

IRON-CATALYZED C—H ALKYLATION AND PHOTOREDOX FRONTAL RING
OPENING METATHESIS POLYMERIZATION

BY

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DISSERTATION

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ABSTRACT

Metal alkylidenes are versatile synthetic intermediates which have revolutionized multiple chemical fields. They have been used in the synthesis of countless natural products, drugs, and polymers and have contributed to a different understanding of the chemistry of carbon. This thesis deals with two very different applications of this intermediate. The development of an iron catalyzed metallocarbene C—H insertion method is the subject of the first two chapters. Investigation of a photoinitiated frontal ring opening metathesis polymerization method comprises the last two chapters.

Iron metallocarbenes are common intermediates in a wide range of synthetic methods, especially cyclopropanation and insertion into heteroatom-hydrogen bonds. Until 2016, there were no catalytic examples of catalytic iron-carbene C—H insertion. The few stoichiometric examples that existed shed some light on the possible kinetic barriers to developing a catalytic version of this protocol. We optimized an iron (III) phthalocyanine method by enhancing the electrophilicity of the metallocarbene intermediate. This method proved effective for a variety of benzylic C—H bonds, including the benzylic position of δ -tocopherol. Mechanistic investigations demonstrated that the C—H insertion mechanism is stepwise. Activity for tertiary C—H bonds was extensively investigated but proved elusive.

Frontal polymerization is a method of polymerizing a resin not by heating the entire mixture, but by heating a small amount, which triggers an autoaccelerated polymerization that travels throughout the resin as a wave, or front. A less common initiation method of frontal polymerization is with light. There are only a handful of photoinitiated frontal ring opening metathesis polymerization protocols reported. We have developed a photoinitiated, thermally propagated method with a less active bis(N-heterocyclic carbene) catalyst which we hoped

would extend storage lifetime from conventional Grubbs second generation catalyzed systems. We did see a marked increase in storage lifetime when the components were split into two separate solutions and these were thoroughly mixed just before ignition. We established some of the materials properties of the resulting polymer and investigated how the frontal polymerization responded to changes in conditions.

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Chapter 1: Introduction to Iron Catalyzed C—H Insertion

1.1 Types of Carbenes

Carbenes are neutral, divalent carbon species with two unshared valence electrons. These species may be stabilized as metallocarbenes, which alters their reactivity. There are four main types of metallocarbenes with a wide range of reactivity, although not all metallocarbenes are necessarily neatly categorized.¹

The first type, a Schrock carbene, is characterized by a high oxidation state metal center and a nucleophilic carbon center.¹ Typically these are triplet state carbenes.¹ These carbenes play an extremely important role in organic synthesis as intermediates in alkene metathesis.¹ Fischer carbenes are characterized by a low oxidation state metal center and an electrophilic metal center.¹ The most common type of Fischer carbene in use is chromium (0) complexes, which are typically used stoichiometrically and have analogous reactivity to carbonyl compounds.² Some examples of their reactivity include 1,2-, 1,4-, and 1,6-nucleophilic additions to saturated, unsaturated, or aryl carbene complexes respectively.² N-heterocyclic carbenes are persistent carbenes usually used as ligands.³ They are characterized by two strong π -donating substituents on the carbene which stabilize it.³ The resulting ligand is a strong σ -donor analogous to phosphine ligands.³ These ligands are useful in a wide variety of organometallic methodologies.³

Metallocarbene compounds exist not only in relatively stabilized forms, but also as short-lived reactive intermediates; discussion of this type of metallocarbene concerns the rest of this document. These reactive intermediates have both electrophilic and nucleophilic character at the carbene carbon, and reactivity more comparable to a free carbene (cyclopropanation, C—H insertion) than the more extensively stabilized Fischer or Schrock carbenes.⁴⁻⁸ They are characterized by electron withdrawing substituents on the carbon center and by late transition

metals with intermediate oxidation states (I-III).⁵⁻⁸ Metallocarbenes of Co (II) are sometimes described as carbene radicals, which have a great deal of radical character.^{9,10} Other carbenes of this type may have more or less radical character. Some react in a concerted fashion with both alkenes and C—H bonds (Rh, Cu) and some in an intermediate fashion, that is in two separate steps but with longer or shorter radical lifetimes.^{9,11-13} In this form they accomplish a wide variety of reactions, including cyclopropanation, C—H insertion, ylide formation and X—H insertion (insertion into heteroatom-proton bonds)¹⁴. These transformations have been catalyzed by a wide variety of metals, including rhodium¹⁵, copper^{16,17}, iron¹⁸, cobalt¹⁹, ruthenium^{20,21}, silver¹⁶, gold^{16,22}, iridium^{23,24}, and palladium^{25,26}. They are not always isolable, but some characterization of even transitory carbene species has been accomplished.²⁷

1.2 Initial Reports of Carbene-Mediated Aliphatic C—H Alkylation

Most metallocarbene intermediates are synthesized from diazo compounds, where the driving force for the carbene formation is the extrusion of nitrogen. Other carbene precursors include various nitrogen species like diazirines,²⁸ triazoles,²⁹ and hydrazones,³⁰ and sulfoxonium³¹ and iodonium ylides.³² There are three major classes of diazo compounds: acceptor, acceptor-donor, and acceptor-acceptor, referring to the substituents on the diazo compound itself.³³ The substituents have a significant impact on the reactivity: more electron-withdrawing groups stabilize the diazo precursor but form a more electrophilic and reactive metallocarbene.³³

The first reports of metal-catalyzed carbene C—H insertion reaction utilized copper (Fig. 1.1).^{13,34} Early developments focused on unligated copper salts, but these systems are generally most effective in intramolecular, rigid systems, and often require high temperatures for reactivity.¹³ Copper bisoxazoline (BOX) systems were used both intra- and inter-molecularly, although

intermolecular reactivity generally requires excess of substrate to achieve high yields. Moderate enantioselectivities can be achieved with copper BOX systems.^{17,35}

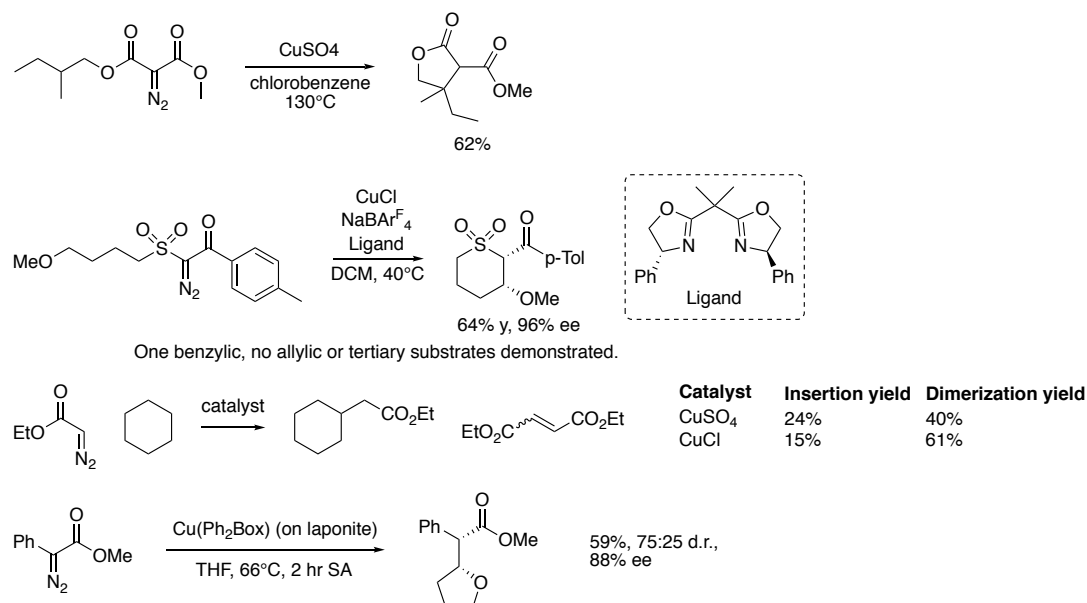


Figure 1.1. Copper catalyzed C—H insertion.

Other coinage metals, including silver and gold, have also been shown to mediate carbene C—H insertion processes.¹⁶ These catalysts are most effective with solvent quantities of simple alkanes and ethyl diazo acetate.¹⁶ Silver, gold, and copper catalyzed systems are also capable of

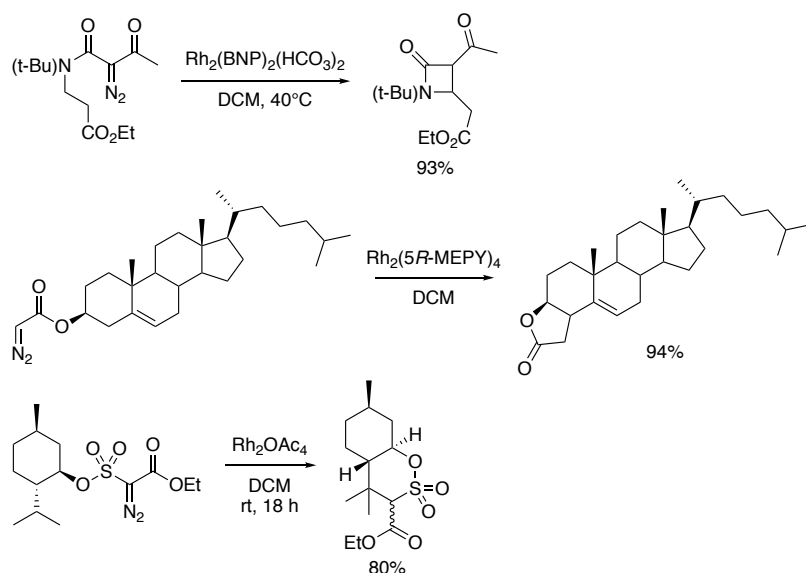


Figure 1.2. Rhodium-catalyzed intramolecular C—H insertion.

aromatic insertion, cyclopropanation, and X—H insertion.^{16,14}

The rhodium catalyzed systems are most well-developed (Fig. 1.2). The mechanism is thought to be a concerted asynchronous

insertion of the metallocarbene

via a three-membered transition state.¹³ Intramolecular reactivity with dirhodium catalysts has been demonstrated for four-, five- and six-membered ring formations with a variety of C—H bond types.^{13,34,36,37} Synthesis of cyclopropanes via C—H insertion is less commonly reported.²⁶ Ketone, ester, and amide tethers all form the five-membered ring preferentially, although this preference may be overturned via electronic or steric bias, most notably in the case of α -N diazoacetamide C—H insertions to form β -lactams.^{13,34,36,37} Sulfonate ester tethers are alone in preferential formation of six-membered rings.³⁸

While rhodium catalysis is capable of insertion into allylic, benzylic, ethereal, α -nitrogen, and unactivated tertiary and secondary aliphatic C—H bonds, there are certain chemoselectivity issues associated particularly with π -functionality, including Buchner reactivity and cyclopropanation.^{37,39,40} In addition, certain rearrangements are possible with nucleophilic heteroatoms which may compete with α -insertion.⁴¹ Selectivities can be altered via different carboxylate ligands on the dirhodium catalysts and via different tethers, as seen below (Fig. 1.3).

^{37,39,40,42}

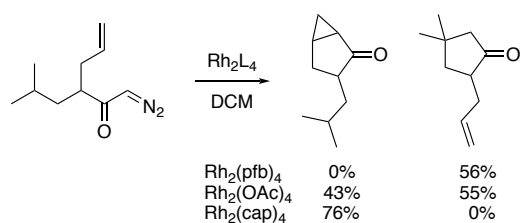


Figure 1.3. Rhodium-catalyzed intramolecular insertion and cyclopropanation.

High enantioselectivities are often obtained, especially in intramolecular insertions, with chiral amide catalysts derived from various amino acids.^{15,36,37,43,44} A large breadth of intermolecular reactivity has also been observed with rhodium,

although the donor-acceptor carbenes are most explored, as acceptor carbenes generally dimerize readily when attempting intermolecular insertions, and acceptor-acceptor carbenes are often too reactive to insert with good regioselectivity.³³ These reactions likewise exhibit chemoselectivity problems with π -functionality.³³ Rhodium carbene mediated insertion protocols have been utilized

for the synthesis of several natural products and pharmaceutical agents ((*R*)-rolipram, Ritalin, sertraline, bakuchiol).^{45,46}

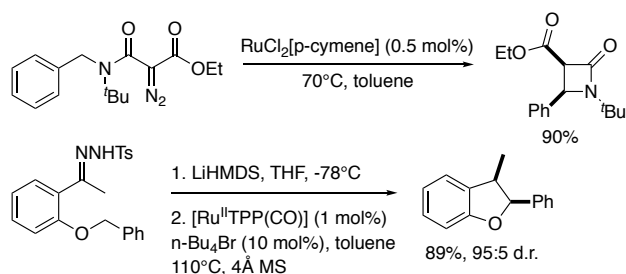


Figure 1.4. Ruthenium catalyzed C—H insertion.

In addition to rhodium, several other metals are also active for intramolecular aliphatic C—H carbene insertion, including ruthenium and cobalt.^{20,21,47,48,19}

Ruthenium carbenes are thought to be more stable than some other metallocarbenes, such as rhodium carbenes, and therefore are less active for C—H insertion.³⁴ However, there are multiple examples of intramolecular ruthenium catalyzed carbene insertions into doubly activated sites (ie. benzylic and α -heteroatom), and some examples at singly activated ethereal sites (Fig. 1.4).^{20,21}

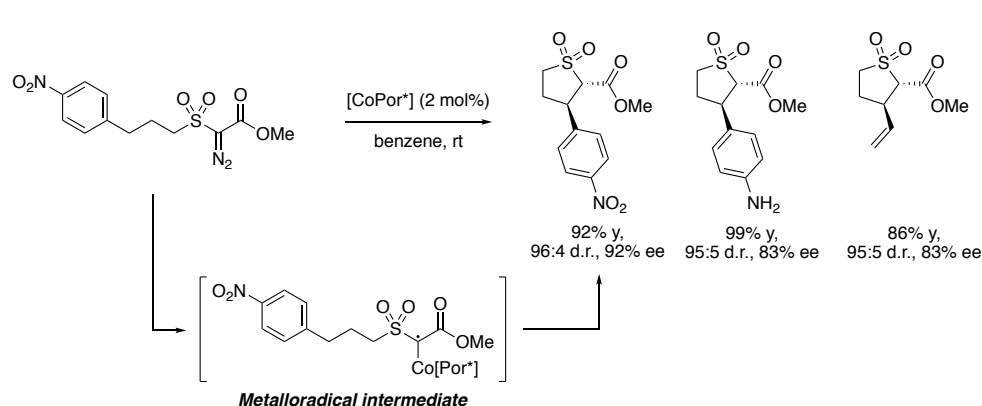


Figure 1.5. Cobalt-catalyzed intramolecular C—H insertion.

Cobalt-catalyzed carbene insertion reactions are thought to proceed through metalloradical intermediates,

where the metal-carbon bond is best represented as a single bond and both the metal and the carbon are open-shell (Fig. 1.5).^{10,49} The increased radical character of these carbenoids has implications for chemoselectivity, substrate scope, and alkene isomerization.¹⁹ The mechanism of insertion is stepwise; the carbenoid abstracts a hydrogen atom and then the resulting carbon-centered radical rebounds to form the carbon-carbon bond.^{10,49,50} Because the insertion into an allylic C—H bond

radicals tend to have reasonably long lifetimes; therefore *Z*-alkenes tend to isomerize partially or fully to the *E*-isomer.¹⁹ The

intermediate is relatively insensitive to substrate electronics, which allows high yields even on electron poor aryl rings.¹⁸

Iron carbene mediated processes are well-precedented in the literature, particularly for cyclopropanation, X—H insertion, and aromatic



insertion (Fig. 1.6).⁵¹ Cyclopropanation reactions have been demonstrated enantioselectively,⁵² in biological systems (both in the presence of bacterial cells^{53,54} and with superb enantio- and diastereo-selectivity via evolved enzymes^{55,56}), and with diazomethane produced in situ.¹⁸ Cyclopropanation of aliphatic olefins is rare aside from intramolecular examples.¹⁸

Iron carbene mediated X—H insertion processes include O—H, N—H, S—H and Si—H insertion^{57–60}. These transformations have been accomplished with high enantioselectivity and have also been demonstrated with enzymes developed via directed evolution.¹⁸

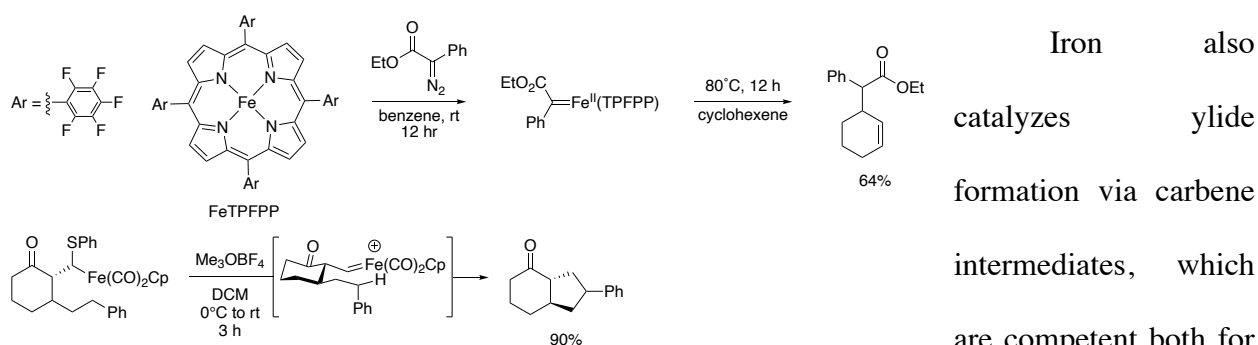


Figure 1.7. Stoichiometric iron carbene C—H insertion.

aldehydes and the Doyle-Kirmse reaction.^{61,62}

Iron carbene aliphatic C—H insertion is less common in the literature than other processes. There are some stoichiometrically generated iron carbenes which are shown to insert into a substrate in a separate synthetic step (Fig. 1.7).^{63–65} This reactivity is either intramolecular or with

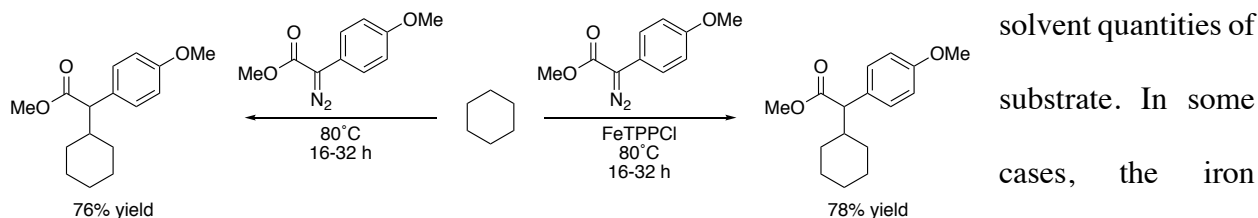
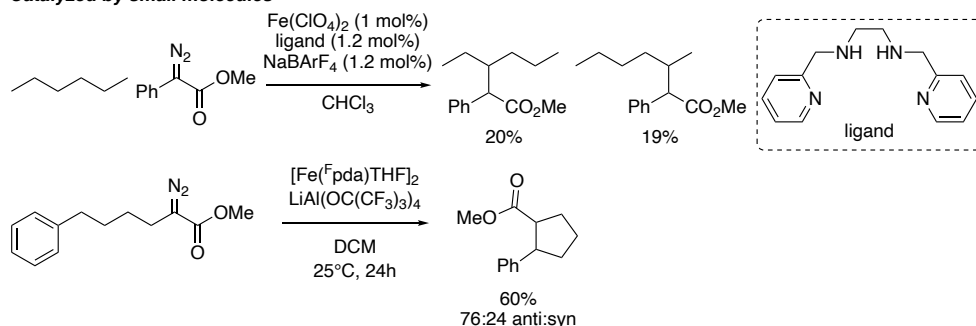


Figure 1.8. Thermal decomposition mistaken for iron-mediated reactivity.

temperature but requires elevated temperatures to undergo C—H insertion.^{13,16} As of 2016, this

was the only type of iron-carbene aliphatic C—H insertion reported. While an iron tetraphenylporphyrin-catalyzed transformation was reported, the reaction gives the same yield of

Catalyzed by small molecules



Catalyzed by unnatural enzymes

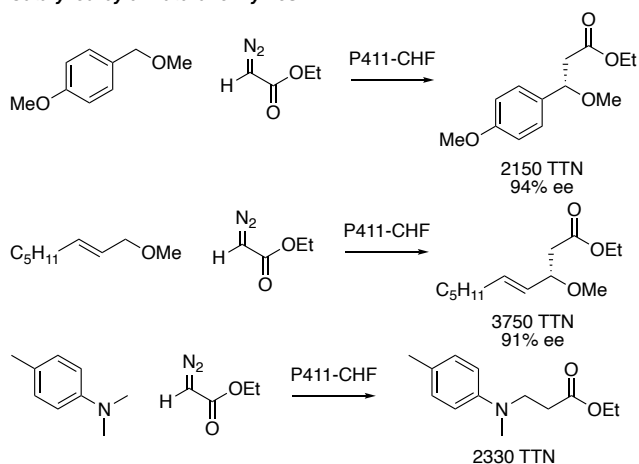


Figure 1.9. Iron catalyzed aliphatic C—H alkylation after carbene was generated at a lower temperature and reacted at a higher temperature.⁶³ This led us to hypothesize that the iron carbene formation may be more kinetically facile than the carbene insertion into the C—H bond. This would be in contrast to other metallocarbene mediated processes whose mechanism has been studied extensively (rhodium, copper). In these systems, the rate-determining step has been shown to be metallocarbene formation rather than C—H insertion.⁵ This may also explain the wealth of precedent of iron carbenes undergoing other, lower energy processes, such as π oxidation.

Since 2016, a handful of catalytic iron carbene aliphatic C—H alkylation protocols have been reported. The first was the work discussed later in the chapter.¹¹ A small molecule catalyst

product with and without catalyst; therefore, it is more likely free carbene than metallocarbene mediated (Fig. 1.8).

In the stoichiometric protocol reported by Che, the

with a tetradentate nitrogen ligand was used by Zhu and coworkers to catalyze intermolecular insertion of EDA, although this process is largely unselective.⁶⁶ Costas demonstrates an intermolecular formation of cyclopentanes with a pre-activation of the diazo precursor with a lithium Lewis acid.⁶⁷ Another was work by Arnold and coworkers, done by directed evolution of unnatural enzymes.^{68,69} These carbenes mostly insert into weaker doubly activated or α -N bonds, often with good enantioselectivity (Fig. 1.9).

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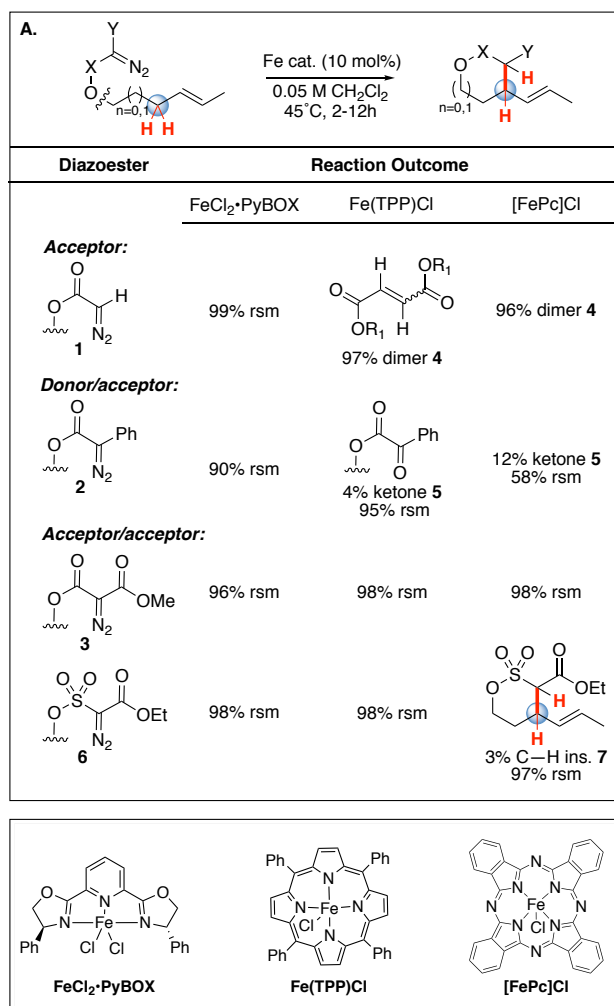
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Chapter 2: Seminal Iron-Catalyzed Aliphatic C—H Alkylation

2.1 Introduction

The carbene literature is vast and widely applicable to a variety of scaffolds; in addition, these methodologies hold a great deal of mechanistic interest. The frequency of aliphatic C—H alkylation with other metals while there were no catalytic reports for iron prior to 2016 suggests some particularity in the reactivity of iron carbenes. Drawing from the stoichiometric example from Che, in which the formation of the iron carbene occurs at a lower temperature than its insertion into a C—H bond, we hypothesized that the C—H insertion may be the rate-determining



step in an iron-catalyzed process.¹ This would be in contrast to copper and rhodium, where metallocarbene formation is rate-determining, producing a high-energy metallocarbene leading to a more kinetically facile C—H insertion step.^{2–7}

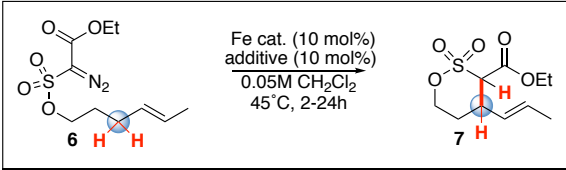
These and other questions, as well as a desire to discover orthogonal reactivity to the catalytic methods in the literature already, lead us to an attempt to optimize an iron-catalyzed methodology for carbene aliphatic C—H alkylation.

2.2 Initial Optimization

We hypothesized that while iron carbene processes have not yet been shown to

Figure 2.1. Initial discovery of reactivity.

undergo catalytic aliphatic C—H insertion, it would be possible to achieve this kind of reactivity with the correct match of iron catalyst and diazo precursor. We began our investigations with intramolecular allylic insertions, both because we judged that intramolecular processes would likely be more facile and because screening with an olefin-containing substrate would show early in the process whether or not the process is chemoselective (Fig. 2.1). Diazoester **1** was unreactive with the iron PyBOX complex. However, with iron porphyrin and phthalocyanine catalysts, it converted to large amounts of olefin dimer (**4**, 93% and 84%, respectively), suggestive of iron carbene formation.⁸ We hypothesized that a more bulky disubstituted diazoester may create a more



entry	catalyst	additive	% yield (% rsm)
1	[Fe ^{III} Pc]Cl	—	3 (97)
2	[Fe ^{III} Pc]Cl [†]	AgSbF ₆	45 (0)
3	[Fe ^{III} Pc]Cl [†]	NaBAR ₄ ^F	48 (0)
4	[Fe ^{III} Cl ₁₆ Pc]Cl	NaBAR ₄ ^F	38 (0)
5	[Fe ^{III} Cl ₈ Pc]Cl	NaBAR ₄ ^F	25 (66)
6	[Fe ^{III} Pc]Cl ^{†‡}	NaBAR ₄ ^F	53 (0)
7	Fe ^{III} (TPP)Cl	NaBAR ₄ ^F	7 (93)
8	[Fe ^{II} Pc]	—	0 (100)
9	—	NaBAR ₄ ^F	0 (96)

Figure 2.2. Optimization of conditions.

sterically demanding environment that disfavors dimerization. Consistent with this, disubstituted donor-acceptor carbene precursor **2** disfavored dimerization with all three catalysts.⁸ However, it was unproductive for C—H alkylation, affording large amounts of recovered starting material and some conversion to alternate oxidation products with Fe(TPP)Cl and [Fe^{III}Pc]Cl (ketone **5**, 4% and 12% respectively).

We hypothesized that augmenting the electrophilicity of the disubstituted diazo compound would increase its reactivity by producing a strongly electrophilic carbene that could more readily engage in higher energy C—H insertion pathways. As demonstrated with rhodium catalysis, acceptor-acceptor diazo compounds are stable and typically require very active catalysts to form the metallocarbene. Once formed, however, the metallocarbene is highly electrophilic and reactive towards C—H insertion.⁹ Acceptor-acceptor

diazoester **3** resulted in predominately recovered starting material for all iron complexes examined. This lack of reactivity may indicate failure to generate a metallocarbene. Alternatively, it could indicate formation of a metallocarbene that was unreactive towards not only C—H bond insertion, but also deleterious side reactions. Exploring this latter possibility, we endeavored to generate a more reactive, electrophilic iron carbene. Upon examination of the ^{13}C shifts of the α -carbon of a variety of different acceptor-acceptor diazo precursors, we observed that sulfonate esters appeared to be the most electrophilic and thus investigated their corresponding diazoesters (**6**) for potential C—H alkylation reactivity.^{10,11} Iron porphyrin and PyBOX complexes exhibited no reactivity for this transformation. However, the catalyst with the greatest π -accepting character, iron phthalocyanine chloride ($[\text{Fe}^{\text{III}}\text{Pc}]\text{Cl}$), formed the C—H alkylated δ -sultone product **7** in low yield (3%), but with no evidence of deleterious side reactions (97% rsm).

We proceeded to test various non-coordinating counterion salts, which had a profound effect on the yield (Fig. 2.2). $\text{NaBAr}^{\text{F}}_4$ gave the highest yield, at 48%. Many carbene-mediated methods benefit from slow addition of the substrate to the catalyst mixture, as this disfavors dimerization pathways, which may decrease yield. Accordingly, we observed a 5% yield increase with a 1-hour slow addition protocol, ultimately arriving at a synthetically useful 53% yield for a simple olefin. Notably, chlorinated iron (III) phthalocyanine derivatives gave decreased yields, and iron (II) phthalocyanine and iron (III) tetraphenylporphyrin failed to catalyze the transformation in appreciable yields. In addition, $\text{NaBAr}^{\text{F}}_4$ alone gave no reactivity.

2.3 Substrate Scope Investigation

We next sought to investigate the yields of the transformation with a variety of sulfonate esters. $[\text{Fe}^{\text{III}}\text{Pc}]$ efficiently catalyzes functionalization of benzylic C—H bonds in the presence of a variety of aryl and heteroaryl functionality (Fig. 2.3). Substrates containing electron-rich aryl

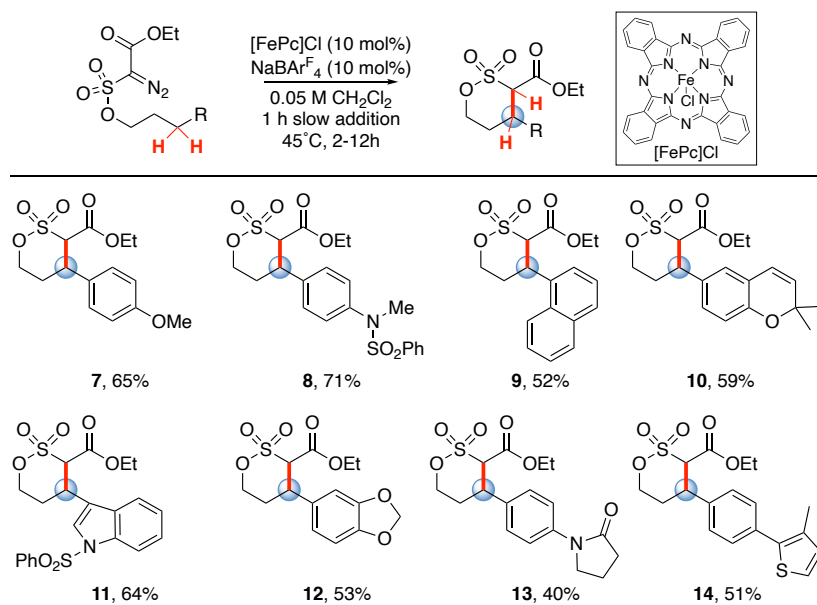


Figure 2.3. Substrate scope.

undergoes benzylic C—H alkylation without competing cyclopropanation (**9**). This iron-catalyzed transformation also exhibits good tolerance towards medically relevant heterocyclic functionality. Despite reactive, proximal alkene functionality, $[\text{Fe}^{\text{III}}\text{Pc}]$ promotes C—H alkylation adjacent to chromene and indole heterocycles, both common in natural products and pharmaceuticals (**10-11**). Additionally, a substrate containing a benzodioxole moiety is readily alkylated under $[\text{Fe}^{\text{III}}\text{Pc}]$ catalysis (**12**), even though these heterocycles have been shown to irreversibly bind to iron heme complexes (Fig. 2.1A).^{12,13} Lactam- and thiophene-containing substrates are also alkylated in moderate yields under iron catalysis (**13-14**) despite the propensity for sulfur and nitrogen moieties to inhibit transition metal catalyzed oxidations.

After establishing the efficacy of the reaction for a variety of simple diazosulfonate esters, we moved on to demonstrating derivatization of a natural product scaffold (Fig. 2.4). Tocopherol was modified via triflate protection and coupling to append the tether, and then underwent iron-

rings are alkylated at the benzylic site in high yield, including *p*-methoxy and *p*-aniline substituted aryl substrates (**7-8**). Notably, a naphthalene-containing diazosulfonate ester, which possesses more readily oxidized π -functionality, also

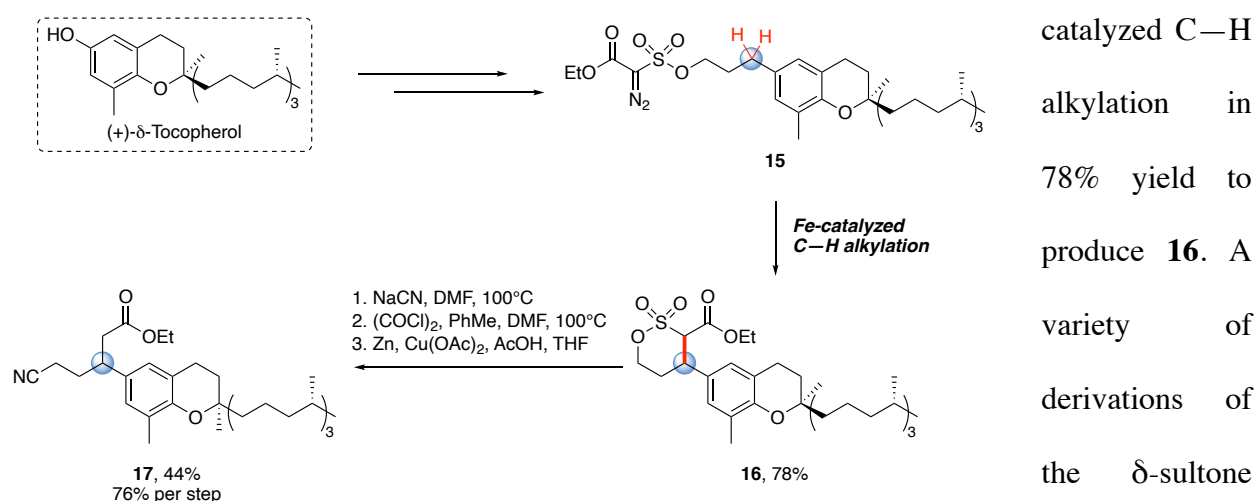


Figure 2.4. Derivatization of δ -tocopherol via C—H insertion.

demonstrated (e.g. nucleophilic displacement, electrophilic substitution α to the ester, ester reduction/ elimination of the resulting alcohol, and oxidative conversion of the δ -sulfone to a γ -lactone).^{9,14,15} A three step elaboration of this δ -sulfone motif via nucleophilic displacement yielded **17**, bearing an unsymmetrical tertiary carbon center with two new functional group handles, in 44% overall yield (76% per step).

2.4 Mechanistic Investigations

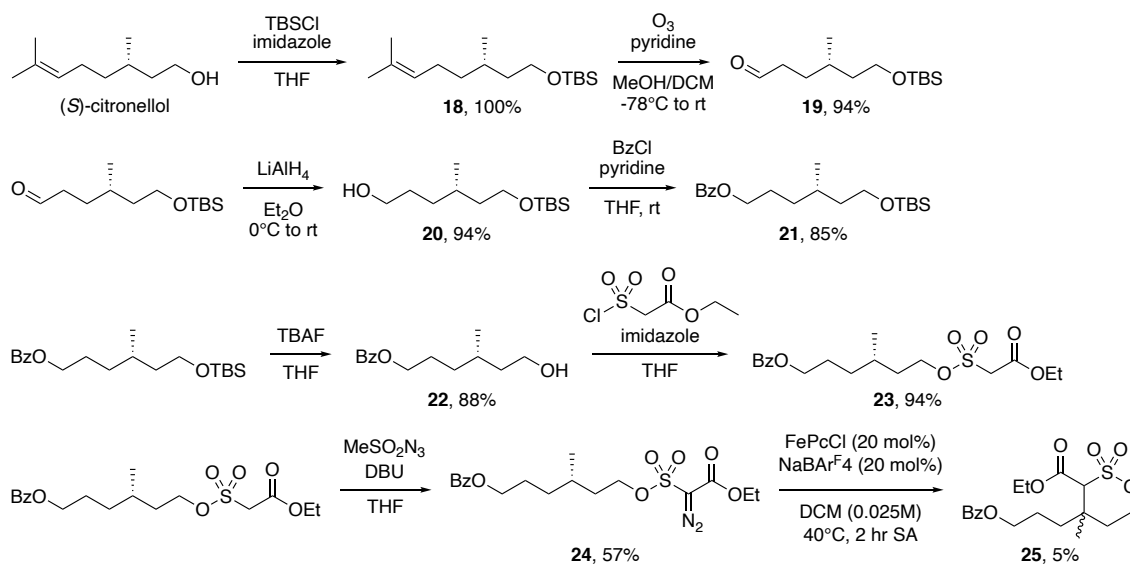


Figure 2.5. Synthesis of enantioenriched tertiary substrate.

Given the variation in radical character of carbenes and intermediates evident in the C—H alkylation literature, we wondered where this novel methodology fit in. One way to probe this was through stereoretention studies. In order to measure whether stereochemistry was retained at the site of C—H activation, it was necessary to formulate an enantioenriched substrate intended for tertiary C—H activation, suitable for analysis via chiral HPLC. This was accomplished via a derivatization of (*S*)-citronellol via oxidative cleavage of the olefin (**19**), reduction (**20**), and benzoate protection to introduce a UV-absorbent moiety for visualization (**21**) (Fig. 2.5).

Unfortunately, the iron phthalocyanine methodology is unreactive with tertiary C—H bonds. Only a 5% yield was obtained even with increased catalyst loading. However, after extensive purification enough material was obtained to test the enantiomeric ratio of the resulting δ -sultone product. This also proved challenging due to the four stereoisomers produced and the necessity of obtaining baseline separation of each, but it was possible after considerable optimization. The resulting partial stereoablation is shown in Table 2.1.

Table 2.1. Enantiomeric ratio of **25** produced with different catalysts.

Catalyst	Enantiomeric ratio of product
Rh(OAc) ₄	98%±1%
FePcCl	81%±3%

This partial stereoablation indicates that this mechanism proceeds through a discrete intermediate after the C—H bond cleavage and before the C—C bond formation; this is likely a carbon-centered radical although a carbocation is also possible. The tertiary alkylation would produce a relatively unstabilized carbon-centered radical. The partial stereoablation indicates that this carbon-centered radical is likely short-lived, but in the benzylic substrates which make up most of the scope of the methodology, the radical would be better stabilized and likely have a

longer lifetime. In contrast, the dirhodium tetraacetate catalyzed methodology produces a product with identical e.r. to the starting material, which is consistent with a concerted process by which the C—H bond cleavage and the C—C bond formation occur in the same step.¹⁶ This demonstrates a clear mechanistic difference between the iron- and rhodium-catalyzed carbene alkylations, which may have chemoselectivity implications.

2.5 Tertiary C—H Bonds

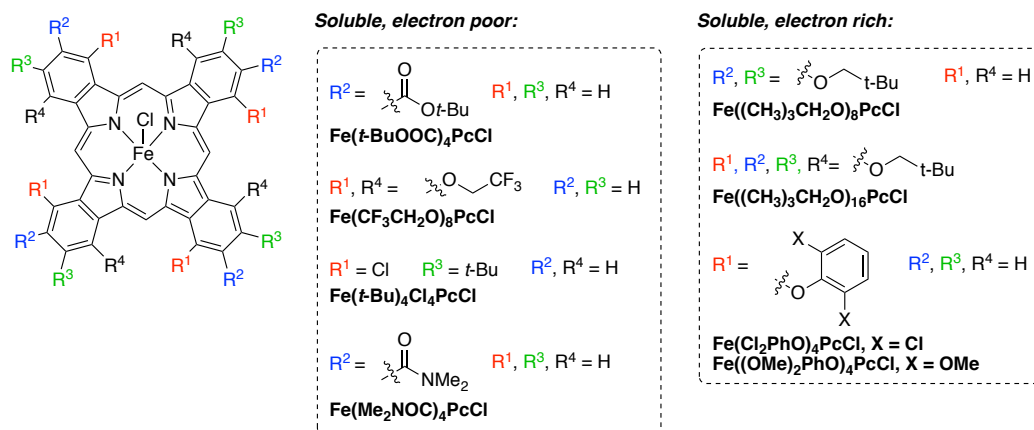
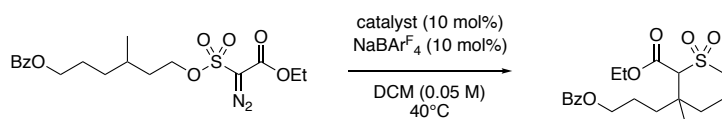


Figure 2.6. Soluble iron phthalocyanines.

While the iron catalyzed C—H alkylation method detailed here can access a variety of C—H bonds, it is incapable currently of accessing unactivated tertiary or secondary C^{sp3}—H bonds. Metallocarbene insertion into tertiary C—H bonds has the potential to generate quaternary centers; if the method were stereoretentive, then nonracemic quaternary centers could be generated from nonracemic tertiary centers.

Initial investigations with a variety of iron and manganese catalysts yielded product only with iron phthalocyanine chloride, which gave 11.4% yield by HPLC (7% isolated yield). A number of derivatives of this catalyst were then investigated. Manganese (III) phthalocyanine chloride and cobalt (II) phthalocyanine gave no reactivity.



Catalyst	diastereomer 1	diastereomer 2	RSM
FePcCl	6.4%	5.4%	19%
Fe(<i>t</i> -BuOOC) ₄ PcCl	6.0%	trace	trace
Fe(<i>t</i> -BuOOC) ₄ PcCl with AgSbF ₆	6.1%	3.3%	59%
Fe(CF ₃ CH ₂ O) ₈ PcCl	5.0%	trace	trace
Fe(<i>t</i> -Bu) ₄ Cl ₄ PcCl	12.0%	1.5%	83%
Fe(Me ₂ NOC) ₄ PcCl	5.2%	0%	20%
Fe((CH ₃) ₃ CH ₂ O) ₈ PcCl	8.6%	6.5%	2.1%
Fe((CH ₃) ₃ CH ₂ O) ₁₆ PcCl	0%	0%	41%
Fe(Cl ₂ PhO) ₄ PcCl	2%	0%	25%
Fe(OMe) ₂ (PhO) ₄ PcCl	0%	0%	93%

Figure 2.7. Activity of soluble phthalocyanines for tertiary C—H insertion.

The metallocarbene intermediate operative in this mechanism is electrophilic, demonstrated by its increased reactivity with electron rich C—H bonds. Increased electrophilicity is generally correlated with increased reactivity, at least in the rhodium-catalyzed case.¹⁷ Therefore, in order to access stronger unactivated tertiary

bonds, we hypothesized that we would need more electrophilic catalysts. However, in addition to electrophilicity, solubility of the catalyst may be important specifically for the phthalocyanine catalysts, as they are relatively insoluble.¹⁸ Developing catalysts that were both electrophilic and

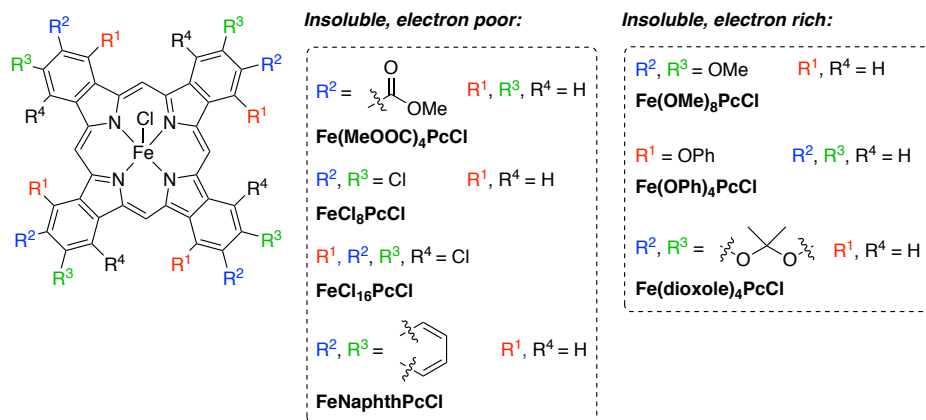
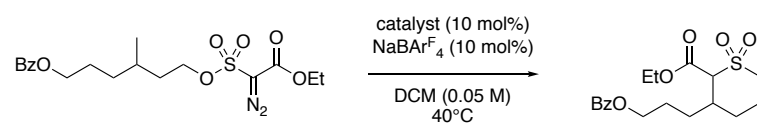


Figure 2.8. Insoluble iron phthalocyanine catalysts.

soluble proved to be an interesting challenge, as many electron-withdrawing substituents (such as halogens) also serve to decrease the solubility

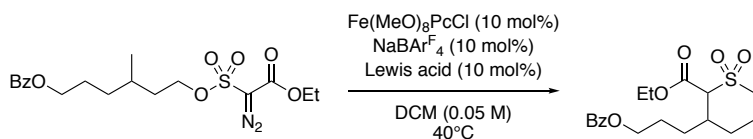
of these catalysts. Strategies generally involved bulky alkyl chains to break up stacking of the phthalocyanines, either fluorinated or paired with an electron withdrawing group (an ester, amide, or halogen) in order to furnish an electrophilic arene (Fig. 2.6). These frameworks did not, in general, increase the yield from the unsubstituted phthalocyanine, although these catalysts did in



Catalyst	diastereomer 1	diastereomer 2	RSM
FePcCl	6.4%	5.4%	19%
Fe(MeOOC) ₄ PcCl	5.3%	trace	105%
FeCl ₈ PcCl	0%	0%	85%
FeCl ₁₆ PcCl	1.9%	trace	92%
FeNaphthPcCl	trace	0%	83%
Fe(MeO) ₈ PcCl	4.9%	2.8%	85%
Fe(PhO) ₄ PcCl	11%	8.6%	3.6%
Fe(dioxole) ₄ PcCl	0%	0%	46%

Figure 2.9. Reactivity for insoluble iron phthalocyanines for tertiary C—H insertion.

electron-rich soluble catalysts in order to disambiguate the low recovered starting material values witnessed with the electron poor, soluble catalysts (Fig. 2.6, 2.7). Long, bulky alkyl ether functionality and biaryl ethers with ortho-substitution both furnished soluble catalysts. These



Lewis Acid	diastereomer 1	diastereomer 2	RSM
none	4.9%	2.8%	83%
Sc(OTf) ₃	4.8%	4.6%	7.7%
Sn(OTf) ₂	8.7%	7.7%	32%
Zn(OAc) ₂	0%	0%	93%
La(OTf) ₃	2.9%	1.7%	32%
Yb(OTf) ₃	4.2%	3.5%	58%
Fe ₂ Cp ₂ (CO) ₂	0%	0%	87%
Bi(OTf) ₃	1.6%	1.6%	2.4%
Me ₃ SiOTf	4.5%	3.9%	2.9%
AlEt ₂ Cl ₂	trace	0%	110%
TiCl ₄	0%	0%	65%
ZrCl ₄	0%	trace	94%
MoO ₃	trace	trace	90%
In(OAc) ₃	2.6%	1.2%	86%
SbF ₃	5.7%	4.9%	8%
SnF ₃	2.2%	1.3%	79%
PtCl ₄	1.9%	1.2%	79%

Figure 2.10. Reactivity with Lewis acid additives.

many cases increase diastereoselectivity, likely due to steric bulk (Fig. 2.7). These also tended to have low recovered starting material values (the Fe(*t*-Bu)₄Cl₄PcCl catalyst is an exception).

Next, we investigated generally also had either low recovered starting material or no reactivity at all. Although the Fe(CH₃)₃CCH₂O)₈PcCl catalyst did increase the yield marginally, these results proved to be irreproducible at higher scale.

Insoluble catalysts were tested to determine whether these would be more selective for desired product over byproducts in their reactivity (Fig. 2.8). Halogens,

esters with smaller alkyl groups, and extended π systems were installed to synthesize insoluble and electron poor catalysts. Electron rich catalysts were synthesized with a variety of ether linkages. The recovered starting material values did increase with insoluble catalysts, though for some that was at the expense of reactivity (Fig. 2.9). The $\text{Fe}(\text{PhO})_4\text{PcCl}$ catalyst gave the highest yield achieved so far, at 19% (16% isolated), although with nearly no starting material recovered. Derivatives of this catalyst were not as effective. The $\text{Fe}(\text{MeO})_8\text{PcCl}$ catalyst gave comparable yields with much higher recovered starting material values than the plain phthalocyanine.

As catalyst modifications did not significantly improve reactivity, additives were investigated. Because Lewis acids have been seen to decompose diazo precursors to free carbenes,^{19,20} and to act cooperatively with metal catalysts to form metallocarbenes,²⁰ we hypothesized that addition of Lewis acids could increase reactivity (Fig. 2.10). A variety of Lewis acids were tested with $\text{Fe}(\text{MeO})_8\text{PcCl}$, due to its low reactivity and high selectivity for product

<i>Catalyst</i>	<i>Lewis acid</i>	<i>diastereomer 1</i>	<i>diastereomer 2</i>	<i>RSM</i>	formation. While three
$\text{Fe}(t\text{-BuOOC})_4\text{PcCl}$ with AgSbF_6	$\text{Sn}(\text{OTf})_2$	8.7%	8.4%	5.4%	Lewis acids gave
$\text{Fe}(t\text{-BuOOC})_4\text{PcCl}$ with AgSbF_6	none	6.1%	3.3%	59%	somewhat increased
$\text{Fe}((\text{CH}_3)_3\text{CH}_2\text{O})_8\text{PcCl}$	$\text{Sn}(\text{OTf})_2$	0%	0%	96%	yields, tin (II) triflate
$\text{Fe}((\text{CH}_3)_3\text{CH}_2\text{O})_8\text{PcCl}$	none	8.6%	6.5%	2.1%	
$\text{Fe}(\text{PhO})_4\text{PcCl}$	$\text{Sn}(\text{OTf})_2$	4.4%	3.9%	3.0%	
$\text{Fe}(\text{PhO})_4\text{PcCl}$	none	11%	8.6%	3.6%	

Figure 2.11. Further investigation into Lewis acid additives. doubled the yield

ordinarily obtained, although the recovered starting material value was much lower. In order to probe the effect of the Lewis acid additive on yield for a variety of catalysts, it was tested with $\text{Fe}(t\text{-BuOOC})_4\text{PcCl}$ with AgSbF_6 , $\text{Fe}((\text{CH}_3)_3\text{CH}_2\text{O})_8\text{PcCl}$, and $\text{Fe}(\text{PhO})_4\text{PcCl}$ (Fig. 2.11). The yield benefited from the Lewis acid additive only when the recovered starting material values were considerable without the additive. Otherwise, the yield suffered. All Lewis acids were shown to produce no product under the reaction conditions without catalyst.

2.6 Conclusion

In conclusion, we have demonstrated the first iron-catalyzed carbene-mediated C—H insertion reaction. This methodology is tolerant of a variety of heterocyclic functionalities and suitable in complex settings, as well as proceeding via a different mechanism from the well-developed rhodium-catalyzed system.

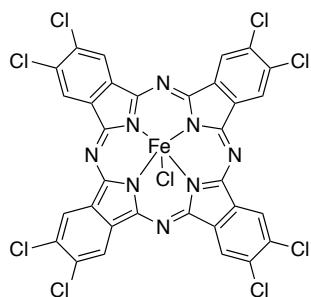
2.7 Supporting Information

General Information

The following commercially obtained reagents were used as received: iron(III) phthalocyanine chloride ([FePc]Cl, Sigma-Aldrich), iron(II) phthalocyanine (FePc, Sigma-Aldrich), 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine iron(III) chloride (Fe(TPP)Cl, Sigma-Aldrich), 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine (PyBOX, Sigma-Aldrich), rhodium(II) acetate dimer (Rh₂(OAc)₄, Strem), and silver hexafluoroantimonate (AgSbF₆, Strem). Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr^F₄)²¹, MeSO₂N₃²², and ClSO₂CH₂CO₂Et²³ were prepared according to literature procedures and stored at rt in the glovebox, 4 °C, and -20 °C, respectively. All reactions were run in flame- or oven-dried glassware under an atmosphere of N₂ or Ar gas with dry solvents unless otherwise stated. All products were filtered through a glass wool plug prior to obtaining a final weight. Solid reagents were stored in a dessicator or glovebox, and anhydrous solvents were purified by passage through a bed of activated alumina immediately prior to use (Glass Countour, Laguna Beach, California). Chloroform-*d* was stored over 3 Å molecular sieves. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized with UV and potassium permanganate stains. Flash chromatography was performed as described by Still²⁴ using American International ZEOprep 60 ECO silica gel (230-400 mesh). Achiral gas chromatographic (GC) analysis was

performed on an Agilent 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25mm), and chiral GC analysis using a CycloSil-B column (30m, 0.25mm, 0.25mm). ¹H-NMR spectra were recorded on a Varian Inova-500 (500 MHz), Varian Unity-500 (500 MHz), Varian Unity Inova-400 (400 MHz), or Bruker (500Mz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, spt = septet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C-NMR spectra were recorded on a Varian Unity-500 (126 MHz) or Bruker (126Mz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.16 ppm). Kinetic isotope effect analyses were recorded on a Varian Inova-600 (600 MHz) spectrometer. IR spectra were recorded by ATR on a Perkin Elmer Frontier FTIR and are reported in frequency of absorption (cm⁻¹). Optical rotations were measured using a 1 mL cell with a 50 mm path length on a Jasco P-1020 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: [α] _{λ} ^TC (*c* = g/100 mL, solvent). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer, and electron ionization (EI) and field desorption (FD) spectra were performed on a Micromass 70-VSE spectrometer.

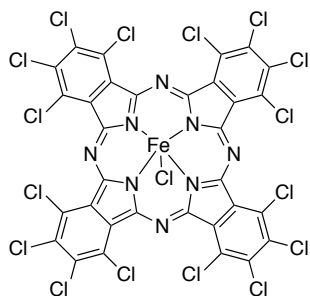
Preparation of $[\text{FeCl}_8\text{Pc}]\text{Cl}$ and $[\text{FeCl}_{16}\text{Pc}]\text{Cl}$



$[\text{FeCl}_8\text{Pc}]\text{Cl}$: A flame dried 25 mL round-bottom flask equipped with a stir bar and reflux condenser (the flask and stir bar should be free of trace metal impurities) was sequentially charged with 4,5-dichlorophthalonitrile (788 mg, 4.0 mmol, 4.0 equiv, TCI America), 1-hexanol (10 mL, freshly distilled over MgSO_4 and degassed), FeCl_3 (162

mg, 1.00 mmol, 1.0 equiv, Sigma-Aldrich) and DBU (597 μL , 4.0 mmol, 4.0 equiv, Sigma-Aldrich). The reaction flask was evacuated under vacuum and refilled with N_2 three times, then heated to 155°C . The reaction mixture changed from brown to turquoise green over 10 min. After stirring at 155°C overnight (12-15h), the heat was ceased and the condenser was removed. After cooling to room temperature, the reaction mixture was filtered. The remaining dark green solid was washed with 10 mL of 1 M HCl , 10 mL of water, and 10 mL of EtOH . The catalyst was dried under high vacuum overnight at 90°C to afford 761 mg (0.867 mmol) of $[\text{FeCl}_8\text{Pc}]\text{Cl}$ as a dark green powder (87% yield).

UV-Vis (H_2SO_4 , $c = 13.4 \mu\text{M}$, $\lambda_{\text{max}} = \text{nm}$, $\epsilon = \text{M}^{-1}\text{cm}^{-1}$): 787 ($\epsilon = 49036$), 305 ($\epsilon = 65655$), 249 ($\epsilon = 107538$).; IR (ATR, cm^{-1}) 2955.86, 2353.03, 1889.14, 1767.7, 1730.25, 1602.19, 1514.22, 1448.96, 1435.09, 1416.2, 1387.01, 1330.14, 1290.86, 1200.89, 1137.03, 1084.38, 1071.49, 962.86, 887.52, 849.38, 824.54, 799.97, 783.39, 749.16, 708.28, 679.24, 660.94, 593.17, 550, 504.; HRMS (EI) $m/z = 839.77$ (M-Cl).



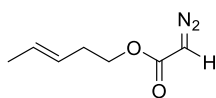
[FeCl₁₆Pc]Cl: A flame dried 25 mL round-bottom flask equipped with a stir bar and reflux condenser (the flask and stir bar should be free of trace metal impurities) was sequentially charged with tetrachlorophthalonitrile (1.06 g, 4.0 mmol, 4.0 equiv, TCI America), 1-hexanol (10 mL, freshly distilled over MgSO₄ and degassed), FeCl₃ (162 mg, 1.00 mmol, 1.0 equiv, Sigma-Aldrich) and DBU (597 μ L, 4.0 mmol, 4.0 equiv, Sigma-Aldrich). The reaction flask was evacuated under vacuum and refilled with N₂ three times, then heated to 155°C. The reaction mixture changed from brown to turquoise green over 10 min. After stirring at 155°C overnight (12-15h), the heat was ceased and the condenser was removed. After cooling to room temperature, the reaction mixture was filtered. The remaining dark green solid was washed with 10 mL of 1 M HCl, 10 mL of water, and 10 mL of EtOH. The catalyst was dried under high vacuum overnight at 90°C to afford 638 mg (0.553 mmol) of [FeCl₁₆Pc]Cl as a dark green powder (55% yield).

UV-Vis (H₂SO₄, c = 8.2 μ M, λ_{max} = nm, ϵ = M⁻¹cm⁻¹): 797 (ϵ = 47290), 770 (ϵ = 47654), 317 (ϵ = 60784).; IR (ATR, cm⁻¹) 3258.78, 2323.85, 2162.01, 2050.37, 1980.01, 1736.67, 1561.44, 1501.78, 1391.32, 1302.37, 1273.49, 1212.62, 1156.98, 1091.91, 955.98, 856.36, 780.41, 770.26, 750.95, 647.41, 607.77, 511.89, 470.91.; HRMS (EI) m/z = 1111.46 (M-Cl).

Reaction Discovery: Traditional Diazo Sources

Preparation of diazoesters:

(*E*)-pent-3-en-1-yl 2-diazoacetate [1].

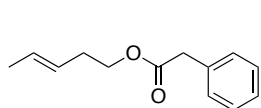


364 mg (2.14 mmol) of (*E*)-pent-3-en-1-yl 3-oxobutanoate was added to a 100 mL round-bottom flask, diluted with acetonitrile (21.4 mL, 0.1 M), and cooled

to 0°C. *p*ABSA (617 mg, 2.57 mmol, 1.2 equiv) and DBU (384 μ L, 2.57 mmol, 1.2 equiv) were added and the reaction was allowed to warm to RT. After stirring for 12 hours, the reaction mixture was diluted with aq. NH₄Cl and extracted with diethyl ether. The organic extracts were combined, dried over NaSO₄, and filtered. After concentration, the crude yellow solid was triturated with a 50/50 mixture of pentane/ether, filtered, and the filtrate was concentrated. This crude mixture was then diluted with acetonitrile (10 mL) and cooled to 0°C. 4% aq. KOH (40 mL) was added and the reaction mixture stirred vigorously until judged complete by TLC (1-5 h). The reaction mixture was extracted three times with diethyl ether, dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography on silica using 10% EtOAc/Hex as eluent gave 191 mg (1.24 mmol) of pure product as a yellow oil (58% yield).

¹H NMR (500 MHz, CDCl₃) δ 5.53 (dqt, *J* = 15.4, 6.3, 1.3 Hz, 1H), 5.38 (dtq, *J* = 15.2, 6.8, 1.6 Hz, 1H), 4.73 (s, 1H), 4.15 (t, *J* = 6.9 Hz, 2H), 2.32 (qp, *J* = 6.8, 1.2 Hz, 2H), 1.66 (dq, *J* = 6.4, 1.3 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 166.80, 128.08, 126.12, 64.47, 46.17, 32.18, 18.00.; IR (ATR, cm⁻¹) 3121.57, 2961.99, 2919.82, 2858.19, 2105.68, 1686.59, 1453.75, 1394.35, 1354.67, 1337.81, 1237.29, 1179.08, 1155.09, 1080.75, 1025.21, 992.16, 965.71, 739.14, 553.27, 468.42.

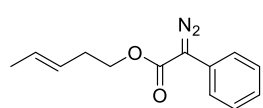
(*E*)-pent-3-en-1-yl 2-phenylacetate [S1].



Synthesized according to literature precedent²⁵. (*E*)-pent-3-en-1-ol (689 mg, 8.0 mmol, 1.0 equiv), phenyl acetyl chloride (1.26 mL, 8.0 mmol, 1.0 equiv), pyridine (1.30 mL, 16 mmol, 2.0 equiv), DMAP (97.8 mg, 0.8 mmol, 0.1 equiv), and CH₂Cl₂ (16 mL, 0.5 M) were used. Flash column chromatography on silica using 0% → 5% ethyl acetate/hexanes as eluent gave 1.40 g (6.85 mmol) of pure product as a clear oil (86% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.36 - 7.24 (m, 5H), 5.55 - 5.42 (m, 1H), 5.35 (dtq, J = 15.0, 6.6, 1.5 Hz, 1H), 4.10 (t, J = 6.8 Hz, 2H), 3.62 (s, 2H), 2.32-2.27 (m, 2H), 1.64 (dq, J = 6.4, 1.3 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 171.66, 134.27, 129.39, 128.63, 128.09, 127.14, 126.32, 64.56, 41.58, 32.05, 18.09.; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 227.1048, found 227.1051.

(*E*)-pent-3-en-1-yl 2-diazo-2-phenylacetate [2].

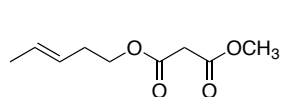


1.43 g (7.00 mmol) of (*E*)-pent-3-en-1-yl 2-phenylacetate [**S1**] was added to a 100 mL round-bottom flask, diluted with acetonitrile (70 mL, 0.1 M), and cooled to 0°C. *p*ABSA (2.02 g, 8.40 mmol, 1.2 equiv) and DBU (1.57 mL, 10.5 mmol, 1.5 equiv) were added and the reaction was allowed to warm to RT. After stirring for 12 hours, the reaction mixture was diluted with aq. NH_4Cl and extracted with diethyl ether. The organic extracts were combined, dried over Na_2SO_4 , and filtered. After concentration, the crude orange solid was triturated with a 50/50 mixture of pentane/ether, filtered, and the filtrate was concentrated. Flash column chromatography on silica using 5% diethyl ether/pentane as eluent gave 669 mg (2.91 mmol) of pure product as an orange oil (42% yield).

^1H -NMR (500 MHz, CDCl_3) δ 7.48 (m, 2H), 7.38 (m, 2H), 7.20-7.16 (m, 1H), 5.57 (dqt, J = 15.2, 6.3, 1.3 Hz, 1H), 5.42 (dtq, J = 15.3, 6.9, 1.5 Hz, 1H), 4.27 (t, J = 6.8 Hz, 2H), 2.38 (qp, J = 6.7, 1.2 Hz, 2H), 1.68 (dq, J = 6.4, 1.3 Hz, 3H). ^{13}C -NMR (126 MHz, CDCl_3) δ 165.27, 129.01, 128.36, 126.19, 125.85, 125.72, 124.05, 64.63, 32.31, 18.12; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}-\text{N}_2]^+$: 203.1072, found 203.1073; IR (ATR, cm^{-1}) 3060.58, 3026.28, 2960.68, 2917.83, 2856.42, 2396.29, 2080.84, 1699.91, 1598.58, 1575.82, 1498.39, 1470.09, 1449.81, 1385.81,

1346.9, 1336.76, 1285.9, 1241.61, 1152.23, 1078.61, 1045.13, 1017.79, 997.6, 965.2, 904.04, 835.72, 752.9, 689.6, 666.78, 619.64, 555.99, 532.68, 493.98

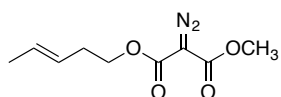
(*E*)-methyl pent-3-en-1-yl malonate [S2].



1.08 g (8.0 mmol) of (*E*)-pent-3-en-1-ol, pyridine (1.21 mL, 16.0 mmol, 2 equiv), DMAP (97.7 mg, 0.8 mmol, 0.1 equiv) and CH₂Cl₂ were added to a flame-dried round-bottom flask and cooled to 0°C. Methyl malonyl chloride (1.09 g, 8.0 mmol, 1 equiv) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was diluted with aq. NH₄Cl and extracted with CH₂Cl₂. The organic extracts were combined, dried over Na₂SO₄, and filtered. After concentration, the crude oil was purified by flash column chromatography on silica using 15% EtOAc/hexanes as eluent, giving 939 mg (5.0 mmol) of pure product as a clear oil (63% yield).

¹H-NMR (500 MHz, CDCl₃) δ 5.58-5.48 (m, 1H), 5.38 (dtq, *J* = 15.3, 6.9, 1.6 Hz, 1H), 4.14 (t, *J* = 6.9 Hz, 2H), 3.75 (s, 3H), 3.38 (s, 2H), 2.37-2.28 (m, 2H), 1.66 (dq, *J* = 6.4, 1.3 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 167.11, 166.58, 128.28, 125.99, 65.27, 52.59, 41.46, 31.85, 18.10.; HRMS (ESI) *m/z* calculated for C₉H₁₄O₄Na [M+Na]⁺: 209.0790, found 209.0786.

(*E*)-1-methyl 3-(pent-3-en-1-yl) 2-diazomalonate [3].



845 mg (4.54 mmol) of (*E*)-methyl pent-3-en-1-yl malonate [S2] was added to a 100 mL flame-dried round-bottom flask, diluted with acetonitrile (45 mL, 0.1 M), and cooled to 0°C. *p*ABSA (1.31 mg, 5.44 mmol, 1.2 equiv) and DBU (815 μL, 5.44 mmol, 1.2 equiv) were added and the reaction was allowed to warm to RT. After stirring for 12 hours, the reaction mixture was diluted with aq. NH₄Cl and extracted with diethyl

ether. The organic extracts were combined, dried over Na₂SO₄, and filtered. After concentration, the crude yellow solid was triturated with a 50/50 mixture of pentane/ether, filtered, and the filtrate was concentrated. Flash column chromatography on silica using 15% EtOAc/hexanes as eluent gave 812 mg (3.83 mmol) of pure product as a yellow oil (84% yield).

¹H-NMR (500 MHz, CDCl₃) δ 5.58 – 5.50 (m, 1H), 5.38 (dtq, *J* = 15.3, 6.9, 1.7 Hz, 1H), 4.22 (t, *J* = 6.9 Hz, 2H), 3.84 (s, 3H), 2.38-2.33 (m, *J* = 6.8, 1.2 Hz, 2H), 1.66 (dq, *J* = 6.4, 1.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.59, 160.70, 128.37, 125.76, 65.02, 52.48, 32.00, 17.96.; HRMS (ESI) *m/z* calculated for C₉H₁₂N₂O₄Na [M+Na]⁺: 235.0695, found 235.0698; IR (ATR, cm⁻¹) 2957.88, 2857.93, 2132.69, 1759.74, 1733.99, 1692.34, 1436.48, 1387.26, 1319.59, 1270.24, 1202.92, 1181.13, 1080.91, 1014.16, 966.47, 830.65, 758.66, 732.78, 647.42, 543.79, 497.46.

General procedure for reaction discovery studies:

Into a 1 dram vial was added catalyst (0.040 mmol, 0.10 equiv) in a glovebox. The vial was sealed, taken out of the box, and the contents were added under a stream of nitrogen to a flame dried three neck 25 mL flask equipped with a stir bar, reflux condenser, glass stopper, and rubber septum. CH₂Cl₂ (5.0 mL, 0.08 M) was added and the flask was heated to reflux (~45°C) for 10 minutes (4 hours for FeCl₃•pybox conditions²⁶). Diazoester (0.40 mmol) was taken up with CH₂Cl₂ (3.0 mL, 0.13 M) in a glass syringe and added dropwise to the refluxing catalyst solution over the course 2-3 minutes (final reaction concentration is 0.05 M). After complete addition of diazoester, the reaction refluxed until judged complete by TLC (2-24 h). The reaction mixture was cooled, adsorbed onto SiO₂ or florisil, and applied directly to a silica column (75 mL SiO₂). Purification conditions are noted for individual entry.

Acceptor diazoester:

FeCl₃•pybox Conditions: (*E*)-pent-3-en-1-yl 2-diazoacetate [**1**] (61.7 mg, 0.400 mmol, 1.0 equiv), FeCl₃ (5.10 mg, 0.040 mmol, 0.10 equiv), 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine (14.8 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 5% → 10% → 15% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (61.6 mg, 0.399 mmol, 100% rsm). Run 2: (60.2 mg, 0.390 mmol, 98% rsm). **Average: 99% yield rsm.**

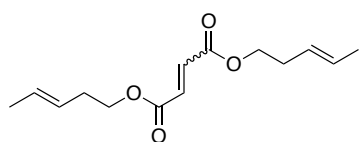
Fe(TPP)Cl Conditions: (*E*)-pent-3-en-1-yl 2-diazoacetate [**1**] (61.7 mg, 0.400 mmol, 1.0 equiv), Fe(TPP)Cl (28.2 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 5% → 10% → 15% EtOAc/hexanes as eluent gave recovered starting material (rsm) and dimer di(pent-3-en-1-yl) fumarate [**4**] as a mixture of olefin isomers.

Run 1: (47.9 mg, 0.190 mmol, 95% dimer), 0% rsm. Run 2: (45.9 mg, 0.182 mmol, 91% dimer), 0% rsm. **Average: 93% yield dimer [4], 0% rsm.**

[FePc]Cl Conditions: (*E*)-pent-3-en-1-yl 2-diazoacetate [**1**] (61.7 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 5% → 10% → 15% EtOAc/hexanes as eluent gave recovered starting material (rsm) and dimer di(pent-3-en-1-yl) fumarate [**4**] as a mixture of olefin isomers.

Run 1: (40.9 mg, 0.162 mmol, 81% dimer), 0% rsm. Run 2: (43.4 mg, 0.172 mmol, 86% dimer), 0% rsm. **Average: 84% yield dimer [4], 0% rsm.**

di(pent-3-en-1-yl) fumarate [4]



$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 6.23 (s, 2H), 5.54 (dqt, $J = 15.4, 6.3, 1.3$ Hz, 2H), 5.39 (dtq, $J = 15.2, 6.8, 1.6$ Hz, 2H), 4.18 (t, $J = 7.0$ Hz, 4H), 2.38-2.32 (m, 4H), 1.66 (dq, $J = 6.4, 1.3$ Hz, 6H); $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 165.32, 129.88, 128.24, 126.08, 65.05, 31.80, 18.12.; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 275.1259, found 275.1257.

Donor/acceptor:

FeCl_3 •pybox Conditions: (*E*)-pent-3-en-1-yl 2-diazo-2-phenylacetate [2] (92.1 mg, 0.400 mmol, 1.0 equiv), FeCl_3 (5.10 mg, 0.040 mmol, 0.10 equiv), 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine (14.8 mg, 0.040 mmol, 0.10 equiv), $\text{NaBAr}^{\text{F}}_4$ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH_2Cl_2 (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (85.1 mg, 0.369 mmol, 92% rsm). Run 2: (80.1 mg, 0.348 mmol, 87% rsm). **Average: 90% rsm.**

$\text{Fe}(\text{TPP})\text{Cl}$ Conditions: (*E*)-pent-3-en-1-yl 2-diazo-2-phenylacetate [2] (92.1 mg, 0.400 mmol), FeTPPCl (28.2 mg, 0.040 mmol, 0.1 equiv), and CH_2Cl_2 (8.0 mL, 0.05 M) were used. Flash column chromatography on silica using 0% petroleum ether to 10% Et_2O /petroleum ether as eluent gave

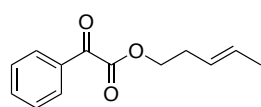
recovered starting material (rsm) and ketone (*E*)-pent-3-en-1-yl 2-oxo-2-phenylacetate [**5**]. Yields partially determined via NMR with mesitylene as an internal standard.

Run 1: (3.5 mg, 0.016 mmol, 4% ketone), (88.9 mg, 0.386 mmol, 97% rsm). Run 2: (2.8 mg, 0.013 mmol, 3% ketone), (85.9 mg, 0.373 mmol, 93% rsm). **Average: 4% yield ketone [**5**], 95% rsm.**

[FePc]Cl Conditions: (*E*)-pent-3-en-1-yl 2-diazo-2-phenylacetate [**2**] (92.1 mg, 0.400 mmol), FePcCl (24.2 mg, 0.040 mmol, 0.1 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used. Flash column chromatography on silica using 0% to 10% Et₂O/petroleum ether as eluent gave recovered starting material (rsm) and ketone (*E*)-pent-3-en-1-yl 2-oxo-2-phenylacetate [**5**]. Yields partially determined via NMR with mesitylene as an internal standard.

Run 1: (10.4 mg, 0.048 mmol, 12% ketone), (53.4 mg, 0.232 mmol, 58% rsm). Run 2: (10.4 mg, 0.048 mmol, 12% ketone), (53.4 mg, 0.232 mmol, 58% rsm). **Average: 12% yield ketone [**5**], 58% rsm.**

(*E*)-pent-3-en-1-yl 2-oxo-2-phenylacetate [5**].**



¹H-NMR (500 MHz, CDCl₃) δ 8.00 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.68-7.64 (m, 1H), 7.51 (dd, *J* = 8.3, 7.4 Hz, 2H), 5.65 - 5.54 (m, 1H), 5.44 (dtq, *J* = 15.3, 6.8, 1.6 Hz, 1H), 4.40 (t, *J* = 6.8 Hz, 2H), 2.51 - 2.41 (m, 2H), 1.68 (dq, *J* = 6.4, 1.4 Hz, 3H).; ¹³C NMR (126 MHz, CDCl₃) δ 186.56, 164.01, 135.02, 132.61, 130.19, 129.00, 128.96, 125.69, 65.86, 32.01, 18.14. HRMS (ESI) *m/z* calculated for C₁₃H₁₄O₃Na [M+Na]⁺: 241.0841, found 241.0849.

Acceptor/acceptor:

FeCl₃•pybox Conditions: (*E*)-1-methyl 3-(pent-3-en-1-yl) 2-diazomalonate [**3**] (84.9 mg, 0.400 mmol, 1.0 equiv), FeCl₃ (5.10 mg, 0.040 mmol, 0.10 equiv), 2,6-bis[(4*R*)-4-phenyl-2-oxazoliny]pyridine(14.8 mg, 0.040 mmol, 0.10 equiv), NaBAR^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (81.9 mg, 0.386 mmol, 97% rsm). Run 2: (81.7 mg, 0.385 mmol, 96% rsm). **Average: 97% yield rsm.**

Fe(TPP)Cl Conditions: (*E*)-1-methyl 3-(pent-3-en-1-yl) 2-diazomalonate [**3**] (84.9 mg, 0.400 mmol, 1.0 equiv), Fe(TPP)Cl (28.2 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (78.7 mg, 0.371 mmol, 93% rsm). Run 2: (83.0 mg, 0.391 mmol, 98% rsm). **Average: 96% rsm.**

[FePc]Cl Conditions: (*E*)-1-methyl 3-(pent-3-en-1-yl) 2-diazomalonate [**3**] (84.9 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (78.5 mg, 0.370 mmol, 93% rsm). Run 2: (82.2 mg, 0.387 mmol, 97% rsm). **Average: 95% rsm.**

Acceptor/acceptor Sulfonate Ester:

FeCl₃•pybox Conditions: Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [**6**] (110.5 mg, 0.400 mmol, 1.0 equiv), FeCl₃ (5.10 mg, 0.040 mmol, 0.10 equiv), 2,6-bis[(4*R*)-4-phenyl-2-oxazoliny]pyridine (14.8 mg, 0.040 mmol, 0.10 equiv), NaBAR^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.5 M) were used. Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (105.6 mg, 0.382 mmol, 96% rsm). Run 2: (110.6 mg, 0.400 mmol, 100% rsm). **Average: 98% yield rsm.**

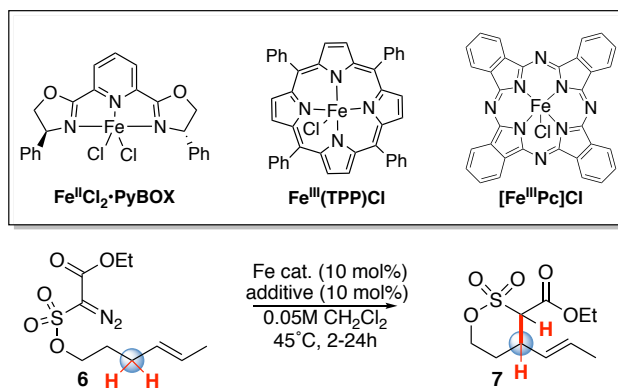
Fe(TPP)Cl Conditions: Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [**6**] (110.5 mg, 0.400 mmol, 1.0 equiv), Fe(TPP)Cl (28.2 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used. Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave recovered starting material (rsm).

Run 1: (108.1 mg rsm, 0.391 mmol, 98%). Run 2: (108.0 mg rsm, 0.391 mmol, 98%). **Average: 0% yield, 98% rsm.**

[FePc]Cl Conditions: Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [**6**] (110.5 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used. Flash column chromatography on silica using 10% → 15% → 20% EtOAc/hexanes as eluent gave recovered starting material (rsm) and ethyl (*E*)-4-(prop-1-en-1-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [**7**] as a mixture of diastereomers.

Run 1: (3.4 mg, 0.014 mmol, 3%), (107.1 mg rsm, 0.388 mmol, 97%). Run 2: (2.4 mg, 0.010 mmol, 2%), (107.0 mg rsm, 0.387 mmol, 97%). **Average: 3% yield [7], 97% rsm.**

Optimization of Fe-Catalyzed Intramolecular C—H Alkylation



entry	catalyst	additive	% yield (% rsm)
1	[Fe ^{III} Pc]Cl	—	3 (97)
2	[Fe ^{III} Pc]Cl ^a	AgSbF ₆	45 (0)
3	[Fe ^{III} Pc]Cl ^a	NaBAR ₄ ^F	48 (0)
4	[Fe ^{III} Cl ₁₆ Pc]Cl	NaBAR ₄ ^F	38 (0)
5	[Fe ^{III} Cl ₈ Pc]Cl	NaBAR ₄ ^F	25 (66)
6	[Fe ^{III} Pc]Cl ^{a,b}	NaBAR ₄ ^F	53 (0)
7	Fe ^{III} (TPP)Cl	NaBAR ₄ ^F	7 (93)
8	[Fe ^{II} Pc]	—	0 (100)
9	—	NaBAR ₄ ^F	0 (96)

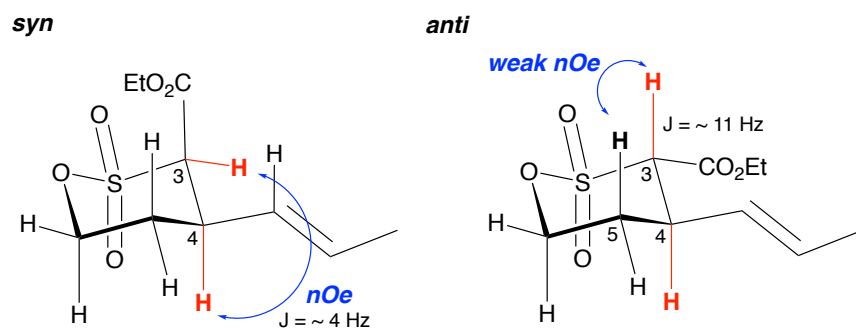
Reaction optimization. Reaction stirred for 24 hours after addition of diazoester unless otherwise noted. ^a Reaction stirred for 2 hours after dropwise addition of diazoester. ^b Diazo added via syringe pump over one hour. Pc = phthalocyanine; TPP = tetraphenylporphyrin; PyBOX = 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine; AgSbF₆ = silver hexafluoroantimonate; NaBAR₄^F = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. Isolated yields are average of two runs. rsm denotes recovered starting material.

Figure 2.12. Initial reaction optimization.

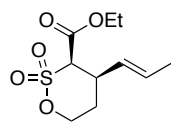
Ethyl (*E*)-4-(prop-1-en-1-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [7].

The relative stereochemistry of the δ -sultones was determined via coupling constant analysis, and confirmed by nOe NMR experiments (500 MHz, CDCl₃) in which the C3 and C4 protons for each diastereomer were irradiated (highlighted in red). Syn δ -sultones have a characteristic nOe between the C3 and C4 equatorial and pseudo-axial hydrogens. Conversely, the C3 and C4

hydrogens in the anti δ -sultones fall on opposite sides of the ring and therefore experience no observable nOe. Instead, for anti allylic C—H alkylation products a weak nOe can be observed between the C3 pseudo-axial hydrogen and the pseudo-axial C5 hydrogen. All products described in this paper are designated with the same relative stereochemistry as **7** as determined by coupling constant analogy. The experimental data are consistent with previously reported studies in the literature^{23,27}. The syn and anti diastereomers were collected from initial purification of crude reaction as a mixture (d.r. 1:1-3:1 syn:anti) and subsequently purified for characterization. In most, but not all, cases, the syn diastereomer was less polar than the anti diastereomer.



Syn diastereomer (major): ¹H-NMR (500 MHz, CDCl₃) δ 5.68 (dqd, J = 15.0, 6.5, 1.1 Hz, 1H),



5.33 (ddd, J = 15.3, 7.6, 1.7 Hz, 1H), 4.68-4.55 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H),

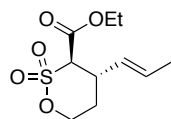
4.05 (d, J = 4.7 Hz, 1H_{C3}), 3.28-3.18 (m, 1H), 2.61 (dtd, J = 14.5, 12.0, 5.6 Hz,

1H), 1.68 (ddd, J = 6.5, 1.7, 0.8 Hz, 3H), 1.64 (ddt, J = 14.6, 4.3, 2.4 Hz, 1H), 1.30 (t, J = 7.1 Hz,

3H); ¹³C-NMR (126 MHz, CDCl₃) δ 164.11, 129.69, 127.73, 73.03, 64.90, 62.37, 40.59, 25.40,

17.99, 14.10.; HRMS (ESI) m/z calculated for C₁₀H₁₇O₅S [M+H]⁺: 249.0797, found 249.0795.

Anti diastereomer (minor): ¹H-NMR (500 MHz, CDCl₃) δ 5.68 (dqd, J = 13.9, 6.5, 0.9 Hz, 1H),



5.23 (ddd, J = 15.3, 8.3, 1.7 Hz, 1H), 4.70-4.61 (m, 1H), 4.52-4.44 (m, 1H), 4.28

(q, J = 7.1 Hz, 2H), 3.78 (d, J = 11.6 Hz, 1H_{C3}), 3.25 (dq, J = 11.4, 8.2 Hz, 1H),

1.92-1.84 (m, 2H), 1.66 (dd, $J = 6.4, 1.4$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C -NMR (126 MHz, CDCl_3) δ 163.35, 130.21, 127.93, 72.54, 68.19, 62.67, 41.70, 30.44, 17.98, 14.16.; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{17}\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 249.0797, found 249.0796.

General procedure for optimization studies (entries 1-9):

Into a 1 dram vial was added catalyst (0.040 mmol, 0.10 equiv) in a glovebox. The vial was sealed, taken out of the box, and the contents were added under a stream of nitrogen to a flame dried three neck 25 mL flask equipped with a stir bar, reflux condenser, glass stopper, and rubber septum. CH_2Cl_2 (5.0 mL, 0.08 M) was added and the flask was heated to reflux ($\sim 45^\circ\text{C}$) for 10 minutes. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate **6** (110.5 mg, 0.400 mmol, 1.0 equiv) was taken up with CH_2Cl_2 (3.0 mL, 0.13 M) in a glass syringe and added dropwise to the refluxing catalyst solution over the course of 2-3 minutes (final reaction concentration is 0.05 M). After complete addition of diazosulfonate, the reaction refluxed until judged complete by TLC (2-24 h). The reaction mixture was cooled, adsorbed onto SiO_2 or florisil, and applied directly to a silica column (75 mL SiO_2) for purification to afford the desired sultone product. The recovered starting material (rsm) and product were eluted with 10% $\rightarrow$ 15% $\rightarrow$ 20% EtOAc/hexanes and isolated separately. Any variation of these reaction conditions is noted for individual entries.

Entry 1. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [**6**] (110.5 mg, 0.400 mmol, 1.0 equiv), $[\text{FePc}]\text{Cl}$ (24.2 mg, 0.040 mmol, 0.10 equiv), and CH_2Cl_2 (8.0 mL, 0.05 M) were used.

Run 1: (3.4 mg, 0.014 mmol, 3%), (107.1 mg rsm, 0.388 mmol, 97%). Run 2: (2.4 mg, 0.010 mmol, 2%), (107.0 mg rsm, 0.387 mmol, 97%). **Average: 3% yield, 97% rsm.**

Entry 2. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), AgSbF₆ (13.7 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Run 1: (45.5 mg, 0.183 mmol, 46%). Run 2: (44.4 mg, 0.179 mmol, 45%). **Average: 45% yield, 0% rsm.**

Entry 3. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Run 1: (47.7 mg, 0.192 mmol, 48%). Run 2: (46.3 mg, 0.186 mmol, 47%). **Average: 48% yield, 0% rsm.**

Entry 4. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), [FeCl₁₆Pc]Cl (46.2 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Run 1: (35.1 mg, 0.141 mmol, 35%). Run 2: (39.6 mg, 0.159 mmol, 40%). **Average: 38% yield, 0% rsm.**

Entry 5. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), [FeCl₈Pc]Cl (35.2 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Run 1: (24.3 mg, 0.098 mmol, 25%), (73.7 mg rsm, 0.267 mmol, 67%). Run 2: (26.0 mg, 0.105 mmol, 26%), (72.6 mg rsm, 0.263 mmol, 66%). **Average: 25% yield, 66% rsm.**

Entry 6. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used. Solution of diazo was added via syringe pump over the course of an hour (see General procedure for [FePc]-catalyzed C—H alkylation).

Run 1: (53.4 mg, 0.215 mmol, 54%). Run 2: (51.9 mg, 0.209 mmol, 53%). **Average: 53% yield, 0% rsm.**

Entry 7. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), Fe(TPP)Cl (28.2 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Run 1: (7.5 mg, 0.030 mmol, 7%), (103.2 mg rsm, 0.373 mmol, 93%). Run 2: (6.3 mg, 0.025 mmol, 6%), (104.7 mg rsm, 0.379 mmol, 94%). **Average: 7% yield, 93% rsm.**

Entry 8. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), [Fe^{II}Pc] (22.7 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Run 1: (108.9 mg rsm, 0.394 mmol, 99%). Run 2: (110.2 mg RSM, 0.399 mmol, 100%). **Average: 0% yield, 100% rsm.**

Entry 9. Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6] (110.5 mg, 0.400 mmol, 1.0 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

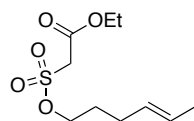
Run 1: (105.7 mg rsm, 0.382 mmol, 96%). Run 2: (106.7 mg rsm, 0.386 mmol, 97%). **Average: 0% yield, 96% rsm.**

Preparation of Sulfonate Ester Starting Materials

General procedure for preparation of sulfonate ester substrates:

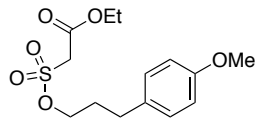
A round-bottom flask equipped with a stir bar and rubber septum was charged with alcohol substrate (1 equiv), imidazole (1.2 equiv), and THF (0.4 M). Ethyl chlorosulfonylacetate (1.5 equiv) was dissolved in THF (0.4 M) and added slowly dropwise to the reaction over the course of 5 mins. The reaction was stirred at room temperature for 1-6 hours, or until complete consumption of starting material as monitored by TLC. The reaction was quenched with H₂O until the mixture turned clear (10-20 mL). The reaction mixture was partitioned between H₂O (15 mL) and CH₂Cl₂ (60 mL) and separated. The aqueous layer was then extracted with CH₂Cl₂ (2x20 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the desired sulfonate ester.

Ethyl (*E*)-2-((hex-4-en-1-yloxy)sulfonyl)acetate [S3].



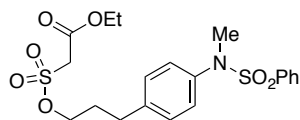
1.00 g (10.0 mmol) of (*E*)-hex-4-en-1-ol were used, along with imidazole (817 mg, 12.0 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (2.80 g, 15.0 mmol, 1.5 equiv), and THF (50 mL, 0.2 M). Flash column chromatography on silica using 10% EtOAc/hexanes as eluent gave 2.30 g (9.20 mmol) of pure product as a pale yellow oil (92% yield).

¹H-NMR (500 MHz, CDCl₃) δ 5.54-5.43 (m, 1H), 5.38 (dt, *J* = 15.2, 6.6 Hz, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 2.11 (dt, *J* = 7.3, 6.6 Hz, 2H), 1.82 (p, *J* = 6.7 Hz, 2H), 1.65 (d, *J* = 6.3 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 162.02, 129.02, 126.58, 71.77, 62.60, 54.67, 28.86, 28.14, 17.84, 13.90.; HRMS (ESI) *m/z* calculated for C₁₀H₁₈O₅SNa [M+Na]⁺: 273.0773, found 273.0771.

Ethyl 2-((3-(4-methoxyphenyl)propoxy)sulfonyl)acetate [S4].

1.58 g (5.00 mmol) of 3-(4-methoxyphenyl)propan-1-ol were used, along with imidazole (408.5 mg, 6 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (1.40 g, 7.50 mmol, 1.5 equiv), and THF (25 mL, 0.2 M). Flash column chromatography on silica using 10% → 20% EtOAc/hexanes as eluent gave 855 mg (2.70 mmol) of pure product as a clear oil (53% yield).

¹H-NMR (500 MHz, CDCl₃) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.31 (t, *J* = 6.3 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 2H), 3.76 (s, 3H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.03 (p, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.2, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 162.08, 158.15, 132.33, 129.45, 114.05, 71.54, 62.79, 55.33, 54.86, 31.04, 30.58, 14.05.; HRMS (ESI) *m/z* calculated for C₁₄H₂₀O₆SNa [M+Na]⁺: 339.0878, found 339.0872.

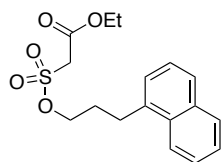
Ethyl 2-((3-(4-(*N*-methylphenylsulfonamido)phenyl)propoxy)sulfonyl)acetate [S5].

1.03 g (3.37 mmol) of *N*-(4-(3-hydroxypropyl)phenyl)-*N*-methylbenzenesulfonamide was used, along with imidazole (275.7 mg, 4.05 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (944.2 mg, 5.06 mmol, 1.5 equiv), and THF (17 mL, 0.2 M). Flash column chromatography on silica using 20% → 50% EtOAc/hexanes as eluent gave 802 mg (1.76 mmol) of pure product as a clear oil (52% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.62 - 7.51 (m, 3H), 7.69 - 7.43 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.34 (t, *J* = 6.3 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 2H), 3.15 (s, 3H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.12 - 2.04 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 162.13, 139.84, 139.74, 136.60, 132.90, 129.06, 128.89, 128.00, 126.97, 71.40, 62.93,

55.04, 38.32, 31.13, 30.74, 14.13.; HRMS (ESI) m/z calculated for $C_{20}H_{26}NO_7S_2$ $[M+H]^+$: 456.1151, found 456.1149.

Ethyl 2-((3-(naphthalen-1-yl)propoxy)sulfonyl)acetate [S6].

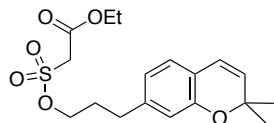


175 mg (0.939 mmol) of 3-(naphthalen-1-yl)propan-1-ol were used, along with imidazole (76.7 mg, 1.13 mmol, 1.2 equiv), $ClSO_2CH_2CO_2Et$ (263 mg, 1.41 mmol, 1.5 equiv), and THF (4.7 mL, 0.2 M). Flash column chromatography on

silica using 10% → 25% EtOAc/hexanes as eluent gave 118 mg (0.351 mmol) of pure product as a clear oil (37% yield).

^1H -NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.55 - 7.47 (m, 2H), 7.41 (dd, J = 8.2, 7.0 Hz, 1H), 7.35 (dd, J = 7.1, 1.5 Hz, 1H), 4.42 (t, J = 6.2 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 3.23 (dd, J = 8.5, 6.8 Hz, 2H), 2.27 - 2.17 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).; ^{13}C -NMR (126 MHz, $CDCl_3$) δ 162.14, 136.44, 134.11, 131.76, 129.06, 127.32, 126.49, 126.24, 125.79, 125.69, 123.58, 71.82, 62.92, 55.07, 30.20, 28.84, 14.13.; HRMS (ESI) m/z calculated for $C_{17}H_{20}O_5SNa$ $[M+Na]^+$: 359.0929, found 359.0927.

Ethyl 2-((3-(2,2-dimethyl-2H-chromen-6-yl)propoxy)sulfonyl)acetate [S7].

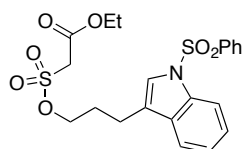


744 mg (3.41 mmol) of 3-(2,2-dimethyl-2H-chromen-6-yl)propan-1-ol was used, along with imidazole (279 mg, 4.10 mmol, 1.2 equiv),

$ClSO_2CH_2CO_2Et$ (955 mg, 5.12 mmol, 1.5 equiv), and THF (17 mL, 0.2 M). Flash column chromatography on silica using 20% → 50% EtOAc/hexanes as eluent gave 896 mg (2.43 mmol) of pure product as a clear oil (71% yield).

^1H -NMR (400 MHz, CDCl_3) δ 6.91 (d, J = 8.4 Hz, 1H), 6.79 (s, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 5.60 (d, J = 9.5 Hz, 1H), 4.33 (t, J = 6.4 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 4.07 (s, 2H), 2.64 (t, J = 7.5 Hz, 2H), 2.05 (p, J = 7.2 Hz, 2H), 1.42 (s, 6H), 1.32 (t, J = 7.2 Hz, 3H).; ^{13}C -NMR (126 MHz, CDCl_3) δ 162.09, 151.45, 132.40, 131.11, 128.99, 126.32, 122.30, 121.36, 116.40, 76.21, 71.59, 62.82, 54.94, 31.00, 30.69, 28.06, 14.08.; HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{25}\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: 369.1372, found 369.1364.

Ethyl 2-((3-(1-(phenylsulfonyl)-1H-indol-3-yl)propoxy)sulfonyl)acetate [S8].

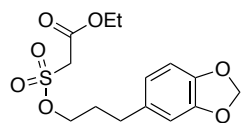


2.30 g (7.28 mmol) of 3-(1-(phenylsulfonyl)-1H-indol-3-yl)propan-1-ol was used, along with imidazole (595 mg, 8.74 mmol, 1.2 equiv), $\text{ClSO}_2\text{CH}_2\text{CO}_2\text{Et}$ (2.04 g, 10.9 mmol, 1.5 equiv), and THF (18 mL, 0.2 M). Flash column

chromatography on silica using 10% $\rightarrow$ 30% EtOAc/hexanes as eluent gave 2.40 g (5.16 mmol) of pure product as a clear oil (71% yield). This compound was isolated with <5% of an unknown impurity that did not appear to affect reactivity.

^1H -NMR (500 MHz, CDCl_3) δ 8.00 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.49 - 7.38 (m, 4H), 7.33 (t, J = 8.0, 1H), 7.24 (m, 1H), 4.35 (t, J = 6.1 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 2.83 (t, J = 7.3 Hz, 2H), 2.14 (p, J = 7.5 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H).; ^{13}C -NMR (126 MHz, CDCl_3) δ 162.13, 138.25, 135.54, 133.88, 130.71, 129.39, 126.87, 125.06, 123.38, 121.38, 119.46, 113.99, 71.20, 62.94, 55.03, 28.57, 20.86, 14.11. (one peak missing due to overlap); HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_7\text{S}_2$ $[\text{M}+\text{H}]^+$: 446.0994, found 446.0993.

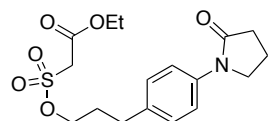
Ethyl 2-((3-(benzo[*d*][1,3]dioxol-5-yl)propoxy)sulfonyl)acetate [S9].



1.26 g (7.0 mmol) of 3-(benzo[d][1,3]dioxol-5-yl)propan-1-ol were used, along with imidazole (571 mg, 8.40 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (1.90 g, 10.5 mmol, 1.5 equiv), and THF (35 mL, 0.2 M). Flash column chromatography on silica using 20% EtOAc/hexanes as eluent gave 1.82 g (5.50 mmol) of pure product as a pale yellow oil (79% yield).

¹H-NMR (500 MHz, CDCl₃) δ 6.74 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 1.5 Hz, 1H), 6.64 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.93 (s, 2H), 4.33 (t, *J* = 6.3 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.04 (p, *J* = 6.4 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 162.11, 147.89, 146.12, 134.13, 121.41, 108.95, 108.43, 101.00, 71.42, 62.87, 55.00, 31.31, 31.14, 14.11.; HRMS (ESI) *m/z* calculated for C₁₄H₁₈O₇SNa [M+Na]⁺: 353.0671, found 353.0672.

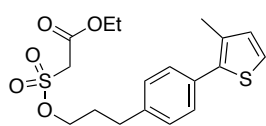
Ethyl 2-((3-(4-(2-oxopyrrolidin-1-yl)phenyl)propoxy)sulfonyl)acetate [S10].



414 mg (1.12 mmol) of 1-(4-(3-hydroxypropyl)phenyl)pyrrolidin-2-one was used, along with imidazole (91.1 mg, 1.34 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (312 mg, 1.67 mmol, 1.5 equiv), and THF (5.6 mL, 0.2 M). Flash column chromatography on silica using 30% → 70% EtOAc/hexanes as eluent gave 245 mg (0.771 mmol) of pure product as a clear oil (69% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 4.34 (t, *J* = 6.3 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.08 (s, 2H), 3.85 (t, *J* = 7.0 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.17 (p, *J* = 7.8 Hz, 2H), 2.08 (p, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 174.25, 162.06, 137.75, 136.52, 128.87, 120.31, 71.44, 62.82, 54.86, 48.91, 32.75, 30.91, 30.84, 18.10, 14.06.; HRMS (ESI) *m/z* calculated for C₁₇H₂₄O₆NS [M+H]⁺: 370.1324, found 370.1325.

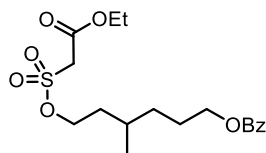
Ethyl 2-((3-(4-(3-methylthiophen-2-yl)phenyl)propoxy)sulfonyl)acetate [S11].



1.06 g (4.56 mmol) of 3-(4-(3-methylthiophen-2-yl)phenyl)propan-1-ol were used, along with imidazole (373 mg, 5.47 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (1.28 g, 6.84 mmol, 1.5 equiv), and THF (24.8 mL, 0.2 M). Flash column chromatography on silica using 10% → 20% EtOAc/hexanes as eluent gave 1.55 g (4.04 mmol) of pure product as a clear oil (89% yield).

¹H-NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 5.1 Hz, 1H), 6.97 (d, *J* = 5.1 Hz, 1H), 4.43 (t, *J* = 6.3 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 2.17 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 162.07, 139.33, 137.63, 133.08, 132.87, 131.19, 129.20, 128.68, 123.29, 71.51, 62.82, 54.88, 31.21, 30.74, 15.00, 14.05.; HRMS (ESI) *m/z* calculated for C₁₈H₂₃O₅S₂ [M+H]⁺: 383.0987, found 383.0985.

7-((2-ethoxy-2-oxoethyl)sulfonyl)-4-methylheptyl benzoate [S12]



0.4391 g (1.858 mmol) of 6-hydroxy-4-methylhexyl benzoate were used, along with imidazole (152 mg, 2.23 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (520. mg, 2.79 mmol, 1.5 equiv), and THF (9.2 mL, 0.2 M). Flash column chromatography on silica using 5% → 15% EtOAc/hexanes as eluent gave 0.495 g (1.29 mmol) of pure product as a clear oil (69% yield).

¹H-NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.16 Hz, 2H), 7.56 (t, *J* = 7.48 Hz, 1H), 7.45 (d, *J* = 7.84 Hz, 2H), 4.45 – 4.22 (m, 6H), 4.08 (s, 2H), 1.90 – 1.71 (m, 2H), 1.74 – 1.43 (m, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H).; ¹³C NMR (126 MHz, CDCl₃) δ 166.64, 162.08,

132.94, 130.38, 129.56, 128.41, 70.72, 65.09, 62.73, 54.83, 35.97, 33.00, 29.10, 26.14, 19.13, 14.01.; HRMS (ESI) m/z calculated for $C_{18}H_{27}O_7S_2$ $[M+H]^+$: 387.1477, found 387.1472.

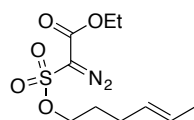
Preparation of Diazosulfonate Starting Materials

General procedure for diazo transfer:

A round-bottom flask equipped with a stir bar and rubber septum was charged with sulfonate ester (1 equiv) and THF (0.4 M) and cooled to -45°C with a dry ice/acetonitrile bath. MeSO_2N_3 (2.2–3.0 equiv) was then added in one portion. DBU (1.5 equiv) was then added slowly dropwise over 2–5 minutes and the solution turned yellow. After the reaction was stirred for 1 hour at -45°C , the cooling bath was removed and 15 mL of sat. aq. $(\text{NH}_4)_2\text{SO}_4$ was immediately added. The mixture was transferred to a separatory funnel with 20 mL of CH_2Cl_2 . The aqueous layer was extracted with 3 x 10 mL CH_2Cl_2 , and the combined organic extracts were washed with 2 x 10 mL 10% NaOH, 2 x 10 mL H_2O , and sat. aq. NaCl. The organic phase was dried over Na_2SO_4 or MgSO_4 , filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel gave the desired diazo product. Some diazoesters were difficult to separate from the sulfonamide byproduct (MeSO_2NH_2 , singlet at 3.30 ppm). In these cases, the diazoester was washed 3x with 20% NaOH, 2x with H_2O , and 1x with brine after column chromatography. We found that this sulfonamide impurity (in trace quantities, <5%) did not affect the reactivity of the diazoesters. Following purification, the diazo compounds were stored at -20°C under argon. The ^{13}C NMR signal for the diazo carbon was typically not detected; Novikov²⁷ and Du Bois²³ noticed similar results. *NOTE: Some diazosulfonate ester compounds exhibited suboptimal reactivity after storing for more than a month; repurification sometimes restored reactivity in these cases. Some*

diazosulfonate ester compounds decomposed during long periods under reduced pressure. These cases are noted below. WARNING: Although we have not experienced problems with the preparation and the handling of MeSO₂N₃ or diazosulfonate esters, sulfonyl azides and diazo compounds can be heat and/or shock sensitive and should be handled with appropriate caution.

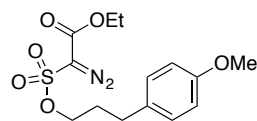
Ethyl (*E*)-2-diazo-2-((hex-4-en-1-yloxy)sulfonyl)acetate [6].



2.30 g (9.20 mmol) of ethyl (*E*)-2-((hex-4-en-1-yloxy)sulfonyl)acetate [S3] were used, along with MeSO₂N₃ (2.40 g, 20.2 mmol, 2.2 equiv), DBU (206 μ L, 13.8 mmol, 1.5 equiv), and THF (23 mL, 0.4 M). Flash column chromatography on silica using 5% EtOAc/hexanes as eluent gave 1.98 g (7.17 mmol) of pure product as a yellow oil (78% yield).

¹H-NMR (500 MHz, CDCl₃) δ 5.53-5.43 (m, 1H), 5.37 (ddd, *J* = 15.2, 6.8, 5.1 Hz, 1H), 4.35 (t, *J* = 6.3 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 2.10 (dt, *J* = 7.7, 7.3 Hz, 2H), 1.81 (p, *J* = 6.7 Hz, 2H), 1.65 (dd, *J* = 6.2, 1.3 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.62, 129.05, 126.88, 72.98, 62.80, 28.77, 28.29, 18.01, 14.39.; HRMS (ESI) *m/z* calculated for C₁₀H₁₆O₅N₂SNa [M+Na]⁺: 299.0678, found 299.0681; IR (ATR, cm⁻¹) 2970, 2940, 2856, 2130, 1721, 1465, 1447, 1373, 1285, 1224, 1178, 1083, 1005, 964, 929, 836, 765, 739, 614, 564, 541, 491.

Ethyl 2-diazo-2-((3-(4-methoxyphenyl)propoxy)sulfonyl)acetate [S13].

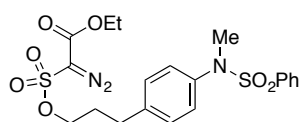


855 mg (2.70 mmol) of ethyl 2-((3-(4-methoxyphenyl)propoxy)sulfonyl)acetate [S4] were used, along with MeSO₂N₃ (761 mg, 8.11 mmol, 3 equiv), DBU (605 μ L, 4.06 mmol, 1.5 equiv), and THF (6.8 mL, 0.4 M). Flash column chromatography on silica using 10% $\rightarrow$ 20% EtOAc/hexanes as eluent gave 721 mg (2.11 mmol)

of pure product as a yellow oil (78% yield). *Note*: the reactivity of this diazoester deteriorated after one week and could not be restored by additional purification.

¹H-NMR (500 MHz, CDCl₃) δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.38 - 4.28 (m, 4H), 3.79 (s, 3H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.04 (p, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.62, 158.25, 132.31, 129.52, 114.13, 72.66, 62.86, 55.42, 30.85, 30.66, 14.43.; HRMS (ESI) *m/z* calculated for C₁₄H₁₉O₆N₂S [M+H]⁺: 343.0964, found 343.0956; IR (ATR, cm⁻¹) 2938.6, 2837.84, 2132.38, 1717.58, 1612.33, 1584.04, 1512.66, 1465.72, 1373.33, 1285.65, 1244.79, 1224.31, 1176.21, 1084.54, 1033.1, 996.13, 830.05, 811.04, 738.66, 698.12, 614.07, 569.25, 554.06, 509.88.

Ethyl 2-diazo-2-((3-(4-(*N*-methylphenylsulfonamido)phenyl)propoxy)sulfonyl) acetate [S14].



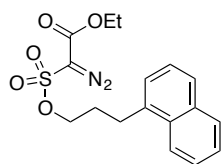
802 mg (1.76 mmol) of ethyl 2-((3-(4-(*N*-methylphenylsulfonamido)phenyl)propoxy)sulfonyl)acetate [S5] were

used, along with MeSO₂N₃ (640.0 mg, 5.28 mmol, 3 equiv), DBU (390 μL, 2.64 mmol, 1.5 equiv), and THF (4.4 mL, 0.4 M). Flash column chromatography on silica using 10% → 40% EtOAc/hexanes as eluent gave 639 mg (1.33 mmol) of pure product as a yellow oil (75% yield).

¹H-NMR (500 MHz, CDCl₃) δ 7.62 - 7.54 (m, 3H), 7.48 (dd, *J* = 8.3, 7.2, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 4.38 (t, *J* = 6.0 Hz, 2H), 4.36 (q, *J* = 7.2, 2H), 3.18 (s, 3H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.00 - 2.04 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.42, 139.74, 139.52, 136.50, 132.76, 128.91, 128.74, 127.86, 126.84, 72.42, 62.75, 38.18, 30.99, 30.38, 14.31. HRMS (ESI) *m/z* calculated for C₂₀H₂₃O₇N₃S₂Na [M+Na]⁺: 504.0875, found 504.0873; IR (ATR, cm⁻¹) 2924.36, 2852.36, 2133.81, 1717.16, 1608.82, 1584.78, 1508.07, 1466.48, 1446.96, 1374.87, 1348.87, 1287.10, 1224.05, 1173.43, 1155.02, 1088.53,

1066.30, 1017.80, 1017.80, 998.66, 926.55, 870.22, 834.43, 722.39, 690.35, 665.65, 649.93, 615.06, 588.85, 572.72, 557.75, 497.97.

Ethyl 2-diazo-2-((3-(naphthalen-1-yl)propoxy)sulfonyl)acetate [S15].

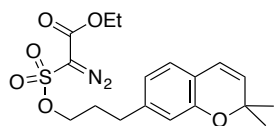


118 mg (0.351 mmol) of ethyl 2-((3-(naphthalen-1-yl)propoxy)sulfonyl)acetate [S6] were used, along with MeSO_2N_3 (127.5 mg, 1.05 mmol, 3 equiv), DBU (78.6 μL , 0.527 mmol, 1.5 equiv), and THF (0.9

mL, 0.4 M). Flash column chromatography on silica using 5% $\rightarrow$ 15% EtOAc/hexanes as eluent gave 86.8 mg (0.240 mmol) of pure product as a yellow oil (67% yield).

^1H -NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.56 - 7.46 (m, 2H), 7.40 (dd, J = 8.1, 7.0 Hz, 1H), 7.34 (d, J = 7.0 Hz, 1H), 4.43 (t, J = 6.1 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.22 (t, J = 7.4 Hz, 2H), 2.29 - 2.17 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).; ^{13}C -NMR (126 MHz, CDCl_3) δ 159.57, 136.33, 134.07, 131.71, 129.04, 127.31, 126.47, 126.22, 125.77, 125.64, 123.54, 72.93, 62.85, 29.86, 28.80, 14.40.; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{19}\text{O}_5\text{N}_2\text{S}$ $[\text{M}+\text{H}]^+$: 363.1015, found 363.1008; IR (ATR, cm^{-1}) 2921.48, 2134.02, 1714.69, 1594.01, 1509.49, 1459.33, 1445.80, 1424.40, 1392.28, 1371.95, 1286.49, 1217.84, 1178.91, 1081.27, 1030.36, 1012.76, 989.32, 925.46, 912.74, 869.31, 854.39, 829.19, 817.01, 796.38, 779.72, 734.26, 648.01, 610.89, 561.82, 549.71, 533.15, 508.97, 496.86, 458.39.

Ethyl 2-diazo-2-((3-(2,2-dimethyl-2H-chromen-6-yl)propoxy)sulfonyl)acetate [S16].



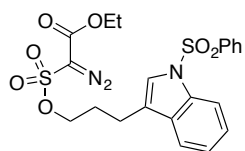
400. mg (1.09 mmol) of ethyl 2-((3-(2,2-dimethyl-2H-chromen-6-yl)propoxy)sulfonyl)acetate [S7] were used, along with MeSO_2N_3 (395

mg, 3.26 mmol, 3 equiv), DBU (243 μL , 1.63 mmol, 1.5 equiv), and THF (2.70 mL, 0.4 M). Flash

column chromatography on silica using 5% → 15% EtOAc/hexanes as eluent gave 228 mg (0.578 mmol) of pure product as a yellow oil (53% yield).

¹H-NMR (500 MHz, CDCl₃) δ 6.93 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.64 (d, *J* = 9.8 Hz, 1H), 4.40 - 4.33 (m, 4H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.07 (p, *J* = 6 Hz, 2H), 1.45 (s, 6H), 1.36 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.53, 151.43, 132.30, 131.11, 128.97, 126.30, 122.27, 121.36, 116.37, 76.20, 72.63, 62.81, 30.69, 30.64, 28.04, 14.38. HRMS (ESI) *m/z* calculated for C₁₈H₂₃O₆N₂S [M+H]⁺: 395.1277, found 395.1273; IR (ATR, cm⁻¹) 2976.12, 2925.41, 2131.58, 1719.37, 1638.37, 1489.48, 1464.88, 1372.12, 1286.63, 1261.45, 1211.27, 118.2, 1151.82, 1127.63, 1084.09, 1001.31, 958.9, 925.35, 923.03, 793.14, 768.19, 738.45, 717.48, 614.17, 584.89, 562.72, 535.86, 510.44, 486.44.

Ethyl 2-((3-(1-(phenylsulfonyl)-1H-indol-3-yl)propoxy)sulfonyl)acetate [S17].



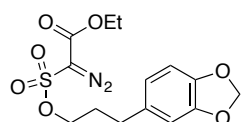
2.30 g (7.28 mmol) of ethyl 2-((3-(1-(phenylsulfonyl)-1H-indol-3-yl)propoxy)sulfonyl)acetate [S8] was used, along with imidazole (595 mg, 8.74 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (2.04 g, 10.9 mmol, 1.5 equiv), and

THF (18 mL, 0.2 M). Flash column chromatography on silica using 10% → 30% EtOAc/hexanes as eluent gave 2.40 g (5.16 mmol) of pure product as a clear oil (71% yield).

¹H-NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.56 - 7.50 (m, 1H), 7.45 (q, *J* = 8.7 Hz, 3H), 7.39 (s, 1H), 7.33 (t, *J* = 9.8 Hz, 1H), 7.25 - 7.21 (m, 1H), 4.38 (t, *J* = 6.0 Hz, 3H), 4.33 (q, *J* = 7.1 Hz, 3H), 2.82 (t, *J* = 7.4 Hz, 3H), 2.13 (p, *J* = 6.5 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 4H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.47, 138.30, 135.54, 133.85, 130.70, 129.36, 126.84, 125.04, 123.36, 123.33, 121.33, 119.42, 113.96, 72.44, 62.87, 28.36, 20.85, 14.37. HRMS (ESI) *m/z* calculated for C₂₁H₂₁NO₇S₂ [M+H]⁺: 514.0719, found 514.0769. IR (ATR, cm⁻¹)

2138.67, 1723.8, 1463.45. 1446.28, 1376.14, 1362.96, 1287.43, 1274.42, 1229.7, 1202.13, 1174.21, 1129.69, 1120.47, 1095.71, 1078.09, 1017.77, 970.87, 943.64, 869.67, 860.01, 821.95, 789.11, 766.62, 748.94, 737.16, 723.89, 685.23, 626.35, 602.94, 591.1, 578.54, 570.31, 549.73, 536.17, 501.85, 478.29.

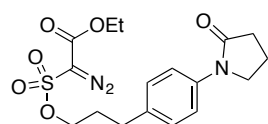
Ethyl 2-((3-(benzo[d][1,3]dioxol-5-yl)propoxy)sulfonyl)-2-diazoacetate [S18].



1.82 g (5.50 mmol) of ethyl 2-((3-(benzo[d][1,3]dioxol-5-yl)propoxy)sulfonyl)acetate [S9] were used, along with MeSO₂N₃ (1.47 g, 12.1 mmol, 2.2 equiv), DBU (1.23 mL, 8.3 mmol, 1.5 equiv), and THF (13.9 mL, 0.4 M). Flash column chromatography on silica using 5% → 10% EtOAc/hexanes as eluent gave 1.47 g (4.13 mmol) of pure product as a yellow oil (75% yield). *Note*: the reactivity of this diazoester deteriorated after one week and could not be restored by additional purification.

¹H-NMR (500 MHz, CDCl₃) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.4 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.93 (s, 2H), 4.38-4.29 (m, 4H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.03 (p, *J* = 6.4 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.50, 147.85, 146.07, 134.00, 121.36, 108.90, 108.37, 100.97, 72.44, 62.81, 31.23, 30.79, 14.37.; HRMS (ESI) *m/z* calculated for C₁₄H₁₆O₇N₂SNa [M+Na]⁺: 379.0576, found 379.0574; IR (ATR, cm⁻¹) 2970, 2941, 2132, 1717, 1608, 1503, 1488, 1442, 1371, 1286, 1243, 1226, 1177, 1121, 1091, 1036, 999, 922, 838, 808, 770.

Ethyl 2-diazo-2-((3-(4-(2-oxopyrrolidin-1-yl)phenyl)propoxy)sulfonyl)acetate [S19].

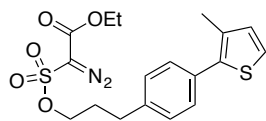


649 mg (1.76 mmol) of ethyl 2-((3-(4-(2-oxopyrrolidin-1-yl)phenyl)propoxy)sulfonyl)acetate [S10] were used, along with MeSO₂N₃

(638 mg, 5.27 mmol, 3 equiv), DBU (390 μ L, 2.64 mmol, 1.5 equiv), and THF (4.4 mL, 0.4 M). Flash column chromatography on silica using 30% $\rightarrow$ 60% EtOAc/hexanes as eluent gave 490 mg (1.24 mmol) of pure product as a yellow oil (70% yield). *Note:* this diazoester decomposes after twelve hours under vacuum at room temperature; for best results use immediately.

^1H -NMR (500 MHz, CDCl_3) δ 7.56 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 4.38 (t, J = 6.2 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 3.88 (t, J = 7.0 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 8.1 Hz, 2H), 2.20 (p, J = 7.3 Hz, 2H), 2.10 (p, J = 6.4 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H).; ^{13}C -NMR (126 MHz, CDCl_3) δ 174.22, 159.47, 137.79, 136.42, 128.85, 120.29, 72.50, 62.80, 48.89, 32.74, 30.91, 30.57, 18.09, 14.36. HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{22}\text{O}_6\text{N}_3\text{S}$ $[\text{M}+\text{H}]^+$: 396.1229, found 396.1221; IR (ATR, cm^{-1}) 2980.9, 2133.8, 1690.4, 1612.35, 1514.75, 1487.79, 1461.43, 1426.78, 1390.72, 1373.34, 1287.34, 1222.81, 1177.02, 1124.05, 1085.38, 1034.71, 996.62, 923.73, 834.88, 801.99, 738.04, 636.79, 613.70, 557.11, 541.11, 508.90.

Ethyl 2-diazo-2-((3-(4-(3-methylthiophen-2-yl)phenyl)propoxy)sulfonyl)acetate [S20].



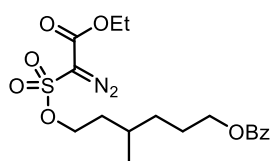
1.55 g (4.04 mmol) of ethyl 2-((3-(4-(3-methylthiophen-2-yl)phenyl)propoxy)sulfonyl)acetate [S11] were used, along with MeSO_2N_3

(1.47 g, 12.1 mmol, 3 equiv), DBU (905 μ L, 6.06 mmol, 1.5 equiv), and THF (10 mL, 0.4 M). Flash column chromatography on silica using 0% $\rightarrow$ 15% EtOAc/hexanes as eluent, and then a second purification using 2% $\rightarrow$ 15% Et_2O /petroleum ether as eluent gave 839 mg (2.05 mmol) of pure product as a yellow oil (51% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.40 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 5.2 Hz, 1H), 6.92 (d, J = 5.0 Hz, 1H), 4.39 (t, J = 6.2 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.32 (s, 3H), 2.11 (p, J = 6.4 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H).; ^{13}C -NMR (126 MHz,

CDCl₃) δ 159.56, 139.29, 137.70, 133.16, 133.04, 131.22, 129.30, 128.70, 123.35, 72.63, 62.85, 31.28, 30.55, 15.02, 14.41.; HRMS (ESI) m/z calculated for C₁₈H₂₁O₅N₂S₂ [M+H]⁺: 409.0892, found 409.0883; IR (ATR, cm⁻¹) 2981.11, 2131.45, 1717.25, 1546.48, 1508.41, 1447.81, 1373.97, 1285.99, 1222.83, 1177.96, 1084.70, 997.25, 925.17, 833.91, 799.89, 736.71, 707.17, 614.44, 554.86, 535.08, 498.08.

6-(((1-diazo-2-ethoxy-2-oxoethyl)sulfonyl)oxy)-4-methylhexyl benzoate [S21]



0.495 g (1.29 mmol) of 6-(((2-ethoxy-2-oxoethyl)sulfonyl)oxy)-4-methylhexyl benzoate [S12] were used, along with MeSO₂N₃ (469 mg, 3.87 mmol, 3 equiv), DBU (290. μ L, 1.93 mmol, 1.5 equiv), and THF (3.5 mL, 0.4 M). Flash column chromatography on silica using 5% $\rightarrow$ 15% EtOAc/hexanes as eluent gave 372 mg (0.903 mmol) of pure product as a yellow oil (70% yield).

¹H NMR (500 MHz, Chloroform-*d*) δ 8.07 – 8.01 (d, J = 7.05 Hz, 2H), 7.59 – 7.53 (t, J = 6.5 Hz, 1H), 7.45 (dd, J = 8.4, 7.1 Hz, 2H), 4.48 – 4.28 (m, 6H), 1.89 – 1.66 (m, 3H), 1.64 – 1.44 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H).; ¹³C NMR (126 MHz, CDCl₃) δ 166.70, 159.55, 130.44, 129.61, 128.51, 128.39, 71.96, 65.13, 62.77, 35.79, 33.06, 29.27, 29.07, 26.22, 19.06, 14.35. HRMS (ESI) m/z calculated for C₁₈H₂₄N₂O₇SN_a [M+Na]⁺: 435.1197, found 435.1202.

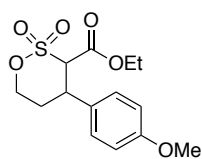
Substrate Scope for Fe-Catalyzed Intramolecular C—H Alkylation

General procedure for [FePc]-catalyzed C—H alkylation:

Into a 1 dram vial was added [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv) and NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv) in a glovebox. The vial was sealed, taken out of the box, and the contents were added under a stream of nitrogen to a flame-dried three neck 25 mL flask equipped with a

stir bar, reflux condenser, glass stopper, and rubber septum. CH₂Cl₂ (5.0 mL, 0.08 M) was added and the flask was heated to reflux (~45°C) for 10 minutes. Diazosulfonate ester (0.40 mmol, 1 equiv) was taken up with CH₂Cl₂ (3.0 mL, 0.13 M) in a 5 mL glass syringe and added to the refluxing catalyst solution over the course of an hour (rate of 3 mL/h) via syringe pump (final reaction concentration is 0.05 M). After complete addition of diazosulfonate, the reaction refluxed until judged complete by TLC (2-12 h). The reaction mixture was cooled, adsorbed onto SiO₂ or florisil, and applied directly to a silica column for purification to afford the desired sultone product. Yields were calculated from a mixture of diastereomers. Subsequent purification afforded the separation of diastereomers for characterization. Relative stereochemistry was assigned *via* coupling constant analysis and analogy from **7**. Some substrates demonstrated improved yields with the addition of activated powdered 3Å molecular sieves. In these cases, the molecular sieves were added to the reaction flask at the same time as [FePc]Cl and NaBAr^F₄. Any further variation of these reaction conditions is noted for individual substrates.

Ethyl 4-(4-methoxyphenyl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [7].



Ethyl 2-diazo-2-((3-(4-methoxyphenyl)propoxy)sulfonyl)acetate [**13**] (137 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), NaBAr^F₄ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used.

Product was purified via flash column chromatography on silica using 10% → 25% EtOAc/hexanes. Pure product was isolated as a clear oil and a 1.1:1 syn:anti mixture of diastereomers. Subsequent purification using 10% → 25% EtOAc/hexanes allowed for separation of diastereomers. The anti diastereomer was isolated with 15% of the syn.

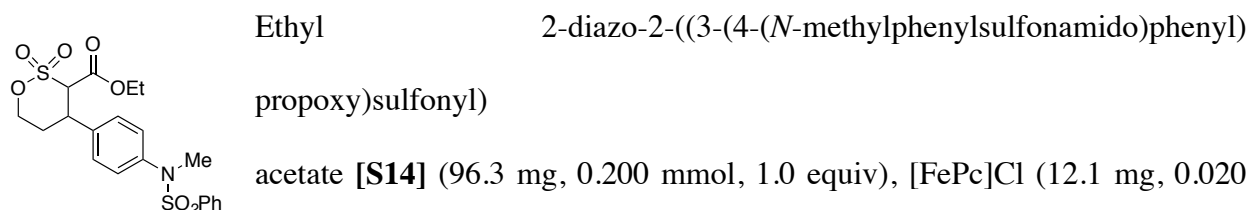
Run 1: (84.1 mg, 0.268 mmol, 67%), 0% rsm. Run 2: (75.0 mg, 0.239 mmol, 60%), 0% rsm. Run 3: (85.5 mg, 0.272 mmol, 68%), 0% rsm. **Average: 65% yield $\pm$ 3.6%, 0% rsm.**

Syn diastereomer (major): $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.15 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.81 – 4.63 (m, 2H), 4.21 (d, J = 4.7 Hz, 1H), 4.18 – 3.93 (m, 2H), 3.87 - 3.80 (m, 1H), 3.79 (s, 3H), 3.16 (tdd, J = 13.9, 11.7, 6.6 Hz, 1H), 1.80 (dd, J = 13.2, 1.8 Hz, 1H), 1.05 (t, J = 7.2, 3H).; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 164.11, 159.43, 129.94, 128.42, 114.45, 73.20, 66.51, 62.26, 55.41, 42.25, 24.34, 13.84.

Anti diastereomer (minor): $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.14 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.74 (ddd, J = 13.4, 11.6, 2.2 Hz, 1H), 4.54 (ddd, J = 11.6, 4.9, 1.5 Hz, 1H), 4.17 (d, J = 12 Hz, 1H), 4.12 - 4.01 (m, 2H), 3.82 - 3.73 (m, 4H), 2.21 (dtd, J = 15.0, 13.0, 4.9 Hz, 1H), 1.99 (d, J = 14.8, 1H), 1.05 (t, J = 7.1 Hz, 3H).; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 162.95, 159.42, 130.63, 128.60, 128.46, 114.52, 72.65, 69.01, 62.67, 55.43, 43.68, 32.53, 13.89.

HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{18}\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$: 337.0721, found 337.0722.

Ethyl 4-(4-(*N*-methylphenylsulfonamido)phenyl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [8].



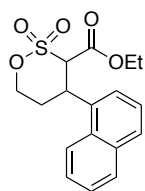
were used. Product was purified via flash column chromatography on silica using 10% $\rightarrow$ 30% EtOAc/hexanes. Pure product was isolated as a clear oil and a 1:1 syn:anti mixture of

diastereomers. The diastereomers were inseparable by column chromatography and were characterized as a mixture.

Run 1: (65.7 mg, 0.145 mmol, 72%), 0% rsm. Run 2: (59.8 mg, 0.132 mmol, 66%), 0% rsm. Run 3: (55.7 mg, 0.123 mmol, 76% (scale: 76.9 mg, 0.160 mmol)), 0% rsm. **Average: 71% yield $\pm$ 4.1%, 0% rsm.**

Mixture of syn and anti diastereomers: ^1H NMR (500 MHz, CDCl_3) δ 7.61 (td, $J = 6.5, 5.5, 3.6$ Hz, 1H D_{syn} + 1H D_{anti}), 7.53 (ddd, $J = 8.3, 4.7, 1.4$ Hz, 2H D_{syn} + 2H D_{anti}), 7.47 (m, 2H D_{syn} + 2H D_{anti}), 7.21 (dd, $J = 8.3, 5.3$ Hz, 2H D_{syn} + 2H D_{anti}), 7.11 (dd, $J = 8.4, 6.1$ Hz, 2H D_{syn} + 2H D_{anti}), 4.82 - 4.71 (m, 1H D_{syn} + 2H D_{anti}), 4.59 (dd, $J = 11.5, 4.5$ Hz, 1H D_{syn}), 4.28 - 4.21 (m, 1H D_{syn}), 4.17 - 4.02 (m, 2H D_{syn} + 2H D_{anti}), 3.92 - 3.80 (m, 1H D_{syn} + 1H D_{anti}), 3.25 - 3.11 (m, 3H D_{syn} + 4H D_{anti}), 2.26 (dq, $J = 13.5, 5.0$ Hz, 1H D_{syn}), 2.04 (dd, $J = 14.7, 3.7$ Hz, 1H D_{anti}), 1.86 (dd, $J = 14.5, 3.2$ Hz, 1H D_{anti}), 1.09 (td, $J = 7.1, 2.3$ Hz, 3H D_{syn} + 3H D_{anti}). ^{13}C NMR (126 MHz, CDCl_3) δ 163.84, 162.73, 141.47, 141.37, 137.64, 136.91, 136.41, 133.05, 128.91, 128.02, 127.86, 127.82, 127.77, 127.75, 127.07, 127.06, 73.11, 72.66, 68.47, 66.11, 62.69, 62.37, 43.81, 42.37, 38.06, 32.15, 24.02, 13.87.; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{24}\text{NO}_7\text{S}_2$ $[\text{M}+\text{H}]^+$: 454.0994, found 454.1003.

Ethyl 4-(naphthalen-1-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [9].



Ethyl 2-((3-(naphthalen-1-yl)propoxy)sulfonyl)acetate [**S15**] (72.4 mg, 0.200 mmol, 1.0 equiv), $[\text{FePc}]\text{Cl}$ (12.1 mg, 0.020 mmol, 0.10 equiv), $\text{NaBAr}^{\text{F}}_4$ (17.7 mg, 0.020 mmol, 0.10 equiv), and CH_2Cl_2 (4.0 mL, 0.05 M) were used. Product was purified

via flash column chromatography on silica using 0.4% Et_2O , 19.6% DCM, 80% hexanes $\rightarrow$ 1.2% Et_2O , 58.8% CH_2Cl_2 , 40% hexanes as eluent. Impure product was isolated as a clear oil and a 1.2:1

syn:anti mixture of diastereomers. Yield was determined with mesitylene as an internal standard. Subsequent purification using 0.4% Et₂O, 19.6% CH₂Cl₂, 80% hexanes → 1% Et₂O, 49% CH₂Cl₂, 50% hexanes as eluent allowed for separation of diastereomers. A trace impurity (<5%) was isolated with the anti product and was factored into yield calculations.

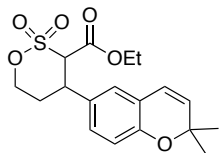
Run 1: (34.8 mg, 0.104 mmol, 52%), 0% rsm. Run 2: (34.8 mg, 0.104 mmol, 52%), 0% rsm. Run 3: (35.4 mg, 0.106 mmol, 53%), 0% rsm. **Average: 52% yield ± 0.5%, 0% rsm.**

Syn diastereomer (major): ¹H-NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.47 – 7.36 (m, 2H), 4.90 (ddd, *J* = 12.9, 11.5, 2.1 Hz, 1H), 4.81 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 4.73 (dt, *J* = 13.1, 3.8 Hz, 1H), 4.47 (d, *J* = 4.4 Hz, 1H), 4.00 – 3.83 (m, 2H), 3.49 (dq, *J* = 16.5, 6 Hz, 1H), 1.89 (d, *J* = 14.3 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 163.93, 134.15, 133.19, 130.46, 129.67, 129.09, 127.57, 126.32, 125.36, 124.31, 121.68, 73.53, 65.10, 62.18, 38.30, 24.31, 13.76.

Anti diastereomer (minor): ¹H-NMR (500 MHz, CDCl₃) δ 8.21 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.60 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 7.1, 1.2 Hz, 1H), 4.89 (td, *J* = 11.6 Hz, 3.7 Hz, 1H), 4.77 (td, *J* = 11.8, 4.7 Hz, 1H), 4.58 (ddd, *J* = 12.0, 4.5, 2.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.01 – 3.88 (m, 2H), 2.27 – 2.13 (m, 2H), 0.85 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃) δ 162.83, 135.58, 134.18, 130.93, 129.22, 128.69, 127.02, 126.37, 125.43, 123.12, 122.57, 72.85, 68.70, 62.76, 38.24, 33.13, 13.66.

HRMS (ESI) *m/z* calculated for C₁₇H₁₉O₅S [M+H]⁺: 335.0953, found 335.0954.

Ethyl 4-(2,2-dimethyl-2*H*-chromen-6-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [10].



Ethyl 2-diazo-2-((3-(2,2-dimethyl-2*H*-chromen-6-yl)propoxy)sulfonyl)acetate

[S16] (75.7 mg, 0.192 mmol, 1.0 equiv), [FePc]Cl (11.6 mg, 0.0192 mmol, 0.10 equiv), NaBAR^F₄ (17.0 mg, 0.0192 mmol, 0.10 equiv), and CH₂Cl₂ (3.80

mL, 0.05 M) were used. Product was purified via flash column chromatography on silica using 10% → 30% EtOAc/hexanes. Pure product was isolated as a clear oil and a 1:1.2 syn:anti mixture of diastereomers. Subsequent purification with 12.5% → 27.5% Et₂O/hexanes separated the diastereomers. The anti diastereomer was isolated with 10% of the syn.

Run 1: (40.1 mg, 0.1094 mmol, 57%), 0% rsm. Run 2: (41.9 mg, 0.1143 mmol, 60%), 0% rsm.

Run 3: (56.3 mg, 0.1536 mmol, 61% (scale: 92.7 mg, 0.253 mmol)), 0% rsm. **Average: 59% yield ± 1.7%, 0% rsm.**

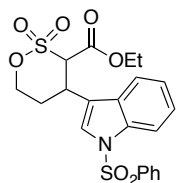
Syn diastereomer (major): ¹H NMR (500 MHz, CDCl₃) δ 6.96 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.83 (d, *J* = 2.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.27 (d, *J* = 9.5 Hz, 1H), 5.64 (d, *J* = 9.8 Hz, 1H), 4.77 - 4.62 (m, 2H), 4.20 (d, *J* = 4.7 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.75 (dt, *J* = 13.4, 4.1 Hz, 1H), 3.14 (tdd, *J* = 13.9, 11.6, 6.5 Hz, 1H), 1.78 (ddt, *J* = 14.3, 3.4, 1.7 Hz, 1H), 1.41 (s, 3H), 1.42 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 164.20, 152.90, 131.71, 130.07, 127.89, 125.17, 121.98, 121.80, 116.95, 76.66, 73.19, 66.49, 62.31, 42.43, 28.10, 24.36, 13.91.

Anti diastereomer (minor): ¹H NMR (500 MHz, CDCl₃) δ 6.94 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 10 Hz, 1H), 5.63 (d, *J* = 9.8 Hz, 1H), 4.73 (ddd, *J* = 13.4, 11.6, 2.2 Hz, 1H), 4.53 (ddd, *J* = 11.6, 4.9, 1.5 Hz, 1H), 4.15 (d, *J* = 12.1 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.72 (td, *J* = 12.5, 3.7 Hz, 1H), 2.20 (dtd, *J* = 14.9, 13.0, 5.0 Hz, 1H), 2.03 - 1.96 (m, 1H), 1.41 (s, 6H), 1.05 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 162.97,

152.83, 131.64, 130.66, 127.95, 125.41, 121.94, 116.89, 76.72, 72.62, 68.96, 62.67, 43.76, 32.45, 28.13, 13.90.

HRMS (ESI) m/z calculated for $C_{18}H_{23}O_6S$ $[M+H]^+$: 367.1215, found 367.1220.

Ethyl 4-(1-(phenylsulfonyl)-1H-indol-3-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [11].



Ethyl 2-diazo-2-((3-(1-(phenylsulfonyl)-1H-indol-3-yl)propoxy)sulfonyl)acetate

[S17] (196.6 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv), $NaBAR^F_4$ (35.4 mg, 0.040 mmol, 0.10 equiv), and CH_2Cl_2 (8.0 mL, 0.05 M)

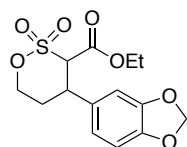
were used. Product was purified via flash column chromatography on silica using 5% → 25% EtOAc/hexanes. Pure product was isolated as a clear oil and a 1.1:1 syn:anti mixture of diastereomers. Diastereomers could not be separated.

Run 1: (118 mg, 0.255 mmol, 64%), 0% rsm. Run 2: (119 mg, 0.256 mmol, 64%), 0% rsm. Run 3: (116 mg, 0.250 mmol, 63%), 0% rsm. **Average: 64% yield ± 0.5%, 0% rsm.**

Mixture of syn and anti diastereomers: ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, $J = 13.0, 8.3$ Hz, 1H D_{maj} + 1H D_{min}), 7.90 - 7.81 (m, 2H D_{maj} + 2H D_{min}), 7.61 - 7.52 (m, 2H D_{maj} + 2H D_{min}), 7.50 - 7.42 (m, 3H D_{min} + 3H D_{min}), 7.41 - 7.23 (m, 2H D_{maj} + 2H D_{min}), 4.88 - 4.66 (m, 2H D_{maj} + 1H D_{min}), 4.57 (ddd, $J = 11.8, 4.8, 1.6$ Hz, 1H D_{min}), 4.37 (d, $J = 4.6$ Hz, 1H D_{maj}), 4.33 (d, $J = 12.0$ Hz, 1H D_{min}), 4.11 (ddd, $J = 12.5, 8.2, 3.8$ Hz, 1H D_{maj} + 1H D_{min}), 4.03 - 3.71 (m, 2H D_{maj} + 2H D_{min}), 3.19 (qd, $J = 13.3, 5.2$ Hz, 1H D_{maj}), 2.34 - 2.21 (m, 1H D_{min}), 2.19 - 2.11 (m, 1H D_{min}), 1.96 - 1.88 (m, 1H D_{maj}), 0.88 (t, $J = 7.1$ Hz, 3H D_{maj}), 0.80 (t, $J = 7.1$ Hz, 3H D_{min}). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.84, 162.73, 141.47, 141.37, 137.64, 136.91, 136.41, 133.05, 128.91, 128.02, 127.90, 127.86, 127.82, 127.77, 127.75, 127.07, 127.06, 73.11, 72.66, 68.47, 66.11, 62.69, 62.37, 43.81,

42.37, 38.06, 32.15, 24.02, 13.87. HRMS (ESI) m/z calculated for $C_{21}H_{22}NO_7S_2$ $[M+H]^+$: 464.0838, found 464.0829.

Ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [12].



Ethyl 2-((3-(benzo[*d*][1,3]dioxol-5-yl)propoxy)sulfonyl)-2-diazoacetate [S18]

(142.5 mg, 0.400 mmol, 1.0 equiv), [FePc]Cl (24.2 mg, 0.040 mmol, 0.10 equiv),

NaBAR₄^F (35.4 mg, 0.040 mmol, 0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.05 M) were used. Product

was purified via flash column chromatography on silica (75 mL SiO₂) using 15% EtOAc/hexanes.

Pure product was isolated as a white solid and a 2:1 syn:anti mixture of diastereomers. Subsequent purification using 15% → 20% → 25% EtOAc/hexanes allowed for separation of diastereomers.

Run 1: (71.1 mg, 0.217 mmol, 54%), 0% rsm. Run 2: (68.8 mg, 0.210 mmol, 52%), 0% rsm. Run

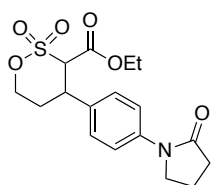
3: (70.6 mg, 0.215 mmol, 54%), 0% rsm. **Average: 53% yield ± 0.8, 0% rsm.**

Syn diastereomer (major): ¹H-NMR (500 MHz, CDCl₃) δ 6.77 (d, *J* = 7.9 Hz, 1H), 6.74 – 6.68 (m, 2H), 5.96 (s, 2H), 4.76 – 4.66 (m, 2H), 4.19 (d, *J* = 4.6 Hz, 1H), 4.16 – 4.03 (m, 2H), 3.77 (dt, *J* = 13.3, 4.0 Hz, 1H), 3.13 (tdd, *J* = 13.8, 11.6, 6.4 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H); ¹³C-NMR (126 MHz, CDCl₃) δ 164.08, 148.26, 147.49, 131.73, 120.74, 108.76, 107.72, 101.43, 73.09, 66.52, 62.39, 42.75, 24.50, 13.91; HRMS (ESI) m/z calculated for C₁₄H₁₇O₇S $[M+H]^+$: 329.0695, found 329.0681.

Anti diastereomer (minor): ¹H-NMR (500 MHz, CDCl₃) δ 6.76 (d, *J* = 8.0 Hz, 1H), 6.71–6.67 (m, 2H), 5.96 (s, 2H), 4.73 (ddd, *J* = 12.9, 11.7, 2.2 Hz, 1H), 4.53 (ddd, *J* = 11.7, 4.9, 1.5 Hz, 1H), 4.18–4.06 (m, 3H), 3.75 (td, *J* = 12.4, 3.7 Hz, 1H), 2.18 (dtd, *J* = 14.8, 12.9, 4.9 Hz, 1H), 2.00 (ddt, *J* = 14.9, 3.6, 1.9 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H); ¹³C-NMR (126 MHz, CDCl₃) δ 162.85, 148.18,

147.43, 132.35, 120.90, 108.76, 107.77, 101.41, 72.58, 68.87, 62.71, 44.05, 32.50, 13.91.; HRMS (ESI) m/z calculated for $C_{14}H_{17}O_7S$ $[M+H]^+$: 329.0695, found 329.0688.

Ethyl 4-(4-(2-oxopyrrolidin-1-yl)phenyl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [13].



Ethyl 2-diazo-2-((3-(4-(2-oxopyrrolidin-1-yl)phenyl)propoxy)sulfonyl)acetate

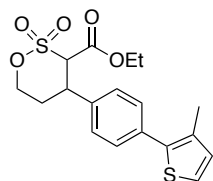
[S19] (75.3 mg, 0.200 mmol, 1.0 equiv), [FePc]Cl (12.1 mg, 0.020 mmol, 0.10 equiv), NaBAR₄^F (17.7 mg, 0.020 mmol, 0.10 equiv), and CH₂Cl₂ (4.0 mL, 0.05

M) were used. Product was purified via flash column chromatography on silica using 30% → 60% EtOAc/hexanes. Product was isolated as a clear oil and a 1.1:1 syn:anti mixture of diastereomers. The diastereomers were inseparable by column chromatography and were characterized as a mixture. Yield was determined via NMR with mesitylene as an internal standard.

Run 1: (29.2 mg, 0.080 mmol, 40%), 0% rsm. Run 2: (28.5 mg, 0.078 mmol, 39%), 0% rsm. Run 3: (29.2 mg, 0.080 mmol, 40%), 0% rsm. **Average: 40% yield ± 0.5%, 0% rsm.**

Mixture of syn and anti diastereomers: ¹H NMR (500 MHz, CDCl₃) δ 7.63 (dd, J = 8.7, 6.9 Hz, 2H D_{maj} + 2H D_{min}), 7.25 (dd, J = 8.5, 5.3 Hz, 2H D_{maj} + 2H D_{min}), 4.82 - 4.69 (m, 2H D_{maj} + 1H D_{min}), 4.56 (dd, J = 11.5, 4.0 Hz, 1H D_{min}), 4.26 (d, J = 3.8 Hz, 1H D_{maj}), 4.24 (d, J = 3.6 Hz, 1H D_{min}), 4.14 - 4.00 (m, 2H D_{maj} + 2H D_{min}), 3.92 - 3.78 (m, 3H D_{maj} + 3H D_{min}), 3.21 (dq, J = 14.0, 6.4 Hz, 1H D_{maj}), 2.63 (td, J = 8.1, 2.9 Hz, 2H D_{maj} + 2H D_{min}), 2.29-2.15 (m, 2H D_{maj} + 3H D_{min}), 2.00 (d, J = 14.5, 1H D_{min}), 1.82 (d, J = 14 Hz, 1H D_{maj}), 1.09 (t, J = 7.1 Hz, 3H D_{maj} + 3H D_{min}). ¹³C NMR (126 MHz, CDCl₃) δ 174.47, 163.98, 162.80, 139.38, 139.28, 134.46, 133.67, 127.88, 127.76, 120.24, 120.17, 73.18, 72.66, 68.58, 66.25, 62.69, 62.36, 48.69, 48.66, 43.70, 42.39, 32.79, 32.34, 24.20, 18.01, 17.98, 13.85, 13.83. HRMS (ESI) m/z calculated for $C_{17}H_{22}NO_6S$ $[M+H]^+$: 368.1168, found 368.1167.

Ethyl 4-(4-(3-methylthiophen-2-yl)phenyl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [14].



Ethyl

2-diazo-2-((3-(4-(3-methylthiophen-2-

yl)phenyl)propoxy)sulfonyl)acetate [S20] (81.7 mg, 0.2 mmol, 1.0 equiv),

[FePc]Cl (12.1 mg, 0.020 mmol, 0.10 equiv), NaBAR₄^F (17.7 mg, 0.020 mmol,

0.10 equiv), and CH₂Cl₂ (8.0 mL, 0.025 M) were used. Product was purified via flash column

chromatography on silica using 0.4% Et₂O, 19.6% CH₂Cl₂, 80% hexanes → 1% Et₂O, 49% CH₂Cl₂,

50% hexanes as eluent. Pure product was isolated as a clear oil and a 1:1.3 syn:anti mixture of

diastereomers. Subsequent purification using 0.4% Et₂O, 19.6% CH₂Cl₂, 80% hexanes → 1%

Et₂O, 49% CH₂Cl₂, 50% hexanes as eluent allowed for separation of diastereomers. Yields were

determined via NMR with mesitylene as an internal standard. The syn diastereomer was isolated

with 10% of the anti, and the anti diastereomer was isolated with 5% syn.

Run 1: (40.4 mg, 0.106 mmol, 53%), 0% rsm. Run 2: (37.9 mg, 0.099 mmol, 49%), 0% rsm. Run

3: (38.2 mg, 0.100 mmol, 52%), 0% rsm. **Average: 51% yield ± 1.7%, 0% rsm.**

Syn diastereomer (major): ¹H-NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3

Hz, 2H), 7.22 (d, *J* = 5.1 Hz, 1H), 6.93 (d, *J* = 5.1 Hz, 1H), 4.82 - 4.70 (m, 2H), 4.28 (d, *J* = 4.6

Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.90 (dt, *J* = 13.5 Hz, 4 Hz, 1H), 3.32 - 3.17 (m, 1H), 2.31 (s,

3H), 1.86 (ddt, *J* = 14.7, 3.5, 1.7 Hz, 1H), 1.04 (t, *J* = 7.1 Hz, 3H).; ¹³C-NMR (126 MHz, CDCl₃)

δ 164.05, 136.92, 136.68, 134.97, 133.68, 131.40, 129.63, 127.53, 123.91, 73.18, 66.24, 62.39,

42.72, 24.11, 15.07, 13.87.

Anti diastereomer (minor): ¹H-NMR (500 MHz, CDCl₃) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* =

8.0 Hz, 2H), 7.21 (d, *J* = 5.1 Hz, 1H), 6.92 (d, *J* = 5.1 Hz, 1H), 4.78 (ddd, *J* = 13.5, 11.5, 2.0 Hz,

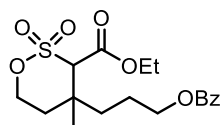
1H), 4.57 (ddd, *J* = 12.4, 5.6, 2.2 Hz, 1H), 4.25 (d, *J* = 12.1 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.87

(td, *J* = 12.4, 3.7 Hz, 1H), 2.33 (s, 3H), 2.30 - 2.23 (m, 1H), 2.06 (d, *J* = 15 Hz, 1H), 1.04 (t, *J* =

7.1 Hz, 3H).; ^{13}C -NMR (126 MHz, CDCl_3) δ 162.90, 137.36, 136.95, 134.93, 133.66, 131.40, 129.65, 127.68, 123.88, 72.67, 68.65, 62.78, 44.16, 32.36, 15.09, 13.87.

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{21}\text{O}_5\text{S}_2$ $[\text{M}+\text{Na}]^+$: 381.0830, found 381.0841.

ethyl 4-(3-(benzyloxy)propyl)-4-methyl-1,2-oxathiane-3-carboxylate 2,2-dioxide [S22]



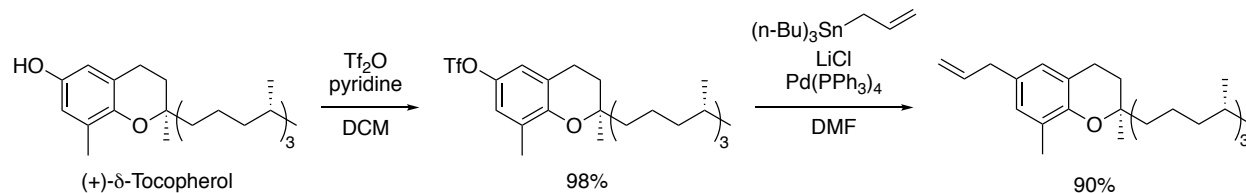
6-(((1-diazo-2-ethoxy-2-oxoethyl)sulfonyl)oxy)-4-methylhexyl benzoate [S21]

(322 mg, 0.706 mmol, 1.0 equiv), Rh_2OAc_4 (6.2 mg, 0.014 mmol, 0.02 equiv), and CH_2Cl_2 (12.5 mL, 0.056 M) were used. Product was purified via flash column chromatography on silica using 10% ether, 90% petroleum ether $\rightarrow$ 40% ether, 60% petroleum ether as eluent. Diastereomers were isolated separately.

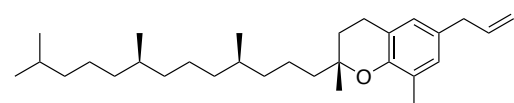
Diastereomer 1: ^1H NMR (500 MHz, Chloroform- d) δ 8.01 (dd, J = 8.2, 1.4 Hz, 2H), 7.60 – 7.53 (m, 1H), 7.45 (t, J = 7.8 Hz, 2H), 4.73 (td, J = 12.1, 2.3 Hz, 1H), 4.55 (ddd, J = 12.0, 4.7, 2.9 Hz, 1H), 4.33 – 4.18 (m, 4H), 3.86 (s, 1H), 2.52 (ddd, J = 14.6, 12.2, 4.7 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.64 – 1.57 (m, 2H), 1.41 (dt, J = 14.7, 2.4 Hz, 1H), 1.26 (dt, J = 12.6, 7.3 Hz, 4H).; ^{13}C NMR (126 MHz, CDCl_3) δ 166.55, 164.65, 133.23, 130.16, 129.62, 128.55, 70.08, 69.96, 64.63, 62.66, 38.75, 37.29, 32.18, 23.11, 22.55, 14.03.

Diastereomer 2: ^1H NMR (500 MHz, Chloroform- d) δ 8.07 – 8.01 (m, 2H), 7.59 – 7.53 (m, 1H), 7.45 (t, J = 7.7 Hz, 2H), 4.70 – 4.56 (m, 2H), 4.38 – 4.23 (m, 4H), 3.93 (s, 1H), 2.33 – 2.24 (m, 1H), 2.04 (ddd, J = 13.5, 11.5, 5.1 Hz, 1H), 1.82 (dddd, J = 13.0, 10.7, 6.5, 4.3 Hz, 2H), 1.75 – 1.57 (m, 2H), 1.43 (d, J = 6.7 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H).; ^{13}C NMR (126 MHz, CDCl_3) δ 166.60, 164.33, 133.16, 130.18, 129.64, 129.61, 128.53, 128.50, 69.85, 68.35, 64.63, 62.61, 38.87, 35.24, 33.02, 23.52, 23.17, 14.09.

Diversification of Complex Molecules



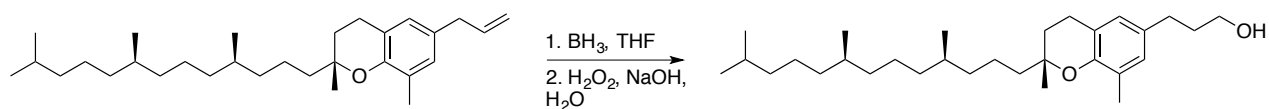
(+)-(R)-6-allyl-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane [S23]



To an oven-dried round-bottom flask with a stir bar was added (+)- δ -tocopherol (3.2 g, 8.0 mmol, 1.0 equiv), CH_2Cl_2 (40 mL, 0.2 M), pyridine (1.94 mL, 12 mmol, 1.5 equiv). The reaction was cooled to 0 °C. Trifluoromethanesulfonic anhydride (1.62 mL, 9.6 mmol, 1.2 equiv) was added dropwise and the reaction was stirred at 0 °C for 30 min. After warming up to room temperature, the reaction was quenched with addition of cold water. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 . The organic layers were combined and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica using 100% hexanes as eluent. The characterization of the resulting compound matched the literature²⁸. To an oven-dried round bottom flask equipped with condenser was added a stir bar, LiCl (477 mg, 11.25 mmol, 3.75 equiv), DMF (7.5 mL, 0.4 M), allyltributylstannane (1.16 mL, 3.75 mmol, 1.25 equiv), (+)- δ -tocopherol triflate (1.60 g, 3 mmol, 1 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (104 mg, 0.09 mmol, 0.03 equiv). The reaction was heated to 100 °C and stirred for 12 hours. Upon completion, the reaction was cooled to room temperature, transferred into a separatory funnel with iced 10% NH_4OH solution (1:1 to DMF) and shake vigorously. Layers were separated, aqueous layer was extracted with ethyl acetate (30 mL x 3). The organic layers were combined and concentrated. The crude mixture was

purified by flash column chromatography on silica using 100% petroleum ether as eluent to give (+)-allylated- δ -tocopherol derivative **[S39]** in 88% yield over two steps.

^1H NMR (500 MHz, CDCl_3) δ 6.80 (d, $J = 2.2$ Hz, 1H), 6.73 (d, $J = 2.1$ Hz, 1H), 5.97 (ddt, $J = 16.8, 10.0, 6.8$ Hz, 1H), 5.13-4.95 (m, 2H), 3.28 (d, $J = 6.8$ Hz, 2H), 2.80-2.61 (m, 2H), 2.16 (s, 3H), 1.86-1.71 (m, 2H), 1.64-1.03 (m, 24H), 0.91-0.84 (m, 12H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.5, 138.5, 130.2, 128.6, 126.8, 126.3, 120.4, 115.2, 75.96, 40.3, 39.7, 39.5, 37.6, 37.6, 37.4, 33.0, 32.9, 31.4, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 22.5, 21.1, 19.9, 19.8, 16.2. HRMS (ESI) m/z calculated for $\text{C}_{30}\text{H}_{50}\text{O}$ $[\text{M}]^+$: 426.3862, found 426.3851. $[\alpha]_{\text{D}}^{22} = +5.6^\circ$ ($c = 1.05$, CHCl_3)



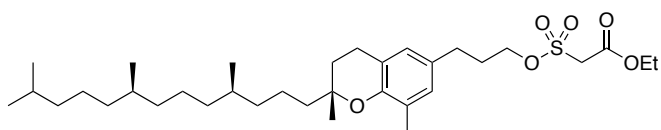
(+)-3-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)propan-1-ol [S24].

The following procedure was adapted from literature precedent²⁹. A round-bottomed flask was flame-dried under vacuum, backfilled with nitrogen, and then charged with 1.28 g (3.0 mmol, 1 equiv) of (*R*)-6-allyl-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane **[S39]** and THF (8.6 mL, 0.35 M). The solution was cooled to 0°C in an ice bath. A 1.0 M BH_3 solution in THF (24 mL, 24 mmol, 8 equiv) was added dropwise. The reaction mixture was removed from the bath and allowed to stir at room temperature for one hour. The mixture was again cooled to 0°C and a 4 M solution of NaOH (2.70 mL) was added dropwise, followed by dropwise addition of 30% H_2O_2 (3.60 mL, 117 mmol, 39 equiv). The reaction was removed from the ice bath and allowed to stir for 40 minutes at room temperature. The mixture was then extracted three times with EtOAc.

The combined organic phases were dried over magnesium sulfate and concentrated in vacuo. Flash column chromatography on silica gel with 5% → 13% EtOAc/hexanes as eluent yielded 644 mg (1.45 mmol) of pure product as a clear oil (48%).

¹H-NMR (500 MHz, CDCl₃) δ 6.79 (d, *J* = 2.7 Hz, 1H), 6.73 (s, *J* = 2.2 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.77 – 2.67 (m, 2H), 2.57 (dd, *J* = 7.3, 7.9 Hz, 2H), 2.14 (s, 3H), 1.92 – 1.68 (m, 4H), 1.63 – 1.00 (m, 25H), 0.92 – 0.81 (m, 12H).; ¹³C-NMR (126 MHz, CDCl₃) δ 150.39, 131.89, 128.51, 126.67, 126.24, 120.40, 75.96, 62.72, 40.38, 39.53, 37.61, 37.57, 37.44, 34.70, 32.95, 32.85, 31.42, 31.40, 28.14, 24.96, 24.60, 24.41, 22.88, 22.79, 22.50, 21.15, 19.91, 19.82, 16.20.; [α]_D²² = +3.80° (c=1.39, CHCl₃); HRMS (ESI) *m/z* calculated for C₃₀H₅₃O₂ [M+H]⁺: 445.4046, found 445.4040.

(+)-Ethyl 2-((3-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)propoxy)sulfonyl)acetate [S25].



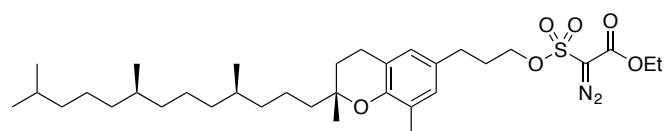
Prepared according to the general procedure for preparation of sulfonate ester substrates.

644 mg (1.45 mmol) of 3-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)propan-1-ol [**S40**] were used, along with imidazole (119 mg, 1.74 mmol, 1.2 equiv), ClSO₂CH₂CO₂Et (406 mg, 2.18 mmol, 1.5 equiv), and THF (7.2 mL, 0.2 M). Flash column chromatography on silica using 5% → 20% Et₂O/petroleum ether as eluent gave 427 mg (0.719 mmol) of pure product as a clear oil (50% yield).

¹H-NMR (500 MHz, CDCl₃) δ 6.80 (d, *J* = 2.2 Hz, 1H), 6.74 (d, *J* = 1.8 Hz, 1H), 4.38 (t, *J* = 6.4 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.11 (s, 2H), 2.79-2.69 (m, 2H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.17 (s, 3H), 2.12 - 2.04 (m, 2H), 1.89 - 1.72 (m, 2H), 1.64 - 1.05 (m, 27H), 0.94 - 0.84 (m, 12H).; ¹³C-

NMR (126 MHz, CDCl₃) δ 162.14, 150.67, 130.33, 128.49, 126.80, 126.42, 120.55, 76.05, 71.88, 62.86, 54.99, 40.40, 39.52, 37.60, 37.57, 37.43, 32.94, 32.85, 31.35, 31.18, 30.73, 28.13, 24.95, 24.60, 24.38, 22.88, 22.78, 22.46, 21.15, 19.90, 19.80, 16.18, 14.12.; $[\alpha]^{22}_{\text{D}}=+3.21^\circ$ (c=0.44, CHCl₃); HRMS (ESI) m/z calculated for C₃₄H₅₉O₆S [M+H]⁺: 595.4032, found 595.4036.

(+)-Ethyl 2-diazo-2-((3-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)propoxy)sulfonyl)acetate [15].

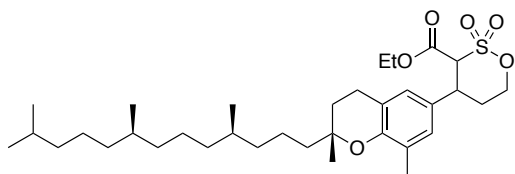


Prepared according to the general procedure for diazo transfer. 427 mg (0.719 mmol) of

ethyl 2-((3-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)propoxy)sulfonyl)acetate [**S40**] were used, along with MeSO₂N₃ (261 mg, 2.16 mmol, 3 equiv), DBU (161 μ L, 1.08 mmol, 1.5 equiv), and THF (1.8 mL, 0.4 M). Flash column chromatography on silica using 1% $\rightarrow$ 8% Et₂O/petroleum ether as eluent gave 280 mg (0.452 mmol) of pure product as a yellow oil (63% yield).

¹H-NMR (500 MHz, CDCl₃) δ 6.75 (d, J = 2.9 Hz, 1H), 6.69 (d, J = 3.0 Hz, 1H), 4.35 (t, J = 6.3 Hz, 2H), 4.33 (q, J = 7.3 Hz, 2H), 2.76 - 2.65 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.13 (s, 3H), 2.07 - 1.98 (m, 2H), 1.85 - 1.67 (m, 2H), 1.60 - 1.00 (m, 27H), 0.91 - 0.81 (m, 12H).; ¹³C-NMR (126 MHz, CDCl₃) δ 159.54, 150.60, 130.22, 128.42, 126.73, 126.31, 120.46, 75.95, 72.85, 62.74, 40.31, 39.45, 37.52, 37.49, 37.36, 32.86, 32.76, 31.29, 30.85, 30.64, 28.05, 24.88, 24.52, 24.31, 22.81, 22.72, 22.39, 21.06, 19.84, 19.75, 16.12, 14.35.; $[\alpha]^{22}_{\text{D}}=+2.58^\circ$ (c=1.99, CHCl₃); HRMS (ESI) m/z calculated for C₃₄H₅₆O₆N₂SNa [M+Na]⁺: 643.3757, found 643.3767; IR (ATR, cm⁻¹) 2925.67, 2867.31, 2130.74, 1723.96, 1598.56, 1480.78, 1464.51, 1376.38, 1288.42, 1222.30, 1180.52, 1151.78, 1092.88, 1006.25, 928.65, 835.62, 738.50, 615.85, 558.77, 538.19, 509.25.

Ethyl 4-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide [16].



Ethyl 2-diazo-2-((3-((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12

trimethyltridecyl)chroman-6-yl)propoxy)sulfonyl)acetate [25] (24.2 mg, 0.200 mmol, 1.0 equiv), [FePc]Cl (12.1 mg, 0.020 mmol, 0.10 equiv), NaBAr^F₄ (17.7 mg, 0.020 mmol, 0.10 equiv), and CH₂Cl₂ (4.0 mL, 0.05 M) were used. Product was purified via flash column chromatography on silica using 2% → 15% EtOAc/hexanes. Pure product was isolated as a yellow oil and a 1.4:1 syn:anti mixture of diastereomers. Subsequent purification using 5% → 20% Et₂O/hexanes allowed for separation of diastereomers. A trace impurity (<5%) was isolated with the syn product and was factored into yield calculations.

Run 1: (96.9 mg, 0.163 mmol, 82%), 0% rsm. Run 2: (85.2 mg, 0.144 mmol, 72%), 0% rsm. Run 3: (94.0 mg, 0.159 mmol, 79%), 0% rsm. **Average: 78% yield ± 4.2%, 0% rsm.**

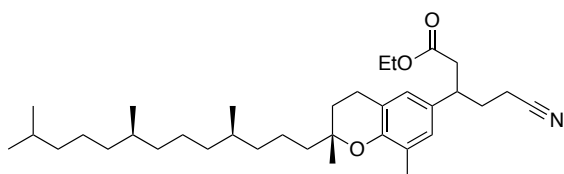
Syn diastereomer (major): ¹H NMR (500 MHz, CDCl₃) δ 6.79 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 4.77 - 4.66 (m, 2H), 4.19 (d, *J* = 4.6 Hz, 1H), 4.14 - 4.00 (m, 2H), 3.71 (dt, *J* = 13.5, 4.1 Hz, 1H), 3.11 (dtd, *J* = 6.5 Hz, 11.6 Hz, 14.0 Hz, 1H), 2.80 - 2.60 (m, 2H), 2.12 (s, 3H), 1.86 - 1.68 (m, 4H), 1.55 - 0.97 (m, 26H), 0.91 - 0.77 (m, 12H).; ¹³C-NMR (126 MHz, CDCl₃) δ ¹³C NMR (126 MHz, CDCl₃) δ 164.32, 152.06, 128.00, 127.24, 127.19, 127.00, 125.73, 125.68, 120.96, 120.94, 76.44, 73.31, 66.67, 62.16, 42.57, 40.30, 40.23, 39.51, 37.60, 37.43, 32.94, 32.87, 32.83, 31.21, 28.13, 24.95, 24.59, 24.56, 24.32, 24.26, 22.88, 22.49, 21.12, 19.90, 19.78, 16.27, 13.91.

Anti diastereomer (minor): ¹H-NMR (500 MHz, CDCl₃) δ 6.78 (d, *J* = 2.3 Hz, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 4.72 (ddd, *J* = 13.4, 11.7, 2.2 Hz, 1H), 4.52 (ddd, *J* = 11.6, 4.9, 1.5 Hz, 1H), 4.15 (d,

$J = 12.0$ Hz, 1H), 4.12 – 4.04 (m, 2H), 3.67 (td, $J = 12.4, 3.6$ Hz, 1H), 2.76 – 2.65 (m, 2H), 2.20 (dtd, $J = 14.8, 12.9, 4.9$ Hz, 1H), 2.12 (s, 3H), 2.01 - 1.94 (m, 1H), 1.82 – 1.70 (m, 2H), 1.59 - 0.99 (m, 27H), 0.87 – 0.83 (m, 12H).; ^{13}C -NMR (126 MHz, CDCl_3) δ 163.10, 151.96, 128.59, 127.25, 127.20, 126.90, 125.99, 125.93, 120.91, 120.90, 76.42, 72.72, 69.11, 62.47, 43.79, 40.37, 40.30, 39.51, 37.60, 37.58, 37.42, 32.94, 32.85, 32.65, 31.17, 28.13, 24.94, 24.59, 24.32, 24.26, 22.87, 22.78, 22.44, 21.11, 19.89, 19.78, 16.26, 13.87.

HRMS (ESI) m/z calculated for $\text{C}_{34}\text{H}_{57}\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: 593.3876, found 593.3865.

Ethyl 5-cyano-3-((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)pentanoate [17].



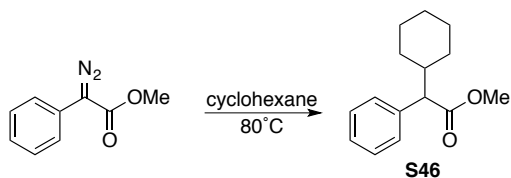
The following procedure was adapted from literature precedent²³. Other examples of sultone eleaboration have been reported³⁰⁻⁴³. A round-

bottomed flask was charged with ethyl 4-((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide (93.9 mg, 0.159 mmol) and DMF (0.45 mL, 0.33 M). Sodium cyanide (8.60 mg, 0.174 mmol, 1.1 equiv) was added and the resulting mixture was heated to 100°C and stirred for three hours. The reaction mixture was then allowed to cool to room temperature and the DMF was removed in vacuo. The resulting brown oil was coevaporated three times with toluene and then allowed to stand under high vacuum for three hours at room temperature. The resulting brown oil was dissolved in toluene (0.63 mL, 0.25 M) and DMF (3.2 μL) and then oxalyl chloride (100.6 mg, 68 μL , 0.793 mmol, 5 equiv) were added. The resulting mixture was heated to 100°C and stirred for twenty minutes, and then allowed to cool to room temperature. The resulting suspension was filtered through a small pad of celite

and the filter cake washed three times with toluene. The filtrate was concentrated in vacuo and the resulting brown oil was redissolved in THF (0.8 mL, 0.2 M). A separate round-bottomed flask was charged with zinc dust (104 mg, 1.59 mmol, 10 equiv), copper (II) acetate monohydrate (31.6 mg, 0.159 mmol, 1 equiv), and glacial acetic acid (0.8 mL). This mixture was stirred for one minute before the substrate solution in THF was added dropwise. The resulting reaction mixture was stirred at room temperature for 2.5 hours. The mixture was diluted with diethyl ether and filtered through a small pad of celite. The filter cake was washed three times with ether. The ether was removed in vacuo. Flash column chromatography on silica gel with 2% → 20% Et₂O/petroleum ether as eluent gave some pure product (19.5 mg, 0.037 mmol, 23%) as a clear oil and some product as a clear oil with minor impurities. The yield was determined via NMR with mesitylene as an internal standard.

Overall: 0.070 mmol, 44% yield. ¹H NMR (500 MHz, CDCl₃) δ 6.75 (s, 1H), 6.71 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.10 – 3.04 (m, 1H), 2.79 – 2.68 (m, 2H), 2.60 (dd, *J* = 7.5, 2.1 Hz, 2H), 2.33 – 2.03 (m, 7H), 1.90 – 1.74 (m, 3H), 1.65 – 1.03 (m, 26H), 0.91 – 0.87 (m, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 171.93, 151.37, 131.18, 127.15, 127.10, 126.70, 126.69, 125.95, 125.90, 120.78, 119.74, 76.22, 60.59, 41.85, 40.64, 40.48, 39.52, 37.62, 37.58, 37.44, 32.95, 31.74, 31.25, 28.13, 24.95, 24.60, 24.37, 24.33, 22.87, 22.78, 22.50, 21.15, 19.90, 19.80, 16.31, 15.52, 14.30.; HRMS (ESI) *m/z* calculated for C₃₅H₅₈NO₃ [M+H]⁺: 540.4417, found 540.4416.

Thermal Decomposition of Diazo Esters



The following procedure was adapted from a literature report³⁴ of an iron catalyzed C—H insertion reaction, wherein a 66% yield of C—H alkylation of cyclohexane was reported with the use of 2 mol% Fe(PPP)Cl at 80°C. We conducted the reaction in the same fashion, but without the addition of catalyst.

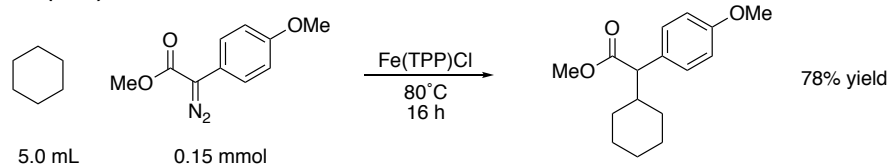
Procedure for metal-free C—H functionalization of cyclohexane:

Methyl 2-phenyldiazoacetate³⁵ (70.5 mg, 0.40 mmol) was added into a new, flame-dried flask equipped with a reflux condenser. Distilled and thoroughly degassed cyclohexane (11.7 mL) was then added and N₂ was bubbled through the solution for 10 minutes. The mixture stirred at 80°C for 24 hours. The mixture was then cooled, concentrated, and purified via flash chromatography on silica using 10% EtOAc/hexanes. Due to co-elution with the diazoester starting material, the yield was determined via NMR with mesitylene as an internal standard. ¹H NMR spectrum matched literature values³⁶. We also repeated this experiment with glassware that had been washed with EDTA (to remove trace metals) and observed the same results.

Run 1: (43.7 mg, 0.188 mmol, 47% yield). Run 2: (29.7 mg, 0.128 mmol, 32% yield). Run 3: (40.9 mg, 0.176 mmol, 44% yield). **Average: 41% yield [S46] ± 6.5.**

These results are consistent with other reports in the literature where a nearly identical yield was achieved without catalyst (**Fig. 2.13**). According to Woo, the following transformation occurred in 78% yield under iron catalysis³⁴. According to Davies, the same transformation occurred in 76% yield without the addition of catalyst³⁷.

Woo (2008):



Davies (2017):

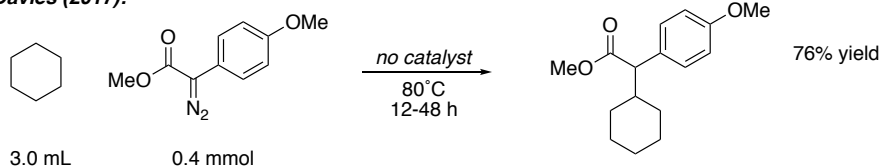
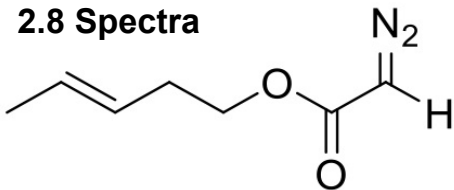
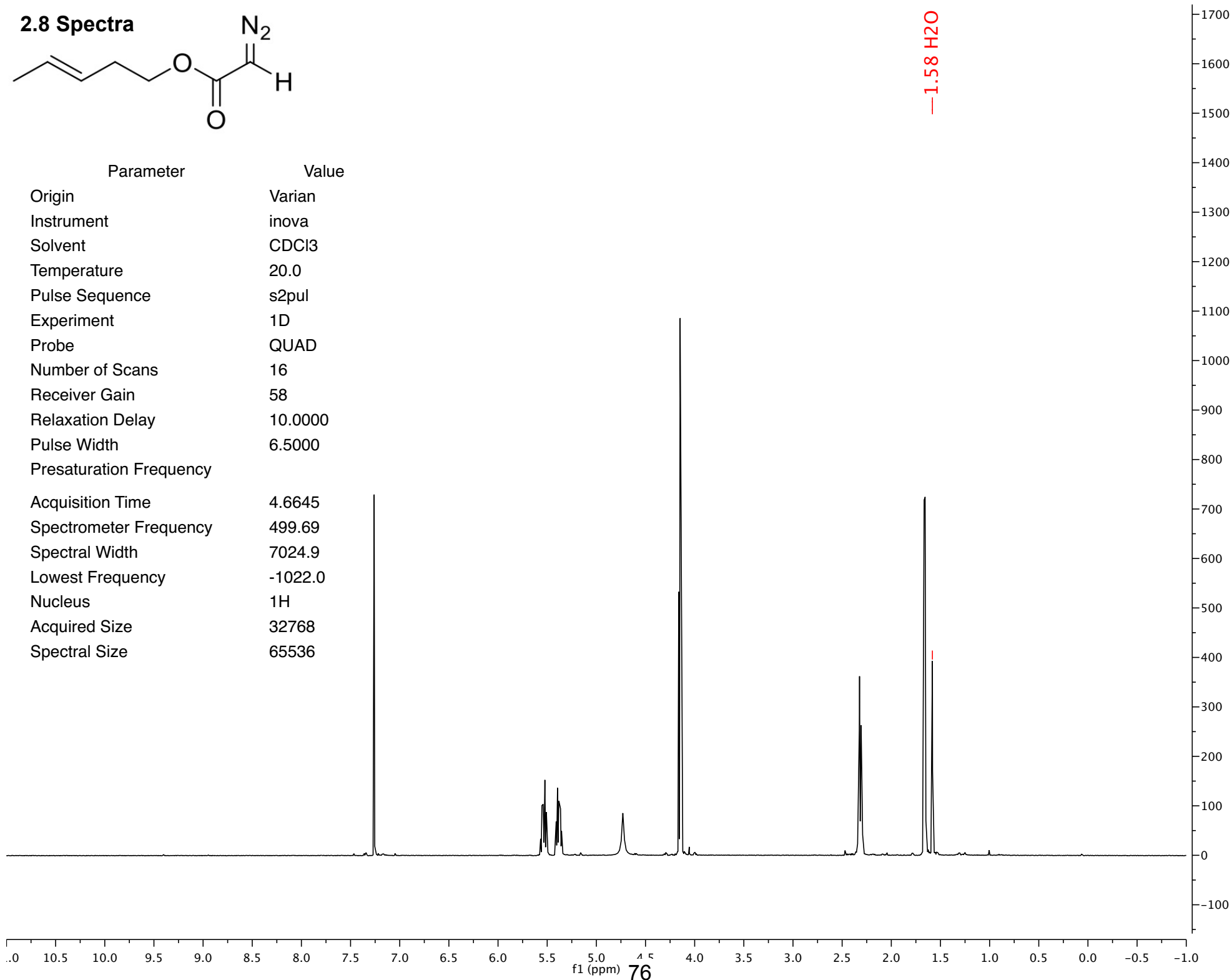


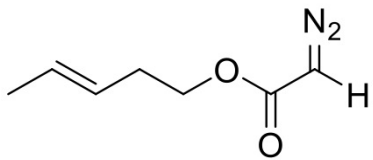
Figure 2.13.

2.8 Spectra

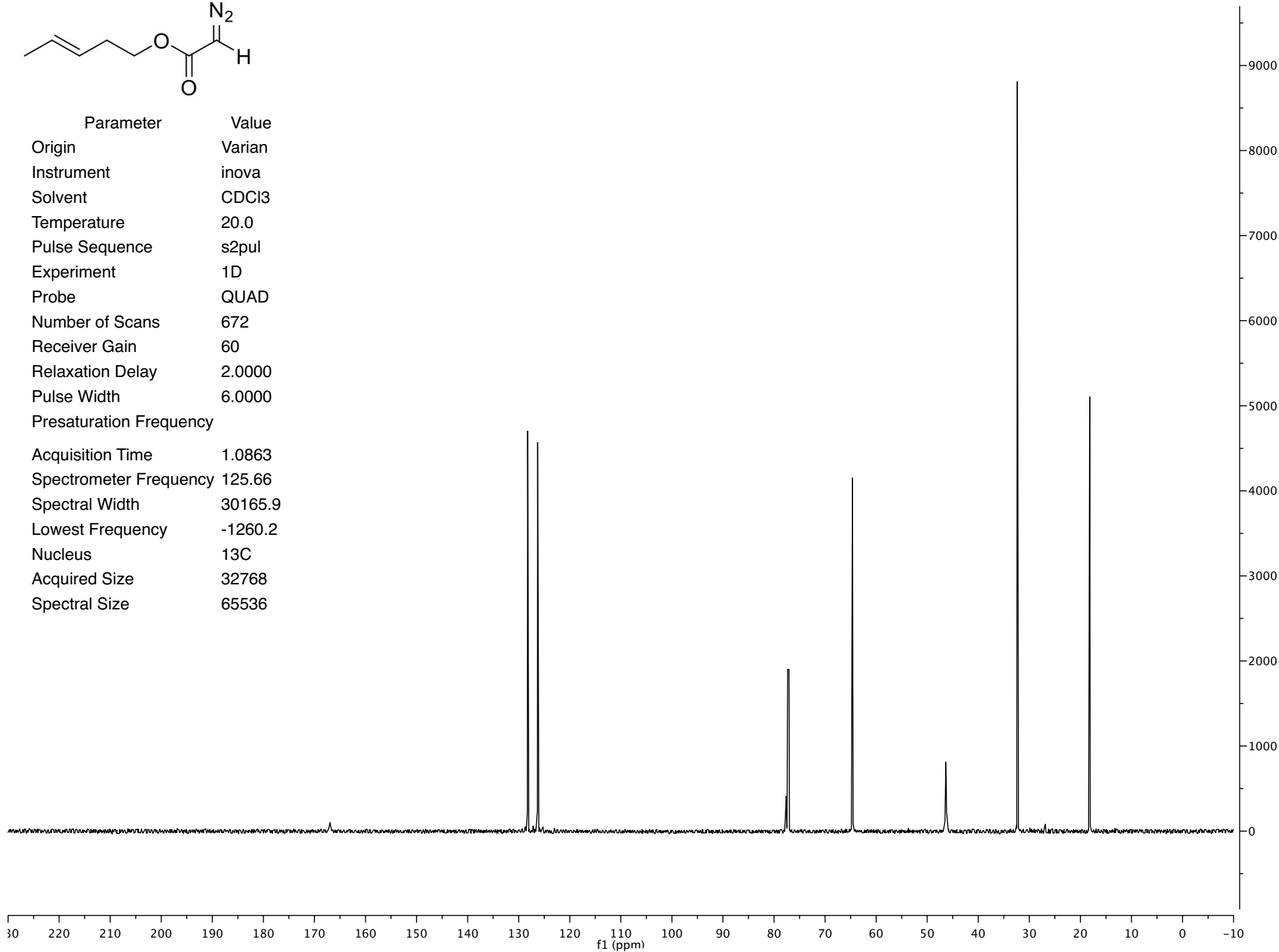


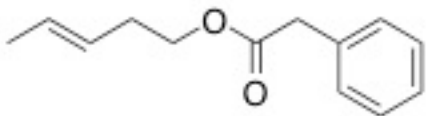
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Experiment	1D
Probe	QUAD
Number of Scans	16
Receiver Gain	58
Relaxation Delay	10.0000
Pulse Width	6.5000
Presaturation Frequency	
Acquisition Time	4.6645
Spectrometer Frequency	499.69
Spectral Width	7024.9
Lowest Frequency	-1022.0
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



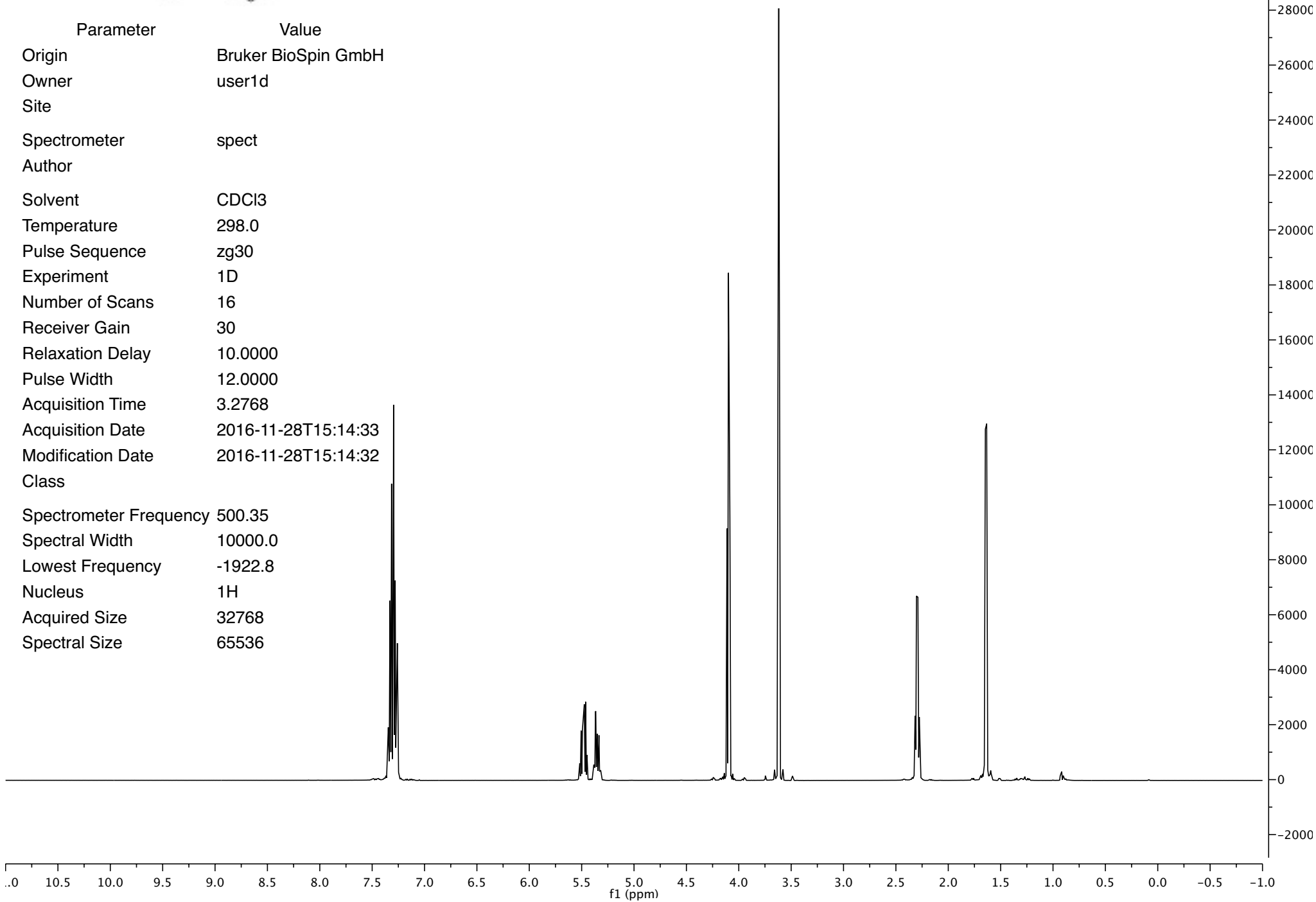


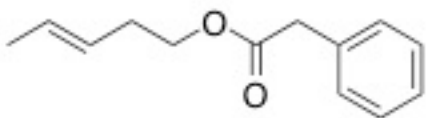
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Nucleus	13C
Acquired Size	32768
Spectral Size	65536



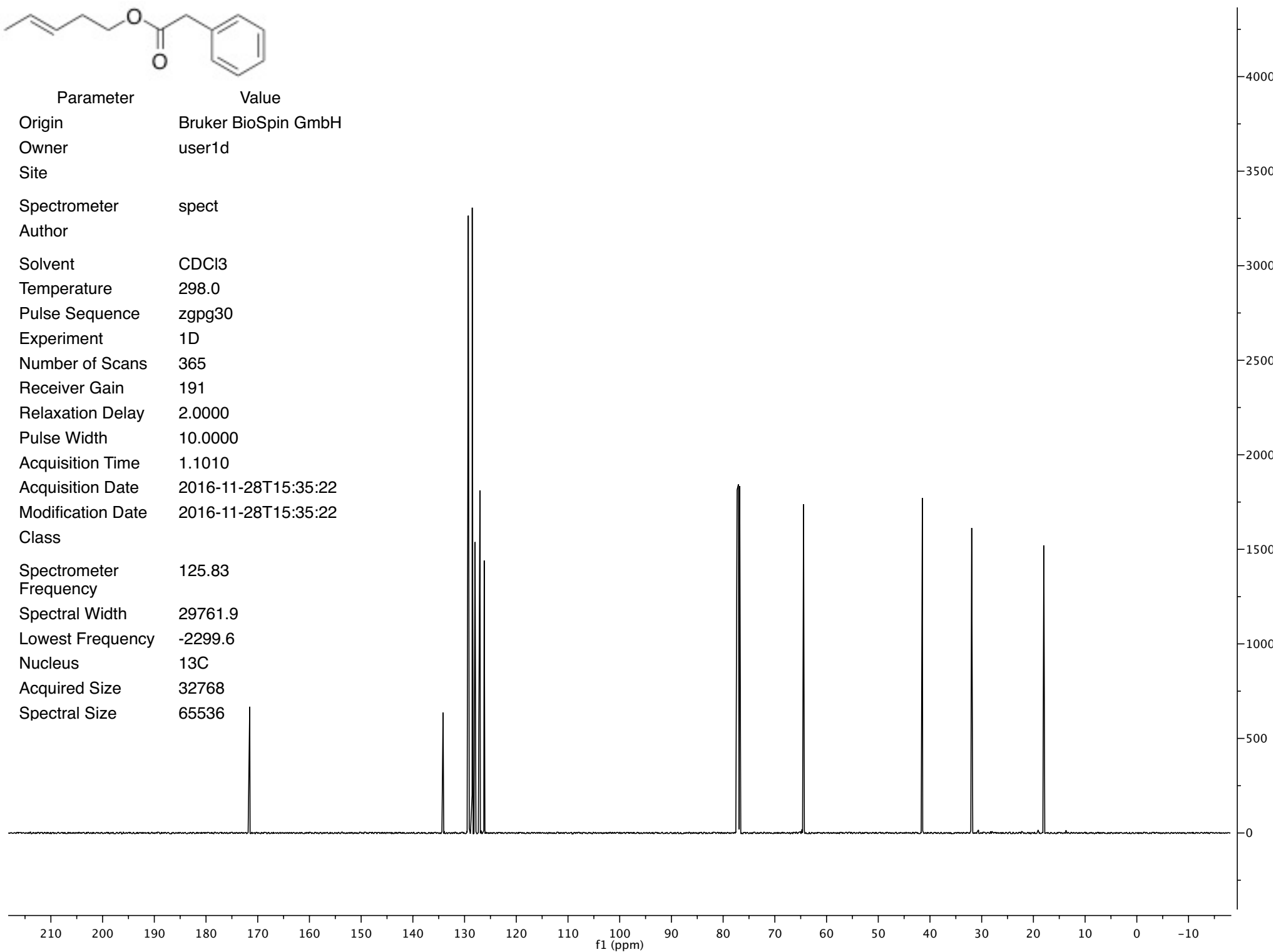


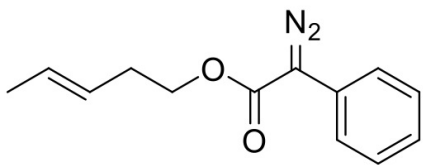
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Author	
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Lowest Frequency	-1922.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



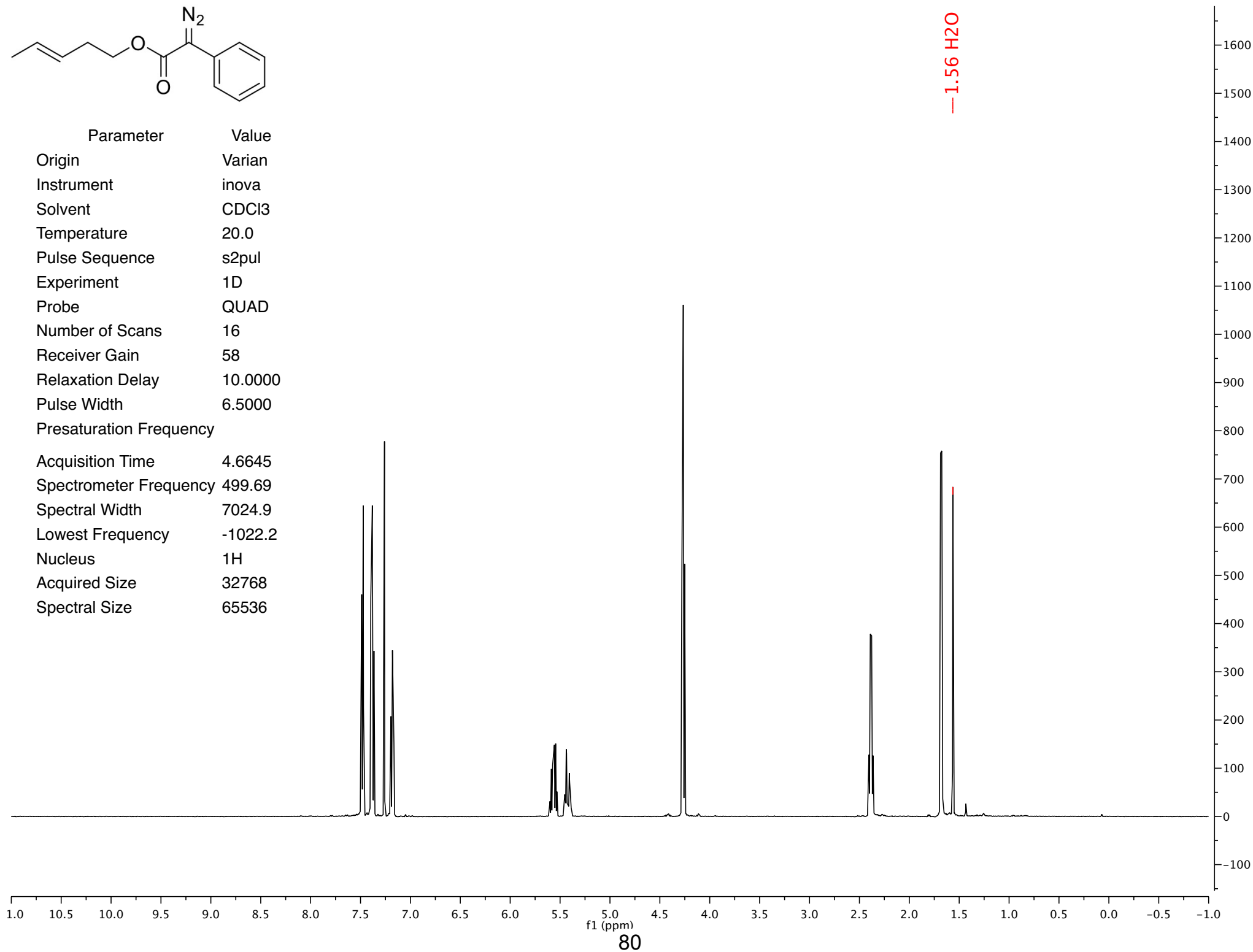


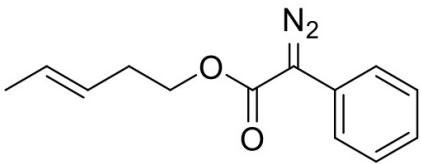
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Author	
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Pulse Width	10.0000
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Modification Date	2016-11-28T15:35:22
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Nucleus	13C
Acquired Size	32768
Spectral Size	65536



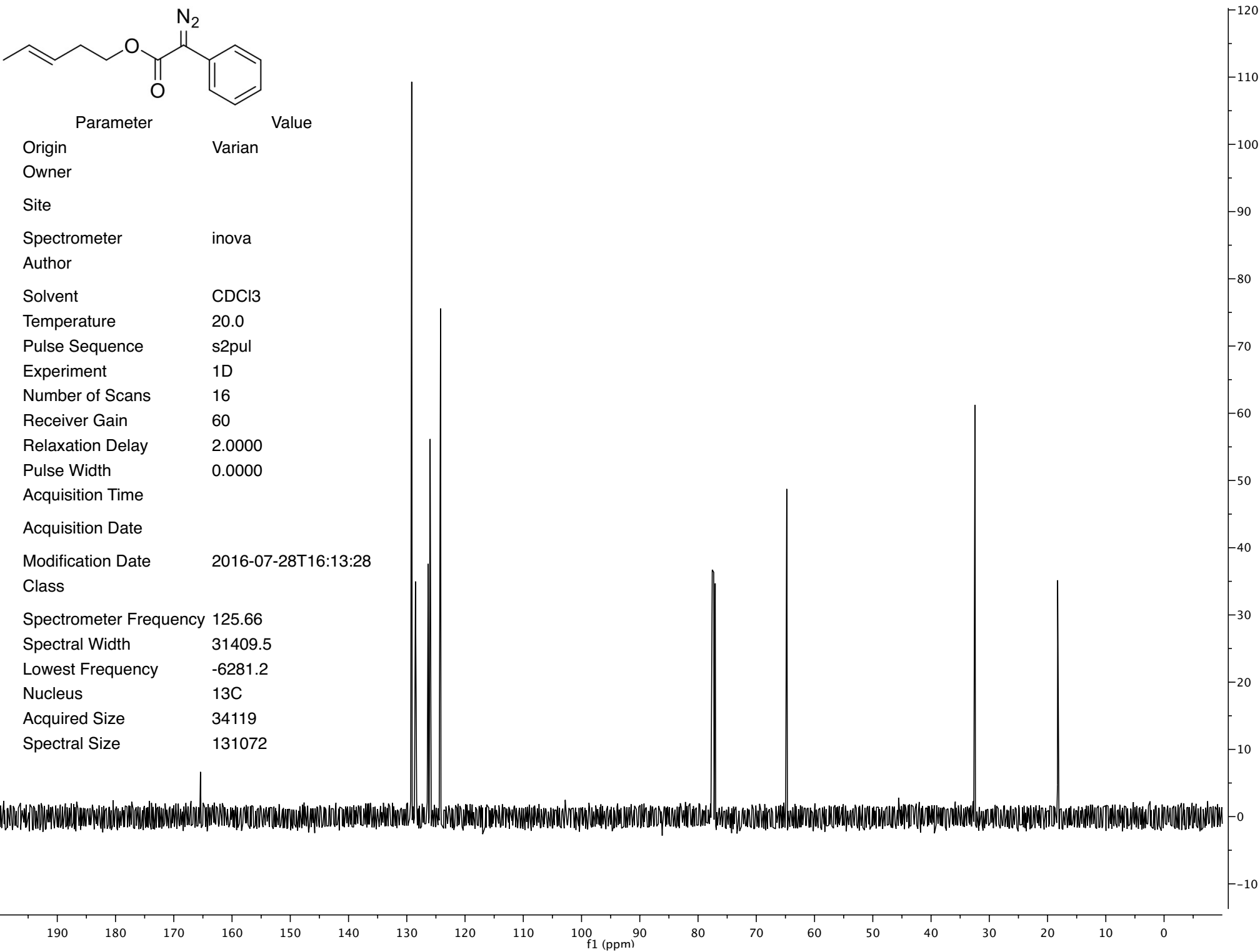


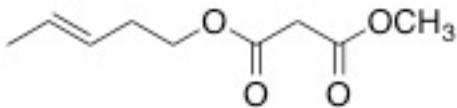
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Probe	QUAD
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Presaturation Frequency	
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Acquired Size	32768
Spectral Size	65536



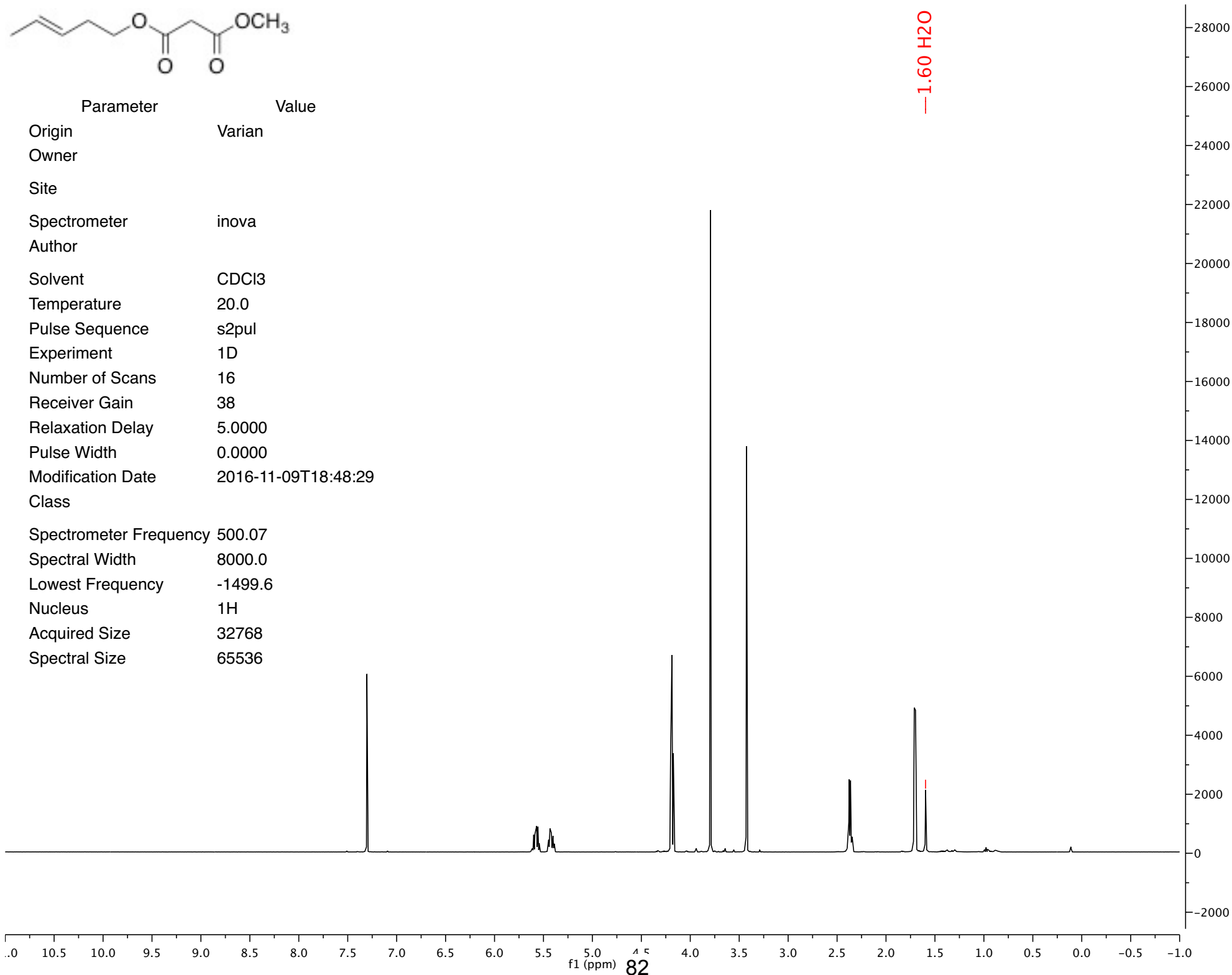


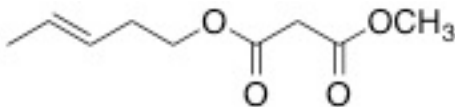
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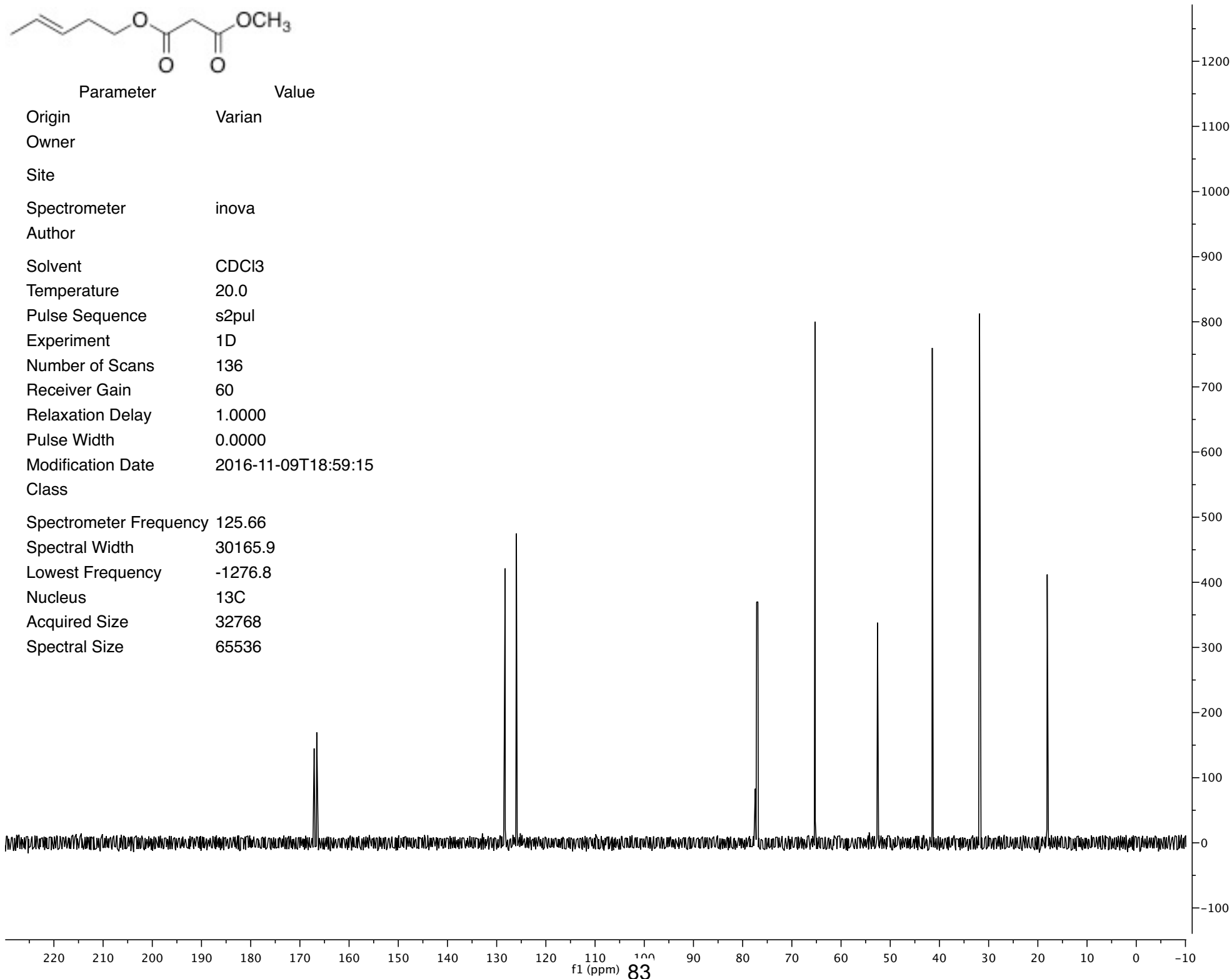


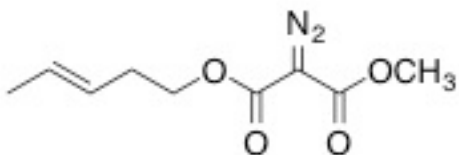
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Nucleus	1H
Acquired Size	32768
Spectral Size	65536



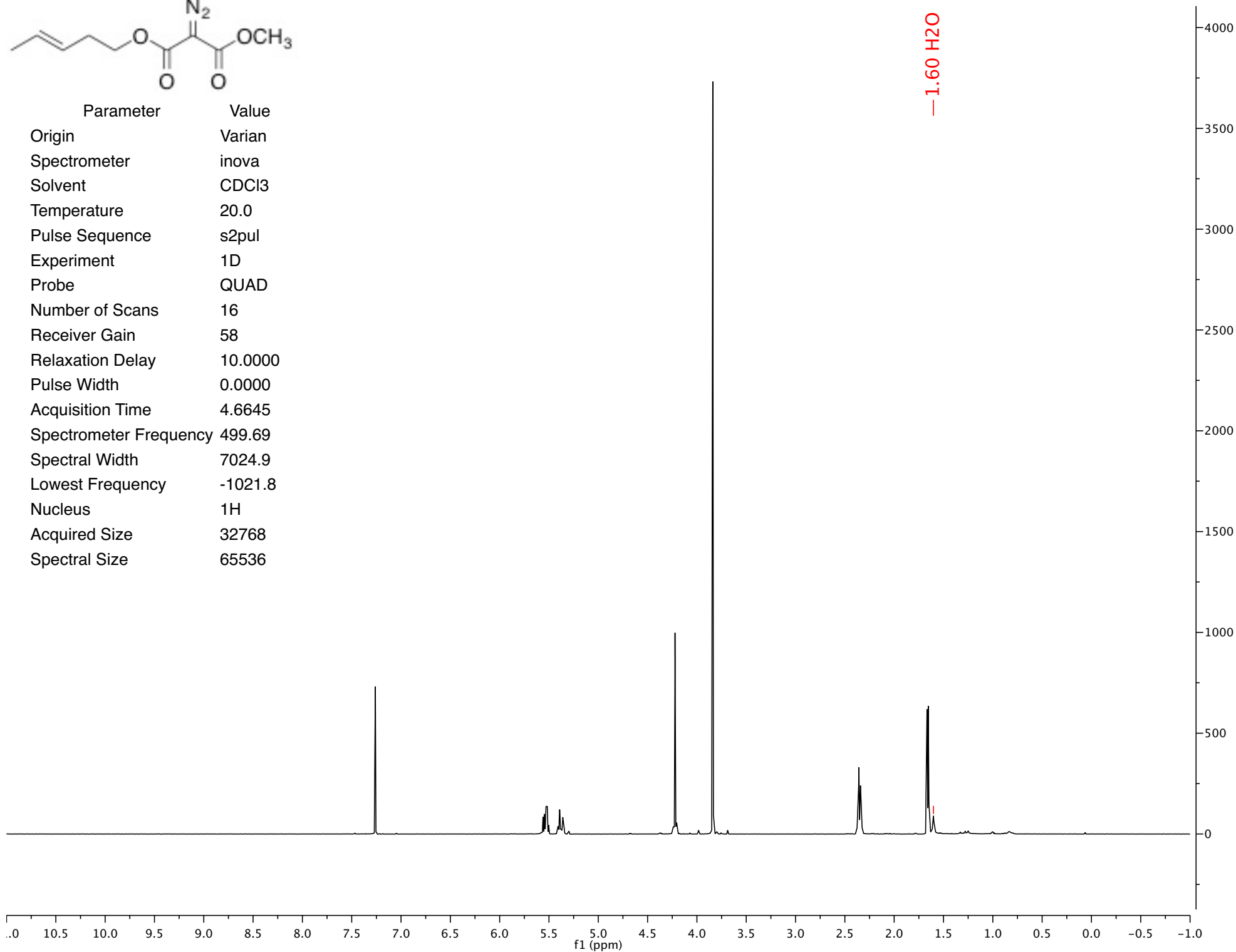


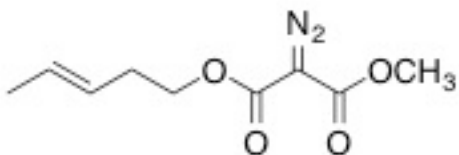
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Experiment	1D
Number of Scans	136
Receiver Gain	60
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Spectral Size	65536



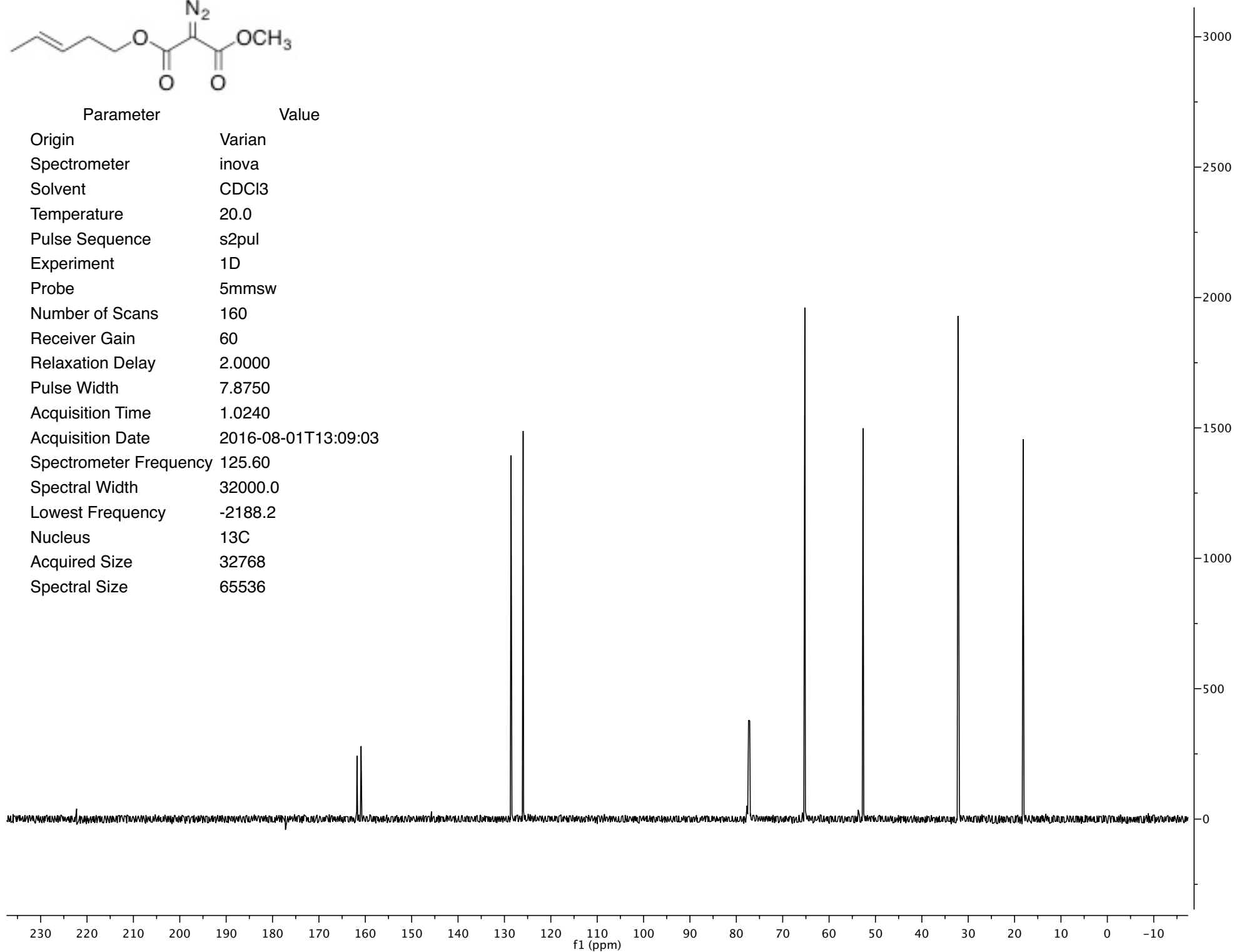


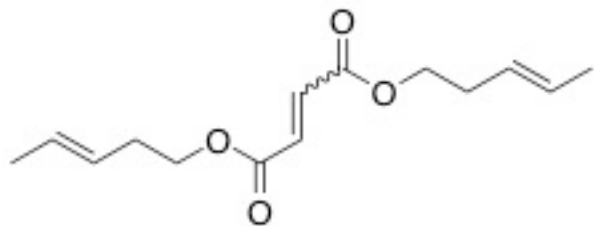
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Probe	QUAD
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Receiver Gain	58
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Pulse Width	0.0000
Acquisition Time	4.6645
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Lowest Frequency	-1021.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536





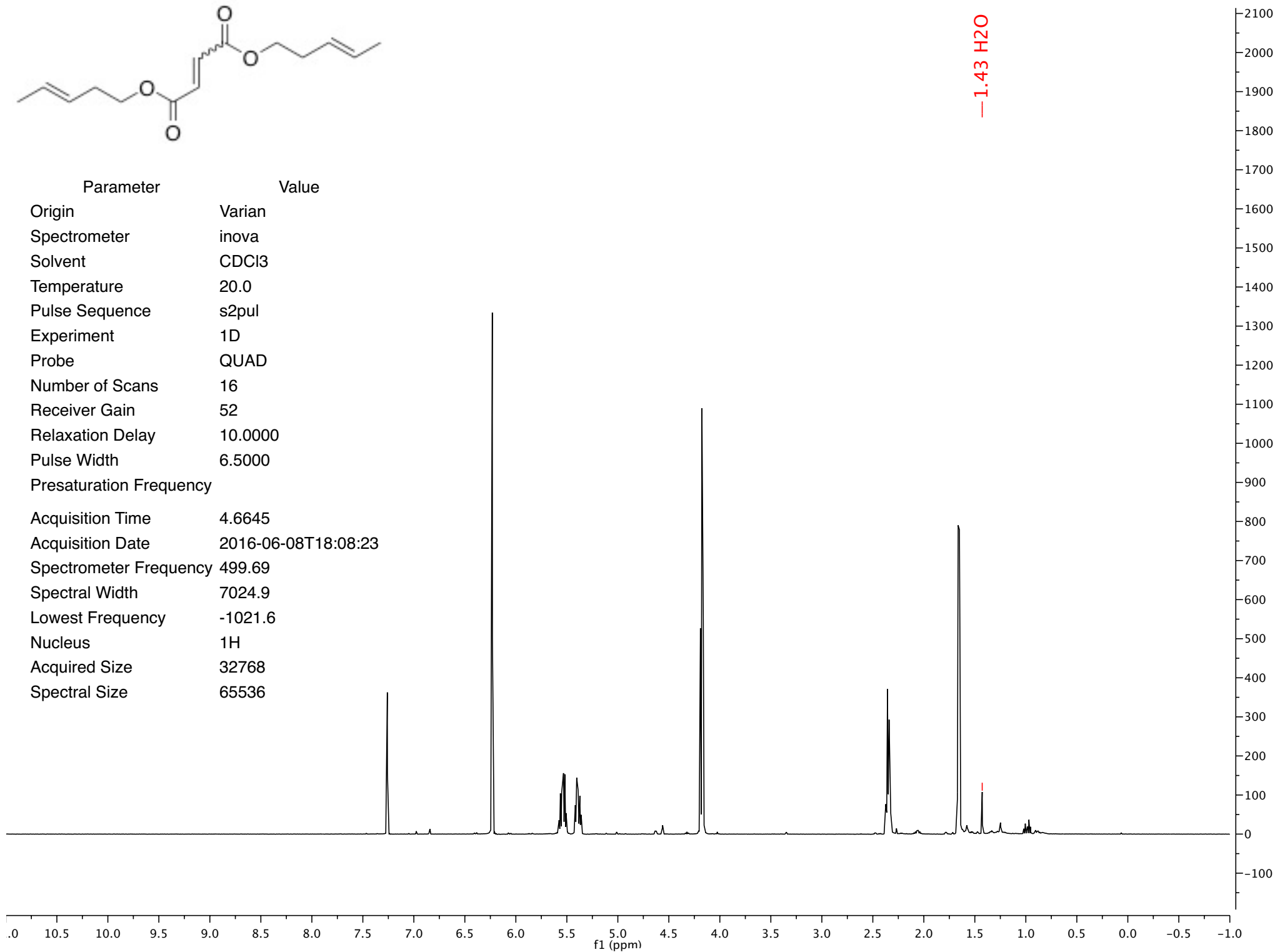
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Acquired Size	32768
Spectral Size	65536

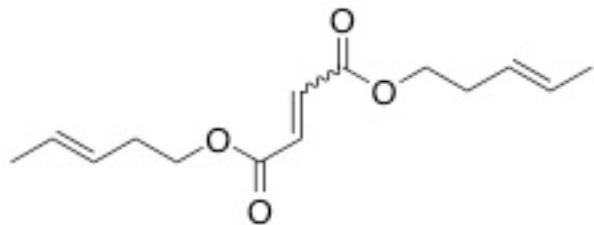




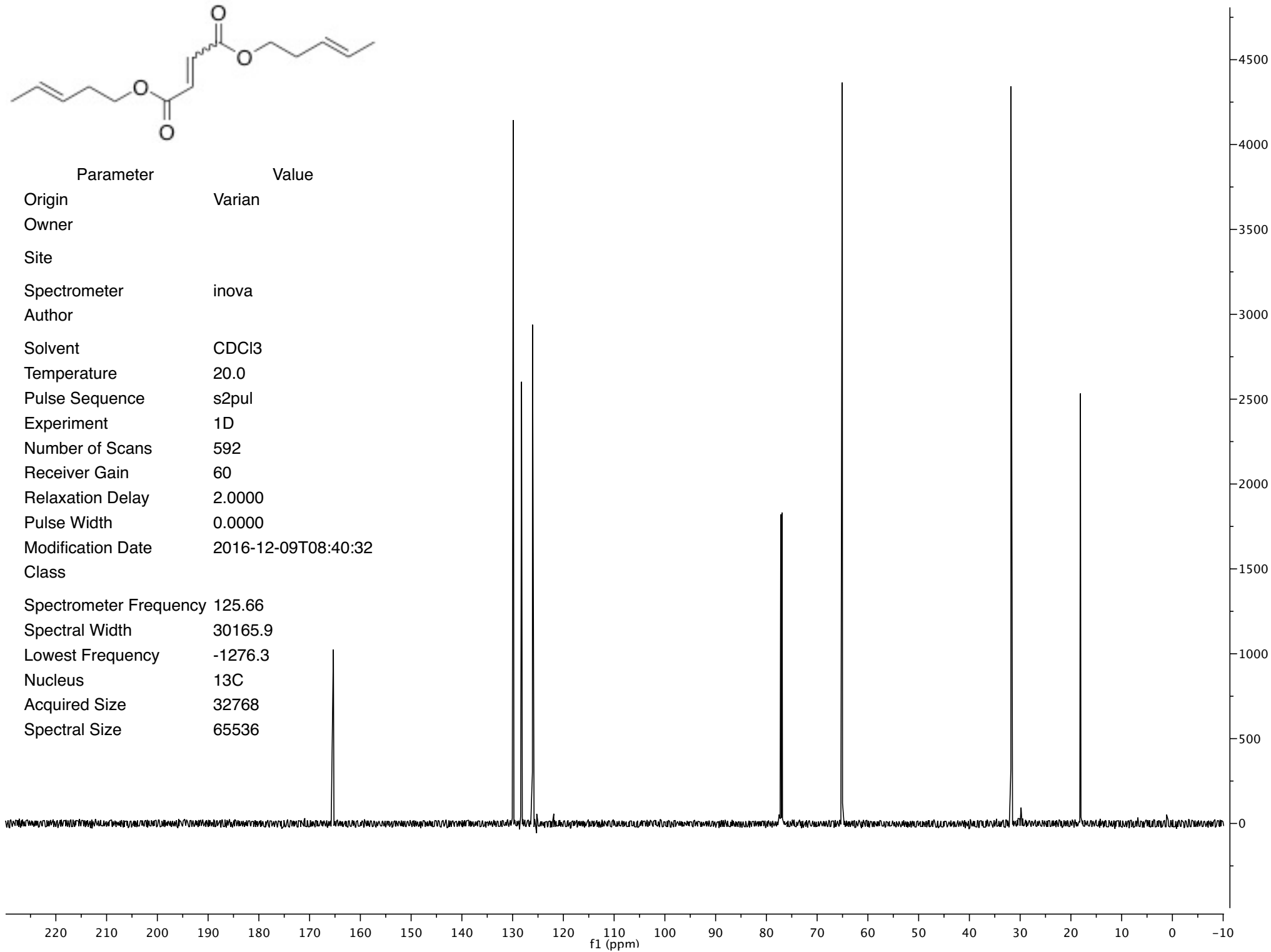
— 1.43 H₂O

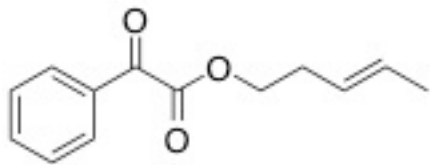
Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Probe	QUAD
Number of Scans	16
Receiver Gain	52
Relaxation Delay	10.0000
Pulse Width	6.5000
Presaturation Frequency	
Acquisition Time	4.6645
Acquisition Date	2016-06-08T18:08:23
Spectrometer Frequency	499.69
Spectral Width	7024.9
Lowest Frequency	-1021.6
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



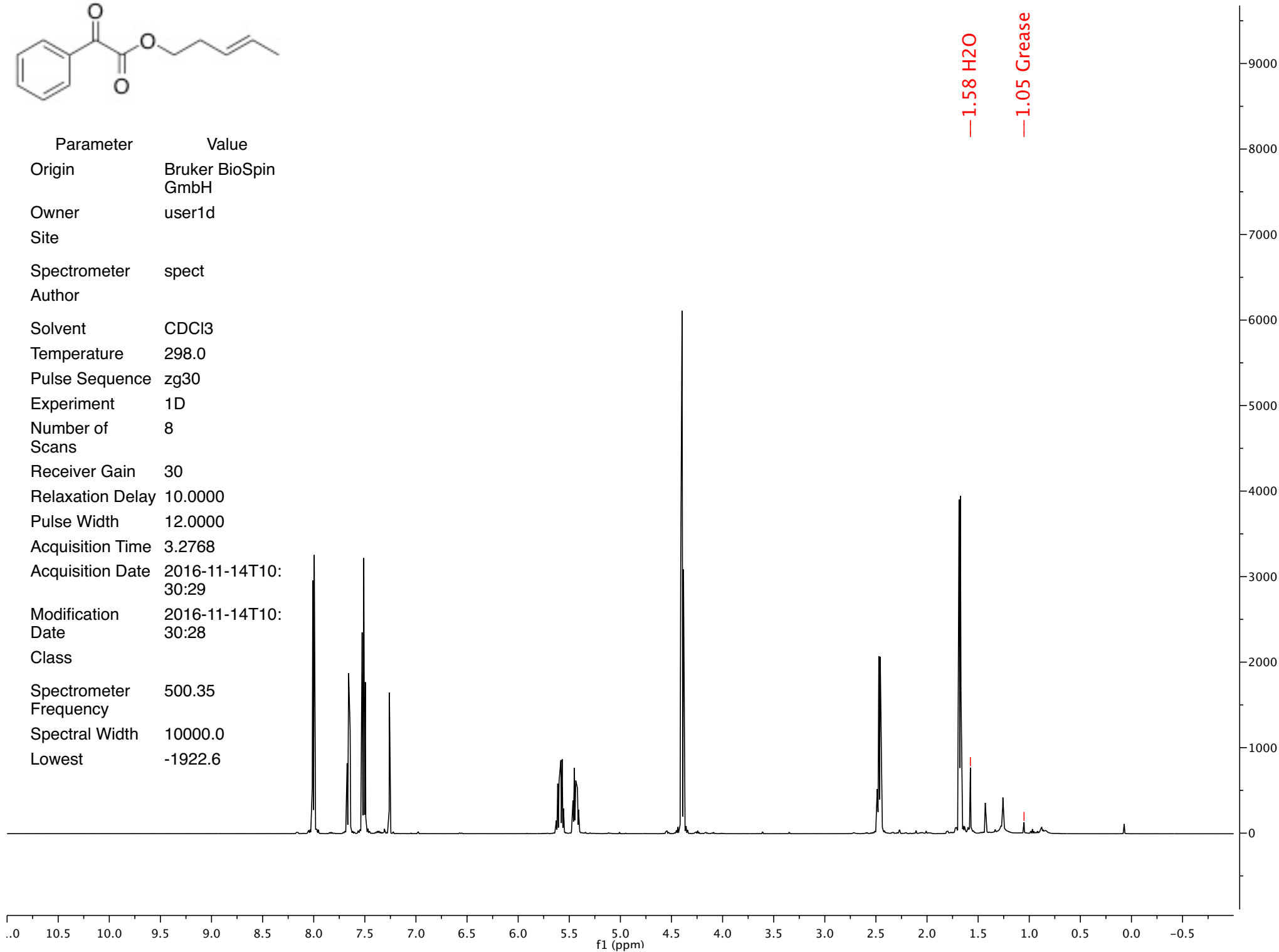


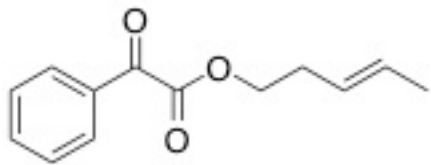
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	592
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-12-09T08:40:32
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1276.3
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



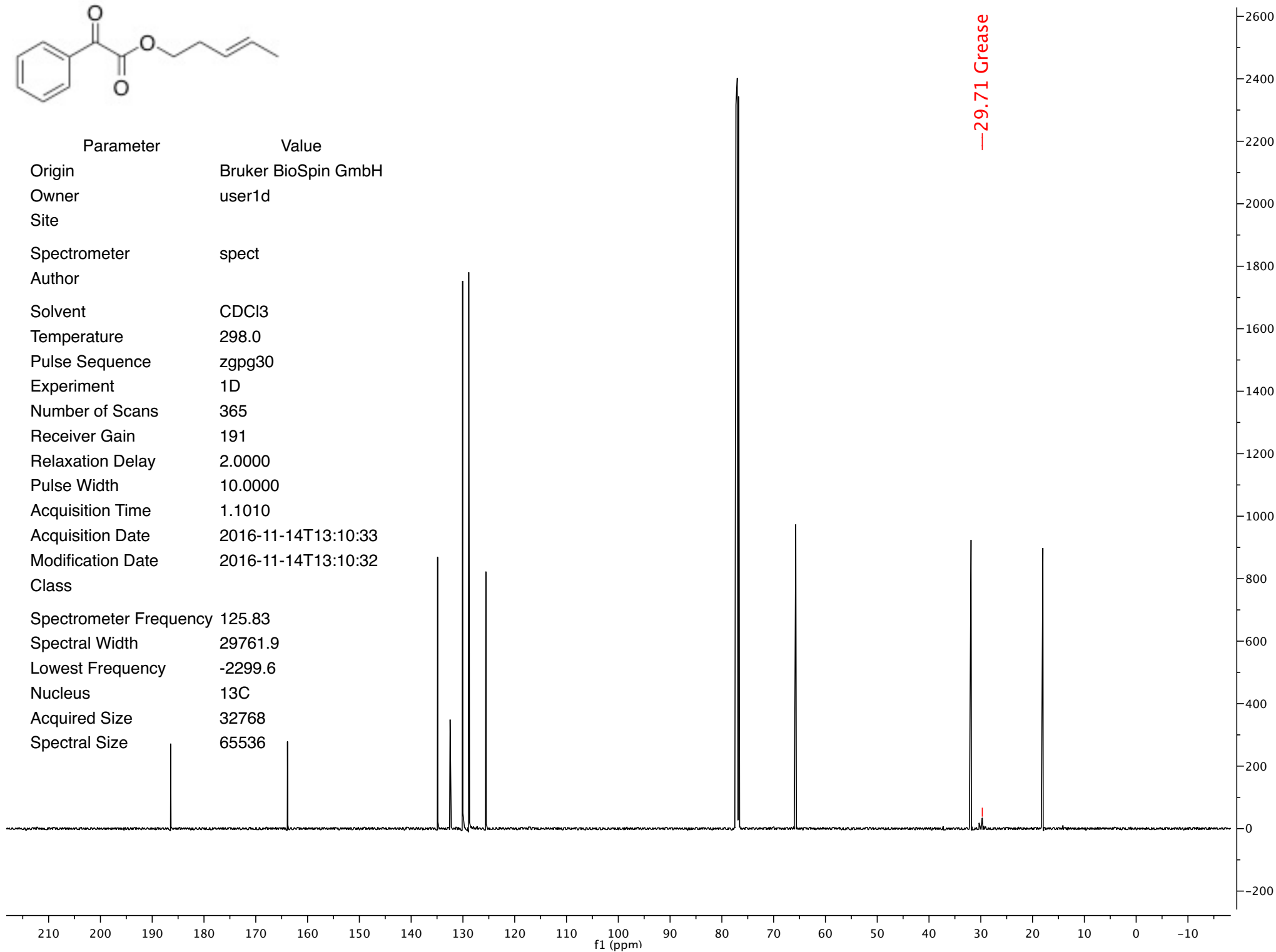


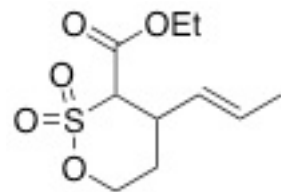
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	8
Receiver Gain	30
Relaxation Delay	10.0000
Pulse Width	12.0000
Acquisition Time	3.2768
Acquisition Date	2016-11-14T10:30:29
Modification Date	2016-11-14T10:30:28
Class	
Spectrometer Frequency	500.35
Spectral Width	10000.0
Lowest	-1922.6





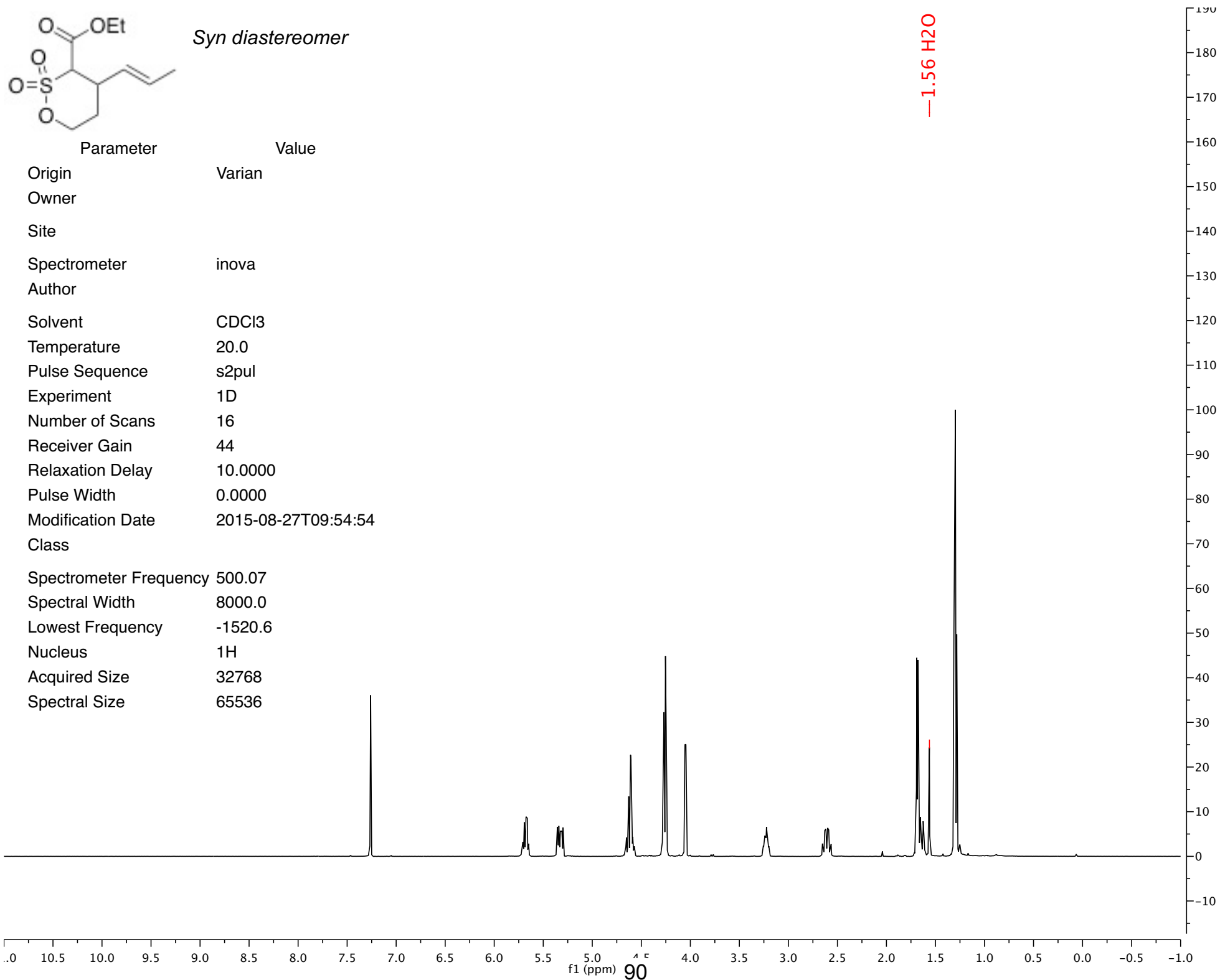
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	365
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-11-14T13:10:33
Modification Date	2016-11-14T13:10:32
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2299.6
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

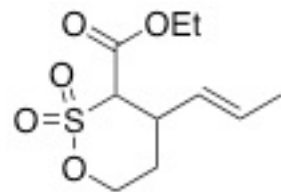




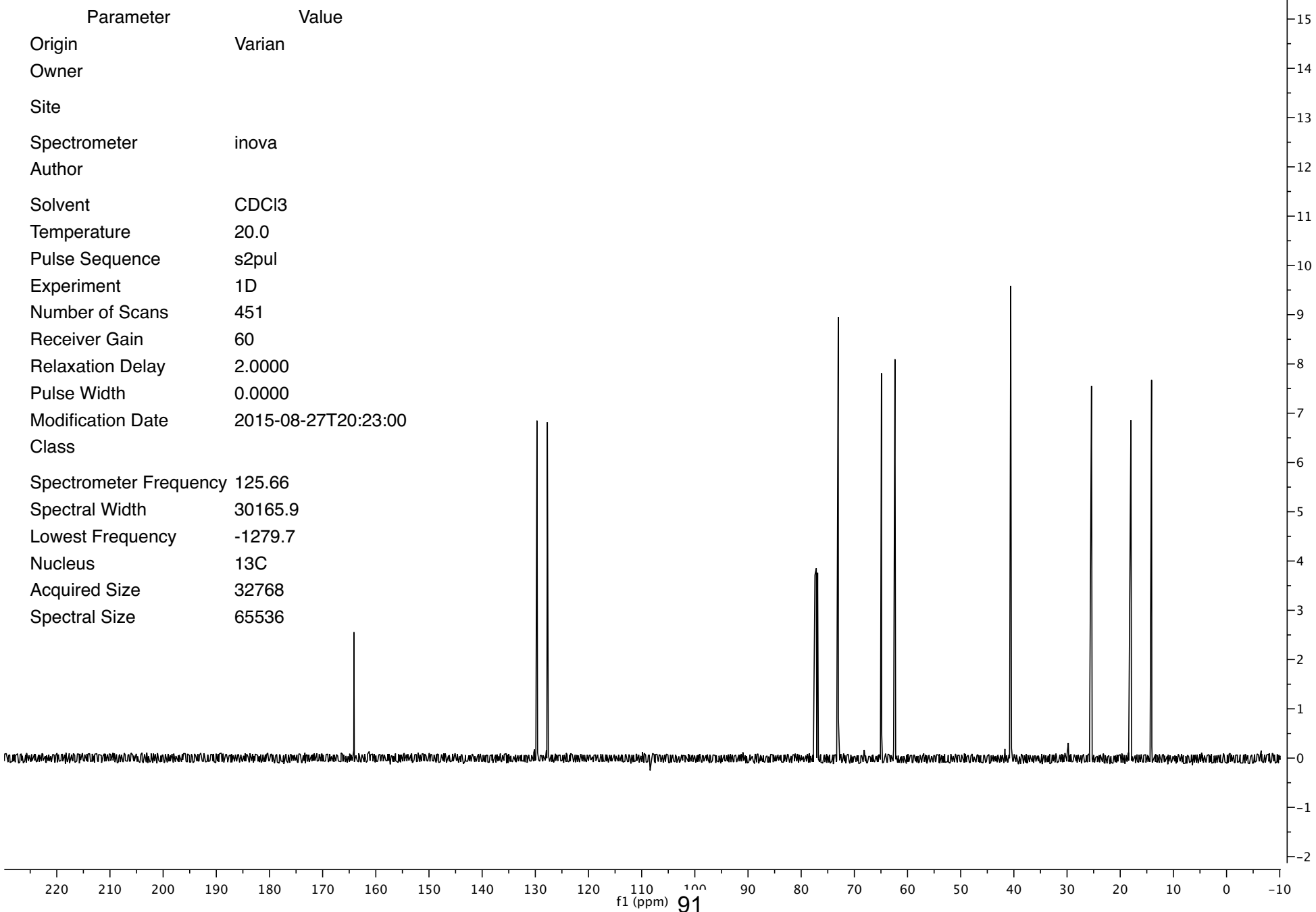
Syn diastereomer

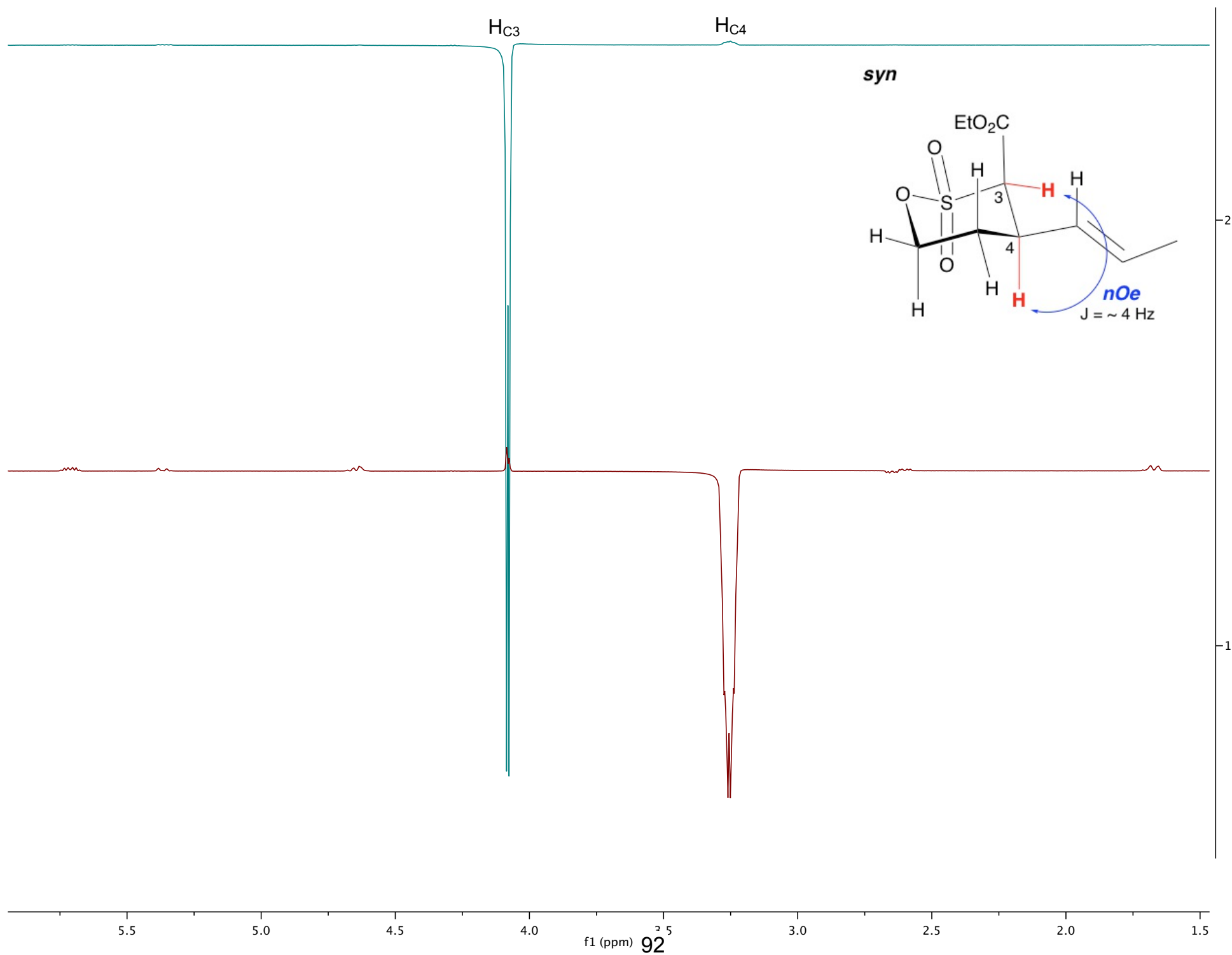
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	44
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2015-08-27T09:54:54
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1520.6
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

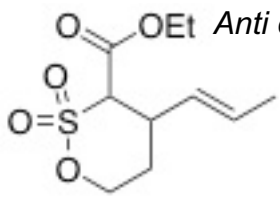




Syn diastereomer



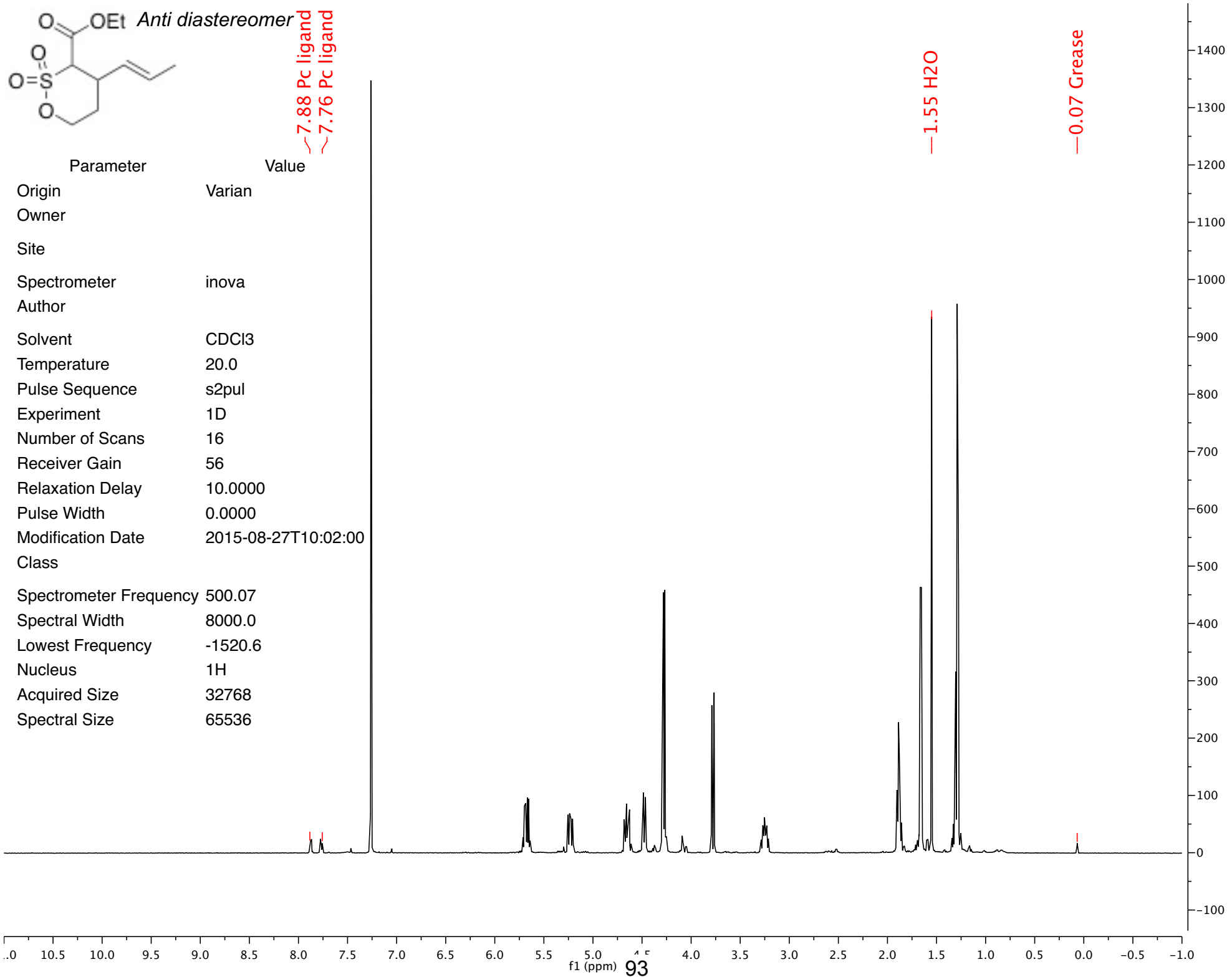


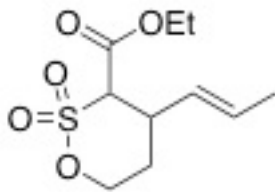


Anti diastereomer

~7.88 Pc ligand
~7.76 Pc ligand

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	56
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2015-08-27T10:02:00
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1520.6
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



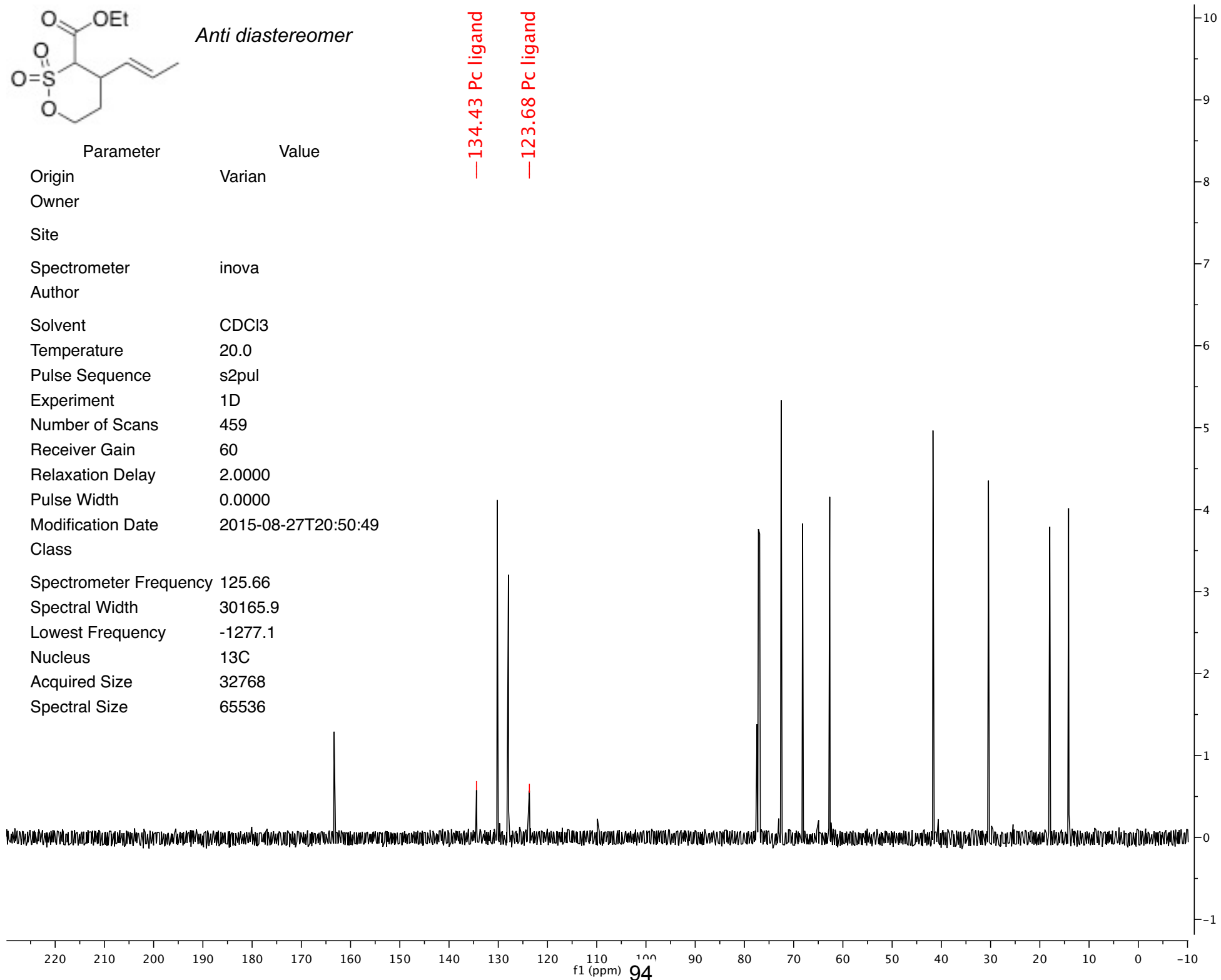


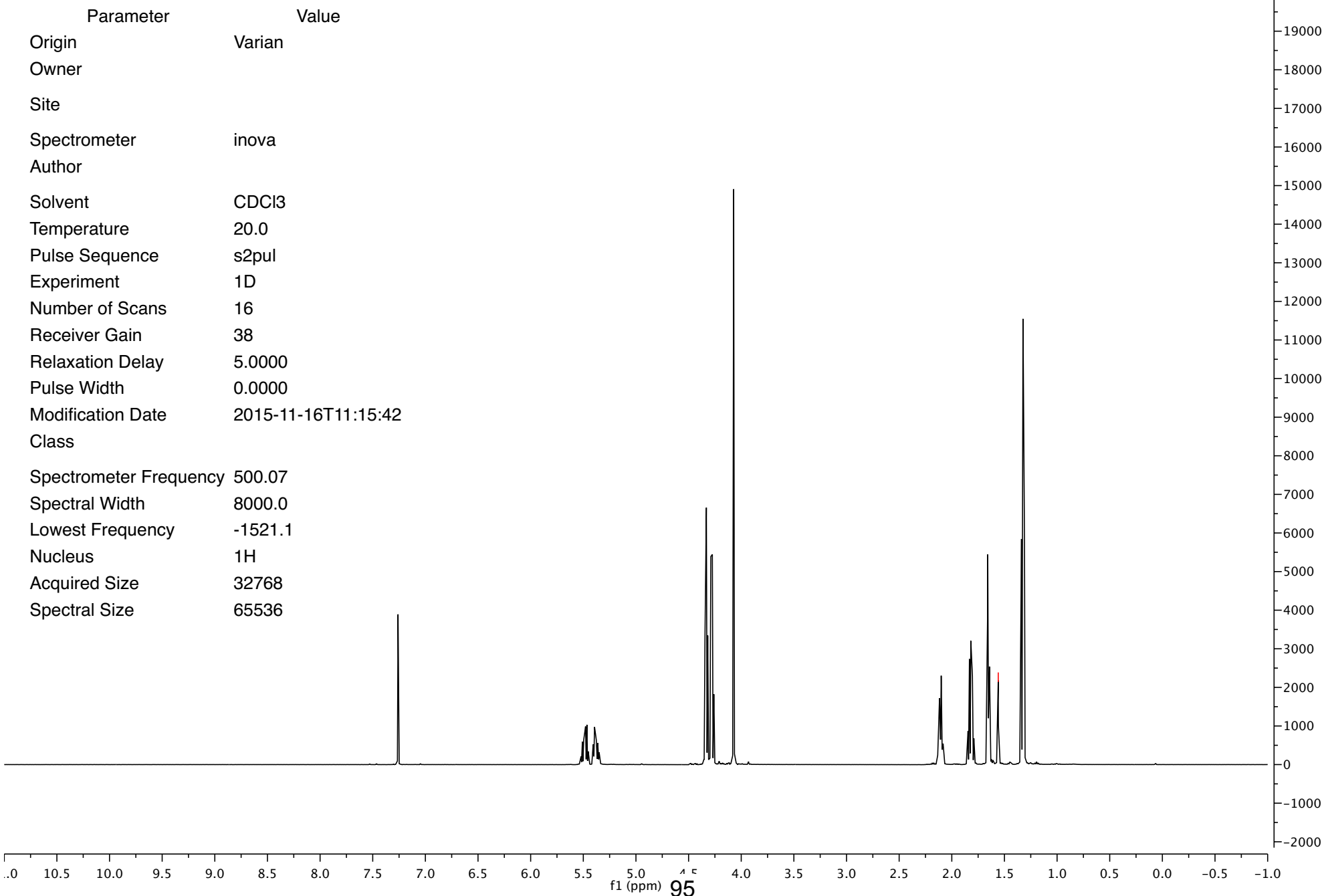
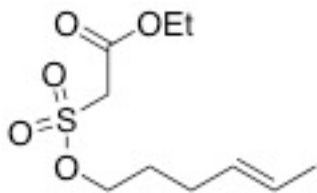
Anti diastereomer

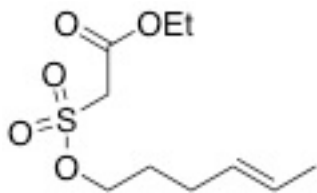
— 134.43 Pc ligand

— 123.68 Pc ligand

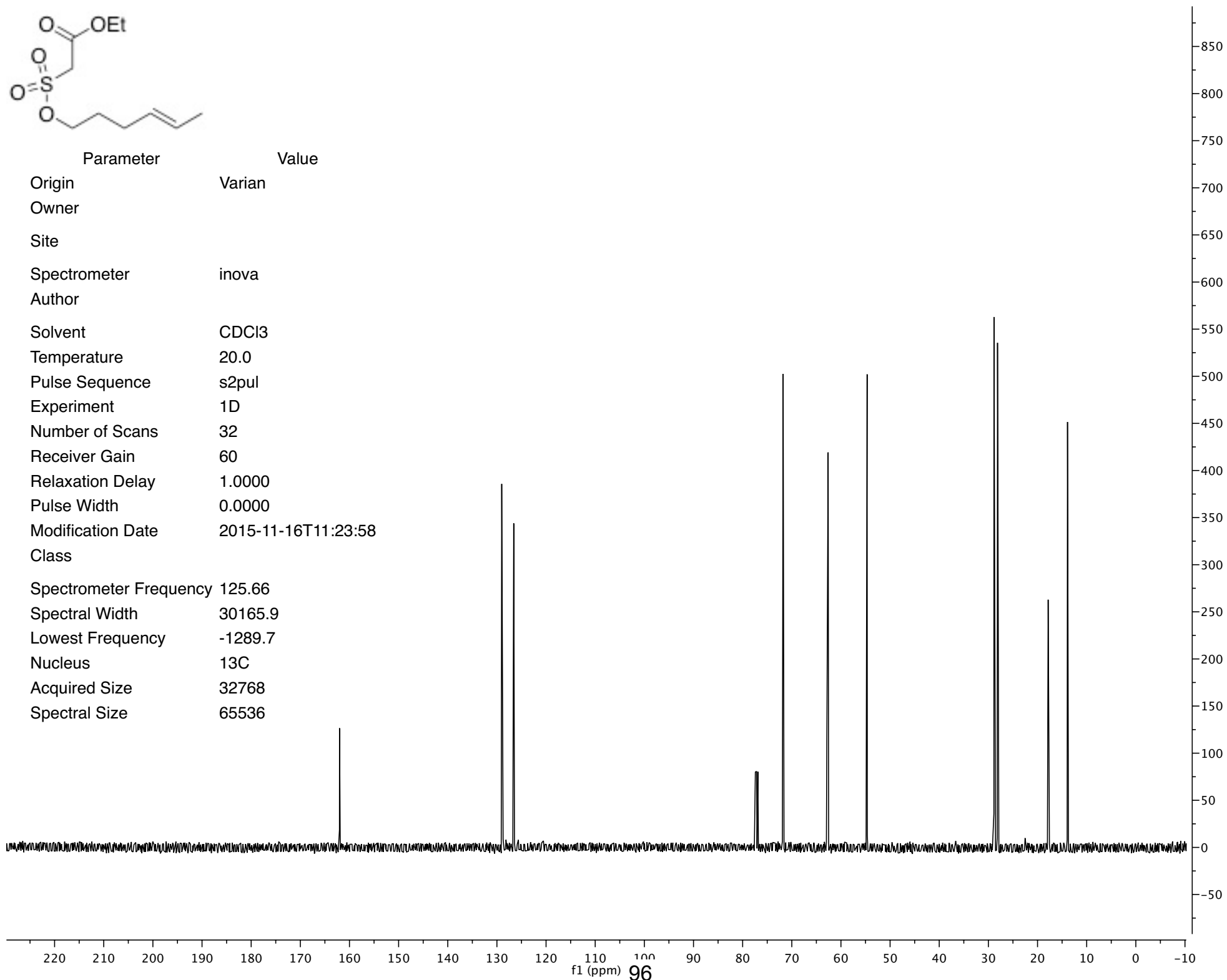
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	459
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2015-08-27T20:50:49
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1277.1
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

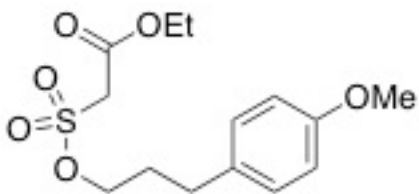




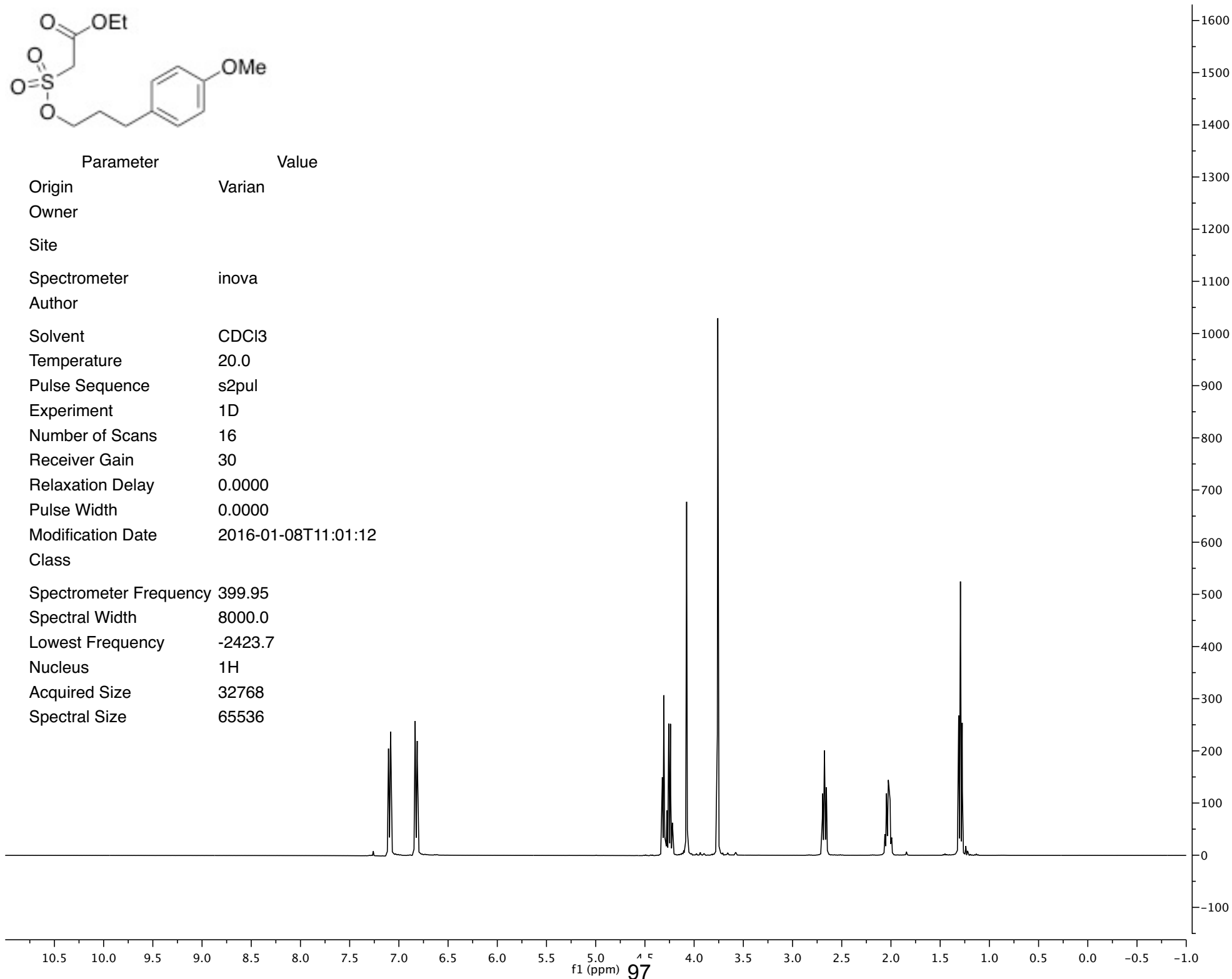


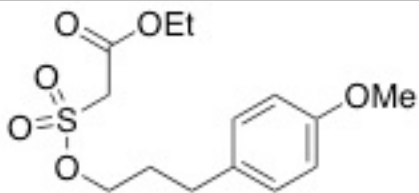
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	32
Receiver Gain	60
Relaxation Delay	1.0000
Pulse Width	0.0000
Modification Date	2015-11-16T11:23:58
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1289.7
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



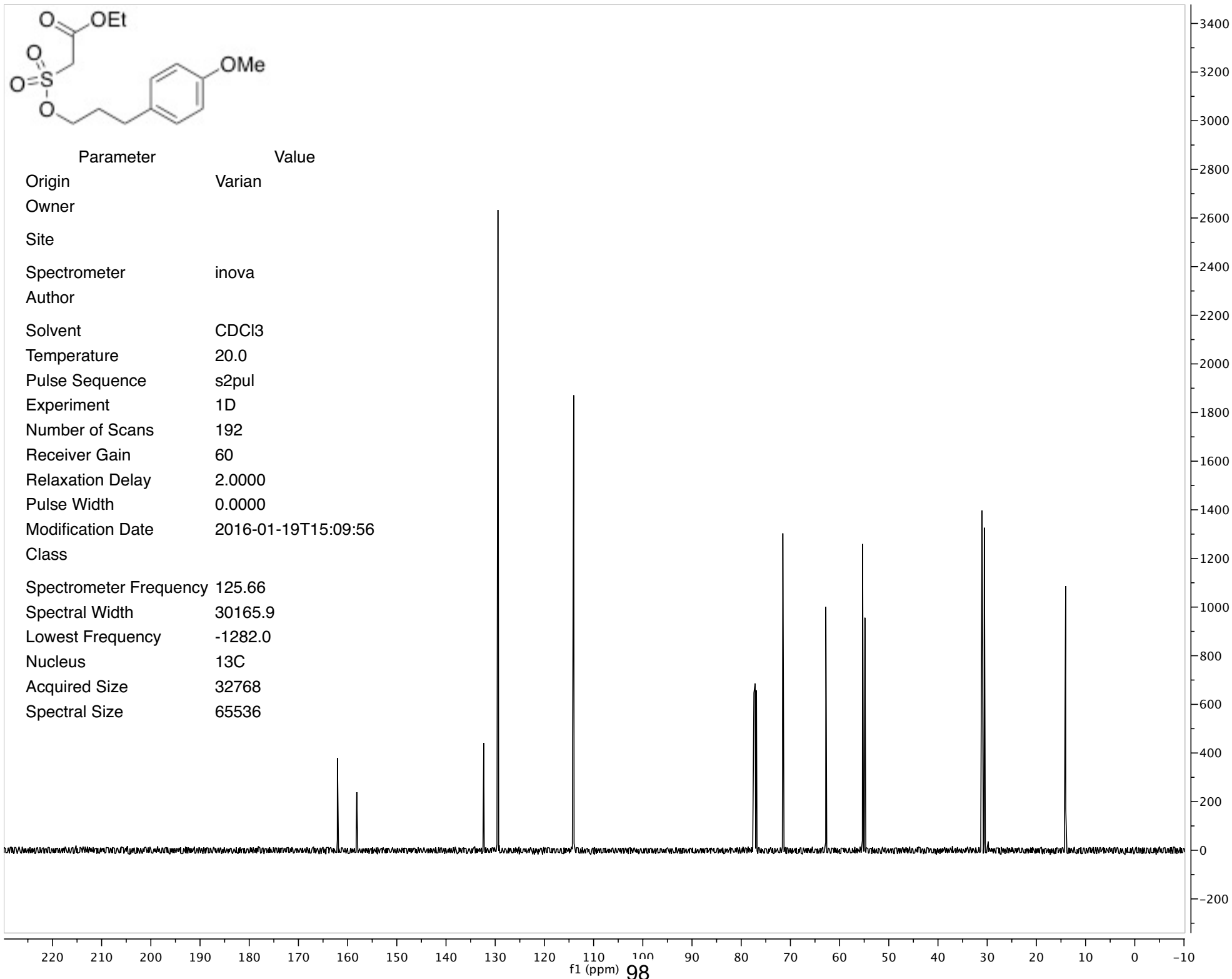


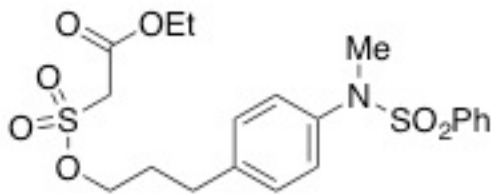
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	30
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-01-08T11:01:12
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2423.7
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



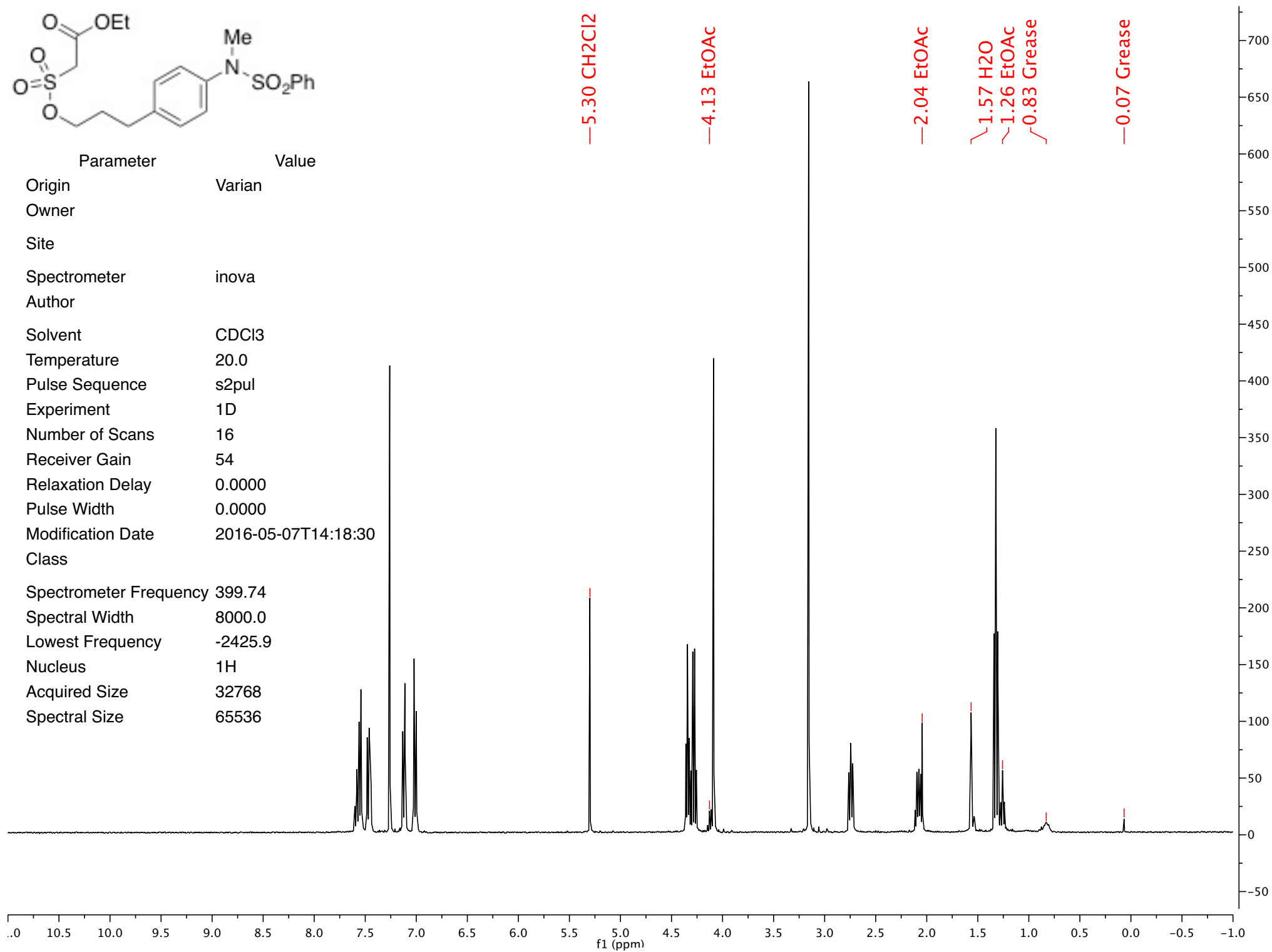


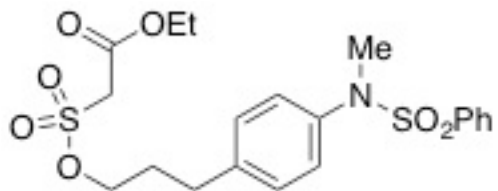
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	192
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-01-19T15:09:56
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1282.0
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



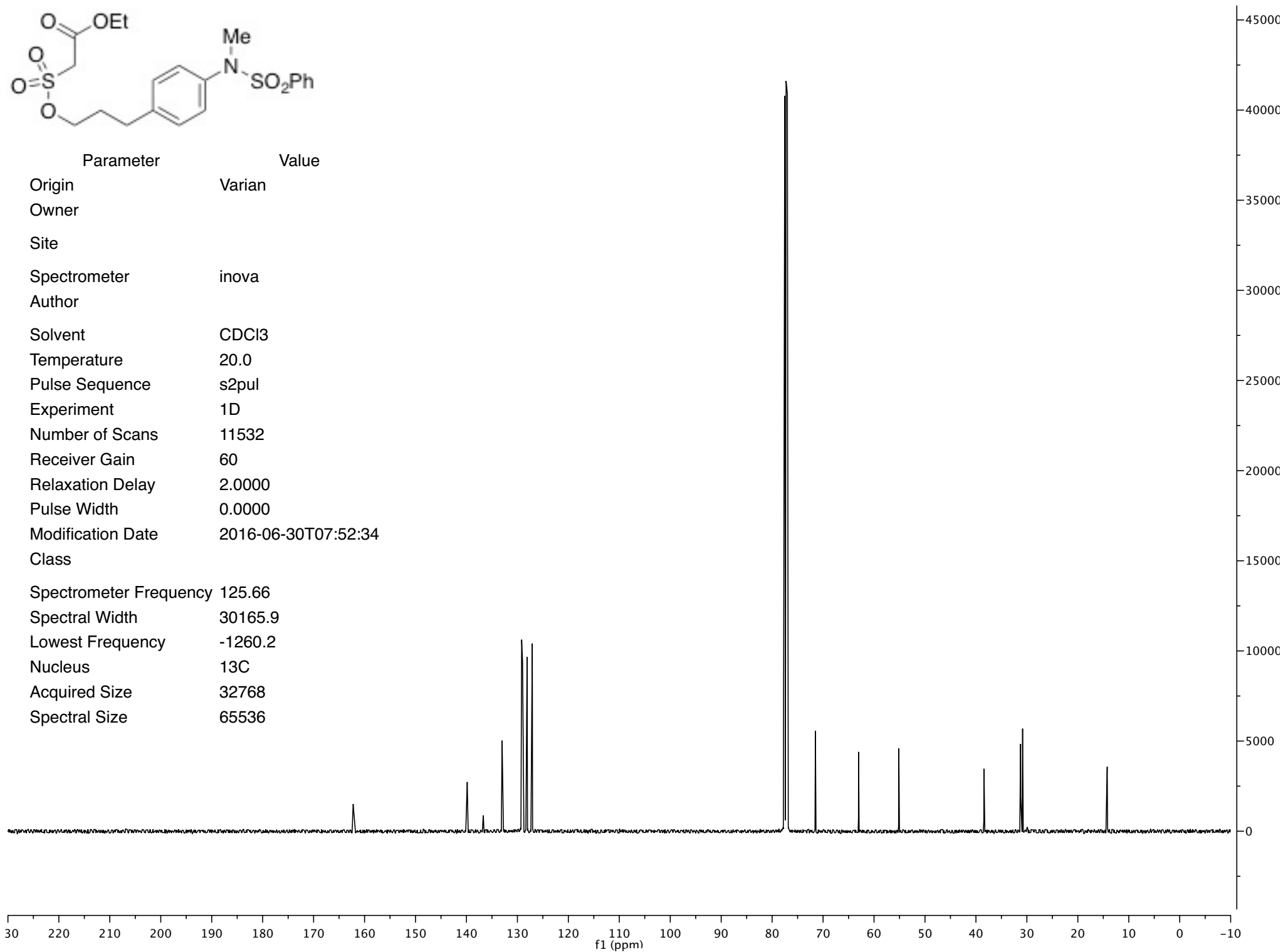


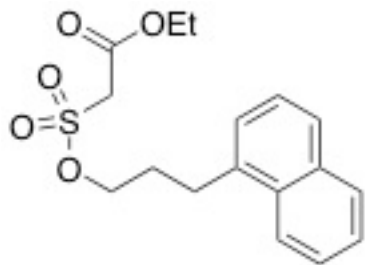
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	54
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-05-07T14:18:30
Class	
Spectrometer Frequency	399.74
Spectral Width	8000.0
Lowest Frequency	-2425.9
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



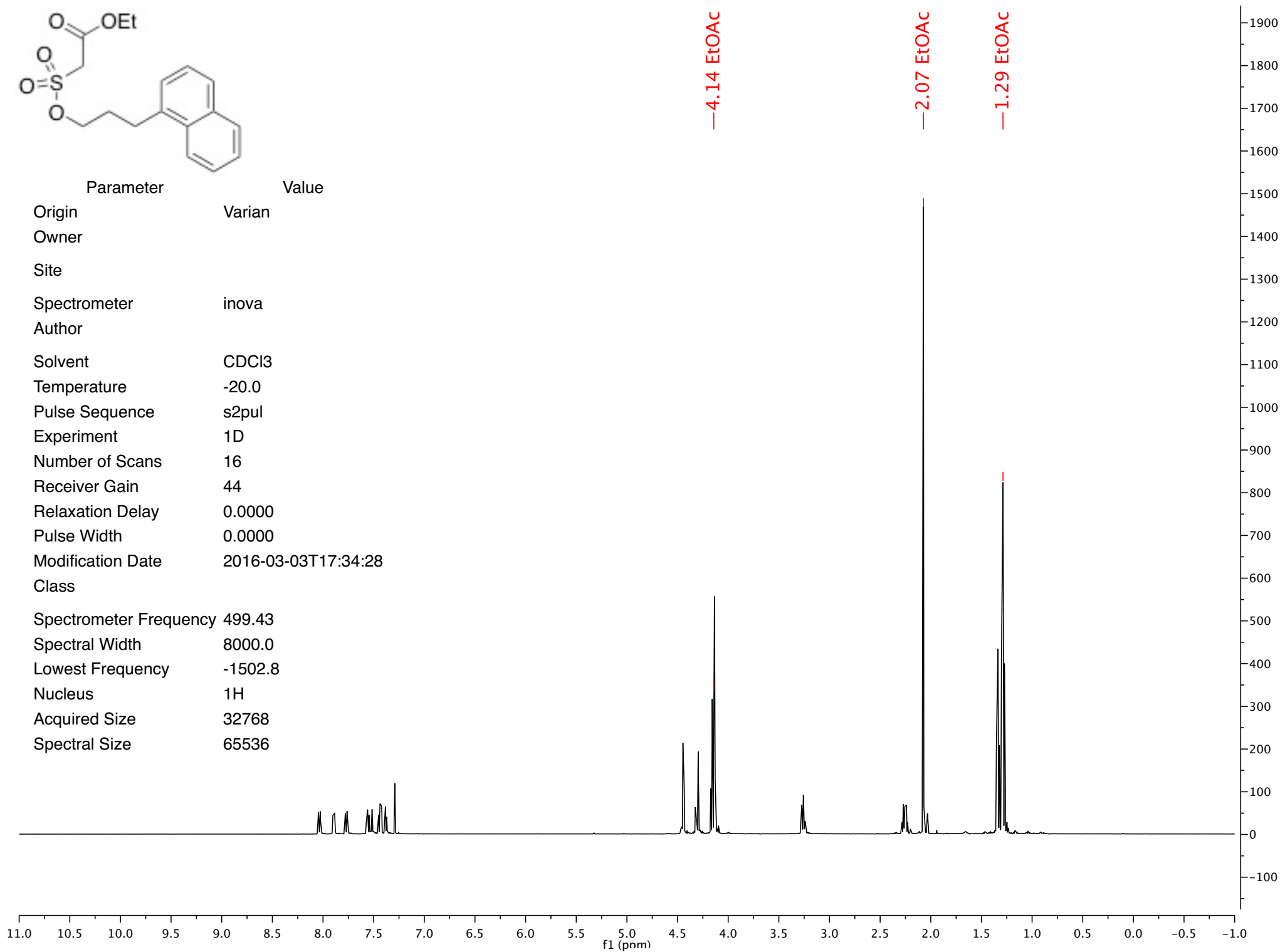


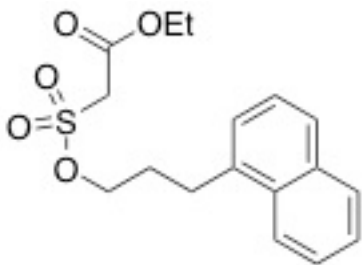
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	11532
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-06-30T07:52:34
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



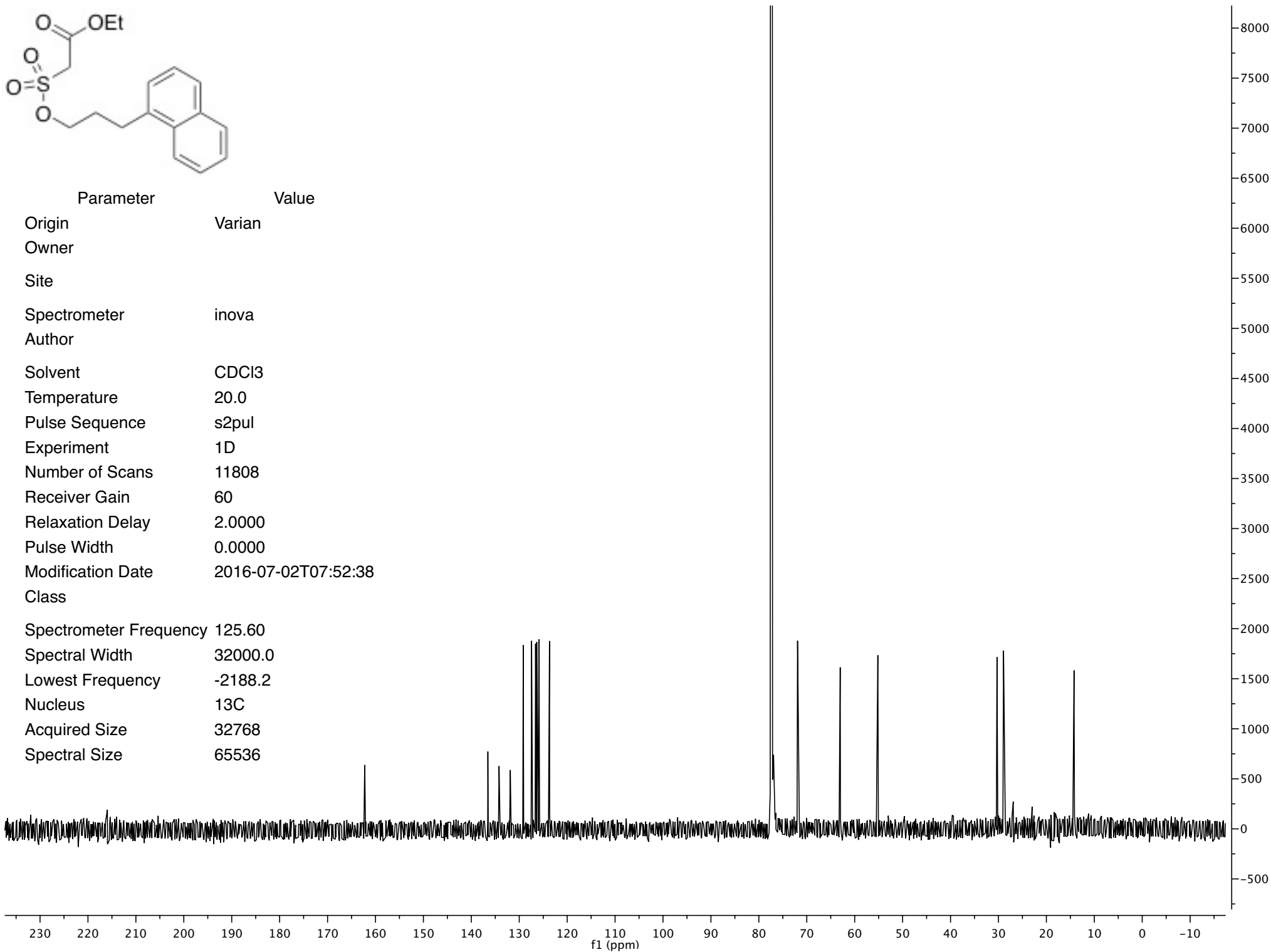


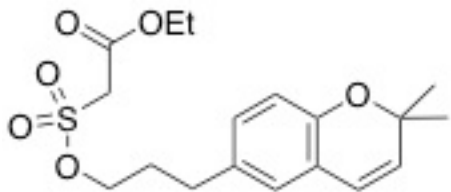
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	-20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	44
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-03-03T17:34:28
Class	
Spectrometer Frequency	499.43
Spectral Width	8000.0
Lowest Frequency	-1502.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536





Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	11808
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-07-02T07:52:38
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2188.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

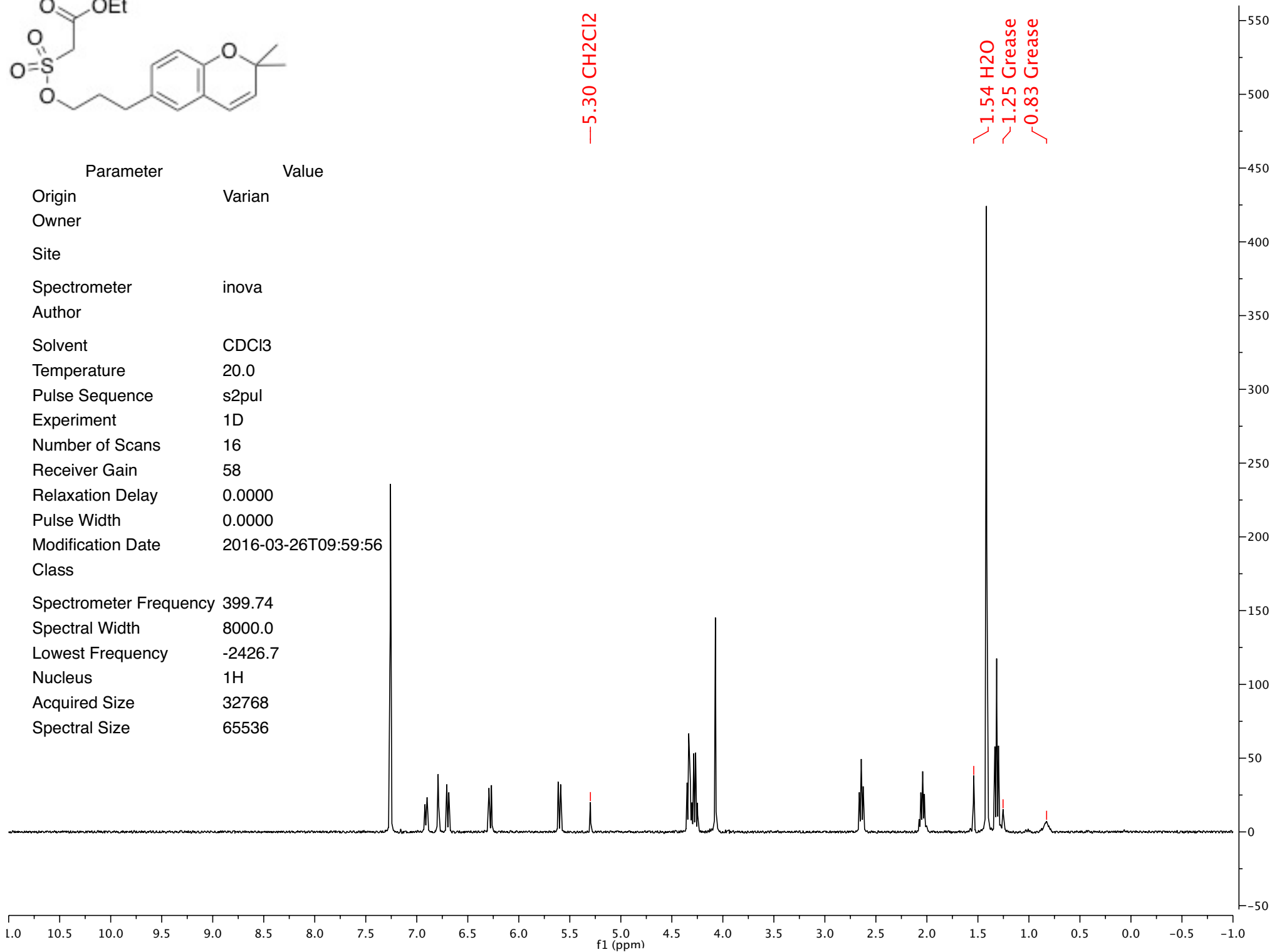


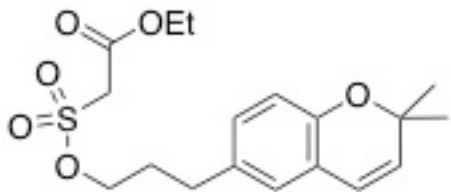


— 5.30 CH₂Cl₂

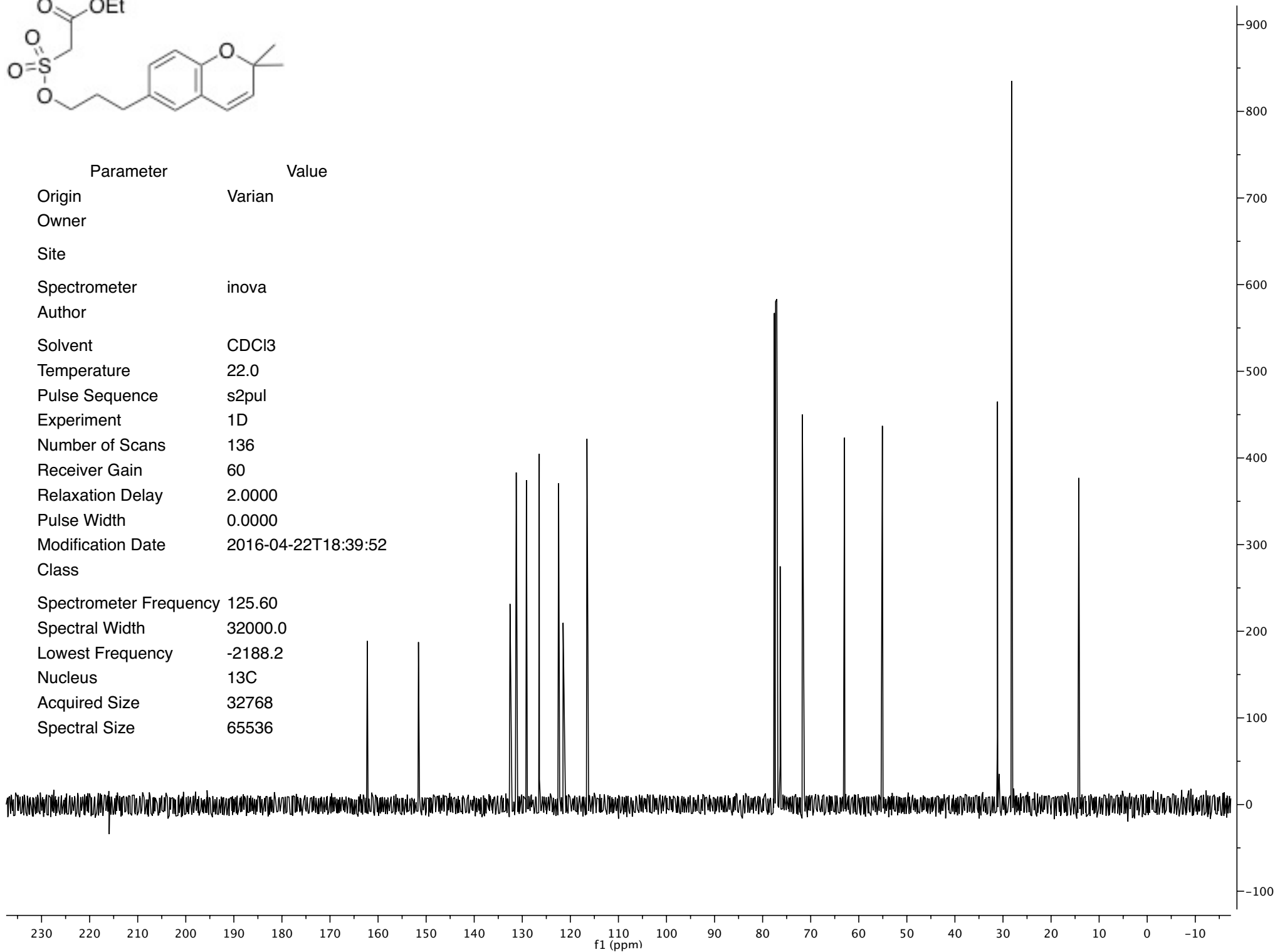
1.54 H₂O
1.25 Grease
0.83 Grease

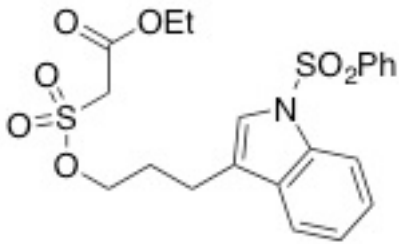
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	58
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-03-26T09:59:56
Class	
Spectrometer Frequency	399.74
Spectral Width	8000.0
Lowest Frequency	-2426.7
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



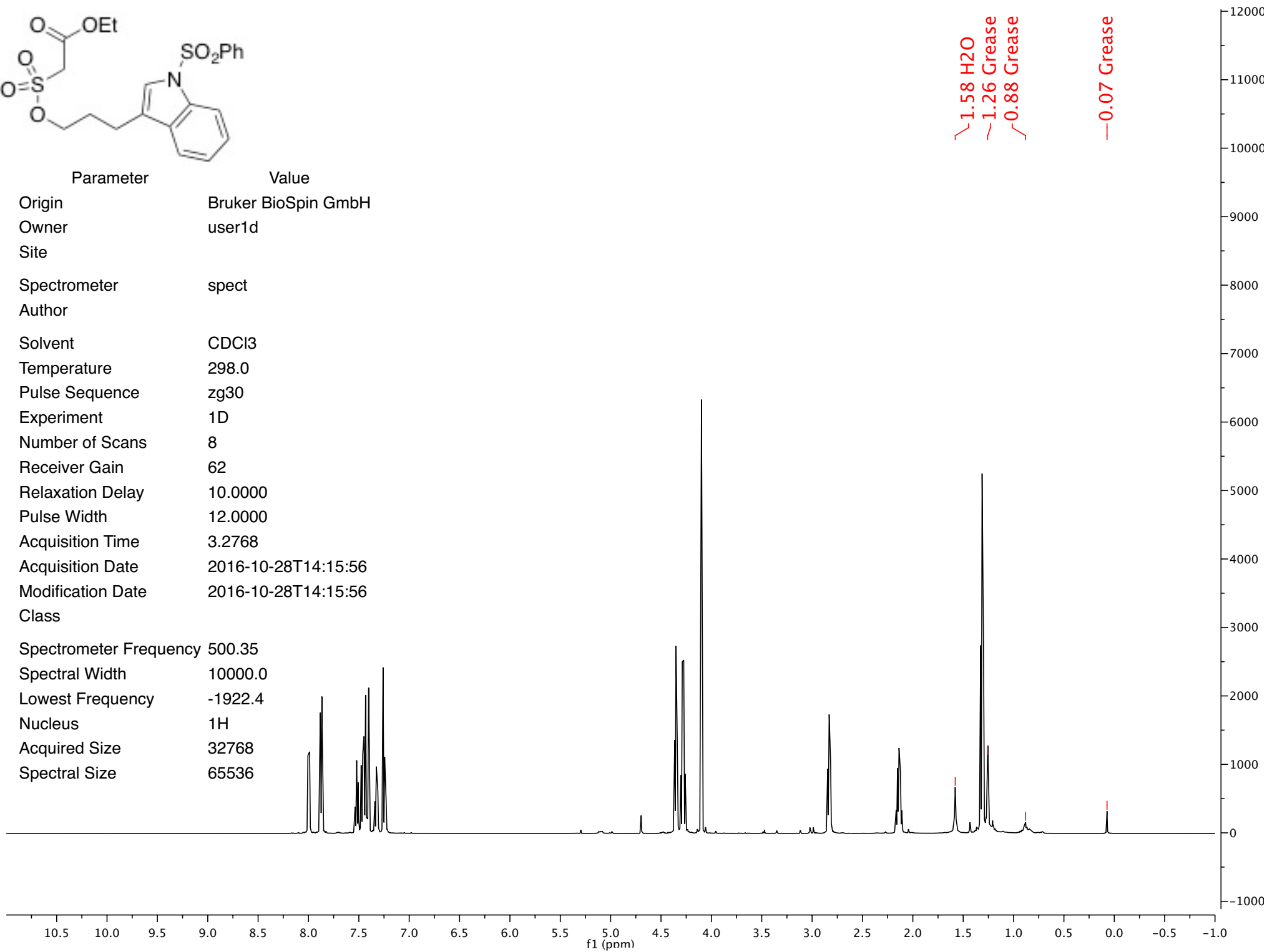


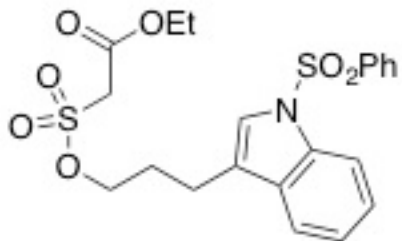
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	22.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	136
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-04-22T18:39:52
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2188.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



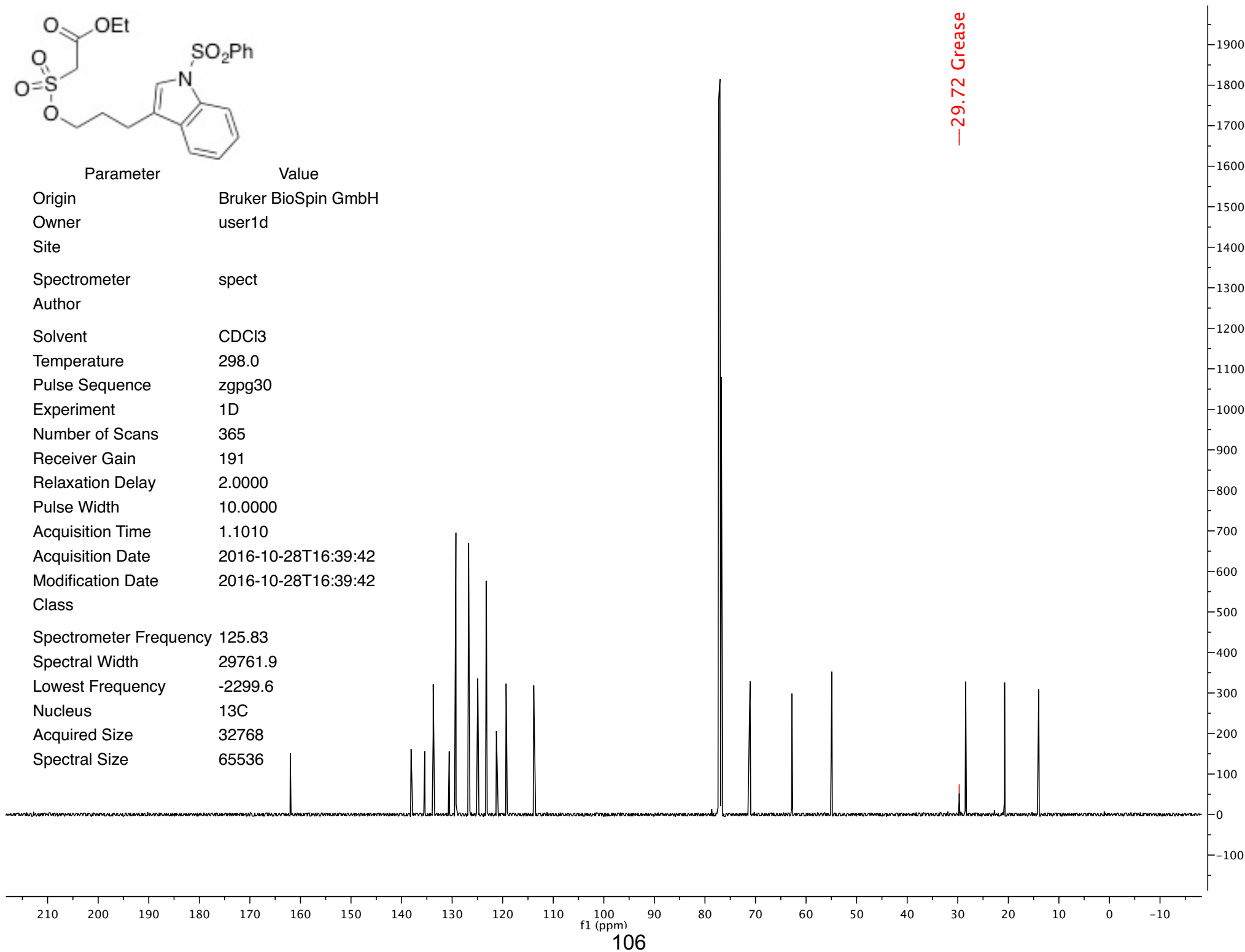


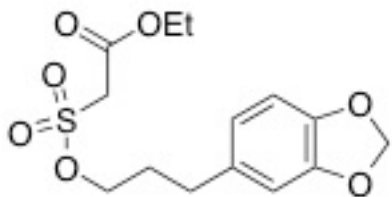
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	8
Receiver Gain	62
Relaxation Delay	10.0000
Pulse Width	12.0000
Acquisition Time	3.2768
Acquisition Date	2016-10-28T14:15:56
Modification Date	2016-10-28T14:15:56
Class	
Spectrometer Frequency	500.35
Spectral Width	10000.0
Lowest Frequency	-1922.4
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



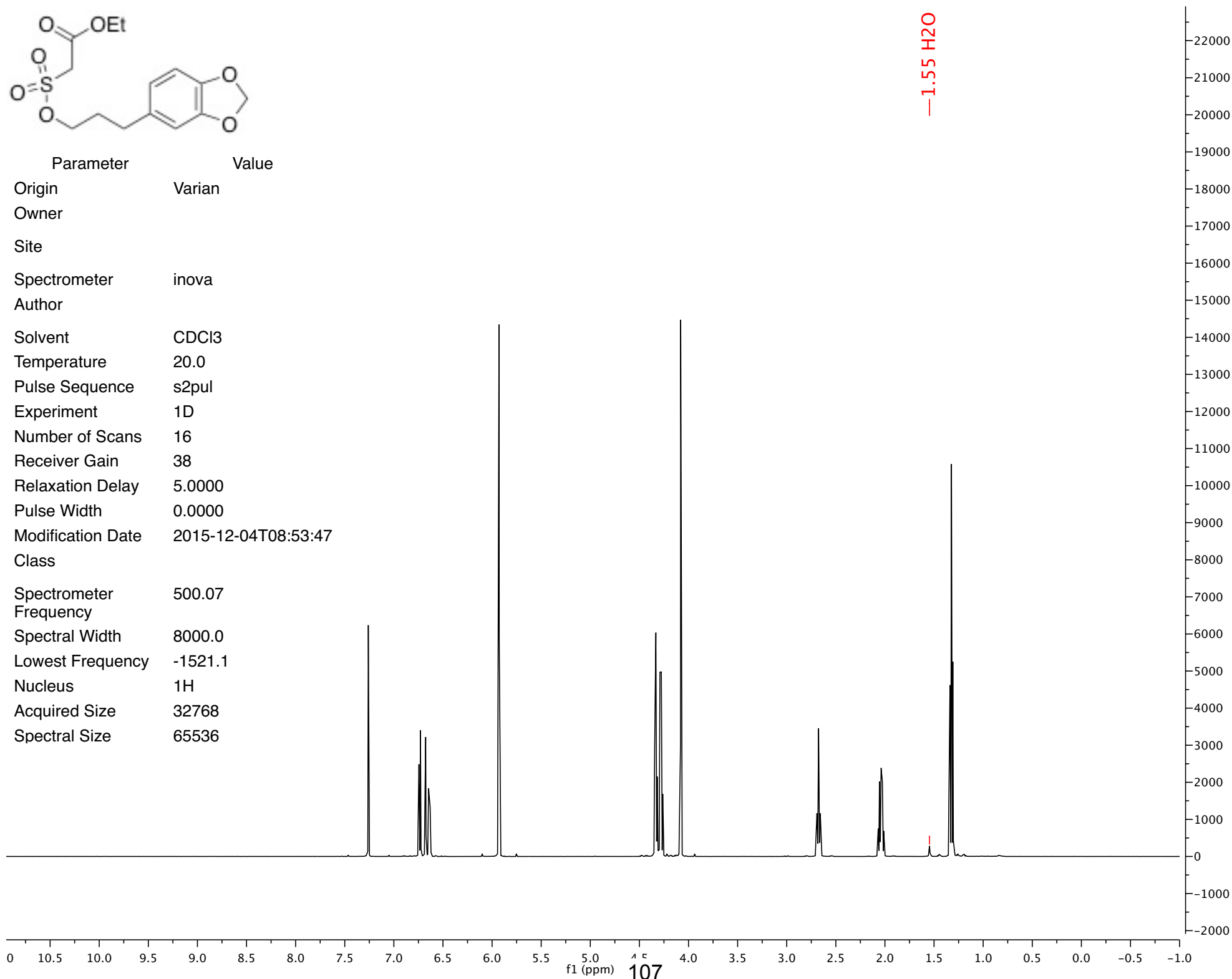


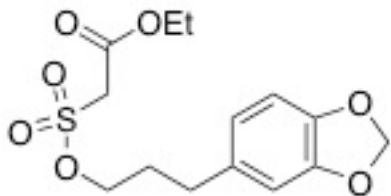
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	365
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-28T16:39:42
Modification Date	2016-10-28T16:39:42
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2299.6
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



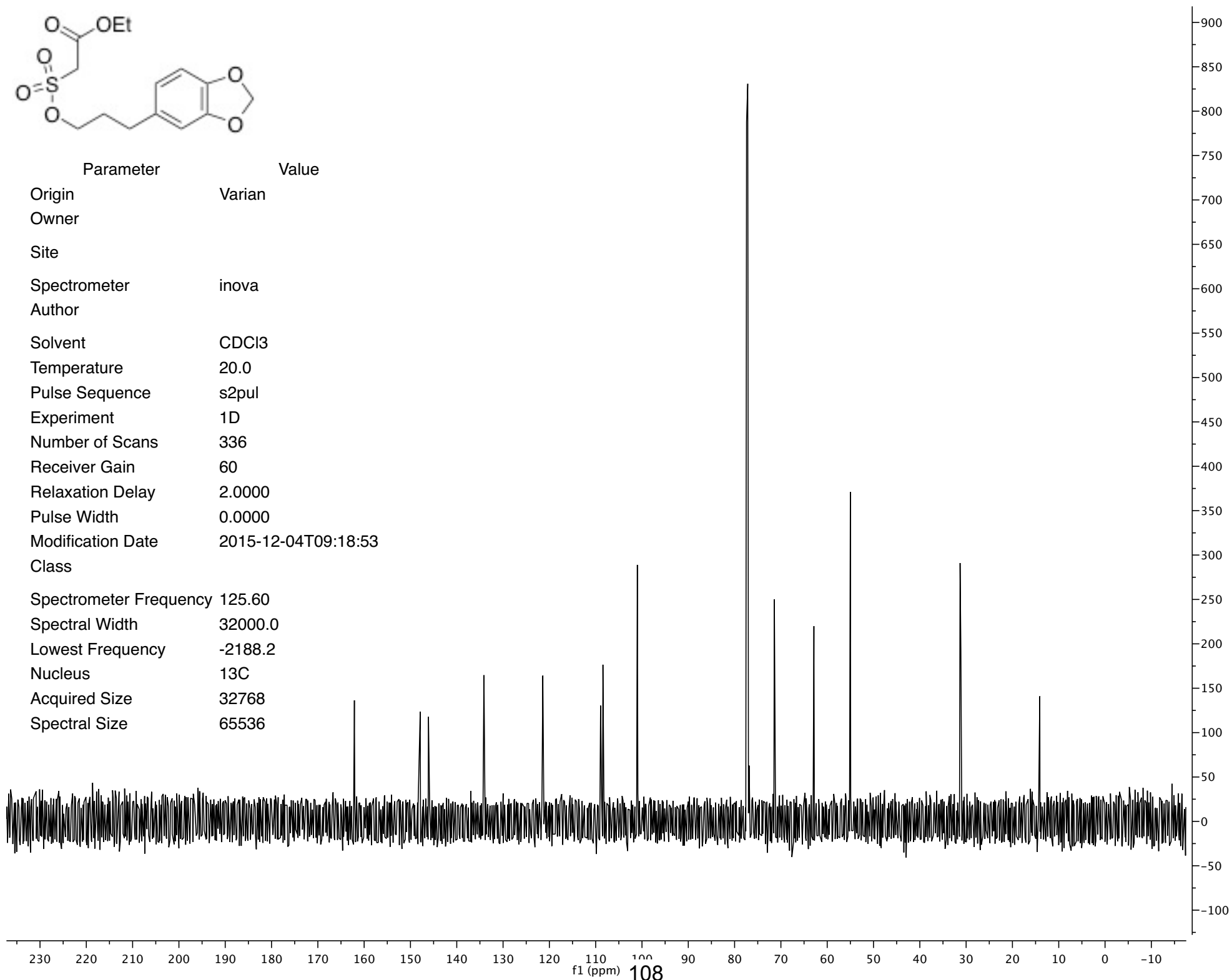


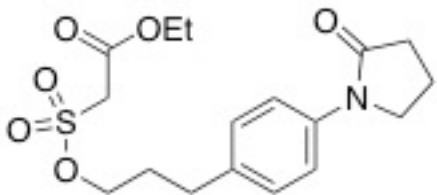
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	38
Relaxation Delay	5.0000
Pulse Width	0.0000
Modification Date	2015-12-04T08:53:47
Class	
Spectrometer	500.07
Frequency	
Spectral Width	8000.0
Lowest Frequency	-1521.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



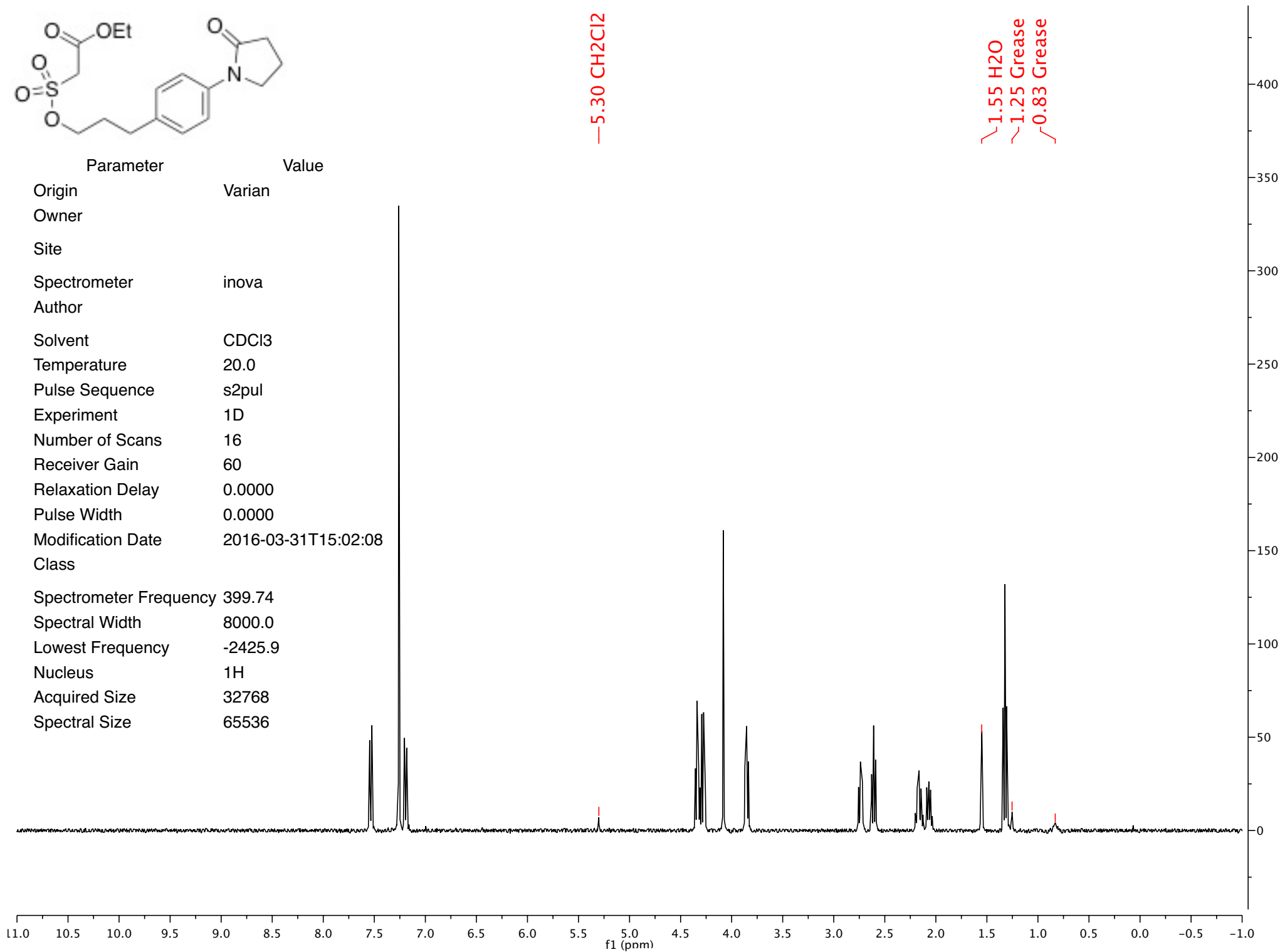


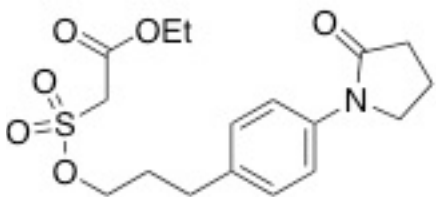
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	336
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2015-12-04T09:18:53
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2188.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



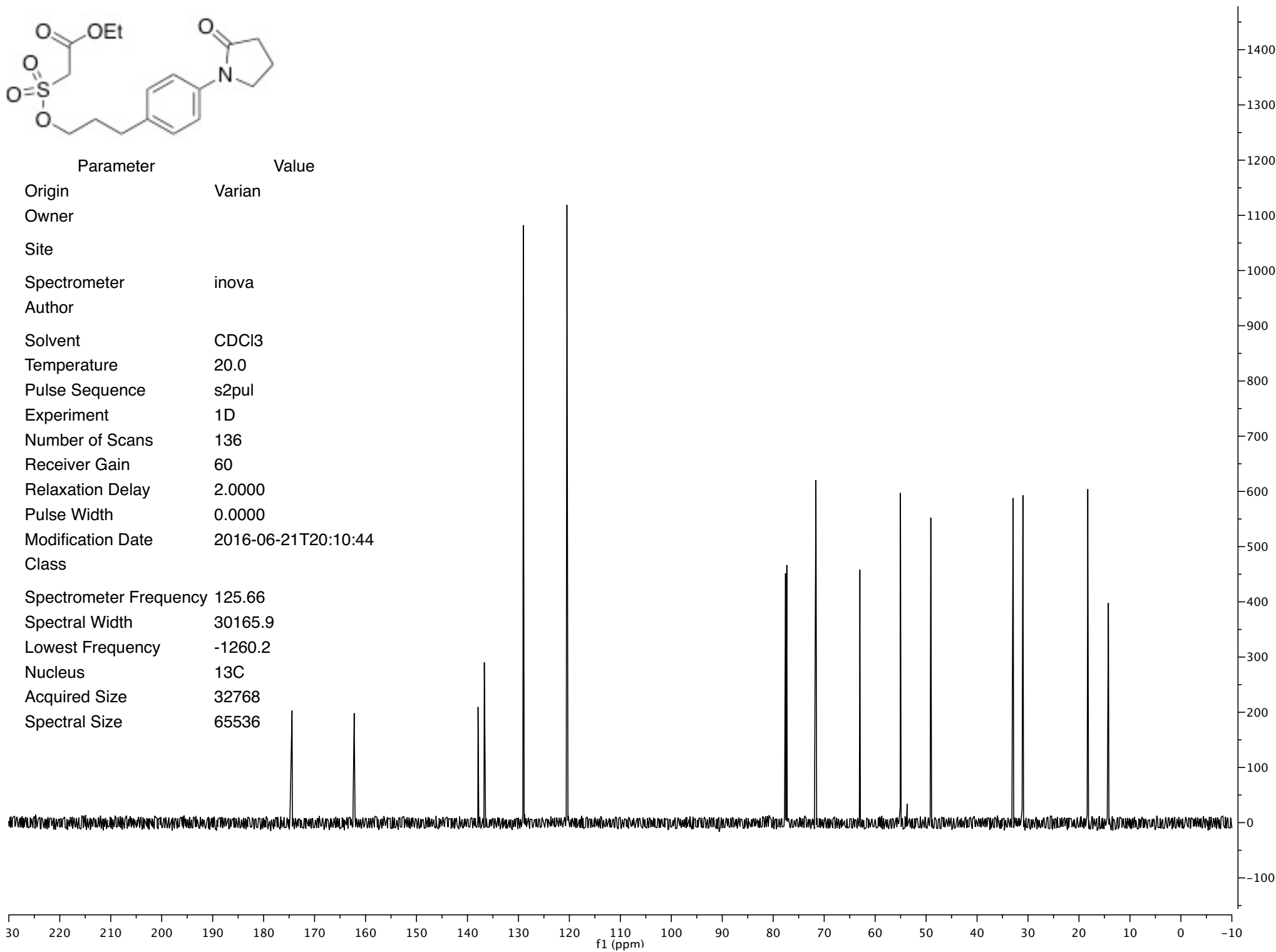


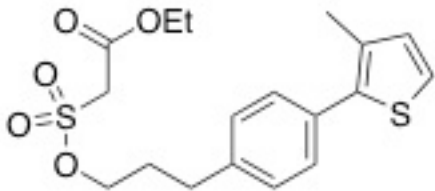
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	60
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-03-31T15:02:08
Class	
Spectrometer Frequency	399.74
Spectral Width	8000.0
Lowest Frequency	-2425.9
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



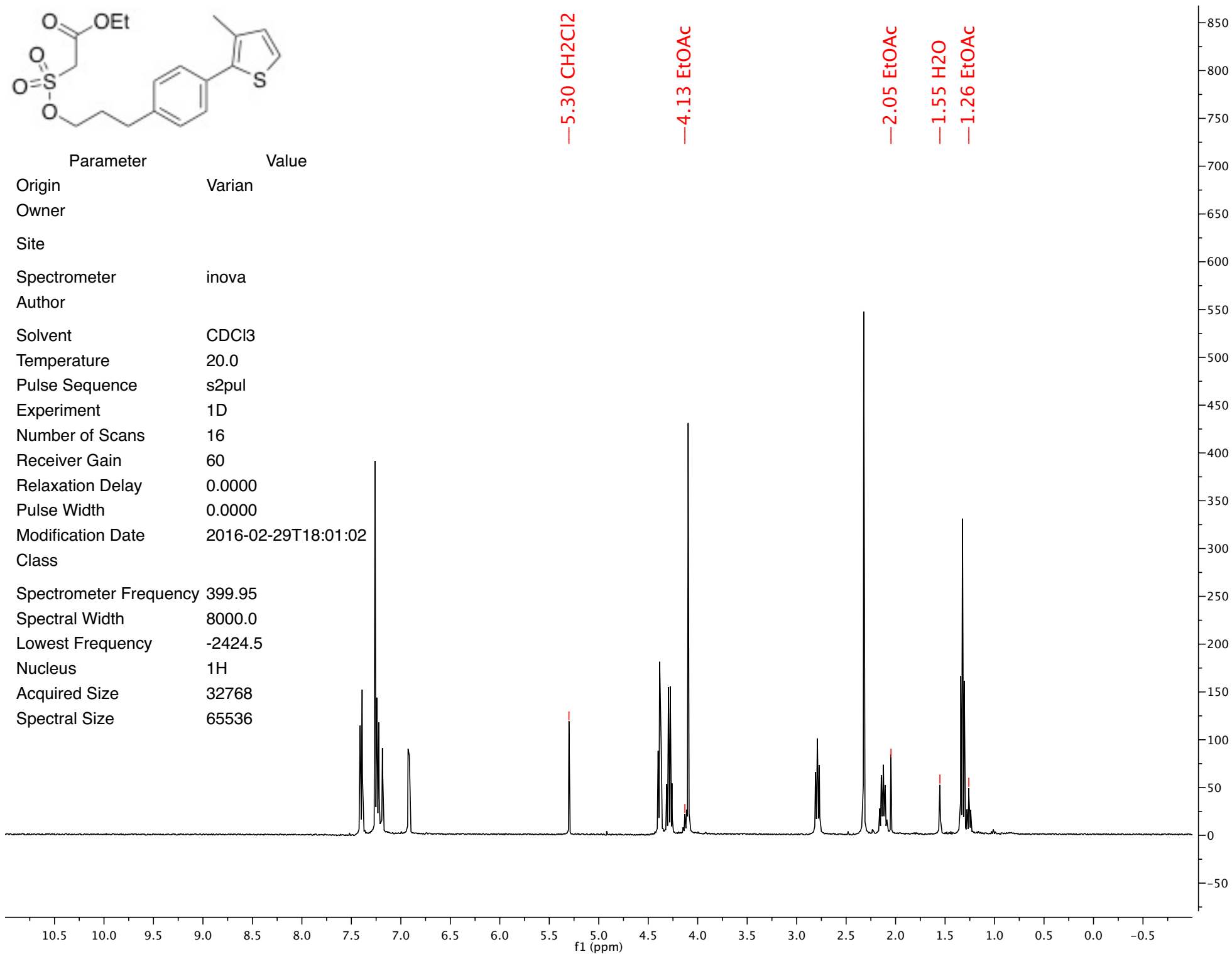


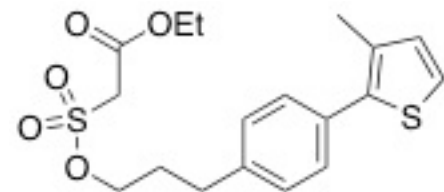
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	136
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-06-21T20:10:44
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



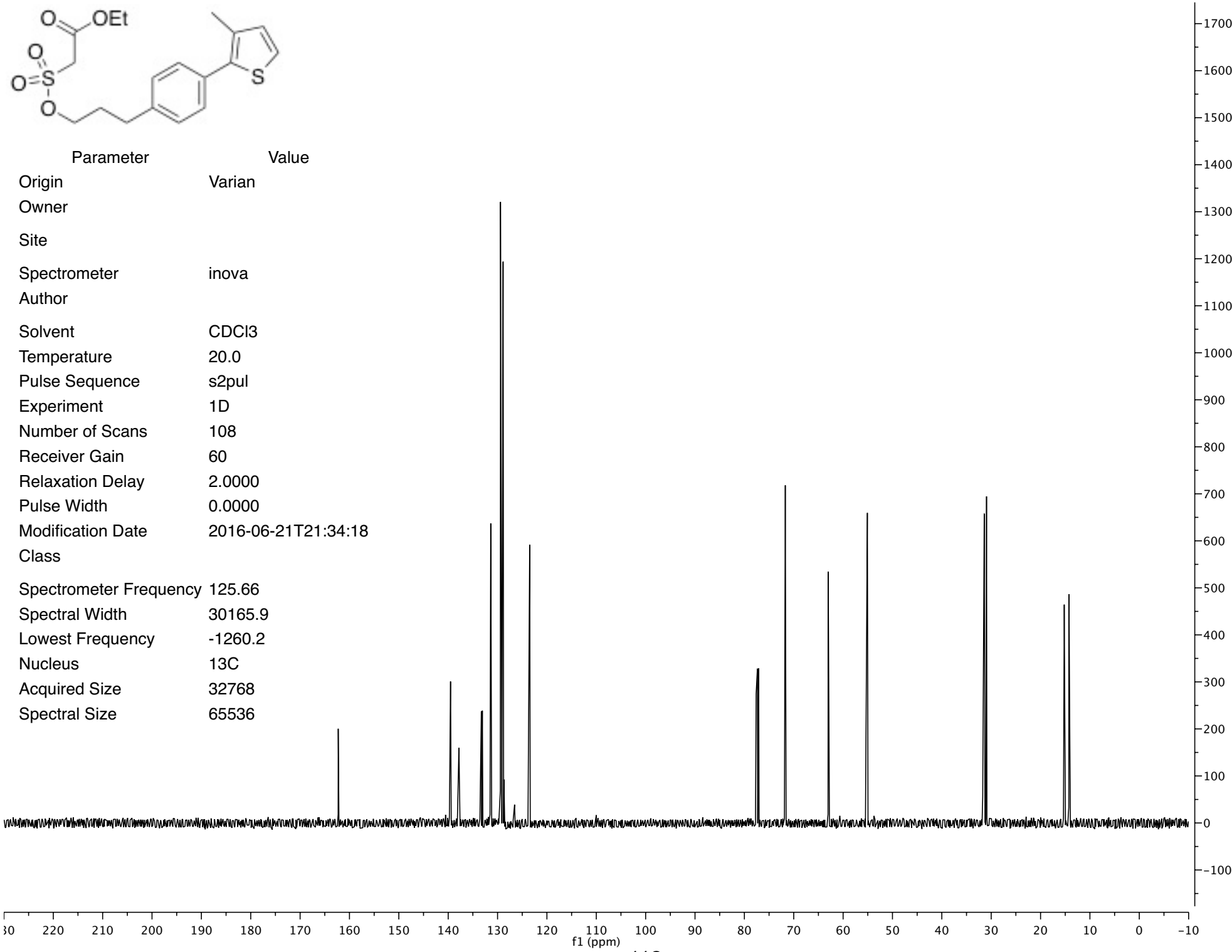


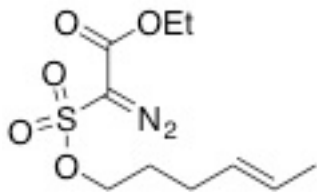
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	60
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-02-29T18:01:02
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2424.5
Nucleus	1H
Acquired Size	32768
Spectral Size	65536





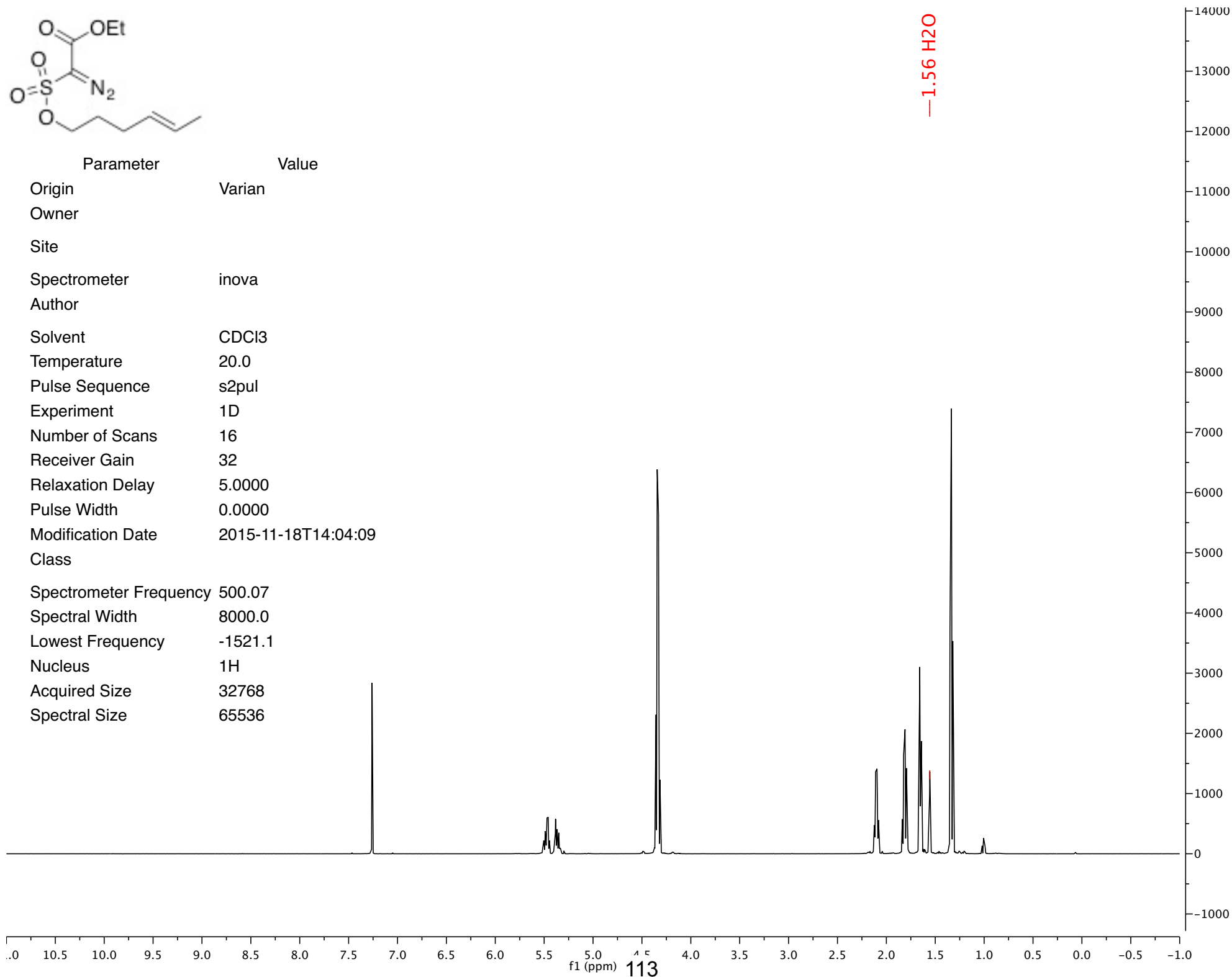
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	108
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-06-21T21:34:18
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

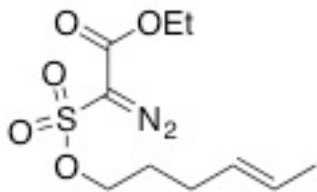




—1.56 H₂O

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	32
Relaxation Delay	5.0000
Pulse Width	0.0000
Modification Date	2015-11-18T14:04:09
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1521.1
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536





Parameter	Value
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Origin	Varian
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Owner	
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Site	
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Spectrometer	inova
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Author	
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Solvent	CDCl3
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Temperature	20.0
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Pulse Sequence	s2pul
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Experiment	1D
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Number of Scans	215
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Receiver Gain	60
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Relaxation Delay	2.0000
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Pulse Width	0.0000
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Modification Date	2015-11-24T13:39:23
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Class	
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Spectrometer Frequency	125.66
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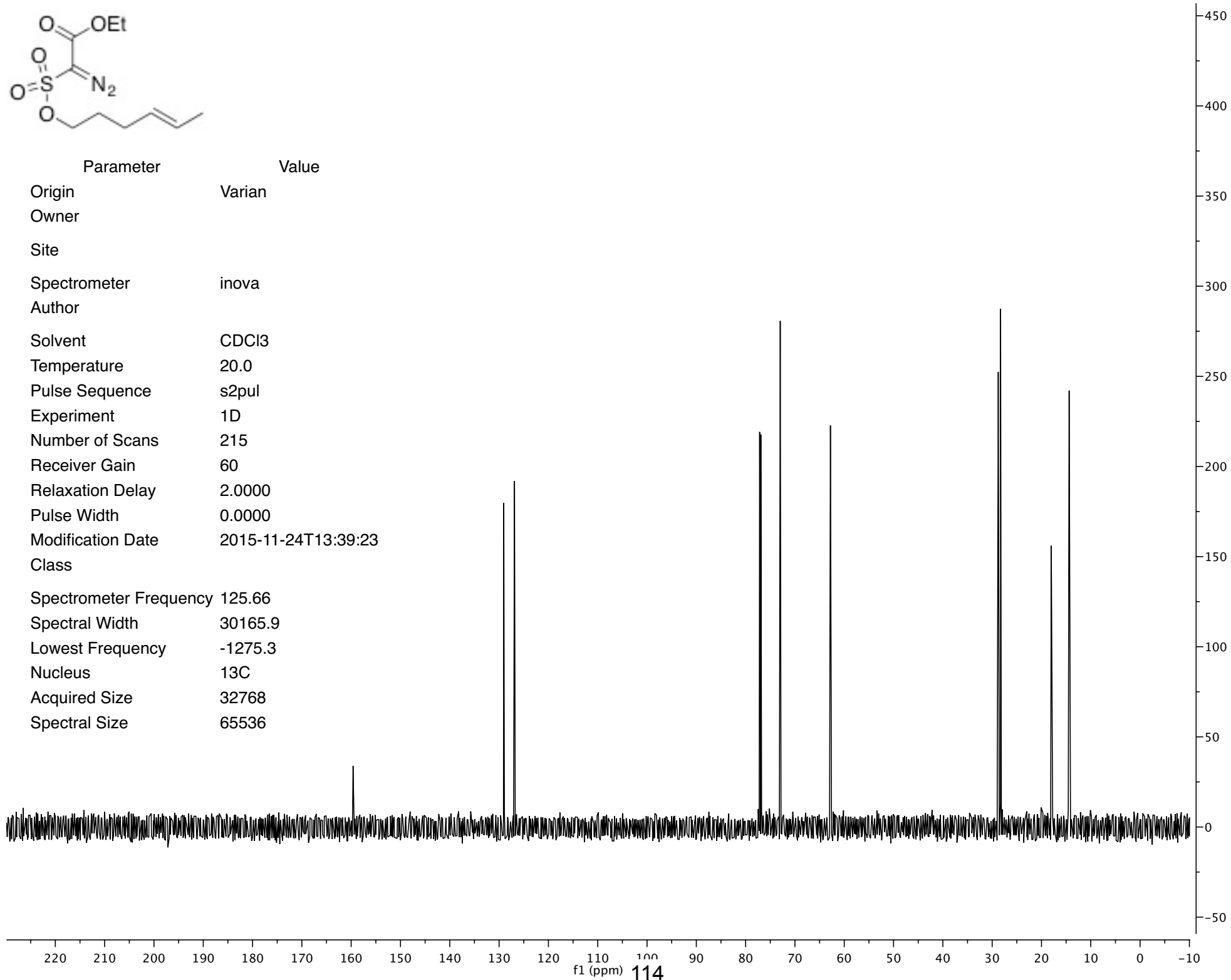
Spectral Width	30165.9
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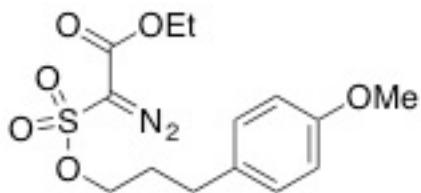
Lowest Frequency	-1275.3
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Nucleus	13C
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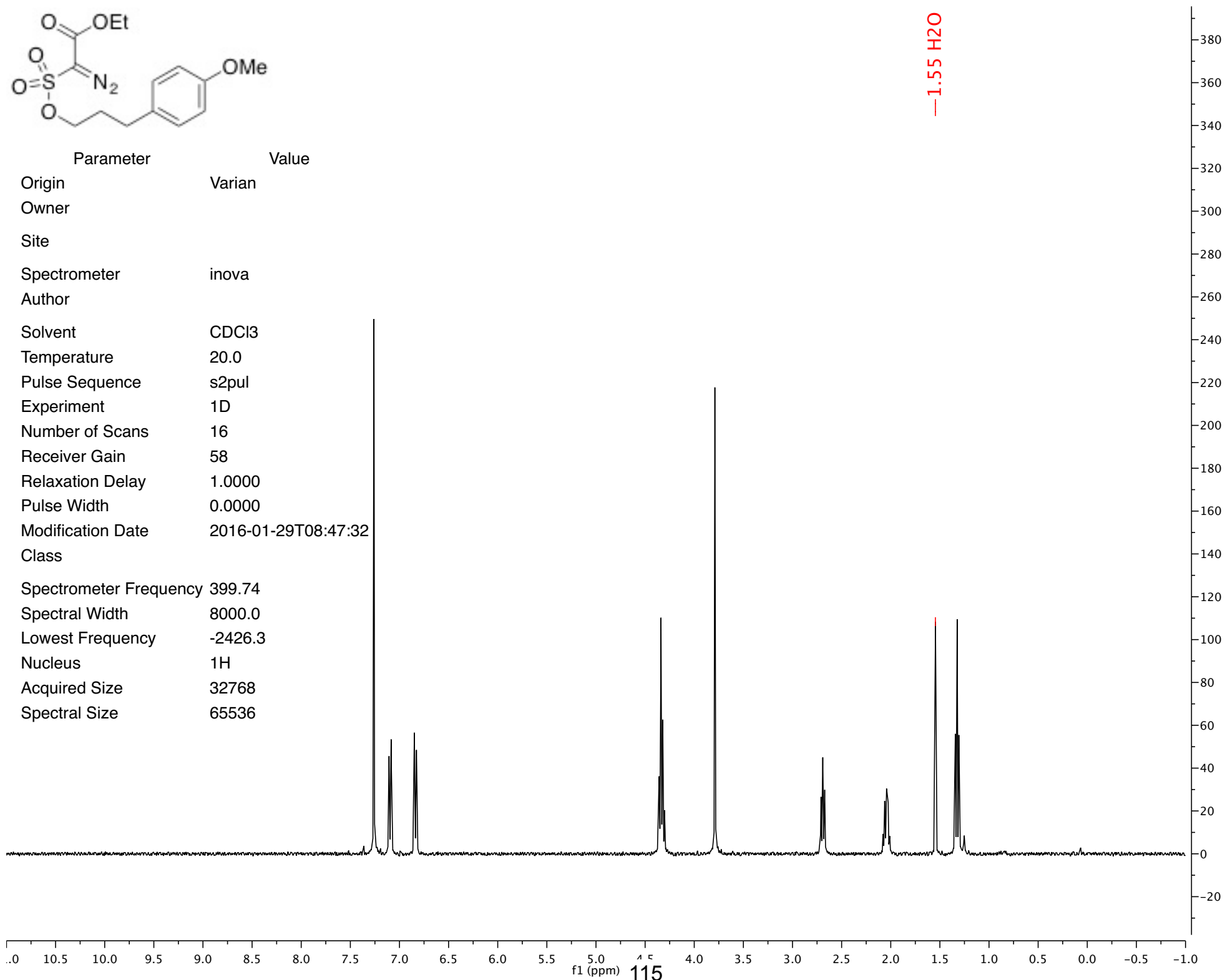
Acquired Size	32768
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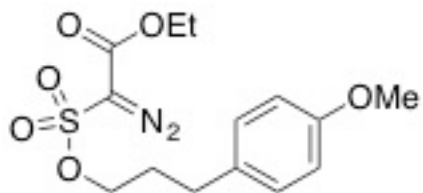
Spectral Size	65536
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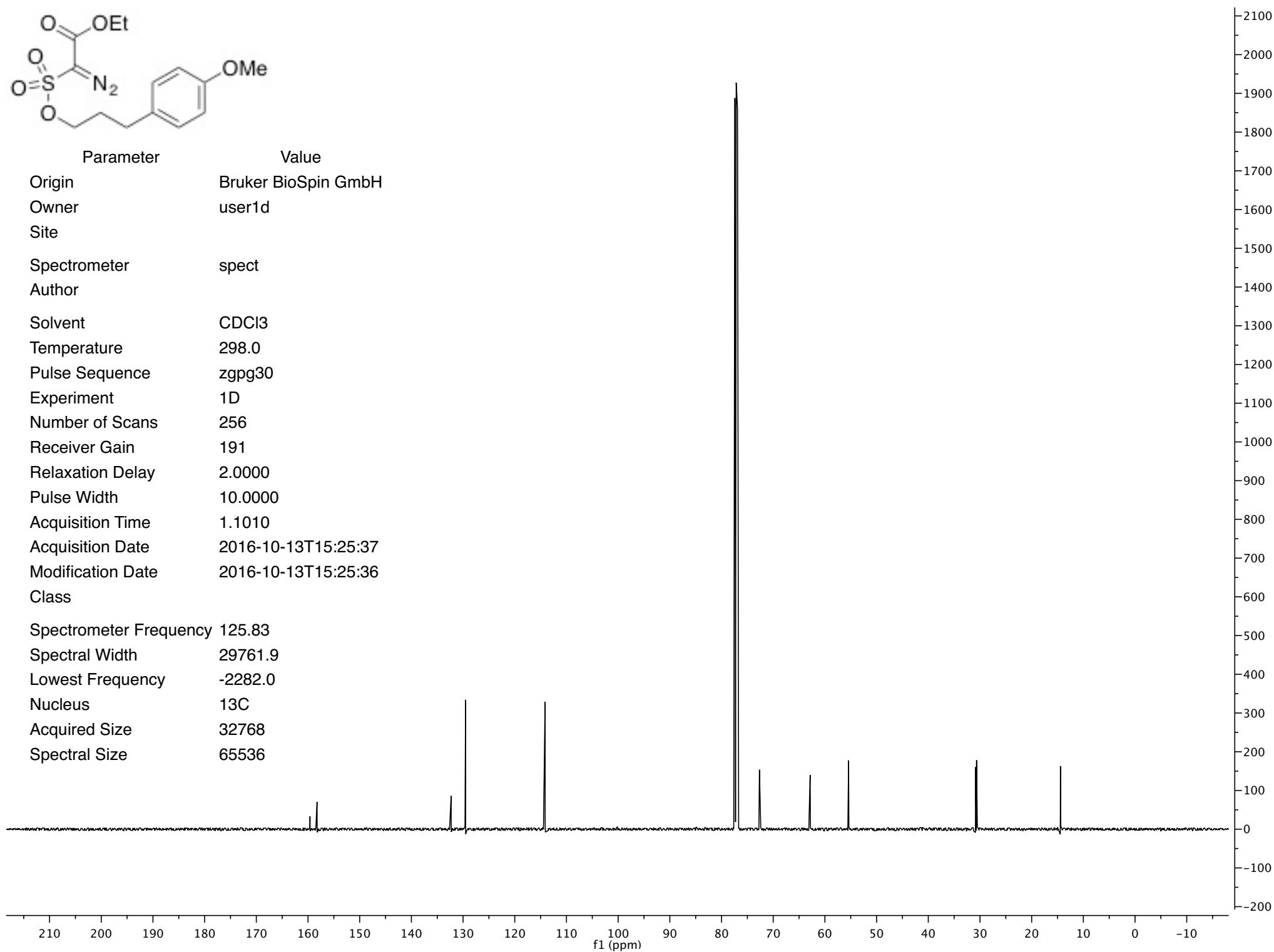


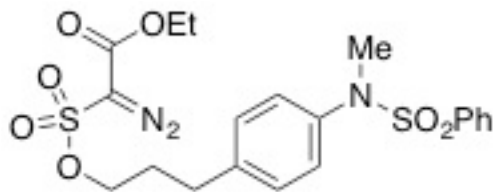
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	58
Relaxation Delay	1.0000
Pulse Width	0.0000
Modification Date	2016-01-29T08:47:32
Class	
Spectrometer Frequency	399.74
Spectral Width	8000.0
Lowest Frequency	-2426.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



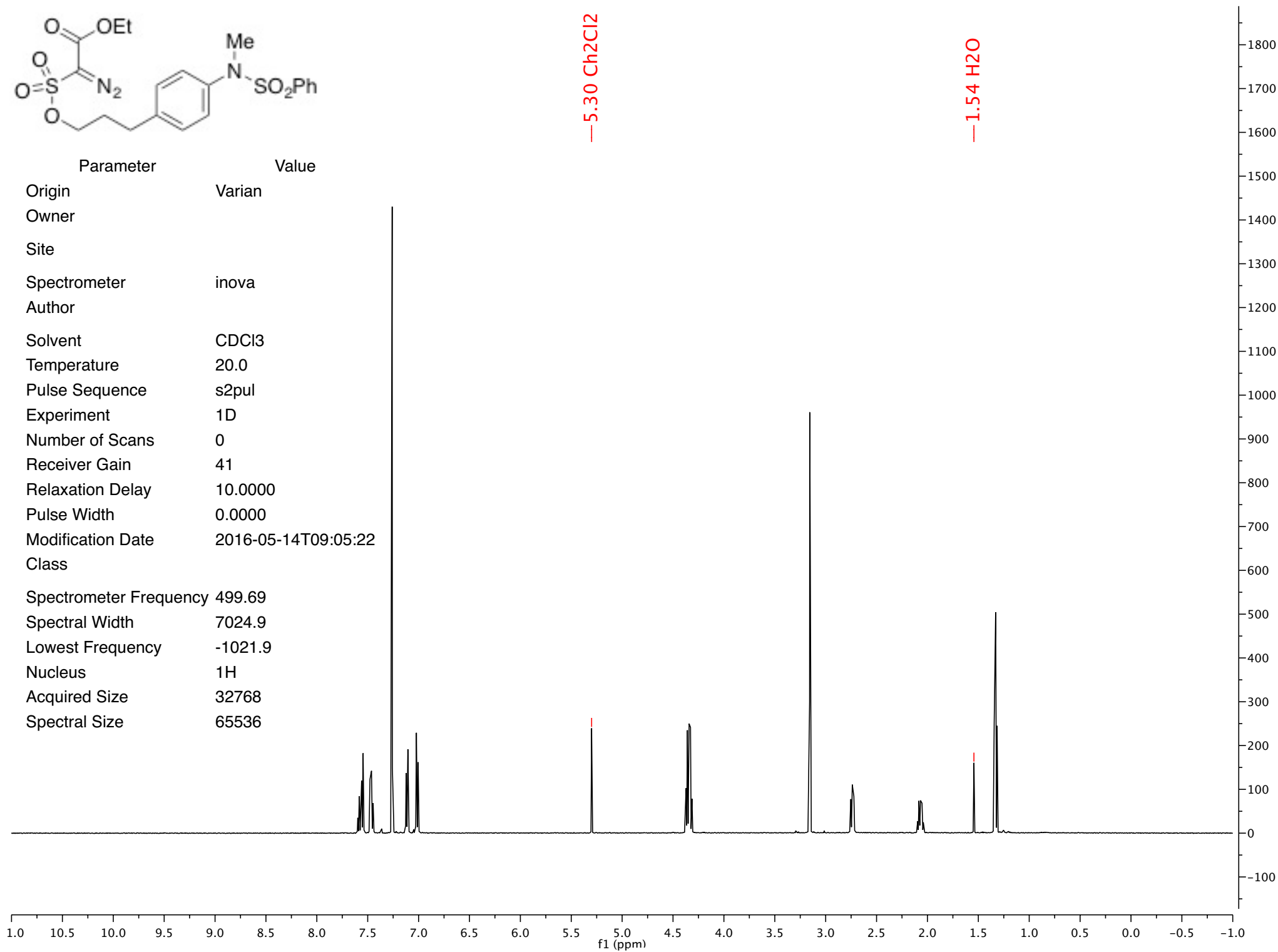


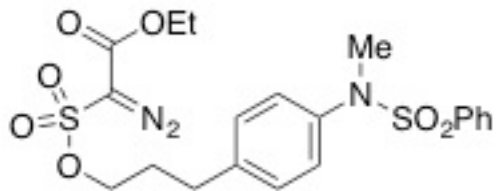
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	256
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-13T15:25:37
Modification Date	2016-10-13T15:25:36
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2282.0
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



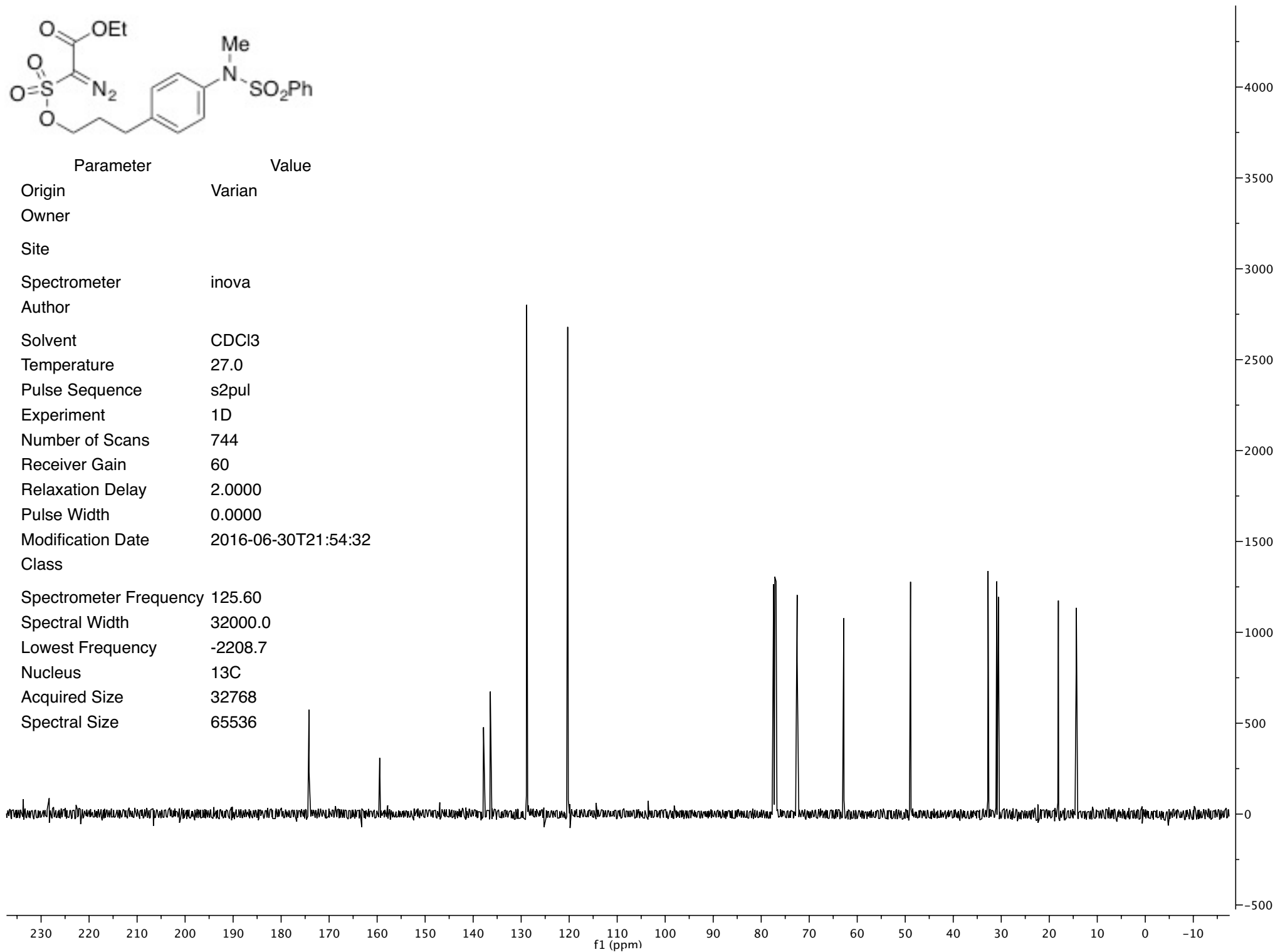


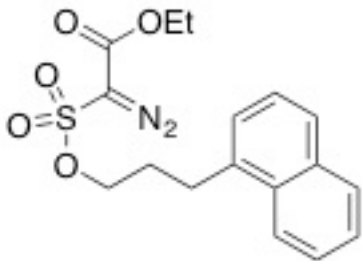
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	0
Receiver Gain	41
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-05-14T09:05:22
Class	
Spectrometer Frequency	499.69
Spectral Width	7024.9
Lowest Frequency	-1021.9
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



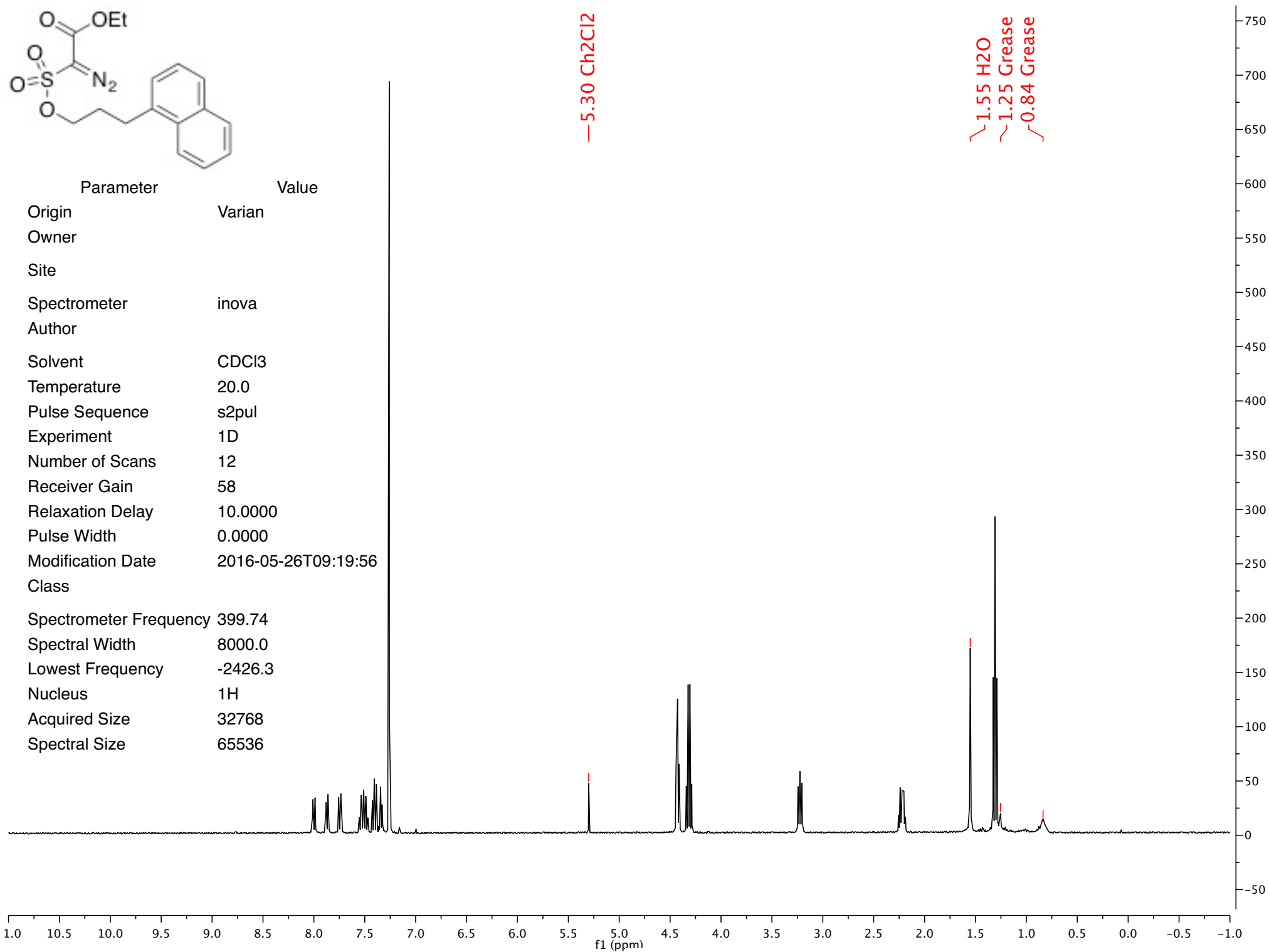


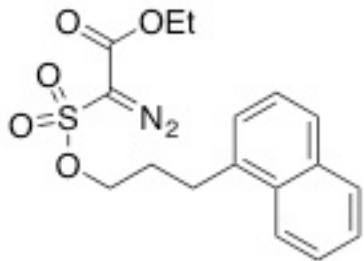
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	27.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	744
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-06-30T21:54:32
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2208.7
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



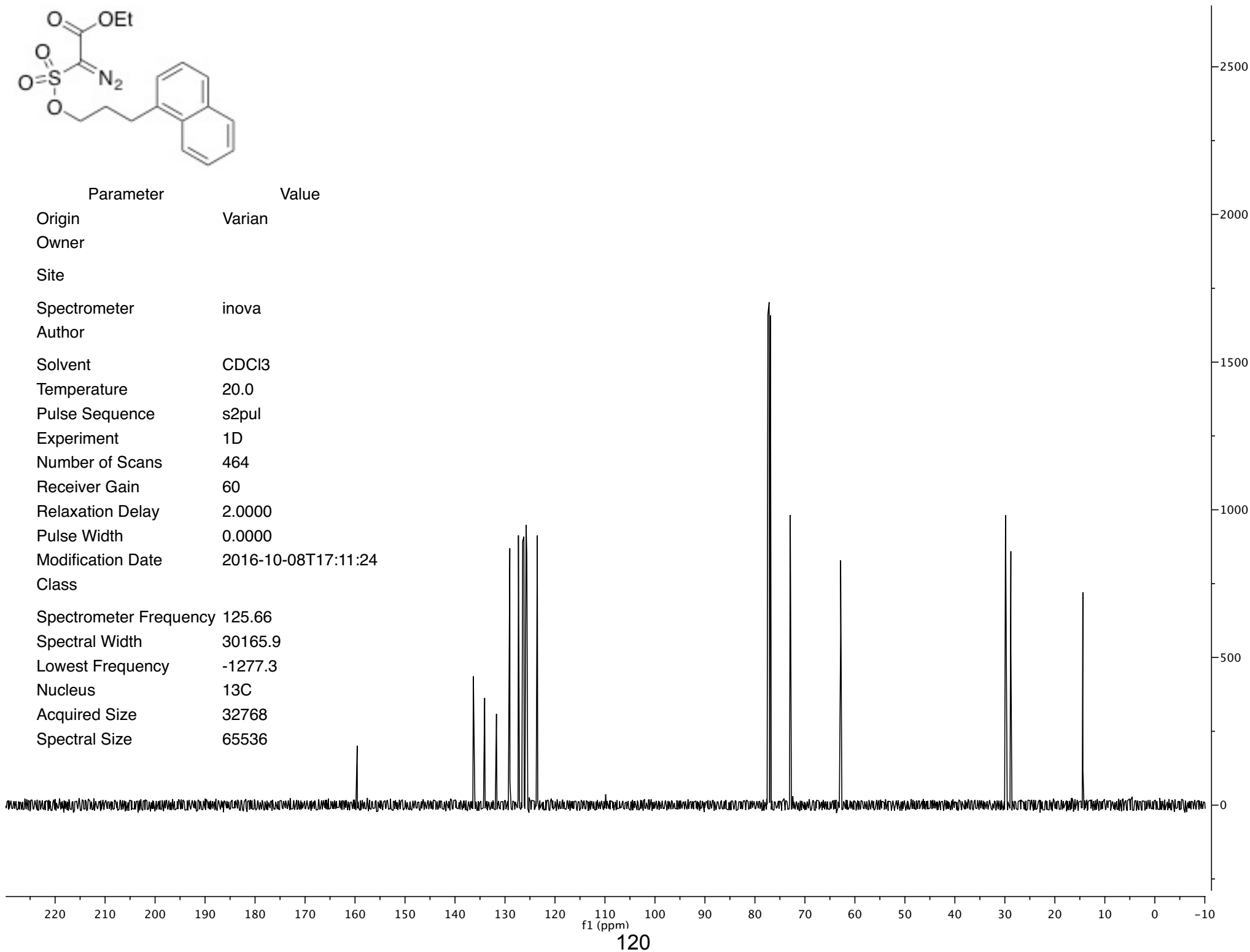


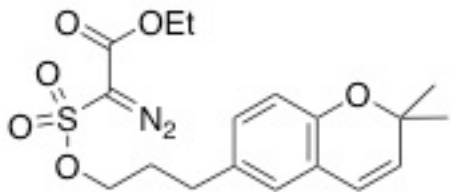
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	12
Receiver Gain	58
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-05-26T09:19:56
Class	
Spectrometer Frequency	399.74
Spectral Width	8000.0
Lowest Frequency	-2426.3
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



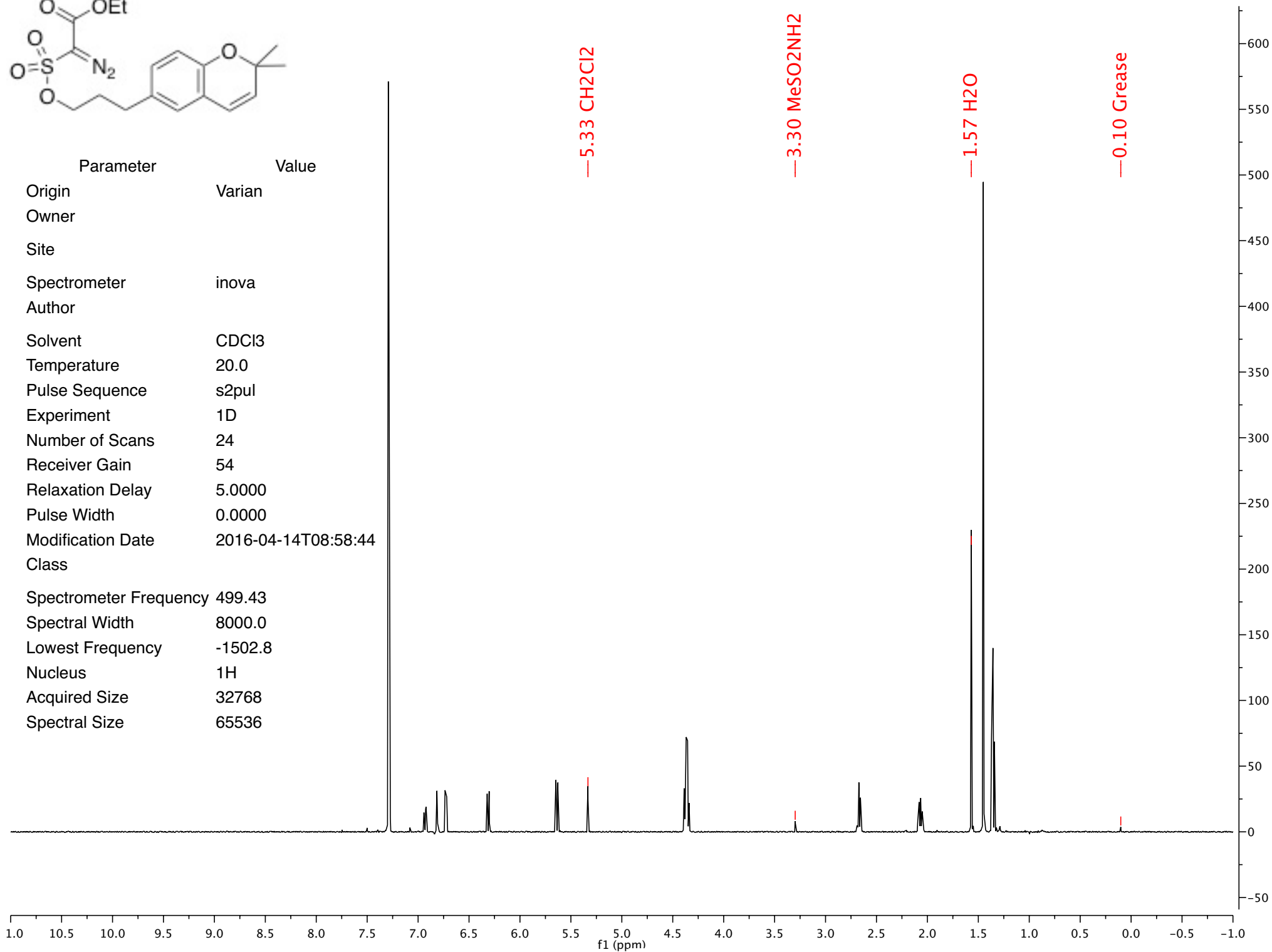


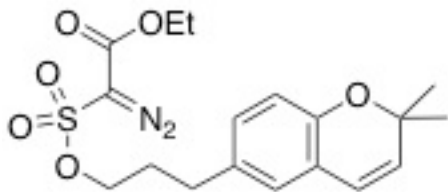
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	464
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-10-08T17:11:24
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1277.3
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



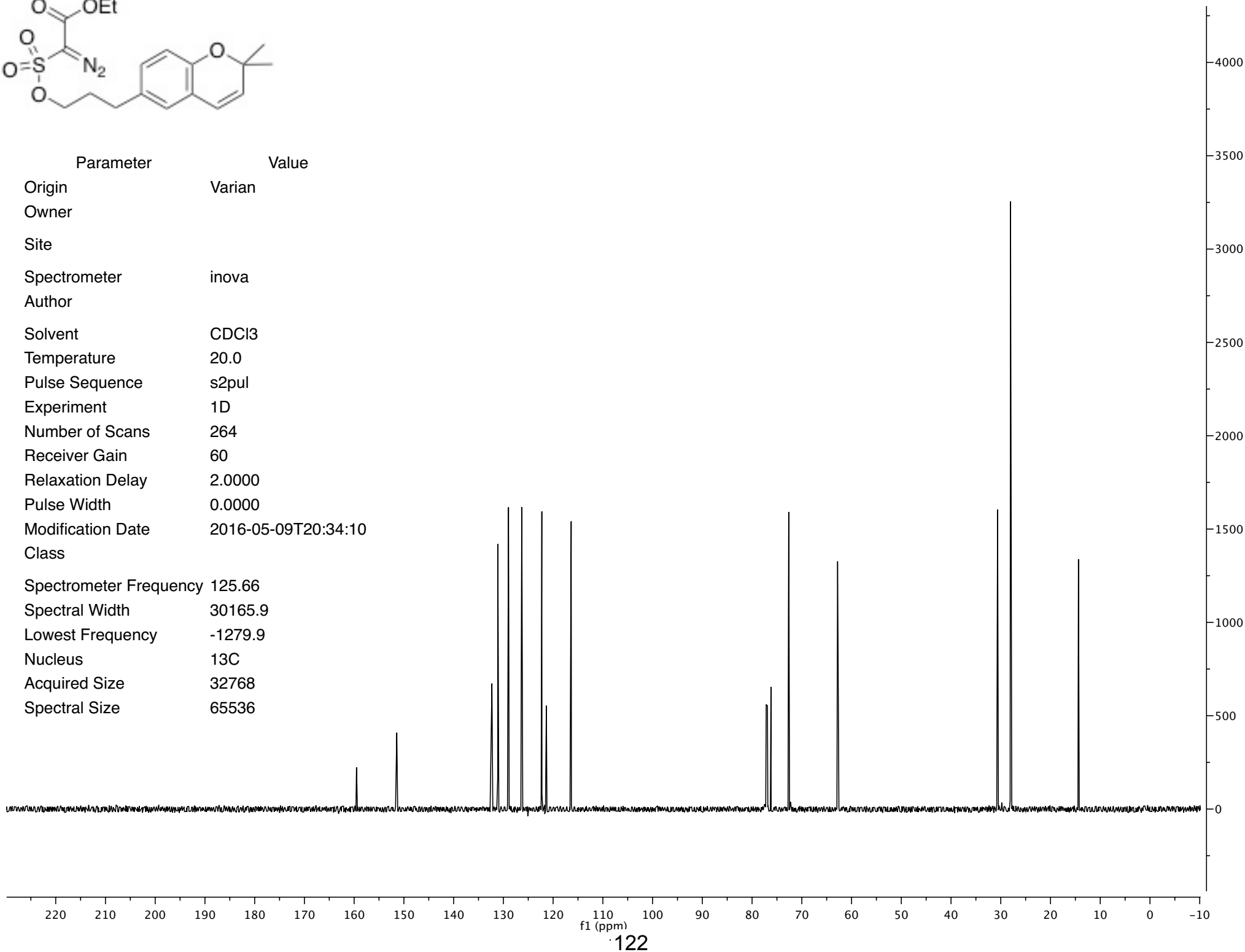


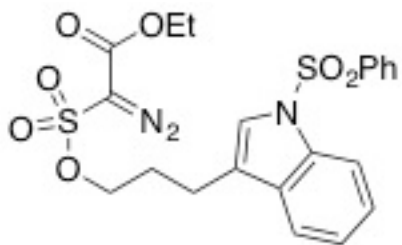
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	24
Receiver Gain	54
Relaxation Delay	5.0000
Pulse Width	0.0000
Modification Date	2016-04-14T08:58:44
Class	
Spectrometer Frequency	499.43
Spectral Width	8000.0
Lowest Frequency	-1502.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



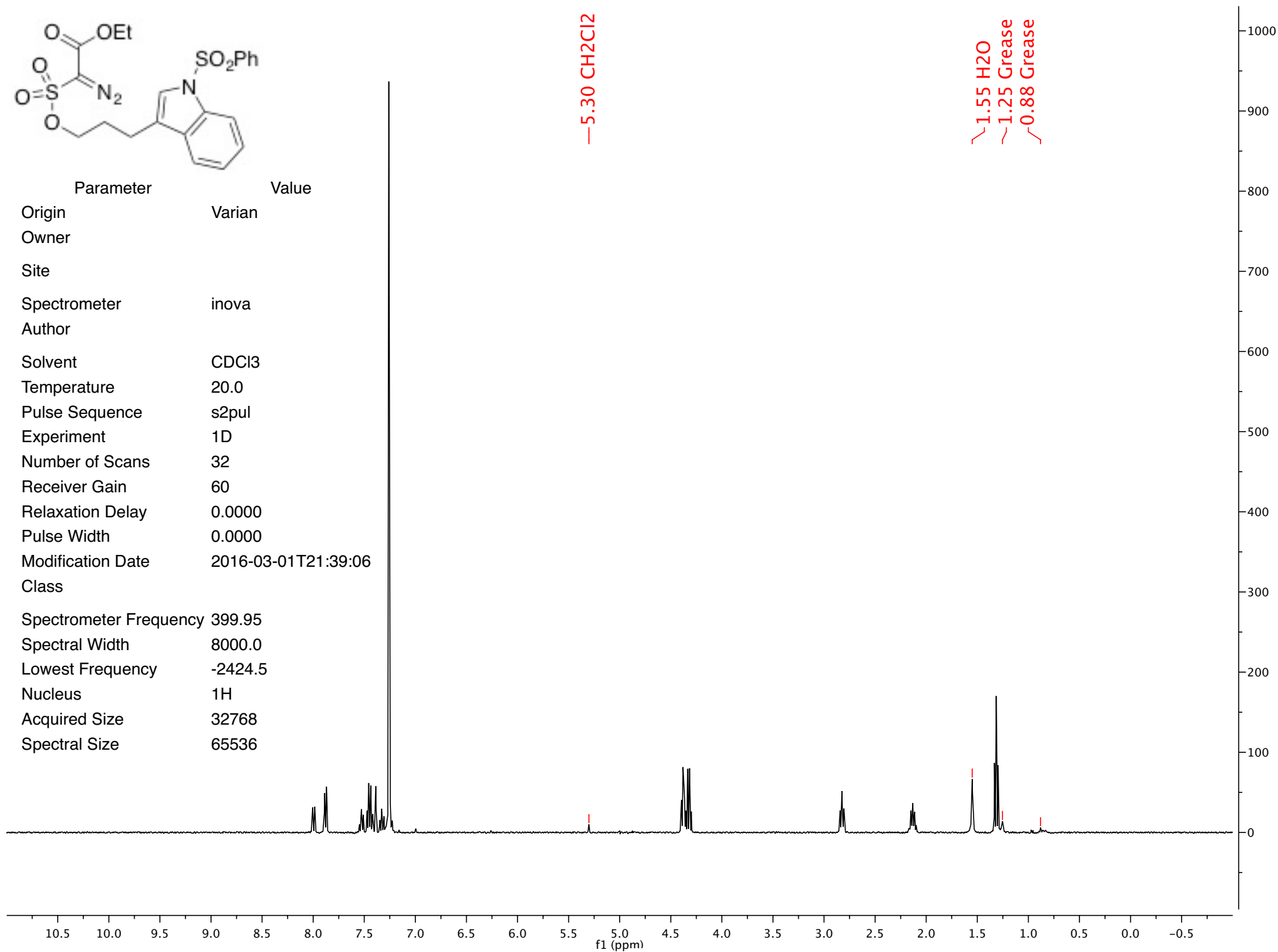


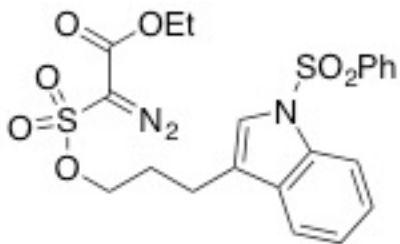
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	264
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-05-09T20:34:10
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1279.9
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



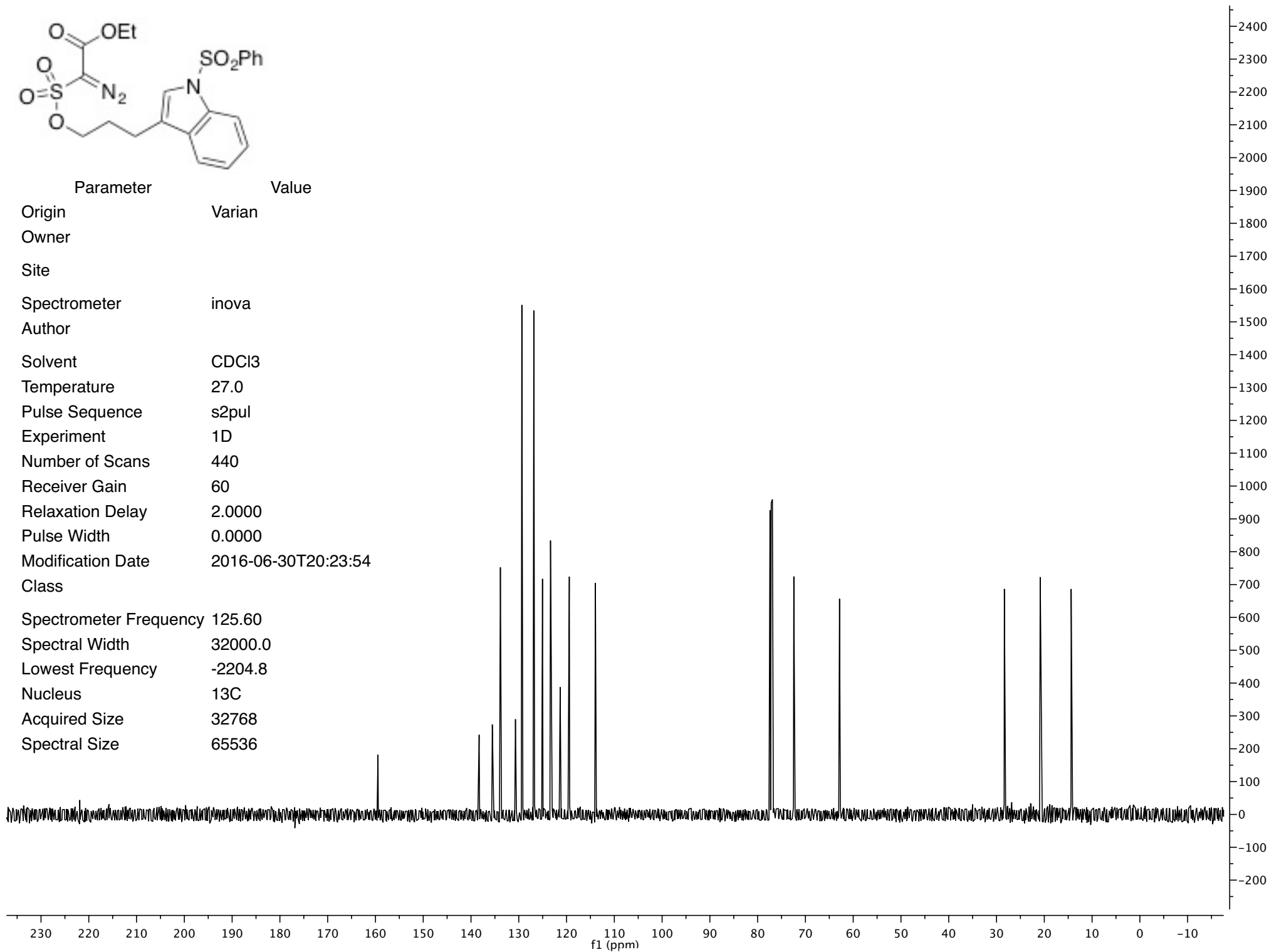


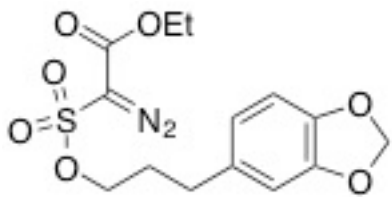
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	32
Receiver Gain	60
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-03-01T21:39:06
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2424.5
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



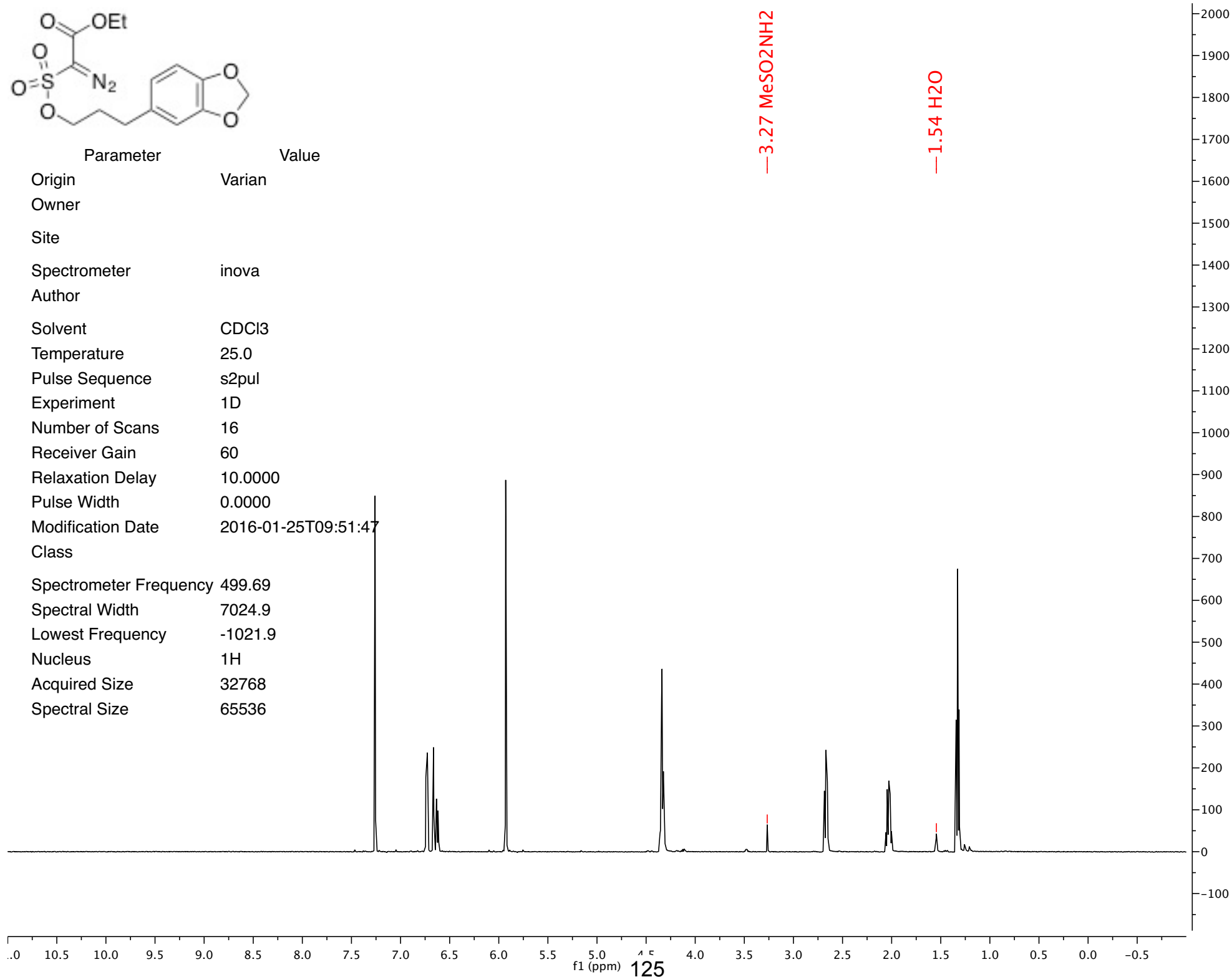


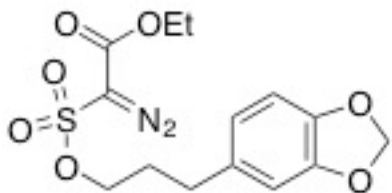
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	27.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	440
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-06-30T20:23:54
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2204.8
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



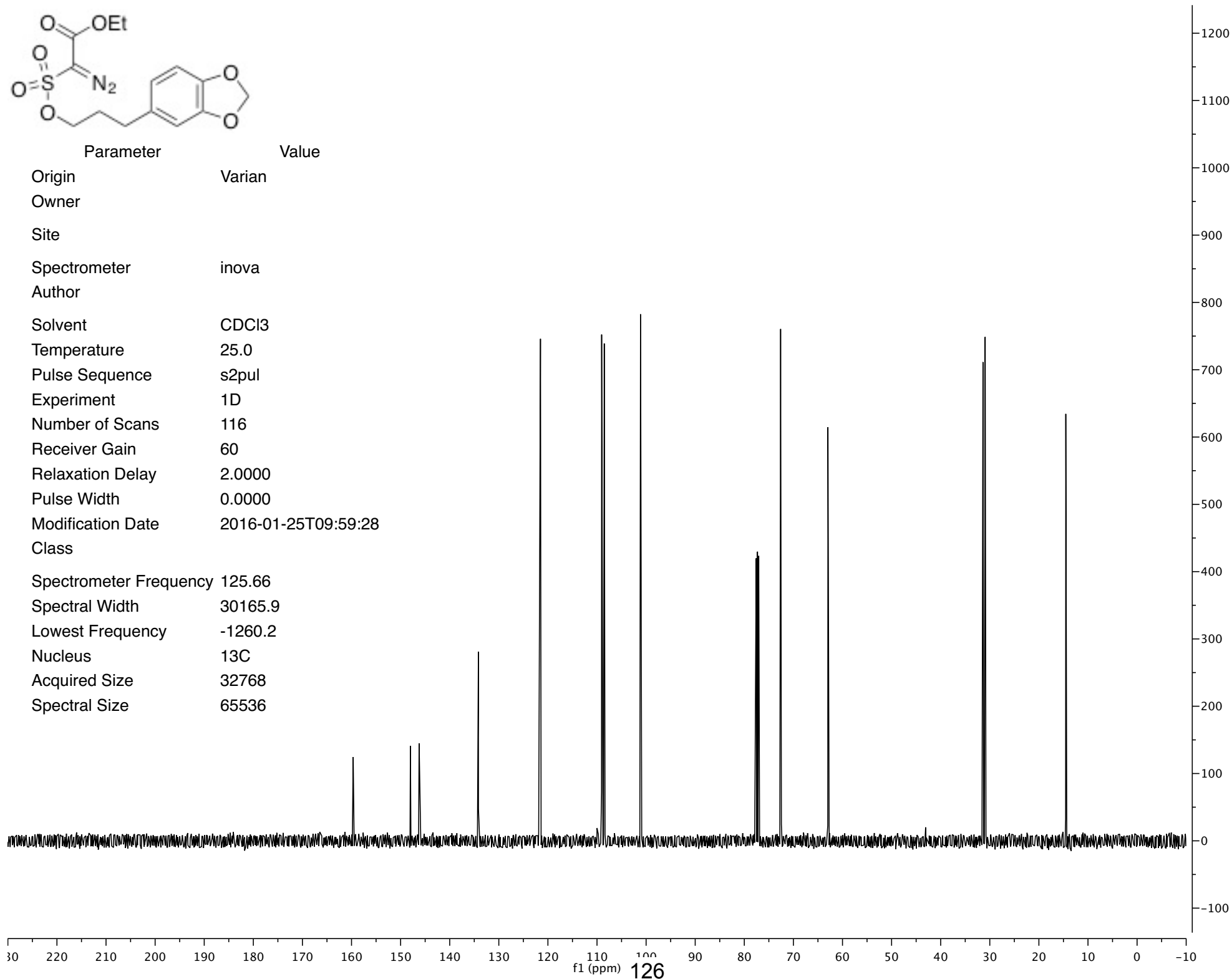


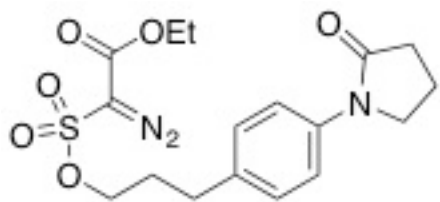
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	60
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-01-25T09:51:47
Class	
Spectrometer Frequency	499.69
Spectral Width	7024.9
Lowest Frequency	-1021.9
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



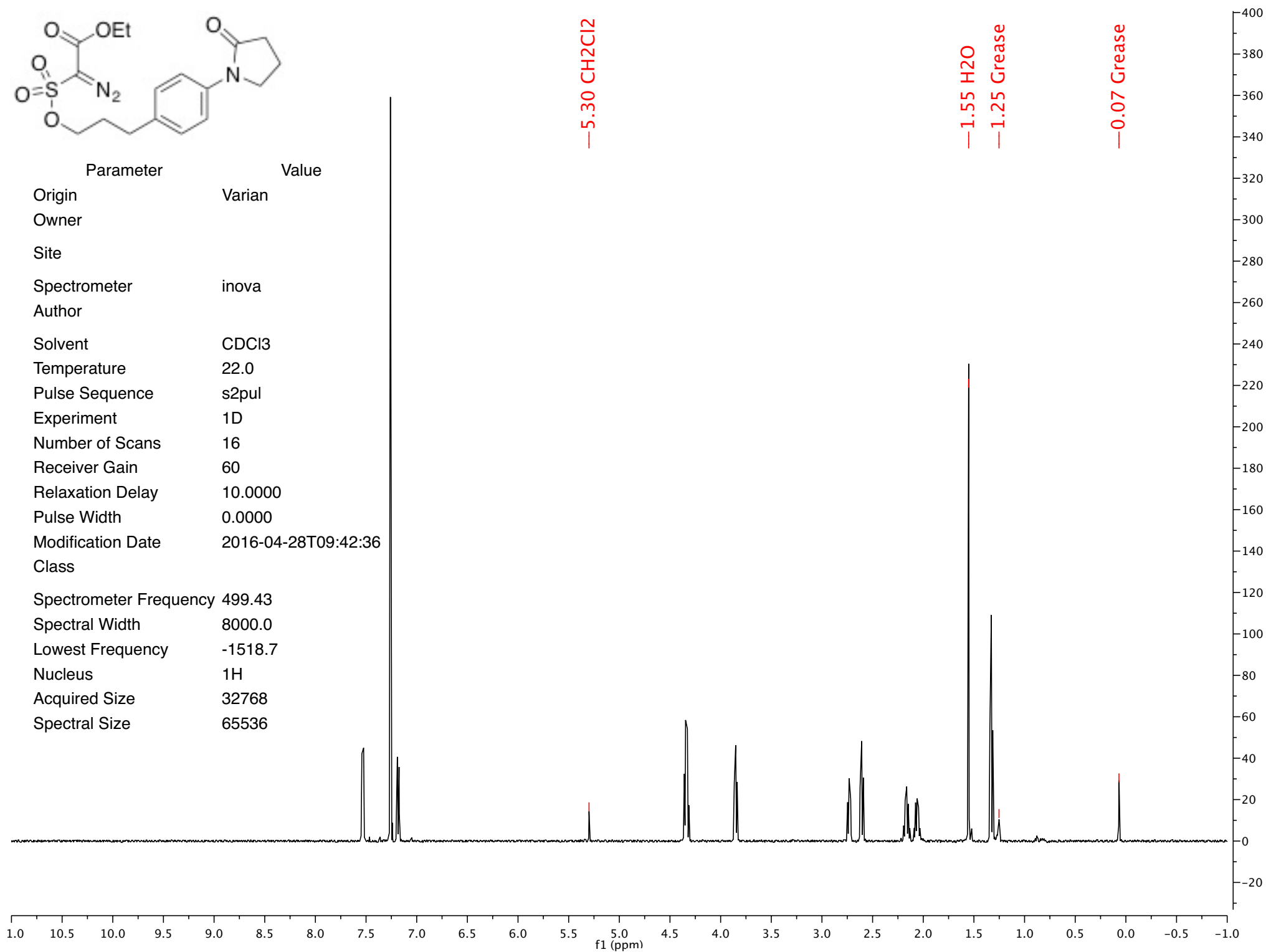


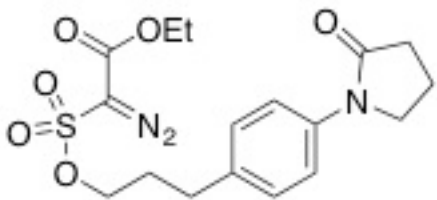
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	116
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-01-25T09:59:28
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



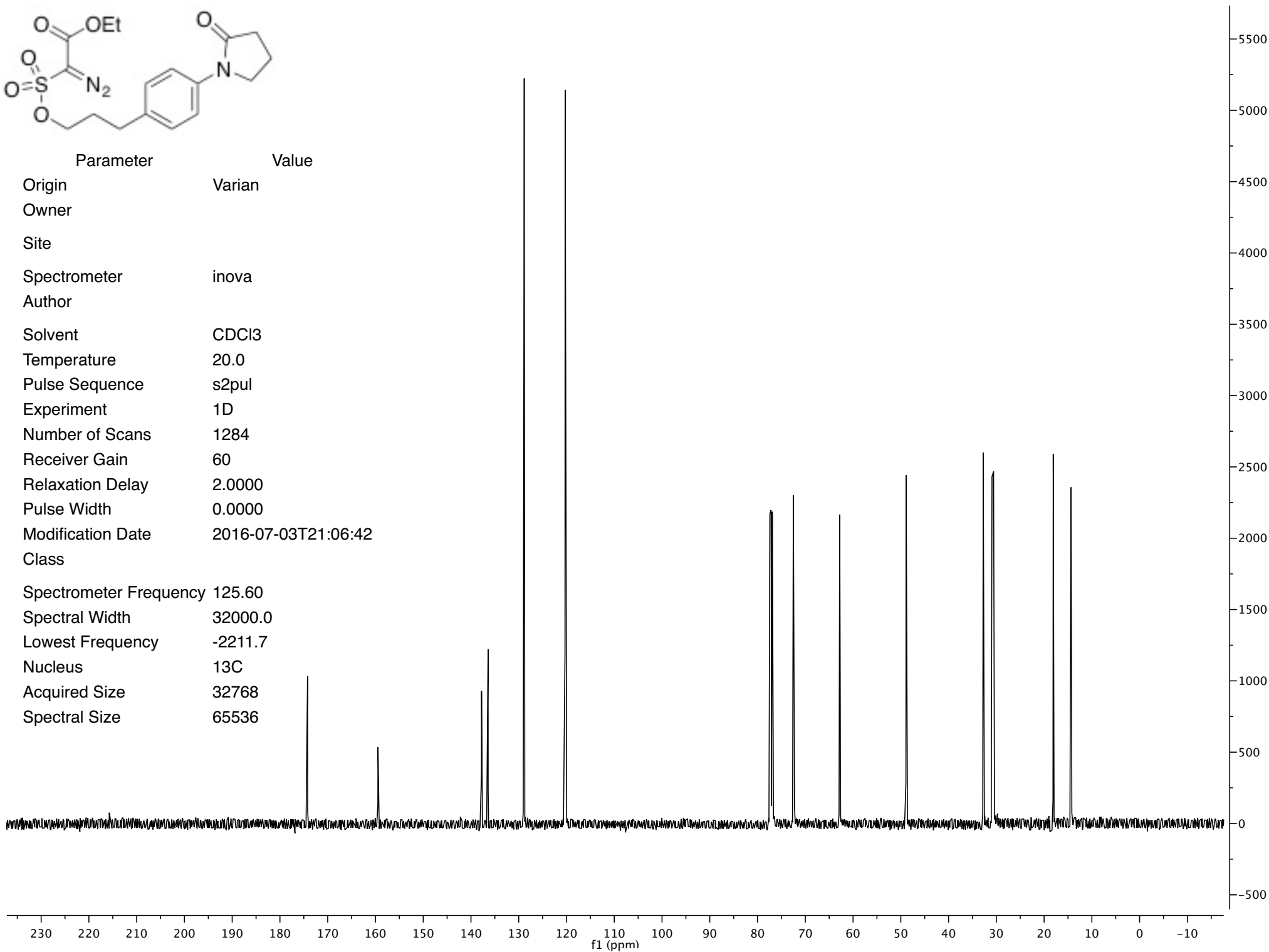


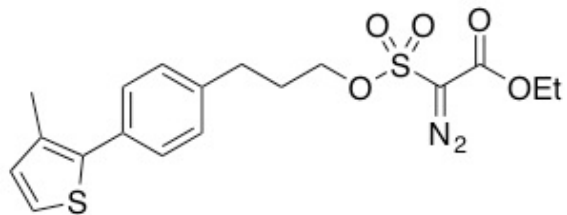
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	22.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	60
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-04-28T09:42:36
Class	
Spectrometer Frequency	499.43
Spectral Width	8000.0
Lowest Frequency	-1518.7
Nucleus	1H
Acquired Size	32768
Spectral Size	65536





Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	1284
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-07-03T21:06:42
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2211.7
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

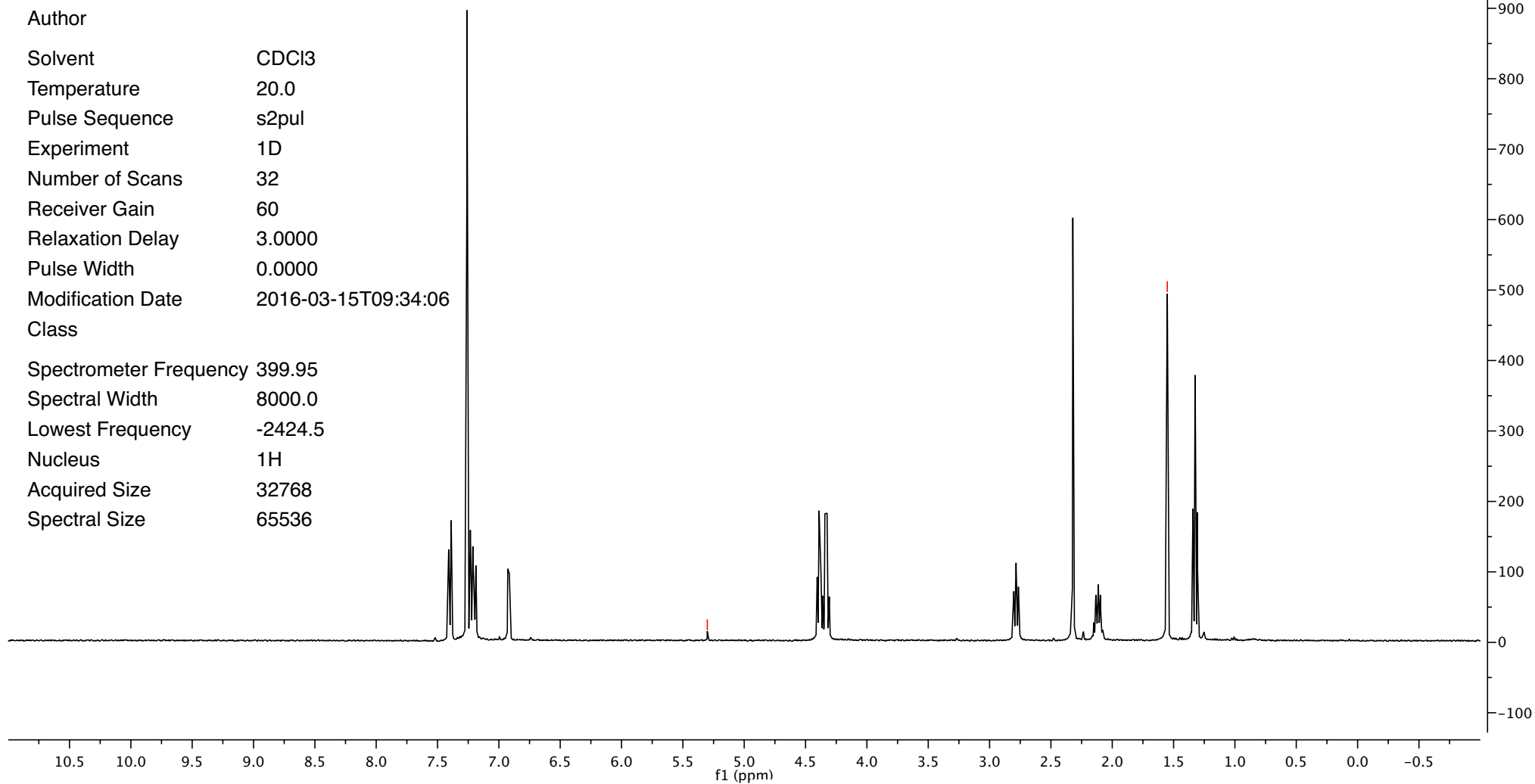


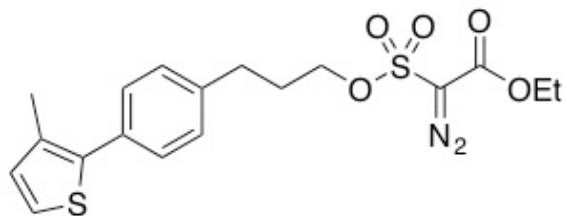


Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	32
Receiver Gain	60
Relaxation Delay	3.0000
Pulse Width	0.0000
Modification Date	2016-03-15T09:34:06
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2424.5
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

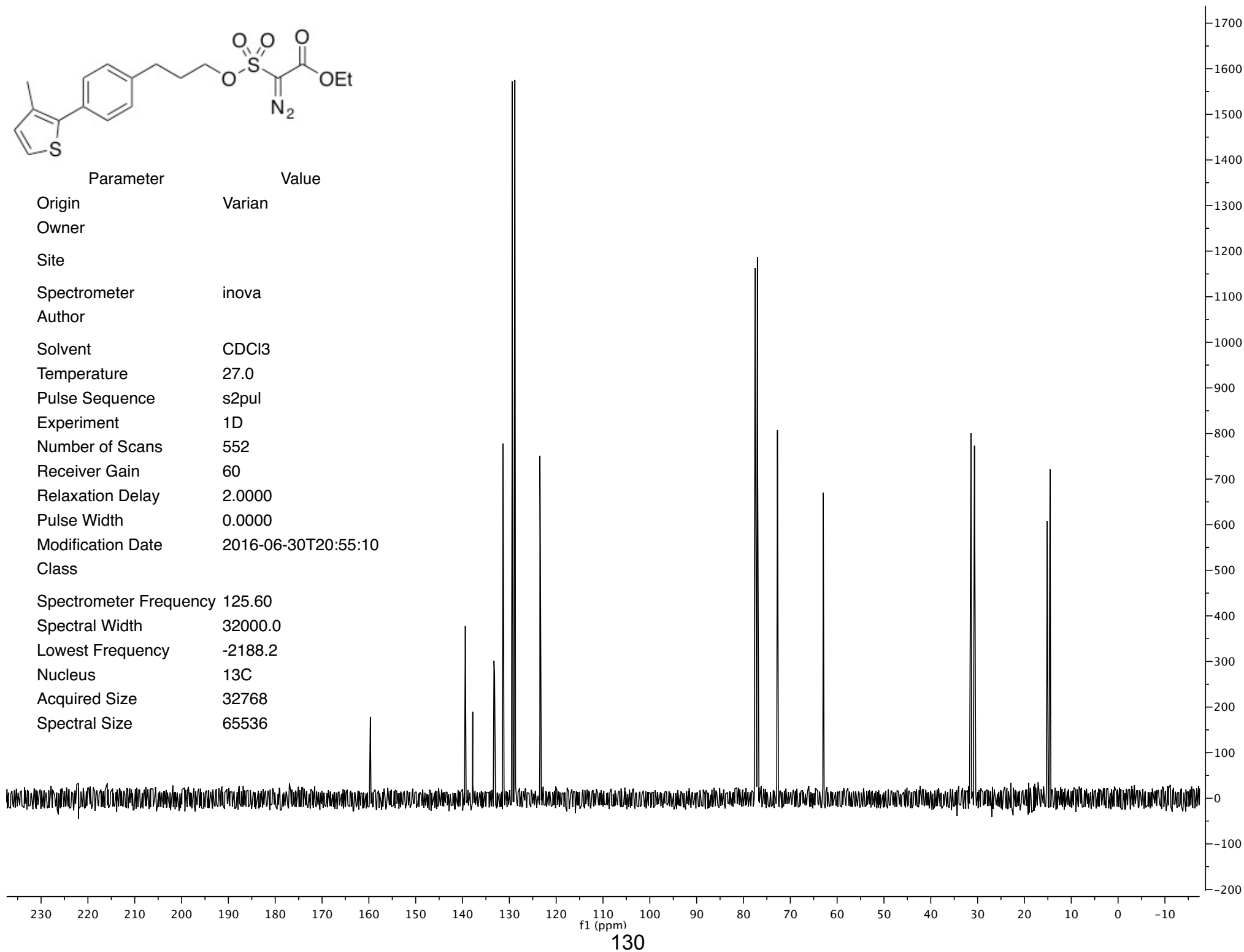
—5.30 CH2Cl2

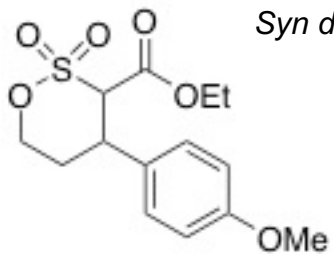
—1.55 H2O





Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	27.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	552
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-06-30T20:55:10
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2188.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

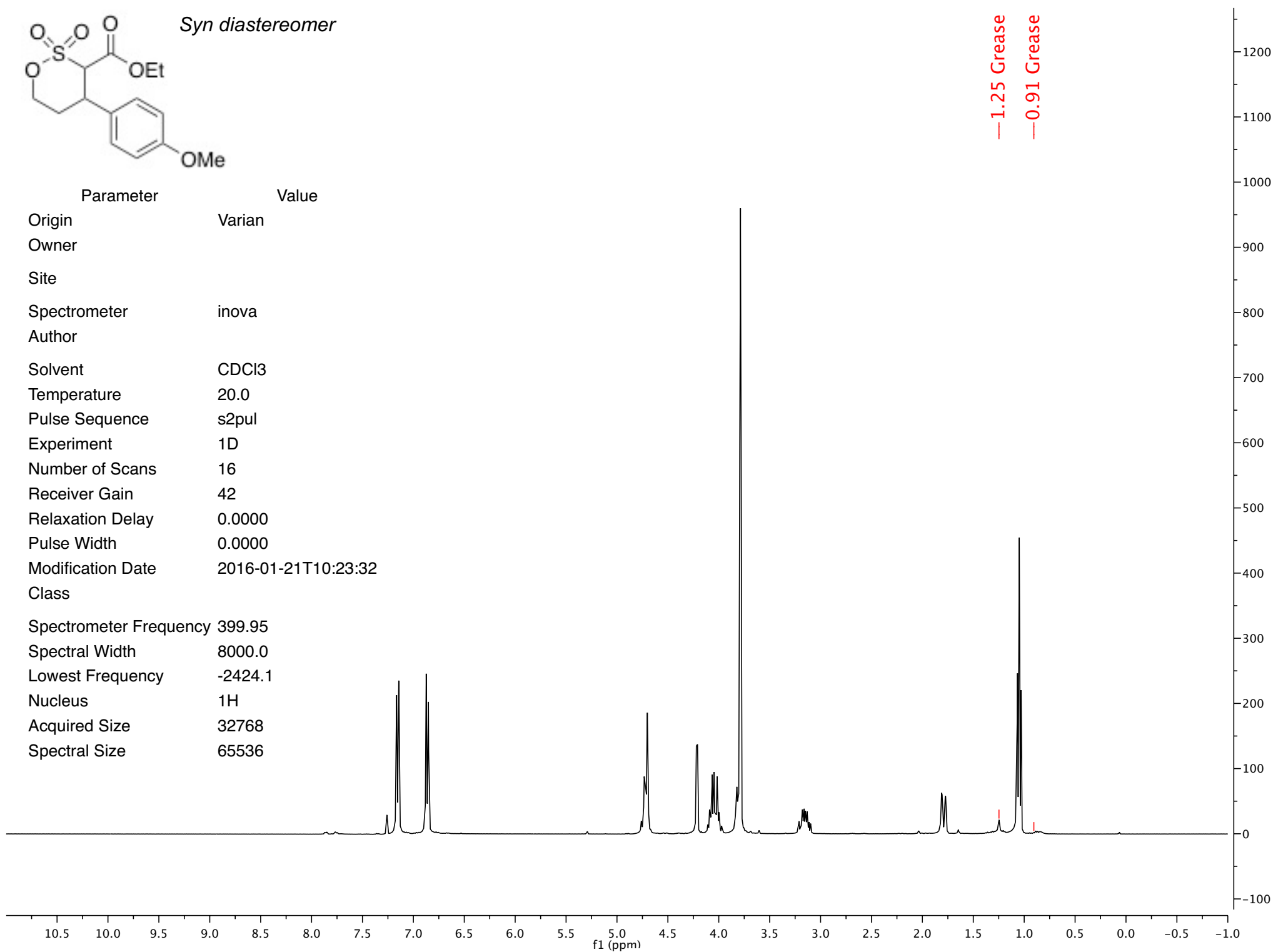




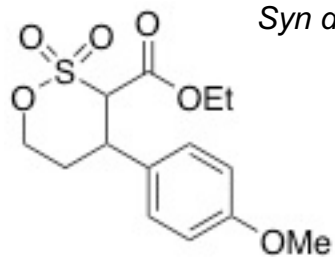
Syn diastereomer

— 1.25 Grease
— 0.91 Grease

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	42
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-01-21T10:23:32
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2424.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

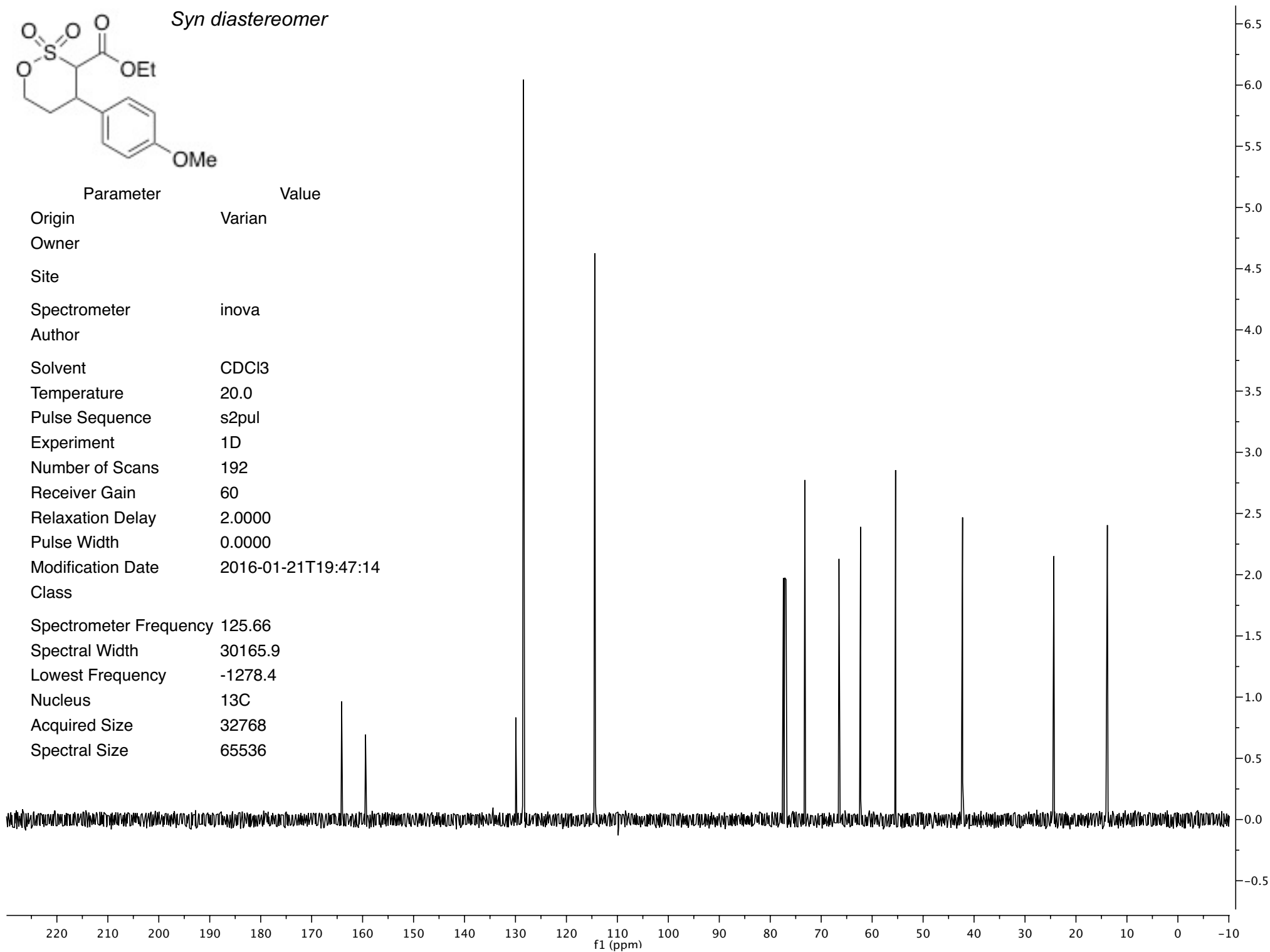


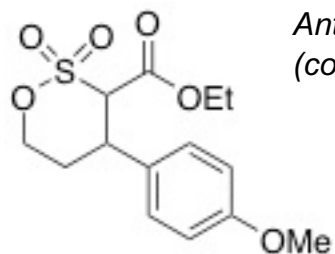
131



Syn diastereomer

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	192
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-01-21T19:47:14
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1278.4
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

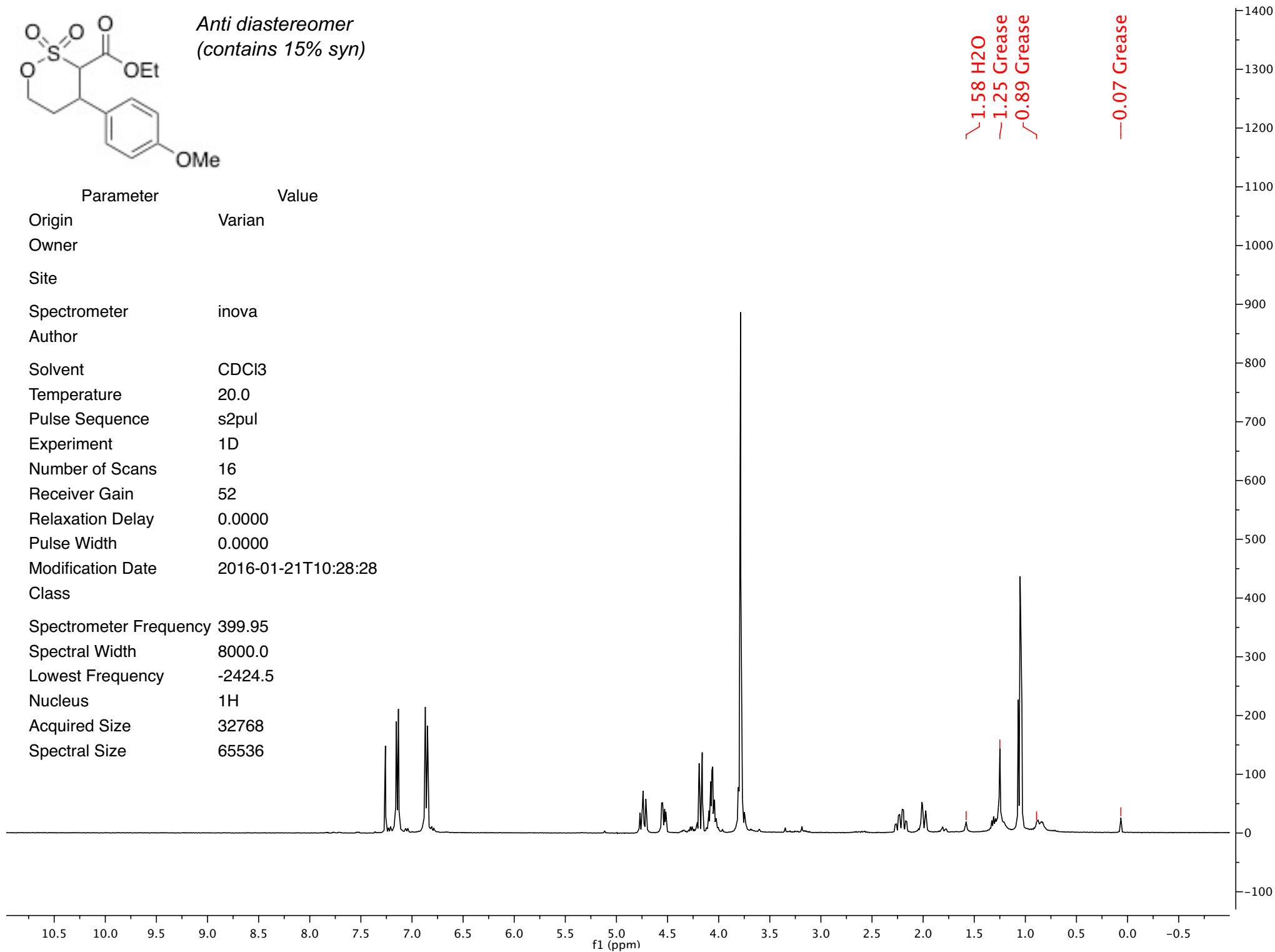




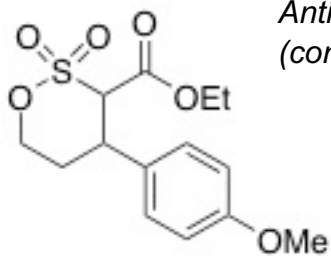
Anti diastereomer
(contains 15% syn)

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	52
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-01-21T10:28:28
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2424.5
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536

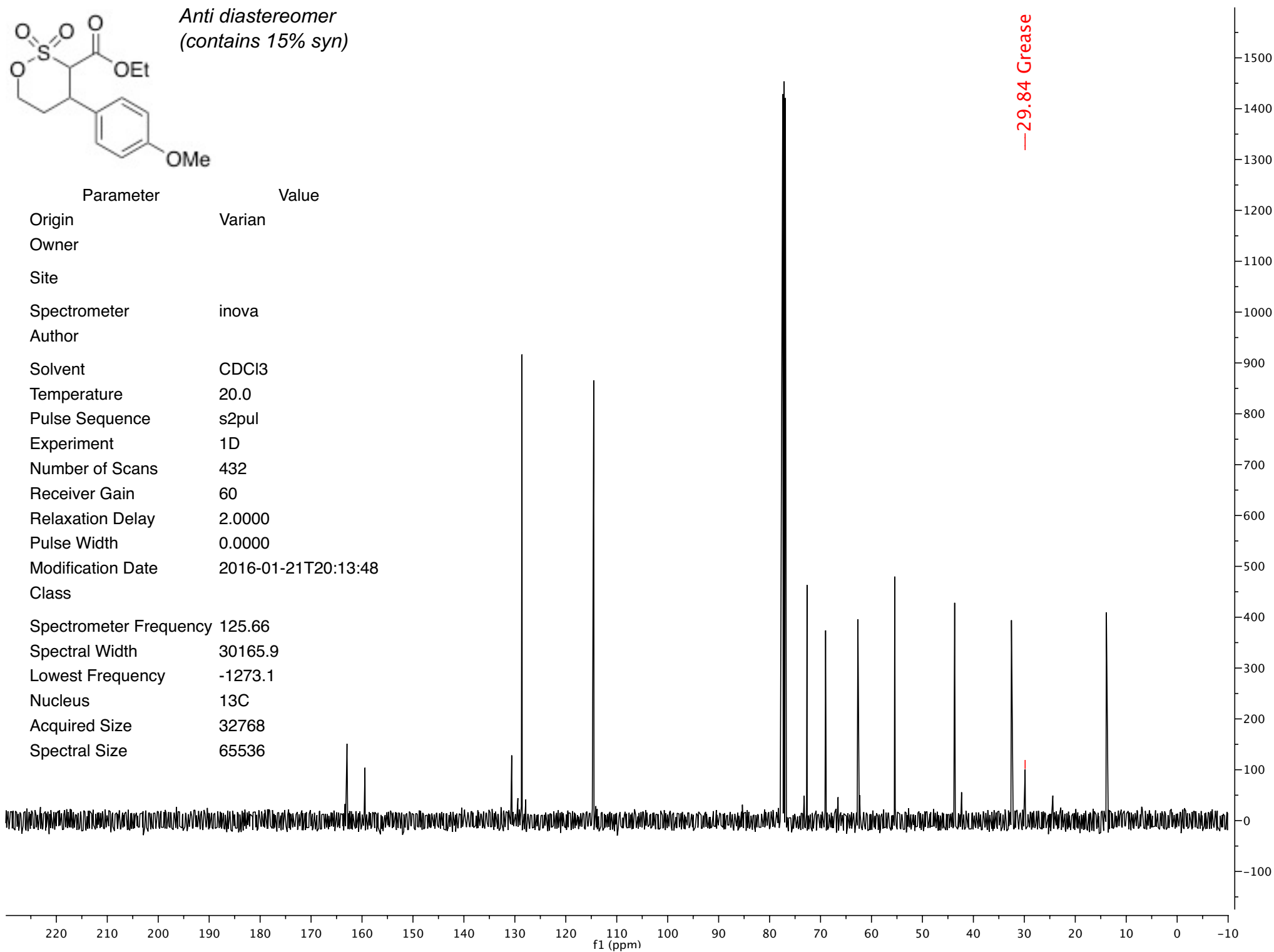
1.58 H₂O
1.25 Grease
0.89 Grease
0.07 Grease

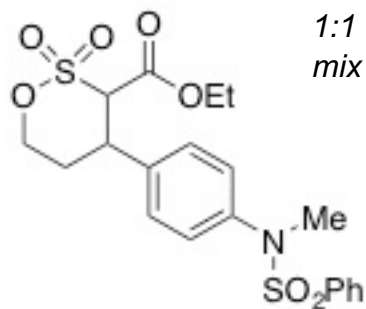


Anti diastereomer
(contains 15% syn)



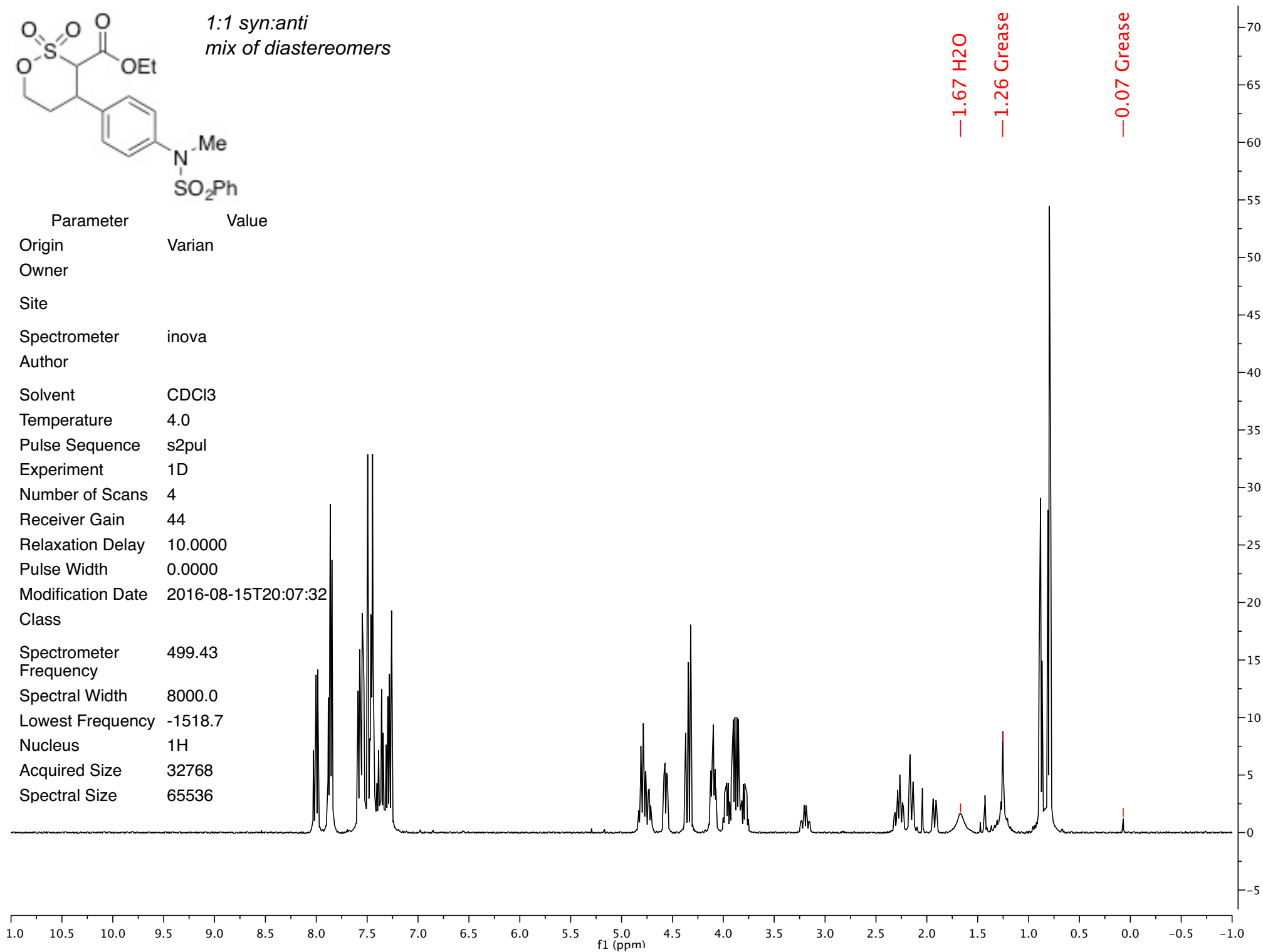
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	432
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-01-21T20:13:48
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1273.1
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

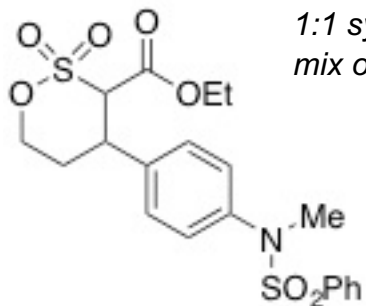




1:1 *syn:anti*
mix of diastereomers

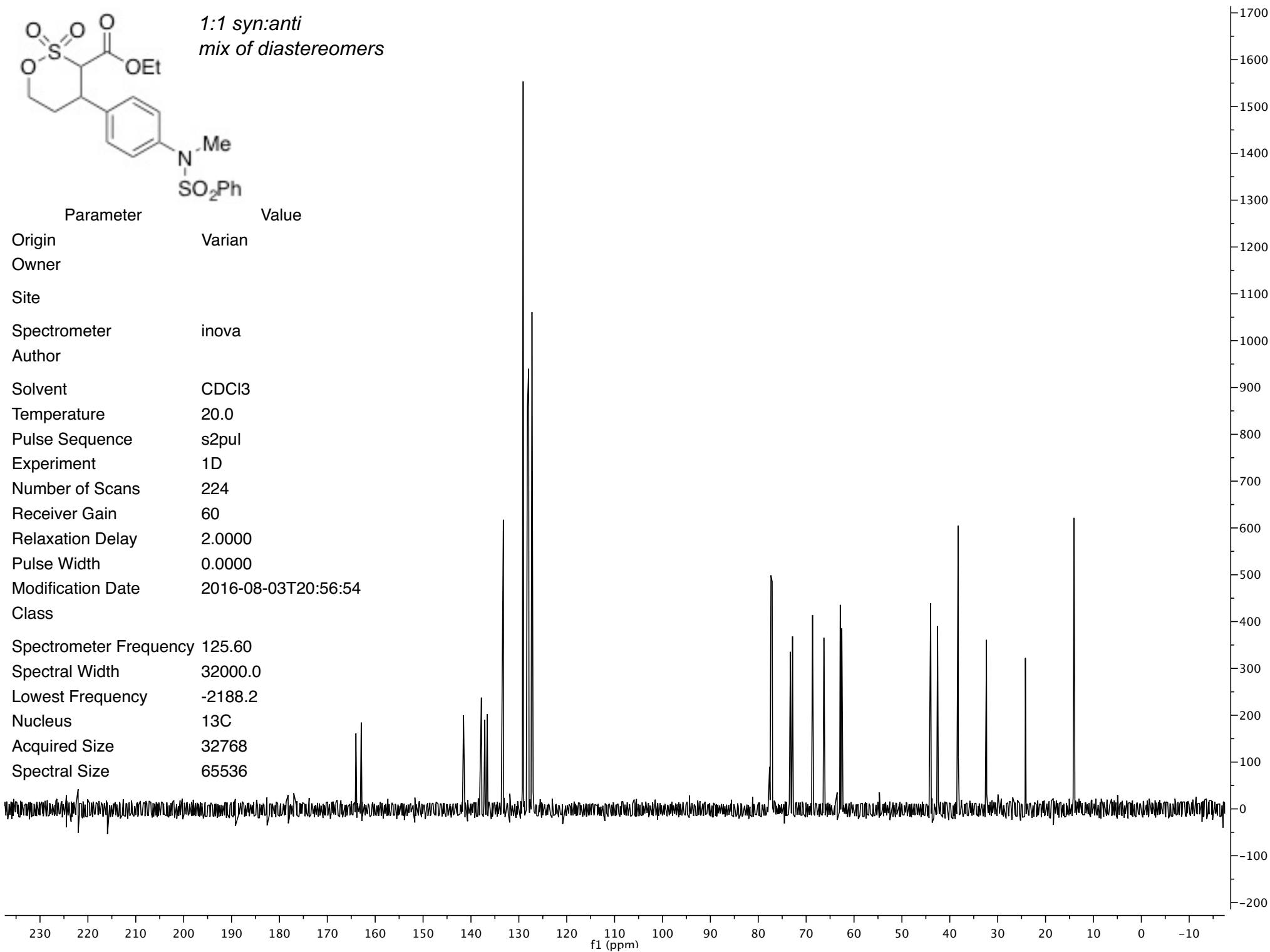
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	4.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	4
Receiver Gain	44
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-08-15T20:07:32
Class	
Spectrometer Frequency	499.43
Spectral Width	8000.0
Lowest Frequency	-1518.7
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536

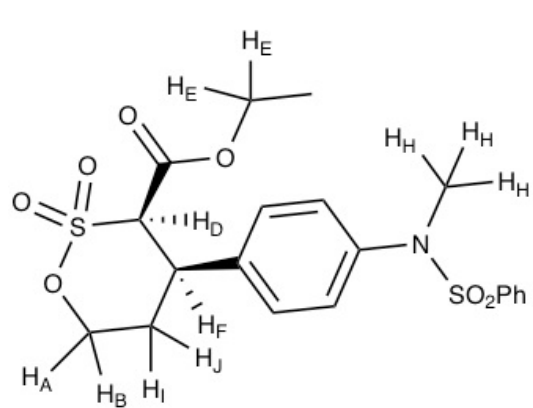




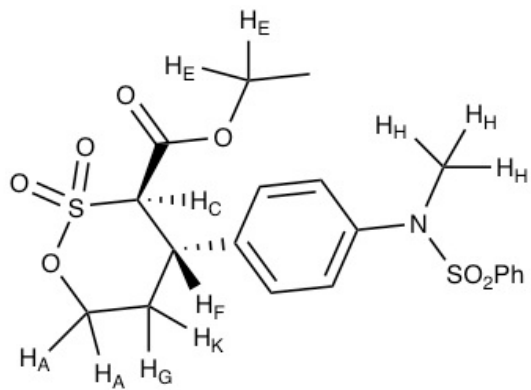
1:1 syn:anti
mix of diastereomers

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	224
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-08-03T20:56:54
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2188.2
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

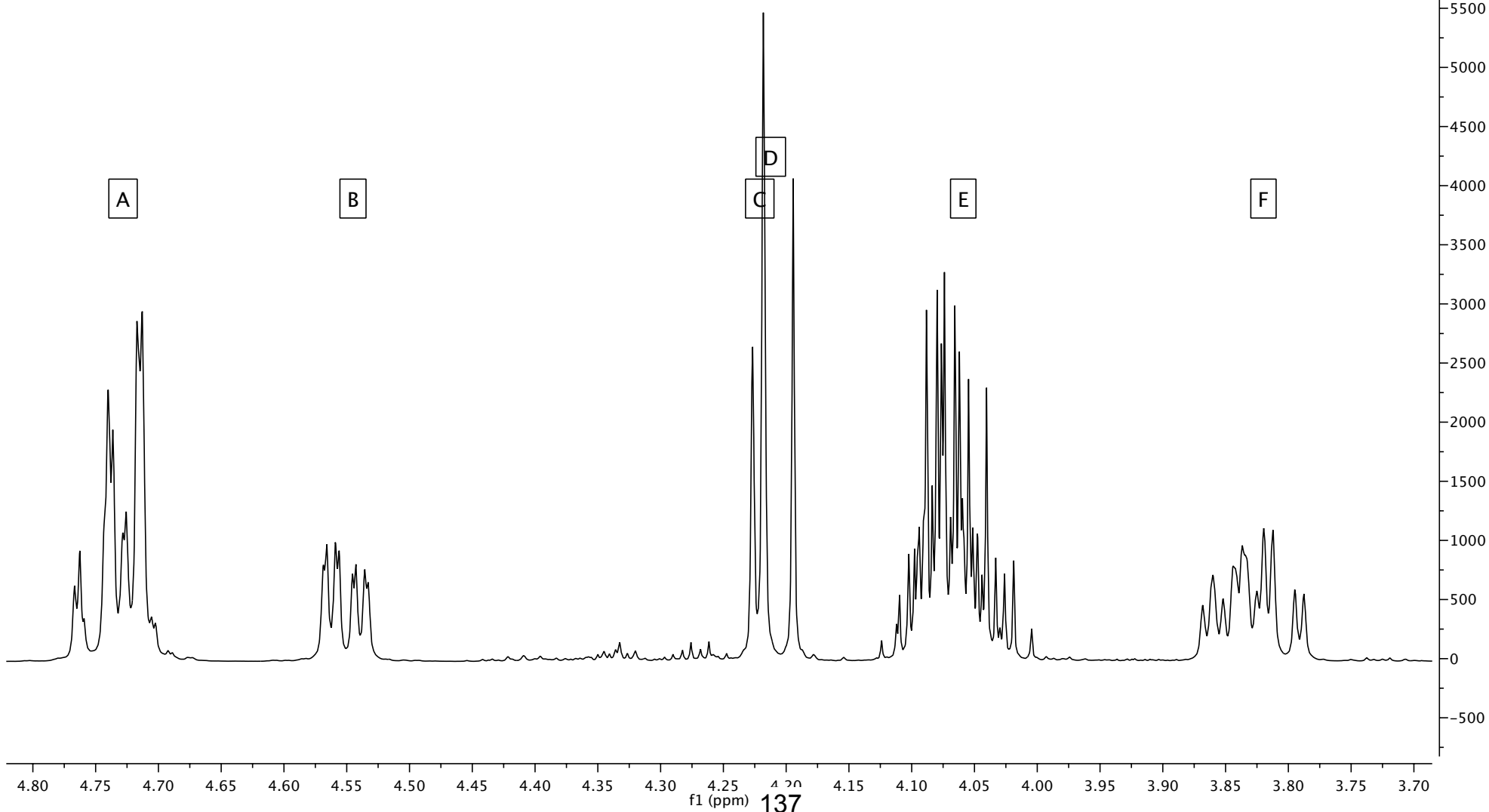


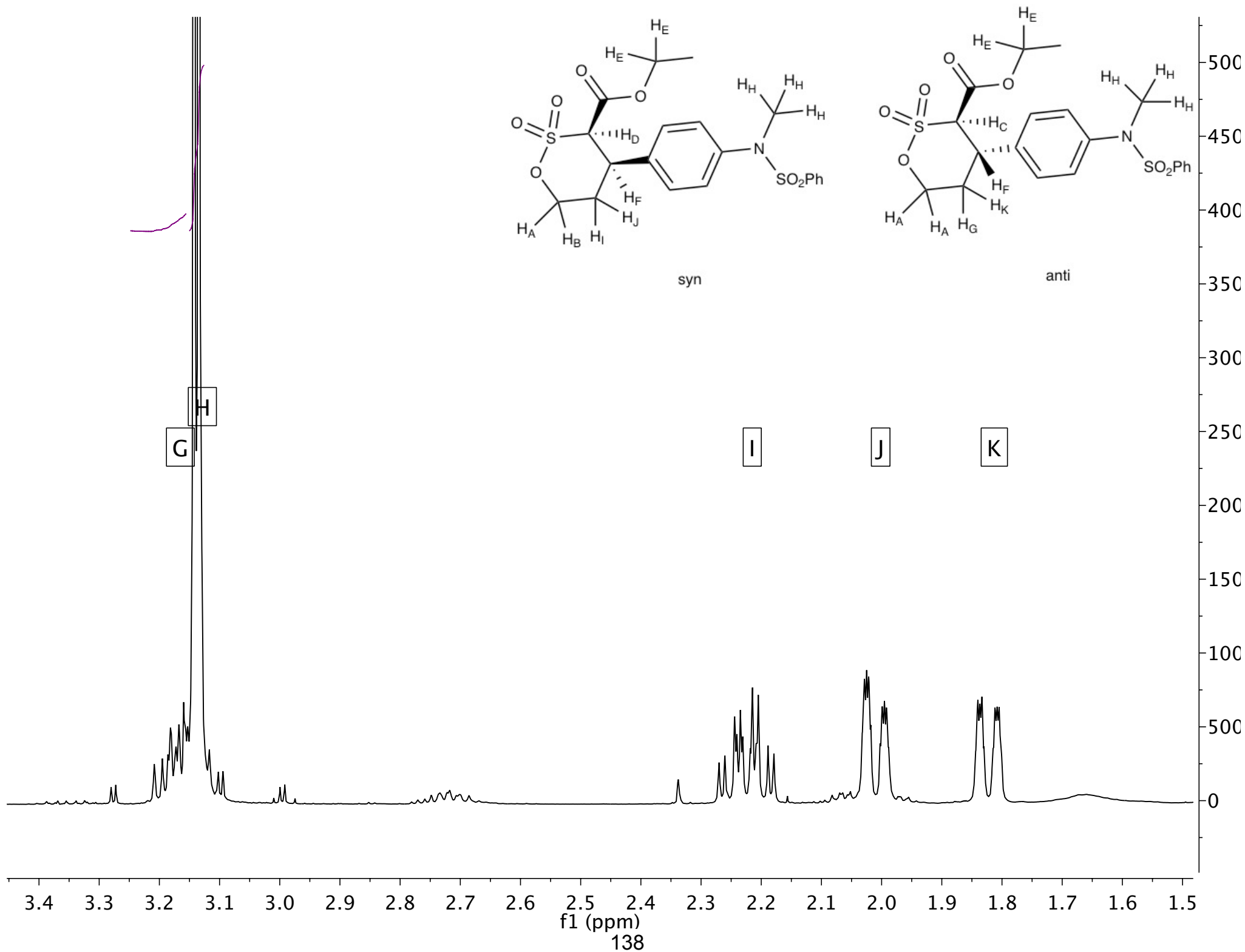


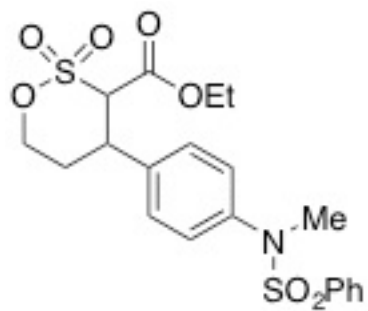
syn



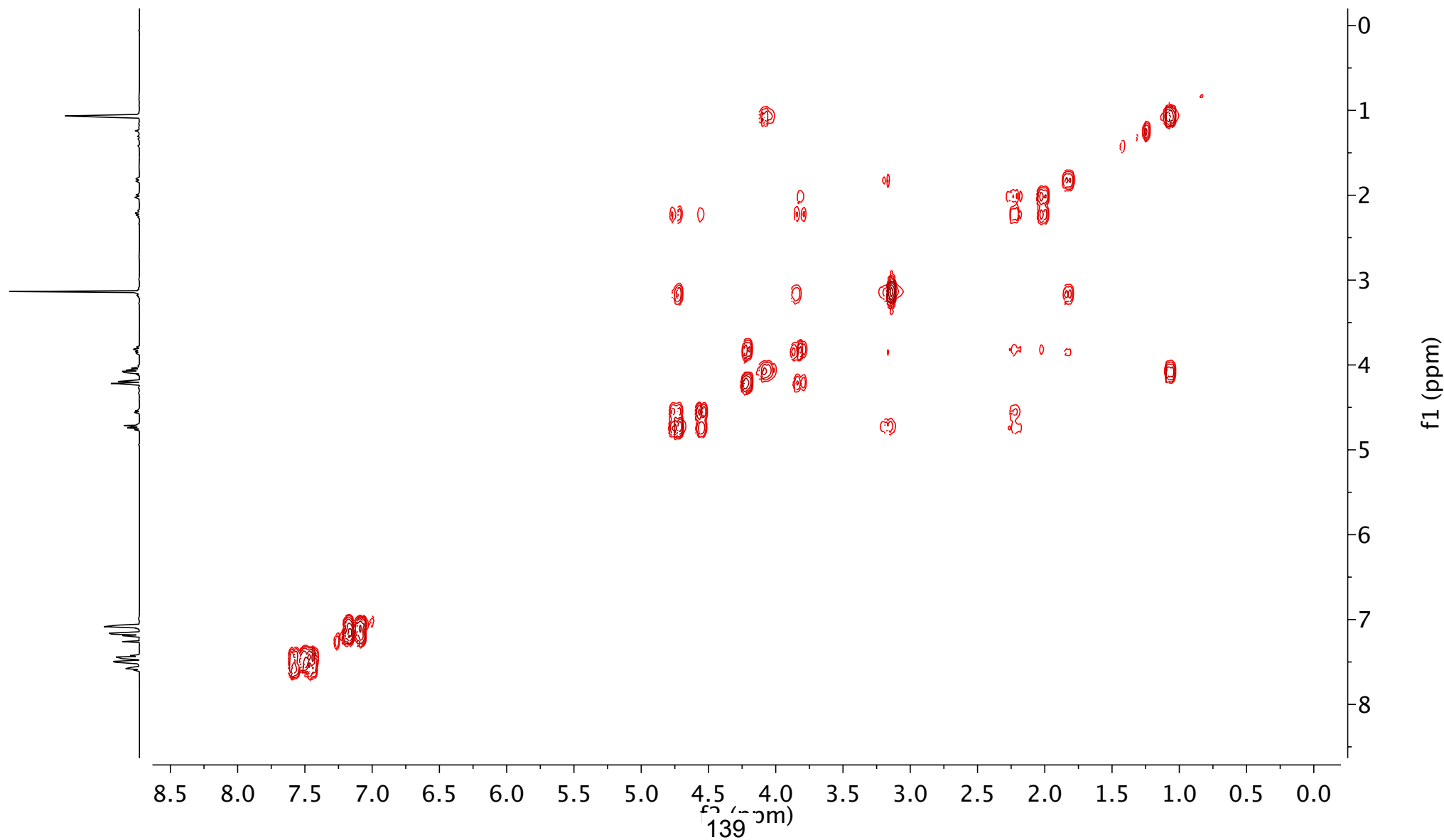
anti

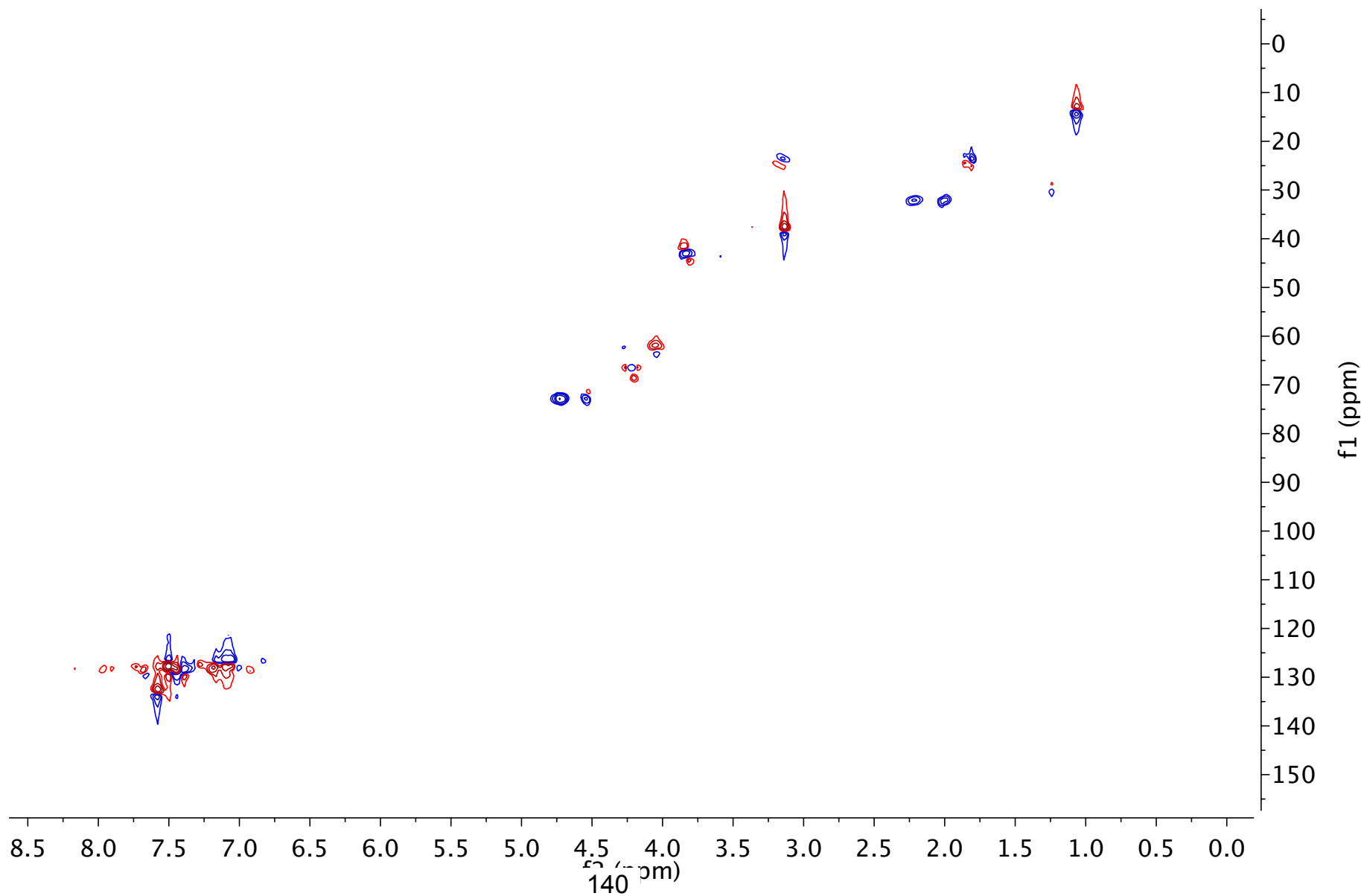
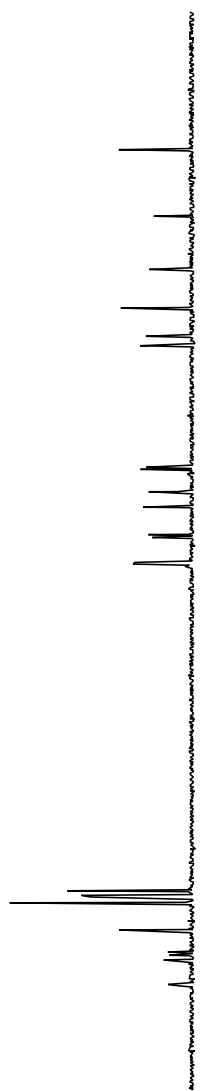
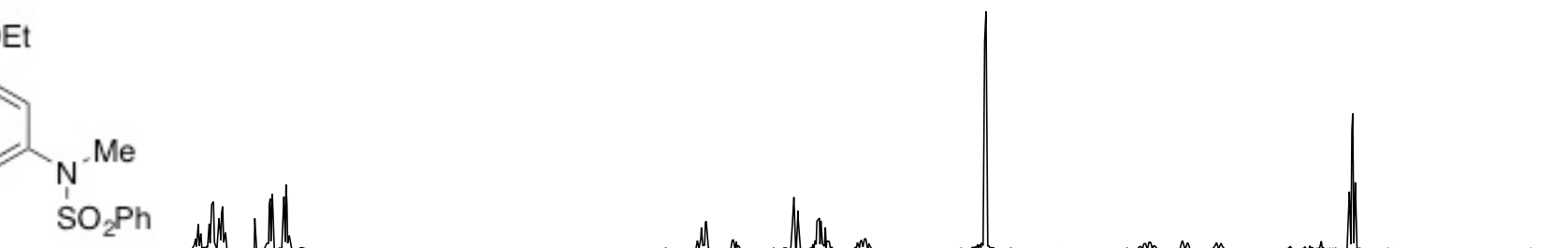
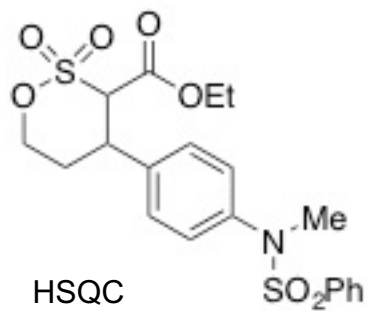


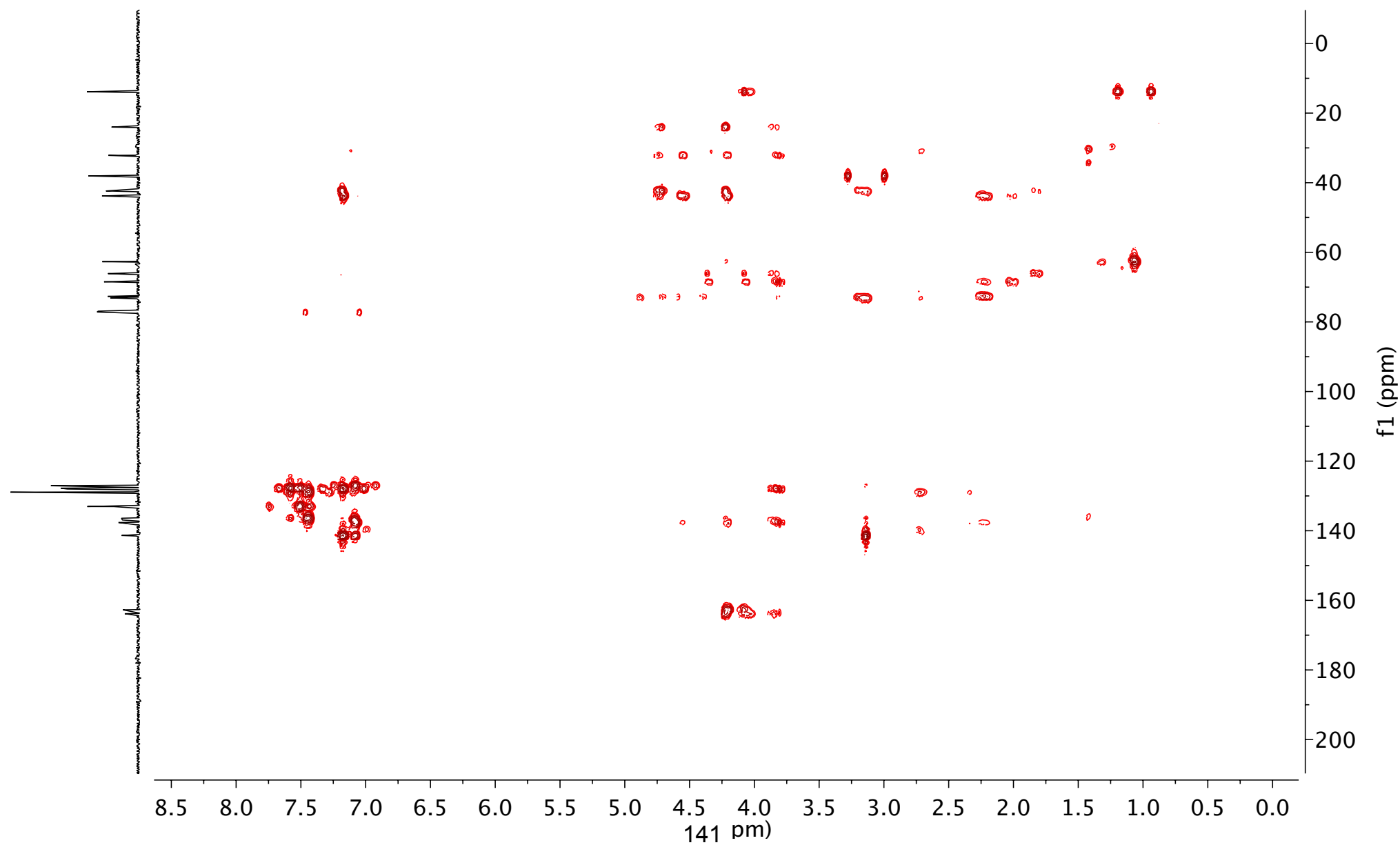
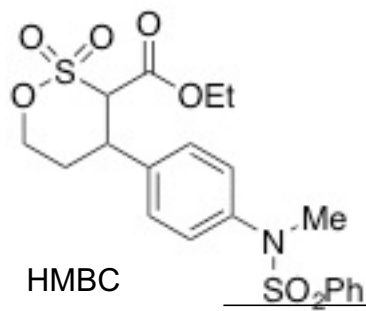


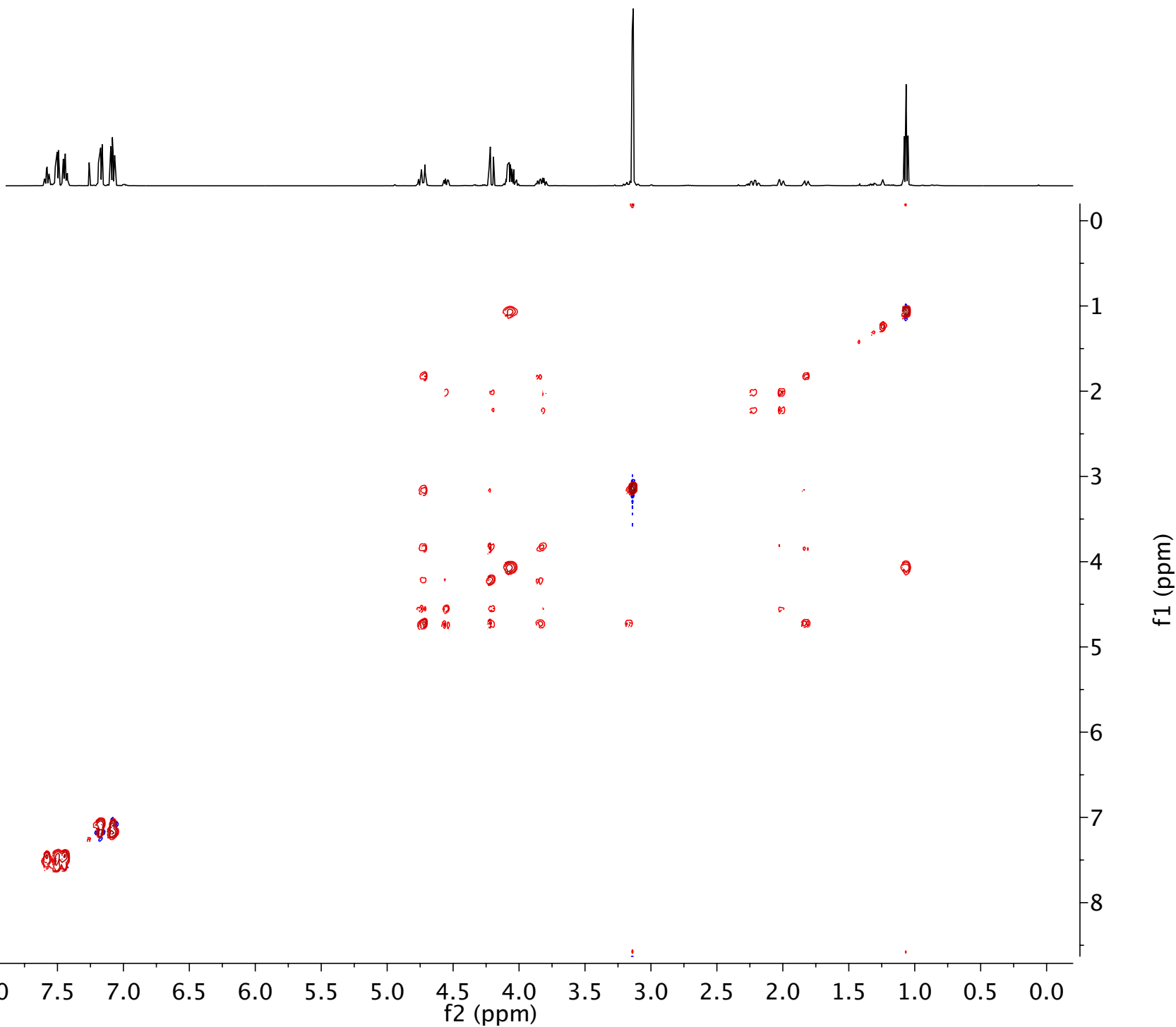
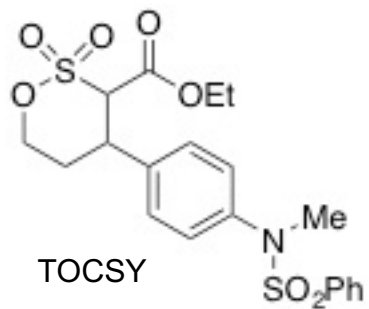


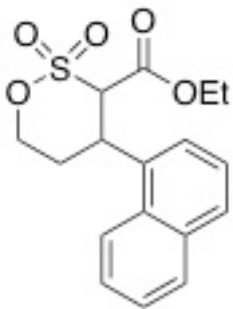
COSY





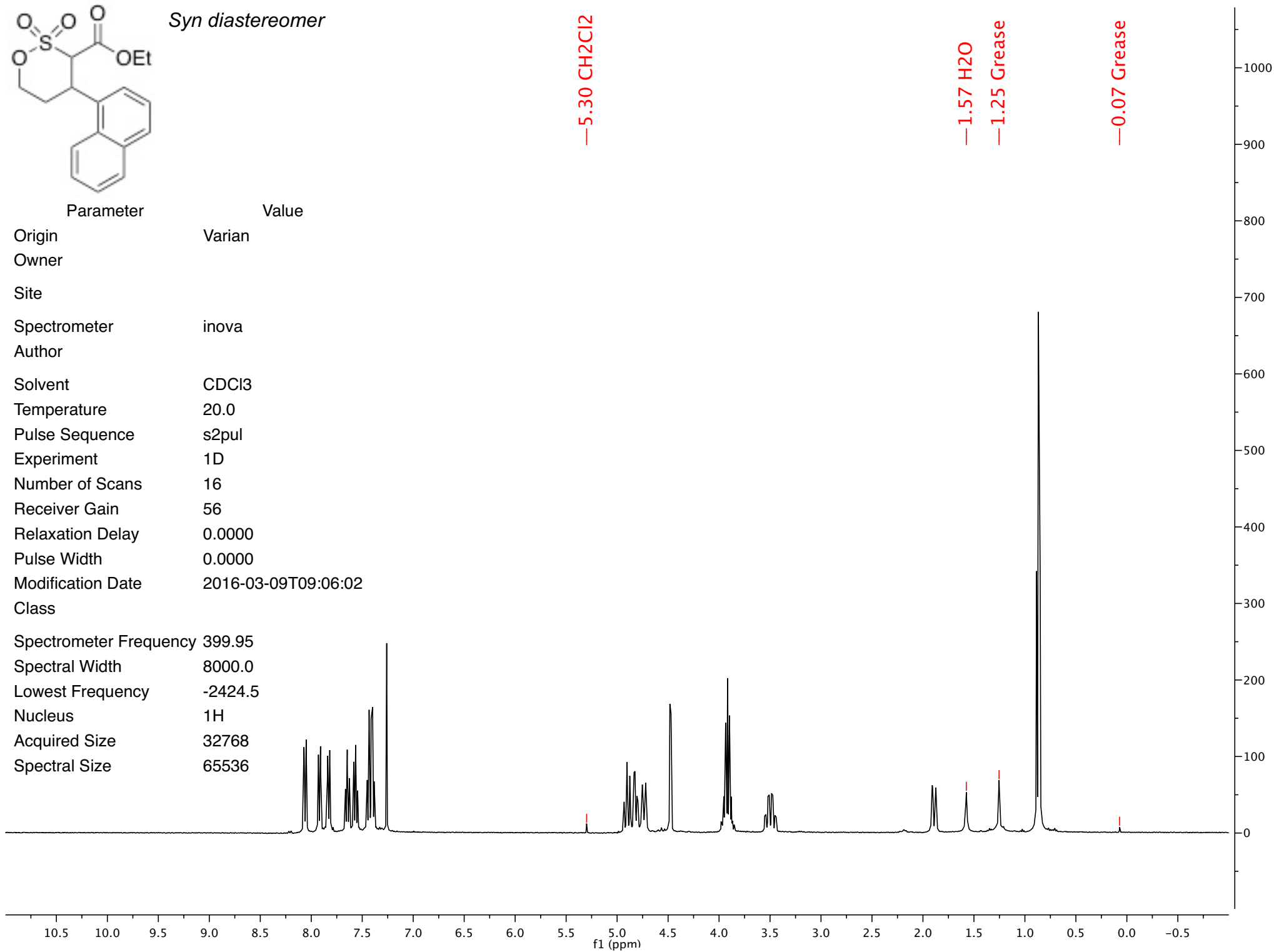


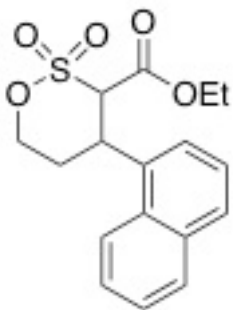




Syn diastereomer

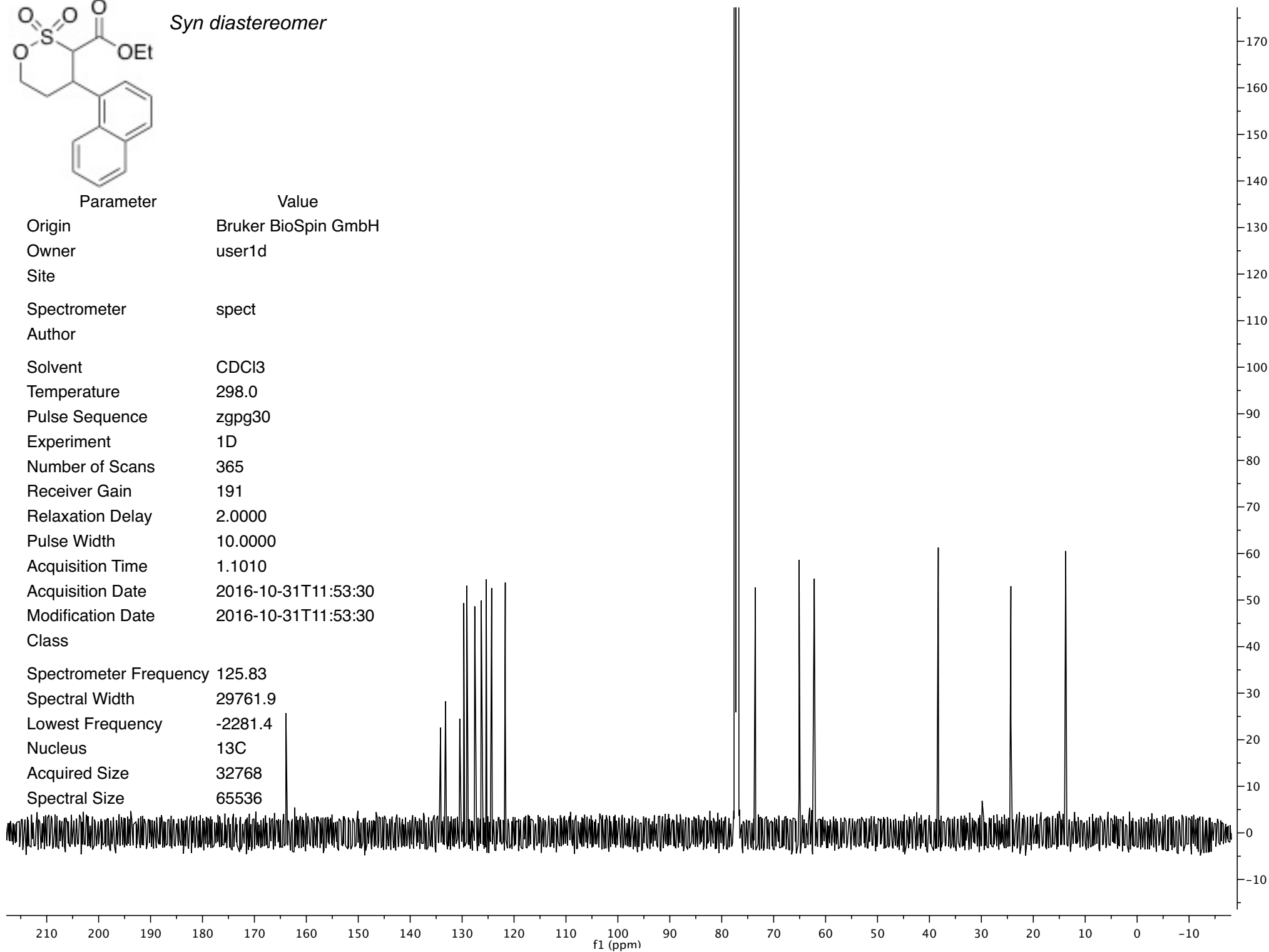
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	56
Relaxation Delay	0.0000
Pulse Width	0.0000
Modification Date	2016-03-09T09:06:02
Class	
Spectrometer Frequency	399.95
Spectral Width	8000.0
Lowest Frequency	-2424.5
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

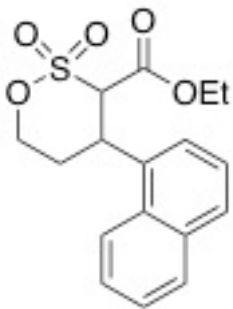




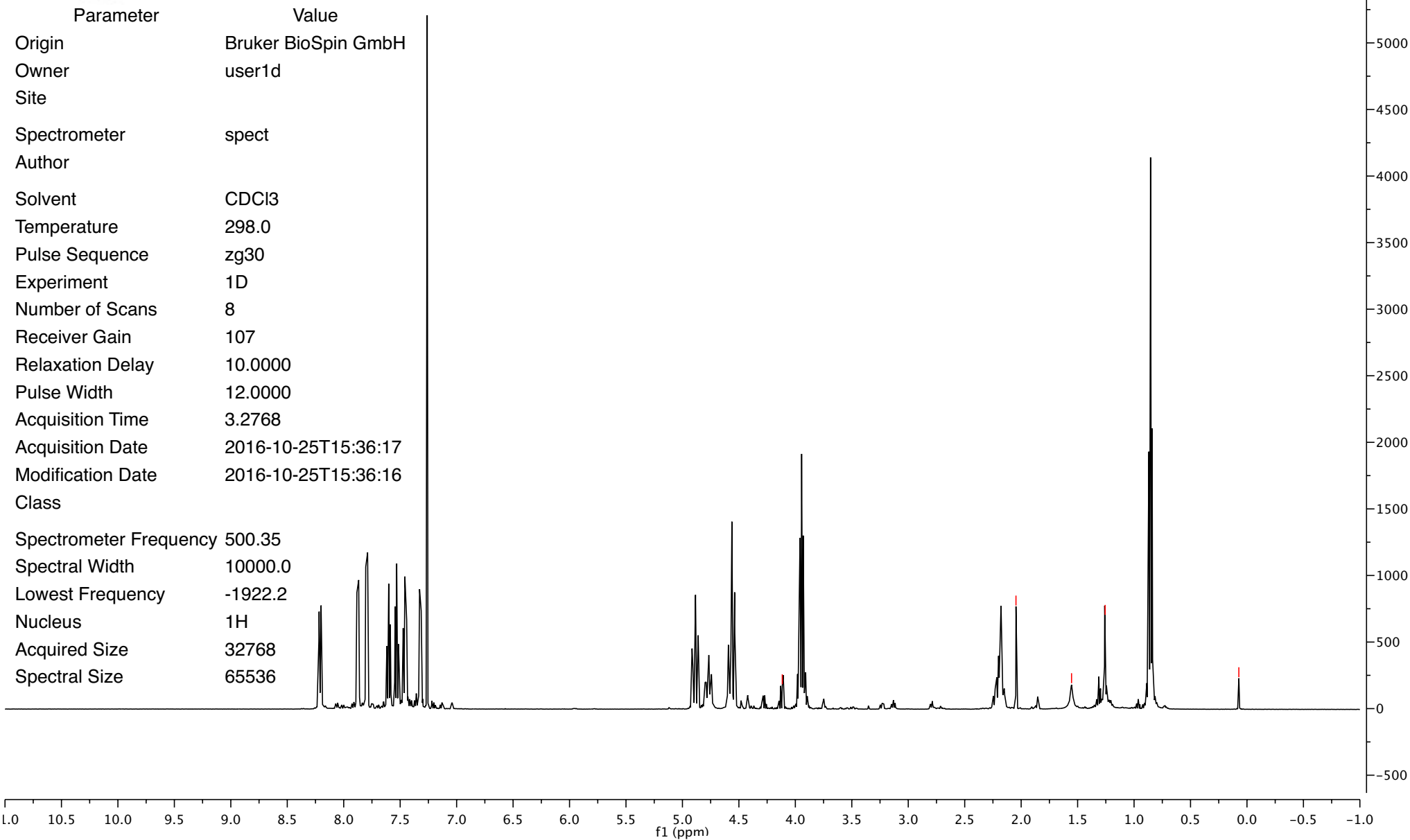
Syn diastereomer

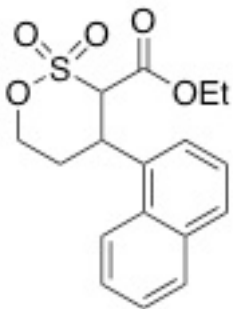
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	365
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-31T11:53:30
Modification Date	2016-10-31T11:53:30
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2281.4
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536





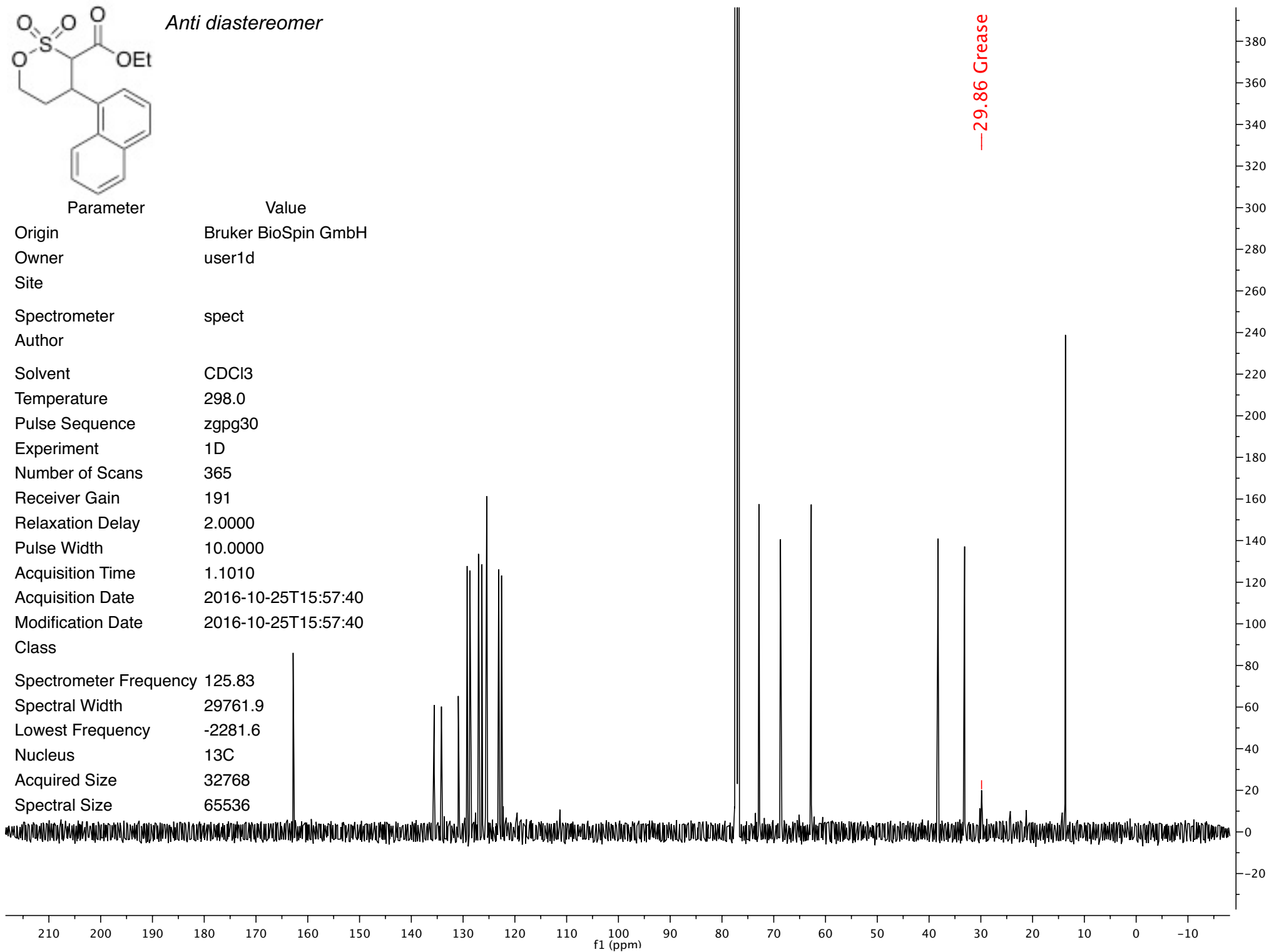
*Anti diastereomer
(contains unknown impurity;
yield determined with internal standard)*





Anti diastereomer

Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	365
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-25T15:57:40
Modification Date	2016-10-25T15:57:40
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2281.6
Nucleus	13C
Acquired Size	32768
Spectral Size	65536





Syn diastereomer

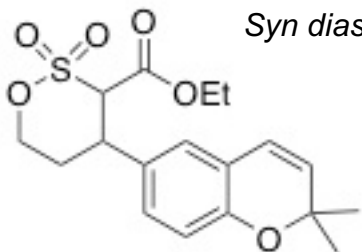
CCOC(=O)C1C2C(C1)C(=C3C=C(C(C3)OC(C2)C)C=C4C=CC(=C(C=C4)C)C)C(=O)O

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	32
Receiver Gain	48
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-04-22T13:48:14
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1520.1
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536

1.54 H₂O
1.25 Grease
0.07 Grease

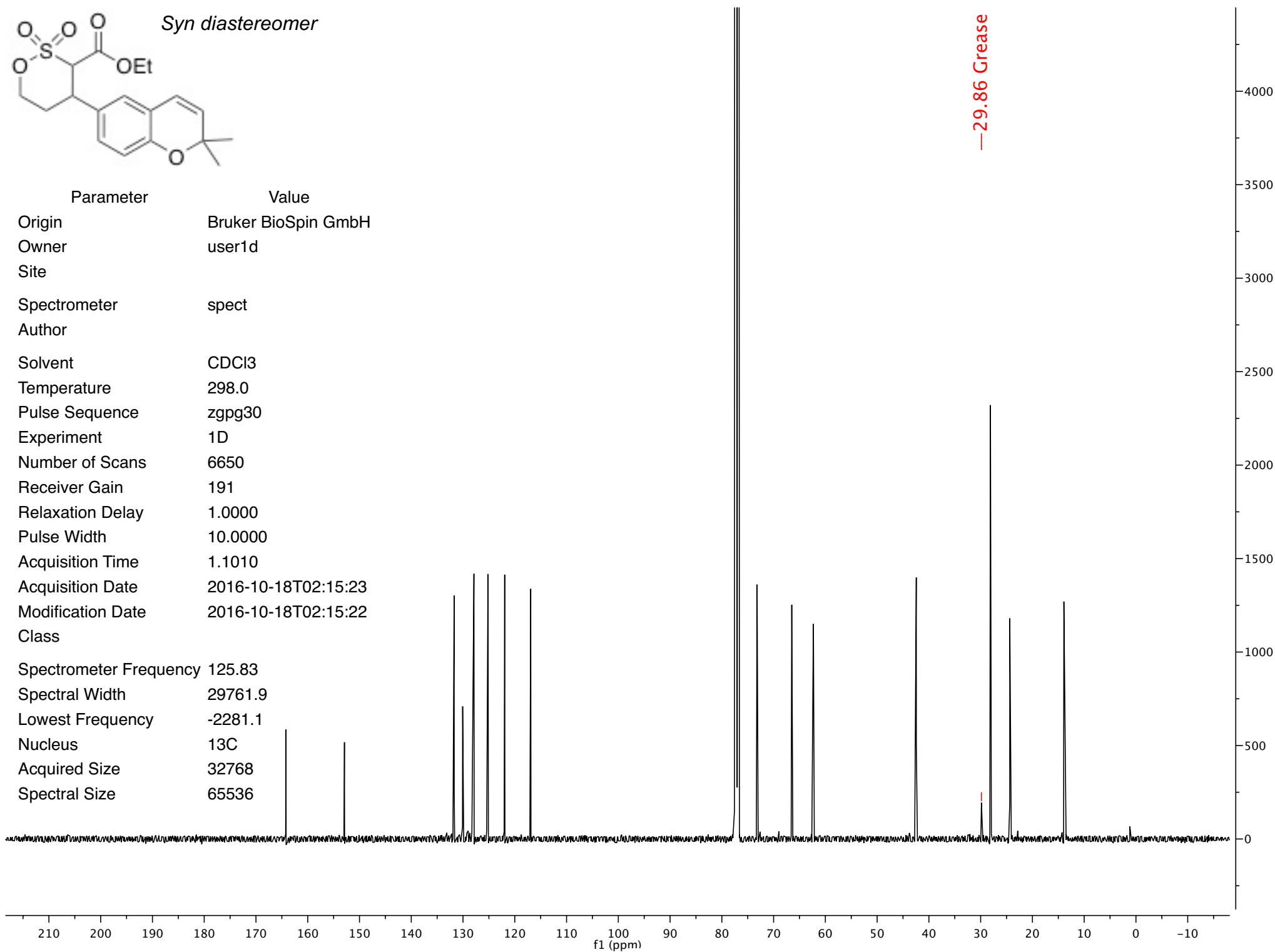
f1 (ppm)

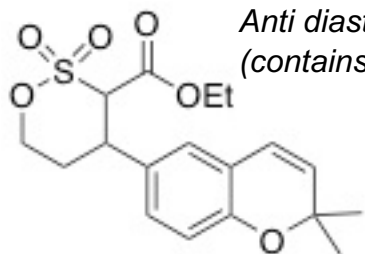
Syn diastereomer



Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	6650
Receiver Gain	191
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-18T02:15:23
Modification Date	2016-10-18T02:15:22
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2281.1
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

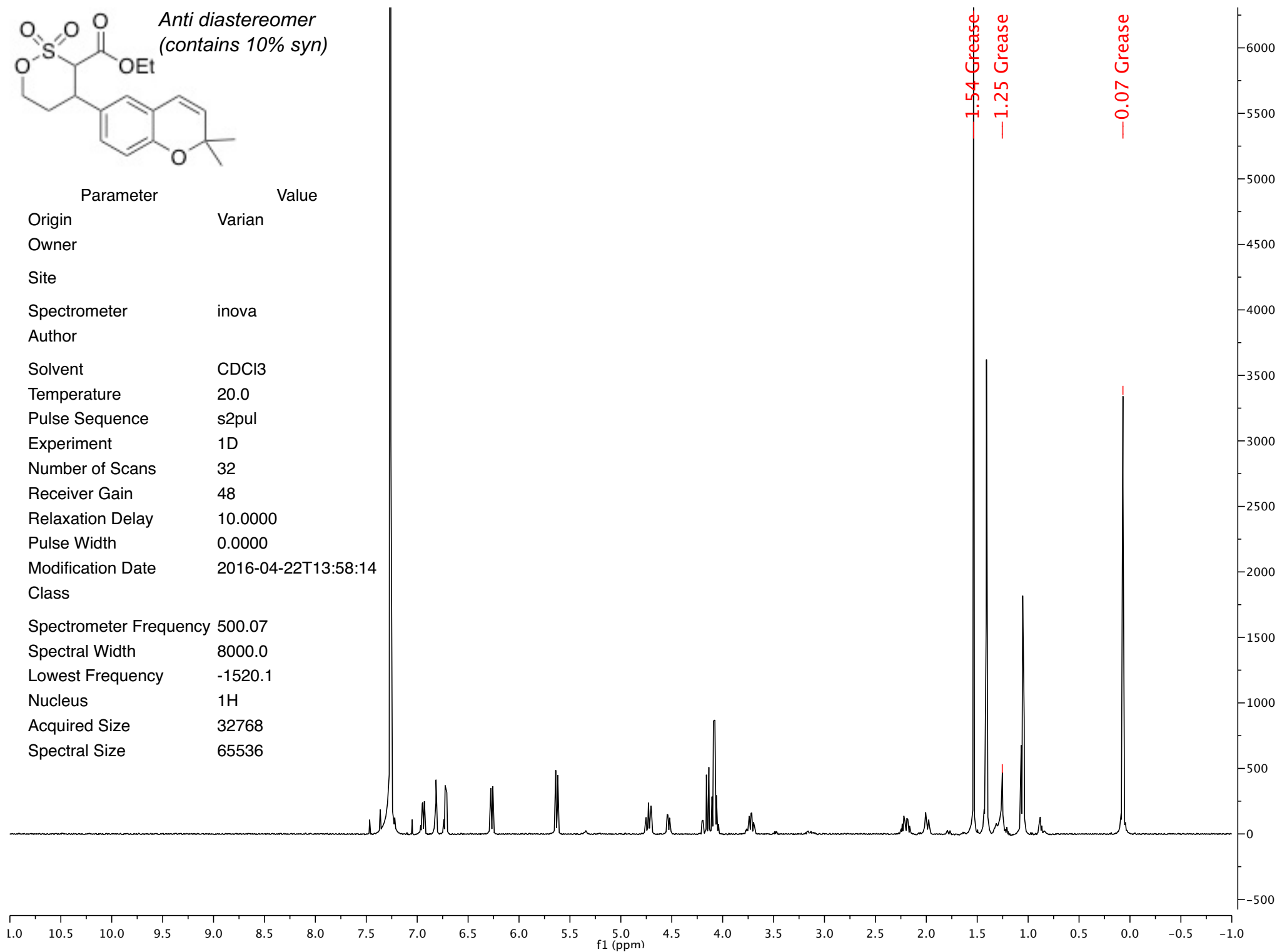
—29.86 Grease

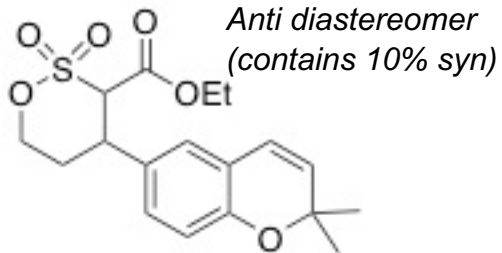




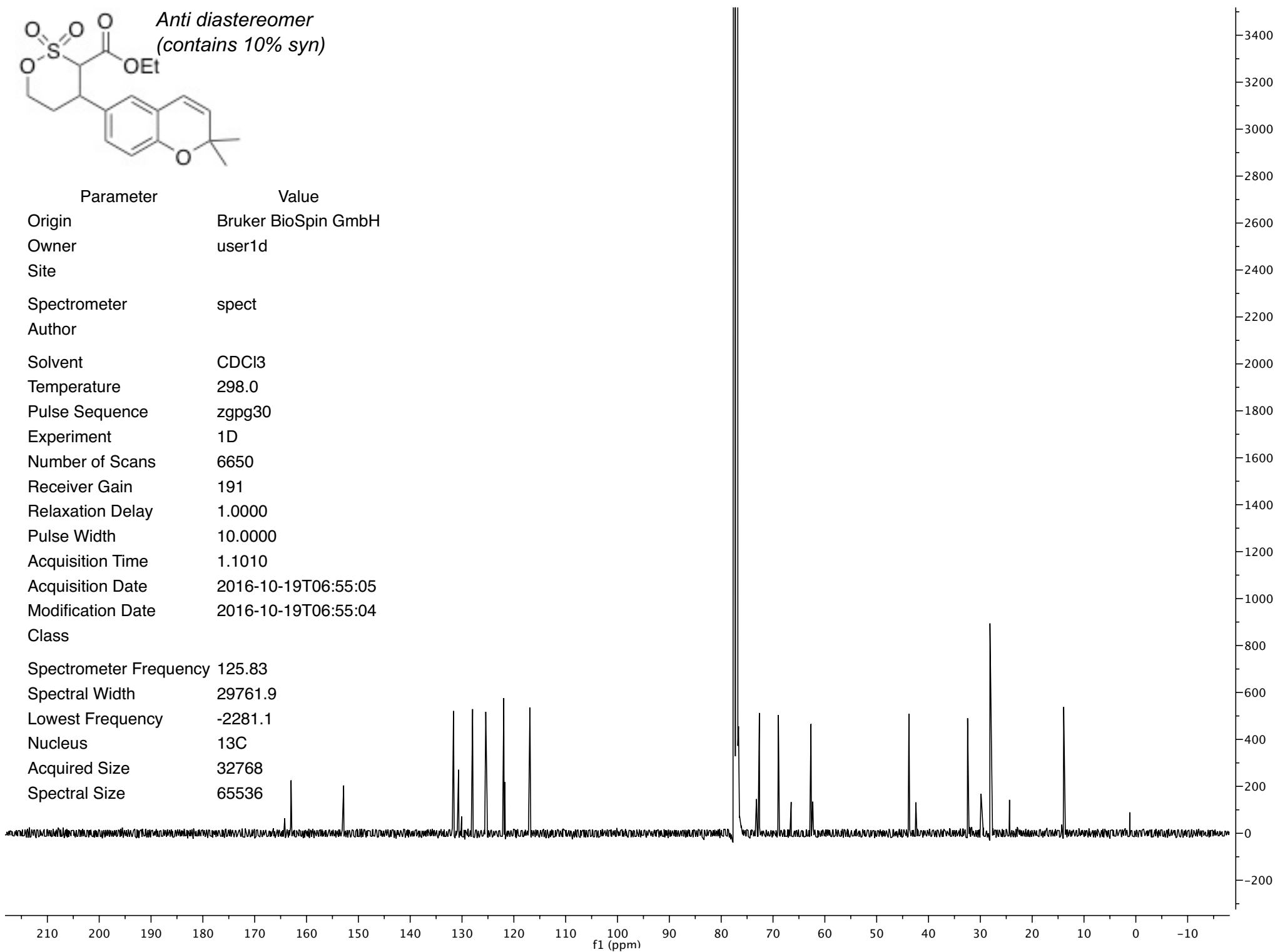
*Anti diastereomer
(contains 10% syn)*

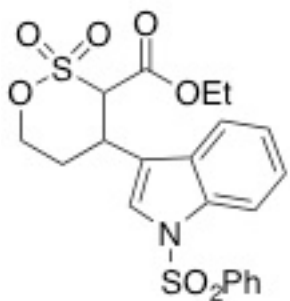
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	32
Receiver Gain	48
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-04-22T13:58:14
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1520.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536





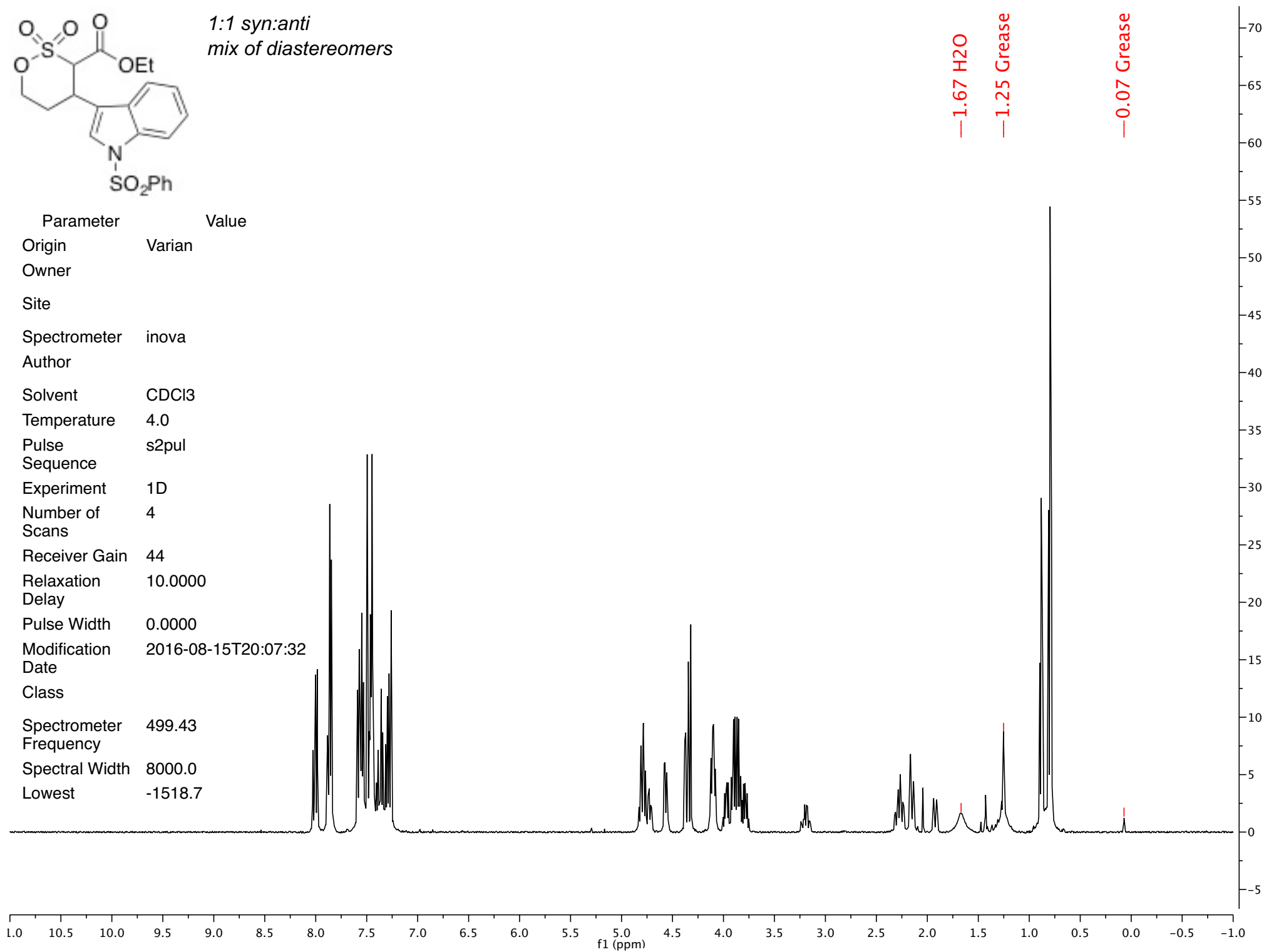
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	6650
Receiver Gain	191
Relaxation Delay	1.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-19T06:55:05
Modification Date	2016-10-19T06:55:04
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2281.1
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

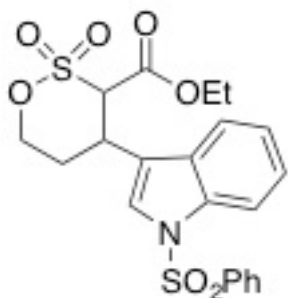




1:1 syn:anti
mix of diastereomers

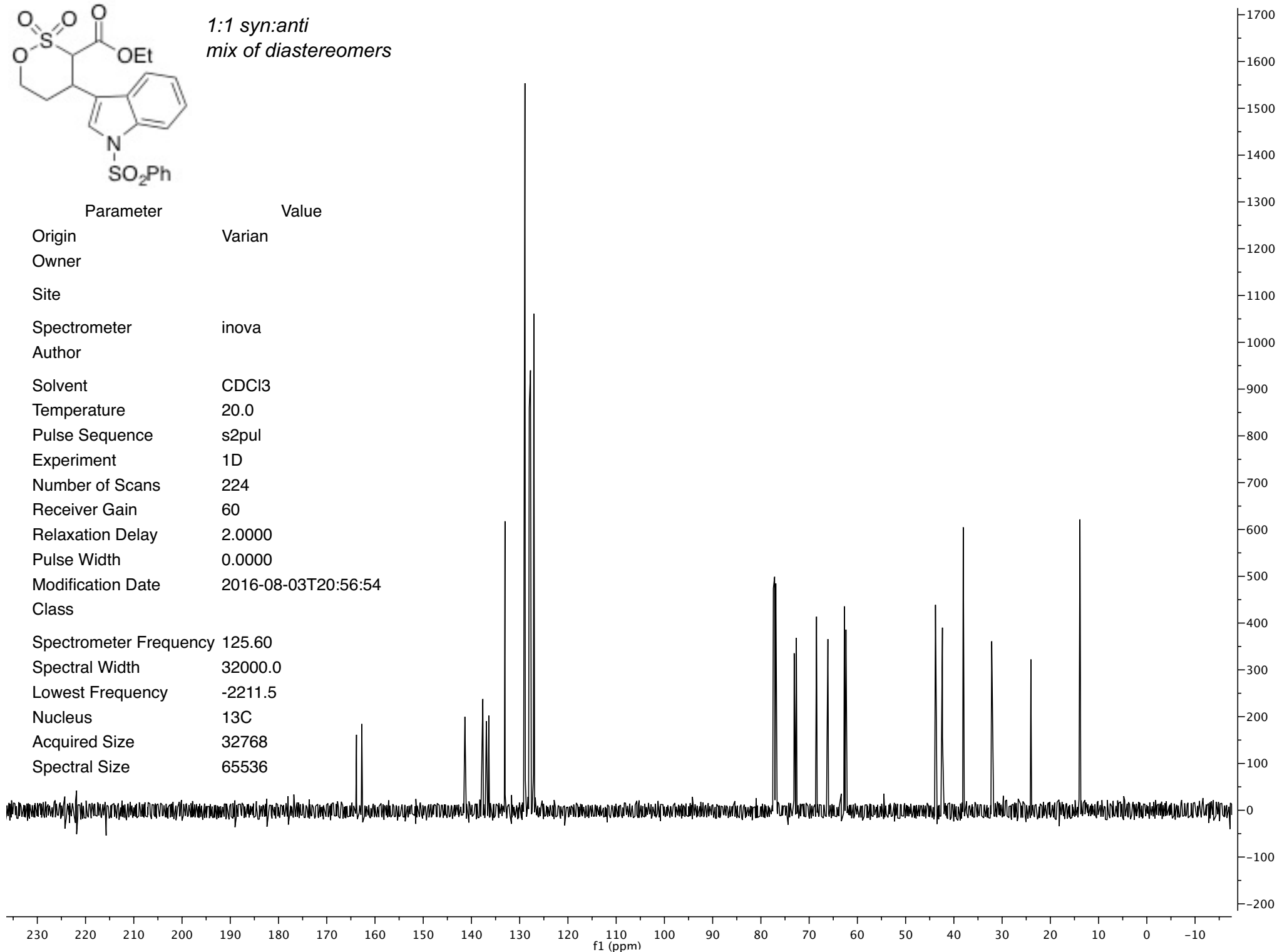
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	4.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	4
Receiver Gain	44
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-08-15T20:07:32
Class	
Spectrometer Frequency	499.43
Spectral Width	8000.0
Lowest	-1518.7

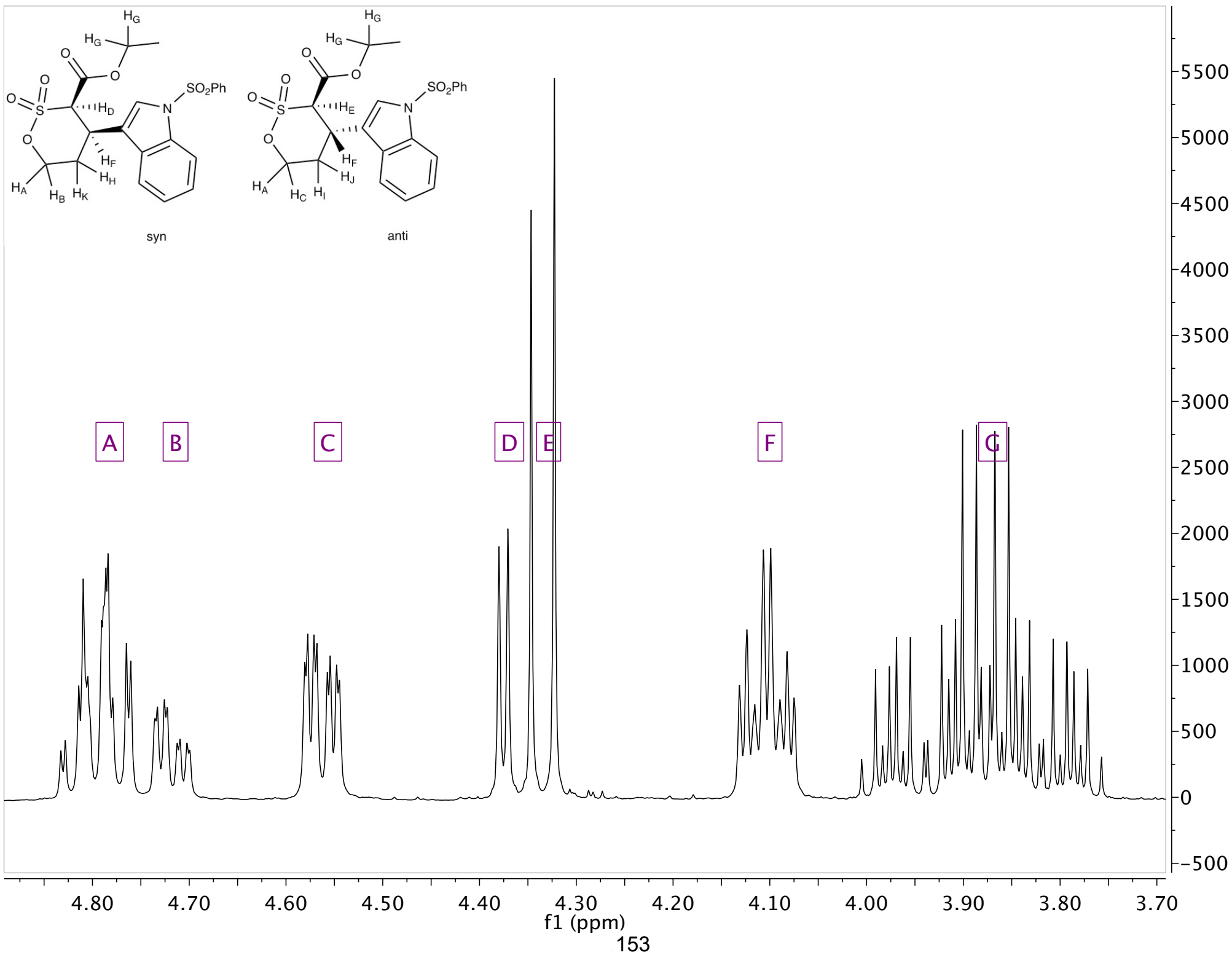


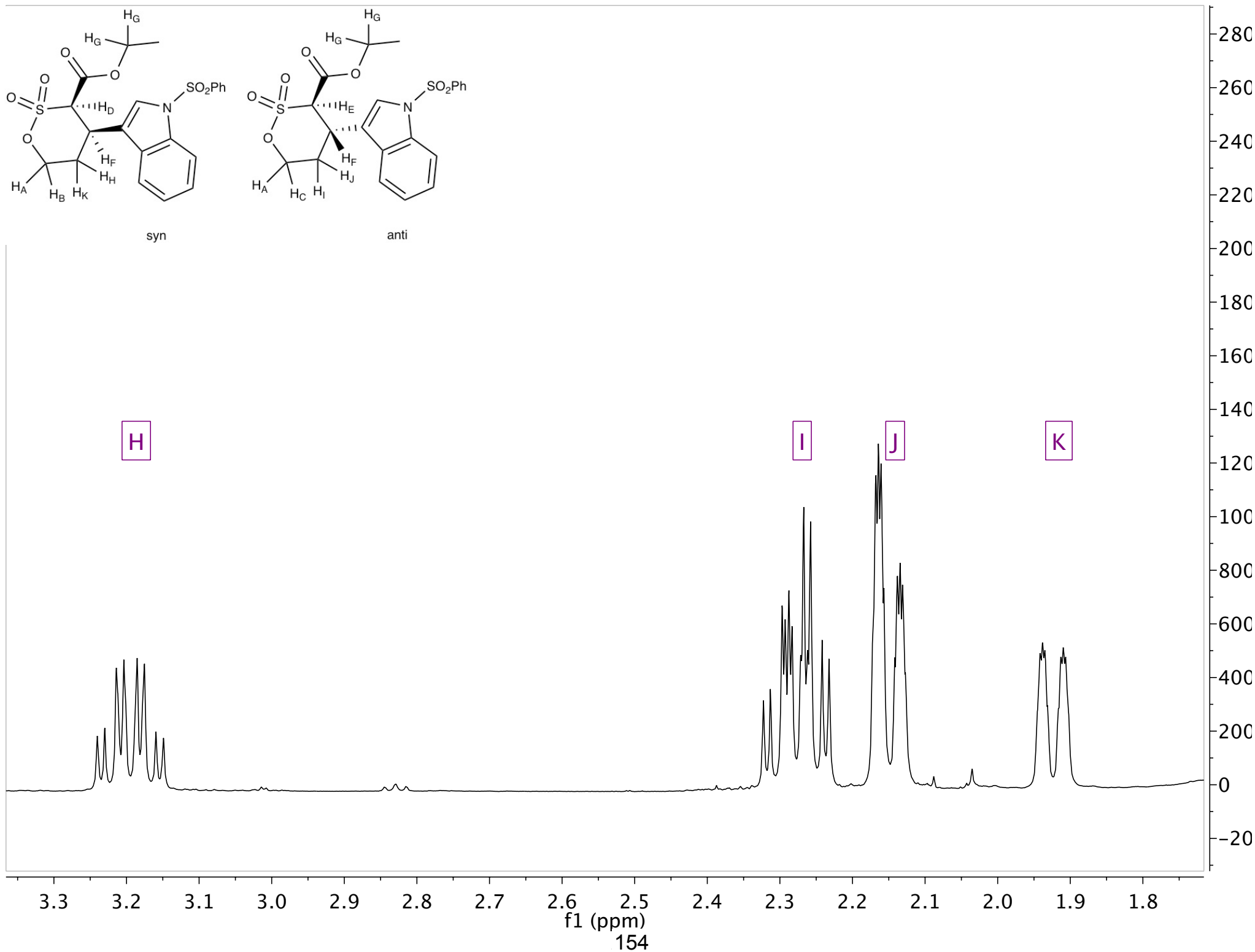


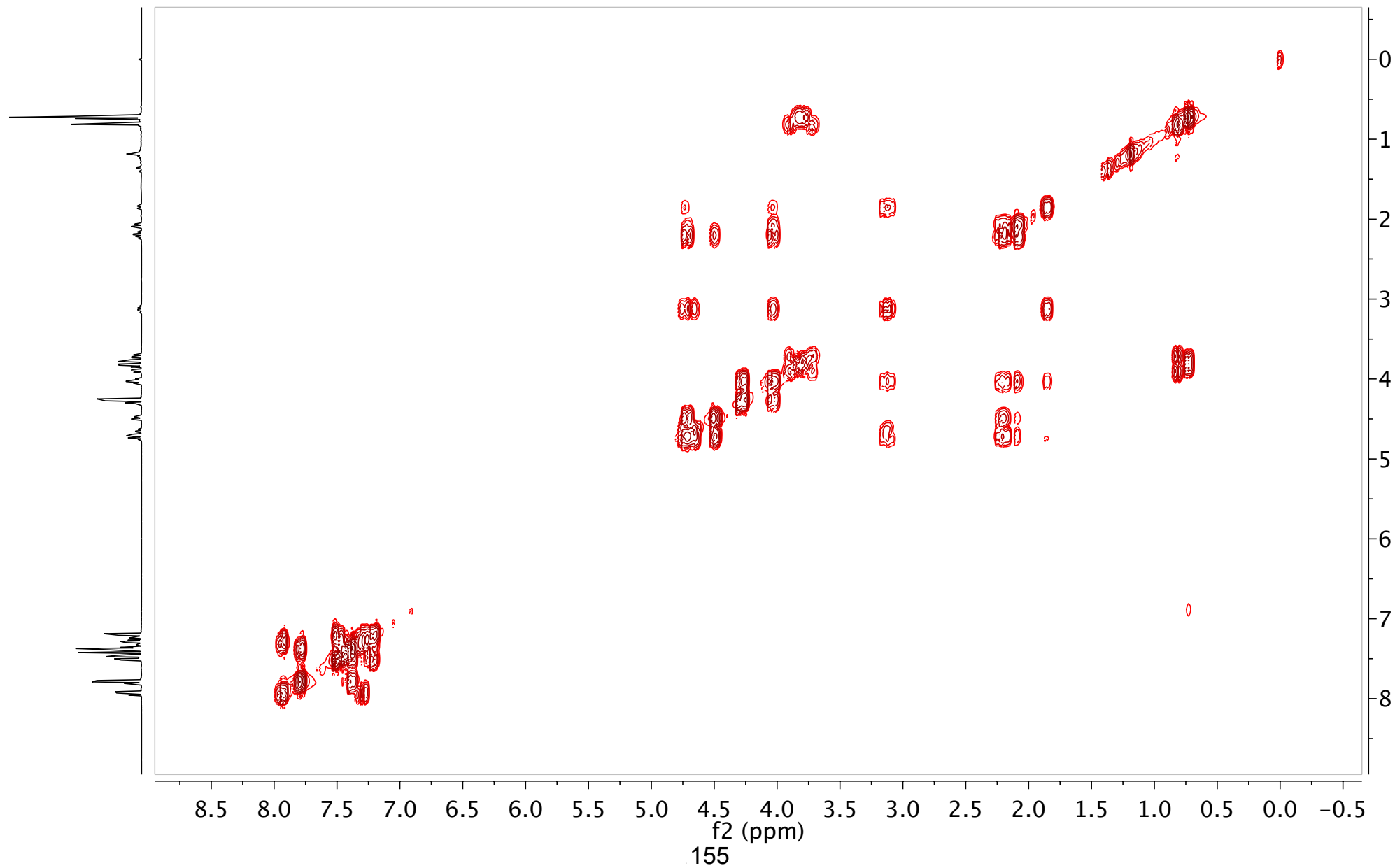
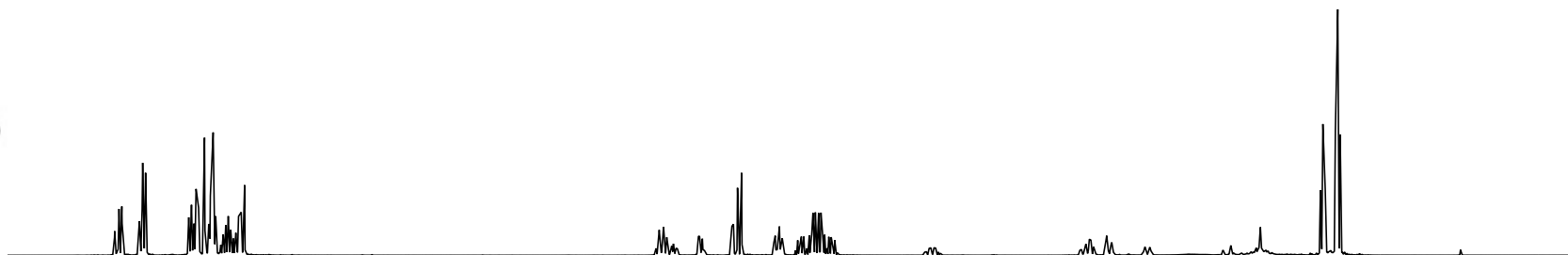
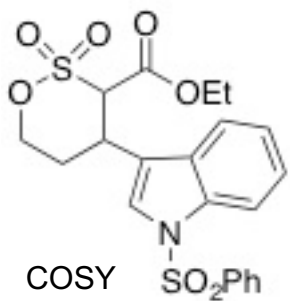
1:1 syn:anti
mix of diastereomers

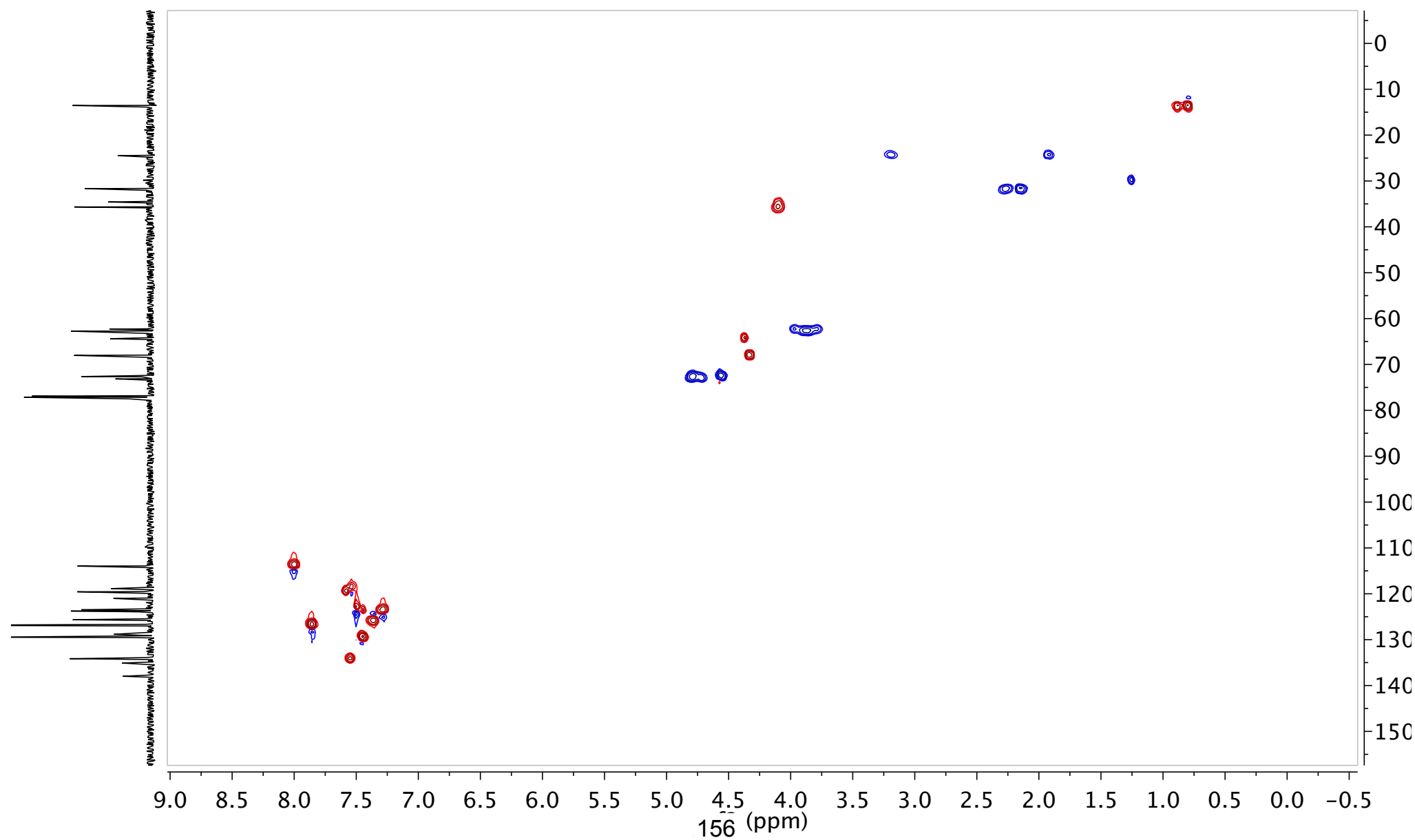
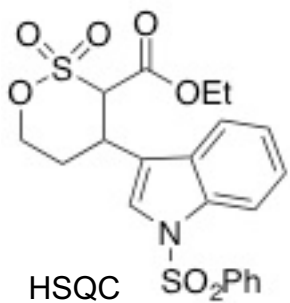
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	224
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-08-03T20:56:54
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2211.5
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

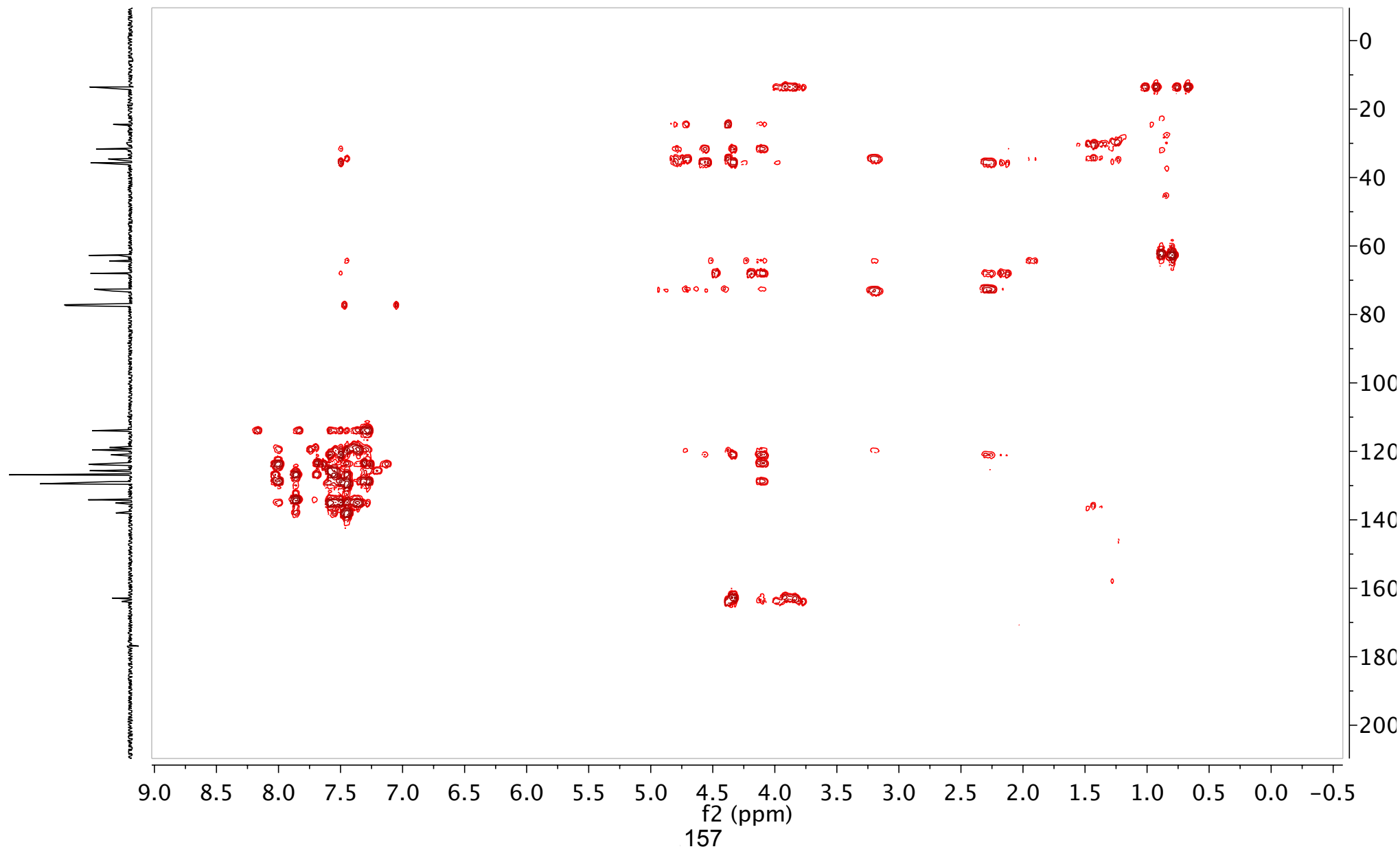
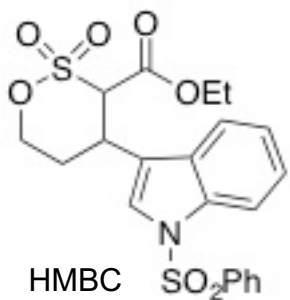


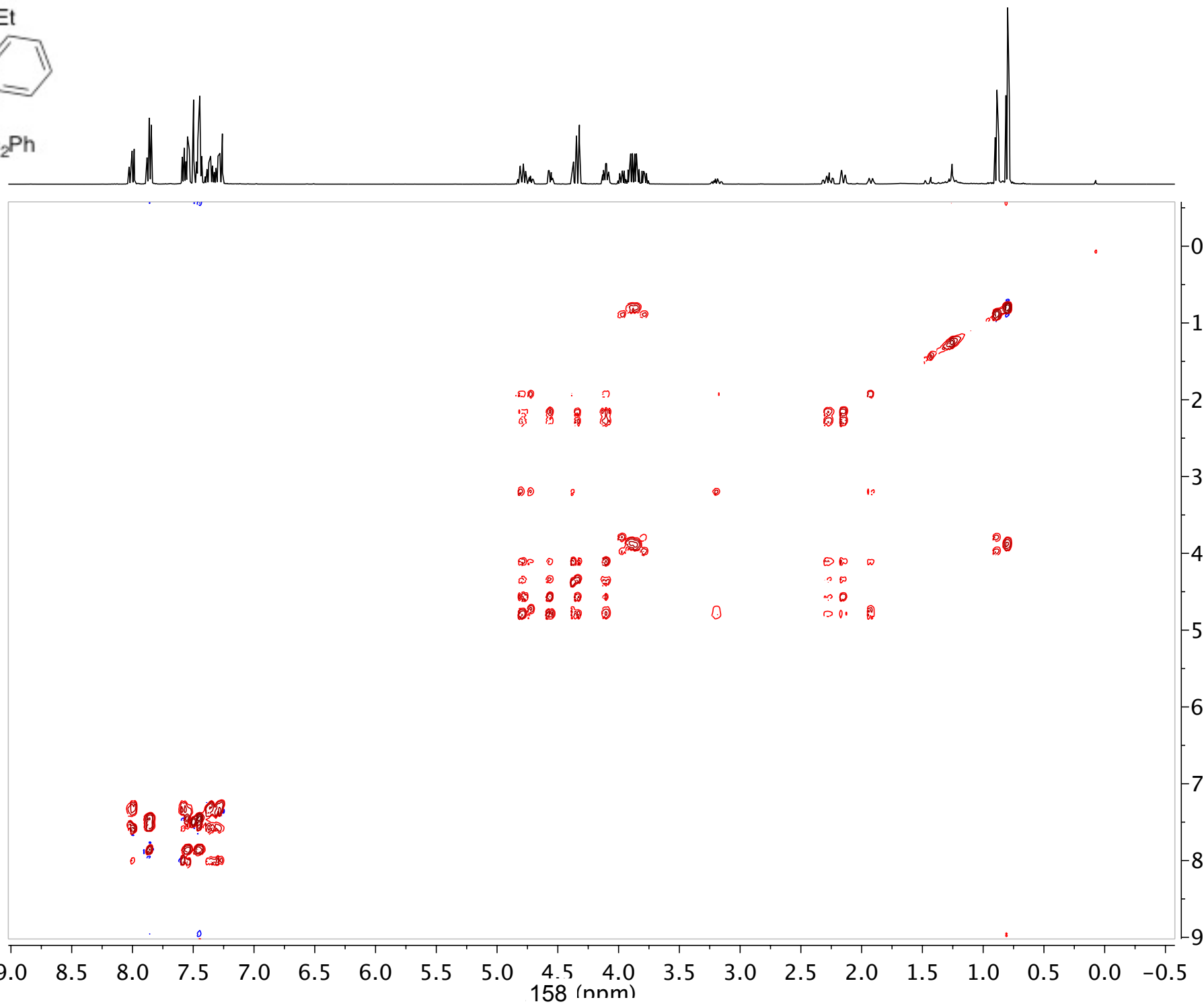
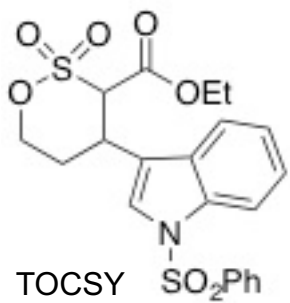


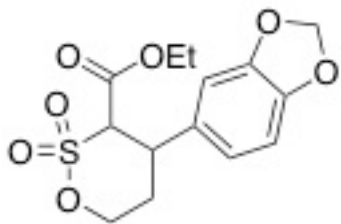












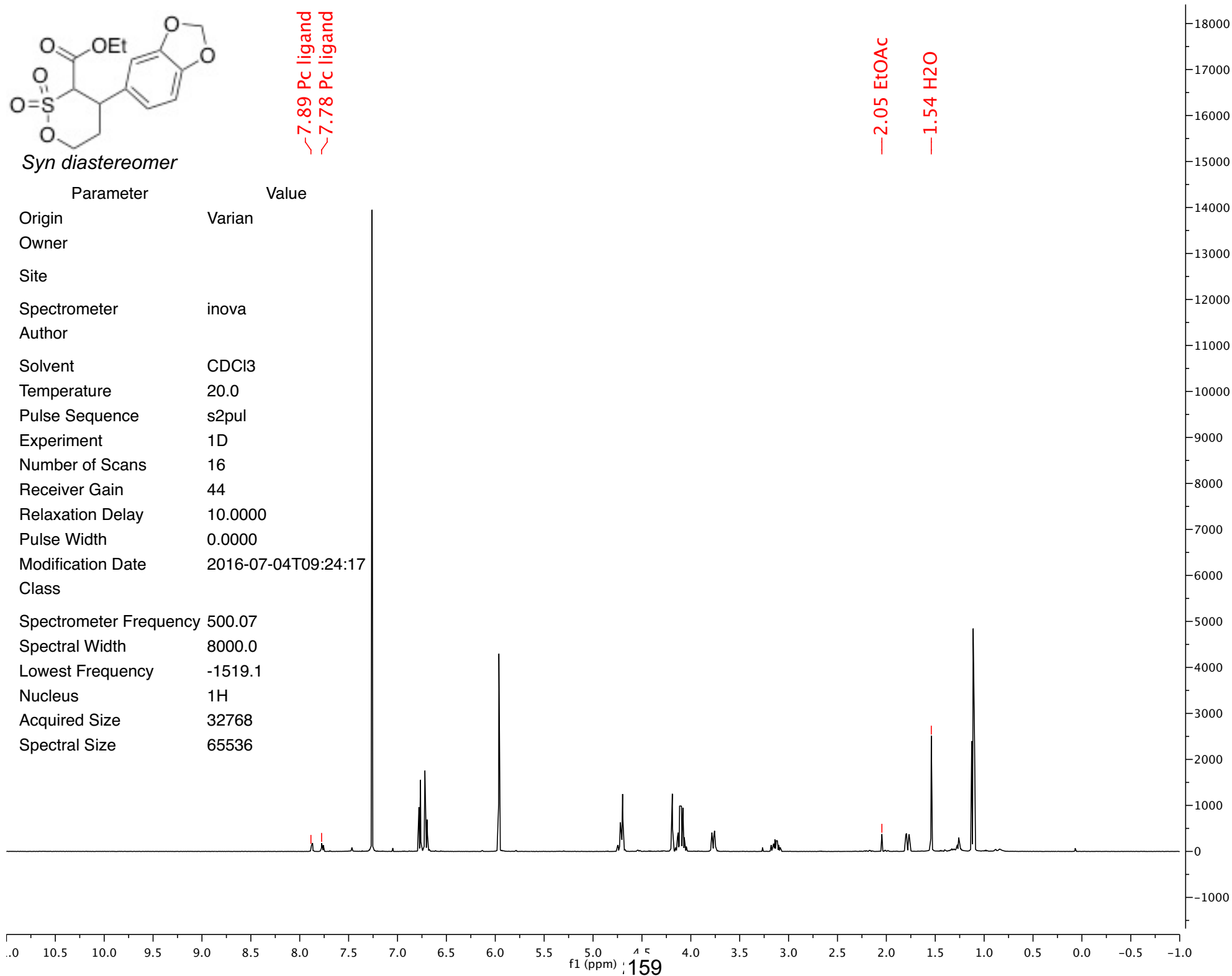
Syn diastereomer

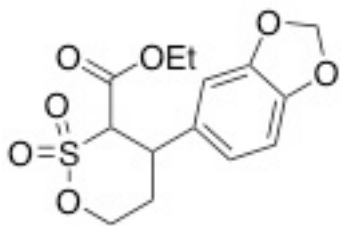
~7.89 Pc ligand
~7.78 Pc ligand

—2.05 EtOAc

—1.54 H2O

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	44
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-07-04T09:24:17
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1519.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



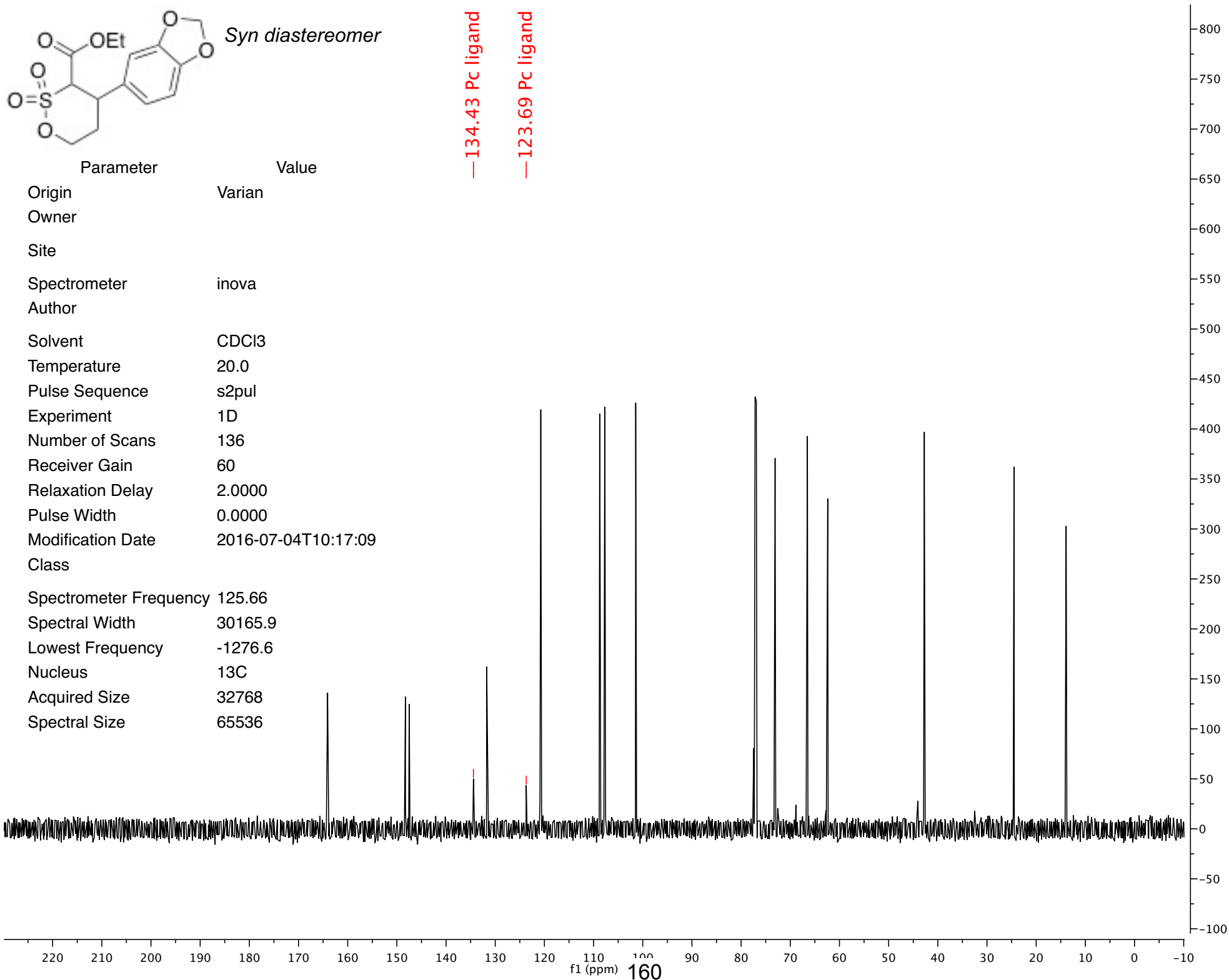


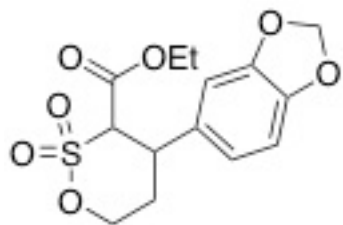
Syn diastereomer

—134.43 Pc ligand

—123.69 Pc ligand

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	136
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-07-04T10:17:09
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1276.6
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

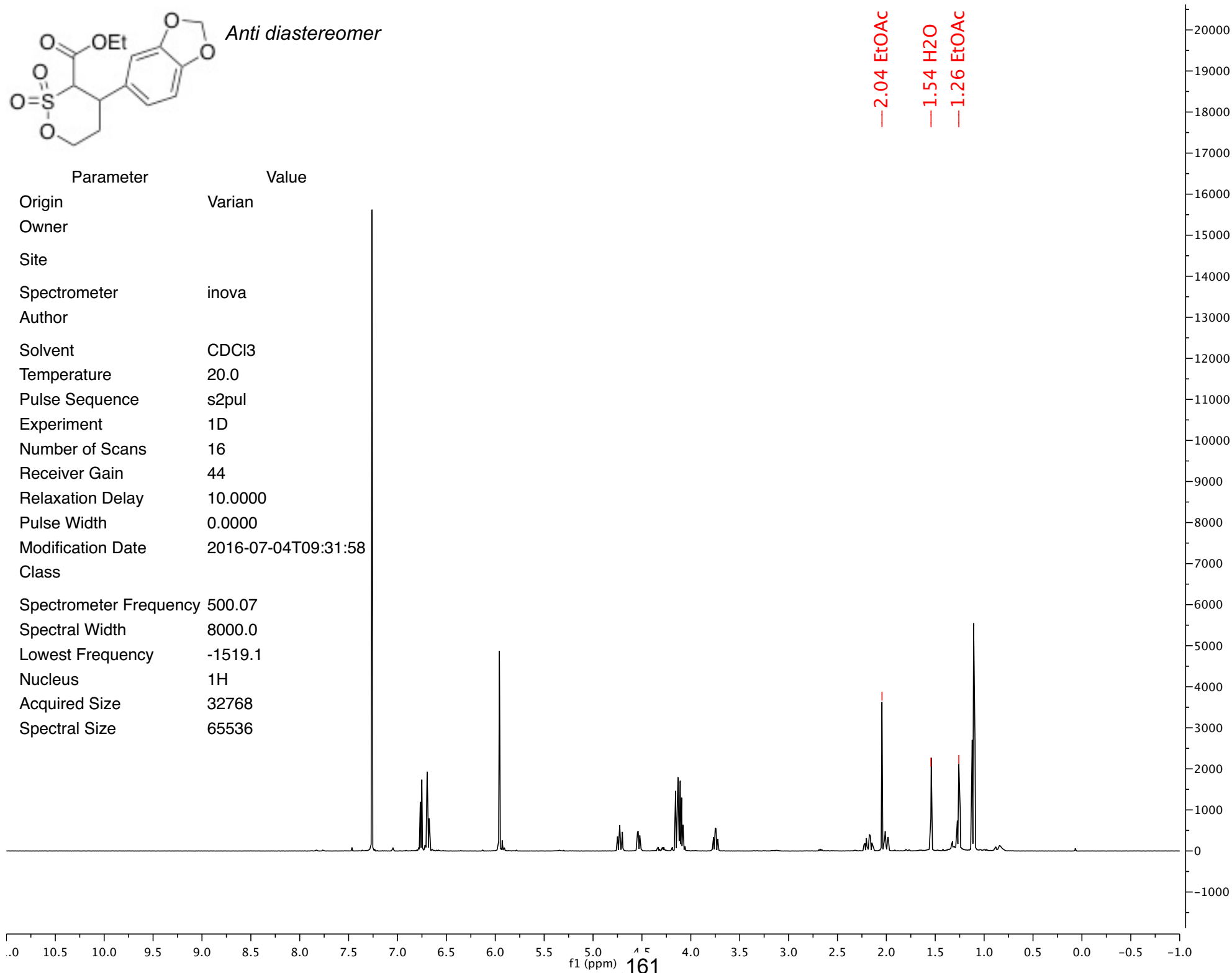


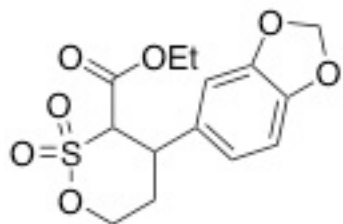


Anti diastereomer

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	44
Relaxation Delay	10.0000
Pulse Width	0.0000
Modification Date	2016-07-04T09:31:58
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1519.1
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

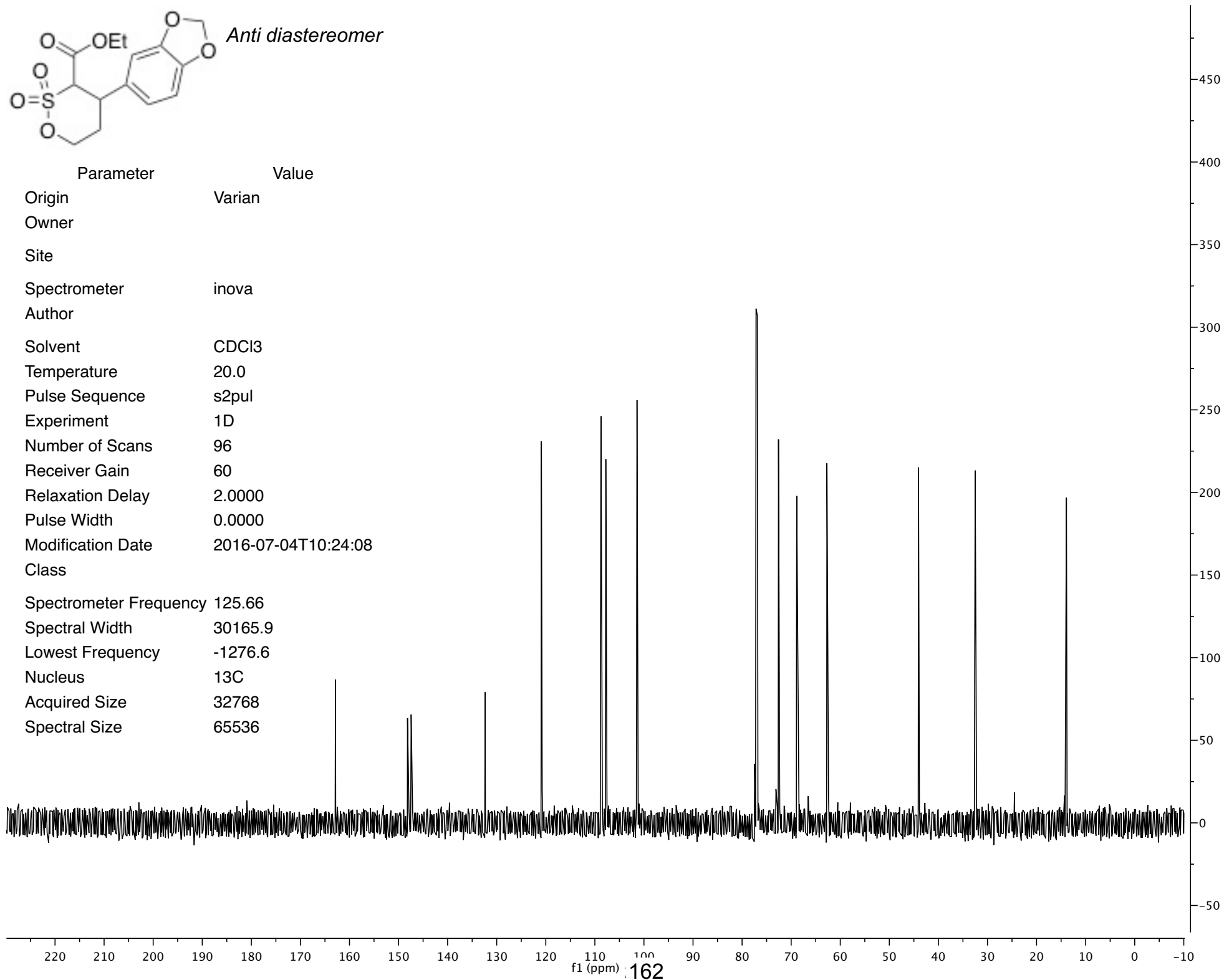
— 2.04 EtOAc
— 1.54 H2O
— 1.26 EtOAc

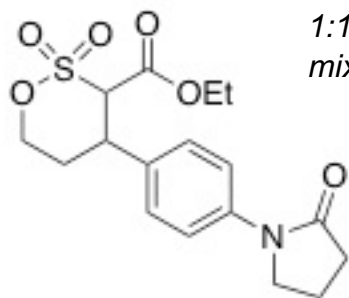




Anti diastereomer

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	96
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-07-04T10:24:08
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1276.6
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536





1:1 syn:anti
mix of diastereomers

—5.28 CH₂Cl₂

Parameter Value
Origin Varian

Owner

Site

Spectrometer inova

Author

Solvent CDCl₃

Temperature 4.0

Pulse Sequence s2pul

Experiment 1D

Number of Scans 4

Receiver Gain 44

Relaxation Delay 10.0000

Pulse Width 0.0000

Modification Date 2016-08-15T20:14:28

Class

Spectrometer 499.43

Frequency

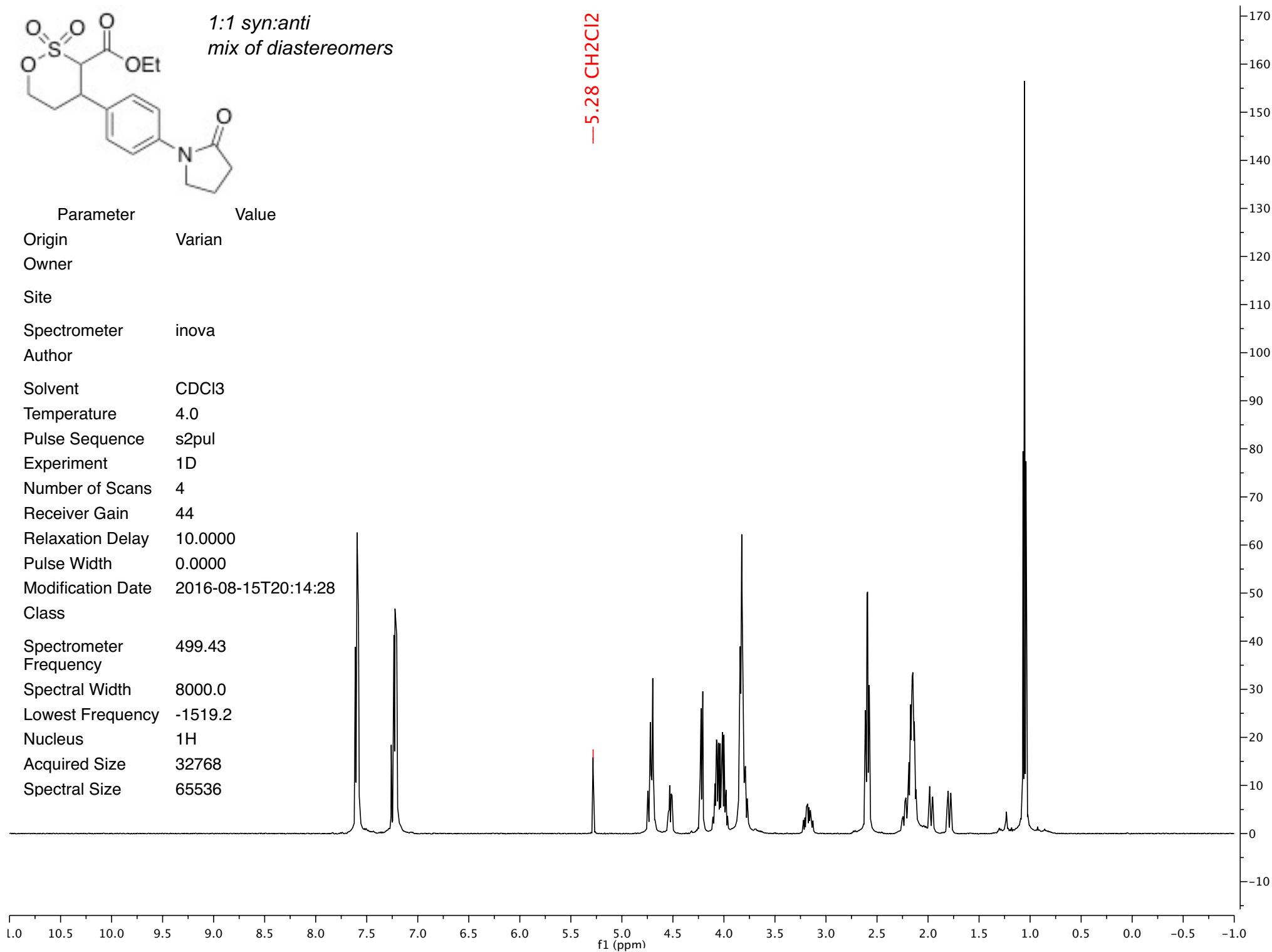
Spectral Width 8000.0

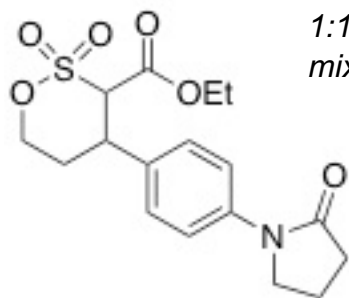
Lowest Frequency -1519.2

Nucleus ¹H

Acquired Size 32768

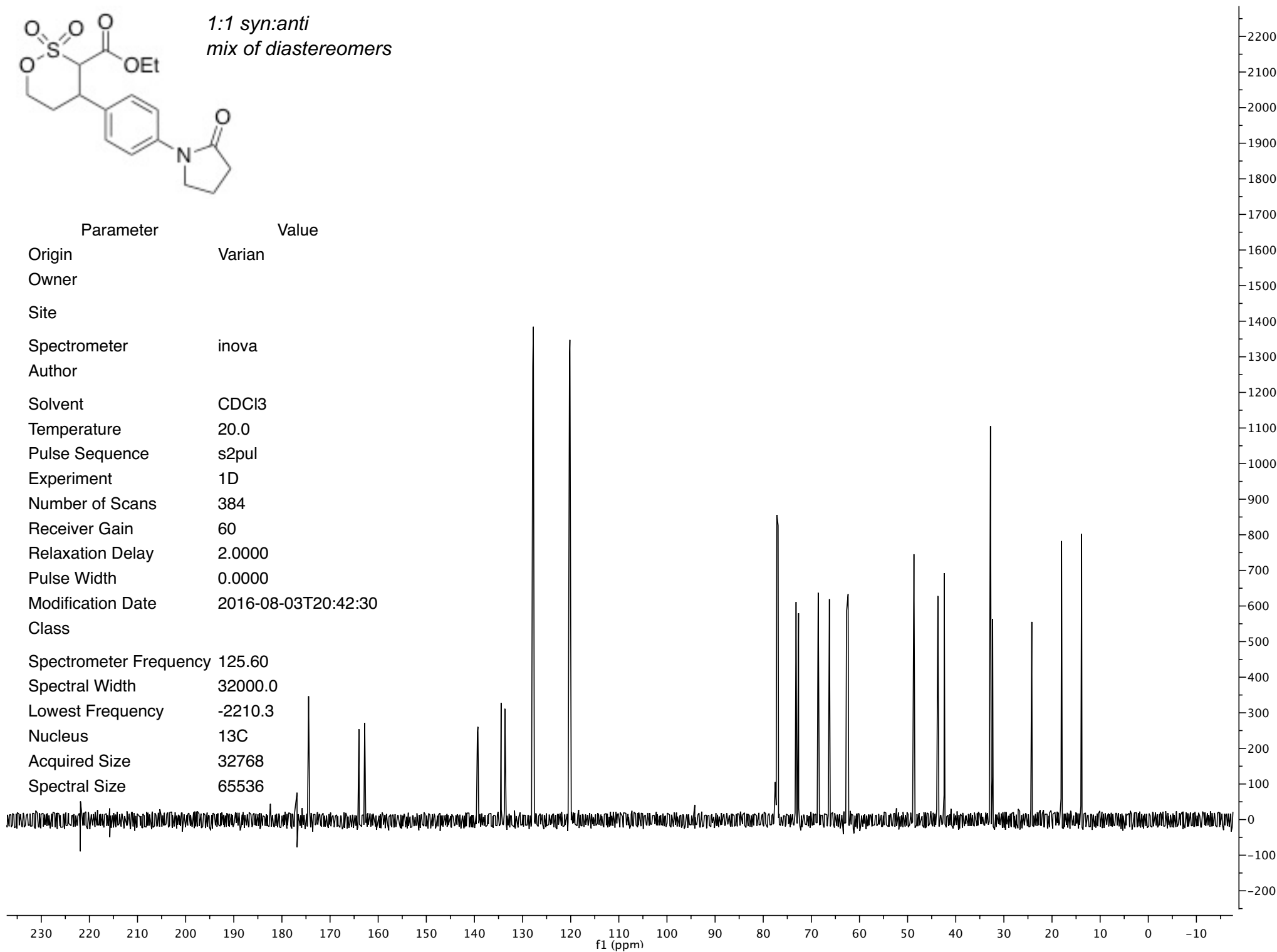
Spectral Size 65536

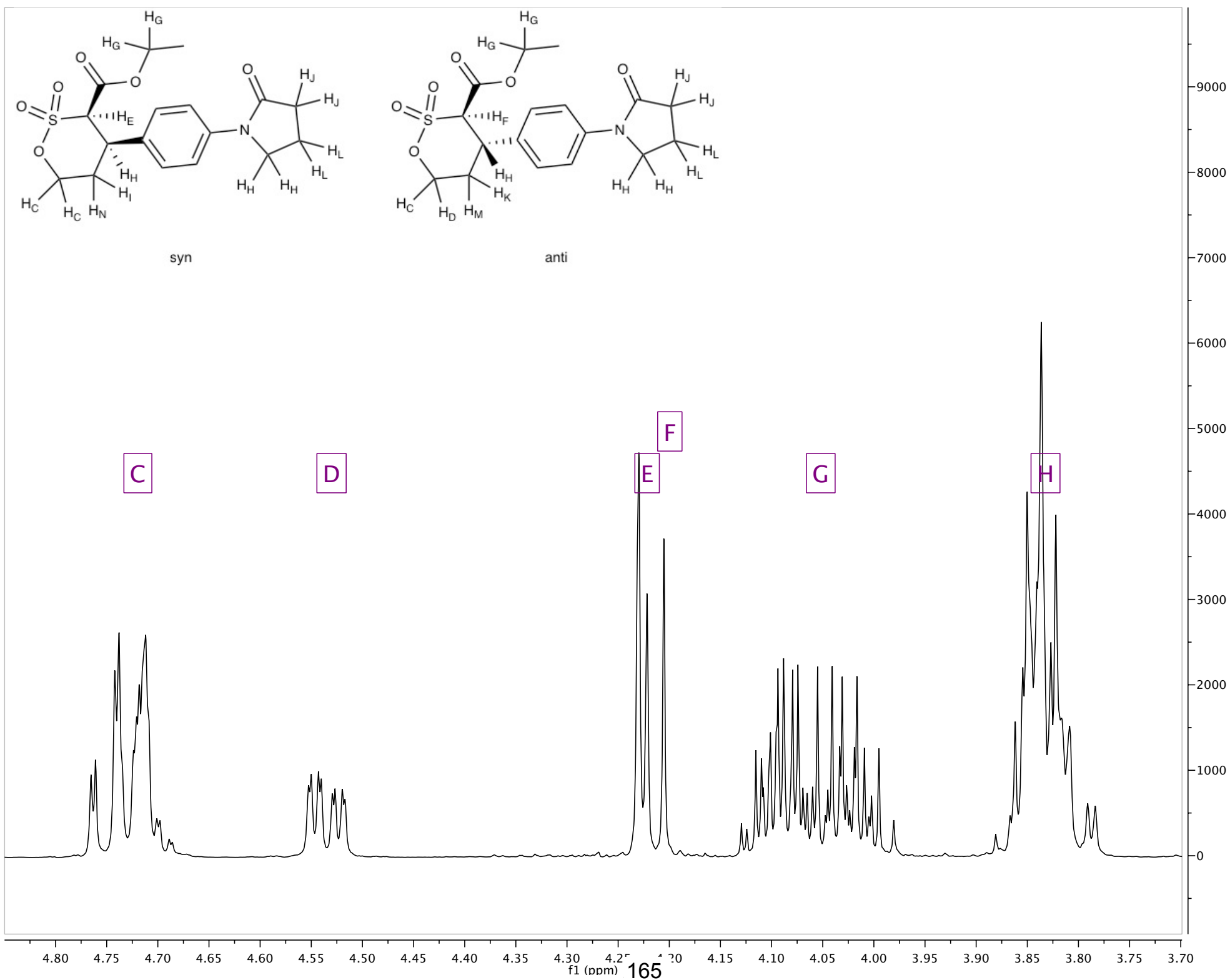


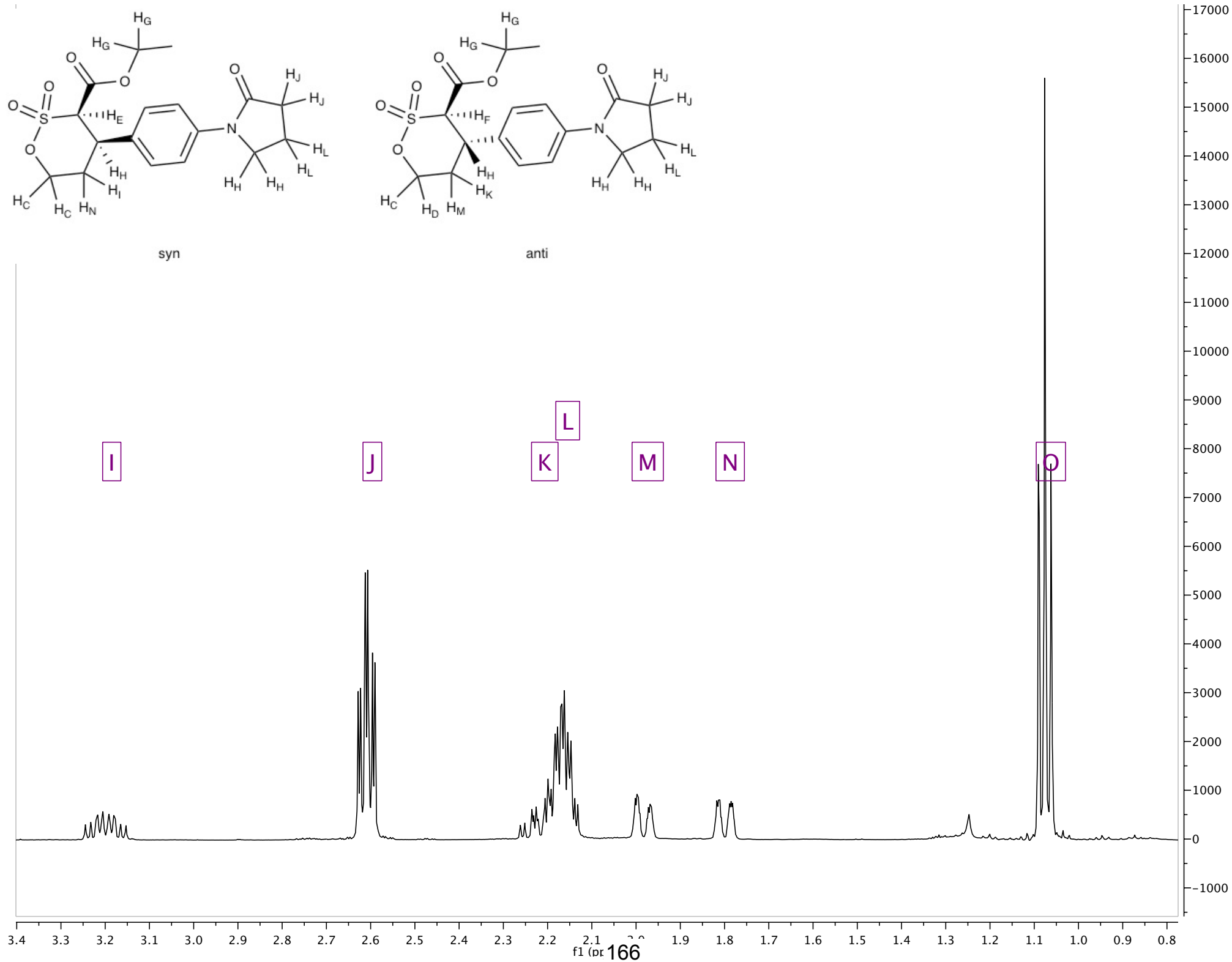


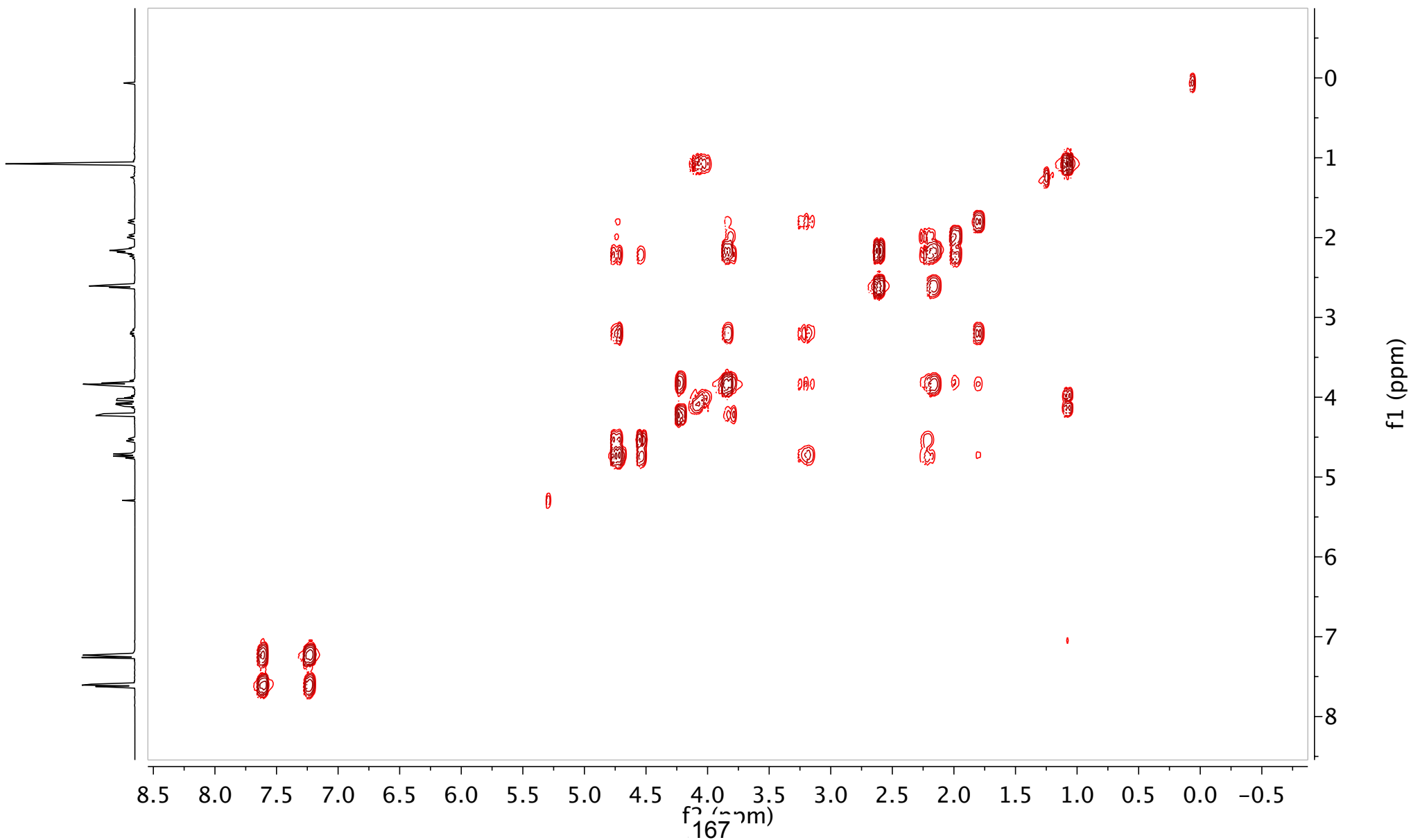
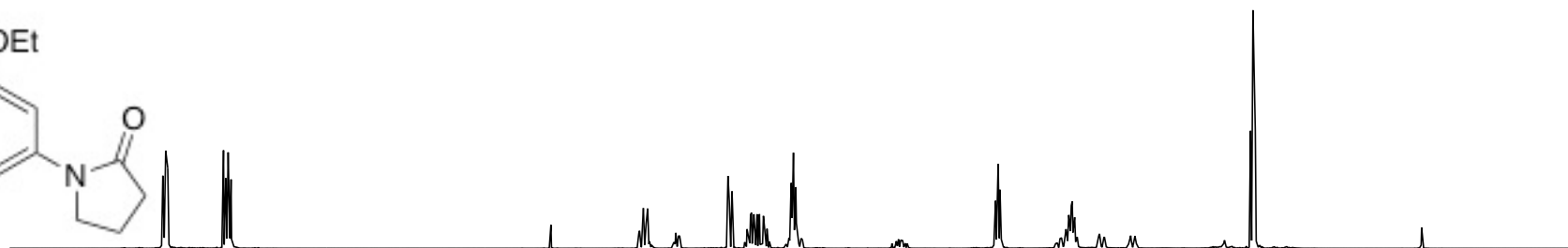
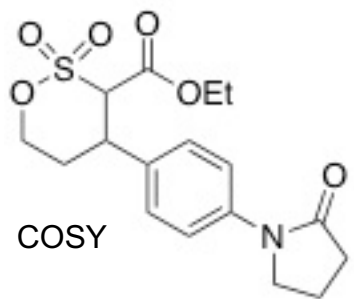
1:1 *syn:anti*
mix of diastereomers

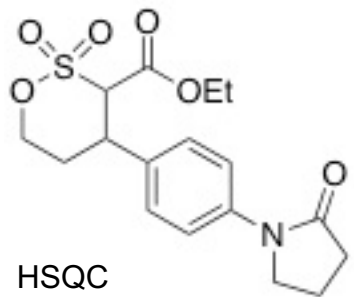
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	384
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-08-03T20:42:30
Class	
Spectrometer Frequency	125.60
Spectral Width	32000.0
Lowest Frequency	-2210.3
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



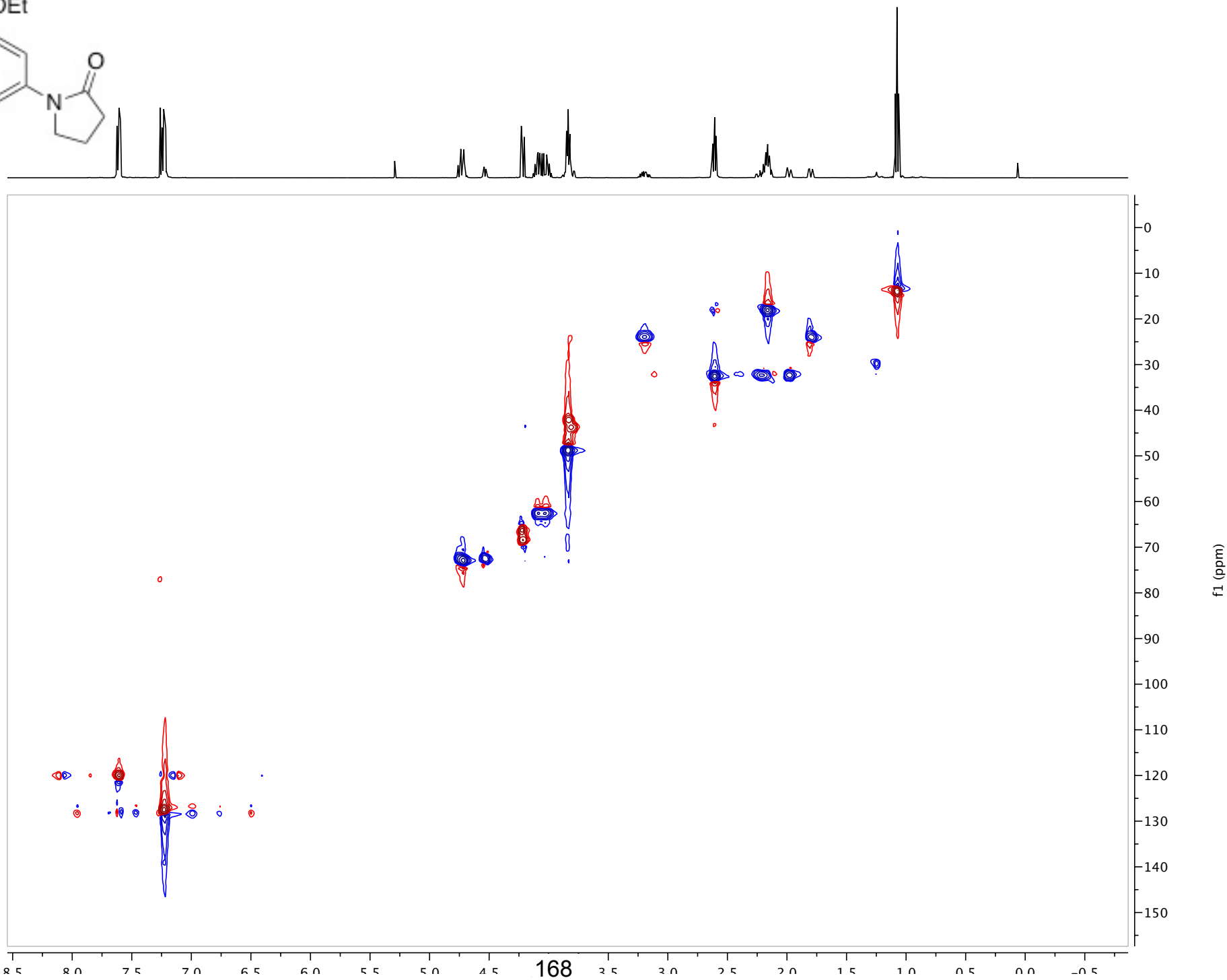


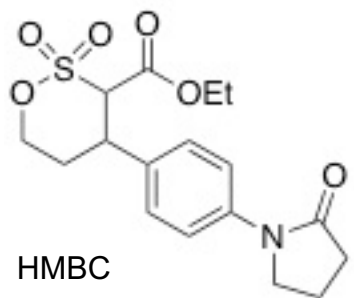




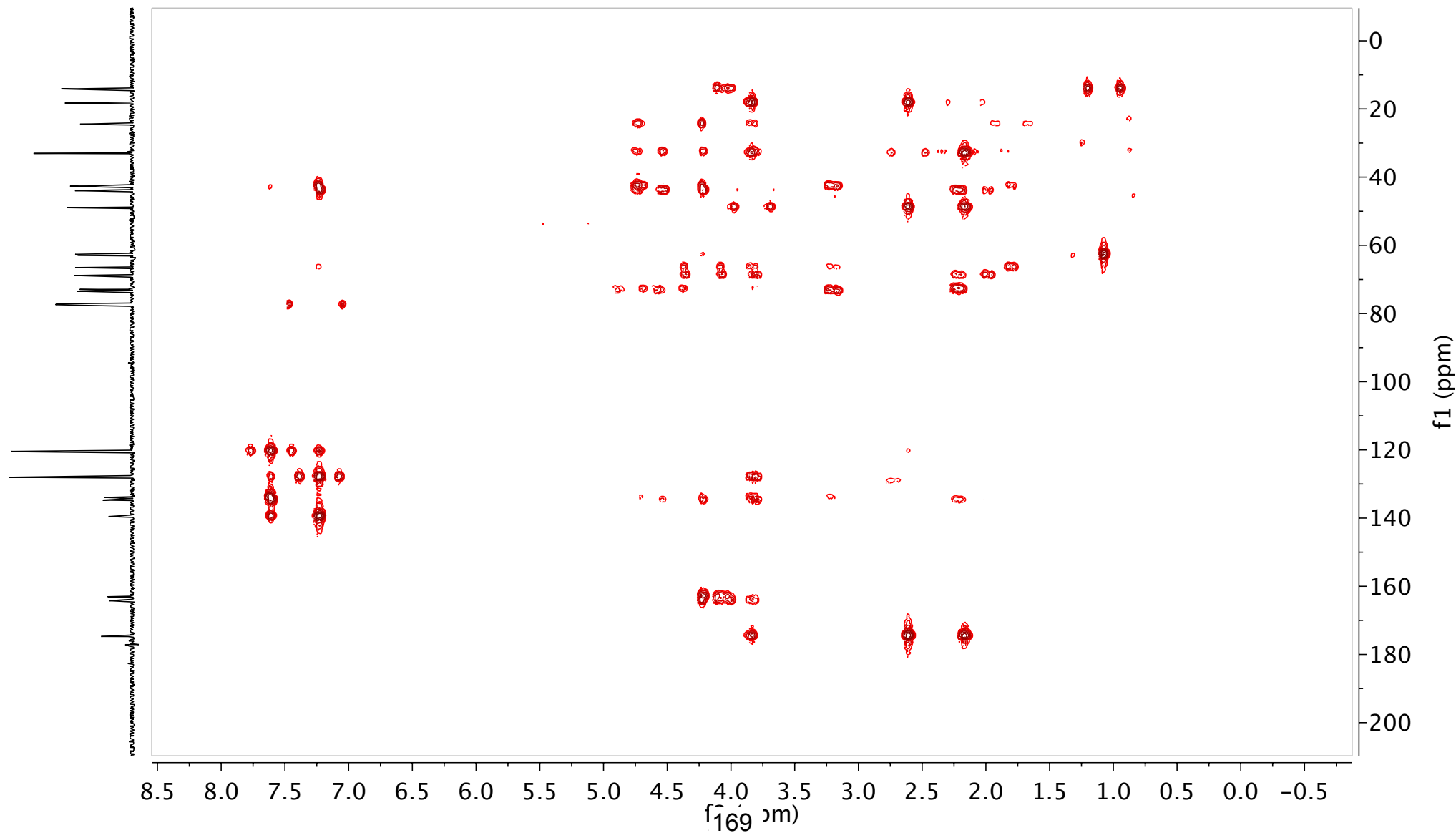
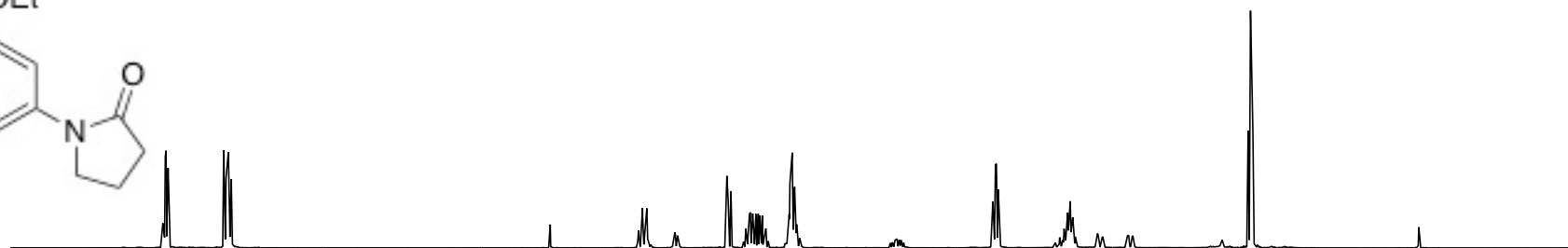


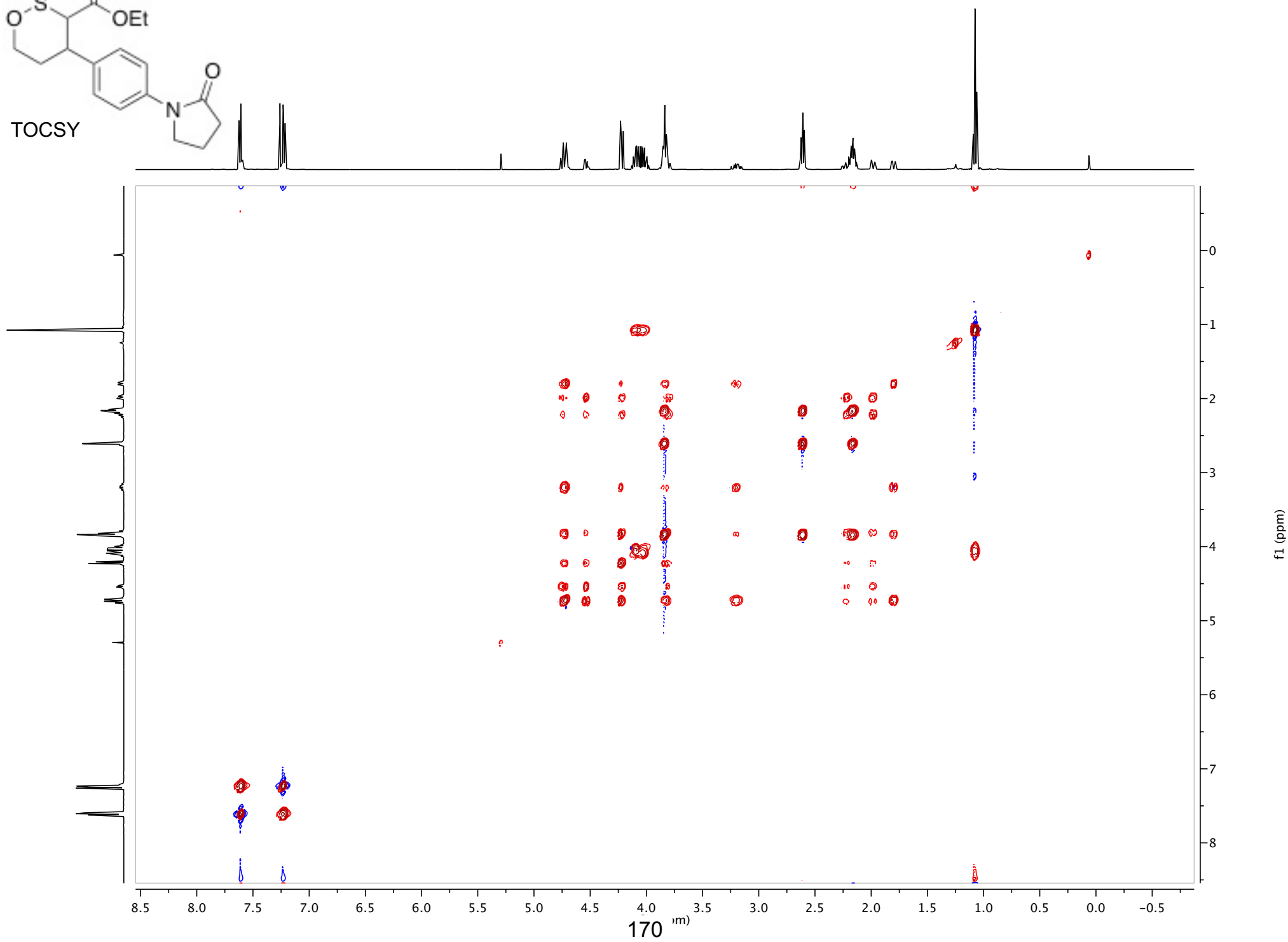
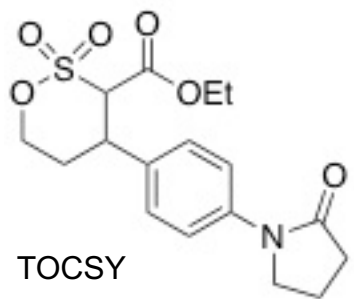
HSQC

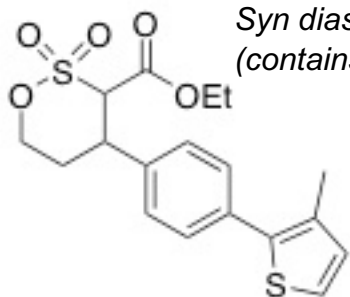




HMBC

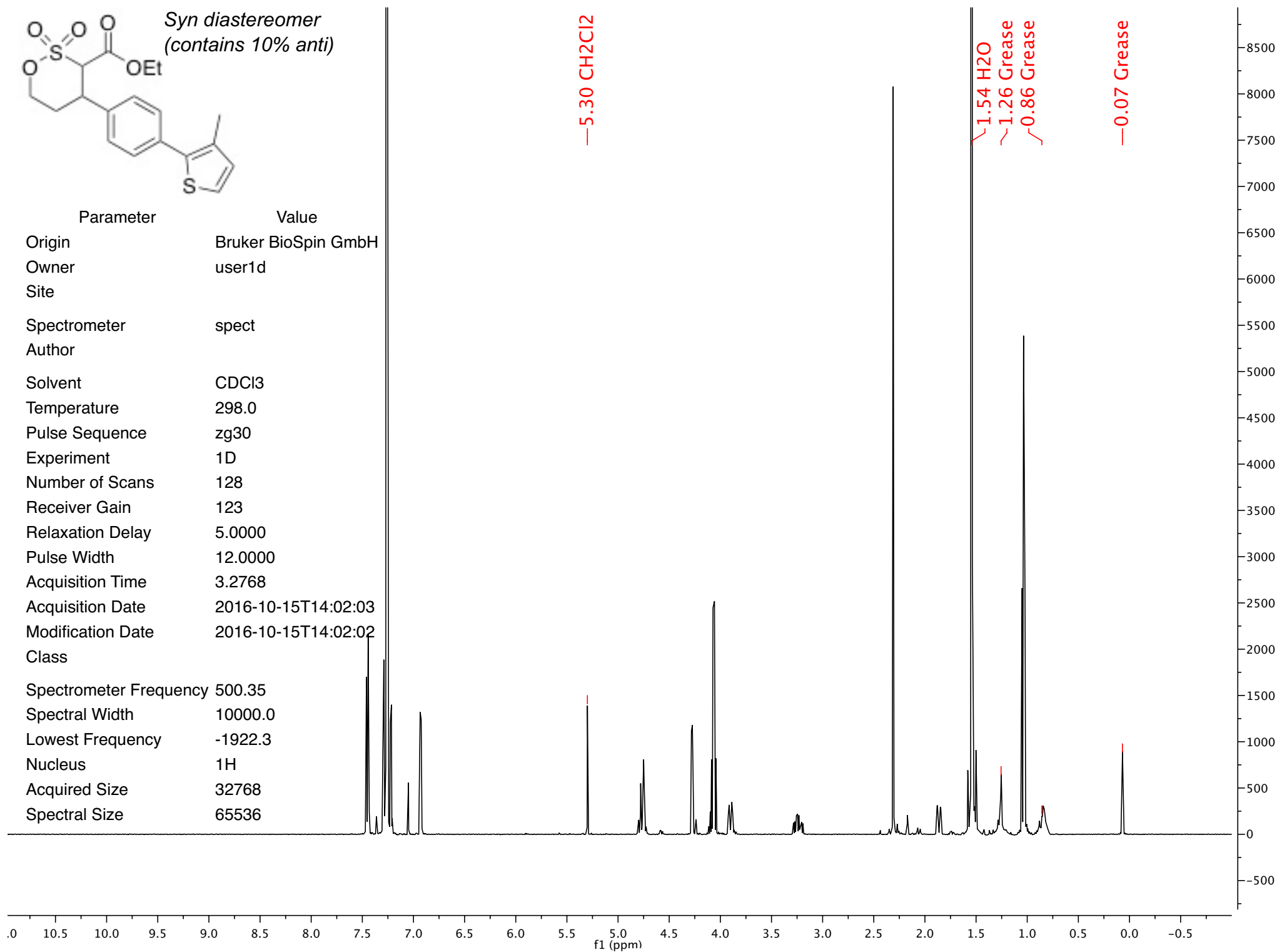




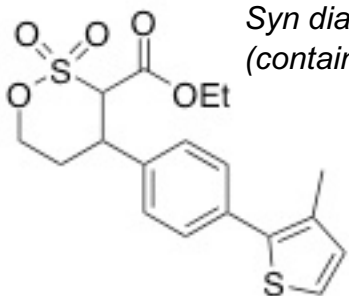


*Syn diastereomer
(contains 10% anti)*

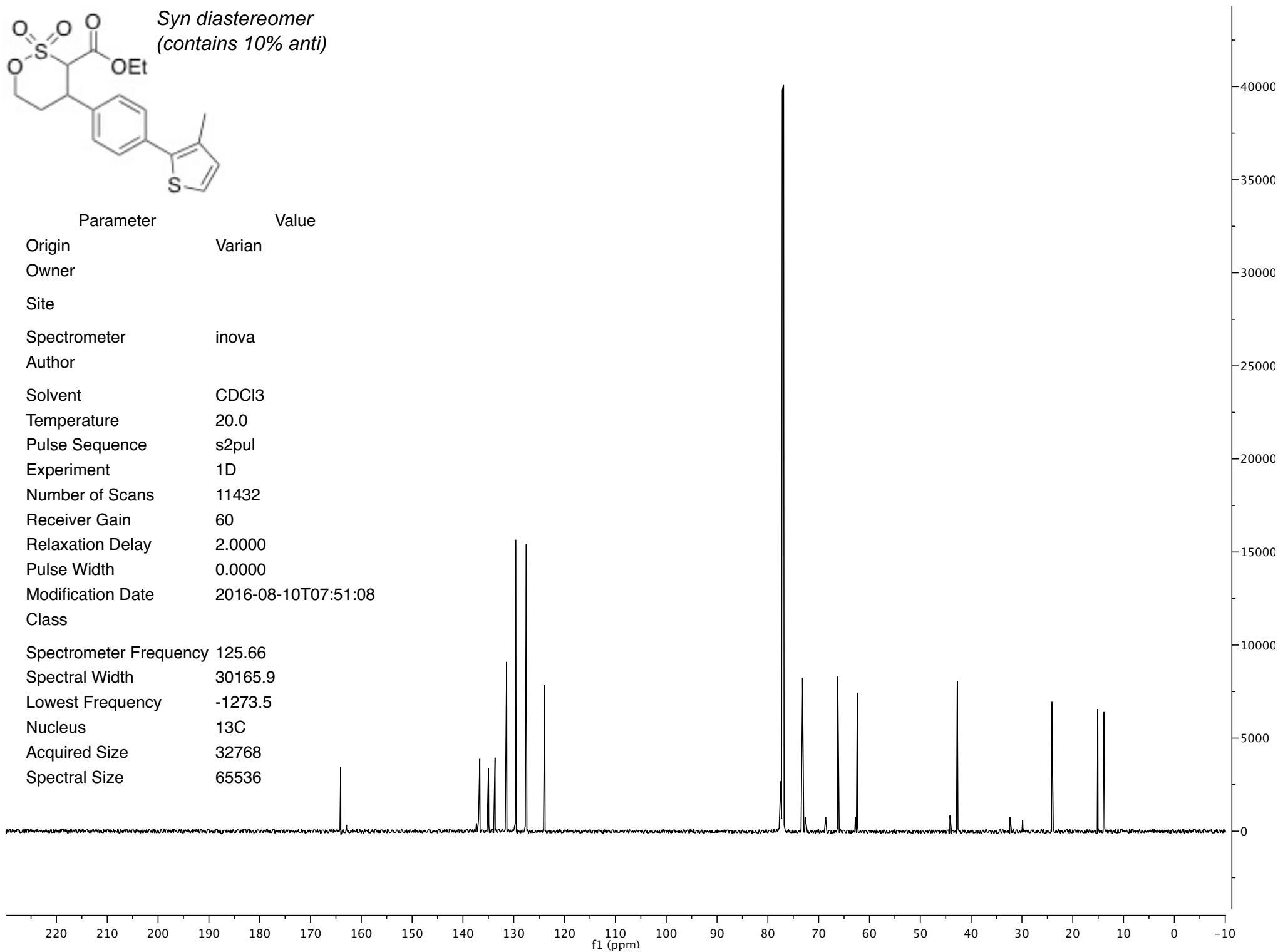
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	128
Receiver Gain	123
Relaxation Delay	5.0000
Pulse Width	12.0000
Acquisition Time	3.2768
Acquisition Date	2016-10-15T14:02:03
Modification Date	2016-10-15T14:02:02
Class	
Spectrometer Frequency	500.35
Spectral Width	10000.0
Lowest Frequency	-1922.3
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536

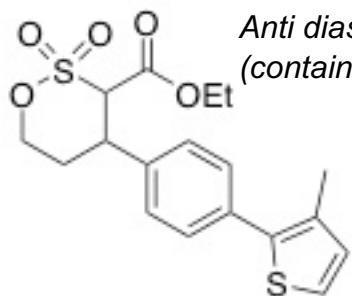


*Syn diastereomer
(contains 10% anti)*



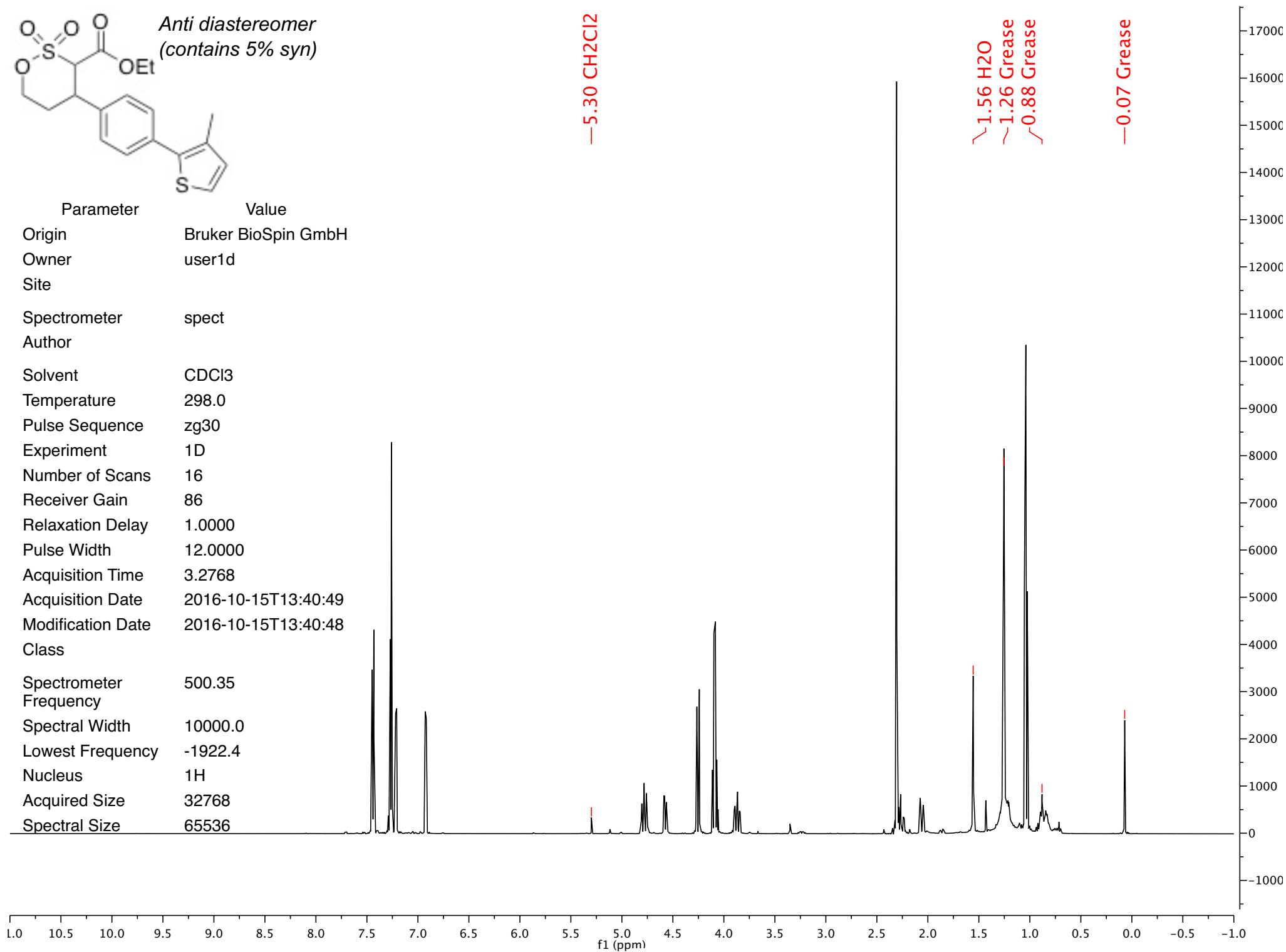
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	11432
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Modification Date	2016-08-10T07:51:08
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1273.5
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

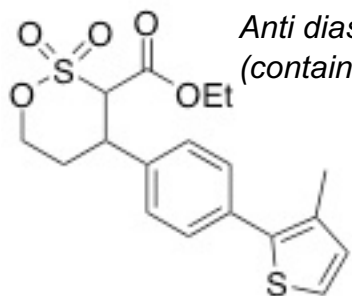




Anti diastereomer
(contains 5% syn)

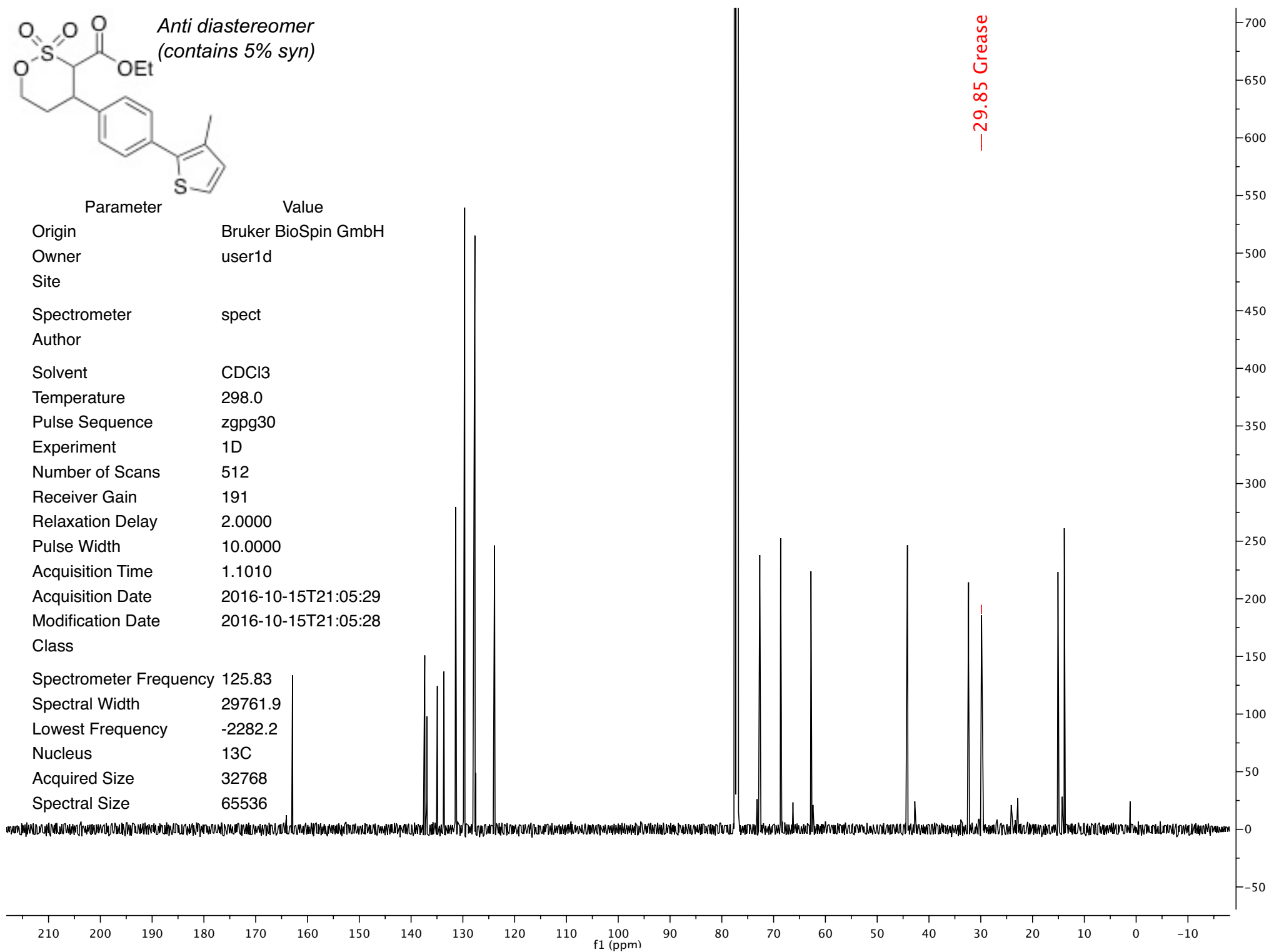
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	86
Relaxation Delay	1.0000
Pulse Width	12.0000
Acquisition Time	3.2768
Acquisition Date	2016-10-15T13:40:49
Modification Date	2016-10-15T13:40:48
Class	
Spectrometer Frequency	500.35
Spectral Width	10000.0
Lowest Frequency	-1922.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

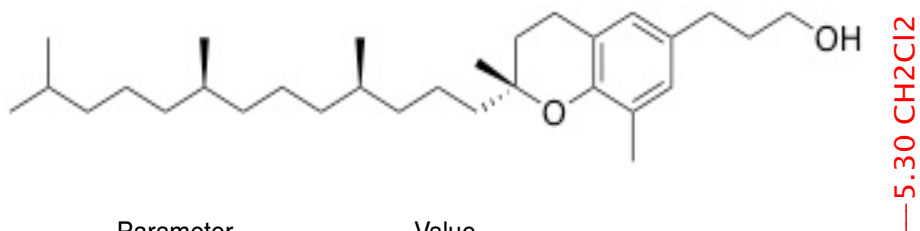




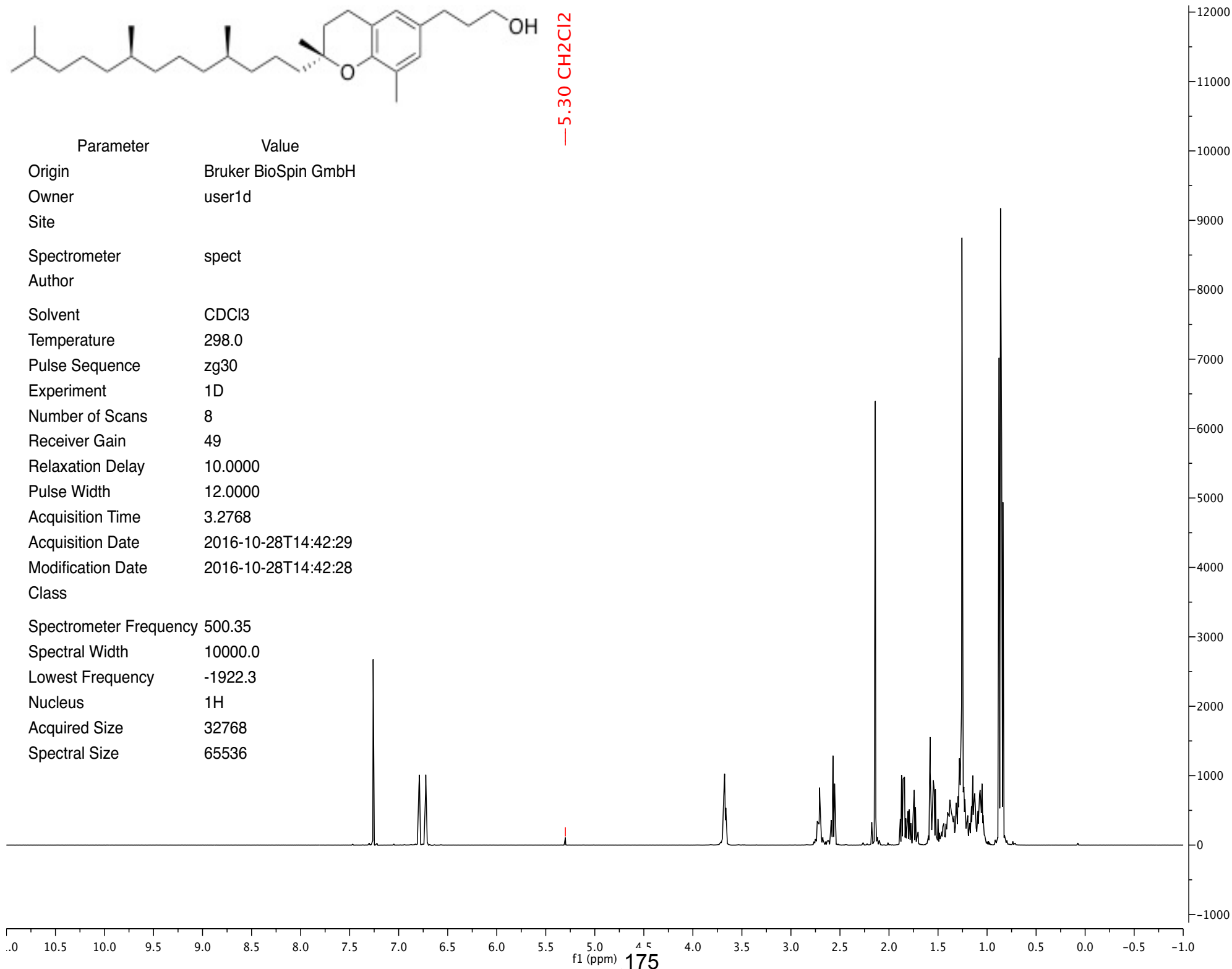
Anti diastereomer
(contains 5% syn)

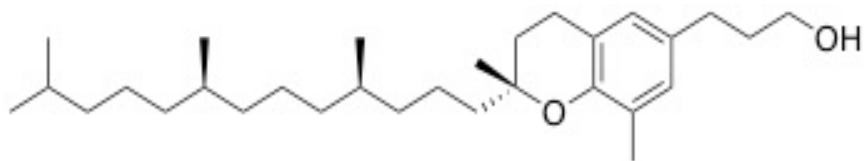
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-15T21:05:29
Modification Date	2016-10-15T21:05:28
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2282.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536





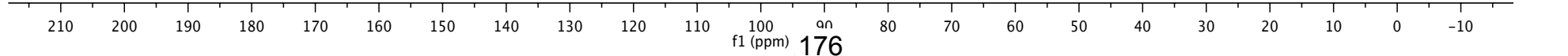
Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	8
Receiver Gain	49
Relaxation Delay	10.0000
Pulse Width	12.0000
Acquisition Time	3.2768
Acquisition Date	2016-10-28T14:42:29
Modification Date	2016-10-28T14:42:28
Class	
Spectrometer Frequency	500.35
Spectral Width	10000.0
Lowest Frequency	-1922.3
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536

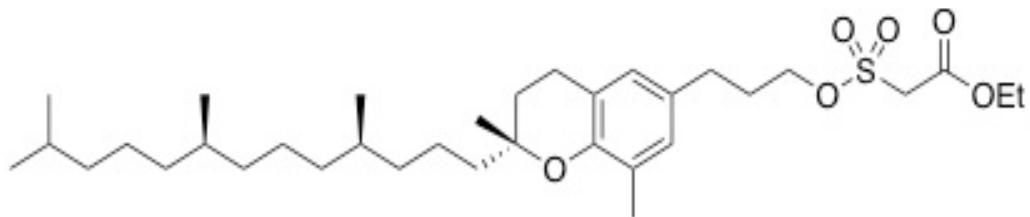




Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl ₃
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	365
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-28T15:03:29
Modification Date	2016-10-28T15:03:28
Class	

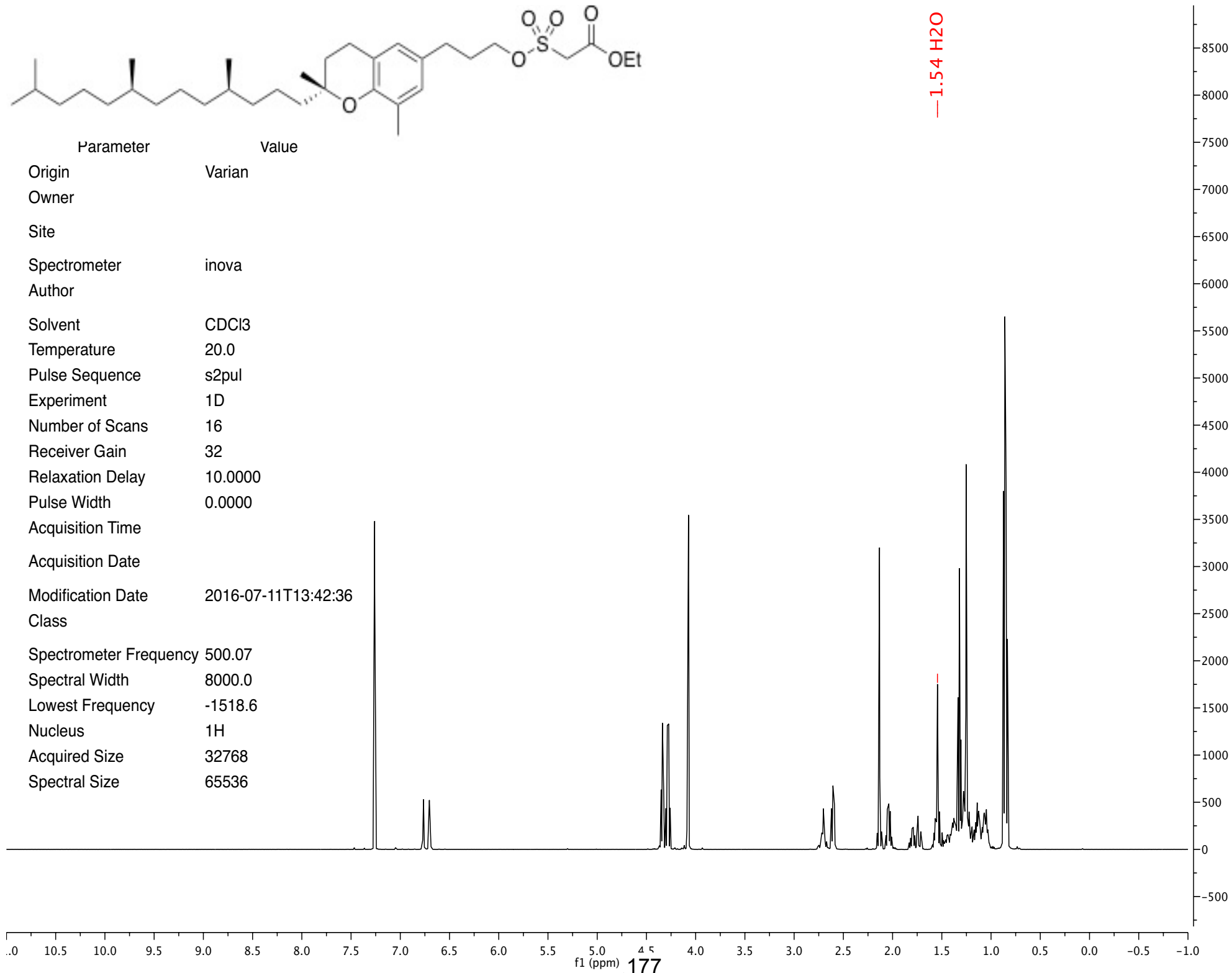
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2299.6
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

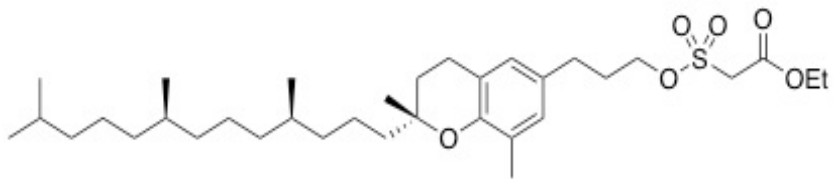




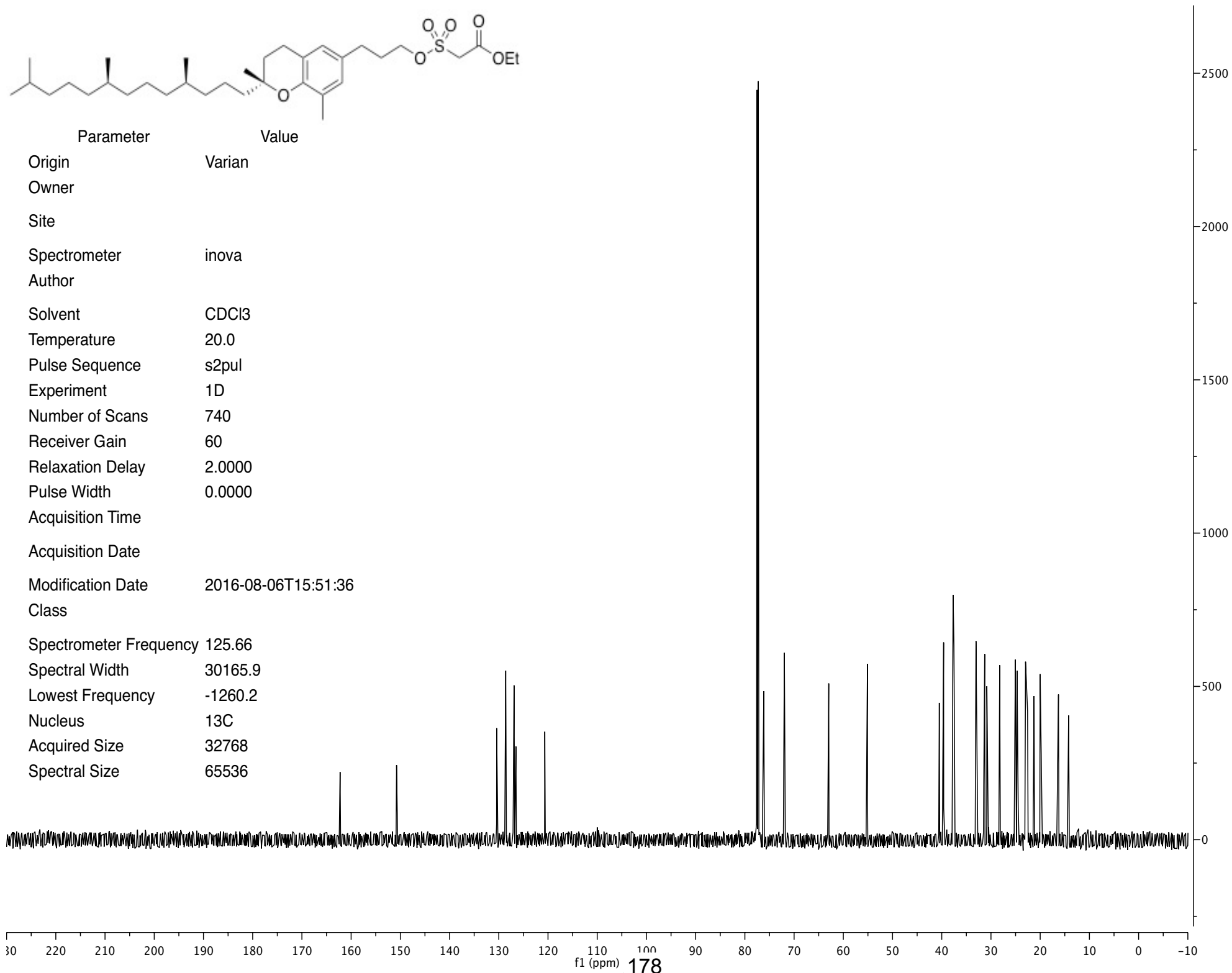
— 1.54 H₂O

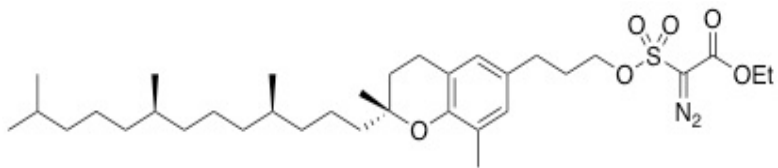
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	32
Relaxation Delay	10.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-07-11T13:42:36
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1518.6
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



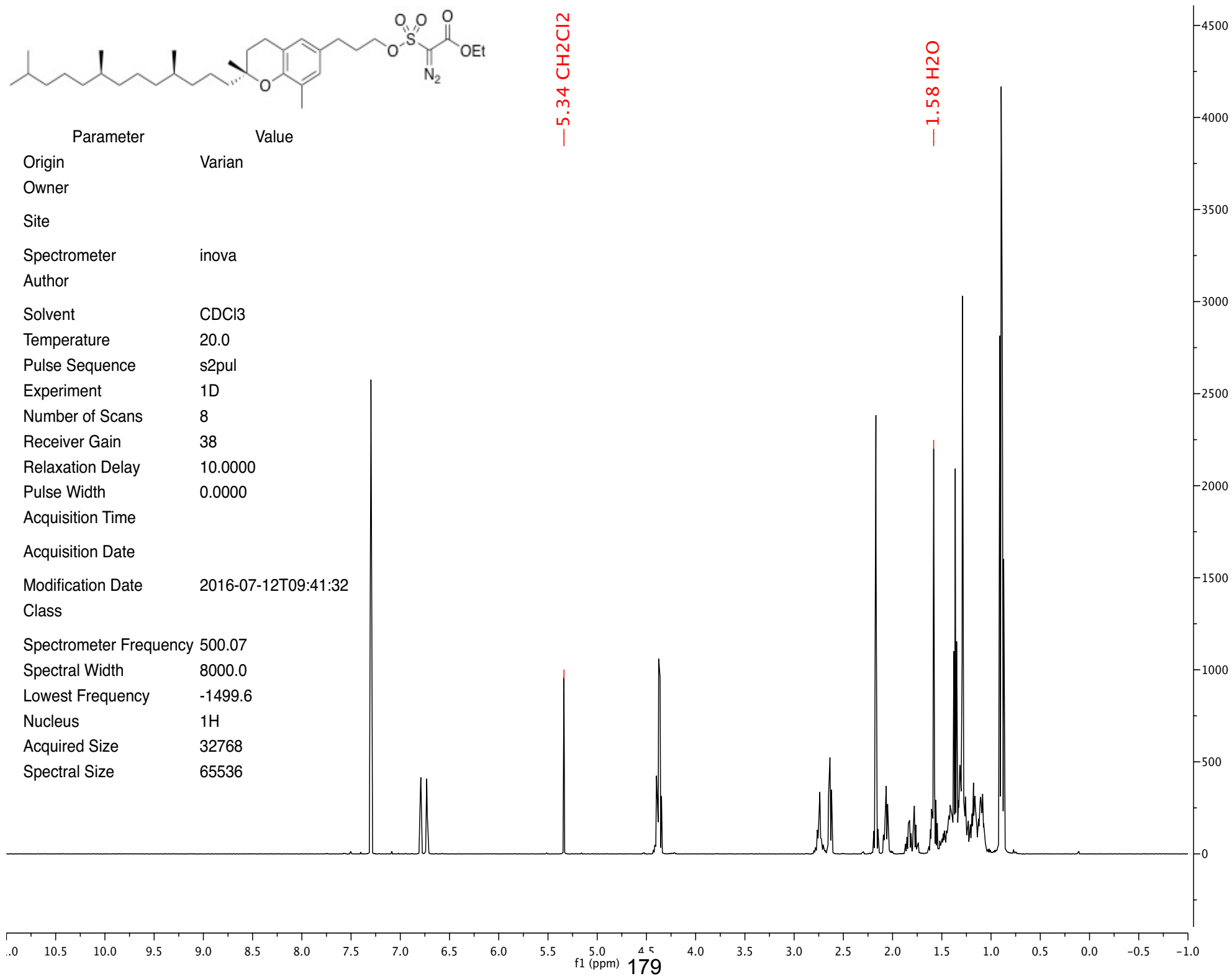


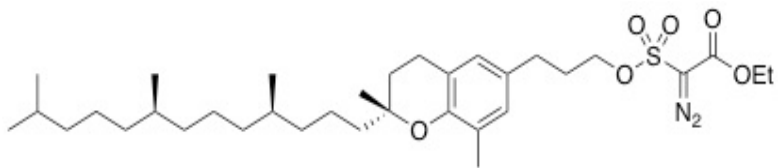
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	740
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-08-06T15:51:36
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



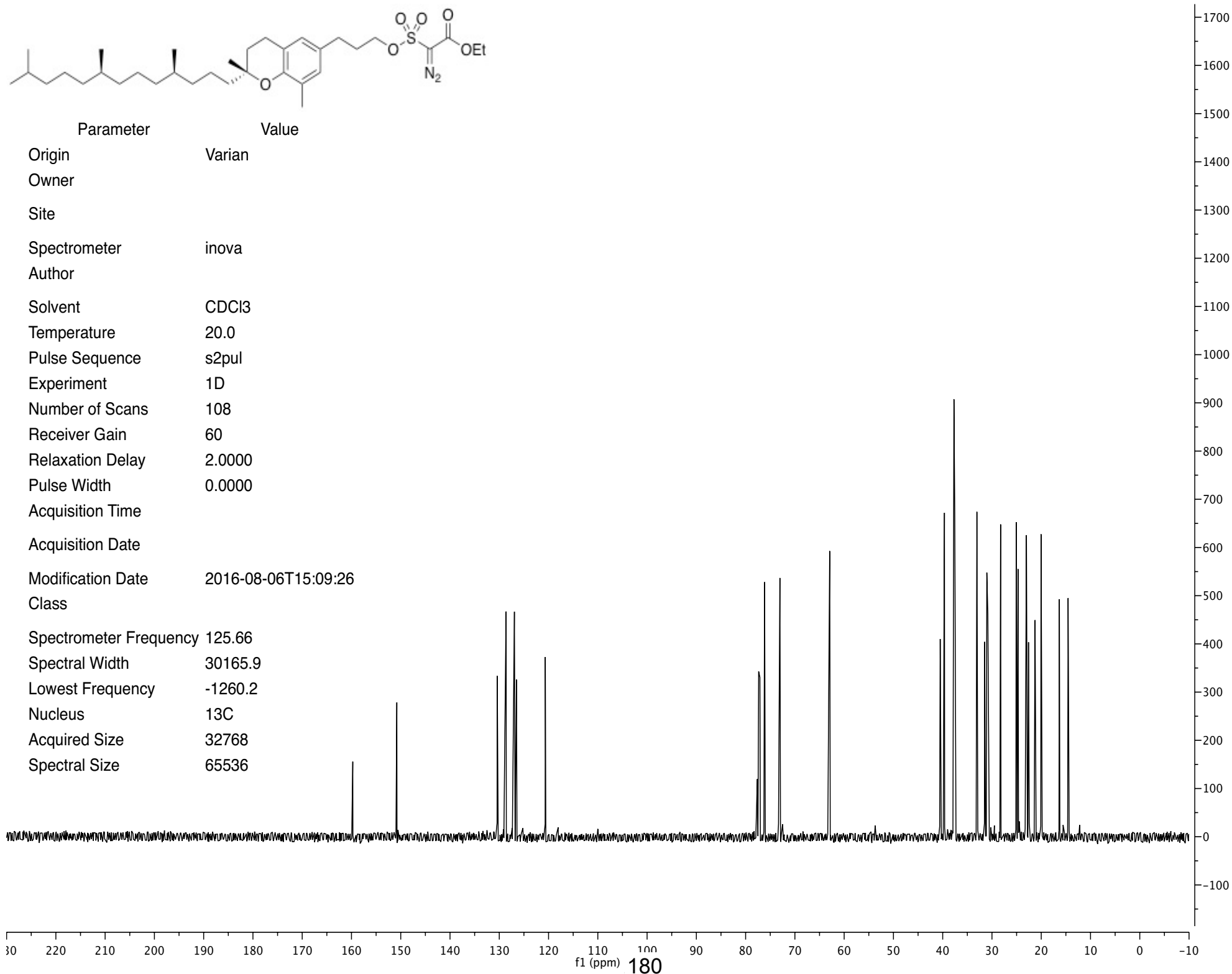


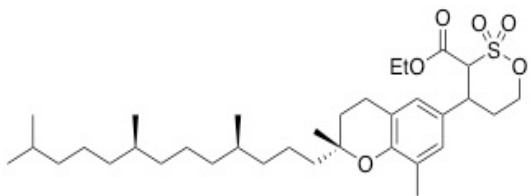
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	8
Receiver Gain	38
Relaxation Delay	10.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-07-12T09:41:32
Class	
Spectrometer Frequency	500.07
Spectral Width	8000.0
Lowest Frequency	-1499.6
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536





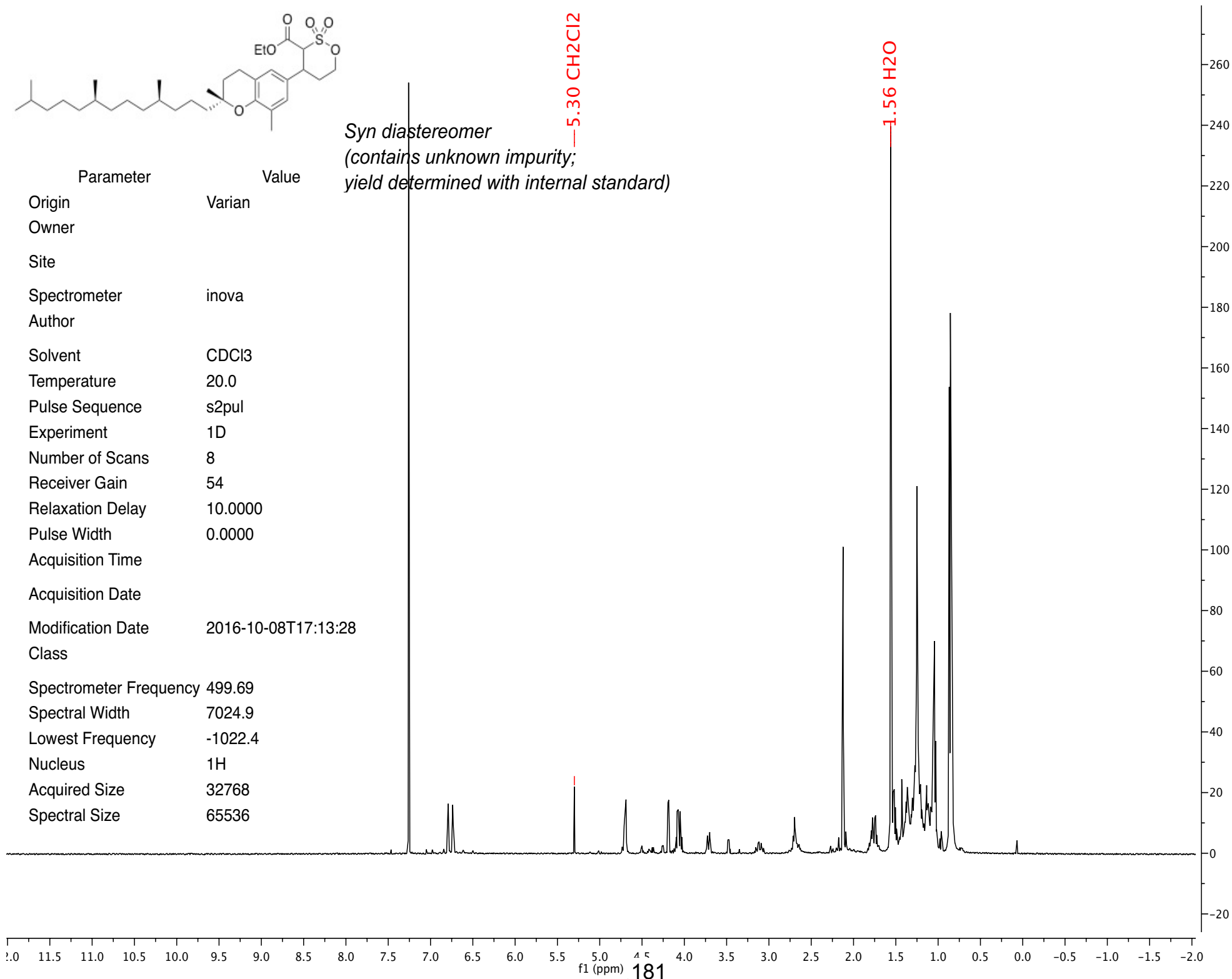
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	108
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-08-06T15:09:26
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

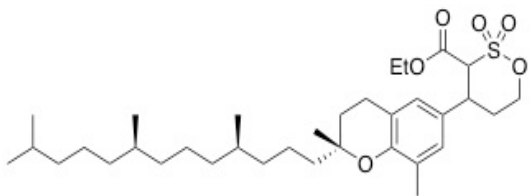




*Syn diastereomer
(contains unknown impurity;
yield determined with internal standard)*

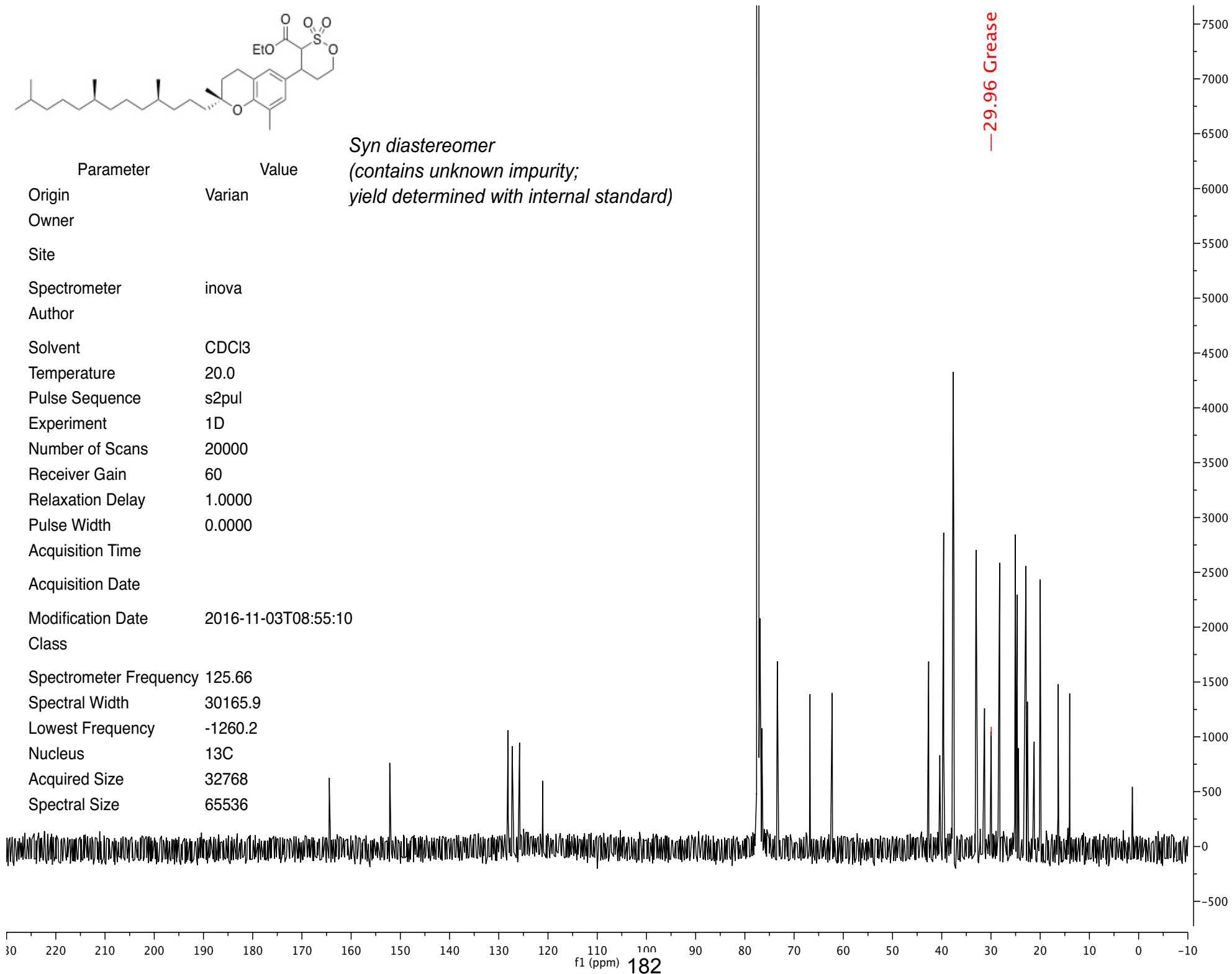
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	8
Receiver Gain	54
Relaxation Delay	10.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-10-08T17:13:28
Class	
Spectrometer Frequency	499.69
Spectral Width	7024.9
Lowest Frequency	-1022.4
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536

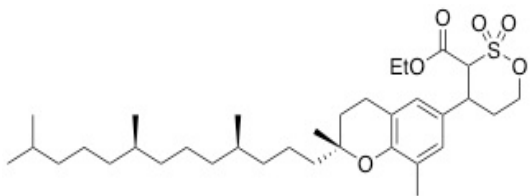




*Syn diastereomer
(contains unknown impurity;
yield determined with internal standard)*

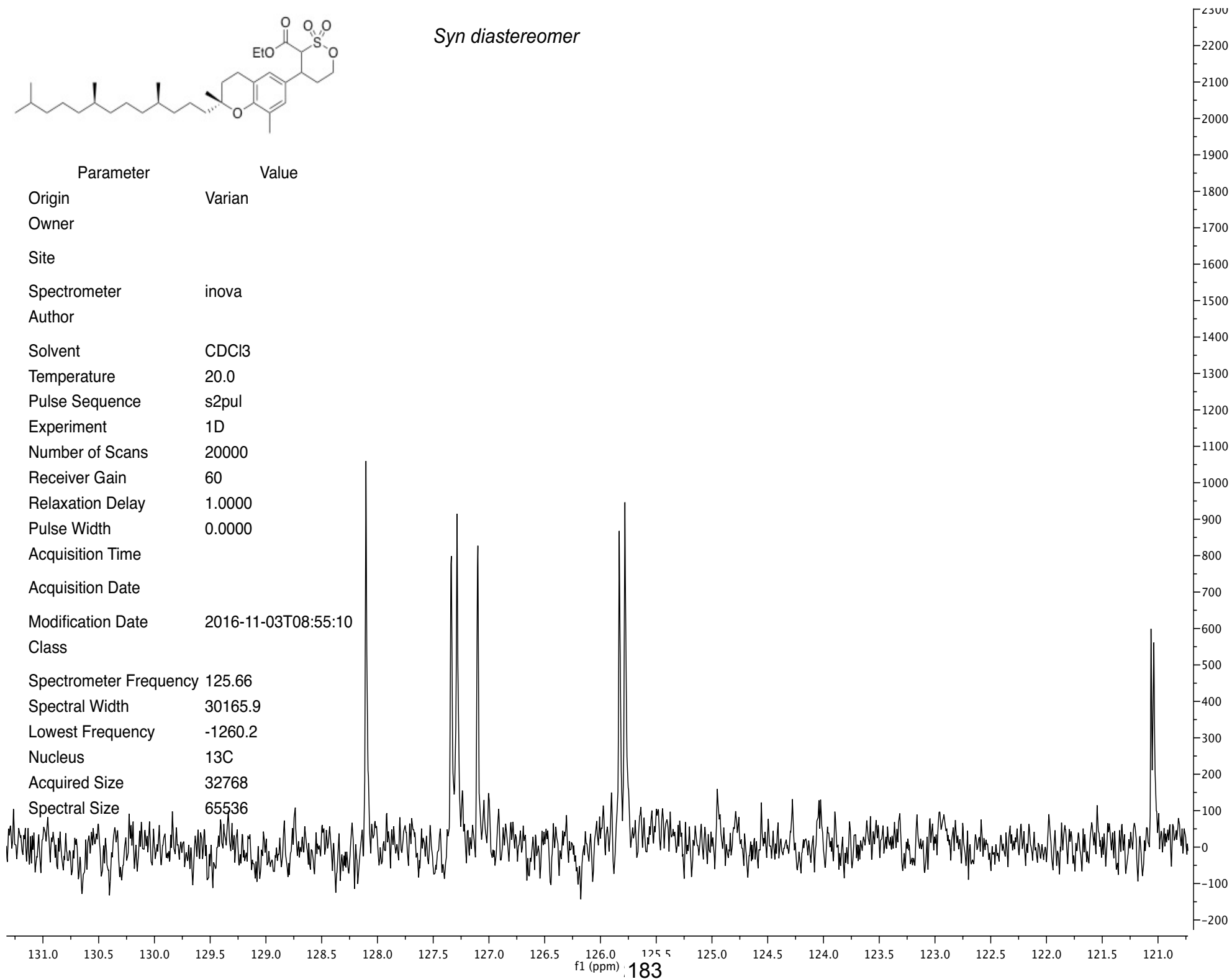
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	20000
Receiver Gain	60
Relaxation Delay	1.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-11-03T08:55:10
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

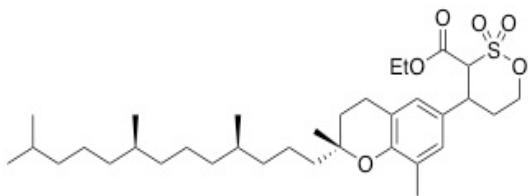




Syn diastereomer

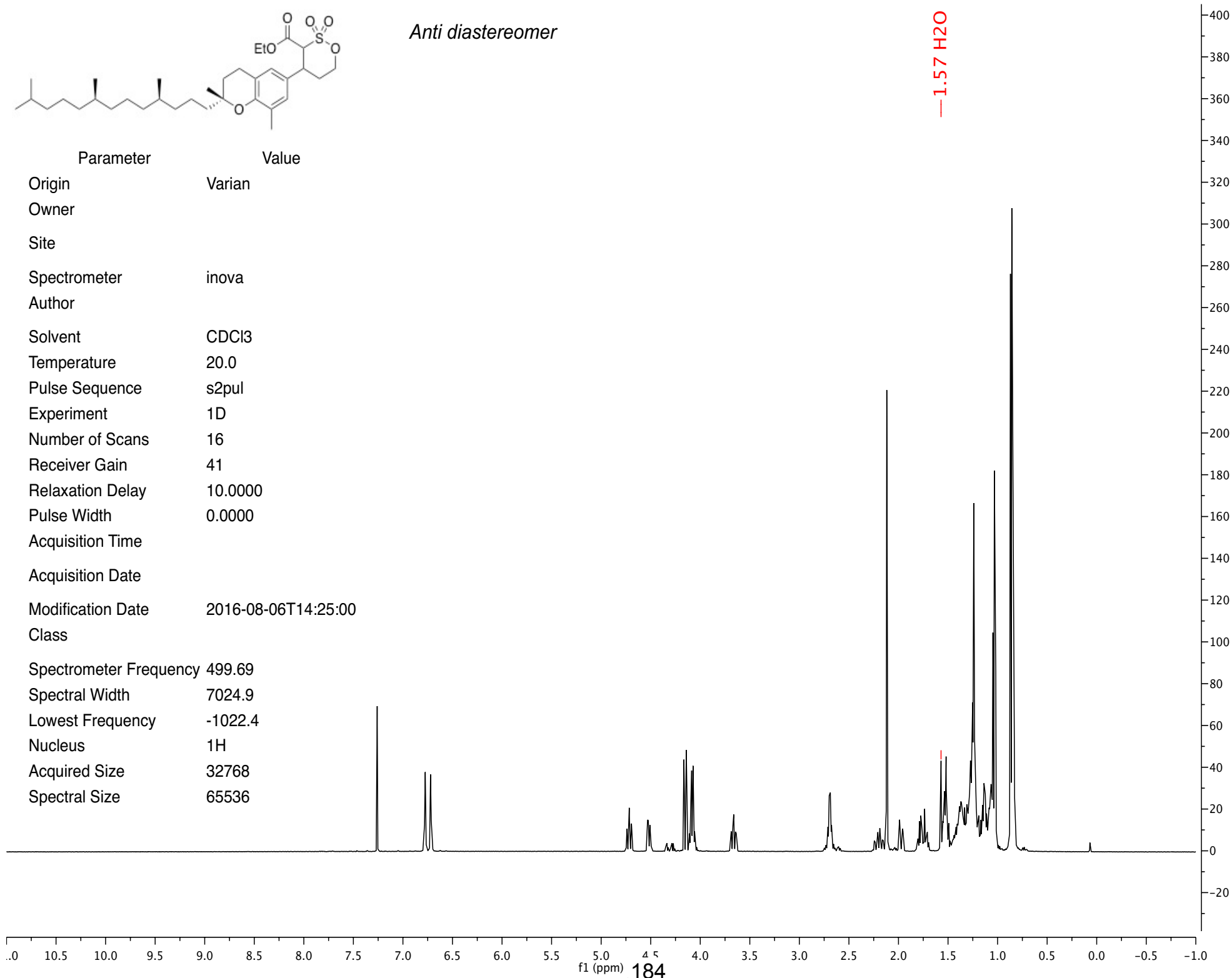
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	20000
Receiver Gain	60
Relaxation Delay	1.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-11-03T08:55:10
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536

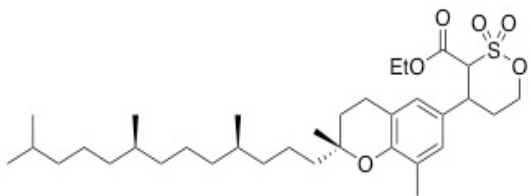




Anti diastereomer

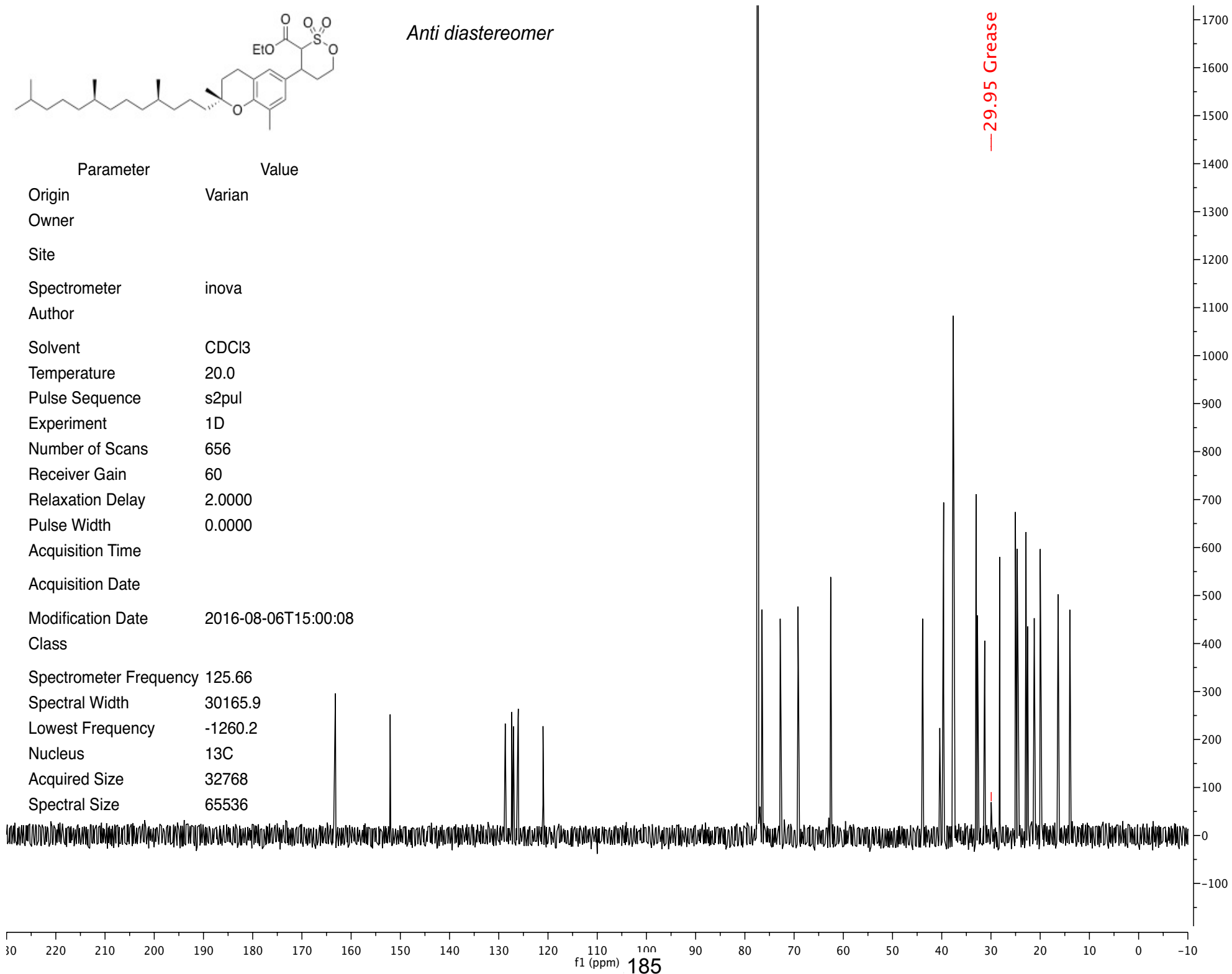
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl3
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	41
Relaxation Delay	10.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-08-06T14:25:00
Class	
Spectrometer Frequency	499.69
Spectral Width	7024.9
Lowest Frequency	-1022.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

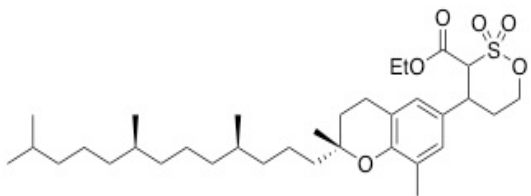




Anti diastereomer

Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	20.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	656
Receiver Gain	60
Relaxation Delay	2.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-08-06T15:00:08
Class	
Spectrometer Frequency	125.66
Spectral Width	30165.9
Lowest Frequency	-1260.2
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536





Anti diastereomer

Parameter	Value
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Origin	Varian
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Owner	
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Site	
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Spectrometer	inova
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Author	
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Solvent	CDCl ₃
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Temperature	20.0
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Pulse Sequence	s2pul
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Experiment	1D
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Number of Scans	656
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Receiver Gain	60
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Relaxation Delay	2.0000
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Pulse Width	0.0000
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Acquisition Time	
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Acquisition Date	
------------------	--

Modification Date	2016-08-06T15:00:08
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Class	
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Spectrometer Frequency	125.66
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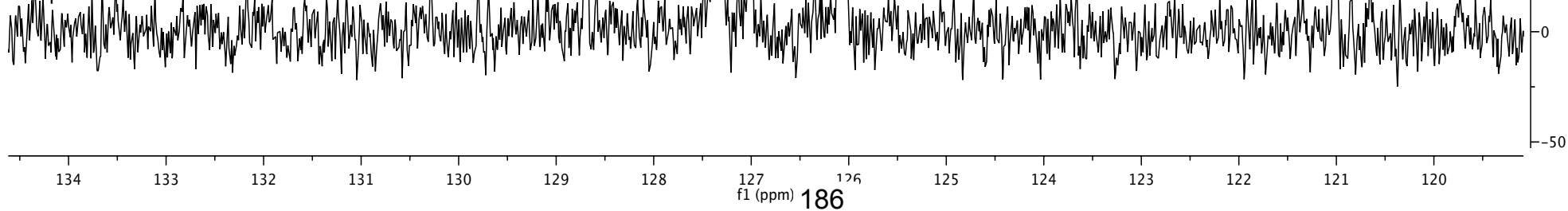
Spectral Width	30165.9
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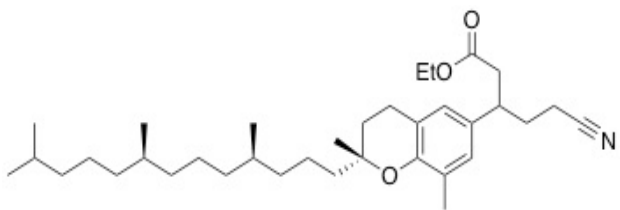
Lowest Frequency	-1260.2
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Nucleus	¹³ C
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Acquired Size	32768
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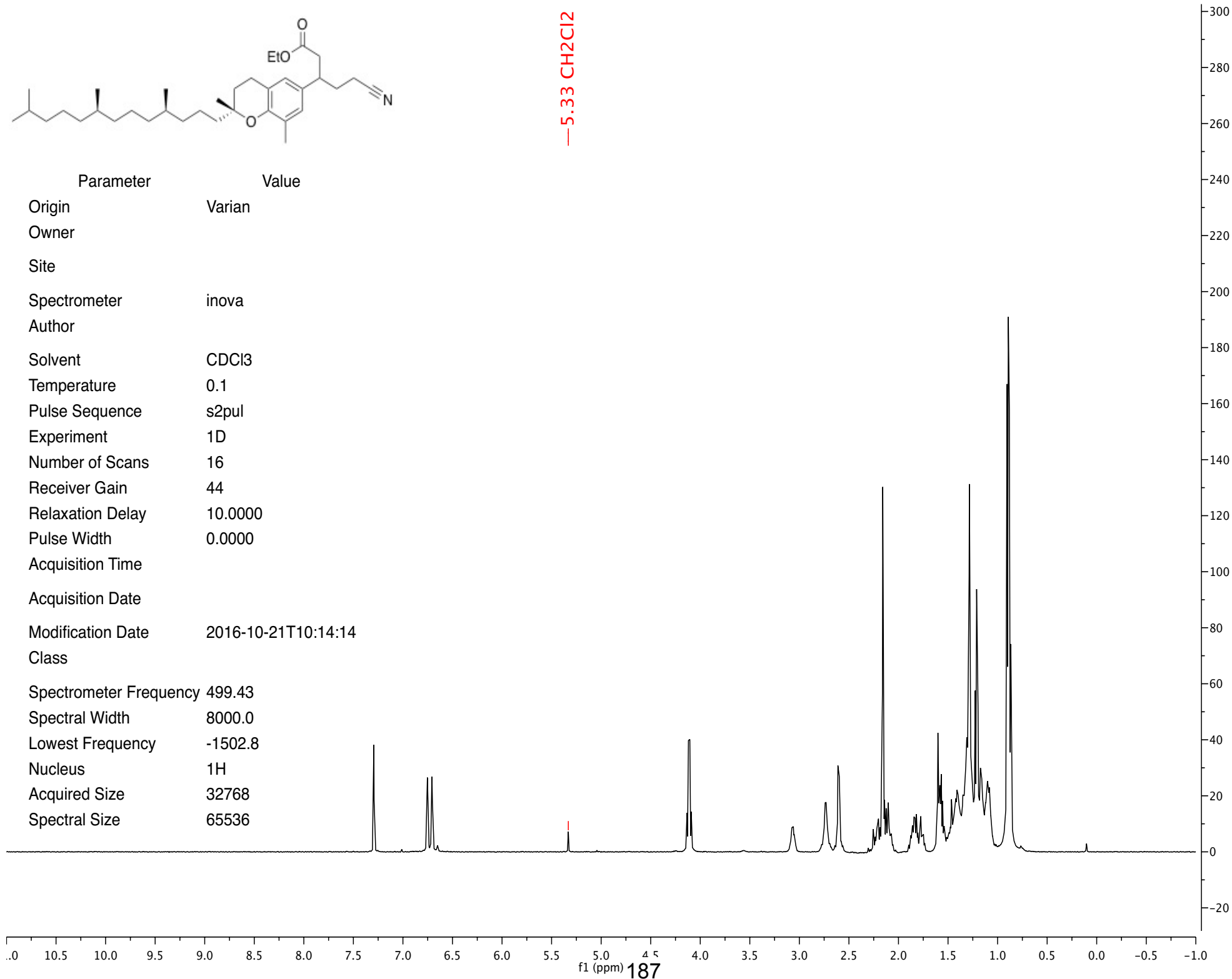
Spectral Size	65536
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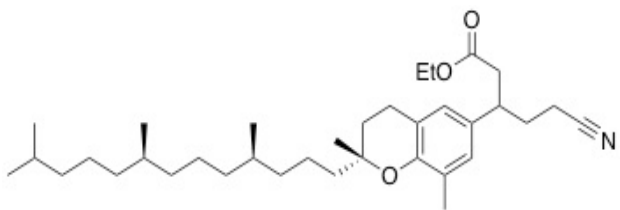




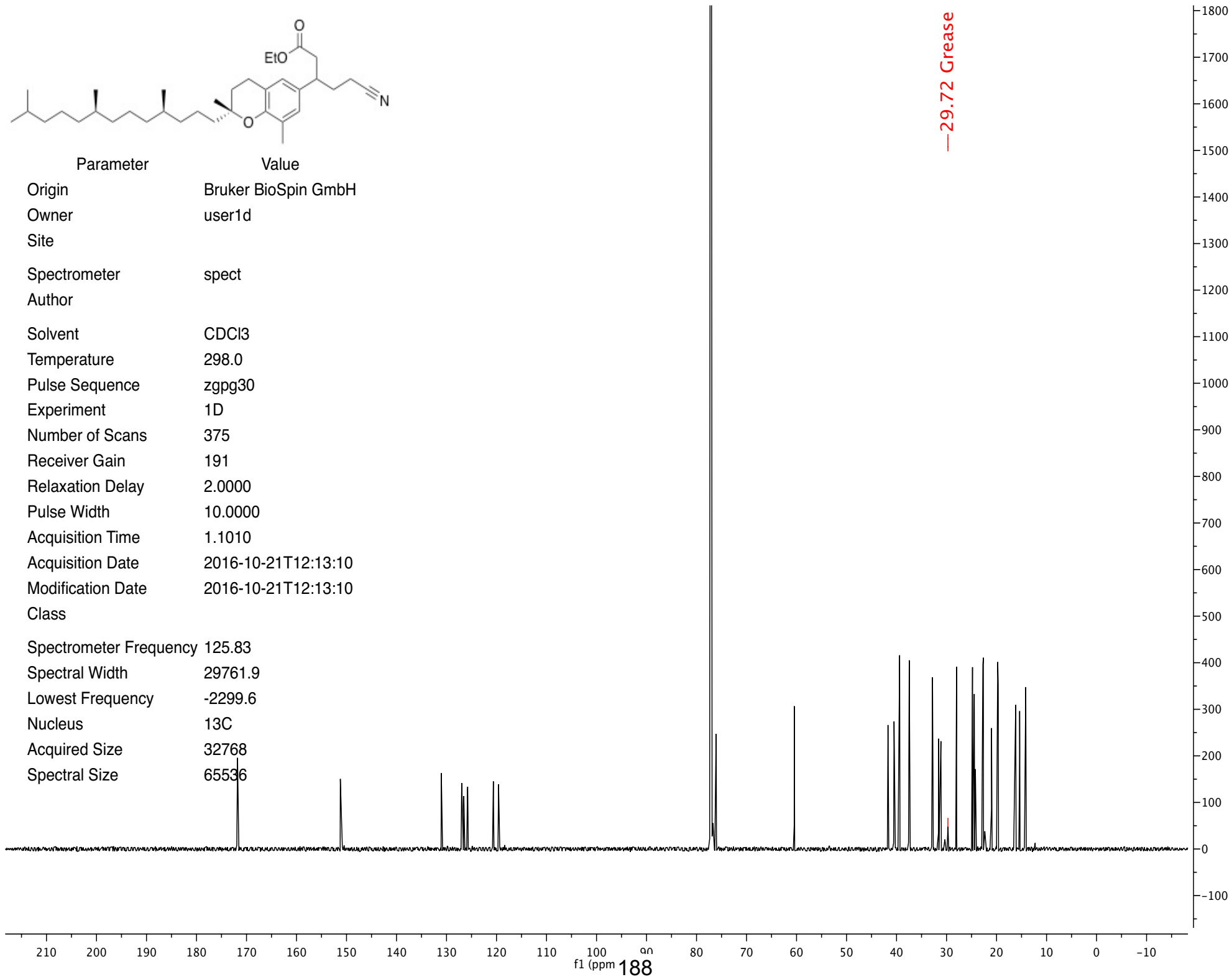
— 5.33 CH₂Cl₂

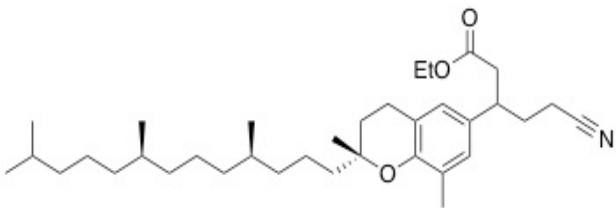
Parameter	Value
Origin	Varian
Owner	
Site	
Spectrometer	inova
Author	
Solvent	CDCl ₃
Temperature	0.1
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	44
Relaxation Delay	10.0000
Pulse Width	0.0000
Acquisition Time	
Acquisition Date	
Modification Date	2016-10-21T10:14:14
Class	
Spectrometer Frequency	499.43
Spectral Width	8000.0
Lowest Frequency	-1502.8
Nucleus	¹ H
Acquired Size	32768
Spectral Size	65536



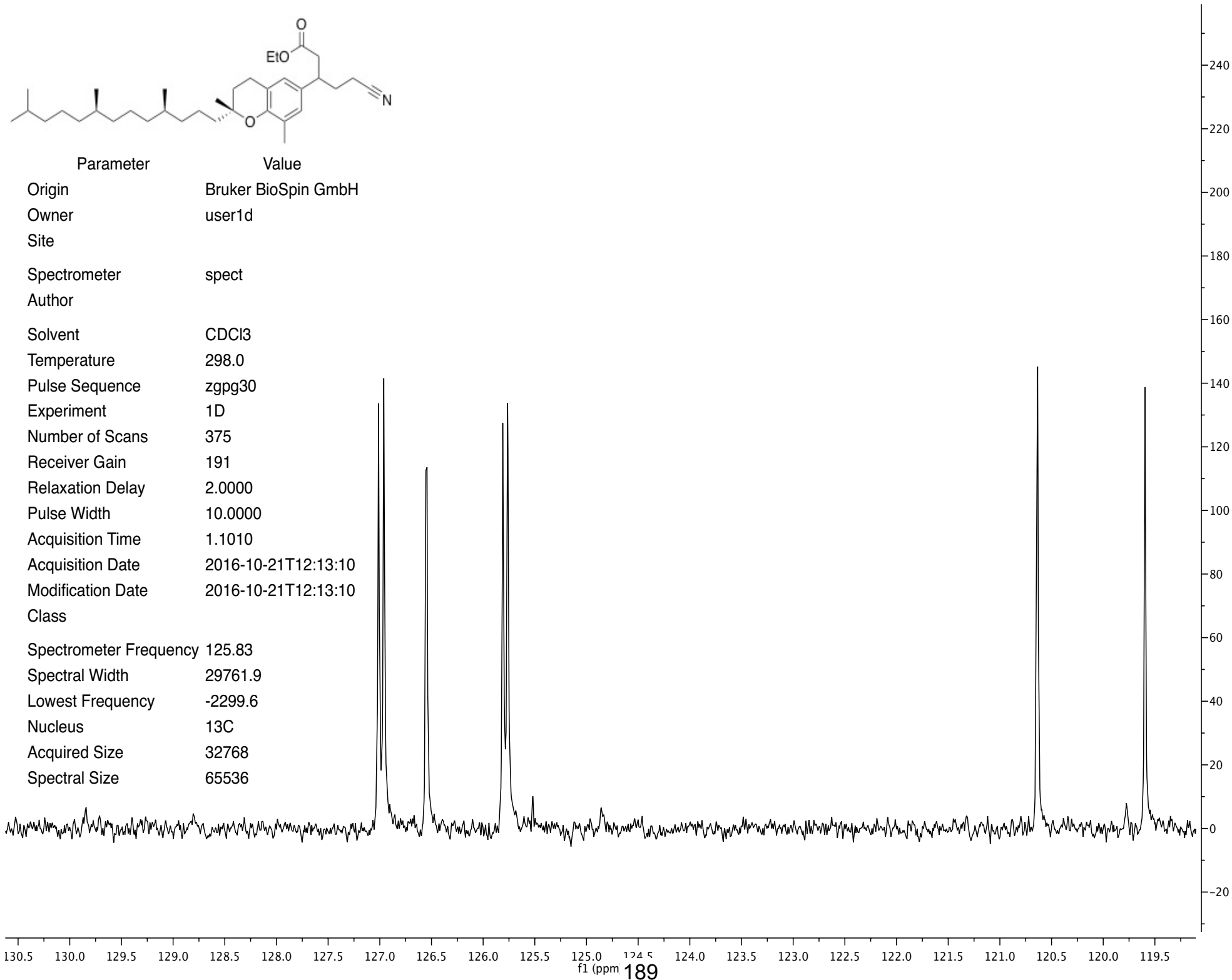


Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	375
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-21T12:13:10
Modification Date	2016-10-21T12:13:10
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2299.6
Nucleus	13C
Acquired Size	32768
Spectral Size	65536





Parameter	Value
Origin	Bruker BioSpin GmbH
Owner	user1d
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	298.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	375
Receiver Gain	191
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.1010
Acquisition Date	2016-10-21T12:13:10
Modification Date	2016-10-21T12:13:10
Class	
Spectrometer Frequency	125.83
Spectral Width	29761.9
Lowest Frequency	-2299.6
Nucleus	¹³ C
Acquired Size	32768
Spectral Size	65536



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Notes

Parts of this chapter are adopted from Griffin, J. R.; Wendell, C. I.; Garwin, J. A.; White, M. C. Catalytic C(Sp³)-H Alkylation via an Iron Carbene Intermediate. *J. Am. Chem. Soc.* **2017**, *139* (39), 13624–13627. The materials are reproduced/adapted with permission. Copyright © 2016 American Chemical Society. This work was produced in close collaboration with Jennifer R. Griffin and Jacob A. Garwin. J.R.G. completed initial optimization of the conditions. J.R.G, C.I.W and J.A.G. all contributed to investigations into tether and catalyst. J.R.G and C.I.W. both worked on confirming the non-catalytic nature of the Woo results. J.R.G. originated substrates **7** and **12**, which were completed by C.I.W. J.R.G. and J.A.G. also completed substrate and mechanistic investigations undiscussed in this thesis.

II)²¹ (Fig. 3.2).

Ring-opening metathesis polymerization (ROMP) utilizes this process for polymerization of cyclic olefins, converting them into linear olefins.^{22–26} The driving force for high-strain

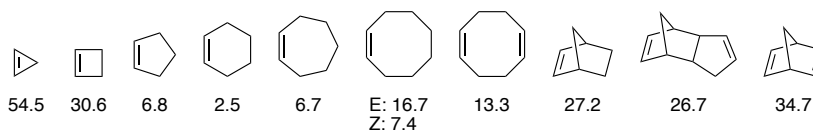


Figure 3.3. Ring strain in kcal/mol.

monomers is the release of ring strain, although it is possible for entropy to play a larger role in the driving force for those monomers with a lower ring strain.^{27–29} Cyclopentene, cyclohexene and cycloheptene tend to have lower ring strain values, whereas smaller rings and bicycles have higher values (Fig. 3.3).^{29–31} It is possible for ROMP to be a living polymerization, where the rate of initiation is much much greater than that of chain transfer or termination, producing monodisperse polymers.^{32–34} A fast-initiating catalyst, like Grubbs III, or other strategies involving ligand or temperature optimization are necessary to achieve this, otherwise inter- or intramolecular chain transfer can interfere.^{18,20,35,36}

3.2 Bulk and Frontal Polymerization

Polymers are widely used in industry and are growing in many applications.^{37–42} They are inexpensive to produce, moldable, and have tunable properties depending on their structure. Most thermoset polymers are made via bulk polymerization, which typically involves raising the temperature of a monomer-initiator mixture gradually and uniformly until the rate of polymerization is high enough that the mixture polymerizes.⁴³ This can be an energy-intensive process. One lifetime analysis of the production of carbon-fiber reinforced composite materials for the fuselage of a Boeing 787 airplane revealed that it took 1.6×10^4 kW h, or 58 GJ to produce.^{39,44} This energy usage has both environmental and economic consequences.⁴⁴ In addition, bulk

polymerization can generate an immense amount of heat, which is both unutilized and a safety hazard.⁴⁵

The large exotherm provided by certain forms of polymerization can be practically put to use through frontal polymerization. This stands in contrast to bulk polymerization; rather than heating the entire mixture, a small amount is heated enough to begin polymerization in this section, and the resulting exotherm drives polymerization in the solution around this region. This produces a front of polymerization which moves throughout the monomer solution like a wave.⁴⁶ Frontal polymerization has a variety of benefits. Since it does not require constant heating over hours, it is typically more energy efficient.⁴³ It is faster, which lowers costs and the required storage lifetimes of materials. It can be beneficial for the dispersal of nanoparticles throughout a resin or the formation of hydrogels, since there is not as much time for settling before polymerization.^{47–49} There is also the potential for more control. In bulk polymerization, the entire mixture polymerizes at once, whereas in frontal polymerization, it is possible to determine which areas will polymerize first. This can enable addition of more resin during the polymerization process with a gradient of materials to produce a final polymer with a gradient of properties.⁵⁰ However, frontal polymerization is associated with a variety of specialized concerns which can complicate this potential for greater control.

3.3 Balance of Forces in Frontal Polymerization

The viability of frontal polymerization requires a sufficiently long storage lifetime of the monomer mixture. The storage lifetime is the time the mixture may be stored without background polymerization that stops it from being activated in the future. This requires that k_p be sensitive to temperature; it must be very low at the storage temperature and very high at the initiation temperature. Per the Arrhenius equation (1), this means that the activation energy of the system

must be high. In practice, the effective activation energy of the system is typically the activation energy of the initiation step, since this is typically higher than the activation energy of the propagation step.⁵¹ The storage lifetime can be especially important for composites, where the monomer mixture must slowly diffuse into an existing framework.⁵²

$$k = Ae^{\frac{-E_a}{RT}} \quad (1)$$

Another concern unique to frontal polymerization is the balance between heat lost to the environment and heat generated by the polymerization itself. If too much heat is generated, then the monomer may polymerize spontaneously. If too much heat is lost, the front may become unable to sustain itself and quench.^{53,54}

Instabilities in the front may also be the result of fluid flow in the mixture. A front propagating upwards can induce convection currents in the monomer which can dissipate heat. A front propagating downwards can produce Trommsdorf-Norrish fingering which can also dissipate heat.⁵⁵⁻⁵⁷ The angle of the propagation with respect to the force of gravity affects front velocity and angle due to these effects.⁵⁸ If some of the materials in the monomer mixture are volatile at the front temperatures they may boil which can consume some heat.⁵⁹ If these effects do not quench the front, they broaden the front by transferring heat ahead of it, slowing and cooling the front. They also typically induce flaws in the final polymer.^{59,60} Spin modes where the front propagates in a helix or double-headed helix are also common and induce materials flaws.⁵⁹⁻⁶¹

Increasing the viscosity of the mixture dampens these effects and may stop a front from quenching. This can be achieved by the addition of fumed silica or kaolin clay which may also improve materials properties, although the additive also reduces the energy density according to its relative concentration.^{46,62-64} The shape and size of the container is also extremely consequential to heat loss to the environment.^{61,65}

3.4 Conditions for Frontal Ring Opening Metathesis Polymerization

The first system reported for frontal polymerization was reported by Enikolopyan and coworkers for the polymerization of methyl methacrylate at pressures >3500 atm.^{66,67} The first example of frontal ring opening metathesis polymerization (FROMP) was in 2001 by Mariani and Pojman using Grubbs first generation catalyst (G1), dicyclopentadiene (DCPD) and a triphenylphosphine inhibitor.⁶⁸ However, the storage lifetime of this system was so short that it had to be flash frozen to prevent spontaneous polymerization. Most FROMP systems utilize norbornene derivatives due to their high ring strain, which contributes to the heat of polymerization. DCPD polymerization releases 353J/g of heat, and is also useful due to its ability to crosslink.⁶⁹ Solid, crosslinked polymers are optimal for FROMP because liquid polymers can display added instabilities due to fluid flow.

Table 3.1. Performance of various inhibitors.^{68,70–72}

Inhibitor	Inhibitor Loading (ppm)	Catalyst Loading (ppm)	Front Speed (cm/min)	T _{max} (°C)	Storage Lifetime (hrs)	Storage Temperature (°C)
PPh ₃	330	122 (G1)	0.6	162	0.3	35
P(OMe) ₃	100-800	100 (G2)	1-7	175-215	1-4	23
P(OEt) ₃	100-800	100 (G2)	1-7	175-215	3-15	23
P(O ⁿ Bu) ₃	100-800	100 (G2)	1-7	175-215	5-30	23
DMAP	170	170 (G1)	0.9	197	0.16	30
DMAP	60-500	60 (G2)	2.2-7.5	197-198	0.3-0.5	30
(R)-limonene	10,000-20,000	80 (G2)	9-29	162-187	0.4-10	22

Because the storage lifetime of G1 and DCPD is very short, it is necessary to add some inhibitors to render the systems more practical. Inhibitors include Lewis bases that bind reversibly to the ruthenium center^{68,70,71} and limonene, which acts as a less reactive monomer.⁷² The performance of these inhibitors are as listed below, as determined from FROMP with DCPD in a

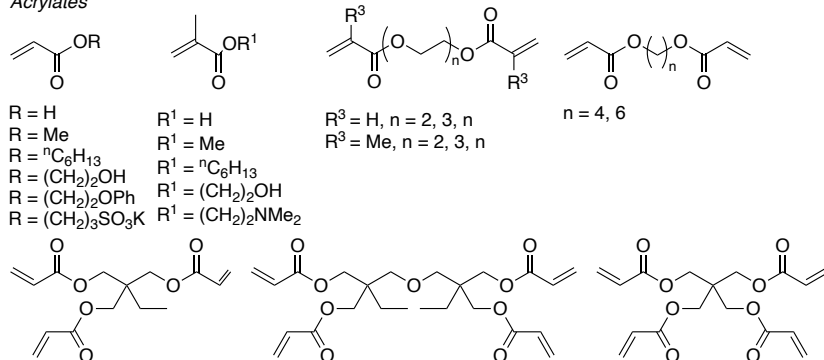
glass test tube of 1.3-1.5 cm diameter (Table 3.1). Grubbs II (G2) is also commonly used.

3.5 Frontal Polymerization of Epoxides

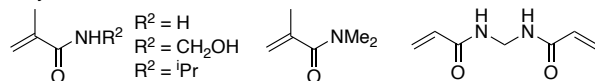
A variety of other kinds of frontal polymerization have been reported. One of the most ubiquitous is cationic epoxide and oxetane polymerization, which is used in a variety of applications, especially aircraft and other applications requiring strong, lightweight materials.^{38,73} Typically this involves an acid-catalyzed opening mechanism where the conjugate base terminates the polymerization.⁷⁴ This polymerization produces less heat than FROMP and displays higher storage lifetimes.^{75,76} Some common initiation reagents include amine-borane adducts, which react with adventitious water to form boric acid,^{63,77,78} cross-linking polyamines,^{79–81} and photoacids in the form of hypervalent iodine reagents.^{78,82–86} Polyamines are crosslinking agents which ultimately form copolymers with the epoxide, and may be used in relatively high concentrations, up to equimolar with the epoxide.⁸⁷

The use of photoacids in cationic epoxide polymerizations is limited by the low

Acrylates



Acrylamides



N-Vinyl Heterocycles

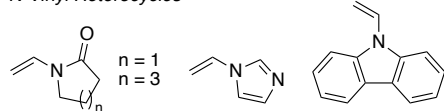


Figure 3.4. Monomers in use for radical frontal

transmission of light through the material. In general, in order to obtain high levels of conversion throughout the material, a radical initiator such as BPO must be added, which drives thermal propagation after a UV initiation event.^{82–86}

3.6 Radical Frontal Polymerization

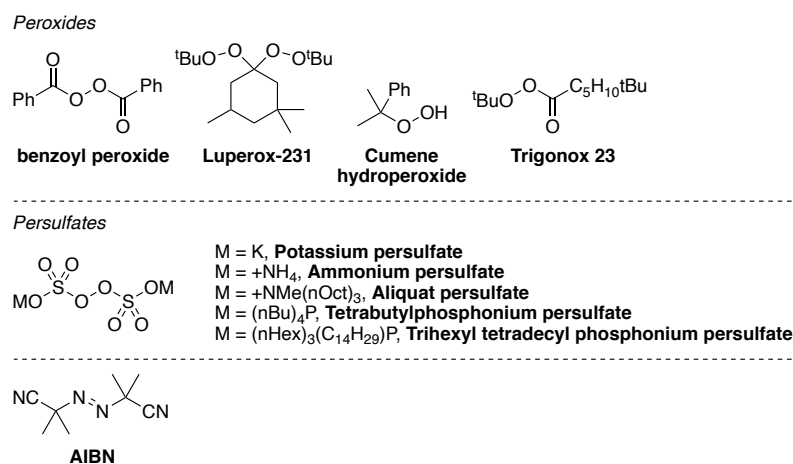


Figure 3.5. Initiators in use for radical frontal

Radical frontal polymerization is the most common type of frontal polymerization.^{56,88} It was also the first reported,^{66,67} and the first reported at ambient pressures, although this first example featured a dispersity of 4 due to

boiling and double diffusive convection instabilities.⁸⁹ Most of the monomers involved are acrylates^{57,58,60,62,64,65,89–113} or acrylamides,^{58,92,98,100,101,110,114–122} less common are enamines (Fig. 3.4).^{95,109,111,117,123–126} The effects of monomers on frontal velocity and front temperature are dependent on a variety of physical parameters, including the heat and rate of polymerization, as well as the mass per olefin, although this may be represented by reporting heat released per gram rather than per mole. Some values for heat released per gram are shown in Table 3.2.

Table 3.2. Some monomers and their heat release during polymerization.

Monomer	ΔH (J/g)	(Hydroxyethyl)methacrylate	385 ⁷⁶
Acrylic acid	930 ⁷⁶	1,6-Hexanediol diacrylate	650 ¹²⁷
Methyl acrylate	907 ⁷⁶	Trimethylolpropane triacrylate	653 ¹²⁷
Hexyl acrylate	500 ⁷⁶	Acrylamide	1120 ⁷⁶
Methacrylic acid	738 ⁷⁶	N-Hydroxymethyl acrylamide	738 ⁷⁶
Methyl methacrylate	560 ⁷⁶	N-Isopropyl acrylamide	700 ⁷⁶
Hexyl methacrylate	344 ⁷⁶	N-Methylene acrylamide	537 ⁷⁶

A variety of radical initiators are also reported for radical frontal polymerization. These undergo homolytic cleavage with some kind of outside stimulus (commonly heat) and initiate the polymerization. Peroxides and AIBN are common but typically produce volatile side products, leading to boiling and corresponding materials flaws.⁵⁶ Persulfates have been developed partially to prevent volatile side products, but are insoluble in most monomers with traditional counterions, leading to the development of bulky counterions to promote solubility.¹⁰⁵ Both frontal speed and storage lifetime are dependent on the reactivity and concentration of initiator, leading to a delicate balance; enhancing one may depreciate the other. Combining peroxides with a metal redox couple can increase front speed without impacting storage lifetime.^{94,96,107,112} Microencapsulated initiators are another strategy to prevent bubbling and lengthen storage lifetime.^{96,107}

Solvents are sometimes used in radical polymerization, whether to promote solubility of certain components or for use in hydrogels.^{49,92,98–100,103,104,109–111,115–117,119,120,122,123,125,126,128–135} Some common solvents include DMSO, glycerol, NMP and water. Solvent concentration is another variable by which the frontal velocity and temperature may be tuned, helpful for use with monomers with smaller working windows, like benzoyl peroxide and AIBN.¹⁰⁵ Fillers are another common additive in radical frontal polymerization, both to alter polymer properties (ie. composites) and to increase viscosity and suppress convective instabilities.^{62,136}

3.7 Photopolymerization

Heat is an accessible and convenient method of activation for a variety of polymerization processes. The exothermic nature of many polymerizations also allows a heat-activated system to be autoaccelerated. However, there are certain applications where heat is not practical or advantageous.¹³⁷ For instance, dental materials which are polymerized in situ cannot reach high temperatures in such close proximity to body tissues.¹³⁸ In addition, heat may damage polymers

and produce volatile organic compounds, which damage materials properties and may be dangerous to inhale. Autoacceleration, while frequently convenient, can also lead to lack of control.

In these contexts, photopolymerization provides many advantages. The use of UV light is common,^{139–144} but lower energy wavelengths are also used.^{137,138,145} In this latter case, the initiation is often very safe and requires very low energy input. LEDs represent a convenient, cheap and safe light source which produce light in a narrow wavelength range. Room temperature reactions are also a safer alternative to high temperature frontal polymerization processes. In addition, depending on the degree of irradiation required, the energy input can be very low. Photopolymerization or photothermal polymerization systems have been developed for acrylate,^{130,141,142,146,147} acrylamide,^{129,131} epoxide,^{78,84,85,145,148} N-vinyl heterocycle,^{131,133} thiol-ene,¹³⁹ polyurethane,¹³³ and ROMP monomers.^{149,150}

However, traditional photopolymerization has one major drawback. The polymerization can only extend as far as the light reaches. Traditionally, in industrial applications this has meant that polymerization only extends up to about 50 μm , and only about 5 μm in the case of highly pigmented paints and inks.¹³⁷ It can also mean that polymerization requires a very high energy dose, defined as irradiance multiplied by irradiation time ($\text{J}\cdot\text{cm}^{-2}$). Pigments tend to absorb in the UV and higher energy end of the visible spectrum, which also tends to be the activation wavelength for most photopolymerization processes. In contrast, monomers tend to only absorb very high energy UV radiation, meaning that they typically do not contribute as much to photoattenuation. Composites and polymers with fillers can also be problematic, since these elements tend to scatter light in the UV/Visible region, whereas the near IR has better transmission.¹⁵¹ Composites and fillers, as well as the geometries of certain practical uses (such as dental fillings) also mean that

monomer solutions have shadow areas where no light reaches at all. Despite these drawbacks, very thin films produced by photopolymerization have found a variety of applications in dentistry, microfluidics, origami, coatings, and paints.^{137–140} The irradiance at depth is calculable based on the Beer-Lambert law (2), where I_0 is the irradiance at the surface, I_x is the irradiance at depth x , and A is the absorbance of the solution at the wavelength of activation.¹³⁷

$$I_x = I_0 \cdot 10^{-x \cdot A} \quad (2)$$

Every strategy used to overcome this problem has an impact on the degree of control that photopolymerization system offers.¹³⁷ This inherent trade off means that systems may need to be tailored to a certain application. Low absorbance monomer solutions and high quantum yield photopolymerization processes can be one way to ameliorate photoattenuation without significant loss of control. For example, high efficiency charge transfer complexes, N-aryl amines and iodoniums, have been used to polymerize 31 cm of clear acrylate with just an LED.^{152–154}

Another strategy is the use of photoinitiators that undergo photobleaching.^{141–143,155} As the photoinitiator absorbs light, it decomposes to species that have much lower absorbance. Therefore, as the upper layers of the material polymerize, they transmit light more effectively down to the lower levels, which can then polymerize and bleach themselves. Traditional photoinitiators in this vein are acylphosphine oxides, which allow 10-15 cm curing of clear acrylates.^{141,156,157} Some other photoinitiators include 1,2 diones like camphorquinone,¹⁵⁸ newly developed Norrish type I photoinitiators like silylglyoxylates,¹⁵⁹ and Norrish type II photoinitiators like benzophenone and thioxanthenes.¹³⁸ This strategy is very common in dental materials.

Near infrared radiation (NIR) tends to have much better penetration through monomer solutions than UV/Visible light. Unfortunately, NIR is generally not high energy enough to promote cleavage in most photoinitiators, and most light emitting particles or compounds emit at

higher wavelengths than they absorb. However, upconversion particles, nanoparticles containing rare earth metals, can combine multiple infrared photons to an ultraviolet photon, albeit at low yields.¹⁶⁰ These particles have been used to convert UV/Vis activated systems into NIR activated systems. They generally require high energy sources of radiation to overcome these low quantum yields. These particles have been used to achieve deep polymerization of acrylate with camphorquinone and benzophenone.¹⁶¹ The Irgacure 784 titanium photocatalyst is frequently used with upconversion particles, for use with acrylates,¹⁶² thiol-ene polymerizations,¹⁶³ and even in highly pigmented samples.¹⁴⁵ Photo-ATRP may also be utilized for low polydispersity results.¹⁶⁴

While these approaches may improve the penetration of photopolymerization and its viability in pigmented samples, they do not solve the fundamental problem of polymerization in shadow areas. One way to tackle this is with latent species produced by light closer to the surface of the mixture which then diffuse outward and initiate polymerization in deeper layers. One common method is with photolatent amines, which can polymerize epoxides when they are unmasked with light.^{165,166} This is generally promoted with an added thiol component. These systems can suffer from low reactivity; they sometimes require heating after being exposed to light in order to fully polymerize. Lower rates of polymerization and longer stability of initiators makes cationic epoxide polymerization better suited to this strategy, but also contributes to its disadvantages. In contrast, these same photocaged amines can interact with a peroxide radical initiator in acrylate polymerization and produce a higher degree of polymerization.¹⁶⁷ A copper photoredox catalyst may also be used to cleave peroxide initiators, which then diffuse through the material to polymerize lower layers.^{168,169} Ultimately latent species diffusion cannot achieve high degree of cure in shadow areas and complete cure requires high durations and temperatures.^{170–174}

These methods of enhancing photopolymerization penetration are inherently limited.

While development of higher efficiency systems may enhance degree of cure at lower levels and in shadow areas, photoattenuation and the limits of diffusion will always be problematic. However, the lack of activity in these areas also allows a degree of control not found in conventional frontal polymerization, and these methods find many specialized applications. In order to overcome these problems entirely, propagation in total darkness must be possible, which inherently sacrifices some this control.

3.8 Photothermal Polymerization

Another strategy to overcome the inherent penetration problem of photopolymerization is to leverage the thermal autoacceleration of frontal polymerization. In these systems, the polymerization requires no outside heating, but is triggered by light. Once the polymerization begins, the exothermic polymerization triggers the next layer of material, so light penetration is not an issue. The entire mixture of monomer is generally polymerized. Benefits of this mode of activation include precise control over the activation of the mixture, the ability to activate it in multiple positions at once, lower energy input (depending on light source), and the ability to activate the mixture remotely. Some of these systems rely only on the heat of polymerization to drive them and there is a direct photochemical mechanism for the initiation of polymerization. Some of them rely on heat generated with light to trigger the polymerization in the first place.

In the latter category are several systems which rely on particles that produce heat from light, or simply on nonradiative relaxation of all the species in the system to generate heat. When no specific heat generating species is used, the light source is typically a higher-powered source.^{95,129} Infrared lasers are also common for this mode of activation.^{130–132} Other protocols rely on particles that convert light into heat (called heaters).¹⁷⁵ Graphene oxide and gold nanorods have been reported for use with broadband light in biological applications.^{176,177} Carbon nanoparticles

have been reported to heat with a broadband light.¹⁵⁰ This system allows the use of broadband light.

Photothermal systems which do not convert heat directly into light must have a dual mechanism of activation. They are activated photochemically, but also activated thermally. This dual mechanism is sometimes carried out by the same species, as in the case of a Grubbs second generation catalyzed polymerization of dicyclopentadiene. The catalyst in this system is inhibited by a phosphite ligand to extend pot life, which must dissociate before the polymerization can begin.¹⁴⁹ This process can be triggered by heat or light. Another example of this type is the bis-acetylacetonate platinum catalyst for hydrosilation, which can trigger polymerization of vinyl silanes with either heat or light.¹⁷⁸

Alternatively, there are a wide variety of systems where these two modes of activation are carried by two separate species. This is common in the polymerization of epoxides, where there is typically a photoinitiator and a thermal initiator. The photoinitiator is commonly a diaryliodonium salt, which acts as a photoacid generator, and some common thermal initiators include peroxides, such as benzoyl peroxide, or 1,1,2,2-tetraphenyl-1,2-ethanediol, both of which undergo homolytic cleavage with heat.^{83–85,179–181} Triphenyl pyrylium tetratfluoroborate has also been employed as a photoinitiator with epoxides.¹⁸² Zhou et al. reported a layered system, where a photoinitiator sulfonium salt mixture was layered over a boron trifluoride amine mixture.⁷⁸ Acrylates are also polymerized with this type of dual system, generally using α -hydroxyketones or phosphinates as photoinitiators, and peroxides or persulfates as thermal initiators.^{64,146,147}

Photothermal processes have been used to form polymers with a variety of applications, including composites^{84,137} and hydrogels.^{129–133,147} They are also compatible with fillers.⁶⁴

3.9 References

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Chapter 4: Photoredox Initiated Frontal Ring Opening Metathesis Polymerization

4.1 Introduction

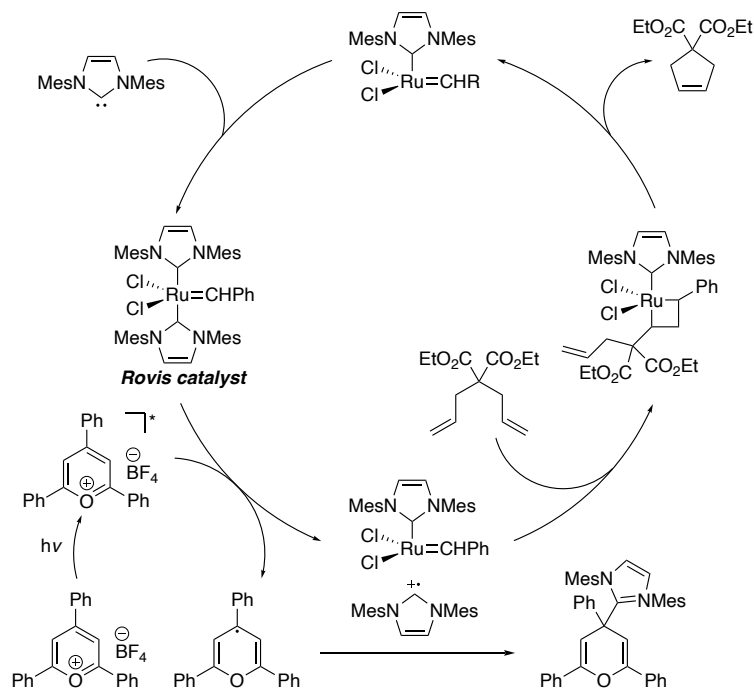


Figure 4.1. Mechanism of Photo-ROMP.

Only a handful of examples of photoinitiated FROMP exist.^{1,2} Both use Grubbs second generation catalyst (G2) and a phosphite inhibitor to polymerize DCPD. This system has certain weaknesses, like a short storage lifetime and a dearth of compatible monomers. The phosphite ligand is labile and not an entirely effective inhibitor; depending on loading and monomer the lifetime can be anywhere from 10-30 hours. We wondered if it were possible to design a less active catalyst, and took inspiration from a photo-ROMP system published by the Rovis group. The catalyst in this system has two NHC ligands, which are less labile than phosphites, and the photocatalyst oxidizes one of the ligands to render the catalyst active for metathesis (Fig. 4.1).³ This reaction does not proceed without blue LED excitation, and can be used to make patterned polymers in thin layers with patterned photomasks. We have had an opportunity to work with Demeta directly on a similar bis-NHC ruthenium catalyst (Fig. 4.2). This catalyst is not active in its resting state and needs to be activated, originally this was done with copper (I) chloride, which undergoes a transmetalation to remove an NHC ligand and furnish a catalyst with an open coordination site.

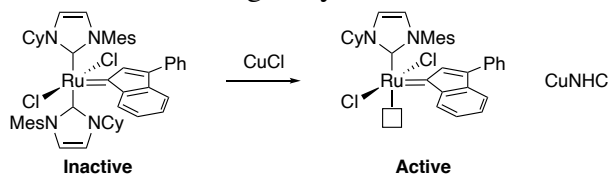


Figure 4.2. Activation of Demeta catalyst.

We wondered whether it would be possible to modify this system to be frontal and photoinitiated. Photoinitiated atom transfer radical polymerization utilizes copper catalysis and is useful for generating block copolymers due to its on/off ability with light.⁴⁻¹¹ In addition, photoredox catalysts have been used in a variety of polymerization methods, including for metal-free ring-opening metathesis.¹²⁻¹⁷

4.2 Development of a Thermal System

The first step was to adapt this catalyst to a frontal system. Key in this attempt was to change the copper source from copper (I) chloride to copper (I) bromide dimethyl sulfide, which

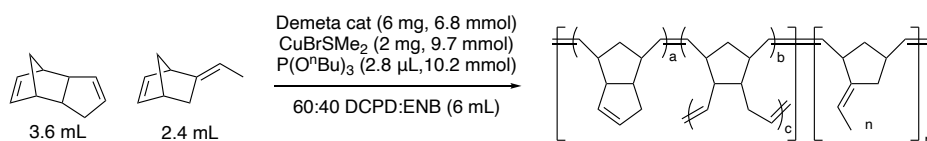


Figure 4.3. Thermal activation of Demeta catalyst for FROMP.

has better solubility. This led to a system which was viable for FROMP (Fig. 4.3). This system requires a larger thermal energy input and has slower front velocities than Grubbs second generation catalyst. The front temperature and velocity are responsive to loadings of copper, inhibitor and catalyst. Gratifyingly, the system may be split into two different monomer solutions: one containing copper and one containing catalyst and inhibitor. The resulting solutions are stable for multiple weeks and can be mixed at any time to undergo frontal polymerization. This represents a significant gain in the problem of storage lifetime.

4.3 Investigation of Photoredox Catalysts for Activation

Due to the similarity of this catalyst to the Rovis catalyst, we wondered if it were possible to activate this with just tetraphenylpyrylium tetrafluoroborate, but unfortunately this did not give FROMP activity. We observed that while copper (I) species readily transmetalate with the NHC to produce an active ruthenium catalyst for metathesis, copper (II) species did not activate the catalyst for FROMP. We were aware of a variety of photoredox literature involving copper redox

cycles,^{18–21} and wondered if a photoredox catalyst would be suitable to reduce a copper (II) source to copper (I) and ultimately activate the bis-NHC Demeta catalyst. We established copper (II) triflate as a copper source due to its solubility in monomer, although it requires a small amount of DMF cosolvent. We began by testing triphenyl pyrylium tetrafluoroborate (TPPT) due to its use with the Rovis catalyst,³ but also tested several other photoredox catalysts. We found especially good results with 9-Mesityl-10-methylacridinium tetrafluoroborate (MesAcr) and tris(bipyridine)ruthenium(II) chloride hexahydrate (Ru(bpy)₃) (Table 4.1). 10-Phenylphenothiazine showed initial promise but proved to be unreproducible over time. Other catalysts that gave no polymerization despite ten minutes of irradiation with an appropriate (UV, blue, or red LED) light source included: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, N-methylquinolinium hexafluorophosphate, N-methyl acridinium hexafluorophosphate, xanthone, Eosin Y, 9,10-anthracene, and Tris[2-phenylpyridinato-C²,N]iridium(III). Other catalysts that gave spontaneous polymerization included: tetrakis(dimethylamino)ethylene, Hantzsch ester, N-methylacridinium iodide.

Table 4.1. Initial identification of effective conditions, all conducted with 6 mL monomer.

Demeta amt	Cu(OTf) ₂ amt	Photocatalyst	DMF amt	DCPD/ENB (v/v)	Wavelength	Time to initiate
6 mg	22 mg/5 eq.	TPPT (10 eq.)	800 μ L	80:20	455 nm	90 s
6 mg	10 mg/5 eq.	MesAcr (1 eq.)	200 μ L	95:5	455 nm	50 s
6 mg	10 mg/5 eq.	Ru(bpy) ₃ (1 eq.)	200 μ L	95:5	455 nm	115 s

In order to ensure that all components were necessary for reactivity, we performed experiments without each critical component (Table 4.2). These controls establish that the Demeta catalyst, the copper source, and the photocatalyst are all necessary for light activation. Demeta and copper (II) triflate can be activated thermally, which is consistent with thermal propagation.

Table 4.2. Control experiments showing no FROMP, all conducted with 3 mL of 95:5 DCPD/ENB.

Demeta amt	Cu(OTf) ₂ amt	Photocatalyst	Photocatalyst amt	DMF amt	Light initiation	Heat initiation
none	5 mg/15 μmol	MesAcr	1.2 mg/3 μmol	100 μL	no	no
none	5 mg/15 μmol	Ru(bpy) ₃	2.3 mg/3 μmol	100 μL	no	--
3 mg/3 μmol	none	MesAcr	1.2 mg/1 eq.	100 μL	no	no
3 mg/3 μmol	none	Ru(bpy) ₃	2.3 mg/3 eq.	100 μL	no	--
3 mg/3 μmol	5 mg/15 μmol	none	n/a	100 μL	no	yes
none	5 mg/15 μmol	none	n/a	100 μL	no	no
3 mg/3 μmol	none	none	n/a	100 μL	no	no

Table 4.3. Effective conditions with inhibitor, all conducted with 6 mL of 95:5 DCPD/ENB.

Demeta amt	Cu(OTf) ₂ amt	Photocatalyst	Inhibitor	DMF amt	Wavelength	Time to initiate
6 mg/6 μmol	5 eq.	MesAcr (2 eq.)	DMAP (8 eq.)	200 μL	455 nm	178 s
9 mg/9 μmol	5 eq.	MesAcr (2 eq.)	PPh ₃ (1.5 eq.)	300 μL	455 nm	104 s
12 mg/12 μmol	3.75 eq.	Ru(bpy) ₃ (1 eq.)	P(O ⁿ Bu) ₃ (1.5 eq.)	400 μL	455 nm	98 s

Because TPPT required extremely high loadings and correspondingly high amounts of DMF to be effective, we moved towards further optimization with only two catalysts: MesAcr and Ru(bpy)₃. We were also curious about the viability of using inhibitors with these systems, since inhibitors are vital to high storage lifetime. We tested four inhibitors which have been used in the past for FROMP with ruthenium catalysts: 4-dimethylaminopyridine (DMAP), tributylphosphite, triphenylphosphine, and limonene.^{22–25} The first four are labile ligands with the ruthenium catalyst, the last undergoes metathesis and then inhibits further metallocyclobutane formation due to steric inhibition. For this reason, it is required in much larger volumes than the other inhibitors. This has a more profound effect on materials properties. Unfortunately, limonene was only viable for FROMP at low percentages (5% by volume) and therefore did not improve the storage lifetime

markedly. We decided to focus on ligand inhibitors, of which all three were viable with FROMP under varying conditions (Table 4.3).

4.4 Temperature and Frontal Velocity

We moved on to investigating the temperature and frontal velocity of our five standard conditions: MesAcr without inhibitor, Ru(bpy)₃ without inhibitor, MesAcr/DMAP, MesAcr/PPh₃, and Ru(bpy)₃/P(OⁿBu)₃ (Table 4.4). Maximum temperature and front speed of the thermal Demeta case vary depending on exact conditions, but most cases are within 140-200°C and 0.2-1.4 mm/s. Temperature for the thermal case is in a similar range, but front speeds tend to be slower. Some of this is due to the presence of DMF in the mixture, not typically included in the thermal case.

Table 4.4. Initial temperatures, initiation times, and frontal velocities of five standard conditions.

Demeta amt	Cu(OTf) ₂ amt	Photocatalyst	Inhibitor	Front speed	Initial front temp	Initiation time
6 mg/6 μmol	10 mg/5 eq.	MesAcr, 1 eq.	none	0.184 mm/s	175°C	50 s
6 mg/6 μmol	10 mg/5 eq.	Ru(bpy) ₃ , 1 eq.	none	0.163 mm/s	184°C	115 s
6 mg/6 μmol	10 mg/30 μmol	MesAcr, 2 eq.	DMAP	0.201 mm/s	205°C	178 s
9 mg/9 μmol	15 mg/5 eq.	MesAcr, 2 eq.	PPh ₃	0.284 mm/s	191°C	104 s
12 mg/12 μmol	15 mg/3.75 eq.	Ru(bpy) ₃ , 1 eq.	P(O ⁿ Bu) ₃	0.199 mm/s	165°C	98 s

These temperature curves are taken a few millimeters into the resin and reveal the

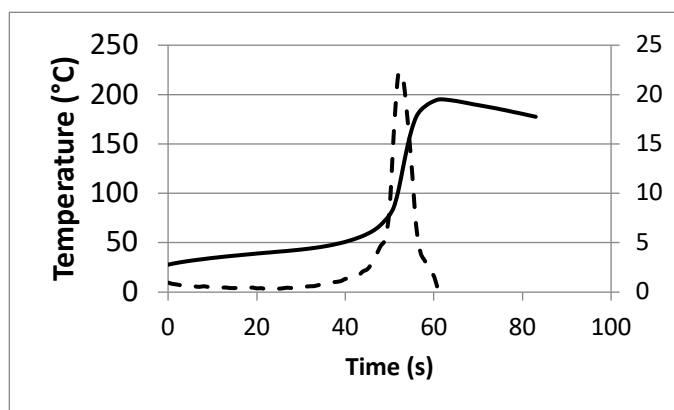


Figure 4.4. Temperature (solid) and first derivative (dashed) of MesAcr initiation over time.

temperature dynamics at the time and place of photoinitiation (Fig. 4.4-4.8). They reveal an uncomplicated single front, as the second derivative shows only one peak. They also show a considerably slower ramp and broader, more gradual derivative peak than the typical Grubbs second generation

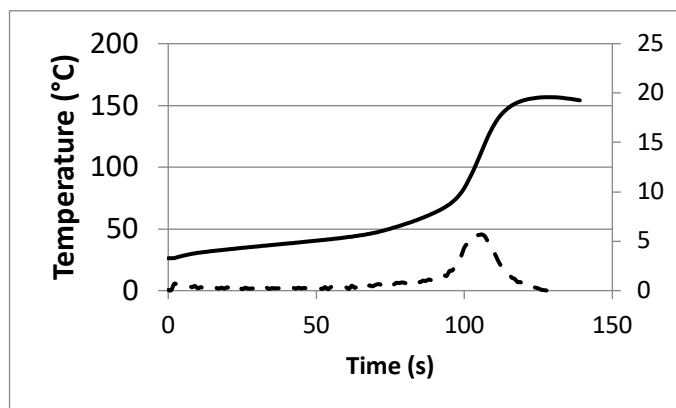


Figure 4.5. Temperature (solid) and first derivative (dashed) of $\text{Ru}(\text{bpy})_3$ initiation over time.

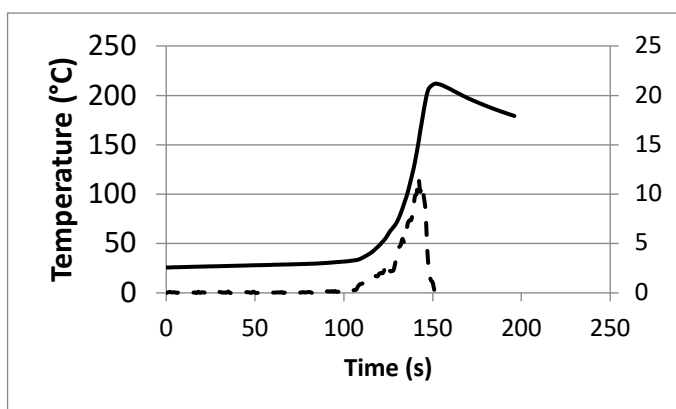


Figure 4.6. Temperature (solid) and first derivative (dashed) of MesAcr/DMAP initiation over time.

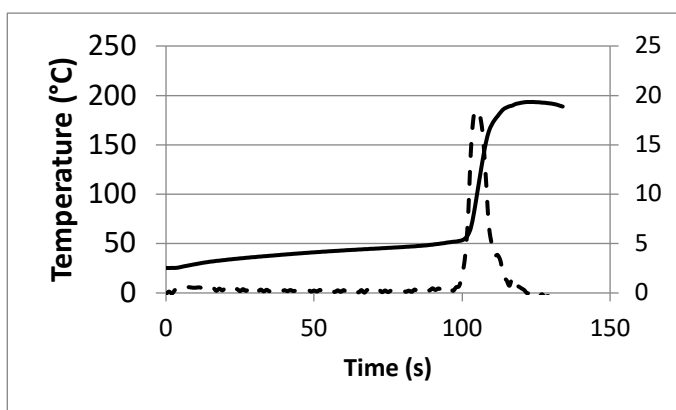


Figure 4.7. Temperature (solid) and first derivative (dashed) of MesAcr/ PPh_3 initiation over time.

monomer is replaced with inert toluene and the temperature measured over a ten minute period (Fig. 4.9). These systems reached a maximum temperature of 56°C without inhibitor and 55°C

FROMP system.²⁶ The temperature curve of the thermal Demeta catalyst system is also broader than that of Grubbs second generation, likely due to the heat required to activate the catalyst. In the photoinitiated system there are two relevant effects. First, the two step mechanism required before the catalyst is activated may lead to a slower initial polymerization, which means the heat build up from polymerization is also slower. In addition, there is heating from the unproductive vibrational relaxation of the photocatalyst. This heating is unlikely to be productive because it does not reach a temperature close to the temperature required for front formation through vibrational heating alone, but it does broaden the temperature profile. Temperature increases from vibrational relaxation alone can be seen when the

with inhibitor, far from the 175°C and 191°C, respectively required to induce fronts in these systems.

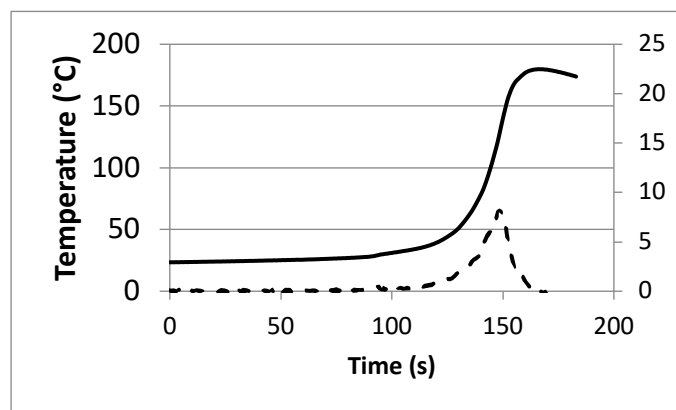


Figure 4.8. Temperature (solid) and first derivative (dashed) of $R(bpy)_3/P(O^nBu)_3$ initiation over time.

After investigating the properties of all five of the standard conditions, we decided to focus on the MesAcr system without inhibitor, and MesAcr with PPh_3 as inhibitor for several reasons. First, the frontal velocity and temperature of both of these systems is fairly high. In addition, the

solubility of MesAcr and PPh_3 in monomer is reasonably good, which in our experience leads to more reproducible results.

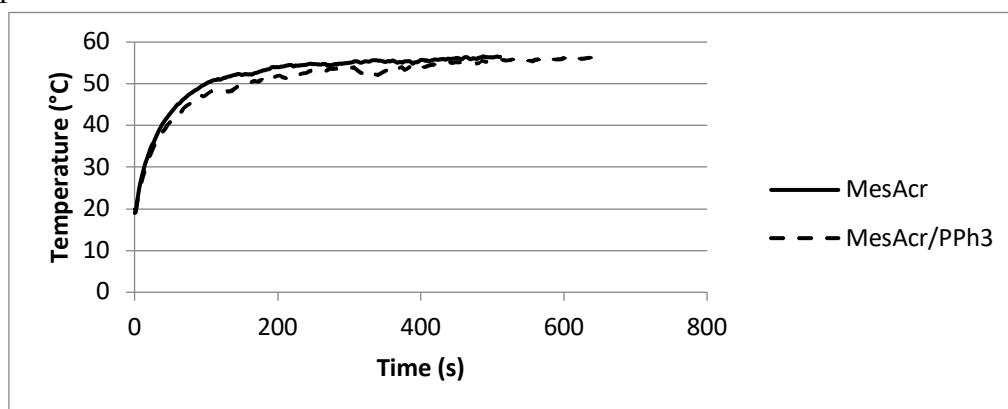


Figure 4.9. Heating due to vibrational relaxation of systems without monomer.

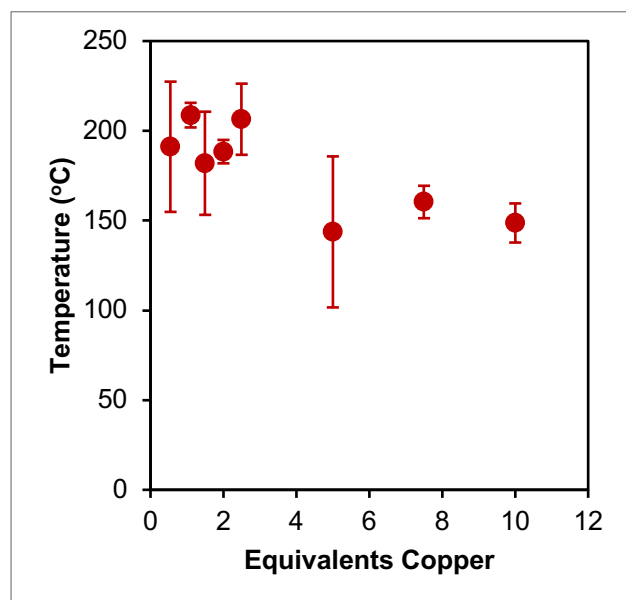
4.5 The Effect of Copper Loading on Temperature, Initiation Time and Front Speed

After the initial optimization and investigation of properties, we sought to further clarify the role of copper (II) triflate in the system by investigating properties as a function of loading. First we investigated the effect of copper in the MesAcr system without inhibitor, then in the MesAcr system with PPh_3 inhibitor.

Table 4.5. Conditions for copper loading experiments.

Demeta amt	Cu(OTf) ₂ amt	Photocatalyst	Inhibitor	DMF amt	DCPD/ENB	Wavelength
6 mg/6 μ mol	variable	MesAcr (1 eq.)	none	100 μ L	95:5, 6 mL	455 nm
9 mg/9 μ mol	variable	MesAcr (2 eq.)	PPh ₃ (1.5 eq.)	300 μ L	95:5, 6 mL	455 nm

Without inhibitor, the MesAcr system can tolerate very low loadings of copper without front instability, as low as 0.55 equivalents of copper with respect to Demeta catalyst (Table 4.5). At lower loadings (less than 3 equivalents), the temperature (Fig. 4.10), frontal velocity (Fig. 4.11), and initiation time (Fig. 4.12) are relatively unaffected by copper loading. At higher loadings, the temperature is lower, the initiation time is higher and the front velocity is slightly lower. These higher loadings are also associated with high error. Our observations indicate that higher loadings of copper cause solids to crash out of solution. We hypothesize that this is due to counterion exchange; at higher loadings of copper (II) triflate, the triflate ion may exchange with either the MesAcr tetrafluoroborate counterion or the Demeta chloride counterions. It is possible that this

**Figure 4.10.** Effect of copper loading on initiation temperature in the MesAcr system.

causes MesAcr to be less soluble in the monomer or the Demeta catalyst to decompose due to the added open coordination site. Either of these pathways explains a longer initiation time and lower initial temperature, but the slower frontal velocities are more likely to be explained by the Demeta catalyst decomposition route than the MesAcr crashing out, because only the

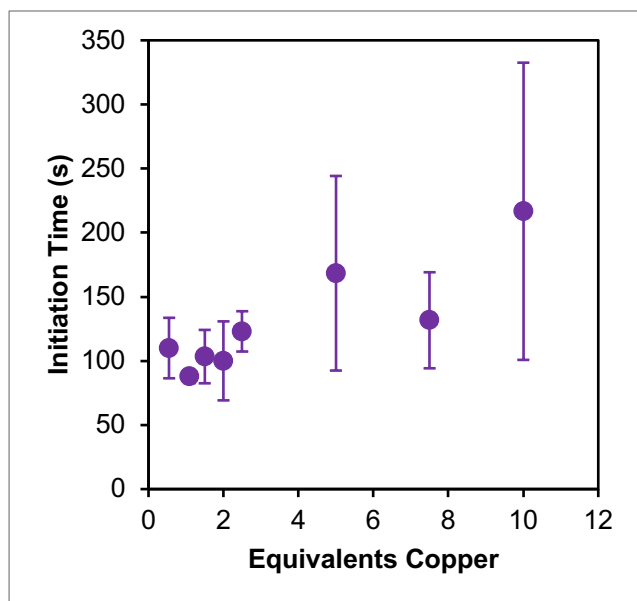


Figure 4.11. Effect of copper loading on initiation time in the MesAcr system.

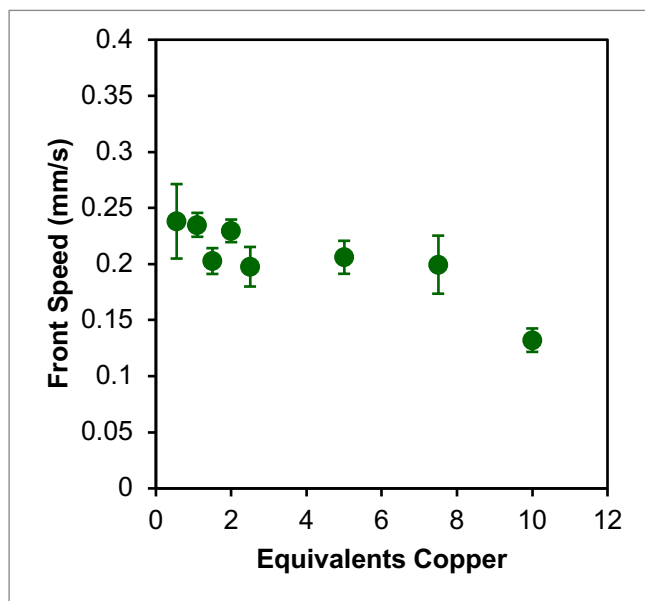


Figure 4.12. Effect of copper loading on front velocity in the MesAcr system.

Demeta catalyst is involved in the thermal propagation.

We next tested the effect of copper loading on the MesAcr system in the presence of the triphenylphosphine inhibitor. The front did not initiate at copper (II) triflate loadings below 3.3 equivalents with respect to Demeta catalyst. Higher loadings were also tolerated without any observed solid crashing out of the monomer system. Consistent with these observations is the fact that initiation temperature (Fig. 4.13), initiation time (Fig. 4.14), and front speed (Fig. 4.15) are relatively unaffected by the copper loadings tested in this case. The presence of triphenyl phosphine clearly makes a significant difference in how the system behaves. Our hypothesis is that the triphenylphosphine coordinates to the copper (II) triflate, rendering it less capable of performing the

transmetalation with the NHC ligand, therefore more copper (II) triflate is needed to promote initiation.

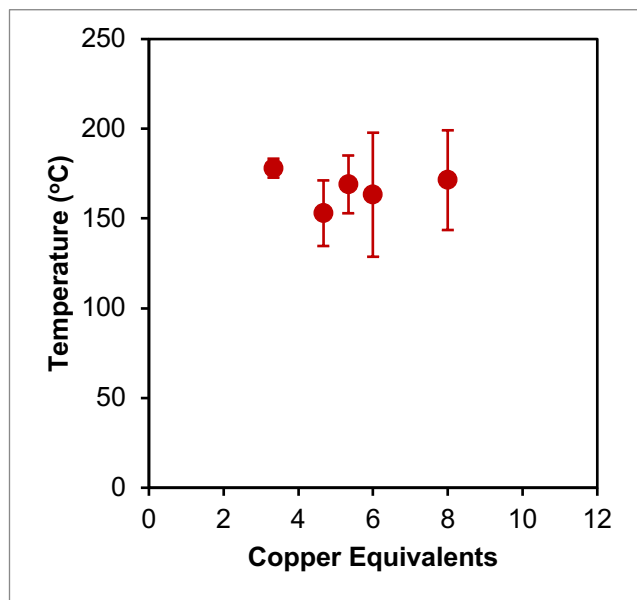


Figure 4.13. Effect of copper loading on initiation temperature in the MesAc/PPh₃

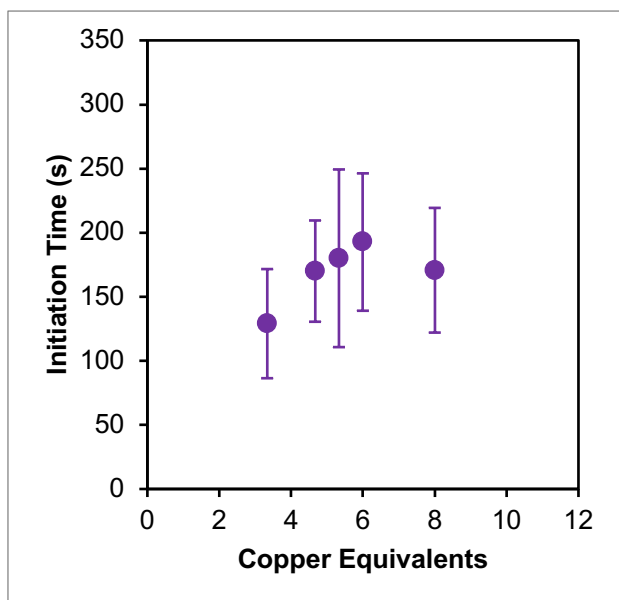


Figure 4.14. Effect of copper loading on initiation time in the MesAc/PPh₃ system.

The triphenylphosphine may also prevent crashing out of solids. The ligand exchange mechanism between copper (II) triflate and Demeta is likely driven by the decreased solubility of copper (II) chloride triflate and copper (II) chloride. The latter we have observed is less soluble in monomer than copper (II) triflate. Triphenylphosphine could coordinate to the copper chloride salts and facilitate their solubility, keeping the chloride ion in equilibrium and preventing further counterion exchange. It is also possible that the triphenylphosphine may promote solubility and stability of the Demeta catalyst after counterion exchange. While it is possible that triphenylphosphine also promotes the solubility of copper (II) tetrafluoroborate salts, it is less likely than copper (II) chloride salts because copper (II) tetrafluoroborate salts are more likely to be

fully soluble in the first place. Therefore, the ability of triphenylphosphine to ameliorate insolubility in the system is another piece of evidence that suggests that higher loadings of copper (II) triflate specifically affect the amount of Demeta catalyst in solution.

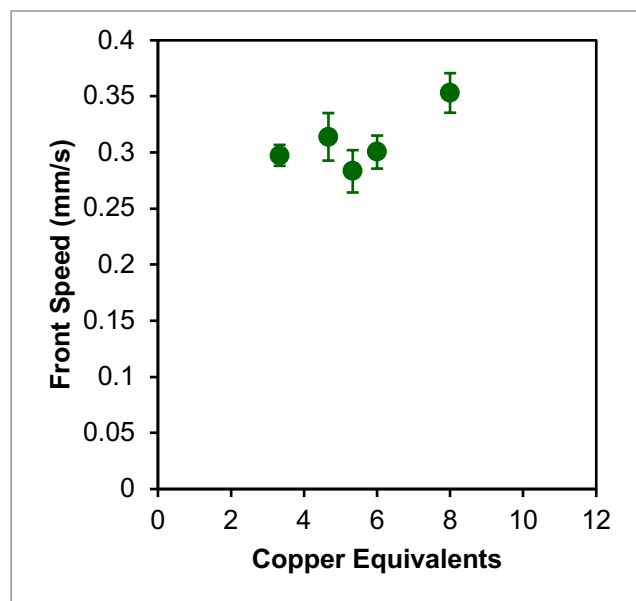


Figure 4.15. Effect of copper loading on front speed in the MesAcr/PPh₃ system.

Ultimately these data suggest that the efficiency of the system is not meaningfully limited by the copper loading, except in those cases where the system is inhibited in an attempt to increase storage lifetime. It also suggests that the inhibitor may coordinate to the copper as well as the ruthenium catalyst.

4.6 The Effect of Demeta Catalyst Loading on Temperature, Initiation Time and Front Speed

Table 4.6. Conditions for Demeta loading experiments.

Demeta amt	Cu(OTf) ₂ amt	MesAcr amt	Inhibitor	DMF amt	DCPD/ENB
variable	2.2 mg, 6 μ mol	2.5 mg/6 μ mol	none	100 μ L	95:5, 6 mL
variable	12 mg, 33 μ mol	7.5 mg/18 μ mol	PPh ₃ , 3.5 mg, 13.5 μ mol	300 μ L	95:5, 6 mL

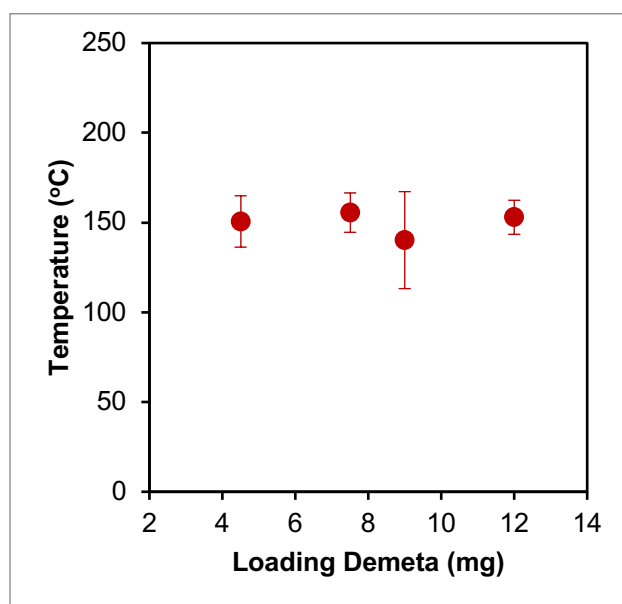


Figure 4.16. The effect of Demeta loading on temperature in the MesAcr system without an inhibitor.

We next wanted to investigate how the loading of the Demeta catalyst affects the system. We investigated this at lower copper loadings than the standard system because we had discovered through our more thorough copper loading investigation that the standard loadings may not be optimal (Table 4.6).

Unsurprisingly, increased Demeta loading increases the front speed (Fig. 4.18). Interestingly, it does not have as much of an

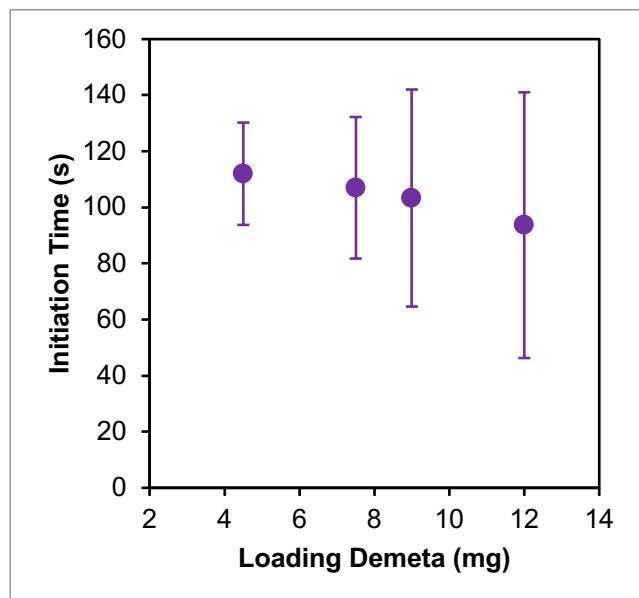


Figure 4.17. The effect of Demeta loading on initiation time in the MesAcr system without inhibitor.

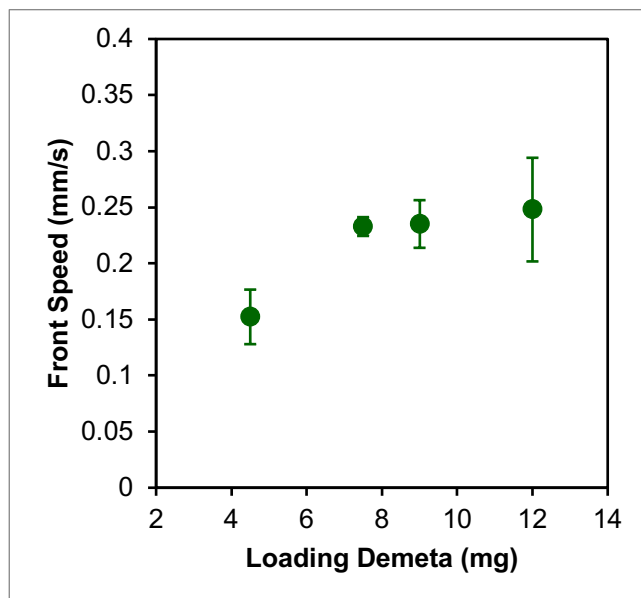


Figure 4.18. The effect of Demeta loading on front speed in the MesAcr system without inhibitor.

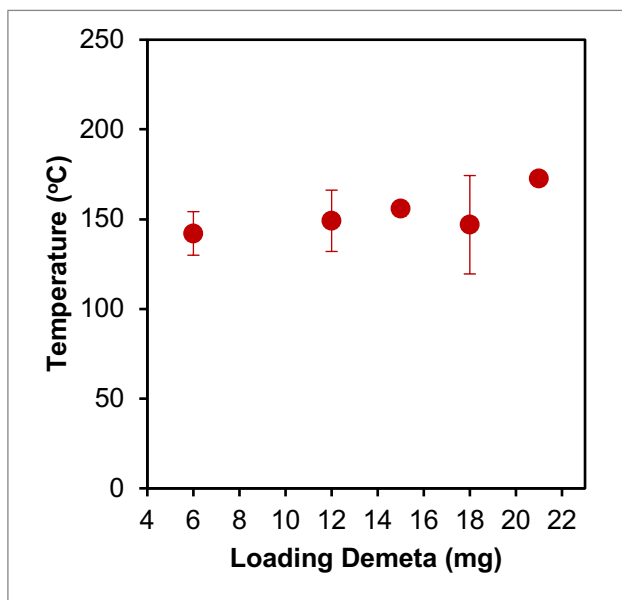


Figure 4.19. The effect of Demeta loading on temperature in the MesAcr system with PPh_3 .

effect on the initiation temperature (Fig. 4.16). It may be that the internal temperature is dependent on Demeta concentration. The initiation time seems to decrease slightly with increased loading, but it is unclear if this effect is significant or just a product of error (Fig. 4.17).

In the case of the inhibited system, we see similar effects of Demeta catalyst loading on temperature and front speed: no effect on

temperature and a clear, but modest, increase in front speed (Fig. 4.18, 4.19). However, there is a marked decrease in initiation time, by almost 50%, when moving from 12 to 15 mg of catalyst (Fig. 4.20). Because the window of viable loadings in the inhibited case is wider, we did not obtain

data higher than 12 mg for the uninhibited system, so it is possible that increasing the loading another increment in the uninhibited case would reveal a similar pattern. However, since we kept the amount of inhibitor constant for each case, it is also possible that the ratio of catalyst:inhibitor was simply high enough at the 15 mg loading to have a large amount of uninhibited catalyst present in the mixture. At 12 mg, the molar ratio of catalyst to inhibitor is 0.99:1. At 15 mg, the molar ratio is 1.24:1.

Regardless, the role of catalyst loading in initiation time contrasts with the relative lack of dependence of initiation time on copper loading, excluding those loadings which contribute to crash out in the uninhibited case. This suggests that the rate determining step of the photoinitiation involves the Demeta catalyst, but does not involve copper.

4.7 Differential Scanning Calorimetry Analysis

Table 4.7. Conditions for DSC experiments and T_g values, as compared to the thermal system.

Demeta amt	Copper source	Copper amt	Photocatalyst	Inhibitor	DMF amt	DCPD/ENB	T_g
6 mg/6 μ mol	Cu(OTf) ₂	2.2 mg, 1 eq.	MesAcr (1 eq.)	none	100 μ L	95:5, 6 mL	123°C
9 mg/9 μ mol	Cu(OTf) ₂	12 mg, 3.7 eq.	MesAcr (2 eq.)	PPh ₃ (1.5 eq.)	300 μ L	95:5, 6 mL	107°C
6 mg/6 μ mol	CuBrSMe ₂	1.8 mg, 1.5 eq.	none	P(O ⁿ Bu) ₃ (1.5 eq.)	none	95:5, 6 mL	156°C

In order to make some determinations about the materials properties of the polymer produced by the photoinitiated system, we analyzed two samples by differential scanning calorimetry (DSC). The resulting curves show no major exotherms during ramp scans, indicating that the frontal polymerization has a high degree of cure (Fig. 4.22).

The thermal system has higher T_g values than the photoinitiated system (Table 4.7). Both systems are lower than the photoinitiated Grubbs second-generation DCPD system, which can be as high as 170°C at high catalyst loadings.¹ However, the thermal system is comparable to other

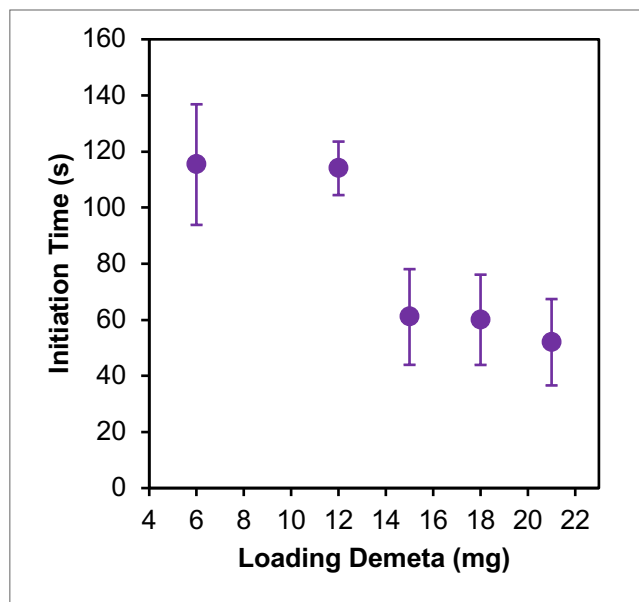


Figure 4.20. The effect of Demeta loading on initiation time in the MesAcr system with PPh₃. Grubbs second generation thermal systems,

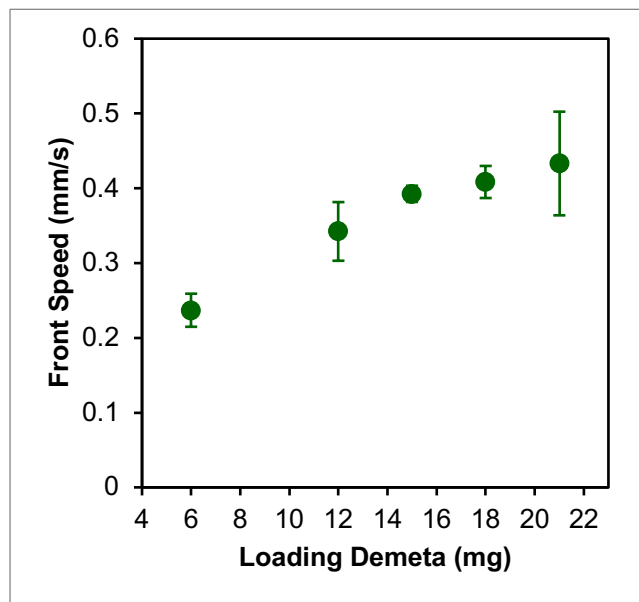


Figure 4.21. The effect of Demeta loading on front speed in the MesAcr system with PPh₃.

although this is dependent on comonomer.²⁷ The photoinitiated system has a lower T_g partially due to the solvent that was included, as demonstrated by the T_g values for a G2/DCPD/DMF system (Table 8). In the future it may be advantageous to develop a system with better monomer solubility to allow solvent-free conditions and therefore higher glass transition temperatures. A more soluble acridinium photocatalyst would need to be developed and more soluble copper (II) sources would be screened.

Table 4.8. Conditions for DSC experiments and T_g values, with G2 and DMF.

G2 amt	P(OnBu) ₃ amt	DMF amt	DCPD/ENB	T _g
5 mg/6 μmol	1.5 μL/1.5 eq.	100 μL	95:5, 6 mL	145.6°C
5 mg/6 μmol	1.5 μL/1.5 eq.	300 μL	95:5, 6 mL	128.3°C

4.8 Storage Lifetime Testing

We were also interested in the storage lifetime of the monomer solutions. We found that

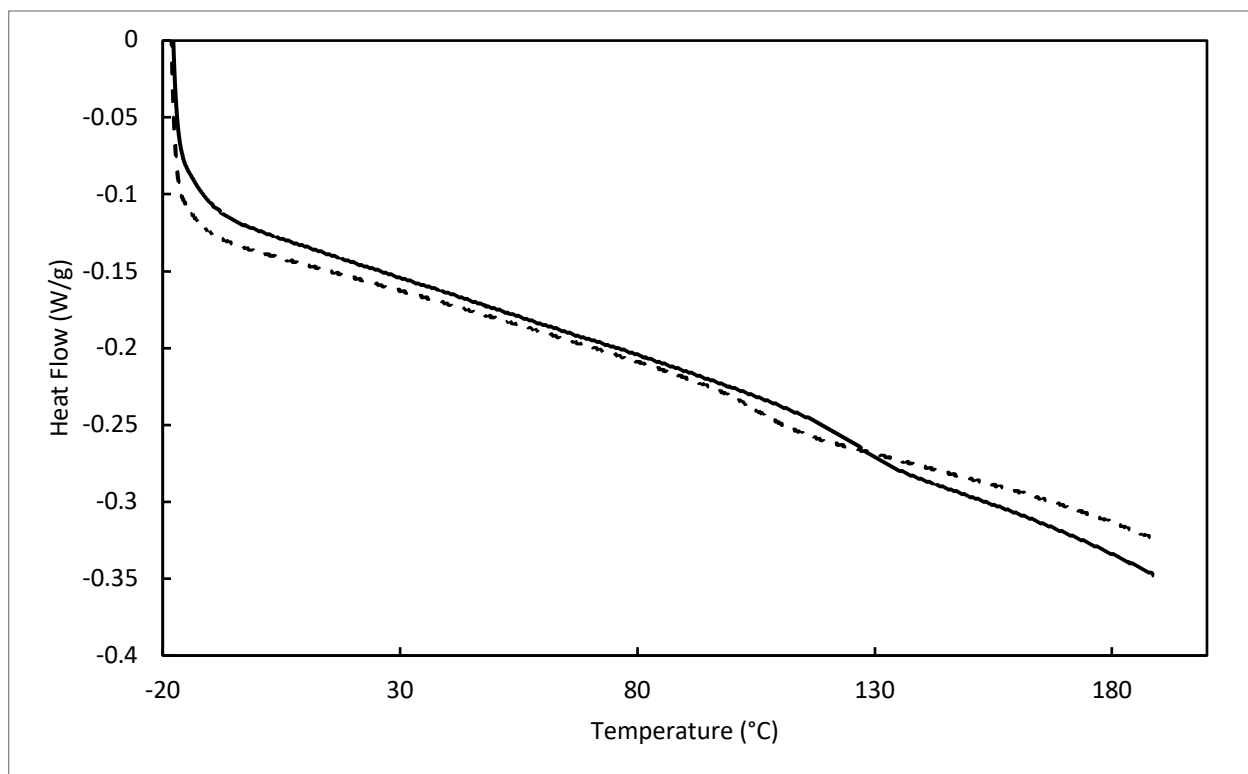


Figure 4.22. DSC ramp scans for the MesAcr uninhibited (solid) and inhibited (dashed) system. none of the monomer solutions remained liquid for 24 hours in the dark at room temperature. The MesAcr system inhibited by DMAP gelled over 24 hours but was also the only system to maintain its activity for 24 hours. The MesAcr system inhibited by triphenylphosphine gels after less than an hour but retains its activity for an hour. In order to extend the stability of the system, we decided to split the solution into two (Table 9). In one solution is the Demeta catalyst and inhibitor, and the other is the copper source and the photocatalyst. Both are kept in the dark at room temperature. At the time of FROMP, they are combined and thoroughly mixed just before initiation. It is worth noting that a mixture of Demeta catalyst, photocatalyst, and inhibitor and a mixture of copper did not FROMP when recombined.

Table 4.9. Conditions for a split stability study.

Solution	Demeta amt	Cu(OTf) ₂ amt	MesAcr amt	PPh ₃	DMF amt	DCPD/ENB
1	18 mg/20 μ mol	none	none	7 mg, 1.4 eq.	150 μ L	95:5, 6 mL
2	none	30 mg, 5 eq.	15 mg/2 eq.	none	150 μ L	95:5, 6 mL

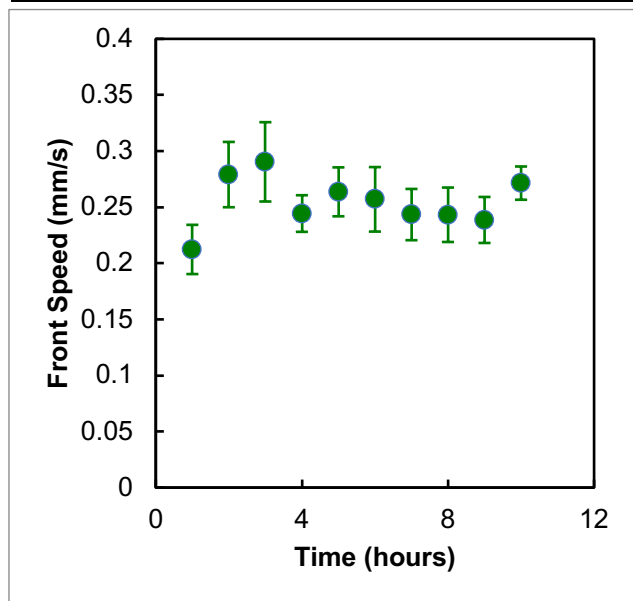


Figure 4.23. Front speed of a split solution MesAcr inhibited system over time.

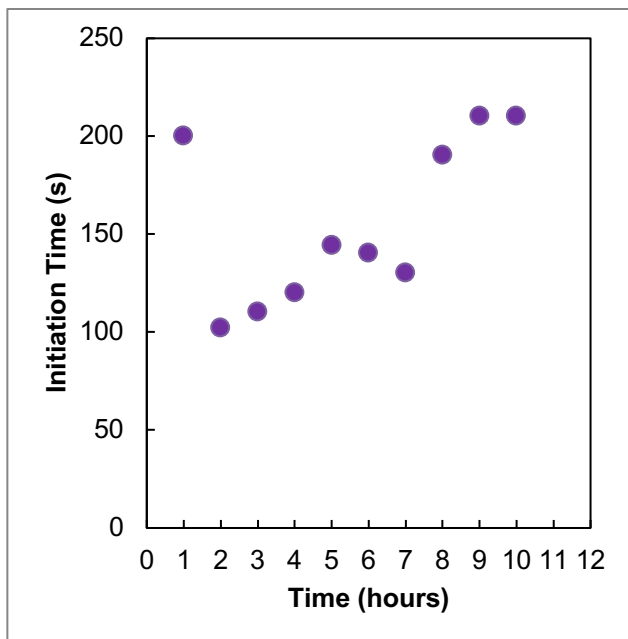


Figure 4.24. Initiation time of a split solution MesAcr inhibited system over time.

First, we monitored the front speed and initiation time of the mixture over the course of ten hours. The front speed of the system with no delay is 0.284 mm/s, and the initiation time is 191 s. We observe an initial drop in initiation time and an initial increase in front speed. We also observe clear crash out in the copper (II) triflate/MesAcr monomer solution, which may contribute to this effect. This is consistent with data from the copper equivalents experiments, which show a slight drop in initiation time and a slight rise in frontal velocity with lower copper equivalents (Fig. 4.23, 4.24). However, over time we observe a flattening of the front speed and an increase in initiation time, so further crash out is unlikely to be beneficial to FROMP parameters.

We moved on to a more long term investigation of the stability of the split

solution system. We found that solution 1 is stable for five days, beyond this point it begins to gel and is eventually inactive. Any degree of gelling makes the solution impossible to mix into the other monomer solution, which makes it untestable. Solution 2 is stable for up to 12 days. While these split solution stabilities are a distinct improvement over typical stabilities of at best 30 hours for a Grubbs second generation/DCPD system, improving the stability should still be a central goal of FROMP investigations in the future.

4.9 Mechanistic Concerns

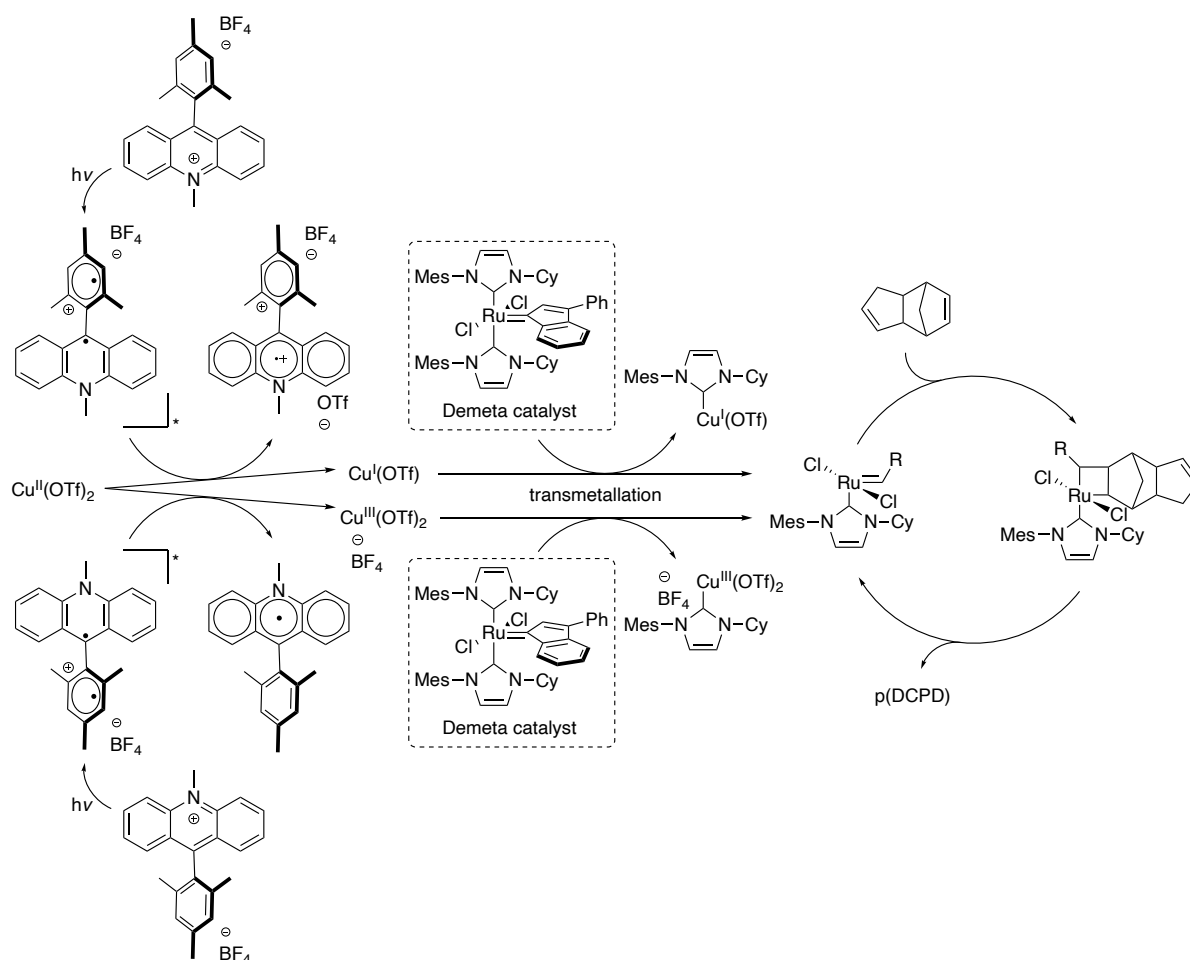


Figure 4.25. Two possible mechanisms for photoinitiated

The mechanism of the photoinitiation is not conclusively known. Since all components are necessary for photoinitiation to operate, one of two possible mechanisms is proposed (Fig. 4.25). It is unclear whether the MesAcr catalyst is acting in an oxidative or reductive manner after

excitation. At high temperatures, that is, after thermal polymerization has taken over from the initial photopolymerization mechanism, a different mechanism is operative (Fig. 4.26). The fact that light does not reach the lower levels of the monomer solution, but polymerization still occurs, indicates that copper (II) triflate is competent to transmetalate only at high temperatures.

Redox potentials of various species in the reaction can shed some light on whether this mechanism is reasonable. These potentials are listed in Table 4.10. Some are from the literature and some have been determined by cyclic voltammetry. The excited MesAcr catalyst is typically not known to perform reductions, but there have been some examples. Although there is no reported oxidation potential, since it is capable of generating $O_2^{\bullet}$, it must have an oxidation potential of at least 0.76 V,^{28–31} this means that the reduction of copper would be energetically favorable, as would its oxidation. 10-Phenyl phenothiazine is also effective, and there are no reported examples of 10-phenyl phenothiazine as an oxidant to our knowledge.³² Therefore, it is very likely that the reductive pathway is operative but possible that the oxidative pathway is operative as well. The reduction potential of $Ru(bpy)_3$ is not high enough for a direct oxidation of the carbene ligands to be energetically feasible, so the mechanism reported in the case of photoredox ROMP with the Rovis catalyst is ruled out (Fig. 4.1).³

More investigation is needed to fully validate the mechanism of the reaction. Possible future testing includes NMR studies to observe either a change in the Demeta catalyst after

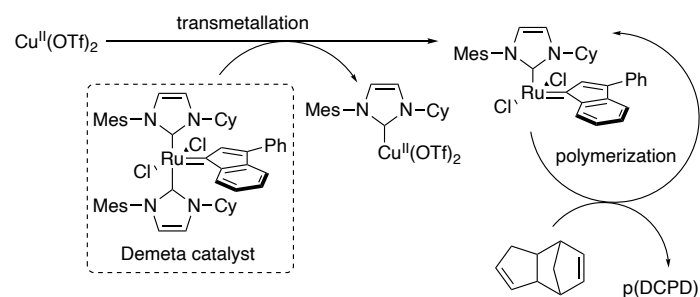


Figure 4.26. Mechanism operative at high temperatures.

transmetalation, or to observe certain byproducts of the photoinitiation mechanism.³ For instance, it is unclear if the MesAcr catalyst is regenerated by the copper species or is quenched

covalently by some species in the mixture, possibly the NHC ligand or the monomer. If one of the latter were captured, this could provide a clue to the mechanism. A Stern-Volmer plot could be another useful tool to examine which species are interacting directly with the MesAcr catalyst.¹⁹

Table 4.10. Oxidation and reduction potentials for reactants.

Compound	Oxidation potential	Reduction potential
MesAcr (excited) ³³	N.R.	2.18 V
Ru(bpy) ₃ (excited) ³⁴	0.81 V	0.77 V
10-Phenyl phenothiazine	2.1 V	N.R.
Cu(I)	-0.28 V ³⁵	0.228 V
D899 Ru	-0.543 V	0.522 V
D899 ligand	-1.873 V	N.D.

4.10 Increased Control in Photothermal Frontal Polymerization

This system has a dual mode of activation; it is photoinitiated but driven by thermal autoacceleration after initiation. The photoinitiation of the system has many advantages, including more precise control over what section of a resin is initiated and when, the possibility of remote initiation, and a lower energy requirement for initiation. However, some of the enhanced control provided by photopolymerization is sacrificed for excellent penetration. Since it is possible to initiate the polymerization with light, we wondered if it was possible to inhibit the polymerization with light in order to recover some lost control over the photopolymerization system. In order to do this, we would need an inhibitor that could be released by light, possibly from a photolabile protecting group. First, we would need to show that it was possible to stop the progress of FROMP by adding a certain inhibitor.

We picked a range of compounds that fit two criteria. First, they are not typically tolerated in alkene metathesis reactions; second, they are known to be viable leaving groups upon irradiation for a photolabile protecting group, either 2-nitrobenzyl or phenacyl, in nonpolar solvents. We initially tested their ability to prevent thermal initiation, and found that in virtually all cases, the frontal polymerization preceded in their presence. Because the thermal case has a faster front than the photothermal case, we decided to test inhibitors with the photothermal case to increase the likelihood of success (Table 11). Concerned that the inhibitor might impede the action of the photocatalyst rather than the thermal propagation, we also moved to a layered system to more accurately represent the desired effect of the inhibitor. We focused on those inhibitors that had at the very least slowed the front in the thermal case.

Table 4.11. Thermal test of inhibitors which may be good leaving groups for photolabile protecting groups.

Demeta amt	CuBrSMe ₂ amt	P(O ⁿ Bu) ₃ amt	Inhibitor	Inhibitor amt	DCPD/ENB	DMF amt	Outcome
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Acetic acid	1.7 μL, 30 μmol	3 mL 95:5	none	Slow front
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Methanol	1.2 μL, 30 μmol	3 mL 95:5	none	Slow front
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Ethanol	1.8 μL, 30 μmol	3 mL 95:5	none	FROMP
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Acetonitrile	1.5 μL, 30 μmol	3 mL 95:5	none	FROMP
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Dimethylamine	3.1 μL, 30 μmol	3 mL 95:5	none	FROMP
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Imidazole	2 mg, 30 μmol	3 mL 95:5	100 μL	FROMP
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Thiophenol	3 μL, 30 μmol	3 mL 95:5	none	Unstable front
3 mg, 3 μmol	1 mg, 5 μmol	1.2 μL, 4.5 μmol	Mesyl acid	2.0 μL, 30 μmol	3 mL 95:5	none	FROMP

We prepared two resins. The first resin contained photocatalyst, Demeta catalyst, copper triflate, DMF, and monomer. The second contained Demeta, copper triflate, DMF, monomer, and inhibitor. The first resin is layered carefully over the second; the mixture is then photoinitiated and the degree of polymerization is observed (Table 12). Certain formulations of the second resin had

lower densities than the first resin, in this case 80:20 DCPD/ENB was used in the first resin because it has a lower density than 95:5 DCPD/ENB and enabled effective layering without mixing (Table 13). All samples either stopped polymerizing at the interface between the resins or polymerized entirely. Unfortunately, none of the tested inhibitors stopped the progress of polymerization. This is likely related to the temperature and monomer concentration of the frontal polymerization process. The temperature promotes a more rapid dissociation/association equilibrium and the high concentration of monomer makes it considerably more likely that monomer will outcompete the inhibitor, even if the inhibitor has a higher binding constant.

Table 4.12. Layered resins for photoinitiation with copper in the propagation layer.

Initiation resin	Demeta amt	Cu(OTf) ₂ amt	DMF amt	Ru(bpy) ₃ amt	DCPD/ENB		
	1 mg/1 μ mol	1.7 mg/4.7 μ mol	47 μ L	1 mg/1.3 μ mol	1 mL 95:5		
Propagation (bottom) resin	Demeta amt	Cu(OTf) ₂ amt	DMF amt	Inhibitor	Inhibitor amt	DCPD/ENB	Outcome
	5 mg/5.5 μ mol	8.3 mg/23 μ mol	83 μ L	none	n/a	5 mL 95:5	FROMP
	5 mg/5.5 μ mol	8.3 mg/23 μ mol	83 μ L	Acetic acid	3.44 μ L/60 μ mol	5 mL 95:5	FROMP
	5 mg/5.5 μ mol	8.3 mg/23 μ mol	83 μ L	Acetic acid	10 μ L/180 μ mol	5 mL 95:5	FROMP
	5 mg/5.5 μ mol	8.3 mg/23 μ mol	83 μ L	Thiophenol	6.1 μ L/60 μ mol	5 mL 95:5	FROMP
	5 mg/5.5 μ mol	8.3 mg/23 μ mol	83 μ L	Water	11 μ L/340 μ mol	5 mL 95:5	FROMP
	5 mg/5.5 μ mol	8.3 mg/23 μ mol	83 μ L	Ethylene Glycol	3.3 μ L/60 μ mol	5 mL 95:5	FROMP

Table 4.13. Layered resins for photoinitiation without copper in the propagation layer.

Initiation resin	Demeta amt	Cu(OTf) ₂ amt	DMF amt	Ru(bpy) ₃ amt	DCPD/ENB		
	1 mg/1 μ mol	2 mg/5.5 μ mol	30 μ L	1 mg/1.3 μ mol	1 mL 80:20		
Propagation (bottom) resin	Demeta amt	DMF amt	Inhibitor	Inhibitor amt	DCPD/ENB	Outcome	
	5 mg/5.5 μ mol	100 μ L	none	n/a	5 mL 95:5	No FROMP	
	5 mg/5.5 μ mol	none	Acetic acid	3.4 μ L/ 60 μ mol	5 mL 95:5	No FROMP	
	5 mg/5.5 μ mol	none	Acetic acid	34 μ L/600 μ mol	5 mL 95:5	FROMP	

The control system with no inhibitor underwent smooth frontal polymerization, whereas the control with just Demeta and no copper did not, suggesting that the mechanism of thermal propagation is as described in Figure 4.26 above. While investigating other possibilities for inhibiting the system, we discovered that acetic acid can also activate the catalyst for thermal propagation, although it is not competent for direct thermal activation with a soldering iron (likely due to boiling). This may be a better system to work with for further attempts to inhibit with light. The ability of the copper source to sequester some inhibitor was demonstrated in the differences in copper loading data between the inhibited and uninhibited system. While the ultimate problems are temperature and monomer concentration, this sequestration is another factor. In contrast, non-basic inhibitors will likely not be as affected by acetic acid. This could also improve the storage lifetime of the fully mixed resin.

4.11 Conclusions and Future Directions

We have developed a system for photothermal frontal ring opening metathesis polymerization. We have elucidated some of the properties of the polymer, including a preliminary test of its glass transition temperature, although more work could be done in the future on its various materials properties. In addition, we have detailed how the initiation time, front speed and initiation temperature vary based on different conditions. We have also investigated the storage lifetime and obtained some evidence in favor of our proposed mechanism.

In the future, there are some parameters that could be improved through optimization, including front speed and initiation time. Storage lifetime may benefit from the development of a copper-free system, and it may also be beneficial to the development of photoreleased inhibitors that can stop FROMP with light. Further evidence of the mechanism would also be a good addition to the work. NMR studies could help confirm the mechanism and shed light on whether and how

the photocatalyst turns over. A Stern-Volmer plot could help prove that the copper directly quenches the photocatalyst.

4.12 Supporting Information

General Information

Equipment:

UV-Vis: UV-Vis absorption spectra were recorded in HPLC grade toluene and dimethylformamide (DMF) on a Shimadzu UV-2401 PC UV-Vis Spectrophotometer.

Differential Scanning Calorimetry (DSC): Differential scanning calorimetry (DSC) liquid resin cure kinetic measurements were performed with a TA Instruments Q250 differential scanning calorimeter. Samples were transferred into aluminum hermetic DSC pans at room temperature and sealed. The sample mass is determined using an analytical balance (XPE205, Mettler-Toledo) and was carefully maintained between 2 mg and 3 mg. The specific heat capacity is determined between 25 °C and 200 °C by comparison with a sapphire standard.

Light Sources: A Novacure N2001 ultraviolet/visible spot cure system (Artisan Technology Group) with a mercury vapor lamp and a fiber optic guide was used as a white light source with an emission spectrum of 250-800 nm and a maximum output intensity of 27 W. A Thor Labs 455 nm mounted LED diode attached to a SM1 lens tube with two lenses for collimation; an aspheric condenser lens ($\varnothing 1"$, $f=16$ mm, $NA=0.79$, ARC: 350-700 nm) and bi-convex lens ($\varnothing 1"$, $f = 150.0$ mm, ARC: 350-700 nm). AT-Cube LED driver set to the continuous mode was used to control the LED intensity. A 375 nm LED diode was also purchased, and easily replaced the 455 nm LED diode on the existing set-up.

Cyclic Voltammogram: CV experiments were performed with a CHI760E (CH Instruments) potentiostat, where all electrochemical measurements were conducted inside an Ar-filled glovebox environment with O_2 and $H_2O < 0.1$ ppm. All voltammetric measurements were taken using a standard three-electrode configuration, a 3 mm glassy carbon macro disk as working electrode, a carbon rod as counter electrode, and a carbon rod as a reference electrode. Potentials are referenced versus ferrocene redox (Fc/Fc^+), which was used as an external standard. Bulk solutions were made by dissolving the compounds in 0.1 M lithium hexafluoroborate ($LiBF_4$) in acetonitrile.

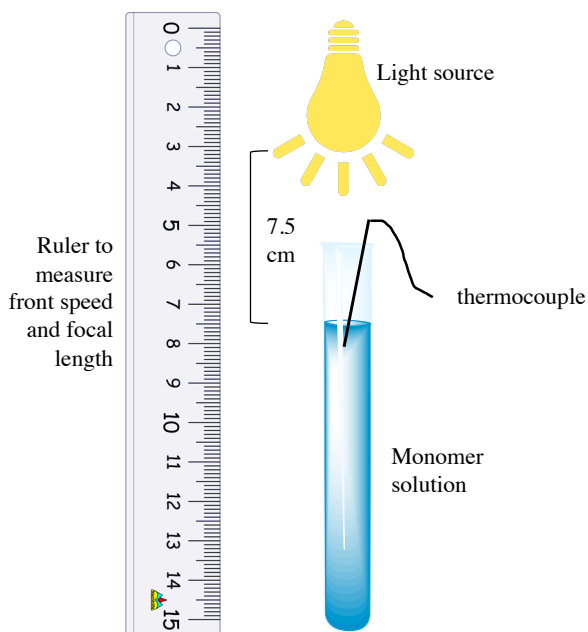


Figure 4.27. Set up of photo-FROMP experiments.

Materials:

Dicyclopentadiene (DCPD), 5-ethylidene-2-norbornene (ENB), tributylphosphite ($P(O^tBu)_3$), 9-mesityl-10-methylacridinium tetrafluoroborate (MesAcr), tris(bipyridine) ruthenium(II) chloride hexahydrate ($Ru(bpy)_3$), 10-phenylphenothiazine, triphenyl pyrylium tetrafluoroborate (TPPT),

tetrakis(dimethylamino)ethylene, 4-dimethylaminopyridine (DMAP), triphenylphosphine, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, N-methylquinolinium hexafluorophosphate, N-methylacridinium hexafluorophosphate, N-methylacridinium iodide, xanthone, Eosin Y, 9,10-anthracene, Hantzsch ester, copper (II) triflate, and limonene were purchased from Millipore Sigma and used as received without further purification. Tris[2-phenylpyridinato-C²,N]iridium(III) was purchased from AstaTech, Inc. and used as received without further purification. Bis(1-cyclohexyl-3-mesityl-2-imidazolidinylidene)(3-phenyl-1*H*-inden-1-ylidene)ruthenium (II) dichloride (Demeta catalyst) was gifted by Demeta S.A.S. and was used as received without further purification. Dimethylformamide was purified under argon by passage through a column of activated alumina.

General photoinitiation procedure:

To a 20 mL scintillation vial was added Demeta catalyst, copper, photocatalyst, and any inhibitor in use. Then the requisite amount of dimethylformamide was added and the mixture was sonicated for 1 minute, or until solids were dissolved. To this mixture was added a pre-mixed solution of DCPD and ENB, which was then vortexed. The resulting solution was transferred to a 13x100 mm test tube, which was clamped under the light source. The height was adjusted to ensure that the level of the fluid was at the focal length of the light source. A thermocouple was inserted approximately 5 mm into the liquid. The light was turned on. Once the front had initiated, video was recorded with an iPhone camera. Front velocities were measured using Tracker®, an open source physics analysis and modeling tool. The built-in point mass tracking feature was used to extract velocity. Each video was analyzed three times, and each velocity was

obtained by averaging velocities from three separate samples. Thermocouple data was used to determine initiation time.

General thermal initiation procedure:

To a 20 mL scintillation vial was added solids, inhibitor, and solvent. The mixture was sonicated for 1 minute, or until solids were dissolved. To this mixture was added a pre-mixed solution of DCPD and ENB, which was then vortexed. The resulting solution was transferred to a 13x100 mm test tube. A thermocouple was inserted approximately 5 mm into the liquid. A hot soldering iron was held to the test tube near the top of the liquid. Once the front had initiated, video was recorded with an iPhone camera. Front velocities were measured using Tracker® as above.

UV/Vis Spectra:

Spectra were taken of the Demeta catalyst, MesAcr, and copper (II) triflate.

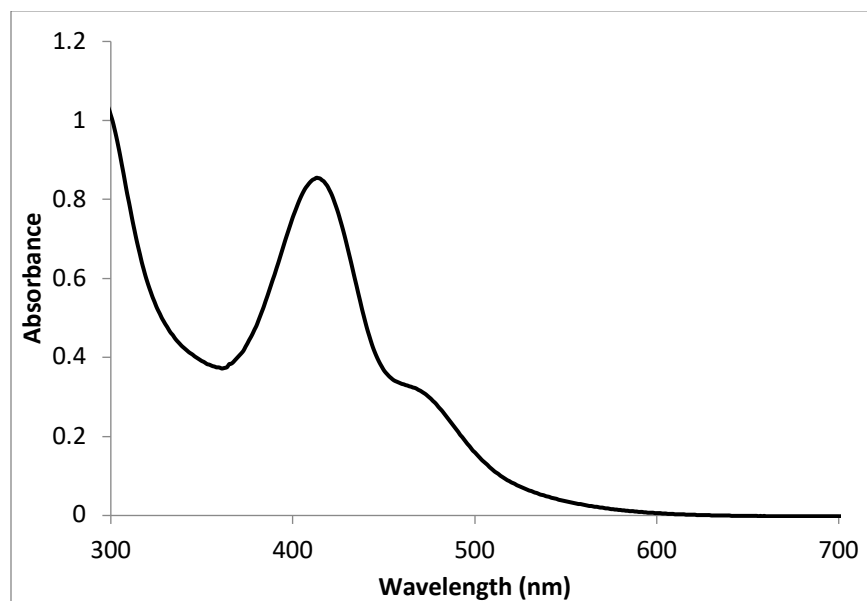


Figure 4.28. UV/Vis spectrum of the Demeta catalyst.

This spectrum was taken in toluene at 69 μ molar. Based on a calibration curve, the extinction coefficient of the Demeta catalyst at the λ_{MAX} of 413 nm is 12,000 $\text{M}^{-1}\cdot\text{cm}^{-1}$.

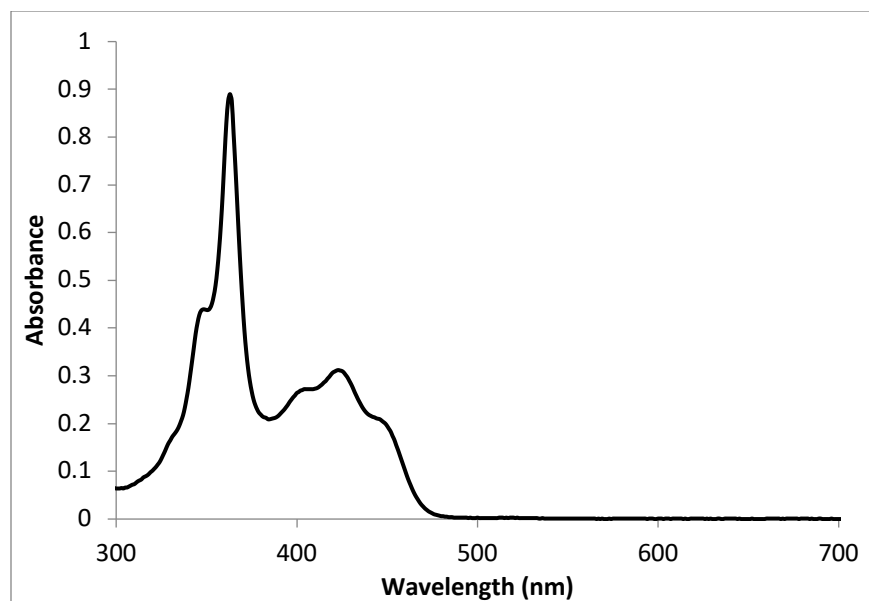


Figure 4.29. UV/Vis spectrum for MesAcr.

This spectrum was taken in DMF at 52 μmolar . Based on a calibration curve, the extinction coefficient of the MesAcr catalyst at the λ_{MAX} of 363 nm is $17,000 \text{ M}^{-1}\cdot\text{cm}^{-1}$, and at the λ_{MAX} of 422 nm is $6,000 \text{ M}^{-1}\cdot\text{cm}^{-1}$. This latter band is associated with the photoredox activity.

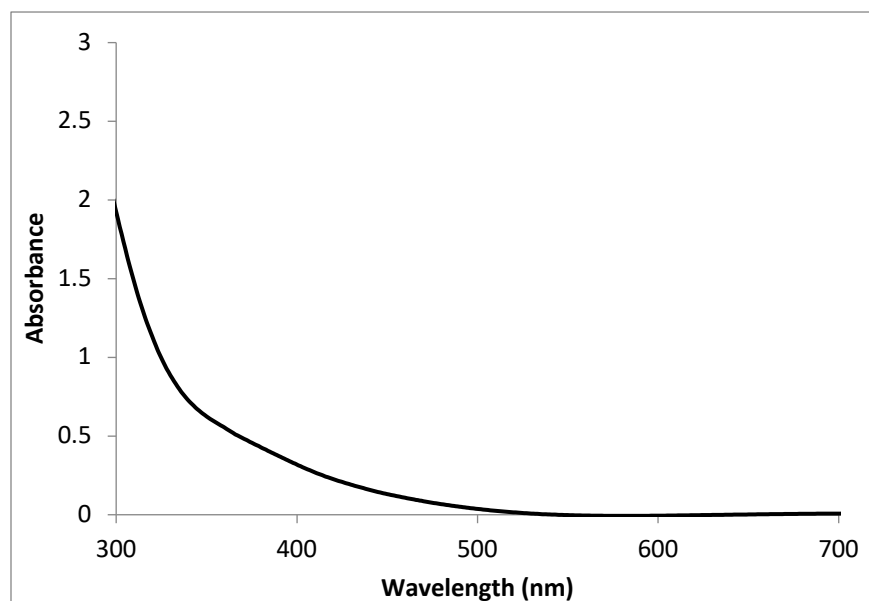


Figure 4.30. UV/Vis spectrum for copper (II) triflate.

This spectrum was taken in toluene at 276 μmolar .

Novacure intensity experiments:

We used the novacure to initiate FROMP because this is a higher intensity light source.

Unfortunately, it did not improve initiation times, likely because it is a broadband light source.

Many of the photocatalysts have multiple absorbance bands, so a broadband light source may delay initiation by exciting to the wrong state, which may not be redox active.

Table 4.14. Initiation time (IT) at different conditions with a 455 nm LED and a broadband novacure.

Demeta amt	Cu(OTf) ₂ amt	Photocat	Inhibitor	DMF amt	DCPD/ENB	IT, LED	IT, novacure
6 mg/6 μ mol	10 mg/30 μ mol	MesAcr, 1 eq.	none	200 μ L	95:5, 6 mL	50 s	150 s
6 mg/6 μ mol	10 mg/30 μ mol	Ru(bpy) ₃ , 1 eq.	none	200 μ L	95:5, 6 mL	115 s	150 s
6 mg/6 μ mol	10 mg/30 μ mol	MesAcr, 2 eq.	DMAP, 8 eq.	200 μ L	95:5, 6 mL	178 s	150 s
9 mg/9 μ mol	15 mg/45 μ mol	MesAcr, 2 eq.	PPh ₃ , 1.5 eq.	300 μ L	95:5, 6 mL	104 s	90 s
12 mg/12 μ mol	15 mg/45 μ mol	Ru(bpy) ₃ , 1 eq.	P(O ⁿ Bu) ₃ , 1.5 eq.	400 μ L	95:5, 6 mL	98 s	60 s
6 mg/6 μ mol	5.4 mg/15 μ mol	MesAcr, 1 eq.	none	200 μ L	95:5, 6 mL	60 s	120 s

Cyclic voltammetry:

Table 4.15. Reduction and oxidation potentials obtained from cyclic voltammetry.

Compound	Reduction Potential		Oxidation Potential	
	(V vs Fc/Fc ⁺)	(V vs SCE)	(V vs Fc/Fc ⁺)	(V vs SCE)
Cu(OTf)₂	0.152	0.228	-	-
D899	0.142	0.522	1.493	1.873

Conversions to SCE were performed by adding 380 mV to the value measured against the Fc/Fc⁺ electrode.³⁶

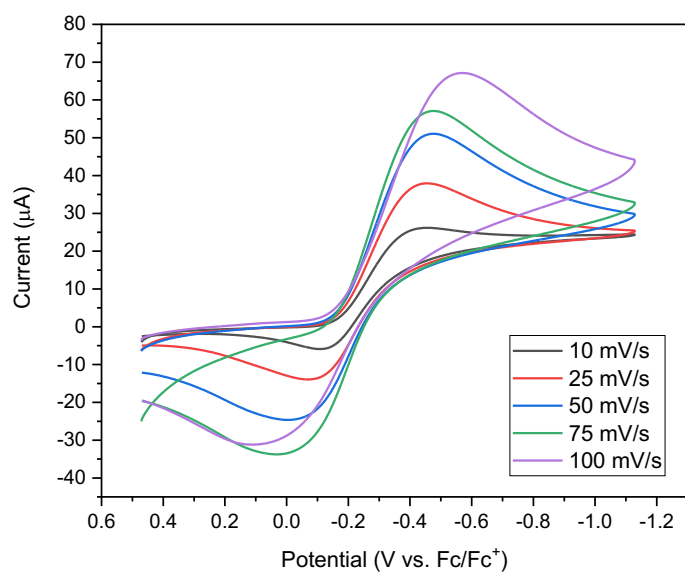


Figure 4.31. Cyclic voltammetry plot of copper (II)

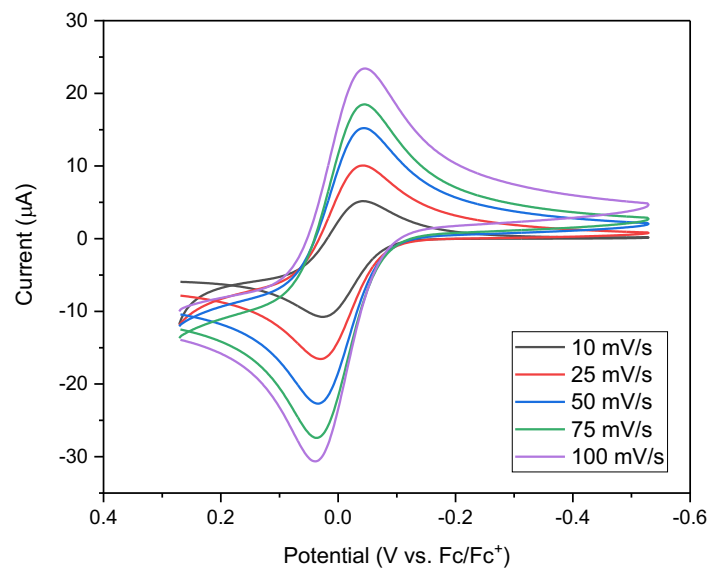


Figure 4.32. Cyclic voltammetry plot of Demeta catalyst.

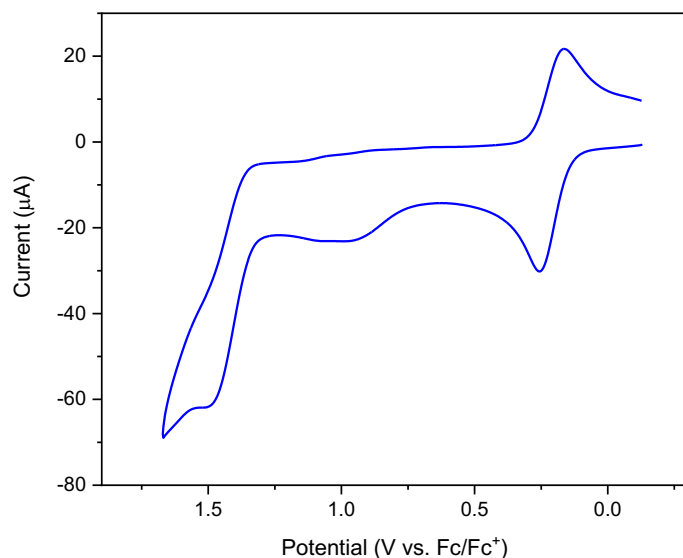


Figure 4.33. Cyclic voltammetry plot of Demeta catalyst.

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Notes

This work was produced in collaboration with Katherine Stawiasz, Benjamin Suslick, and Nafisa Ibrahim. K.J.S. and I did nearly all the experiments together. I did the layered experiments alone and K.J.S. did the radiation intensity experiments alone. B.A.S. was responsible for the first experiment with 2,4,6-triphenyl pyrylium tetrafluoroborate with K.J.S. and C.I.W. consulting. N.B.I. was responsible for cyclic voltammetry experiments and consultation about their interpretation.