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Three-Component Carbenylative Coupling Reaction Involving Palladium Alkylidene Intermediates

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Organic Chemistry

by

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2015

DEDICATION

To

my parents, family, teachers, and friends

who have great influence on me

as a person, a student, and a friend

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ACKNOWLEDGMENTS

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ABSTRACT OF THE THESIS

Three-Component Carbenylative Coupling Reaction Involving Palladium Alkylidene Intermediates

By

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Master of Science in Organic Chemistry

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Professor David L. Van Vranken, Chair

In Chapter 1, an overview of the literature of palladium-catalyzed carbenylative coupling reaction was reviewed. Palladium alkylidene intermeditates derived from *N*-tosylhydrazones and diazo compounds were used in the carbenylative reactions with facile β-hydride elimination, which erased the stereogenic center formed during carbene insertion. The review also covered palladium-catalyzed carbenylative coupling reaction without β-hydride elimination.

In Chapter 2, a palladium-catalyzed three-component intermolecular carbenylative amination and alkylation reaction of vinyl iodides, *N*-tosylhydrazones and nucleophiles were successfully carried out to yield products resulting from nucleophilic attack on the least hindered side of the η^3-allylpalladium complexes. With the optimized reaction conditions, a variety of *N*-tosylhydrazones and nucleophiles were explored. The reaction works well with cyclic secondary amines and stabilized enolates and moderately with primary amines. A variety of alkyl *N*-tosylhydrazones have been demonstrated to work with the reaction conditions as well. Good yields were obtained under conditions that minimized the palladium-catalyzed ionization of allylic amines and addition of metalated hydrazones to η^3-allylpalladium complexes.

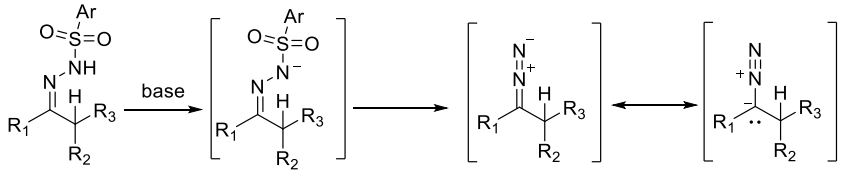
In Chapter 3, vinyl iodides, carbon or nitrogen based nucleophiles and trimethylsilyldiazomethane (TMSD) were utilized to form vinylsilanes via palladium-catalyzed carbenylative cross-coupling reactions. These vinylsilanes were then subjected to iododesilylation conditions to generate new vinyl iodides capable of undergoing a second palladium-catalyzed cross-coupling reaction. This two-step process could be used iteratively to form new C–C and C–N bonds that quickly increased molecular complexity.

Chapter 1. Carbenylative Coupling Involving Palladium Alkylidene Intermediates

1.1. Alkylidene precursors for palladium-catalyzed carbenylative coupling reaction

A wide variety of transformations proceed via palladium carbene intermediates.[1] Diazo compounds are common precursors to carbene ligands. Diazo compounds are stabilized anions and are usually stabilized by π acceptor groups such as carbonyls and aromatics. Carbene ligands are electron-deficient and are most stabilized by lone pair or π donor groups. Carbene ligands with simple alkyl substituents, referred to here as alkylidenes, are among the most interesting participants in palladium-catalyzed reactions. There are two common types of alkylidene precursors used in palladium-catalyzed insertion reactions: diazoalkanes and alkyl *N*-sulfonylhydrazones. Unstabilized diazoalkanes are dangerous because of their toxicity and explosive tendency as many incidents have been reported.[2] As a result, alkyl *N*-sulfonylhydrazones are preferred as carbene precursors because they are safer to work with and react *in situ* to form a reactive diazo intermediate. In the presence of a base, alkyl *N*-sulfonylhydrazones decompose to generate the corresponding diazo compounds through the Bamford-Stevens reaction (Scheme 1-1).[3]

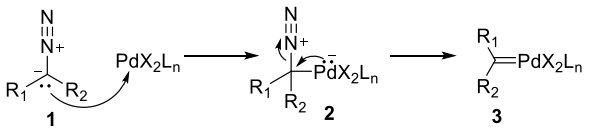
Scheme 1-1. Generation of Diazo Compounds from *N*-Sulfonylhydrazones through the Bamford-Stevens Reaction.



Regardless of how the diazoalkane is formed, it is assumed that the diazoalkane adds to palladium(II), in this case, to give a zwitterionic palladate **2**, which is followed by expulsion of nitrogen gas to afford the palladium alkylidene intermediate **3** (Scheme 1-2). This intermediate can then participate in a variety of useful synthetic reactions. In addition to diazo compounds and

N-sulfonylhydrazones, there are several other less common sources of carbene precursors for palladium reactions such as tethered alkynes,[4] diazirines,[5] Fischer carbenes,[6] and chloroform.[7]

Scheme 1-2. Formation of Palladium(II) Alkylidenes from Diazoalkane



1.2. Carbenylative coupling processes involving β-hydride elimination

1.2.1. β-Hydride elimination in carbenylative coupling processes involving alkylidene precursors

Historically, palladium alkylidene intermediates were used in cyclopropanation.[8] More recently, palladium(II) alkylidenes have been exploited in carbenylative coupling processes involving alkylidene precursors and aryl halides or their equivalents. When the alkylidene ligands have hydrogens adjacent to the carbene center, the carbene center usually ends up as a sp^2 center due to rapid β-hydride elimination.

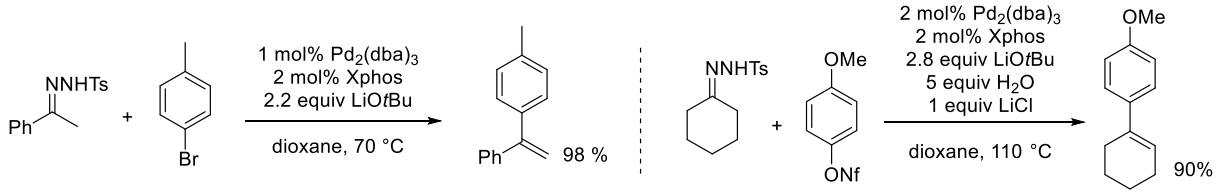
1.2.1.1. Carbenylative coupling processes with elimination involving ketone *N*-tosylhydrazones

1.2.1.1.1. Carbenylative coupling processes involving ketone hydrazones and ArPdX derived from halides or pseudohalides

N-Tosylhydrazones were first used to generate diazo compounds in situ in a rhodium-catalyzed reaction by Aggarwal and co-workers.[9] Later, Barluenga and co-workers demonstrated that *N*-tosylhydrazones were also suitable in palladium-catalyzed carbenylative coupling reactions (Scheme 1-3).[10] Aryl alkyl ketone *N*-tosylhydrazones have been widely used in carbenylative coupling reactions because they are easily accessed from their corresponding ketone starting materials. The scope of alkylidenes was previously limited by the stability of

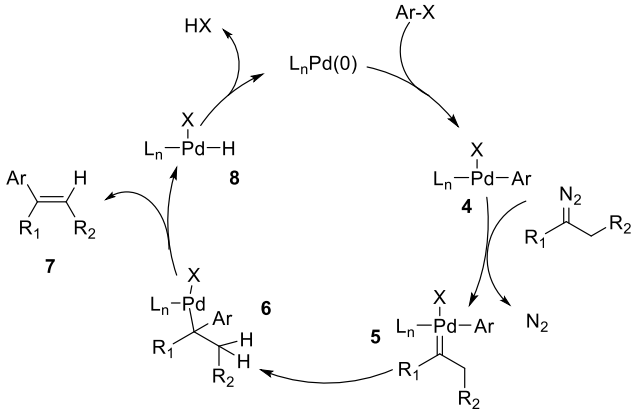
diazo precursors; however, the use of *N*-tosylhydrazones greatly increased the scope of alkylidene groups. Many groups have adopted *N*-tosylhydrazones in carbenylative coupling reactions. These reactions work with aryl halides[11] and pseudohalides such as nonaflates[12] as well as alkenyl pseudohalides such as alkenyl tosylates.[13]

Scheme 1-3. Representative Examples of Palladium-Catalyzed Carbenylative Coupling Reaction of Ketone *N*-Tosylhydrazones and Aryl Halides/Pseudohalides.



The proposed reaction mechanism of this carbenylative coupling reaction is shown in Scheme 1-4. Aryl halide undergoes oxidative addition to palladium to generate arylpalladium halide intermediate **4**. The diazo compound is generated in situ from *N*-tosylhydrazone and then adds to palladium to form arylpalladium alkylidene intermediate **5**. Migratory insertion of the

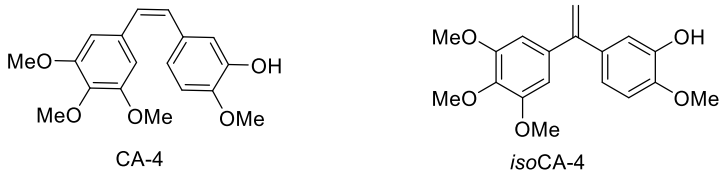
Scheme 1-4. Proposed Mechanism of Palladium(II)-Catalyzed Carbenylative Coupling Reaction.



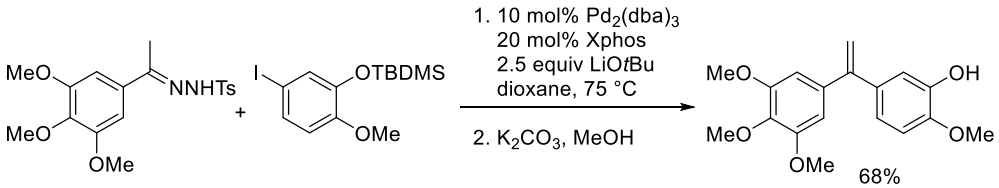
aryl group to the alkylidene ligand generates alkylpalladium intermediate **6**, which undergoes β-hydride elimination to yield alkene product **7**. Palladium(0) is regenerated by reductive elimination of HX from palladium(II) hydride intermediate **8**.

Palladium-catalyzed carbenylative coupling reactions with ketone *N*-sulfonylhydrazones has proved to be a valuable transformation in medicinal chemistry. This process has been used in the synthesis of combrestatin A-4 (CA-4) and its analogs. Combretastatin A-4, a *Z*-stilbene extracted by Petit and co-workers from an African tree, *Combretum caffrum*, is a potent cytotoxic agent to a variety of cancer cells.[14] It is the most studied example of vascular disrupting agents that binds on β-tubulin at the colchicine binding site.[15] Despite its potency, CA-4 can easily isomerize into its inactive (*E*)-isomer over time reducing its potency. Derivatives of CA-4, which contain a 1,1-diarylethylene motif, include *iso*combretastatin A-4 (*iso*CA-4), *iso*NH_2CA-4, *iso*FCA-4. These derivatives have shown nanomolar level of cytotoxicity against various cancer cell lines. The 1,1-diarylethylene motif can be synthesized by using carbenylative coupling reactions between *N*-tosylhydrazones and aryl halides, or their equivalents, using catalytic palladium.[16] The reaction also allows for a quick synthesis of analogues by changing either coupling partner: aryl halides or *N*-tosylhydrazone.

Scheme 1-5. Structures of Combretastatin A-4 (CA-4) and *iso*Combretastatin A-4 (*iso*CA-4)



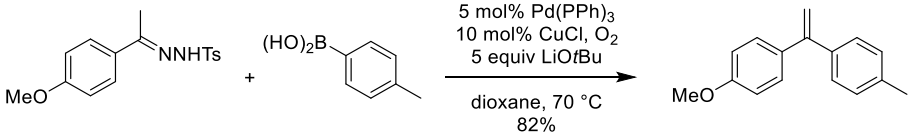
Scheme 1-6. Synthesis of isoCA-4 by Carbenylative Coupling Reaction of Aryl Halide and *N*-Tosylhydrazone.



1.2.1.1.2. Carbenylative Coupling Processes Involving Ketone *N*-Tosylhydrazones and ArPdX Derived from Nucleophiles and Oxidants

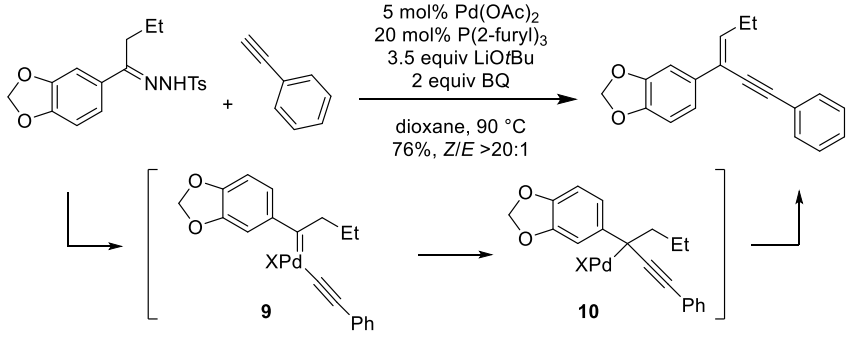
Carbene precursors—such as *N*-tosylhydrazones or diazo compounds—can react with nucleophiles such as boronic acids[17] or indole[18] under oxidative conditions (Scheme 1-7) in the presence of palladium catalysts. The mechanism for the oxidative carbenylative coupling reaction is similar to the one shown in Scheme 1-4 except that the palladium(II) alkylidene intermediates were accessed by oxidation of palladium(0) by various oxidants such as molecular oxygen,[17b,d,18a] benzoquinone,[17a,c] or iodobenzene.[18b,c]

Scheme 1-7. Palladium-Catalyzed Carbenylative Coupling of *N*-Tosylhydrazone and Boronic Acid



Terminal alkynes were used in palladium-catalyzed Sonogashira cross-coupling reactions to introduce alkynyl groups to organic molecules. Under oxidative conditions, terminal alkynes can be used in a palladium-catalyzed carbenylative coupling reaction (Scheme 1-8). A weak electron-rich ligand such as tris-(2-furyl)phosphine was used to promote the formation of the alkynylpalladium(II) alkylidene intermediate **9**.[19] The reaction works well with a wide variety of both *N*-tosylhydrazones and terminal alkyne substrates. *N*-Tosylhydrazones with both electron-donating and electron-withdrawing groups on the aromatic ring gave good yields. Terminal alkynes with aliphatic, aromatic, and heteroaryl group substituents were shown to be suitable substrates. Conjugated enynes were also obtained with high stereoselectivity (*Z*/*E* >20:1) (Scheme 1-8).

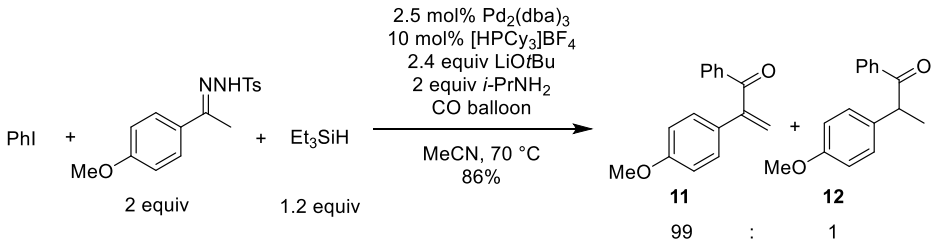
Scheme 1-8. Palladium-Catalyzed Oxidative Carbenylative Coupling of *N*-Tosylhydrazone and Terminal Alkyne



1.2.1.1.3. Carbenylative Coupling Processes Involving Ketone *N*-Tosylhydrazones and ArPdX Derived from Tandem Reactions to Access ArPdX or ArCOPdX Intermediates

N-Tosylhydrazones can also participate in a tandem carbonylative cross-coupling reaction as demonstrated by Wang and co-workers.[20] Under a carbon monoxide (CO) atmosphere, the aryl group on the palladium intermediate migrates to a carbon monoxide ligand, forming a benzoyl group. The benzoyl group then migrates to the alkylidene group on palladium to form alkylpalladium complex. Subsequent β-hydride elimination results in the formation of alkene product (Scheme 1-9). The choice of palladium pre-catalyst greatly affected the yield and ratio of products **11** and **12**.

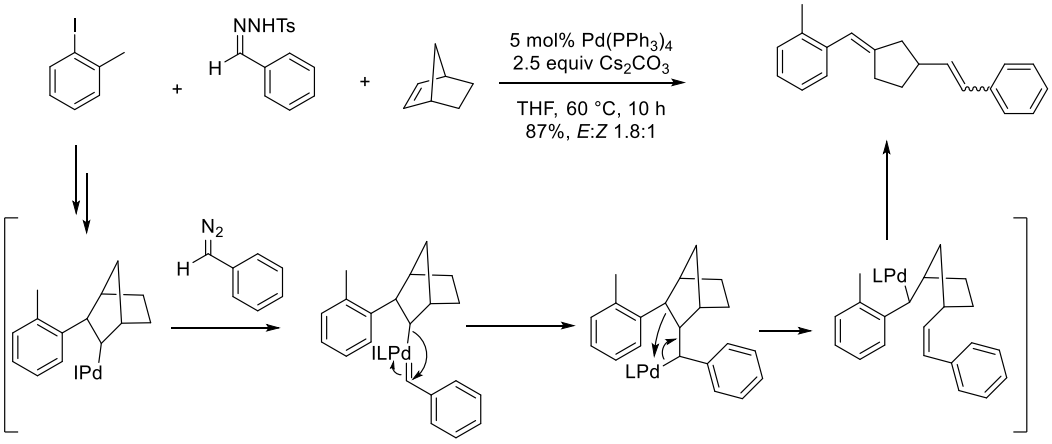
Scheme 1-9. Palladium-Catalyzed Carbenylative Coupling of *N*-Tosylhydrazone, Aryl Halide and CO.



N-Tosylhydrazones can also participate in multi-step domino reactions with aryl halides and norbornene resulting in ring-opening of norbornene to form methylenecyclopentane

derivatives.[21] The reaction worked with a wide range of aryl iodides and aryl aldehyde *N*-tosylhydrazones. Substrates with electron-donating groups on aryl iodides gave moderate to high yields, while electron-withdrawing groups greatly lowered the yield. The reaction was also highly chemoselective. Bromide and chloride substituents were left intact under the reaction conditions. This transformation involved carbopalladation of norbornene, followed by carbene migratory insertion, C–C bond cleavage and β-hydride elimination (Scheme 1-10).

Scheme 1-10. Tandem Carbenylative Reaction involving Ring-Opening of Norbornene for Methylenecyclopentane.

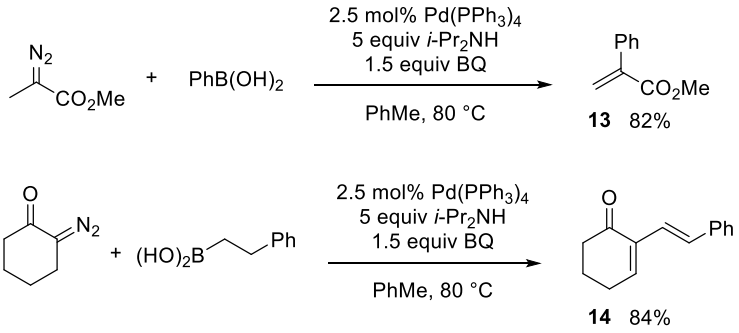


1.2.1.2. Carbenylative Coupling Processes with Elimination Involving Diazo Compounds

Relative to *N*-tosylhydrazones, few diazo compounds have been used in carbenylative coupling reactions because of their lack of stability. Wang and Peng reported the first example of palladium-catalyzed carbenylative reaction of α-diazocarbonyl compounds with arylboronic acids to access to α-aryl substituted α,β-unsaturated carbonyl compounds (**13**) (Scheme 1-11).[17a] The reaction was greatly affected by the electronic properties of the boronic acids. The electron-donating groups favored product formation, while electron-withdrawing groups lower the yield. Vinylboronic acids were also found to be compatible with the reaction conditions to generate 1,3-diene compounds (**14**) from cyclic α-diazocarbonyls.[17c] The reaction featured a wide scope,

tolerating a variety of vinylboronic acids and cyclic α-diazocarbonyls. α-Aryl vinylboronic acids and diazo compounds containing five-membered rings did not work.

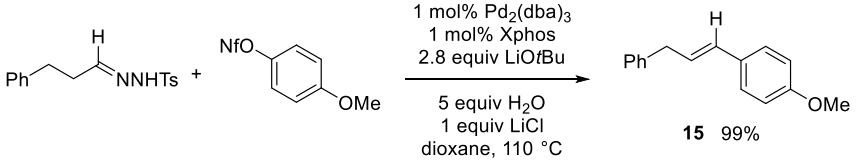
Scheme 1-11. Palladium-Catalyzed Carbenylative Coupling of α-Diazocarbonyl and Boronic Acids.



1.2.1.3. Carbenylative Coupling Processes with Elimination Involving Aldehyde *N*-Tosylhydrazones

In contrast with ketone *N*-tosylhydrazones, which have been widely used in palladium-catalyzed carbenylative coupling reactions, there is only a few examples of using aldehyde *N*-tosylhydrazones.[22] Barluenga and co-workers reported the carbenylative coupling between aldehyde *N*-tosylhydrazones and aryl nonaflates to afford elimination product **15** in excellent yield (Scheme 1-12). Aldehyde *N*-tosylhydrazones can couple with aryl halides and pseudohalides and gave similar yields as with ketone *N*-tosylhydrazones.

Scheme 1-12. Palladium-Catalyzed Carbenylative Coupling of Aldedhyde *N*-Tosylhydrazone and Aryl Nonaflates.

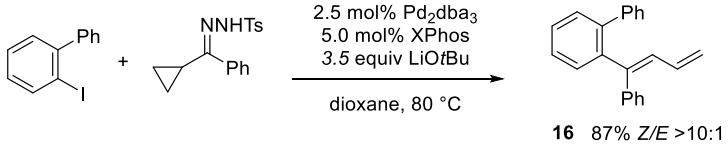


1.2.1.4. Carbenylative Coupling Processes with Cyclopropyl Ketone *N*-Tosylhydrazones

When both a cyclopropyl group and hydrogen are at the beta position on the alkylpalladium intermediate, β-hydride elimination is slower than β-alkyl elimination of a

strained carbon-carbon bond, which results in the formation of 1,3-butadiene **16**. The formation of 1,3-butadiene through carbenylative coupling was reported by Wang and Yu, respectively (Scheme 1-13).[23] Wang and co-workers had reported that when the cyclopropyl group came from either *N*-tosylhydrazones or cyclopropyl halides, the 1,3-diene product was still obtained from the carbenylative coupling reaction. The reaction conditions yield high *Z*/*E* selectivity depending on the steric bulk on the aryl halides.

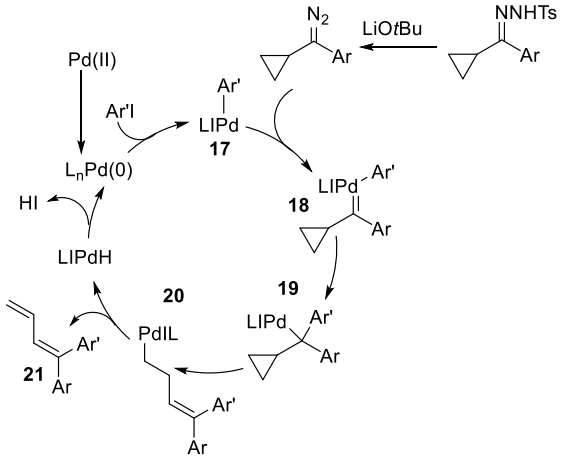
Scheme 1-13. Formation of 1,3-Diene from Aryl Halide and *N*-Tosylhydrazone with Adjacent Cyclopropyl Group.



16 87% *Z*/*E* >10:1

The mechanism for formation of 1,3-dienes is proposed in Scheme 1-14. Aryl iodide undergoes oxidative addition to form arylpalladium complex **17**. Then, the diazo compound adds to palladium to form cyclopropylcarbenylpalladium intermediate **18**, which undergoes migratory insertion to form cyclopropylcarbinylpalladium intermediate **19**. β-Alkyl elimination outcompetes β-hydride elimination to form homoallylpalladium intermediate **20**. β-Hydride elimination results in the formation of 1,3-diene product **21**. The palladium(II) complex undergoes reductive elimination to regenerate palladium(0).

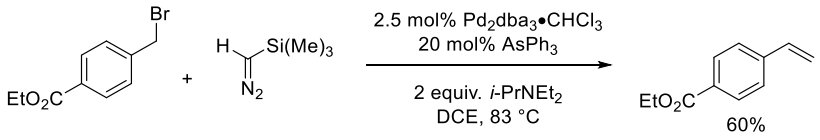
Scheme 1-14. The Proposed Catalytic Cycle of Carbenylative Coupling of Aryl Halide and *N*-Tosylhydrazone with Adjacent Cyclopropyl Group.



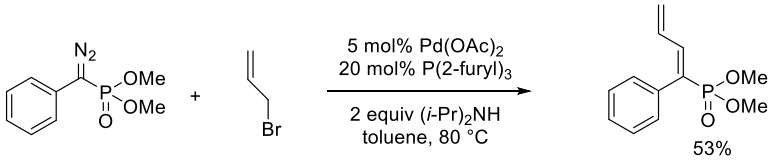
1.2.2. Carbenylative Coupling Processes with β-Hydride Elimination toward the Alkyl Halides

Benzyl and allyl halides had been used as electrophiles in palladium-catalyzed reactions.[24] Benzyl and allyl halides also have been shown to be compatible in carbenylative coupling reactions. In these reactions, β-hydride elimination can also occur on the electrophile when there is no hydrogen adjacent to the alkylidene carbon. The first practical carbenylative coupling of this type was reported by Van Vranken and co-workers using (trimethylsilyl)diazomethane ($TMSCHN_2$), benzyl halides and catalytic palladium to synthesize styrene derivatives (Scheme 1-15).[25] Triphenylarsine was used instead of triphenylphosphine ligand to prevent the phosphine from attacking benzyl bromide.[26] In similar reaction conditions with allyl halides, using tris-(2-furyl)phoshine ligand also led to improved yields compared to triphenylphosphine ligand (Scheme 1-16).[27]

Scheme 1-15. Formation of Styrene Derivatives Using Benzyl Halide and Diazo Compound.



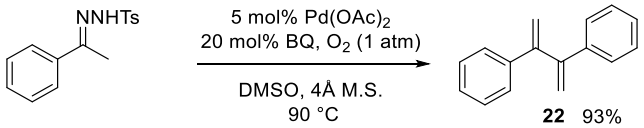
Scheme 1-16. Formation of 1,3-Diene Using Allyl Halide and Diazo Compound.

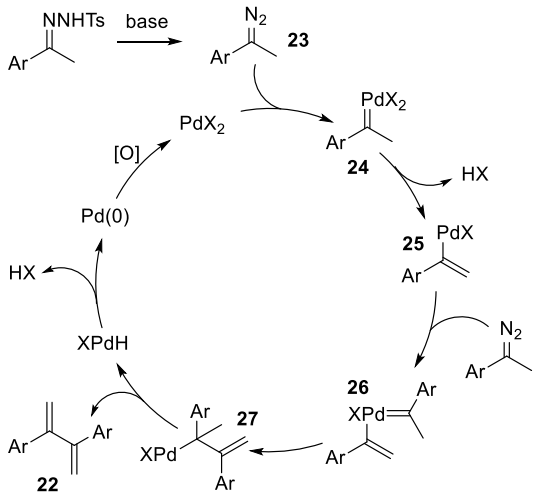


1.3. Carbenylative Homo-Coupling Processes involving β-Hydride Elimination

N-Tosylhydrazones can undergo homo-coupling reaction under oxidative conditions (Scheme 1-17).[28,29] Substrates with electron-donating groups afford 2,3-diaryl-1,3-diene in high yields, while substrates with electron-withdrawing groups gave slightly lower yields. The reaction proceeds with high chemoselectivity as halide substituents were intact under reaction conditions. A plausible mechanism for the formation of homo-coupling product is proposed in Scheme 1-17. *N*-Tosylhydrazone undergoes the Bamford-Stevens reaction to generate diazo compound **23** that react with palladium to form palladium(II) carbene intermediate **24**. The authors propose that the alkylidene ligand undergoes loss of an alpha proton to form vinylpalladium intermediate **25**, which reacts with another diazo compound **23** to form vinylpalladium alkylidene complex **26**. Migratory insertion of the vinyl group to the carbene generates η^1-allylpalladium intermediate **27**. The diene product **22** is formed by β-hydride elimination. Palladium(0) is then oxidized by benzoquinone and oxygen to regenerate palladium(II) in the reaction.

Scheme 1-17. Proposed Catalytic Cycle for Homo-Coupling Product Formation of Aryl *N*-Tosylhydrazones.



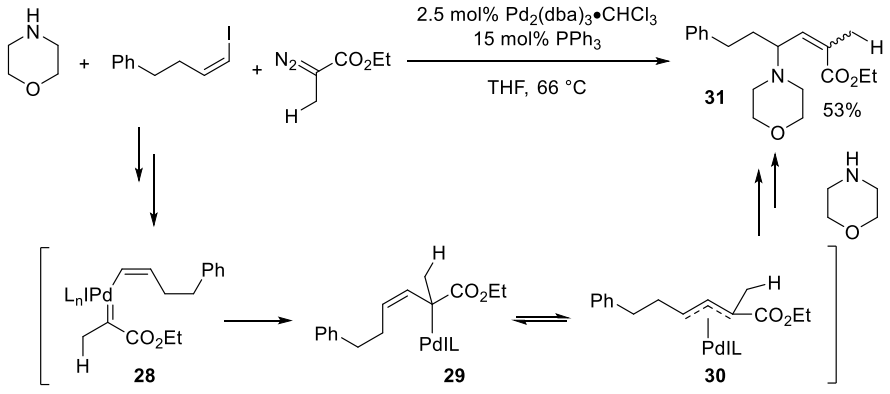


1.4. Carbenylative Coupling Processes without Elimination

1.4.1. π-Allyl/Oxa-Allyl formation prior to β-hydride elimination

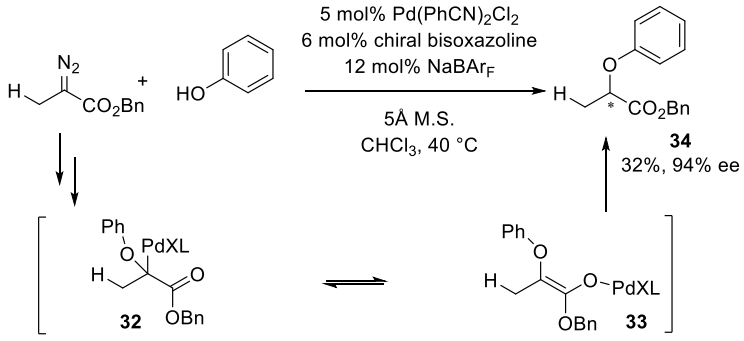
A few reports had demonstrated that β-hydride elimination can be avoided by interrupting the elimination with other processes. One way to prevent β-hydride elimination is to form π-allyl intermediate. Van Vranken and co-workers showed that palladium-catalyzed reactions with vinyl iodide and diazo compound form η^1- allylpalladium intermediate **28**, which isomerize to η^3-allylpalladium intermediates **30**.[30] Then the η^3-allylpalladium intermediate can be trapped by a nucleophile to form allyl amine **31** without β-hydride elimination (Scheme 1-18).

Scheme 1-18. π-Allyl Formation Prevents β-Hydride Elimination.



Similarly, oxa-allyl transition has been shown to outcompete β-hydride elimination as shown by Zhou and co-workers (Scheme 1-19).[31,17a] In this example, the phenoxide group on palladium migrates to the alkylidene group to form a *C*-palladium enolate **32**, which can isomerize into *O*-palladium enolate **33**. Chiral ligands led to enantioselective protonation of the enolate to generate chiral α-aryl-α-aryloxyacetate product **33** without β-hydride elimination.

Scheme 1-19. Oxa-Allyl Transition Prevents β-Hydride Elimination.

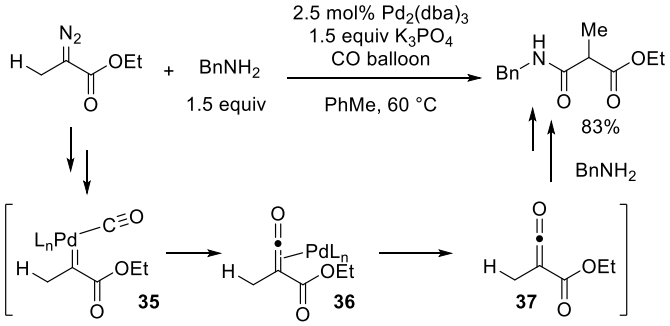


1.4.2. Ketene/Ketenamine Formation Prevent β-Hydride Elimination

Palladium-catalyzed carbonylation is a powerful method to construct molecules containing carbonyl groups. Typically, CO insertion into Pd–C bond generates acyl-palladium intermediates; however, CO insertion into palladium alkylidene results in formation of ketene that is a useful intermediate in synthetic applications such as benzannulation reactions (Dötz reaction)[32] and [2+2] cycloaddition reactions of ketene–imine substrates.[33] In 2011, Wang and co-workers reported carbonylation of diazo compounds affording reactive ketene intermediates in high yield.[34] In contrast with existing reaction conditions,[35] which require high pressure of carbon monoxide and high reaction temperatures, the reaction occurs at moderate temperature and atmospheric CO (Scheme 1-20). The reaction works with a variety of diazo compounds as well as *N*-tosylhydrazones, which greatly expand the substrate scope of the reaction. Mechanistically, carbon monoxide ligand bound palladium intermediate **35** migrates over the

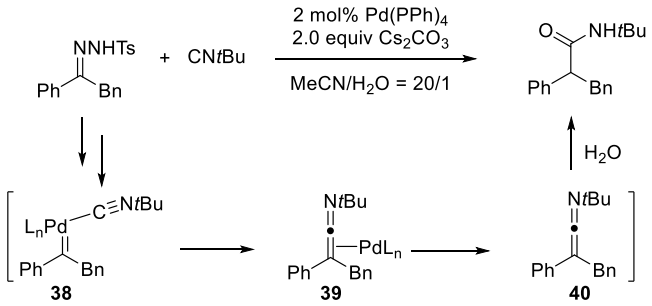
alkylidene ligand to generate ketene intermediate **37**. The ketene intermediates is then trapped by a variety of nucleophiles such as primary and secondary amines as well as phenol and primary alcohols. Nucleophilic trapping outcompetes β- hydride elimination.

Scheme 1-20. Ketene Formation in the Coupling Reaction Prevents β-Hydride Elimination.



Isocyanide is isoelectronic to carbon monoxide and can undergo a similar transformation to generate a ketenimine intermediate.[36] When there are hydrogens next to the carbene center, isocyanide insertion is much more favorable than β-hydride elimination (Scheme 1-21). The ketenimine intermediates react with water to generate amides as the products. The reaction can tolerate a variety of *N*-tosylhydrazones derived from aryl aldehyde and ketones. When the aryl aldehydes have electron-donating groups such as methyl or methoxide, high yields were achieved. However, electron-withdrawing groups gave moderate yields. The authors speculate that the palladium-carbene intermediate is destabilized by the electron-withdrawing groups on the aryl ring. Alkyl ketones give moderate yields, while alkyl aldehydes yielded small amount of products.

Scheme 1-21. Ketenamine Formation Prevents β-Hydride Elimination.



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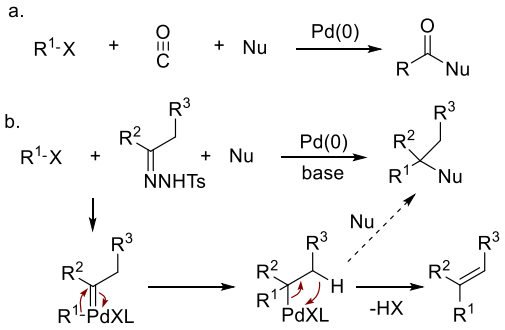
Chapter 2. Intermolecular Carbenylative Amination and Alkylation involving Palladium Alkylidene Intermediates

2.1. Introduction

Palladium-catalyzed reactions have been widely utilized as indispensable tools in organic synthesis.[1] Palladium-catalyzed carbonylation and carbopalladation insertion processes have been robust and reliable methods to generate new bonds. Palladium-catalyzed carbenylative insertion processes are gaining increasing attention because they are analogous to carbonylation insertion processes. Palladium-catalyzed carbenylative insertion reactions are a powerful method for joining molecular fragments through one-carbon units and building molecular complexity. Diazo compounds have been widely used as the major sources of carbene precursors, but *N*-tosylhydrazone anions have been used to expand the scope of carbene precursors to include benzylidene and alkylidene derivatives.[2] Palladium-catalyzed carbene insertion processes usually involve RPdX intermediates usually derived from oxidative addition of aryl

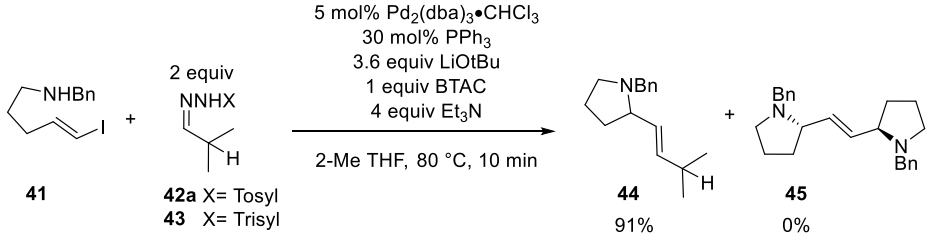
Scheme 2-1. β-Hydride Elimination Outcompetes Nucleophilic Trapping



halides/pseudohalides,[3] benzylic and allylic halides.[4] Additionally, RPdX intermediates can also be obtained from addition of nucleophiles to palladium(II).[5] Migratory insertion of the R ligand to the carbene center is usually followed by β-hydride elimination, which is much more facile than nucleophilic trapping. This elimination erases any stereochemical information created in the carbene insertion step (Scheme 2-1b).

In this work, a palladium-catalyzed carbenylative coupling reaction of alkyl *N*-tosylhydrazones, vinyl iodides, and nucleophiles was demonstrated to proceed without β-hydride elimination by going through an η^1-to η^3-allyl transition. In an initial stage of this work, an intramolecular carbenylative amination reaction was investigated by my co-worker, Udara Premachandra.[6] The carbenylative insertion reaction of ω-aminovinyl iodide **41** and isobutyraldehyde *N*-tosylhydrazone **42a** was carried out using published conditions used in previous work on the carbenylative amination of benzaldehyde *N*-tosylhydrazones.[7] The only product isolated from the reaction was known dimer **45** (31%) and a large amount of unreacted vinyl iodide **41** (68%) was recovered (Scheme 2-2). The low solubility of lithiated *N*-tosylhydrazone was responsible for its failure to generate diazo fast enough for it to engage in the reaction. When *N*-trisylhydrazone **43** was employed as the alkylidene precursor, the lithiated *N*-trisylhydrazone exhibited better solubility allowing generation of the diazo compound at a rate which it can react in the palladium-catalyzed reaction. After optimizing various additives like amines and solubilizing agents (water and quaternary ammonium salts), the reaction yielded pyrrolidine product **44** in 91%.

Scheme 2-2. Intramolecular Carbenylative Amination with Alkylidene Precursors **42a** and **43**

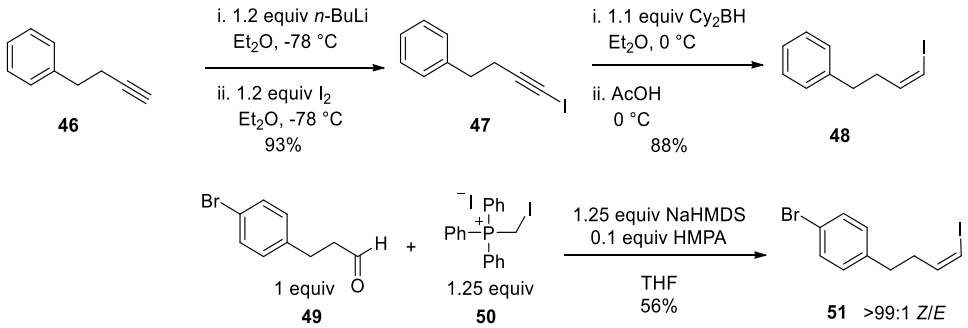


2.2. Results and Discussion

2.2.1. Synthesis of Vinyl Iodides

Using the optimized reaction conditions for the intramolecular carbenylative amination reaction, I set out to investigate a three-component intermolecular carbenylative reaction. First, vinyl iodides were synthesized by following known procedures from the literature.[7,8] *Z*-Vinyl iodide **48** was synthesized in two steps from alkyne **46** (Scheme 2-3). Lithiated acetylene was formed by deprotonation of alkyne **46** using *n*-BuLi and subsequent iodination yielded iodoalkyne **47** in excellent yield. Hydroboration of iodoalkyne **47** followed by protodeboronation afforded (*Z*)-vinyl iodide **48** in 88% yield. Vinyl iodide **51** containing a *p*-bromophenyl

Scheme 2-3. Stereoselective Synthesis of Vinyl Iodides **48** and **51**.



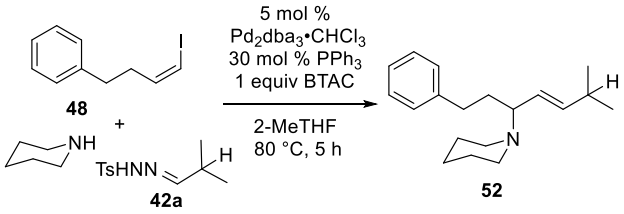
substituent, was prepared from 3-(4-bromophenyl)propanal, **49**. The aldehyde **49** was treated with the phosphonium ylide generated in situ from iodomethylphosphonium iodide and sodium bis(trimethylsilyl)amide (NaHMDS) to afford a 10:1 *Z*/*E* mixture. Upon column chromatography, the *Z*-vinyl iodide isomer **51** was isolated in 56% yield (>99:1 *Z*/*E*).

2.2.2. Optimization of the Intermolecular Carbenylative Coupling Reaction

A three-component carbenylative coupling reaction was investigated with *Z*-vinyl iodide **8** and piperidine as the external nucleophile (Table 2-1). Using the conditions optimized by my co-worker for the intramolecular reaction, the desired allylamine **52**, resulting from the trapping of vinyl iodide **48** with piperidine was not observed even with the complete disappearance of *N*-trisylhydrazone **43** (entry 1). Under these conditions, *N*-trisylhydrazone **43** was too reactive as a

carbene source. When *N*-tosylhydrazone **42a** was used along with four equivalents of piperidine, the desired allylamine **52** was obtained in 56% yield (entry 2). Because of the presence of excess piperidine, triethylamine additive can be omitted from the reaction conditions. The amounts of piperidine affected the yield of the reaction. The yield increased from 56% to 68% when the equivalents of piperidine were increased from four to 10 equivalents likely due to increasing the amount of nucleophile to trap the π-allyl intermediate to form allylamine **52**. After varying the amount of piperidine, five equivalents were determined to be optimal amount for the reaction. The phase transfer catalyst, benzyltriethylammonium chloride (BTAC), was important in the reaction. The yield dropped significantly when BTAC was omitted from the reaction (entry 5). The phase transfer catalyst increased the solubility of lithiated *N*-tosylhydrazones and thus sped up the rate of formation of diazo compounds. Finally, three equivalents of *N*-tosylhydrazone **42a**

Table 2-1. Optimization of Conditions for Intermolecular Carbenylative Amination with *N*-tosylhydrazone **42a**



entry	equiv of **42a**	equiv of LiO*t*Bu	equiv of piperidine	yield of **52**
1[a]	2	3.6	4	0%
2	2	3.6	4	56%
3	2	3.6	5	66%
4	2	3.6	10	68%
5[b]	2	3.6	5	29%
6[c]	2	3.6	5	54%
7	**3**	**5.4**	**5**	**75%**
8	4	7.2	5	60%

Conditions: [a]2 equiv isobutyraldehyde trisylhydrazone **43** and 4 equiv Et_3N was utilized. [b] no BTAC used. [c] 20 equiv of H_2O added

and 5.4 equivalents of lithium *tert*-butoxide gave optimal yield of carbenylative amination product **52** in 75% yield (entry 7). The yield drops significantly when the *E*-isomer of vinyl iodide **48** is used in the reaction instead of using the *Z*-isomer (55%). It is unknown what causes

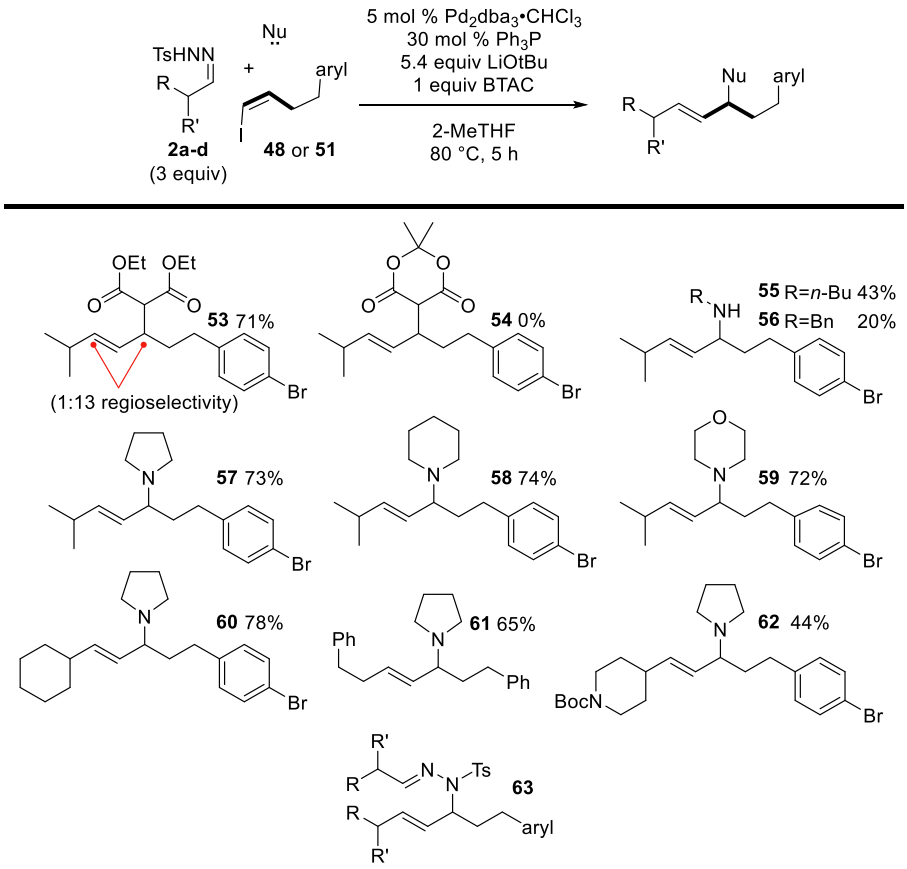
the difference in reactivity between the two isomers. Previous reports from the group had shown that both *Z*- and *E*-vinyl iodides gave comparable yields in the intramolecular carbenylative amination.[7]

2.2.3. Substrate Scope of the Intermolecular Three-Component Coupling Reaction

With the optimized conditions for the intermolecular carbenylative cross-coupling reaction on hand, the substrate scope of the reaction was explored with various alkylidene precursors **42a-d**, vinyl iodides **48** and **51**, and nucleophiles (Scheme 2-4). It is surprising that the *N*-sulfonylhydrazone anions compete with other nucleophiles in the reaction by attacking the η^3-allylpalladium intermediate. The formation of *N*-allylated hydrazone **63** accounts for 20-30% of the mass balance based on NMR of the crude reaction mixtures. When the nucleophile is omitted from the reaction, a mixture of diene products resulting from β-hydride elimination, was observed along with adduct **63**. Diethyl malonate anion afforded good yield and resulted in a 13:1 regioisomeric mixture of allylic alkylation products **53** favoring the nucleophilic attack on the least hindered side of the π-allyl intermediate. When Meldrum's acid was utilized as the nucleophile, the desired product **54** was not obtained and the starting material vinyl iodide was recovered. The failure may be attributable to the weaker nucleophilicity of the conjugate base of Meldrum's acid (pK_a' = 7.43) compared to diethyl malonate anion (pK_a' = 16.4) in DMSO. Primary amines such as butylamine and benzylamine gave modest yields of the desired coupling products **55** and **56**, respectively. When the cyclic secondary amines such as pyrrolidine, piperidine and morpholine were used, allylamines were obtained in good yields (**57**, **58**, and **59**, respectively). The superiority of cyclic amines in three-component carbenylative amination reactions was reported in previous studies.[7,9] My co-worker, Eugene Gutman, tried to use oxygen nucleophiles such as pivalic acid and *N*-hydroxyphthalimide, but they did not engage in the

reaction, probably due to the weak nucleophilicity of the oxygen nucleophiles. The carbenylative amination and alkylation reactions proceeded with high chemoselectivity; the product of oxidative addition across the Ar–Br bond was not observed. Different alkyl *N*-tosylhydrazones were also explored and the coupling reactions afforded yields up to 78% (**60-62**).

Scheme 2-4. Scope of the Intermolecular Carbenylative Alkylation and Amination with Alkylidene Precursors.

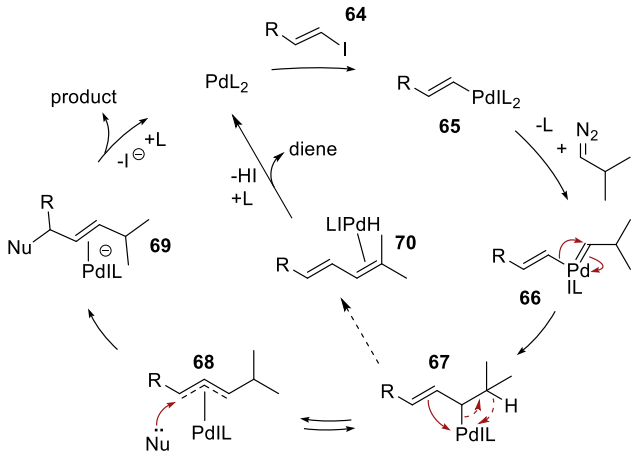


2.2.4. Proposed Mechanism

The proposed mechanism for carbenylation is described in Scheme 2-5. First, vinyl iodide **64** undergoes oxidative addition across palladium(0) to generate vinylpalladium intermediate **65**. Then the diazo compound, generated from the base decomposition of *N*-

sulfonylhydrazone, adds to vinylpalladium **65** to form vinylpalladium alkylidene intermediate **66**. Migratory insertion of the vinyl group to the alkylidene ligand generates η^1-allylpalladium intermediate **67**, which can undergo two pathways: nucleophilic trapping or β-hydride elimination. In the nucleophilic trapping pathway, η^1-allylpalladium intermediate **67** isomerizes into η^3-allylpalladium intermediate **68**, which is trapped by a nucleophile to generate intermediate **69**. Dissociation of palladium from intermediate **69** forms the product and regenerates palladium(0). The other alternative is intermediate **67** undergoing β-hydride elimination to generate diene products. In this pathway, the palladium(0) is regenerated by reductive elimination of HI from palladium(II) intermediate **70**.

Scheme 2-5. Proposed Catalytic Cycle of Carbenylative Amination and Alkylation

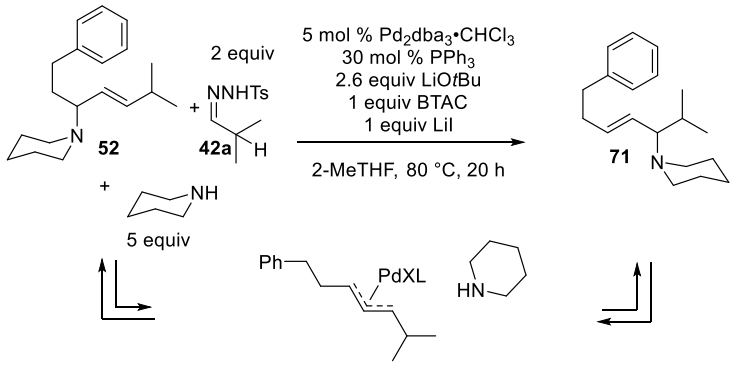


2.2.5. Study of Isomerizaton of Allylamines

Mechanistically, the formation of product **52** involved intermolecular attack of piperidine on the least hindered side of an η^3-allylpalladium intermediate.[10] During optimization, when the reaction was stopped at 20 h, a mixture of regioisomer allylamines **52** (55%) and **71** (25%) was obtained. The poor regioselectivity can be explained by a palladium-catalyzed equilibration of the protonated forms of allylamine **52** to form allylamine **71** during the reaction. To test this

hypothesis, allylamine **52** was submitted to the palladium-catalyzed reaction conditions that mimic the end of the reaction without vinyl iodide starting material for 20 h (Scheme 2-6). A mixture of 80:20 of allylamines **52** and **71** was obtained. This result indicated that regioisomer **71** indeed arises from the isomerization of **52** rather than being formed simultaneously.

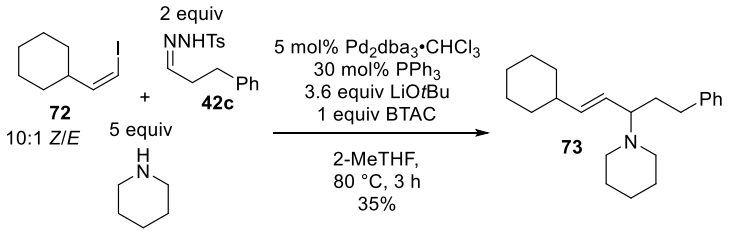
Scheme 2-6. Isomerization of Allylamines under less Basic Reaction Conditions



2.2.6. Study of Steric Hindrance on π-Allyl System

The preferred formation of regioisomer **52** over regioisomer **71** indicates that regioisomer **52** is the kinetic product resulting from nucleophilic attack on the least hindered side of the η^3-allylpalladium intermediate (Table 2-1). The η^3-allylpalladium intermediate was generated from vinyl iodide **48** containing a primary alkyl chain and *N*-tosylhydrazone **42a** containing a secondary alky group. If such is the case, then altering the substituents on the coupling components should still result in a nucleophilic attack on the least hindered side of the η^3-allylpalladium intermediate. When vinyl iodide **73** containing a secondary alkyl group reacted with hydrocinnamaldehyde *N*-tosylhydrazone **42c** in a carbenylative coupling reaction, piperidine preferentially attacked the least hindered side of allylic system to generate allylamine **73** (Scheme 2-7). The result from this experiment indicates that regioselectivity of the nucleophilic attack of an allylic system is greatly sensitive to the steric bulk of the substituents.

Scheme 2-7. Carbenylative Cross-Coupling with a Hindered Vinyl Iodide



2.3. Conclusion

In conclusion, a palladium-catalyzed three-component intermolecular carbenylative amination and alkylation reaction of vinyl iodides, *N*-tosylhydrazones and nucleophiles were successfully carried out to yield products resulting from nucleophilic attack on the least hindered side of the η^3-allylpalladium complexes. With the optimized reaction conditions, a variety of *N*-tosylhydrazones and nucleophiles were explored. The reaction works well with cyclic secondary amines and stabilized enolates and moderately with primary amines. A variety of alkyl *N*-tosylhydrazones have been demonstrated to work with the reaction conditions as well. Good yields were obtained under conditions that minimized the palladium-catalyzed ionization of allylic amines and addition of metalated hydrazones to η^3-allylpalladium complexes.

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2.5. Supporting Information

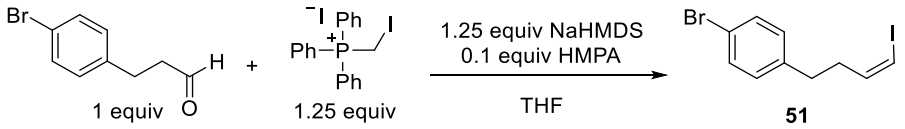
2.5.1. General Experimental Procedures

NMR spectral data were recorded at room temperature using a Bruker 500 or 600 MHz spectrometer. The NMR data are reported as follows: chemical shifts in ppm from an internal tetramethylsilane standard on the δ scale, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration.

Analytical thin layer chromatography (TLC) was performed using EMD Reagents 0.25 mm silica gel 60-F plates. "Flash" chromatography on silica gel was performed using Silicycle silica gel (40-63 μm). All reactions were carried out under an atmosphere of nitrogen in glassware that was evacuated and back-filled with nitrogen three times. Reactions were carried out at room temperature unless otherwise indicated. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Amines were distilled from calcium hydride. THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs and coworkers.[1]

2.5.2. Experimental

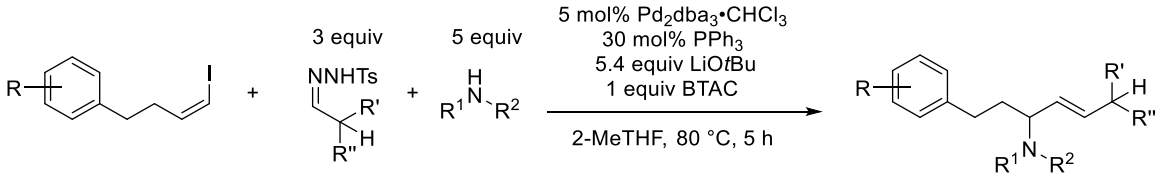
Synthesis of (*Z*)-1-bromo-4-(4-iodobut-3-en-1-yl)benzene, 51.[2]



An oven-dried 200 mL round-bottom flask was charged with iodomethylphosphonium iodide (5.1 g, 9.6 mmol, 1.25 equiv) and a stir bar. The flask was fitted with a septum and purged with nitrogen. Tetrahydrofuran (30 mL) was added and the yellow slurry was stirred at room temperature. A solution of NaHMDS (1.0 M in THF) (9.6 mL, 9.6 mmol, 1.25 equiv) was slowly added to the slurry. The reaction mixture was cooled to -60 ºC, and then HMPA (130 μL, 0.77 mmol, 0.1 equiv) was added. The reaction mixture was cooled to -78 ºC, and then 3-(4-bromophenyl)propanal (1.6 g, 7.7 mmol, 1.0 equiv) was added drop-wise via a syringe. The reaction was stirred at -78 ºC for 30 min and let warm to room temperature over an hour. The reaction mixture was poured into brine (12 mL) and extracted with pentane (3x30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give orange oil. The oil was purified by flash chromatography with hexanes to afford *Z*-isomer **51** as a colorless

liquid with 10:1 *Z*/*E* isomer (1.6 g, 4.3 mmol, 56 %). R_f = 0.59 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 7.4 Hz, 1H), 6.17 (q, *J* = 7.0 Hz, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.44 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 139.8, 131.5, 130.3, 119.9, 83.6, 36.2, 33.5; IR (thin film) 2925, 1608, 1487, 1283, 1071, 1011 cm^{-1}; HRMS (ESI): m/z calculated for $C_{10}H_{10}BrI$ $[M]^+$ 335.9011, found 335.9022.

2.5.3. General procedure for intermolecular carbenylation



An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (5.0 mol%), PPh_3 (30 mol%), and a stir bar. The flask was fitted with a septum and purged with nitrogen. 2-MeTHF was added to make a 0.01 M solution, and the brown slurry was then stirred for 20 min at room temperature to give a clear yellow catalyst solution.

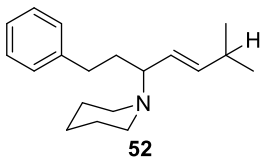
Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*-tosylhydrazone (3.0 equiv), benzyltriethylammonium chloride (1.0 equiv), lithium *tert*-butoxide base (5.4 equiv), and a stir bar was evacuated and back-filled with N_2 three times, and then capped with a septum. A solution of the vinyl iodide (1.0 equiv, 0.5 M in 2-MeTHF) was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Next, amine (5.0 equiv) was added to the round-bottom flask.

Finally, the catalyst solution was transferred to the reaction vessel via syringe, the remaining catalyst solution was transferred using 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in an 80 °C oil

bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature.

The reaction was monitored by thin layer chromatography (20:79:1 EtOAc/hex/Et_3N) to check for depletion of the vinyl iodide. The reactions reached completion between ca. 3 and 5 h depending on *N*-tosylhydrazone. Upon consumption of the vinyl iodide, the reaction was allowed to cool to room temperature and 1% (w/v) aq. NaOH was added to the reaction vessel. The mixture was extracted with EtOAc three times and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The pyrrolidine was purified by silica gel chromatography.

(*E*)-1-(6-methyl-1-phenylhept-4-en-3-yl)piperidine, 52.



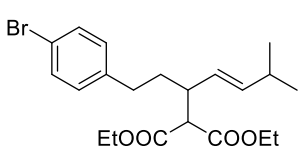
52

An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (8.6 mg, 0.0083 mmol), PPh_3 (13 mg, 0.050 mmol), and a stir bar. The flask was fitted with a septum and purged with nitrogen. 2-MeTHF (0.2 mL) was added, and the brown slurry was then stirred for 20 min at room temperature to give a clear yellow catalyst solution.

Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*-tosylhydrazone (0.12 g, 0.50 mmol), benzyltriethylammonium chloride (46 mg, 0.17 mmol), lithium *tert*-butoxide base (72 mg, 0.90 mmol), and a stir bar was evacuated and back-filled with N_2 three times, and then capped with a septum. A solution of the (*Z*)-(4-iodobut-3-en-1-yl)benzene **48** (43 mg, 0.17 mmol) in 0.2 mL of 2-MeTHF was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Next, piperidine (82 μL, 0.83 mmol) was added to the round-bottom flask.

Finally, the catalyst solution was transferred to the reaction vessel via syringe, the remaining catalyst solution was transferred 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in a 80 °C oil bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature. The reaction reached completion within 10 min and was allowed to cool to room temperature; then 2 mL 1% (w/v) aq. NaOH was added to the reaction vessel. The mixture was extracted with 3x10 mL EtOAc and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The pyrrolidine was purified by silica gel chromatography (10:85:5 EtOAc/Hex/Et_3N) to provide of pyrrolidine **52** (29 mg, 91%), as a yellow oil. TLC R_f = 0.45 (10:90:5 EtOAc/Hexanes/Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.21 (m, 2H), 7.20-7.08 (m, 3H), 5.47 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.30 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.73-2.69 (m, 1H), 2.65-2.59 (m, 1H), 2.56-2.45 (m, 3H), 2.42-2.26 (m, 3H), 2.07-1.82 (m, 1H), 1.83-1.64 (m, 1H), 1.64-1.47 (m, 4H), 1.46-1.33 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 141.5, 128.5, 128.3, 125.6, 125.5, 67.5, 50.6, 34.4, 33.0, 31.2, 26.4, 24.9, 22.9, 22.8; IR (thin film) 2929, 2856, 2791, 1495, 1453, 1101 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{19}H_{29}NH$ $(M+H)^+$ 272.2378, found 272.2384.

Diethyl (*E*)-2-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)malonate, 53.



53

Diethyl malonate (0.23 mL, 1.5 mmol, 12 equiv) was slowly added to a suspension of NaH (0.055 g, 1.4 mmol, 11 equiv) in THF (1.0 mL) at 0 °C. The mixture was stirred at room temperature for 10 min and set aside.

An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (6.5 mg, 0.0063 mmol, 0.05 equiv), PPh_3 (9.4 mg, 0.038 mmol, 0.3 equiv), and a stir bar. The flask was fitted

with a septum and purged with nitrogen. 2-MeTHF (0.3 mL) was added, and the brown slurry was then stirred for 20 min at room temperature to give a clear orange catalyst solution.

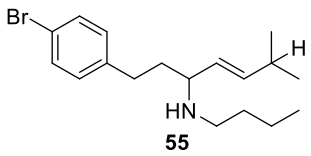
Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*- tosylhydrazone (91 mg, 0.38 mmol, 3.0 equiv), benzyltriethylammonium chloride (35 mg, 0.13 mmol, 1.0 equiv), lithium *tert*-butoxide base (55 mg, 0.68 mmol, 5.4 equiv), and a stir bar. The reaction vessel was evacuated and back-filled with N_2 three times, and then capped with a septum. A solution of the vinyl iodide **51** (48 mg, 0.13 mmol, 1.0 equiv) in 0.2 mL of 2-MeTHF was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Sodium malonate solution was added via syringe to the round-bottom flask.

Finally, the catalyst solution was transferred to the reaction vessel via syringe, the remaining catalyst solution was transferred 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in a 80 °C oil bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature. The reaction reached completion within 3 h. The resulting orange mixture was cooled to room temperature and quenched with a saturated NH_4Cl solution. The resulting solution was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated by rotary evaporation to give an orange oil.

The crude reaction mixture was purified by silica gel chromatography (1:9 EtOAc/Hex) to afford **53 (**24 mg, 71%), as a colorless oil. TLC R_f = 0.56 (10:90 EtOAc/Hex). Isolated as a mixture of 2 regioisomers, 13% of the minor regioisomer was inseparable by column chromatography. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.9 Hz,

1H), 5.48 (dd, *J* = 15.3, 6.7 Hz, 1H), 5.21 (dd, *J* = 15.3, 9.6 Hz, 1H), 4.22-4.04 (m, 4H), 3.30 (d, *J* = 8.9, 1H), 2.76-2.39 (m, 2H), 2.27 (dq, *J* = 13.5, 6.6 Hz, 1H), 1.83-1.48 (m, 1H), 1.29-1.20 (m, 6H), 0.97 (dd, *J* = 10.9, 6.8 Hz, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 168.2, 141.8, 140.9, 131.4, 131.3, 130.3, 130.2, 125.9, 119.5, 61.3, 61.2, 57.5, 42.6, 34.2, 32.9, 31.2, 25.8, 22.6, 22.5, 14.2, 14.2; IR (thin film) 2958, 1731, 1488, 1367, 1242, 1149 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{21}H_{29}BrO_4Na$ $(M+Na)^+$ 447.1147, found 447.1154.

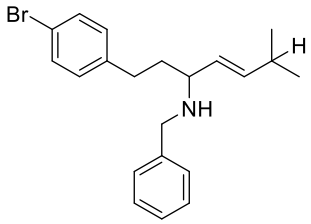
(*E*)-1-(4-bromophenyl)-*N*-butyl-6-methylhept-4-en-3-amine, 55.



55

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (54 mg, 0.14 mmol) gave **55** (21 mg, 43%) as a yellow oil. TLC R_f = 0.41 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 1H), 5.49 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.14 (dd, *J* = 15.4, 8.4 Hz, 1H), 2.93-2.88 (m, 1H), 2.67-2.49 (m, 2H), 2.46-2.41(m, 2H), 2.36-2.27 (m, 1H), 1.81-1.74 (m, 1H), 1.68-1.60 (m, 1H), 1.47-1.38 (m, 2H), 1.35-1.29 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 6H), 0.9(t, J = 7.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 131.4, 130.3, 119.4, 66.9, 60.6, 46.7, 31.8, 31.0, 22.69, 22.64, 20.5, 14.0; IR (thin film) 2956, 2926, 2867, 1488, 1464, 1072, 1012 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{18}H_{28}NBrH$ $(M+H)^+$ 338.1483, found 338.1496.

(*E*)-*N*-benzyl-1-(4-bromophenyl)-6-methylhept-4-en-3-amine, 56.

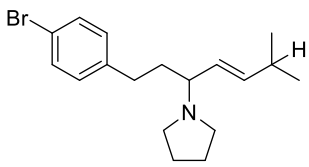


56

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (150 mg, 0.44 mmol) gave **56** (34 mg, 21%) as a colorless oil. TLC R_f = 0.9 (20:79:1 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.32-7.22 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.50 (dd, *J* = 15.4, 6.7 Hz, 1H), 5.19 (ddd, *J* = 15.4, 8.5, 1 Hz, 1H), 3.80 (d, *J* =

13.2 Hz, 1H), 3.62 (d, *J* = 13.2, 1H), 2.96 (m, 1H), 2.57 (m, 2H), 2.37-2.30 (m, 1H), 1.81-1.74 (m, 1H), 1.71-1.64 (m, 1H), 1.02 (dd, *J* = 6.8, 3.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 140.8, 140.7, 131.4, 130.2, 129.2, 128.4, 128.3, 126.9, 119.4, 59.7, 51.2, 37.5, 31.8, 31.0, 22.74, 22.70; IR (thin film) 2923, 1727, 1488, 1454, 1288, 1105, 1072, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{21}H_{26}BrNH$ $(M+H)^+$ 372.1327, found 372.1328.

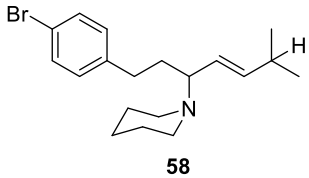
(*E*)-1-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)pyrrolidine, 57.



57

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (51 mg, 0.14 mmol) gave **57** (32 mg, 70 %) as a yellow oil. TLC R_f = 0.43 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.50 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.31(ddd, *J* = 15.4, 8.9, 0.6 Hz, 1H), 2.64-2.41 (m, 6H), 2.35-2.29 (m, 1H), 2.01-1.94 (m, 1H), 1.75-1.65 (m, 6H), 1.01 (dd, *J* = 6.8, 3.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 140.7, 131.3, 130.3, 127.9, 119.4, 67.1, 51.6, 35.7, 31.9, 31.0, 23.2, 22.7; IR (thin film) 2957, 2867, 2782, 1487, 1458, 1361, 1121, 1071, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{18}H_{26}BrNH$ $(M+H)^+$ 336.1327, found 336.1330.

(*E*)-1-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)piperidine, 58.

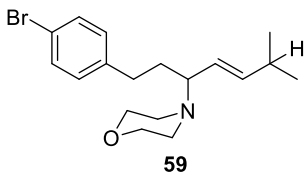


58

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (50.0 mg, 0.13 mmol) gave **58** (34 mg, 74%) as a yellow oil. TLC R_f = 0.45 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42-7.33 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.44 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.31-5.25 (m, 1H), 2.68-2.65 (m, 1H), 2.61-2.56 (m, 1H), 2.50-2.45 (m, 3H), 2.33-2.29 (m, 3H), 1.94-1.86 (m, 1H), 1.71-1.61 (m, 1H), 1.61-1.48 (m, 4H), 1.43-1.35 (m, 2H), 1.01 (dd, *J* = 6.7, 2.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 141.6, 131.3, 130.3, 125.4, 119.3, 67.2, 50.6,

34.2, 32.4, 31.2, 26.5, 24.9, 22.9, 22.8; IR (thin film) 2929, 2855, 2791, 1660, 1487, 1452, 1095, 1071, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{19}H_{28}BrNH$ $(M+H)^+$ 350.1483, found 350.1482.

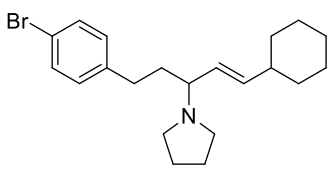
(*E*)-4-(1-(4-bromophenyl)-6-methylhept-4-en-3-yl)morpholine, 59.



59

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (48 mg, 0.13 mmol) gave **59** (32 mg, 72%) as a colorless oil. TLC R_f = 0.41 (10:90:5 EtOAc/Hex/Et_3N). ^1H NMR (600 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 5.44 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.31-5.25 (ddd, *J* = 15.5, 6.6, 1.2 Hz, 1H), 3.76-3.62 (m, 4H), 2.68-2.58 (m, 2H), 2.58-2.46 (m, 3H), 2.43-2.37 (m, 2H), 2.36-2.29 (m, 1H), 1.97-1.87 (m, 1H), 1.70-1.61 (m, 1H), 1.01 (dd, *J* = 6.8, 1.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 141.4, 131.4, 130.3, 125.0, 119.4, 67.4, 67.0, 50.1, 33.6, 32.0, 31.2, 22.8, 22.7; IR (thin film) 2954, 2853, 2810, 1487, 1452, 1117, 1071, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{18}H_{26}BrNOH$ $(M+H)^+$ 352.1276, found 352.1278.

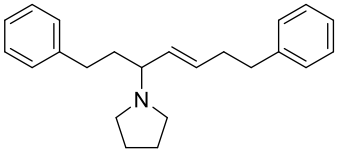
(*E*)-1-(5-(4-bromophenyl)-1-cyclohexylpent-1-en-3-yl)piperidine, 60.



60

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (54 mg, 0.16 mmol) gave **60** (47 mg, 78%) as a yellow oil. TLC R_f = 0.59 (5:95:3 EtOAc/Hex/Et_3N). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.33-7.24 (d, *J* = 8.1 Hz, 2H), 5.48 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.31 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.70-2.31 (m, 8H), 1.99-1.94 (m, 2H), 1.80-1.60 (m, 9H), 1.35-1.00 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 139.6, 131.3, 130.3, 128.3, 119.3, 67.2, 51.6, 40.6, 35.7, 33.2, 33.3, 31.9, 26.2, 26.1, 23.2; IR (thin film) 2921, 1652, 1487, 1447, 1122, 1072, 1011 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{21}H_{30}BrNH$ $(M+H)^+$ 376.1640, found 376.1637.

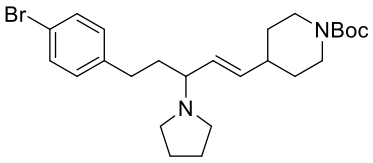
(*E*)-1-(1,8-diphenyloct-4-en-3-yl)piperidine, 61.



61

Following the general procedure for intermolecular carbenylation, vinyl iodide **48** (49 mg, 0.19 mmol) gave **61** (34 mg, 57%) as a yellow oil. TLC R_f = 0.39 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 4H), 7.20-7.13 (m, 6H), 5.56 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.41-5.37 (m, 1H), 2.75-2.72 (m, 2H), 2.62-2.56 (m, 2H), 2.48-2.39 (m, 5H), 2.00-1.94 (m, 1H), 1.73-1.67 (m, 4H), 1.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 141.8, 132.2, 128.5, 128.4, 128.33, 128.30, 125.8, 125.6, 67.3, 51.6, 35.83, 35.80, 34.1, 32.4, 23.2; IR (thin film) 2925, 2782, 1603, 1495, 1454 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{23}H_{29}NH$ $(M+H)^+$ 320.2378, found 320.2379.

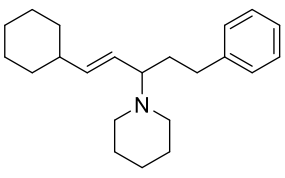
***tert*-Butyl (*E*)-4-(5-(4-bromophenyl)-3-(piperidin-1-yl)pent-1-en-1-yl)piperidine-1-carboxylate, 62.**



62

Following the general procedure for intermolecular carbenylation, vinyl iodide **51** (50.0 mg, 0.15 mmol) gave **62** (35 mg, 50%) as a yellow oil. TLC R_f = 0.27 (10:90:5 EtOAc/Hex/Et_3N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.49 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.38 (dd, *J* = 15.7, 8.7 Hz, 1H), 4.10 (m, 2H), 2.82-2.69 (m, 2H), 2.63-2.40 (m, 7H), 2.19-2.12 (m, 1H), 2.02-1.96 (m, 1H), 1.75-1.67 (m, 6H), 1.46 (s, 9H), 1.35-1.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 141.3, 137.5, 131.4, 130.2, 129.6, 119.4, 79.4, 67.0, 51.6, 38.8, 35.4, 32.0, 31.8, 29.8, 28.5, 23.2; IR (thin film) 2927, 2853, 1689, 1422, 1364, 1274, 1231, 1162 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{25}H_{37}BrN_2O_2H$ $(M+H)^+$ 477.2117, found 477.2126.

(*E*)-1-(1-cyclohexyl-5-phenylpent-1-en-3-yl)piperidine, 73.

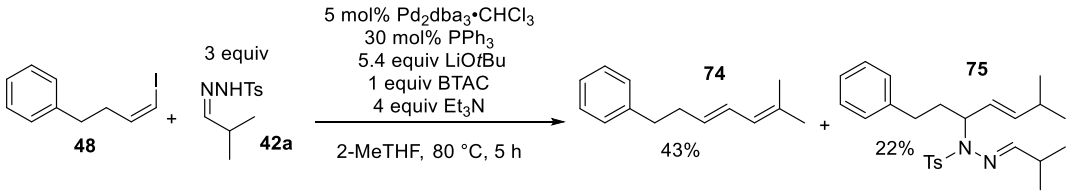


73

Following the general procedure for intermolecular carbenylation, vinyl iodide **72** (39 mg, 0.16 mmol) gave **73** (15 mg, 35%) as a yellow oil.

TLC R_f = 0.45 (10:90:5 EtOAc/Hex/Et_3N). ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 7.17-7.14 (m, 3H), 5.44 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.30 (ddd, *J* = 15.5, 9.0, 0.9 Hz, 1H), 2.71-2.59 (m, 2H), 2.54-2.48 (m, 3H), 2.38-2.96 (m, 2H), 2.03-1.92 (m, 2H), 1.76-1.53 (m, 7H), 1.60-1.50 (m, 4H), 1.43-1.39 (m, 2H), 1.33-1.24 (m, 3H), 1.22-1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 140.3, 128.5, 128.3, 126.1, 125.6, 67.6, 50.6, 40.8, 34.4, 33.4, 33.3, 33.0, 26.5, 26.3, 26.1, 24.9; IR (thin film) 2922, 2850, 1730, 1495, 1449, 1271, 1116 cm^{-1}; HRMS (ESI): *m/z* calc'd for $C_{22}H_{33}NH$ $(M+H)^+$ 312.2691, found 312.2698.

Control experiment: Carbenylation in the absence of the amine nucleophile.



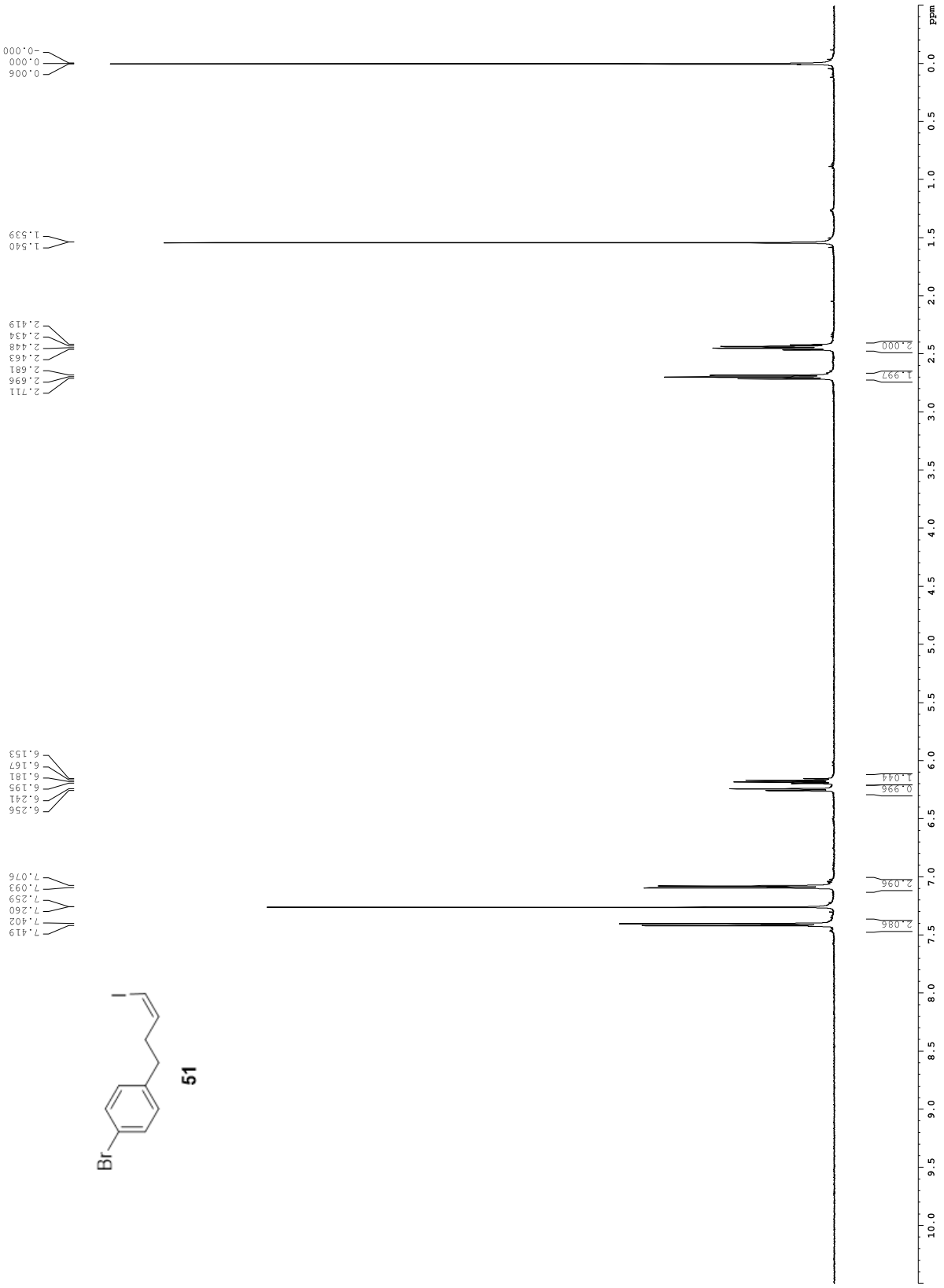
An oven-dried 5 mL pear-shaped flask was charged with Pd_2dba_3•$CHCl_3$ (7.6 mg, 0.0073 mmol), PPh_3 (12 mg, 0.044 mmol), and a stir bar. The flask was fitted with a septum and purged with nitrogen. 2-MeTHF (0.2 mL) was added, and the brown slurry was then stirred for 20 min at room temperature to give a clear yellow catalyst solution.

Meanwhile, a separate oven-dried 5 mL round-bottom flask containing of *N*- tosylhydrazone **42a** (0.11 g, 0.44 mmol), benzyltriethylammonium chloride (41 mg, 0.15 mmol), lithium *tert*-butoxide base (64 mg, 0.79 mmol), and a stir bar was evacuated and back-filled with N_2 three times, and then capped with a septum. A solution of the (*Z*)-(4-iodobut-3-en-1-yl)benzene **48** (38 mg, 0.15 mmol) in 0.2 mL of 2-MeTHF was transferred from a pear-shaped flask by syringe to the dry reagents in the round-bottom flask. The residual vinyl iodide in the pear-shaped flask was transferred to the reaction vessel using 2x0.15 mL 2-MeTHF. Next, triethylamine (78 μL, 0.59 mmol) was added to the round-bottom flask.

Finally, the catalyst solution was transferred to the reaction vessel via syringe; the remaining catalyst solution was transferred 2x0.2 mL 2-MeTHF. The reaction vessel was fitted with a reflux condenser and capped with a septum. The reaction vessel was immersed in a 80 °C oil bath up to the level of the flask contents, and the stirred slurry rapidly reached reflux temperature. The reaction reached completion within 3 h and was allowed to cool to room temperature; then 2 mL 1% (w/v) aq. NaOH was added to the reaction vessel. The mixture was extracted with 3x10 mL EtOAc and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude reaction mixture was analyzed by GC/MS (EI). In the absence of an amine nucleophile, the reaction conditions resulted in 43% of β-hydride eliminated diene **74**, 22% of **75** and 10% of remaining starting vinyl iodide 4**8**.

2.6. Reference

S.1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518 – 1520.
S.2. Menzel, K.; Fu, G. C. *J*. *Am*. *Chem*. *Soc*. **2003**, *125*, 3718–3719.
S.3. Khanna, A., Maung, C., Johnson, K. R., Luong, T. T., Van Vranken, D. L. *Org*. *Lett*. **2012**, *14*, 3233–3235.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2.448
2.434
2.419
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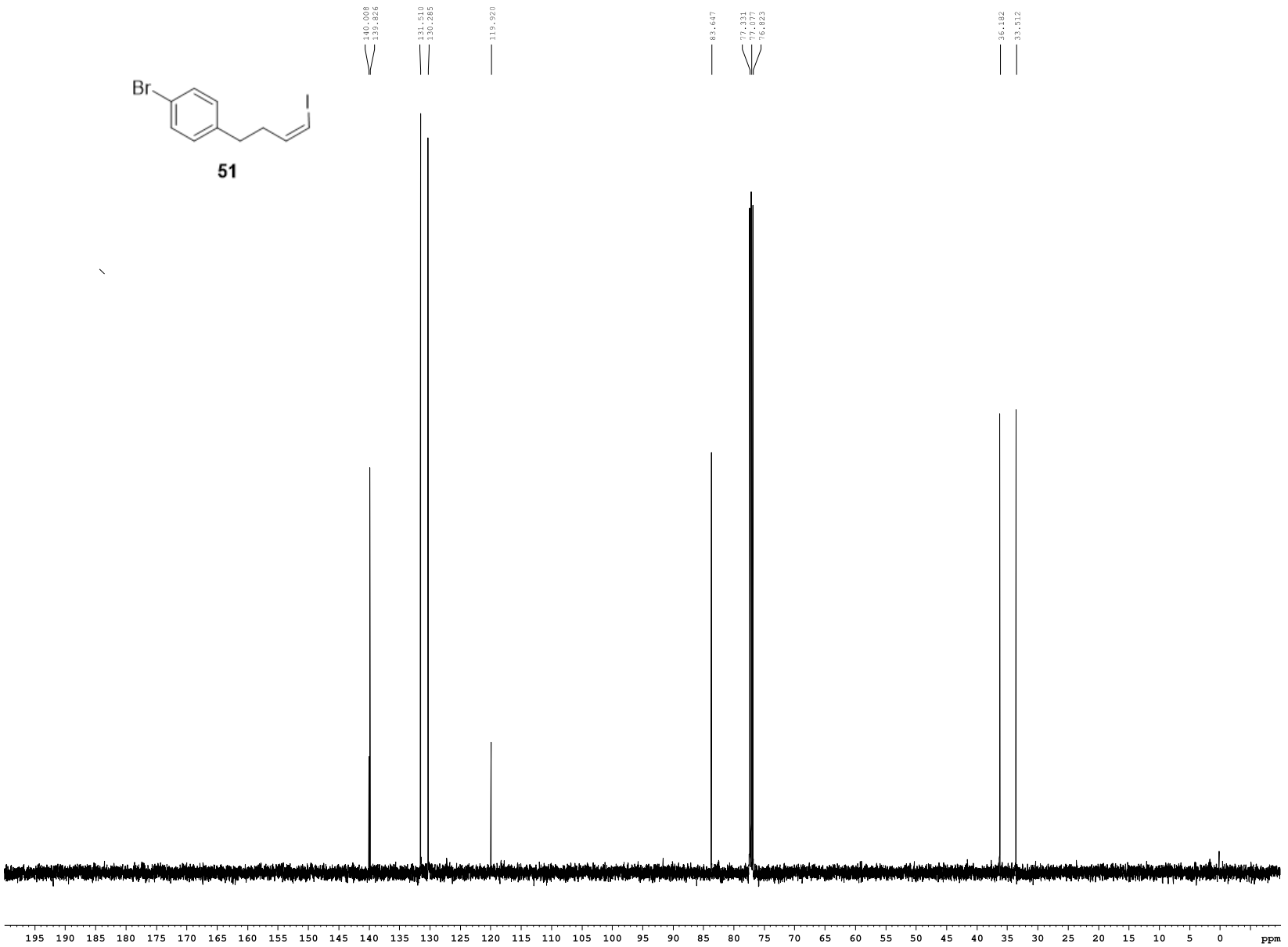
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51
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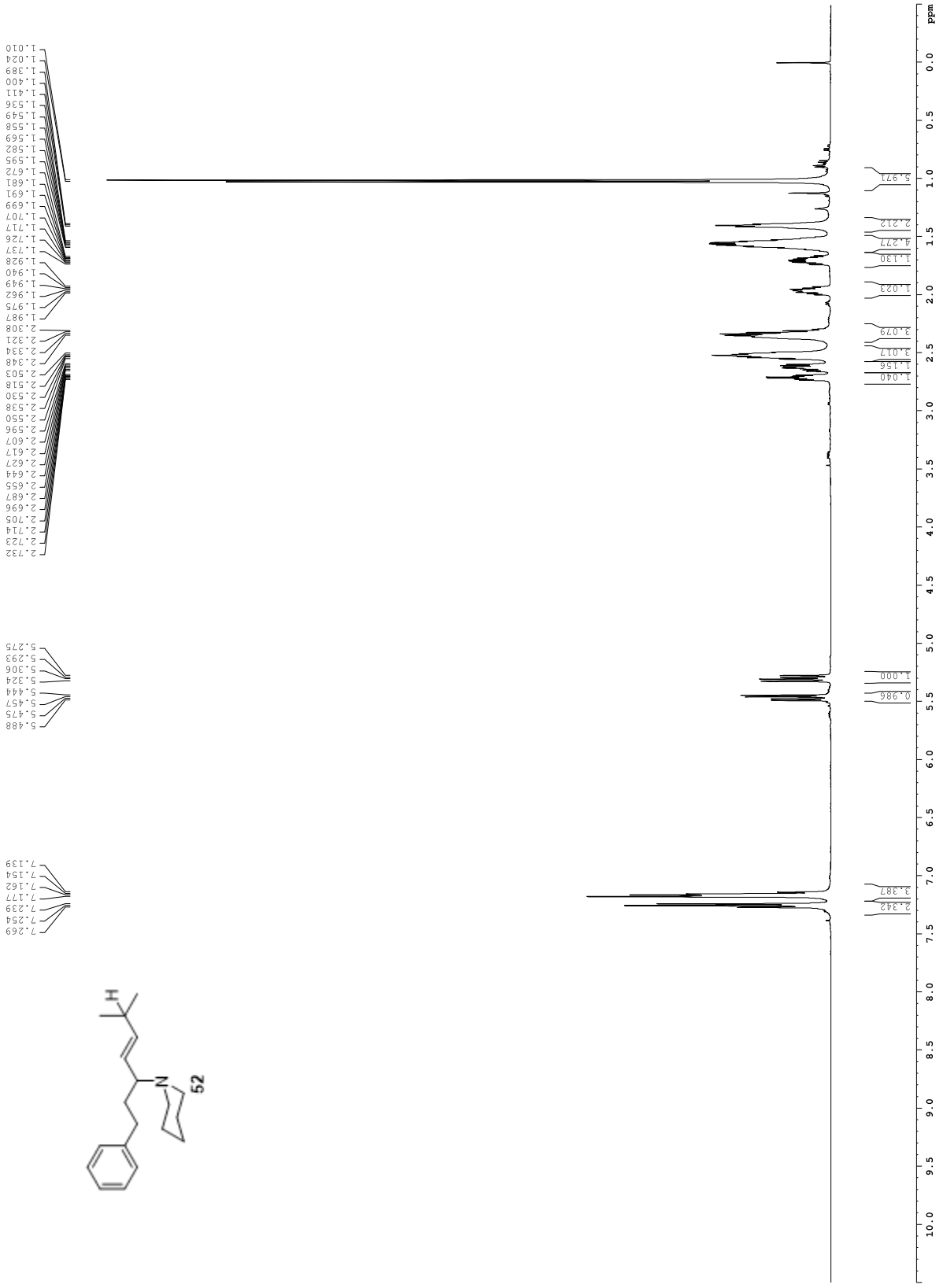
ppm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2.705
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2.687
2.655
2.644
2.627
2.617
2.607
2.596
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1.717
1.707
1.699
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1.681
1.672
1.595
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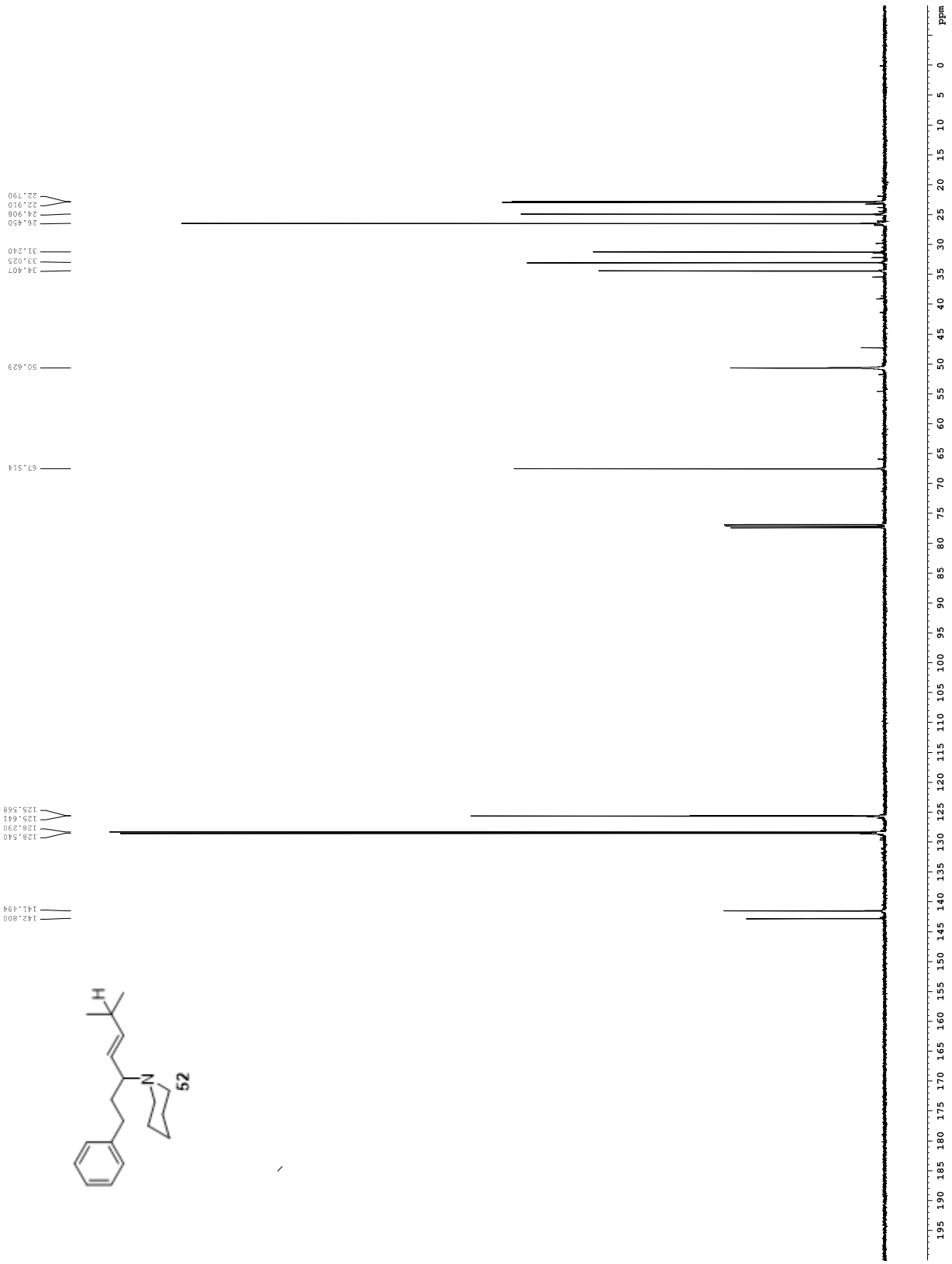
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H
N
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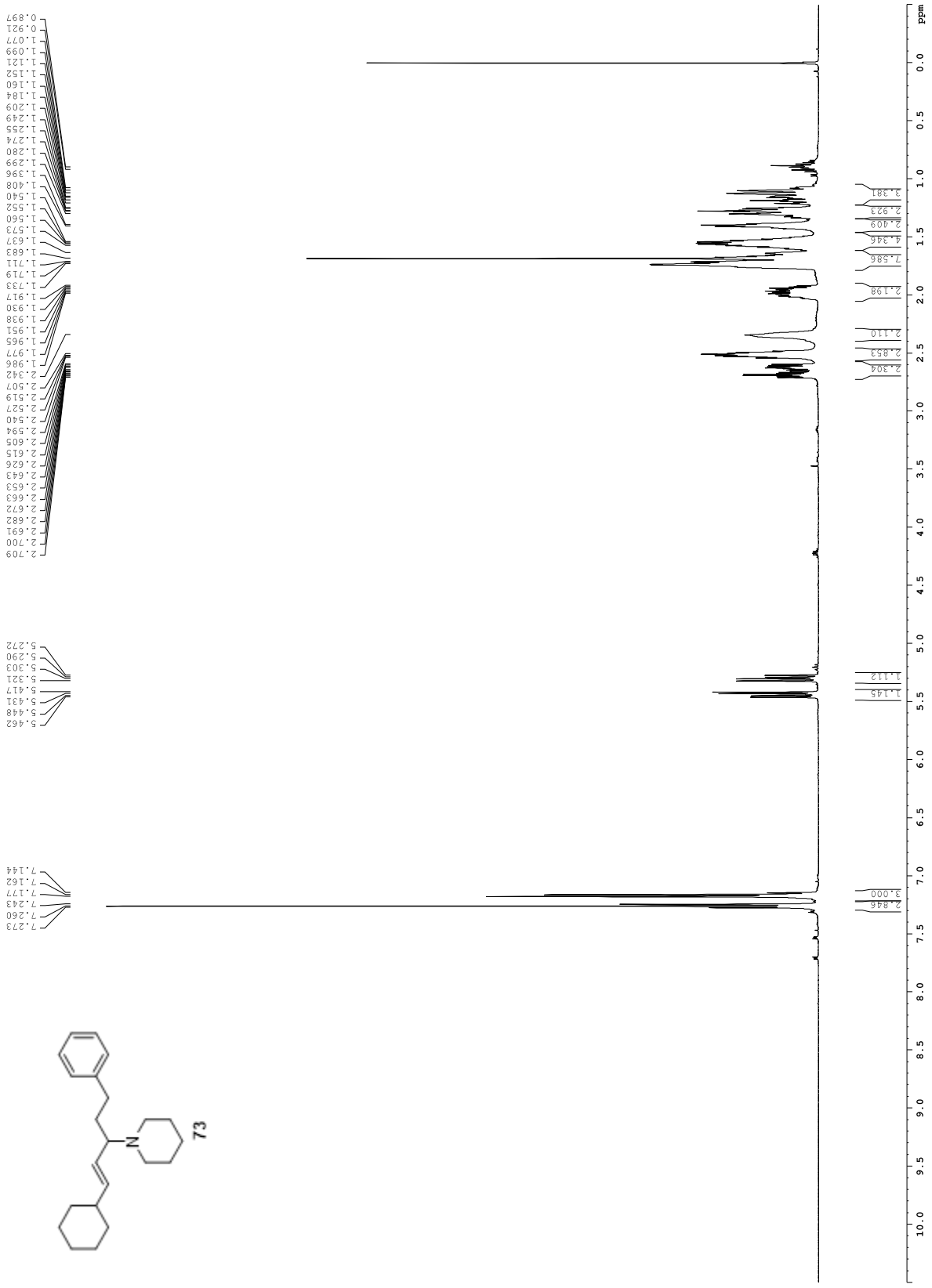
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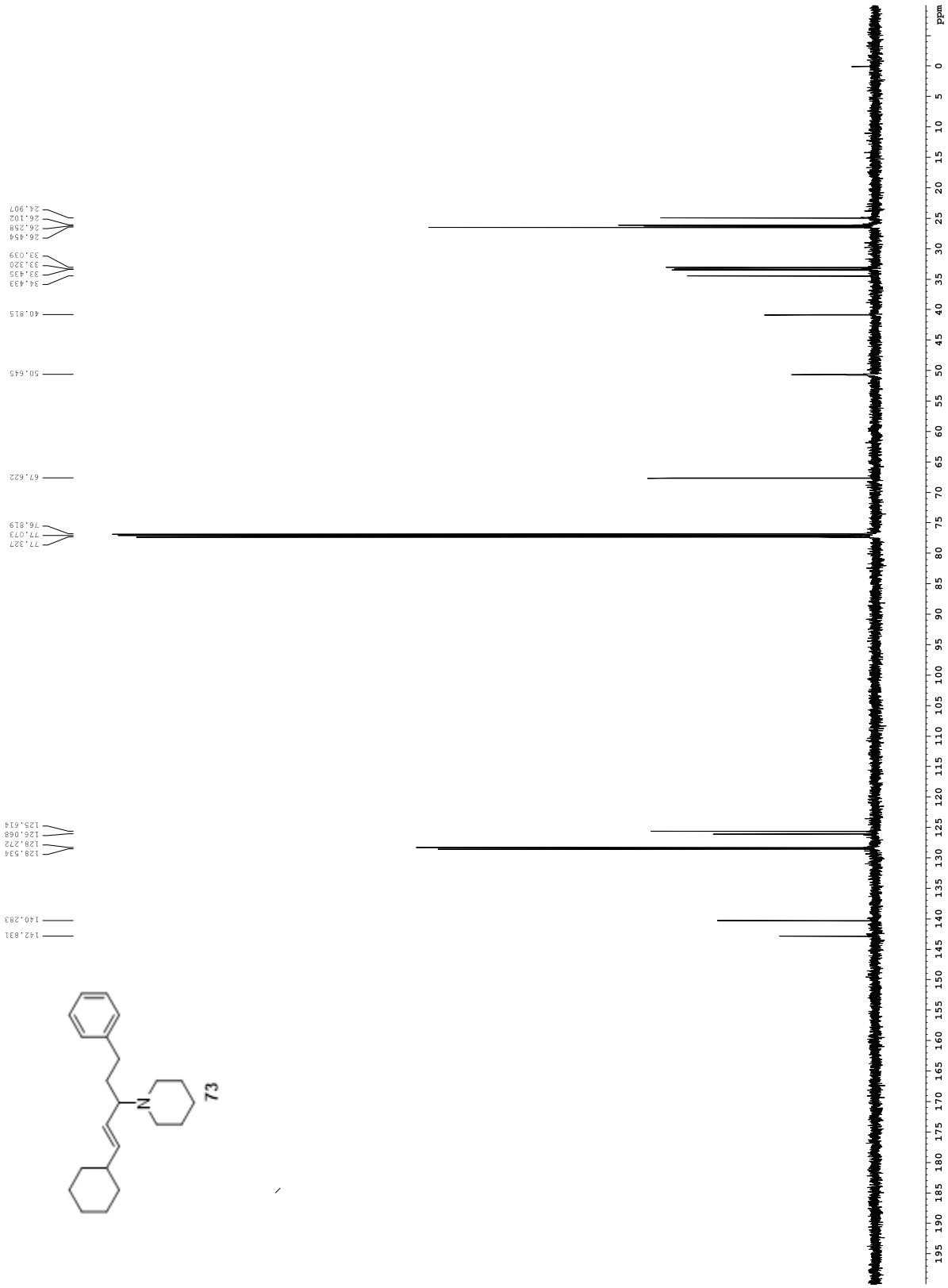
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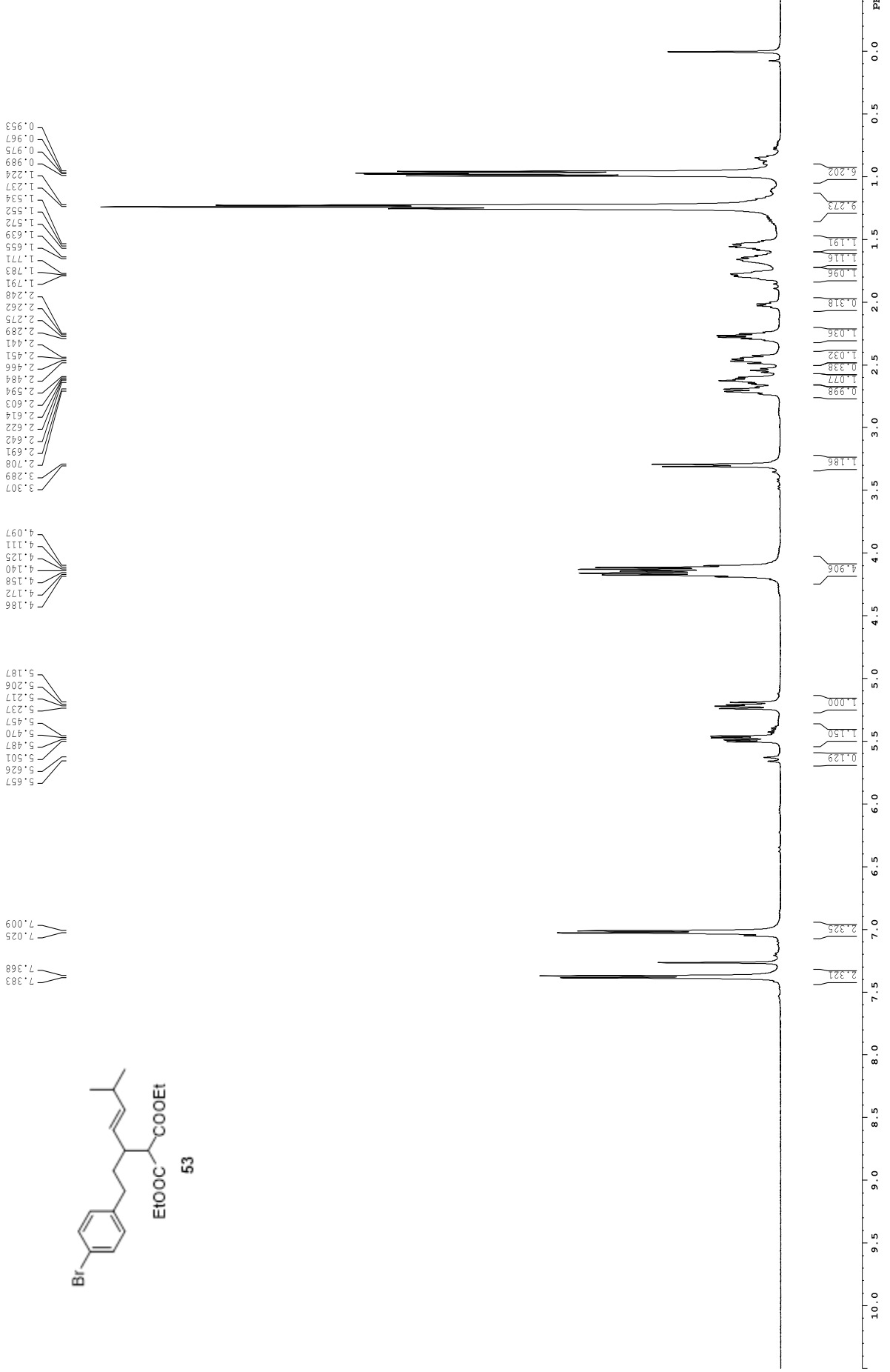
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2.594
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EtOOC
COOEt
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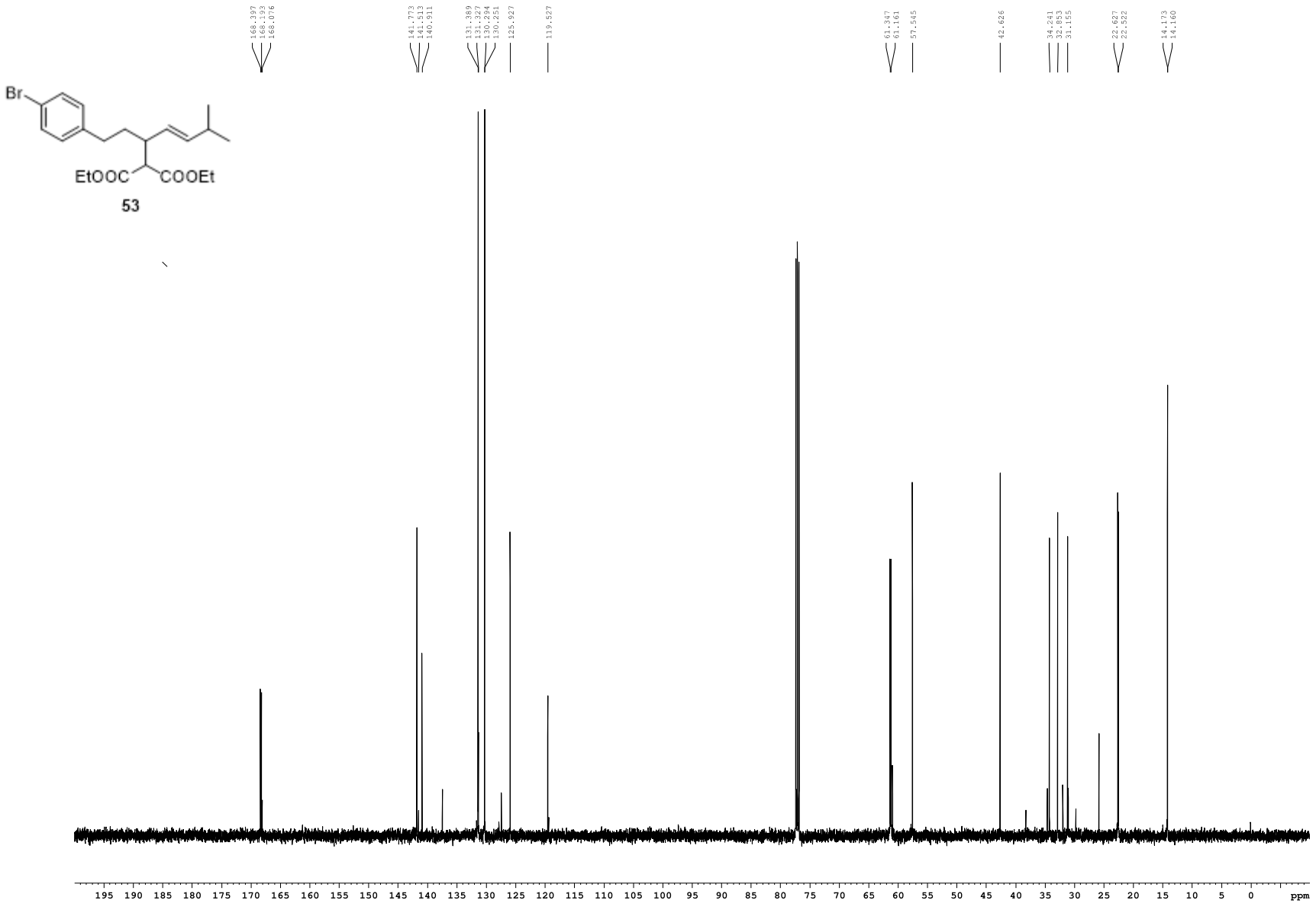
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31.155
22.627
22.522
14.173
14.160
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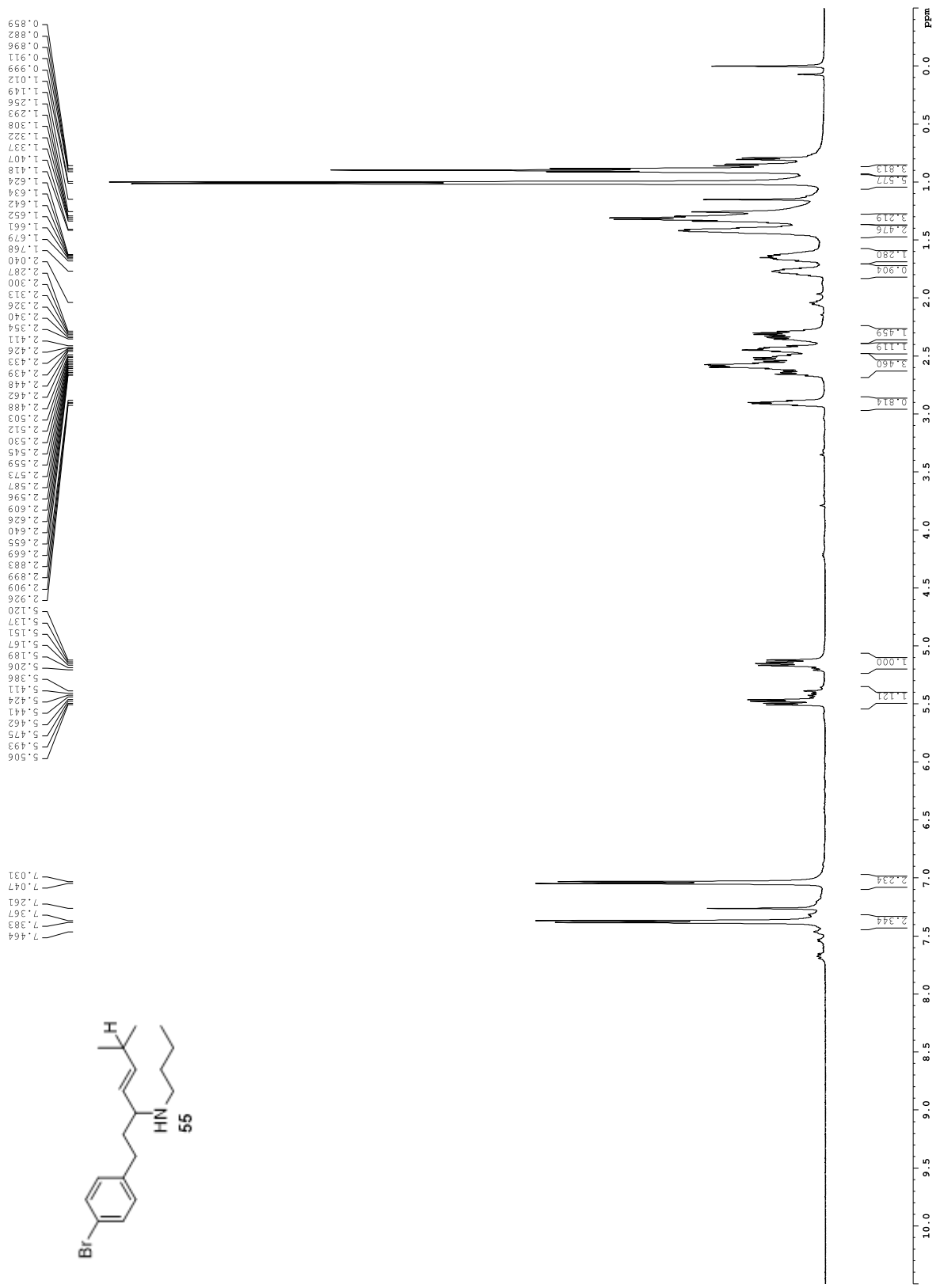
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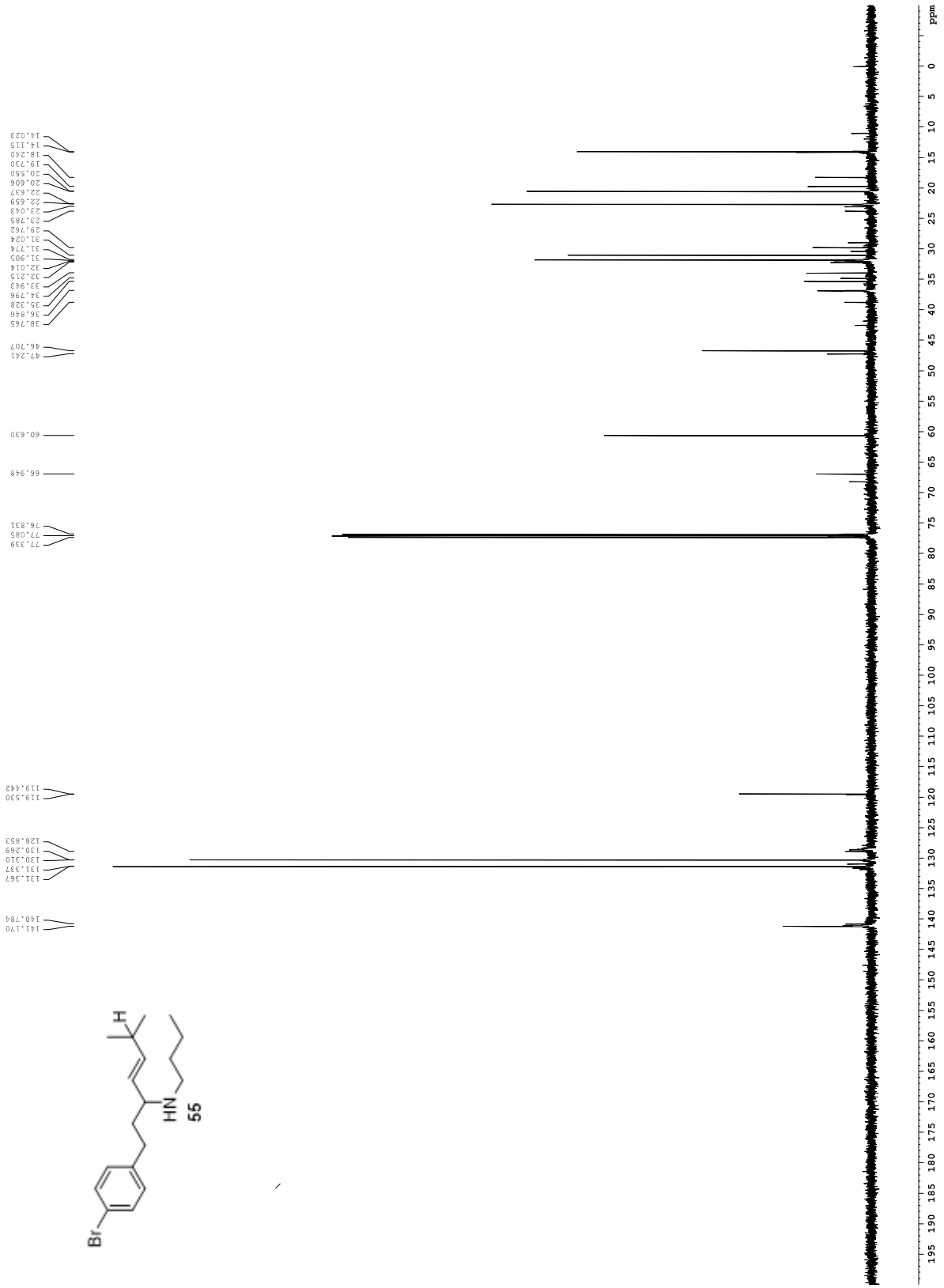
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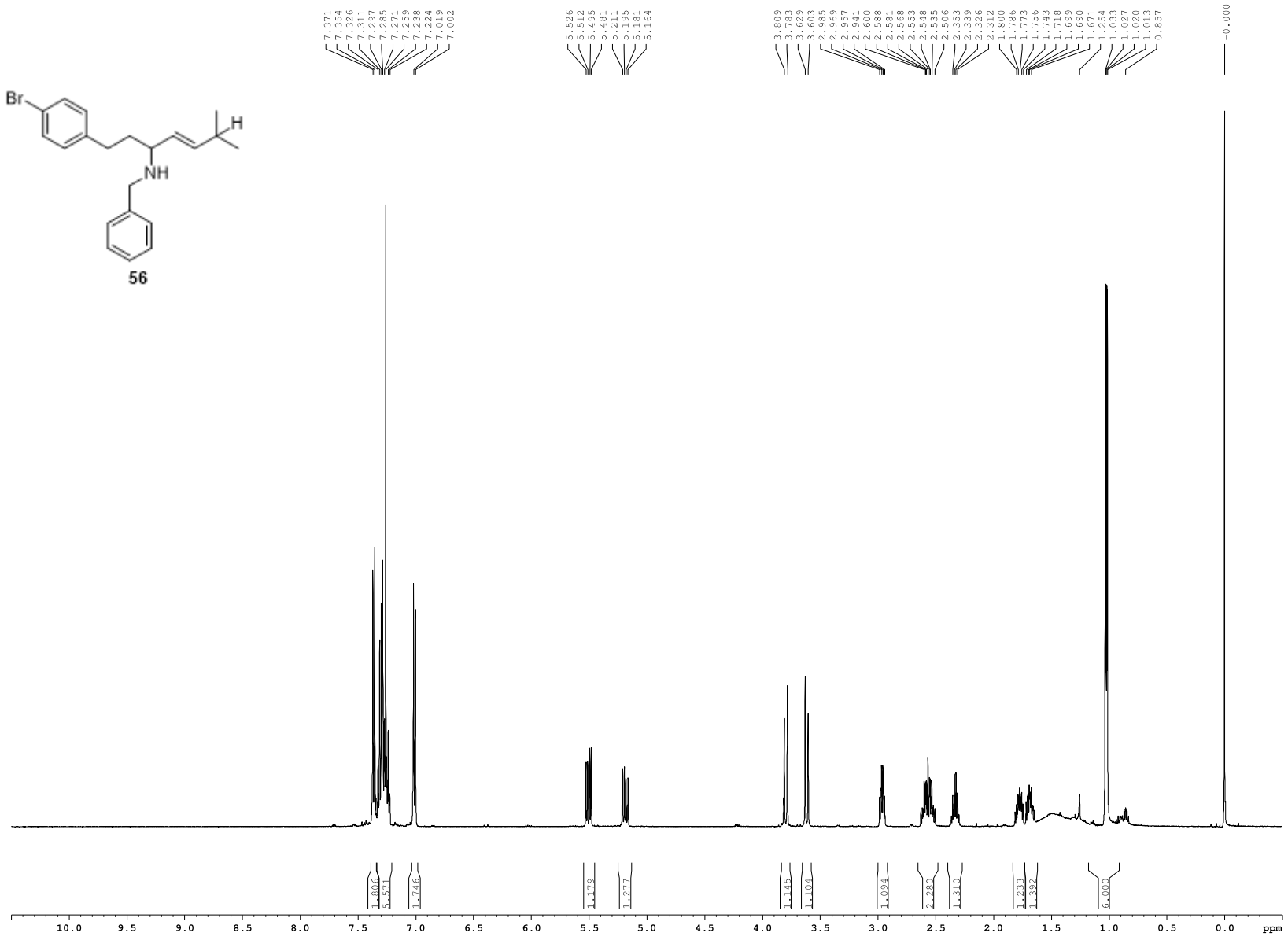
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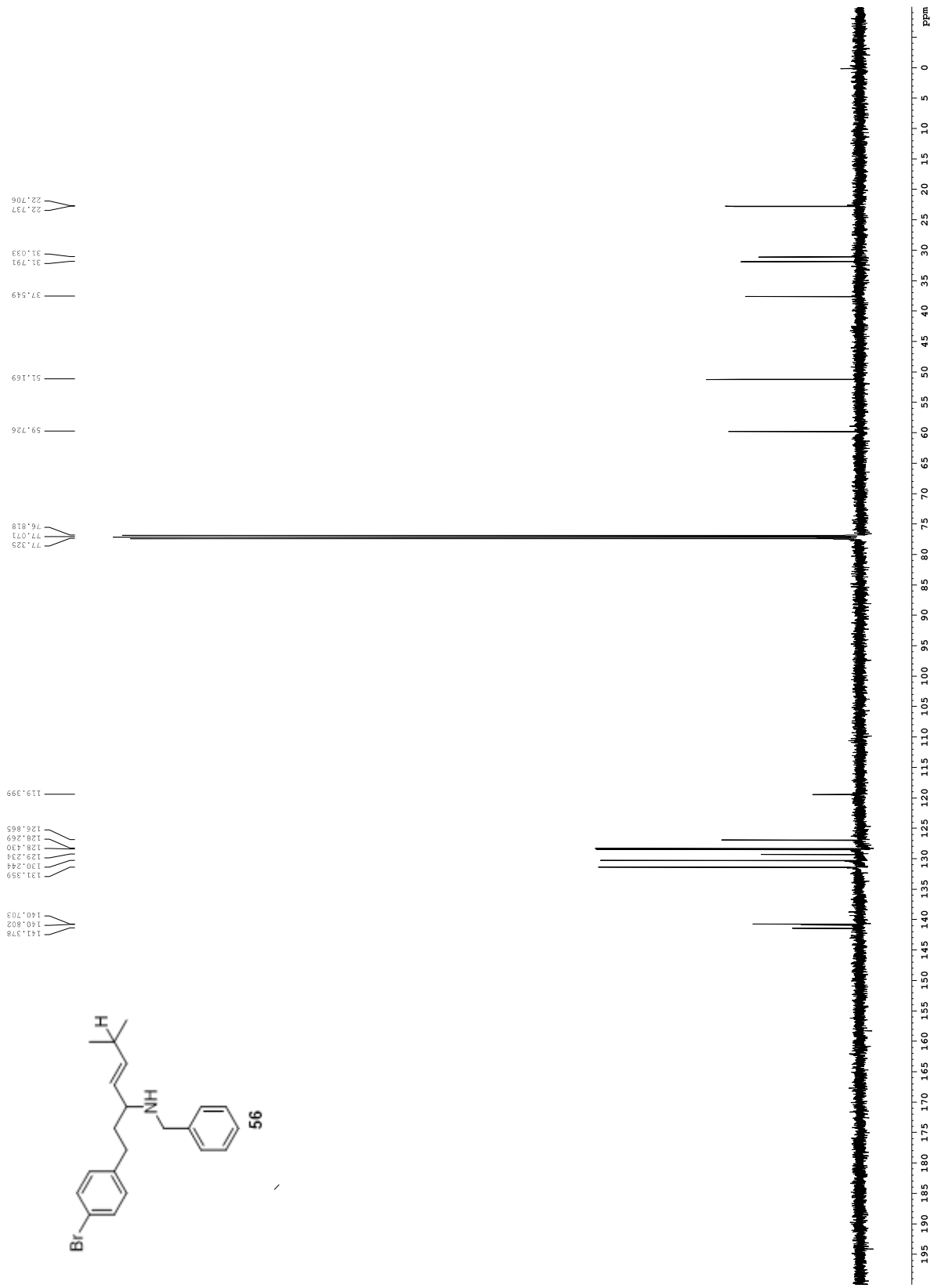
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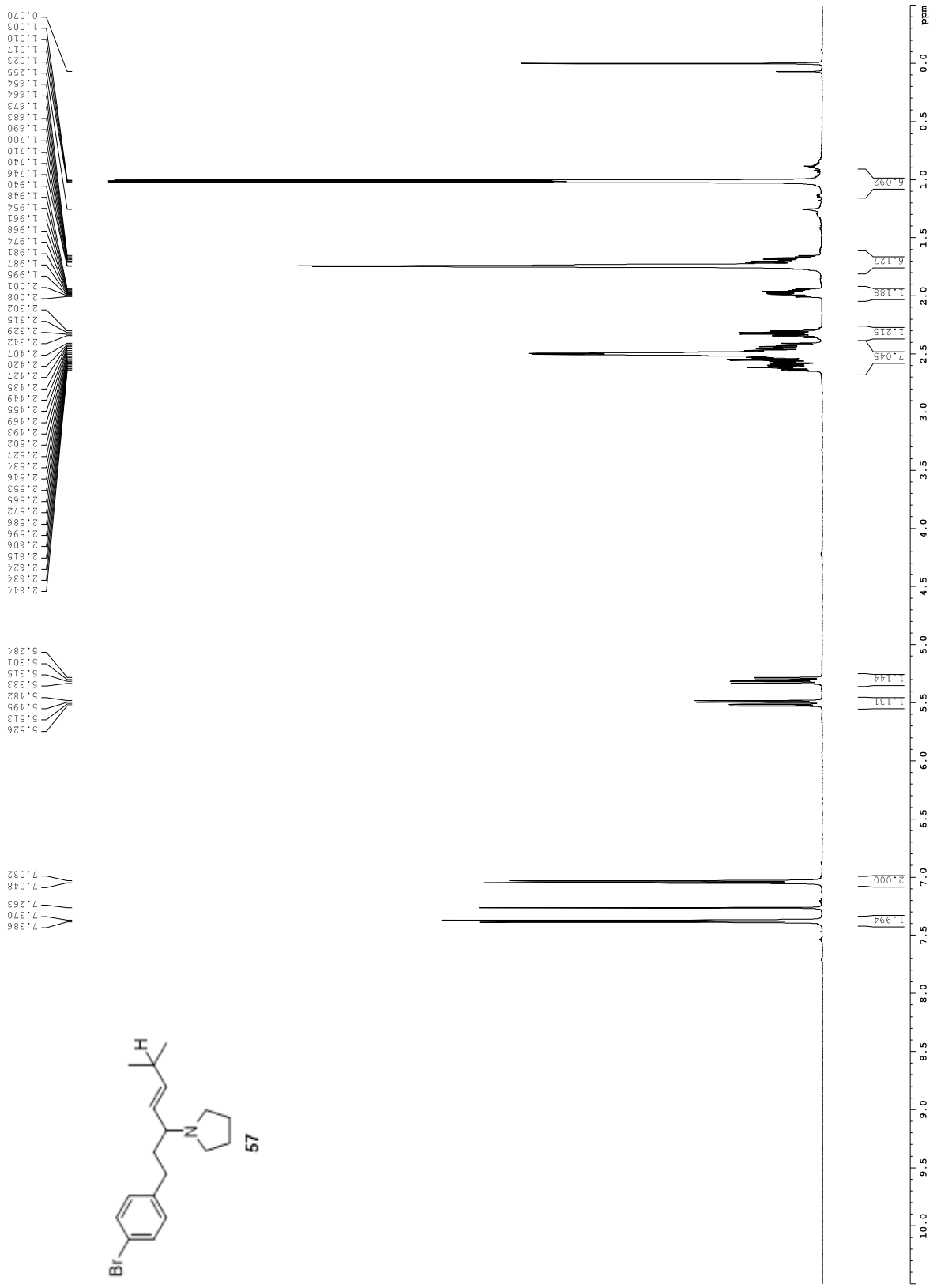
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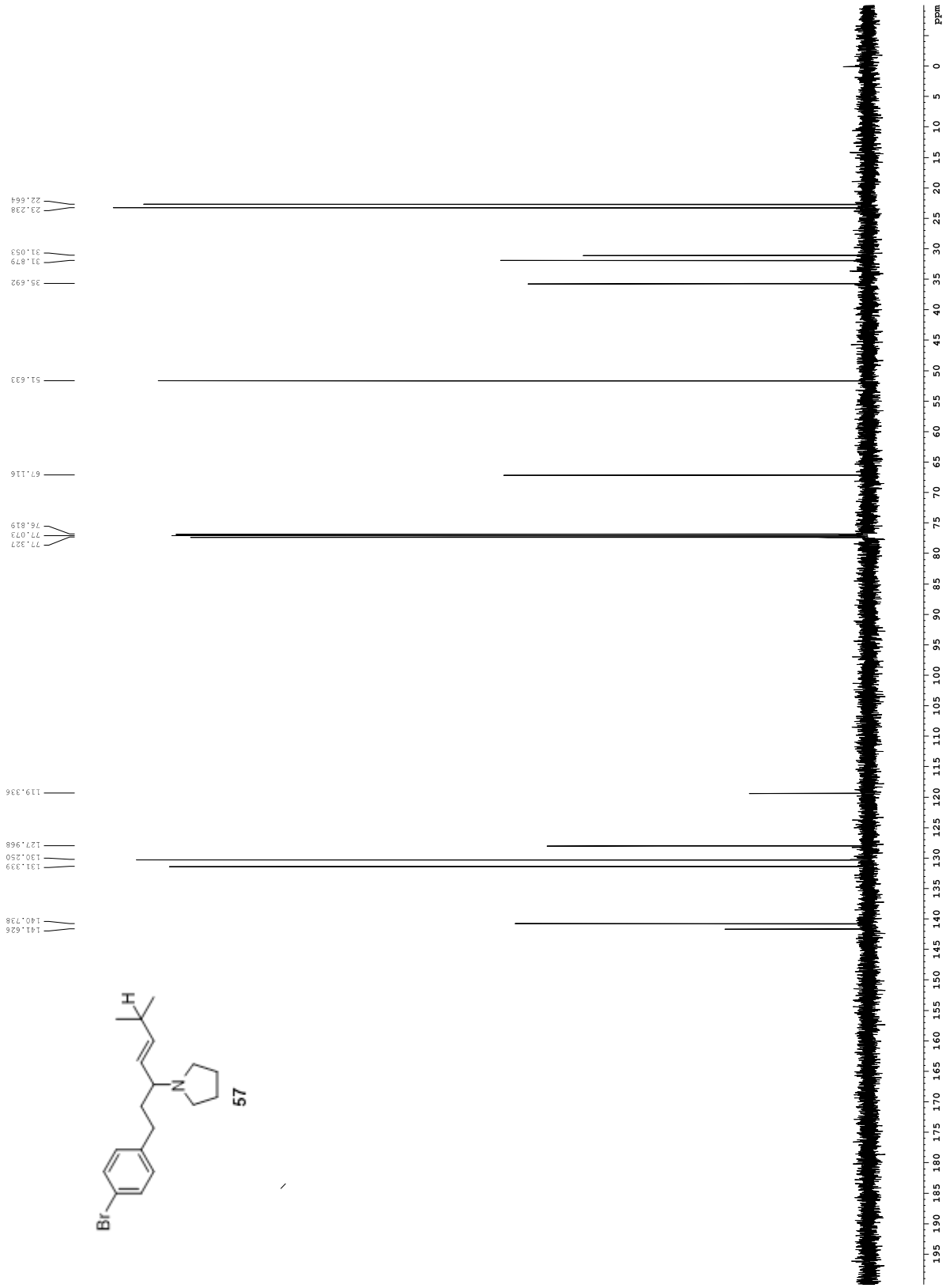
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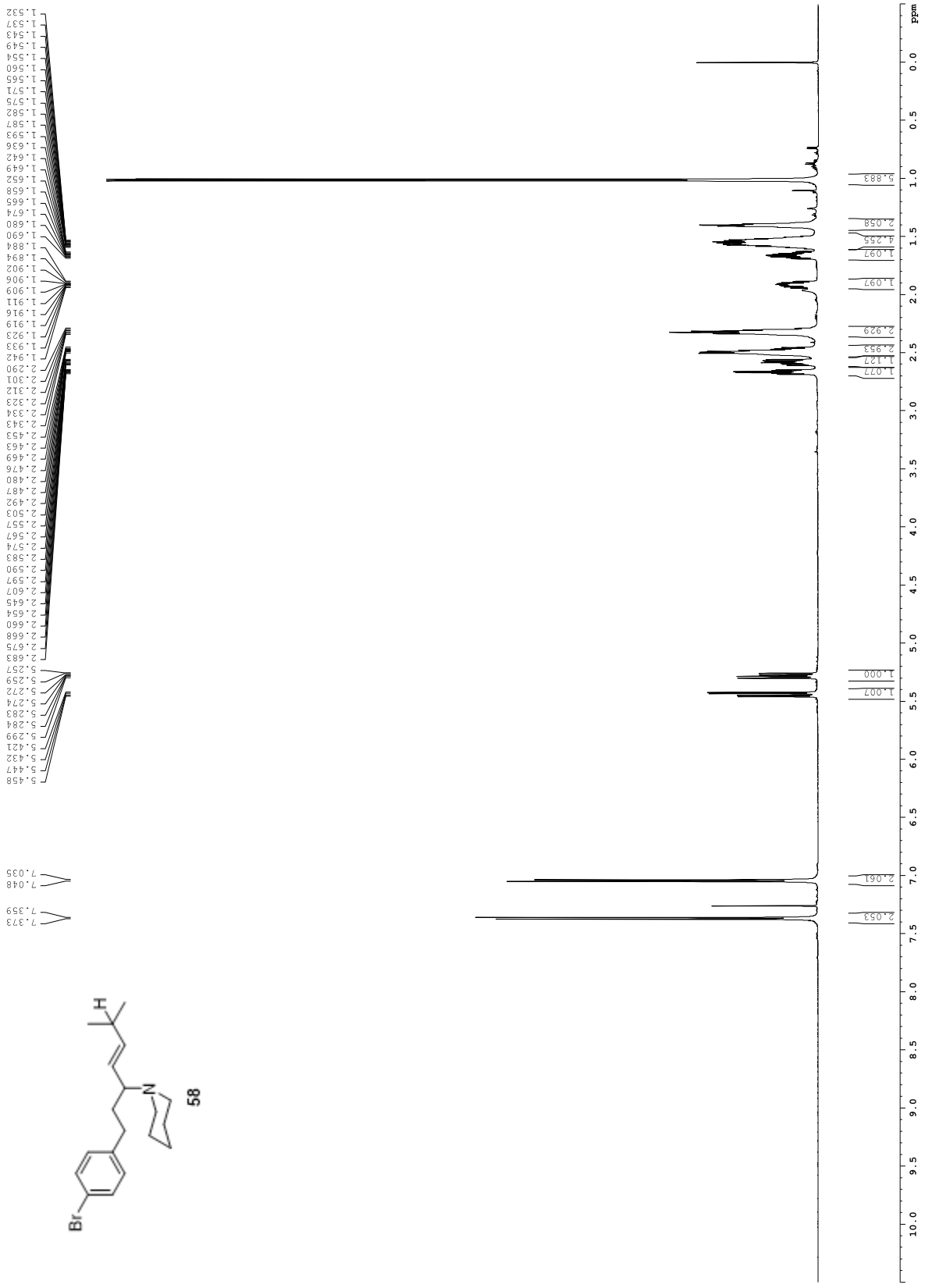
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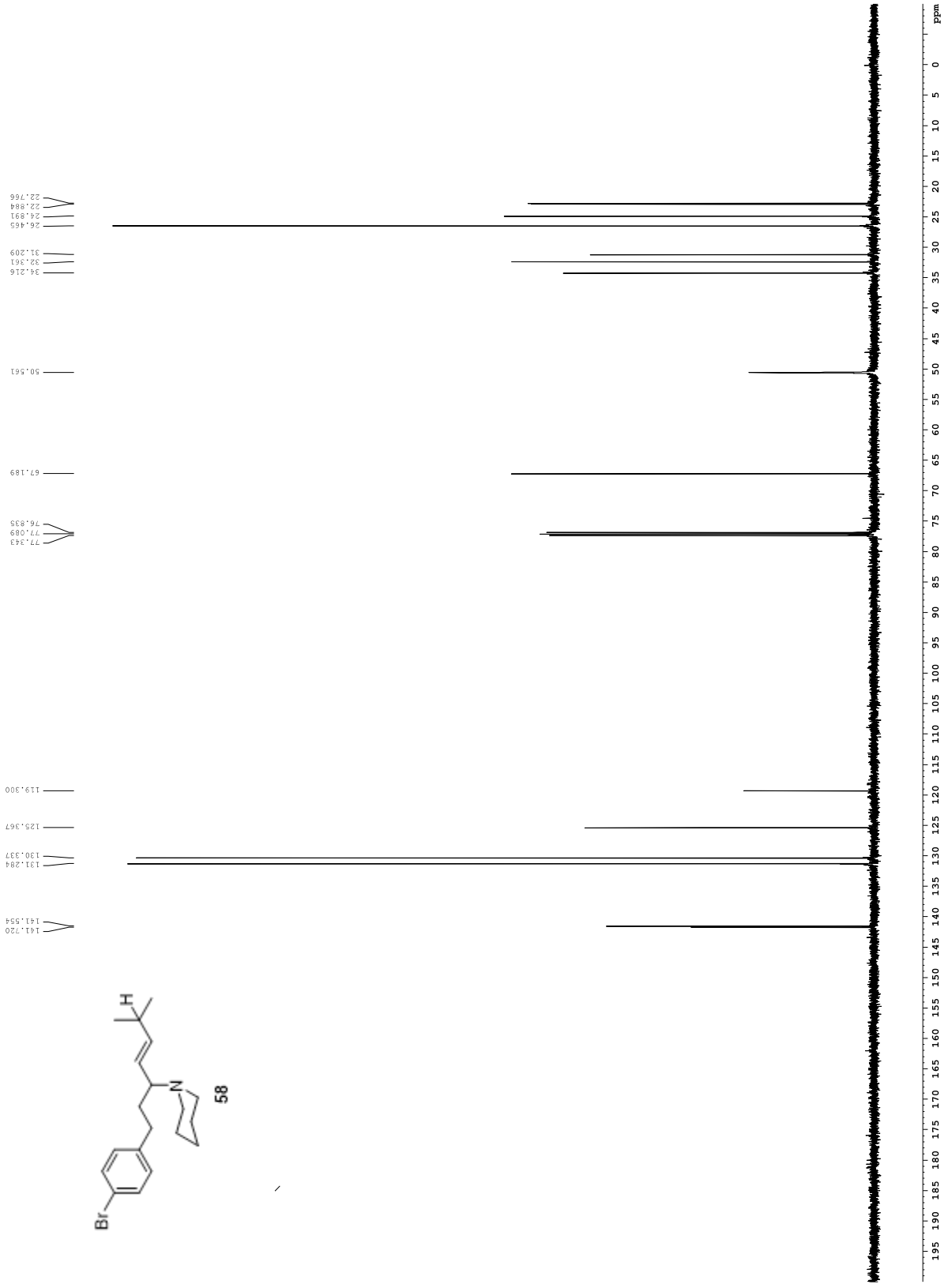
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H
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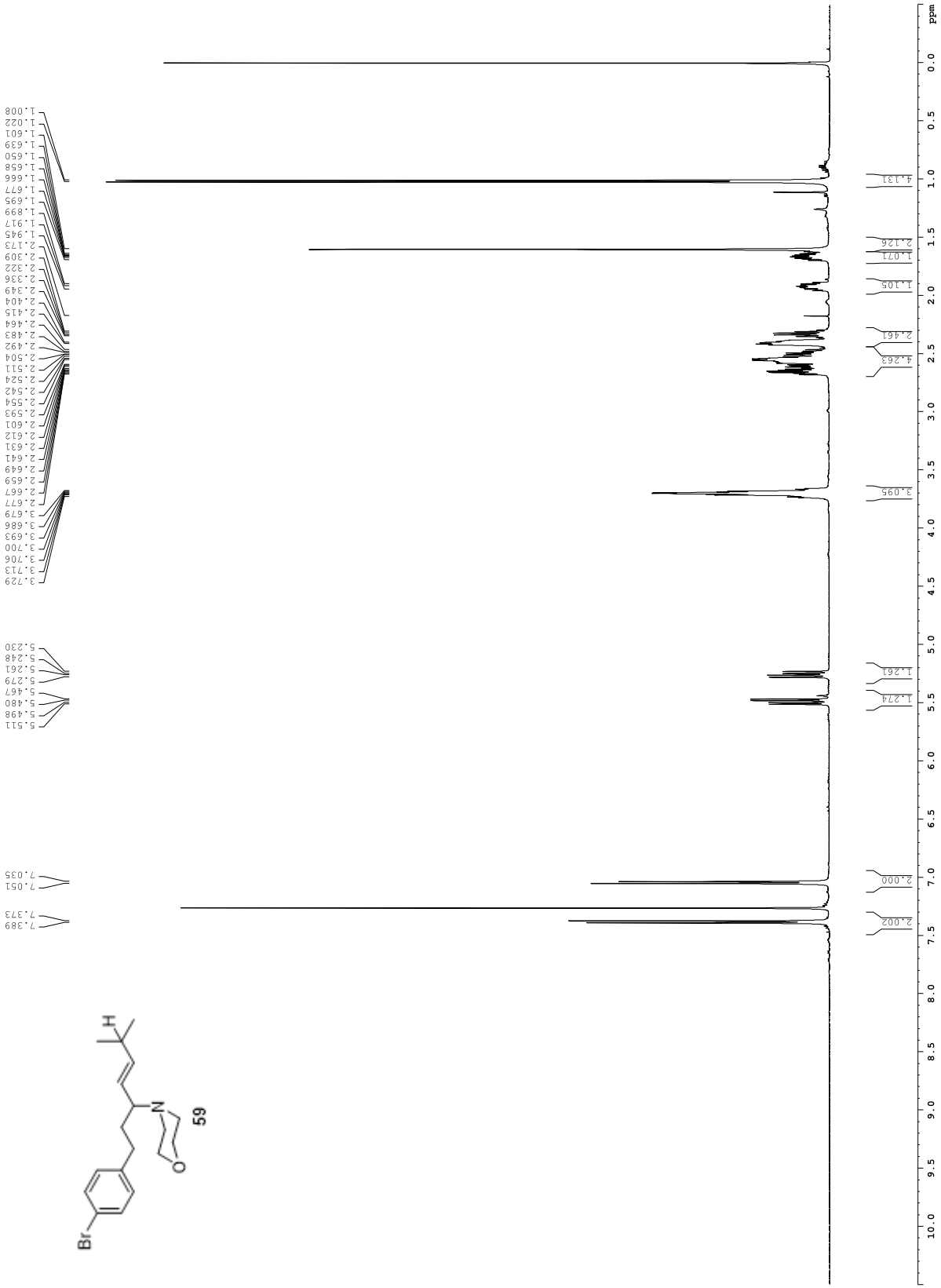
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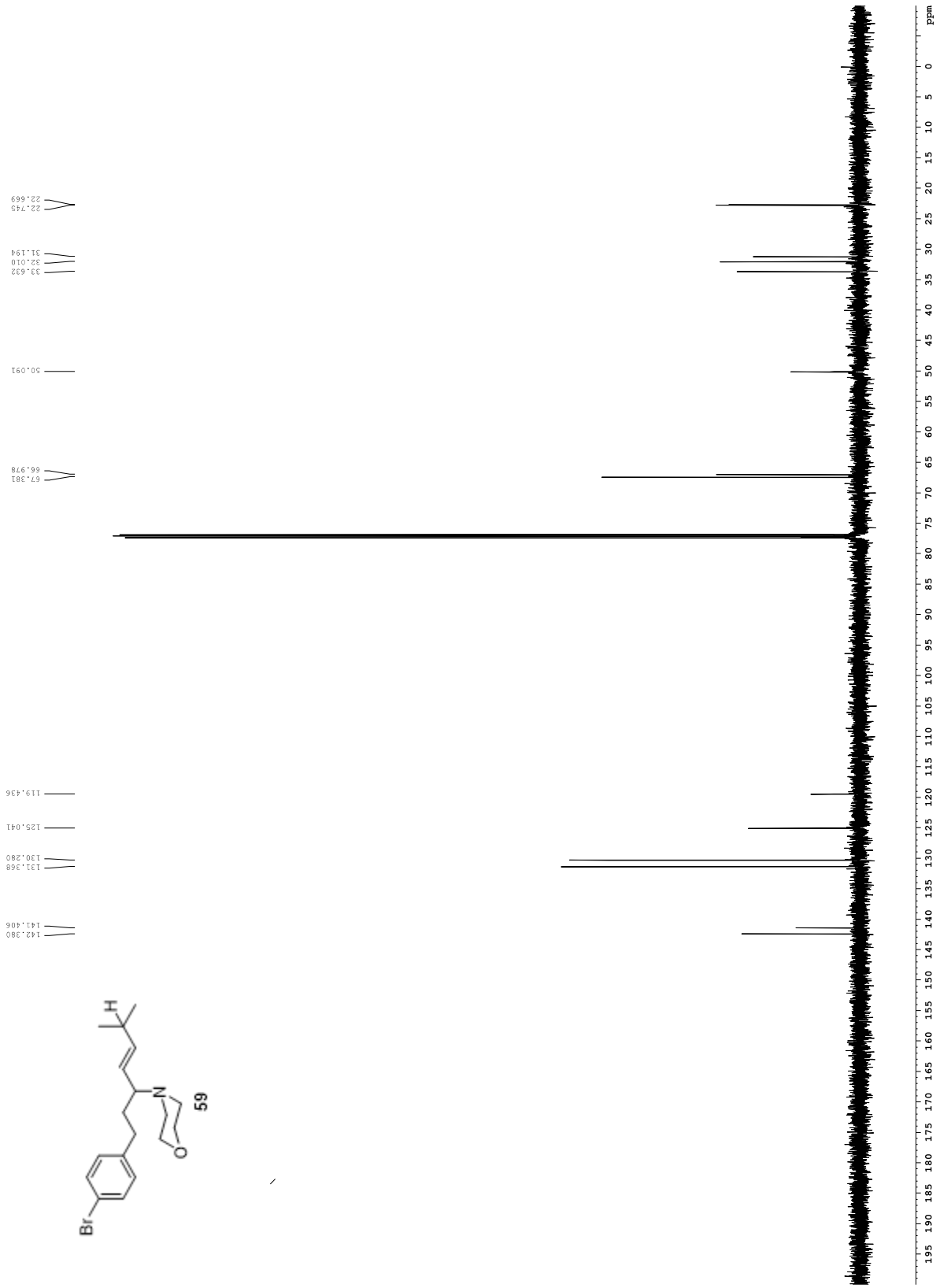
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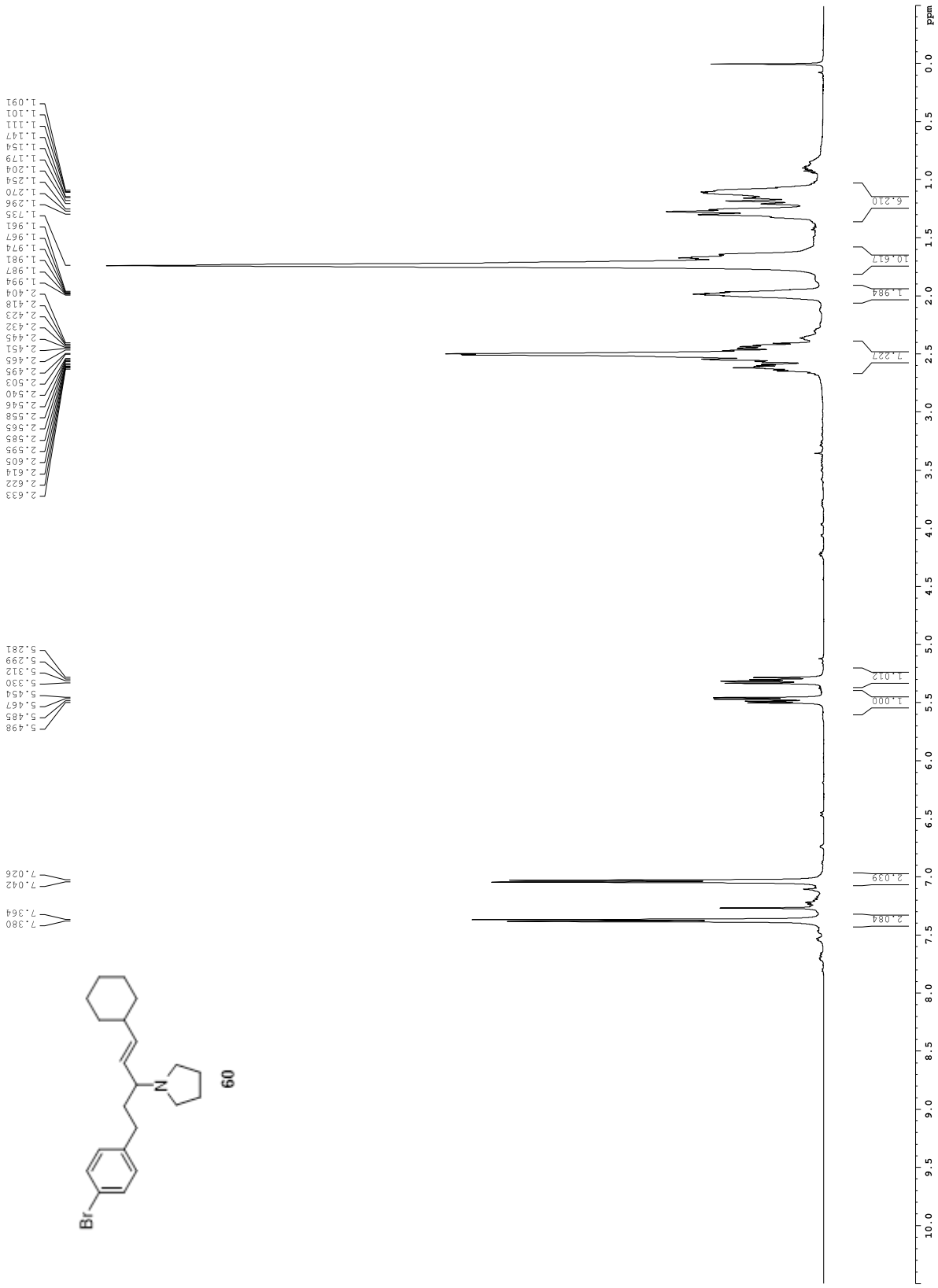
H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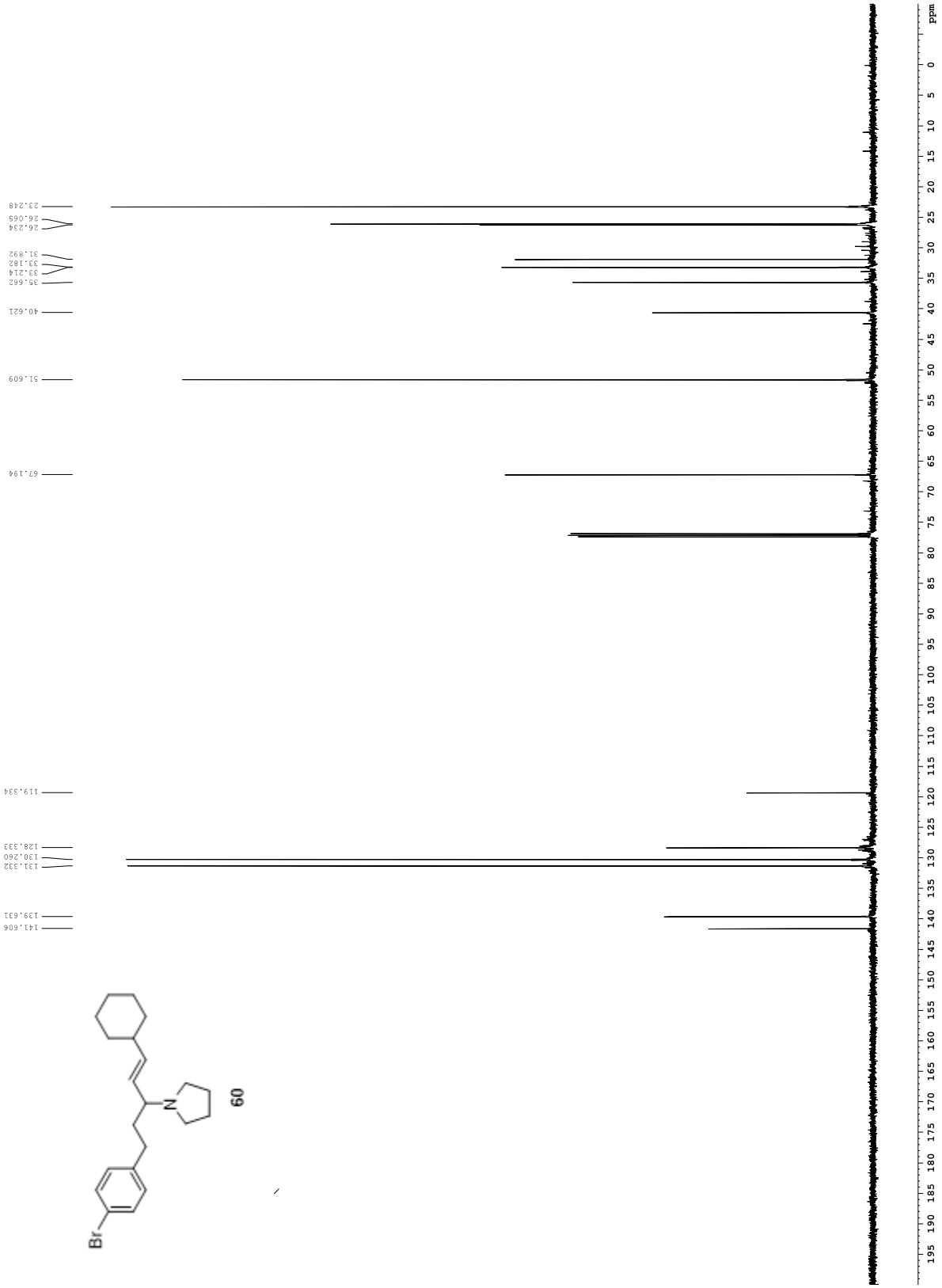
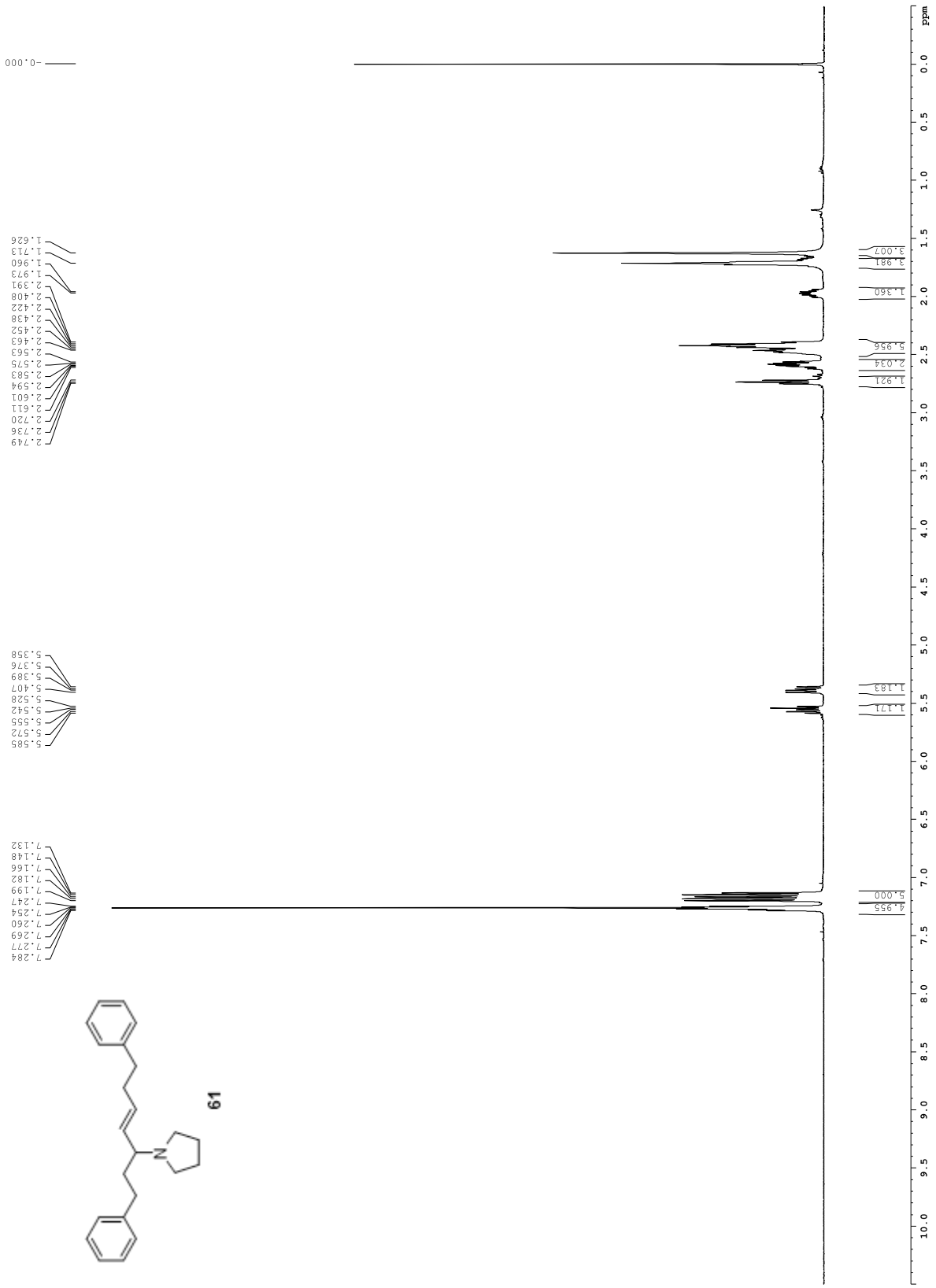
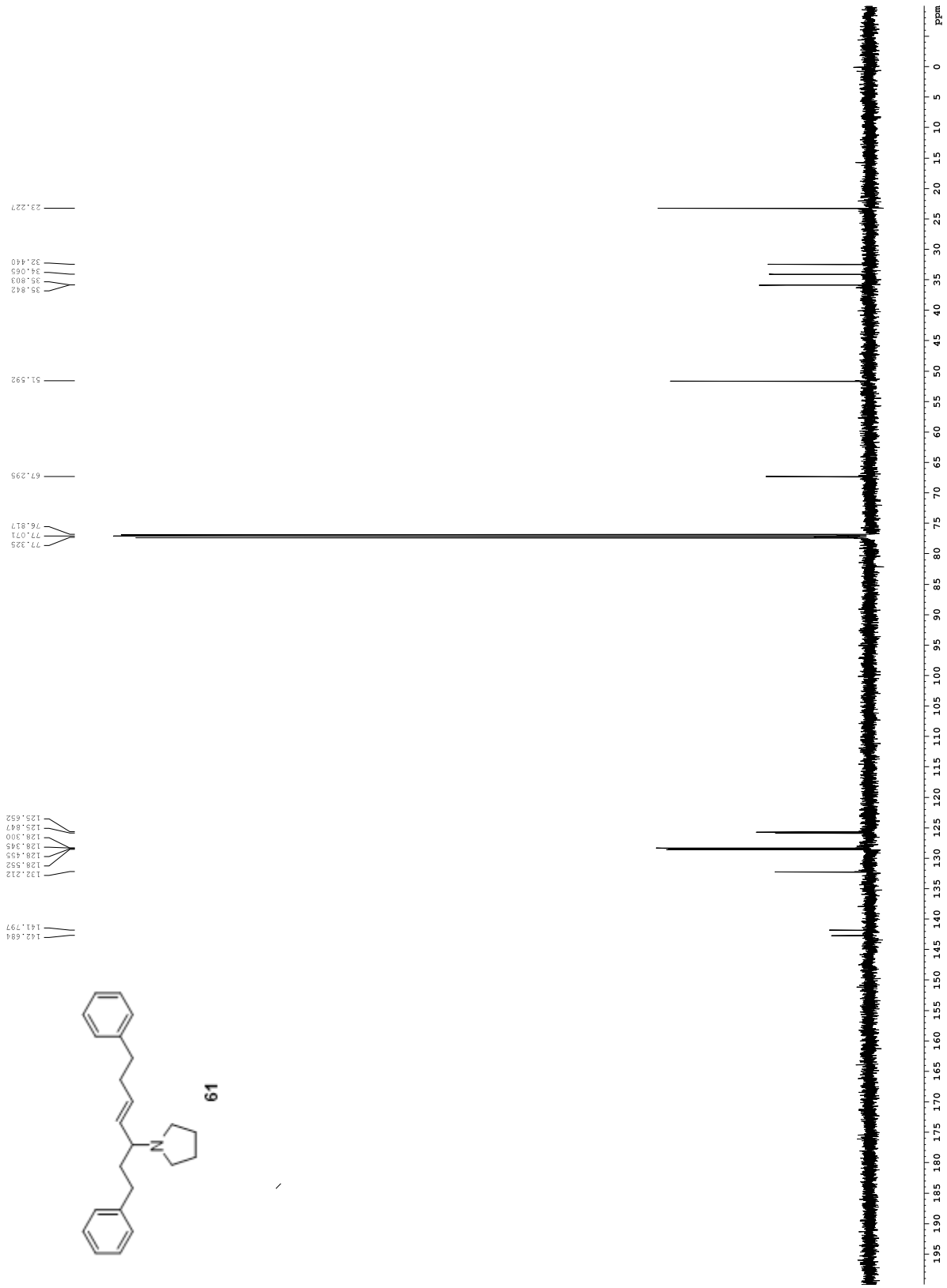
N
60


23.248
26.065
26.234
31.892
33.162
33.214
35.662
40.621
51.609
67.194
119.334
128.333
130.260
131.332
139.631
141.606
ppm
Br
N
60


61
ppm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32.440
34.065
35.803
35.842
51.592
67.295
76.817
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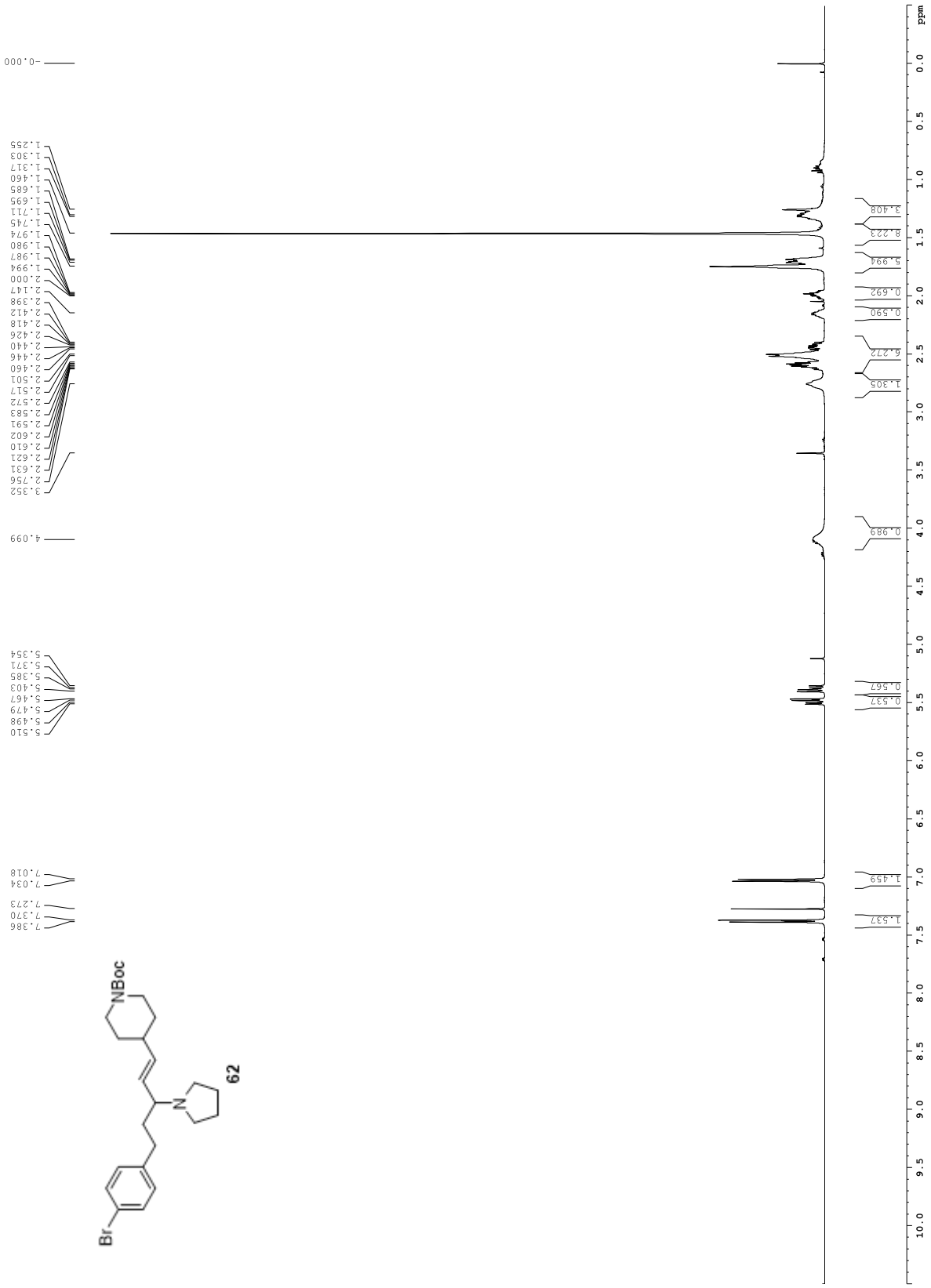
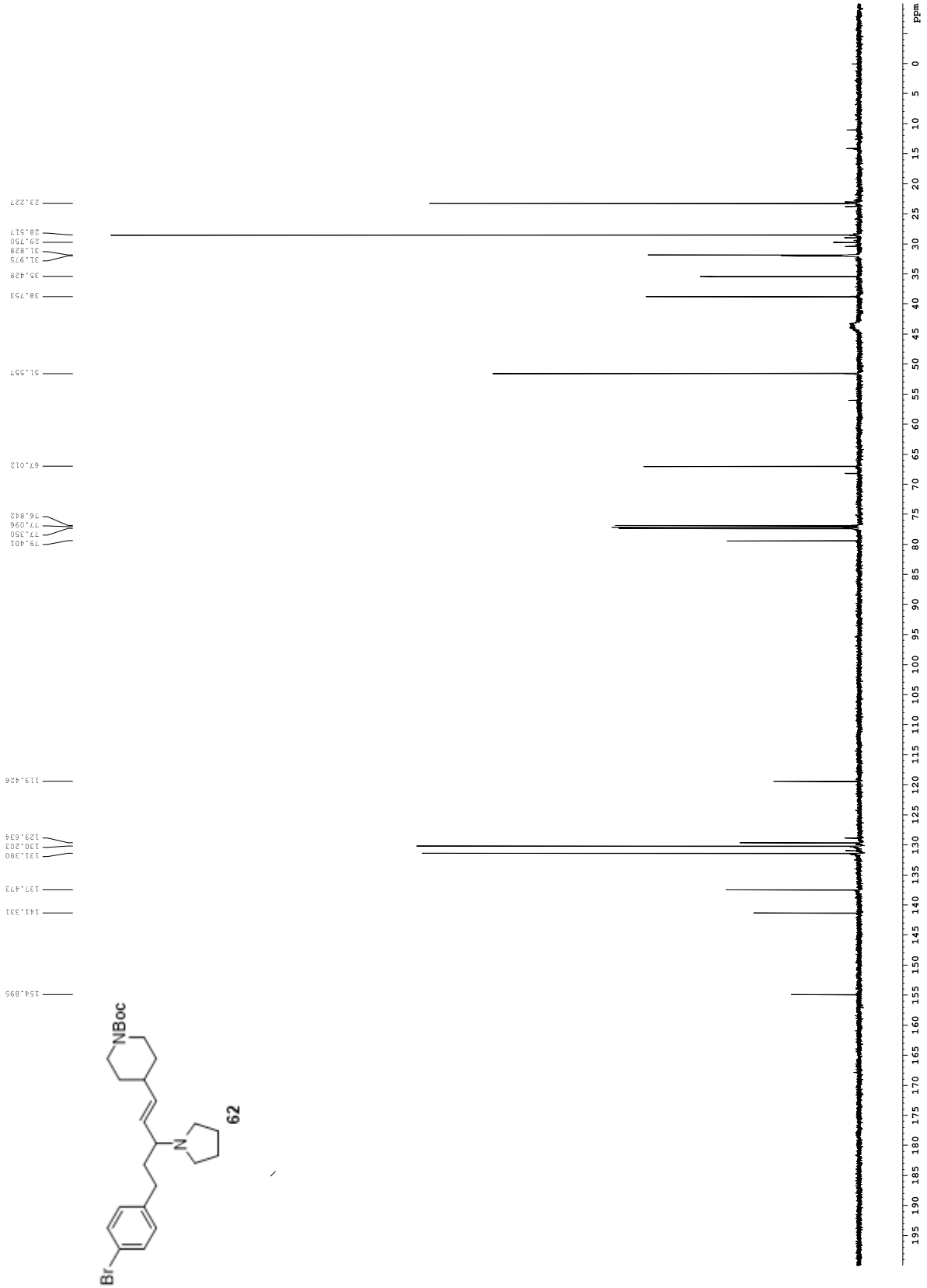
142.684
61
ppm


NBoc
N
Br
62


154.895
141.331
137.473
131.380
130.203
129.634
119.426
79.401
77.350
77.096
76.842
67.012
51.557
38.753
35.428
31.975
31.828
29.750
28.517
23.227
ppm
NBoc
N
Br
62

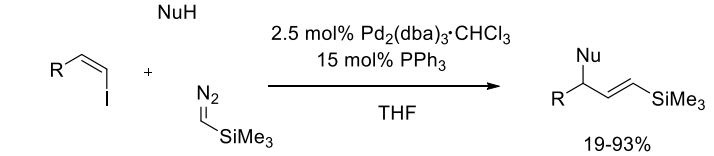
Chapter 3. Progress toward Iterative Palladium-Catalyzed Carbenylative Insertion of Vinyl Iodides

3.1. Introduction

Iterative processes have been utilized in synthetic organic chemistry to effectively access the core structures of various challenging molecules such as polyenes,[1] polyheterocyclics,[2] polycyclic ethers,[3] and polyketides.[4] Most iterative processes rely on robust reactions such as transition metal catalyzed cross-couplings and on the ability to reintroduce functional groups to reliably control the elongation of the molecule. For example, Burke and co-workers reported an iterative Suzuki–Miyaura coupling reaction utilizing boron-protected haloalkenylboronic acid to construct the polyene segment of amphotericin B.[1] Metal carbenes have also been utilized as intermediates in iterative processes as well. West and McDonald reported an iterative carbene insertion using copper[5] and tungsten[6] in progress towards the synthesis of brevetoxins by making trans-fused pyran ring. Recently, there has been growing interest in migratory insertion to palladium carbenes to construct new C–C bonds.[7] In this report I discuss the utility of such process to access useful synthetic substrates that can be potentially used in an iterative fashion.

In 2001, Van Vranken and co-workers reported the first catalytic cross-coupling that demonstrated a palladium carbene migratory insertion process.[8] In this reaction, benzyl halide

Scheme 3-1. General Three-Component Coupling of Vinyl Iodide, TMSD, and Nucleophiles.



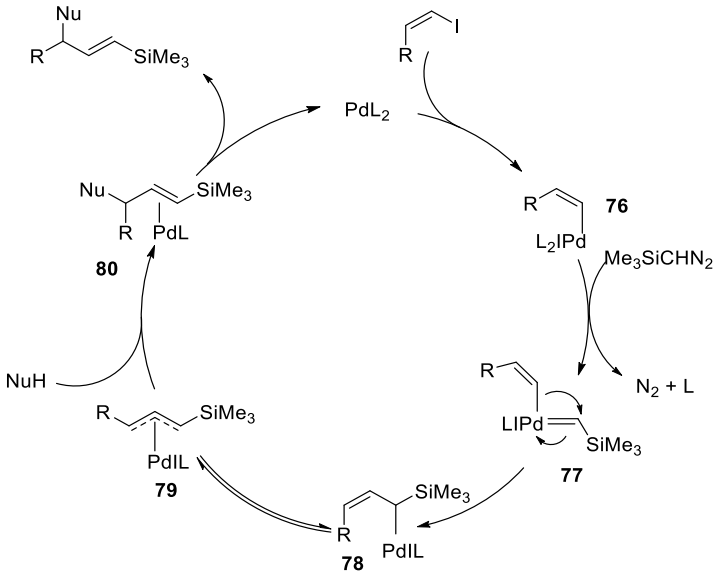
R: alkyl
NuH: malonates, malononitrile, ethyl cyanoacetate, cyclic secondary amines

oxidatively adds across palladium and then migrates to the subsequently formed palladium carben center from trimethylsilyldiazomethane (TMSD) as the key step in the reaction, which affords styrene derivatives. Later, this transformation was expanded to a three-component coupling of vinyl halides, TMSD and various nucleophiles (Scheme 3-1).[9,10]

The proposed mechanism for this coupling is shown in Scheme 3-2. Vinyl iodide undergoes oxidative addition across palladium to generate vinylpalladium complex **76**. Then, TMSD reacts with **76** to generate vinylpalladium-carbene complex **77.** Migratory insertion of vinyl group to carbene carbon form η^1-allylpalladium intermediate **78**, which is in equilibrium with η^3-allylpalladium **79**. An external nucleophile then attacks the η^3-allylpalladium to form **80**, which dissociates into product and catalytic palladium(0). The result of this transformation is the addition of a nucleophile, the extension of one carbon unit, and the formation of a vinylsilane.

In a subsequent transformation, the vinylsilane can be converted to vinyl iodide by iododesilylation. This new vinyl iodide can then be employed in a second palladium reaction.

Scheme 3-2. Proposed Mechanism for Palladium-Catalyzed Three-Component Coupling Reaction.



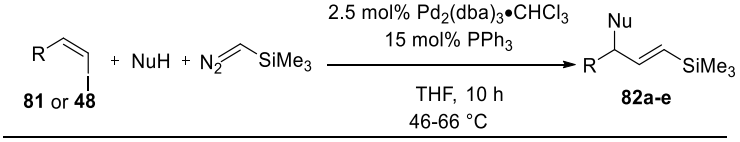
The two-step process of carbene insertion followed by iododesilylation to obtain a new vinyl iodide can be used in an iterative fashion. Such a process is yet to be developed. The goal of this research is to investigate iterative carbene insertion. This involves two steps: investigating iododesilylation conditions for the vinylsilanes generated in the first palladium reaction to subsequently yield vinyl iodides, and then utilizing the newly formed vinyl iodide substrates in a second palladium-catalyzed carbene insertion.

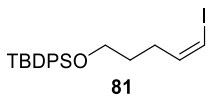
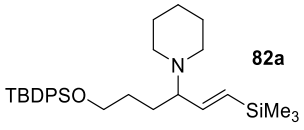
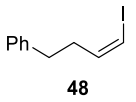
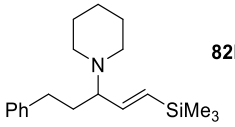
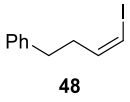
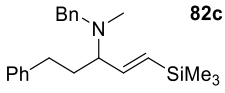
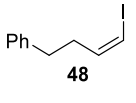
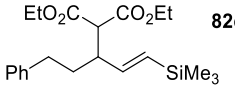
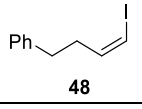
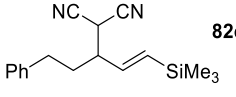
3.2. Results and Discussion

3.2.1. Palladium-catalyzed Reaction

Vinylsilanes were synthesized using conditions previously published in the Van Vranken's group (Table 3-1).[9,10] Treatment of vinyl iodides, **81** and **48**, a nucleophile, and slow

Table 3-1. Synthesis of Vinylsilanes from Pd-Catalyzed Coupling of Vinyl Iodide, TMSD, and Nucleophiles



Starting material	Product		Yield[a]
 **81**		**82a**	76%
 **48**		**82b**	86%
 **48**		**82c**	60%
 **48**		**82d**	73%
 **48**		**82e**	74%

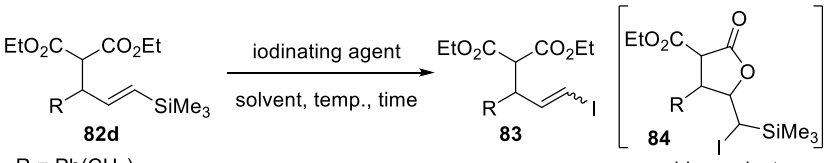
[a]Isolated yield after column chromatography

addition of TMSD by syringe pump in the catalytic palladium (0), resulted in vinylsilanes **82a-e** in 60-86% yields.

3.2.2. Iododesilylation Reaction

Vinylsilane **82d** was submitted to traditional iododesilylation condition by using iodine in DCM as the first reaction (Table 3-2, entry 1). Surprisingly, the isolated product was identified to be the protodesilylation product and was confirmed by the NMR of the reported compound.[10] Recently, Zakarian and co-worker reported a new iododesilylation condition. They treated alkyl vinylsilane with *N*-iodosuccinimide (NIS) in hexafluoroisopropanol (HFIP).[11] This condition

Table 3-2. Effect of Lewis Acids on Iododesilylation



82d **83** **84**

R = $Ph(CH_2)_2$ side product

Entry	Iodating agent (equiv)	Solvent (1.0 M)	Lewis acid (equiv)	**83** (%) (*E*/*Z*)
1[a]	I_2 (1.1)	DCM	–	–
2	NIS (2.2)	HFIP	–	67 (3:1)
3	NIS (2.2)	HFIP	Ag_2CO_3 (0.3)	62 (1:4)
4	NIS (2.2)	HFIP	$SnCl_4$ (2.0)	30 (1:4)
5	NIS (1.1)	HFIP	$SnCl_4$ (2.0)	73 (1:2)
6[b]	NIS (1.1)	HFIP	$ZnCl_2$ (2.0)	0
7[c]	NIS (1.1)	HFIP	$TiCl_4$ (2.0)	0
8	I_2 (2.2)	DCM	$AlCl_3$ (2.0)	32 (1:4)
9	NIS (1.1)	MeCN	$SnCl_4$ (2.0)	80 (1:2)
10	I_2 (1.1)	DCM	$SnCl_4$ (2.0)	93 (1:1)

[a] 55% protodesiylation product. [b] No vinyl proton was observed by ^1H NMR spectrum. [c] 22% protodesilylation product.

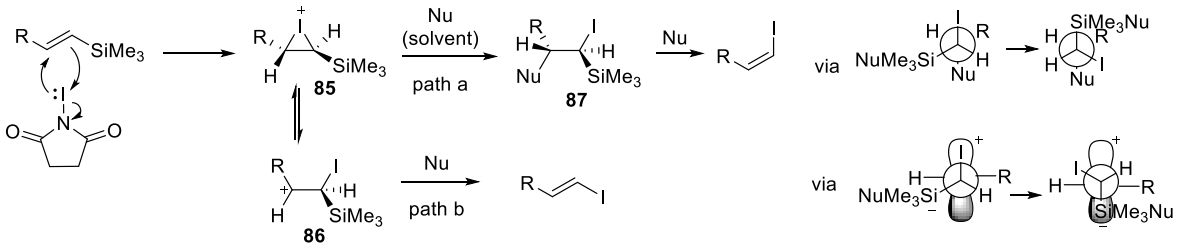
gave higher yields and better regioselectivities compared to other reported iododesilylation conditions such as NIS in monochloroacetonitrile.[12] So Zakarian's iododesilylation condition was used on vinylsilane **82d**. Vinyl iodide **83** was observed for the first time in 67% yield and 3:1 *E*:*Z* ratio after the reductive workup with saturated solution of $Na_2S_2O_3$ and 1 M HCl (Table 3-2, entry 2).

During isolation of the vinyl iodide **83**, iodolactonization side product **84** was isolated in 15-20% yield, which results from the participation of pendant ester group in iododesilylation process. To prevent iodolactonization, Lewis acids were used to deactivate the nucleophilicity of the lone pair on oxygen carbonyl ester.[13] When $SnCl_4$ is used in Zakarian's condition with 2.2 equivalents of NIS, vinyl iodide **83** was obtained in 30% yield and lactone byproduct **84** was isolated in 52% yield (Table 3-2, entry 3). Reducing the equivalent of NIS to 1.1 increased the yield to 73% (Table 3-2, entry 4). When $ZnCl_2$ was used, there was no vinyl proton on the ^1H NMR spectrum (Table 3-2, entry 6). Protodesilylation product was observed in 22% yield when $TiCl_4$ was used (Table 3-2, entry 7). The effect of solvents was also tested because of the use of HFIP as solvent is not economical if the stereoselectivity was not as good as expected. When solvent was switched to acetonitrile, the vinyl iodide **83** was obtained in good yield (Table 3-2, entry 8). The best yield of vinyl iodide **83** was obtained in 1:1 *E*/*Z* when iododesilylation was carried out with iodine in DCM with $SnCl_4$ as Lewis acid. Since the optimization conditions were obtained recently, the following results and discussion were using condition in entry 2. After vinyl iodide **83** was obtained, it was submitted to the second palladium-catalyzed carbenylative coupling to demonstrate iterative process.

A rationalization for the low stereoselectivity can be explained as shown in Scheme 3-3.[13] In general, the iodonium **85** was formed when iodinating agent deliver iodide to the vinylsilane. The iodonium **85** can be in equilibrium with β-silyl cation intermediate **86** depending on the solvent polarity. A nucleophilic attack on silyl group on the intermediate **86** sequentially yields vinyl iodide with retention of stereocenter as shown by Newman projection (path b). On the other hand, nucleophilic attack from either solvent or actual nucleophile can open the iodonium **85** to form **87**. A nucleophilic attack of the silyl group will eventually afford vinyl iodide with

the inversion of stereochemistry. The pendant malonate on **82d** can also act as a nucleophile because of the nucleophilic lone pair on the carbonyl oxygen, which can explain for low *E*/*Z* selectivity.

Scheme 3-3. Rationalization of the Formation of *E*- and *Z*-Isomers in Iododesilylation



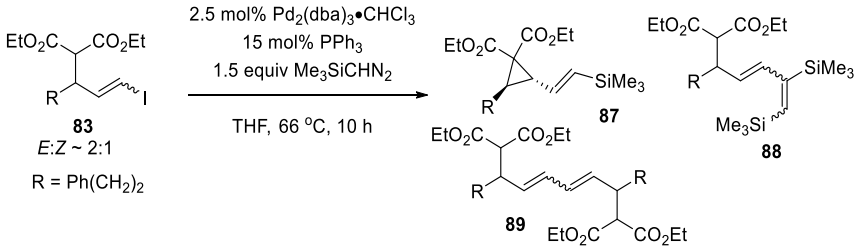
3.2.3. Second Palladium-Catalyzed Carbenylative Insertion Reaction

To demonstrate the iterative nature of this sequence of reactions, the newly formed vinyl iodide **83** was used in a second palladium-catalyzed carbenylative insertion reaction. Instead of using an external nucleophile such as diethylmalonate anion, the pendant diethyl malonate on **83** was utilized to trap the expected π-allylpalladium intermediate (see Scheme 3-2). If the second palladium reaction followed the proposed mechanism, it would result in formation of cyclopropane vinylsilane **87**.

Vinyl iodide **83** was treated with NaH to generate internal malonate anion and added to palladium (0) catalyst with slow addition of TMSD over 10 h (Table 3-3). The first reaction was run with 1.1 equiv of NaH, 1.5 equiv of TMSD over 10 h, there were 6% recovered vinyl iodide **83** with only *Z*-isomer, 10% of cyclopropane **87**, 32% of bis-TMS **88**, and 55% of homo-coupling **89** (entry 1). To prevent the formation of homo-coupling, the concentration of vinyl iodide **83** was reduced half while other reagents were kept at the same concentration (entry 2). The formation of cyclopropane and other by-products did not change significantly. Because bis-TMS product formed in a significant amount indicate a high concentration of TMSD in the reaction. When the rate of TMSD was decreased in half, no change in the result compared to

entry 1. Because the reaction was run in a small scale, due to the errors occurred in measuring, it is possible that the amount of NaH used to deprotonate **83** might be lower than the required amount, so NaH was doubled in the next reaction. To ensure malonate was deprotonated, the equivalent of NaH was double (entry 4). However, the formation of cyclopropane and other by-products was similar to entry 1. When the reaction was run without the addition of TMSD, only

Table 3-3. Optimization of Iterative Carbene Insertion Reaction with Pendant Nucleophile.



Entry	Base (equiv)	**4** (equiv)	Rec.**4**(%)	Yield (%)		
				87[a]	**88**[b,c]	**89**[d]
1	NaH (1.1)	1	6	7	26	50
2	NaH (1.1)	0.5	5	10	20	40
3[e]	NaH (1.1)	1	16	2	25	52
4	NaH (2.2)	1	0	10	27	40
5	NaH (1.1)	1	16	0	0	53

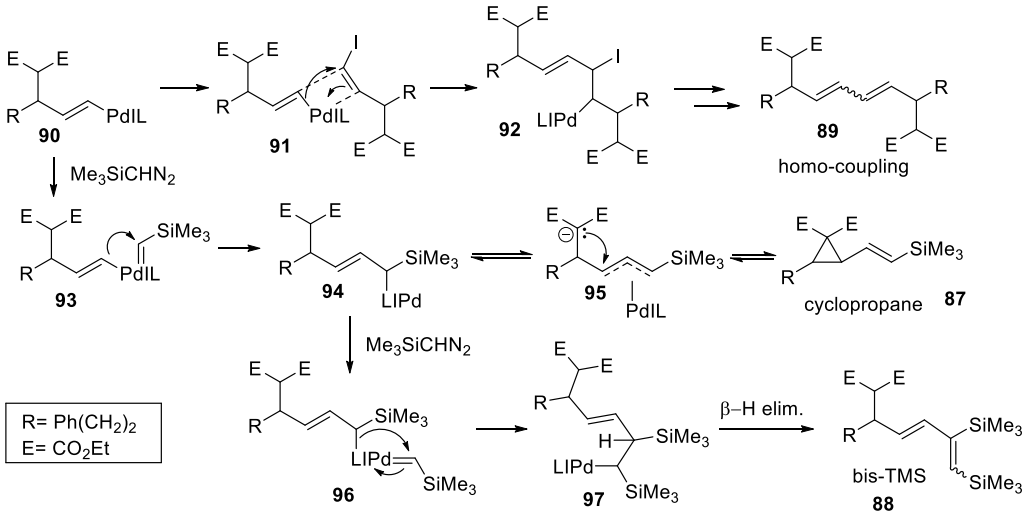
[a]Z-isomer only. [b]The yield was determined by ^{1}H NMR spectroscopy using 1,4-dimethoxy -benzene as internal standard.[c] **88** and **89** were isolated as a mixture. The yield of **88** was based on mass difference. [d]Isolated yield after column chromatography. [e]TMSD was diluted in half

homo-coupling product **89** was formed (entry 5). It is interesting that for the first few minutes of the reaction, the homo-coupling product was observed before product and other by-products.

A proposed mechanism for the formation of cyclopropane vinylsilane **87** and other by-products is shown in Scheme 3-4. Oxidative addition of vinyl iodide **83** across palladium results in the formation of vinylpalladium complex **90**. This complex can undergo carbopalladation with vinyl iodide starting material to form homo-coupling product **89**. In the presence of TMSD, complex **90** can generate vinylpalladium carbene intermediate **93**. Migratory insertion of vinyl group generates η^1-allylpalladium complex **94** that can isomerize to η^3-allylpalladium complex

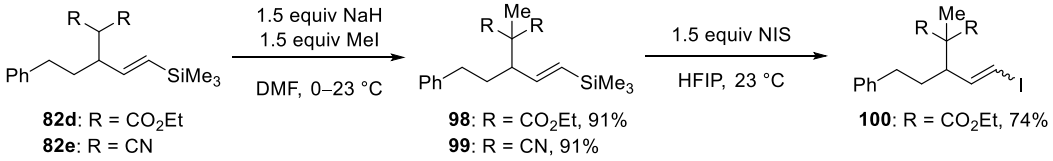
95. The internal malonate nucleophile then attacks the η^3-allylpalladium complex to generate the strained cyclopropane vinylsilane **87**. Alternatively if cyclopropane formation is unfavorable, complex **94** can react with another TMSD to generate palladium carbene complex **96**. Migratory insertion followed by β-hydride elimination results in the formation of bis-TMS from **88**. The formation of cyclopropane vinylsilane is the first example of iterative carbenylative homologation.

Scheme 3-4. Possible Pathways to Form Cyclopropane **87** and Side Products **88** and **89**.



In order to carry out the three-component cross-coupling reaction, the new vinyl iodide is methylated to prevent the internal nucleophile attack of η^3-allylpalladium intermediate. First, vinylsilane **82d** was depronated by NaH followed by addition of MeI to obtain methylated vinylsilane **98** (Scheme 3-5). Then methylated vinylsilane underwent iododesilylation condition

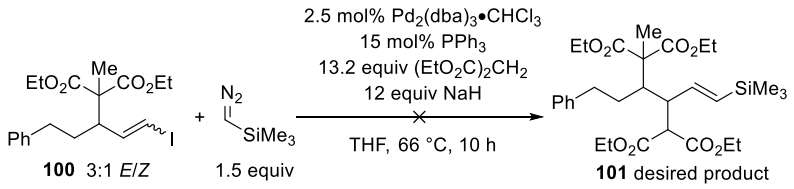
Scheme 3-5. Synthesis of Methylated Vinyl Iodide **100**



to obtain methylated vinyl iodide **100**. The methylated vinylsilane **99** did not convert to vinyl iodide under the same iododesilylation condition.

Then vinyl iodide **100** was then submitted to palladium-catalyzed carbenylative coupling reaction as showed in Scheme 3-6 with diethylmalonate as nucleophile. The reaction did not yield the desired product **101** with the addition of second nucleophile; instead, vinyl iodide **100** was recovered in 40% and bis-TMS and homo-coupling products were detected by mass spectroscopy because ^{1}H NMR spectrum was hard to decipher in the vinyl proton region. A plausible explanation for this outcome is that the steric bulk on both sides of allyl intermediate generated in the reaction prevents the trapping of a nucleophile, which results in unproductive pathways to generate homo-coupling and bis-TMS products. To prevent the steric bulk, vinylsilanes with nitrogen nucleophile was used next.

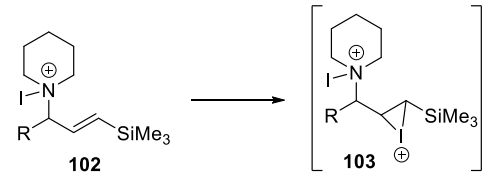
Scheme 3-6. Second Pd-catalyzed Carbenylative Coupling with Vinyl Iodide **100**



Without any successes from the second palladium-catalyzed carbenylative cross coupling reaction with carbon nucleophile, allyl amine vinylsilane were investigated. Vinylsilanes **82a** and **82b** were submitted to Zakarian's iododesilylation condition. Surprisingly, vinylsilanes did not undergo iododesilylation. The ^{1}H NMR spectrum of the crude mixture contained many signals in the alkene region. A small amount of vinylsilane **82a** and **82b** were recovered and no desired iododesilylation product was observed. Other iododesilylation conditions did not yield desired product.[14] The nucleophilic character of the tertiary amine in vinylsilanes **82a** and **82b** may be the reason for these results. The lone pair on tertiary amine can attack iodinating agents to

generate an *N*-iodoammonium intermediate **102** that would prevent the formation of adjacent iodonium in **103** (Scheme 3-7).

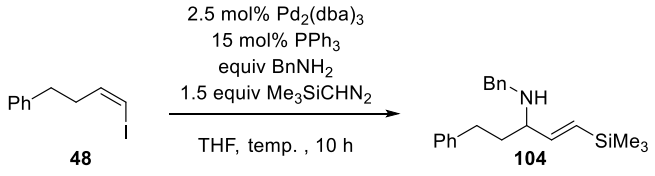
Scheme 3-7. An *N*-Iodoammonium is Expected to Destabilize the Formation of Iodonium **103**



102a: R = $TBDPSO(CH_2)_3$
102b: R = $Ph(CH_2)_2$

To prevent the formation of *N*-iodoammonium species, primary amine was used as a nucleophile in the first palladium-catalyzed reaction so that it can be protected after the formation of vinylsilane. From previous report,[9] vinylsilane **104** was obtained in 30% using benzylamine as a nucleophile. A few parameters of the reaction were investigated to improve the yield (Table 3-4). From the report, increasing reaction temperature from 46 to 66 ºC improves the yield from 19 to 30% (entry 1 and 2). So the reaction was run at 80 ºC, however, the yield lowered by half (entry 3). Double the palladium load did not improve the yield (entry 5). The recovered vinyl iodide also decreased significantly indicated that vinyl iodide participated in

Table 3-4. Optimization of the Formation of Vinylsilane **104**



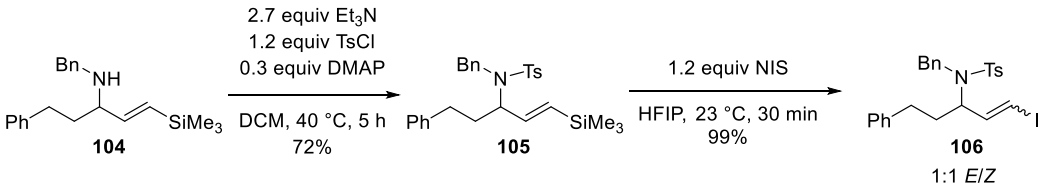
Entry	$BnNH_2$ (equiv)	Temp. (°C)	Rec. **48** (%)	Product (%)
1[a]	4	46	50	19
2	2	66	48	30
3	2	80	20	17
4	2	66	48	29
5[b]	2	66	14	30
6	4	66	54	16

[a] Reported in ref. 9. [b] 5 mol% $Pd_2(dba)_3$ and 30 mol% PPh_3

other side-reactions. Changing the amount of benzylamine decreased the yield (entry 5 and 6). So vinylsilane **104** was synthesized according to the condition in entry 2. The low yields can be attributed to the lower nucleophilicity of primary amines compared to secondary, which benefit from the extra hyperconjugation from C-H bond next to the nitrogen.

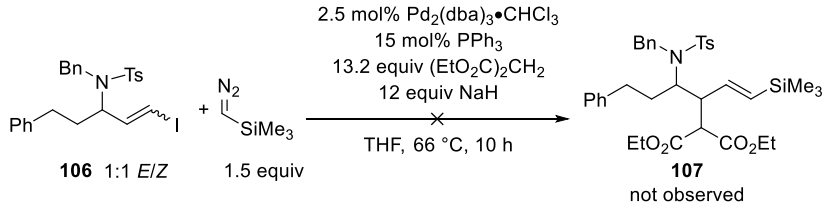
The amine group on vinylsilane **104** was protected with the tosyl group so that the lone pair on the nitrogen will not interfere with iododesilylation.[15] Indeed, tosylated vinylsilane **105** smoothly underwent iododesilylation to form **106** in high yield (Scheme 3-8). The second

Scheme 3-8. Synthesis of Allyl Sulfonamide Vinyl Iodide **106**.



palladium-catalyzed carbenylative was carried out with vinyl iodide **106** in the presence of diethylmalonate anion and piperidine as a nucleophile (Scheme 3-9). However, starting material was recovered in 40% and 60%, respectively. Homo-coupling and bis-TMS by-products were also observed in ^{1}H NMR and mass spectroscopy. High recovered vinyl iodide indicated low catalytic turnover for this reaction.

Scheme 3-9. Second Pd-catalyzed Carbenylative Coupling with Vinyl Iodide **106** and Diethyl Malonate Anion



3.3. Conclusion

In conclusion, iododesilylation of vinylsilanes from three-component coupling was obtained only for vinylsilanes with diethylmalonate **82d** and with protected amine **105**. When

nucleophile was cyclic secondary amine or malononitrile, iododesilylation product was not formed. The resulting vinyl iodide **83** with appending malonate as a nucleophile was submitted to palladium-catalyzed carbenylative reaction. As expected, the cyclopropane vinylsilane **87** was obtained in low yield due to possible palladium-assisted ring opening of cyclopropane vinylsilane.

The second palladium-catalyzed carbenylative coupling reaction with vinyl iodides **100** and **106** and an external nucleophile were not successful due to the steric bulk on both sides of π-allyl intermediate, which was generated in the reaction. The formation of homo-coupling and bis-TMS products indicated that nucleophilic trapping of π-allyl intermediate pathway had to compete with other unproductive pathways.

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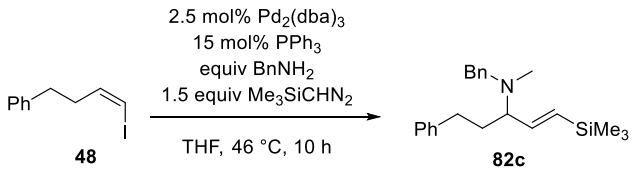
3.5. Supporting Information

3.5.1. General Procedures

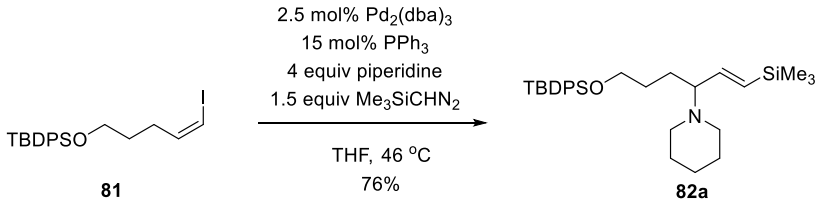
NMR spectral data were recorded at room temperature using either a Bruker 500 MHz or 600 MHz spectroscopy. The NMR data are reported as follows: chemical shift in ppm from tetramethylsilane internal standard on the δ scale, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. All IR spectra were recorded on a PerkinElmer FT-IR Spectrum Two. All reactions were monitored by thin layer chromatography (TLC) technique using EMD Reagent 0.25 mm silica gel 60-F. UV light, $KMnO_4$ and *p*-anisaldehyde stain were used for TLC visualization. Silica gel for "flash" column chromatography was purchased from Silicycle (SiliaFlash® F60, 40-60 μm, 60Å). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. All reactions were evacuated and back-filled with nitrogen three times. Unless otherwise noted, all reagents were commercially obtained. Dry THF, Et_2O, and CH_2Cl_2 were obtained by filtration through alumina according to the procedure of Grubbs and co-workers.[1]

3.5.2. Experimental Section



Synthesis of (*E*)-N-benzyl-N-methyl-5-phenyl-1-(trimethylsilyl)pent-1-en-3-amine, 82c. The compound **82c** was synthesized according to the method of Devine, *et al*.[2] A flame-dried 5 mL round-bottom flask was charged with vinyl iodide **48** (0.067 g, 0.26 mmol), $Pd_2(dba)_3$•$CHCl_3$ (0.067 g, 0.065 mmol), triphenylphosphine (0.010 g, 0.039 mmol) and a stir-bar. The flask was fit with a septum and purged with nitrogen. THF (1.0 mL) was added and the resulting purple

suspension was stirred at room temperature until a clear orange solution was obtained (about 10 min). *N*-Benzylmethylamine (0.14 mL, 1.0 mmol) was added to the flask by syringe and the resulting green solution was stirred at 46 °C in a preheated oil bath. Trimethylsilyldiazomethane (TMSD) (2.0 M in diethyl ether, 0.20 mL, 0.39 mmol) was added by syringe pump over 10 h. The resulting orange solution was then cooled to room temperature and poured into a separatory funnel containing 1% NaOH solution (1x3 mL). The resulting mixture was extracted with EtOAc (3x5 mL). The combined extracts were washed with brine (1x5 mL), dried over Na_2SO_4, and concentrated in vacuo to give an orange oil. Purification by silica gel chromatography (3:95:2 EtOac/hexanes/Et_3N) afforded vinylsilane **82c**, as a colorless oil (0.053 g, 0.16 mmol, 60%). TLC R_f = 0.34 (5:95 EtOAc/hexanes)**;** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.23 (m, 7H), 7.19–7.15 (m, 3H), 6.01 (dd, *J* = 18.5, 8.0 Hz, 1H), 5.75 (d, *J* = 18.5 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.41 (d, *J* = 13.5 Hz, 1H), 2.98 (q, 1H), 2.69-2.64 (m, 2H), 2.17 (s, 3H), 2.04-1.96 (m, 1H), 1.84–1.75 (m, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 142.8, 140.1, 128.9, 128.6, 128.5, 128.4, 128.3, 126.8, 125.7, 67.9, 58.1, 37.7, 33.9, 32.8, -0.9; IR (thin film) 1604, 1247 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{31}NSi$ $(M + H)^+$ 338.2304, found 338.2301.



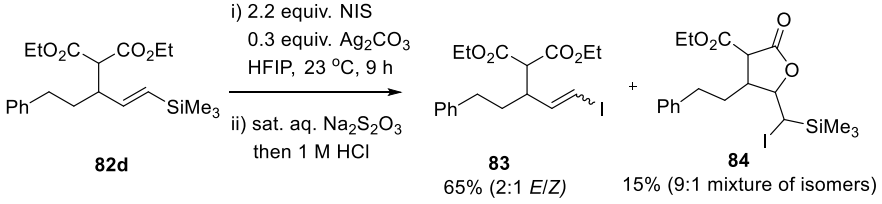
Synthesis of (*E*)-1-(6-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)hex-1-en-3-yl)piperidine, 2a. The compound **82a** was synthesized according to the method of Devine, *et al*.[2] Vinyl iodide **81** was reacted with piperidine to generate allylamine **82a**. Purification by silica gel chromatography (5:95:1 EtOac/hexanes/Et_3N) afforded vinylsilane **82a**, as a colorless oil (0.25 g, 0.50 mmol, 76%). TLC R_f = 0.40 (1:10:1EtOAc/hexanes/Et_3N); ^{1}H NMR (600 MHz, $CDCl_3$) δ

7.66 (dd, *J* = 7.2, 1.2 Hz, 4H), 7.41 (t, *J* = 7.2 Hz, 3H), 7.37 (t, *J* = 7.2 Hz, 1H), 5.87 (dd, *J* = 18.6, 8.4 Hz, 1H), 5.66 (d, *J* = 18.4 Hz, 1H), 3.65 (t, *J* = 5.4 Hz, 2H), 2.70–2.67 (m, 1H), 2.48 (app s, 2H), 2.39 (app s, 2H), 1.86 (app s, 2H), 1.72–1.68 (m, 1H), 1.59-1.52 (m, 5H), 1.50–1.47 (m, 2H), 1.41(app t, *J*= 5.4 Hz, 2H), 1.04 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 135.6, 134.2, 134.1, 133.1, 129.5, 127.6, 71.3, 64.1, 50.9, 29.7, 27.8, 26.9, 26.4, 24.9, 19.3, –1.0; IR (thin film) 1253, 1091 cm^{-1}; HRMS (CI): *m/z* calcd for $C_{30}H_{48}NOSi_2$ $(M + H)^+$ 494.3275, found 494.3284.

Synthesis of (*E*)-1-(5-Phenyl-1-(trimethylsilyl)pent-1-en-3-yl)piperidine, 82b. The compound **82b** was synthesized according to the method of Devine, *et al*.[2] ^{1}H and ^{13}C NMR data for vinylsilane **82b** matched that previously published.[2]

Synthesis of Diethyl (*E*)-2-(5-phenyl-1-(trimethylsilyl)pent-1-en-3-yl)malonate, 82d. The compound **82d** was synthesized according to the method of Devine, *et al*.[3] ^{1}H and ^{13}C NMR data for vinylsilane **82d** matched that previously published.[3]

Synthesis of (*E*)-2-(5-Phenyl-1-(trimethylsilyl)pent-1-en-3-yl)malononitrile, 82e. The compound **82e** was synthesized according to the method of Devine, *et al*.[3] ^{1}H and ^{13}C NMR data for vinylsilane **82e** matched that previously published.[3]



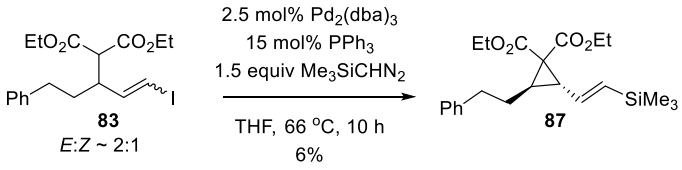
Synthesis of diethyl 2-(1-iodo-5-phenylpent-1-en-3-yl)malonate, 83.[4] A flame-dried 5 mL round-bottom flask containing a stir bar was charged with vinylsilane **82d** (0.51 g, 1.4 mmol). HFIP (0.68 mL) was added to the flask and the solution was stirred at room temperature. *N*-Iodosuccinimide (0.67 g, 3.0 mmol, 2.2 equiv) was added to **82d** in one portion. Upon addition,

the solution turned from colorless to light pink within 30 seconds. The flask was then covered with aluminum foil. After 9 h, the reaction mixture was filtered through a celite pad, washed with EtOAc (1x200 mL), and concentrated in vacuo to yield an orange oil. Then the orange oil was then taken up in EtOAc (10 mL), transferred to a separatory funnel, and washed vigorously with saturated $Na_2S_2O_3$ (3x10 mL), 1 M HCl (3x5 mL), and saturated NaCl (1x5 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification by silica gel chromatography (5:95 to 10:90 EtOAc/hexanes) yielded vinyl iodide **83** as a colorless oil containing inseparable 2:1 mixture of *E* and *Z* isomers (0.37 g, 0.86 mmol, 65%) and lactone **84** as a colorless oil containing 9:1 mixture of isomers (86 mg, 15%).

Vinyl iodide **83**: TLC R_f = 0.41 (10:90 EtOAc/hexanes); ^{1}H NMR for the major isomer (600 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 7.20–7.13 (m, 3H), 6.48–6.44 (dd, *J*= 14.4, 4.8 Hz, 1H), 6.18 (d, *J* = 14.4 Hz, 1H), 4.19–4.14 (m, 4H), 3.35 (d, *J* = 8.4Hz, 1H), 2.85 (ddd, *J* = 18.6, 10.2, 3.6 Hz, 1H), 2.71–2.61 (m, 1H), 2.52 (ddd, *J* = 16.8, 9.6, 7.2 Hz, 1H), 1.83–1.73 (m, 1H), 1.67 (ddd, *J* = 18.6, 10.2, 5.4 Hz, 1H), 1.28–1.23 (m, 6H); ^{13}C NMR for both isomers (125 MHz, $CDCl_3$) δ 168.0, 167.9, 167.8, 167.7, 145.2, 141.7, 141.2, 140.9, 128.6, 128.5, 128.4, 128.1, 126.1, 126.0, 85.5, 78.5, 61.7, 61.6, 61.58, 61.53, 56.2, 55.4, 46.2, 44.3, 34.0, 33.5, 33.4, 14.3, 14.2; IR (thin film) 1723, 1221, 1142 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{18}H_{23}IO_4Na$ $(M+Na)^+$ 453.0539, found 453.0527.

Lactone **84**: TLC R_f = 0.33 (10:90 EtOAc/hexanes); ^{1}H NMR for the major diastereomer (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.0 Hz, 2H), 7.22 (d, *J* = 7.0 Hz, 1H), 7.18 (app t, *J* = 7.0 Hz, 2H), 4.43 (dd, *J* = 8.5, 4.5 Hz, 0.9H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.38 (app t, *J* = 8.0 Hz, 1.8H), 2.91–2.6 (m, 0.9H), 2.75–2.62(m, 2H), 2.12–2.04 (m, 1H), 1.87–1.79 (m, 1H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR for both isomers (125 MHz, $CDCl_3$) δ 170.6, 168.0, 140.3, 128.7, 128.4,

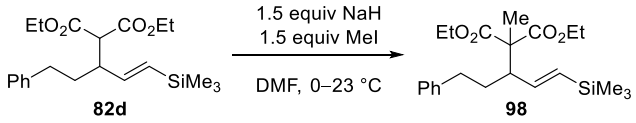
126.5, 87.4, 62.6, 53.5, 46.0, 36.5, 33.1, 20.7, 14.1, –0.7; IR (thin film) 1786, 1739, 1258, 1153 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{27}IO_4SiNa$ $(M+Na)^+$ 497.0621, found 497.0616.



Synthesis of diethyl (*E*)-2-phenethyl-3-(2-(trimethylsilyl)vinyl)cyclopropane-1,1-dicarboxylate, 87.[5] A flame-dried pear-shaped flask containing vinyl iodide **83** (0.049 g, 0.11 mmol) was evacuated and back-filled with nitrogen (3x). The flask was fit with a septum and THF (0.2 mL) was added. The second flame-dried pear-shape flask was charged with NaH (60% in mineral oil, 2.9 mg, 0.12 mmol) and a stir-bar. After the flask was evacuated and back-filled with nitrogen (3x) and fit with a septum, THF was added (0.3 mL). The solution of vinyl iodide **83** was slowly added to the suspension of NaH at 0 °C to form a vinyl iodide salt. The reaction was stirred for 10 minutes and set aside. A third flame-dried round-bottom flask was charged with $Pd_2(dba)_3 \bullet CHCl_3$ (2.9 mg, 2.8 μmol), triphenylphosphine (4.5 mg, 0.017 mmol), and a stir-bar. THF (0.3 mL) was added and the purple solution was stirred until an orange solution was obtained (10 min). The vinyl iodide salt was then added to the third flask containing catalyst and the reaction mixture was stirred in a 66 °C oil bath. Vinylsilyldiazomethane (2 M in diethyl ether, 0.085 mL, 0.17 mmol) was added by a syringe pump over 10 h. The resulting orange solution was cooled to room temperature and quenched with a saturated NH_4Cl solution (3 mL). The aqueous layer was extracted with diethyl ether (3x10 mL). The combined extracts were washed with brine (1x5 mL), dried over Na_2SO_4, and concentrated in vacuo to give an orange oil. Multiple purifications by silica gel chromatography afforded vinylsilane **87**, as colorless oil (2.6 mg, 6% in over 95% purity). TLC R_f = 0.46 (10:90 EtOAc/hexanes); ^1H NMR (500 MHz,

$CDCl_3$) δ 7.27 (t, *J* = 8.5 Hz, 2H), 7.17 (dd, *J* = 16.4, 7.2 Hz, 3H), 5.89 (d, *J* = 18.5 Hz, 1H), 5.54 (dd, *J* = 18.5, 8.4 Hz, 1H), 4.20–4.14 (m, 4H), 2.71–2.64 (m, 2H), 2.43 (t, *J* = 8.0 Hz, 1H), 2.11 (q, *J* = 7.5 Hz, 1H), 1.78–1.70 (m, 2H), 1.26 (q, *J* = 7.0 Hz, 6H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.8, 141.3, 140.6, 134.5, 128.6, 128.4, 128.3, 126.0, 125.8, 61.6, 61.4, 61.3, 61.2, 42.1, 38.1, 35.1, 2.1, 29.3, 14.4, 14.3, -1.2; IR (thin film) 1723, 1294, 1247, 1200 cm^{-1}; HRMS (CI): *m/z* calcd for $C_{18}H_{24}IO_4$ $(M+H)^+$ 389.2148, found 389.2139**.**

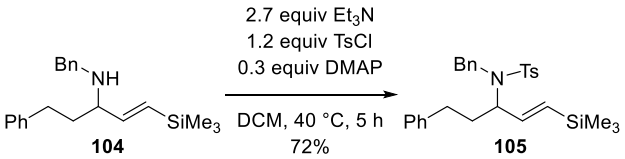
Synthesis of (*E*)-N-benzyl-5-phenyl-1-(trimethylsilyl)pent-1-en-3-amine, 15. The compound **15** was synthesized according to the method of Devine, *et al*.[2] ^{1}H and ^{13}C NMR data for vinylsilane **15** matched that previously published.[2]



Synthesis of diethyl (*E*)-2-methyl-2-(5-phenyl-1-(trimethylsilyl)pent-1-en-3-yl)malonate, 98. The compound **98** was synthesized according to the method reported by Katz, *et al*.[6] A flame-dried 10 mL round-bottom flask containing a stir bar was charged with vinylsilane **82d** (0.055 g, 0.15 mmol). DMF (2.5 mL) was added to the flask and the solution was stirred at 0 ºC. NaH (60% in mineral oil, 0.0088 g, 0.22 mmol, 1.5 equiv) was added in one portion. The reaction was stirred for 10 min and MeI (0.015 mL, 0.22 mmol, 1.5 equiv) was added through a syringe. Upon addition of MeI, the solution turned solid and the reaction was let warmed to room temperature. After 20 min., the reaction was diluted with EtOAc (10 mL) and transferred to a separatory funnel. The organic layer was washed with distilled H_2O (5**x**10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give colorless oil. Purification by silica gel chromatography (5:95 EtOAc/hexanes) afforded methylated vinylsilane **98** as a colorless oil (0.052 g, 0.13 mmmol, 91%). Vinylsilane **98**: TLC R_f = 0.50 (10:90 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t,

J = 7.5 Hz, 2H), 7.16 (q, *J* = 7.5 Hz, 3H), 5.81 (dd, *J* = 18.5, 8.5 Hz, 1H), 5.75 (d, *J* = 18.5 Hz, 1H), 4.16–4.08 (m, 4H), 2.80–2.76 (m, 1H), 2.67–2.61 (m, 1H), 2.51–2.45 (m, 1H), 1.88–1.81 (m, 1H), 1.64–1.58 (m, 1H), 1.36 (s, 3H), 1.22 (dt, *J* = 7.0, 1.5 Hz, 6H); ^{13}C NMR for both isomers (125 MHz, $CDCl_3$) δ 171.4, 171.3, 144.4, 142.3, 135.6, 128.5, 128.3, 125.8, 61.2, 57.5, 51.4, 34.2, 31.7, 17.2, 14.2, 14.1, -1.2; IR (thin film) 1730, 1613, 1380, 1245, 1101 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{34}O_4SiNa$ $(M + Na)^+$ 413.2124, found 413.2138.

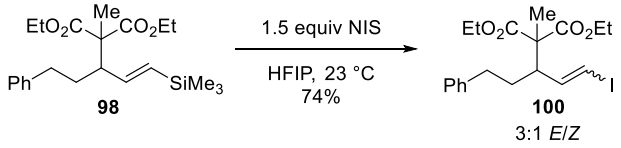
Synthesis of (*E*)-2-methyl-2-(5-phenyl-1-(trimethylsilyl)pent-1-en-3-yl)malononitrile, 99. Follow the reaction conditions for vinylsilane **98**. Vinylsilane **82e** (0.057 g, 0.20 mmol) was treated with NaH (60% in mineral oil, 0.012 g, 0.30 mmol) and methyl iodide (0.020 mL, 0.30 mmol) to affored methylated vinylsilane **99** as a colorless oil (0.054 g, 0.18 mmmol, 91%). Vinylsilane **10**: TLC R_f = 0.49 (10:90 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.0 Hz, 2H), 7.23 (dd, *J* = 16.5, 7.0 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 2.8–2.75 (m, 1H), 6.24 (d, *J* = 14.4 Hz, 1H), 4.23–4.17 (m, 4H), 2.76–2.66 (m, 1H), 2.58–2.51 (m, 1H), 2.54–2.48 (m, 1H), 2.36–2.32 (m, 1H), 2.24–2.17 (m, 1H), 1.98-1.90 (m, 1H), 1.68 (s, 3H), 0.14 (s, 9H); ^{13}C NMR for both isomers (125 MHz, $CDCl_3$) δ 141.6, 140.3, 139.4, 128.69, 128.68, 128.49, 128.47, 126.4, 116.0, 115.3, 53.2, 35.9, 32.9, 31.9, 23.3, -1.4; IR (thin film) 1496, 1454, 1248, 995 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{24}N_2SiNa$ $(M + Na)^+$ 319.1606, found 319.1617.



Synthesis of (E)-N-benzyl-4-methyl-N-(5-phenyl-1-(trimethylsilyl)pent-1-en-3-yl)benzenesulfonamide, 105. Vinylsilane **105** was synthesized according to the method of Huy et al.[7] A flame-dried 5 mL round-bottom flask containing a stir bar was charged with vinylsilane

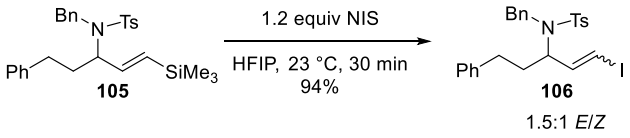
104 (0.21 g, 0.63 mmol). DCM (1.3 mL) was added to the flask and the solution was stirred at room temperature. Triethylamine (0.24 mL, 1.7 mmol), 4-(dimethylamino)pyridine (0.023 g, 0.19 mmol), and *p*-toluenesulfonyl chloride (0.14 g, 0.76 mmol) were added to **104** in order. The reaction was stirred at 40 ºC in a preheat oil bath. After five hour, the reaction mixture was diluted with 1 M HCl (1x5 mL), extracted with Et_2O (3x10 mL), and washed with brine (1x10 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil. Purification by silica gel chromatography (5:95-10:90 EtOAc/hexanes) yielded **105** as a colorless oil (0.11 g, 0.45 mmol, 72%). TLC R_f = 0.45 (10:90 EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.33–7.28 (m, 5H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 2H), 5.57 (d, *J* = 19 Hz, 1H), 5.49 (dd, *J* = 19, 5.5 Hz, 1H), 4.57 (d, *J* = 15.5 Hz, 1H), 4.38–4.34 (m, 1H), 4.12 (d, *J* = 15.5 Hz, 1H), 2.49–2.43 (m, 5H), 1.70–1.67 (m, 1H), 1.61–1.56 (m, 1H); ^{13}C NMR for both isomers (150 MHz, $CDCl_3$) δ 143.2, 142.7, 141.8, 138.3, 138,2, 134.3, 129.7, 128.6, 128.5, 128.4, 128.2, 127.7, 127.6, 127.3, 125.8, 61.9, 48.3, 33.9, 32.7, 21.5, -1.56; IR (thin film) 1338, 1247, 1158, 1092 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{35}NO_2SSiNa$ $(M + Na)^+$ 500.2055, found 500.2060.

Iododesilylation Procedures



Synthesis of diethyl (*E*/*Z*)-2-(1-iodo-5-phenylpent-1-en-3-yl)-2-methylmalonate, 100. Iododesilylation was carried out according to the procedure reported by Zakarian et al.[8] A flame-dried 5 mL round-bottom flask containing a stir bar was charged with vinylsilane **98** (0.13 g, 0.33 mmol). HFIP (0.17 mL) was added to the flask and the solution was stirred at room temperature. NIS (0.039 g, 0.17 mmol, 2.0 equiv) was added to **98** in one portion. The flask was

then covered with aluminum foil. After one hour, the reaction mixture was diluted with EtOAc (1x20 mL), transferred to a separatory funnel, and washed vigorously with saturated $Na_2S_2O_3$ (3x10 mL), 1 M HCl (3x10 mL), and saturated NaCl (1x10 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification by silica gel chromatography (5:95-10:90 EtOAc/hexanes) yielded vinyl iodide **100** as a colorless oil containing inseparable 3:1 mixture of *E* and *Z* isomers (0.11 g, 0.25 mmol, 74%). TLC R_f = 0.44 (10:90 EtOAc/Hex). ^{1}H NMR for the major isomer (500 MHz, $CDCl_3$) δ 7.28 (q, *J* = 7.0 Hz, 2H), 7.16 (m, 3H), 6.41 (dd, *J* = 14.5, 7.5 Hz, 1H), 4.20–4.13 (m, 4H), 2.77 (t, *J* = 11.0 Hz, 1H), 2.68–2.63 (m, 1H), 2.56–2.45 (m, 1H), 1.81–1.74 (m, 1H), 1.68–1.61 (m, 2H), 1.37 (s, 3H), 1.27–1.21 (m, 6H); ^{13}C NMR for both isomers (125 MHz, $CDCl_3$) δ 171.2, 171.1, 170.94, 170.88, 144.8, 142.2, 141.5, 140.2, 86.4, 78.8, 61.51, 61.50, 61.4, 57.2, 56.9, 51.2, 49.0, 34.0, 32.7, 31.2, 18.2, 17.5, 14.2, 14.1; IR (thin film) 1726, 1239, 1101, 1021 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{25}IO_4Na$ $(M + Na)^+$ 467.0695, found 467.0699.



Synthesis of (*E*/*Z*)-N-benzyl-N-(1-iodo-5-phenylpent-1-en-3-yl)-4-methylbenzenesulfonamide, 106. A flame-dried 5 mL round-bottom flask containing a stir bar was charged with vinylsilane **105** (0.15 g, 0.31 mmol). HFIP (0.3 mL) was added to the flask and the solution was stirred at room temperature. NIS (0.076 g, 034 mmol) was added to in one portion. The flask was then covered with aluminum foil. After two hour, the reaction mixture was diluted with EtOAc (1x20 mL), transferred to a separatory funnel, and washed vigorously with saturated $Na_2S_2O_3$ (3x10 mL), 1 M HCl (3x10 mL), and saturated NaCl (1x10 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to give yellow oil.

Purification by silica gel chromatography (5:95 EtOAc/hexanes) yielded vinyl iodide **106** as a colorless oil containing inseparable 1.5:1 mixture of *E*- and *Z*-isomers (0.15 g, 0.29 mmol, 94%). TLC R_f = 0.45 (10:90 EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.37–7.25 (m, 5 H), 7.18 t, *J* = 7.0 Hz, 3H), 7.14 (d, *J* = 7 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.82 (d, 2H), 6.30 (d, *J* = 7.5 Hz, 1H), 6.23–6.16 (m, 2H), 6.01 (*J* = 7.0 Hz, 1 H), 4.55–4.46 (m, 2H), 4.35 (d, *J* = 15.5 Hz, 1H), 4.24–4.16 (m, 2H), 2.45 (d, *J* = 13.0 Hz, 6H), 1.90–175 (m, 2H), 1.70–1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 143.4, 141.1, 140.9, 138.8, 37.7, 137.6, 137.5, 137.4, 129.8, 129.6, 128.68, 128.66, 128.53, 128.51, 128.38, 128.31, 127.88, 127.84, 127.6, 127.3, 126.0, 125.9, 85.4, 80.7, 62.9, 61.9, 50.0, 48.8, 35.3, 34.1, 32.5, 32.4, 21.6; IR (thin film) 1599, 1494, 1328, 1153 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{26}INO_2SNa$ $(M + Na)^+$ 554.0627, found 554.0619.

3.6. References

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S.3. Devine, S. K. J.; Van Vranken, D. L. *Org*. *Lett*, **2008**, *10*, 1909-1911.
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S.5. Thorimbert, S.; Malacria, M. *Tet*. *Lett*. **1998**, *39*, 9659–9660.
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S.8. Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org*. *Lett*. **2008**, *10*, 1727.

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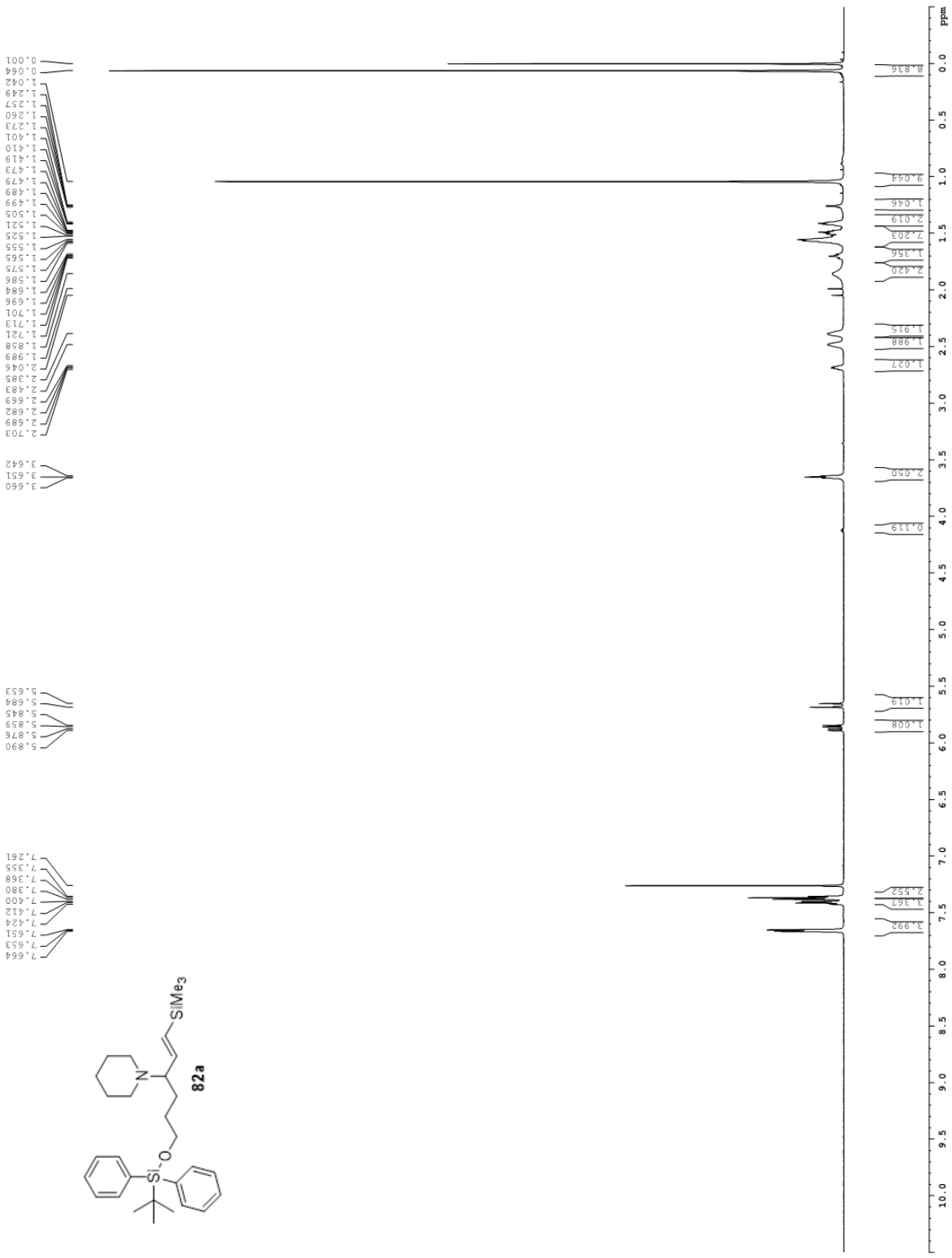
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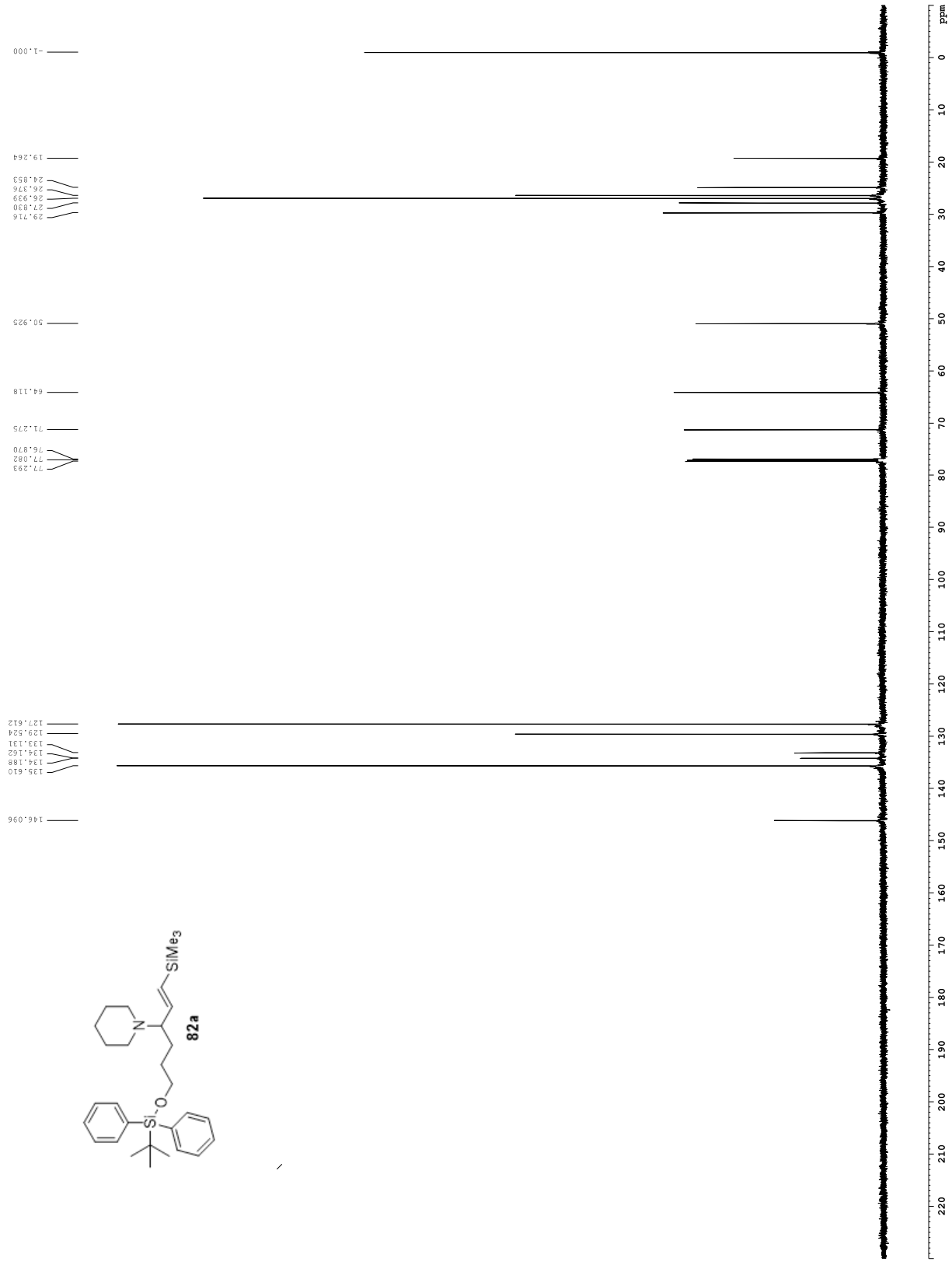
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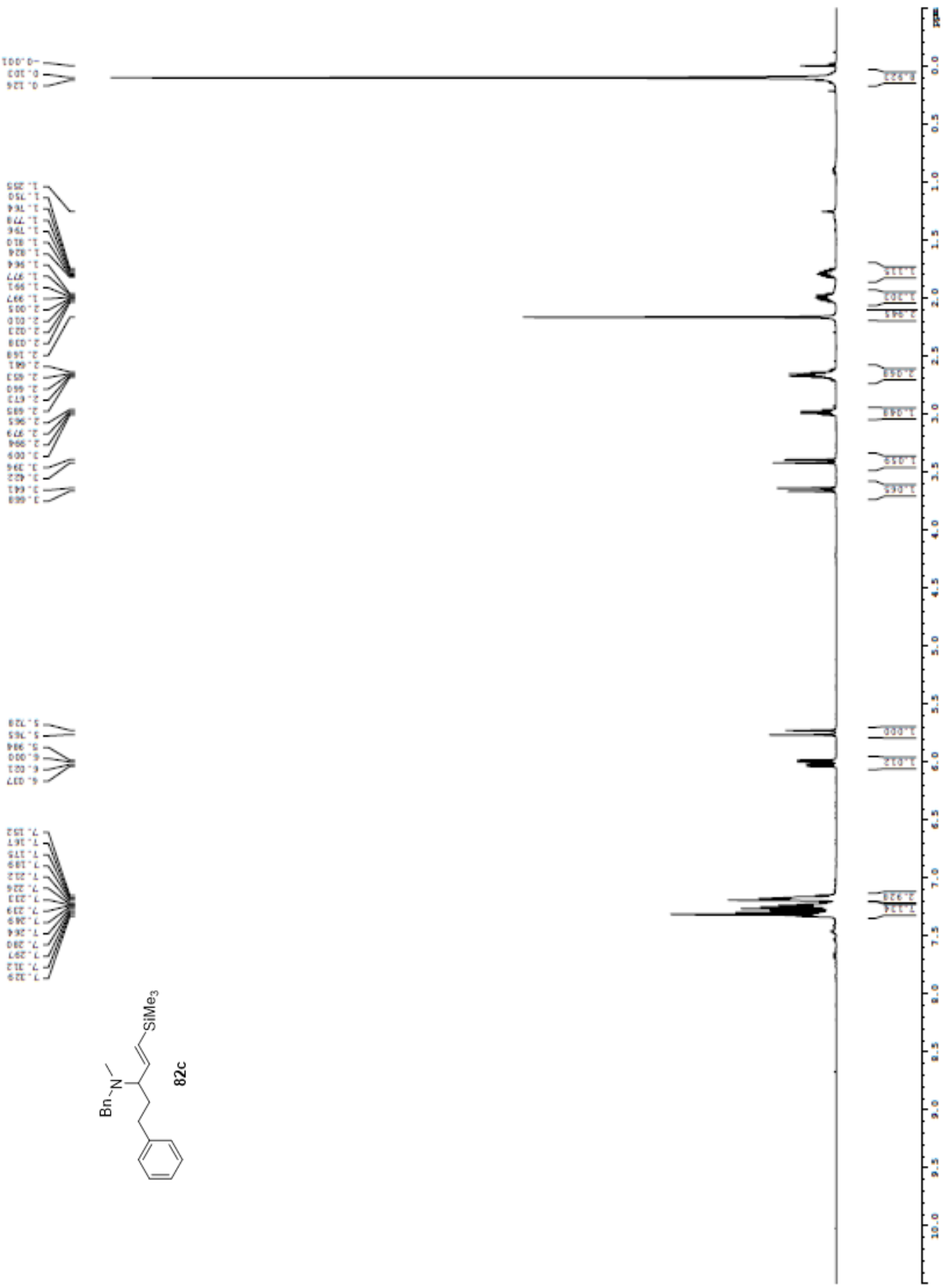
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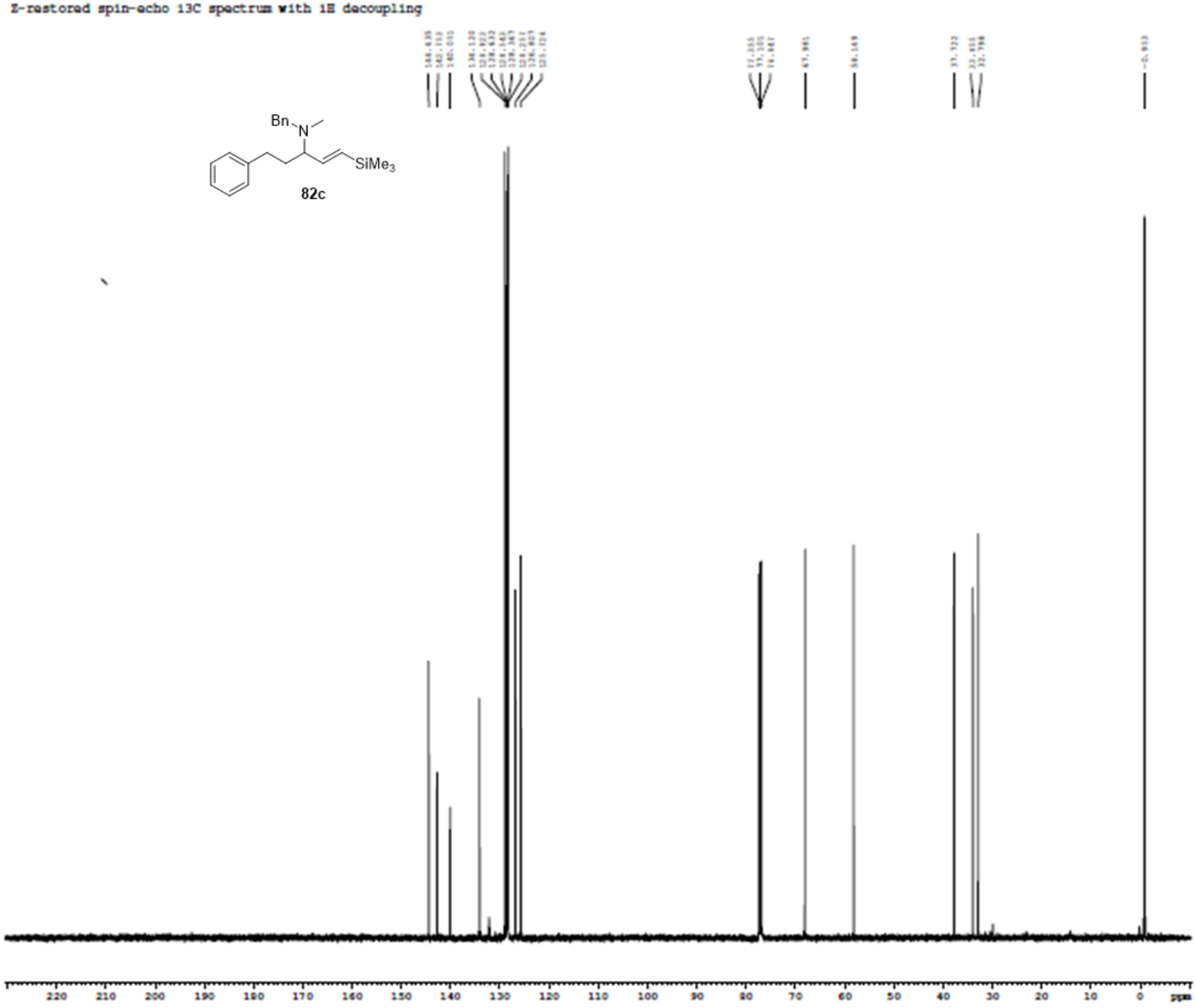
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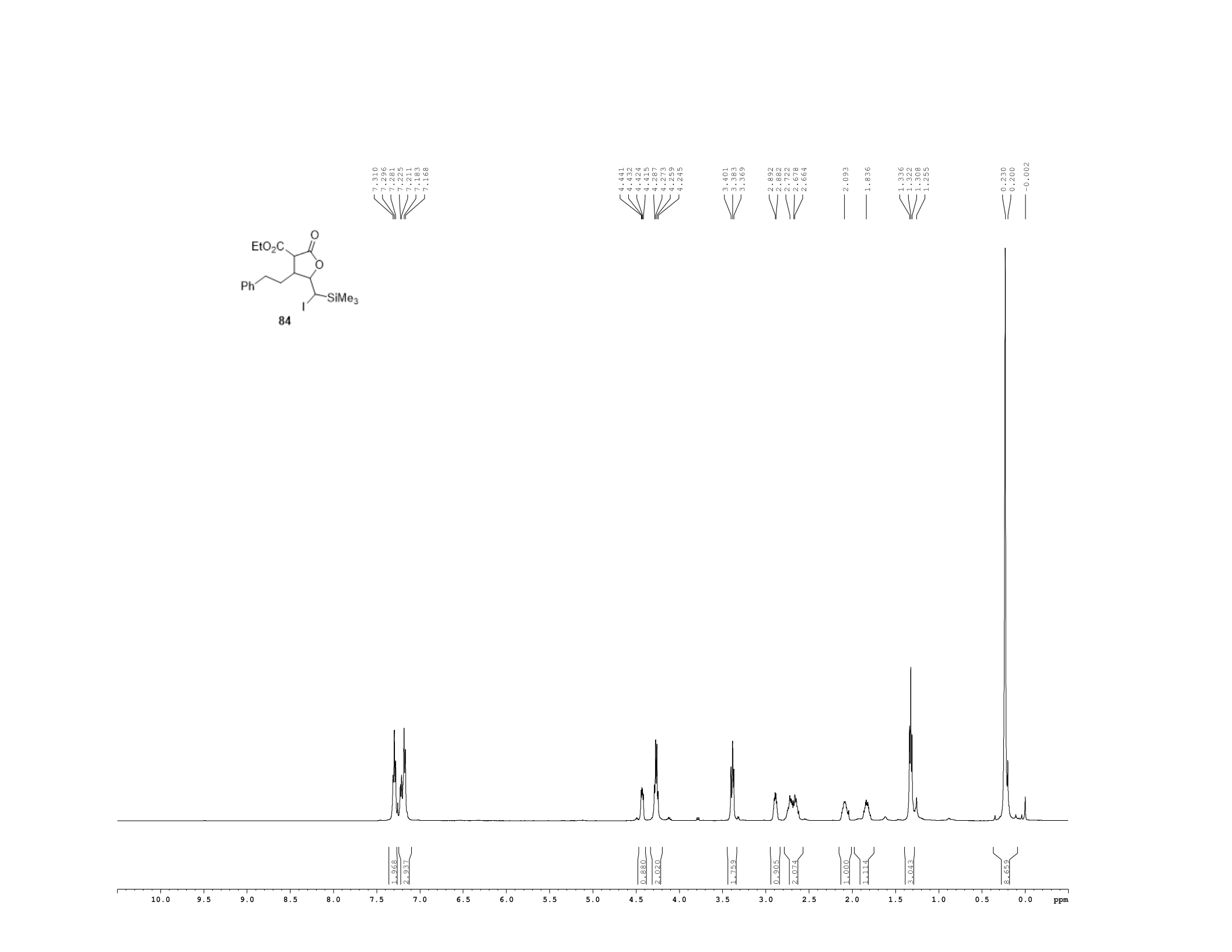
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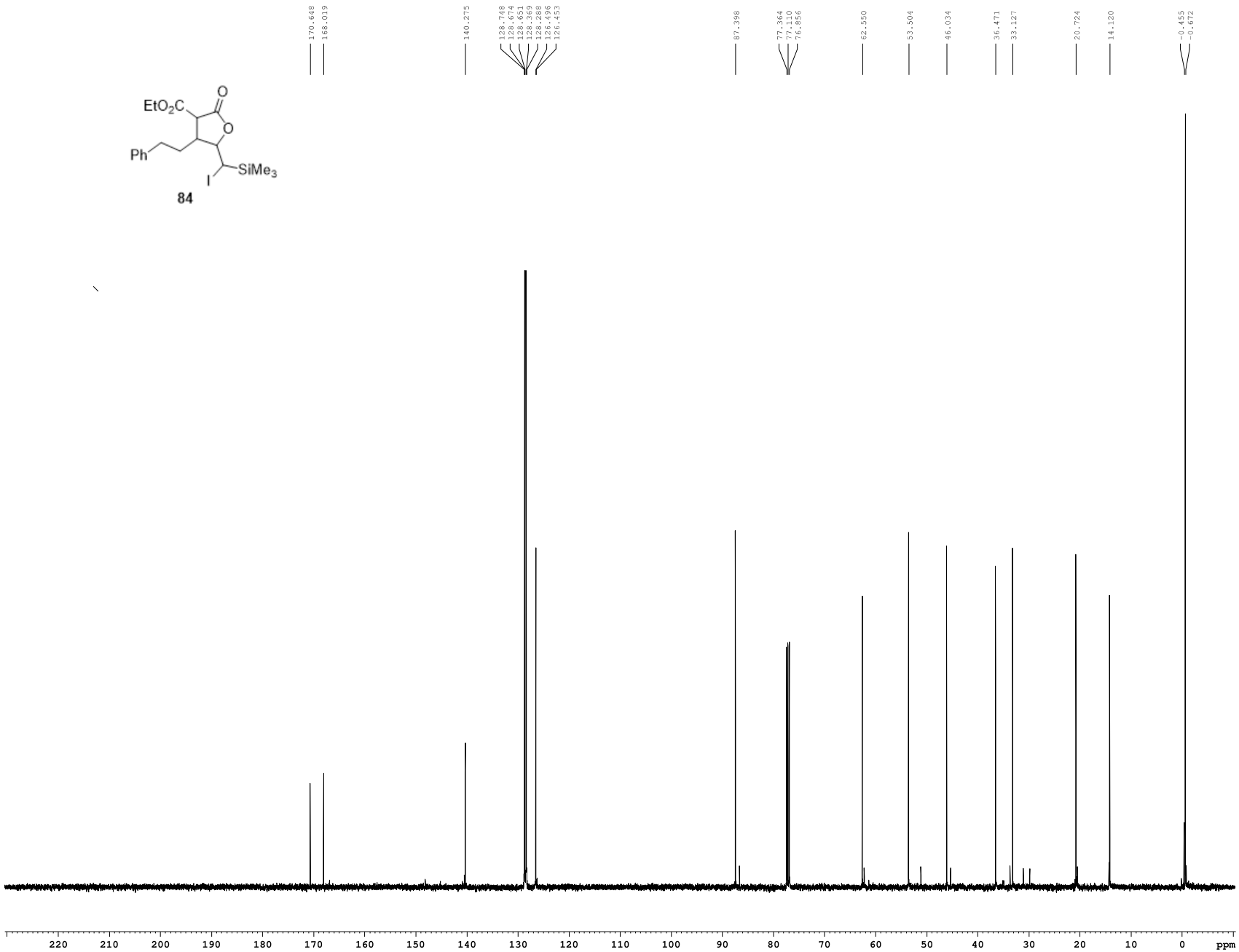
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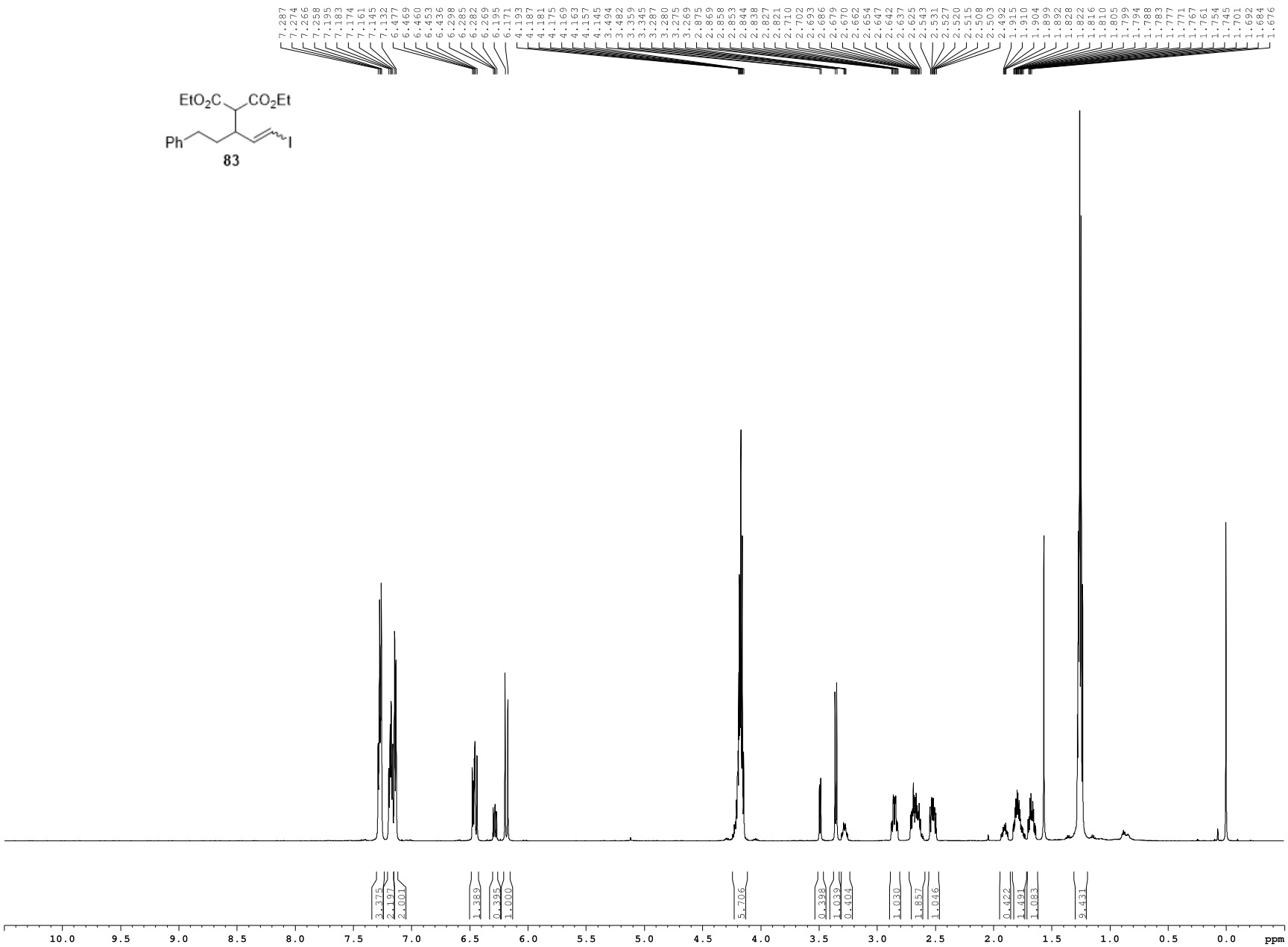
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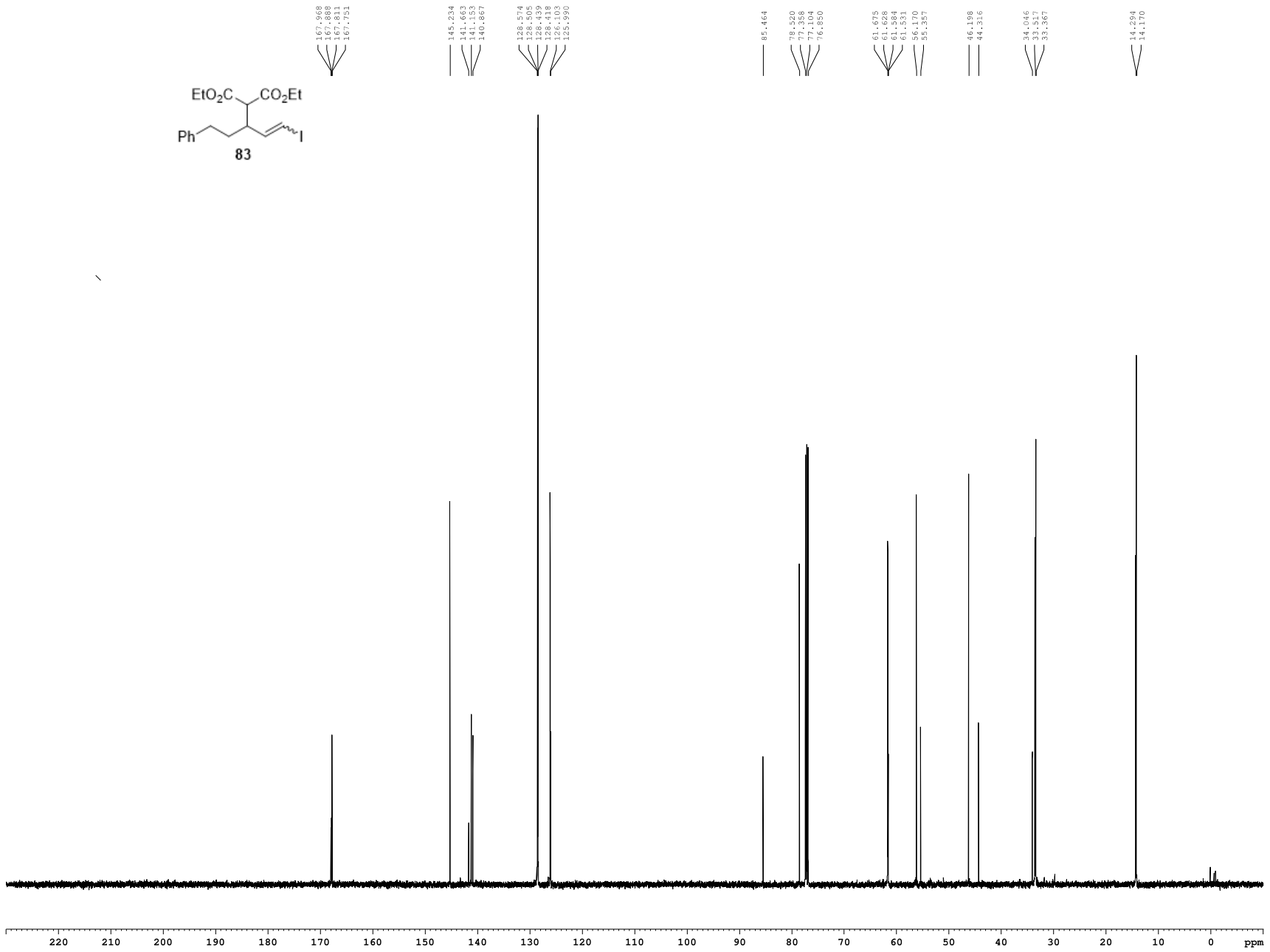
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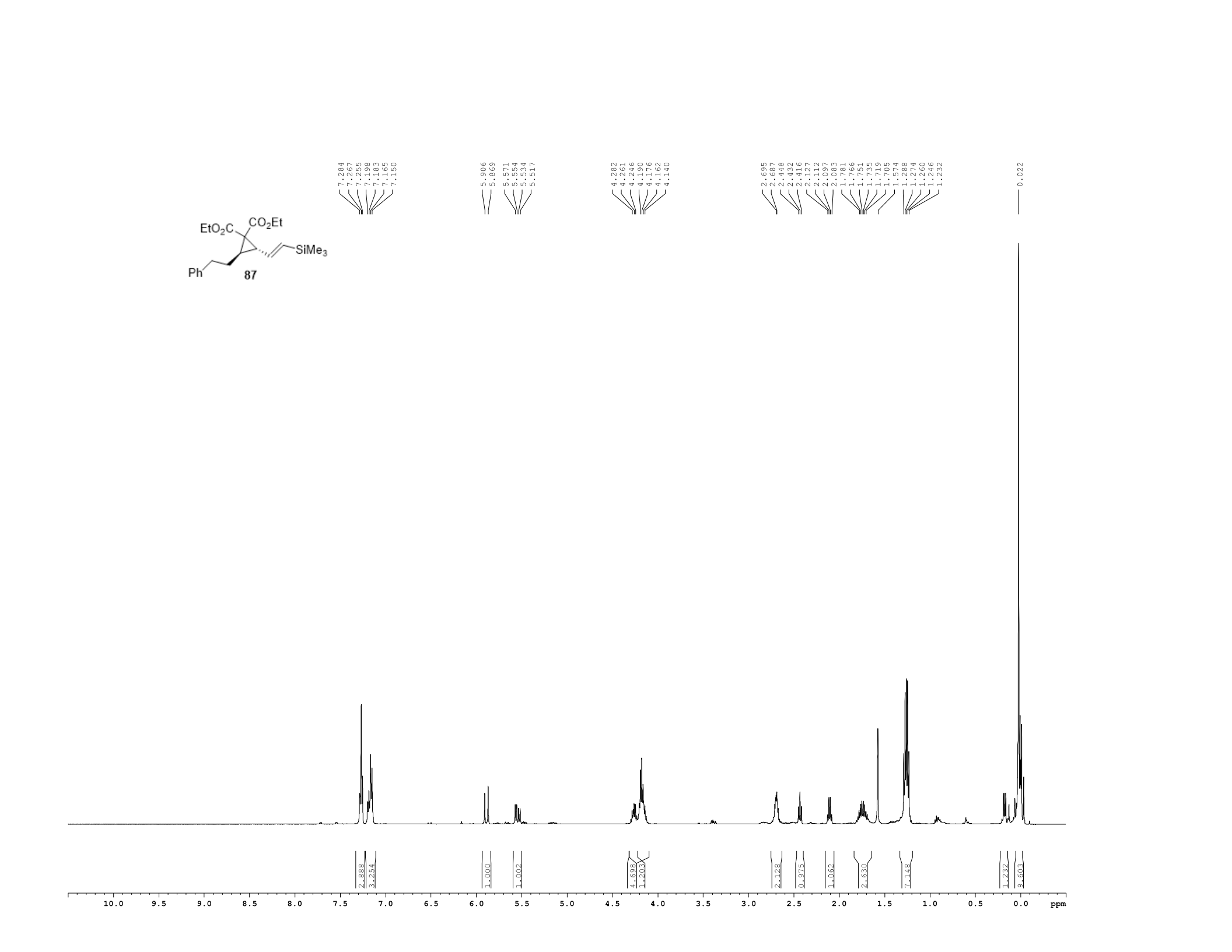
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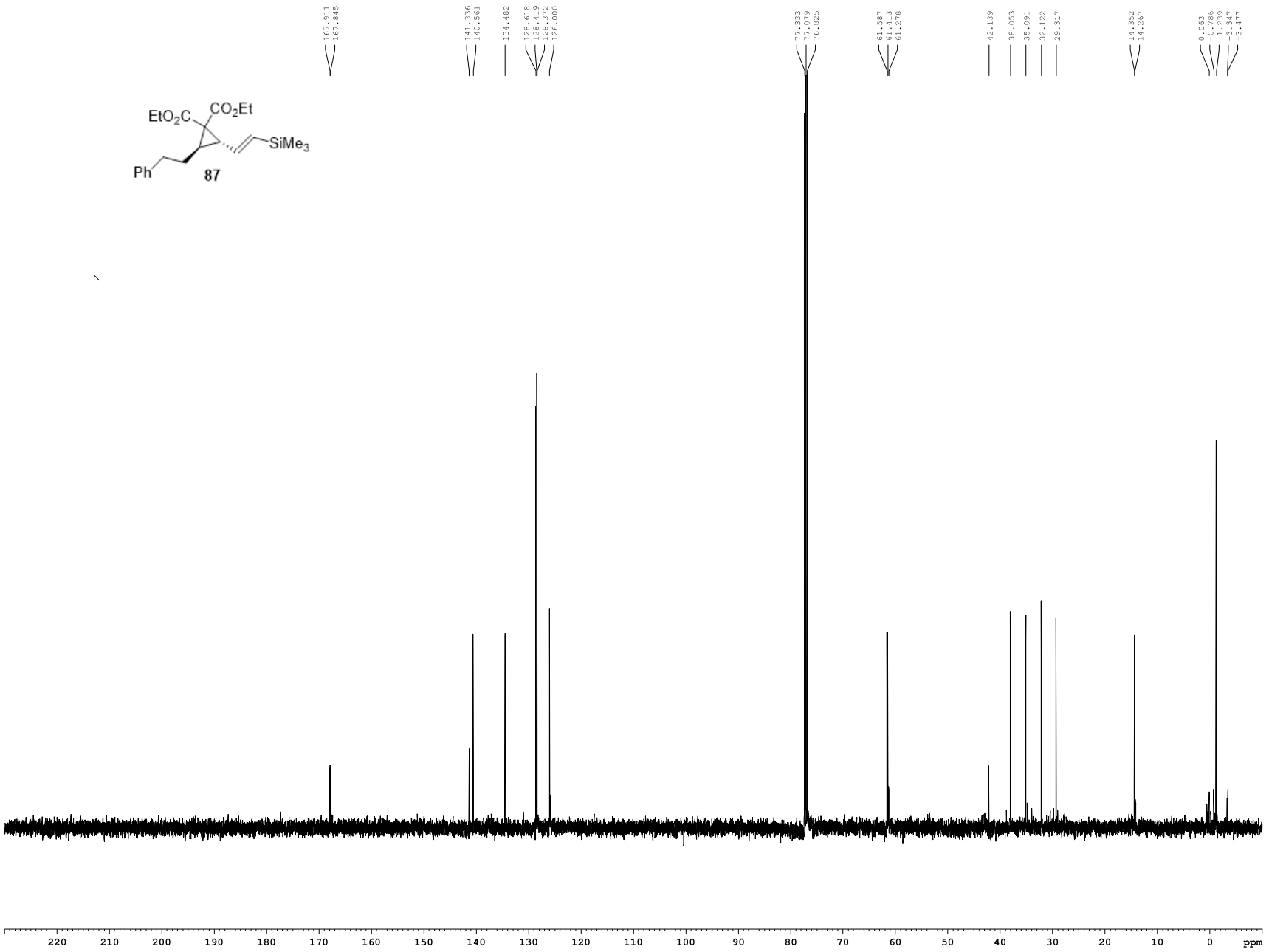
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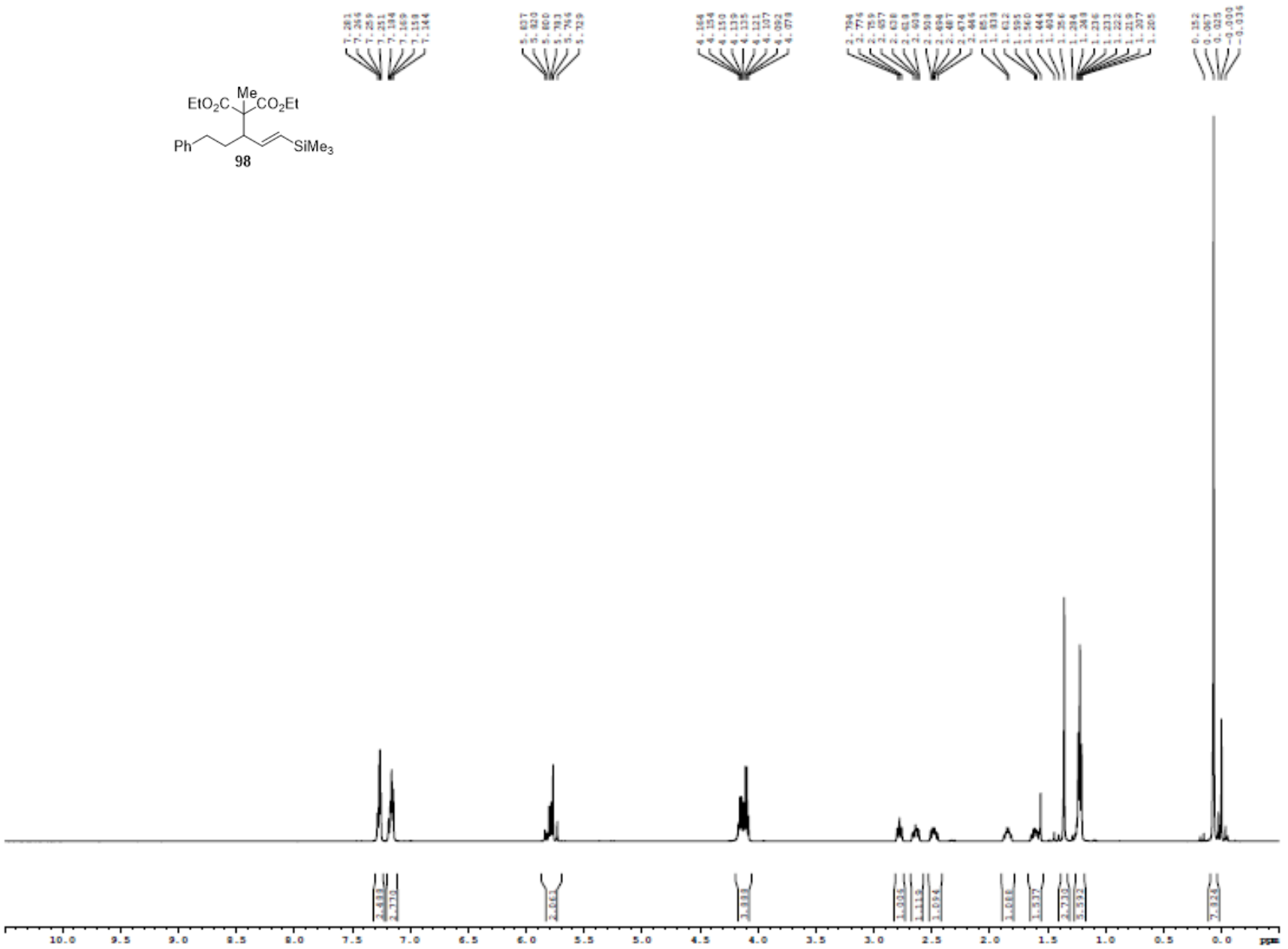
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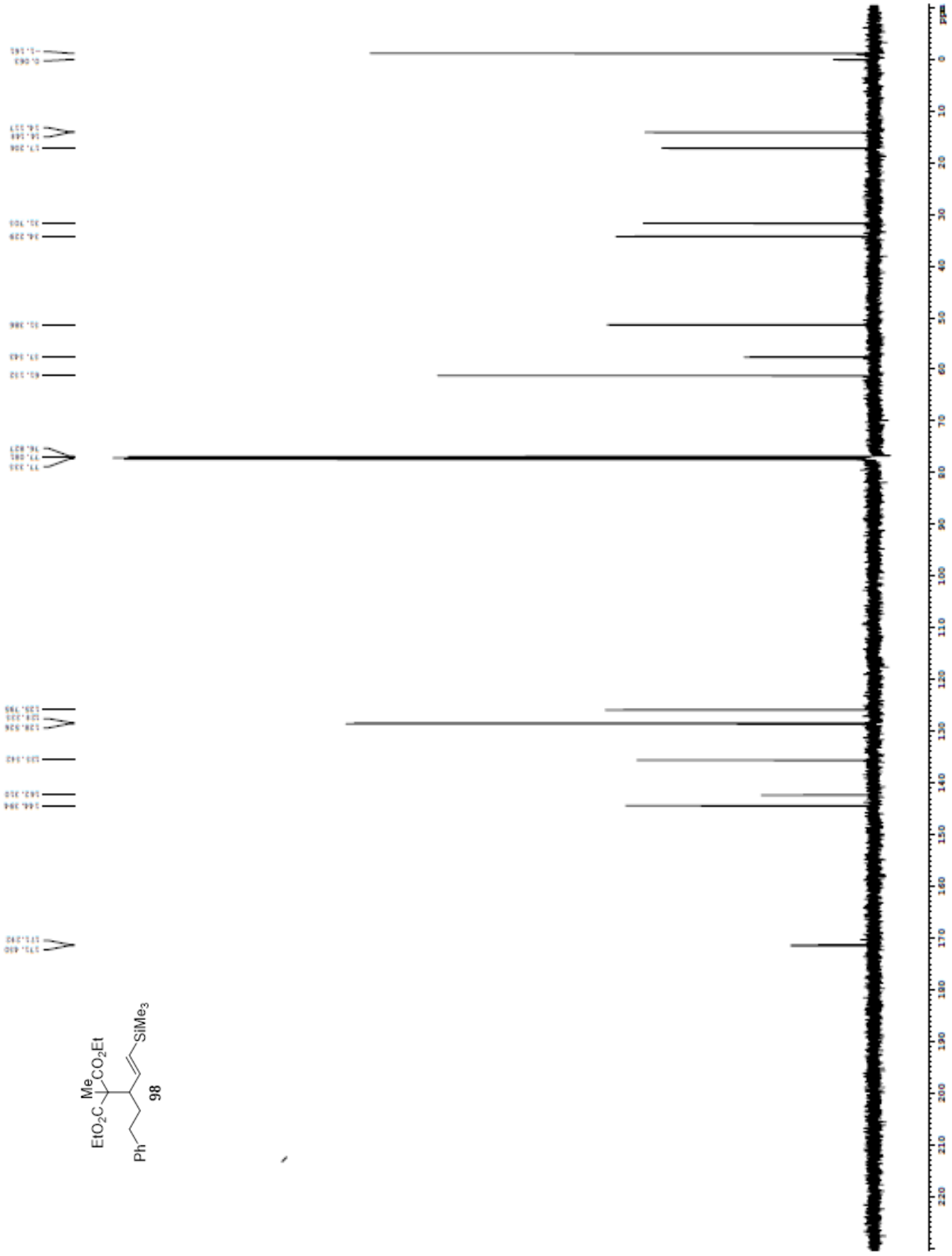
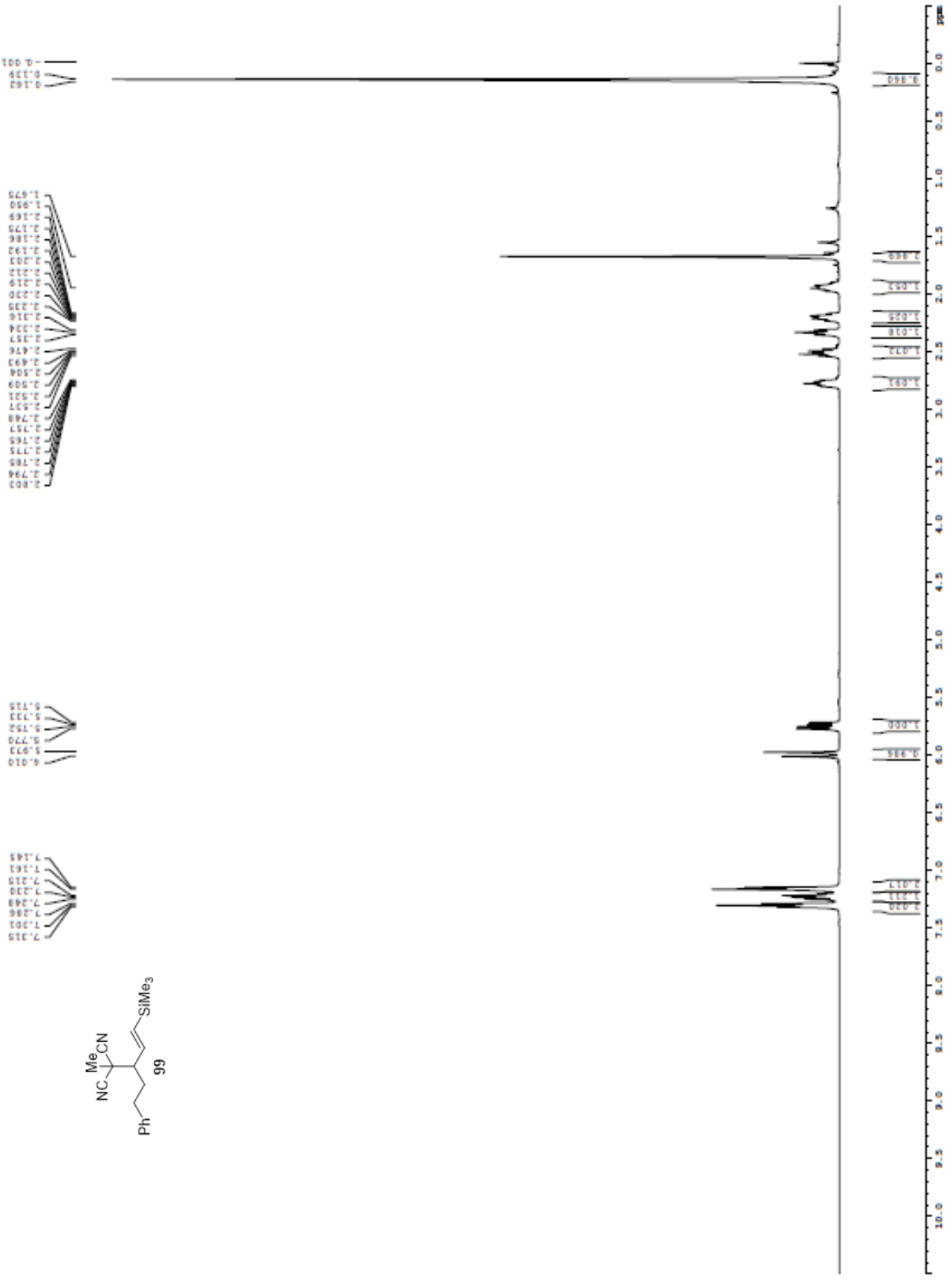
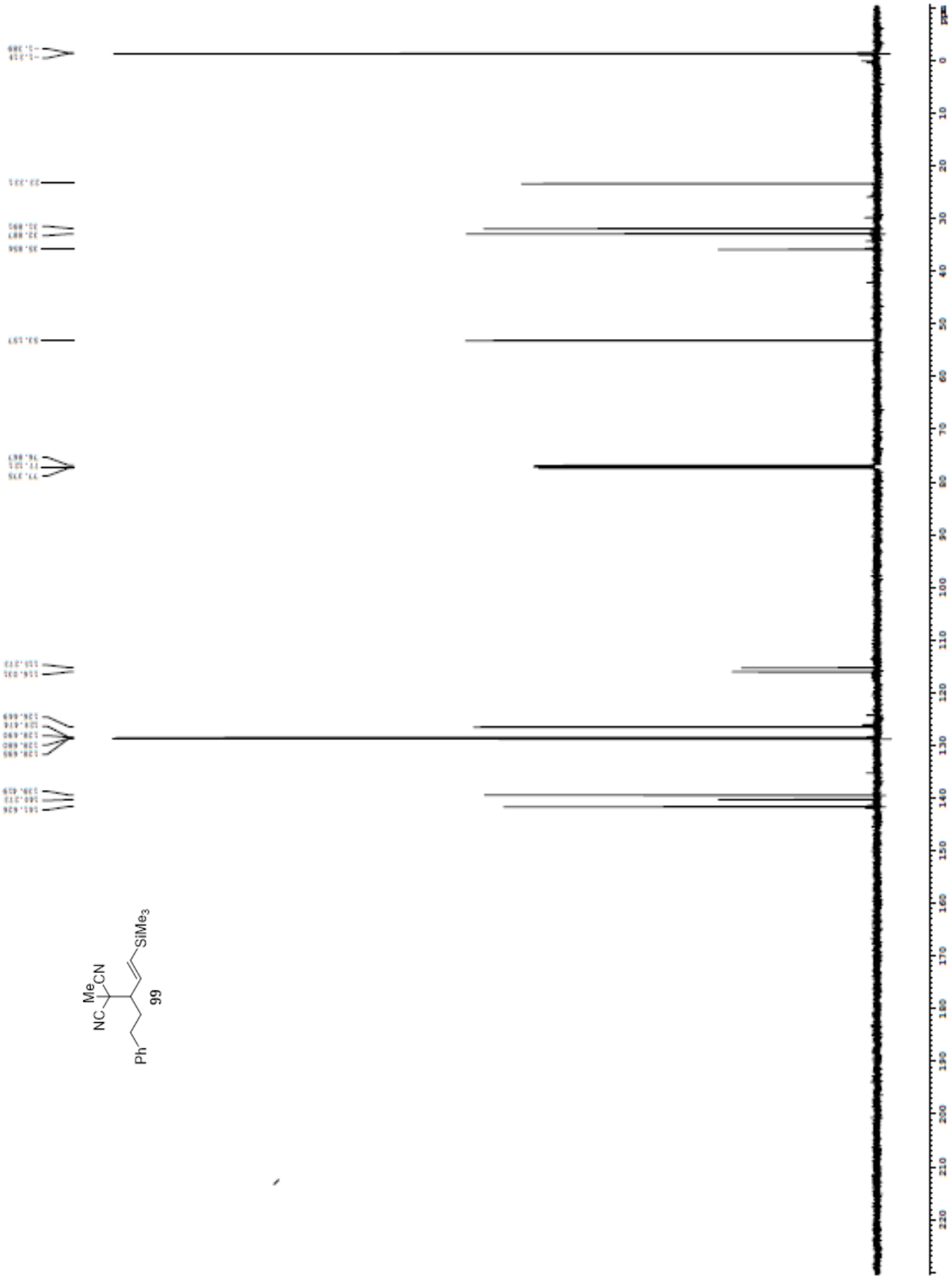
CO2Et
Ph
SiMe3
98


Me
CO_2Et
$SiMe_3$
EtO_2C
Ph
98


SiMe3
Me
CN
NC
Ph
99


SiMe3
Me
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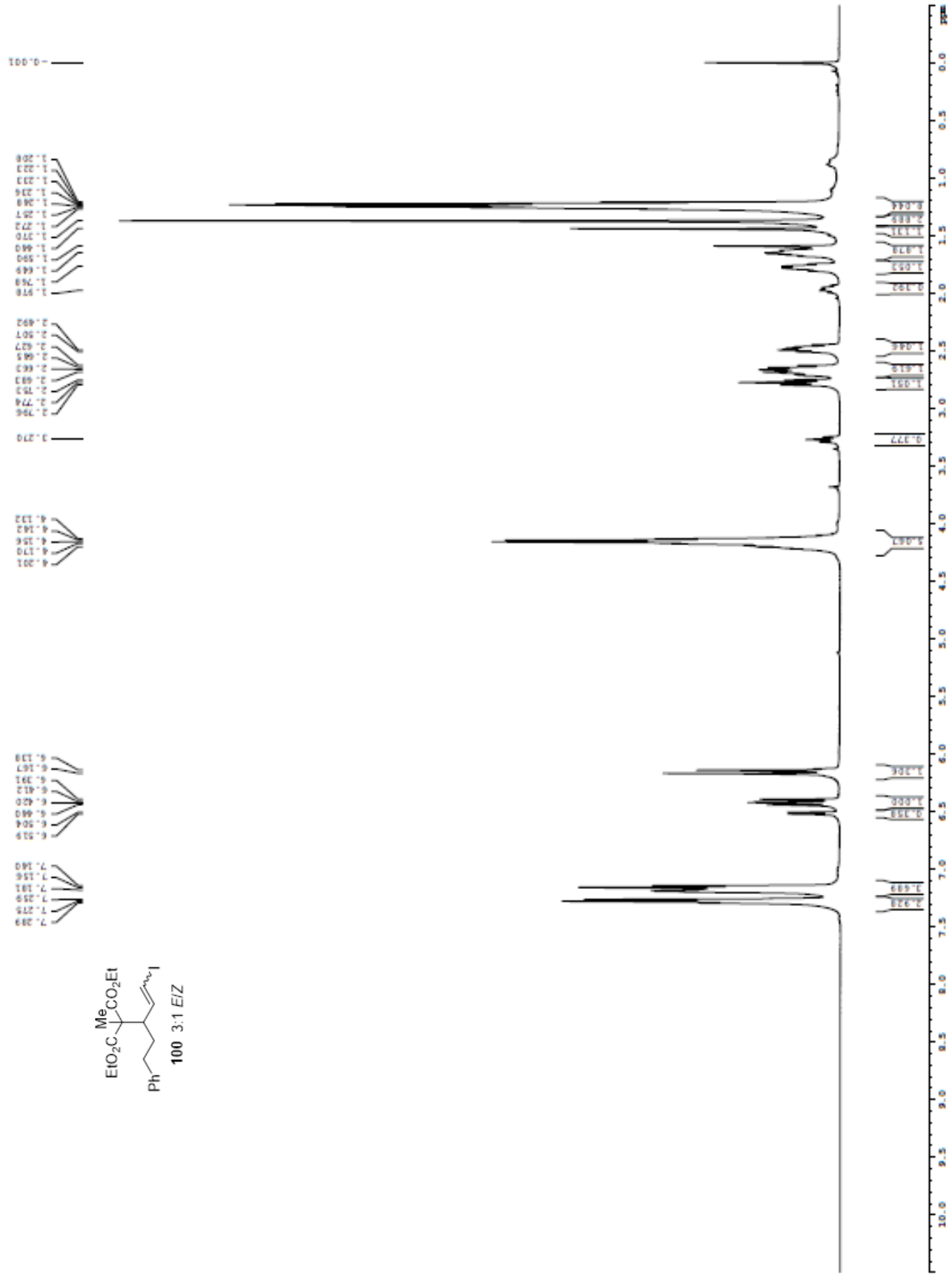
Ph
99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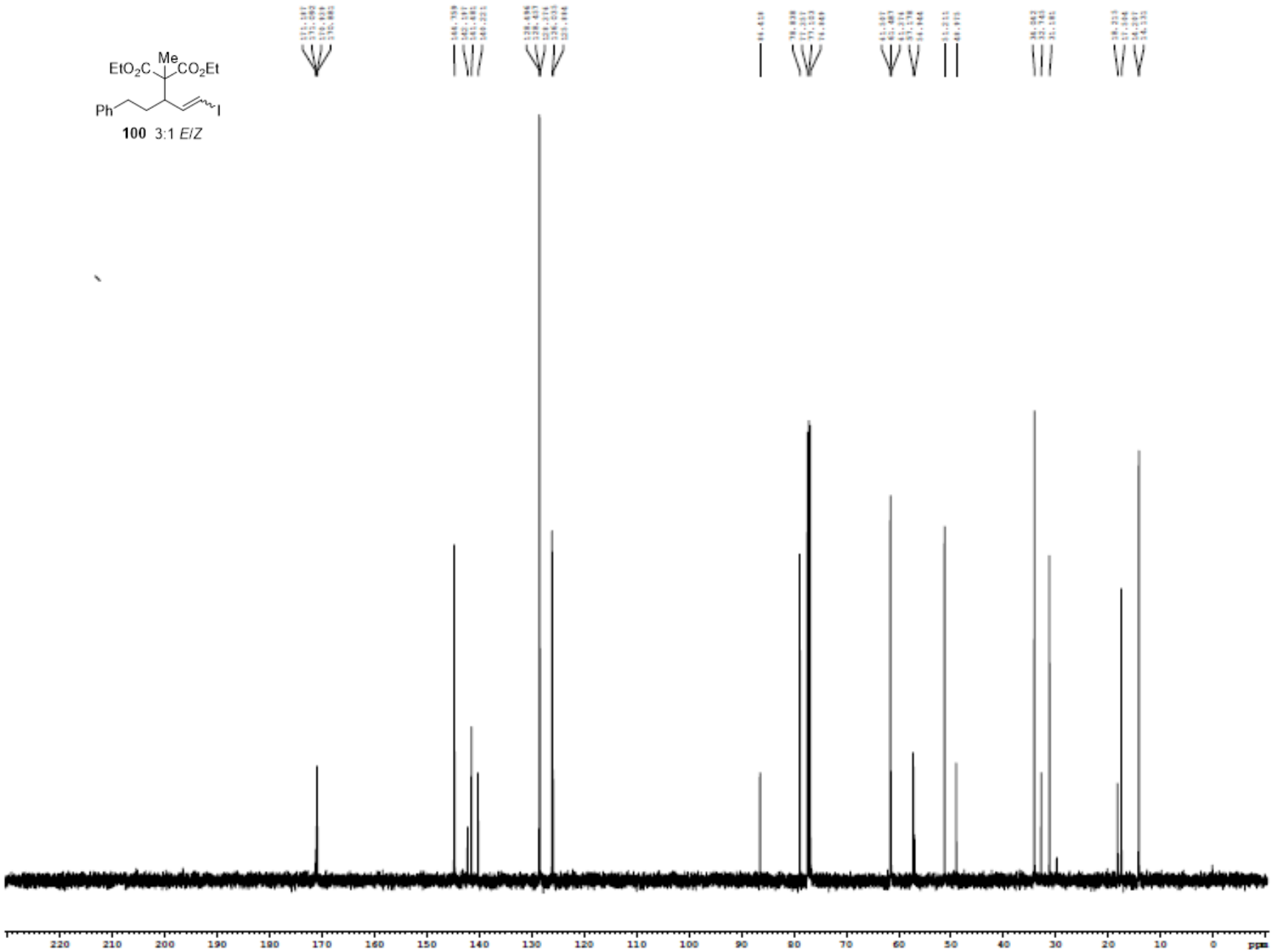
Ph
100 3:1 E/Z


EtO2C
Me
CO2Et
Ph
I
100 3:1 E/Z
220
210
200
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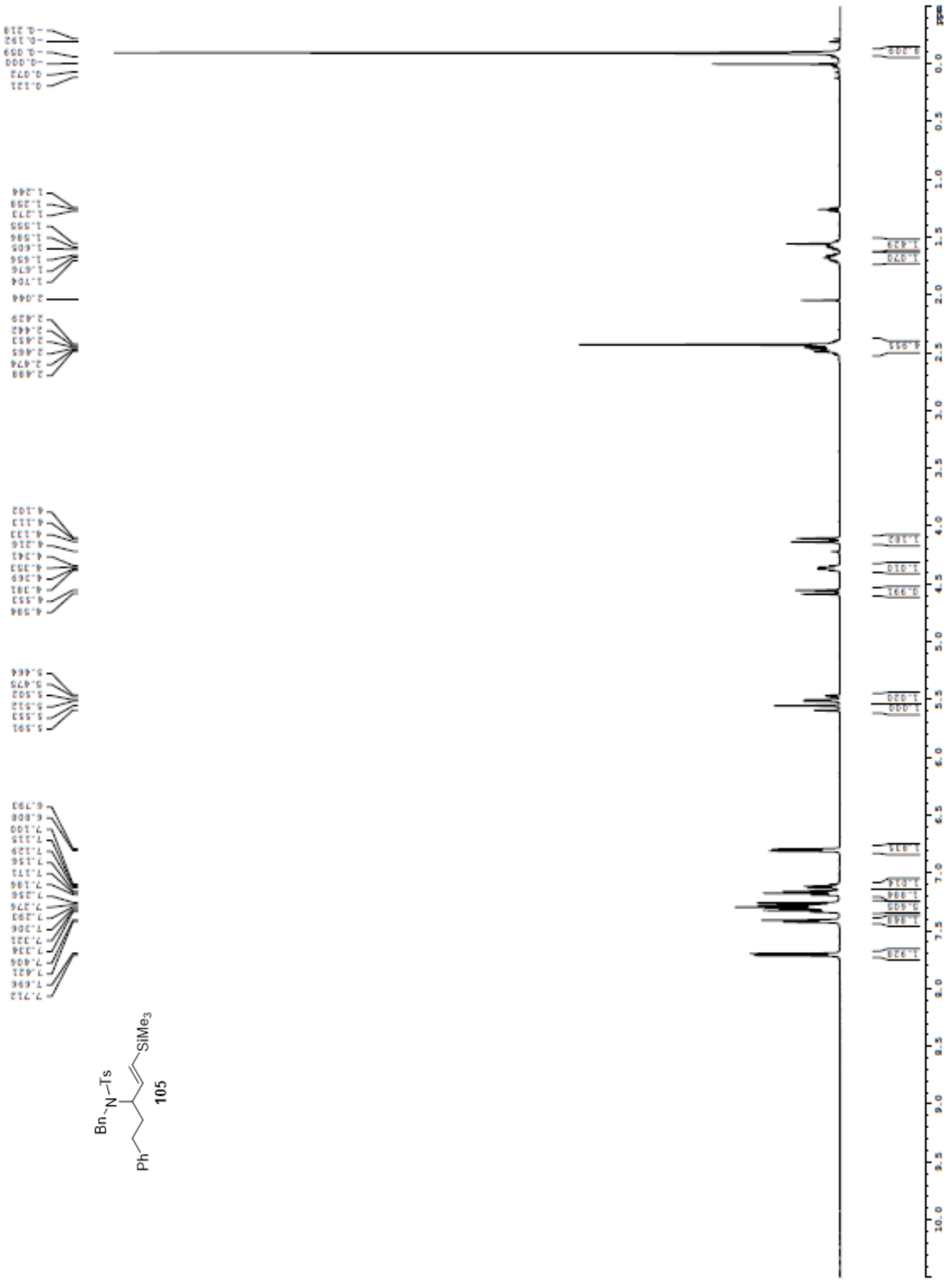
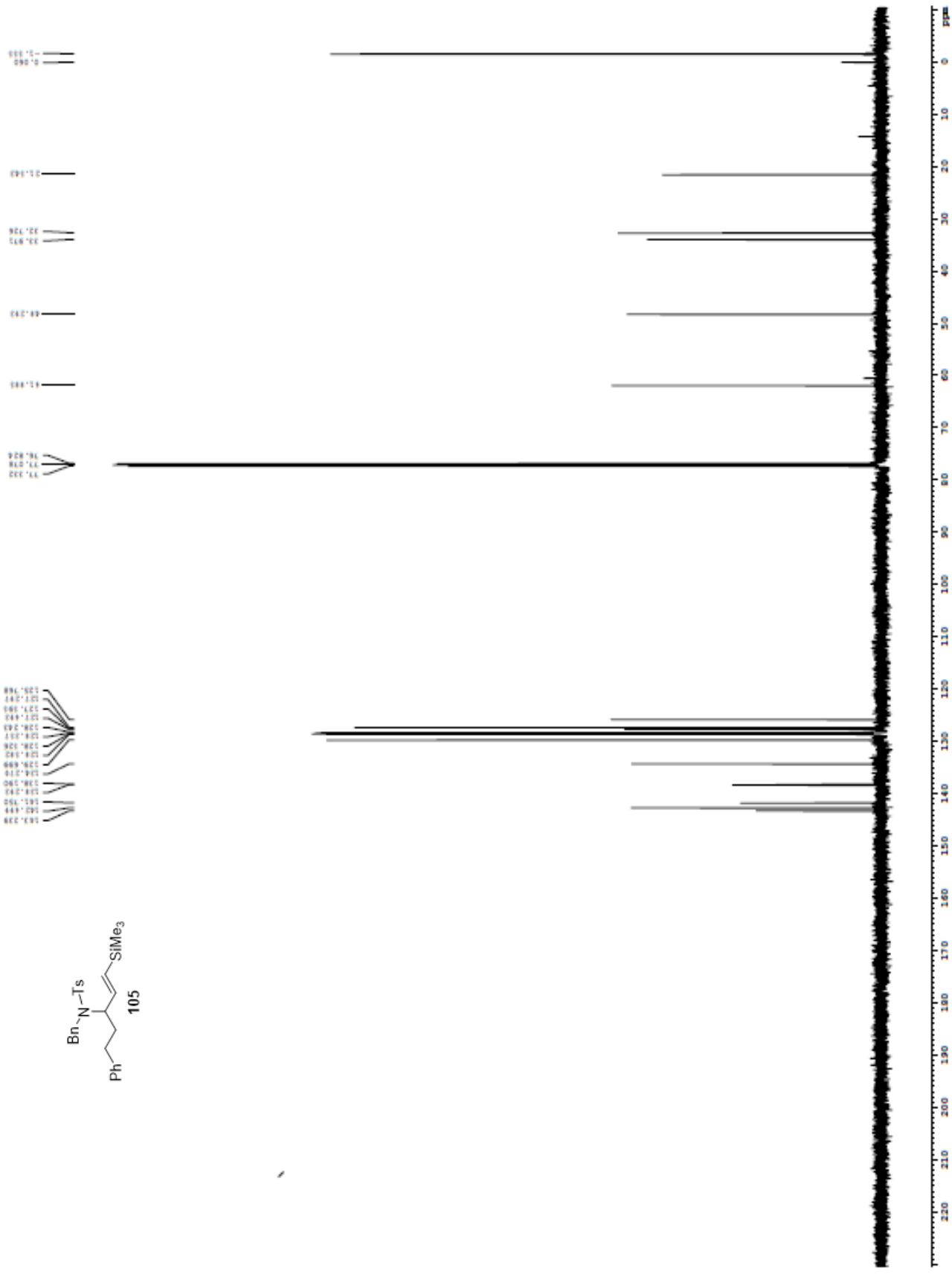

Bn
N
Ts
Ph
SiMe3
105


Bn
N
Ts
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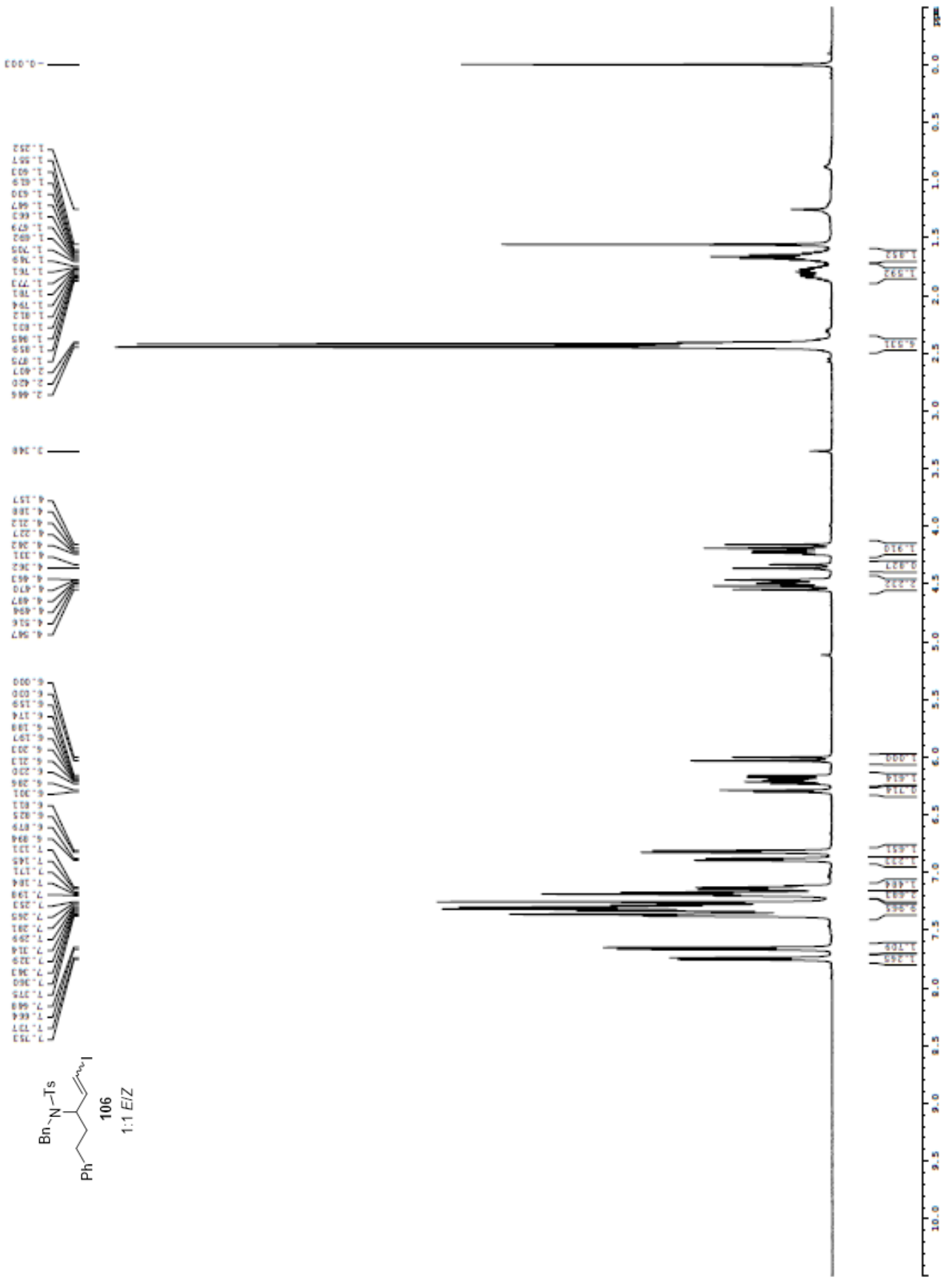
SiMe3
105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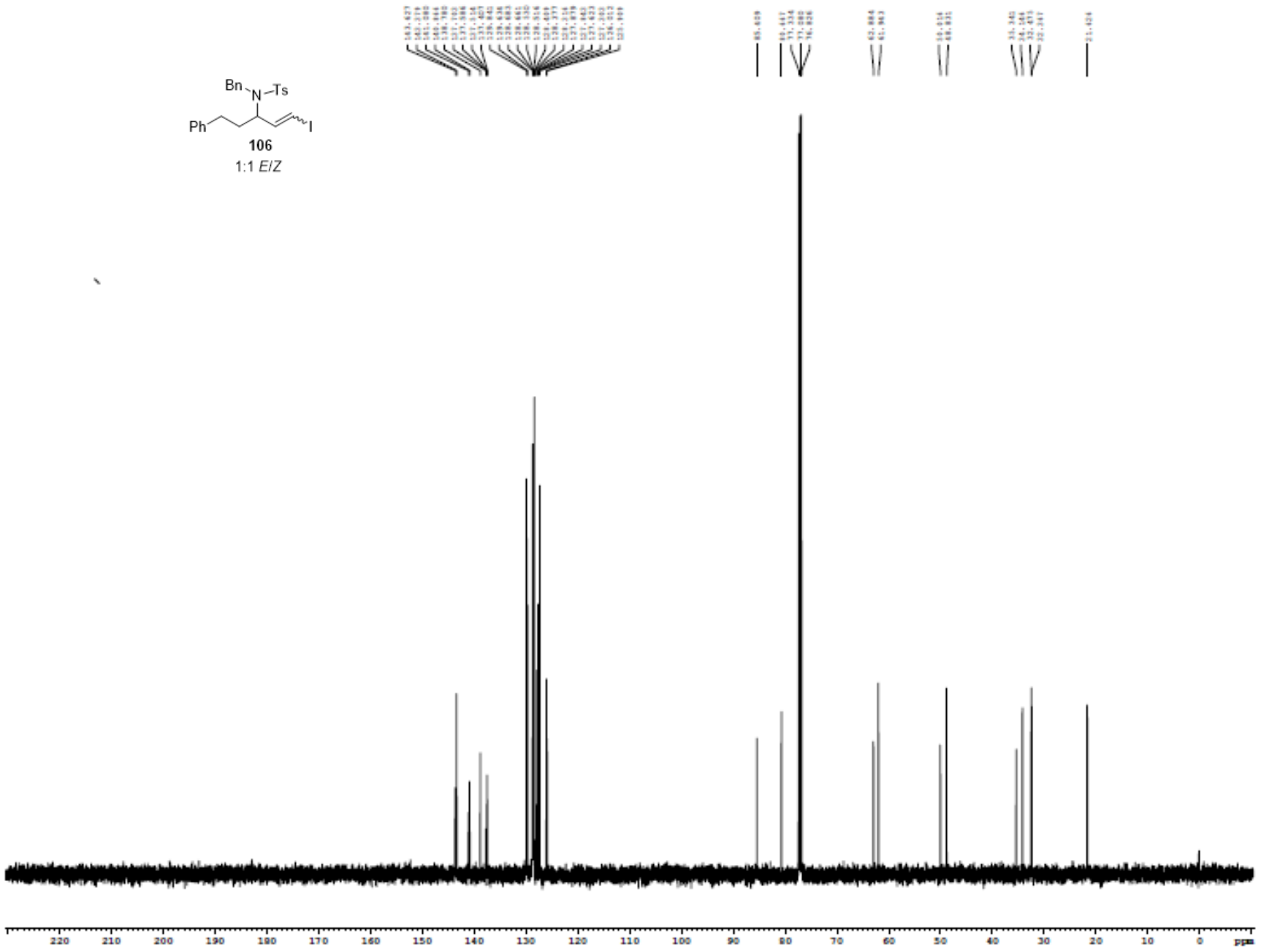
Ts
Ph
I
106
1:1 E/Z


Bn
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Ts
Ph
I
106
1:1 E/Z
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100
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ppm