DISCOVERY AND DEVELOPMENT OF COPPER CATALYSTS FOR THE C-ALKYLATION OF NITROALKANES

by

Peter G. Gildner

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry and Biochemistry

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ABSTRACT

Nitroalkanes are useful reagents for building complex molecules in organic synthesis by acting as powerful intermediates for forming new carbon-carbon (C-C) bonds, and serving as precursors for a variety of functional groups. Despite this wealth of established reactivity, the carbon alkylation of nitroalkanes with alkyl electrophiles remains undeveloped. Despite the seeming simplicity and high value of this potential transformation, general conditions for this reaction are not known. The discovery and development of catalytic conditions to promote the *C*-alkylation of nitroalkanes with several classes of alkyl electrophiles are reported.

The success of this newly developed *C*-alkylation methodology is dependent on copper bromide together with diketoimine (nacnac) ligands to catalyze the alkylation of nitroalkanes in a thermal redox pathway. The utility of this method is first demonstrated with the *C*-alkylation of various functionalized nitroalkanes with a variety of functional group bearing benzyl bromides. It is proposed that a stabilized radical intermediate is generated by single electron transfer (SET) or atom transfer (AT) from an electron-rich Cu(I)-nacnac complex. Subsequent radical-anion coupling, followed by the transfer of an electron back to the copper catalyst, leads to the observed product. The broad application of this *C*-alkylation method for nitroalkanes is further established by the successful coupling of several additional radical-stabilizing substrate classes including α-bromocarbonyls, α-bromonitroalkanes, α-bromocyanoalkanes, and a trifluoromethyl radical source. Detailed accounts of the optimization and scope of each of these substrate classes are described herein.

Given the synthetic utility of nitroalkanes as intermediates for building molecular complexity, the value of the functional group dense nitrogen-containing products obtained, and the importance of enantioselective methods, detailed investigations into an asymmetric *C*-alkylation method are also reported. While the development of several potential strategies are described, the success of this challenging goal is ultimately realized using either copper or nickel catalysts formed from chiral diamine ligands. Promising yields and enantioselectivities are reported using α-bromoamide electrophiles. The enantioenriched nitroalkane products also serve successfully as intermediates to incorporate asymmetry into even more complex products.

Chapter 1

INTRODUCTION

1.1 Nitroalkanes as Intermediates

Nitroalkanes are versatile reagents for assembling complex molecules in organic synthesis.[1] Their ease of deprotonation and subsequent ability to act as carbon nucleophiles by addition to carbonyls (Henry reaction) and addition to electron deficient alkenes (Michael addition) have made them powerful reagents for forming new carbon-carbon (C-C) bonds.[1] Nitroalkanes are also known to react in transition metal catalyzed processes to form C-C bonds through arylation[2] and allylation.[3] Additionally they are widely used as synthons for heterocycles in cycloaddition reactions[1] and radical precursors.[4] The nitro group is easily converted to alternative functional groups through hydrolysis to carbonyls, reduction to amines, and radical cleavage to denitrated alkanes.[1] Despite this wealth of established reactivity, the carbon alkylation of nitroalkanes with alkyl electrophiles remains undeveloped. Despite the seeming simplicity and high value of this potential transformation, general conditions for this reaction are not known.

As a whole this dissertation will describe the discovery and development of catalytic conditions for the *C*-alkylation of nitroalkanes with alkyl electrophiles. The versatile classes of reactivity already known to nitroalkanes, as well as a primary remaining gap in reactivity with respect to the ability of nitroalkanes to undergo *C*-alkylation with simple alkyl electrophiles, will be outlined. Despite published attempts to promote this general transformation, the *C*-alkylation of nitroalkanes has remained

an open challenge. This text will describe our efforts to identity effective catalytic conditions for such a general method for the alkylation of nitroalkanes with several classes of radical-stabilizing alkyl electrophiles. Additionally in this dissertation I will describe our multi-faceted efforts for the development of an enantioselective method for *C*-alkylating nitroalkanes.

The following sections of this chapter will present a brief introduction to the most commonly used synthetic transformations of nitroalkanes in carbon-carbon (C-C) bond formation. Additionally, several methods for transforming the nitro group to other useful functional groups will be highlighted.

1.1.1 Henry Reaction

First discovered in 1895 by Henry,[5] the nitro-aldol (Henry Reaction) is a powerful method for accessing β-nitro alcohols through the addition of a nitroalkane to a carbonyl compound. These products are themselves useful intermediates for accessing nitroalkanes, nitroalkanes, α-nitro ketones, and β-amino alcohols.[1] In a typical reaction β-nitro alcohols are obtained in good yield when a catalytic amount of base is added to the nitroalkane and aldehyde compounds (Figure 1.1).[6,7] Using more sterically hindered substrates such as secondary nitroalkanes and ketones can lead to decreased reactivity. In the cases when aryl aldehydes are used the products can easily undergo elimination of water to form nitroalkenes. Careful control in workup conditions allows for the selective formation of either β-nitro alcohol or nitroalkene products. These general conditions lead to a mixture of diastereomers and enantiomers. Selectivity is made challenging by the reversible nature of the addition and epimerization that occurs easily at the nitro-substituted carbon, although methods to control selectivity have been devised.[8]

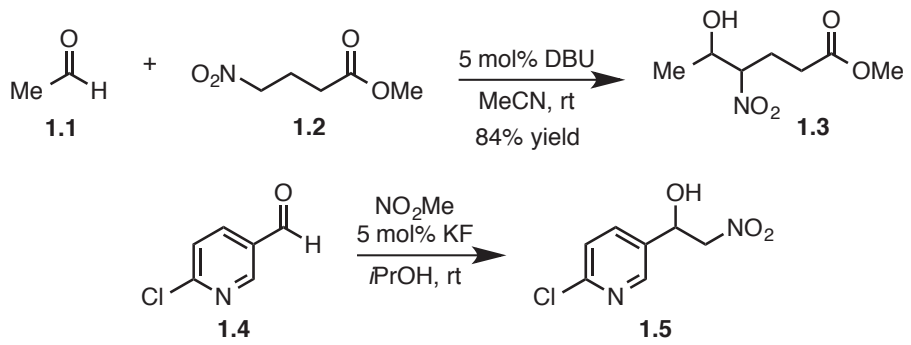


Figure 1.1: General reaction conditions for nitro Aldol reaction

While the general basic conditions for the nitro aldol reaction don't allow for stereoselective control, progress has been made in the design of appropriate catalysts to afford the nitro addition products in high diastereo- and enantioselectivities. In 1992, the Shibasaki group, published the first catalytic asymmetric nitro aldol reaction using rare earth metal alkoxides together with enantiopure binol.[9] Subsequent modification of their heterobimetallic catalysts led to the development of chiral Schiff bases which have been used in a *syn*-selective nitro mannich (Aza-Henry) reaction to from enantioenriched β-nitro amines (Figure 1.2, top). Later in 2008, they published an *anti*-selective nitro aldol reaction with good diastereo- and enantioselectivity by simply switching the metals used in their chiral Schiff base catalyst (Figure 1.2, bottom).[10] While investigations to understand the mechanism and active catalyst are underway, they demonstrated through several control reactions that both metals and the catalytic phenol additive are all crucial for good diastereo- and enantiocontrol. They proposed that the heterobimetallic catalyst acts as an activator for both the nucleophilic nitronate and the electrophilic imine or aldehyde. The Bronsted basic rare earth metal portion of the catalyst likely deprotonates the alpha proton of the

nitroalkane forming a nitronate bound intermediate. The bound transition metal may datively bind the imine nitrogen or aldehyde oxygen holding it in the proper environment for selectivity in the bond-forming step.[10]

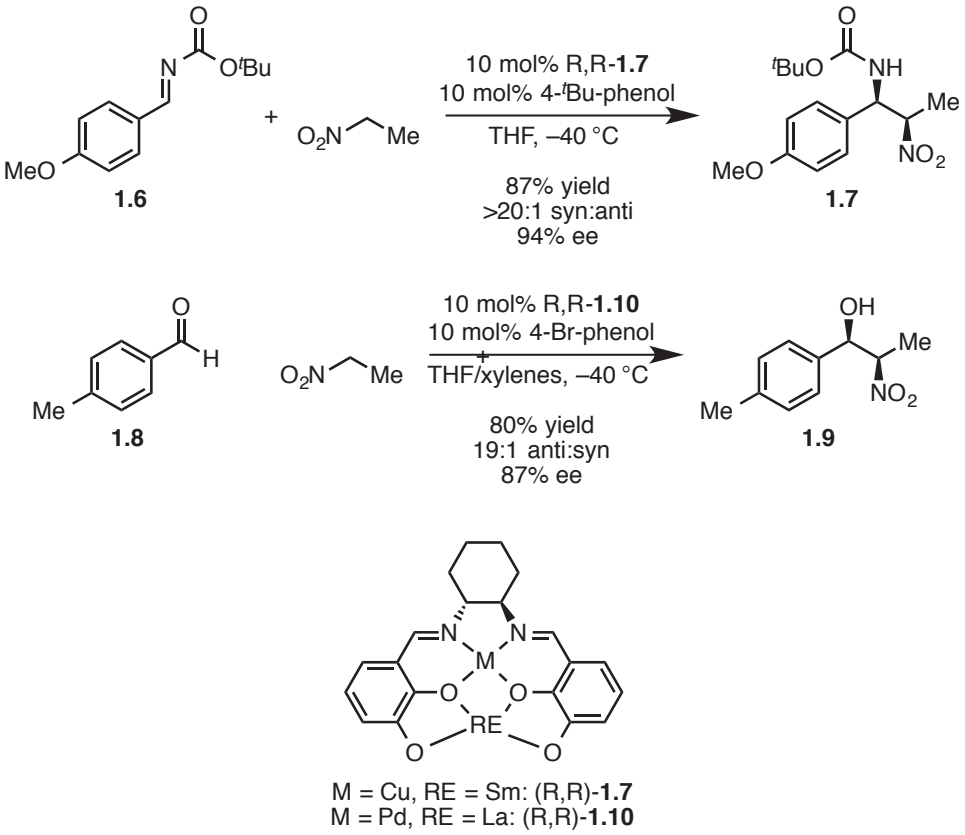


Figure 1.2: Enantioselective nitro Mannich and nitro Aldol reactions using chiral heterobimetallic Schiff bases

1.1.2 Michael Addition

Conjugate addition of a nitroalkane to α,β-unsaturated carbonyls (Michael addition) is a powerful transformation for C-C bond formation that often benefits from the versatility of the resultant nitro group. In 1998, the Crossley group used the

addition of nitroalkanes to dehydroalanines to form γ-nitro-α-amino acids in high yields (Figure 1.3).[11] Using the nitro group within the resultant products as a synthetic handle, this method proved useful for accessing various side-chain modified α-amino acids via denitration, Nef hydrolysis, and reduction.[12]

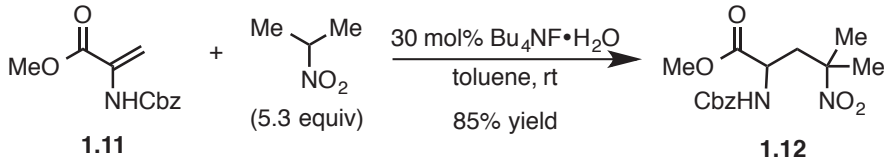


Figure 1.3: Crossley group formation of γ-nitro-α-amino acids

In 1999, the Amri group used the addition of primary nitroalkanes to Baylis-Hillman acetates such as **1.13** to form 1,4-nitroketones as the single trans isomer (Figure 1.4).[13] With the ultimate aim of forming 1,4-diketone products, useful for accessing cyclopentenones, the 1,4-nitroketone products were readily hydrolyzed through the Nef reaction in good yield. The Dondoni group published a highly syn-selective addition of nitromethane to enantiopure γ,δ-dialkoxy enones in high yield and diastereoselectivity (Figure 1.5).[14] These products proved useful intermediates for forming sialic acid analogues.

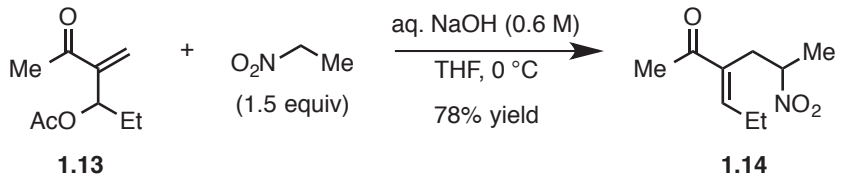


Figure 1.4: Michael addition of nitroalkanes to Baylis-Hillman acetates

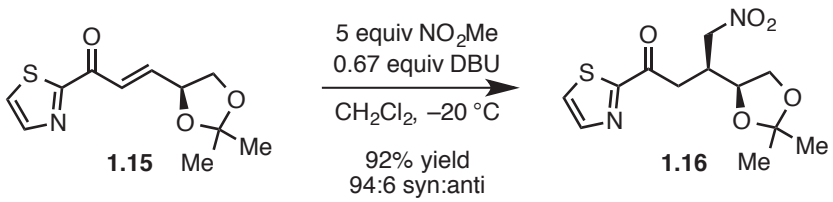


Figure 1.5: Dondoni group syn-selective addition of nitromethane to γ,δ-dialkoxy enones

Additionally, many classes of organocatalysts have proven effective for the enantioselective conjugate addition of nitroalkanes.[15] In 2008, the Ye group identified a particularly potent class of cinchona alkaloid derived primary amine thioureas (**1.19**) for catalyzing the addition of nitroalkanes to cyclic and acyclic enones in good yields with high enantioselectivity (Figure 1.6).[16] Importantly this methodology is useful for the construction of quaternary stereocenters with high selectivity.

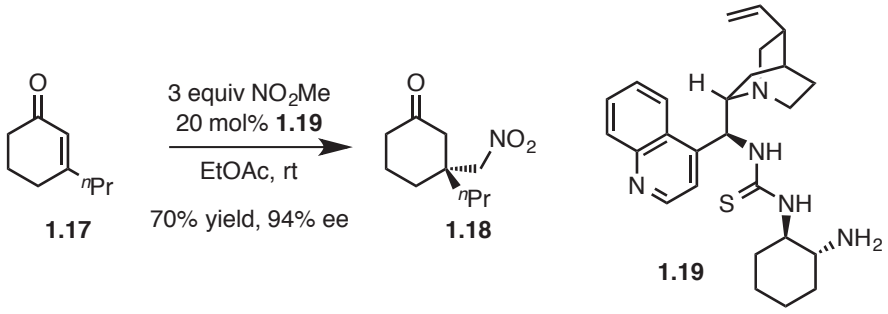


Figure 1.6: Organocatalytic enantioselective Michael addition of nitromethane using thiourea **1.19**

1.1.3 Allylation

In 1982, the Wade[3e] and Aleksandrowicz[3a] groups reported successful examples of palladium-catalyzed allylation of nitroalkanes. These initial reports demonstrate alkylation of simple nitroalkanes with allylic alcohols, acetates, and phenyl ethers in low to moderate yields (Figure 1.7). With coupling partners bearing additional substituents mixtures of allylic rearrangement products were obtained likely due to competitive sites of alkylation of the resultant π-allyl-palladium intermediate.[3e]

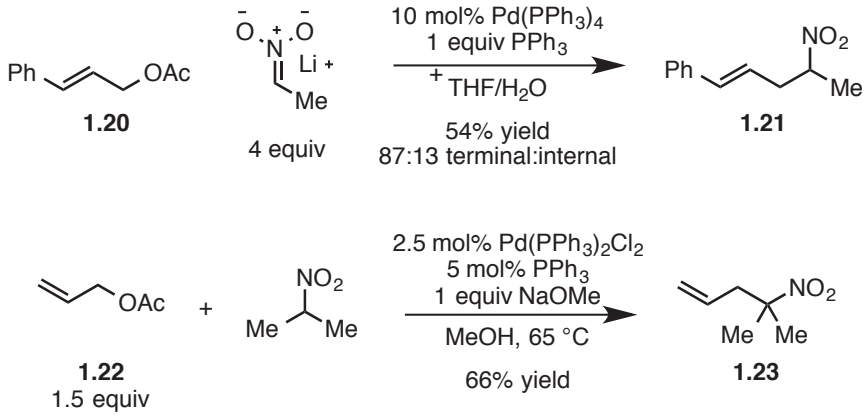
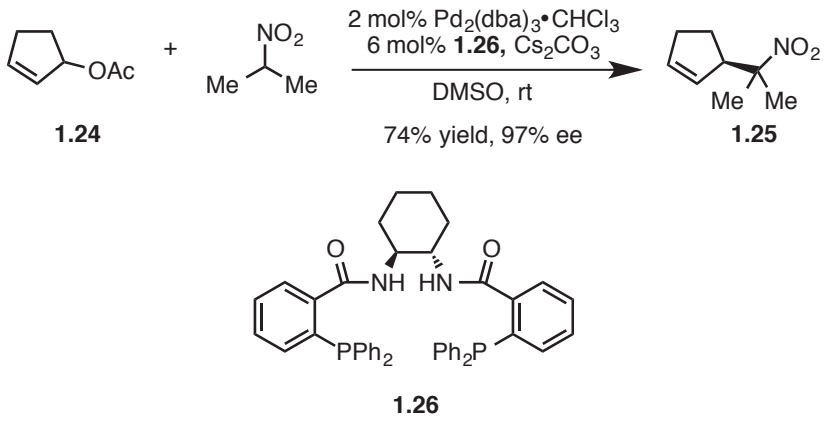


Figure 1.7: Initial reports of allylation of nitroalkanes by Wade and Aleksandrowicz

The Trost group later investigated catalyst conditions for an asymmetric transition-metal catalyzed allyic alkylation. Using catalytic palladium together with chiral diamine **1.26** the successful alkylation of simple nitroalkanes with racemic cyclic allyl esters to afford nitroalkane products such as **1.25** in high yield and enantioselectivity (Figure 1.8).[17] Though poor results were obtained when using nitromethane, simply switching the base from cesium carbonate to *N*,*O*-bis-(trimethylsilyl)acetamide led to similarly high yields and enantiomeric excess. The

authors proposed that the cesium nitronate may have been acting as a competitive ligand to palladium leading to diminished reactivity.



1.24 **1.25** **1.26**

Figure 1.8: Trost asymmetric allylic alkylation of nitroalkanes

In 2007, the Shibasaki group published conditions addressing the previous limitations to the nitroalkane coupling partner using catalytic base.[3b] Bulky secondary nitroalkanes were successfully alkylated with allyl carbonates using highly polar DMSO to further stabilize the ionic π-allyl-palladium and nitronate intermediates (Figure 1.9). It was proposed that after deprotonating the nitroalkane the protonated DBU was neutralized by the *tert*-butoxide anion generated after oxidative addition of the allylic carbonates to palladium.

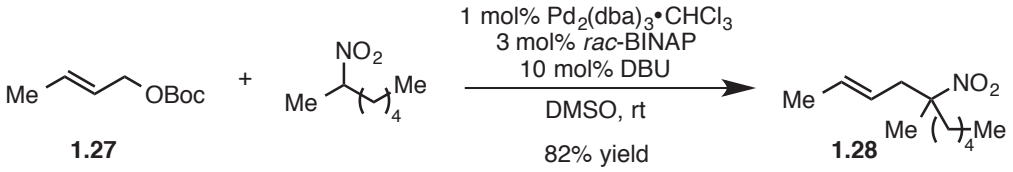


Figure 1.9: Additional scope of allylation of secondary nitroalkanes

1.1.4 Arylation

In the process of expanding their work on the palladium-catalyzed α-arylation of carbonyls,[18] the Buchwald group found that the combination of a di-*tert*butyl phosphine ligand with Pd^0, while inactive in the aforementioned reaction, is uniquely suited for the arylation of nitroalkanes.[2] In basic reaction media a wide range of nitroalkanes are chemoselectively mono-arylated even in the presence of enolizable ketones and esters (Figure 1.10). Even when employing incorporating alkenes the desired products are obtained in good yield with no Heck-type product observed.

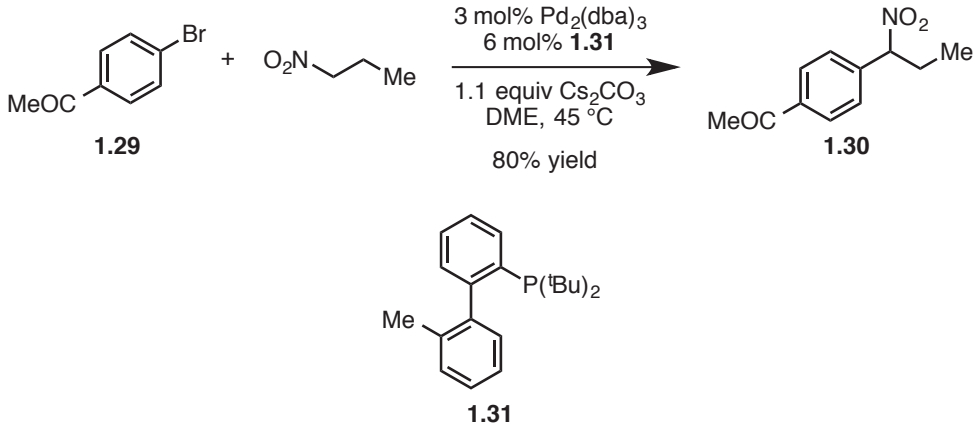


Figure 1.10: Buchwald arylation of nitroalkanes

While the use of nitromethane led to poor yields and multiple products using the Buchwald group's conditions, the Kozlowski group subsequently found optimal conditions to couple nitromethane with aryl halides.[19] The use of di-cyclohexylphosphine ligands such as XPhos (**1.34**) with Pd^0 when using nitromethane as the solvent in otherwise similar reaction conditions led to good yields of monoarylated nitroalkanes (Figure 1.11).

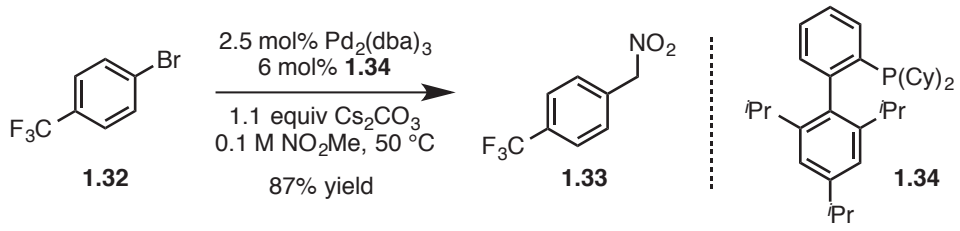
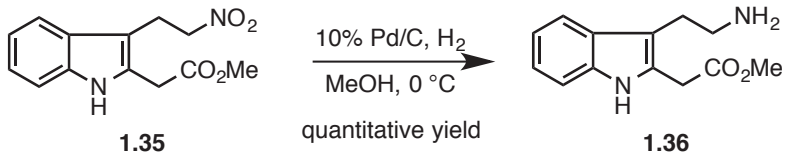


Figure 1.11: Kozlowski monoarylation of nitromethane

1.1.5 Reduction to Amines

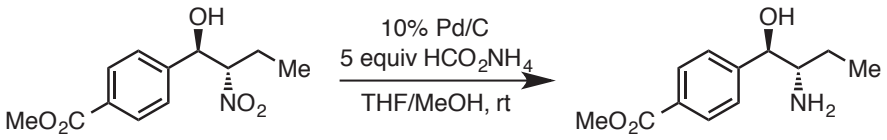
A common way of accessing amines is through the reduction of aliphatic nitroalkanes.[1] Hydrogenation in the presence of palladium on carbon under hydrogen is commonly used to access amines from the corresponding nitroalkanes even at reduced temperatures (Figure 1.12).[20] Many elegant methods have been developed to access enantioenriched β-nitro alcohols and conjugate addition products as intermediates towards enantioenriched amine products. Therefore the reduction step of the nitro group to the amine must be stereoretentive. Palladium on carbon with excess ammonium formate gives access to amines with stereoretention and requires only a simple filtration (Figure 1.13).[21] An alternative method catalyzed by Raney nickel

under atmospheric or high pressure hydrogen can be used to access amines as in the stereoretentive reduction to amino sugar **1.40** (Figure 1.14).[22]



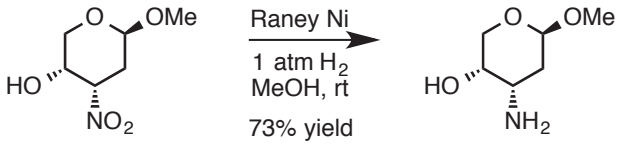
1.35 **1.36**

Figure 1.12: Palladium on carbon reduction



1.37 **1.38**

Figure 1.13: Palladium on carbon with ammonium formate stereoretentive reduction



1.39 **1.40**

Figure 1.14: Raney nickel reduction with retention of stereochemistry

Additionally the combination of sodium borohydride with cobalt chloride acts as a mild, but efficient reducing agent of nitroalkanes through the *in situ* formation of cobalt hydride (Figure 1.15). The Ley group used this functional group tolerant method in their racemic total synthesis of indolactam V in 1986.[23] The reduction of secondary nitroindole **1.41** proceeded in good yield to afford aminoindole **1.42**.

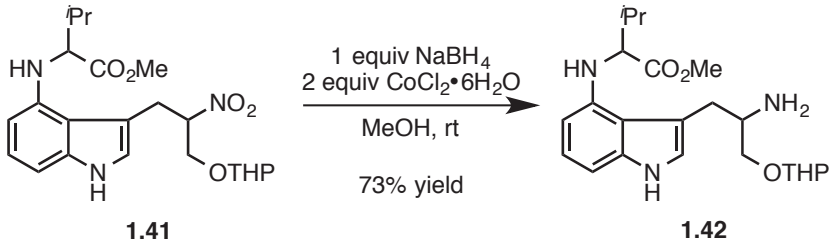


Figure 1.15: Sodium borohydride reduction of nitroalkanes in the presence of transition metal salts

1.1.6 Hydrolysis to Carbonyls

The usefulness of the nitro group as a means of accessing other intermediates is further demonstrated in the various conditions used to hydrolyze a nitro group into a carbonyl.[24] This reaction was first discovered in 1894 by Nef and has since changed from a proof of concept requiring conditions intolerant of most other functional groups to a useful transformation utilized even in late stage total synthesis.[25] The original work by Nef described the hydrolysis of the nitronate in a strongly acidic environment (Figure 1.16). The necessity of maintaining a pH <1 to avoid oxime and other side product formation has spurred the development of less harsh methods to affect the same transformation.

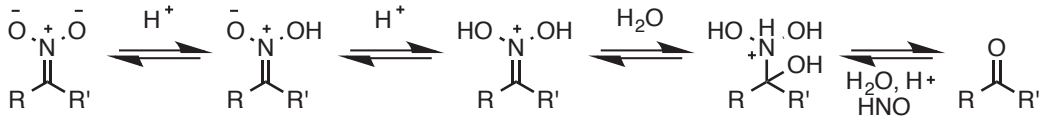
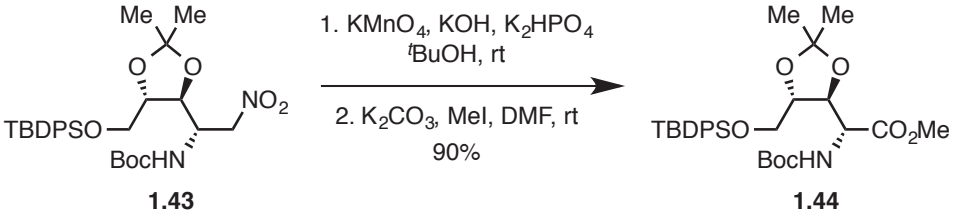


Figure 1.16: Nef hydrolysis of nitronate to carbonyl

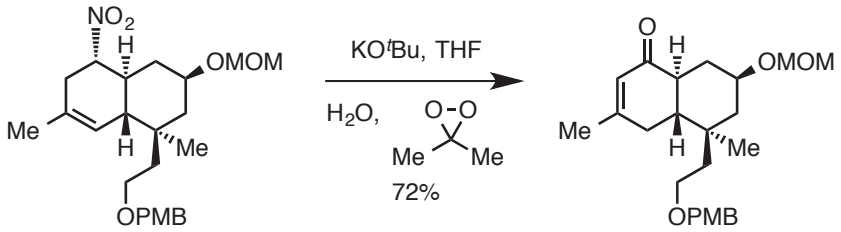
Oxidative procedures to affect the Nef reaction start with deprotonation of the nitroalkane to access the nitronate salt. Cleavage of the carbon-nitrogen double bond

then leads to carbonyl formation. Potassium permanganate ($KMnO_4$) is the most commonly used oxidant for this reaction. By controlling the pH of solution primary nitroalkanes can be oxidized to either aldehydes or carboxylic acids. Petrini et al. used this strategy in the treatment of the nitronate of **1.43** with $KMnO_4$ to access intermediate **1.44** after subsequent esterification in a combined yield of 90% over two steps (Figure 1.17).[26] The use of dimethyldioxirane (DMD) is an alternative strong oxidant used in the Nef reaction. The Williams group used this method in a late stage reaction to construct the AB ring system of norzoanthamine.[27] The hydrolysis of the nitro group in cyclic **1.45** and migration of the double bond into conjugation yields the α,β-unsaturated ketone **1.46** in good yield (Figure 1.18).



1.43 **1.44**

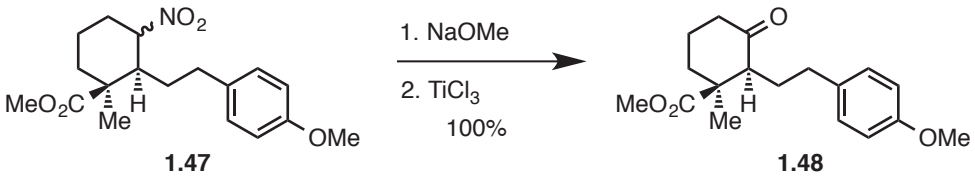
Figure 1.17: Oxidative Nef reaction with potassium permanganate



1.45 **1.46**

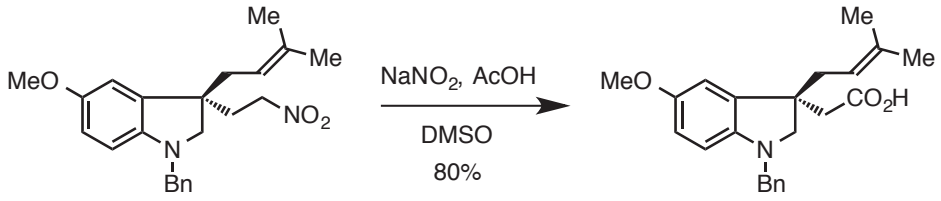
Figure 1.18: Oxidative Nef reaction with DMD

In addition to the oxidative strategies to accessing carbonyls from nitronates several alternatives exist proceeding through reductive and more neutral conditions. Among the reductive methods for accessing carbonyls from nitroalkanes, the McMurry method using $TiCl_3$ is the most commonly used. $TiCl_3$ is effective in reducing either the nitroalkane or the corresponding nitronate. Both modes of reactivity are proposed to access a common oxime intermediate, which is further reduced to an imino derivative on the way to the final carbonyl product. The Fuji group used the McMurry method in their total synthesis of (+)-podocarpic acid to give ketone **1.48** in quantitative yield (Figure 1.19).[28] The same group later chose more neutral conditions to form carboxylic acid **1.50** from primary nitroalkane **1.49** towards their total synthesis of (–)-horsfiline (Figure 1.20).[29]



1.47 **1.48**

Figure 1.19: Nef reaction using the reductive McMurry method

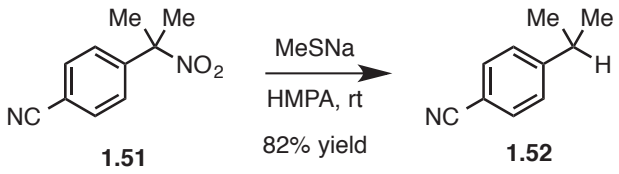


1.49 **1.50**

Figure 1.20: Neutral Nef reaction with sodium nitrite

1.1.7 Denitration

With significant progress made in methodology to replace nitro groups with hydrogen, the nitroalkane can be viewed as an alkyl anion. Due to the relative acidity of nitroalkanes (pKa = ca. 10 for RCH_2NO_2),[1] nitronates are more easily generated than alkyl anions. The ease and functional group compatibility of denitration methods make this strategy a powerful one for complex molecule synthesis. The first radical denitration was published in 1979 by Kornblum and utilized the sodium salt of methyl mercaptan to cleave the carbon-nitrogen bond of mostly tertiary-substituted nitroalkanes via a radical mechanism in moderate to good yields (Figure 1.21).[4a]



1.51 **1.52**

Figure 1.21: First radical denitration of nitroalkanes

In 1981, the Ono[30] and Tanner[31] groups separately published the use of tributyltin with either azobisisobutyronitrile (AIBN) or benzoyl peroxide as a catalytic radical initiator. Their initial results demonstrated the successful removal of tertiary nitro groups and even some secondary examples at radical stabilizing positions in good yields in the presence of functional groups (Figure 1.22). Tin hydride has since become the most widely employed reagent for removal of aliphatic nitro groups to give alkanes.[1]

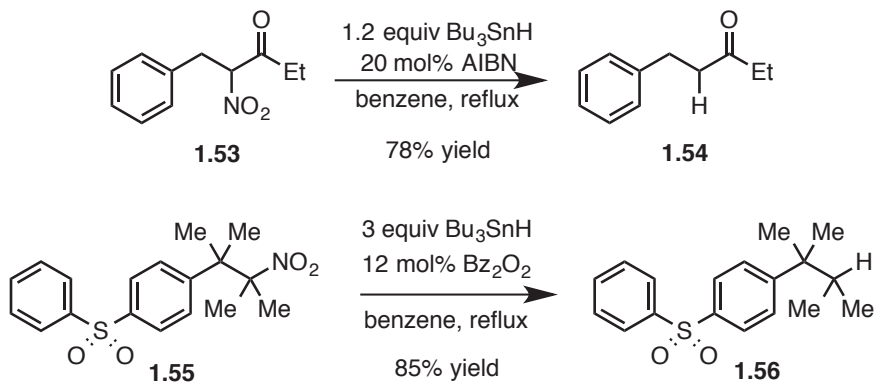


Figure 1.22: Advent of trialkyltin reagents for denitration by Ono and Tanner

The usefulness of denitration with trialkyltin reagents is further demonstrated in the cleavage of non-activated secondary nitro groups as shown by the Ono group's denitration of nitrolactone **1.57** in moderate yield (Figure 1.23).[32] The Yamaguchi group demonstrated complete stereoretention in the cleavage of the C-N bond of the enantioenriched Michael addition product **1.59** (Figure 1.24).[33] With the useful stereoselective methods developed for nitro aldol and conjugate addition this method enhances the utility of the resultant products as enantioenriched intermediates for further reactivity.

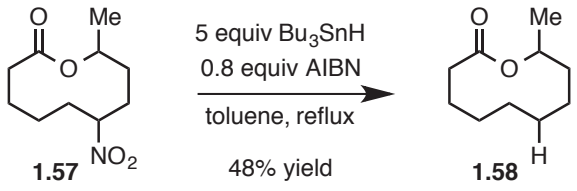


Figure 1.23: Denitration of secondary nitroalkanes

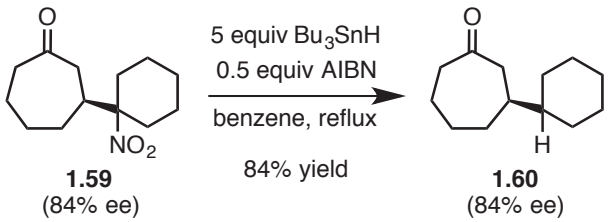


Figure 1.24: Denitration of secondary nitroalkanes

Due to stoichiometric and sometimes super stoichiometric amounts of tributyltin for denitration and the inherent toxicity of alkyl tin reagents, methods have been developed that utilize catalytic quantities of trialkyltin in the presence of silicon hydride reducing agents. In 1998, the Fu group published an efficient method using 10 mol% tributyltin and phenylsilane as a reducing agent.[4b] Product yields are comparable to the stoichiometric method in the denitration of secondary and tertiary nitroalkanes even in the presence of functional groups (Figure 1.25).

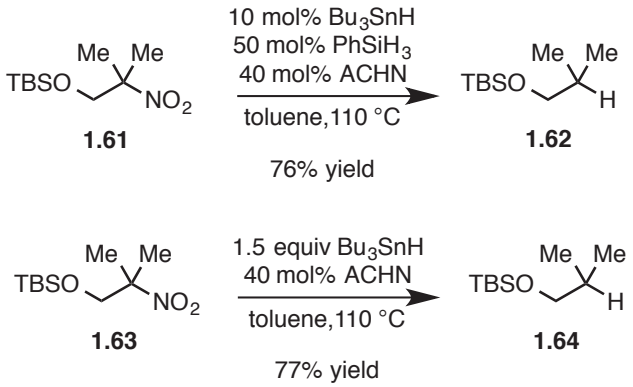


Figure 1.25: Denitration of secondary nitroalkanes

1.2 Alkylation of Nitroalkanes

For over a century investigations have been reported with respect to the competing sites of alkylation of nitroalkanes.[34] Deprotonation of a nitroalkane leads to the formation of a nitronate salt, which can undergo two possible sites of alkylation. Alkylation at oxygen of the nitronate leads to unstable nitronic esters, which break down to give an oxime and carbonyl. Alkylation at carbon of the nitronate forms a new C-C bond and keeps the nitro group intact (Figure 1.26). Given the widespread use of the existing methods of creating new C-C bonds with nitroalkanes (nitro-aldol addition, conjugate addition, and allylation), the ability to selectively *C*-alkylate nitroalkanes with alkyl electrophiles would fill a significant gap in the existing literature. Despite the apparent value and seeming simplicity of such a *C*-alkylation method for nitroalkanes with alkyl electrophiles, reports as early as 1908 have documented failed attempts to perform such a general transformation. *O*-alkylation of nitroalkanes in the presence of alkyl electrophiles predominates in all but very select cases.

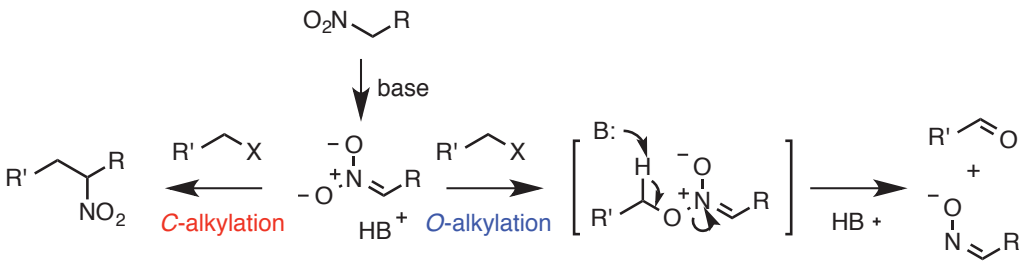
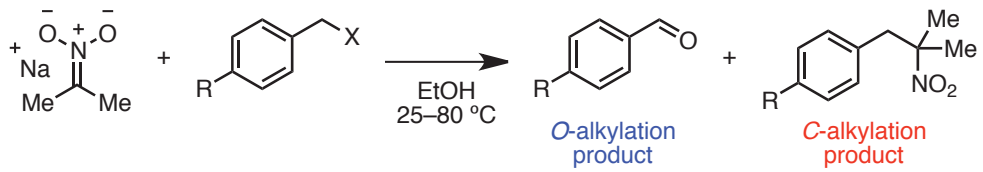


Figure 1.26: Alkylation of nitroalkanes

1.2.1 Inherent *O*-Alkylation of Nitroalkanes

In 1949, Hass and Bender published the reaction of the sodium salt of 2-nitropropane with various benzyl halides.[35] The results of this investigation summarize the various previous findings with respect to the alkylation patterns of nitronate salts. When the sodium salt of 2-nitropropane (chosen to avoid over alkylation) reacts with a range of benzyl halides eight out of the nine substrates shown react at oxygen to give substituted benzaldehydes in good yields ranging from 68-77% without any observance of the *C*-alkylated product (Table 1.1).

Table 1.1: Hass and Bender inherent alkylation of nitroalkanes



entry	R	X	yield *O*-alk	yield *C*-alk	entry	R	X	yield *O*-alk	yield *C*-alk
1	Me	Br	70%	0%	5	CF_3	Br	77%	0%
2	Br	Br	75%	0%	6	$NMe_3^+I^-$	I	68%	0%
3	CO_2Me	Br	72%	0%	7	H	Cl	73%	0%
4	CN	Br	70%	0%	8	NO_2	Cl	1%	83%

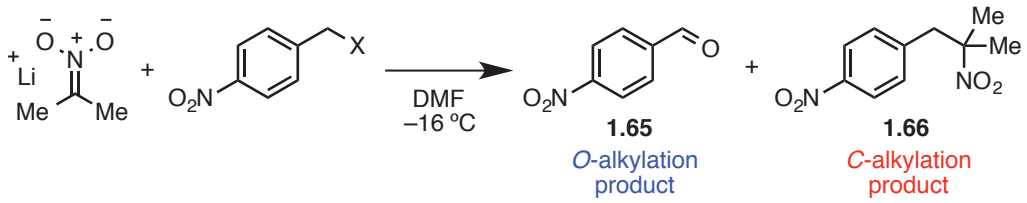
The authors noted that similar trends were observed with other alkyl halides as indicated by the formation of 2-octanone in 54% yield from 2-bromooctane using the same general reaction conditions. The single case of *C*-alkylation of sodium 2-propanenitronate occurs when using *p*-nitrobenzyl chloride as the alkylating partner. This isolated instance led to 83% yield of the *C*-alkylated product and only trace *p*-

nitrobenzaldehyde (1% yield) from *O*-alkylation (Table 1.1, entry 8). Similar moderate yields of *C*-alkylated product are observed when reacting several simple primary and secondary nitroalkanes with *p*-nitrobenzyl chloride.[36]

1.2.2 Kornblum Mechanistic Studies

In 1961, Kornblum et al. discussed the likelihood of two distinct mechanisms as an explanation for the two divergent pathways for alkylation of nitroalkanes. When investigating this idea they found that in addition to the para-nitro group, a difficultly displaced leaving group was also required for *C*-alkylation (Table 1.2). When using other alkylating partners with more easily displaced leaving groups such as *p*-nitrobenzyl iodide and -bromide, they observed *p*-nitrobenzaldehyde (**1.65**) in good yields with diminished yields of the *C*-alkylated product (**1.66**).[37] Kornblum et al. proposed that *C*-alkylation occurs through a radical mechanism, while *O*-alkylation predominates through an S_N2 displacement when the radical pathway is disfavored.

Table 1.2: Effects of leaving groups on nitroalkylation

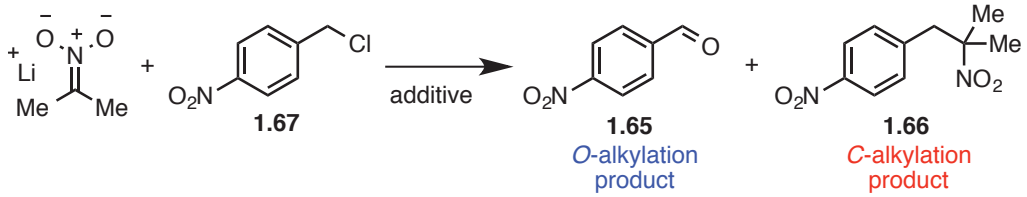


entry	X	yield **1.65**	yield **1.66**
1	Cl	1%	95%
2	OTos	32%	40%
3	Br	65%	17%

4	I	81%	7%

In support of this mechanistic idea several additives were studied to ascertain their effect on the *C*-alkylation reaction. Kerber hypothesized that easily reduced nitroarenes might intercept a radical before loss of the chloride took place in the p-nitrobenzyl chloride starting material.[38] This electron transfer event should prevent *C*-alkylation while leaving the competing *O*-alkylation pathway unaffected. Indeed, with the addition of one equivalent of 1,4-dinitrobenzene to the reaction of the lithium 2-propanenitronate with *p*-nitrobenzyl chloride (**1.67**) only 2% of the *C*-alkylated product (**1.66**) was observed and the substituted benzaldehyde (**1.65**) was obtained in 72% yield. Other nitroarenes substantiated this trend with various levels of inhibition of *C*-alkylation relative to their ease of one electron reduction (Table 1.3). At this time, the proposed radical pathway for *C*-alkylation was revised to a radical chain mechanism. The key step in this reaction is a radical anion coupling (Figure 1.27).[39]

Table 1.3: Effect of nitroarene additives on nitroalkylation



entry	additive (equiv)	yield **1.65**	yield **1.66**
1	none	6%	92%
2	$PhNO_2$	7%	84%
3	*m*-DNB (1)	29%	61%
4	*m*-DNB (1)	48%	40%

5	*p*-DNB (0.2)	88%	6%
6	*p*-DNB (1)	72%	2%

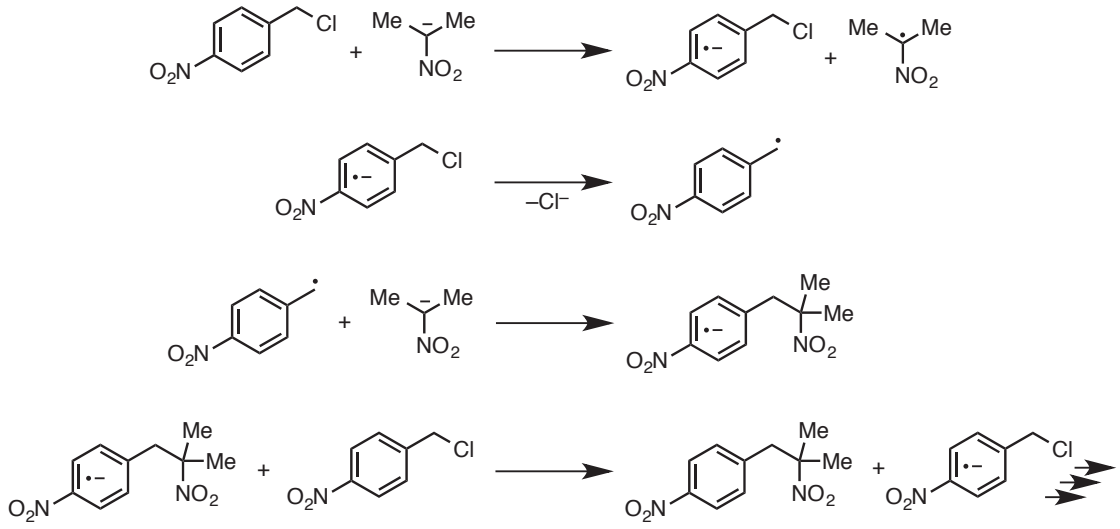


Figure 1.27: Radical chain reaction from nitronate to electron poor benzyl halide

1.3 Attempts Toward *C*-Alkylation Method for Nitroalkanes

Recognizing the significant utility of a general method for the *C*-alkylation of nitroalkanes with alkyl electrophiles, several attempts have been made to overcome the inherent *O*-alkylation. The following sections will discuss the past efforts towards *C*-alkylating nitroalkanes. As is discussed below, each of the following methods, however, suffers from limitations that prevent it from being used as a general method for the *C*-alkylation of nitroalkanes.

1.3.1 Seebach Dianion *C*-Alkylation of Nitroalkanes

Aware of the usefulness of nitroalkanes as synthetic building blocks, Seebach and Lehr investigated the *C*-alkylation of nitronate dianions. These reagents are

generated by double deprotonation of primary nitroalkanes using butyl lithium. When singly deprotonated they observed the inherent *O*-alkylation of nitroalkanes. However, with a second equivalent of butyl lithium at reduced temperatures (–90 °C) in a THF/HMPA mixture, the nucleophilicity at carbon of the nitrodianions significantly increases. Several examples of carbonates, anhydrides, chloroformates, and ketones act as suitable electrophiles for *C*-alkylation. They also found that two examples of simple alkyl halides (1-bromopentane and 1-iodohexane) alkylate the dianion of a thiol nitroalkane. When attempting *C*-alkylation with non-thiol based nitrodianions, hydrolysis occurs during the HCl quench of the alkylated nitronate to give Nef products.[40] A follow-up publication reported an alternative workup procedure to address this issue. The use of a 14 h temperature gradient from –78 °C to 15 °C and subsequent addition of glacial acetic acid leads to simple *C*-alkylated nitroalkane products in 35-80% yield (Figure 1.28).[41] While offering a proof of concept, the challenging conditions of this work prevent this method from being used as a general means for alkylating nitroalkanes.

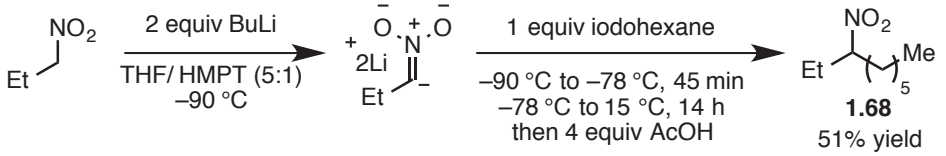


Figure 1.28: Seebach dianion *C*-alkylation of nitroalkanes

1.3.2 Katritzky *N*-Substituted Pyridiniums

In an attempt to explore other methods to *C*-alkylate nitroalkanes the Katritzky group demonstrated that sterically protected N-substituted-pyridinium salts[42] and later

superior –quinolinium salts[43] alkylate nitronates. These relatively complex starting materials must be prepared from the corresponding chalcone and ketone. Reaction of the resulting pyrylium or chromenylium salt with the appropriate amine leads to the formation of the pyridinium or quinolinium salt respectively. For the desired *C*-alkylation reaction, three equivalents of the nitronate salts (prepared separately) are subjected to the quinolinium salt in DMSO under nitrogen and reacted at temperatures ranging from rt to 80 °C (Figure 1.29). The alkyl chains successfully transferred to the nitronates vary in length but do not bear functional groups. A separate class of 2,4,6-triphenyl substituted quinolinium salts transfers simple secondary alkyl chains in yields ranging from 36-69%. Additionally, with respect to the nitroalkane starting materials, no functional groups are present making it unclear as to whether this method tolerates the formation of more complex nitroalkanes. The present alkylation is proposed to proceed from a non-chain radical mechanism involving electron transfer from the electron rich nitronate to the electron poor heterocyclic salts. Loss of the N-substituted alkyl radical and recombination with the nitroalkyl radical furnishes a new C-C bond (Figure 1.30).

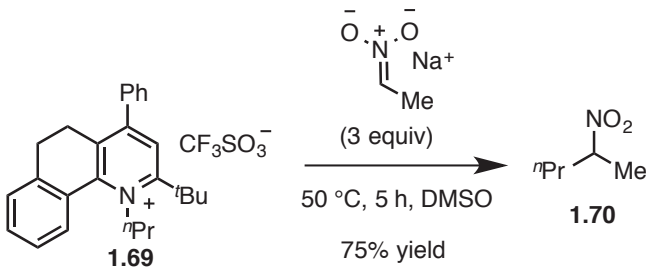


Figure 1.29: Katritzky *N*-substituted-quinolinium salts for *C*-alkylation of nitroalkanes

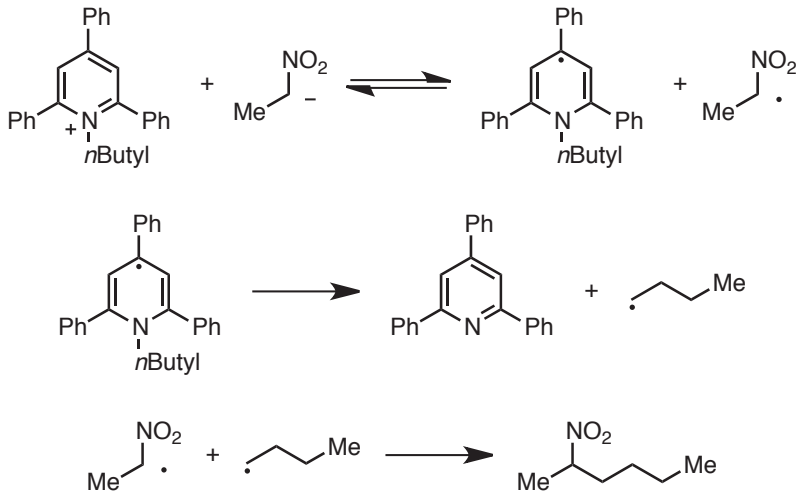


Figure 1.30: Katritzky non-chain radical mechanism

1.3.3 Russell Alkyl Mercury

In studying free-radical chain reactions the Russell group observed that stoichiometric primary and secondary alkylmercury chlorides or bromides react with simple nitroalkanes such as 2-nitropropane in an $S_{RN}1$ process. The photolytic reaction proceeds in good yields in polar solvents such as DMF and DMSO.[44] In a subsequent study the rate of this reaction was investigated by the reaction of the anion of 2-nitropropane with the 5-hexenyl radical. Electron transfer to hexenylmercury chloride and loss of the chloride ion and mercury (0) yields the 5-hexenyl radical known to cyclize at a rate of 1.7 X 10^5 s^{-1} at 40 ºC (K_C). With this value and the ratio of non-cyclized to cyclized nitrocoupling product the rate of radical anion coupling was estimated at ~1 X 10^6 L/mol s^{-1} at 40 ºC (Figure 1.31).[45]

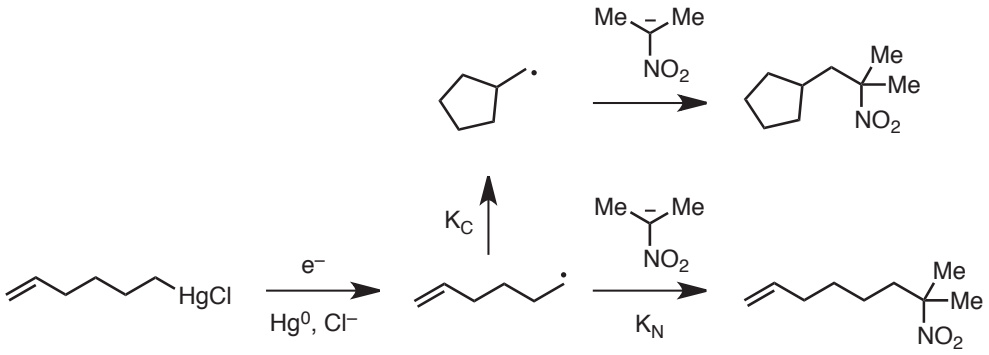


Figure 1.31: Russell rate studies of radical anion coupling

1.3.4 Branchaud Alkyl Cobalt

Additionally, the Branchaud group found success in stoichiometric cobaloxime mediated alkyl-alkenyl and alkyl-heteroaromatic cross-couplings to form new C-C bonds. Aware of the extremely high rate of reactivity of nitroalkyl anions with nucleophilic alkyl radicals, Branchaud examined the potential of coupling their alkyl cobaloximes to react with nitroalkyl anions. For example 5-hexenyl radical is known to react faster with the anion of 2-nitropropane (~2.5 X 10^5 L/mol s^{-1} at 40 ºC) than with unsubstituted styrene (~8.7 X 10^4 L/mol s^{-1} at 45 ºC).[45] Provided the nitroalkyl anion was used in excess (10 equivalents) the anions of nitromethane and 1-nitropropane could be coupled to add a decyl chain in 85% and 83% respectively in a 5% H_2O solution in ethanol (Figure 1.32). The transfer of secondary alkyl chains using the alkylcobalt complex was less favorable with yields ranging from 5% to 62% when using 20 equivalents of sodium nitronate.[46]

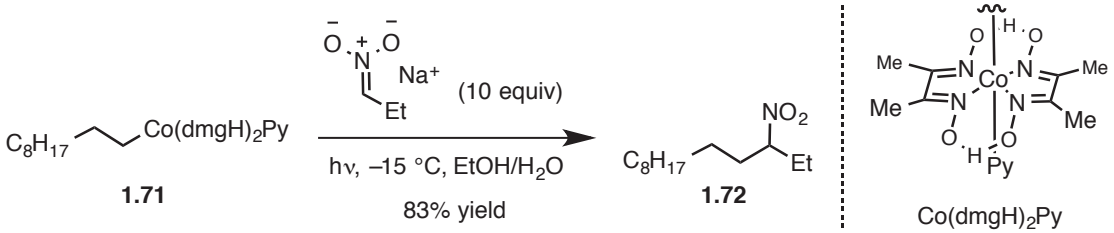


Figure 1.32: Branchaud *C*-alkylation of nitroalkanes with alkyl cobaloximes

1.4 Transition Metal Catalyzed Alkylation of Carbon Nucleophiles

In considering ways in which to realize a *C*-alkylation method for nitroalkanes I was drawn to the significant advances in the field of transition metal-catalyzed alkylation of carbon nucleophiles with various alkyl electrophiles. Given the recent progress in this field towards increasing the tolerance of functional groups and broadening the array of suitable organometallic reagents, I was drawn to these methods. Additionally many of the following methods are thought to proceed through radical intermediates.[47]

1.4.1 Challenges in C(sp^3)- C(sp^3) Cross-Coupling

In the last several decades there have been numerous advances in the cross-couplings of alkyl halides with carbon nucleophiles.[47] Cross-couplings of C(sp^3)-X bonds face a number of new challenges as compared to the more extensively utilized couplings of C(sp^2)-X bonds. The more electron rich C(sp^3)-X bonds make oxidative addition more sluggish. Even after successful oxidative addition of a C(sp^3)-X bond, the resulting intermediate is less stable owing to a lack of π electrons useful in stabilizing the empty d orbitals of the metal center. β-Hydride elimination again competes with transmetallation and the final reductive elimination step (Figure 1.33). Despite the numerous challenges associated with alkyl halide cross-couplings,

significant advancements have been made in the tolerance of activated and non-activated primary and secondary alkyl electrophiles.[48] This field is well reviewed with respect to the use of various transition metals, the organometallic reagent, and the classes of tolerated alkyl electrophiles.[47-49] The following sections will describe several successful examples of $C(sp^3)$-$C(sp^3)$ cross-couplings using highly effective transition metal complexes with varying organometallic reagents.

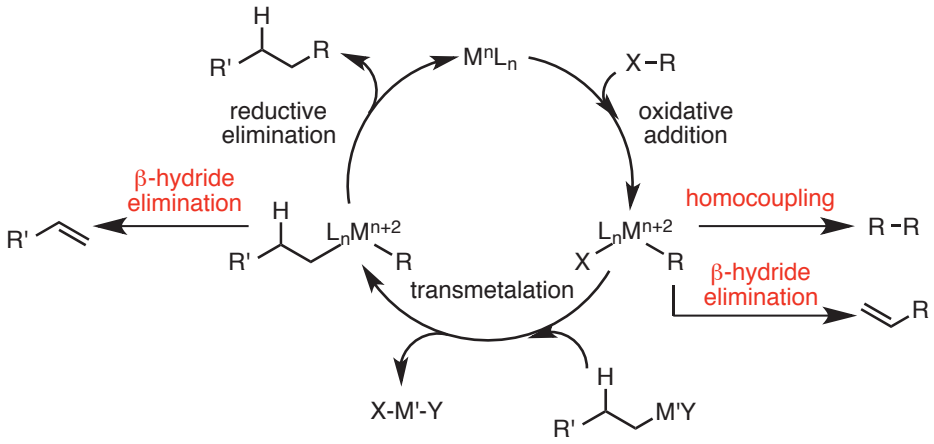


Figure 1.33: General catalytic cycle for cross-coupling of alkyl halides

1.4.2 Advances in $C(sp^3)$-$C(sp^3)$ Cross-Couplings with Palladium and Nickel Catalysts

Many developments in $C(sp^3)$-$C(sp^3)$ cross-couplings have benefitted from palladium and nickel catalysts to overcome the challenges associated with these difficult reactions.[47] In 2009, the Organ group published the use of an *N*-heterocyclic (NHC) based palladium catalyst for the Suzuki-Miyaura coupling of unactivated alkyl bromides with alkyl 9-BBN reagents.[50] They demonstrated the utility of their novel air

and moisture stable palladium catalyst **1.76** in the coupling of functional group bearing alkyl bromides and alkyl boranes in high yields at room temperature (Figure 1.34).

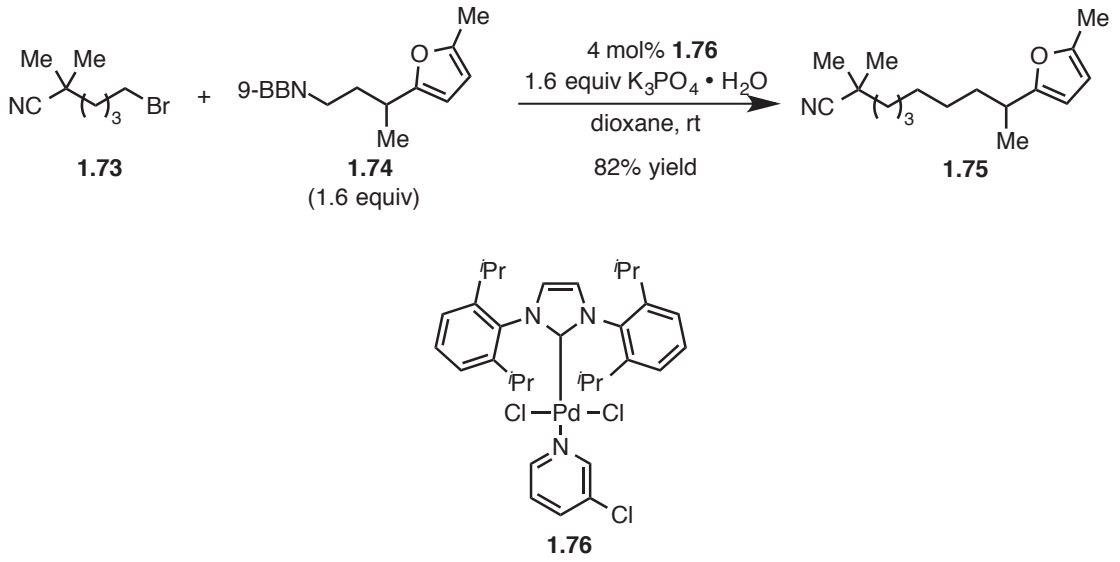


Figure 1.34: Organ group use of NHC-based palladium catalyst **1.76**

In 2002, the Kambe group demonstrated the first Ni-catalyzed $C(sp^3)$-$C(sp^3)$ cross-coupling of alkyl magnesium reagents.[51] Using 1,3-butadiene instead of phosphine ligands led to the reactive catalyst. It was proposed that nickel(0) arising from reduction of nickel(II) with two equivalents of the Grignard reagent **1.78** forms a crucial bis-π-allyl complex with two equivalents of 1,3-butadiene. The same nickel-catalyzed conditions were used to overcome issues of functional group tolerance in the Kumada cross-coupling of unactivated alkyl halides with alkyl Grignards in good yields (Figure 1.35).[52]

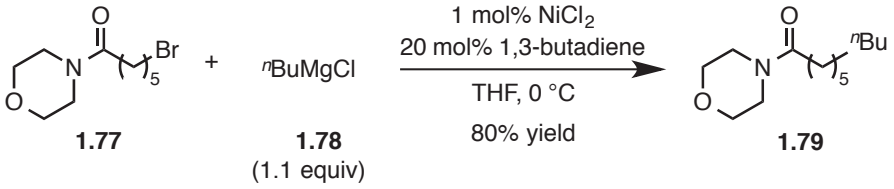


Figure 1.35: Kambe group functional group tolerance in $C(sp^3)$-$C(sp^3)$ Kumada cross-coupling

In 2010, the Fu group published an enantioselective Suzuki arylation of activated secondary α-bromo- and α-chloroamides using nickel (II) and chiral diamines ligands.[53] High yields and enantioselectivities of α-arylated amides are obtained as in the coupling of α-chlorobutyramide **1.80** with aryl borane **1.81** to give arylated **1.82** in 88% yield and 91% ee (Figure 1.36). They have since expanded their methodology to the cross-couplings of unactivated alkyl halides. In 2011 they published the coupling of γ-chlorocarbonyl compounds with alkyl boranes using a similar chiral 1,2-diamine catalyst (**1.87**) to control selectivity remote from the carbonyl group with high yields and enantioselectivities (Figure 1.37).[54]

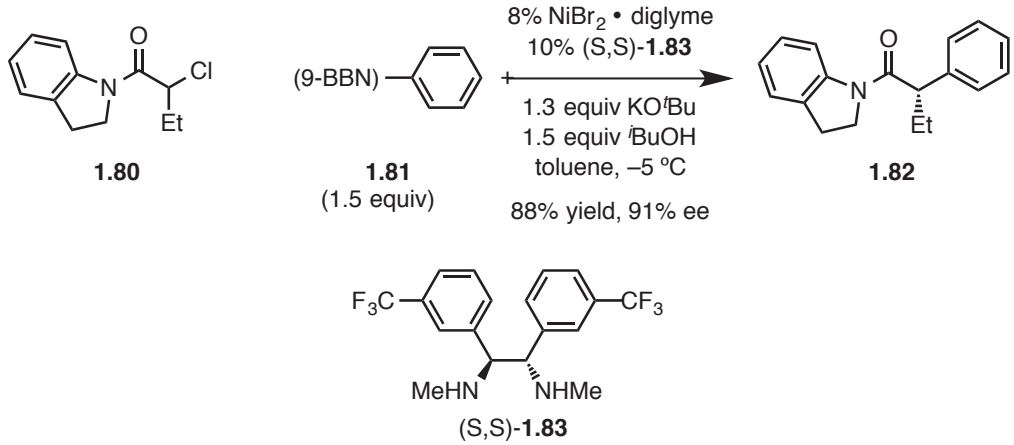


Figure 1.36: Fu group Suzuki arylation of activated secondary α-chloroamides

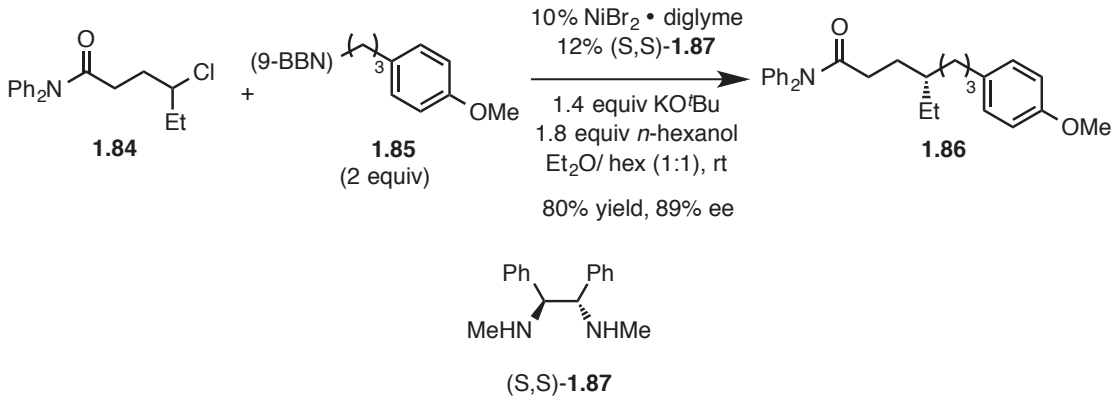


Figure 1.37: Fu group enantioselective γ-alkylation of diphenylamides

Even more recently in 2013 the Reisman group published mild, base-free conditions for the enantioconvergent reductive coupling of acid chlorides with racemic secondary benzyl chlorides.[55] Manganese was identified as a suitable reductant for nickel, with 2,6-dimethylbenzoic acid (DMBA) and molecular sieves used to suppress the formation of carboxylic acid formation from the acyl chloride starting material. α-Aryl-α-alkyl ketones such as **1.90** are obtained in good yield with high enantioselectivities (Figure 1.38).

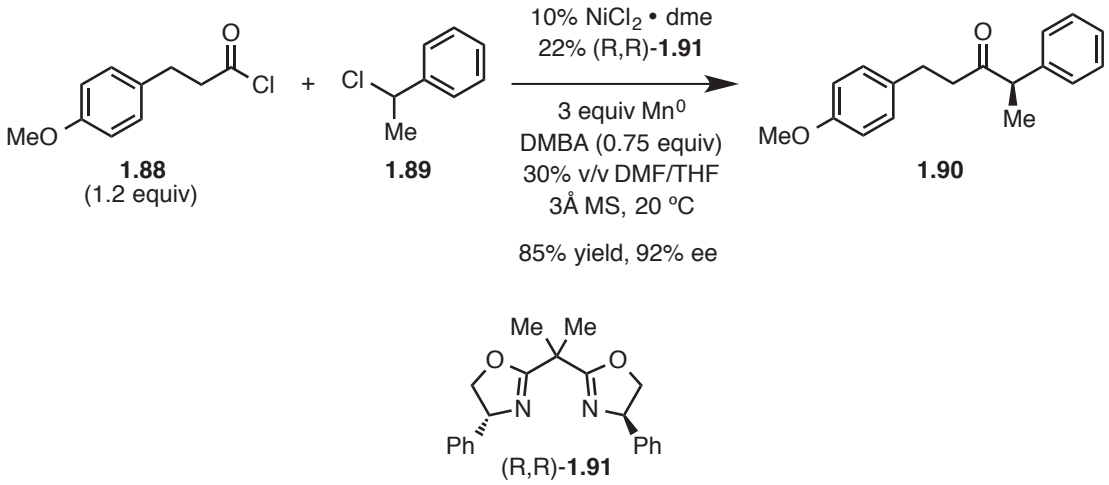


Figure 1.38: Reisman's enantioselective Ni-catalyzed reductive acyl cross-coupling

1.4.3 Advances in $C(sp^3)$-$C(sp^3)$ Cross-Couplings with Iron and Cobalt Catalysts

In addition to the many advancements in $C(sp^3)$-$C(sp^3)$ cross-couplings using palladium and nickel, remarkable progress has been made when using iron[49a] and cobalt[49b] for overcoming the same obstacles. In 2007 the Chai group published the first $C(sp^3)$-$C(sp^3)$ coupling of Grignard reagents with unactivated alkyl halides using Xantphos **1.95** as the best ligand for iron(II) acetate (Figure 1.39).[56] While only primary alkyl chains were demonstrated in this initial work, further scope and application will likely result due to the need for more sustainable metal catalysts.

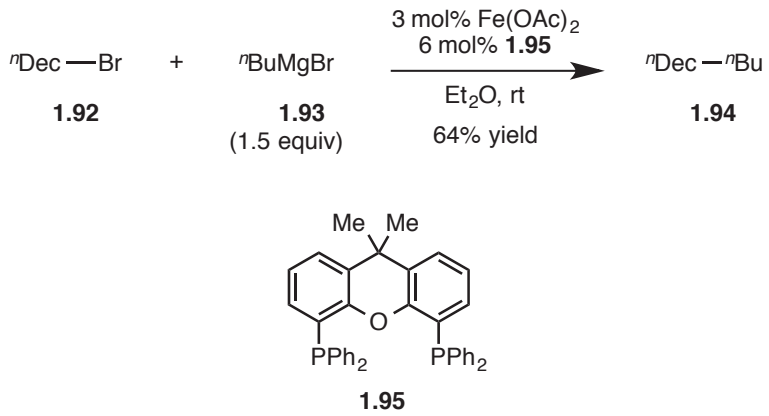


Figure 1.39: Iron-catalyzed $C(sp^3)$-$C(sp^3)$ coupling of Grignard reagents with unactivated alkyl halides

The utility of cobalt in cross-couplings of alkyl halides has also been examined with several key discoveries expanding the scope of reactivity.[49b] Successful reports of cobalt together with catalytic TMEDA and lithium iodide reported by the Cahiez group have led to the coupling of primary and secondary unactivated alkyl bromides in good to excellent yields.[57] Several examples of functional group tolerance were demonstrated in addition to the first example of a chemoselective $C(sp^3)$-$C(sp^3)$ coupling from a functional group bearing secondary alkyl bromide (Figure 1.40).

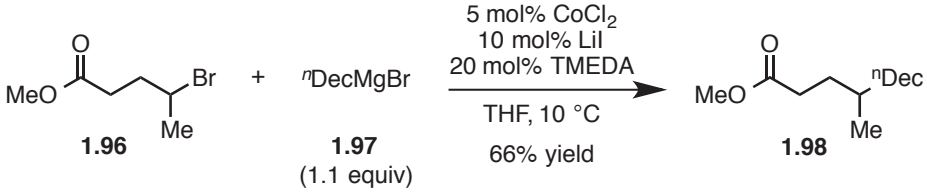


Figure 1.40: Cahiez coupling of secondary alkyl bromide **1.96** with Grignard **1.97**

1.5 Atom Transfer Radical Addition

In addition to the advances in methods for alkylating carbon nucleophiles I was aware of the established field of atom transfer chemistry. In the 1940's, the addition of halogenated methane to alkenes using either light or a radical initiator was demonstrated.[58] Since that initial report, atom transfer radical addition (ATRA) has become a powerful synthetic tool typically catalyzed by transition metal complexes using Ru, Fe, Ni and Cu to form the mono-addition adduct.[59] From this original mode of reactivity has come a variety of controlled/ living radical polymerization (CRP) systems.[60] Of the most promising of these, atom transfer radical polymerization (ATRP), involves mediating a small amount of growing free radicals with a large amount of dormant alkyl halides to synthesize polymers of well-defined composition. The rapid growth of this field and increasing reports in this area have contributed to improvements in reduced catalyst loading down to ppm quantities, heightened control of polymer distribution, and tolerance of functional groups.[61]

1.5.1 Introduction and Discovery

The Kharasch addition was first discovered in the 1940's as a means of adding halogenated methanes to alkenes by using light or radical initiators.[58] Today this process, commonly referred to as atom transfer radical addition (ATRA), is accepted to occur through a free radical mechanism. While this reaction proved quite high yielding in the case of halogenated methane with simple olefins using 2,2'-azobis(2-methylpropionitrile) (AIBN) as the radical initiator, the use of more reactive alkene partners such as styrene lead to oligomerization. While decreasing radical concentration did lead to less undesired radical-radical coupling the rates of polymerization could not be suppressed. The competition between halide recapture to

form a monoadduct and polymerization to form oligomers with additional equivalents of alkene, led to additional studies with transition metals to control these rates.[61]

1.5.2 Transition Metal ATRA

The desire to selectively access monoadduct products from atom transfer reactions led to the investigation of transition metal complexes as catalysts. Recognizing that metal catalysts transfer halogens more effectively than alkyl halides it was hypothesized that polymerization could be more successfully suppressed. Indeed, complexes using Cu, Fe, Ru, and Ni have all been used extensively in ATRA. Among these copper is one of the most promising due to the inexpensive cost and availability of copper halides, their ease of use in one electron redox catalysis, and simplicity in work up.[62] In addition to favoring monoadduct products with great selectivity, the discovering of potent catalysts has led to an increase in the reaction partners for this transformation. Halogenated starting materials such as alkyl and aryl halides, alkyl sulfonyl halides, and *N*-chloroamines all participate with good reactivity. With respect to the olefin, a variety of alkenes such as styrenes, alkyl acrylates, and acrylonitriles are all suitable partners leading to monoadduct products.

The accepted mechanism for this transition metal catalyzed process with copper involves first the formation of the active catalyst from a copper (I) halide and a suitable ligand (Figure 1.41). A single electron transfer event with the halogenated starting material generates a copper (II) complex and an organic radical. The radical species then reacts in one of several pathways. Unproductively the alkyl radical can dimerize thus terminating the cycle. The reverse process of reacting with the catalyst to regenerate an alkyl halide is also possible. In the productive pathway, the alkyl radical reacts with the alkene to form a new C-C bond and generate a new

alkyl radical. For success in this overall transformation, the new alkyl radical that is formed should be more reactive than the original alkyl radical formed in the first step. This favors quick halogen abstraction from the copper (II) complex to give the monoadduct product.[61]

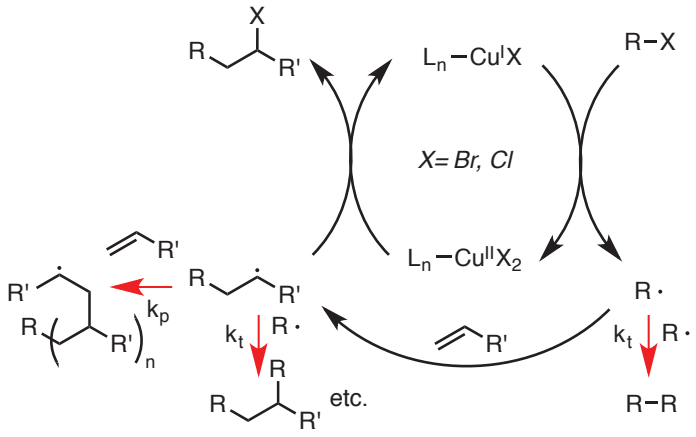


Figure 1.41: ATRA transition metal catalyzed radical mechanism

1.5.3 Atom Transfer Radical Cyclization Chemistry

The power and utility of atom transfer chemistry has been further demonstrated in the synthesis of functionalized ring systems through atom transfer radical cyclization (ATRC) chemistry. Many commonly used radical cyclization methods are mediated by organostannane reagents and are quenched through the addition of a hydrogen atom to the final product in an overall reductive pathway. In addition to losing two functional groups in this transformation the reagents are toxic and can complicate the purification process. Conversely ATRC reactions retain the halide after cyclization, which can be used in subsequent reactions as a handle for additional elaboration. The Nagashima group first used this method in the successful formation

of gamma-lactones from alkenyl trichloroacetates (Figure 1.42).[63] Subsequent investigation into the nature of the catalyst has lead to dramatically increased reactivity when investigating the role of nitrogen-based ligands (Table 1.4).[62]

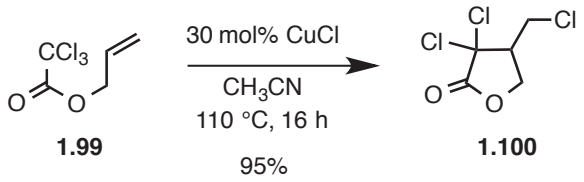
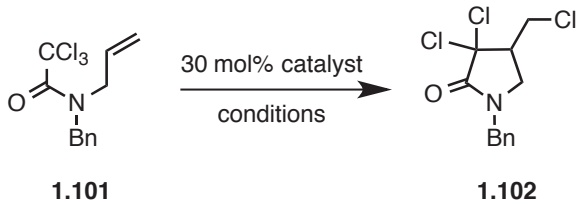


Figure 1.42: First example of ATRC

Table 1.4: Improved catalysts for ATRC



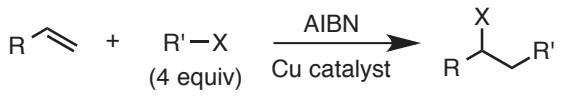
entry	catalyst	temp	time	yield **1.102**
1	CuCl	80 °C	18 h	68%
2	CuCl-bipy	rt	1 h	98%

1.5.4 Improving Catalyst Efficiency

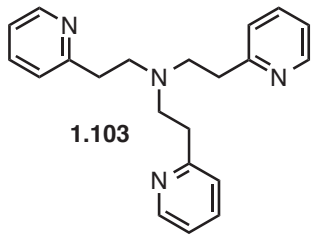
Numerous studies examining the properties of the nitrogen ligand on copper have highlighted its impact on reactivity. More than just solubilizing the copper, nitrogen ligands have been found to affect reaction rate with respect to steric bulk and stereoelectronic effects.[62] Careful ligand design in addition to other modifications such

as the use of biphasic systems using fluorous solvents and solid supported catalysts have led to remarkable reactivity in atom transfer chemistry using only ppm amounts of copper catalysts.[61] One of the most active catalysts in copper-mediated ATRP is formed from tetradentate ligand **1.103** with copper chloride and bromide salts (Table 1.5). Using air stable $Cu^{II}Cl_2$(**1.103**) led to similar results as when using $Cu^{I}Cl$(**1.103**) demonstrating that azobisisobutyronitrile (AIBN) is suitable for regenerating the copper (I) complex.[64] Increased reactivity was observed when using $Cu^{II}Br_2$(**1.103**) due to the weaker C-Br and Cu-Br bonds compared to the equivalent chloride bonds. One of the highest turnover numbers (TON) for any metal-mediated ATRA process was reported when using $Cu^{II}Br_2$(**1.103**) for the ATRA of carbon tetrabromide to styrene (Table 1.5, entry 4).[59]

Table 1.5: ATRA of polyhalogenated compounds to alkenes using copper **1.103** catalysts



entry	alkene	RX	catalyst	yield	TON
1	1-hexene	$CHCl_3$	$Cu^{I}Cl$(**1.103**)	56%	$5.6X10^2$
2	1-hexene	$CHBr_3$	$Cu^{II}Br_2$(**1.103**)	61%	$6.1X10^3$
3	styrene	CCl_4	$Cu^{I}Cl$(**1.103**)	85%	$2.1X10^2$
4	styrene	CBr_4	$Cu^{II}Br_2$(**1.103**)	95%	$1.9x10^5$



1.103

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Chapter 2

BENZYLATION OF NITROALKANES USING COPPER-CATALYZED THERMAL REDOX CATALYSIS: TOWARD THE FACILE *C*-ALKYLATION OF NITROALKANES

2.1 Introduction: Reactivity of Nitroalkanes

A discussed in Chapter 1, the ability of nitroalkanes to form C-C bonds greatly contributes to the value of nitroalkanes as tools for building molecular complexity. However, as outlined in detail in the preceding chapter, there are no general methods to *C*-alkylate nitroalkanes with alkyl electrophiles. With the goal of finding means to affect the *C*-alkylation of nitroalkanes, I was particularly drawn to the potential of radical chemistry. In addition to the radical pathways elucidated by Kornblum[1] and Katritzky,[2] photogenerated alkyl radicals, generated via the homolytic fragmentation of mercury- or cobalt-alkyls, have been shown to react with nitronate anions at carbon.[3] Although of limited synthetic utility, these reactions demonstrate that radical-anion coupling involving nitronate anions is feasible.

Simultaneously, I was cognizant of recent work in the area of metal-catalyzed alkylation of carbon nucleophiles using alkyl halides.[4] Many of these reactions have been shown to involve radical intermediates. I was particularly drawn to the copper-based catalyst systems used in the mechanistically related Atom Transfer Radical Addition (ATRA) and Atom Transfer Radical Polymerization (ATRP) reactions, in which Cu(I) catalysts initiate radical reactions of substituted alkenes by undergoing an SET reaction with alkyl halides bearing a wide range of radical stabilizing groups.[5]

Given the propensity of nitronate anions to undergo reactions with radical intermediates, I reasoned that a copper-based catalyst might promote *C*-alkylation using readily prepared or commercially available alkyl halides via a pathway involving SET followed by radical-anion coupling (Figure 2.1).

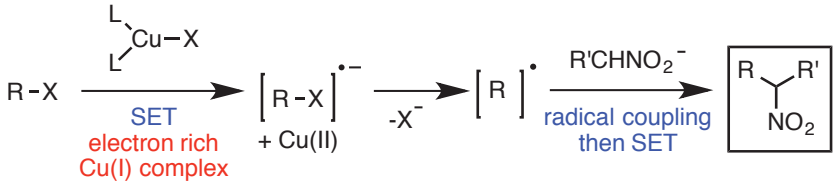
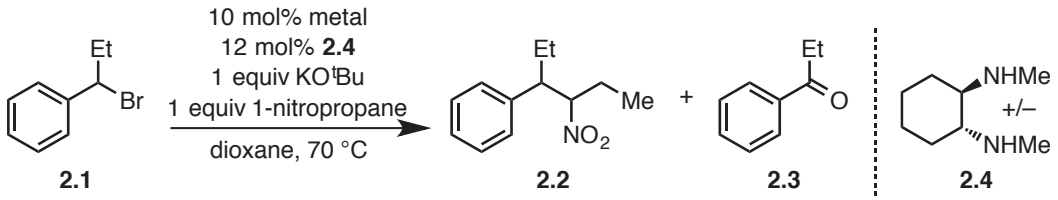


Figure 2.1: Electron-rich copper catalysts to promote nitroalkane alkylation

2.2 Identifying and Optimizing Reaction Conditions

Initially I began by examining the use of various first row transition metals to catalyze the reaction of 1-nitropropane with 1-bromo-1-phenylpropane (**2.1**) (Table 2.1). Minimal *C*-alkylation to form nitroalkane (**2.2**) was observed, and in all cases competitive *O*-alkylation to ketone (**2.3**) was observed. To avoid diastereomer formation (all *C*-alkylated products in Table 2.1 obtained in 1:1 dr) I moved to a primary alkyl electrophile, benzyl bromide (**2.5**).

Table 2.1: Initial studies towards *C*-alkylation of 1-nitropropane with 1-bromo-1-phenylpropane using first row transition metal catalysts

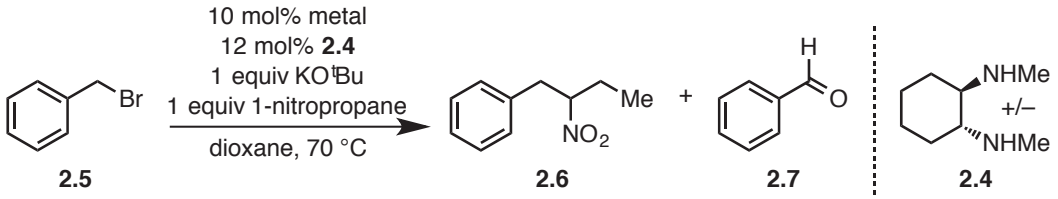


2.1 **2.2** **2.3** **2.4**

entry	metal	yield **2.2**	yield **2.3**
1	CuI	7%	2%
2	$CoCl_2$	3%	10%
3	$FeCl_3$	trace	9%
4	$Ni(COD)_2$	4%	8%

Encouragingly moving to a primary benzyl bromide (**2.5**) as an alkylating partner for 1-nitropropane led to formation of *C*-alkylated nitroalkane **2.6** in 43% yield with only minimal *O*-alkylated product, benzaldehyde (**2.7**), when using copper bromide with diamine **2.4** (Table 2.2, entry 1). Interestingly all other transition metal sources tested led to significant benzaldehyde (**2.7**) with only minimal *C*-alkylation (entries 2-6). Using nickel (0) led to the second best results with 12% yield of nitroalkane **2.6**. I selected copper as the most promising transition metal and performed additional screening to evaluate the nature of the ligand in affecting *C*-alkylation.

Table 2.2: Initial studies towards *C*-alkylation of 1-nitropropane with benzyl bromide using first row transition metal catalysts



entry	metal	yield **2.6**	yield **2.7**
1	CuBr	43%	5%
2	$CoCl_2$	2%	29%
3	$FeCl_3$	2%	24%
4	$Ni(COD)_2$	12%	24%
5	Pd_2dba_3	2%	12%
6[a]	Pd_2dba_3	4%	32%

[a]12 mol% PCy_3 used as ligand.

Under basic conditions in the absence of catalyst, only trace desired 1-phenyl-2-nitrobutane (**2.6**) was observed (<5% by NMR). The major product in these reactions was benzaldehyde (**2.7**) (12% by NMR, Table 2.3, entry 1) along with unreacted starting material. With CuBr, and simple ligands such as PPh_3 or bipyridyl **2.8**, a modest increase in the desired product was seen (entries 2 and 3). Interestingly, the neutral polydentate ligands **2.9** and **2.10**, which are often very effective ligands in ATRA/ATRP reactions, were less effective (entries 4 and 5).

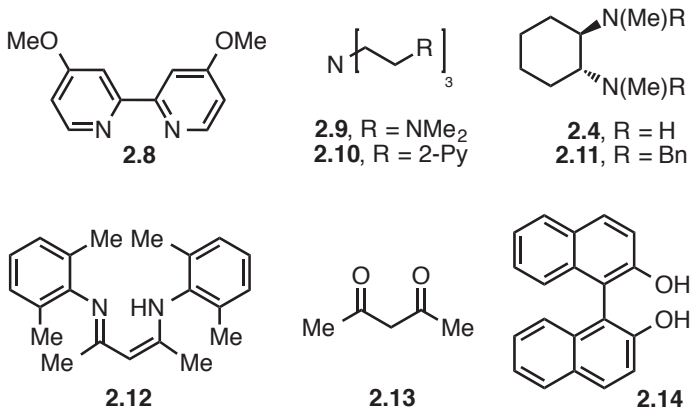
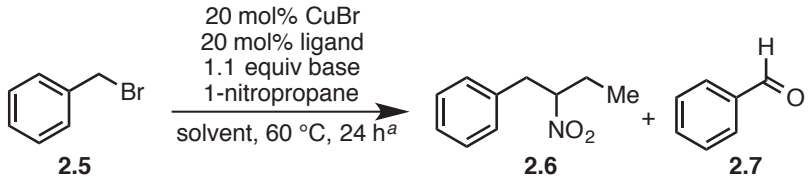


Figure 2.2: Examples of ligands examined in the benzylation

Table 2.3: Identification of reaction conditions



entry	ligand	base	solvent	yield **2.6**[b]	yield **2.7**[b]
1	none[c]	KO^{t}Bu	C_6D_6	trace	12%
2	PPh_3	KO^{t}Bu	C_6D_6	18%	13%
3	**2.8**	KO^{t}Bu	C_6D_6	17%	19%
4	**2.9**	KO^{t}Bu	C_6D_6	8%	14%
5	**2.10**	KO^{t}Bu	C_6D_6	10%	2%
6	**2.4**	KO^{t}Bu	C_6D_6	45%	8%

7	**2.11**	KO^{t}Bu	C_6D_6	15%	22%
8	**2.12**	KO^{t}Bu	C_6D_6	64%	2%
9	**2.13**	KO^{t}Bu	C_6D_6	3%	10%
10	**2.14**	KO^{t}Bu	C_6D_6	7%	8%
11 [d]	**2.12**	KO^{t}Bu	C_6D_6	72%	2%
12 [d]	**2.12**	LiO^{t}Bu	C_6D_6	0%	1%
13[d]	**2.12**	NaO^{t}Bu	C_6D_6	78%	2%
14 [d]	**2.12**	NaO^{t}Bu	hexanes	85%[e]	trace

[a] Unless otherwise noted: 1.15 equiv nitropropane; [b] Unless otherwise noted: yields determined by NMR; [c] No copper, no ligand; [d] Conditions: 1.25 equiv nitropropane, 1.2 equiv base, 25 mol% **2.12**; [e] Isolated yield.

In contrast, as was noted in the preliminary transition metal screens (Tables 2.1 and 2.2), *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (**2.4**), a ligand that has been used in copper-catalyzed Goldberg-type reactions[6] but not often used in atom-transfer reactions, led to more promising results. Using this ligand, **2.6** was observed in 45% yield (Table 2.3, entry 6). Unfortunately, efforts to optimize this ligand design were unsuccessful. However, during these studies I noted a major byproduct from the reaction was the dibenzylated ligand **2.11**. Independent preparation of **2.11** revealed that it was ineffective as a ligand in the catalytic reaction (entry 7).[7] Similar results were observed for other tetra-alkyl diamine ligands, leading me to speculate that the protic N–H bond of **2.4** might be integral to its success in the reaction; I postulated

that the active catalyst might arise from deprotonation of the ligand under the reaction conditions leading to the formation of a highly electron-rich Cu(I)-amido species.

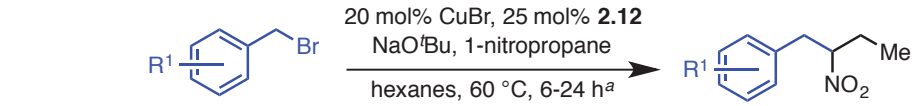
This line of reasoning led me to examine the use of 1,3-diketimine (nacnac) ligands in the reaction. I predicted that the acidic nature of the nacnac backbone would rapidly result in the formation of a neutral Cu(I)-nacnac under the basic reaction conditions.[8] Further, I hoped that the steric bulk of the nacnac architecture would prevent competitive alkylation of the ligand. Using nacnac **2.12**, a 64% yield of **2.6** was observed under the initial screening conditions. Extensive attempts to optimize the reaction through modulation of the nacnac structure proved unsuccessful (see Section 2.9: Experimental); however further studies revealed a significant effect of the base counter-ion, with sodium proving optimal in terms of yield and ease of use (entry 12 vs. 13).[9,10] Non-polar solvents were also generally favored, with hexanes being the most effective in the screening reaction. Using these optimized conditions, the desired 2° nitroalkane could be isolated in 85% yield on a 1 mmol scale (entry 14).[11]

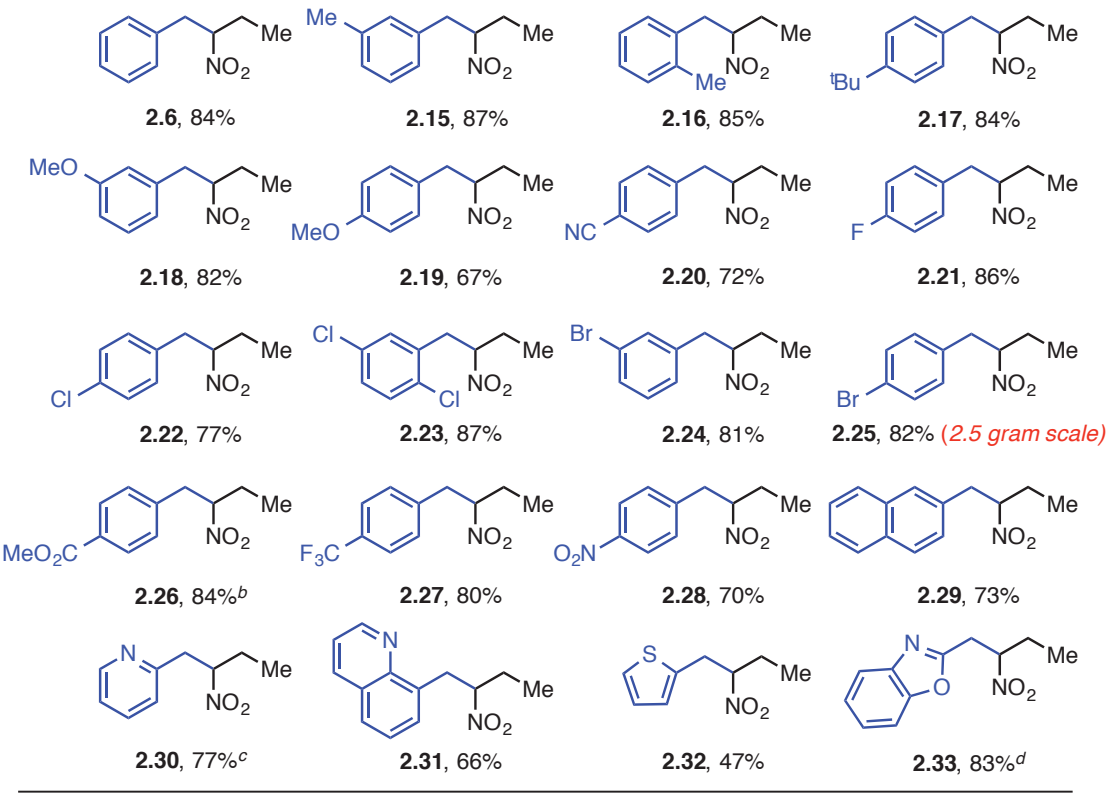
2.3 Reaction Scope with Respect to Benzyl Bromides

The scope of the reaction with respect to benzyl bromide is broad (Table 2.4). A wide-range of functional groups are tolerated, including fluorides, chlorides, bromides, nitriles, esters, ethers, and trifluoromethyl groups. Both electron-rich (**2.19**) and electron-poor (**2.20**, **2.26,** and **2.27**) benzyl bromides participate in the reaction, and there is remarkably little variance in the yield of product due to the electronic effects of the arene substituent. The reactions of more sterically encumbered benzyl bromides, such as those containing an *ortho* methyl group (**2.16**), and polyaromatic substrates (**2.29**) also proceed without incident. *Para*-nitrobenzyl bromide also reacts to provide the *C*-alkylated product under the copper-catalyzed reaction conditions

(**2.28**).[12] Finally, bromomethyl-substituted heteroaromatic compounds also can be used in the reaction. For example, treatment of 2-bromomethylpyridine hydrobromide with 1-nitropropane lead to nitropyridine **2.30**. Other heteroaromatics, including quinolones (**2.31**), thiophenes (**2.32**), and benzoxazoles (**2.33**) are also efficient substrates.[13] The reaction was easily scaled; compound **2.25** was isolated in 82% yield from a 2.5 gram reaction. In all cases, only trace amounts aldehyde (1-5%) were observed. The major byproduct detected (NMR and GC) was the bibenzyl resulting from dimerization of the alkylating reagent.

Table 2.4: Scope with respect to benzyl bromides





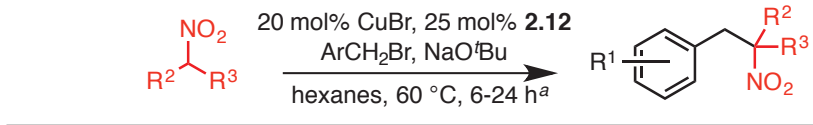
[a] Unless otherwise noted, conditions: 1 equiv benzyl bromide, 1.25 equiv 1-nitropropane, 20 mol% CuBr, 25 mol% **2.12**, 1.2 equiv NaO^{t}Bu; [b] Base = NaOMe; [c] 2.2 mmol of NaO^{t}Bu, solvent = benzene; starting material = HCl salt; [d] Solvent = benzene, base = $NaOSiMe_3$.

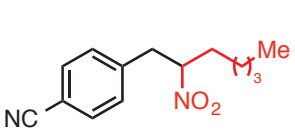
2.4 Reaction Scope with Respect to Nitroalkanes

The reaction also enjoys wide substrate scope with respect to the nitroalkane (Table 2.5). Longer aliphatic nitroalkanes, such as nitrohexane, participated in the reaction well (**2.34**). Branching beta to the nitro group was tolerated (**2.35**). A range of functional groups on the nitroalkane proved compatible with the transformation,

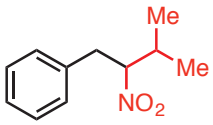
including alkenes, esters, amides and acyl-protected alcohols (**2.36**-**2.39**). All of these reactions proceeded in good yield under the standard reaction conditions or slight modifications thereof. Nitromethane can also be alkylated using this catalyst system in good yield (73%, **2.40**), provided it is used in excess (7.5 equiv). Under these conditions, good selectivity for the monoalkylated product is observed; with less nitromethane double alkylation competes.

Table 2.5: Scope with respect to nitroalkanes

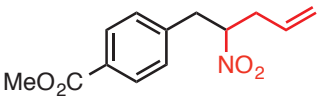




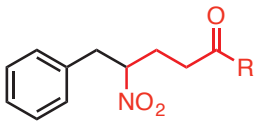
2.34, 67%



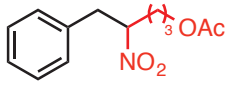
2.35, 66%[b]



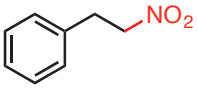
2.36, 70%[c]



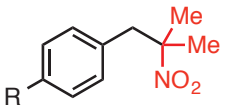
2.37, R = OMe, 64%[c]
2.38, R = NMe_2, 79%[b]



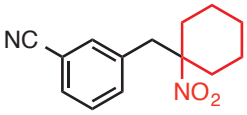
2.39, 66%



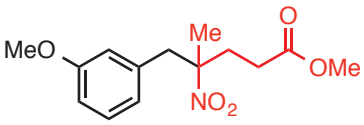
2.40, 73%[d]



2.41, R = H, 71%[e]
2.42, R = Me, 71%[e]



2.43, 73%



2.44, 53%[f]

[a] Unless otherwise noted, conditions: 1 equiv benzyl bromide, 1.25 equiv 1-nitroalkane, 20 mol% CuBr, 25 mol% **2.12**, 1.2 equiv NaO^{t}Bu; [b] Solvent = dioxane; [c] Base = NaOMe; [d] 20 mol% CuBr, 20 mol% **2.12**, 7.5 equiv NO_2Me, solvent = dioxane; [e] 1.15 equiv nitroalkane, 20 mol% **2.12**, solvent = cyclohexane, 48 h; [f] 1.15 equiv nitroalkane, solvent = cyclohexane, base = $NaOSiMe_3$, 24 h, reaction performed in glovebox.

Importantly, secondary nitroalkanes are also tolerated in the reaction. For example, benzylation of 2-nitropropane resulted in a 71% isolated yield of **2.41** (Table 2.5). This transformation allows for the direct construction of a fully substituted carbon bearing a nitrogen substituent, which remains a challenging problem in organic synthesis.[14] Not surprisingly, this reaction proceeded more slowly than those employing primary nitroalkanes. Interestingly, however, this reaction was very sensitive to the choice of solvent, and cyclohexane provided consistently higher yields than hexanes, which was employed in the other reactions. The reason for this solvent effect is not clear – no additional byproducts, such as reduced starting materials, were detected. Other secondary nitroalkanes can participate in the reaction, including nitrocyclohexane (**2.43**) and those bearing functional groups (**2.44**).[15]

2.5 Sequential Alkylation of Nitroalkane Products

The ability of secondary nitroalkanes to participate in the reaction opens the possibility for sequential alkylation reactions (Figure 2.3). For example, as reported above, alkylation of nitropropane with 4-bromobenzyl bromide gave rise to nitroalkane **2.25** in 82% yield. Subsequent alkylation of that product with methyl 4-(bromomethyl)-benzoate resulted in tertiary nitroalkane **2.45** in 65% yield. Such sequential alkylation reactions promise the ability to rapidly prepare complex nitroalkanes and amines from very simple starting materials.

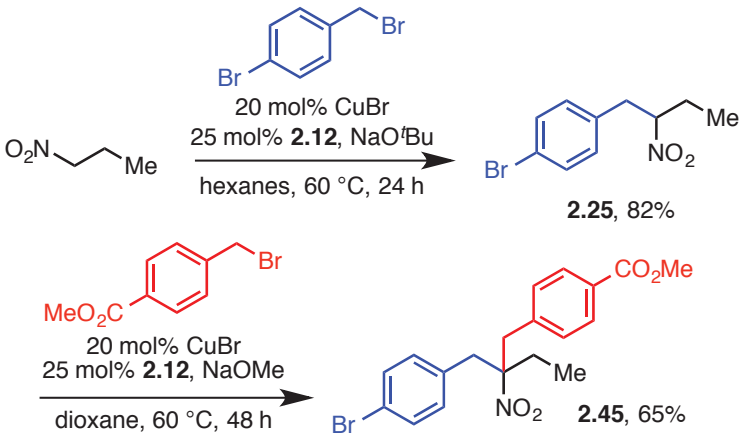


Figure 2.3: Sequential double benzylation of nitroalkanes

2.6 Reduction to Phenethylamines

There is clear relevance of the nitroalkane products from the copper-catalyzed benzylation reaction to the preparation of bioactive molecules. Phenethylamines are important medicinal agents, which have found wide use in the treatment of obesity and other metabolic diesases.[16] These compounds can be readily prepared from β-phenyl nitroalkanes.[17] As an illustration of the utility of our catalytic process, simple hydrogenolysis of nitroalkane **2.41** provided the tertiary amine phentermine (**2.46**) in high yield (Figure 2.4). Phentermine is a clinically prescribed anorectic (appetite suppressant) for the treatment for obesity.[18] It is typically prepared via the Henry reaction of benzaldehyde and 2-nitropropane followed by a multi-step reduction sequence,[19] or via a Ritter reaction of the corresponding tertiary alcohol and subsequent hydrolysis,[20] both of which require more steps than the sequence reported herein.

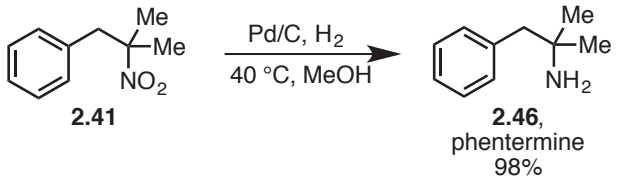


Figure 2.4: Reduction to phentermine

2.7 Mechanistic Hypothesis

Mechanistically, we postulate that these reactions are proceeding via a thermal redox mechanism involving single electron transfer (SET) from the electron-rich Cu(I)-nacnac complex to the benzyl bromide. Upon loss of halide, this process generates a neutral benzylic radical. Alternatively atom transfer (AT) of a bromine atom from the substrate to the Cu(I)-nacnac complex also generates a stabilized benzylic radical (Figure 2.5). This benzylic radical can undergo coupling with the nitronate anion in a radical-anion coupling step. Electron transfer from the resulting nitronate radical would regenerate the copper catalyst, closing the catalytic cycle. The observation of bibenzyl side products is consistent with a single electron pathway.[21]

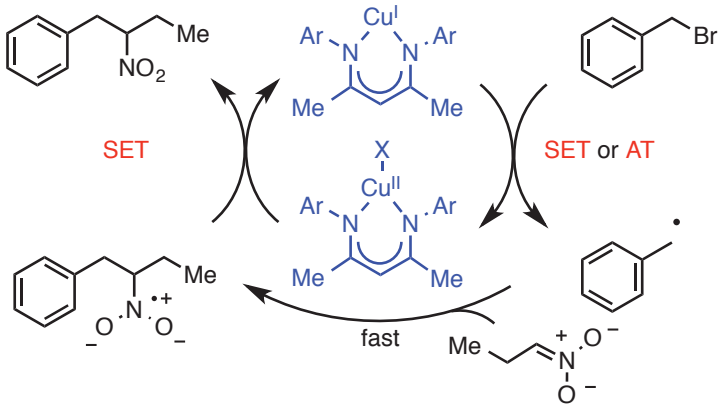


Figure 2.5: Possible mechanistic pathway

2.8 Conclusion

In summary, with my colleagues Amber Gietter and Di Cui, I have developed a catalytic system for the benzylation of nitroalkanes that utilizes readily available benzyl halides and related hetereoaromatic compounds.[22] This protocol addresses a century-old gap in C–C bond construction and provides the first example of alkylation of nitroalkanes using readily available starting materials under mild reaction conditions. This reaction allows for the conversion of simple starting materials to complex nitroalkanes, which are important synthetic intermediates in the preparation of bioactive molecules, such as phenethylamines. The key to this discovery was the identification of a highly electron-rich Cu(I)-nacnac complex, which can be prepared *in situ* and is capable of facile reduction of the benzyl halide to the corresponding radical. This thermally driven process clearly bears mechanistic resemblance to catalytic photoredox systems, the synthetic utility of which has been elegantly demonstrated by several groups.[23,24]

2.9 Experimental

2.9.1 General Experimental Details

Toluene and dioxane were dried on alumina according to published procedures.[25] Hexanes and benzene were purchased in an anhydrous septa sealed bottle. Copper bromide and sodium *tert*-butoxide were purchased commercially; the bulk was stored in a nitrogen filled glovebox; samples were removed from the glovebox and stored in a desiccator under air for up to one week prior to use. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. β-Diketiminate ligand **2.12** was synthesized according to a published procedure.[26] Substrates 8-(bromomethyl)-quinoline[27], 2-(bromomethyl)thiophene[28], 2-

bromomethyl-benzooxazole[29], 2-methyl-1-nitropropane[30], and 4-nitro-1-butene[31], methyl-4-nitrobutyrate[32], N,N-dimethyl-4-nitro-butanamide[33], 4-nitrobutyl acetate[34], nitrocyclohexane[35], and methyl 4-nitropentanoate[36] were prepared according to the literature procedure. All other substrates and reagents were purchased in highest analytical purity from commercial suppliers and used as received. Reactions reported in tables 2.1, 2.2, and 2.3 were carried out in a glovebox (N_2 atmosphere) on a 500 μmol scale in 16 mm X 100 mm threaded test tubes sealed with Teflon lined caps and were heated in an aluminum block-heater with stirring. Product yields in Tables 2.1 and 2.2 obtained by GC. Product yields in Table 2.3 obtained by NMR unless otherwise noted. Product yields in Table 2.6 obtained by GC with dodecane as an internal standard. All other reactions, except that producing nitroalkane **2.44**, were set up using Schlenk technique and heated with stirring in temperature controlled oil baths. "Double manifold" refers to a standard Schlenk-line gas manifold equipped with nitrogen and vacuum (ca. 100 mtorr).

2.9.2 Instrumentation and Chromatography

400 MHz ^{1}H, 101 MHz ^{13}C, and 376 MHz ^{19}F spectra were obtained on a 400 MHz FT-NMR spectrometer equipped with a Bruker CryoPlatform. 600 MHz ^{1}H and 151 MHz ^{13}C spectra were obtained on a 600 MHz FT-NMR spectrometer equipped with a Bruker SMART probe. ^{13}C spectra were recorded using Attached Proton Test phase pulse sequence; carbons with an odd number of protons are phased down and those with an even number of protons are phased up.[37] All samples were analyzed in the indicated deutero-solvent and were recorded at ambient temperatures. Chemical shifts are reported in ppm. ^{1}H NMR spectra were calibrated using the residual protio-signal in deutero-solvents as a standard. ^{13}C NMR spectra were calibrated using the

deutero-solvent as a standard. IR spectra were recorded on an FT-IR spectrometer as thin films. Unless otherwise noted, column chromatography was performed with 40-63 μm silica gel with the eluent reported in parentheses. In specially marked reactions 5-20 μm silica gel was used to improve separation. Analytical thin-layer chromatography (TLC) was performed on precoated glass plates and visualized by UV or by staining with $KMnO_4$. GC samples were run on a Shimadzu GC 2010 Plus using a Thermo Scientific TR-1 column (10m X 0.1mm, ID 0.1μm film). All reported GC yields are corrected using dodecane as an internal standard. All NMR yields are reported using 1,3,5-trimethoxybenzene or hexamethylbenzene as an internal standard. GCMS data was collected using an Agilent 6850 series GC and 5973 MS detector. Low resolution ESI data was collected on a Thermo LCQ Advantage running in positive ion mode. High resolution mass spectrometry data was obtained at the University of Illinois at Urbana-Champaign.

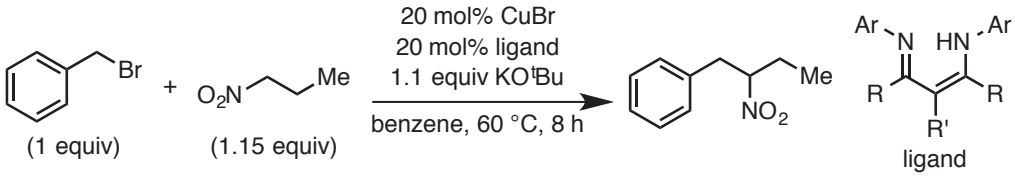
Yields reported in Tables 2.1-2.5 reflect the average isolated yields of at least two independent runs; any deviation between these yields and those reported in this experimental section reflect the difference between individual and average yields.

2.9.3 Additional Optimization of β-Diketiminate Ligands

Outlined in Table 2.6 is the series of experiments aimed at the optimization of the β-diketiminate ligand in the copper catalyzed nitroalkane benzylation reaction. Although a range of substituents were explored on both the nitrogen-aryl substituents, as well as the 1,3-diketone backbone, none of these derivatives proved more successful than the 2,6-dimethyl aniline derived ligand **2.12**. Due to its ease of synthesis and low cost, ligand **2.12** was selected as the ligand for further optimization (see main text). Synthesis of ligands **2.12**, **2.47**, and **2.50-2.64** were carried out via the

condensation of the appropriate 1,3 diketones and the corresponding aniline using a Dean-Stark condenser as described in the literature[26]. All reactions were run under air with the exception of **2.55**, which was run under N_2. Ligands **2.48**[38] and **2.49**[39] were prepared by modification of published procedures.

Table 2.6: Ligand optimization



entry	ligand	R	R'	Ar	yield (%)[a]
1	**2.12**	Me	H	2,6-Me-C_6H_3	77
2	**2.47**[b,c]	Et	H	2,6-Me-C_6H_3	76
3	**2.48**[b,c]	^{i}Pr	H	2,6-Me-C_6H_3	80
4	**2.49**[b,d]	^{t}Bu	H	2,6-Me-C_6H_3	40
5	**2.50**[b,e]	Ph	H	2,6-Me-C_6H_3	4
6	**2.51**[b,e]	Me	H	2-OMe-C_6H_4	44
7	**2.52**	Me	H	2,6-^{i}Pr-C_6H_3	44
8	**2.53**[b]	Me	Me	2,6-Me-C_6H_3	69
9	**2.54**[b,f]	Me	H	2,6-Et-C_6H_3	78
10	**2.55**[b]	Me	H	2,6-Me, 4-OMe-C_6H_2	79
11	**2.56**	Me	H	2,4,6-Me-C_6H_2	80
12	**2.57**	Me	H	2-CF_3-C_6H_4	37
13	**2.58**[b]	Me	H	2-OCF_3-C_6H_4	64
14	**2.59**	Me	H	2-Me, 4-OMe-C_6H_3	64
15	**2.60**	Me	H	2,4,6-OMe-C_6H_2	47
16	**2.61**[b,e]	Me	H	2-Me-C_6H_4	55
17	**2.62**	Me	H	C_6H_5	28
18	**2.63**	Me	H	4-OMe-C_6H_4	33
19	**2.64**	Me	H	4-CF_3-C_6H_4	18
20	**2.65**	Me	H	3,5-CF_3-C_6H_3	17

[a] All yields determined by GC with internal standard. [b] Toluene [0.17M] used as solvent. [c]Reaction time 28 h. [d]Reaction time 17 h. [e]Reaction time 12 h. [f]Reaction time 20 h.

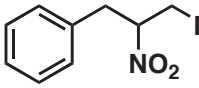
2.9.4 General Protocols for Nitroalkylation

General Protocol A. Synthesis of Nitroalkanes with Liquid Benzyl Bromide Substrates: A hot 25 mL Schlenk flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and CuBr (0.2 equiv), ligand **2.12** (0.25 equiv), and base (1.2 equiv) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with nitrogen five times. Anhydrous solvent (6 mL), the nitroalkane (1.25 equiv), and the benzyl bromide (1.0 equiv) were added to the flask sequentially via syringe. The resulting suspension was heated in a 60 °C oil bath with rapid stirring for the indicated time. The reactor was cooled to rt, the flask was opened to air and the reaction mixture was diluted with diethyl ether (20 mL). The solution was washed twice with saturated ammonium chloride (25 mL) and once with brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by silica gel flash chromatography.

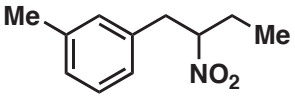
General Protocol B. Synthesis of Nitroalkanes with Solid Benzyl Bromide Substrates: A hot 25 mL Schlenk flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and CuBr (0.2 equiv), ligand **2.12** (0.25 equiv), base (1.2 equiv), and the benzyl bromide (1.0 equiv) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with nitrogen five times. Anhydrous solvent (6 mL) and the nitroalkane

(1.25 equiv) were added to the flask sequentially via syringe. The resulting suspension was heated in a 60 °C oil bath with rapid stirring for the indicated time. The reactor was cooled to rt, the flask was opened to air and the reaction mixture was diluted with diethyl ether (20 mL). The solution was washed twice with saturated ammonium chloride (25 mL) and once with brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by silica gel flash chromatography.

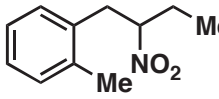
2.9.5 Benzylation of Nitroalkanes



(**2.6**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and benzyl bromide (120 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.6** (153 mg, 85%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.34 – 7.23 (m, 3H), 7.20 – 7.12 (m, 2H), 4.63 (dddd, *J* = 9.7, 8.4, 5.9, 4.4 Hz, 1H), 3.26 (dd, *J* = 14.2, 8.6 Hz, 1H), 3.03 (dd, *J* = 14.2, 5.8 Hz, 1H), 2.03 (ddq, *J* = 14.5, 9.4, 7.3 Hz, 1H), 1.84 (dqd, *J* = 14.8, 7.5, 4.4 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 135.8, 128.98, 128.95, 127.5, 91.5, 39.9, 27.0, 10.4; FTIR (cm^{-1}): 2975, 1549, 1456, 1374, 749, 699; GC/MS (EI) 179.2 $(M)^+$, 132.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{13}NO_2]^+$: 179.0946; found: 179.0936.

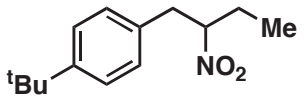


(**2.15**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 3-methylbenzyl bromide (135 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.15** (164 mg, 85%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.20 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 2H), 4.62 (dddd, *J* = 9.7, 8.1, 5.9, 4.3 Hz, 1H), 3.23 (dd, *J* = 14.1, 8.5 Hz, 1H), 2.99 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.33 (s, 3H), 2.02 (ddq, *J* = 14.6, 9.4, 7.3 Hz, 1H), 1.84 (dqd, *J* = 14.8, 7.5, 4.3 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 138.6, 135.7, 129.8, 128.8, 128.2, 126.0, 91.6, 39.8, 27.0, 21.5, 10.4; FTIR (cm^{-1}): 2975, 2936, 1550, 1459, 1374, 782, 700; GC/MS (EI) 193.3 $(M)^+$, 146.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO_2]^+$: 193.1103; found: 193.1086.

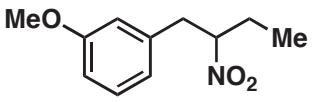


(**2.16**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 2-methylbenzyl bromide (134 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.16** (164 mg, 85%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.19 – 7.11 (m, 3H),

7.08 (d, J = 6.8 Hz, 1H), 4.62 (dddd, J = 10.0, 8.3, 6.1, 4.3 Hz, 1H), 3.28 (dd, J = 14.4, 8.3 Hz, 1H), 3.06 (dd, J = 14.4, 6.2 Hz, 1H), 2.34 (s, 3H), 2.06 (ddq, J = 14.6, 9.6, 7.3 Hz, 1H), 1.84 (dqd, J = 14.8, 7.5, 4.3 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 136.3, 134.0, 130.8, 129.8, 127.6, 126.5, 90.4, 37.3, 27.0, 19.5, 10.5; FTIR (cm^{-1}): 2974, 2937, 1550, 1458, 1373, 745; GC/MS (EI) 193.3 $(M)^+$, 146.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO_2]^+$: 193.1103; found: 193.1111.

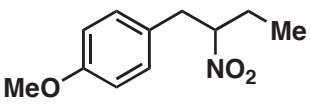


(**2.17**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 4-(*tert*-butyl)benzyl bromide (184 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.17** (196 mg, 83%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.35 – 7.29 (m, 2H), 7.12 – 7.06 (m, 2H), 4.62 (dddd, *J* = 9.7, 8.6, 6.0, 4.4 Hz, 1H), 3.24 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.99 (dd, *J* = 14.2, 6.0 Hz, 1H), 2.01 (ddq, *J* = 14.6, 9.4, 7.3 Hz, 1H), 1.84 (dqd, *J* = 14.8, 7.5, 4.3 Hz, 1H), 1.30 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 150.4, 132.7, 128.7, 125.9, 91.5, 39.4, 34.6, 31.4, 27.0, 10.4; FTIR (cm^{-1}): 2966, 2870, 1551, 1458, 1373; GC/MS (EI) 235.2 $(M)^+$, 188.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{14}H_{21}NO_2]^+$: 235.1572; found: 235.1557.



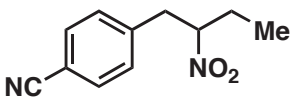
(**2.18**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-

butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 µL, 1.25 mmol), and 3-methoxybenzyl bromide (140 µL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.18** (171 mg, 82%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.22 (t, *J* = 8.0 Hz, 1H), 6.80 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.69 (t, *J* = 2.0 Hz, 1H), 4.63 (dddd, *J* = 9.7, 8.3, 6.0, 4.3 Hz, 1H), 3.79 (s, 3H), 3.24 (dd, *J* = 14.1, 8.5 Hz, 1H), 3.00 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.01 (ddq, *J* = 14.6, 9.8, 7.3 Hz, 1H), 1.84 (dqd, *J* = 14.8, 7.5, 4.3 Hz, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 159.9, 137.3, 130.0, 121.2, 114.8, 112.7, 91.4, 55.3, 39.9, 27.0, 10.4; FTIR (cm^{-1}): 2972, 2935, 1548, 1263, 1155, 1042, 781, 696; GC/MS (EI) 209.2 $(M)^+$, 162.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO_3]^+$: 209.1052; found: 209.1058.

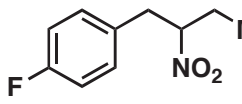


(**2.19**). According to general protocol A: CuBr (28.7 mg, 200 µmol), ligand **2.12** (76.6 mg, 250 µmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 µL, 1.25 mmol), and 4-methoxybenzyl bromide (146 µL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:2:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:2 hexanes : ethyl acetate) to afford nitroalkane **2.19** (141 mg, 67%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.07 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.58

(dddd, J = 9.7, 8.6, 5.8, 4.4 Hz, 1H), 3.78 (s, 3H), 3.19 (dd, J = 14.3, 8.6 Hz, 1H), 2.97 (dd, J = 14.3, 5.8 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.83 (dqd, J = 14.8, 7.5, 4.3 Hz, 1H), 0.97 (t, J = 7.4 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 158.9, 130.0, 127.7, 114.3, 91.8, 55.4, 39.1, 26.9, 10.4; FTIR (cm^{-1}): 2972, 1548, 1514, 1249, 1179, 1034; GC/MS (EI) 209.2 $(M)^+$, 162.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO_3]^+$: 209.1052; found: 209.1057.

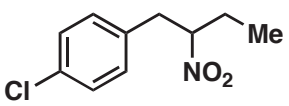


(**2.20**). According to general protocol B: CuBr (28.7 mg, 200 µmol), ligand **2.12** (76.6 mg, 250 µmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 µL, 1.25 mmol), and 4-cyanobenzyl bromide (196 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:10:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:10 hexanes : ethyl acetate) to afford nitroalkane **2.20** (147 mg, 72%) as a white solid (97% pure with trace bibenzyl byproduct): mp = 40–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.60 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.63 (tt, *J* = 9.4, 4.8 Hz, 1H), 3.30 (dd, *J* = 14.4, 9.4 Hz, 1H), 3.08 (dd, *J* = 14.4, 5.0 Hz, 1H), 2.11 – 1.97 (m, 1H), 1.86 (dqd, *J* = 14.7, 7.4, 4.7 Hz, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 141.2, 132.8, 129.8, 118.6, 111.6, 90.8, 39.6, 27.3, 10.3; FTIR (cm^{-1}): 2975, 2229, 1548, 1373, 863, 564; GC/MS (EI) 157.2 $(M–HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{13}N_2O_2]^+$: 205.0977; found: 205.0982.



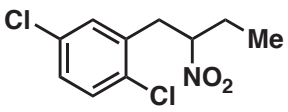
(**2.21**). According to general protocol A: CuBr (28.7 mg, 200

μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 4-fluorobenzyl bromide (125 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.21** (165 mg, 83%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.15 – 7.09 (m, 2H), 7.03 – 6.95 (m, 2H), 4.63 – 4.55 (m, 1H), 3.22 (dd, J = 14.3, 9.0 Hz, 1H), 3.01 (dd, J = 14.3, 5.5 Hz, 1H), 2.02 (ddq, J = 14.6, 9.4, 7.3 Hz, 1H), 1.84 (dqd, J = 14.8, 7.5, 4.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 162.2 (d, J = 245.9 Hz), 131.5 (d, J = 3.3 Hz), 130.5 (d, J = 8.1 Hz), 115.9 (d, J = 21.4 Hz), 91.6, 39.0, 27.0, 10.4; ^{19}F NMR (376 MHz, $CDCl_3$) ∂ -115.0 – -115.2 (m); FTIR (cm^{-1}): 2975, 1550, 1373, 1224, 825; GC/MS (EI) 196.9 $(M)^+$, 150.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{12}NO_2F]^+$: 197.0852; found: 197.0838.

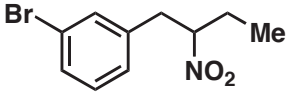


(**2.22**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 4-chlorobenzyl bromide (206 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.22** (169 mg, 79%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.28 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 4.63 –

4.55 (m, 1H), 3.22 (dd, J = 14.3, 9.0 Hz, 1H), 3.00 (dd, J = 14.3, 5.5 Hz, 1H), 2.02 (ddq, J = 14.6, 9.4, 7.3 Hz, 1H), 1.84 (dqd, J = 14.8, 7.5, 4.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 134.2, 133.5, 130.3, 129.1, 91.3, 39.1, 27.0, 10.4; FTIR (cm^{-1}): 2975, 1549, 1493, 1374, 1094, 1016, 805; GC/MS (EI) 166.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{12}NO_2Cl]^+$: 213.0556; found: 213.0546.

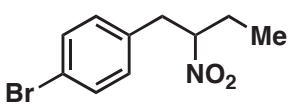


(**2.23**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 2,5-dichlorobenzyl bromide (240 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.23** (207 mg, 84%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.31 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 8.5, 2.5 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 4.75 (ddd, J = 14.0, 9.0, 5.1 Hz, 1H), 3.30 – 3.17 (m, 2H), 2.13 – 2.01 (m, 1H), 1.95 – 1.82 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 135.3, 133.1, 132.4, 131.3, 131.0, 129.3, 89.1, 37.3, 27.4, 10.4; FTIR (cm^{-1}): 2975, 1550, 1471, 1373, 1098, 815; GC/MS (EI) 247.2 $(M)^+$, 200.1 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{11}NO_2Cl_2]^+$: 247.0167; found: 247.0148.



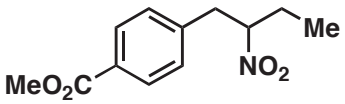
(**2.24**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-

butoxide (115 mg, 1.2 mmol), 3-bromobenzyl bromide (250 mg, 1.0 mmol), anhydrous hexanes (6 mL) and 1-nitropropane (112 μL, 1.25 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.24** (212 mg, 82%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.40 (ddd, *J* = 8.0, 1.7, 1.2 Hz, 1H), 7.32 (t, *J* = 1.7 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.12 – 7.05 (m, 1H), 4.66 – 4.56 (m, 1H), 3.23 (dd, *J* = 14.3, 8.9 Hz, 1H), 3.00 (dd, *J* = 14.3, 5.5 Hz, 1H), 2.02 (ddq, *J* = 14.6, 9.3, 7.3 Hz, 1H), 1.84 (dqd, *J* = 14.8, 7.5, 4.5 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 138.0, 132.0, 130.7, 130.5, 127.6, 122.9, 91.1, 39.3, 27.1, 10.4; FTIR (cm^{-1}): 2975, 1549, 1374, 1073, 780, 693; GC/MS (EI) 257.1 $(M)^+$, 210.1 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{12}NO_2Br]^+$: 257.0051; found: 257.0057.

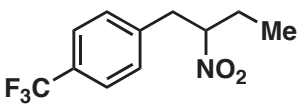


(**2.25**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 4-bromobenzyl bromide (250 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.25** (210 mg, 81%) as a white solid: mp = 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.43 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 4.64 – 4.54 (m, 1H), 3.21 (dd, J = 14.3, 9.0 Hz, 1H), 2.99 (dd, J = 14.3, 5.5

Hz, 1H), 2.02 (ddq, J = 14.6, 9.4, 7.3 Hz, 1H), 1.84 (dqd, J = 14.9, 7.6, 4.4 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 134.7, 132.1, 130.7, 121.6, 91.2, 39.2, 27.1, 10.4; FTIR (cm^{-1}): 2974, 1549, 1489, 1373, 1073, 1012, 801; GC/MS (EI) 257.0 $(M)^+$, 210.1 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{12}NO_2Br]^+$: 257.0051; found: 257.0067.

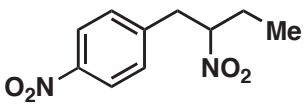


(**2.26**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium methoxide (64.8 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and methyl 4-(bromomethyl)benzoate (229 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:5:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:5 hexanes : ethyl acetate) to afford nitroalkane **2.26** (206 mg, 87%) as a clear oil (96% pure with trace bibenzyl byproduct): ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.98 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 4.69 – 4.60 (m, 1H), 3.92 (s, 3H), 3.31 (dd, J = 14.2, 9.0 Hz, 1H), 3.09 (dd, J = 14.2, 5.5 Hz, 1H), 2.04 (ddq, J = 14.6, 9.3, 7.3 Hz, 1H), 1.85 (dqd, J = 14.8, 7.5, 4.5 Hz, 1H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 167.2, 141.1, 130.3, 129.3, 129.1, 91.0, 52.4, 39.6, 27.1, 10.4; FTIR (cm^{-1}): 2953, 1721, 1550, 1436, 1282, 1181, 1111; GC/MS (EI) 190.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{12}H_{15}NO_4]^+$: 237.1001; found: 237.1020.



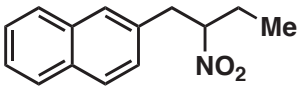
(**2.27**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-

butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 4-(trifluoromethyl)benzyl bromide (155 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.27** (200 mg, 81%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.57 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.69 – 4.60 (m, 1H), 3.32 (dd, J = 14.3, 9.1 Hz, 1H), 3.09 (dd, J = 14.3, 5.3 Hz, 1H), 2.05 (ddq, J = 14.6, 9.3, 7.3 Hz, 1H), 1.87 (dqd, J = 14.8, 7.5, 4.5 Hz, 1H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 139.8 (q, *J* = 1.1 Hz), 130.1 (q, *J* = 32.7 Hz), 129.4, 125.9 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.4 Hz), 91.0, 39.4, 27.2, 10.4; ^{19}F NMR (376 MHz, $CDCl_3$) ∂ –62.6 (s); FTIR (cm^{-1}): 1549, 1326, 1161, 1123, 1068, 863; GC/MS (EI) 200.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{11}F_3]^+$: 200.0813; found: 200.0821.

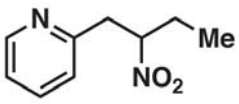


(**2.28**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 4-nitrobenzyl bromide (216 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:5:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:5 hexanes : ethyl acetate) to afford nitroalkane **2.28** (163 mg, 72%) as a clear oil (97% pure with trace bibenzyl byproduct): ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.16 (d, J = 8.6

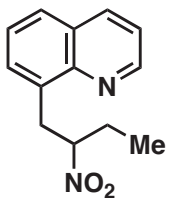
Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 4.67 (tt, J = 9.4, 4.7 Hz, 1H), 3.36 (dd, J = 14.4, 9.6 Hz, 1H), 3.14 (dd, J = 14.4, 4.9 Hz, 1H), 2.07 (ddq, J = 14.6, 9.3, 7.3 Hz, 1H), 1.90 (dqd, J = 14.8, 7.4, 4.6 Hz, 1H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 147.4, 143.2, 129.9, 124.2, 90.7, 39.3, 27.3, 10.3; FTIR (cm^{-1}): 2976, 1606, 1549, 1520, 1348, 870; GC/MS (EI) 224.1 $(M)^+$, 177.2 $(M–HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{13}N_2O_4]^+$: 225.0875; found: 225.0877.



(**2.29**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 2-(bromomethyl)naphthalene (221 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:1 hexanes : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.29** (164 mg, 72%) as a yellow solid: mp = 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.84 – 7.76 (m, 3H), 7.62 (s, 1H), 7.52 – 7.44 (m, 2H), 7.28 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.74 (dddd, *J* = 9.8, 8.6, 6.0, 4.3 Hz, 1H), 3.44 (dd, *J* = 14.2, 8.5 Hz, 1H), 3.20 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.08 (ddq, *J* = 14.6, 9.4, 7.3 Hz, 1H), 1.89 (dqd, *J* = 14.9, 7.5, 4.3 Hz, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 133.5, 133.2, 132.6, 128.7, 127.9, 127.79, 127.78, 126.8, 126.5, 126.1, 91.4, 40.0, 27.0, 10.4; FTIR (cm^{-1}): 2974, 1545, 1521, 1373, 817, 749; GC/MS (EI) 229.2 $(M)^+$, 182.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{14}H_{15}NO_2]^+$: 229.1103; found: 229.1118.

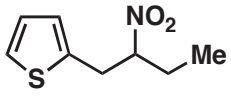


(**2.30**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (211 mg, 2.2 mmol), anhydrous benzene (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 2-(bromomethyl)pyridine hydrobromide (253 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography using 5-20 μm silica gel (100:10 hexanes : ethyl acetate**)** to afford nitroalkane **2.30** (134 mg, 74%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.54 (d, J = 4.0 Hz, 1H), 7.61 (td, J = 7.7, 1.5 Hz, 1H), 7.20 – 7.10 (m, 2H), 5.03 (tt, J = 9.3, 4.8 Hz, 1H), 3.44 (dd, J = 14.6, 9.3 Hz, 1H), 3.17 (dd, J = 14.6, 4.8 Hz, 1H), 2.05 (tt, J = 15.5, 7.4 Hz, 1H), 1.92 (dp, J = 14.6, 7.5, 5.0 Hz, 1H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 156.1, 149.8, 136.9, 123.8, 122.4, 89.4, 41.2, 27.4, 10.3; FTIR (cm^{-1}): 2974, 1592, 1549, 1476, 1439, 1375, 759; GC/MS (EI) 134.1 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{13}N_2O_2]^+$: 181.0977; found: 181.0982.

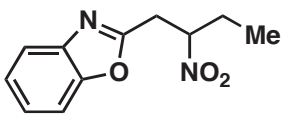


(**2.31**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and 8-(bromomethyl)-quinoline (222 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography using 5-20 μm silica gel (50:50 benzene : petroleum ether) to afford nitroalkane **2.31** (157 mg, 68%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 8.91 (dd, J = 4.2, 1.7 Hz, 1H), 8.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.74 (dd, J = 8.1, 1.4 Hz, 1H),

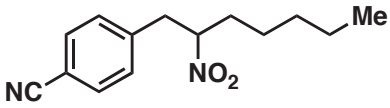
7.50 (d, J = 6.3 Hz, 1H), 7.47 – 7.39 (m, 2H), 5.14 (tt, J = 9.3, 4.5 Hz, 1H), 3.94 (dd, J = 13.6, 4.6 Hz, 1H), 3.56 (dd, J = 13.6, 9.6 Hz, 1H), 2.13 (ddq, J = 14.6, 9.4, 7.3 Hz, 1H), 1.99 (dqd, J = 14.7, 7.5, 4.4 Hz, 1H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 149.8, 146.6, 136.6, 134.5, 130.5, 128.5, 127.9, 126.4, 121.4, 91.0, 36.5, 27.7, 10.5; FTIR (cm^{-1}): 2970, 1547, 1499, 1373, 858, 794; GC/MS (EI) 230.1 $(M)^+$, 184.1 $(M–NO_2)^+$. HRMS (EI) m/z, calculated for $[C_{13}H_{14}N_2O_2]^+$: 230.1055; found: 230.1046.



(**2.32**). According to general protocol A: CuBr (28.7 mg, 200 µmol), ligand **2.12** (76.6 mg, 250 µmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous dioxane (6 mL), 1-nitropropane (112 µL, 1.25 mmol), and 2-(bromomethyl)thiophene (110 µL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:2:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:2 hexanes : ethyl acetate) to afford nitroalkane **2.32** (80 mg, 43%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.19 (dd, J = 5.2, 1.1 Hz, 1H), 6.94 (dd, J = 5.1, 3.5 Hz, 1H), 6.86 – 6.82 (m, 1H), 4.69 – 4.59 (m, 1H), 3.51 (dd, J = 15.2, 8.6 Hz, 1H), 3.24 (dd, J = 15.2, 5.5 Hz, 1H), 2.02 (ddq, J = 14.7, 9.1, 7.3 Hz, 1H), 1.89 (dqd, J = 14.8, 7.5, 4.5 Hz, 1H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 137.3, 127.3, 126.8, 125.0, 91.3, 33.7, 26.9, 10.3; FTIR (cm^{-1}): 2974, 1550, 1440, 1374, 858, 703; GC/MS (EI) 185.1 $(M)^+$, 138.1 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_8H_{11}NO_2S]^+$: 185.0511; found: 185.0517.

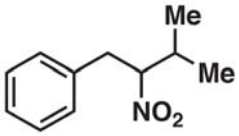


(**2.33**). According to general procedure A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium trimethylsilanolate (135 mg, 1.2 mmol), anhydrous benzene (6 mL), 1-nitropropane (112 μL, 1.25 mmol), and melted 2-bromomethyl-benzooxazole (132 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography using 5-20 μm silica gel (100:7:1 hexanes : diethyl ether : trifluoroacetic acid → 100:7 hexanes : diethyl ether) to afford nitroalkane **2.33** (183 mg, 83%) as a pale yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.74 – 7.70 (m, 1H), 7.55 – 7.51 (m, 1H), 7.40 – 7.35 (m, 2H), 5.07 (ddd, *J* = 13.6, 8.6, 5.1 Hz, 1H), 3.77 (dd, *J* = 16.3, 8.8 Hz, 1H), 3.45 (dd, *J* = 16.3, 5.0 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.09 – 2.01 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 162.4, 150.7, 139.7, 125.9, 125.2, 119.7, 111.0, 85.9, 31.7, 27.3, 10.0; FTIR (cm^{-1}): 2975, 1575, 1509, 1241, 1159, 747; GC/MS (CI) 174.1 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{13}N_2O_3]^+$: 221.0926; found: 221.0929.



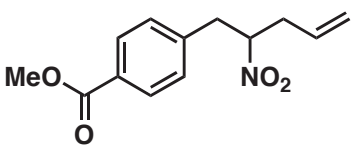
(**2.34**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 1-nitrohexane (174 μL, 1.25 mmol), and 4-cyanobenzyl bromide (196 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:8:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:8 hexanes : ethyl acetate) to afford nitroalkane **2.34** (176 mg, 71%) as a clear oil: ^{1}H

NMR (400 MHz, $CDCl_3$) ∂ 7.61 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 4.69 (tt, *J* = 9.5, 4.7 Hz, 1H), 3.30 (dd, *J* = 14.4, 9.5 Hz, 1H), 3.08 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.83 – 1.71 (m, 1H), 1.41 – 1.23 (m, 6H), 0.91 – 0.84 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 141.2, 132.8, 129.8, 118.6, 111.6, 89.5, 39.9, 33.9, 31.1, 25.5, 22.4, 14.0; FTIR (cm^{-1}): 2957**,** 2930, 2229, 1550, 1506, 565; GC/MS (EI) 199.3 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{14}H_{19}N_2O_2]^+$: 247.1447; found: 247.1443.

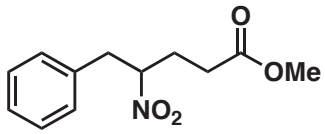


(**2.35**). CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), and sodium *tert*-butoxide (115 mg, 1.2 mmol) were added to a 25 mL Schlenk flask equipped with stir bar. The flask was sealed with a rubber septum, attached to a double manifold, and evacuated and backfilled with nitrogen five times. Anhydrous dioxane (6 mL) was added and the resulting mixture was heated in a 60 °C oil bath with rapid stirring for 5 h. 2-methyl-1-nitropropane (135 μL, 1.25 mmol) and benzyl bromide (120 μL, 1.0 mmol) were then added and the resulting viscous mixture was allowed to continue heating at 60 °C with rapid stirring for 24 h. The flask was then cooled to rt, opened to air, and the reaction mixture was diluted with diethyl ether (20 mL). The solution was washed twice with saturated ammonium chloride (25 mL) and once with brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.35** (126 mg, 65%) as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) ∂ 7.33 – 7.22 (m, 3H), 7.17 – 7.13 (m, 2H), 4.50 (ddd, *J* = 11.0, 7.4, 3.9 Hz, 1H), 3.21 (dd, *J* = 14.5, 10.6 Hz, 1H), 3.10 (dd, *J* = 14.5, 3.9 Hz,

1H), 2.31 – 2.17 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 136.2, 128.9, 128.8, 127.4, 96.2, 37.2, 32.4, 19.2, 18.9; FTIR (cm^{-1}): 2971, 1548, 1456, 1374, 699; GC/MS (EI) 146.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO_2]^+$: 193.1103; found: 193.1084.

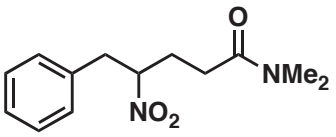


(**2.36**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium methoxide (64.8 mg, 1.2 mmol), anhydrous hexanes (6 mL), 4-nitro-1-butene (128 μL, 1.25 mmol), and methyl 4-(bromomethyl)benzoate (229 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:3:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:3 hexanes : ethyl acetate) to afford nitroalkane **2.36** (179 mg, 72%) as a white solid: mp = 52–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.98 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 5.78 – 5.66 (m, 1H), 5.22 – 5.14 (m, 2H), 4.76 (tt, J = 8.8, 5.3 Hz, 1H), 3.91 (s, 3H), 3.32 (dd, J = 14.3, 9.0 Hz, 1H), 3.12 (dd, J = 14.3, 5.4 Hz, 1H), 2.78 – 2.68 (m, 1H), 2.61 – 2.53 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 166.9, 140.7, 131.1, 130.3, 129.5, 129.1, 120.3, 88.8, 52.4, 39.2, 37.8; FTIR (cm^{-1}): 2953, 1721, 1552, 1436, 1282, 1182, 1112, 764**;** GC/MS (EI) 202.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{13}H_{15}NO_4]^+$: 249.1001; found: 249.0994.



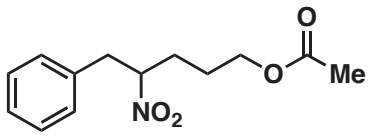
(**2.37**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium methoxide (64.8 mg, 1.2 mmol), anhydrous hexanes (6

mL), methyl 4-nitrobutyrate (160 µL, 1.25 mmol), and benzyl bromide (120 µL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 6 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:5:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:5 hexanes : ethyl acetate) to afford nitroalkane **2.37** (150 mg, 63%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.35 – 7.24 (m, 3H), 7.16 (d, J = 7.1 Hz, 2H), 4.86 – 4.74 (m, 1H), 3.69 (s, 3H), 3.29 (dd, J = 14.2, 8.4 Hz, 1H), 3.07 (dd, J = 14.2, 5.9 Hz, 1H), 2.49 – 2.11 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 172.7, 135.2, 129.02, 128.99, 127.7, 88.8, 52.2, 40.2, 30.1, 28.3; FTIR (cm^{-1}): 1734, 1550, 1437, 1364, 1202, 701; GC/MS (EI) 190.2 $(M–HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{16}NO_4]^+$: 238.1079; found: 238.1084.

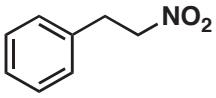


(**2.38**). According to general protocol A: CuBr (28.7 mg, 200 µmol), ligand **2.12** (76.6 mg, 250 µmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous dioxane (6 mL), N,N-dimethyl-4-nitro-butanamide (181 µL, 1.25 mmol), and benzyl bromide (120 µL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (50:50:1 hexanes : ethyl acetate : trifluoroacetic acid → 50:50 hexanes : ethyl acetate) to afford nitroalkane **2.38** (194 mg, 77%) as a green oil: ^{1}H NMR (400 MHz, DMSO) ∂ 7.33 – 7.16 (m, 5H), 5.00 – 4.90 (m, 1H), 3.15 (qd, *J* = 14.3, 7.2 Hz, 2H), 2.89 (s, 3H), 2.79 (s, 3H), 2.38 – 2.30 (m, 2H), 2.11 – 2.03 (m, 2H); ^{13}C NMR (101 MHz, DMSO) ∂ 170.1, 135.9, 128.7, 128.4, 126.9, 88.9, 36.3, 34.7, 28.5, 28.2; FTIR (cm^{-1}): 1653, 1549, 1200, 1147, 701; GC/MS (CI) 251.2 $(M+H)^+$

204.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{13}H_{19}N_2O_3]^+$: 251.1396; found: 251.1403.

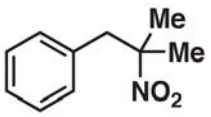


(**2.39**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous hexanes (6 mL), 4-nitrobutyl acetate (175 μL, 1.25 mmol), and benzyl bromide (120 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (100:5:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:5 hexanes : ethyl acetate) to afford nitroalkane **2.39** (171 mg, 68%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.35 – 7.25 (m, 3H), 7.18 – 7.13 (m, 2H), 4.73 (dddd, *J* = 9.9, 8.6, 6.1, 4.0 Hz, 1H), 4.15 – 4.02 (m, 2H), 3.28 (dd, *J* = 14.1, 8.4 Hz, 1H), 3.04 (dd, *J* = 14.1, 6.0 Hz, 1H), 2.16 – 2.02 (m, 4H), 1.92 – 1.80 (m, 1H), 1.75 – 1.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 172.3, 135.3, 129.03, 128.98, 127.7, 89.5, 63.7, 40.2, 30.0, 25.0, 21.0; FTIR (cm^{-1}): 1734**,** 1550, 1507, 1457, 1240, 668; GC/MS (EI) 204.2 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{13}H_{18}NO_4]^+$: 252.1236; found: 252.1250.



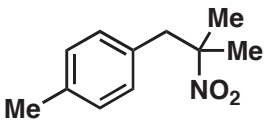
(**2.40**). According to general protocol A: CuBr (28.7 mg, 200 μmol), ligand **2.12** (61.3 mg, 200 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous dioxane (6 mL), nitromethane (403 μL, 7.5 mmol), and benzyl bromide (120 μL, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 4 h. The reaction was worked up according to the general

protocol and purified by flash silica chromatography (100:2:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:2 hexanes : ethyl acetate) to afford nitroalkane **2.40** (110 mg, 73%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.40 – 7.25 (m, 3H), 7.24 – 7.17 (m, 2H), 4.62 (t, *J* = 7.4 Hz, 2H), 3.33 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 135.8, 129.1, 128.7, 127.6, 76.4, 33.6; FTIR (cm^{-1}): 3032, 1551, 1497, 1456, 1378, 699**;** GC/MS (EI) 151.1 $(M)^+$. HRMS (EI) m/z, calculated for $[C_8H_9O_2N]^+$: 151.0633; found: 151.0629.

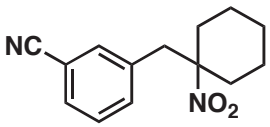


(**2.41**). CuBr (86.1 mg, 600 μmol), ligand **2.12** (184 mg, 600 μmol), and sodium *tert*-butoxide (346 mg, 3.6 mmol) were added to a 50 mL Schlenk flask equipped with stir bar. The flask was sealed with a rubber septum, attached to a double manifold, and evacuated and backfilled with nitrogen five times. Anhydrous cyclohexane (15 mL) was added and the resulting mixture was heated in a 60 °C oil bath with rapid stirring for 1 h. 2-Nitropropane (310 μL, 3.45 mmol) and benzyl bromide (359 μL, 3.0 mmol) were then added and the resulting viscous mixture was allowed to continue heating at 60 °C with rapid stirring for 48 h. The flask was then cooled to rt, opened to air, and the reaction mixture was diluted with diethyl ether (60 mL). The solution was washed twice with saturated ammonium chloride (75 mL) and once with brine (75 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.41** (394 mg, 73%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.33 – 7.27 (m, 3H), 7.13 – 7.09 (m, 2H), 3.20 (s, 2H), 1.58 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 135.0, 130.2, 128.6, 127.6, 88.8, 46.9,

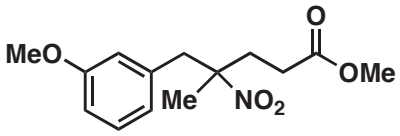
25.7; FTIR (cm^{-1}): 2990, 1538, 1456, 1397, 1349, 702; GC/MS (EI) 179.1 $(M)^+$, 132.1 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{10}H_{13}NO_2]^+$: 179.0946; found: 179.0937.



(**2.42**). CuBr (86.1 mg, 600 μmol), ligand **2.12** (184 mg, 600 μmol), and sodium *tert*-butoxide (346 mg, 3.6 mmol) were added to a 50 mL Schlenk flask equipped with stir bar. The flask was sealed with a rubber septum, attached to a double manifold, and evacuated and backfilled with nitrogen five times. Anhydrous cyclohexane (15 mL) was added and the resulting mixture was heated in a 60 °C oil bath with rapid stirring for 1 h. 2-Nitropropane (310 μL, 3.45 mmol) and 4-methylbenzyl bromide (419 μL, 3.0 mmol) were then added and the resulting viscous mixture was allowed to continue heating at 60 °C with rapid stirring for 48 h. The flask was then cooled to rt, opened to air, and the reaction mixture was diluted with diethyl ether (60 mL). The solution was washed twice with saturated ammonium chloride (75 mL) and once with brine (75 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (100:1:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:1 hexanes : ethyl acetate) to afford nitroalkane **2.42** (409 mg, 71%) as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) ∂ 7.10 (d, J = 7.7 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 3.15 (s, 2H), 2.32 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 137.3, 132.0, 130.1, 129.3, 88.8, 46.5, 25.7, 21.2; FTIR (cm^{-1}): 2988, 2925, 1539, 1516, 1396, 1372, 1348, 793; GC/MS (EI) 193.1 $(M)^+$, 146.1 $(M–HNO_2)^+$. HRMS (EI) m/z, calculated for $[C_{11}H_{15}NO_2]^+$: 193.1103; found: 193.1097.

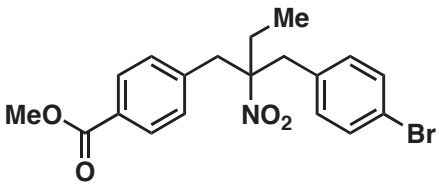


(**2.43**). According to general protocol B: CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium *tert*-butoxide (115 mg, 1.2 mmol), anhydrous dioxane (6 mL), nitrocyclohexane (154 μL, 1.25 mmol), and 3-cyanobenzyl bromide (196 mg, 1.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography using 5-20 μm silica gel (5% EtOAc in hexanes with 0.1M trifluoroacetic acid) to afford nitroalkane **2.43** (178 mg, 73%) as a white solid: mp = 63–64 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.57 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.35 (s, 1H), 7.27 (d, J = 8.7 Hz, 1H), 3.12 (s, 2H), 2.38 (d, J = 13.3 Hz, 2H), 1.71 – 1.58 (m, 5H), 1.45 – 1.35 (m, 2H), 1.35 – 1.28 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 135.8, 134.4, 133.4, 131.4, 129.5, 118.6, 112.6, 91.7, 46.3, 34.0, 24.7, 22.3; FTIR (cm^{-1}): 2940, 2230, 1535, 1449, 1345, 692; GC/MS (EI) 198.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{17}N_2O_2]^+$: 245.1290; found: 245.1284.



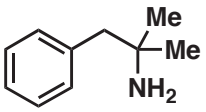
(**2.44**). In a nitrogen glovebox, CuBr (14.3 mg, 100 μmol), ligand **2.12** (38.3 mg, 125 μmol), sodium trimethylsilanolate (67.3 mg, 600 μmol), and anhydrous cyclohexane (3 mL) were added to a dry threaded 16 mm test tube equipped with a stir bar. The tube was sealed with a Telfon lined cap and heated in an aluminum block on a temperature controlled stir plate to 60°C with vigorous stirring for 1 hour. After the allotted time, the reaction was removed from the aluminum block and allowed to cool to rt. Once cooled, methyl 4-nitropentanoate (82 μL, 575 μmol) and 3-methoxybenzyl bromide (70 μL, 500 μmol) were added to the reaction vessel.

The reaction was returned to the aluminum block and heated to 60 °C with rapid stirring for 24 h. The reaction was then removed from the glovebox, allowed to cool to rt, and exposed to air. The solution was diluted with diethyl ether (10 mL), washed twice with saturated ammonium chloride (10 mL), and once with brine (10 mL). The organic layer was dried with magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (100:3:1 hexanes : ethyl acetate : trifluoroacetic acid → 100:3 hexanes : ethyl acetate) to afford nitroalkane **2.44** (74.5 mg, 53%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.21 (t, *J* = 7.9 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 6.63 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.33 (d, *J* = 13.9 Hz, 1H), 3.03 (d, *J* = 13.9 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.42 – 2.26 (m, 2H), 2.16 – 2.10 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 172.6, 159.6, 135.7, 129.6, 122.4, 115.9, 112.9, 91.0, 55.2, 52.0, 46.2, 34.2, 28.9, 21.3; FTIR (cm^{-1}): 2870, 1734, 1540, 1507, 1457, 1143; GC/MS (CI) 281.1 $(M)^+$, 235.1 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{19}NO_5]^+$: 281.1263; found: 281.1257.



(**2.45**). CuBr (28.7 mg, 200 μmol), ligand **2.12** (76.6 mg, 250 μmol), sodium methoxide (64.8 mg, 1.2 mmol), nitroalkane **2.25** (323 mg, 1.25 mmol), and methyl 4-(bromomethyl)benzoate (229 mg, 1.0 mmol) were added to a 25 mL Schlenk flask equipped with stir bar. The flask was sealed with a rubber septum, attached to a double manifold, and evacuated and backfilled with nitrogen five times. Anhydrous dioxane (6 mL) was added and the resulting mixture was heated in a 60 °C oil bath with rapid stirring for 48 h. The flask was then cooled to rt, opened to air, and the reaction mixture was diluted with diethyl

ether (20 mL). The solution was washed twice with saturated ammonium chloride (25 mL) and once with brine (25 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash silica chromatography (70:30:1 petroleum ether : benzene : trifluoroacetic acid → 60:40 petroleum ether : benzene). The resulting residue was washed with hexanes to afford nitroalkane **2.45** (264 mg, 65%) as a white solid: mp = 92–93 °C; ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 7.97 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 3.91 (s, 3H), 3.44 (d, *J* = 14.4 Hz, 1H), 3.36 (d, *J* = 14.5 Hz, 1H), 3.21 (d, *J* = 14.4 Hz, 1H), 3.13 (d, *J* = 14.5 Hz, 1H), 1.81 (q, *J* = 7.4 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) ∂ 166.8, 139.8, 133.5, 132.0, 131.7, 130.1, 130.0, 129.8, 122.0, 95.7, 52.3, 42.1, 41.7, 25.5, 9.0; FTIR (cm^{-1}): 2949, 1719, 1539, 1281, 1110; GC/MS (CI) 406.1 $(M)^+$, 359.1 $(M–HNO_2)^+$**.** HRMS (CI) m/z, calculated for $[C_{19}H_{20}NO_4Br]^+$: 405.0576; found: 405.0590.



(**2.46**). Nitroalkane **2.41** (179 mg, 1.0 mmol) and methanol were added to a 25 mL recovery flask equipped with stir bar. Using a T joint adapter the flask was evacuated and backfilled with nitrogen several times. The adapter was removed and Palladium on carbon was quickly added. The adapter was replaced and the flask was evacuated and backfilled five times with nitrogen. A hydrogen balloon was added to the T joint and the flask was evacuated and backfilled ten times with hydrogen. The resulting suspension was heated in a 40 °C oil bath for 24 h. The flask was then cooled to rt, vented, and the suspension was poured through a fritted funnel with celite. The solution was concentrated *in vacuo* to afford amine **2.46** (146 mg, 98%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 7.34 –

7.15 (m, 5H), 2.66 (s, 2H), 1.26 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 138.5, 130.5, 128.0, 126.3, 51.1, 50.1, 30.4; FTIR (cm^{-1}): 2962, 1452, 1386, 1381, 854, 724, 702; ESI+ 150.0 $(M+H)^+$. HRMS (QTOF) m/z, calculated for $[C_{10}H_{16}N]^+$: 150.1283; found: 150.1281.

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(9) In all cases, the alkylation reactions are heterogeneous, which we believe is due to the low solubility of the nitronate anions in the apolar media. We believe that the failure of the reactions involving lithium salts stems from the very low solubility of the lithium nitronates.

(10) Screening reactions were set up inside a nitrogen-filled glovebox. The use of NaOtBu, due to its limited hydroscopicity compared to KOtBu, also allowed the reactions to be performed on the bench, using standard Schlenk techniques. With the exception of 38, all isolated yields refer to reactions run on the bench. All reported isolated yields are the average of at least two independent experiments.

(11) Lower catalyst loading resulted in lower yields.

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(13) In some cases, particularly those involving more polar substrates, pre-forming the catalyst in situ, the use of alternative solvents, such as 1,4-dioxane, or weaker bases, such as sodium silanolate, proved superior to the standard conditions. When substrates contained methyl esters, sodium methoxide was used as the base.

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(15) The reaction providing 38 proved very sensitive to oxygen and was performed in a nitrogen-filled glovebox.

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Chapter 3

A GENERAL ROUTE FOR PREPARING β-NITROCARBONYL COMPOUNDS USING COPPER THERMAL REDOX CATALYSIS

3.1 Synthesis of α-Nitrocarbonyls

Among nitroalkanes, nitrocarbonyl compounds are a particularly interesting class, as the two functionalities have widely orthogonal reactivity, making them highly versatile intermediates in complex molecule synthesis.[1] α-Nitrocarbonyls can be easily prepared by acylation of a nitronate anion.[2] In 1982, the Mosher group published a route to α-nitroketones and -esters by the addition of nitronates to aromatic and aliphatic acylimidazoles. Good yields of the resulting α-nitrocarbonyls are obtained when using the lithium salts of primary nitronates (Figure 3.1).[2c] The Katritzky group later published an improved method to the same classes of products using *N*-acylbenzotriazoles to acylate primary nitroalkanes.[2d] The *N*-acylbenzotriazoles, readily available from the parent carboxylic acid in a single step, react with nitroalkanes deprotonated *in situ* with potassium *tert*-butoxide in good yield (Figure 3.2). *N*-acylbenzotriazoles from aliphatic, aromatic, heteroaromatic, and *N*-protected α-amino carboxylic acids all readily alkylate a range of primary nitroalkanes allowing access to a wide range of α-nitrocarbonyls.

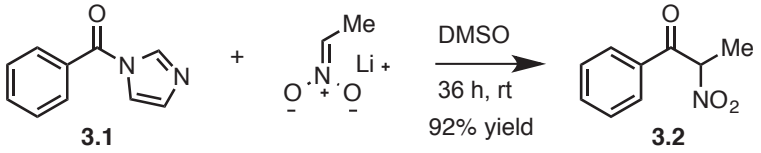


Figure 3.1: Mosher's formation of α-nitro ketone **3.2**

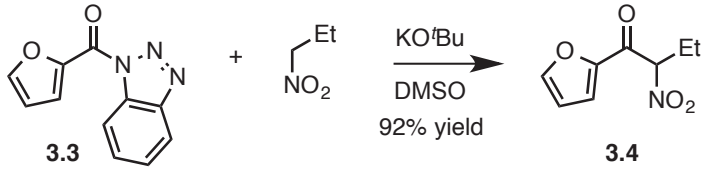


Figure 3.2: Katritzky Acylation of 1-Nitropropane with *N*-Acylbenzotriazole **3.3**

A less general method of accessing α-nitrocarbonyls involves nitration of a carbonyl. Kornblum found that α-iodoesters undergo substitution with silver nitrite in good yield (Figure 3.3).[3] Nitration of cyclic 1,3-diones[4] by dropwise addition of nitric acid leads to α-nitrodiones in moderate yield as in the conversion of tetrahydroindan-1,3-dione **3.7** to α-nitrodione **3.8** by the Buckle group (Figure 3.4).[5] Due to the high cost of silver nitrite and low stability of alkyl iodides in addition to the impractical use of nitric acid, α-nitrocarbonyls are typically accessed through the acylation method discussed above (Figures 3.1 and 3.2).

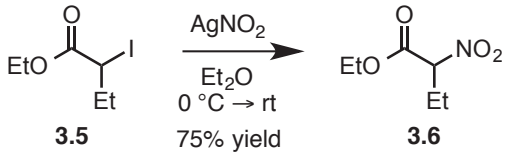


Figure 3.3: Kornblum's nitration of α-iodoesters

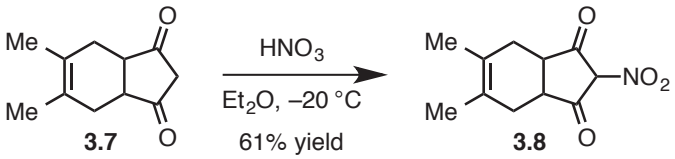


Figure 3.4: Nitration of cyclic 1,3-diones with nitric acid

3.2 Synthesis of γ-Nitrocarbonyls

Routes to γ-nitrocarbonyls are similarly well established by conjugate addition of a nitronate anion to an α,β-unsaturated carbonyl.[6] Ongoing efforts in this reaction class are aimed at improving enantioselectivity and efficiency. An elegant example by the Jacobsen group in 2005 demonstrated the potential of chiral (salen)Al complex **3.11** to catalyze the addition of nitroalkanes to α,β-unsaturated ketones in high yield and excellent enantioselectivity (Figure 3.5).[7]

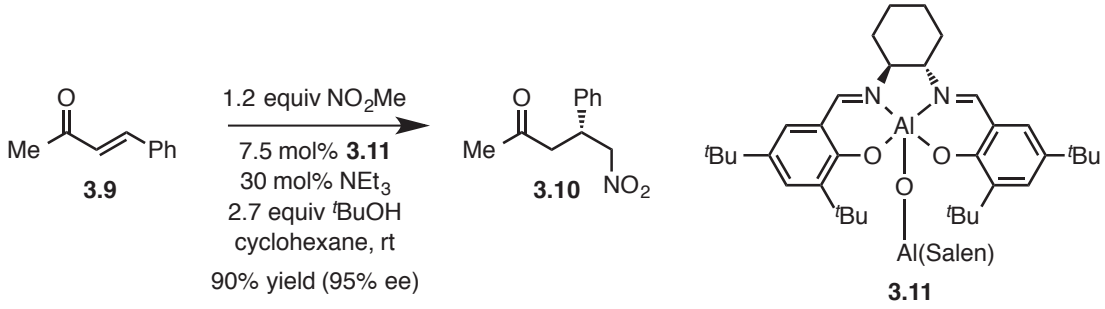


Figure 3.5: Jacobsen's enantioselective addition of nitroalkanes to α,β-unsaturated ketones

The Michael addition of an enolate to a nitroalkene is another route to γ-nitrocarbonyls that has received considerable attention.[8] Many chiral secondary amines have been investigated to catalyze the Michael addition of carbonyls to

aliphatic and aromatic nitroalkenes. One such general example from the Ma group in 2008 used trimethylsilyl-protected di-phenylprolinol **3.15** to catalyze the formation of a wide range of γ-nitroaldehydes in excellent yield, diastereoselectivity, and enantioselectivity (Figure 3.6).[9]

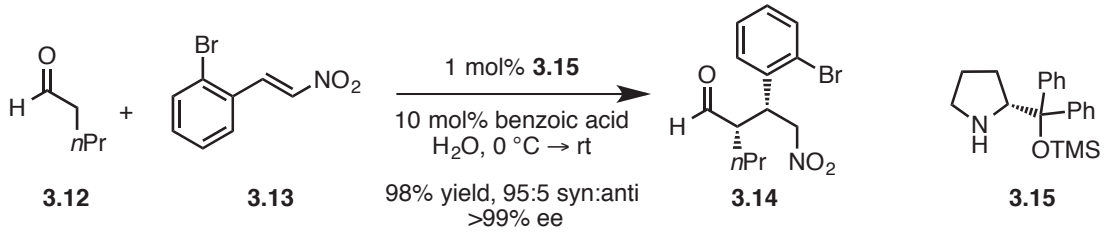


Figure 3.6: Ma's enantioselective and diastereoselective addition of aldehydes to nitroalkenes

3.3 Limited Routes to β-Nitrocarbonyls

In contrast, however, the synthesis of β-nitrocarbonyls is considerably more challenging (Figure 3.7). In 1970, Kornblum demonstrated that several examples of tertiary α-nitrocarbonyls can undergo coupling with nitronate anions to prepare β-nitroesters and ketones (Figure 3.8).[10] The reactions to form β-nitroesters were set up with exposure to a 20 W fluorescent light source, with significantly slower rates observed for reactions run in darkness. For the formation of β-nitroketones no significant difference was observed when switching from a light source to darkness. These conditions have not been widely adopted, possibly due to the need for preparation of α-nitrocarbonyl starting materials.

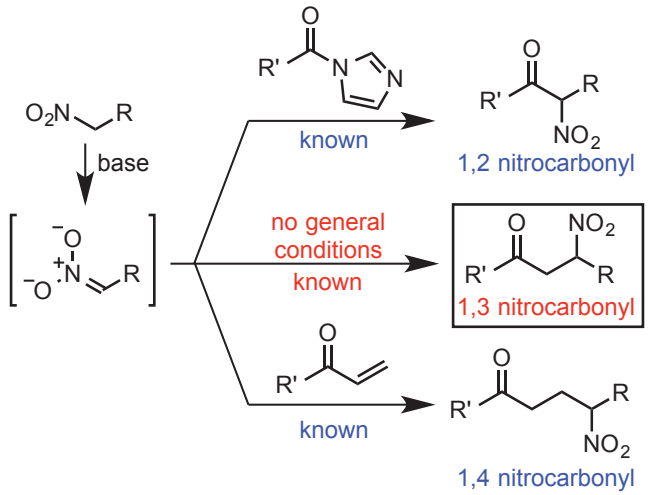


Figure 3.7: Synthesis of nitrocarbonyl compounds

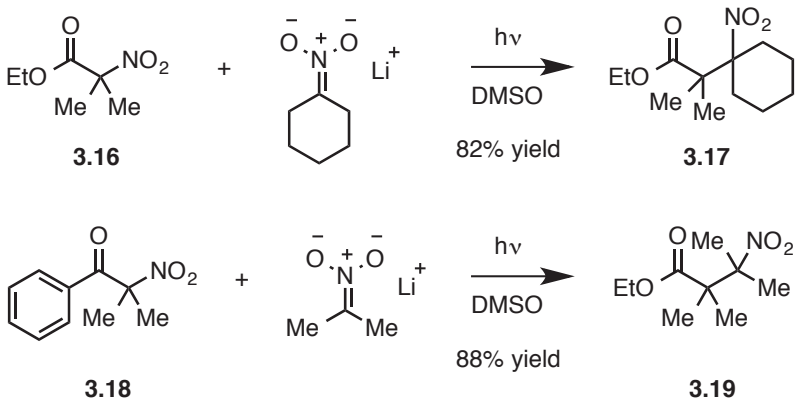
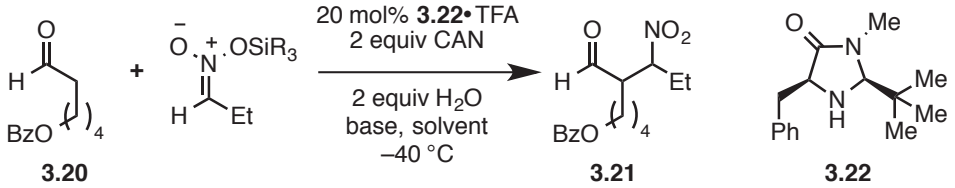


Figure 3.8: Kornblum photolytic alkylation of nitronates with tertiary α-nitroketones and –esters

More recently, MacMillan reported the enantioselective α-nitroalkylation of aldehydes using silylnitronates and organo-SOMO catalysis (Table 3.1). Interestingly depending on the lability of the silyl group in the reaction conditions, good selectivity for either the anti or syn diastereomer is achieved. The reaction conditions are altered such that the silyl group is maintained for the C-C bond-forming step leading to

preferential formation of the anti diastereomer (entry 1) or the silyl group is cleaved from the nitronate before the C-C bond forming step, which leads to the syn diastereomer preferentially. While this latter method is extremely elegant and efficient, it is limited to preparation of β-nitroaldehydes.[11]

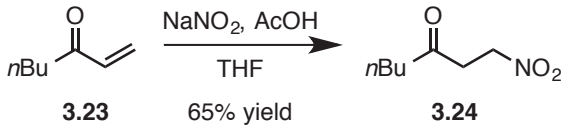
Table 3.1: MacMillan's α-nitroalkylation of primary aldehydes



entry	SiR_3	base	solvent	yield **3.21** (anti:syn)	ee (%)
1	TIPS	$NaHCO_3$	THF	78% (4:1)	90
2	TBS	NaO_2CCF_3	acetone	74% (1:6)	94

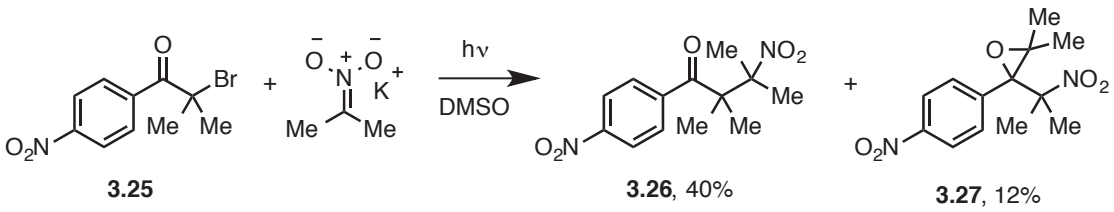
A few additional sundry methods exist to access β-nitrocarbonyls. The Miyakoshi group used sodium nitrite to add to several alkyl vinyl ketones in moderate yield to access unsubstituted β-nitroketones (Figure 3.9).[12] In 1982, Russell published the alkylation of the potassium salt of 2-nitropropane with electron poor α-halobenzophenones using photolytic conditions in low yields (Figure 3.10).[13] Competitive oxirane formation supports the proposed radical mechanism established by Kornblum.[14] Alternatively for accessing β-nitroketones the Ioffe group published a convergent multi-step sequence. Addition of ammonium fluoride initiates the coupling of nitronate **3.28** with disilylated **3.29** (previously prepared) to give β-nitrooxime **3.30**

(Figure 3.11). Subsequent treatment with Jones' Reagent gives the β-nitroketone **3.31**.[15] Beyond these limited methods, to date no general method has been reported for the preparation of β-nitrocarbonyls that is both general for a wide variety of carbonyl groups with varying substitution and proceeds under synthetically tractable conditions.



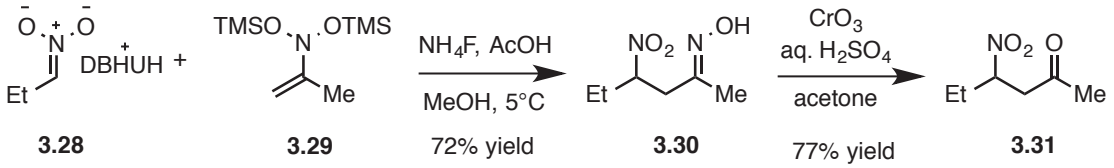
3.23 **3.24**

Figure 3.9: Sodium nitrite addition to alkyl vinyl ketones



3.25 **3.26**, 40% **3.27**, 12%

Figure 3.10: Russell alkylation of nitronates with α-haloketones



3.28 **3.29** 72% yield **3.30** 77% yield **3.31**

Figure 3.11: Ioffe group multi-step synthesis of β-nitroketones

3.4 Copper-Catalyzed Synthesis of β-Nitrocarbonyls: Our Work

One potential entry to β-nitrocarbonyls involves the alkylation of a nitronate anion by a readily available α-bromocarbonyl compound. However, this reaction has been shown to lead to a complex mixture of products, presumably due to the strong

preference for nitronate-anions to undergo alkylation at oxygen in reactions involving alkyl halide electrophiles (Figure 3.12, top).[10, 16,17]

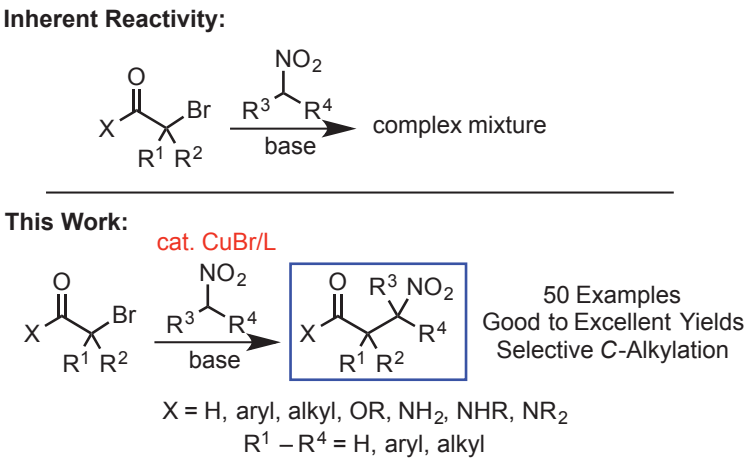


Figure 3.12: Alkylation of nitroalkanes using α-bromocarbonyls

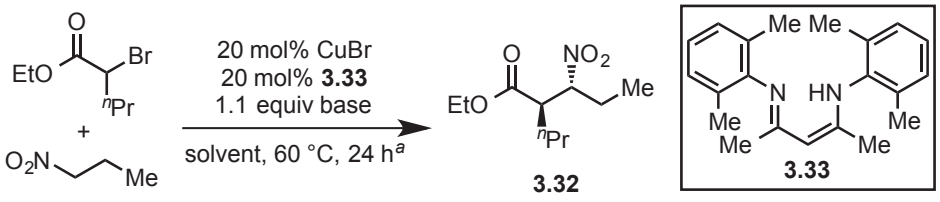
In Chapter 2 I discussed our first report of a simple copper catalyst, prepared *in situ* from copper bromide and a 1,3-diketimine (nacnac) ligand, that successfully catalyzes the *C*-alkylation of nitroalkanes using benzyl bromides.[18] I believe this reaction proceeds via a benzyl-stabilized radical, which suggests that other alkyl bromides bearing radical-stabilizing groups might be viable coupling partners for the reaction. Towards this end, together with Amber Gietter and Andrew Cinderella, I explored the potential coupling of α-bromocarbonyls with nitroalkanes in the presence of our previously utilized copper catalyst.

3.5 Optimizing Reaction Conditions

I began by studying the reaction of ethyl 2-bromovalerate with 1-nitropropane (Table 3.2). Starting with the optimized conditions for alkylation of nitroalkanes using

benzyl bromides (20 mol % CuBr, 20 mol% diketimine **3.33**, NaOEt, benzene, 60 °C), I was pleased to observe a 75% yield of the desired product **3.32** (entry 1). The nitroester was observed as a 58:42 mixture of diastereoisomers, which was later shown to favor the erythro-isomer, as shown (see below). In the absence of catalyst, none of the desired product was observed (entry 2). When $NaOSiMe_3$ was used as the base, **3.32** was observed in 92% yield (89% isolated yield) with a similar diastereomeric ratio as above (entry 3). Further studies revealed that the reaction was tolerant of a range of solvents. Whereas, non-polar solvents generally provided the highest yields, moderate to good yields were observed in all but the most polar solvents investigated (entries 4-9). Particularly effective solvents include benzene, hexanes, and methylene chloride, all of which provide excellent yield in the model reaction. In subsequent studies benzene proved to be the most general solvent, and was therefore used most often. In many cases, however, hexanes could also be employed. For the sake of comparison, yields in both solvents are reported in some of the studied examples described below. In a few cases, often those involving more polar substrates, other solvents such as dioxane, cyclohexane, or methylene chloride provided superior yields. These cases are denoted in the tables.

Table 3.2: Optimization of reaction conditions



entry	base	solvent	yield **3.32**[b]	dr [b]
1	NaOEt	benzene	75%	58:42
2	NaOEt	benzene	0%[c]	n/a
3	$NaOSiMe_3$	benzene	92% (89%)	59:41
4	$NaOSiMe_3$	toluene	69%	61:39
5	$NaOSiMe_3$	hexanes	94% (90%)	62:38
6	$NaOSiMe_3$	Et_2O	68%	62:38
7	$NaOSiMe_3$	dioxane	77%	56:44
8	$NaOSiMe_3$	CH_2Cl_2[d]	96% (94%)	62:38
9	$NaOSiMe_3$	DMF	4%	~50:50

[a]1.2 equiv 1-nitropropane; [b]Yield and diastereomeric ratio (dr) determined by NMR using 1,3,5-trimethoxybenzene or mesitylene as an internal standard, parenthetical yields are isolated yields of pure material; [c]No copper, no ligand; [d]40 °C.

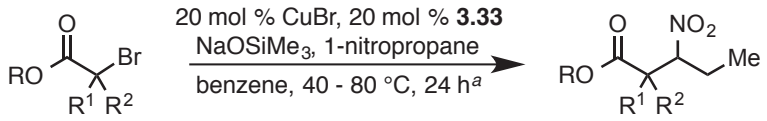
3.6 Reaction Scope with Respect to α-Bromoesters

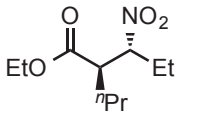
The optimized reaction conditions are highly general for the preparation of β-nitrocarbonyl compounds. As shown in Table 3.3, a broad range of α-bromoesters bearing diverse substitution and functionality participate in the reaction. Branching and aromatic substitution at the α-position (**3.34** and **3.35**) do not adversely affect the yield of the reaction. Both primary and tertiary α-bromoesters are also effective substrates. With primary substrates (**3.36** and **3.40**) I have found that increased catalyst loading is required to achieve good yields. I assume this relates to the difficultly in

forming a primary radical intermediate. However, given the cost of the catalyst, I do not believe this to be a serious impediment.

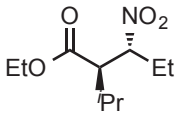
In contrast, tertiary α-bromoesters react very smoothly with standard catalyst loadings to provide highly substituted β-nitroesters (e.g. **3.37** and **3.38**). A variety of esters can also can be used in the reaction, including methyl (**3.39**), *tert*-butyl (**3.40** and **3.41**), and benzylic esters (**3.42**, **3.43** and **3.45**). Finally, β-nitrolactones can also be prepared using this route (**3.44**).

Table 3.3: Scope with respect to α-bromoesters

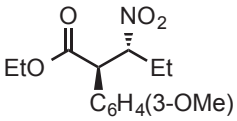




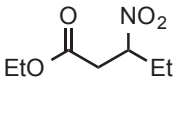
3.32, 89% (59:41)
90% (62:38, hexanes)



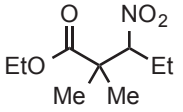
3.34, 82%
(64:36, CH_2Cl_2)



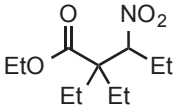
3.35, 61%
(36:64, hexanes)



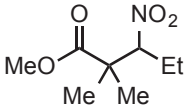
3.36, 68% (CH_2Cl_2)[b]



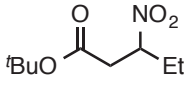
3.37, 72%
77% (hexanes)



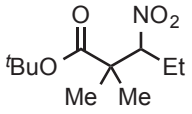
3.38, 72%



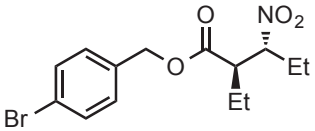
3.39, 70%



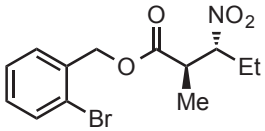
3.40, 52% (CH_2Cl_2)[b]



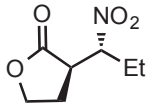
3.41, 70%



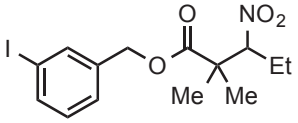
3.42, 85% (59:41)



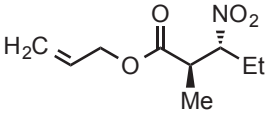
3.43, 81% (56:44)



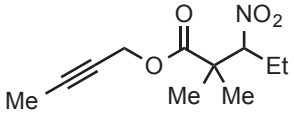
3.44, 78% (48:52, CH_2Cl_2)
X-ray of minor



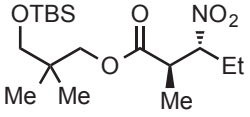
3.45, 81%



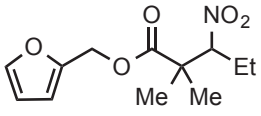
3.46, 47% (57:43)[c]



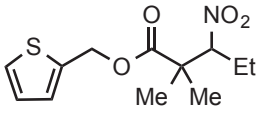
3.47, 64%



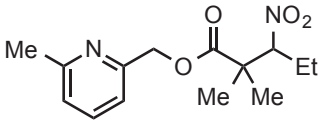
3.48, 84% (60:40)



3.49, 67% (*4g scale)*



3.50, 67%



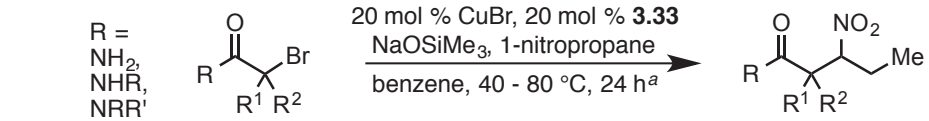
3.51, 80%

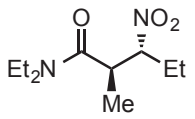
[a] Conditions: 1 equiv α-bromocarbonyl, 1.2 - 1.4 equiv nitroalkane, 20 mol % CuBr, 20 mol % **3.33**, and 1.1 - 1.3 equiv $NaOSiMe_3$, see Experimental for exact conditions. Diastereomeric ratio determined from NMR of crude product using mesitylene as internal standard. [b] 50 mol % CuBr and **3.33**. [c] 48 h.

3.7 Reaction Scope with Respect to α-Bromoamides

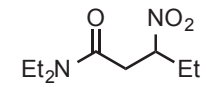
α-Bromoamides also serve as alkylating reagents in this transformation (Table 3.4). *N,N*-Dialkyl amides bearing a secondary α-bromide react in excellent yield under the optimized reaction conditions (**3.52**). As with the ester substrates, primary bromide substrates can also be used, but the yield is slightly attenuated and higher catalyst loading is required (**3.53**). With tertiary amides bearing a tertiary halogen, the facility of the reaction depends greatly on the nature of the nitrogen substituents. With amides bearing two alkyl groups, low yield of the desired product (**3.54**) was observed, even when forcing conditions were employed. I attribute this to the extreme steric encumbrance imparted by the *s-trans* amide substituent in the putative radical intermediate.[19] This hypothesis is supported by the fact that formation of the pyrrolidine-derived product **3.55**, in which the *s-trans* substituent is constrained, is formed in much higher yield under the standard conditions. α-Bromoamides bearing other nitrogen substituents can also be used in the reaction. This includes protic primary (**3.56**) and secondary amides (**3.57**). Weinreb amide substrates are also very good substrates in the reaction: products derived from both secondary (**3.58**) and tertiary bromides (**3.59**) can be obtained in high yield. The versatility of the Weinreb amide products will allow for a broad range of downstream synthetic manipulations.[20]

Table 3.4: Scope with respect to α-bromoamide

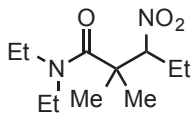




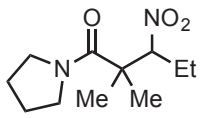
3.52, 93% (68:32)



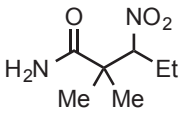
3.53, 54% (CH_2Cl_2)[b]



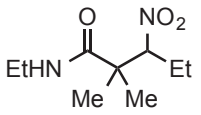
3.54, 25%



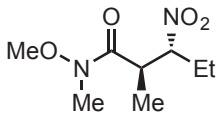
3.55, 60%



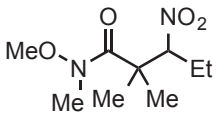
3.56, 58%



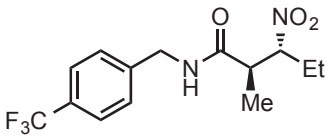
3.57, 81%
88% (hexanes)



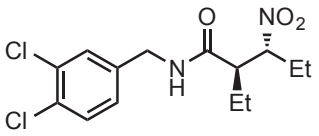
3.58, 82% (68:32)



3.59, 73%



3.60, 83% (60:40)



3.61, 75% (54:46)
X-ray of major

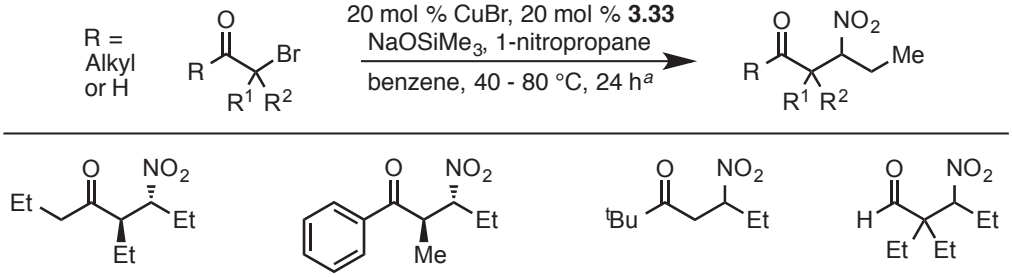
[a] Conditions: 1 equiv α-bromocarbonyl, 1.2 - 1.4 equiv nitroalkane, 20 mol % CuBr, 20 mol % **3.33**, and 1.1 - 1.3 equiv $NaOSiMe_3$, see Experimental for exact conditions. Diastereomeric ratio determined from NMR of crude product using mesitylene as internal standard. [b] 50 mol % CuBr and **3.33.**

3.8 Reaction Scope with Respect to α-Bromoketones and –aldehydes

Finally, with respect to the scope of the α-bromocarbonyl substrate, both α-bromoketones and -aldehydes can be used (Table 3.5). Ketones both with (**3.62**) and without (**3.63**) enolizable protons at the adjacent α-center performed equally well. As with previous examples, reduced substitution at the bromide center of the starting material decreased the yield of the product (**3.64**). With aldehydes, the degree of substitution at the halogen center proved highly critical. Only tertiary α-

bromoaldehydes provided useful yields in the reaction (**3.65**). In this way, the current reaction is highly complementary to the transformation reported by MacMillan described above.[11]

Table 3.5: Scope with respect to α-bromoketones and –aldehydes



[a] Conditions: 1 equiv α-bromocarbonyl, 1.2 - 1.4 equiv nitroalkane, 20 mol % CuBr, 20 mol % **3.33**, and 1.1 - 1.3 equiv $NaOSiMe_3$, see Experimental for exact conditions. Diastereomeric ratio determined from NMR of crude product using mesitylene as internal standard. [b] 48 h.

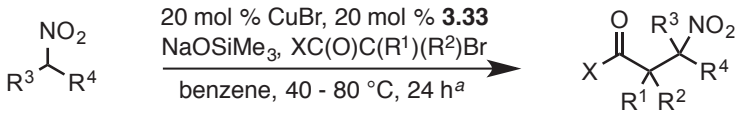
3.9 Reaction Scope with Respect to Nitroalkanes

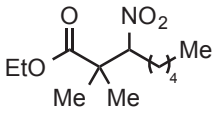
The reaction is also highly robust with respect to the nitroalkane coupling partner (Table 3.6). Longer aliphatic nitroalkanes (**3.66**), as well as those with β-branching (**3.67**) are well tolerated. The alkylation of nitromethane proceeded without incident (**3.72**). Most strikingly, secondary nitroalkanes could also be alkylated using this protocol. This includes the use of both secondary (**3.74** and **3.75**) *as well as tertiary* (**3.76** – **3.82**) α-bromocarbonyls. In the latter case, both simple secondary nitroalkanes, such as 2-nitropropane and nitrocyclohexane, as well as more complex nitroalkanes participated in the reaction with equal facility (**3.80** and **3.82**). The

products from these reactions contain fully-substituted vicinal carbons bearing a nitrogen center, which are highly challenging to prepare by other means.[21] There does, however, appear to be a steric limit in these reactions (see **3.78** and **3.81**); very highly encumbered products are formed in only limited yield.

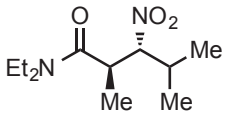
Finally, more complex nitroalkanes bearing additional functionality were also well tolerated in the reaction (**3.68** – **3.71** and **3.80** – **3.82**). These examples, as well as the additional examples in Table 3.6, demonstrate the broad functional group compatibility observed with this transformation. In total, compatible functional groups include aromatic chlorides (**3.61**), bromides (**3.42** and **3.43**), and iodides (**3.45**), trifluoromethyl arenes (**3.60**), alkenes (**3.46**), internal alkynes (**3.47**), silyl ethers (**3.48**), esters (**3.68**) and amides (**3.69**) located away from the reaction center, acyl protected alcohols (**3.70**), and secondary Boc-protected amines (**3.71**). In addition, a variety of heterocyclic substrates are tolerated in the reaction, including lactones (mentioned above, **3.44**), furans (**3.49**), thiophenes (**3.50**), and pyridines (**3.51**). Finally, it is notable that the preparation of **3.49** was accomplished on multi-gram scale, demonstrating the scalability of these reactions, even on more complex substrates.

Table 3.6: Scope with respect to nitroalkane

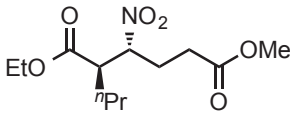




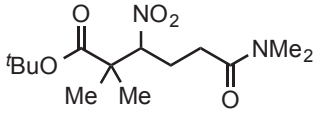
3.66, 79%[b]



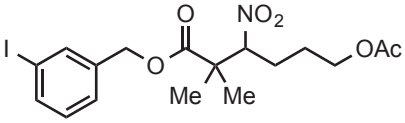
3.67, 88% (62:38)



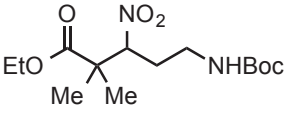
3.68, 89% (61:39)



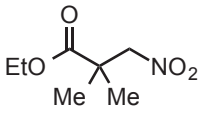
3.69, 69% (CH_2Cl_2)



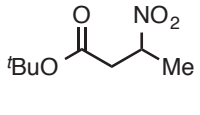
3.70, 71%



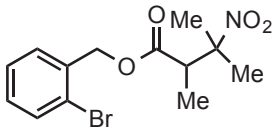
3.71, 75% (dioxane)



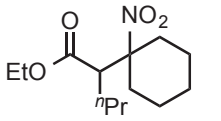
3.72, 89% (CH_2Cl_2)



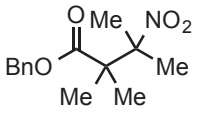
3.73, 63% (CH_2Cl_2)[c]



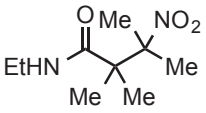
3.74, 71% (CyH)



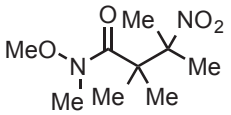
3.75, 68% (dioxane)



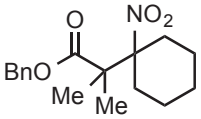
3.76, 44% (CyH)[d]



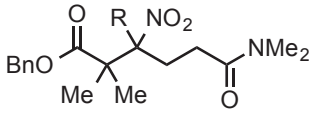
3.77, 43% (CyH)[d]



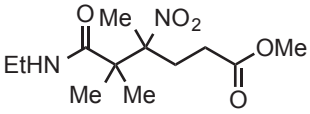
3.78, ~10% (CyH, NMR)[d]



3.79, 33% (^{t}BuOH)[e]



3.80, R = Me, 68% (^{t}BuOH)[e]
3.81, R = Et, ~17% (NMR, ^{t}BuOH)[e]



3.82, 41% (^{t}BuOH)[e]

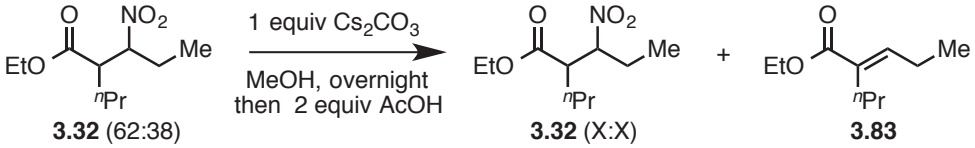
[a] Conditions: 1 equiv α-bromocarbonyl, 1.2 - 1.6 equiv nitroalkane, 20 mol % CuBr, 20 mol % **3.33**, and 1.1 - 1.7 equiv $NaOSiMe_3$, see Supporting Information for exact conditions. [b] 48 h. [c] 50 mol % CuBr and **3.33**. [d] 30 mol % CuBr and **3.33**, 48 h. [e] 40 mol % CuBr and **3.33**.

3.10 Identifying Diastereomers and Epimerization Studies

Only modest levels of diastereoselectivity were observed in cases where stereoisomers were possible. In most cases, however, the stereoisomers were readily separated by simple chromatography, and in several cases one of the isomers could be characterized via X-ray crystallography (see Tables 3.3, 3.4, and 3.5). Correlation of these structures to their ^{1}H NMR spectra revealed that the erythro-isomer consistently displayed downfield shifts at the hydrogen atom alpha to the nitro group compared to the threo-isomer.[22] Based upon this analysis, I was able to determine that the erythro-isomer was the predominant product in all but two cases (the exceptions were for the aromatic product **3.35** and the lactone **3.44**).[23]

In an effort to better understand the diastereoselectivity in terms of a kinetic or thermodynamic preference, β-nitrocarbonyl product **3.32** as a mixture of diastereomers (62:38) was stirred under basic conditions overnight (Table 3.7). After addition of glacial acetic acid the reactions were filtered through a short plug of magnesium sulfate and concentrated *in vacuo*. A reversal of diastereoselectivity was observed at rt (entry 1), but further efforts to increase the diastereoselectivity resulted in undesired elimination to form α,β-unsaturated ester, **3.83** (entry 2). Heating **3.32** in the absence of base did not change the diastereomeric ratio (entry 3).

Table 3.7: Epimerization studies of β-nitrocarbonyl **3.32**



3.32 (62:38) → **3.32** (X:X) + **3.83**

entry	temp (°C)	yield **3.32** (%)[a]	yield **3.83** (%)[a]
1	rt	79 (37:63)	8
2	40	24 (50:50)	29
3[b]	rt	99 (63:37)	0

[a] Yield determined by NMR using 1,3,5-trimethoxybenzene as an internal standard; [b] No Cs_2CO_3 added.

3.11 Nitroalkane Products as Intermediates for Additional Alkylation

The products from the alkylation reaction are highly useful intermediates for further synthetic manipulations. For example, the products can be elaborated by C-C bond forming reactions. This includes traditional reactions, such as their use as nucleophiles in conjugate addition reactions (e.g. Figure 3.13, top)[24] or our previously reported copper-catalyzed benzylation reaction (e.g. Figure 3.13, bottom).[18] Notably, both of these reactions form congested nitrogen-bearing fully-substituted carbons. The ability to further functionalize alpha to the nitro group highlights the importance of this transformation compared to other protocols for preparing β-azocarbonyl compounds, such as the β-aminocarbonyls that result from Mannich reactions.[21]

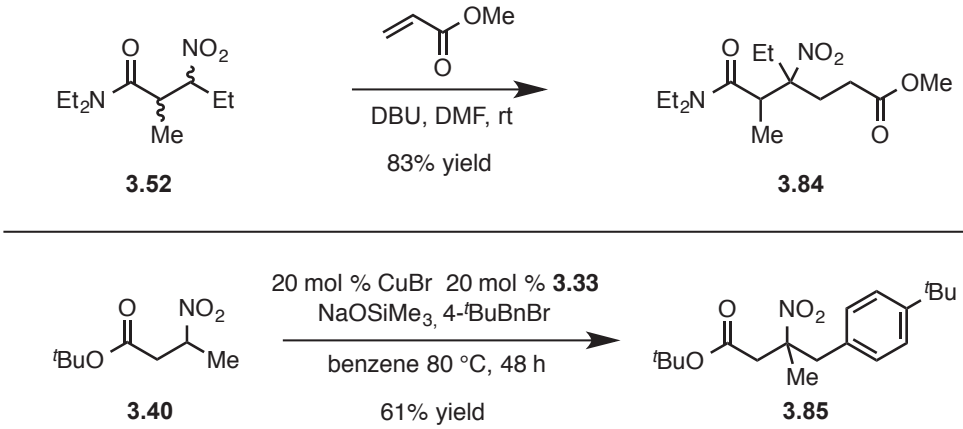


Figure 3.13: Subsequent *C-C* bond forming reactions of alkylation products

3.12 Reduction to β-Amino Acids and β-Amino Esters

Moreover, β-nitrocarbonyls are excellent precursors for β-amino acids and their derivatives.[25] For example, Zn/AcOH provides a high yielding, mild reagent for the selective reduction of the nitro group to the corresponding amine (Figure 3.14, top). Alternatively, Pd/C catalyzed hydrogenolysis of benzyl ester derivatives leads cleanly to the unprotected β-amino acids in very high yield (Figure 3.14, bottom). It is particularly notable that this latter reaction works efficiently to prepare a range of highly substituted β-amino acids, including those bearing additional functional groups.

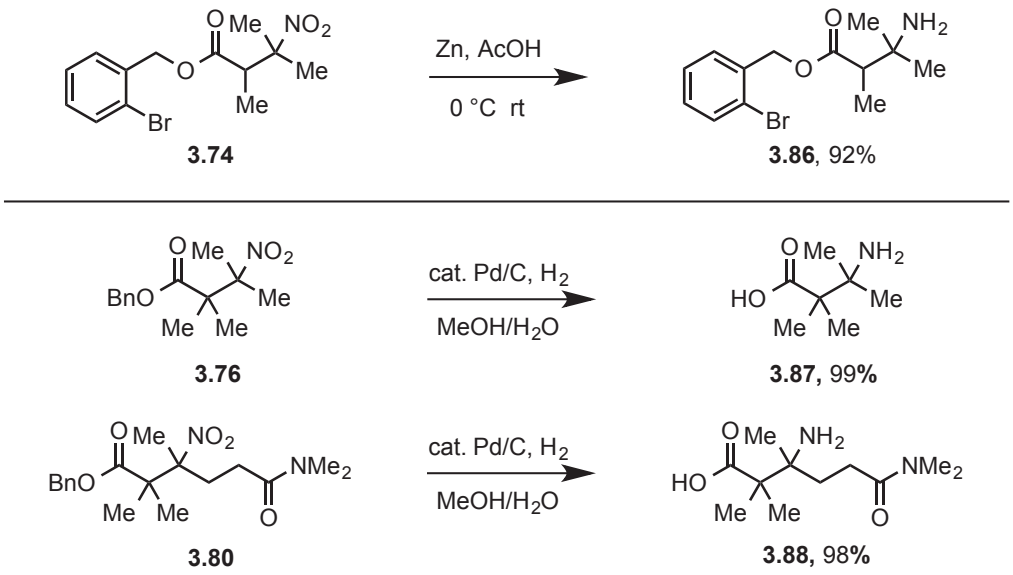


Figure 3.14: Reduction of alkylation products

3.13 Conclusion

In summary, using copper-catalyzed thermal redox catalysis, with my colleagues Amber Gietter and Andrew Cinderella, I have developed a general and high yielding route for the preparation of β-nitrocarbonyl compounds from readily

available α-bromocarbonyls.[26] The method is applicable to the synthesis of nitroesters, -amides, -ketones, and -aldehydes, and the mild reaction conditions are compatible with a vast range of functional groups. Importantly, this method also demonstrates remarkable steric tolerance, and allows for the synthesis of β-nitrocarbonyls containing fully substituted vicinal carbons at both the alpha and beta positions. The versatile products from the reaction offer a range of options for additional synthetic manipulations, including ready access to highly substituted β-amino acids and their derivatives.

3.14 Experimental

3.14.1 General Experimental Details

Benzene, toluene, diethyl ether, dimethylformamide, dichloromethane, hexanes, and dioxane were dried on alumina according to a published procedure.[27] Cyclohexane was sparged with N_2 prior to use and stored over molecular sieves. *tert*-Butanol was distilled from calcium hydride, sparged with N_2, and stored under N_2 in a sealed vessel. Copper bromide and sodium trimethylsilanolate were purchased commercially; the bulk was stored in a N_2 filled glovebox; samples were removed from the glovebox and stored in a desiccator under air for up to two weeks prior to use. Triethylamine was distilled from calcium hydride and sparged with N_2 prior to use. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. β-Diketiminate ligand **3.33** was synthesized according to a published procedure.[28] Substrates ethyl 2-bromo-2-ethylbutanoate,[29] allyl 2-bromopropionate,[30] 2-bromo-*N,N*-diethylpropionamide,[31] 2-bromo-*N,N*-diethylacetamide,[31] 2-bromo-*N*-methoxy-*N*-methylpropanamide,[32] 2-bromo-2-

ethylbutanal,[33] benzyl 2-bromoisobutyrate,[34] 2-methyl-1-nitropropane,[35] methyl-4-nitrobutyrate,[36] *N,N*-dimethyl-4-nitrobutanamide,[37] 4-nitrobutyl acetate,[38] *tert*-butyl 3-nitropropylcarbamate,[39] nitrocyclohexane,[40] and *N,N*-dimethyl-4-nitropentamide[41] were synthesized according to published procedures. All other substrates and reagents were purchased in highest analytical purity from commercial suppliers and used as received. Reaction optimization (Tables 3.2 and 3.8) was conducted in a glovebox (N_2 atmosphere) on a 250 mmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. All NMR yields and diastereoselectivity are reported using mesitylene or 1,3,5-trimethoxybenzene as an internal standard. All other reactions were set up using standard Schlenk technique and heated with stirring in temperature controlled oil baths. "Double manifold" refers to a standard Schlenk-line gas manifold equipped with N_2 and vacuum (ca. 0.1 mm Hg).

Yields reported in Tables 3.2 - 3.6 reflect the average isolated yields of at least two independent runs; any deviation between these yields and those reported in this supporting information reflect the difference between individual and average yields.

3.14.2 Instrumentation and Chromatography

400 MHz ^{1}H, 101 MHz ^{13}C, and 376 MHz ^{19}F spectra were obtained on a 400 MHz FT-NMR spectrometer equipped with a Bruker CryoPlatform. 600 MHz ^{1}H and 151 MHz ^{13}C spectra were obtained on a 600 MHz FTNMR spectrometer equipped with a Bruker SMART probe. ^{13}C spectra were recorded using Attached Proton Test phase pulse sequence; carbons with an odd number of protons are phased down and those with an even number of protons are phased up.[42] All samples were analyzed in the indicated deutero-solvent and were recorded at ambient temperatures. Chemical shifts are reported in ppm. ^{1}H NMR spectra were calibrated using the residual protio-

signal in deutero-solvents as a standard. ^{13}C NMR spectra were calibrated using the deutero-solvent as a standard. IR spectra were recorded on a Nicolet Magma-IR 560 FT-IR spectrometer as thin films on NaCl plates or using KBr pellets. Unless otherwise noted, column chromatography was performed with 40-63 μm silica gel with the eluent reported in parentheses. Where noted 5-20 μm silica gel was used to improve separation. Analytical thin-layer chromatography (TLC) was performed on precoated glass plates and visualized by UV or by staining with $KMnO_4$. GCMS data was collected using an Agilent 6850 series GC and 5973 MS detector. Low resolution ESI data was collected on a Thermo LCQ Advantage running in positive ion mode. High resolution MS data was obtained on a Waters GCT Premier spectrometer using chemical ionization (CI) or liquid injection field desorption ionization (LIFDI).

3.14.3 Determination of Relative Stereochemistry

X-ray crystal structures were obtained for **3.44B**, **3.61B**, and **3.63B**. As shown below, these structures showed a relative erythro orientation of the β-nitro group and the α-substituent. Comparing the NMR data from these compounds, it was determined the α-nitro proton (labeled H_A below, ppm range 4.97-4.68) was shifted further downfield than the corresponding signal from the threo isomer. From this data, all other spectra were assigned accordingly.

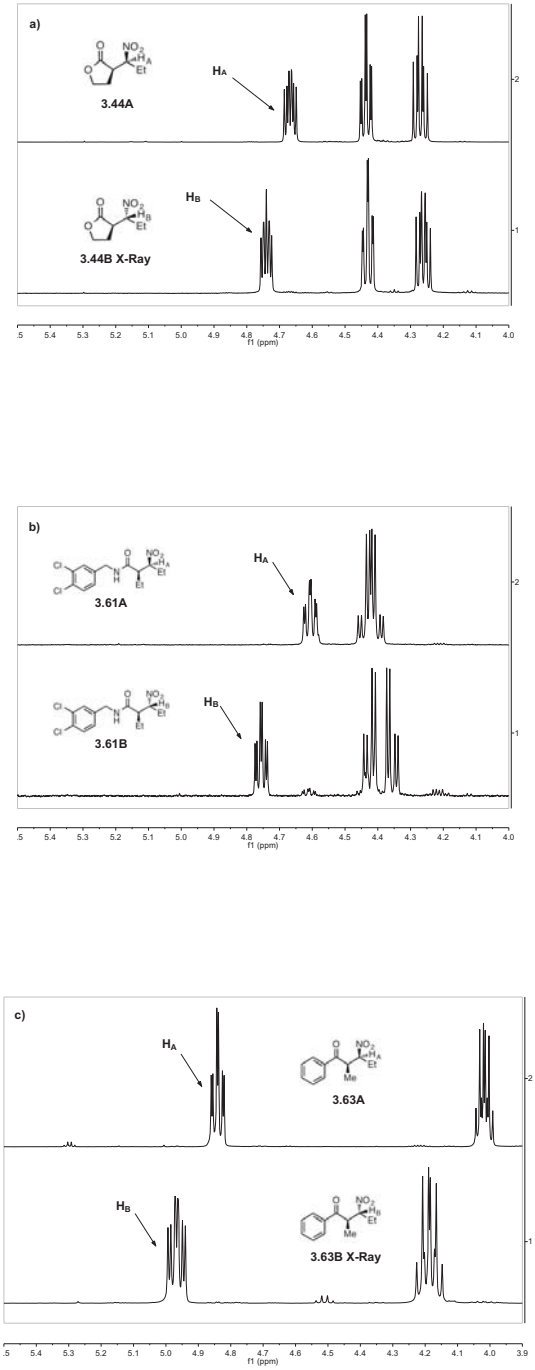
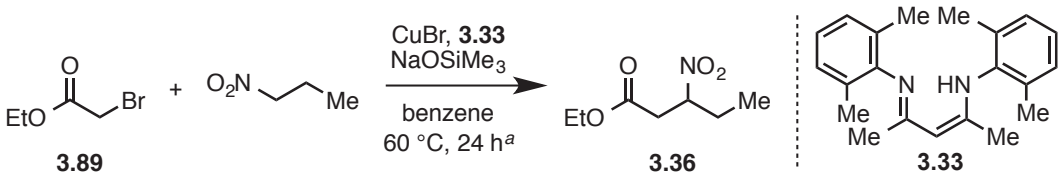


Figure 3.15: NMR and X-ray comparison of a) compound **3.44**, b) compound **3.61**, and c) compound **3.63** to determine relative stereochemistry

3.14.4 Optimization of Primary α-Bromoesters and α-Bromoamides

Table 3.8: Optimization of primary α-bromoesters and α-bromoamides



3.89 **3.36** **3.33**

entry	Cu/Nac Nac	$NaOSiMe_3$	yield **3.36** (%)[b]
1	20 mol%	1.1 equiv	30
2	30 mol%	1.2 equiv	33
3	40 mol%	1.3 equiv	36
4	50 mol%	1.4 equiv	38
5	1 equiv	1.9 equiv	20
6[c]	50 mol%	1.1 equiv	54
7[c]	50 mol%	1.4 equiv	59
8[c,d]	50 mol%	1.4 equiv	62

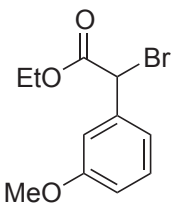
[a] 1.2 equiv 1-nitropropane; [b] Yield determined by NMR using 1,3,5-trimethoxybenzene as an internal standard; [c] CH_2Cl_2 used as solvent; [d] 1.3 equiv 1-nitropropane.

3.14.5 General Protocol for Synthesis of Previously Unknown α-Bromocarbonyls

General Protocol A. Synthesis of α-bromocarbonyl derivatives using solid alcohols or amines: A hot round bottom flask equipped with a magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and the solid alcohol or amine (1 equiv) was added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 three times. Anhydrous dichloromethane, triethylamine (1.1 equiv), and α-bromoacylbromide (1 equiv) were added to the flask

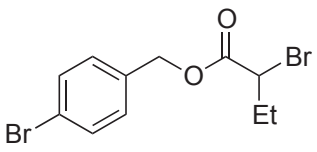
sequentially via syringe. The resulting homogenous reaction was stirred at room temperature overnight. The septum was removed and the reaction was diluted with dichloromethane and washed with water (1x). The aqueous layer was washed with dichloromethane (1x). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The product was purified by silica gel flash chromatography.

General Protocol B. Synthesis of α-bromocarbonyl derivatives using liquid alcohols or amines: A hot round bottom flask equipped with a magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was evacuated and backfilled with N_2 three times. Anhydrous dichloromethane, triethylamine (1.1 equiv), alcohol or amine (1 equiv) and α-bromoacylbromide (1 equiv) were added to the flask sequentially via syringe. The resulting homogenous reaction was stirred at room temperature overnight. The septum was removed and the reaction was diluted with dichloromethane and washed with water (1x). The aqueous layer was washed with dichloromethane (1x). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The product was purified by silica gel flash chromatography.



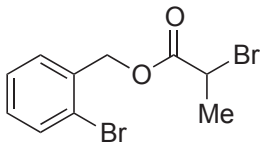
(**3.90**). A hot 50 mL round bottom flask equipped with a magnetic stir bar, reflux condenser, and a rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the reflux condenser was removed, and N-bromosuccinimide (1.91 g, 10.8 mmol) and azobisisobutyronitrile (169 mg, 1.03 mmol) were added. The reflux condenser was replaced and the system was evacuated and backfilled with N_2 three

times. Anhydrous cyclohexane (25 mL) and ethyl 2-(3-methoxyphenyl)acetate (1.88 mL, 10.3 mmol) were added to the flask sequentially via syringe. The resulting mixture was heated to 80 °C in an oil bath for 1 h. The reflux condenser was removed and the reaction mixture was filtered and the solid was washed with hexanes (10 mL, 2x) and the resulting filtrate was concentrated *in vacuo*. The crude oil was purified via fractional distillation (110 °C, 0.20 mm Hg) to afford **3.90** as a clear oil (1.04 g, 37%): ^{1}H NMR (600 MHz, C_6D_6) d 7.21 (s, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 7.9 Hz, 1H), 6.64 (dd, J = 8.2, 2.1 Hz, 1H), 5.19 (s, 1H), 3.88 – 3.76 (m, 2H), 3.22 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) d 168.1, 160.3, 137.9, 130.0, 121.3, 115.6, 114.4, 62.3, 54.7, 47.2, 13.8; FTIR (cm^{-1}): 2982, 1746, 1600, 1491, 1261, 1144, 1025, 548; GC/MS (EI): 272.0 $(M)^{+}$. HRMS (CI) m/z, calculated for $[C_{11}H_{14}O_3Br]^{+}$: 273.0126; found: 273.0133.

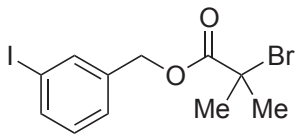


(**3.91**). According to general protocol A: 4-bromobenzyl alcohol (4.68 g, 25.0 mmol), anhydrous dichloromethane (250 mL), triethylamine (3.83 mL, 27.5 mmol) and a-bromobutyryl bromide (3.02 mL, 25.0 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (90:10 hexanes : ethyl acetate) to afford α-bromoester **3.91** (7.34 g, 87%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.52 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.20 - 5.13 (q, 2H), 4.21 (t, J = 7.2 Hz, 1H), 2.13 (hept, 1H), 2.04 (hept, 1H), 1.03 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 169.6, 134.3, 131.9, 130.0, 122.7, 66.8, 47.5, 28.5, 12.0; FTIR

(cm^{-1}): 2972, 1741, 1490, 1150, 631, 518; GC/MS (EI): 337.9 $(M)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{12}O_2Br_2]^+$: 335.9179; found: 335.9205.

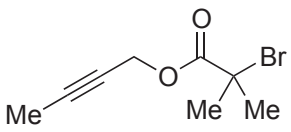


(**3.92**). According to general protocol A: 2-bromobenzyl alcohol (4.68 g, 25.0 mmol), anhydrous dichloromethane (100 mL), triethylamine (3.83 mL, 27.5 mmol) and 2-bromopropionyl bromide (2.62 mL, 25.0 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (90:10 hexanes : ethyl acetate) to afford α-bromoester **3.92** (6.83 g, 85%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.59 (dd, 1H), 7.45 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.34 (td, 1H), 7.22 (td, *J* = 7.8, 1.6 Hz, 1H), 5.28 (q, 2H), 4.45 (q, *J* = 6.9 Hz, 1H), 1.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 169.9, 134.7, 133.0, 130.1, 130.0, 127.7, 123.5, 67.2, 40.0, 21.8; FTIR (cm^{-1}): 2978, 1743, 1153, 751, 659, 589; GC/MS (EI) 243.0 $(M\text{-}Br)^+$; HRMS (CI) m/z, calculated for $[C_{10}H_{11}O_2Br_2]^+$: 320.9126; found: 320.9131.

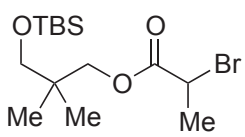


(**3.93**). According to general protocol A: 3-iodobenzyl alcohol (2.56 g, 11.0 mmol), anhydrous dichloromethane (37 mL), triethylamine (1.53 mL, 11.0 mmol) and a-bromoisobutyryl bromide (1.45 mL, 9.20 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (90:10 hexanes : ethyl acetate) to afford α-bromoester **3.93** (3.42 g, 81%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.73 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.11 (t, *J* =

7.8 Hz, 1H), 5.14 (s, 2H), 1.96 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.5, 137.8, 137.5, 136.9, 130.5, 127.2, 94.4, 66.5, 55.6, 30.9; FTIR (cm^{-1}): 3059, 1736, 1271, 1156, 596; GC/MS (EI): 383.9 $(M)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{13}O_2BrI]^+$: 384.9123; found: 384.9110.

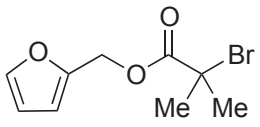


(**3.94).** According to general protocol B: Anhydrous dichloromethane (100 mL), triethylamine (1.53 mL, 11.0 mmol), 2-butyn-1-ol (748 mL, 10.0 mmol) and a-bromoisobutyryl bromide (1.24 mL, 10.0 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (95:5 hexanes: ethyl acetate) to afford α-bromoester **3.94** (1.70 g, 78%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.73 (q, *J* = 2.4 Hz, 2H), 1.95 (s, 6H), 1.86 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 171.4, 83.9, 72.6, 55.5, 54.5, 30.9, 3.9; FTIR (cm^{-1}): 2241, 1734,1274, 1157, 668; GC/MS (EI): 139.1 $(M\text{-}Br)^+$. HRMS (CI) m/z, calculated for $[C_8H_{12}O_2Br]^+$: 221.0000; found: 221.0015.

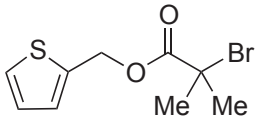


(**3.95**). According to general protocol B: Anhydrous dichloromethane (40 mL), triethylamine (1.67 mL, 12.0 mmol) 3-(*tert*-butyl-dimethylsilanyloxy)-2,2'-dimethyl-propan-1-ol (2.62 g, 12.0 mmol) and 2-bromopropionyl bromide (1.67 mL, 1.00 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (97:3 hexanes : ethyl acetate) to afford α-bromoester **3.95** (3.02 g, 86%) as a clear oil:

^{1}H NMR (600 MHz, $CDCl_3$) d 4.38 (q, *J* = 6.9 Hz, 1H), 4.01 (d, *J* = 10.5 Hz, 1H), 3.94 (d, *J* = 10.5 Hz, 1H), 3.35 (s, 2H), 1.83 (d, *J* = 6.9 Hz, 3H), 0.92 - 0.86 (m, 15H), 0.03 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 170.3, 70.8, 68.4, 40.5, 36.7, 26.0, 21.9, 21.5, 18.4, -5.42; FTIR (cm^{-1}): 1742, 1258, 1100, 775, 668; GC/MS (EI): 297.1 $(M-C_4H_9)^+$; HRMS (CI) m/z, calculated for $[C_{14}H_{30}O_3SiBr]^+$: 355.1127; found: 355.1152.

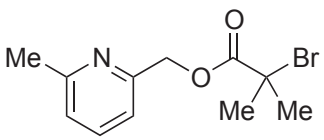


(**3.96).** According to general protocol B: Furfuryl alcohol (10.0 g, 101 mmol), anhydrous dichloromethane (400 mL), triethylamine (15.5 mL, 111 mmol), and 2-bromo-2-methylpropionyl bromide (16.0 mL, 101 mmol) were combined under N_2 and stirred rapidly at room temperature for 20 h. The reaction was extracted with diethyl ether and water, dried over $MgSO_4$, filtered, and concentrated. Purified by flash silica chromatography (95:5 hexanes : ethyl acetate) to afford α-bromoester **3.96** (22.7 g, 91%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.44 – 7.43 (m, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.37 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.16 (s, 2H), 1.93 (s, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.3, 148.8, 143.4, 111.0, 110.6, 59.5, 6.6, 30.7; FTIR (cm^{-1}): 3453, 2977, 1734, 1463, 1274, 1159, 1108, 747; GC/MS (EI) 248.0, 245.9 $(M)^+$. HRMS (CI) m/z, calculated for $[C_9H_{12}O_3Br]^+$: 246.9970; found: 246.9968.

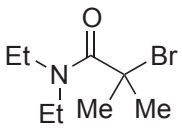


(**3.97).** According to general protocol B: Anhydrous dichloromethane (80 mL), triethylamine (3.62 mL, 26.0 mmol), 2-thiophenemethanol (1.89 mL, 20.0 mmol) and α-bromoisobutyryl bromide (4.08 mL, 26.0 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general

procedure and purified by flash silica chromatography (95:5 hexanes: ethyl acetate) to afford α-bromoester **3.97** (2.57 g, 49%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.33 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 6.99 (m, *J* = 5.1, 3.5 Hz, 1H), 5.36 (s, 2H), 1.93 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.4, 137.3, 128.4, 127.1, 126.9, 62.2, 55.7, 30.8; FTIR (cm^{-1}): 3108, 1735, 1271, 1155, 708, 526; GC/MS (EI): 264.0 $(M)^{+}$. HRMS (CI) m/z, calculated for $[C_9H_{12}O_2SBr]^{+}$: 264.9721; found: 264.9702.

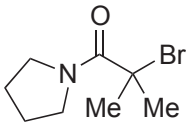


(**3.98**). According to general protocol A: 6-Methyl-2-pyridinemethanol (2.96 g, 24.0 mmol), anhydrous dichloromethane (80 mL), triethylamine (3.35 mL, 24 mmol) and α-bromoisobutyryl bromide (3.15 mL, 26.2 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (85:15 hexanes: ethyl acetate) to afford α-bromoester **3.98** (4.678 g, 72%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.62 - 7.57 (m, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 5.30 (s, 2H), 2.55 (s, 3H), 1.99 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.4, 158.3, 154.9, 137.2, 122.6, 118.2, 68.1, 55.7, 31.0, 24.5; FTIR (cm^{-1}): 2977, 1739, 1161, 1109, 668; GC/MS (EI) 273.0 $(M)^{+}$. HRMS (CI) m/z, calculated for $[C_{11}H_{15}NO_2Br]^{+}$: 274.0266; found: 274.0269.



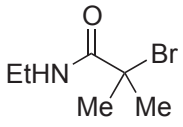
(**3.99**). A hot 500 mL round bottom flask equipped with a magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was evacuated and backfilled with N_2

three times. Diethylamine (7.97 mL, 77.0 mmol) and anhydrous diethyl ether (150 mL) were added and the flask was cooled to 0 °C using an ice bath. 2-Bromoisobutyryl bromide (4.76 mL, 38.5 mmol) was added and the flask was allowed to warm to room temperature stirring for 4 h. The resulting suspension was filtered and the filtrate was washed with saturated ammonium chloride (200 mL), saturated sodium bicarbonate (200 mL), and a saturated brine solution (200 mL). After drying with magnesium sulfate the solution was filtered and concentrated *in vacuo* to afford a pale yellow oil pure by NMR. The oil was further distilled (50 °C, 0.500 mm Hg) to afford α-bromoamide **3.99** (7.90 g, 92%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 3.95 – 3.11 (m, 4H), 1.95 (s, 6H), 1.38 – 0.94 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) d 169.6, 57.5, 43.4, 41.7, 33.0, 13.8, 12.3; FTIR (cm^{-1}): 2975, 1636, 1464, 1424, 1277, 1128, 1107; GC/MS (EI) 221.0 $(M-H)^+$. HRMS (CI) m/z, calculated for $[C_8H_{17}NOBr]^+$: 222.0494; found: 222.0490.

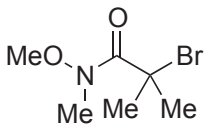


(**3.100**). According to general protocol B: Anhydrous dichloromethane (80 mL), triethylamine (3.35 mL, 24.0 mmol), pyrrolidine (1.97 mL, 24.0 mmol) and α-bromoisobutyryl bromide (3.15 mL, 20.0 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (75:25 hexanes: ethyl acetate) to afford α-bromoamide **3.100** (2.71 g, 62%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) d 3.82 (bs, 2H), 3.52 (bs, 2H), 2.00 - 1.91 (m, 8H), 1.84 (bs, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) d 169.1, 58.5, 49.0, 48.6, 32.0, 27.2, 23.4; FTIR (cm^{-1}): 2361, 1635, 1106, 668; GC/MS

(EI) 219.0 $(M\text{-}H)^+$. HRMS (CI) m/z, calculated for $[C_8H_{15}NOBr]^+$: 222.0317; found: 222.0329; mp = 60-63 °C.

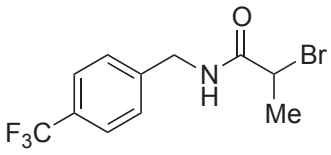


(**3.101**). According to general protocol B: Excess 2.0 M ethylamine in THF (65.3 mL, 131 mmol) used in place of triethylamine, anhydrous dichloromethane (400 mL), and 2-bromo-2-methylpropionyl bromide (5.38 mL, 43.5 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash chromatography (90:10 hexanes : ethyl acetate) to afford α-bromoamide **3.101** (6.50 g, 77%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 6.70 (s, 1H), 3.36 – 3.22 (m, 2H), 1.94 (s, 6H), 1.17 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 171.9, 63.6, 35.5, 32.8, 14.7; FTIR (cm^{-1}): 3350, 2976, 1653, 1539, 1457, 1194, 1113; GC/MS (EI) 193.0 $(M\text{-}H)^+$. HRMS (CI) m/z, calculated for $[C_6H_{13}NOBr]^+$: 194.0181; found: 194.0182; mp = 59-60 °C.

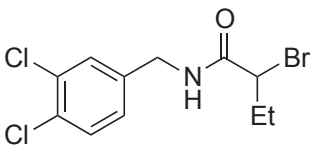


(**3.102**). According to general protocol A: *N*,*O*-dimethylhydroxylamine·HCl (4.86 g, 49.8 mmol), anhydrous dichloromethane (166 mL), triethylamine (6.94 mL, 49.8 mmol), and α-bromoisobutyryl bromide (5.00 mL, 41.5 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica chromatography (80:20 hexanes : ethyl acetate) to afford α-bromoamide **3.102** (5.89 g, 68%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) d 3.80 (s, 3H), 3.26 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) d 171.4, 60.7, 55.8, 34.2, 31.7; FTIR (cm^{-1}) 2978, 1740, 1653, 1458, 1366, 1164,

1112, 995; GC/MS (EI) 209.0 $(M)^+$. HRMS (CI) m/z, calculated for $[C_6H_{13}NO_2Br]^+$: 210.0130; found: 210.0139.



(**3.103**). According to general protocol B: 4-(trifluoromethyl)benzyl amine (3.42 mL, 24.0 mmol), anhydrous dichloromethane (80 mL), triethylamine (3.35 mL, 24.0 mmol) and 2-bromopropionyl bromide (2.10 mL, 20.0 mmol) were combined under N_2 and stirred at room temperature for 24 h. The reaction was worked up according to the general procedure and purified by flash chromatography (70:30 hexanes : ethyl acetate) to afford α-bromoamide **3.103** (5.09 g, 82%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.61 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 4.58 – 4.45 (m, 3H), 1.92 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 169.6, 141.7, 130.1 (q, *J* = 32.5 Hz), 127.9, 125.9 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.1 Hz), 45.2, 43.7, 23.3; ^{19}F NMR (376 MHz, $CDCl_3$) d -62.56 (s); FTIR (cm^{-1}): 3277, 1653, 1558, 1328, 1111, 1069; GC/MS (EI) 291.9 $(M-F)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{12}NOBrF_3]^+$: 310.0054; found: 310.0064; mp = 92-93 °C.



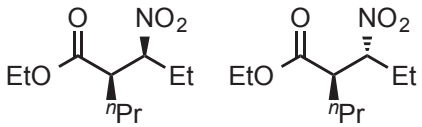
(**3.104**). According to general protocol A: 3,4-dichlorobenzylamine (3.20 g, 24.0 mmol), anhydrous dichloromethane (80 mL), triethylamine (3.35 mL, 24.0 mmol) and 2-bromobutyryl bromide (2.41 mL, 20.0 mmol) were combined under N_2 and stirred at room temperature for 16 h. The reaction was worked up according to the general procedure and purified by flash silica

chromatography (90:10 hexanes : ethyl acetate) to afford α-bromoamide **3.104** (3.65 g, 56%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.41 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 1.9 Hz, 1H), 7.12 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.77 (s, 1H), 4.47 - 4.38 (m, 2H), 4.35 (dd, *J* = 7.7, 5.0 Hz, 1H), 2.24 - 2.15 (m, 1H), 2.09 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 168.8, 138.1, 133.0, 131.9, 130.9, 129.7, 127.0, 53.7, 43.1, 29.5, 11.8; FTIR (cm^{-1}): 3272, 3079, 1652, 814, 668; GC/MS (EI) 246.0 $(M\text{-}Br)^{+}$. HRMS (CI) m/z, calculated for $[C_{11}H_{13}NOCl_2Br]^{+}$: 327.9499; found: 327.9508; mp = 85-89 °C.

3.14.6 General Protocols for Nitroalkylation

General Protocol C. Synthesis of nitroalkanes with liquid α-bromocarbonyl substrates: A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed, and CuBr (0.2 equiv), ligand **3.33** (0.2 equiv), and sodium trimethylsilanolate (1.1 equiv) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous solvent, nitroalkane (1.2 equiv), and α-bromocarbonyl (1 equiv) were added via syringe. The resulting suspension was heated to the indicated temperature in an oil bath with rapid stirring for the indicated time. Once completed, the reaction was cooled to room temperature, the septum was removed and the reaction mixture was diluted with diethyl ether (10 mL). The crude reaction mixture was filtered through a plug of magnesium sulfate and concentrated *in vacuo*. The product was purified by silica gel flash chromatography.

General Protocol D. Synthesis of nitroalkanes with primary at bromine α-bromocarbonyl substrates: A hot 50 mL reaction vessel equipped with a magnetic stir bar and a threaded Kontes valve was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the Teflon valve was removed, and CuBr (0.5 equiv), ligand **3.33** (0.5 equiv), and sodium trimethylsilanolate (1.4 equiv) were added. The valve was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. The valve was removed and quickly replaced with a rubber septum and vent needle under positive N_2. Anhydrous dichloromethane, 1-nitropropane (1.3 equiv), and α-bromocarbonyl (1 equiv) were added via syringe. The reaction vessel was sealed under N_2. The vessel was removed from the manifold and the suspension was heated to 60 °C fully submerged in an oil bath with rapid stirring for the indicated time. Once completed, the reaction was cooled to room temperature, the valve was removed and the reaction mixture was diluted with diethyl ether (20 mL). The crude reaction mixture was filtered through a plug of magnesium sulfate and concentrated *in vacuo*. The product was purified by silica gel flash chromatography.



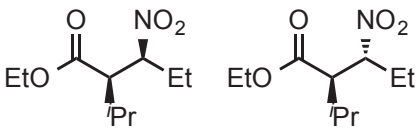
3.32A **dr: 41 : 59** **3.32B**

(**3.32**). According to general protocol C: CuBr (143 mg, 1.00 mmol), ligand **3.33** (306 mg, 1.00 mmol), sodium trimethylsilanolate (617 mg, 5.50 mmol), anhydrous benzene (30 mL), 1-nitropropane (536 μL, 6.00 mmol), and ethyl 2-bromovalerate (850 mL, 5.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 41:59 mixture of syn and

anti isomers. These products were separated and purified by flash silica chromatography (98:2:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.32** (976 mg, 90% combined).

3.32A (393 mg, 36%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.56 (td, *J* = 10.3, 3.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.93 (td, *J* = 10.1, 3.5 Hz, 1H), 1.97 (ddq, *J* = 14.5, 10.6, 7.3 Hz, 1H), 1.74 (dqd, *J* = 14.8, 7.5, 3.2 Hz, 1H), 1.66 (tdd, *J* = 12.1, 7.1, 3.0 Hz, 1H), 1.43 – 1.30 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (ddt, *J* = 8.7, 7.1, 4.5 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.8, 91.9, 61.2, 49.1, 31.8, 25.6, 20.0, 14.1, 13.7, 10.3; FTIR (cm^{-1}): 2965, 1735, 1554, 1375, 1182, 811; GC/MS (EI) 171.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{20}NO_4]^+$: 218.1392; found: 218.1398.

3.32B (584 mg, 54%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.68 (td, *J* = 9.1, 3.6 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.04 (td, *J* = 9.1, 4.9 Hz, 1H), 2.01 (dqd, *J* = 15.0, 7.5, 3.6 Hz, 1H), 1.91 (ddq, *J* = 14.6, 8.8, 7.3 Hz, 1H), 1.64 – 1.54 (m, 2H), 1.43 – 1.27 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 172.3, 89.5, 61.2, 47.3, 30.5, 24.1, 19.9, 14.1, 13.9, 9.6; FTIR (cm^{-1}): 2965, 1734, 1553, 1375, 1189, 810; GC/MS (EI) 171.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{20}NO_4]^+$: 218.1392; found: 218.1383.



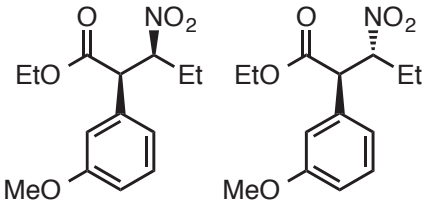
3.34A **dr: 36 : 64** **3.34B**

(**3.34**). According to general protocol C: CuBr (86.1 mg, 600 μmol), ligand **3.33** (184 mg, 600 μmol), sodium trimethylsilanolate (428 mg, 3.80 mmol),

anhydrous dichloromethane (18 mL), 1-nitropropane (321 μL, 3.60 mmol), and ethyl 2-bromo-3-methylbutyrate (492 μL, 3.00 mmol) were combined under N_2 and heated at 40 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 36:64 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (93:7:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.34** (544 mg, 84% combined).

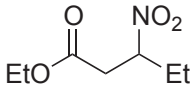
3.34A (368 mg, 57%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.73 (td, *J* = 10.5, 2.9 Hz, 1H), 4.26 - 4.13 (m, 2H), 2.91 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.01 - 1.91 (m, 1H), 1.89 - 1.72 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 1H), 1.03 - 0.92 (m, 9H);^{13}C NMR (151 MHz, $CDCl_3$) d 170.6, 89.8, 61.1, 54.8, 28.4, 25.9, 21.3, 17.8, 14.4, 10.5; FTIR (cm^{-1}): 1733, 1554, 1183, 1026, 668; GC/MS (EI) 171.2 $(M\text{-}HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{20}NO_4]^+$: 218.1392; found: 218.1381.

3.34B (175 mg, 27%) yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.78 (ddd, *J* = 10.2, 8.6, 3.7 Hz, 1H), 4.20 - 4.12 (m, 2H), 2.96 (dd, *J* = 10.2, 4.4 Hz, 1H), 2.10 - 2.03 (m, 1H), 2.01 - 1.96 (m, 1H), 1.89 (hept, *J* = 15.6, 7.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.0, 88.5, 61.1, 52.9, 27.2, 24.7, 21.9, 17.8, 14.3, 9.5; FTIR (cm^{-1}): 1731, 1554, 1190, 1029, 667; GC/MS (EI) 172.2 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{20}NO_4]^+$: 218.1392; found: 218.1387.



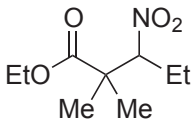
3.35A **dr: 64 : 36** **3.35B**

(**3.35**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous hexanes (6 mL), 1-nitropropane (107 μL, 1.20 mmol), and **3.90** (273 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 64:36 mixture of syn and anti isomers. The reaction was purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid to afford an inseparable mixture of diastereomers of nitroester **3.35** (169 mg, 60%) as a pale yellow oil: ^{1}H NMR (600 MHz, C_6D_6: mixture of diastereomers; useful diagnostic peaks for each compound are listed. See attached spectra for details) d **3.35A**: 6.68 (d, *J* = 7.5 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.88 (dq, *J* = 10.5, 7.1 Hz, 1H), 1.41 (tp, *J* = 14.9, 11.3, 7.5, 3.9 Hz, 1H), 1.31 – 1.21 (m, 1H); **3.35B**: 7.08 (s, 1H), 4.10 (d, *J* = 11.0 Hz, 1H), 3.81 (dq, *J* = 10.9, 7.1 Hz, 1H), 1.85 – 1.70 (m, 2H); ^{13}C NMR (101 MHz, C_6D_6) d **3.35A**: 170.8, 160.3, 134.9, 130.5, 120.7, 114.2, 113.9, 89.5, 61.9, 55.4, 53.7, 24.8, 14.0, 9.4; **3.35B**: 170.2, 159.9, 135.0, 130.1, 120.5, 114.2, 114.0, 92.0, 61.9, 55.4, 55.1, 26.6, 14.1, 10.5; FTIR (cm^{-1}): 2977, 2940, 2839, 1732, 1553, 1262, 1182, 1048; GC/MS (EI) 281.1 $(M)^+$; 281.1 $(M)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{19}NO_5]^+$: 282.1337; found: 282.1340; found: 282.1346.

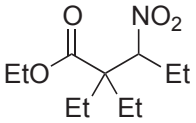


(**3.36**). According to general protocol D: CuBr (144 mg, 1.00 mmol), ligand **3.33** (306 mg, 1.00 mmol), sodium trimethylsilanolate (314 mg, 2.80 mmol), anhydrous dichloromethane (12 mL), 1-nitropropane (232 μL, 2.60

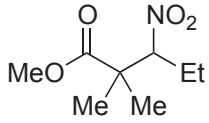
mmol), and ethyl bromoacetate (222 μL, 2.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography using 5-20 μm silica gel (94:6:2 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.36** (241 mg, 69%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.86 – 4.80 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.13 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.67 (dd, *J* = 17.2, 4.4 Hz, 1H), 2.03 – 1.88 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 169.5, 84.6, 61.5, 36.9, 27.2, 14.2, 10.0; FTIR (cm^{-1}): 2981, 1734, 1558, 1380, 1341, 1194; GC/MS (EI) 130.0 $(M–C_2H_5O)^+$. HRMS (CI) m/z, calculated for $[C_7H_{14}NO_4]^+$: 176.0923; found: 176.0919.



(**3.37**). According to general protocol C: CuBr (144 mg, 1.00 mmol), ligand **3.33** (306 mg, 1.00 mmol), sodium trimethylsilanolate (617 mg, 5.50 mmol), anhydrous benzene (30 mL), 1-nitropropane (536 μL, 6.00 mmol), and ethyl α-bromoisobutyrate (734 μL, 5.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.37** (755 mg, 74%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.73 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.16 - 2.03 (m, 1H), 1.67 (ddd, *J* = 14.7, 7.4, 2.4 Hz, 1H), 1.33 - 1.23 (m, 9H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 174.3, 95.7, 61.7, 45.8, 23.2, 22.9, 20.4, 14.2, 11.3; FTIR (cm^{-1}):1735, 1552, 1254, 1148, 1024, 810; GC/MS (EI) 158.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{18}NO_4]^+$: 204.1236; found: 204.1235.

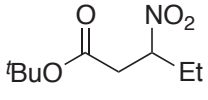


(**3.38**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.4 mmol), and ethyl 2-bromo-2-ethylbutanoate (178 μL, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (98:2:2 hexanes : ethyl acetate : acetic acid to afford nitroester **3.38** (162 mg, 70%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.56 (dd, J = 11.9, 2.3 Hz, 1H), 4.23 – 4.16 (m, 2H), 2.22 – 2.13 (m, 1H), 1.93 – 1.76 (m, 3H), 1.69 – 1.55 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.96 – 0.89 (m, 6H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.8, 94.8, 61.3, 52.2, 25.1, 23.6, 22.6, 14.2, 11.4, 8.4, 8.3; FTIR (cm^{-1}): 2979, 1733, 1554, 1458, 1227, 1143; GC/MS (EI) 185.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{22}NO_4]^+$: 232.1549; found: 232.1545.

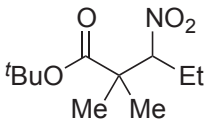


(**3.39**). According to general protocol C: CuBr (144 mg, 1.0 mmol), ligand **3.33** (306 mg, 1.0 mmol), sodium trimethylsilanolate (617 mg, 5.5 mmol), anhydrous benzene (30 mL), 1-nitropropane 536 μL, 6.0 mmol), and methyl α-bromoisobutyrate (647 μL, 5.0 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (95:5:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.39** (695 mg, 74%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.71 (dd, J = 11.6, 2.4 Hz, 1H), 3.72 (s, 3H), 2.14 - 2.04 (m, 1H), 1.66 (dqd, J = 14.8, 7.4, 2.4 Hz, 1H), 1.29 (d, J = 6.9 Hz,

6H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 174.8, 95.7, 52.7, 45.9, 23.1, 22.7, 20.5, 11.2; FTIR (cm^{-1}) 1734, 1558, 1257, 1148, 668; GC/MS (EI) 158.1 $(M\text{-}C_4H_9O)^+$. HRMS (CI) m/z, calculated for $[C_8H_{16}NO_4]^+$: 190.1079; found: 190.1069.

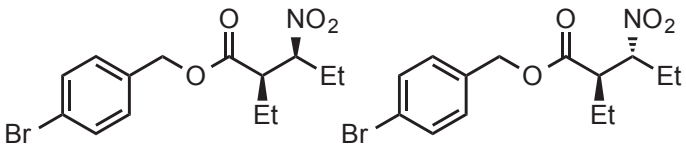


(**3.40**). According to general protocol D: CuBr (143 mg, 1.00 mmol), ligand **3.33** (306 mg, 1.00 mmol), sodium trimethylsilanolate (314 mg, 2.80 mmol), anhydrous dichloromethane (12 mL), 1-nitropropane (232 μL, 2.60 mmol), and *tert*-butyl bromoacetate (295 μL, 2.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.40** (210 mg, 52%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.81 – 4.74 (m, 1H), 3.04 (dd, J = 17.1, 9.6 Hz, 1H), 2.60 (dd, J = 17.1, 4.3 Hz, 1H), 2.01 – 1.84 (m, 2H), 1.43 (s, 9H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 168.6, 84.9, 82.2, 38.1, 28.1, 27.2, 10.1; FTIR (cm^{-1}): 1733, 1555, 1370, 1256, 1159; GC/MS (EI): 148.1 $(M\text{-}C_4H_7)^+$. HRMS (CI) m/z, calculated for $[C_9H_{18}NO_4]^+$: 204.1236; found: 204.1235.



(**3.41**). According to general protocol C: CuBr (144 mg, 1.00 mmol), ligand **3.33** (306 mg, 1.00 mmol), sodium trimethylsilanolate (617 mg, 5.50 mmol), anhydrous benzene (30 mL), 1-nitropropane (536 μL, 6.00 mmol), and *tert*-butyl α-bromoisobutyrate (933 μL, 5.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h.

The reaction was worked up according to the general protocol and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.41** (830 mg, 72%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.68 (dd, *J* = 11.5, 2.4 Hz, 1H), 2.15 - 2.02 (m, 1H), 1.70 - 1.61 (m, 1H), 1.45 (s, 9H), 1.24 (d, *J* = 10.4 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.3, 95.8, 82.0, 46.3, 28.0, 23.2, 22.9, 20.5, 11.4; FTIR (cm^{-1}): 1733, 1552, 1369, 1144, 848; GC/MS (EI) 158.1 $(M\text{-}C_4H_9O)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{22}NO_4]^+$: 232.1549; found: 232.1560.



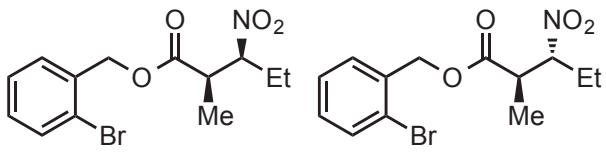
3.42A **dr: 41 : 59** **3.42B**

(**3.42**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.2 mg, 200 μmol), sodium trimethylsilanolate (145 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and **3.91** (336 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 41:59 mixture of syn and anti isomers. These products were purified by flash silica chromatography (95:5:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.42** (297 mg, 87%).

3.42A (128 mg, 37%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 7.51 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 5.14 – 5.08 (m, 1H), 4.58 (td, *J* = 10.3, 3.2 Hz, 1H), 2.92 (td, *J* = 9.8, 3.9 Hz, 1H), 1.93 (ddq, *J* = 14.4, 10.6, 7.2 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.58 – 1.51 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR

(151 MHz, $CDCl_3$) d 171.4, 134.2, 131.9, 130.2, 122.7, 90.8, 66.2, 50.5, 25.6, 23.0, 11.0, 10.3; FTIR (cm^{-1}) 2971, 1736, 1552, 1490, 1376, 1272, 1170, 806; GC/MS (EI) 256.0 $(M\text{-}C_2H_4NO_2)^+$. HRMS (LIFDI) m/z, calculated for $[C_{14}H_{18}NO_4Br]^+$: 343.0414; found: 343.0415.

3.42B (169 mg, 49%, yellow oil): ^1H NMR (600 MHz, $CDCl_3$) d 7.51 – 7.47 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 5.08 (s, 1H), 4.70 (td, *J* = 9.1, 3.7 Hz, 1H), 3.06 (td, *J* = 9.2, 4.2 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.89 (ddq, *J* = 14.7, 8.8, 7.3 Hz, 1H), 1.79 – 1.69 (m, 1H), 1.63 (ddq, *J* = 14.5, 8.9, 7.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.9, 134.3, 131.8, 130.0, 122.6, 88.9, 66.2, 48.3, 24.1, 21.7, 10.8, 9.5; FTIR (cm^{-1}) 2973, 1735, 1551, 1489, 1375, 1184, 808; GC/MS (EI) 256.0 $(M\text{-}C_2H_4NO_2)^+$. HRMS (LIFDI) m/z, calculated for $[C_{14}H_{18}NO_4Br]^+$: 343.0414; found: 343.0431.

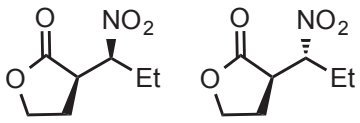


3.43A **dr: 44 : 56** **3.43B**

(**3.43**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and **3.92** (323 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 44:56 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.43** (256 mg, 78% combined).

3.43A (110 mg, 34%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 7.61 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.34 (td, *J* = 7.5, 1.0 Hz, 1H), 7.23 (td, *J* = 7.8, 1.7 Hz, 1H), 5.25 (d, *J* = 12.6 Hz, 1H), 5.23 (d, *J* = 12.6 Hz, 1H), 4.63 (td, *J* = 9.9, 3.6 Hz, 1H), 3.08 - 3.01 (m, 1H), 2.05 - 1.95 (m, 1H), 1.83 - 1.74 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 172.1, 134.6, 133.2, 130.7, 130.4, 127.8, 124.0, 91.7, 67.0, 43.5, 25.8, 14.5, 10.5; FTIR (cm^{-1}) 2925, 1740, 1557, 1457, 1154**;** GC/MS (EI) 250.1 $(M\text{-}Br)^{+}$. HRMS (CI) m/z, calculated for $[C_{13}H_{17}NO_4Br]^{+}$: 330.0341; found: 330.0346.

3.43B (147 mg, 44%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 7.59 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 7.33 (td, *J* = 7.5, 1.0 Hz, 1H), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H), 5.22 (s, 2H), 4.73 (td, *J* = 8.6, 3.9 Hz, 1H), 3.29 - 3.22 (m, 1H), 2.02 - 1.89 (m, 2H), 1.28 (d, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H);^{13}C NMR (151 MHz, $CDCl_3$) d 172.6, 134.8, 133.1, 130.4, 130.2, 127.8, 123.8, 89.7, 66.9, 41.9, 23.7, 13.5, 9.6; FTIR (cm^{-1}) 2930, 1739, 1554, 1257, 1100, 812; GC/MS (EI) 250.1 $(M\text{-}Br)^{+}$. HRMS (CI) m/z, calculated for $[C_{13}H_{17}NO_4Br]^{+}$: 330.0341; found: 330.0331.



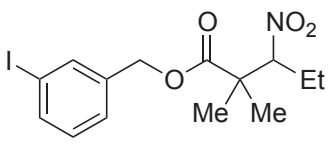
3.44A **dr: 52 : 48** **3.44B**

(**3.44**). According to general protocol C: CuBr (86.1 mg, 600 μmol), ligand **3.33** (184 mg, 600 μmol), sodium trimethylsilanolate (438 mg, 3.90 mmol), anhydrous dichloromethane (18 mL), 1-nitropropane (321 μL, 3.60 mmol), and a-bromo-g-butyrolactone (287 μL, 3.00 mmol) were combined under N_2 and heated at 40 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 52:48 mixture of syn and anti

isomers. These products were separated and purified by flash silica chromatography (85:15:1 hexanes : ethyl acetate : acetic acid → 80:20:1 hexanes : ethyl acetate: acetic acid) to afford nitrolactone **3.44** (413 mg, 80% combined).

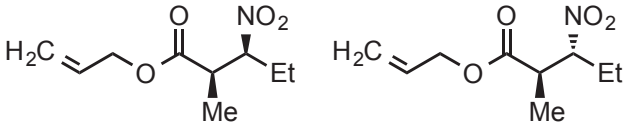
3.44A (227 mg, 44%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.72 - 4.61 (m, 1H), 4.44 (td, *J* = 9.0, 2.7 Hz, 1H), 4.27 (td, *J* = 9.4, 6.9 Hz, 1H), 3.08 - 3.02 (m, 1H), 2.42 - 2.35 (m, 1H), 2.35 - 2.22 (m, 2H), 2.21 - 2.12 (m, 1H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 174.6, 88.7, 66.4, 41.9, 25.7, 25.5, 10.4; FTIR (cm^{-1}) 1771, 1550, 1377, 1173, 1022, 805; GC/MS (EI) 127.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_7H_{12}NO_4]^+$: 174.0766; found: 174.0762.

3.44B (186 mg, 36%, yellow solid): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.79 - 4.68 (m, 1H), 4.43 (td, *J* = 9.0, 2.0 Hz, 1H), 4.26 (td, *J* = 9.7, 6.6 Hz, 1H), 3.32 (ddd, *J* = 11.6, 9.1, 5.5 Hz, 1H), 2.49 - 2.37 (m, 1H), 2.33 - 2.22 (m, 1H), 2.19 - 2.08 (m, 1H), 1.86 - 1.74 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 174.5, 87.9, 66.6, 42.3, 24.7, 23.9, 10.6; FTIR (cm^{-1}) 1769, 1553, 1378, 1175, 1022, 807; GC/MS (EI) 126.1 $(M\text{-}HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_7H_{12}NO_4]^+$: 174.0766; found: 174.0746; mp = 54 - 57°C. Crystals used for X-ray analysis were obtained by slow evaporation of dichloromethane.



(**3.45**). According to general protocol C: CuBr (28.7 mg, 200 µmol), ligand **3.33** (61.2 mg, 200 µmol), sodium trimethylsilanolate (145 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 µL, 1.40 mmol), and **3.93** (383 mg, 1.00 mmol)

were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.45** (307 mg, 79%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.69 – 7.67 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 5.14 – 5.02 (m, 2H), 4.71 (dd, *J* = 11.6, 2.4 Hz, 1H), 2.09 (ddq, *J* = 14.3, 11.6, 7.1 Hz, 1H), 1.61 (dqd, *J* = 14.8, 7.5, 2.4 Hz, 1H), 1.31 (d, *J* = 2.2 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.8, 137.6, 137.5, 137.1, 130.4, 127.4, 95.5, 94.3, 66.2, 45.9, 23.0, 22.7, 20.4, 11.1; FTIR (cm^{-1}) 2977, 1734, 1550, 1472, 1251, 1144, 779; GC/MS (EI) 391.0 $(M)^+$. HRMS (LIFDI) m/z, calculated for $[C_{14}H_{18}NO_4I]^+$: 391.0276; found: 391.0251.

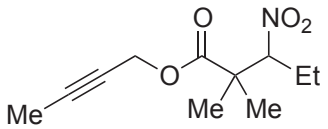


3.46A **dr: 43 : 57** **3.46B**

(**3.46**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and allyl 2-bromopropionate (192 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 48 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 43:57 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (95:5:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.46** (95.8 mg, 48% combined).

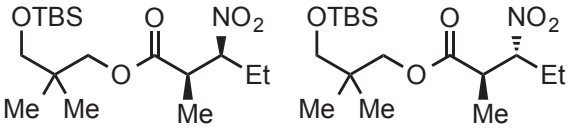
3.46A (40.5 mg, 20%, clear oil): ^{1}H NMR (600 MHz, C_6D_6) d 5.62 (ddt, *J* = 16.2, 11.3, 5.7 Hz, 1H), 5.04 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.93 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.42 (dt, *J* = 8.5, 4.2 Hz, 1H), 4.37 – 4.28 (m, 2H), 2.95 – 2.88 (m, 1H), 1.40 – 1.30 (m, 2H), 0.74 (d, *J* = 7.3 Hz, 3H), 0.54 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, C_6D_6) d 172.3, 132.1, 118.3, 89.7, 65.7, 41.8, 23.7, 13.2, 9.3; FTIR (cm^{-1}): 2980, 1737, 1650, 1552, 1188, 937, 810; GC/MS (EI) 155.1 $(M\text{-}NO_2)^+$. HRMS (LIFDI) m/z, calculated for $[C_9H_{15}NO_4]^+$: 201.0996; found: 201.1026.

3.46B (55.3 mg, 28%, clear oil): ^{1}H NMR (600 MHz, C_6D_6) d 5.70 (ddd, *J* = 22.9, 11.0, 5.8 Hz, 1H), 5.13 (dq, 1H), 5.03 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.57 (ddd, *J* = 10.0, 8.9, 3.8 Hz, 1H), 4.44 - 4.36 (m, 2H), 2.84 - 2.77 (m, 1H), 1.83 - 1.75 (m, 1H), 1.53 - 1.43 (m, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.68 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) d 171.7, 132.0, 128.6, 118.5, 91.5, 65.6, 43.3, 25.4, 13.9, 10.3; FTIR (cm^{-1}): 2979, 1735, 1557, 1373, 810; GC/MS (EI) 155.1 $(M\text{-}NO_2)^+$. HRMS (LIFDI) m/z, calculated for $[C_9H_{15}NO_4]^+$: 201.0996; found: 201.0999.



(**3.47**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous benzene (6 mL), 1-nitropropane (107 μL, 1.20 mmol), and **3.94** (219 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. The crude reaction mixture was passed through a short plug of silica gel (80:20:1 hexanes : ethyl acetate : acetic acid). All fractions were pooled, concentrated *in vacuo*, and resubjected to silica gel flash

chromatography (95:5 hexanes : ethyl acetate) to afford nitroester **3.47** (149 mg, 66%) as a yellow oil: NOTE: **3.47** is not stable under prolonged exposure to glacial acetic acid. ^{1}H NMR (600 MHz, $CDCl_3$) d 4.75 (dd, *J* = 11.6, 2.4 Hz, 1H), 4.71 (dq, *J* = 15.1, 2.3 Hz, 0H), 4.65 (dq, *J* = 15.1, 2.3 Hz, 0H), 2.16 - 2.06 (m, 1H), 1.86 (t, *J* = 2.4 Hz, 3H), 1.67 (dtd, *J* = 14.8, 7.5, 5.0 Hz, 1H), 1.31 (d, *J* = 7.1 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.7, 95.5, 83.8, 72.7, 53.9, 46.0, 23.3, 22.9, 20.1, 11.2, 3.8; FTIR (cm^{-1}): 2240, 1734, 1553, 1142, 114, 668; GC/MS (EI) 158.1 $(M\text{-}C_4H_5O)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{18}NO_4]^+$: 228.1236; found: 228.1237.



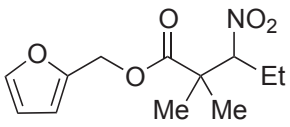
3.48A **dr: 40 : 60** **3.48B**

(**3.48**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and **3.95** (353 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 40:60 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (99:1:1 hexanes : diethyl ether : acetic acid) to afford nitroester **3.48** (312 mg, 86% combined).

3.48A (123 mg**,** 34%, clear oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.59 (td, *J* = 9.9, 3.5 Hz, 1H), 3.93 (d, *J* = 1.9 Hz, 2H), 3.33 (s, 2H), 3.04 - 2.93 (m, 1H), 2.04 - 1.93 (m, 1H), 1.85 - 1.75 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 - 0.88

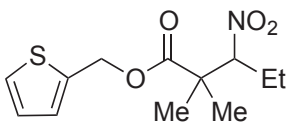
(m, 15H), 0.03 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 172.4, 91.9, 70.4, 68.4, 43.7, 36.3, 26.0, 25.8, 21.6, 18.4, 14.7, 10.54 -5.43; FTIR (cm^{-1}) 1739, 1556, 1257, 1099, 838, 668; GC/MS (EI) 304.1 $(M\text{-}C_4H_9)^+$. HRMS (CI) m/z, calculated for $[C_{17}H_{36}NO_5Si]^+$: 362.2363; found: 362.2358.

3.48B (189 mg, 52%, clear oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.69 (td, *J* = 8.6, 4.0 Hz, 1H), 3.91 (q, *J* = 2.9 Hz, 2H), 3.31 (q, *J* = 2.6 Hz, 2H), 3.23 - 3.15 (m, 1H), 2.02 - 1.89 (m, 2H), 1.25 (d, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 - 0.86 (m, 15H), 0.03 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 172.8, 89.8, 70.5, 68.6, 42.1, 36.4, 26.0, 23.8, 21.5, 18.5, 13.5, 9.7, -5.45; FTIR (cm^{-1}): 1734, 1558, 1099, 838, 668; GC/MS (EI) 304.1 $(M\text{-}C_4H_9)^+$. HRMS (CI) m/z, calculated for $[C_{17}H_{36}NO_5Si]^+$: 362.2363; found: 362.2390.

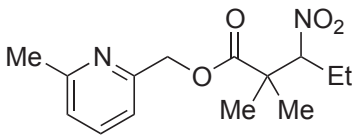


(**3.49**). According to general protocol C: CuBr (464 mg, 3.20 mmol), ligand **3.33** (995 mg, 3.20 mmol), sodium trimethylsilanolate (2.36 mg, 21.0 mmol), anhydrous benzene (95 mL), 1-nitropropane (2.02 mL, 22.7 mmol), and **3.96** (4.00 g, 16.2 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (95:5:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.49** (2.91 g, 70%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.44 - 7.40 (m, 1H), 6.42 (d, *J* = 3.2 Hz, 1H), 6.38 - 6.36 (m, 1H), 5.16 (d, *J* = 13.1 Hz, 1H), 5.06 (d, *J* = 13.1 Hz, 1H), 4.71 (dd, *J* = 11.5, 2.3 Hz, 1H), 2.12 - 2.01 (m, 1H), 1.62 - 1.51 (m, 1H), 1.28 (d, *J* = 2.9 Hz, 6H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 173.9,

149.0, 143.6, 111.1, 110.7, 95.5, 59.0, 46.0, 23.3, 22.8, 20.1, 11.2; FTIR (cm^{-1}): 2979, 1734, 1552, 1249, 1153, 748, 600; GC/MS (EI) 129.1 $(M\text{-}C_6H_5O_3)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{17}NO_5]^+$: 255.1102; found: 255.1105.

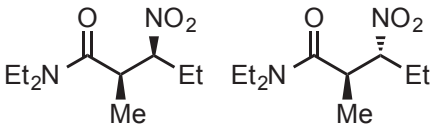


(**3.50**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous benzene (6 mL), 1-nitropropane (107 μL, 1.20 mmol), and **3.97** (263 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.50** (177 mg, 65%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.33 (d, *J* = 5.1 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.99 (t, *J* = 4.3 Hz, 1H), 5.36 (d, *J* = 12.7 Hz, 1H), 5.27 (d, *J* = 12.7 Hz, 1H), 4.72 (dd, *J* = 11.6, 2.2 Hz, 1H), 2.12 - 2.02 (m, 1H), 1.62 - 1.52 (m, 1H), 1.28 (d, *J* = 4.5 Hz, 6H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.9, 137.4, 128.5, 127.2, 127.0, 95.5, 61.6, 45.9, 23.3, 22.8, 20.1, 11.2; FTIR (cm^{-1}): 2978, 1734, 1551, 1248, 1141; GC/MS (EI) 129.1 $(M\text{-}C_6H_5O_2S)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{17}NO_4S]^+$: 271.0873; found: 271.0859.



(**3.51**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (126 μL, 1.40 mmol), and **3.98** (272 mg, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction

was worked up according to the general protocol and purified by flash silica chromatography (65:35:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.51** (221 mg, 79%) as a dark yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.60 (t, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 11.3, 7.7 Hz, 2H), 5.27 - 5.18 (m, 2H), 4.78 (dd, *J* = 11.6, 2.4 Hz, 1H), 2.55 (s, 3H), 2.16 - 2.06 (m, 1H), 1.74 - 1.66 (m, 1H), 1.34 (d, *J* = 3.8 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 174.0, 158.5, 154.6, 137.2, 122.8, 118.8, 95.6, 67.9, 46.1, 24.5, 23.4, 22.9, 20.3, 11.2; FTIR (cm^{-1}) 2957, 1739, 1557, 1256, 1100, 838; GC/MS (EI) 234.2 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{21}N_2O_4]^+$: 281.1501; found: 281.1493.



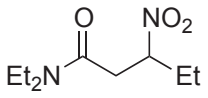
3.52A **dr: 32 : 68** **3.52B**

(**3.52**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and 2-bromo-*N,N*-diethylpropionamide (162 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 32:68 mixture of syn and anti isomers. These isomers were separated and purified by flash silica chromatography using 5-20 μm silica gel (80:20:2 hexanes : ethyl acetate : acetic acid) to afford nitroamide **3.52** (209 mg, 97% combined).

3.52A (66.7 mg, 31%, clear oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.72 – 4.66 (m, 1H), 3.45 – 3.30 (m, 4H), 3.12 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.88 – 1.73 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H);

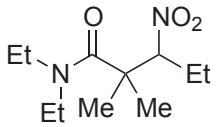
^{13}C NMR (101 MHz, $CDCl_3$) d 171.3, 93.9, 42.4, 40.9, 40.2, 26.1, 16.0, 15.2, 13.1, 10.6; FTIR (cm^{-1}): 2975, 1636, 1550, 1457, 1436, 1375; GC/MS (EI) 170.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{21}N_2O_3]^+$: 217.1552; found: 217.1543.

3.52B (142 mg, 66%, clear oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.84 (td, *J* = 9.4, 3.4 Hz, 1H), 3.41 – 3.24 (m, 5H), 2.12 – 2.02 (m, 1H), 1.89 – 1.79 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.3, 90.8, 42.2, 40.7, 38.4, 24.2, 14.7, 14.5, 13.0, 9.6; FTIR (cm^{-1}): 2976, 1652, 1636, 1558, 1548, 1457, 1376; GC/MS (EI) 170.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{21}N_2O_3]^+$: 217.1552; found: 217.1561.

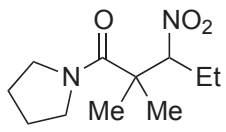


(**3.53**). According to general protocol D: CuBr (144 mg, 1.00 mmol), ligand **3.33** (306 mg, 1.00 mmol), sodium trimethylsilanolate (314 mg, 2.80 mmol), anhydrous dichloromethane (12 mL), 1-nitropropane (232 μL, 2.60 mmol), and 2-bromo-*N,N*-diethylacetamide (282 μL, 2.00 mmol) were combined under N_2 in a sealed reaction vessel and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (90:10:2 hexanes : acetone : acetic acid) to afford nitroamide **3.53** (215 mg, 53%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 5.05 – 4.99 (m, 1H), 3.41 – 3.28 (m, 4H), 3.16 (dd, *J* = 16.5, 8.9 Hz, 1H), 2.58 (dd, *J* = 16.5, 4.4 Hz, 1H), 2.01 – 1.89 (m, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 167.4, 85.3, 42.0, 40.6, 35.7, 27.4, 14.3, 13.1, 10.3; FTIR (cm^{-1}):

2975, 1645, 1551, 1458, 1437, 1378, 1268; GC/MS (EI) 156.1 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{19}N_2O_3]^+$: 203.1396; found: 203.1394.

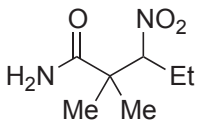


(**3.54**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.2 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and **3.99** (176 μL, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (65:32:3:1 hexanes : toluene : ethyl acetate : acetic acid) to afford nitroester **3.54** (57.6 mg, 25%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.94 (dd, *J* = 11.3, 1.8 Hz, 1H), 3.47 (s, 2H), 3.33 (s, 2H), 2.07 (ddq, *J* = 14.3, 11.4, 7.1 Hz, 1H), 1.70 (dqd, *J* = 14.9, 7.5, 1.9 Hz, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.18 – 1.14 (m, 6H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.6, 96.3, 45.8, 42.3, 23.3, 23.3, 20.6, 11.4; GC/MS (EI) 184.2 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{23}N_2O_3]^+$: 231.1709; found: 231.1689.



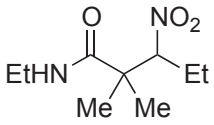
(**3.55**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol) and **3.100** (220 mg, 1.00 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous benzene (6

mL) and 1-nitropropane (126 μL, 1.40 mmol) were added via syringe and the resulting mixture was heated at 80 °C with rapid stirring for 24 h. The flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and concentrated *in vacuo*. The crude reaction was purified via column chromatography (80:20:1 hexanes : ethyl acetate : acetic acid → 50:50:1 hexanes: ethyl acetate: acetic acid) to afford nitroamide **3.55** (131 mg, 57%) as a brown oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.99 (dd, J = 11.4, 1.8 Hz, 1H), 3.53 (bs, 4H), 2.09 - 1.74 (m, 6H), 1.74 - 1.66 (m, 1H), 1.38 (s, 3H), 1.31 (s, 3H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 172.2, 96.1, 48.5 (b), 46.0, 27.4 (b), 23.1, 22.8, 19.9, 11.3; FTIR (cm^{-1}): 2975, 1616, 1558, 1542, 1340, 668; GC/MS (EI) 182.2 $(M\text{-}HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{21}N_2O_3]^+$: 229.1552; found: 229.1557.



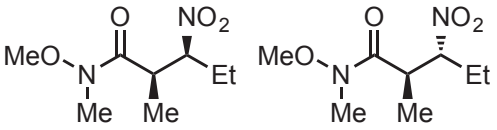
(**3.56**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol) and 2-bromo-2-methylpropionamide (166 mg, 1.00 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous benzene (6 mL) and 1-nitropropane (107 μL, 1.20 mmol) were added via syringe and the resulting mixture was heated at 60 °C with rapid stirring for 24 h. The flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and

concentrated *in vacuo*. The crude reaction was purified via column chromatography (50:50:1 hexanes : ethyl acetate : acetic acid) to afford nitroamide **3.56** (101 mg, 58%) as a yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 5.77 (s, 1H), 5.46 (s, 1H), 4.82 (dd, *J* = 11.7, 2.3 Hz, 1H), 2.14 - 2.02 (m, 1H), 1.76 - 1.67 (m, 1H), 1.32 (d, *J* = 13.7 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 176.6, 95.9, 45.6, 24.1, 22.8, 20.4, 11.2; FTIR (cm^{-1}): 3356, 3200, 1668, 1547, 1371, 812; GC/MS (EI) 128.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_7H_{15}N_2O_3]^+$: 175.1083; found: 175.1085; mp = 98-100 °C.



(**3.57**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), and sodium trimethylsilanolate (123 mg, 1.10 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous hexanes (3 mL) and 1-nitropropane (107 μL, 1.20 mmol) were added via syringe. To a separate hot 25 mL conical flask prepared as above was added **3.101** (194 mg, 1.00 mmol). The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. The solid was dissolved in anhydrous hexanes (2 mL) and added to the Schlenk flask. Additional anhydrous hexanes (1 mL) was used to rinse the flask. The resulting mixture was heated at 60 °C with rapid stirring for 24 h. The flask was then cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and concentrated *in vacuo*. The crude

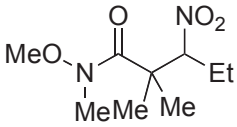
reaction was purified by flash silica chromatography (70:30:2 hexanes : ethyl acetate : acetic acid) to afford nitroamide **3.57** (175 mg, 87%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 5.80 (s, 1H), 4.82 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.31 – 3.25 (m, 2H), 2.07 – 1.98 (m, 1H), 1.64 (dqd, *J* = 14.8, 7.4, 2.4 Hz, 1H), 1.27 (d, *J* = 13.4 Hz, 6H), 1.14 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 173.6, 96.1, 45.5, 35.0, 24.0, 22.6, 20.0, 14.8, 11.2; FTIR (cm^{-1}): 3356, 2977, 1652, 1549, 1457, 1373; GC/MS (EI) 156.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{19}N_2O_3]^+$: 203.1396; found: 203.1391.



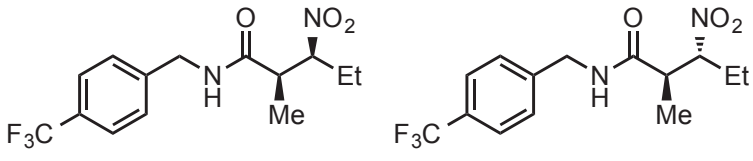
3.58A **dr: 32 : 68** **3.58B**

(**3.58**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (126 μL, 1.40 mmol), and 2-bromo-*N*-methoxy-*N*-methylpropanamide (196 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 32:68 mixture of syn and anti isomers. The crude reaction was purified by flash silica chromatography (70:30:1 hexanes : ethyl acetate : acetic acid) to afford an inseparable mixture of diastereomers of nitroamide **3.58** (168 mg, 82%) as a dark yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$: mixture of diastereomers; useful diagnostic peaks for each compound are listed. See attached spectra for details) d **3.58A**: 4.63 (td, *J* = 10.6, 3.0 Hz, 1H), 3.74 (s, 3H), 3.46 - 3.38 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H); **3.58B**: 4.81 (ddd, *J* = 10.0, 8.8, 3.5 Hz, 1H), 3.78 (s, 3H), 3.56 - 3.48 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d **3.58A**: 173.1, 92.9, 61.9, 38.2, 32.1,

26.0, 15.2, 10.4; **3.58B:** 173.6, 89.7, 61.5, 39.5, 32.3, 24.0, 13.7, 9.4; FTIR (cm^{-1}): 1662, 1653, 1558, 1550, 993, 668; GC/MS (EI) retention time= 9.339, 158.1 ($M\text{-}NO_2$); retention time= 9.582, 158.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_8H_{17}N_2O_4]^+$: 205.1188; found: 205.1206; found: 205.1180.



(**3.59**). According to general protocol C: CuBr (28.7 mg, 200 µmol), ligand **3.33** (61.2 mg, 200 µmol), sodium trimethylsilanolate (145 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 µL, 1.40 mmol), and **3.102** (210 mg, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (94:6:1 hexanes : ethyl acetate : acetic acid) to afford nitroalkane **3.59** (164 mg, 75%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 5.07 (dd, J = 11.6, 2.2 Hz, 1H), 3.73 (s, 3H), 3.19 (s, 3H), 2.16 – 2.05 (m, 2H), 1.58 (dqd, J = 14.8, 7.4, 2.2 Hz, 1H), 1.34 (s, 6H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 174.7, 94.3, 60.8, 46.6, 34.2, 22.4, 22.1, 20.3, 11.1; FTIR (cm^{-1}) 2978, 1653, 1549, 1458, 1366, 997; GC/MS (EI) 172.1 $(M\text{-}NO_2)^+$. HRMS (LIFDI) m/z, calculated for $[C_9H_{18}N_2O_4]$: 218.1267; found: 218.1281.



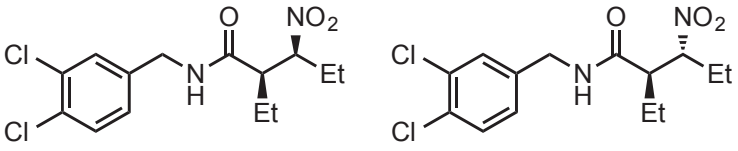
(**3.60**). According to general protocol C: CuBr (28.7 mg, 200 µmol), ligand **3.33** (61.3 mg, 200 µmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous benzene (6

mL), 1-nitropropane (107 μL, 1.20 mmol), and **3.103** (310 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 40:60 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography using 5-20 μm silica gel (80:20:2 hexanes : acetone : acetic acid) to afford nitroamide **3.60** (258 mg, 81% combined).

3.60A (102 mg, 32%, white solid): ^{1}H NMR (400 MHz, $CDCl_3$) d 7.60 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.13 (s, 1H), 4.63 (td, *J* = 10.3, 3.4 Hz, 1H), 4.56 – 4.43 (m, 2H), 2.74 (dq, *J* = 9.5, 6.8 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.73 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 171.8, 141.8, 130.2 (q, *J* = 32.6 Hz), 128.0, 125.9 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 273.2, 271.9 Hz), 92.5, 45.2, 43.3, 25.8, 15.7, 10.5; ^{19}F NMR (376 MHz, $CDCl_3$) d -62.6 (s); FTIR (cm^{-1}): 3307, 1652, 1636, 1540, 1558, 1338, 1111; GC/MS (EI) 272.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{18}F_3N_2O_3]^+$: 319.1270; found: 319.1273; mp = 123-125 °C.

3.60B (156 mg, 49%, white solid): ^{1}H NMR (400 MHz, $CDCl_3$) d 7.58 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 1H), 4.76 (td, *J* = 9.3, 3.5 Hz, 1H), 4.53 (dd, *J* = 15.3, 6.2 Hz, 1H), 4.41 (dd, *J* = 15.3, 5.6 Hz, 1H), 2.92 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.93 – 1.81 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.8, 142.0, 130.0 (q, *J* = 32.5 Hz), 127.9, 125.8 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 271.9 Hz), 90.6, 43.5, 43.2, 24.2, 14.7, 9.5; ^{19}F NMR (376 MHz, $CDCl_3$) d -62.5 (s); FTIR (cm^{-1}): 3284, 1651, 1548, 1326, 1123, 1068; GC/MS

(EI) 272.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{18}F_3N_2O_3]^+$: 319.1270; found: 319.1273; mp = 123-125 °C.



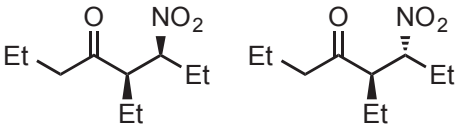
3.61A **dr: 46 : 54** **3.61B**

(**3.61**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), and sodium trimethylsilanolate (146 mg, 1.30 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous benzene (2 mL) and 1-nitropropane (126 μL, 1.40 mmol) were added via syringe. A separate hot 10 mL round bottom flask equipped with a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the septum was removed and **3.104** (325 mg, 1.00 mmol) was added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous benzene (3 mL) was added via syringe. The solution was added to the Schlenk flask via syringe. Anhydrous benzene (1 mL) was used to rinse the 10 mL round bottom flask and was then transferred via syringe to the 25 mL Schlenk flask. The resulting mixture was heated to 80 °C with rapid stirring in an oil bath for 24 h. Once the reaction was completed, the flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and concentrated *in vacuo*. NMR analysis revealed a 46:54 mixture of syn and anti

isomers. These products were separated and purified by flash silica chromatography (75:25:1 hexanes: ethyl acetate: glacial acetic acid) to afford nitroamide **3.61** (240 mg, 72% combined).

3.61A (127 mg, 37%, white solid): ^{1}H NMR (600 MHz, $CDCl_3$) d 7.42 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.13 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.00 (s, 1H), 4.61 (td, *J* = 10.5, 3.0 Hz, 1H), 4.48 - 4.37 (m, 3H), 2.54 (td, *J* = 10.0, 3.6 Hz, 1H), 1.93 - 1.84 (m, 1H), 1.82 - 1.74 (m, 4H), 1.51 - 1.42 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.90 (t, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) d 170.8, 138.1, 133.0, 132.0, 130.9, 129.9, 127.2, 91.9, 52.7, 42.8, 25.8, 23.6, 11.5, 10.5; FTIR (cm^{-1}): 3290, 3084, 1642, 1541, 1217, 820; GC/MS (EI) 288.0 $(M\text{-}HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{19}N_2O_3Cl_2]^+$: 335.0743; found: 335.0761; mp = 144-147 °C.

3.61B (117 mg, 35%, white solid): ^{1}H NMR (600 MHz, $CDCl_3$) d 7.40 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.09 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.89 (s, 1H), 4.76 (td, *J* = 9.6, 3.5 Hz, 1H), 4.46 - 4.33 (m, 2H), 2.68 (dt, *J* = 10.0, 5.0 Hz, 1H), 2.10 - 2.01 (m, 1H), 1.94 - 1.84 (m, 1H), 1.74 - 1.65 (m, 1H), 1.65 - 1.58 (m, 1H), 0.96 (td, *J* = 7.4, 3.2 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.7, 138.3, 132.9, 131.8, 130.9, 129.7, 127.1, 90.5, 51.1, 42.7, 24.5, 22.1, 11.7, 9.7; FTIR (cm^{-1}): 3292, 3086, 1650, 1549, 1472, 809; GC/MS (EI) 288.0 $(M\text{-}HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{19}N_2O_3Cl_2]^+$: 335.0743; found: 335.0723; mp = 133-136. Crystals used for X-ray analysis were obtained by slow evaporation of diethyl ether. .



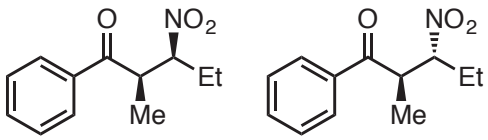
3.62A **dr: 48 : 52** **3.62B**

(**3.62**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.2 mg, 200 μmol), sodium trimethylsilanolate (145 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitropropane (125 μL, 1.40 mmol), and 3-bromo-4-heptanone (193 mg, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 48:52 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroketone **3.62** (148 mg, 74% combined).

3.62A (71.6 mg, 36%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.64 (td, *J* = 10.6, 2.9 Hz, 1H), 3.06 (ddd, *J* = 10.3, 8.1, 3.9 Hz, 1H), 2.53 – 2.40 (m, 2H), 1.86 (ddq, *J* = 14.4, 11.0, 7.2 Hz, 1H), 1.69 – 1.52 (m, 5H), 0.92 (q, *J* = 7.3 Hz, 6H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 210.1, 90.9, 55.5, 46.9, 25.9, 23.0, 16.75, 13.8, 10.6, 10.4; FTIR (cm^{-1}): 2970, 1713, 1551, 1461, 1376, 807; GC/MS (EI) 155.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{20}NO_3]^+$: 202.1443; found: 202.1433.

3.62B (76.7 mg, 38%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.78 (ddd, *J* = 10.2, 8.6, 3.5 Hz, 1H), 3.23 (ddd, *J* = 10.4, 7.7, 4.0 Hz, 1H), 2.50 (qt, *J* = 17.6, 7.4 Hz, 2H), 2.03 (dqd, *J* = 14.9, 7.5, 3.5 Hz, 1H), 1.83 (dp, *J* = 15.0, 7.4 Hz, 1H), 1.71 (dqd, *J* = 15.2, 7.6, 4.0 Hz, 1H), 1.66 – 1.55 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 210.6, 88.4, 53.1, 45.2, 24.2, 21.2, 16.8, 13.8, 10.4, 9.4; FTIR (cm^{-1}): 2970, 1713, 1551, 1461, 1375,

809; GC/MS (EI) 155.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{10}H_{20}NO_3]^+$: 202.1443; found: 202.1427.



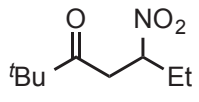
3.63A **dr: 27 : 73** **3.63B**

(**3.63**). According to general protocol C: CuBr (63.9 mg, 600 μmol), ligand **3.33** (183 mg, 600 μmol), sodium trimethylsilanolate (375 mg, 3.30 mmol), anhydrous benzene (18 mL), 1-nitropropane (320 μL, 3.60 mmol), and 2-bromopropiophenone (640 mg, 3.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 27:73 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (99:1:1 hexanes : ethyl acetate : acetic acid) to afford nitroketone **3.63** (606 mg, 91% combined).

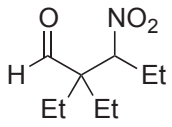
3.63A (166 mg, 25%, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 8.00 – 7.97 (m, 2H), 7.67 – 7.61 (m, 1H), 7.52 (dd, *J* = 8.3, 7.3 Hz, 2H), 4.84 (td, *J* = 10.4, 3.1 Hz, 1H), 4.02 (dq, *J* = 10.2, 7.0 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.80 – 1.75 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 199.7, 135.5, 134.0, 129.0, 128.5, 92.9, 44.1, 26.1, 16.1, 10.5; FTIR (cm^{-1}) 2975, 1682, 1549, 1374, 1210, 947; GC/MS (EI) 175.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{16}NO_3]^+$: 222.1130; found: 222.1145.

3.63B (440 mg, 66%, orange solid): ^{1}H NMR (400 MHz, $CDCl_3$) d 8.01 – 7.95 (m, 2H), 7.64 – 7.57 (m, 1H), 7.53 – 7.47 (m, 2H), 4.97 (ddd, *J* = 9.5, 8.4, 3.5 Hz, 1H),

4.19 (dq, *J* = 9.5, 7.3 Hz, 1H), 2.16 (dqd, *J* = 15.1, 7.6, 3.6 Hz, 1H), 1.96 (ddq, *J* = 14.6, 8.3, 7.4 Hz, 1H), 1.24 (d, *J* = 7.3 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 200.3, 135.1, 133.7, 128.9, 128.5, 89.4, 42.4, 23.9, 14.3, 9.4; FTIR (cm^{-1}) 2977, 1683, 1548, 1378, 1215, 975; GC/MS (EI) 145.0 $(M\text{-}C_6H_5)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{16}NO_3]^+$: 222.1130; found: 222.1113; mp= 70 – 71 °C. Crystals used for X-ray analysis were obtained by slow evaporation of dichloromethane.

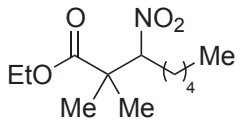


(**3.64**). According to general protocol C: CuBr (57.4 mg, 400 µmol), ligand **3.33** (123 mg, 400 µmol), sodium trimethylsilanolate (247 mg, 2.20 mmol), anhydrous benzene (12 mL), 1-nitropropane (214 µL, 2.40 mmol), and 1-bromopinacolone (270 µL, 2.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (95:5:2) hexanes : ethyl acetate : acetic acid to afford nitroketone **3.64** (193 mg, 52%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.93 – 4.87 (m, 1H), 3.41 (dd, *J* = 18.2, 9.0 Hz, 1H), 2.74 (dd, *J* = 18.3, 4.3 Hz, 1H), 1.98 – 1.84 (m, 2H), 1.16 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 211.5, 84.0, 44.2, 39.1, 27.2, 26.3, 10.2; FTIR (cm^{-1}): 2973, 1707, 1552, 1507, 1458, 1374; GC/MS (EI) 83.1 $(M–C_4H_{10}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{18}NO_3]^+$: 188.1287; found: 188.1290.

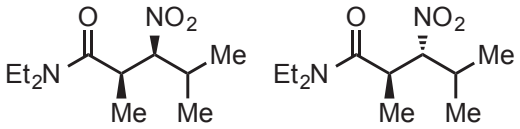


(**3.65**). According to general protocol C: CuBr (28.7 mg, 200 µmol), ligand **3.33** (61.3 mg, 200 µmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous benzene (6 mL), 1-nitropropane (107 µL, 1.20

mmol), and 2-bromo-2-ethylbutanal (138 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 48 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (95:5:1 hexanes : ethyl acetate : acetic acid) to afford nitroaldehyde **3.65** (99.0 mg, 53%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 9.67 (s, 1H), 4.56 (dd, *J* = 12.1, 2.7 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.88 (dqd, *J* = 14.8, 7.4, 2.7 Hz, 1H), 1.83 – 1.68 (m, 2H), 1.67 – 1.58 (m, 1H), 1.58 – 1.49 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 202.9, 94.9, 53.0, 22.4, 21.9, 21.4, 11.1, 7.6, 7.4; FTIR (cm^{-1}): 2976, 2946, 1724, 1557, 1458, 1373; GC/MS (EI) 141.1 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{18}NO_3]^+$: 188.1287; found: 188.1286.



(**3.66**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 1-nitrohexane (195 μL, 1.40 mmol), and ethyl α-bromoisobutyrate (147 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 48 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (99:1:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.66** (188 mg, 77%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.81 (dd, *J* = 11.6, 2.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.14 – 2.04 (m, 1H), 1.59 – 1.51 (m, 1H), 1.36 – 1.22 (m, 15H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 174.3, 93.9, 61.7, 45.9, 31.1, 29.4, 26.3, 23.3, 22.4, 20.2, 14.2, 14.0; FTIR (cm^{-1}): 2960, 2932, 1737, 1552, 1468, 1367, 1257, 1146; GC/MS (EI) 199.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{24}NO_4]^+$: 246.1705; found: 246.1721.



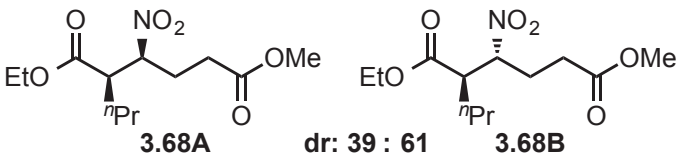
3.67A **dr: 38 : 62** **3.67B**

(**3.67**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 2-methyl-1-nitropropane (151 μL, 1.40 mmol), and 2-bromo-*N,N*-diethylpropionamide (162 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 38:62 mixture of syn and anti isomers. These products were separated and purified by flash silica chromatography (80:20:1 hexanes : ethyl acetate : acetic acid) to afford nitroamide **3.67** (207 mg, 90% combined).

3.67A (79.0 mg, 34%, clear oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.78 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.43 - 3.33 (m, 4H), 3.31 - 3.21 (m, 1H), 2.18 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 171.4, 96.7, 42.2, 40.6, 37.6, 30.4, 20.1, 17.2, 16.6, 14.9, 12.9; FTIR (cm^{-1}): 1636, 1545, 1457, 1374, 1134; GC/MS (EI) 184.2 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{23}N_2O_3]^+$: 231.1709; found: 231.1711.

3.67B (128 mg, 56%, clear oil): ^{1}H NMR (600 MHz, $CDCl_3$) d 4.87 (dd, *J* = 10.5, 2.9 Hz, 1H), 3.42 - 3.33 (m, 4H), 3.26 (dq, *J* = 14.0, 7.1 Hz, 1H), 2.23 - 2.16 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.06 (t, *J* = 7.1

Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 172.4, 94.2, 42.2, 40.7, 36.9, 28.0, 20.7, 15.8, 14.8, 14.5, 13.0; FTIR (cm^{-1}): 1636, 1544, 1458, 1377, 1099; GC/MS (EI) 184.2 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{11}H_{23}N_2O_3]^+$: 231.1709; found: 231.1707.

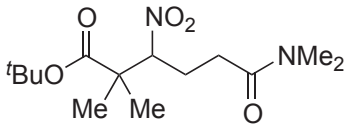


(**3.68**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous benzene (6 mL), methyl 4-nitrobutyrate (154 μL, 1.20 mmol), and ethyl 2-bromovalerate (171 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol. NMR analysis revealed a 39:61 mixture of syn and anti isomers. The products were purified by flash silica chromatography (90:10:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.68** as a mixture of diastereomers (244 mg, 89%) as a clear oil. Further chromatography allowed for purification of analytically pure samples of each diastereomer for characterization.

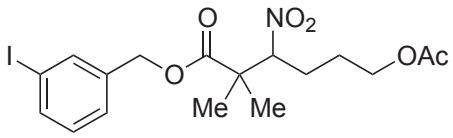
3.68A: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.73 – 4.67 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.67 (s, 3H), 2.95 (td, J = 9.7, 3.6 Hz, 1H), 2.42 – 2.28 (m, 2H), 2.28 – 2.19 (m, 1H), 2.12 – 2.04 (m, 1H), 1.72 – 1.63 (m, 1H), 1.43 – 1.20 (m, 6H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.1, 171.5, 88.7, 61.5, 52.1, 49.2, 31.7, 30.1, 27.0, 20.1, 14.3, 13.8; FTIR (cm^{-1}): 2962, 1738, 1554, 1439, 1375, 1178; GC/MS (EI)

229.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{22}NO_6]^+$: 276.1447; found: 276.1446.

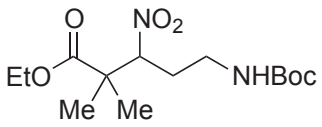
3.68B: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.79 (td, *J* = 10.1, 2.9 Hz, 1H), 4.16 (q, *J* = 6.3 Hz, 2H), 3.69 (s, 3H), 3.02 (td, *J* = 9.0, 4.3 Hz, 1H), 2.47 – 2.32 (m, 2H), 2.32 – 2.25 (m, 1H), 2.17 – 2.08 (m, 1H), 1.70 – 1.57 (m, 2H), 1.44 – 1.19 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.4, 172.0, 87.4, 61.5, 52.1, 48.1, 30.5, 29.7, 26.0, 19.9, 14.2, 14.0; FTIR (cm^{-1}): 2962, 1737, 1553, 1440, 1194, 1024; GC/MS (EI) 229.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{22}NO_6]^+$: 276.1447; found: 276.1431.



(**3.69**). According to general protocol C: CuBr (86.1 mg, 600 μmol), ligand **3.33** (184 mg, 600 μmol), sodium trimethylsilanolate (359 mg, 3.20 mmol), anhydrous dichloromethane (18 mL), *N,N*-dimethyl-4-nitrobutanamide (470 μL, 3.60 mmol), and *tert*-butyl α-bromoisobutyrate (560 μL, 3.00 mmol) were combined under N_2 and heated at 40 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (92:8:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.69** (612 mg, 67%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.72 (dd, *J* = 11.1, 2.3 Hz, 1H), 2.85 (d, *J* = 8.2 Hz, 6H), 2.30 - 2.18 (m, 2H), 2.17 - 2.04 (m, 2H), 1.34 (s, 9H), 1.17 (d, *J* = 12.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.2, 170.8, 93.3, 82.0, 46.4, 37.1, 35.6, 29.7, 27.9, 24.9, 22.1, 21.9; FTIR (cm^{-1}): 1730, 1653, 1550, 1149, 848; GC/MS (EI) 255.2 $(M-NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{27}N_2O_5]^+$: 303.1920; found: 303.1921.

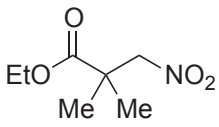


(**3.70**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), 4-nitrobutyl acetate (225 mg, 1.40 mmol), and **3.93** (382 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (92:8:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.70** (315 mg, 68%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.71 - 7.65 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.82 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.08 - 4.00 (m, 2H), 2.22 - 2.11 (m, 1H), 2.04 (s, 3H), 1.69 - 1.59 (m, 3H), 1.31 (d, *J* = 3.4 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.8, 171.0, 137.74, 137.7, 137.2, 130.5, 127.5, 94.5, 93.3, 66.4, 63.3, 46.1, 26.2, 25.9, 23.0, 21.0, 20.6; FTIR (cm^{-1}): 2954, 1737, 1551, 1241, 1139, 852; GC/MS (EI) 232.0 $(M\text{-}C_7H_6IO)^+$. HRMS (CI) m/z, calculated for $[C_{17}H_{23}INO_6]^+$: 464.0570; found: 464.0550.

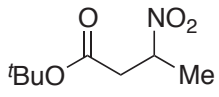


(**3.71**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.2 mg, 200 μmol), sodium trimethylsilanolate (145 mg, 1.30 mmol), anhydrous dioxane (6 mL), *tert*-butyl 3-nitropropylcarbamate (286 mg, 1.40 mmol), and ethyl 2-bromo-2-methyl propionate (195 mg, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (91:9:1 hexanes : ethyl

acetate : acetic acid) to afford nitroester **3.71** (243 mg, 76%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.90 – 4.85 (m, 1H), 4.72 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.32 – 3.25 (m, 1H), 3.04 (td, *J* = 14.4, 6.2 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.01 – 1.94 (m, 1H), 1.43 (s, 9H), 1.29 – 1.25 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) d 174.2, 156.0, 90.9, 79.8, 61.8, 45.8, 37.9, 29.5, 28.5, 22.5, 21.0, 14.1; FTIR (cm^{-1}) 3391, 2980, 1717, 1553, 1367, 1253, 1172; GC/MS (EI) 259.1 $(M\text{-}CO_2NH)^+$. HRMS (LIFDI) m/z, calculated for $[C_{14}H_{27}N_2O_6]^+$: 319.1869; found: 319.1884.

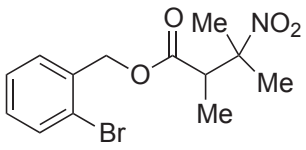


(**3.72**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous dichloromethane (6 mL), nitromethane (409 μL, 7.50 mmol), and ethyl α-bromoisobutyrate (147 μL, 1.00 mmol) were combined under N_2 and heated at 40 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography using 5-20 μm silica gel (90:10:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.72** (157 mg, 90%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.56 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.31 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 174.3, 82.4, 61.7, 42.3, 23.1, 14.2; FTIR (cm^{-1}): 2984, 1788, 1726, 1564, 1552, 1391, 1377, 1213, 1150; GC/MS (EI) 130.1 $(M\text{-}C_2H_5O)^+$. HRMS (CI) m/z, calculated for $[C_7H_{14}NO_4]^+$: 176.0923; found: 176.0931.



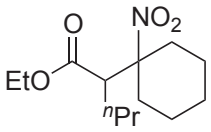
(**3.73**). According to general protocol D: CuBr (574 mg, 4.00 mmol), ligand **3.33** (1.22 g, 4.00 mmol), sodium

trimethylsilanolate (1.26 g, 11.2 mmol), anhydrous dichloromethane (47 mL), nitroethane (744 μL, 10.4 mmol), and *tert*-butyl bromoacetate (1.18 mL, 8.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (49.5:49.5:1:1 hexanes : toluene : diethyl ether : acetic acid) to afford nitroester **3.73** (937 mg, 62%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.89 (dqd, *J* = 8.7, 6.9, 5.0 Hz, 1H), 3.05 (dd, *J* = 17.0, 8.8 Hz, 1H), 2.61 (dd, *J* = 17.0, 4.9 Hz, 1H), 1.59 (d, *J* = 6.9 Hz, 2H), 1.44 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 168.4, 82.3, 78.9, 40.0, 28.1, 19.5; FTIR (cm^{-1}): 1733, 1558, 1369, 1160, 668; GC/MS (EI) 134.1 (M-C_4H_9O)$^+$. HRMS (CI) m/z, calculated for $[C_8H_{16}NO_4]^+$: 190.1079; found: 190.1061.



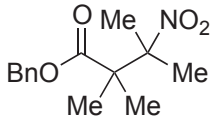
(**3.74**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), and sodium trimethylsilanolate (146 mg, 1.30 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous cyclohexane (6 mL) was added and the resulting mixture was heated with vigorous stirring in an oil bath at 60 °C for 1 h. 2-Nitropropane (126 μL, 1.40 mmol) and **3.92** (323 mg, 1.00 mmol) were added via syringe and the resulting mixture was allowed to continue heating at 60 °C with rapid stirring for 24 h. The flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through

magnesium sulfate and concentrated *in vacuo*. The crude reaction was purified via column chromatography (97:3:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.74** (239 mg, 73%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.59 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.33 (td, *J* = 7.5, 1.1 Hz, 1H), 7.21 (td, *J* = 7.7, 1.8 Hz, 1H), 5.20 (d, *J* = 4.2 Hz, 2H), 3.45 (q, *J* = 7.2 Hz, 1H), 1.66 (s, 3H), 1.62 (s, 3H), 1.25 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.1, 134.7, 133.1, 130.4, 130.2, 127.8, 123.8, 89.6, 66.7, 47.1, 23.8, 23.8, 13.2; FTIR (cm^{-1}): 2978, 1734, 1541, 753, 668**;** GC/MS (EI) 250.2 $(M\text{-}Br)^{+}$. HRMS (CI) m/z, calculated for $[C_{13}H_{17}NO_4Br]^{+}$: 330.0341; found: 330.0325.

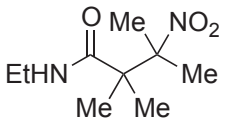


(**3.75**). According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (123 mg, 1.10 mmol), anhydrous dioxane (6 mL), nitrocyclohexane (148 μL, 1.20 mmol), and ethyl 2-bromovalerate (171 μL, 1.00 mmol) were combined under N_2 and heated at 60 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (99:1:2 hexanes : ethyl acetate : acetic acid) followed by basic workup of product mixture: 1M NaOH (1x), sat. NH_4Cl (1x), brine (1x), and filtration through basic alumina to afford nitroester **3.75** (172 mg, 67%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 4.21 – 4.12 (m, 2H), 2.83 (dd, *J* = 12.2, 2.7 Hz, 1H), 2.61 – 2.55 (m, 1H), 2.45 (dd, *J* = 14.6, 2.8 Hz, 1H), 1.85 – 1.60 (m, 5H), 1.53 – 1.44 (m, 1H), 1.44 – 1.12 (m, 9H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 171.8, 93.3, 61.2, 55.2, 33.3, 29.9, 29.3, 24.6, 22.4, 22.2, 21.1, 14.3, 13.9; FTIR (cm^{-1}): 2938, 1734, 1542, 1451, 1373, 1179,

1031; GC/MS (EI) 211.2 $(M–NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{13}H_{24}NO_4]^+$: 258.1705; found: 258.1723.

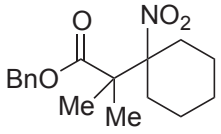


(**3.76**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (43.0 mg, 300 μmol), ligand **3.33** (91.8 mg, 300 μmol), and sodium trimethylsilanolate (157 mg, 1.40 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous cyclohexane (6 mL) was added and the resulting mixture was heated with vigorous stirring in an oil bath at 60 °C for 1 h. 2-Nitropropane (126 μL, 1.40 mmol) and benzyl 2-bromoisobutyrate (257 mg, 1.00 mmol) were added via syringe and the resulting mixture was allowed to continue heating at 80 °C with rapid stirring for 48 h. The flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and concentrated *in vacuo*. The crude reaction was purified via column chromatography (98:2:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.76** (118 mg, 45%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.40 - 7.32 (m, 5H), 5.13 (s, 2H), 1.65 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.9, 135.6, 128.7, 128.5, 128.4, 92.7, 67.4, 49.0, 23.4, 22.1; FTIR (cm^{-1}): 2990, 1728, 1539, 1267, 1121, 853; GC/MS (EI) 219.2 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{20}NO_4]^+$: 266.1392; found: 266.1373.

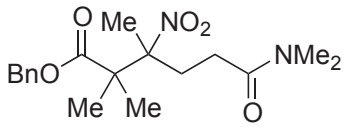


(**3.77**). A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (43.0 mg, 300 μmol), ligand **3.33** (91.8 mg, 300 μmol), and sodium trimethylsilanolate (157 mg, 1.40 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous cyclohexane (2 mL) was added and the resulting mixture was heated with vigorous stirring in an oil bath at 60 °C for 1h. 2-Nitropropane (126 μL, 1.40 mmol) was added via syringe. A separate hot 10 mL round bottom flask equipped with a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the septum was removed and **3.101** (194 mg, 1.00 mmol) was added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous cyclohexane (3 mL) was added via syringe. The solution was added to the Schlenk flask via syringe. Anhydrous cyclohexane (1 mL) was used to rinse the 10 mL round bottom flask and was then transferred via syringe to the 25 mL Schlenk flask. The resulting mixture was heated to 80 °C with rapid stirring in an oil bath for 48 h. Once the reaction was completed, the flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and concentrated *in vacuo*. The crude reaction was purified by flash silica gel chromatography (75:25:1 hexanes: ethyl acetate: glacial acetic acid) to afford nitroamide **3.77** (86.9 mg, 43%) as an orange solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 5.62 (s, 1H), 3.30 - 3.24 (m, 2H), 1.68 (s, 6H), 1.30 (s, 6H), 1.14 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 173.1, 93.5, 48.0, 35.0, 23.4, 22.0, 14.6; FTIR (cm^{-1}):

3378, 1636, 1533, 851, 668; GC/MS (EI) 156.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_9H_{19}N_2O_3]^+$: 203.1396; found: 203.1384; mp = 51 - 53°C.

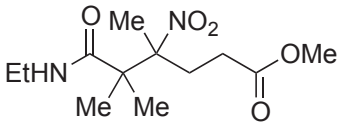


(**3.79**); According to general protocol C: CuBr (57.4 mg, 400 μmol), ligand **3.33** (122 mg, 400 μmol), sodium trimethylsilanolate (191 mg, 1.70 mmol), anhydrous *tert*-butanol (6 mL), nitrocyclohexane (197 μL, 1.60 mmol), and benzyl 2-bromoisobutyrate (257 mg, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (50: 50: 1 hexanes: ethyl acetate: glacial acetic acid) to afford nitroester **3.79** (101 mg, 33%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.41 - 7.32 (m, 5H), 5.11 (s, 2H), 2.61 (d, *J* = 13.1 Hz, 2H), 1.68 (d, *J* = 14.3 Hz, 2H), 1.62 - 1.52 (m, 3H), 1.27 (s, 6H), 1.19 (qt, *J* = 14.0, 3.3 Hz, 2H), 1.04 (qt, *J* = 13.2, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) d 173.6, 135.5, 128.7, 128.5, 128.5, 96.3, 67.4, 49.7, 30.1, 24.4, 22.6, 21.7; FTIR (cm^{-1}):1733, 1540, 1147, 1123, 845, 668; GC/MS (EI) 259.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{17}H_{23}O_2]^+$: 259.1698; found: 259.1708.



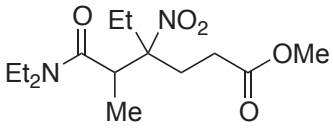
(**3.80**): According to general protocol C: CuBr (57.4 mg, 400 μmol), ligand **3.33** (122 mg, 400 μmol), sodium trimethylsilanolate (191 mg, 1.70 mmol), anhydrous *tert*-butanol (6 mL), *N,N*-dimethyl-4-nitropentamide (279 mg, 1.60 mmol), and benzyl 2-bromoisobutyrate (257 mg, 1.00 mmol) was combined under N_2 and heated at 80 °C with rapid stirring for 24 h. The reaction was worked up according to the general

protocol and purified by flash silica chromatography (55:45:1 hexanes: ethyl acetate: glacial acetic acid) and a second column (25:75 hexanes: ethyl acetate → 50:50 hexanes : ethyl acetate) to afford nitroester **3.80** (248 mg, 71%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.38 - 7.30 (m, 5H), 5.11 (d, *J* = 1.9 Hz, 2H), 2.94 (d, *J* = 1.5 Hz, 6H), 2.74 (ddd, *J* = 14.8, 10.3, 5.3 Hz, 1H), 2.31 - 2.11 (m, 3H), 1.54 (s, 3H), 1.34 (d, *J* = 15.9 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.5, 171.3, 135.5, 128.7, 128.5, 128.4, 95.5, 67.4, 50.1, 37.3, 35.8, 30.2, 28.4, 22.1, 18.8; FTIR (cm^{-1}): 1950, 1730, 1651, 1540, 1266, 1147, 699; GC/MS (EI) 212.1 $(M\text{-}C_7H_8NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{18}H_{27}N_2O_5]^+$: 351.1920; found: 351.1949.



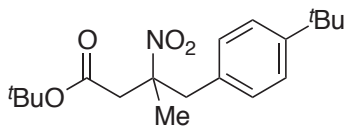
(**3.82**): A hot 25 mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the flask was backfilled with N_2, the septum was removed and CuBr (57.4 mg, 400 μmol), ligand **3.33** (122 mg, 400 μmol), and sodium trimethylsilanolate (191 mg, 1.40 mmol) were added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 five times. Anhydrous *tert*-butanol (2 mL) and *N,N*-dimethyl-4-nitropentamide (258 mg, 1.60 mmol) was added via syringe. A separate hot 10 mL round bottom flask equipped with a rubber septum was attached to a double manifold and cooled under vacuum. Once cool, the septum was removed and **3.101** (194 mg, 1.00 mmol) was added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_x five times. Anhydrous *tert*-butanol (3 mL) was added via syringe. The solution was added to the Schlenk flask via syringe. Anhydrous *tert*-butanol (1 mL) was used to rinse the 10 mL

round bottom flask and was then transferred via syringe to the 25 mL Schlenk flask. The resulting mixture was heated to 80 °C with rapid stirring in an oil bath for 24 h. Once the reaction was completed, the flask was cooled to room temperature, the septum was removed and diethyl ether (10 mL) was added. The solution was filtered through magnesium sulfate and concentrated *in vacuo*. The crude reaction was purified by flash silica gel chromatography (75:25:1 hexanes: ethyl acetate: glacial acetic acid) to afford nitroamide **3.82** (112 mg, 41%) as a yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 5.63 (s, 1H), 3.68 (s, 3H), 3.27 (dtd, *J* = 12.9, 7.3, 2.1 Hz, 2H), 2.81 (ddd, *J* = 14.6, 11.4, 4.6 Hz, 1H), 2.37 - 2.26 (m, 2H), 2.13 (ddd, *J* = 17.0, 11.3, 4.8 Hz, 1H), 1.58 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) d 172.8, 172.7, 95.8, 52.1, 48.9, 35.1, 30.0, 29.4, 22.0, 18.7, 14.6; FTIR (cm^{-1}):3375, 1740, 1653, 1540, 1201, 1177, 668; GC/MS (EI) 228.1 $(M\text{-}NO_2)^+$. HRMS (CI) m/z, calculated for $[C_{12}H_{22}NO_3]^+$: 228.1600; found: 228.1598; mp = 65 - 68 °C.

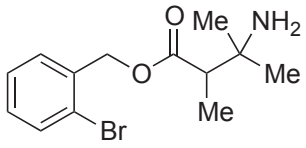


(**3.84**): To a 10 mL round bottom flask equipped with a magnetic stir bar was added b-nitroamide **3.52** (100 mg, 463 μmol), dimethylformamide (4.63 mL), 1,8-diazabicycloundec-7-ene (126 μL 1.39 mmol), and methyl acrylate (208 μL, 1.39 mmol). The reaction was stirred at room temperature for 5.5 h. Dichloromethane (5 mL) was added and the reaction was extracted with brine (10 mL, 4x). The aqueous layers were combined and extracted with dichloromethane (10 mL). The combined organic layers were dried with magnesium sulfate, filtered, concentrated *in vacuo*, and placed under vacuum until the pressure was under 0.20 mm Hg. The resulting oil was

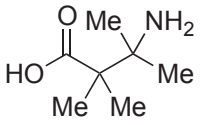
loaded onto a plug of silica gel and eluted with 1:1 ethyl acetate : hexanes to afford nitroamide **3.84** as a clear oil (117 mg, 84%, single diastereomer): ^{1}H NMR (600 MHz, $CDCl_3$) d 3.69 (s, 3H), 3.51 - 3.42 (m, 3H), 3.35 - 3.21 (m, 2H), 2.71 - 2.65 (m, 1H), 2.60 (ddd, *J* = 16.1, 11.4, 4.7 Hz, 1H), 2.52 (ddd, *J* = 16.1, 11.4, 4.9 Hz, 1H), 2.48 - 2.41 (m, 1H), 2.21 - 2.14 (m, 1H), 2.05 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.25 - 1.21 (m, 6H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 173.3, 171.3, 96.3, 52.0, 42.7, 41.6, 40.9, 29.4, 28.7, 28.0, 14.8, 14.7, 12.9, 8.9; FTIR (cm^{-1}): 1739, 1636, 1540, 1436, 1085, 668; GC/MS (EI) 271.1 $(M\text{-}CH_3O)^+$. HRMS (CI) m/z, calculated for $[C_{14}H_{27}N_2O_5]^+$: 303.1920; found: 303.1922.



(**3.85**): According to general protocol C: CuBr (28.7 mg, 200 μmol), ligand **3.33** (61.3 mg, 200 μmol), sodium trimethylsilanolate (146 mg, 1.30 mmol), anhydrous benzene (6 mL), **3.40** (265 mg, 1.40 mmol), and 4-*tert*-butylbenzyl bromide (184 μL, 1.00 mmol) were combined under N_2 and heated at 80 °C with rapid stirring for 48 h. The reaction was worked up according to the general protocol and purified by flash silica chromatography (99:1:1 hexanes : ethyl acetate : acetic acid) to afford nitroester **3.85** (212 mg, 64%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.31 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 3.27 - 3.20 (m, 2H), 3.05 (d, *J* = 16.5 Hz, 1H), 2.69 (d, *J* = 16.5 Hz, 1H), 1.65 (s, 3H), 1.44 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) d 168.3, 150.7, 131.3, 130.1, 125.7, 88.9, 82.1, 60.6, 45.3, 43.2, 31.5, 28.1, 23.0; FTIR (cm^{-1}): 2963, 1732, 1540, 1364, 1234, 1138**;** GC/MS (EI) 288.1 $(M\text{-}HNO_2)^+$. HRMS (CI) m/z, calculated for $[C_{19}H_{28}NO_4]^+$: 334.2018; found: 334.2002**;** mp = 111-114 °C.

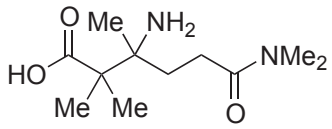


(**3.86**): Nitroester **3.74** (200 mg, 605 μmol) and acetic acid (2 mL) were added to a 10 mL round bottom flask equipped with a magnetic stir bar. The flask was cooled to 0 °C and Zn dust (346 mg, 6.05 mmol) was added portion wise. The mixture was warmed to room temperature and stirred for 6 h. The resulting solution was filtered through Celite and rinsed with ethyl acetate (5 mL, 2x). The organic filtrate was concentrated *in vacuo*, redissolved in ethyl acetate (10 mL) and washed with saturated $NaHCO_3$ (10 mL, 3x) to remove excess acetic acid. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford β-aminoester **3.86** (164 mg, 90%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) d 7.57 (d, J = 8.0 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.19 (td, J = 7.7, 1.5 Hz, 1H), 5.19 (s, 2H), 2.51 (q, J = 7.1 Hz, 1H), 1.20 (d, J = 7.1 Hz, 3H), 1.14 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) d 175.4, 135.4, 133.0, 130.4, 130.0, 127.6, 123.8, 65.9, 51.2, 50.5, 29.6, 28.0, 12.9; FTIR (cm^{-1}): 3378, 3061, 2969, 1731, 1210, 1146, 752; GC/MS (EI) 284.0 (M-CH_3)$^+$. HRMS (LIFDI) m/z, calculated for $[C_{13}H_{19}NO_2Br]^+$: 300.0599; found: 300.0605.



(**3.87**): Nitroester **3.76** (100 mg, 390 μmol), methanol (6.43 mL), water (1.13 mL), and Pd/C were added to a 25 mL round bottom flask equipped with a magnetic stir bar. Using a T joint adaptor the flask was evacuated and backfilled five time with N_2. A H_2 balloon was added to the T joint and the flask was evacuated and backfilled twenty times with H_2. The flask was heated in a 40 °C oil bath with rapid stirring for 18 h. The flask was cooled to room

temperature and the mixture was filtered through Celite. The solution was concentrated *in vacuo* to afford β-amino acid **3.87** (56.1 mg, 99%) as a white solid: ^{1}H NMR (400 MHz, MeOD) d 1.69 (s, 6H), 1.28 (s, 6H); ^{13}C NMR (101 MHz, DMSO) d 175.2, 92.6, 48.1, 22.8, 21.9; FTIR (cm^{-1}): 3019, 1701, 1540, 931, 697, 648; HRMS (LIFDI) m/z, calculated for $[C_7H_{16}NO_2]^+$: 146.1181; found: 146.1172; mp = 216 - 218 °C.



(**3.88**): Nitroester **3.80** (70.0 mg, 200 μmol), methanol (6.43 mL), water (1.13 mL), and Pd/C were added to a 25 mL round bottom flask equipped with a magnetic stir bar. Using a T joint adaptor the flask was evacuated and backfilled five times with N_2. A H_2 balloon was added to the T joint and the flask was evacuated and backfilled twenty times with H_2. The flask was heated in a 40 °C oil bath with rapid stirring for 18 h. The flask was cooled to room temperature and the mixture was filtered through Celite. The solution was concentrated *in vacuo* to afford β-amino acid **3.88** (45.2 mg, 98%) as a white solid: ^{1}H NMR (400 MHz, MeOD) d 2.89 (s, 1H), 2.79 (s, 1H), 2.67 – 2.57 (m, 1H), 2.33 – 2.25 (m, 1H), 2.17 – 2.09 (m, 1H), 2.02 – 1.95 (m, 1H), 1.49 (s, 1H), 1.20 (s, 1H), 1.14 (s, 1H); ^{13}C NMR (101 MHz, DMSO) d 174.9, 170.6, 95.2, 49.1, 36.6, 35.0, 29.7, 27.6, 21.8, 21.7, 18.4; FTIR (cm^{-1}): 2985, 2552, 1701, 1621, 1533, 1259, 834, 709; HRMS (LIFDI) m/z, calculated for $[C_{11}H_{23}N_2O_3]^+$: 231.1709; found: 231.1737; mp = 179 - 180 °C.

3.14.7 X-ray Structural Solution and Refinement

X-ray structural analysis for **3.44B**, **3.61B**, and **3.63B**: Crystals were mounted using viscous oil onto a glass fiber and cooled to the data collection temperature. Data

were collected on a Bruker-AXS APEX II CCD diffractometer with graphite-monochromated Mo-Kα radiation (l=0.71073 Å). Unit cell parameters were obtained from 36 data frames, 0.3º w, from three different sections of the Ewald sphere. The systematic absences in the diffraction data are consistent with $P2_1$ and $P2_1/m$ for **3.63B**, and, uniquely, for $P2_1/c$ for **3.61B**, and $P2_12_12_1$ for **3.44B**. For **3.63B**, the chiral nature of the molecule is consistent only in the noncentrosymmetric space group option, which yielded chemically reasonable and computationally stable results of refinement. The data-sets were treated with SADABS absorption corrections based on redundant multiscan data.[43] The structures were solved using direct methods and refined with full-matrix, least-squares procedures on F^2. For **3.63B**, refinement of the absolute structure parameter yielded nil indicating the true hand of the data-set had been determined consistent with absolute chirality in the molecule that is invariant during synthesis. The absolute chirality in **3.44B** was assigned to be consistent with the synthetic method. Structure **3.61B** was refined as a two-component psuedomerohedral twin with 56/44 refined ratio caused by a 0.38 ° rotation on a two-fold direct axis (1 0 0), reciprocal axis [4 0 1]. The lower than ideal C-C precision alert level B observed in **3.61B** is possibly an artifact of the pseudomerohedral twinning. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were treated as idealized contributions with geometrically calculated positions and with U_{eq} equal to 1.2, or 1.5 for methyl, U_{iso} of the attached atom. Structure factors are contained in the SHELXTL 6.12 program library.[43]

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(22) See section 3.14.3 for further details regarding this analysis.

(23) See section 3.14.3 for further details regarding this analysis. Note: With the possible exceptions of **3.35** and **3.44**, we believe this product mixture to be kinetic in origin. See section 3.10 for further details.

(24) Interestingly, although a 63:37 mixture of diastereoisomers was taken into the reaction, only a single diastereomer of the conjugate addition product was formed (as determined by NMR), suggesting that the reaction is highly diastereoselective. Future studies will be directed at determining the generality and stereoselectivity of this process.

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Chapter 4

ADDITIONAL NITROALKANE *C*-ALKYLATION PARTNERS

The following reactions discussed in this chapter represent preliminary studies aimed at expanding the scope of the copper-catalyzed *C*-alkylation of nitroalkanes. While not yet published, the research described herein has established the potential of several new classes of electrophilic *C*-alkylation coupling partners. The elaboration of these results into publishable work is either currently being pursued by other co-workers or will be investigated by future co-workers in the Watson lab.

4.1 Towards 1,2- and 1,3-Diamines

Recognizing the potential of our group's newly developed *C*-alkylation conditions for nitroalkanes I looked for other classes of electrophiles that might suitably act as alkylating agents for nitroalkanes at carbon. In both of the previously studies (Chapters 2 and 3) I successfully demonstrated nitroalkanes could be alkylated using alkyl halides bearing radical stabilizing groups. Both nitro and nitrile groups have been shown to stabilize alkyl radicals. Moreover, both α-halonitroalkanes (**4.1**) and α-halonitriles (**4.2**) have previously been shown to participate in radical mediated reactions, including as radical initiators in atom transfer radical polymerization (ATRP) chemistry.[1] I recognized that if these classes of electrophiles successfully participated in the copper catalyzed *C*-alkylation of nitroalkanes, 1,2-dinitroalkanes (**4.3**) and 1,2-cyanonitroalkanes (**4.4**) would result, respectively (Figure 4.1). These products would allow facile access to 1,2- and 1,3-diamines (**4.5** and **4.6**) upon

reduction. Additionally, all stereocenters in the alkylated products are readily epimerizable, which might allow for interesting routes to control diastereomeric ratios in the products.

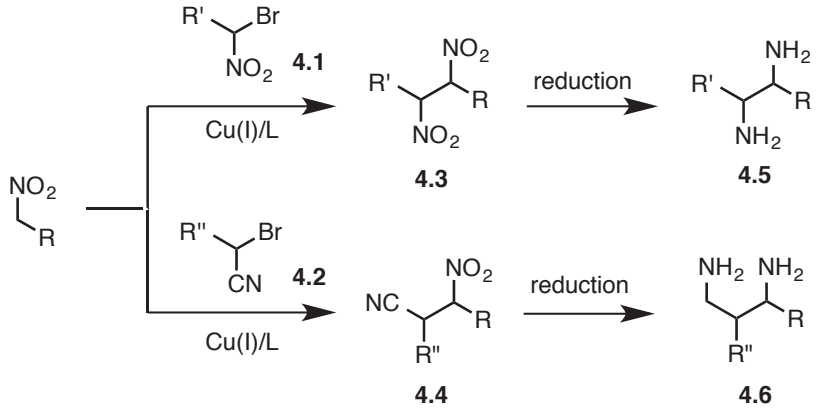


Figure 4.1: Proposed access to 1,2- and 1,3-diamines

4.2 Photolytic Formation of 1,2-Dinitro- and 1,2-Cyanonitroalkanes

In parallel studies to use α-nitroesters and –ketones as alkylating agents for nitroalkanes, the Kornblum group investigated the use of both 1,1-dinitroalkanes[2] and α-nitrocyanoalkanes[2-3] as coupling partners for the lithium salt of 2-nitropropane using photolytic conditions. They found that both dinitroalkane **4.7** and α-nitrocyanoalkane **4.9** served as alkylating partners for the lithium salt of 2-nitropropane (Figure 4.2). While the simple non-functionalized alkylation partners investigated suggest nitro- and cyano-stabilized radicals might serve as alkylating agents for nitroalkanes, the starting materials required for this coupling severely limit the usefulness of the transformation in synthesis.

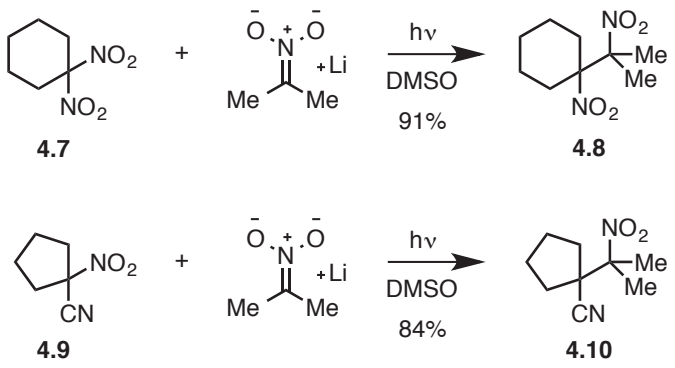


Figure 4.2: Kornblum photolytic formation of 1,2-dinitro- and 1,2-cyanonitroalkanes

4.3 Previous Formation of Cyanonitroalkanes

After Kornblum's initial findings[2] the Ros group published another photolytic method to 1,2-cyanonitroalkanes using α-bromoisobutyronitrile (**4.11**) and five simple non-fuctionalized nitroalkanes. Isolated yields ranged from 36% to 76% (Figure 4.3).[4] The potassium nitronate was prepared *in situ* by a 30 min prestir of potassium *tert*-butoxide and nitroalkane in HMPA. An attempt to use α-bromocyanoalkane **4.13** in the alkylation reaction led to minimal alkylation product **4.10** in favor of elimination product **4.14** (Figure 4.4).

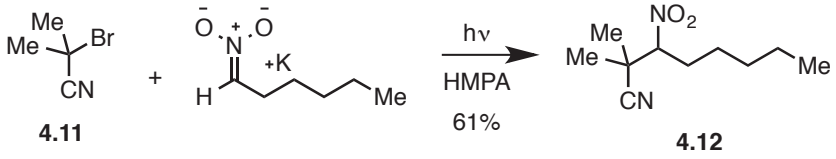


Figure 4.3: Ros photolytic formation of 1,2-cyanonitroalkanes

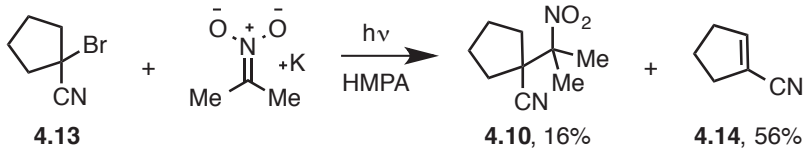


Figure 4.4: Elimination of 1,2-cyanonitroalkane product **4.10**

More recently in 2008, the Anderson group published a more general route to β-cyanonitroalkanes through the hydrocyanation of nitroalkanes (Figure 4.5).[5] The cyanide ion is solubilized in acetonitrile using acetone cyanohydrin **4.16** and catalytic quantities 18-crown-6 and potassium cyanide. Presumably, acetone and cyanide are formed from the decomposition of cyanohydrin **4.16**. In addition to the use of highly toxic cyanide starting materials, the nitroalkene starting materials must be synthesized in a two-step sequence. A Henry reaction of the corresponding nitroalkane and aldehyde is followed by removal of the hydroxyl group by mesylation and elimination. Despite their limitations, to my knowledge, these efforts constitute the best routes to these valuable 1,2-cyanonitroalkane intermediates to date.

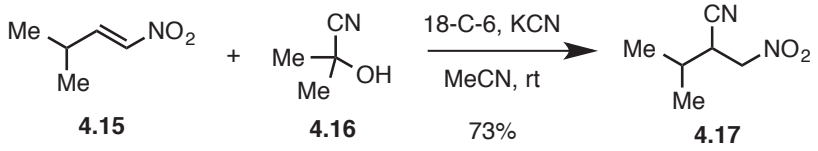


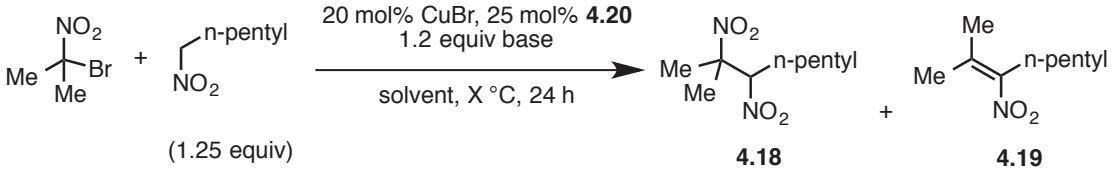
Figure 4.5: Anderson hydrocyanation of nitroalkenes

4.4 Copper-Catalyzed Alkylation of Nitroalkanes with α-Halonitroalkanes: Towards 1,2-Diamines

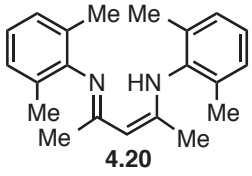
To explore the use α-halonitroalkanes as electrophiles in the copper-catalyzed alkylation of nitroalkanes, 2-bromo-2-nitropropane and 1-nitrohexane were selected as

model substrates (Table 4.1). These reagents were subjected to the previously optimized conditions at room temperature, and while none of the desired product **4.18** was observed, nitroalkene **4.19** was detected by ^{1}H NMR in 16% NMR yield (Table 4.1, entry 1). This byproduct is likely formed by elimination of the desired dinitroalkane **4.18** in the basic reaction conditions. Examination of other ethereal solvents led to similar results (entry 2) albeit with trace yield of the desired dinitroalkane. However, the use of more polar solvents such as CH_2Cl_2 and even polar protic, ^{t}BuOH, reversed this trend (entries 3 and 4) with a more appreciable formation of dinitroalkane **4.18** despite the presence of some nitroalkene **4.19**. Increasing the reaction temperature to 40 °C in ^{t}BuOH led to higher conversion, albeit completely to the elimination product, **4.19**. Rationalizing that the elimination product was the result of an E_1 process, I investigated weaker bases. In accord with this hypothesis, using $NaOSiMe_3$ (pKa 12.7 in water)[6] as a base proved superior and led to increased yields of *C*-alkylation product **4.18** in dichloromethane (entry 7). At 50 °C, the best results to date were achieved in a 44% yield of the nitroalkylation product **4.18** and 12% of the elimination product **4.19**. The structure of dinitroalkane **4.18** was confirmed by subsequent isolation and characterization by NMR (^{1}H and ^{13}C). Finally, I have verified that this new reaction is a copper-catalyzed process; in the absence of copper and diketiminate **4.20** only minimal product formation is observed (entry 10). These results are the best to date for this transformation and will be optimized further at a future date by the Watson group.

Table 4.1: *C*-Alkylation of 1-nitrohexane with 2-bromo-2-nitropropane



entry	base	solvent	temp	yield **4.18** (%)	yield **4.19** (%)
1	NaO^{t}Bu	hexanes	rt	0	16
2	NaO^{t}Bu	Et_2O	rt	1	5
3	NaO^{t}Bu	CH_2Cl_2	rt	12	5
4	NaO^{t}Bu	^{t}BuOH	rt	22	15
5	NaO^{t}Bu	^{t}BuOH	40 °C	0	56
6	NaO^{t}Bu	CH_2Cl_2	40 °C	10	8
7	$NaOSiMe_3$	CH_2Cl_2	40 °C	25	12
8	$NaOSiMe_3$	CH_2Cl_2	50 °C	44	12
9	$NaOSiMe_3$	CH_2Cl_2	60 °C	36	20
10[a]	$NaOSiMe_3$	CH_2Cl_2	40 °C	2	7



4.20

4.5 Copper-Catalyzed Synthesis of β-Cyanonitroalkanes

With encouraging preliminary results for the formation of 1,2-dinitroalkanes, the formation of β-cyanonitroalkanes was investigated. After successful formation of β-cyanonitroalkanes, subsequent reduction leads to 1,3-diamines. Similar to 1,2-dinitroalkanes the β-cyanonitroalkane products bear readily epimerizable centers, which may prove useful for enantio- or diastereoselective reduction.

Towards this end, 1-bromocyclohexylnitrile **4.21** and 1-nitropropane were subjected to the previously optimized conditions for the *C*-alkylation of nitroalkanes with benzyl bromides.[7] With no further screening the initial reaction led to quantitative yield of β-cyanonitroalkane **4.22** (Figure 4.6). The structure was confirmed by subsequent isolation and characterization by NMR (^{1}H and ^{13}C). A subsequent control reaction without catalyst demonstrated that the *C*-alkylation product is formed in only trace yields. The preparation of 1,2-cyanonitroalkanes, and their subsequent reduction to 1,3-diamines, is currently being pursued by another researcher within the Watson group.

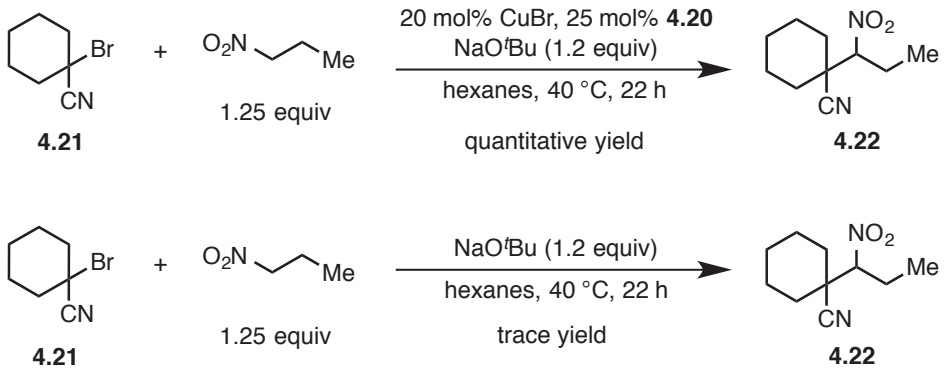


Figure 4.6: *C*-Alkylation of 1-nitropropane with 1-bromocyclohexylnitrile

Taken in total, the successful participation of both α-bromonitroalkanes and α-bromonitriles further supports the hypothesis that the copper-catalyzed alkylation of nitroalkanes proceeds via stabilized radical intermediates. Furthermore, these results promise to greatly expand the types of nitroalkane products that are accessible from this general catalytic manifold.

4.6 Methods for Adding Trifluoromethyl Groups into Organic Molecules

Given the importance and prevalence of nitrogen in pharmaceutical molecules,[8] and the observance that fluorine imparts altered properties in those molecules,[9] additional methods of accessing fluorinated amines are of great utility. Among various fluorinated molecules, trifluoromethyl-substituted compounds have drawn significant interest due in part to their unique polarity, thermal and metabolic stabilities, and high lipophilicity that can increase bioavailablility.[10] Recent efforts to add trifluoromethyl groups into organic molecules have utilized nucleophilic, electrophilic, radical, or transition metal catalyzed processes.[11] The instability of the naked trifluoromethyl anion makes nucleophilic trifluoromethylation challenging. Because of destabilizing interactions between the anion on carbon and the lone pairs of the fluorine, the anion dissociates rapidly to form a fluoride anion and a difluorocarbene stabilized by the electron donation of the lone pairs on fluorine into the empty orbital. Conversely the trifluoromethyl radical is well stabilized. The fluorine atoms of the trifluoromethyl radical exert a strong inductive effect through the C-F σ-bond, but also stabilize the radical as a weak π-donor with overlap from the lone pairs on the F substituents with the singly occupied molecular orbital (SOMO) on carbon.[12]

4.7 Nucleophilic Trifluoromethylation

A common way of accessing α-trifluoromethylated amines is by using the nucleophilic addition of trifluoromethyltrimethylsilane ($TMSCF_3$, Ruppert-Prakash Reagent) to imines.[13] This reagent successfully circumvents the stability issues normally associated with the trifluoromethyl anion. It is proposed that the anion is stabilized by the formation of a pentacoordinate silicon intermediate (Figure 4.9).

These methods utilize the increased electrophilicity of activated imines or strained azirine to aid the addition of the trifluoromethyl group.

In 1994, the Laurent group found that azirines were suitably reactive for the nucleophilic addition of $TMSCF_3$ to give solely the trans isomer (Figure 4.7).[14] Imines were not successfully employed in this reaction.

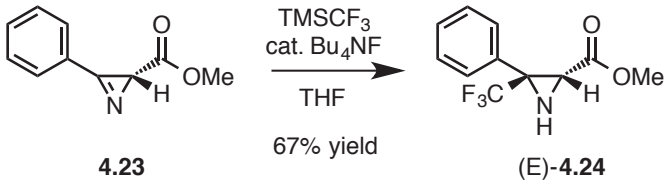


Figure 4.7: Addition of Ruppert's reagent to azirines

In 2001 Prakash and Olah overcame the lower reactivity of sulfinylimines[15] by using a nonmetallic fluoride source, tetrabutylammonium difluorotriphenylsilicate (TBAT), first used by DeShong.[16] The use of this reagent favorably increased the conversion of imine and prevented the undesired deprotonation of imines bearing an α-hydrogen that was observed when using cesium fluoride (CsF). High diastereoselectivity was achieved when using chiral sulfinimines as the electrophilic partner (Figure 4.8). While these methods elegantly incorporate CF_3 groups into molecules with neighboring amines, some limitations remain. Aldimines are typically used, which limits the substitution available on carbon.[15, 17] Also these strategies often require a subsequent deprotection step to access the primary trifluoromethylated amines (Figure 4.8).

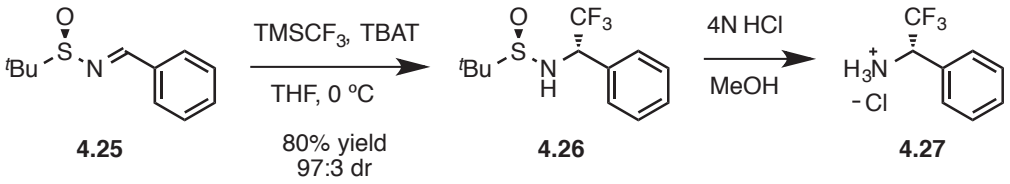


Figure 4.8: Addition of Ruppert's reagent to chiral sulfinimines

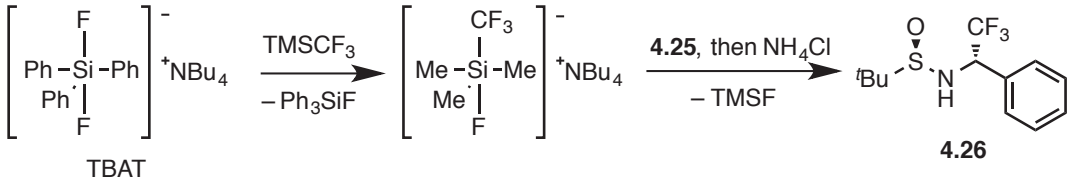


Figure 4.9: Pentacoordinate silicon intermediate in nucleophilic trifluoromethylation with Ruppert-Prakash reagent

4.8 Radical Trifluoromethylation

Despite the effectiveness of the Ruppert-Prakash Reagent for nucleophilic trifluoromethylation the inherent stability of the trifluoromethyl radical as compared to the trifluoromethyl anion or cation has led to many elegant methods using trifluoromethyl radical sources for trifluoromethylation. Recently the MacMillan group published a follow up report to their enantioselective conditions for radical α-trifluoromethylation of aldehydes with Togni's reagent,[18] which described the formation of α-trifluoromethylated carbonyl compounds using trifluoromethyl iodide and a simple household light source (Figure 4.10).[19]

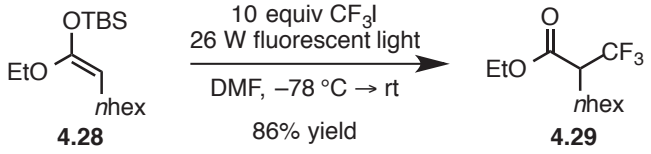


Figure 4.10: MacMillan trifluoromethylation of silyl ketene acetal **4.28**

The Buchwald group has also published a number of methods for introducing trifluoromethyl groups via transition metal catalysis and radical trifluoromethyl sources.[20] The most recent example involves the radical trifluoromethylation of an alkene followed by enantioselective C-O bond formation aided by a chiral copper catalyst to afford trifluoromethyl lactones such as **4.32** in good yield with high enantioselectivities (Figure 4.11).[20c]

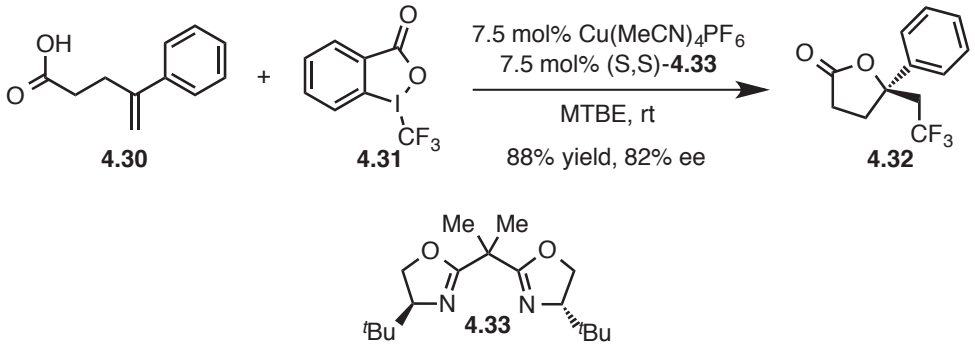


Figure 4.11: Buchwald copper-catalyzed enantioselective oxytrifluoromethylation of alkenes

Aware of the potential of radical trifluoromethylation as demonstrated by these and other examples, I sought to develop conditions for a transition metal catalyzed trifluoromethylation of nitroalkanes using radical trifluoromethylation. Given the

likelihood for a radical anion coupling mechanism for our *C*-alkylation chemistry, I proposed to first examine sources known to produce trifluoromethyl radicals.

4.9 Photolytic Perfluoroalkylation of Nitronate Anion

In 1983, Feiring demonstrated the successful coupling of two examples of perfluoroalkyl iodides with the 2-nitropropyl anion (Figure 4.12).[21] Using photolysis, the nitronate anion was successfully perfluoroalkylated with perfluorohexyl or perfluorooctyl iodide. Trifluoromethyliodide was not studied in this transformation, presumably because it is a gas at room temperature. Radical trapping agents, such as 1,4-dinitrobenzene (**4.36**), were found to compete with the formation of α-perfluoroalkylated **4.35** in the photolytic reaction (Figure 4.13). One electron reduction of dinitroarene **4.36** and loss of a nitrite ion leads to an arene radical competitively intercepted by the lithium salt of 2-nitropropane to form nitroalkane **4.37**. This result strongly supports the presence radical intermediates in the transformation.

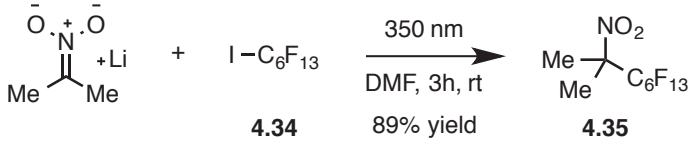


Figure 4.12: Photolytic perfluoroalkylation of lithium 2-nitropropane anion

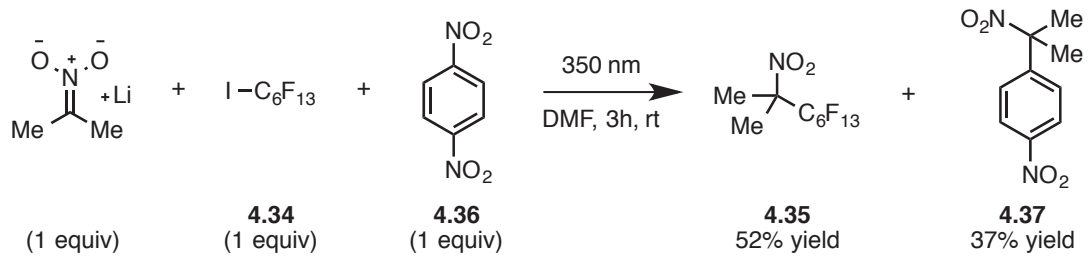


Figure 4.13: Competition experiment for photolytic perfluoroalkylation

The Feiring group demonstrated the ability to access α-perfluoroalkylamines from these α-perfluoroalkylnitroalkanes in the successful reduction of α-perfluoroalkylated **4.35** to α-perfluoroalkylamine **4.38** under elevated hydrogen pressure in the presence of palladium on carbon (Figure 4.14).[21] The necessity of using the previously isolated lithium salt of 2-nitropropane or the equivalent tetrabutylammonium salt (isolated and rigorously dried) limits the usefulness of this transformation. Additionally while nitroalkane products bearing α-perfluorohexyl and α-perfluorooctyl groups are successfully formed, the formation of α-trifluoromethyl nitroalkanes are not demonstrated.

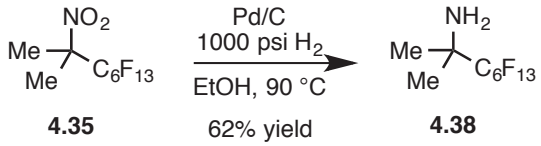


Figure 4.14: Reduction of α-perfluoroalkylated **4.35** to α-perfluoroalkylamine **4.38**

4.10 Copper-Catalyzed α-Trifluoromethylation of Nitroalkanes

Recognizing the potential of a catalytic method for the incorporation of α-trifluoromethyl groups into nitroalkanes as a means to prepare α-trifluoroamines, I

investigated the use of our previously optimized *C*-alkylation conditions with several trifluoromethyl sources previously shown to produce CF_3 radicals. I hypothesized that using the copper diketimine catalyst might lead to the formation of an electrophilic trifluoromethyl radical,[22] which could then be intercepted by the nucleophilic nitronate salt formed *in situ* from a simple nitroalkane. Due to stabilizing properties of the CF_3 radical,[12] I hypothesized that it might be suitably long-lived to undergo radical-anion coupling with the nitronate.

I began screening this desired reaction using **4.39** as the nitroalkane partner and a range of radical CF_3 sources. While many variations of conditions were evaluated for the transformation, the results can be neatly summarized in Figure 4.15. The use of trifluoromethanesulfonyl chloride (**4.42**) known to generate a CF_3 radical under photoredox conditions did not yield any of the desired product (**4.40**).[23] The Sanford group found that using the Ruppert-Prakash Reagent (**4.43**) with superstoichiometric AgOTf and KF led to the formation of trifluoromethyl-substituted benzene derivatives presumably through a radical-pathway mechanism.[24] Using the copper catalyzed reaction conditions found suitable for benzyl bromides no conversion of the nitroalkane starting material was observed. Perhaps not surprisingly, sodium trifluoromethanesulfinate (Langlois' reagent), traditionally oxidized using a copper (II) source to form a CF_3 radical after elimination of SO_2,[25] also did not lead to conversion of the nitroalkane starting material.

However, when switching to 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (the Shreeve-Umemoto Reagent, **4.44**), typically used as an electrophilic trifluoromethyl source,[11] I observed the formation of α-trifluoromethyl nitroester **4.40** in 31% NMR yield. The structure was confirmed by subsequent

isolation and characterization by NMR (^{1}H, ^{13}C, and ^{19}F) as well as mass spectrometry. In the absence of catalyst only 4% of **4.40** is observed, supporting our hypothesis that the copper diketimine catalyst is aiding the formation of a transient CF_3 radical. These conditions were also successfully applied to the α-trifluoromethylation of secondary nitroalkane **4.45** in 40% yield (Figure 4.16).[21] Efforts are ongoing in our lab to further optimize and probe the scope of this valuable transformation.

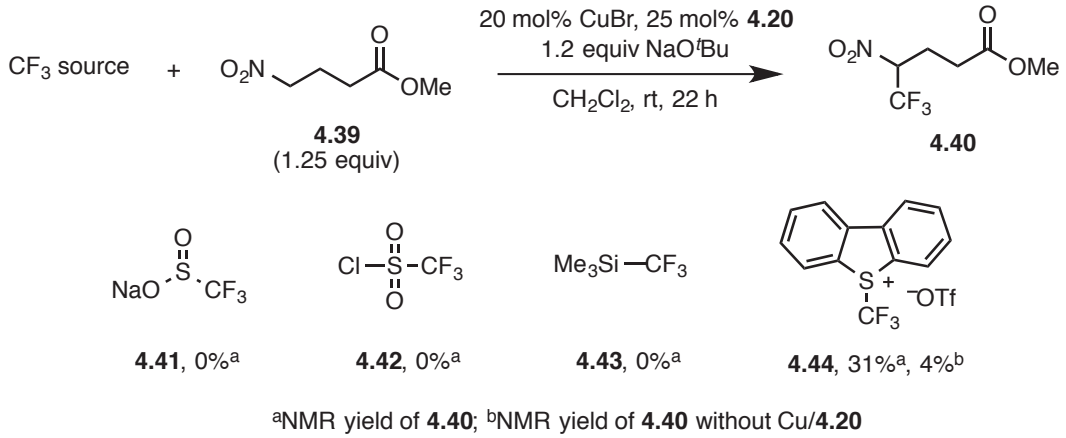


Figure 4.15: Preliminary screening for copper catalyzed *C*-trifluoromethylation of nitroester **4.39**

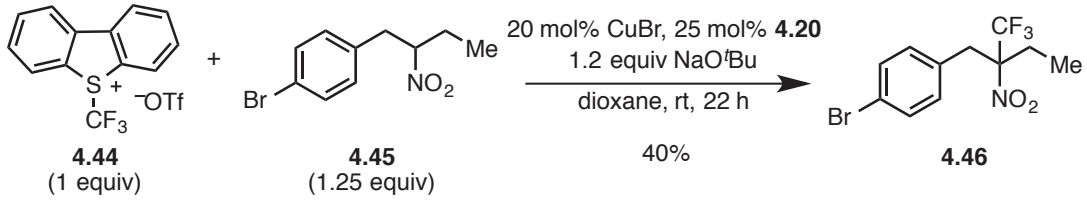


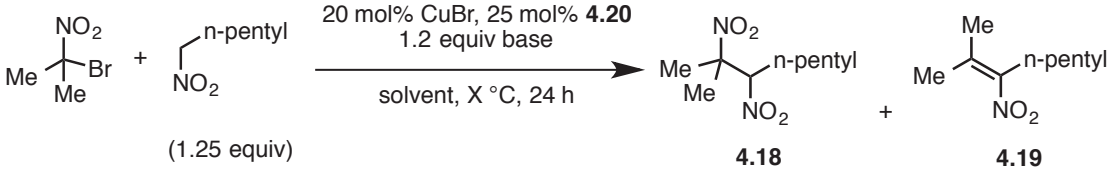
Figure 4.16: Copper catalyzed C-trifluoromethylation of secondary nitroalkane **4.45**

4.11 Experimental

4.11.1 General Experimental Details

Hexanes, dioxane, diethyl ether, and dichloromethane were dried on alumina according to published procedures.[26] *tert*-Butanol was distilled from calcium hydride, sparged with N_2, and stored under N_2 in a sealed vessel. Copper bromide, sodium *tert*-butoxide, and sodium trimethylsilanolate were purchased commercially; the bulk was stored in a nitrogen filled glovebox; samples were removed from the glovebox and stored in a desiccator under air for up to one week prior to use. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. b-Diketiminate ligand **4.20** was synthesized according to a published procedure.[27] Substrates α-bromonitrile **4.21**,[28] methyl-4-nitrobutyrate[29], and nitroalkane **4.45**[7] were prepared according to the literature procedure. All other substrates and reagents were purchased in highest analytical purity from commercial suppliers and used as received. Reactions reported in Figures 4.6 and 4.15 were carried out in a glovebox (N_2 atmosphere) on a 250 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Reactions reported in Table 4.1 and Figure 4.16 were carried out in a glovebox (N_2 atmosphere) on a 125 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Product yields in Table 4.1 and Figures 4.6, 4.15, and 4.16 were obtained by NMR using 1,3,5-trimethoxybenzene as an internal standard.

4.11.2 Procedure for Optimization Towards 1,2-Dinitroalkanes (Table 4.1)

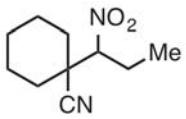


See notebook pages: PGG03266 – PGG03293 and PGG05139

In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (3.6 mg, 25 μmol), ligand **4.20** (9.6 mg, 31.3 μmol), either sodium *tert*-butoxide (14.4 mg, 150 μmol) or sodium trimethylsilanolate (16.9 mg, 150 μmol) (see above), either hexanes, diethyl either, dichloromethane, or *tert*-butanol (750 μL) (see above), 1-nitrohexane (21.9 μL, 156 μmol), and 2-bromo-2-nitropropane (13.3 μL, 125 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at the above temperature for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (10.5 mg, 63 μmol) was added and the mixture was diluted with dichloromethane (approximately 750 μL). The solution was passed through a plug of celite and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. The crude product was purified by flash silica chromatography (hexanes → 99:1 hexanes : ethyl acetate) to afford a mixture of dinitroalkane **4.18** and 1-nitrohexane as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) ∂ 5.13 (dd, J = 11.7, 2.3 Hz, 1H), 2.17 – 2.04 (m, 1H), 1.73 – 1.66 (m, 6H), 1.63 – 1.52 (m, 1H), 1.41 – 1.22 (m, 6H), 0.93 – 0.83 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 92.8, 88.5, 30.9, 28.9, 25.9, 24.0, 22.3, 22.1, 14.0.

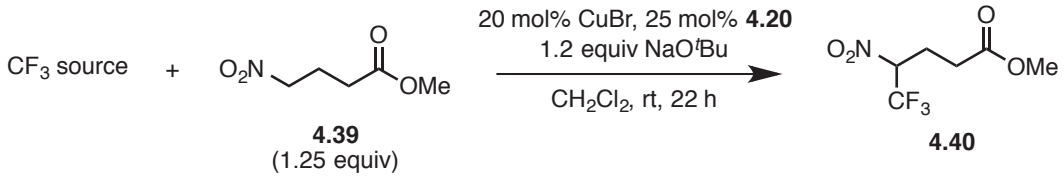
4.11.3 Synthesis of α-Cyanonitroalkane 4.22 (Figure 4.6)

See notebook pages: PGG04034, PGG04037, and PGG04042



(**4.22**) In a nitrogen glovebox, CuBr (7.2 mg, 50 μmol), ligand **4.20** (19.2 mg, 63 μmol), sodium *tert*-butoxide (28.8 mg, 300 μmol), anhydrous hexanes (1.5 mL), 1-nitropropane (27.9 μL, 313 μmol), and 1-bromocyclohexylnitrile (39.0 μL, 250 μmol) were added to a dry 15 x 45 mm vial equipped with a stir bar. The vial was sealed with a Telfon lined cap and heated in an aluminum block on a temperature controlled stir plate to 40°C with vigorous stirring for 24 h. The reaction was then removed from the glovebox, allowed to cool to rt, and exposed to air. 1,3,5-Trimethoxybenzene (21.0 mg, 125 μmol) was added, the solution was diluted with diethyl ether (1.5 mL), and the mixture was passed through a plug of celite. The resulting homogeneous solution was concentrated *in vacuo*. **4.22** was formed in quantitative yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. The crude product was purified by flash silica chromatography (90:10:1 hexanes : ethyl acetate : trifluoroacetic acid) to afford nitroalkane **4.22** as a pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 4.26 (dd, J = 11.9, 2.7 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.10 – 2.03 (m, 1H), 1.99 (dqd, J = 14.8, 7.4, 2.7 Hz, 1H), 1.88 – 1.75 (m, 4H), 1.75 – 1.60 (m, 2H), 1.47 (td, J = 13.1, 3.4 Hz, 1H), 1.31 (td, J = 12.9, 3.5 Hz, 1H), 1.23 – 1.14 (m, 1H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 119.2, 95.5, 42.4, 33.8, 32.1, 24.8, 23.1, 22.5, 22.5, 10.6.

4.11.4 Procedure for Screening Trifluoromethyl Sources (Figure 4.15)

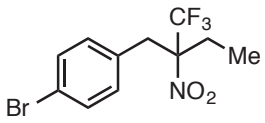


See notebook pages: PGG03238 – PGG03299 and PGG05138

In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (7.2 mg, 50 μmol), ligand **4.20** (19.2 mg, 63 μmol), sodium *tert*-butoxide (28.8 mg, 300 μmol), CF_3 source (250 μmol), dichloromethane (1.5 mL), and methyl 4-nitrobutyrate (40.0 μL, 313 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at room temperature for 24 h. The vials were then removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (21.0 mg, 125 μmol) was added and the mixture was diluted with dichloromethane (approximately 1.5 mL). The mixture was passed through a plug of celite and the resulting homogeneous solution was concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. The crude product was purified by flash silica chromatography (99:1 hexanes : ethyl acetate → 97:3 hexanes : ethyl acetate) to afford α-trifluoromethylnitroester **4.40** (7.6 mg, 14%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) ∂ 5.25 – 5.18 (m, 1H), 3.73 (s, 3H), 2.60 – 2.49 (m, 2H), 2.47 – 2.36 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 171.6, 121.4 (q, J = 281.6 Hz), 85.2 (q, J = 31.3 Hz), 52.4, 28.7, 22.9; ^{19}F NMR (376 MHz, $CDCl_3$) ∂ -72.77.

4.11.5 Synthesis of Trifluoromethylated Secondary Nitroalkane 4.46 (Figure 4.16)

See notebook page: PGG04009



(**4.46**) In a nitrogen glovebox, CuBr (3.6 mg, 25 μmol), ligand **4.20** (9.6 mg, 31.3 μmol), sodium *tert*-butoxide (14.4 mg, 150 μmol), nitroalkane **4.45** (40.3 mg, 156 μmol), 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (50.3 mg, 125 μmol), and anhydrous dioxane (750 μL) were added to a dry 15 x 45 mm vial equipped with a stir bar. The vial was sealed with a Telfon lined cap and vigorously stirred for 22 h. The reaction was then removed from the glovebox and exposed to air. 1,3,5-Trimethoxybenzene (10.5 mg, 63 μmol) was added and the solution was diluted with diethyl ether (750 μL). The solution was then washed once with saturated ammonium chloride (1.5 mL) and once with brine (1.5 mL), passed through a plug of magnesium sulfate and concentrated *in vacuo*. **4.46** was formed in 40% yield by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. The crude product was purified by flash silica chromatography (hexanes → 100:1 hexanes : ethyl acetate) to afford nitroalkane **4.46** as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 7.03 – 6.99 (m, 2H), 3.51 (d, J = 14.7 Hz, 1H), 3.34 (d, J = 14.7 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.05 (dq, J = 14.9, 7.3 Hz, 1H), 1.07 (td, J = 7.4, 1.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ∂ 132.1, 132.0, 131.0, 123.2 (q, J = 286.0 Hz), 122.6, 94.24 (q, J = 25.9 Hz), 39.0, 26.1, 8.37 (d, J = 1.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) ∂ –69.5 (s).

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Chapter 5

CHIRAL CROWN SYNTHESIS

5.1 Proposing an Enantioselective *C*-Alkylation of Nitroalkanes

The ability to enantioselectively *C*-alkylate nitroalkanes with simple alkyl halides would significantly enhance the usefulness of the catalytic *C*-alkylation method developed in our lab. Despite the great value of such a transformation, several problematic factors complicate the realization of an enantioselective variant to this transformation. Epimerization of the proton alpha to the nitro group in the basic reaction media could destroy any enantioenrichment that is achieved in an enantioselective coupling. Also, traditional methods of catalyst controlled asymmetric cross-coupling reactions would not prove viable if our mechanistic hypothesis for outer sphere C-C bond formation is correct (Figure 5.1). These apparent challenges led me to consider alternative methods to induce enantioselectivity.

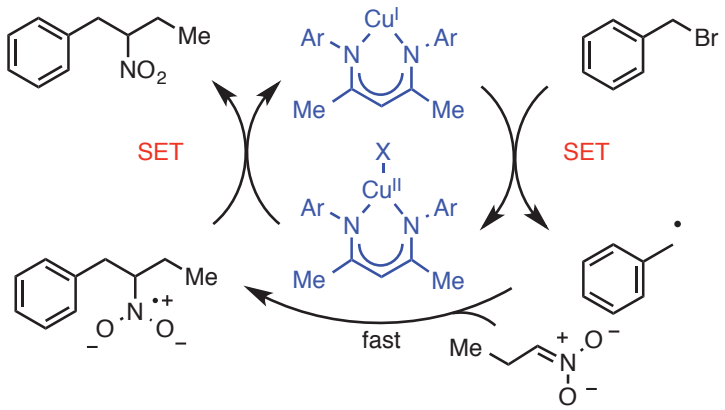
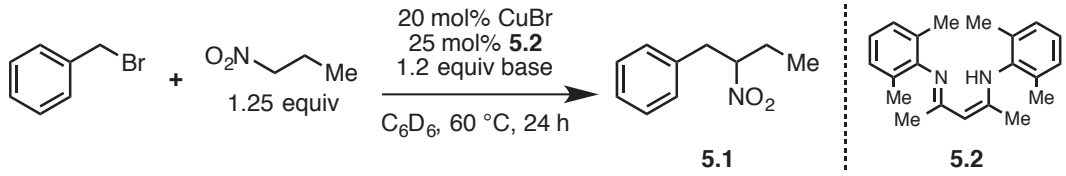


Figure 5.1: Proposed mechanism for *C*-benzylation of nitroalkanes

While optimizing the method for the benzylation of nitroalkanes I observed a peculiar cation effect when using alkoxide bases.[1] While potassium and sodium *tert*-butoxide proved nearly equivalent in their effectiveness as bases, using lithium *tert*-butoxide did not lead to any *C*-alkylated product **5.1** (Table 5.1). I hypothesized that the due to the heterogeneous nature of the reaction and the sparing solubility of the nitronate salt, the lithium nitronate is likely completely insoluble in the non-polar reaction media. In this case, no reaction takes place and the benzyl bromide starting material remains untouched.

Table 5.1: Cation effect of alkoxide bases in *C*-benzylation of nitroalkanes



entry	base	Yield **5.1** (%)
1	KO^{t}Bu	72
2	NaO^{t}Bu	78
3	LiO^{t}Bu	0

I wondered if these conditions might prove useful in the presence of a chiral phase transfer catalyst (Figure 5.2). The use lithium *tert*-butoxide presumably results in the formation of a completely insoluble lithium nitronate, which remains out of the liquid phase of the reaction. A chiral phase transfer catalyst might reversibly form an ion pair with the nitronate that is not only soluble in the reaction media, but is also

held in a chiral environment. The anion radical coupling of this soluble prochiral nitronate with the resultant benzyl radical (formed after reduction and loss of halide) could lead to an enantioenriched *C*-alkylated nitroalkane product.

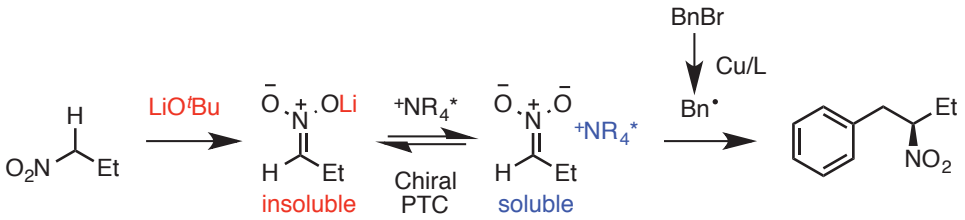


Figure 5.2: Proposed enantioselective *C*-alkylation with chiral phase transfer catalyst

5.2 Use of Chiral Phase Transfer Catalysts with Nitroalkanes

The use of several classes of chiral phase transfer catalysts to achieve highly enantioselective C-C bond forming reactions with nitroalkanes supported our proposal to use chiral phase transfer reagents.[2] In 2003 the Maruoka group demonstrated that chiral C_2-symmetric quaternary ammonium bifluorides could be used to achieve high levels of enantioselectivity in the Henry Reaction of simple silyl-protected nitronates with several aromatic aldehydes. High yields and excellent enantioselectivities were obtained in catalyst loadings of only 2 mol% (Figure 5.3).[3] The Maruoka group later used the same chiral ammonium as the bromide salt for the conjugate addition of nitroalkanes to alkylidenemalonates[4] and later cyclic α,β-unsaturated cyclic ketones[5] in high yields with excellent levels of enantio- and diastereoselectivity.

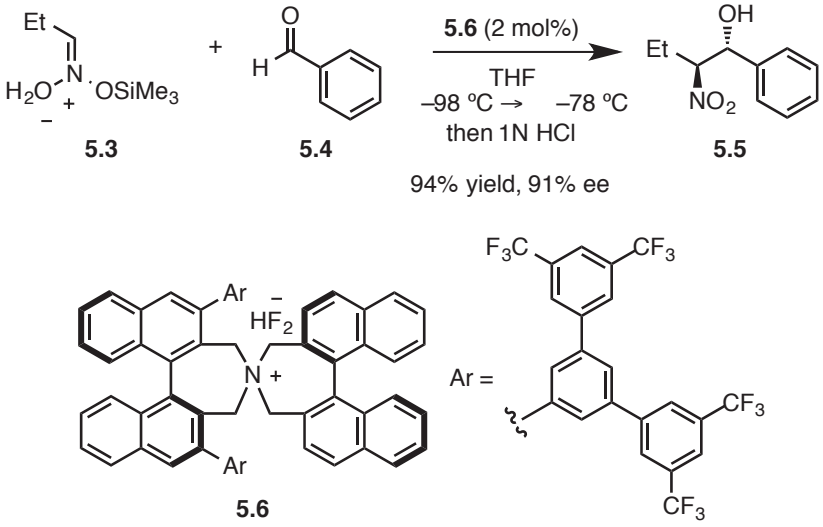


Figure 5.3: Enantioselective Henry reaction using chiral quaternary ammonium salt **5.6**

The Palomo Group in 2005 found that N-benzyl quininium chloride **5.9** was effective as a catalyst for the aza-Henry addition of nitromethane to aromatic *and* aliphatic N-carbamoyl imines generated *in situ* from the corresponding α-amino sulfones (Figure 5.4, top).[6] The presence of the unprotected hydroxyl group in **5.9** was found to be critical for achieving high yields indicating that hydrogen bonding between the hydroxyl group and the oxygen of the nitro group and/or the nitrogen of the azomethine may be playing a role in the reaction. At the same time Herrera, Bernardi, et al. published the same enantioselective aza-Henry reaction with the same quininium catalyst **5.9** using potassium hydroxide instead of cesium hydroxide with equally high yields and enantioselectivities (Figure 5.4, bottom).[7]

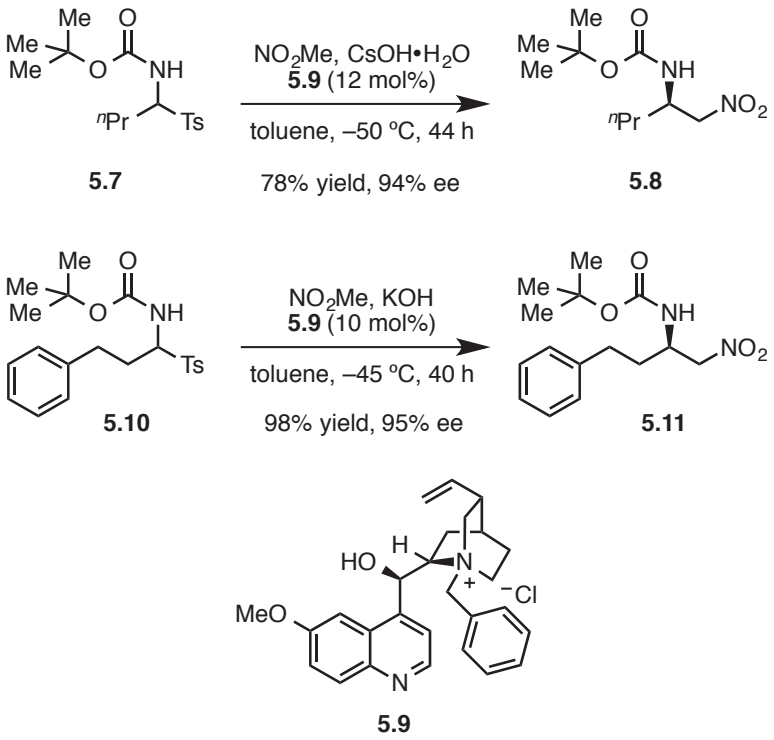


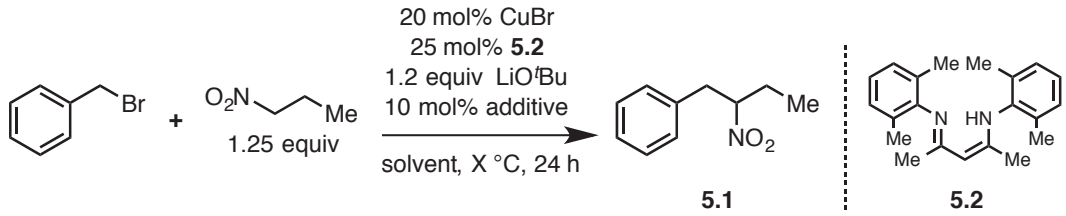
Figure 5.4: Enantioselective aza-Henry reaction with N-benzyl quininium chloride **5.9**

5.3 Examining Phase Transfer Catalysts for *C*-Alkylation of Nitroalkanes

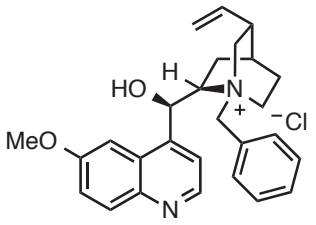
In an effort to examine the viability of quaternary ammonium salts as phase transfer catalysts in the *C*-alkylation of nitroalkanes, benzyl bromide and 1-nitropropane were reacted under conditions previously optimized for the *C*-alkylation of nitroalkanes with benzyl bromides[1] using lithium *tert*-butoxide as the base. Indeed as noted above (Table 5.1), in the absence of a phase transfer additive none of the *C*-alkylated product, **5.1**, was formed (Table 5.2, entry 1). The use of N-benzyl quininium chloride **5.9**, previously found to be an effective chiral phase transfer catalyst in conjunction with nitronate salts, disappointingly did not catalyze the desired reaction (entries 2 and 3). Other non-chiral quaternary ammonium salts, used

simply to monitor conversion, also failed to lead to any *C*-alkylated product. In all cases little to no conversion of starting material was observed.

Table 5.2: Effect of ammonium additives on lithium nitronate reactivity



entry	additive	solvent (°C)	yield **5.1** (%)
1	none	benzene (60)	0
2	**5.9**	hexanes (30)	0
3	**5.9**	benzene (60)	2
4	Bu_4NBr	hexanes (30)	0
5	Bu_4NBr	benzene (60)	2
6	$Pent_4NBr$	benzene (60)	1

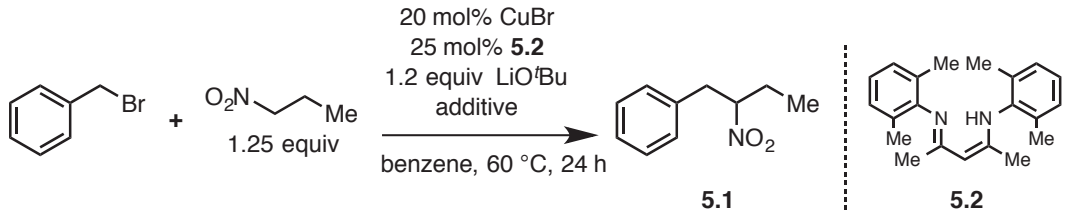


5.9

To better understand the role of the lithium ion in the reaction, several additives known to preferentially solvate lithium were examined (Table 5.3).[8] While a modest increase in formation of **5.1** was observed when using the solvating

hexamethylphosphoramide (HMPA) in one equivalent relative to lithium *tert*-butoxide (entry 2), the use of less toxic, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), as a co-solvent (1:3 DMPU : benzene) did not afford appreciable product (entry 3). A more remarkable effect was observed when using 12-crown-4. I was pleased to observe 64% yield of the *C*-alkylated product (entry 4) presumably due to the solvation of the lithium nitronate back into solution with benzyl bromide and catalyst. Moving to catalytic amounts of 12-crown-4 unfortunately lead to diminished yields (entries 5 and 6). Encouragingly nitroalkanes with increased steric bulk, such as those possessing β-branching, reacted in even higher yield when using 12-crown-4 demonstrating the potential for more complex substrates (Table 5.4). This considerable improvement in reactivity led me to consider chiral variants around this core structure.

Table 5.3: Effect of lithium binding additives on *C*-alkylation reactivity



entry	additive	yield **5.1** (%)
1	none	0
2	(1.2 equiv) HMPA	6
3	(co-solvent) DMPU	trace
4	(1.2 equiv) 12-C-4	64
5	(0.5 equiv) 12-C-4	25

6	(10 mol%) 12-C-4	5

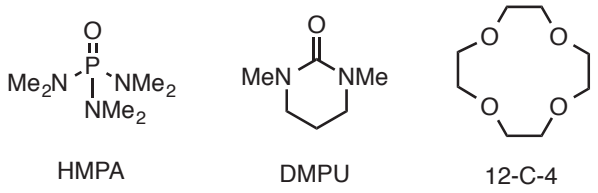
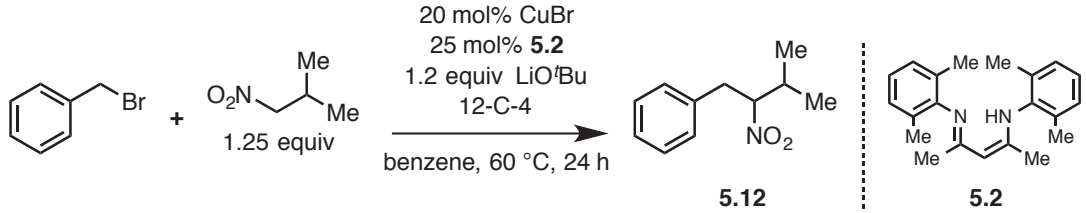


Table 5.4: Formation of nitroalkane **5.12** using 12-crown-4



entry	additive	yield **5.12** (%)
1	none	5
2	(1.2 equiv) 12-C-4	82

5.4 Synthesis and Reactivity of Chiral Crowns

Though the synthesis of chiral 12-crown-4 rings have not been investigated to the same extent as larger crowns, there is precedent for their formation.[9] The Chênevert group published a multi-step synthesis of chiral crowns **5.13** and **5.14** (and their derivatives *en route*) bearing the 12-crown-4 core starting from commercially available (+)-diethyl L-tartrate (Figure 5.5).[10] Chiral crowns have also been used for asymmetric reactions of nitroalkanes such as the Michael addition of 2-nitropropane to chalcones and several heterocyclic derivatives in good yield and high

enantioselectivity using the Tőke group's monoaza-15-crown-5 sugar based chiral crown **5.17** (Figure 5.6).[11]

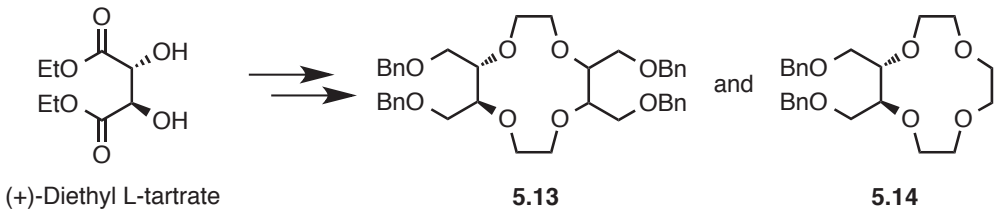


Figure 5.5: Chênevert synthesis of (+)-diethyl L-tartrate derived chiral crowns

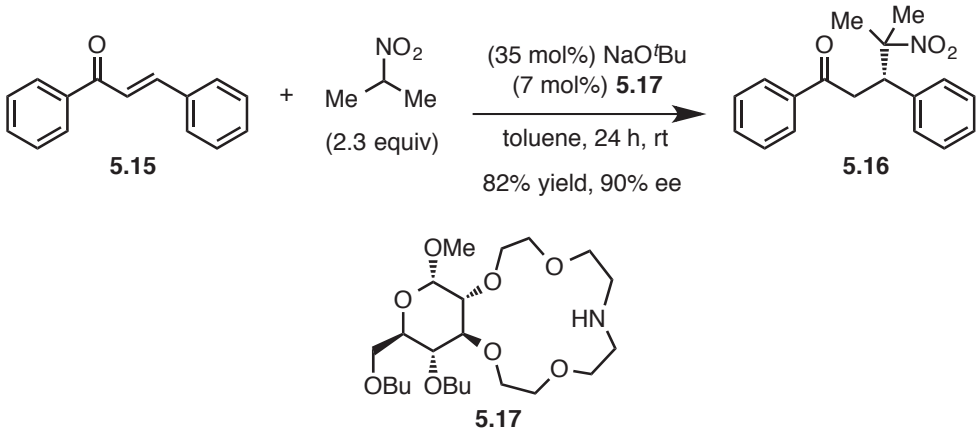


Figure 5.6: Tőke group enantioselective Michael addition of 2-nitropropane using chiral monoaza-15-crown-5 **5.17**

5.5 Synthesis of Chiral Crown AT

Inspired by the high catalytic efficiency and promising enantioselectivity of binol derived chiral crowns I began developing a synthetic route to 12-crown-4 resembling **5.23**. With a smaller ring I envisioned a better differentiating chiral environment to improve upon the moderate enantioselectivities observed with larger

binol derived chiral crowns.[9a] Towards this end I began the synthesis by silyl protecting 2-bromoethanol (Figure 5.7).[12] Under basic conditions two subsequent S_N2 displacements of silyl protected **5.19** by (R)-binol led to the doubly protected ether **5.20**. Stirring **5.20** at room temperature in the presence of tetrabutylammonium fluoride for several hours led to diol **5.21** in 61% yield over two steps after column chromatography.

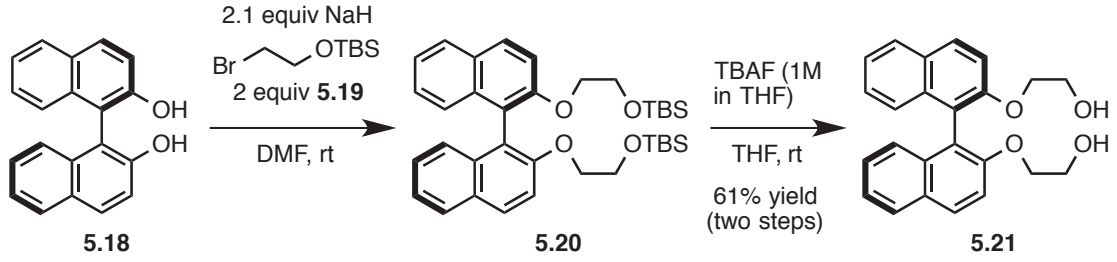


Figure 5.7: Synthesis of diol **5.21** from (R)-binol

While the conversion of diol **5.21** to the ditosylate proceeded in quantitative yield (not shown), subsequent steps to displace the primary tosylated alcohols with another equivalent of (R)-binol led to complex mixtures with no product observed. Presumably elimination occurred in preference to alkylation. The bromination of diol **5.21**, which occurred in high yield, led to a more reactive coupling partner for the final coupling step (Figure 5.8).

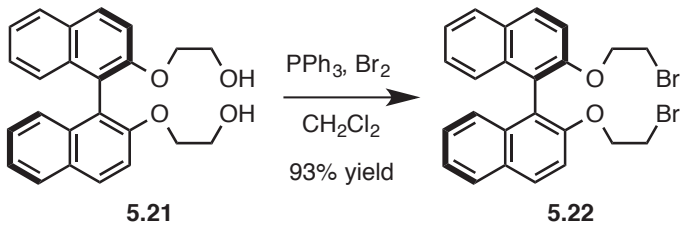


Figure 5.8: Bromination of diol **5.21**

The final step requiring the alkylation of phenolic **5.18** with dibromo **5.22** to form the 16 membered **5.23** proved quite problematic. Given the remarkably low reported yields for similar ring closing steps in macrocycle formation this was not unexpected. The Chênevert group in their ring-closing step to form chiral **5.13** (Figure 5.5) reported a 27% yield in a 7-day reaction requiring several warming and cooling steps with periodic additions of base.[10] Additionally they noted that any deviations from the reported procedure resulted in significantly decreased yields. Ultimately **5.23** was obtained in 13% yield after column purification by alkylating (R)-binol with dibromo **5.22** in the presence of sodium hydride (Figure 5.9). To evaluate the potential of the newly synthesized **5.23**, the chiral crown was used in the reaction of benzyl bromide with 2-methyl-1-nitropropane using our previously optimized *C*-alkylation conditions. Though the same reaction conditions had proved quite effective when using 12-crown-4 to solubilize the nitronate (Table 5.4), disappointingly **5.23** not only failed to form appreciable *C*-alkylated product **5.1**, but also did not break symmetry (Figure 5.10).

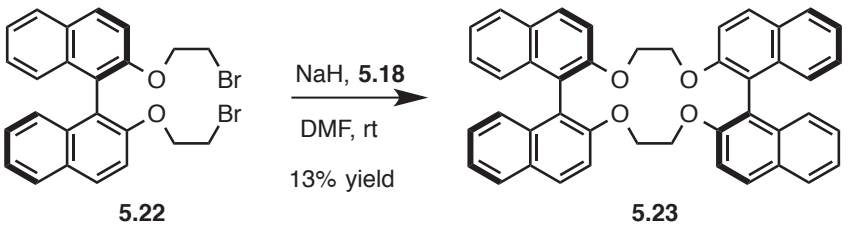


Figure 5.9: Final step of chiral crown **5.23**

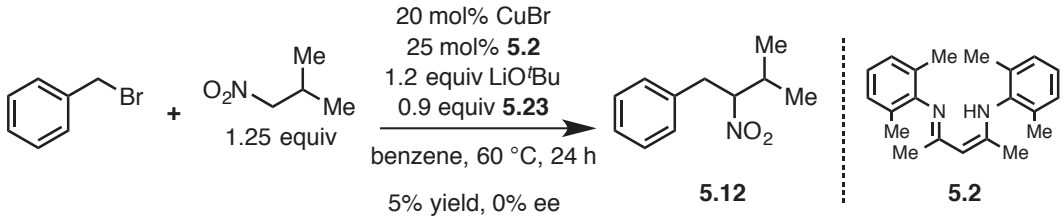


Figure 5.10: Chiral crown **5.23** in benzylation of 2-methyl-1-nitropropane

5.6 Synthesis of Chiral 12-Crown-4 5.14

While chiral crown **5.23** was predicted to have a deeper chiral pocket to induce enantioselectivity, the poor results led us to reconsider a more traditional 12-membered ring structure better suited for binding lithium. Towards this end I began the synthesis of known chiral 12-crown-4 **5.14** (Figure 5.11).[10] Starting with (+)-diethyl L-tartrate **5.24** formation of acetonide **5.25** proceeded in near quantitative yield.[13] Lithium aluminum hydride reduction of diester **5.25** led cleanly to diol **5.26** in 93% yield. Protection of the diol **5.26** with two equivalents of benzyl bromide led to dibenzyl ether **5.27**, which was subjected to a methanolic HCl solution without prior purification. Diol **5.28** was obtained in 80% yield over two steps.[14]

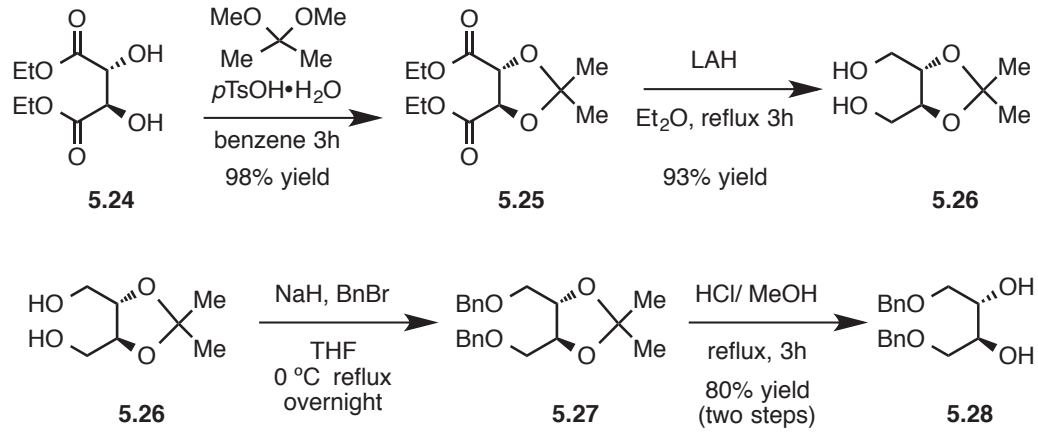


Figure 5.11: Initial steps to chiral crown **5.14**

To close the ring and complete the synthesis of 12-crown-4 **5.14**, triethylene glycol was tosylated to give ether **5.29** in near quantitative yield (Figure 5.12). Reacting diol **5.28** with ditosylated **5.29** using Chênevert's carefully optimized conditions led to chiral crown **5.14** obtained in 18% yield after column purification. Unfortunately, despite possessing a 12-crown-4 core, chiral crown **5.14** did not promote the *C*-alkylation of 2-methyl-1-nitropropane when using lithium *tert*-butoxide (Figure 5.13). HPLC analysis revealed the trace product to be racemic.

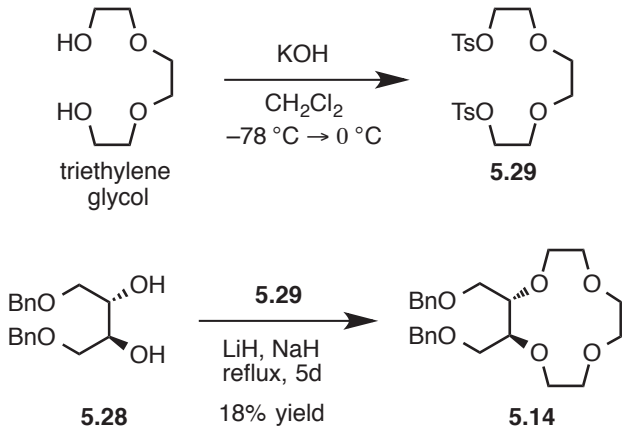


Figure 5.12: Final step of synthesis of chiral crown **5.14**

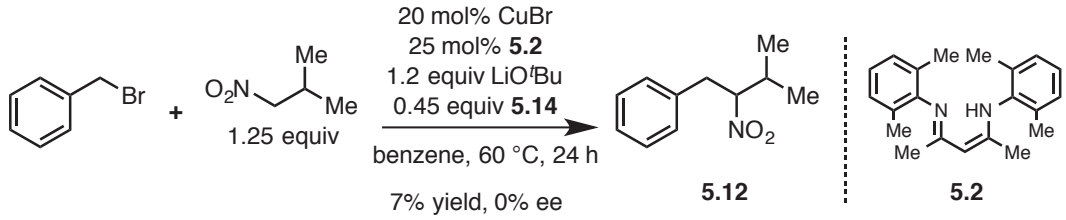


Figure 5.13: Chiral crown **5.14** in benzylation of 2-methyl-1-nitropropane

5.7 Synthesis of Chiral 12-Crown-4 5.32

In a final attempt to examine chiral 12-crown-4 additives in the *C*-benzylation of nitroalkanes with lithium *tert*-butoxide, the two-step synthesis to previously unknown 1,2-diphenyl-substituted chiral crown **5.32** was proposed (Figure 5.14). Possessing a 12-crown-4 core and larger steric bulk close to the site of lithium chelation, chiral crown **5.32** was thought to be a more promising target. The first step using Sharpless asymmetric dihydroxylation conditions proceeded in high yield with greater than 99% ee. With enantioenriched hydrobenzoin **5.31** in hand, conditions modified from Chênevert's ring closing procedure were used to afford 1,2-diphenyl-

substituted chiral crown **5.32**.[10] The results when using chiral crown **5.32** in the optimized *C*-alkylation conditions were disappointingly similar to the aforementioned reactions with only trace product formation and no observance of enantioselectivity (Figure 5.15).

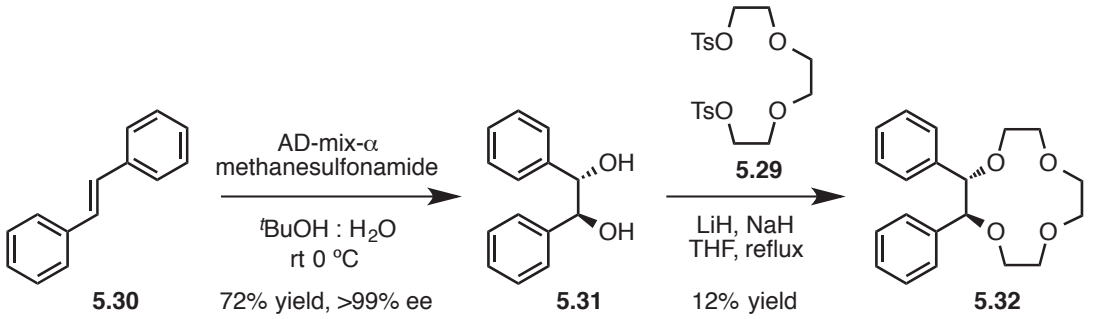


Figure 5.14: Synthesis of chiral crown **5.32**

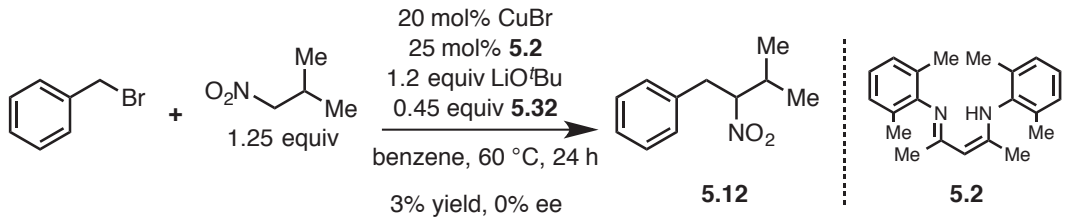


Figure 5.15: Chiral crown **5.32** in benzylation of 2-methyl-1-nitropropane

5.8 Conclusion

Despite the lack of reactivity in the *C*-benzylation of nitroalkanes of the three chiral crowns discussed in this chapter, future efforts to utilize these chiral additives for other enantioselective transformations may result. Synthetic routes to two previously unknown chiral crown structures are described herein. Further efforts to better understand the role of lithium in our *C*-alkylation conditions are underway.

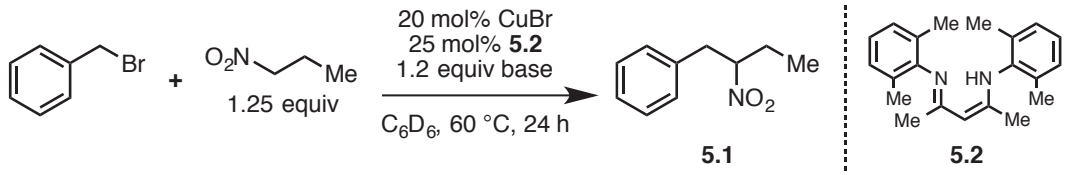
5.9 Experimental

5.9.1 General Experimental Details

Benzene, hexanes, dimethylformamide, tetrahydrofuran, dichloromethane, and diethyl ether were dried on alumina according to published procedures.[15] *tert*-Butanol was distilled from calcium hydride, sparged with N_2, and stored under N_2 in a sealed vessel. Methanol and ethanol was purchased in ACS grade, stored under air and used without further manipulation. Copper bromide, potassium *tert*-butoxide, sodium *tert*-butoxide, and lithium *tert*-butoxide were purchased commercially; the bulk was stored in a nitrogen filled glovebox; samples were removed from the glovebox and stored in a desiccator under air for up to one week prior to use. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. β-Diketiminate ligand **5.2** was synthesized according to a published procedure.[16] Nitroalkane substrate 2-methyl-1-nitropropane was prepared according to the literature procedure.[17] All other substrates and reagents were purchased in highest analytical purity from commercial suppliers and used as received. Reactions reported in Table 5.1 were carried out in a glovebox (N_2 atmosphere) on a 500 μmol scale in 16 x 100 mm threaded test tubes with Teflon lined caps and heated in an aluminum block with stirring. Reactions reported in Tables 5.2, 5.3, and 5.4 were carried out in a glovebox (N_2 atmosphere) on a 250 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Figures 5.9, 5.13, and 5.15 were carried out in a glovebox (N_2 atmosphere) on a 125 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Product yields in Tables 5.1, 5.2, and 5.3 and Figures 5.9, 5.13, and 5.15 were obtained by NMR using 1,3,5-trimethoxybenzene as an internal standard. Product yields in Table 5.4 were obtained

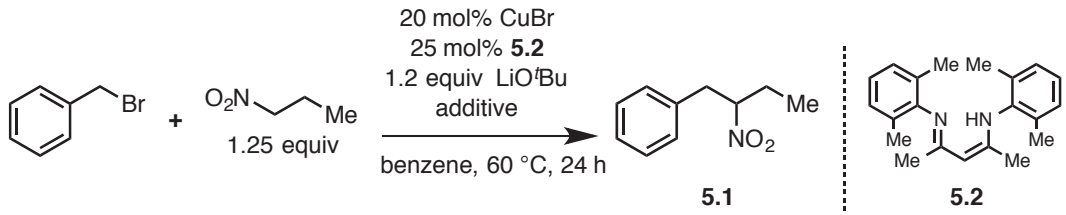
by NMR using mesitylene as an internal standard. All other reactions were set up using Schlenk technique and heated with stirring in temperature controlled oil baths. "Double manifold" refers to a standard Schlenk-line gas manifold equipped with nitrogen and vacuum (ca. 100 mtorr).

5.9.2 Procedure for Alkoxide Base Screen



In a glovebox under N_2 atmosphere, to a 16 x 100 mm threaded test tube containing a stir bar was added sequentially CuBr (14.3 mg, 100 μmol), ligand **5.2** (38.3 mg, 125 μmol), base (600 μmol), *d*-benzene (3 mL), 1-nitropropane (55.8 μL, 625 μmol), and benzyl bromide (59.8 μL, 500 μmol). The vial was sealed with a Telfon lined cap and heated in an aluminum block on a temperature controlled stir plate to 60°C with vigorous stirring for 24 h. The vials were then removed from the N_2 atmosphere and opened to air and 1,3,5-Trimethoxybenzene (42.0 mg, 250 μmol) was added. The solution was washed once with saturated ammonium chloride (6 mL) and once with brine (6 mL), passed through a plug of magnesium sulfate and analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields.

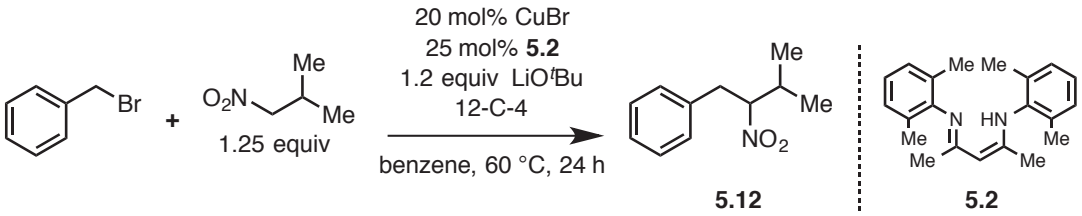
5.9.3 Procedure for Phase Transfer Additive Screens



See notebook pages: PGG03104, PGG03122, PGG03123, and PGG03124

In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (7.2 mg, 50 μmol), ligand **5.2** (19.2 mg, 63 μmol), lithium *tert*-butoxide (24.0 mg, 300 μmol), phase transfer additive (25-300 μmol), solvent (1.5 mL), 1-nitropropane (27.9 μL, 313 μmol), and benzyl bromide (29.9 μL, 250 μmol). The vial was sealed with a Telfon lined cap and heated in an aluminum block on a temperature controlled stir plate to 60°C with vigorous stirring for 24 h. The vials were then removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (21.0 mg, 125 μmol) was added and the mixture was diluted with diethyl ether (approximately 1.5 mL). The solution was washed once with saturated ammonium chloride (3 mL) and once with brine (3 mL), passed through a plug of magnesium sulfate and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields.

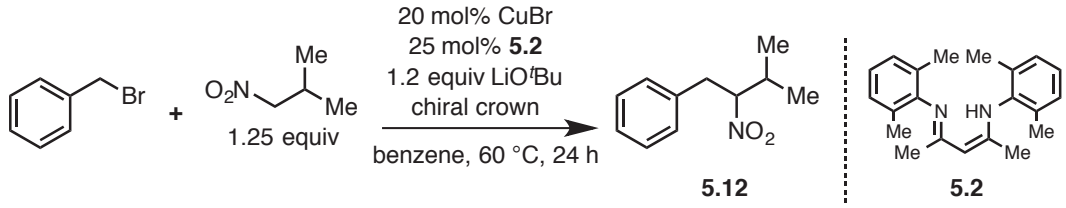
5.9.4 Procedure for Formation of Nitroalkane 5.12 Using 12-Crown-4



See notebook page: PGG04083

In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (7.2 mg, 50 μmol), ligand **5.2** (19.2 mg, 63 μmol), lithium *tert*-butoxide (24.0 mg, 300 μmol), benzene (1.5 mL), 12-crown-4 (48.5 μL, 300 μmol), 2-methyl-1-nitropropane (33.7 μL, 313 μmol), and benzyl bromide (29.9 μL, 250 μmol). The vial was sealed with a Telfon lined cap and heated in an aluminum block on a temperature controlled stir plate to 60°C with vigorous stirring for 24 h. The vials were then removed from the N_2 atmosphere and opened to air. Mesitylene (17.3 μL, 125 μmol) was added and the mixture was diluted with diethyl ether (approximately 1.5 mL). The solution was washed once with saturated ammonium chloride (3 mL) and once with brine (3 mL), passed through a plug of magnesium sulfate and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using mesitylene as an internal standard to report yields.

5.9.5 Procedure for Using Synthesized Chiral Crowns in Benzylation of 2-Methyl-1-Nitropropane

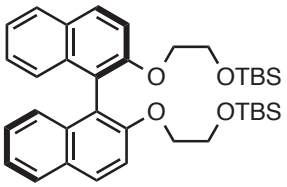


See notebook pages: PGG04081, PGG04289, and PGG04290

In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (3.6 mg, 25 μmol), ligand **5.2** (9.6 mg, 31.3 μmol), lithium *tert*-butoxide (12.0 mg, 150 μmol), chiral crown (56 – 113 μmol), benzene (750 μL), 2-methyl-1-nitropropane (16.8 μL, 156 μmol), and benzyl bromide (15.0 μL, 125 μmol). The vial was sealed with a Telfon lined cap and heated in an aluminum block on a temperature controlled stir plate to 60°C with vigorous stirring for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (10.5 mg, 63 μmol) was added and the mixture was diluted with diethyl ether (approximately 750 μL). The solution was washed once with saturated ammonium chloride (1.5 mL) and once with brine (1.5 mL), passed through a plug of magnesium sulfate and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. Reverse phase HPLC analysis (Chiralcel OJ-RH column, 1:1 H_2O : MeCN) indicates 0% ee. Enantiomers elute at 9.90 and 10.67 minutes.

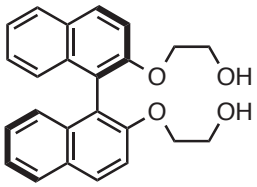
5.9.6 Synthesis of Chiral Crown 5.23

See notebook pages: PGG03291 – PGG04082



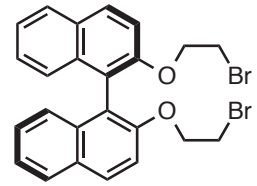
5.20

A hot 100 mL recovery flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and sodium hydride (0.672 g, 16.8 mmol) as a 60% dispersion in mineral oil was added. The septum was replaced and the flask was flushed with N_2 using a vent needle for 5 minutes. To a second 100 mL recovery flask prepared as above, (R)-binol, **5.18** (2.29 g, 8.0 mmol) was added, the septum was replaced, and the flask was flushed with N_2 using a vent needle for 5 minutes. Anhydrous DMF was added to dissolve the (R)-binol and the solution was transferred via syringe to the first flask at room temperature. Bubbling was observed and the solution turned yellow. Additional anhydrous DMF (10 mL) was used to rinse of the remaining (R)-binol. After 20 min the mixture was cooled to 0 °C using an ice bath. To a separate 25 mL conical flask prepared as above, was added silyl protected **5.19** (3.83 g, 16 mmol). Anhydrous DMF (8 mL) was added and the solution was added dropwise to the first flask previously cooled to 0 °C. The solution was allowed to warm to room temperature and stirred for an additional 14 h. Product formation by TLC was observed and the reaction was opened to air, diluted with diethyl ether (50 mL) and extracted two times with brine (100 mL). The organic layer was dried with magnesium sulfate, filtered and rotovapped to give silyl protected **5.20** and some remaining (R)-binol, **5.18**. The crude reaction mixture was rotovapped onto celite, loaded onto a short plug of silica gel and eluted with 1:10 ethyl acetate : hexanes to remove remaining (R)-binol, **5.18**. Silyl protected **5.20** was carried on directly without characterization.



5.21

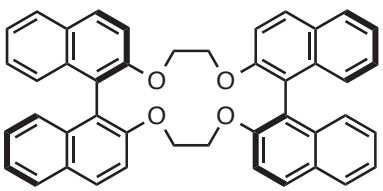
To a 250 mL round-bottom flask equipped with magnetic stir bar containing silyl protected **5.20** as an oil carried on from the previous step was added a 1M solution of HCl in ethanol (2.8 mL concentrated HCl in 95 mL ethanol). The solution was sealed with a rubber septum under air and stirred overnight. The reaction was diluted with dichloromethane (100mL) and carefully quenched with sodium bicarbonate (100mL). Using a separatory funnel the aqueous layer was extracted twice with dichloromethane (100mL). The organic layers were combined, dried with magnesium sulfate, filtered, and rotovapped to give a diol **5.21** as a white solid with some remaining silyl byproducts. Washing this solid with hexanes (20 mL) afforded diol **5.21** (1.80 g, 60% over two steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.37 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 2H), 7.29 – 7.22 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 4.24 (ddd, *J* = 10.3, 6.4, 2.6 Hz, 2H), 4.04 (ddd, *J* = 10.4, 5.7, 2.6 Hz, 2H), 3.66 – 3.50 (m, 4H), 2.29 (t, *J* = 6.6 Hz, 2H) .



5.22

A hot 25 mL recovery flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and triphenylphosphine (0.890g 3.39 mmol) was added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 three times. Anhydrous dichloromethane (4 mL) was added, the solution was cooled to 0 °C using an ice bath, and bromine (170 μL, 3.31 mmol) was added dropwise. To a separate 25 mL conical

flask prepared as above containing diol **5.21** (0.620 g, 1.66 mmol) was added dichloromethane (3 mL). The resulting homogeneous solution of diol **5.21** in dichloromethane was added dropwise to the first flask previously cooled to 0 °C, using additional dichloromethane (1 mL) to rinse the flask. After 24 h TLC shows full conversion of diol **5.21**. The crude reaction mixture was rotovapped onto celite and purified by flash column chromatography (1:9 ethyl acetate : hexanes → 3:7 ethyl acetate : hexanes) to afford dibromo **5.22** (0.722 g, 87%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 4.25 (dt, *J* = 10.7, 6.8 Hz, 2H), 4.18 (dt, *J* = 10.7, 6.6 Hz, 2H), 3.24 – 3.20 (m, 4H).



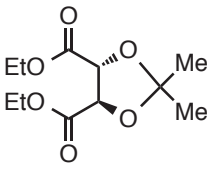
5.23

A hot 25 mL recovery flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and sodium hydride (32.8 mg, 820 μmol) was added. The septum was replaced and the flask was flushed with N_2 using a vent needle for 5 minutes. To a separate 25 mL conical flask prepared as above and containing (R)-binol (115 mg, 400 μmol) was added anhydrous dimethylformamide (2 mL). The solution was transferred to the first flask with bubbling. An additional aliquot of dimethylformamide (2 mL) was used to rinse the flask. The mixture was stirred at room temperature for 20 min. To a third 25 mL conical flask prepared as above containing dibromo **5.22** (200 mg, 400 μmol) was added anhydrous dimethylformamide (2 mL). This solution was added to the first flask at 0 °C using an

ice bath. An additional aliquot of dimethylformamide (2 mL) was used to rinse the flask. The reaction mixture was allowed to warm to room temperature and continue stirring for 48 h. The septum was removed and the reaction mixture was diluted and moved to a separatory funnel with ethyl acetate (10 mL) and brine (10 mL). The organic layer was washed three times with brine (10 mL) then dried with magnesium sulfate, filtered, and rotovapped to give a yellow solid. This crude yellow solid was purified by flash column chromatography (1:9 ethyl acetate : hexanes) to afford chiral crown **5.23** (17.6 mg, 7%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 4H), 7.54 (d, J = 9.0 Hz, 4H), 7.34 (t, J = 7.4 Hz, 4H), 7.20 (t, J = 7.5 Hz, 4H), 7.09 – 7.00 (m, 8H), 4.11 (s, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 134.0, 129.4, 129.3, 128.0, 126.3, 125.6, 123.6, 119.8, 115.5, 68.9.

5.9.7 Synthesis of Chiral Crown 5.14

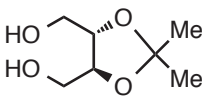
See notebook pages: PGG04276 – PGG04282



5.25

According to literature procedure[13] a hot 3-neck 100 mL round-bottom flask equipped with magnetic stir bar, rubber septum, and two ground glass stoppers, was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, and anhydrous benzene (20 mL), (+)-diethyl L-tartrate **5.24** (8.59 mL, 50.0 mmol), 2,2-dimethoxypropane (7.38 mL, 60.0 mmol) were added. The septum was removed and *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol) was added and a distillation head fitted with a thermometer and 100 mL recovery flask was attached using a "T" joint to bubble N_2 through the full apparatus. The solution was refluxed using a variac temperature controller with sand bath and the benzene-methanol

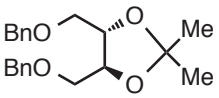
azeotrope (bp 58 °C) was distilled into the 100 mL recovery flask. After the distilling temperature had risen to 75 °C after 6 h the reaction was cooled to room temperature. The septum was removed, the flask was opened to air, and potassium carbonate (50 mg) was added to quench the residual acid. The resulting oil was distilled at 90 °C at 0.1 mm Hg using a kugelrohr apparatus to afford diester **5.25** (12.03 g, 98%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.76 (s, 2H), 4.28 (q, J = 7.1 Hz, 4H), 1.50 (s, 6H), 1.31 (t, J = 7.1 Hz, 6H).



5.26

According to literature procedure[18] a hot 3-neck 100 mL round-bottom flask equipped with magnetic stir bar, rubber septum, ground glass stopper, and condenser was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and lithium aluminum hydride (4.03 g, 105.4 mmol) was added. The septum was replaced and the flask was flushed with N_2 using a vent needle for 5 minutes. Anhydrous diethyl ether (35 mL) was added and the resulting suspension was refluxed for 30 min using an oil bath with temperature controller. To a separate 100 mL recovery flask prepared as above and containing diester **5.25** (11.8 g, 47.9 mmol) was added anhydrous diethyl ether (50 mL). To the flask containing the suspension of lithium aluminum hydride in diethyl ether previously cooled to room temperature was carefully added the solution of **5.25**. The rate of addition was monitored so as not to exceed a gentle reflux of the ether suspension. After addition the mixture was refluxed for an additional 3 h. After cooled to room temperature ethyl acetate (5 mL) was carefully added and the solution was cooled to 0 °C using an ice bath. After successive cautious additions of H_2O (4 mL), 4 M sodium hydroxide (4 mL), and H_2O (12.5 mL),

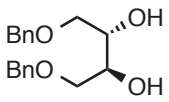
the inorganic precipitate was removed by filtration and extracted with ethyl acetate (100 mL). The combined organic extracts were dried with magnesium sulfate, filtered and rotovapped to give diol **5.26** (7.25 g, 93%) as an oil and used without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.04 – 3.97 (m, 2H), 3.80 (d, J = 11.5 Hz, 2H), 3.70 (d, J = 11.4 Hz, 2H), 2.21 (s, 2H), 1.43 (s, 6H).



5.27

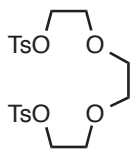
According to literature procedure[14] a hot 100 mL recovery flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and sodium hydride (1.70 g, 42.4 mmol) as a 60% dispersion in mineral oil was added. The septum was replaced, the flask was flushed with N_2 using a vent needle for 5 minutes, and then anhydrous tetrahydrofuran (12 mL) was added. To a separate 50 mL recovery flask prepared as above and containing diol **5.26** (2.93 g, 18.1 mmol), was added tetrahydrofuran (12 mL). This solution was added dropwise to the first flask containing the suspension of sodium hydride at room temperature with bubbling observed. An additional aliquot of tetrahydrofuran (5 mL) was used to rinse the flask. The reaction was stirred for 1 h then benzyl bromide was added (4.75 mL, 39.7 mmol) dropwise. Stirring at room temperature was continued overnight, then a reflux condenser was added and the solution was refluxed for an additional 2 h using an oil bath with temperature controller. The reaction mixture was then cooled to 0 °C using an ice bath and H_2O (3 mL) was added to quench any unreacted sodium hydride. The tetrahydrofuran was removed by rotovap and the resulting yellow residue was moved to a separatory funnel with benzene (50 mL) and brine (50 mL). The aqueous layer was extracted with

benzene (50 mL) once more,and then the combined organic layers were dried with magnesium sulfate, filtered, and rotovapped to give mostly pure dibenzyl ether **5.27** with some remaining benzyl bromide a yellow oil which was carried on without further purification.



5.28

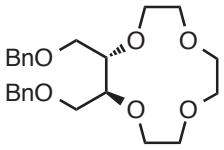
According to literature procedure[14] a 100 mL round-bottom flask equipped with a magnetic stir bar open to air, containing dibenzyl ether **5.27** carried on directly from the previous step, was charged with 4M HCl in methanol (16 mL). To the flask was added a distillation head fitted with a thermometer, 50 mL recovery flask, and "T" joint to bubble N_2 through the full apparatus. The solution was refluxed using a variac temperature controller with sand bath and the acetone-methanol azeotrope was distilled into the 50 mL recovery flask. After about 15 mL had distilled over an additional portion of 4M HCl in methanol (3 mL) was added. The mixture was rotovapped to remove excess methanol then moved to a separatory funnel with benzene (50 mL) and washed once with aqueous saturated sodium bicarbonate (50 mL), and once with brine (50 mL). The resulting organic layer was dried with magnesium sulfate, filtered and rotovapped to give a yellow oil that solidified upon removal of trace volatiles by hivac. Washing this pale yellow solid with cold hexanes (20 mL) afforded diol **5.28** (4.37g, 80% yield over two steps) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 10H), 4.55 (q, J = 11.9 Hz, 4H), 3.91 – 3.85 (m, 2H), 3.65 – 3.56 (m, 4H), 2.80 – 2.77 (m, 2H).



5.29

According to literature procedure[19] a hot 3-neck 200 mL round-bottom flask equipped with magnetic stir bar, rubber septum, and ground glass

stopper, was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and *p*-toluenesulfonyl chloride (19.5 g, 102 mmol) was added. The septum was replaced, the flask was flushed with N_2 using a vent needle for 5 minutes, and then anhydrous dichloromethane (50 mL), and triethylene glycol (6.67 mL, 50 mmol) were added. The flask was cooled to 0 °C using an ice bath, the septum was removed under positive N_2 and potassium hydroxide (22.44 g, 400 mmol) was added in portions. After complete addition of base, the reaction was allowed to warm to room temperature and stir for an additional 3 h. The reaction mixture was then moved to a separatory funnel with dichloromethane (50 mL) and ice water (60 mL). The aqueous layer was extracted an additional two times with dichloromethane (50 mL), and then the combined organic layers were dried with magnesium sulfate, filtered, and rotovapped to afford **5.29** as a white solid used without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 4H), 7.34 (d, *J* = 8.0 Hz, 4H), 4.16 – 4.12 (m, 4H), 3.67 – 3.64 (m, 4H), 3.53 (s, 4H), 2.45 (s, 6H).



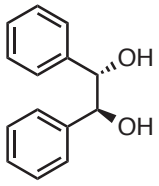
5.14

Modified from literature procedure[10] a hot 3-neck 100 mL round-bottom flask equipped with magnetic stir bar, rubber septum, and ground glass stopper, was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and diol **5.28** (200 mg, 662 μmol), lithium hydride (11.0 mg, 1.39 mmol), and sodium hydride (55.6 mg, 1.39 mmol) as a 60% dispersion in mineral oil were added. A reflux condenser was added and the flask was flushed with N_2 using a vent needle for 5 minutes. Anhydrous tetrahydrofuran (33 mL) was added and stirred at

45 °C for 3 h using an oil bath with temperature controller. To a separate 25 mL conical flask prepared as above containing tosylated **5.29** (319 mg, 695 μmol) was added anhydrous tetrahydrofuran (10 mL). The solution of ditosylated **5.29** was added to the first flask at 45 °C then the temperature was increased to reflux. The refluxing mixture was stirred for an additional 5 days. The septum was removed and chloroform (10 mL) was used to move the reaction mixture to a separatory funnel. H_2O (10 mL) was added and the aqueous layer was extracted three times with chloroform (10 mL). The combined organic fractions were dried with magnesium sulfate, filtered, and rotovapped to give an oily residue. Purification by flash column chromatography (4:6 ethyl acetate : hexanes → 9:1 ethyl acetate : hexanes) afforded **5.14** (49.1 mg, 18%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 7H), 7.24 – 7.20 (m, 3H), 4.48 – 4.41 (m, 4H), 3.77 – 3.44 (m, 18H).

5.9.8 Synthesis of Chiral Crown 5.32

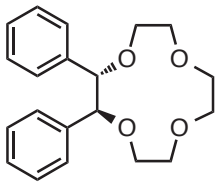
See notebook pages: PGG04088 – PGG04283



5.31

According to literature procedure[20] a 25 mL round-bottom flask equipped with a magnetic stir bar open to air, was charged with *tert*-butanol (5 mL), H_2O (5 mL), and AD-mix-α (1.4 g). Stirring at room temperature produced two clear phases; the lower aqueous phase appears yellow. Methanesulfonamide (95.1 mg, 1 mmol) was added and the mixture was cooled to 0 °C using a cryocool unit and 2:1 isopropanol : water bath whereupon the solution turned heterogeneous orange. Trans-stilbene (180.3 mg, 1 mmol) was added and the flask was sealed under with a rubber septum. After 3 days complete conversion of starting material was observed by TLC and the mixture appeared as a

yellow suspension. Sodium sulfite (1.5 g) was added and the mixture was allowed to warm to room temperature and stir for an additional 1.5 h. The reaction was diluted with ethyl acetate (10 mL) and the aqueous layer was subsequently extracted three times with ethyl acetate (10 mL). The organic layers were combined and washed with 2M potassium hydroxide (30 mL), dried with magnesium sulfate, filtered and rotovapped to give the desired product and some unreacted starting material. The reaction was purified by flash silica chromatography (1:3 ethyl acetate : hexanes) to afford hydrobenzoin **5.31** (155 mg, 72%, >99% ee) as a white crystalline solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 6H), 7.14 (dd, J = 6.7, 2.9 Hz, 4H), 4.72 (s, 2H), 2.80 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 128.3, 128.1, 127.1, 79.3.



5.32

Modified from literature procedure[10] a hot 3-neck 100 mL round-bottom flask equipped with magnetic stir bar, rubber septum, and ground glass stopper, was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and hydrobenzoin **5.31** (100 mg, 467 μmol), lithium hydride (7.8 mg, 980 μmol), and sodium hydride (39.2 mg, 980 μmol) as a 60% dispersion in mineral oil were added. A reflux condenser was added and the flask was flushed with N_2 using a vent needle for 5 minutes. Anhydrous tetrahydrofuran (23 mL) was added and stirred at 45 °C for 3 h using an oil bath with temperature controller. To a separate 25 mL conical flask prepared as above containing tosylated **5.29** (225 mg, 490 μmol) was added anhydrous tetrahydrofuran (7 mL). The solution of ditosylated **5.29** was added to the first flask at 45 °C, rinsing with an additional aliquot of tetrahydrofuran (1.5 mL) then the temperature was increased to reflux. The refluxing mixture was stirred

for an additional 5 days. The septum was removed and chloroform (10 mL) was used to move the reaction mixture to a separatory funnel. H_2O (10 mL) was added and the aqueous layer was extracted three times with chloroform (10 mL). The combined organic fractions were dried with magnesium sulfate, filtered, and rotovapped to give an oily residue. Purification by flash column chromatography (1:4 ethyl acetate : hexanes → 1:1 ethyl acetate : hexanes) afforded **5.32** (18.2 mg, 12%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 6H), 7.04 – 6.98 (m, 4H), 4.51 (s, 2H), 3.87 – 3.78 (m, 4H), 3.78 – 3.70 (m, 4H), 3.61 (t, J = 4.5 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.9, 128.0, 127.9, 127.6, 86.8, 71.1, 71.0, 69.5.

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Chapter 6

ENANTIOSELECTIVE *C*-ALKYLATION OF NITROALKANES

6.1 Enantioselective Cross-Coupling of Alkyl Halides with Carbon Nucleophiles

As discussed in Chapter 1, despite the numerous challenges associated with cross-couplings of alkyl halides with carbon nucleophiles, significant progress has been made in the field using transition metal catalysis.[1] The identification of suitable chiral ligands for these catalysts has greatly expanded the scope of asymmetric methods for forming $C(sp^3)$-$C(sp^3)$ bonds. Aware of the versatility of nickel catalysts for cross-coupling alkyl halides, I was especially drawn to the pioneering work of the Fu group. In 2005, they published the first catalytic enantioselective cross-coupling of secondary alkyl electrophiles as demonstrated in the Negishi type coupling of α-bromoamide **6.1** with organozinc reagent **6.2** using chiral pybox ligand **6.4** (Figure 6.1).[2]

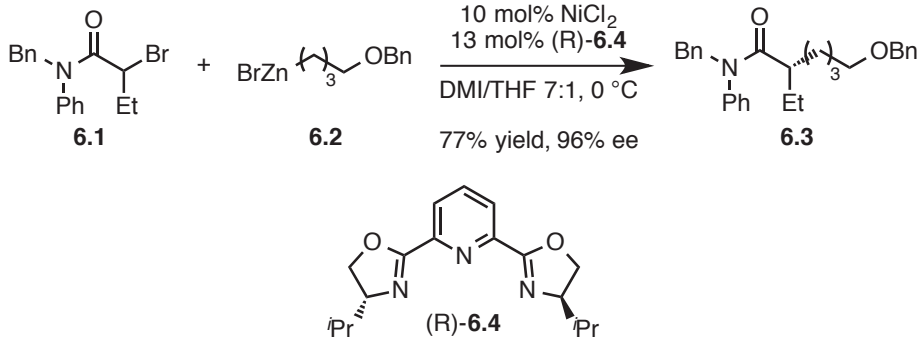


Figure 6.1: First enantioselective cross-coupling of secondary alkyl electrophiles by the Fu Group

Later in 2008, the Fu group reported the first asymmetric cross-coupling of unactivated alkyl electrophiles using the versatile chiral diamine **6.8**.[3] The Suzuki coupling of homobenzylic bromide **6.5** with alkylborane **6.6** led to formation of enantioenriched alkane **6.7** in 86% yield and 86% enantioselectivity (Figure 6.2). These examples and those presented in Chapter 1 highlight the recent advancements in the field of enantioselective $C(sp^3)$-$C(sp^3)$ cross-couplings. As will be discussed further in the following sections, new results led me to reconsider the presence of the ligand in the bond-forming step of our *C*-alkylation conditions when using lithium nitronates. These preliminary results led me to examine chiral ligands as a means of inducing asymmetry in the *C*-alkylation of nitroalkanes.

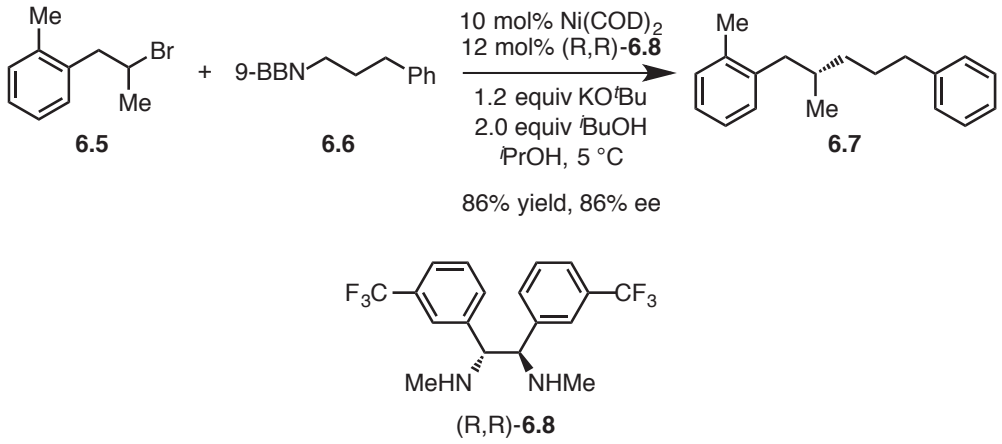


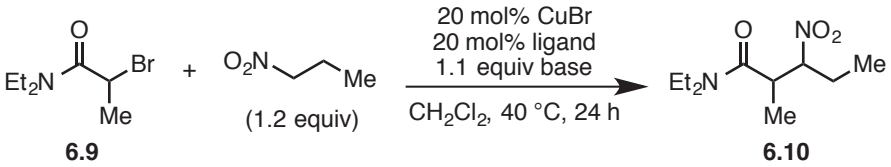
Figure 6.2: Fu group enantioselective cross-coupling of unactivated homobenzylic bromides

6.2 Towards Enantioselective *C*-Alkylation of Nitroalkanes: Effect of Lithium Counterion on Diastereoselectivity of β-Nitrocarbonyl Formation

Despite the unsuccessful attempts of inducing enantioselectivity when using chiral crown ethers in the presence of lithium alkoxide bases, I was eager to better

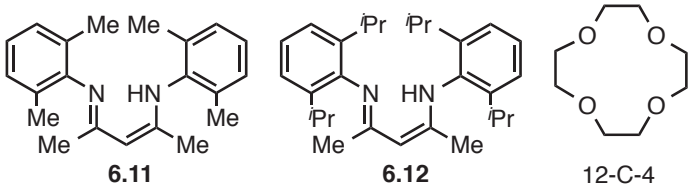
understand the role and reactivity of lithium in our *C*-alkylation reactions. Towards this end Vijayarajan Devannah examined the use of lithium bases in the formation of β-nitrocarbonyls. In our group's prior work for the formation of β-nitrocarbonyls, sodium trimethylsilanolate gave high yields but modest diastereoselectivities (52:48 to 77:33) in all but two cases for the anti-diastereomer. Potassium trimethylsilanolate gave similar diastereoselectivity, albeit with diminished yields (Table 6.1, entry 1). When using lithium bases with more polar solvents such as dichloromethane reactivity was observed for the first time in our copper-catalyzed *C*-alkylation of nitroalkanes (Table 6.1, entry 2). Despite low yields of *C*-alkylated product, interestingly the diastereoselectivity increased to a ratio of 11:89 in favor of the opposite syn-diastereomer. Using lithium methoxide further increased the selectivity for the syn-diastereomer up to 5:95. To evaluate this apparent cation effect, 12-crown-4 was added to the reaction when using lithium methoxide. The observance of a 56:44 diastereomeric ratio of the resultant product (a similar ratio as when using the corresponding potassium or sodium base) supports apparent involvement of lithium in the bond-forming step when it is coordinated to the nitronate. A minor, but reproducible, change in yield and diastereoselectivity was observed when using β-diketimine **6.12** as a catalyst, which led me to reconsider the possibility of ligand interaction in the bond-forming step. Together these observations led me to investigate chiral ligands as possible means of imparting asymmetry in our *C*-alkylation reaction.

Table 6.1: Effect of lithium bases on diastereoselectivity



entry	ligand	base	yield **6.10** (anti:syn dr)
1	**6.11**	$KOSiMe_3$	33 (67:33)
2	**6.11**	$LiOSiMe_3$	27 (11:89)
3	**6.11**	LiOMe	27 (5:95)
4[a]	**6.11**	LiOMe	25 (56:44)
5	**6.12**	LiOMe	34 (10:90)

[a]1.1 equiv 12-C-4



6.3 Examining Chiral Ligands for the *C*-Alkylation of Nitroalkanes

In the initial stages of ligand optimization for the benzylation of nitroalkanes the class of 1,2-cyclohexyldiamines showed promise (Figure 6.3). Ultimately this ligand scaffold was abandoned due to undesired *N*-alkylation of the ligand with the benzyl bromide starting material. The absence of a proton on nitrogen in this alkylated ligand prevented it from being an effective catalyst. However, I believed the secondary and tertiary bromide α-bromocarbonyl starting materials would be less likely to act as alkylating agents for the ligand. This ligand class might therefore serve as an effective chiral catalyst to form *C*-alkylated nitroalkanes enantioselectively.

Gratifyingly this proved to be the case as Weinreb amide **6.16** and 1-nitropropane in suitably polar ^{t}BuOH with lithium methoxide, and copper bromide gave *C*-alkylated product **6.17** in 40% yield and an encouraging 10% ee (Figure 6.4). Despite achieving only modest enantioenrichment, this initial result for the first time demonstrated it was possible to set a stereocenter alpha to the nitro group using a chiral ligand with our catalytic *C*-alkylation conditions.

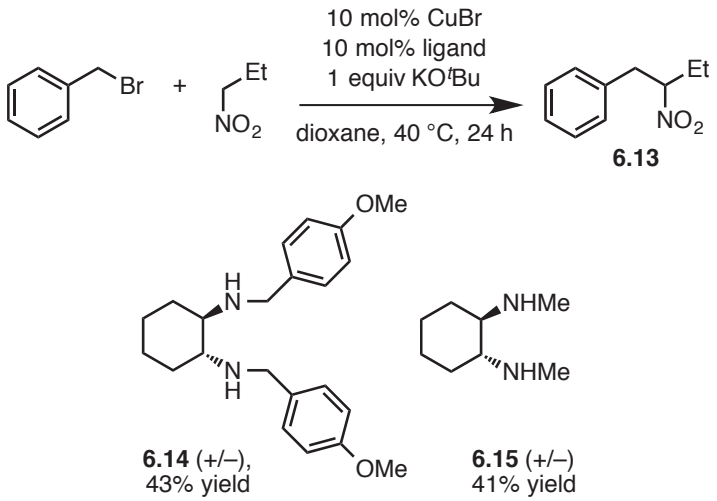


Figure 6.3: 1,2-Cyclohexyl diamine ligands in benzylation of 1-nitropropane

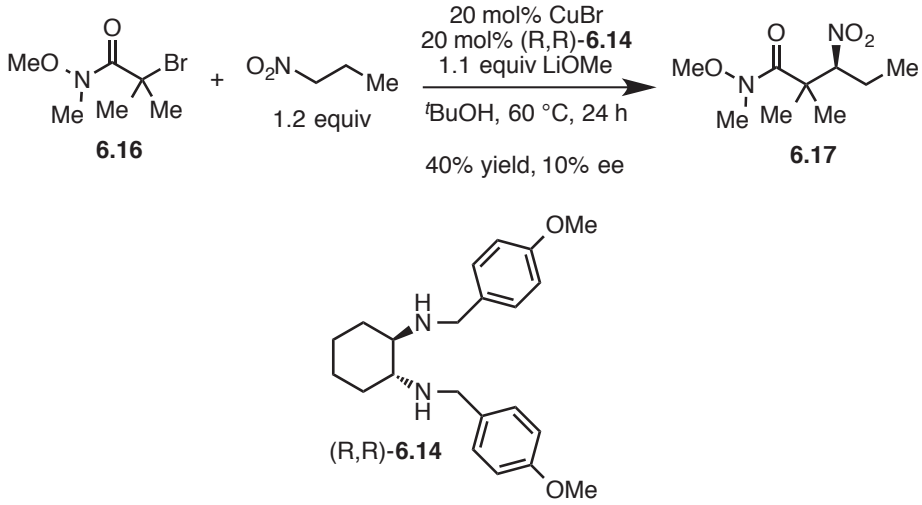
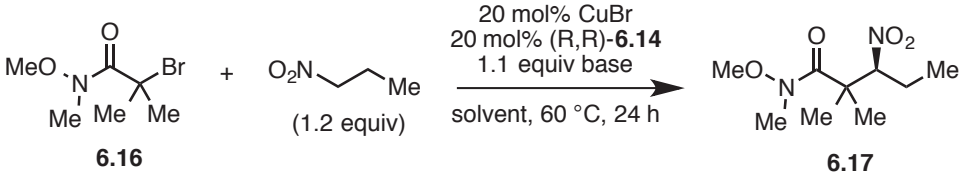


Figure 6.4: Enantioselectivity achieved with chiral 1,2-diamine ligand **6.14**

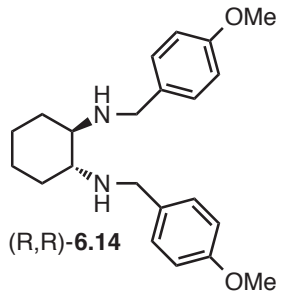
6.4 Optimization of Enantioselective Copper-Catalyzed *C*-Alkylation of Nitroalkanes with α-Bromoamides

A subsequent investigation of the reaction conditions when using diamine **6.14** with copper bromide led to several key improvements in both yield and enantioselectivity. Despite the previous results that suggested a unique role of lithium in promoting a more ordered transition state (Table 6.1) switching to sodium trimethylsilanolate led to a significant improvement in yield (71%) and enantioselectivity (22%) in the formation of nitroamide **AH** (Table 6.2, entry 2). Moving to less polar dichloromethane, while decreasing the yield of nitroamide **AH** to 41%, significantly improved the ee to 42% (entry 3).

Table 6.2: Effect of base and solvent on enantioselective *C*-alkylation of Weinreb amide **6.16**



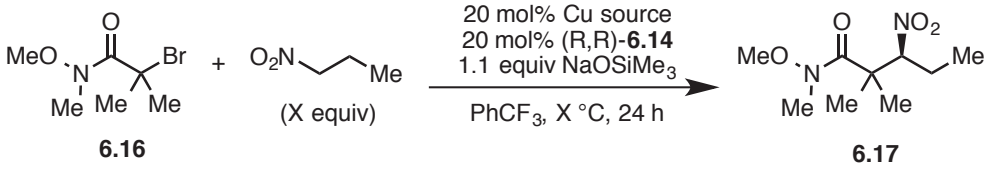
entry	base	solvent	yield **6.17** (%)	ee **6.17** (%)
1	LiOMe	^{t}BuOH	40	10
2	$NaOSiMe_3$	^{t}BuOH	71	22
3	$NaOSiMe_3$	CH_2Cl_2	41	42



(R,R)-**6.14**

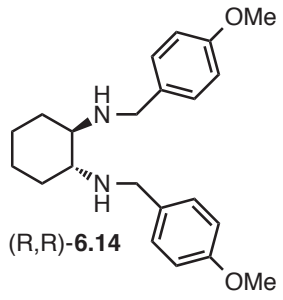
Further investigation of solvents ultimately led to halogenated trifluorotoluene as the best solvent to date in forming nitroamide **6.17** in 47% yield with 48% ee (Table 6.3, entry 1). Moving to lower temperature with a less coordinating copper source, tetrakis(acetonitrile)copper(I) hexafluorophosphate, improved yield and enantioselectivity (entries 2 and 3). A slight reduction in the equivalents of 1-nitropropane led to our best conditions to date to form nitroamide **6.17** when using a copper catalyst: 80% yield, with 65% ee (entry 4).

Table 6.3: Effect of copper source and temperature on enantioselective *C*-alkylation of Weinreb amide **6.16**



entry	Cu source	temp	yield **6.17** (%)	ee **6.17** (%)
1	CuBr	60 °C	47	48
2	CuBr	40 °C	57	51
3	$Cu(MeCN)_4PF_6$	40 °C	74	64
4[a]	$Cu(MeCN)_4PF_6$	40 °C	80	65

[a]1.1 equiv 1-nitropropane



(R,R)-**6.14**

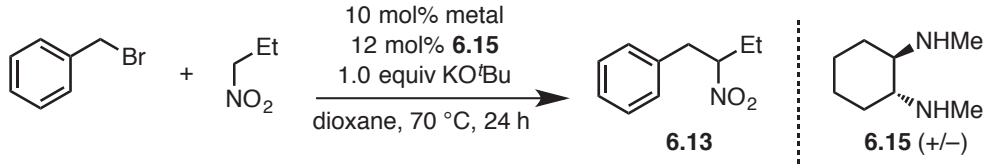
6.5 Discovery and Optimization of Enantioselective Nickel-Catalyzed *C*-Alkylation of Nitroalkanes with α-Bromoamides

While copper (I) salts thus far have proved to be effective toward the development of an enantioselective *C*-alkylation of nitroalkanes, I was cognizant of the recent advances in enantioselective nickel catalyzed cross-couplings of alkyl halides with carbon nucleophiles.[1a] The similar structure of the activated α-haloamide substrates in the work of the Fu group (Figure 6.4)[4] to the α-bromocarbonyls suitable for our *C*-alkylation conditions, as well as their use of chiral diamines led Vijayarajan

Devannah and I to examine nickel as a potential catalyst in the enantioselective transformations.

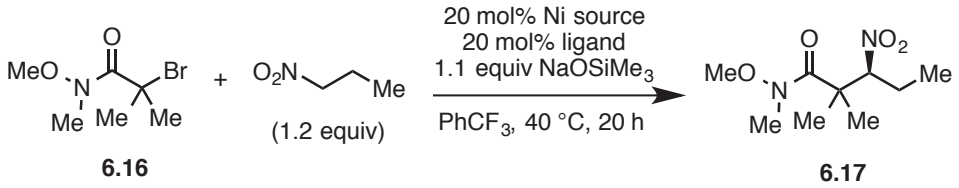
Earlier in the initial optimization of our *C*-alkylation conditions when using benzyl bromides and 1-nitropropane I observed modest reactivity when using bis(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$). Ultimately optimization was continued with the superior copper(I) bromide (Table 6.4). However, when using nickel (II) bromide with chiral 1,2-diphenyldiamine **6.18** in the enantioselective *C*-alkylation of 1-nitropropane with Weinreb amide **6.16** Vijayarajan observed, despite a modest yield of 22% of the *C*-alkylated product **6.17**, a significant enantioselectivity of 60% ee (Table 6.5, entry 1). Moving to cyclohexyldiamine **6.14,** which had shown promise in the copper-catalyzed conditions, led to increased enantioselectivity with slightly diminished yield (entry 2). Addition of catalytic amounts of Zn powder as a reductant did not significantly alter reactivity (entry 3). However, using $Ni(COD)_2$ as a nickel (0) source led to improved yields with only a slight decrease in enantioselectivity (entry 4).

Table 6.4: Comparing copper and nickel with diamine ligand **6.15**



entry	metal	yield **6.13** (%)
1	CuBr	43
2	$Ni(COD)_2$	12

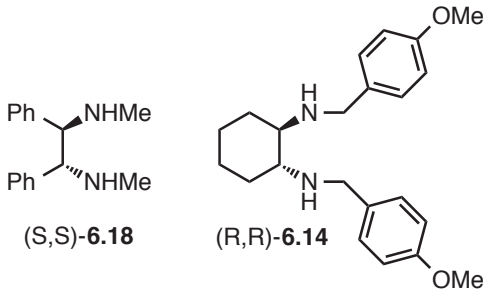
Table 6.5: Examining nickel catalyst in enantioselective *C*-alkylation of Weinreb amide **6.16**



6.16 **6.17**

entry	Ni source	ligand	yield **6.17** (%)	ee **6.17** (%)
1	$NiBr_2$ • diglyme	**6.18**	22	60
2	$NiBr_2$ • diglyme	**6.14**	12	71
3[a]	$NiBr_2$ • diglyme	**6.14**	9	73
4	$Ni(COD)_2$	**6.14**	40	63

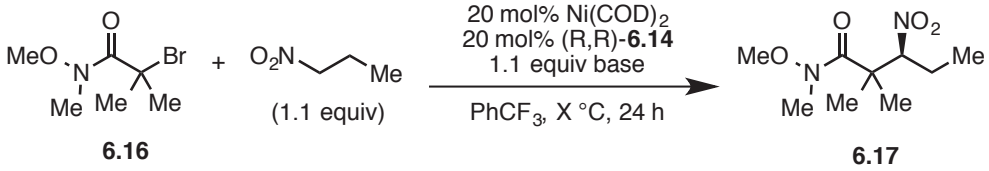
[a]40 mol% Zn powder added



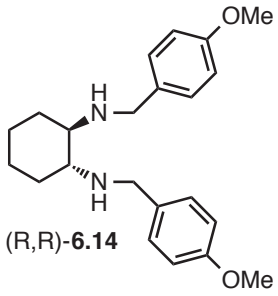
(S,S)-**6.18** (R,R)-**6.14**

Optimizing further with $Ni(COD)_2$ together with chiral diamine **6.14** as the most promising nickel catalyst to date, I observed improved yields of nitroamide **6.17** when using the organic base 1,8-Diazabicycloundec-7-ene (DBU) (Table 6.6, entry 2). Lower temperatures led to increased product formation and higher enantioselectivity. To date the best results using a nickel catalyst are observed in the *C*-alkylation of 1-nitroproane with weinreb amide **6.16** in 74% yield with 75% ee. Efforts to further optimize these conditions, examine the role of the chiral 1,2-diamine ligand, and understand the mechanism for the enantioselective pathway are underway.

Table 6.6: Optimizing conditions for nickel catalyst in enantioselective *C*-alkylation of Weinreb amide **6.16**



entry	base	temp	yield **6.17** (%)	ee **6.17** (%)
1	$NaOSiMe_3$	40 °C	40	63
2	DBU	40 °C	60	62
3	DBU	rt	73	64
4	DBU	0 °C	74	75



(R,R)-**6.14**

6.6 Diastereoselective Conjugate Addition of Enantioenriched β-Nitroamides

In an effort to explore the scope with respect to substitution of our group's newly discovered nickel-catalyzed *C*-alkylation conditions, secondary α-bromo Weinreb amide **6.19** was subjected to the optimized enantioselective nickel-catalyzed *C*-alkylation conditions in the presence of 1-nitrohexane (Figure 6.5). Gratifyingly without additional optimization nitroamide **6.20** was isolated in 57% yield as a mixture of diastereomers (72:28 syn:anti). Enantioenrichment was observed in both of

these diastereomers with 68% ee for the syn diastereomer and 33% ee for the anti diastereomer.

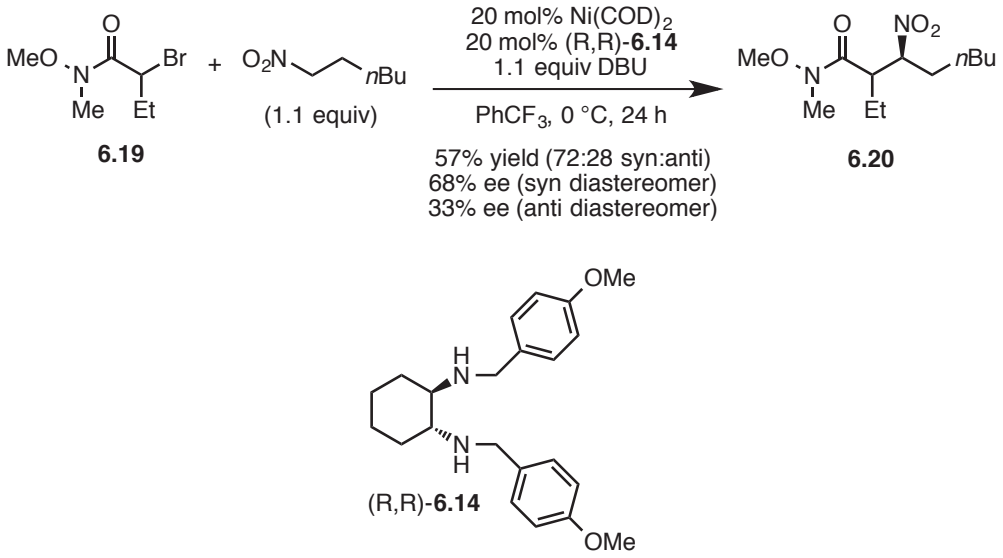


Figure 6.5: Enantioselective *C*-alkylation of secondary Weinreb amide **6.19** with 1-nitrohexane

In our group's previous work detailing the *C*-alkylation of nitroalkanes with α-bromocarbonyls,[5] we demonstrated the utility of resulting 1,3-nitrocarbonyls as intermediates towards products with nitrogen-bearing fully-substituted carbons, a motif challenging to access with alternative strategies.[6] One such demonstration involved the conjugate addition of nitroamide **6.10** (reacted as a 68:32 anti:syn mixture of diastereomers) to methyl acrylate (Figure 6.6). The resultant tertiary nitroester **6.21** was formed in 83% yield as a single observable diastereomer. Encouraged by these results, I sought to examine whether these conditions might prove highly diastereoselective for enantioenriched nitroalkane products such as **6.20**

to form sterically congested, functional group dense nitroalkane products with high diastereo- and enantioselectivity.

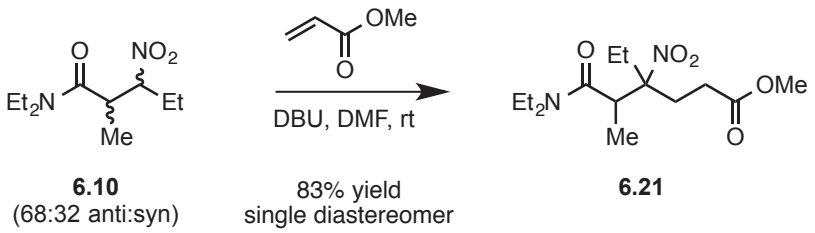


Figure 6.6: Diastereoselective Michael addition of nitroamide **6.10** to methyl acrylate

Towards this end I subjected nitroamide **6.20** as a mixture of diastereomers (66:34 syn:anti) to the previously optimized diastereoselective conjugate additions conditions (Figure 6.7, top). The conjugate addition product **6.22** was obtained with 52% ee as a single observable diastereomer. Performing the same reaction with just the syn diastereomer of nitroamide **6.20** gave the conjugate addition product **6.22** as the same single diastereomer (Figure 6.7, bottom). Efforts at this time are underway to determine if the conjugate addition is selective when using the anti diastereomer and, in all three cases, which diastereomer of product **6.22** is formed. The expansion of these initial results, with regards to ligand design optimization and expansion of scope, should lead to new useful methods for accessing complex nitroalkane products in high diastereo- and enantioselectivity.

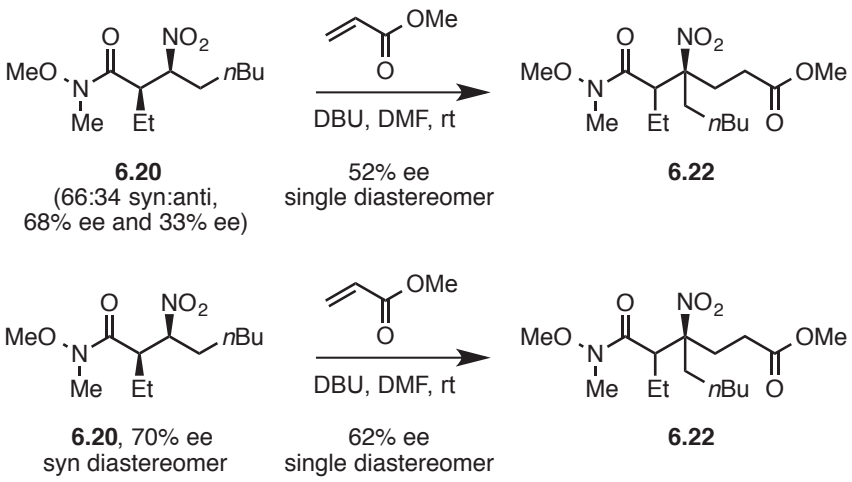


Figure 6.7: Diastereoselective Michael addition of nitroamide **6.20** to methyl acrylate

Using the diastereomeric and enantiomeric ratios of nitroamide **6.20** (Figure 6.7, top), I calculated the percentages of each isomer introduced into the Michael addition with methyl acrylate (Figure 6.8, top). With the percentage of each isomer known (Figure 6.8, top right), and given the complete diastereoselectivity of the Michael addition, we could then calculate the predicted enantioselectivity of the resultant product (Figure 6.8, bottom). Since deprotonation should occur exclusively alpha to the nitro group the stereocenter alpha to the carbonyl should be preserved. The measured enantioselectivity of Michael addition product **6.22** (52% ee) closely matches the calculated enantioselectivity of the Michael addition product assuming retention of stereochemistry alpha to the carbonyl (56% ee).

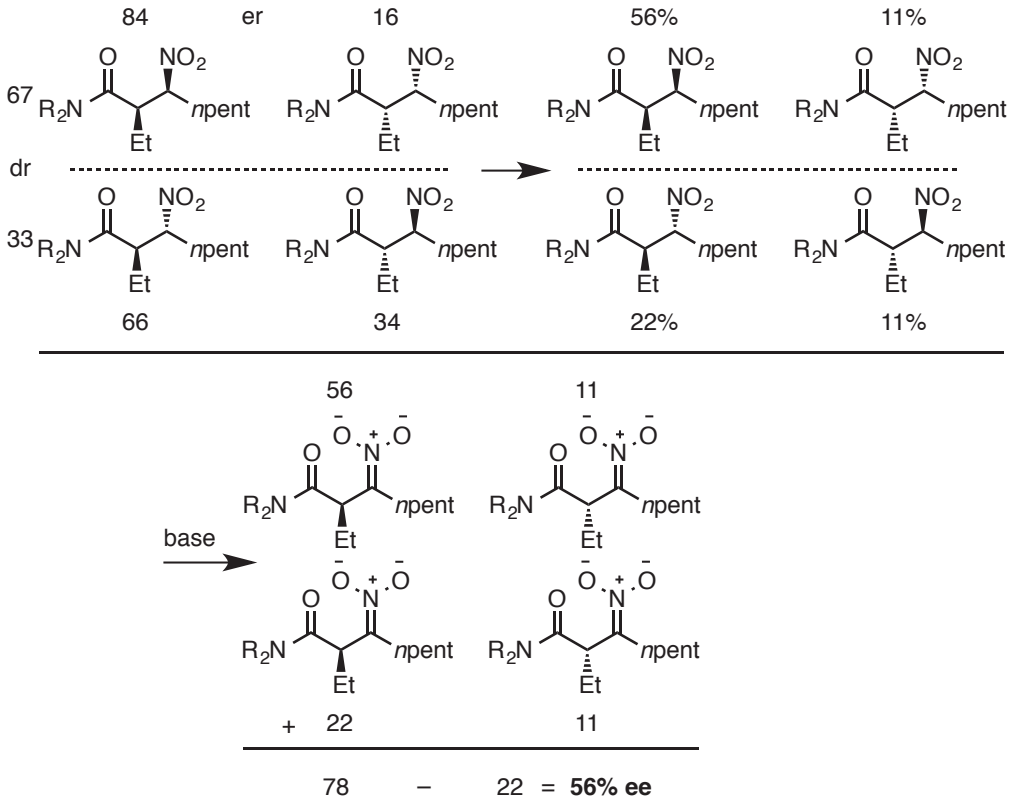


Figure 6.8: Prediction of enantioselectivity of conjugate addition based on relative percentages of isomers

6.7 Conclusion

In summary the results described herein constitute the first steps towards the identification of general conditions for the enantioselective *C*-alkylation of nitroalkanes. The realization of these conditions was dependent on the identification of 1,2-cyclohexyldiamines as suitable chiral ligands with both copper and nickel to impart enantioselectivity. While the promising results have thus far utilized secondary and tertiary α-bromo Weinreb amides as coupling partners, expansion of scope is underway. Additionally the ability to set stereocenters adjacent to the nitro and carbonyl group in the 1,3-nitroamide products further extends the usefulness of this

method as a means to access more complex enantioenriched nitrogen containing molecules after subsequent alkylation.

In total my work in the Watson lab has focused on the discovery and development of copper-catalyzed conditions for the *C*-alkylation of nitroalkanes with alkyl electrophiles. This method has proven general with respect to the *C*-alkylation of nitroalkanes with several classes of radical-stabilizing alkyl electrophiles including benzyl bromides, α-bromocarbonyls, α-bromonitroalkanes, α-bromocyanoalkanes, and a radical trifluoromethyl source. Additionally a copper- and nickel-catalyst has been identified for the enantioselective *C*-alkylation of nitroalkanes with Weinreb amides. In addition to publication, my work has led to the creation of several new projects that are being investigated by other members of the Watson lab. In total my research in the Watson Lab has addressed a significant gap in the reactivity and potential of nitroalkanes as versatile synthons for C-C bond formation.

6.8 Experimental

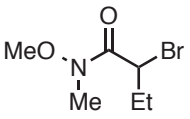
6.8.1 General Experimental Details

Dichloromethane, dioxane, and dimethylformamide were dried on alumina according to published procedures.[7] *tert*-Butanol was distilled from calcium hydride, sparged with N_2, and stored under N_2 in a sealed vessel. Copper bromide, copper tetrakis(acetonitrile) hexafluorophosphate, potassium *tert*-butoxide, lithium methoxide, potassium trimethylsilanolate, sodium trimethylsilanolate, and lithium trimethylsilanolate were purchased commercially; the bulk was stored in a nitrogen filled glovebox; samples were removed from the glovebox and stored in a desiccator under air for up to one week prior to use. Bis(1,5-cyclooctadiene)nickel was purchased

commercially and stored in a nitrogen filled glovebox freezer at –35 °C; samples were weighed in a nitrogen atmosphere at room temperature. All hot glassware was oven dried for a minimum of two hours or flame-dried under vacuum prior to use. Synthesis of b-diketiminate ligands **6.11** and **6.12** were carried out via the condensation of the appropriate 1,3 diketones and the corresponding aniline under air using a Dean-Stark condenser as described in the literature.[8] Diamine ligands **6.15**[9] and **6.14**[10] were prepared according to the literature procedure. Substrates α-bromoamide **6.9**[11] and α-bromo Weinreb amide **6.16**[12] were prepared according to the literature procedure. All other substrates and reagents were purchased in highest analytical purity from commercial suppliers and used as received. Reactions reported in tables 6.2, 6.3, 6.5 and 6.6 (entries 1-3) and Figure 6.4 were carried out in a glovebox (N_2 atmosphere) on a 125 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Reactions reported in Figure 6.3 were carried out in a glovebox (N_2 atmosphere) on a 500 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Reactions reported in tables 6.1 and 6.4 were carried out in a glovebox (N_2 atmosphere) on a 250 μmol scale in 15 x 45 mm vials with Teflon lined caps and heated in an aluminum block with stirring. Reactions reported in table 6.6 (entry 4) and Figure 6.5 were set up in a glovebox (N_2 atmosphere) on a 125 μmol scale in 15 x 45 mm vials, sealed with a septum cap, removed from the glovebox, and submerged in a cryocool bath at reduced temperature for the duration of the reaction. Reactions reported in Figures 6.6 and 6.7 were set up in 15 x 45 mm vials and sealed with Teflon lined caps under air and stirred at room temperature. Product yields in tables 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6 and Figures 6.3 and 6.4 were obtained by NMR using 1,3,5-trimethoxybenzene as an internal standard.

6.8.2 Synthesis of α-Bromo Weinreb Amide 6.19

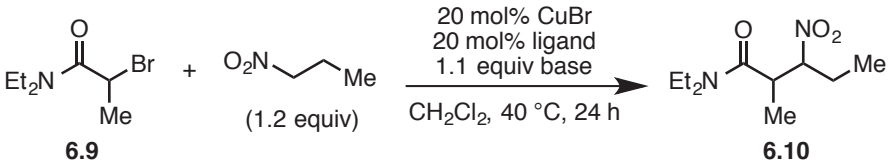
See notebook page: PGG05120



6.19

A hot 500 mL round bottom flask equipped with a magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with N_2, the septum was removed, and *N*,*O*-dimethylhydroxylamine • HCl (6.79 g, 69.6 mmol) was added. The septum was replaced, the flask was attached to a double manifold, and evacuated and backfilled with N_2 three times. Anhydrous dichloromethane (200 mL), triethylamine (9.70 mL, 69.6 mmol), and 2-bromobutyryl bromide (7.00 mL, 58.0 mmol) were added to the flask sequentially via syringe. The resulting homogenous reaction was stirred at room temperature overnight. The septum was removed and the reaction was diluted with dichloromethane and washed with brine (1x). The aqueous layer was washed with dichloromethane (1x). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (70:30 hexanes : ethyl acetate) to afford α-bromo Weinreb amide **6.19** as a pale yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.72 – 4.63 (m, 1H), 3.78 (s, 3H), 3.23 (s, 3H), 2.15 – 2.06 (m, 1H), 2.06 – 1.98 (m, 1H), 1.00 (t, *J* = 7.3 Hz, 3H).

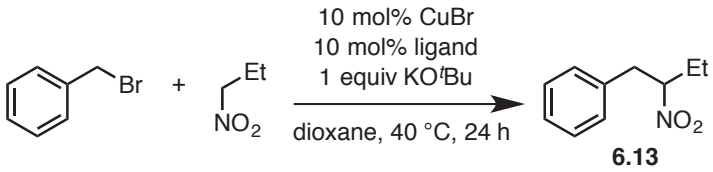
6.8.3 Procedure for Examining Effect of Base on Diastereoselectivity



In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (7.2 mg, 50 μmol), ligand (50 μmol), base (275 μmol), anhydrous dichloromethane (750 μL), 1-nitropropane (26.8 μL, 300 μmol), and α-bromoamide **6.9** (52.0 mg, 250 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at 40 °C for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (10.5 mg, 63 μmol) was added and the mixture was diluted with dichloromethane (approximately 750 μL). The solution was passed through a plug of celite and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. The product peaks matched those reported for **6.10** in the experimental section of Chapter 3.

6.8.4 Procedure for Using 1,2-Cyclohexyl Diamine Ligands in Benzylation of 1-Nitropropane

See notebook pages: PGG01139 and PGG01140

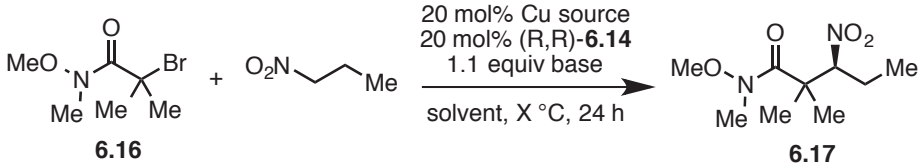


6.13

In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially CuBr (7.2 mg, 50 μmol), ligand (50 μmol), potassium *tert*-butoxide (56.1 mg, 500 μmol), anhydrous dioxane (3 mL), 1-nitropropane (44.6 μL, 500 μmol), and benzyl bromide (59.8 μL, 500 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at 40 °C for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. Dodecane (114 μL, 500 μmol) was added and the mixture was diluted with diethyl ether (3 mL). The solution was washed twice with saturated ammonium chloride (6 mL) and once with brine (6 mL), dried through a plug of magnesium sulfate and concentrated *in vacuo*. The reactions were analyzed by GC using dodecane as an internal standard to report yields. The product peaks matched those reported for **6.13** in the experimental section of Chapter 2.

6.8.5 Procedure for Optimization of Enantioselective Copper-Catalyzed *C*-Alkylation of α-Bromo Weinreb Amide 6.16

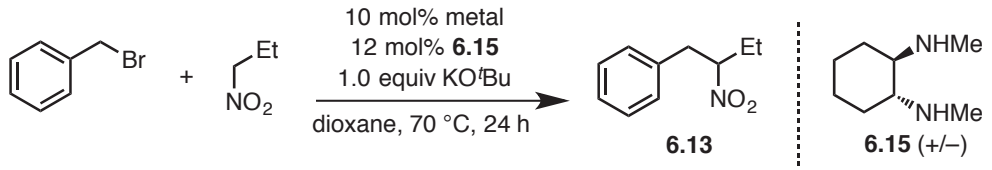
See notebook pages: PGG05003, PGG05004, PGG05009, PGG05022, and PGG05072



In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially copper source (25 μmol), ligand (R,R)-**6.14** (8.9 mg, 25 μmol), base (138 μmol), solvent (750 μL), 1-nitropropane (13.4 μL, 150 μmol), and α-bromoweinreb amide **6.16** (26.3 mg, 125 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at the given temperature for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (10.5 mg, 63 μmol) was added and the mixture was diluted with dichloromethane (approximately 750 μL). The solution was passed through a plug of celite and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. The product peaks matched those reported for **6.17** in the experimental section of Chapter 3.

6.8.6 Procedure for Comparing Copper and Nickel with Diamine Ligand 6.15

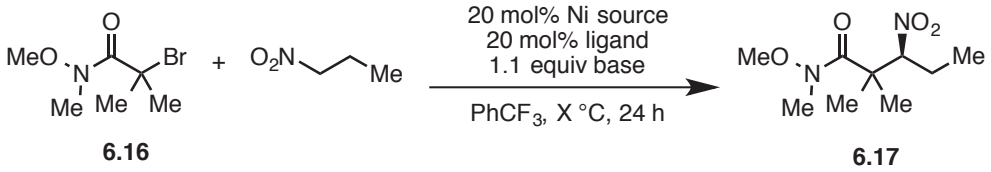
See notebook pages: PGG01101 and PGG01105



In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially metal source (25 μmol), cyclohexyl diamine **6.15** (4.3 mg, 30 μmol), potassium *tert*-butoxide (28.1 mg, 250 μmol), anhydrous dioxane (1.5 mL), 1-nitropropane (22.3 μL, 250 μmol), and benzyl bromide (30.0 μL, 250 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at 70 °C for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. 1,3,5-Trimethoxybenzene (21.0 mg, 125 μmol) was added and the mixture was diluted with diethyl ether (1.5 mL). The solution was washed twice with saturated ammonium chloride (3.0 mL) and once with brine (3.0 mL), dried through a plug of magnesium sulfate and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. The product peaks matched those reported for **6.13** in the experimental section of Chapter 2.

6.8.7 Procedure for Optimization of Enantioselective Nickel-Catalyzed *C*-Alkylation of α-Bromo Weinreb Amide 6.16

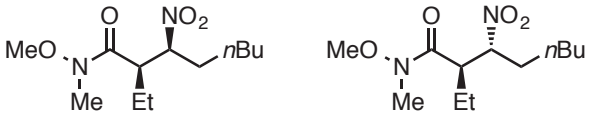
See notebook pages: PGG05096, PGG05102, and PGG05103



In a glovebox under N_2 atmosphere, to a 15 x 45 mm vial containing a stir bar was added sequentially nickel source (25 μmol), diamine ligand (25 μmol), base (138 μmol), anhydrous trifluorotoluene (750 μL), 1-nitropropane, and α-bromo Weinreb amide **6.16** (26.3 mg, 125 μmol). The vial was sealed with a Teflon lined cap, and the heterogeneous mixture was stirred at the given temperature for 24 h. After cooling to room temperature the vials were removed from the N_2 atmosphere and opened to air. For entry 4 of Table 6.TAF the vial was sealed with a septum cap, removed from the glovebox, and submerged in an isopropanol bath at 0 °C chilled using a cryocool. A nitrogen spaghetti line was added and α-bromo Weinreb amide **6.16** (26.3 mg, 125 μmol) was added via syringe using Schlenk technique. The reaction was allowed to continue stirring at 0 °C for 24 h then warmed to room temperature and opened to air. For all reactions 1,3,5-trimethoxybenzene (10.5 mg, 63 μmol) was then added and the mixture was diluted with dichloromethane (approximately 750 μL). The solution was passed through a plug of celite and concentrated *in vacuo*. The reactions were analyzed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard to report yields. The product peaks matched those reported for **6.17** in the experimental section of Chapter 3.

6.8.8 Synthesis of β-Nitroamide 6.20

See notebook page: PGG05130



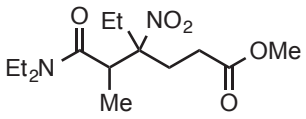
6.20A dr: 66:34 **6.20B**

In a glovebox under N_2 atmosphere, to a 17 x 60 mm vial containing a stir bar was added sequentially $Ni(COD)_2$ (27.5 mg, 100 μmol), diamine (R,R)-**6.14** (35.4 mg, 100 μmol), DBU (82.3 μL, 550 μmol), anhydrous trifluorotoluene (3.0 mL), and 1-nitrohexane (76.7 μL, 550 μmol). The vial was sealed with a septum cap, removed from the glovebox, and submerged in an isopropanol bath at 0 °C chilled using a cryocool. A nitrogen spaghetti line was added and α-bromoweinreb amide **6.19** (80.0 μL, 500 μmol) was added via syringe using schlenk technique. The reaction was allowed to continue stirring at 0 °C for 24 h. After warming to room temperature the vial was opened to air. 1,3,5-Trimethoxybenzene (42.0 mg, 250 μmol) was added, the mixture was diluted with dichloromethane (approximately 750 μL), and the solution was passed through a plug of celite and concentrated *in vacuo*. Nitroamide **6.20** was formed in 58% yield (72:28 syn:anti diastereoselectivity) by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. The crude product was purified by flash silica chromatography (97:3 hexanes : ethyl acetate → 96:4 hexanes : ethyl acetate) to afford nitroamide **6.20** (74.2 mg, 57% yield, in 67:33 syn:anti diastereoselectivity) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$: mixture of diastereomers; useful diagnostic peaks for each compound are listed) δ **6.20A**: 4.69 (td, J = 11.0, 2.6 Hz, 1H), 3.42 (td, J = 9.9, 3.4 Hz, 1H); **6.20B**: 4.85 (td, J = 9.6, 3.7 Hz, 1H), 3.53 – 3.46 (m, 1H). HPLC analysis of syn diastereomer (IA column, 1% isopropanol in hexanes, 0.2 mL/ min) indicates 68% ee. Enantiomers elute at 30.5 and 31.8 minutes. HPLC analysis of anti diastereomer (IA column, 1% isopropanol in

hexanes, 1.0 mL/ min) indicates 33% ee. Enantiomers elute at 13.8 and 16.8 minutes. Further flash silica chromatography of the 67:33 syn:anti mixture of diastereomers (hexanes → 96:4 hexanes : ethyl acetate) afforded the syn enantiomer of nitroamide **6.20** (11.4 mg, 9% yield) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.68 (td, J = 10.9, 2.6 Hz, 1H), 3.74 (s, 3H), 3.42 (td, J = 9.9, 3.5 Hz, 1H), 3.22 (s, 3H), 1.95 – 1.85 (m, 1H), 1.76 – 1.66 (m, 1H), 1.65 – 1.55 (m, 1H), 1.54 – 1.45 (m, 1H), 1.34 – 1.16 (m, 6H), 0.92 – 0.81 (m, 6H). HPLC analysis (IA column, 1% isopropanol in hexanes, 0.2 mL/ min) indicates 70% ee. Enantiomers elute at 28.7 and 29.4 minutes.

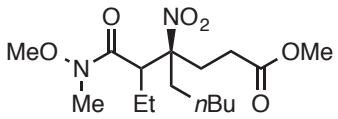
6.8.9 Synthesis of Nitroalkane Michael Addition Products

See notebook pages: PGG05133 - PGG05137



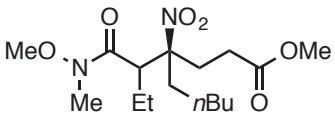
6.21

The procedure for the synthesis of β-Nitroamide **6.21** is reported in the experimental section of Chapter 3. To a 10 mL round bottom flask equipped with a magnetic stir bar was added β-nitroamide **6.10** as a (68:32 anti:syn) mixture of diastereomers (100 mg, 463 μmol), dimethylformamide (4.63 mL), 1,8-Diazabicycloundec-7-ene (126 μL 1.39 mmol), and methyl acrylate (208 μL, 1.39 mmol). The reaction was stirred at room temperature for 5.5 h. Dichloromethane (5 mL) was added and the reaction was extracted four times with brine (10 mL). The aqueous layers were combined and extracted with dichloromethane (10 mL). The combined organic layers were dried with magnesium sulfate, filtered, concentrated *in vacuo*, and placed under vacuum until the pressure was below 0.20 mm Hg. The resulting oil was loaded onto a plug of silica gel and eluted with 1:1 ethyl acetate : hexanes to afford nitroamide **6.21** as a clear oil (117 mg, 84%, single diastereomer).



6.22

To a 15 x 45 mm vial equipped with a magnetic stir bar was added under air β-nitroamide **6.20** (25.3 mg, 97.2 μmol) as a 67:33 (syn:anti) mixture of diastereomers, dimethylformamide (1.0 mL), DBU (43.6 μL 292 μmol), and methyl acrylate (26.3 μL, 292 μmol). The reaction was stirred at room temperature for 14 h. Dichloromethane (2 mL) was added and the reaction was extracted three times with brine (2 mL). The aqueous layers were combined and extracted once with dichloromethane (6 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo*. ^{1}H NMR of the resulting clear oil shows nearly pure product **6.22** as a single diastereomer. HPLC analysis (IB column, 3% isopropanol in hexanes, 0.5 mL/ min) indicates 52% ee. Enantiomers elute at 15.8 and 27.6 minutes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 – 3.63 (m, 6H), 3.47 (dd, J = 11.7, 2.6 Hz, 1H), 3.20 (s, 3H), 2.67 – 2.48 (m, 2H), 2.48 – 2.35 (m, 1H), 2.35 – 2.22 (m, 1H), 2.22 – 2.10 (m, 1H), 1.96 – 1.79 (m, 2H), 1.50 – 1.38 (m, 1H), 1.34 – 1.17 (m, 5H), 1.04 (ddd, J = 13.4, 8.4, 5.1 Hz, 1H), 0.91 – 0.80 (m, 6H).



6.22

To a 15 x 45 mm vial equipped with a magnetic stir bar was added under air β-nitroamide **6.20** (10.3 mg, 39.6 μmol) as the syn diastereomer (68% ee), dimethylformamide (0.7 mL), DBU (17.8 μL 119 μmol), and methyl acrylate (10.7 μL, 119 μmol). The reaction was stirred at room temperature for 14 h. Dichloromethane (1 mL) was added and the reaction was extracted three times with brine (1 mL). The aqueous layers were combined and extracted once with

dichloromethane (3 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo*. ^{1}H NMR of the resulting clear oil shows nearly pure product **6.22** as a single diastereomer. HPLC analysis (IB column, 3% isopropanol in hexanes, 0.5 mL/ min) indicates 62% ee. Enantiomers elute at 15.8 and 27.7 minutes: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.72 – 3.67 (m, 6H), 3.48 (dd, *J* = 11.7, 2.5 Hz, 1H), 3.21 (s, 3H), 2.62 (ddd, *J* = 15.7, 11.4, 4.5 Hz, 1H), 2.55 (ddd, *J* = 15.4, 11.2, 4.3 Hz, 1H), 2.43 (ddd, *J* = 15.7, 11.1, 4.9 Hz, 1H), 2.30 (ddd, *J* = 15.7, 11.5, 4.8 Hz, 1H), 2.20 – 2.12 (m, 1H), 1.94 – 1.82 (m, 2H), 1.49 – 1.40 (m, 1H), 1.32 – 1.20 (m, 5H), 1.11 – 1.01 (m, 1H), 0.91 – 0.82 (m, 6H).

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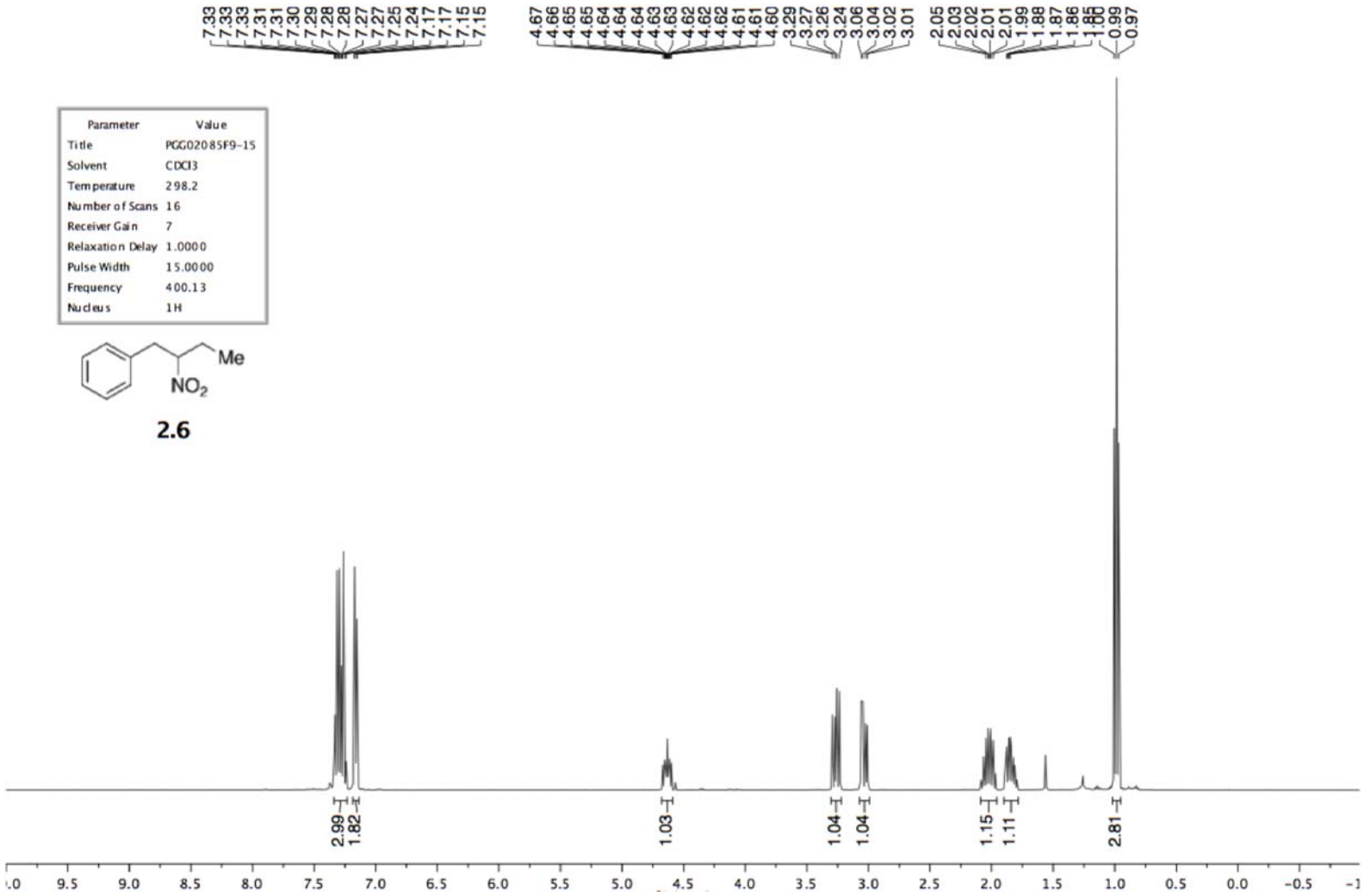
Appendix A

SPECTRAL DATA FOR CHAPTER 2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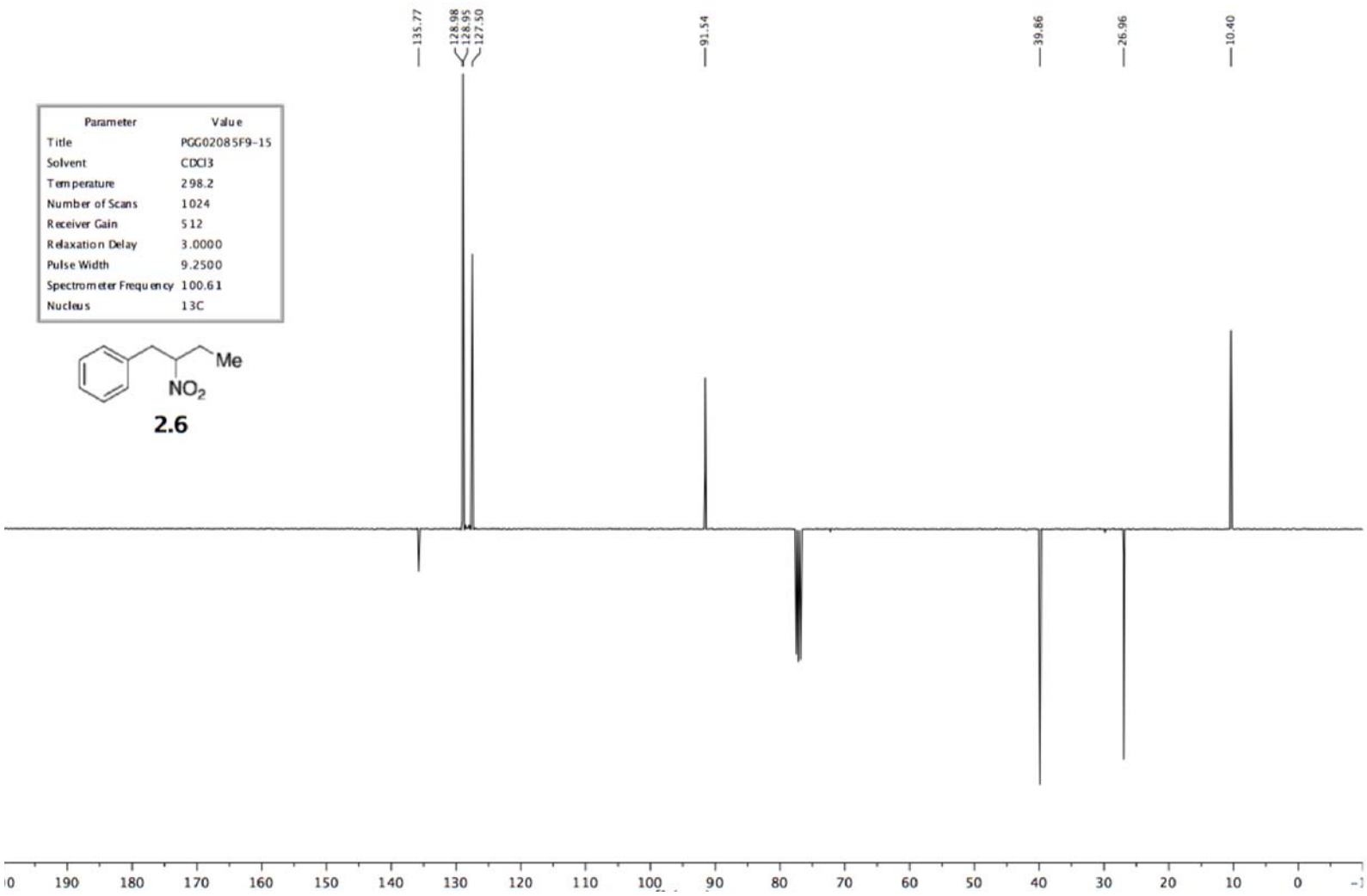
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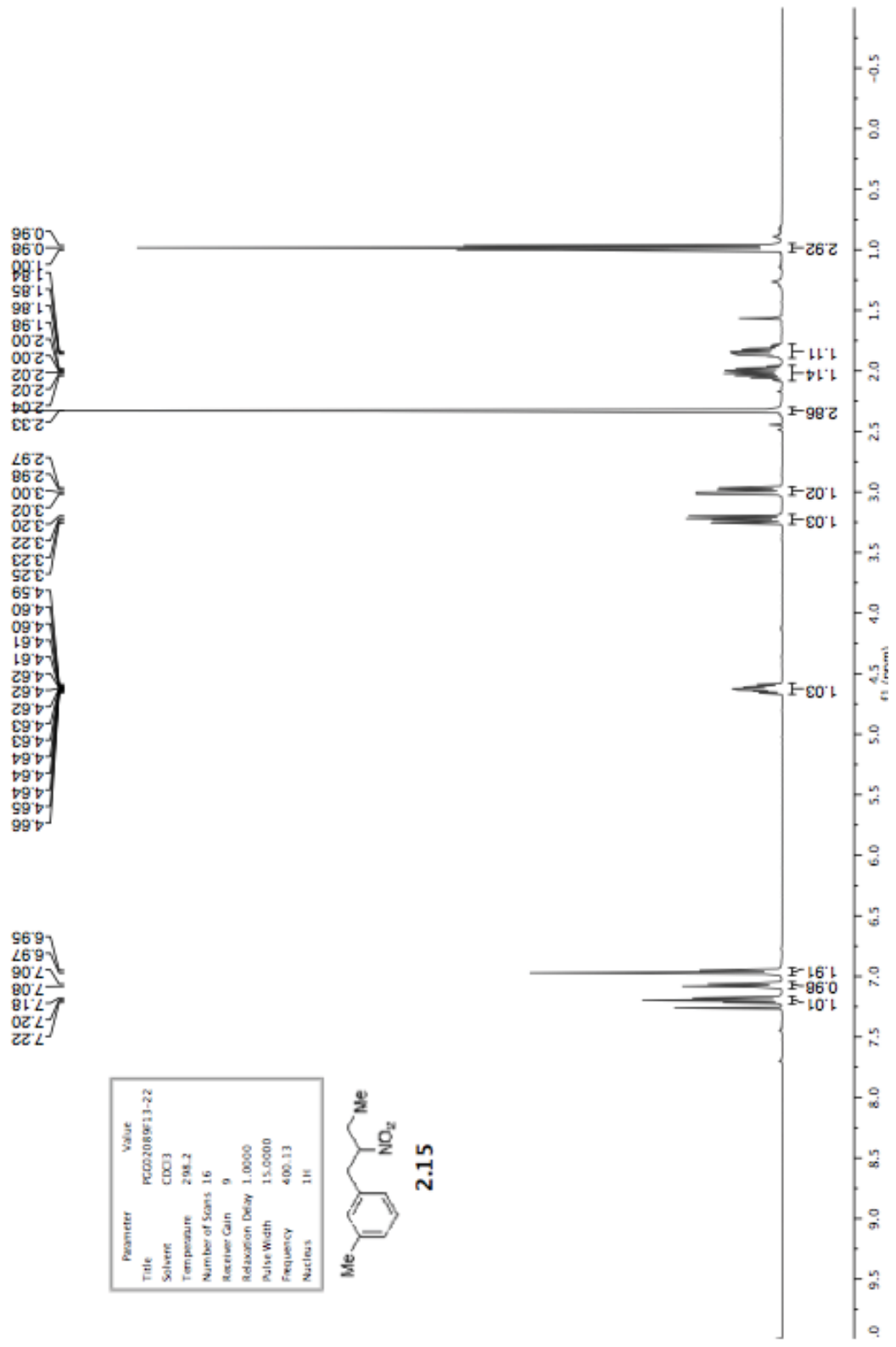
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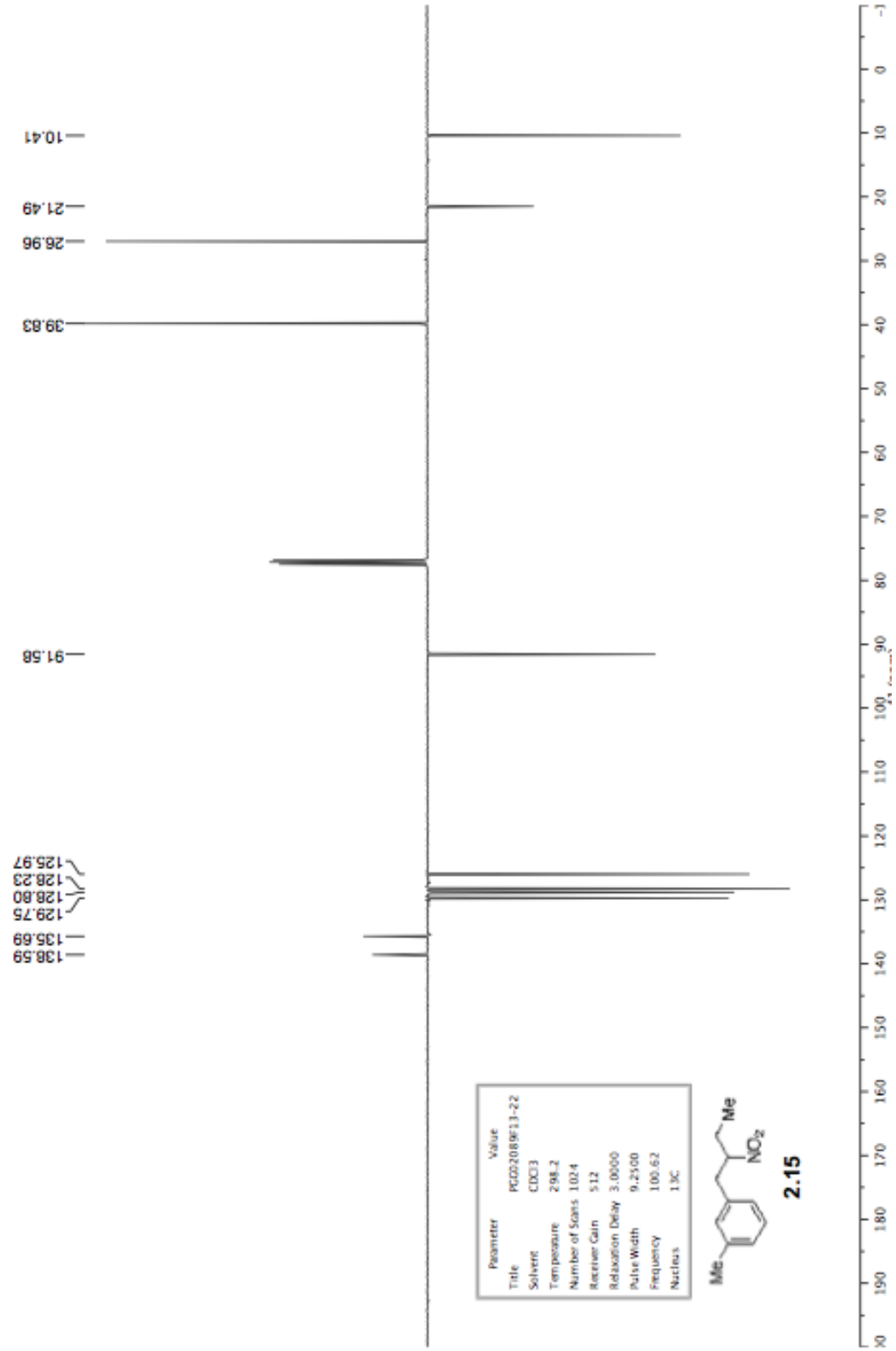
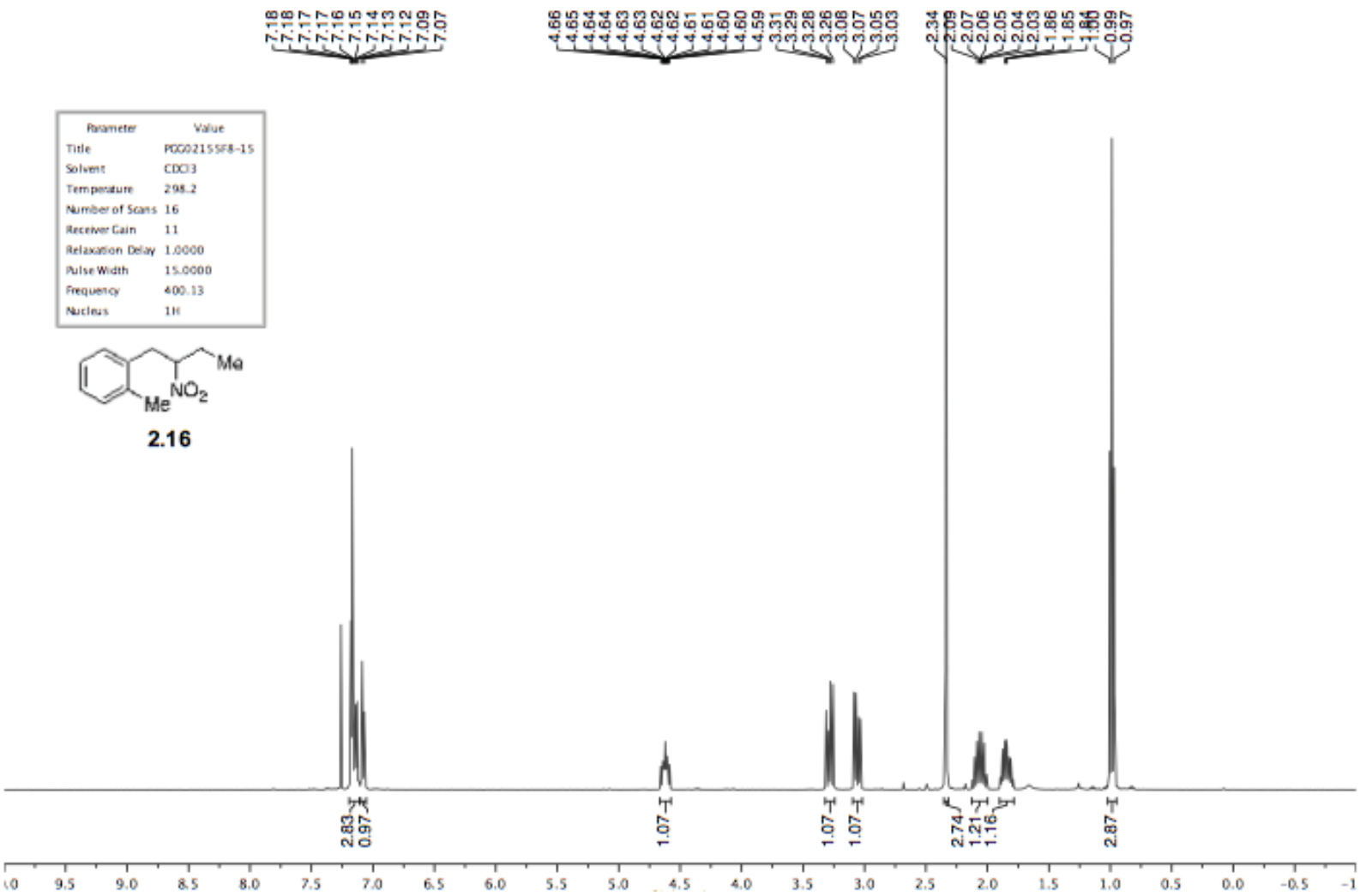
Me
2.15


10.41
21.49
26.96
39.83
91.58
125.97
128.23
128.80
129.75
135.69
138.59
Parameter Value
Title PGD20809E13-22
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
Me
2.15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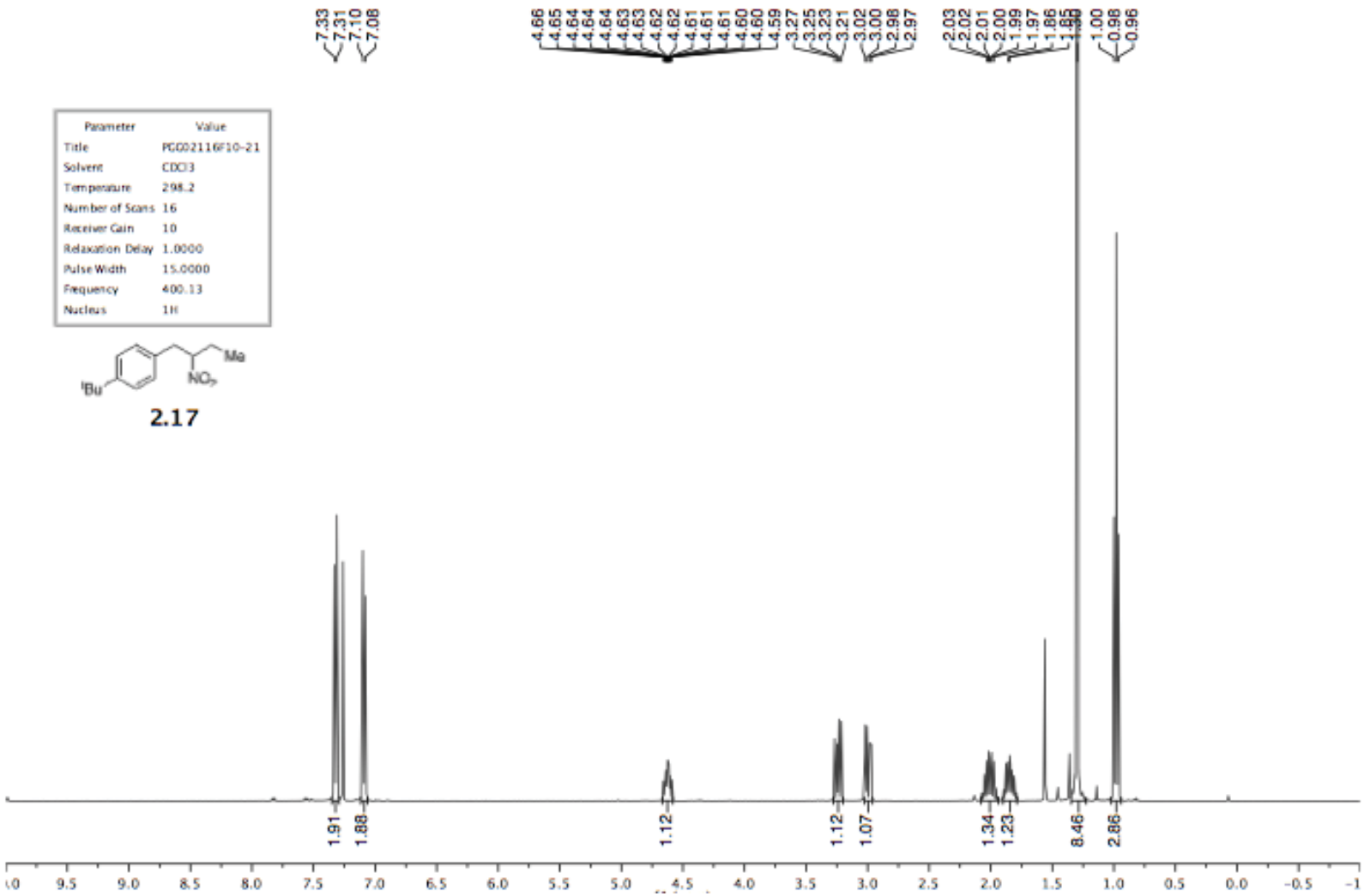
Title PGG02155F8-15
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 11
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
Me
2.16
7.18 7.18 7.17 7.17 7.16 7.15 7.14 7.13 7.12 7.09 7.07
4.66 4.65 4.64 4.64 4.63 4.63 4.62 4.62 4.61 4.61 4.60 4.60 4.59
3.31 3.29 3.28 3.26 3.08 3.07 3.05 3.03
2.34 2.09 2.07 2.06 2.05 2.04 2.03 1.86 1.85 0.99 0.97
2.83 0.97 1.07 1.07 1.07 2.74 1.21 1.16 2.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

10.51
19.52
27.05
37.32
90.42
126.50
127.65
129.75
130.85
134.02
136.28
Parameter Value
Title PD022155F8-15
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
Me
2.16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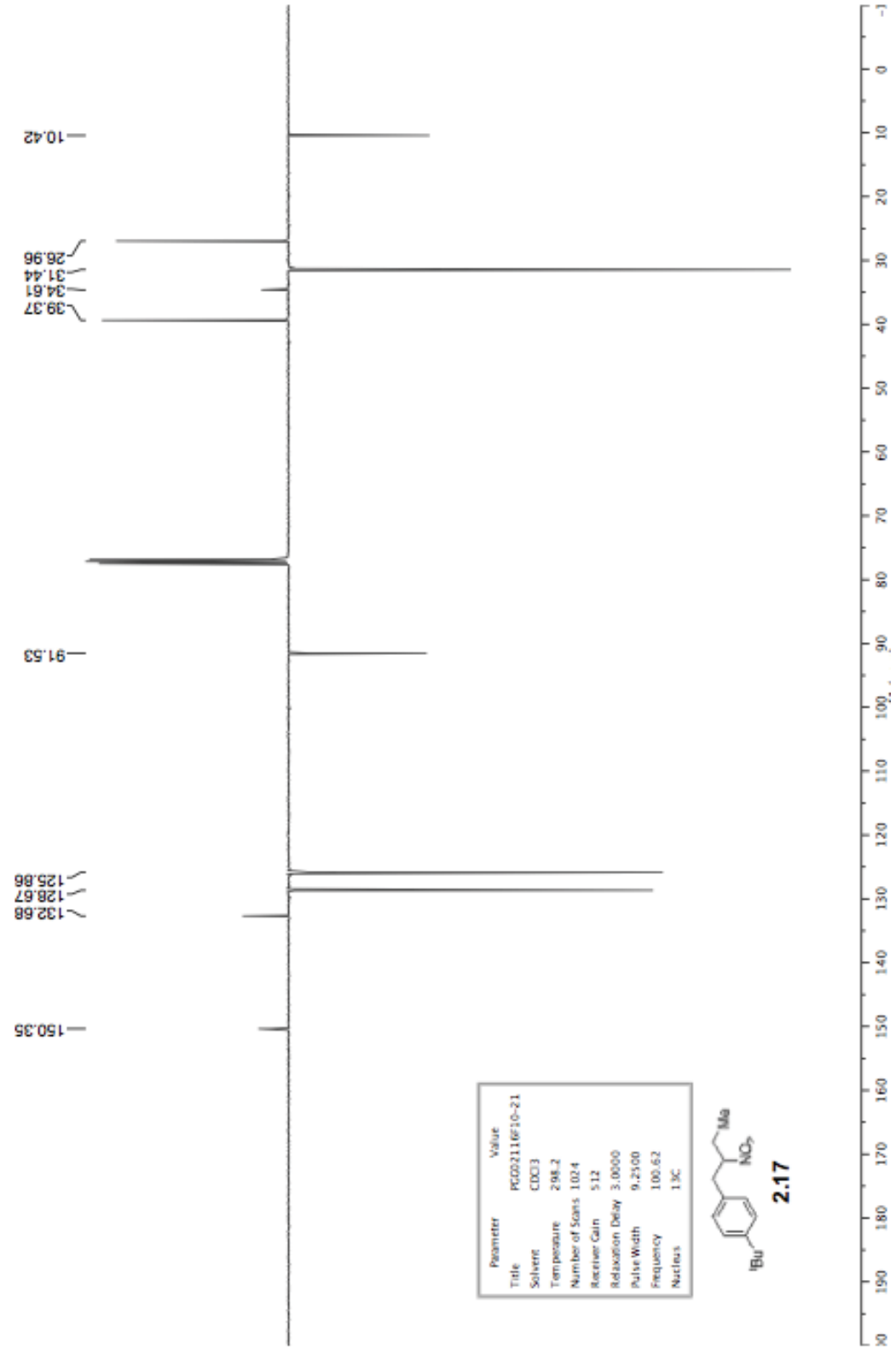
Title PGD02116F10-21
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 10
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
tBu
Me
NO2
2.17
7.33 7.31 7.10 7.08
4.66 4.65 4.64 4.64 4.64 4.63 4.63 4.62 4.62 4.61 4.61 4.61 4.60 4.60 4.59
3.27 3.25 3.23 3.21 3.02 3.00 2.98 2.97
2.03 2.02 2.01 2.00 1.99 1.97 1.86 1.85 1.00 0.98 0.96
1.91 1.88 1.12 1.12 1.07 1.34 1.23 8.46 2.86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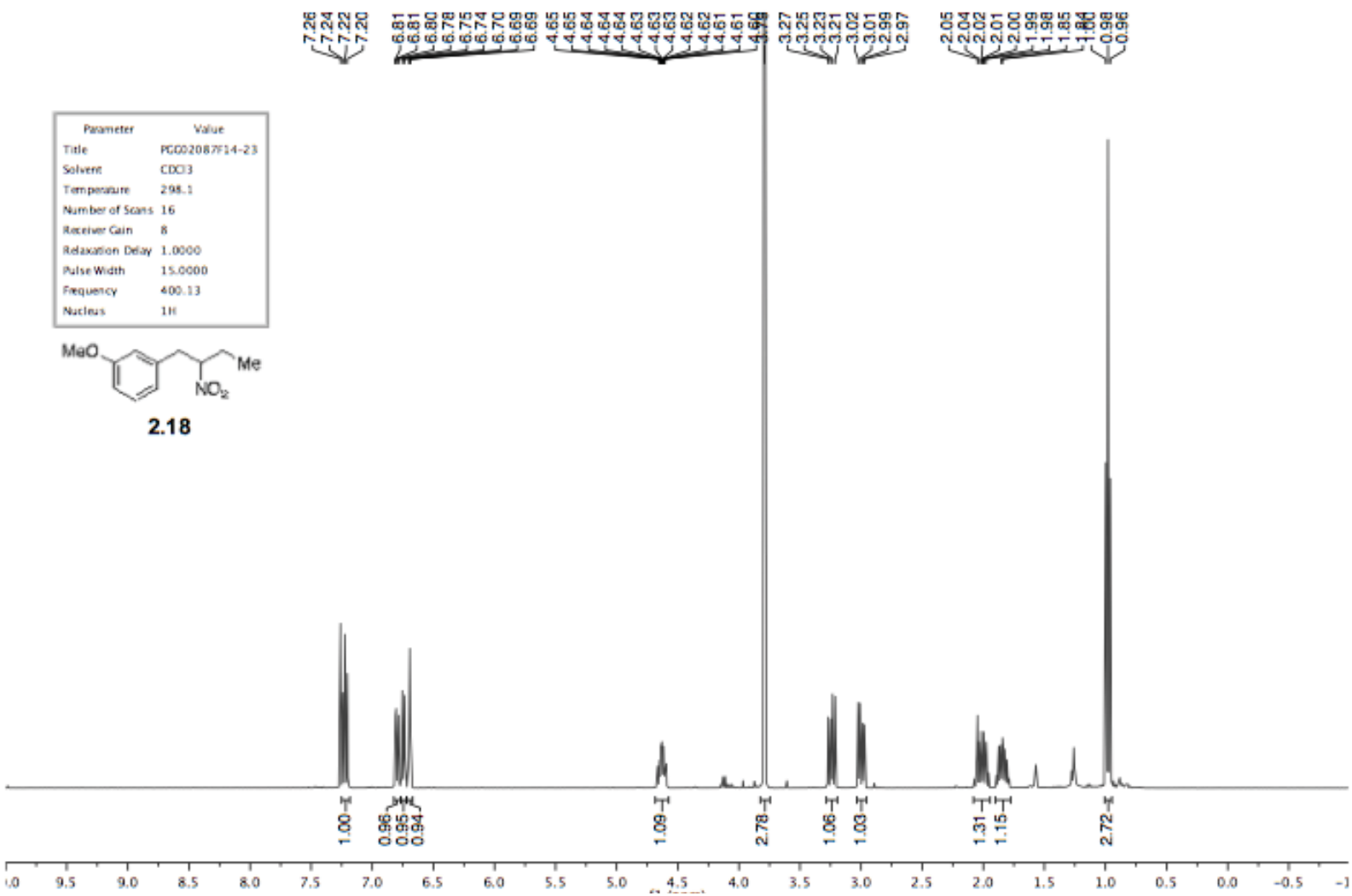
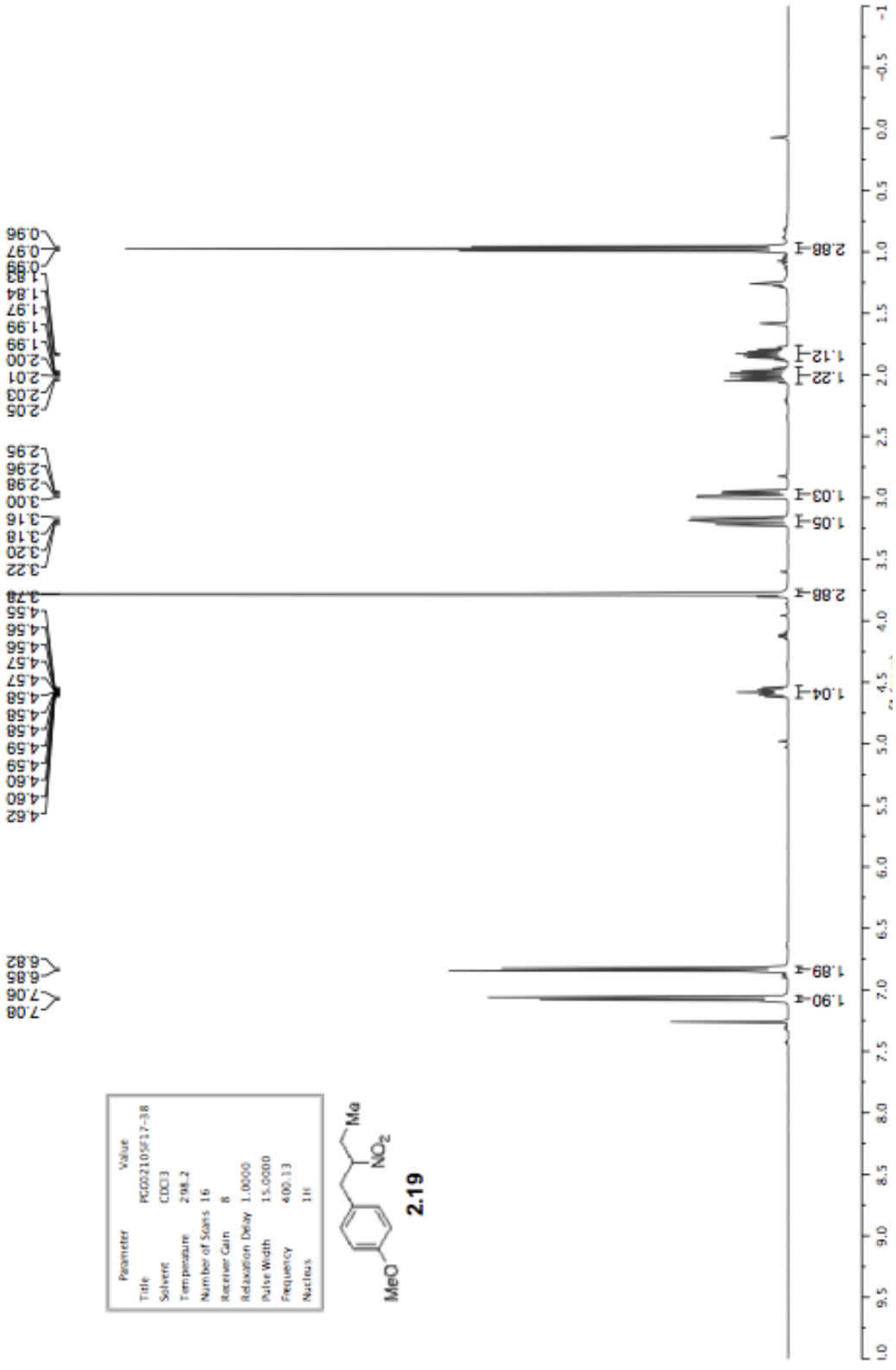
26.96
31.44
34.61
39.37
91.53
125.86
128.67
132.68
150.35
Parameter Value
Title PGD021116f10-21
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
tBu
2.17


Parameter Value
Title PGD02087F14-23
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
MeO
Me
NO2
2.18

10.40
26.98
39.87
55.32
91.42
112.71
114.81
121.24
129.97
137.28
159.93
Parameter Value
Title PGD20807514-23
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
MeO
Me
NO2
2.18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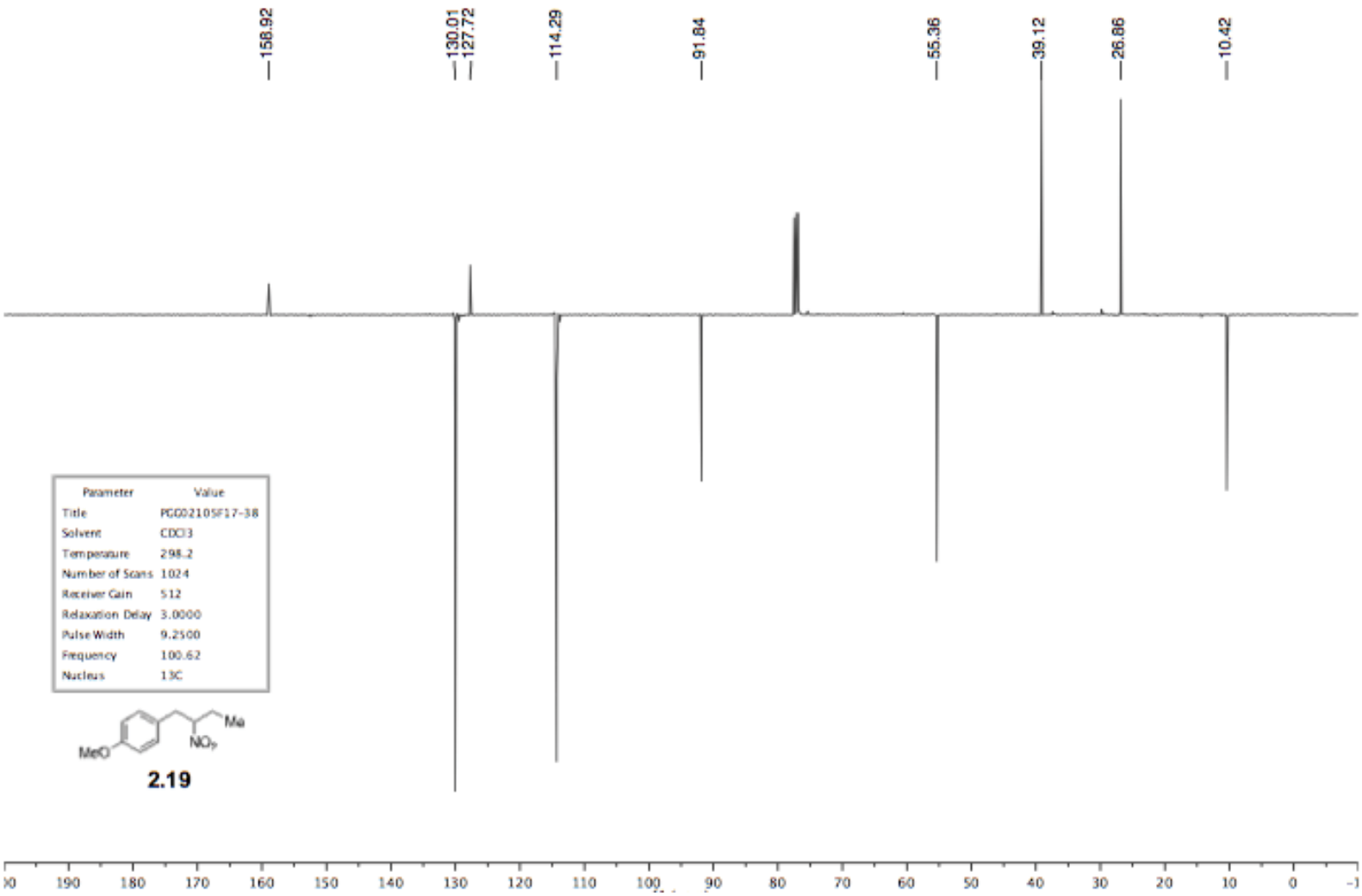
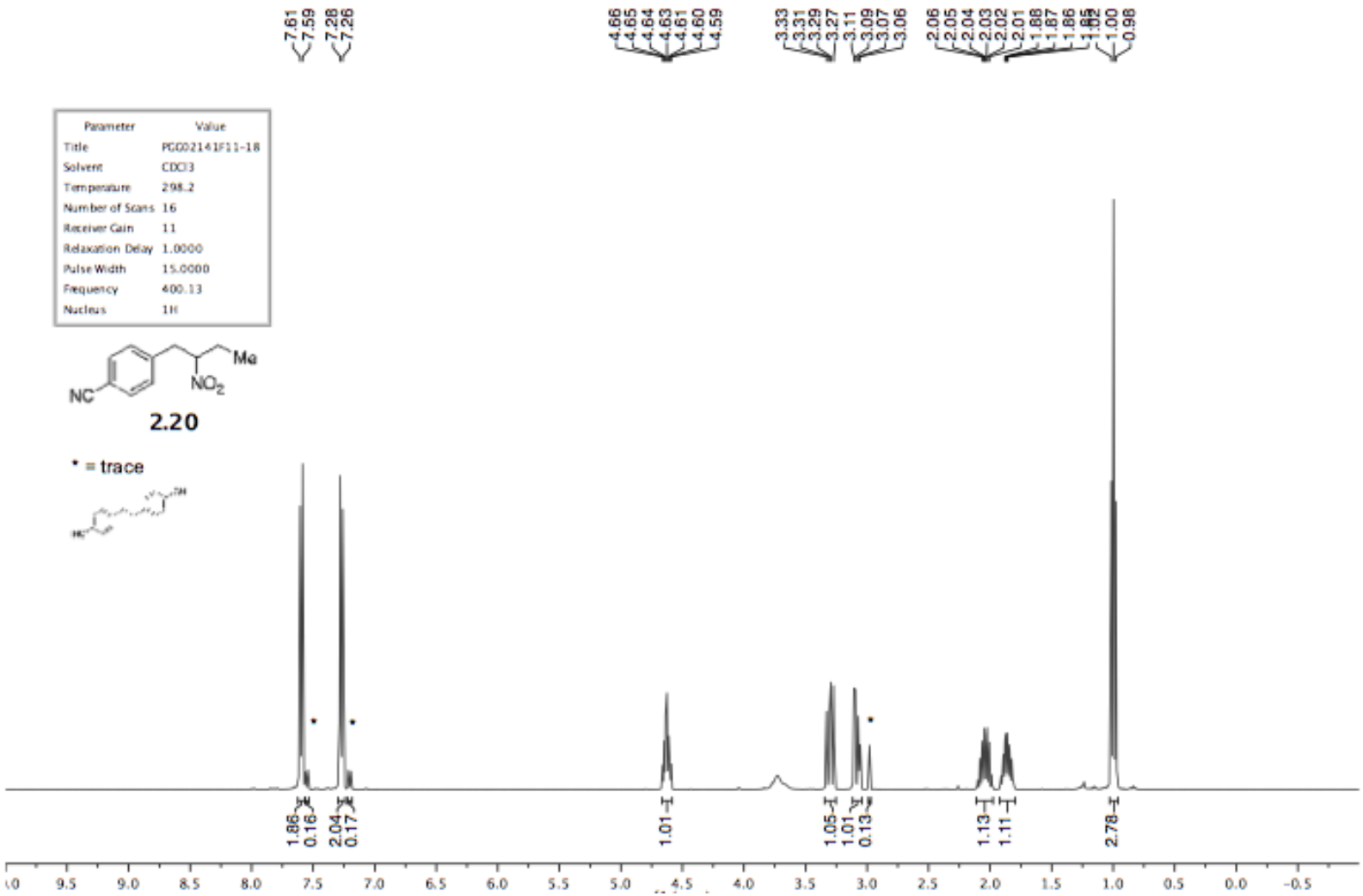
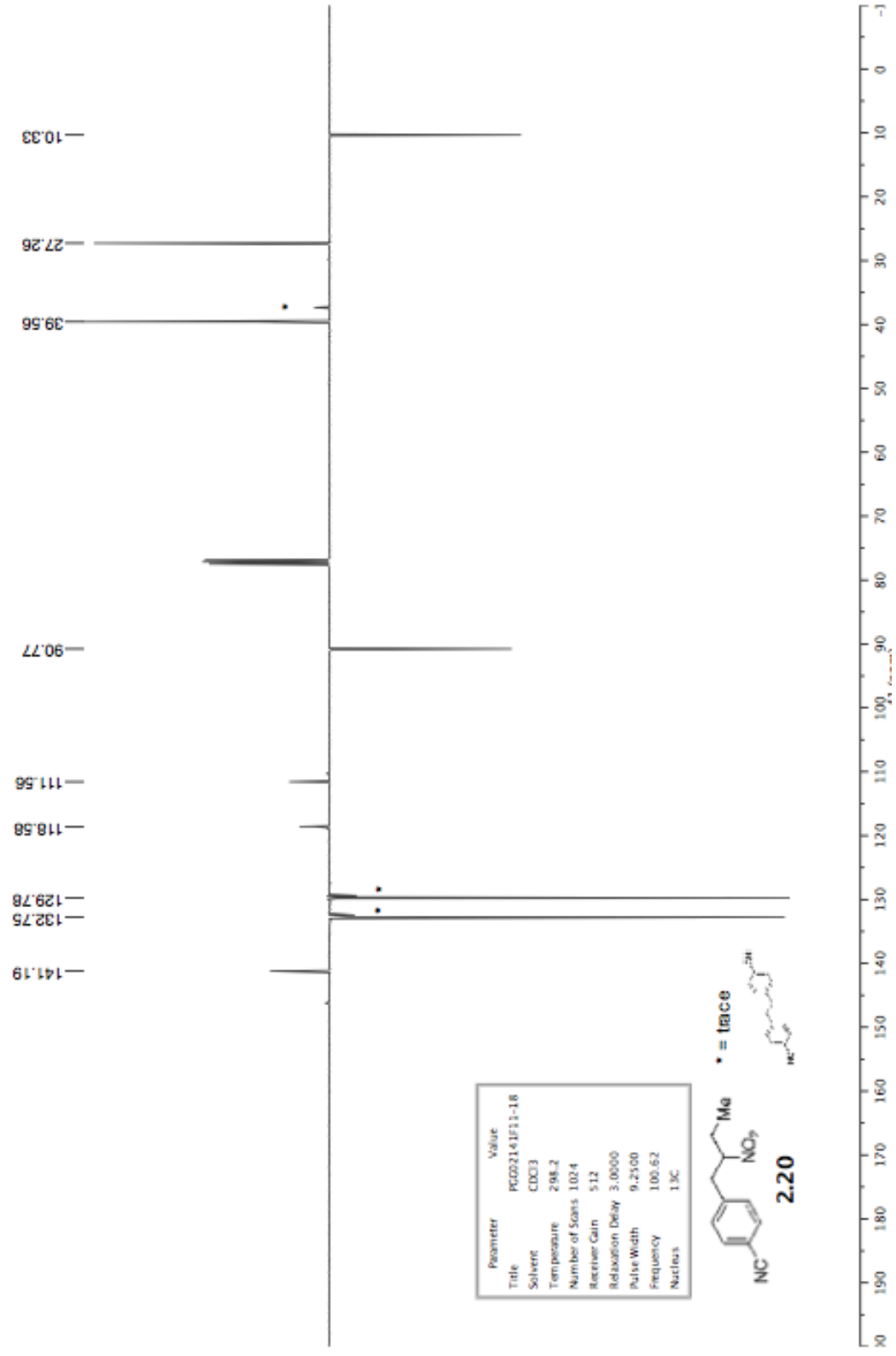
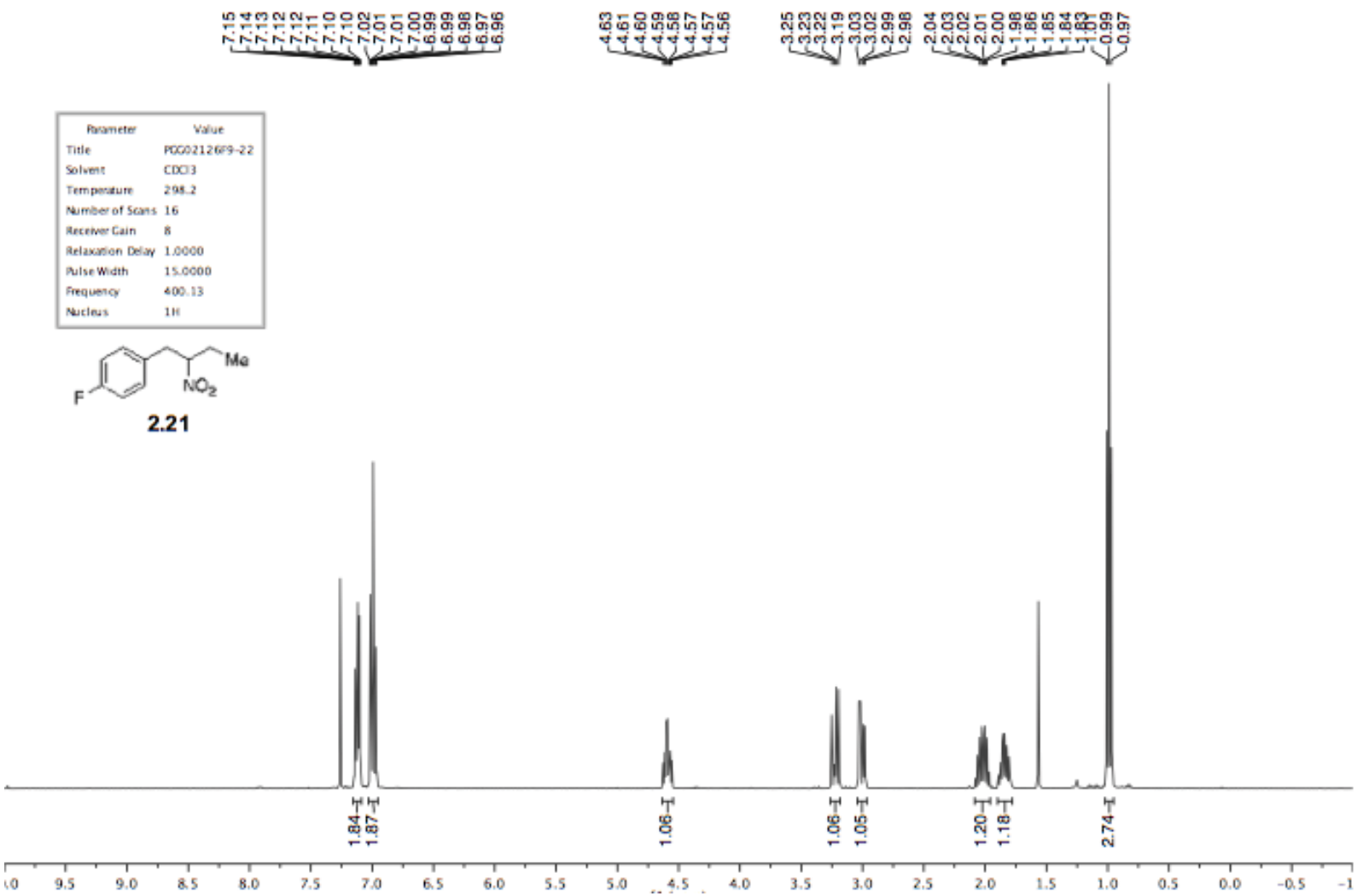
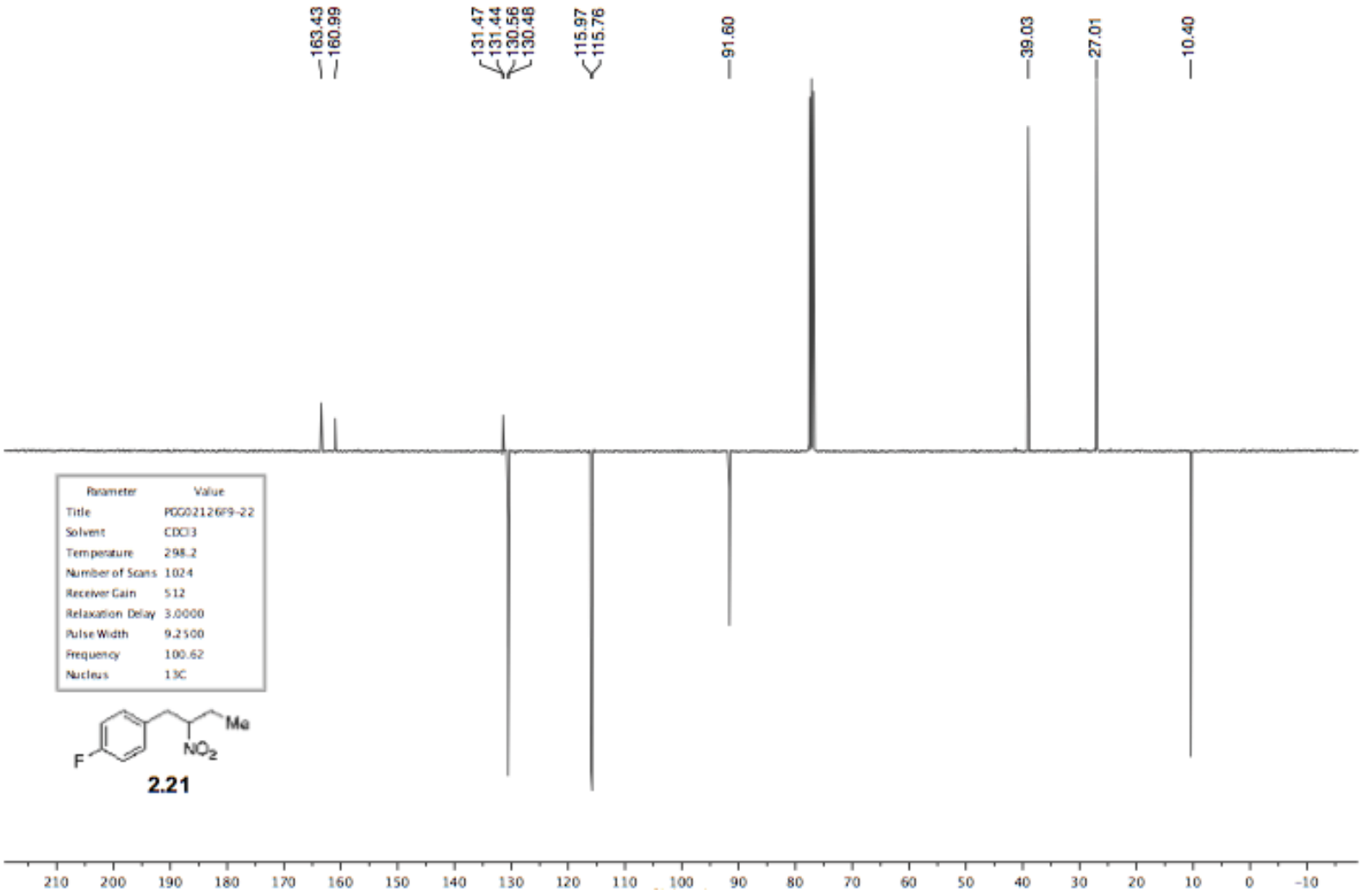
Title PGD221005F17-38
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
MeO
2.19

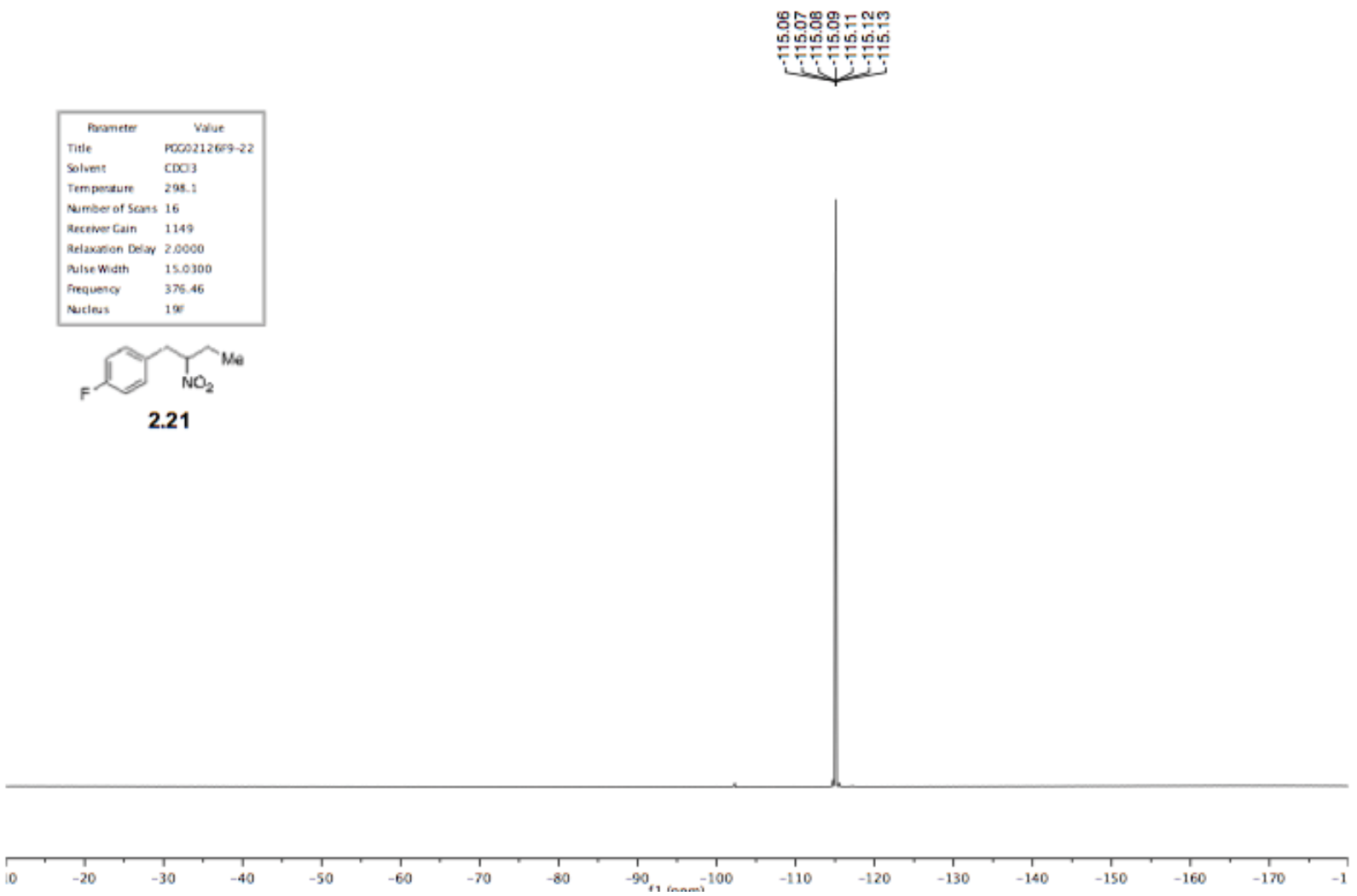

158.92
130.01
127.72
114.29
91.84
55.36
39.12
26.86
10.42
Parameter Value
Title PGD0210SF17-38
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
MeO
NO2
Me
2.19
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

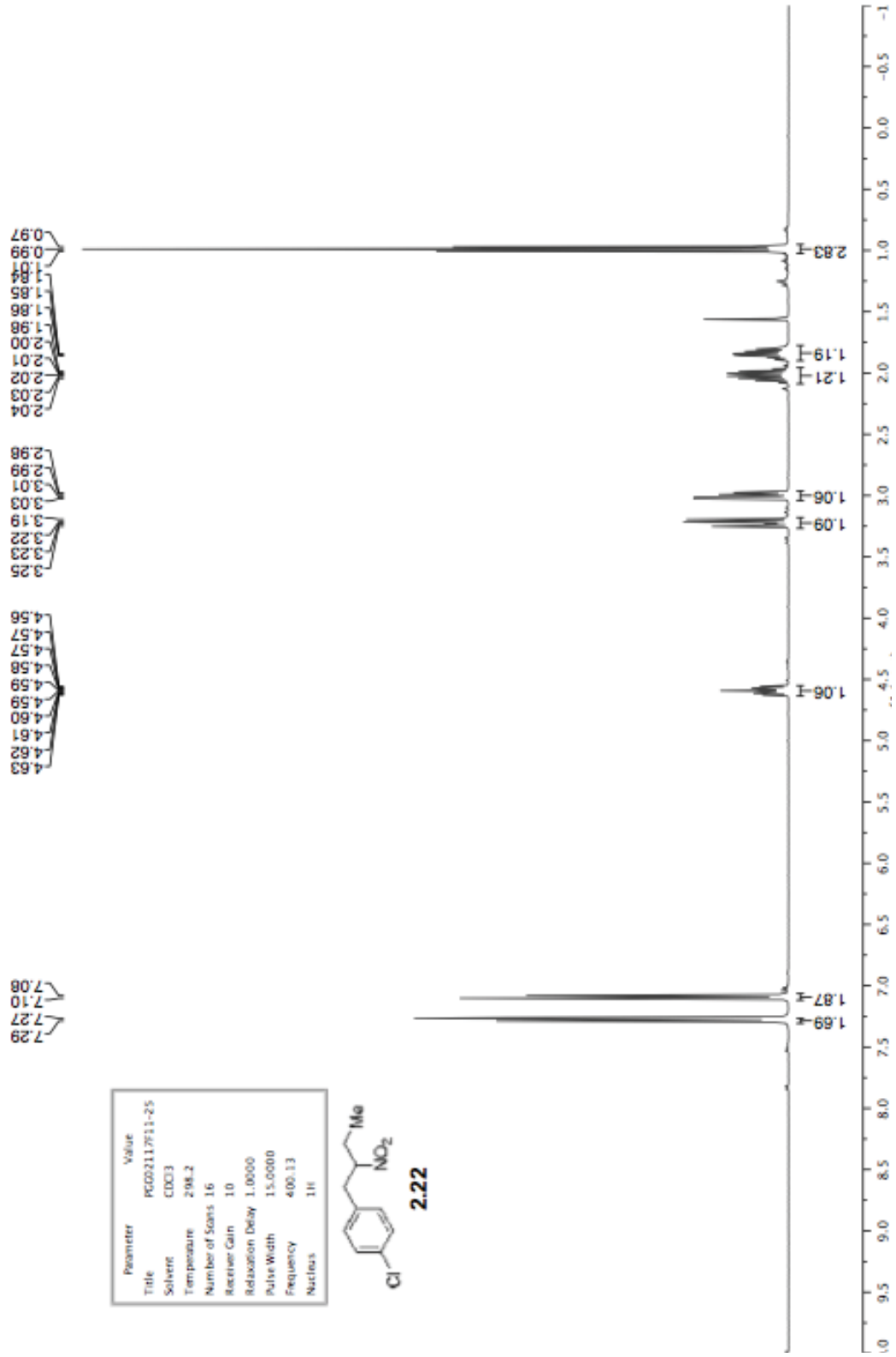

7.61
7.59
7.28
7.26
4.66
4.65
4.64
4.63
4.61
4.60
4.59
3.33
3.31
3.29
3.27
3.11
3.09
3.07
3.06
2.06
2.05
2.04
2.03
2.02
2.01
1.88
1.87
1.86
1.00
0.98
Parameter Value
Title PG002141F11-18
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 11
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NC
NO2
2.20
* = trace
1.86
0.16
2.04
0.17
1.01
1.05
1.01
0.13
1.13
1.11
2.78
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

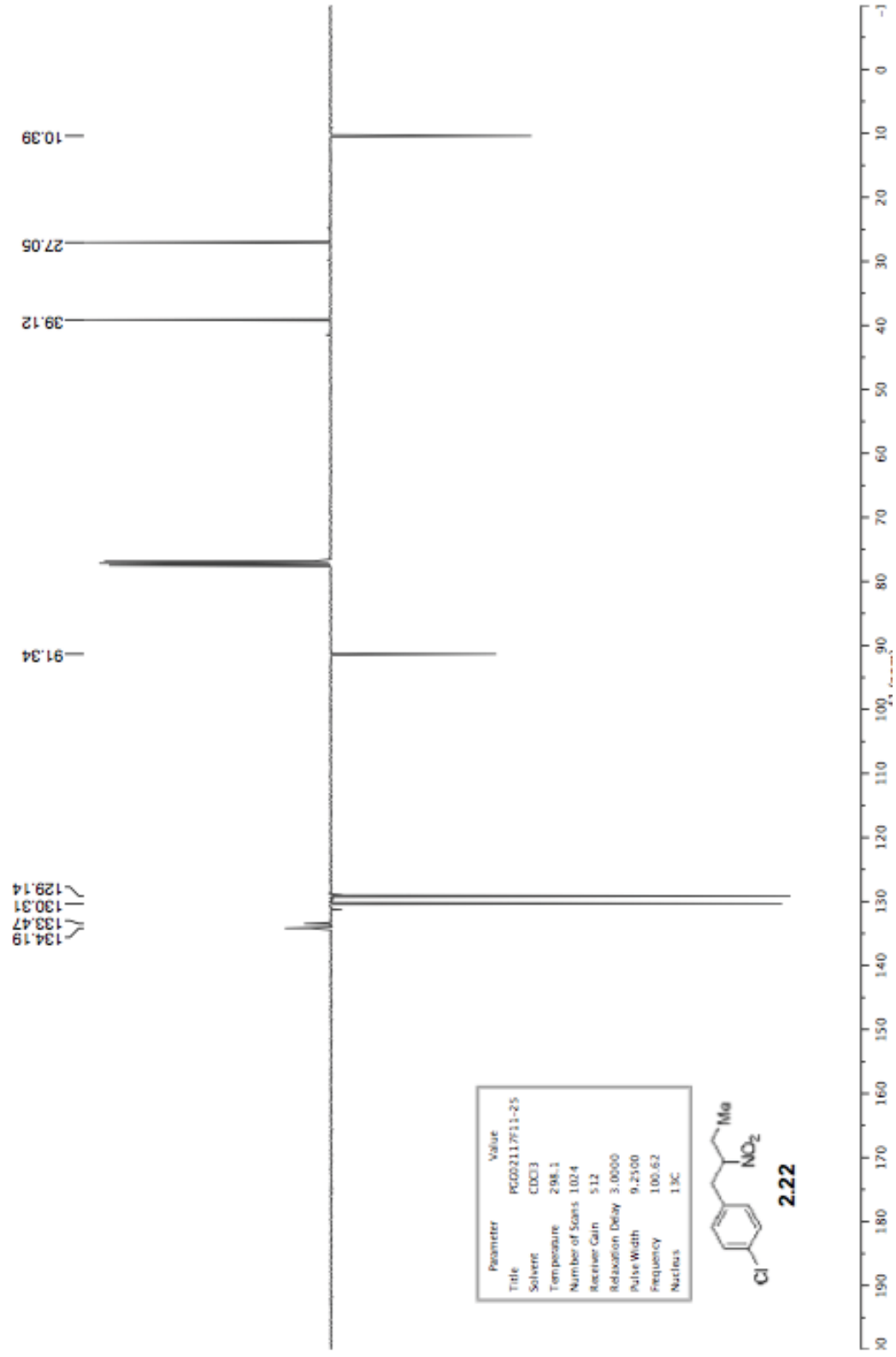

10.33
27.26
39.56
90.77
111.56
118.58
129.78
132.75
141.19
Parameter Value
Title PGD2141F11-1B
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
* = trace
Me
NO2
NC
2.20


7.15
7.14
7.13
7.12
7.12
7.11
7.10
7.10
7.02
7.01
7.01
7.00
6.99
6.99
6.98
6.97
6.96
4.63
4.61
4.60
4.59
4.58
4.57
4.57
4.56
3.25
3.23
3.22
3.19
3.03
3.02
2.99
2.98
2.04
2.03
2.02
2.01
2.00
1.98
1.86
1.85
1.84
1.83
1.01
0.99
0.97
Parameter Value
Title PGG02126F9-22
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
F
2.21
1.84
1.87
1.06
1.06
1.05
1.20
1.18
2.74
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1


163.43
160.99
131.47
131.44
130.56
130.48
115.97
115.76
91.60
39.03
27.01
10.40
Parameter Value
Title PDG02126F9-22
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
F
NO2
Me
2.21
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


-115.06
-115.07
-115.08
-115.09
-115.11
-115.12
-115.13
Parameter Value
Title PDG0212619-22
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 1149
Relaxation Delay 2.0000
Pulse Width 15.0300
Frequency 376.46
Nucleus 19F
Me
NO2
F
2.21
0 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -1
f1 (ppm)


Parameter Value
Title PGD021117F11-25
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 10
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
Cl
2.22
7.29
7.27
7.10
7.08
4.63
4.62
4.61
4.60
4.59
4.59
4.58
4.57
4.57
4.56
3.25
3.23
3.22
3.19
3.03
3.01
2.99
2.98
2.04
2.03
2.02
2.01
2.00
1.98
1.86
1.85
1.84
1.01
0.99
0.97
1.87
1.69
1.06
1.09
1.06
1.21
1.19
2.83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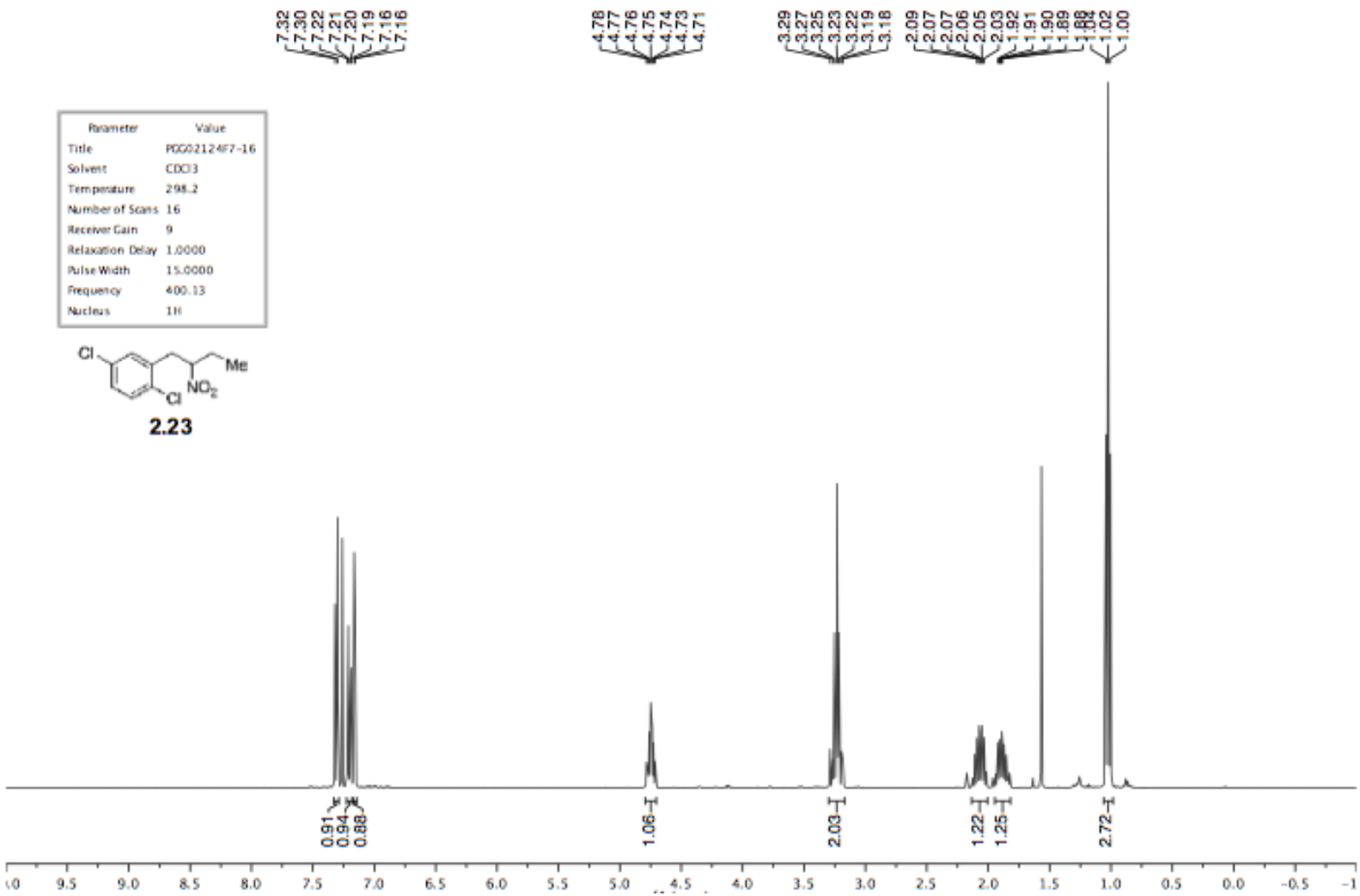
27.05
39.12
91.34
129.14
130.31
133.47
134.19
Parameter Value
Title PEG0211?911-25
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
Cl
2.22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7.30
7.22
7.21
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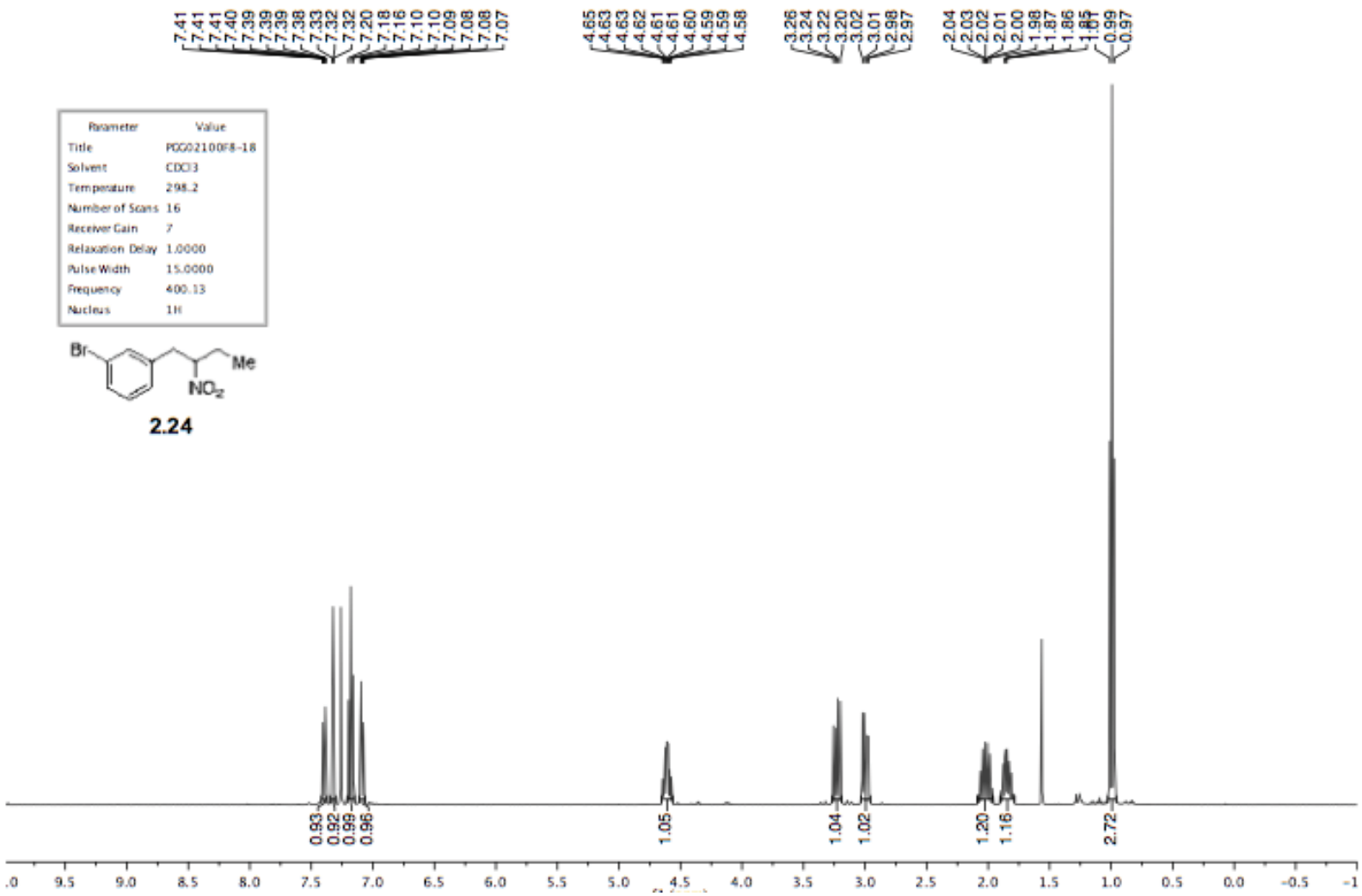
7.19
7.16
7.16
4.78
4.77
4.76
4.75
4.74
4.73
4.71
3.29
3.27
3.25
3.23
3.22
3.19
3.18
2.09
2.07
2.07
2.06
2.05
2.03
1.92
1.91
1.90
1.89
1.02
1.00
Parameter Value
Title PDG0212417-16
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 9
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Cl
Me
NO2
Cl
2.23
0.91
0.94
0.88
1.06
2.03
1.22
1.25
2.72

10.35
27.41
37.32
89.13
129.27
130.98
131.29
132.41
133.12
135.26
Parameter Value
Title PDD2212467-16
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
Cl
Cl
2.23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7.41
7.41
7.40
7.39
7.39
7.39
7.38
7.33
7.32
7.32
7.20
7.18
7.16
7.10
7.09
7.08
7.08
7.07
4.65
4.63
4.63
4.62
4.61
4.61
4.60
4.59
4.59
4.58
3.26
3.24
3.22
3.20
3.02
3.01
2.98
2.97
2.04
2.03
2.02
2.01
2.00
1.98
1.87
1.86
1.85
1.01
0.99
0.97
Parameter Value
Title PDG02100F8-18
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 7
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Br
Me
NO2
2.24
0.93
0.92
0.99
0.96
1.05
1.04
1.02
1.20
1.16
2.72
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

10.37
27.07
39.26
91.13
122.92
127.62
130.51
130.72
132.02
138.00
Parameter Value
Title PDZ0210DF8-1B
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Br
Me
NO2
2.24

Parameter Value
Title PGD021118f12-26
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
Br
2.25
7.44
7.42
7.04
7.02
4.63
4.61
4.61
4.60
4.59
4.58
4.57
4.57
4.56
3.24
3.22
3.20
3.18
3.01
3.00
2.97
2.96
2.04
2.03
2.02
2.01
2.00
1.98
1.86
1.85
1.84
1.01
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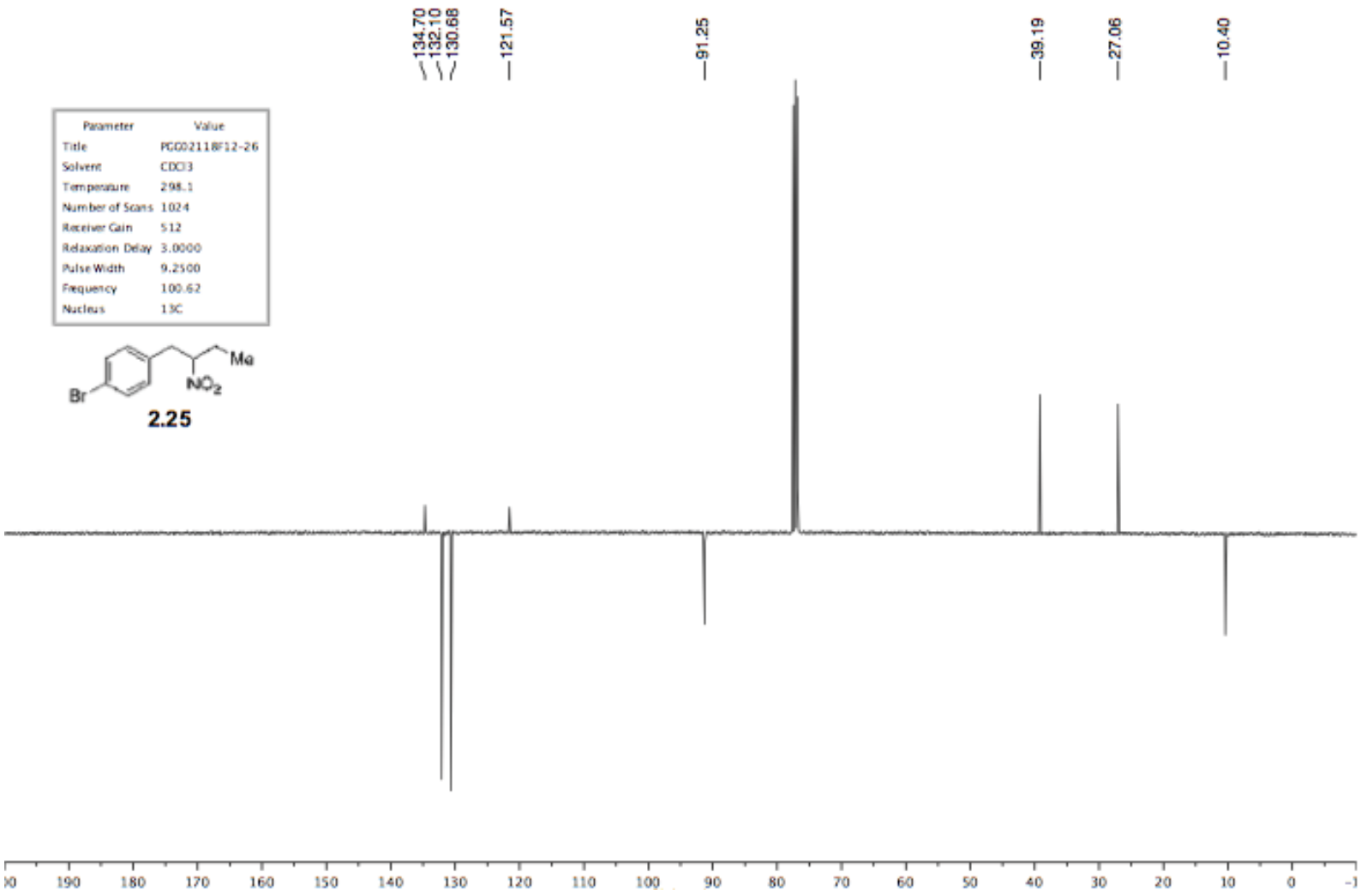
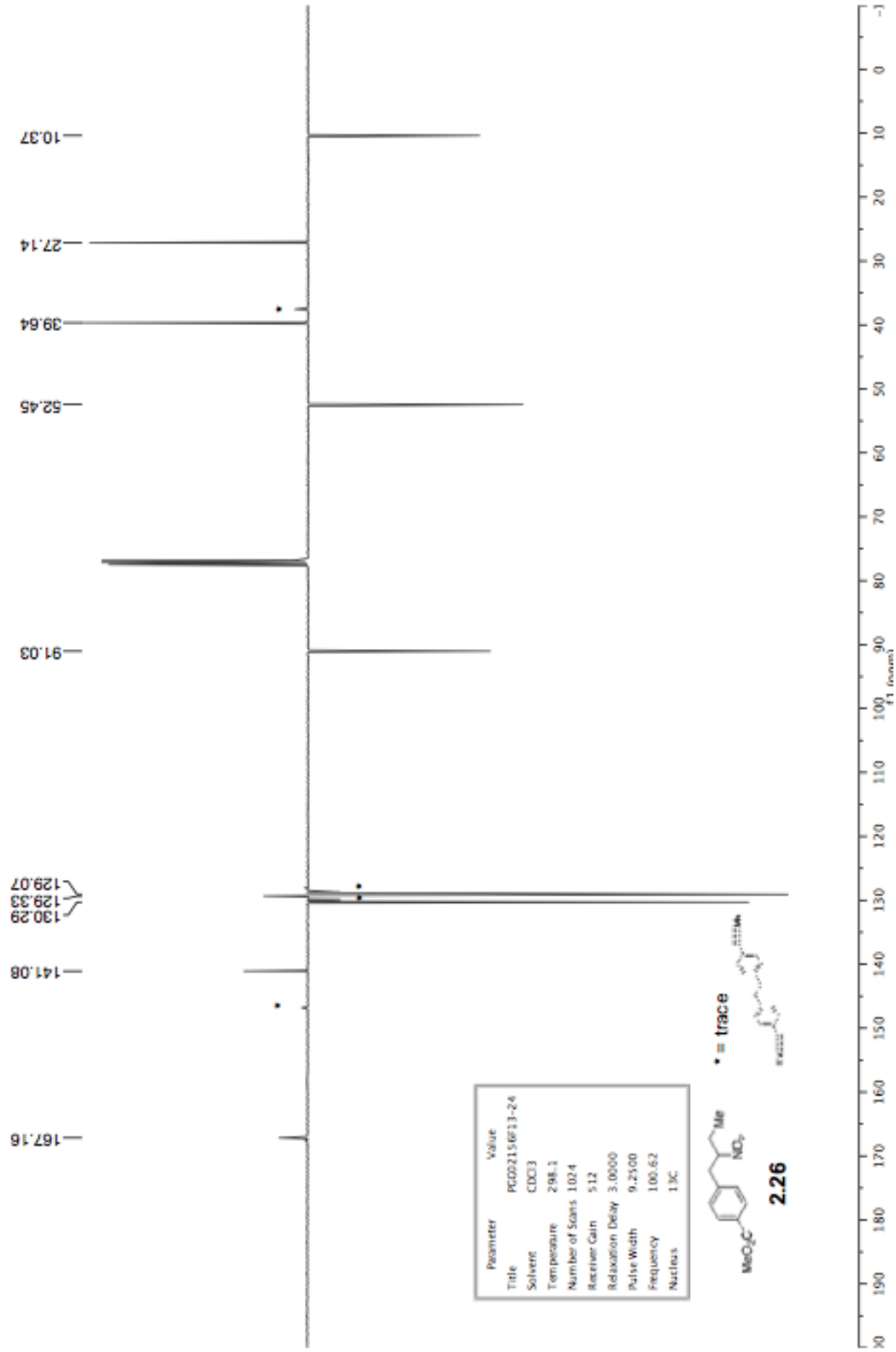
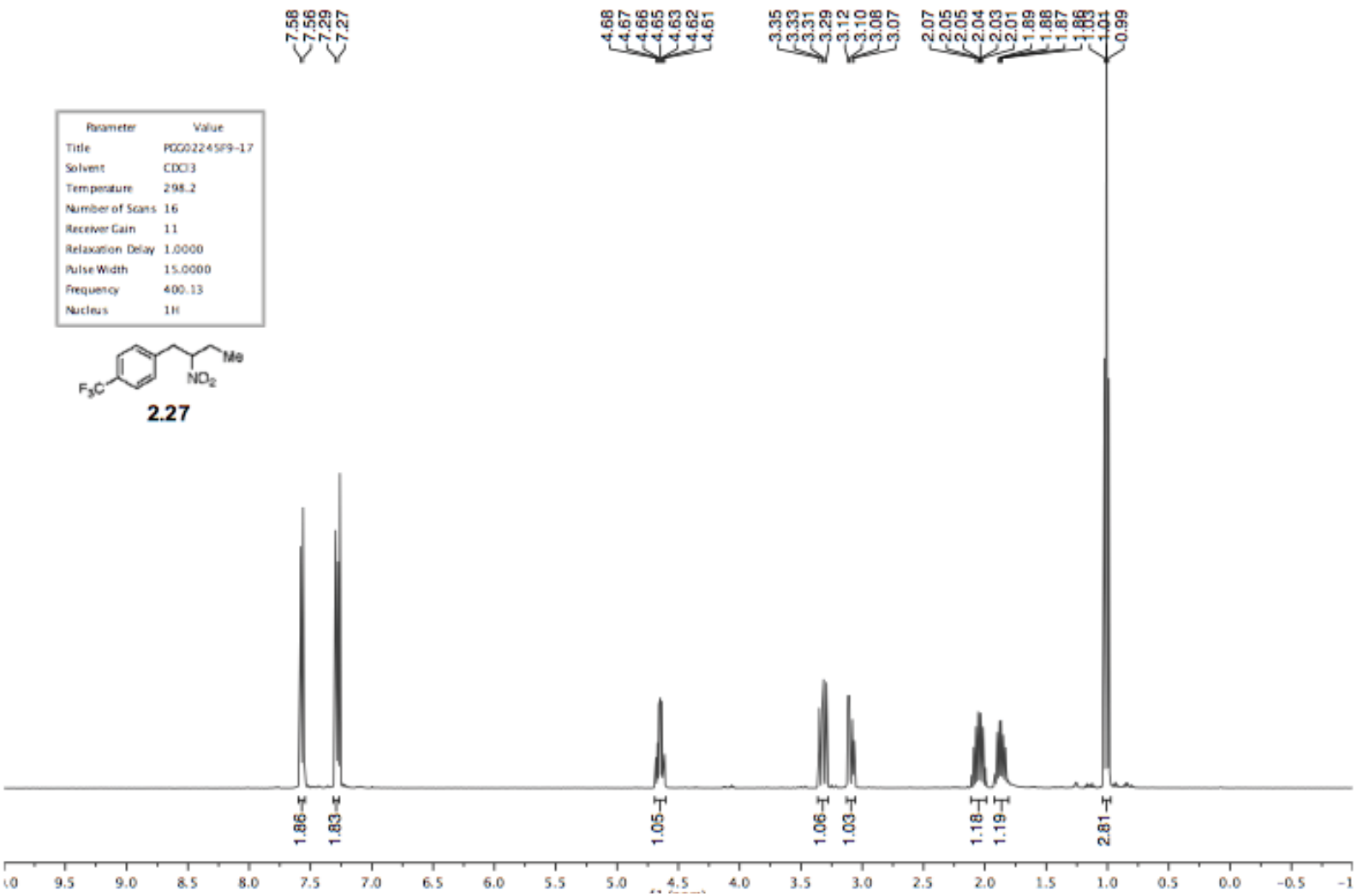
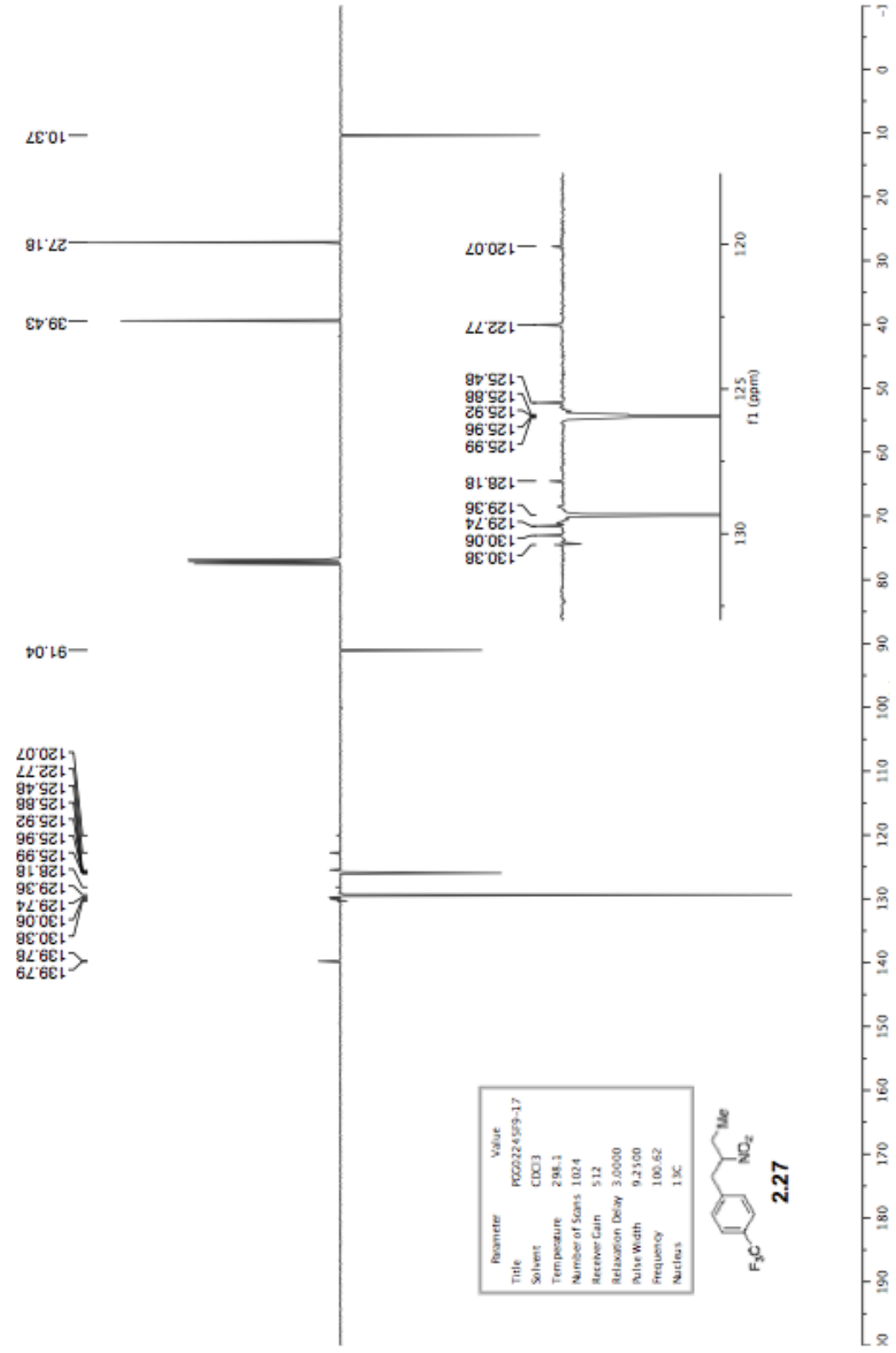
0.97
1.60
1.58
1.21
1.16
1.15
1.55
1.43
2.31


134.70
132.10
130.68
121.57
91.25
39.19
27.06
10.40
Parameter Value
Title PGD02118F12-26
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
Br
2.25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

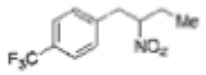
Parameter Value
Title PGD0215613-24
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 11
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
2.26
* = trace


10.37
27.14
39.64
52.45
91.03
129.07
129.33
130.29
141.08
167.16
Parameter Value
Title PGO215F13-24
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
• = trace
2.26
f1 (ppm)


Parameter Value
Title PDG0224SP9-17
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 11
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
F3C
2.27
7.58
7.56
7.29
7.27
4.68
4.67
4.66
4.65
4.63
4.62
4.61
3.35
3.33
3.31
3.29
3.12
3.10
3.08
3.07
2.07
2.05
2.05
2.04
2.03
2.01
1.89
1.88
1.87
1.04
0.99
1.86
1.83
1.05
1.06
1.03
1.18
1.19
2.81

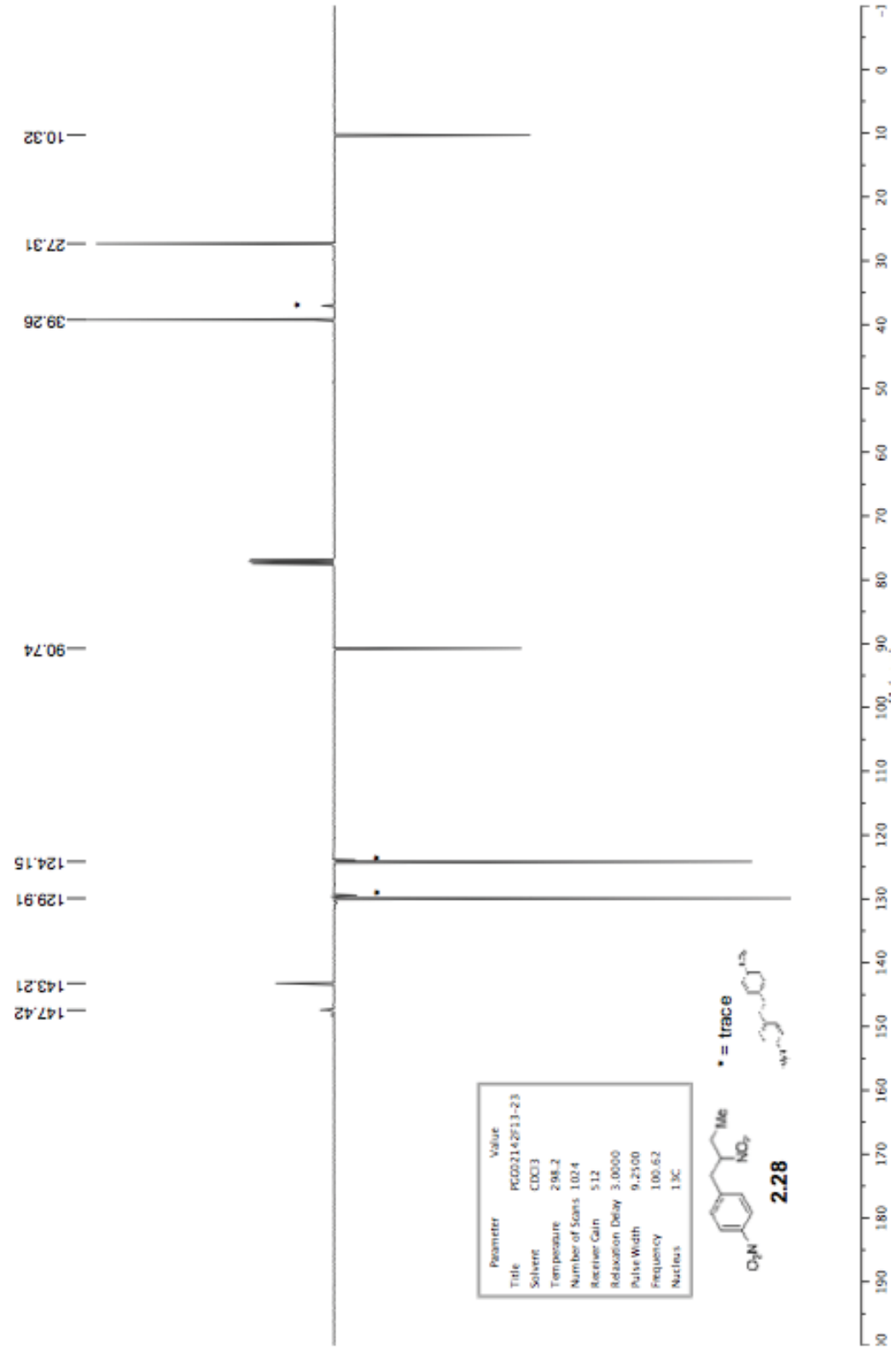

10.37
27.18
39.43
91.04
120.07
122.77
125.48
125.88
125.92
125.96
125.99
128.18
129.36
129.74
130.06
130.38
139.78
139.79
Parameter Value
Title PD20224509-17
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
ND2
F3C
2.27
f1 (ppm)

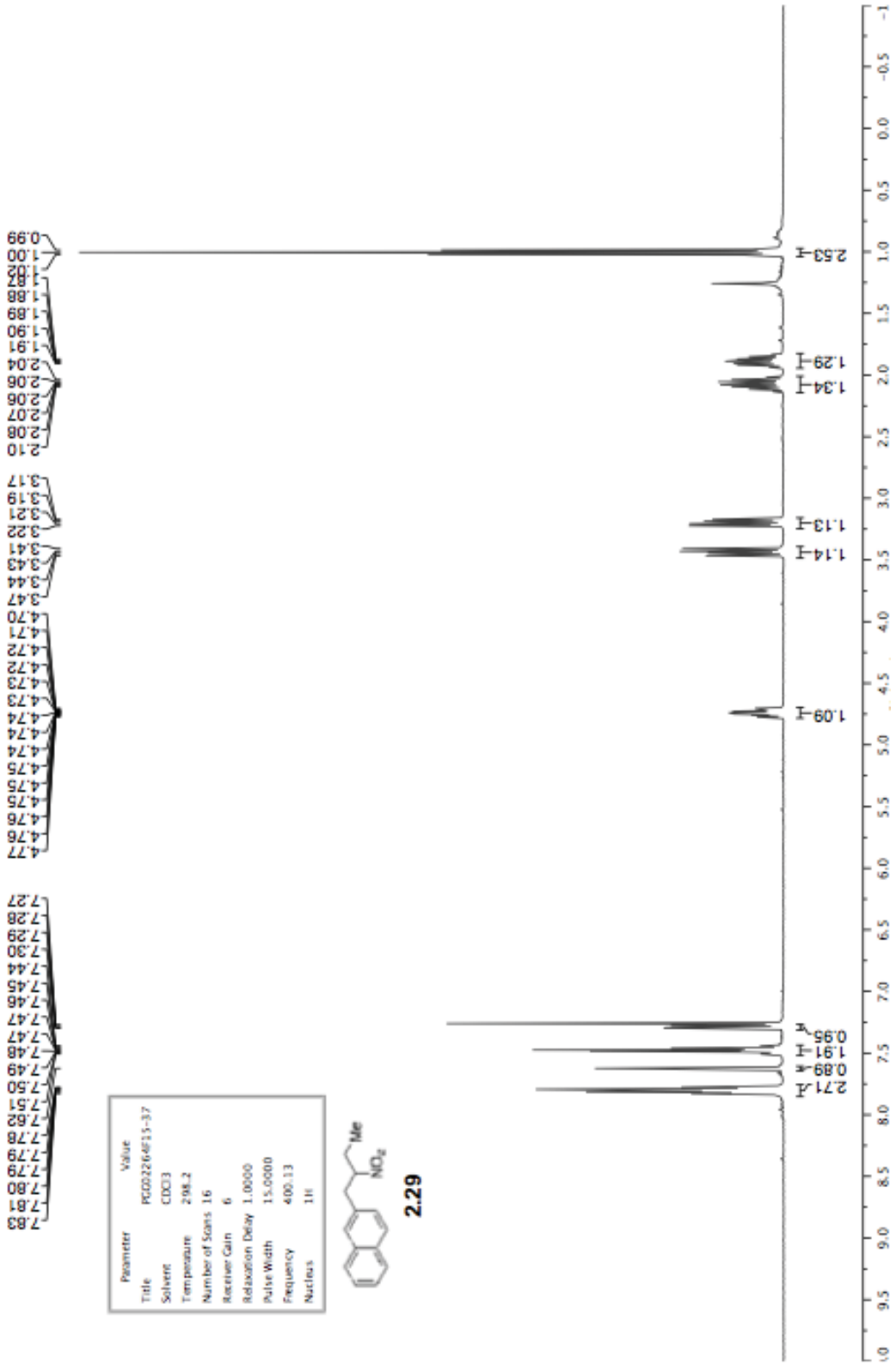
Parameter	Value
Title	PGG0224SF9-17
Solvent	CDCl3
Temperature	298.2
Number of Scans	16
Receiver Gain	645
Relaxation Delay	2.0000
Pulse Width	15.0300
Frequency	376.46
Nucleus	19F

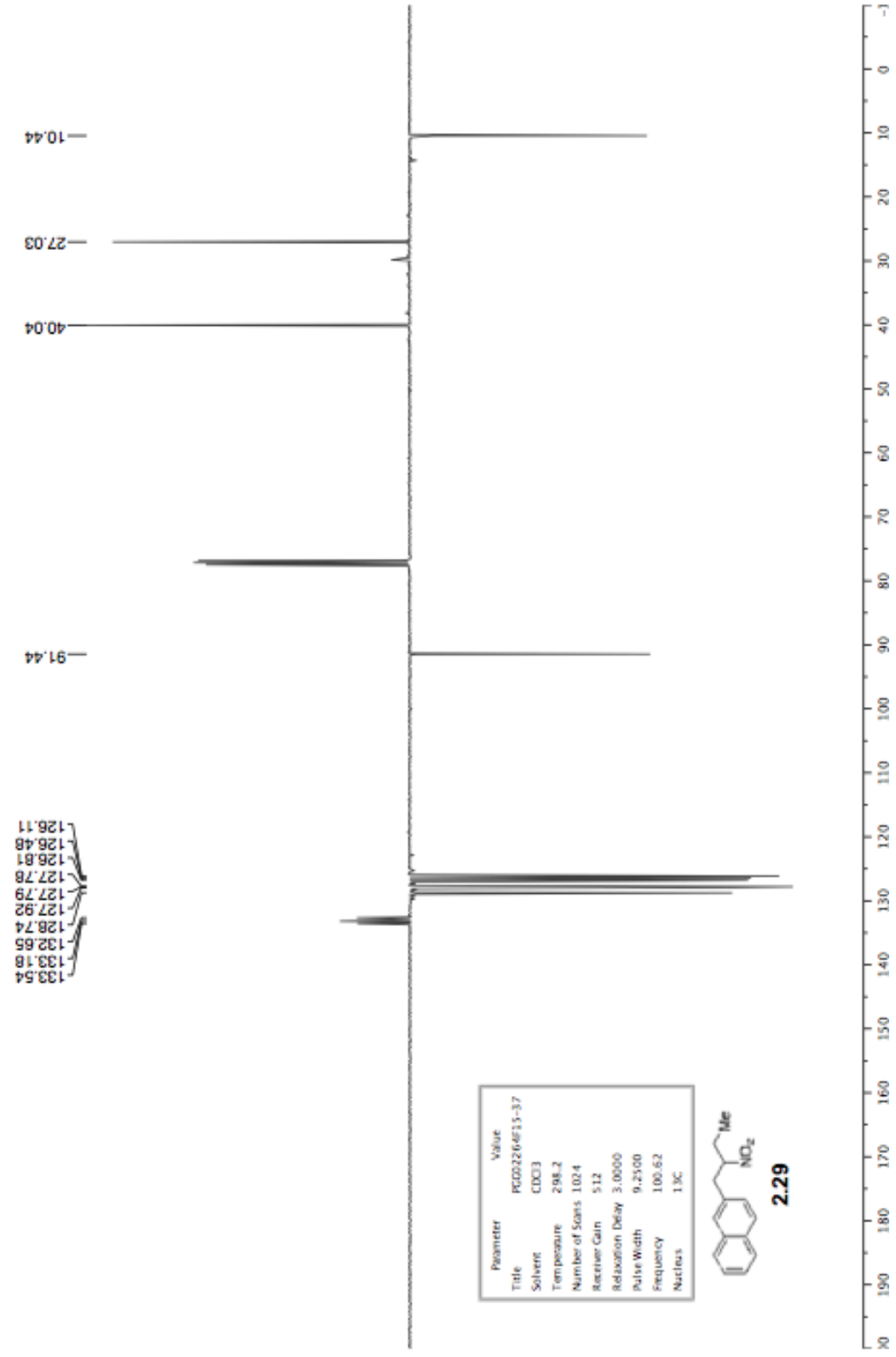


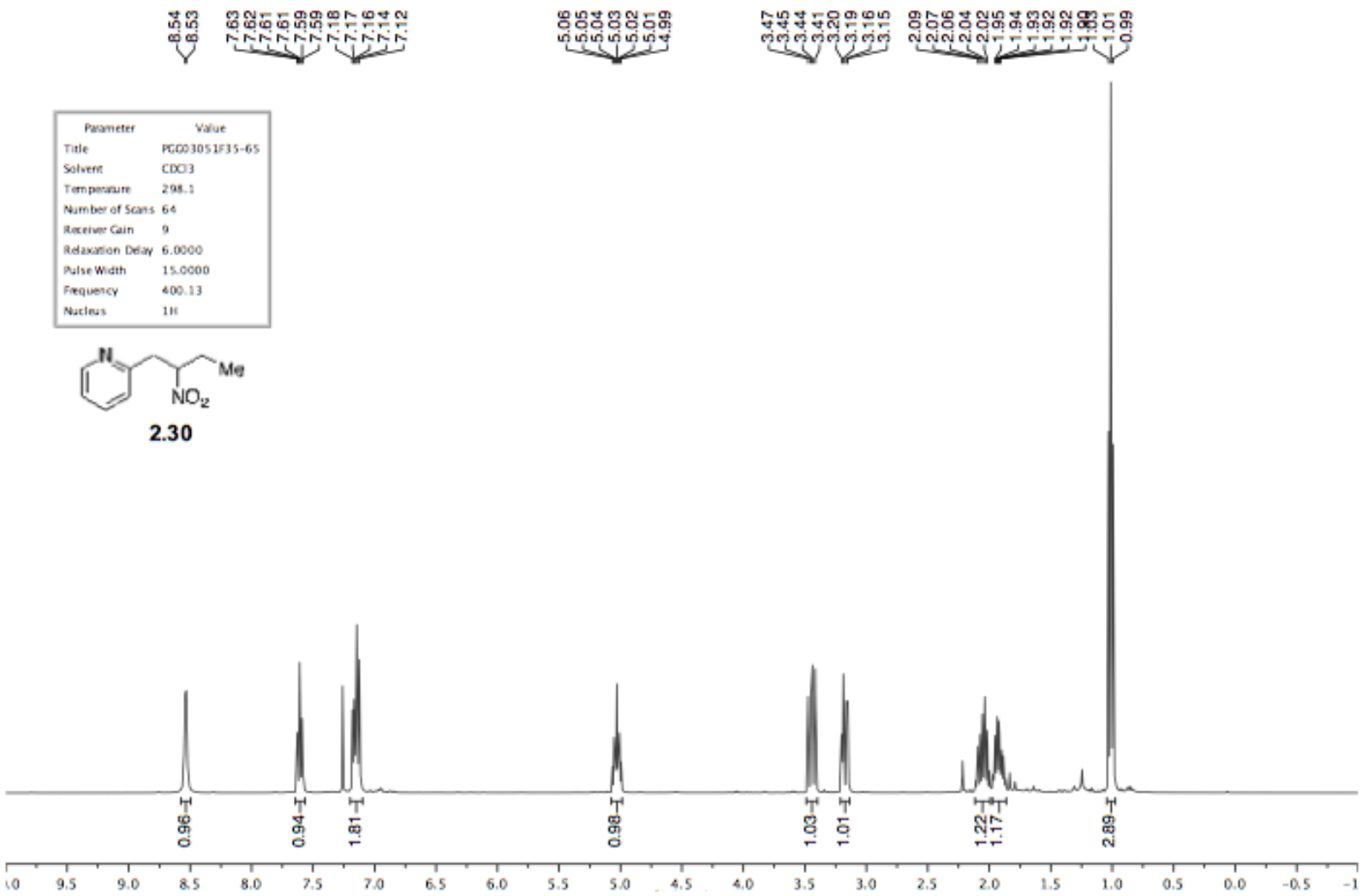
2.27

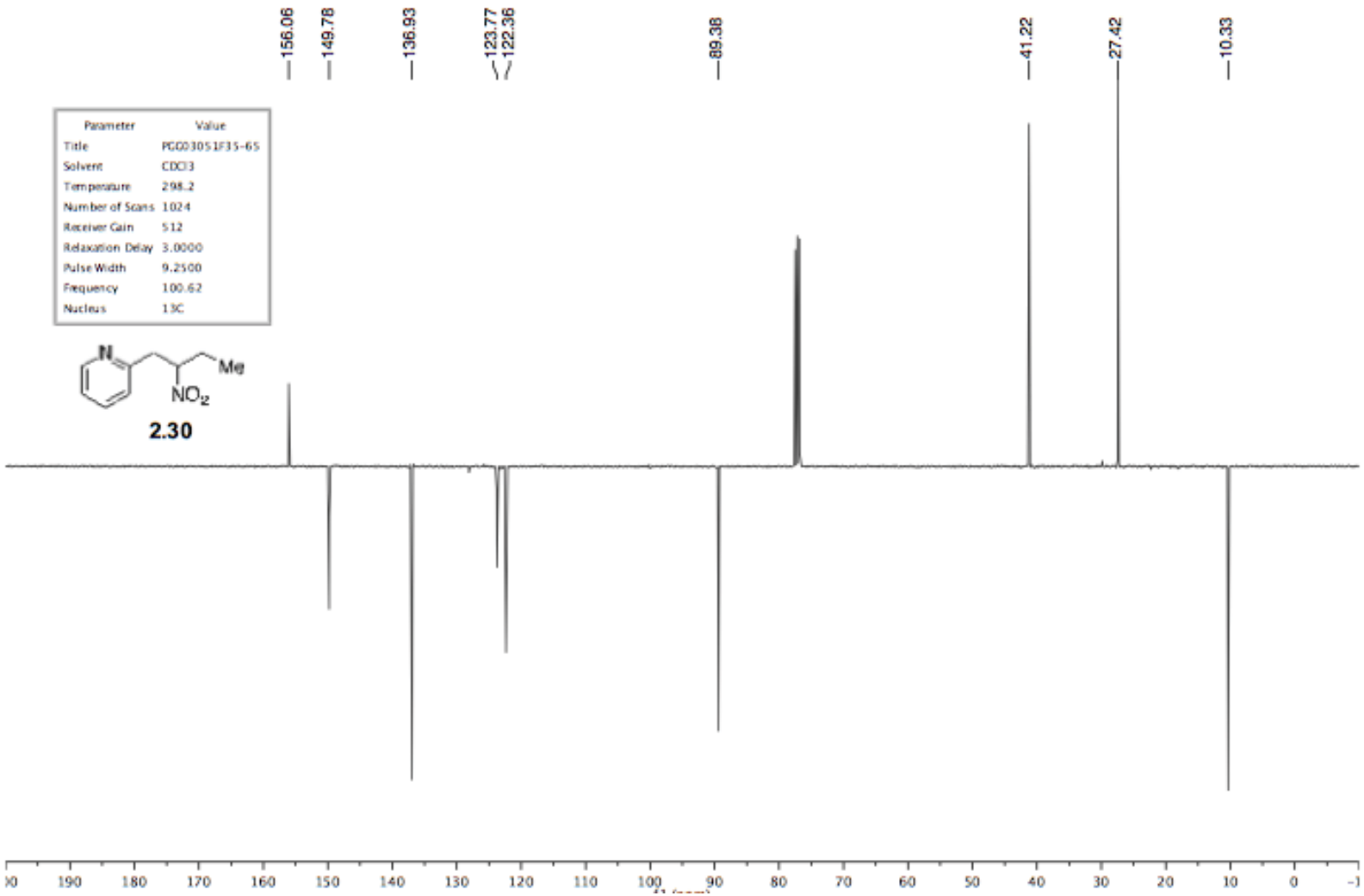
Parameter Value
Title PGD021427S13-23
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
O2N
2.28
• = trace
1.85
0.13
1.94
0.16
1.02
1.05
1.03
0.11
1.12
1.10
2.89

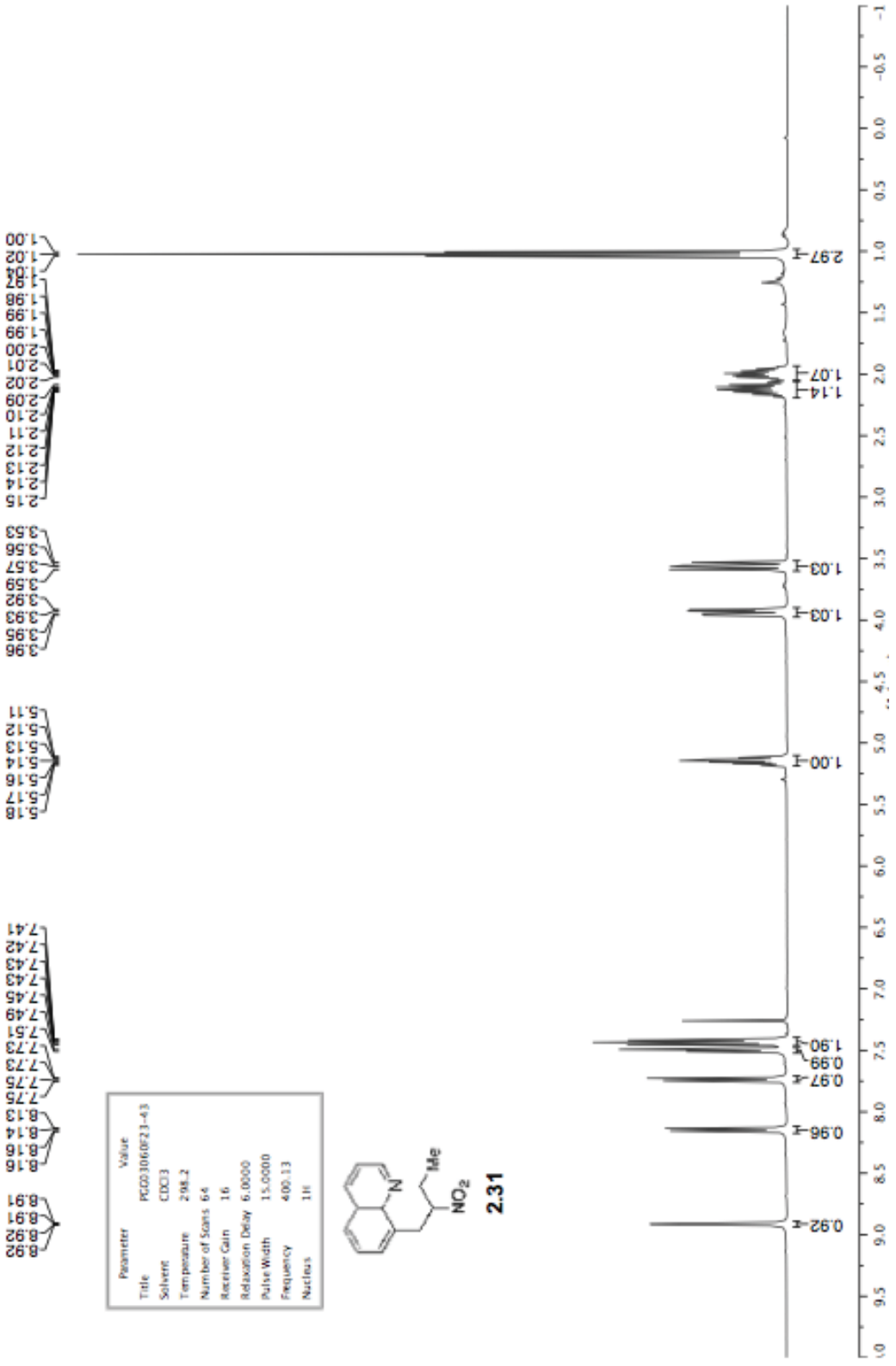

10.32
27.31
39.26
90.74
124.15
129.91
143.21
147.42
Parameter Value
Title PGD0214f313-23
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
• = trace
2.28

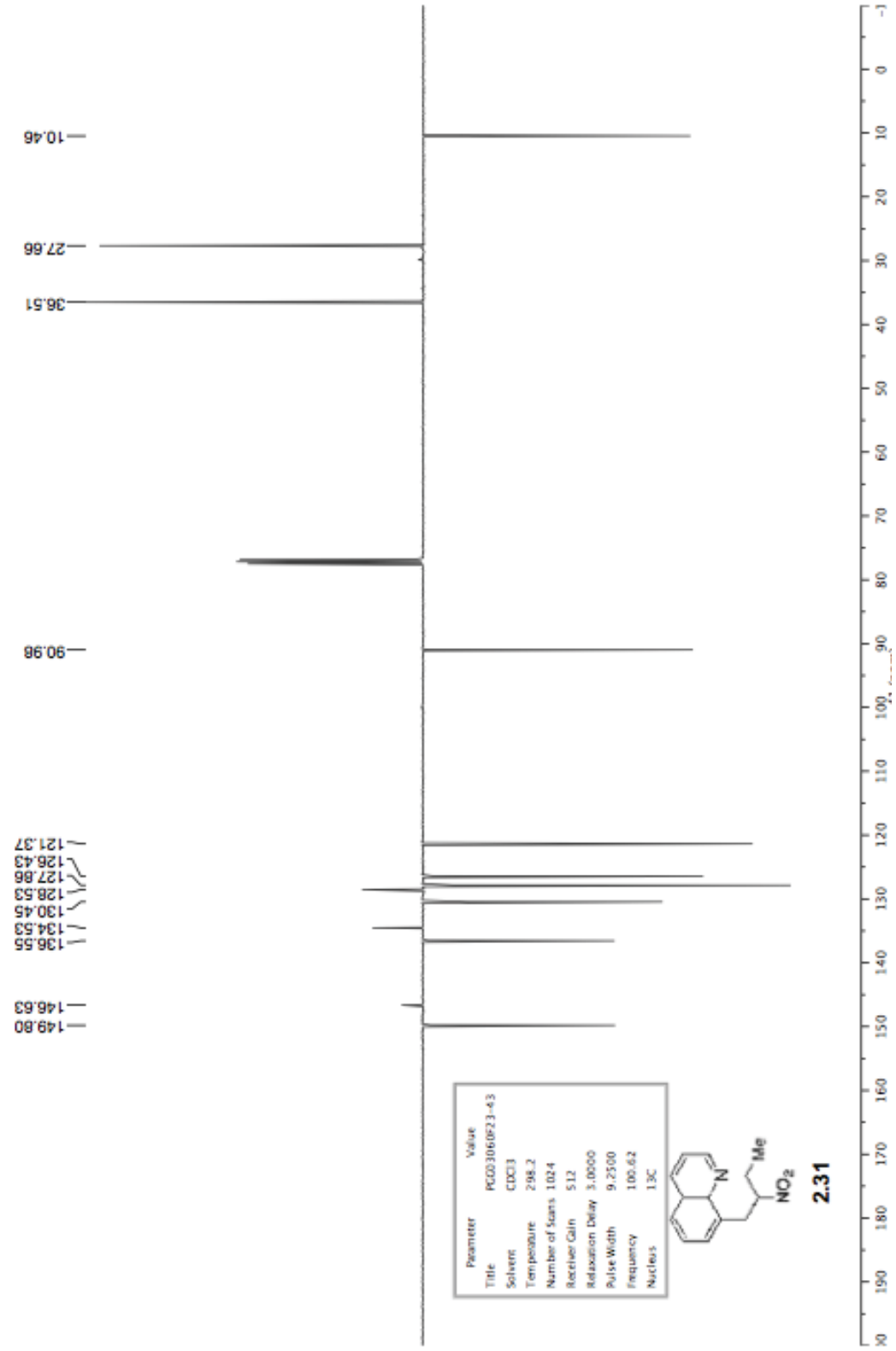

Parameter Value
Title PEG02264F15-37
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 6
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
2.29
Me
NO2
0.99
1.00
1.02
1.87
1.88
1.89
1.90
1.91
2.04
2.06
2.06
2.07
2.08
2.10
3.17
3.19
3.21
3.22
3.41
3.43
3.44
3.47
4.70
4.71
4.72
4.72
4.73
4.73
4.74
4.74
4.74
4.75
4.75
4.75
4.76
4.76
4.77
7.27
7.28
7.29
7.30
7.44
7.45
7.46
7.47
7.47
7.48
7.49
7.50
7.51
7.62
7.78
7.79
7.79
7.80
7.81
7.83
2.53
1.29
1.34
1.13
1.14
1.09
0.95
1.91
0.89
2.71

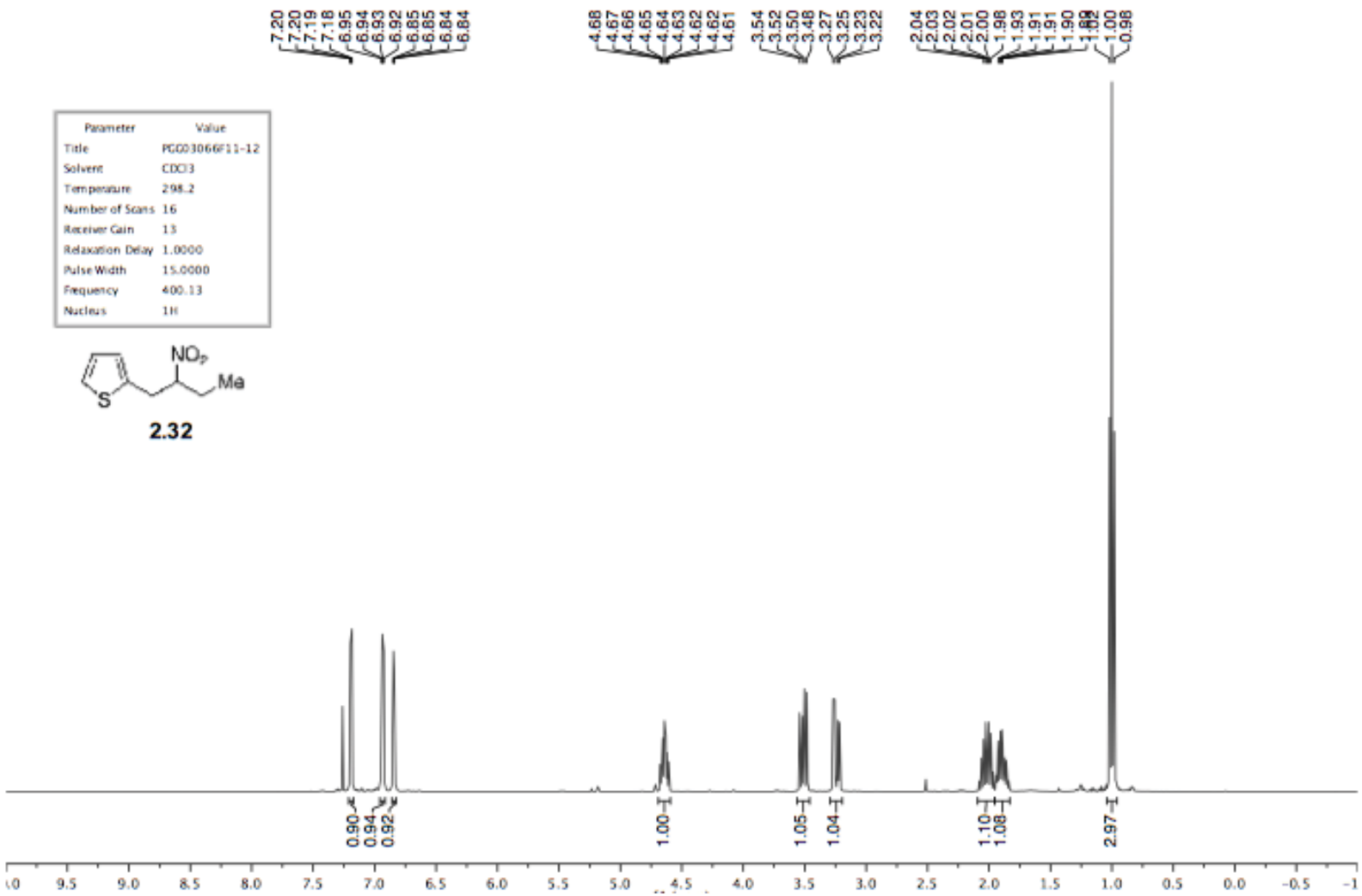

10.44
27.03
40.04
91.44
126.11
126.48
126.81
127.78
127.79
127.92
128.74
132.65
133.18
133.54
Parameter Value
Title PGD2264F15-37
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
2.29

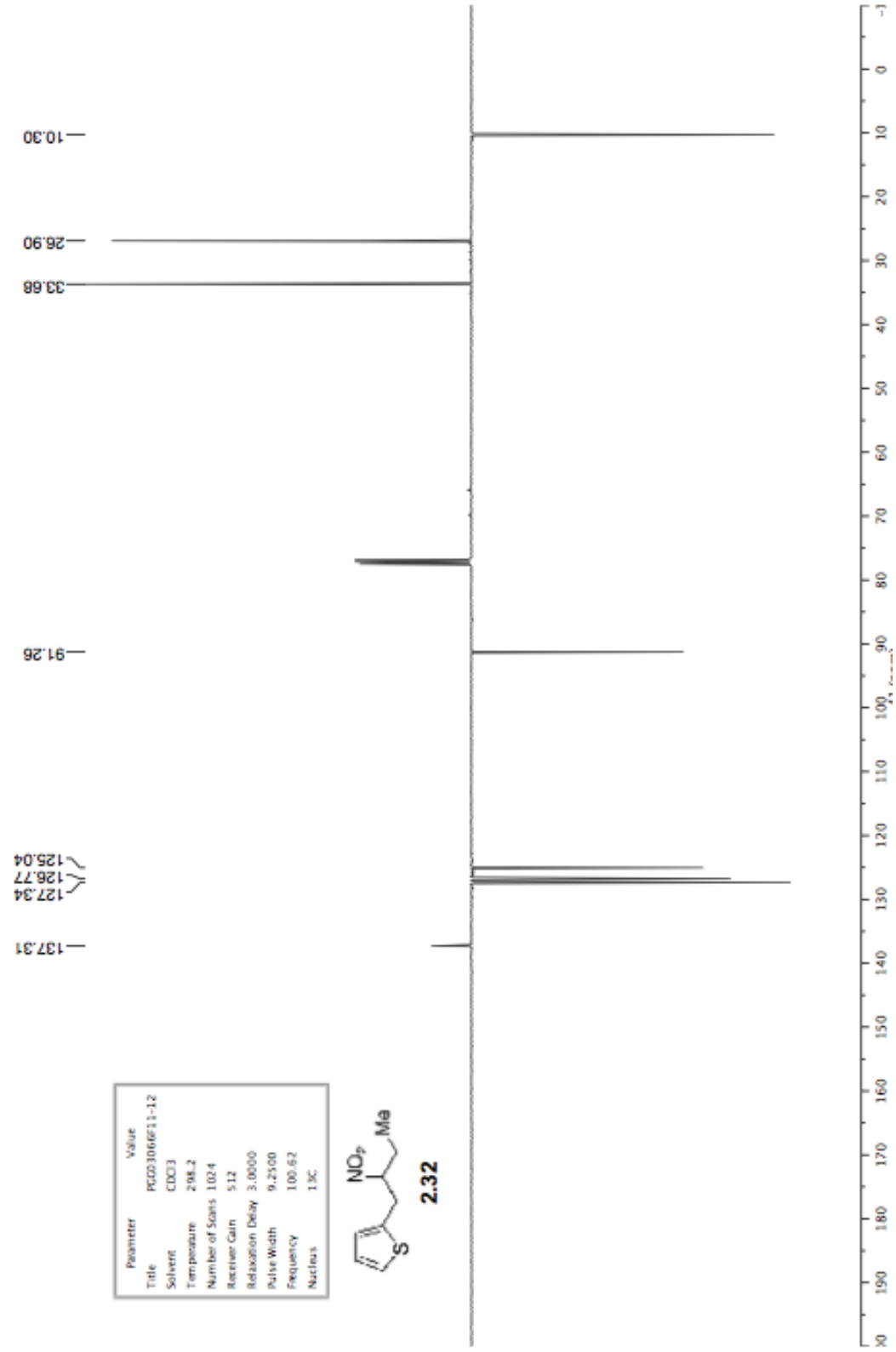

8.54
8.53
7.63
7.62
7.61
7.61
7.59
7.59
7.18
7.17
7.16
7.14
7.12
5.06
5.05
5.04
5.03
5.02
5.01
4.99
3.47
3.45
3.44
3.41
3.20
3.19
3.16
3.15
2.09
2.07
2.06
2.04
2.02
1.95
1.94
1.93
1.92
1.92
1.01
0.99
Parameter Value
Title PGD03051F35-65
Solvent CDCl3
Temperature 298.1
Number of Scans 64
Receiver Gain 9
Relaxation Delay 6.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
N
Me
NO2
2.30
0.96
0.94
1.81
0.98
1.03
1.01
1.22
1.17
2.89
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

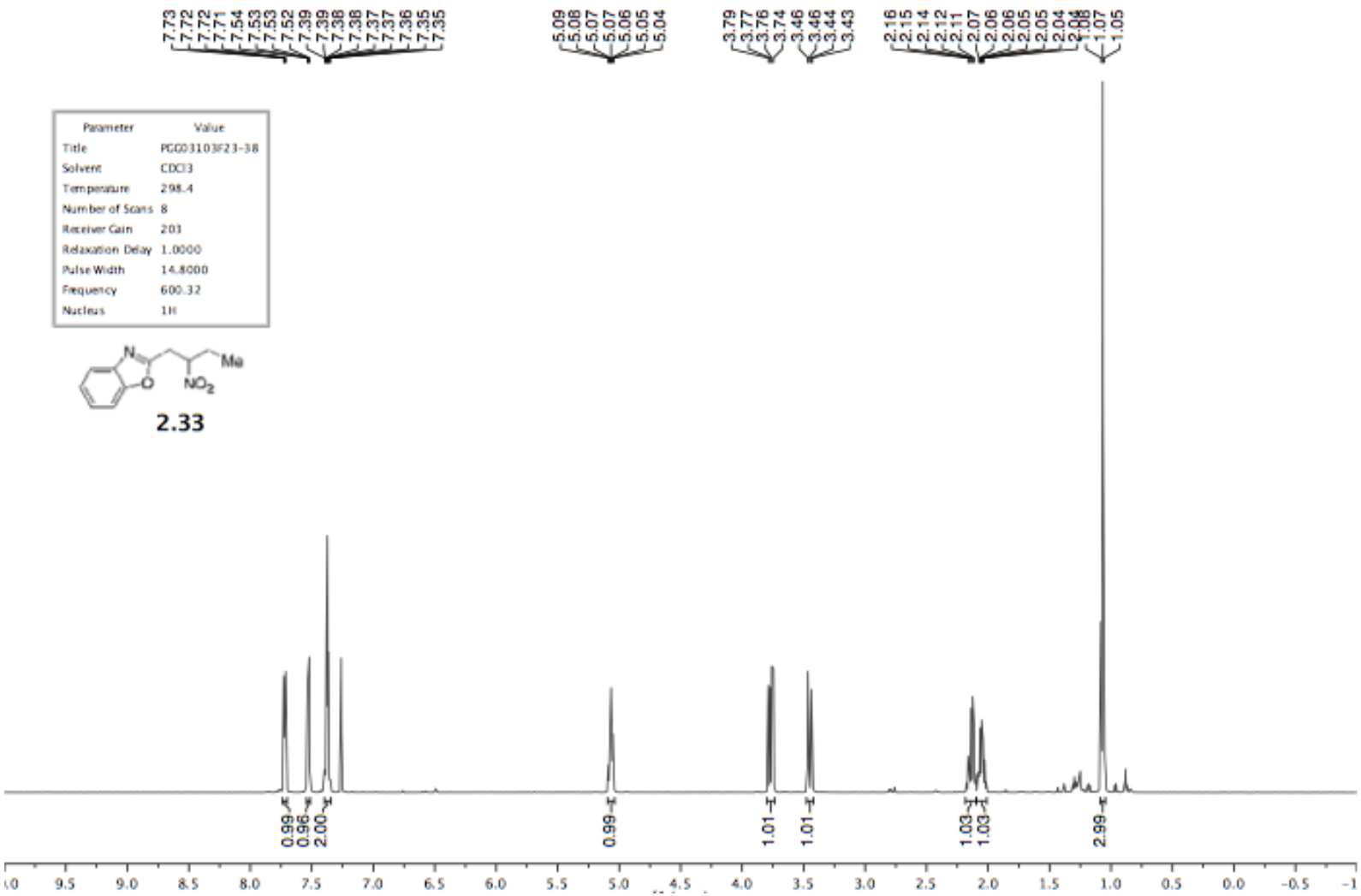

156.06
149.78
136.93
123.77
122.36
89.38
41.22
27.42
10.33
Parameter Value
Title PGD03051F35-65
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
N
Me
NO2
2.30
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

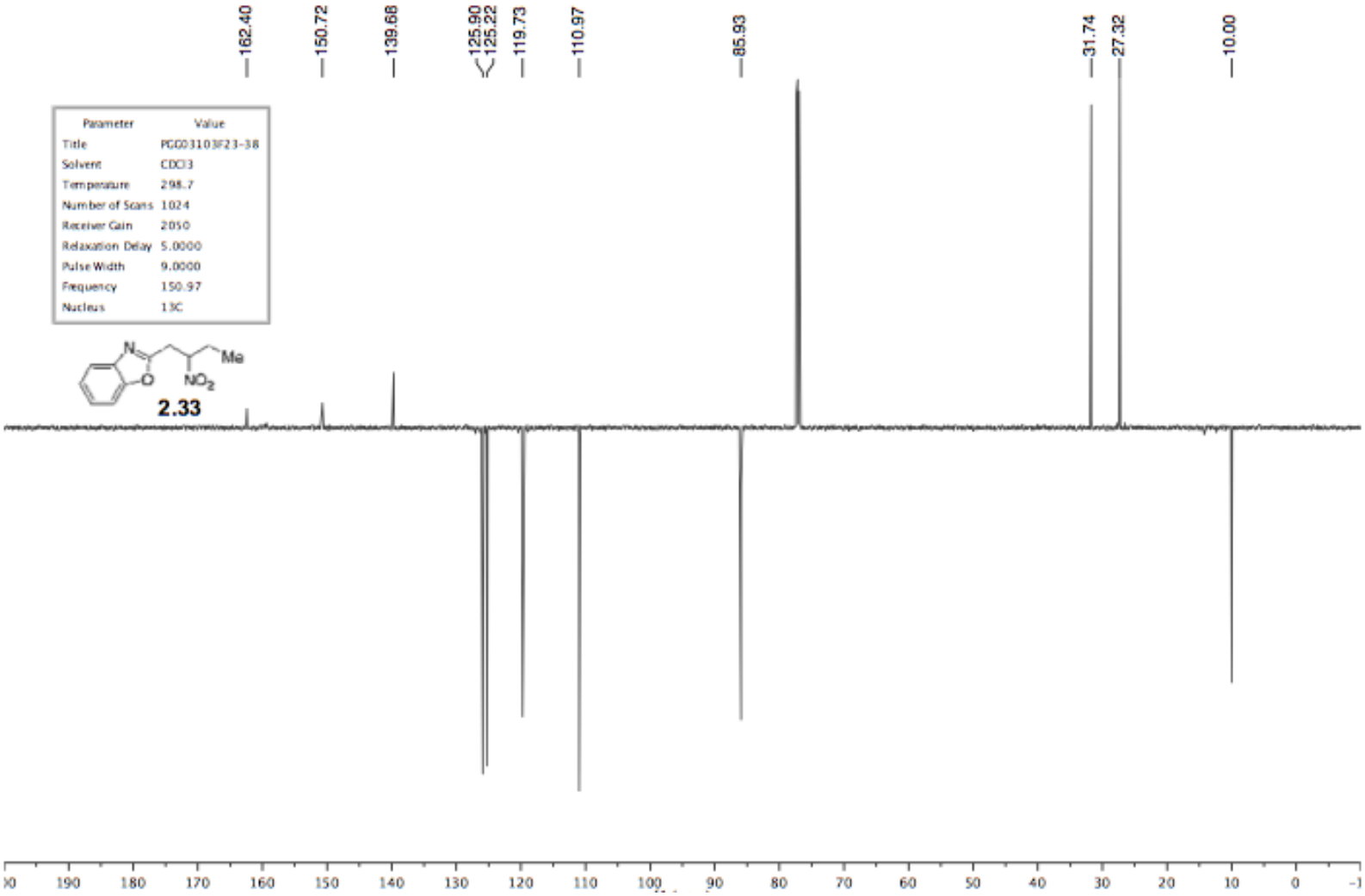

Parameter Value
Title PGD3060F23-43
Solvent CDCl3
Temperature 298.2
Number of Scans 64
Receiver Gain 16
Relaxation Delay 6.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
2.31


10.46
27.66
36.51
90.98
121.37
126.43
127.86
128.53
130.45
134.53
136.55
146.63
149.80
Parameter Value
Title PG03060P23-43
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
N
Me
NO2
2.31


7.20
7.20
7.19
7.18
6.95
6.94
6.93
6.92
6.85
6.85
6.84
6.84
4.68
4.67
4.66
4.65
4.64
4.63
4.62
4.62
4.61
3.54
3.52
3.50
3.48
3.27
3.25
3.23
3.22
2.04
2.03
2.02
2.01
2.00
1.98
1.93
1.91
1.91
1.90
1.00
0.98
Parameter Value
Title PGD3066F11-12
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 13
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
NO2
Me
S
2.32
0.90
0.94
0.92
1.00
1.05
1.04
1.10
1.08
2.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


10.30
26.90
33.68
91.26
125.04
126.77
127.34
137.31
Parameter Value
Title PGD03066F11-12
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Me
S
2.32


7.73 7.72 7.72 7.71 7.54 7.53 7.53 7.52 7.39 7.38 7.38 7.37 7.37 7.36 7.35 7.35
5.09 5.08 5.07 5.07 5.06 5.05 5.04
3.79 3.77 3.76 3.74 3.46 3.46 3.44 3.43
2.16 2.15 2.14 2.12 2.11 2.07 2.06 2.06 2.05 2.05 2.04 2.04 2.03 1.07 1.05
Parameter Value
Title PGD03103F23-38
Solvent CDCl3
Temperature 298.4
Number of Scans 8
Receiver Gain 203
Relaxation Delay 1.0000
Pulse Width 14.8000
Frequency 600.32
Nucleus 1H
N
O
Me
NO2
2.33
0.99 0.96 2.00 0.99 1.01 1.01 1.03 1.03 2.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1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150.72
139.68
125.90
125.22
119.73
110.97
85.93
31.74
27.32
10.00
Parameter Value
Title PGC03103F23-38
Solvent CDCl3
Temperature 298.7
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 9.0000
Frequency 150.97
Nucleus 13C
N
O
Me
NO2
2.33
190
180
170
160
150
140
130
120
110
90
80
70
60
50
40
30
20
10
0

Parameter Value
Title PDG2223865-12
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 14
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
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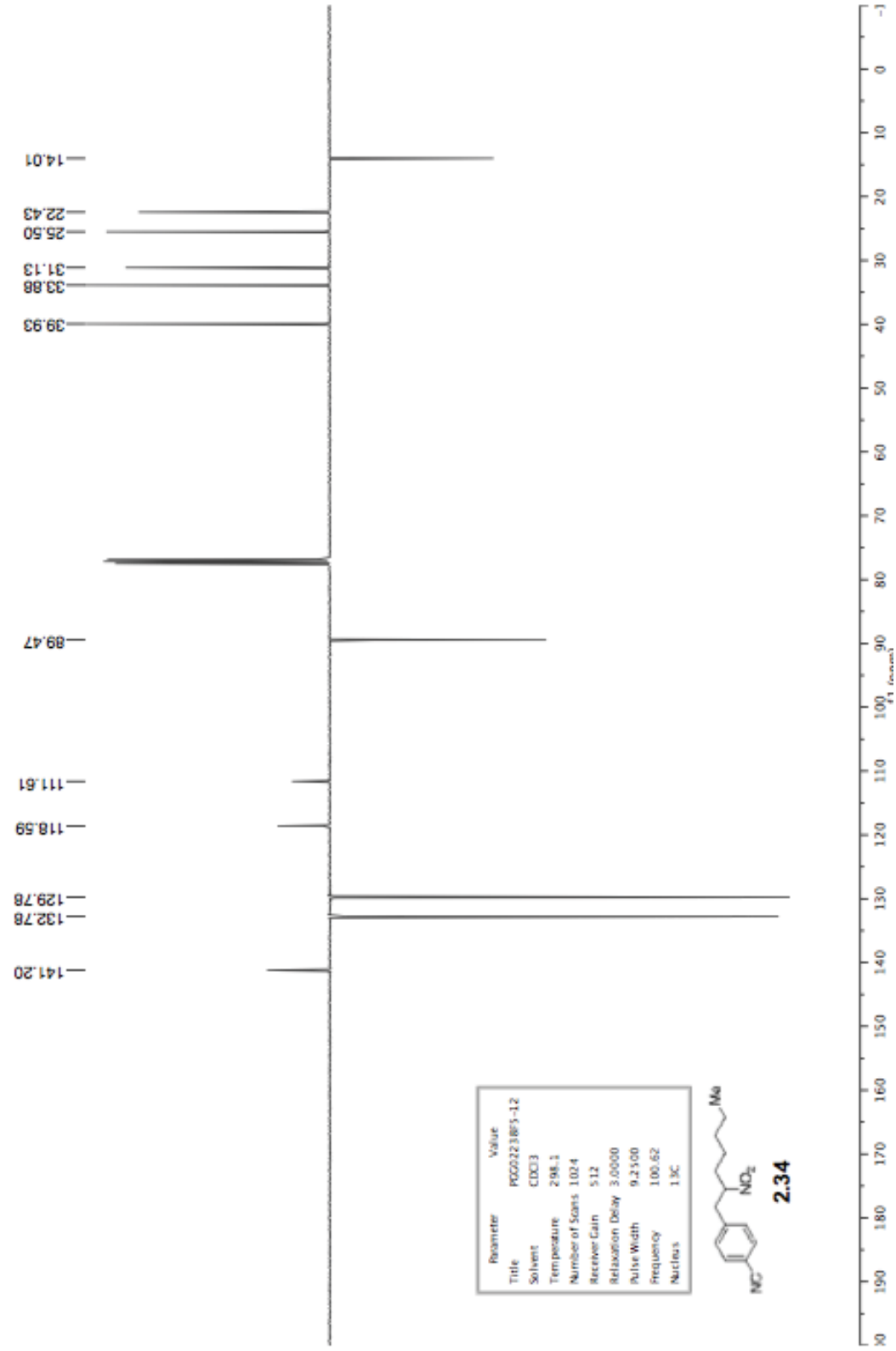
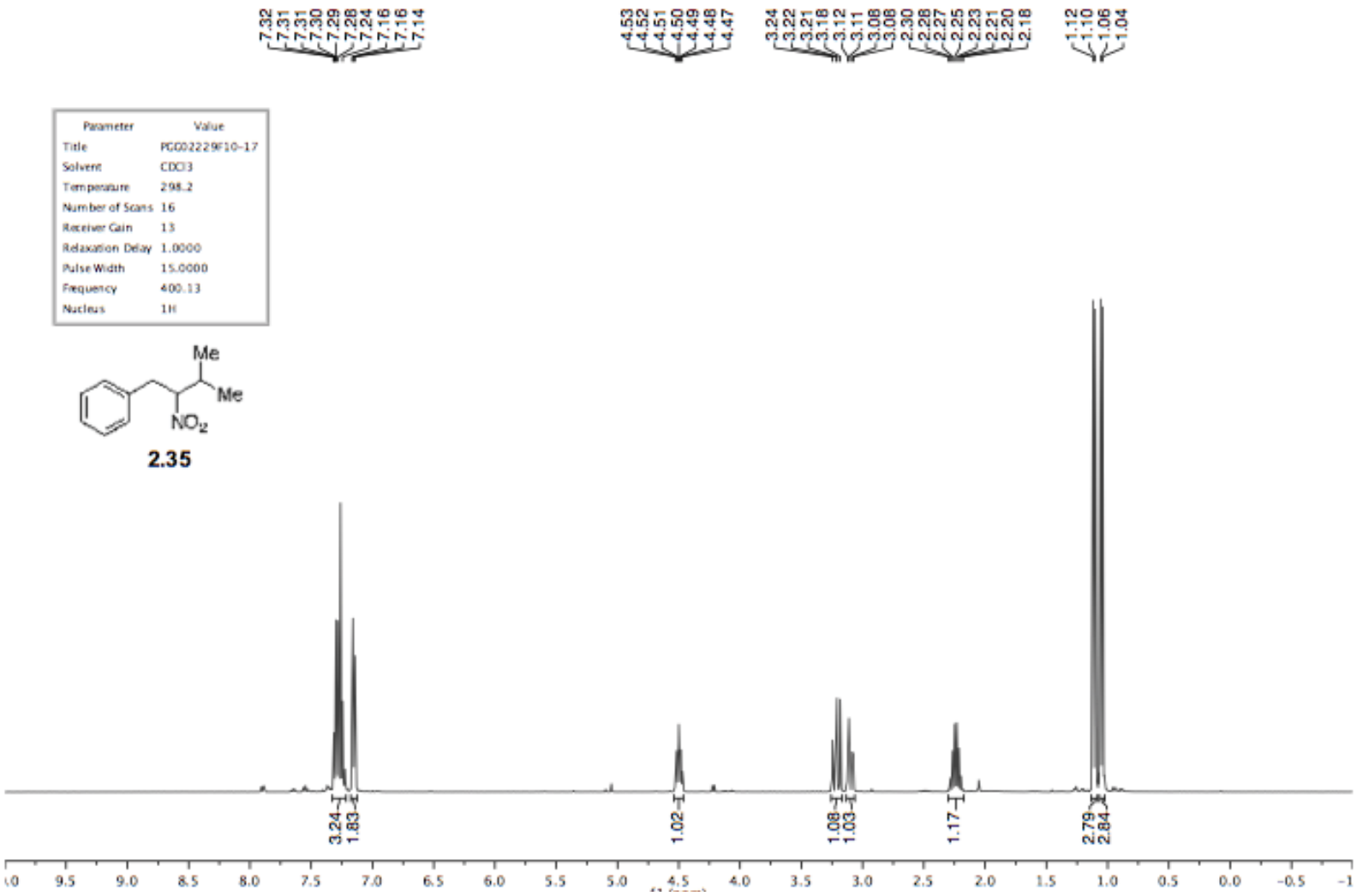
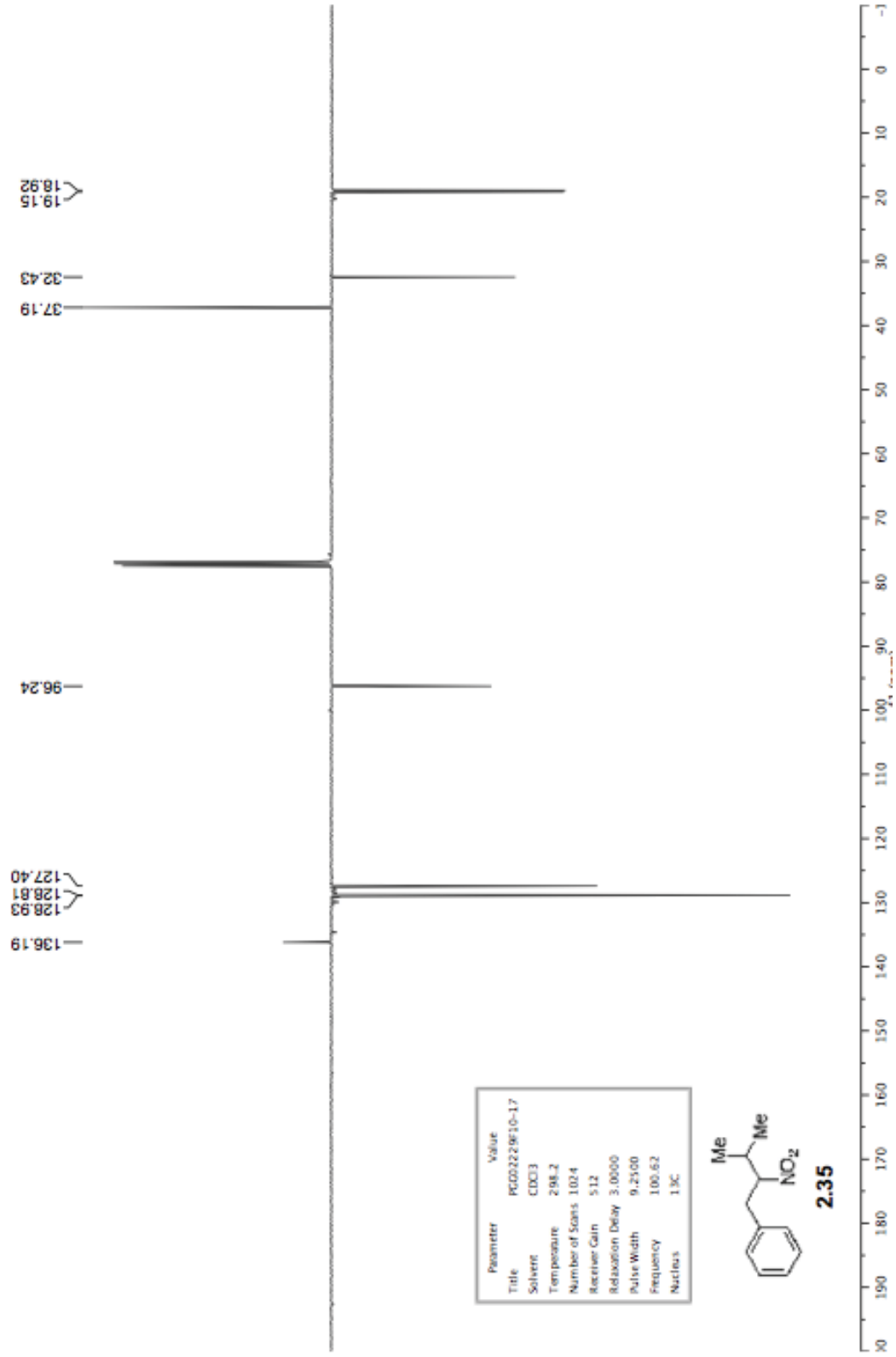
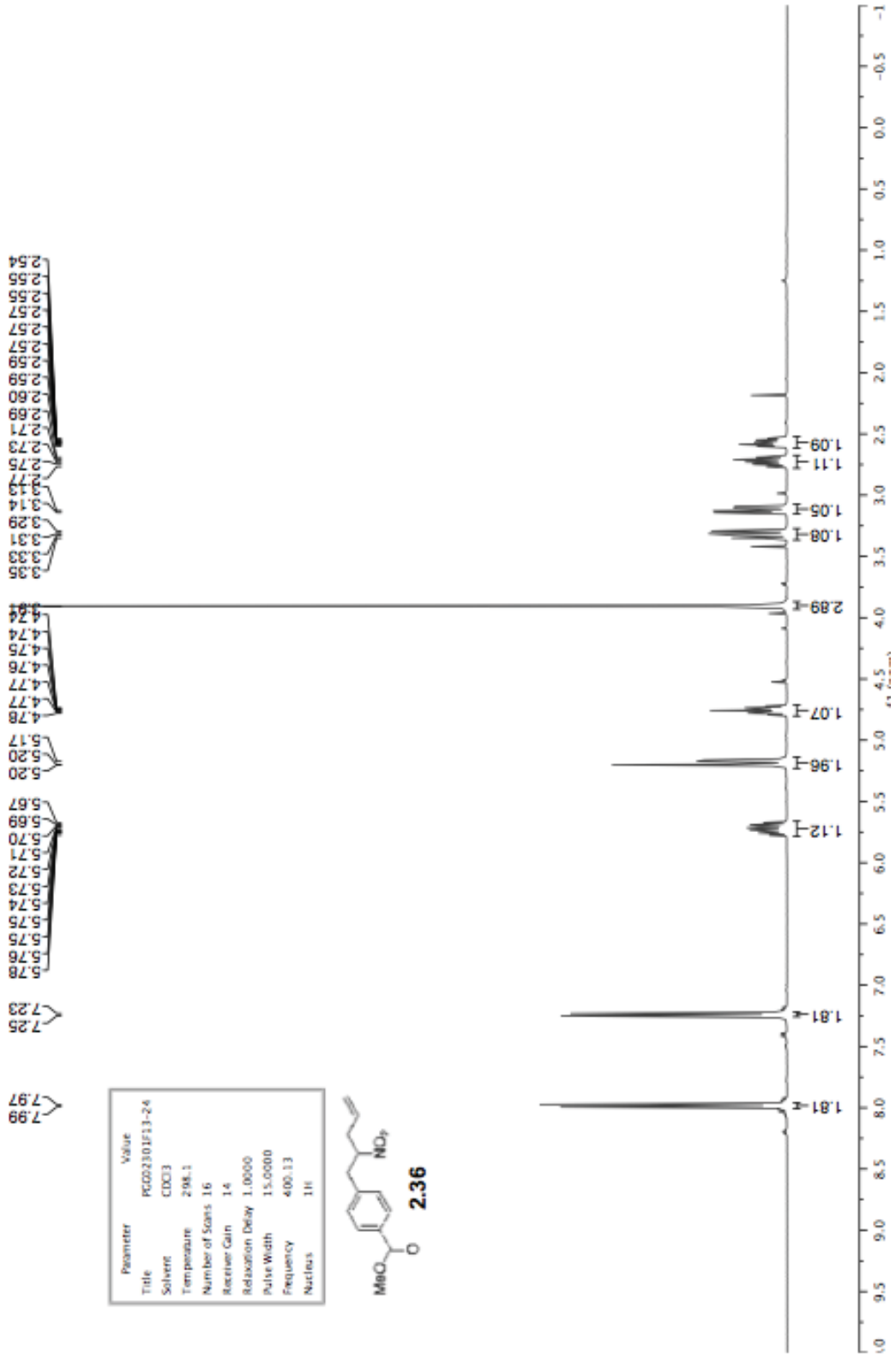
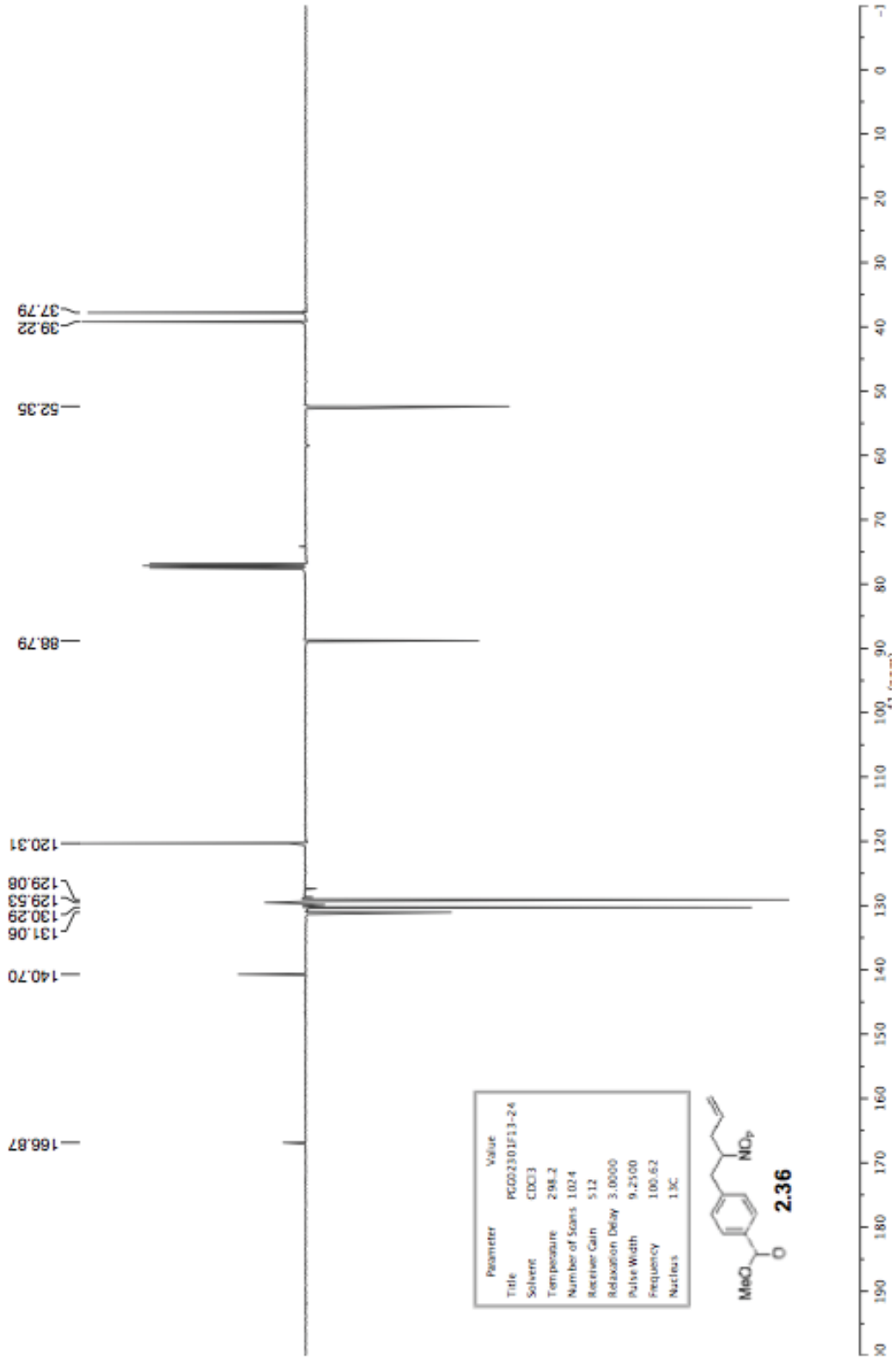
1.71
1.86
1.10
1.09
1.06
1.20
1.14
5.92
2.91

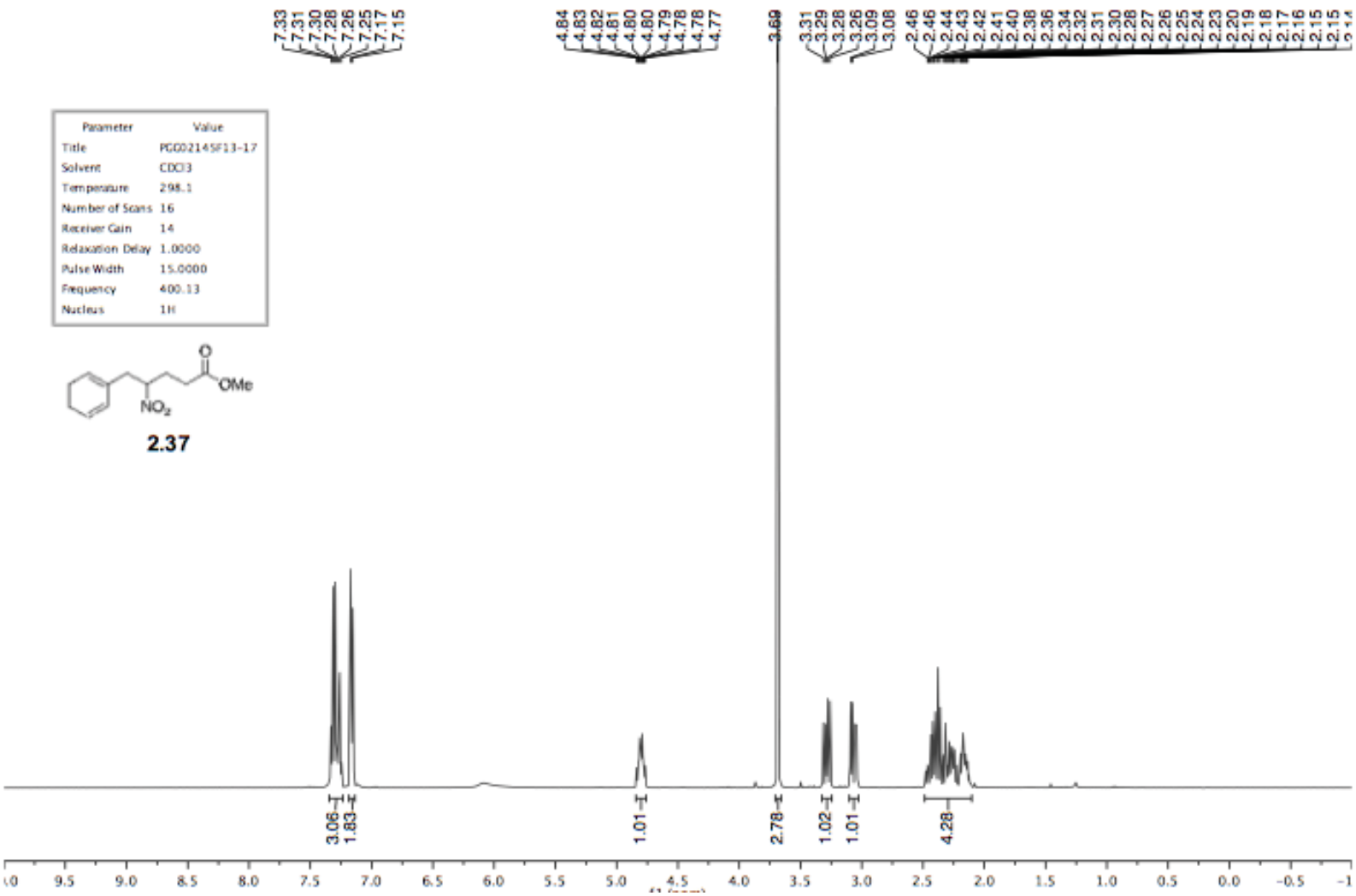

14.01
22.43
25.50
31.13
33.86
39.93
89.47
111.61
118.59
129.78
132.78
141.20
Parameter Value
Title PDD223865-12
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NC
NO2
Na
2.34

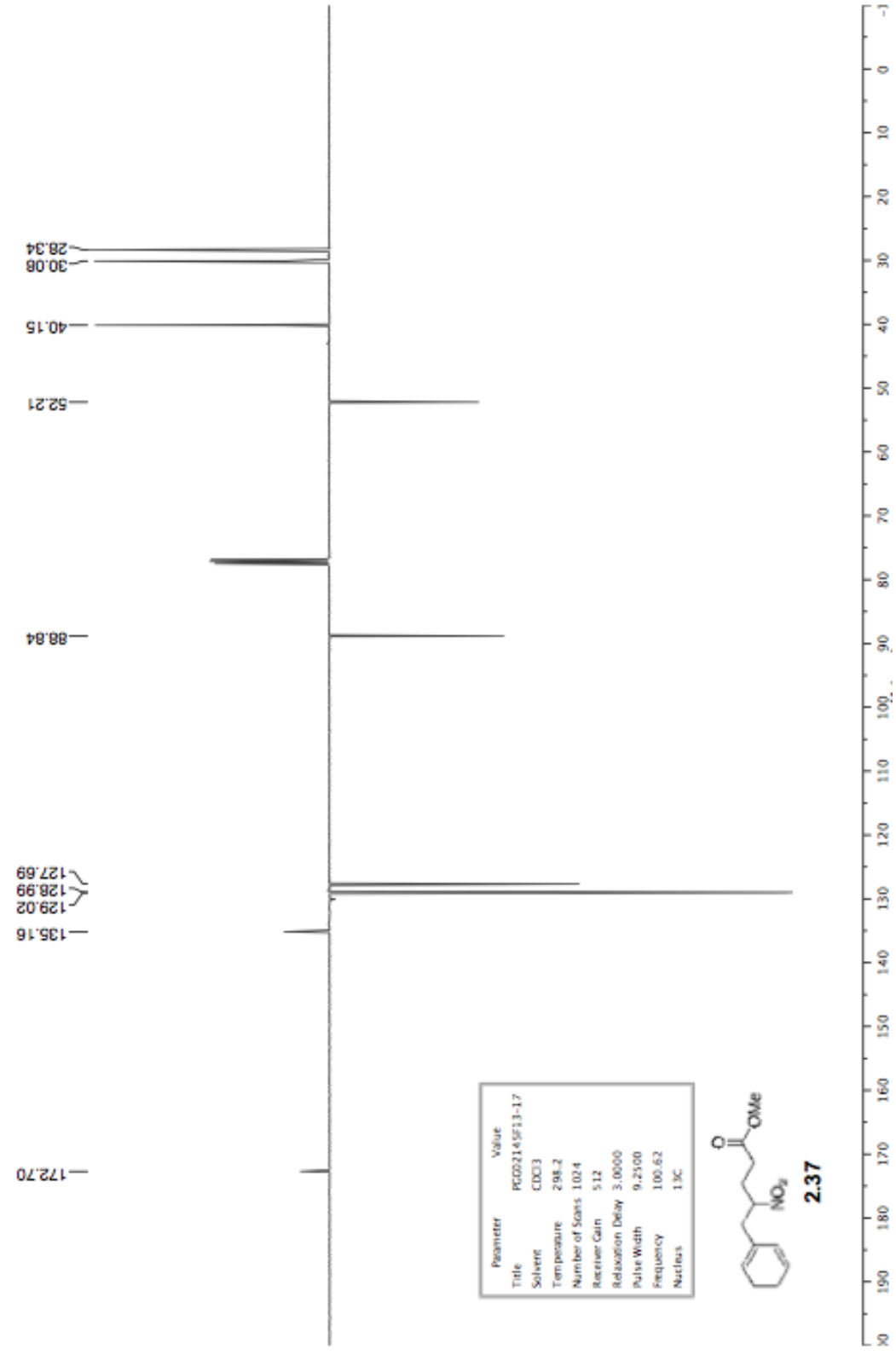

7.32
7.31
7.31
7.30
7.29
7.28
7.24
7.16
7.16
7.14
4.53
4.52
4.51
4.50
4.49
4.48
4.47
3.24
3.22
3.21
3.18
3.12
3.11
3.08
3.08
2.30
2.28
2.27
2.25
2.23
2.21
2.20
2.18
1.12
1.10
1.06
1.04
Parameter Value
Title PGD02229F10-17
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 13
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
Me
NO2
2.35
3.24
1.83
1.02
1.08
1.03
1.17
2.79
2.84

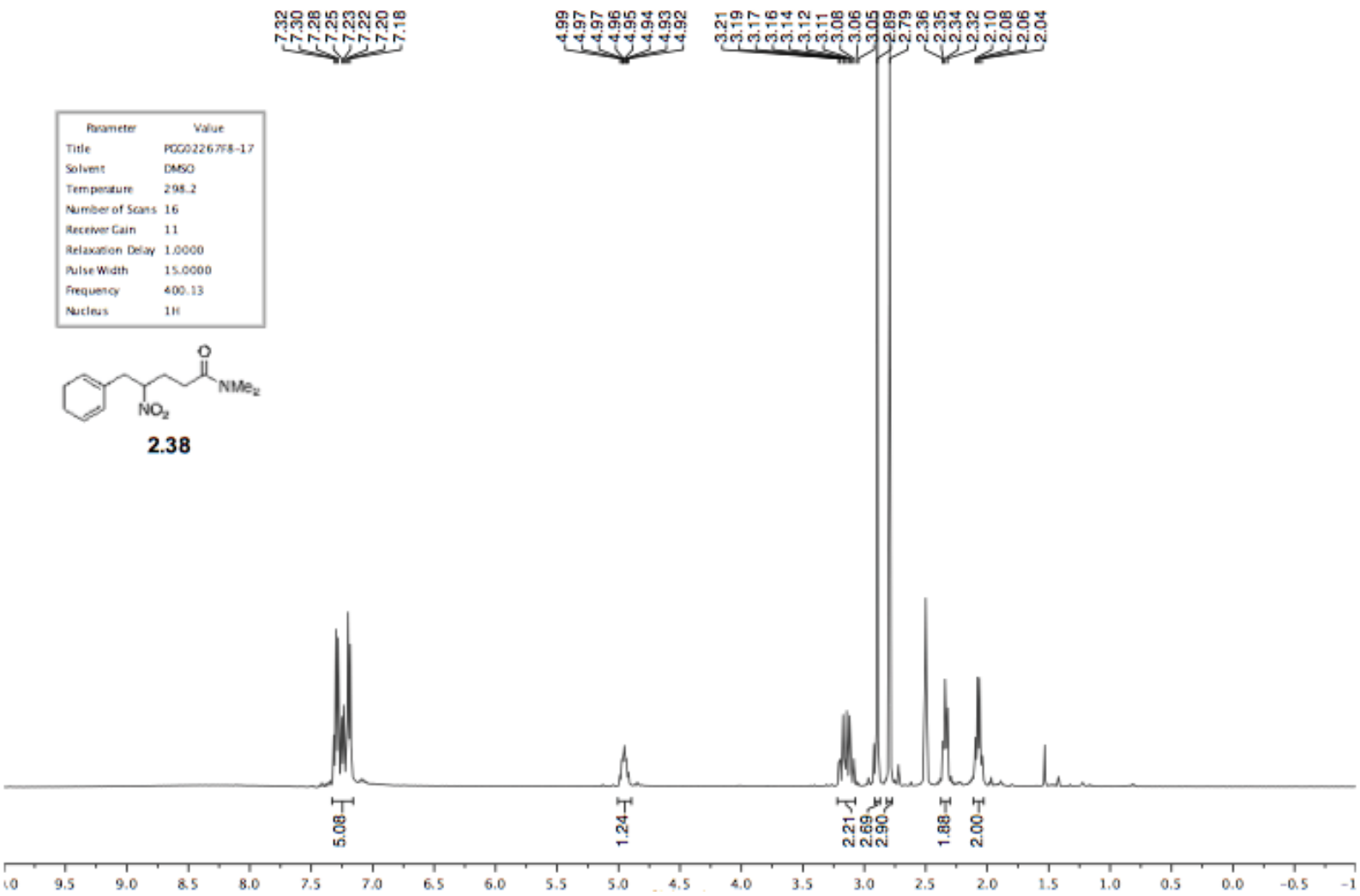

19.15
18.92
32.43
37.19
96.24
128.93
128.81
127.40
136.19
Parameter Value
Title PE0222910-17
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
Me
NO2
2.35

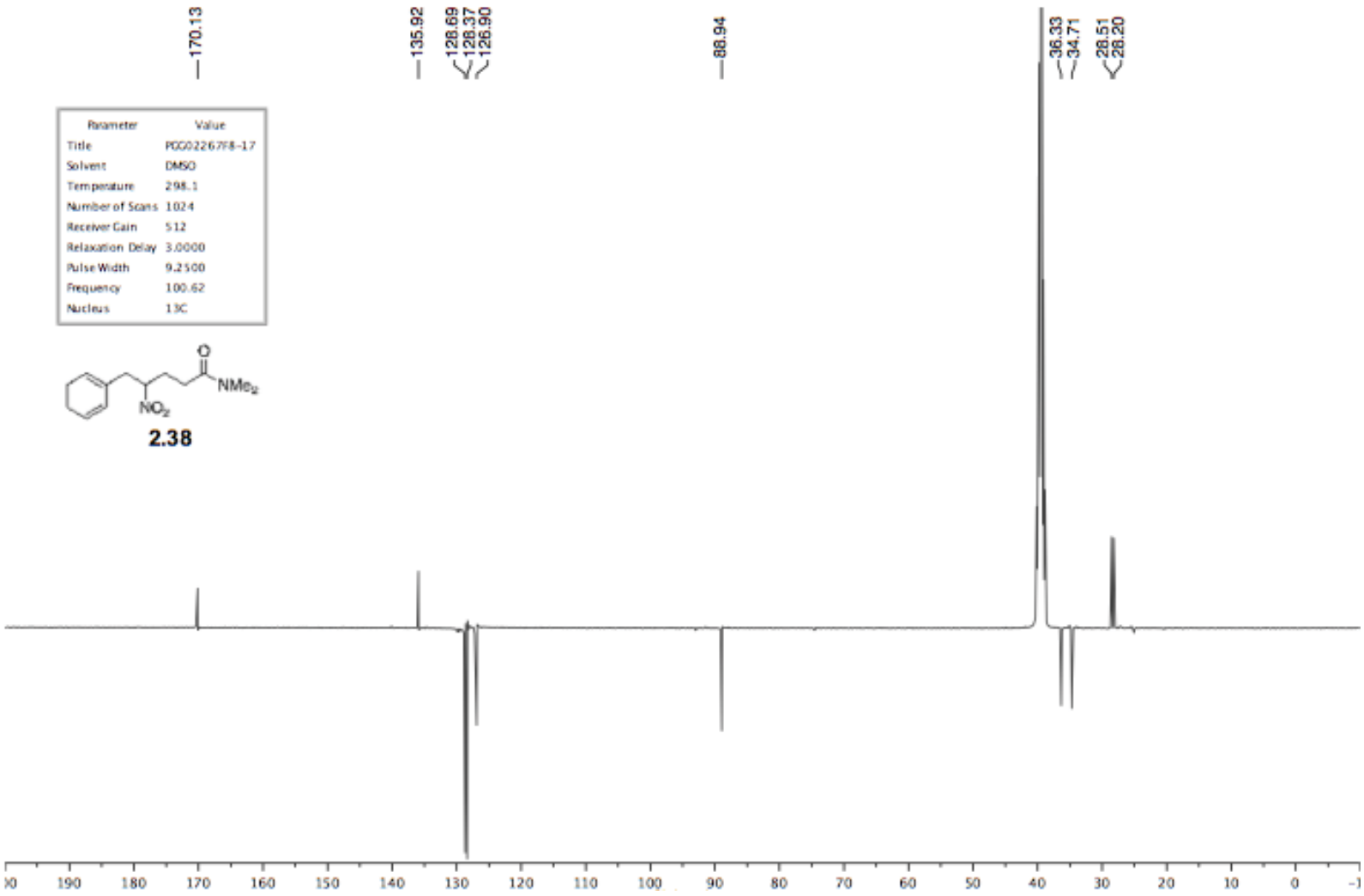

Parameter Value
Title PG023801F33-24
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 14
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
2.36
MeO
NO2
1.81
1.81
1.12
1.96
1.07
2.89
1.08
1.05
1.11
1.09

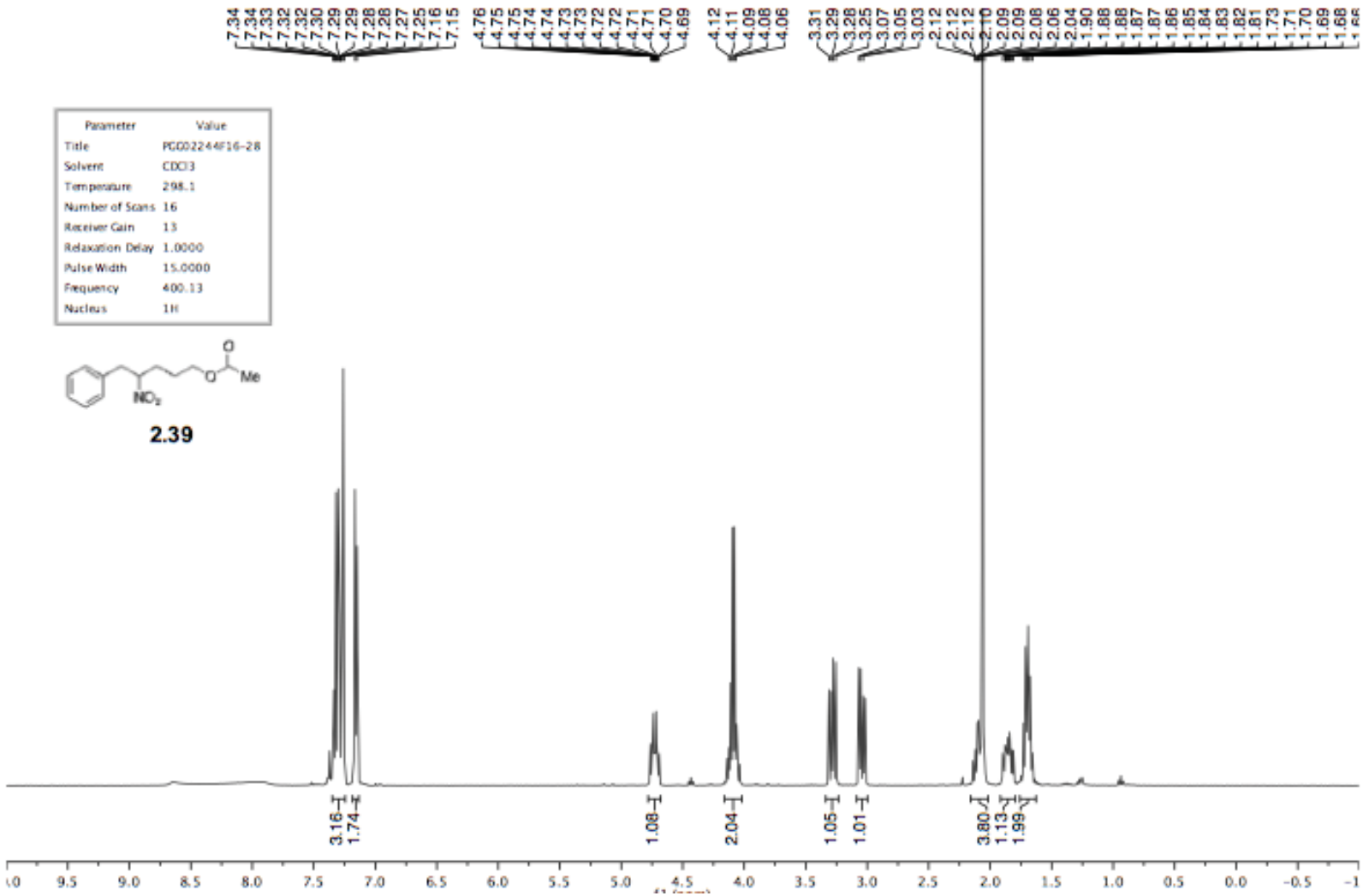

37.79
39.22
52.35
86.79
120.31
129.08
129.53
130.29
131.06
140.70
166.87
Parameter Value
Title PGD2301F13-24
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
MeO
O
NO2
2.36

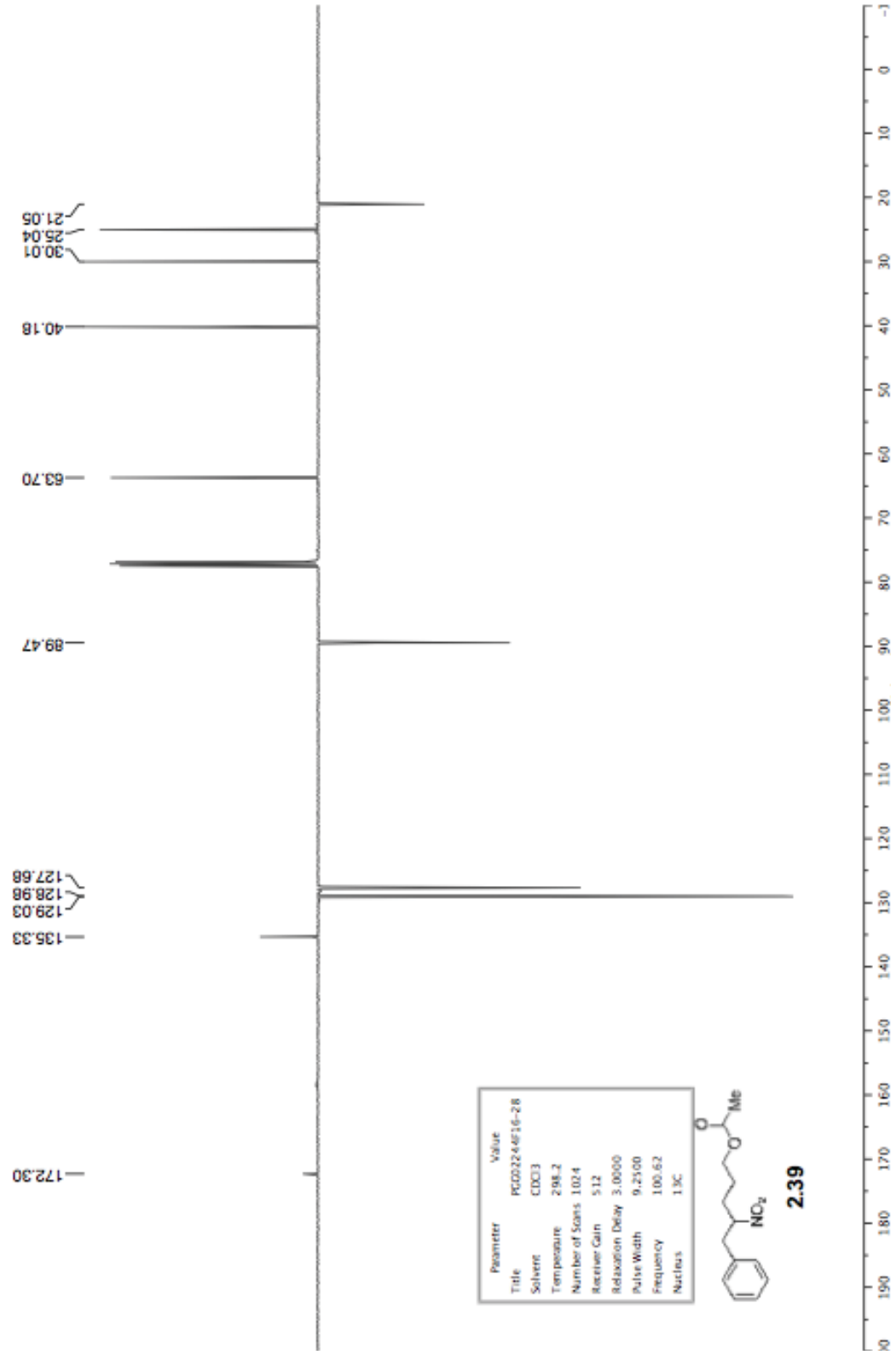

Parameter Value
Title PGD0214SF13-17
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 14
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
OMe
NO2
2.37
7.33 7.31 7.30 7.28 7.26 7.25 7.17 7.15
4.84 4.83 4.82 4.81 4.80 4.80 4.79 4.78 4.78 4.77
3.69
3.31 3.29 3.28 3.26 3.09 3.08
2.46 2.46 2.44 2.43 2.42 2.41 2.40 2.38 2.36 2.34 2.32 2.31 2.30 2.28 2.27 2.26 2.25 2.24 2.23 2.20 2.19 2.18 2.17 2.16 2.15 2.15
3.06
1.83
1.01
2.78
1.02
1.01
4.28
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

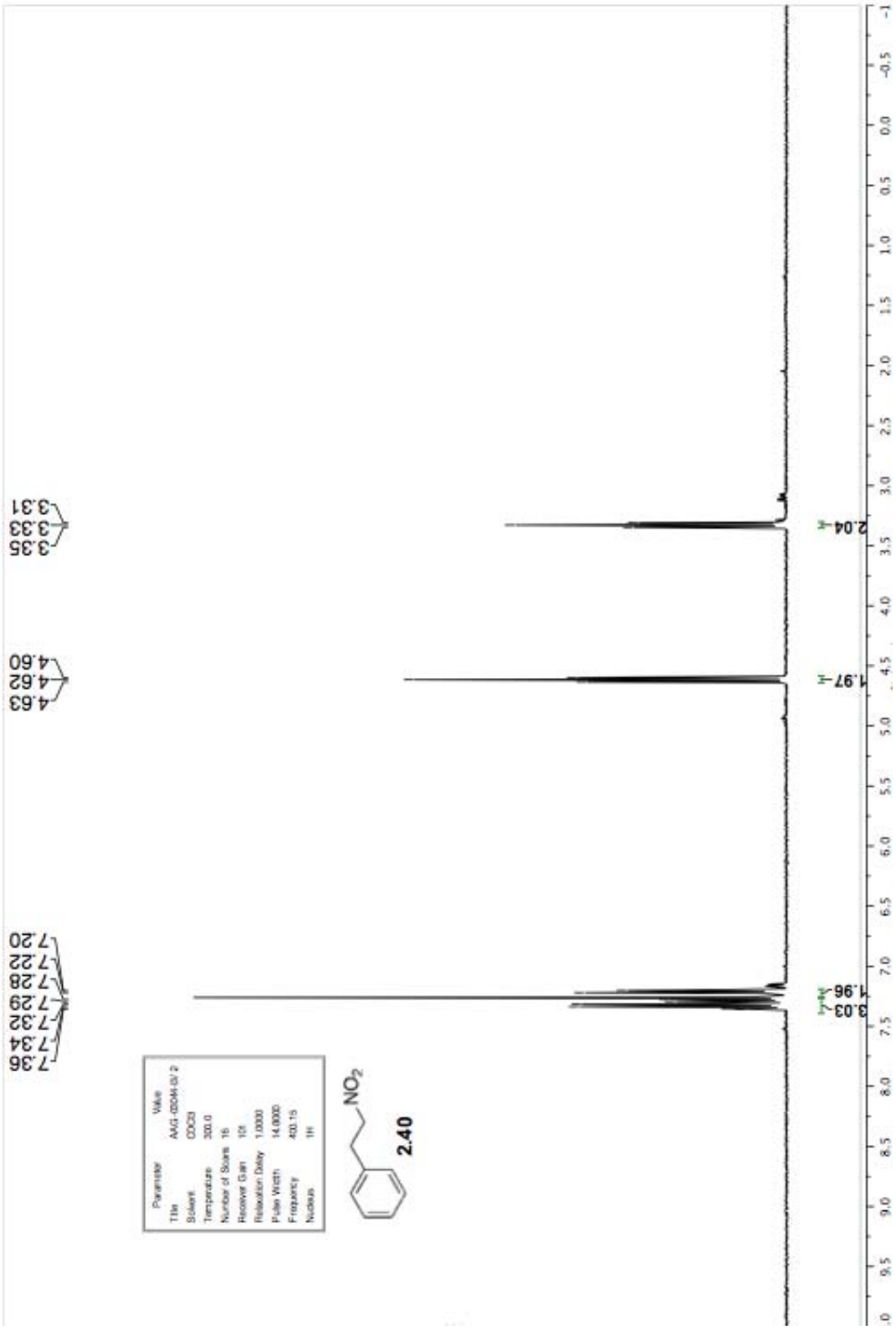

28.34
30.08
40.15
52.21
88.84
127.69
128.99
129.02
135.16
172.70
Parameter Value
Title PGD221455133-17
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
OMe
NO2
2.37

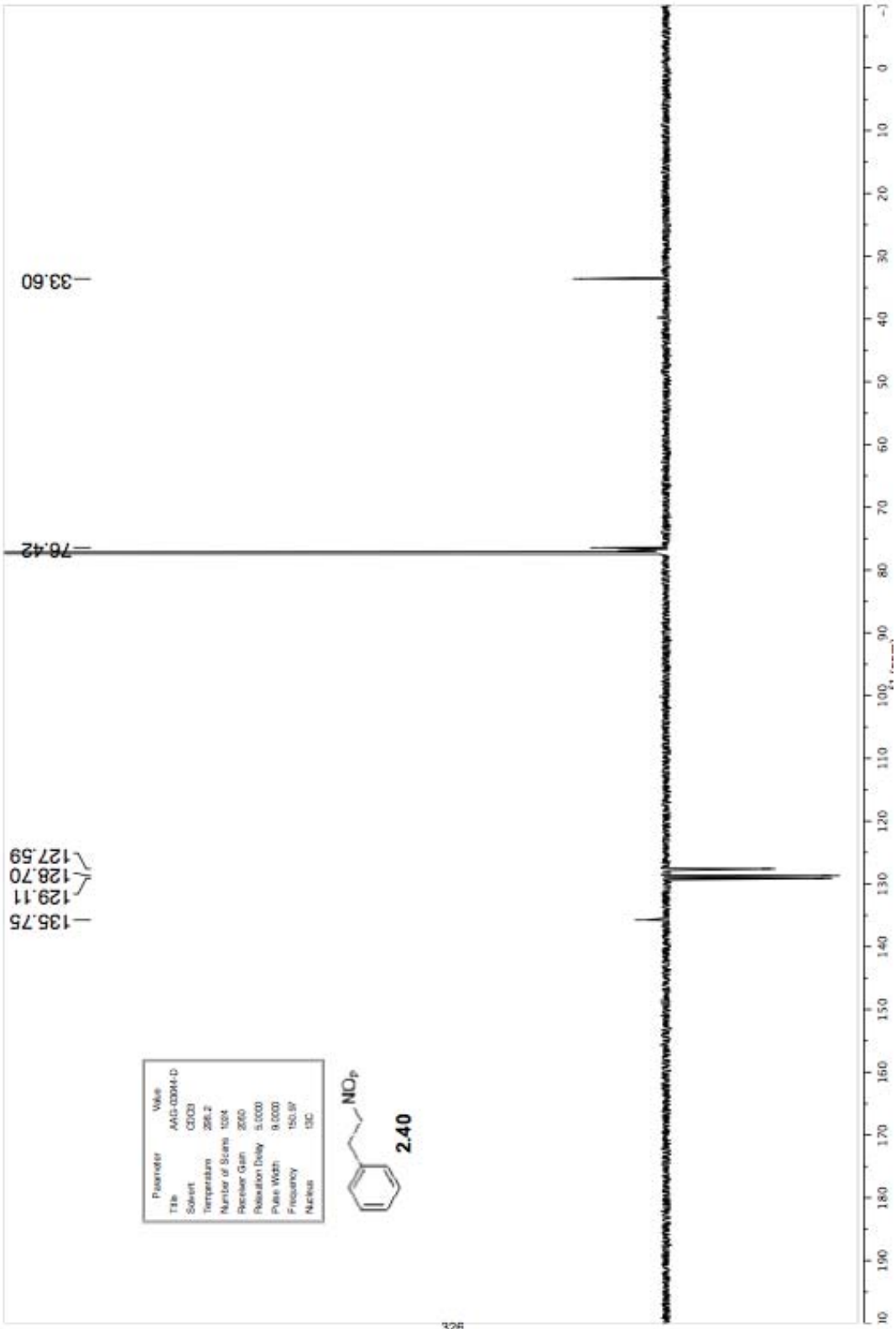

7.32
7.30
7.28
7.25
7.23
7.22
7.20
7.18
4.99
4.97
4.97
4.96
4.95
4.94
4.93
4.92
3.21
3.19
3.17
3.16
3.14
3.12
3.11
3.08
3.06
3.05
2.89
2.79
2.36
2.35
2.34
2.32
2.10
2.08
2.06
2.04
Parameter Value
Title PDG022677f8-17
Solvent DMSO
Temperature 298.2
Number of Scans 16
Receiver Gain 11
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
O
NMe2
NO2
2.38
5.08
1.24
2.21
2.69
2.90
1.88
2.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1


170.13
135.92
128.69
128.37
126.90
88.94
36.33
34.71
28.51
28.20
Parameter Value
Title PDG022677F8-17
Solvent DMSO
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
NMe2
NO2
2.38
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

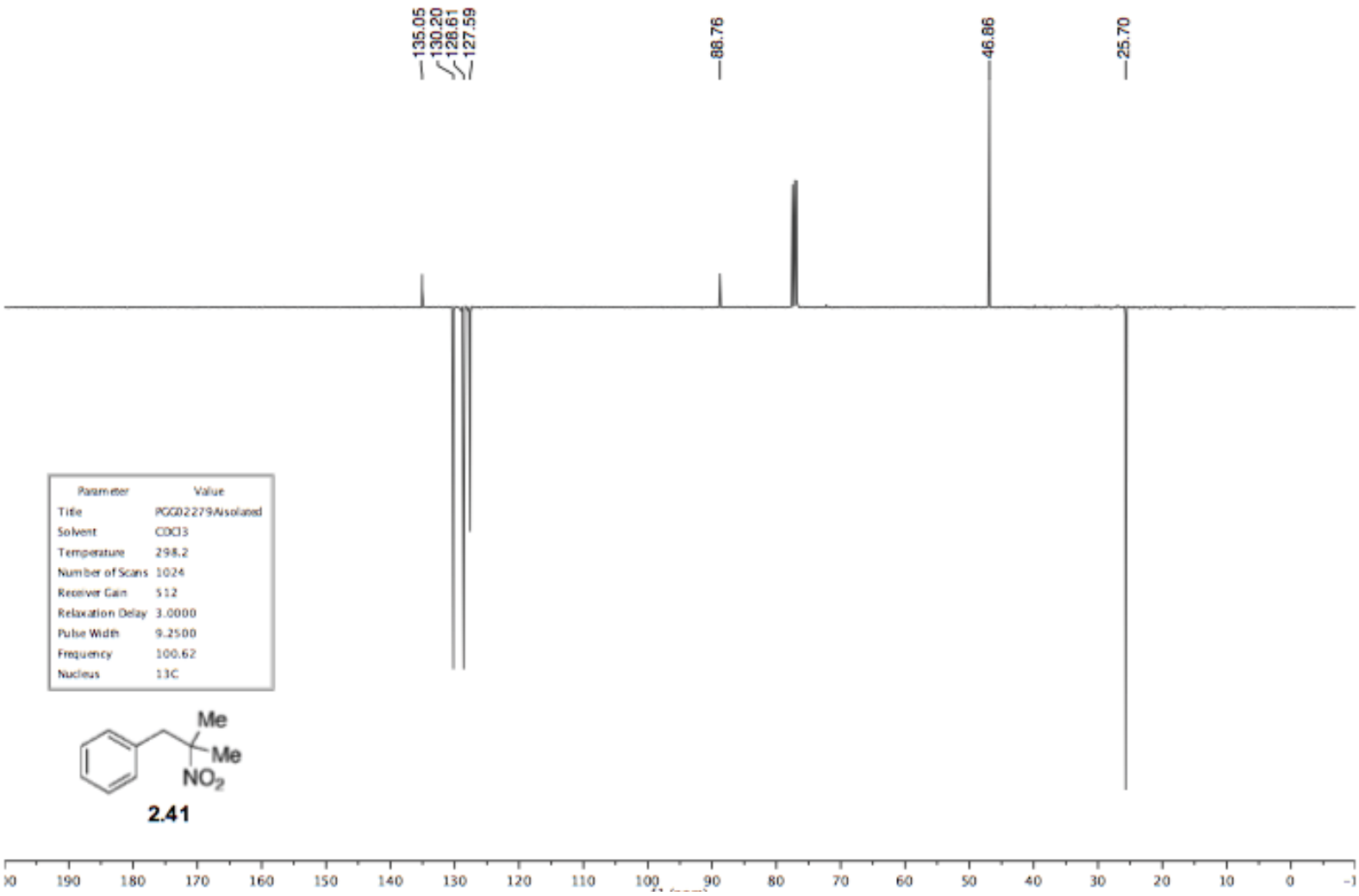

Parameter Value
Title PGD02244F16-28
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 13
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
NO2
2.39
3.16
1.74
1.08
2.04
1.05
1.01
3.80
1.13
1.99


172.30
135.33
129.03
128.98
127.68
89.47
63.70
40.18
30.01
25.04
21.05
Parameter Value
Title PGD0224#16-28
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
2.39

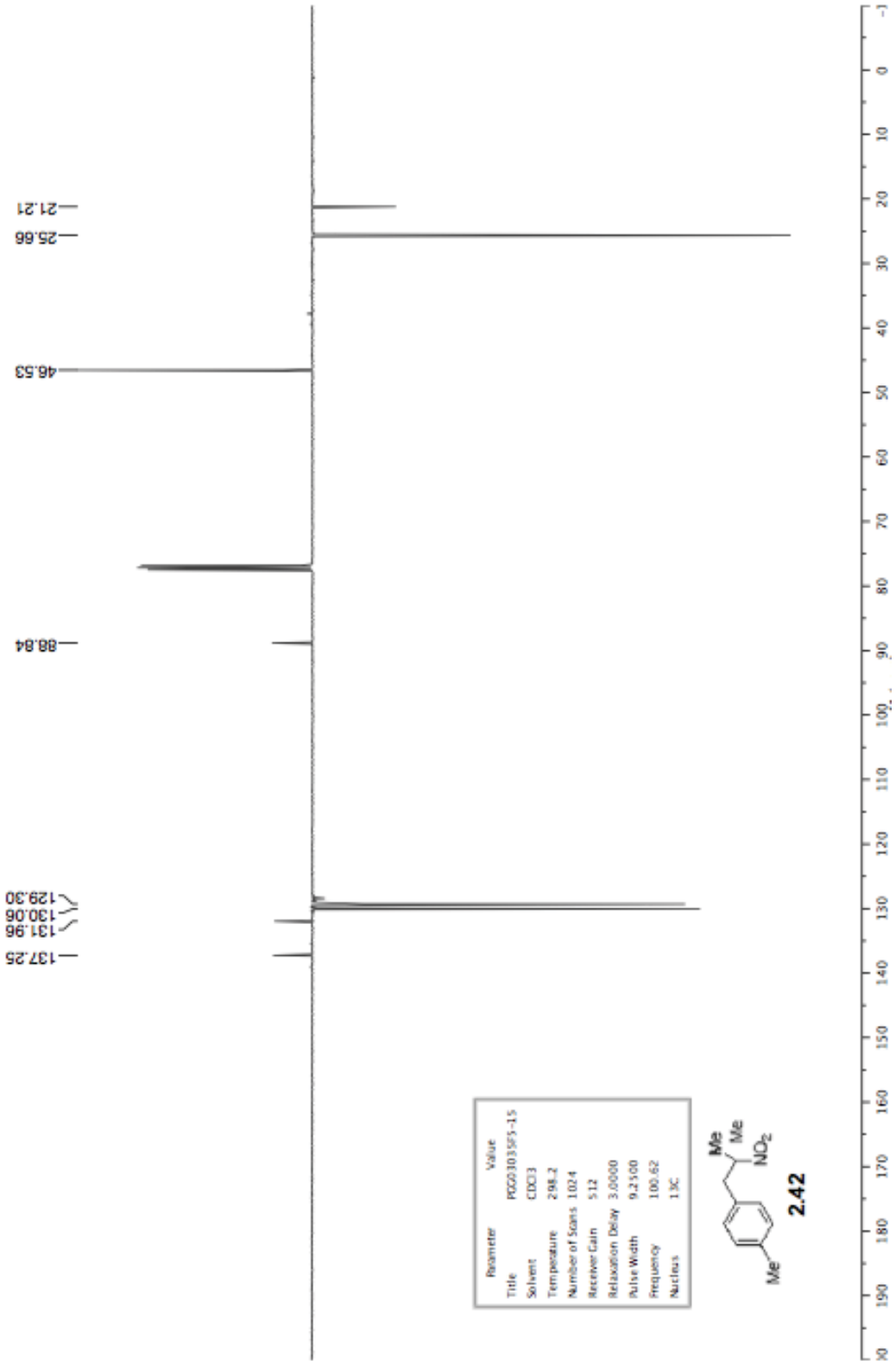

7.36
7.34
7.32
7.29
7.28
7.22
7.20
4.63
4.62
4.60
3.35
3.33
3.31
3.03
1.96
1.97
2.04
NO2
2.40

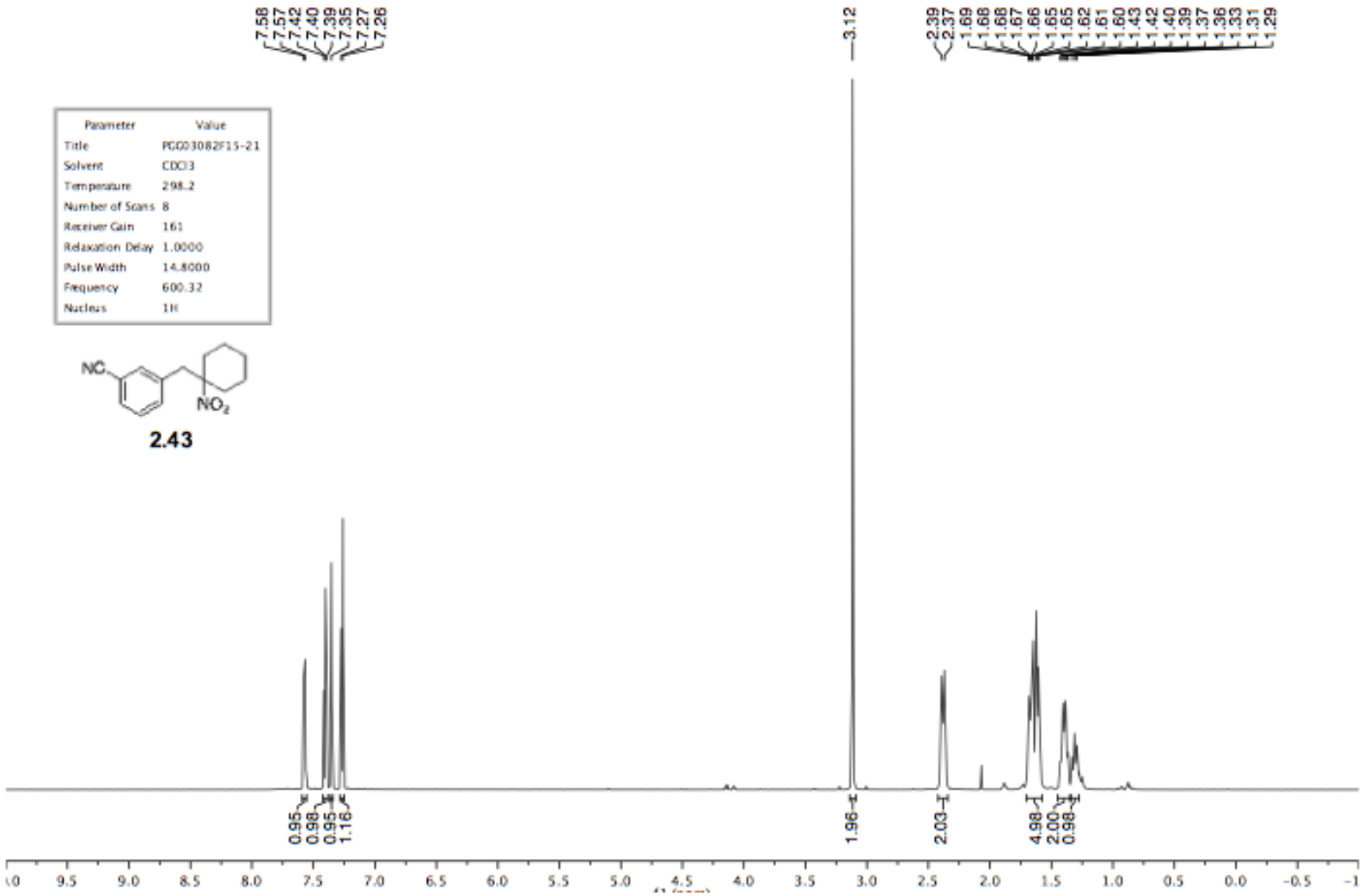

33.60
76.42
135.75
129.11
128.70
127.59
NO2
2.40

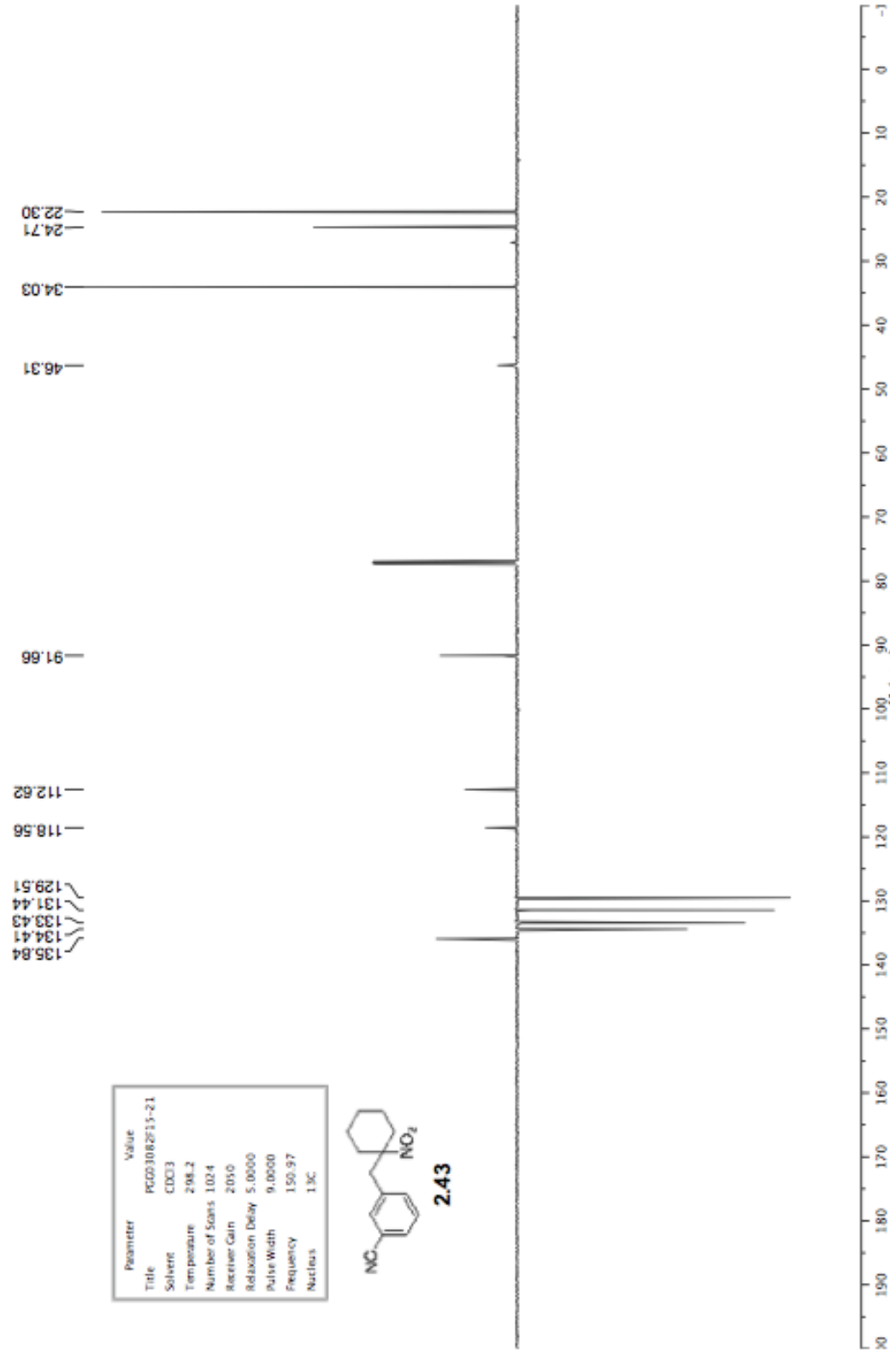
7.32
7.30
7.29
7.27
7.12
7.11
7.10
7.09
3.20
1.58
6.00
2.04
2.93
2.04
Parameter Value
Title PGD2279Isolated
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 10
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
Me
NO2
2.41

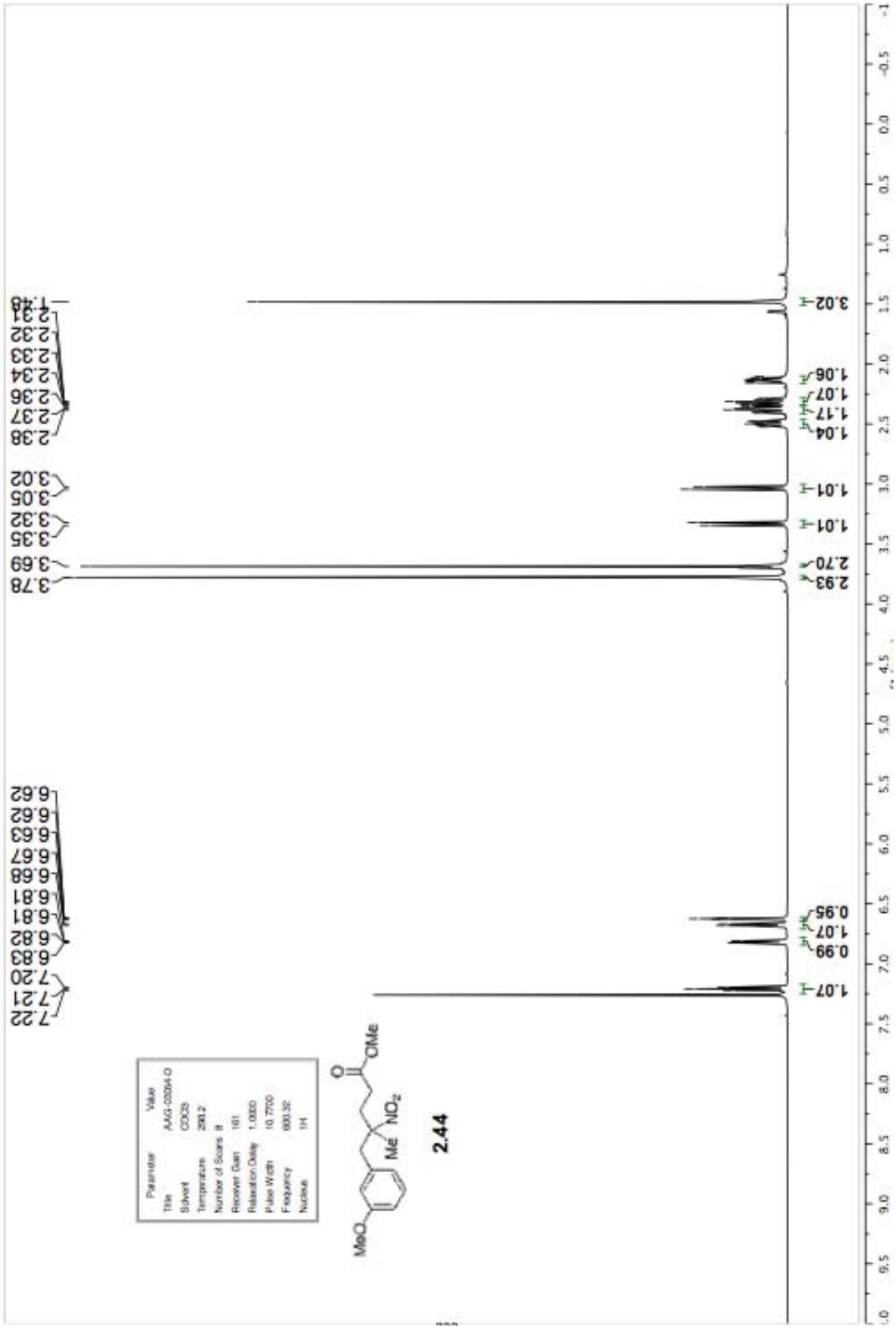

135.05
130.20
128.61
127.59
88.76
46.86
25.70
Parameter Value
Title PGD2279Aisolated
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
Me
NO2
2.41
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

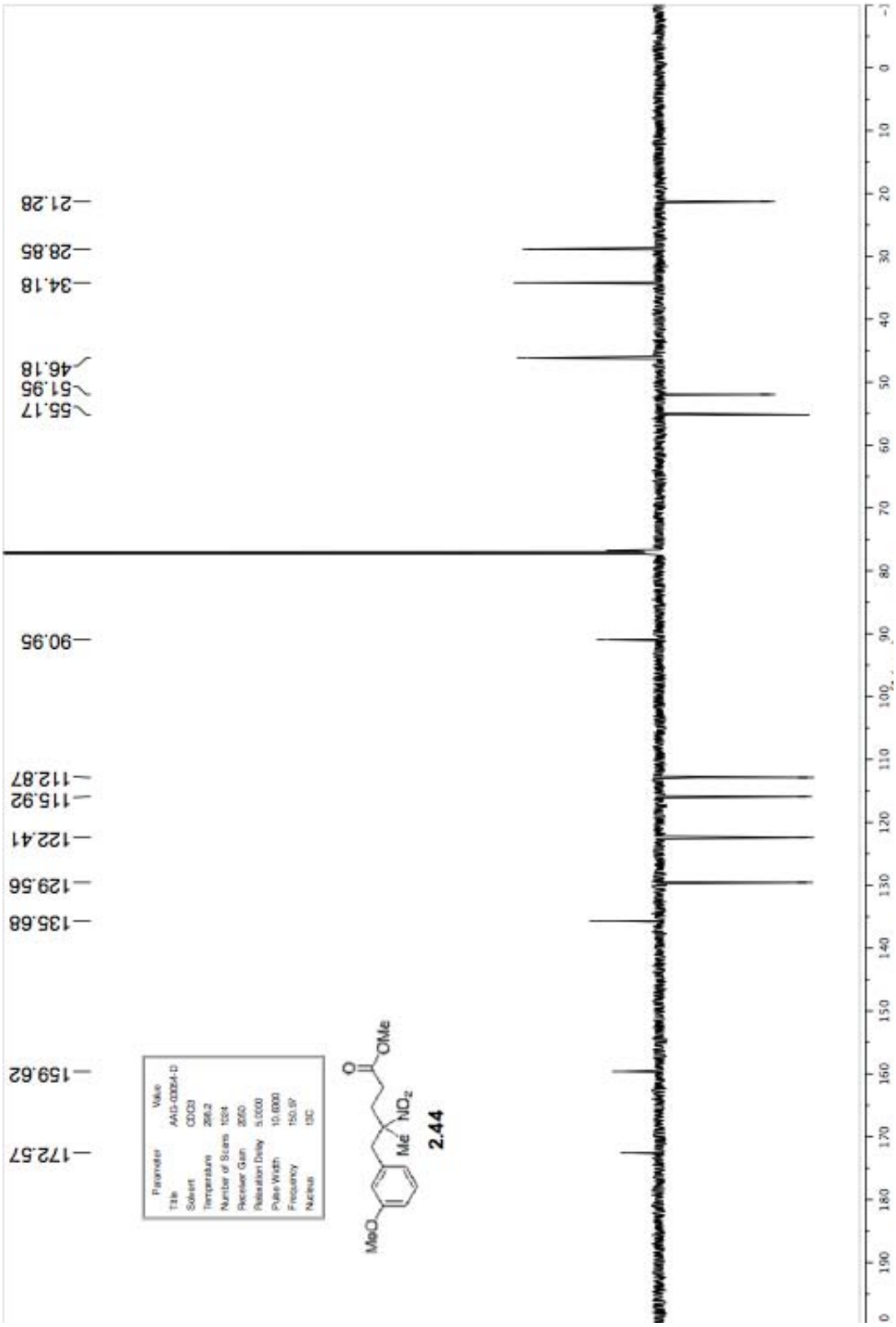
7.11
7.09
7.00
6.98
3.15
2.32
1.56
2.08
2.00
1.87
3.04
6.02
Parameter Value
Title PDD0303SF5-1S
Solvent CDCl3
Temperature 298.2
Number of Scans 64
Receiver Gain 14
Relaxation Delay 6.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
Me
NO2
Me
2.42

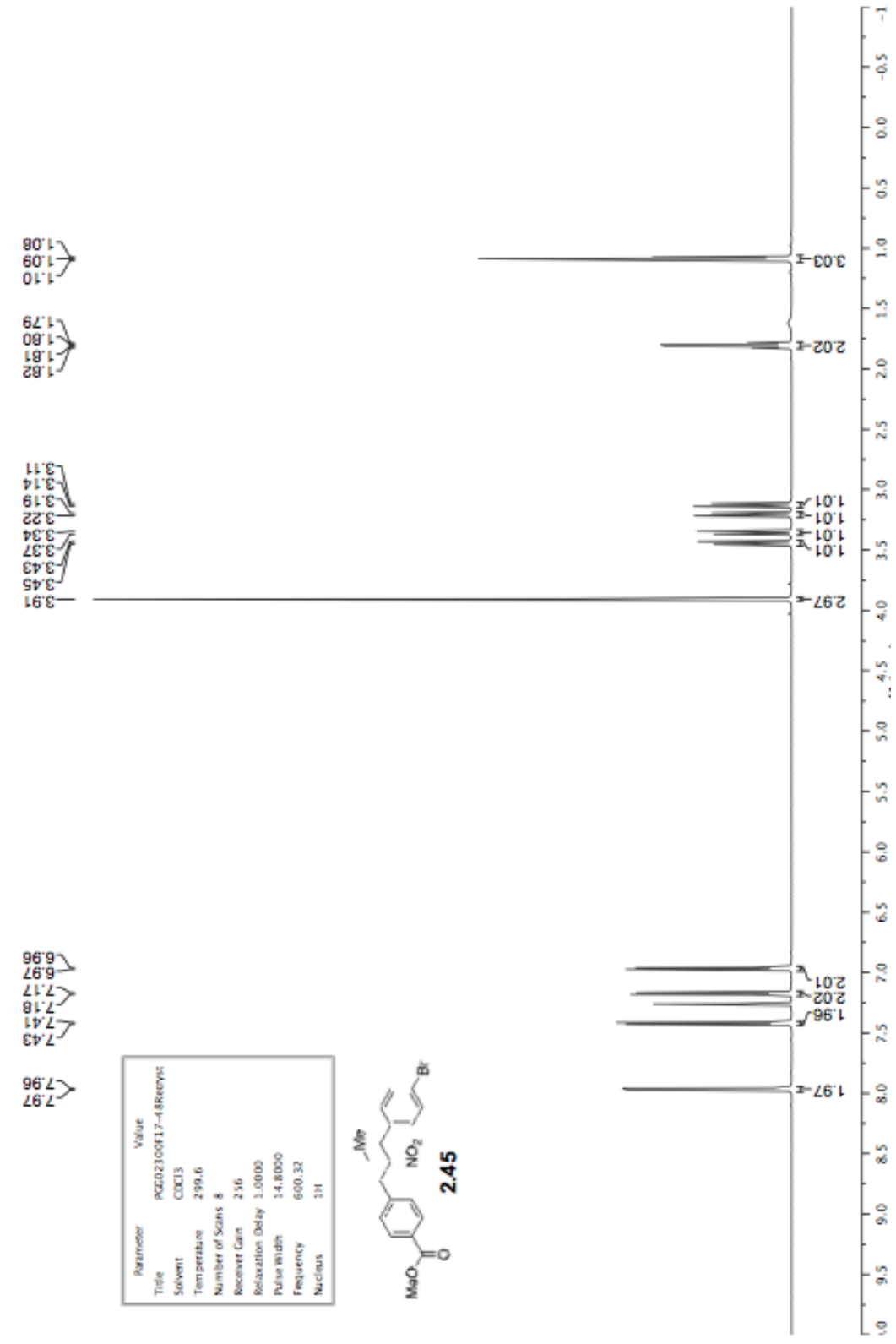

21.21
25.66
46.53
88.84
129.30
130.06
131.96
137.25
Parameter Value
Title PDG030SPS-15
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
Me
NO2
Me
2.42


7.58
7.57
7.42
7.40
7.39
7.35
7.27
7.26
3.12
2.39
2.37
1.69
1.68
1.68
1.67
1.66
1.65
1.65
1.62
1.61
1.60
1.43
1.42
1.40
1.39
1.37
1.36
1.33
1.31
1.29
Parameter Value
Title PGD030820F15-21
Solvent CDCl3
Temperature 298.2
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 14.8000
Frequency 600.32
Nucleus 1H
NC
NO2
2.43
0.95
0.98
0.95
1.16
1.96
2.03
4.98
2.00
0.98


22.30
24.71
34.03
46.31
91.66
112.62
118.56
129.51
131.44
133.43
134.41
135.84
Parameter Value
Title PGD3082F15-21
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 9.0000
Frequency 150.97
Nucleus 13C
NC
NO2
2.43


Parameter Value
Title AAG-03264-D
Solvent CDCl3
Temperature 298.2
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.52
Nucleus 1H
2.44
MeO
Me
NO2
OMe
O
7.22
7.21
7.20
6.83
6.82
6.81
6.81
6.68
6.67
6.63
6.62
6.62
3.78
3.69
3.35
3.32
3.05
3.02
2.38
2.37
2.36
2.34
2.33
2.32
2.31
1.48
1.07
0.95
0.99
1.07
3.02
1.06
1.07
1.17
1.04
1.01
1.01
2.70
2.93


172.57
159.62
135.68
129.56
122.41
115.92
112.87
90.95
55.17
51.95
46.18
34.18
28.85
21.28
Parameter Value
Title AAS-03824-1
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.91
Nucleus 13C
MeO
Me
NO2
OMe
O
2.44


Parameter Value
Title PGD02300F17-48Recryst
Solvent CDCl3
Temperature 299.6
Number of Scans 8
Receiver Gain 256
Relaxation Delay 1.0000
Pulse Width 14.8000
Frequency 600.32
Nucleus 1H
Me
NO2
Br
MeO
O
2.45
7.97
7.96
7.43
7.41
7.18
7.17
6.97
6.96
3.91
3.45
3.43
3.37
3.34
3.22
3.19
3.14
3.11
1.82
1.81
1.80
1.79
1.10
1.09
1.08
1.97
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2.02
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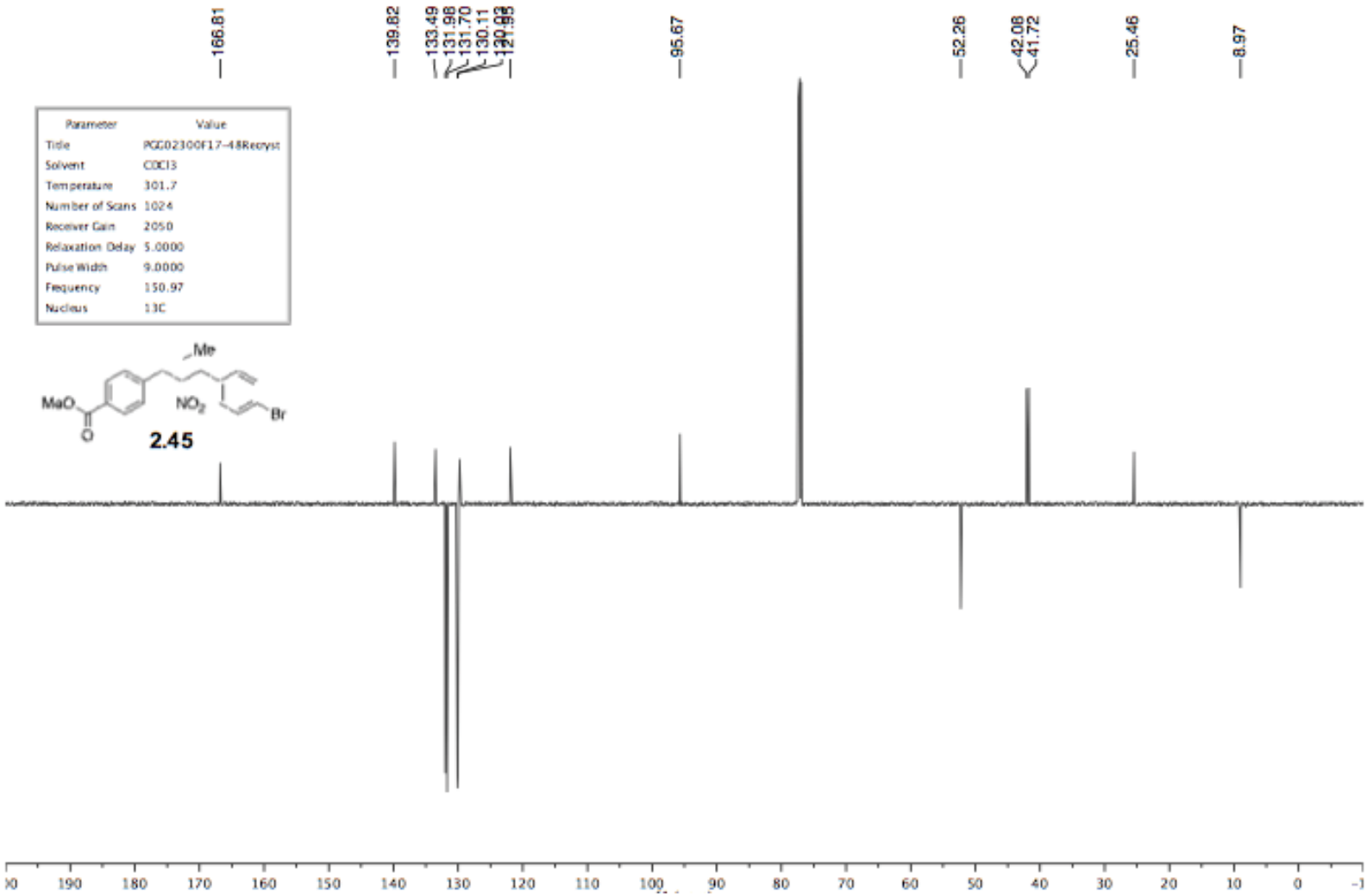
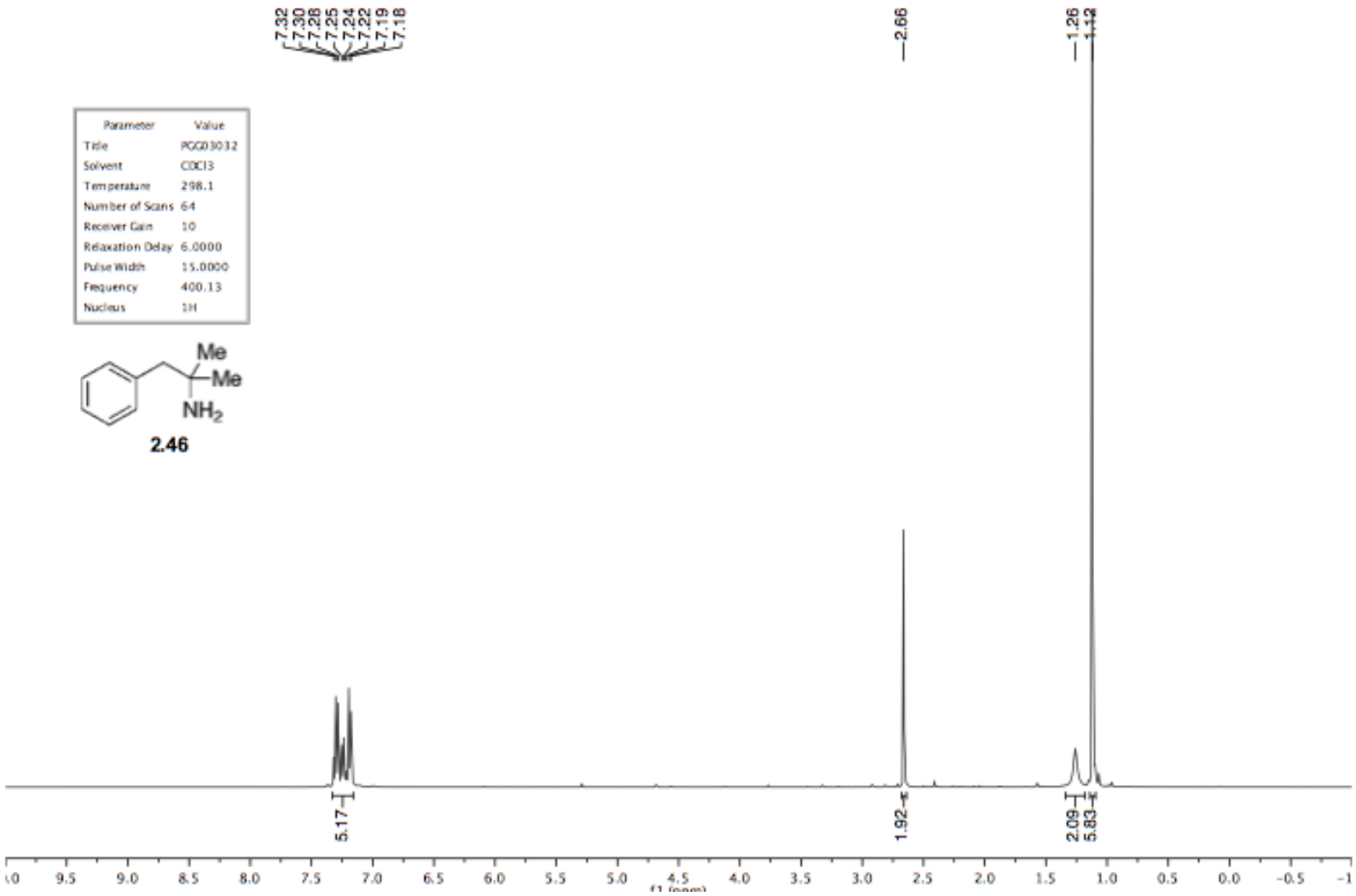
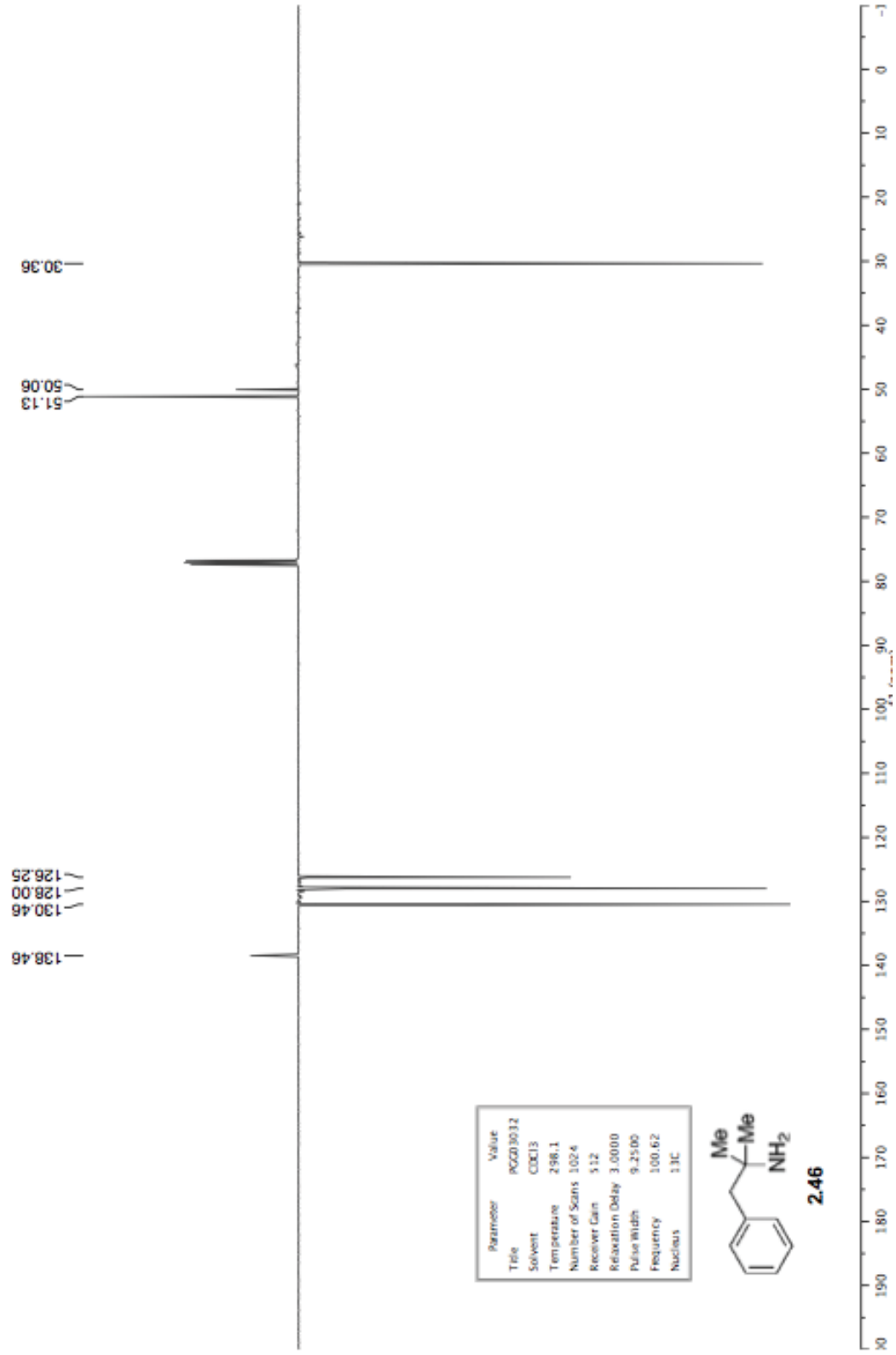
1.01
1.01
1.01
1.01
3.03
2.02

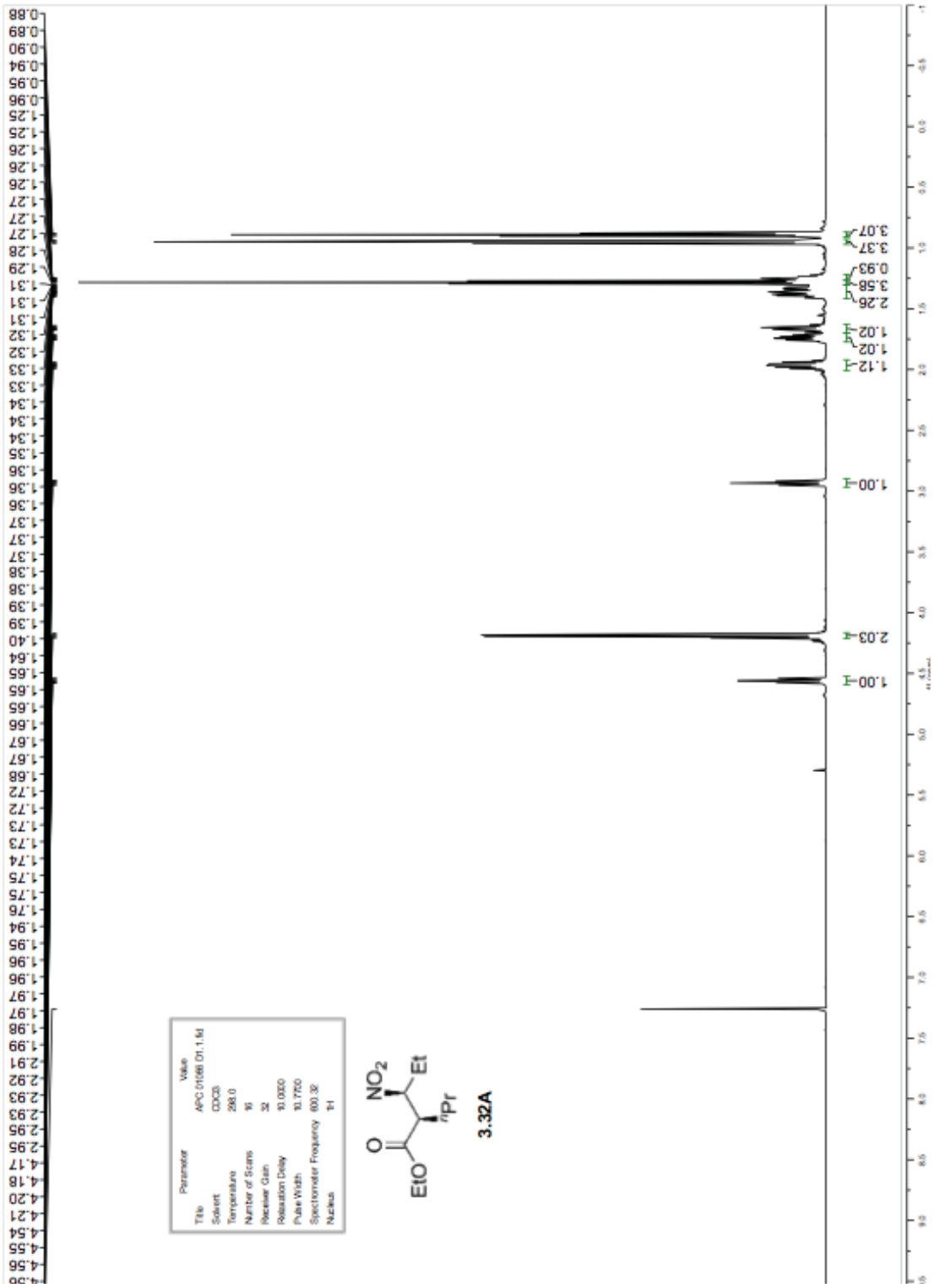

166.81
139.82
133.49
131.98
131.70
130.11
95.67
52.26
42.08
41.72
25.46
8.97
Parameter Value
Title PGD0230OF17-48Recryst
Solvent CDCl3
Temperature 301.7
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 9.0000
Frequency 150.97
Nucleus 13C
Me
MeO
NO2
Br
O
2.45
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

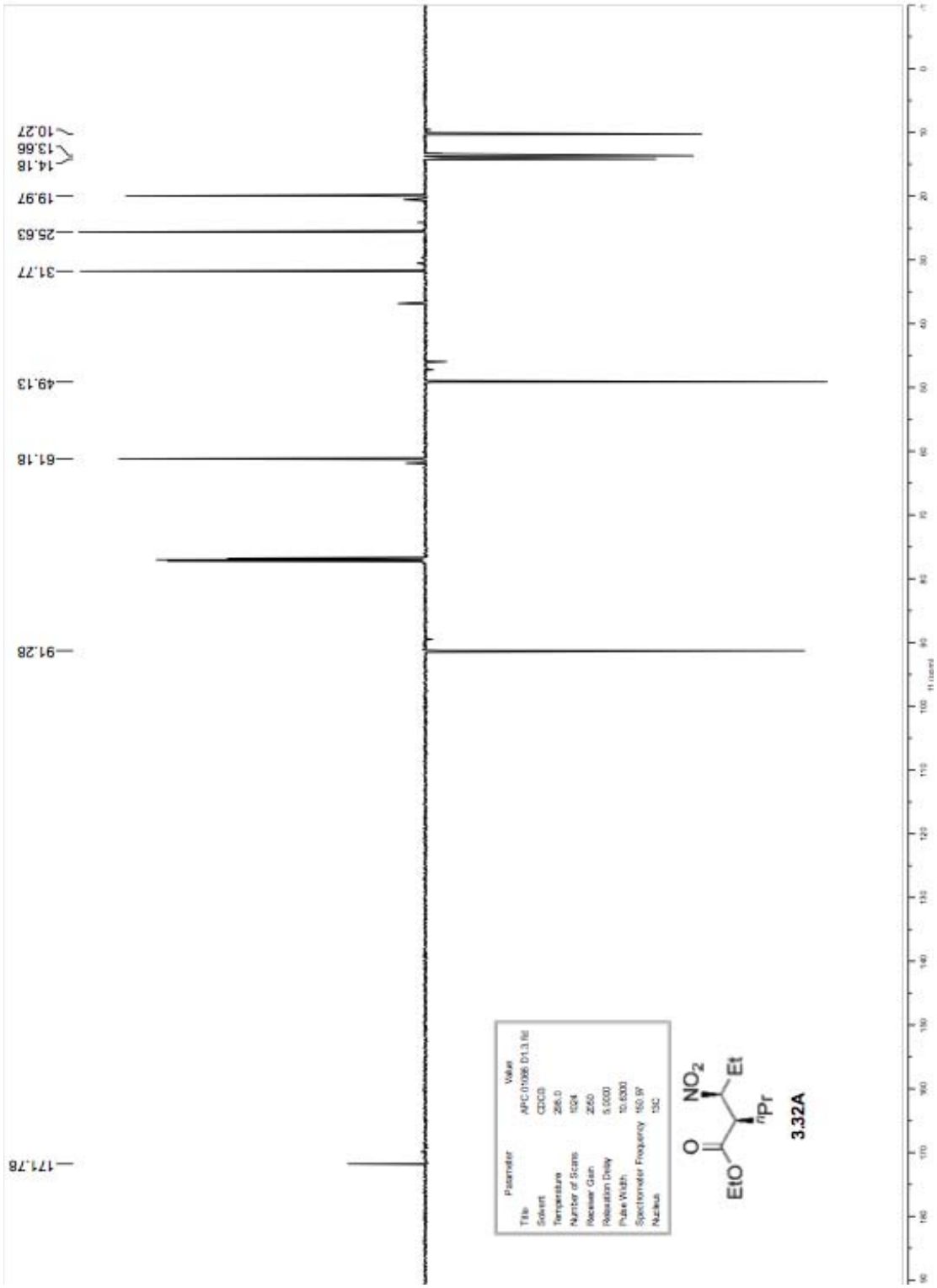

7.32
7.30
7.28
7.25
7.24
7.22
7.19
7.18
2.66
1.26
1.12
Parameter Value
Title PGCD3032
Solvent CDCl3
Temperature 298.1
Number of Scans 64
Receiver Gain 10
Relaxation Delay 6.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
Me
Me
NH2
2.46
5.17
1.92
2.09
5.83
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

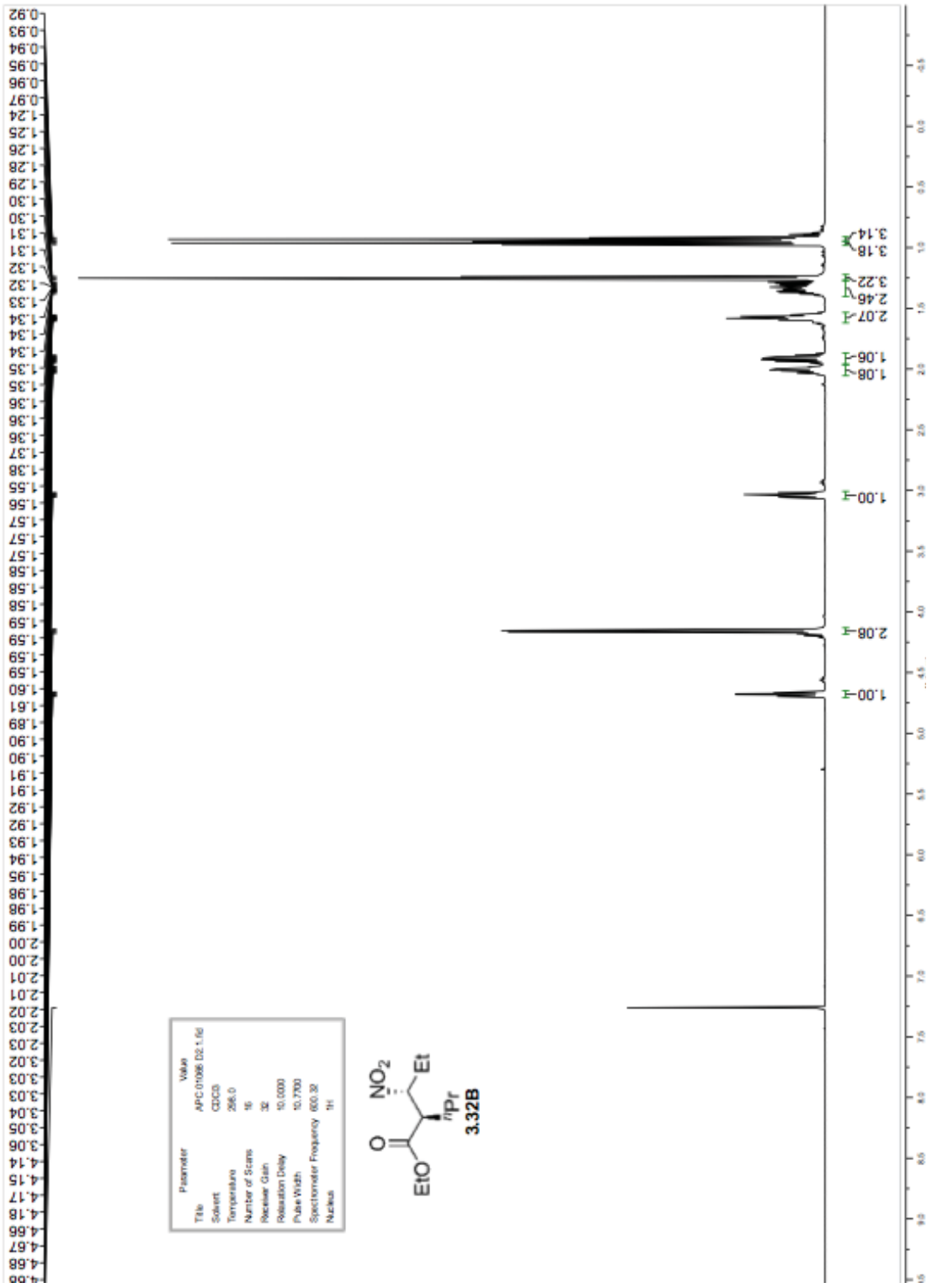

30.36
51.13
50.06
126.25
128.00
130.46
138.46
Parameter Value
Title PGD3032
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
Me
NH2
2.46

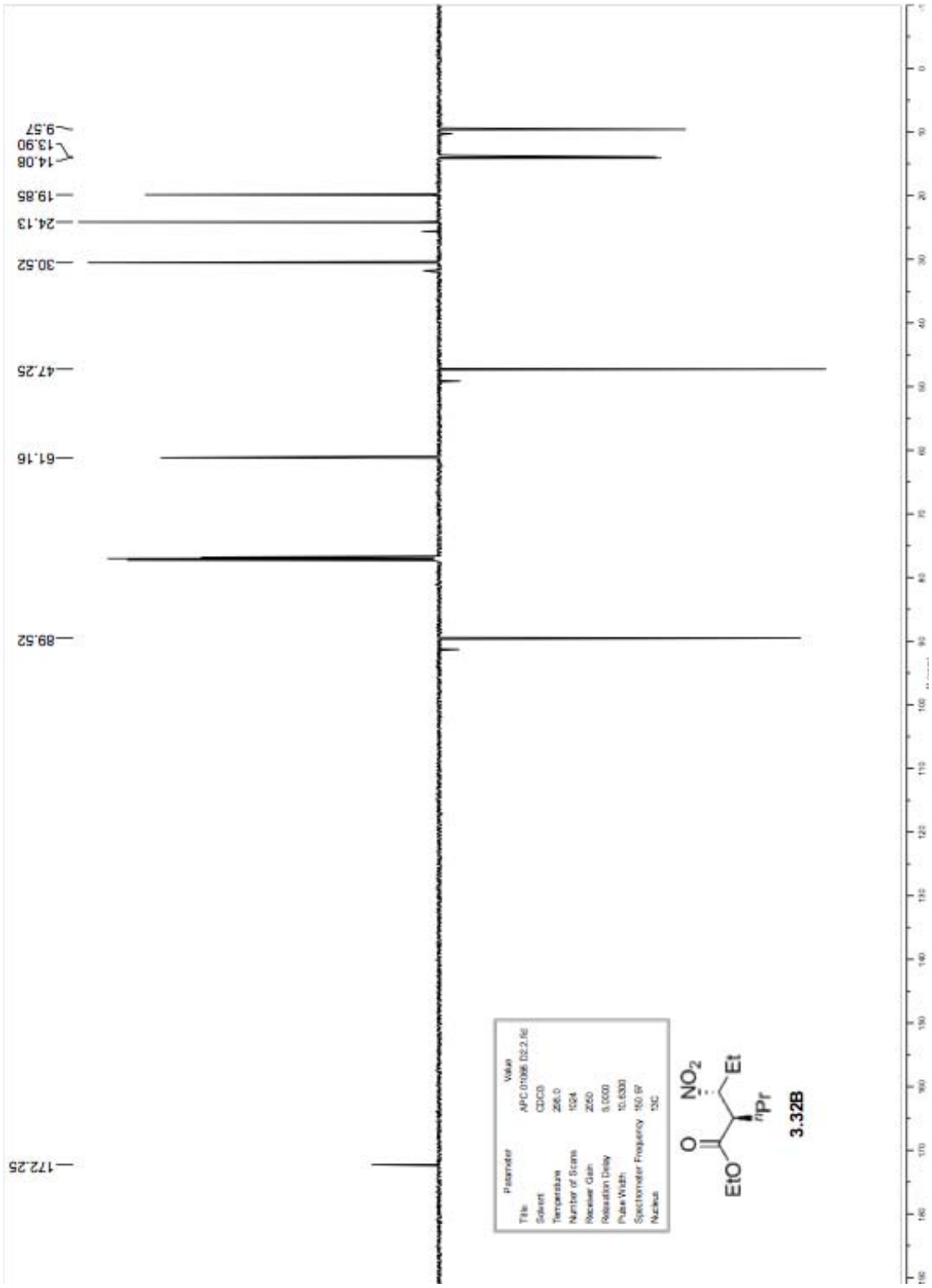
Appendix B

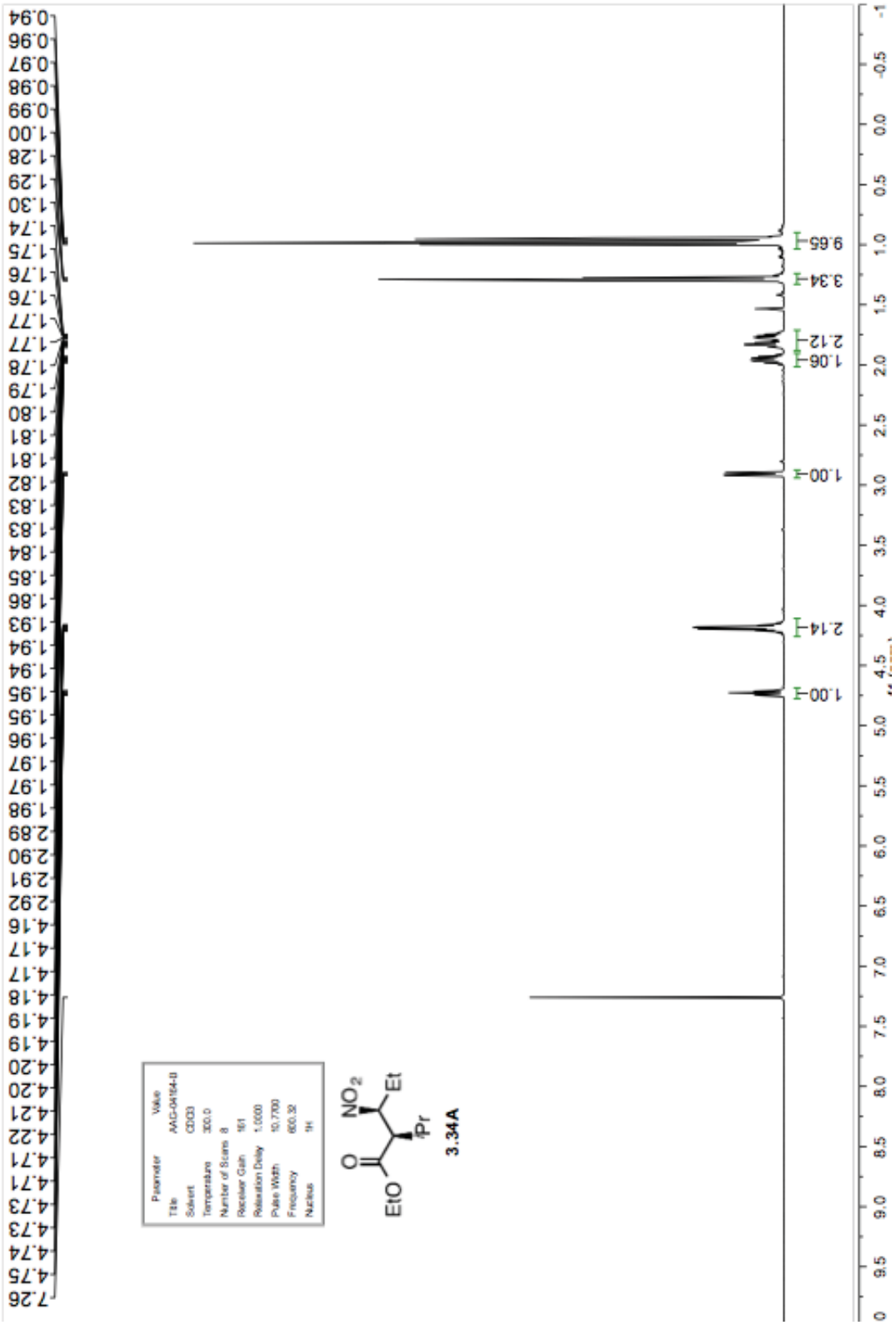
SPECTRAL DATA FOR CHAPTER 3

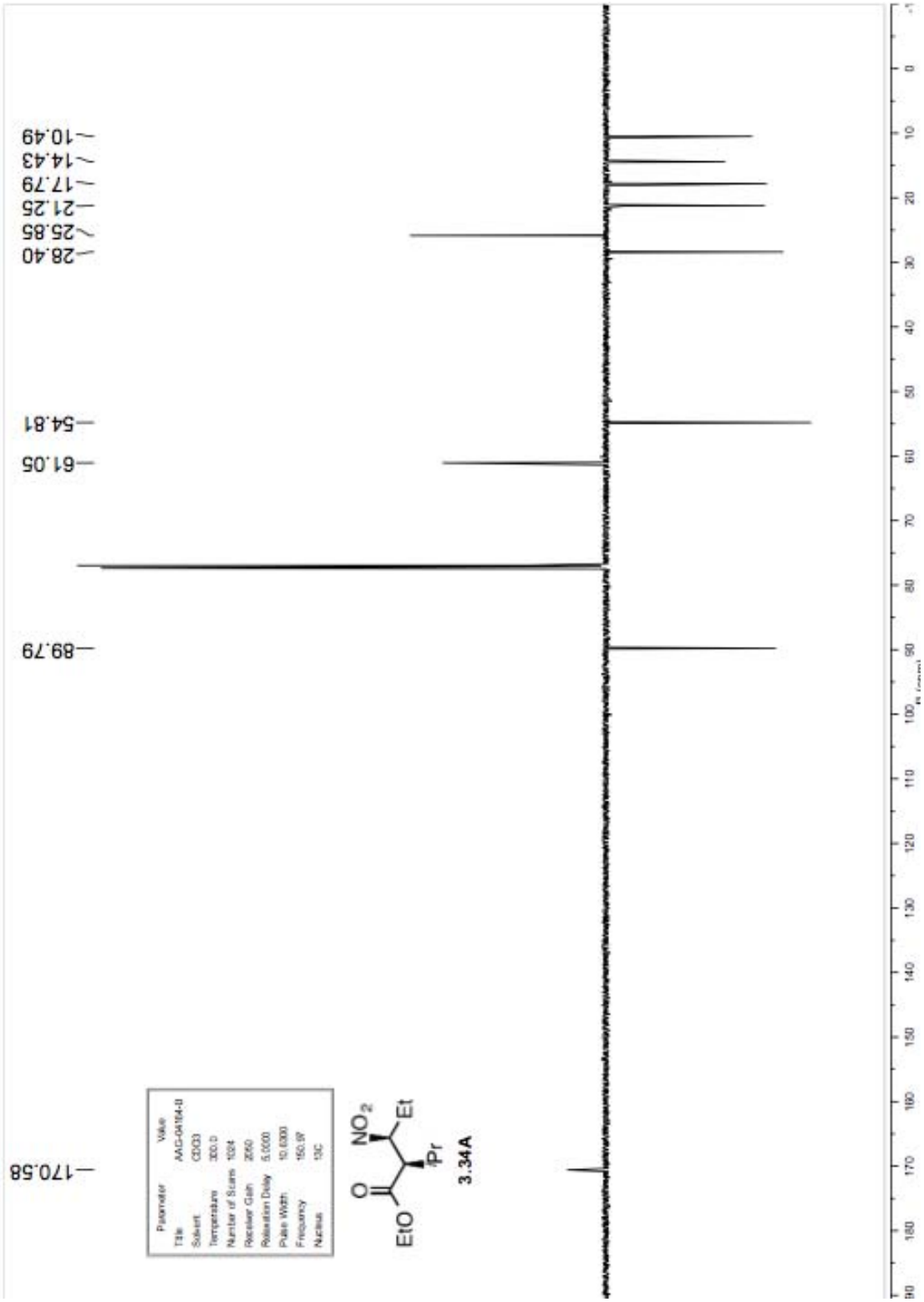

3.07
3.37
0.93
3.58
2.26
1.02
1.02
1.12
1.00
2.03
1.00
Parameter Value
Title APC 01066 D1 1 fid
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 32
Relaxation Delay 10.0000
Pulse Width 10.7700
Spectrometer Frequency 600.32
Nucleus 1H
O
NO2
Et
EtO
nPr
3.32A

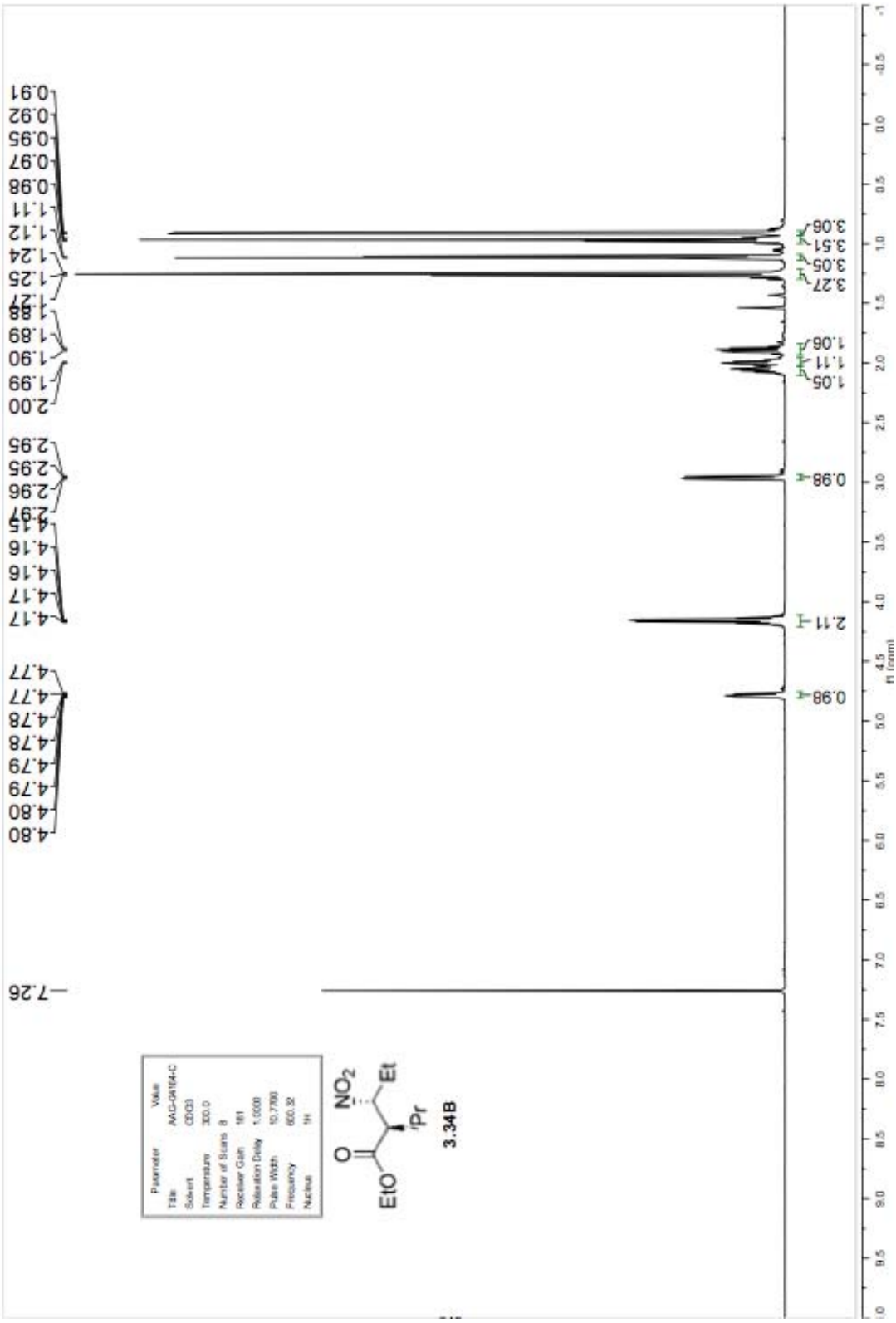

10.27
13.66
14.18
19.97
25.63
31.77
49.13
61.18
91.28
171.78
Parameter Value
Title APC-01006 D13.fid
Solvent CDCl3
Temperature 295.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Spectrometer Frequency 150.91
Nucleus 13C
O
NO2
Et
EtO
nPr
3.32A

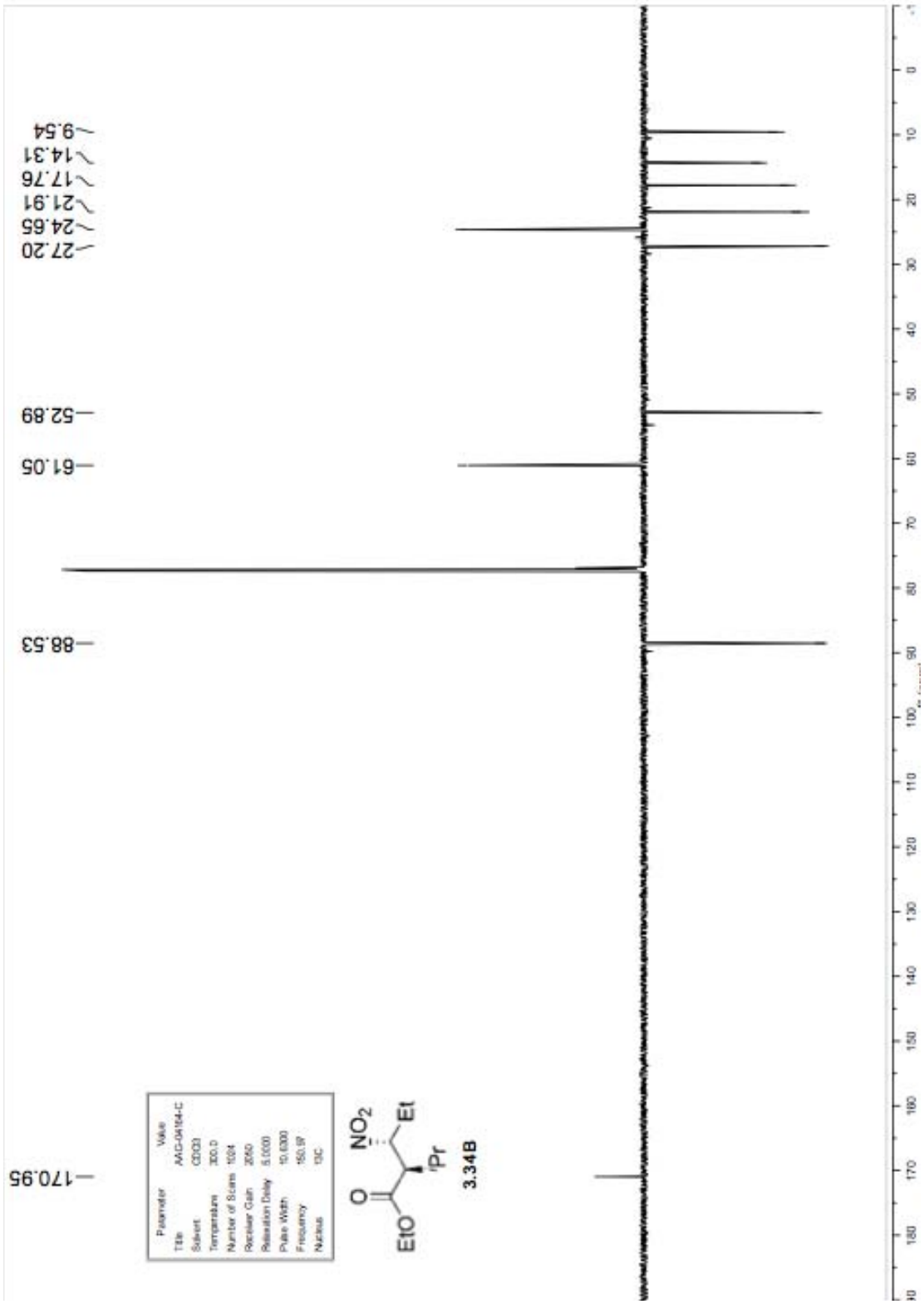

Parameter Value
Title APC-01008 (02.1.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 32
Relaxation Delay 10.0000
Pulse Width 10.7000
Spectrometer Frequency 600.32
Nucleus 1H
3.14
3.18
3.22
2.46
2.07
1.08
1.06
1.00
2.08
1.00
EtO
O
NO2
Et
nPr
3.32B

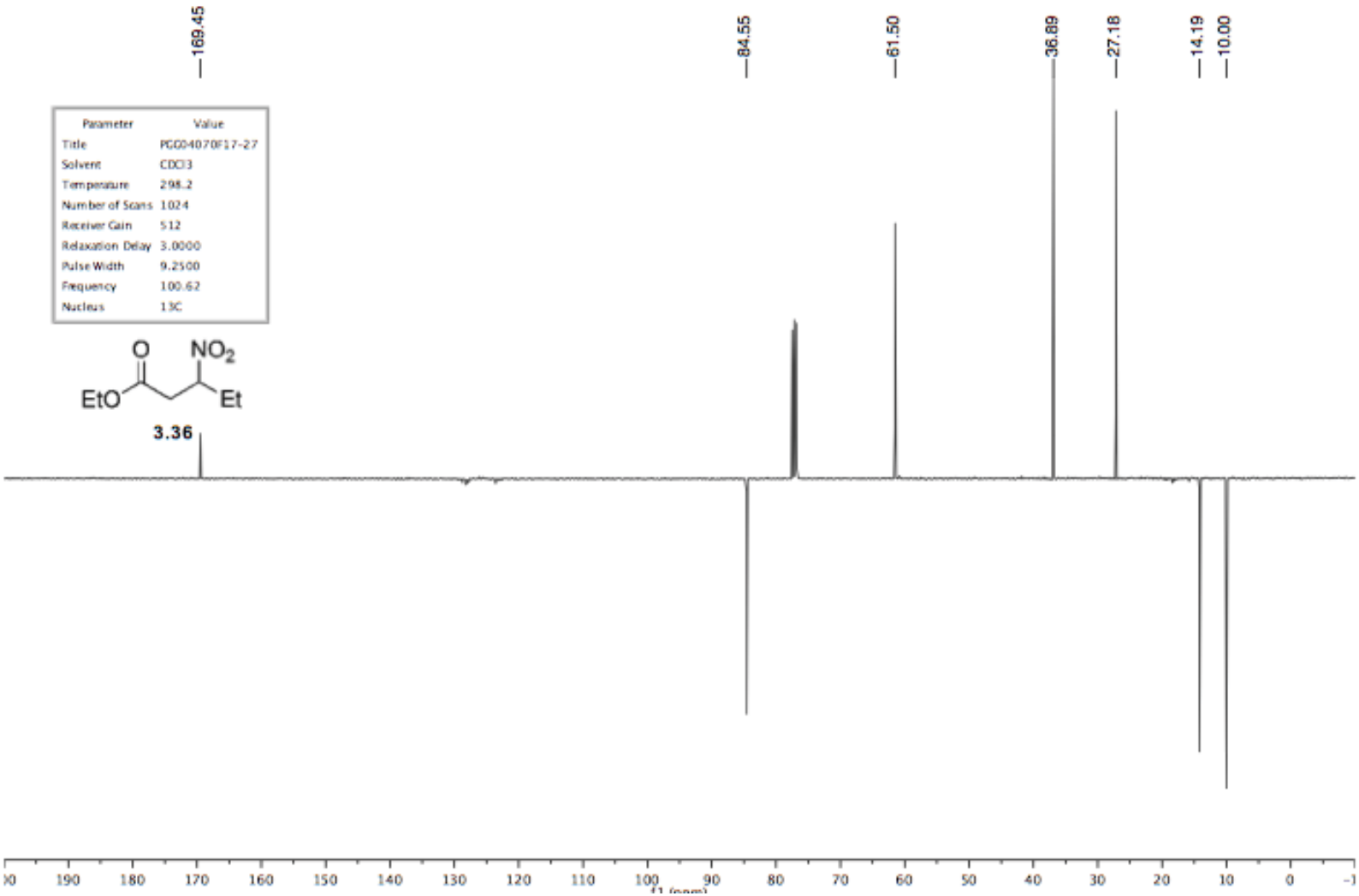

9.57
13.90
14.08
19.85
24.13
30.52
47.25
61.16
89.52
172.25
Parameter Value
Title APC-01096 D2-3-fid
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 3.0000
Pulse Width 10.6300
Spectrometer Frequency 150.87
Nucleus 13C
O
NO2
Et
EtO
nPr
3.32B

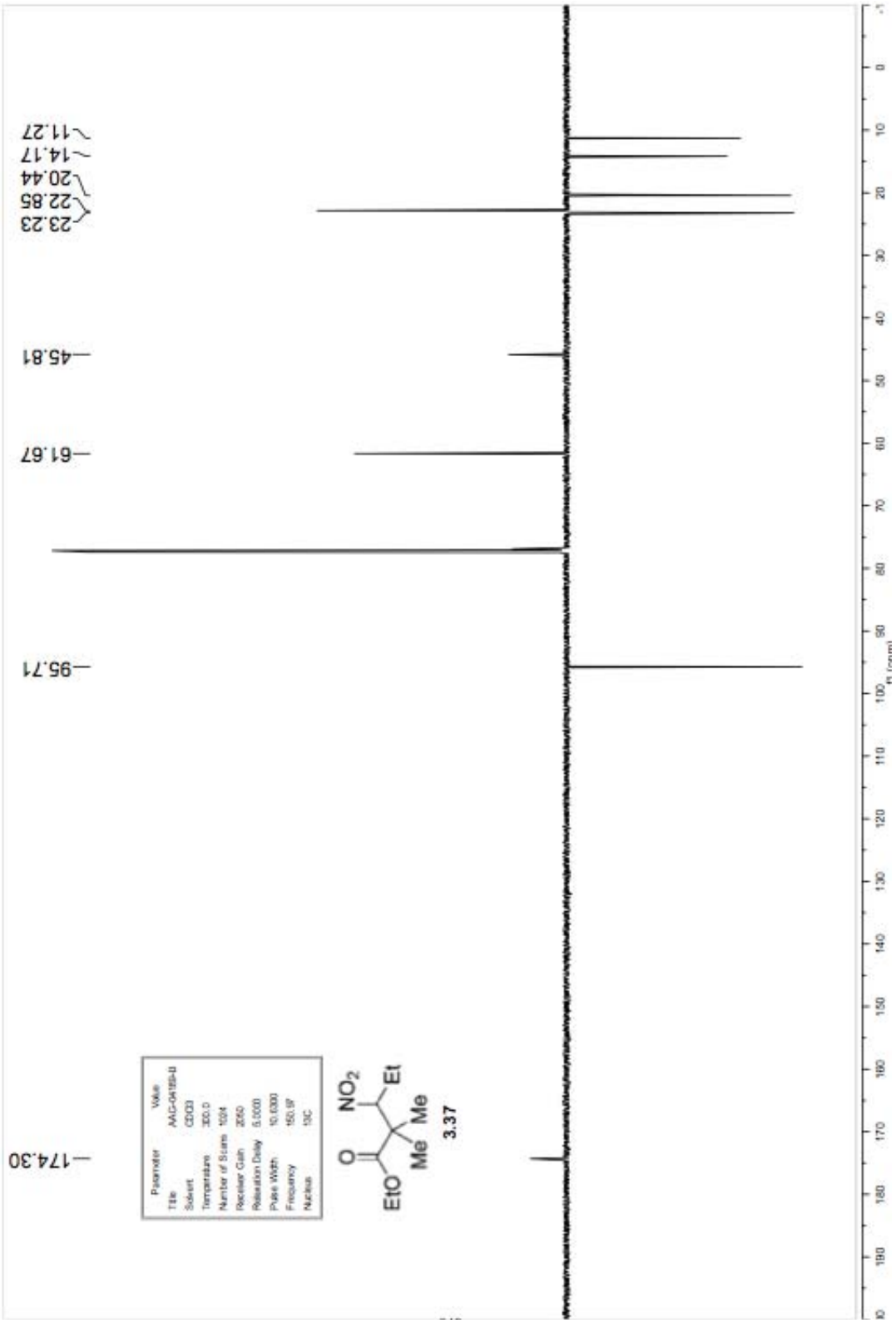

Parameter Value
Title AAG-04164-B
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
NO2
Et
iPr
O
EtO
3.34A
9.65
3.34
2.12
1.06
1.00
2.14
1.00

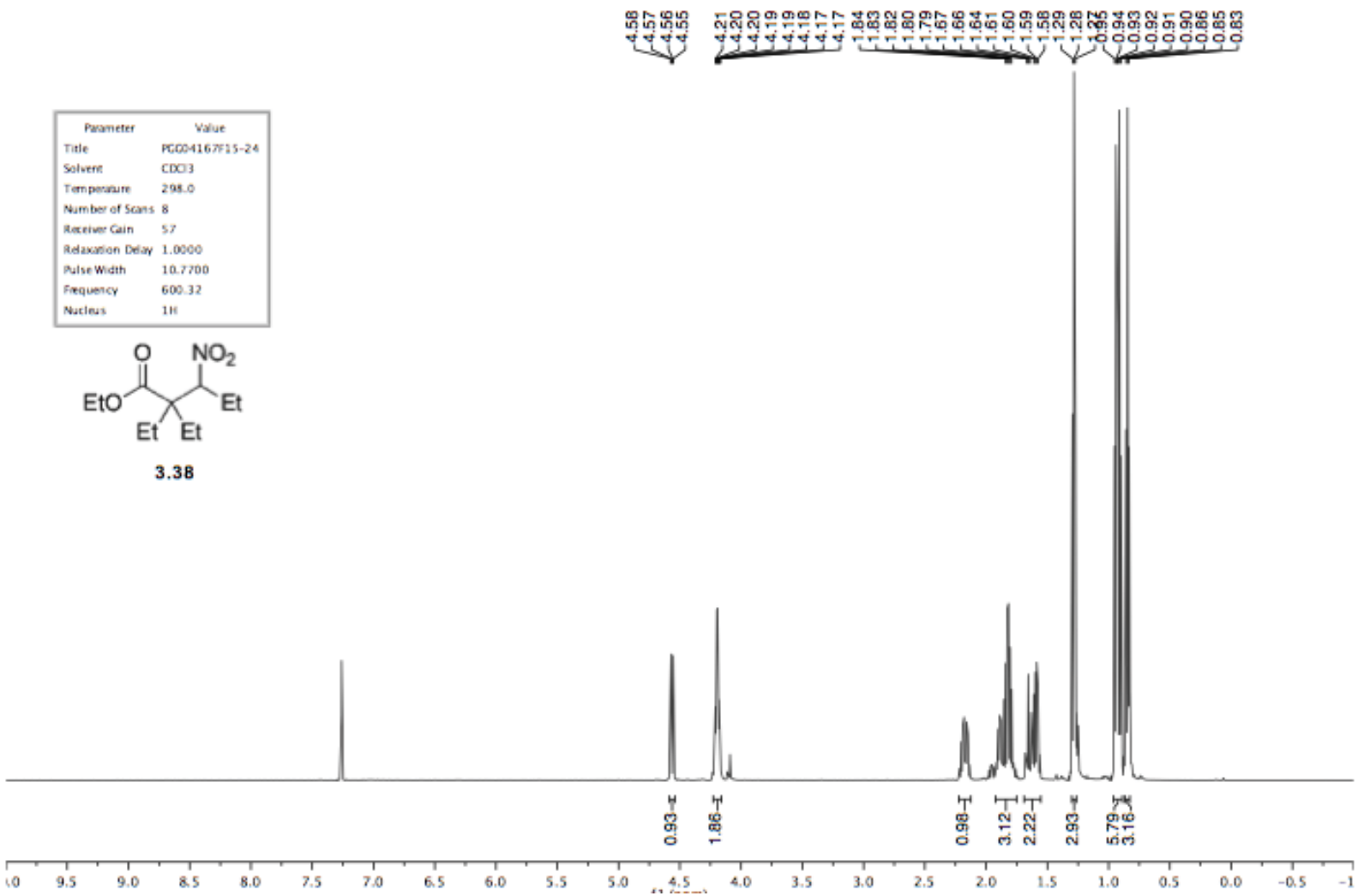

10.49
14.43
17.79
21.25
25.85
28.40
54.81
61.05
89.79
170.58
Parameter Value
Title AAG-04164-II
Solvent CDCl3
Temperature 300.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.97
Nucleus 13C
NO2
Et
iPr
O
EtO
3.34A


Parameter Value
Title AAG-04164-C
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7300
Frequency 660.32
Nucleus 1H
NO2
Et
iPr
O
EtO
3.34B
7.26
4.80
4.80
4.79
4.79
4.78
4.78
4.77
4.77
4.17
4.17
4.16
4.16
4.15
2.97
2.96
2.95
2.95
2.00
1.99
1.90
1.89
1.88
1.27
1.25
1.24
1.12
1.11
0.98
0.97
0.95
0.92
0.91
0.98
2.11
0.98
1.05
1.11
1.06
3.27
3.05
3.51
3.06
f1 (ppm)


170.95
88.53
61.05
52.89
27.20
24.65
21.91
17.76
14.31
9.54
Parameter Value
Title AAC-04164-C
Solvent CDCl3
Temperature 300.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.91
Nucleus 13C
EtO
O
NO2
Et
iPr
3.34B


169.45
84.55
61.50
36.89
27.18
14.19
10.00
Parameter Value
Title PGD04070F17-27
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
NO2
EtO
Et
3.36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1


174.30
95.71
61.67
45.81
23.23
22.85
20.44
14.17
11.27
Parameter Value
Title AAG-04189-II
Solvent CDCl3
Temperature 300.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0300
Frequency 150.97
Nucleus 13C
NO2
Et
O
EtO
Me
Me
3.37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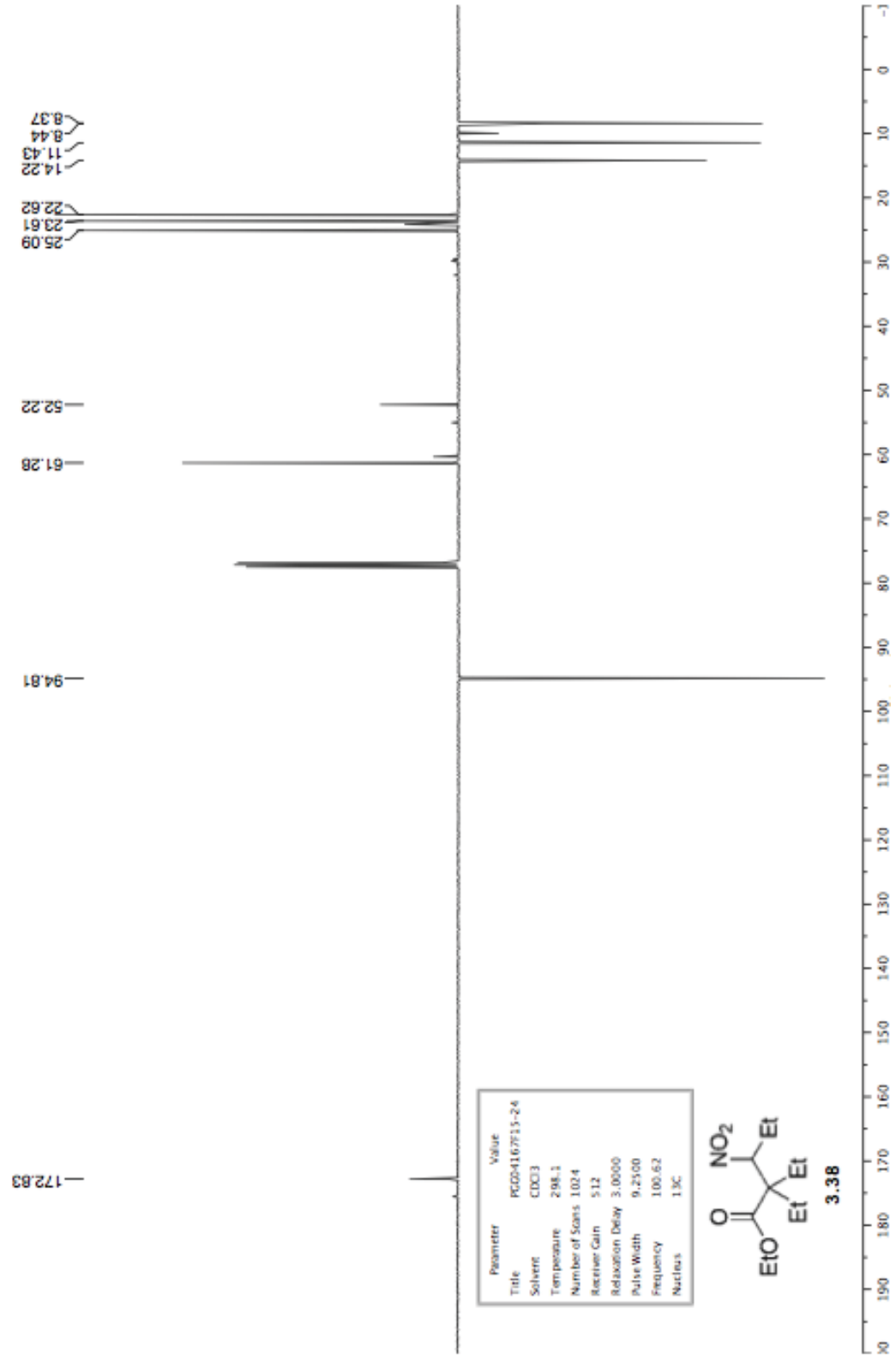
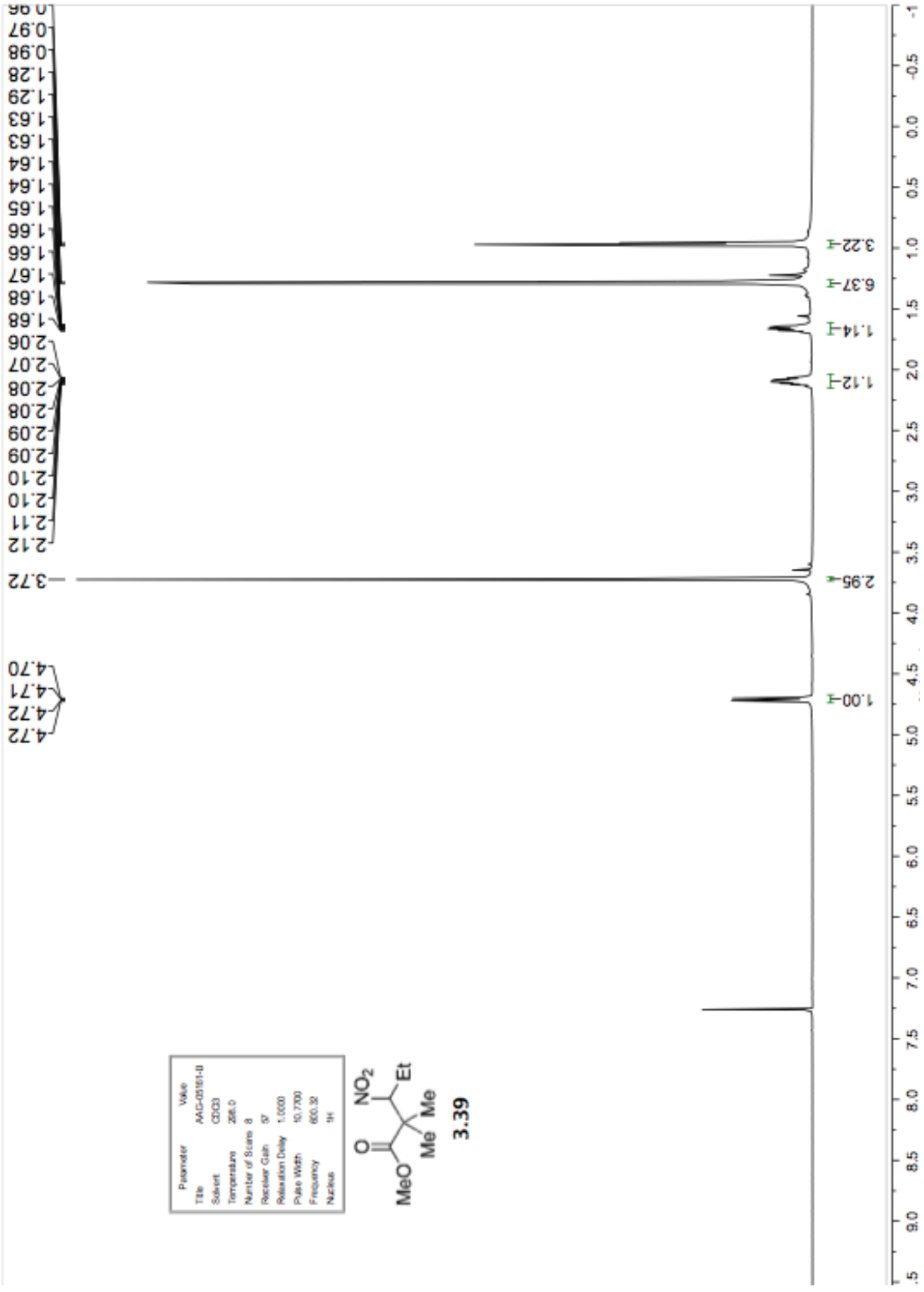
Title PGD04167F15-24
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
EtO
Et
Et
Et
3.38
4.58 4.57 4.56 4.55 4.21 4.20 4.20 4.19 4.19 4.18 4.17 4.17 1.84 1.83 1.82 1.80 1.79 1.67 1.66 1.64 1.61 1.60 1.59 1.58 1.29 1.28 0.95 0.94 0.93 0.92 0.91 0.90 0.86 0.85 0.83
0.93 1.86 0.98 3.12 2.22 2.93 5.79 3.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


172.83
94.81
61.28
52.22
25.09
23.61
22.62
14.22
11.43
8.44
8.37
Parameter Value
Title PGD-416.7f15-24
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtO
O
NO2
Et
Et
Et
3.38


Parameter Value
Title AAG-05161-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
NO2
Et
O
MeO
Me
Me
3.39
4.72
4.71
4.70
3.72
2.12
2.11
2.10
2.10
2.09
2.09
2.08
2.08
2.07
2.06
1.68
1.68
1.67
1.66
1.66
1.65
1.64
1.64
1.63
1.63
1.29
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0.96
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2.95
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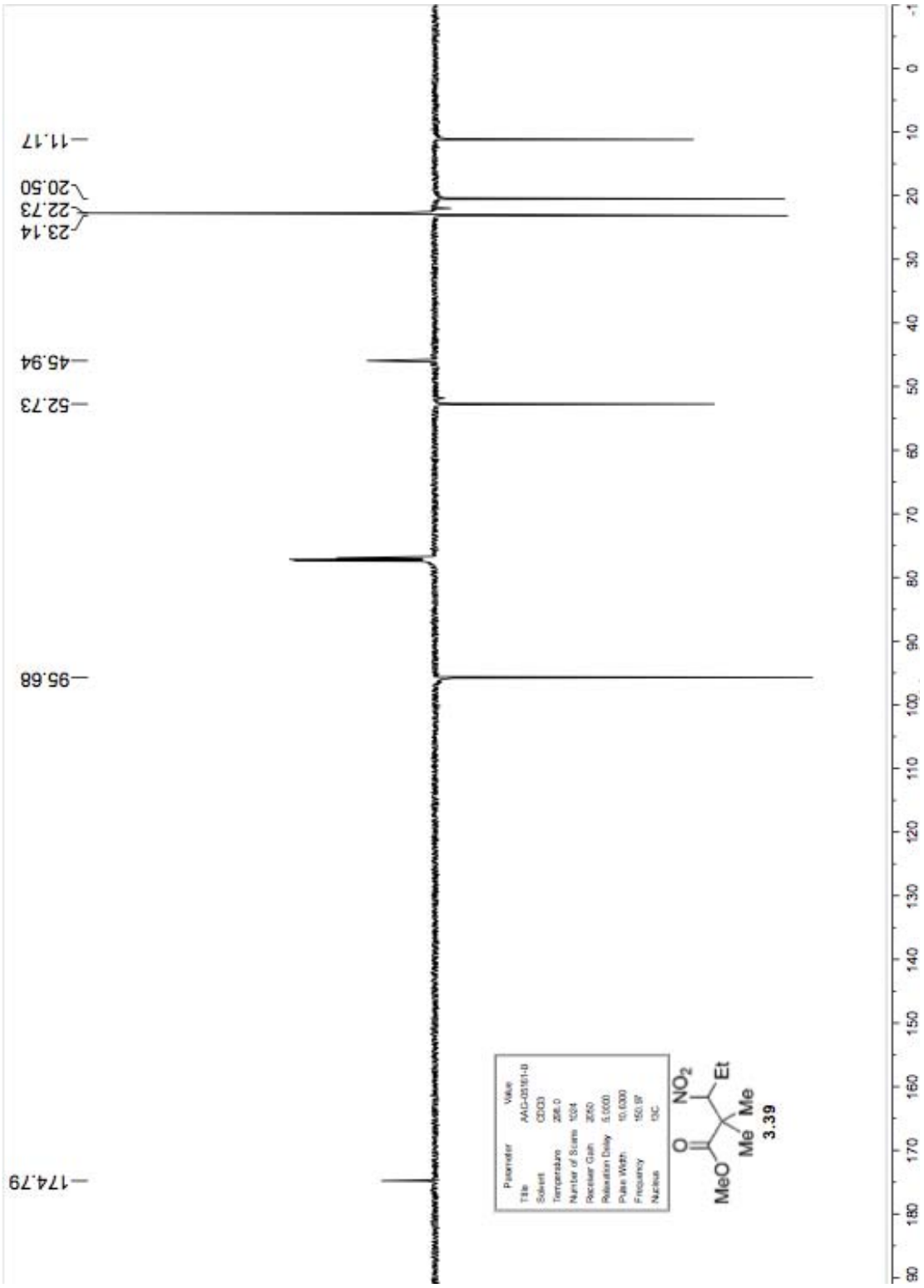
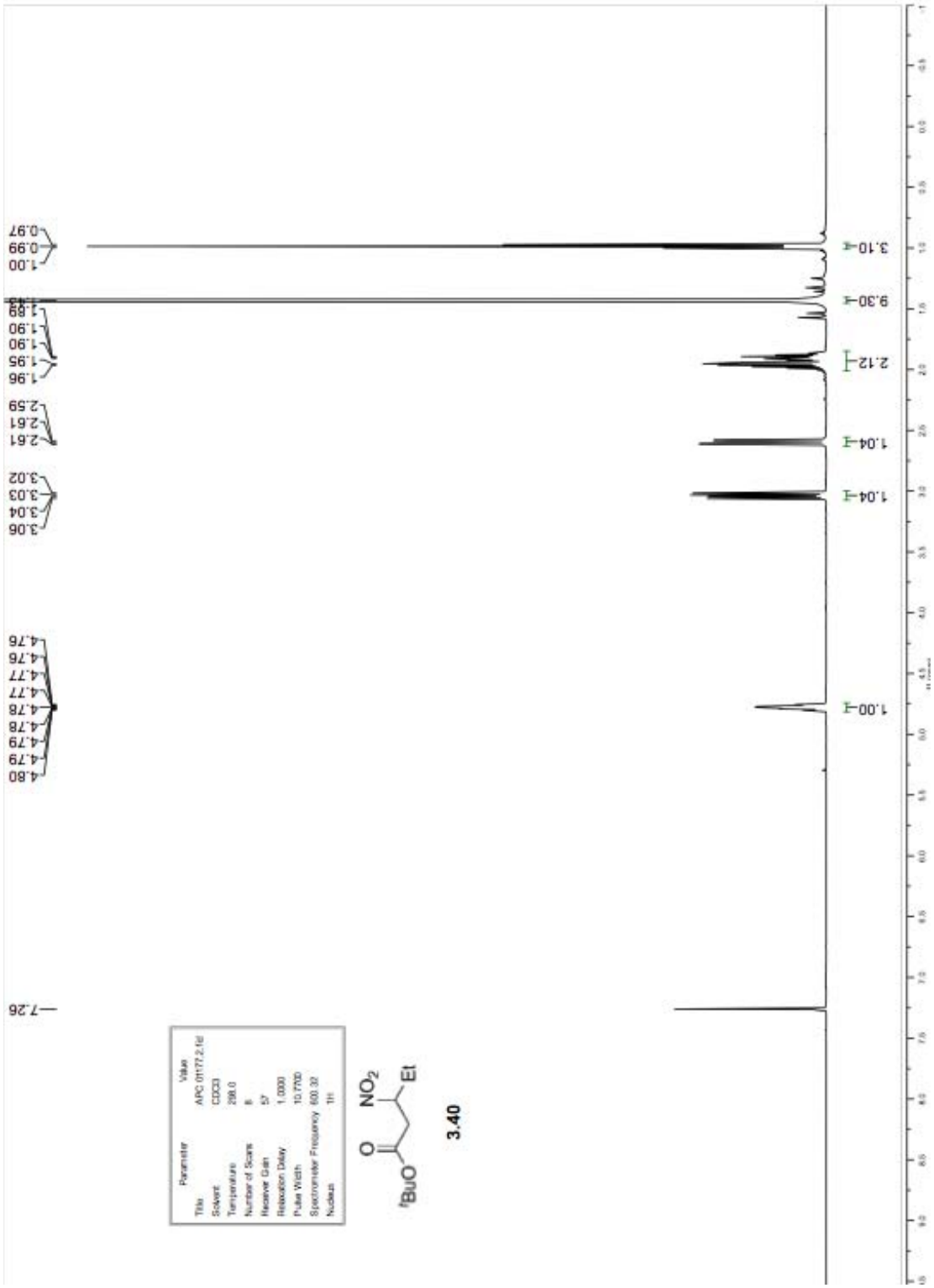
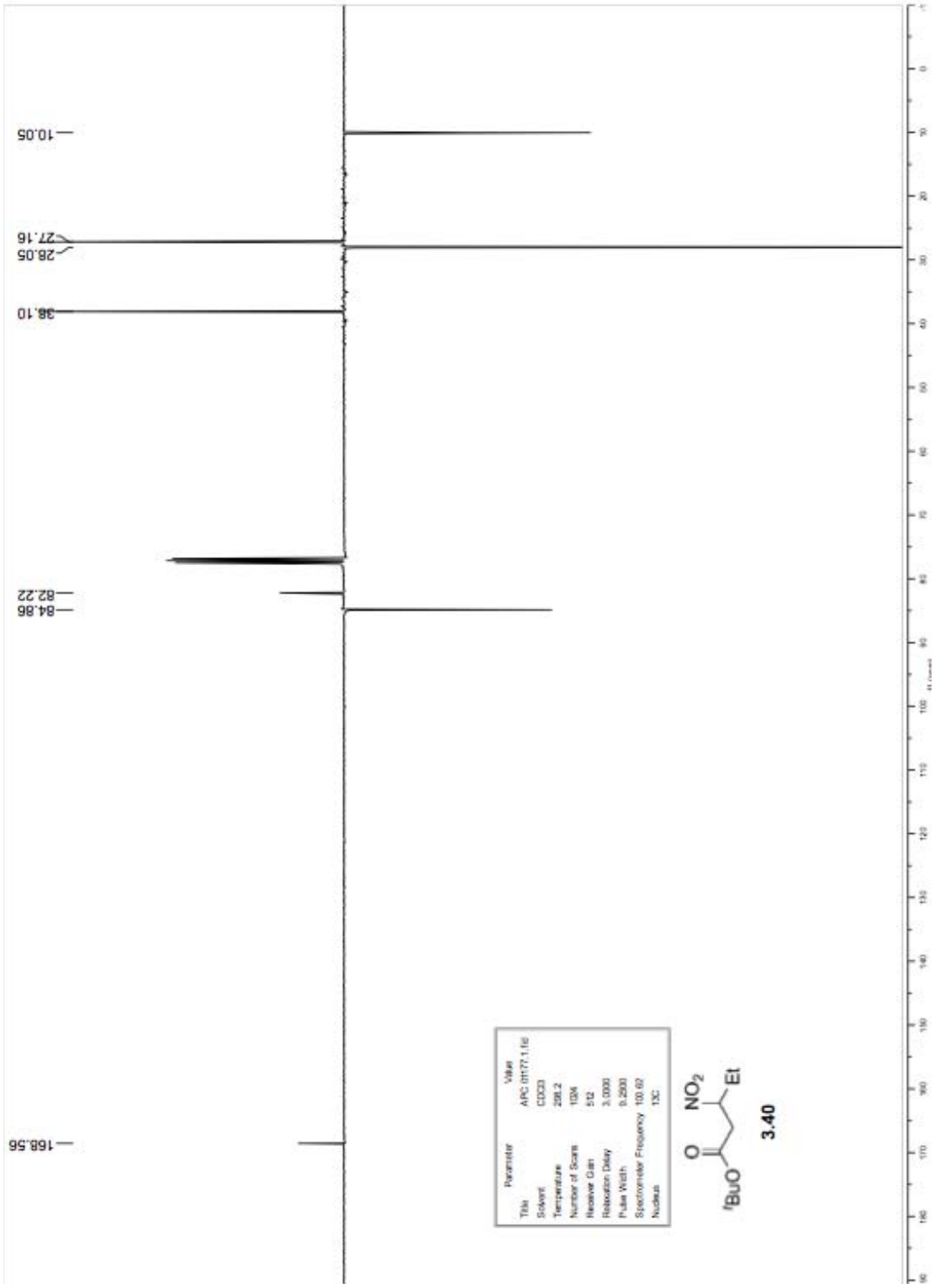
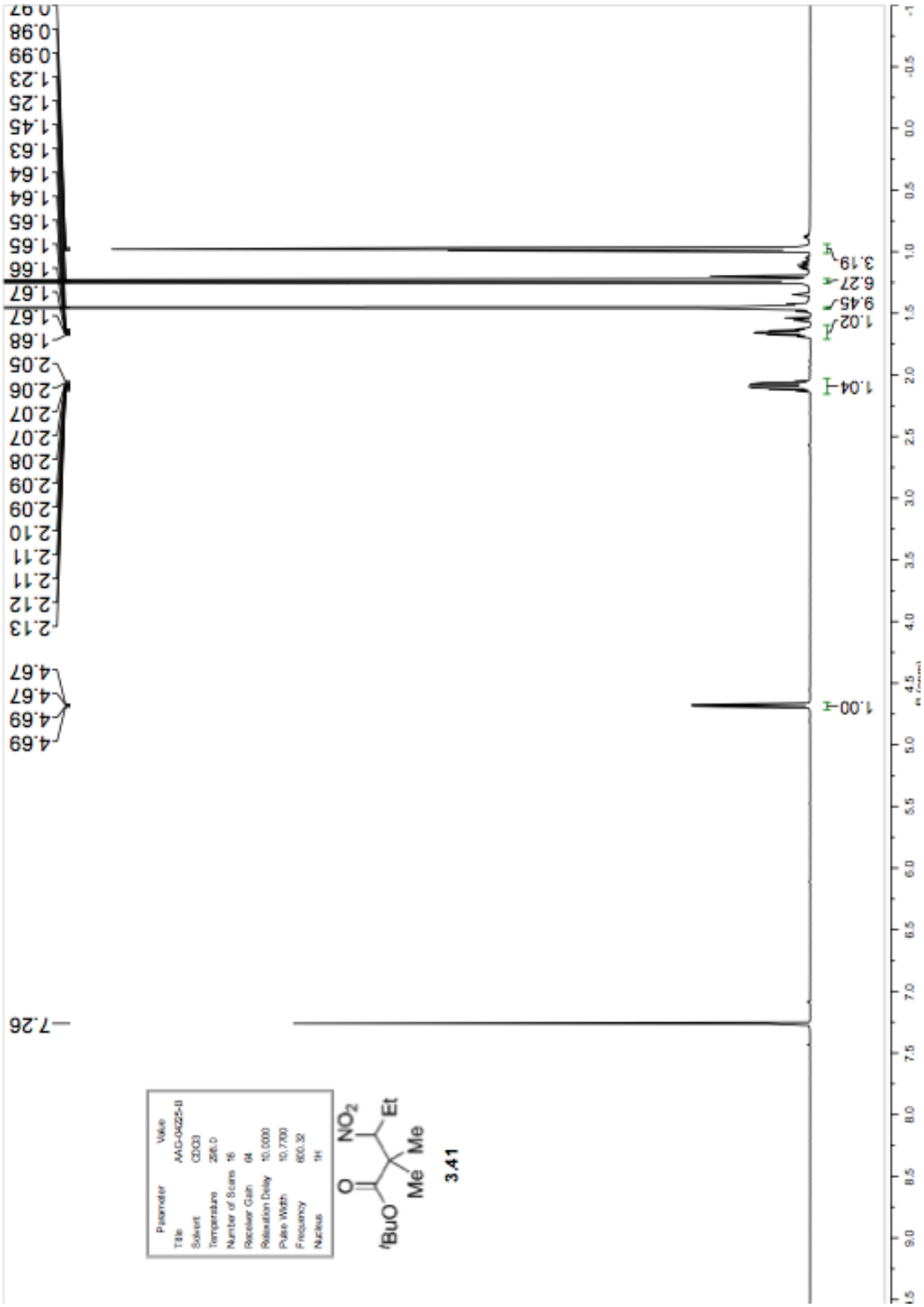
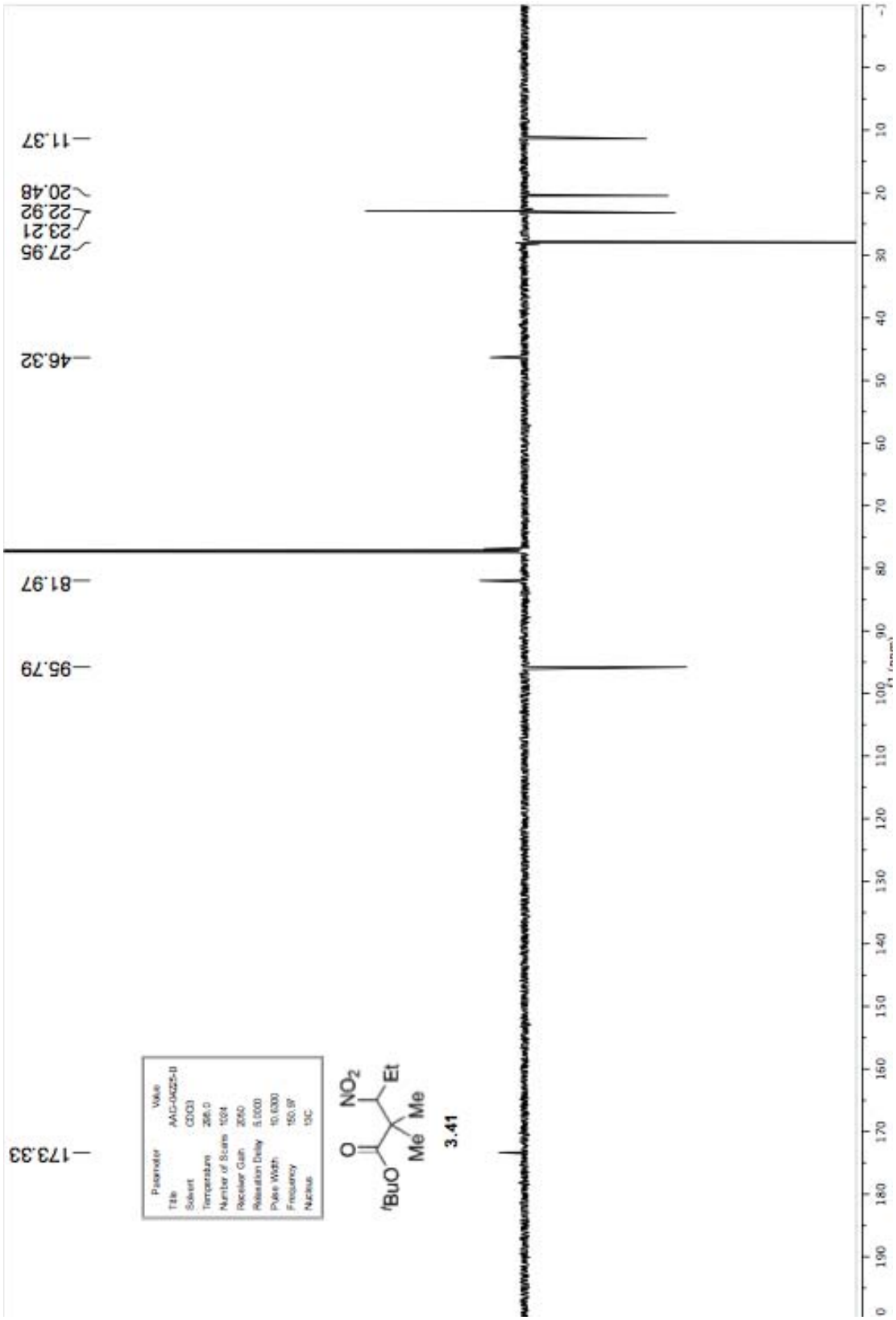
1.14
6.37
3.22

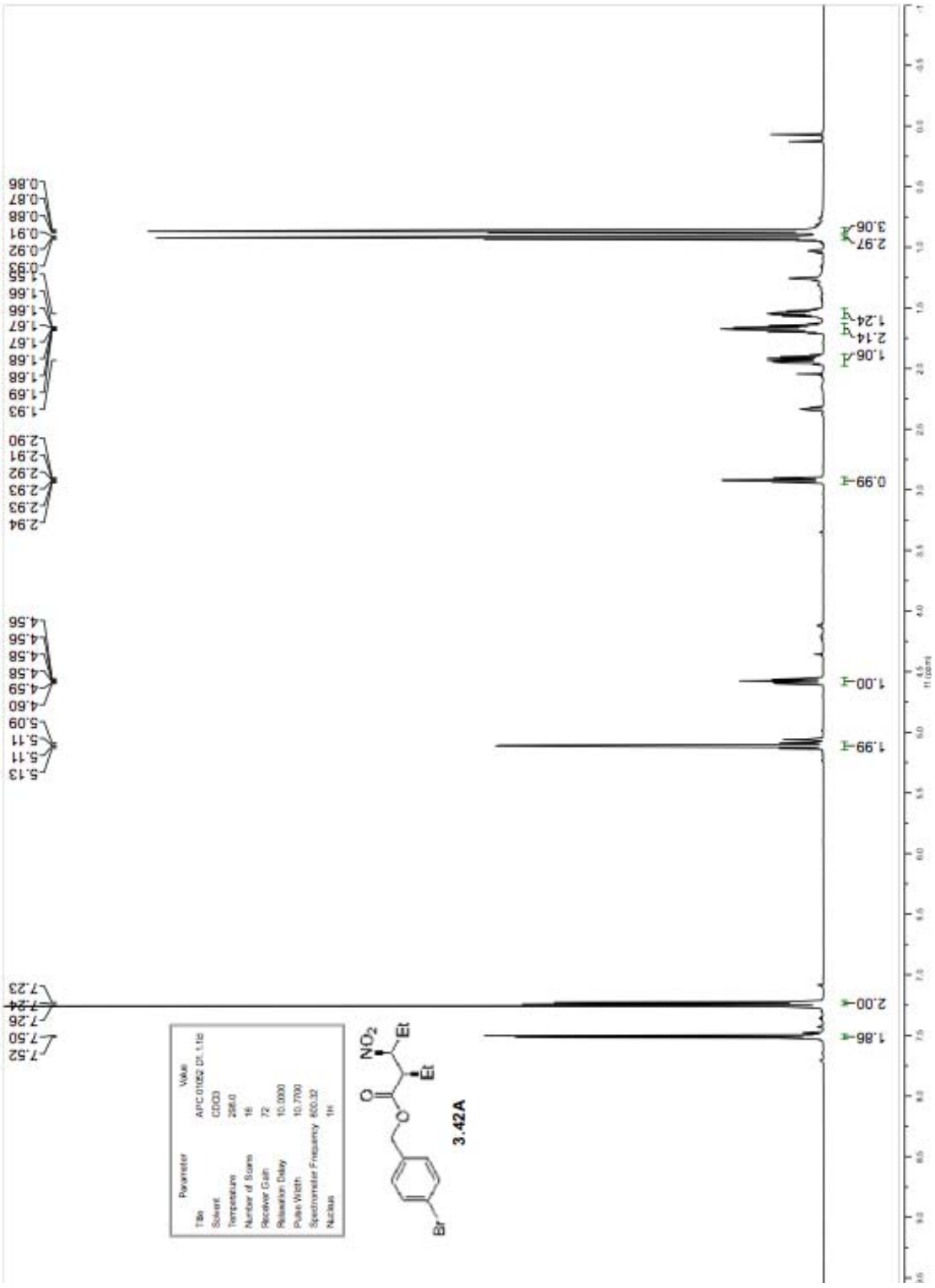

174.79
95.68
52.73
45.94
23.14
22.73
20.50
11.17
Parameter Value
Title AAD-05161-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0000
Frequency 150.97
Nucleus 13C
NO2
Et
Me
Me
MeO
O
3.39

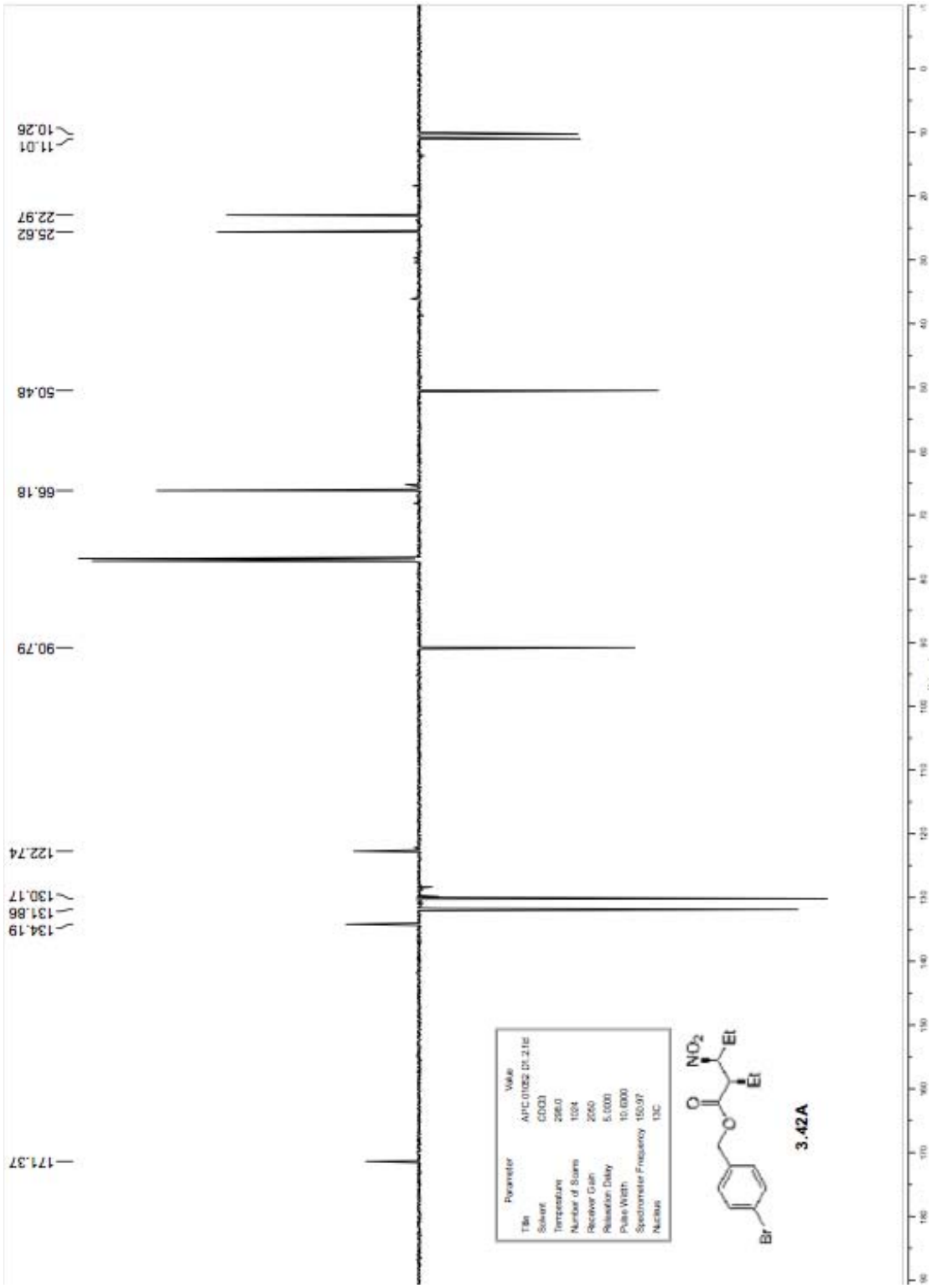

0.97
0.99
1.00
1.89
1.90
1.90
1.95
1.96
2.59
2.61
3.02
3.03
3.04
3.06
4.76
4.76
4.77
4.77
4.78
4.78
4.79
4.79
4.80
7.26
3.10
9.30
2.12
1.04
1.04
1.00
Parameter
Value
Title
APC 01177-2.fid
Solvent
CDCl3
Temperature
298.0
Number of Scans
8
Receiver Gain
57
Relaxation Delay
1.0000
Pulse Width
10.7700
Spectrometer Frequency
600.32
Nucleus
1H
O
NO2
Et
tBuO
3.40

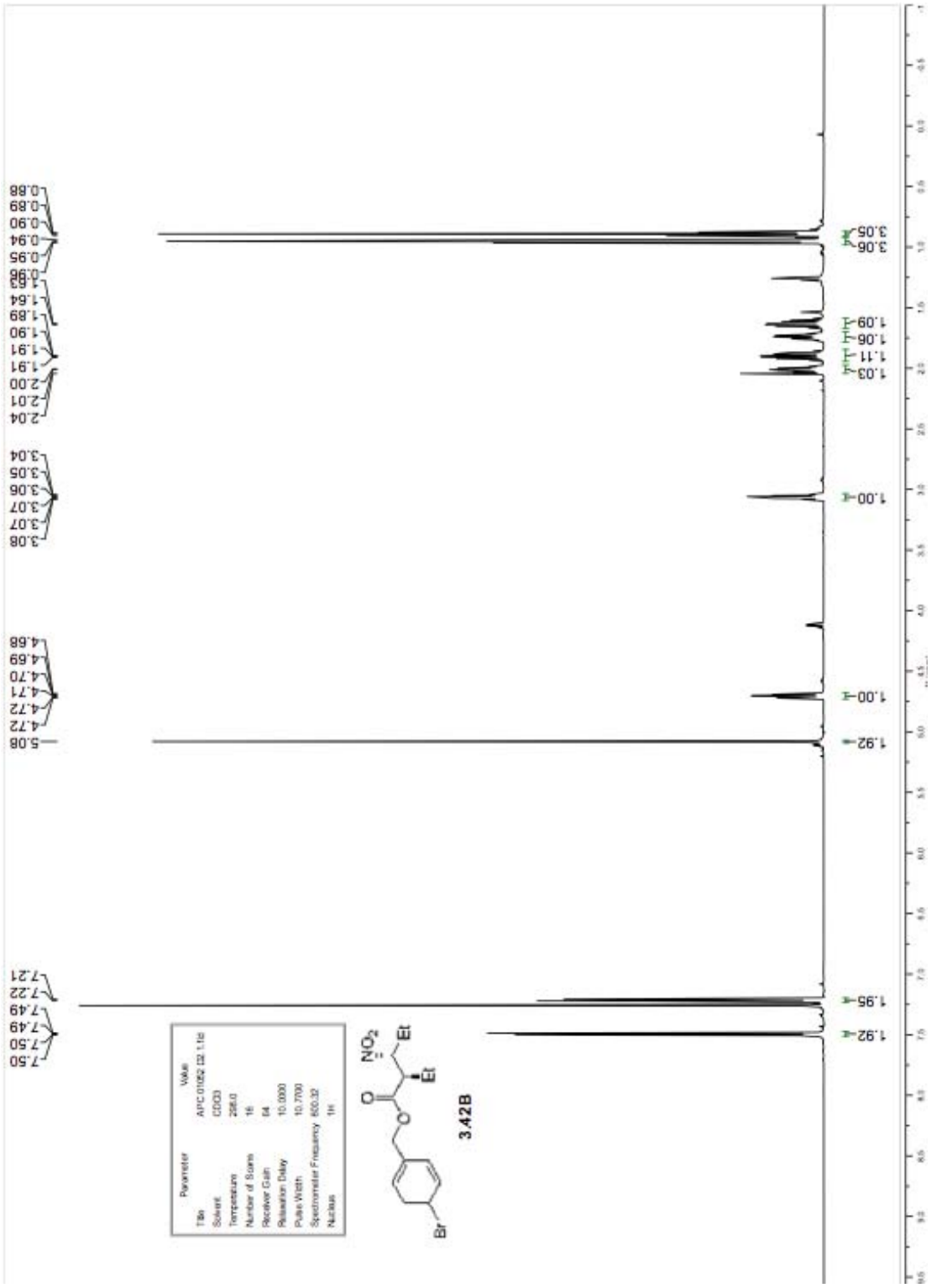

10.05
27.16
28.05
38.10
82.22
84.86
168.56
Parameter Value
Title APC 01177.1.fid
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Spectrometer Frequency 100.62
Nucleus 13C
NO2
Et
O
tBuO
3.40

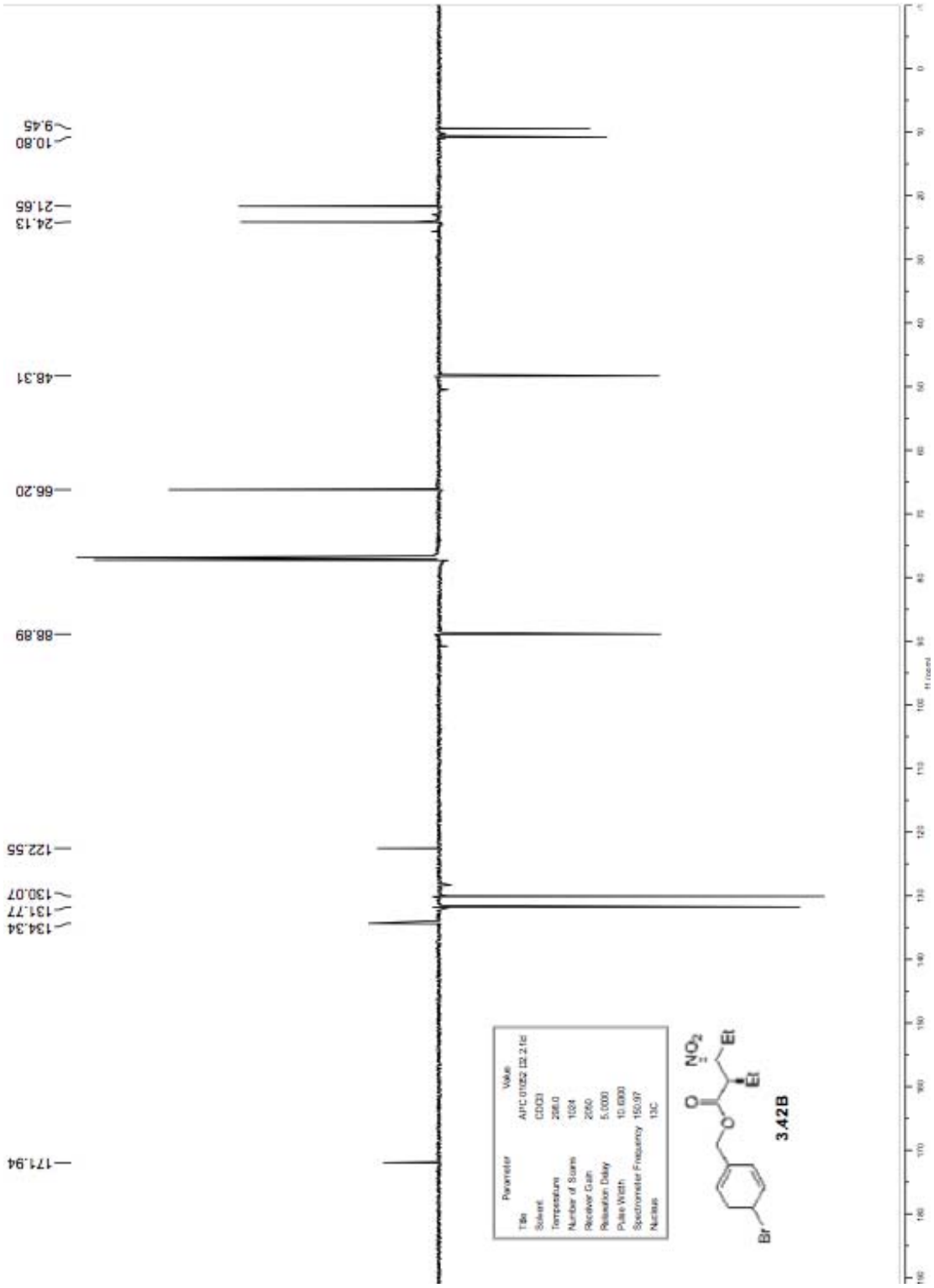

Parameter Value
Title AAG-0422-II
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 64
Relaxation Delay 10.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
tBuO
O
NO2
Et
Me
Me
3.41
7.26
4.69
4.67
4.67
4.69
2.13
2.12
2.11
2.11
2.10
2.09
2.09
2.08
2.07
2.07
2.06
2.05
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.64
1.63
1.45
1.25
1.23
0.99
0.98
0.97
1.00
1.04
1.02
9.45
6.27
3.19

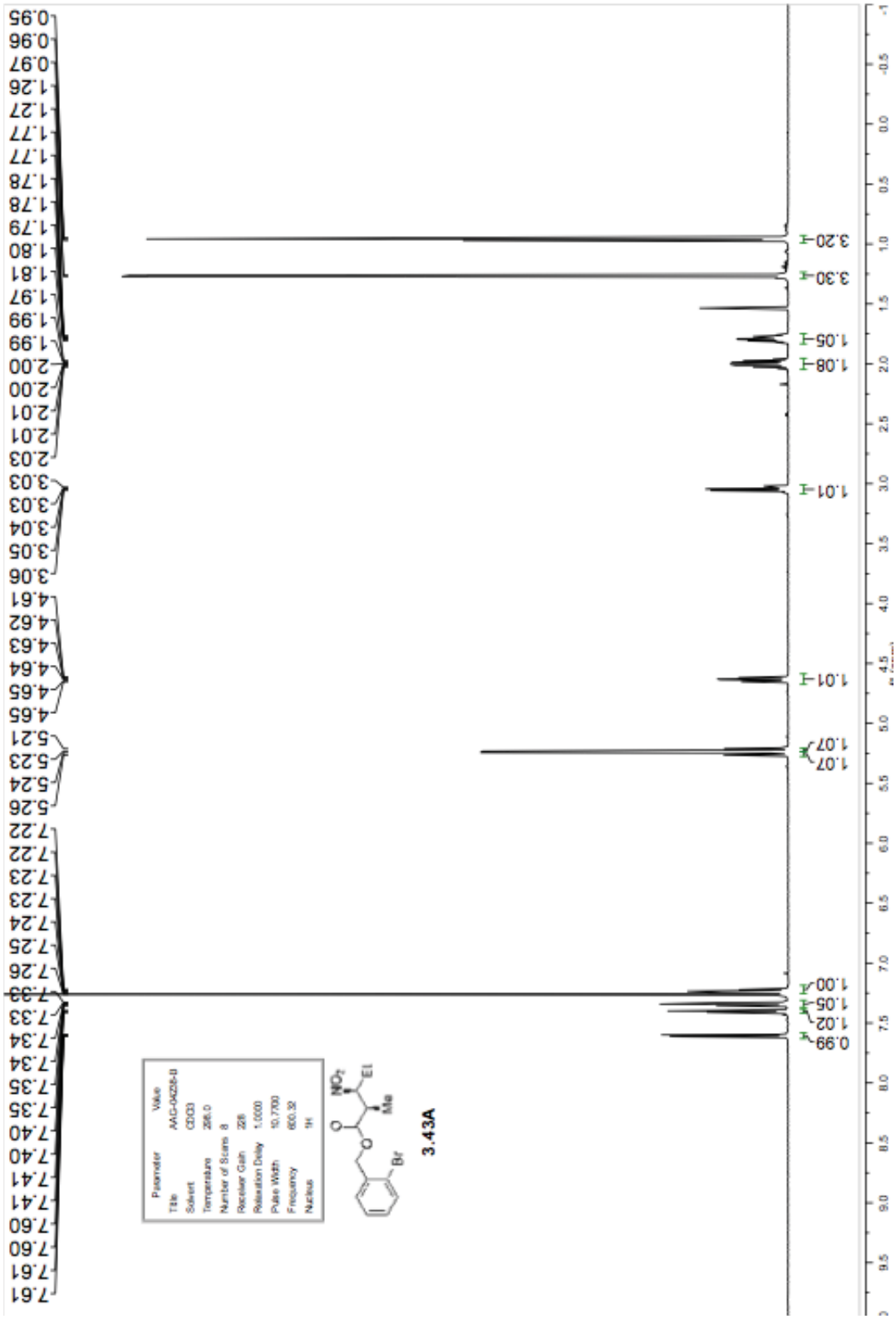

173.33
81.97
95.79
46.32
27.95
23.21
22.92
20.48
11.37
Parameter Value
Title AAD-04225-II
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.87
Nucleus 13C
NO2
Et
O
tBuO
Me
Me
3.41


Parameter Value
Title APC 01052 (2) 1.1ti
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 72
Relaxation Delay 10.0000
Pulse Width 10.7700
Spectrometer Frequency 600.32
Nucleus 1H
NO2
Et
Et
O
O
Br
3.42A
7.52
7.50
7.26
7.24
7.23
5.13
5.11
5.09
4.60
4.59
4.58
4.58
4.58
4.56
4.56
2.94
2.93
2.93
2.92
2.91
2.90
1.93
1.69
1.68
1.68
1.67
1.67
1.66
1.66
1.55
0.93
0.92
0.91
0.88
0.87
0.86
2.97
3.06
1.24
2.14
1.06
0.99
1.00
1.99
2.00
1.86


10.26
11.01
22.97
25.62
50.48
66.18
90.79
122.74
130.17
131.86
134.19
171.37
Parameter Value
Title APC 01052 01-21d
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Spectrometer Frequency 150.97
Nucleus 13C
NO2
Et
Et
O
O
Br
3.42A


Parameter Value
Title APC 0182 [32 1 1c]
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 84
Relaxation Delay 10.0000
Pulse Width 10.7000
Spectrometer Frequency 600.32
Nucleus 1H
3.42B
Et
Et
Br
7.50
7.49
7.49
7.50
7.22
7.21
4.72
4.71
4.70
4.69
4.68
5.08
3.08
3.07
3.07
3.06
3.05
3.04
2.04
2.01
2.00
1.91
1.91
1.90
1.89
1.64
1.63
0.98
0.95
0.94
0.90
0.89
0.88
1.92
1.95
1.92
1.00
1.00
1.03
1.11
1.06
1.09
3.06
3.05


9.45
10.80
21.65
24.13
48.31
66.20
86.89
122.55
130.07
131.77
134.34
171.94
Parameter Value
Title APC 01052 [2] 2 1d
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0000
Spectrometer Frequency 150.97
Nucleus 13C
NO2
Et
Et
O
O
Br
3.42B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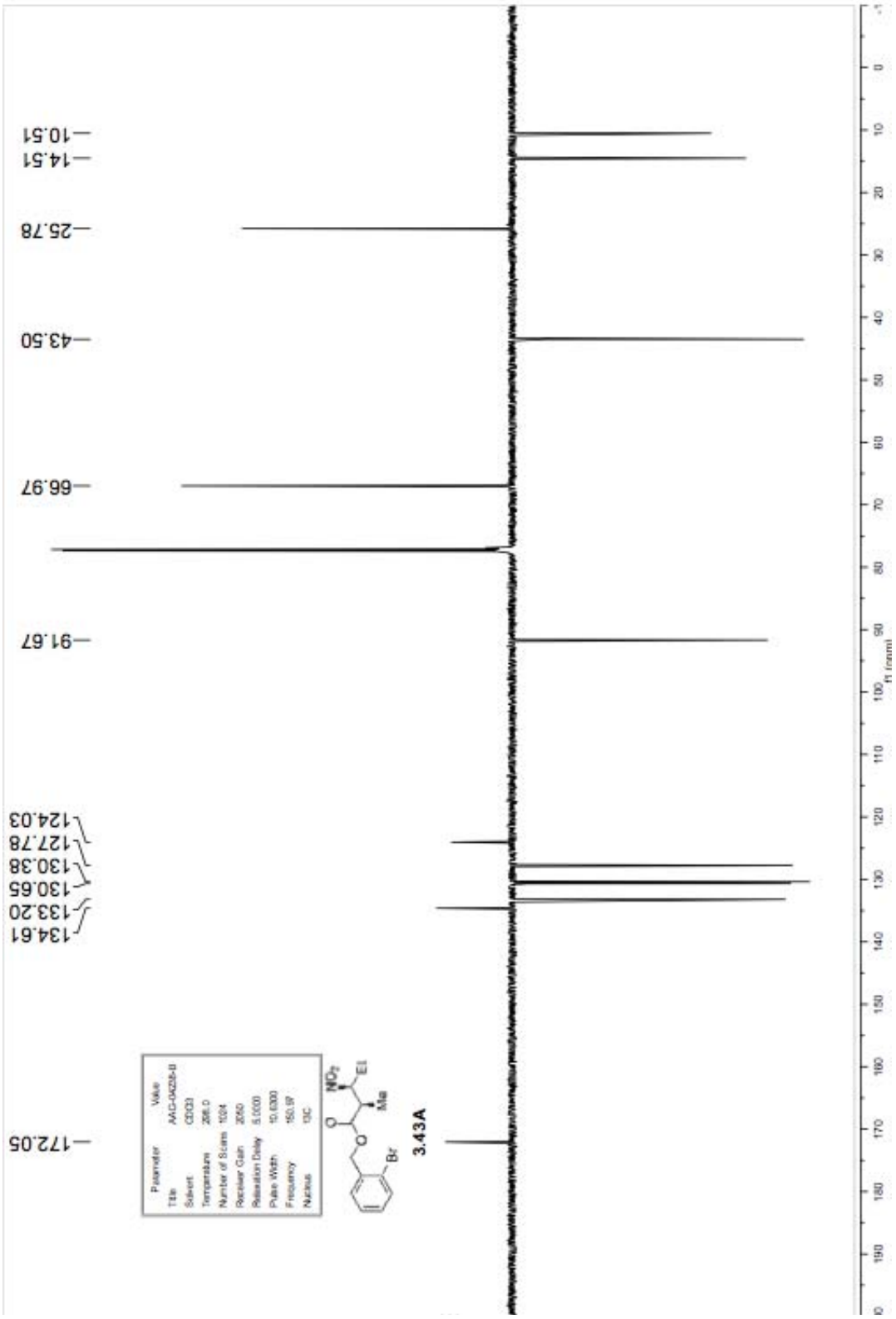
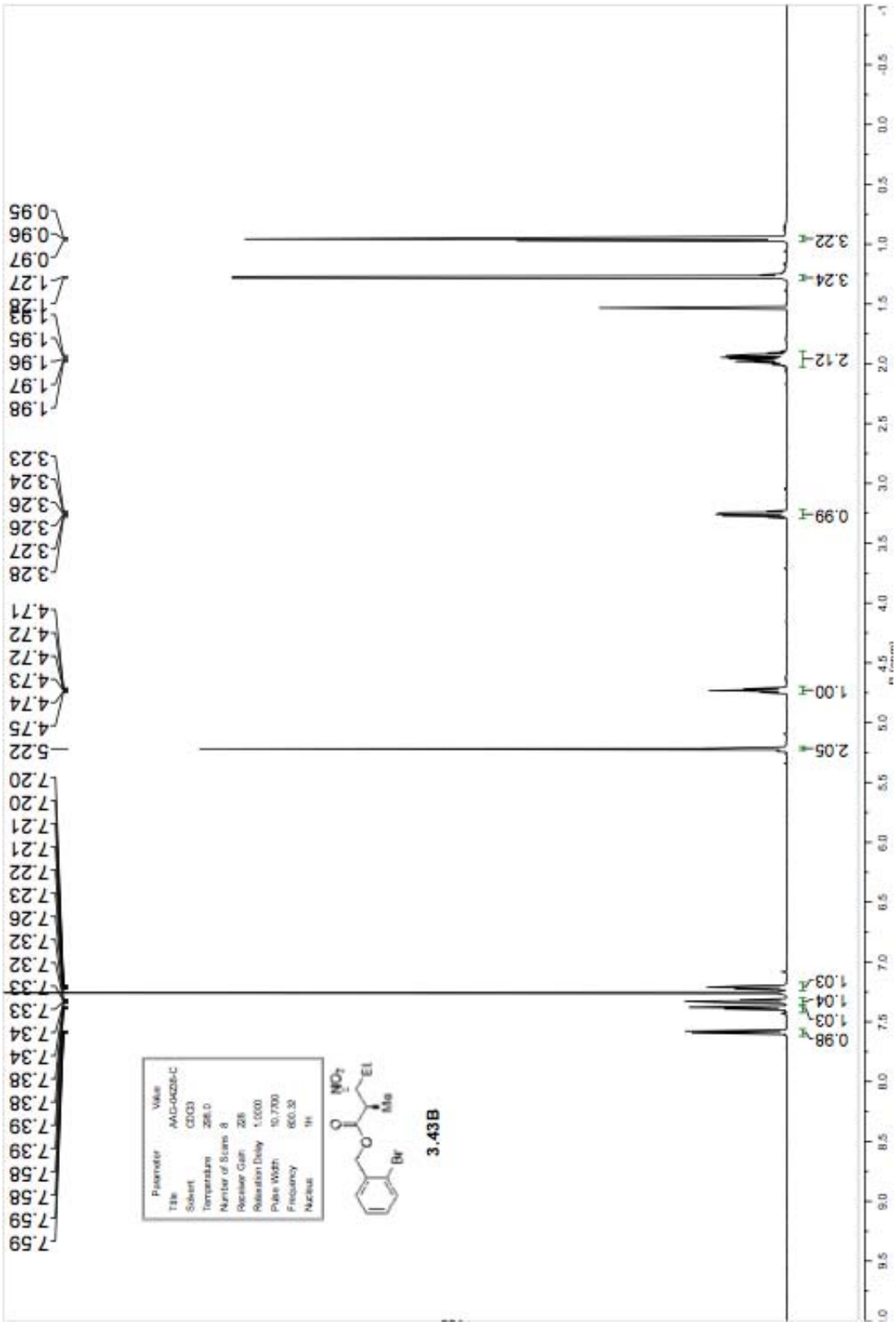
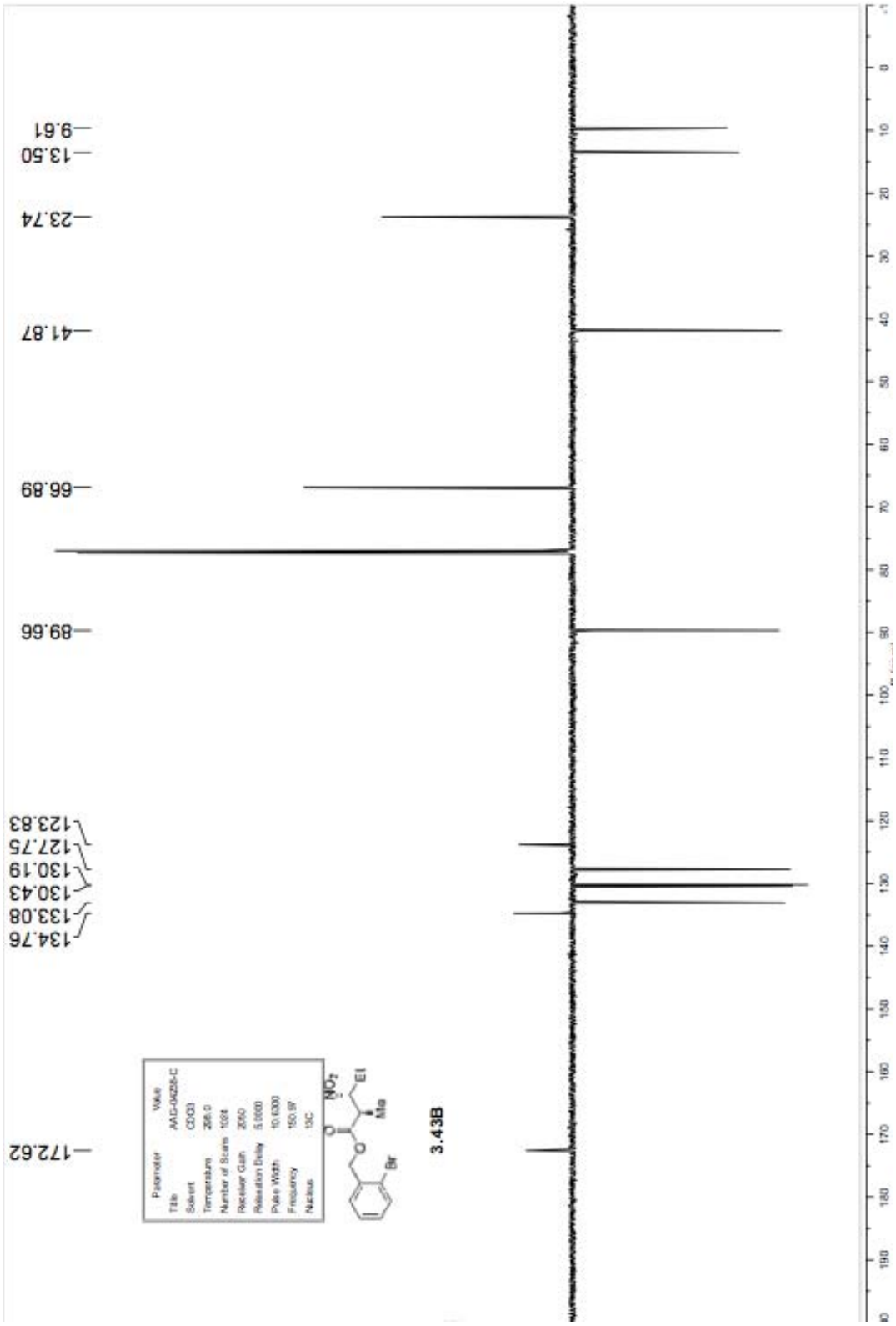
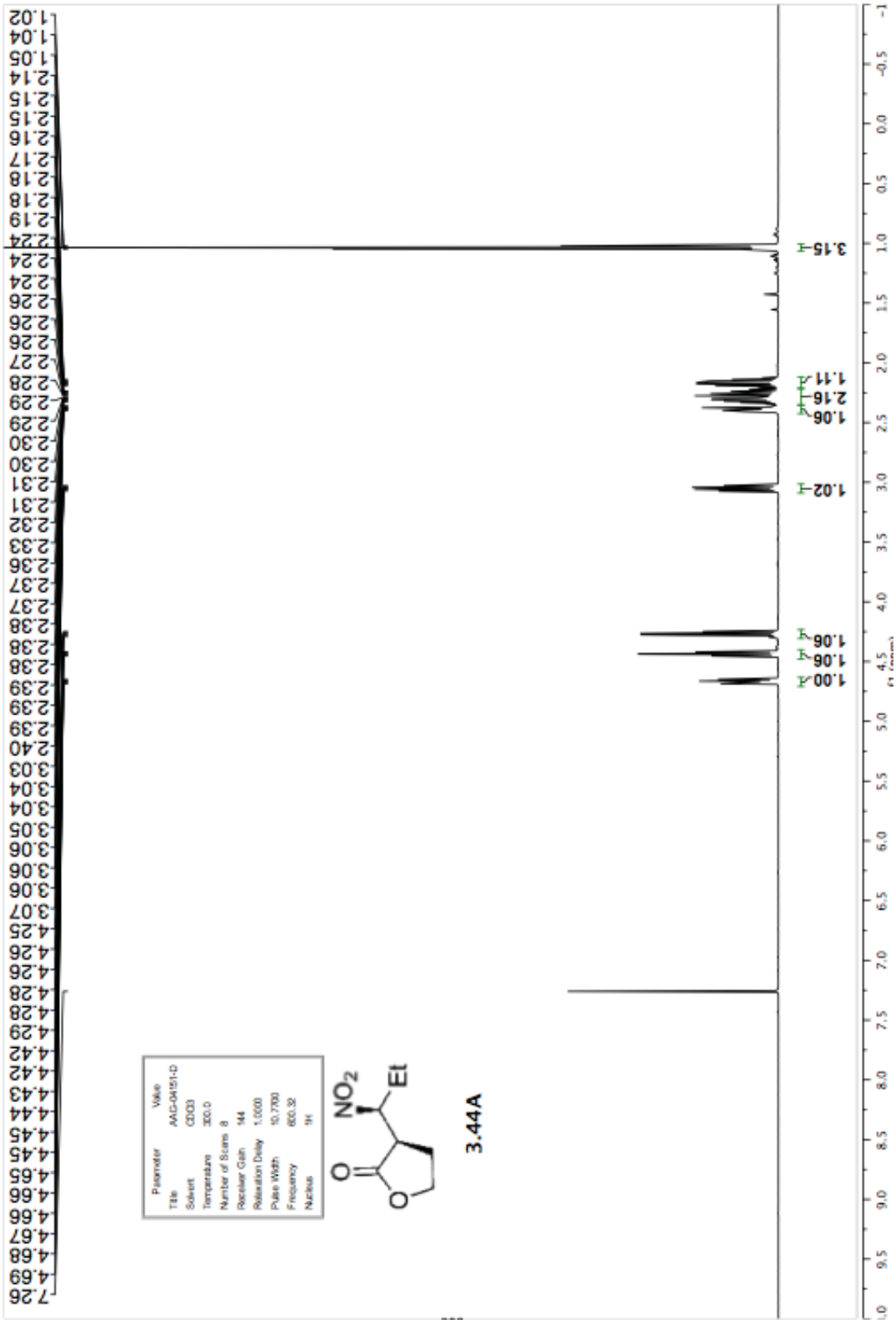
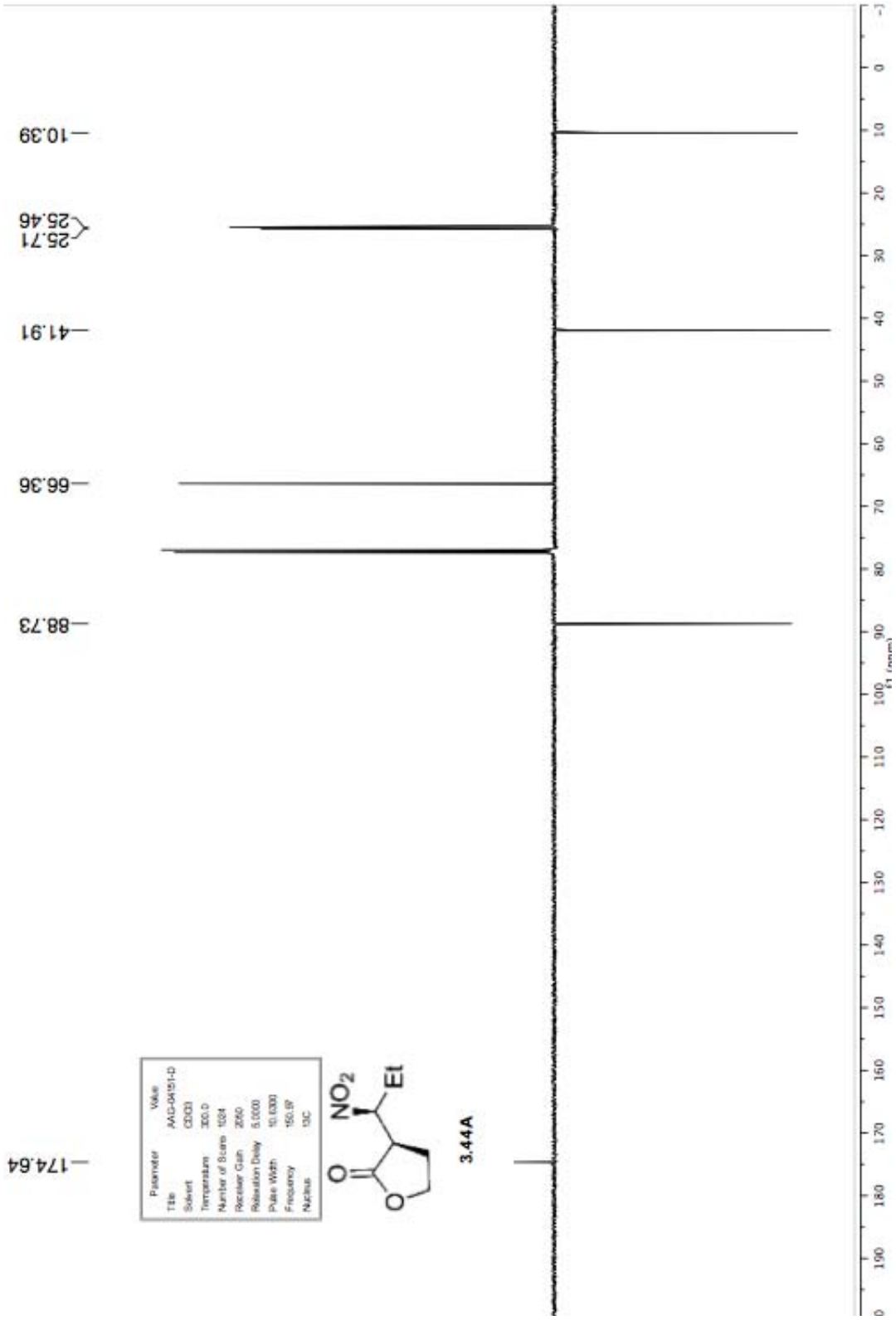
Title AAG-04258-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 228
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
3.43A
Br
Me
Et
NO2
0.99
1.02
1.05
1.00
1.07
1.07
1.01
1.01
1.08
1.05
3.30
3.20

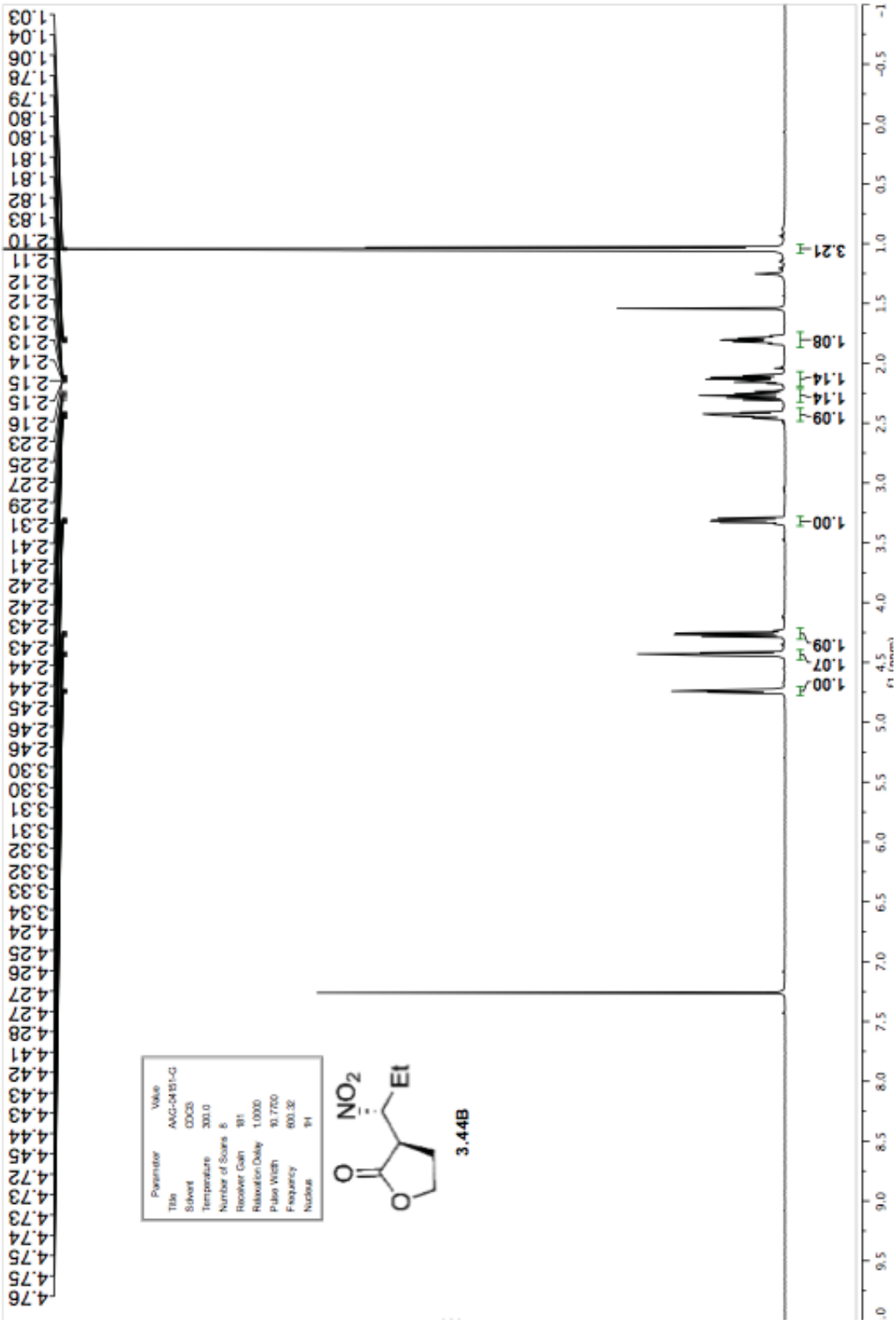

10.51
14.51
25.78
43.50
66.97
91.67
124.03
127.78
130.38
130.65
133.20
134.61
172.05
Parameter Value
Title AAD-0422B-II
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.97
Nucleus 13C
NO2
Et
Me
O
O
Br
3.43A
f1 (ppm)


3.43B


9.61
13.50
23.74
41.87
66.89
89.66
123.83
127.75
130.19
130.43
133.08
134.76
172.62
Parameter Value
Title AAD-04228-C
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.91
Nucleus 13C
NO2
Et
Me
O
O
Br
3.43B


Parameter Value
Title AAG-04181-D
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 144
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Et
O
O
3.44A
3.15
1.02
1.06
2.16
1.11
1.00
1.06
1.06


174.64
88.73
66.36
41.91
25.71
25.46
10.39
Parameter Value
Title AAD-04151-D
Solvent CDCl3
Temperature 300.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.9
Nucleus 13C
NO2
Et
O
O
3.44A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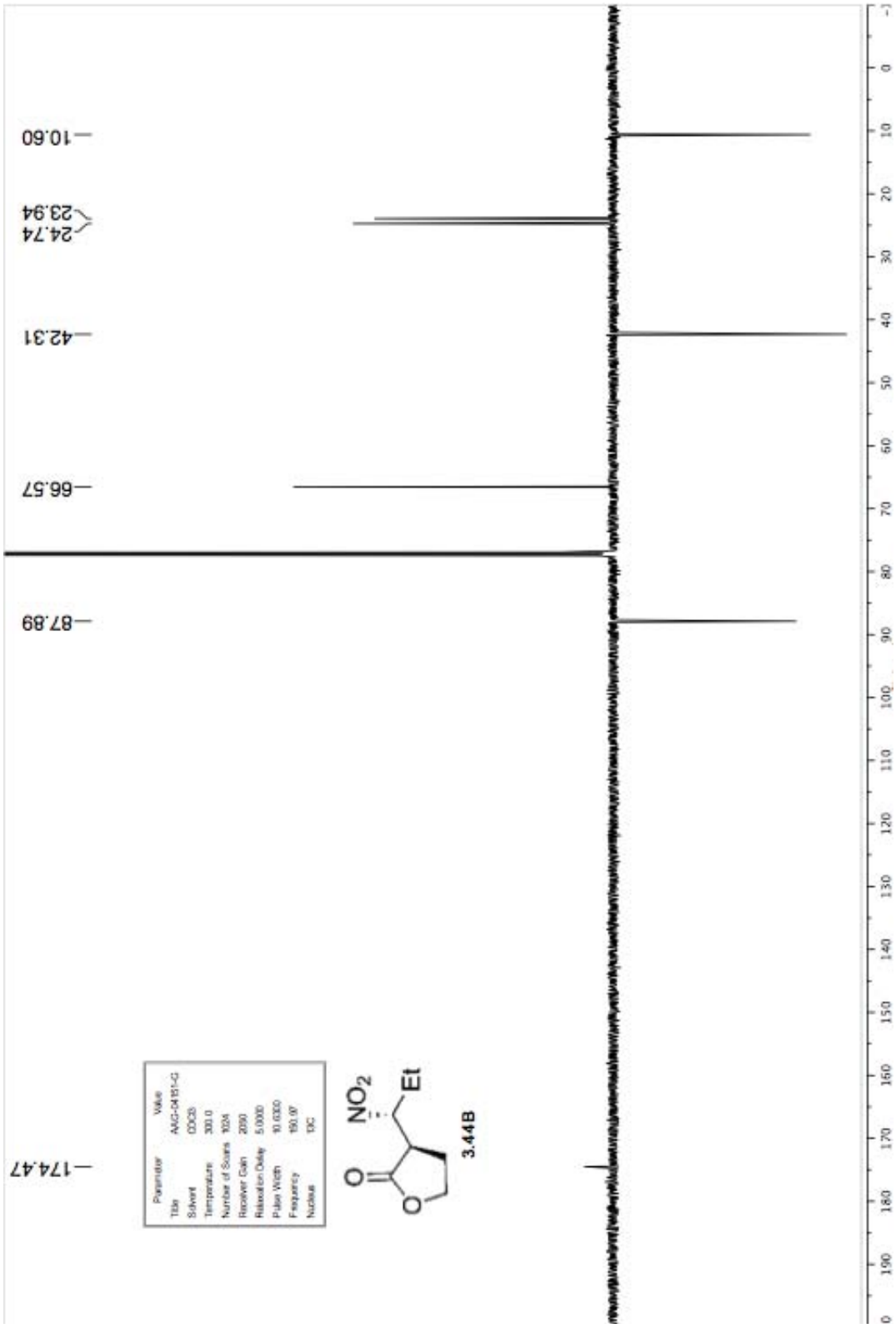
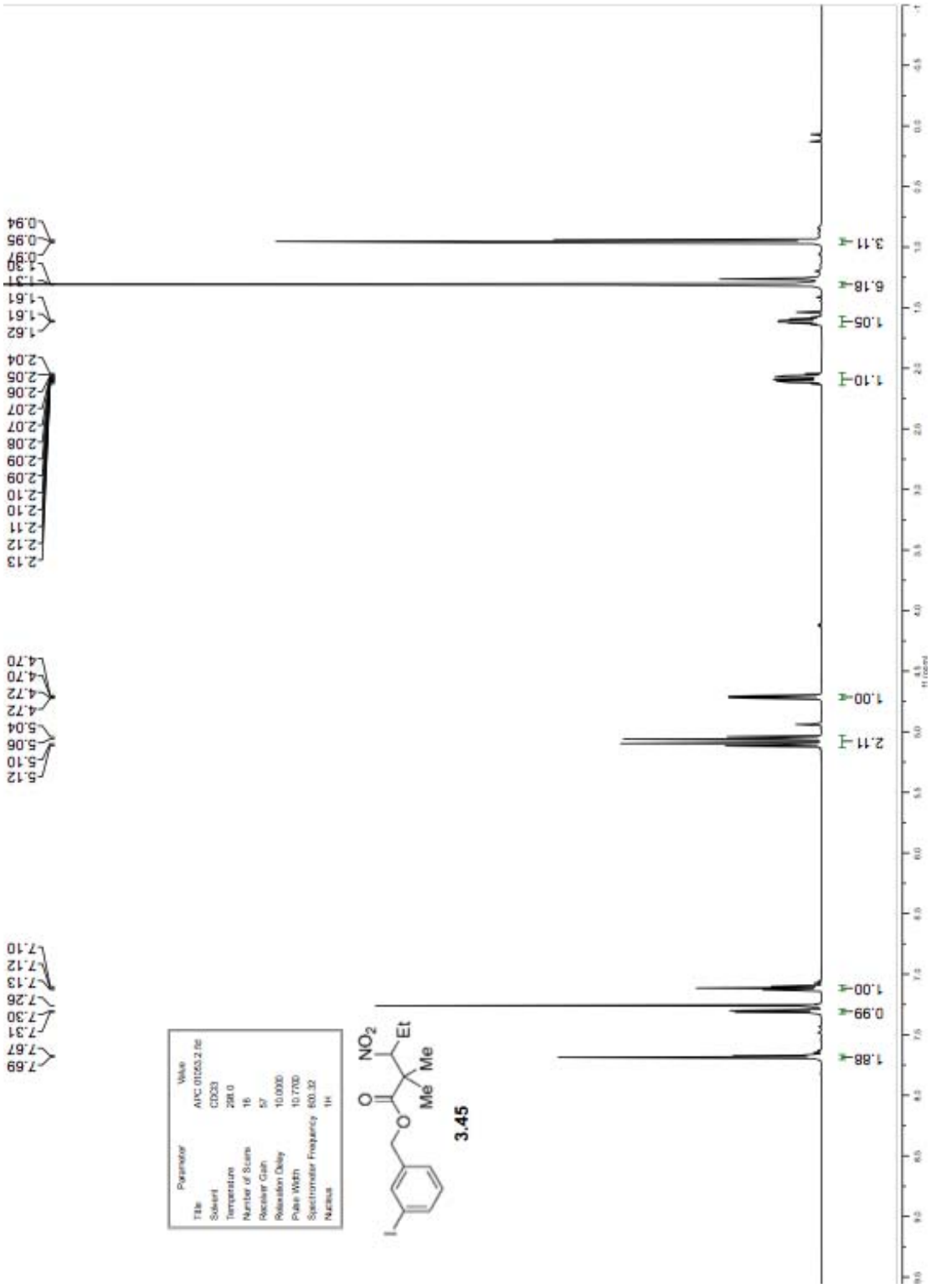
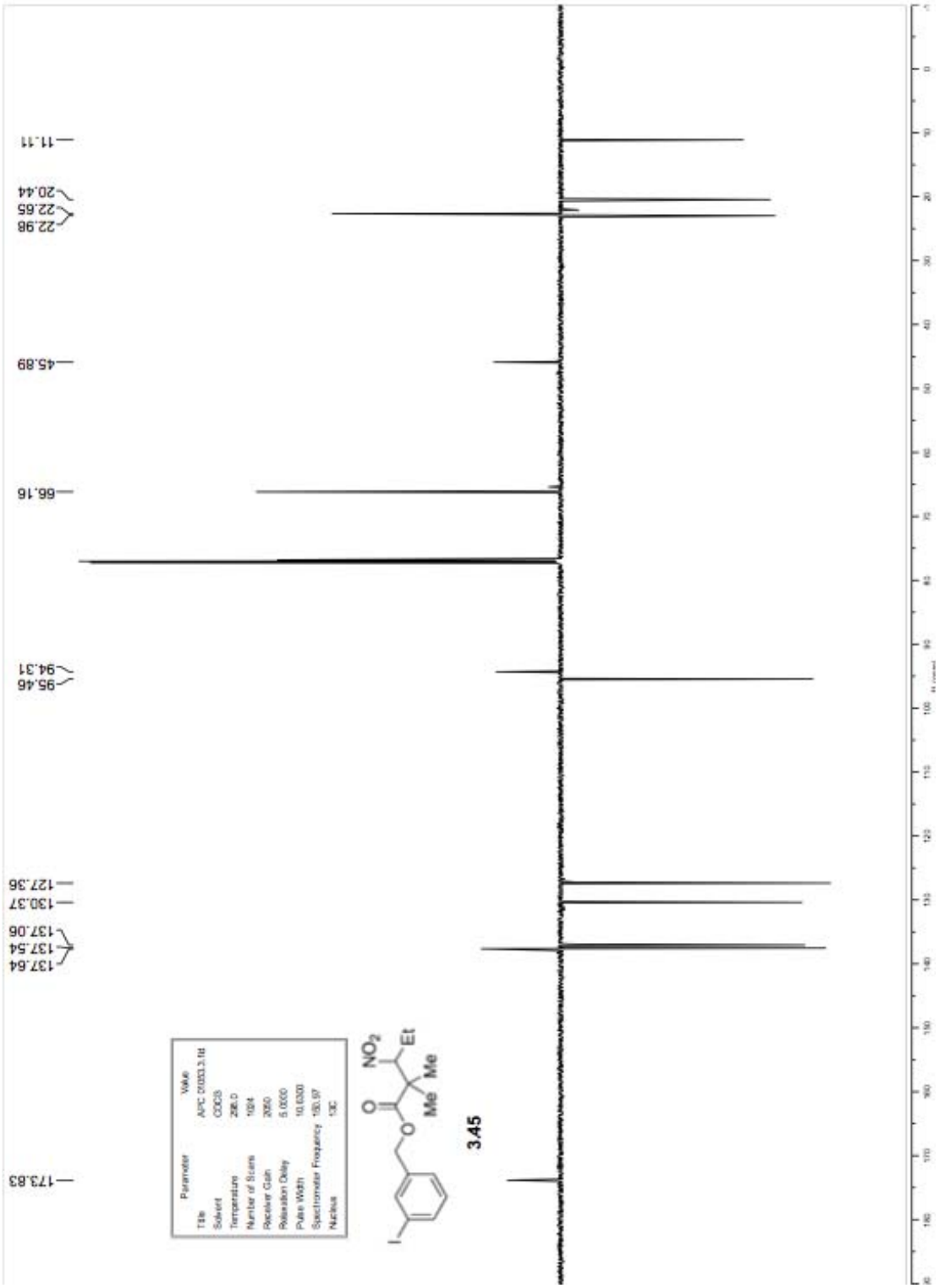
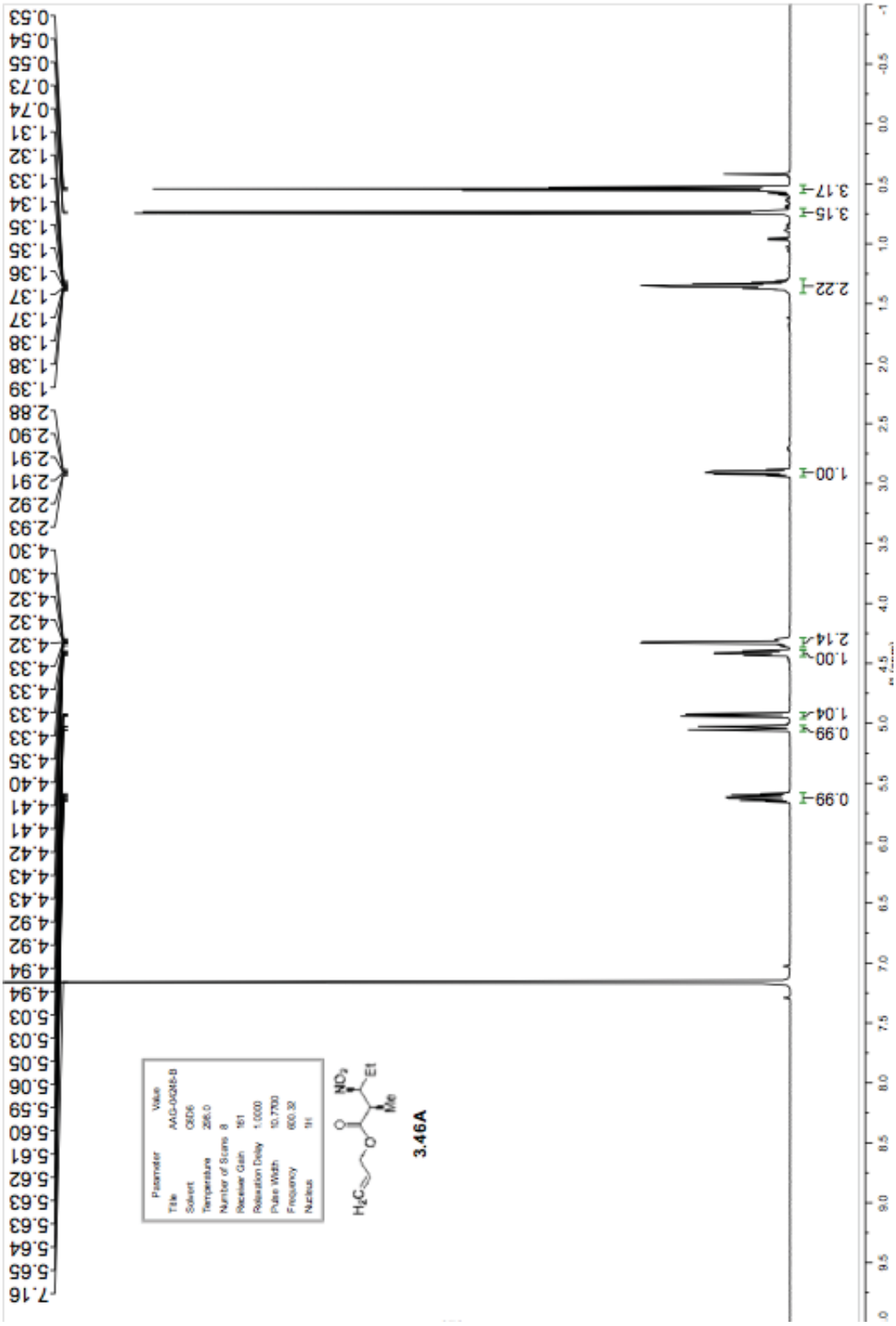
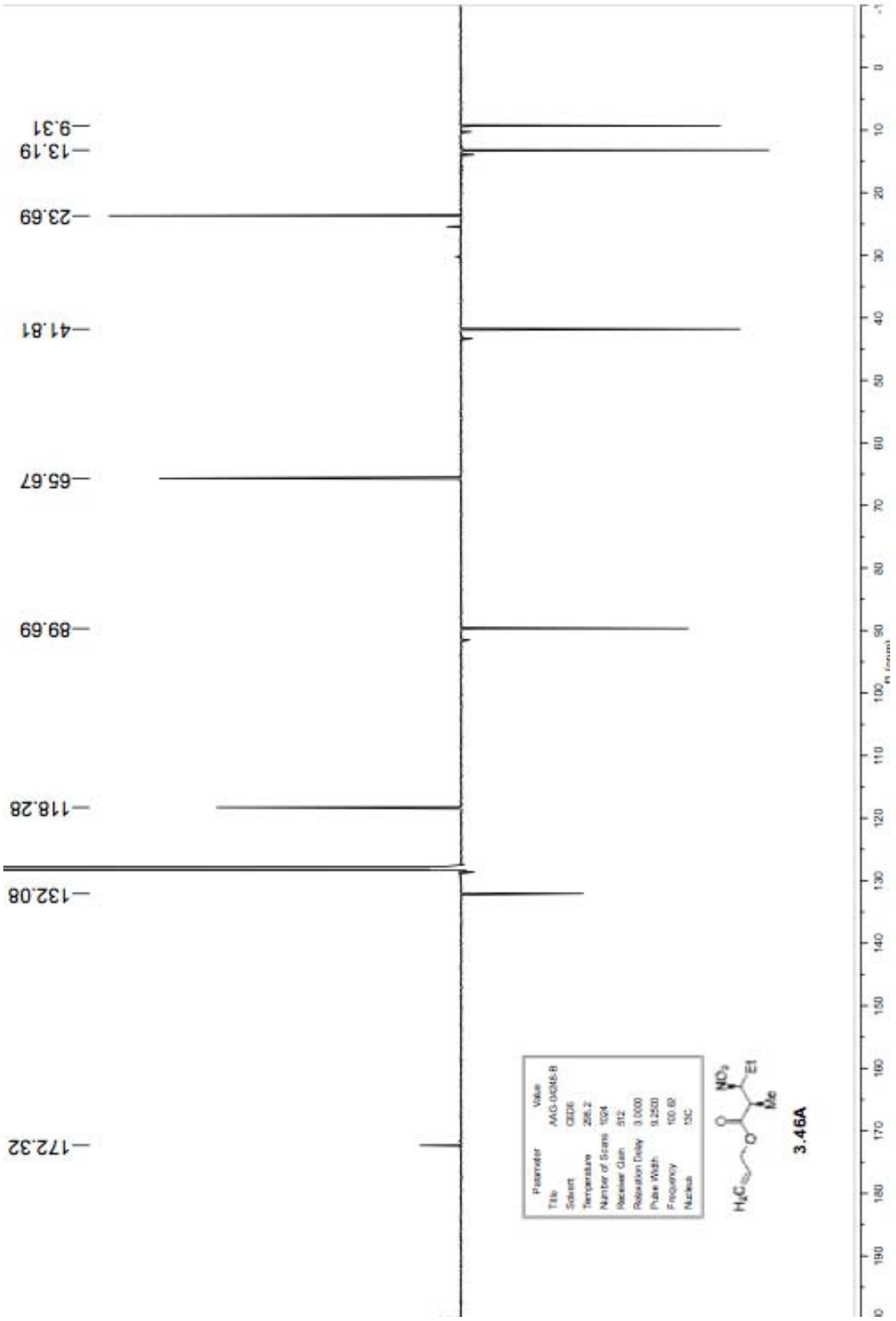
Title AAG-04161-G
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7720
Frequency 600.32
Nucleus 1H
NO2
Et
O
O
3.44B
3.21
1.08
1.14
1.14
1.09
1.00
1.09
1.07
1.00

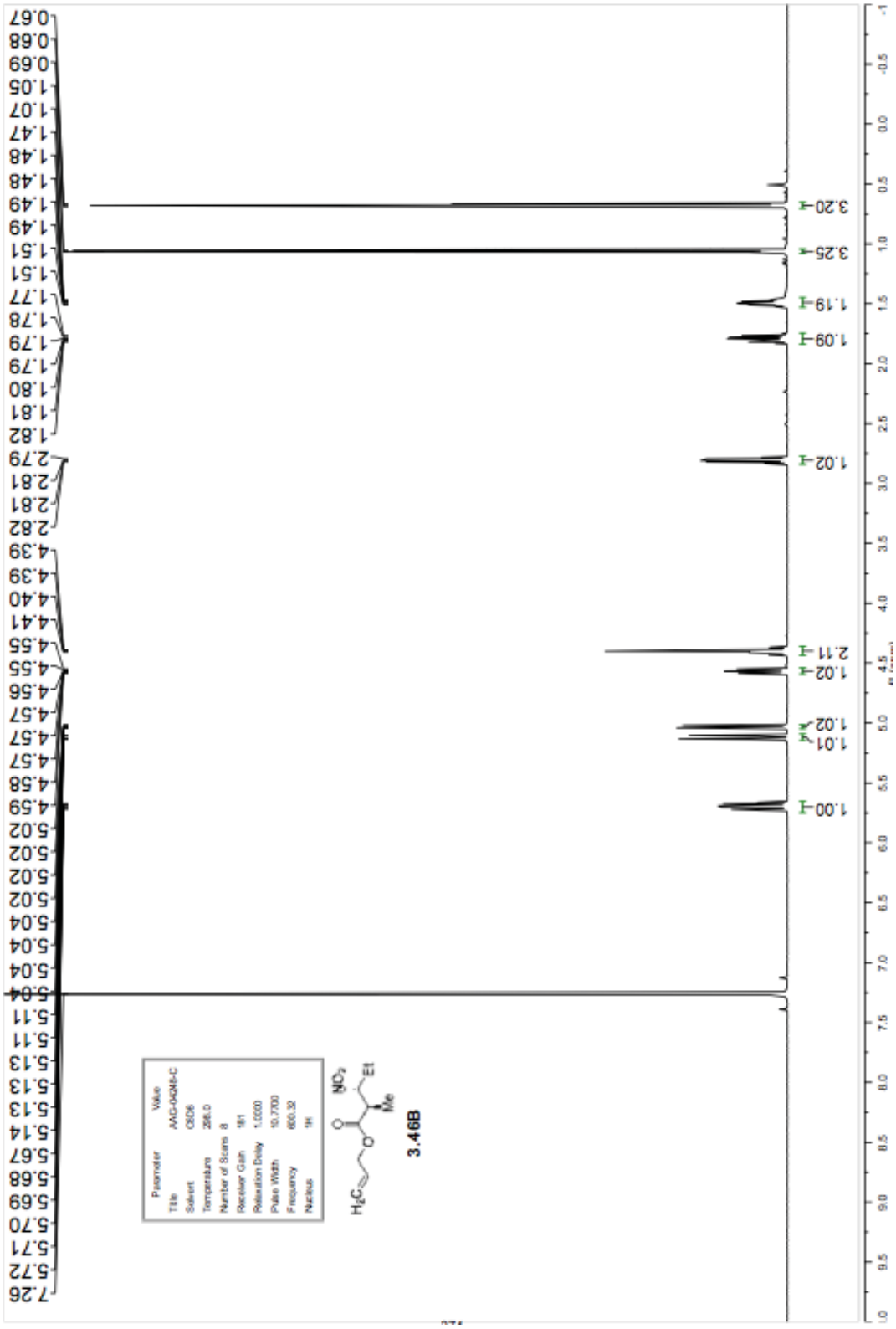

174.47
87.89
66.57
42.31
24.74
23.94
10.60
Parameter Value
Title AAG-0451-G
Solvent CDCl3
Temperature 300.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.97
Nucleus 13C
O
NO2
Et
O
3.44B

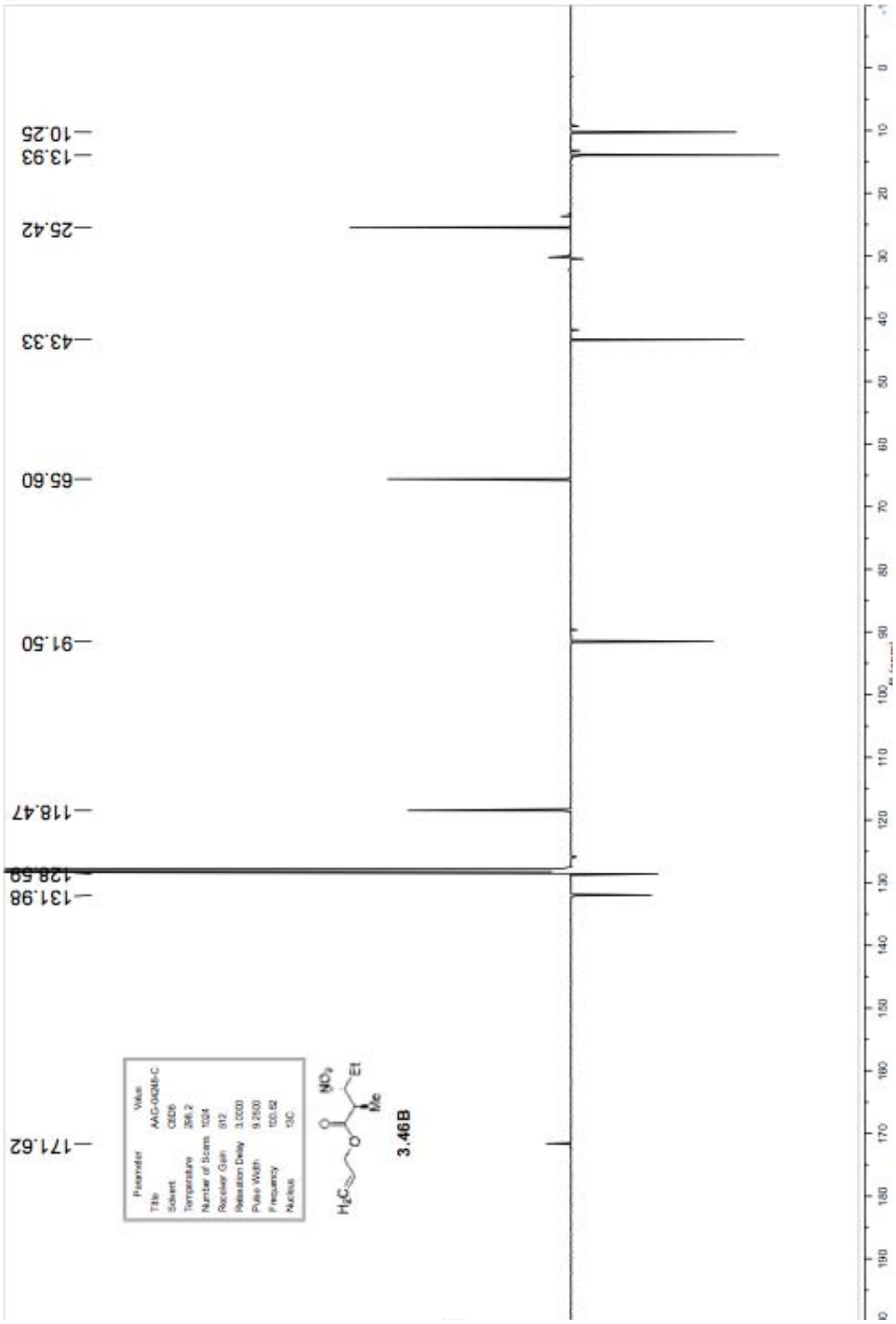

Parameter Value
Title AYC 01553.2.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 57
Relaxation Delay 10.000
Pulse Width 10.700
Spectrometer Frequency 600.32
Nucleus 1H
3.45

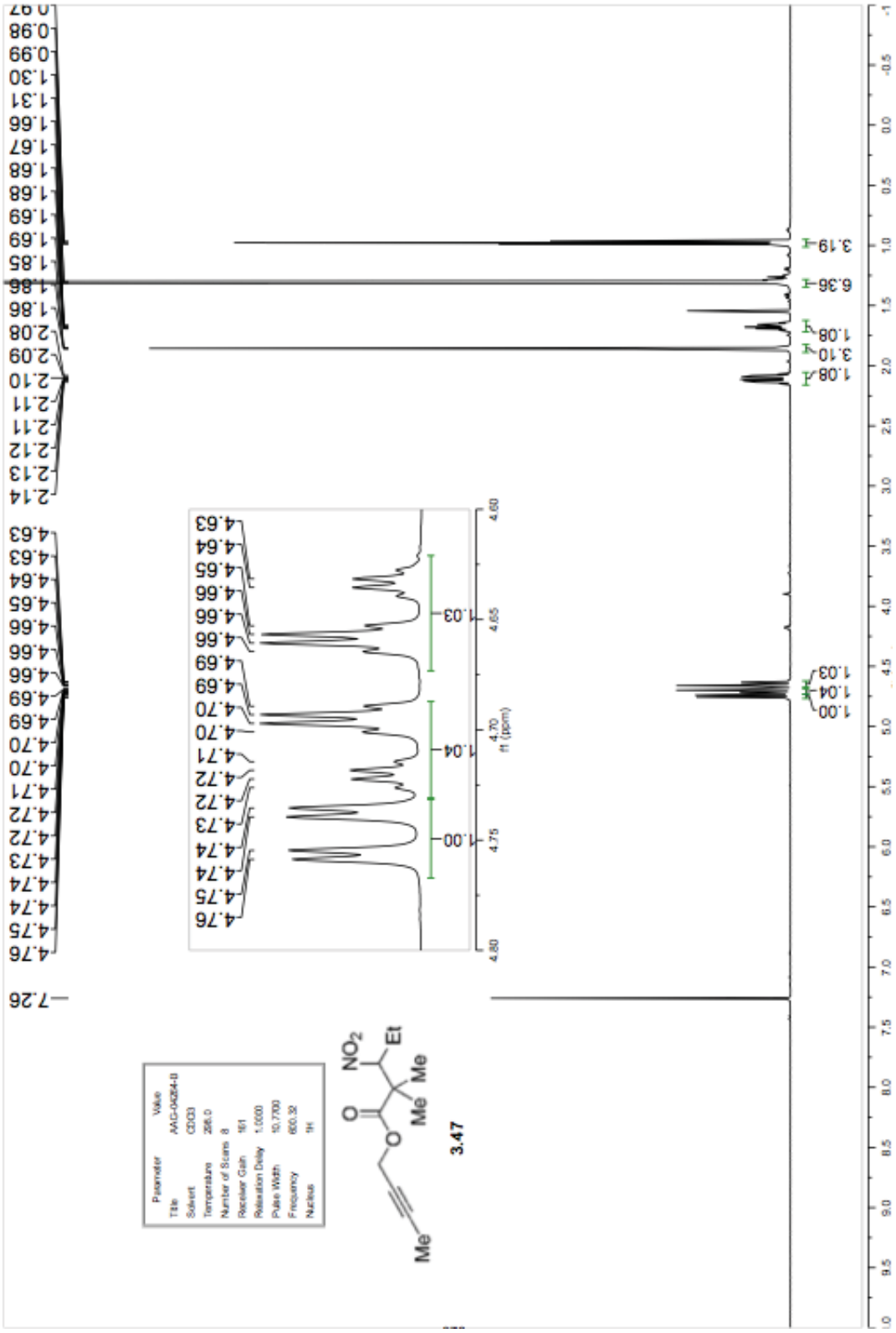

11.11
20.44
22.65
22.98
45.89
66.16
94.31
95.46
127.36
130.37
137.06
137.54
137.64
173.83
Parameter Value
Title APC 010313.1H
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Spectrometer Frequency 150.87
Nucleus 13C
NO2
Et
Me
Me
O
O
I
3.45

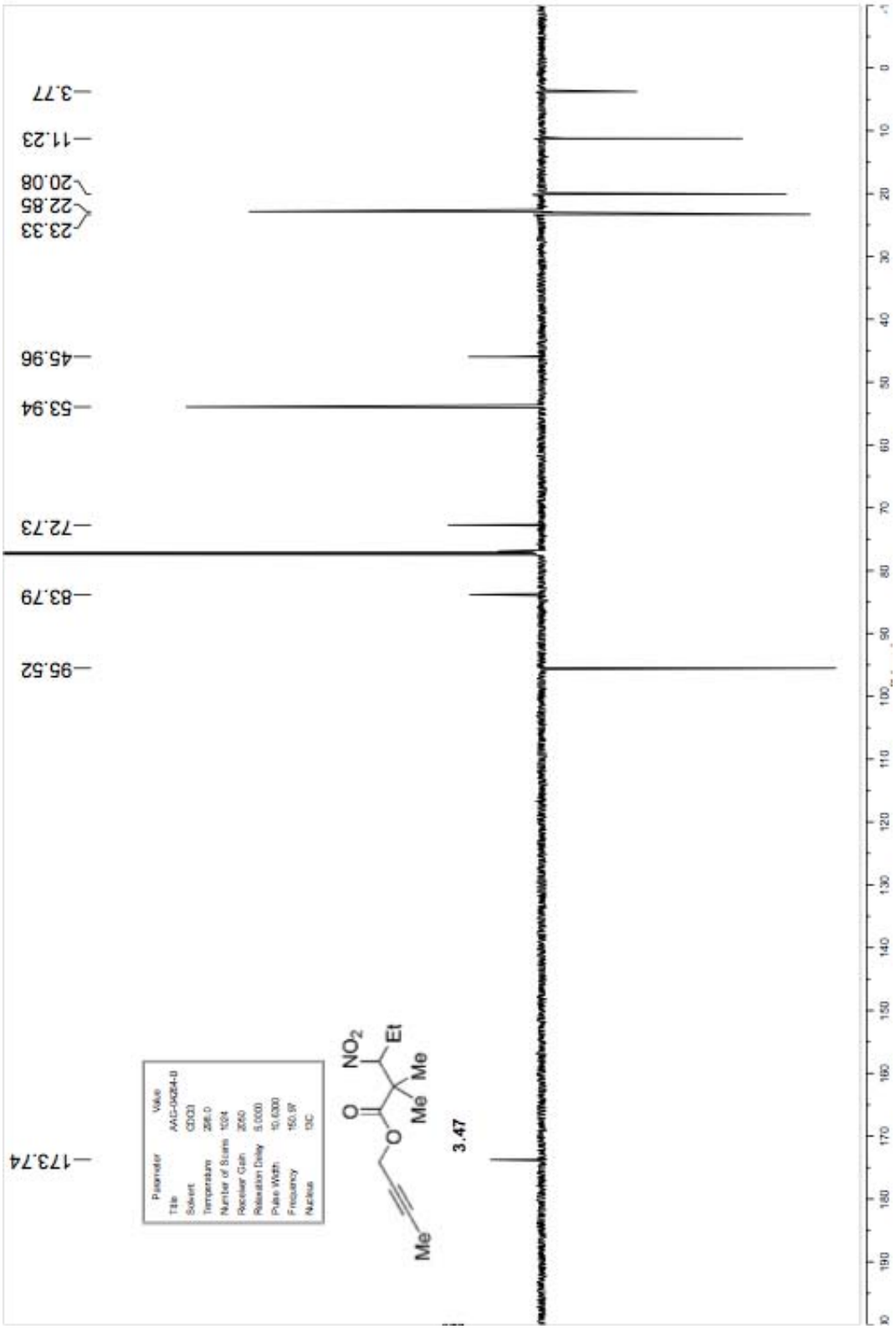

Parameter Value
Title AAG-0426-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Et
Me
3.46A
3.17
3.15
2.22
1.00
2.14
1.00
1.04
0.99
0.99

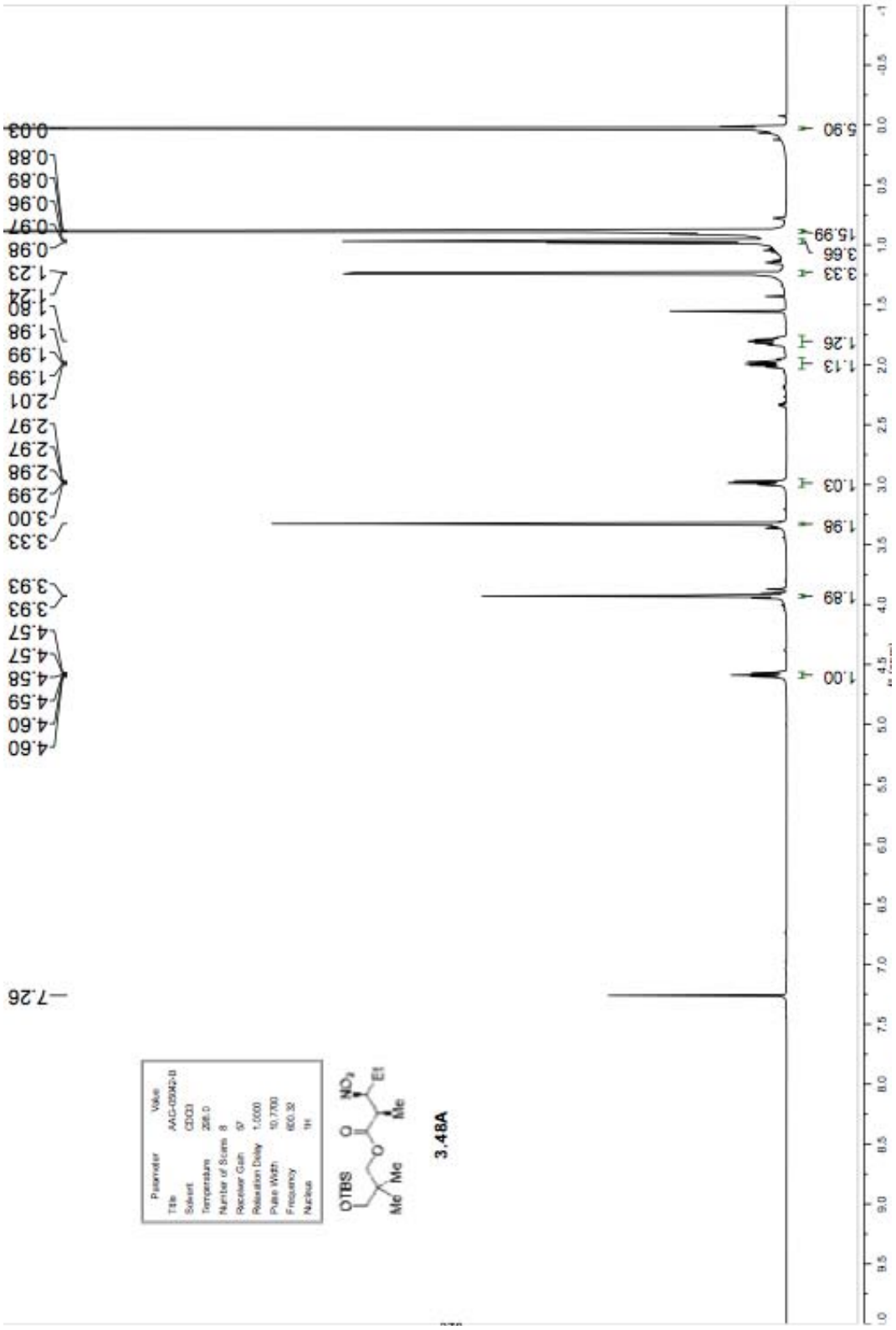

9.31
13.19
23.69
41.81
65.67
89.69
118.28
132.08
172.32
Parameter Value
Title AAG-0436-B
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Et
Me
O
O
H2C
3.46A


Parameter Value
Title AAC-0426-C
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
NO2
Et
Me
O
O
H2C
3.46B
3.20
3.25
1.19
1.09
1.02
2.11
1.02
1.01
1.02
1.00


10.25
13.93
25.42
43.33
65.60
91.50
118.47
128.59
131.98
171.62
Parameter Value
Title AAG-04086-C
Solvent CDCl3
Temperature 296.2
Number of Scans 1024
Receiver Gain 812
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Et
Me
O
O
H2C
3.46B


Parameter Value
Title AAG-04264-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Et
Me
Me
O
O
Me
3.47
f1 (ppm)


3.77
11.23
20.08
22.85
23.33
45.96
53.94
72.73
83.79
95.52
173.74
Parameter Value
Title AAG-0424-0
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.91
Nucleus 13C
NO2
Et
Me
Me
O
O
Me
3.47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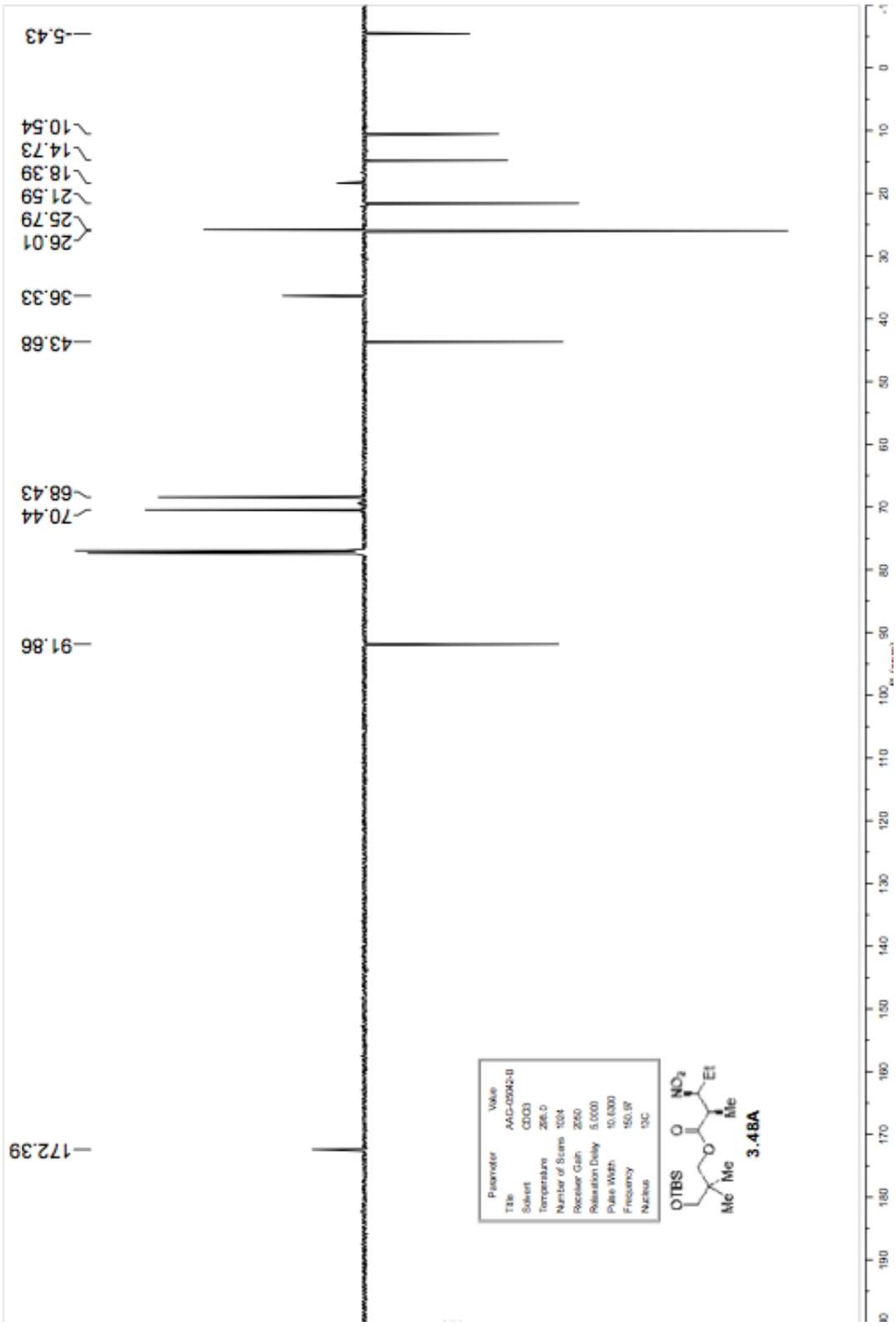
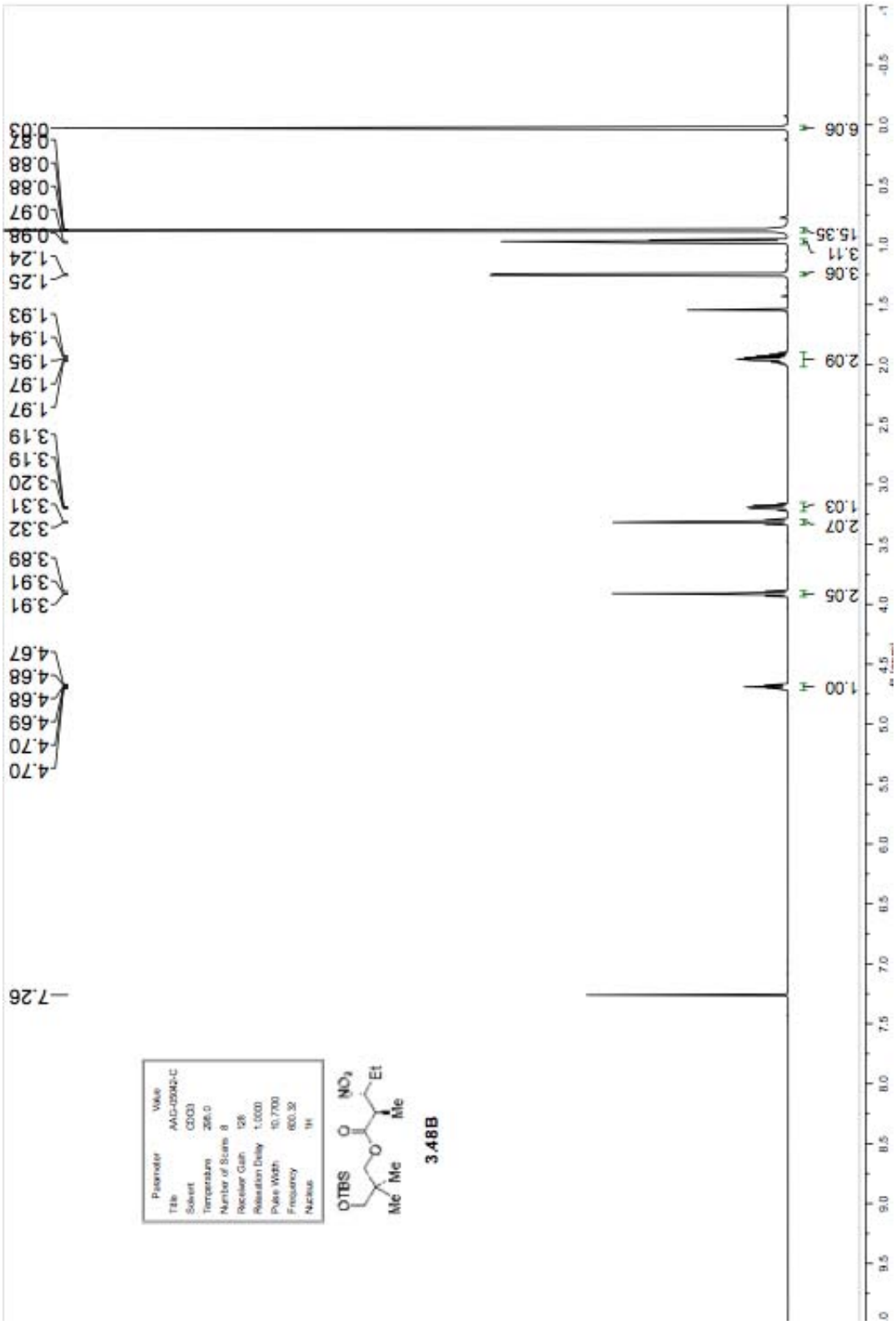
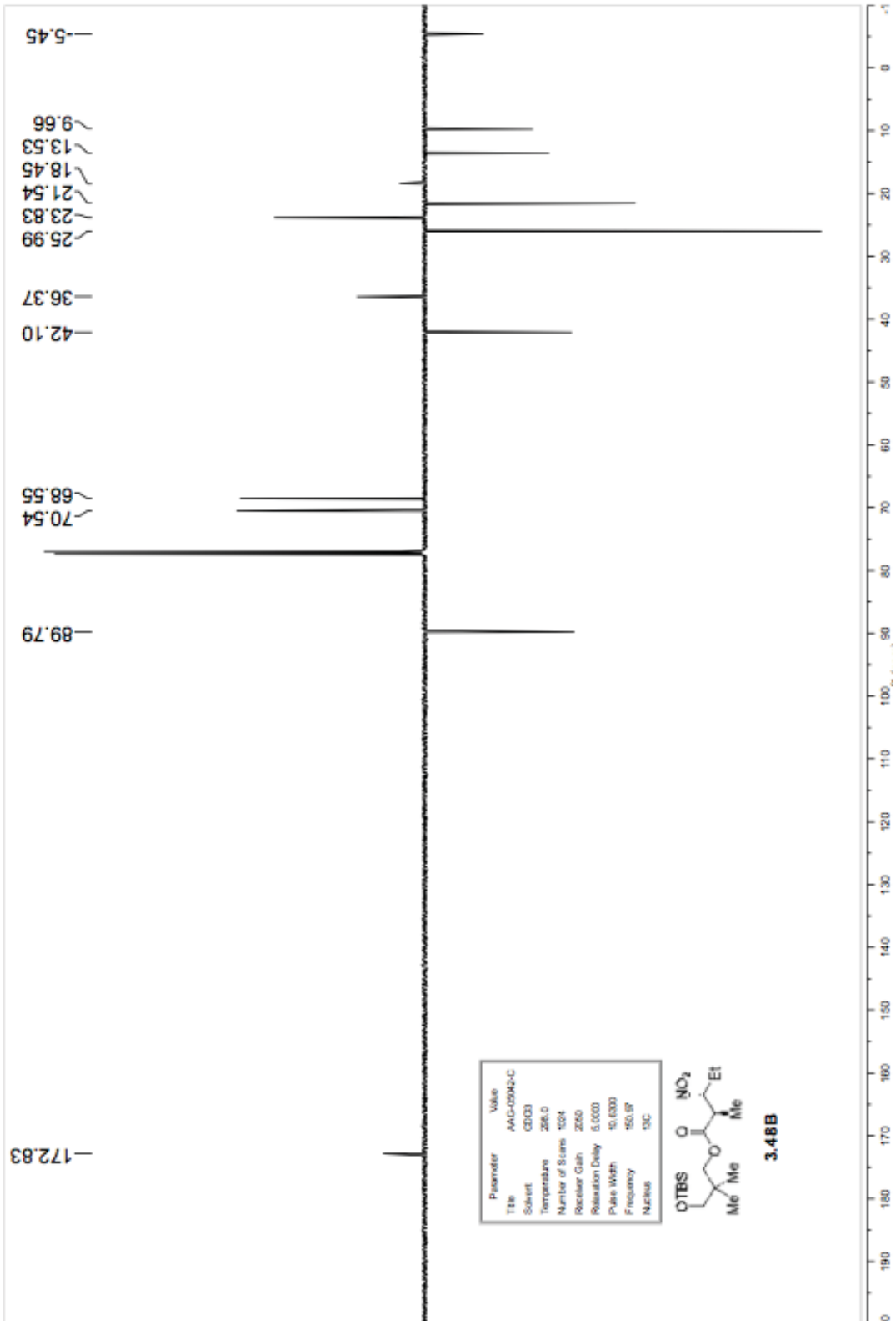
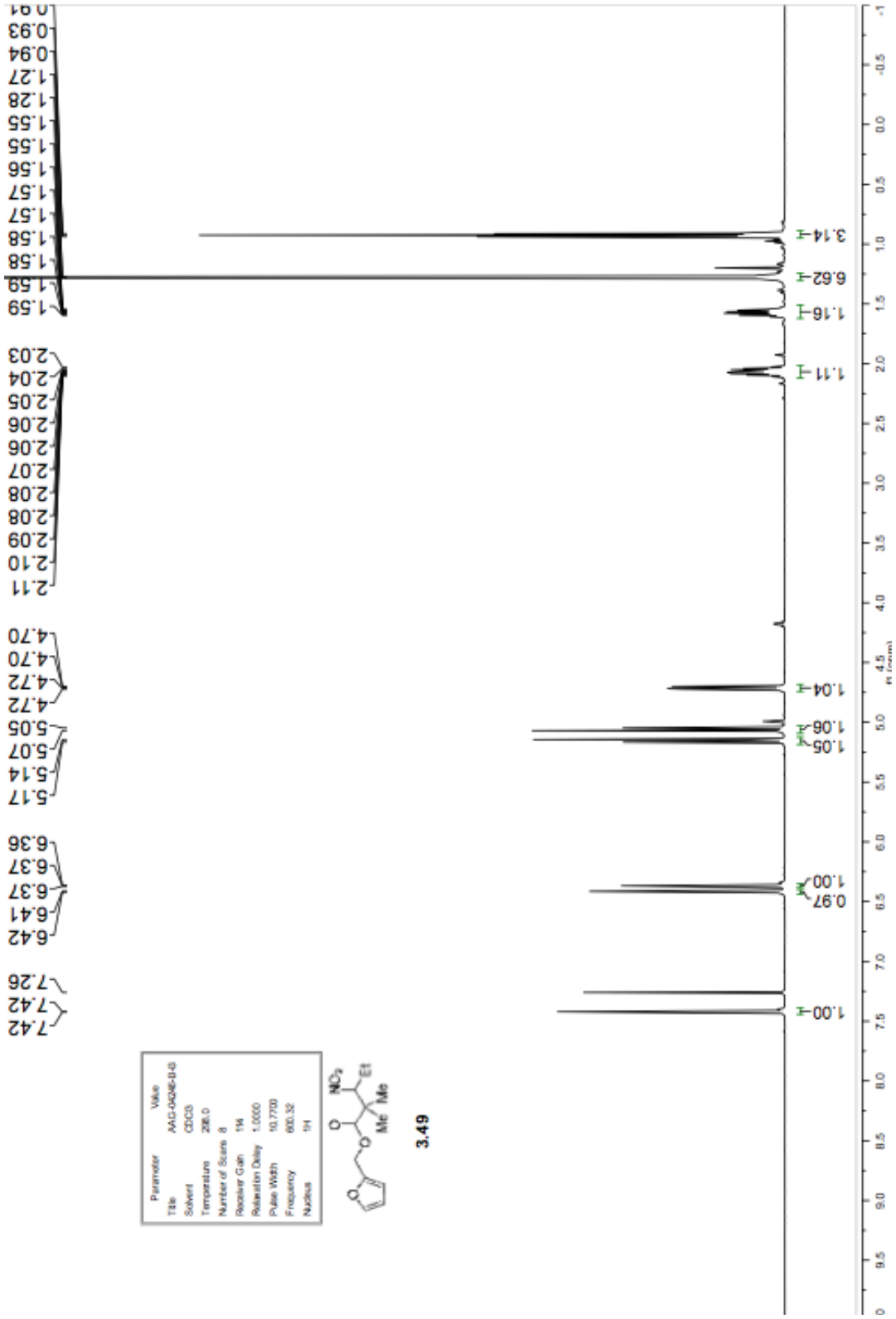
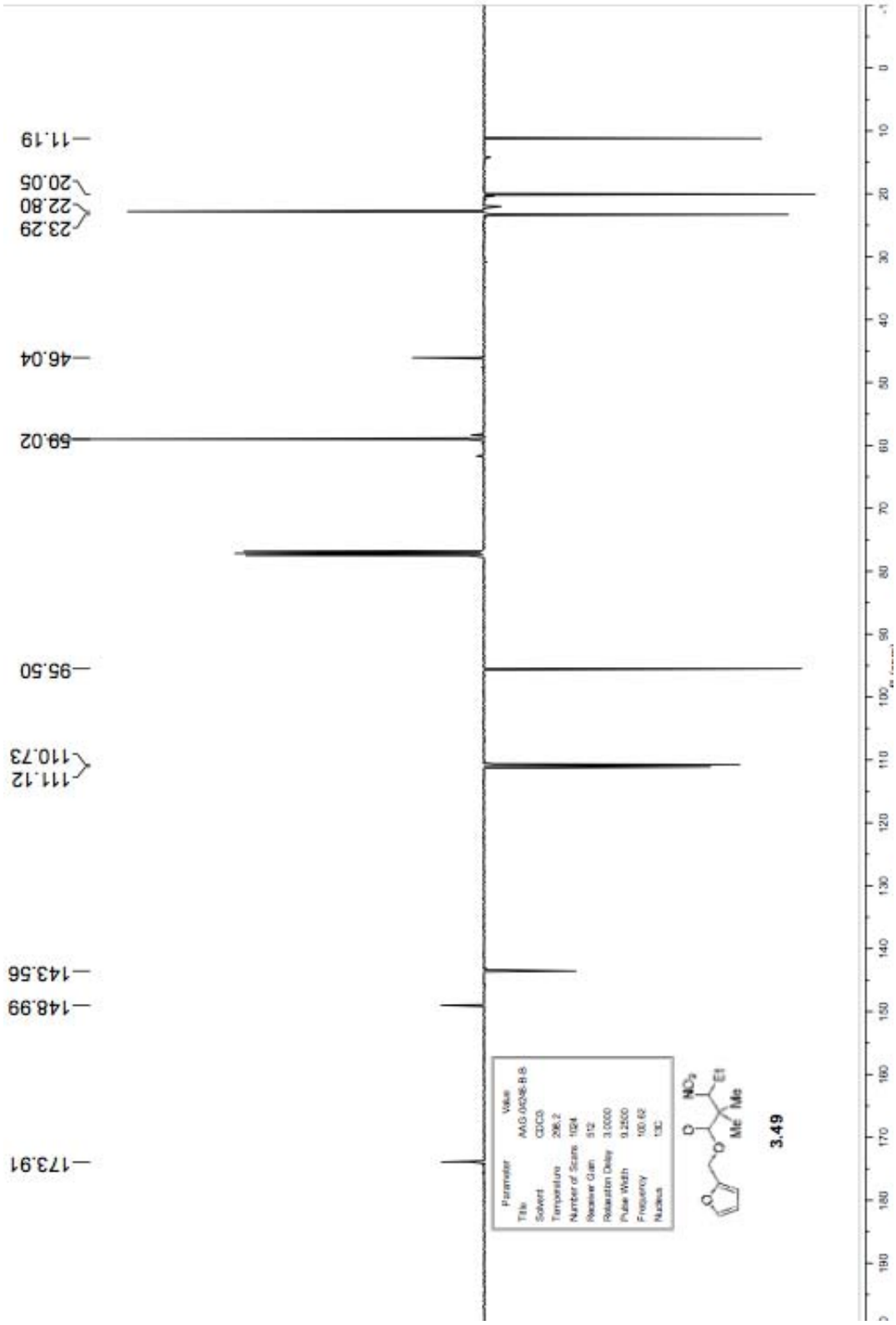
0.88
0.89
0.96
0.97
0.98
1.23
1.24
1.80
1.98
1.99
1.99
2.01
2.97
2.97
2.98
2.99
3.00
3.33
3.93
3.93
4.57
4.57
4.58
4.59
4.60
4.60
5.90
15.99
3.66
3.33
1.26
1.13
1.03
1.98
1.89
1.00
Parameter Value
Title AAC-0504z-8
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
OTBS
NO2
Et
Me
Me
Me
3.48A

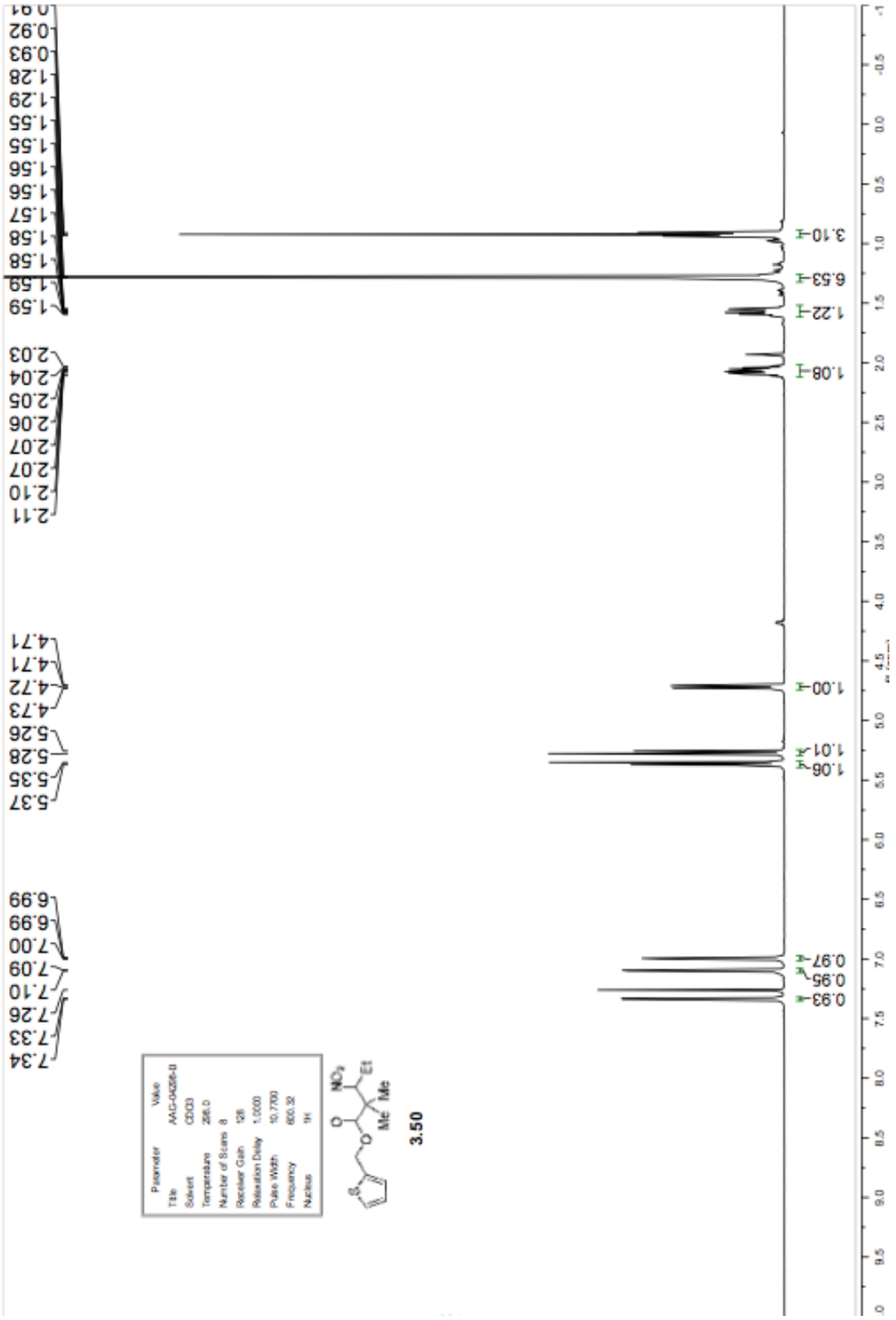

-5.43
10.54
14.73
18.39
21.59
25.79
26.01
36.33
43.68
68.43
70.44
91.86
172.39
Parameter Value
Title AAG-05942-II
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
OTBS
Me Me
NO2
Et
Me
3.48A

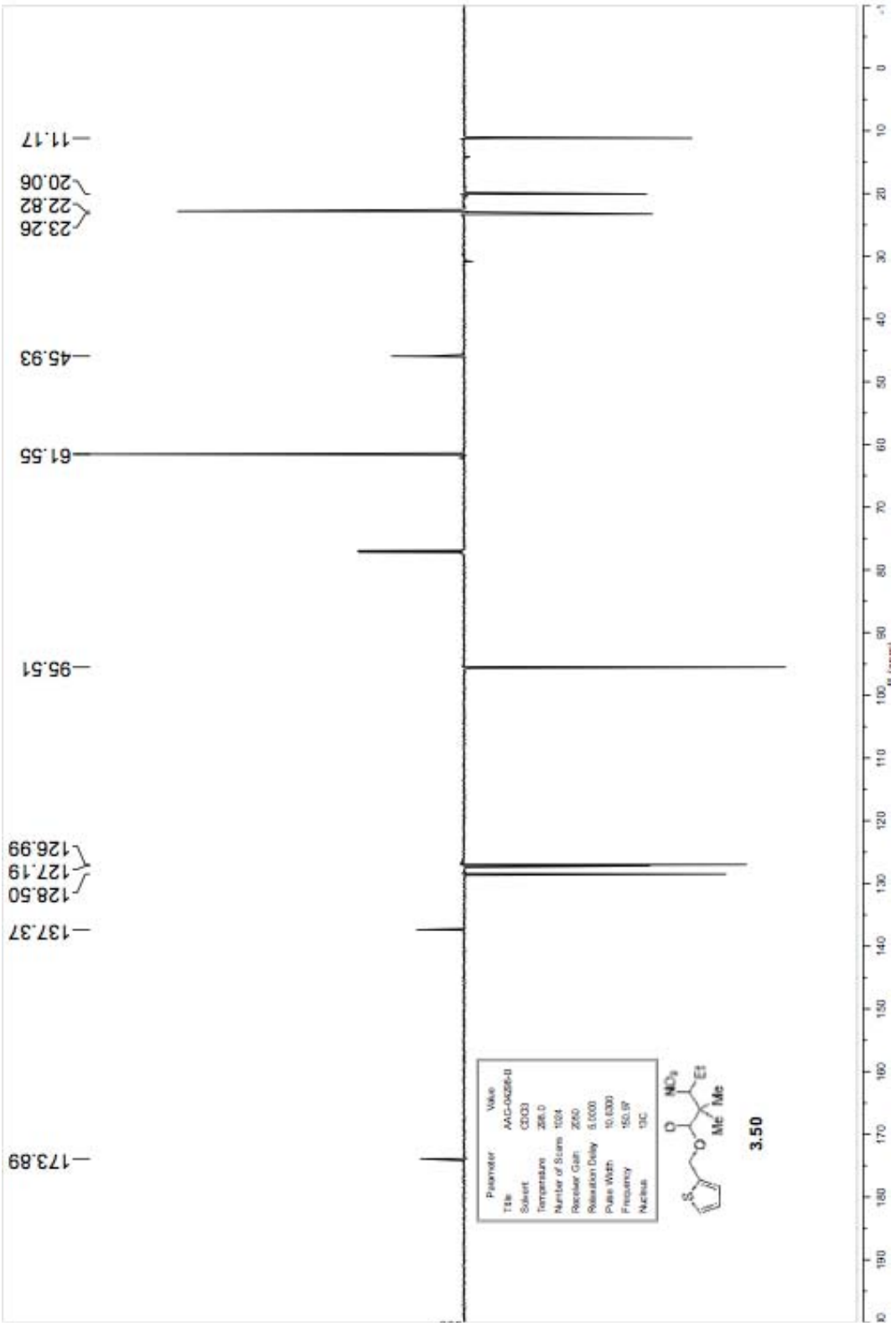

Parameter Value
Title AAD-05042-C
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 126
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
OTBS
O
NO2
Et
Me
Me
Me
3.48B
0.03
0.87
0.88
0.88
0.97
0.98
1.24
1.25
1.93
1.94
1.95
1.97
1.97
3.19
3.19
3.20
3.31
3.32
3.89
3.91
3.91
4.67
4.68
4.68
4.69
4.70
4.70
7.26
6.06
15.35
3.11
3.06
2.09
1.03
2.07
2.05
1.00

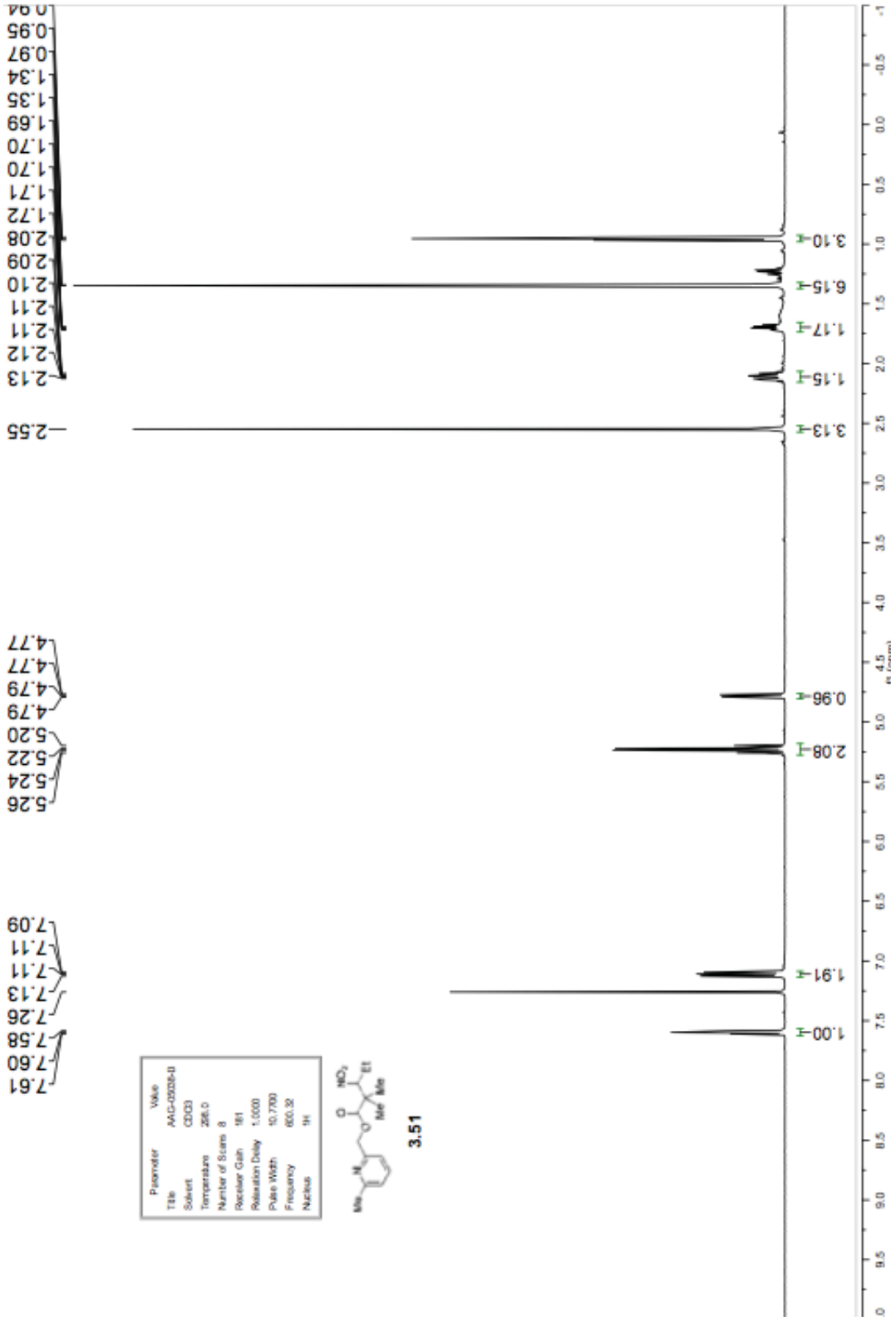

-5.45
9.66
13.53
18.45
21.54
23.83
25.99
36.37
42.10
68.55
70.54
89.79
172.83
Parameter Value
Title AAG-09342-C
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.97
Nucleus 13C
OTBS
O
NO2
Et
Me
Me
Me
3.48B

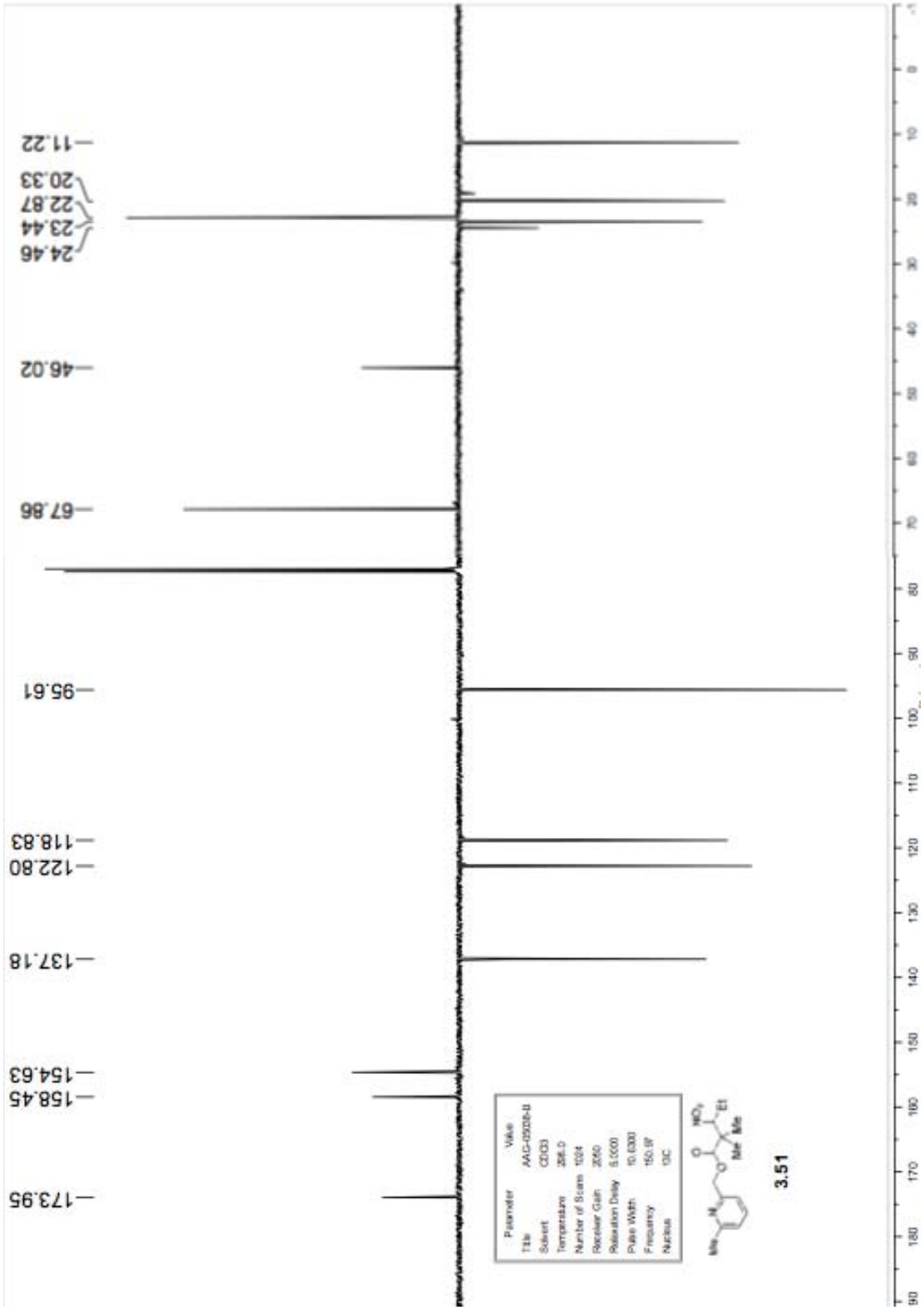

Parameter Value
Title AAG-04046-01-S
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 114
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
3.49


11.19
20.05
22.80
23.29
46.04
59.02
95.50
110.73
111.12
143.56
148.99
173.91
Parameter Value
Title AAG-0606-B-B
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Et
Me
Me
3.49


Parameter Value
Title AAG-04268-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 128
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
3.50


11.17
20.06
22.82
23.26
45.93
61.55
95.51
126.99
127.19
128.50
137.37
173.89
Parameter Value
Title AAG-04356-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0300
Frequency 150.91
Nucleus 13C
3.50


Parameter Value
Title AAG-03028-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
3.51
0.94
0.95
0.97
1.34
1.35
1.69
1.70
1.70
1.71
1.72
2.08
2.09
2.10
2.11
2.11
2.12
2.13
2.55
4.77
4.77
4.79
4.79
5.20
5.22
5.24
5.26
7.09
7.11
7.11
7.13
7.26
7.58
7.60
7.61
3.10
6.15
1.17
1.15
3.13
0.96
2.08
1.91
1.00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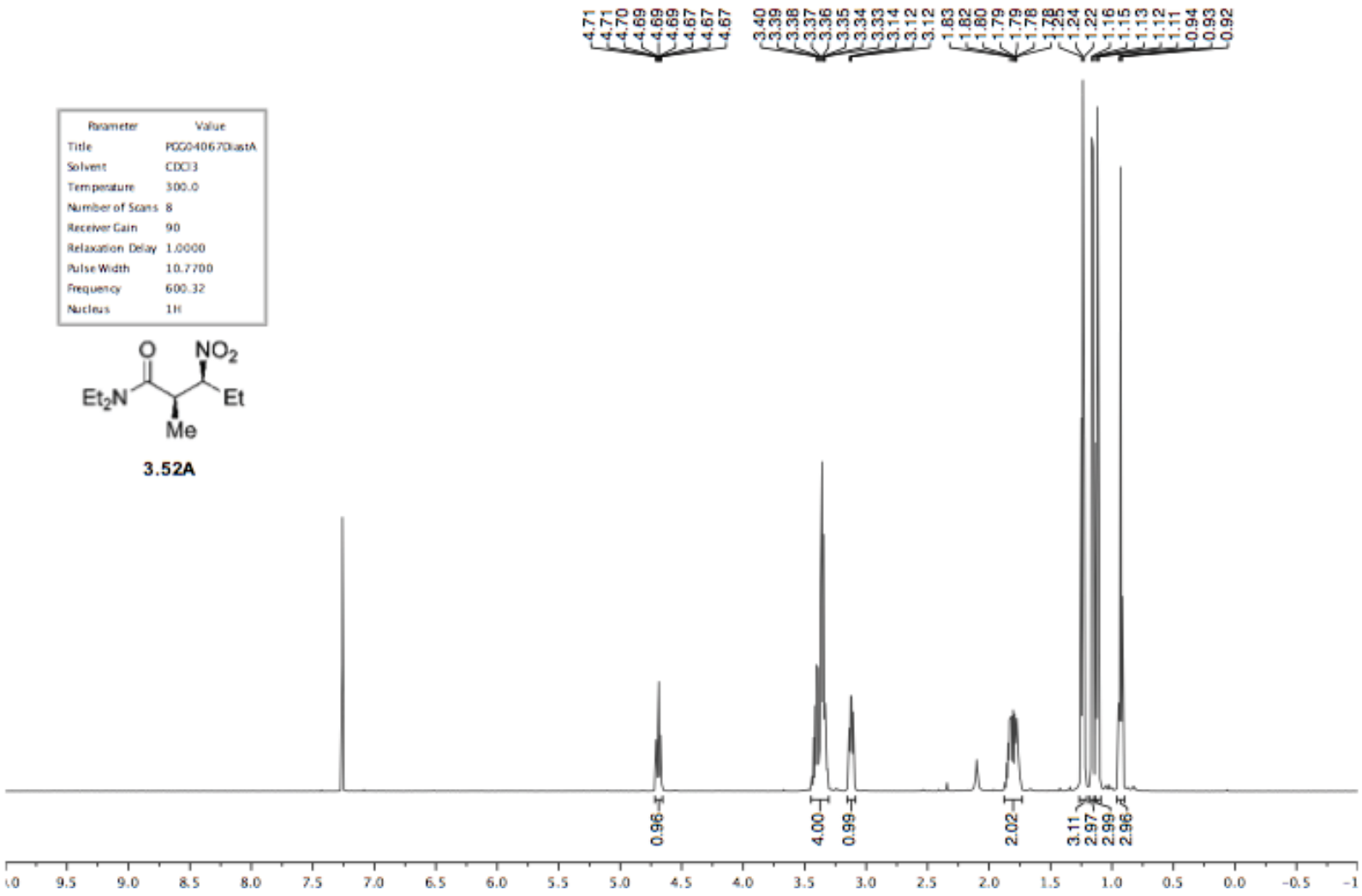
20.33
22.87
23.44
24.46
46.02
67.86
95.61
118.83
122.80
137.18
154.63
158.45
173.95
Parameter Value
Title AAC-09208-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0300
Frequency 150.91
Nucleus 13C
3.51


4.71
4.71
4.70
4.69
4.69
4.69
4.67
4.67
4.67
3.40
3.39
3.38
3.37
3.36
3.35
3.34
3.33
3.14
3.12
3.12
1.83
1.82
1.80
1.79
1.79
1.78
1.78
1.25
1.24
1.22
1.16
1.15
1.13
1.12
1.11
0.94
0.93
0.92
Parameter Value
Title PGG040670lastA
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 90
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
Et2N
Et
Me
3.52A
0.96
4.00
0.99
2.02
3.11
2.97
2.99
2.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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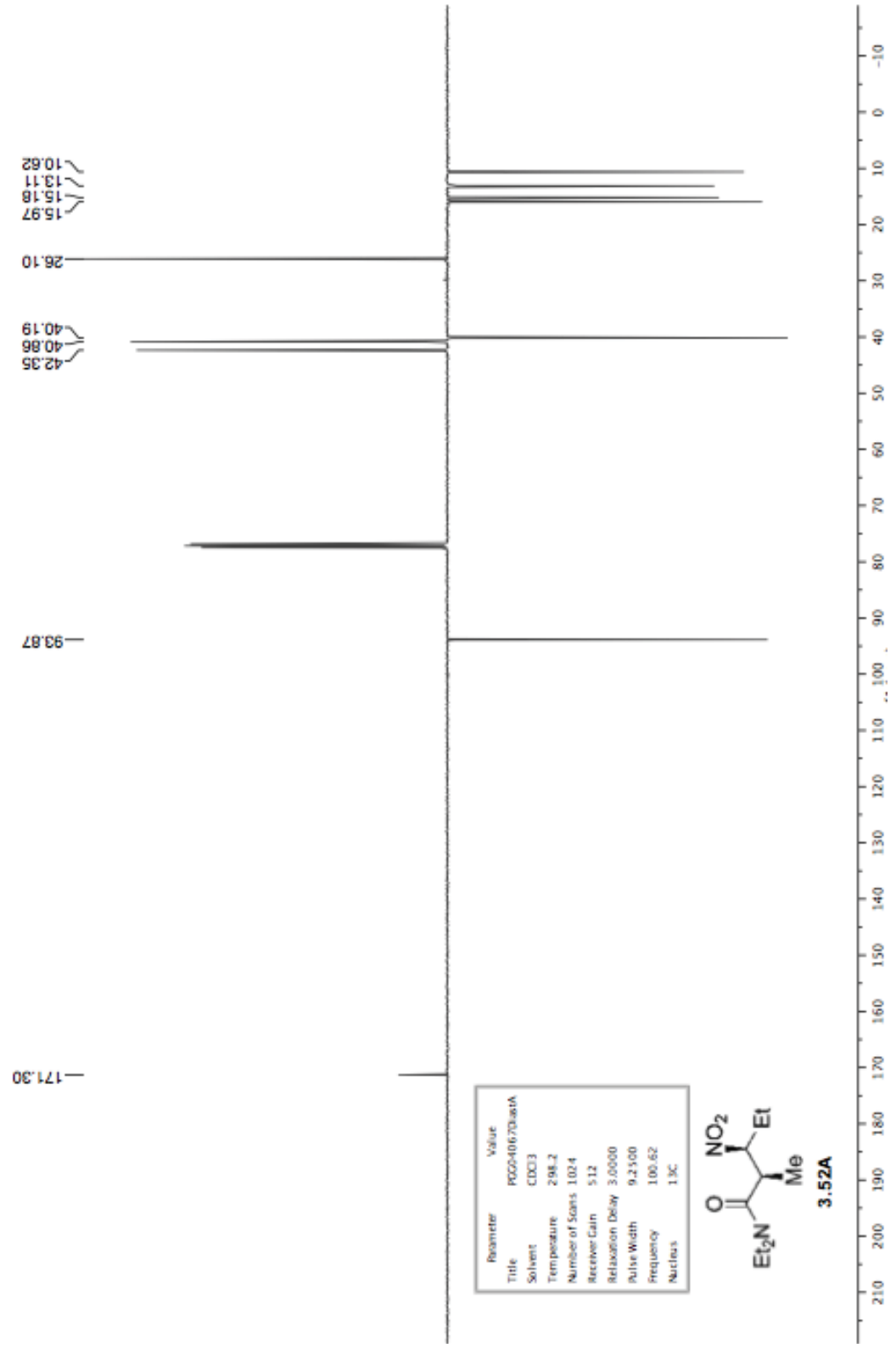
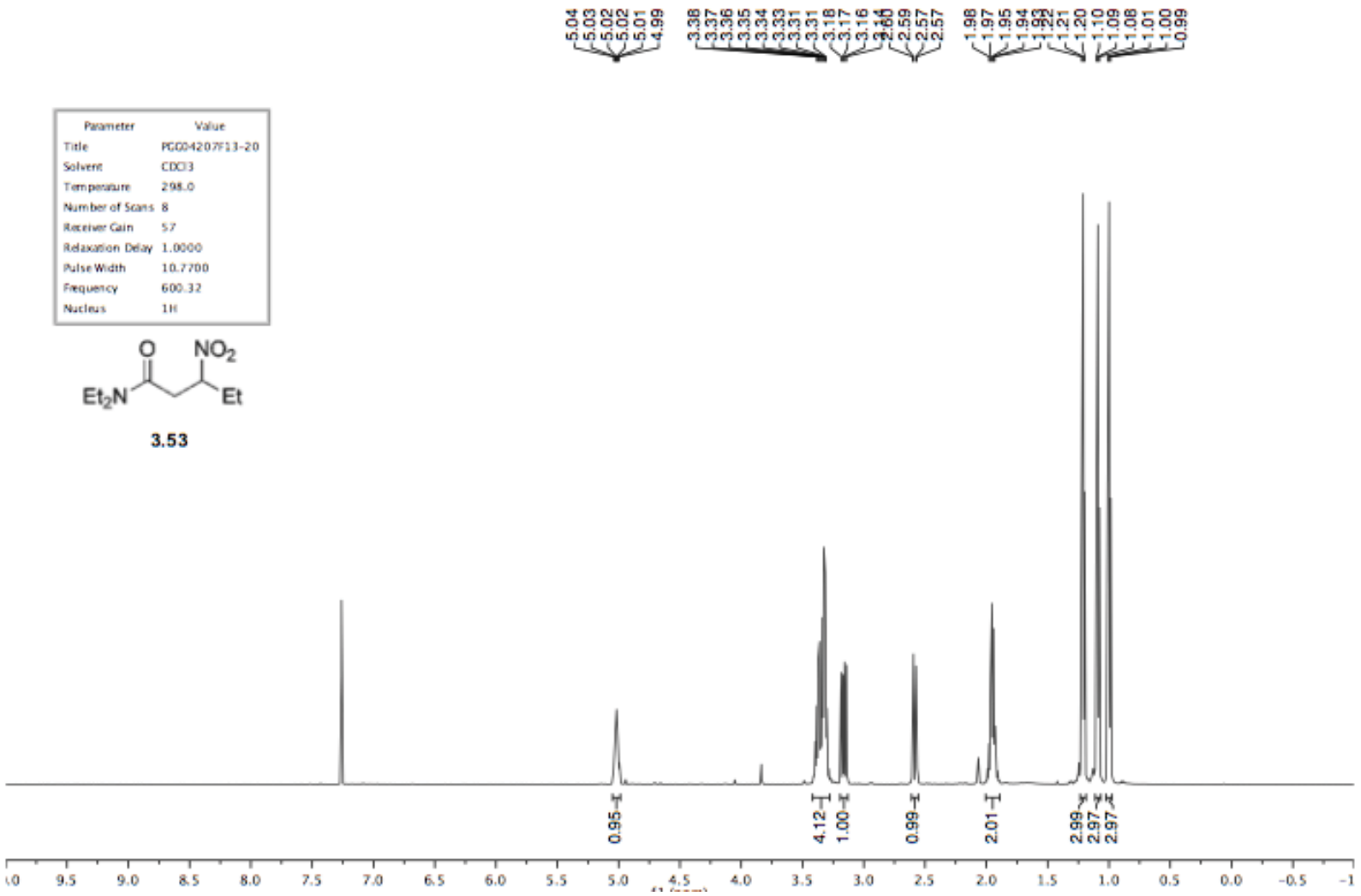
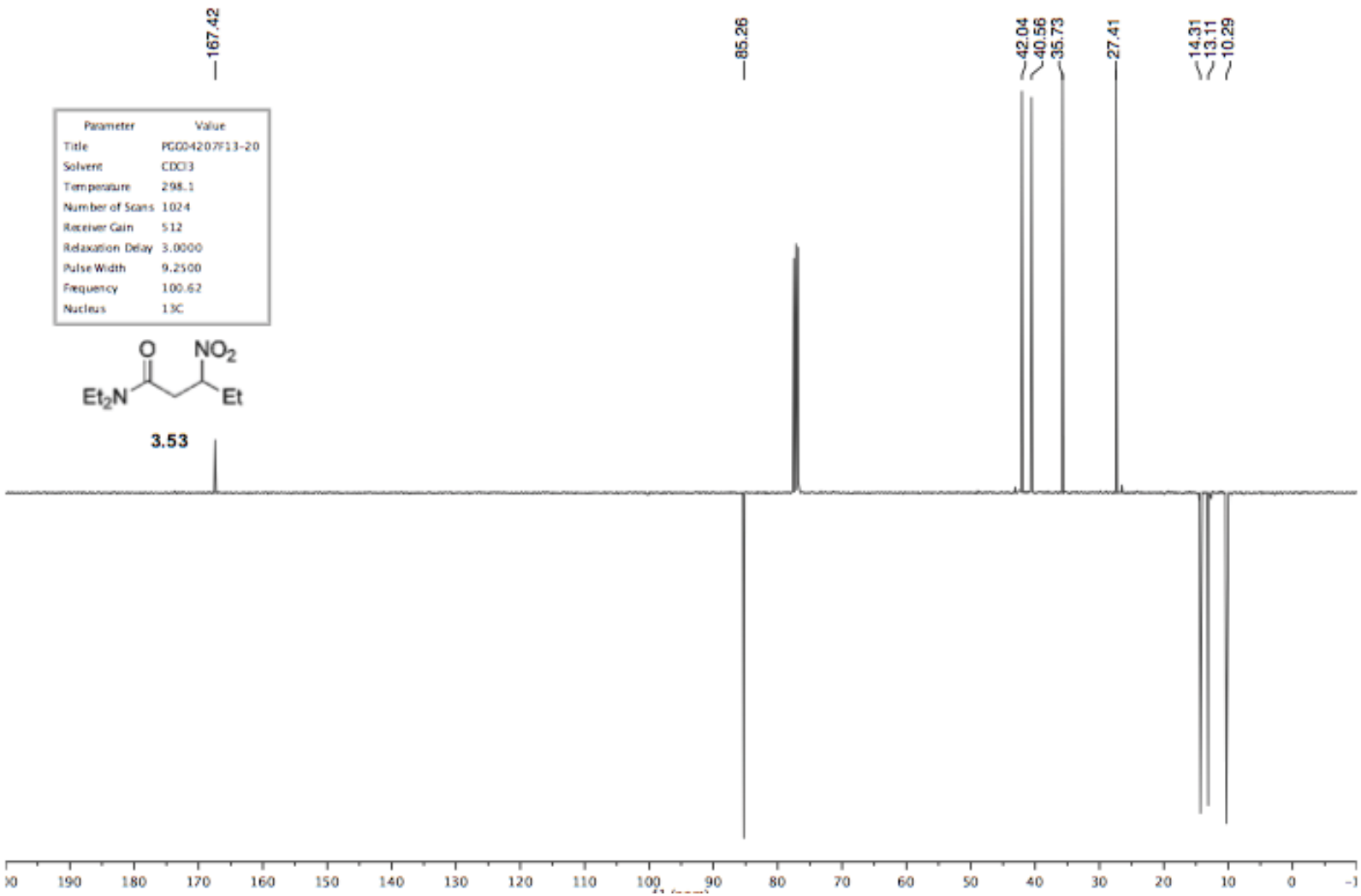
0.0
-0.5

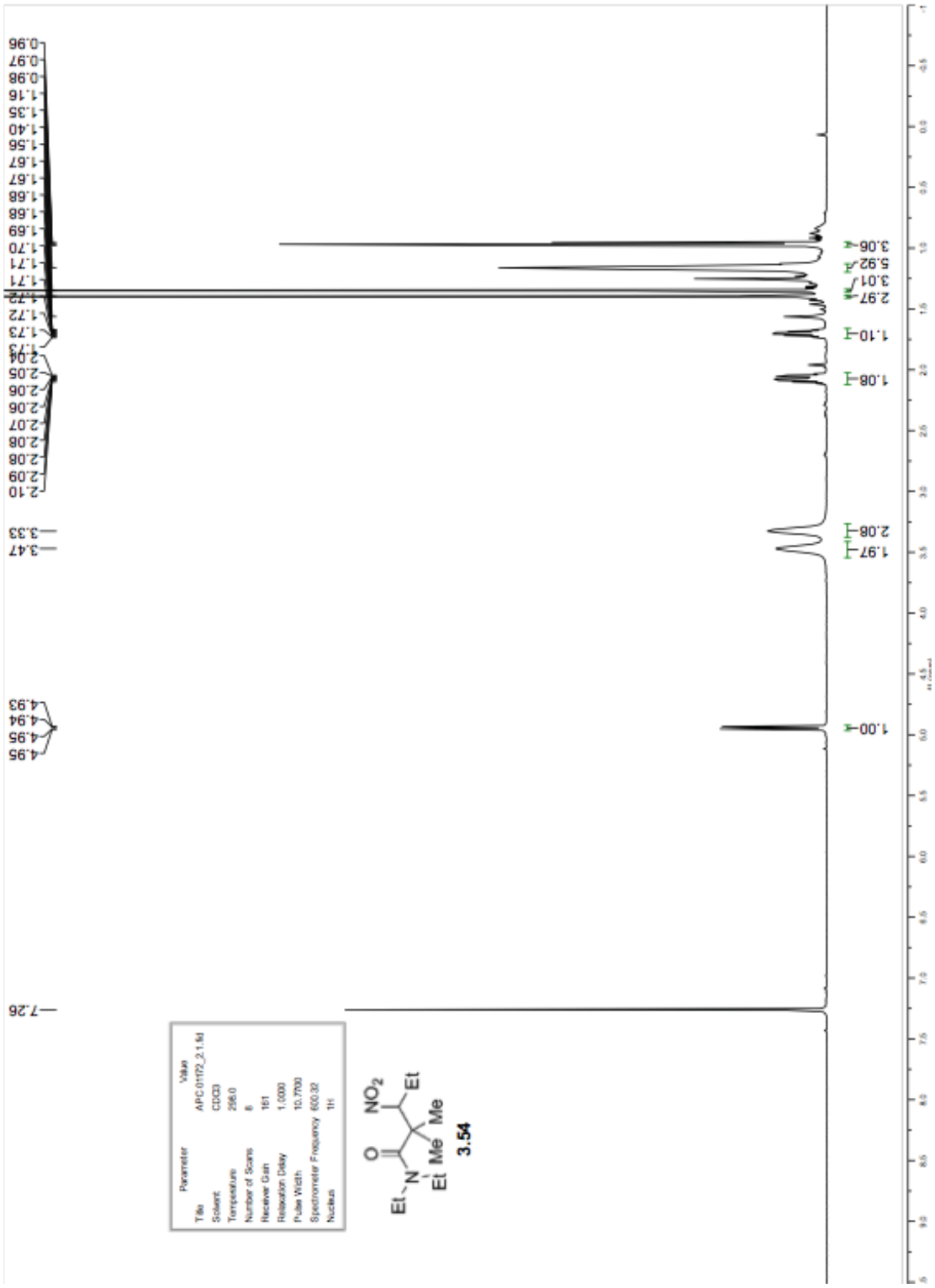

171.30
93.87
42.35
40.86
40.19
26.10
15.97
15.18
13.11
10.62
Parameter Value
Title PDD2406703astA
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
NO2
Et
Et2N
Me
3.52A

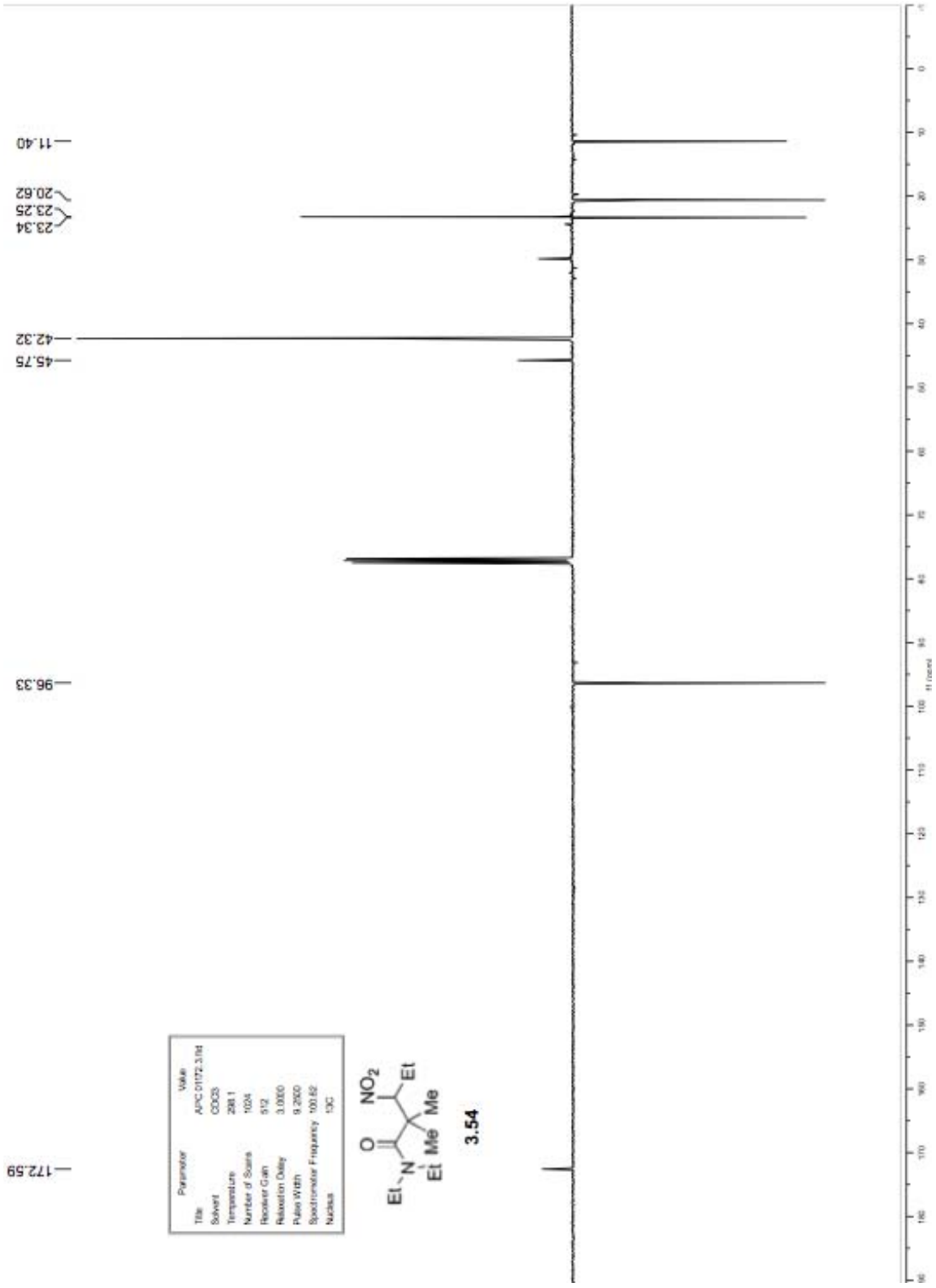
Parameter Value
Title PGD04067Dia68
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Et
O
Et2N
Me
3.52B
0.93
4.97
1.33
0.97
3.00
3.01
2.89
2.91

172.25
90.75
42.17
40.72
38.38
24.24
14.71
14.51
12.98
9.64
Parameter Value
Title PGE040607Bas8
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Et
Me
O
Et2N
3.52B


Parameter Value
Title PGD04207F13-20
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
Et2N
Et
3.53
5.04 5.03 5.02 5.02 5.01 4.99
3.38 3.37 3.36 3.35 3.34 3.33 3.31 3.31 3.18 3.17 3.16 2.60 2.59 2.57 2.57
1.98 1.97 1.95 1.94 1.93 1.92 1.21 1.20 1.10 1.09 1.08 1.01 1.00 0.99
0.95 4.12 1.00 0.99 2.01 2.99 2.97 2.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


167.42
85.26
42.04
40.56
35.73
27.41
14.31
13.11
10.29
Parameter Value
Title PGD04207F13-20
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
NO2
Et2N
Et
3.53


Parameter Value
Title APC-01172_2.1.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7000
Spectrometer Frequency 600.32
Nucleus 1H
NO2
Et
O
N
Et
Me
Me
Et
3.54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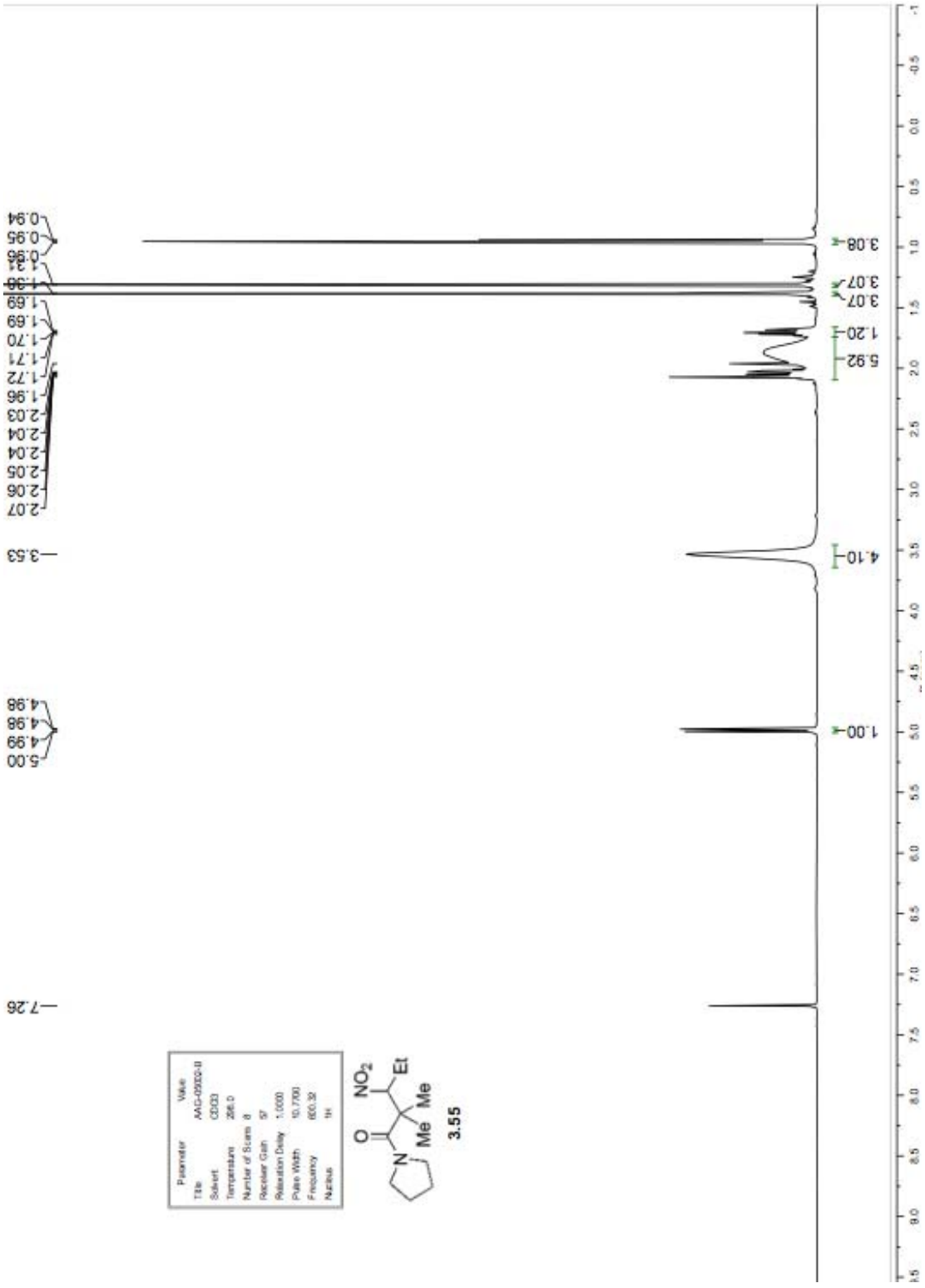
20.62
23.25
23.34
42.32
45.75
96.33
172.59
Parameter Value
Title APC 01172-3.fid
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Spectrometer Frequency 100.62
Nucleus 13C
O
NO2
Et
Et
N
Et
Me
Me
3.54


0.94
0.95
0.96
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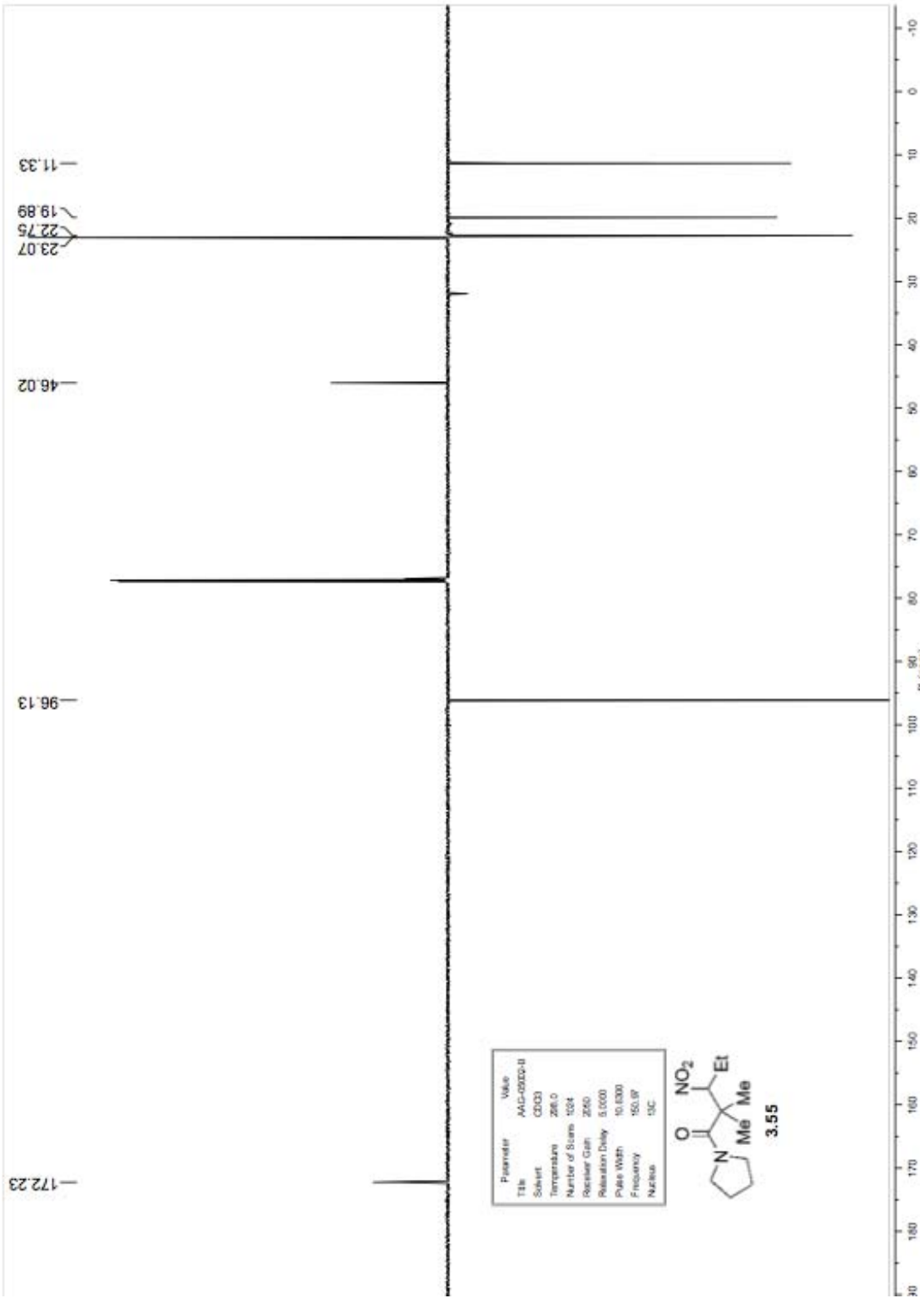
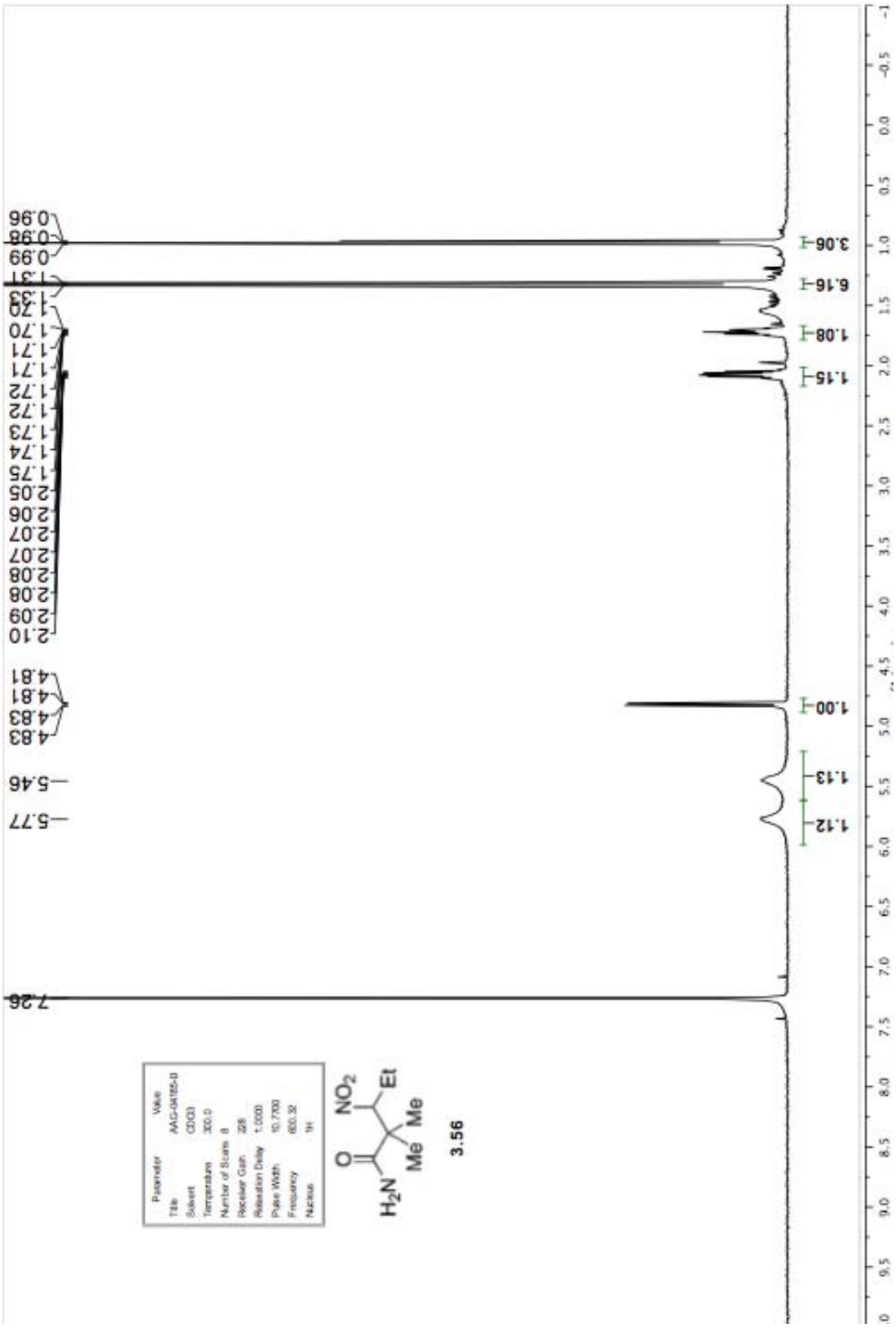
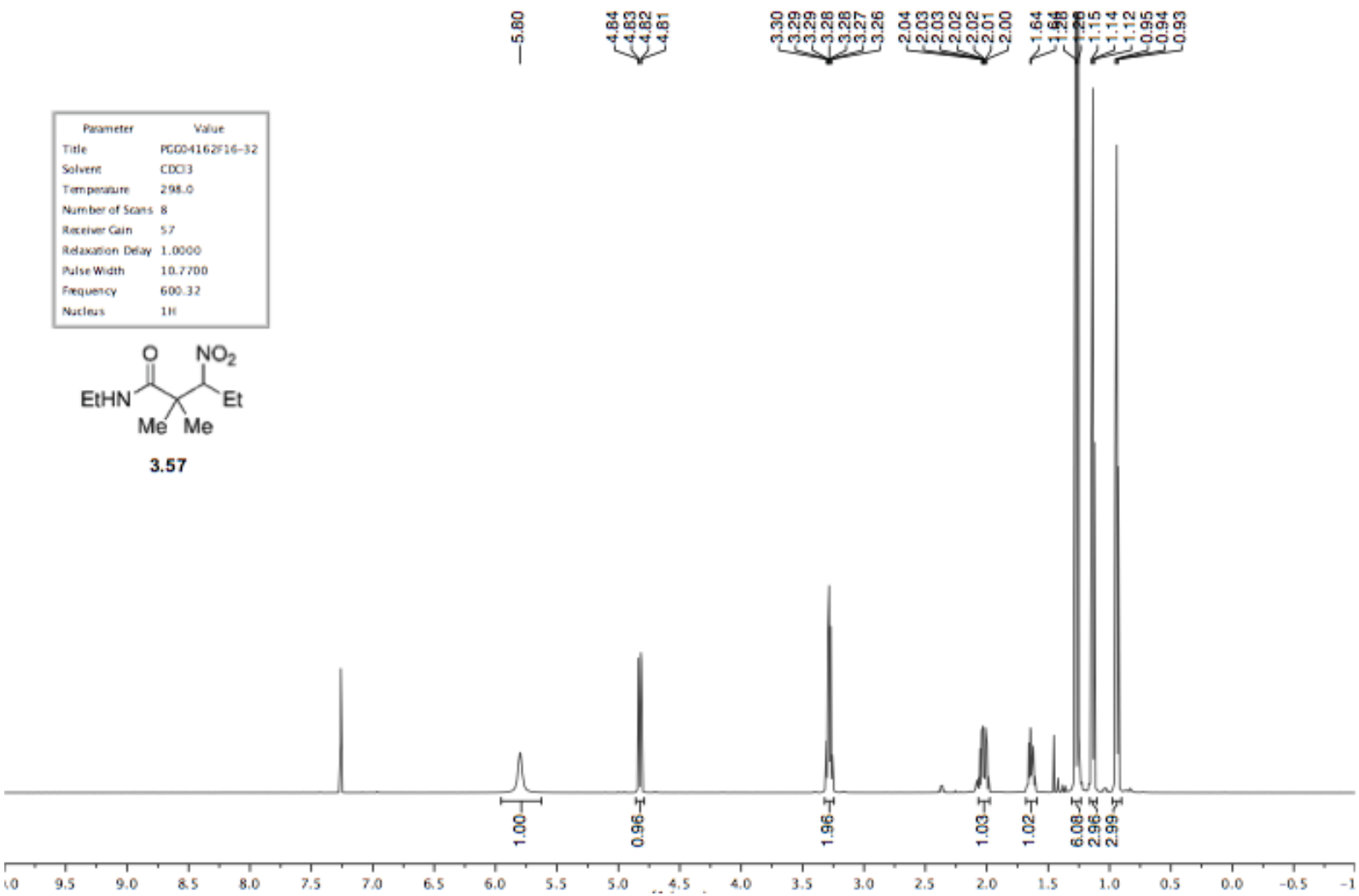
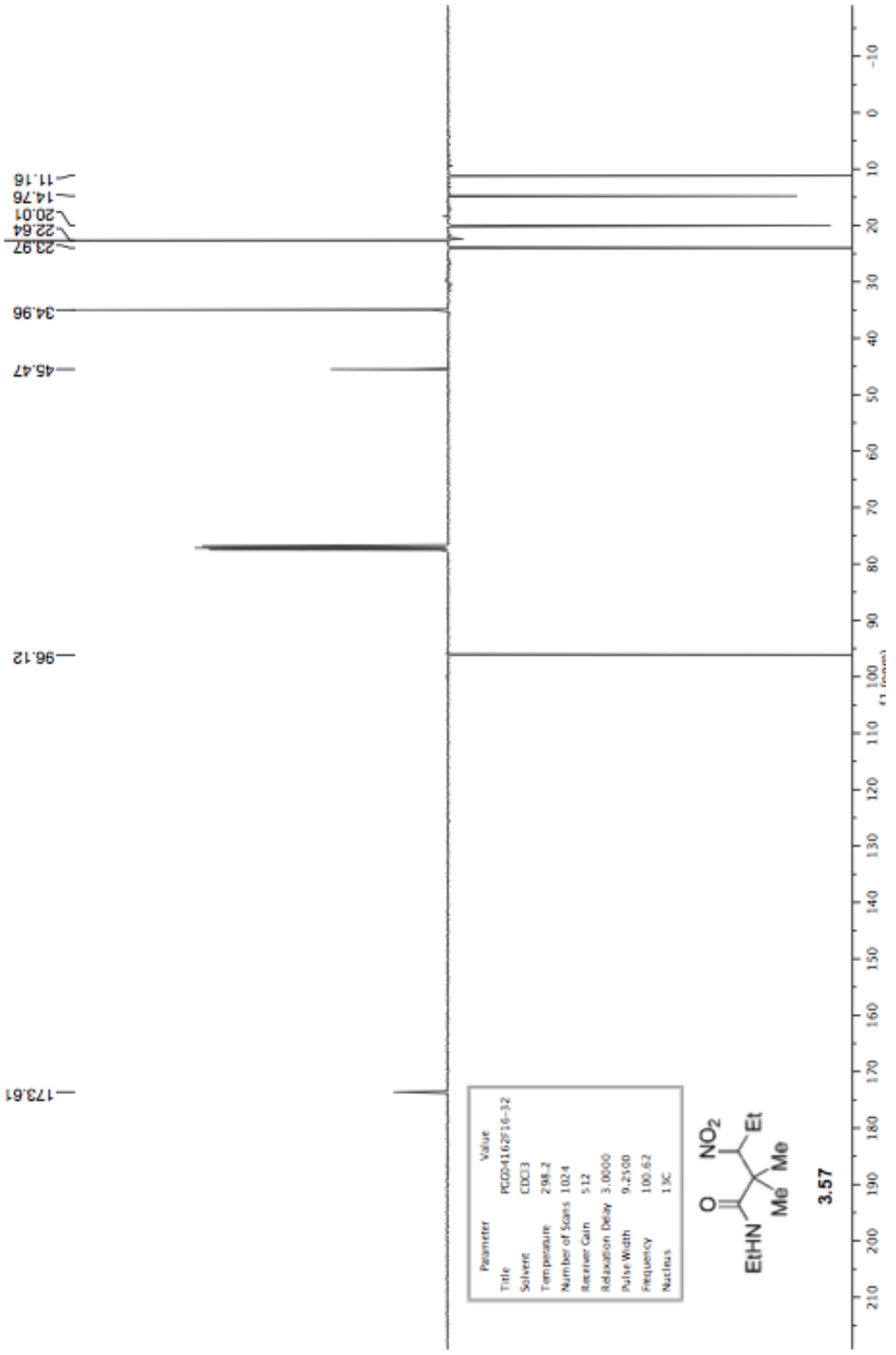
1.69
1.69
1.70
1.71
1.72
1.96
2.03
2.04
2.04
2.05
2.06
2.07
3.53
4.98
4.98
4.99
5.00
7.26
3.08
3.07
3.07
1.20
5.92
4.10
1.00
Parameter Value
Title AAD-03032-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 97
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
O
NO2
Et
Me
Me
N
3.55

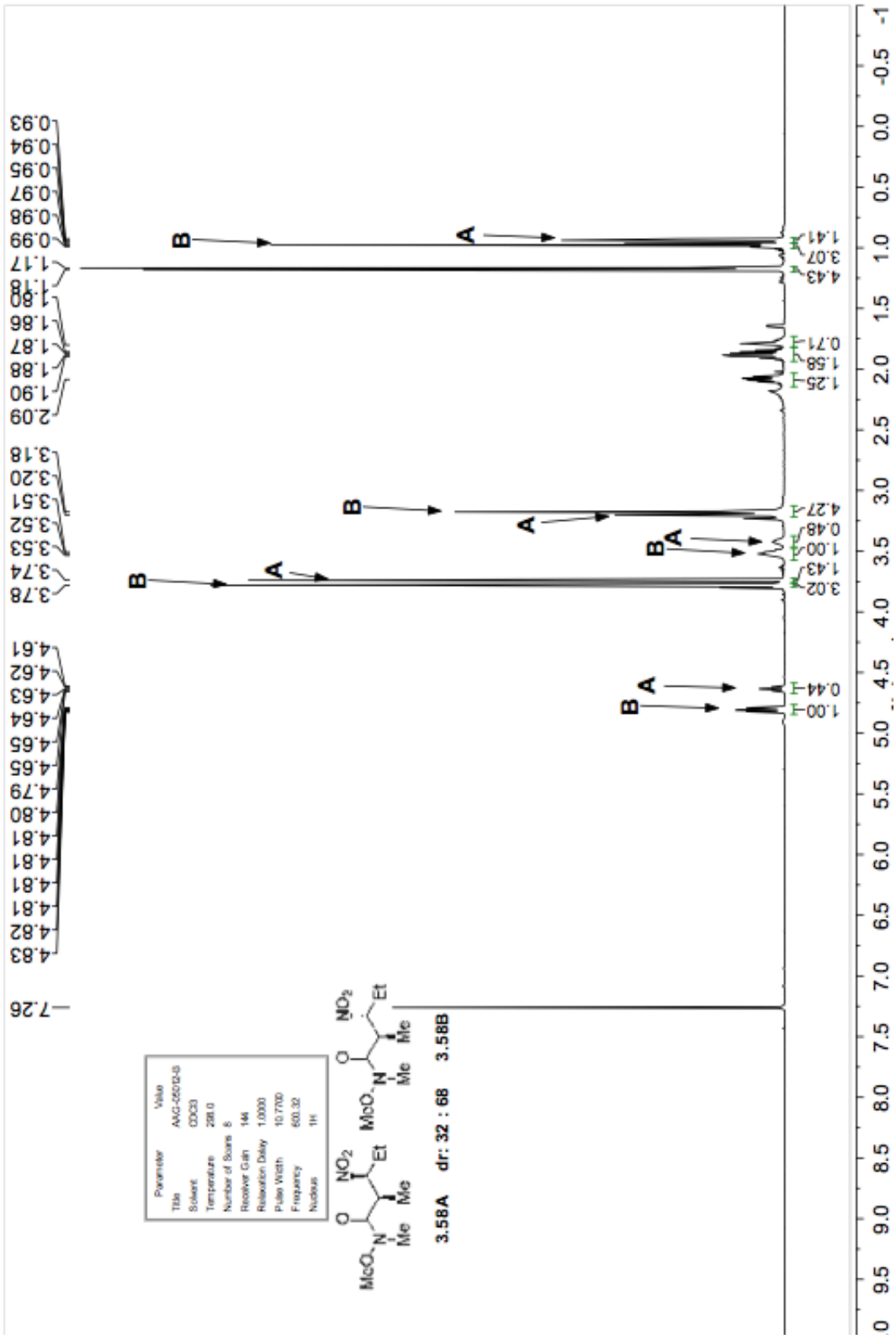

11.33
19.89
22.75
23.07
46.02
96.13
172.23
Parameter Value
Title AAG-0302-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0000
Frequency 150.97
Nucleus 13C
O
NO2
Et
N
Me
Me
3.55

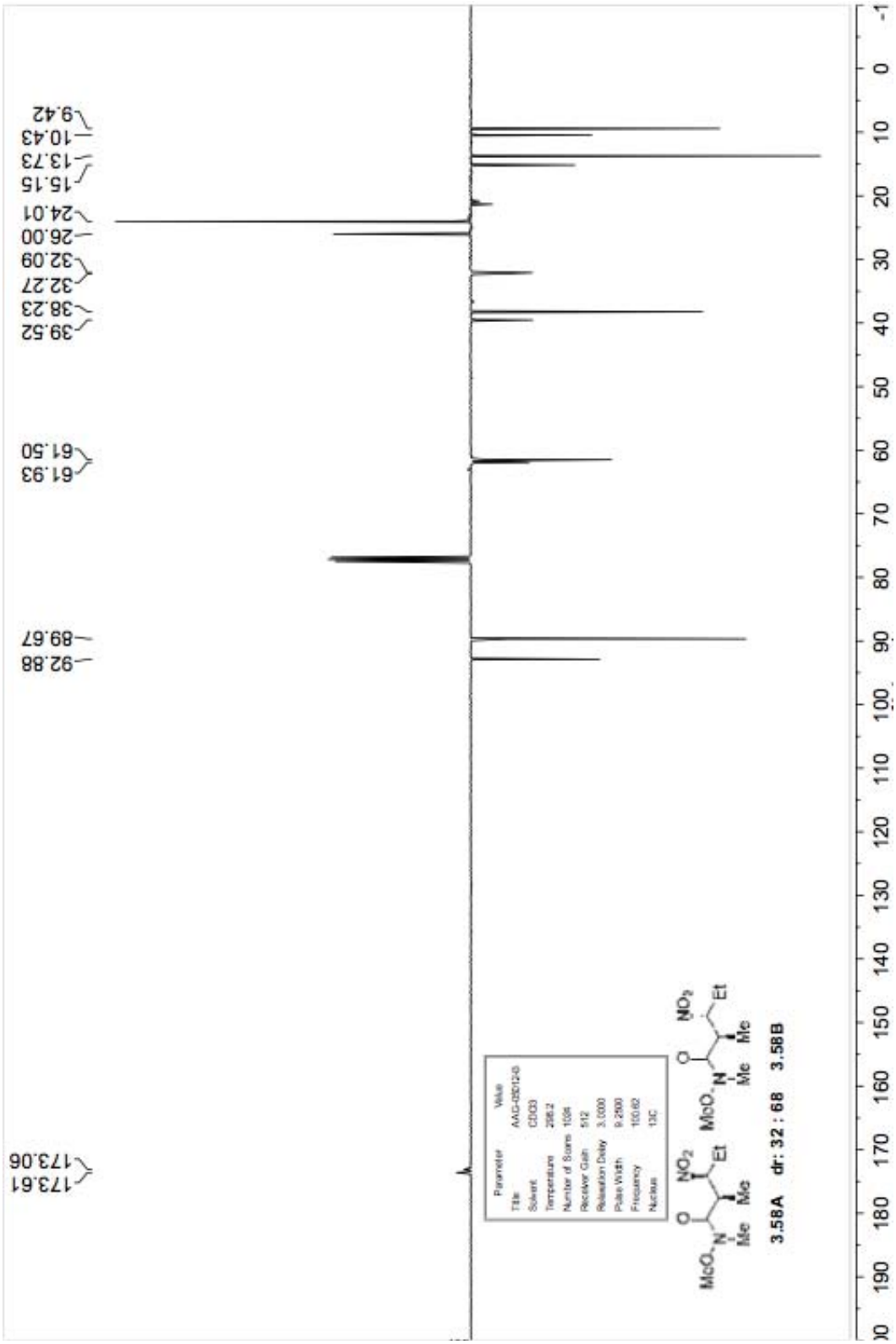

Parameter Value
Title AAG-04185-II
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 226
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
Et
H2N
Me
Me
3.56
0.96
0.98
0.99
1.31
1.33
1.70
1.71
1.71
1.72
1.72
1.73
1.74
1.75
2.05
2.06
2.07
2.07
2.08
2.08
2.09
2.10
4.81
4.81
4.83
4.83
5.46
5.77
7.26
3.06
6.16
1.08
1.15
1.00
1.13
1.12

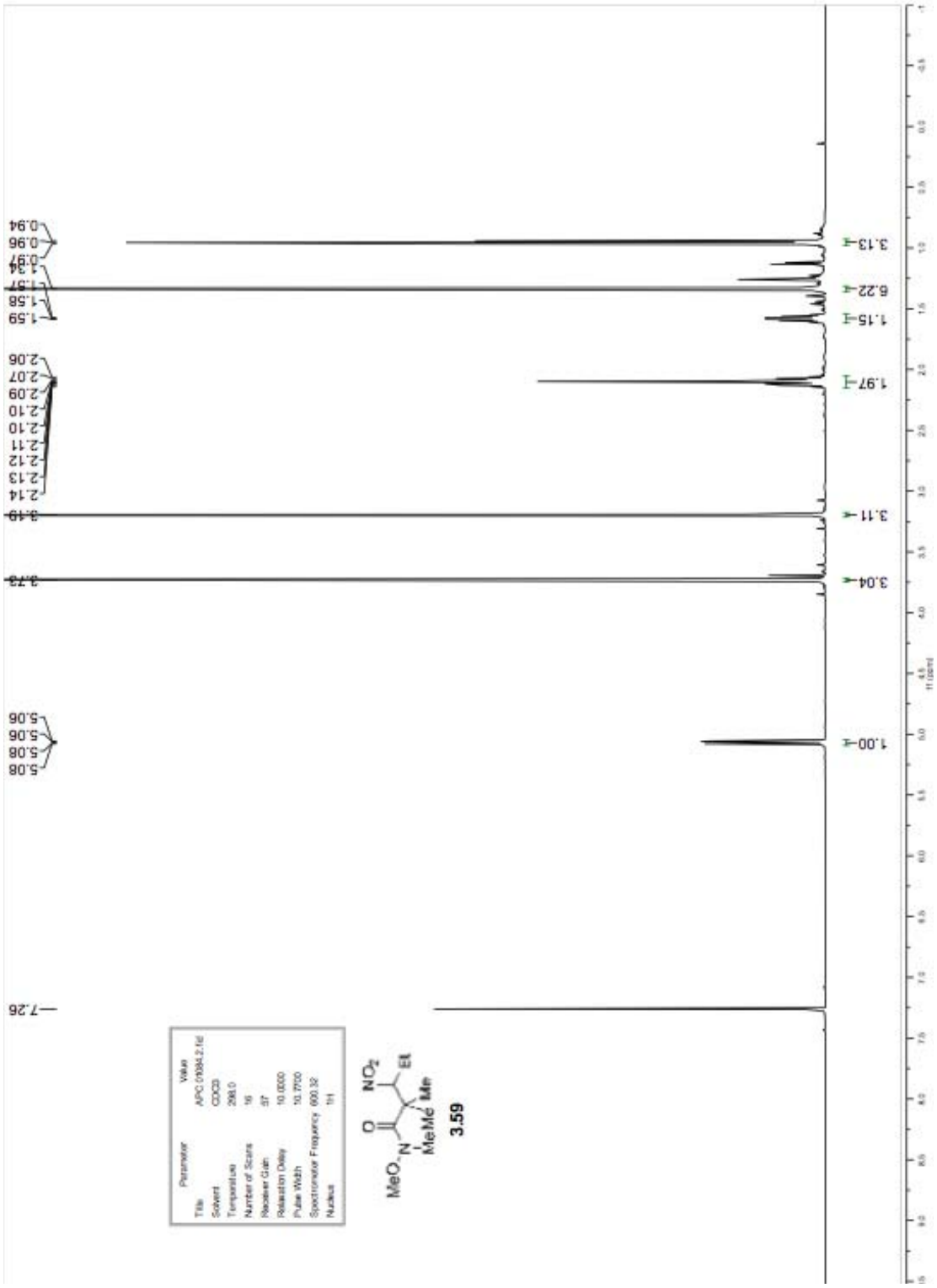
176.59
95.92
45.56
24.12
22.80
20.39
11.19
Parameter Value
Title AAG-04185-II
Solvent CDCl3
Temperature 300.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 6.0000
Pulse Width 10.0000
Frequency 150.9?
Nucleus 13C
O
NO2
Et
H2N
Me
Me
3.56
f1 (ppm)

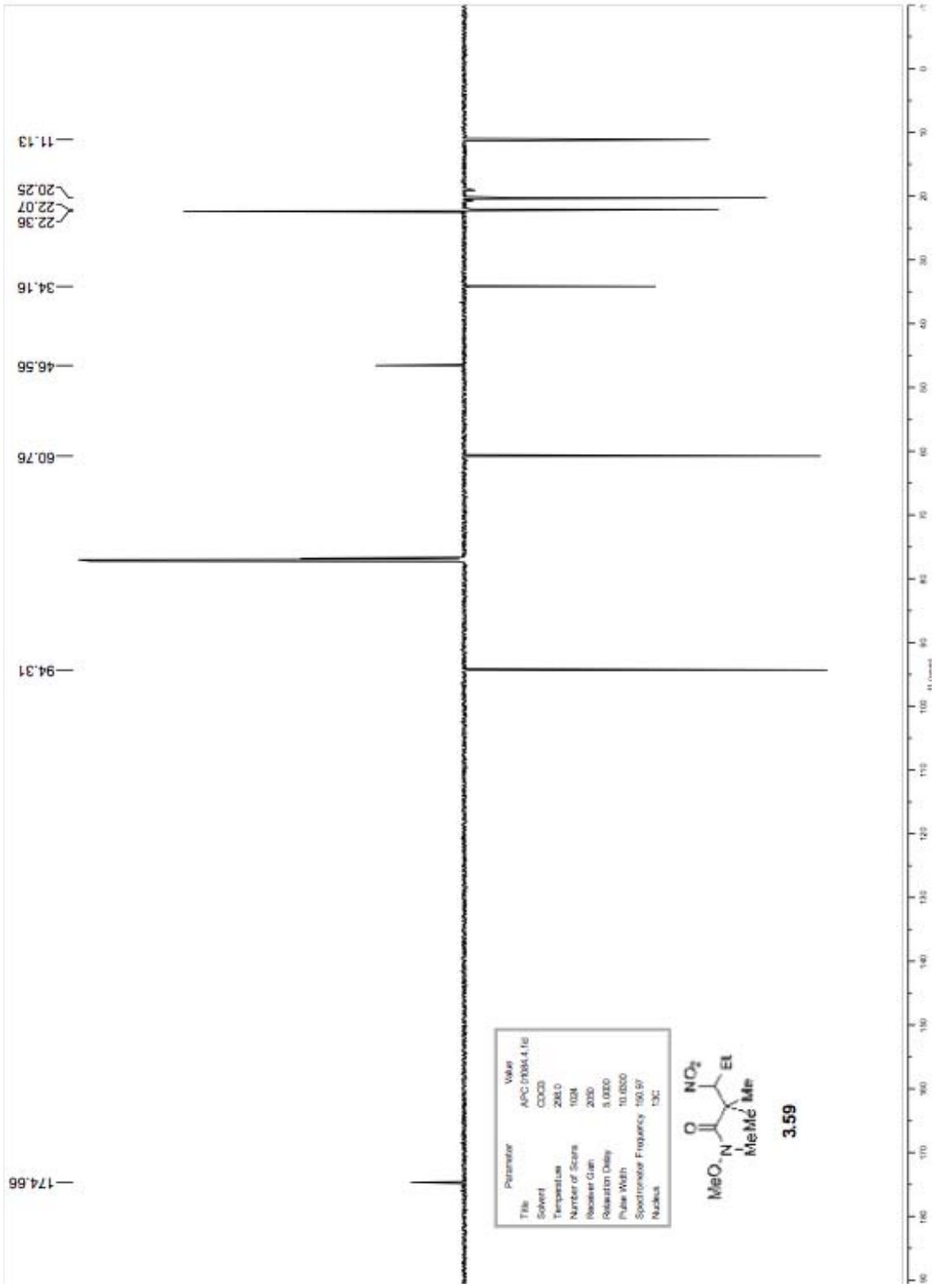

Parameter Value
Title PGD04162F16-32
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
EtHN
Et
Me Me
3.57
5.80
4.84 4.83 4.82 4.81
3.30 3.29 3.29 3.28 3.28 3.27 3.26
2.04 2.03 2.03 2.02 2.02 2.01 2.00
1.64
1.15 1.14 1.12 0.95 0.94 0.93
1.00
0.96
1.96
1.03
1.02
6.08
2.96
2.99

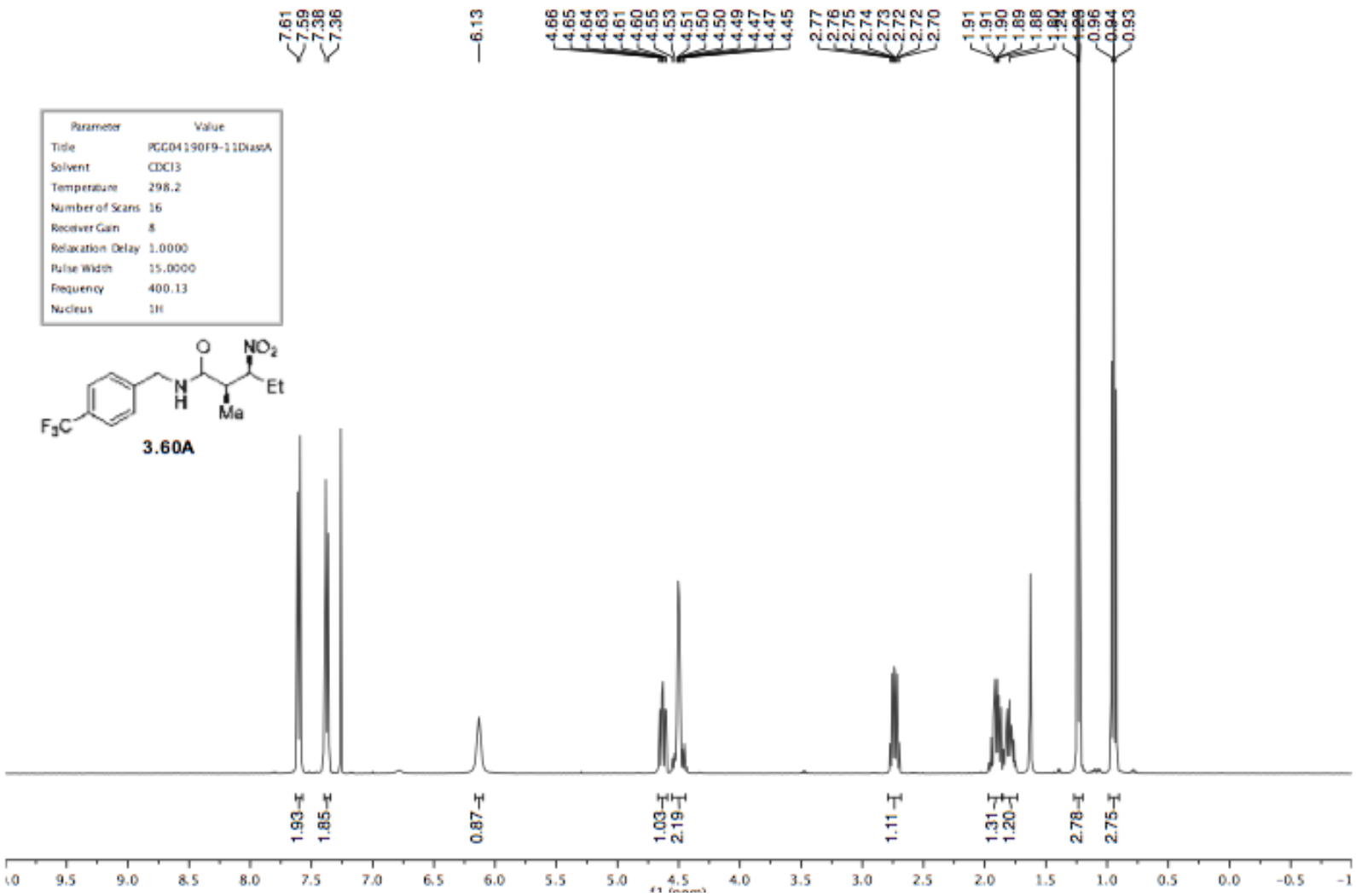

173.61
96.12
45.47
34.96
23.97
22.64
20.01
14.76
11.16
Parameter Value
Title PCD-416-2516-32
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtHN
O
NO2
Et
Me
Me
3.57

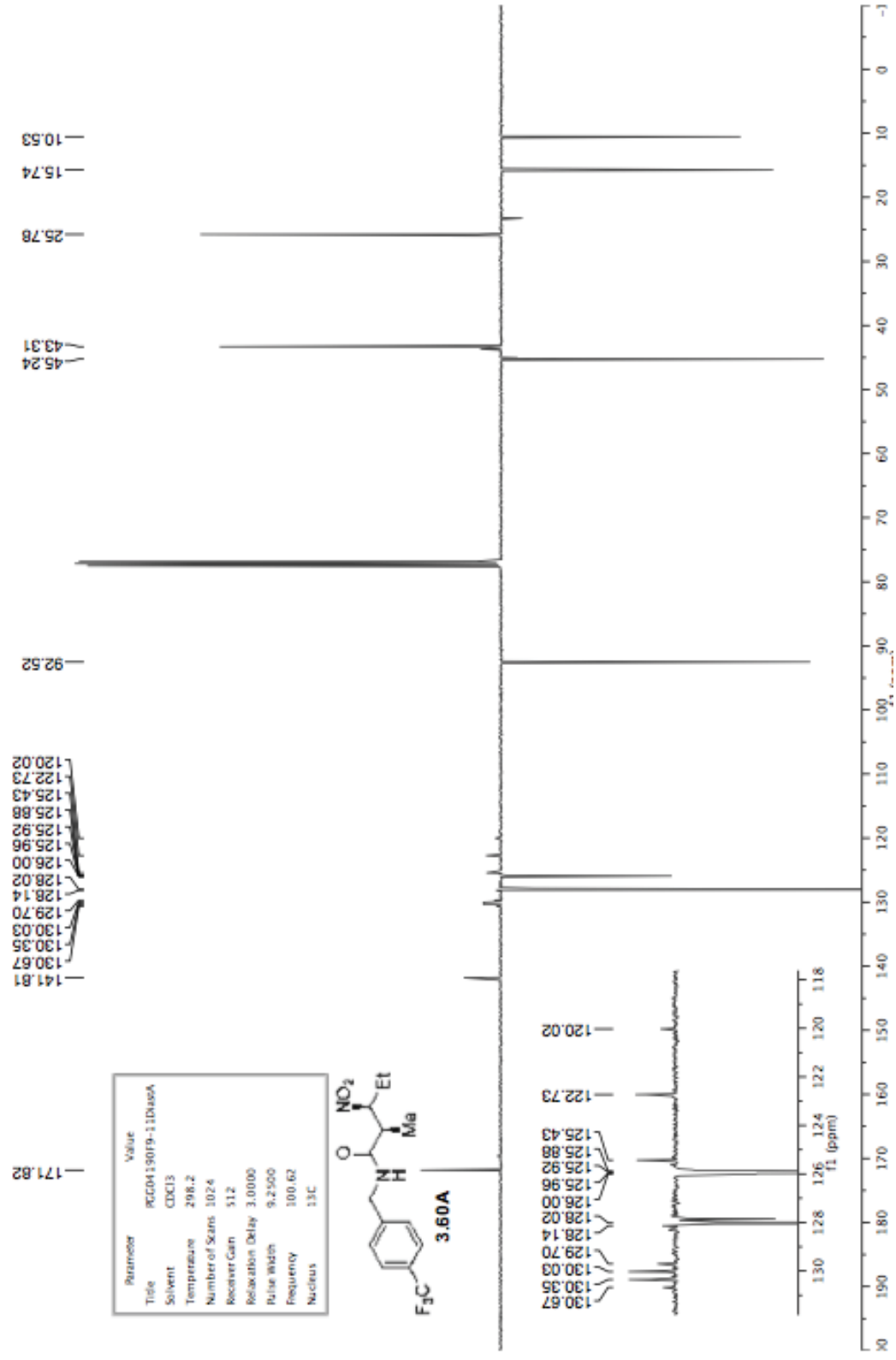

Parameter Value
Title AAG-250702-5
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 144
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
3.58A dr: 32 : 68 3.58B

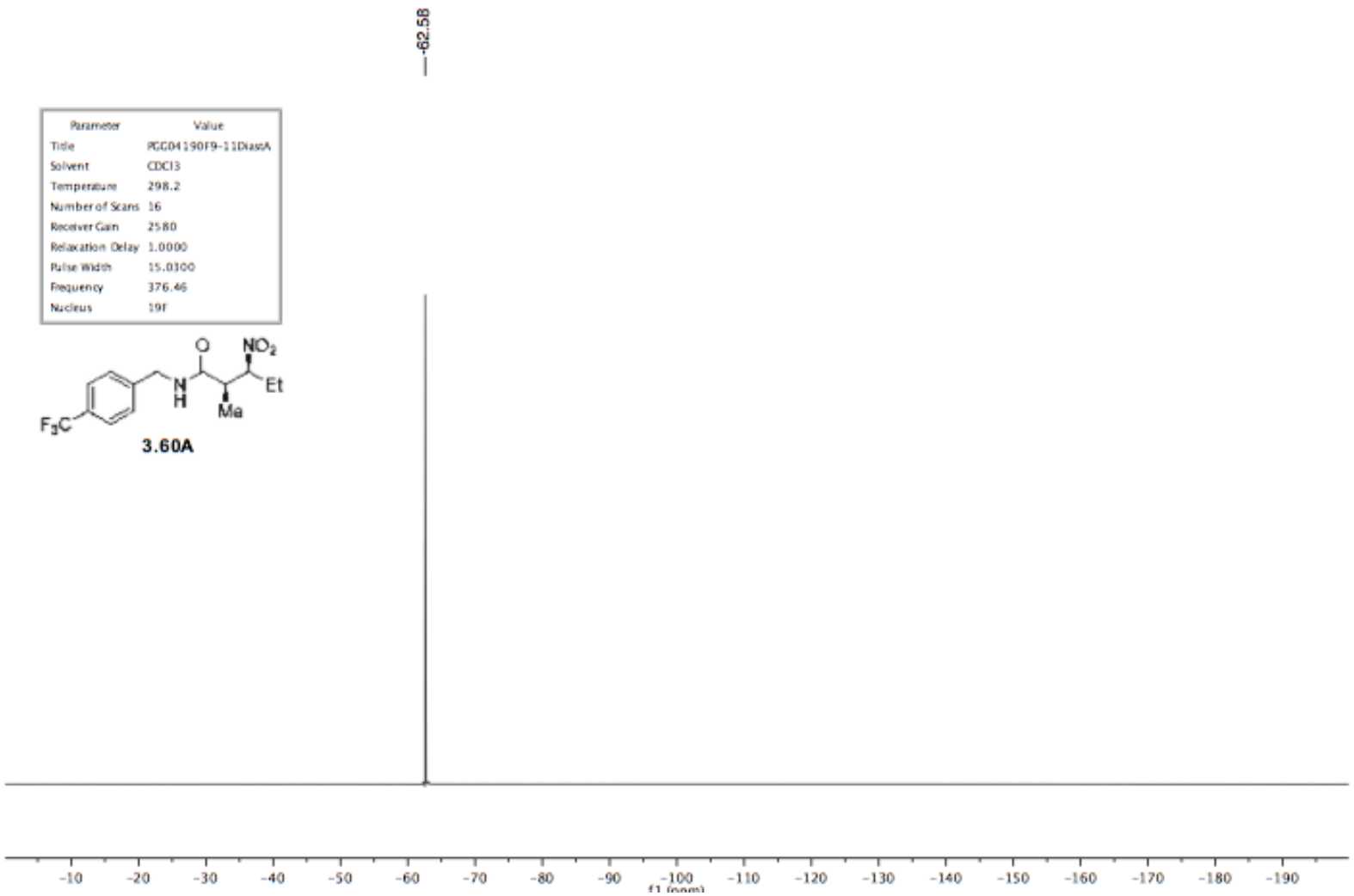

173.61
173.06
92.88
89.67
61.93
61.50
39.52
38.23
32.27
32.09
26.00
24.01
15.15
13.73
10.43
9.42
Parameter Value
Title AAG-080124
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
3.58A dr: 32 : 68 3.58B

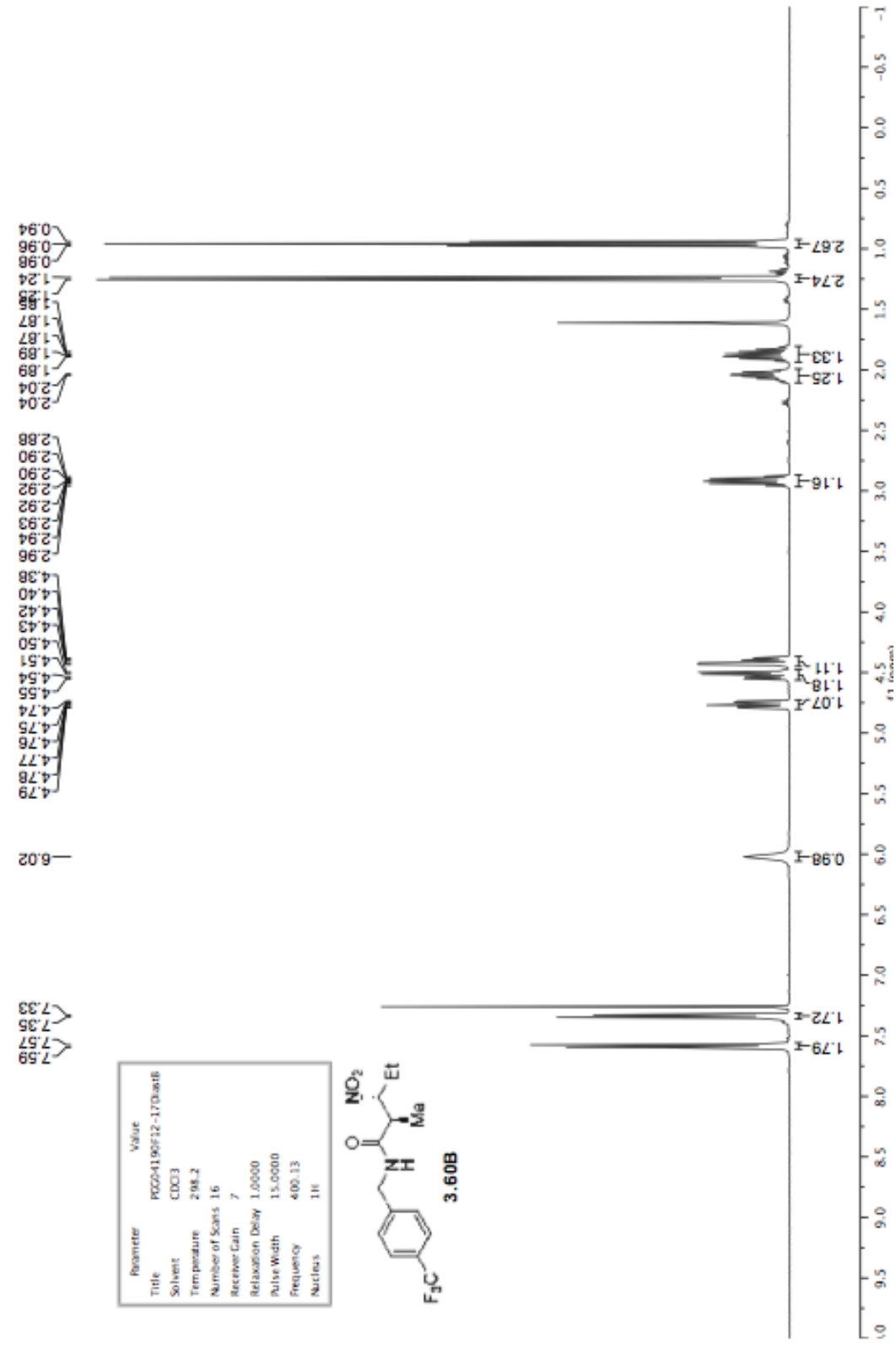

0.94
0.96
0.97
1.34
1.57
1.58
1.59
2.06
2.07
2.09
2.10
2.10
2.11
2.12
2.13
2.14
3.19
3.73
5.06
5.06
5.06
5.08
7.26
3.13
6.22
1.15
1.97
3.11
3.04
1.00
Parameter Value
Title APC 0084-2.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 57
Relaxation Delay 10.0000
Pulse Width 10.7700
Spectrometer Frequency 600.32
Nucleus 1H
MeO
N
O
NO2
Et
Me
Me
3.59

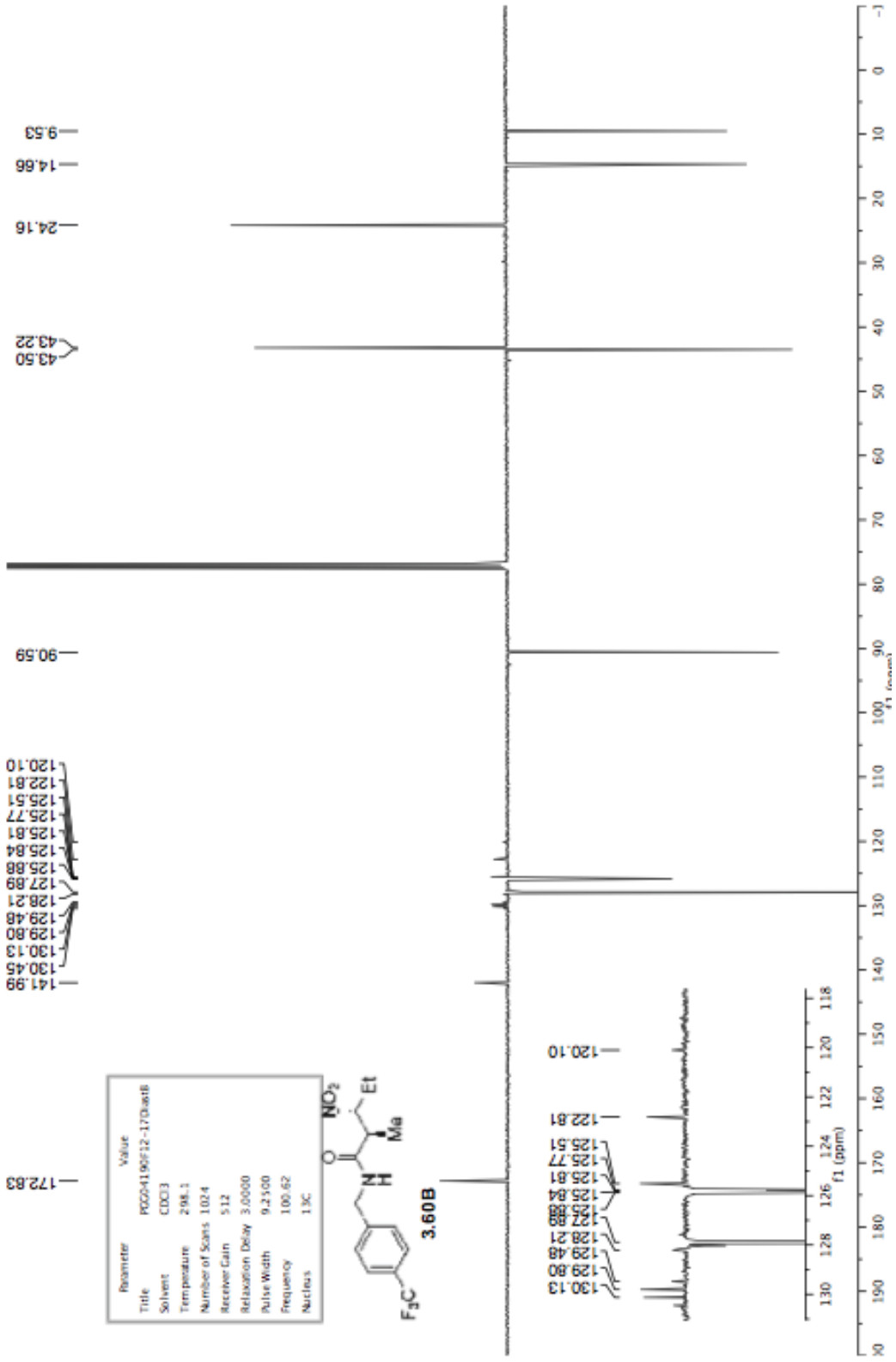

11.13
20.25
22.07
22.36
34.16
46.56
60.76
94.31
174.66
Parameter Value
Title APC 01084.4.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2030
Relaxation Delay 5.0000
Pulse Width 10.6000
Spectrometer Frequency 150.97
Nucleus 13C
MeO
N
O
NO2
Et
Me
Me
3.59


7.61
7.59
7.38
7.36
6.13
4.66
4.65
4.64
4.63
4.61
4.60
4.55
4.53
4.51
4.50
4.50
4.49
4.47
4.47
4.45
2.77
2.76
2.75
2.74
2.73
2.72
2.72
2.70
1.91
1.91
1.90
1.89
1.88
0.96
0.94
0.93
Parameter Value
Title PGD04190F9-11DiastA
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
O
NO2
N
H
Et
Me
F3C
3.60A
1.93
1.85
0.87
1.03
2.19
1.11
1.31
1.20
2.78
2.75
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

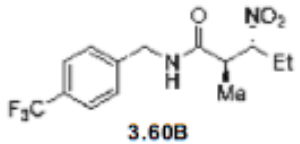

Parameter Value
Title RGE041130F9-11DiastA
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
3.60A
171.82
141.81
130.67
130.35
130.03
129.70
128.14
128.02
126.00
125.96
125.92
125.88
125.43
122.73
120.02
92.52
45.24
43.31
25.78
15.74
10.53
f1 (ppm)


-62.58
Parameter Value
Title PGD04190F9-11DiastA
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 2580
Relaxation Delay 1.0000
Pulse Width 15.0300
Frequency 376.46
Nucleus 19F
O
NO2
Et
N
H
Me
F3C
3.60A
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

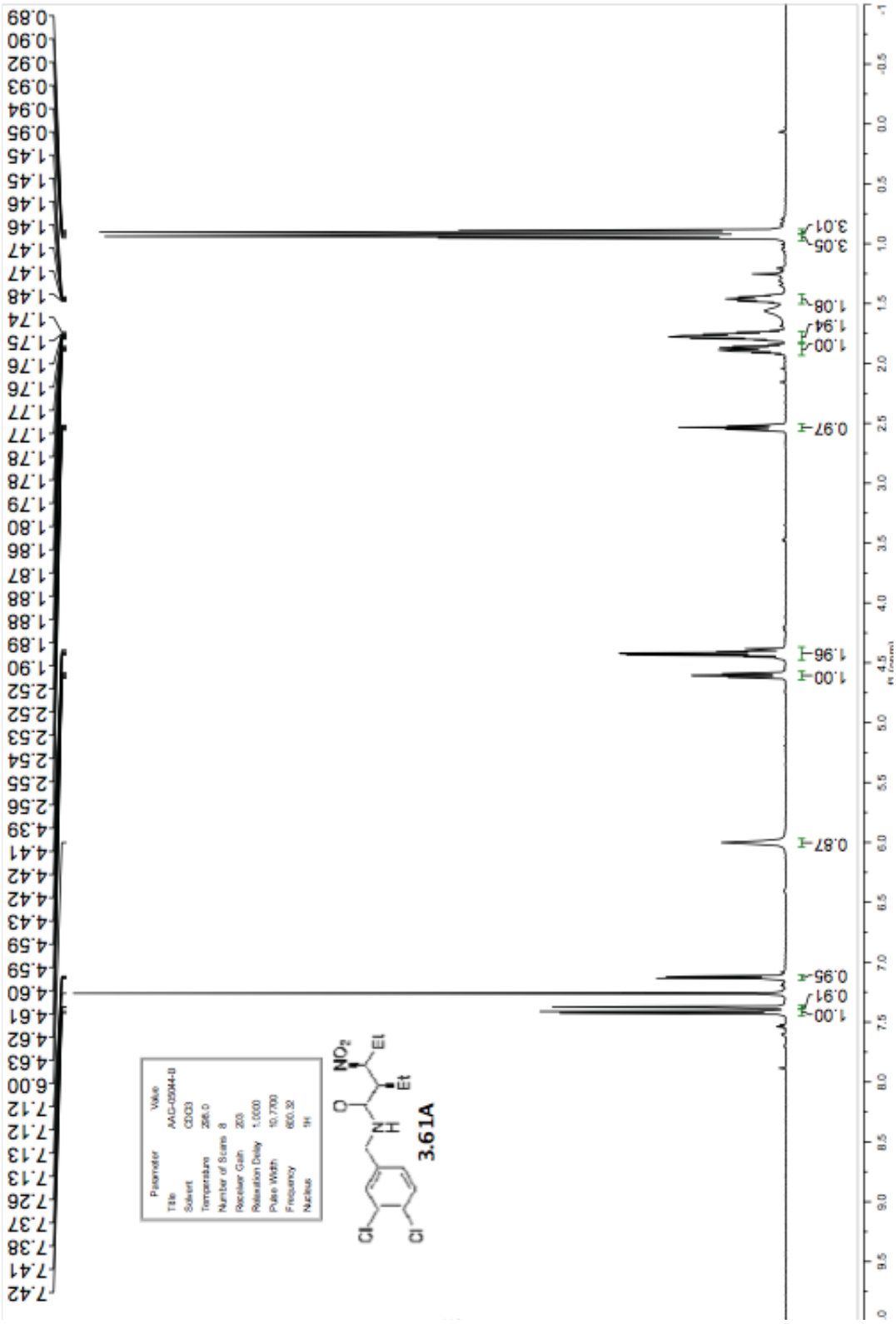

Parameter Value
Title PDC041905F12-17Dast8
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 7
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
NO2
Et
Me
O
N
H
F3C
3.60B

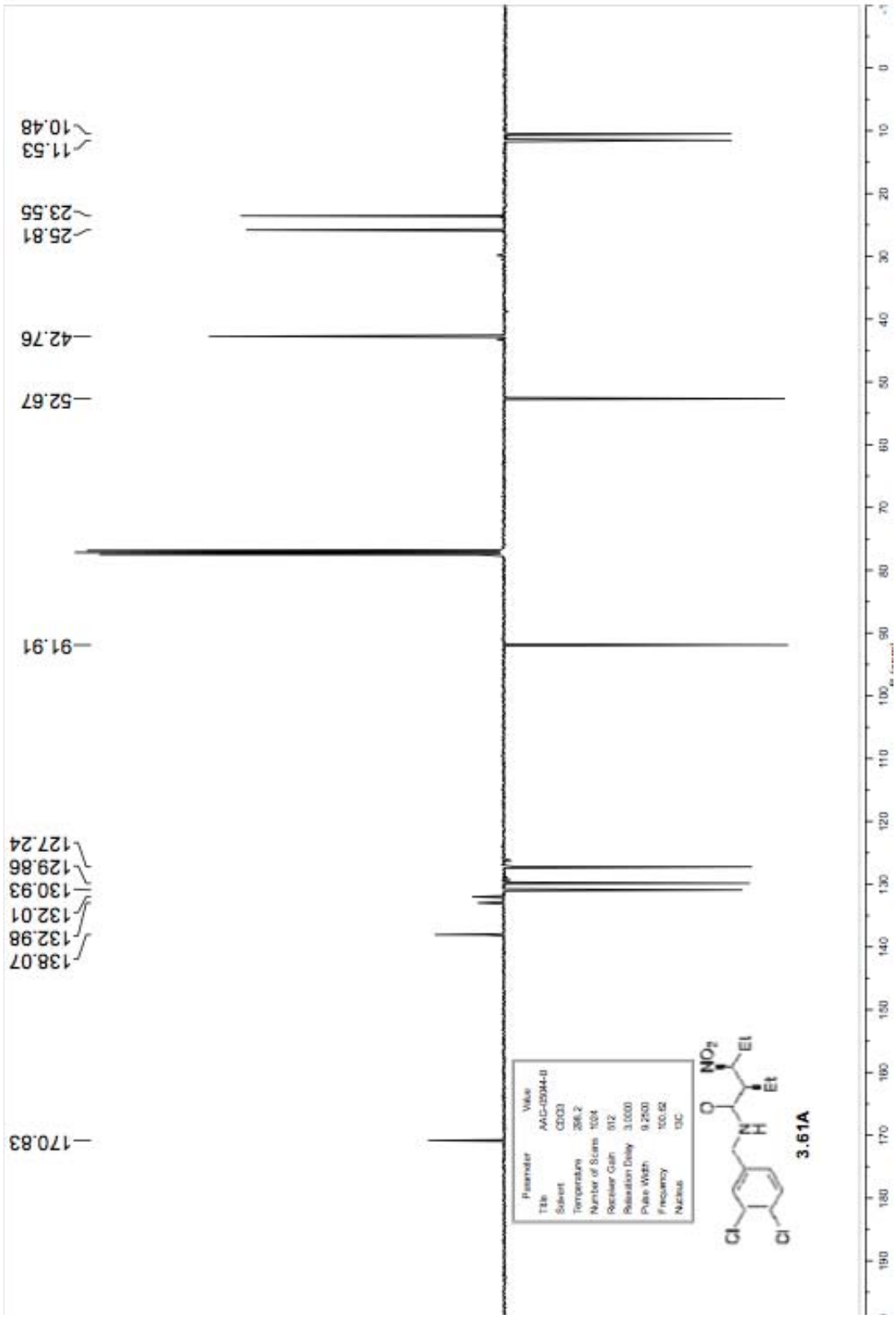

Parameter Value
Title PGD04190F12-17Oct18
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2100
Frequency 100.62
Nucleus 13C
3.60B
Et
Me
NO2
F3C
172.83
141.99
130.45
130.13
129.80
129.48
128.21
127.89
125.88
125.84
125.81
125.77
125.51
122.81
120.10
90.59
43.50
43.22
24.16
14.66
9.53
f1 (ppm)

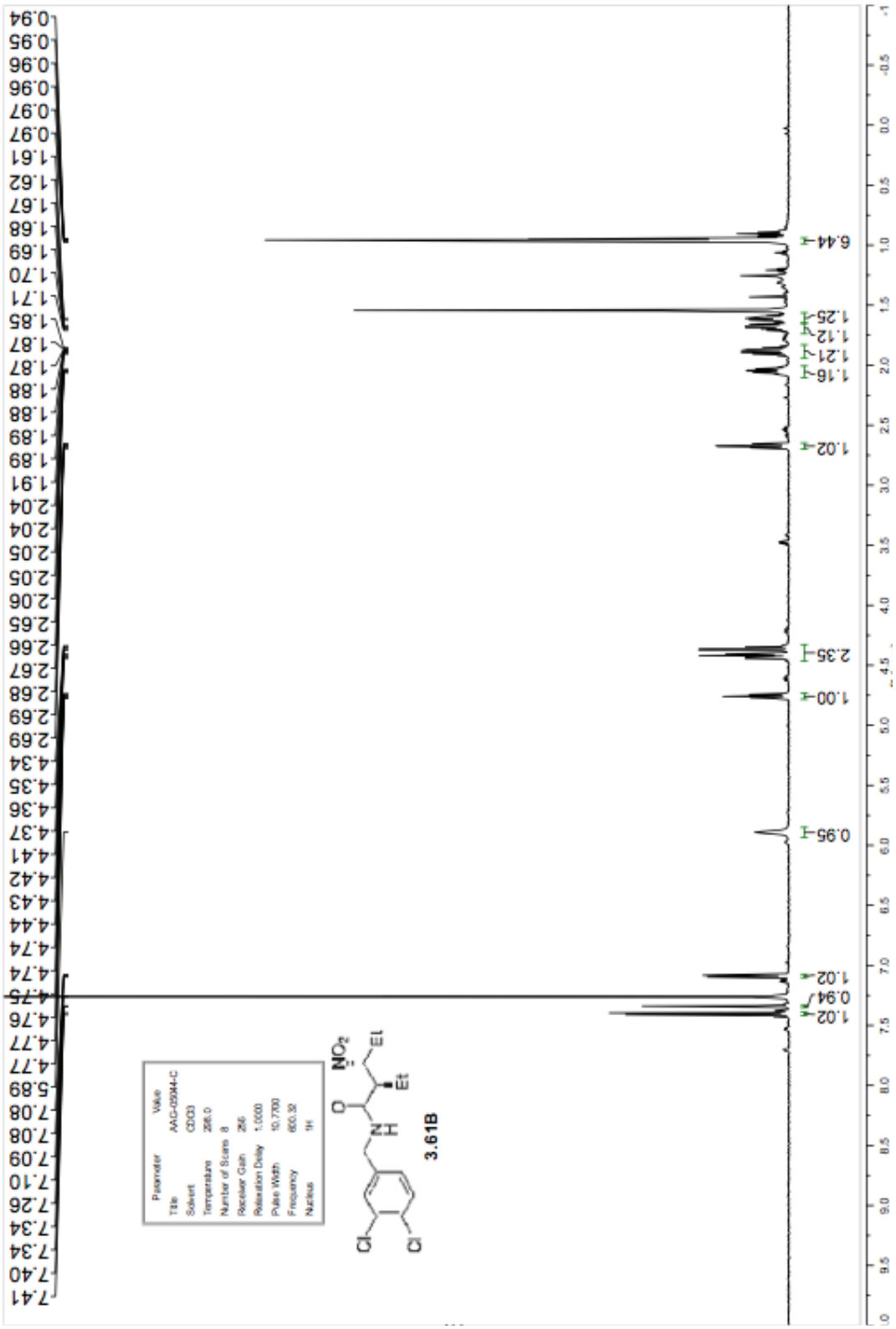
Parameter	Value
Title	PDG04190F12-17Diast8
Solvent	CDCl3
Temperature	298.2
Number of Scans	16
Receiver Gain	2580
Relaxation Delay	1.0000
Pulse Width	15.0300
Frequency	376.46
Nucleus	19F

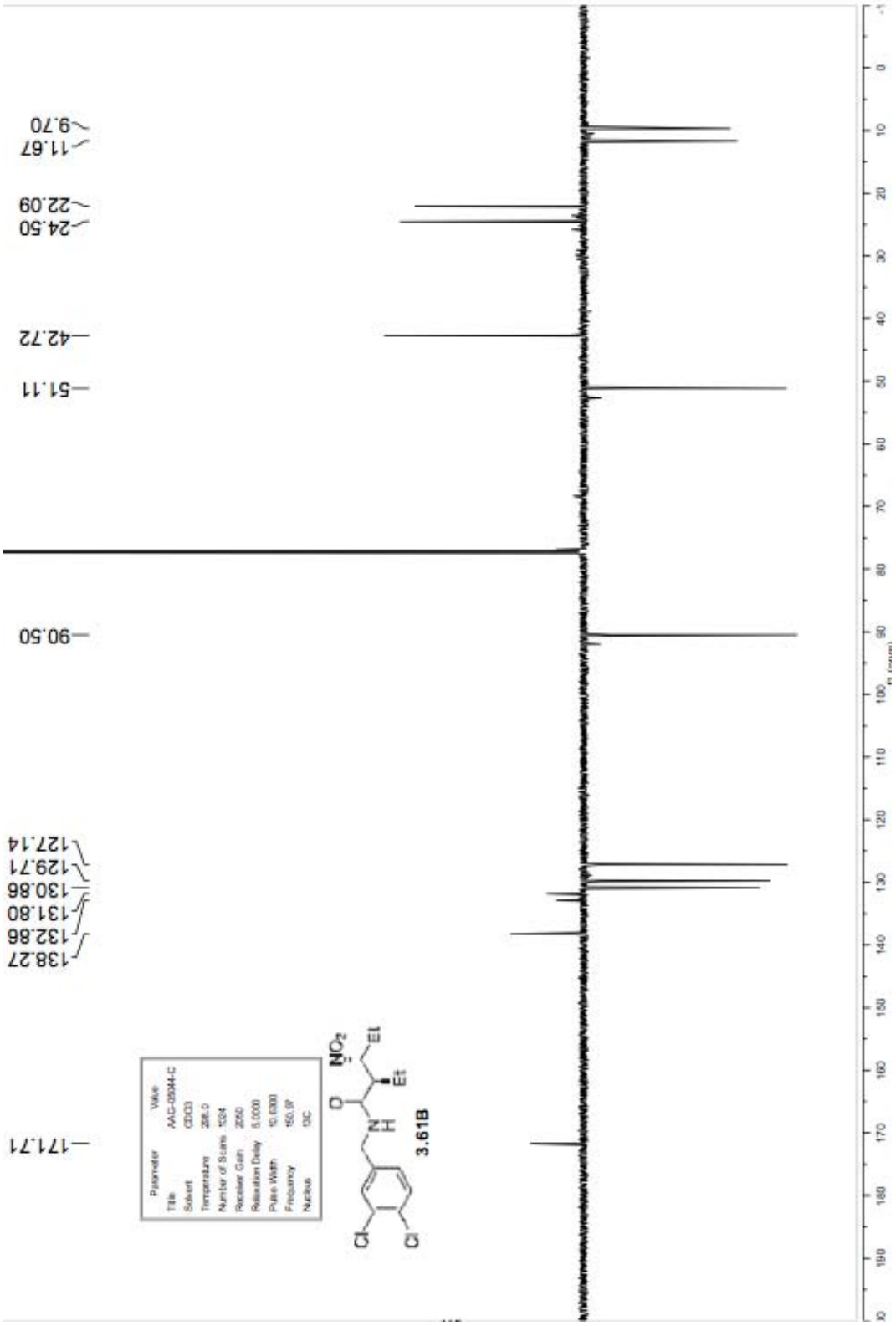


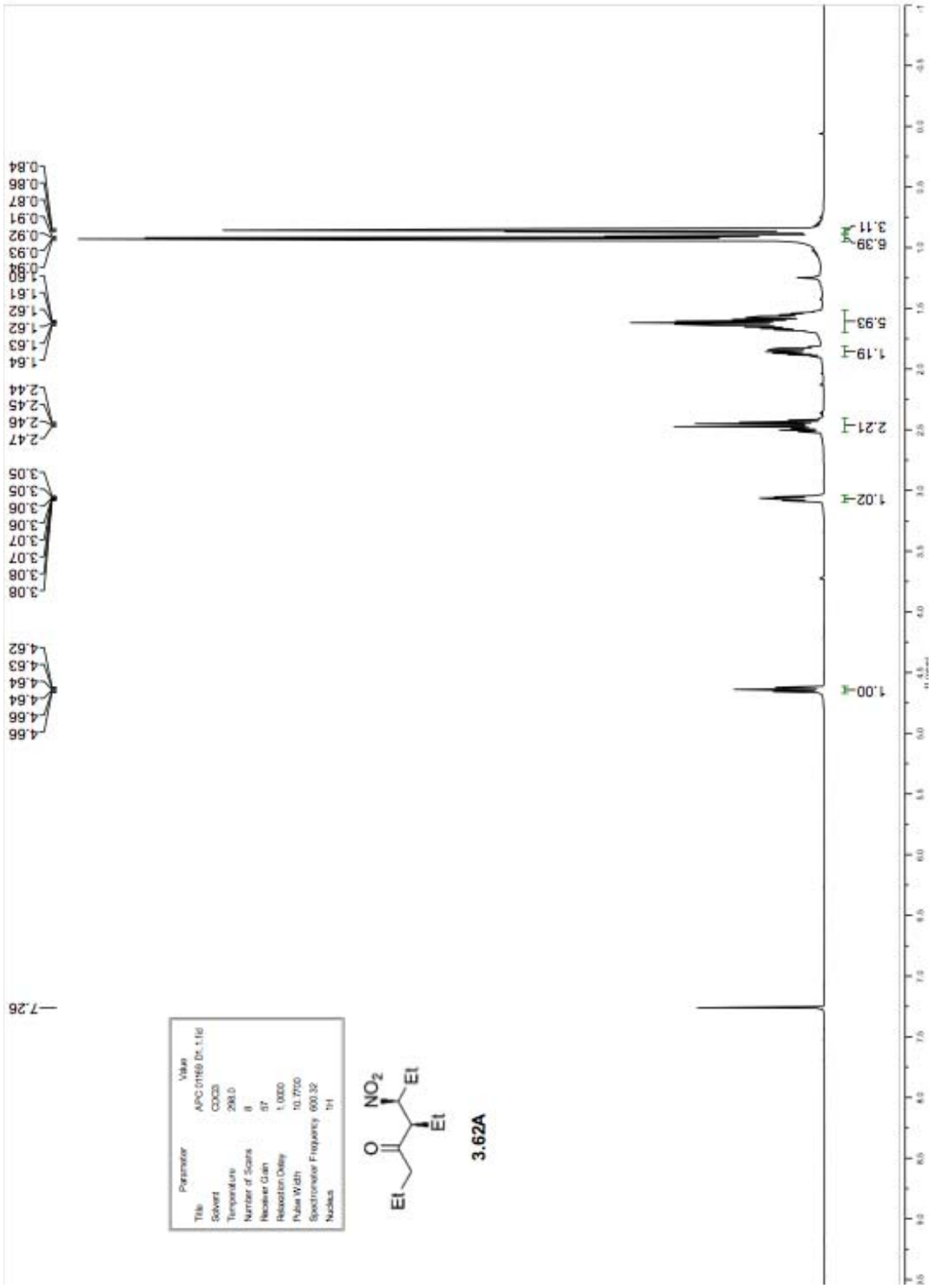
3.60B

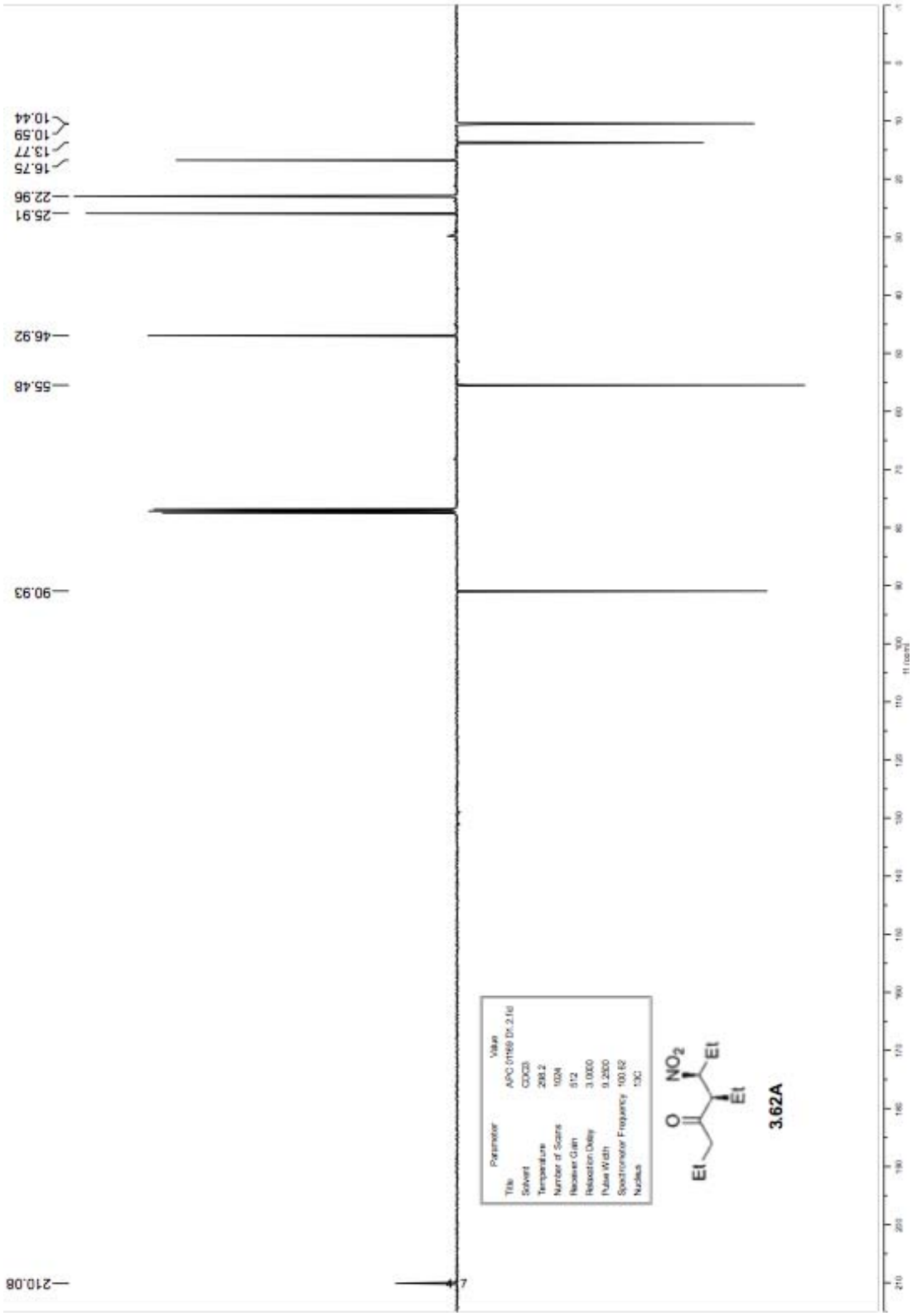

Parameter Value
Title AAG-09W44-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 203
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
3.61A

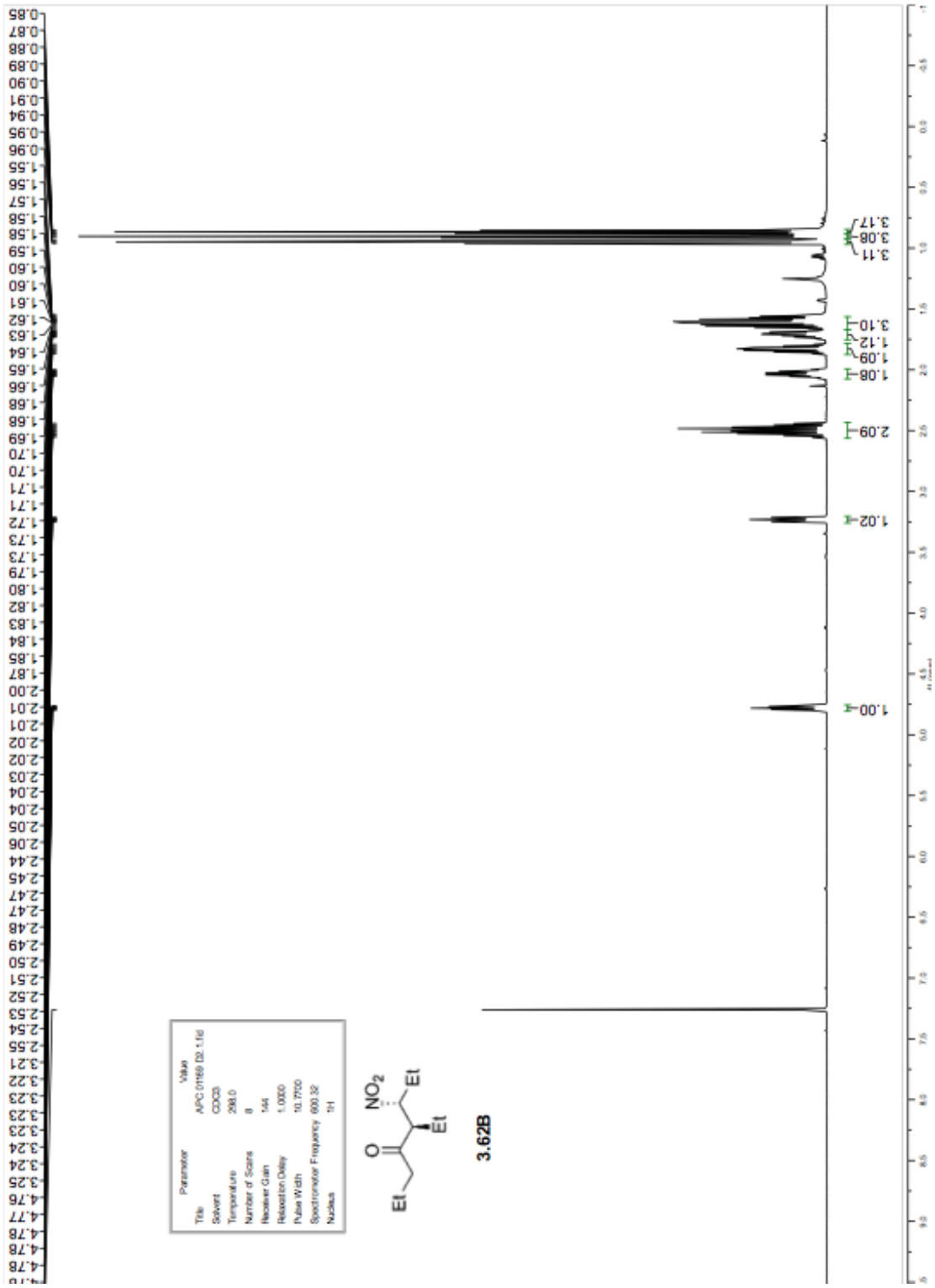

10.48
11.53
23.55
25.81
42.76
52.67
91.91
127.24
129.86
130.93
132.01
132.98
138.07
170.83
Parameter Value
Title AAC-05044-0
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 912
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Et
Et
O
N
H
Cl
Cl
3.61A

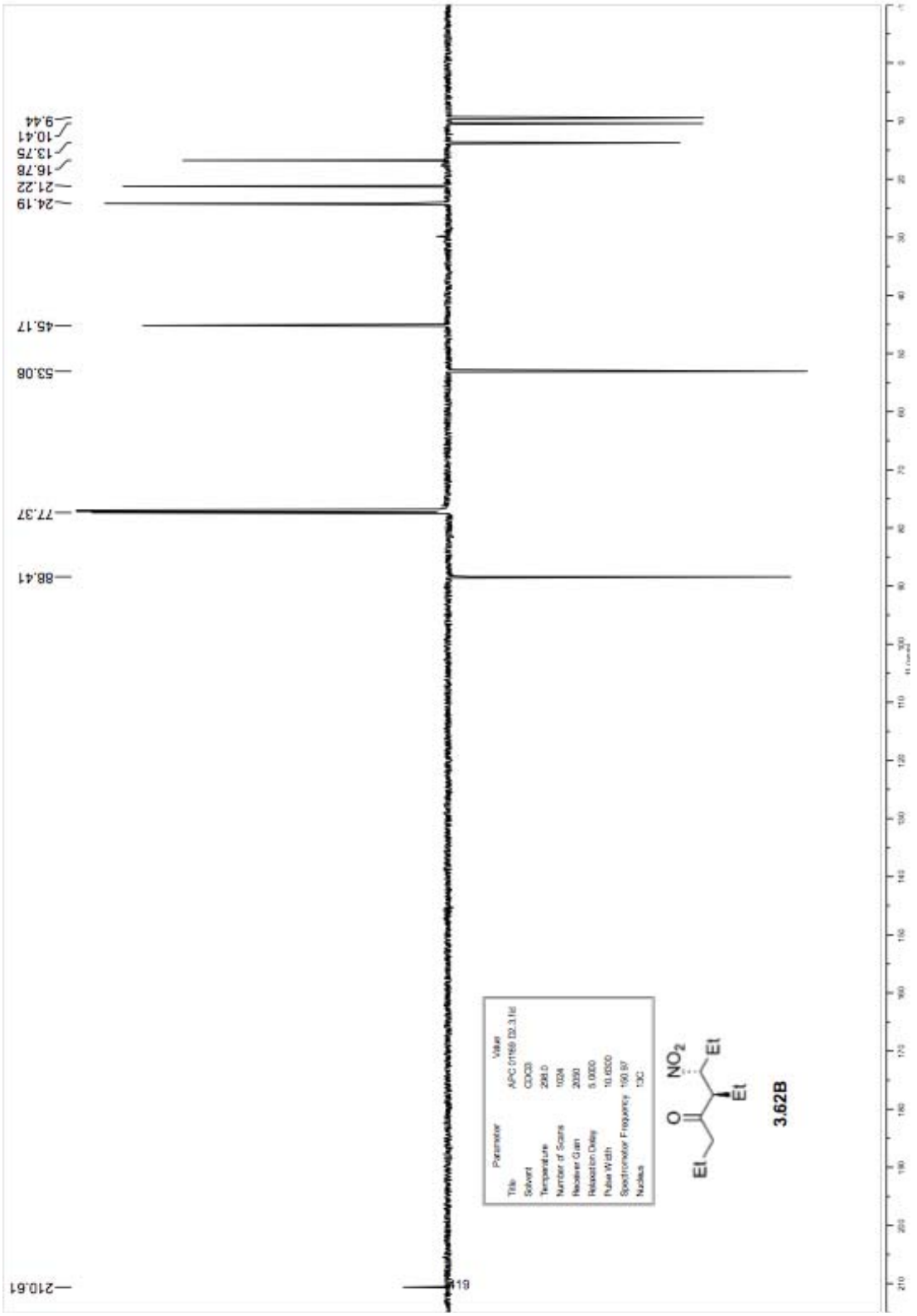

Parameter Value
Title AAG-05944-C
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 256
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
3.61B
6.44
1.25
1.12
1.21
1.16
1.02
2.35
1.00
0.95
1.02
0.94
1.02

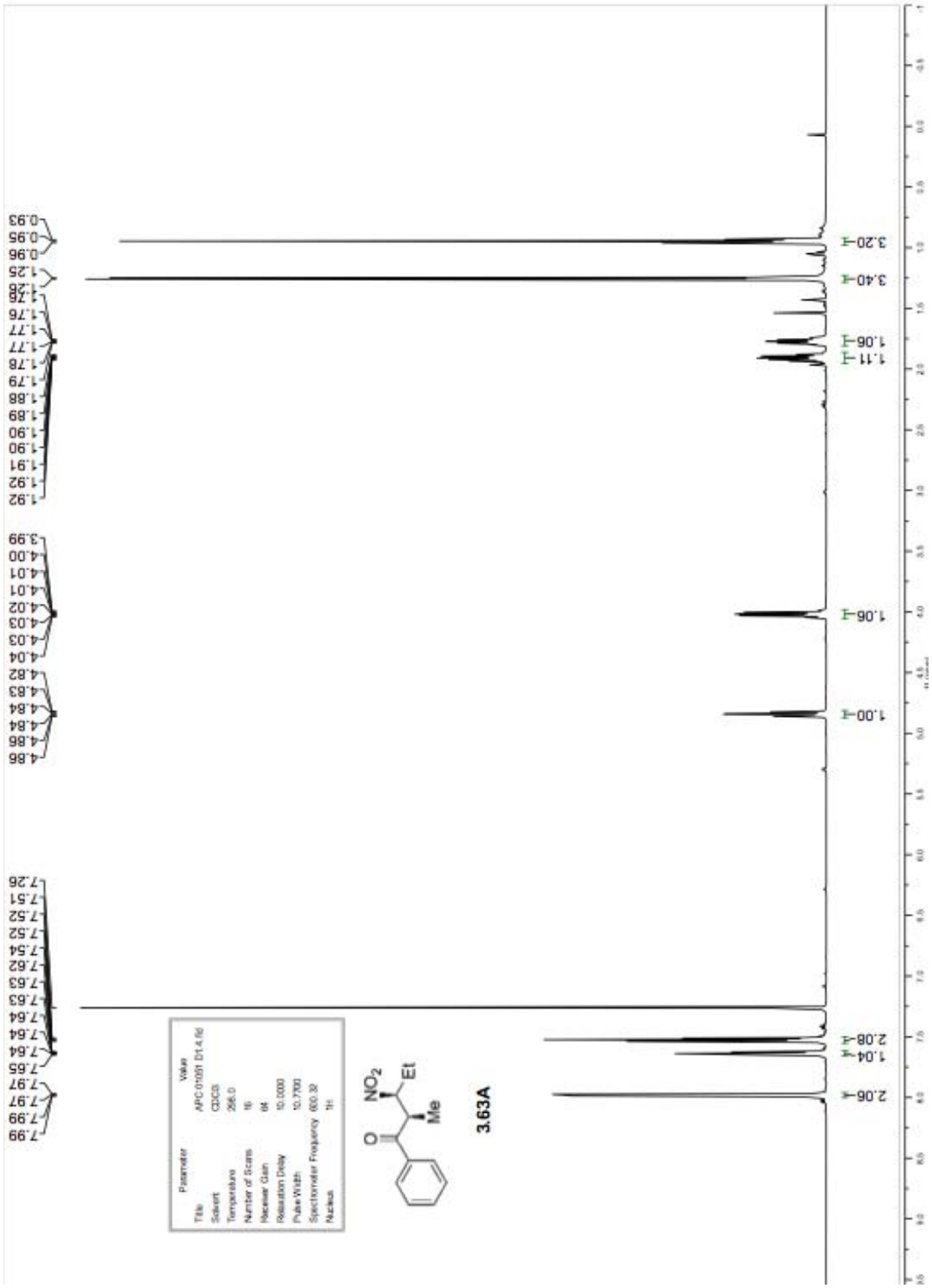

9.70
11.67
22.09
24.50
42.72
51.11
90.50
127.14
129.71
130.86
131.80
132.86
138.27
171.71
Parameter Value
Title AAG-05044-C
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 3.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
3.61B


7.26
4.66
4.66
4.64
4.64
4.63
4.62
3.08
3.08
3.07
3.07
3.06
3.06
3.05
3.05
2.47
2.46
2.45
2.44
1.64
1.63
1.62
1.62
1.61
1.60
0.94
0.93
0.92
0.91
0.87
0.86
0.84
1.00
1.02
2.21
1.19
5.93
6.39
3.11
Parameter
Value
Title
APC-01169 Dr. 1 1d
Solvent
CDCl3
Temperature
298.0
Number of Scans
8
Receiver Gain
57
Relaxation Delay
1.0000
Pulse Width
10.7700
Spectrometer Frequency
600.32
Nucleus
1H
O
NO2
Et
Et
Et
3.62A


10.44
10.59
13.77
16.75
22.96
25.91
46.92
55.48
90.93
210.08
Parameter
Value
Title
APC 01169 DX 2.1d
Solvent
CDCl3
Temperature
298.2
Number of Scans
1024
Receiver Gain
512
Relaxation Delay
3.0000
Pulse Width
9.2500
Spectrometer Frequency
100.62
Nucleus
13C
O
NO2
Et
Et
Et
3.62A


Parameter Value
Title APC 01169 D2.1.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 144
Relaxation Delay 1.0000
Pulse Width 10.7700
Spectrometer Frequency 600.32
Nucleus 1H
NO2
Et
Et
O
Et
3.62B
1.00
1.02
2.09
1.08
1.09
1.12
3.10
3.11
3.06
3.17


9.44
10.41
13.75
16.78
21.22
24.19
45.17
53.08
77.37
88.41
210.61
Parameter
Value
Title
APC (1H) 02.3.fid
Solvent
CDCl3
Temperature
298.0
Number of Scans
1024
Receiver Gain
2030
Relaxation Delay
5.0000
Pulse Width
10.6500
Spectrometer Frequency
150.97
Nucleus
13C
O
NO2
Et
Et
Et
3.62B


3.63A
Parameter Value
Title APC 01001 D1 4.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 64
Relaxation Delay 10.0000
Pulse Width 10.7700
Spectrometer Frequency 600.30
Nucleus 1H
NO2
Et
Me
O
0.93
0.95
0.96
1.25
1.26
1.76
1.77
1.77
1.78
1.79
1.88
1.89
1.90
1.90
1.91
1.92
1.92
3.99
4.00
4.01
4.01
4.02
4.03
4.03
4.04
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4.84
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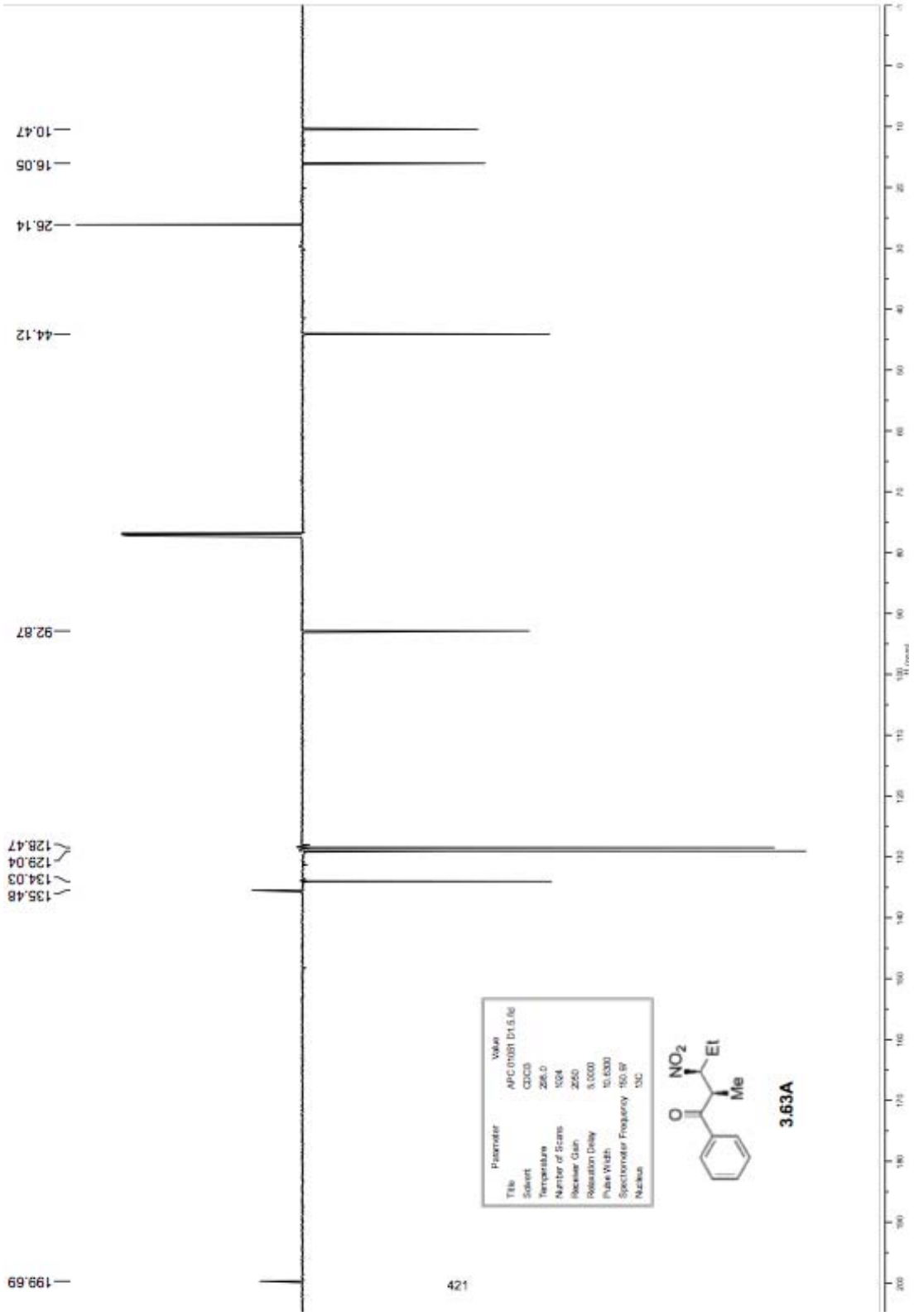
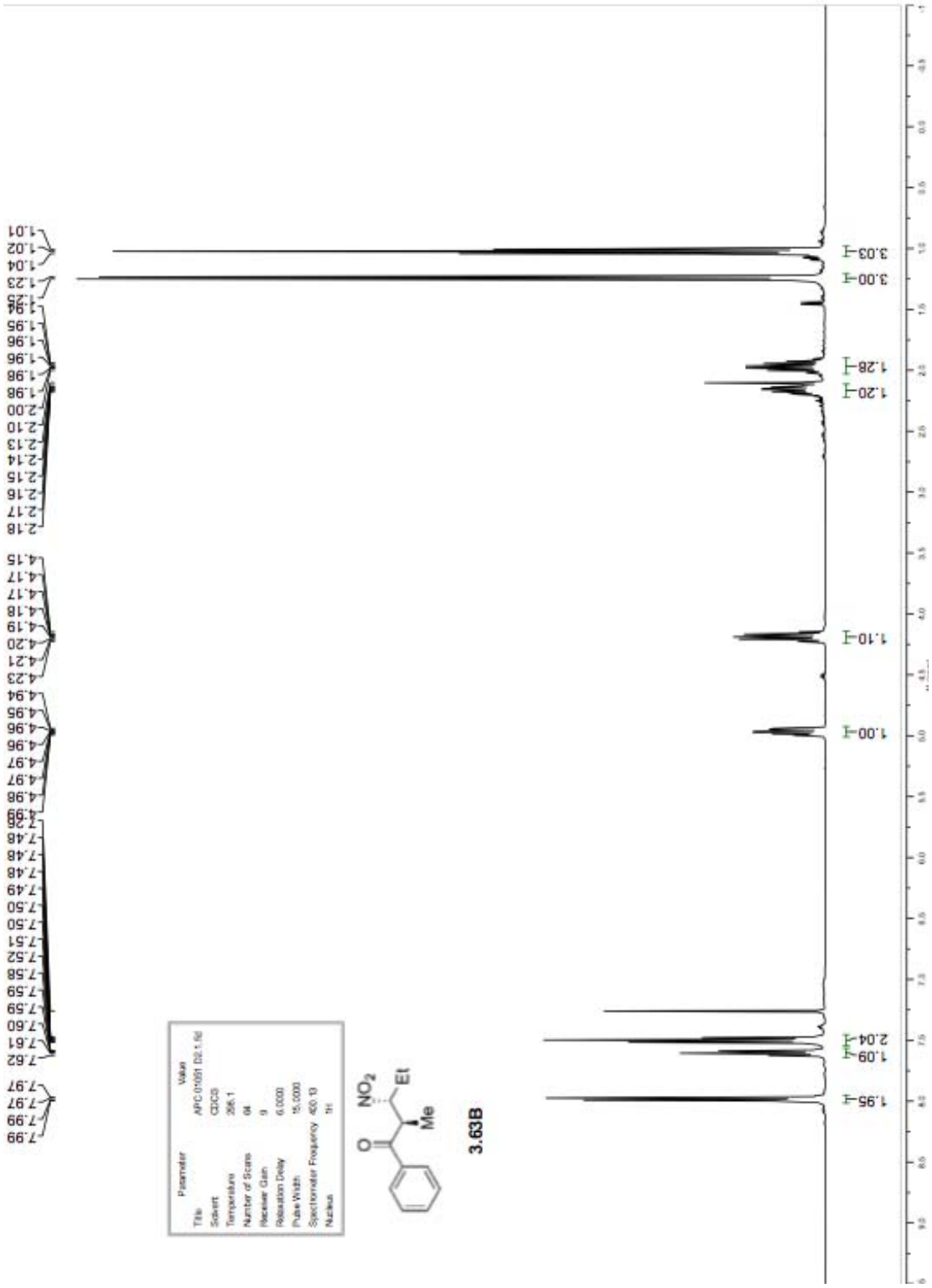
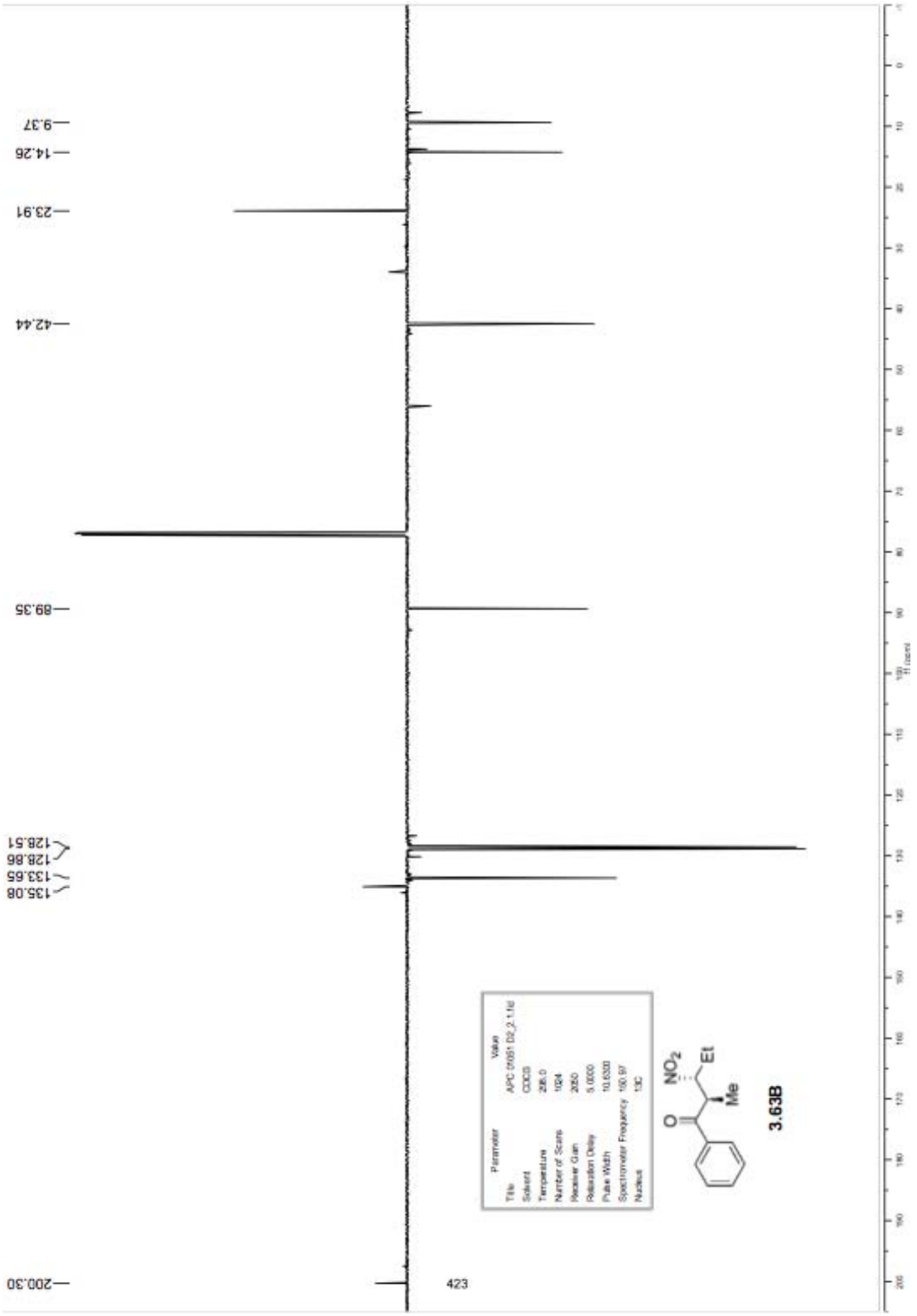
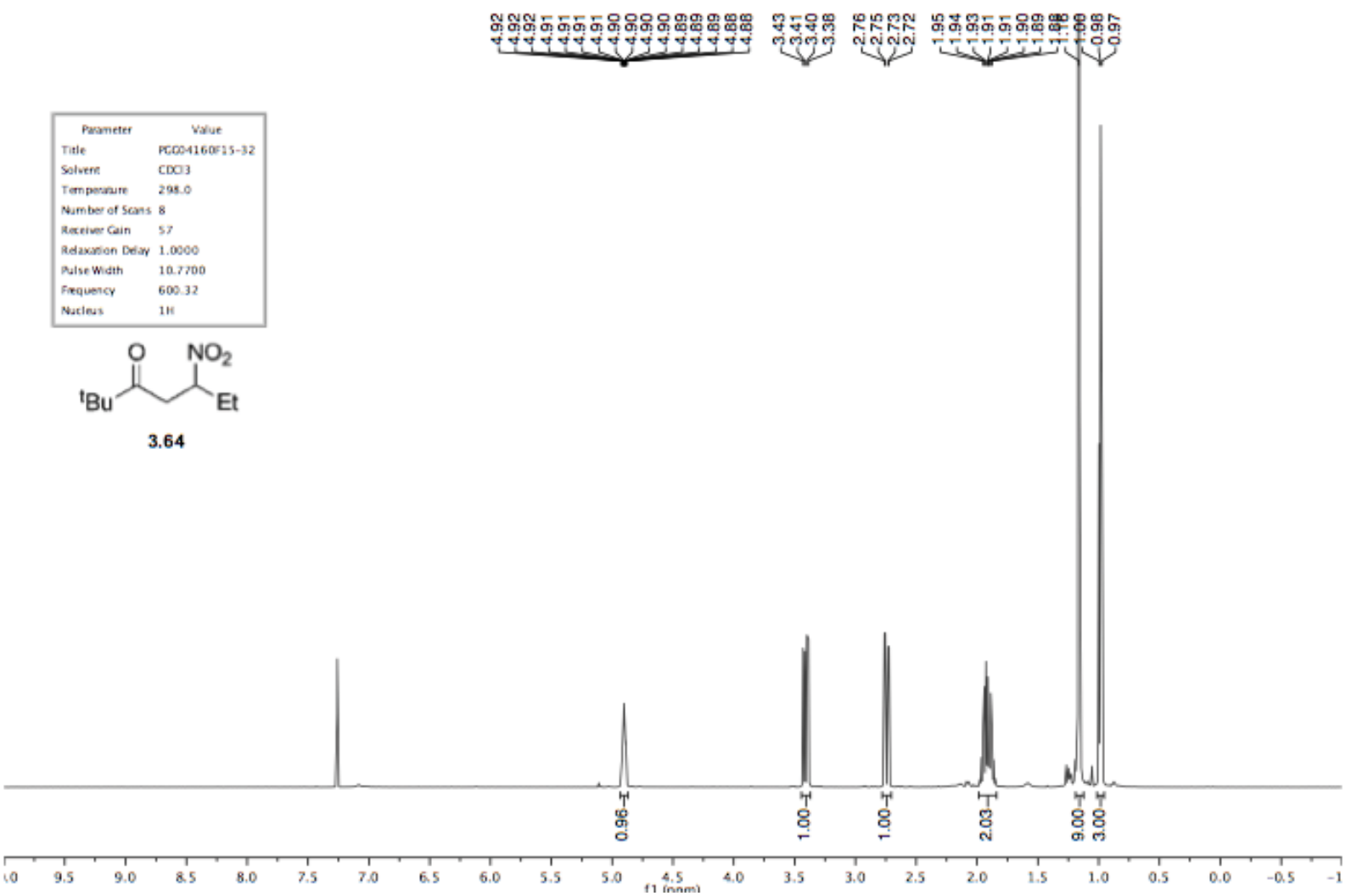
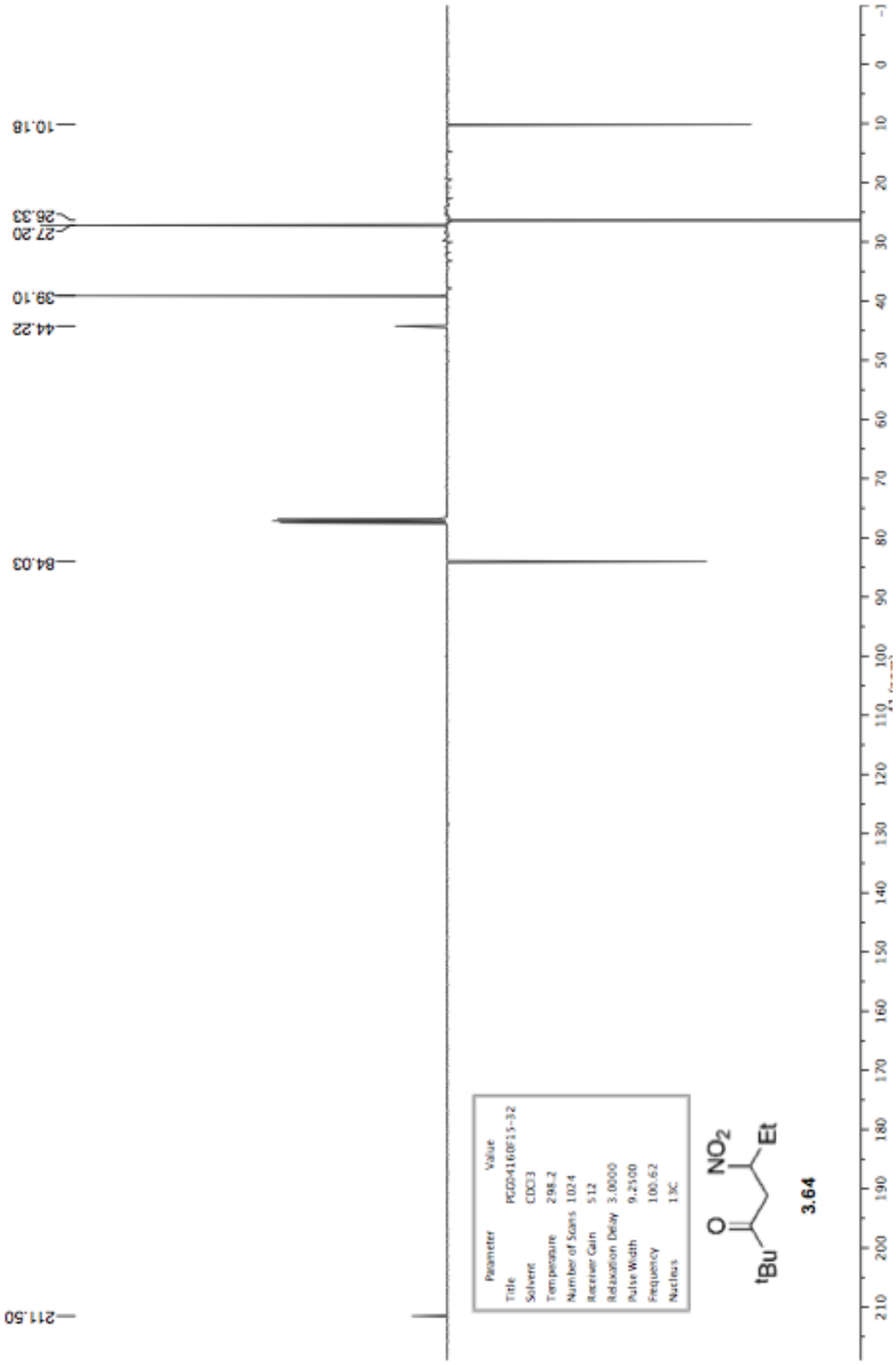
1.11
1.06
1.00
2.08
1.04
2.06

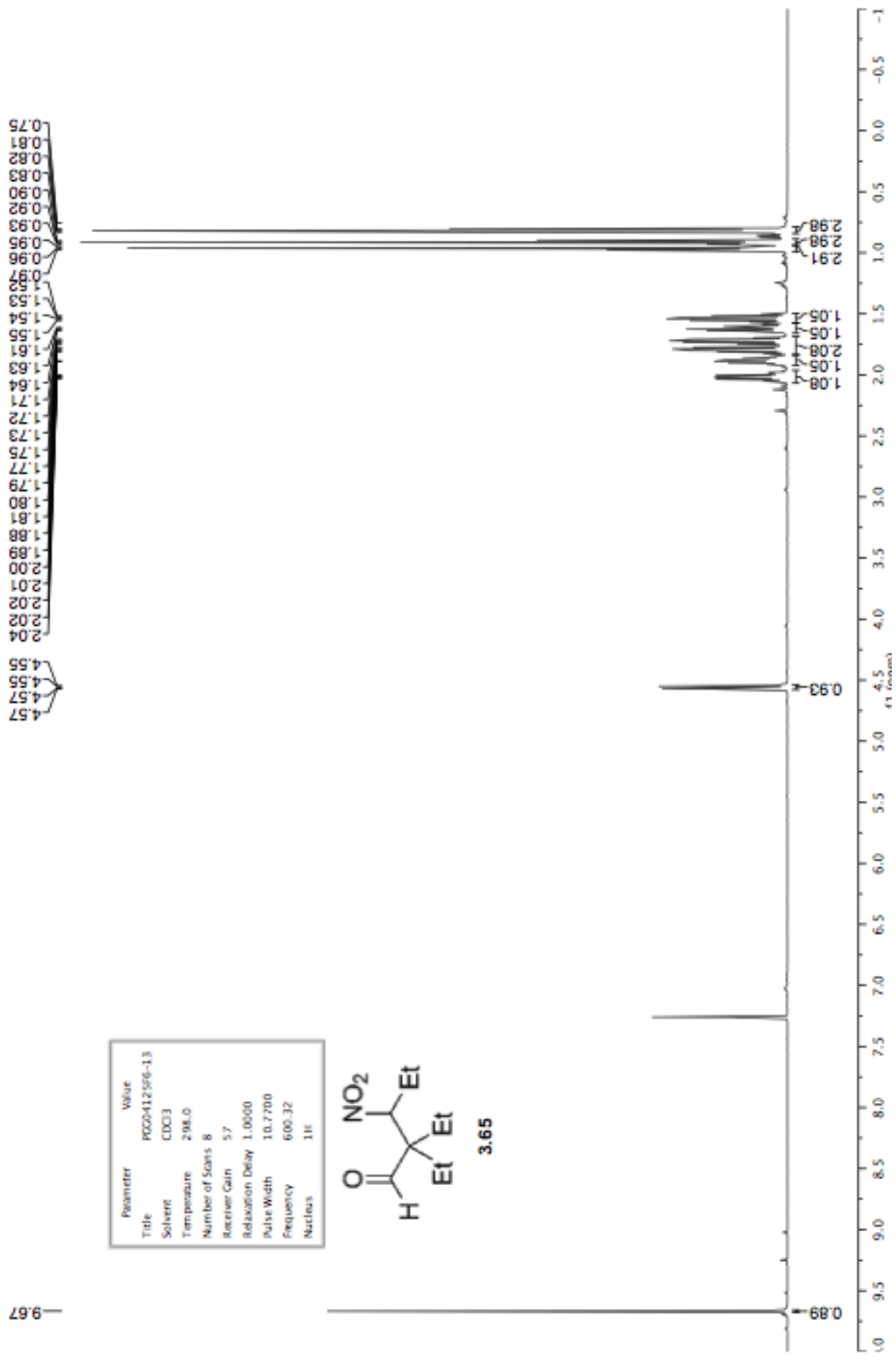

10.47
16.05
26.14
44.12
92.87
128.47
129.04
134.03
135.48
199.69
421
Parameter Value
Title APC 07091 D1 5.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2550
Relaxation Delay 5.0000
Pulse Width 10.6300
Spectrometer Frequency 150.91
Nucleus 13C
O
NO2
Et
Me
3.63A

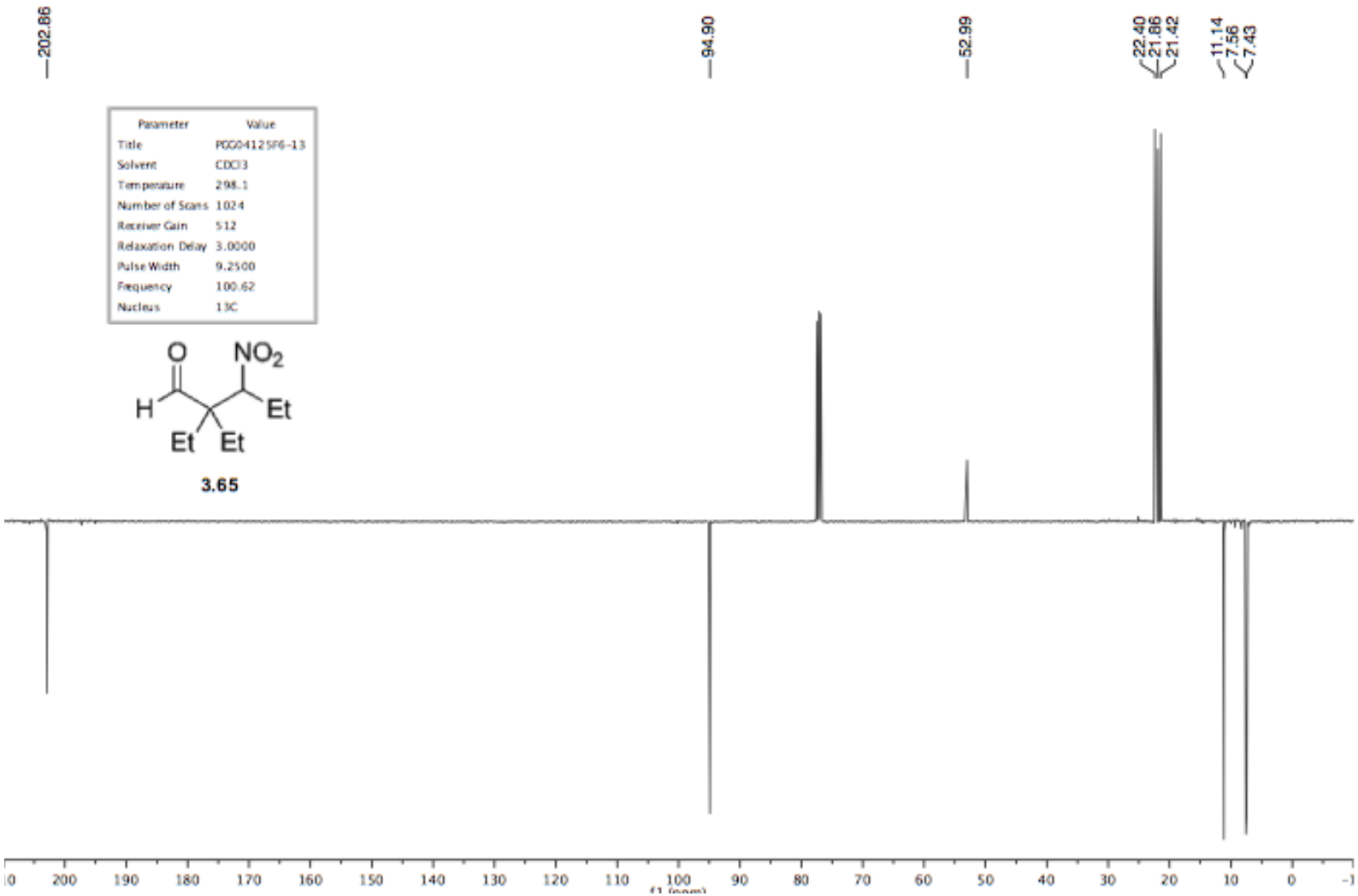

Parameter Value
Title APC 01001 D2.1.fid
Solvent CDCl3
Temperature 298.1
Number of Scans 64
Receiver Gain 9
Relaxation Delay 6.0000
Pulse Width 15.0000
Spectrometer Frequency 400.13
Nucleus 1H
NO2
Et
Me
O
3.63B
1.01 1.02 1.04 1.23 1.25 1.94 1.95 1.96 1.96 1.98 1.98 2.00 2.10 2.13 2.14 2.15 2.16 2.17 2.18
4.15 4.17 4.17 4.18 4.19 4.20 4.21 4.23 4.94 4.95 4.96 4.96 4.97 4.97 4.98 4.99
7.25 7.48 7.48 7.48 7.49 7.50 7.50 7.51 7.52 7.58 7.59 7.59 7.60 7.61 7.62
7.97 7.97 7.99 7.99
1.95 1.09 2.04 1.00 1.10 1.20 1.28 3.00 3.03

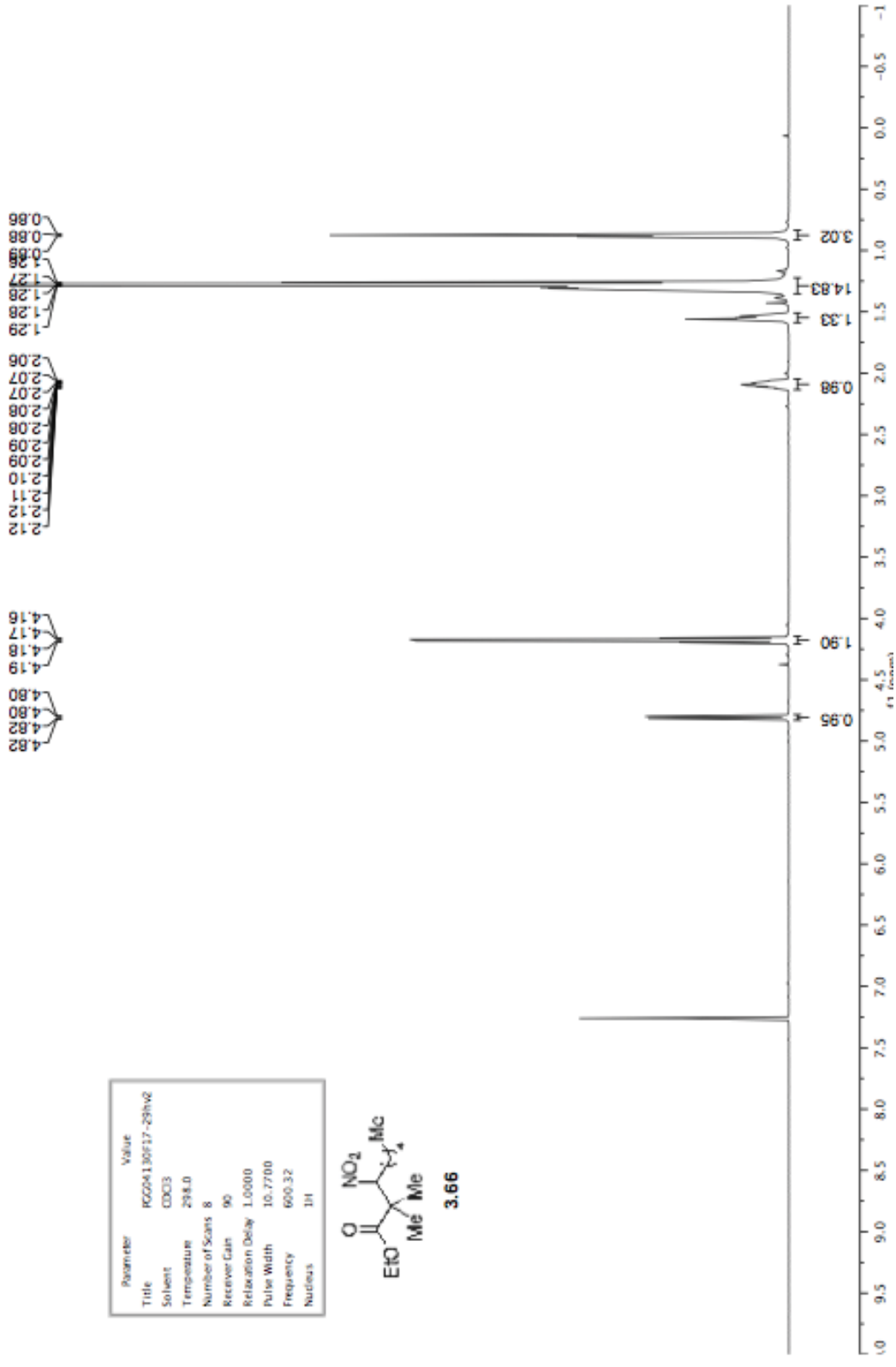

9.37
14.26
23.91
42.44
89.35
128.51
128.86
133.65
135.08
200.30
423
Parameter
Value
Title
APC-0691 D2-2 1-1d
Solvent
CDCl3
Temperature
298.0
Number of Scans
1024
Receiver Gain
2050
Relaxation Delay
5.0000
Pulse Width
10.6300
Spectrometer Frequency
150.97
Nucleus
13C
NO2
Et
Me
O
3.63B

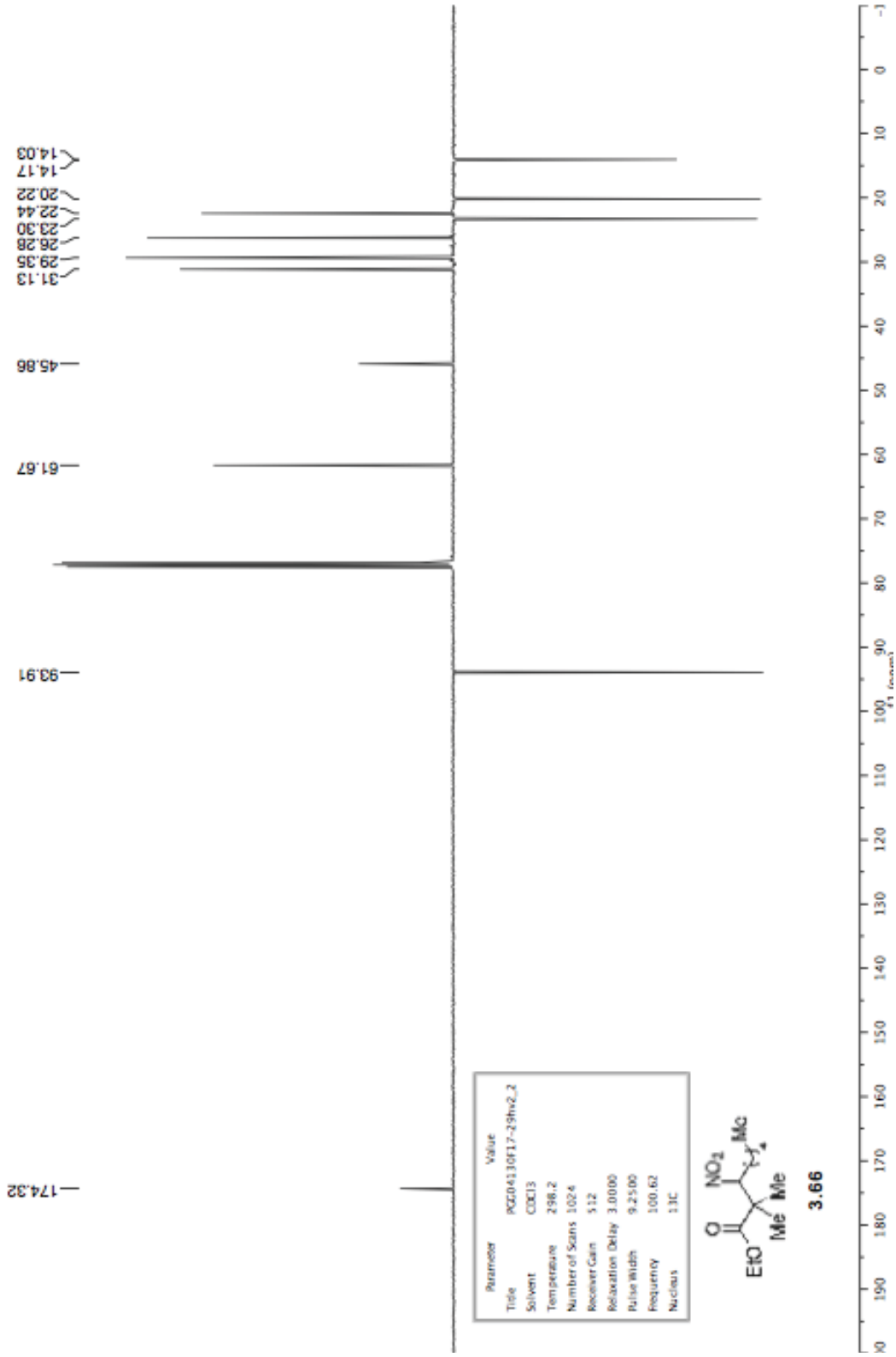

Parameter Value
Title PGD04160F15-32
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
tBu
Et
3.64
4.92 4.92 4.92 4.91 4.91 4.91 4.91 4.90 4.90 4.90 4.90 4.89 4.89 4.89 4.88 4.88
3.43 3.41 3.40 3.38
2.76 2.75 2.73 2.72
1.95 1.94 1.93 1.91 1.91 1.90 1.89
0.98 0.97
0.96 1.00 1.00 2.03 9.00 3.00
f1 (ppm)

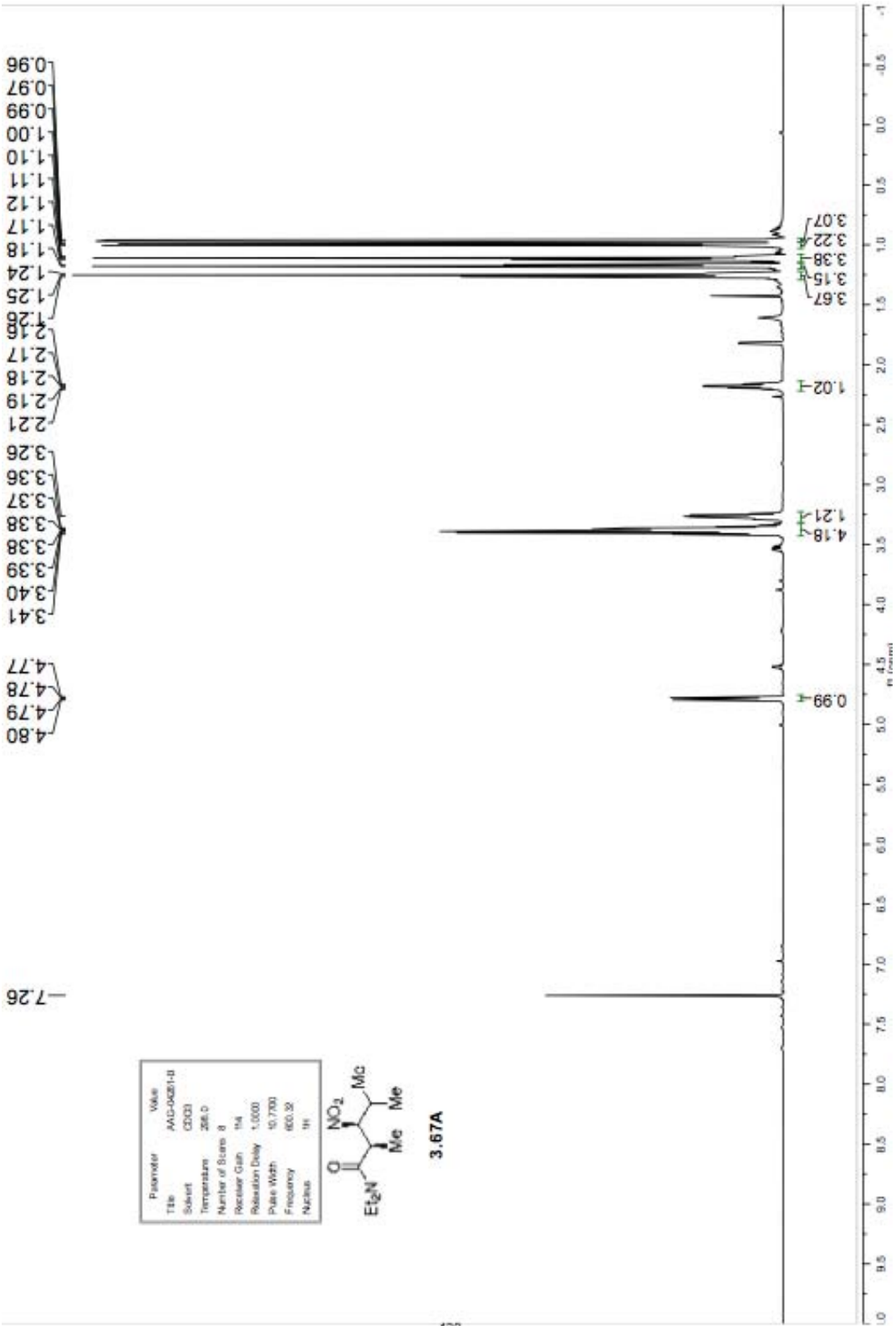

211.50
84.03
44.22
39.10
27.20
26.33
10.18
Parameter Value
Title PGD-4160F15-32
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
NO2
Et
tBu
3.64


Parameter Value
Title PGD0412SP6-13
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Et
Et
Et
O
H
3.65


202.86
94.90
52.99
22.40
21.86
21.42
11.14
7.56
7.43
Parameter Value
Title PDG0412SF6-13
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
NO2
H
Et
Et
Et
3.65
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Parameter Value
Title RGDM130517-29hv2
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 90
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Me
EtO
Me
Me
3.66
0.95
1.90
0.98
1.33
14.83
3.02


174.32
93.91
61.67
45.86
31.13
29.35
26.28
23.30
22.44
20.22
14.17
14.03
Parameter Value
Title PGE041316F17-23hr2_2
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtO
NO2
Me
Me
Me
3.66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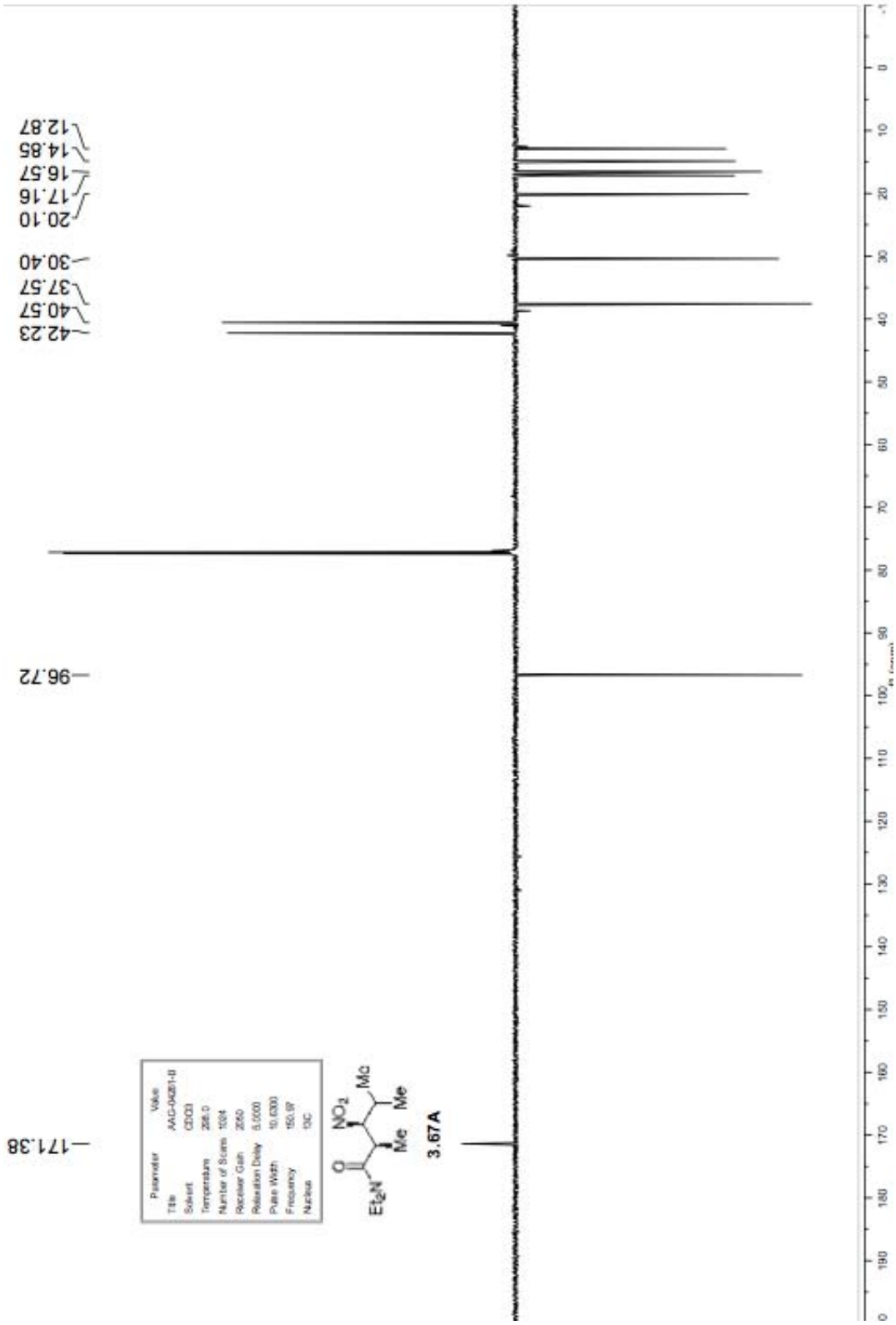
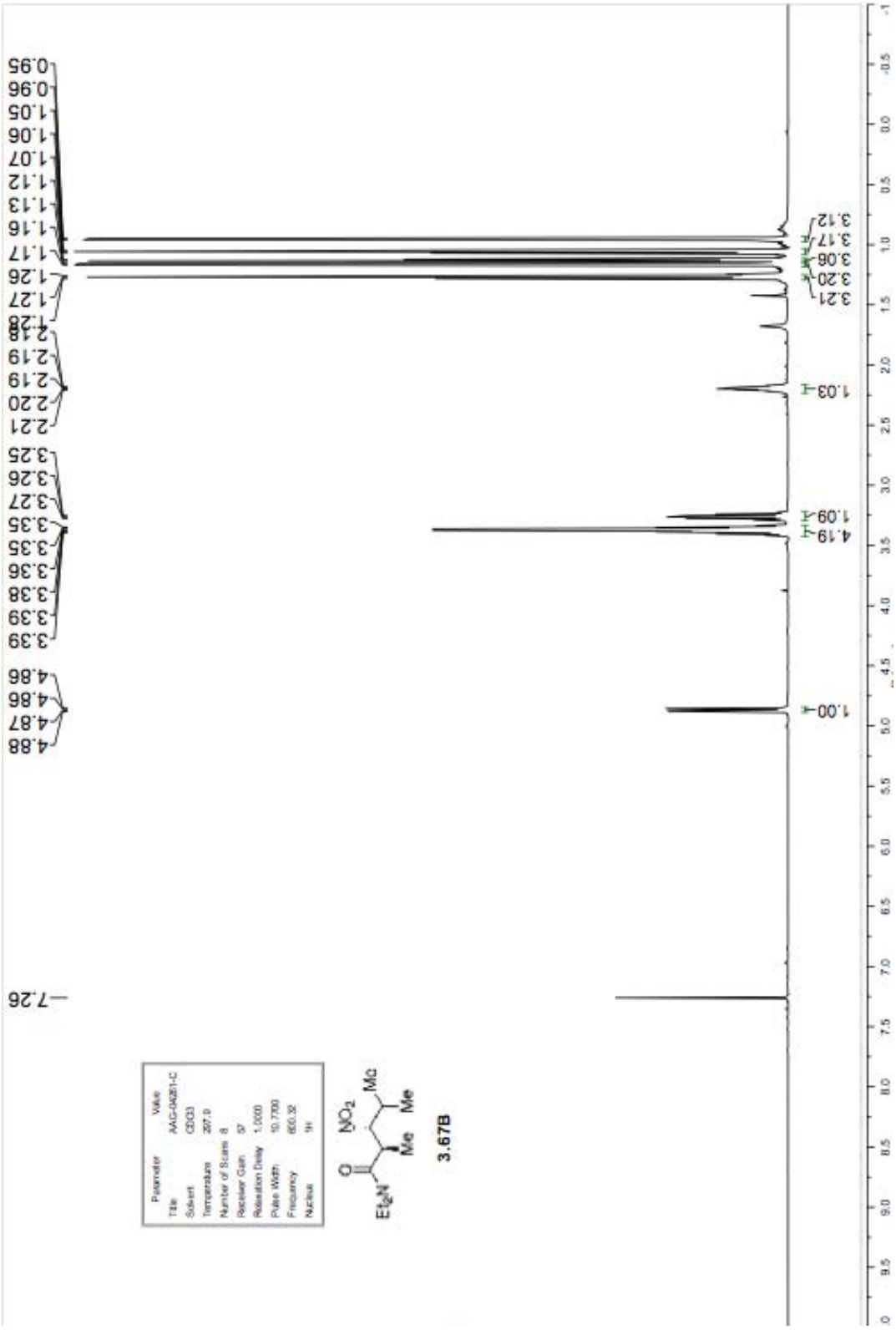
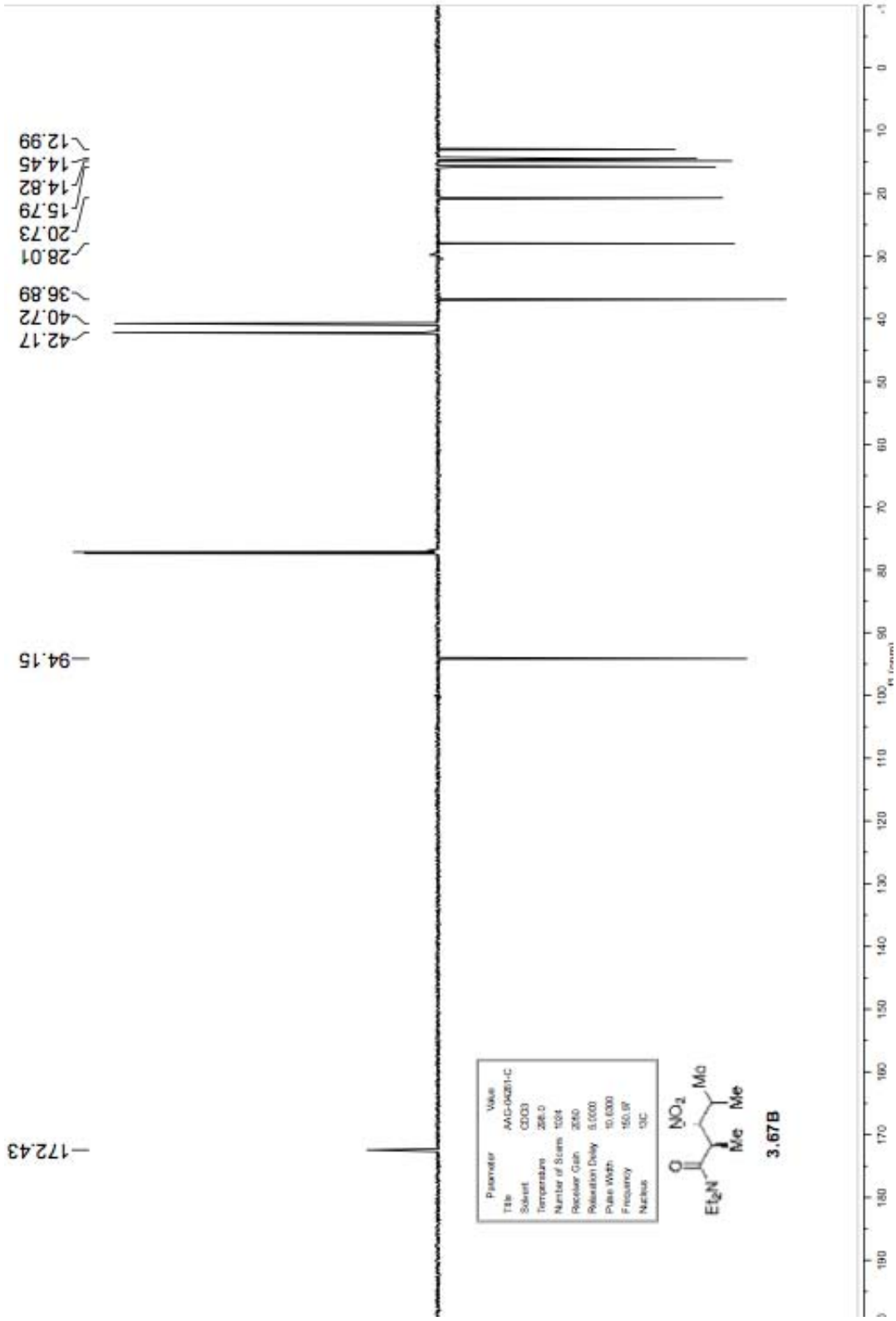
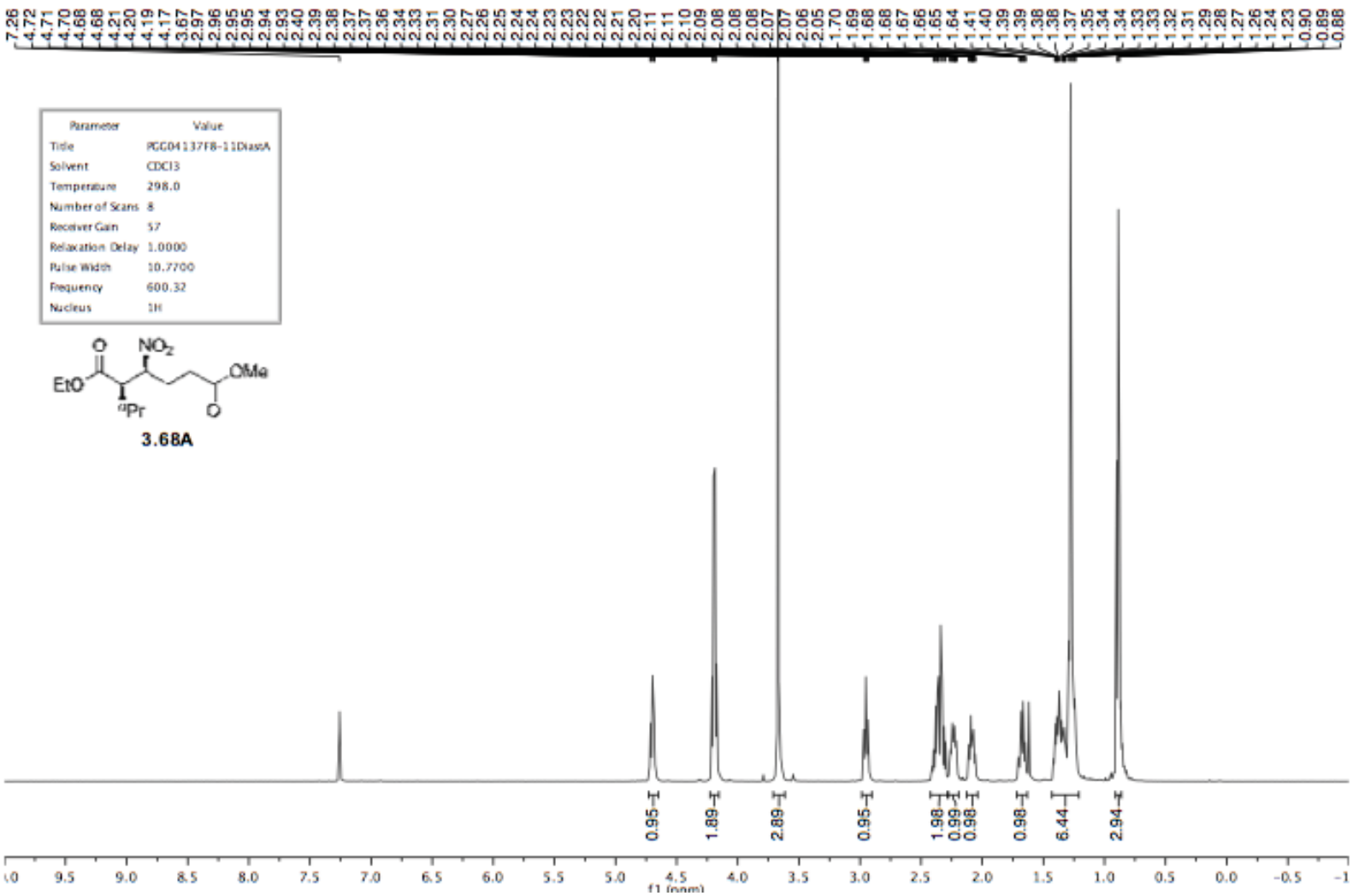
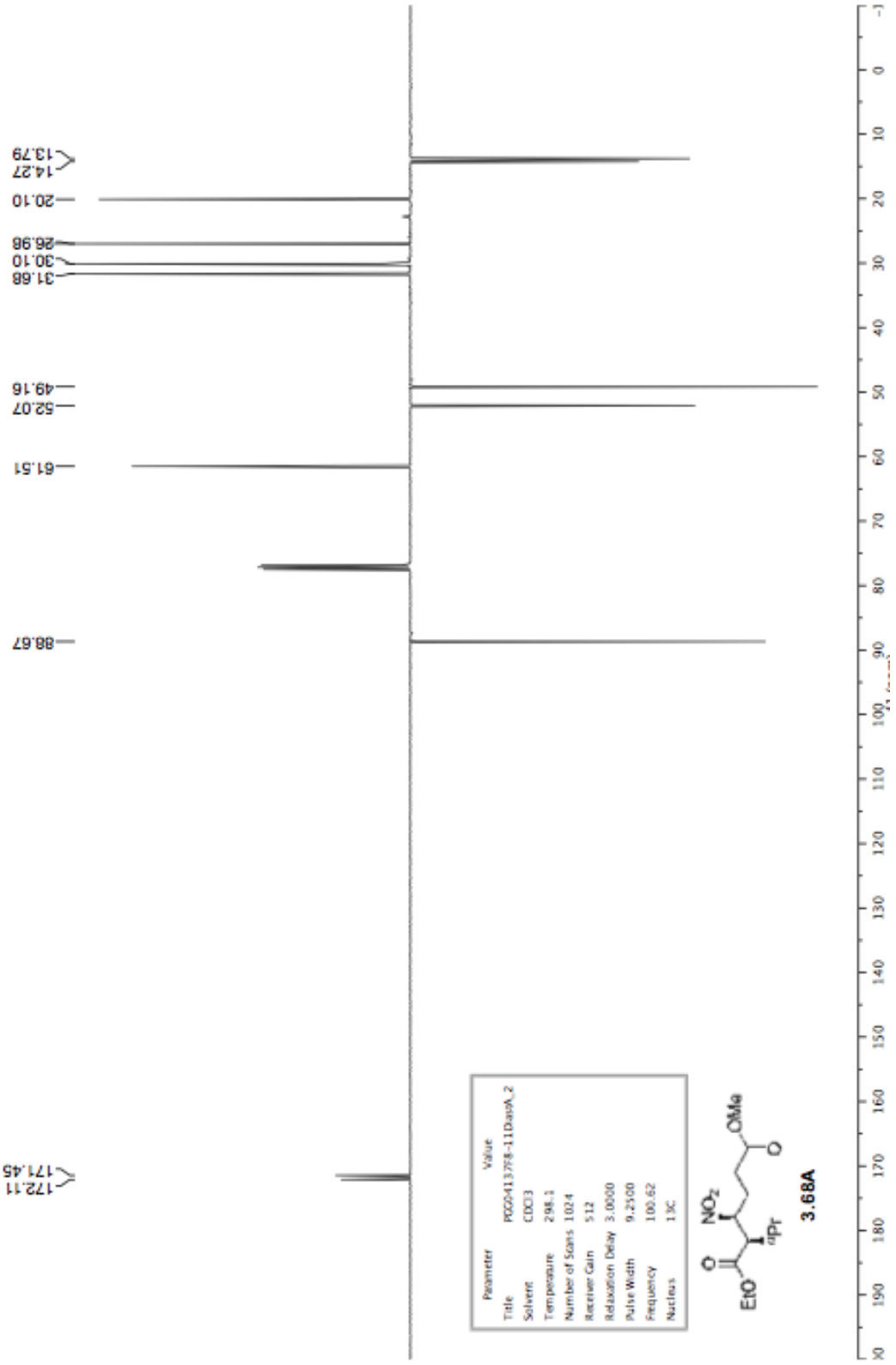
0.97
0.99
1.00
1.10
1.11
1.12
1.17
1.18
1.24
1.25
1.26
2.16
2.17
2.18
2.19
2.21
3.26
3.36
3.37
3.38
3.38
3.39
3.40
3.41
4.77
4.78
4.79
4.80
7.26
3.67
3.15
3.38
3.22
3.07
1.02
4.18
1.21
0.99
Parameter Value
Title AAD-0426-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 114
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Me
Me
Me
O
Et2N
3.67A

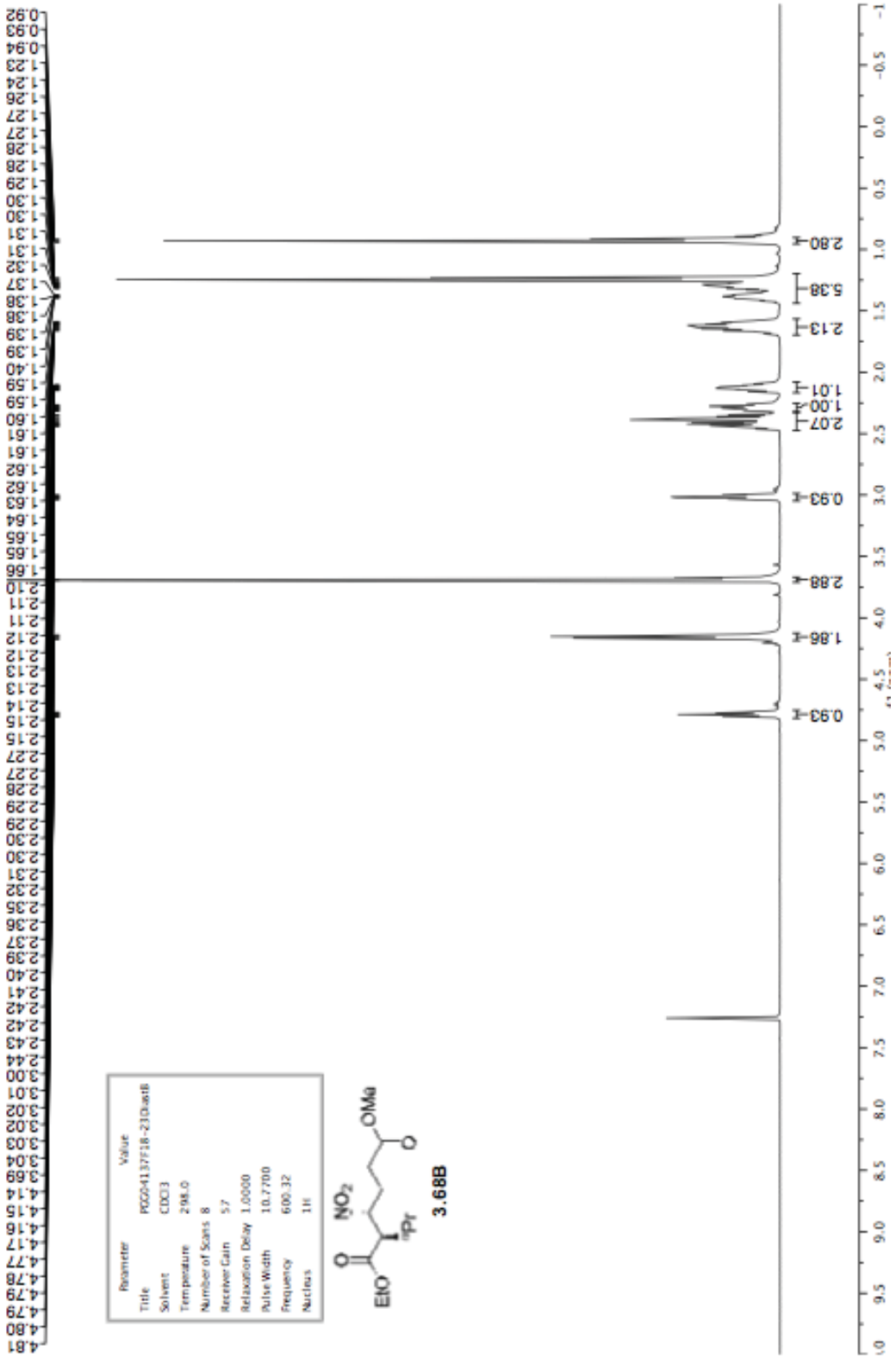

12.87
14.85
16.57
17.16
20.10
30.40
37.57
40.57
42.23
96.72
171.38
Parameter Value
Title AAG-04081-II
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
Et3N
NO2
Me
Me
Me
O
3.67A


Parameter Value
Title AAG-04261-C
Solvent CDCl3
Temperature 297.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.92
Nucleus 1H
NO2
Me
Me
Me
Et2N
O
3.67B

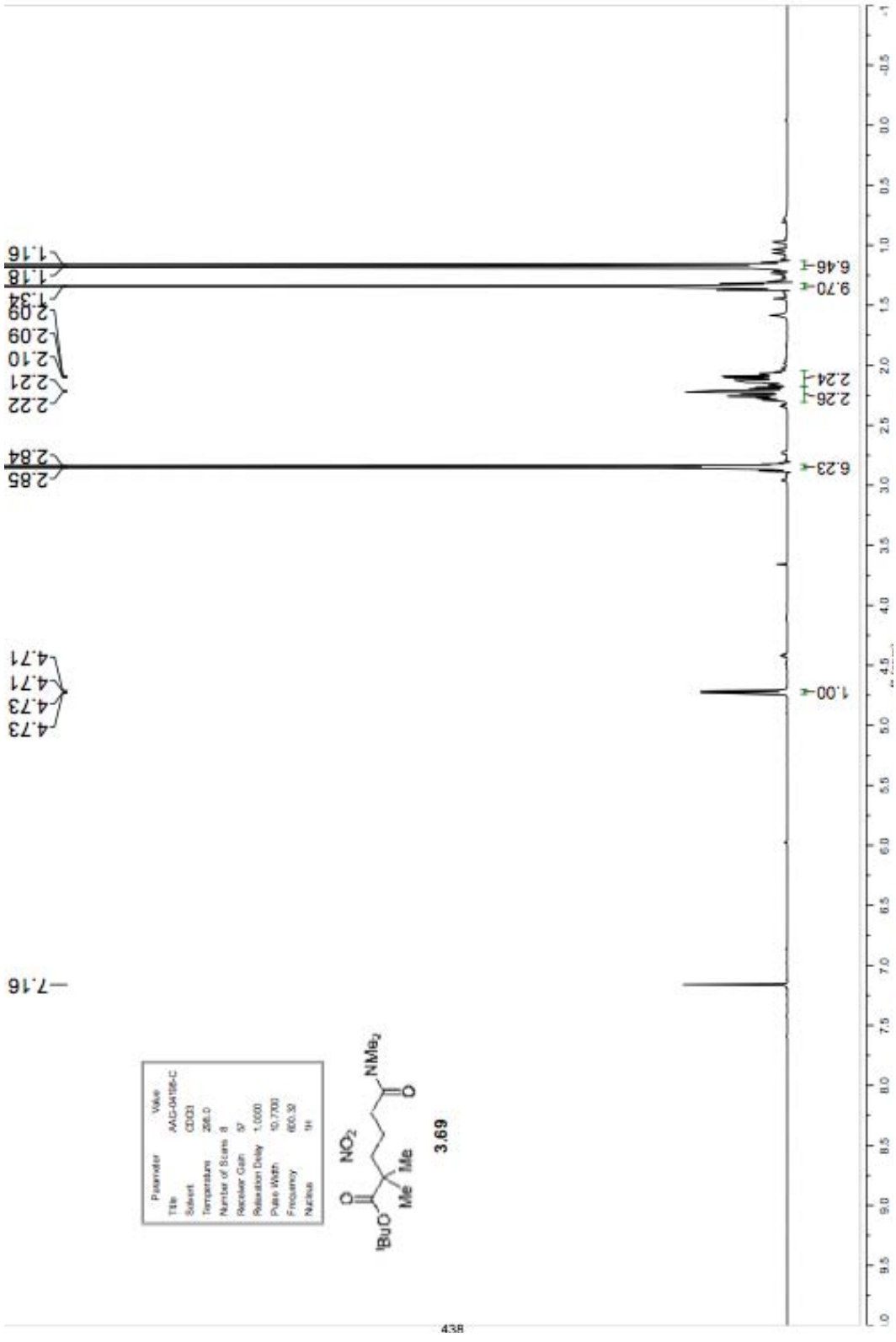

172.43
94.15
42.17
40.72
36.89
28.01
20.73
15.79
14.82
14.45
12.99
Parameter Value
Title AAD-0426-1-C
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.91
Nucleus 13C
O
NO2
Me
Et2N
Me
Me
3.67B

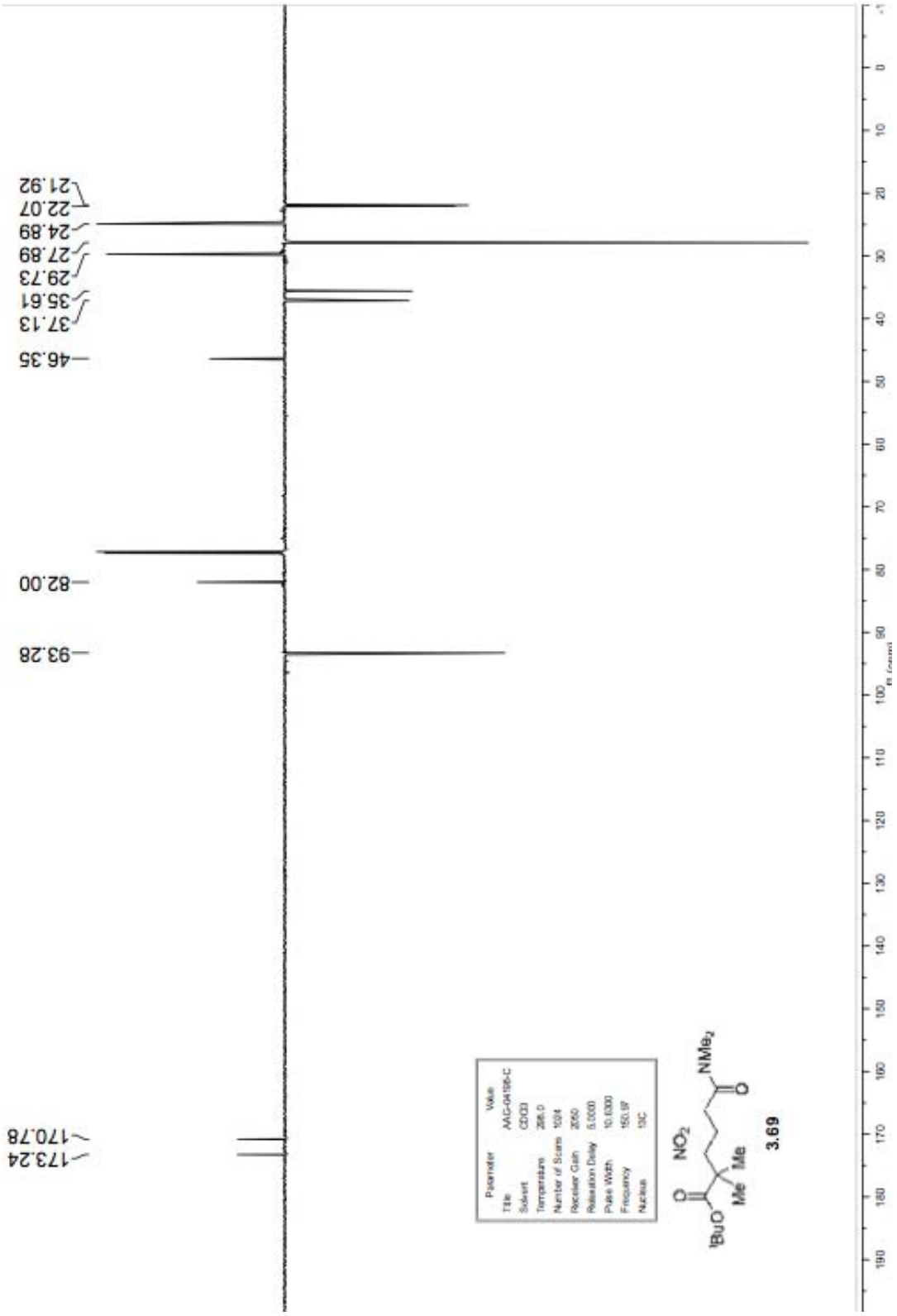

Parameter Value
Title PGD04137F8-11DiastA
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
EtO
NO2
OMe
iPr
O
3.68A
0.95
1.89
2.89
0.95
1.98
0.99
0.98
0.98
6.44
2.94
f1 (ppm)

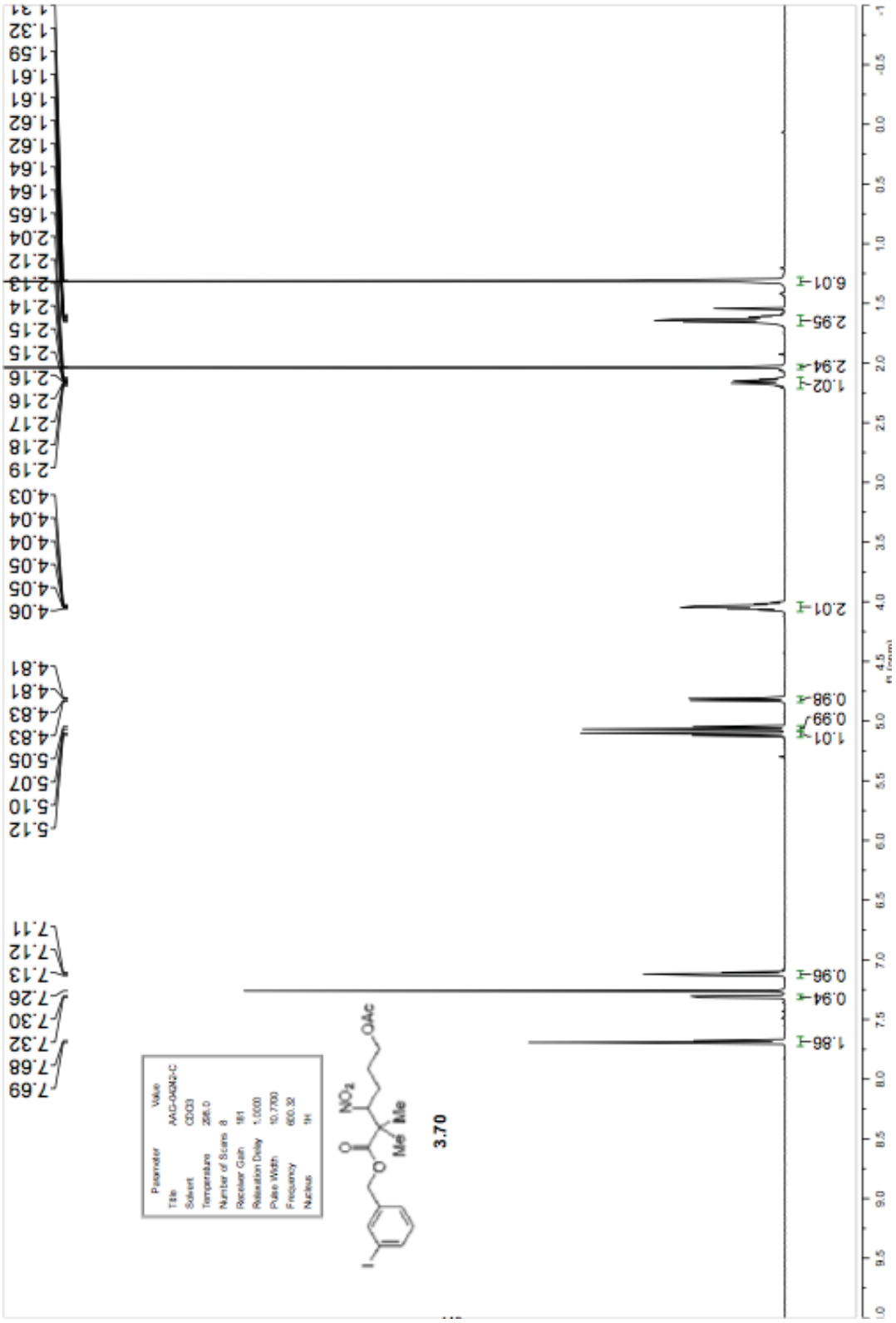

172.11
171.45
88.67
61.51
52.07
49.16
31.68
30.10
26.98
20.10
14.27
13.79
Parameter Value
Title PDG041378-11DaysA_2
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtO
O
NO2
nPr
OMe
O
3.68A

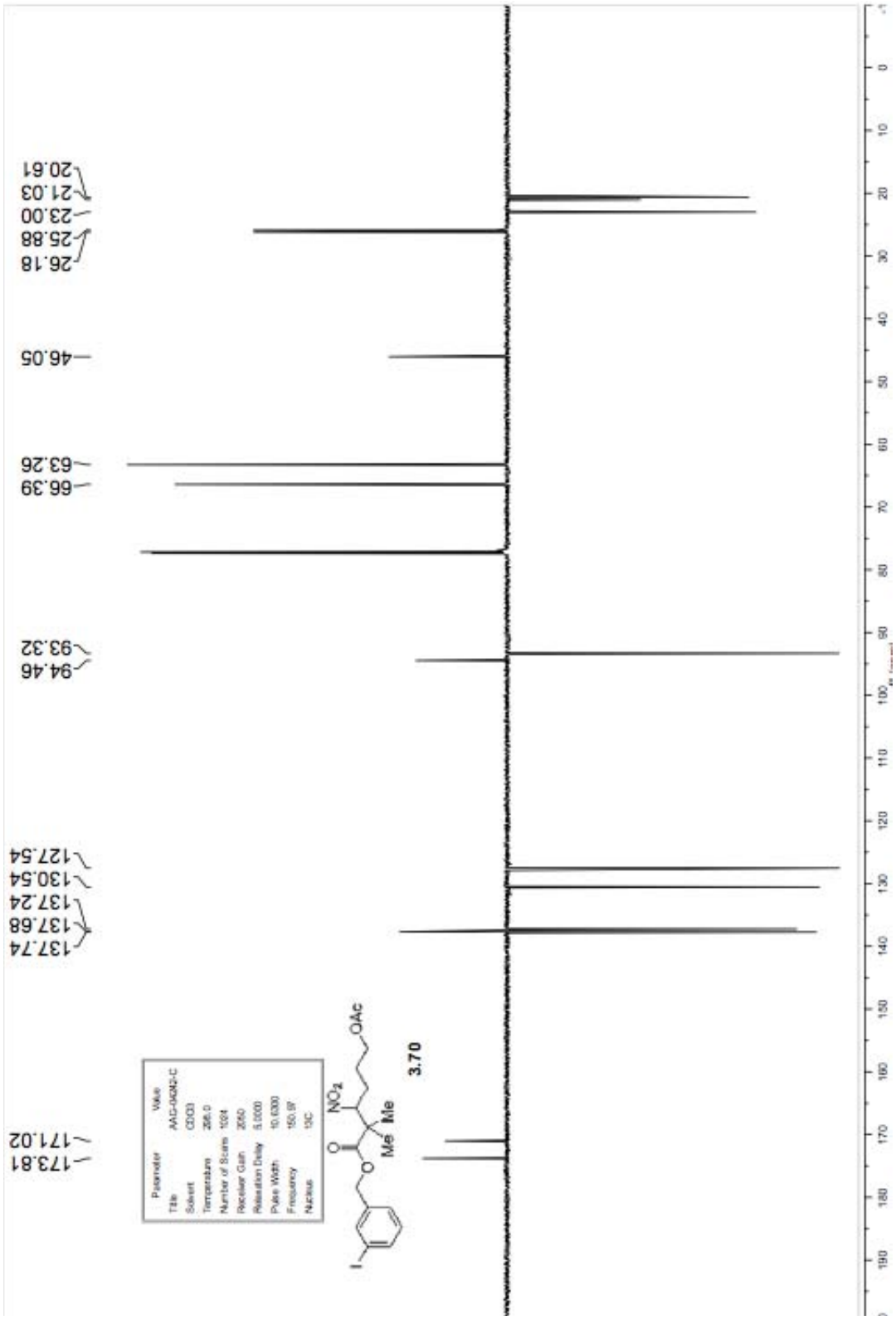

Parameter Value
Title PCC041377518-230ast8
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
EtO
NO2
iPr
OMe
3.68B
0.93
1.86
2.88
0.93
2.07
1.00
1.01
2.13
5.38
2.80

172.36
171.95
87.36
61.45
52.08
48.08
30.51
29.74
26.03
19.94
14.19
14.02
Parameter Value
Title PDG041137F18-230ast8
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtO
O
NO2
nPr
OMe
O
3.68B
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


7.16
4.73
4.73
4.71
4.71
2.85
2.84
2.22
2.21
2.10
2.09
2.09
1.34
1.18
1.16
1.00
6.23
2.26
2.24
9.70
6.46
Parameter Value
Title AAC-04156-C
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
O
NO2
NMe2
O
tBuO
Me
Me
3.69
438


21.92
22.07
24.89
27.89
29.73
35.61
37.13
46.35
82.00
93.28
170.78
173.24
Parameter Value
Title AAG-04156-C
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.0300
Frequency 150.97
Nucleus 13C
NMe2
NO2
Me
Me
tBuO
3.69


Parameter Value
Title AAG-0424-C
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7300
Frequency 600.32
Nucleus 1H
NO2
OAc
Me
Me
3.70
1.86
0.94
0.96
7.11
7.12
7.13
7.26
7.30
7.32
7.68
7.69
5.12
5.10
5.07
5.05
4.83
4.83
4.81
4.81
0.98
0.99
1.01
2.01
4.03
4.04
4.04
4.05
4.05
4.06
2.19
2.18
2.17
2.16
2.16
2.15
2.15
2.14
2.13
2.12
2.04
1.65
1.64
1.64
1.62
1.62
1.61
1.61
1.59
1.32
1.31
6.01
2.95
2.94
1.02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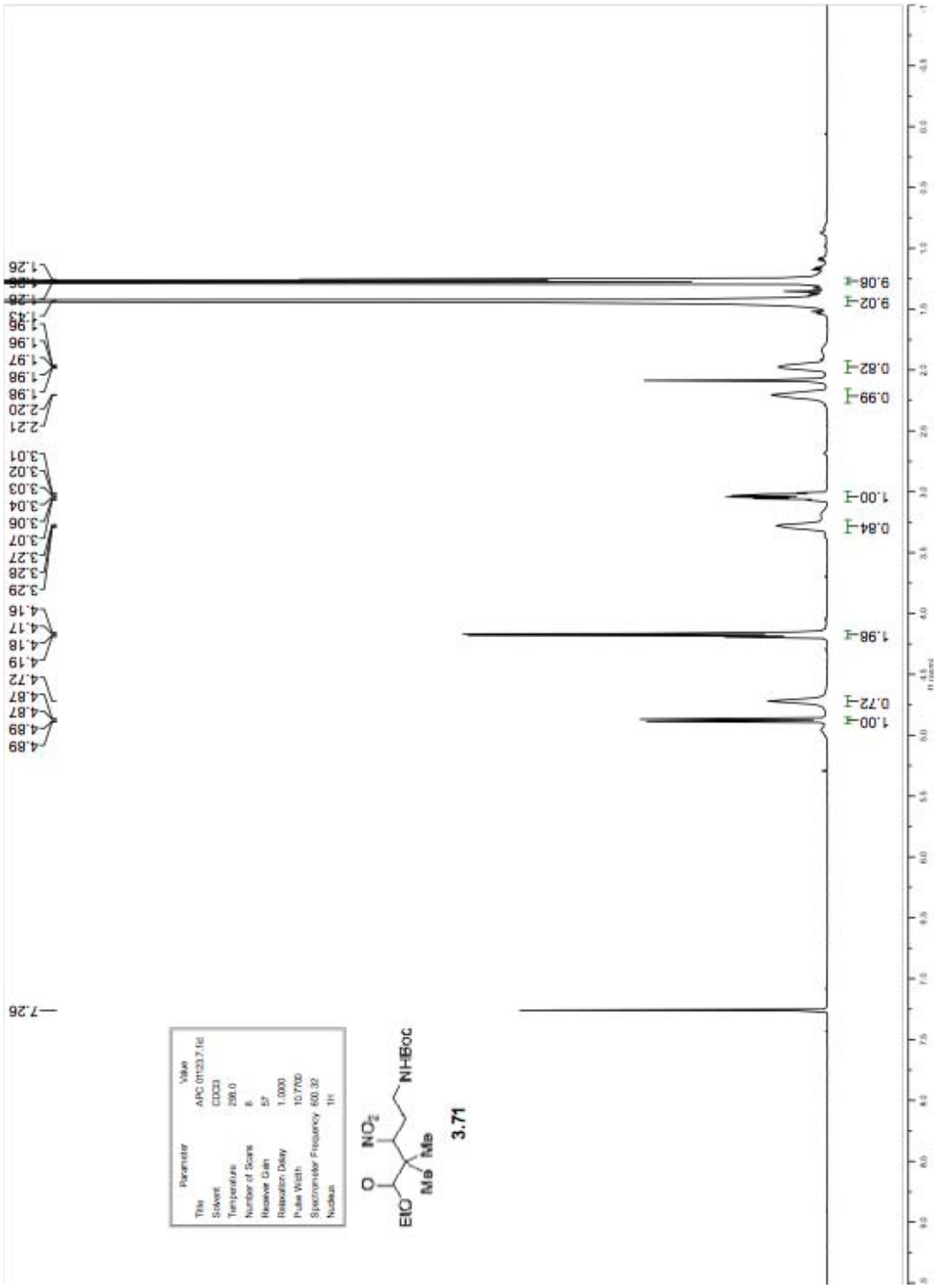
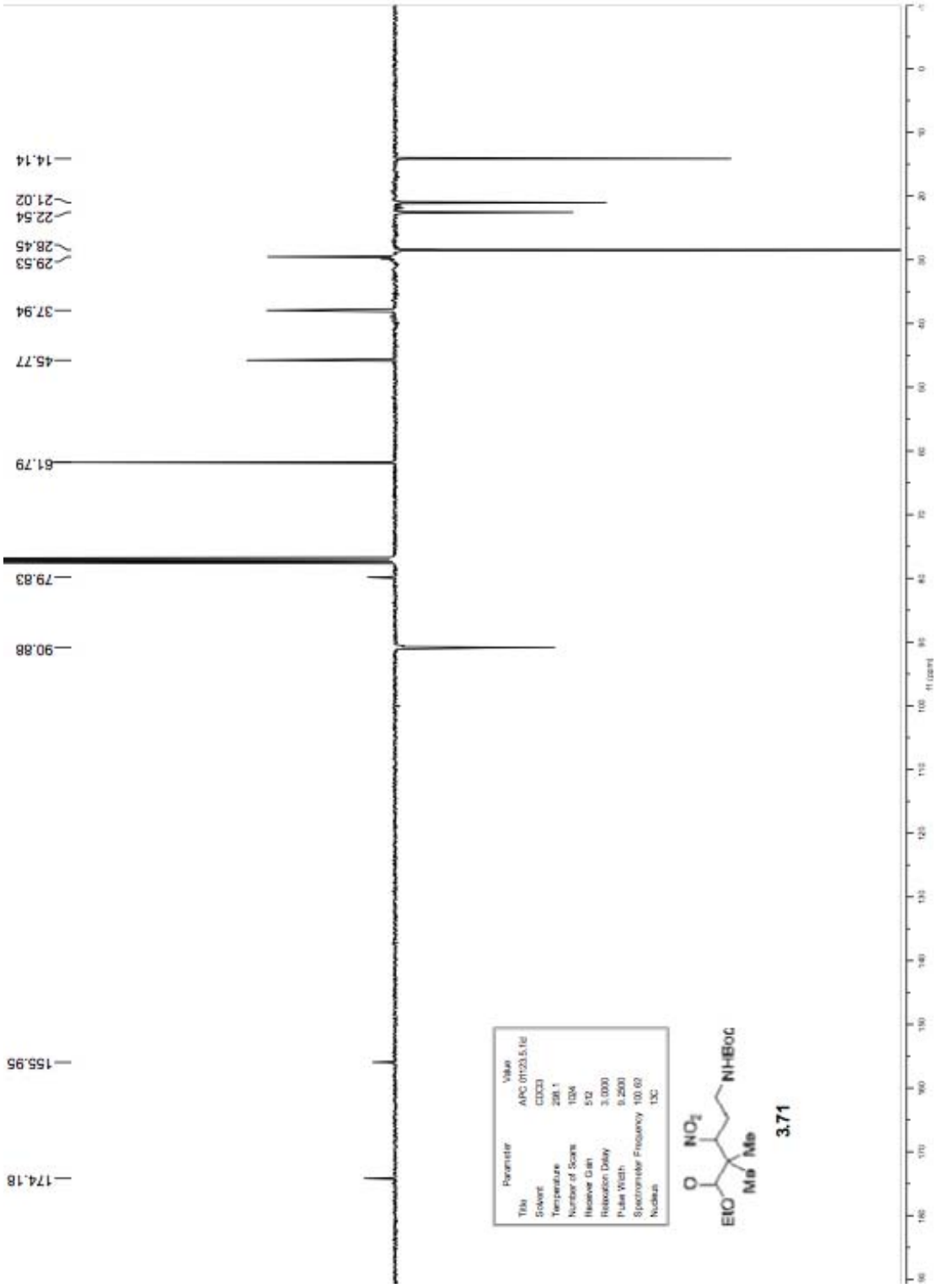
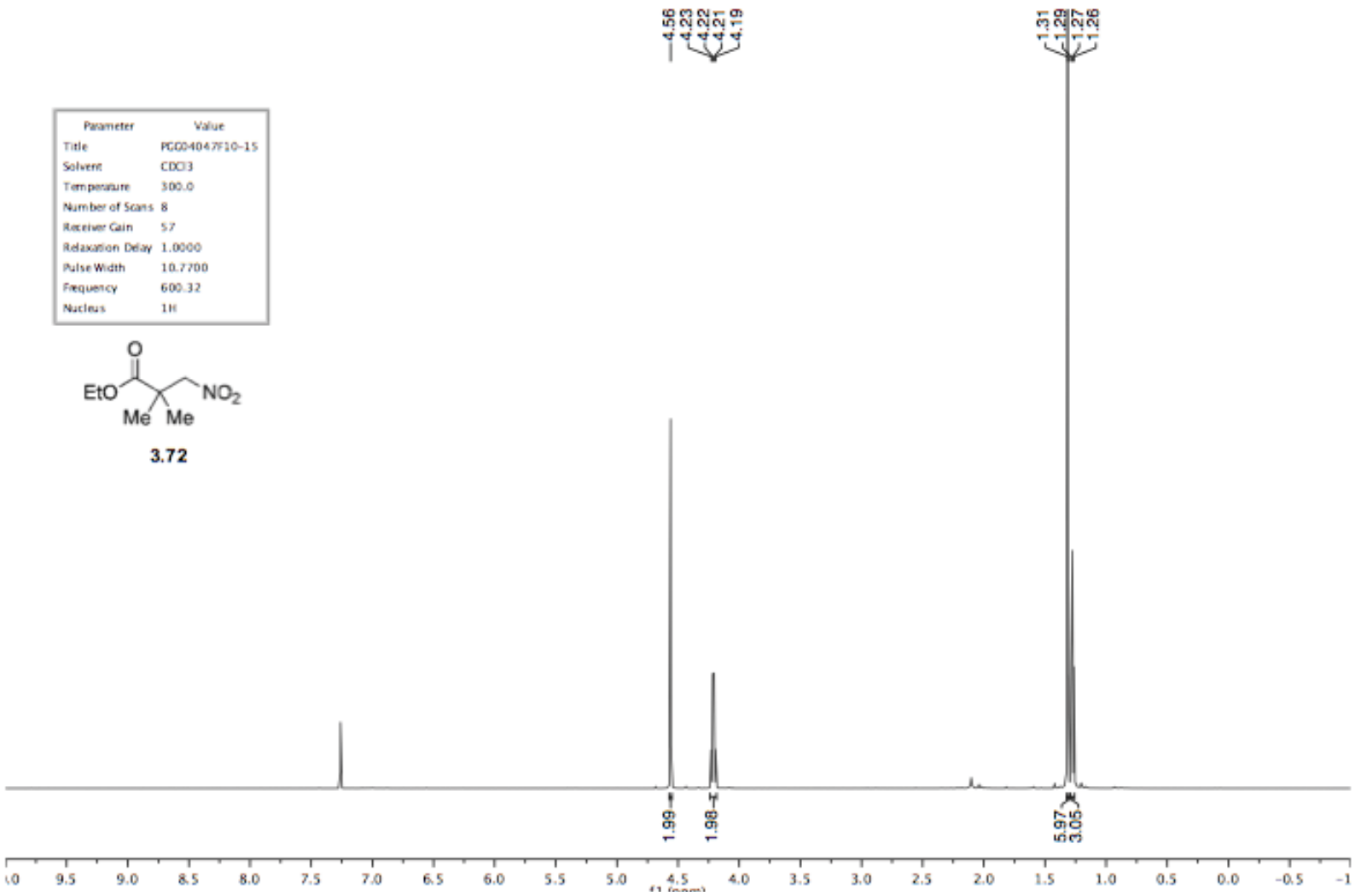
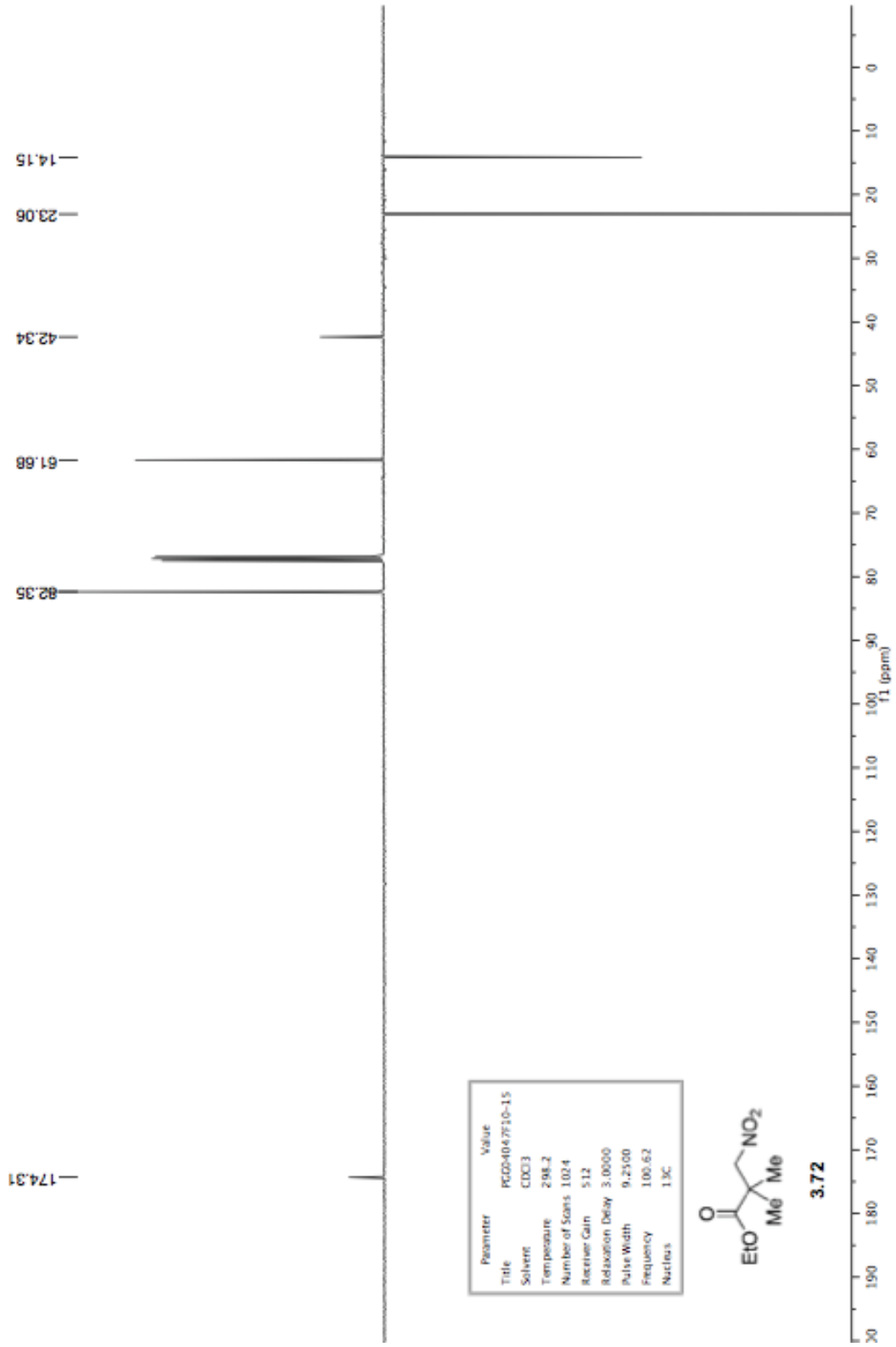
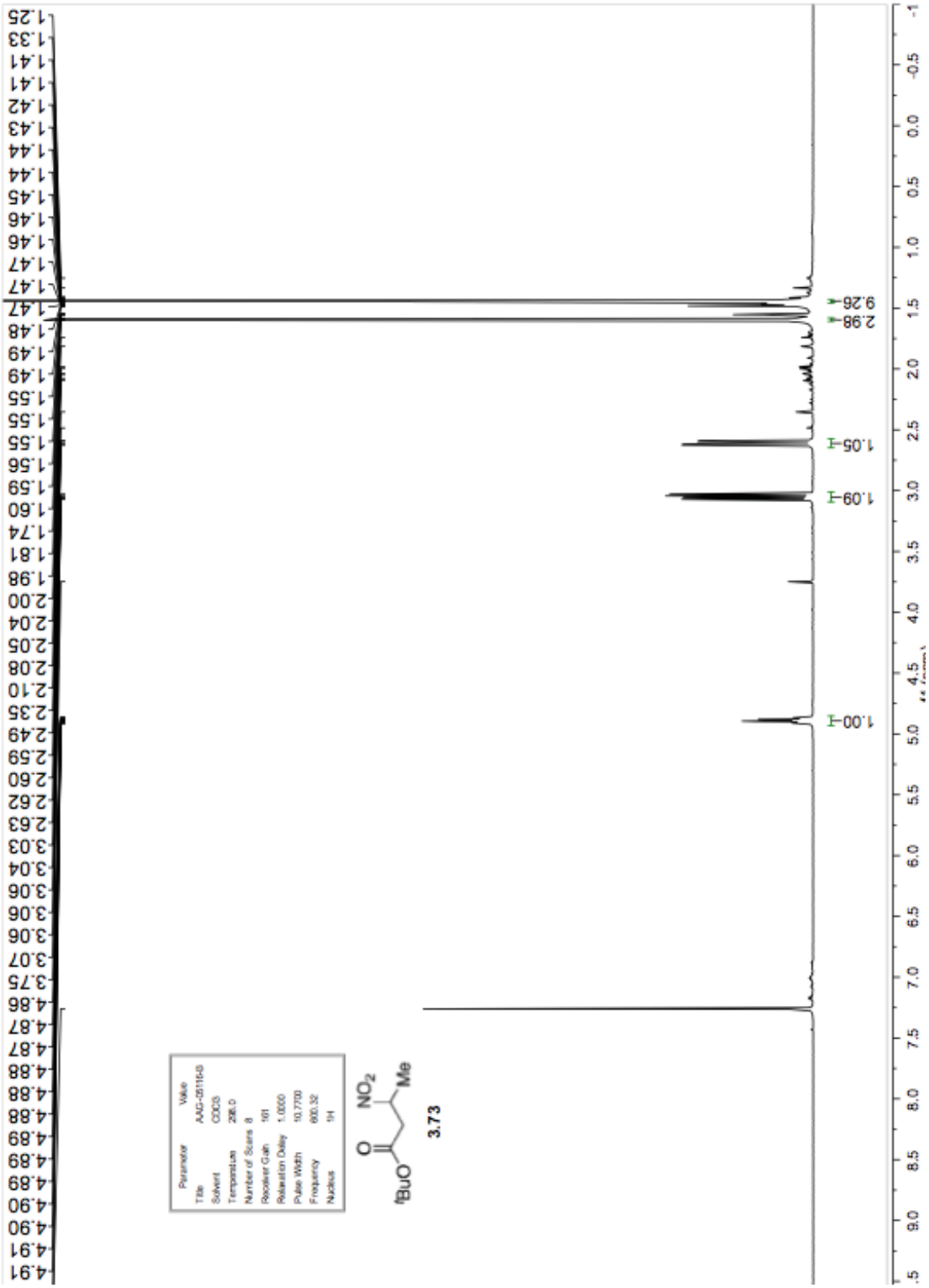
21.03
23.00
25.88
26.18
46.05
63.26
66.39
93.32
94.46
127.54
130.54
137.24
137.68
137.74
171.02
173.81
Parameter Value
Title AAD-0404-C
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.97
Nucleus 13C
NO2
OAc
Me Me
3.70
I

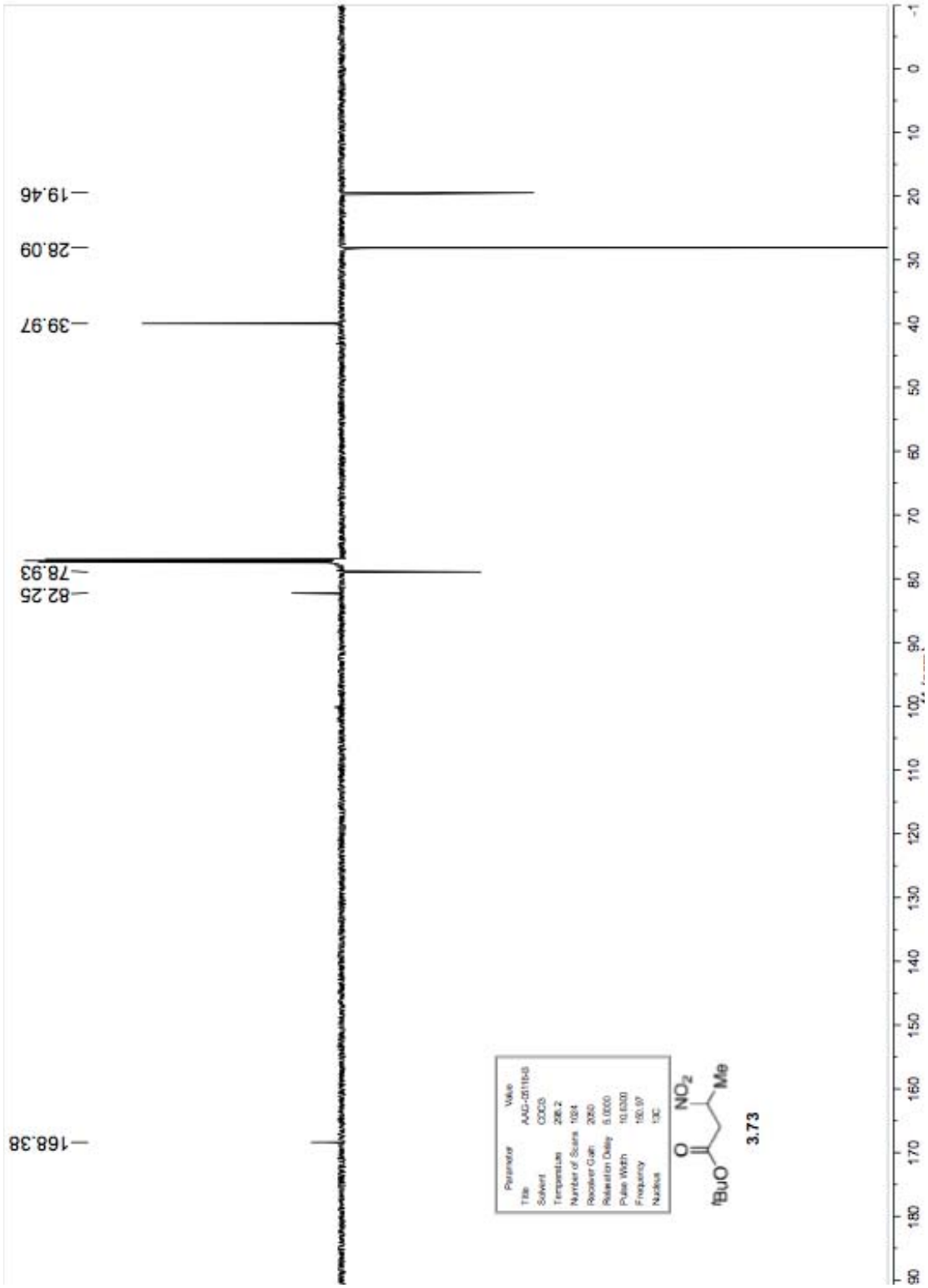

7.26
4.89
4.89
4.87
4.87
4.72
4.19
4.18
4.17
4.16
3.29
3.28
3.27
3.07
3.06
3.04
3.03
3.02
3.01
2.21
2.20
1.98
1.97
1.96
1.96
1.43
1.28
1.26
9.06
9.02
0.82
0.99
1.00
0.84
1.98
0.72
1.00
Parameter
Value
Title
APC 01123.7.fid
Solvent
CDCl3
Temperature
299.0
Number of Scans
8
Receiver Gain
57
Relaxation Delay
1.0000
Pulse Width
10.7700
Spectrometer Frequency
600.32
Nucleus
1H
O
NO2
NHBoc
EtO
Me
Me
3.71

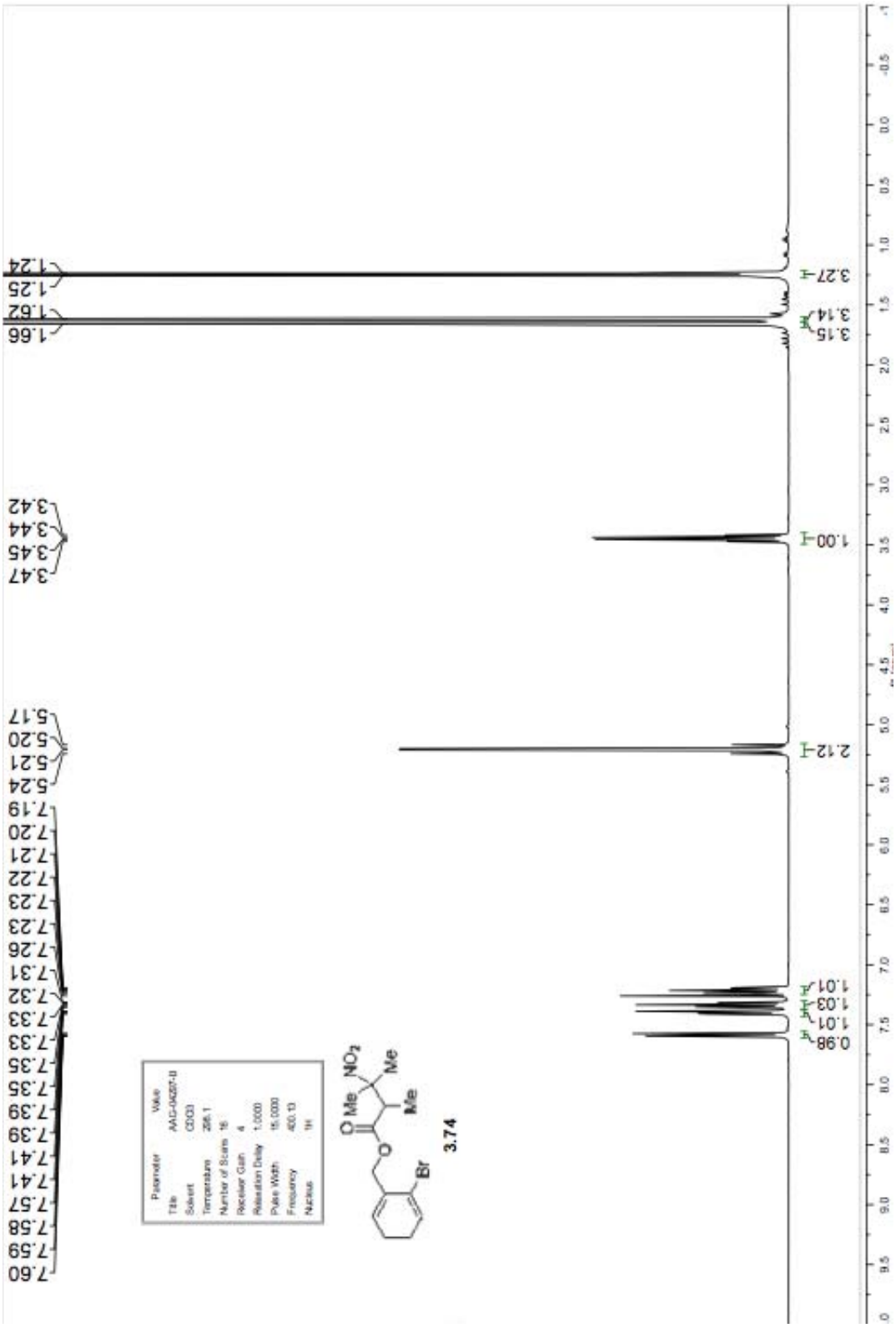

14.14
21.02
22.54
28.45
29.53
37.94
45.77
61.79
79.83
90.88
155.95
174.18
Parameter
Value
Title
APC 01123.5.1d
Solvent
CDCl3
Temperature
298.1
Number of Scans
1024
Receiver Gain
512
Relaxation Delay
3.0000
Pulse Width
9.2500
Spectrometer Frequency
100.62
Nucleus
13C
NO2
NHBoc
O
EtO
Me
Me
3.71

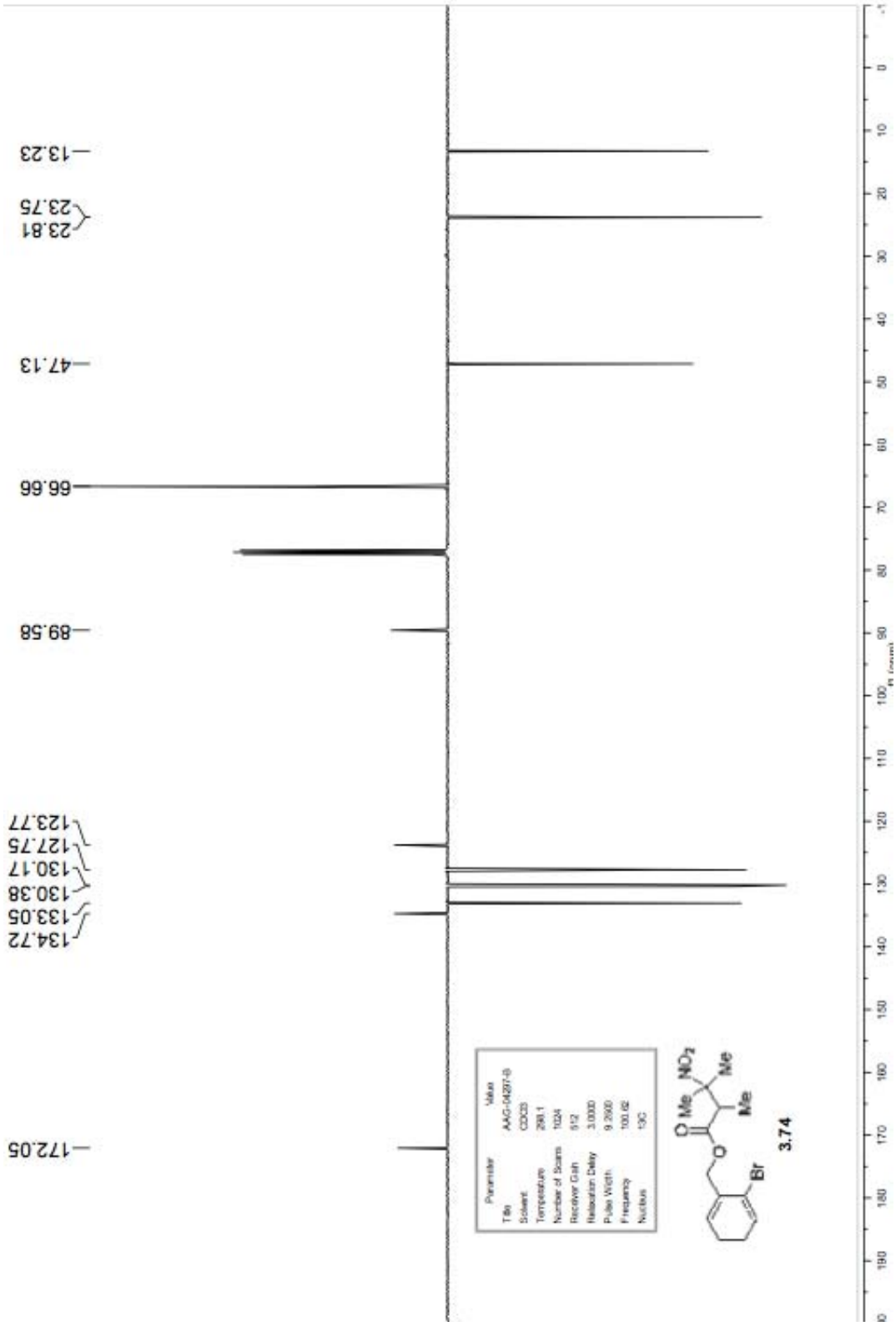

Parameter Value
Title PGD04047F10-15
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
EtO
NO2
Me Me
3.72
4.56
4.23
4.22
4.21
4.19
1.31
1.29
1.27
1.26
1.99
1.98
5.97
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

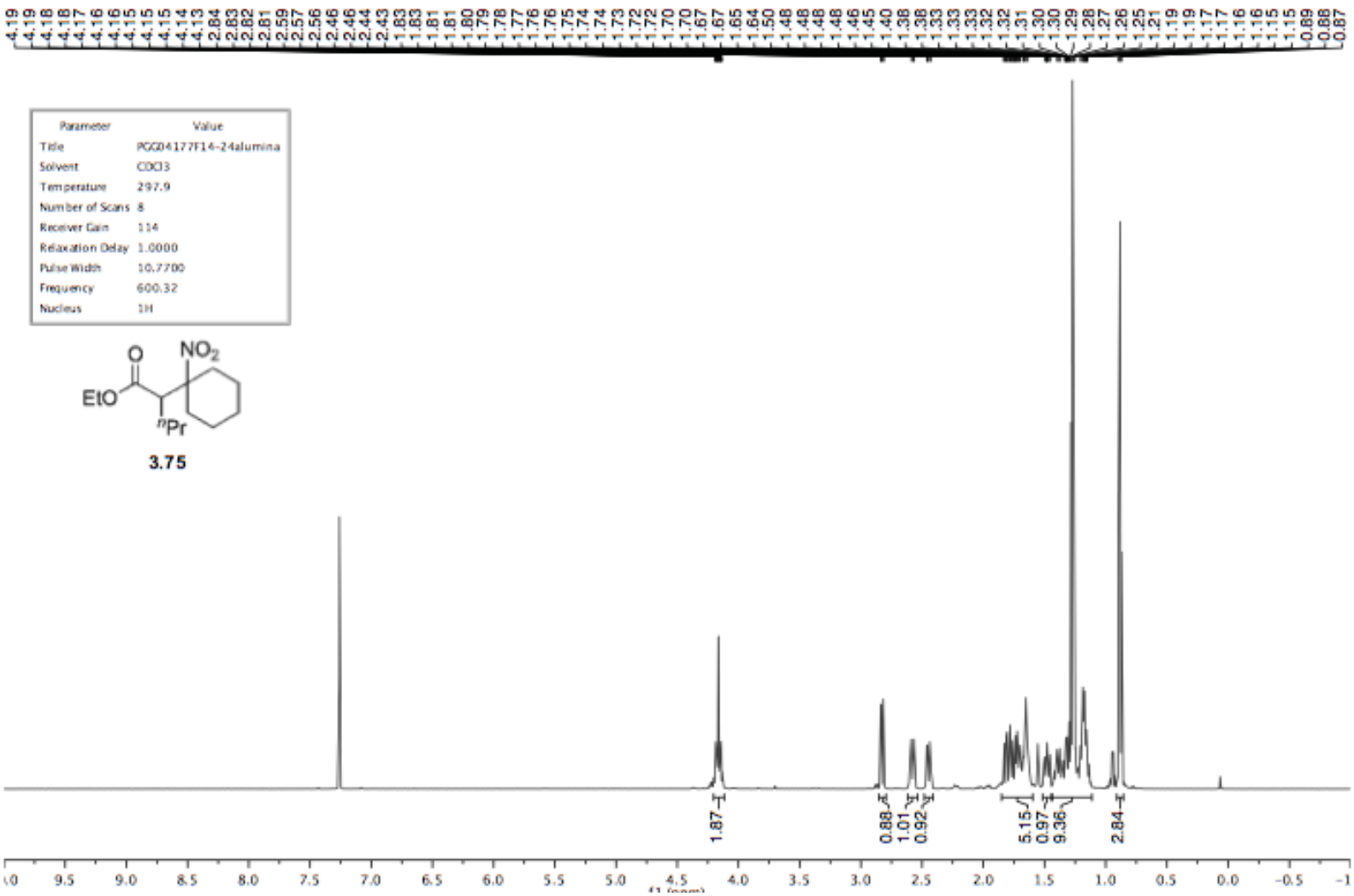

174.31
82.35
61.68
42.34
23.06
14.15
f1 (ppm)
Parameter Value
Title PE004047F10-15
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtO
O
Me
Me
NO2
3.72

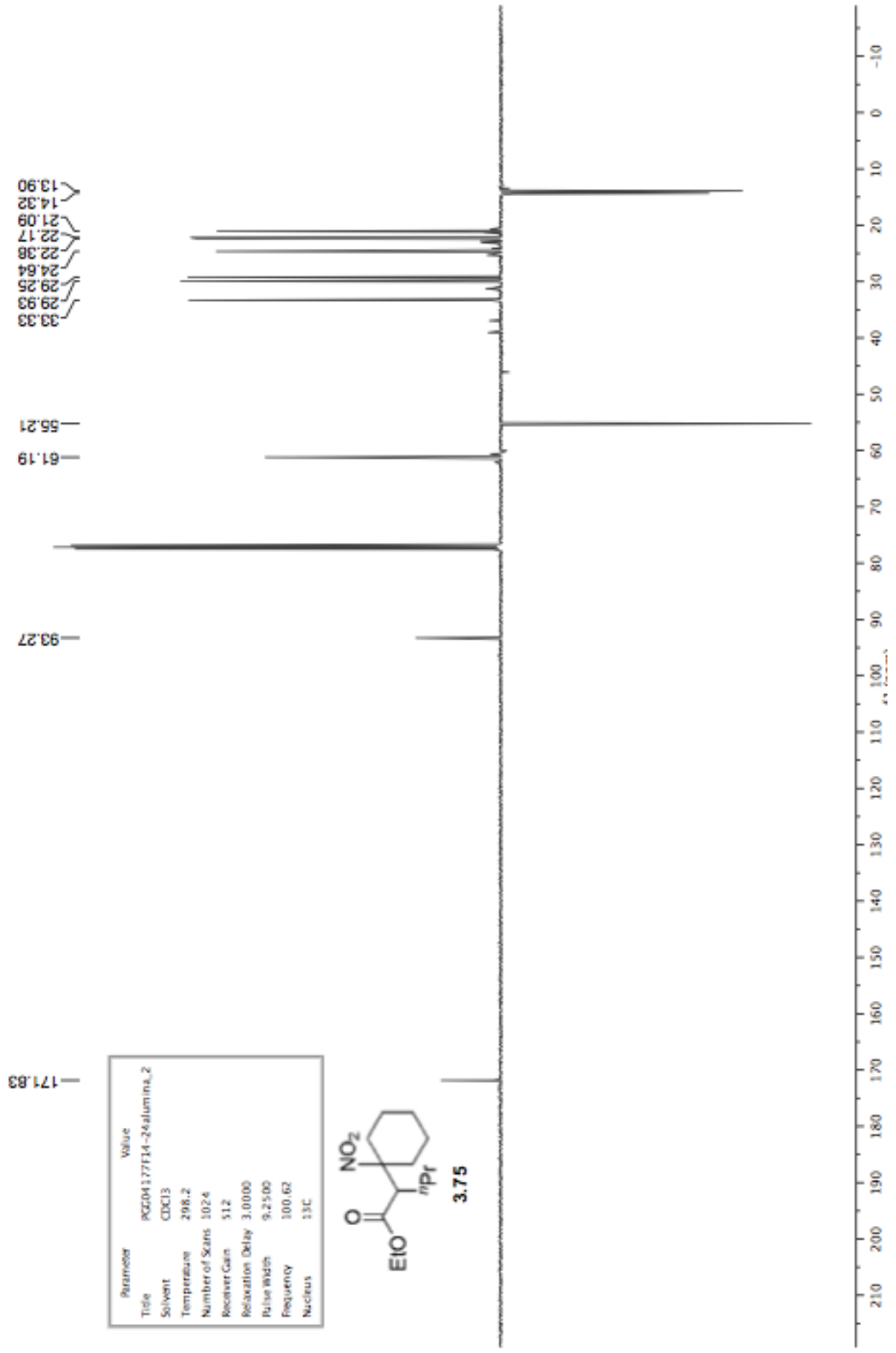

Parameter Value
Title AAG-051104
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 101
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Me
O
tBuO
3.73
9.26
2.98
1.05
1.09
1.00

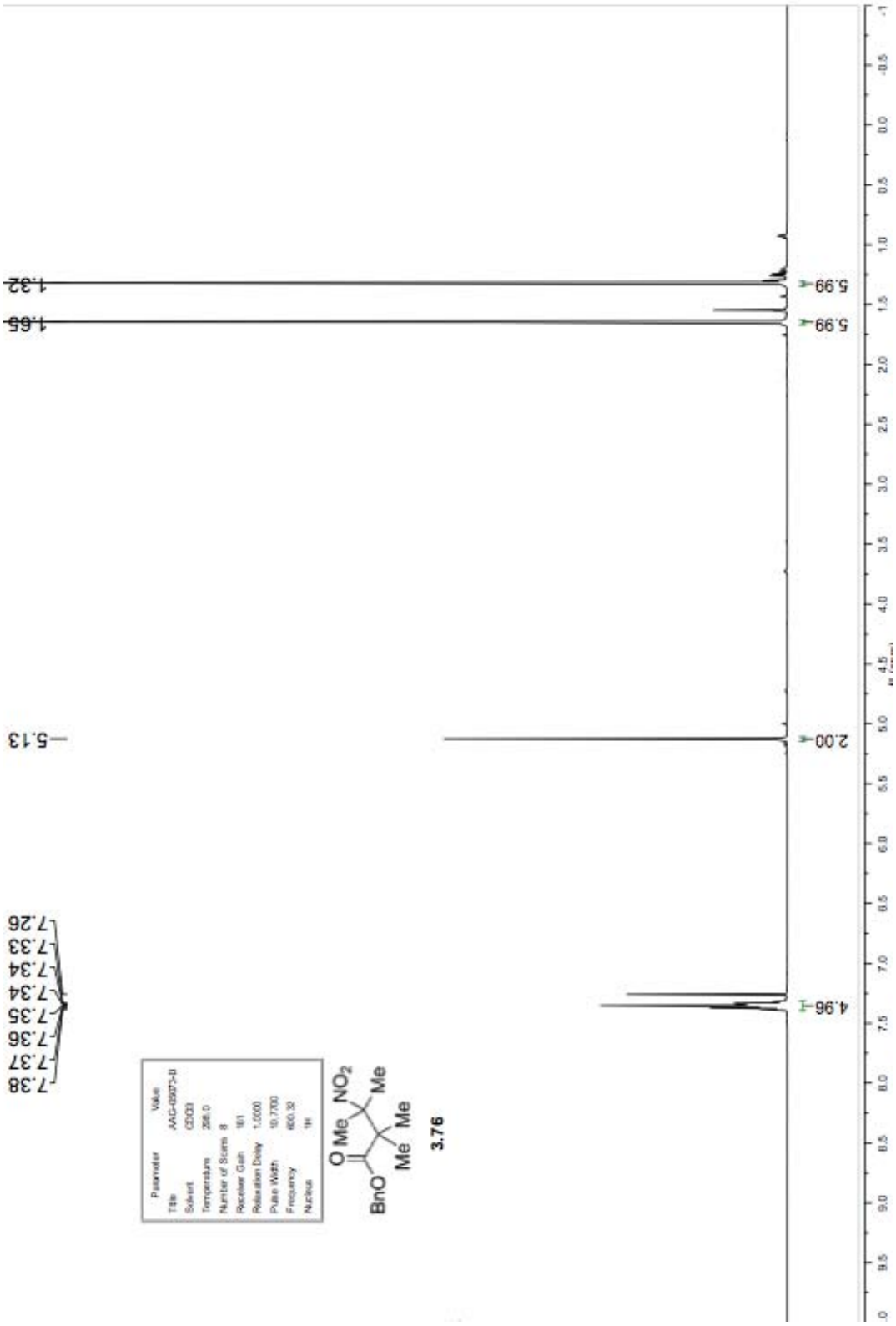

19.46
28.09
39.97
78.93
82.25
168.38
Parameter Value
Title AAD-051845
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6500
Frequency 150.97
Nucleus 13C
NO2
Me
O
tBuO
3.73

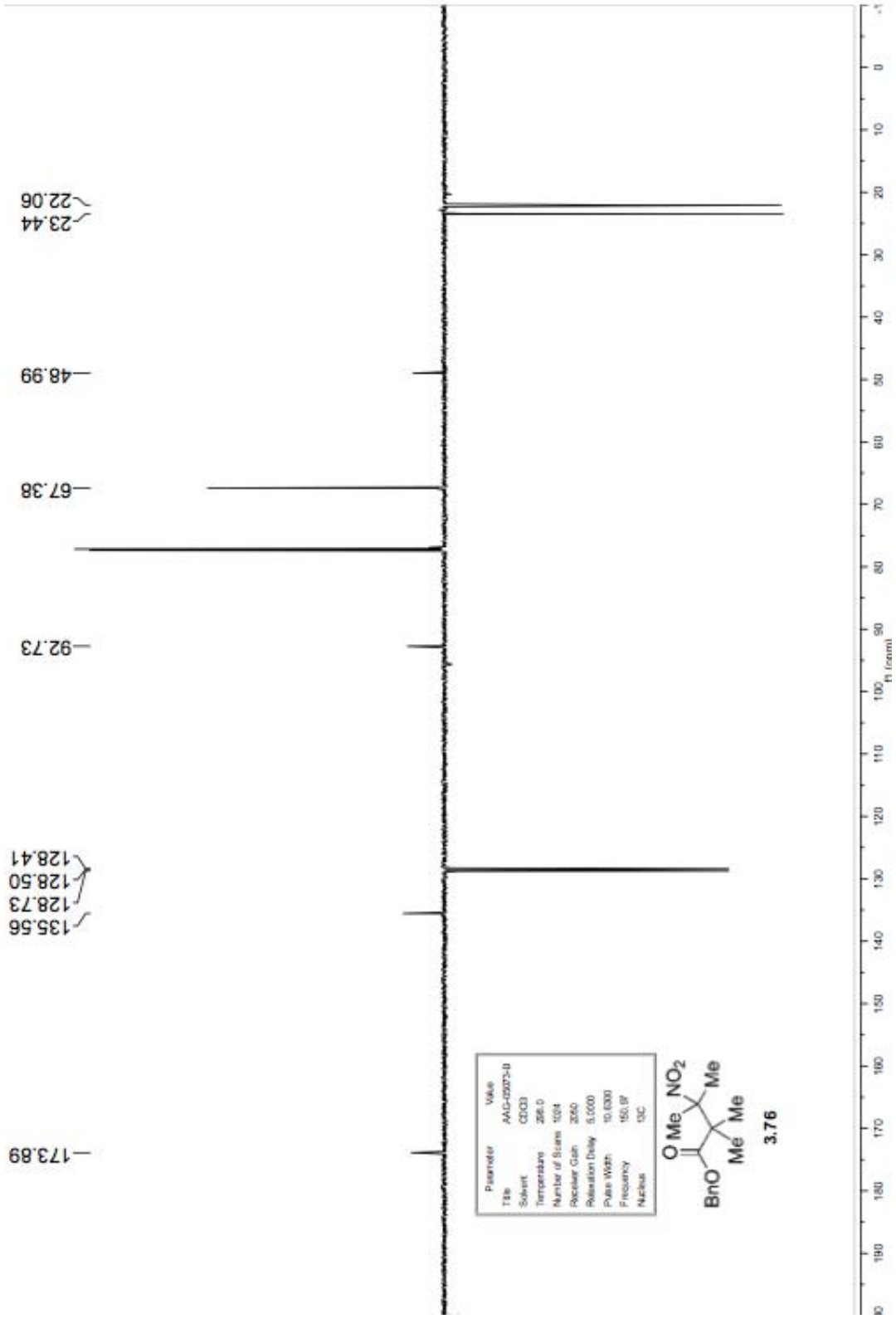

1.24
1.25
1.62
1.66
3.42
3.44
3.45
3.47
5.17
5.20
5.21
5.24
7.19
7.20
7.21
7.22
7.23
7.23
7.26
7.31
7.32
7.33
7.33
7.35
7.35
7.39
7.39
7.41
7.41
7.57
7.58
7.59
7.60
3.27
3.15
3.14
1.00
2.12
1.01
1.03
1.01
0.98
Parameter Value
Title AAD-04287-II
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 4
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
NO2
Me
Me
Me
O
O
Br
3.74

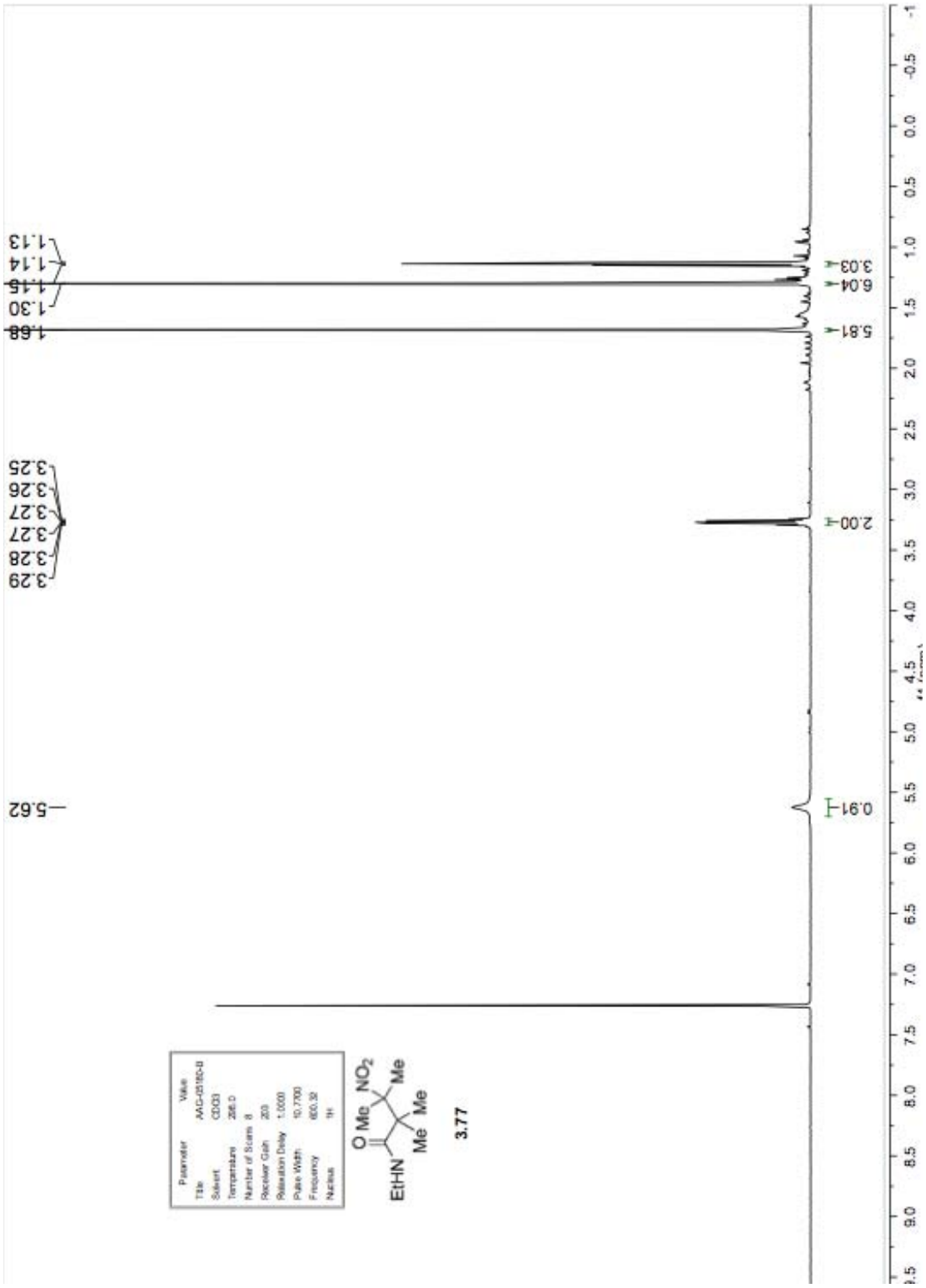

172.05
134.72
133.05
130.38
130.17
127.75
123.77
89.58
66.66
47.13
23.81
23.75
13.23
Parameter Value
Title AAG-04297-b
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Me
NO2
Me
Me
O
O
Br
3.74

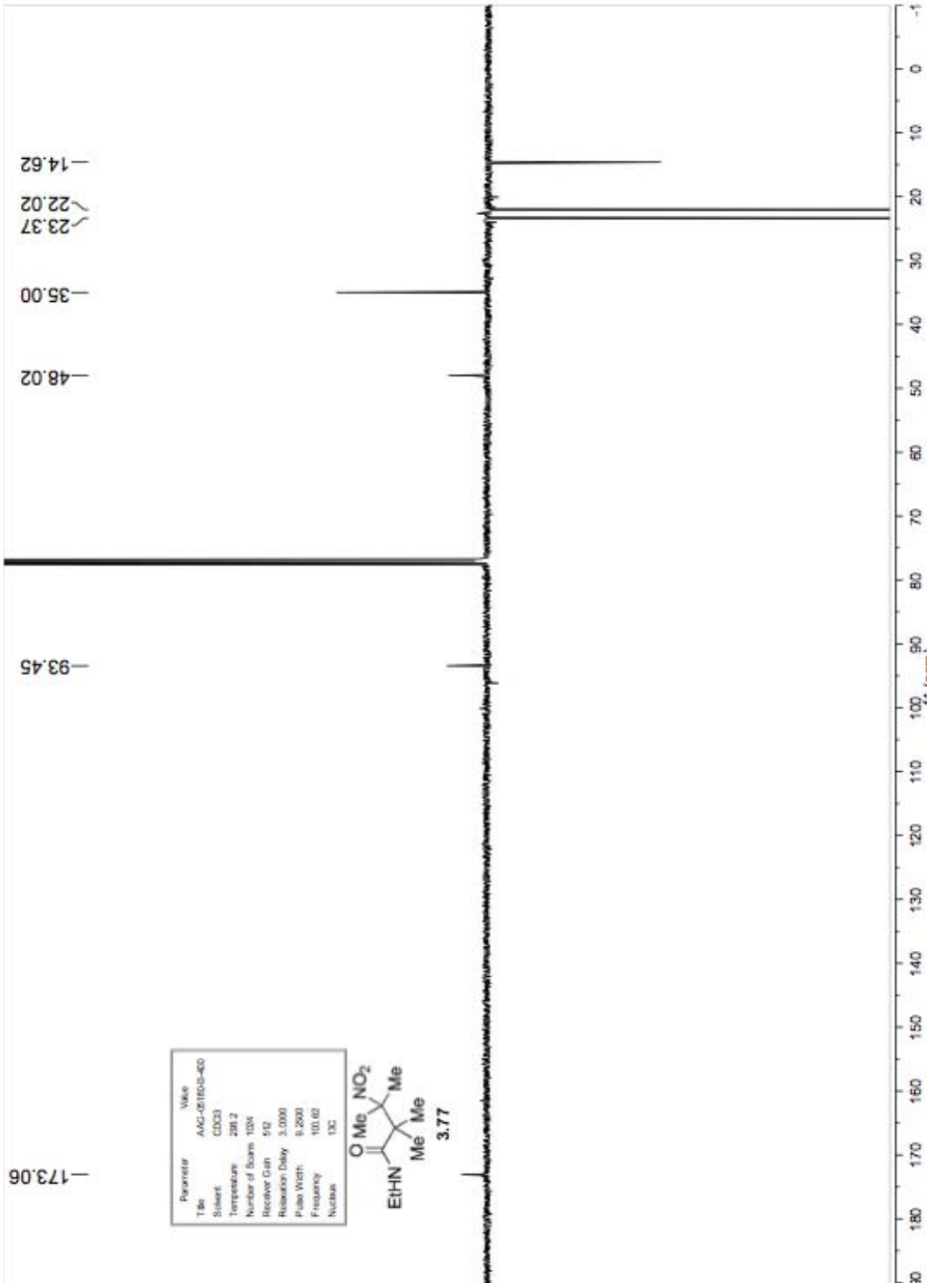

Parameter Value
Title PGD4177F14-24alumina
Solvent CDCl3
Temperature 297.9
Number of Scans 8
Receiver Gain 114
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
NO2
EtO
nPr
3.75
1.87
0.88
1.01
0.92
5.15
0.97
9.36
2.84

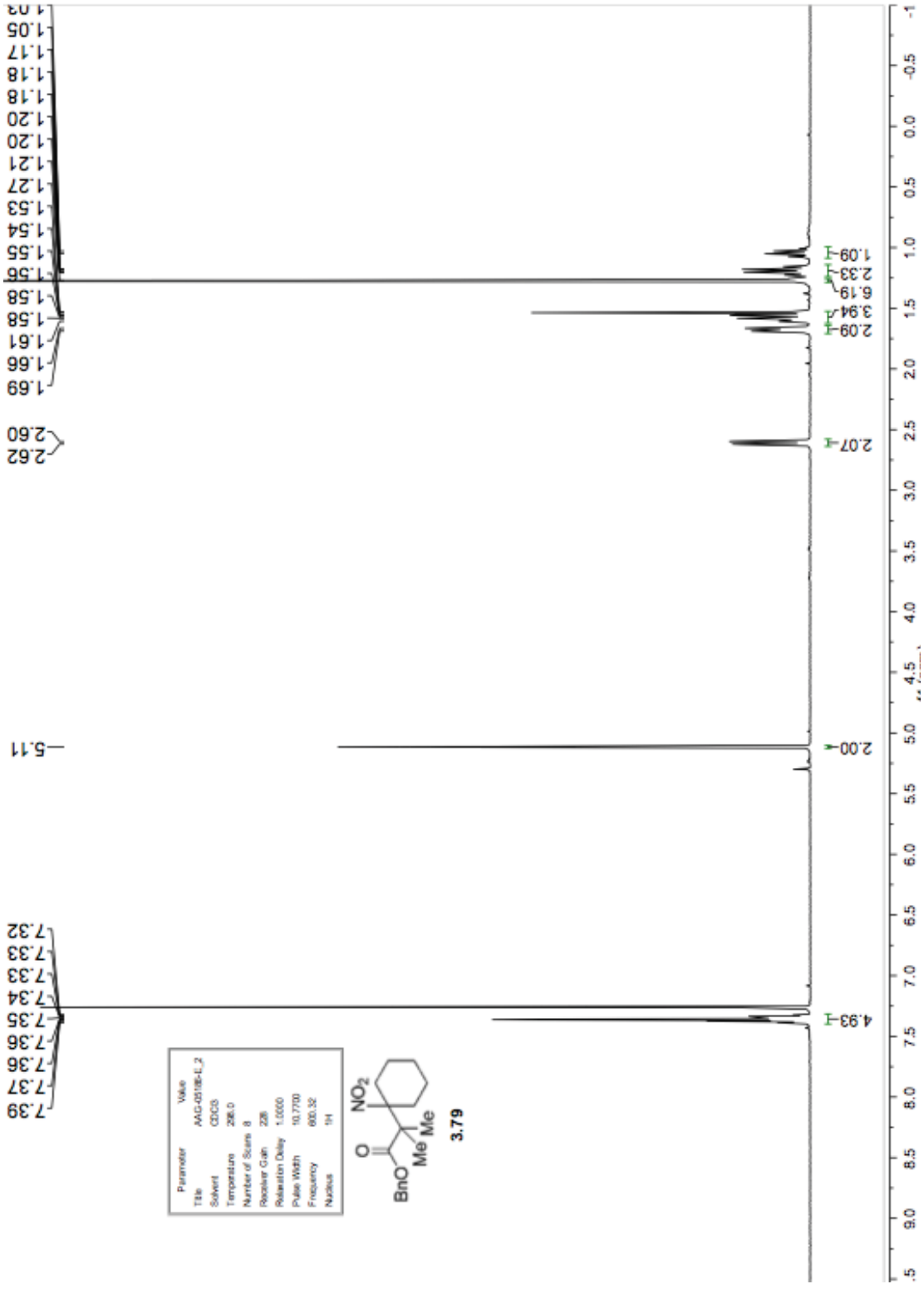

171.83
93.27
61.19
55.21
33.33
29.93
29.25
24.64
22.38
22.17
21.09
14.32
13.90
Parameter Value
Title PGE041777F14-24alumina_2
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtO
O
NO2
nPr
3.75

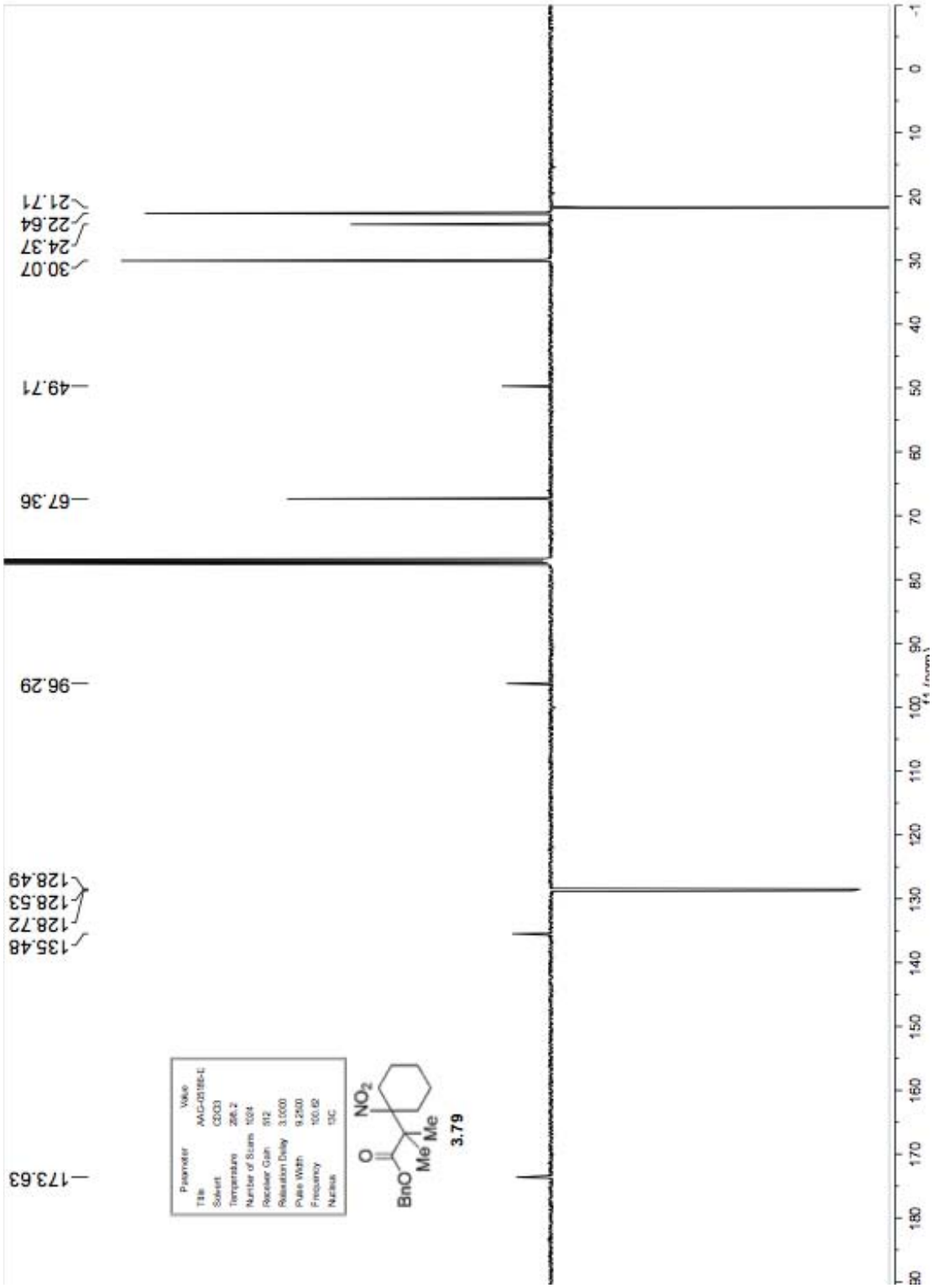

7.38
7.37
7.36
7.35
7.34
7.34
7.33
7.26
5.13
1.65
1.32
5.99
5.99
2.00
4.96
Parameter Value
Title AAG-05073-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
BnO
O
Me
NO2
Me
Me
Me
3.76

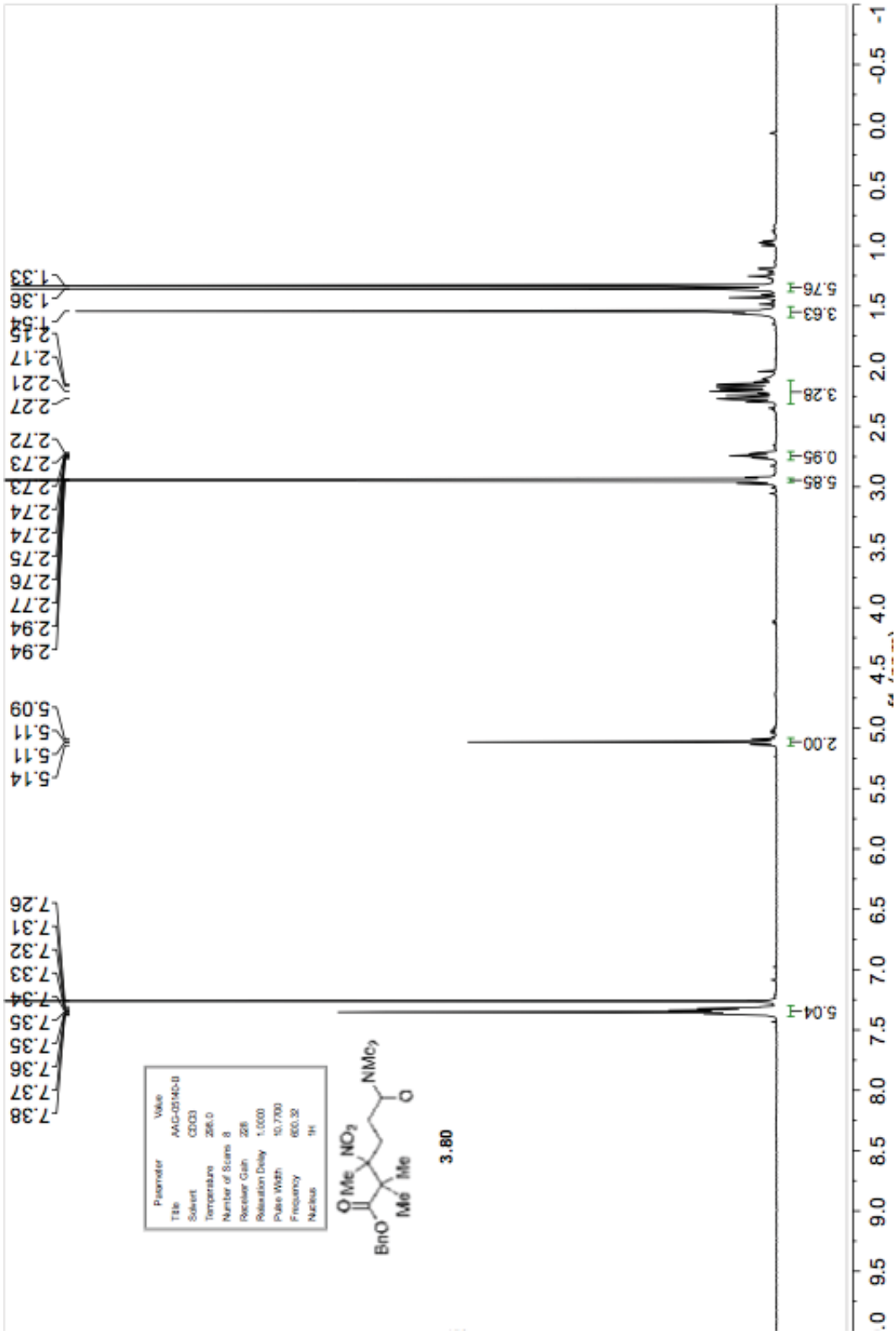

173.89
135.56
128.73
128.50
128.41
92.73
67.38
48.99
23.44
22.06
Parameter Value
Title AAG-0507-II
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.91
Nucleus 13C
BnO
O
Me
Me
Me
NO2
Me
3.76
f1 (ppm)

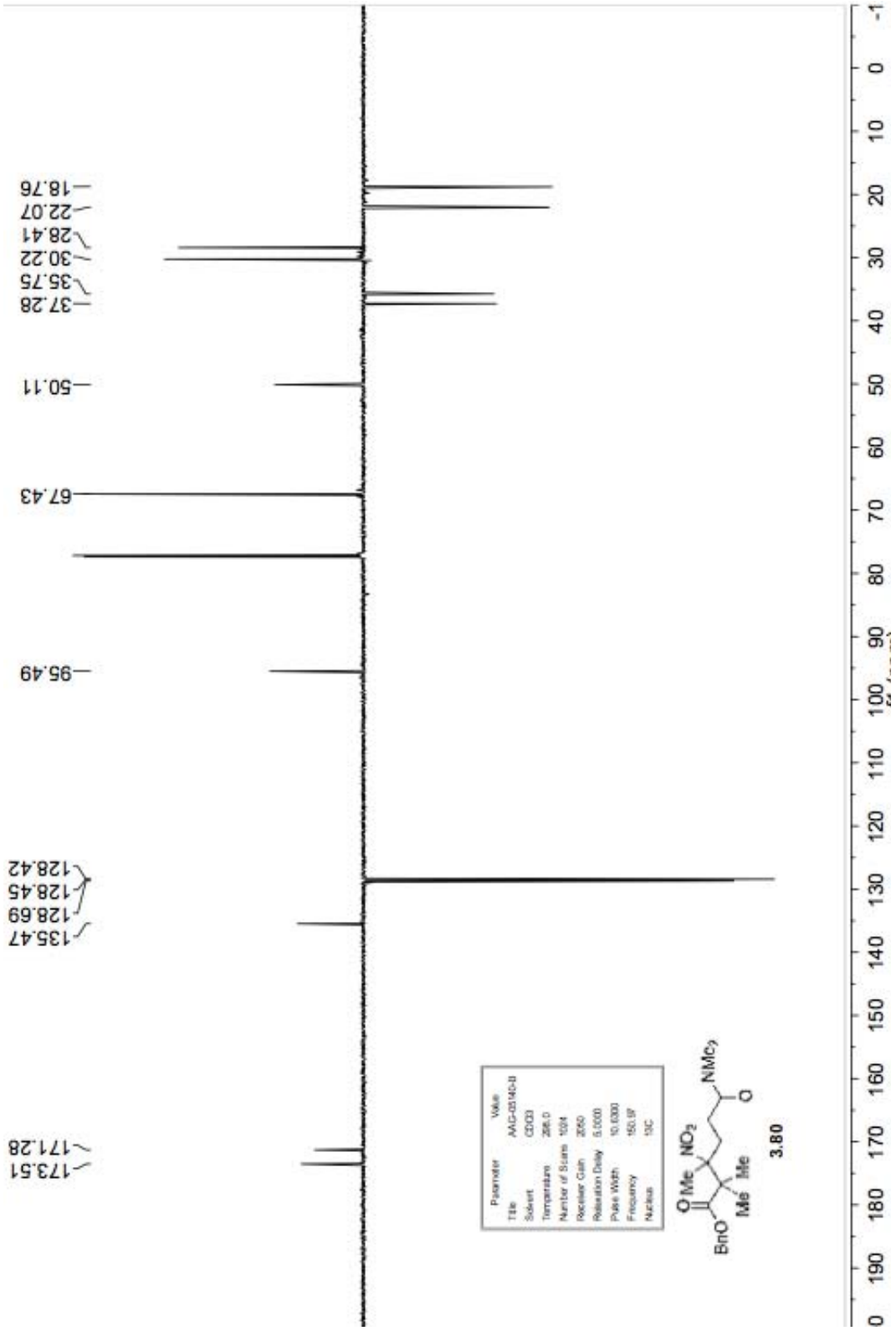

Parameter Value
Title AAD-05180-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 203
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
1.68
1.30
1.15
1.14
1.13
3.29
3.28
3.27
3.27
3.26
3.25
5.62
0.91
2.00
5.81
6.04
3.03
O
Me
NO2
Me
EtHN
Me
Me
3.77

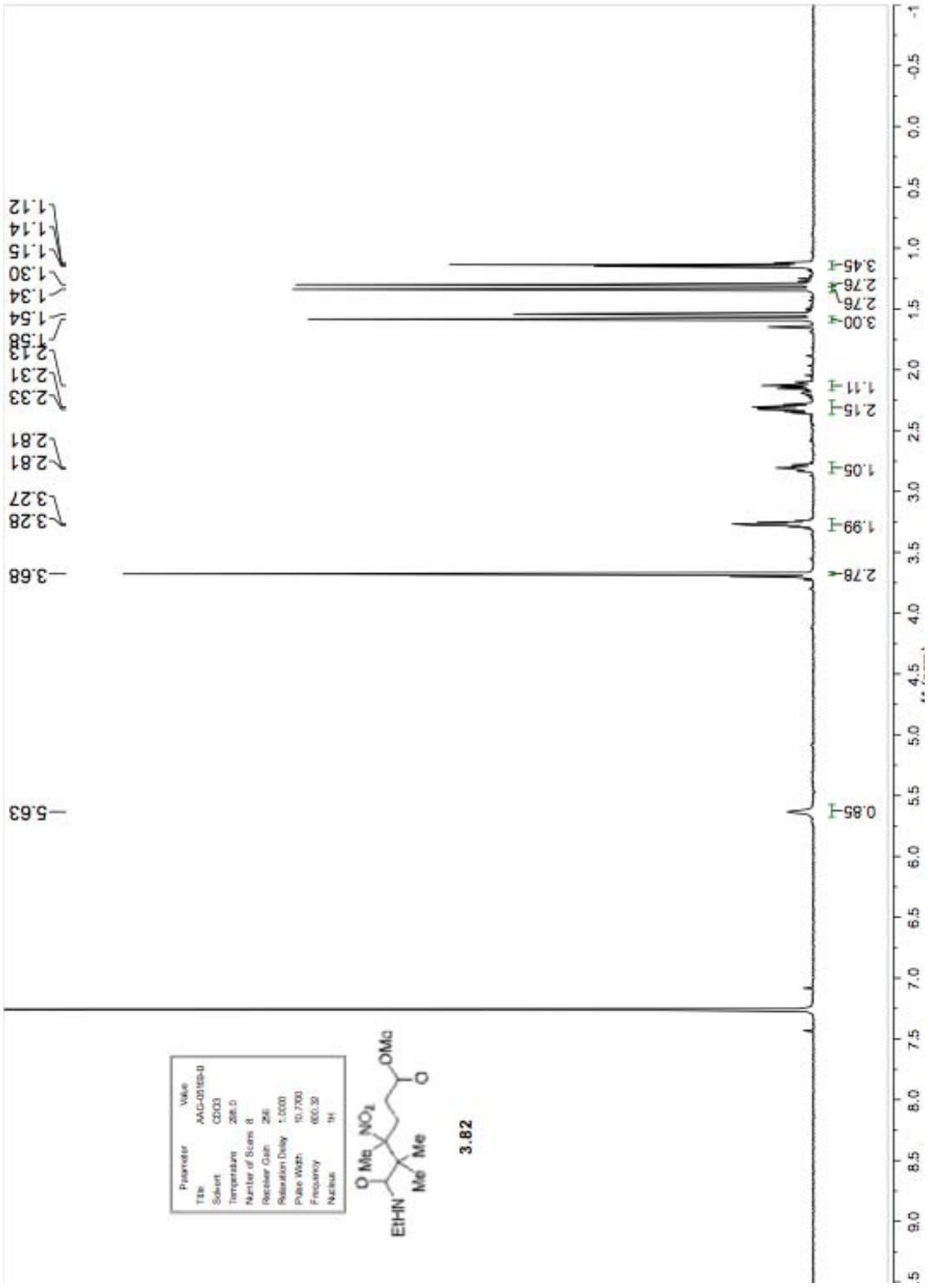

173.06
93.45
48.02
35.00
23.37
22.02
14.62
Parameter Value
Title AAG-IB1808-400
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O Me NO2
EtHN Me
Me Me
3.77

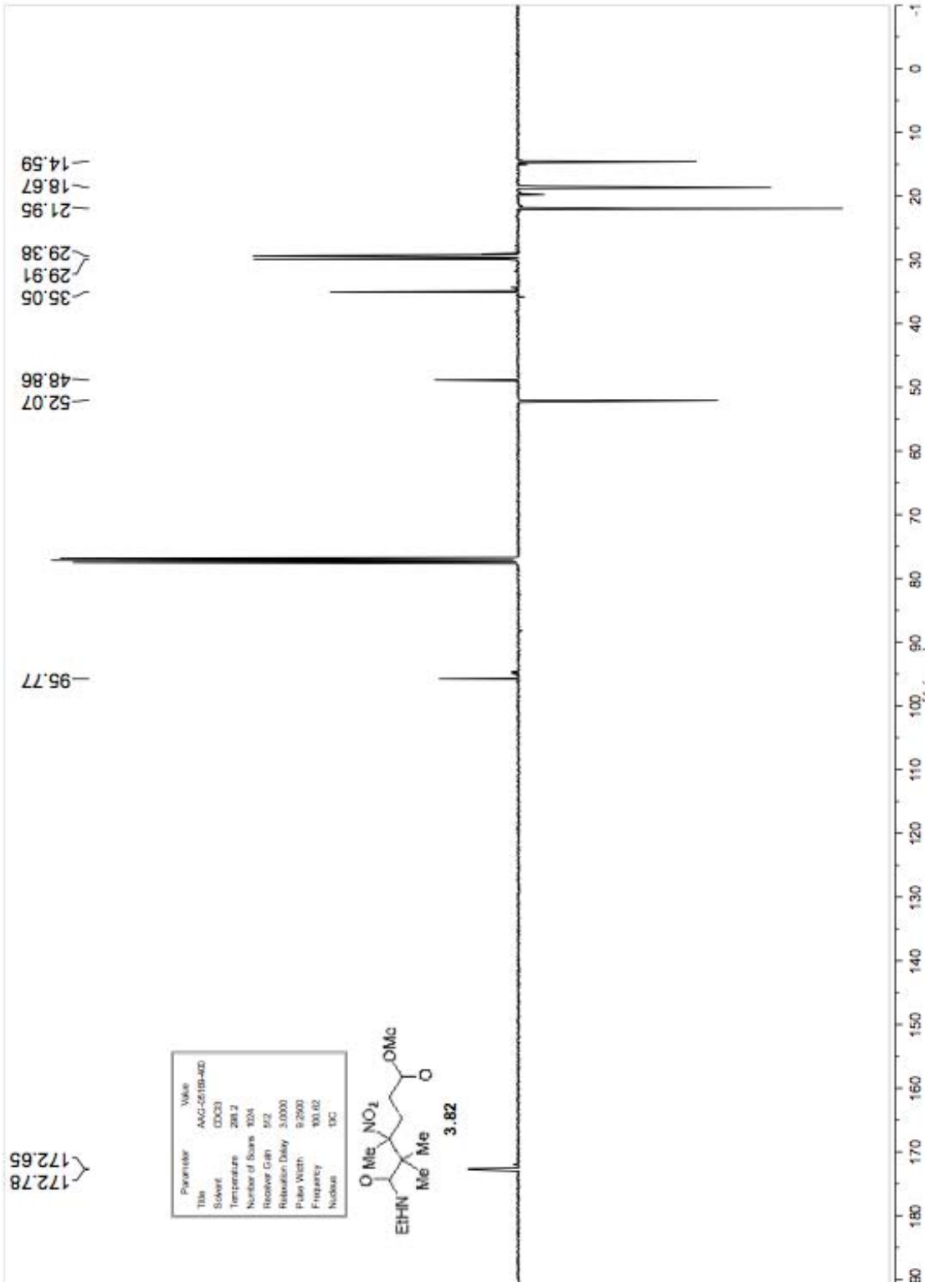

Parameter Value
Title AAG-05188-E_2
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 228
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
O
BnO
Me
Me
3.79

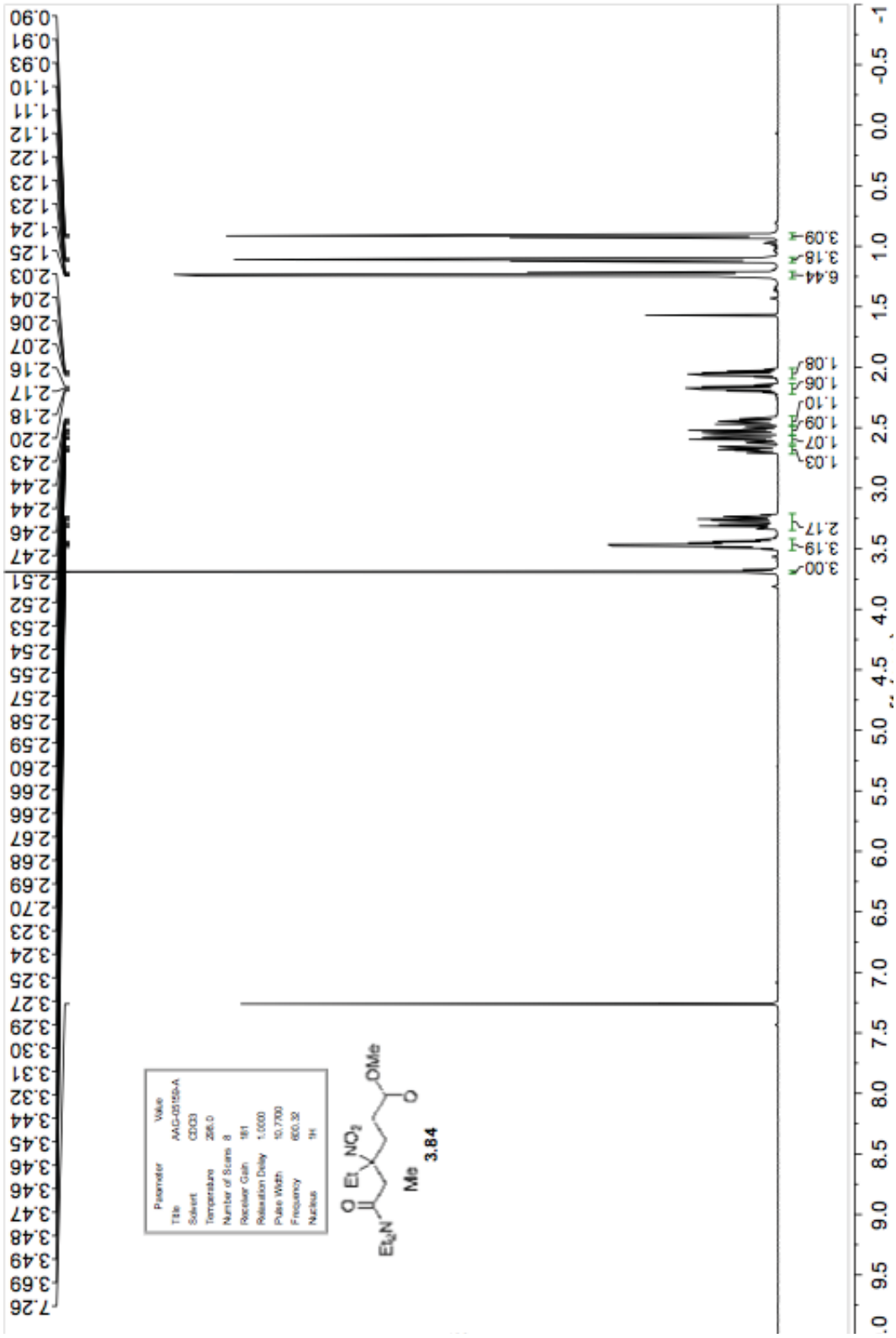

173.63
135.48
128.72
128.53
128.49
96.29
67.36
49.71
30.07
24.37
22.64
21.71
Parameter Value
Title AAD-03188-E
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
O
BnO
Me
Me
3.79

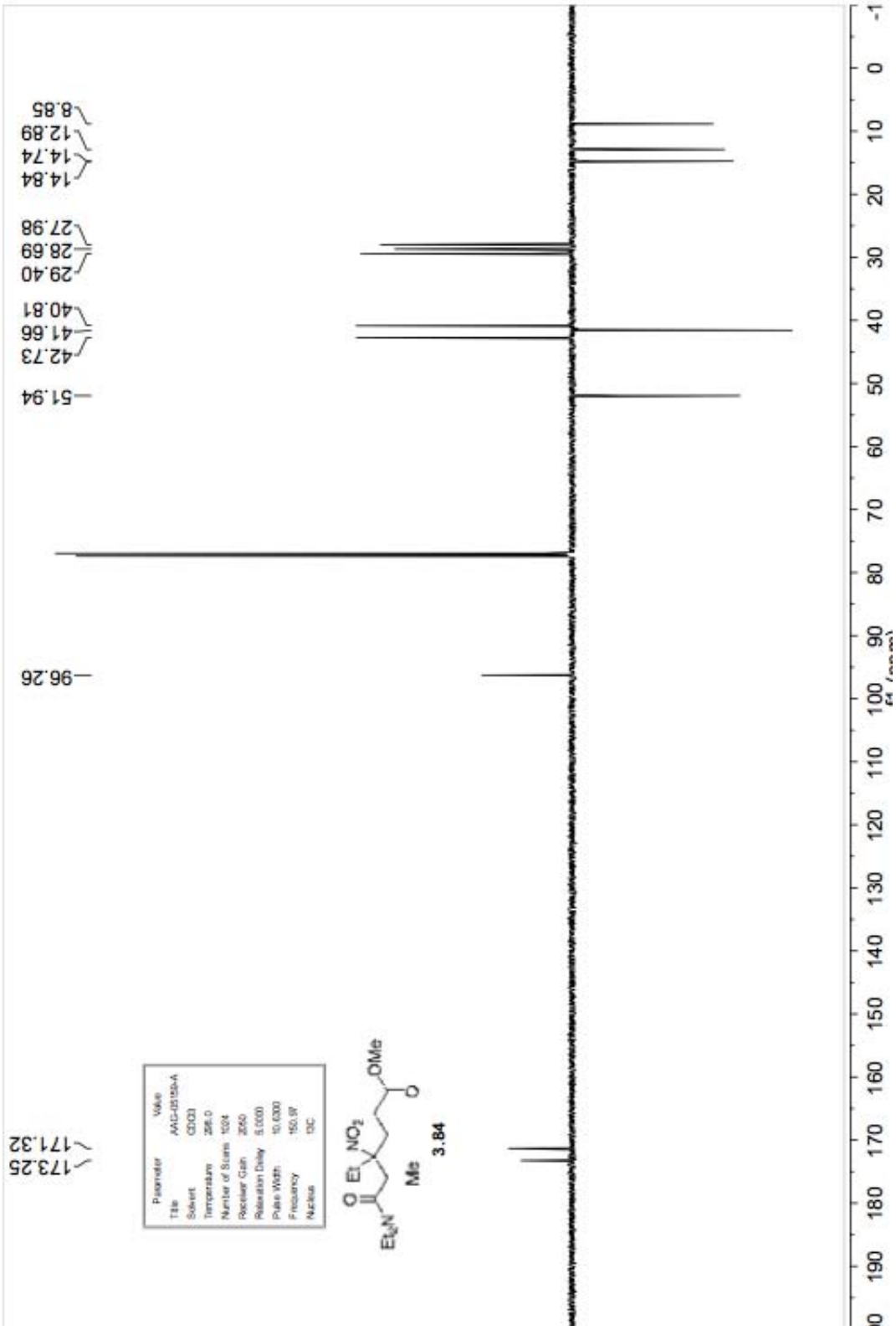

Parameter Value
Title AAG-05140-II
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 228
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
3.80
7.38
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.26
5.14
5.11
5.11
5.09
2.94
2.94
2.77
2.76
2.75
2.74
2.74
2.73
2.73
2.72
2.27
2.21
2.17
2.15
1.54
1.36
1.33
5.04
2.00
5.85
0.95
3.28
3.63
5.76

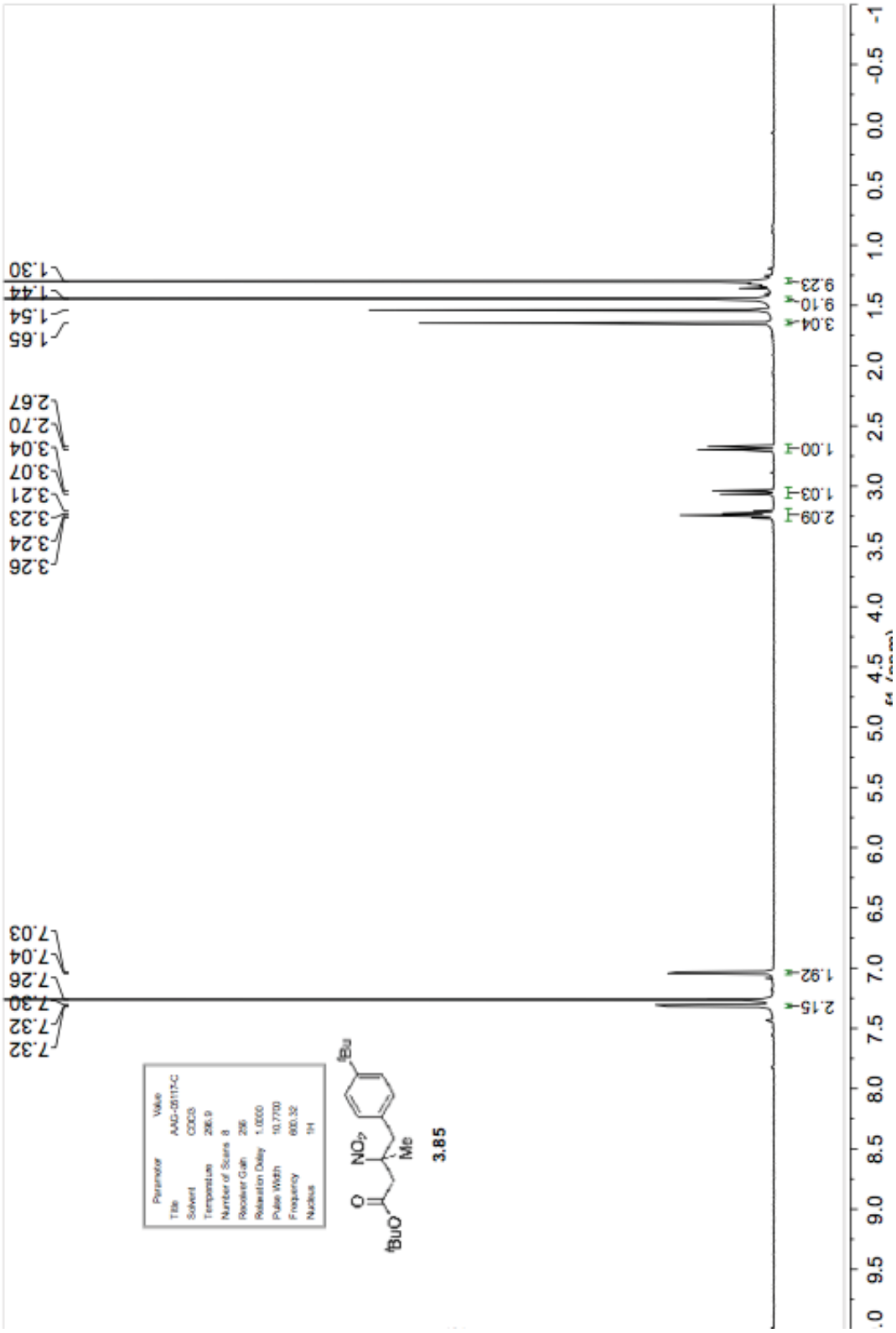

173.51
171.28
135.47
128.69
128.45
128.42
95.49
67.43
50.11
37.28
35.75
30.22
28.41
22.07
18.76
Parameter Value
Title AAG-05140-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.9F
Nucleus 13C
BnO
O
Me
NO2
Me
Me
NMc2
O
3.80

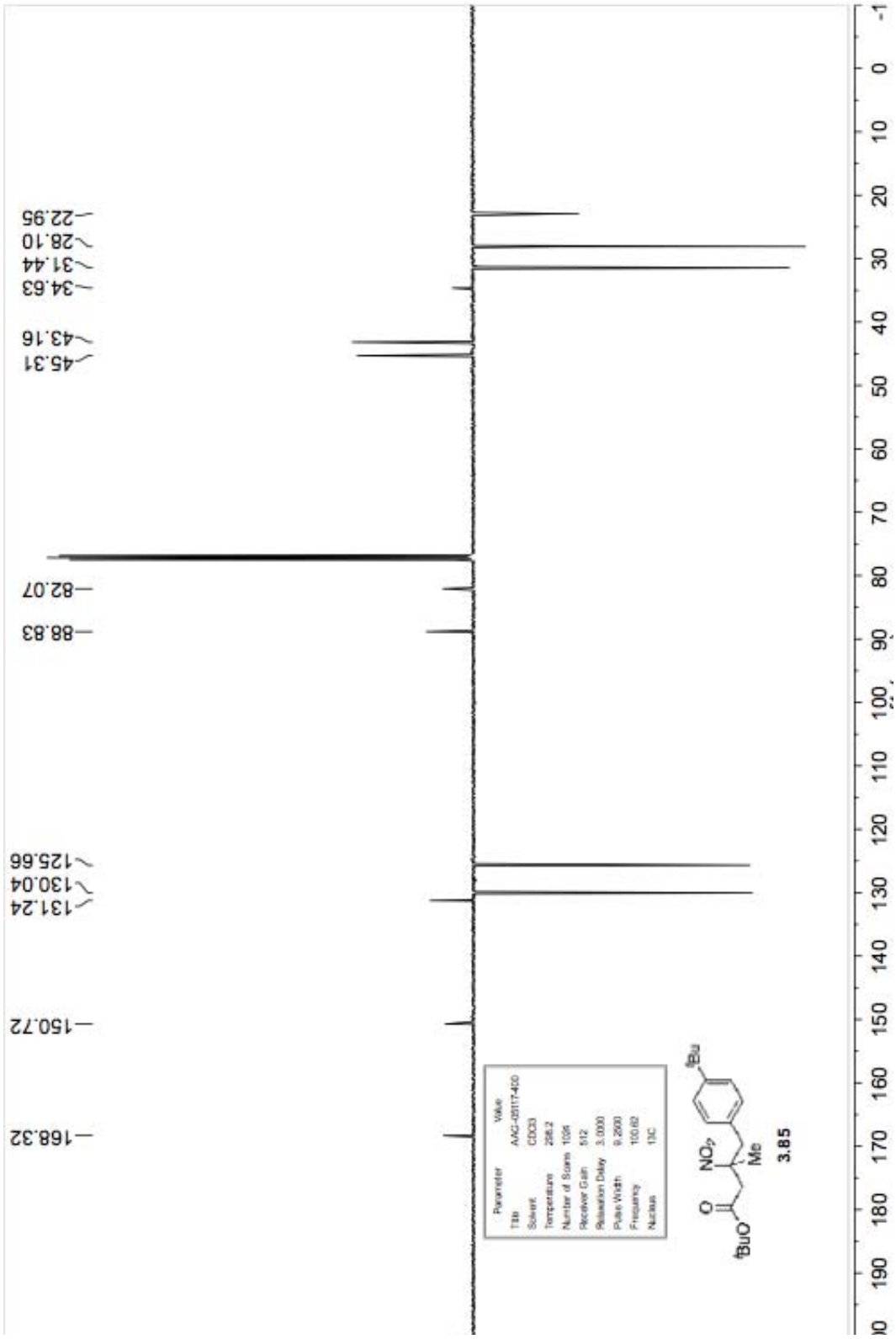

Parameter Value
Title AAG-05169-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 256
Relaxation Delay 1.0000
Pulse Width 10.7000
Frequency 600.32
Nucleus 1H
3.82
5.63
3.68
3.28
3.27
2.81
2.81
2.33
2.31
2.13
1.58
1.54
1.34
1.30
1.15
1.14
1.12
0.85
2.78
1.99
1.05
2.15
1.11
3.00
2.76
2.76
3.45

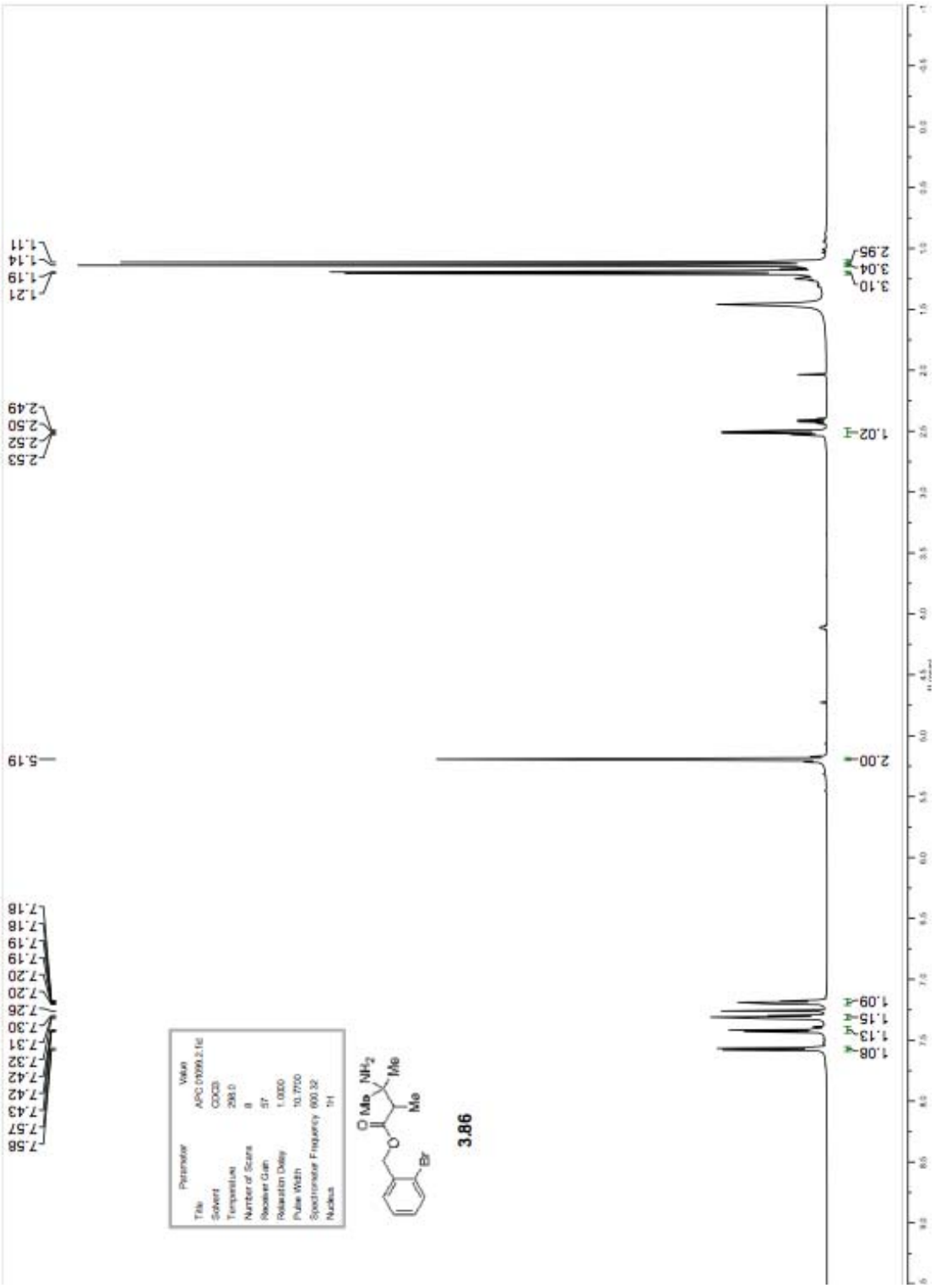

172.78
172.65
95.77
52.07
48.86
35.05
29.91
29.38
21.95
18.67
14.59
Parameter Value
Title AAG-26188-400
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
EtHN
O
Me
NO2
OMe
O
Me
Me
3.82

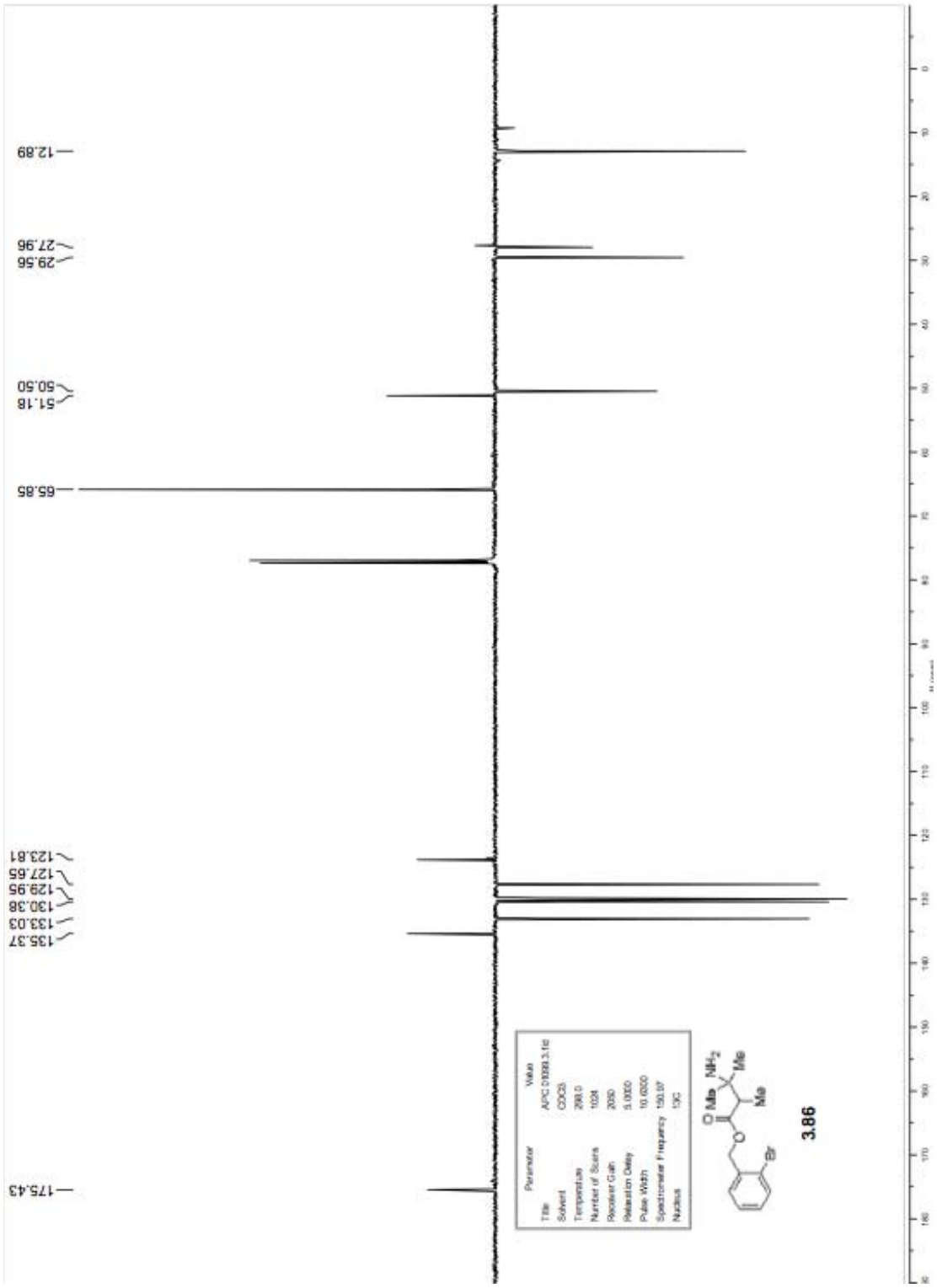

Parameter Value
Title AAG-05155-A
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
Et
NO2
OMe
O
Et3N
Me
3.84
3.00
2.17
3.19
1.03
1.07
1.09
1.10
1.06
1.08
6.44
3.18
3.09


173.25
171.32
96.26
51.94
42.73
41.66
40.81
29.40
28.69
27.98
14.84
14.74
12.89
8.85
Parameter Value
Title AAG-05159-A
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6000
Frequency 150.97
Nucleus 13C
O
Et
NO2
OMe
O
Et2N
Me
3.84
f1 (ppm)


7.32
7.32
7.30
7.26
7.04
7.03
3.26
3.24
3.23
3.21
3.07
3.04
2.70
2.67
1.65
1.54
1.44
1.30
2.15
1.92
2.09
1.03
1.00
3.04
9.10
9.23
Parameter Value
Title AAG-05117-C
Solvent CDCl3
Temperature 298.9
Number of Scans 8
Receiver Gain 256
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
tBu
NO2
Me
O
tBuO
3.85

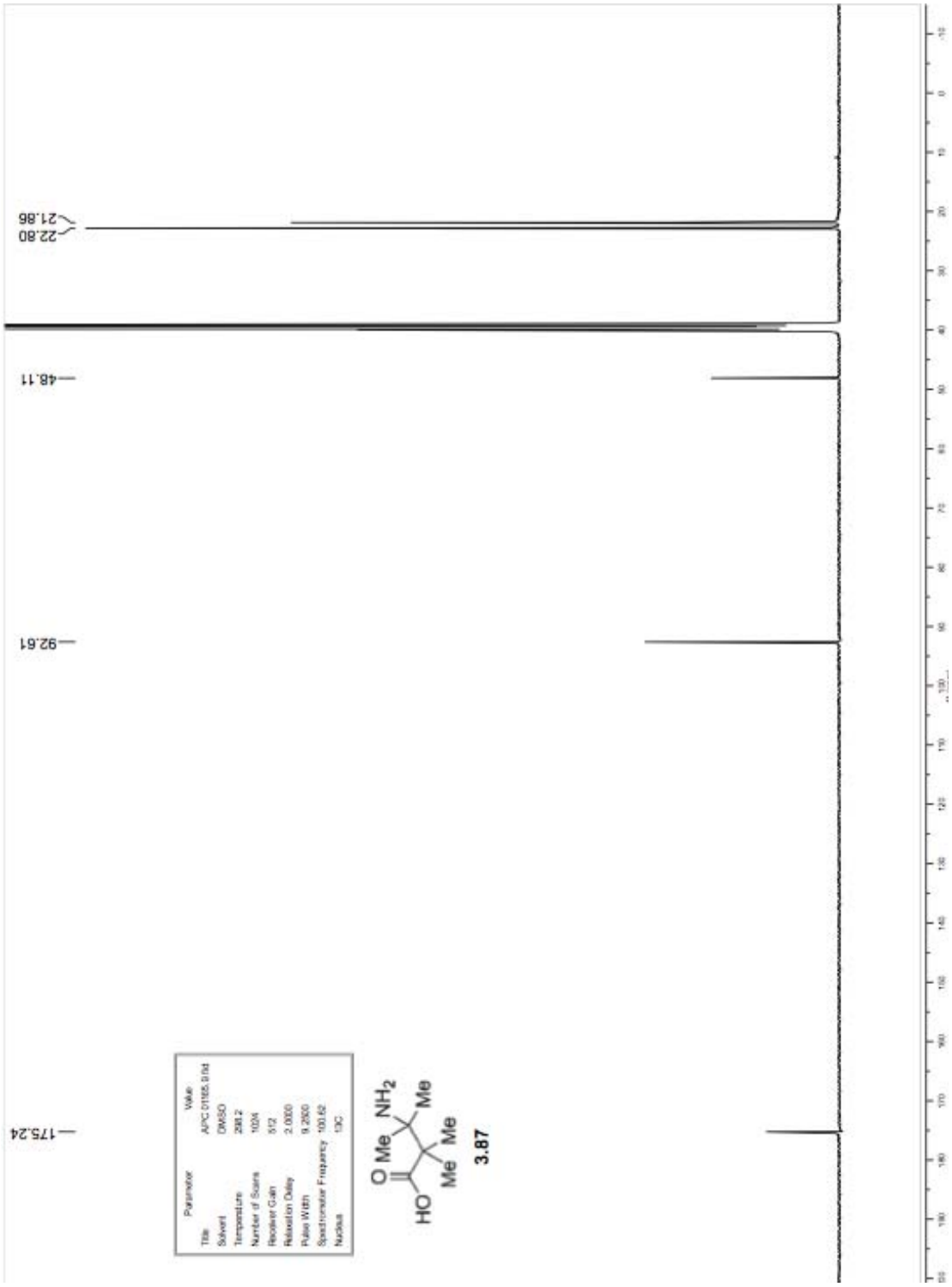

168.32
150.72
131.24
130.04
125.66
82.07
88.83
45.31
43.16
34.63
31.44
28.10
22.95
Parameter Value
Title AAG-05117-400
Solvent CDCl3
Temperature 298.2
Number of Scans 1026
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
tBu
NO2
Me
O
tBuO
3.85

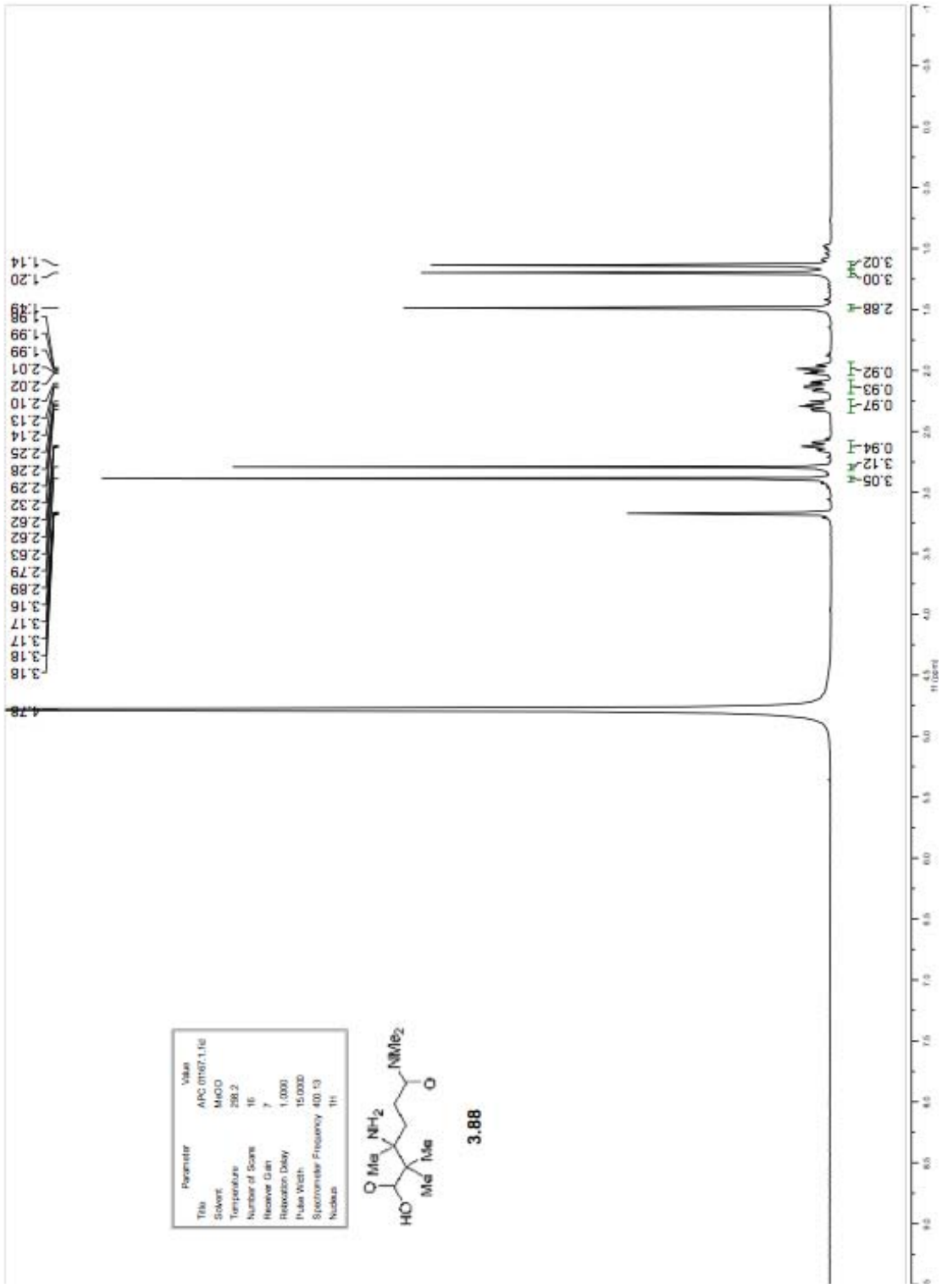

1.21
1.19
1.14
1.11
2.53
2.52
2.50
2.49
5.19
7.58
7.57
7.43
7.42
7.42
7.32
7.31
7.30
7.26
7.20
7.20
7.19
7.19
7.18
7.18
3.10
3.04
2.95
1.02
2.00
1.09
1.15
1.13
1.08
Parameter Value
Title APC 01699.2.1d
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7720
Spectrometer Frequency 600.32
Nucleus 1H
Me
NH2
Me
Me
O
O
Br
3.86

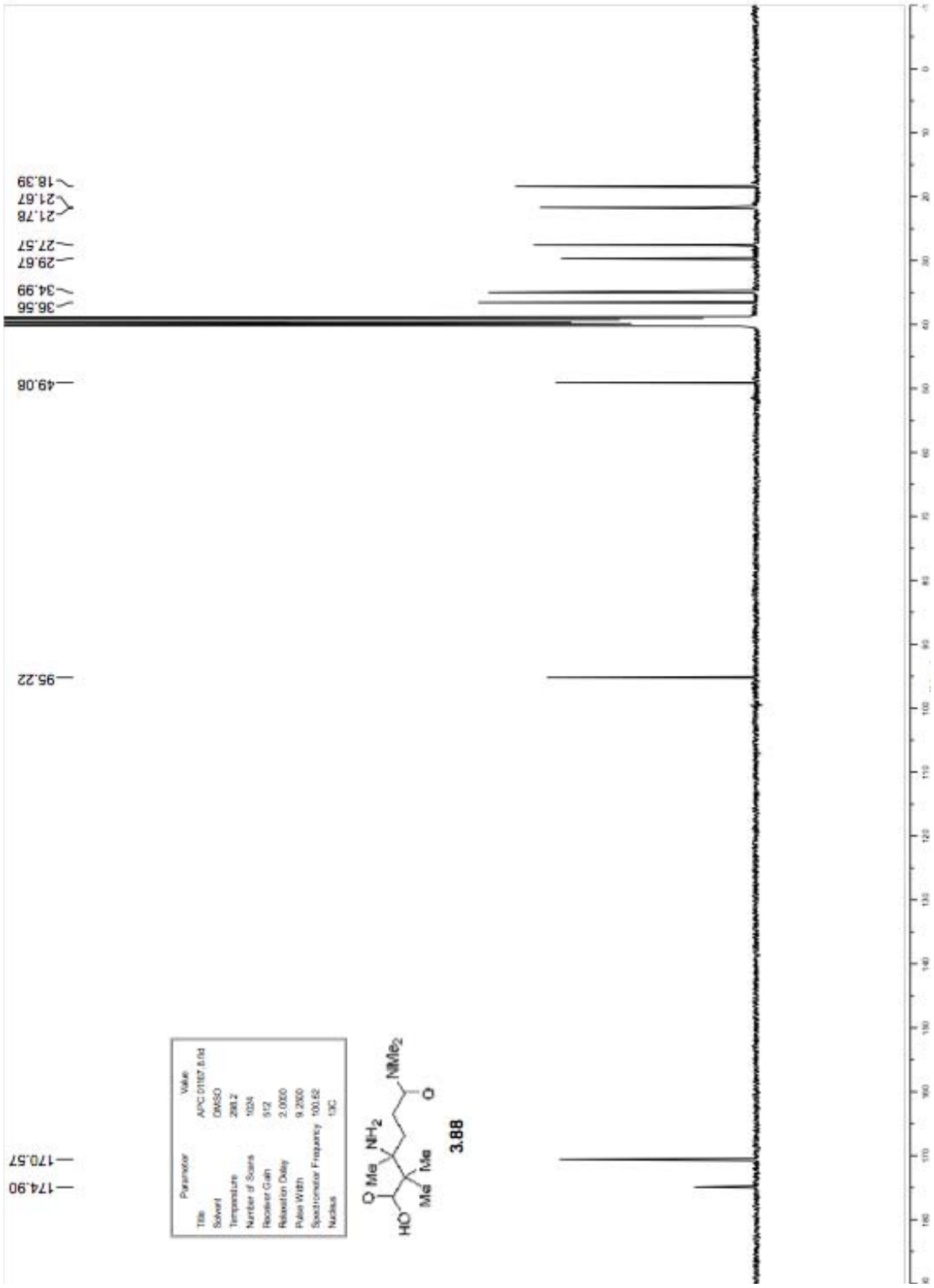

175.43
135.37
133.03
130.38
129.95
127.65
123.81
65.85
51.18
50.50
29.56
27.96
12.89
Parameter
Value
Title
APC 0308.3.10
Solvent
CDCl3
Temperature
298.0
Number of Scans
1024
Receiver Gain
2050
Relaxation Delay
5.0000
Pulse Width
10.0000
Spectrometer Frequency
150.97
Nucleus
13C
3.86

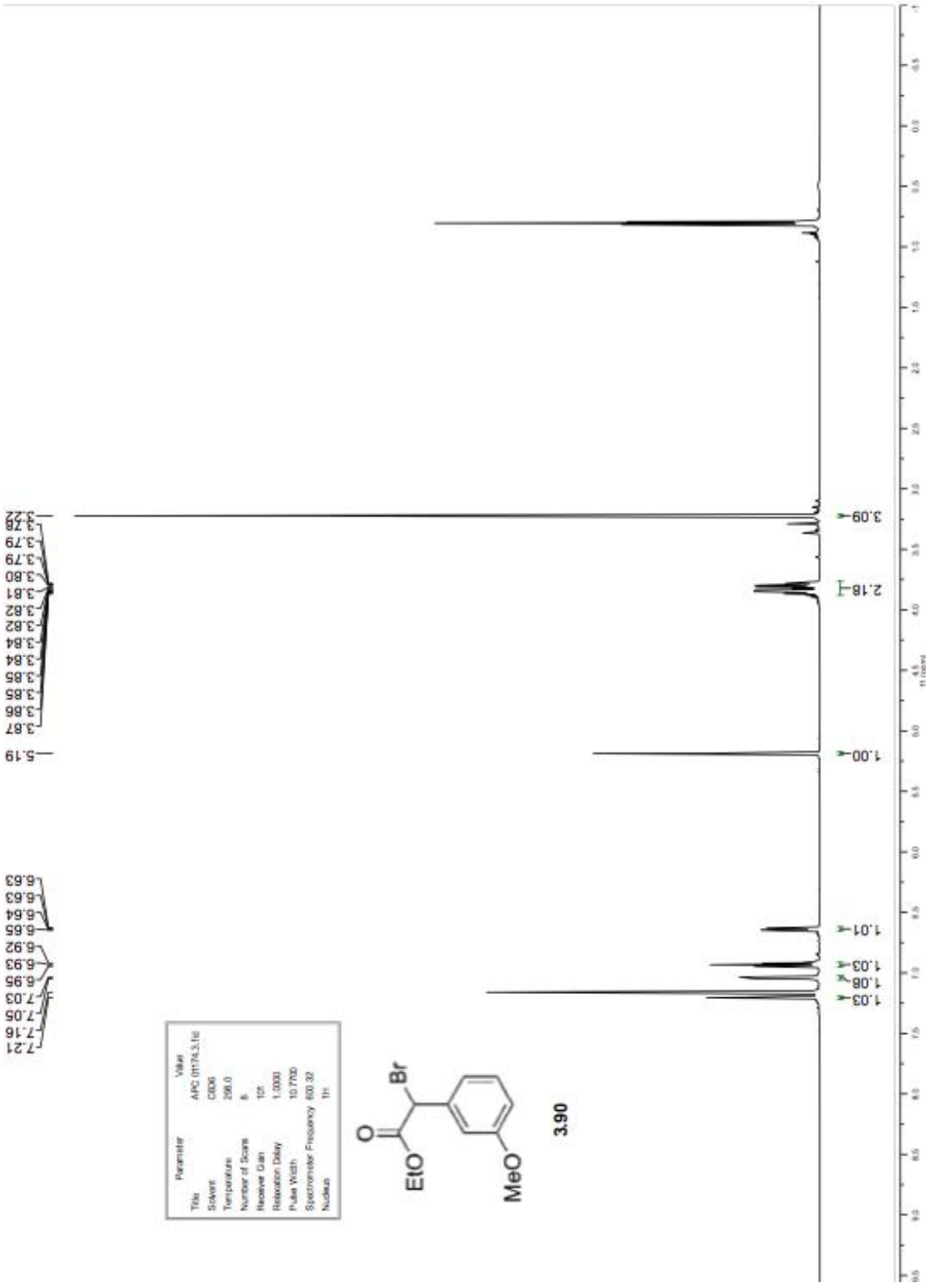
4.92
3.32
3.31
3.31
3.31
3.30
1.69
1.28
6.00
6.06
Parameter Value
Title APC 01165.1.fid
Solvent MeOD
Temperature 298.2
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Spectrometer Frequency 400.13
Nucleus 1H
O
HO
Me
NH2
Me
Me
Me

3.87


175.24
92.61
48.11
22.80
21.86
Parameter Value
Title APC 0165.9.fid
Solvent DMSO
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 2.0000
Pulse Width 9.2500
Spectrometer Frequency 100.62
Nucleus 13C
O
Me
NH2
Me
HO
Me
Me
3.87


Parameter Value
Title APC 01107.1.1r
Solvent MeOD
Temperature 298.2
Number of Scans 16
Receiver Gain 7
Relaxation Delay 1.0000
Pulse Width 15.0000
Spectrometer Frequency 400.13
Nucleus 1H
3.88
NMe2
NH2
Me
Me
HO
Me
O
O
4.78
3.18
3.18
3.17
3.17
3.16
2.89
2.79
2.63
2.62
2.62
2.32
2.29
2.28
2.25
2.14
2.13
2.10
2.02
2.01
1.99
1.99
1.98
1.79
1.20
1.14
3.05
3.12
0.94
0.97
0.93
0.92
2.88
3.00
3.02


174.90
170.57
95.22
49.08
36.56
34.99
29.67
27.57
21.78
21.67
18.39
Parameter Value
Title APC 0167 B fid
Solvent DMSO
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 2.0000
Pulse Width 9.2500
Spectrometer Frequency 100.62
Nucleus 13C
HO
Me
NH2
NMe2
O
Me
Me
Me
3.88


Parameter Value
Title APC (11743.1.1d)
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 101
Relaxation Delay 1.0000
Pulse Width 10.7100
Spectrometer Frequency 600.32
Nucleus 1H
Br
O
EtO
MeO
3.90
7.21
7.16
7.05
7.03
6.95
6.93
6.92
6.65
6.64
6.63
6.63
5.19
3.87
3.86
3.85
3.85
3.84
3.84
3.82
3.82
3.81
3.80
3.79
3.79
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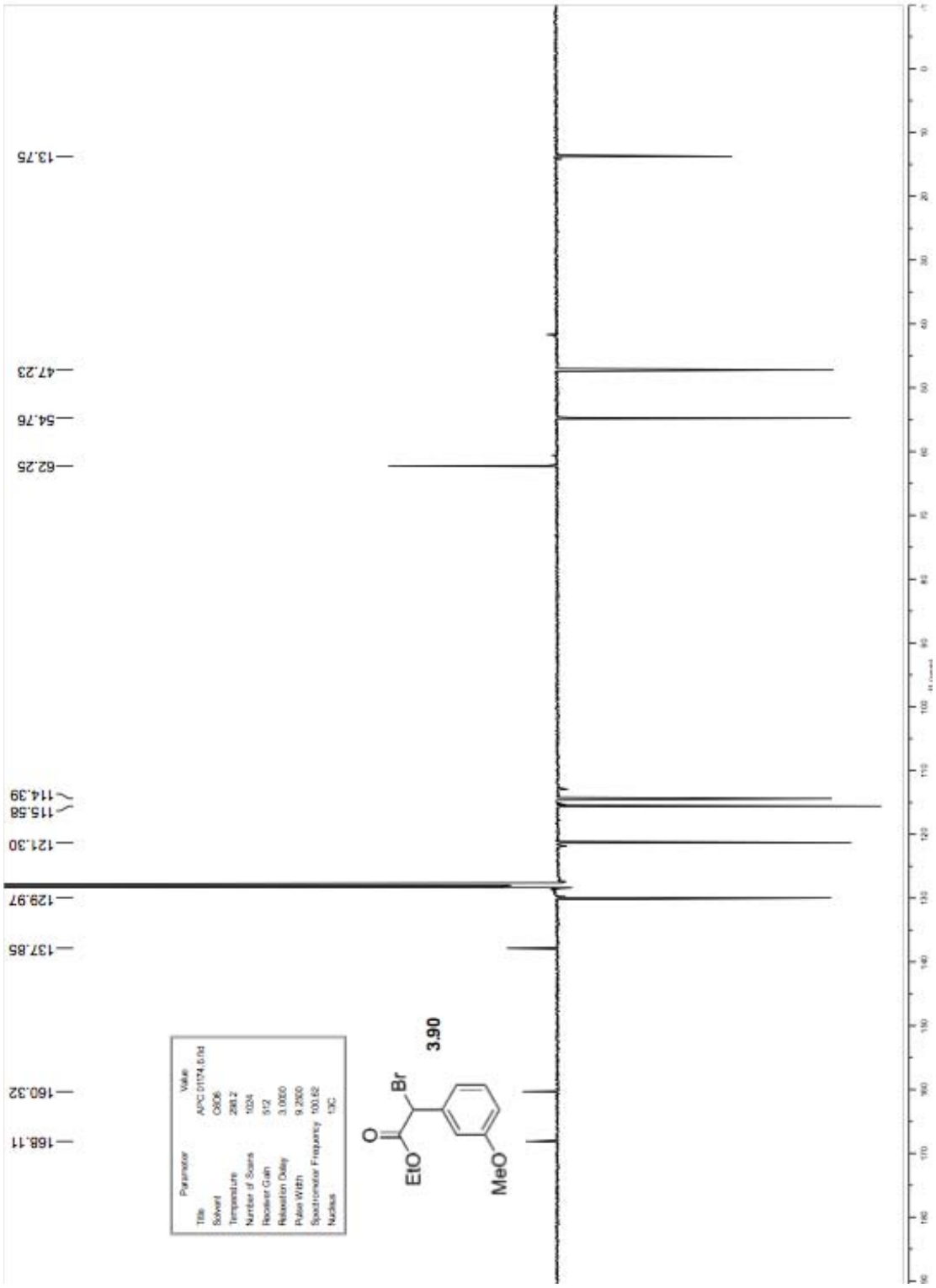
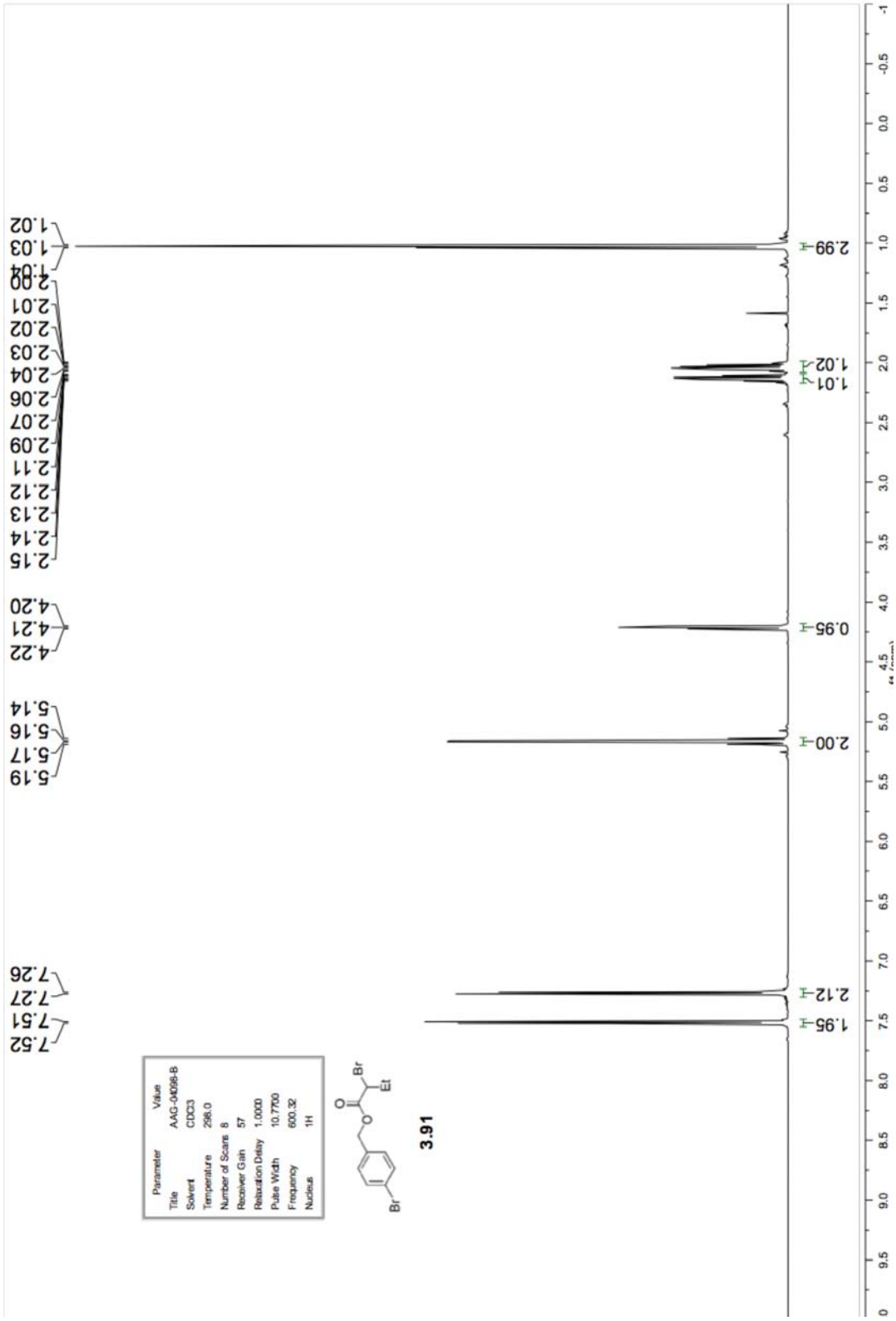
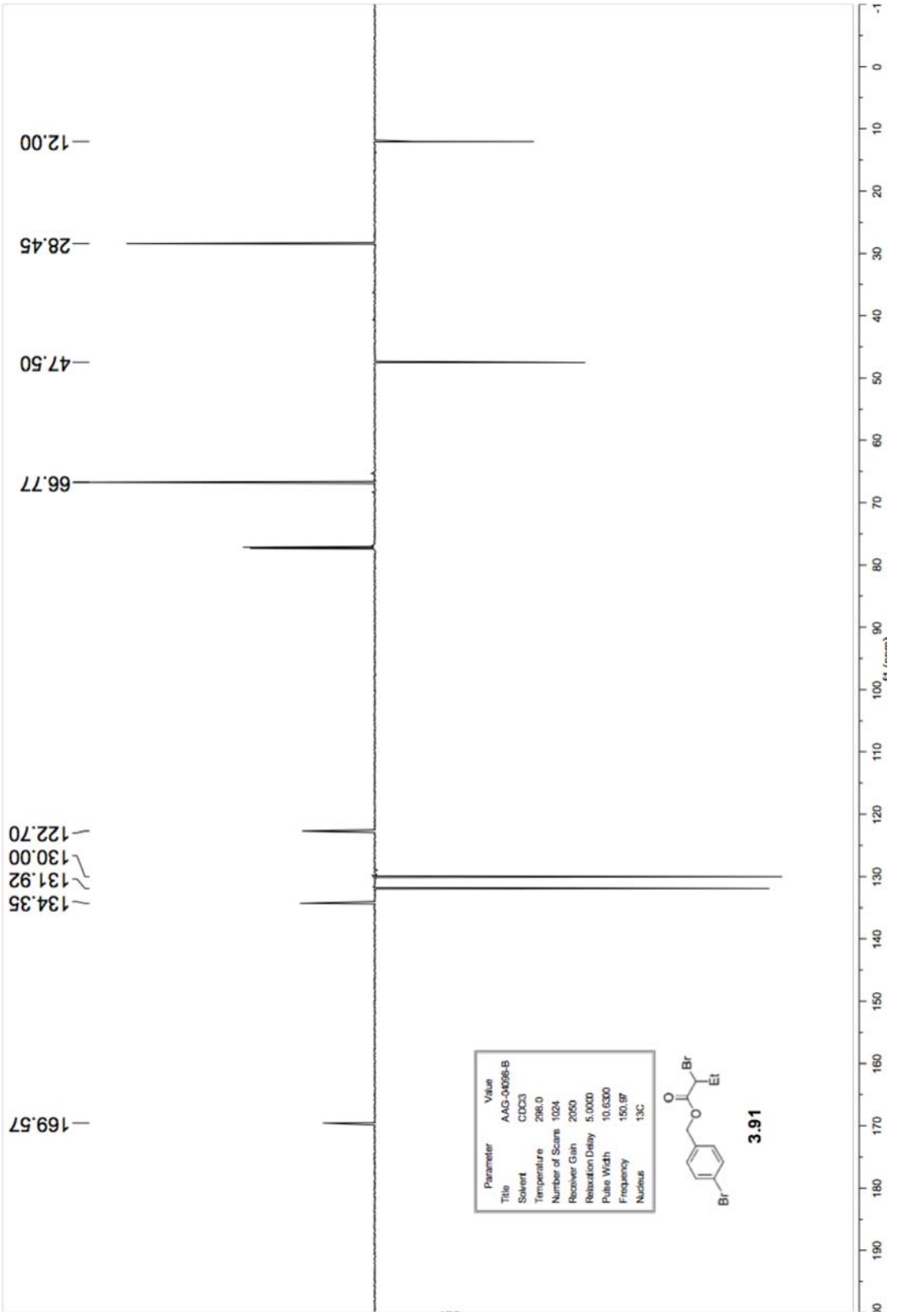
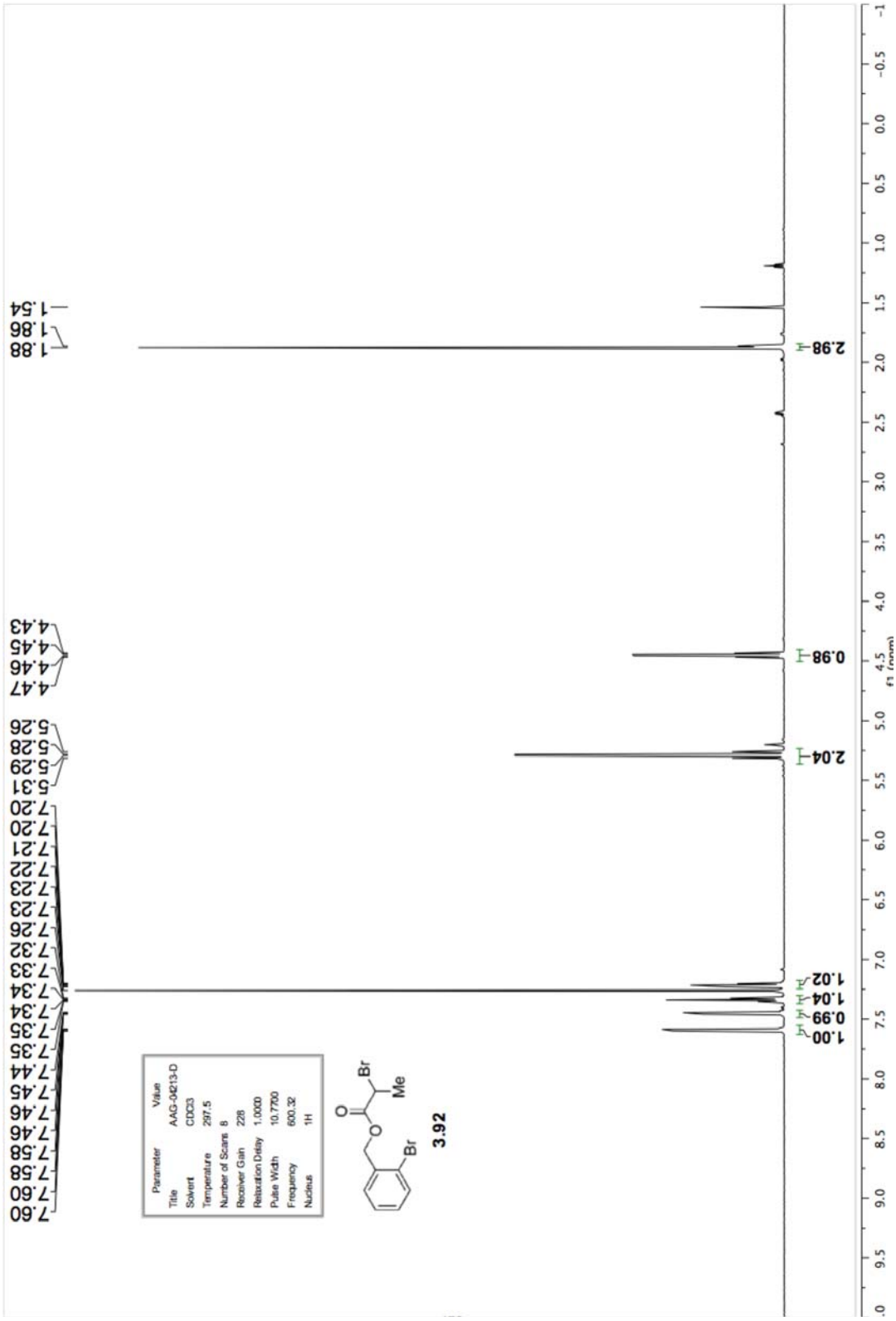
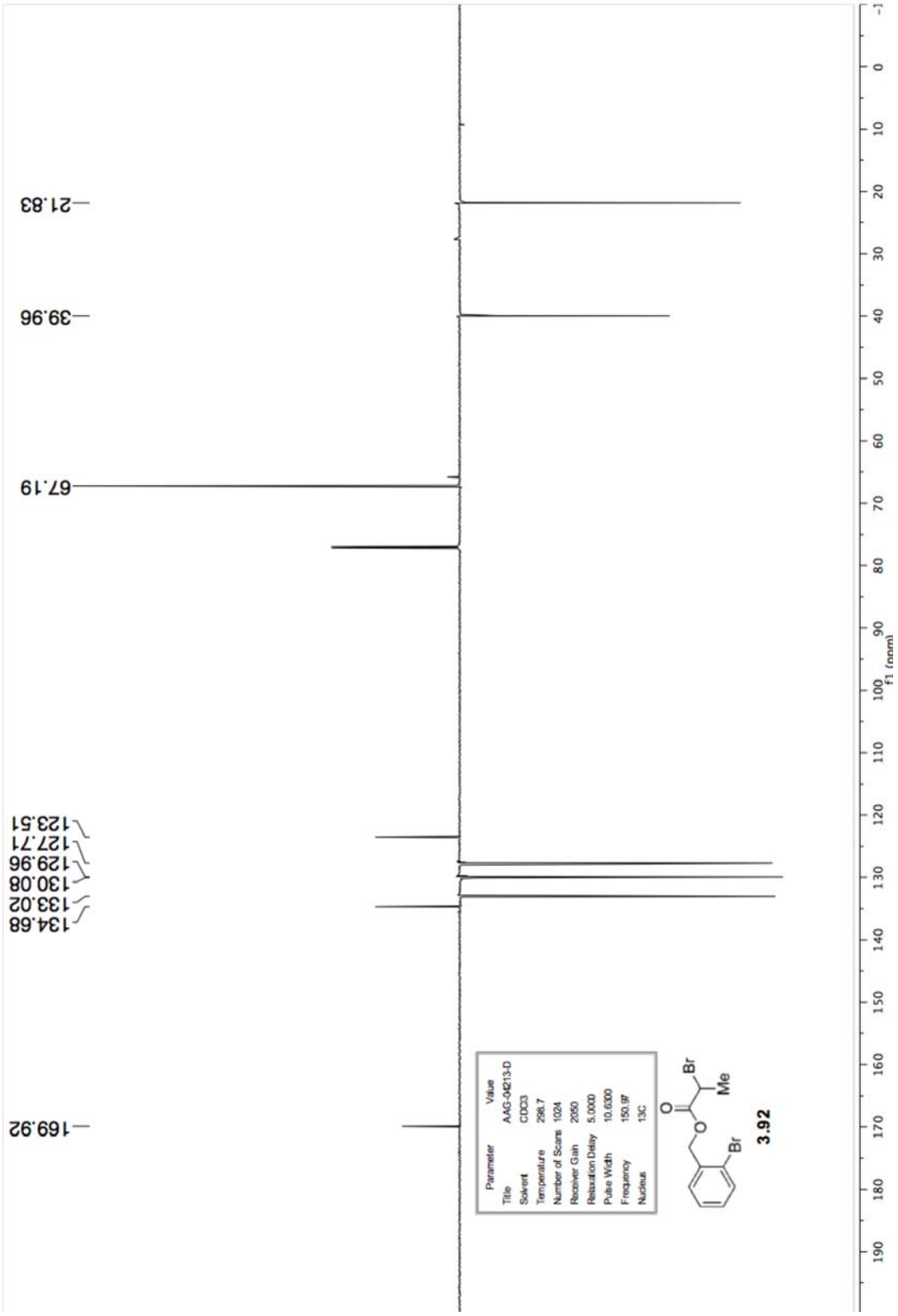
2.18
1.00
1.01
1.03
1.08
1.03

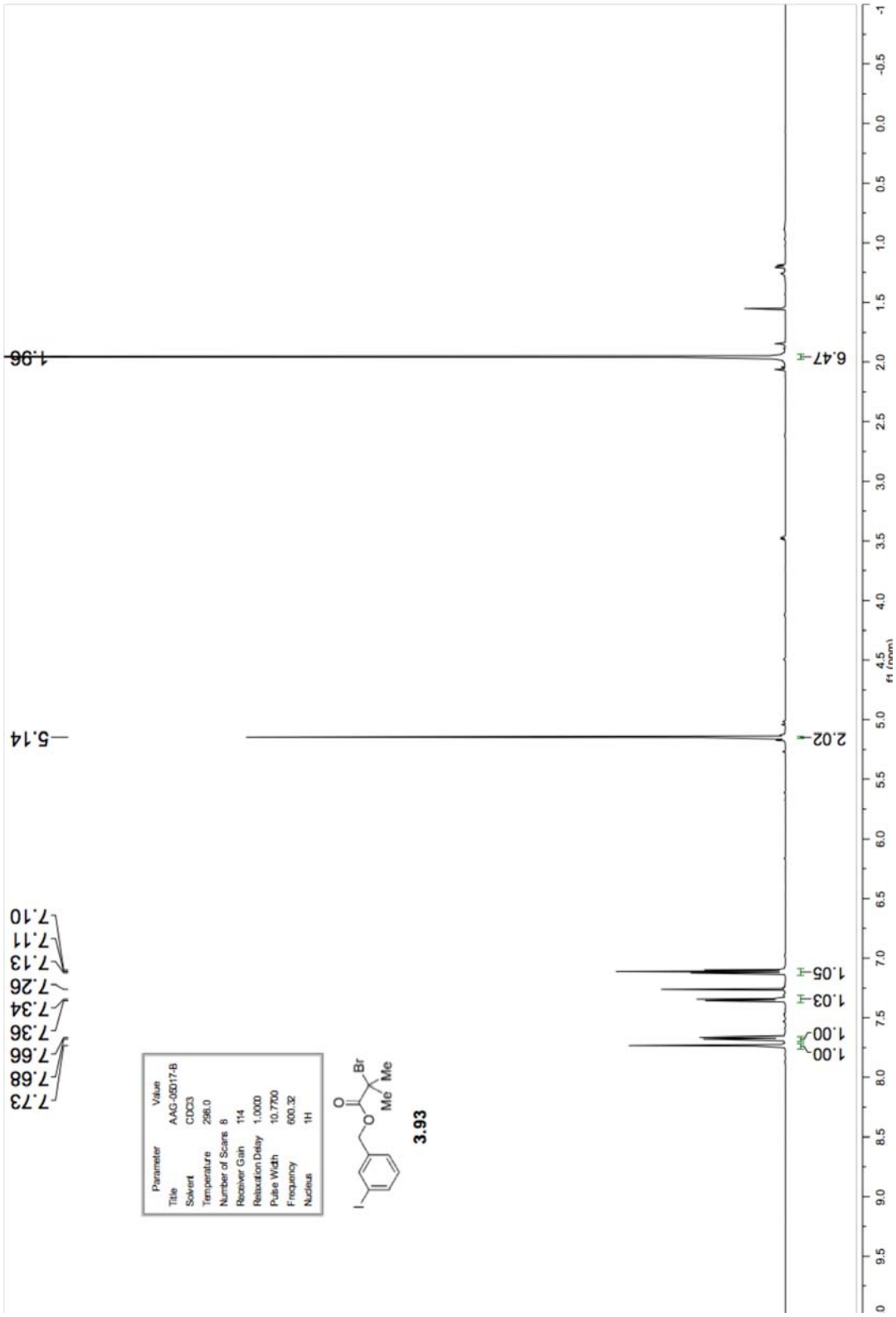

13.75
47.23
54.76
62.25
114.39
115.58
121.30
129.97
137.85
160.32
168.11
Parameter Value
Title APC-01174-5.fid
Solvent CHCL
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Spectrometer Frequency 100.62
Nucleus 13C
3.90
Br
O
EtO
MeO

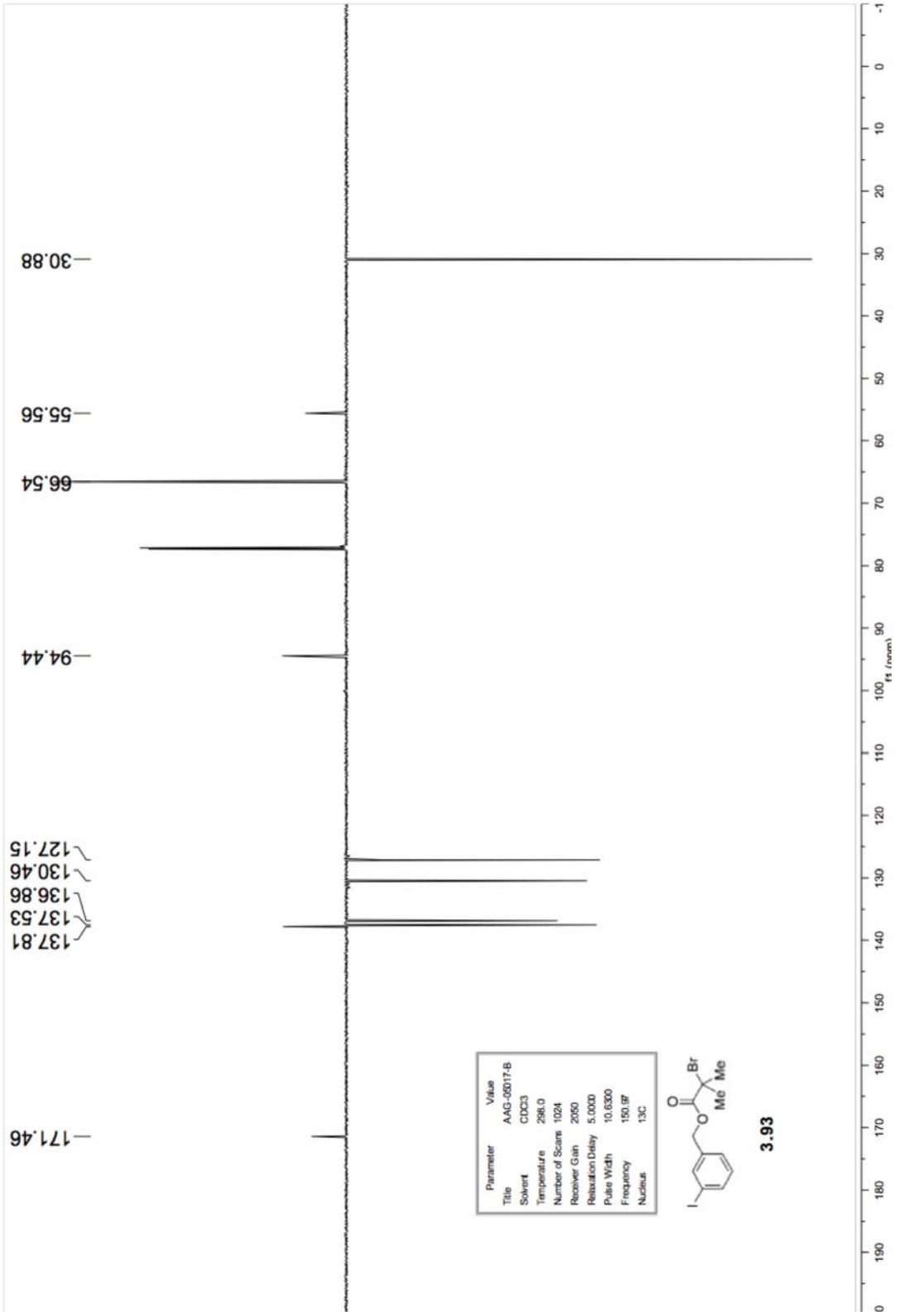

Parameter Value
Title AAG-04098-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
3.91
7.52
7.51
7.27
7.26
5.19
5.17
5.16
5.14
4.22
4.21
4.20
2.15
2.14
2.13
2.12
2.11
2.09
2.07
2.06
2.04
2.03
2.02
2.01
2.00
1.04
1.03
1.02
1.95
2.12
2.00
0.95
1.01
2.99

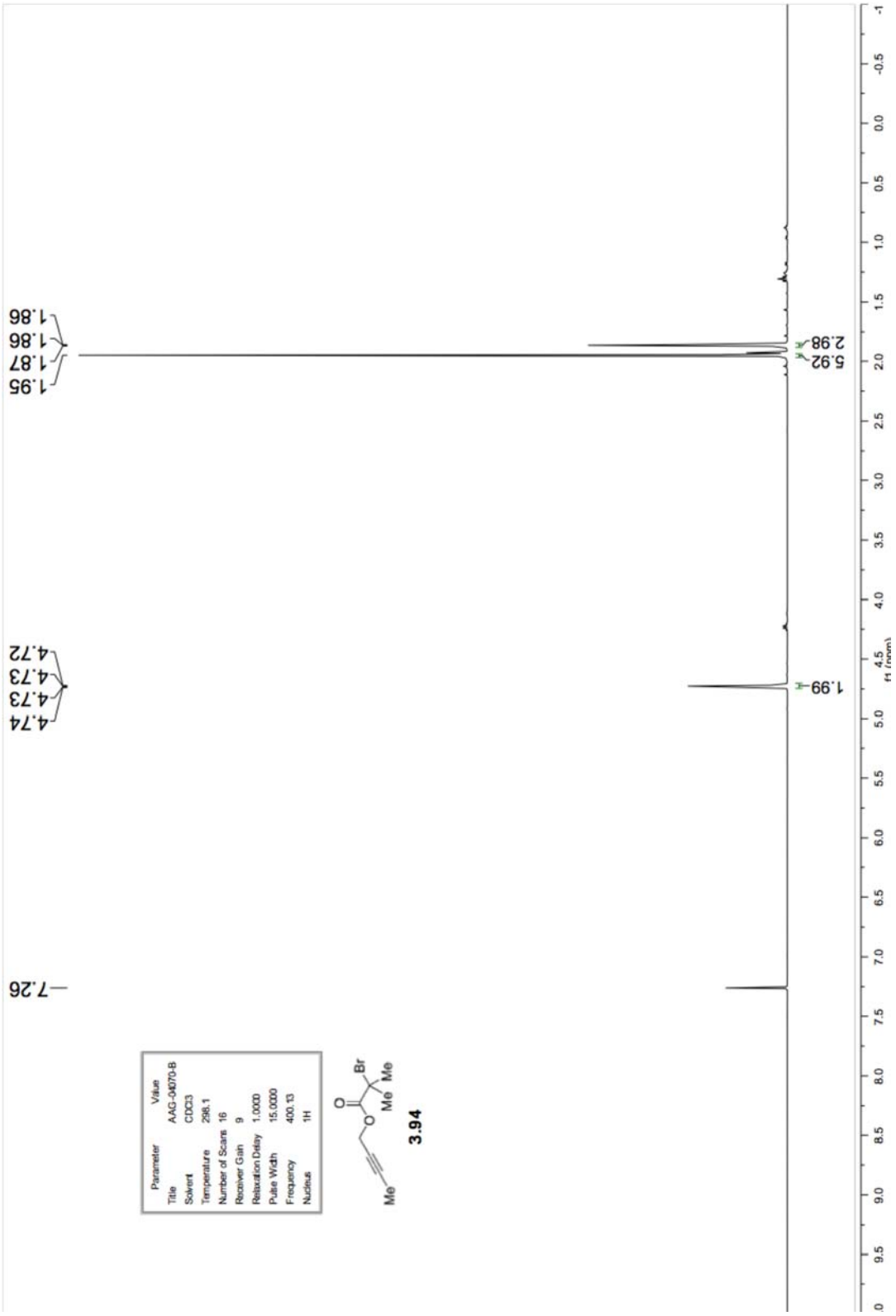

12.00
28.45
47.50
66.77
122.70
130.00
131.92
134.35
169.57
Parameter Value
Title AAG-04098-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
Br
Et
O
O
Br
3.91

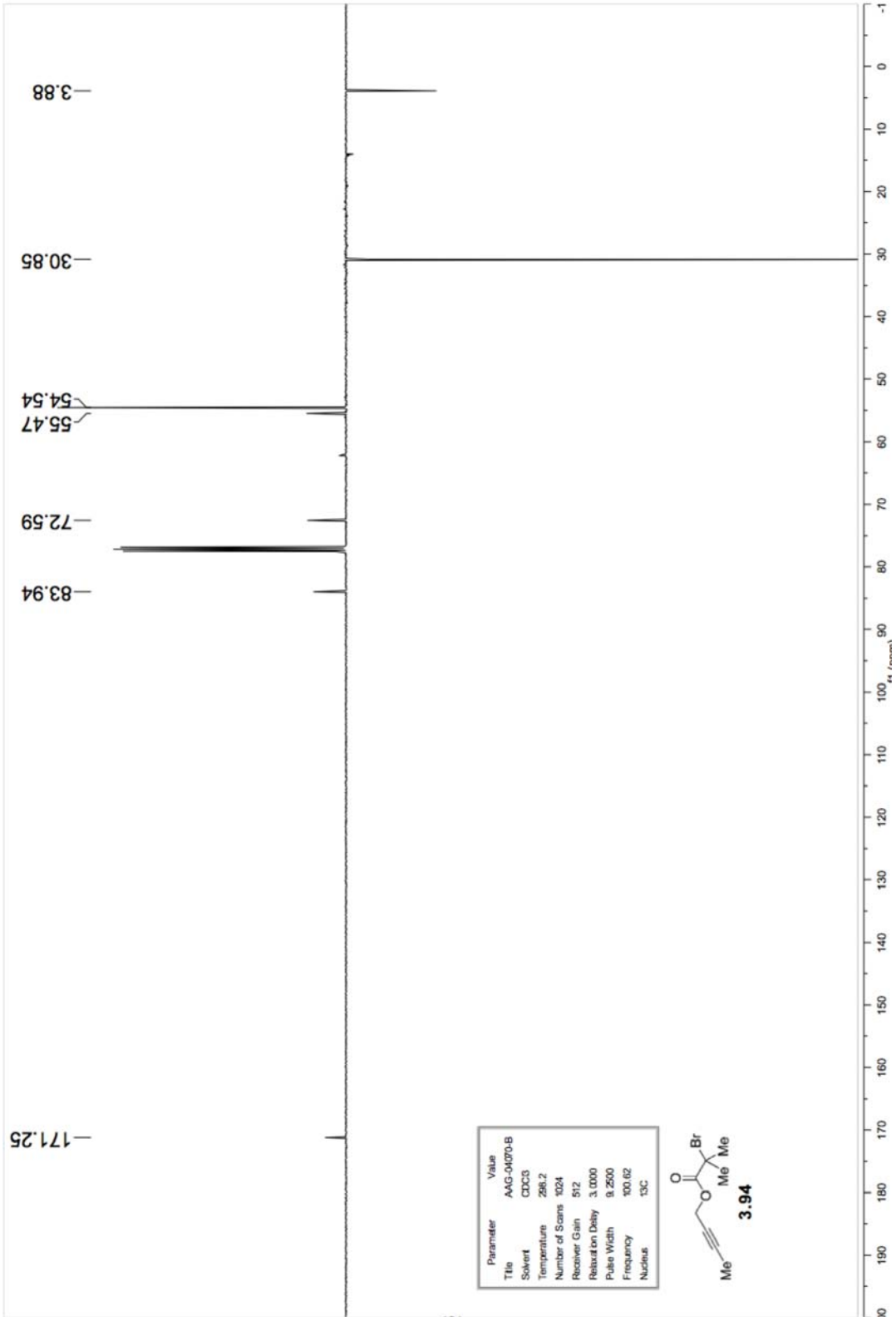

Parameter Value
Title AAG-04213-D
Solvent CDCl3
Temperature 297.5
Number of Scans 8
Receiver Gain 228
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
Br
Me
O
O
Br
3.92
1.00
0.99
1.04
1.02
2.04
0.98
2.98
7.60
7.60
7.58
7.58
7.46
7.46
7.45
7.44
7.35
7.35
7.34
7.34
7.33
7.32
7.26
7.23
7.23
7.22
7.21
7.20
7.20
5.31
5.29
5.28
5.26
4.47
4.46
4.45
4.43
1.88
1.86
1.54

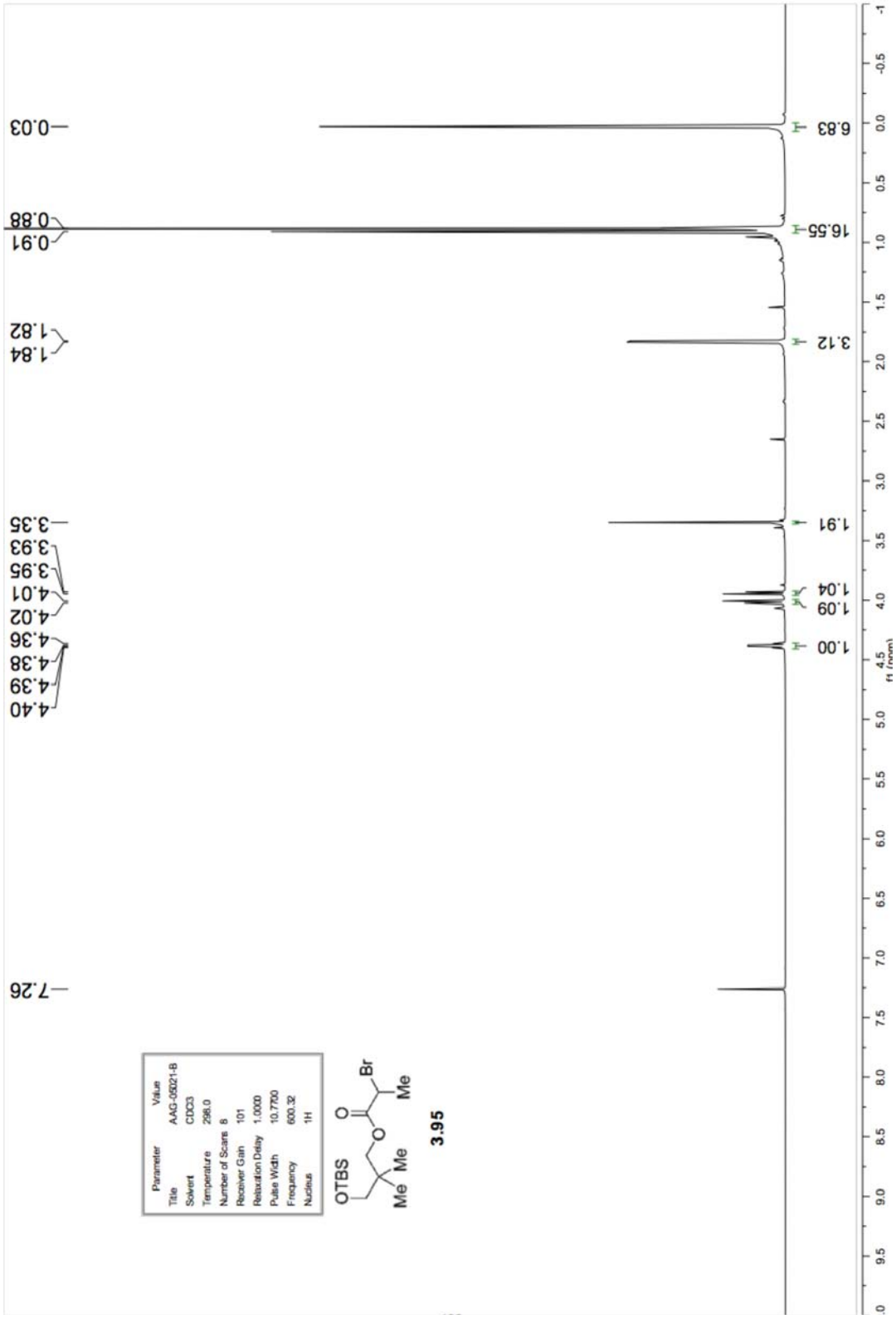

169.92
134.68
133.02
130.08
129.96
127.71
123.51
67.19
39.96
21.83
Parameter Value
Title AAG-04213-D
Solvent CDCl3
Temperature 298.7
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.9F
Nucleus 13C
O
O
Br
Me
Br
3.92
f1 (ppm)

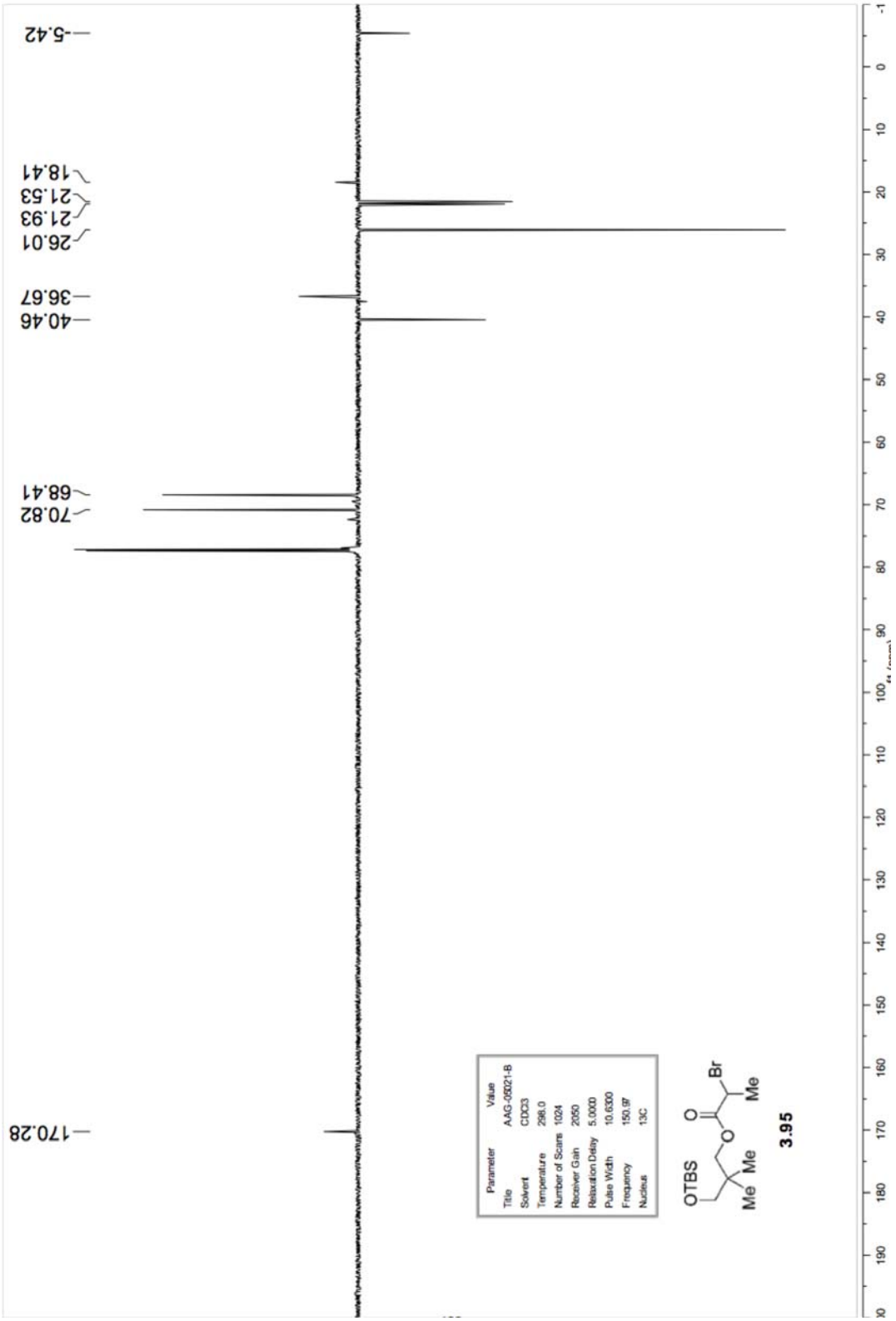

7.73
7.68
7.66
7.36
7.34
7.26
7.13
7.11
7.10
5.14
1.96
Parameter Value
Title AAG-06017-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 114
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
Br
O
Me Me
I
3.93
6.47
2.02
1.05
1.03
1.00
1.00
f1 (ppm)

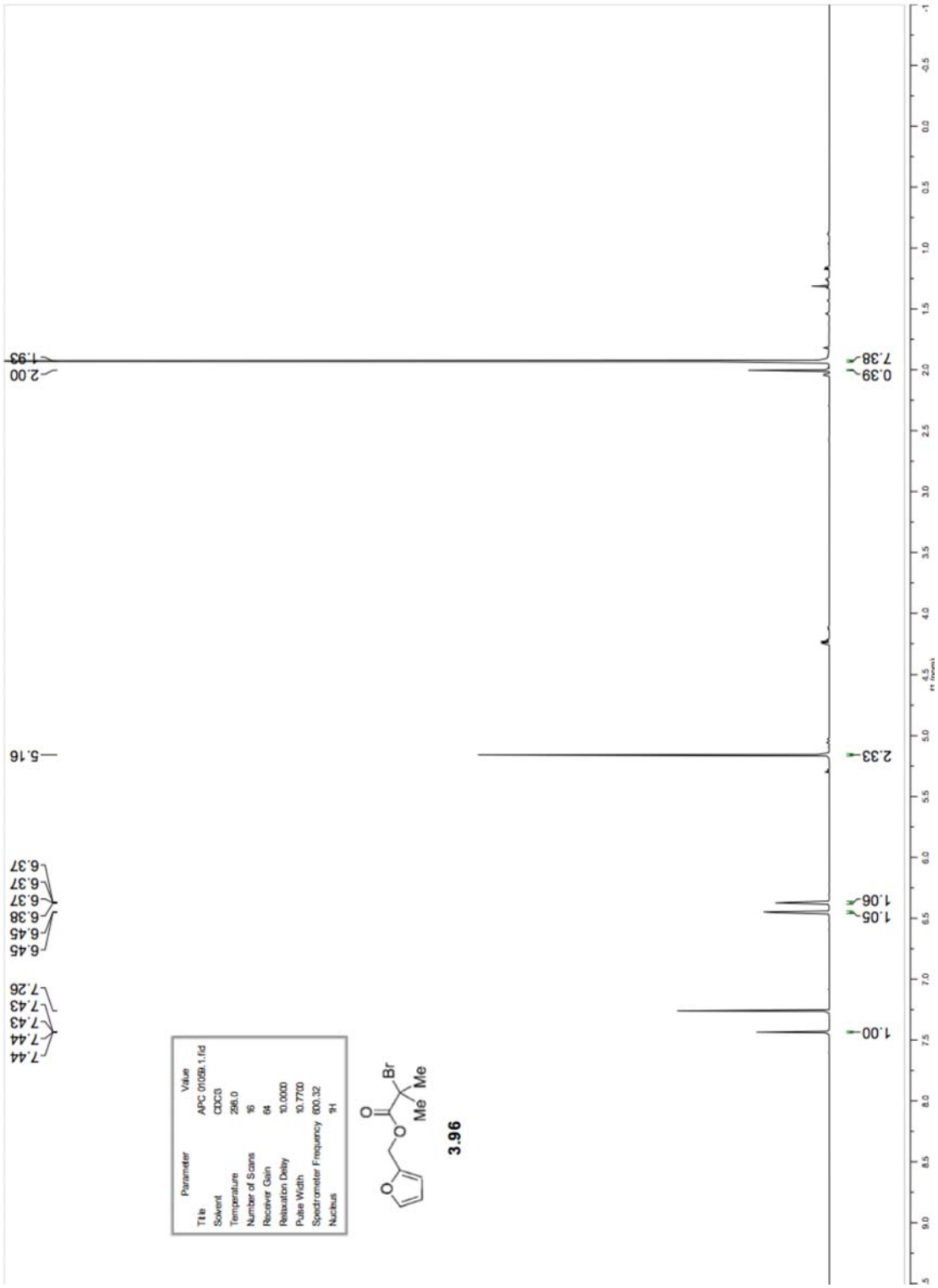

30.88
55.56
66.54
94.44
127.15
130.46
136.86
137.53
137.81
171.46
Parameter Value
Title AAG-05017-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.9F
Nucleus 13C
Br
Me
Me
O
O
I
3.93
f1 (ppm)

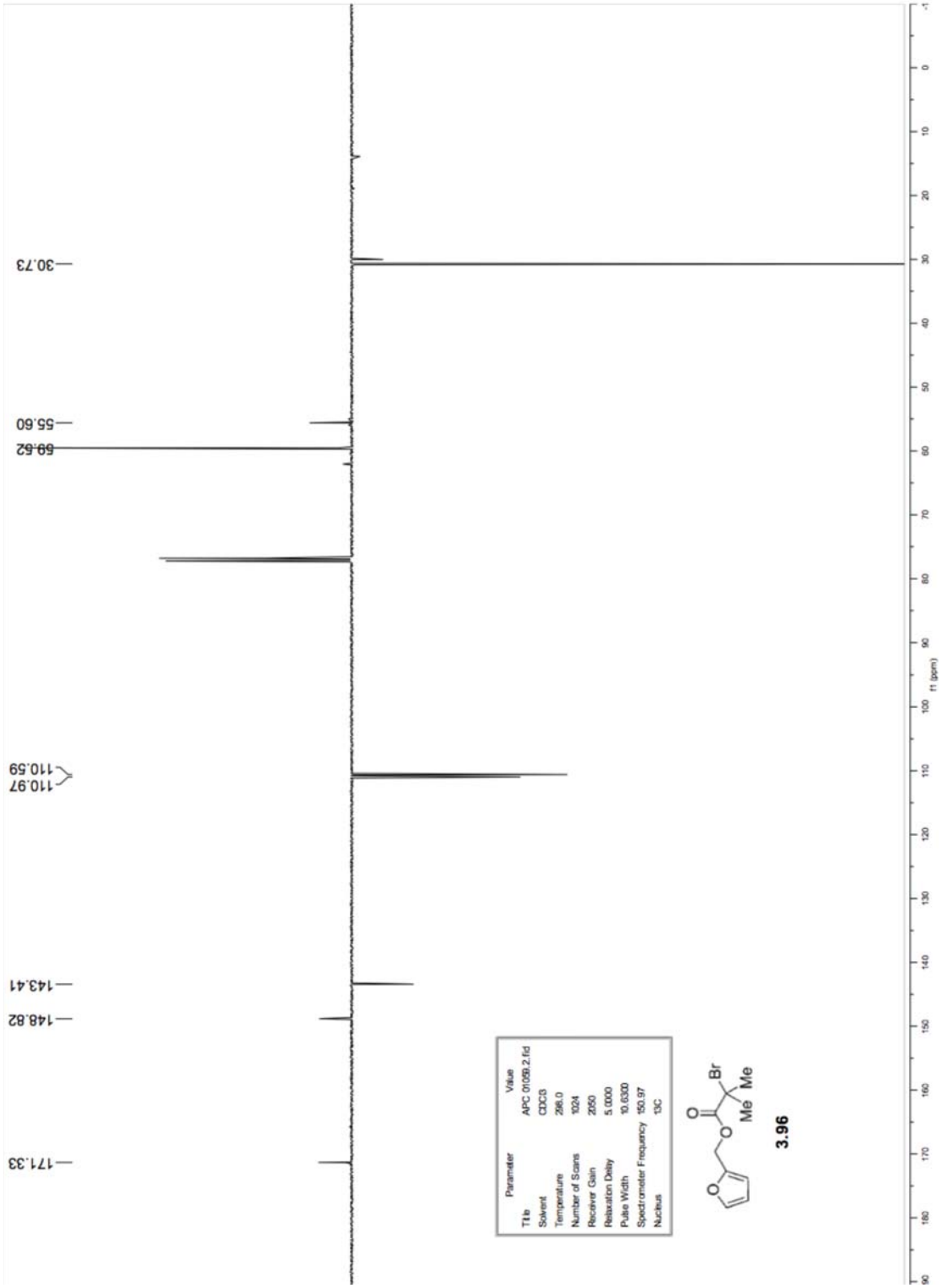

7.26
4.74
4.73
4.73
4.72
1.95
1.87
1.86
1.86
1.99
5.92
2.98
Parameter Value
Title AAG-04070-B
Solvent CDCl3
Temperature 298.1
Number of Scans 16
Receiver Gain 9
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
O
Br
O
Me
Me
Me
3.94


171.25
83.94
72.59
55.47
54.54
30.85
3.88
Parameter Value
Title AAG-04070-B
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
Br
Me
Me
O
O
Me
3.94

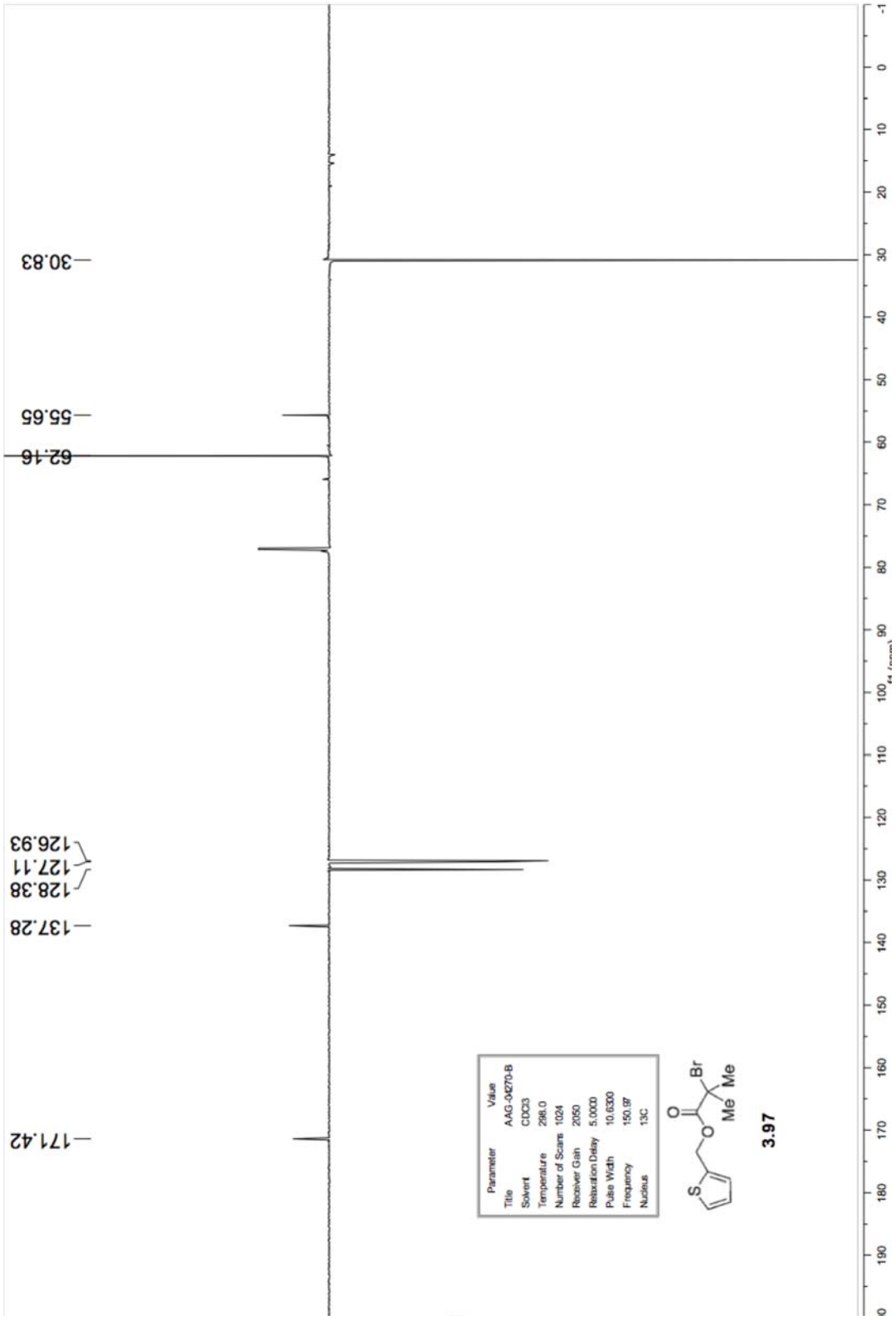

Parameter Value
Title AAG-05021-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 101
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
OTBS
O
Br
Me Me
Me
3.95
7.26
4.40
4.39
4.38
4.36
4.02
4.01
3.95
3.93
3.35
1.84
1.82
0.91
0.88
0.03
6.83
16.55
3.12
1.91
1.04
1.09
1.00
f1 (ppm)

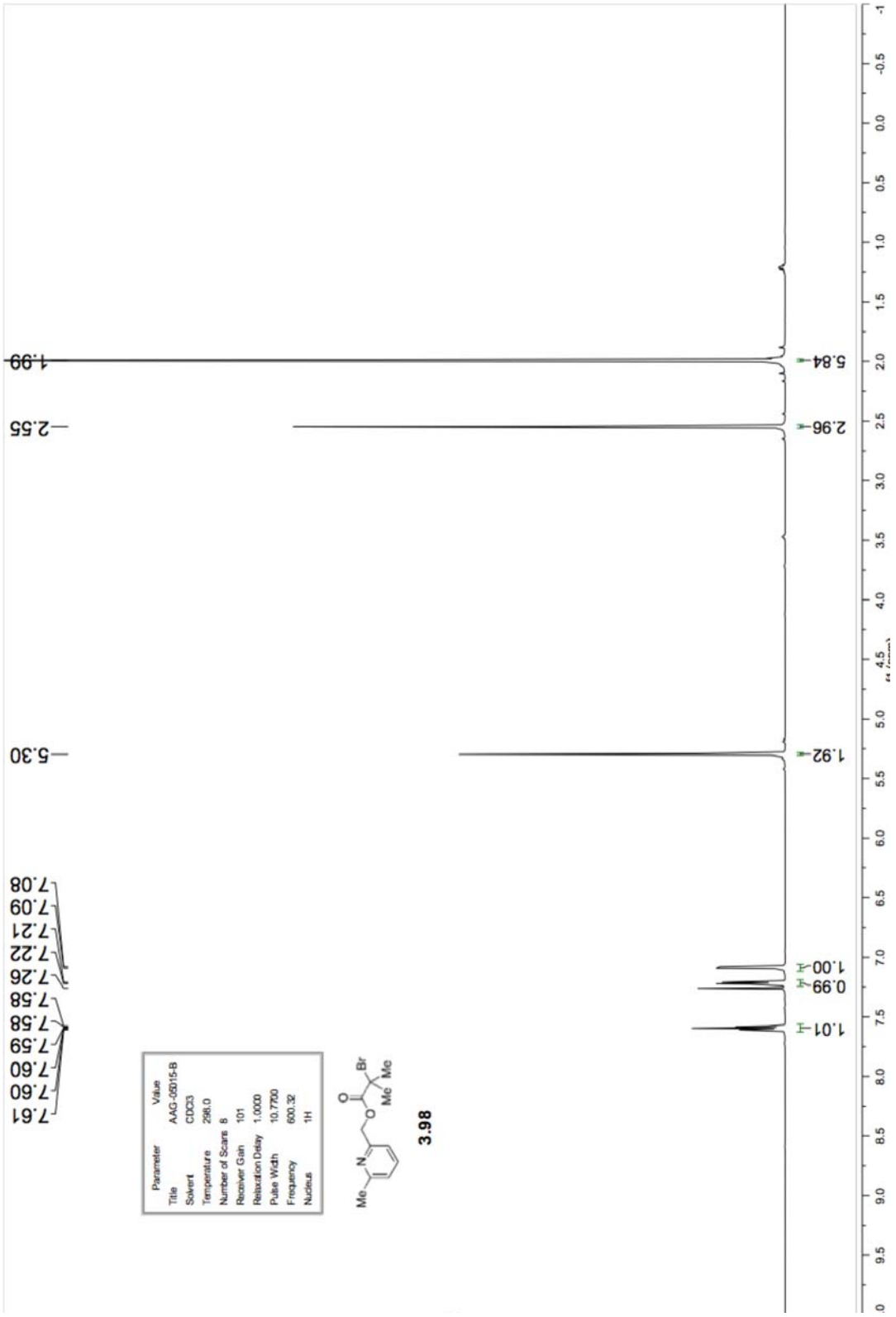

-5.42
18.41
21.53
21.93
26.01
36.67
40.46
68.41
70.82
170.28
Parameter Value
Title AAG-08021-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.87
Nucleus 13C
OTBS
O
Br
O
Me
Me
Me
3.95

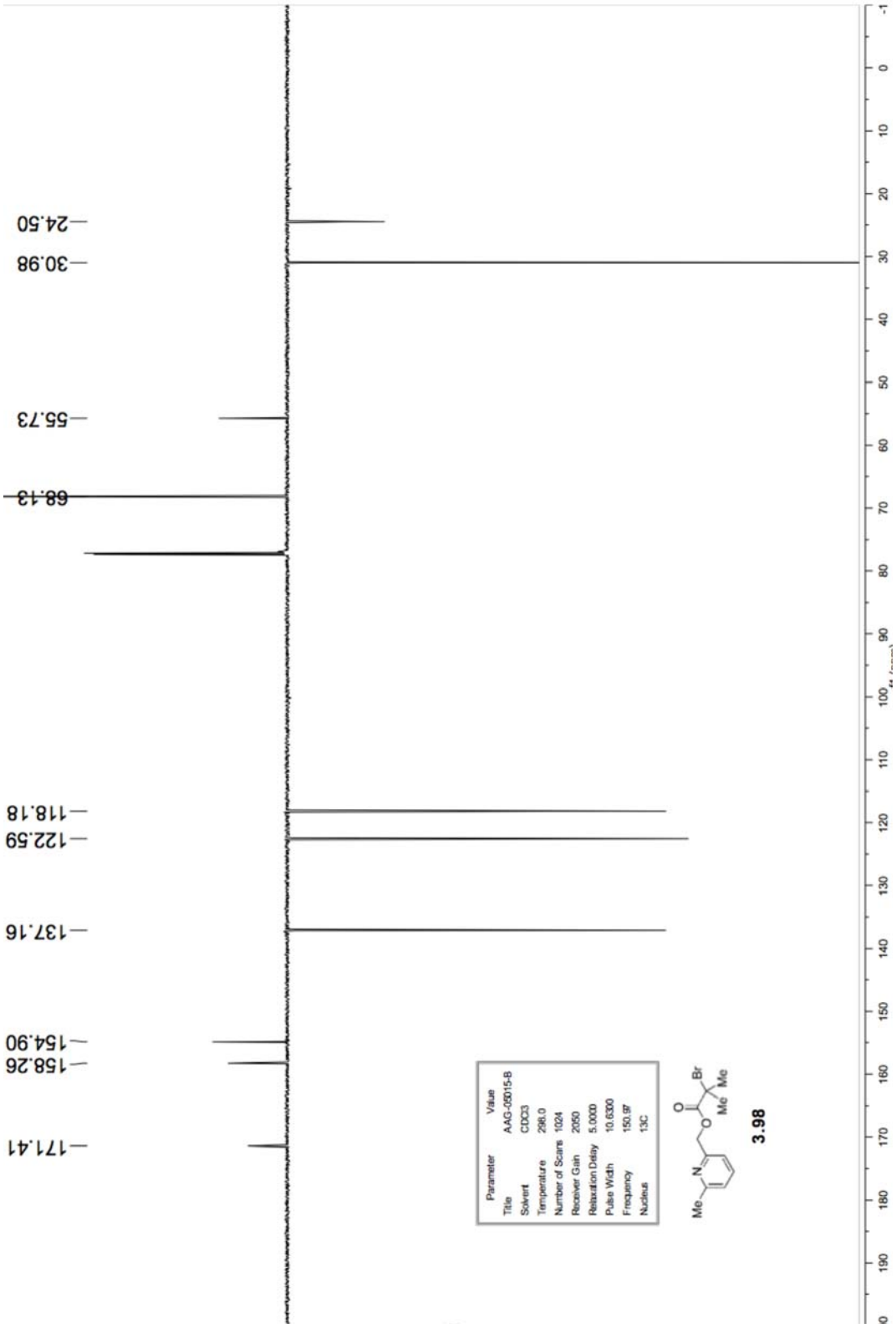

7.44
7.44
7.43
7.43
7.26
6.45
6.45
6.38
6.37
6.37
6.37
6.37
5.16
2.00
1.93
1.00
1.05
1.06
2.33
0.39
7.38
Parameter
Value
Title
APC 01089.1.fid
Solvent
CDCl3
Temperature
298.0
Number of Scans
16
Receiver Gain
64
Relaxation Delay
10.0000
Pulse Width
10.7700
Spectrometer Frequency
600.32
Nucleus
1H
Br
Me
Me
3.96


30.73
55.60
59.62
110.97
110.59
143.41
148.82
171.33
f1 (ppm)
Parameter Value
Title APC 01059.2.fid
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Spectrometer Frequency 150.97
Nucleus 13C
Br
Me
Me
O
O
O
3.96

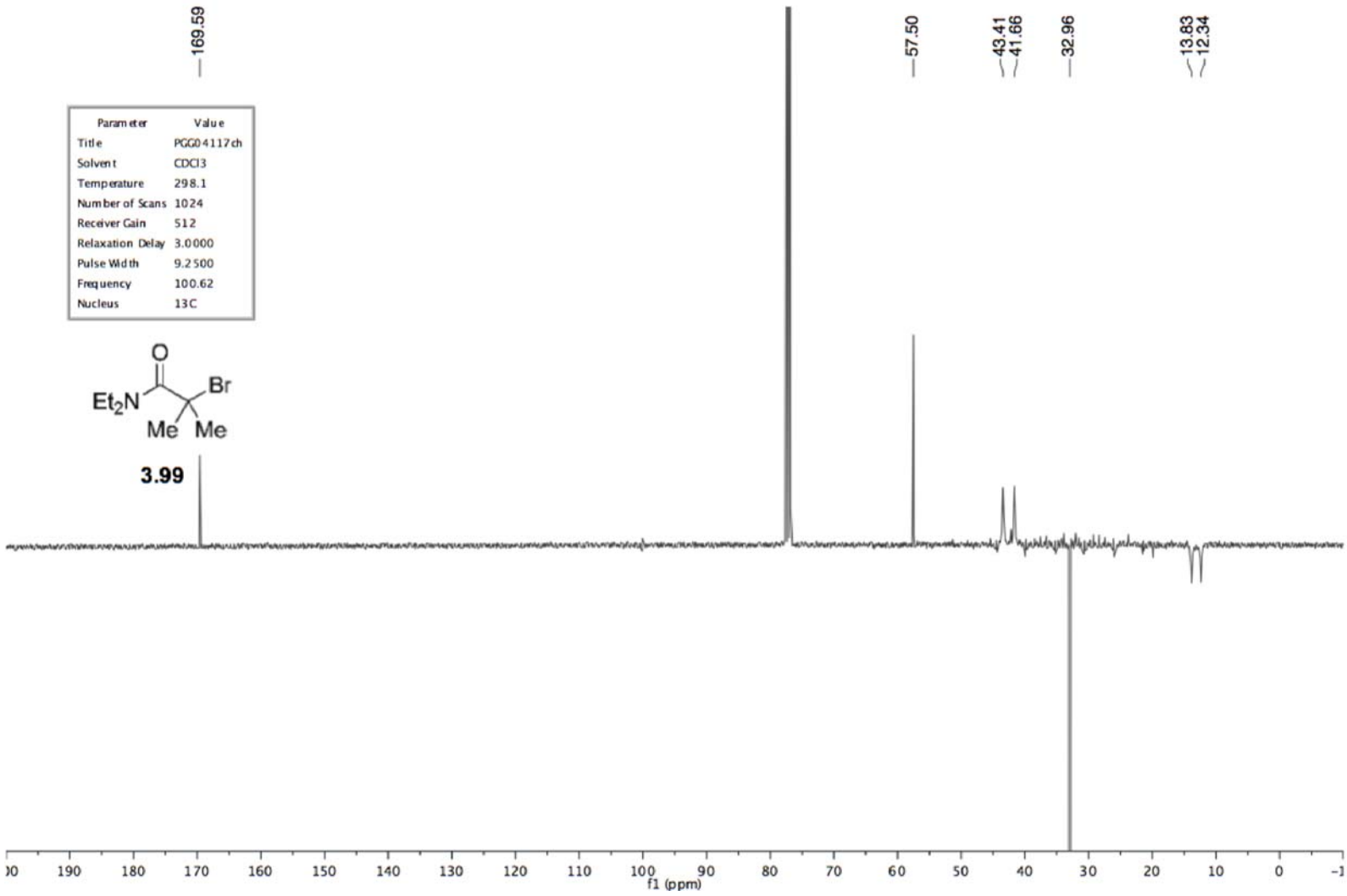
7.34
7.33
7.33
7.33
7.33
7.26
7.13
7.12
7.00
7.00
6.99
6.99
5.36
1.93
Parameter Value
Title AAG-04270-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
Br
O
S
Me Me
3.97
6.34
2.00
0.87
0.93
0.93

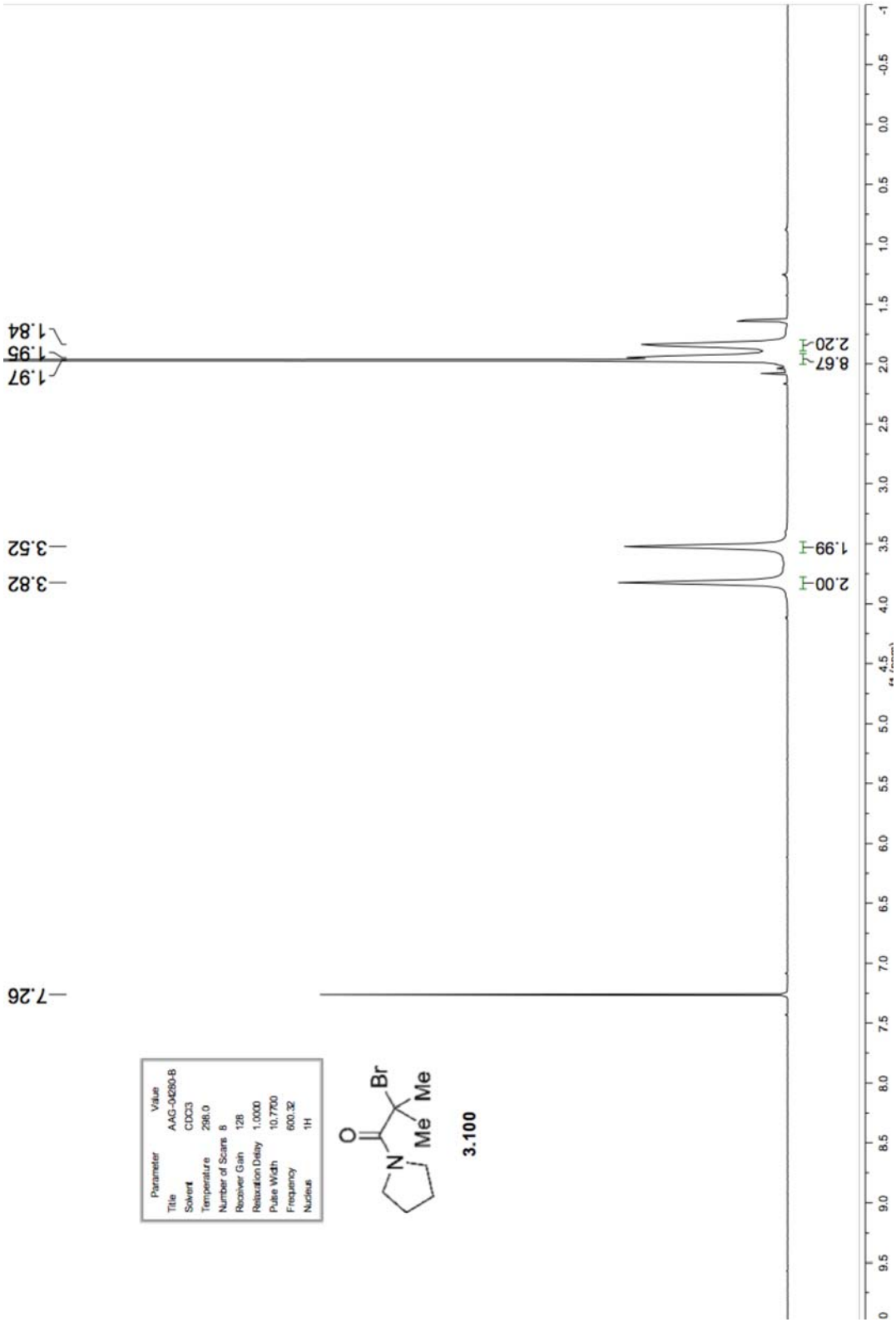

30.83
55.65
62.16
126.93
127.11
128.38
137.28
171.42
Parameter Value
Title AAG-04270-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
Br
Me
Me
O
O
S
3.97

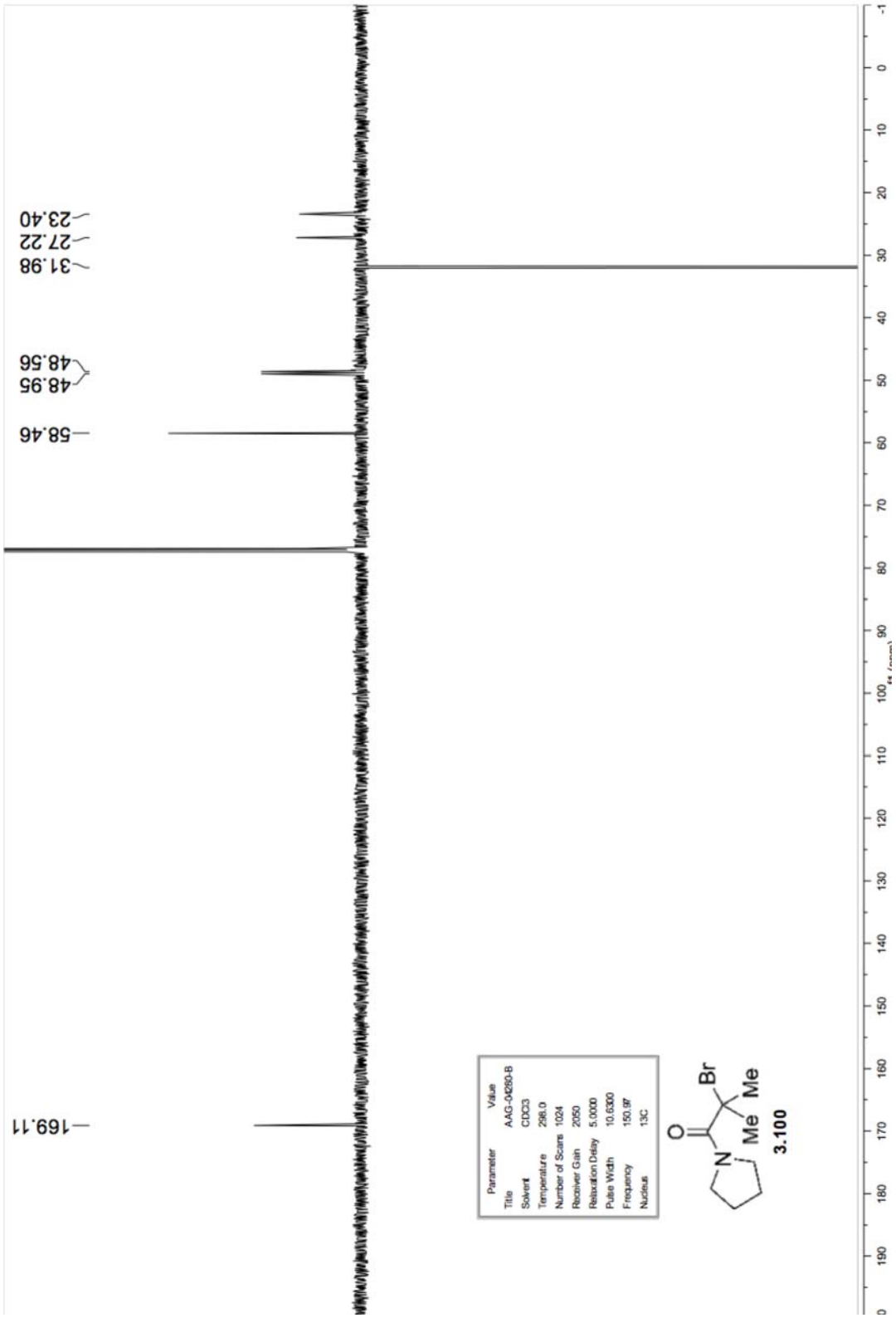

7.61
7.60
7.60
7.59
7.58
7.58
7.26
7.22
7.21
7.09
7.08
5.30
2.55
1.99
1.01
0.99
1.00
1.92
2.96
5.84
Parameter Value
Title AAG-06015-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 101
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
Me
N
O
O
Br
Me
Me
3.98


24.50
30.98
55.73
68.13
118.18
122.59
137.16
154.90
158.26
171.41
Parameter Value
Title AAG-05015-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.9F
Nucleus 13C
Br
Me
Me
O
O
N
Me
3.98

Parameter Value
Title PCC04117ch
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
Et2N
O
Br
Me
Me
3.99
3.72
3.35
1.95
1.22
1.14
4.02
5.93
6.05


169.59
57.50
43.41
41.66
32.96
13.83
12.34
Parameter Value
Title PGG04117ch
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
Et2N
Br
Me Me
3.99
f1 (ppm)


7.26
3.82
3.52
1.97
1.95
1.84
2.00
1.99
2.20
8.67
Parameter Value
Title AAG-04080-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 128
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
N
Br
Me
Me
3.100

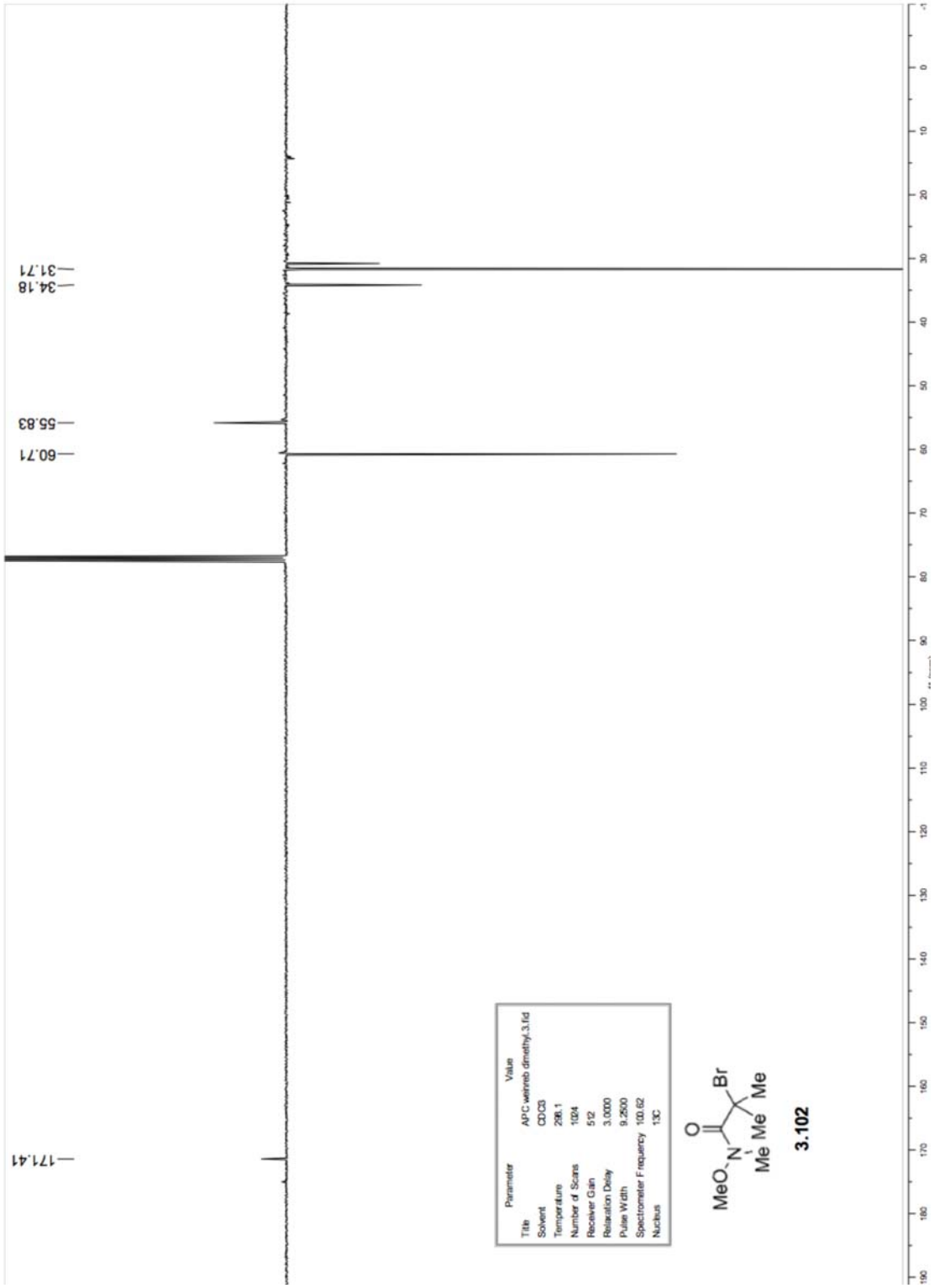

169.11
58.46
48.95
48.56
31.98
27.22
23.40
Parameter Value
Title AAG-04260-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.9F
Nucleus 13C
O
N
Br
Me
Me
3.100

Parameter Value
Title secamidech
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
Br
EtHN
Me
Me
3.101
6.70
3.32
3.31
3.30
3.30
3.29
3.28
3.27
1.94
1.18
1.17
1.16
0.97
1.99
6.04
3.00

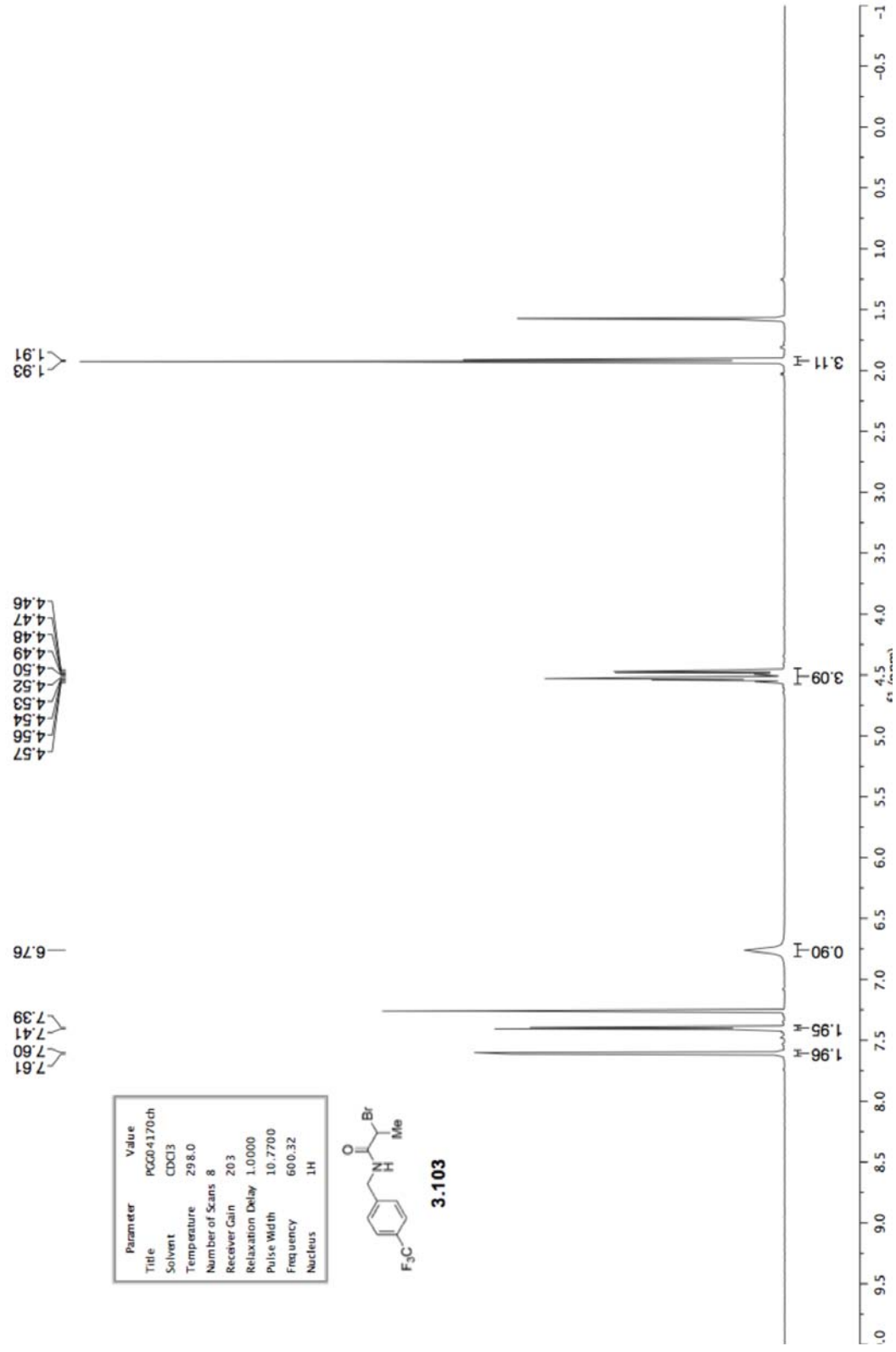
171.92
63.59
35.45
32.75
14.65
Parameter Value
Title secamidech
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
O
Br
EtHN
Me
Me
3.101
f1 (ppm)

7.26
1.97
3.26
3.80
5.93
2.96
3.00
Parameter Value
Title APC weinreb dimethyl.2.fid
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Spectrometer Frequency 400.13
Nucleus 1H
MeO
N
Me
Me
O
Br
Me
Me

3.102

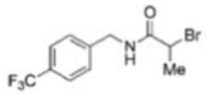

171.41
60.71
55.83
34.18
31.71
Parameter Value
Title APC weinreb dimethyl.3.fid
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Spectrometer Frequency 100.62
Nucleus 13C
MeO
N
Me
Me
O
Br
Me
Me

3.102

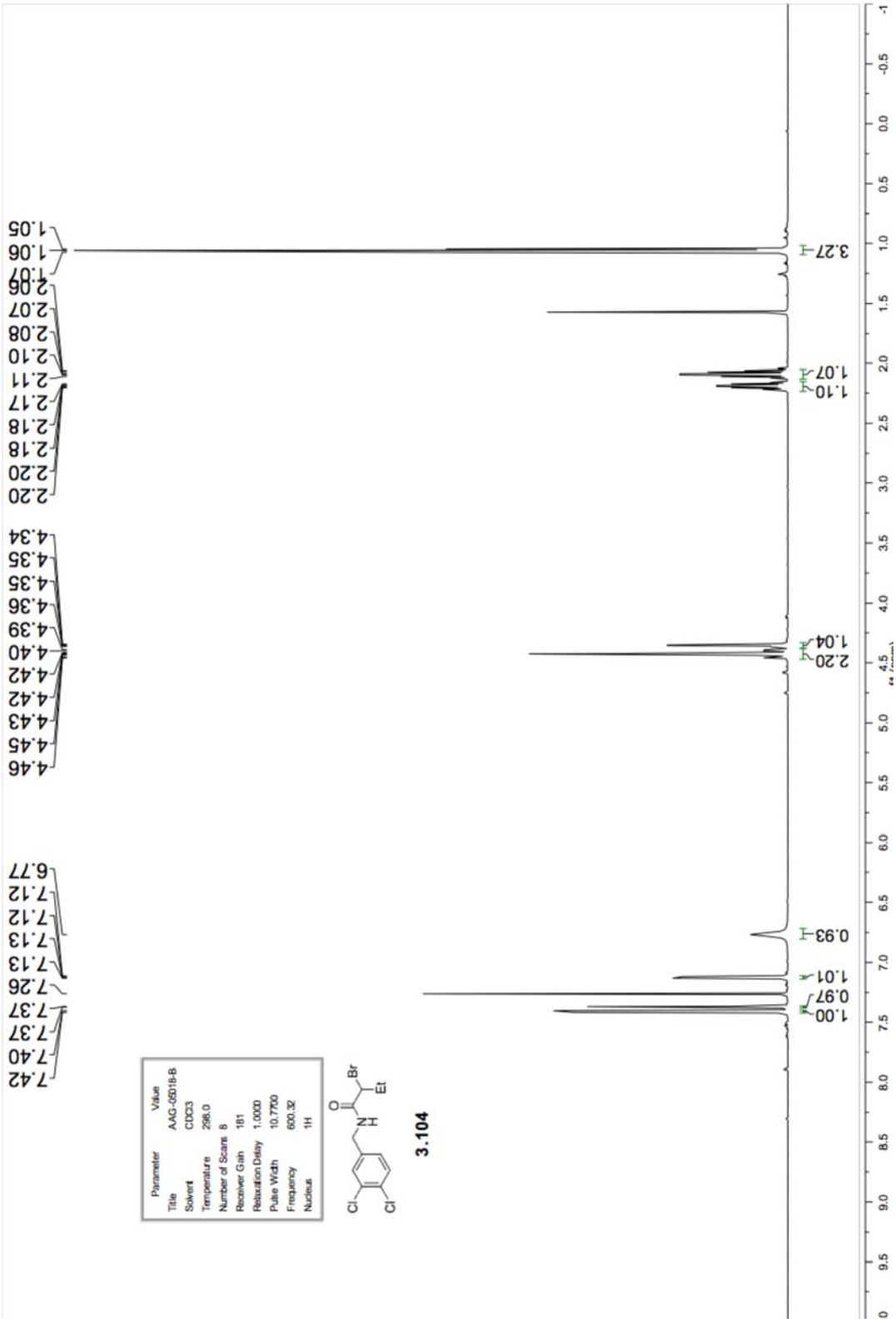

Parameter Value
Title PGC04170ch
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 203
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
3.103
7.61
7.60
7.41
7.39
6.76
4.57
4.56
4.54
4.53
4.52
4.50
4.49
4.48
4.47
4.46
1.93
1.91
1.96
1.95
0.90
3.09
3.11

169.55
141.74
130.57
130.24
129.92
129.60
128.20
127.89
125.95
125.91
125.87
125.83
125.49
122.79
120.09
45.18
43.70
23.32
Parameter Value
Title PGC04170dh
Solvent CDCl3
Temperature 298.1
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
3.103
f1 (ppm)

Parameter	Value
Title	PGG04170ch
Solvent	CDCl3
Temperature	298.2
Number of Scans	16
Receiver Gain	2299
Relaxation Delay	1.0000
Pulse Width	15.0300
Frequency	376.46
Nucleus	19F



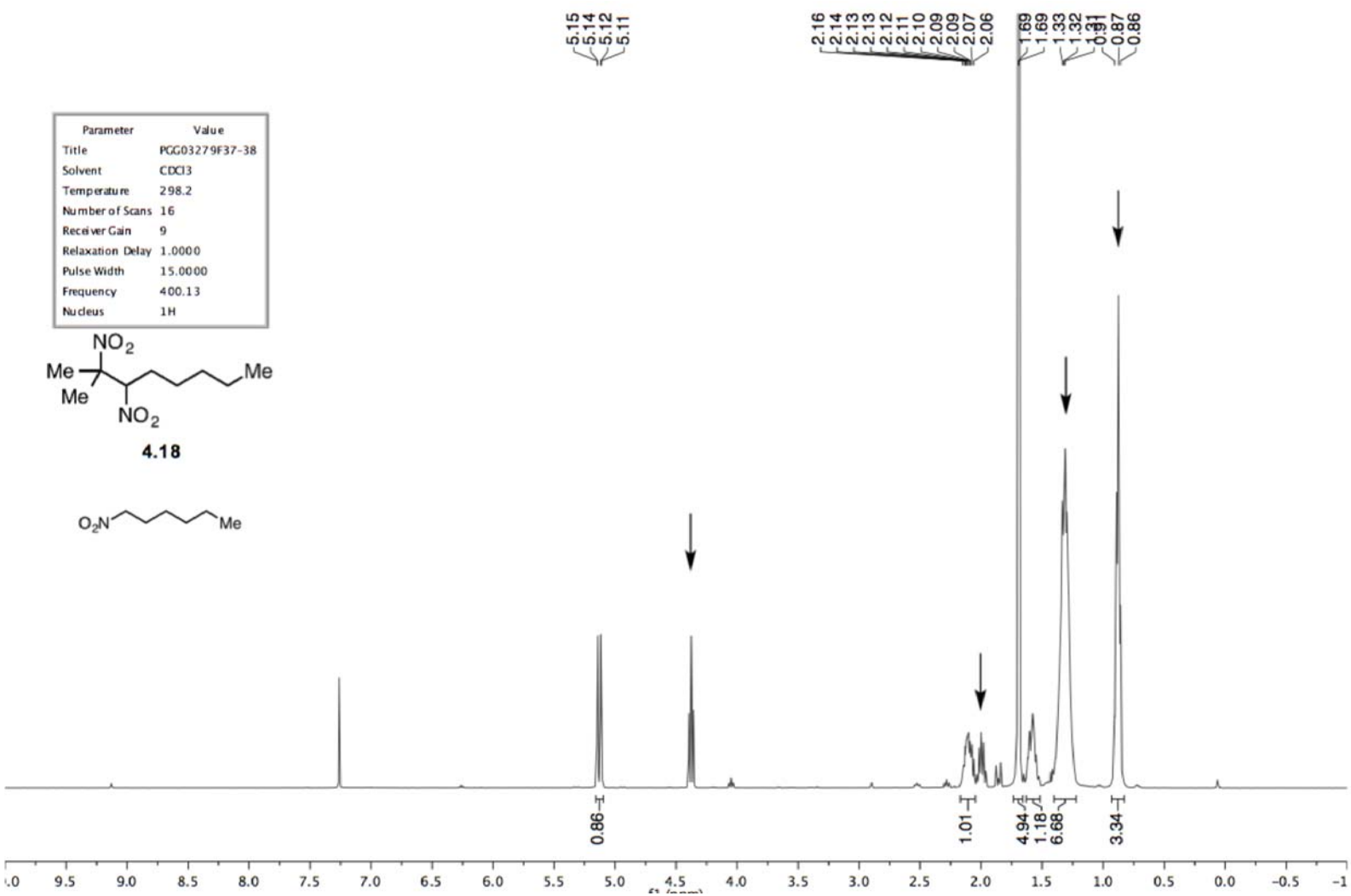
3.103

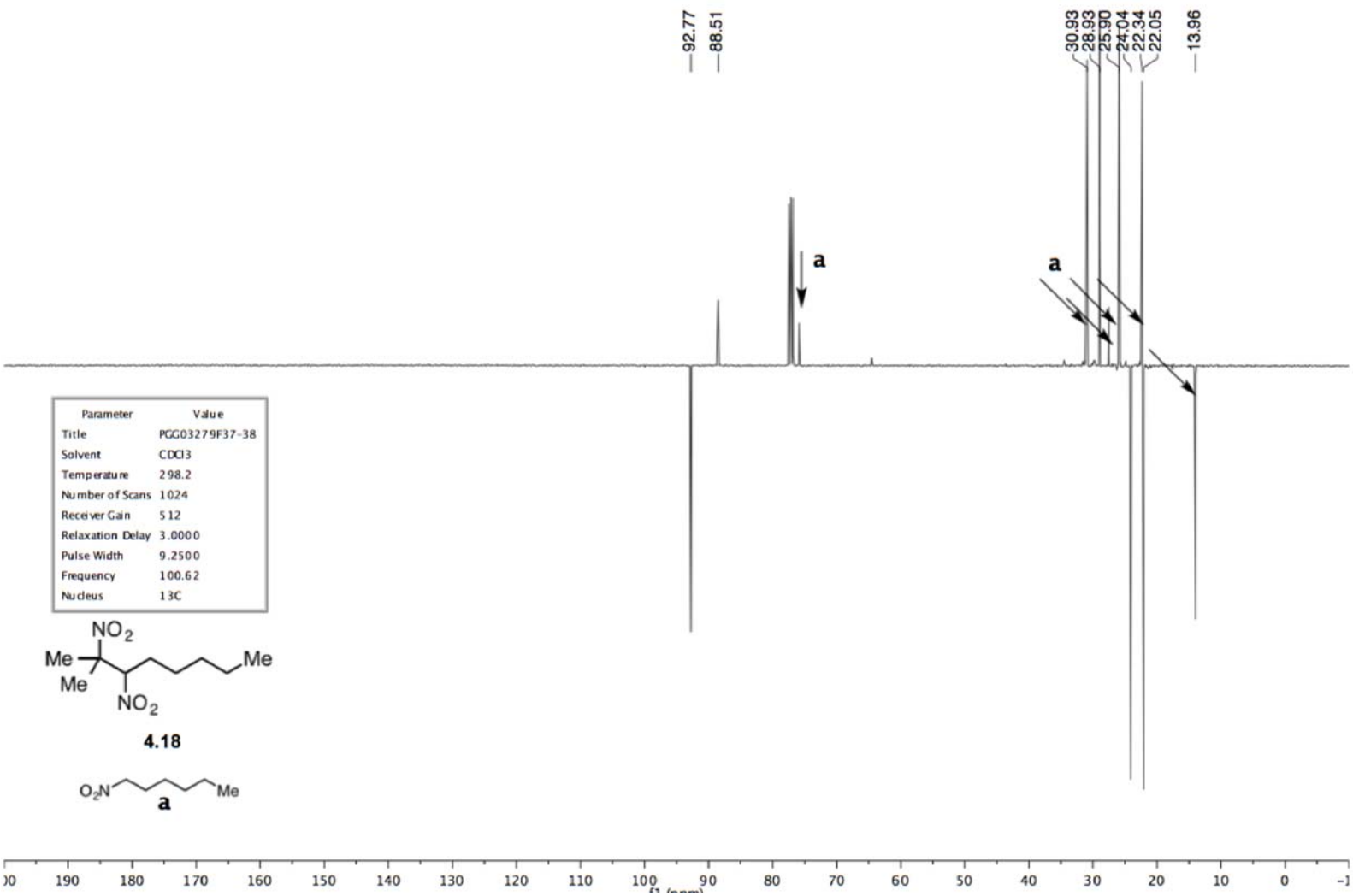

Parameter Value
Title AAG-06018-B
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
3.104
Cl
Cl
O
N
H
Br
Et
7.42
7.40
7.37
7.37
7.26
7.13
7.13
7.12
7.12
6.77
4.46
4.45
4.43
4.42
4.42
4.40
4.39
4.36
4.35
4.35
4.34
2.20
2.18
2.18
2.17
2.11
2.10
2.08
2.07
2.06
1.07
1.06
1.05
1.00
0.97
1.01
0.93
2.20
1.04
1.10
1.07
3.27

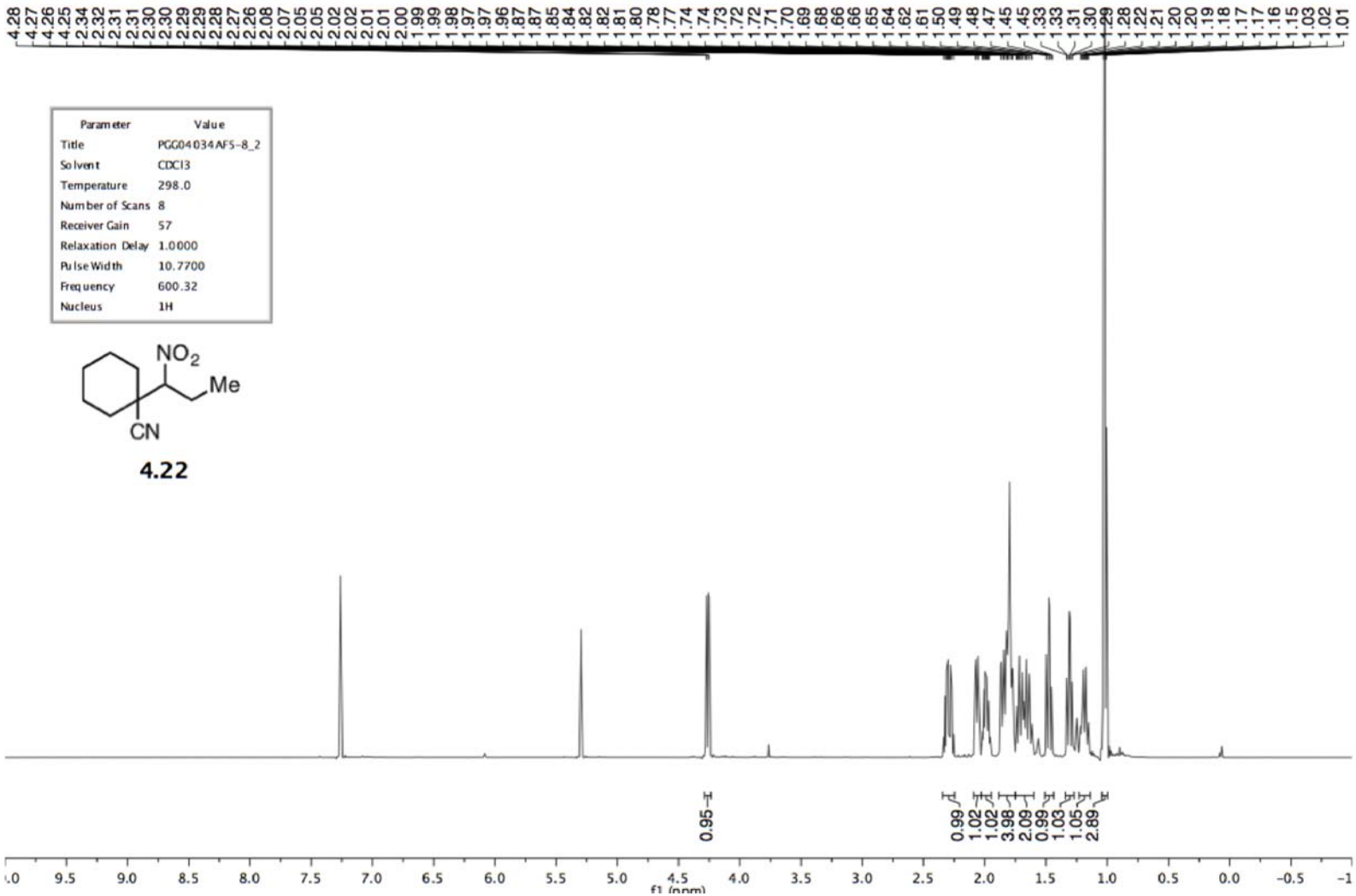
11.83
29.49
43.10
53.70
127.03
129.67
130.89
131.91
132.97
138.10
168.84
Parameter Value
Title AAG-05018-B
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
3.104

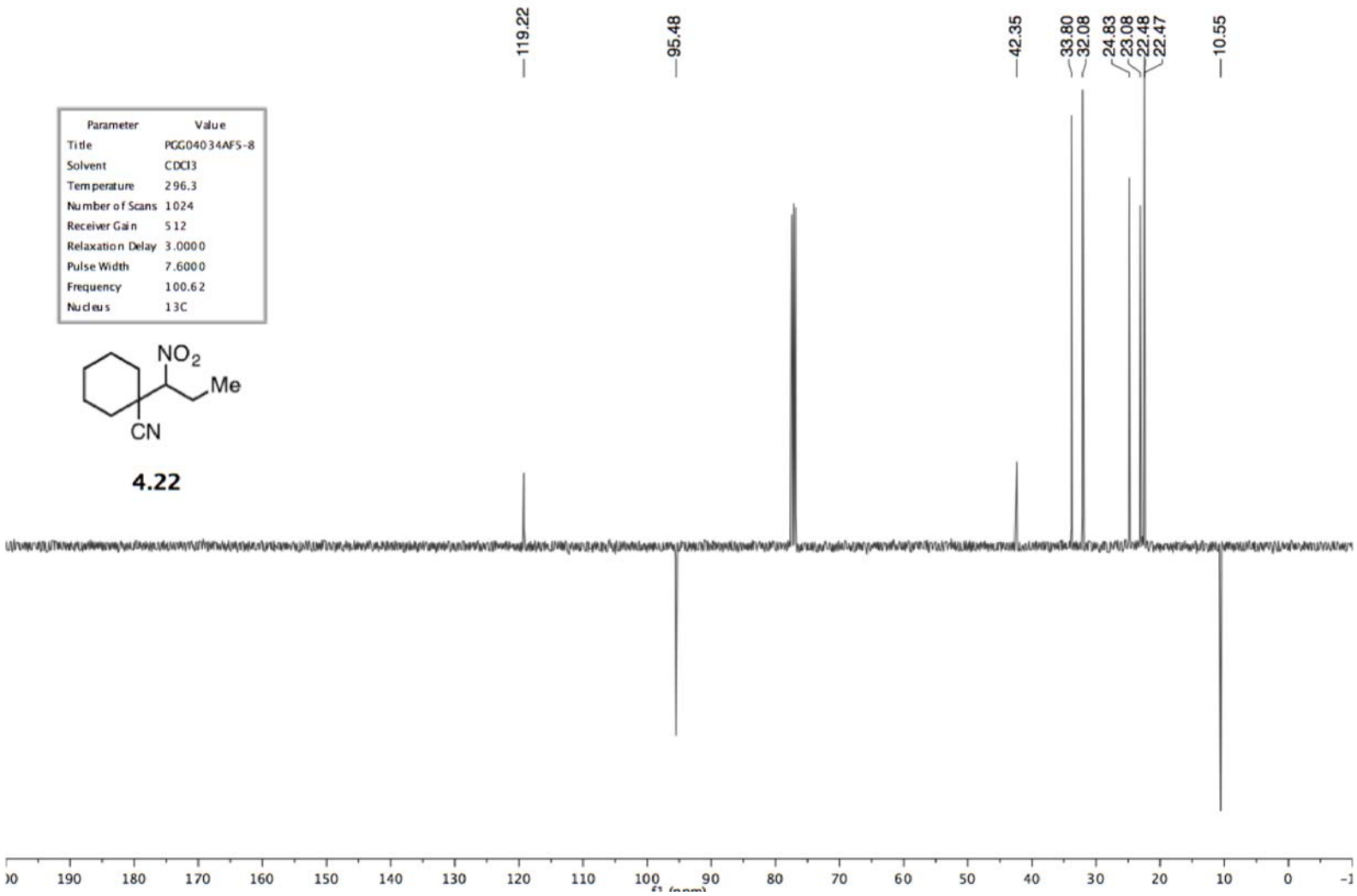
Appendix C

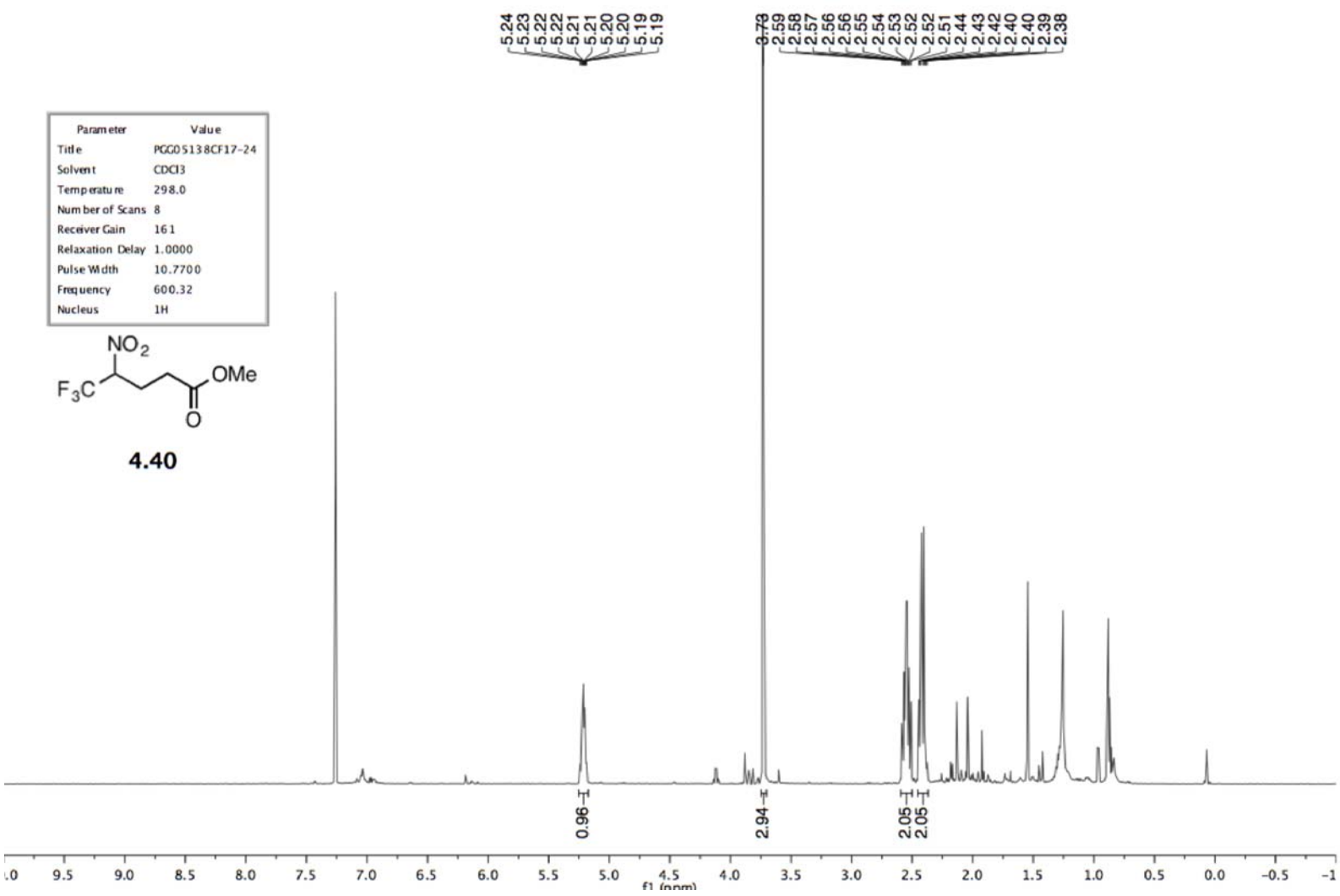
SPECTRAL DATA FOR CHAPTER 4

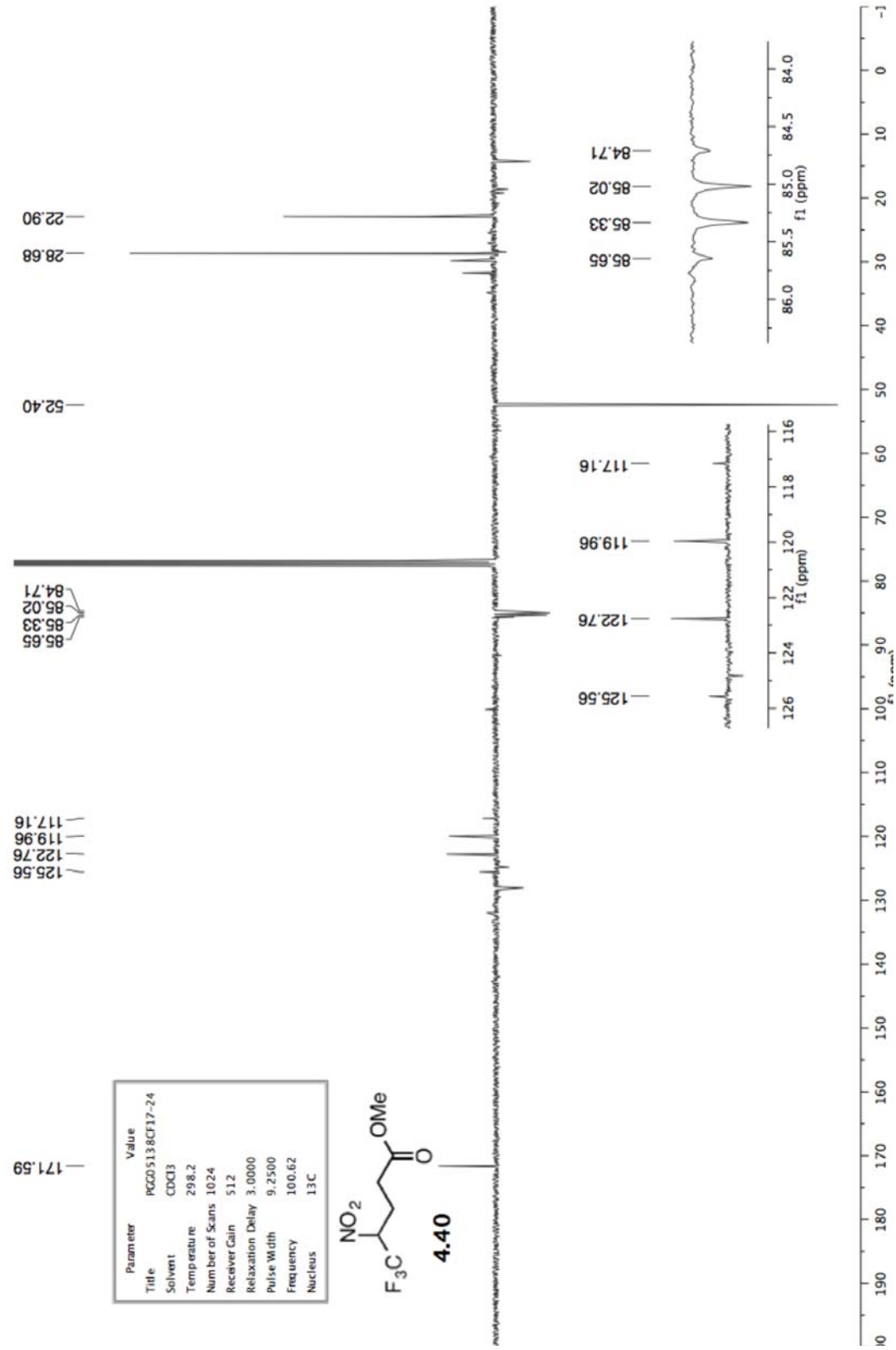

Parameter Value
Title PGG03279F37-38
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 9
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
NO2
Me
Me
Me
NO2
4.18
O2N
Me
5.15
5.14
5.12
5.11
2.16
2.14
2.13
2.13
2.12
2.11
2.10
2.09
2.09
2.07
2.06
1.69
1.69
1.33
1.32
0.91
0.87
0.86
0.86
1.01
4.94
1.18
6.68
3.34
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1


92.77
88.51
30.93
28.93
25.90
24.04
22.34
22.05
13.96
a
a
Parameter Value
Title PGG03279F37-38
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
NO2
Me
Me
Me
NO2
4.18
O2N
Me
a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

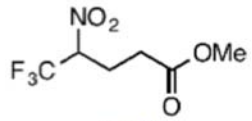

Parameter Value
Title PGG04034AF5-8_2
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
Me
CN
4.22
0.95
0.99
1.02
1.02
3.98
2.09
0.99
1.03
1.05
2.89
f1 (ppm)


119.22
95.48
42.35
33.80
32.08
24.83
23.08
22.48
22.47
10.55
Parameter Value
Title PGG04034AF5-8
Solvent CDCl3
Temperature 296.3
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 7.6000
Frequency 100.62
Nucleus 13C
NO2
Me
CN
4.22
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

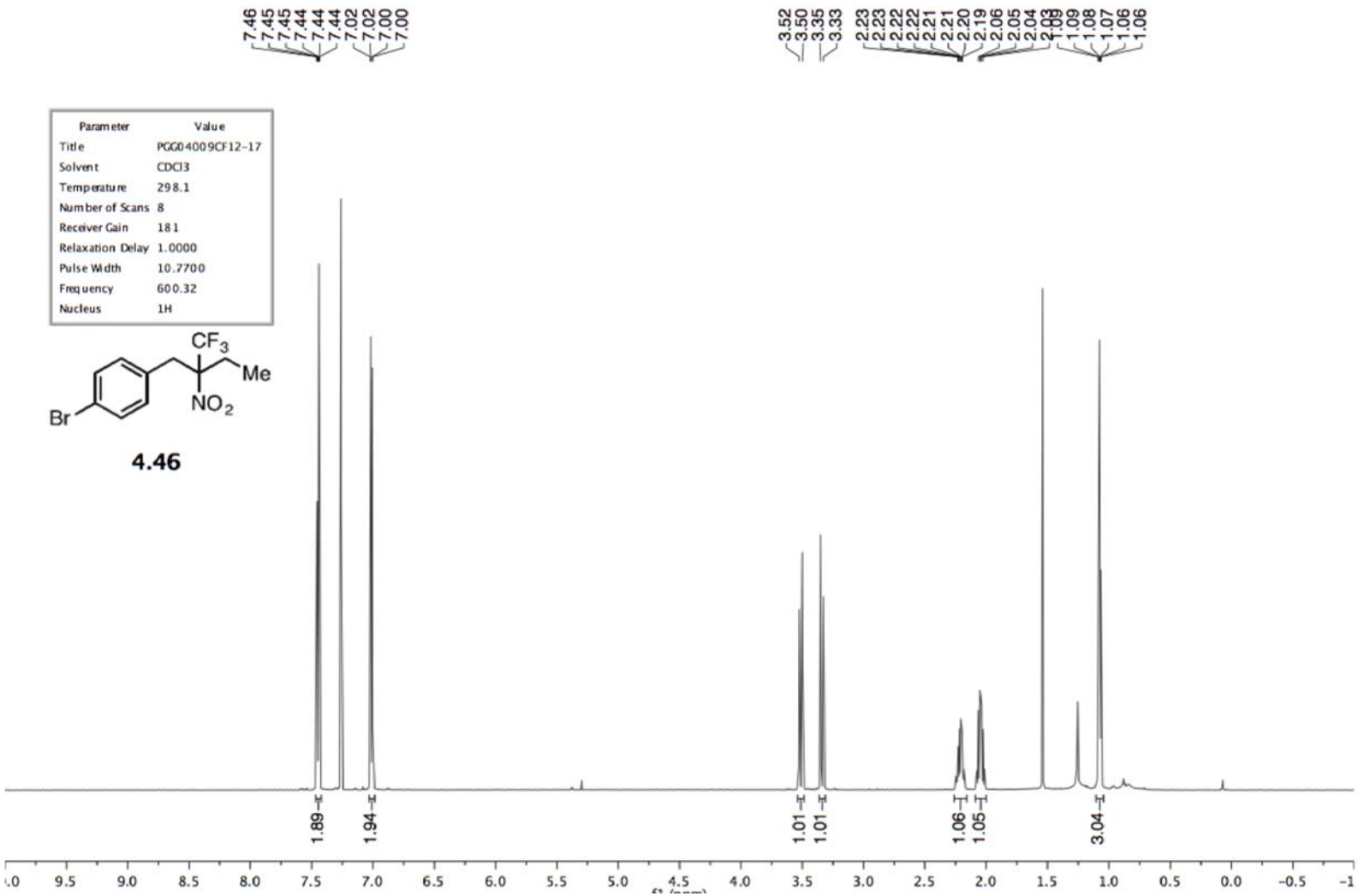

5.24
5.23
5.22
5.22
5.21
5.21
5.20
5.20
5.19
5.19
3.78
2.59
2.58
2.57
2.56
2.56
2.55
2.54
2.53
2.52
2.52
2.51
2.44
2.43
2.42
2.40
2.40
2.39
2.38
Parameter Value
Title PGG05138CF17-24
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
NO2
F3C
OMe
O
4.40
0.96
2.94
2.05
2.05
f1 (ppm)


Parameter Value
Title PGC05138CF17-24
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
171.59
125.56
122.76
119.96
117.16
85.65
85.33
85.02
84.71
52.40
28.68
22.90
NO2
OMe
O
F3C
4.40
f1 (ppm)

Parameter	Value
Title	PGG05138CF17-24
Solvent	CDCl3
Temperature	298.2
Number of Scans	16
Receiver Gain	1626
Relaxation Delay	1.0000
Pulse Width	15.0300
Frequency	376.46
Nucleus	19F



4.40

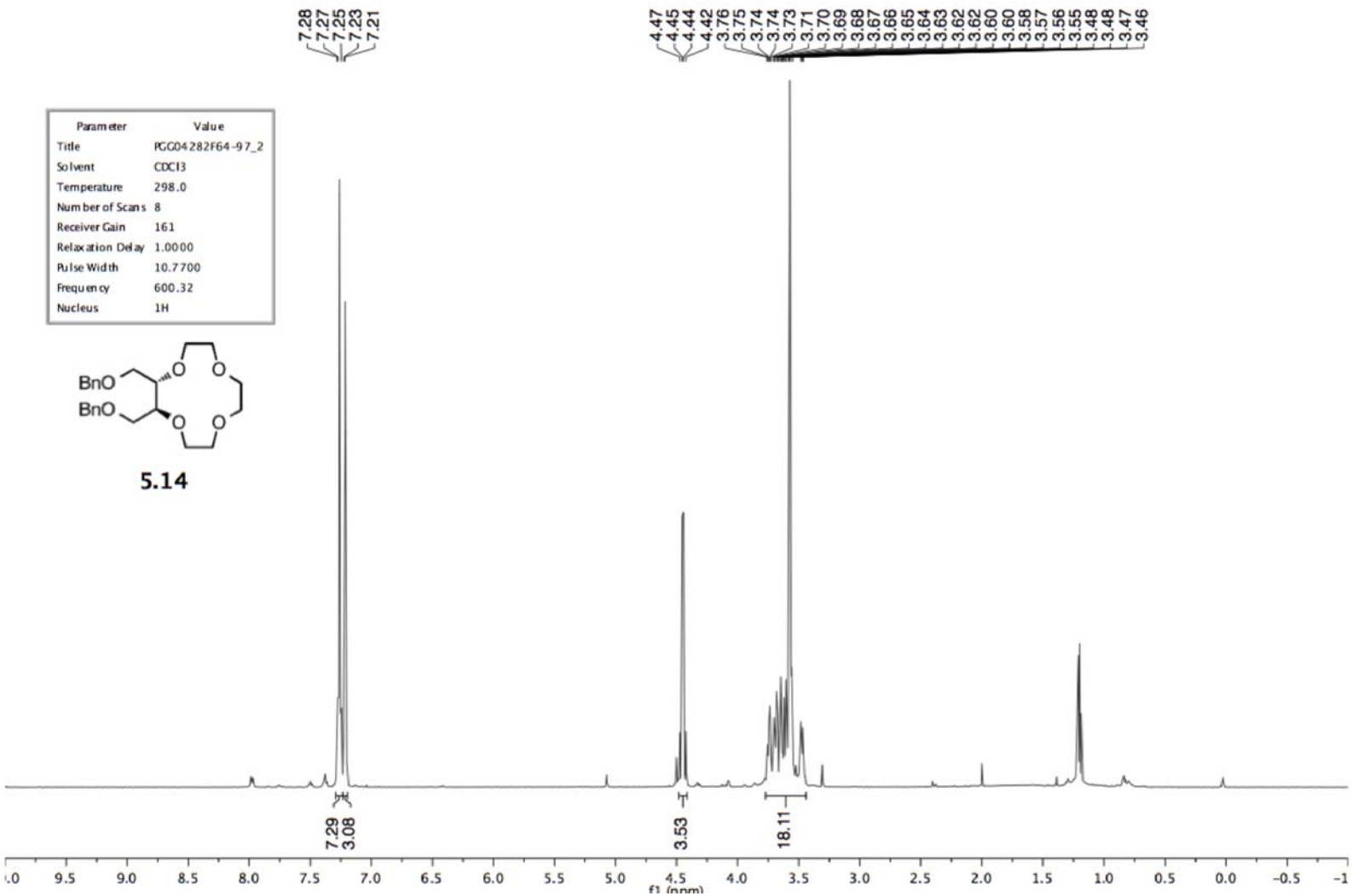

7.46
7.45
7.45
7.44
7.44
7.44
7.02
7.02
7.00
7.00
3.52
3.50
3.35
3.33
2.23
2.23
2.22
2.22
2.21
2.21
2.20
2.19
2.06
2.05
2.04
1.09
1.09
1.08
1.07
1.06
1.06
Parameter Value
Title PGG04009CF12-17
Solvent CDCl3
Temperature 298.1
Number of Scans 8
Receiver Gain 181
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
CF3
Me
NO2
Br
4.46
1.89
1.94
1.01
1.01
1.06
1.05
3.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

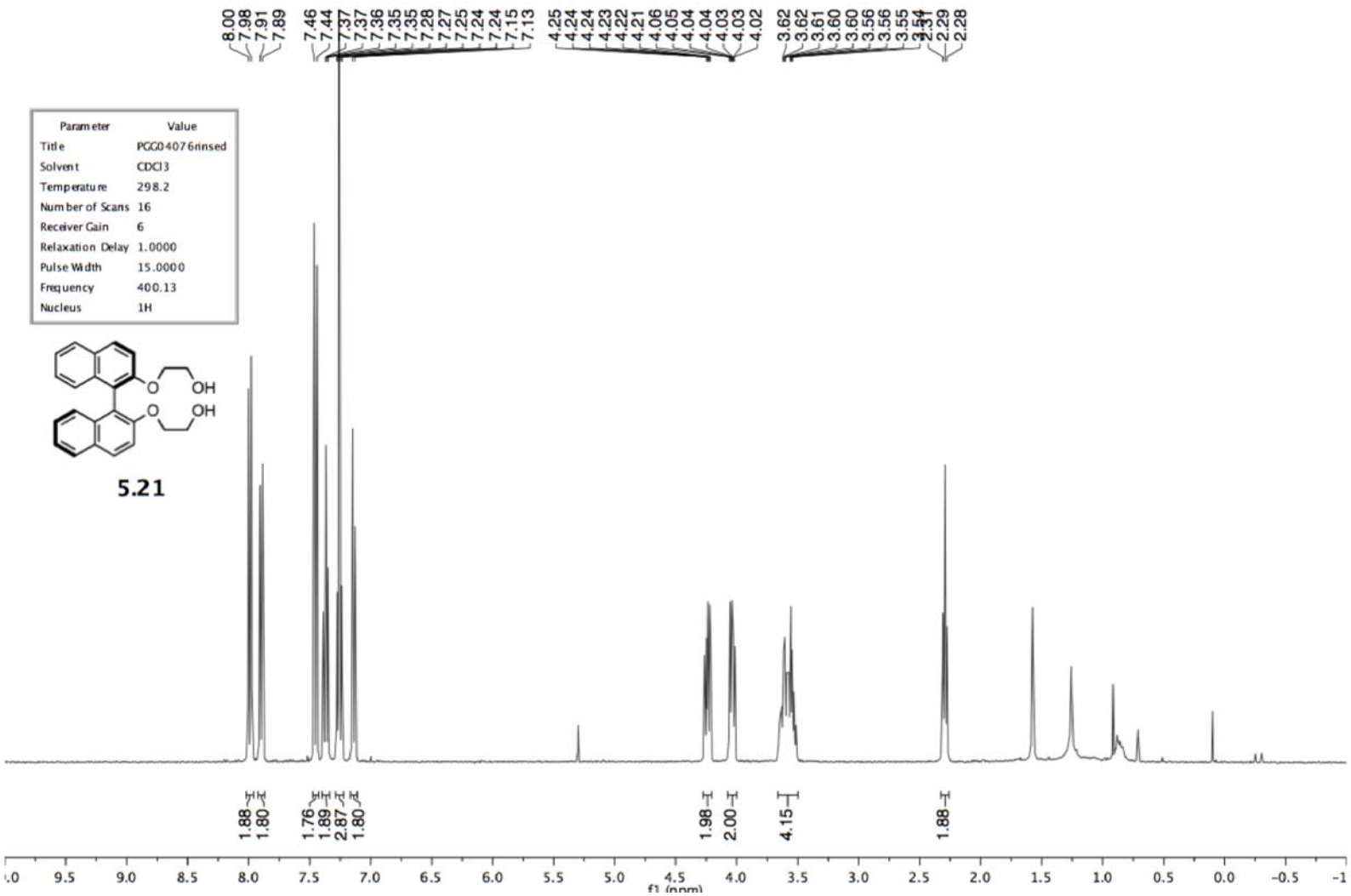
8.38
8.36
26.11
38.95
93.86
94.11
94.37
94.63
132.06
132.04
130.96
127.41
124.57
122.64
121.73
118.89
f1 (ppm)
Parameter Value
Title RGG04009CF12-17_2
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
CF3
Me
NO2
Br
4.46

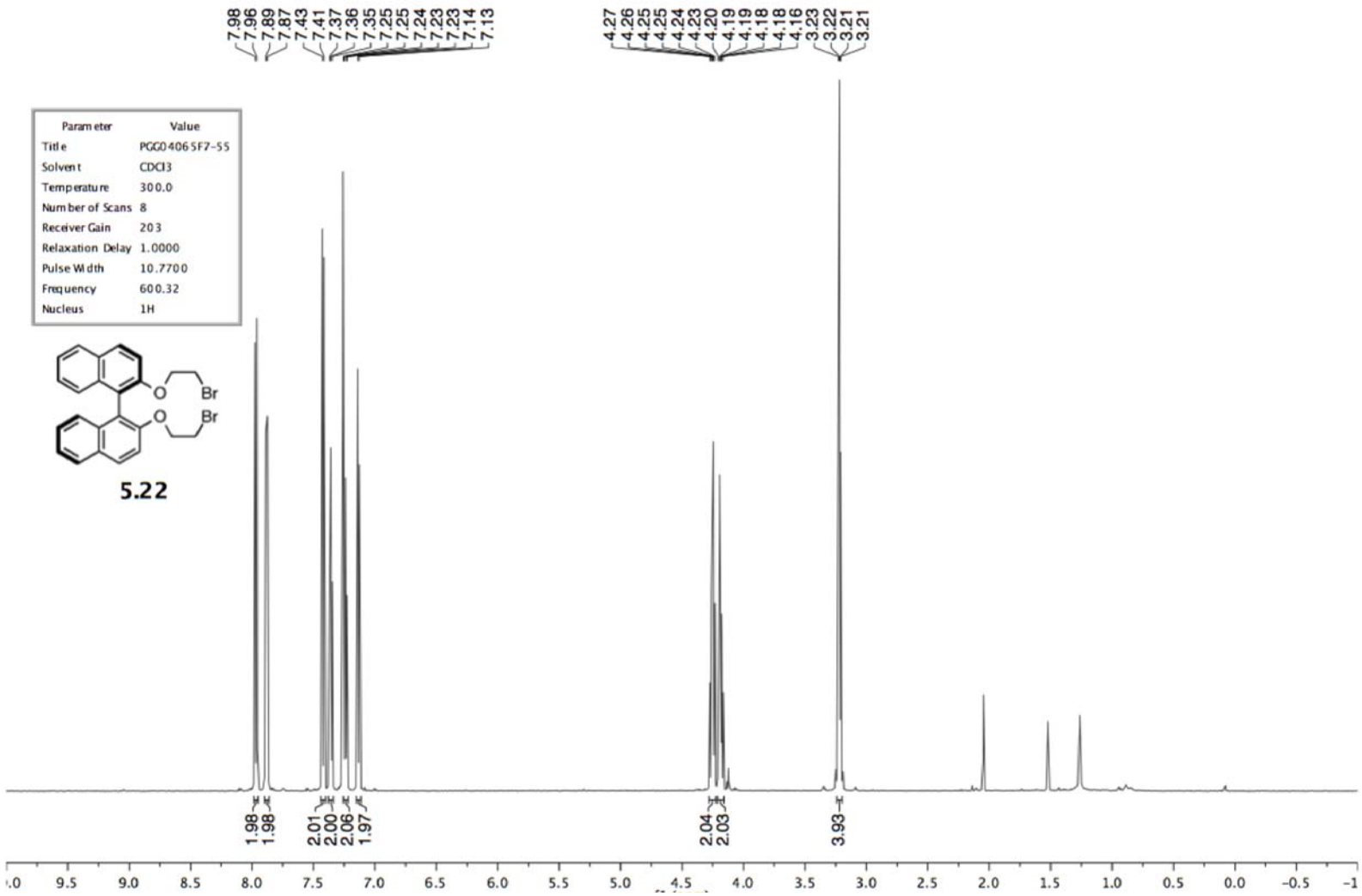
-69.50
Parameter Value
Title PGD4009CF12-17
Solvent CDCl3
Temperature 298.1
Number of Scans 32
Receiver Gain 144
Relaxation Delay 3.0000
Pulse Width 11.6200
Frequency 564.81
Nucleus 19F
CF3
Me
NO2
Br
4.46
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2

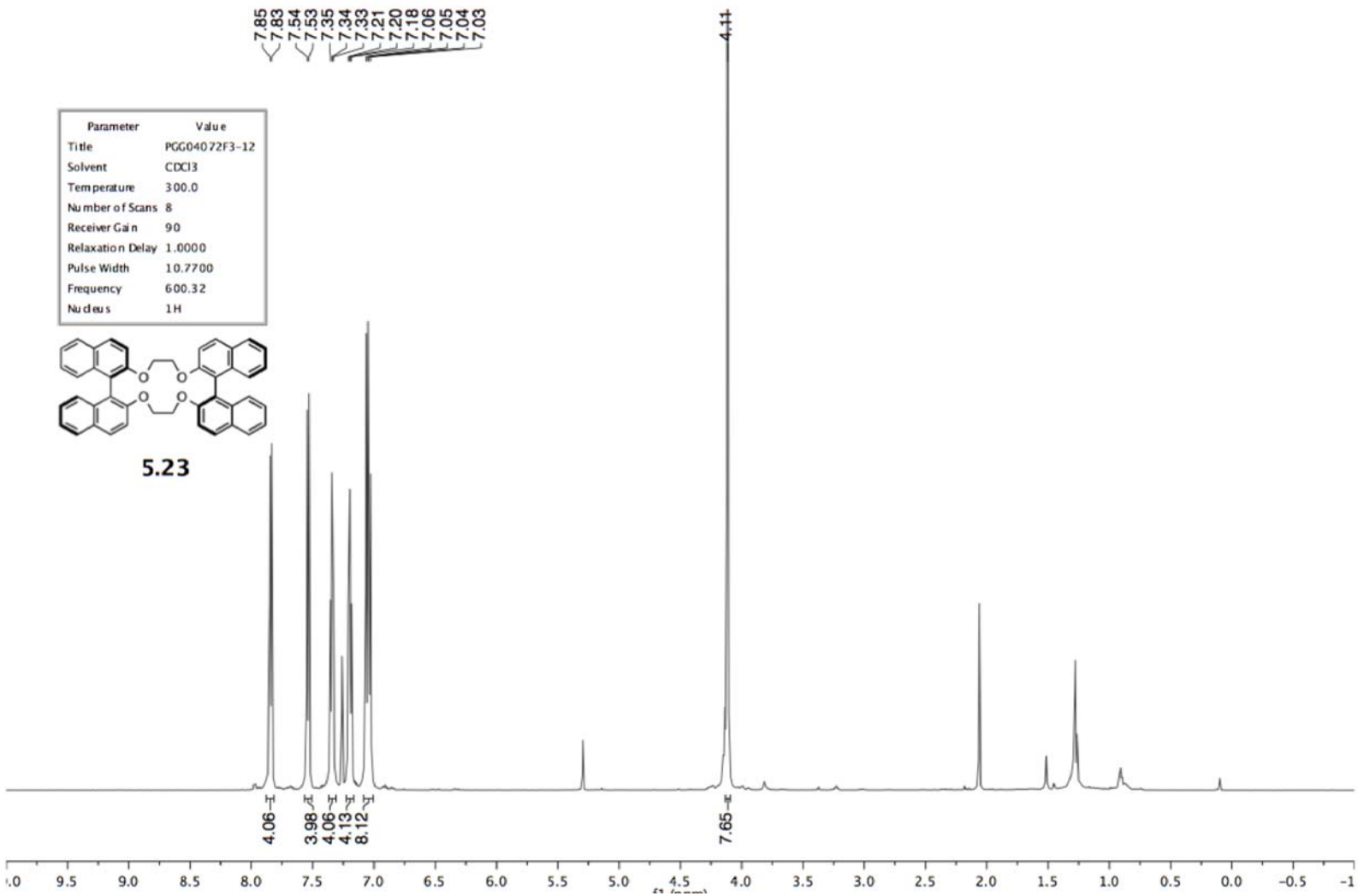
Appendix D

SPECTRAL DATA FOR CHAPTER 5

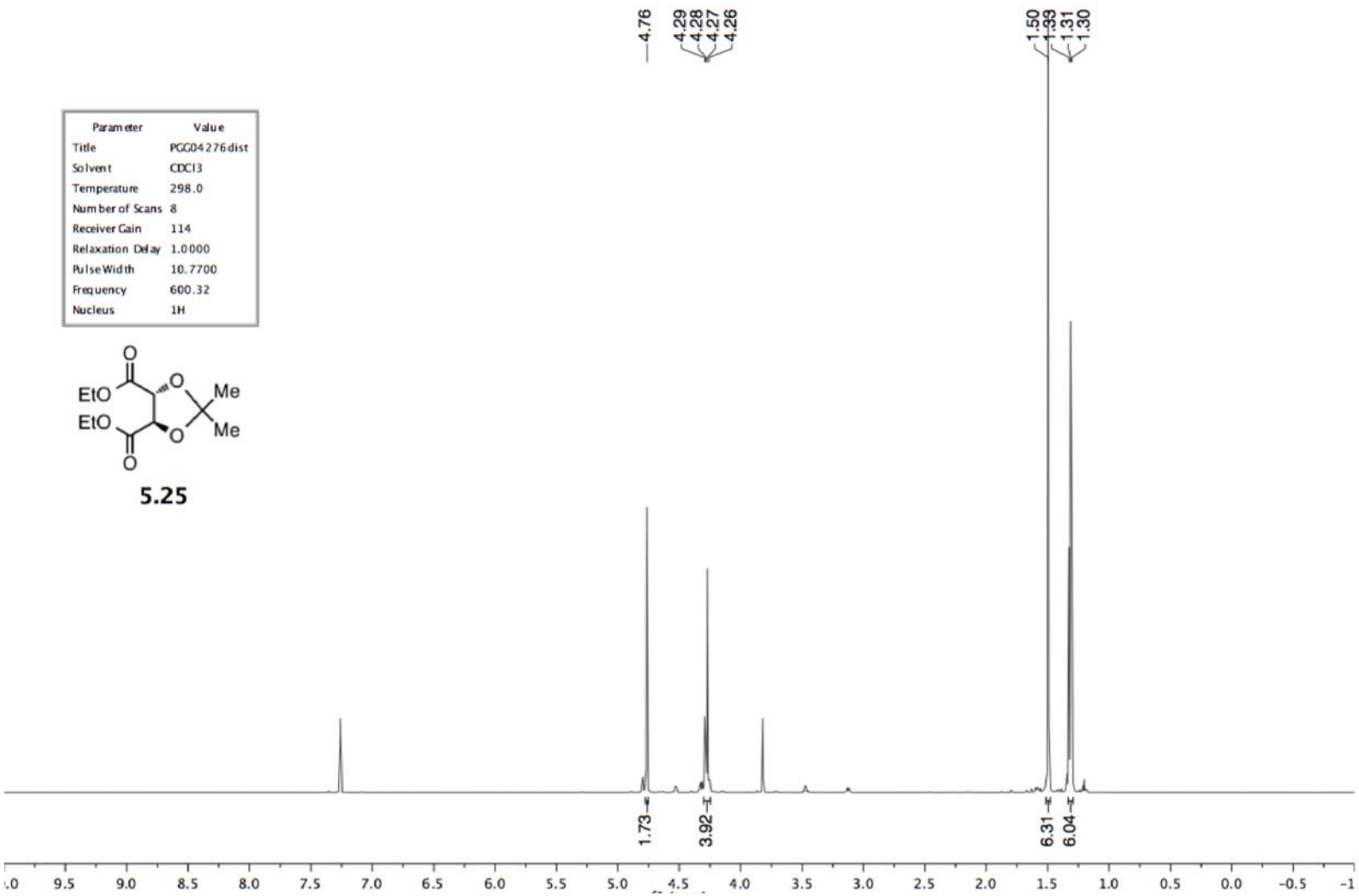

7.28
7.27
7.25
7.23
7.21
4.47
4.45
4.44
4.42
3.76
3.75
3.74
3.74
3.73
3.71
3.70
3.69
3.68
3.67
3.66
3.65
3.64
3.63
3.62
3.62
3.60
3.60
3.58
3.57
3.56
3.55
3.48
3.48
3.47
3.46
Parameter Value
Title PGG04282F64-97_2
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 161
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
BnO
BnO
5.14
7.29
3.08
3.53
18.11
f1 (ppm)

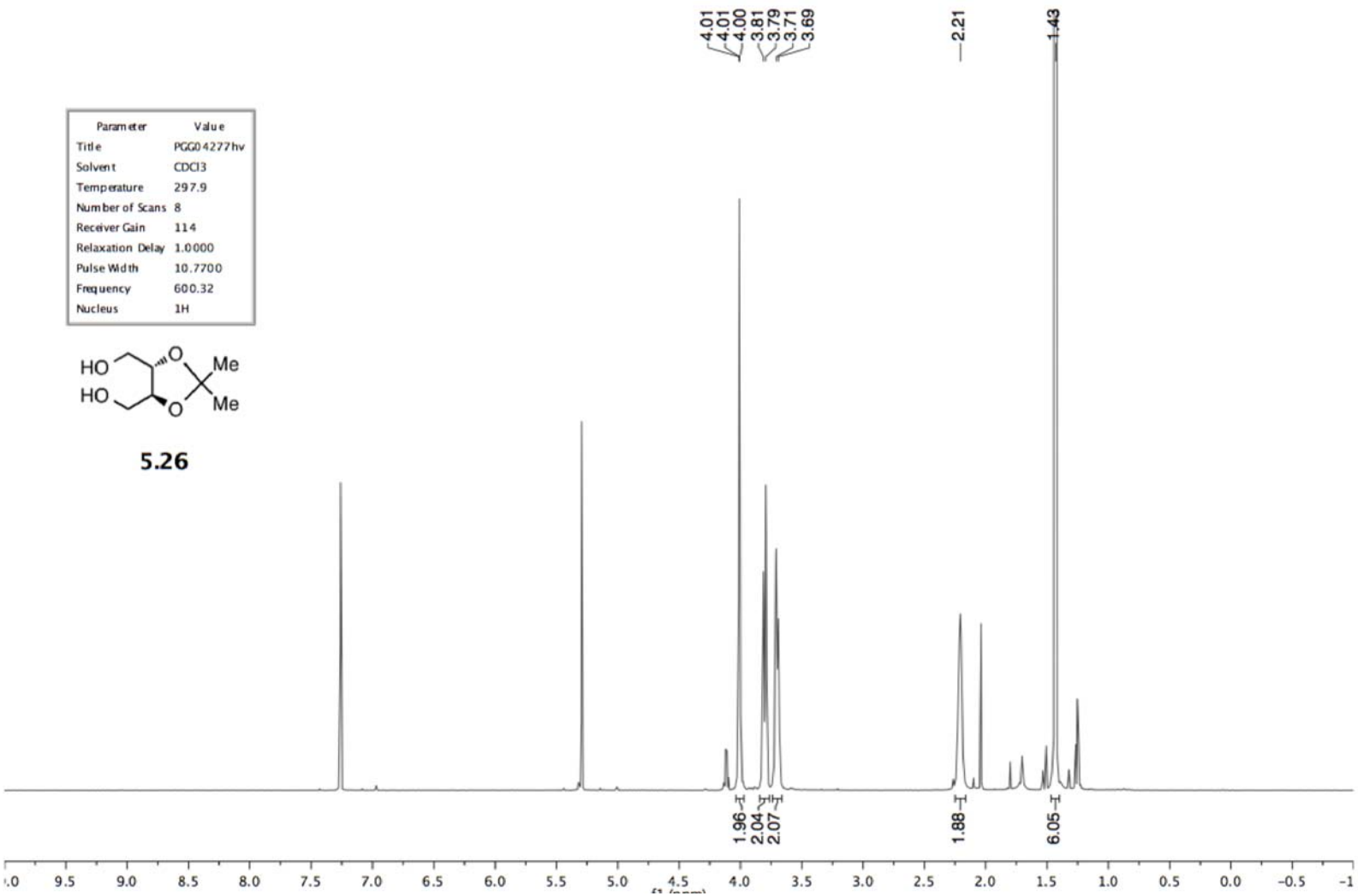

8.00
7.98
7.91
7.89
7.46
7.44
7.37
7.37
7.36
7.35
7.35
7.28
7.27
7.25
7.24
7.24
7.15
7.13
4.25
4.24
4.24
4.23
4.22
4.21
4.06
4.05
4.04
4.04
4.03
4.03
4.02
3.62
3.62
3.61
3.60
3.60
3.56
3.55
2.29
2.28
Parameter Value
Title PGG04076rinsed
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 6
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
OH
OH
5.21
1.88
1.80
1.76
1.89
2.87
1.80
1.98
2.00
4.15
1.88
f1 (ppm)

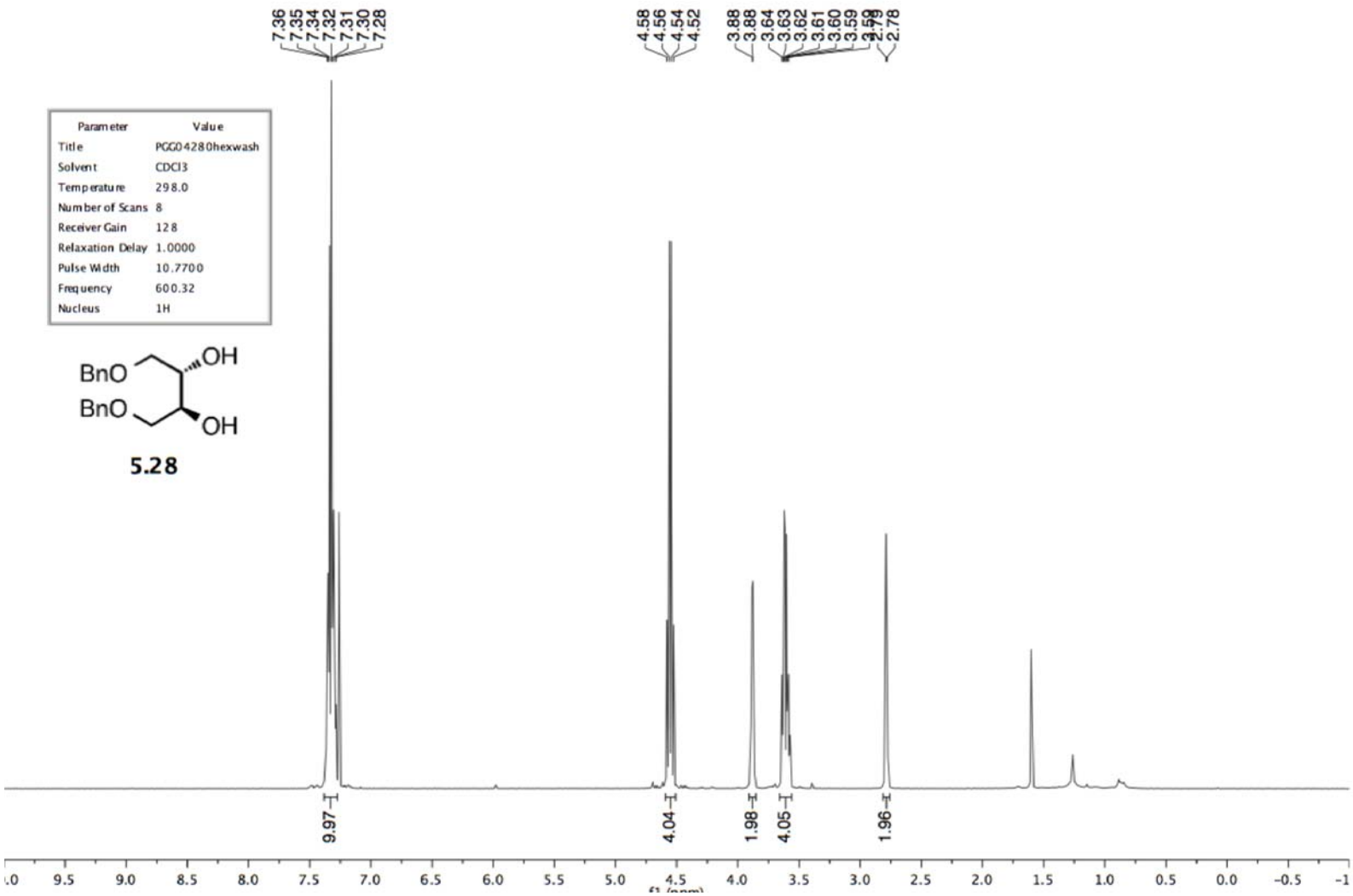

7.98
7.96
7.89
7.87
7.43
7.41
7.37
7.36
7.35
7.25
7.25
7.24
7.23
7.23
7.14
7.13
4.27
4.26
4.25
4.25
4.24
4.23
4.20
4.19
4.19
4.18
4.18
4.16
3.23
3.22
3.21
3.21
Parameter Value
Title PGG0406 5F7-55
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 203
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
O
Br
O
Br
5.22
1.98
1.98
2.01
2.00
2.06
1.97
2.04
2.03
3.93
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1


7.85
7.83
7.54
7.53
7.35
7.34
7.33
7.21
7.20
7.18
7.06
7.05
7.04
7.03
4.11
Parameter Value
Title PGG04072F3-12
Solvent CDCl3
Temperature 300.0
Number of Scans 8
Receiver Gain 90
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
5.23
4.06
3.98
4.06
4.13
8.12
7.65
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

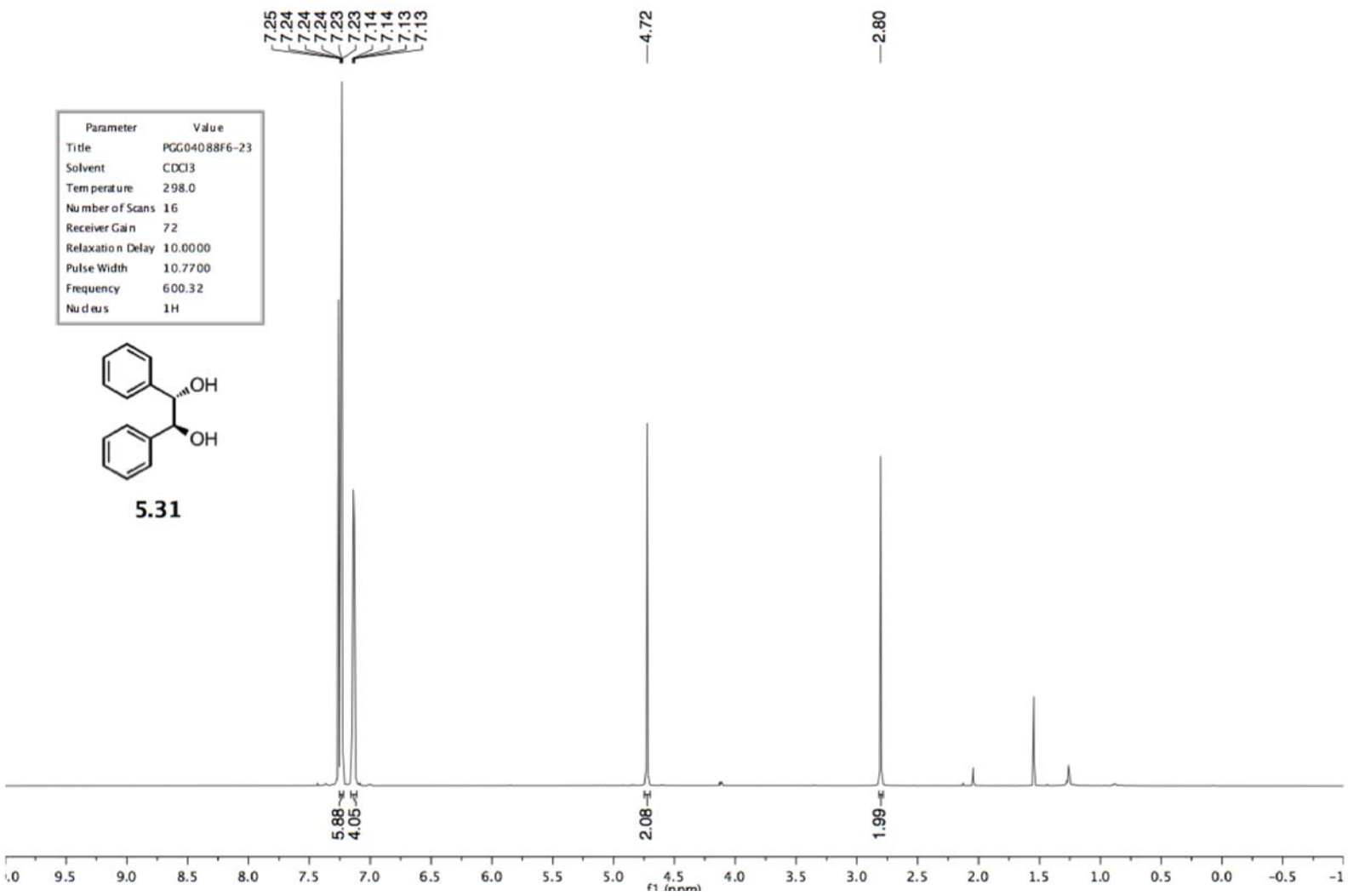
68.94
115.47
119.82
123.59
125.60
126.27
127.95
129.30
129.38
134.02
154.66
Parameter Value
Title PGG040723-12
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
5.23


4.76
4.29
4.28
4.27
4.26
1.50
1.33
1.31
1.30
Parameter Value
Title PGG04276dist
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 114
Relaxation Delay 1.0000
PulseWidth 10.7700
Frequency 600.32
Nucleus 1H
EtO
EtO
O
O
O
O
Me
Me
5.25
1.73
3.92
6.31
6.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

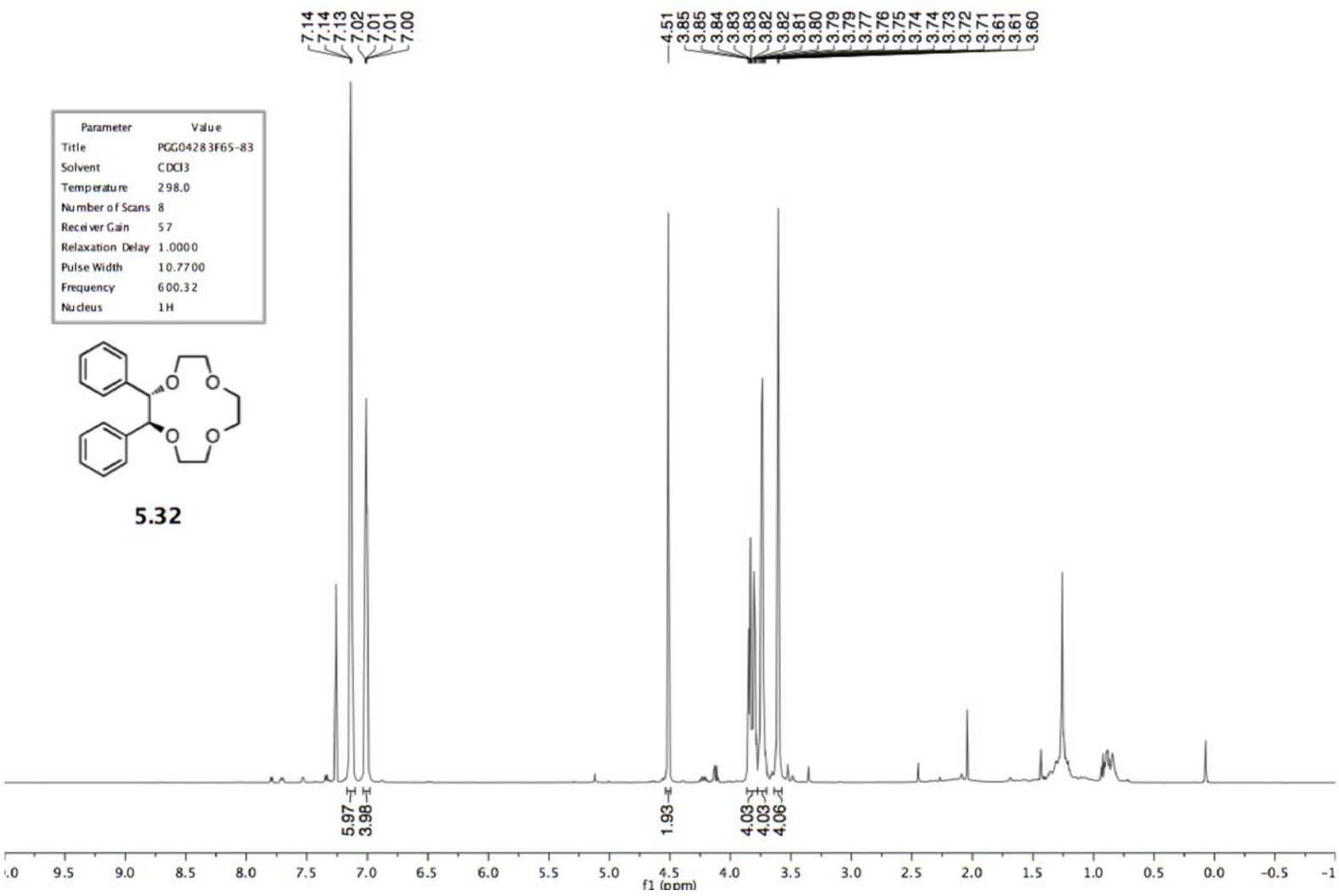

4.01
4.01
4.00
3.81
3.79
3.71
3.69
2.21
1.43
Parameter Value
Title PGG04277hv
Solvent CDCl3
Temperature 297.9
Number of Scans 8
Receiver Gain 114
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
HO
HO
O
O
Me
Me
5.26
1.96
2.04
2.07
1.88
6.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

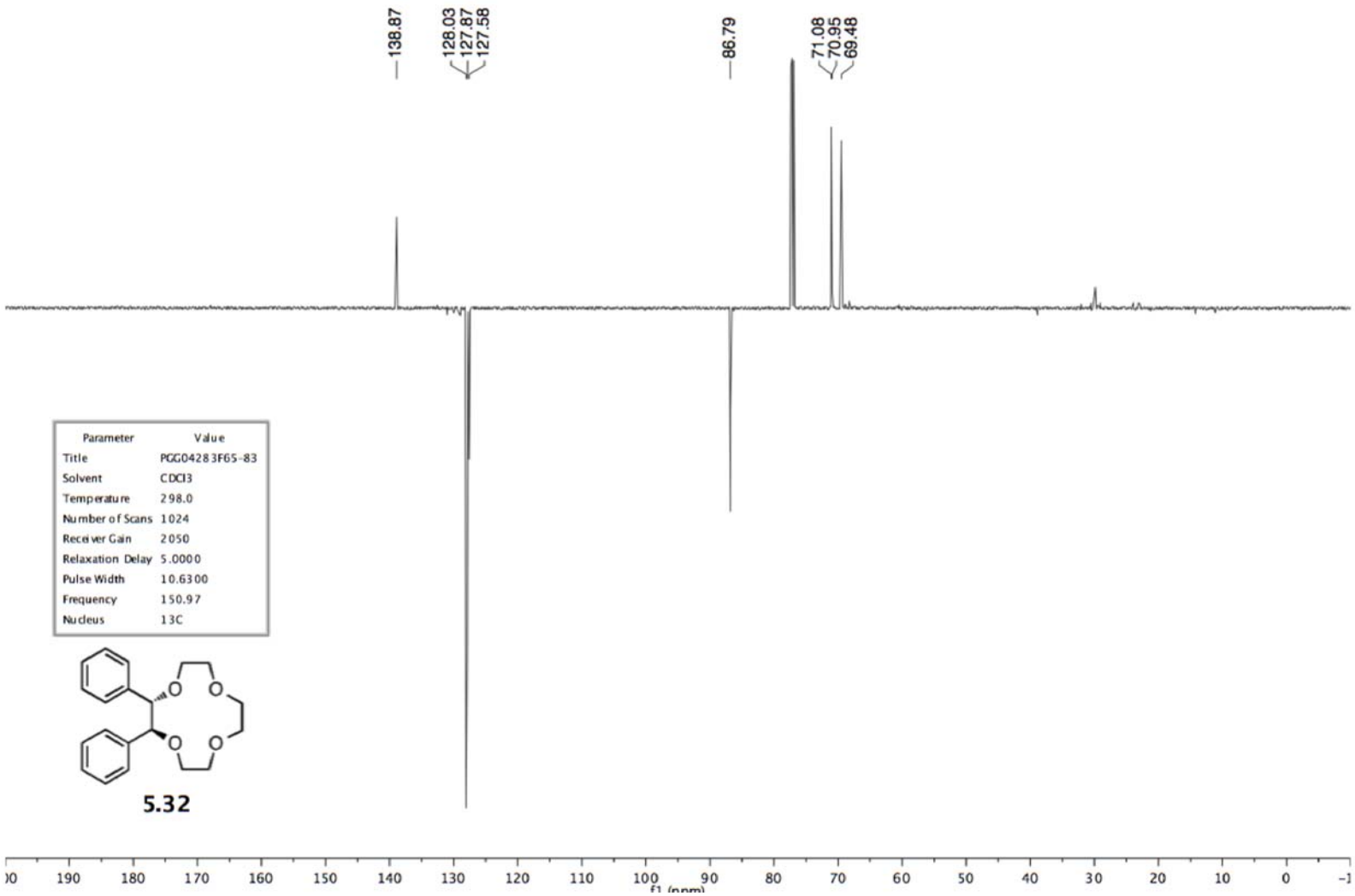

7.36
7.35
7.34
7.32
7.31
7.30
7.28
4.58
4.56
4.54
4.52
3.88
3.88
3.64
3.63
3.62
3.61
3.60
3.59
2.79
2.78
Parameter Value
Title PGG04280hexwash
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 128
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
BnO
BnO
OH
OH
5.28
9.97
4.04
1.98
4.05
1.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

Parameter Value
Title RCG04279
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 203
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
TsO
TsO
5.29
7.80
7.78
7.35
7.33
4.15
4.14
4.13
3.66
3.65
3.65
3.53
2.45
3.83
3.94
3.99
4.01
4.03
6.20


7.25
7.24
7.24
7.24
7.23
7.23
7.14
7.14
7.13
7.13
4.72
2.80
Parameter Value
Title PGG04088F6-23
Solvent CDCl3
Temperature 298.0
Number of Scans 16
Receiver Gain 72
Relaxation Delay 10.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
OH
OH
5.31
5.88
4.05
2.08
1.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

79.27
139.92
128.28
128.09
127.06
Parameter Value
Title PGG040888F6-23
Solvent CDCl3
Temperature 298.2
Number of Scans 1024
Receiver Gain 512
Relaxation Delay 3.0000
Pulse Width 9.2500
Frequency 100.62
Nucleus 13C
OH
OH
5.31

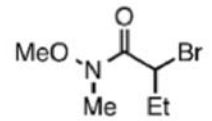

7.14
7.14
7.13
7.02
7.01
7.01
7.00
4.51
3.85
3.85
3.84
3.83
3.83
3.82
3.82
3.81
3.80
3.79
3.79
3.77
3.76
3.75
3.74
3.74
3.73
3.72
3.71
3.61
3.61
3.60
Parameter Value
Title PGG04283F65-83
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
5.32
5.97
3.98
1.93
4.03
4.03
4.06
f1 (ppm)


138.87
128.03
127.87
127.58
86.79
71.08
70.95
69.48
Parameter Value
Title PGG04283F65-83
Solvent CDCl3
Temperature 298.0
Number of Scans 1024
Receiver Gain 2050
Relaxation Delay 5.0000
Pulse Width 10.6300
Frequency 150.97
Nucleus 13C
5.32
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

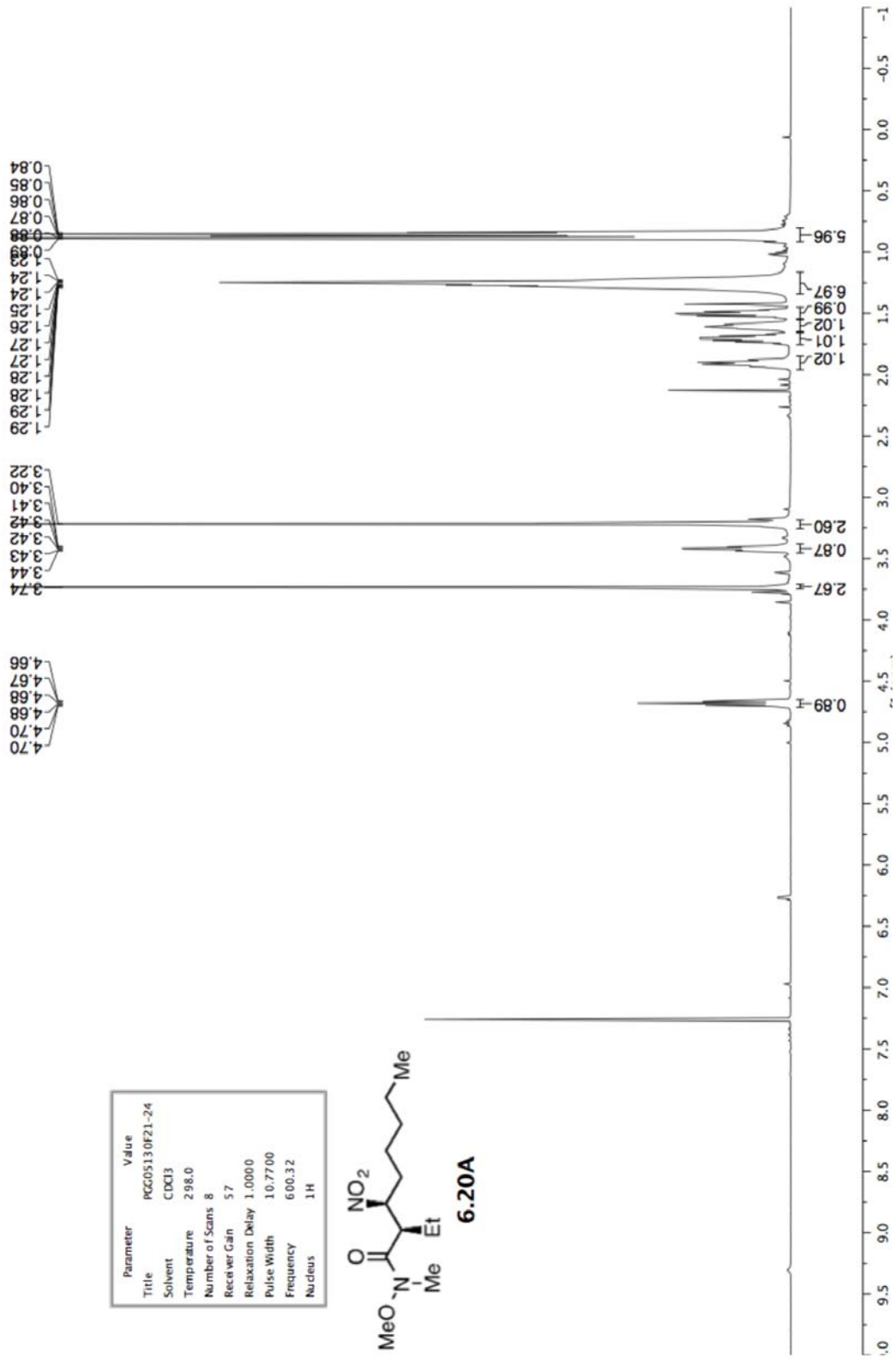
Appendix E

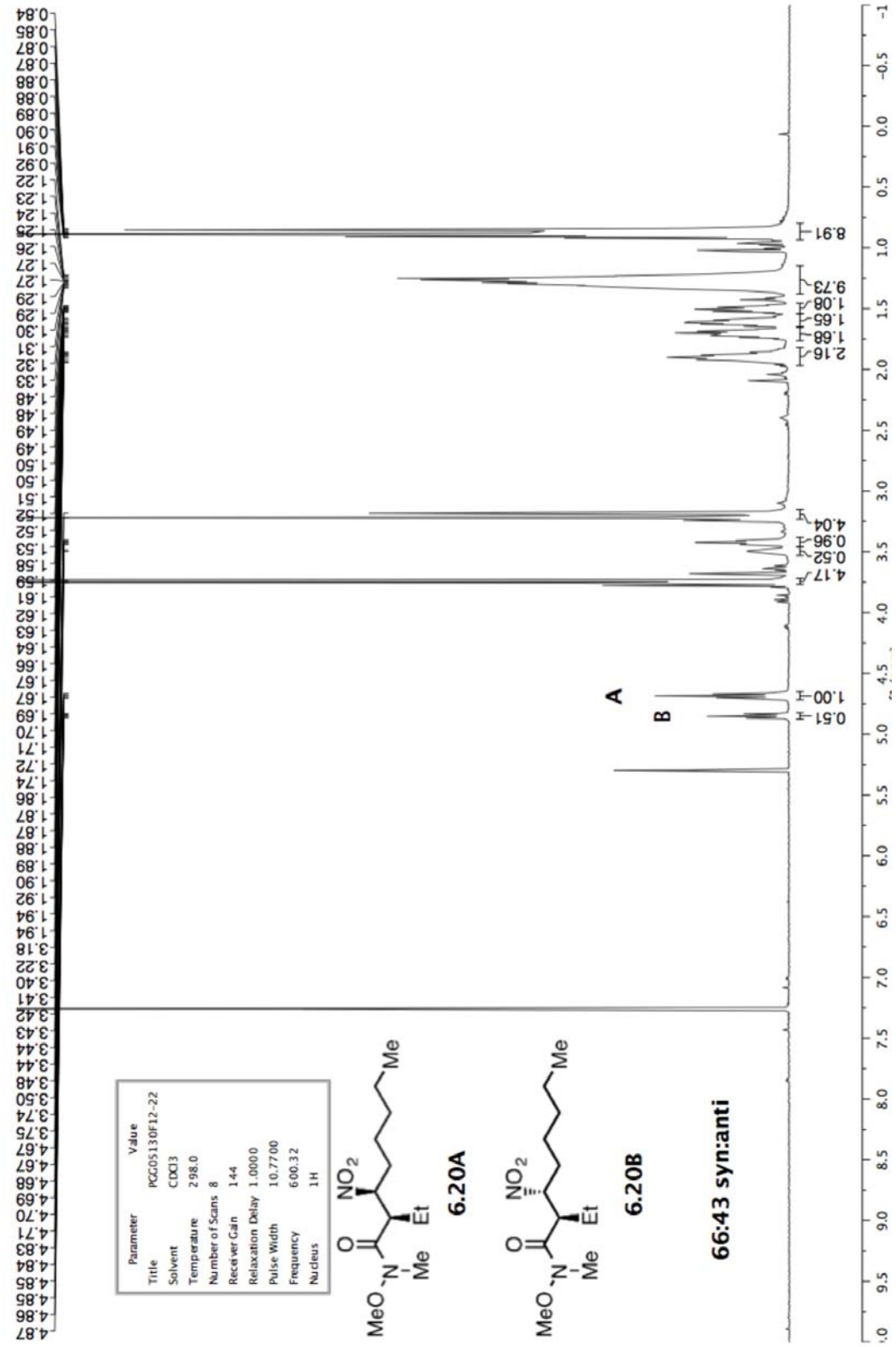
SPECTRAL DATA FOR CHAPTER 6

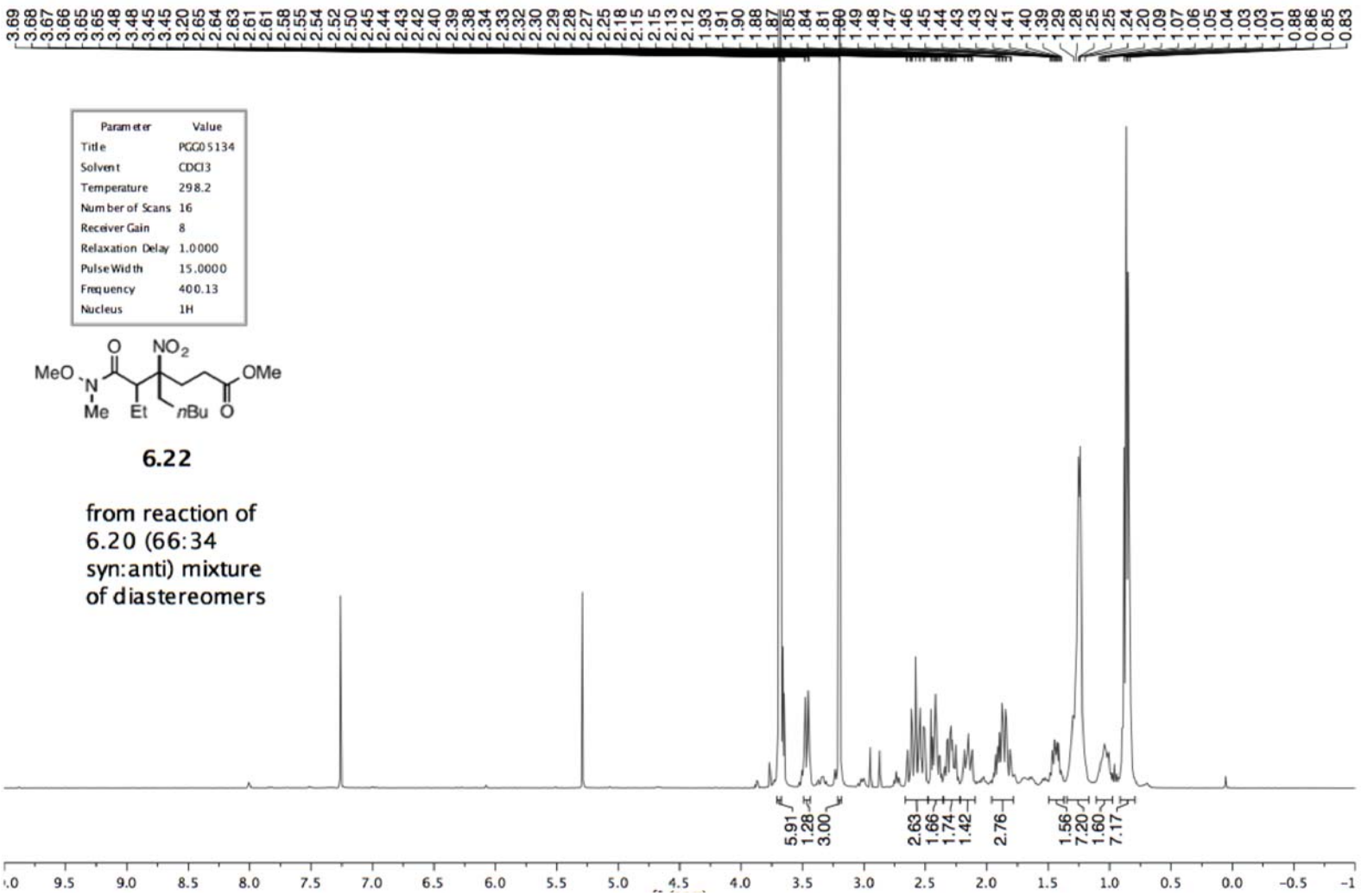
Parameter	Value
Title	PGG05120F4-12
Solvent	CDCl3
Temperature	298.0
Number of Scans	8
Receiver Gain	57
Relaxation Delay	1.0000
Pulse Width	10.7700
Frequency	600.32
Nucleus	1H



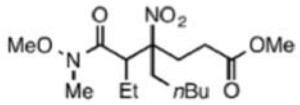
6.19


Parameter Value
Title PGC05130F21-24
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 57
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
6.20A


Parameter Value
Title PGC051130F12-22
Solvent CDCl3
Temperature 298.0
Number of Scans 8
Receiver Gain 144
Relaxation Delay 1.0000
Pulse Width 10.7700
Frequency 600.32
Nucleus 1H
A
B
0.51
1.00
4.17
0.52
0.96
4.04
2.16
1.68
1.65
1.08
9.73
8.91
6.20A
6.20B
66:43 syn:anti


Parameter Value
Title PGG05134
Solvent CDCl3
Temperature 298.2
Number of Scans 16
Receiver Gain 8
Relaxation Delay 1.0000
Pulse Width 15.0000
Frequency 400.13
Nucleus 1H
MeO
N
Me
O
NO2
Et
nBu
O
OMe
6.22
from reaction of 6.20 (66:34 syn:anti) mixture of diastereomers
5.91
1.28
3.00
2.63
1.66
1.74
1.42
2.76
1.56
7.20
1.60
7.17

Parameter	Value
Title	PGG05137
Solvent	CDCl3
Temperature	298.0
Number of Scans	8
Receiver Gain	101
Relaxation Delay	1.0000
Pulse Width	10.7700
Frequency	600.32
Nucleus	1H



6.22

from reaction of 6.20A (syn diastereomer only)

Appendix F

PERMISSION LETTERS