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MODULAR SYNTHESIS OF WEINREB AMIDES OF 2-FLUORO-2,4-DIENOIC ACIDS

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MODULAR SYNTHESIS OF WEINREB AMIDES OF 2-FLUORO-2,4-DIENOIC ACIDS

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CHAPTER 1: INTRODUCTION

In 1886, H. Moissan first synthesized fluorine by the electrolysis of solution of KF and he was awarded Nobel prize for his discovery in 1906. The unique properties of fluorine are the highest electronegativity (3.98 χ_p), high electron affinity (79.5 kcal/mol), high ionization energy (401.8 kcal/mol), low polarizability and small size (1.47 Å)^3 which make it a special element in periodic table.[1] Good overlap between 2s and 2p orbitals of fluorine with those of carbon gives rise to high stability of fluorocarbons which can be explained by comparing the bond energies of C-H (99 kcal/mol) and C-F (116 kcal/mol).[2]

1.1 **Fluorocarbons**

Compound that containing C-F bond are called fluorocarbons. Due to high thermal stability of fluorocarbons, these are used in almost all areas of our daily life. Fluoroorganic chemistry is a growing field of science in the present decade due to the diverse application of these compounds. Introduction of fluorine into the organic molecules changes their physical and chemical properties which may lead to change in the biological activities of these compounds. It also increases the lipophilicity and hydrophobicity of organic compounds.[3] The small van der Waals volume of fluorine (1.47 Å)^3 is comparable with that of H (1.20 Å)^3 and O (1.52 Å)^3 and replacement of hydrogen by fluorine does not bring much steric change in the molecule.[1] These unique properties of organofluorine compounds led to numerous applications in various fields; for example, they are used as refrigerants, solvents, anesthetics, polymers, pharmaceuticals and agrochemicals.

1.1.1 **Organofluorine compounds in pharmaceutical industry**

Organofluorine compounds are more stable due to high bond dissociation energy of C-F. In addition fluorine substitution may also alter the biological activities of organic compounds. Because of these unique properties a large number of organofluorine compounds are now used as pharmaceutical drugs or as intermediates to synthesize

pharmaceutical drugs.[3b,4-5] It has been reported that over 25 years fluorine containing drugs increased 3.9 times whereas the number of other drugs 2.3 times.[6] Examples of some fluorinated drugs are fluorouracil (anticancer)[7] and ciprofloxacin (antibiotic) (Figure 1).

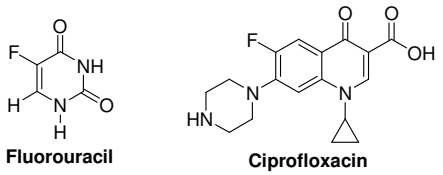


Figure 1. Examples of Fluorinated Drugs

1.1.2 **Organofluorine compounds as solvents**

Organofluorine compounds are also used as solvents in various fields. Dichlorofluoromethane and chlorofluoromethane were used as refrigerants. Nowadays perfluorohydrocarbons are used as refrigerants. Fluorinated hydrocarbons are also used as artificial oxygen carrier to the lungs.[8-10] Among organofluorine solvents perfluoro alkanes are very nonpolar solvents whereas fluorinated alcohols {eg. CF_3CH_2OH and $(CF_3)_3CHOH$} are highly polar.

1.1.3 **Organofluorine compounds in agrochemistry**

Fluorinated organic compounds are often used as herbicides, insecticides and fungicides and display more efficiency compared to their nonfluorinated analogues.[11a] It has been reported that fluoro agrochemicals increased 4% to 9 % of all agrochemicals over last 15 years.[11b] Examples of some fluorinated agrochemicals are Diflubenzuron (insecticide), Triflularin (herbicide) and Mefluidide (herbicide) (Figure 2).

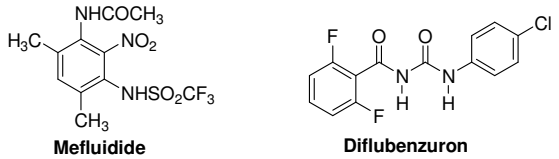


Figure 2. Examples of Fluorinated Agrochemicals

1.2 **Approaches to the synthesis of fluorinated compounds**

Fluorinated compound can be synthesized either by direct introduction of fluorine atom or via the use of fluorinated building blocks.

1.2.1 **Direct introduction of fluorine atom**

Fluorine can be introduced into organic molecules using several fluorinating reagents.[2a] Some of these are:

1. F_2 gas, diluted with N_2, the content of F_2 is in the range of 1-10%, typically 1-3%.
2. Sulfur tetrafluoride and its derivatives are commonly used in fluorodeoxygenation reactions.
3. Nucleophilic fluorinating reagents range from alkali metal fluorides and hydrogen fluoride, to tetraalkylammonium fluorides and TASF.
4. Electrophilic fluorinating reagents include CF_3OF, XeF_2, $CsSO_4F$ and *N*-fluoro containing reagents. The latter are widely used today, whereas the use of the former has substantially declined due to either difficult preparation or problems associated with safety and handling or price.
5. Trifluoromethylating reagents.

Some examples of fluorinating and trifluoromethylating reagents are shown in Figure 3.

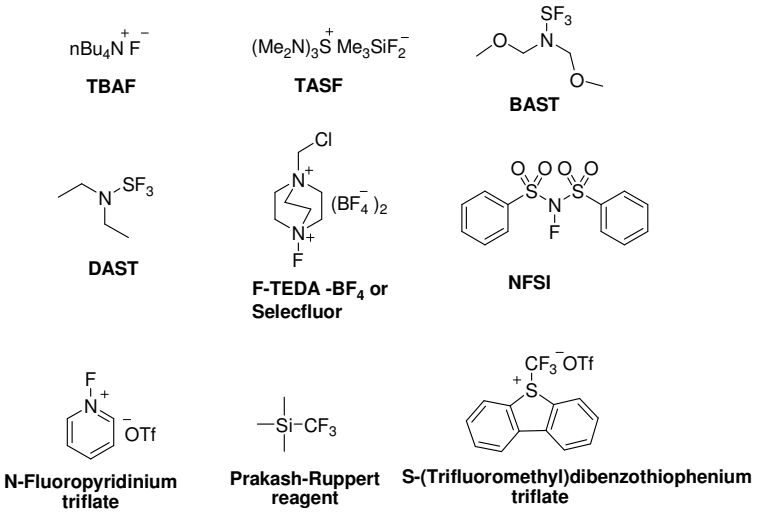


Figure 3. Reagents for Direct Introduction of Fluorine

Despite numerous reagents, methods for regioselective introduction of fluorine into organic molecules are still lacking.

1.2.2 **Synthesis of organofluorine compounds using fluorinated building blocks**

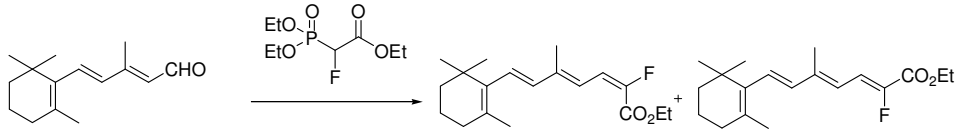
The use of fluorinated building block approach is a tactic for the synthesis of fluorinated organic molecules using smaller functionalized fluorinated molecules.[12a] Some examples of fluorinated building blocks are ethylbromofluroacetate, chlorodifluoroacetic acid, diethylfluoromalonate, C_6F_5Br and CF_3X (X= Br, I) (Figure 4).

Chlorodifluoroacetic acid **Ethyl Bromodifluoroacetate**

Figure 4. Fluorinated Building Blocks

Compounds that contain a fluorine atom and an electron withdrawing group on the same carbon atom are used as effective fluorinated building blocks to synthesize organofluorine compounds. These kinds of building blocks are treated with base to form fluoro-carbanions, which again react with electrophiles. For example, triethyl 2-fluoro-2-phosponoacetate produces carbanion when treated with base which further reacts with aldehydes and ketones to form alkenes (Scheme 1).[12b]

Scheme 1. Synthesis of Organofluorine Compound by the Use of Fluorinated Building Block



1.3 **Alkenes and Fluoroalkenes**

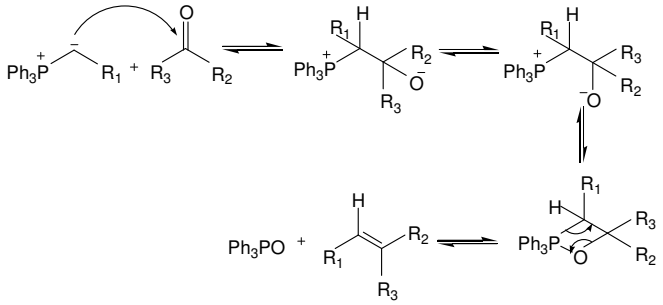
Alkenes are useful synthetic intermediates and can be synthesized via different methods. Modular approaches involve reactions of carbonyl compounds with appropriate reagents.

Most commonly used methods are Wittig reaction, Horner-Wadsworth-Emmons (HWE) olefination, Peterson olefination and Julia olefination.

1.3.1 **Wittig reaction**

Witttig reaction is an important and widely used synthetic methodology for the preparation of olefins.[13-15] In this reaction, aldehyde or ketone react with triphenyl phosphonium ylide to produce an olefin and triphenylphosphine oxide (Scheme 2).

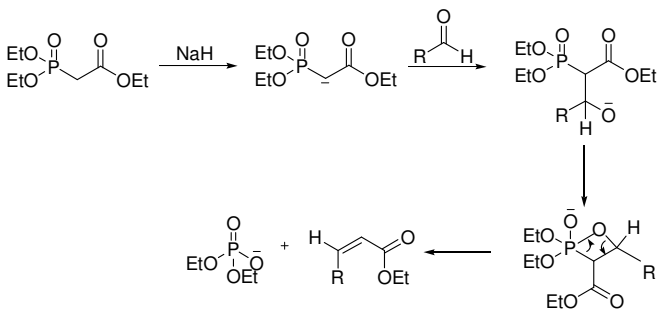
Scheme 2. Synthesis of Olefins via Wittig Olefination



1.3.2 **Horner-Wadsworth-Emmons Reaction**[16]

In this reaction stabilized phosphonate carbanions react with aldehydes or ketones to yield alkenes. Compared to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbanions are more nucleophilic and more basic and can be alkylated (Scheme 3).

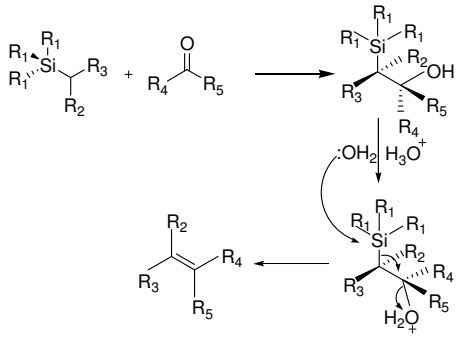
Scheme 3. Synthesis of Olefins by Horner-Wadsworth -Emmons Reaction



1.3.3 **Peterson Olefination**[17]

Peterson olefination reaction involves the synthesis of olefin from α-silyl carbanions. Depending on reaction conditions, either cis or trans alkenes can be synthesized using the same β-hydroxysilane. In this reaction α-silyl carbanions react with ketones or aldehydes to form a β-hydroxysilane as an intermediate, which eliminates to form alkenes.

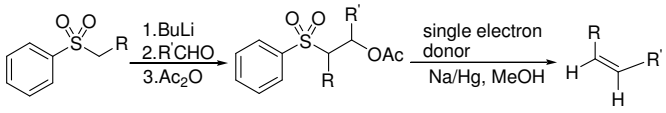
Scheme 3. Synthesis of Olefins by Horner-Wadsworth -Emmons Reaction



1.3.4 **Julia Olefination**[18-24]

Classical Julia olefination involves addition of alpha metalated phenyl sulfones to an aldehyde or ketone, acylation of the resulting beta alkoxy sulfones, followed by its reductive elimination using single electron donor to give the alkenes.[18,19]

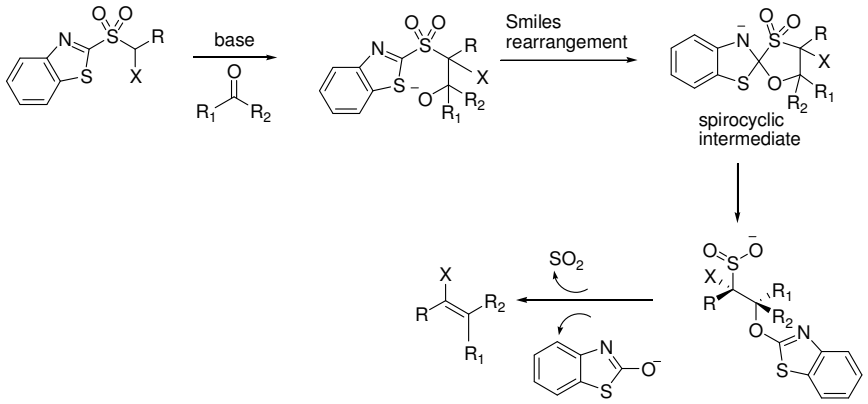
Scheme 5. Synthesis of Olefins via Classical Julia Reaction



A convenient route for olefination is via the modified Julia reaction.[20, 21] Modified Julia olefination uses the heteroaryl sulfones instead of phenyl sulfone used in classical method. Here the initial beta alkoxy heteroaryl sulfone is very labile and quickly undergoes Smiles rearrangement to form spirocyclic intermediate. This brakes down via

C-S bond cleavage to form another unstable intermediate, sulfinate salt, which eliminates sulfur dioxide and salt of benzothiazol-2-ol, to give the alkene.

Scheme 6. Synthesis of Olefins via Modified Julia Olefination



The use of fluorinated ylides for the synthesis of fluoroalkenes has been demonstrated in the literature.[23,24] Julia olefination on the other hand, did not gain much attention for the synthesis of fluoroalkenes until recently.[22]

1.4 **Dienes and Fluorinated Dienes**

Dienes are important synthetic intermediates, that are used in addition, polymerization, and cycloaddition reactions, such as Diels-Alder reaction. Recently, complex functionalized five membered rings were prepared via metal-catalyzed diene-yne, diene-ene and diene-allene cycloaddition reactions.[25] Further, conjugated diene/polyene structural moiety can be found in various natural products, i.e. pheromones, juvenile hormones and retinoids. Moreover, polyene amide structural unit is found in many natural products with biological activity.[26] Despite wide use of dienes in synthetic chemistry, there is only a handful of methods that were developed for the synthesis of regiospecifically fluorinated dienes.[27] These were subsequently used in Diels-Alder reactions.[27a,c-d] Among biologically relevant compounds, synthesis of fluorinated analogs of retinoic acids has been reported[28] and some fluorinated carotenoids have been prepared as well.[29]

CHAPTER 2: OBJECTIVES

Fluorinated olefins are of great value as synthetic intermediates and fluorovinyl moiety is also found in biologically active compounds.[3b,30] For example, terminal fluoroalkenes are known to be mechanism-based enzyme inhibitors.[31] Various methods have been developed for the synthesis of fluoroalkenes.[22-24,32] On the other hand, methods for synthesis of regiospecifically fluorinated dienes with defined stereochemistry are scarce.[27b] We were therefore interested in the development of a new synthetic method for regiospecifically fluorinated functionalized dienes.

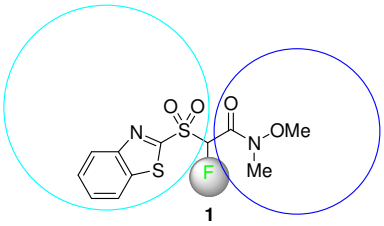


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Figure 5. Fluorinated Julia Weinreb Amide Moiety

Our target compounds were regiospecifically fluorinated dienes containing Weinreb amide moiety that would allow further conversions.These would include Michael addition,

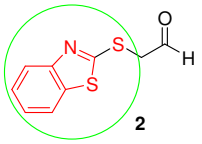

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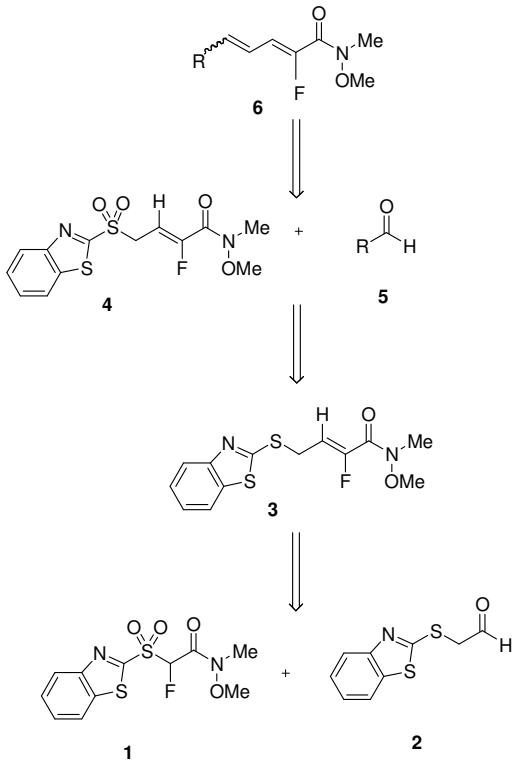
Figure 6. Aldehyde attached to "Julia Olefination Handle" Precursor

Scheme 7. Retro Synthetic Synthesis of Fluorinated Dienes

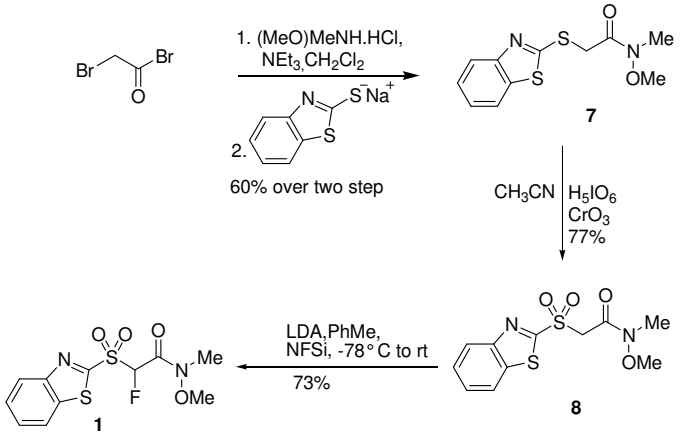


cycloadditions or conversions of Weinreb amide moiety. In our laborotatory a fluorinated building block containing Weinreb amide moiety has been synthesized and used in modified Julia olefinations (**1**, Figure 5).[33] Condensation of reagent **1** (Figure 5) with an aldehyde **2** (Figure 6**)** that contains a handle for further Julia olefination would provide access to regiospecifically fluorinated dienes containing Weinreb amide moiety. Scheme 7 shows a retrosynthetic plan for our approach. Briefly, reaction of Julia reagent **1** with aldehyde **2** would introduce α-fluorovinyl Weinreb amide moiety (**3**, Scheme 7). Oxidation of **3** would result in "second generation" Julia reagent **4.** Condensation of **4** with carbonyl compounds **5** would yield the desired functionalized fluorodiene **6**.

CHAPTER 3: RESULTS AND DISCUSSION

Fluorinated Weinreb amide reagent, 2-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylacetamide (**1**) was synthesized as reported.[33] Synthesis is shown in Scheme 8.

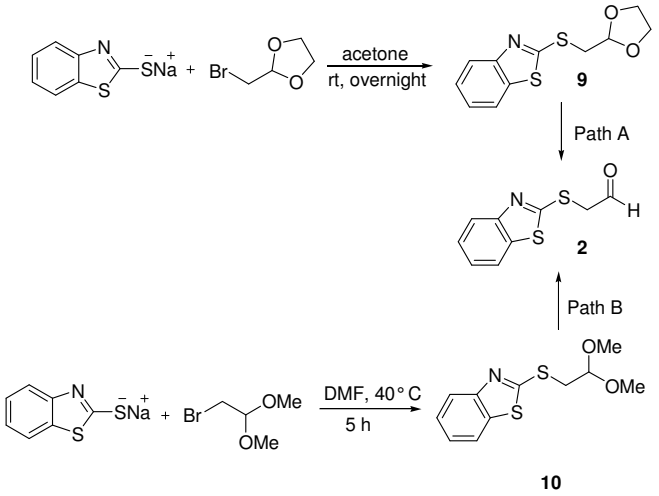
Scheme 8. Synthesis of Fluoro Julia Weinreb Amide Reagent **1**



A known BT-sulfide **7** was synthesized by the reaction of the sodium salt of 2-mercapto-1,3-benzothiazole with 2-bromo-*N*-methoxy-*N*-methylacetamide, that was prepared by the reaction of bromoacetyl bromide and (MeO)MeNH.HCl in DCM in the presence of NEt_3 (Scheme 8). Periodic oxidation of BT-sulfide **7** in the presence of chromium oxide in CH_3CN yielded the known sulfone, **8**. Sulfone **8** was subjected to metalation-fluorination with LDA and NFSI in toluene to give the monofluoro derivative **1** in 73 % yield.

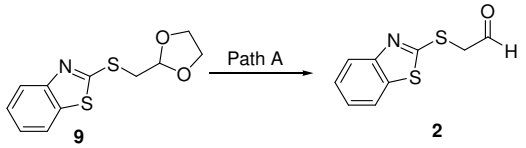
Our second goal was synthesis of 2-(benzo[*d*]thiazol-2-ylthio)acetaldehyde **2**.[34] Our initial attempt was synthesis of aldehyde **2** via acid hydrolysis of corresponding dioxolane **9** (path A, Scheme 9). For this purpose dioxalane **9** was synthesized in reaction of 2-mercapto-1,3-benzothiazole and 2-(bromomethyl)-1,3-dioxolane in acetone at room temperature (**9**, 44%).

Scheme 9. Synthesis of Aldehyde via Path A and Path B



Deprotection of 2-[(1,3-dioxolan-2-yl)methylthio]benzo[*d*]thiazole, **9** was attempted under several conditions (Table 1). Treatment of **9** with 2N H_2SO_4 in CH_3CN-H_2O (3:1) at room temperature showed unreacted starting material after 24 h (entry 1). The use of 2N H_2SO_4 in toluene at higher temperature was also ineffective (entry 2).

Table 1. Attempts at Synthesis of 2-(Benzo[*d*]thiazol-2-ylthio)acetaldehyde **2**, via Path A



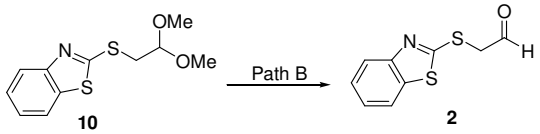
Entry	Reagent	Solvent	T (°C)	Time	Conversion[a]
1	H_2SO_4 (2N)	CH_3CN-H_2O (3:1)	rt	overnight	0
2	H_2SO_4 (2N)	toluene	90 °C	overnight	0
3	PPTS	acetone- H_2O (3:1)	40 °C	24 h	0
4	I_2	acetone	55 °C	overnight	0
5	CBr_4	CH_3CN-H_2O (1:3)	rt	4 h	0
6	CBr_4	CH_3CN-H_2O (1:3)	80 °C	overnight	0
7[b]	HCl (2N)	acetone-H_2O (2:1)	75 °C	3 days	small conversion

[a] Determined by thin layer chromatography. [b] Conversion determined by ^{1}H NMR and thin layer chromatography. Complex reaction mixture was obtained.

Pyridinium *p*-toluenesulfonate (PPTS) in acetone-H_2O (3:1) or I_2 in acetone did not give the desired product (entries 3 and 4). Use of CBr_4 in CH_3CN-H_2O was unsuccessful either at room temperature or at 80 °C (entries 5 and 6). Use of 2N HCl was unsuccessful, although a small conversion of starting material in acetone-H_2O (2:1) solvent at 75 °C was observed (entry 7). We were unable to isolate the product formed and complex reaction mixture was obtained upon chromatography.

Since we were unable to deprotect compound **9** (Scheme 9, Path A) we considered the use of dimethylacetal protecting group (Scheme 9, Path B). Compound **10** was prepared in the reaction of 2-mercapto-1,3-benzothiazole with 2-bromo-1,1-dimethoxyethane in DMF at 40° C by displacement of bromine. Several conditions were also attempted for removal of dimethylacetal in **10** (Table 2).

Table 2. Synthesis of 2-(Benzo[*d*]thiazol-2-ylthio)acetaldehyde **2**, via Path B



10 **2**

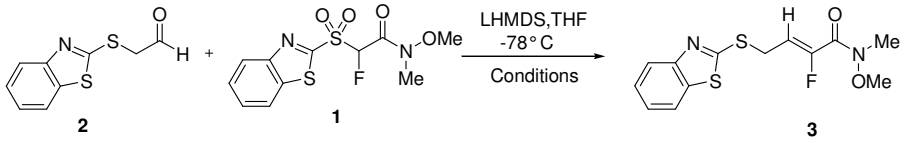
Entry	Reagent	Solvent	T (° C)	Time	Yields[a] (%)
1	I_2	acetone	rt	overnight	0[b]
2	CBr_4	CH_3CN-H_2O (1:3)	80 °C	3 d	0[b]
3	PTSA	THF-H_2O (1:1)	rt	3 d	0[b]
4	HCl (4N)	acetone	40 °C	24 h	20[c]
5	HCl (4N)	acetone	40 °C	4 h	56
6	HCl (12N)	acetone	55 °C	30 m	81
7	HCl (12N)	acetone -H_2O (10:1)	55 °C	40 m	84

[a] Yield was determined for the crude product without purification, unless stated otherwise. Aldehyde **2** was unstable under chromatography either on silica gel or alumina. [b] Conversion judged by thin layer chromatography and ^{1}H NMR. Only starting material was observed. [c] Isolated yield after column chromatography.

The overnight reaction with I_2 in acetone at room temperature did not show any conversion of **10** (entry 1). Use of CBr_4 at 80 °C in CH_3CN-H_2O (1:3) solvent did not show any consumption of starting material either (entry 2). Reaction with PTSA in THF-H_2O (1:1) at rt for 3 days showed only the presence of **10** and no desired product (entry 3). The use of 4N HCl hydrolyzed starting materials completely but aldehyde **2** was obtained in only 20% yield after column chromatography. Later it was established that the desired aldehyde **2** synthesized in path B (entry 4) was unstable on silica gel or on alumina supported column chromatography. The use of 4N HCl in acetone solvent at 40 °C then improved the yield to 56% (without column chromatography) (entry 5). Increasing the temperature and the use of 12N HCl showed the complete consumption of the starting material within 30 minutes and gave the desired aldehyde in 81% yield after workup (entry 6). Due to water solubility of the aldehyde the method was unrepeatable. We attempted several techniques to resolve this problem. For example, adding excess solid $NaHCO_3$ to the reaction mixture or evaporating the acetone before extraction, etc. None of these techniques worked well. We were finally pleased to find out that the best yield of **2**, that was repeatable, was obtained when no workup was used upon completion of the reaction. Acetal **10** was stirred in acetone-H_2O (10:1) for 40 minutes at 55 °C using 12 N HCl and showed complete consumption of starting compound. Solid $NaHCO_3$ was then added portionwise to neutralize the reaction at 0° C and excess water was removed by adding anhydrous Na_2SO_4. The solution was then passed through a bed of anhydrous Na_2SO_4 and solvent was evaporated to get more than 80% of pure aldehyde **2** (as determined by ^1H NMR). Reaction showed complete conversion under these conditions (acetone-water, 10:1) but its crude product showed the presence of byproduct that could be the result of condensation of acetone and **2**. So the use of water seems to be crucial to minimize the condensation byproduct and to improve the quality of the aldehyde.

With both desired building blocks in hand, that is fluoro Julia Weinreb reagent **1** and benzothiazole derived aldehyde **2**, we tested reaction conditions for olefination reaction (Table 3).

Table 3. LHMDS Mediated Condensation Reaction of Sulfone **1** with Aldehyde **2**



2 **1** **3**

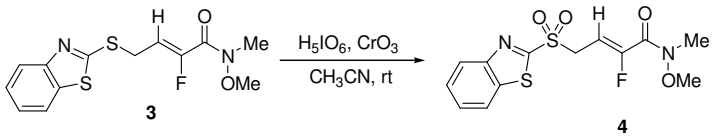
Entry	Aldehyde:Sulfone:LHMDS (molar ratio)	Time	Yield[a] (%)
1	1:1.5:1.5	3 h	32
2	1:1:2	2.5 h	20
3[b]	3:1:5	4 h	60
4[b]	2:1:3	3.5 h	76

[a] Yield of the isolated purified compound. Reaction was monitor by ^{19}F NMR for completion. [b] Sulfone was used as limiting reagent.

All reactions were performed at -78 °C using LHMDS as base. Critical for conversion was the ratio of aldehyde:sulfone:base. Our initial attempt was to use aldehyde as a limiting reactant. A 1:1.5:1.5 molar ratio of aldehyde (**2**) to sulfone (**1**) to base produced only 32 % of desired product after 3 hours (entry 1). The yield decreased to 20%, when a 1:1:2 molar ratio was used (entry 2). A much higher 60% yield of the desired product was obtained when sulfone was a limiting reagent and a 3:1:5 ratio of **1**, **2** and LHMDS was used (entry 3**)**. The best 76% yield of compound **3** was obtained when reaction was performed for 3 h and the molar ratio of aldehyde, sulfone and base was 2:1:3, respectively (entry 4).

Sulfide **3** was subjected to oxidation using periodic acid in the presence of a catalytic amount of chromium trioxide, to afford sulfone **4** in good yield (65%, Scheme 10).

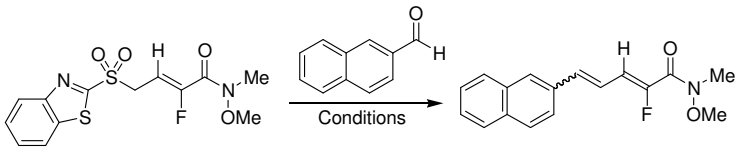
Scheme 10. Periodic Oxidation of Sulfide **3**



3 **4**

With desired reagent **4** in hand, we screened the reactivity of the reagent. Various reaction conditions were tested in condensation reactions with 2-napthaldehyde (Table 4).

Table 4. Condensation Reactions of **4** with 2-Napthaldehyde



4 (2*Z*, 4*E*/*Z*)-**6**

Entry	Reagent	Solvent	T	Time	4*E*/4*Z* ratio[a,b]	Yield[c]
1	LHMDS	THF	-78 °C to 0 °C	overnight	--	- -[d]
2	LHMDS	THF	0 °C to rt	12 h	--	- -[d]
3	DBU	THF	rt	2 h	--	- -[d]
4	DBU	THF	-78 °C to 0 °C	overnight	57/43,	35%
5	Cs_2CO_3	THF	0 °C	overnight	--	- -[d]
6	DBU	THF	0 °C	overnight	42/57,	55%
7	Cs_2CO_3	DCM	0 °C	overnight	--	- -[d]
8	DBU	DCM	0 °C	overnight	35/65,	66%

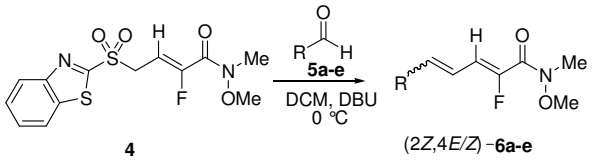
[a] The *E*/*Z* ratio refers to the double bond formed in the reaction. [b] Relative ratio of isomers in the crude reaction mixture determined by ^{19}F NMR prior to isolation. No change in relative ratio was observed after purification. [c] Yields of the isolated purified compounds. [d] No product was detected either by ^{19}F NMR or by TLC.

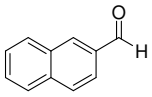
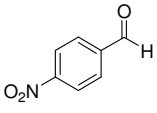
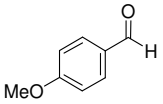
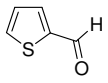
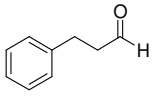
As evident from Table 4, selectivity or product yields depended on reaction conditions. No product was obtained using LHMDS as base in THF at -78 °C to 0 °C for 24 h or at 0 °C to rt for 12 h (entries 1 and 2). Room temperature olefination using DBU as a base in THF for 2 h did not show any product at all (entry 3). Changing the base from DBU to Cs_2CO_3 in THF or in DCM at 0 °C for 24 h did not give any condensation product (entries 5 and 7). Moderate 4*E* selectivity but a low yield (35%) was observed in the DBU mediated overnight condensation in THF at -78 °C to 0 °C (entry 4). A much better 55% yield, with opposite selectivity (compared to entry 4) was observed at 0 °C (entry 6).

The best yield (66%) and selectivity was obtained when condensation reaction was performed overnight using DBU as base in DCM at 0 °C (entry 8).

Next, generality of olefination conditions with **4** (DBU, DCM, 0° C) was tested with a series of aldehydes (Table 5).

Table 5. Reactions of **4** with Aldehydes



Entry	RCHO (**5a-e**)	Product (**6a-e**); (%)*E/Z* ratio[a]; Yield[b]	^{19}F NMR data: δ (ppm); mult, *J* (Hz)
1		**6a**; 35/65; 65%	4*E* isomer -123.5; d, 30.5 4*Z* isomer -121.1; d, 30.5
2		**6b**; 40/60; 74%	4*E* isomer -119.6; d, 30.5 4Z isomer -118.5; d, 27.5
3		**6c**; 20/80; 51%	4*E* isomer -125.2; d, 33.6 4Z isomer -122.6; d, 33.6
4		**6d**; 10/90; 63%	4*E* isomer -123.7; d, 30.5 4Z isomer -120.7; d, 33.6
5		**6e**; 16/84; 51%	4*E* isomer -125.6; d, 30.5 4Z isomer -124.3; d, 30.5

[a] Relative ratio of isomers in the crude reaction mixture determined by ^{19}F NMR prior to isolation. No change in relative ratio was observed after purification.
[b] Yields of the isolated, purified compounds.

Table 5 displays the DBU mediated olefination reactions of sulfone **4** with different aldehydes in DCM at 0 °C overnight. Moderate 4*Z* selectivity and good yield (65%) was obtained with 2-napthaldehyde **5a** (entry 1). *p*-Nitrobenzaldehyde (**5b**) gave product **6b** in good 74% yield, but with poor selectivity (entry 2). *p*-Methoxybenzaldehyde (**5c**),

thiophene-2-carbaldehyde (**5d**), 3-phenylpropanal (**5e**) gave products **6c-e** in 51%, 63% and 51% yield, respectively. Reactions of **4** with **5c-e** showed higher 2*Z*,4*E*-selectivity (entries 3-5).

Upon chromatographic purification, partial isomerization of 2*Z*,4*Z*-isomer to 2*Z*,4*E*-isomer was observed. We therefore attempted complete isomerization of 2*Z*,4*Z*-isomer to 2*Z*,4*E*-isomer. Several techniques were tested to get the desired 2*Z*,4*E*-isomer. Exposure of the isomer mixture to light (20 watt bulb) overnight did not show any isomerization at all. Treatment of the isomer mixtures with silica powder in $CHCl_3$ at rt or at 0 °C showed the desired isomerization, but isomerization did not proceed to completion. Alan T. McGown et al[35] described a convenient method for the isomerization of *Z*-isomer to its *E*-isomer using I_2 catalyst in $CHCl_3$ at rt (Table 6).

Table 6. Isomerization of 2*Z*,4*Z*-isomer to 2*Z*,4*E*-isomer

(2*Z*,4*Z*)-**6a-d** / (2*Z*,4*E*)-**6a-d** $\xrightarrow[\text{rt}]{I_2,\ CHCl_3}$ (2*Z*,4*E*)-**6a-d**

Entry	Isomer mixture: 2*Z*,4*Z* and 2*Z*,4*E*	T	Product (2*Z*,4*E*)[a]	Yield[b] (%)
1	**6a**	3 h	(2*Z*,4*E*)-**6a**	75%
2	**6b**	1.5 h	(2*Z*,4*E*)-**6b**	88%
3	**6c**	3 h	(2*Z*,4*E*)-**6c**	85%
4	**6d**	overnight	(2*Z*,4*E*)-**6d**	91%

[a] Determined by ^{19}F NMR. [b] Yield of the purified isomer.

Table 6 shows the time required for complete isomerization of 2*Z*,4*Z*-isomers to 2*Z*,4*E*-isomers along with the yields of the desired isomers.

CHAPTER 4: CONCLUSIONS

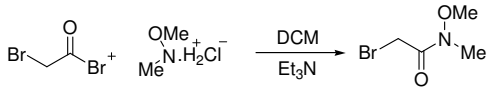
We have developed a new synthetic method for synthesis of regiospecifically fluorinated functionalized dienes. Two key substrates, a fluorinated building block containing Weinreb amide moiety 2-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylacetamide and 2-(benzo[d]thiazol-2-ylthio)acetaldehyde **2** have been synthesized and used for the preparation of (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide via modified Julia olefination. Reagent (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide undergoes reactions with different aldehydes under DBU mediated conditions to yield fluorinated functionalized dienes. Under the conditions used, formation of 2*Z*,4*Z*-isomer was predominant. Mixtures of (2*Z*,4*Z*)- and (2*Z*,4*E*)-isomers were isomerized to (2*Z*,4*E*)-isomer.

CHAPTER 5: EXPERIMENTAL SECTION

DCM, hexane and EtOAc were distilled over $CaCl_2$. Toluene and THF were distilled from sodium wire prior to use. LHMDS, LDA, DBU, DMF, NFSI, CH_3CN and all others chemicals and solvents were obtained from commercial sources and used without purification. All reactions were conducted in oven-dried glassware. For reactions that were performed under nitrogen atmosphere, glassware was flame dried under vacuum. Column chromatographic separation was performed on 200-300 mesh silica powder. Analytical thin layer chromatography and preparative thin layer chromatography were performed on Analtech 250 μm and 1000 μm silica plates. Visualization of developed TLC plates was accomplished by UV light and sometimes with I_2. ^1H NMR spectra were recorded at 500 MHz in $CDCl_3$. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as internal standard. Chemical shifts are reported in δ (parts per million) and coupling constants are in hertz (*J*).

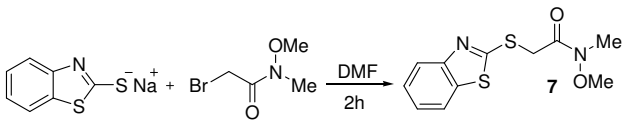
SYNTHESIS OF WEINREB AMIDE **1**

Synthesis of 2-bromo-N-methoxy-N-methylacetamide



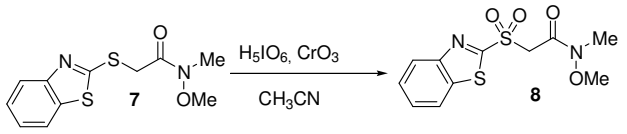
To a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (4.10 g, 42.0 mmol, 1.0 molar equiv) and bromoacetyl bromide (8.57 g, 42.4 mmol, 1.0 molar equiv) in distilled CH_2Cl_2 (200 mL) was added NEt_3 (12.1 mL, 8.50 g, 2.0 molar equiv) at room temperature. The reaction mixture was allowed to stir for 1 hour at room temperature, diluted with CH_2Cl_2 and washed with water. The water layer was extracted with CH_2Cl_2 (3 × 30 mL), combined organic layer was washed with saturated NH_4Cl (30 mL), brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield 3.84 g of 2-bromo-*N*-methoxy-*N*-methylacetamide (R_f = 0.43, SiO_2, 20% EtOAc in hexanes) as a yellow paste which was subjected to the next step without any purification.

Synthesis of 2-(benzo[d]thiazol-2-ylthio)-N-methoxy-N-methylacetamide ***7***



To a solution of crude 2-bromo-*N*-methoxy-*N*-methylacetamide (3.84 g, 21.0 mmol, 1.0 molar equiv) in DMF (70.0 mL) was added the sodium salt of 2-mercapto-1,3-benzothiazole (5.97 g, 31.5 mmol, 1.5 molar equiv) at room temperature. The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed with water. The water layer was extracted with EtOAc (3 × 30 mL), combined organic layer was washed with saturated NH_4Cl (30 mL), brine, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, 20%, 30% and 40% EtOAc in hexanes) to obtain product 2-(benzo[*d*]thiazol-2-ylthio)-*N*-methoxy-*N*-methylacetamide (**7**, 4.42 g, 79%) as a yellow solid (R_f = 0.43, SiO_2, 40% EtOAc in hexanes). Spectral data were in agreement with those reported in the literature.[32]

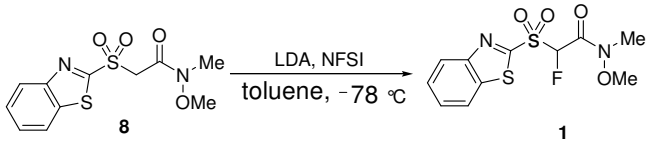
Synthesis of 2-(benzo[d]thiazol-2-ylsulfonyl)-N-methoxy-N-methylacetamide ***8***



H_5IO_6 (2.54 g, 11.1 mmol, 3.0 molar equiv) was dissolved in CH_3CN (140 mL) by vigorous stirring at rt for 20 min. CrO_3 (60.0 mg, 0.60 mmol) was added and the reaction mixture was stirred for an additional 5 min to give an orange colored solution. A solution of 2-(benzo[*d*]thiazol-2-ylthio)-*N*-methoxy-*N*-methylacetamide (**7**, 1.00 g, 3.72 mmol) in CH_3CN (10.0 mL) was added slowly and dropwise to this mixture, resulting in an exothermic reaction and formation of a yellowish precipitate. After complete addition the reaction mixture was stirred for three hours, at which time TLC (SiO_2, 20% EtOAc in hexanes) showed a complete consumption of 2-(benzo[*d*]thiazol-2-ylthio)-*N*-methoxy-*N*-methylacetamide (**7**). The reaction mixture was filtered through a Celite pad, the Celite was washed with CH_3CN, and the filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc (3 × 30 mL), then the combined organic layer was washed with

saturated aq $NaHCO_3$ (5 × 30 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 10% and 15% EtOAc in hexanes) to afford 2-(benzo[*d*]thiazol-2-ylsulfonyl)-*N*-methoxy-*N*-methylacetamide (**8**, 8.60 g, 77%) (R_f = 0.43, SiO_2, 20% EtOAc in hexanes) as a yellow solid. Spectral data were in agreement with those reported in the literature.[36]

*Synthesis of 2-(benzo[d]thiazol-2-ylsulfonyl)-2-fluoro-N-methoxy-N-methylacetamide **1***



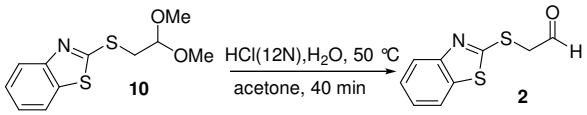
Under nitrogen atmosphere, a solution of 2-(benzo[*d*]thiazol-2-ylsulfonyl)-*N*-methoxy-*N*-methylacetamide (**8**, 0.90 g, 2.99 mmol, 1.0 molar equiv) in dry toluene (50.0 mL) was cooled to -78 °C (dry ice/*iso*-PrOH) and LDA (1.79 mL, 2 M solution in heptane/THF/EtPh, 3.58 mmol, 1.2 molar equiv) was added dropwise to the reaction mixture. After 15 min solid NFSI (1.13 g, 3.59 mmol, 1.2 molar equiv) was added. The mixture was allowed to stir at -78 °C (dry ice/*iso*-PrOH) for 50 min, then warmed to rt and stir for an additional 50 min. Saturated aq NH_4Cl was added and the mixture was extracted with EtOAc (3 × 30 mL) and washed with H_2O (30 mL), brine solution (30 mL), and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, 10%, and 20% EtOAc in hexanes) to obtain product 2-(benzo[*d*]thiazol-2-ylthio)-2-fluoro-*N*-methoxy-*N*-methylacetamide (**1**, 0.69 g, 73%) as a white solid (R_f = 0.43, SiO_2, 40% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, 1H, Ar-H, J = 7.8 Hz), 8.04 (d, 1H, Ar-H, J = 7.8 Hz), 7.68-7.61 (m, 2H, Ar-H), 6.58 (d, 1H, CHF, $^2J_{HF}$ = 47.8 Hz), 3.90 (s, 3H, OCH_3), 3.32 (s, 3H, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ -181.4 (d, $^2J_{HF}$ = 45.7 Hz).

SYNTHESIS OF ALDEHYDE **2**

*Synthesis of 2-(2,2-dimethoxyethylthio)benzo[d]thiazole **10***

To a solution of sodium salt of 2-mercapto-1,3-benzothiazole (1.67 g, 8.86 mmol, 1.5 molar equiv) in 20 mL of DMF was added 2-bromo-1,1-dimethoxyethane (1.00 g, 5.91 mmol) and the reaction mixture was allowed to stir at 40 °C for 4 hours. At the completion of the reaction (TLC monitoring), the reaction mixture was diluted with ethyl acetate and washed with water. The water layer was extracted with EtOAc (3 × 30 mL), combined organic layer was washed with saturated $NaHCO_3$ (30 mL), brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2) using 20% EtOAc in hexanes to obtain pure compound 2-(2,2-dimethoxyethylthio)benzo(*d*)thiazole (**10**, 0.769 g, 51%) as a white paste (R_f = 0.40, SiO_2, 20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, 1H, Ar-H, J = 7.8 Hz), 7.75 (d, 1H, Ar-H, J = 8.3 Hz), 7.41 (t, 1H, Ar-H, J = 7.8 Hz), 7.90 (t, 1H, Ar-H, J = 7.8 Hz), 4.72 (t, 1H, CH, J = 5.3 Hz), 3.58 (d, 2H, CH_2, J = 5.3 Hz), 3.44 (s, 6H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 153.2, 135.5, 126.1, 124.4, 121.6, 121.1, 103.0, 54.3 and 35.5. HRMS (ESI) calcd. for $C_{11}H_{14}NS_2O_2$ $[M + H]^+$ 256.0460, found 256.0462.

*Synthesis of 2-(benzo[d]thiazol-2-ylthio)acetaldehyde **2***

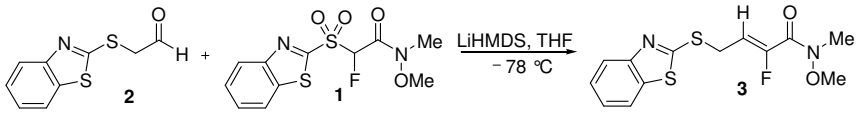


To a stirred solution of 2-(2,2-dimethoxyethylthio)benzo[*d*]thiazole (**10**, 1.60 g, 6.26 mmol) in 48 mL of acetone was added a solution of 10.6 mL of HCl (12N) and 5.2 mL of water slowly at room temperature. The reaction mixture was stirred for 40 minutes at 50 °C. At the completion of the reaction (TLC monitoring), the reaction mixture was quenched by portionwise addition of solid $NaHCO_3$ at 5 °C up to the neutralization point and then passed through anhydrous Na_2SO_4 bed. The eluent was dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain 2-(benzo[*d*]thiazol-2-ylthio)acetaldehyde (**2**, 1.10 g, 84%), (R_f = 0.29, SiO_2, 20% EtOAc in hexanes) which was used in the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (s, 1H, CHO), 7.85 (d, 1H, Ar-H, *J* = 7.9 Hz), 7.76 (d, 1H, Ar-H, *J* = 8.2 Hz), 7.42 (t, 1H, Ar-H, *J* = 7.6 Hz), 7.32 (t, 1H, Ar-H, *J* = 7.6 Hz) 4.09 (d, 2H, CH_2, *J* = 1.8 Hz).

SYNTHESIS OF SECOND-GENERATION JULIA REAGENT **4**

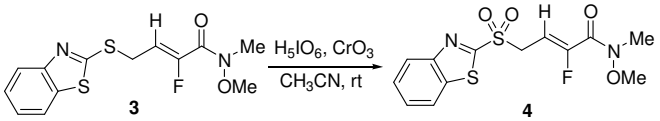
*Synthesis of (Z)-4-(benzo[d]thiazol-2-ylthio)-2-fluoro-N-methoxy-N-methylbut-2-enamide **3***



To a stirred solution of 2-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylacetamide (**1**, 0.700 g, 2.19 mmol) and 2-(benzo[*d*]thiazol-2-ylthio)acetaldehyde (**2**, 0.93 g, 4.44 mmol, 2.0 molar equiv) in dry THF (48.0 mL) at -78 °C (dry ice/*iso*-PrOH), was added dropwise LHMDS (6.57 mL, 1 M, 6.57 mmol, 3.0 molar equiv) under N_2 atmosphere. The reaction was allowed to stir at -78 °C (dry ice/*iso*- PrOH) until consumption of sulfone was observed by ^{19}F NMR (small sample was removed by syringe and checked by NMR). The reaction mixture was quenched with saturated NH_4Cl solution, the solvent was partially removed under reduce pressure and the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with 5% NaOH solution, followed by water and brine. Organic layer was dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and crude product was purified by column chromatography (SiO_2, 10%, 15% and 20% EtOAc in hexanes) to afford (*Z*)-4-(benzo[*d*]thiazol-2-ylthio)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide as a yellow paste (**3**, 0.523 g, 76%) (R_f = 0.54, SiO_2, 30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.76 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.43-7.40 (m, 1H, Ar-H), 7.32-7.29 (m, 1H, Ar-H,), 6.22 (dt, 1H, CH=, $^3J_{HF}$ = 32.7 Hz, $^3J_{HH}$ = 8.0 Hz), 4.15 (dd, 2H, CH_2, *J* = 8.0 Hz, 1.5 Hz), 3.69 (s, 3H, OCH_3), 3.22 (s, 3H, CH_3).^{13}C NMR(125 MHz, $CDCl_3$): δ 165.2, 161.8 (d, $^2J_{CF}$ = 27.9 Hz), 153.3, 152.4 (d,

$^{1}J_{CF}$ = 271.9 Hz), 135.7, 126.3, 124.6, 121.9, 121.2, 113.0 (d, $^{2}J_{CF}$ = 10.5 Hz), 62.1, 33.9 and 26.9 (d, $^{3}J_{CF}$ = 5.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -119.9 (d, $^{3}J_{HF}$ = 30.5 Hz). HRMS (ESI) calcd. for $C_{13}H_{14}FN_2S_2O_2$ $[M + H]^+$ 313.0475, found 313.0480.

*Synthesis of (Z)-4-(benzo[d]thiazol-2-ylsulfonyl)-2-fluoro-N-methoxy-N-methylbut-2-enamide **4***

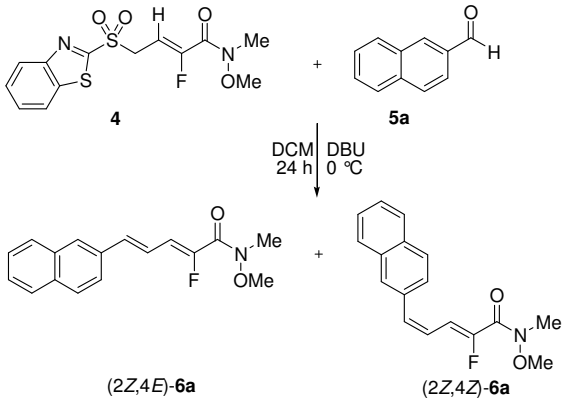


H_5IO_6 (0.47 g, 2.09 mmol, 3.0 molar equiv) was dissolved in CH_3CN (80.0 mL) by vigorous stirring at rt for 20 min. CrO_3 (25.0 mg, 0.25 mmol) was added and the reaction mixture was stirred for an additional 5 min to give an orange colored solution. A solution of (*Z*)-4-(benzo[*d*]thiazol-2-ylthio)-2-fluoro-*N*-methoxy-*N*-methybut-2-enamide **(3,** 0.21 g, 0.69 mmol) in CH_3CN (10.0 mL) was added dropwise to this mixture, resulting in an exothermic reaction and formation of a yellowish precipitate. After complete addition the reaction mixture was stirred for three hours, at which time TLC (SiO_2, 25% EtOAc in hexanes) showed a complete consumption of (*Z*)-4-(benzo[*d*]thiazol-2-ylthio)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide, **3**. The reaction mixture was filtered through a Celite pad, the Celite was washed with CH_3CN, and the filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc (3 × 30 mL), then the combined organic layer was washed with saturated aq $NaHCO_3$ (5 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 15%, 20% and 25% EtOAc in hexanes) to afford (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide as a yellow solid (**4**, 0.152 g, 63%, R_f = 0.43, SiO_2, 40% ethyl acetate in hexanes).^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, 1H, Ar-H, *J* = 7.8 Hz), 8.02 (d, 1H, Ar-H, *J* = 7.8 Hz), 7.67-7.59 (m, 2H, Ar-H), 5.96 (dt, 1H, CH=, $^{3}J_{HF}$ = 31.2 Hz, $^{3}J_{HH}$ = 8.3 Hz), 4.43 (dd, 2H, CH_2, *J* = 8.3 Hz, 1.5 Hz), 3.53 (s, 3H, OCH_3), 3.17 (s, 3H, CH_3).^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 160.8 (d, $^{2}J_{CF}$ = 28.4 Hz), 155.6 (d, $^{1}J_{CF}$ = 279.7 Hz,), 152.8, 137.2, 128.4, 127.9, 125.8, 122.6, 102.7 (d, $^{2}J_{CF}$ = 10.1 Hz), 62.1, 51.1 (d, $^{2}J_{CF}$ = 4.6 Hz)

and 33.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ 113.6 (d, $^3J_{HF}$ = 30.5 Hz). HRMS (ESI) calcd. for $C_{13}H_{14}FN_2S_2O_4$ $[M + H]^+$ 345.0374, found 345.0376.

CONDENSATION REACTIONS OF **4**

Synthesis of (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-5-(naphthalen-2-yl)penta-2,4-dienamide ***6a***

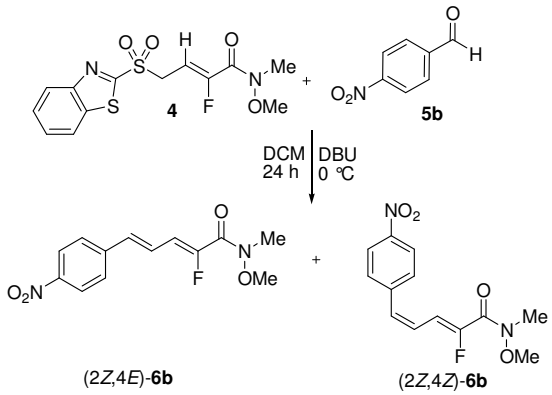


To a stirred solution of napthaldehyde (**5a**, 31.2 mg, 0.20 mmol) in dry DCM (10.0 mL) was added DBU (121.6 mg, 0.80 mmol, 4.0 molar equiv) and the mixture was cooled to 0 °C. A solution of (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide (**4**, 103.3 mg, 0.29 mmol, 1.5 equiv) in dry DCM (10.0 mL) was then added slowly and dropwise (for about 90 minutes). The reaction mixture was allowed to stir overnight at 0 °C. After completion of the reaction, analysis of the crude reaction mixture by ^{1}H and ^{19}F NMR showed the 4*E*/4*Z* product ratio 35:65. Reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 10%, 15% and 20% EtOAc in hexanes) to afford (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(naphthalen-2-yl)penta-2,4-dienamide (**6a**, 38.0 mg, 66%) as a white solid (R_f = 0.58 for 4*E*-isomer and R_f = 0.49 for 4*Z*-isomer, SiO_2, 30% EtOAc in hexanes). ^{1}H NMR (500 MHz ,$CDCl_3$): δ 7.85-7.80 (m, Ar-H, 4H, 4*E*-isome*r* and 4H, 4*Z*-isomer), 7.68 (m, 1H, Ar-H, 4*E*-isomer) 7.50-7.45 (m, Ar-H, 2H, 4*E*- and 3H, 4*Z*-isomer), 7.50-7.45 (m, Ar-H , 4*E*- and 4*Z*-isomer), 7.21 (dd, 1H, CH=, *J* = 15.6 Hz and 11.2 Hz, 4*E*-isomer), 7.06 (dd, 1H, CH=, $^3J_{HF}$ = 32.7 Hz, $^3J_{HH}$ = 12.0 Hz, $^4J_{HH}$ = 1.0 Hz 4*Z*-isomer), 6.91 (d, 1H, Ar-CH, *J* = 15.6 Hz, 4*Z*-isomer), 6.97 (d,

1H, Ar-CH, J = 11.2 Hz, 4*E*-isomer), 6.72 (dd, 1H, CH=, $^{3}J_{HF}$ = 32.5 Hz, $^{3}J_{HH}$ = 11.5 Hz, 4*E*-isomer), 6.66 (t, 1H, CH=, J = 11.7 Hz, 4*Z*-isomer), 3.80 (s, 3H, OMe, 4*E*-isomer), 3.76 (s, 3H, OMe, 4*Z*-isomer), 3.29 (s, 3H, Me, 4*E*-isomer), 3.25 (s, 3H, Me, 4*Z*-isomer). ^{19}F (282 MHz, $CDCl_3$): δ -121.1 (d, $^{3}J_{HF}$ = 30.5 Hz, 4*Z*-isomer), -123.4 (d, $^{3}J_{HF}$ = 30.5 Hz, 4*E*-isomer). HRMS (ESI) calcd. for $C_{17}H_{17}FNO_2$ $[M + H]^+$ 286.1238, found 286.1242.

[Note: the mixture of 4*E*- and 4*Z*-isomers was analyzed and characterized based on the ^{1}H NMR; assignment and integration of olefinic proton at δ 7.21 ppm and 6.66 ppm allowed for other peaks to be characterized based on the integration, along with comparison to pure 2*Z*,4*E*-isomer. Assignment of ^{19}F NMR signals to 4*E*- and 4*Z*-isomers was based on the integration.]

Synthesis of (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-5-(4-nitrophenyl)penta-2,4-dienamide ***6b***

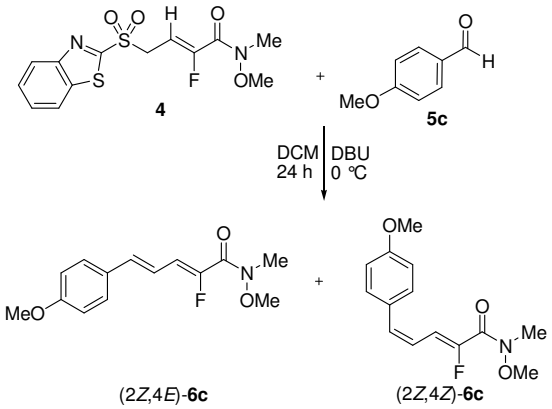


To a stirred solution of *p*-nitrobenzaldehyde (**5b**, 30.2 mg, 0.20 mmol) in dry DCM (10.0 mL) was added DBU (121.7 mg, 0.8 mmol, 4.0 molar equiv) and the mixture was cooled to 0 °C. A solution of (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide (**4**, 103.3 mg, 0.20 mmol, 1.5 molar equiv) in dry DCM (10.0 mL) was then added slowly and dropwise (for about 90 minutes).The reaction mixture was allowed to stir overnight at 0 °C. After completion of the reaction, analysis of the crude reaction mixture by ^{1}H and ^{19}F NMR showed the 4*E*/4*Z* product ratio 4:6. Reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 8%, 15% and 20% EtOAc in hexanes) to afford (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(4-nitrophenyl)penta-2,4-

dienamide (**6b**, 41.3 mg, 74%) as a yellow solid (R_f = 0.47 for 4*E*- and R_f = 0.72 for 4*Z*-isomers, SiO_2, 30% EtOAc in hexanes). The ratio of isomers after column chromatography was 4*E*/4*Z* 3:7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, 2H, Ar-H, *J* = 9.0 Hz, 4*Z*-isomer), 8.21 (d, 2H, Ar-H, *J* = 8.7 Hz, 4*E*-isomer), 7.60 (d, 2H, Ar-H, *J* = 8.8 Hz, 4*E*-isomer), 7.48 (d, 2H, Ar-H, *J* = 8.3 Hz, 4*Z*-isomer), 7.23 (dd, 1H, CH=, *J* = 15.9 Hz, 11.5 Hz, 4*E*-isomer), 6.86-6.61(m, 3H, 4*Z*-isomer and 2H, 4*E*-isomer), 3.79 (s, 3H, OMe, 4*E*-isomer), 3.77 (s, 3H, OMe, 4*Z*-isomer), 3.28 (s, 3H, Me, 4*E*-isomer), 3.25 (s, 3H, Me, 4*Z*-isomer). ^{19}F NMR (282 MHz, $CDCl_3$): δ -118.4 (d, $^3J_{HF}$ = 30.5 Hz, 4*Z*-isomer), -119.6 (d, $^3J_{HF}$ = 30.5 Hz, 4*E*-isomer). HRMS (ESI) calcd for $C_{13}H_{14}FN_2O_4$ [M + H]$^+$ 281.0932, found 281.0935.

[Note: the mixture of 4*E*- and 4*Z*-isomers was analyzed and characterized based on the ^{1}H NMR; assignment and integration of olefinic proton at δ 7.23 ppm and 6.86-6.61 ppm allowed for other peaks to be characterized based on the integration, along with comparison to pure 2*Z*,4*E*-isomer. Assignment of ^{19}F NMR signals to 4*E*- and 4*Z*-isomers was based on the integration.]

Synthesis of (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-5-(4-methoxyphenyl)penta-2,4-dienamide ***6c***

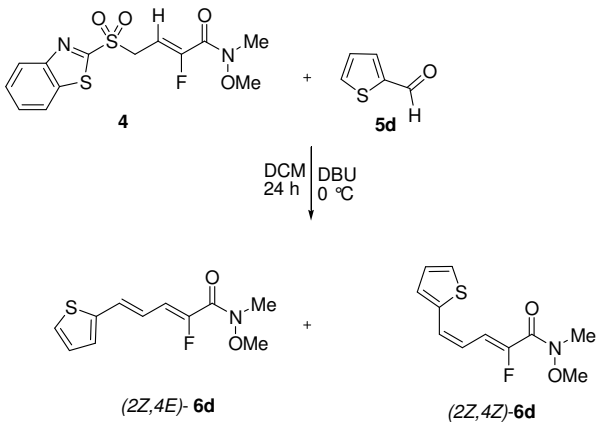


To a stirred solution of *p*-methoxybenzaldehyde (**5c**, 27.2 mg, 0.2 mmol) in dry DCM (10.0 mL) was added DBU (121.7 mg, 0.80 mmol, 4.0 molar equiv) and the mixture was cooled to 0 °C. A solution of (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide (**4**, 103.3 mg, 0.29 mmol, 1.5 equiv) in dry DCM (10.0 mL) was then added slowly and dropwise (for about 90 minutes).The reaction mixture was allowed

to stir overnight at 0 °C. After completion of the reaction, analysis of the crude reaction mixture by ^{1}H and ^{19}F NMR showed the 4*E*/4*Z* product ratio 1:4. Reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 8%, 15% and 20% EtOAc in hexanes) to afford (2*Z*, 4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(4-methoxyphenyl)penta-2,4-dienamide (**6c**, 26.5 mg, 51%) as a white paste (R_f = 0.53, SiO_2, 30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, 1H, Ar-H, *J* = 8.8 Hz, 4*E*-isomer), 7.29 (d, 1H, Ar-H, *J* = 8.8 Hz, 4*Z*-isomer), 6.99 (ddd, 1H, CH=, $^{3}J_{HF}$ = 32.7 Hz, $^{3}J_{HH}$ = 11.7 Hz, $^{4}J_{HH}$ = 0.9 Hz, 4*Z*-isomer), 6.95 (dd, 1H, CH=, *J* = 15.6 Hz, 11.2 Hz, 4*E*-isomer), 6.91-6.87 (m, Ar-H, 2H, 4*E*-isomer and 2H, 4*Z*-isomer), 6.75 (d, 1H, Ar-CH, *J* = 15.6 Hz, 4*E*-isomer), 6.69 (br d, 1H, CH=, *J* = 11.7 Hz, 4Z-isomer), 6.65 (dd, 1H, $^{3}J_{HF}$ = 32.7 Hz, $^{3}J_{HH}$ = 11.4, 4*E*-isomer), 6.47 (t, 1H, *J* = 11.7 Hz, 4*Z*-isomer), 3.83 (s, 3H, Ar-OMe, 4*E*-isomer), 3.82 (s, 3H, Ar-OMe, 4*Z*-isomer), 3.77 (s, 3H, OMe, 4*E*-isomer), 3.76 (s, 3H, OMe, 4*Z*-isomer), 3.27 (s, 3H, CH_3, 4*E*-isomer), 3.25 (s, 3H, CH_3, 4*Z*-isomer). ^{19}F (282 MHz, $CDCl_3$): δ -122.6 (d, $^{3}J_{HF}$ = 33.6, 4*Z*-isomer), -125.2 (d, $^{3}J_{HF}$ = 33.6, 4*E*-isomer) and. HRMS (ESI) calcd. for $C_{14}H_{17}FNO_3$ $[M + H]^+$ 266.1187, found 266.1191.

[Note: the mixture of 4*E*- and 4*Z*-isomers was analyzed and characterized based on the ^{1}H NMR; assignment and integration of olefinic proton at δ 6.95 ppm and 6.47 ppm allowed for other peaks to be characterized based on the integration, along with comparison to pure 2*Z*,4*E*-isomer. Assignment of ^{19}F NMR signals to 4*E*- and 4*Z*-isomer was based on the integration.]

Synthesis of (2 Z,4E/Z)-2-fluoro–N-methoxy-N-methyl-5-(thiophen-2-yl)penta-2,4-dienamide ***6d***

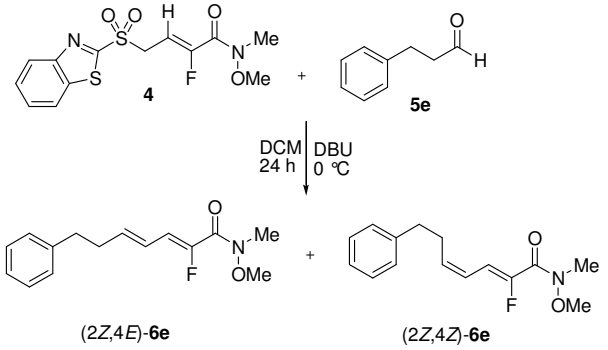


To a stirred solution of thiophene-2-carbaldehyde (**5d**, 22.4 mg, 0.20 mmol) in dry DCM (10.0 mL) was added DBU (121.7 mg, 0.80 mmol, 4.0 molar equiv) and the mixture was cooled to 0 °C. A solution of (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide (**4**, 103.3 mg, 0.29 mmol, 1.5 molar equiv) in dry DCM (10.0 mL) was then added slowly and dropwise (for about 90 minutes). The reaction mixture was allowed to stir overnight at 0 °C. After completion of the reaction analysis of the crude reaction mixture by ^{19}F NMR showed the 4*E*/4*Z* product ratio 1:9. Reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 8%, 15% and 20% EtOAc in hexanes) to afford (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(thiophen-2-yl)penta-2,4-dienamide (**6d**, 30.2 mg, 63%) as a yellow paste (R_f = 0.34, SiO_2, 30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (dd, 1H, Ar-H, J = 6.4 Hz, 1.5 Hz, 4*E*-isomer), 7.36 (d, 1H, Ar-H, J = 4.9 Hz, 4*Z*-isomer), 7.26 (ddd, 1H, CH=, $^3J_{HF}$ = 31.7 Hz, $^3J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 1.0 Hz, 4*Z*-isomer), 7.12 (d, 1H, Ar-H, J = 3.4 Hz, 4*Z*-isomer), 7.09 (d, 1H, Ar-H, J = 3.4 Hz, 4*E*-isomer), 7.04 (dd, 1H, Ar-H, J = 5.1 Hz, 3.7 Hz, 4*Z*-isomer), 7.00 (dd, 1H, Ar-H, J = 5.13 Hz, 3.7 Hz, 4*E*-isomer), 6.90 (d, 1H, Ar-CH, J = 15.6 Hz, 4*E*-isomer), 6.86 (dd, 1H, CH=, J = 15.6 Hz, 10.7 Hz, 4*E*-isomer), 6.76 (br d, 1H, Ar-CH, J = 11.2 Hz, 4Z-isomer), 6.61 (dd, 1H, CH=, $^3J_{HF}$ = 32.2 Hz, $^3J_{HH}$ = 10.7 Hz, 4*E*-isomer), 6.42 (t, 1H, J = 12.0 Hz, 4*Z*-isomer), 3.78 (s, 3H, OMe, 4*Z*-isomer), 3.77 (s, 3H, OMe, 4*E*-isomer), 3.28 (s, 3H, Me, 4*Z*- isomer), 3.26 (s, 3H, Me, 4*E*-isomer). ^{19}F (282 MHz,$CDCl_3$): δ -120.7

(d, $^3J_{HF}$ = 33.6 Hz, 4*Z*-isomer), -123.7 (d, $^3J_{HF}$ = 30. 5 Hz, 4*E*-isomer). HRMS (ESI) calcd. for $C_{11}H_{13}FNO_2S$ $[M + H]^+$ 242.0646, found 242.0647.

[Note: the mixture of 4*E*- and 4*Z*-isomers was analyzed and characterized based on the ^{1}H NMR; assignment and integration of olefinic proton at δ 6.86 ppm and 6.42 ppm allowed for other peaks to be characterized based on the integration, along with comparison to pure 2*Z*,4*E*-isomer. Assignment of ^{19}F NMR signals to 4*E*- and 4*Z*- based on the integration.]

Synthesis of (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-7-phenylhepta-2,4-dienamide ***6e***



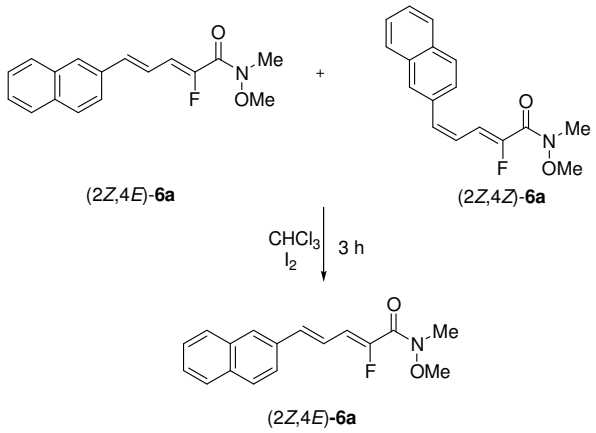
To a stirred solution of 3-phenylpropanal (**5e**, 26.8 mg, 0.20 mmol) in dry DCM (10.0 mL) was added DBU (121.6 mg, 0.80 mmol, 4.0 equiv) and the mixture was cooled to 0 °C. A solution of (*Z*)-4-(benzo[*d*]thiazol-2-ylsulfonyl)-2-fluoro-*N*-methoxy-*N*-methylbut-2-enamide (**4**, 103.3 mg, 0.20 mmol, 1.5 equiv) in dry DCM (10.0 mL) was added slowly and dropwise (for about 90 minutes). The reaction mixture was allowed to stir overnight at 0 °C. After completion of the reaction analysis of the crude reaction mixture by ^{19}F NMR showed the 4*E*/4*Z* product ratio 16:84. Reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, 8%, 15% and 20% EtOAc in hexanes) to afford (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-7-phenylhepta-2,4-dienamide (**6e**, 26.5 mg, 51%) as a white liquid (R_f = 0.30, SiO_2, 30% EtOAc in hexanes). We were able to resolve the ^{1}H NMR signals for the major (2*Z*,4*Z*)-isomer only. ^{1}H NMR (500 MHz ,$CDCl_3$) of (2*Z*,4*Z*)-isomer: δ 7.30-7.27 (m, 2H, Ar-H), 7.20-7.18 (m, 3H, Ar-H), 6.34 (t, 1H, CH=, *J* = 11.2 Hz), 5.80 (dt, 1H, CH=, J = 10.7 Hz, 7.8 Hz), 3.74 (s, 3H, OMe), 3.24 (s, 3H, CH_3), 2.73 (t, 2H, CH_2, *J* = 7.8 Hz), 2.55 (q, 2H, CH_2, *J* = 7.8 Hz). ^{19}F (282 MHz, $CDCl_3$): δ -124.2 (d, $^3J_{HF}$ = 30.5 Hz), -

125.6 (d, $^{3}J_{HF}$ = 30.5 Hz). HRMS (ESI) calcd for $C_{17}H_{17}FNO_2$ $[M + H]^+$ 264.1394, found 264.1407

[Note: 4*Z*-isomer was characterized based on the olefinic proton at δ 6.34 ppm which allowed for other peaks to be characterized based on the integration. Assignment of ^{19}F NMR signals to 4*E*- and 4*Z*-isomers was characterized based on the integration.]

ISOMERIZATION OF (2*Z*,4*E*/*Z*)**6a-d** TO (2*Z*,4*E*)**6a-d**

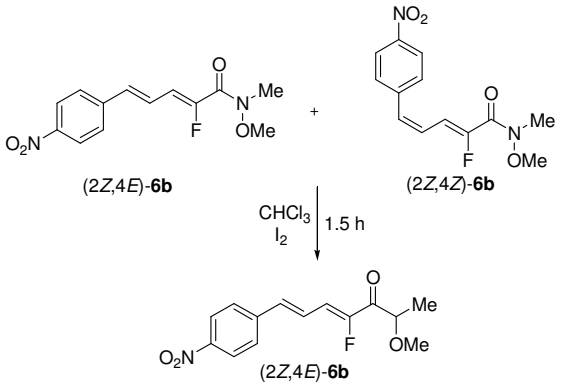
*Isomerization of (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-5-(naphthalen-2-yl)penta-2,4-dienamide (2Z,4E/Z)-**6a** to (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-5-(naphthalen-2-yl)-penta-2,4-dienamide (2Z,4E)-**6a***



To a stirred solution of (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(naphthalen-2-yl)penta-2,4-dienamide (**6a**, 16.0 mg, 0.05 mmol) in dry $CHCl_3$ (8.0 mL) was added I_2 (1.26 mg, 5.0×10^{-3} mmol, 10 mol%) and allowed to stirr for 3 h at rt. Reaction was monitored by ^{19}F NMR. When only one isomer was observed in ^{19}F NMR (3 h), the reaction mixture was extracted with EtOAc (30 mL) and washed with water, saturated aq $Na_2S_2O_3$ (2 × 10 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the desired isomer (2*Z*,4*E*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(naphthalen-2-yl)penta-2,4-dienamide {(2*Z*,4*E*)-**6a**, 12.0 mg, 75%} as a white paste (R_f = 0.58, SiO_2, 30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83-7.80 (m, 4H, Ar-H), 7.69 (dd, 1H, Ar-H, J = 8.3 Hz, 1.5 Hz), 7.50-7.46 (m, 2H, Ar-H), 7.21 (dd, 1H, CH=, J = 15.8 Hz, 11.3 Hz), 6.97 (d, 1H, J = 15.8 Hz), 6.72 (dd, 1H, $^{3}J_{HF}$ = 32.4 Hz, $^{3}J_{HH}$ = 11.3 Hz), 3.80 (s, 3H, OMe), 3.29 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.8

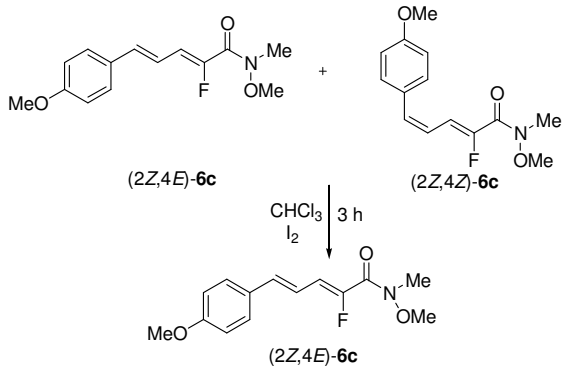
(d, C=O, $^{2}J_{CF}$ = 26.5 Hz), 150.2 (d, C-F, $^{1}J_{CF}$ = 275.6 Hz), 137.9 (d, $^{4}J_{CF}$ = 4.5 Hz), 134.1, 133.7, 128.7, 128.4, 128.01, 128.0, 127.9, 126.8, 126.7, 123.6, 119.7 (d, $^{3}J_{CF}$ = 3.6 Hz), 118.2 (d, $^{2}J_{CF}$ = 9.2 Hz), 62.2 and 34.3. ^{19}F (282 MHz, $CDCl_3$): δ -123.4 (d, $^{3}J_{HF}$ = 30.5 Hz). HRMS (ESI) calcd. for $C_{17}H_{17}FNO_2$ $[M + H]^+$ 286.1238, found 286.1242.

*Isomerization of (2Z,4E/Z)-2-fluoro-N-methoxy-N-methyl-5-(4-nitrophenyl)penta-2,4-dienamide (2Z,4E/Z)-**6b** to (2Z,4E)-2-fluoro -N-methoxy-N-methyl-5-(4-nitrophenyl)penta-2,4-dienamide (2Z,4E)-**6b***



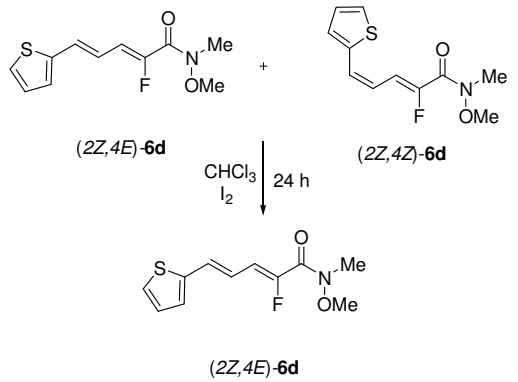
To a stirred solution of (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(4-nitrophenyl)penta-2,4- dienamide (**6b**, 4.5 mg, 0.01 mmol) in dry $CHCl_3$ (1.6 mL) was added I_2 (0.25 mg, 1.0×10^{-3} mmol, 10 mol%) and allowed to stir for 1.5 h at rt. Reaction was monitored by ^{19}F NMR. When only one isomer was observed in ^{19}F NMR (1.5 h), the reaction mixture was extracted with EtOAc (30 mL) and washed with water, saturated aq $Na_2S_2O_3$ (2×10 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford desired isomer (2*Z*,4*E*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(4-nitrophenyl)penta-2,4-dienamide {(2*Z*,4*E*)-**6b**, 4.0 mg, 88%) as a white paste (R_f = 0.47, SiO_2, 30% EtOAc in hexanes) . ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, Ar-H, 2H, *J* = 8.8 Hz), 7.60 (d, Ar-H, 2H, *J* = 8.8 Hz), 7.23 (dd, 1H, *J* = 15.8 Hz, 11.4 Hz), 6.83 (d, 1H, *J* = 15.8 Hz), 6.65 (dd, 1H, $^{3}J_{HF}$ = 31.6 Hz, $^{3}J_{HH}$ = 11.3 Hz), 3.79 (s, 3H, OMe), 3.28 (s, 3H, Me).^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3 (d, C=O, $^{2}J_{CF}$ = 26.6 Hz), 151.8 (d, C-F, $^{1}J_{CF}$ = 280.4 Hz), 147.6, 142.9, 134.7 (d, $^{4}J_{CF}$ = 4.6 Hz), 127.6, 124.4, 123.6 (d, $^{3}J_{CF}$ = 3.7 Hz), 116.8 (d, $^{2}J_{CF}$ = 9.2 Hz), 62.3 and 34.2. ^{19}F (282 MHz, $CDCl_3$): δ -119.6 (d, $^{3}J_{HF}$ = 30.5 Hz). HRMS (ESI) calcd. for $C_{13}H_{14}FN_2O_4$ $[M + H]^+$ 281.0932, found 281.0935.

*Isomerization of (2Z,4E/Z)-2-fluoro–N-methoxy-N-methyl-5-(4-methoxyphenyl)penta-2,4-dienamide (2Z,4E/Z)-**6c** to (2Z,4E)-2-fluoro-N-methoxy-N-methyl-5-(4-methoxyphenyl)penta-2,4-dienamide (2Z,4E)-**6c***



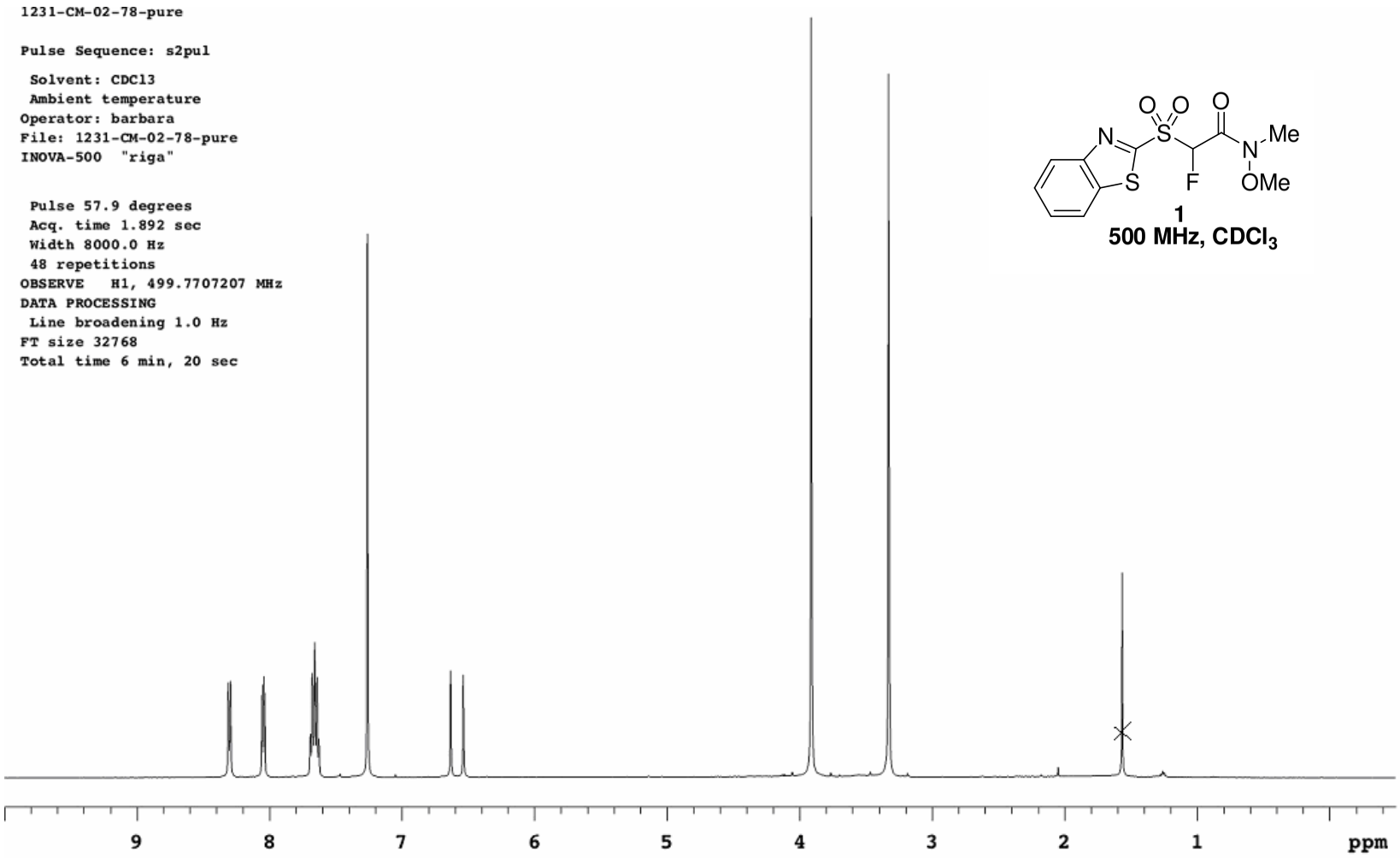
To a stirred solution of (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(4-methoxyphenyl)penta-2,4-dienamide (**6c**, 14.0 mg, 0.05 mmol) in dry $CHCl_3$ (8.0 mL) was added I_2 (1.26 mg, 4.9×10^{-3} mmol, 10 mol%) and allowed to stir for 3 h at rt. Reaction was monitored by ^{19}F NMR. When only isomer was observed in ^{19}F NMR (3 h), the reaction mixture was extracted with EtOAc (30 mL) and washed with water, saturated aq $Na_2S_2O_3$ (2 × 10 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the desired isomer (2*Z*,4*E*)-2-fluoro–*N*-methoxy-*N*-methyl-5-(4-methoxyphenyl)penta-2,4-dienamide {(2*Z*,4*E*)-**6c**, 12.0 mg, 85%) as a white paste (R_f = 0.53, SiO_2, 30% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, 2H, Ar-H, J = 7.1 Hz), 6.95 (dd, 1H, CH=, J = 15.6 Hz, 11.2 Hz), 6.88 (d, 2H, Ar-H, J = 7.1 Hz), 6.75 (d, 1H, Ar-CH, J = 15.6 Hz), 6.65 (dd, 1H, CH=, $^3J_{HF}$ = 32.5 Hz, $^3J_{HH}$ = 11.3 Hz), 3.83 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.27 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9 (d, C=O, $^2J_{CF}$ = 26.8 Hz), 160.4, 149.5 (d, C-F, $^1J_{CF}$ = 272.8 Hz), 137.5, 129.5, 128.7, 118.7 (d, $^2J_{CF}$ = 9.1 Hz), 117.2, 114.5, 62.1, 55.6, 34.3. ^{19}F (282 MHz, $CDCl_3$): δ -125.1 (d, $^3J_{HF}$ = 33.6 Hz). HRMS (ESI) calcd for $C_{14}H_{17}FNO_3$ $[M + H]^+$ 266.1187, found 266.1191.

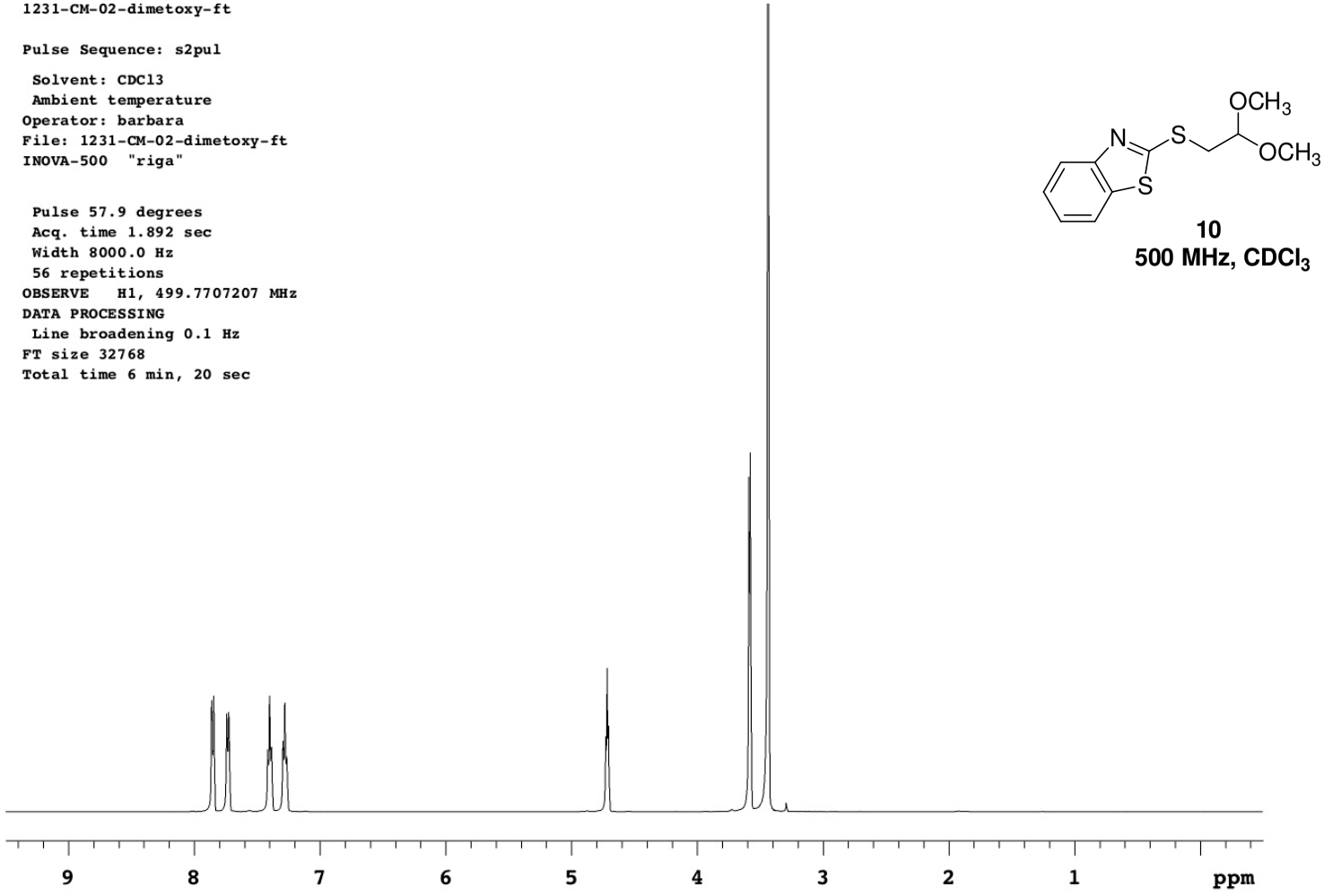
Isomerization of (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(thiophen-2-yl)penta-2,4-dienamide (2*Z*,4*E/Z*)-**6d** to (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(thiophen-2-yl)penta-2,4- dienamide (2*Z*,4*E*)-**6d**



To a stirred solution of (2*Z*,4*E/Z*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(thiophen-2-yl)penta-2,4-dienamide (**6d**, 12.0 mg, 0.04 mmol) in dry $CHCl_3$ (7.5 mL) was added I_2 (1.01 mg, 4.0×10^{-3} mmol, 10 mol%) and allowed to stir overnight at rt. Reaction was monitored by ^{19}F NMR. When only one isomer was observed in ^{19}F NMR (24 h), the reaction mixture was extracted with EtOAc (30 mL) and washed with water, saturated aq $Na_2S_2O_3$ (2 × 10 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the desired isomer (2*Z*,4*E*)-2-fluoro-*N*-methoxy-*N*-methyl-5-(thiophen-2-yl)penta-2,4-dienamide {(2*Z*,4*E*)-**6d** , 11.0 mg, 91%} as a yellow paste (R_f = 0.34, SiO_2, 30% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 1H, Ar-H, J = 5.4 Hz), 7.09 (d, 1H, Ar-H, J = 3.4 Hz), 7.0 (dd , 1H, Ar-H, J = 5.1 Hz, 3.7 Hz), 6.93 (d, 1H, J = 15.7 Hz), 6.86 (dd, 1H, J = 15.6 Hz, 10.4 Hz), 6.61 (dd, 1H, $^3J_{HF}$ = 32.2 Hz, $^3J_{HH}$ = 10.7 Hz), 3.77 (s, 3H, OMe), 3.26 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7 (d, C=O, $^2J_{CF}$ = 26.5 Hz), 150.1 (d, C-F, $^1J_{CF}$ = 275.5 Hz), 142.1, 130.4 (d, $^4J_{CF}$ = 5.0 Hz), 128.1, 126.5 (d, J = 1.38 Hz), 118.9 (d, $^3J_{CF}$ = 3.2 Hz), 117.9 (d, $^2J_{CF}$ = 9.6 Hz), 62.1, 34.3. ^{19}F (282 MHz, $CDCl_3$): δ -123.7 (d, $^3J_{HF}$ = 30.5 Hz). HRMS (ESI) calcd for $C_{11}H_{13}FNO_2S$ $[M + H]^+$ 242.0646, found 242.0647.

APPENDIX: ^{1}H NMR AND ^{13}C NMR SPECTRA


1231-CM-02-78-pure
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-CM-02-78-pure
INOVA-500 "riga"
Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 6 min, 20 sec
O
O
O
N
S
Me
N
S
F
OMe
1
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
ppm



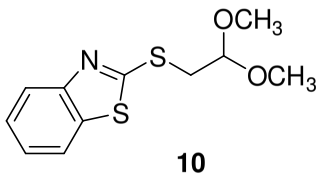
10
500 MHz, $CDCl_3$

1231-CM-02-dimethoxy-sulfide-13C

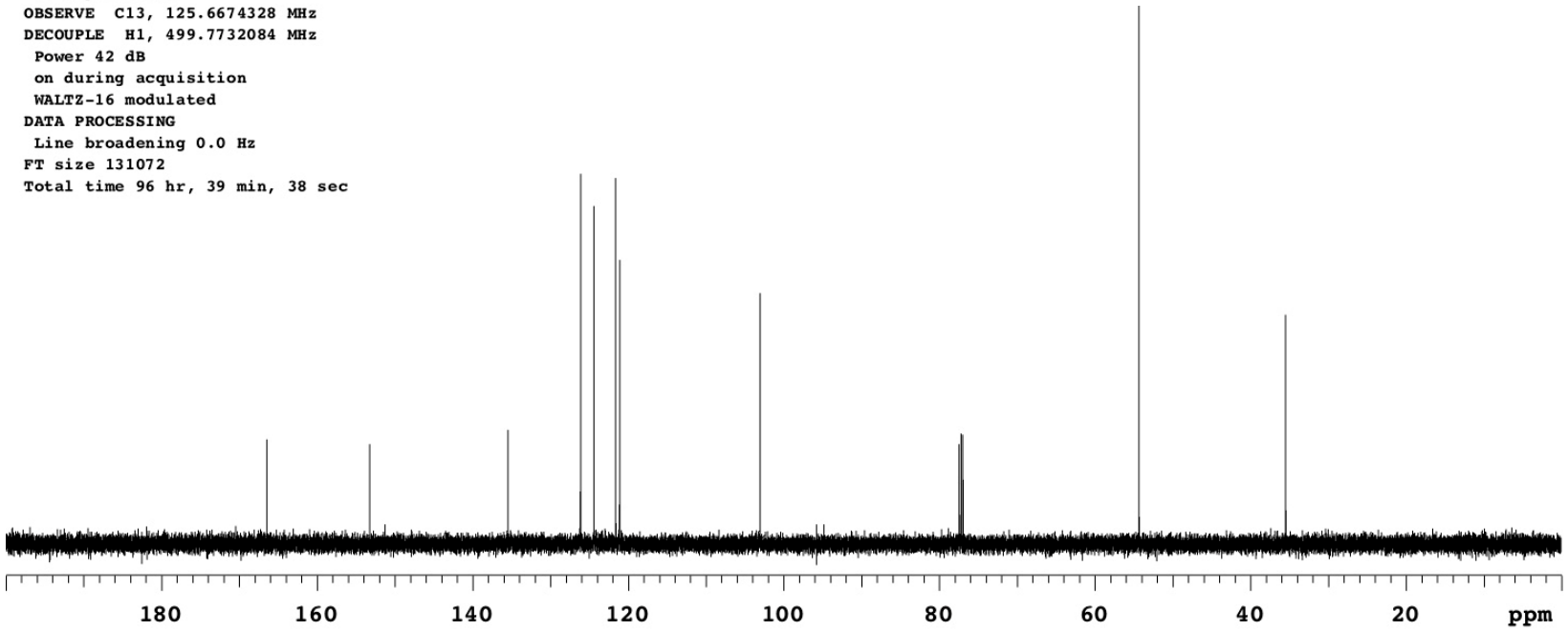
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-CM-02-dimethoxy-sulfide-13C
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
44 repetitions
OBSERVE C13, 125.6674328 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



10
125 MHz, $CDCl_3$

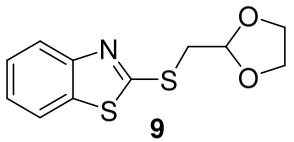


1222-CM-01-19-pure

Pulse Sequence: s2pul

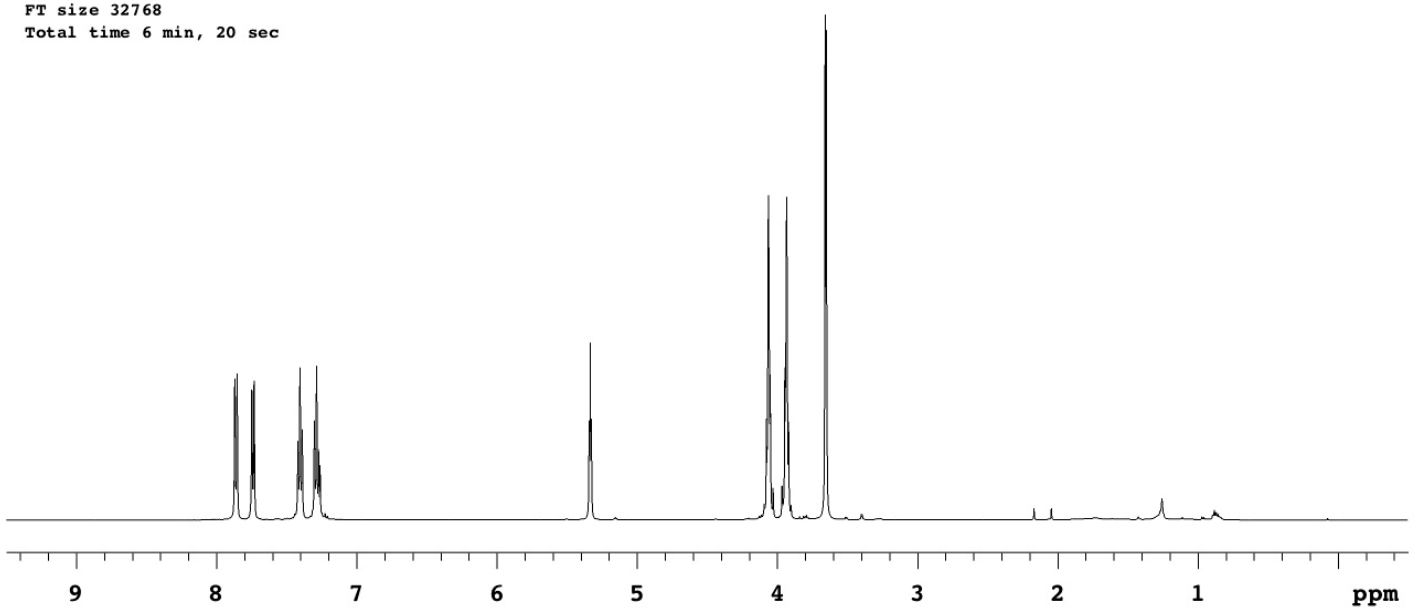
Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1222-CM-01-19-pure
INOVA-500 "riga"

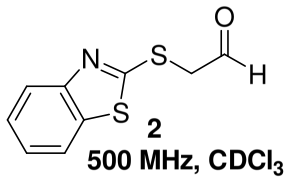
Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
28 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 6 min, 20 sec



9

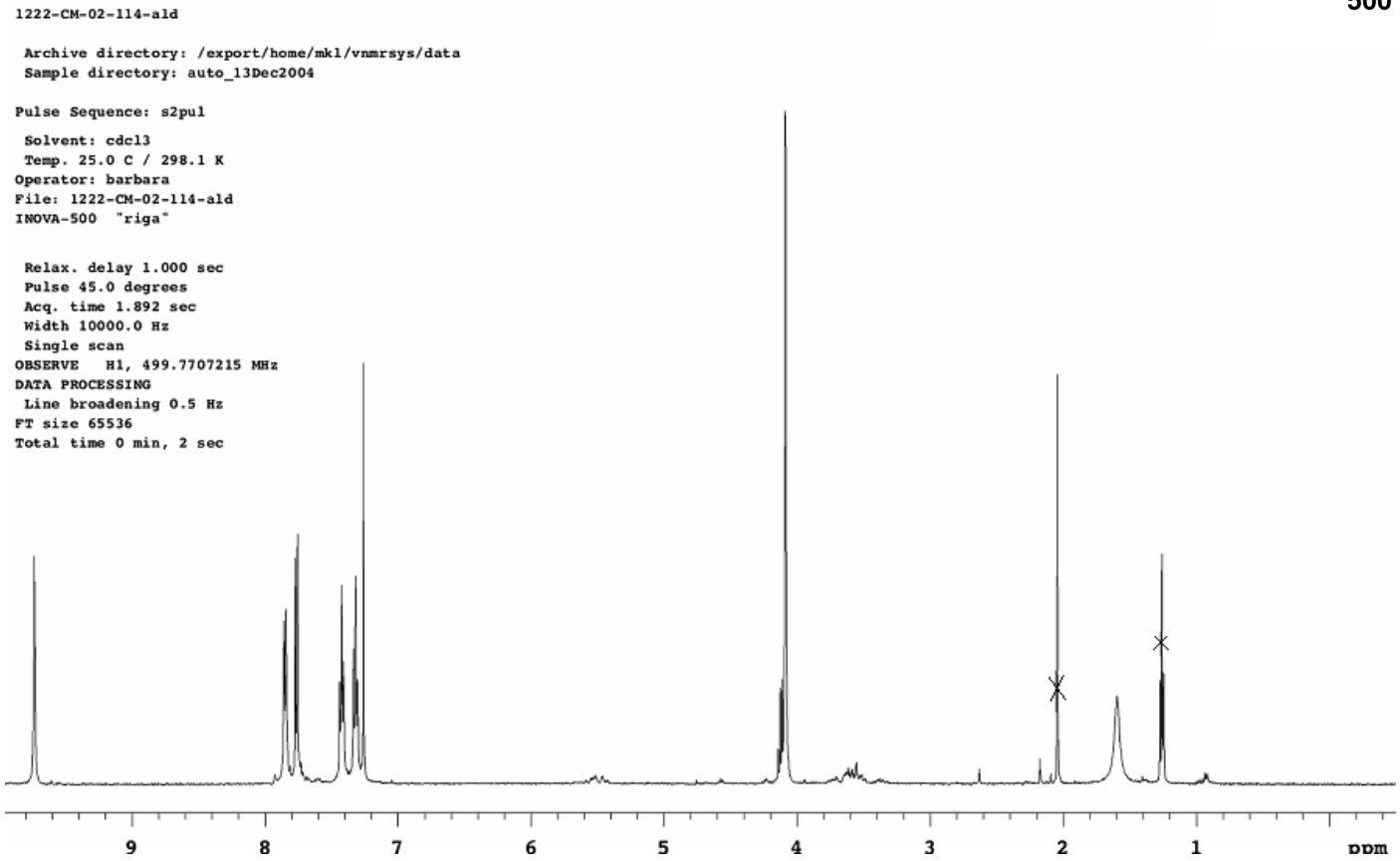
500 MHz, $CDCl_3$

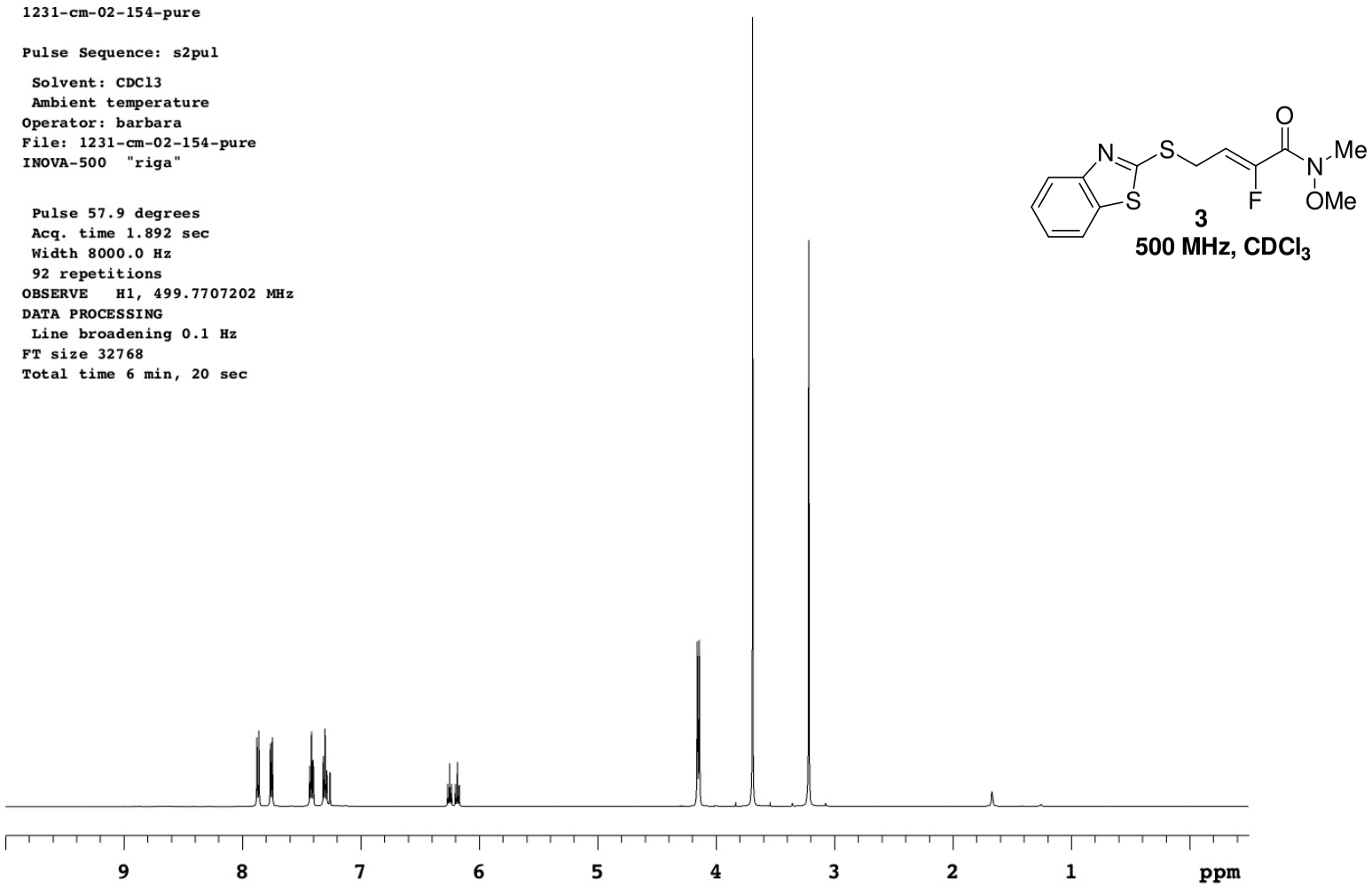




2

500 MHz, $CDCl_3$



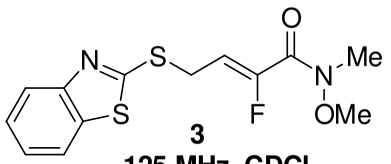

1231-cm-02-154-pure
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-cm-02-154-pure
INOVA-500 "riga"
Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
92 repetitions
OBSERVE H1, 499.7707202 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
N
S
S
O
N
Me
OMe
F
3
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
ppm

1231-CM-02-116-13c

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-CM-02-116-13c
INOVA-500 "riga"

Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1176 repetitions
OBSERVE C13, 125.6674302 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



3

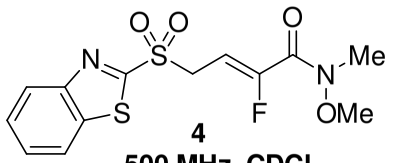
125 MHz, $CDCl_3$

1231-CM-02-117-ft

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-CM-02-117-ft
INOVA-500 "riga"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec



4

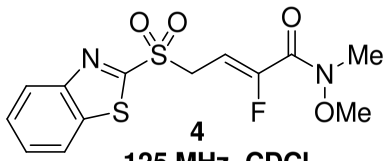
500 MHz, $CDCl_3$

1231-CM-02-117-13C

Pulse Sequence: s2pul

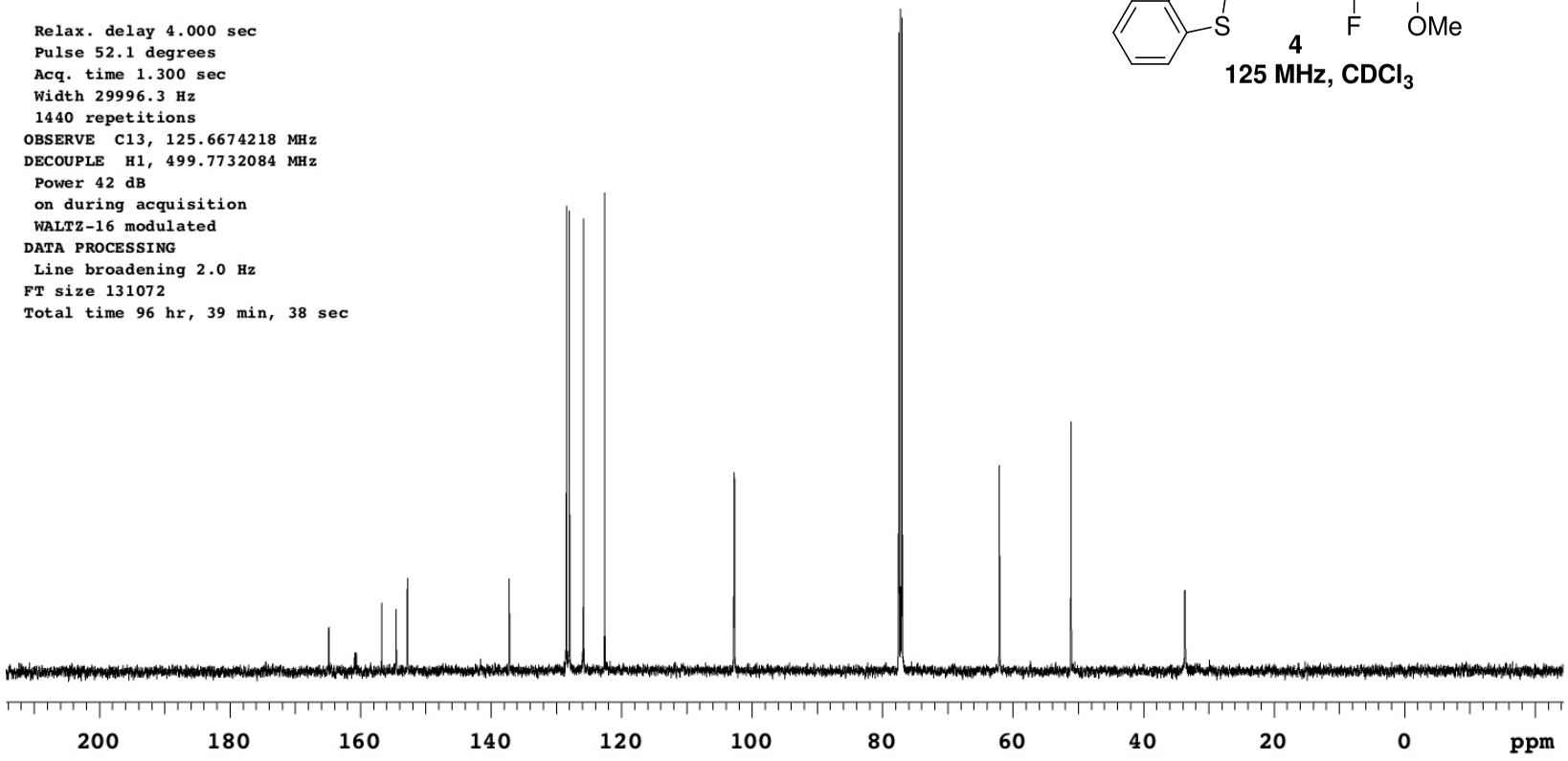
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-CM-02-117-13C
INOVA-500 "riga"

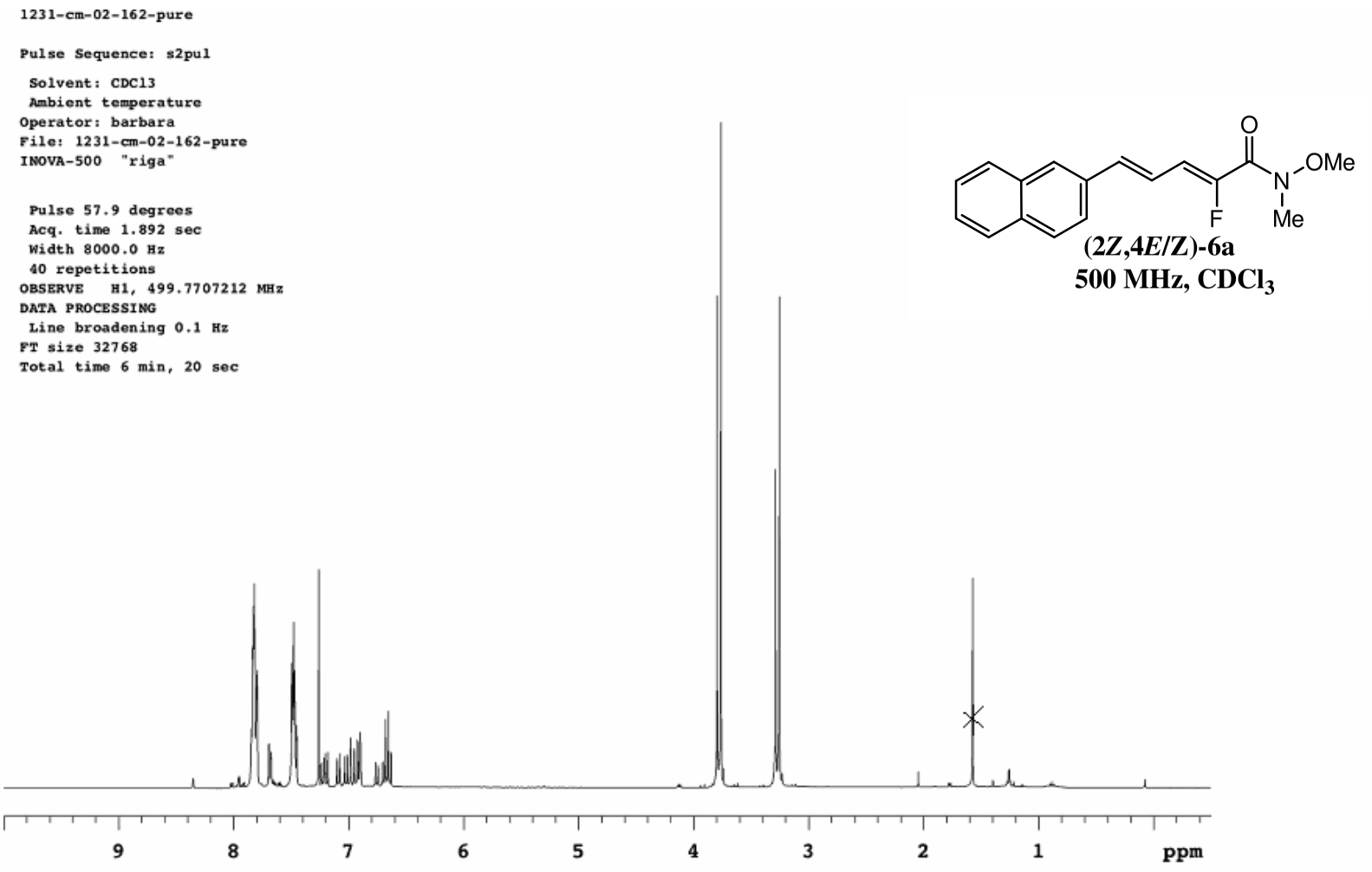
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
1440 repetitions
OBSERVE C13, 125.6674218 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec



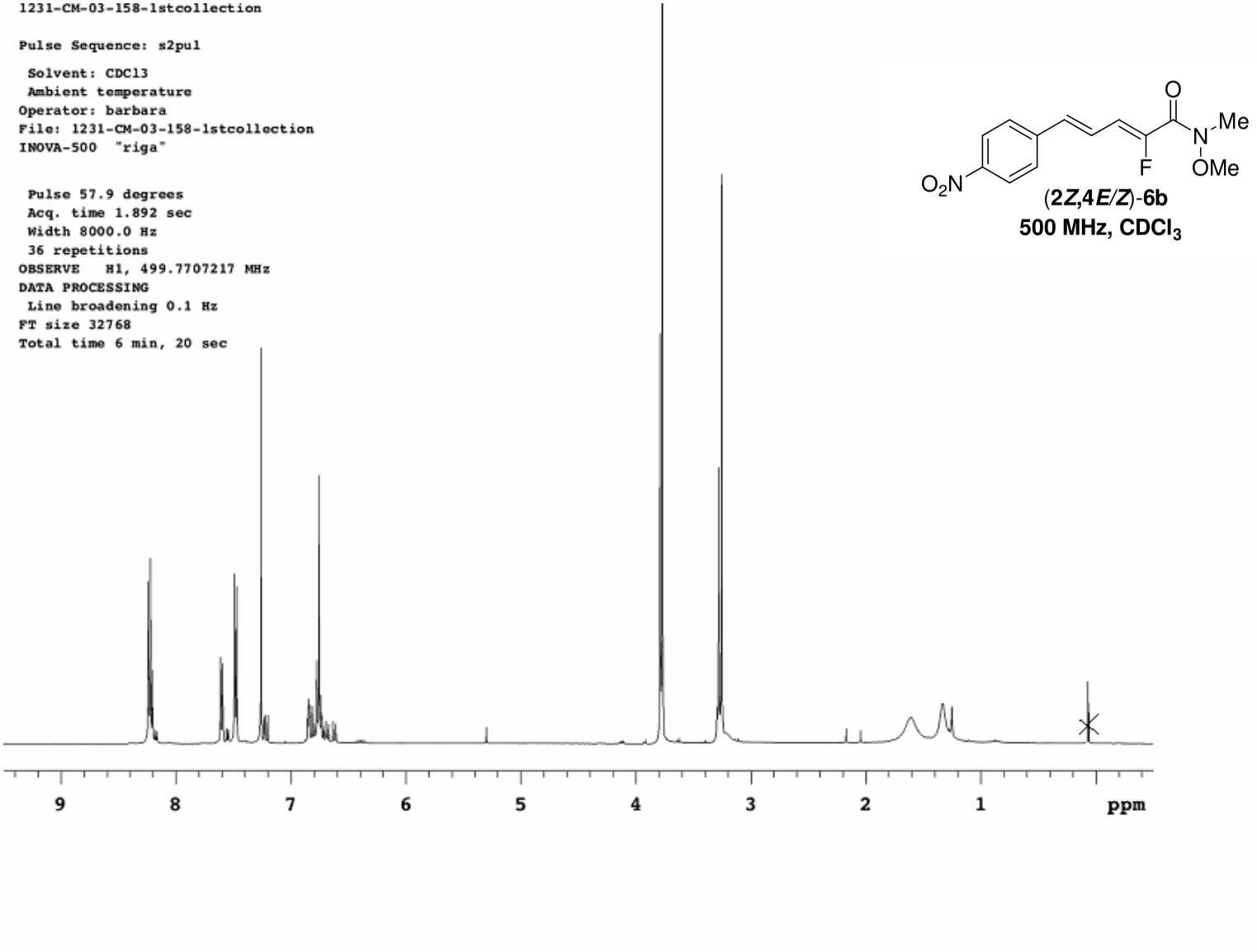
4

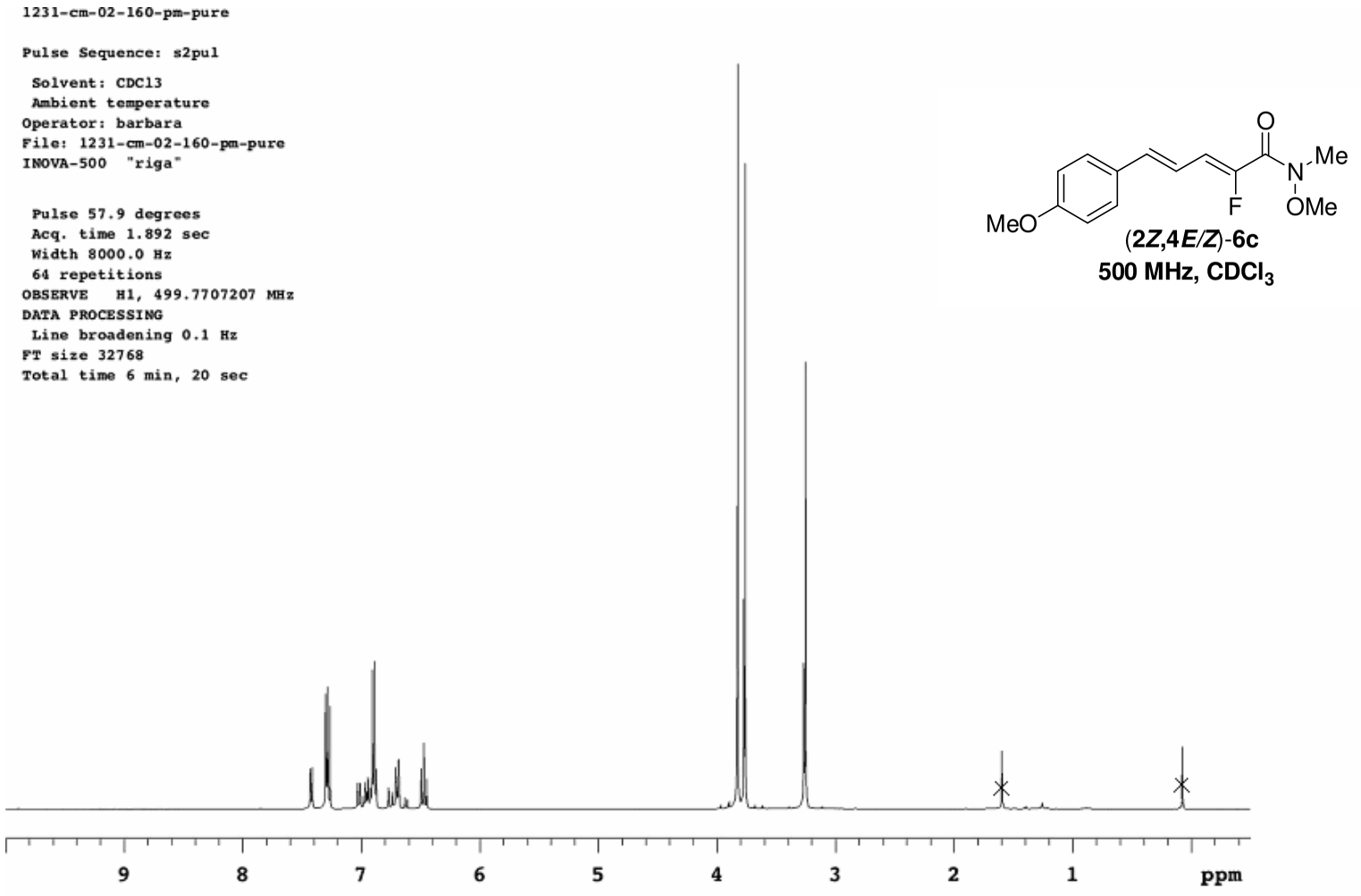
125 MHz, $CDCl_3$





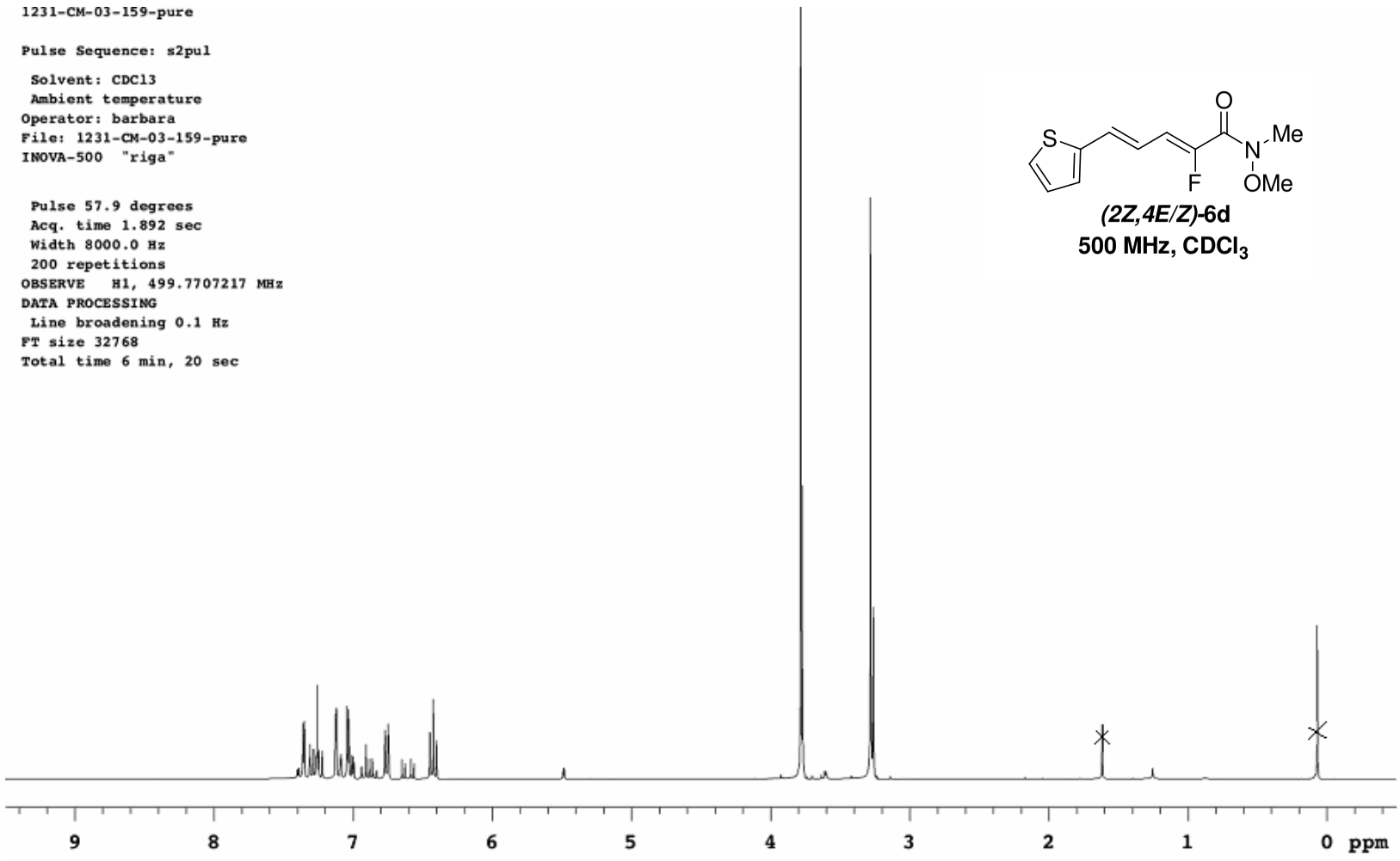
(2Z,4*E*/Z)-6a
500 MHz, $CDCl_3$


1231-CM-03-158-1stcollection
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-CM-03-158-1stcollection
INOVA-500 "riga"
Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
36 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
O
N
Me
OMe
F
O2N
(2Z,4E/Z)-6b
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
ppm



(2*Z*,4*E*/*Z*)-**6c**

500 MHz, $CDCl_3$



***(2Z,4E/Z)*-6d**

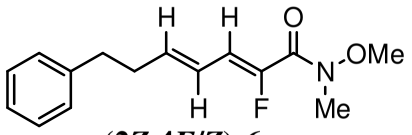
500 MHz, $CDCl_3$

1231-cm-03-161-pure

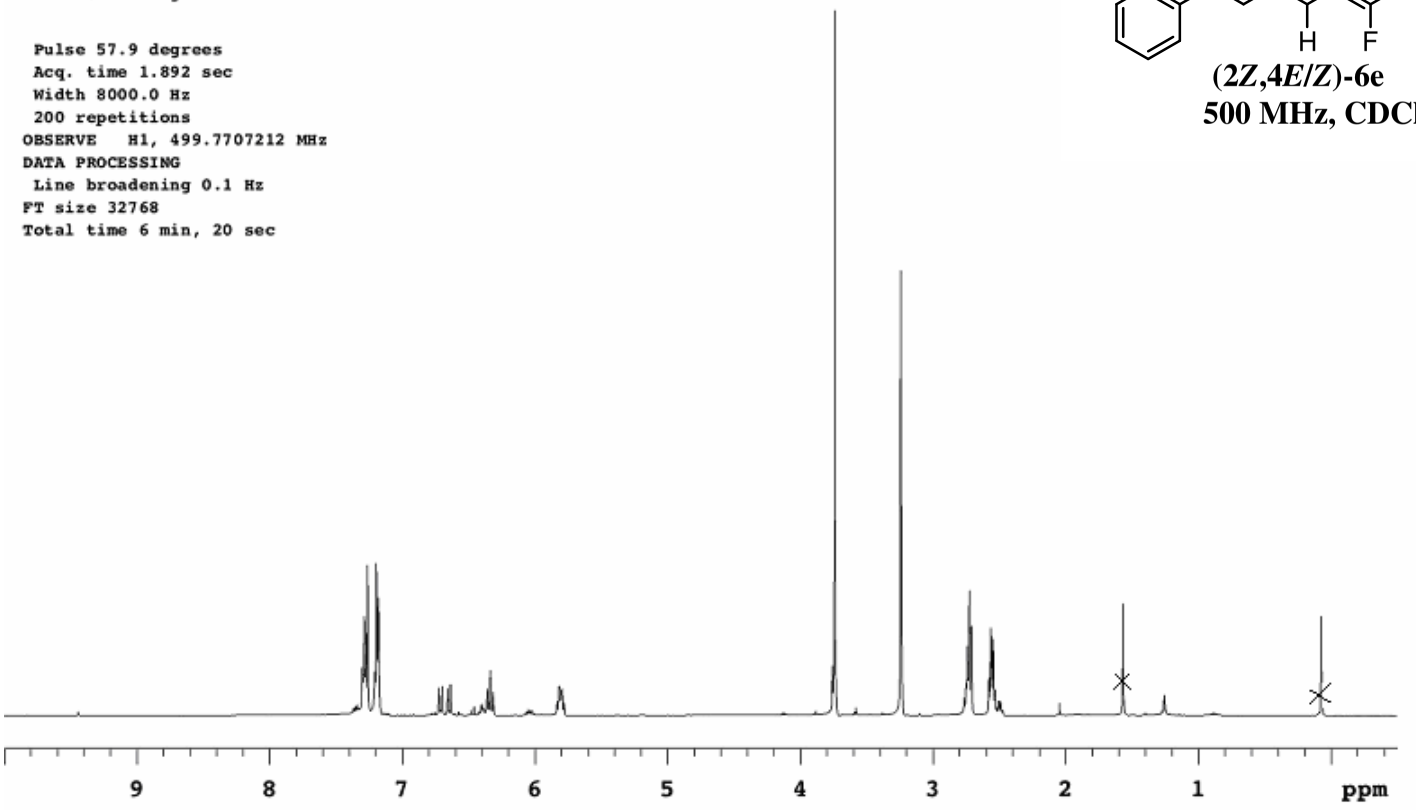
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-cm-03-161-pure
INOVA-500 "riga"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
200 repetitions
OBSERVE H1, 499.7707212 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec



(2*Z*,4*E*/*Z*)-6e
500 MHz, $CDCl_3$

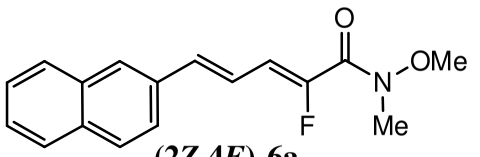


1231-cm-03-162-eenapafterPEPtlc

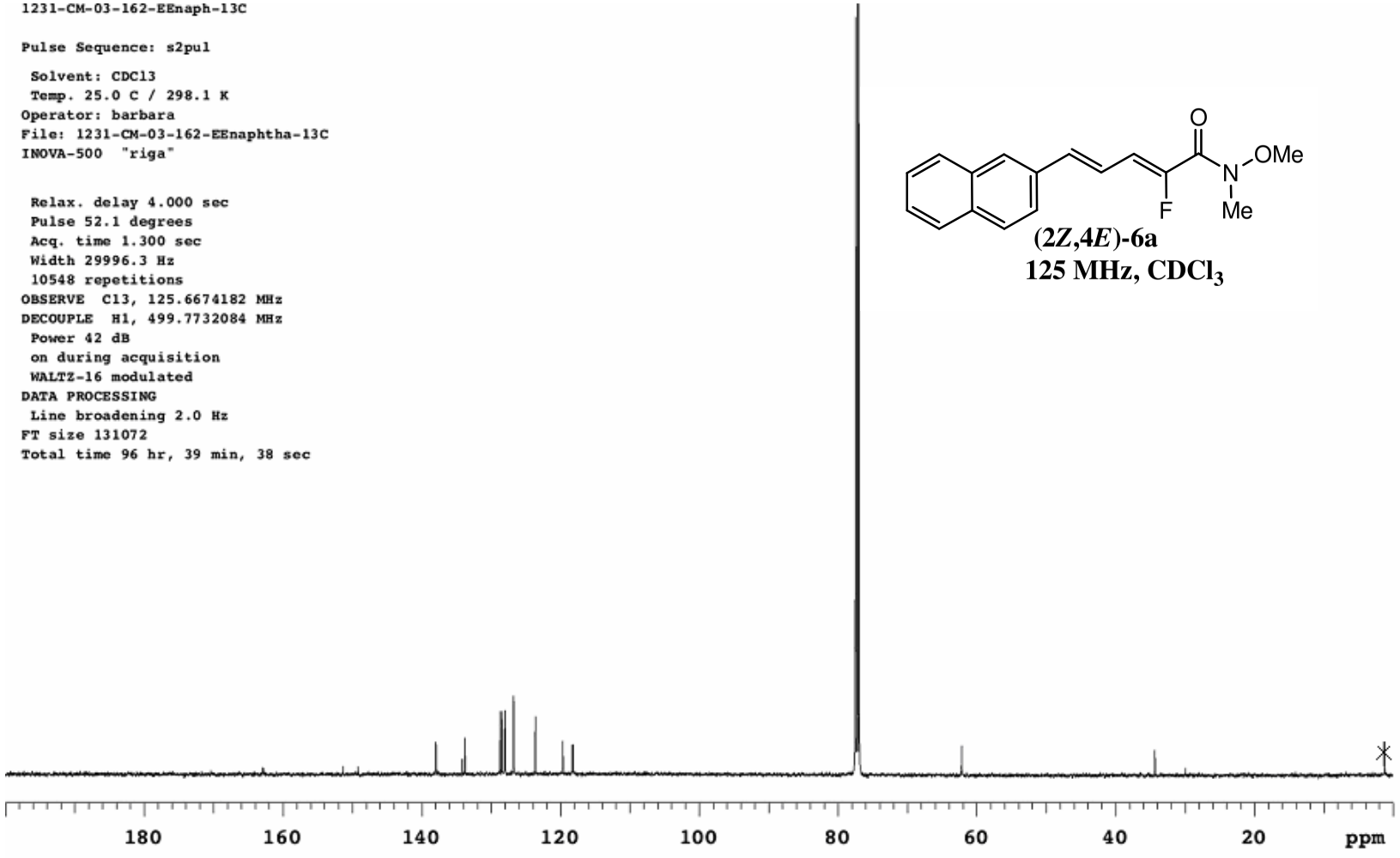
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-cm-03-162-eenapafterPEPtlc
INOVA-500 "riga"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
176 repetitions
OBSERVE H1, 499.7707222 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec



(2*Z*,4*E*)-6a
500 MHz, $CDCl_3$



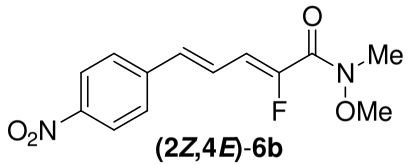
(2*Z*,4*E*)-6a
125 MHz, $CDCl_3$

1231-cm-03-158-2ndspot-pure

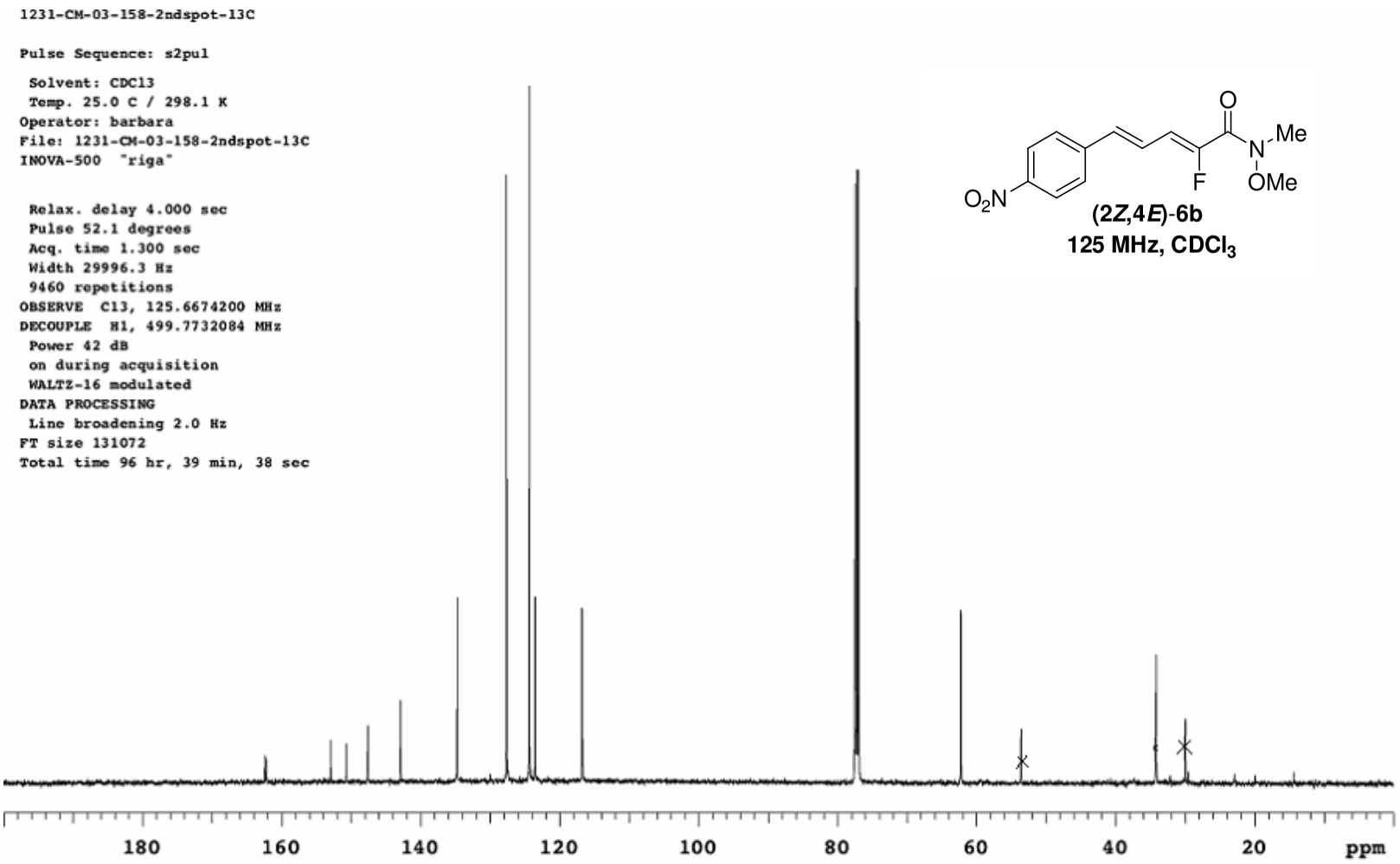
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-cm-03-158-2ndspot-pure
INOVA-500 "riga"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
200 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec

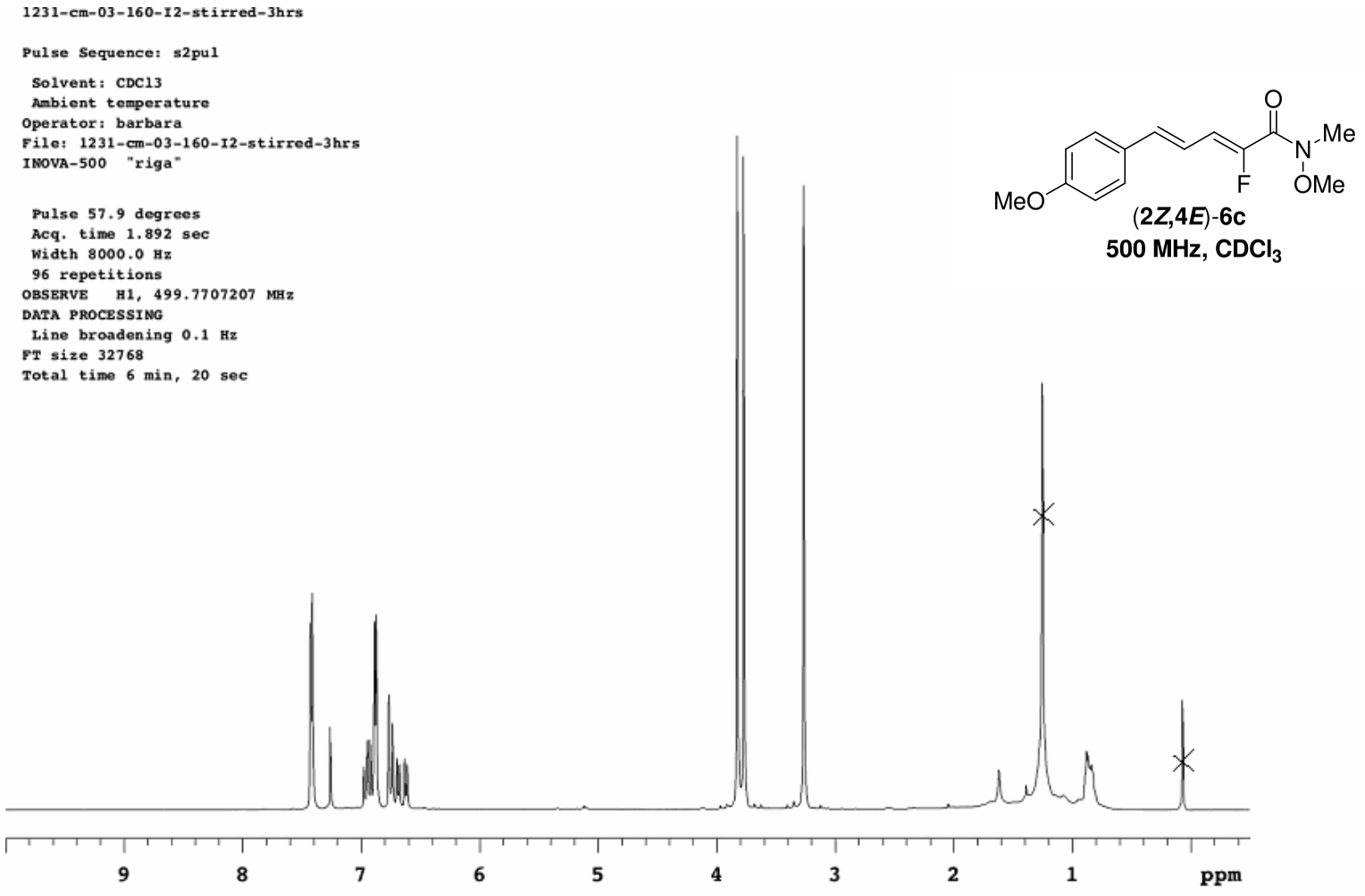


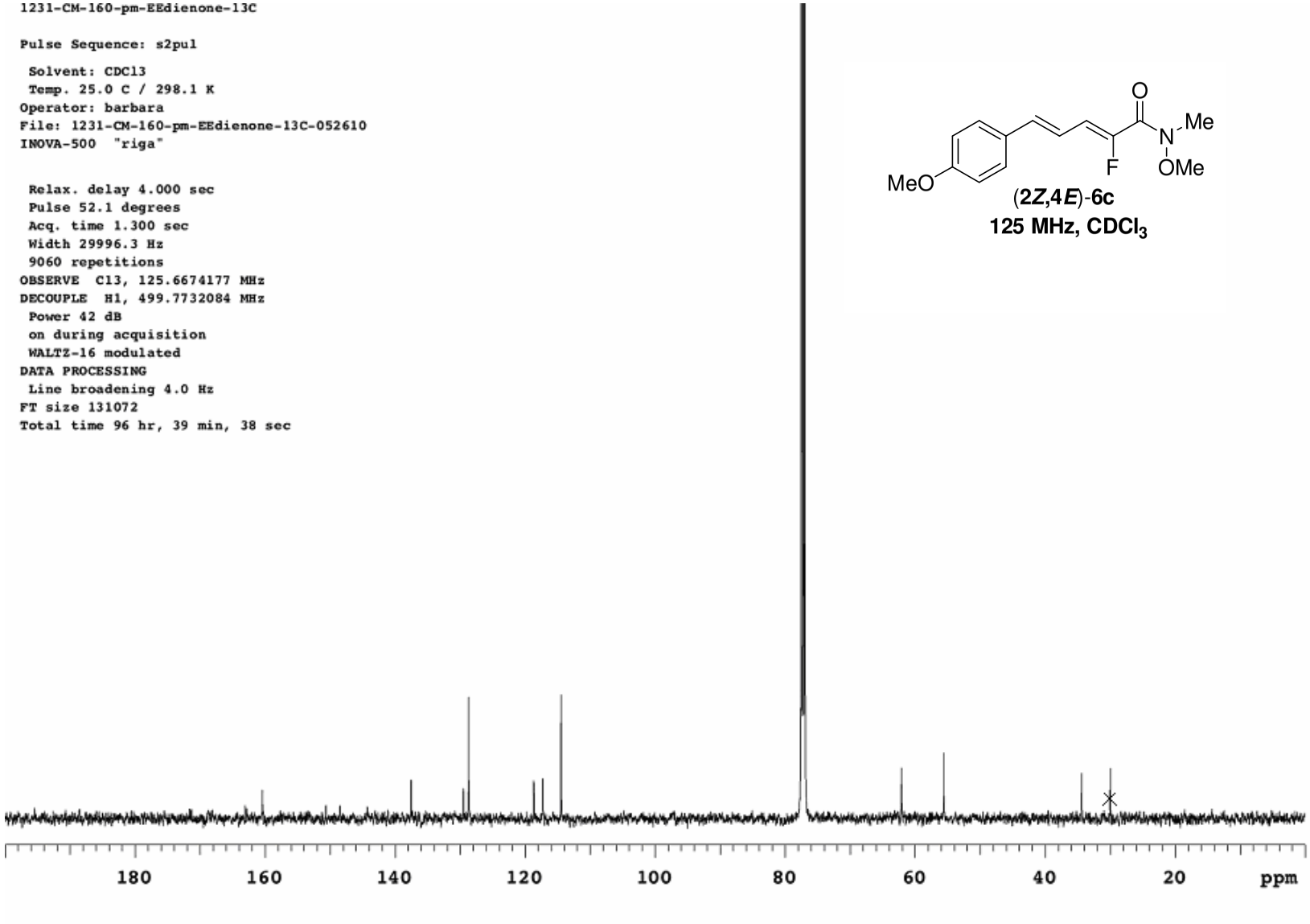
(2*Z*,4*E*)-6b
500 MHz, $CDCl_3$



(2*Z*,4*E*)-6b

125 MHz, $CDCl_3$


1231-cm-03-160-I2-stirred-3hrs
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-cm-03-160-I2-stirred-3hrs
INOVA-500 "riga"
Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
96 repetitions
OBSERVE H1, 499.7707207 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec
O
N
Me
OMe
F
MeO
(2Z,4E)-6c
500 MHz, CDCl3
9
8
7
6
5
4
3
2
1
ppm

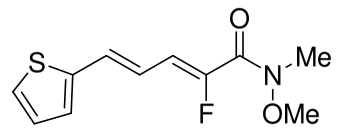

1231-CM-160-pm-EEdienone-13C
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Operator: barbara
File: 1231-CM-160-pm-EEdienone-13C-052610
INOVA-500 "riga"
Relax. delay 4.000 sec
Pulse 52.1 degrees
Acq. time 1.300 sec
Width 29996.3 Hz
9060 repetitions
OBSERVE C13, 125.6674177 MHz
DECOUPLE H1, 499.7732084 MHz
Power 42 dB
on during acquisition
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 131072
Total time 96 hr, 39 min, 38 sec
O
Me
N
F
OMe
MeO
(2Z,4E)-6c
125 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

1231-cm-03-159-EEthiophene-I2stirred-overnight

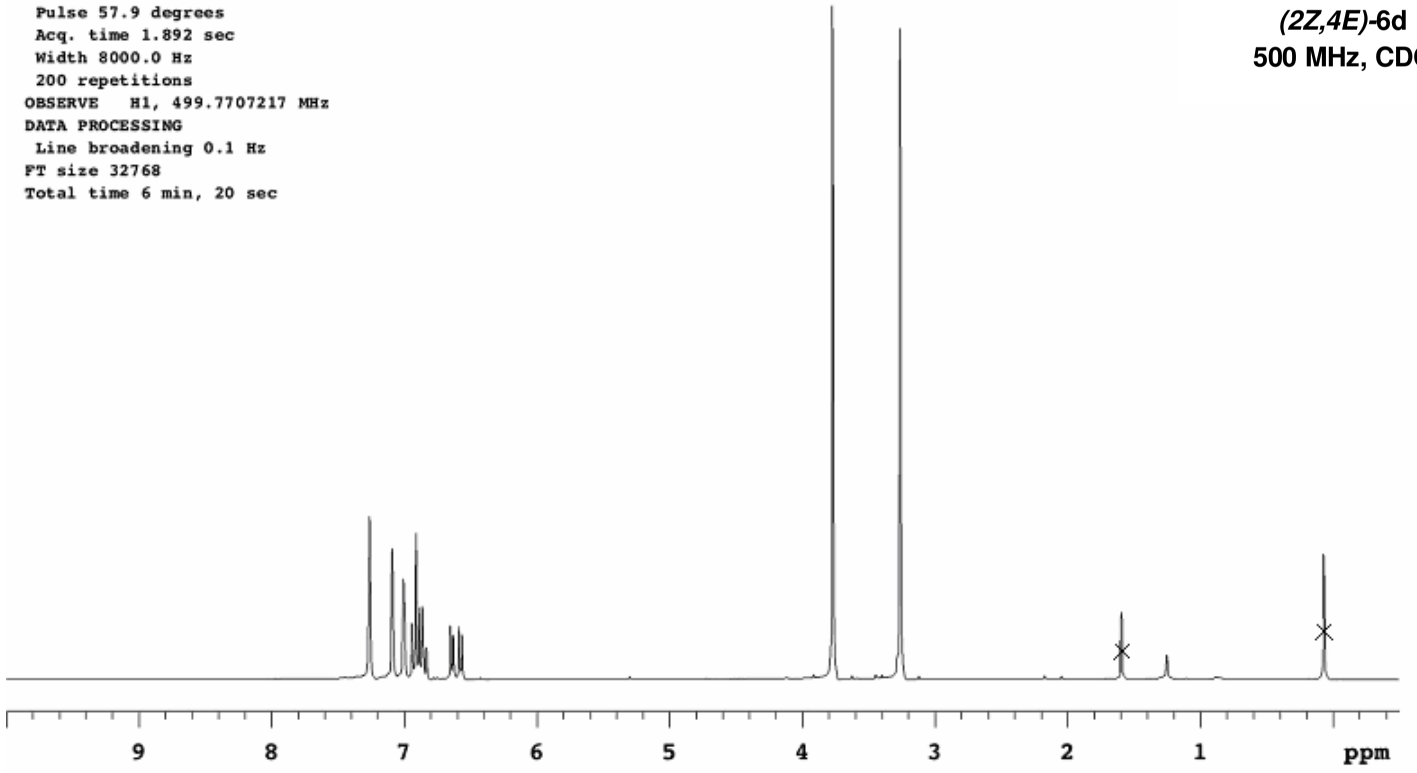
Pulse Sequence: s2pul

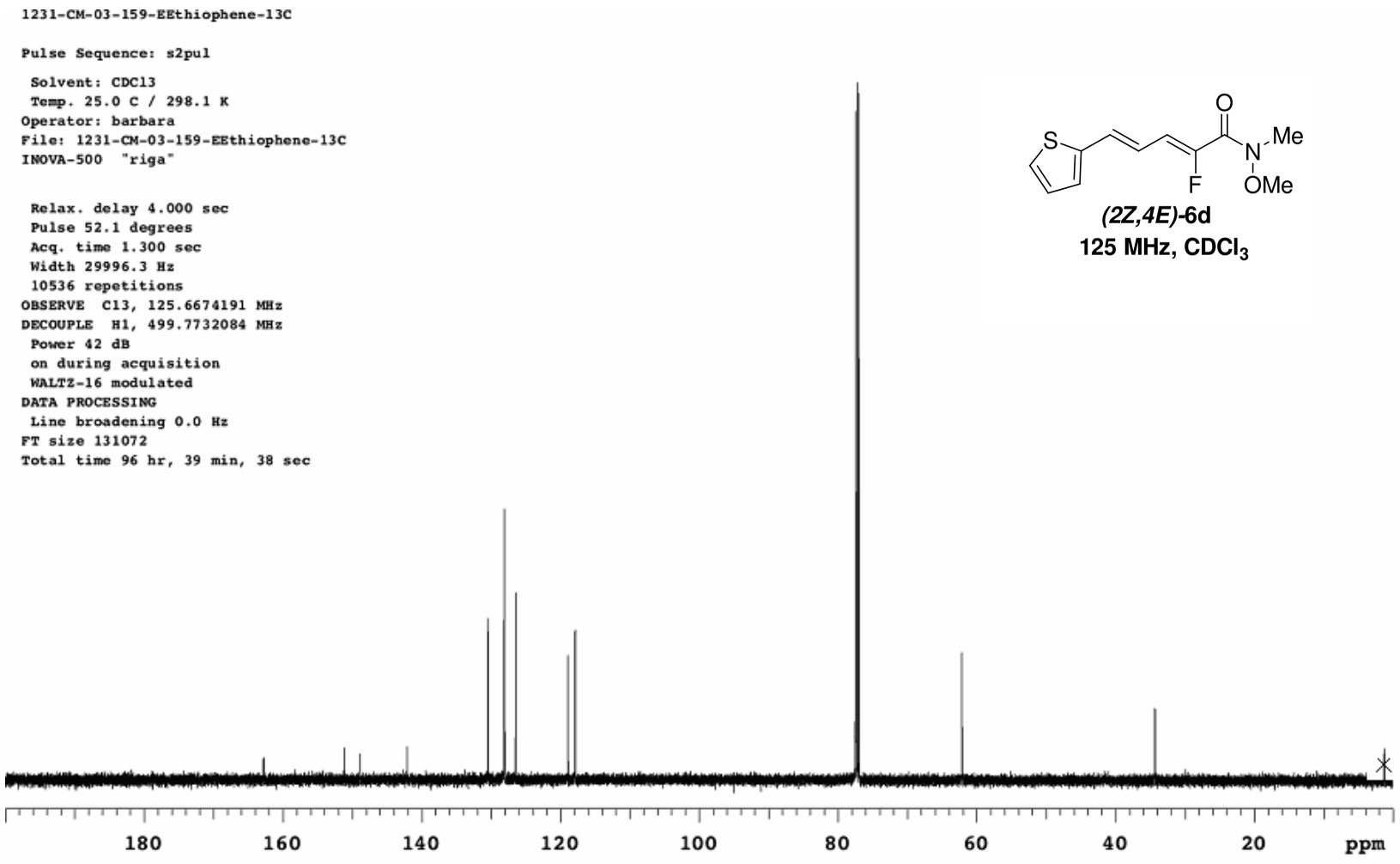
Solvent: CDCl3
Ambient temperature
Operator: barbara
File: 1231-cm-03-159-EEthiophene-I2stirred-overnight
INOVA-500 "riga"

Pulse 57.9 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
200 repetitions
OBSERVE H1, 499.7707217 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 6 min, 20 sec



***(2Z,4E)*-6d**
500 MHz, $CDCl_3$





***(2Z,4E)*-6d**

125 MHz, $CDCl_3$

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