AN INVESTIGATION OF THE UNEXPECTED RING-OPENING MECHANISM OF 2,2-DIFLUOROCYCLOPROPANECARBONYL CHLORIDE DURING FRIEDEL-CRAFTS ACYLATION

By

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To my family and friends for supporting me

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By

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Major: Chemistry

In an attempt to synthesize aryl 2,2-difluorocyclopropyl ketones through an alternate route, 2,2-difluorocyclopropanecarbonyl chloride underwent a Friedel-Crafts acylation reaction with aromatic compounds using aluminum chloride as the catalyst. However, the reaction produced previously-unreported aryl propyl ketones with terminal chlorodifluoromethyl groups instead of or along with the expected products, indicating that the 2,2-difluorocyclopropyl ring opened during the reaction between the carbon connected to the acyl chloride and the difluorinated carbon. Experimental evidence and thermodynamic calculations indicated that the ring-opening mechanism directly competed with the acylation reaction and that the type of aromatic compound and, to a lesser extent, its concentration affected the ratio of ring-intact and ring-opened products along with the yields. Ultimately, this reaction proved most useful in either synthesizing exclusively the ring-opened aryl 3-chloro-3,3-difluorocyclopropyl ketones from arenes of low reactivity or mostly the ring-intact aryl 2,2-difluorocyclopropyl ketones from arenes of high reactivity. Both the ring-opened and ring-intact products could potentially be

used in the synthesis of larger, more complex fluorinated products such as medicinal drugs.

CHAPTER 1
BACKGROUND

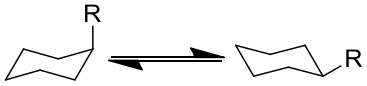
1.1 Introduction

1.1.1 Fluorine

1.1.1.1 Properties of fluorine atoms

Fluorine is of significant importance to organic and medicinal chemistry due to the atom's small size and its high electronegativity. In terms of physical size, fluorine is second only to hydrogen as the smallest atom capable of binding to carbon atoms. Much like hydrogen, fluorine only requires a single covalent bond to complete its octet. This makes the fluorine atom the smallest possible substituent to replace a hydrogen atom on an organic compound.[1,2] This is seen in calculations on the steric effects of various substituents on the equilibrium between axial and equatorial substitution of cyclohexane, where the energy difference between fluorine and hydrogen atoms themselves were negligible and the replacement of methyl and ethyl groups with fluorinated analogs only increased the steric effects slightly (Table 1-1).[1]

Table 1-1. Relative steric impact of common substituents on the axial-equatorial equilibrium of cyclohexane[1]



R	-ΔG° (kcal/mol)	R	-ΔG° (kcal/mol)
H	[0]	F	0.2
OH	0.5	OCF_3	0.8
OCH_3	0.6	SCF_3	1.2
CH_3	1.7	CH_2F	1.6
C_2H_5	1.8	CHF_2	1.9
i-C_3H_7	2.2	CF_3	2.4
Ph	2.8	C_2F_5	2.7

However, fluorine has the highest electronegativity of all elements and thus produces strong electron-withdrawing inductive effects on the molecule it is bonded with, thereby altering the molecule's overall polarity and chemical reactivity of its other

functional groups. For example, the electron-withdrawing effect of fluorine atoms and trifluoromethyl groups weaken the oxygen-hydrogen bond of nearby carboxylic acids and hydroxyl groups on the molecule, thereby increasing its dissociation and thus the acidity of the molecule (Tables 1-2 & 1-3).[1,3] Even replacing the terminal methyl group of butanoic acid, which is three carbon atoms away from the carboxylic acid functional group itself, with a trifluoromethyl group increases its acidity slightly, demonstrating the strength of the electron-withdrawing effects of the substituent.[1,4] The withdrawal effects of fluorine substituents also hinder the binding power of an amine's lone pair, thereby decreasing its basicity (Table 1-4).[1,3,4]

Table 1-2. Acidity of carboxylic acids[1,3,4]

Carboxylic acid	pKa
CH_3CO_2H	4.8
FCH_2CO_2H	2.6
$CF_3CH_2CO_2H$	2.9
CF_3CO_2H	0.2
$CH_3CH_2CH_2CO_2H$	4.8
$CF_3CH_2CH_2CO_2H$	4.2

Table 1-3. Acidity of alcohols[1,3,4]

Alcohol	pKa
CH_3CH_2OH	15.9
CF_3CH_2OH	12.4
$(CF_3)_2CHOH$	9.3
$(CF_3)_3COH$	5.4
C_6H_5OH	10.0
C_6H_5FO (2-fluorophenol)	8.7
C_6H_5FO (3-fluorophenol)	9.3
C_6H_5FO (4-fluorophenol)	9.9

Table 1-4. Basicity of amines[1,3,4]

Amine	pKb
$CH_3CH_2NH_2$	3.3
$CF_3CH_2CH_2NH_2$	5.3
$CF_3CH_2NH_2$	8.3
$C_6H_5NH_2$	9.1
C_6H_7FN (2-fluoroaniline)	10.8
C_6H_7FN (3-fluoroaniline)	10.4
C_6H_7FN (4-fluoroaniline)	9.4

Fluorine's high electronegativity and small atomic size make the carbon-fluorine bond the strongest and one of the shortest single bonds in organic chemistry. This makes the fluorine atom a poor leaving group and thus relatively unreactive compared to other substituents. Furthermore, the high electron density around the fluorine atom repels negatively-charged species and thus, along with fluorine's short bond length with carbon, prevents direct nucleophilic attack (S_N2 reaction) on the carbon it is attached to.[5] For difluorinated carbons, S_N2-like reactions have only been reported under very specific and unusual circumstances.[5,6]

Despite having the highest electronegativity and producing strong inductive effects, fluorine atoms are still capable of donating its electrons to stabilize a carbocation through resonance.[7] Thermodynamic tests have shown that fluoromethyl and difluoromethyl carbocations are significantly more stable than primary carbocations.[7] Our group previously demonstrated that (2,2-difluorocyclopropyl)methyl tosylates at high temperatures in acidic condition, notably with trifluoroacetic acid, rearranged to stabilize a primary carbocation that formed, opening their difluorocyclopropyl ring and producing a difluorocarbocation intermediate, which reacted further to produce their observed products (Figure 1-1).[8]

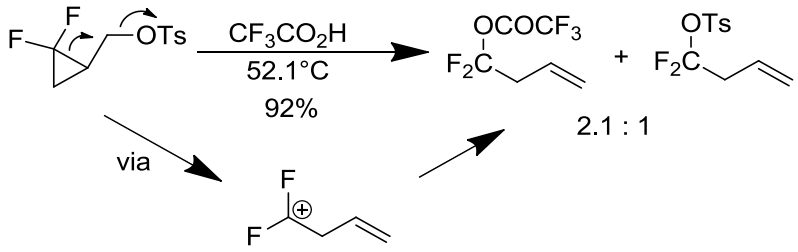


Figure 1-1. Rearrangement reaction of (2,2-difluorocyclopropyl)methyl tosylate in triflic acid[8]

1.1.1.2 Fluorine in the medicinal field

The effects of fluorine on organic molecules and reactions have been most notably seen in the pharmaceutical field, where fluorinated drugs have exhibited more potent effects on the behavior of biological agents and processes compared to other halogen-containing and non-halogenated drugs.[2,9-12] In fact, there are over 150 medicinal compounds currently on the market containing fluorine in its molecular structure.[9] Analogs of natural products where fluorine substituted hydrogen have worked most effectively due to biological agents failing to detect the size difference between fluorine and hydrogen atom, thereby accepting the analog as if it were the natural substrate.[2] Then, the fluorine atom's electronic properties altered the agent's properties such as hydrogen bonding or conformation, ultimately altering its normal behavior such as its ability to bind with other substrates, its ability to absorb and transport nutrients, and its metabolism of various chemicals.[9-12] Thus, there has been increased interest in the synthesis of fluorinated analogs of natural products, which in turn has increased the need for the discovery of new synthetic reactions involving fluorine as well as the development of new fluorinated precursors.

1.1.2 Friedel-Crafts Acylation

Friedel-Crafts acylation is an electrophilic aromatic substitution reaction in which an acyl halide or anhydride reacts with an aromatic ring with the assistance of a Lewis acid catalyst to produce an aryl ketone. An excess of 1 equivalent of Lewis acid with respect to the acylating agent is required for the reaction. During the reaction, one Lewis acid molecule first coordinates with the carbonyl oxygen of the acylating agent while a second Lewis acid molecule removes the halide or anhydride connected to the carbonyl, forming the acylium cation. The aromatic ring then uses one of its double

bond to attack the acylium cation on the carbonyl carbon. The removed halide or anhydride then detaches from its Lewis acid, regenerating it for reaction with another molecule, and removes the hydrogen on the aromatic ring carbon atom that the acyl group bonded to, thereby reforming the double bond and the ring's aromaticity. The Lewis acid still coordinated to the carbonyl oxygen is eventually removed during work-up (Figure 1-2).[13]

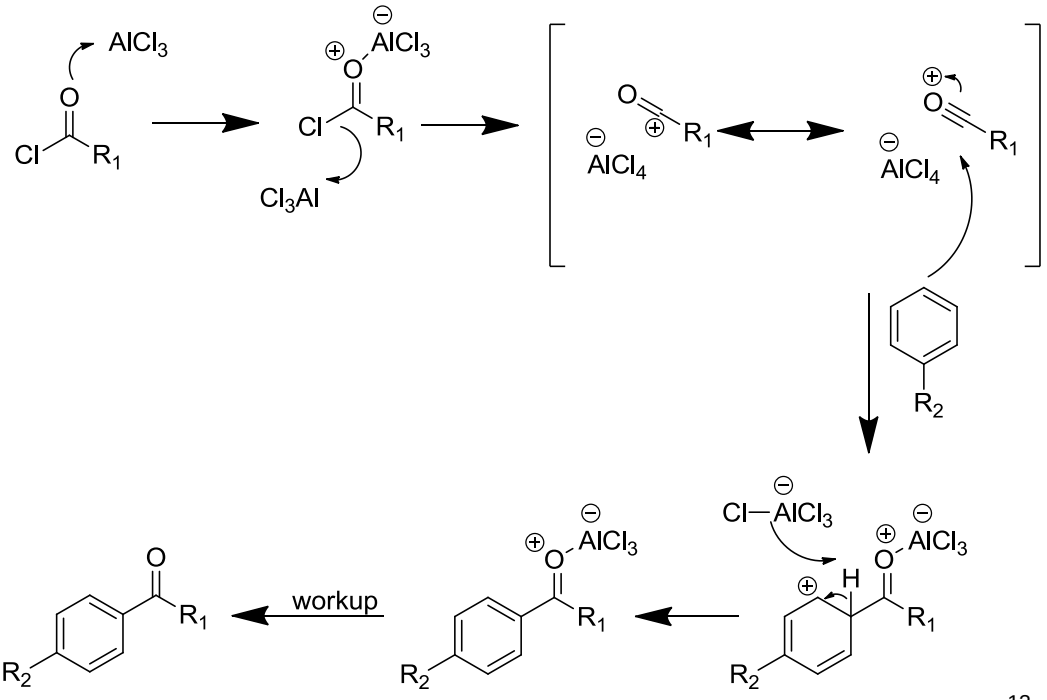


Figure 1-2. Mechanism of Friedel-Crafts acylation with monosubstituted arene[13]

The type of substituents on the aromatic ring determines its reactivity. Electron-donating substituents increase the reactivity of the aromatic ring, whereas electron-withdrawing substituents decrease reactivity. In most instances, the activation and deactivation of aromatic rings through resonance has a greater effect on reactivity than activation and deactivation through inductive effects. Thus, the resonance effects from methoxy groups and anilines increase reactivity greater than the induction from alkyl groups. Likewise, resonance from acyl and nitro groups strongly reduces reactivity

greater than the induction from halogenated methyl groups. In fact, the withdrawal effects of acyl groups almost always surpasses the effects of most electron-donating substituents, hence why Friedel-Crafts acylation almost never occurs more than once per aromatic ring. Halogens are the notable exception as their inductive-withdrawing effects outweigh their resonance-donation effects in terms of reactivity.[13]

Along with reactivity, substituents also dictate the position of acylation on the aromatic ring. All electron-donating groups on benzene analogs promote acylation on the ortho-position or para-position to itself, with para-positioning often favored for steric reasons. Most electron-withdrawing substituents direct the acylation reaction to the meta-position, assuming that Friedel-Crafts acylation can occur on the deactivated phenyl ring. Despite their electron-withdrawing inductive effects being stronger than their electron-donating resonance effects, halogens still promote ortho-positioning and para-positioning through resonance. If an aromatic ring contains two or more substituents, the stronger group (usually activating) dominates positioning.[13]

Friedel-Crafts acylation has been performed using a variety of acylating agents, catalysts, and solvents. Although acyl halides and anhydrides are most commonly used, Friedel-Crafts acylation has occurred using carboxylic acids, esters, and even ketenes as the acylating agents under specific conditions.[13,14] The most frequently used Lewis acid catalyst is aluminum chloride, although aluminum bromide, zinc chloride, ferric chloride, and scandium triflate are common alternatives.[13,14] Common solvents for acylation include dichloromethane, carbon disulfide, acetonitrile, nitromethane, nitrobenzene, and 1,2-dichloroethane.[13-17] An excess of the aromatic ring can also be used as both solvent and reactant.[13,17]

1.2 Events Leading to This Research

1.2.1 Trimethylsilyl Fluorosulfonyldifluoroacetate (TFDA)

TFDA is a difluorocarbene reagent that reacts with alkenes using a catalytic amount of sodium fluoride to synthesize 2,2-difluorocyclopropyl groups. During the reaction, the fluoride anion reacts with and removes TFDA's trimethylsilyl group, which subsequently results in decarboxylation and the generation of sulfur dioxide, the difluorocarbene, and another fluoride anion. The difluorocarbene then reacts with the alkene to form the 2,2-difluorocyclopropyl group (Figure 1-3).[18]

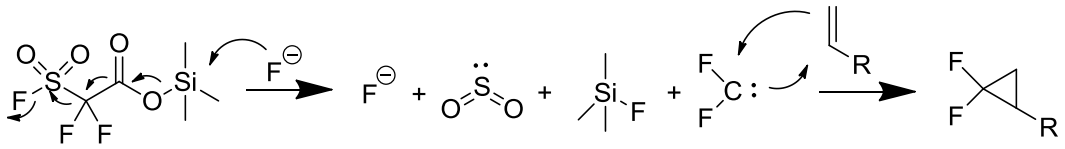


Figure 1-3. Mechanism of TFDA Reaction to form 2,2-difluorocyclopropyl groups[18]

TFDA is prepared by refluxing fluorosulfonyldifluoroacetic acid and trimethylsilyl chloride. Although commercially available, the fluorosulfonyldifluoroacetic acid precursor is expensive. However, it can be prepared in a 3-step process by reacting relatively inexpensive tetrafluoroethylene and sulfur trioxide together, followed by using catalytic amounts of triethylamine on the resulting sulfone, and then reacting the fluorosulfonyldifluoroacetyl fluoride result with water in petroleum ether to form the precursor (Figure 1-4).[18]

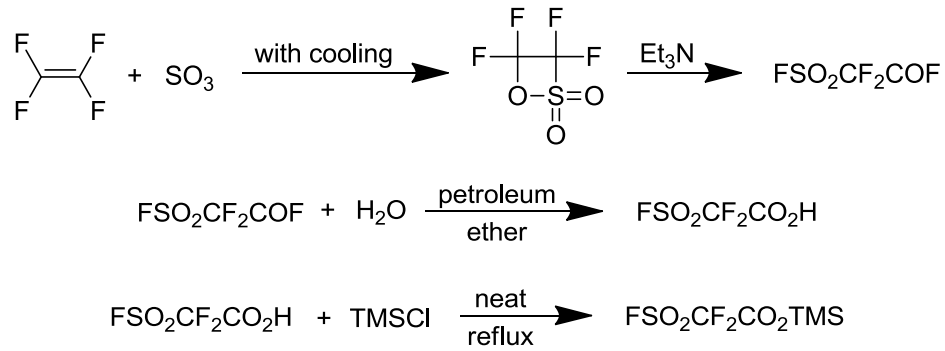


Figure 1-4. Synthesis of TFDA[18]

TFDA has several advantages over other common difluorocarbene reagents such as sodium chlorodifluoroacetate and hexafluoropropylene oxide. The reaction can be performed under relatively mild conditions compared to other difluorocarbene reagents which require high temperatures or pressure.[18,19] When using TFDA directly on the alkene with no solvent or additives other than the sodium fluoride catalyst, the reaction produces only gaseous byproducts trimethylsilyl fluoride, carbon dioxide and sulfur dioxide, thus simplifying the purification processes at the end.[18,19] The reaction usually requires at most 2 equivalents of TFDA to produce sufficient yields.[18,19] Most importantly, TFDA can react with a wide variety of alkenes, including relatively unreactive alkenes such as acrylate esters.[18,19]

1.2.2 Aryl 2,2-Difluorocyclopropyl Ketones

1.2.2.1 Uses of aryl 2,2-difluorocyclopropyl ketones

Aryl 2,2-difluorocyclopropyl ketones serve both as a precursor for adding 2,2-difluorocyclopropyl groups to complex molecules as well as starting material for the synthesis of both nonfluorinated and fluorinated precursors, usually through a ring-opening mechanism. In one set of reactions performed by our group, when treated with magnesium iodide in the presence of aryl imines, aryl 2,2-difluorocyclopropyl ketones underwent a series of ring-opening, elimination, and reductive-elimination mechanisms to produce 2-alkylideneazetidines devoid of fluorine. When the reaction was carried out in the absence of imines, the intermediate reacted with iodine by-product formed in the reaction and then cyclized to produce 2,5-diaryl-3-iodofurans that also lacked fluorine atoms (Figure 1-5).[20]

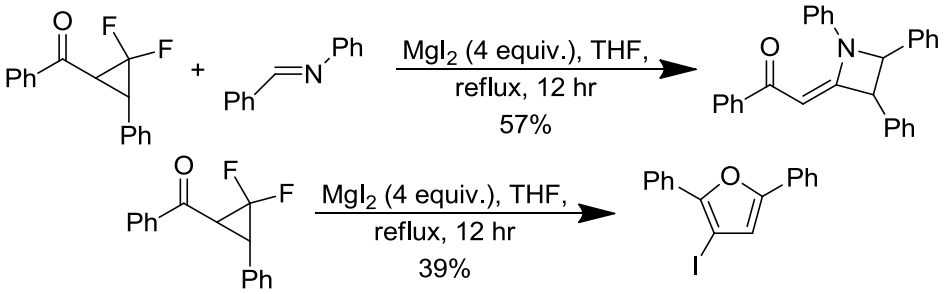


Figure 1-5. Reactions of aryl 2,2-difluorocyclopropyl ketones with magnesium iodide[20]

In another reaction our group carried out, when aryl 2,2-difluorocyclopropyl ketones were dissolved in ionic liquid N-pentylpyridinium bromide at 70°C and then treated with either trifluoroacetic acid or triflic acid, the reaction produced high yields of novel aryl 3-bromo-2,2-difluoropropyl ketones (Figure 1-6). This reaction occurred through an S_N2 mechanism where, after the ketone was protonated by the acid, a bromide anion nucleophilically attacked the unsubstituted cyclopropyl carbon, thereby opening the ring between the nonfluorinated carbons to produce an enol. The enol intermediate immediately tautomerized back into a ketone to produce the product (Figures 1-7).[21]

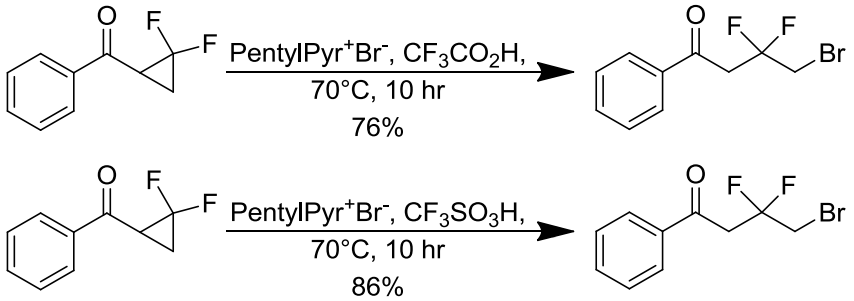


Figure 1-6. Reactions of aryl 2,2-difluorocyclopropyl ketones with ionic liquid[21]

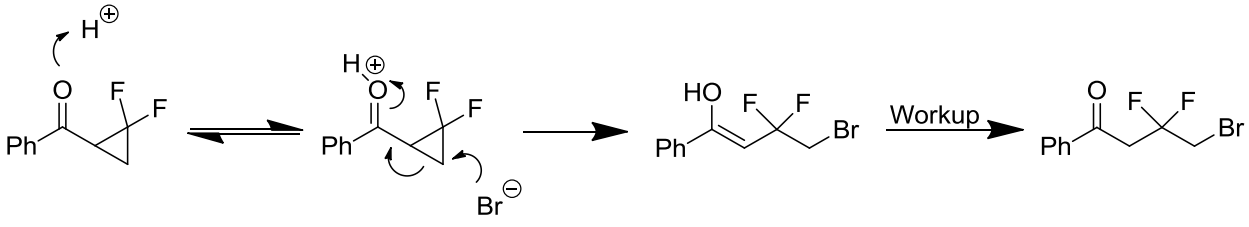


Figure 1-7. S_N2 mechanism of aryl 2,2-difluorocyclopropyl ketones with ionic liquid[21]

1.2.2.2 Synthesis of aryl 2,2-difluorocyclopropyl ketones

Aryl 2,2-difluorocyclopropyl ketones were previously synthesized by our group through a 3-step sequence.[21] In the first reaction, the desired aromatic compound underwent Friedel-Crafts acylation with 3-chloropropionyl chloride to produce aryl 3-chloropropanone. The aryl 3-chloropropanone then underwent an elimination reaction using triethylamine as the base to produce the aryl vinyl ketone. Both reactions produced high yields for all aromatic compounds of their respective products (Figure 1-8).[21] In the third step, the aryl vinyl ketone reacted with the difluorocarbene reagent TFDA using sodium fluoride catalyst and high temperatures to produce the desired aryl 2,2-difluorocyclopropyl ketone. However, these conditions also favored polymerization of the aryl vinyl ketone which effectively competed with the difluorocarbene addition reaction. The most optimal conditions discovered to favor the desired product only produced yields ranging from 45-55%, which is insufficient for large-scale production of the precursor (Figure 1-9).[21]

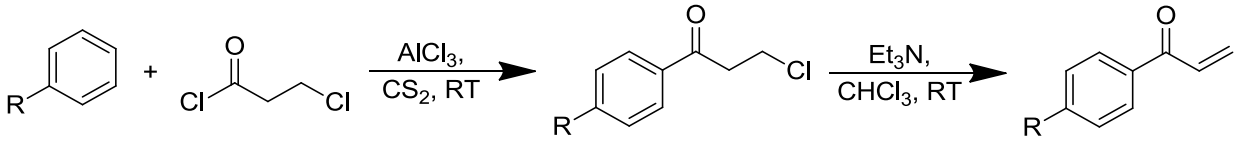


Figure 1-8. First two steps in synthesis of aryl 2,2-difluorocyclopropyl ketones[21]

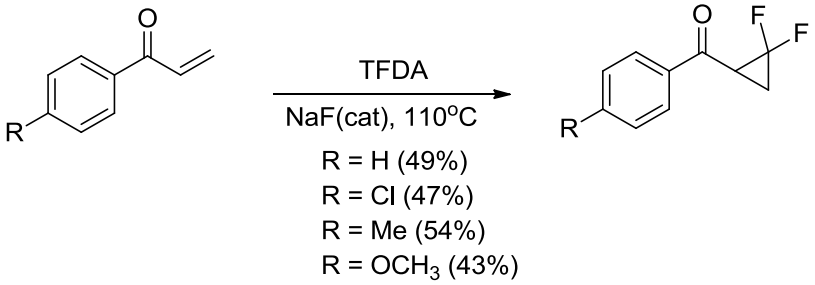


Figure 1-9. Third step in synthesis of aryl 2,2-difluorocyclopropyl ketones with yields[21]

1.2.2.3 Proposed alternative synthesis using Friedel-Crafts acylation

Since directly reacting TFDA with aryl vinyl ketones provided undesirable yield, an alternate synthesis was proposed in which 2,2-difluorocyclopropanecarbonyl chloride would be synthesized and then used in a Friedel-Crafts acylation with aromatic compounds to produce aryl 2,2-difluorocyclopropyl ketones. The acyl chloride itself could be prepared from reacting TFDA with butyl acrylate, followed by a hydrolysis of the ester product, and then converting the resulting carboxylic acid with thionyl chloride into the acyl chloride (Figure 1-10).[18,22,23] Previous experiments have shown that the nonfluorinated analog cyclopropanecarbonyl chloride successfully underwent Friedel-Crafts acylation with a variety of arenes with no effect on the cyclopropyl group, including those with steric hindrance such as mesitylene and even a self-acylation reaction (Figure 1-11).[15-17] Furthermore, the dichlorinated analog 2,2-dichlorocyclopropanecarbonyl chloride also underwent Friedel-Crafts acylation with toluene and mesitylene, producing high yields of the expected ring-intact product (Figure 1-12).[24] Thus, it was expected that 2,2-difluorocyclopropanecarbonyl chloride would react similarly.

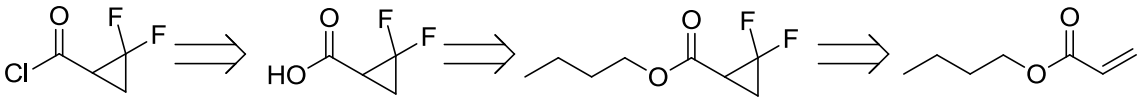


Figure 1-10. Retrosynthetic scheme for 2,2-difluorocyclopropanecarbonyl chloride

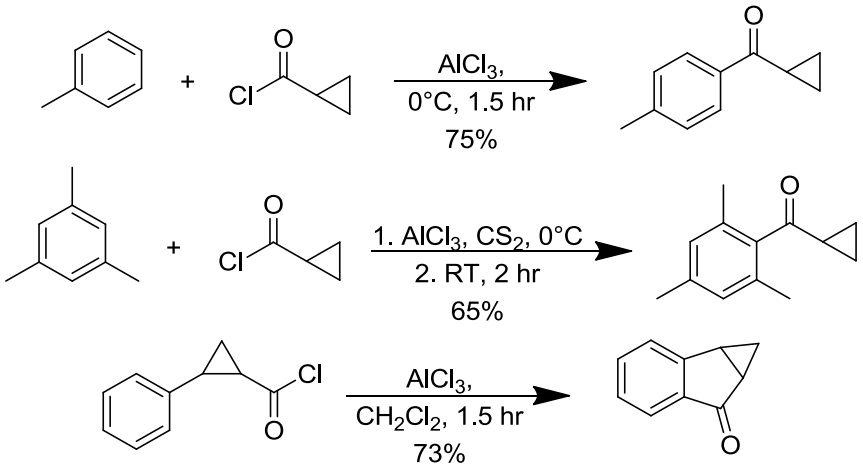


Figure 1-11. Previous Friedel-Crafts reactions with cyclopropanecarbonyl chloride[16-17]

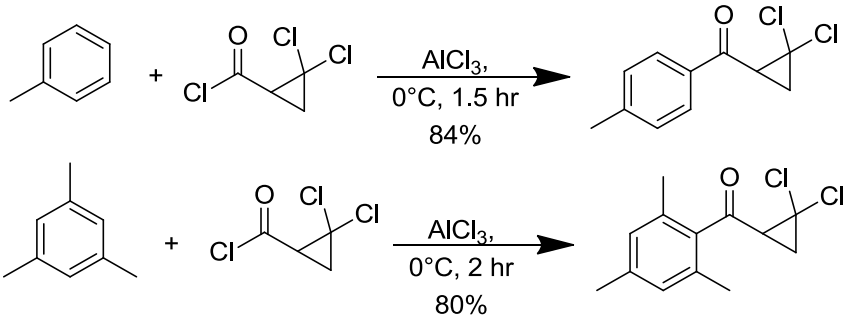


Figure 1-12. Previous Friedel-Crafts reactions with 2,2-dichlorocyclopropanecarbonyl chloride[24]

CHAPTER 2
RESULTS

2.1 Synthesis of 2,2-Difluorocyclopropanecarbonyl Chloride (3)

Commercially available butyl acrylate reacted with trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) using sodium fluoride as catalyst to produce butyl 2,2-difluorocyclopropanecarboxylate **1**.[18] Although butyl acrylate does normally polymerize under the required reaction conditions, polymerization never occurred or effectively competed when the TFDA reaction was performed quickly enough. The resulting ester **1** then underwent hydrolysis with potassium hydroxide in refluxing water to synthesize 2,2-difluorocyclopropanecarboxylic acid **2**.[22] Finally, carboxylic acid **2** was converted into the desired acyl chloride **3** by reaction with thionyl chloride.[23] All three reactions produced high yields of their respective products (Figure 2-1).

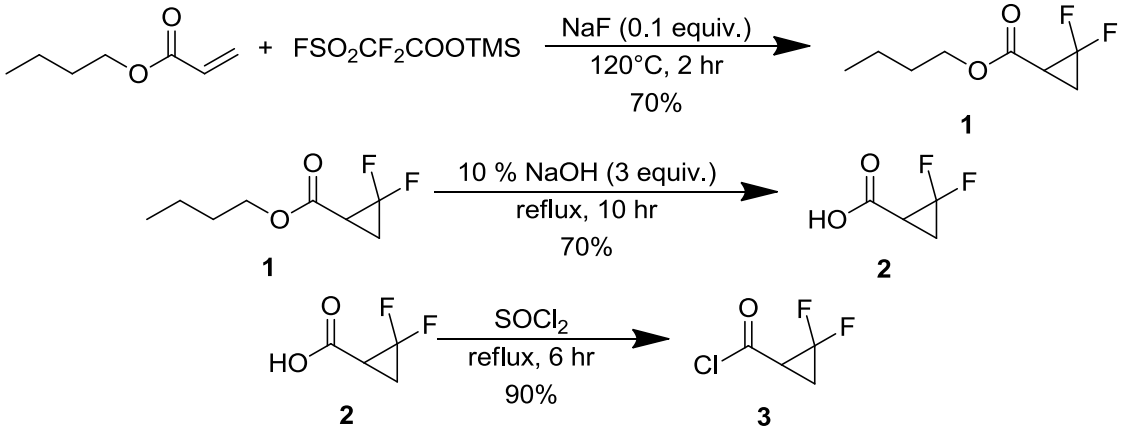


Figure 2-1. Synthesis of 2,2-difluorocyclopropanecarbonyl chloride **3**

2.2 Friedel-Crafts Acylation With 2,2-Difluorocyclopropanecarbonyl Chloride (3)

2.2.1 Initial Experiments Using 1 Equivalent of Aromatic Compound

When 2,2-difluorocyclopropanecarbonyl chloride **3** underwent Friedel-Crafts acylation with 1 equivalent of benzene in 20 mL of dichloromethane at 0°C using aluminum chloride as the catalyst for 2 hours, the reaction produced a 50% yield of

exclusively ring-opened phenyl 3-chloro-3,3-difluoropropyl ketone **4a**. Surprisingly, none of the expected ring-intact phenyl 2,2-difluorocyclopropyl ketone **5a** was produced. When the same reaction was performed using 1 equivalent of the relatively more-reactive alkyl aromatic substrates such as toluene, ethylbenzene and p-xylene, the only products obtained were their analogous ring-opened products **4b**, **4c**, and **4d** in 72%, 78% and 78% yields respectively (Figure 2-2, Table 2-1). No reaction occurred when chlorobenzene was used as the aromatic substrate.

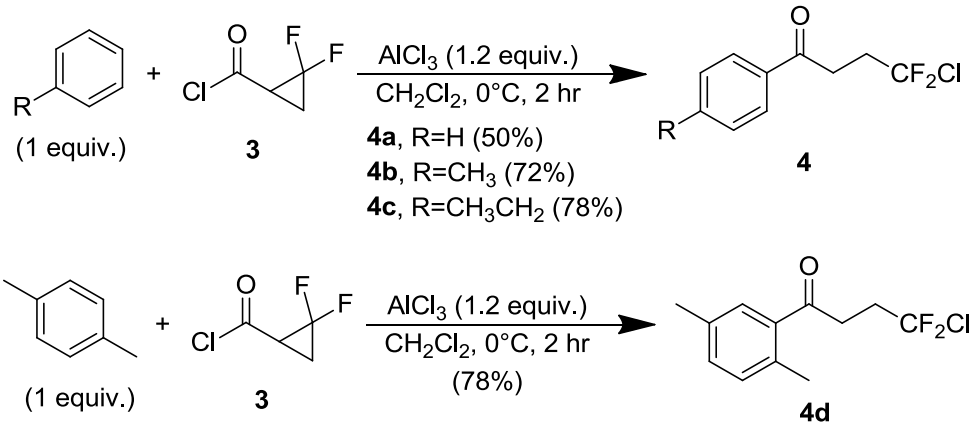


Figure 2-2. Initial Friedel-Crafts reaction with **3** on alkylated benzenes

The expected ring-intact products were first observed when 1 equivalent of highly reactive anisole was used as the aromatic substrate, which produced a 52% yield of a 25:75 mixture of ring-opened product **4e** and ring-intact product **5e**. One equivalent of naphthalene also strongly favored the intended Friedel-Crafts reaction, yielding an 18:82 ratio of rearranged and ring-intact products **4f** and **5f** respectively, although the overall yield only averaged around 45%. Strangely, anisole and naphthalene's overall average yields were lower than those of toluene and p-xylene despite the fact that both are far more reactive than the alkylated benzenes. Performing the reaction using 1 equivalent of highly reactive thiophene produced an 86% yield of almost exclusively ring-intact product **5g** (Figure 2-3, Table 2-1).

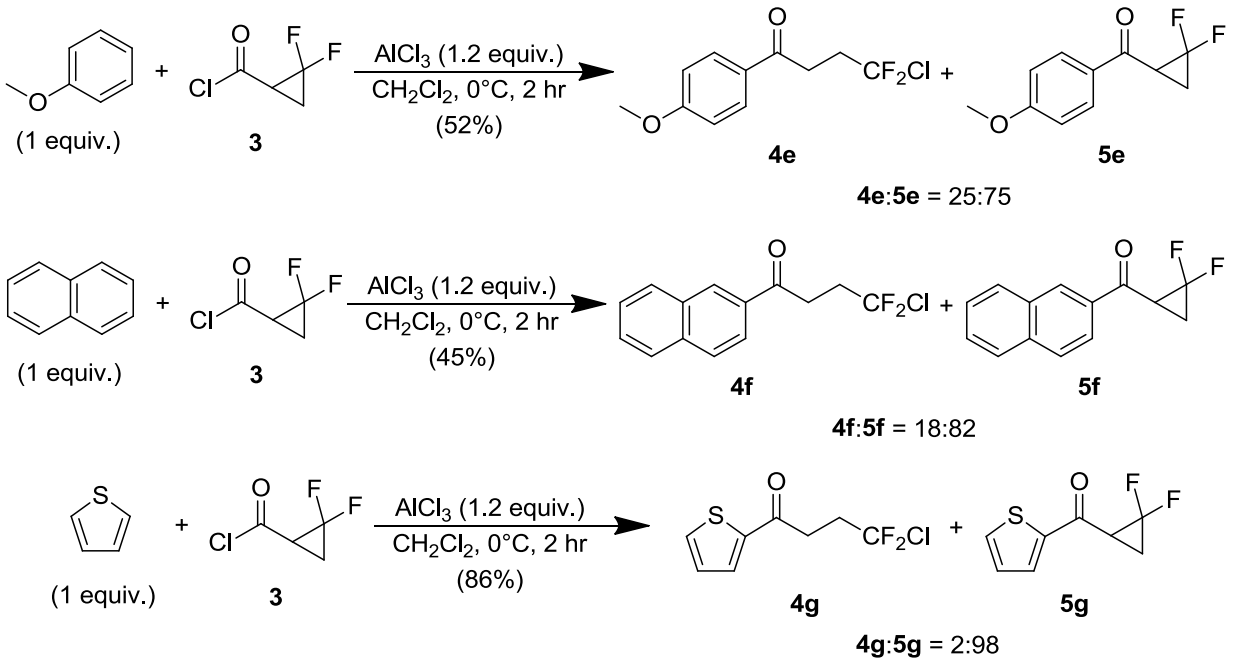


Figure 2-3. Initial Friedel-Crafts reaction with **3** on highly-reactive aromatic compounds

For all single-substituted benzene derivatives, acylation exclusively occurred in the para-position, regardless of whether ring-cleavage occurred or not. For thiophene, the reaction occurred on carbon-2 as expected. Acylation occurred only on carbon-1 of naphthalene for both ring-intact and ring-opened products.

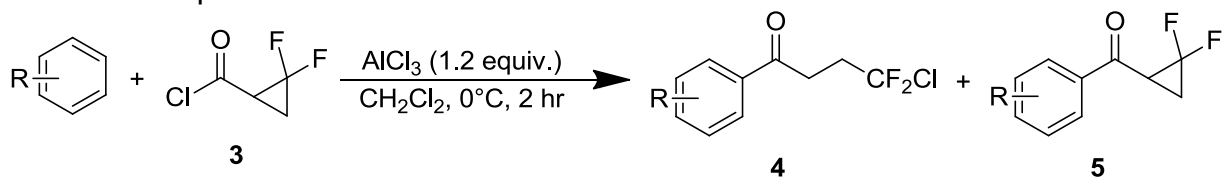
2.2.2 Experiments on the Effects of Concentration on the Reaction

2.2.2.1 Experiments using 5 equivalents of the aromatic compound

Using 5 equivalents of benzene instead of 1 equivalent under the same reaction conditions as the initial experiment resulted in a 55% yield with a 80:20 mixture of ring-opened **4a** to ring-intact **5a**. Interestingly, 5 equivalents of toluene provided a 70% yield favoring mostly ring-intact product **5b**, a stark contrast to the results produced using 1 equivalent of toluene which yielded exclusively rearranged product **5a**. On the other hand, p-xylene still exclusively gave the rearranged product **4d** with roughly the same yield despite the higher concentration. Raising the amount of anisole to 5 molar equivalents slightly increased its overall yield to 60% with a 12:88 ratio of rearranged

product **4e** to expected product **5e**. No notable changes to yields or product ratio occurred when the molar amount of naphthalene was increased (Table 2-1).

Table 2-1. Friedel-Crafts acylation with **3** of various molar equivalents of aromatic compounds



3 **4** **5**

Aromatic compound	Molar equivalents	Average percent yield[α]	Ratio of product **4**	**5**
benzene	1	50%	**4a**: 100	**5a**: 0
benzene	5	55%	**4a**: 80	**5a**: 20
toluene	1	72%	**4b**: 100	**5b**: 0
toluene	5	70%	**4b**: 10	**5b**: 90
ethylbenzene	1	78%	**4c**: 100	**5c**: 0
p-xylene	1	78%	**4d**: 100	**5d**: 0
p-xylene	5	75%	**4d**: 100	**5d**: 0
anisole	1	52%	**4e**: 25	**5e:** 75
anisole	5	60%	**4e**: 12	**5e**: 88
naphthalene	1	45%	**4f**: 18	**5f**: 82
naphthalene	5	40%	**4f**: 15	**5f**: 85
thiophene	1	86%	**4g**: 2	**5g**: 98

[α]All percent yields were calculated from ^{19}F nuclear magnetic resonance (NMR) integration of crude product using known amount of α,α,α-trifluorotoluene

It was peculiar that toluene provided mostly ring-intact product after its concentration increase whereas p-xylene, the more reactive of the two species, still produced none. Thus, an additional experiment was conducted where a mixture of 5 equivalents of toluene and 5 equivalents of p-xylene acted as the aromatic substrate. The acyl chloride reacted exclusively with toluene, producing a 70% yield with a 22:78 ratio of ring-opened **4b** to ring-intact **5b**. This result, along with the lack of ortho-positioned products detected throughout our investigation, hinted that steric hindrance of p-xylene's methyl groups interfered with the Friedel-Crafts reaction (Figure 2-4).

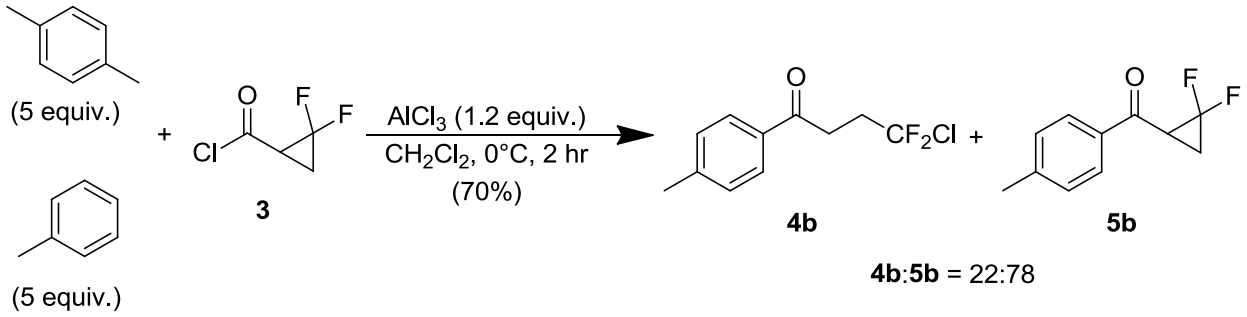
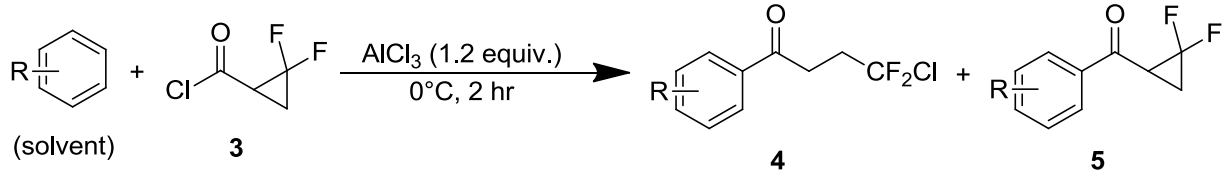


Figure 2-4. Comparison experiment between toluene and p-xylene

2.2.2.2 Experiments using the aromatic compound as solvent

Since using higher equivalents of aromatic compound generally resulted in an increased amount of ring-intact product produced, it seemed reasonable that using the substrates as the solvent would accentuate the results further. However, all experiments involving the aromatic substrate as both reactant and solvent while under the same conditions as the initial reaction reduced the overall percent yields between 10-20% compared to using 5 equivalents in 20 mL of dichloromethane with no major changes in product ratio (Table 2-2).

Table 2-2. Friedel-Crafts acylation with **3** with aromatic substrates as solvent



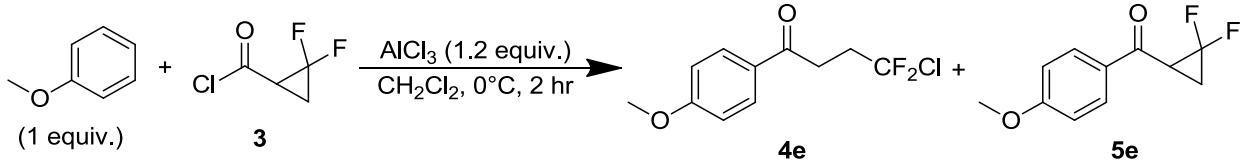
Aromatic compound	Average percent yield[α]	Ratio of products **4**	**5**
benzene	40%	**4a**: 90	**5a**: 10
toluene	55%	**4b**: 10	**5b**: 90
p-xylene[β]	52%	**4d:** 100	**5d**: 0
anisole	48%	**4e**: 10	**5e**: 90

[α]All percent yields were calculated from ^{19}F NMR integration of crude product using known amount of α,α,α-trifluorotoluene
[β]Reaction done at 25°C

2.2.2.3 Experiments on the effects of dilution on the reaction

Due to the potential use of the ring-opened anisole product **4e**, several attempts were performed to promote the rearrangement mechanism. Since concentration displayed some effect on anisole's product ratio and since 1 equivalent of anisole produced a mixture of its products in comparison to 1 equivalent of the other aromatic compounds, which favored mostly one product, decreasing the concentration of anisole through higher solvent volume should theoretically synthesize more ring-opened product without significantly affecting the overall yields. When the Friedel-Crafts reaction of 1 equivalent of anisole was performed with a concentration of 0.1 M instead of the original 0.3 M, the reaction actually produced a 70% yield but had little effect on the product ratio. However, performing the same reaction with a concentration of 0.05 M drastically dropped the yield to 40% with little fluctuation of the product ratio, indicating that further dilution would prevent reaction altogether (Table 2-3).

Table 2-3. Effect of dilution on Friedel-Crafts reaction of **3** on anisole



Anisole concentration	Average percent yield	**4e** to **5e** product ratio
0.3 M	52%	25:75
0.1 M	70%	28:72
0.05 M	40%	30:70

2.2.3 Experiment on the Effects of Temperature on the Reaction

To determine whether temperature would affect the Friedel-Crafts reaction for anisole, 1 equivalent of the aromatic compound underwent Friedel-Crafts acylation in refluxing dichloromethane (40°C) for 2 hours. Although the reaction yield averaged 70%, the product ratio was 36:64, still favoring ring-intact product **5e** (Figure 2-5).

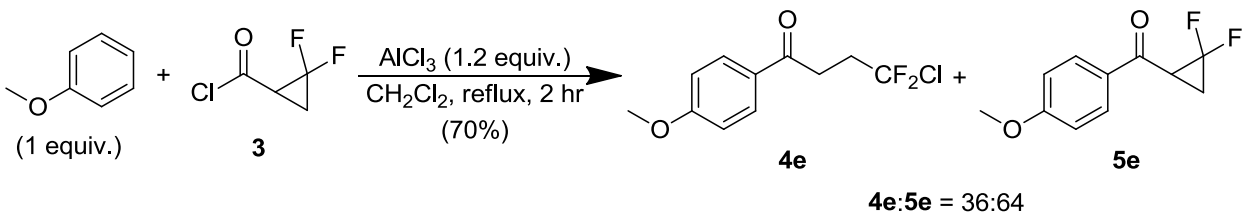


Figure 2-5. Effect of temperature on Friedel-Crafts reaction of **3** on anisole

2.2.4 Experiments on the Effects of Time on the Reaction

Two sets of experiments were conducted to determine if reaction time would promote more ring-cleavage during the reaction. In the first set of experiments, since using 1 equivalent of anisole produced a mixture of ring-opened and ring-intact products compared to the other aromatic substrates, its reaction was repeated under the same conditions as its respective initial reaction except that the reaction time was extended to 6 hours. Although the reaction yield increased slightly to an average of 60%, it retained the exact product ratio as the initial 2 hour experiment (Figure 2-6).

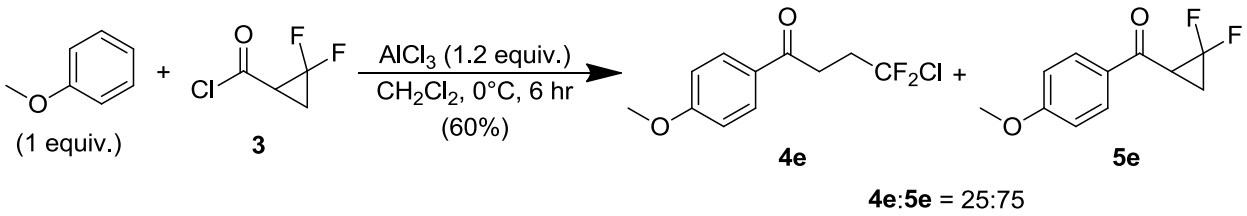
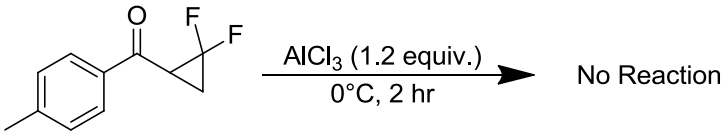


Figure 2-6. Friedel-Crafts reaction of **3** with anisole for 6 hours

In the second set of experiments, the ring-intact product of the toluene reaction, tolyl 2,2-difluorocyclopropyl ketone **5b**, was mixed with 1.2 equivalents of aluminum chloride in different solvents at 0°C for 2 hours in order to induce the ring-opening mechanism. However, no ring-opening occurred in either dichloromethane, 1,2-dichloroethane, or acetonitrile. Furthermore, heating the contents to reflux in acetonitrile for 2 hours failed to promote any reaction. These results indicated that the reaction time had no effect on the products produced and that cleavage occurred during the acylation reaction, not after the ring-intact product had already formed (Figure 2-7).



5b

Figure 2-7. Ring-intact product **5b** in Friedel-Craft conditions without acylating agent

2.2.5 Experiments on the Effects of Solvent on the Reaction

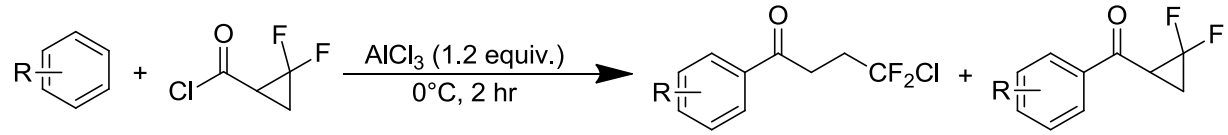
Since the primary product that toluene synthesized in dichloromethane depended heavily on the aromatic concentration and since anisole always produced both products in dichloromethane regardless of concentration, both aromatic substrates were used to determine the effects of other common solvents on the product ratio of the Friedel-Crafts acylation (Table 3-4). Interestingly, decomposition of the starting material occurred with both substrates when the reaction was performed in highly polar solvents such as acetonitrile, nitromethane, and nitrobenzene, resulting in no acylated products. Using carbon disulfide resulted in poor overall yields for both aromatic substrates, with 1 equivalent of toluene producing only a 19% overall yield and 1 equivalent of anisole producing a 32% overall yield, a sharp contrast to their respective 78% and 52% yields from dichloromethane. Furthermore, the reactions were less selective for both aromatic substrates compared to dichloromethane, producing a noticeable mixture of ring-intact and ring-opened product

Surprisingly, when 1,2-dichloroethane was used as the solvent, both aromatic compounds produced high yields of mostly ring-intact product, though rearrangement was still not entirely prevented. The reaction with 1 equivalent of toluene in 1,2-dichloroethane produced a 74% overall yield with a 22:78 ratio of ring-opened **4b** and ring-intact **5b**, which is unusual in that the same reaction in dichloromethane produced exclusively the rearranged product. Using 1 equivalent of anisole resulted in

a 72% yield of a 10:90 ratio of ring-opened **4e** to ring-intact **5e**, a general increase in both yield and expected product.

After witnessing these results, additional Friedel-Crafts reactions were performed in 1,2-dichloroethane using benzene, another aromatic substrate that yielded ring-intact products only when higher molar equivalents were used. Using 1 equivalent of benzene produced a 50% yield, much like in dichloromethane, but had a ring-opened to ring-intact product ratio of 65:35. Using 5 equivalents of benzene increased the yield to 57% but only altered the ratio slightly to 55:45 favoring **4a**, thus demonstrating that the type of aromatic ring dictated the product distribution in 1,2-dichloroethane more than the concentration, much like in dichloromethane (Table 2-4).

Table 2-4. Friedel-Crafts acylation of aromatic compounds with **3** in various solvents



(1 equiv.) **3** **4** **5**

Aromatic compound	Solvent (20 mL)	Average percent yield[α]	Product ratio **4**	**5**
toluene	CH_2Cl_2	72%	**4b**: 100	**5b**: 0
anisole	CH_2Cl_2	52%	**4e**: 25	**5e**: 75
toluene	CS_2	19%	**4b**: 60	**5b**: 40
anisole	CS_2	32%	**4e**: 31	**5e**: 69
toluene	CH_3NO_2	decomposition	-	-
anisole	CH_3NO_2	decomposition	-	-
toluene	$C_6H_5NO_2$	decomposition	-	-
anisole	$C_6H_5NO_2$	decomposition	-	-
toluene	CH_3CN	decomposition	-	-
anisole	CH_3CN	decomposition	-	-
toluene	$ClCH_2CH_2Cl$	74%	**4b**: 22	**5b**: 78
anisole	$ClCH_2CH_2Cl$	72%	**4e**: 10	**5e**: 90
benzene	$ClCH_2CH_2Cl$	50%	**4a**: 65	**5a**: 35
benzene[β]	$ClCH_2CH_2Cl$	57%	**4a**: 55	**5a**: 45

[α]All percent yields were calculated from ^{19}F NMR integration of crude product using known amount of α,α,α-trifluorotoluene
[β]Second benzene reaction used 5 molar equivalents

2.2.6 Experiments on the Effects of Aluminum Bromide as the Catalyst

Being an analog of aluminum chloride and a stronger Lewis acid than its counterpart, aluminum bromide was tested as a catalyst not only to determine how it would affect yields and product ratio, but also to see if aryl 3-bromo-3,3-difluoropropyl ketones **6** would be synthesized. However, when 1 equivalent of benzene underwent Friedel-Crafts acylation using 1.2 equivalents of aluminum bromide, the reaction unexpectedly produced a relatively equal mixture of four different products for a combined 33% yield; one product being the usual open-ringed product **4a**, another product being the anticipated aryl propyl ketone with the terminal bromodifluoromethyl group **6a**, and the unexpected final two products being α-brominated analogs of the former two products **7a** and **8a** (Figure 2-8). When the same reaction was performed using 1 equivalent of toluene, the reaction produced a 21% yield of ring-intact product **5b** and a combined 39% yield of the tolyl counterparts of the ring-opened products obtained from the benzene reaction. Unlike the results with benzene, the majority of the ring-opened tolyl ketones were the bromodifluoromethyl product **6b** and its respective α-brominated analog **8b** (Figure 2-9). None of the ring-opened products could be successfully isolated from one another, limiting the use of this reaction.

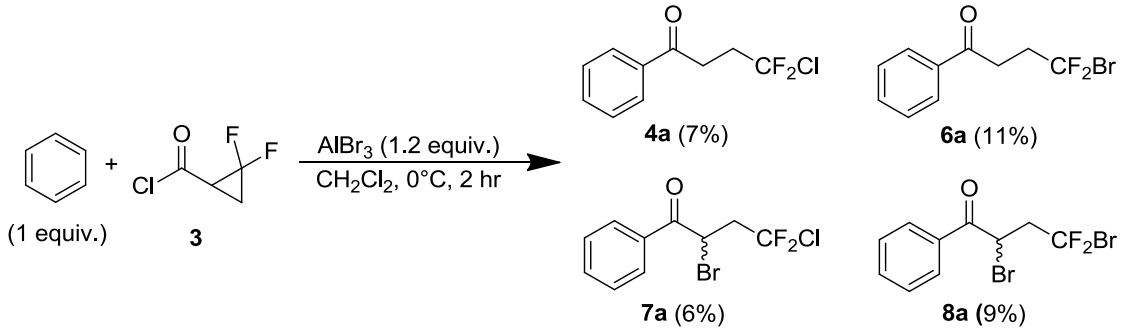


Figure 2-8. Friedel-Crafts reaction of **3** with 1 equivalent of benzene using aluminum bromide

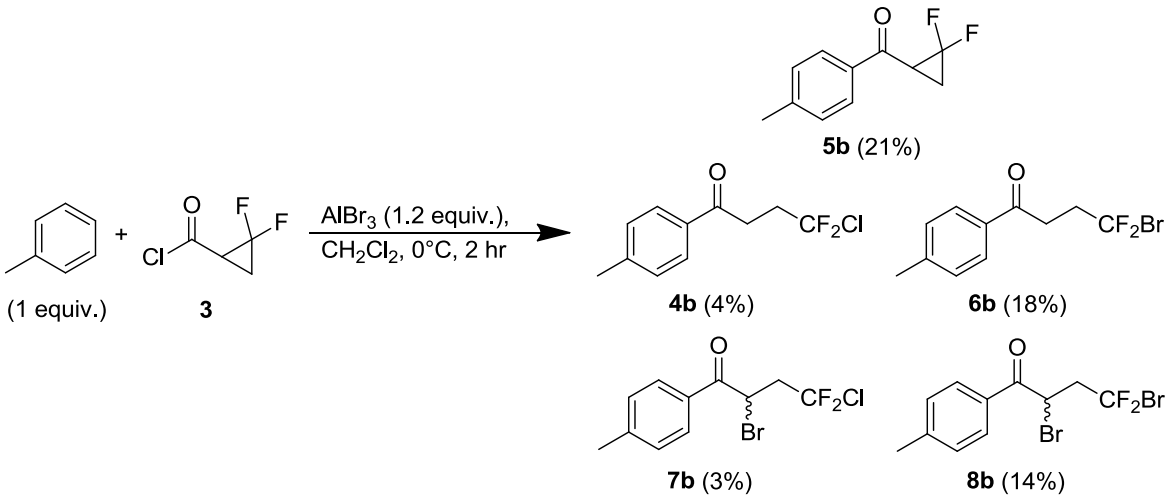
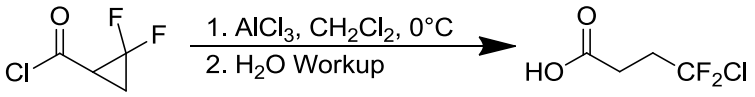


Figure 2-9. Friedel-Crafts reaction of **3** with 1 equivalent of benzene using aluminum bromide

2.3 Attempted Synthesis of Ring-Opened Starting Material (9)

Since all evidence pointed to the ring-opening mechanism occurring during the acylation reaction, attempts were made to synthesize 4-chloro-4,4-difluorobutanoic acid **9**, an open-ringed carboxylic acid version of 2,2-difluorocyclopropanecarbonyl chloride **3**, by placing the starting material under the conditions for Friedel-Crafts acylation but without aromatic substrate and then hydrolyzing the product during work-up. However, when the reaction was performed as in the initial experiment without aromatic substrate, only a 9% yield of the desired product was obtained with only 4% of the starting material recovered (as its carboxylic acid form). When the starting material was mixed with 0.1 equivalents of aluminum chloride, only a 4% yield was obtained with 70% of the starting material recovered. Using 0.3 and 0.5 equivalents of the catalyst produced respective yields of 36% and 43% with respective starting material recovery of 24% and 12%. No effects were observed when the reaction was allowed to run for 6 hours (Table 2-5). Along with the unimpressive yields, numerous byproducts formed in the reaction which could not be identified nor separated from the desired product.

Table 2-5. Effect of aluminum chloride amount on synthesis of **9**



3 **9**

Equivalents of $AlCl_3$	Reaction time	Crude percent yield[α]	Starting material recovery[α]
0.1	2 hr	4%	70%
0.1	6 hr	3%	74%
0.3	2 hr	36%	24%
0.5	2 hr	43%	12%
1.2	2 hr	9%	4%

[α]All percent yields and starting material recovery were calculated from ^{19}F NMR integration of crude product using known amount of α,α,α-trifluorotoluene

CHAPTER 3
DISCUSSION

3.1 Thermodynamic Calculations of Possible Carbocations

The ring-opening mechanism was unexpected because previous Friedel-Crafts acylation reactions with the analogs cyclopropanecarbonyl chloride and 2,2-dichlorocyclopropanecarbonyl chloride produced ring-intact products as expected, showing no evidence of any form of rearrangement.[15-17,24] Furthermore, when rearrangement occurred during the Friedel-Crafts reaction of 2,2-difluorocyclopropanecarbonyl chloride **3**, the only rearranged product received were aryl 3-chloro-3,3-difluoropropyl ketones **4**. No aryl 3-chloro-2,2-difluoropropyl ketones were obtained throughout our investigation, indicating that the cyclopropyl ring exclusively cleaved between the carbon connected to the acyl chloride and the difluorinated carbon. In order to obtain further insight into the mechanism, thermodynamic calculations were performed by group member Henry Martinez.

Calculations on the cyclopropane ring strain from geminal chlorines and fluorines were performed using Wiberg and Marquez's method (Table 3-1).[25] The ground states of several cyclopropane-substituted cations and their respective possible ring-opened carbocations were calculated in the gas phase at HF and MP2/6-31G(d) levels of theory using Gaussian 03 Rev. E01 package. The stability that dichloromethane provided for the cations were also calculated using the Onsager model for both HF and MP2 methods (Table 3-2). The procedures for both calculations are described in further detail within our previous publication of this investigation.[26]

Table 3-1. Isodesmic equations on the effect of geminal fluorine and chlorine substituents on cyclopropyl ring strain

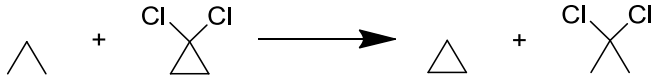
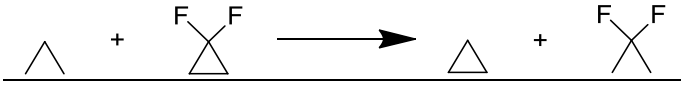
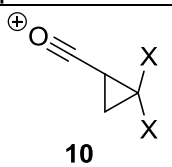
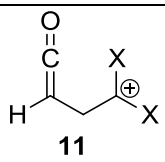
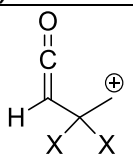
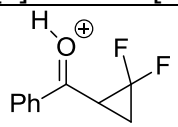
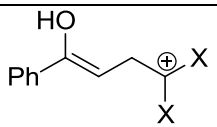
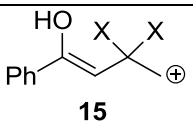
Equation	HF/6-31 g(d)	MP2/6-31 g(d)
	-4.42	-5.51
	-12.37	-13.29

Table 3-2. Computed ground states of cyclopropane-substituted carbocations and their respective ring-opened cations (*ab initio* HF and MP2/6-31G(d))

		Cyclopropyl acylium ion  **10**		 **11**		 **12**	
X	CH_2Cl_2?	HF	MP2	HF	MP2	HF	MP2
X = H	no	[0]	[0]	+45.1	+55.0	+45.1	+55.0
	yes	[0]	[0]	+40.9	+52.6	+40.9	+52.6
X = Cl	no	[0]	[0]	+16.2	+19.9	+38.0	+39.2
	yes	[0]	[0]	+17.3	+20.9	+44.8	+47.7
X = F	no	[0]	[0]	+12.4	+19.8	+52.0	+61.8
	yes	[0]	[0]	**+10.4**	+18.2	+49.7	+59.4
		Protonated cyclopropyl ketone  **13**		 **14**		 **15**	
X	CH_2Cl_2?	HF	MP2	HF	MP2	HF	MP2
X = H	no	[0]	[0]	+43.2	+54.6	+43.2	+54.6
	yes	[0]	[0]	+38.0	+48.8	+38.0	+48.8
X = F	no	[0]	[0]	+20.9	+24.0	+55.0	+61.2
	yes	[0]	[0]	**+15.6**	+17.9	+48.8	+56.2

The calculations indicated that the acylium cations **10** produced from cyclopropanecarbonyl chloride, 2,2-dichlorocyclopropanecarbonyl chloride, and 2,2-difluorocyclopropanecarbonyl chloride were all more stable than the two possible ring-opened ketene carbocations **11** and **12** that each could respectively reproduce. In every case, the ring-opening to produce a primary carbocation **12** was highly

unfavorable, which was expected due to their high instability and the adverse inductive effects of β-halogens on cations. However, the energy difference between the acylium cation from the fluorinated analog $\mathbf{10_F}$ and the ring-opened difluorocarbocation $\mathbf{11_F}$ (+10.4 kcal/mol) was much lower than the energy difference between their chlorinated analogs $\mathbf{10_{Cl}}$ and $\mathbf{11_{Cl}}$ (+17.3 kcal/mol), which itself was greatly lower than the difference from the nonhalogenated analogs $\mathbf{10_H}$ and $\mathbf{11_H}$ (+40.9 kcal/mol). The low energy differences of the halogenated species compared to the nonhalogenated ones was due to the release of cyclopropane ring strain to which the halogens contributed. Most notably, our cyclopropane ring strain calculations showed that geminal fluorine atoms caused significantly greater ring strain than geminal chlorine atoms, hence why the energy difference of the fluorinated cation species $\mathbf{10_F}$ and $\mathbf{11_F}$ was lower than the difference of the chlorinated counterparts $\mathbf{10_{Cl}}$ and $\mathbf{11_{Cl}}$. Ultimately, our calculations demonstrated that the energy required for rearrangement of the fluorinated acylium cation $\mathbf{10_F}$ is low enough to occur whereas the energy required to rearrange the chlorinated and nonhalogenated acylium cations, $\mathbf{10_{Cl}}$ and $\mathbf{10_H}$, are too high, hence why their rearrangement have not been observed thus far.

The thermodynamic calculations also indicated that protonated phenyl cyclopropyl ketones **13** were more stable than either of the possible ring-opened cation species **14** and **15** that could be produced. Much like cyclopropyl acylium cations **10**, the ring-opening of phenyl cyclopropyl ketones **13** to produce primary carbocations **15** was highly unfavorable. Also, the energy difference between the protonated phenyl 2,2-difluorocyclopropyl ketone $\mathbf{13_F}$ and the difluorocarbocation produced from ring-opening $\mathbf{14_F}$ is lower than the energy difference from opening the nonhalogenated

version. However, the energy difference in opening the fluorinated cyclopropyl ring of the protonated ketone **13$_F$** is greater than that of opening the fluorinated cyclopropyl ring of the acylium cation **10$_F$**, which are +15.6 kcal/mol and +10.4 kcal/mol respectively in dichloromethane.

3.2 Proposed Mechanism

Our previous work with aryl 2,2-difluorocyclopropyl ketones in ionic liquids showed that nucleophilic attack on the cyclopropyl ring would occur on the unsubstituted carbon instead of the difluorinated carbon, ruling out an S_N2 mechanism for the newly-discovered mechanism.[19] Furthermore, the newly-discovered mechanism resembled the ring-opening mechanism of (2,2-difluorocyclopropyl)methyl tosylates in acidic conditions.[6] Thus, when we first discovered the ring-opening mechanism that occurs during Friedel-Crafts acylation using 2,2-difluorocyclopropanecarbonyl chloride **3**, two mechanisms were considered based on the observed products, the results of the previous related reactions, and general knowledge of Friedel-Crafts acylation and fluorine.

In the first proposed mechanism, the Friedel-Crafts reaction occurred as expected to produce the ring-intact product but before work-up, the cyclopropyl ring would open to produce the difluorocarbocation enolate. The cation would then react with the chloride anion, the enolate would be protonated, and then tautomerize to form the ring-opened product (Figure 3-1). The reason why highly reactive aromatic compounds such as anisole and thiophene would show less rearrangement would be because they could stabilize the ketone through resonance.

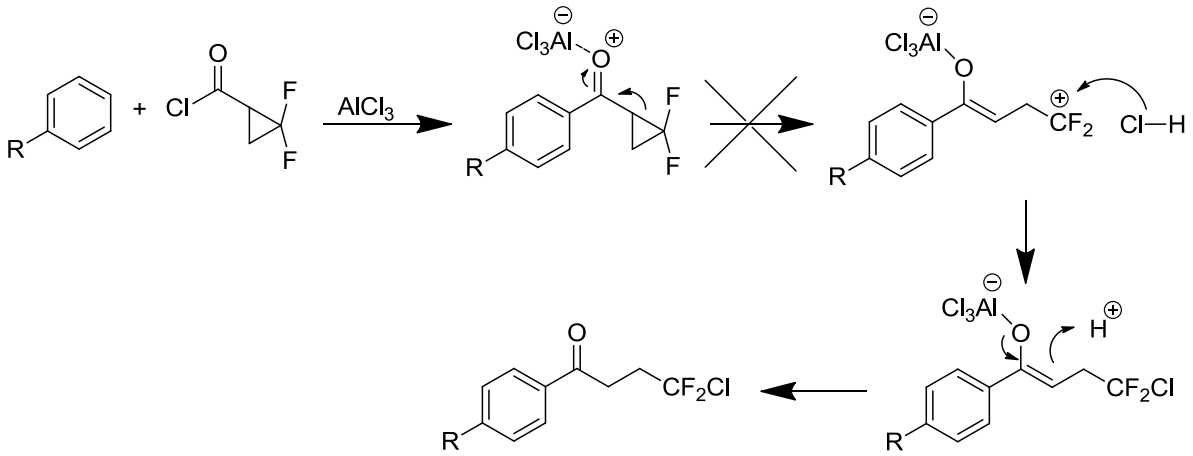


Figure 3-1. Rejected first proposed mechanism: rearrangement after acylation

However, if this first mechanism were to be true, eventually all of the product would become ring-opened product over enough time as the cyclopropane ring would be unable to be restored once the difluorocarbocation reacted with an anion. Both time experiments performed in this investigation disproved this mechanism as prolonging the reaction showed no effect on product ratio and placing ring-intact product in Friedel-Craft conditions never induced rearrangement.

In the second proposed mechanism, after the acylium cation was formed, the intermediate would rearrange to produce the ketene and the difluorocarbocation. The difluorocarbocation would react with a chloride anion to produce the chlorodifluoromethyl group. The ketene would undergo the Friedel-Crafts reaction to produce the observed ring-opened product (Figure 3-2). The reason why highly reactive arenes such as anisole and thiophene produced mostly ring-intact products was because they effectively competed with the rearrangement mechanism. If this second mechanism were true, then increasing the concentration of aromatic compound would theoretically increase likelihood of Friedel-Crafts reaction before the rearrangement occurred.

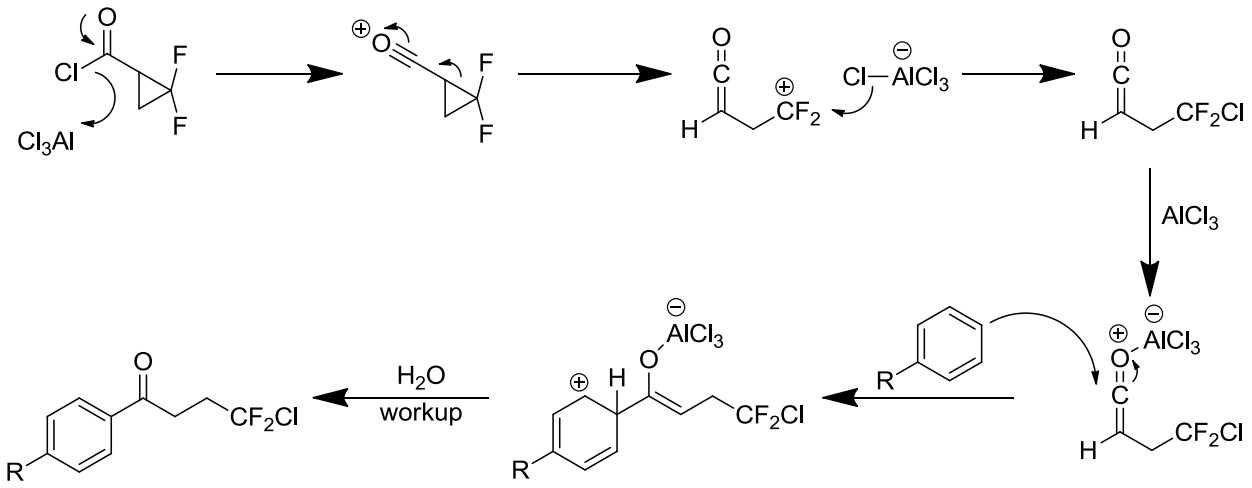


Figure 3-2. Accepted second proposed mechanism: rearrangement before acylation

Both thermodynamic calculations and experimental data supported the second proposed mechanism. The thermodynamic calculations indicated that rearrangement would more likely occur from the acylium cation intermediate than from the protonated ring-intact product. Furthermore, the concentration experiments showed that increasing the equivalents of aromatic compound resulted in generally more ring-intact product being produced, notably with relatively low reactive benzene and toluene which didn't produce ring-intact products at all until higher amounts were used.

The sole outlier was p-xylene which always produced ring-opened products despite being more electron-rich than benzene or toluene. However, this could be explained by the fact that only ortho-substitution can occur on p-xylene and that its methyl groups sterically hindered the acylation reaction, allowing ring-opening to occur first. The fact that no ortho-substituted products other than the p-xylene product were received throughout the investigation and that the experiment where using 5 equivalents each of both toluene and p-xylene only produced toluene products seemed to support this steric hindrance explanation. The fact that p-xylene produced no ring-intact product

due to steric reasons doesn't contradict the second proposed mechanism, which is based on kinetics.

3.3 Reaction Limitations

Although the concentration of aromatic compound showed some effect on the product ratio, the type of aromatic substrate itself ultimately determined both the yields and product ratios received from the reaction with low reactive substrates producing ring-opened products and highly reactive substrates forming the expected ring-intact products. Only toluene's product ratio could be effectively controlled with 1 equivalent producing exclusively ring-opened product **4b** while using 5 equivalents produced mostly ring-intact product **5b**. Being the least reactive aromatic substrate that effectively underwent acylation, benzene produced mostly rearranged product **4a** even at high concentrations. No reaction occurred with the less reactive chlorobenzene as expected. Due to steric interference from its methyl groups, p-xylene could only produce the ring-opened product **4d**. Highly reactive anisole, naphthalene, and thiophene all produced mostly their expected ring-intact products **5e**, **5f**, and **5g** with thiophene's being almost exclusively ring-intact **5g**. Dilution and higher temperatures were not effective enough in inducing rearrangement for anisole, the highly reactive substrate most affected by concentration fluctuations.

In terms of solvent, dichloromethane proved to be most ideal due to the exclusive synthesis of rearranged products **4** for low concentrations of benzene and alkylated benzene derivatives and the synthesis of mostly ring-intact products **5** for higher concentrations of toluene and the stronger aromatic substrates, along with the positive properties of dichloromethane itself such as its low boiling point and wider range of organic material it can dissolve. The only effective alternative solvent was

1,2-dichloroethane, most likely because it is a halogenated hydrocarbon like dichloromethane with similar physical properties and polarity. Using 1,2-dichloroethane as the solvent produced high yields of mostly ring-intact products **5b** and **5e** using 1 equivalent of toluene and anisole and could possibly be a good alternative for synthesizing ring-intact products of more reactive aromatic compounds. However, the reaction with benzene in that solvent produced a mixture of products **4a** and **5a** regardless of the amount of molar equivalents used, indicating that the aromatic substrate itself was the biggest factor in determining product yields and ratio. Using carbon disulfide as the solvent provided insufficient yields and highly polar solvents such as nitromethane, nitrobenzene, and acetonitrile resulted in decomposition of the starting material, producing no discernable products.

Despite being similar to aluminum chloride except slightly stronger as a Lewis acid, using aluminum bromide proved ineffective as an alternate catalyst. In the reactions performed, the chloride anion from the acyl chloride and the bromide anion from the catalyst competed with one another for the difluorocarbocation. Also, α-bromination reactions occurred for some of the products, possibly through bromine byproduct either formed during the reaction or present in the catalyst as impurity reacting with the enolate intermediate. Most importantly, no techniques effectively separated the bromide and chloride analogs from one another.

3.4 Comparison to Previous Synthesis of Aryl 2,2-Difluorocyclopropyl Ketones

The synthesis of aryl 2,2-difluorocyclopropyl ketones through Friedel-Crafts acylation using 2,2-difluorocyclopropanecarbonyl chloride **3** proved to be an effective alternative route when anisole, thiophene and higher equivalents of toluene were used as the substrate, notably with 1,2-dichloroethane as the solvent. However, the original

synthetic route using the reaction of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) with aryl vinyl ketones is still better for synthesizing aryl 2,2-difluorocyclopropyl ketones from relatively low reactive substrates such as benzene, p-xylene, and chlorobenzene.

CHAPTER 4
CONCLUSION

When various aromatic compounds underwent Friedel-Crafts acylation with 2,2-difluorocyclopropanecarbonyl chloride **3** using aluminum chloride as the catalyst and dichloromethane as solvent, the reaction produced novel aryl 3-chloro-3,3-difluoropropyl ketones **4** instead of or along with the expected aryl 2,2-difluorocyclopropyl ketones **5**. Both thermodynamic calculations and experimental evidence indicated that the ring-opening rearrangement mechanism occurred after the formation of the acylium cation but before the acylation step. The difluorocarbocation ketene intermediate that was formed reacted immediately with chloride anion and the ketene then underwent the acylation step. Thus, this rearrangement-acylation mechanism competed with the direct Friedel-Crafts acylation reaction.

However, the yield and product-ratio of Friedel-Crafts acylation with this particular acyl chloride depended mostly on the aromatic compound used, with benzene producing mostly if not exclusively mediocre yields of ring-opened product **4a**, chlorobenzene being too deactivated to react, the sterically-hindered p-xylene always producing high yields of ring-opened product **4d**, and highly reactive substrates such as anisole, thiophene, and naphthalene mostly producing their expected ring-intact products **5e**, **5f**, and **5g** respectively. The notable exception was toluene which produced high yields of exclusively rearranged product **4b** when 1 equivalent was used and mostly ring-intact product **5b** when 5 equivalents were used. Therefore, this reaction would be most synthetically useful for creating exclusively ring-opened products from 1 equivalent of relatively unreactive arenes or mostly ring-intact products from higher molar amounts of highly reactive arenes.

Using 1,2-dichloroethane as the solvent produced high yields of mostly ring-intact products for toluene and anisole and could potentially be used in synthesizing ring-intact product from more reactive aromatic substrates, but would not be synthetically practical for less reactive substrates such as benzene nor useful for making any ring-opened products. Otherwise, no other solvent or catalyst tested thus far proved practical for this particular reaction. Also, no alternate route to synthesize the rearranged product has been discovered yet.

CHAPTER 5
EXPERIMENTAL

5.1 General Information

Unless otherwise specified, proton, fluorine and carbon nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ at 300, 282, and 75.46 MHz, respectively, and chemical shifts are reported in parts per million (ppm) upfield relative to tetramethylsilane (TMS) for proton and carbon, and upfield of fluorotrichloromethane ($CFCl_3$) for fluorine. All percent yields were calculated from ^{19}F NMR integration of crude product using known amount of α,α,α-trifluorotoluene and are averages of three trials within a 3% range from the listed value.

5.2 Preparation of 2,2-Difluorocyclopropanecarbonyl Chloride (3)

5.2.1 n-Butyl 2,2-Difluorocyclopropanecarboxylate (1)

Under nitrogen at room temperature, sodium fluoride (0.654 g, 0.1 equiv.) was mixed in n-butyl acrylate (20 g, 1 equiv.). The glassware containing the contents was lowered into a 120°C oil bath and stirred for 5 minutes. Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) (50.8 g, 1.3 equiv.) was added dropwise via addition funnel into the mixture until all TFDA was consumed. The solution was allowed to stir overnight under nitrogen at 120°C to allow further reaction of n-butyl acrylate. The solution was then allowed to cool to room temperature. The crude product was then purified via distillation under reduced pressure to give n-butyl 2,2-difluorocyclopropanecarboxylate **1** as a transparent yellow liquid (19.5 g, 70%). ^1H NMR δ 0.90 (t, 3H), 1.60 (m, 2H), 1.70 (m, 1H), 2.00 (m, 1H), 2.38 (m, 1H), 4.12 (t, 2H); ^{19}F NMR δ -126.48 (dtd, 1F), -141.27 (ddd, 1F)

5.2.2 2,2-Difluorocyclopropanecarboxylic Acid (2)

Potassium hydroxide (18.4 g, 3 equiv.) was dissolved in 93 mL of deionized water. n-Butyl 2,2-difluorocyclopropanecarboxylate **1** (19.5 g, 1 equiv.) was added to the solution and the mixture was heated to reflux and stirred for 10 hours. The solution was cooled to room temperature and then underwent rotary evaporation under reduced pressure to remove water and butanol until crude solid was obtained. Deionized water was added to the crude solid dropwise until it dissolved. Concentrated hydrochloric acid was added dropwise until the solution obtained a pH of 2. The acidic solution then underwent extraction with diethyl ether. Afterwards, the diethyl ether layer was then dried with anhydrous $MgSO_4$, filtered, and removed via rotary evaporation to provide 2,2-difluorocyclopropanecarboxylic acid **2** as a pale yellow solid (9.4 g, 70%). The acid was used without further purification in the next step. ^{1}H NMR δ 1.83 (m, 1H), 2.10 (m, 1H), 2.46 (m, 1H) 11.00 (broad s, 1H); ^{19}F NMR δ -125.68 (dtd, 1F), -140.59 (ddd, 1F)

5.2.3 2,2-Difluorocyclopropanecarbonyl Chloride (3)

2,2-Difluorocyclopropanecarboxylic acid **2** (9.0 g, 1 equiv.) was dissolved in thionyl chloride (75 mL, 14 equiv.) under nitrogen. The solution was then heated to 60°C and stirred for 6 hours. The crude product underwent distillation at atmospheric pressure to provide 2,2-difluorocyclopropanecarbonyl chloride **3** as a transparent, colorless liquid (9.3 g, 90%). bp 106-107 $^{o}C^{23}$; ^{1}H NMR δ 1.98 (m, 1H), 2.27 (m, 1H), 3.02 (m, 1H); ^{19}F NMR δ -124.6 (dm, *J* = 149 Hz, 1F), -138.3 (dm, *J* = 149 Hz, 1F)

5.3 General Procedure for Friedel-Crafts Acylation Reactions with2,2-Difluorocyclopropanecarbonyl Chloride (3)

Under nitrogen, anhydrous aromatic compound was added via syringe to 20 mL of anhydrous dichloromethane at 0°C. 2,2-Difluorocyclopropanecarbonyl chloride **3**

(0.5 mL, 0.84 g, 1 equiv.) was added to the solution at 0°C. Aluminum chloride (0.956 g, 1.2 equiv.) was slowly added to the solution and the mixture was stirred under nitrogen for two hours at 0°C. Water was slowly added to the mixture until two distinct layers form and bubbling ceases. The entire solution was added to $NaHCO_3$ solution and the products were extracted using dichloromethane. The dichloromethane layer was then dried with anhydrous $MgSO_4$, filtered, and then removed via rotary evaporation under reduced pressure, leaving behind a liquid crude mixture of aromatic compound and product. Relative amounts of products were determined through ^{19}F NMR analysis of the crude mixture. The products were purified through column chromatography using silica gel and hexane as eluent.

5.3.1. 4-Chloro-1-phenyl-4,4-difluorobutan-1-one (4a)

Solid, mp 37-38 ^{o}C, 50% and 44% yield when using 1 and 5 equiv. of benzene respectively; ^{1}H NMR δ 2.79 (m, 2H), 3.30 (t, *J*= 7.2 Hz, 2H), 7.47 (m, 2H), 7.59 (m, 1H), 7.97 (d, *J* = 8.1 Hz, 2H); ^{19}F NMR δ -51.4 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 32.73 (t, J_{FC} = 2.6 Hz), 36.53 (J_{FC} = 25.2 Hz), 128.25, 128.99, 129.98 (J_{FC} = 291 Hz), 133.81, 136.38, 196.49; HRMS (EI) calcd for $C_{10}H_9OF_2Cl$, $[M+H]^+$, 218.0304, found 218.0305; Anal. Calcd for $C_{10}H_9OF_2Cl$: C, 54.94; H, 4.15. Found: C, 55.01; H, 4.08.

5.3.2. 4-Chloro-1-(4-methylphenyl)-4,4-difluorobutan-1-one (4b)

Solid, mp 61-63.5 ^{o}C, 72% and 7% yield when using 1 and 5 equiv. of toluene respectively; ^{1}H NMR δ 2.43 (s, 3H), 2.79 (m, 2H), 3.29 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H); ^{19}F NMR δ -51.4 (t, *J* = 14.7 Hz, 2F); ^{13}C NMR δ 21.91, 32.64 (t, J_{FC} = 3.0 Hz), 36.61 (t, J_{FC} = 24.7 Hz), 129.38, 129.67, 129.97 (t, J_{FC} = 291 Hz), 133.92, 144.74, 196.23; HRMS (EI) calcd for $C_{11}H_{11}OF_2Cl$, $[M+H]^+$, 233.0539,

found 233.0387. Anal. Calcd for $C_{11}H_{11}OF_2Cl$: C, 56.79; H, 4.77. Found: C, 56.88; H, 4.68.

5.3.3. 4-Chloro-1-(4-ethylphenyl)-4,4-difluorobutan-1-one (4c)

Liquid, bp 132 ^{o}C/10 mmHg, 78% yield when using 1 equiv. of ethylbenzene; ^{1}H NMR δ 1.27 (t, *J*= 7.8 Hz, 3H), 2.68-2.86 (m, 4H), 3.29 (t, *J*= 7.8 Hz, 2H), 7.30 (d, *J*= 8.1 Hz, 2H), 7.90 (d, *J*= 8.1 Hz, 1H); ^{19}F NMR δ -51.45 (t, *J*= 12.4 Hz, 2F); ^{13}C NMR δ 15.34, 29.14, 32.58, 36.54 (t, *J* = 25.0 Hz), 128.44, 129.94 (t, *J* = 291 Hz), 133.80, 134.06, 150.84, 196.18; HRMS (EI) calcd for $C_{12}H_{13}OF_2Cl$, $[M]^+$, 246.0623, found 246.0604. Anal. Calcd for $C_{12}H_{13}OF_2Cl$: C, 58.43; H, 5.31. Found: C, 58.08; H, 5.28.

5.3.4. 4-Chloro-1-(2,5-dimethylphenyl)-4,4-difluorobutan-1-one (4d)

Liquid, bp 91 ^{o}C/10 mmHg, 78% yield when using 1 equiv. of p-xylene; ^{1}H NMR δ 2.38 (s, 3H), 2.46 (s, 3H), 2.77 (m, 2H), 3.23 (t, *J*= 6.0 Hz, 2H), 7.20 (m, 2H), 7.48 (s, 1H); ^{19}F NMR δ -51.43 (t, *J*= 12.4 Hz, 2F); ^{13}C NMR δ 21.00, 21.14, 35.08 (t, *J* = 2.5 Hz), 36.60 (t, *J* = 25.4 Hz), 129.37, 129.90 (t, *J* = 292 Hz), 132.27, 132.80, 135.56, 135.66, 136.67, 199.96; HRMS (EI) calcd for $C_{12}H_{13}OF_2Cl$, $[M+H]^+$, 246.0623, found 246.0616; Anal. Calcd for $C_{12}H_{13}OF_2Cl$: C, 58.43; H, 5.31; Found: C, 58.16; H, 5.32.

5.3.5. 4-Chloro-1-(4-methoxyphenyl)-4,4-difluorobutan-1-one (4e)

Solid, mp 40.5-43.0 ^{o}C, 13% and 8% yield when using 1 and 5 equiv. of anisole respectively; ^{1}H NMR δ 2.77 (m, 2H), 3.25 (m, 2H), 3.88 (s, 3H), 6.95 (dm, *J* = 9 Hz, 2H), 7.96 (dm, *J* = 9 Hz, 2H); ^{19}F NMR δ -51.4 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 32.33, 36.64 (t, *J* = 18.5 Hz), 55.71, 114.10, 129.43, 130.03 (t, *J* = 291 Hz), 130.53, 164.07, 195.06; HRMS (EI) calcd for $C_{11}H_{11}O_2F_2Cl$, $[M+H]^+$, 249.0494, found 249.0473; Anal. Calcd for $C_{11}H_{11}O_2F_2Cl$: C, 53.13; H, 4.46. Found: C, 53.50; H, 4.33.

5.3.6. 4-Chloro-4,4-difluoro-1-(naphthalen-1-yl)butan-1-one (4f)

An 8% yield when using 1 equiv. of naphthalene; ^{1}H NMR δ 2.90 (m, 2H), 3.54 (m, 2H), 7.76 (m, 4H), 8.10 (m, 1H), 8.20 (m, 1H), 8.62 (d, 1H); ^{19}F NMR δ -51.305 (t, 2F)

5.3.7. 4-Chloro-4,4-difluoro-1-(thiophen-2-yl)butan-1-one (4g)

Liquid, 2% yield when using 1 equivalent of thiophene; ^{1}H NMR, δ 2.79 (m, 2H), 3.30 (m, 2H), 7.00 (t, *J* = 4.5 Hz, 1H), 7.16 (dd, *J* = 5.7 & 1.2 Hz, 1H), 7.21 (dd, *J* = 3.8 & 1.0 Hz, 1H); ^{19}F NMR, δ - 51.5 (t, *J* = 12.4 Hz)

5.3.8. (2,2-Difluorocyclopropyl)(phenyl)methanone (5a)[21]

Liquid, 11% yield when using 5 equiv. of benzene; ^{1}H NMR δ 1.80 (m, 1H), 2.42 (m, 1H), 3.38 (m, 1H), 7.46 (m, 2H), 7.60 (m, 1H), 8.02 (m, 2H); ^{19}F NMR δ -124.72 (dtd, 1F), -140.58 (ddd, 1F)

5.3.9 (2,2-Difluorocyclopropyl)(p-tolyl)methanone (5b)[21]

Solid, mp 37-38°C, 63% yield when using 5 equiv. of toluene; ^{1}H NMR δ 1.75 (m, 1H), 2.39 (m, 1H), 2.40 (s, 3H), 3.35 (m, 1H), 7.49 (m, 2H), 7.66 (m, 2H); ^{19}F NMR δ -124.70 (dtd, 1F), -140.70 (ddd, 1F)

5. 3.10. (2,2-Difluorocyclopropyl)(4-methoxyphenyl)methanone (5e)[21]

Liquid, 39% and 51% yields when using 1 and 5 equiv. of anisole respectively; ^{1}H NMR δ 1.68 (m, 1H), 2.30 (m, 1H), 3.36 (m, 1H), 3.72 (s, 3H), 6.96 (m, 2H), 7.54 (m, 2H); ^{19}F NMR δ -124.74 (ddt, 1F), -140.80 (ddd, 1F)

5.3.11. (2,2-Difluorocyclopropyl)(naphthalen-1-yl)methanone (5f)

Solid, mp 93-95°C, 37% and 34% yields when using 1 and 5 equiv. of naphthalene respectively; ^{1}H NMR δ 1.84 (m, 1H), 2.48 (m, 1H), 3.54 (m, 1H), 7.58 (m, 4H), 7.90 (m, 1H), 8.02 (m, 1H), 8.52 (d, 1H); ^{19}F NMR: -124.54 (dtd, 1F); -140.46 (ddd, 1F); ^{13}C NMR δ 16.0 (t, J = 9 Hz), 30.2 (t, J = 11 Hz) , 111.9, 124.0, 127.3, 128.1, 129.0, 129.1,

130.0, 130.7, 132.7, 134.6, 136.1, 190.6; Anal. Calcd for $C_{14}H_{10}OF_2$: C, 72.41; H, 4.34. Found: C, 72.26; H, 4.21

5.3.12. (2,2-Difluorocyclopropyl)(thiophen-2-yl)methanone (5g)

Solid, mp 47-49°C, 84% yield when using 1 equiv. of thiophene; ^{1}H NMR δ 1.81 (m, 1H), 2.40 (m, 1H), 3.30 (m, 1H), 7.19 (t, *J* = 4.5 Hz, 1H), 7.72 (dd, *J* = 5.7 & 1.2 Hz, 1H), 7.82 (dd, *J* = 3.8 & 1.0 Hz, 1H); ^{19}F NMR δ - 124.6 (dtd *J* = 149,12.4 & 6.2 Hz, 1F), -140.9 (ddd, *J* = 148, 21 & 4.2 Hz, 1F); ^{13}C NMR δ 16.2 (t, J = 9 Hz), 30.2 (t, J = 11 Hz), 111.7 (t, J = 289 Hz), 128.7, 133.2, 135.0, 144.4, 183.2; HRMS (EI) calcd for $C_8H_6OF_2S$ $[M + H]^+$ 189.0180, found 189.0190. Anal. Calcd for $C_8H_6OF_2S$: C, 51.06; H, 3.21. Found: C, 50.94; H, 3.11

5.3.13. 4-Bromo-4,4-difluoro-1-phenylbutan-1-one (6a)

An 11% yield when using 1.2 equiv. aluminum bromide and 1 equiv. of benzene, 1 trial only; ^{1}H NMR δ 3.34 (m, 2H), 3.50 (m, 2H), 7.52 (m, 2 H), 7.80 (m, 1H), 8.03 (dd, 2H); ^{19}F NMR δ -44.398 (t, 2F)

5.3.14. 4-Bromo-4,4-difluoro-1-p-tolylbutan-1-one (6b)

An 18% yield when using 1.2 equiv. aluminum bromide and 1 equiv. of toluene, 1 trial only; ^{1}H NMR δ 2.42 (s, 3H), 3.42 (m, 2H), 3.48 (t, 2H), 7.30 (dd, 2H), 7.92 (dd, 2H); ^{19}F NMR δ -44.339 (t, 2F)

5.3.15. 2-Bromo-4-chloro-4,4-difluoro-1-phenylbutan-1-one (7a)

A 6% yield when using 1.2 equiv. aluminum bromide and 1 equiv. of benzene, 1 trail only; ^{1}H NMR δ 3.72 (qd, 1H), 4.60 (qd, 1H), 5.43 (qt, 1H), 7.54 (dd, 2 H), 7.63 (dd, 1H), 8.07 (dd, 2H); ^{19}F NMR δ -50.408 (qt, 2F)

5.3.16. 2-Bromo-4-chloro-4,4-difluoro-1-p-tolylbutan-1-one (7b)

A 3% yield when using 1.2 equiv. aluminum bromide and 1 equiv. of toluene, 1 trial only; ^{1}H NMR δ 2.51 (s, 3H), 3.10 (m, 1H), 3.65 (m, 1H), 5.37 (m, 1H), 7.32 (d, 1H), 7.93 (d, 2H); ^{19}F NMR δ -50.437 (qt, 2F)

5.3.17. 2,4-Dibromo-4,4-difluoro-1-phenylbutan-1-one (8a)

A 9% yield when using 1.2 equiv. aluminum bromide and 1 equiv. of benzene, 1 trial only; ^{1}H NMR δ 3.15 (m, 1H), 3.74 (m, 1H), 5.39 (m, 1H), 7.52 (dd, 2 H), 7.66 (dd, 1H), 8.03 (dd, 2H); ^{19}F NMR δ -44.100 (qt, 2F)

5.3.18. 2,4-Dibromo-4,4-difluoro-1-p-tolylbutan-1-one (8b)

A 14% yield when using 1.2 equiv. aluminum bromide and 1 equiv. of toluene, 1 trial only; ^{1}H NMR δ 2.44 (s, 3H), 3.17 (m, 1H), 3.76 (m, 1H), 5.37 (m, 1H), 7.32 (d, 1H), 7.93 (d, 2H); ^{19}F NMR δ -44.101 (qt, 2F)

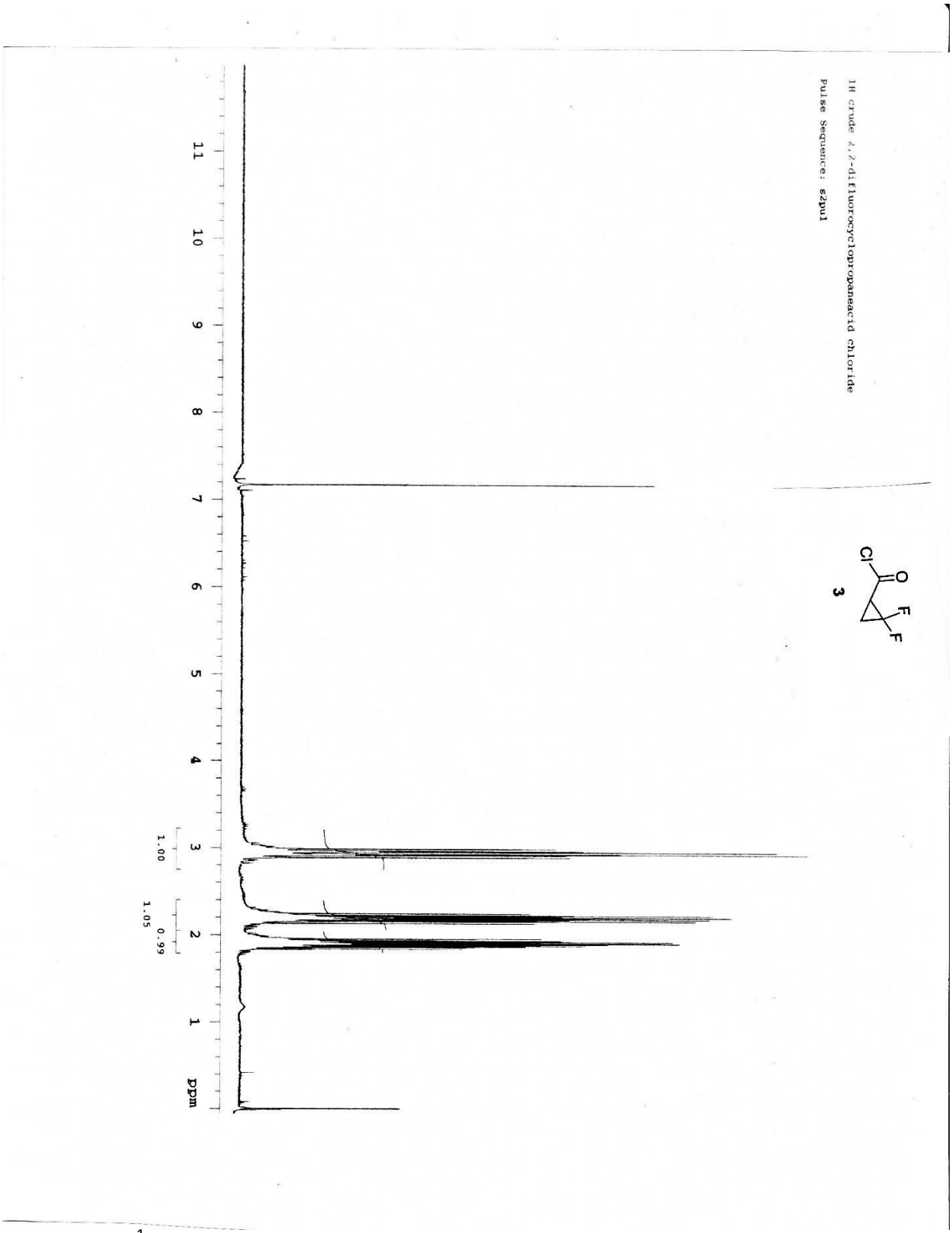


Figure A-1. ^{1}H NMR of 2,2-difluorocyclopropanecarbonyl Chloride **3**

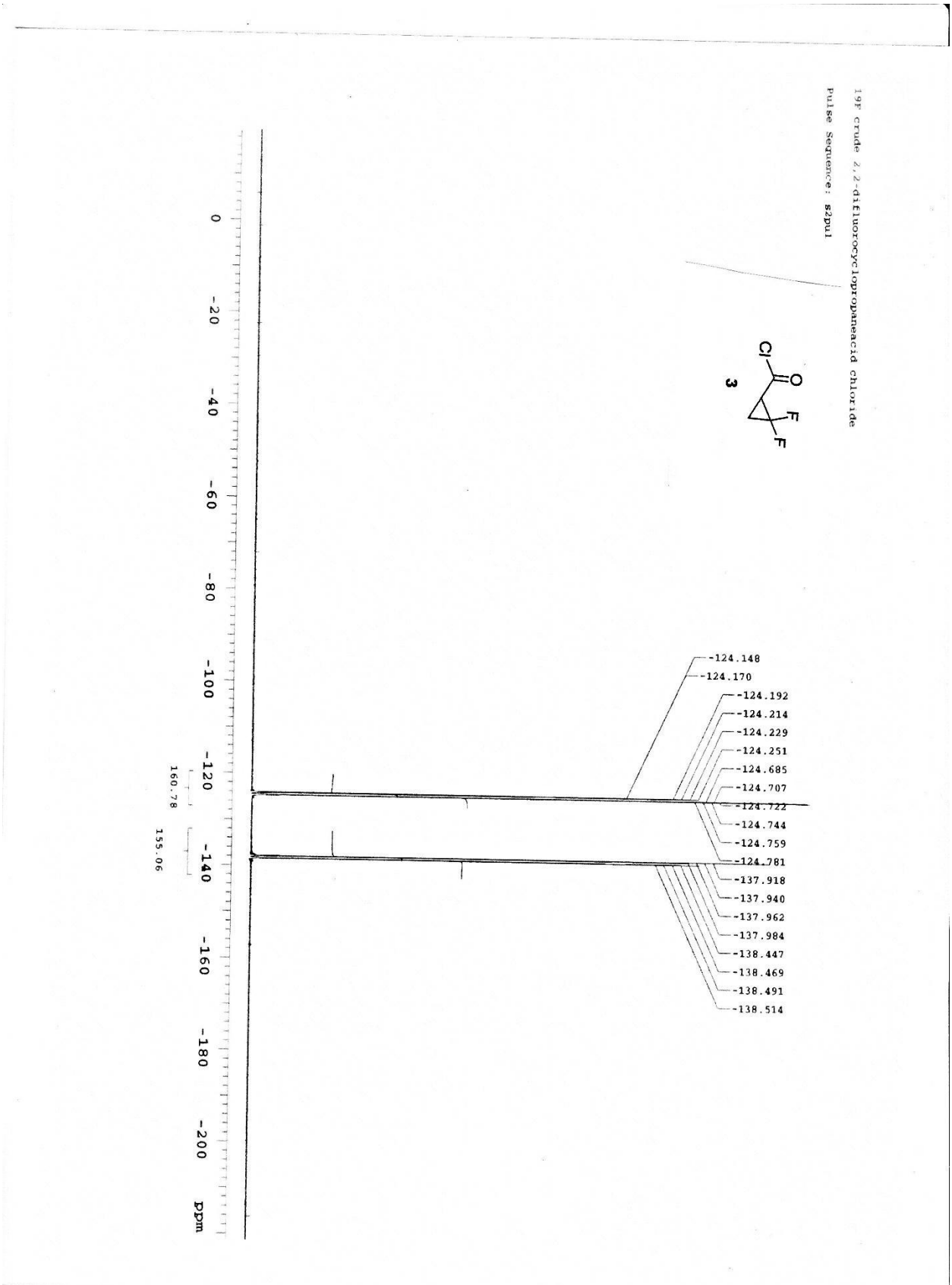


Figure A-2. ^{19}F NMR of 2,2-difluorocyclopropanecarbonyl Chloride **3**

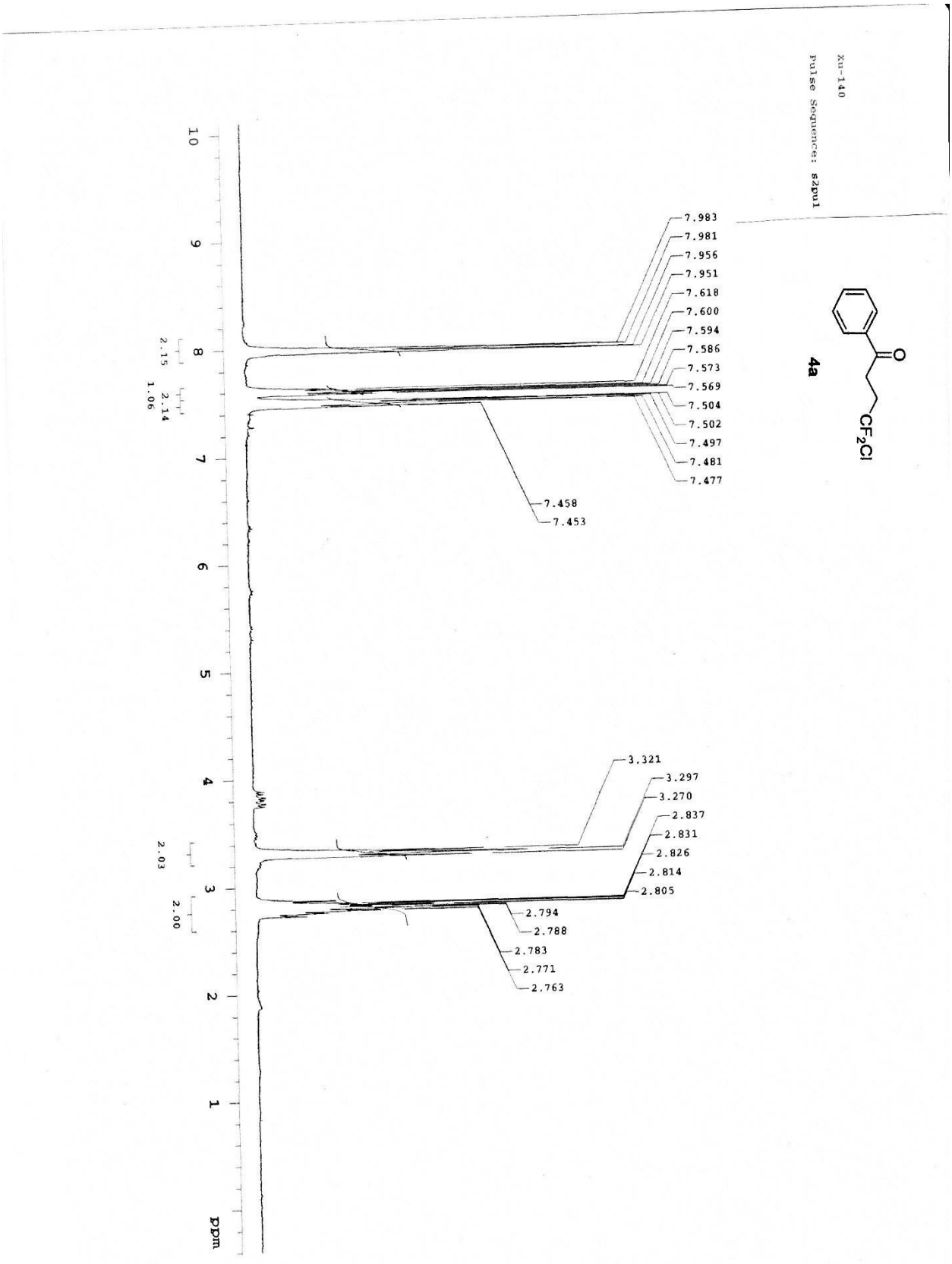


Figure A-3. ^{1}H NMR of 4-chloro-1-phenyl-4,4-difluorobutan-1-one **4a**

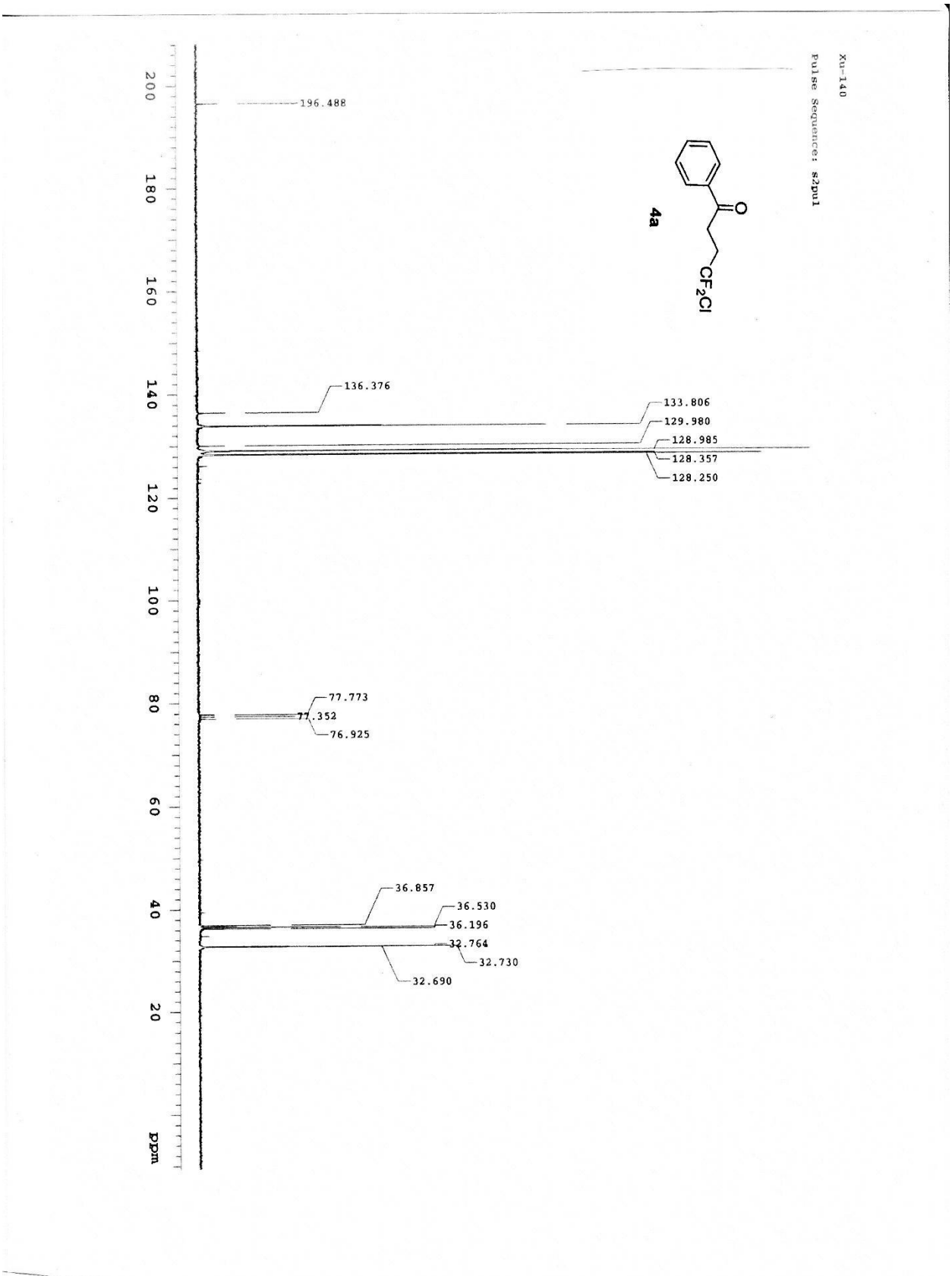
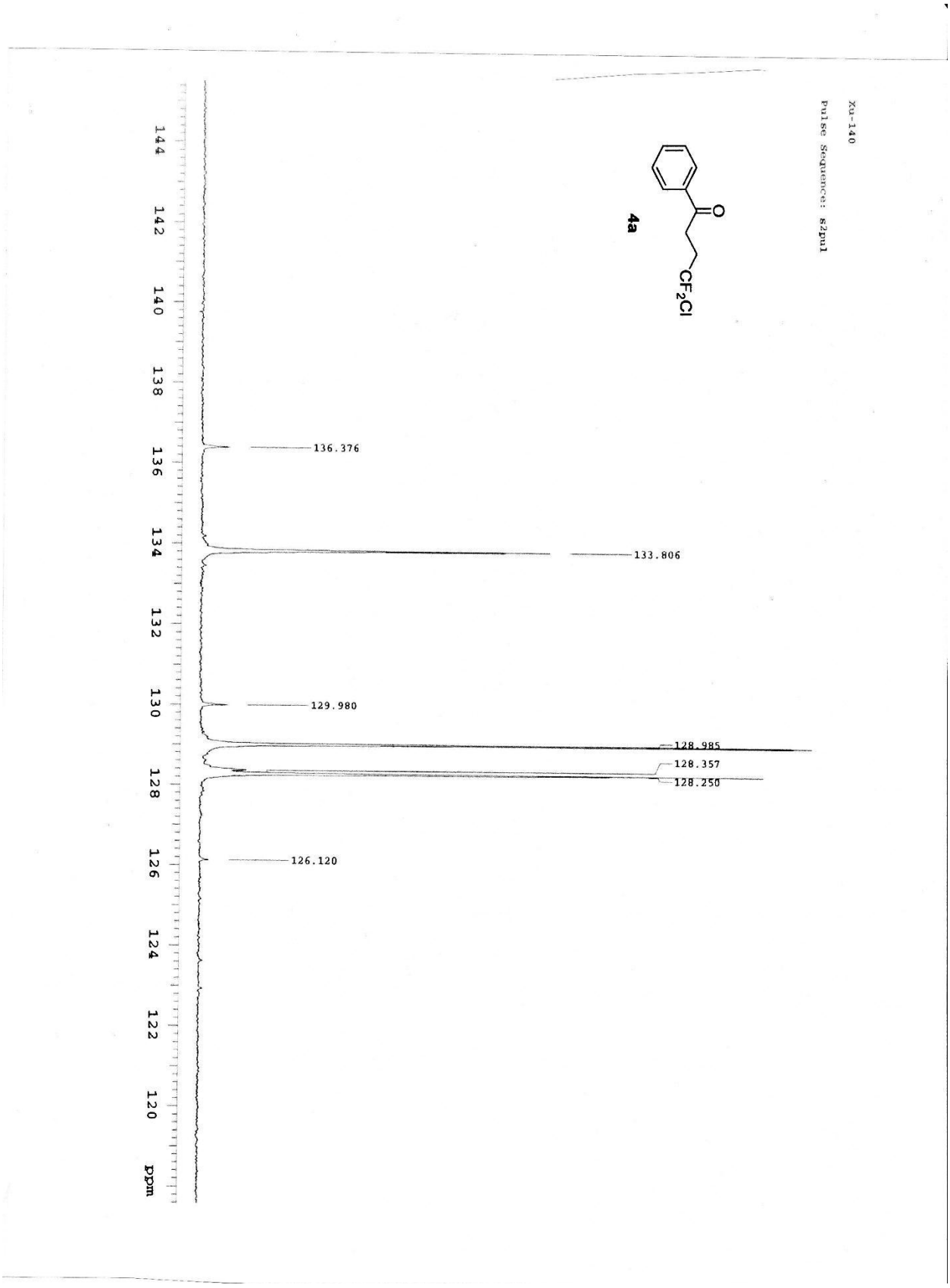


Figure A-4. ^{13}C NMR of 4-chloro-1-phenyl-4,4-difluorobutan-1-one **4a**



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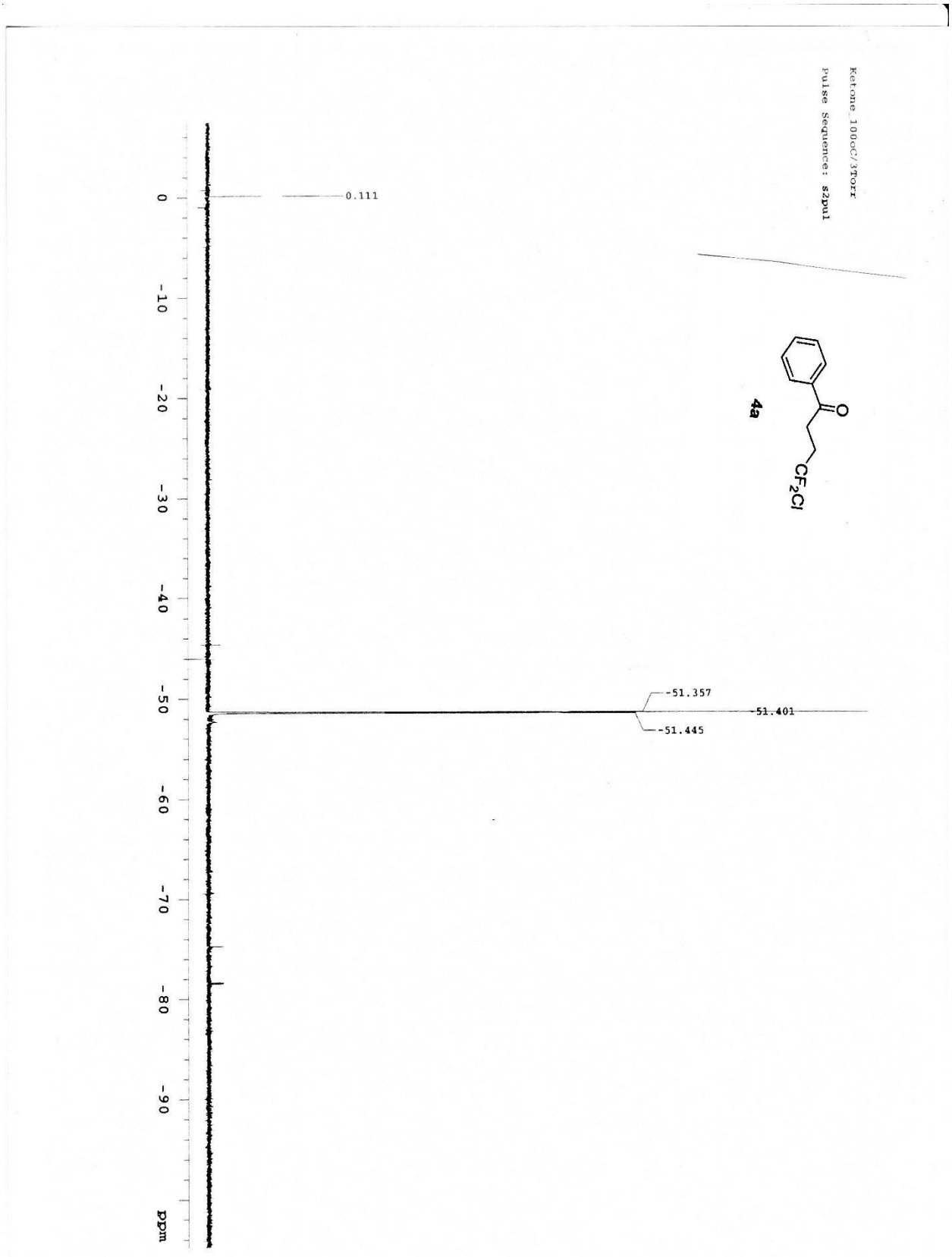


Figure A-5. ^{19}F NMR of 4-chloro-1-phenyl-4,4-difluorobutan-1-one **4a**

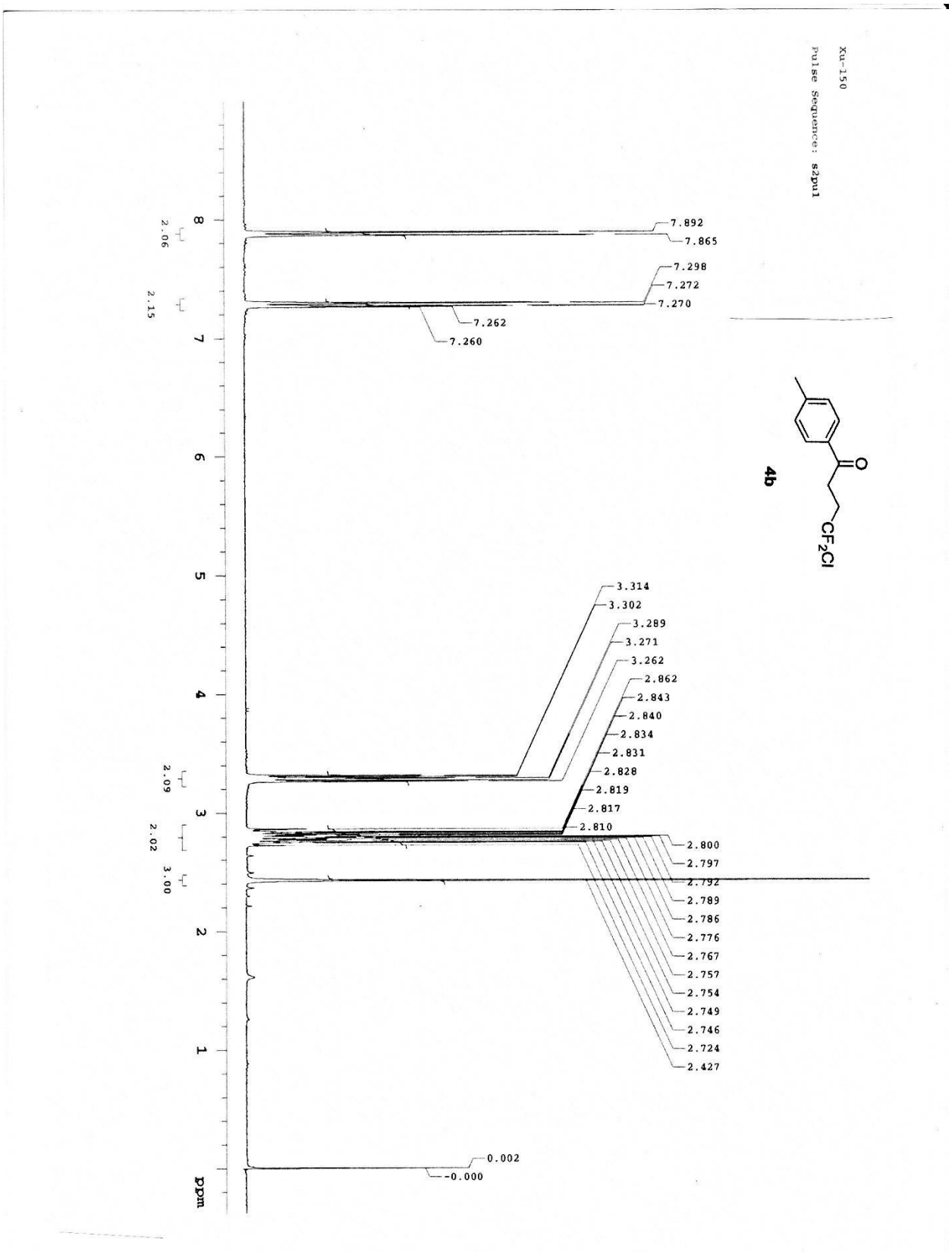


Figure A-6. ^{1}H NMR of 4-chloro-1-(4-methylphenyl)-4,4-difluorobutan-1-one **4b**

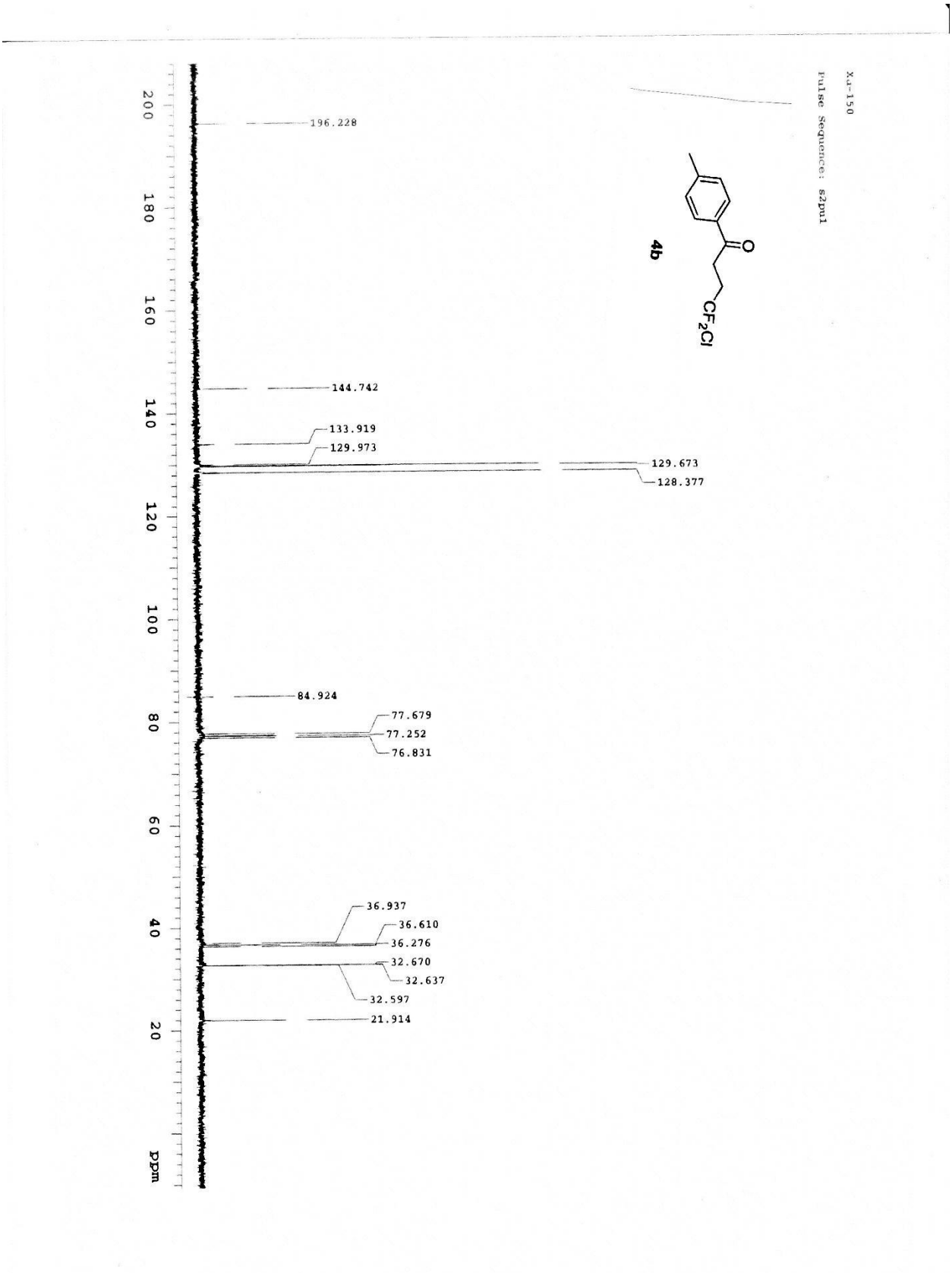


Figure A-7. ^{13}C NMR of 4-chloro-1-(4-methylphenyl)-4,4-difluorobutan-1-one **4b**

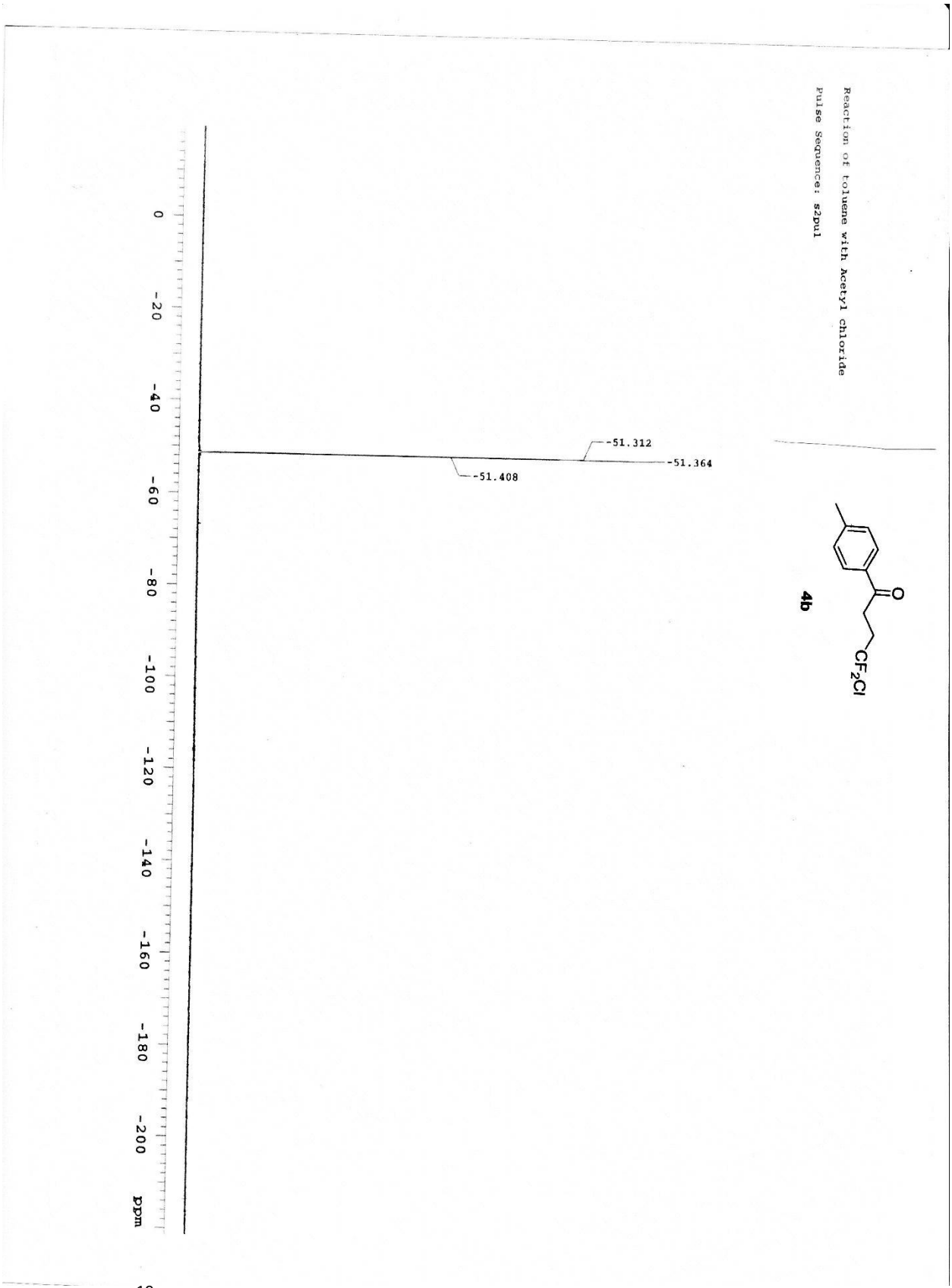


Figure A-8. ^{19}F NMR of 4-chloro-1-(4-methylphenyl)-4,4-difluorobutan-1-one **4b**

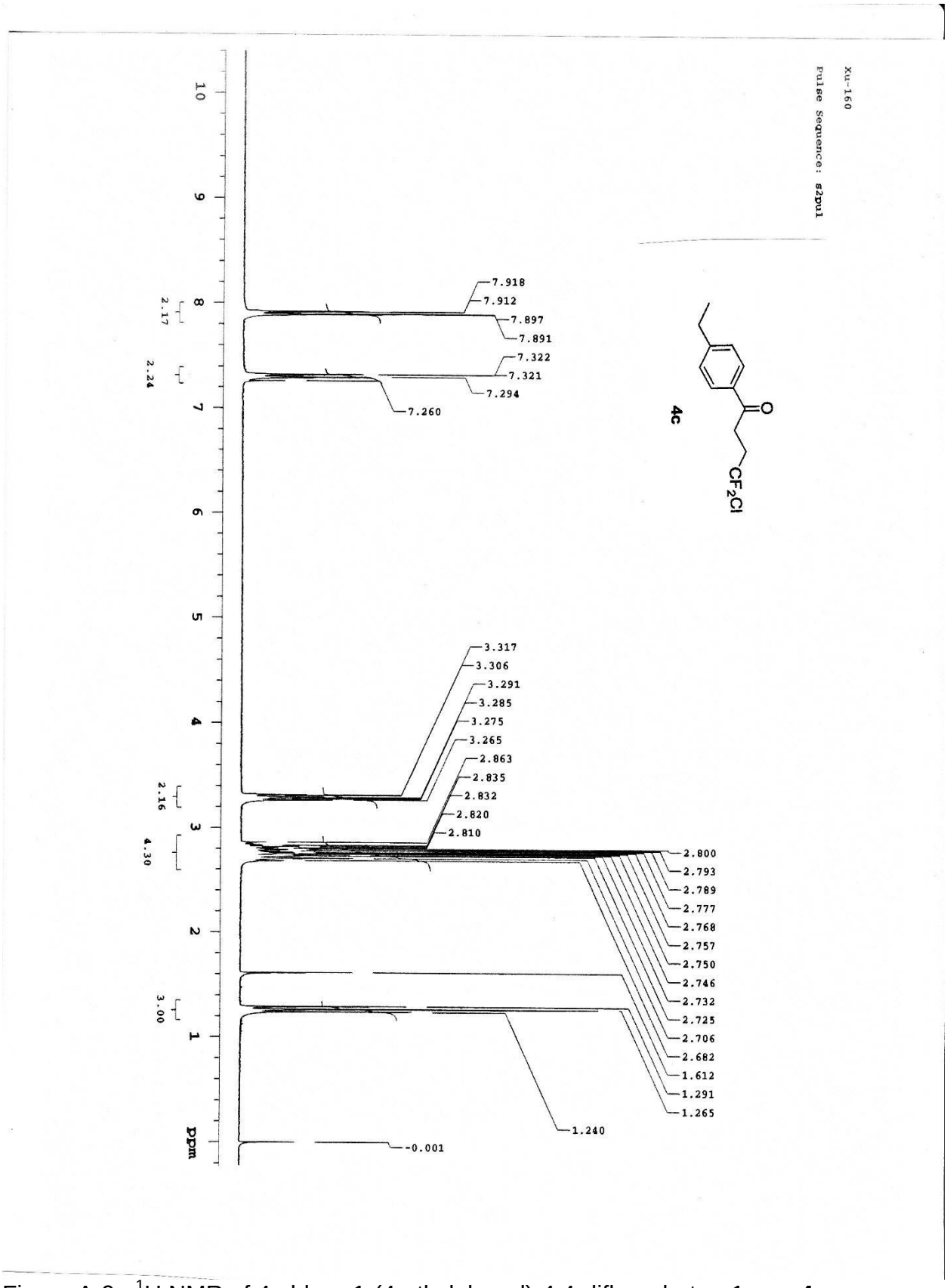


Figure A-9. ^{1}H NMR of 4-chloro-1-(4-ethylphenyl)-4,4-difluorobutan-1-one **4c**

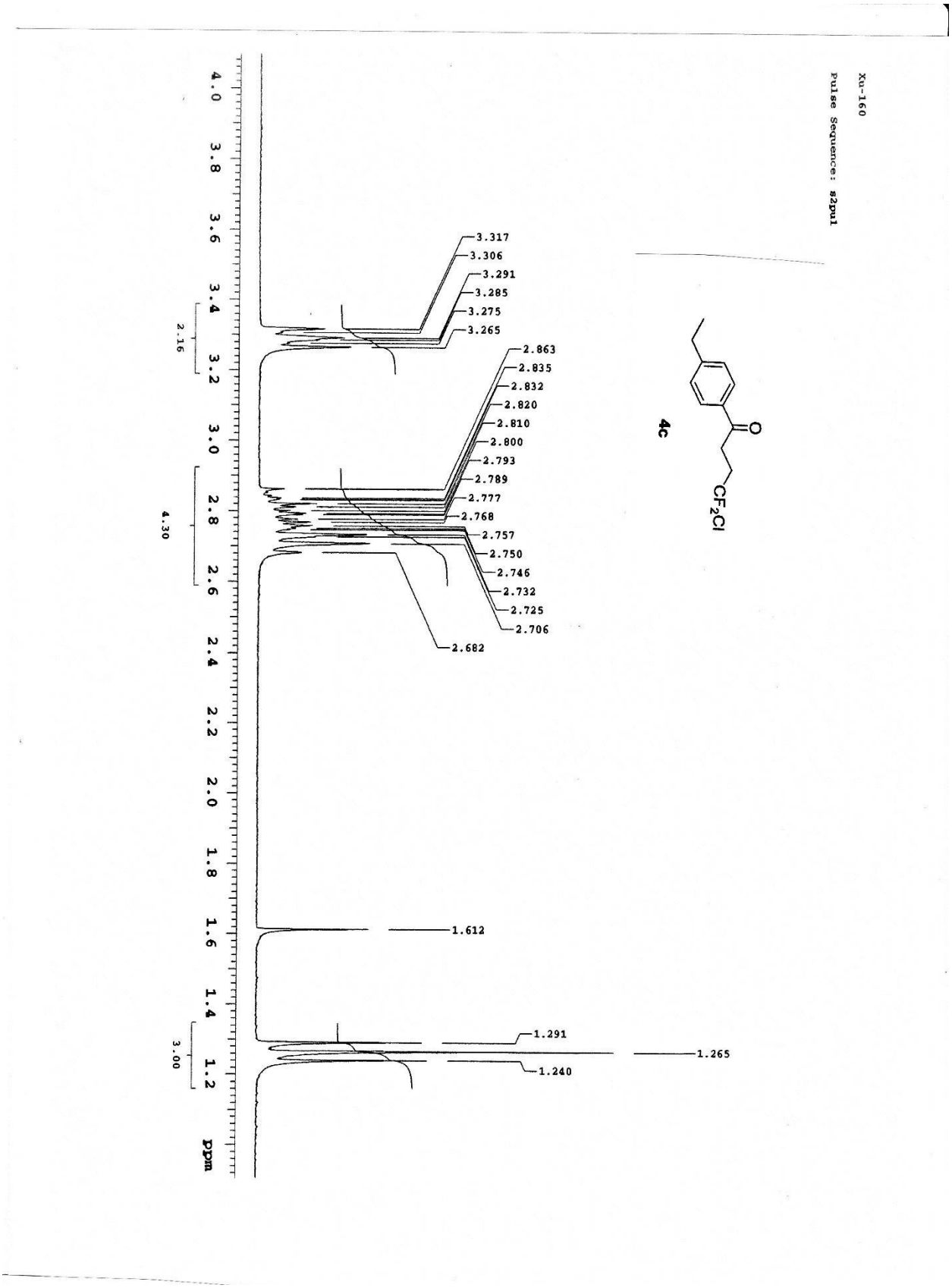


Figure A-9. Continued

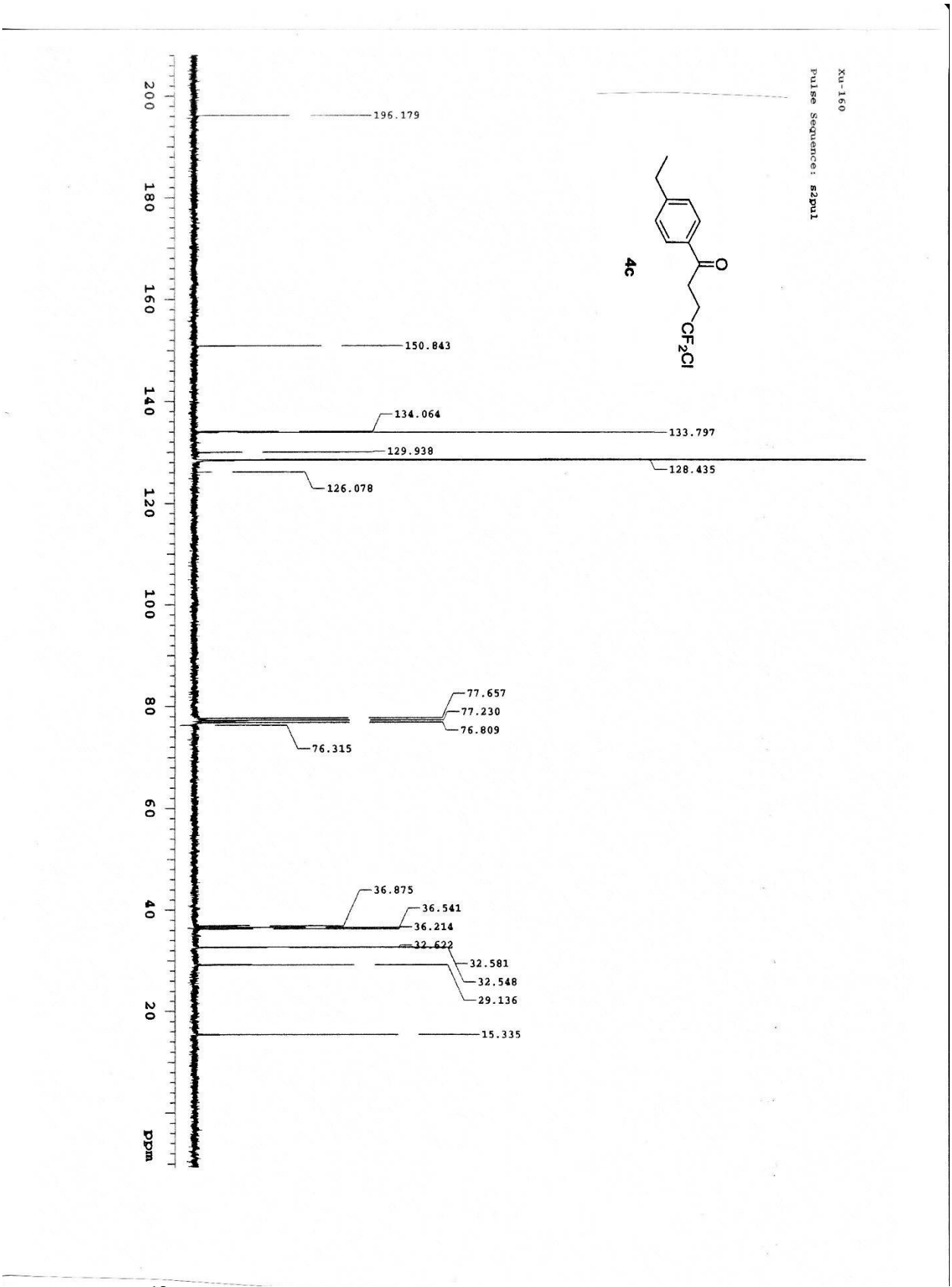
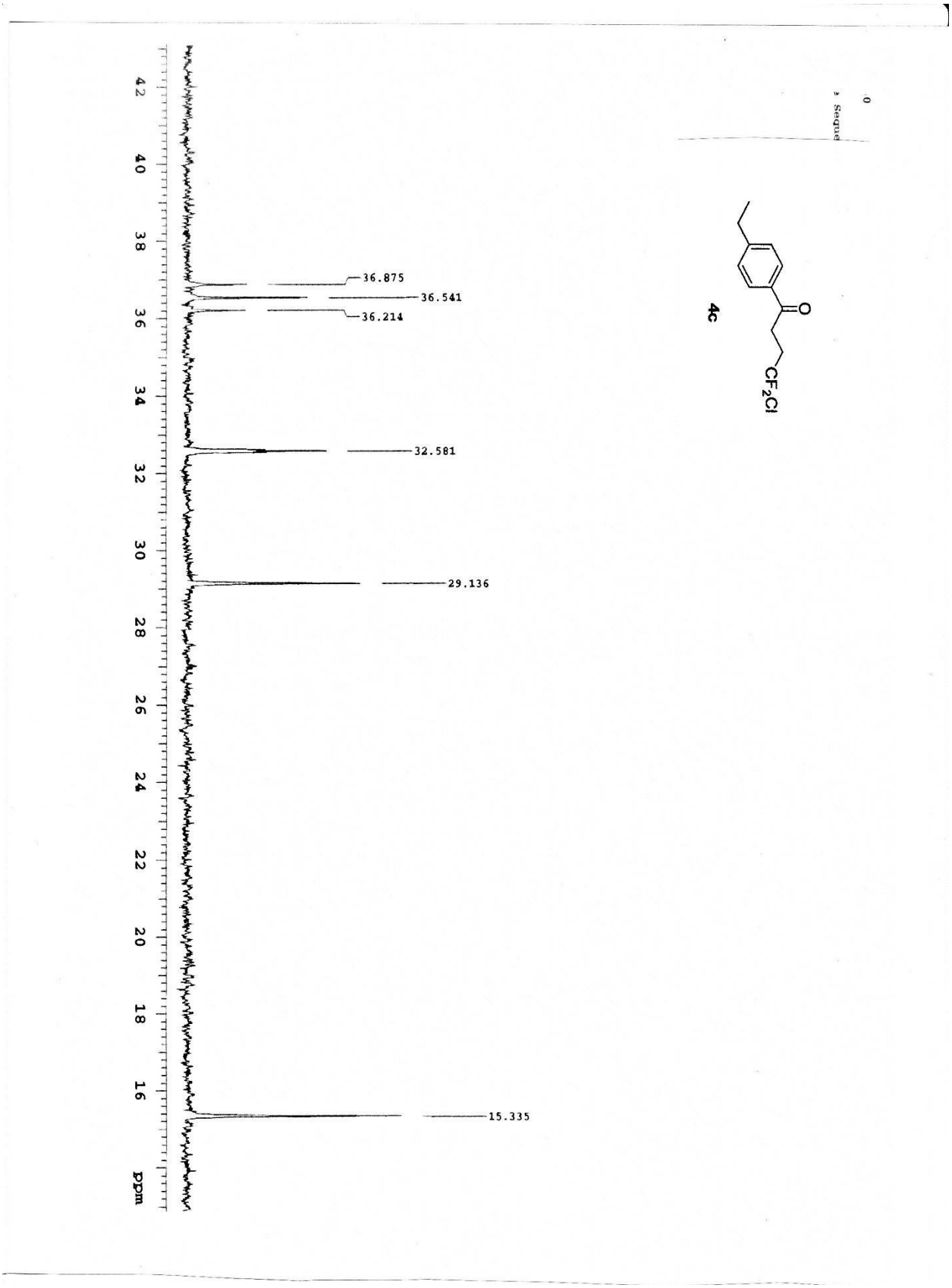


Figure A-10. ^{13}C NMR of 4-chloro-1-(4-ethylphenyl)-4,4-difluorobutan-1-one **4c**



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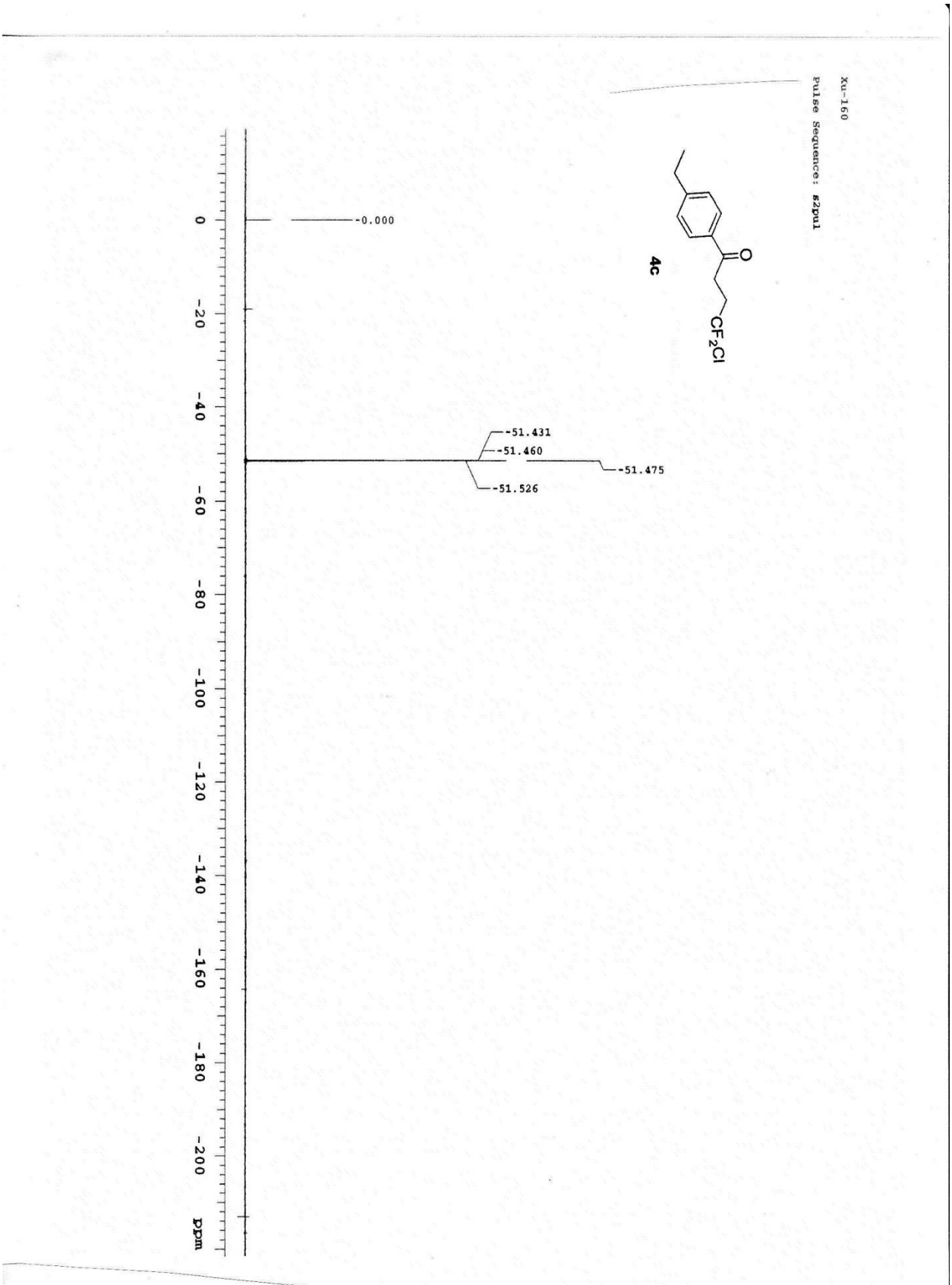


Figure A-11. ^{19}F NMR of 4-chloro-1-(4-ethylphenyl)-4,4-difluorobutan-1-one **4c**

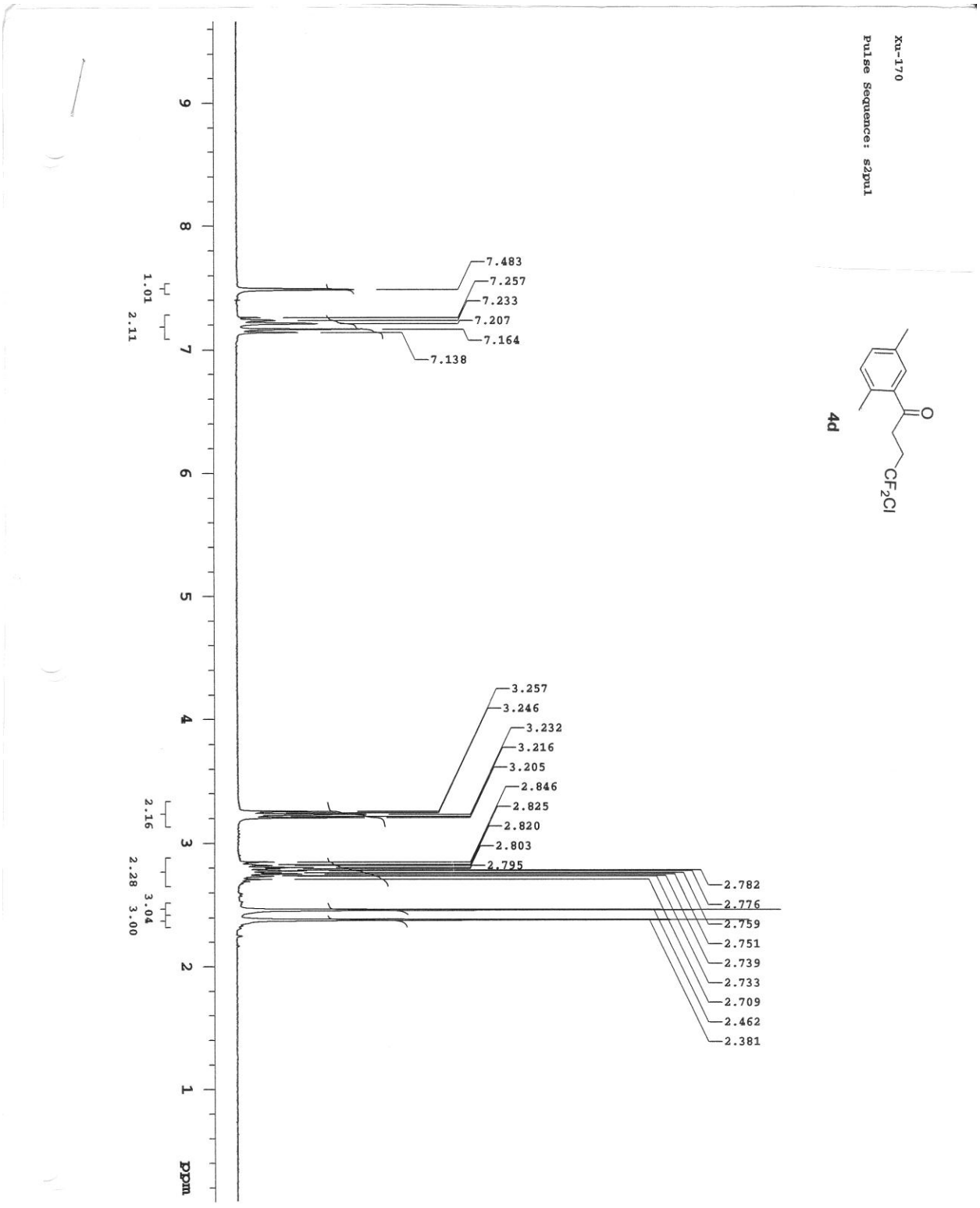


Figure A-12. ^{1}H NMR of 4-chloro-1-(2,5-dimethylphenyl)-4,4-difluorobutan-1-one **4d**

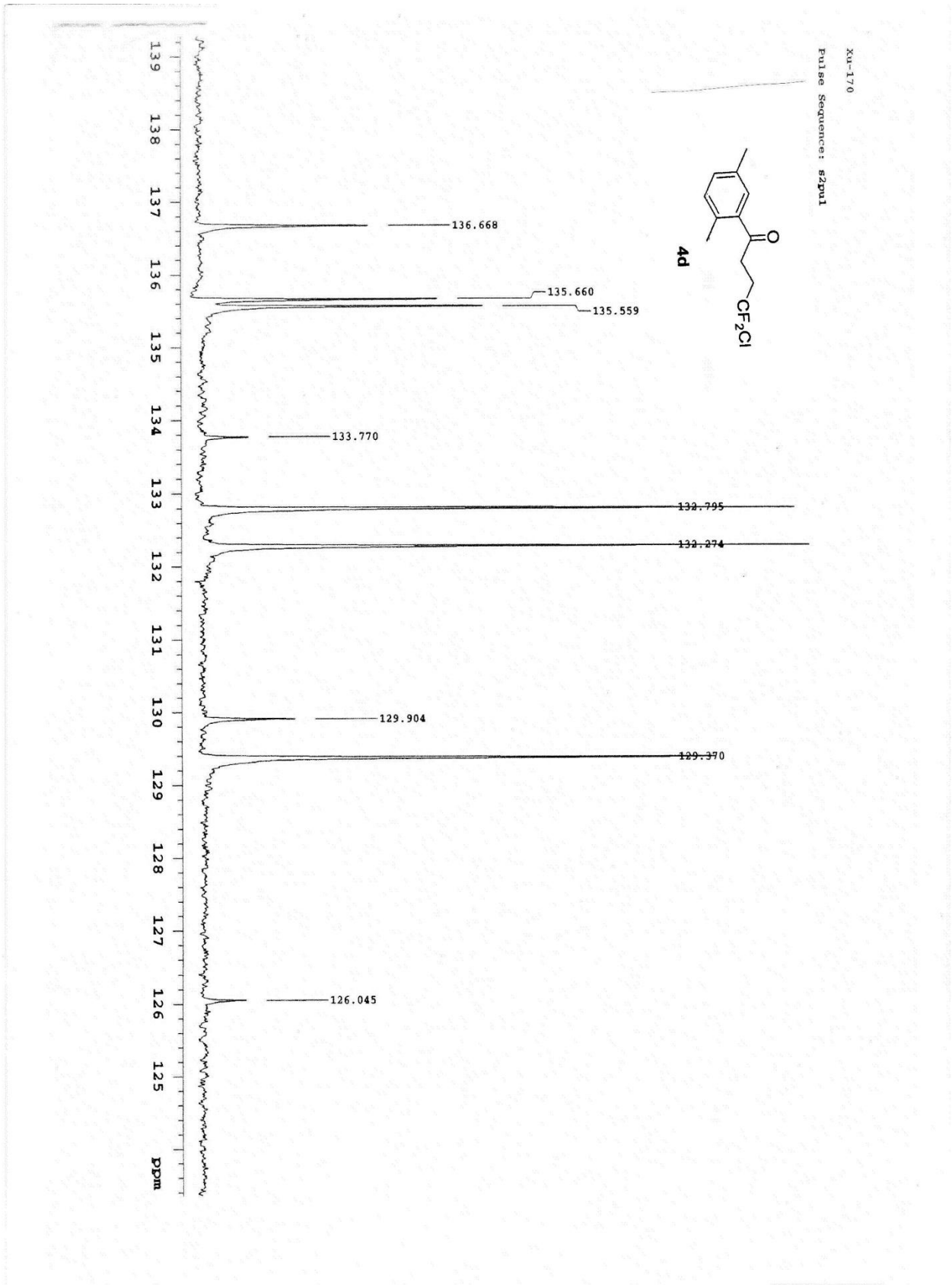
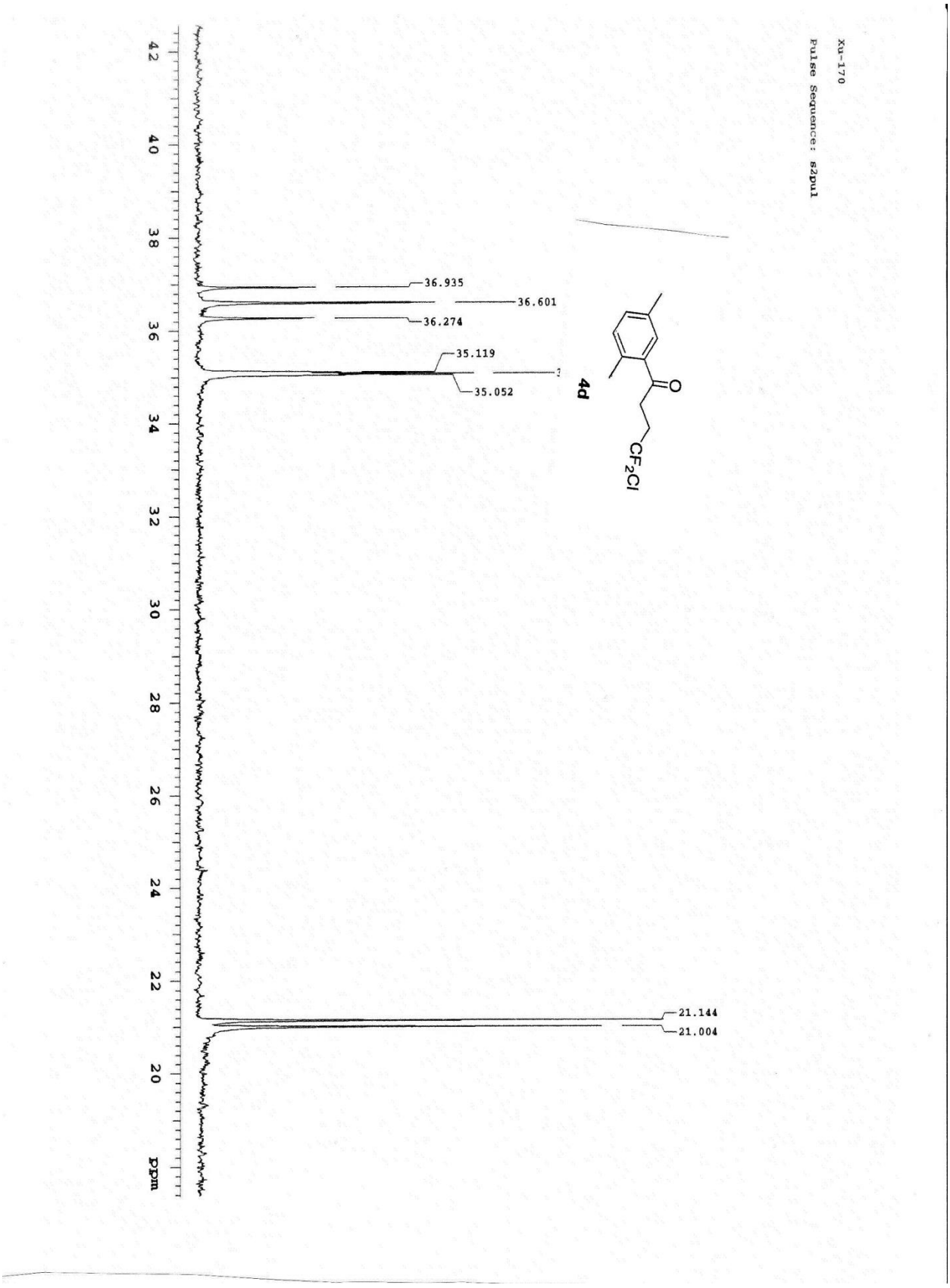


Figure A-13. ^{13}C NMR of 4-chloro-1-(2,5-dimethylphenyl)-4,4-difluorobutan-1-one **4d**



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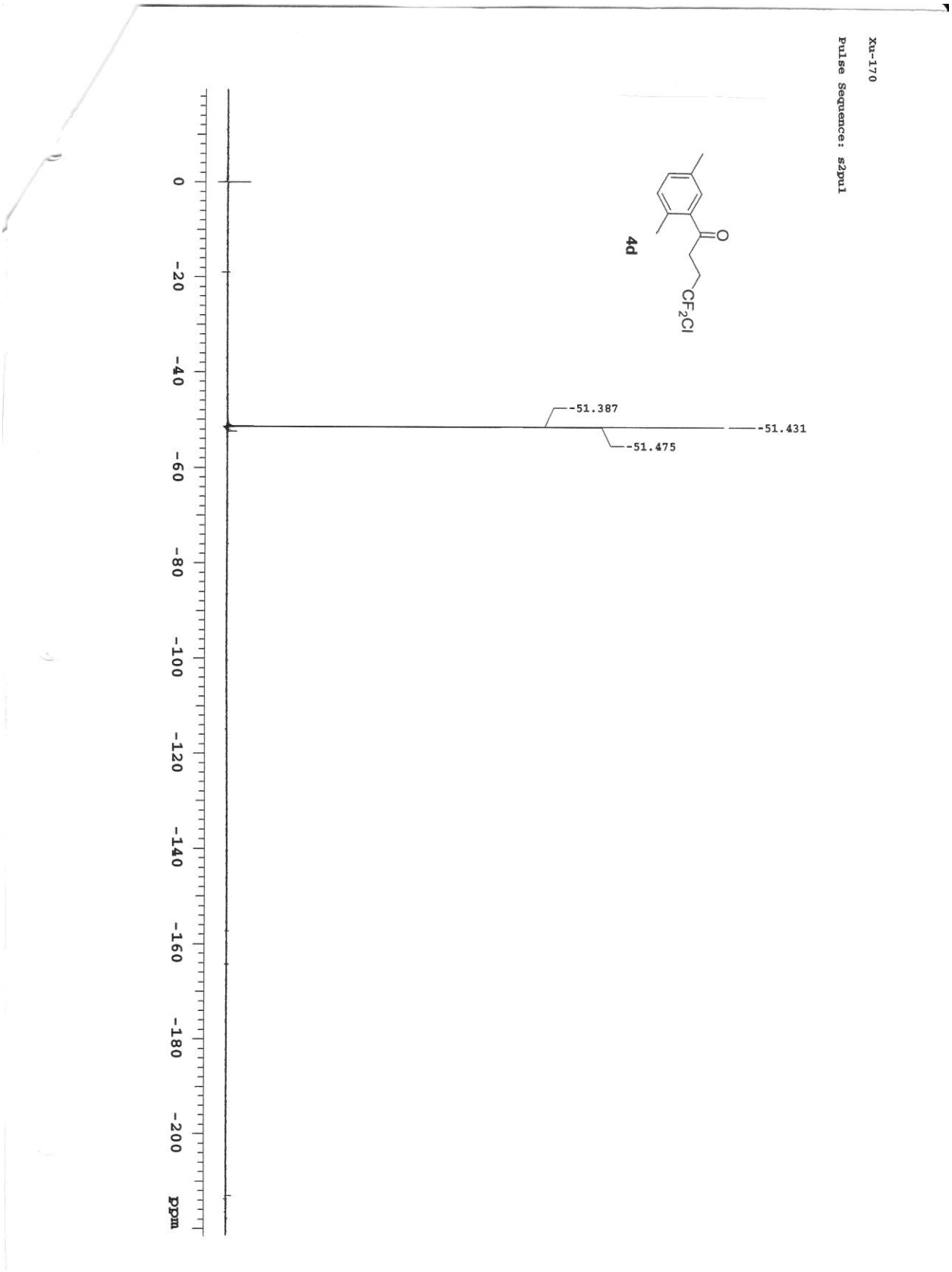


Figure A-14. ^{19}F NMR of 4-chloro-1-(2,5-dimethylphenyl)-4,4-difluorobutan-1-one **4d**

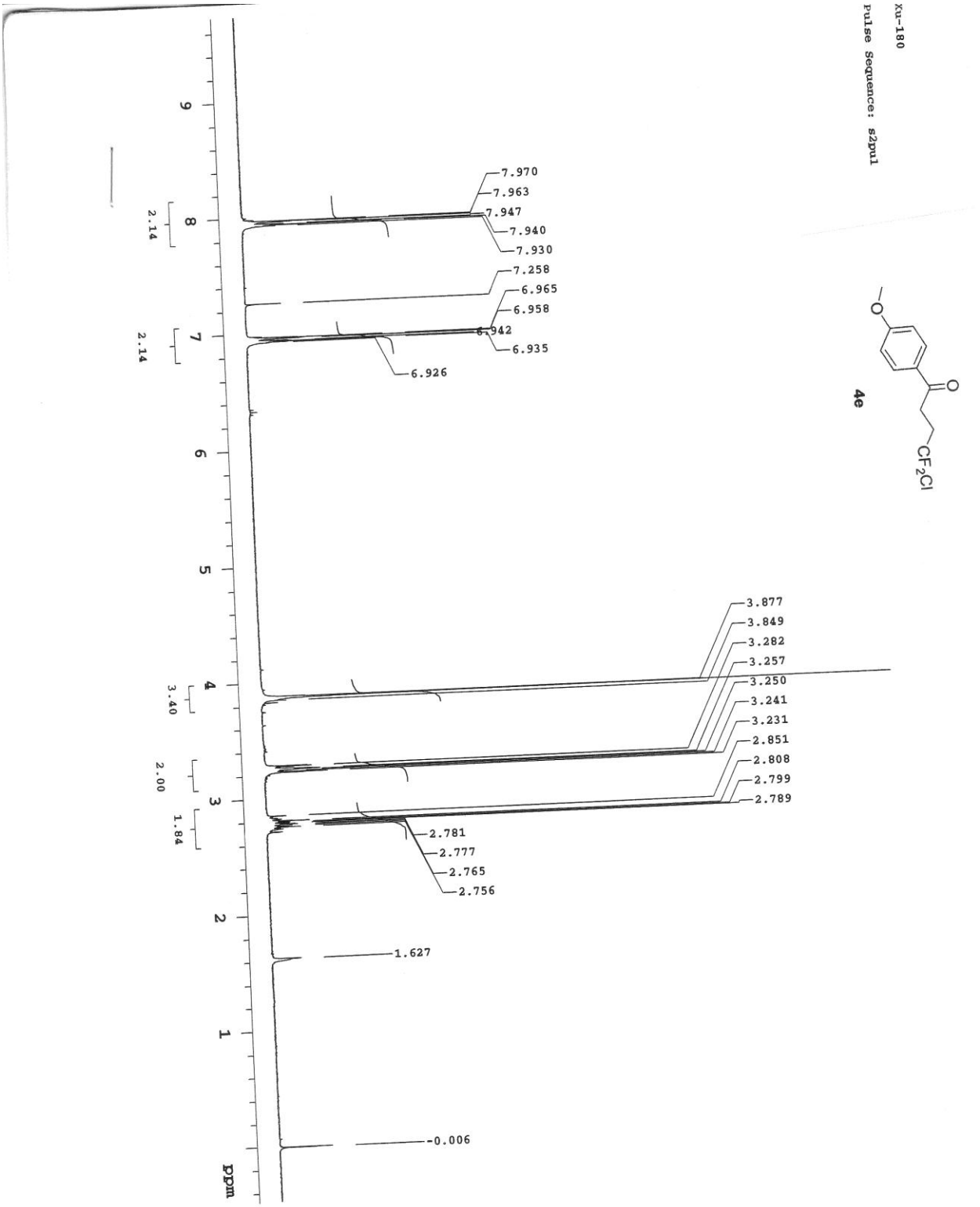


Figure A-15. ^{1}H NMR of 4-chloro-1-(4-methoxyphenyl)-4,4-difluorobutan-1-one **4e**

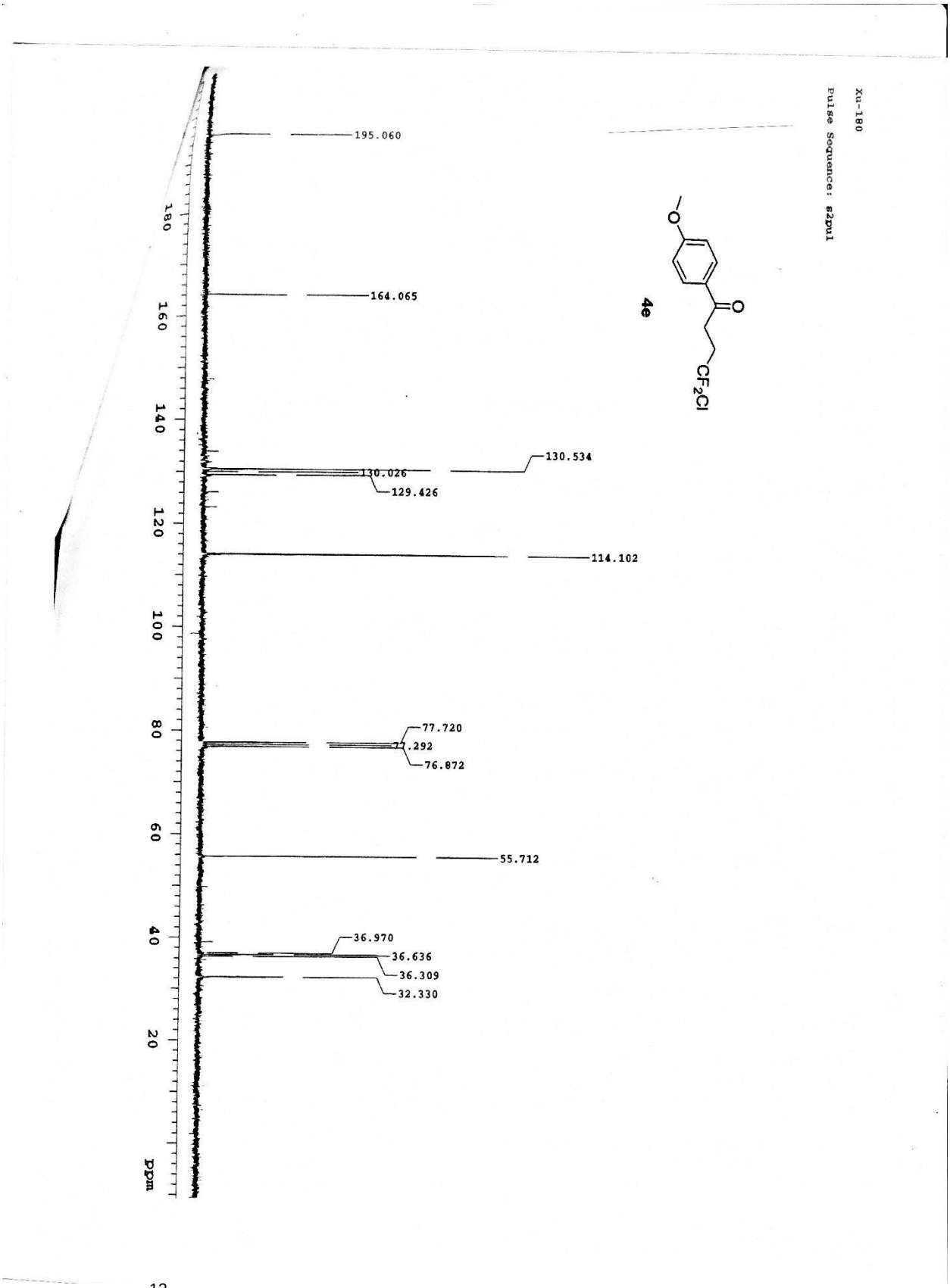
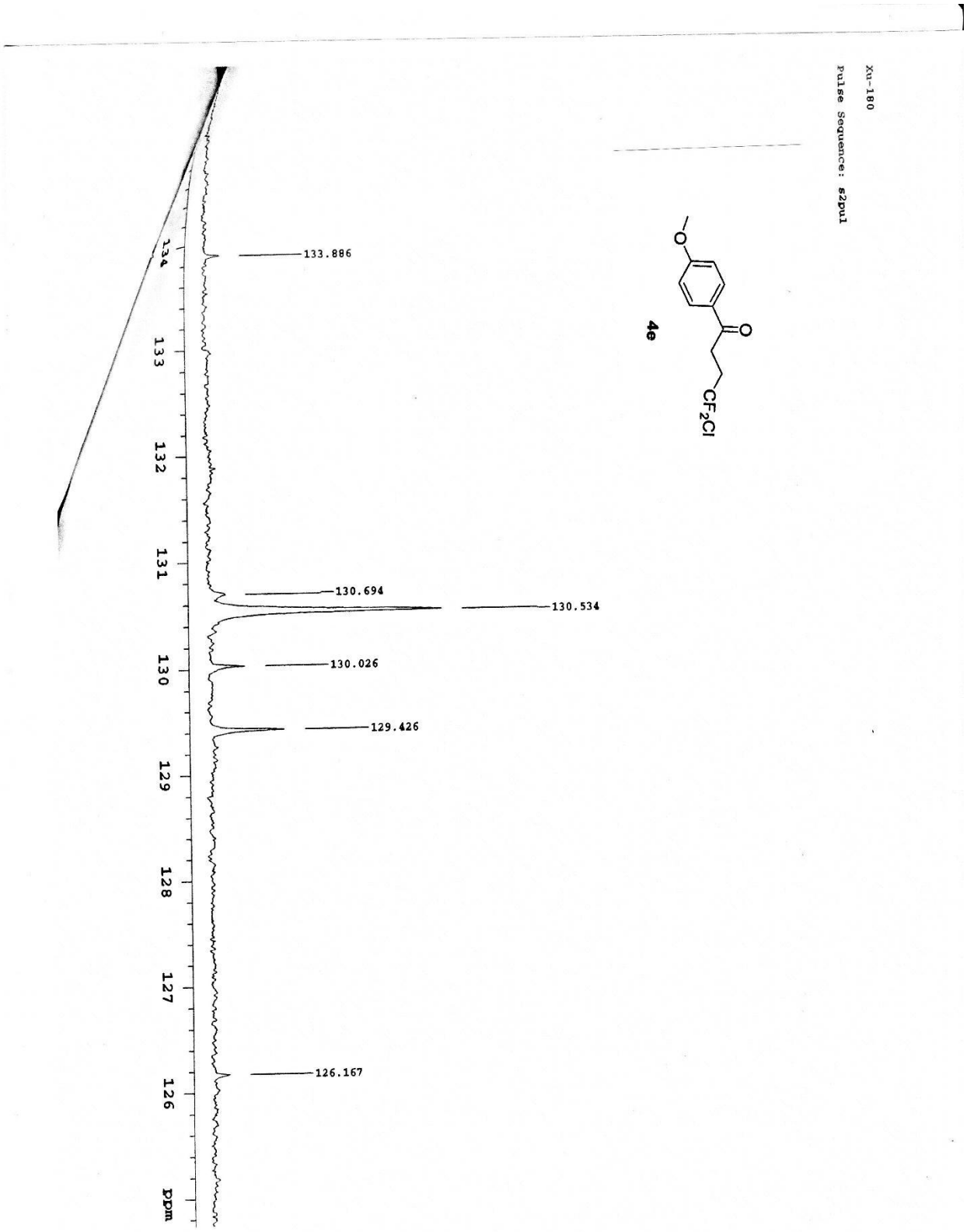


Figure A-16. ^{13}C NMR of 4-chloro-1-(4-methoxyphenyl)-4,4-difluorobutan-1-one **4e**



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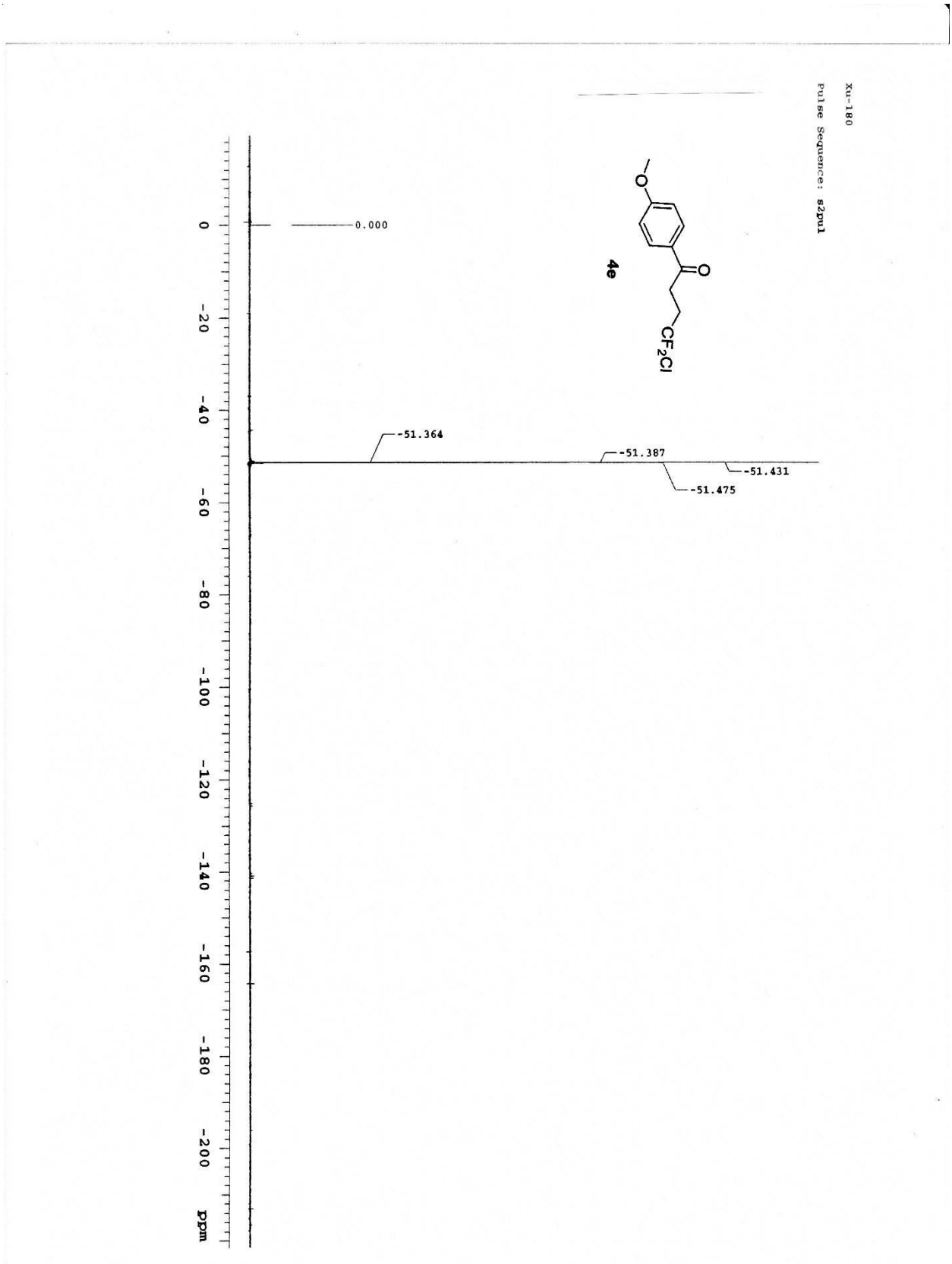

Figure A-17. ^{19}F NMR of 4-chloro-1-(4-methoxyphenyl)-4,4-difluorobutan-1-one **4e**

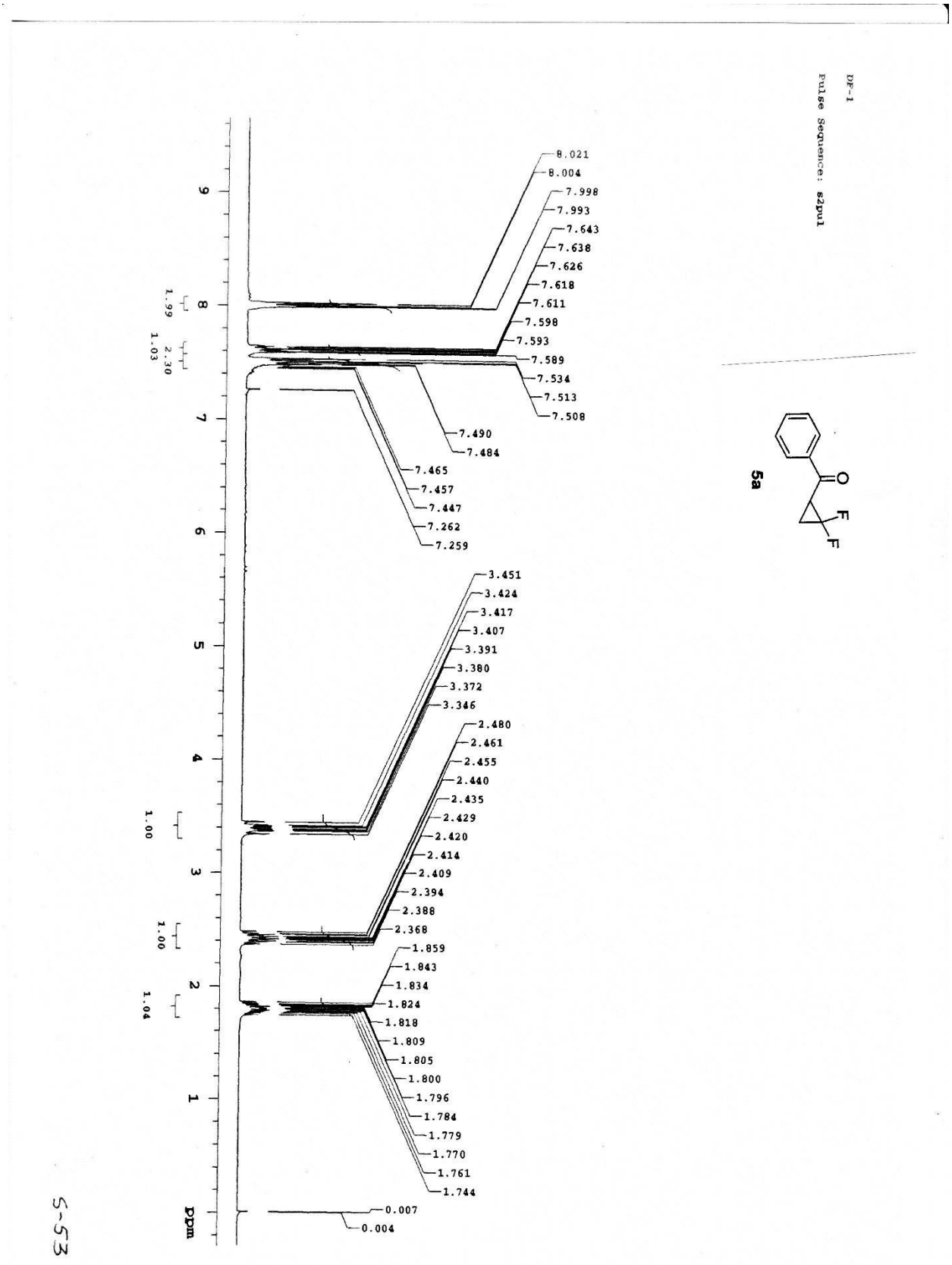

Figure A-18. ^{1}H NMR of (2,2-difluorocyclopropyl)(phenyl)methanone **5a**

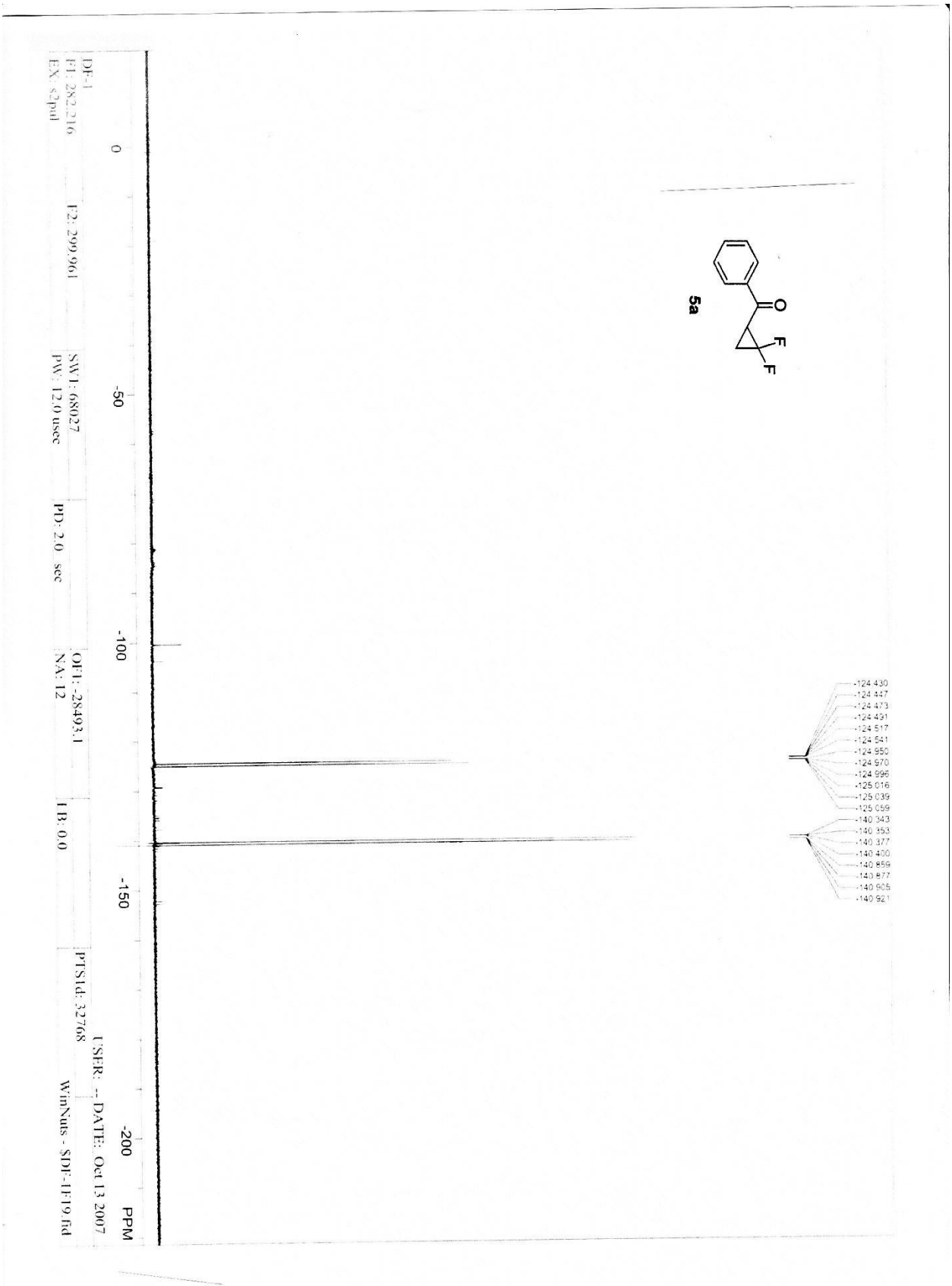

Figure A-19. ^{19}F NMR of (2,2-difluorocyclopropyl)(phenyl)methanone **5a**

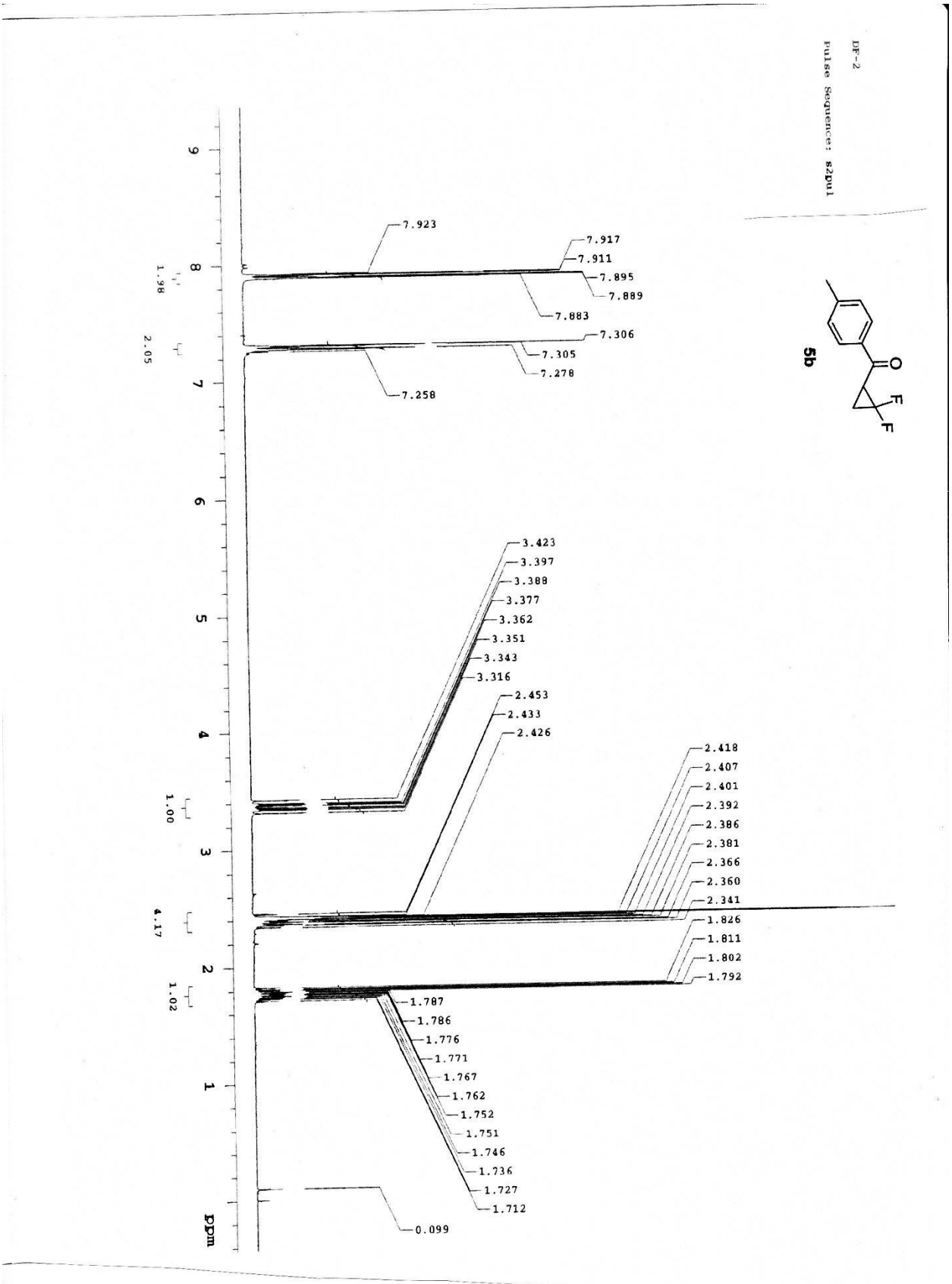

Figure A-20. ^{1}H NMR of (2,2-difluorocyclopropyl)(p-tolyl)methanone **5b**

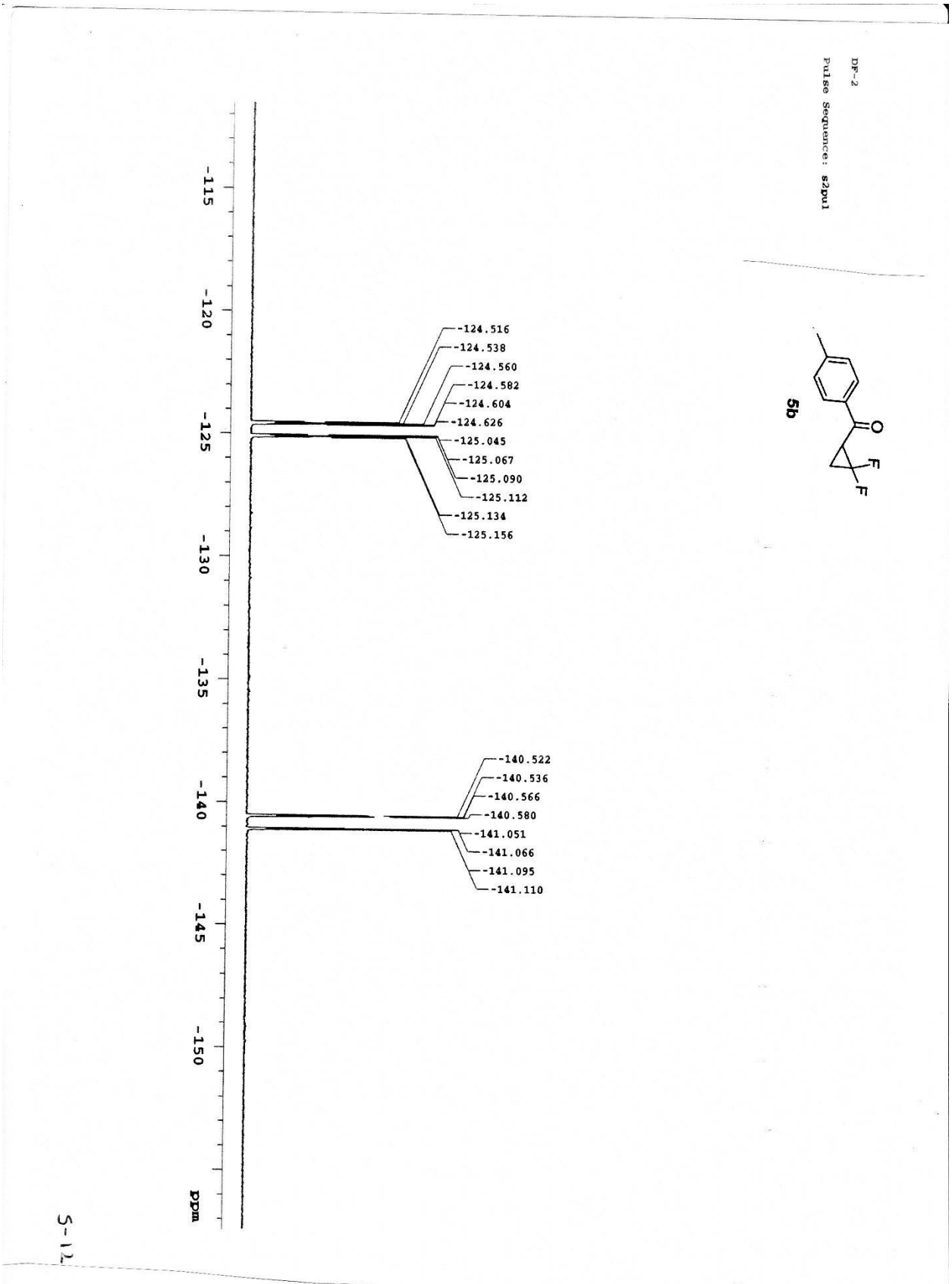

Figure A-21. ^{19}F NMR of (2,2-difluorocyclopropyl)(p-tolyl)methanone **5b**

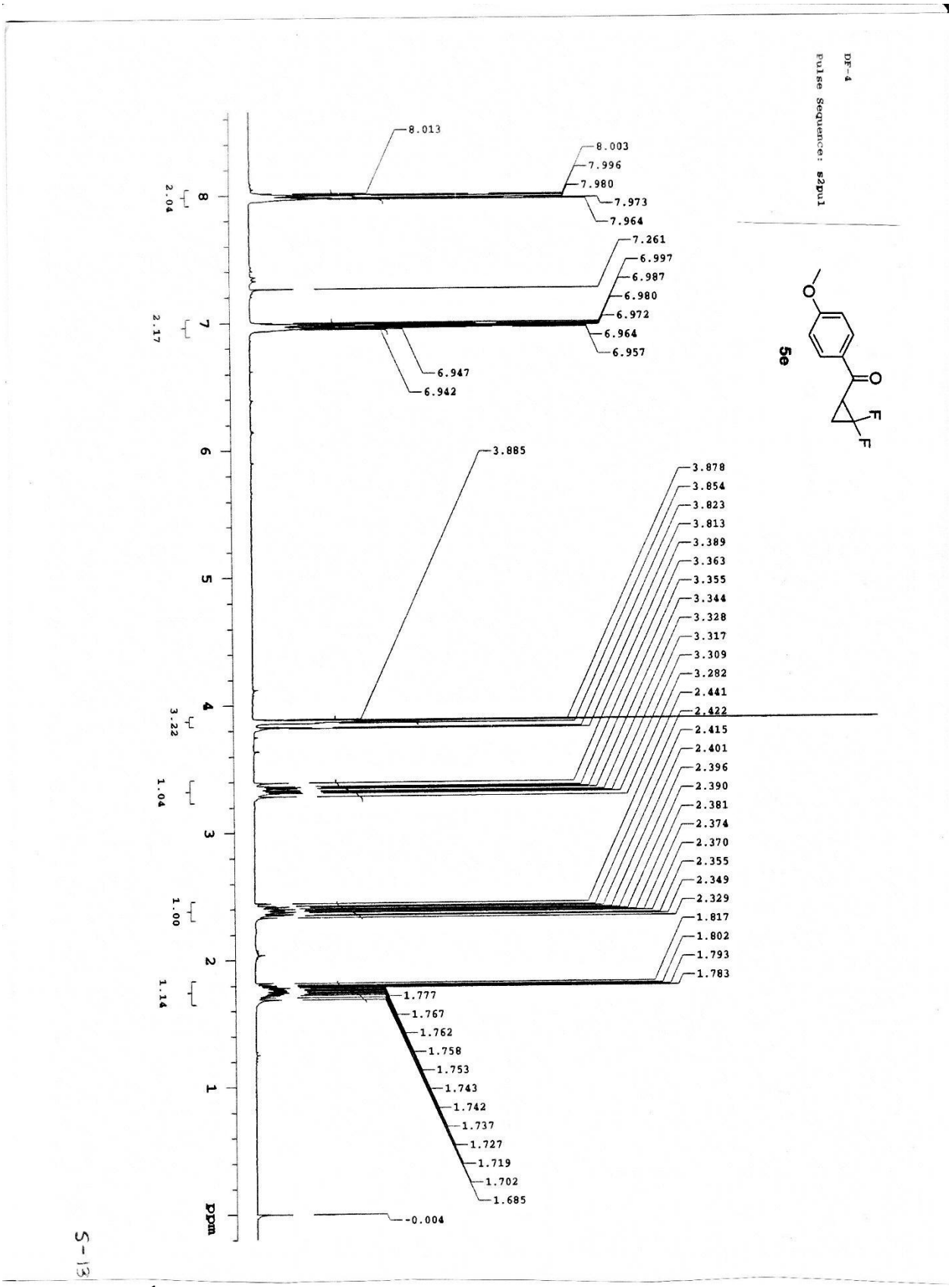

Figure A-22. ^{1}H NMR of (2,2-difluorocyclopropyl)(4-methoxyphenyl)methanone **5e**

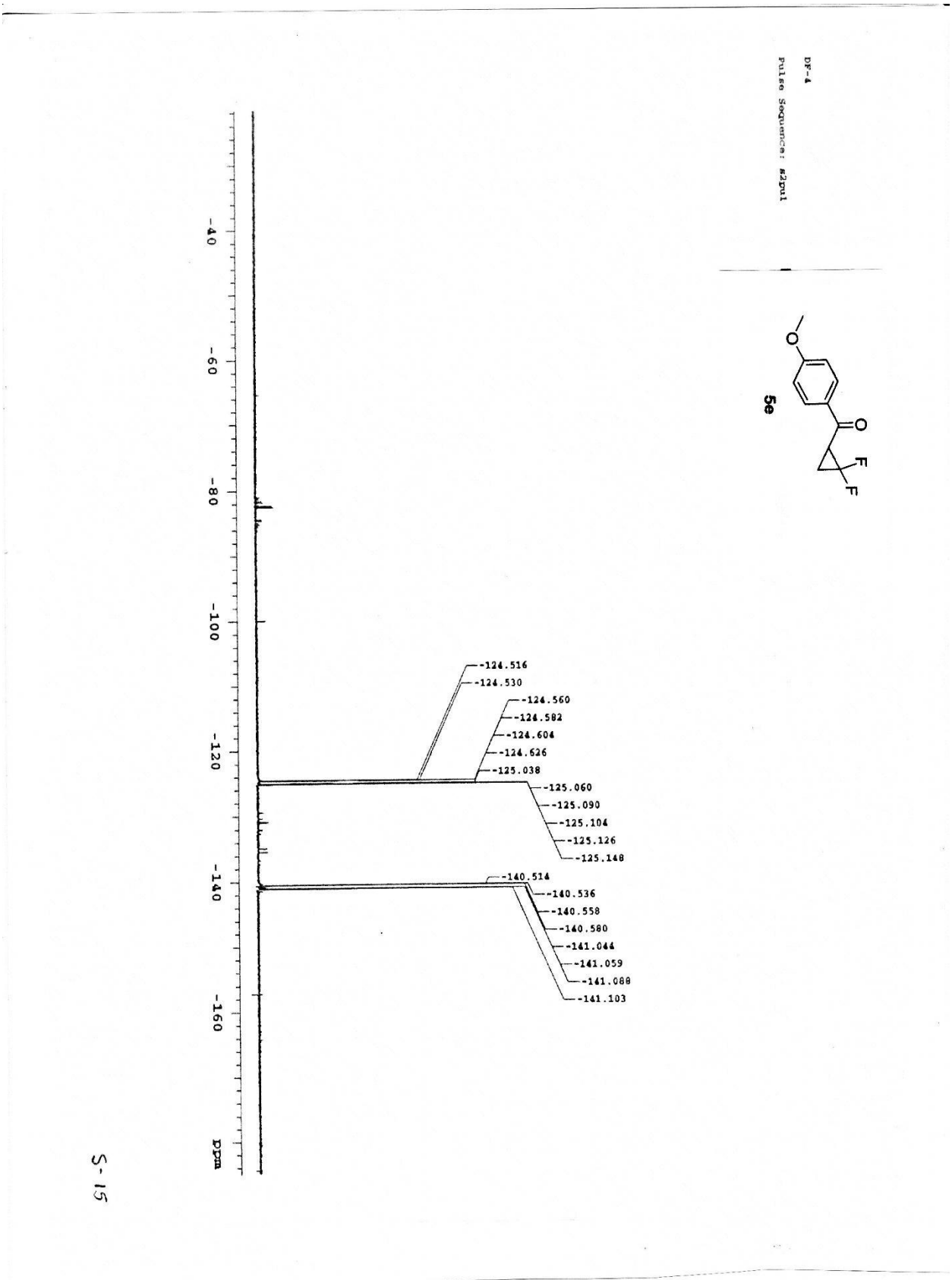

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Figure A-23. ^{19}F NMR of (2,2-difluorocyclopropyl)(4-methoxyphenyl)methanone **5e**

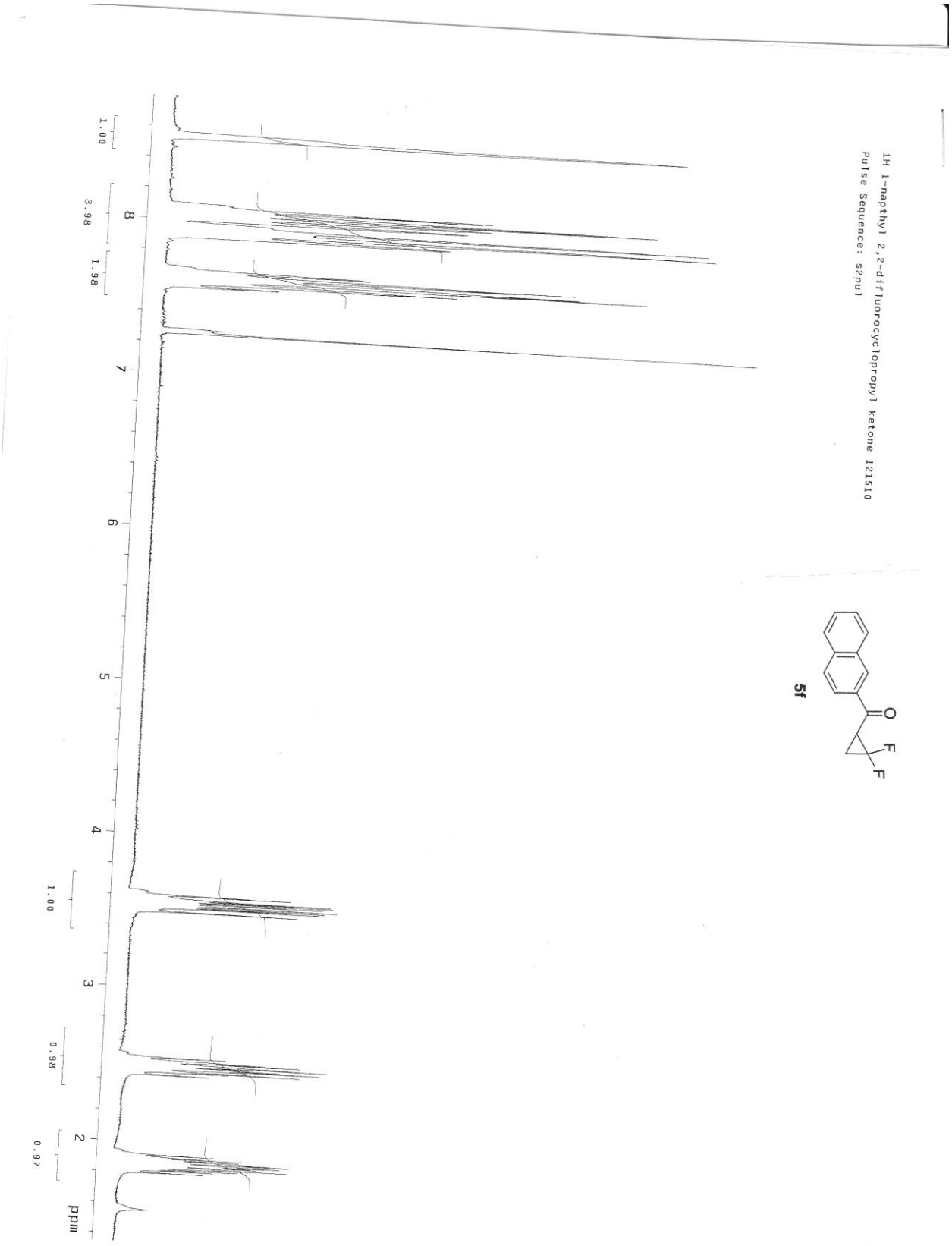


Figure A-24. ^{1}H NMR of (2,2-difluorocyclopropyl)(naphthalen-1-yl)methanone **5f**

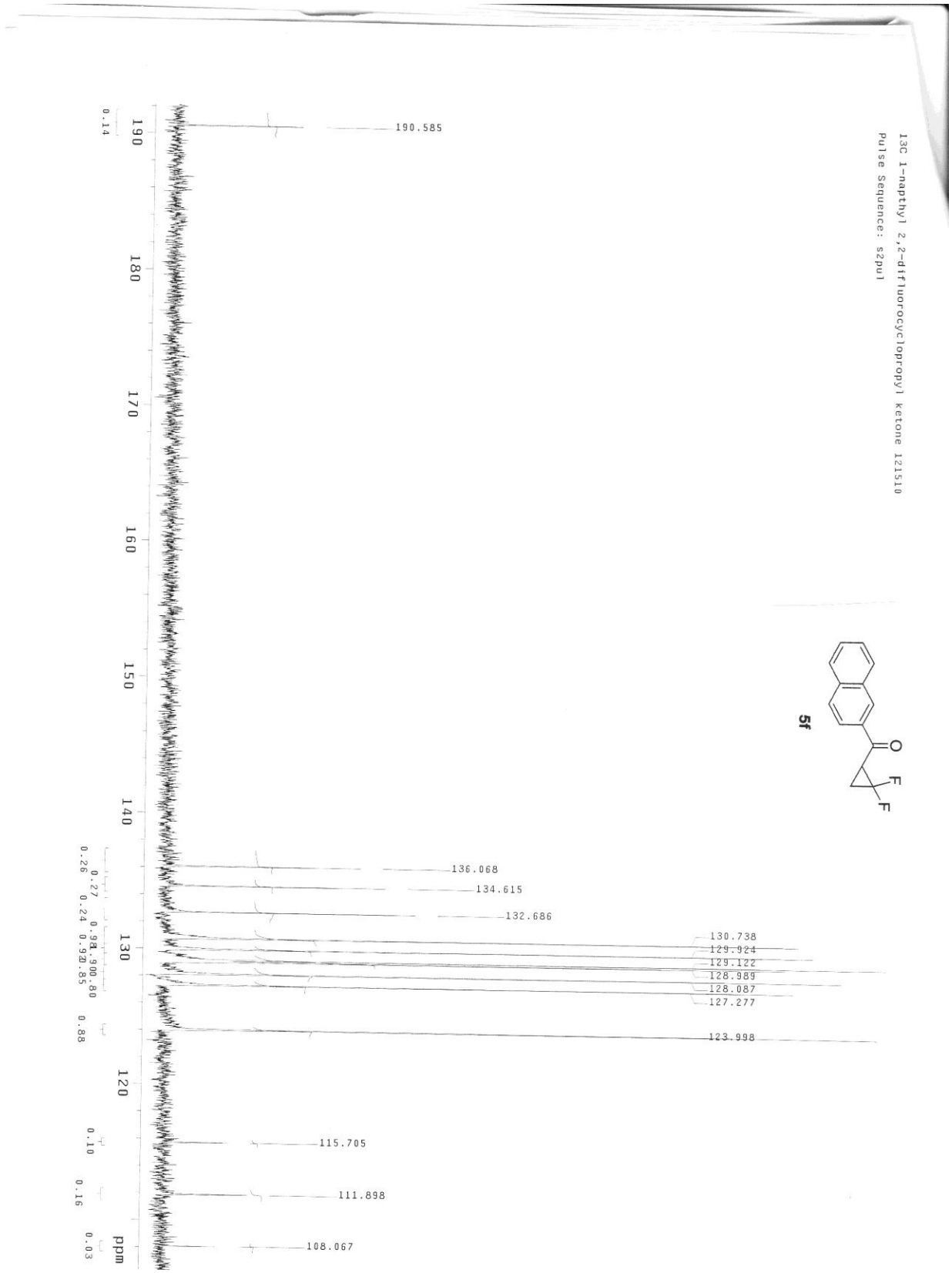
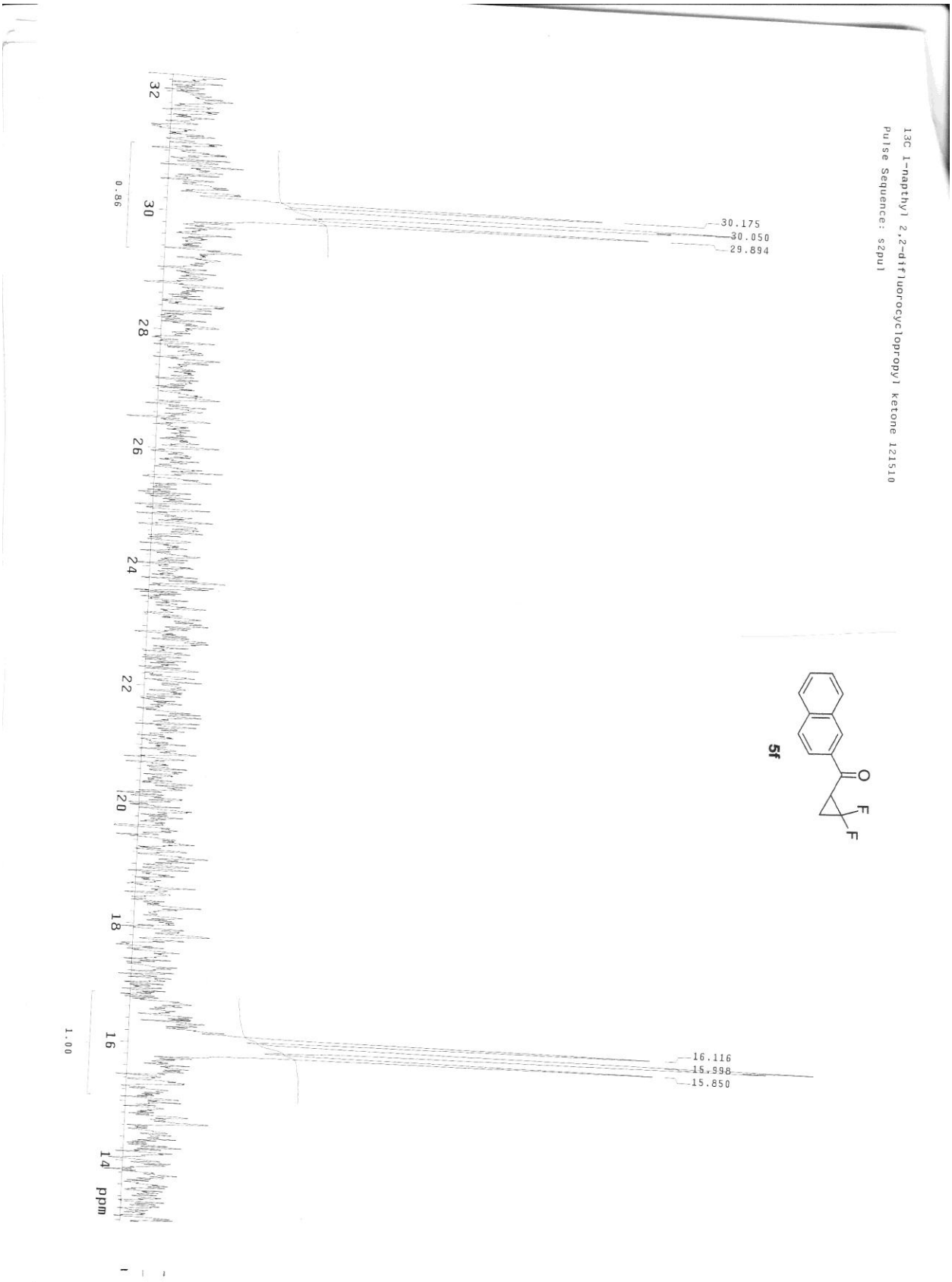


Figure A-25. ^{13}C NMR of (2,2-difluorocyclopropyl)(naphthalen-1-yl)methanone **5f**



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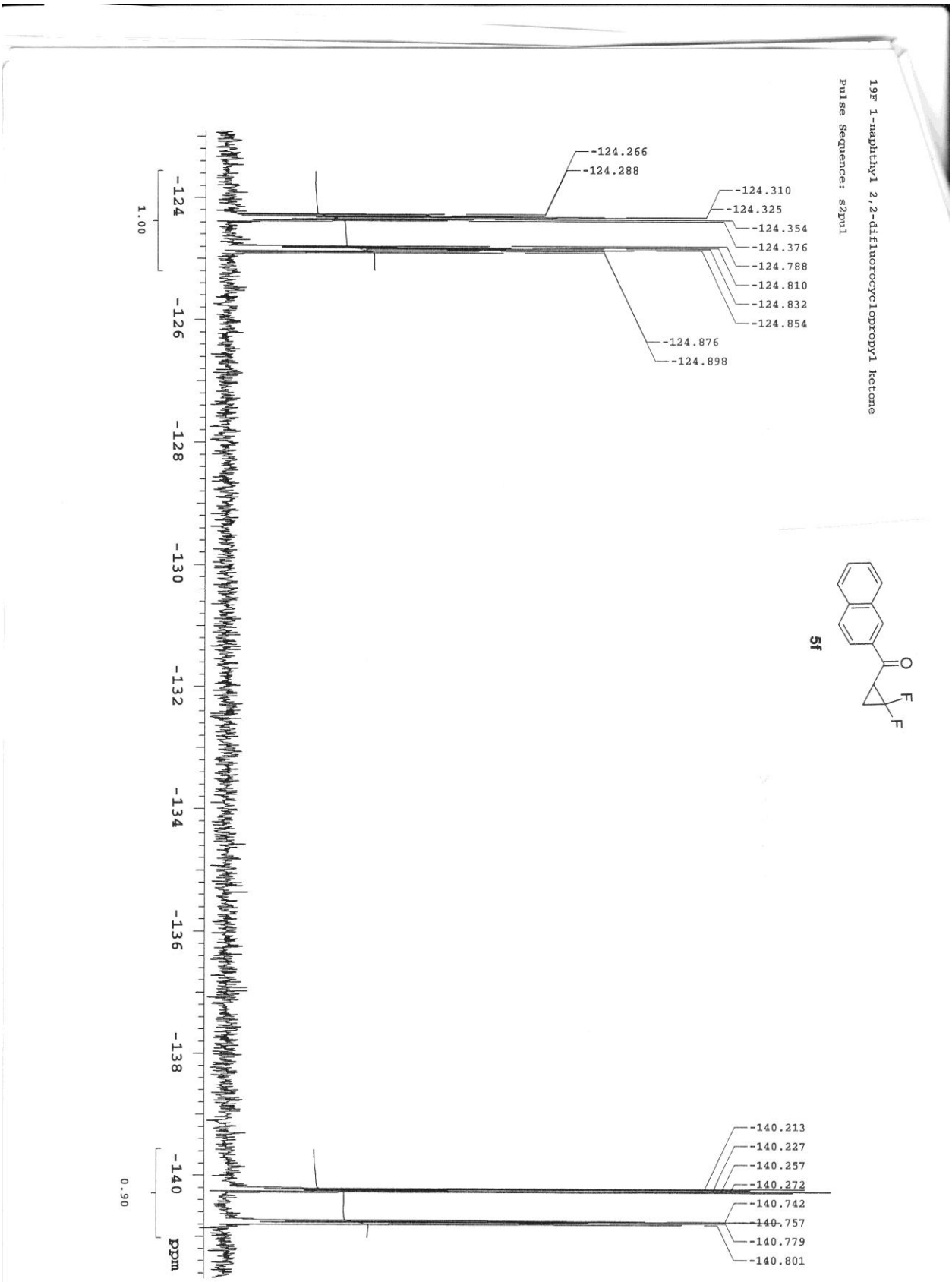

Figure A-26. ^{19}F NMR of (2,2-difluorocyclopropyl)(naphthalen-1-yl)methanone **5f**

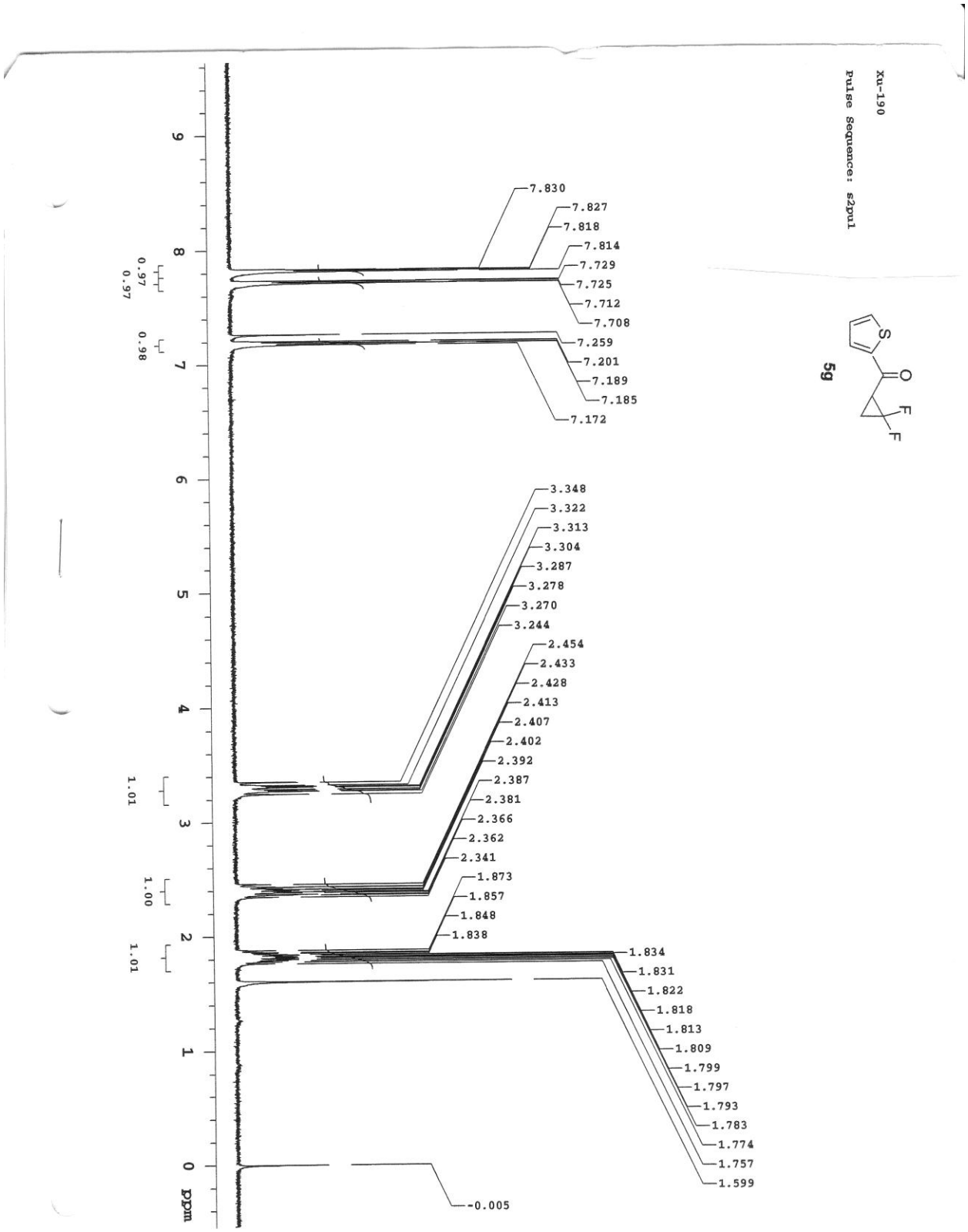

Figure A-27. ^{1}H NMR of (2,2-difluorocyclopropyl)(thiophen-2-yl)methanone **5g**

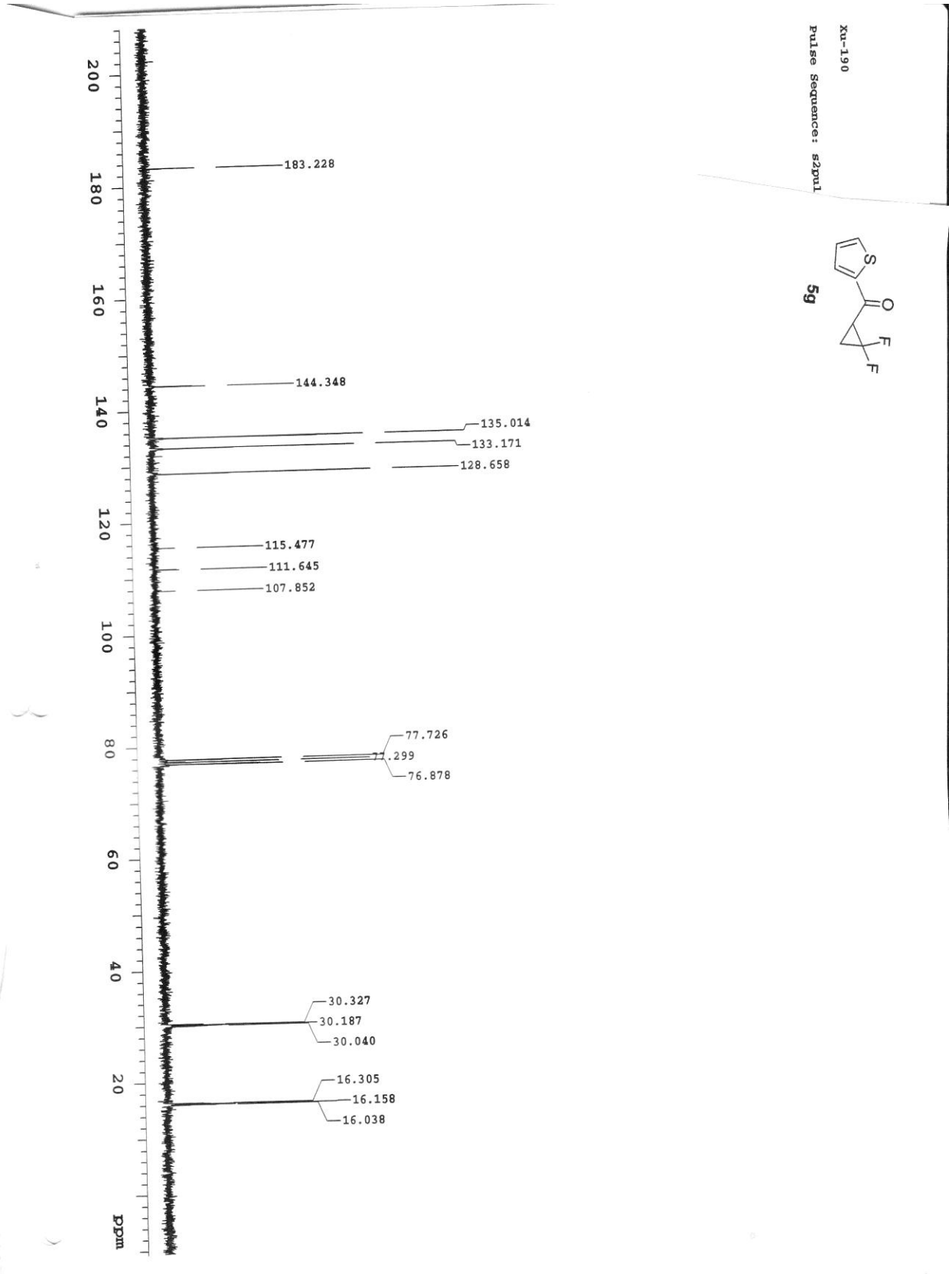

Figure A-28. ^{13}C NMR of (2,2-difluorocyclopropyl)(thiophen-2-yl)methanone **5g**

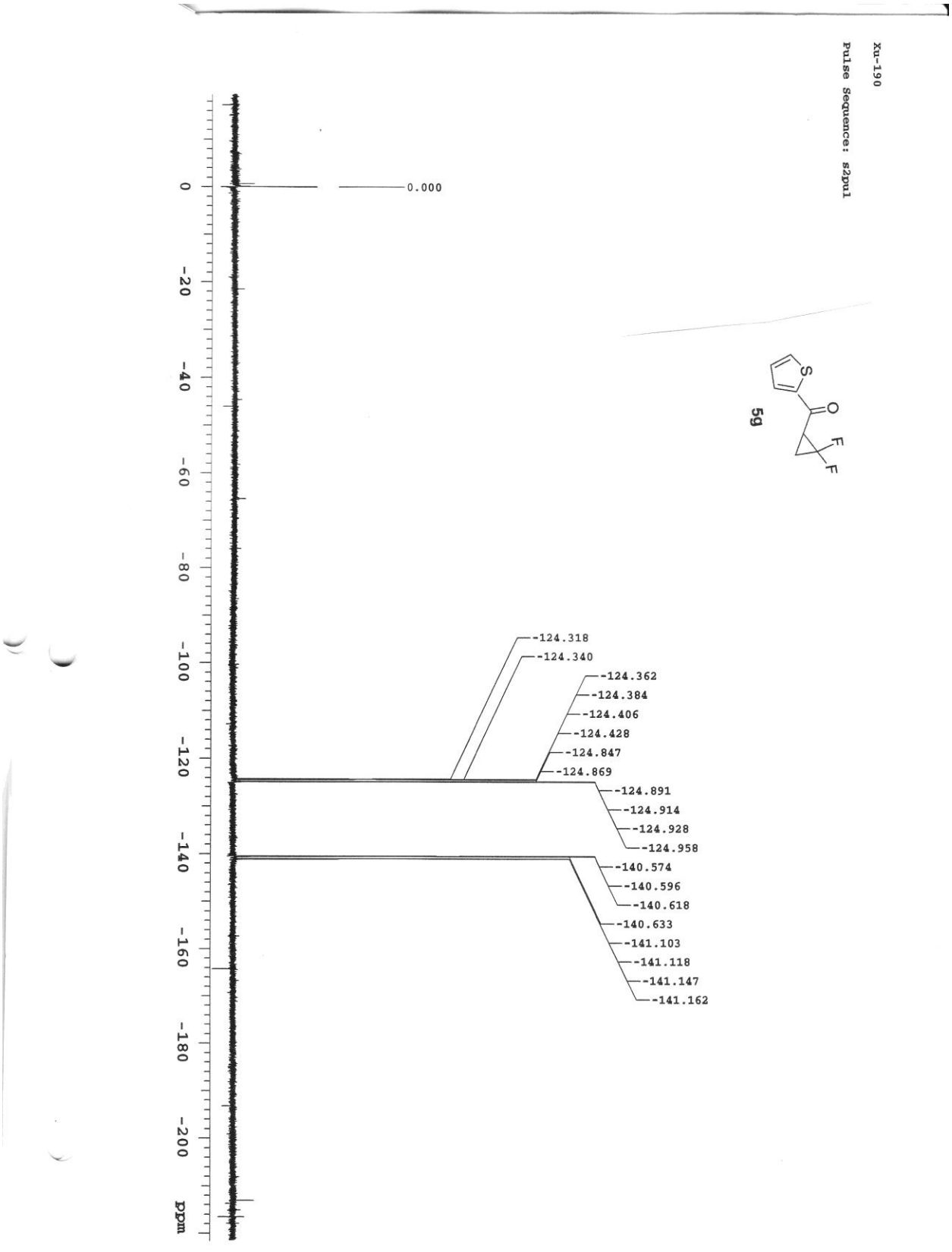

Figure A-29. ^{19}F NMR of (2,2-difluorocyclopropyl)(thiophen-2-yl)methanone **5g**

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BIOGRAPHICAL SKETCH

Eric Alan Cornett was born in Dayton, Ohio. Shortly after his birth, he moved to Orlando, Florida where he grew up throughout his childhood. He graduated valedictorian at Winter Park High School in 2003. He then attended University of Central Florida in Fall 2003, where he first pursued an engineering degree but then switched to the field of chemistry. He performed his undergraduate studies in synthesis of medicines under the advisement of Dr. Otto Phanstiel. He graduated magna cum laude in Fall 2007, majoring in chemistry with a minor in mathematics. He enrolled into the University of Florida in Fall 2008 as a graduate student in organic chemistry under the direction of Dr. William R. Dolbier Jr., where he studied organic chemistry involving fluorine.