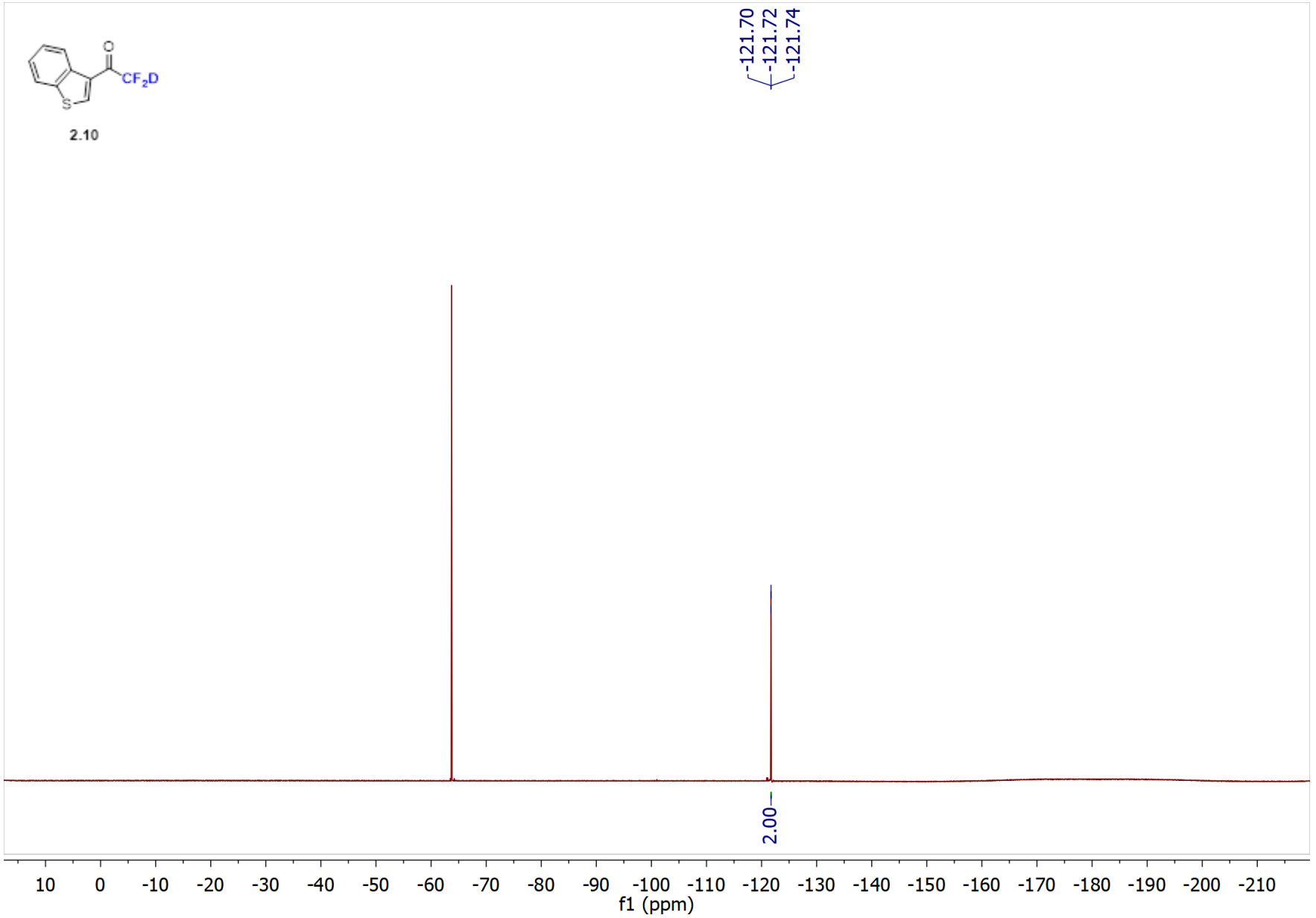
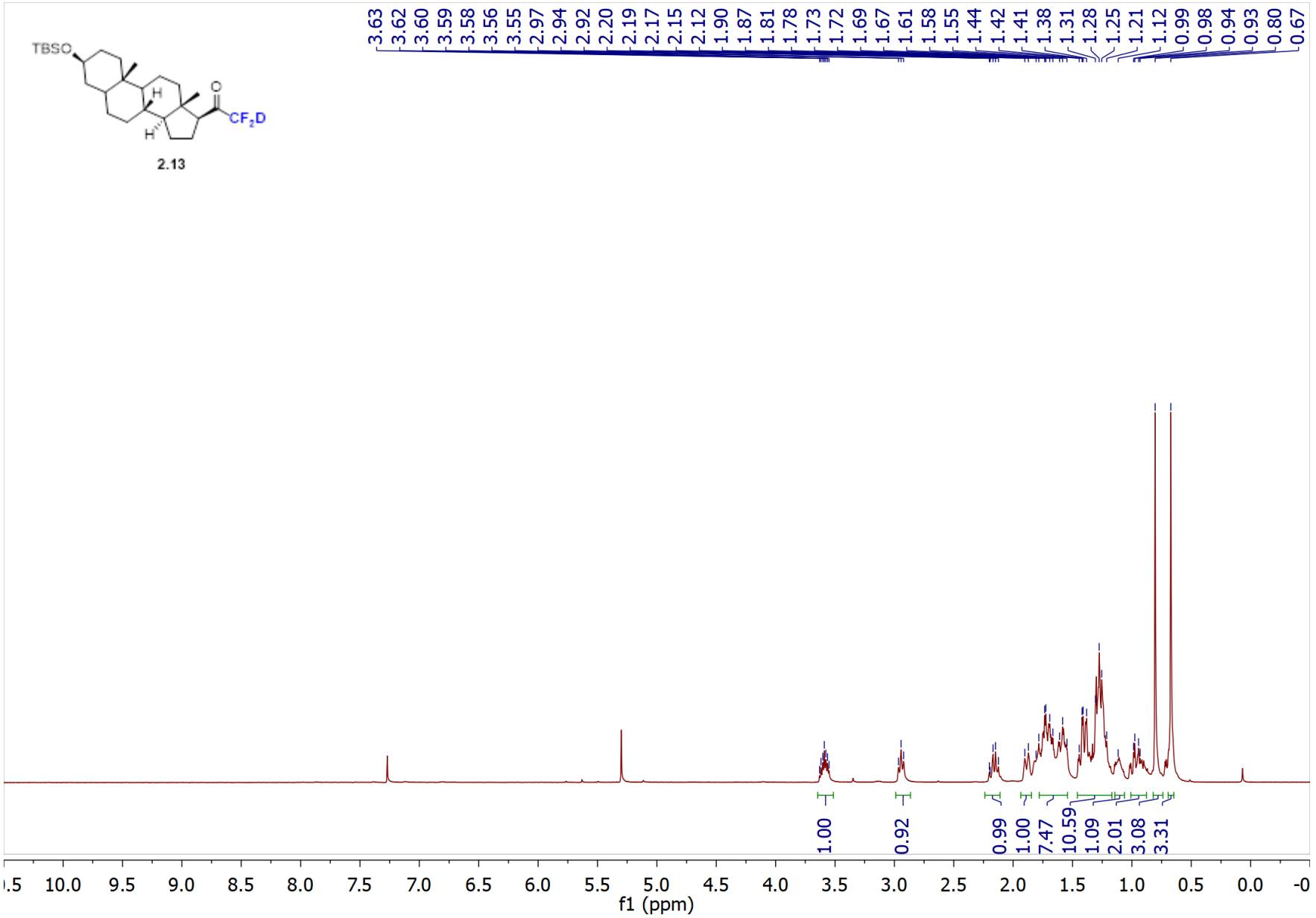
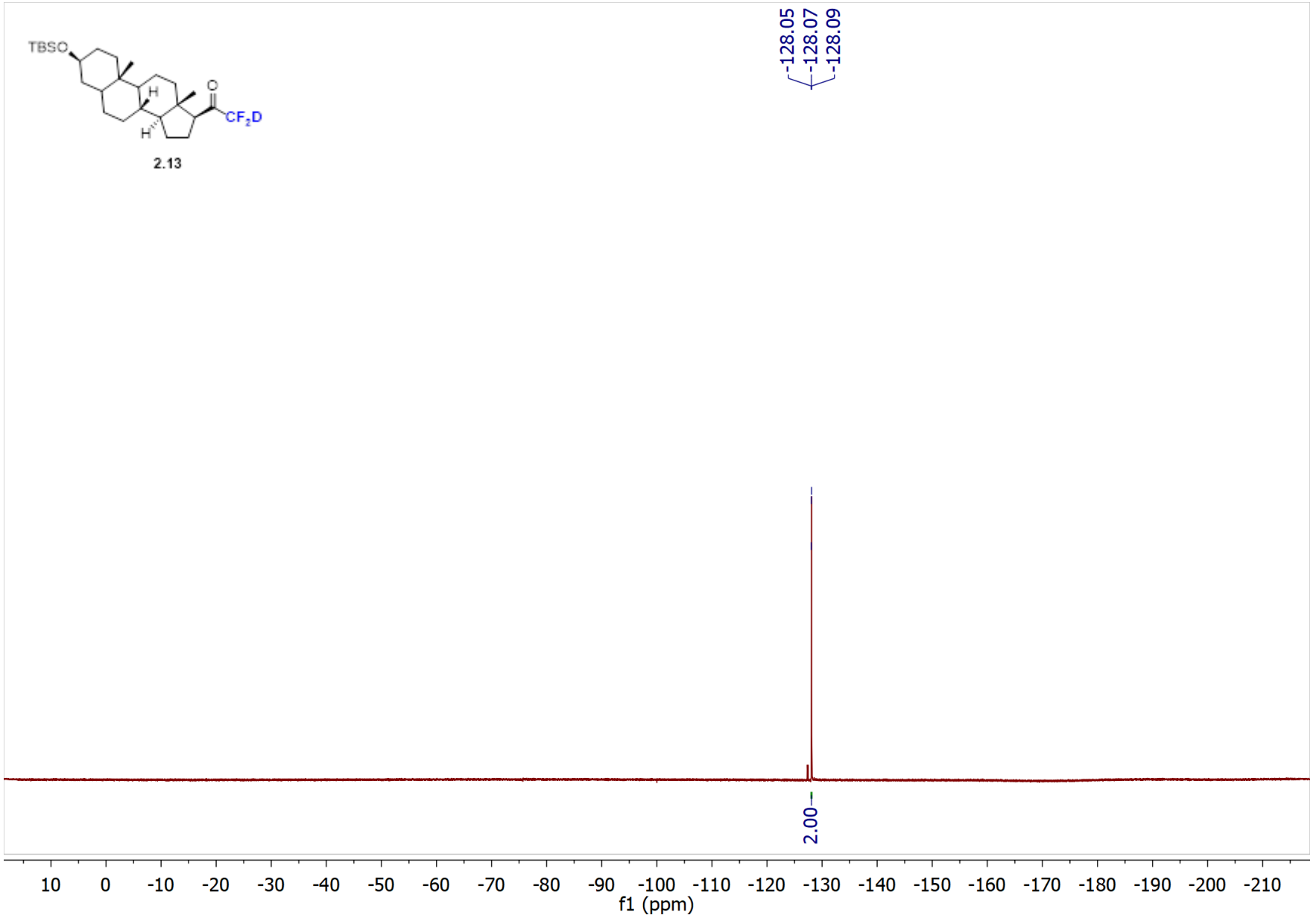
1.0
0.5
0.0
f1 (ppm)


-121.70
-121.72
-121.74
O
CF2D
S
2.10
2.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


TBSO
H
H
O
CF2D
2.13
3.63 3.62 3.60 3.59 3.58 3.56 3.55 2.97 2.94 2.92 2.20 2.19 2.17 2.15 2.12 1.90 1.87 1.81 1.78 1.73 1.72 1.69 1.67 1.61 1.58 1.55 1.44 1.42 1.41 1.38 1.31 1.28 1.25 1.21 1.12 0.99 0.98 0.94 0.93 0.80 0.67
1.00 0.92 0.99 1.00 7.47 10.59 1.09 2.01 3.08 3.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)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H
O
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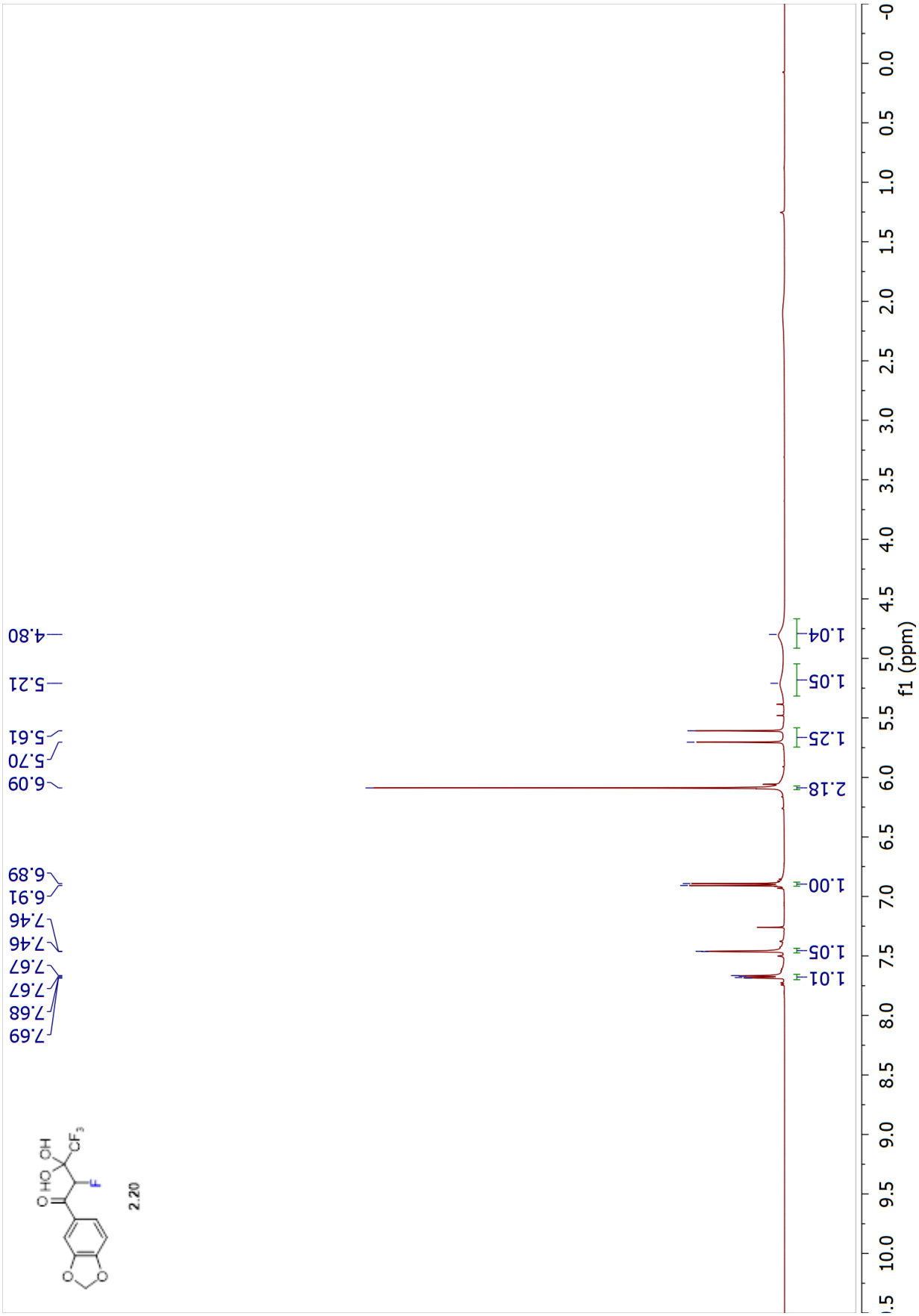
f1 (ppm)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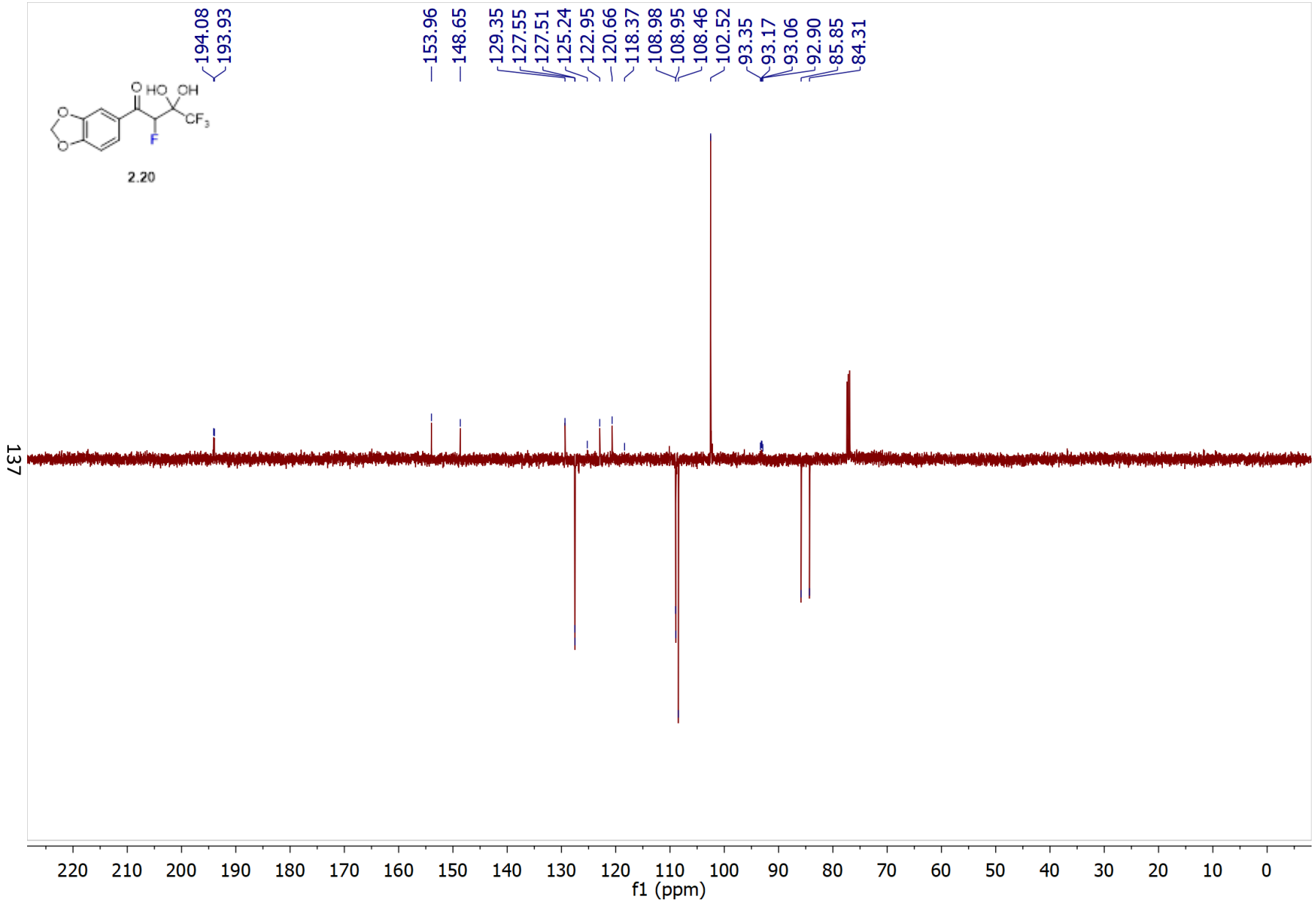
1.00
1.05
1.01
f1 (ppm)
2.20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120.66
118.37
108.98
108.95
108.46
102.52
93.35
93.17
93.06
92.90
85.85
84.31
HO
OH
F
CF3
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137
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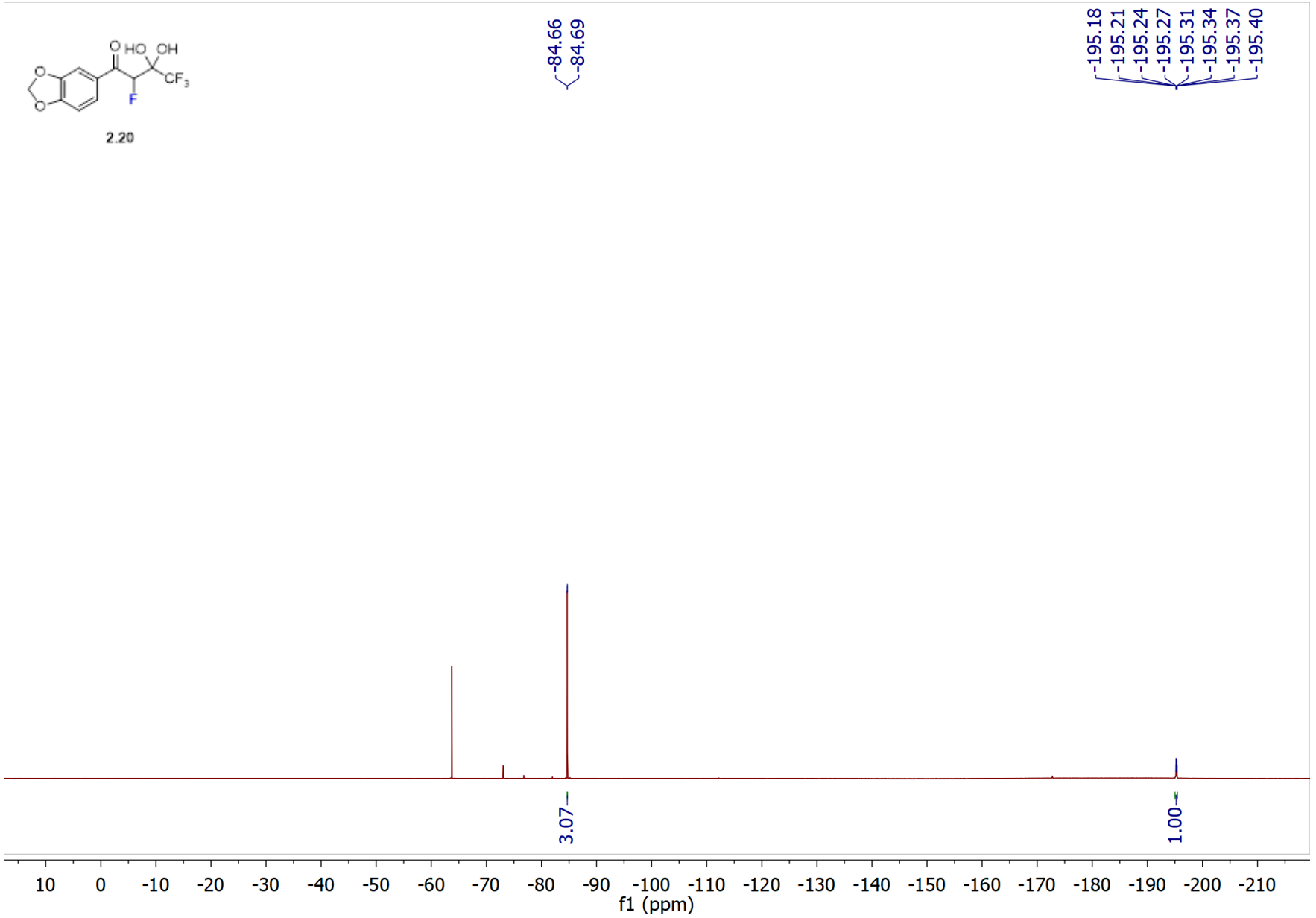
f1 (ppm)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-195.34
-195.37
-195.40
3.07
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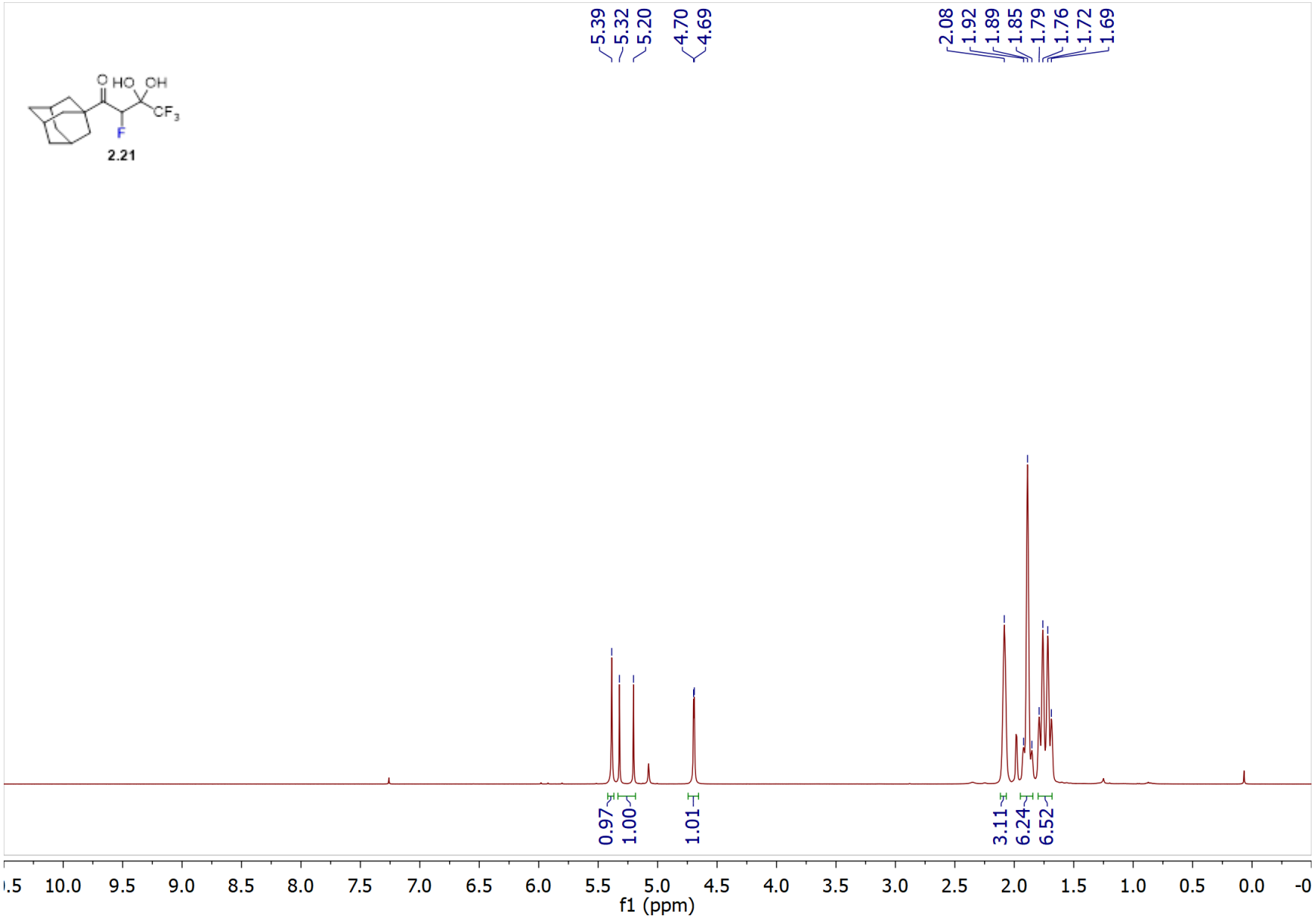
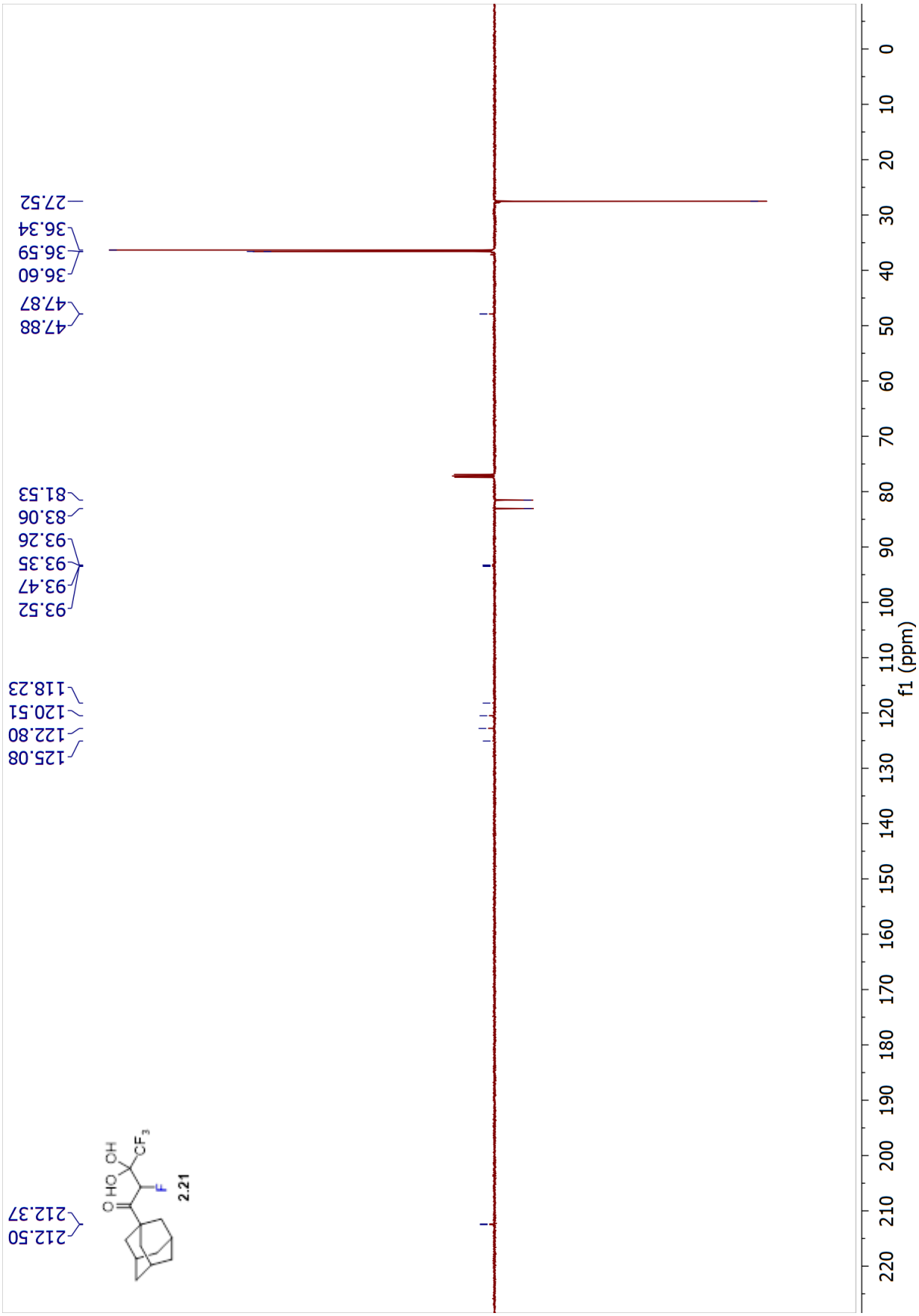
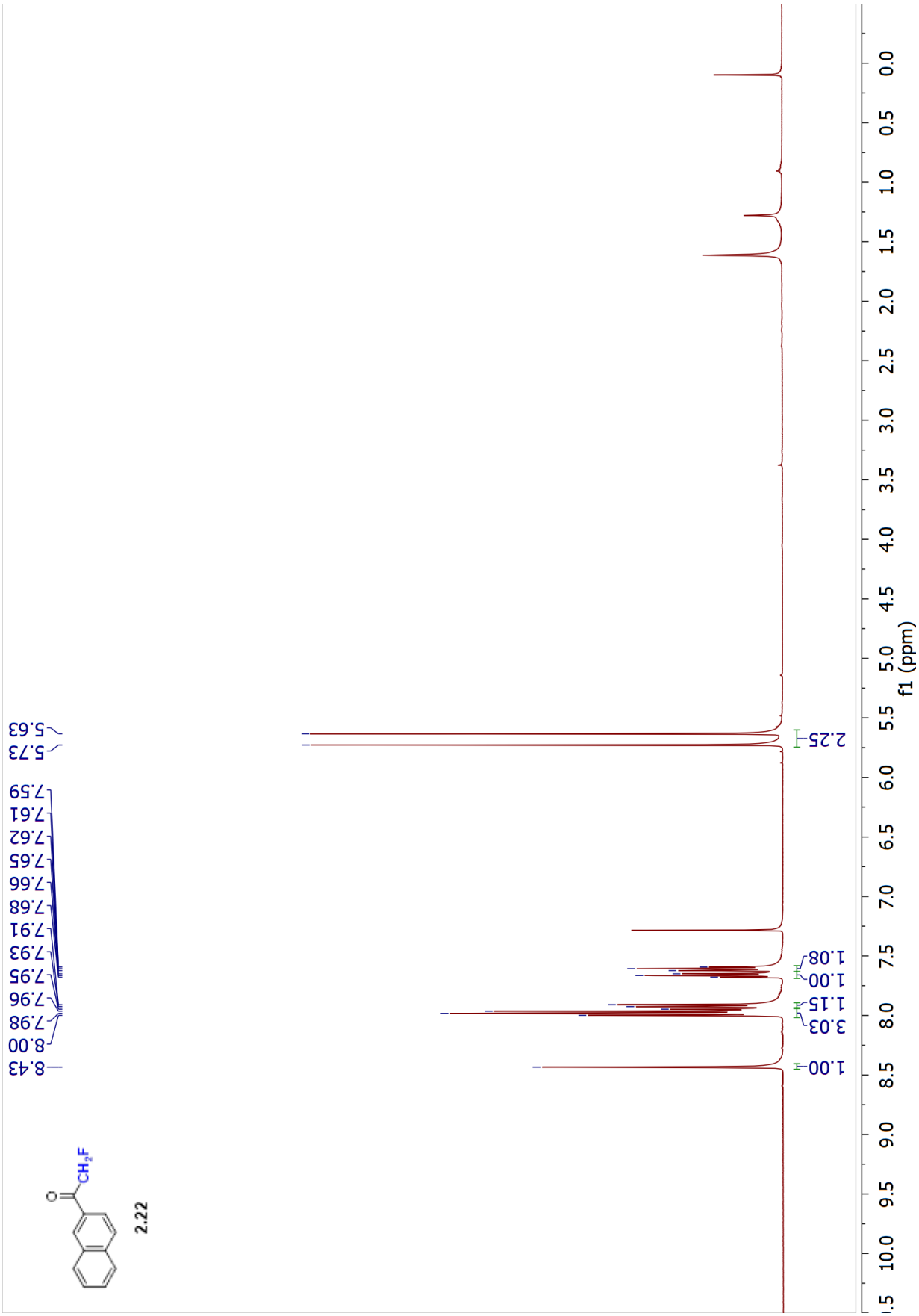
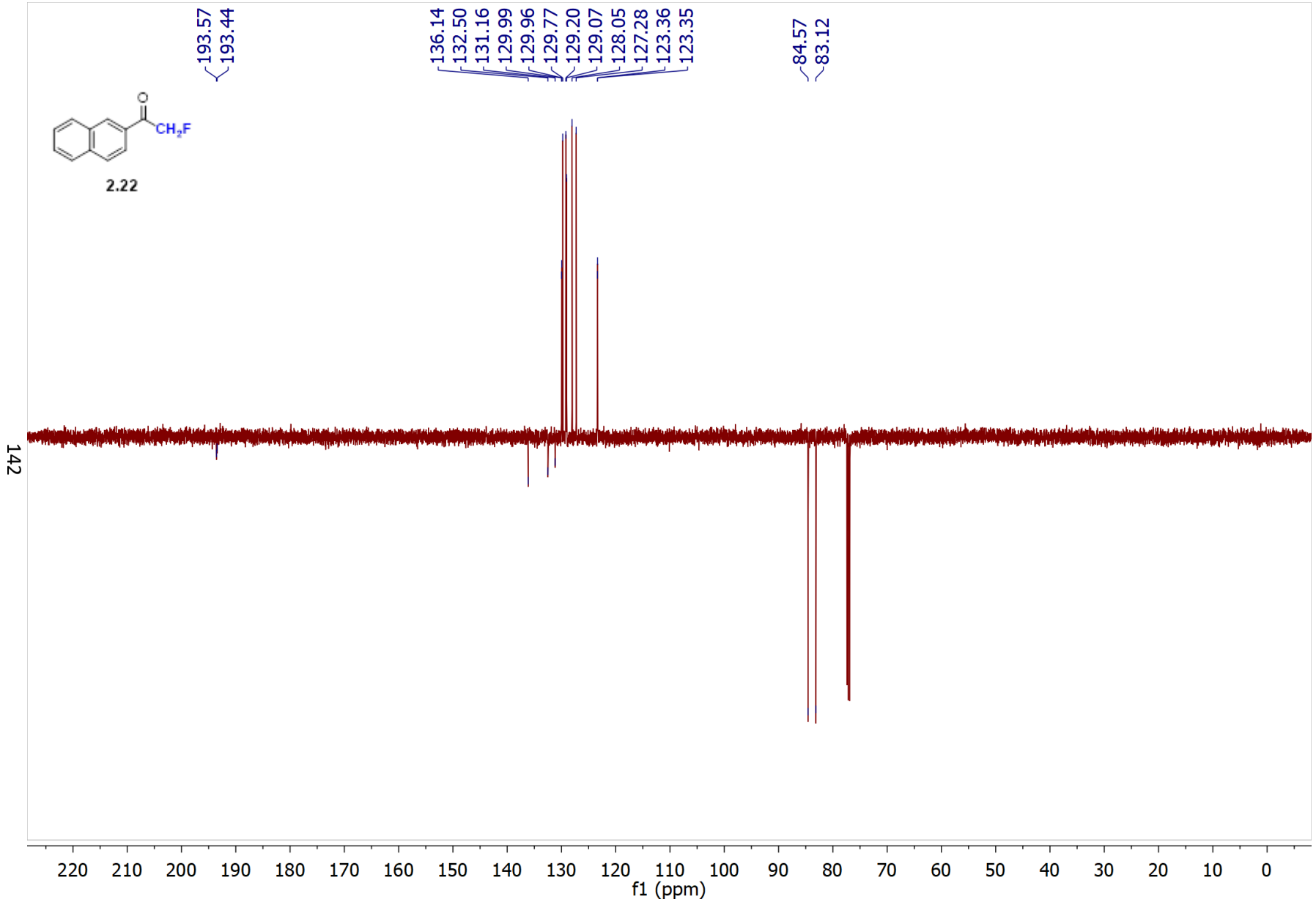
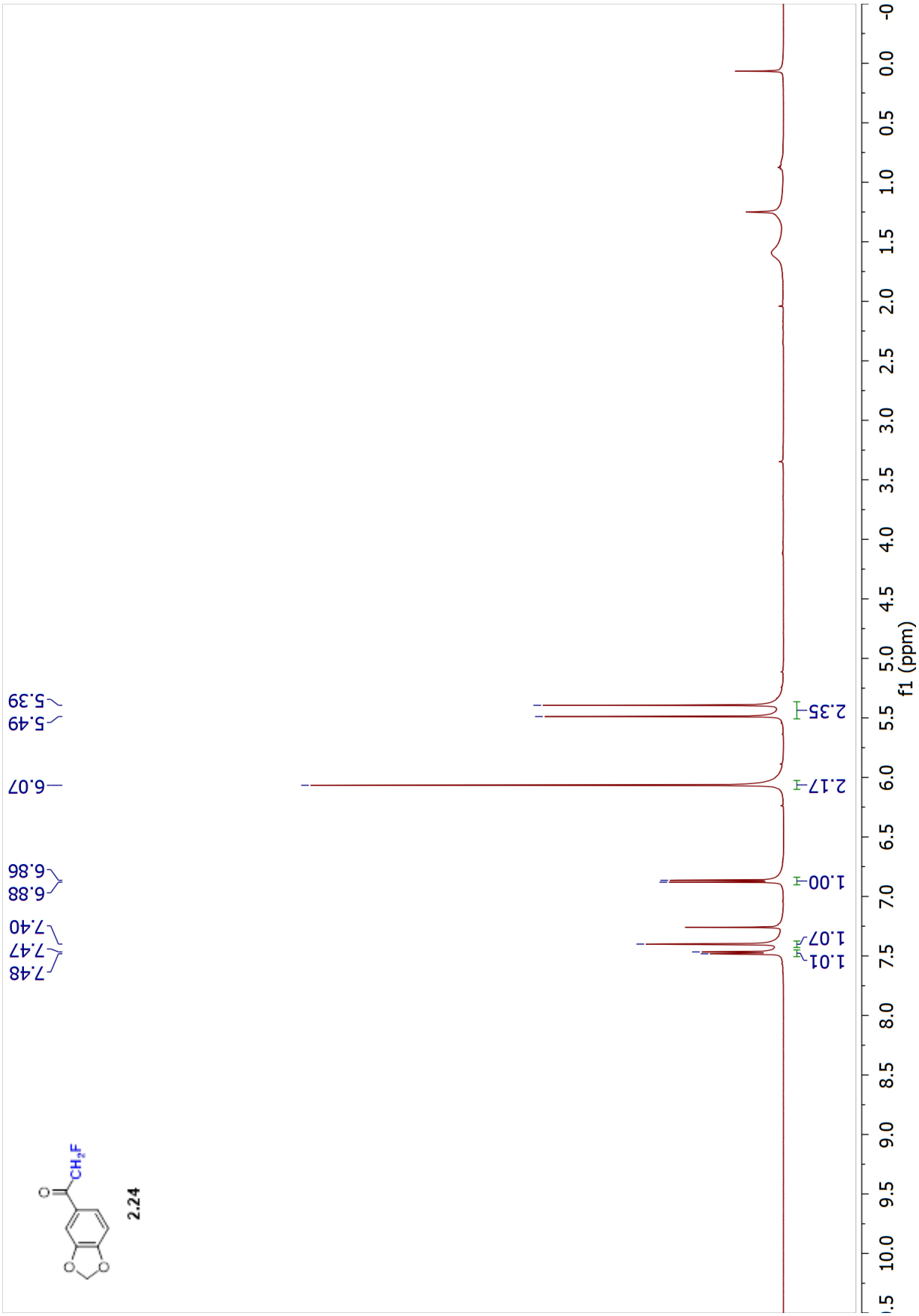
f1 (ppm)

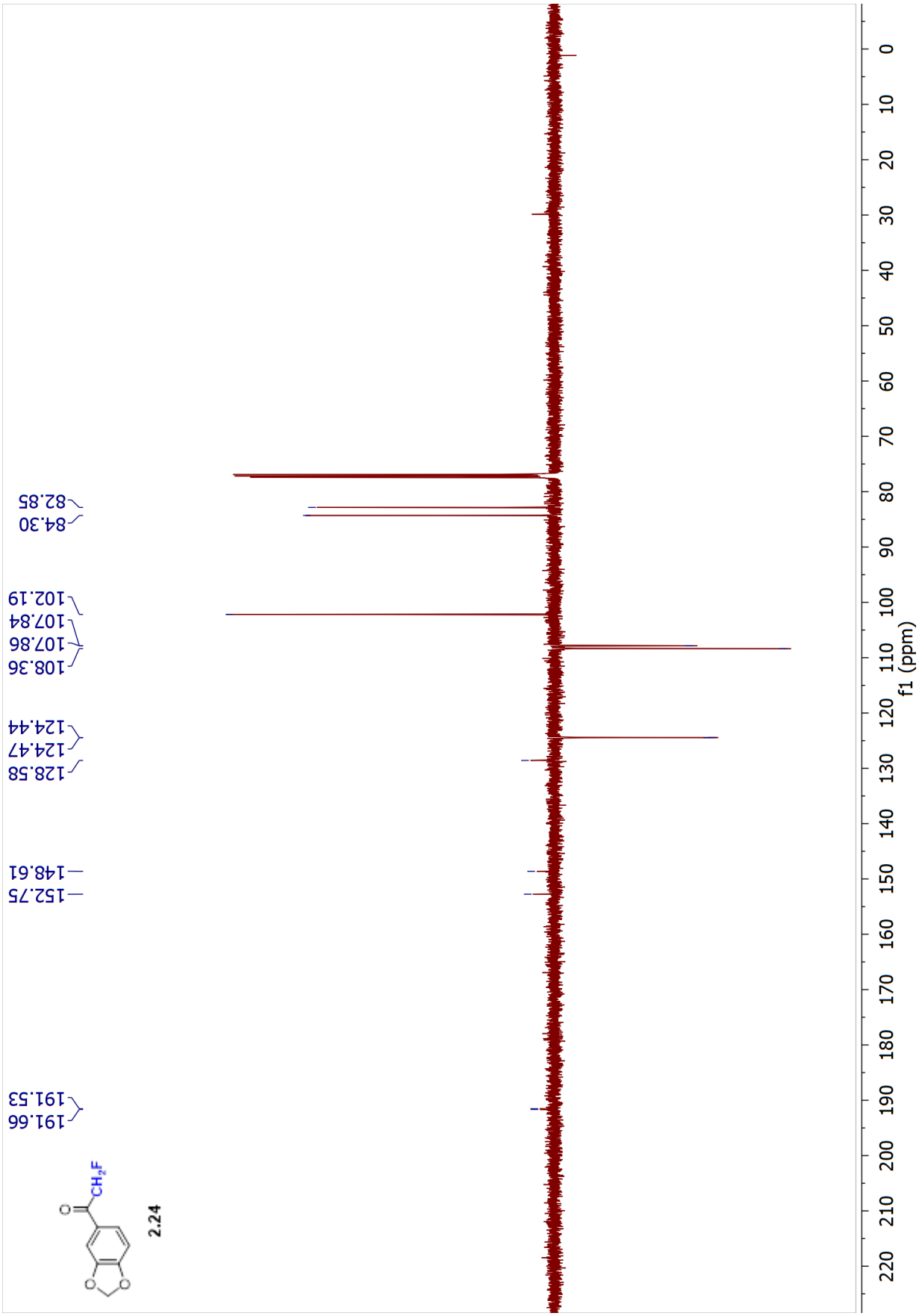

5.39
5.32
5.20
4.70
4.69
2.08
1.92
1.89
1.85
1.79
1.76
1.72
1.69
O HO OH
CF3
F
2.21
0.97
1.00
1.01
3.11
6.24
6.52
f1 (ppm)

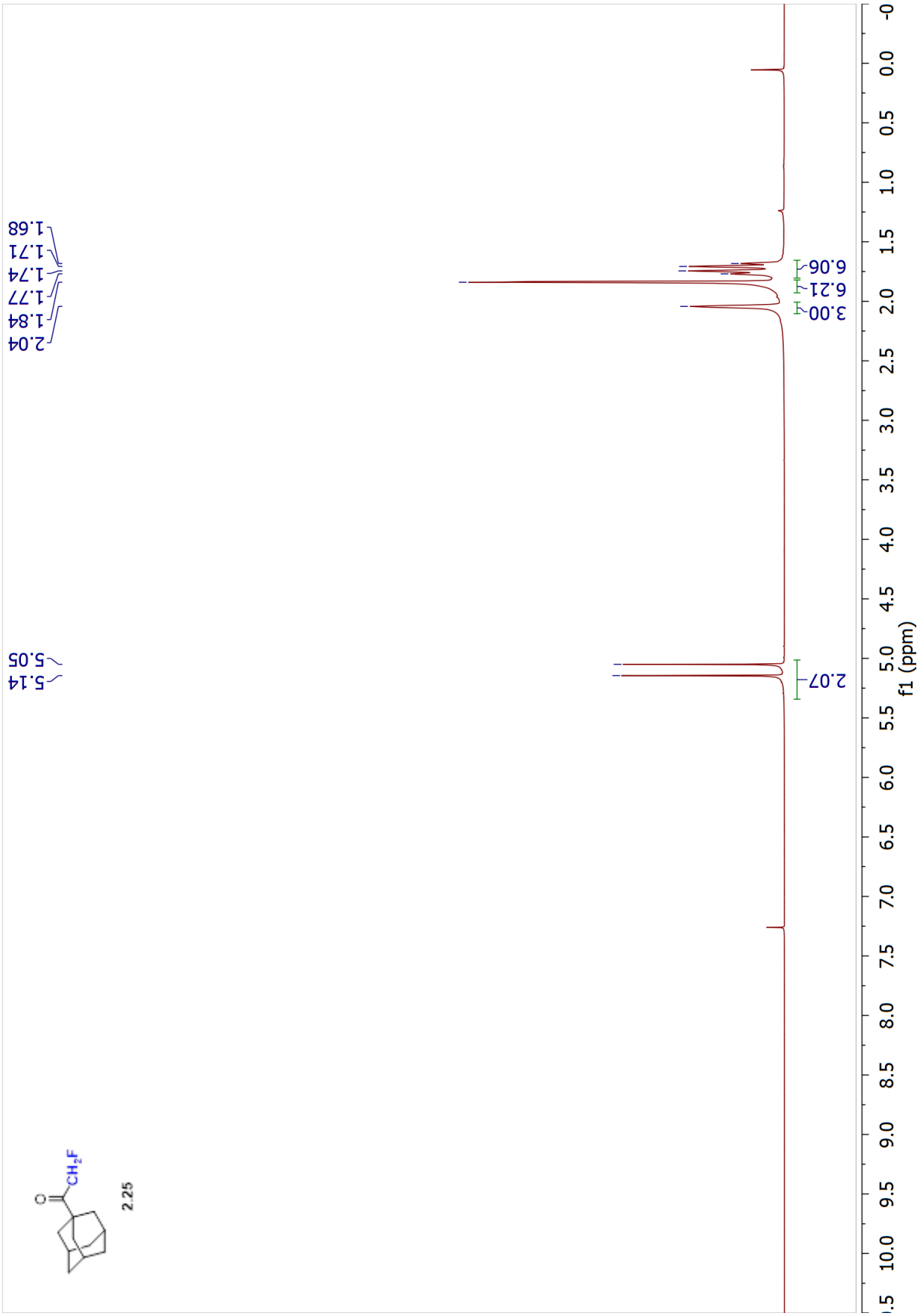

212.50
212.37
125.08
122.80
120.51
118.23
93.52
93.47
93.35
93.26
83.06
81.53
47.88
47.87
36.60
36.59
36.34
27.52
f1 (ppm)
2.21

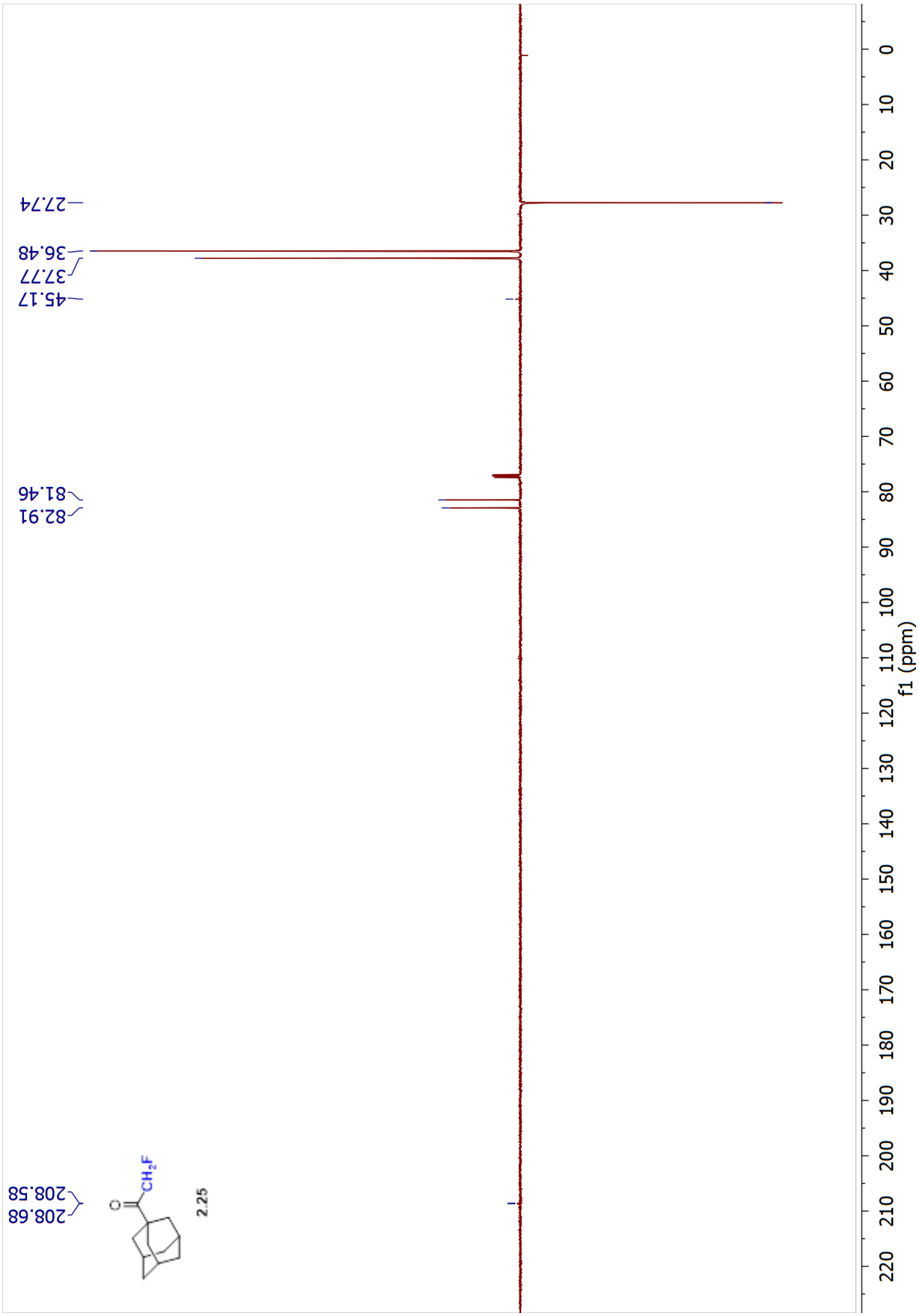

8.43
8.00
7.98
7.96
7.95
7.93
7.91
7.68
7.66
7.65
7.62
7.61
7.59
5.73
5.63
1.00
3.03
1.15
1.00
1.08
2.25
f1 (ppm)
2.22

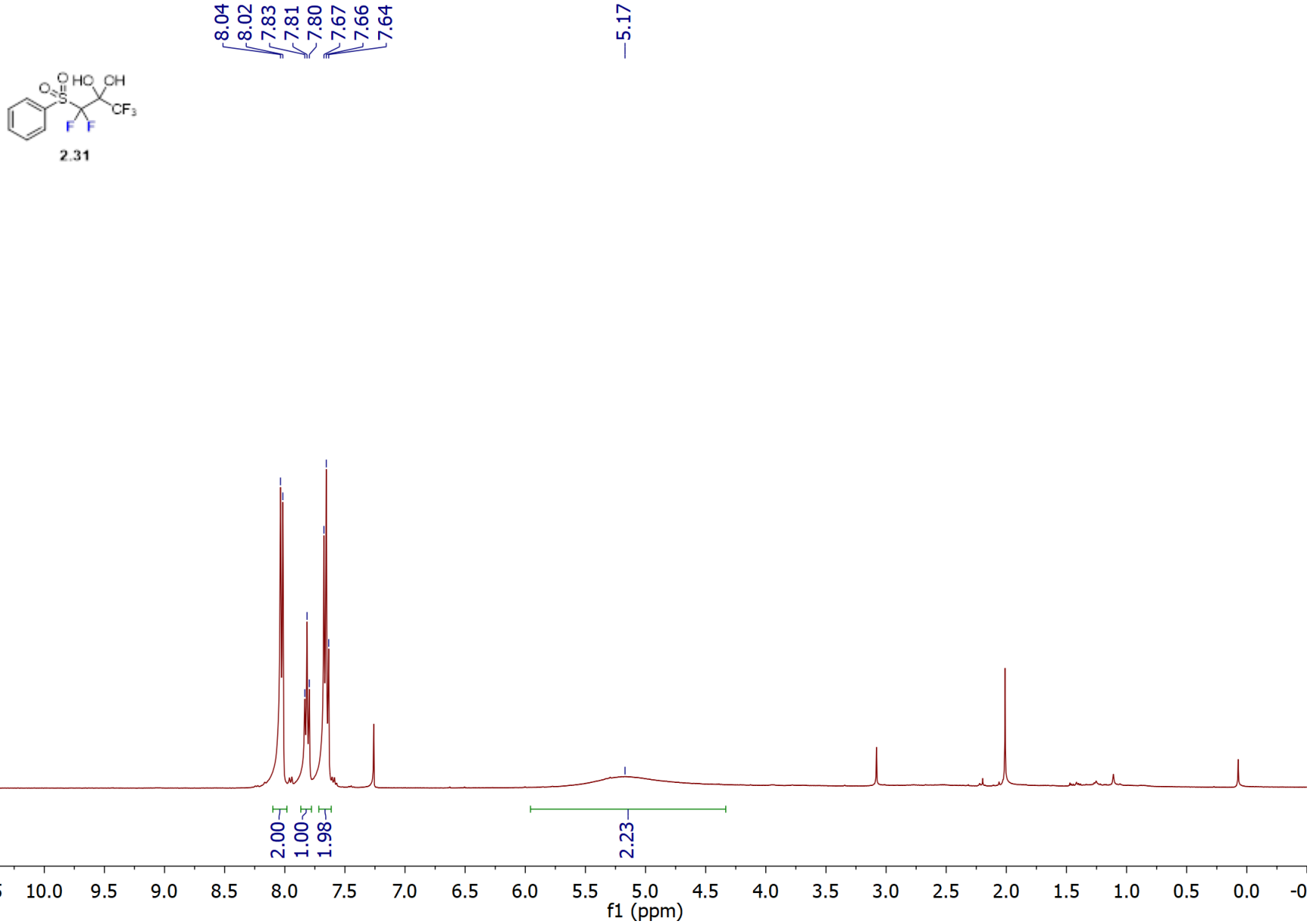

193.57
193.44
136.14
132.50
131.16
129.99
129.96
129.77
129.20
129.07
128.05
127.28
123.36
123.35
84.57
83.12
CH2F
2.22
142
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

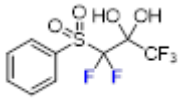

7.48
7.47
7.40
6.88
6.86
6.07
5.49
5.39
1.01
1.07
1.00
2.17
2.35
f1 (ppm)
2.24


191.66
191.53
152.75
148.61
128.58
124.47
124.44
108.36
107.86
107.84
102.19
84.30
82.85
2.24
f1 (ppm)


1.68
1.71
1.74
1.77
1.84
2.04
5.05
5.14
2.07
3.00
6.21
6.06
f1 (ppm)
2.25


208.68
208.58
O
CH2F
2.25
27.74
36.48
37.77
45.17
81.46
82.91
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)


8.04
8.02
7.83
7.81
7.80
7.67
7.66
7.64
5.17
HO
OH
O
S
O
F
F
CF3
2.31
147
2.00
1.00
1.98
2.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



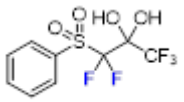
2.31

136.62
132.70
131.22
129.88
125.09
122.20
119.51
119.32
116.49
116.27
113.47
94.11
94.03
93.78
93.70
93.53
93.45
93.20
93.11

148

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

f1 (ppm)



2.31

-82.44
-82.46
-82.48

-111.13
-111.15
-111.16
-111.18

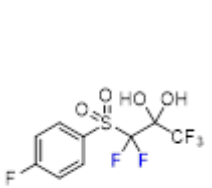
149

3.05

2.00

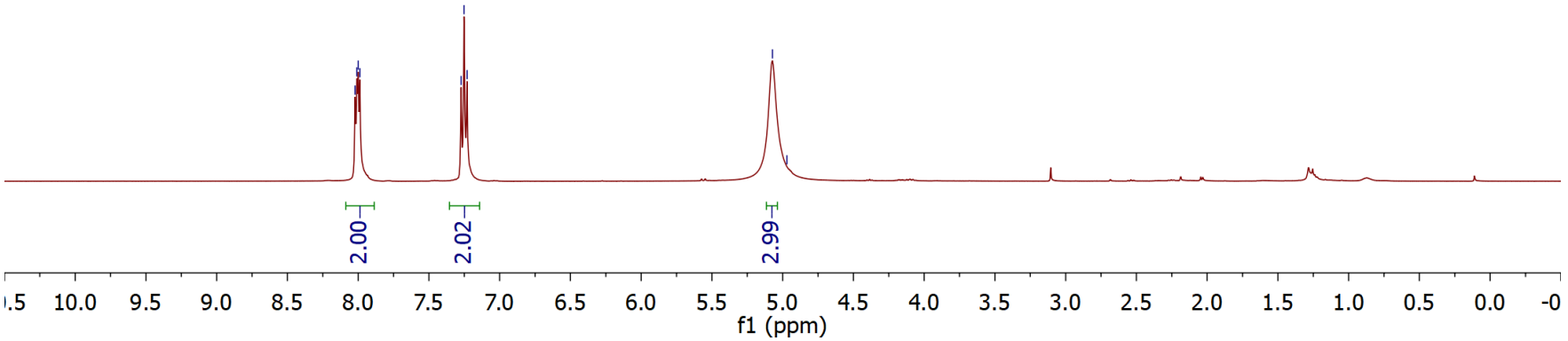
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

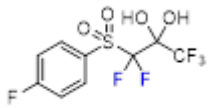
f1 (ppm)



2.32

8.02
8.01
8.00
7.99
7.27
7.25
7.23
5.07
4.97





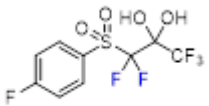
2.32

168.82
166.23
134.16
134.06
128.53
128.50
125.15
122.33
120.03
119.44
117.24
117.01
116.54
114.01
93.92
93.84
93.59
93.50
93.34
93.26
93.00
92.92

151

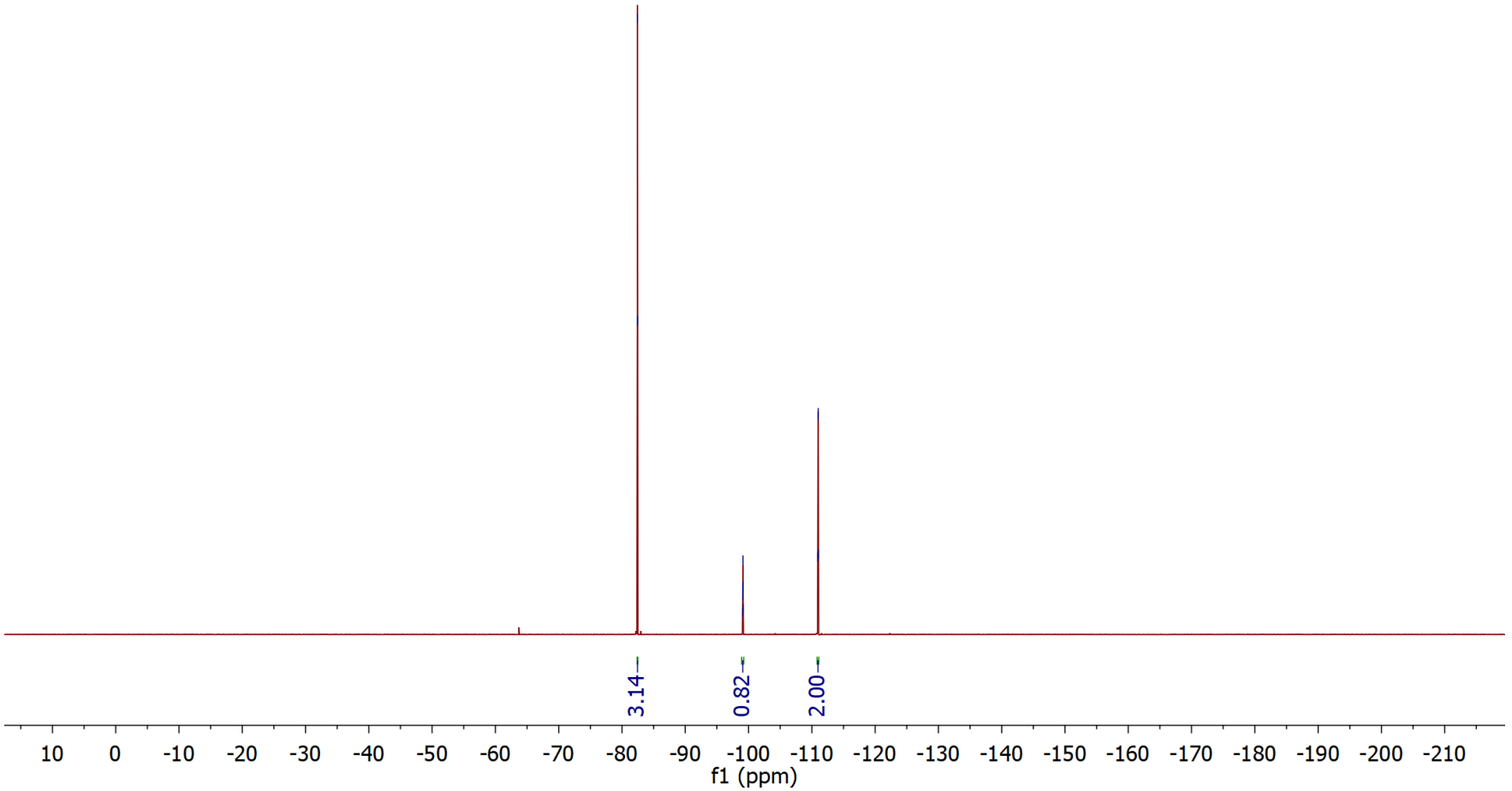
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

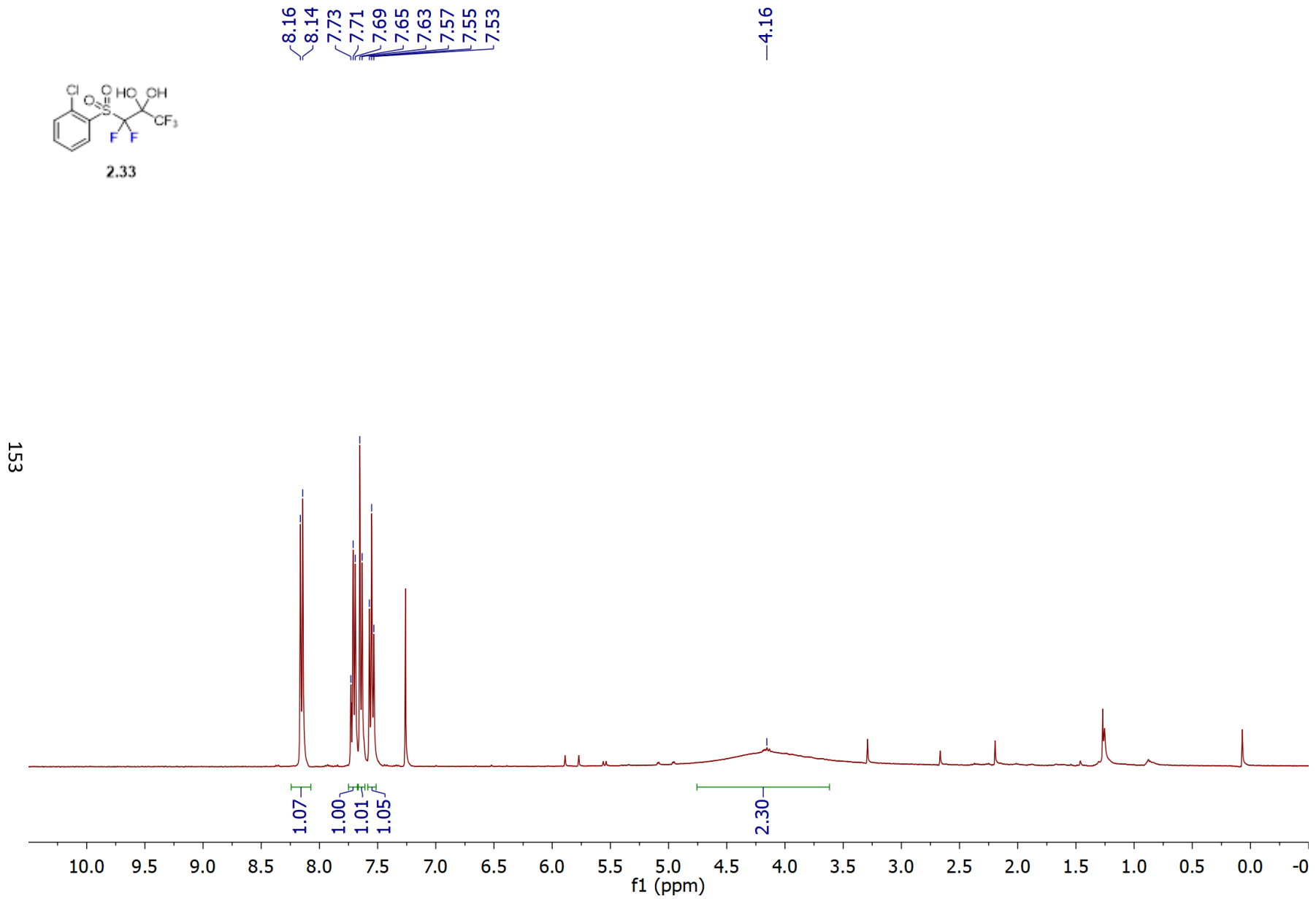
f1 (ppm)

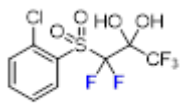


2.32

-82.42
-82.45
-82.48
-99.08
-99.10
-99.10
-99.12
-99.13
-99.14
-99.15
-110.95
-110.98
-111.01
-111.04




8.16
8.14
7.73
7.71
7.69
7.65
7.63
7.57
7.55
7.53
4.16
Cl
O
O
S
HO
OH
CF3
F
F
2.33
153
1.07
1.00
1.01
1.05
2.30
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)



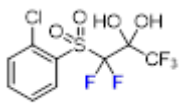
2.33

136.15
135.25
133.76
132.07
130.13
126.81
123.81
120.93
118.94
115.90
112.86
92.60
92.35
92.27
92.02
91.93

154

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

f1 (ppm)



2.33

-82.36
-82.39
-82.42
-108.98
-109.01
-109.04
-109.07
3.00
1.88
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

2.34

148.13
131.03
130.32
129.36
125.01
122.15
119.43
119.26
116.42
113.41
93.90
93.82
93.57
93.49
93.32
93.24
93.11
92.99
92.91
92.84
21.94

156

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

f1 (ppm)

2.34

-82.43
-82.47
-82.49
-82.50

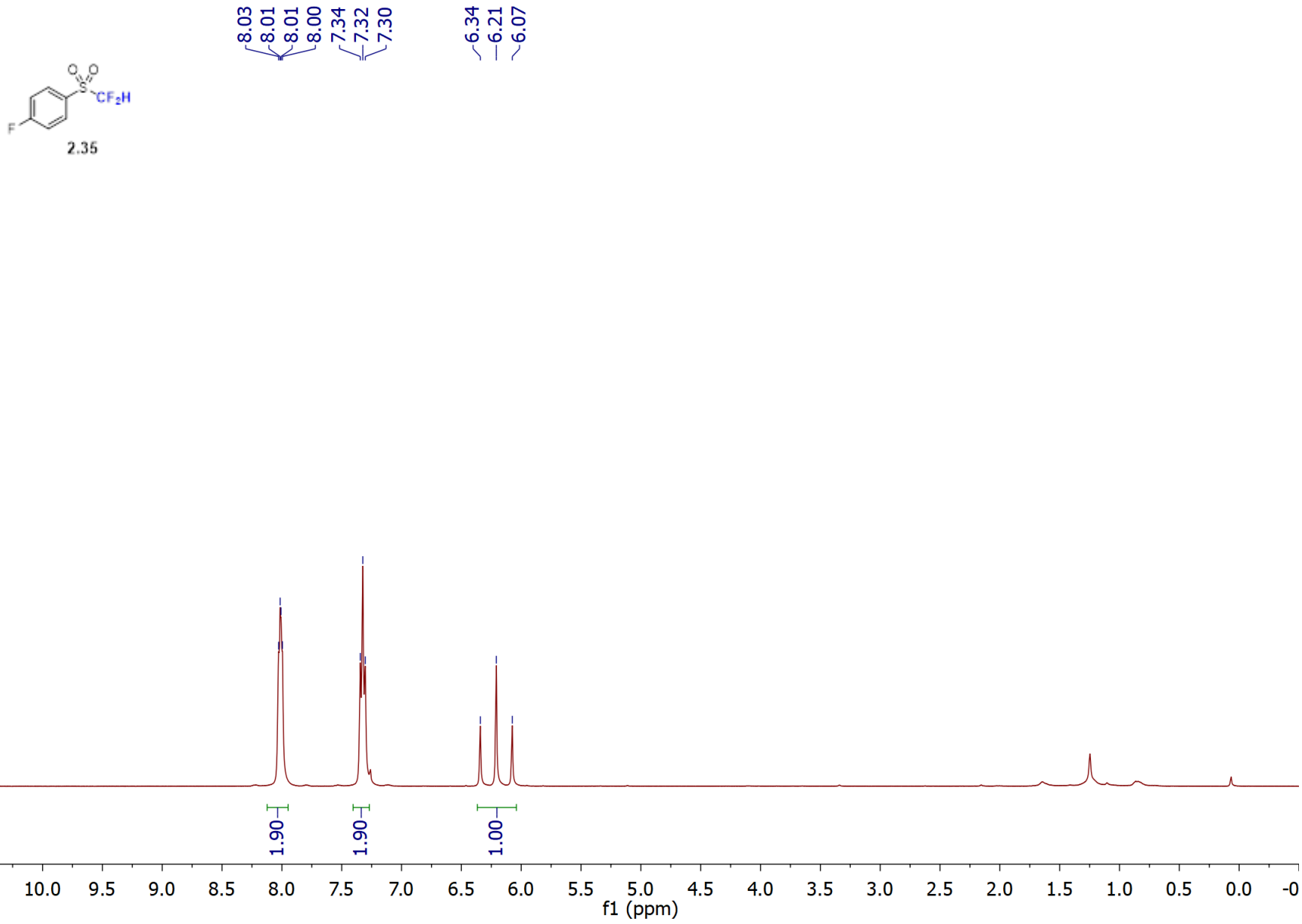
-111.52
-111.54
-111.56
-111.58

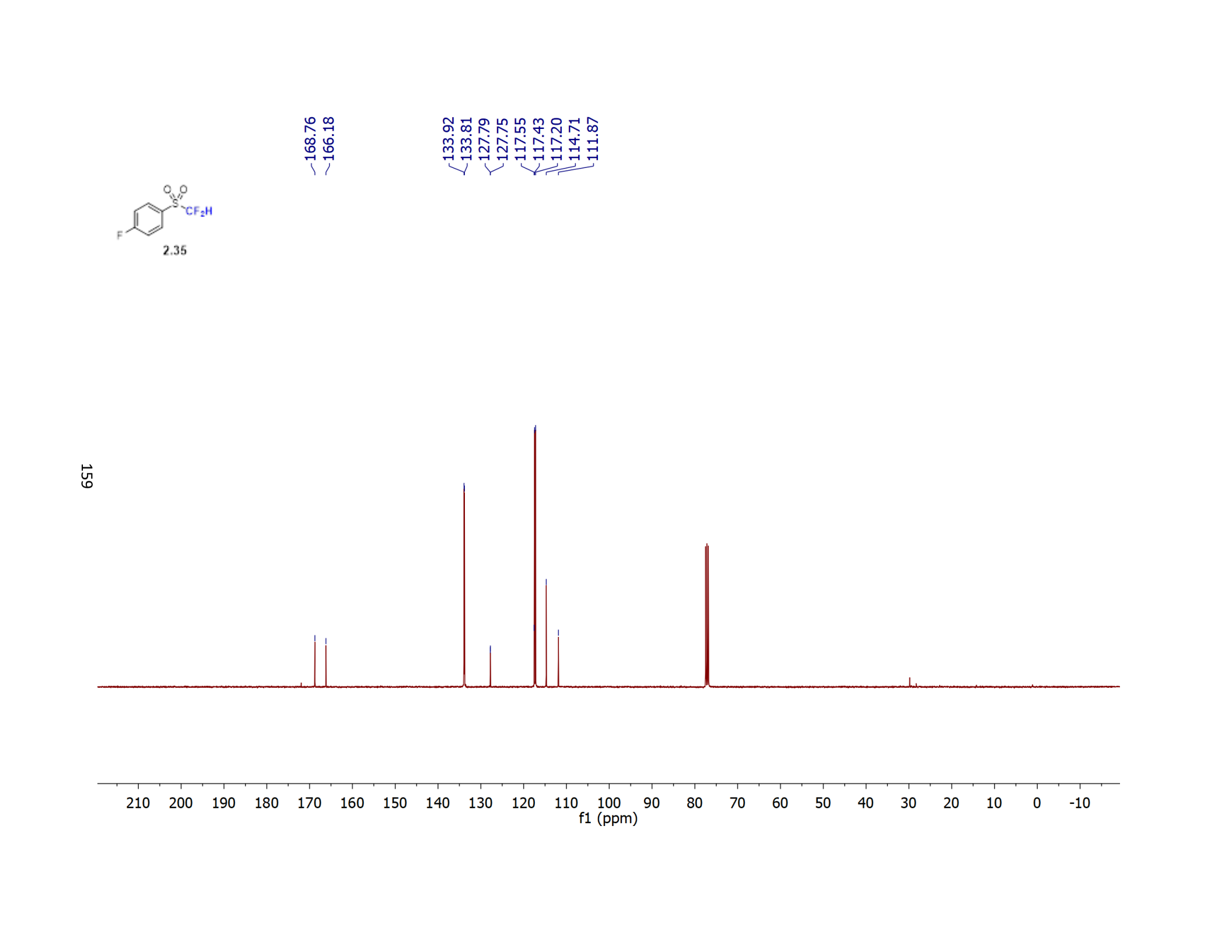
3.07

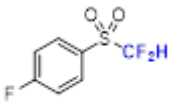
2.02

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

f1 (ppm)

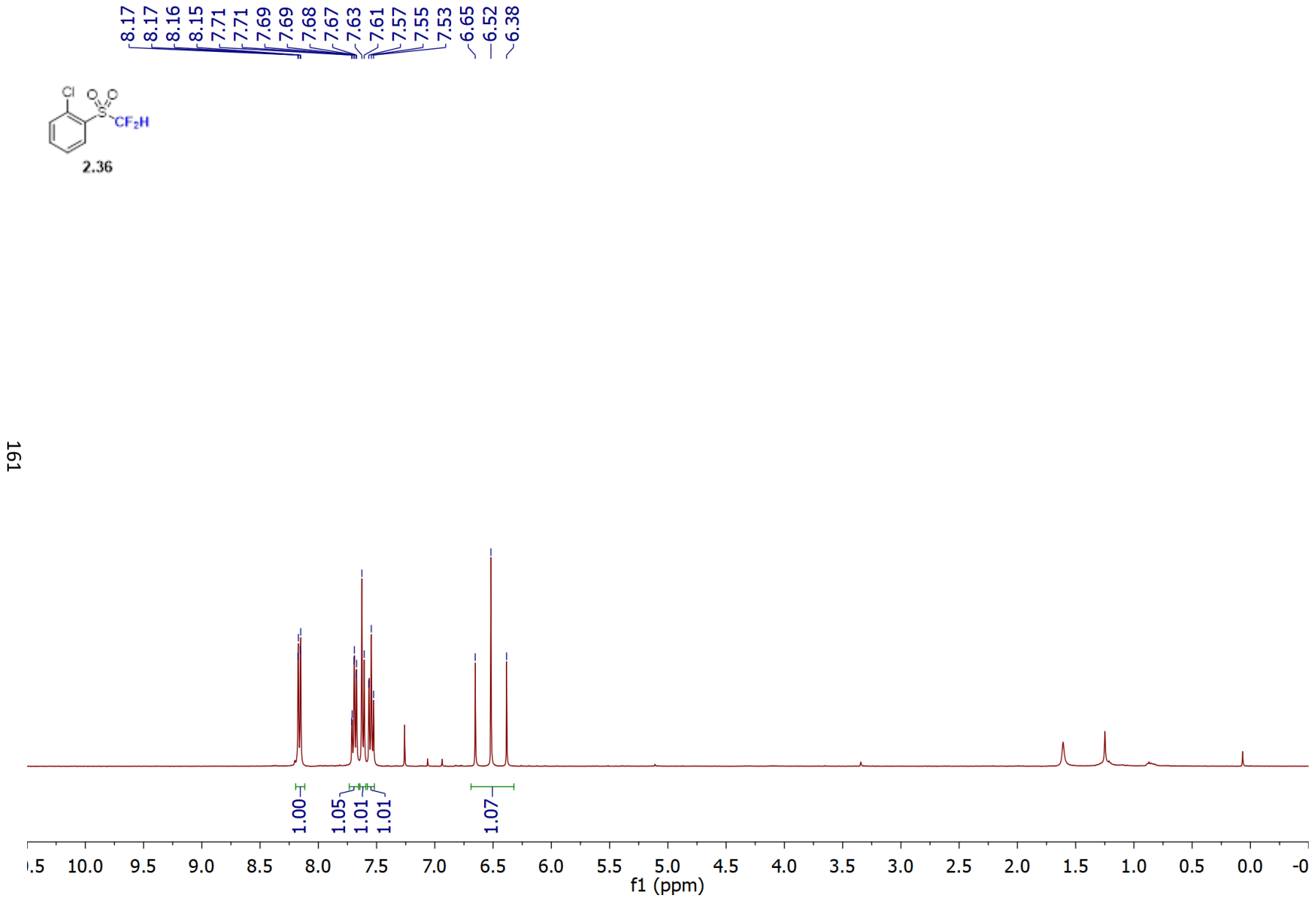

8.03
8.01
8.01
8.00
7.34
7.32
7.30
6.34
6.21
6.07
CF2H
F
2.35
158
1.90
1.90
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

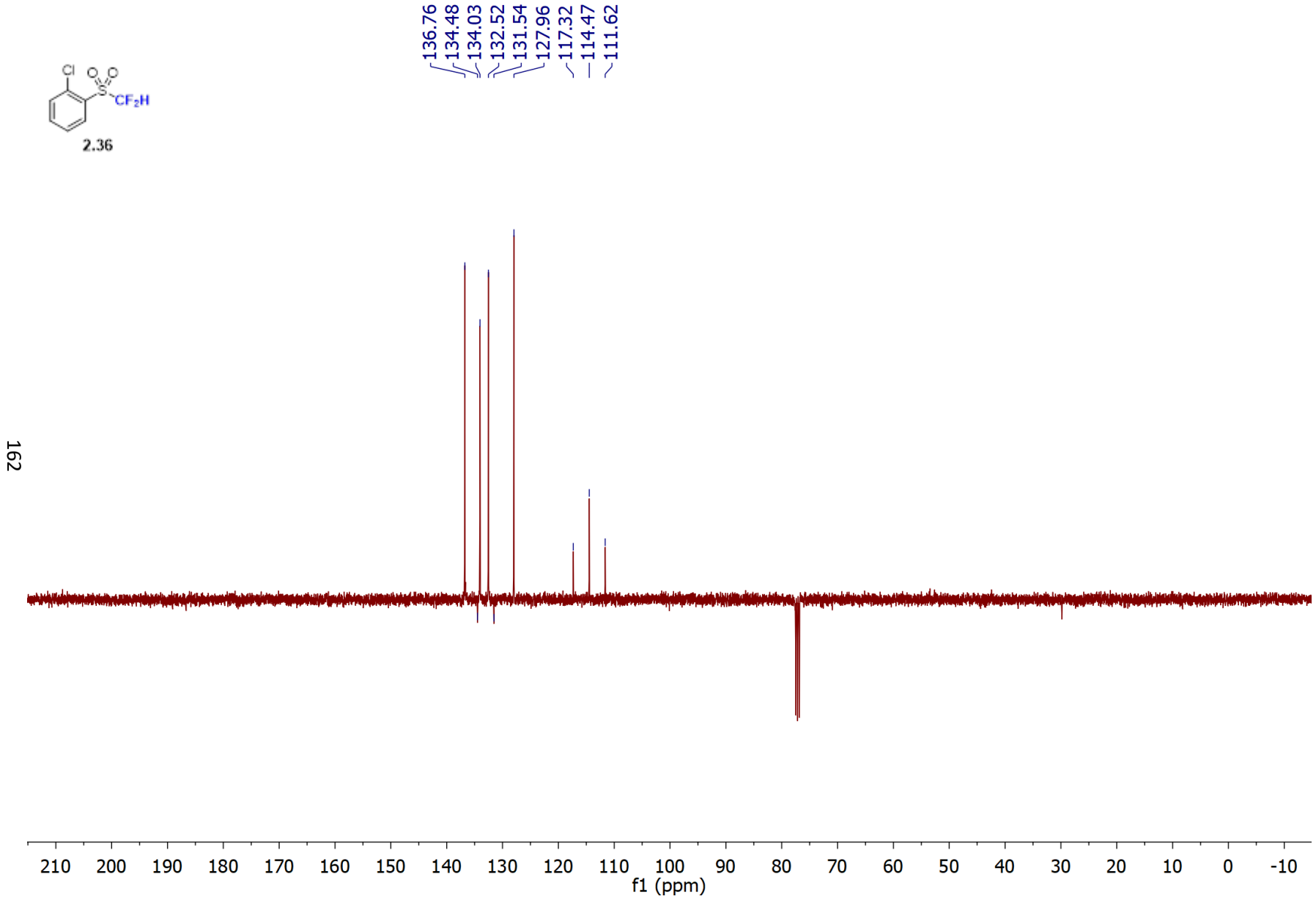

168.76
166.18
133.92
133.81
127.79
127.75
117.55
117.43
117.20
114.71
111.87
F
S
O
O
CF2H
2.35
159
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

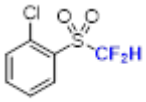

O
O
S
CF2H
F

2.35

-100.31
-100.33
-100.33
-100.35
-100.36
-100.37
-100.38
-122.37
-122.51
160
1.00
2.38
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


8.17
8.17
8.16
8.15
7.71
7.71
7.69
7.69
7.68
7.67
7.63
7.61
7.57
7.55
7.53
6.65
6.52
6.38
Cl
O
O
S
CF2H
2.36
161
1.00
1.05
1.01
1.01
1.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


136.76
134.48
134.03
132.52
131.54
127.96
117.32
114.47
111.62
Cl
O
O
S
CF2H
2.36
162
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



2.36

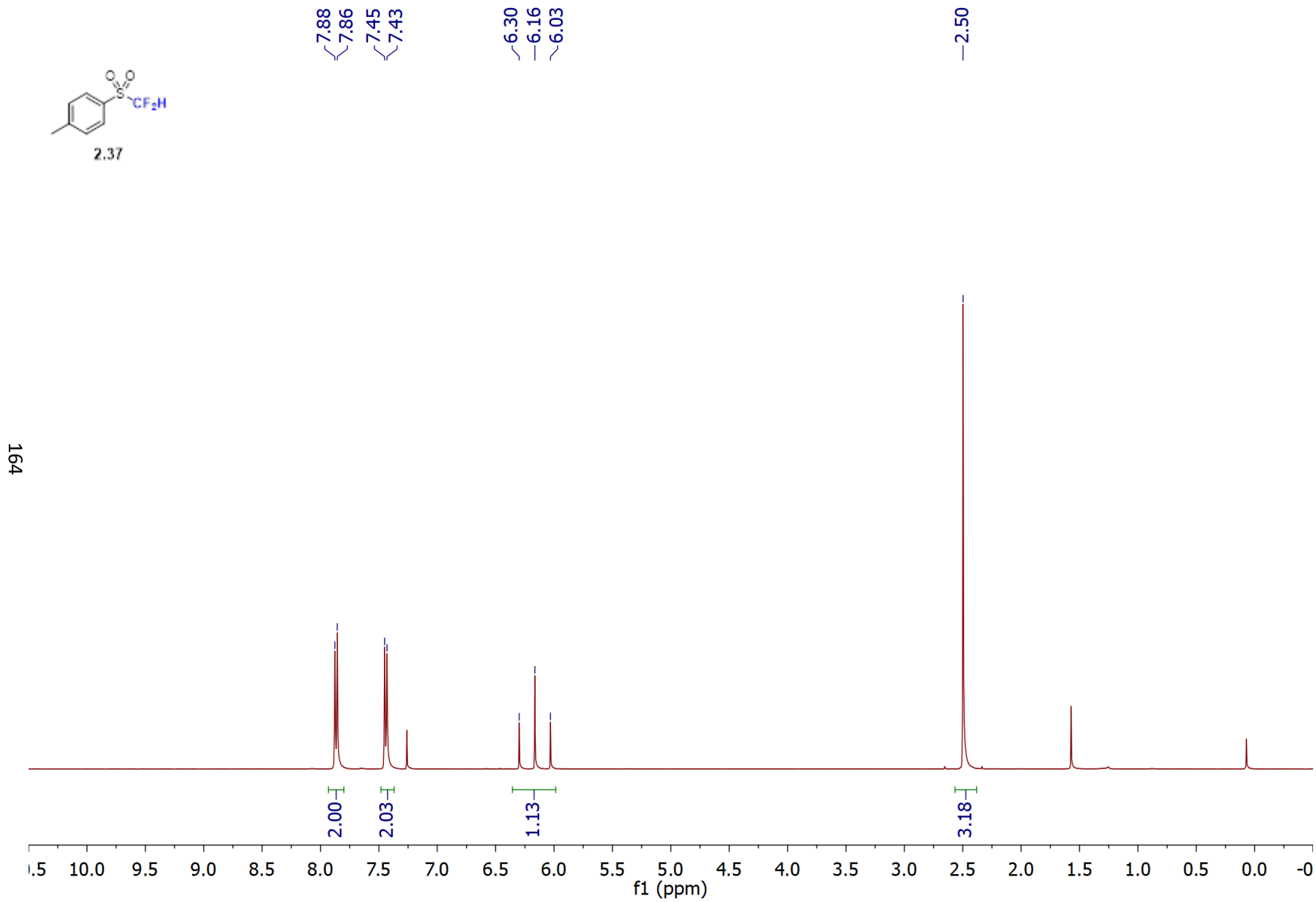
-122.84
-122.98

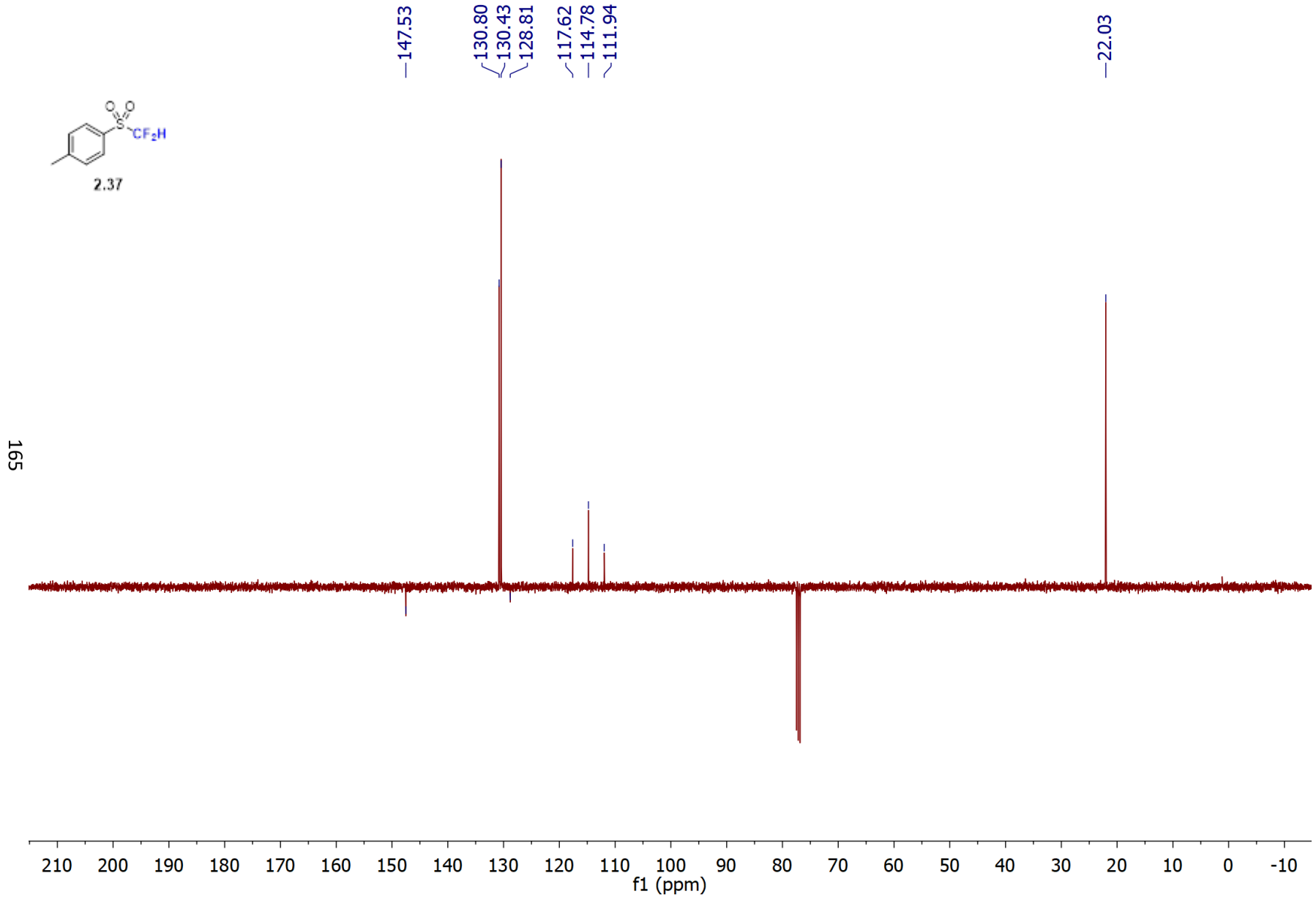
163

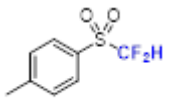
2.00

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

f1 (ppm)


7.88
7.86
7.45
7.43
6.30
6.16
6.03
2.50
CF2H
2.37
164
2.00
2.03
1.13
3.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


147.53
130.80
130.43
128.81
117.62
114.78
111.94
22.03
CF2H
2.37
165
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



2.37

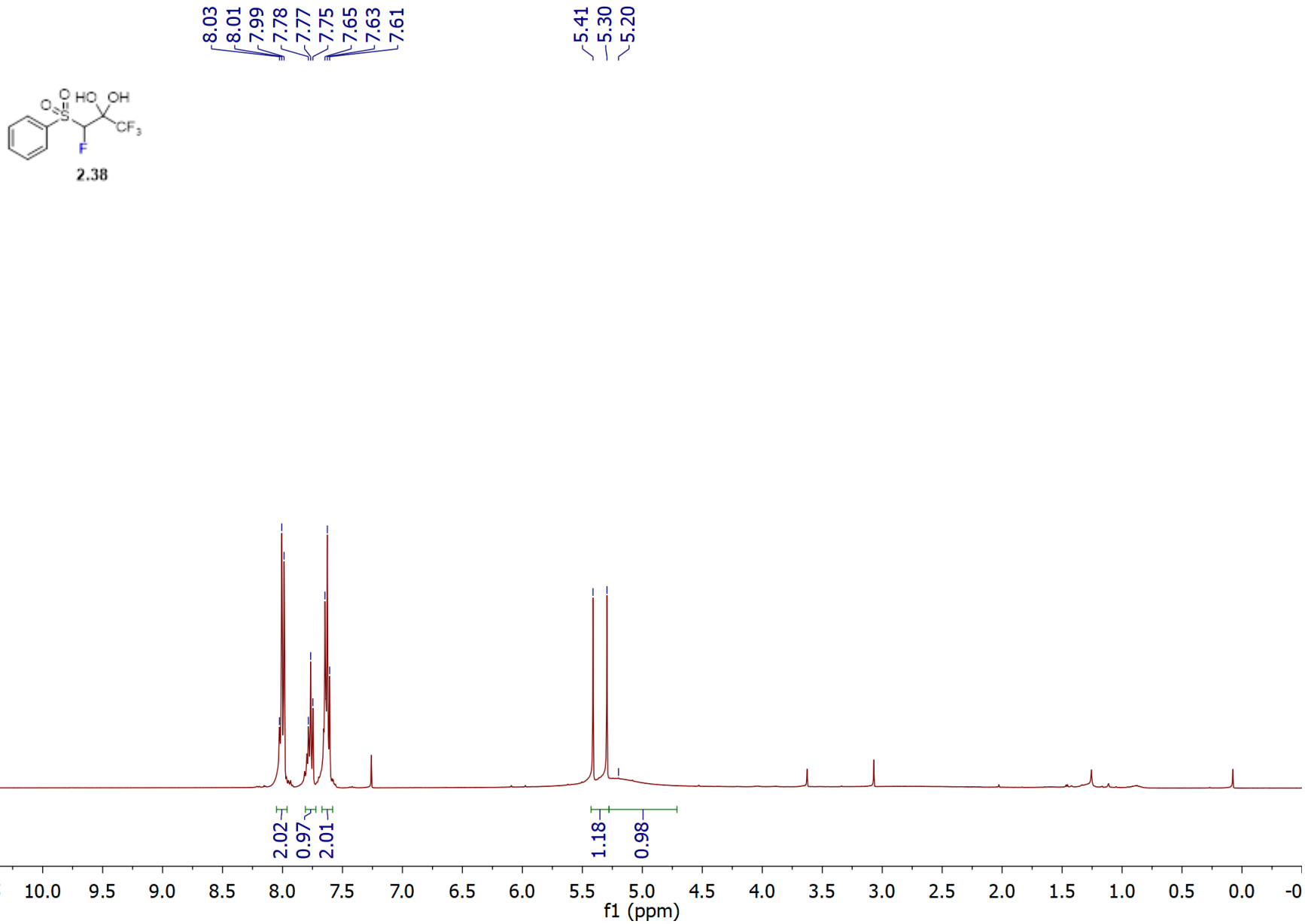
-122.65
-122.80

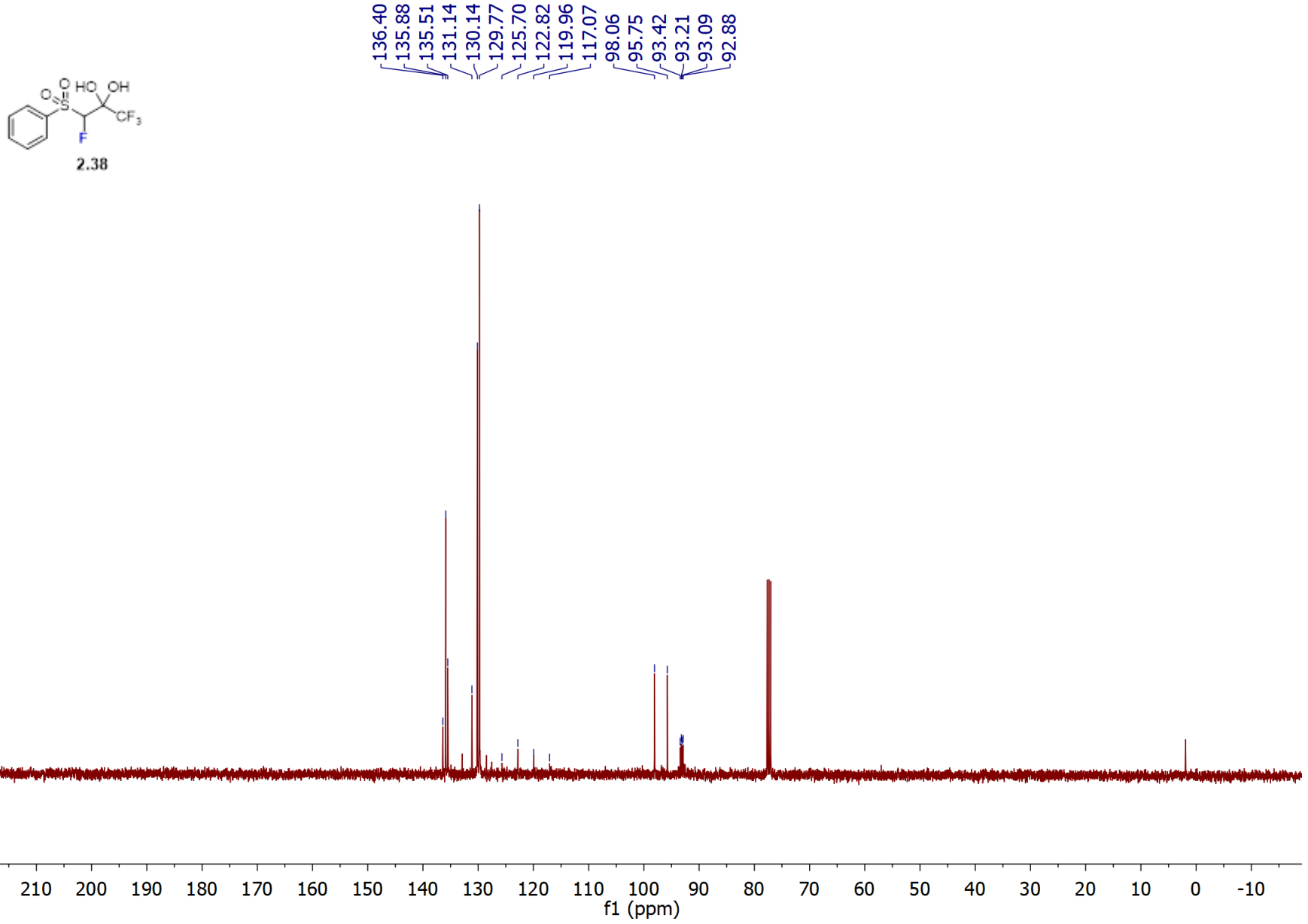
166

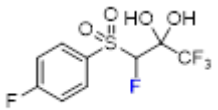
2.00

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

f1 (ppm)

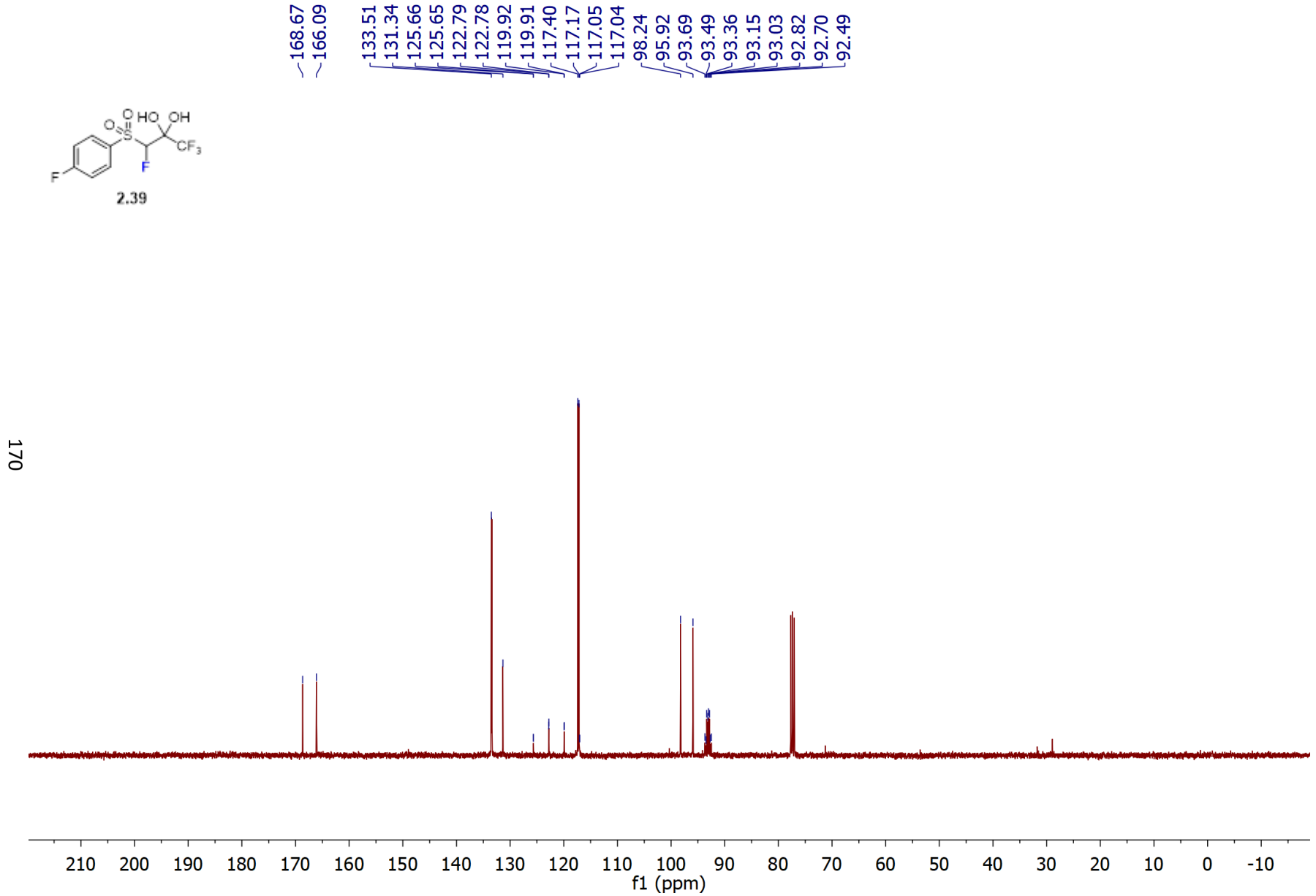

8.03
8.01
7.99
7.78
7.77
7.75
7.65
7.63
7.61
5.41
5.30
5.20
HO
OH
CF3
F
2.38
2.02
0.97
2.01
1.18
0.98
f1 (ppm)


136.40
135.88
135.51
131.14
130.14
129.77
125.70
122.82
119.96
117.07
98.06
95.75
93.42
93.21
93.09
92.88
HO
OH
CF3
F
2.38
168
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



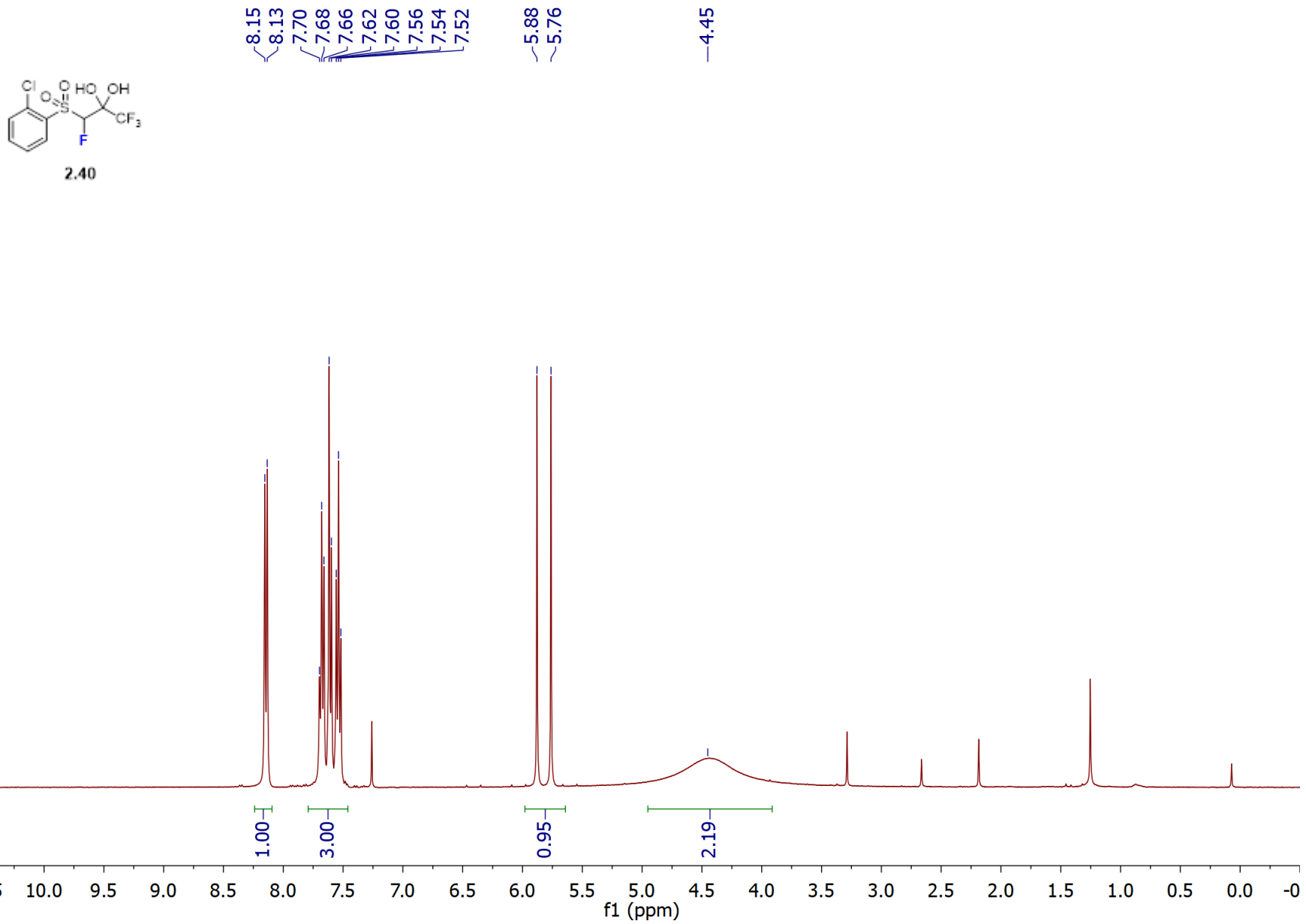
2.39

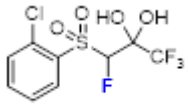
8.03
8.02
8.01
8.00
7.31
7.29
7.27
5.41
5.29
4.99
2.00
2.15
1.07
1.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


168.67
166.09
133.51
131.34
125.66
125.65
122.79
122.78
119.92
119.91
117.40
117.17
117.05
117.04
98.24
95.92
93.69
93.49
93.36
93.15
93.03
92.82
92.70
92.49
HO
OH
CF3
F
F
2.39
170
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

2.39

-84.87
-84.89
-100.35
-185.23
-185.24
-185.26
-185.28
-185.31
-185.33
-185.35
-185.37
171
3.15
1.14
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


8.15
8.13
7.70
7.68
7.66
7.62
7.60
7.56
7.54
7.52
5.88
5.76
4.45
Cl
O
O
S
HO
OH
CF3
F
2.40
172
1.00
3.00
0.95
2.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



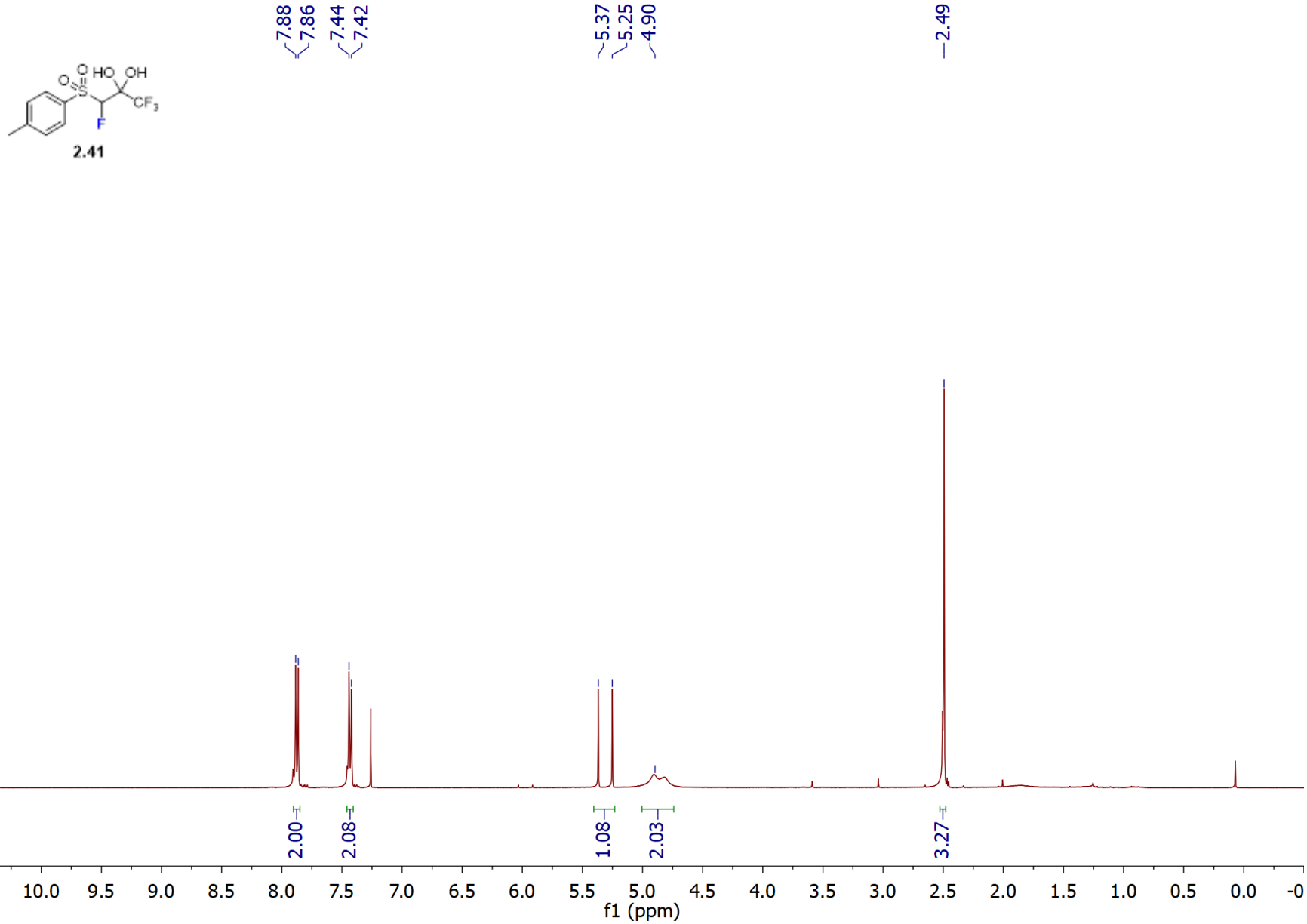
2.40

136.80
134.00
133.71
133.32
132.56
128.14
125.57
122.70
122.69
119.84
119.82
116.99
96.37
94.05
93.80
93.58
93.46
93.25

173

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

f1 (ppm)


7.88
7.86
7.44
7.42
5.37
5.25
4.90
2.49
HO
OH
CF3
F
2.41
174
2.00
2.08
1.08
2.03
3.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

2.41

147.63
132.33
130.48
130.27
125.61
122.75
119.88
117.02
97.70
95.38
93.44
93.23
93.11
92.90
22.10

175

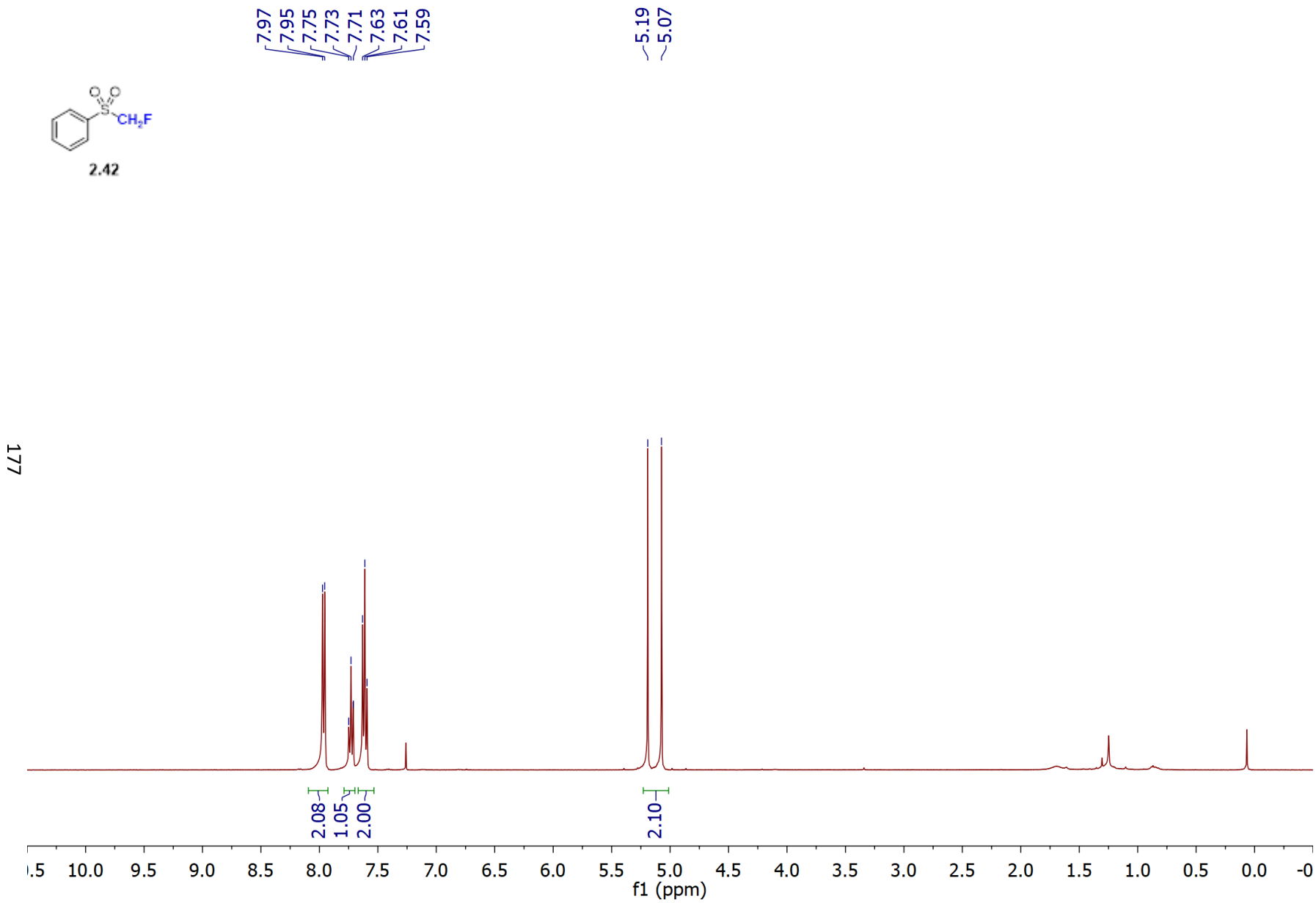
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

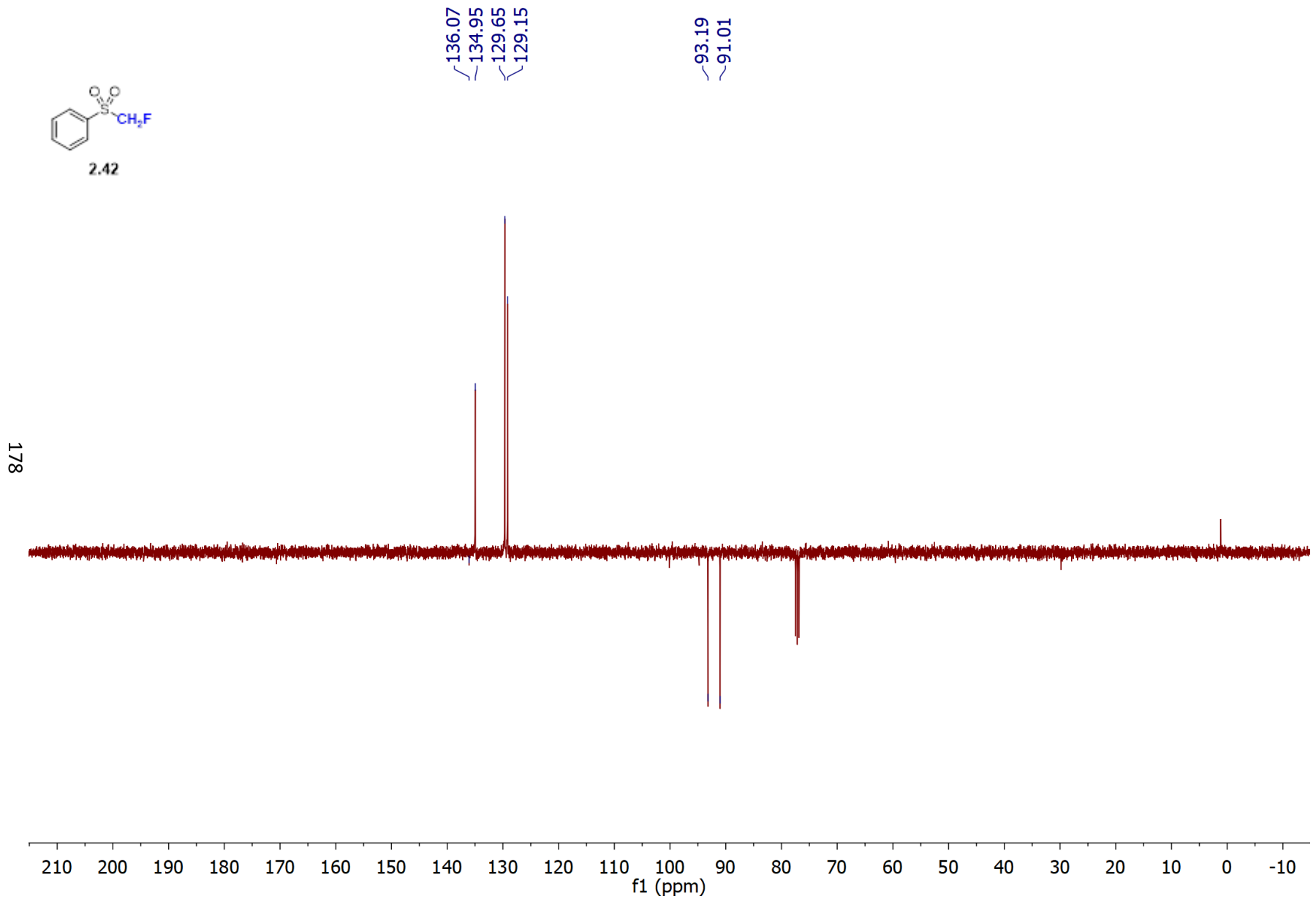
f1 (ppm)

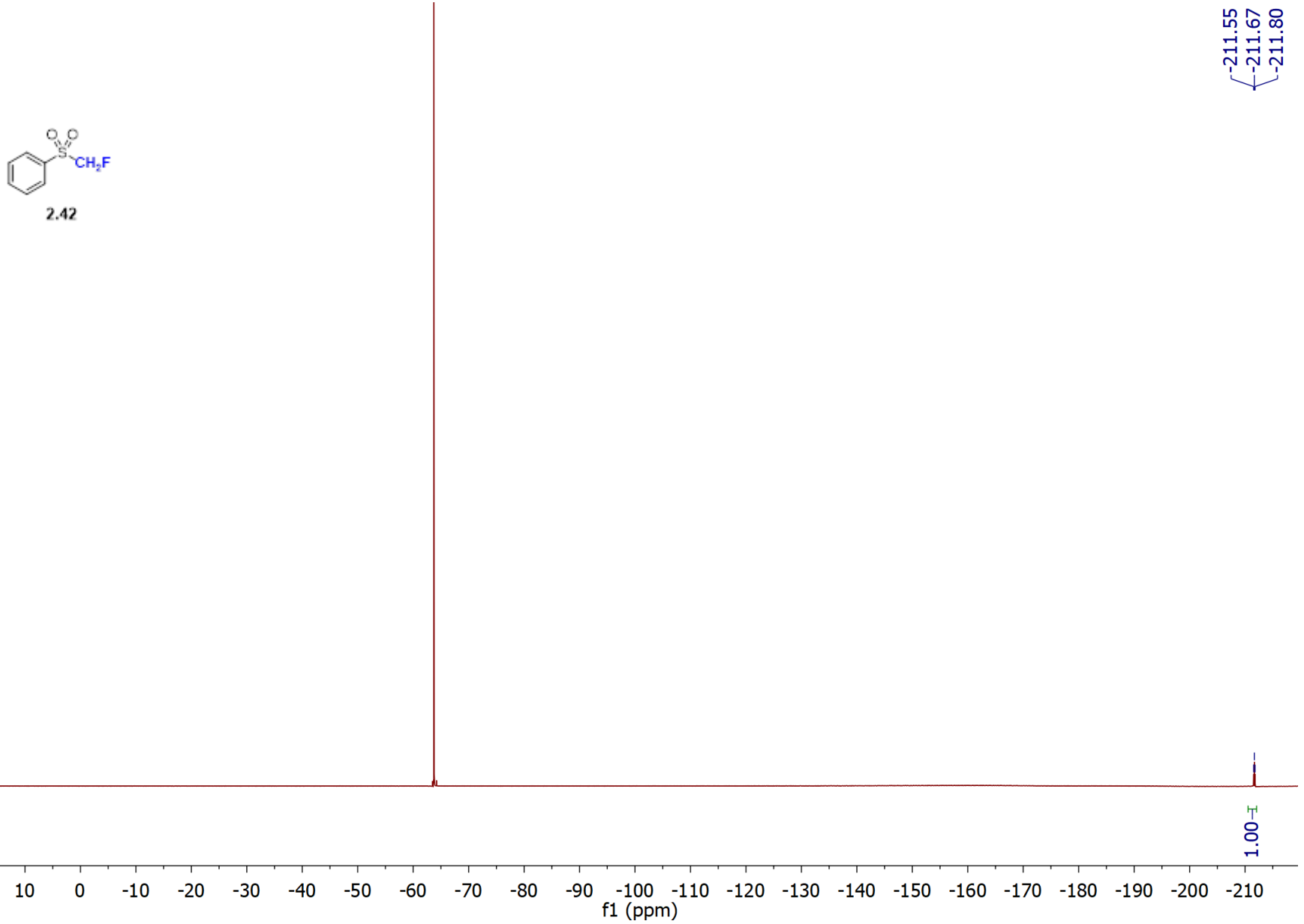

O
O
S
HO
OH
CF3
F

2.41

-84.89
-84.91
-185.53
-185.55
-185.57
-185.59
-185.61
-185.63
-185.65
-185.67
176
3.09
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


7.97
7.95
7.75
7.73
7.71
7.63
7.61
7.59
5.19
5.07
CH2F
2.42
177
2.08
1.05
2.00
2.10
f1 (ppm)

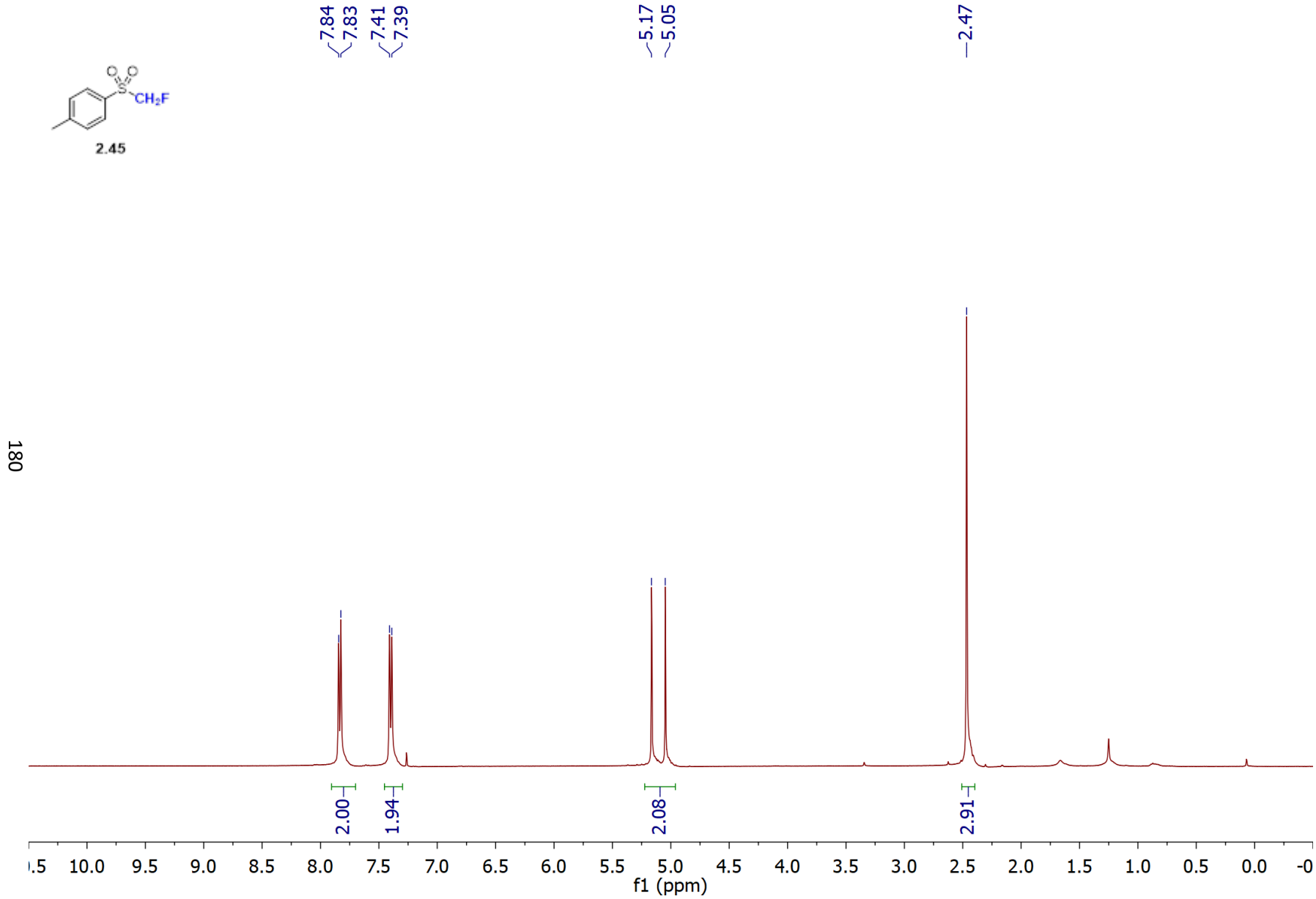

136.07
134.95
129.65
129.15
93.19
91.01
CH2F
2.42
178
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

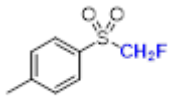

-211.55
-211.67
-211.80
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

O
O
S
CH2F

2.42

179


7.84
7.83
7.41
7.39
5.17
5.05
2.47
CH2F
2.45
180
2.00
1.94
2.08
2.91
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



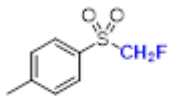
2.45

146.23
133.03
130.28
129.16
93.25
91.07
21.87

181

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

f1 (ppm)



2.45

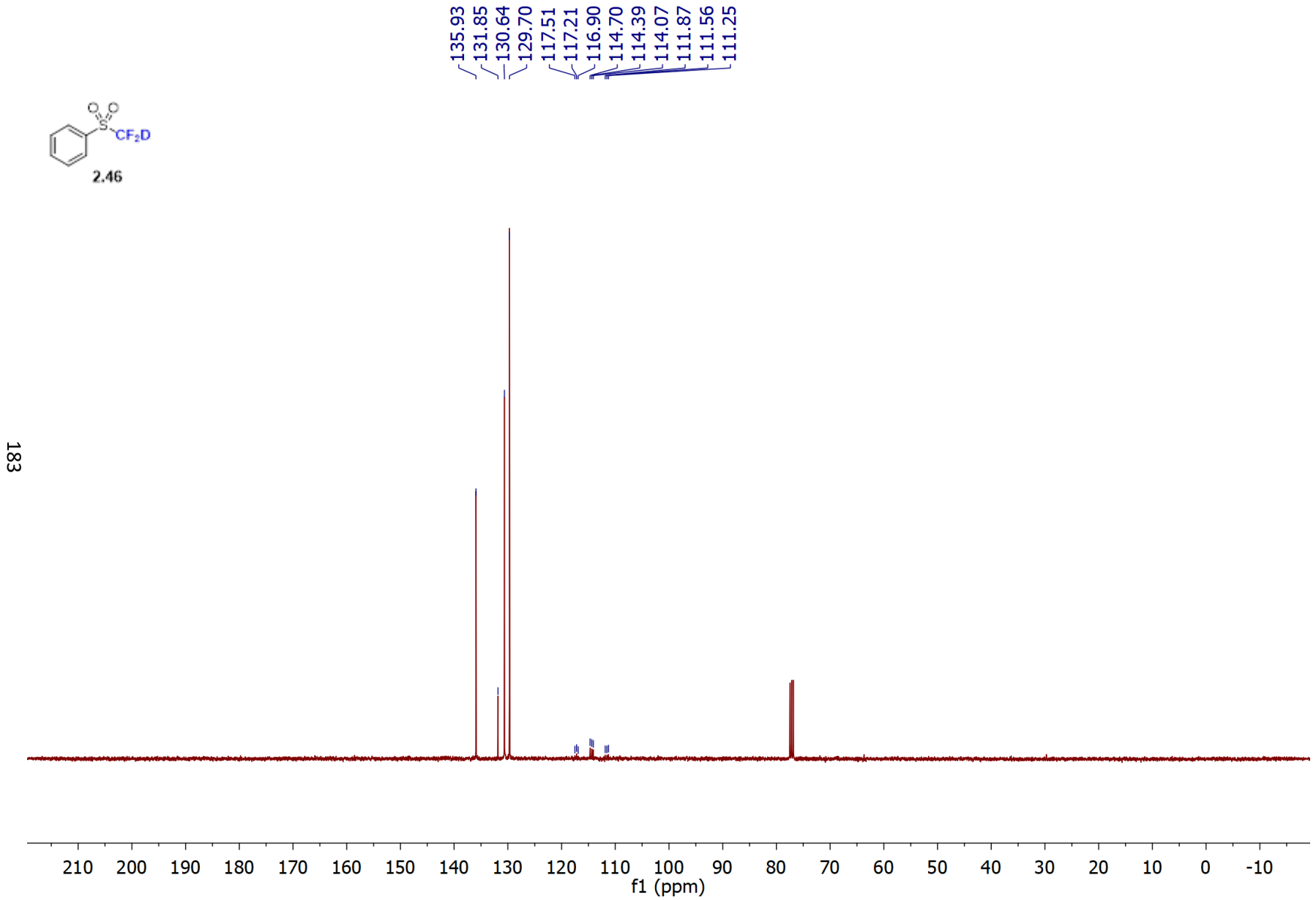
182

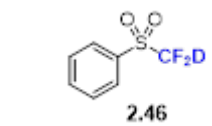
-211.54
-211.67
-211.79

1.00

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

f1 (ppm)


135.93
131.85
130.64
129.70
117.51
117.21
116.90
114.70
114.39
114.07
111.87
111.56
111.25
CF2D
2.46
183
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



2.46

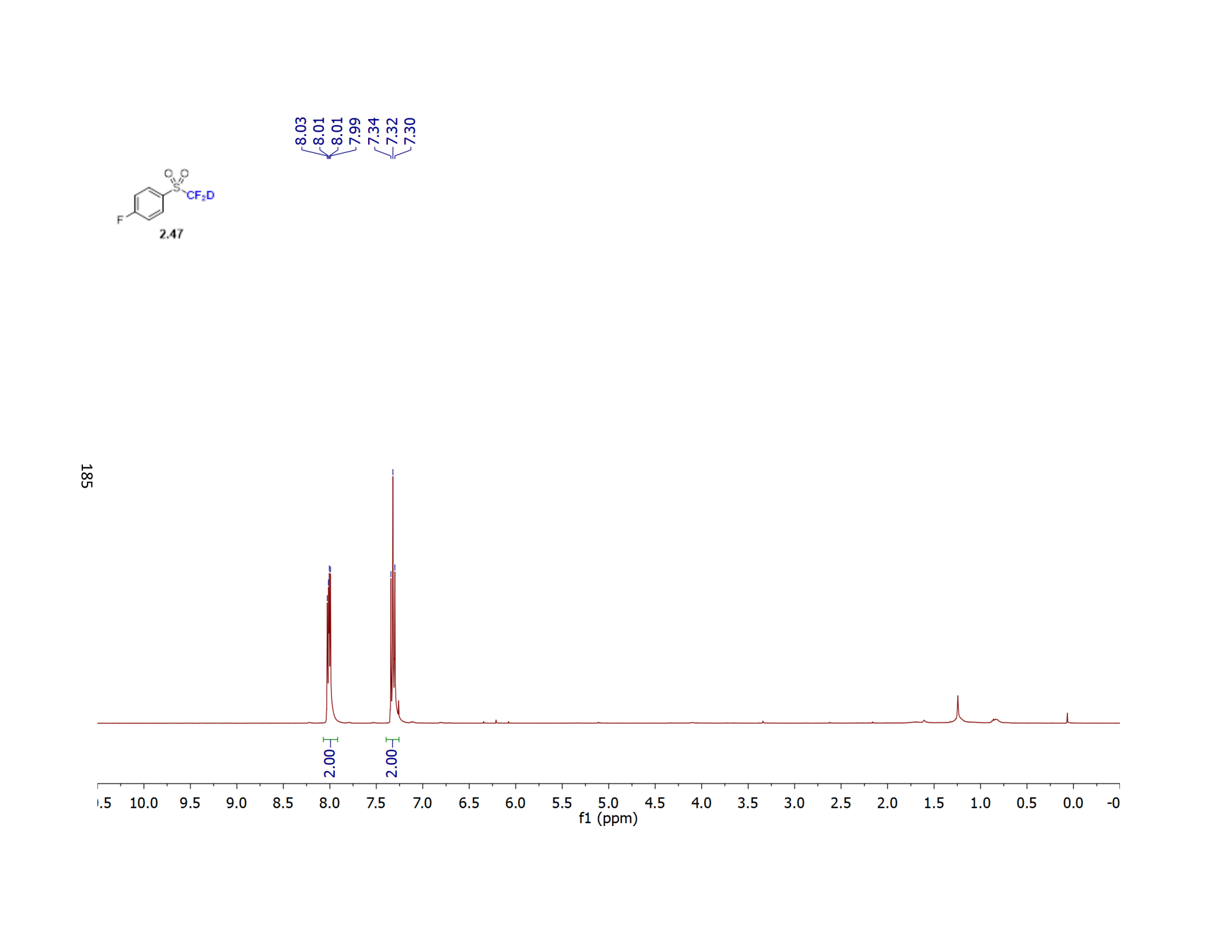
-122.82
-122.96

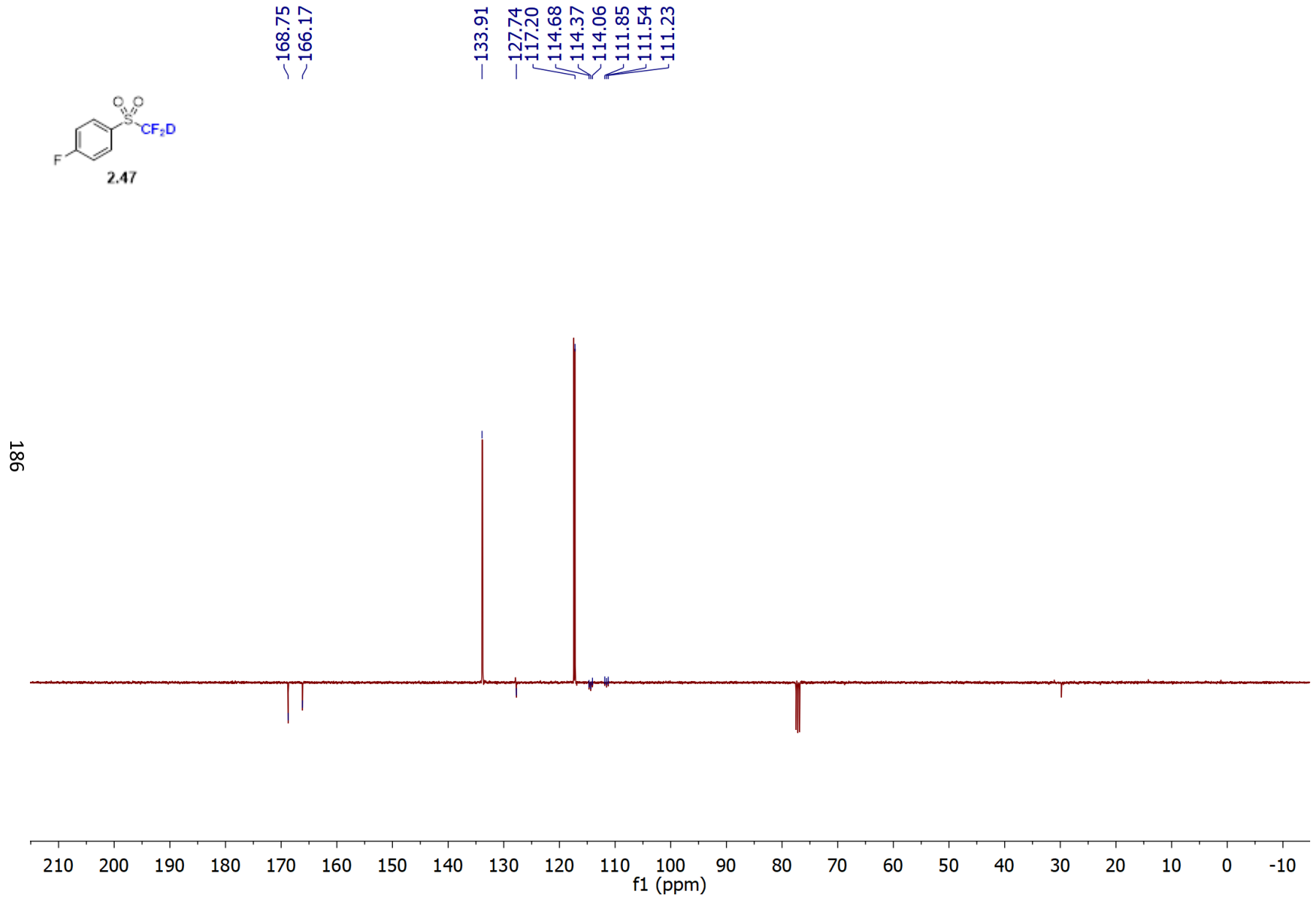
184

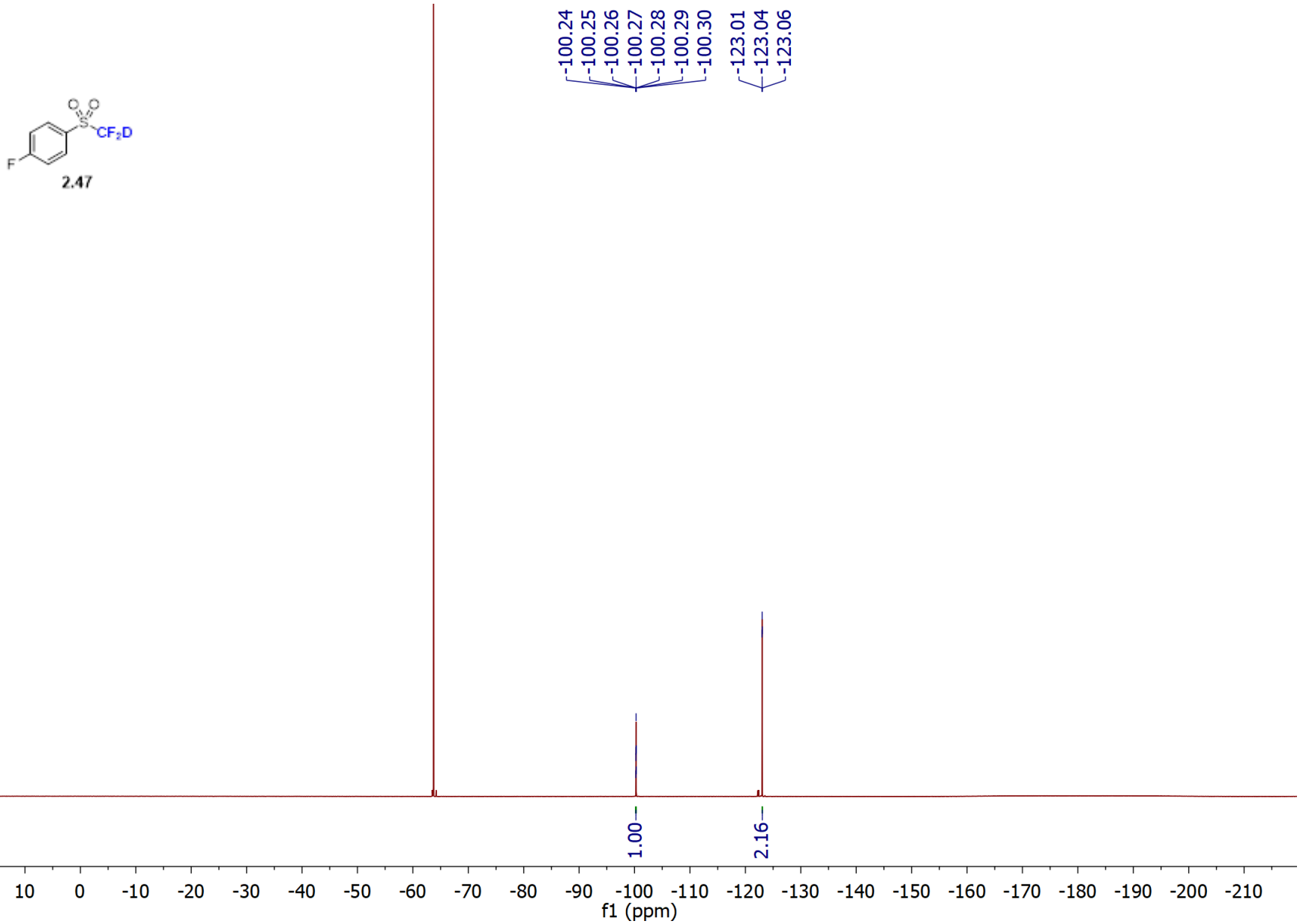
2.00

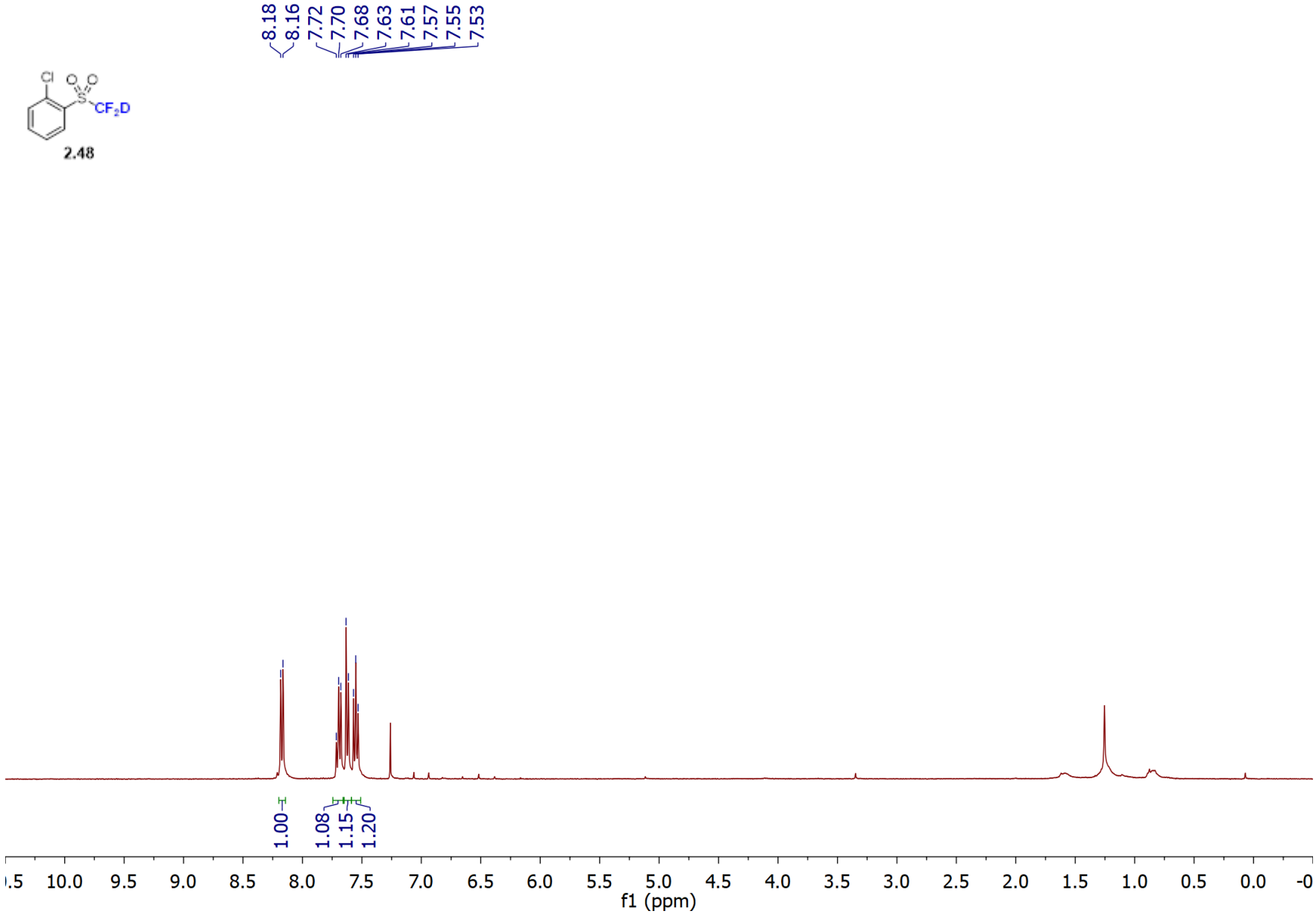
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

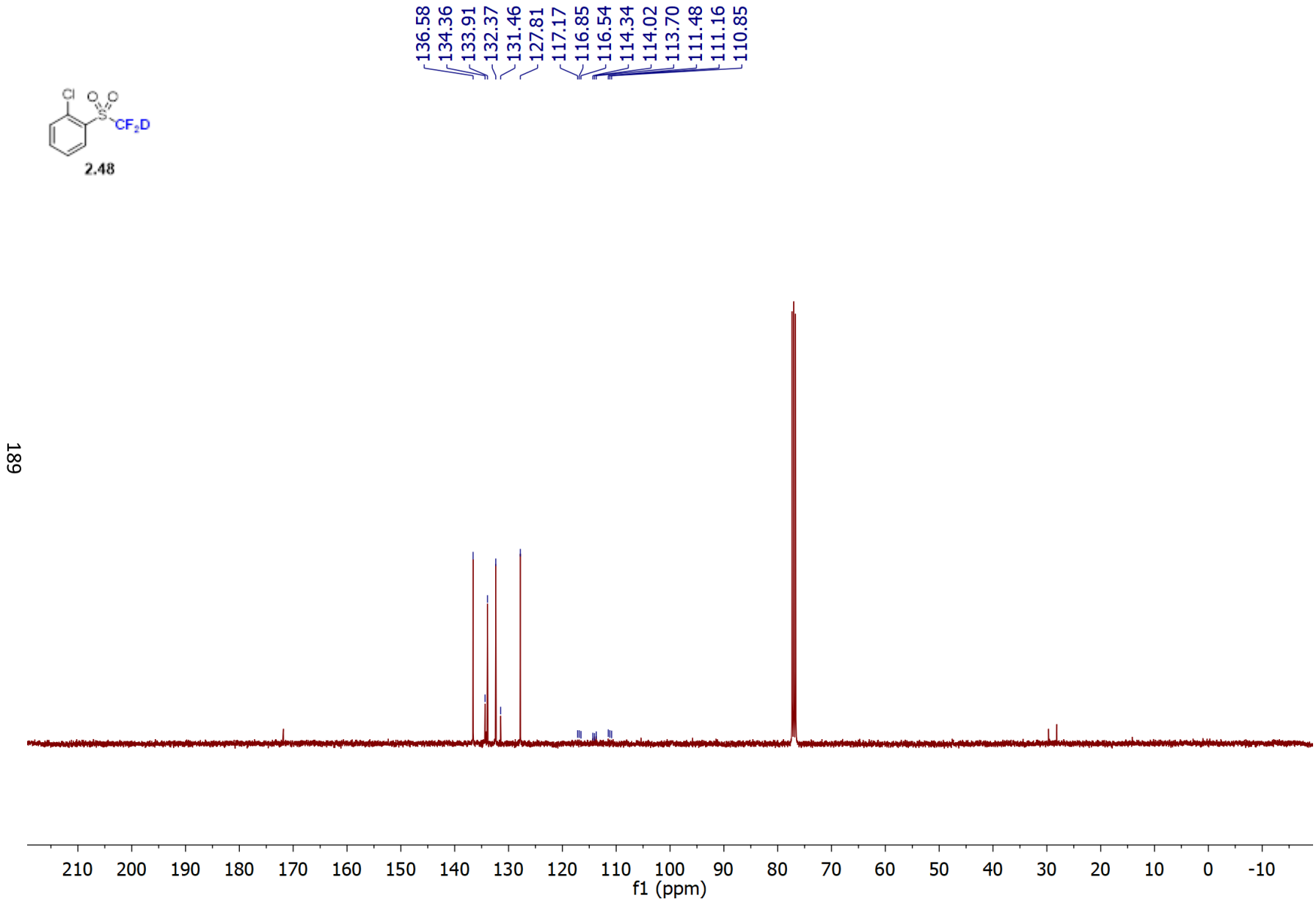
f1 (ppm)

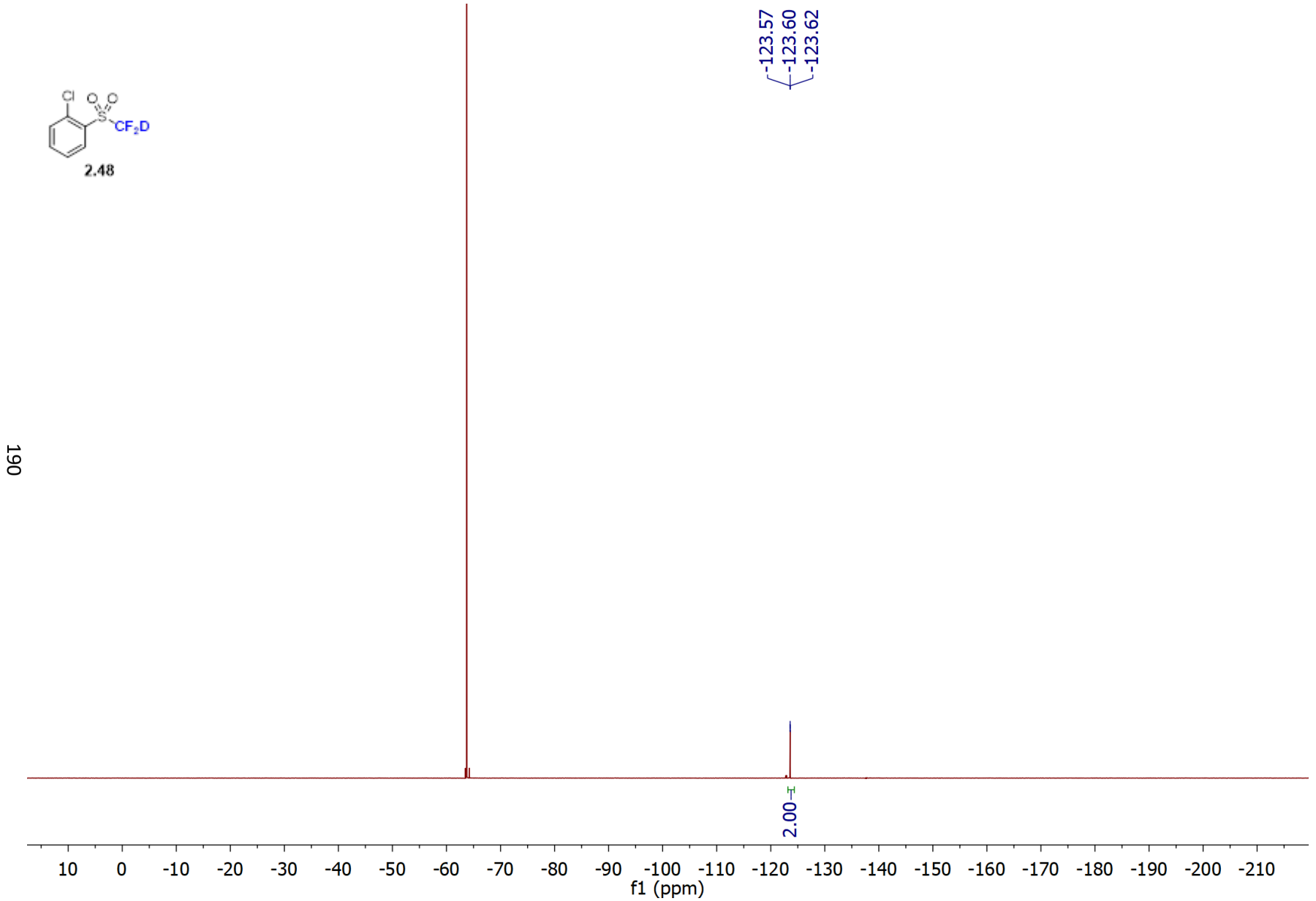

8.03
8.01
8.01
7.99
7.34
7.32
7.30
CF2D
F
2.47
185
2.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

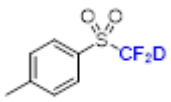

168.75
166.17
133.91
127.74
117.20
114.68
114.37
114.06
111.85
111.54
111.23
CF2D
F
2.47
186
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-100.24
-100.25
-100.26
-100.27
-100.28
-100.29
-100.30
-123.01
-123.04
-123.06
F
CF2D
2.47
187
1.00
2.16
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


8.18
8.16
7.72
7.70
7.68
7.63
7.61
7.57
7.55
7.53
Cl
O
O
S
CF2D
2.48
188
1.00
1.08
1.15
1.20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


136.58
134.36
133.91
132.37
131.46
127.81
117.17
116.85
116.54
114.34
114.02
113.70
111.48
111.16
110.85
Cl
O
O
S
CF2D
2.48
189
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Cl
O
O
S
CF2D
2.48
-123.57
-123.60
-123.62
190
2.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)



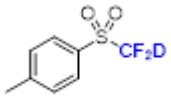
2.49

7.86
7.84
7.43
7.41
2.47

191

2.00
2.03
3.03

f1 (ppm)



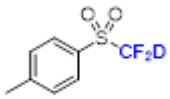
2.49

147.53
130.70
130.40
128.75
117.53
117.21
116.91
114.70
114.39
114.08
111.88
111.57
111.26
21.94

192

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

f1 (ppm)



2.49

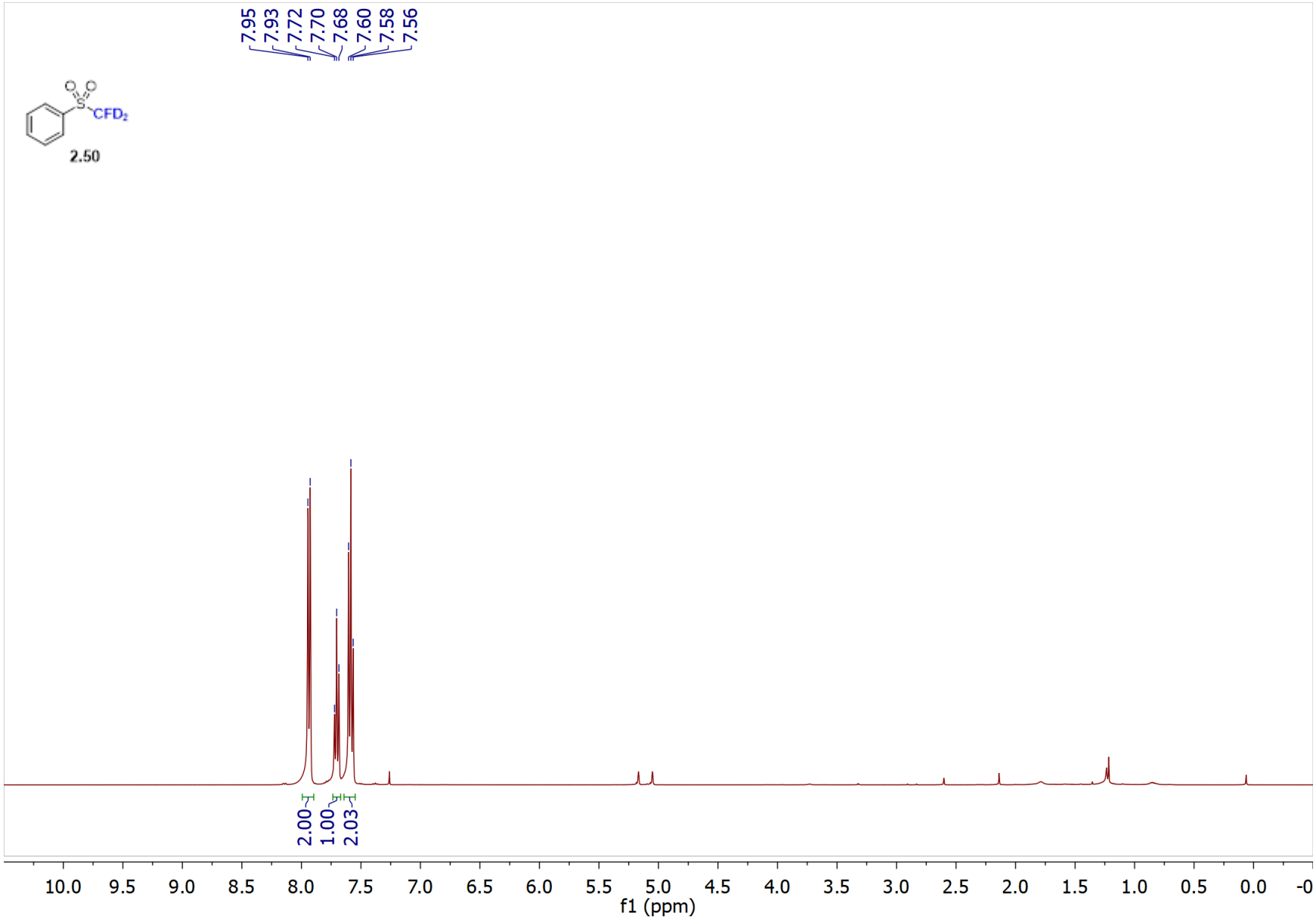
-123.58
-123.60
-123.63

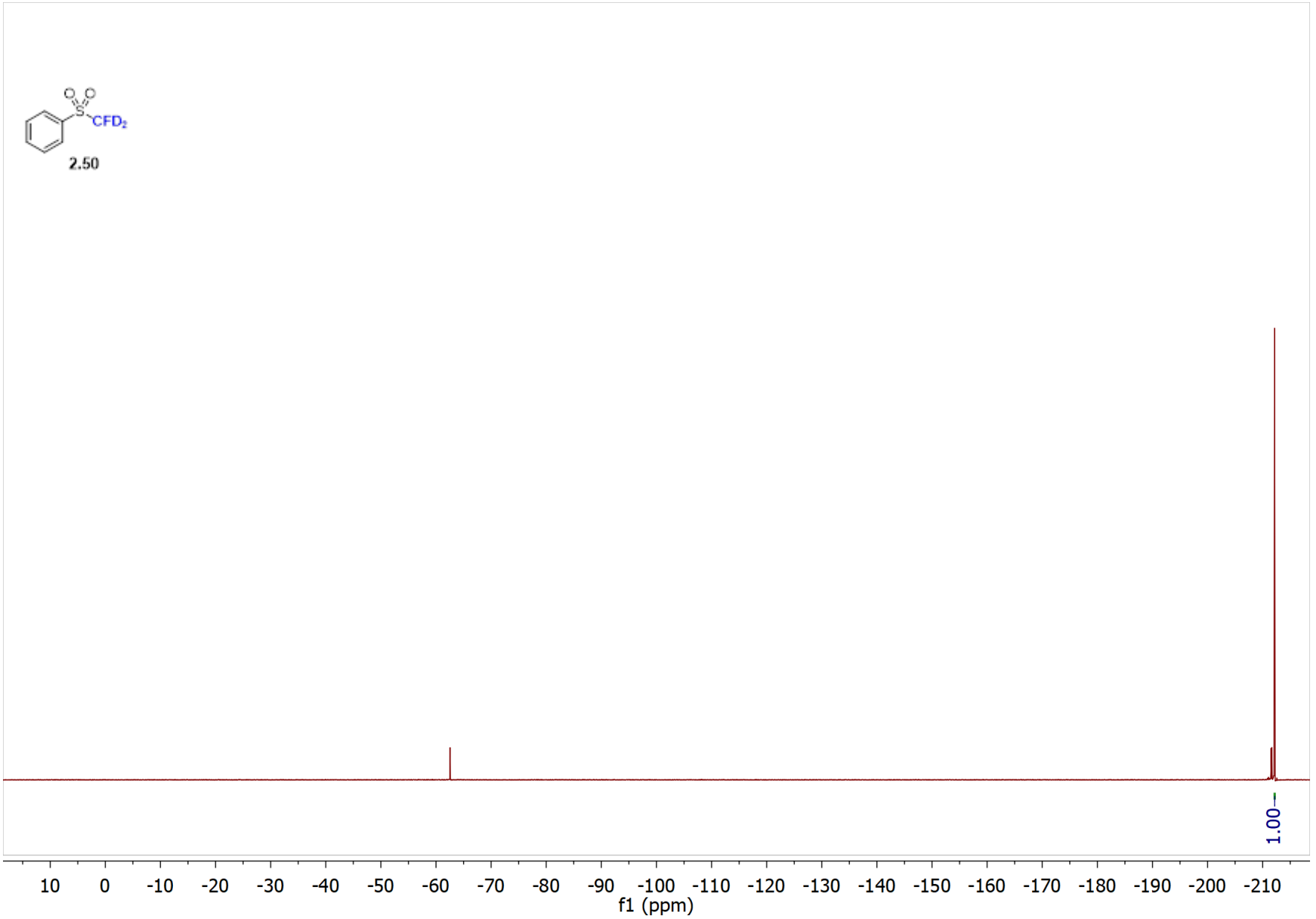
193

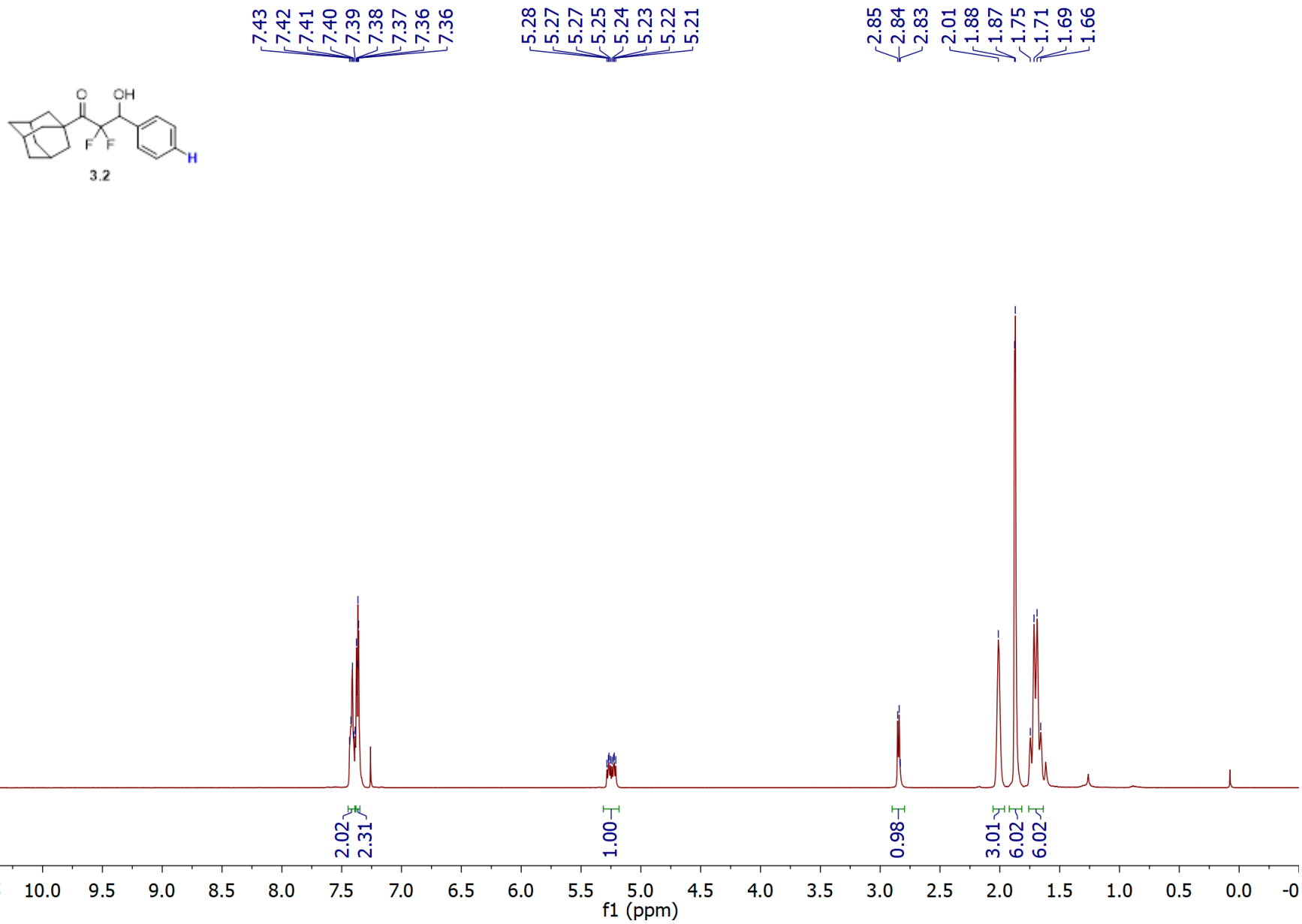
2.01

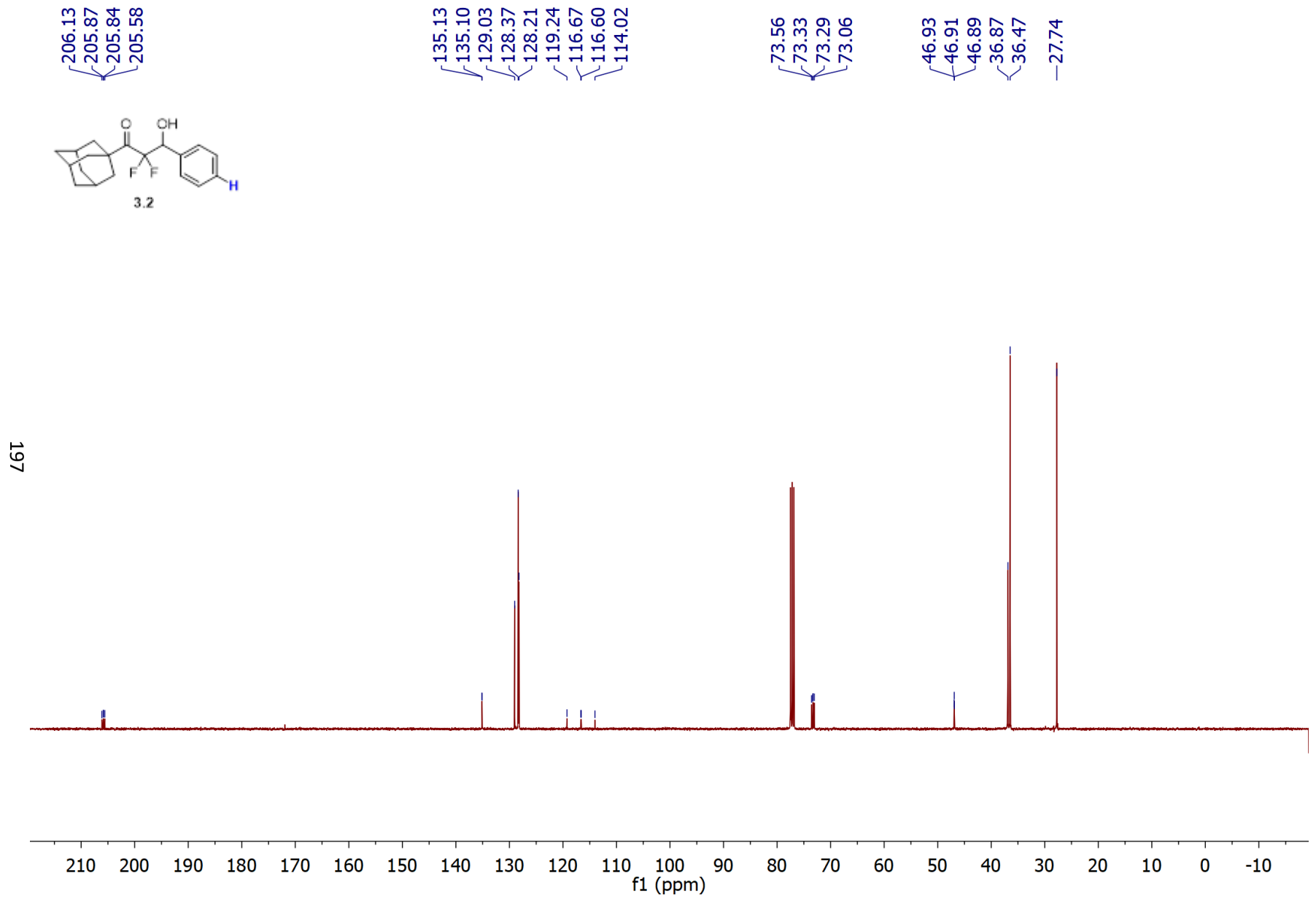
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

f1 (ppm)


7.95
7.93
7.72
7.70
7.68
7.60
7.58
7.56
CFD2
2.50
2.00
1.00
2.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


CFD2
2.50
195
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.36
5.28
5.27
5.27
5.25
5.24
5.23
5.22
5.21
2.85
2.84
2.83
2.01
1.88
1.87
1.75
1.71
1.69
1.66
O
OH
F
F
H
3.2
196
2.02
2.31
1.00
0.98
3.01
6.02
6.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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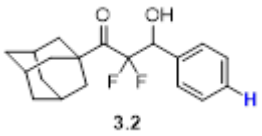
205.87
205.84
205.58
135.13
135.10
129.03
128.37
128.21
119.24
116.67
116.60
114.02
73.56
73.33
73.29
73.06
46.93
46.91
46.89
36.87
36.47
27.74
O
OH
F
F
H
3.2
197
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



3.2

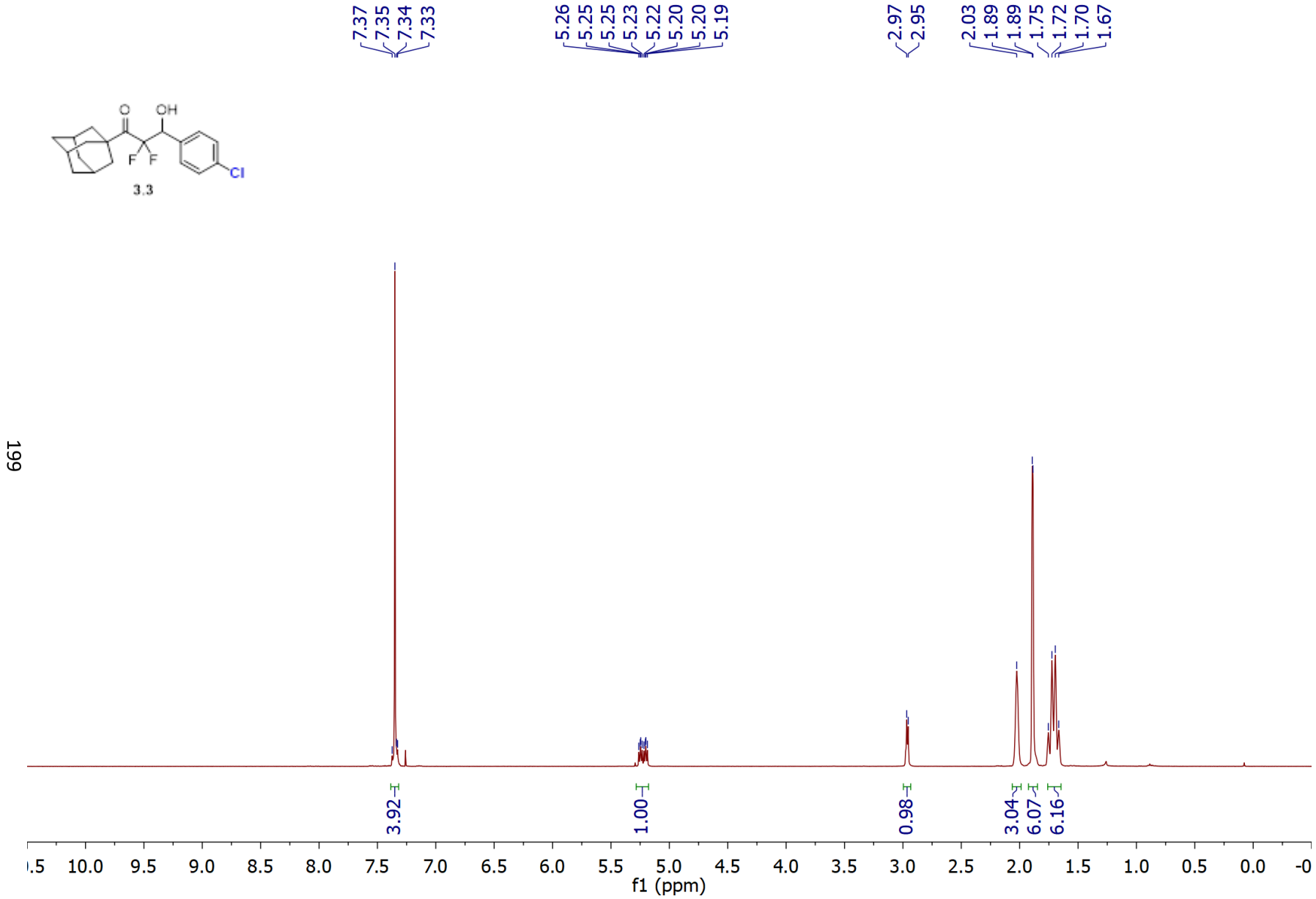
-107.79
-107.81
-108.55
-108.57
-118.62
-118.67
-119.38
-119.42

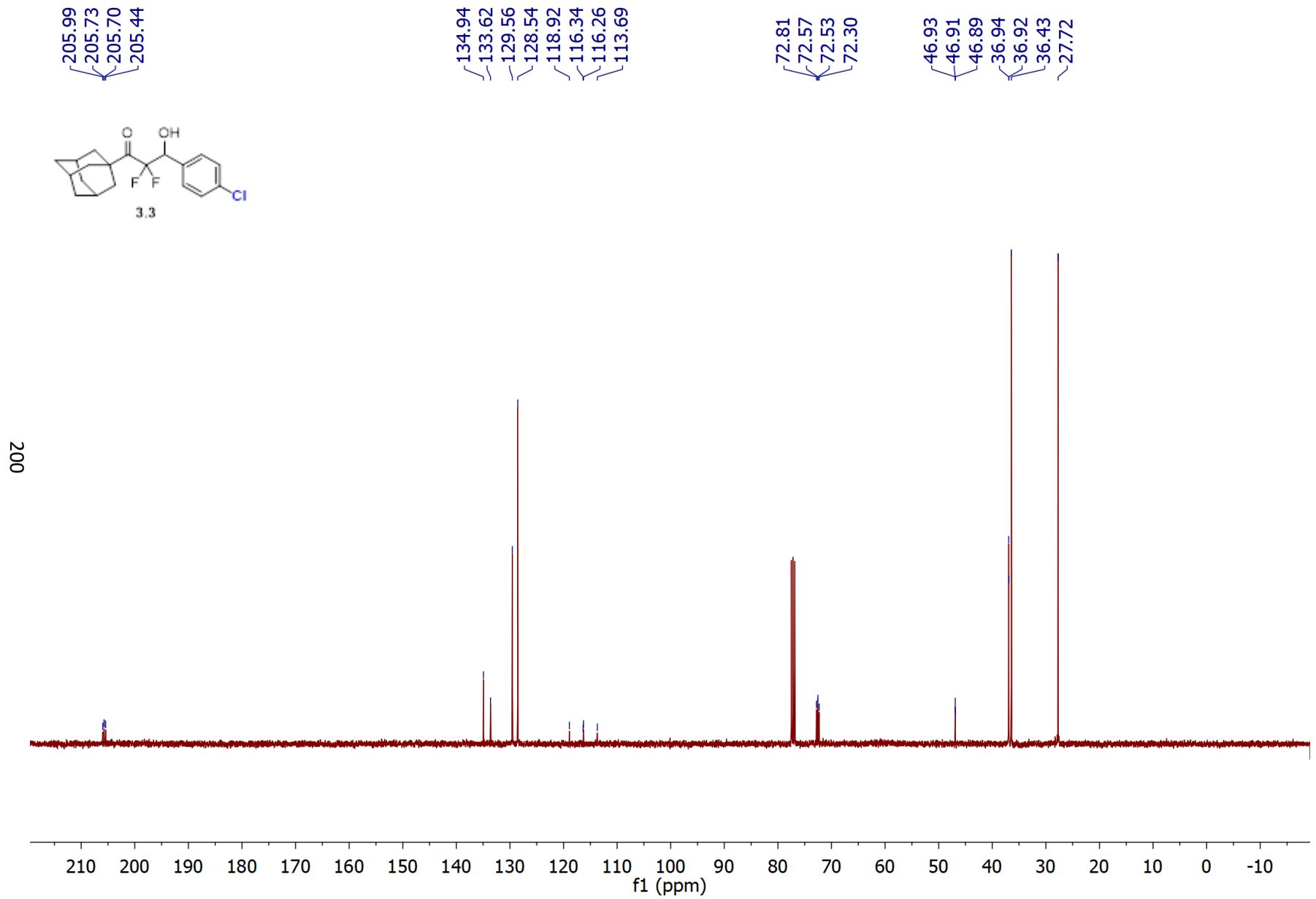
198

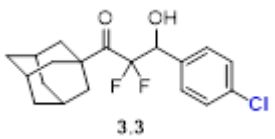
1.04
1.00

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

f1 (ppm)


7.37
7.35
7.34
7.33
5.26
5.25
5.25
5.23
5.22
5.20
5.20
5.19
2.97
2.95
2.03
1.89
1.89
1.75
1.72
1.70
1.67
O
OH
F F
Cl
3.3
199
3.92
1.00
0.98
3.04
6.07
6.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


205.99
205.73
205.70
205.44
134.94
133.62
129.56
128.54
118.92
116.34
116.26
113.69
72.81
72.57
72.53
72.30
46.93
46.91
46.89
36.94
36.92
36.43
27.72
O
OH
F F
Cl
3.3
200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



3.3

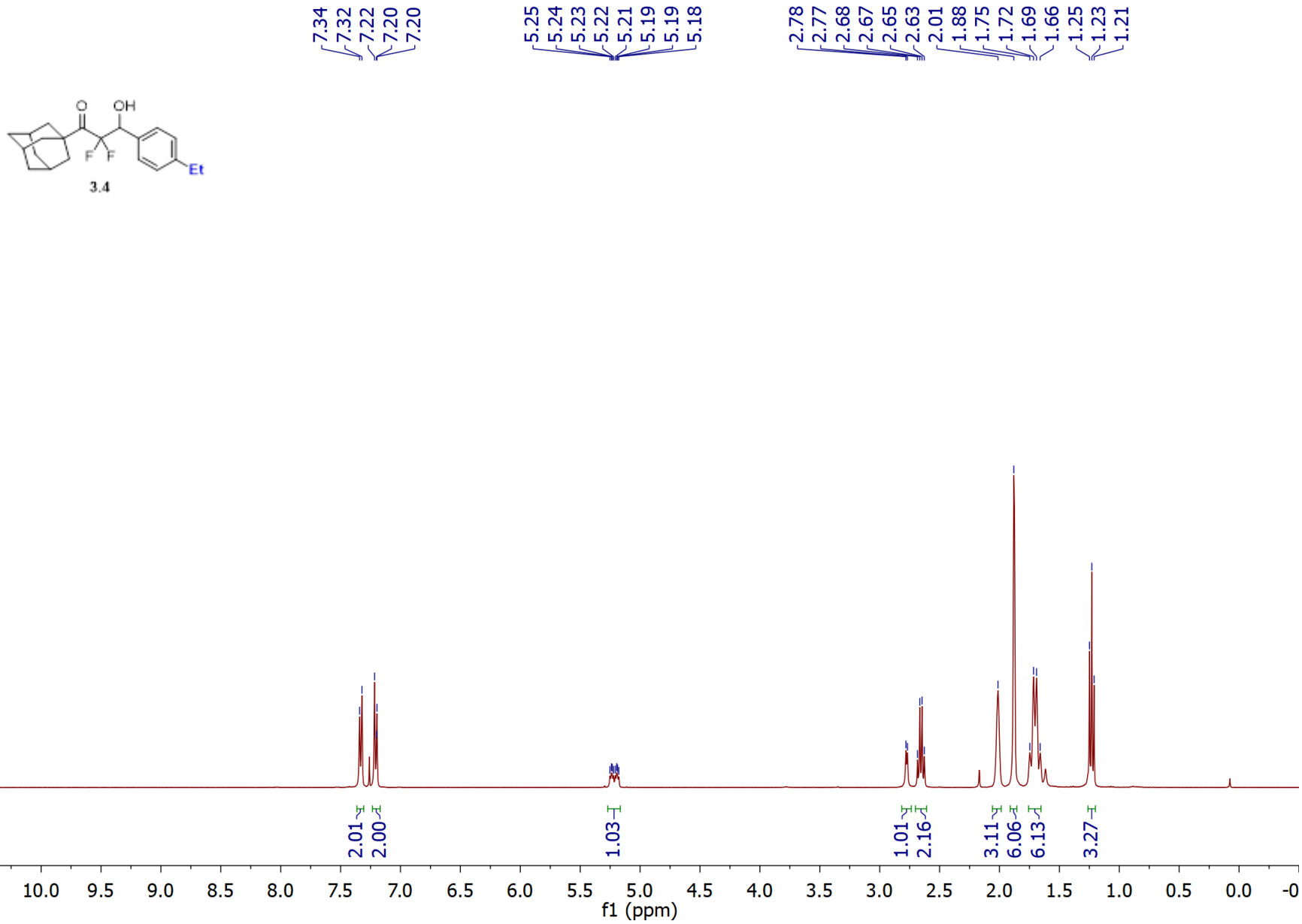
-106.07
-106.09
-106.84
-106.85
-118.54
-118.59
-119.31
-119.35

201

1.00
1.00

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

f1 (ppm)


7.34
7.32
7.22
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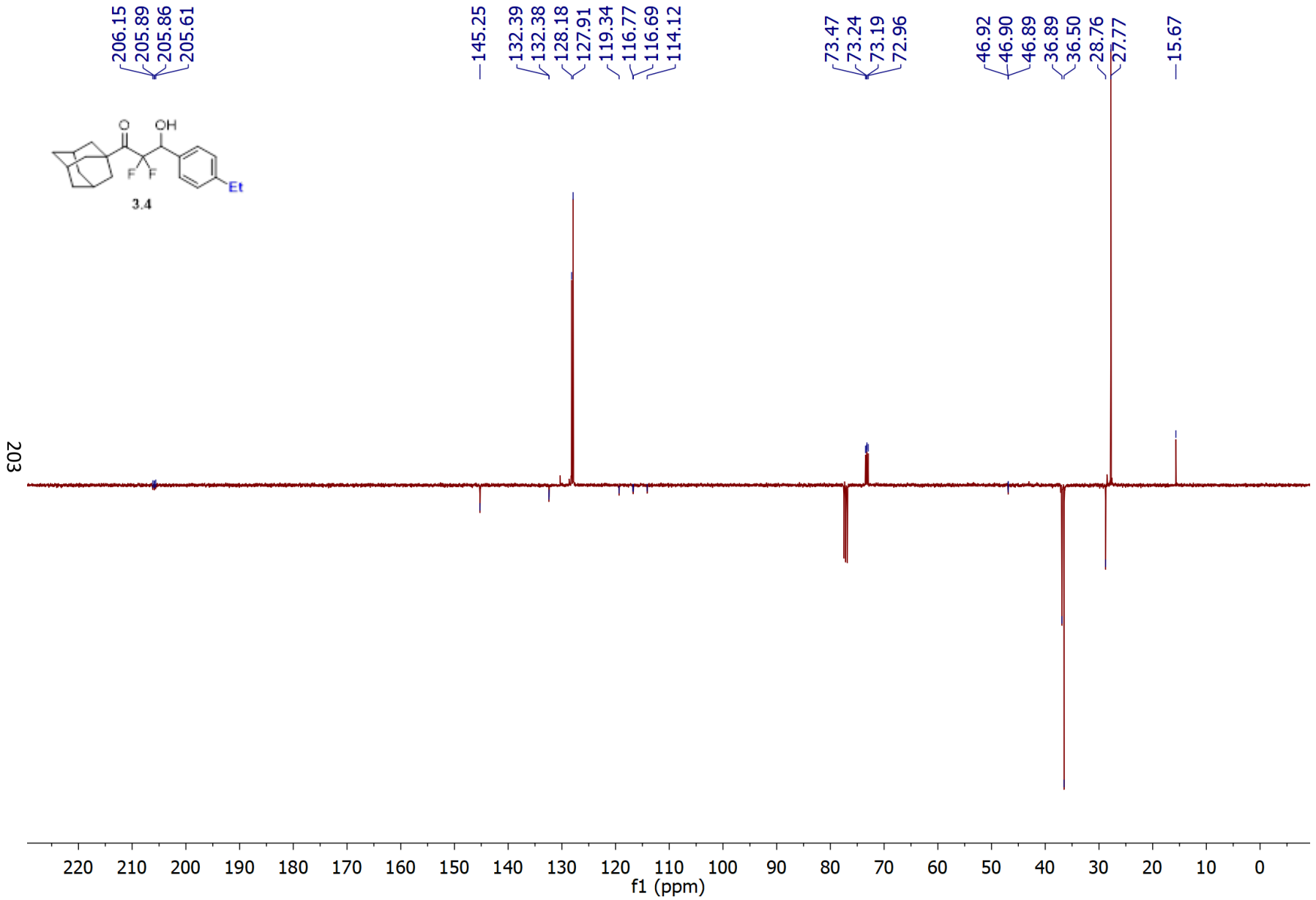
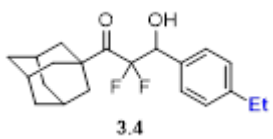
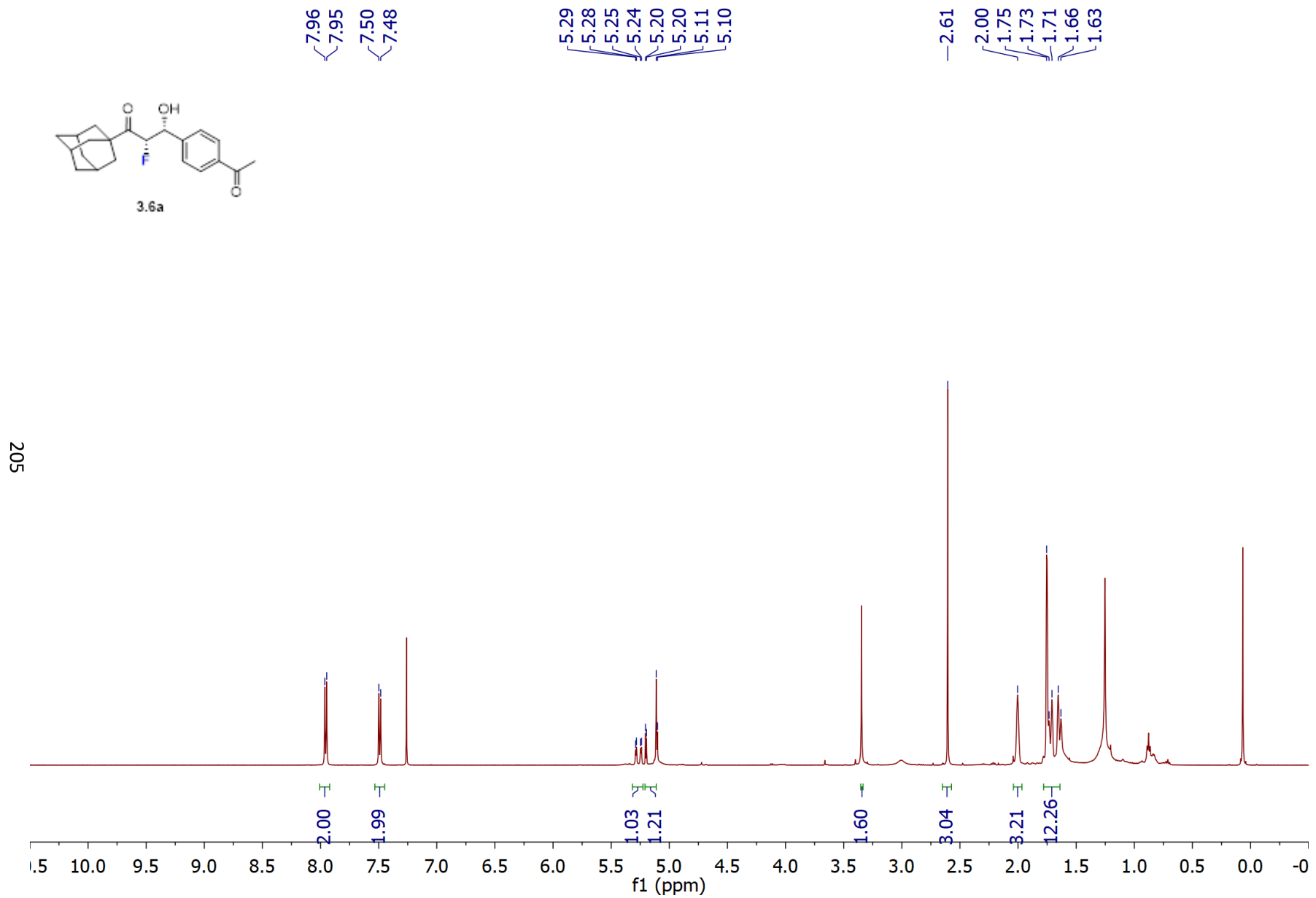
7.20
5.25
5.24
5.23
5.22
5.21
5.19
5.19
5.18
2.78
2.77
2.68
2.67
2.65
2.63
2.01
1.88
1.75
1.72
1.69
1.66
1.25
1.23
1.21
O
OH
F
F
Et
3.4
202
2.01
2.00
1.03
1.01
2.16
3.11
6.06
6.13
3.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

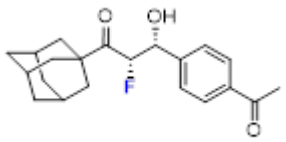

206.15
205.89
205.86
205.61
145.25
132.39
132.38
128.18
127.91
119.34
116.77
116.69
114.12
73.47
73.24
73.19
72.96
46.92
46.90
46.89
36.89
36.50
28.76
27.77
15.67
O
OH
F
F
Et
3.4
203
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OH
F
F
Et

3.4

-107.62
-108.38
-118.86
-118.91
-119.62
-119.66
1.00
1.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


7.96
7.95
7.50
7.48
5.29
5.28
5.25
5.24
5.20
5.20
5.11
5.10
2.61
2.00
1.75
1.73
1.71
1.66
1.63
OH
O
F
O
3.6a
205
2.00
1.99
1.03
1.21
1.60
3.04
3.21
12.26
f1 (ppm)



3.6a

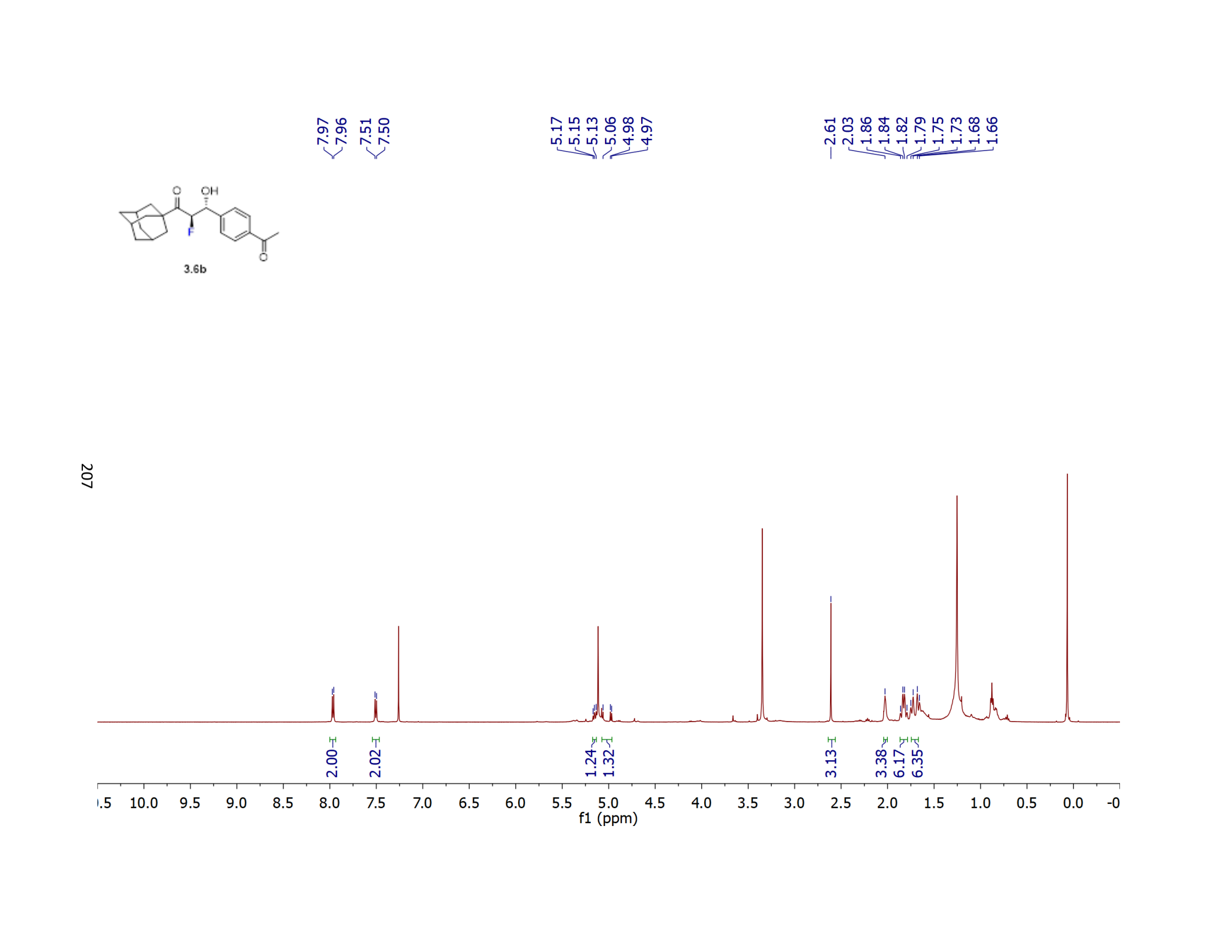
-196.56
-196.61
-196.66
-196.71

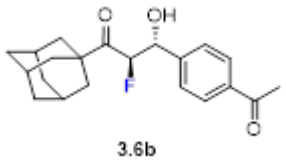
206

1.00

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

f1 (ppm)


7.97
7.96
7.51
7.50
5.17
5.15
5.13
5.06
4.98
4.97
2.61
2.03
1.86
1.84
1.82
1.79
1.75
1.73
1.68
1.66
O
OH
F
O
3.6b
207
2.00
2.02
1.24
1.32
3.13
3.38
6.17
6.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



3.6b

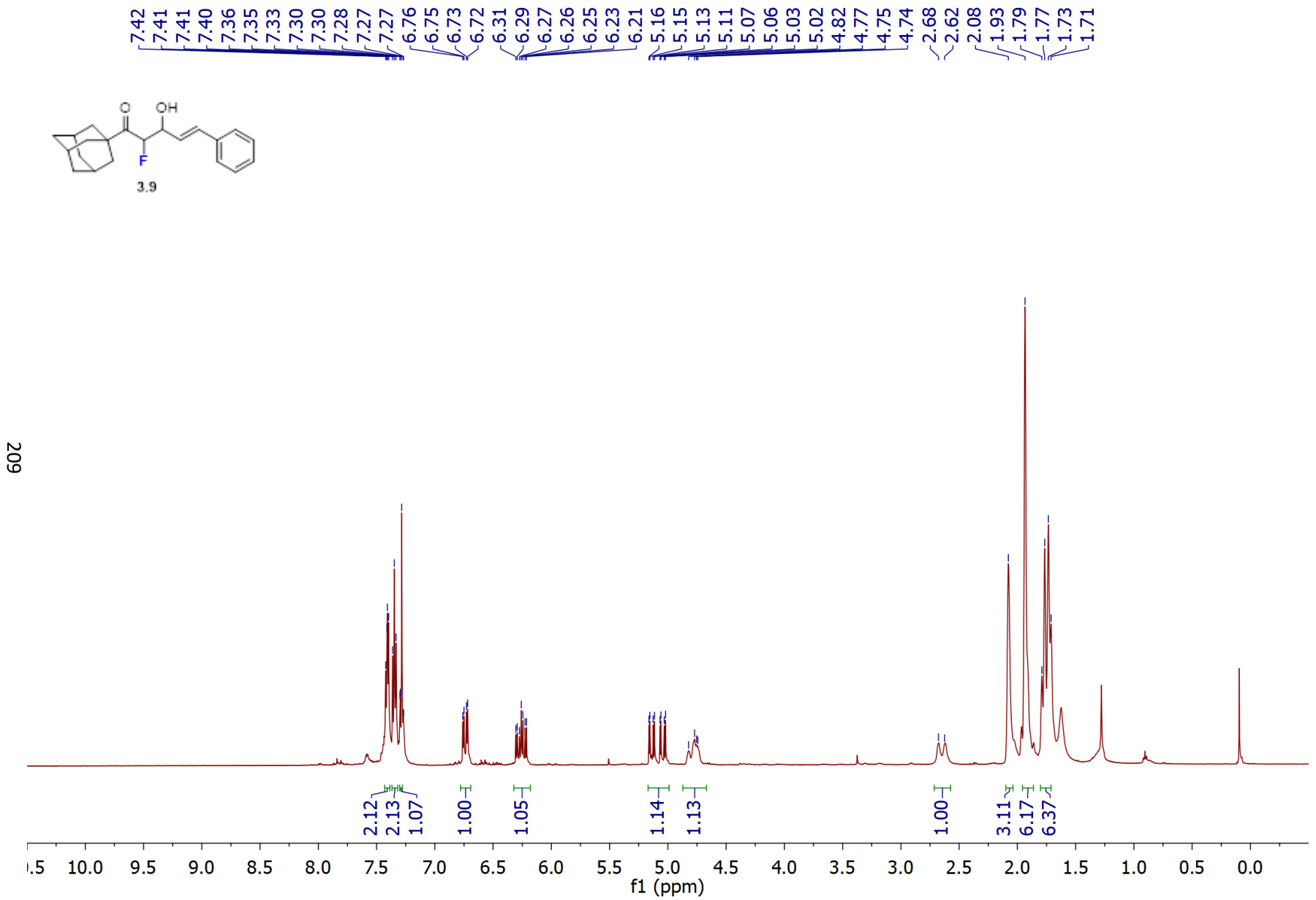
-190.36
-190.38
-190.46
-190.48

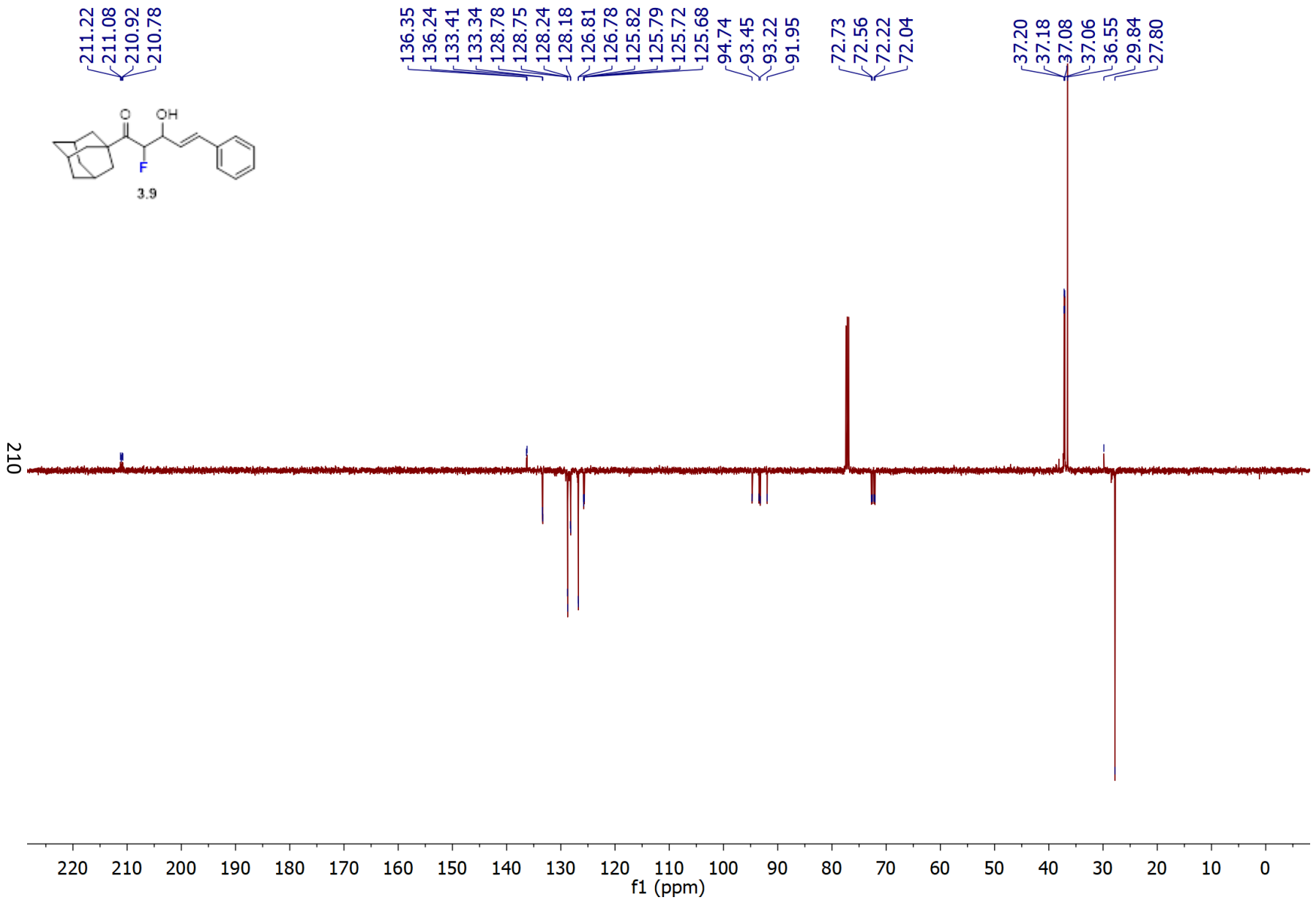
208

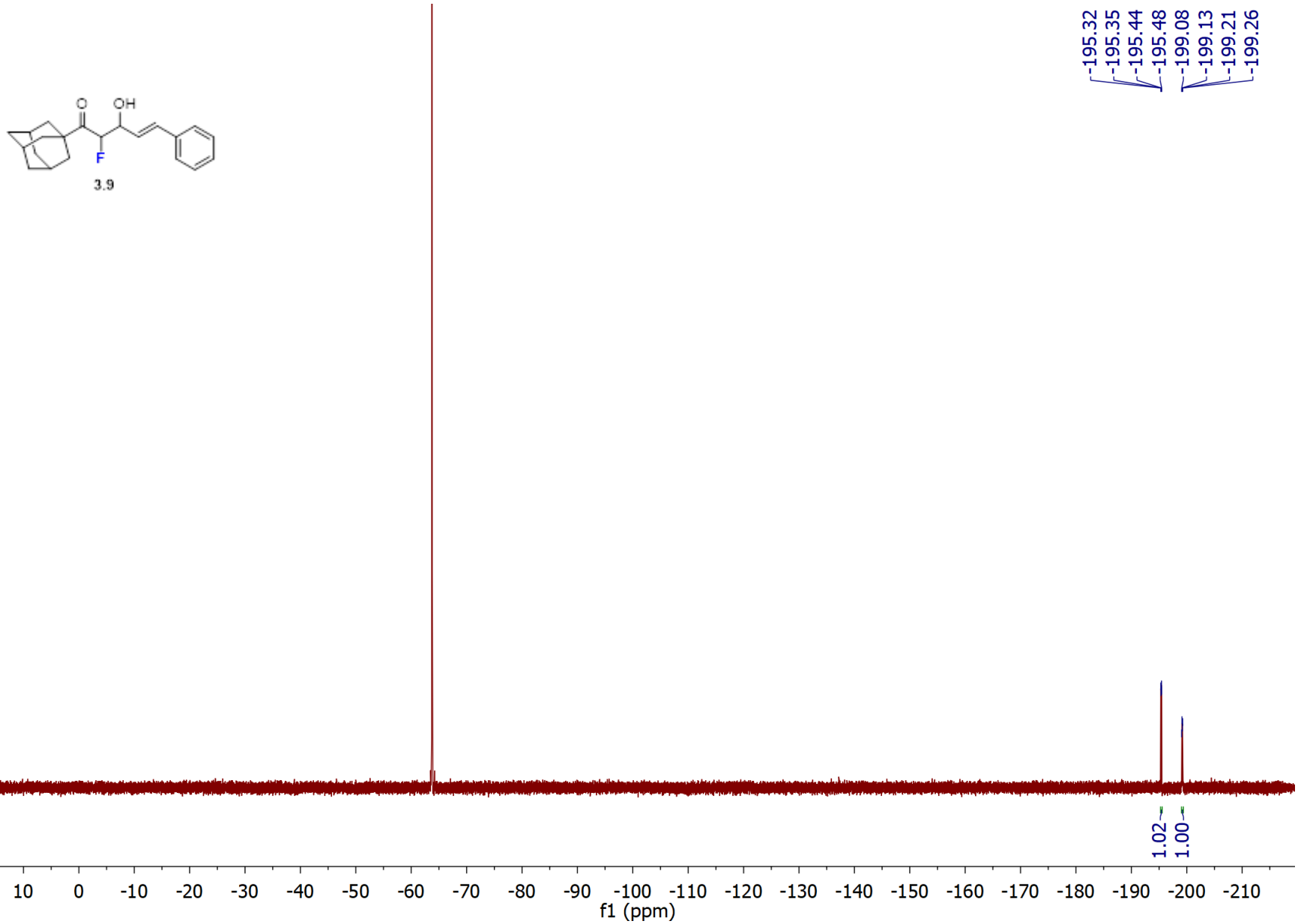
1.00

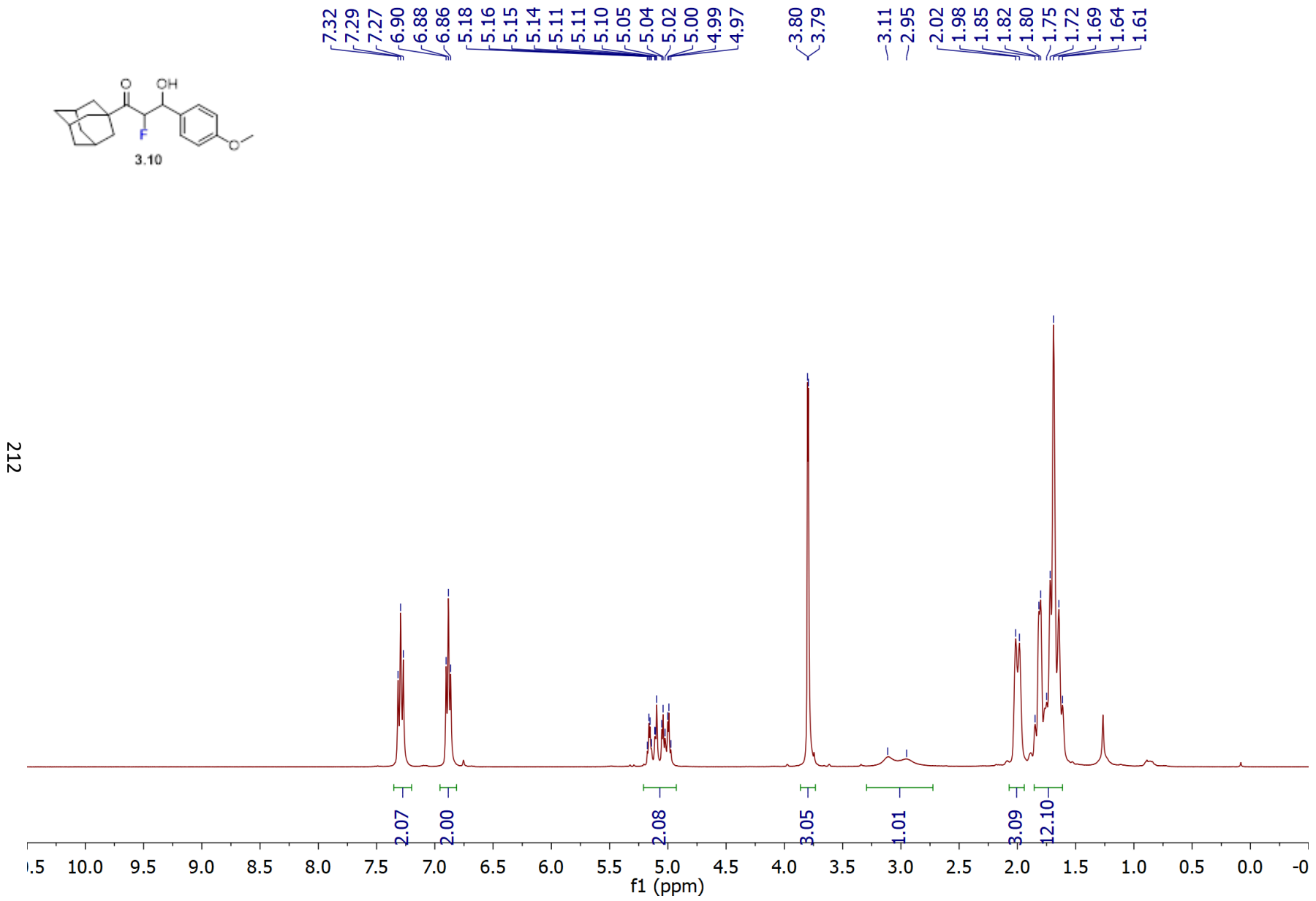
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

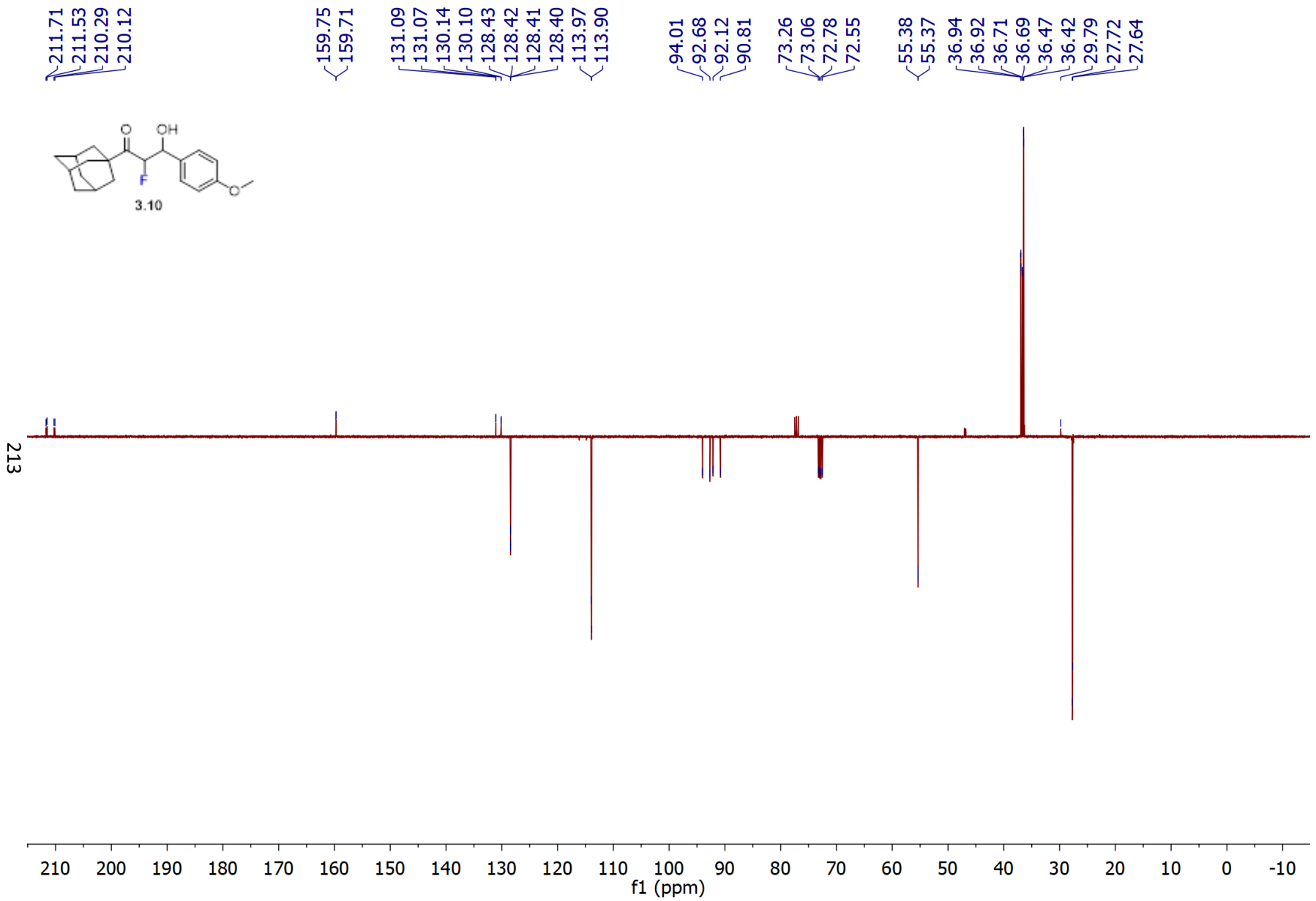
f1 (ppm)

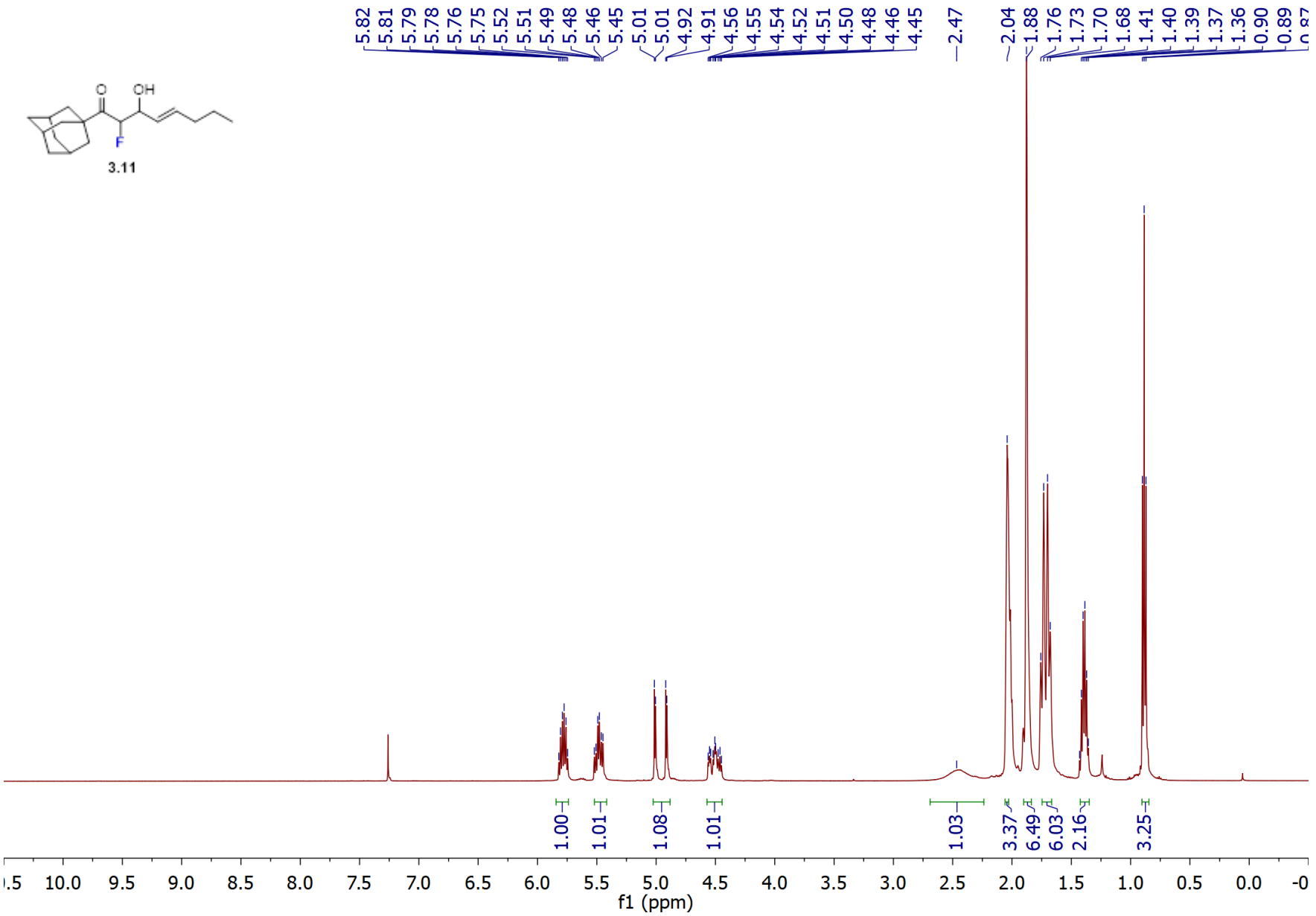

7.42
7.41
7.41
7.40
7.36
7.35
7.33
7.30
7.30
7.28
7.27
7.27
6.76
6.75
6.73
6.72
6.31
6.29
6.27
6.26
6.25
6.23
6.21
5.16
5.15
5.13
5.11
5.07
5.06
5.03
5.02
4.82
4.77
4.75
4.74
2.68
2.62
2.08
1.93
1.79
1.77
1.73
1.71
O
OH
F
3.9
209
2.12
2.13
1.07
1.00
1.05
1.14
1.13
1.00
3.11
6.17
6.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

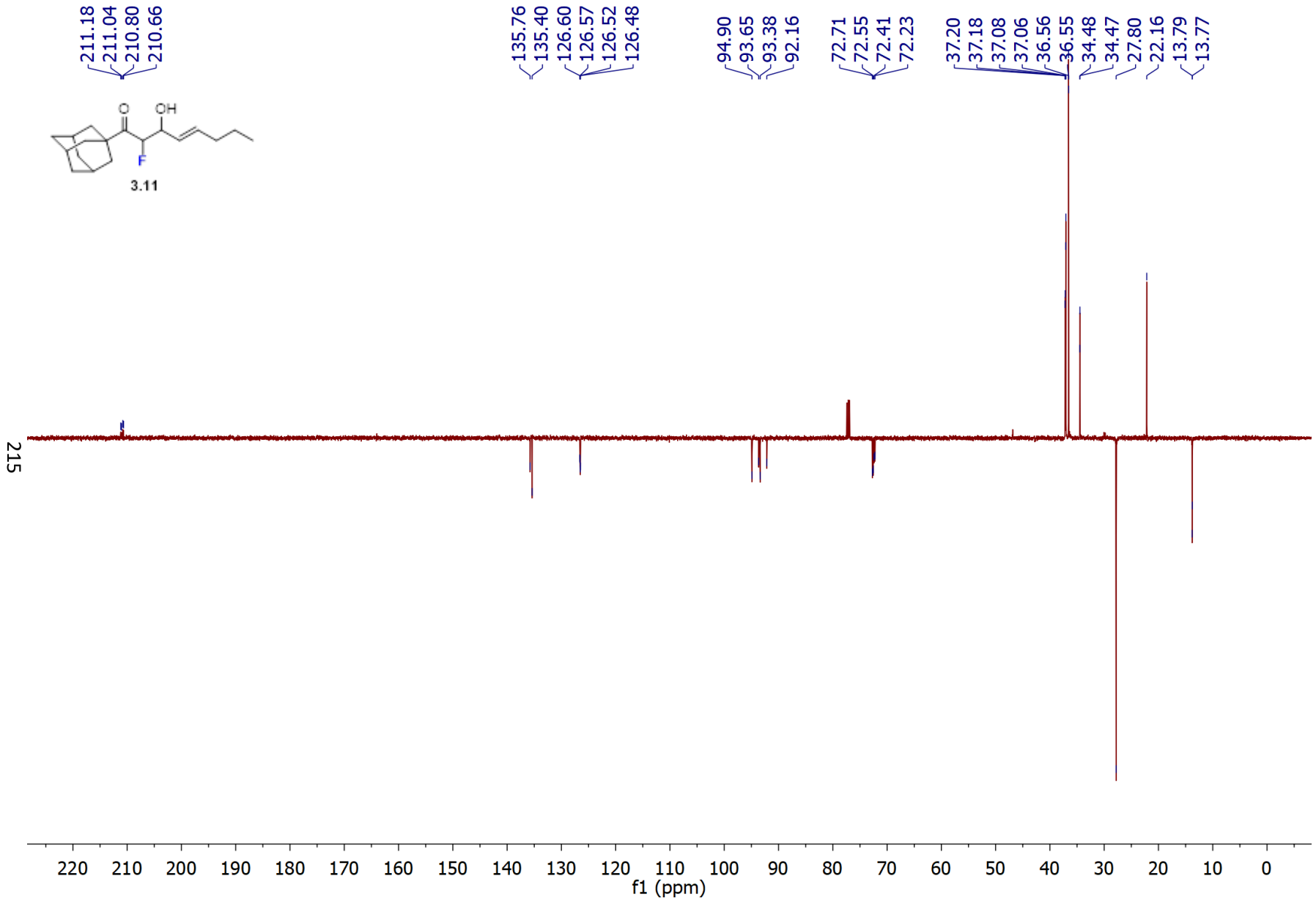

211.22
211.08
210.92
210.78
136.35
136.24
133.41
133.34
128.78
128.75
128.24
128.18
126.81
126.78
125.82
125.79
125.72
125.68
94.74
93.45
93.22
91.95
72.73
72.56
72.22
72.04
37.20
37.18
37.08
37.06
36.55
29.84
27.80
O
OH
F
3.9
210
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OH
F
3.9
-195.32
-195.35
-195.44
-195.48
-199.08
-199.13
-199.21
-199.26
1.02
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


7.32
7.29
7.27
6.90
6.88
6.86
5.18
5.16
5.15
5.14
5.11
5.11
5.10
5.05
5.04
5.02
5.00
4.99
4.97
3.80
3.79
3.11
2.95
2.02
1.98
1.85
1.82
1.80
1.75
1.72
1.69
1.64
1.61
O
OH
F
O
3.10
2.07
2.00
2.08
3.05
1.01
3.09
12.10
f1 (ppm)


211.71
211.53
210.29
210.12
159.75
159.71
131.09
131.07
130.14
130.10
128.43
128.42
128.41
128.40
113.97
113.90
94.01
92.68
92.12
90.81
73.26
73.06
72.78
72.55
55.38
55.37
36.94
36.92
36.71
36.69
36.47
36.42
29.79
27.72
27.64
O
OH
F
O
3.10
213
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
OH
F
3.11
5.82
5.81
5.79
5.78
5.76
5.75
5.52
5.51
5.49
5.48
5.46
5.45
5.01
5.01
4.92
4.91
4.56
4.55
4.54
4.52
4.51
4.50
4.48
4.46
4.45
2.47
2.04
1.88
1.76
1.73
1.70
1.68
1.41
1.40
1.39
1.37
1.36
0.90
0.89
1.00
1.01
1.08
1.01
1.03
3.37
6.49
6.03
2.16
3.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


211.18
211.04
210.80
210.66
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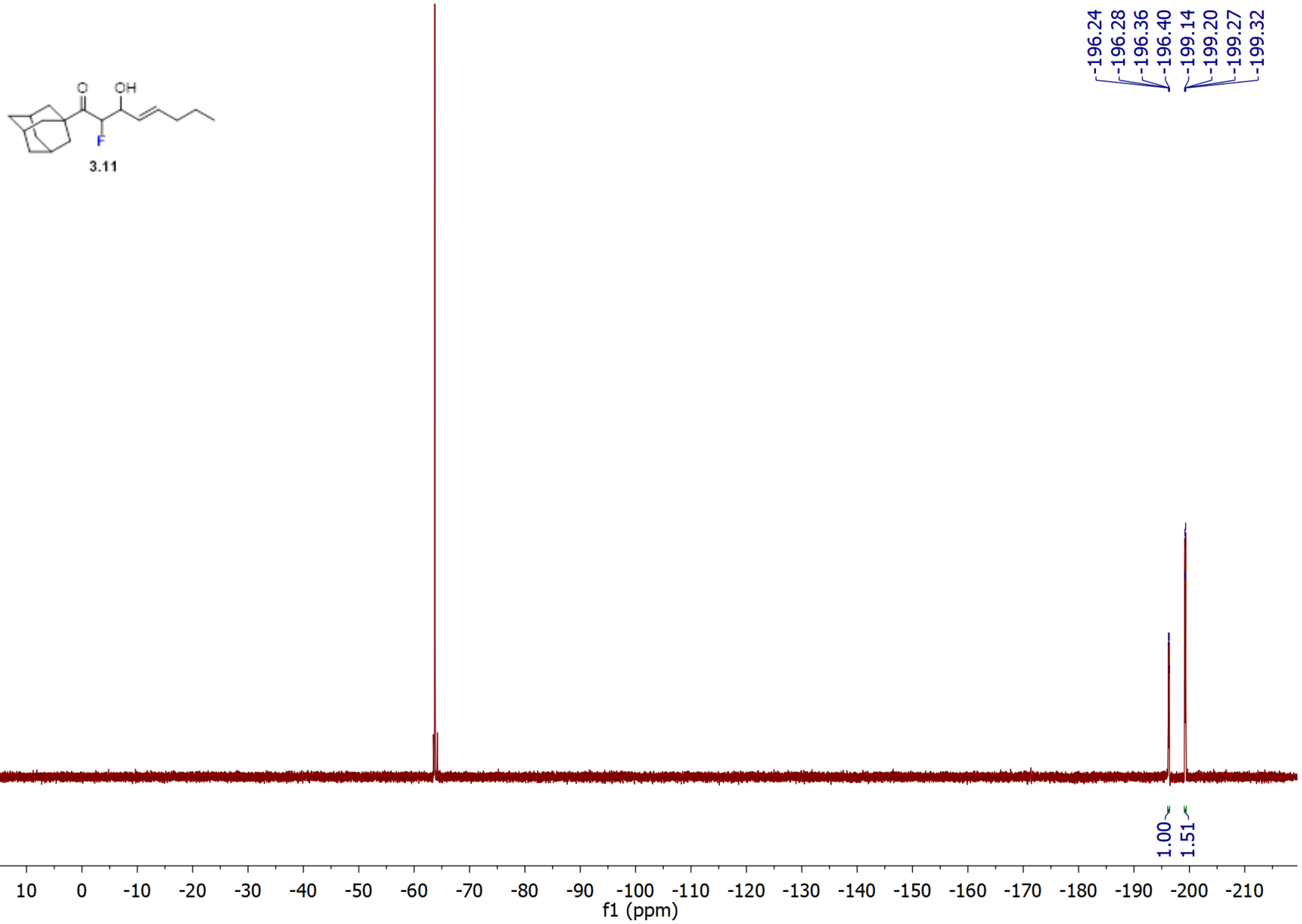
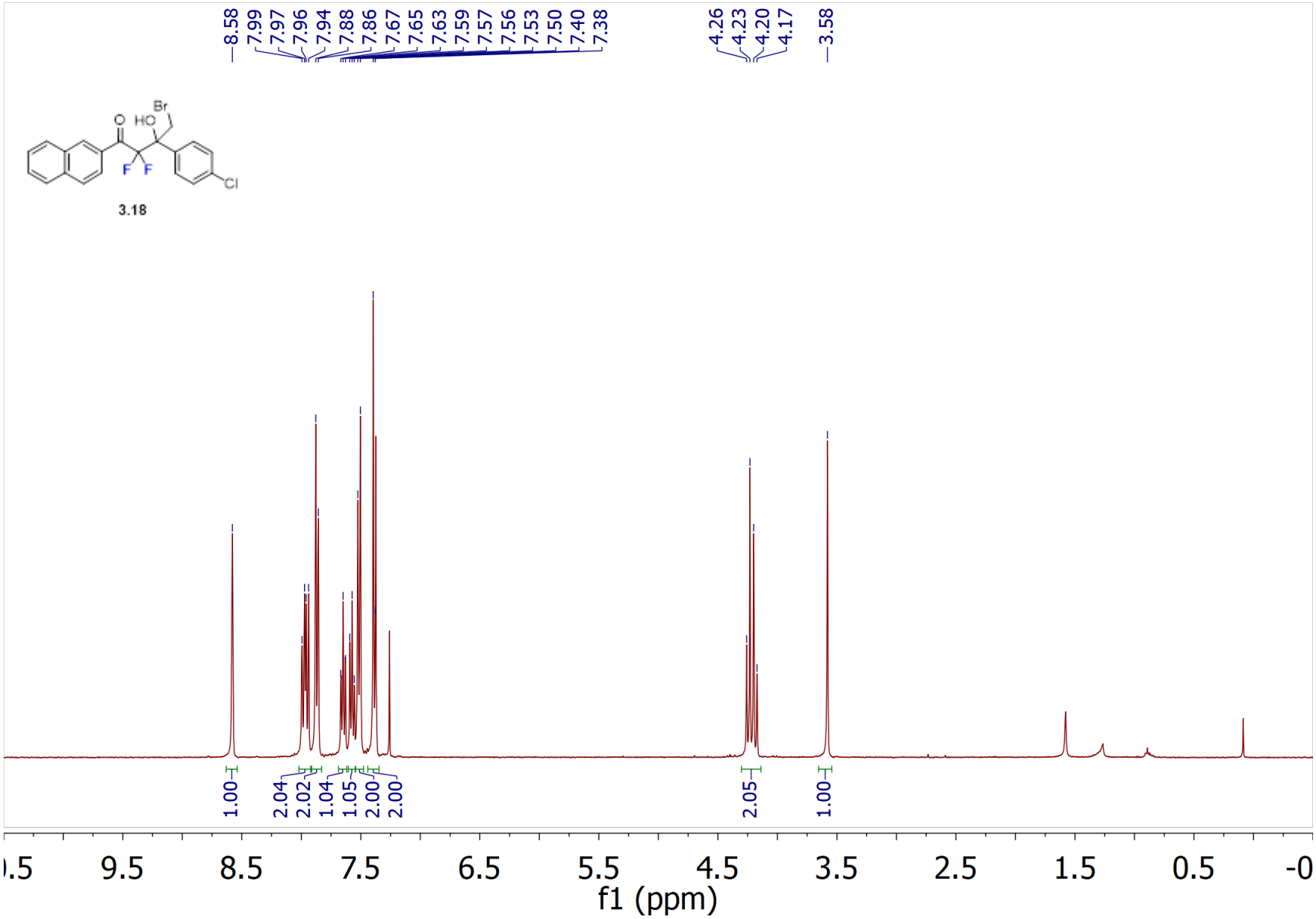
135.40
126.60
126.57
126.52
126.48
94.90
93.65
93.38
92.16
72.71
72.55
72.41
72.23
37.20
37.18
37.08
37.06
36.56
36.55
34.48
34.47
27.80
22.16
13.79
13.77
O
OH
F
3.11
215
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OH
F
3.11
-196.24
-196.28
-196.36
-196.40
-199.14
-199.20
-199.27
-199.32
1.00
1.51
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


8.58
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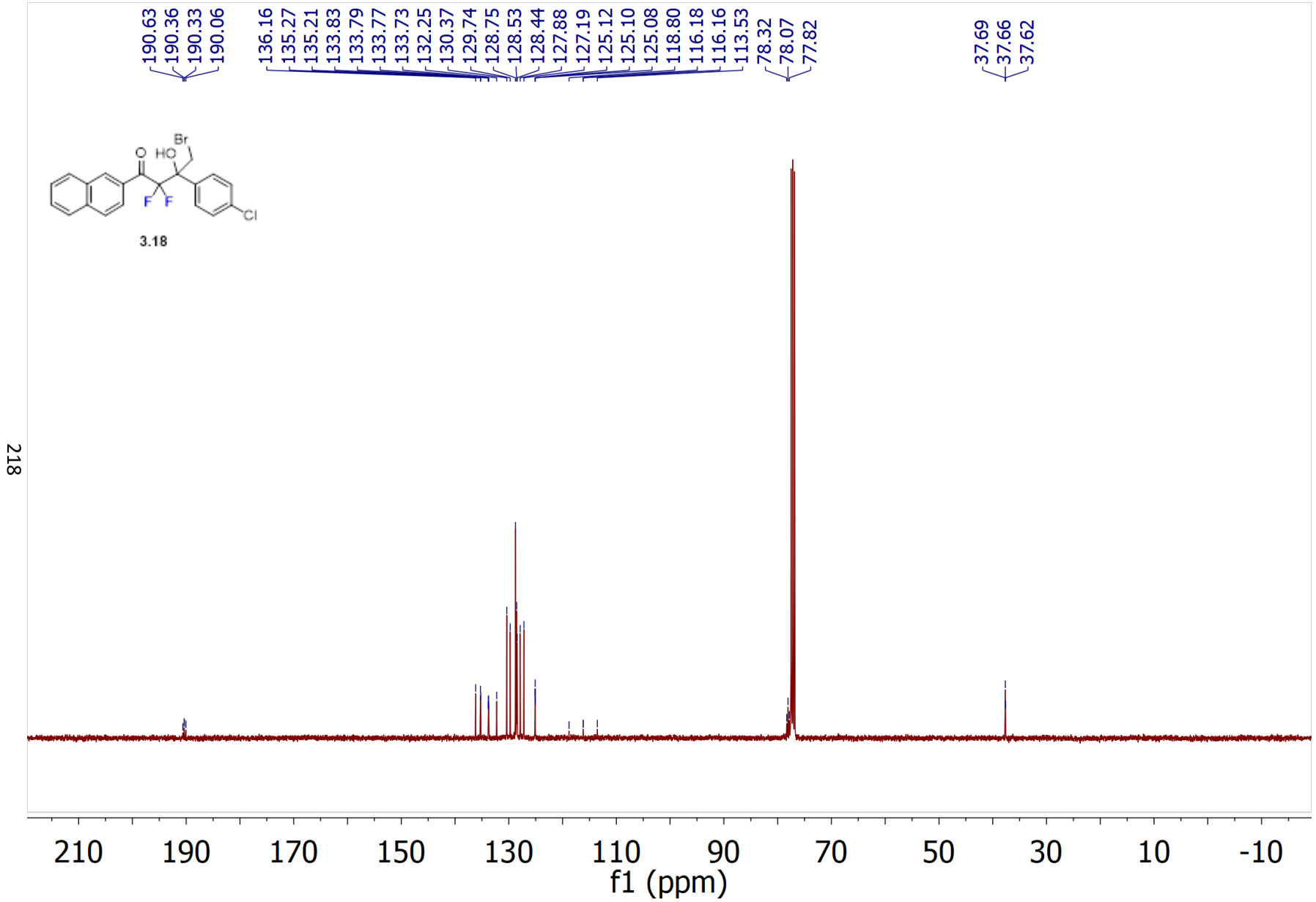
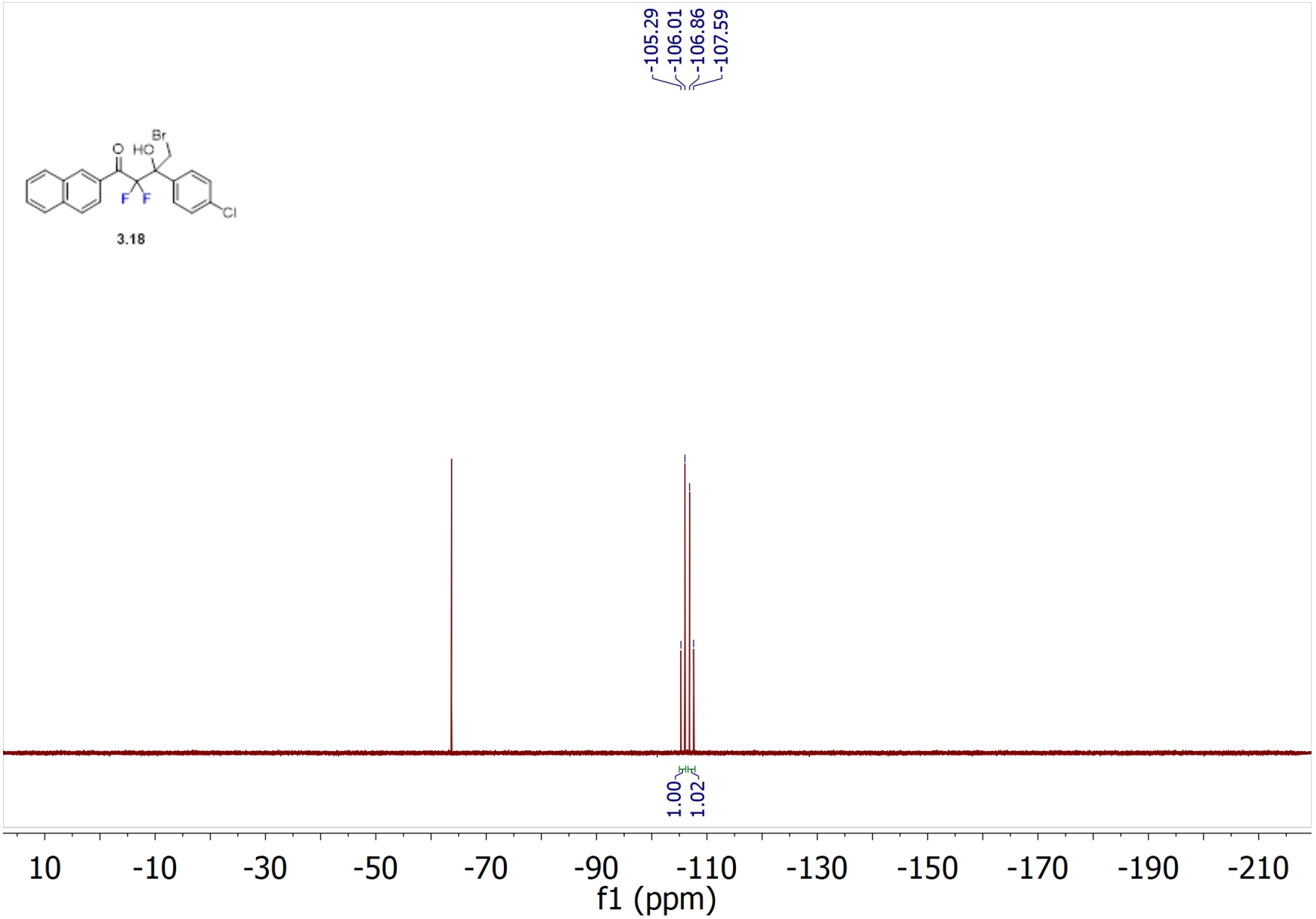
7.97
7.96
7.94
7.88
7.86
7.67
7.65
7.63
7.59
7.57
7.56
7.53
7.50
7.40
7.38
4.26
4.23
4.20
4.17
3.58
Br
HO
O
F
F
Cl
3.18
1.00
2.04
2.02
1.04
1.05
2.00
2.00
2.05
1.00
f1 (ppm)


190.63
190.36
190.33
190.06
136.16
135.27
135.21
133.83
133.79
133.77
133.73
132.25
130.37
129.74
128.75
128.53
128.44
127.88
127.19
125.12
125.10
125.08
118.80
116.18
116.16
113.53
78.32
78.07
77.82
37.69
37.66
37.62
Br
HO
O
F F
Cl
3.18
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


-105.29
-106.01
-106.86
-107.59
Br
HO
O
F
F
Cl
3.18
1.00
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-30
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-70
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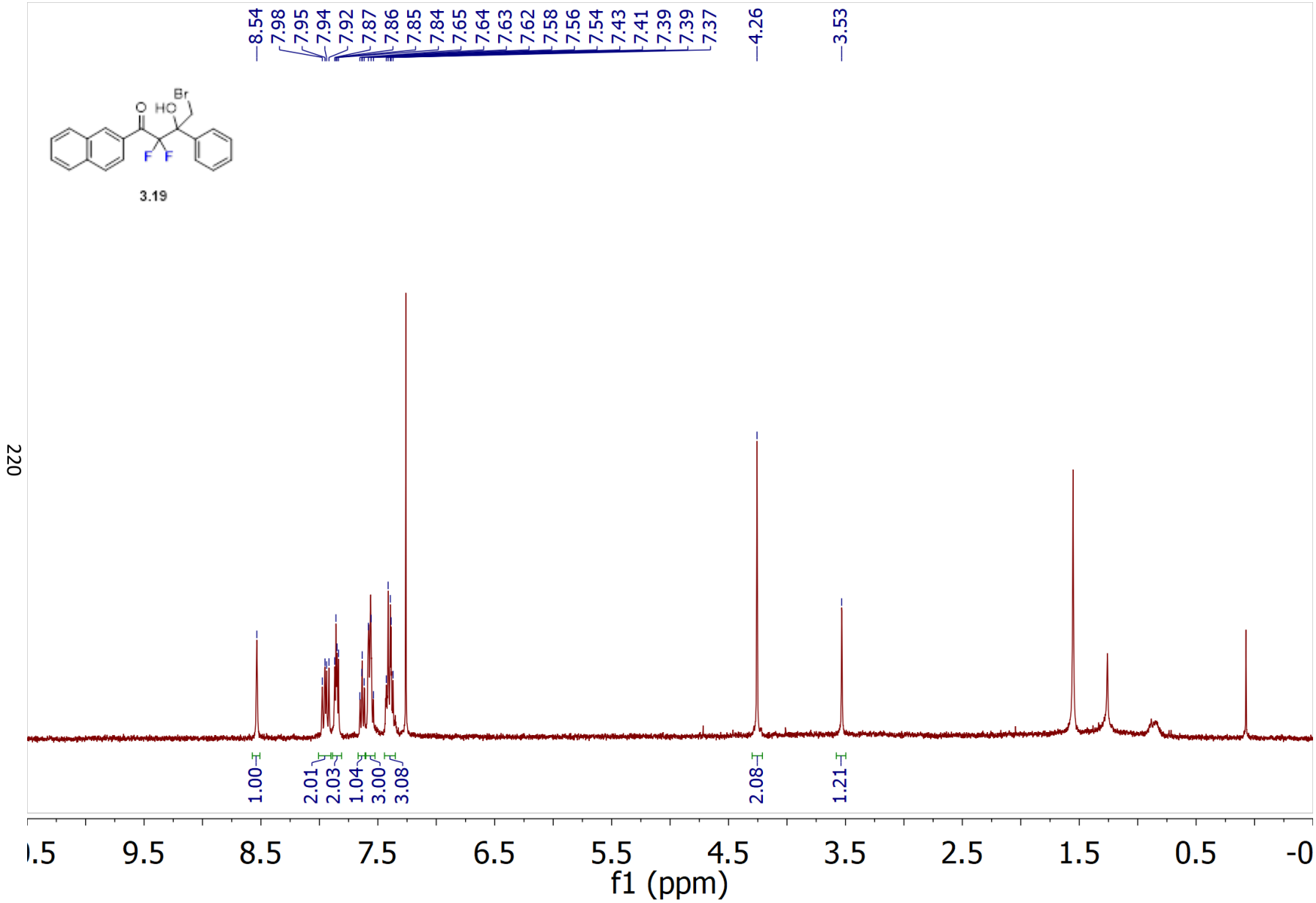
-110
-130
-150
-170
-190
-210
f1 (ppm)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7.85
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7.63
7.62
7.58
7.56
7.54
7.43
7.41
7.39
7.39
7.37
4.26
3.53
Br
HO
O
F F
3.19
1.00
2.01
2.03
1.04
3.00
3.08
2.08
1.21
220
9.5
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7.5
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4.5
3.5
2.5
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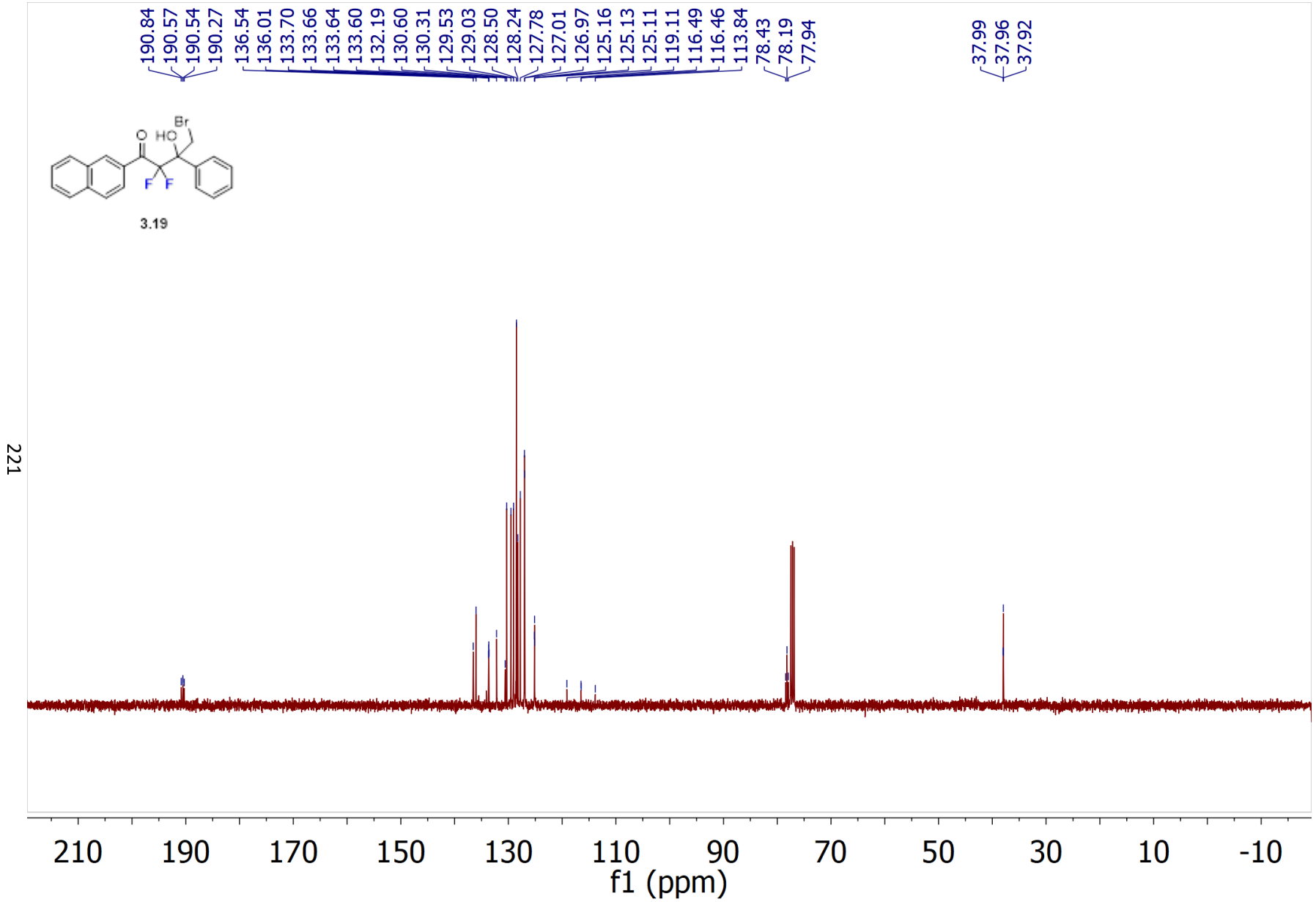
0.5
f1 (ppm)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132.19
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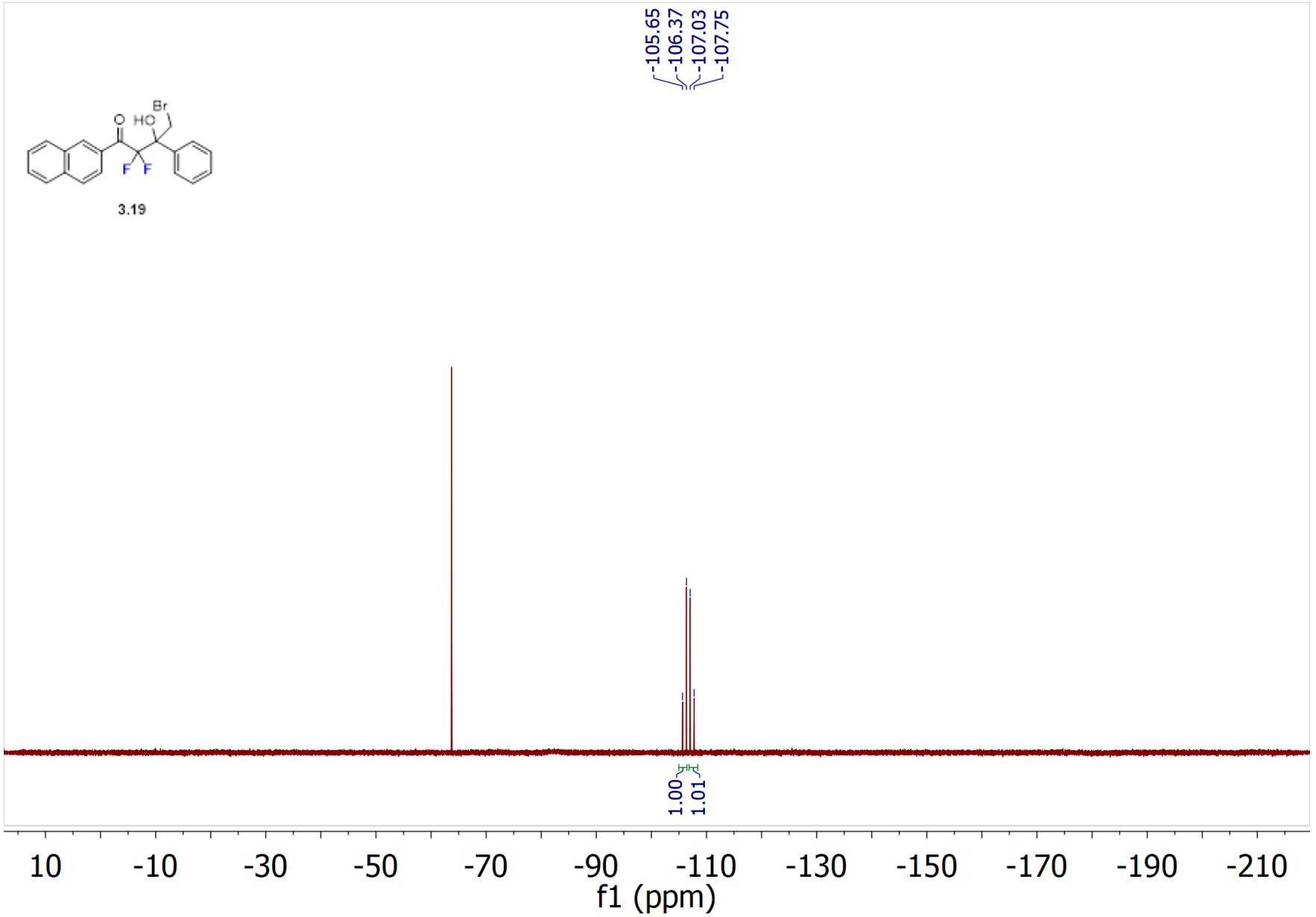
130.31
129.53
129.03
128.50
128.24
127.78
127.01
126.97
125.16
125.13
125.11
119.11
116.49
116.46
113.84
78.43
78.19
77.94
37.99
37.96
37.92
Br
HO
O
F F
3.19
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)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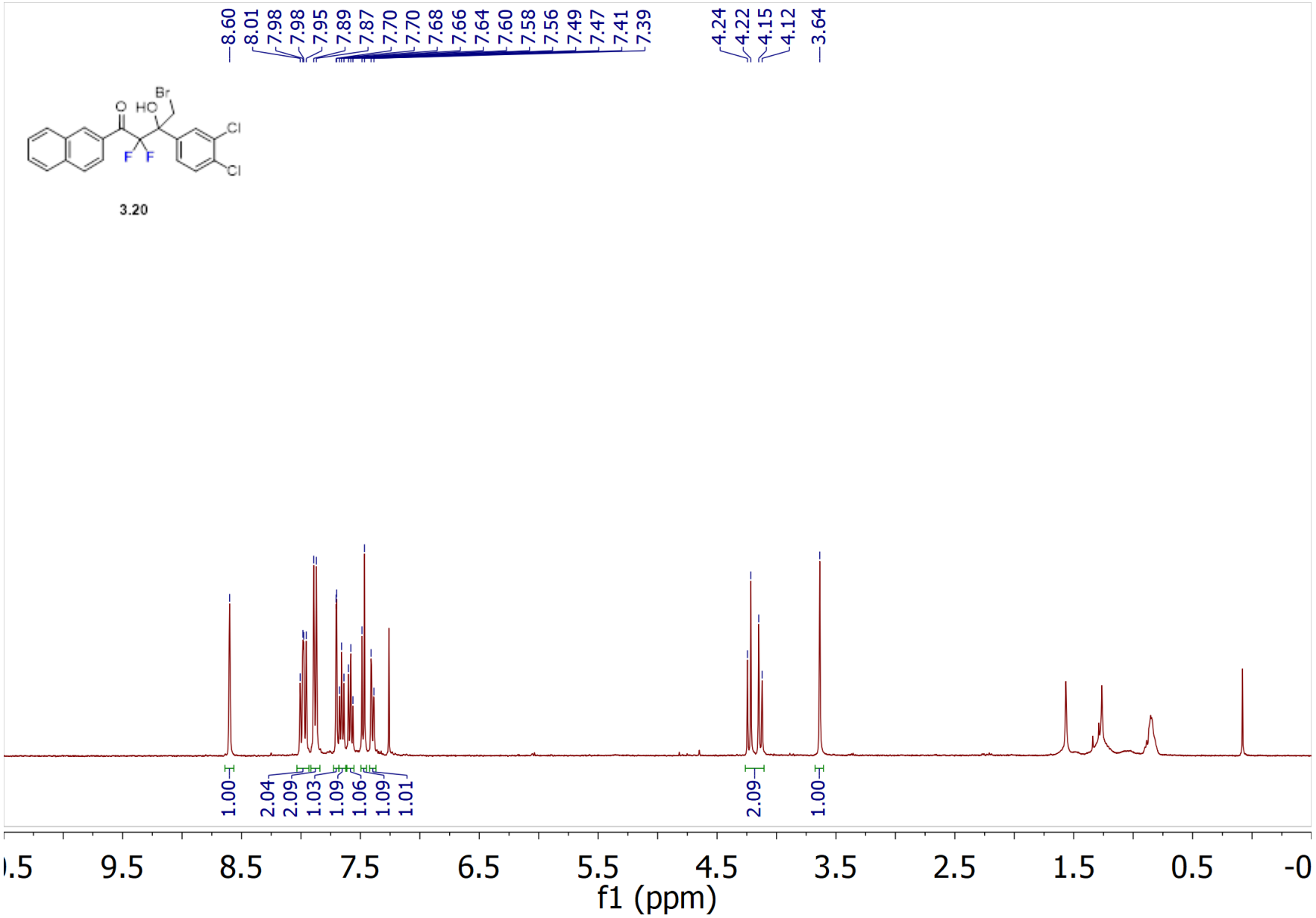
-106.37
-107.03
-107.75
Br
HO
O
F F
3.19
1.00
1.01
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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7.68
7.66
7.64
7.60
7.58
7.56
7.49
7.47
7.41
7.39
4.24
4.22
4.15
4.12
3.64
Br
HO
O
Cl
Cl
F
F
3.20
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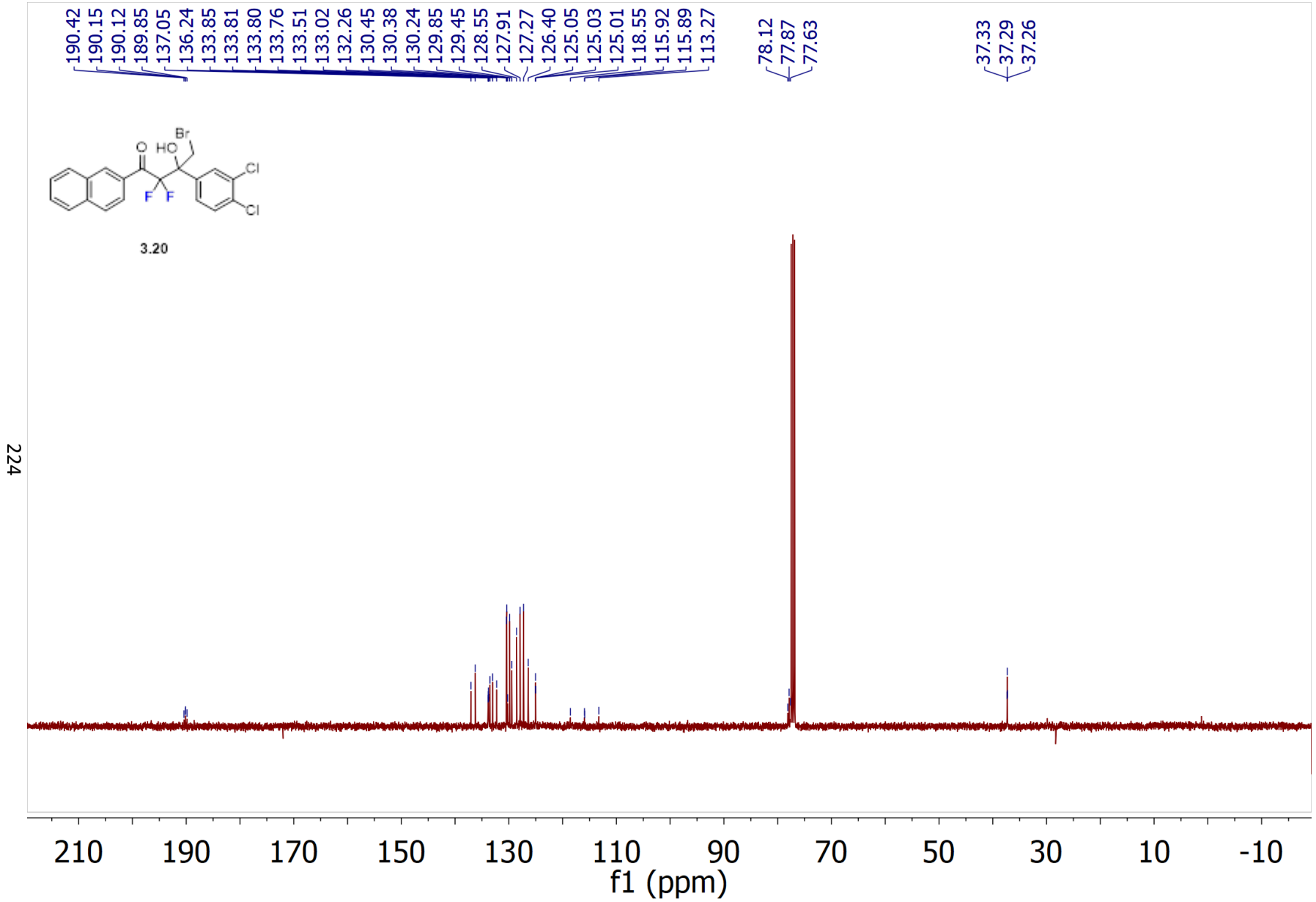
2.04
2.09
1.03
1.09
1.06
1.09
1.01
2.09
1.00
f1 (ppm)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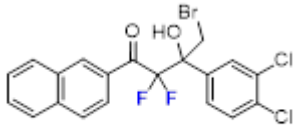
133.51
133.02
132.26
130.45
130.38
130.24
129.85
129.45
128.55
127.91
127.27
126.40
125.05
125.03
125.01
118.55
115.92
115.89
113.27
78.12
77.87
77.63
37.33
37.29
37.26
O
HO
Br
F
F
Cl
Cl
3.20
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


Br
O
HO
Cl
F
F
Cl

3.20

-104.94
-105.67
-106.55
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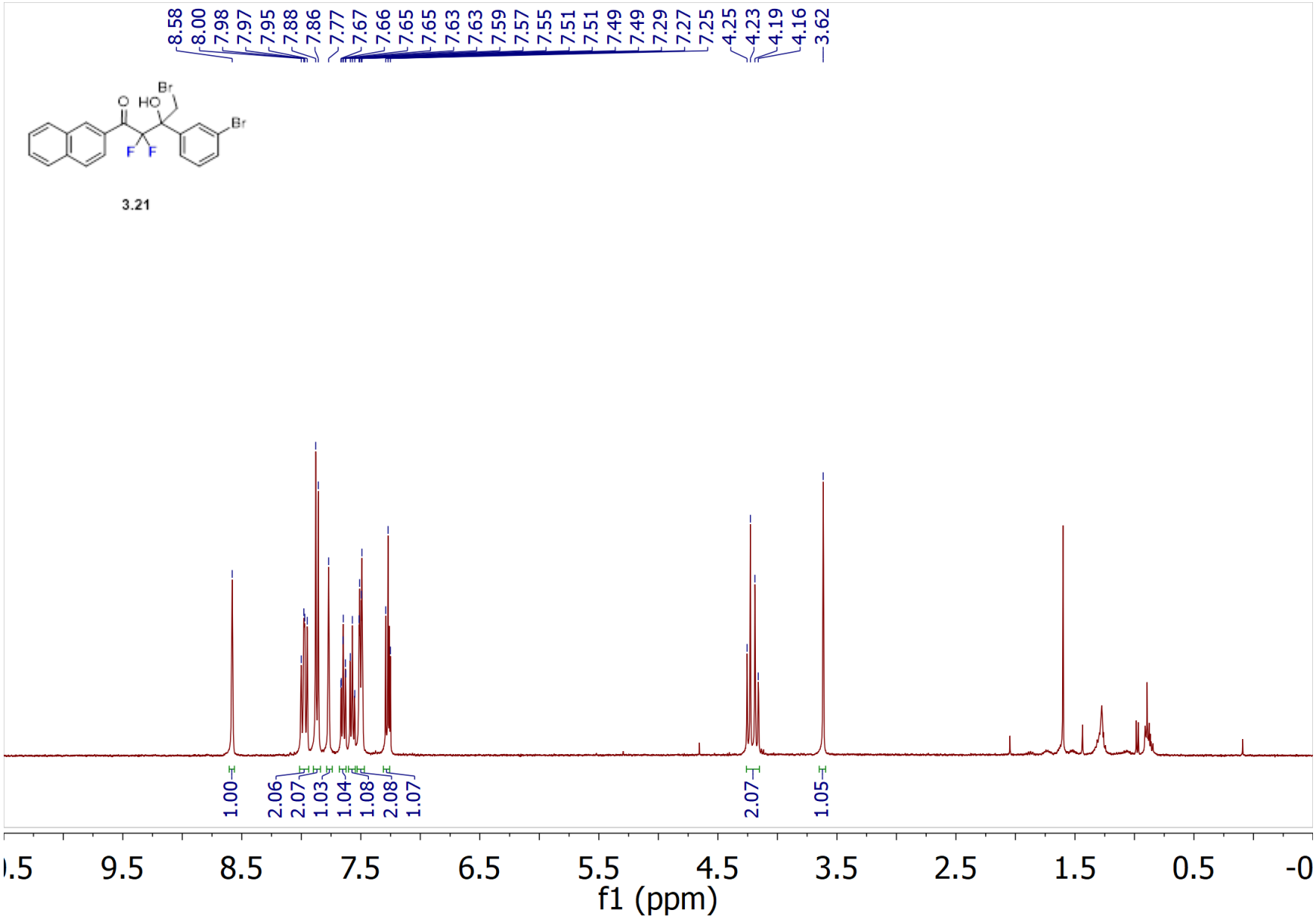
1.00
1.06
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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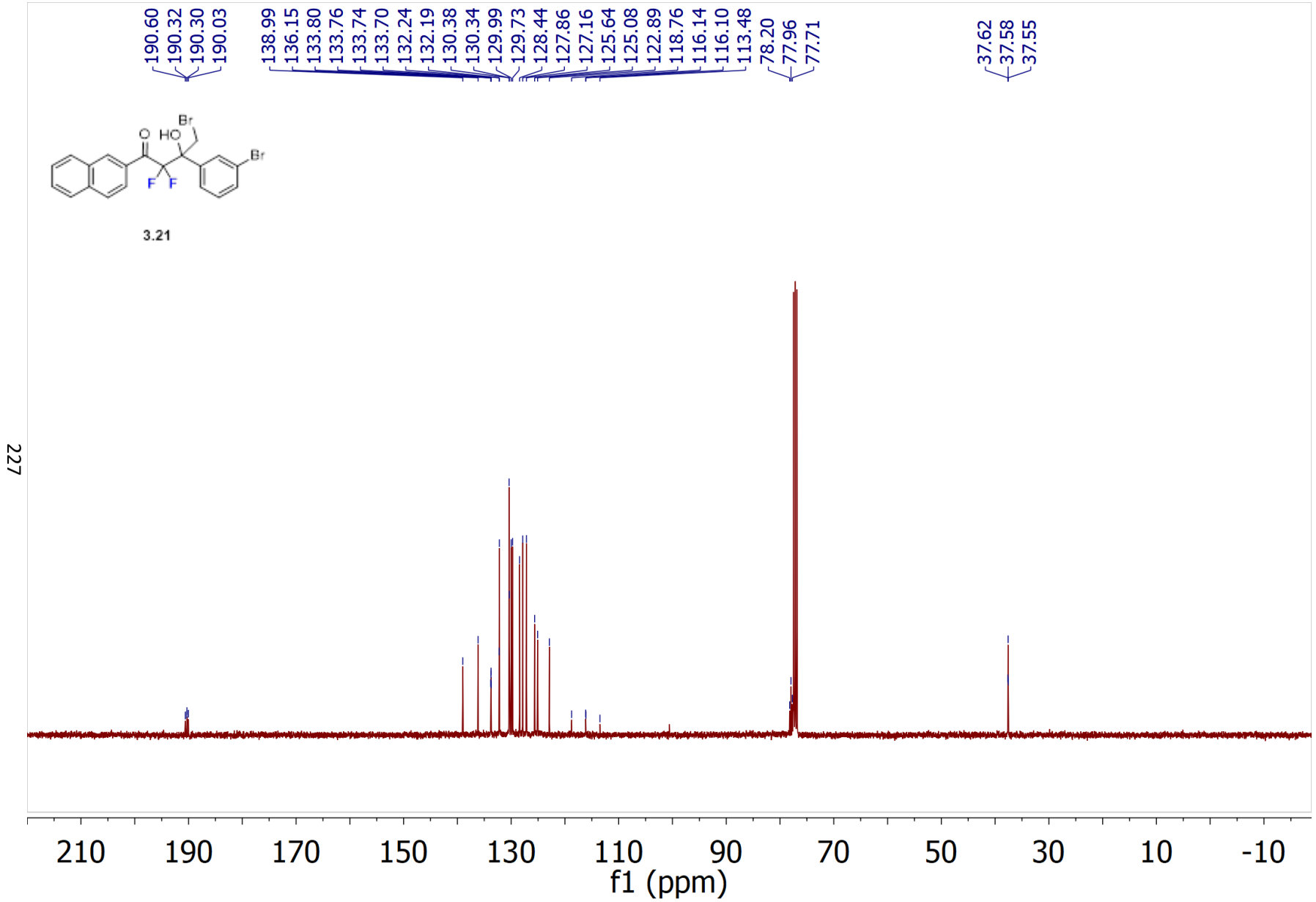
7.77
7.67
7.66
7.65
7.65
7.63
7.63
7.59
7.57
7.55
7.51
7.51
7.49
7.49
7.29
7.27
7.25
4.25
4.23
4.19
4.16
3.62
Br
O
HO
Br
F
F
3.21
1.00
2.06
2.07
1.03
1.04
1.08
2.08
1.07
2.07
1.05
f1 (ppm)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190.32
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190.03
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136.15
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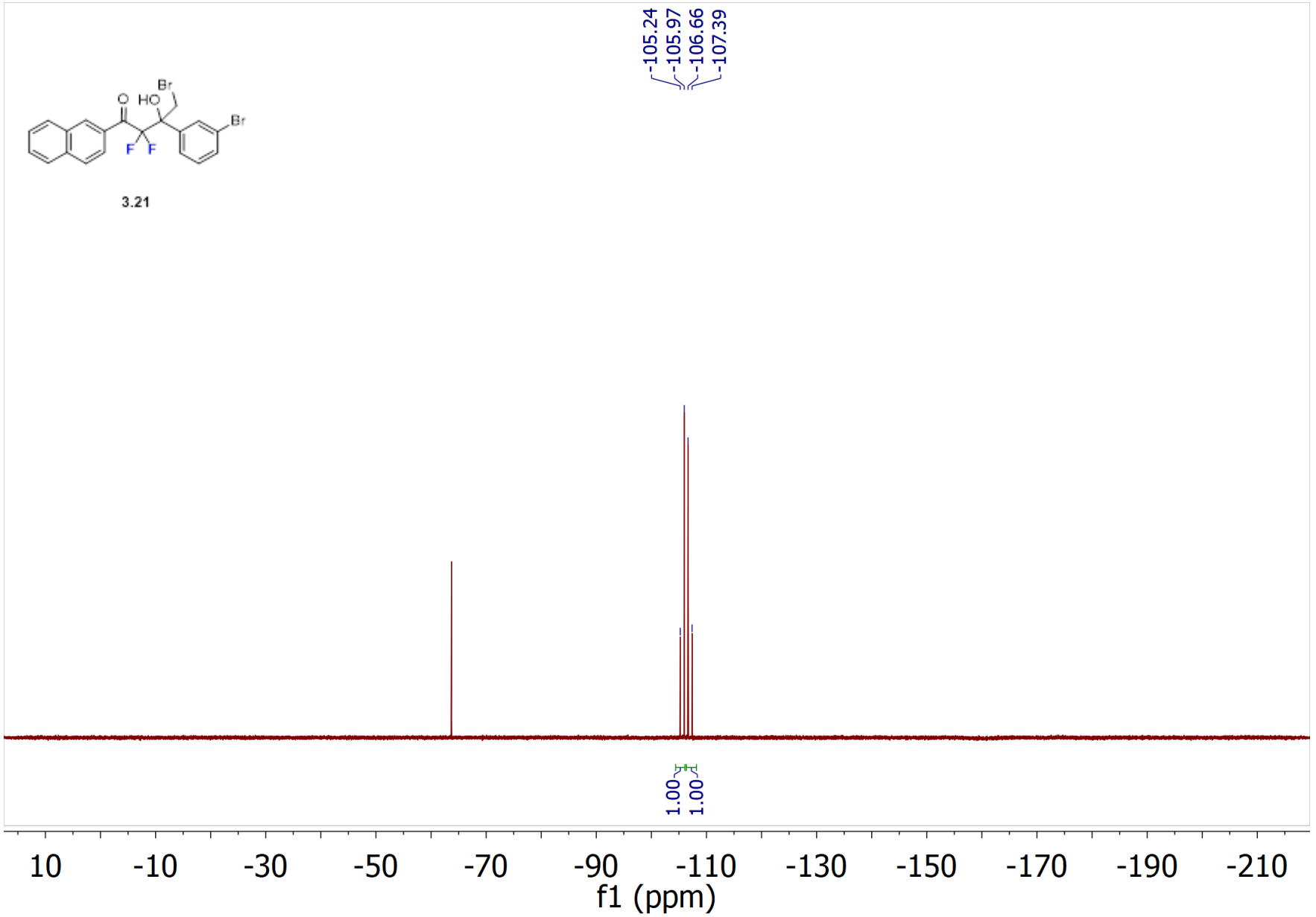
133.76
133.74
133.70
132.24
132.19
130.38
130.34
129.99
129.73
128.44
127.86
127.16
125.64
125.08
122.89
118.76
116.14
116.10
113.48
78.20
77.96
77.71
37.62
37.58
37.55
Br
O
HO
Br
F
F
3.21
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)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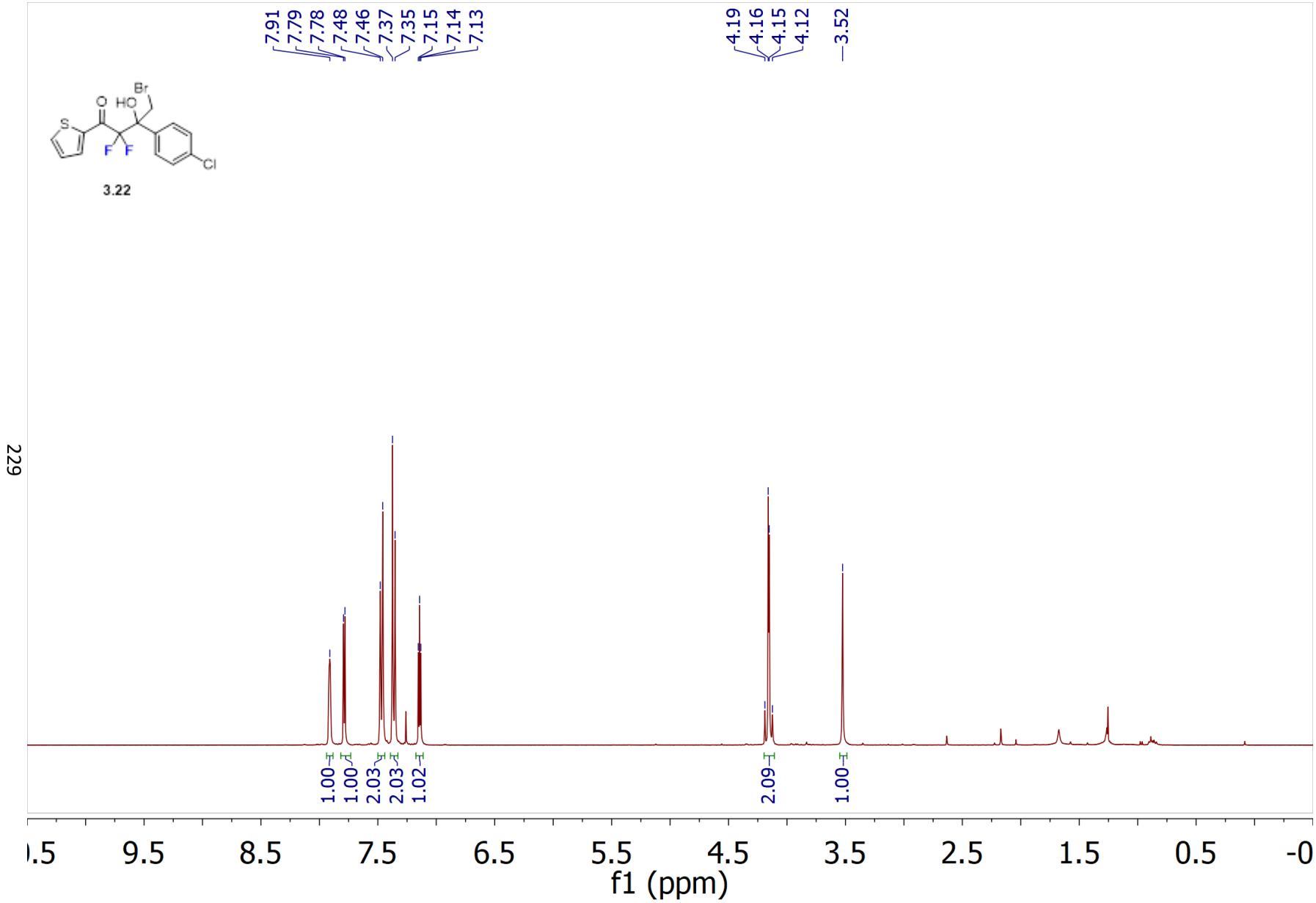
-106.66
-107.39
Br
O
HO
Br
F
F
3.21
1.00
1.00
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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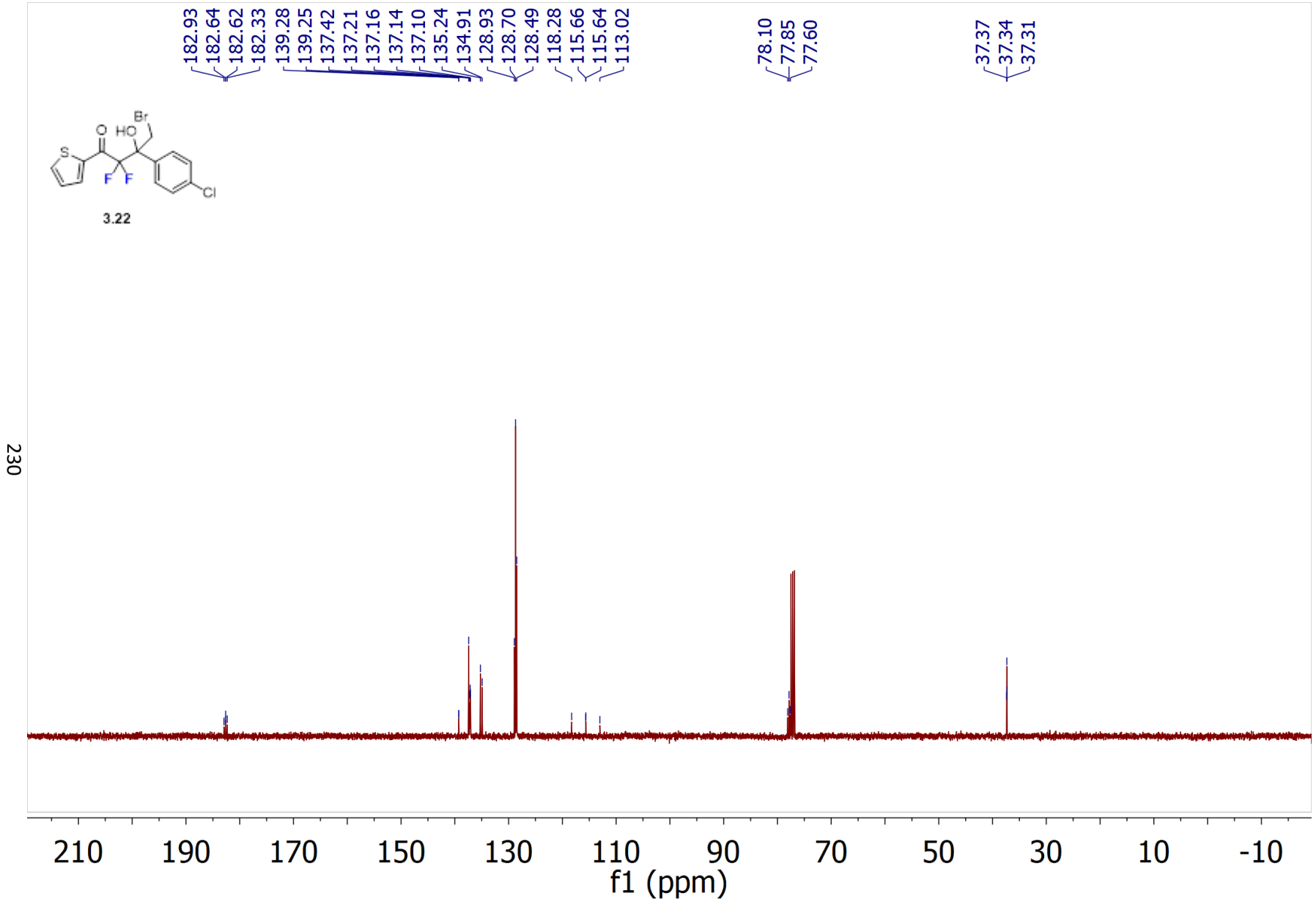
7.79
7.78
7.48
7.46
7.37
7.35
7.15
7.14
7.13
4.19
4.16
4.15
4.12
3.52
Br
O
HO
S
F
F
Cl
3.22
1.00
1.00
2.03
2.03
1.02
2.09
1.00
f1 (ppm)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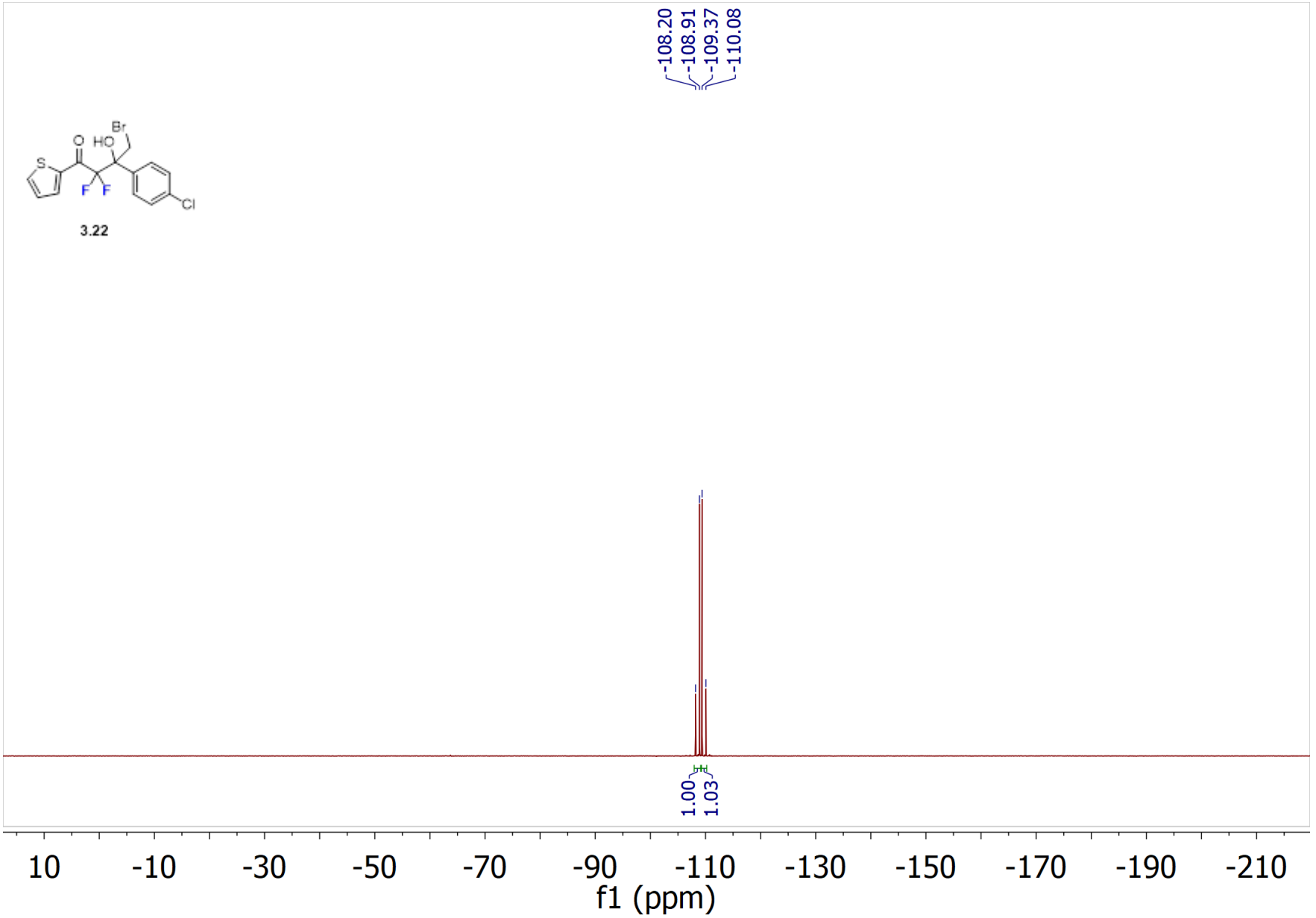
182.62
182.33
139.28
139.25
137.42
137.21
137.16
137.14
137.10
135.24
134.91
128.93
128.70
128.49
118.28
115.66
115.64
113.02
78.10
77.85
77.60
37.37
37.34
37.31
O
HO
Br
S
F
F
Cl
3.22
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)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-108.91
-109.37
-110.08
Br
HO
O
S
F
F
Cl
3.22
1.00
1.03
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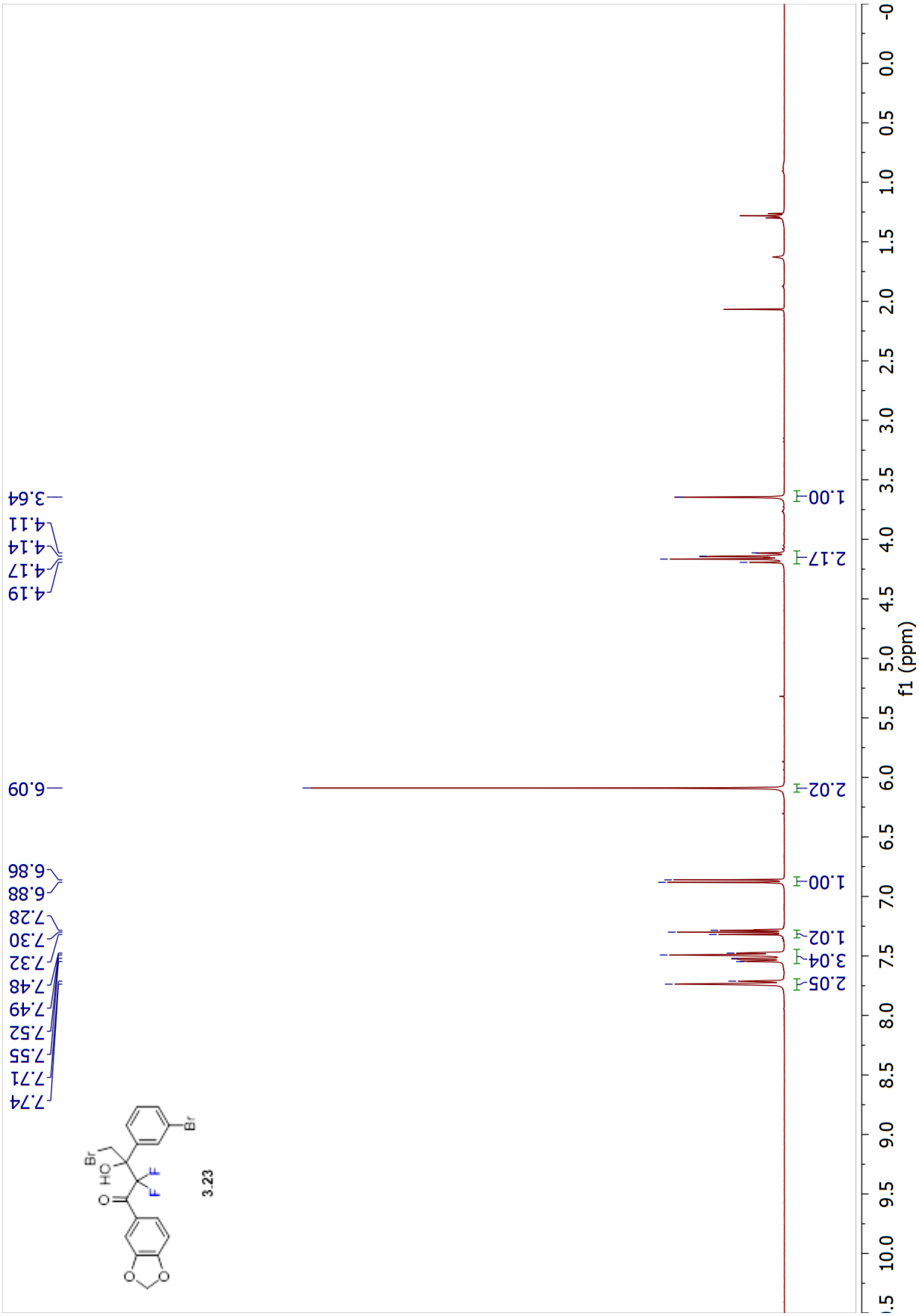
-130
-150
-170
-190
-210
f1 (ppm)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7.32
7.30
7.28
6.88
6.86
6.09
4.19
4.17
4.14
4.11
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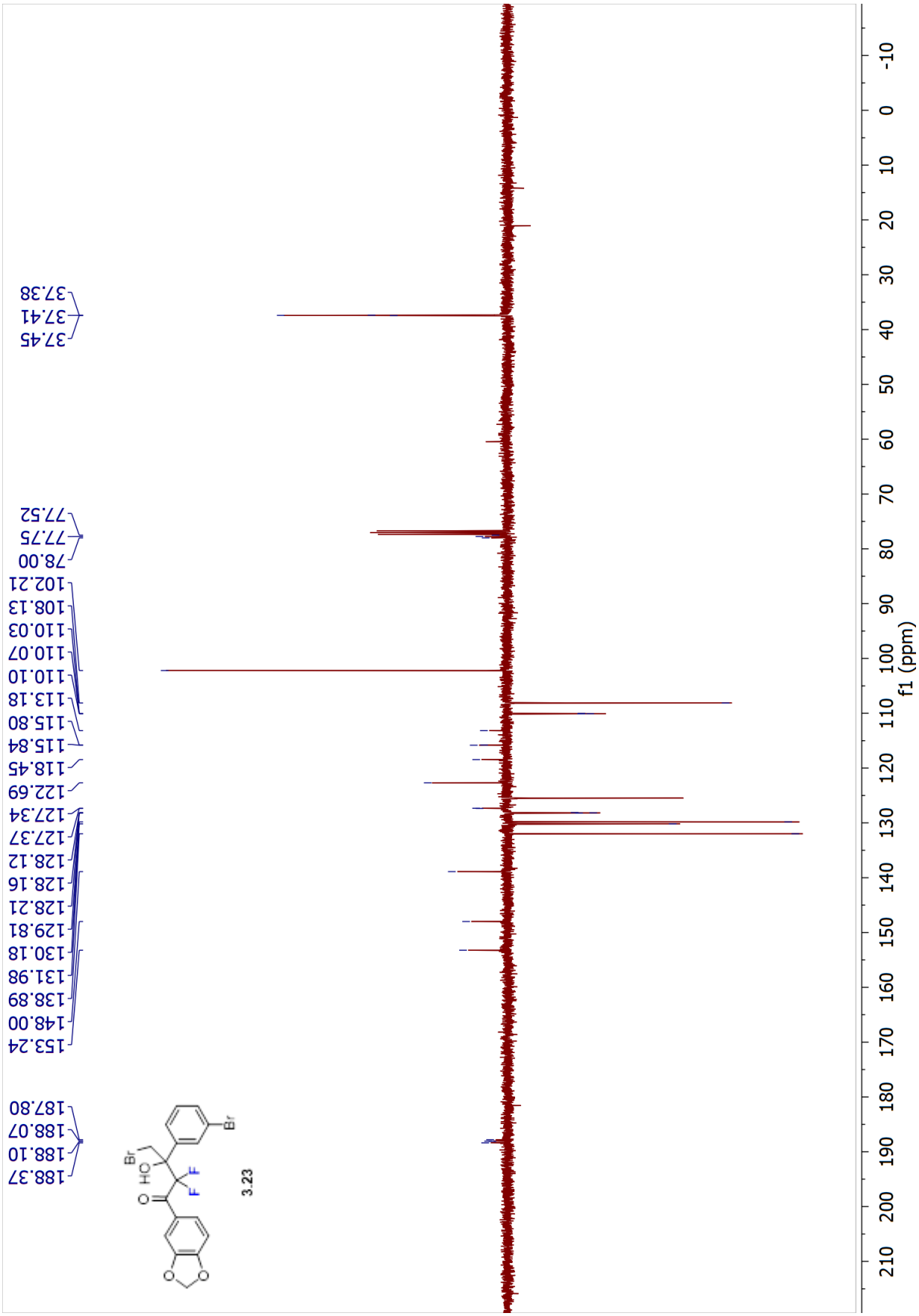
3.04
1.02
1.00
2.02
1.00
2.17
1.00
f1 (ppm)
3.23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77.75
78.00
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110.03
110.07
110.10
113.18
115.80
115.84
118.45
122.69
127.34
127.37
128.12
128.16
128.21
129.81
130.18
131.98
138.89
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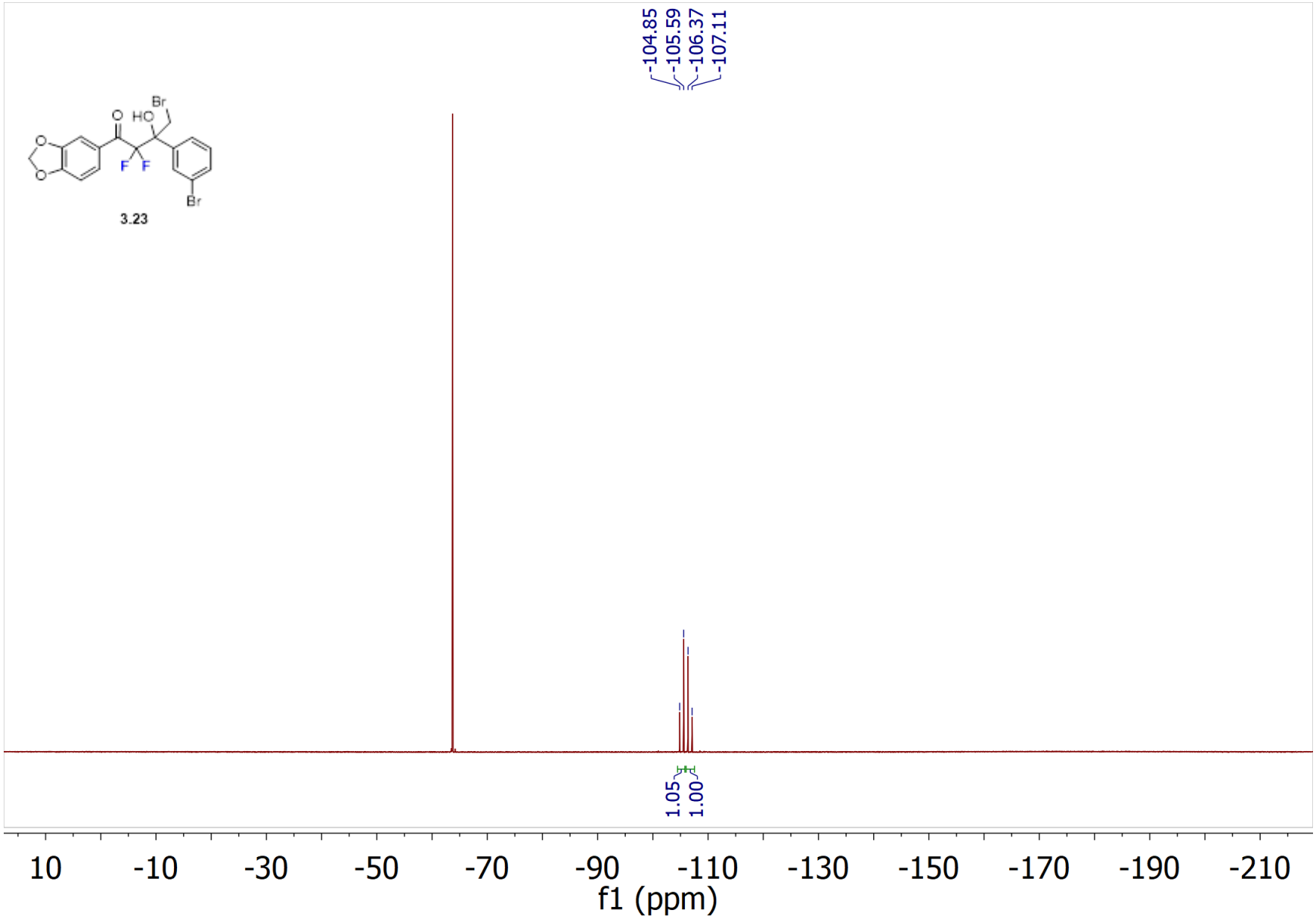
153.24
187.80
188.07
188.10
188.37
Br
HO
O
F
F
Br
3.23
f1 (ppm)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-105.59
-106.37
-107.11
Br
HO
O
F F
O
O
Br
3.23
1.05
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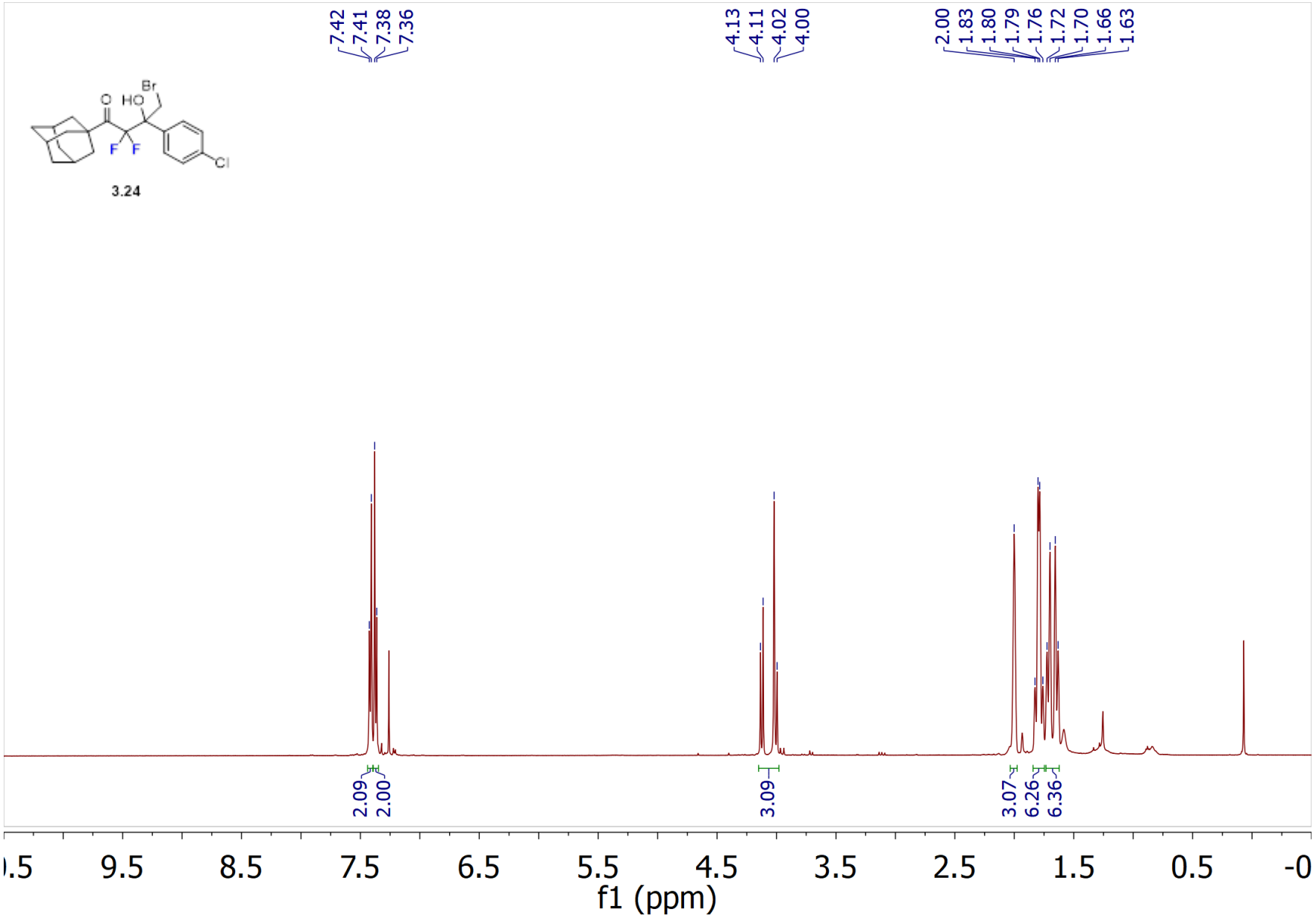
-130
-150
-170
-190
-210
f1 (ppm)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4.11
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1.76
1.72
1.70
1.66
1.63
Br
O
HO
F
F
Cl
3.24
2.09
2.00
3.09
3.07
6.26
6.36
9.5
8.5
7.5
6.5
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3.5
2.5
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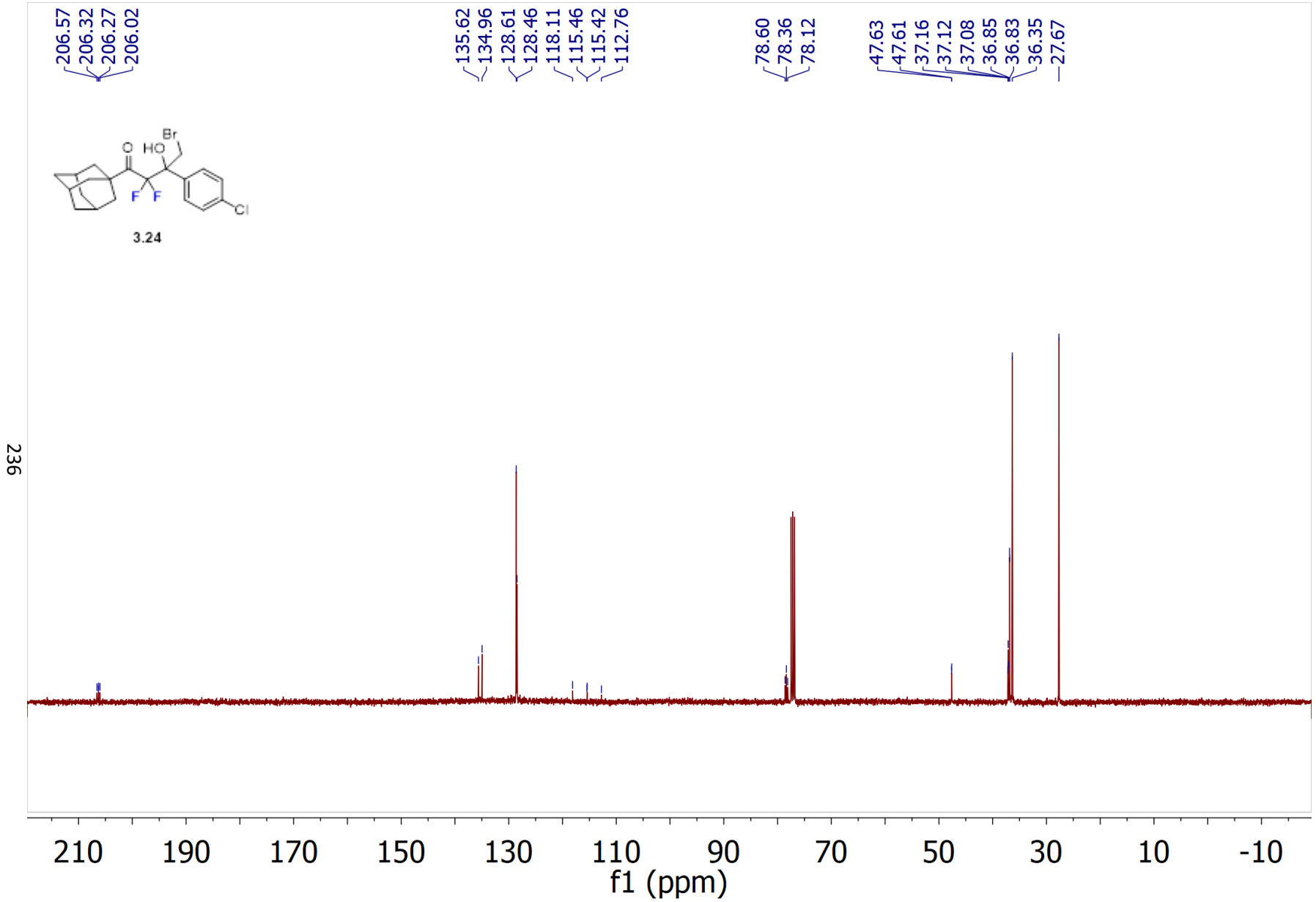
f1 (ppm)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115.42
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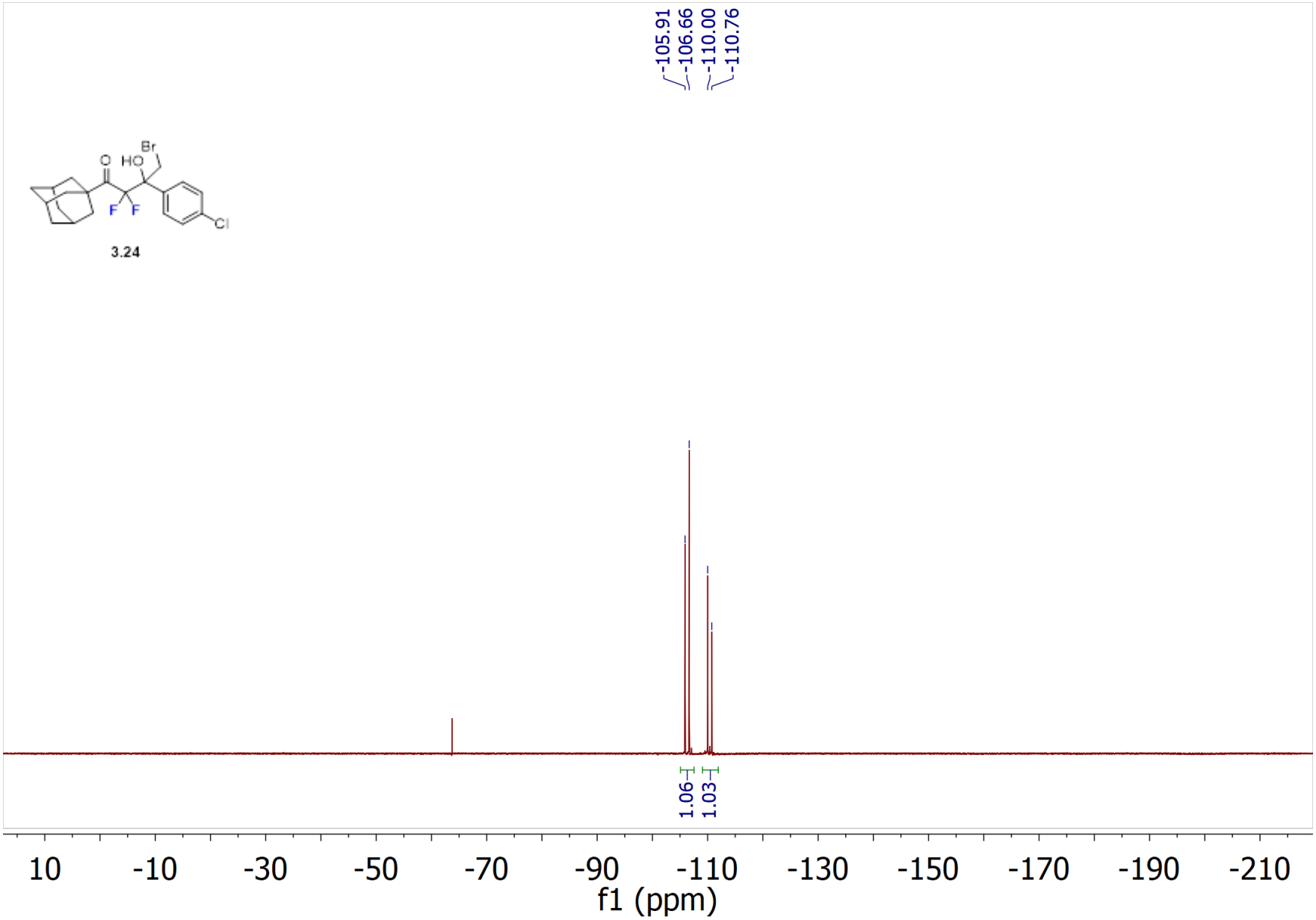
78.36
78.12
47.63
47.61
37.16
37.12
37.08
36.85
36.83
36.35
27.67
O
HO
Br
F
F
Cl
3.24
236
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)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-106.66
-110.00
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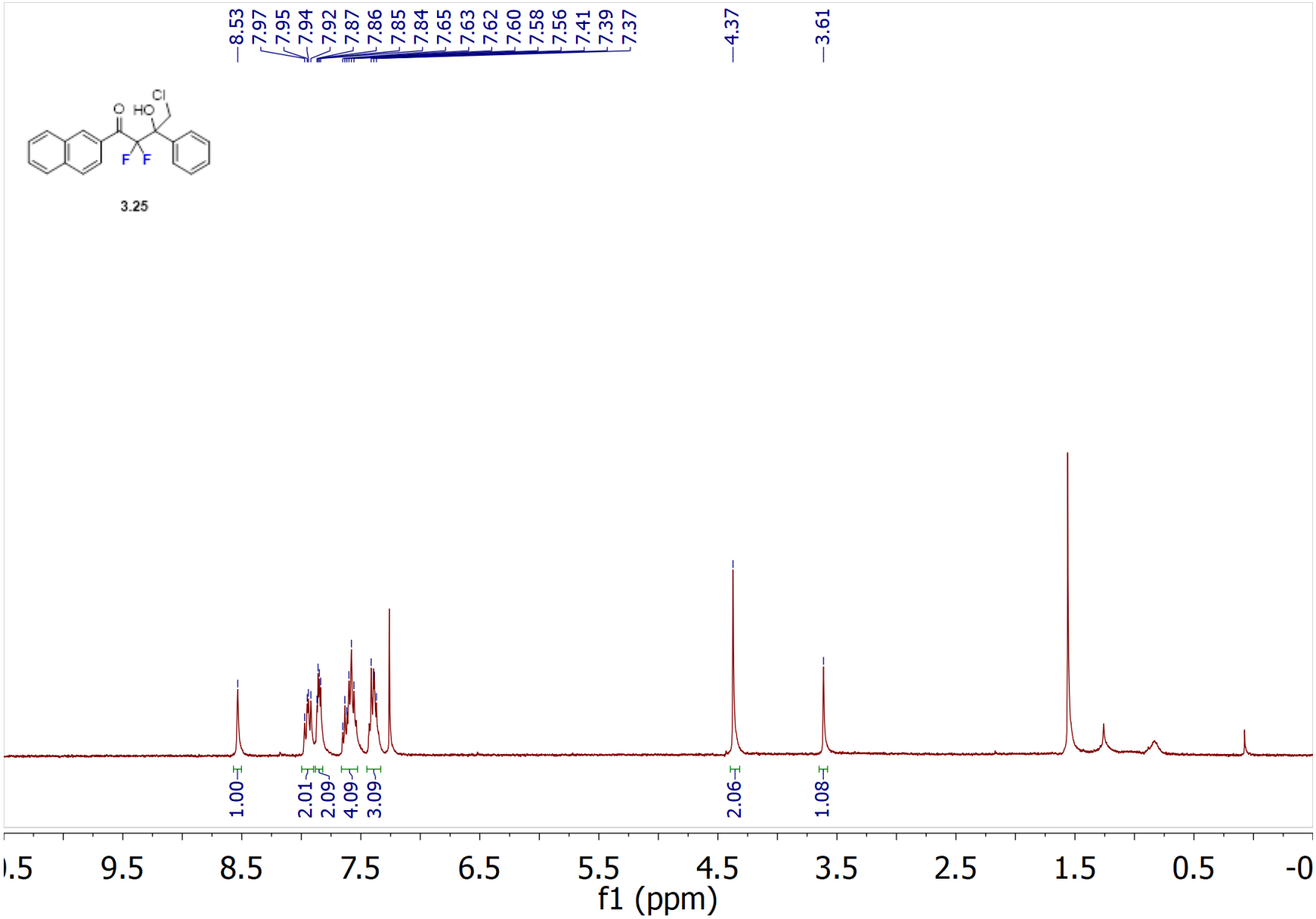
Br
O
HO
F
F
Cl
3.24
1.06
1.03
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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7.63
7.62
7.60
7.58
7.56
7.41
7.39
7.37
4.37
3.61
O
HO
Cl
F
F
3.25
1.00
2.01
2.09
4.09
3.09
2.06
1.08
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7.5
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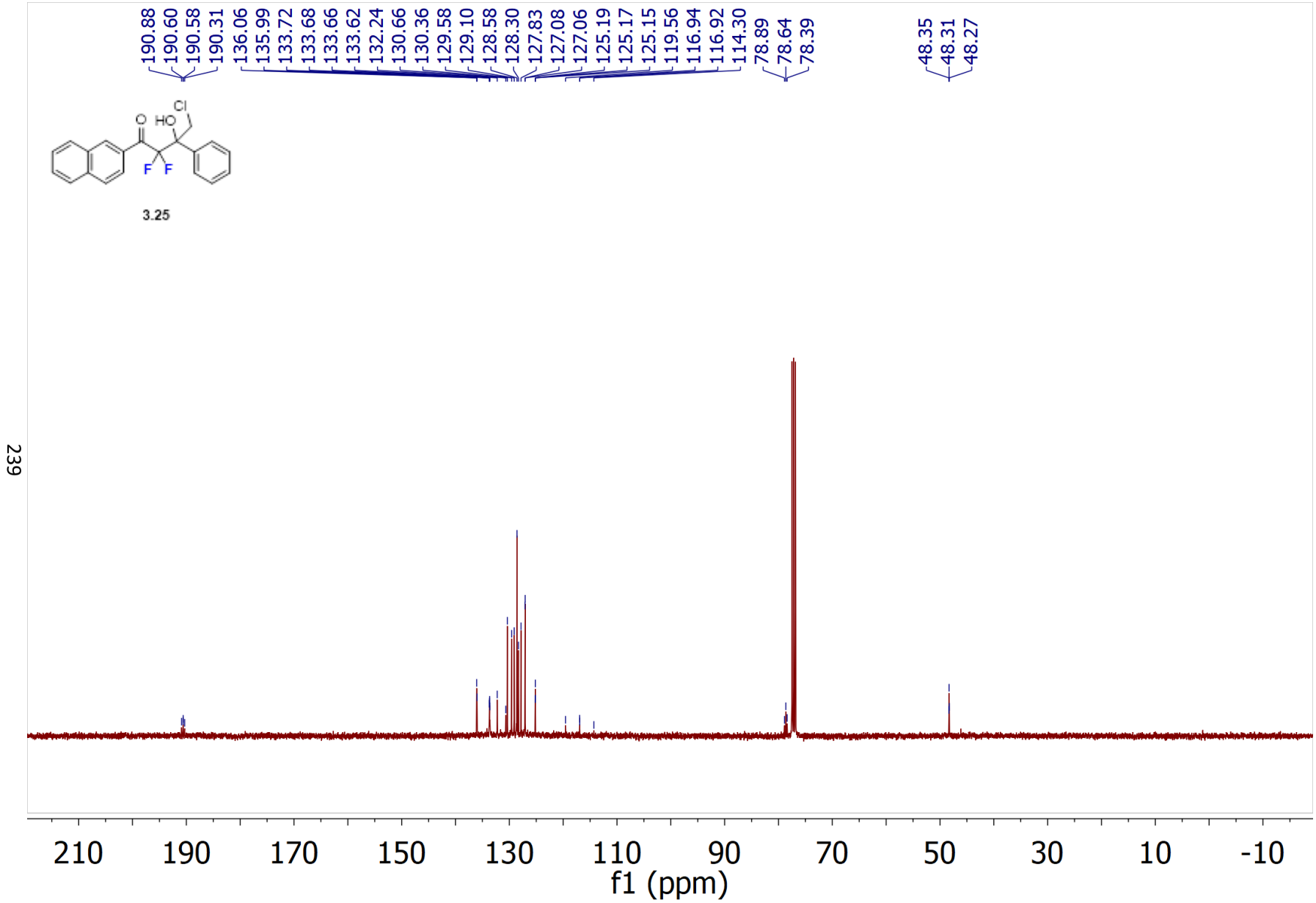
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)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133.68
133.66
133.62
132.24
130.66
130.36
129.58
129.10
128.58
128.30
127.83
127.08
127.06
125.19
125.17
125.15
119.56
116.94
116.92
114.30
78.89
78.64
78.39
48.35
48.31
48.27
O
HO
Cl
F
F
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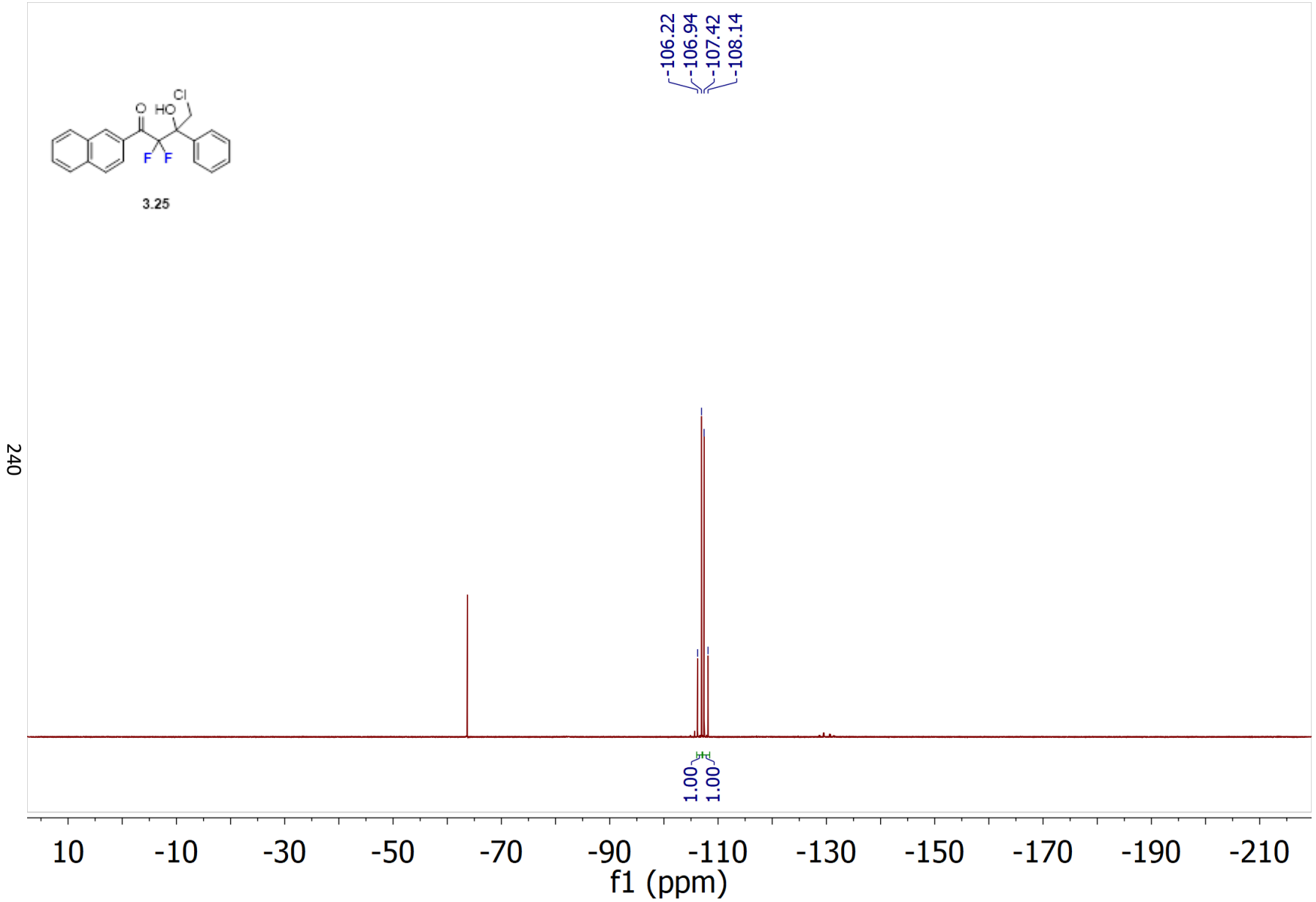
239
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)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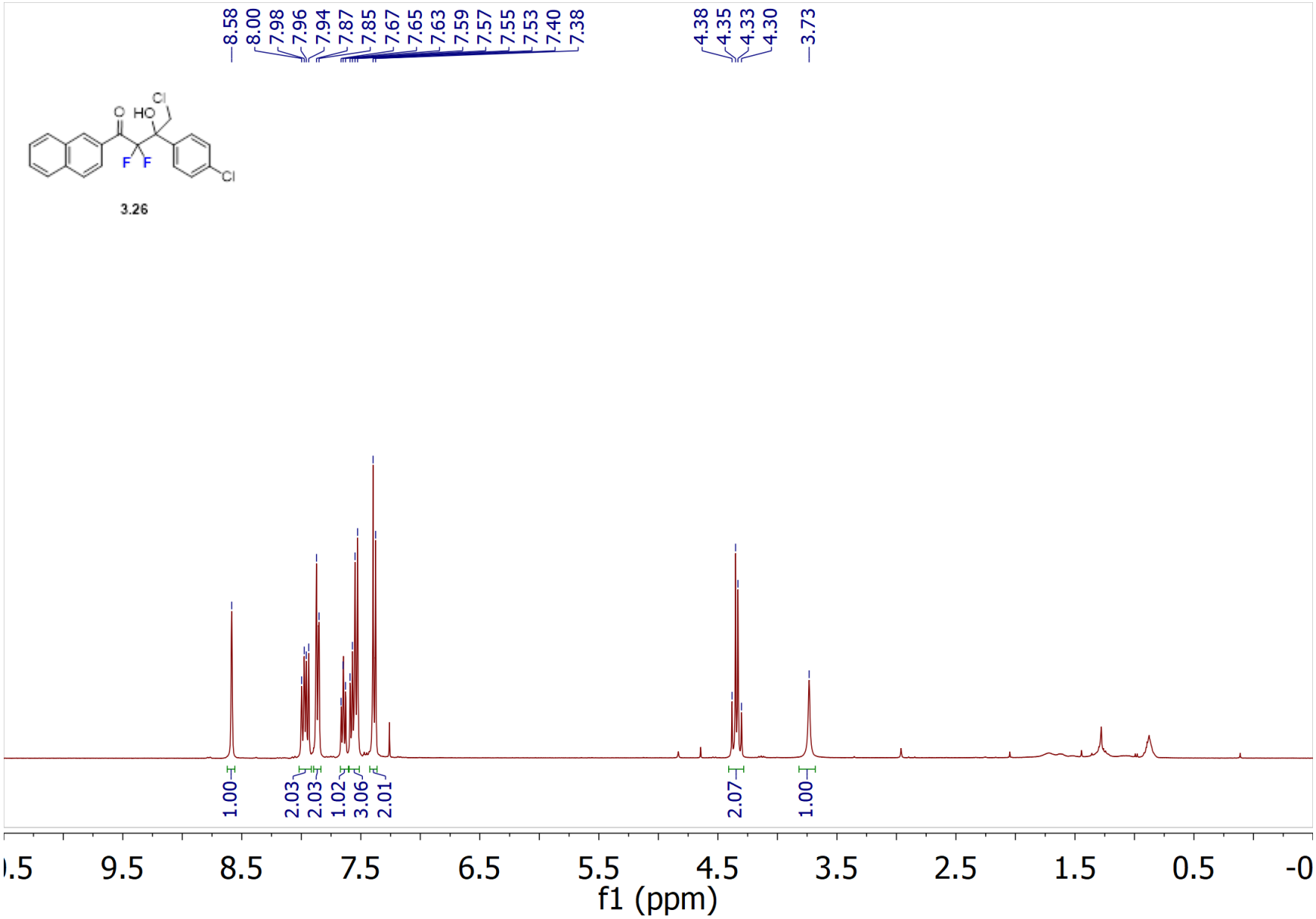
-106.94
-107.42
-108.14
Cl
HO
O
F F
3.25
240
1.00
1.00
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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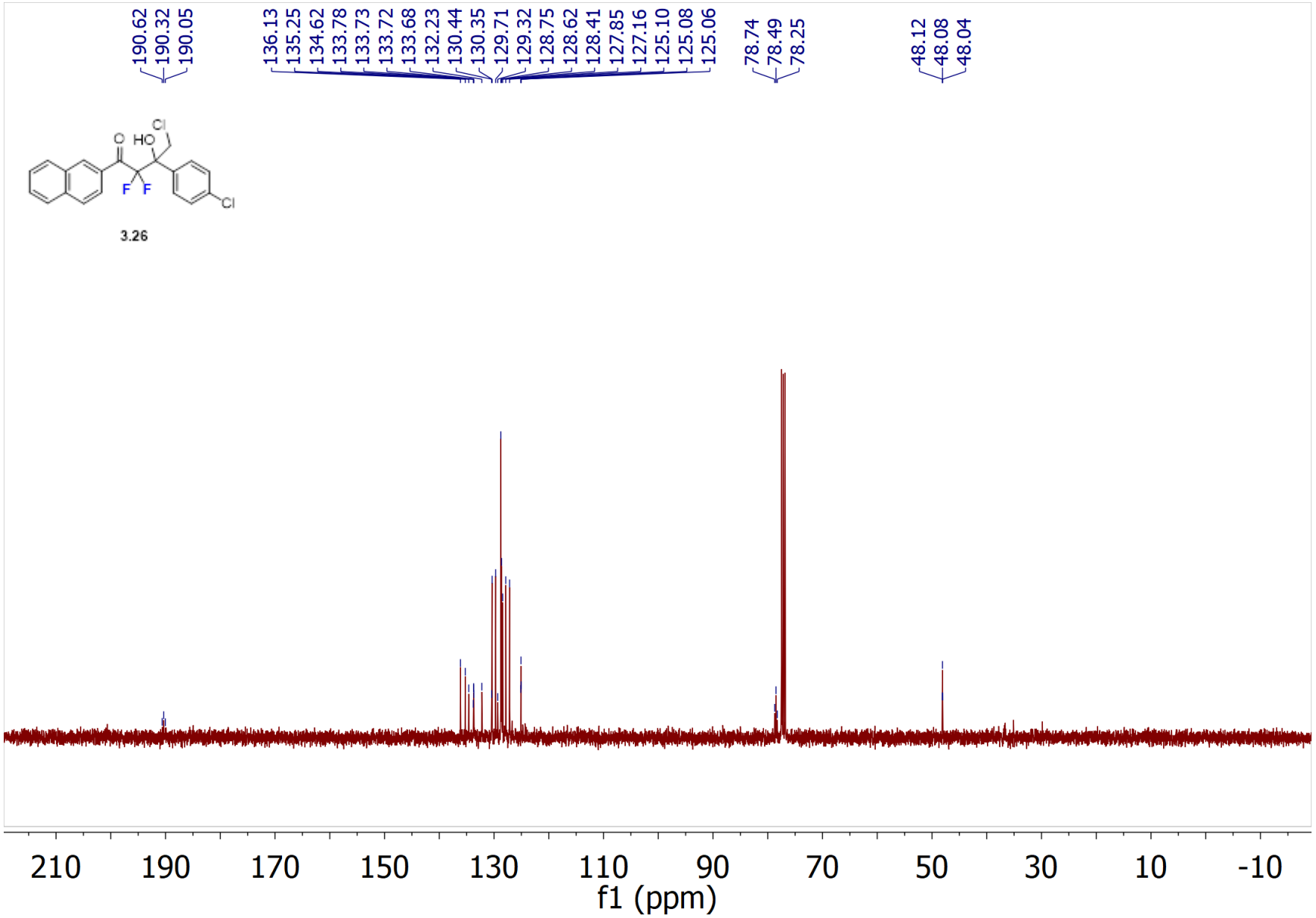
7.63
7.59
7.57
7.55
7.53
7.40
7.38
4.38
4.35
4.33
4.30
3.73
O
HO
Cl
F F
Cl
3.26
1.00
2.03
2.03
1.02
3.06
2.01
2.07
1.00
f1 (ppm)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132.23
130.44
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129.71
129.32
128.75
128.62
128.41
127.85
127.16
125.10
125.08
125.06
78.74
78.49
78.25
48.12
48.08
48.04
Cl
O
HO
F
F
Cl
3.26
210
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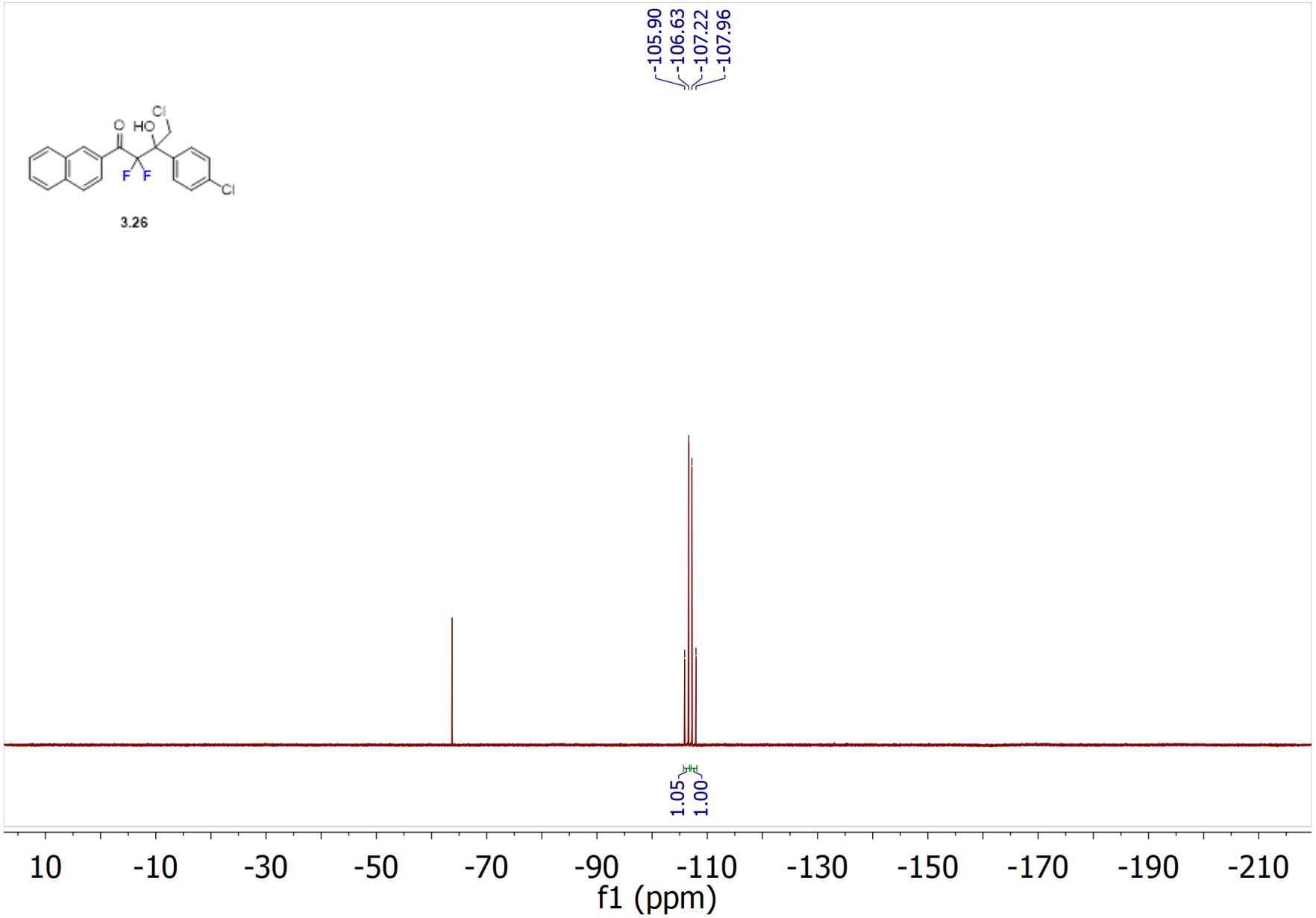
150
130
110
90
70
50
30
10
-10
f1 (ppm)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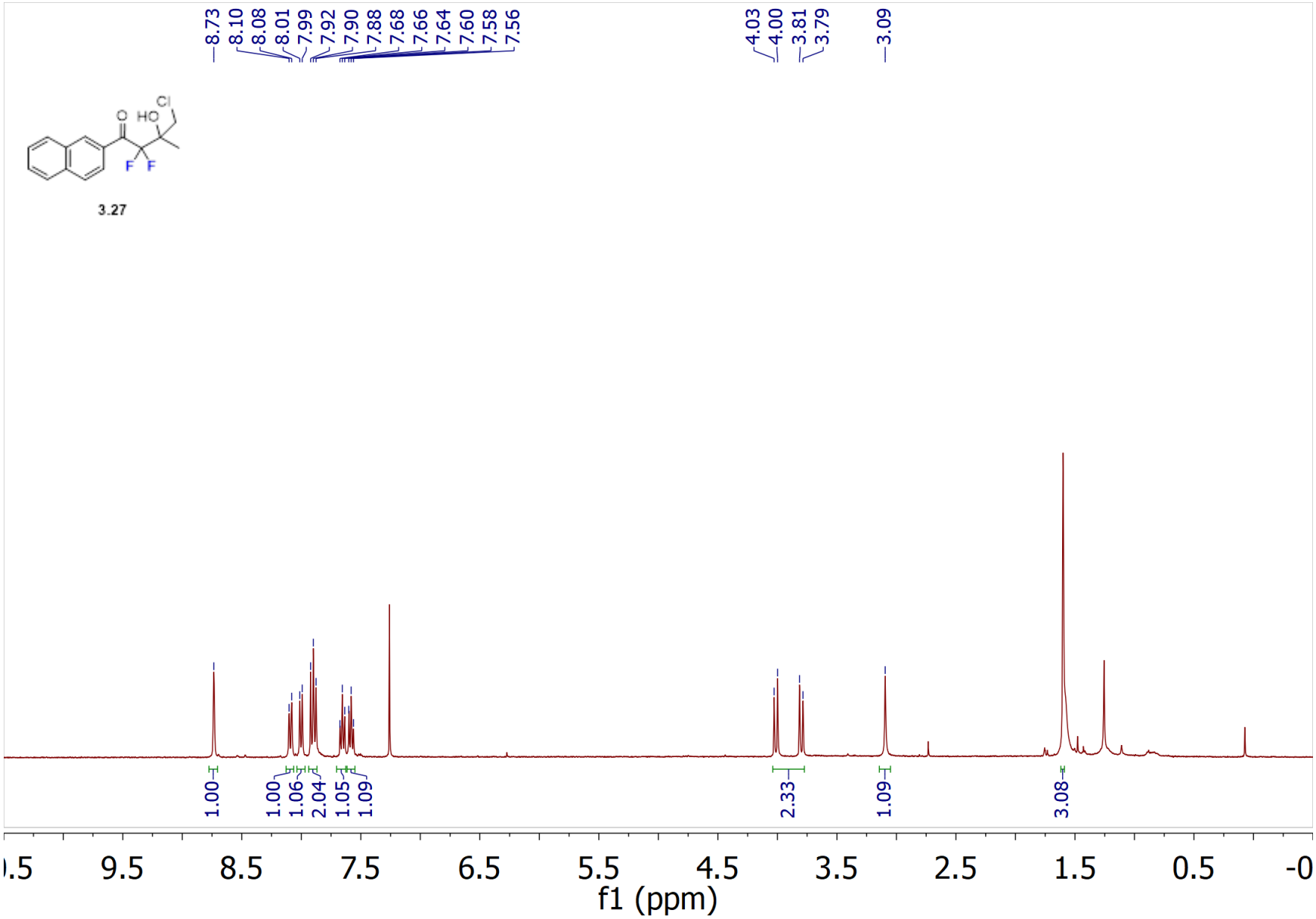
-107.96
O
HO
Cl
F
F
Cl
3.26
1.05
1.00
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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7.92
7.90
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7.68
7.66
7.64
7.60
7.58
7.56
4.03
4.00
3.81
3.79
3.09
O
HO
Cl
F
F
3.27
1.00
1.00
1.06
2.04
1.05
1.09
2.33
1.09
3.08
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7.5
6.5
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2.5
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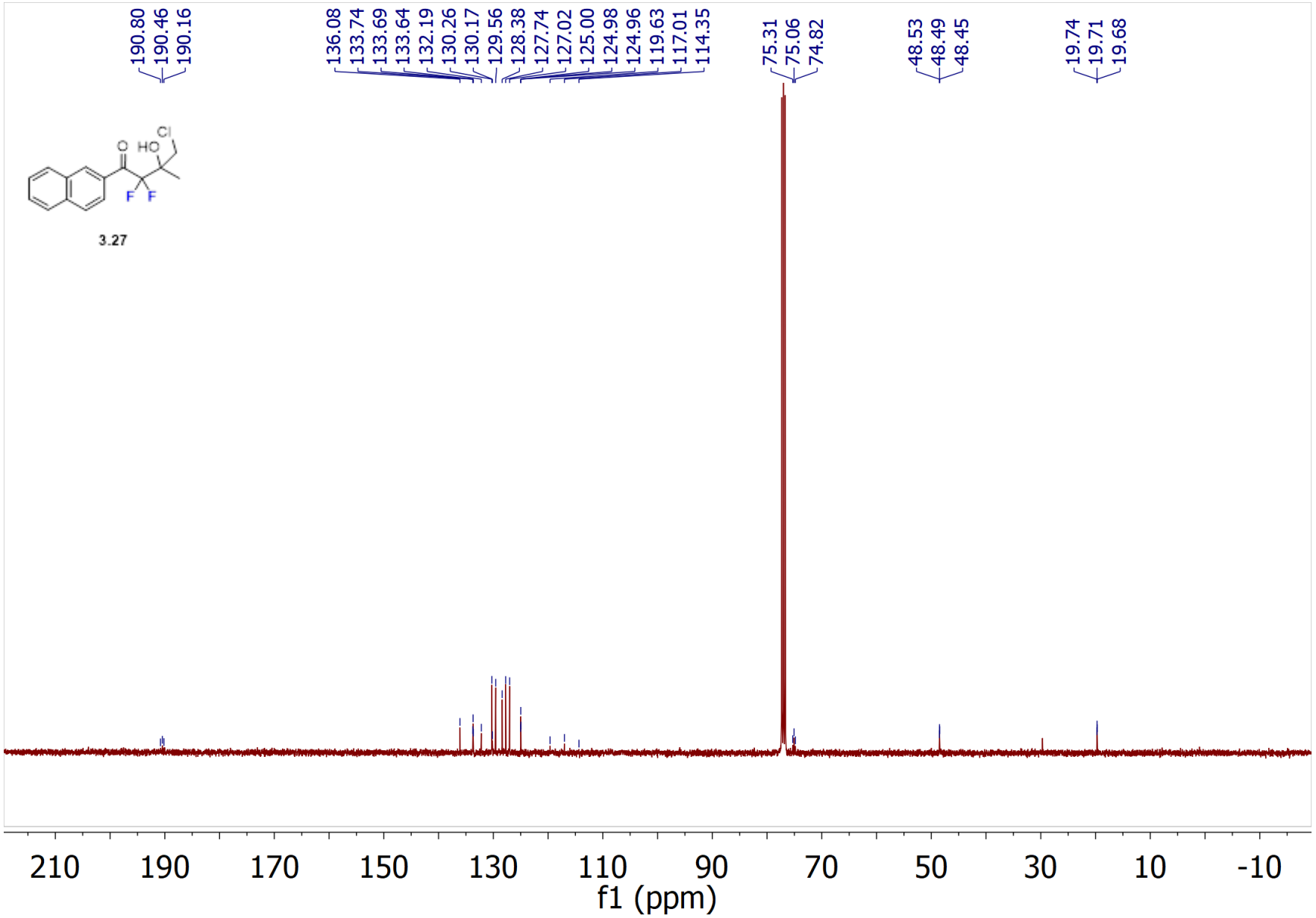
f1 (ppm)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133.69
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132.19
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127.74
127.02
125.00
124.98
124.96
119.63
117.01
114.35
75.31
75.06
74.82
48.53
48.49
48.45
19.74
19.71
19.68
O
HO
Cl
F
F
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90
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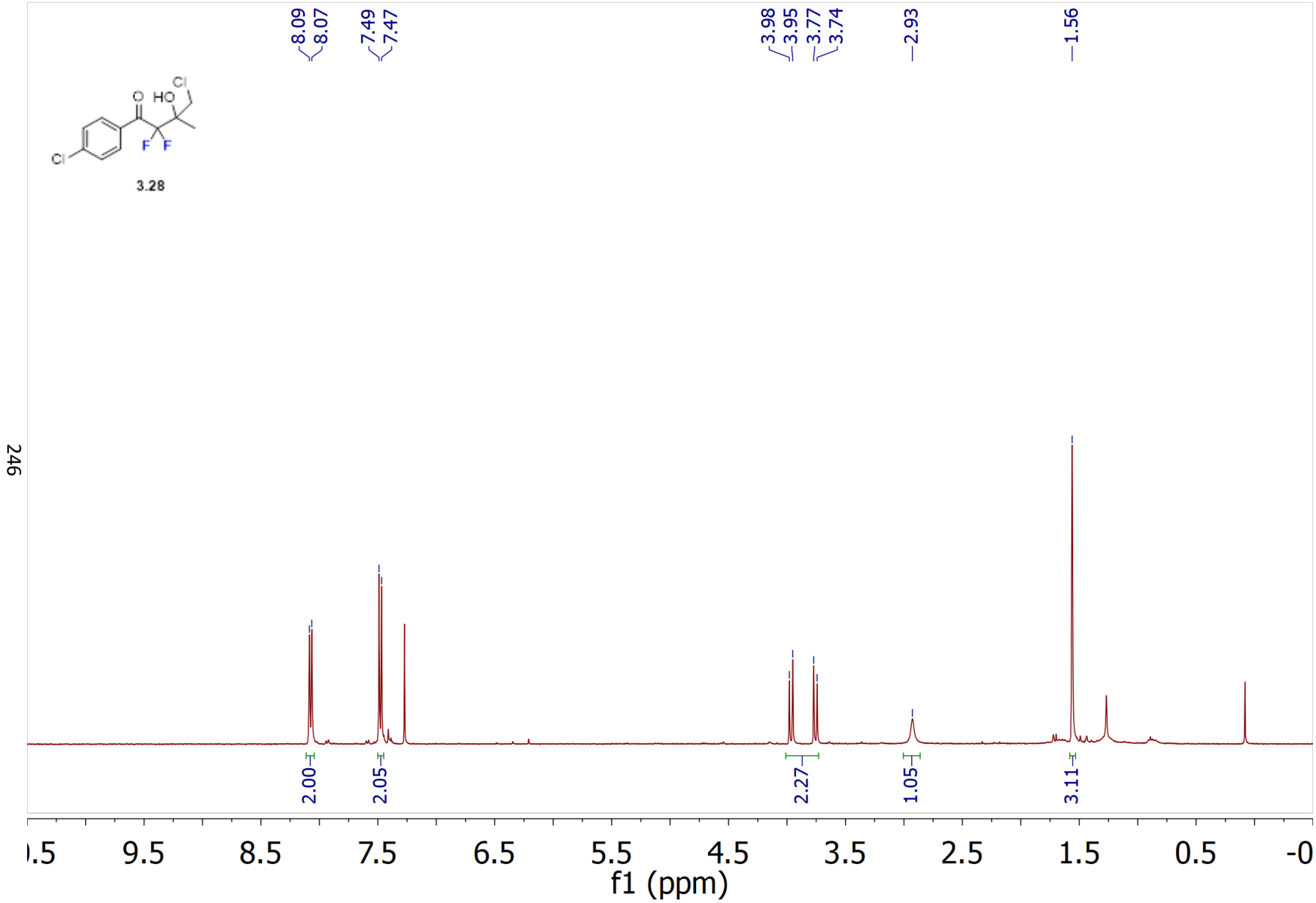
f1 (ppm)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3.77
3.74
2.93
1.56
Cl
O
HO
Cl
F
F
Cl
3.28
2.00
2.05
2.27
1.05
3.11
246
.5
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6.5
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4.5
3.5
2.5
1.5
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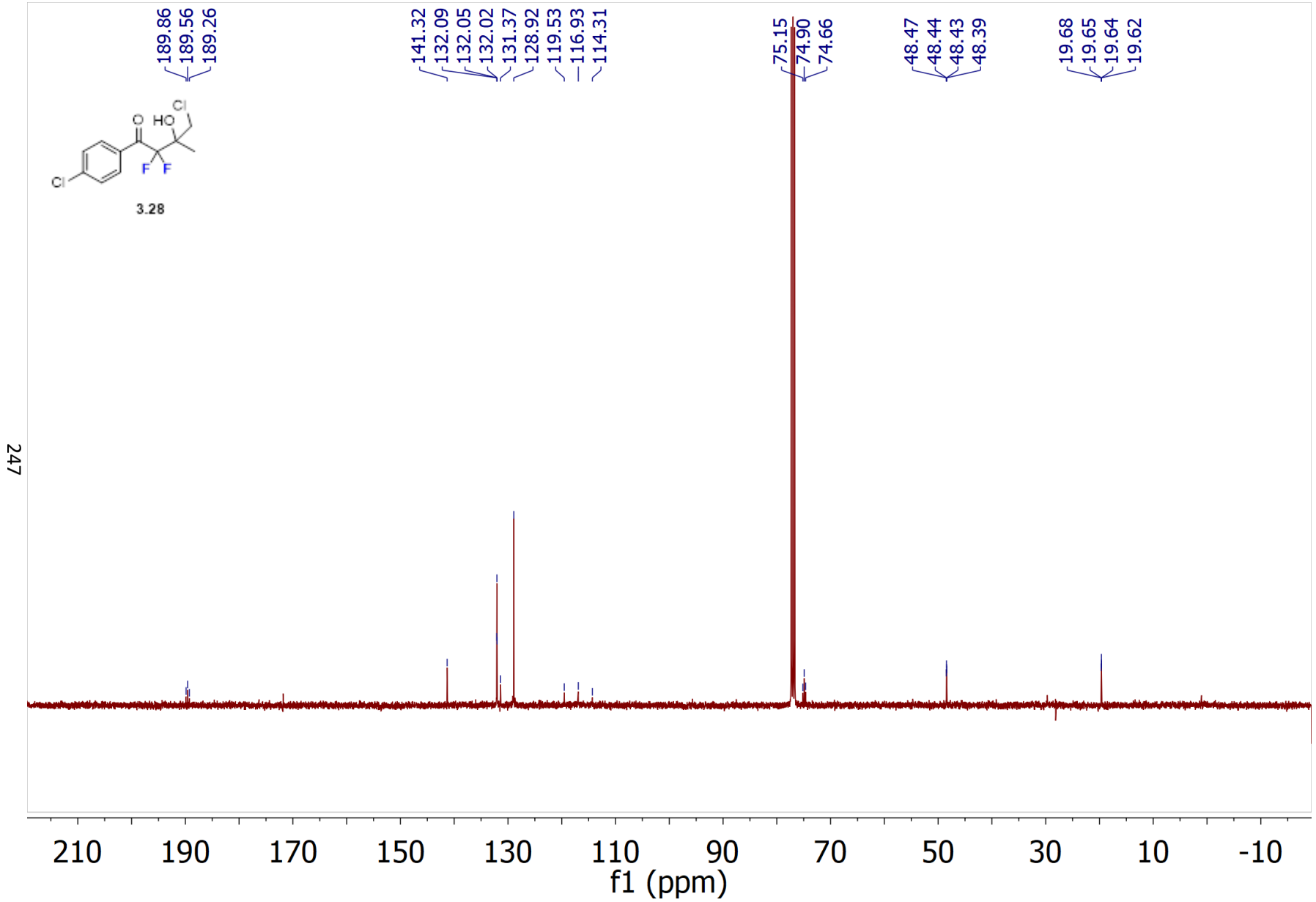
f1 (ppm)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114.31
75.15
74.90
74.66
48.47
48.44
48.43
48.39
19.68
19.65
19.64
19.62
O
HO
Cl
F
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90
70
50
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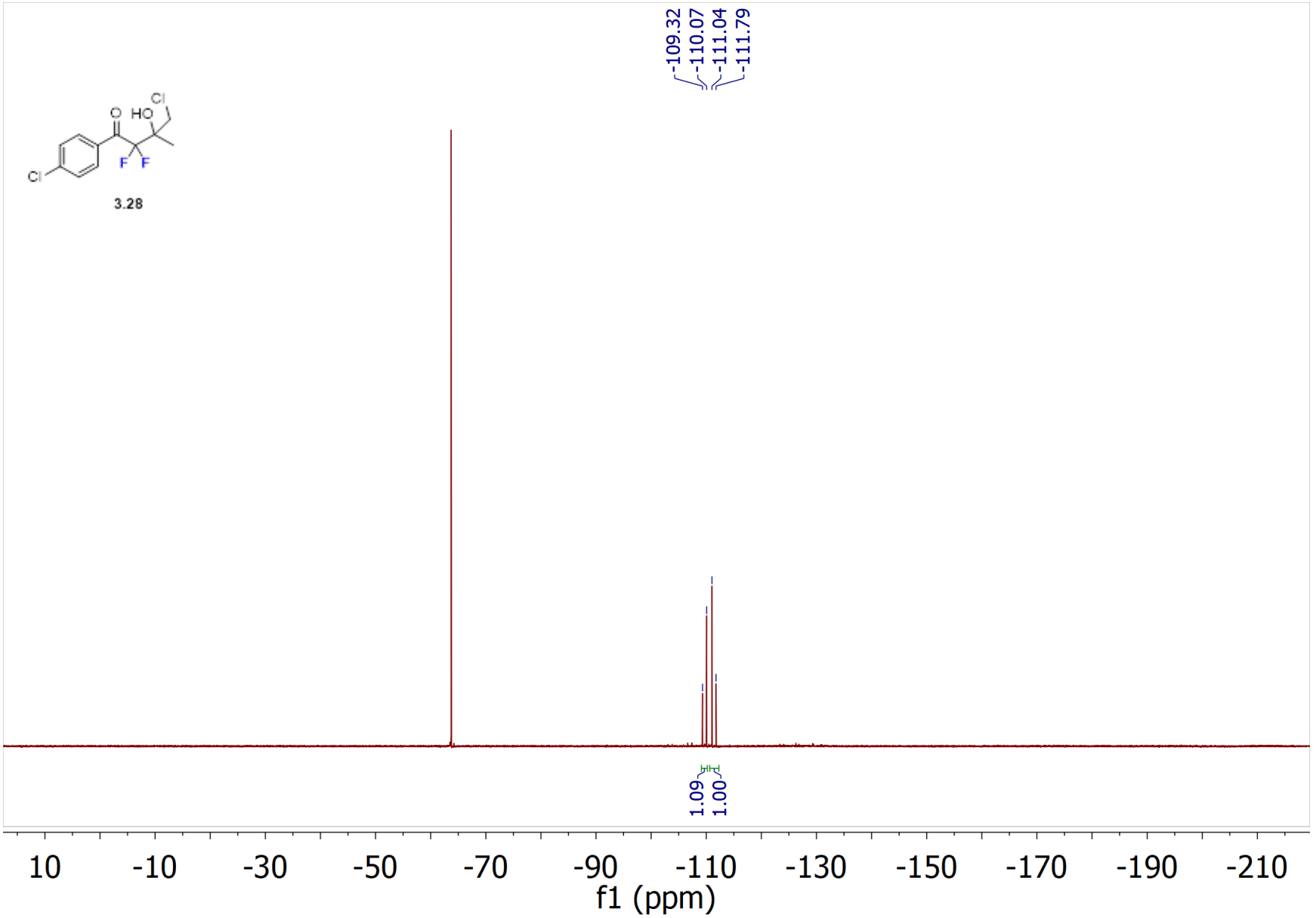
10
-10
f1 (ppm)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-111.04
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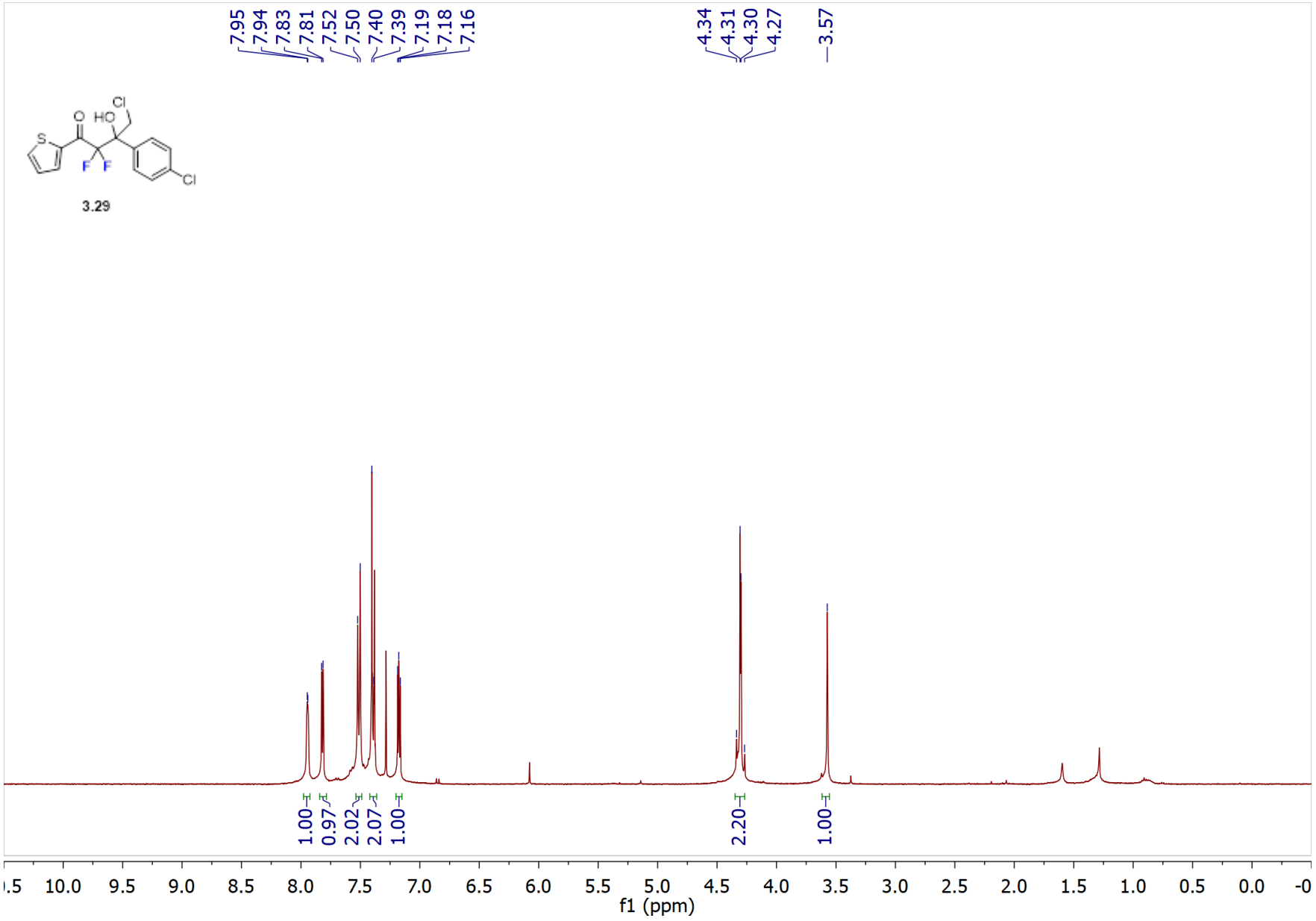
Cl
O
HO
F
F
Cl
3.28
1.09
1.00
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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7.94
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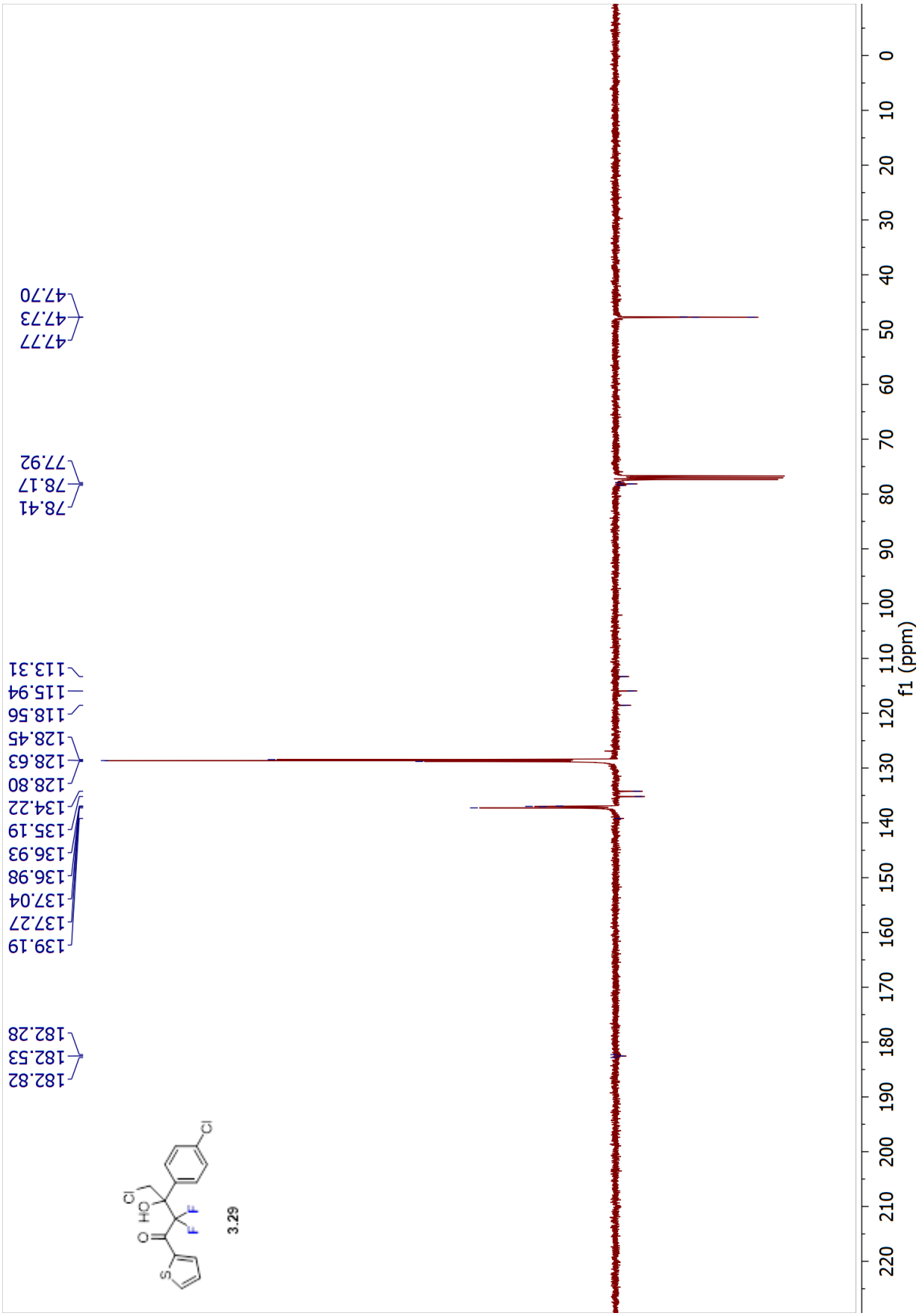
7.40
7.39
7.19
7.18
7.16
4.34
4.31
4.30
4.27
3.57
Cl
HO
O
S
F F
Cl
3.29
1.00
0.97
2.02
2.07
1.00
2.20
1.00
f1 (ppm)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182.53
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137.04
136.98
136.93
135.19
134.22
128.80
128.63
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113.31
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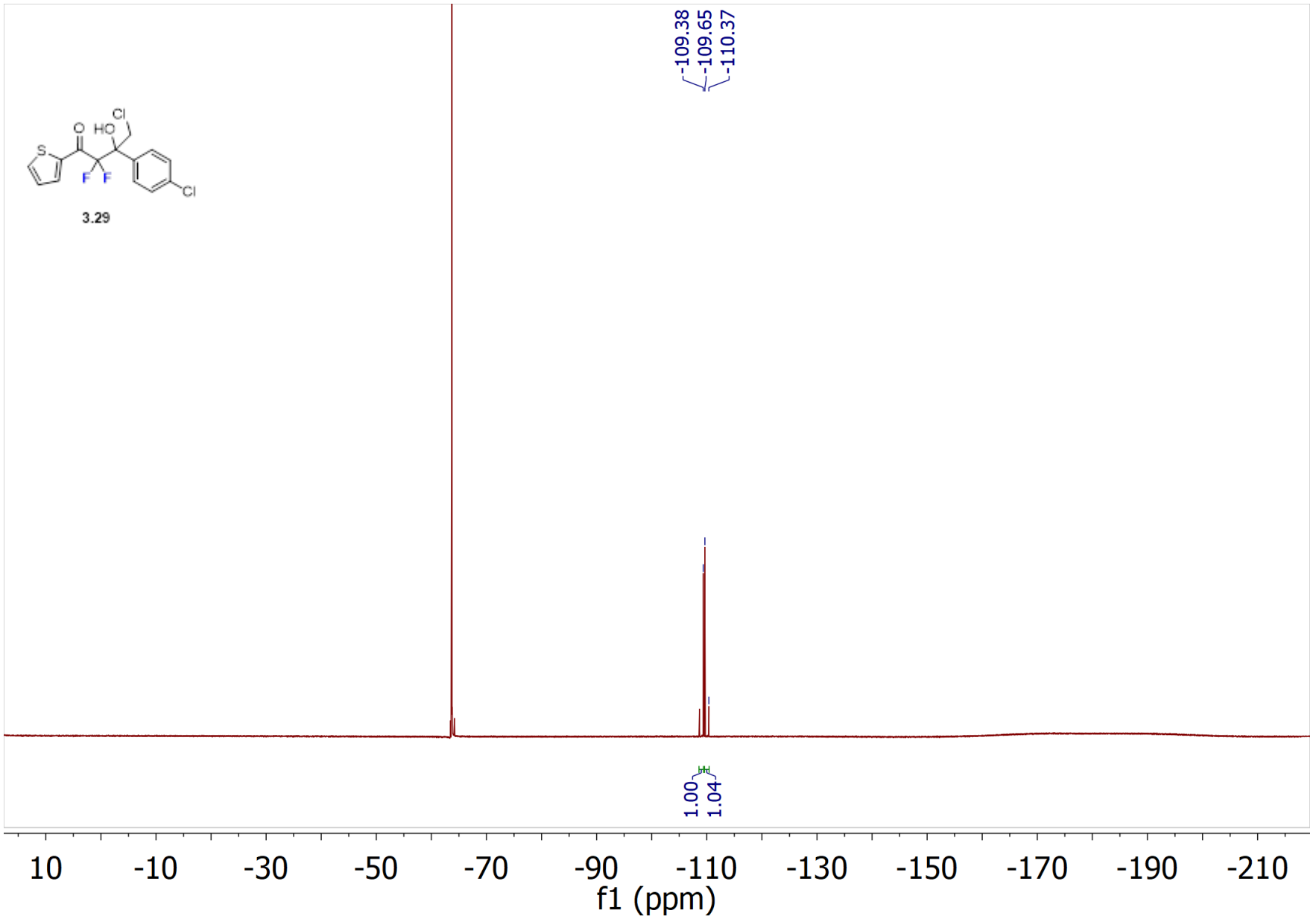
78.17
77.92
47.77
47.73
47.70
f1 (ppm)
3.29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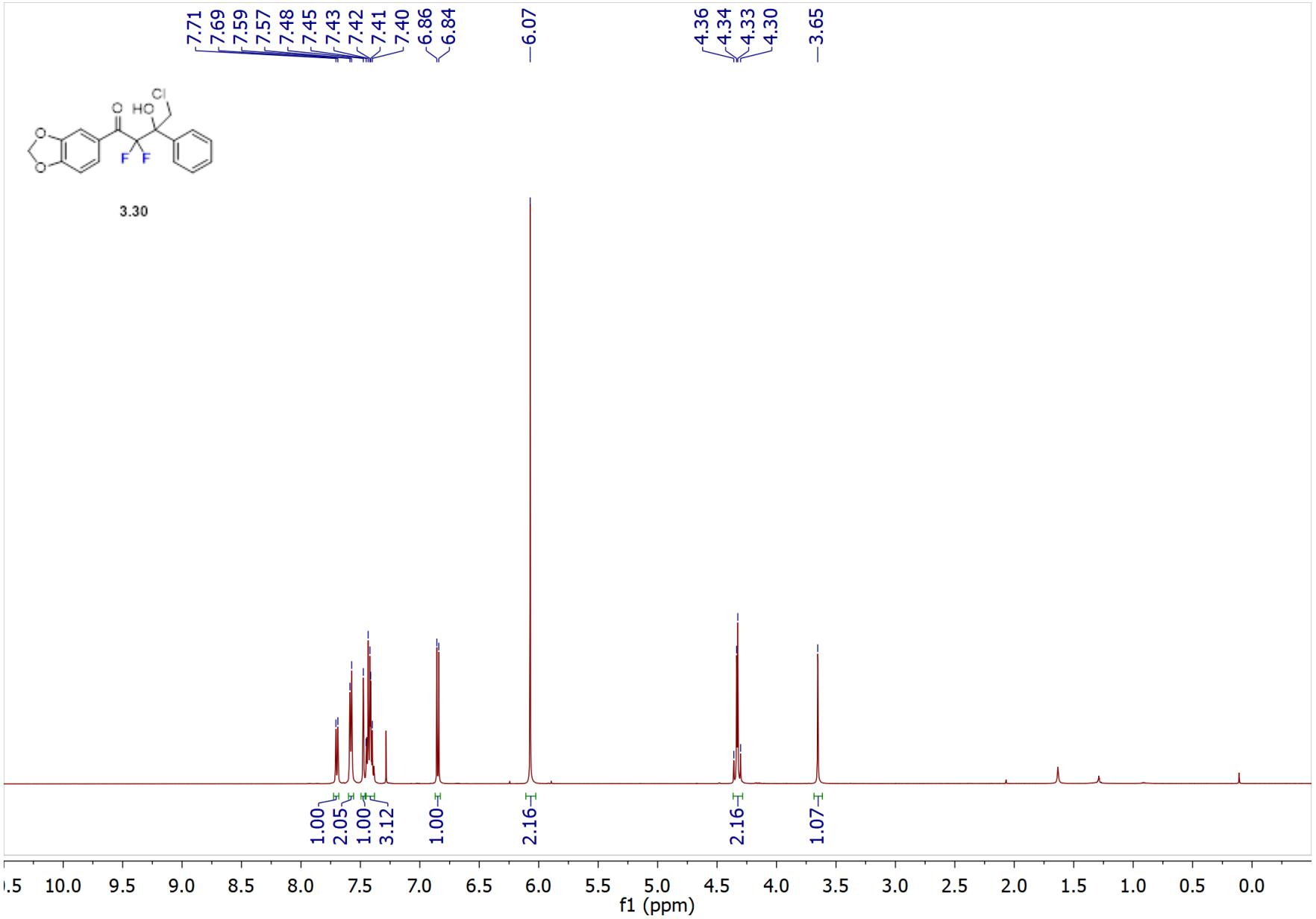
-109.65
-110.37
Cl
HO
O
S
F F
Cl
3.29
1.00
1.04
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)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7.69
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7.57
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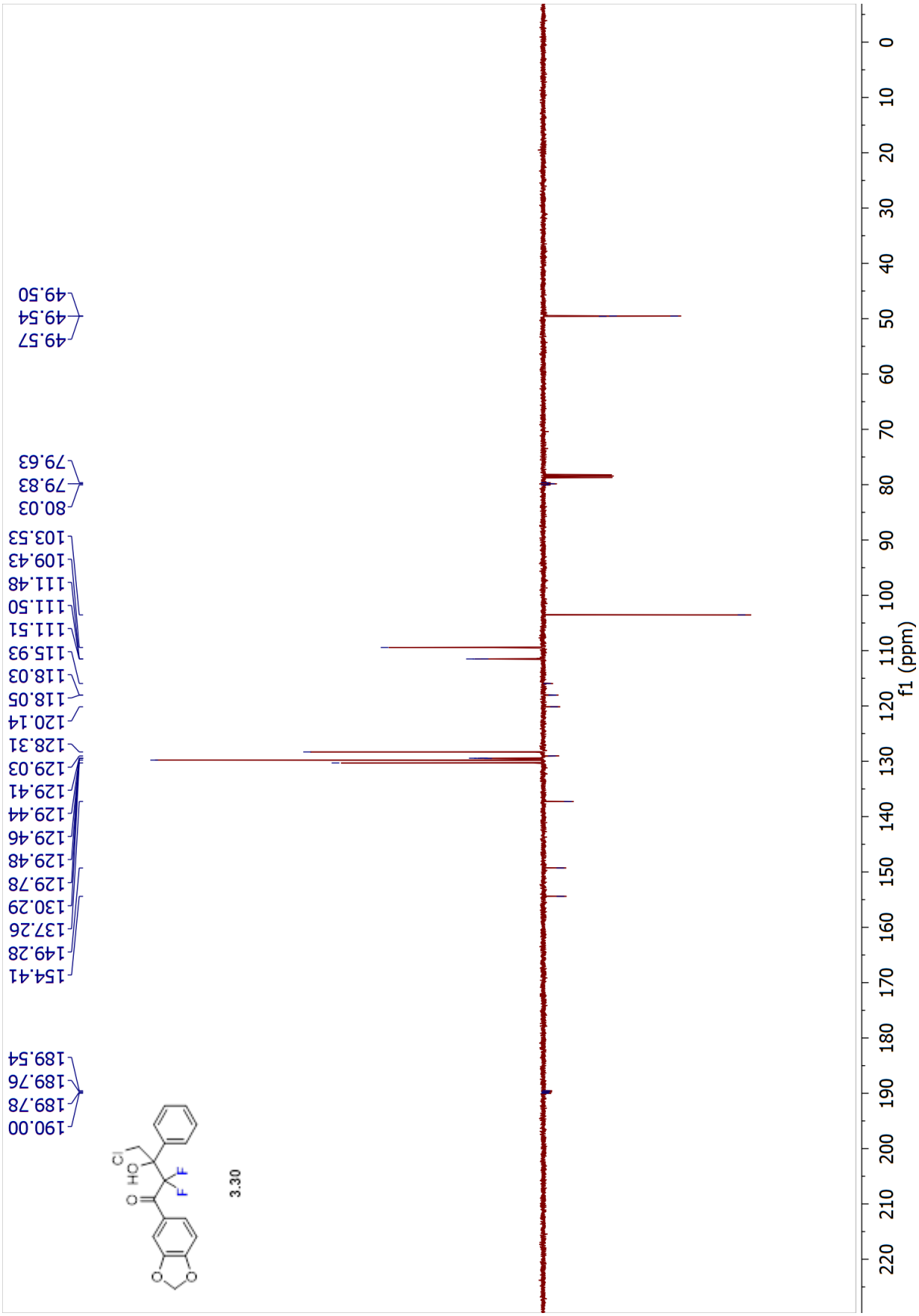
7.45
7.43
7.42
7.41
7.40
6.86
6.84
6.07
4.36
4.34
4.33
4.30
3.65
Cl
HO
O
F
F
3.30
1.00
2.05
1.00
3.12
1.00
2.16
2.16
1.07
f1 (ppm)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189.76
189.54
154.41
149.28
137.26
130.29
129.78
129.48
129.46
129.44
129.41
129.03
128.31
120.14
118.05
118.03
115.93
111.51
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111.48
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103.53
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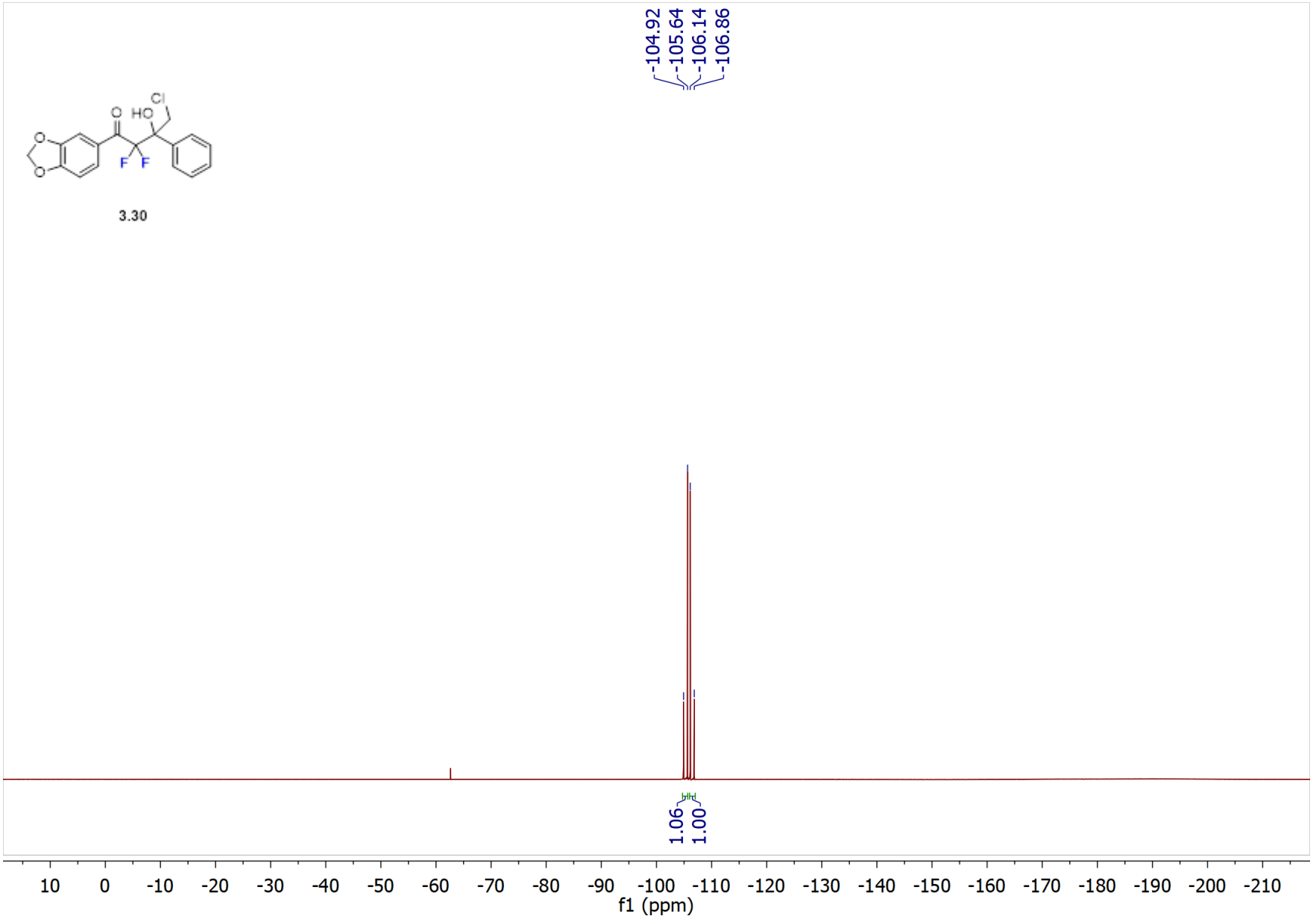
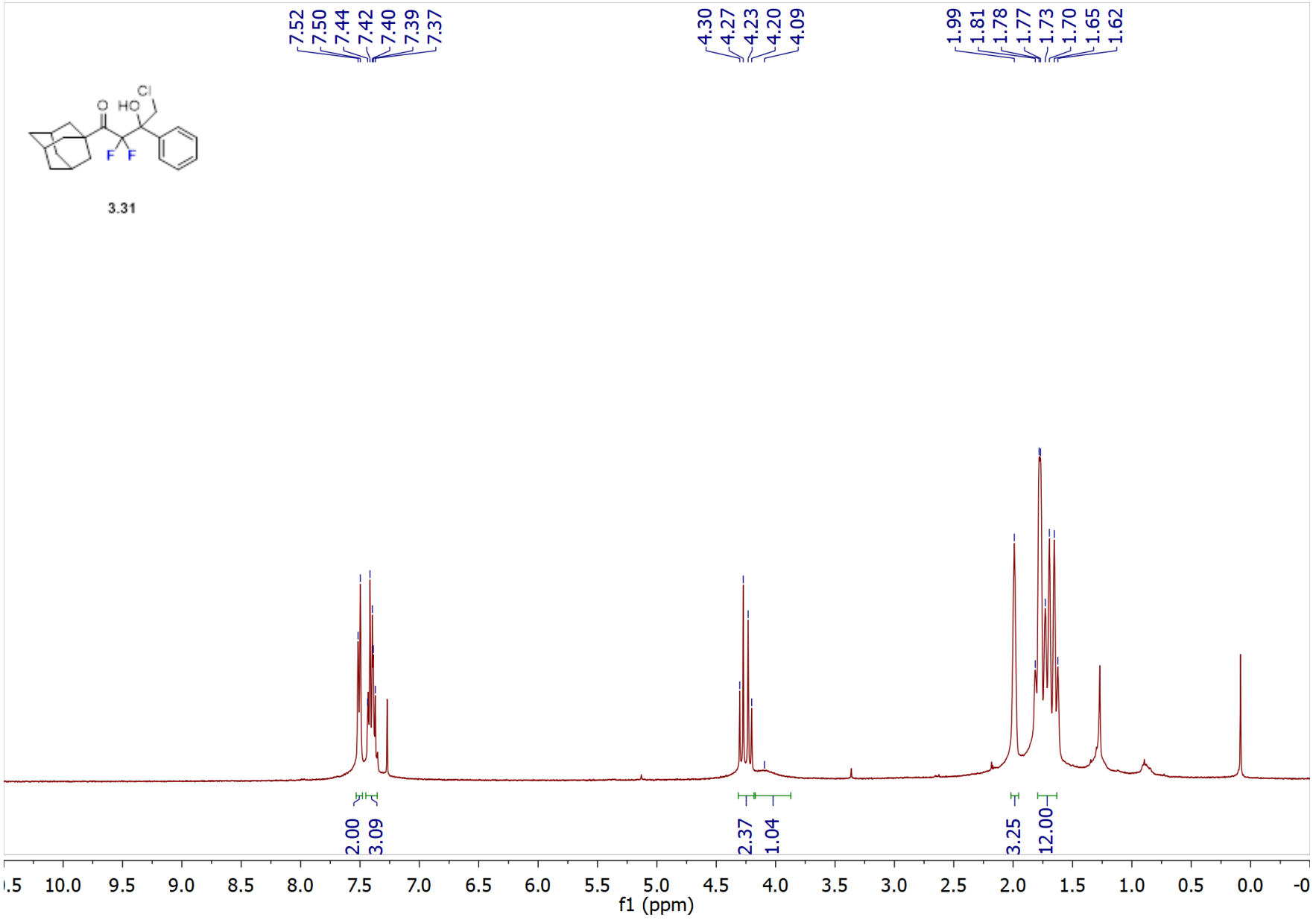
79.83
79.63
49.57
49.54
49.50
3.30
f1 (ppm)


-104.92
-105.64
-106.14
-106.86
Cl
HO
O
F F
3.30
1.06
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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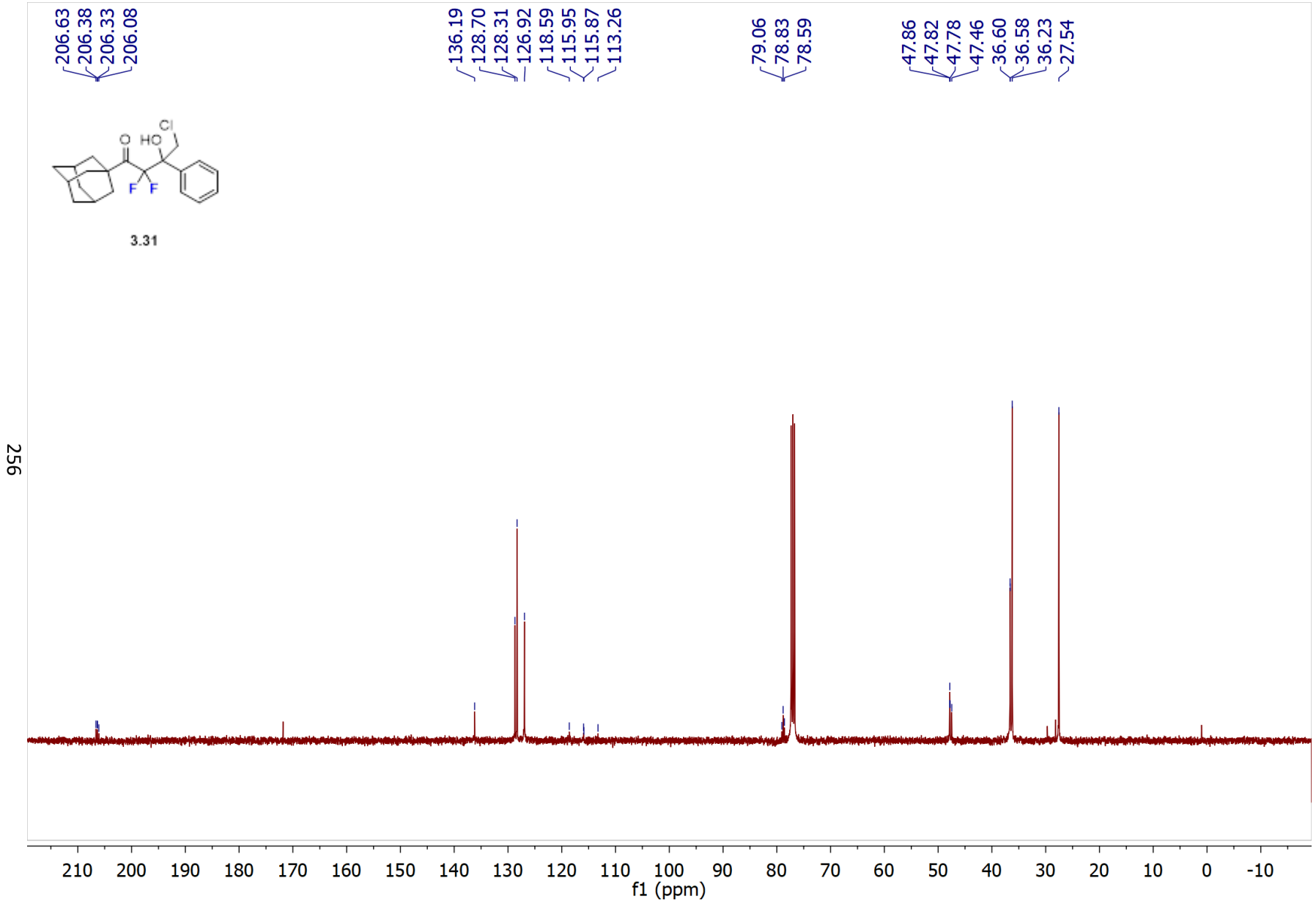
7.50
7.44
7.42
7.40
7.39
7.37
4.30
4.27
4.23
4.20
4.09
1.99
1.81
1.78
1.77
1.73
1.70
1.65
1.62
O
HO
Cl
F
F
3.31
2.00
3.09
2.37
1.04
3.25
12.00
f1 (ppm)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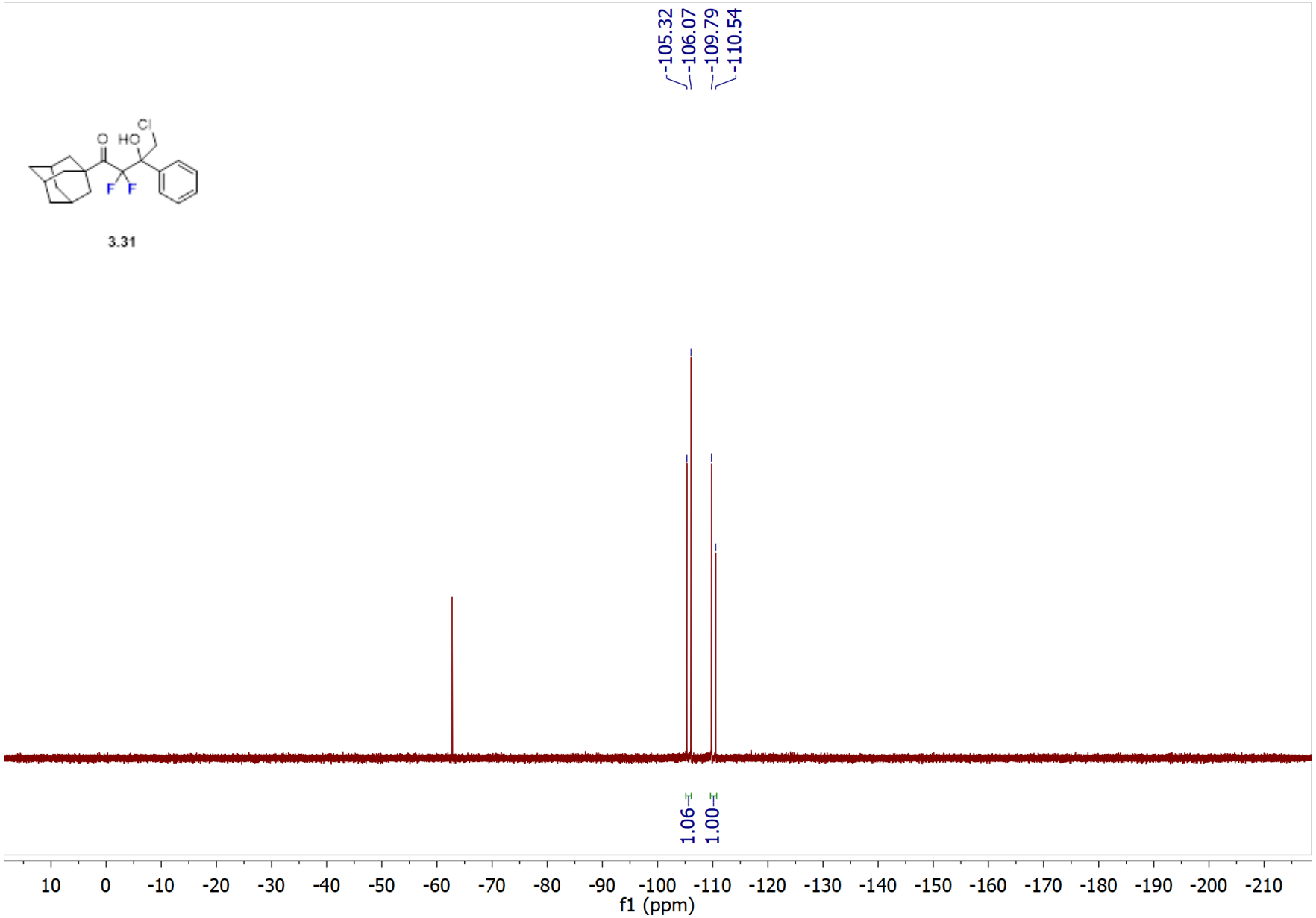
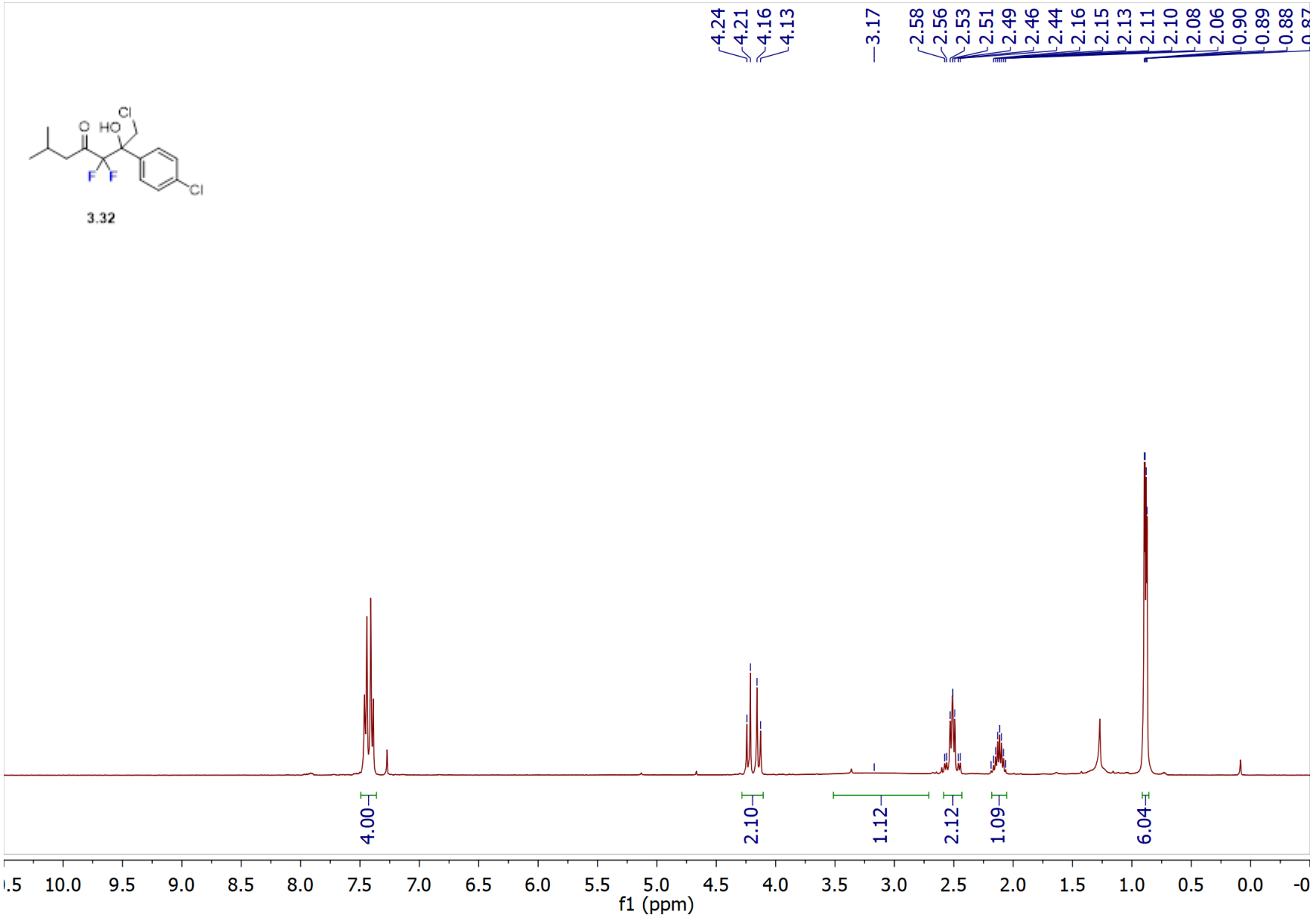
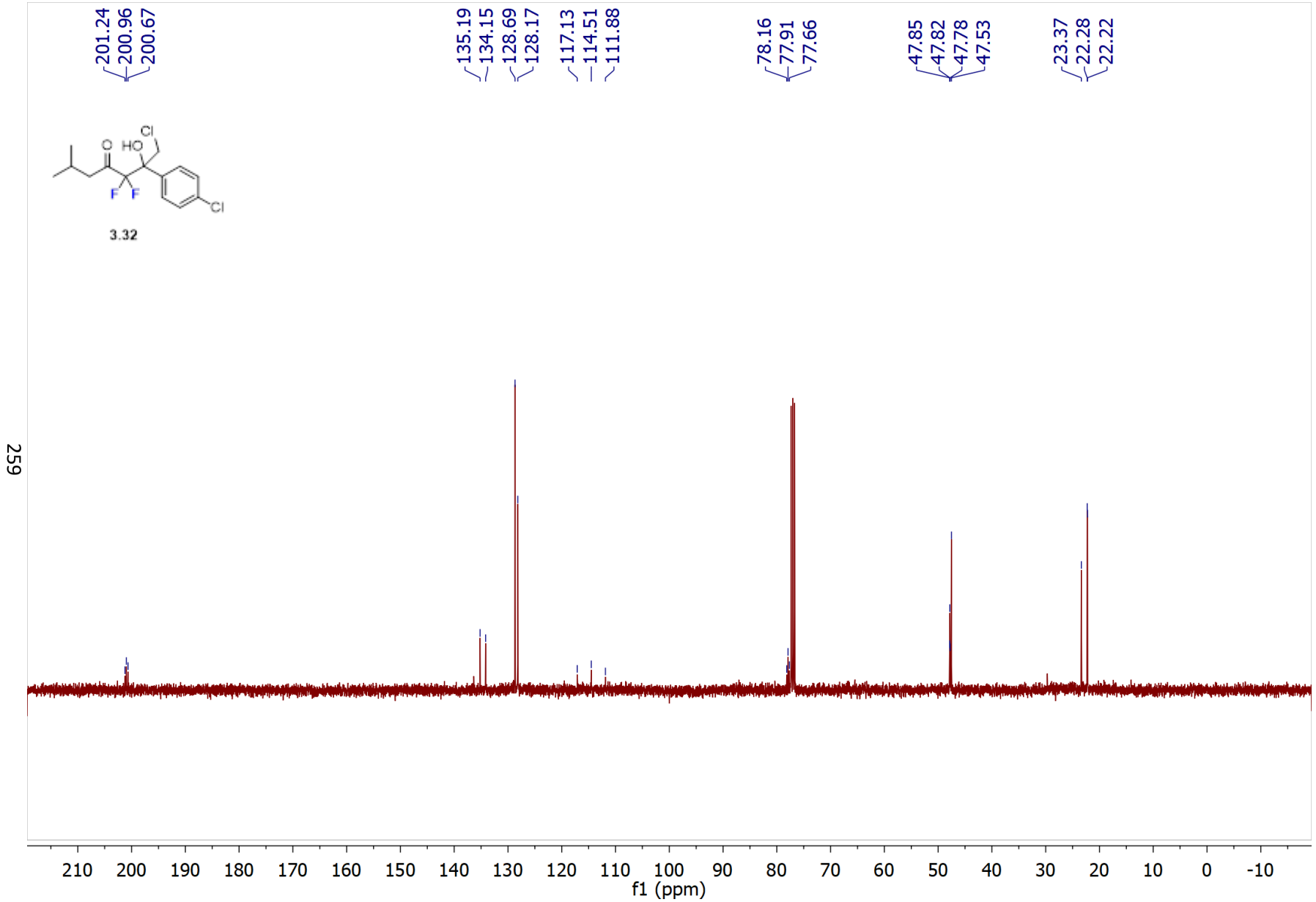
206.38
206.33
206.08
136.19
128.70
128.31
126.92
118.59
115.95
115.87
113.26
79.06
78.83
78.59
47.86
47.82
47.78
47.46
36.60
36.58
36.23
27.54
Cl
O
HO
F
F
3.31
256
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-105.32
-106.07
-109.79
-110.54
O
HO
Cl
F
F
3.31
1.06
1.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


4.24
4.21
4.16
4.13
3.17
2.58
2.56
2.53
2.51
2.49
2.46
2.44
2.16
2.15
2.13
2.11
2.10
2.08
2.06
0.90
0.89
0.88
O
HO
Cl
F
F
Cl
3.32
4.00
2.10
1.12
2.12
1.09
6.04
f1 (ppm)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200.96
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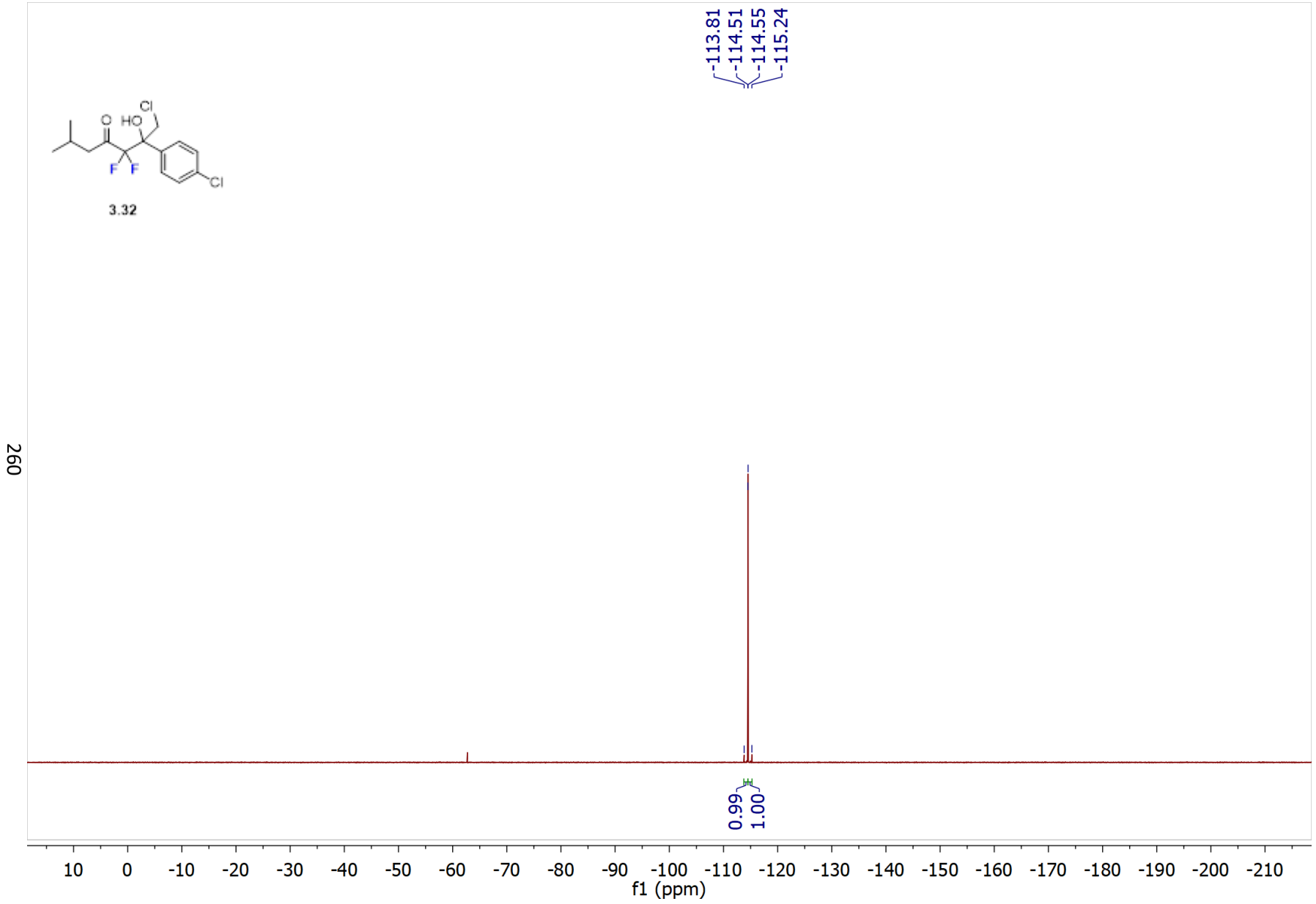
135.19
134.15
128.69
128.17
117.13
114.51
111.88
78.16
77.91
77.66
47.85
47.82
47.78
47.53
23.37
22.28
22.22
O
HO
Cl
F
F
Cl
3.32
259
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-113.81
-114.51
-114.55
-115.24
Cl
O
HO
F
F
Cl
3.32
260
0.99
1.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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-100
-110
-120
-130
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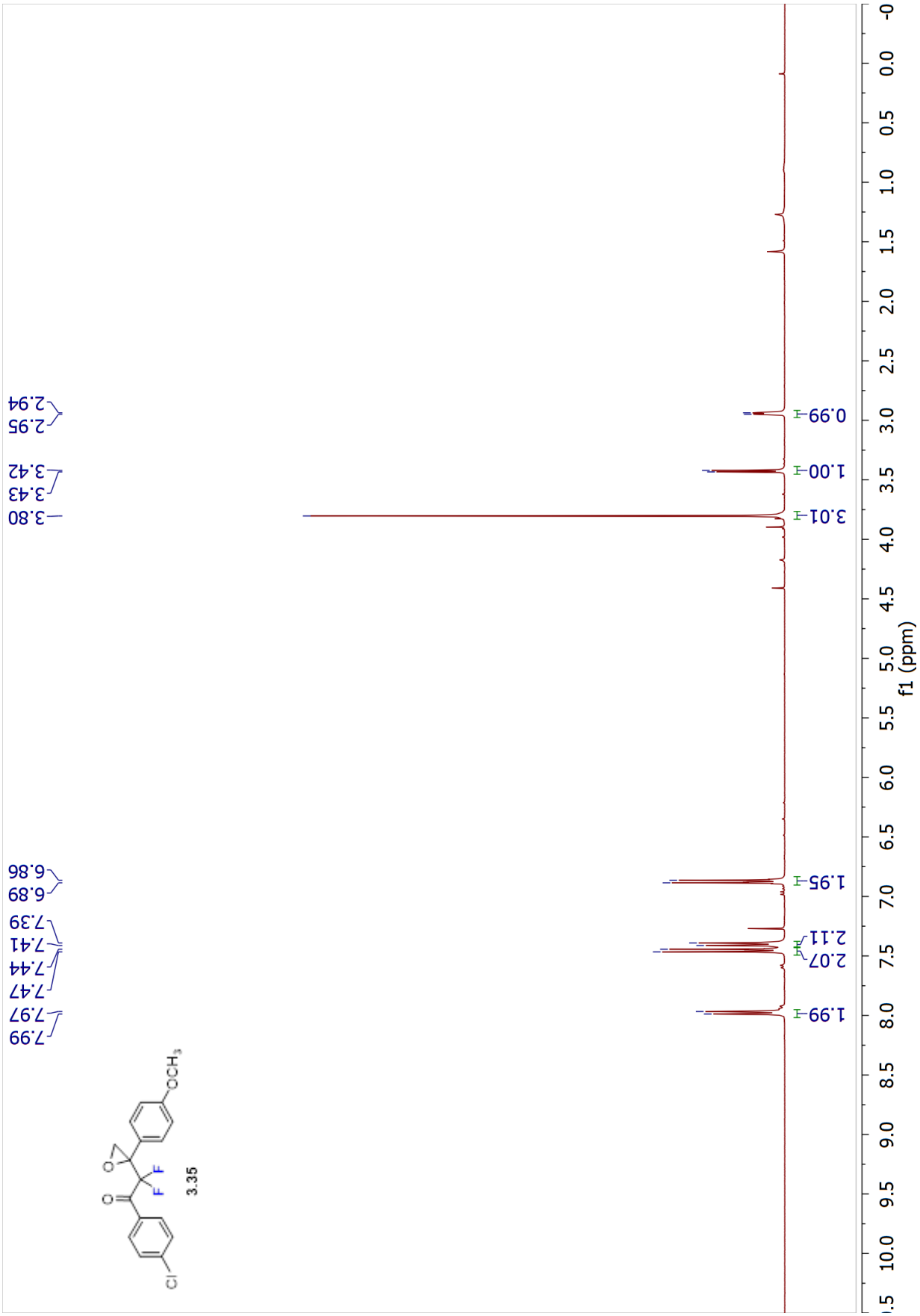
-170
-180
-190
-200
-210
f1 (ppm)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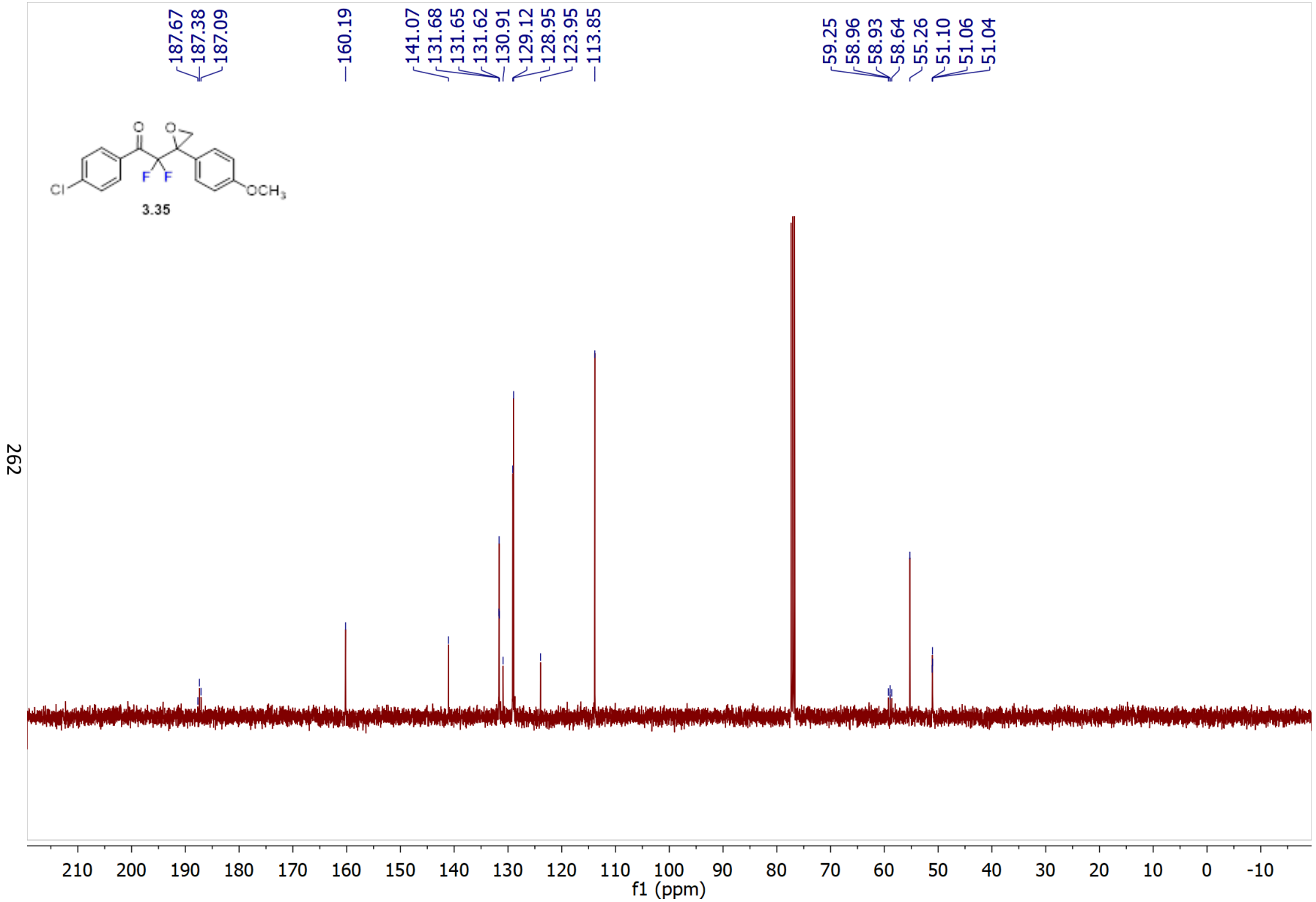
7.97
7.47
7.44
7.41
7.39
6.89
6.86
3.80
3.43
3.42
2.95
2.94
1.99
2.07
2.11
1.95
3.01
1.00
0.99
f1 (ppm)
3.35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187.38
187.09
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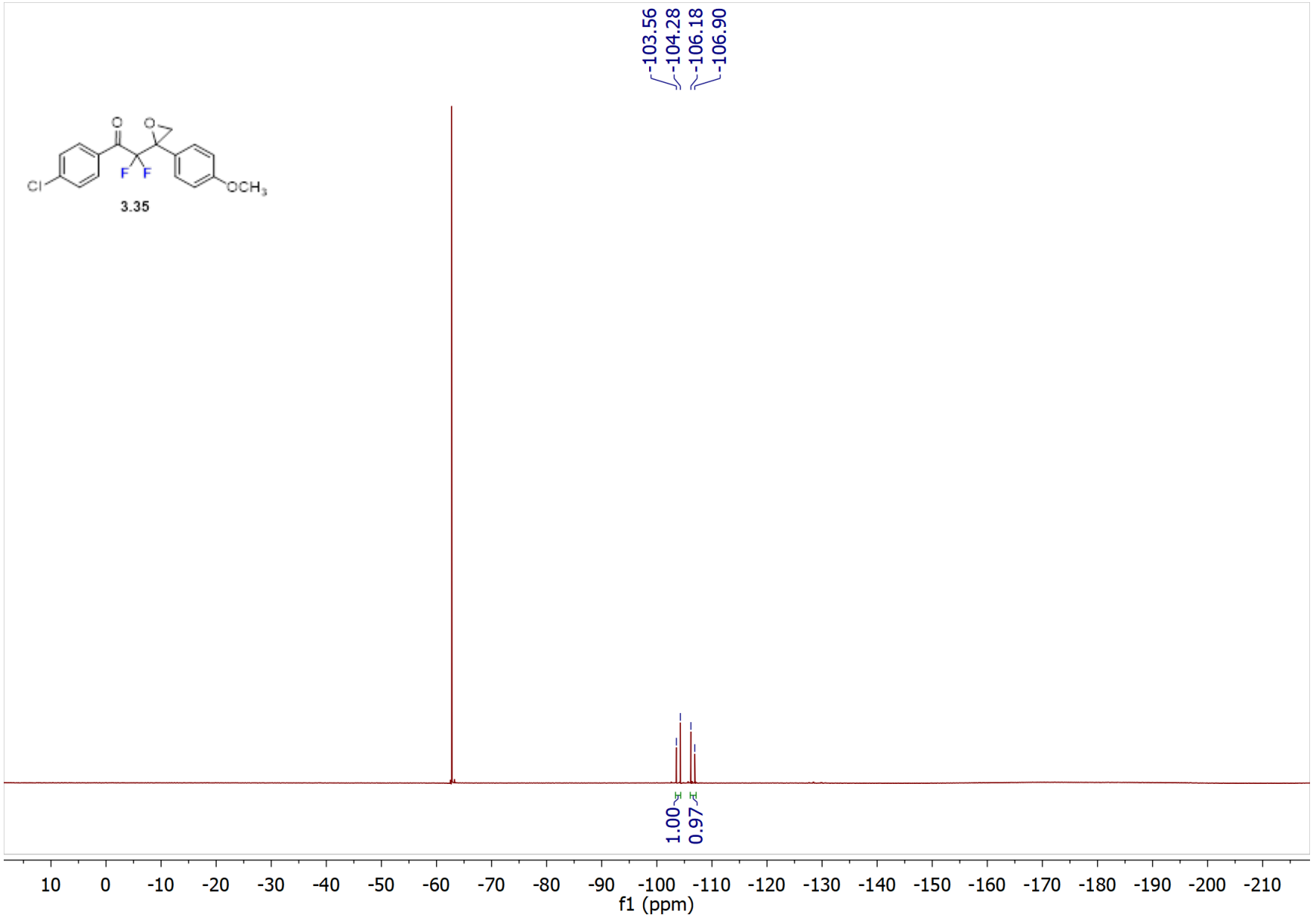
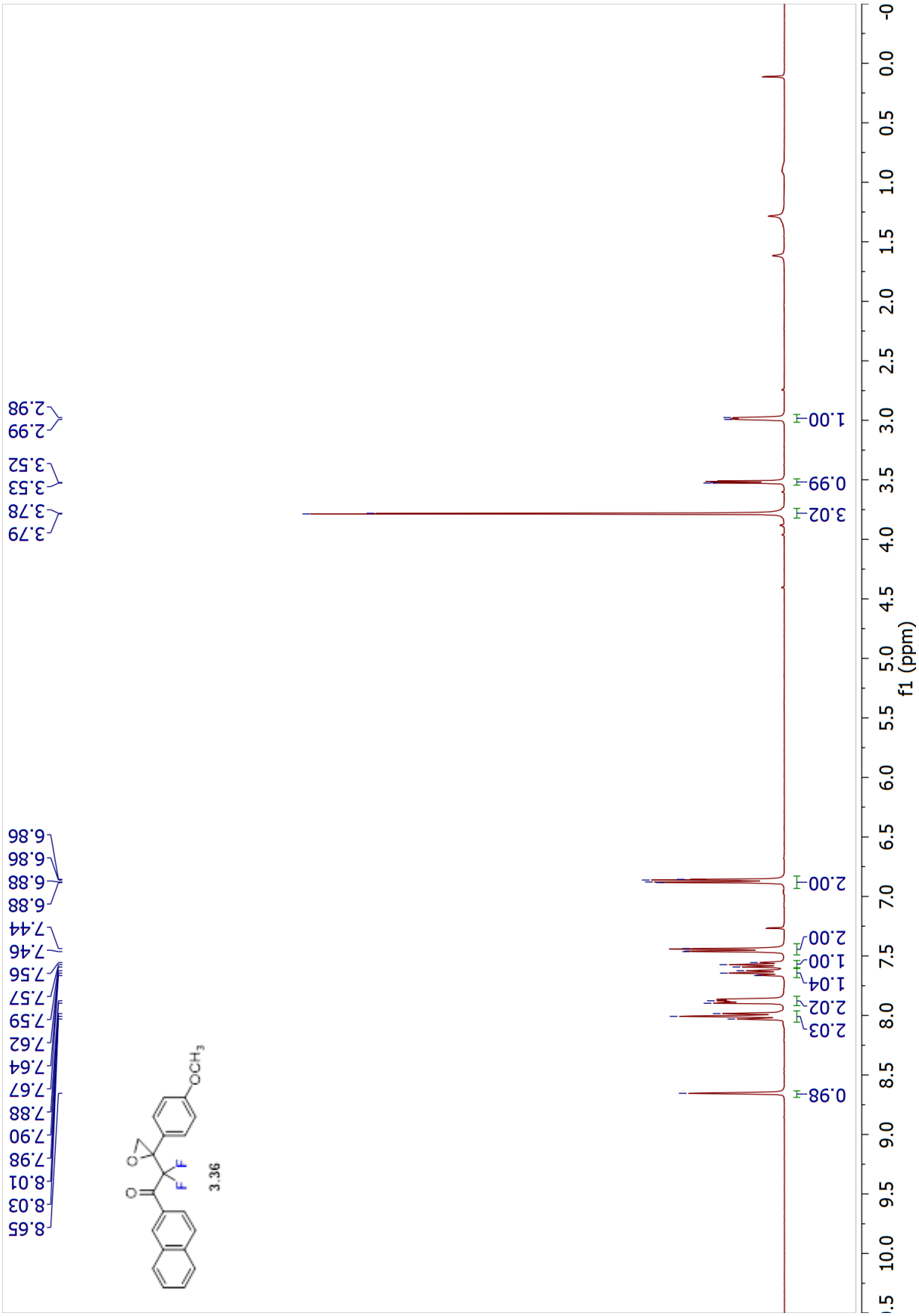
131.65
131.62
130.91
129.12
128.95
123.95
113.85
59.25
58.96
58.93
58.64
55.26
51.10
51.06
51.04
O
O
F
F
Cl
OCH3
3.35
262
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-103.56
-104.28
-106.18
-106.90
Cl
F F
OCH3
3.35
1.00
0.97
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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8.01
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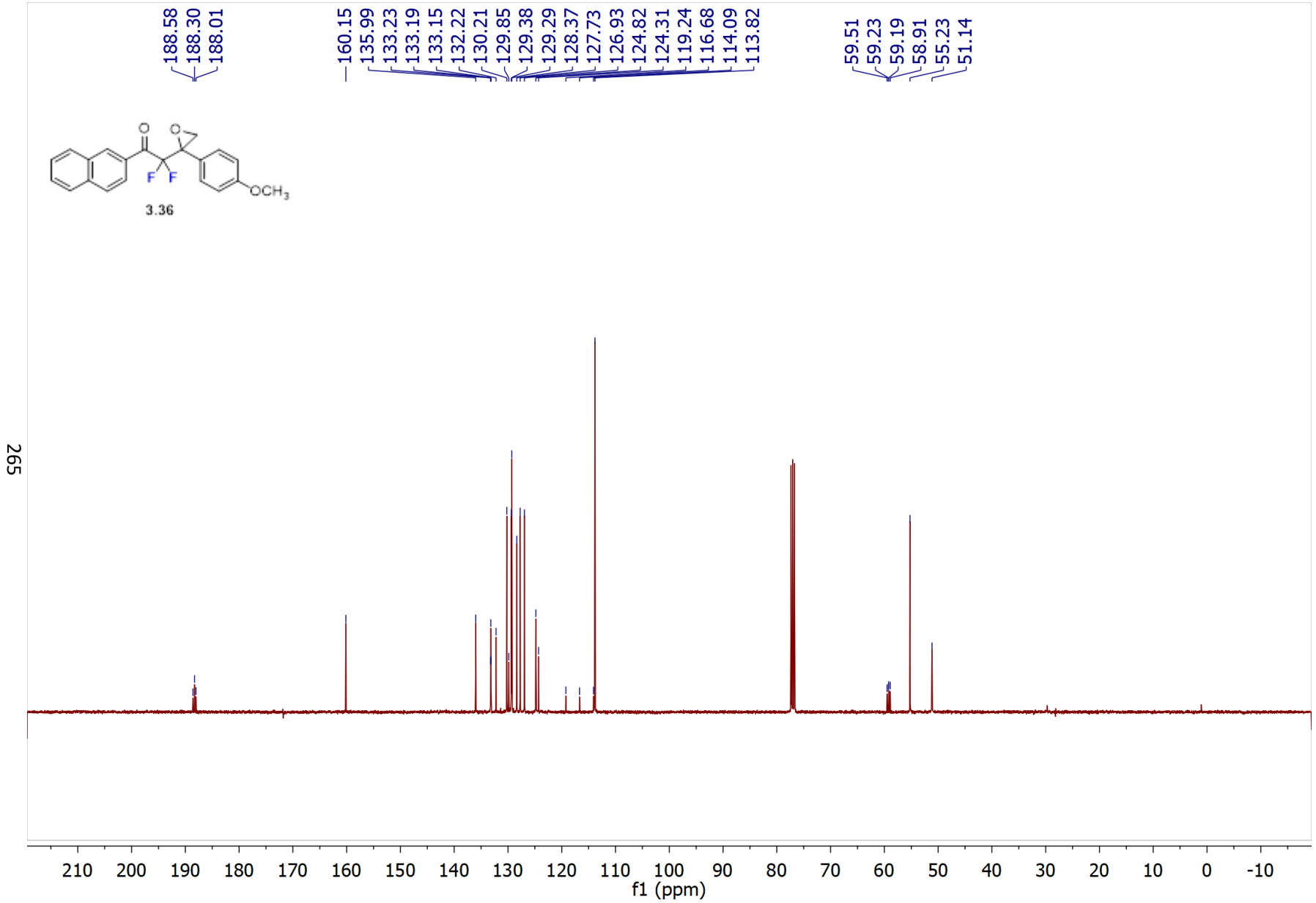
7.64
7.62
7.59
7.57
7.56
7.46
7.44
6.88
6.88
6.86
6.86
3.79
3.78
3.53
3.52
2.99
2.98
0.98
2.03
2.02
1.04
1.00
2.00
2.00
3.02
0.99
1.00
O
F F
OCH3
3.36
f1 (ppm)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133.23
133.19
133.15
132.22
130.21
129.85
129.38
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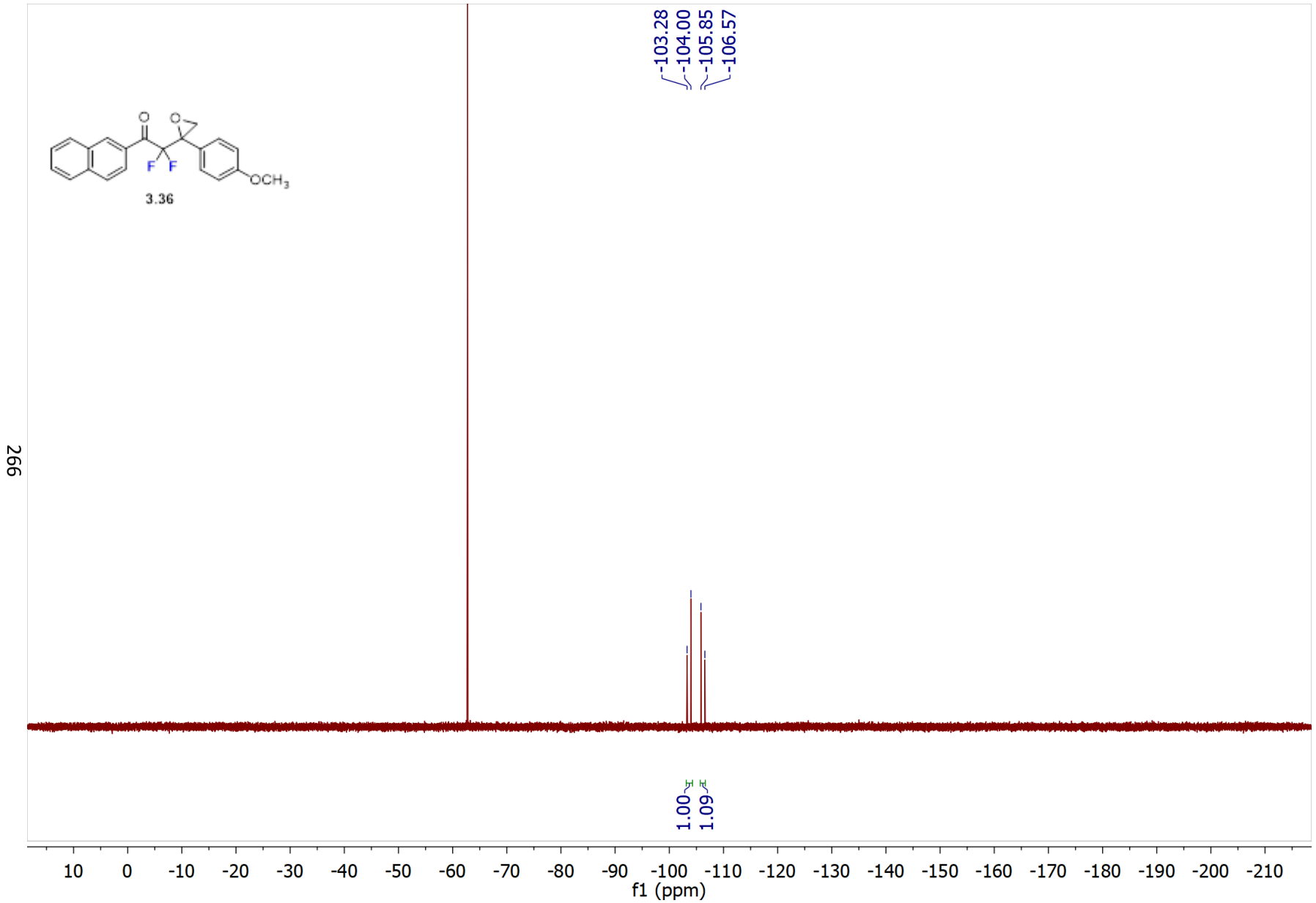
128.37
127.73
126.93
124.82
124.31
119.24
116.68
114.09
113.82
59.51
59.23
59.19
58.91
55.23
51.14
O
O
F F
OCH3
3.36
265
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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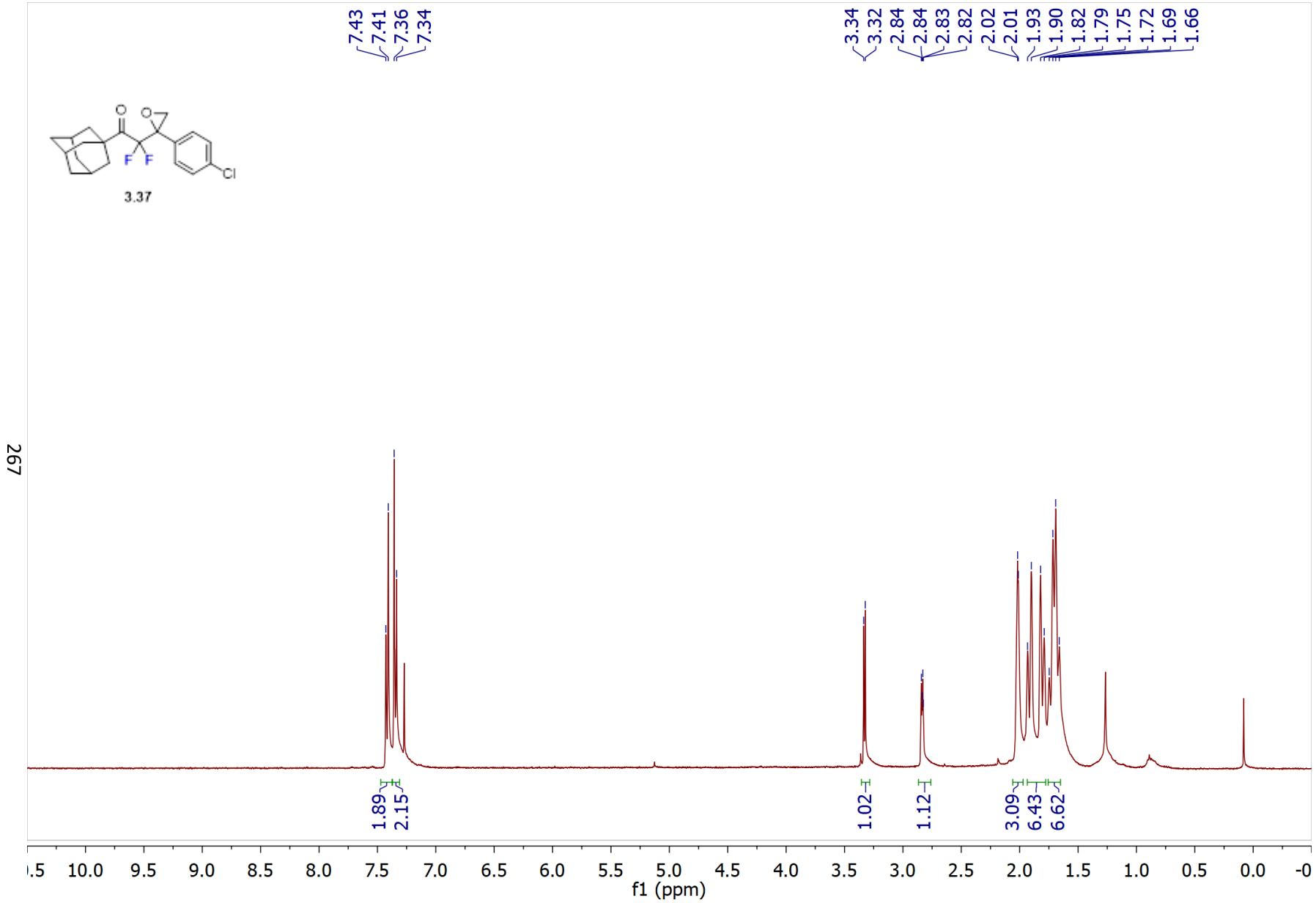
-104.00
-105.85
-106.57
O
O
F F
OCH3
3.36
266
1.00
1.09
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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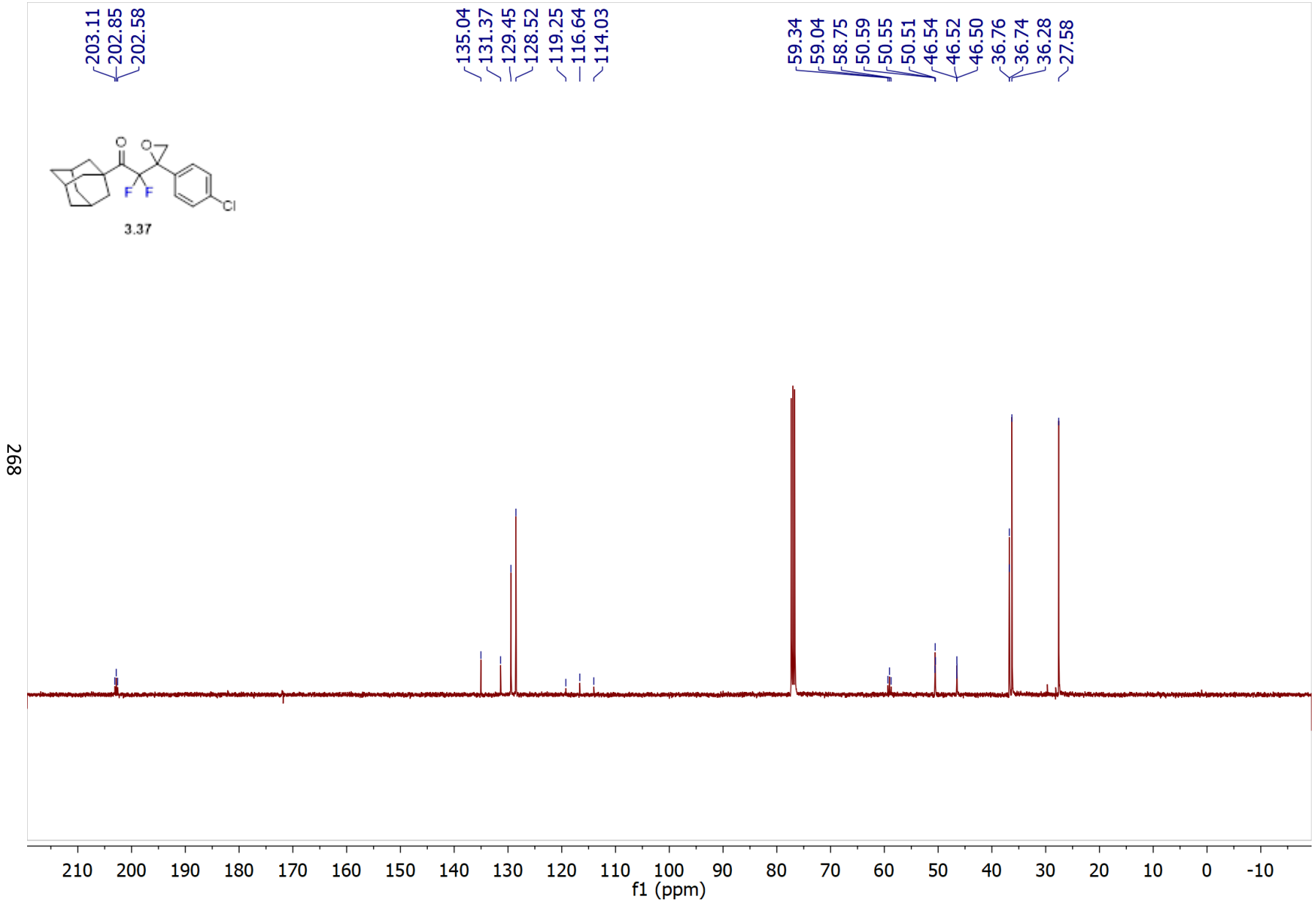
7.41
7.36
7.34
3.34
3.32
2.84
2.84
2.83
2.82
2.02
2.01
1.93
1.90
1.82
1.79
1.75
1.72
1.69
1.66
F F
Cl
3.37
1.89
2.15
1.02
1.12
3.09
6.43
6.62
f1 (ppm)


203.11
202.85
202.58
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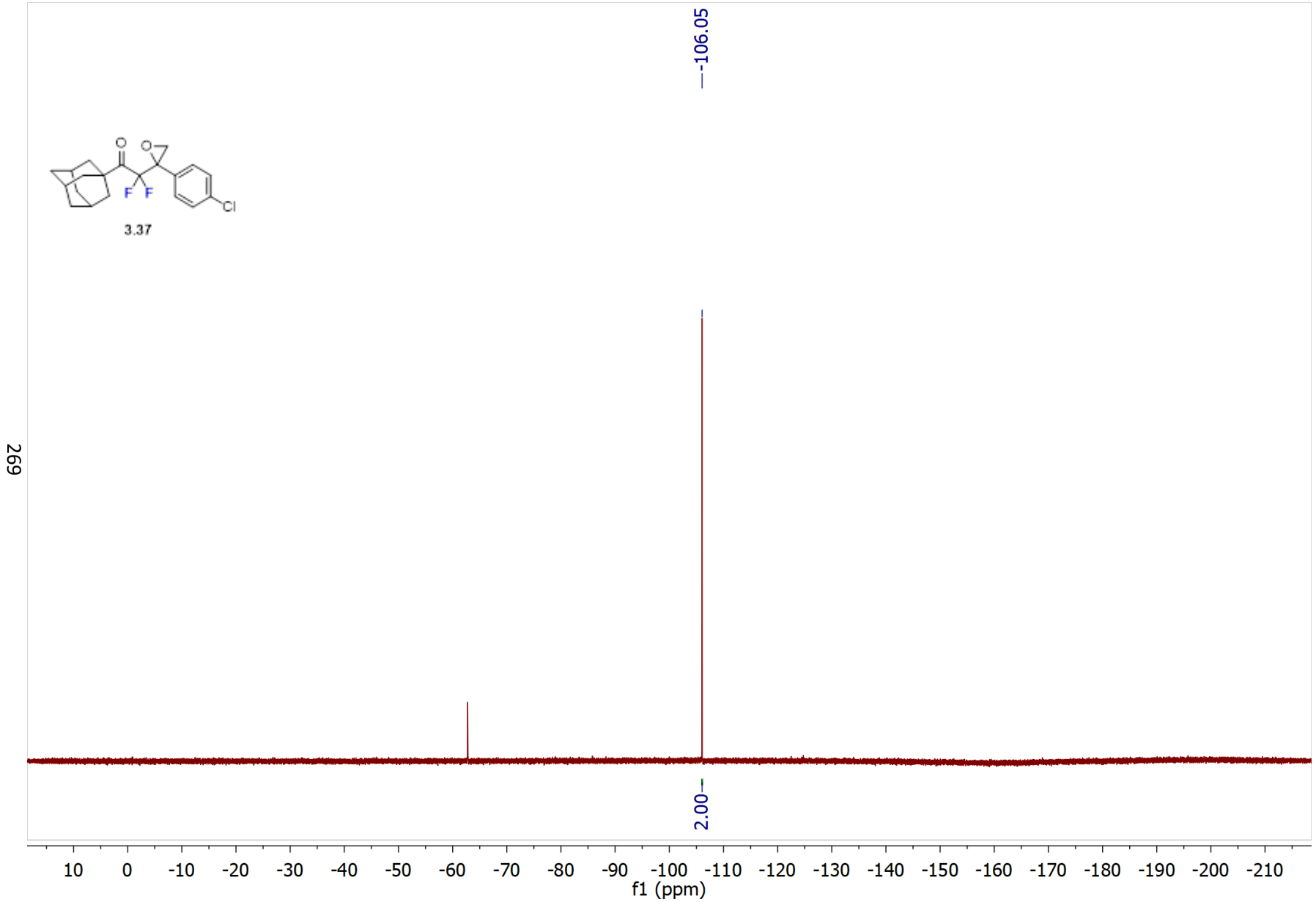
131.37
129.45
128.52
119.25
116.64
114.03
59.34
59.04
58.75
50.59
50.55
50.51
46.54
46.52
46.50
36.76
36.74
36.28
27.58
F F
Cl
3.37
268
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-106.05
F F
Cl
3.37
269
2.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

8.71
8.08
8.05
8.01
7.99
7.91
7.89
7.87
7.66
7.64
7.63
7.59
7.57
7.55
4.47
4.46
4.45
4.43
3.60
3.59
2.16
2.12
2.09
2.06
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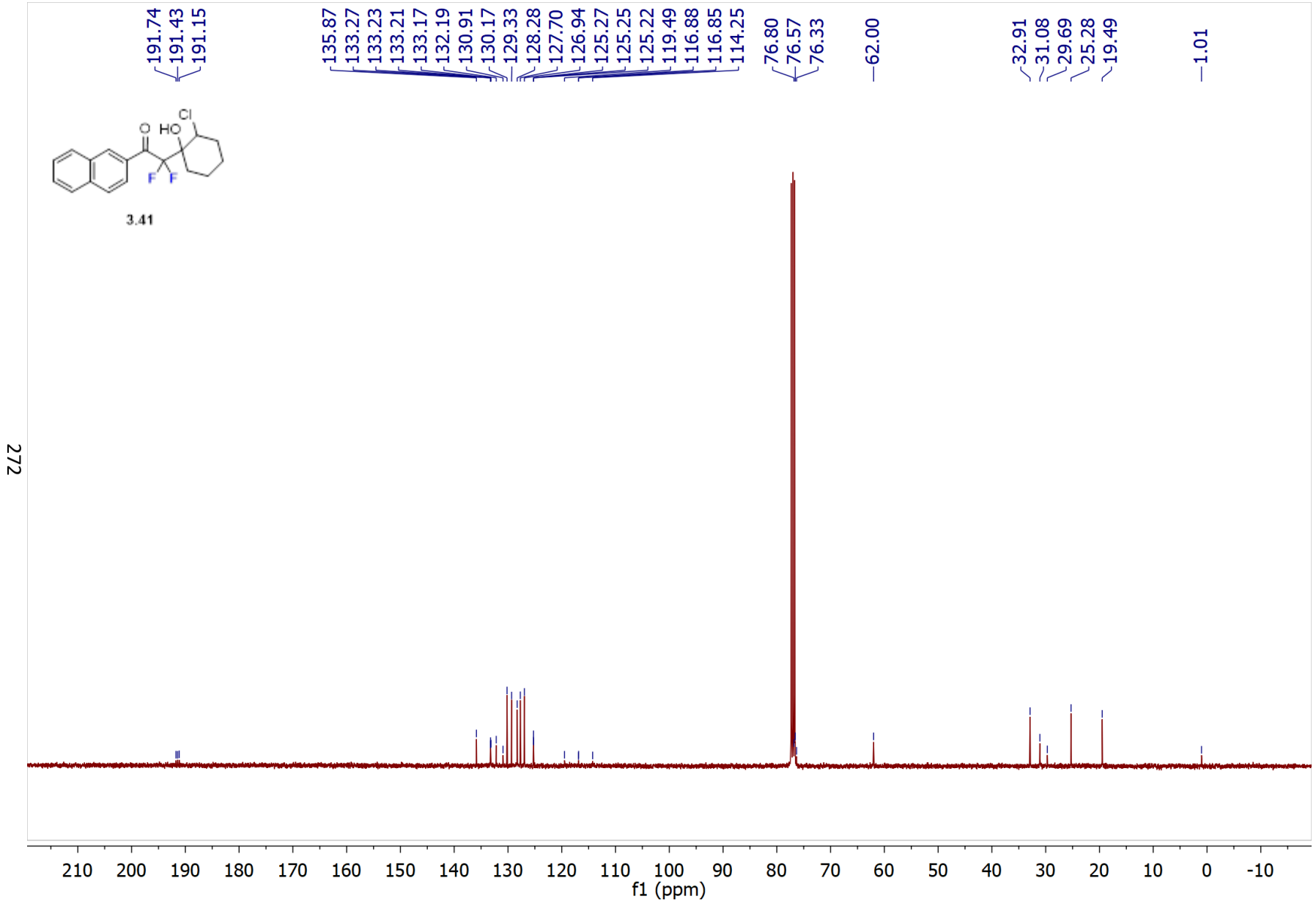
1.68
1.62
1.60
1.43
1.39
1.33
1.00
1.09
1.04
2.21
1.08
1.10
0.99
0.99
1.20
2.12
2.31
2.41
1.26
f1 (ppm)
Cl
HO
O
F
F
3.41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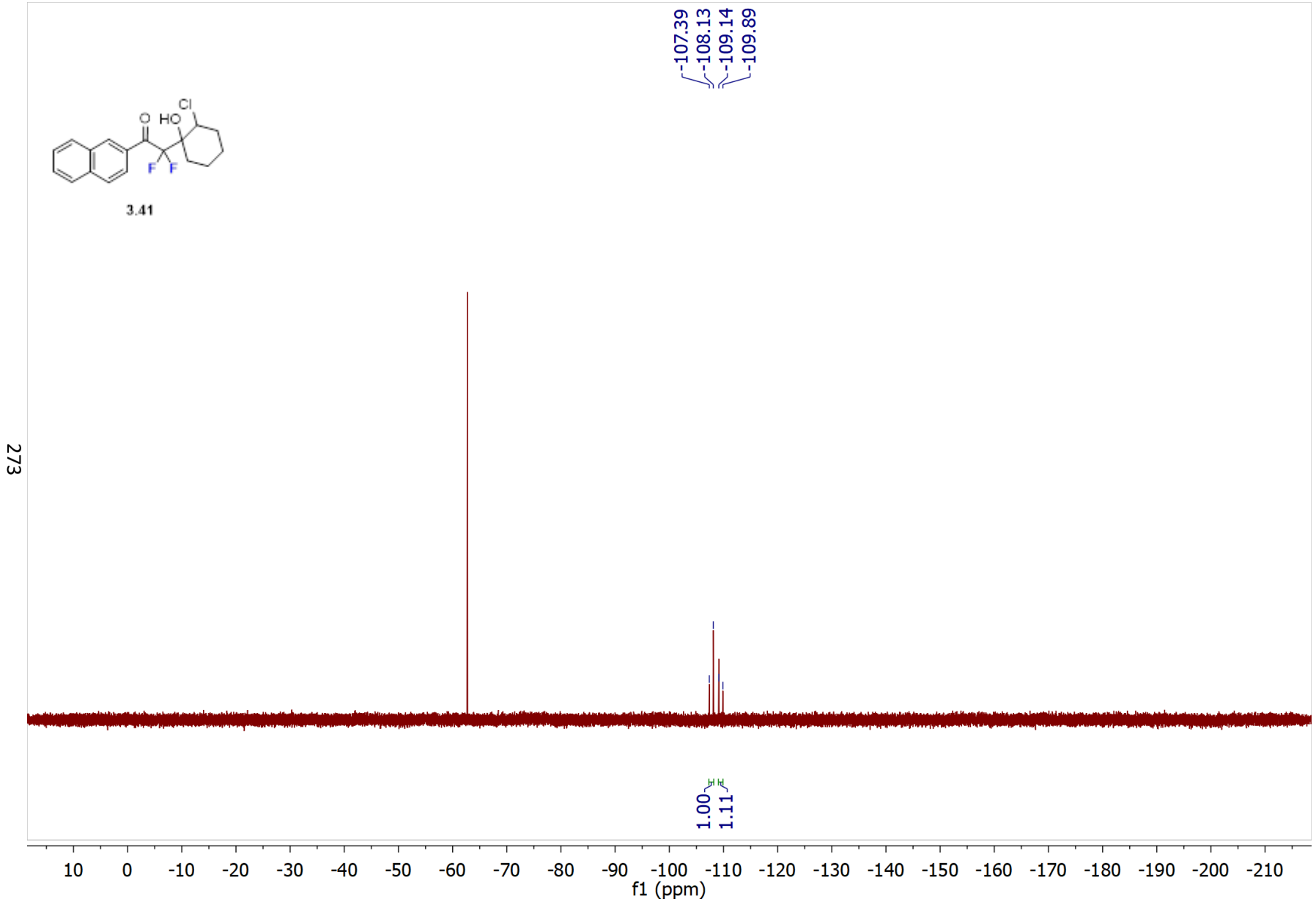
191.43
191.15
135.87
133.27
133.23
133.21
133.17
132.19
130.91
130.17
129.33
128.28
127.70
126.94
125.27
125.25
125.22
119.49
116.88
116.85
114.25
76.80
76.57
76.33
62.00
32.91
31.08
29.69
25.28
19.49
1.01
O
HO
Cl
F
F
3.41
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-107.39
-108.13
-109.14
-109.89
O
HO
Cl
F
F
3.41
1.00
1.11
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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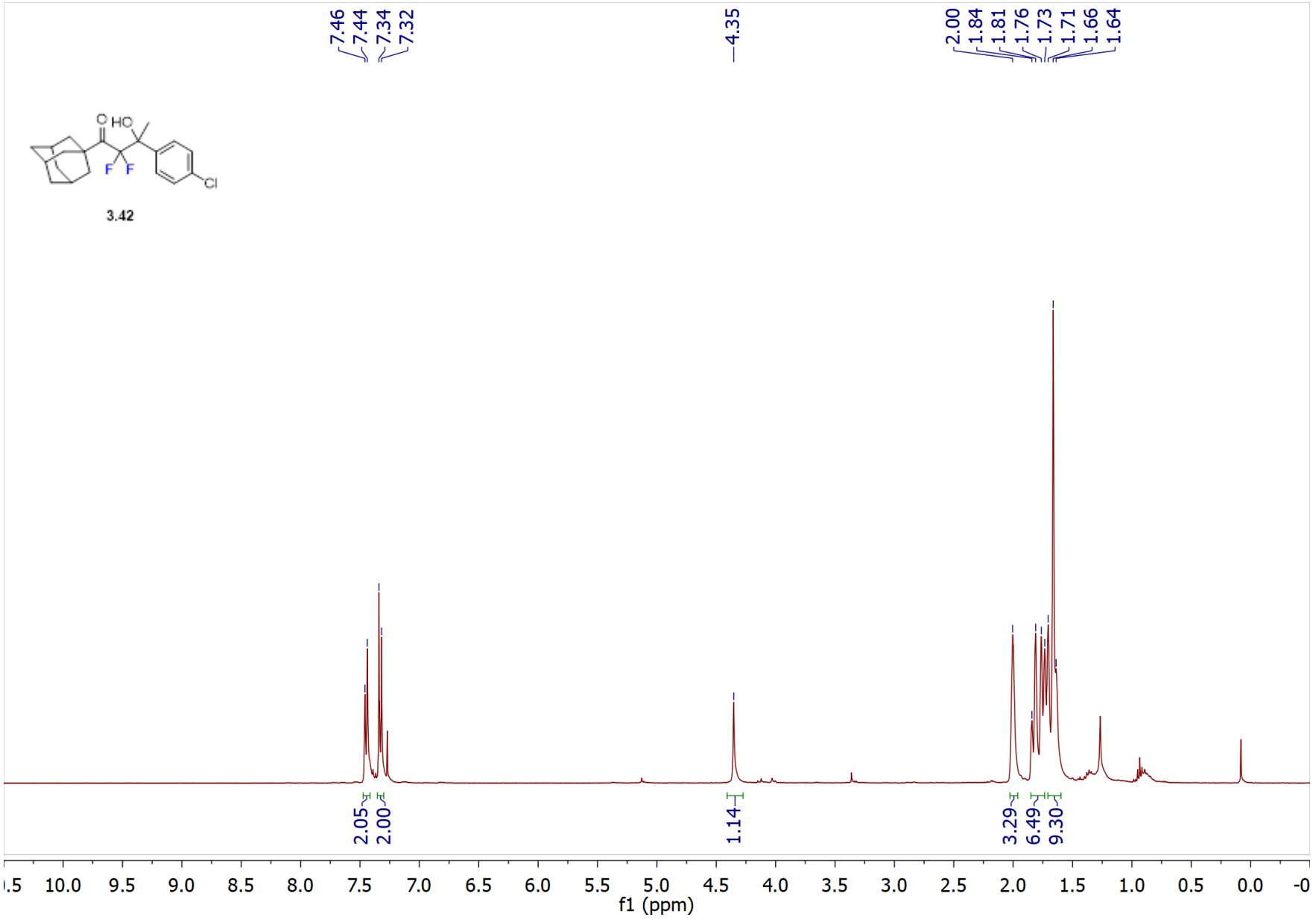
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)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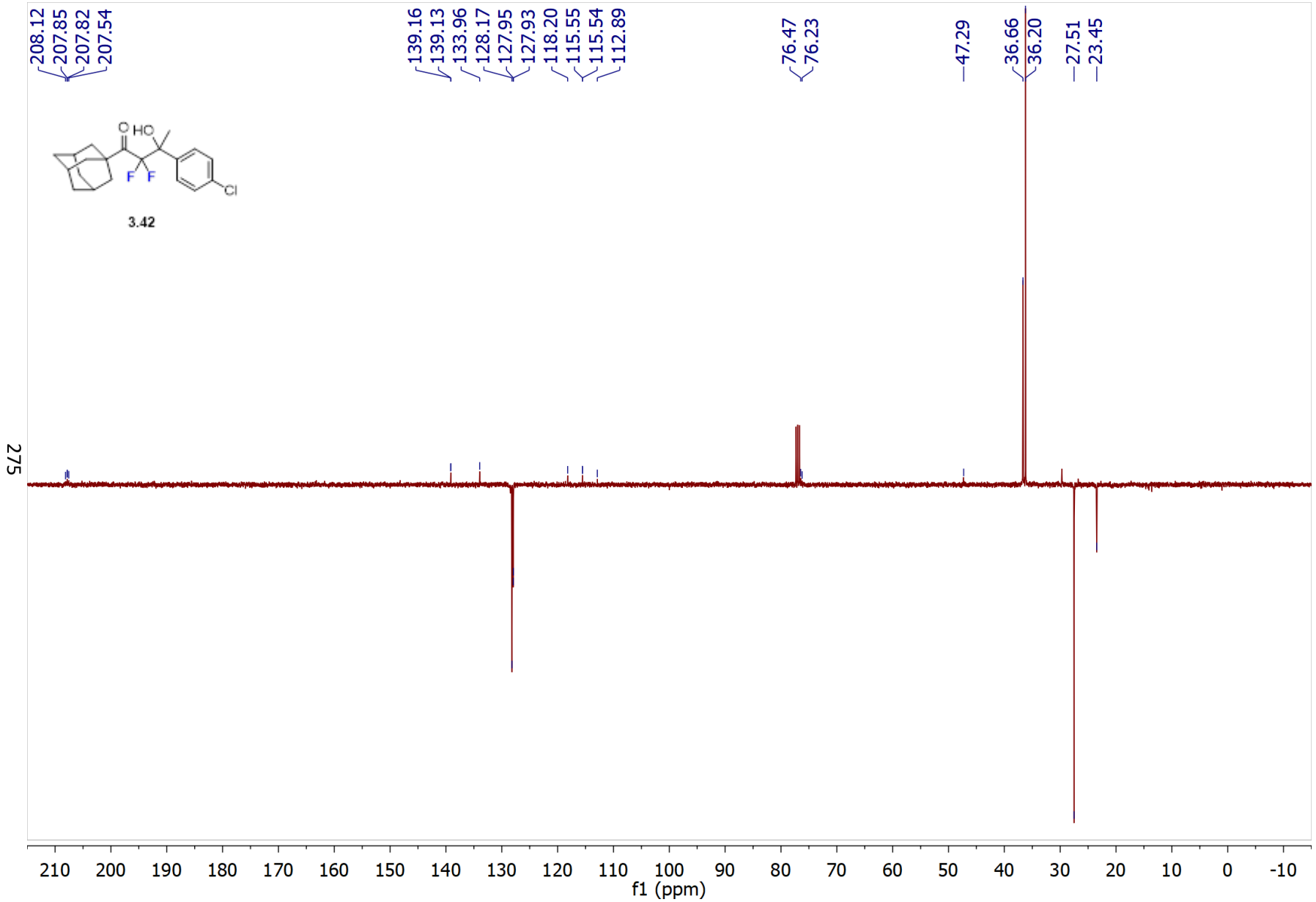
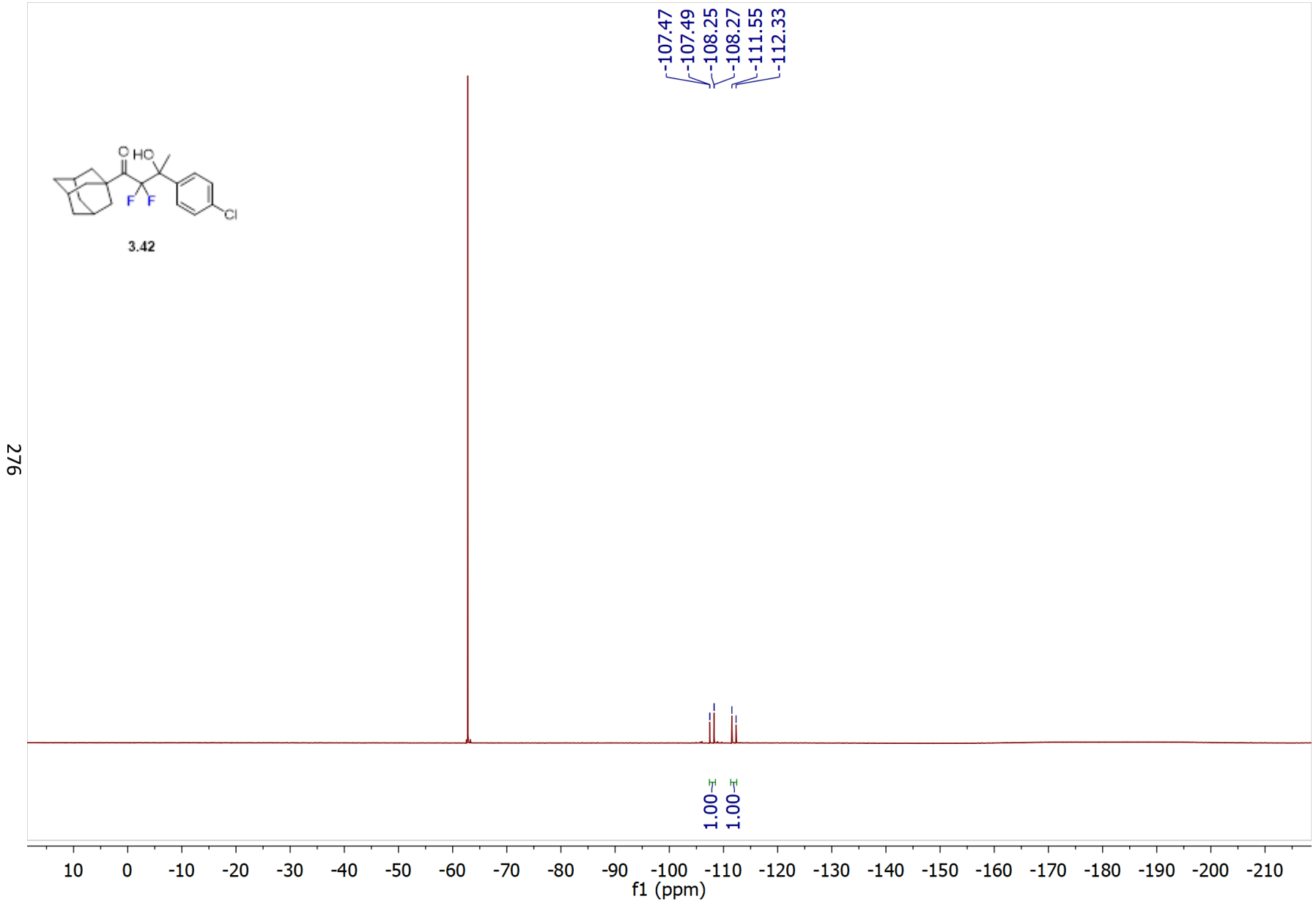
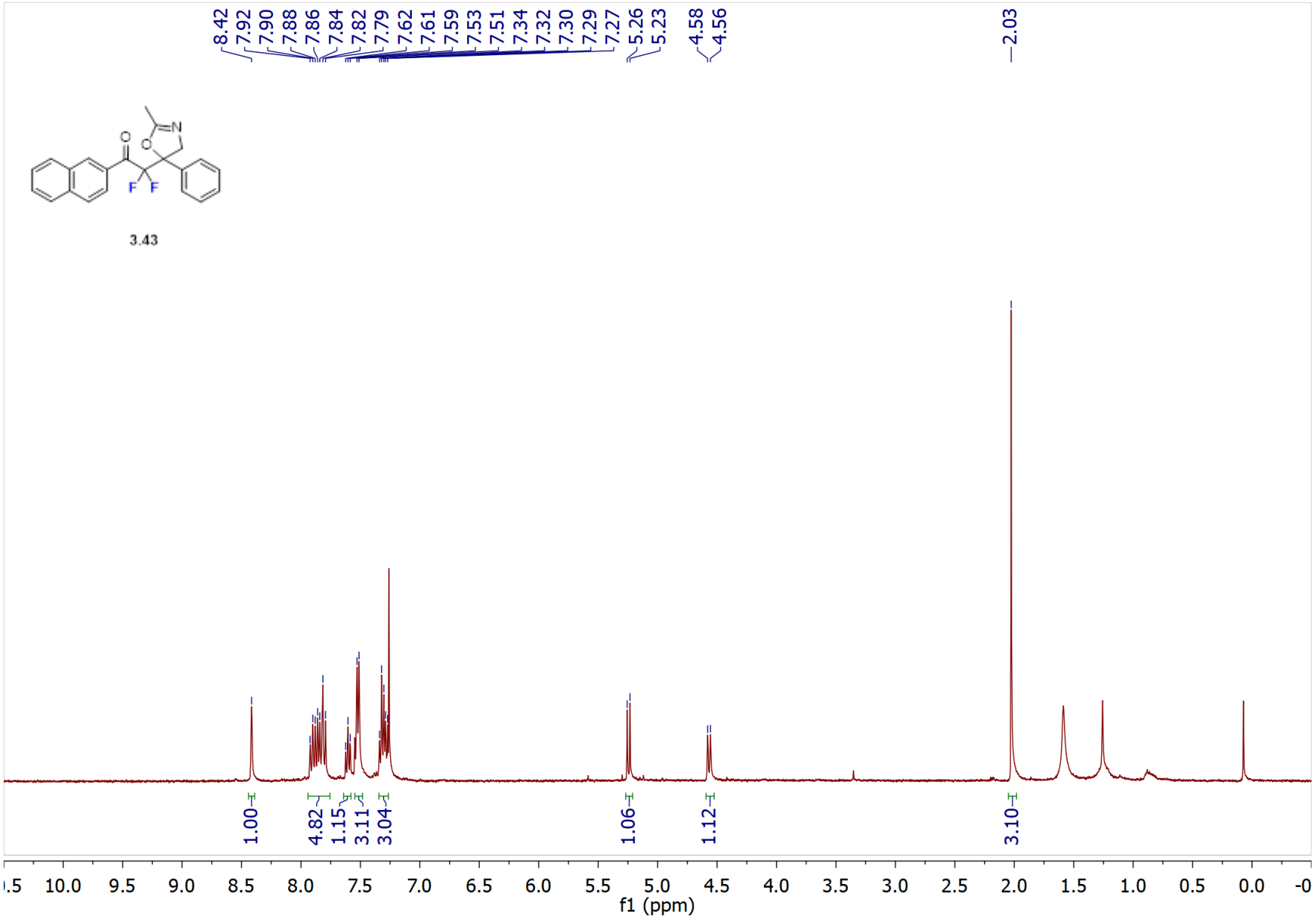
7.44
7.34
7.32
4.35
2.00
1.84
1.81
1.76
1.73
1.71
1.66
1.64
O
HO
F
F
Cl
3.42
2.05
2.00
1.14
3.29
6.49
9.30
f1 (ppm)


208.12
207.85
207.82
207.54
139.16
139.13
133.96
128.17
127.95
127.93
118.20
115.55
115.54
112.89
76.47
76.23
47.29
36.66
36.20
27.51
23.45
O
HO
F
F
Cl
3.42
275
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-107.47
-107.49
-108.25
-108.27
-111.55
-112.33
O
HO
F
F
Cl
3.42
276
1.00
1.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)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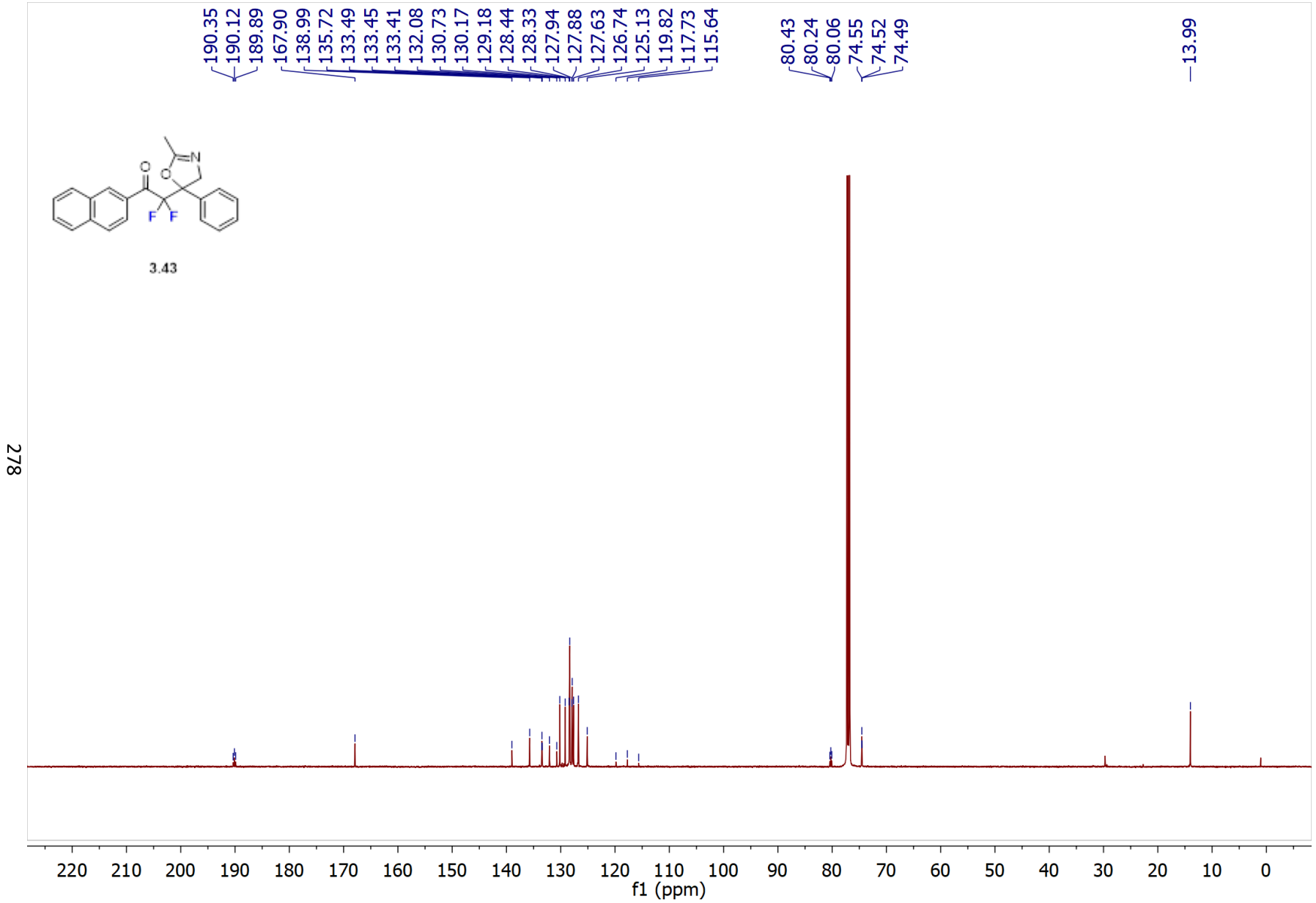
7.92
7.90
7.88
7.86
7.84
7.82
7.79
7.62
7.61
7.59
7.53
7.51
7.34
7.32
7.30
7.29
7.27
5.26
5.23
4.58
4.56
2.03
O
N
O
F
F
3.43
1.00
4.82
1.15
3.11
3.04
1.06
1.12
3.10
f1 (ppm)


190.35
190.12
189.89
167.90
138.99
135.72
133.49
133.45
133.41
132.08
130.73
130.17
129.18
128.44
128.33
127.94
127.88
127.63
126.74
125.13
119.82
117.73
115.64
80.43
80.24
80.06
74.55
74.52
74.49
13.99
O
N
O
F
F
3.43
278
220
210
200
190
180
170
160
150
140
130
120
110
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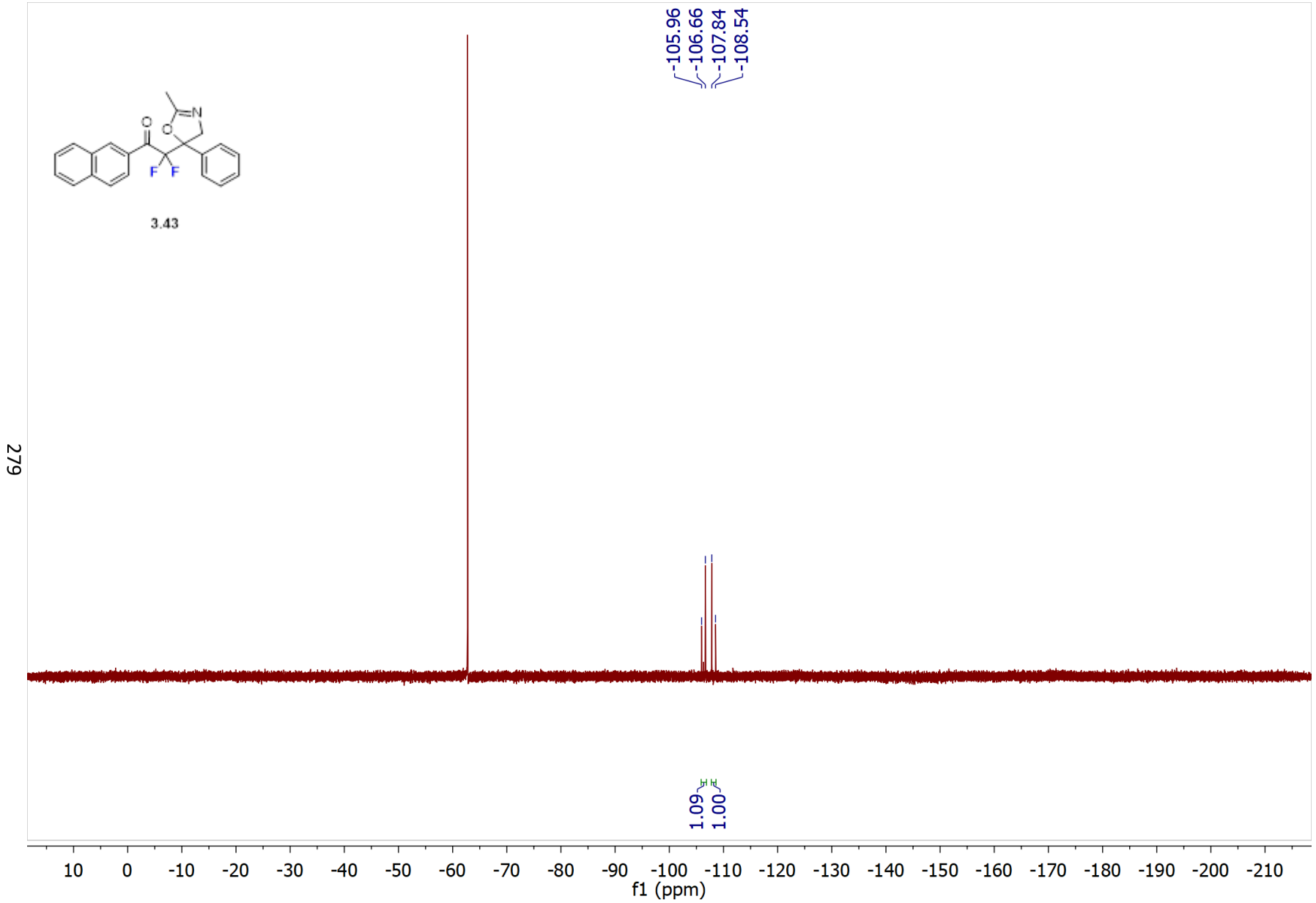
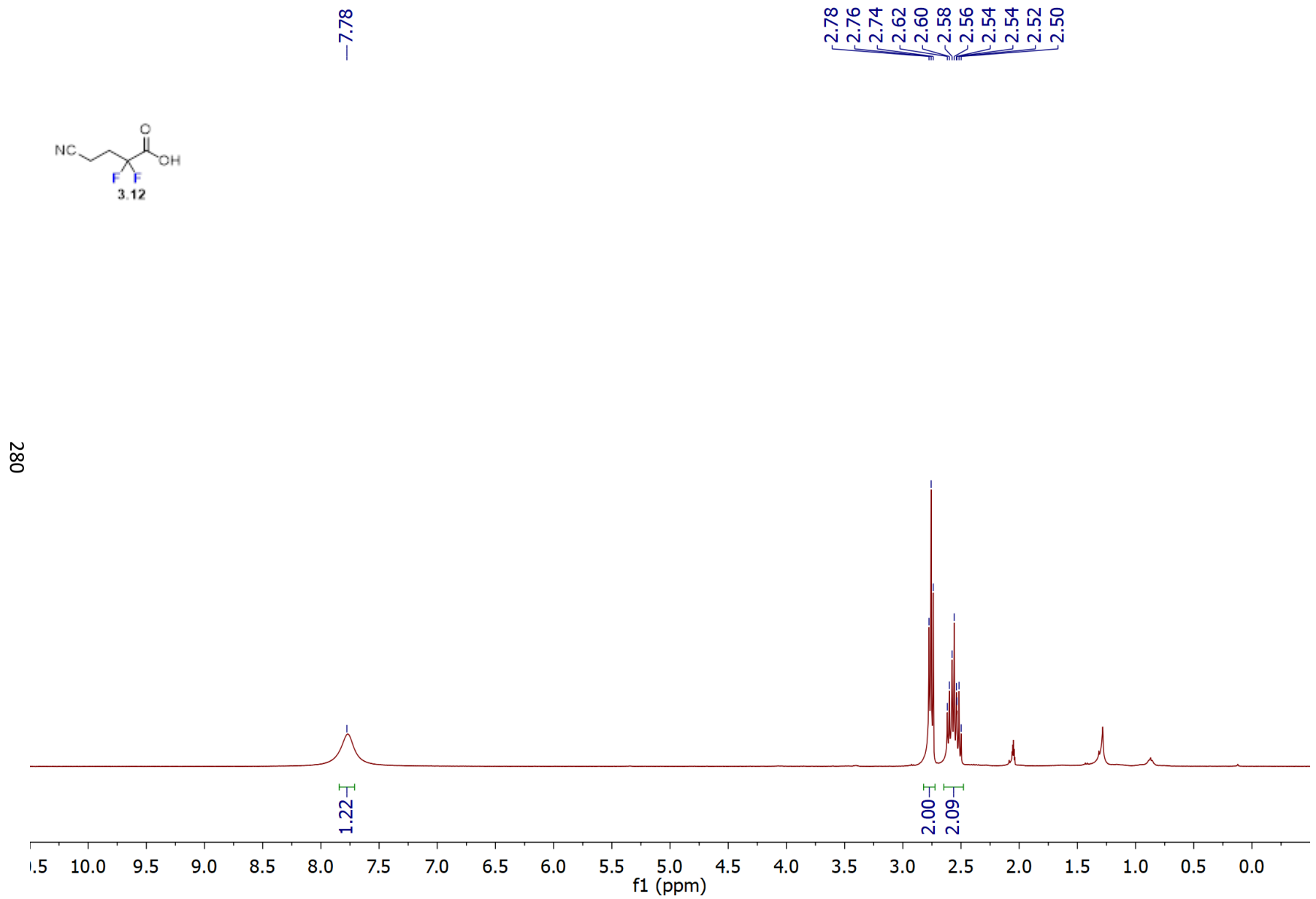
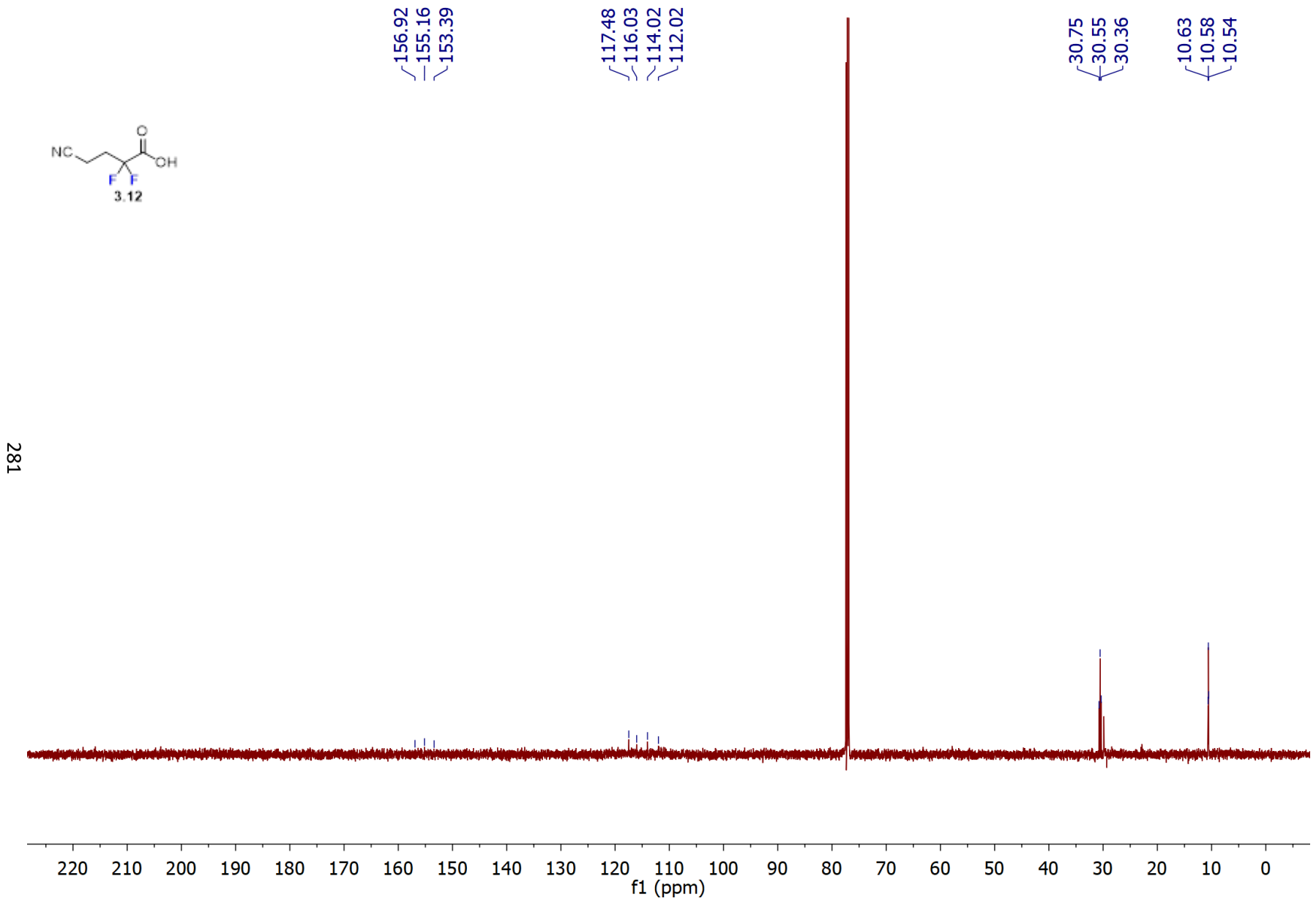
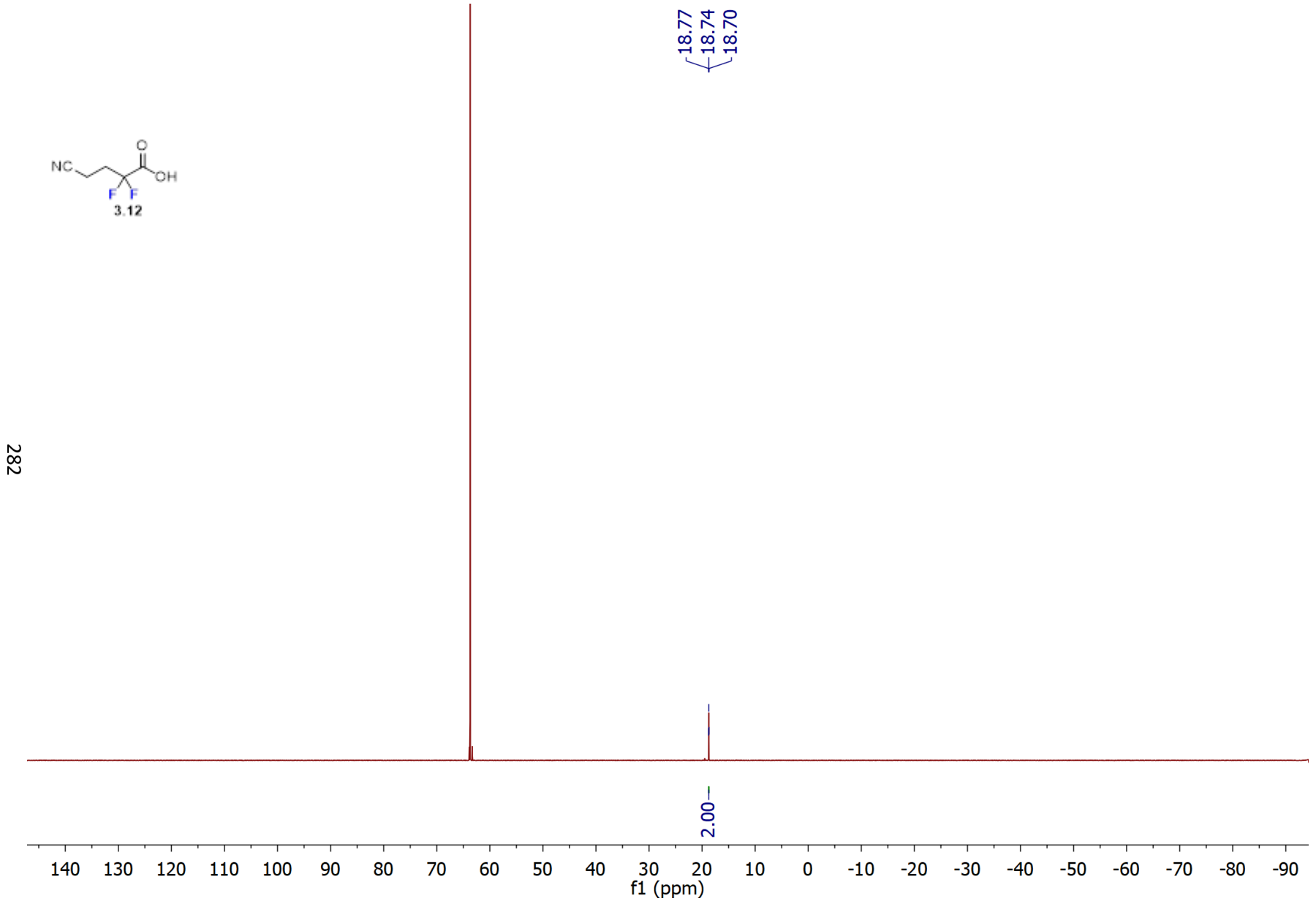
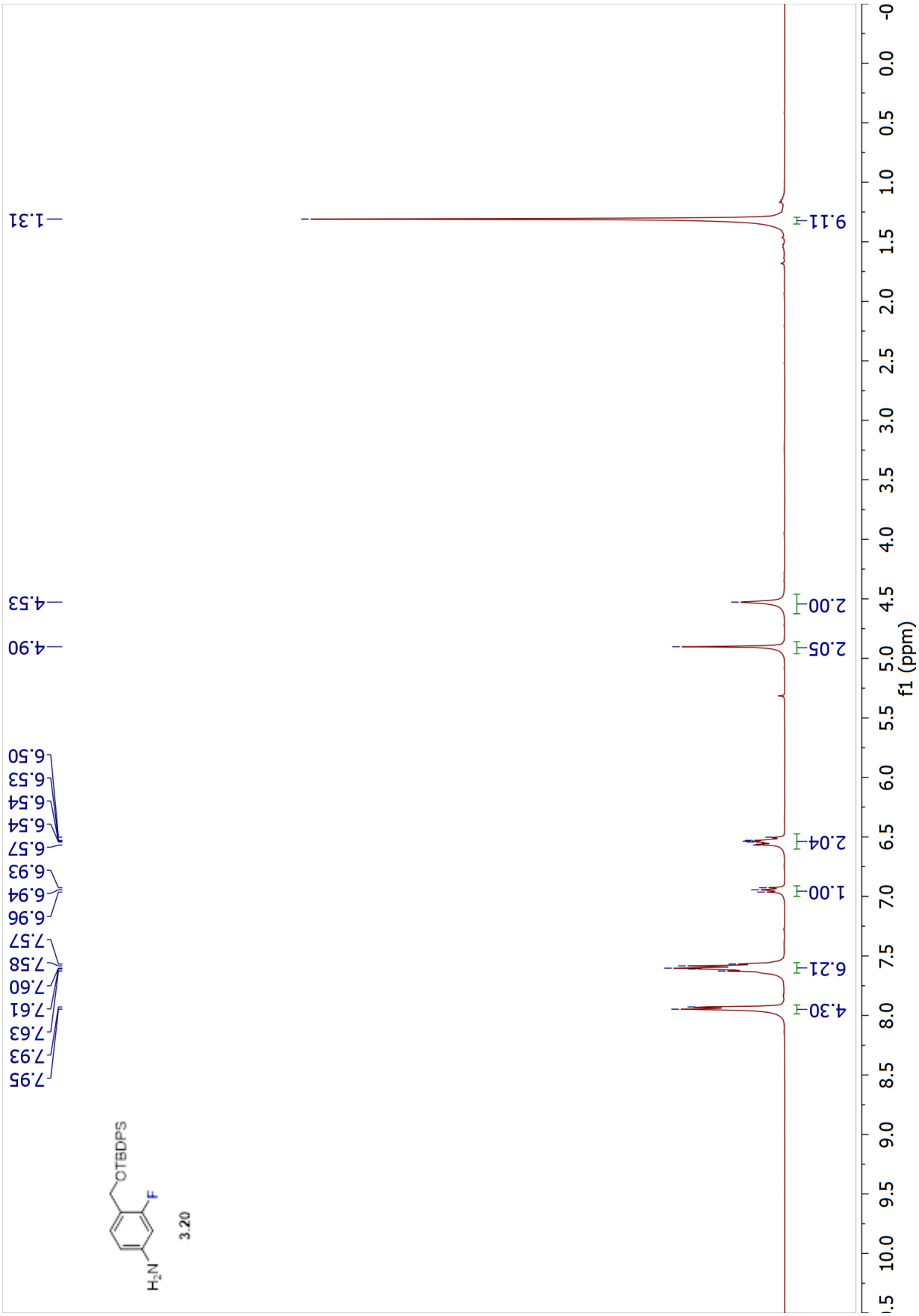
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

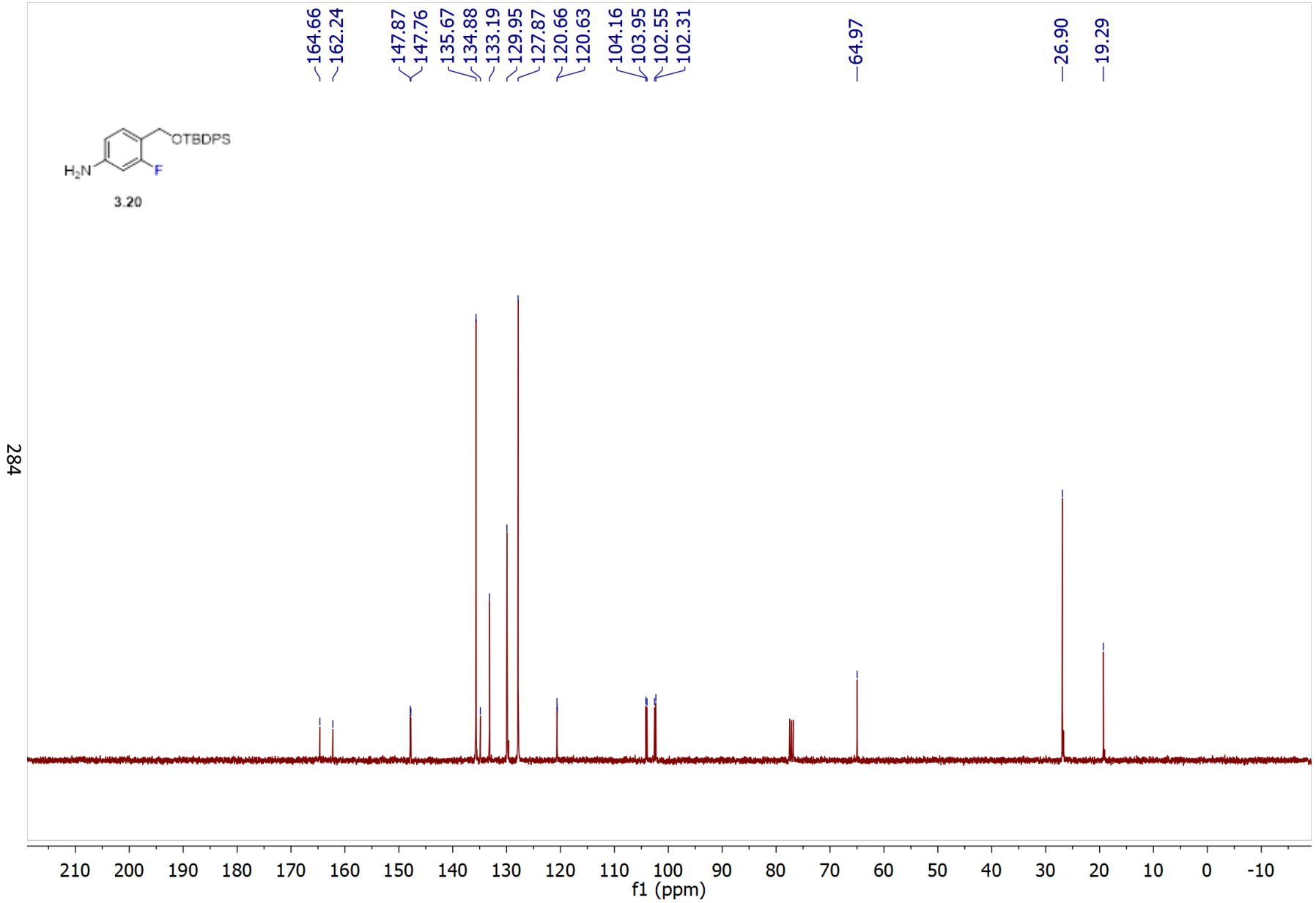

-105.96
-106.66
-107.84
-108.54
O
N
O
F
F
3.43
279
1.09
1.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

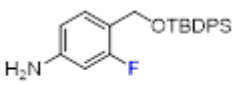

7.78
2.78
2.76
2.74
2.62
2.60
2.58
2.56
2.54
2.54
2.52
2.50
NC
O
OH
F
F
3.12
280
1.22
2.00
2.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


156.92
155.16
153.39
117.48
116.03
114.02
112.02
30.75
30.55
30.36
10.63
10.58
10.54
NC
O
OH
F F
3.12
281
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


18.77
18.74
18.70
NC
O
OH
F F
3.12
2.00
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)


OTBDPS
F
H2N
3.20
7.95
7.93
7.63
7.61
7.60
7.58
7.57
6.96
6.94
6.93
6.57
6.54
6.54
6.53
6.50
4.90
4.53
1.31
4.30
6.21
1.00
2.04
2.05
2.00
9.11
f1 (ppm)


164.66
162.24
147.87
147.76
135.67
134.88
133.19
129.95
127.87
120.66
120.63
104.16
103.95
102.55
102.31
64.97
26.90
19.29
OTBDPS
H2N
F
3.20
f1 (ppm)



3.20

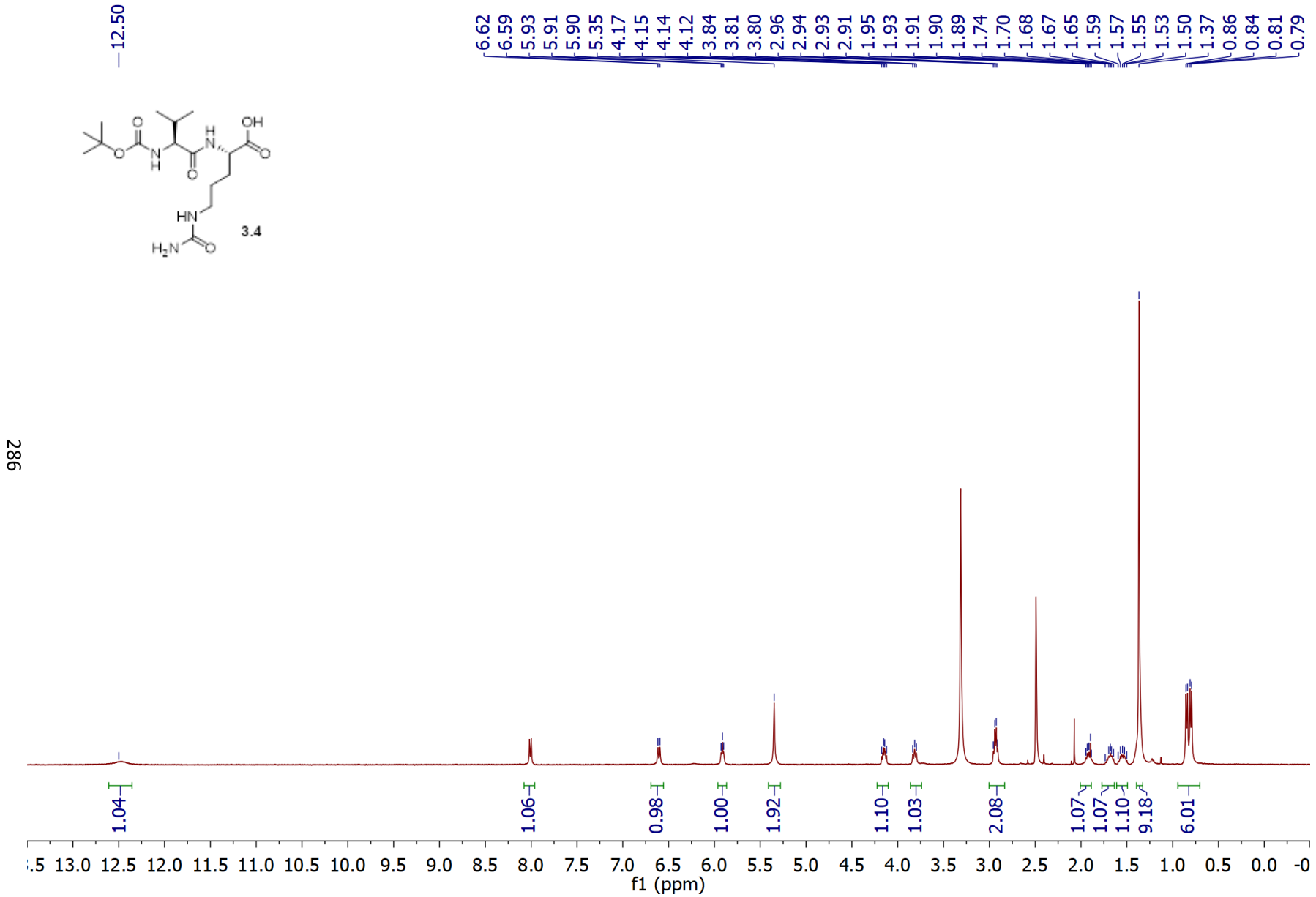
-115.47
-115.49
-115.51
-115.52
-115.54
-115.59

285

0.99

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

f1 (ppm)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6.62
6.59
5.93
5.91
5.90
5.35
4.17
4.15
4.14
4.12
3.84
3.81
3.80
2.96
2.94
2.93
2.91
1.95
1.93
1.91
1.90
1.89
1.74
1.70
1.68
1.67
1.65
1.59
1.57
1.55
1.53
1.50
1.37
0.86
0.84
0.81
0.79
OH
HN
3.4
286
1.04
1.06
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1.00
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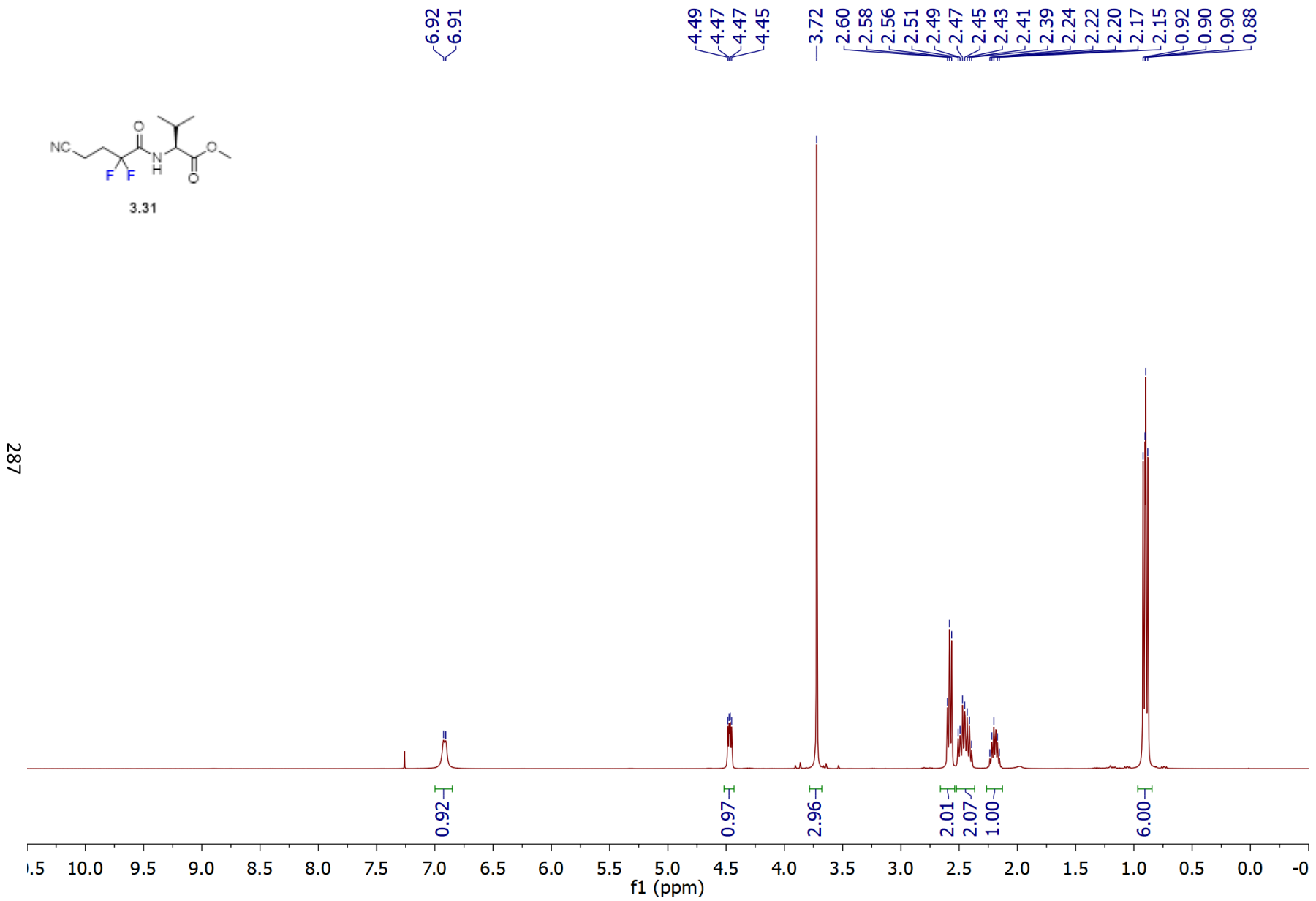
1.10
1.03
2.08
1.07
1.07
1.10
9.18
6.01
f1 (ppm)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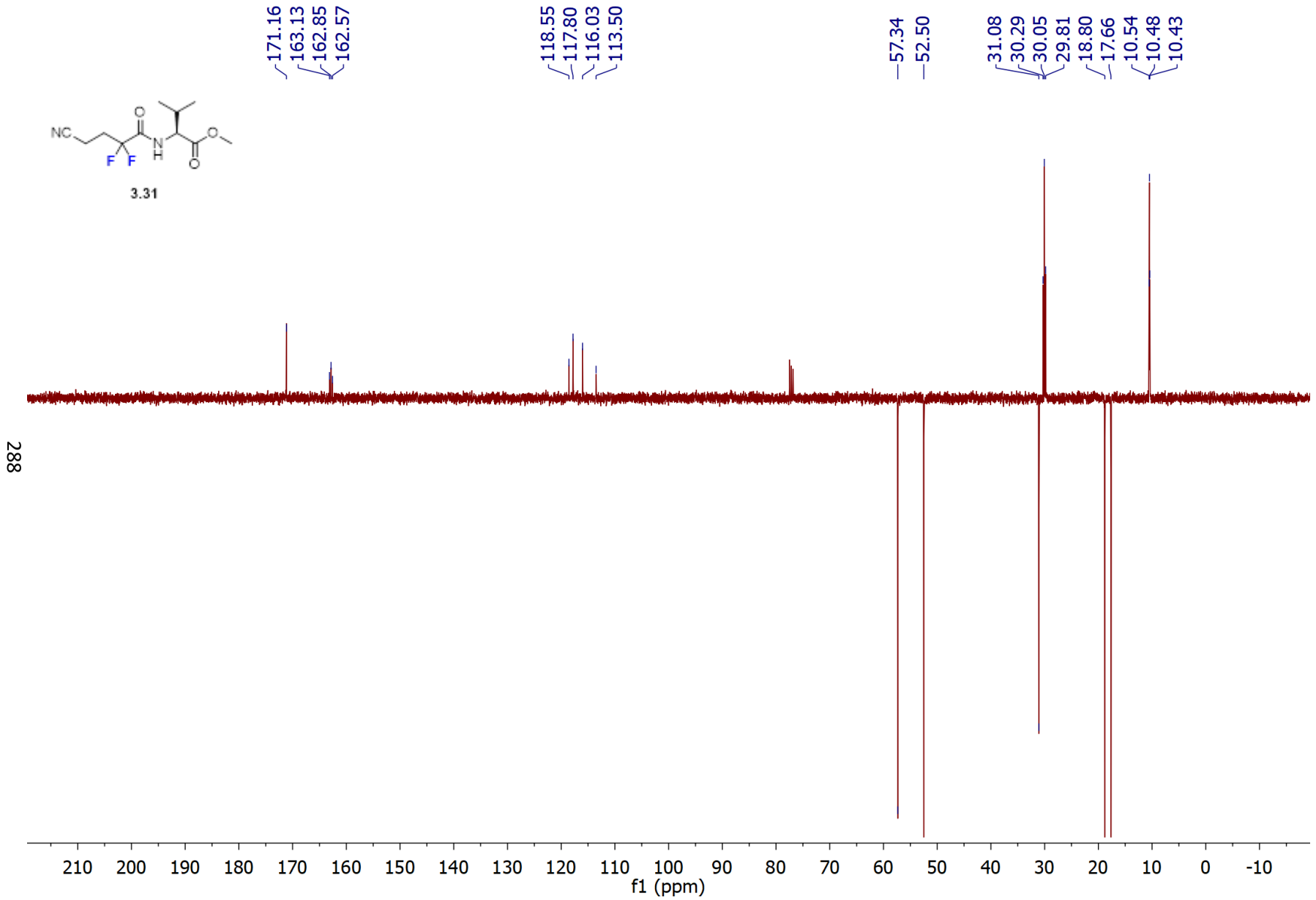
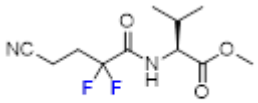
6.91
4.49
4.47
4.47
4.45
3.72
2.60
2.58
2.56
2.51
2.49
2.47
2.45
2.43
2.41
2.39
2.24
2.22
2.20
2.17
2.15
0.92
0.90
0.90
0.88
NC
O
N
H
F F
O
O
3.31
287
0.92
0.97
2.96
2.01
2.07
1.00
6.00
f1 (ppm)


171.16
163.13
162.85
162.57
118.55
117.80
116.03
113.50
57.34
52.50
31.08
30.29
30.05
29.81
18.80
17.66
10.54
10.48
10.43
NC
O
N
H
O
O
F F
3.31
288
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



3.31

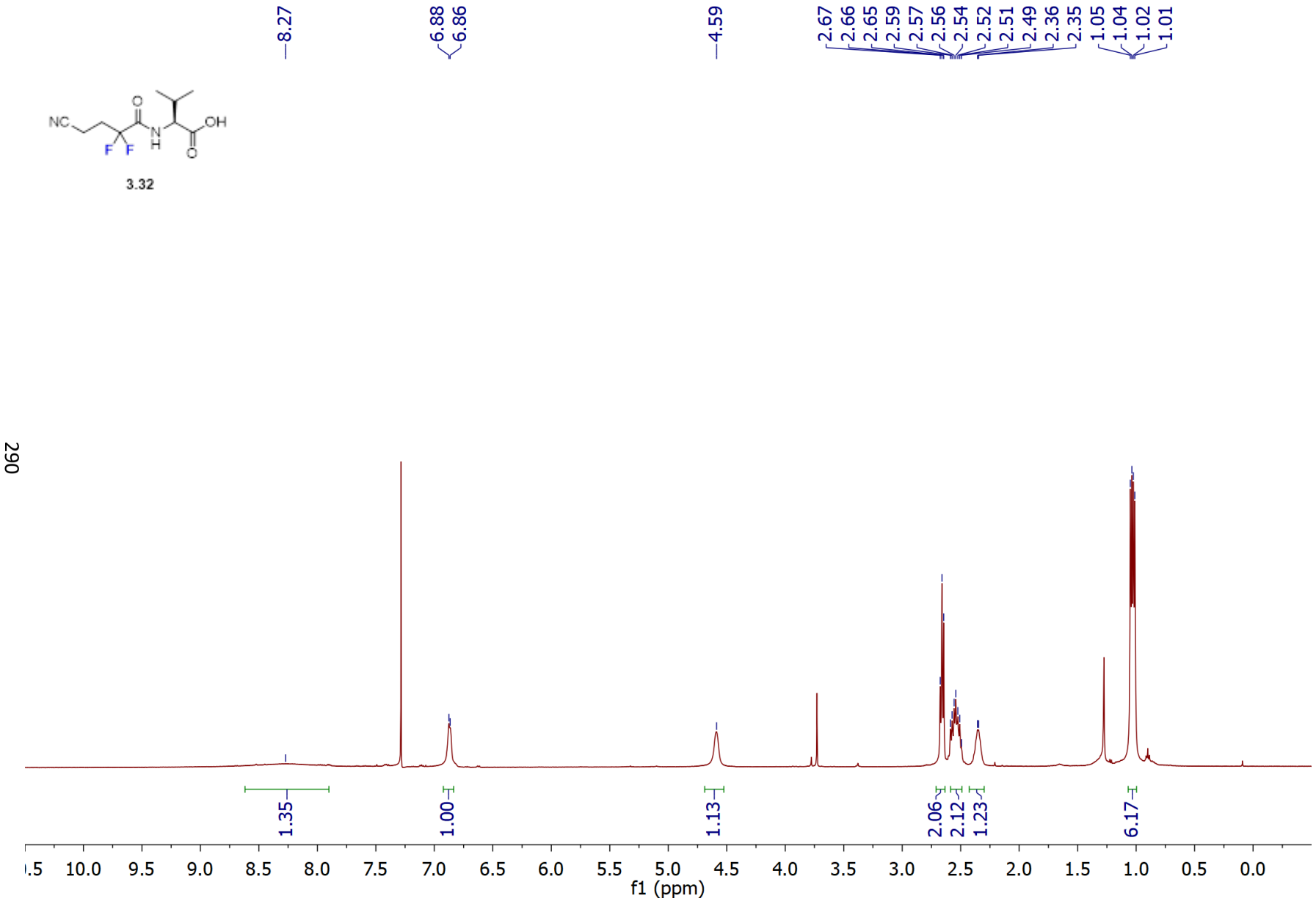
-106.55
-106.60
-106.64
-107.25
-107.29
-107.33
-108.78
-108.83
-108.87
-109.48
-109.52
-109.56

289

1.00
1.02

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

f1 (ppm)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2.67
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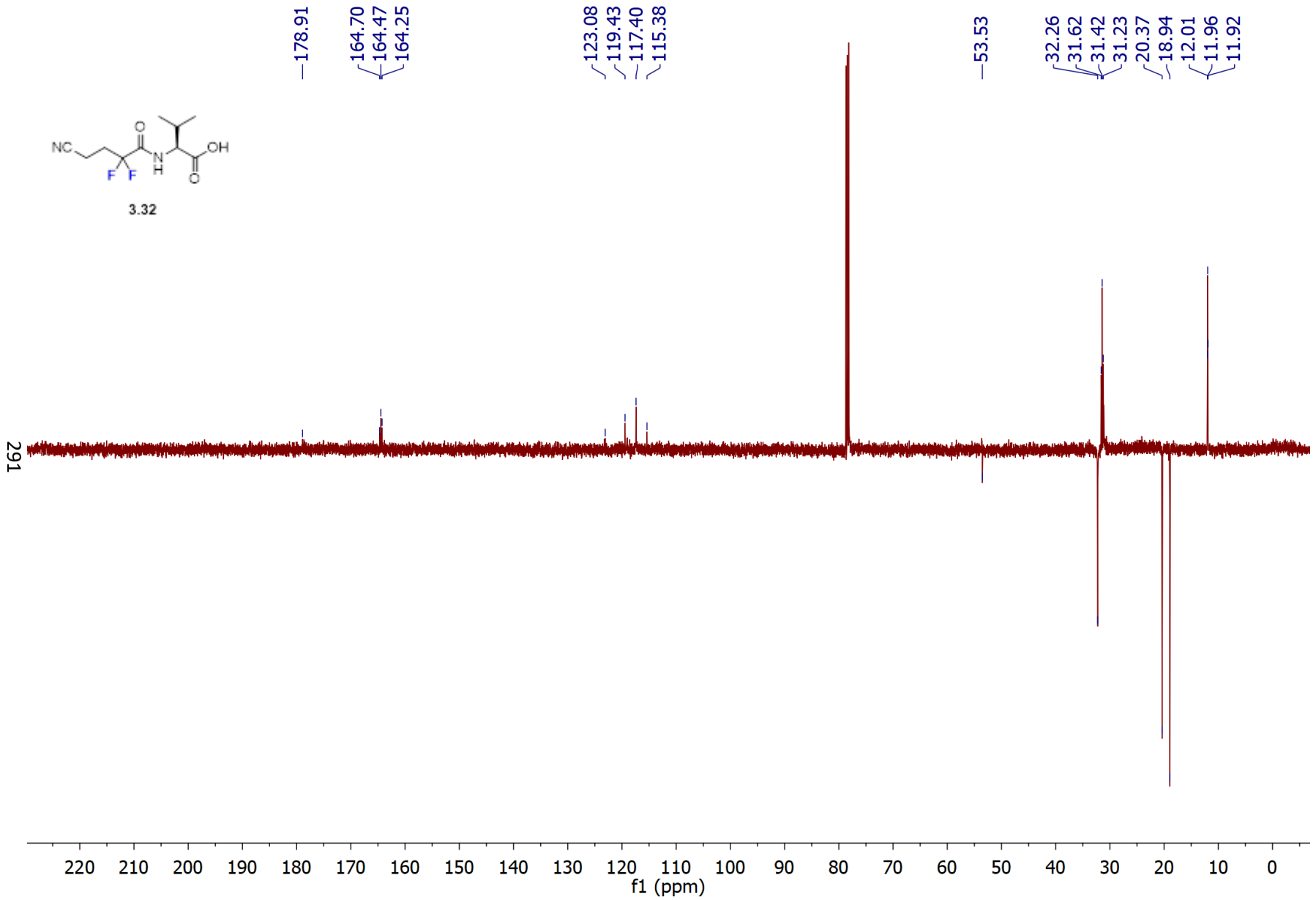
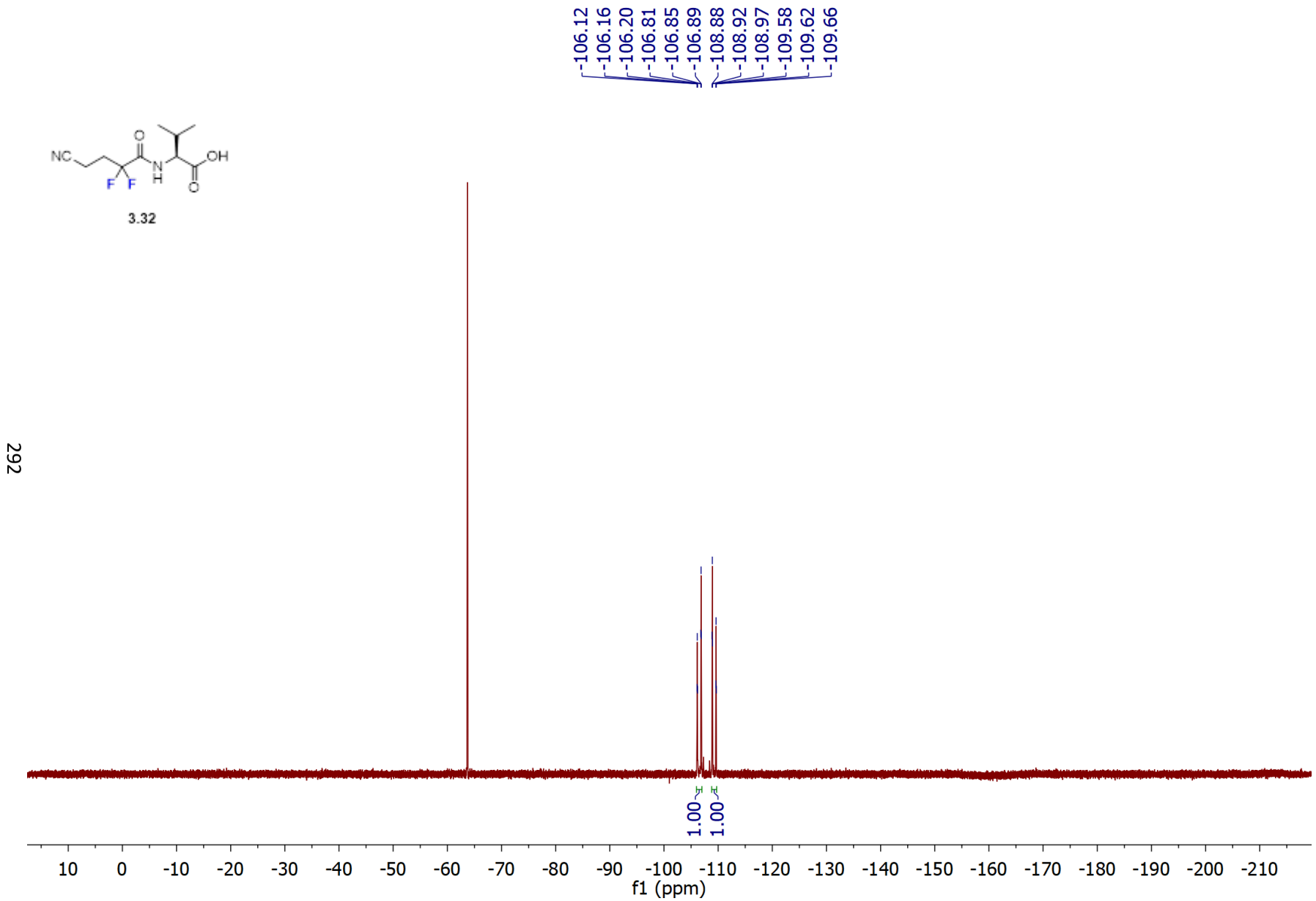
2.65
2.59
2.57
2.56
2.54
2.52
2.51
2.49
2.36
2.35
1.05
1.04
1.02
1.01
NC
O
N
H
OH
O
F F
3.32
290
1.35
1.00
1.13
2.06
2.12
1.23
6.17
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


178.91
164.70
164.47
164.25
123.08
119.43
117.40
115.38
53.53
32.26
31.62
31.42
31.23
20.37
18.94
12.01
11.96
11.92
NC
O
N
H
OH
F F
O
3.32
291
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-106.12
-106.16
-106.20
-106.81
-106.85
-106.89
-108.88
-108.92
-108.97
-109.58
-109.62
-109.66
NC
O
N
H
OH
O
F F
3.32
292
1.00
1.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

VITA

Munia F. Sowaileh was born in Amman, Jordan. She received her degree in pharmacy in 2010 and her M.S. degree in medicinal chemistry in 2013 from Jordan University of Science and technology. She started her Ph.D. at Purdue University in 2013 where she joined Professor David A. Colby's group and moved with the group to the University of Mississippi. She's currently a Ph.D. candidate at the Department of BioMolecular Sciences at the University of Mississippi where she is conducting her graduate research with a focus on the development of new methods in fluorine chemistry and the use of fluorinated organic molecules in medicinal chemistry and drug design