DIETHYL ZINC MEDIATED INTRAMOLECULAR METALLOAMINATION OF *N,N*-DIMETHYLHYDRAZINES: EXPANDING A NOVEL APPROACH TO FUNCTIONALIZED PYRROLIDINES AND PIPERIDINES. UTILIZING SYNTHESIS AS A TOOL FOR MEDICINAL CHEMISTRY, ENVIRONMENTAL REMEDIATION, AND NONLINEAR OPTICAL CHROMOPHORE CONSTRUCTION

by

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of

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in

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This dissertation is dedicated to my wife, Sarah Partovi,
and my parents, Lin and Brian Mickelsen.

“Think no small thoughts, take no big steps.”

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PREFACE

Organic synthesis is an extremely broad field that has been heavily studied, in the past, organic chemistry focused on expanding methodology for bond forming and bond breaking reactions in order to assemble complex natural products. However, more recently, synthesis has emerged as a tool for constructing interesting molecules rationally designed for specific purposes. With decades of research focusing on organic methodologies, almost any envisioned molecule can be produced. Throughout this document, organic synthesis was used towards the advancement of an array of scientific topics, including organic materials, specifically organic nonlinear optical chromophores, and environmental remediation of carbon tetrachloride. Additionally, synthetic chemistry was used in a traditional fashion, generating new methodologies towards medicinally relevant, biologically active molecules.

Chapter one revolves around the construction of ferroelectric-like liquid crystal containing organic nonlinear optical chromophores for the desire to develop a supramolecular system that favors unidirectional organization. Environmental remediation methods for the destruction of aqueous carbon tetrachloride were explored in chapter two. Lastly, chapters 4-6 focused on synthetic methodologies for producing functionalized piperidines and pyrrolidines for medicinal chemistry. Chapter seven discusses the next logical steps for the continuation of each of these projects.

ABSTRACT

When attempting to develop a novel material for increased second-order nonlinear activity, a strategy was devised to rationally design an architecture that would allow for optimized acentric supramolecular organization. By coupling a liquid crystal tolane to a well-understood NLO chromophore via strategic synthesis, a set of novel chromophores was created. The ferroelectric liquid crystal-like molecules intrinsically favor unidirectional chromophore order while simultaneously containing a high β chromophore along the polar axis. This system has shown potential for high terminal stability as well as increased nonlinear optical susceptibilities.

Carbon tetrachloride poses a large threat to the environment and is the focus of ongoing remediation efforts. It is a well-known carcinogenic pollutant that has contaminated groundwater beneath former grain storage and industrial sites, such as the Department of Energy's Hanford site. Remediation through the use of a small molecule, PDTC, when complexed with copper has been shown to lead to complete dechlorination, resulting in conversion to non-toxic end-products (mostly CO_2) and complete removal of the problematic carbon-chlorine bonds. Synthetic chemistry was employed to develop a modified procedure for large-scale production of PDTC that eliminates harmful byproducts and excess toxic reagents used. Additionally, structural derivatives for increased water solubility have been envisaged from citrazinic acid, which could allow for aqueous destruction of carbon tetrachloride.

In medicinal and pharmaceutical chemistry, routes to nitrogenous heterocycles are of great importance due to their prevalence in bioactive molecules. Diethylzinc mediated metalloamination/cyclization of unsaturated *N,N*-dimethylhydrazines with subsequent electrophilic functionalization could prove to be a powerful tool for constructing pyrrolidines and piperidines. This method was extended to the use of 1,2-disubstituted alkenes as N-Zn migratory insertion acceptors, including various vinylcyclopropyl hydrazines. The potential behind the irreversible cyclopropane scission and development of a new alkene make this class of substrates extremely desirable. The metalloamination-alkylation of N,N-dimethylhydrazinoalkenes was shown to be effectively catalyzed by $CuBr•SMe_2$, CuCN and CuI. This novel method obviates the prior methodology involving use of stoichiometric $CuCN(LiCl)_2$ as a promoter for the electrophilic functionalization.

CHAPTER ONE

RATIONAL DESIGN OF NOVEL CHROMOPHORES FOR INTRINSIC UNIDIRECTIONAL ORDER

1.1 Abstract

Ferroelectric liquid crystal-like molecules intrinsically favor unidirectional order while simultaneously containing a highly polar molecule normal to the axis of liquid cystallinity. By coupling a liquid crystal tolane to a well-understood nonlinear optical (NLO) chromophore via strategic synthesis, a set of novel ferroelectric liquid crystal containing NLO chromophores was created. These chromophores have shown potential for high terminal stability as well as increased nonlinear optical susceptibilities.

1.2 Introduction

Organic synthesis, aided by computational simulations, can be employed for the preparation of specialized molecular architectures intended to create unnatural materials with remarkable electromagnetic (specifically optical) properties.[1] Organic materials exhibiting extraordinarily large second-order nonlinear optical (NLO) susceptibilities, $\chi^{(2)}$, have been of particular interest because of their potential in creating low-cost, high-performance electro-optic (EO) devices.

For years, research has focused largely on manipulating chromophore structures in order to create a larger first molecular hyperpolarizability (β).[2] In the case of the most commonly employed classes of dipolar chromophores, increased permanent dipole

moment accompanies improvements in β. Thus, improvements in β have resulted in significant increases in achievable organic nonlinear optical activity. However, due to the overwhelming dipole-dipole interactions between chromophores with such large permanent dipoles, the chromophore number density is limited to an optimum value, beyond which the acentric organization is dramatically reduced.[1,3,4]

Second-order organic nonlinear optical materials currently only achieve about 10-15% of their potential second-order nonlinear optical activity due to the inability to create and stabilize long-range unidirectional organization.[2] Molecular organization plays a major role in not only defining electronic and photonic properties, but it also governs physical properties. Therefore, a better understanding of how to create specific long-range order in organic nonlinear optical materials, using noncovalent forces, is absolutely essential. Recently, Walba[5,6] and Zhang[7-9] have introduced a chiral smectic ferroelectric liquid crystal as a new type of organic NLO material. Ferroelectric liquid crystals exemplify a case where a molecule with both polar and mesogenic properties spontaneously forms a polar ordered phase, analogous to that needed for nonzero $\chi^{(2)}$.[10,11] Their work shows that molecular design, with respect to long-range supramolecular order, can also provide materials with potentially useful NLO and EO properties.

1.3 The Electro-Optic Effect

In organic materials, the electro-optic (EO) or Pockels effect arises from a bulk material comprised of many nonlinear optically active organic molecules, or chromophores. Chromophores (dyes) are structurally rigid, electronically asymmetric, organic molecules consisting of an electron donor, electron acceptor, and an extended π-conjugated bridge that allows for efficient nonlinear polarization of electron density in response to an applied electric field. These organic nonlinear optically (ONLO) active molecules can be combined to create a bulk material as neat (pure) compounds or dispersed into an optically inactive (host) medium such as a polymer or dendrimer.[1,3]

In order to understand nonlinear optical (NLO) effects we must look at both the polarization of a single chromophore at the molecular level and the corresponding effect at the macroscopic level. At the molecular level, the polarization, p, of the electron density of the chromophore in response to a weak electro-magnetic field can be described by equation 1.1 shown below where p_0 is the equilibrium polarization of the chromophore, α_{ij} represents a particular tensor element of the linear polarizability, and E_j is the vector component of the applied electric field.

$$p = p_0 + \alpha_{ij} E_j \qquad (1.1)$$

$$P = P_0 + \chi_{ij}^{(1)} E_j \qquad (1.2)$$

Equation 1.2 above shows the analogous relationship at the macroscopic level where the linear polarizability of the individual chromophore is extrapolated to the linear susceptibility ($\chi_{ij}^{(1)}$) of the bulk material. When a particular optical frequency interacts

with a material the incident electro-magnetic wave is altered in such a way that the resultant wave created is of the same frequency (Figure 1), but phase-shifted in time. The amount the resultant field is phase-shifted is proportional to the magnitude of the index of refraction, η, of the material.[3,4]

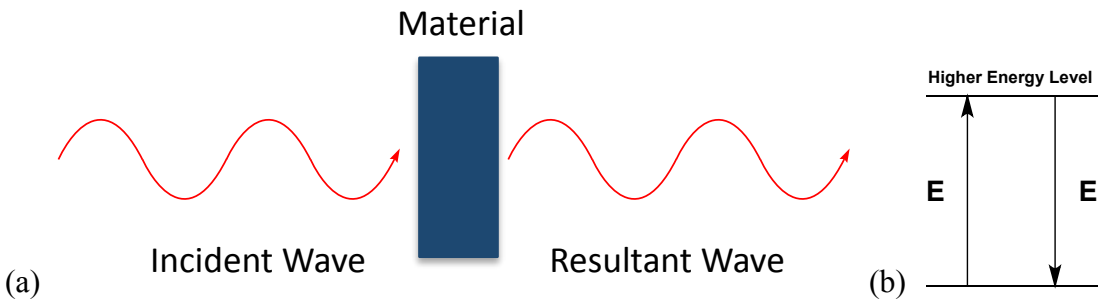


Figure 1.1a. Shows the creation of an identical frequency wave phase-shifted in time after passing through a linear optically material. Figure 1.1b. Shows the energy level diagram of the emitted photon.

With higher power optical fields, such as those produced by lasers, equation 1.2 above becomes an inadequate representation of the response observed. Therefore, there is a need to amend the mathematical representation to include higher order, nonlinear, polarization terms. As in the previous equations, we must look first at the single chromophore level and expand to the bulk material, or macroscopic level.

$$p = p_0 + \alpha_{ij} + \beta_{ijk} E_j E_k + \gamma_{ijkl} E_j E_k E_l \qquad (1.3)$$

$$P = P_0 + \chi^{(1)}_{ij} + \chi^{(2)}_{ijk} E_j E_k + \chi^{(3)}_{ijkl} E_j E_k E_l \qquad (1.4)$$

At the single molecule level, equation 1.3, the molecular first and second hyperpolarizabilities are represented by β_{ijk} and γ_{ijkl}, respectively. While in equation 1.4, the expansion to the bulk material uses $\chi^{(2)}_{ijk}$ and $\chi^{(3)}_{ijkl}$ to represent the second- and third-order nonlinear susceptibilities, respectively. As discussed above, in linear optics as the

electromagnetic wave passed through the material the resultant field was of the same frequency as the incident field (Figure 1.1). With the addition of a nonlinear susceptibility contribution, this is not necessarily the case. For example, in the case of materials with nonzero $\chi^{(2)}$, degenerate and non-degenerate wave mixing effects may occur giving rise to second harmonic generation, sum-frequency generation, and other similar effects. Figure 1.2 below shows the nonlinear effect known as second harmonic generation (SHG), a nonlinear optical property directly related to the first nonlinear susceptibility. As shown above in Figure 1.2, SHG, also known as frequency doubling, is commonly described in quantum mechanical terms as the interaction of two identical photons resulting in a virtual higher energy level. Upon relaxation of this state, a new wave of double the incident photons' frequency is generated. The linear component of this interaction is responsible for refractive index and linear absorption. The nonlinear component of this interaction gives rise to the Pockels and second harmonic generation, $\chi^{(2)}$, as well as Kerr effects and third harmonic generation, $\chi^{(3)}$, etc.[3,4]

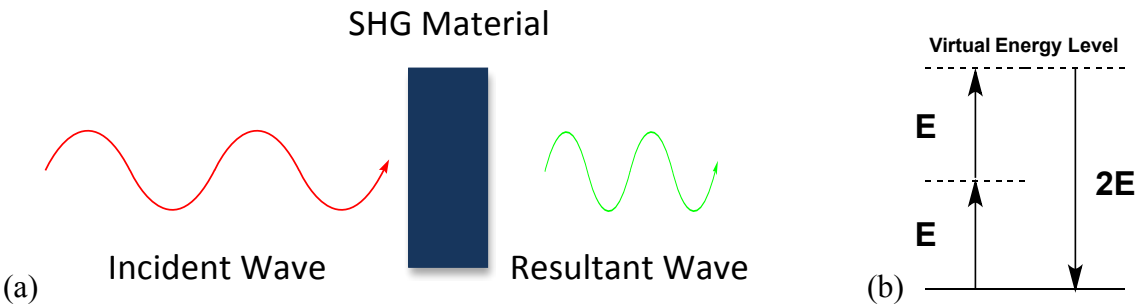


Figure 1.2a. Shows an electro-magnetic wave passing through a SHG material creating a new wave of twice the frequency of the incident wave. Figure 1.2b. Shows the combined two-photon interaction that results in the new wave that is twice the frequency of the incident wave.

1.4 Second-Order Nonlinear Optics

Second-order nonlinear susceptibility differs greatly from linear and third-order susceptibilities due to the requirement for a noncentrosymmetric, or acentric, alignment of the constituent highly dipolar chromophores. In order to achieve nonzero $\chi^{(2)}$ (proportional to the EO effect), these asymmetric chromophores must be arranged into a bulk material that is also asymmetric. The relationship between the second-order nonlinear response and composition/organization of the material can be defined by equation 1.5 where β_{zzz}, is the molecular first hyperpolarizability.

$$\chi^{(2)}_{zzz}(\omega) = N\beta_{zzz}\langle\cos^3\theta\rangle g(\omega) \qquad (1.5)$$

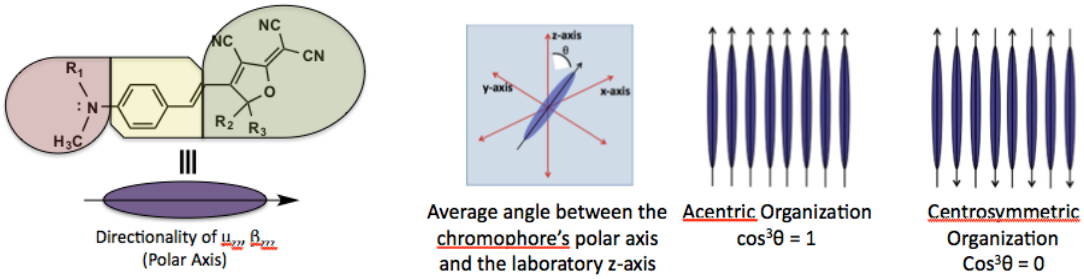


Figure 1.3. Example of a nonlinear optical chromophore, showing the direction of β_{zzz} and how the supramolecular organization of the chromophores can affect the overall $\chi^{(2)}_{zzz}$.

Equation 1.5 describes β_{zzz} as dependent on both frequency of the incident field, ω, and the dielectric permittivity, ε, of the electro-optic material. The dominant second-order nonlinear susceptibility tensor element (in the laboratory z-axis) is also dependent upon the number density of active chromophores, N (molecules/cm^3), and the overall average of the dipolar alignment, $\cos^3\theta$, within the bulk material. Lastly, the scalar quantity, g(ω), is the wavelength dependent Lorentz-Onsager local field factor. Figure

1.3 shows an example of a chromophore and how the overall material must be aligned in order to observe a second-order nonlinear response as defined by equation 1.5.

$$r_{33}(\omega) = \frac{-2\chi^{(2)}_{zzz}}{\eta^4} \qquad (1.6)$$

The experimentally measurable electro-optic coefficient, r_{33}, is related to $\chi^{(2)}$ according to the relationship shown in equation 1.6. It is clear from these relationships that in order to increase the observed EO coefficient one must increase $\chi^{(2)}_{zzz}$.

Another property inherent to the first nonlinear susceptibility, as mentioned previously, is the Pockels effect. The Pockels effect presents the ability to alter the refractive index (η) of a material through the use of an applied electric field. This effect is directly proportional the optimization of r_{33}, and in turn $\chi^{(2)}_{zzz}$. The relationship between the EO coefficient and the change in refractive index is represented by equation 1.7.

$$\Delta\eta(E) = \eta - \frac{r\eta^3 E}{2} \qquad (1.7)$$

The change in refractive index, in a defined field, is dependent upon the innate refractive index of the material as well as the EO coefficient (r_{33}) in relation to the applied field.[3] It is clear that though the optimization of the EO coefficient one can increase the resulting strength of the Pockels effect. This can be accomplished through simultaneous optimization of the three major contributors to $\chi^{(2)}_{zzz}$: N; β_{zzz}; and $\langle\cos^3\theta\rangle$.

For years, research has focused largely on manipulating chromophore structures in order to create a larger β_{zzz}.[2] In the case of the most commonly employed classes of dipolar chromophores, increased permanent dipole moment accompanies improvements in β_{zzz}. Due to the overwhelming dipole-dipole interactions between chromophores with

such large permanent dipoles, N is limited to an optimum value, beyond which <cos$^3\theta$> is dramatically reduced.[1,3,4] Thus, improvements in β_{zzz} have resulted in most increases in achievable r_{33}.

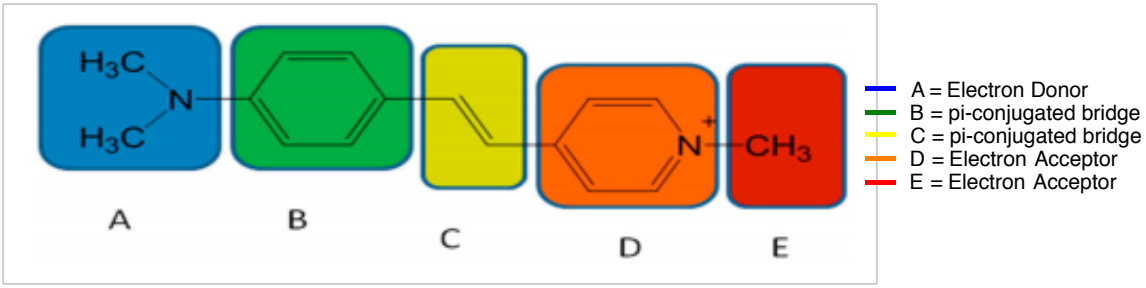


Figure 1.4. Structure of a nonlinear chromophore with defined regions

A generic chromophore that exhibits second order nonlinear optical properties can be seen in Figure 1.4, where region A is the electron donor, regions B-C are the π-conjugated bridge, and regions D-E are the electron acceptor, commonly referred to as D-π-A molecules. It is well known that the utilization of stronger electron acceptors and electron donors as well as extending the π-conjugated bridge generally leads to higher β_{zzz} chromophores.[3] Of these three building blocks, development of high β_{zzz} chromophores is largely based on the producing novel electron acceptors. Jen[12] and Dalton[3,4] have developed an outstanding electron acceptor that has helped to advance the field of nonlinear optical (NLO) chromophores. Basic structures of powerful NLO chromophores reliant on large β_{zzz} to increase second order nonlinear activity can be seen in Figure 1.5.

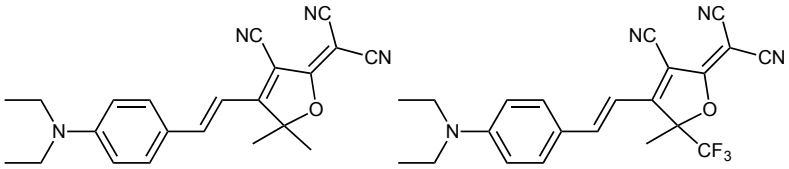


Figure 1.5. NLO chromophores utilizing powerful electron acceptors for increasing β_{zzz}

However, by increasing the strength of β_{zzz}, typically the supramolecular organization diminishes due to the strongly repulsive intermolecular interactions. Several laboratories have tried to combat these unfavorable interactions through electric poling,[3] use of dendrimers,[4] and utilizations of liquid crystals.[5-9, 12, 16]

1.5 Liquid Crystals

The challenge in creating a highly efficient $\chi^{(2)}$ material system comes through the need for a closely packed system of high β_{zzz} chromophores that still support long-range molecular order. Liquid crystals are known to display long-range supramolecular order. However, most liquid crystals only display long-range organization in two dimensions, rather than all three, as required for $\chi^{(2)}_{zzz}$. Liquid crystals are materials that simultaneously possess the mobility of a liquid and the anisotropic characteristics normally associated with solids (birefringence).[13] Liquid crystalline mesophases are formed due to a number of specific intermolecular interactions that accompany distinct molecular structures. Liquid crystals are often long, narrow, rod-like molecules that contain a structurally rigid backbone with the concurrent incorporation of both strong dipoles and easily polarizable moieties.[13,14] There are two major forms of liquid

crystalline (LC) mesophases that exist: smectic (Figure 1.6a) and nematic phases(Figure 1.6b). Smectic phases form at lower temperature and are more ordered than nematic.

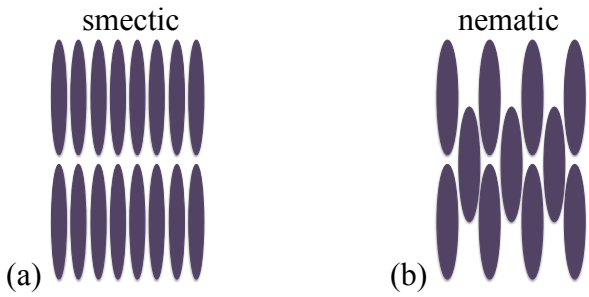


Figure 1.6a. Shows cartoon representation of a smectic liquid crystalline phase. Figure 1.6b. Shows a nematic liquid crystalline phase.

Both of these two phases contain sub-phases to describe a number of different possible local molecular orientations that can form but retain the overall ordering characteristic of either smectic or nematic. Nematic describes LC phases in which molecular orientational correlation exists, but positional correlation does not. In contrast, smectic phases exhibit both positional and orientational correlation. In Figure 1.6a and 1.6b, both smectic and nematic phases are shown, respectively.

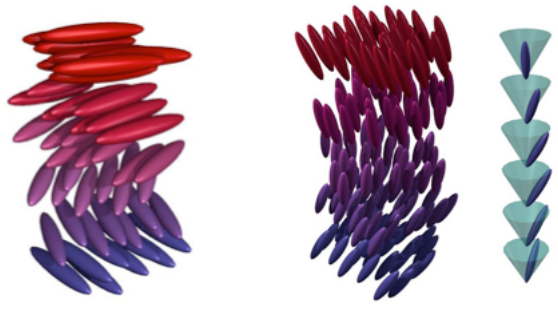


Figure 1.7. Helical twist of a chiral liquid crystal.

Two examples of sub-phases mentioned above are chiral-nematic and chiral-smectic LC phases, typically represented with an asterisk (*). Chirality can be introduced either through a chiral center on the liquid crystal molecule or a chiral dopant added to induce a chiral phase. In chiral liquid crystals (Figure 1.7), as layers form or stack on one another they develop a helical twist from the asymmetry of the chiral center. The resulting helical pitch can be tuned with the concentration and type of dopant to have a specific helical pitch length.[15]

Ferroelectric liquid crystals are a division of liquid crystals that contain two rigid, rod-like axes *normal* to one another (Figure 1.8). The first axis is that of the liquid crystal (mesogen) itself and the second axis is one that contains a permanent polarization. Clark and Lagerwall[10] discovered that anti-ferroelectric formations could be avoided using surface stabilization; that is, if a chiral ferroelectric liquid crystal is put into a cell gap, via capillary action, that is less than that of one full helical rotation, then no anti-ferroelectric formations were observed. All liquid crystal axes would lie in the plane of the surface, while all permanently polarized axes would lie in the direction of the applied field. After the field is applied, it can be removed and the surface stabilizations and intermolecular interactions will allow for the created phase to be preserved, this is known as surface stabilized ferroelectric liquid crystals.[10,11]

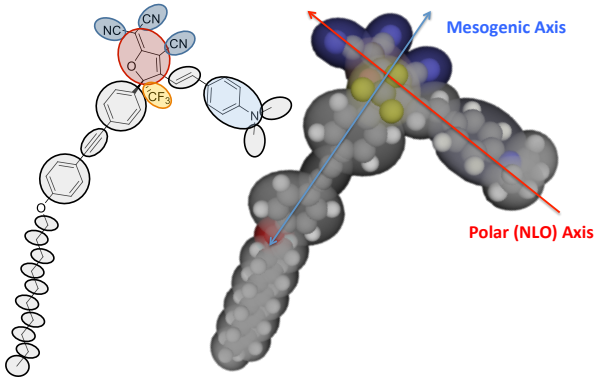
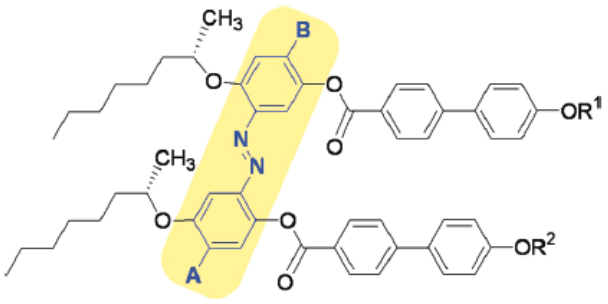
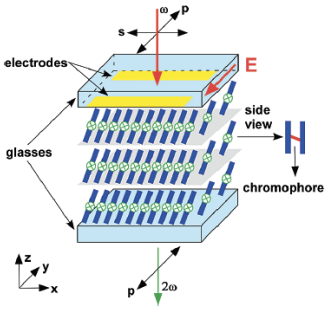


Figure 1.8. Shown is a ferroelectric liquid crystal represented as dipolar ellipsoids, showing the axis of liquid crystallinity normal to that of the polar axis

Zhang and co-workers[7-9] are pushing the forefront of building a spontaneously organized second-order nonlinear optical chromophore system using H-shaped ferroelectric liquid crystals, seen in Figure 1.9. The advantage to this system is the development of highly ordered systems gained through intelligent design of the liquid crystal (LC) base tethered by a nonlinear optical chromophore. Albeit an excellent system Zhang and co-workers have designed, their intent could be furthered with the use of a stronger β chromophore.



(a)



(b)

Figure 1.9a. Basic design of the H-shaped NLO chromophore/LC molecule, where B = electron donor and A = electron acceptor of the NLO chromophore defined in the yellow box.[7] Figure 1.9b. Model of how the ferroelectric LC-NLO chromophore is used in a second harmonic generation experiment.[7]

Shown in Figure 1.10 below is how a rationally designed chromophore/liquid crystal molecule could be used in a analogous fashion to the Zhang[7,8,9] group to induce spontaneous long-range unidirectional order, while incorporating a chromophore with a much larger β_{zzz} than previously used in these systems.

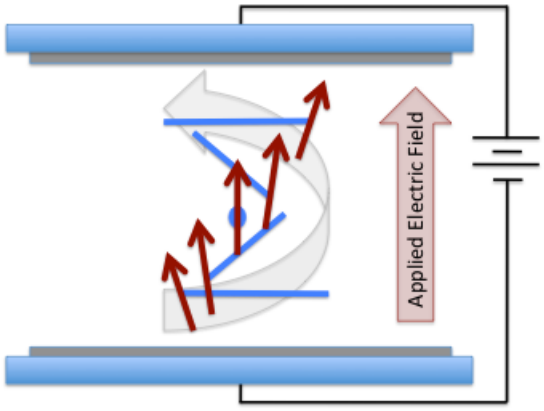


Figure 1.10. Proposed development of a ferroelectric-like chromophore where a large β chromophore (red) could be coupled with a highly ordered liquid crystal (blue).

In order to optimize acentric order within the overall system one must design a molecule, which still possesses the characteristics necessary to have a large hyperpolarizablity, but also bears the appropriate structural elements for directing order. The opportunity to couple a polar axis (large β chromophore) and a mesogenic axis (directing order) within one molecule makes materials similar to ferroelectric liquid crystals an attractive system for creating organic nonlinear optical materials. Coupling two methods previously discussed in order to rationally design an organic ferroelectric liquid crystal-like material that intrinsically favors acentric chromophore order while still

containing a high β chromophore along the polar axis for increased and stabilized second-order nonlinear optical potential.

With the understanding that a material must be engineered at the molecular level to achieve reproducible macroscopic electromagnetic properties, development of a chromophore using a bottom up approach began.

1.6 Results and Discussion

To allow for overall unidirectional order within the material system we needed to design a dye with strong mesogenic properties to direct liquid crystalline-like order. A tolane group (diphenylacetylene) was selected for the mesogenic moiety because of its strong liquid crystal (nematic and/or smectic phase formation) character, synthetic ease, and thermal stability.[17-21] It was also essential to incorporate a high β chromophore along polar axis, normal to the mesogenic axis. Thankfully, high β chromophores have been intensely studied.[1-4, 22-24] Therefore, a para-amino phenyl-TCF (tricyanofuran) structure was chosen due to its status as one of the best NLO chromophores known to date. The pendent group (mesogen) was then fashioned to include a saturated tail containing a point of possible chirality, because chirality adds another element of symmetry breaking. Nematic/smectic LC mesophases are already asymmetric in two dimensions. The addition of chirality to the system helps break symmetry in the third dimension,[10] as is required for the induction of $\chi^{(2)}$. The aliphatic tail was introduced to modulate crystallinity, reducing melting temperatures. The end molecular architecture selected (**1**, Figure 1.11), based on potential for spontaneous order and overall increased $\chi^{(2)}$ is shown

below

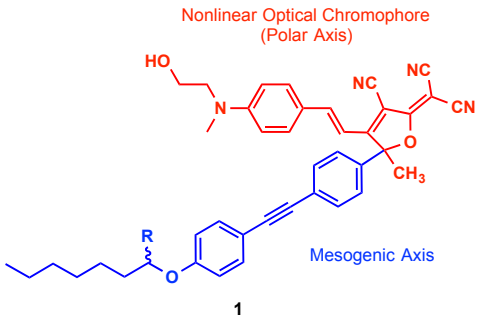
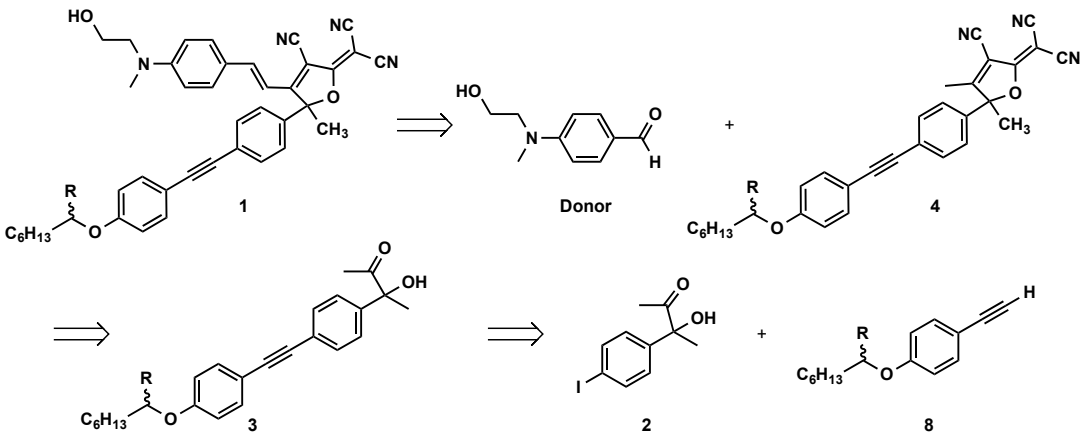


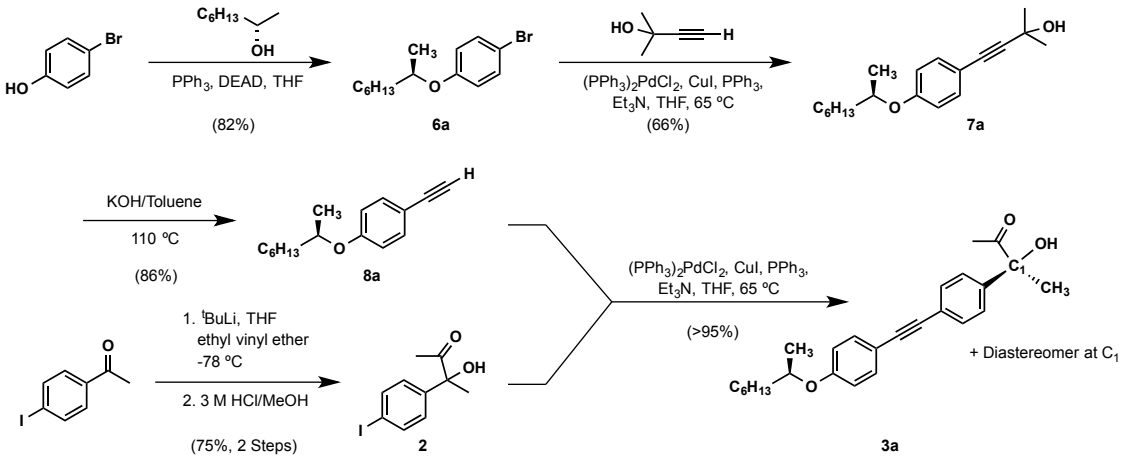
Figure 1.11. Model of desired ferroelectric-like LC nonlinear optical chromophore (**1**)

Retro-synthetic analysis was used in order determine logical starting materials for the production of the desired NLO chromophores. A retro-condensation separates the chromophore into the specialized electron acceptor (**4**) and commercially available electron donor. The electron acceptor, **4**, can be constructed from two equivalents of malononitrile and the β-hydroxyketone **3** seen in Scheme 1.1, which could be envisaged through the cross-coupling of simple 3-hydroxy-3-(4-iodophenyl)-butan-2-one (**2**) and the terminal acetylene **8** shown below.

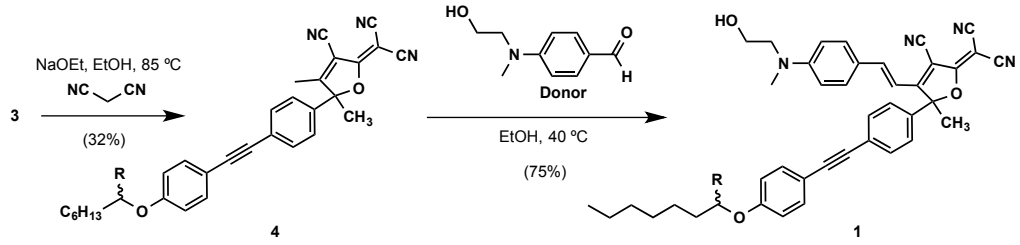


Scheme 1.1. Retrosynthetic pathway for producing the chromophore of interest (**1**)

Scheme 1.2 shows specifically the production of chiral tolane **3a** which was created in an analogous manner to the tolane construction of Yelamaggad.[17] The Mitsunobu inversion employed was only used to convert 4-bromophenol to (R)-1-bromo-4-(octan-2-yloxy)benzene (**6a**) using (S)-2-octanol (shown in Scheme 1.2), and racemic 1-bromo-4-(octan-2-yloxy)benzene utilizing 2-octanol (**6b**, not shown). 1-bromo-4-(heptyloxy)benzene (**6c**, not shown) was made according to a previously reported procedure[25] performing a simple S_N2 displacement on bromoheptane. An additional alteration to the Yelamaggad method was using 5% palladium (II) catalyst loading for the Sonogashira cross-coupling reaction to provide the protected (R)-2-methyl-4-(4-(octan-2-yloxy)phenyl)but-3-yn-2-ol (**7a**, Scheme 1.2), racemic 2-methyl-4-(4-(octan-2-yloxy)phenyl)but-3-yn-2-ol (**7b**, not shown), and 4-(4-(heptyloxy)phenyl)-2-methylbut-3-yn-2-ol (**7c**, not shown), which were deprotected with potassium hydroxide in toluene to afford the respective terminal acetylenes (**8a-c**). 3-hydroxyl-3-(4-iodophenyl)butan-2-one (**2**, Scheme 1.2) was easily obtained in good yields through a lithiated addition of ethyl vinyl ether into 4'-iodoacetophenone in dry THF at reduced temperature. This produced intermediate 3-ethoxy-2-(4-iodophenyl)but-3-en-2-ol, which was readily deprotected with the addition of 3M HCl in methanol. Similar molecules have been previously synthesized using this route.[26] The first tolanes (**3**, Scheme 1.2) were produced through a second Sonogashira reaction between α-hydroxyketone **2** and the terminal acetylenes **8** using bis(triphenylphosphine)palladium(II) dichloride as the catalyst (5 mol%). **3a-c** were purified via flash column chromatography and carried into the preparation of NLO electron acceptors **4a-c** (Scheme 1.3).



Scheme 1.2. Synthetic pathway to key intermediate **3a**



Scheme 1.3. Construction of the FLC-nonlinear optical chromophore **1**

The electron acceptors, **4a-c**, were made utilizing a Knoevenagel condensation with the addition of 2 equivalent of malononitrile, employing a method described for the construction of comparable molecules.[24,26,27-30] Upon completion of the NLO electron acceptors, the corresponding final mesogen containing chromophore was prepared through a simple condensation reaction between N-methyl-N-(2-hydroxyethyl)-4-aminobenzaldehyde (**Donor**) and **4a-c**. Similar transformations, joining an electron acceptor to an electron donor and creating the polar axis of the chromophore have been shown to proceed in high yield.[22,24,28] Thus completed the construction of three novel ferroelectric-like nonlinear optical liquid crystal containing chromophores **1a-c** (Figure

1.12).

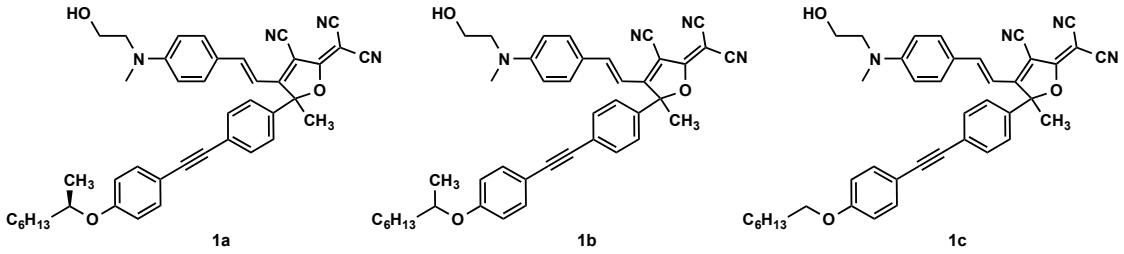


Figure 1.12. Series of novel NLO chromophores

Compound **5** (Figure 1.13), which has been shown to be a strong NLO chromophore,[31] was prepared according to a previously reported method[32] as a control compound. A representative UV-Vis spectra of compound **1** was taken. Figure 1.13 shows that the addition of the mesogenic tolane onto the electron acceptor results in a slight red shift of the λ_{max} compared to that of reference compound **5** (Table 1.1). This can be easily explained by the additional electron donation from the tolane; it can also be seen that an additional peak from the tolane is present at 308 nm.

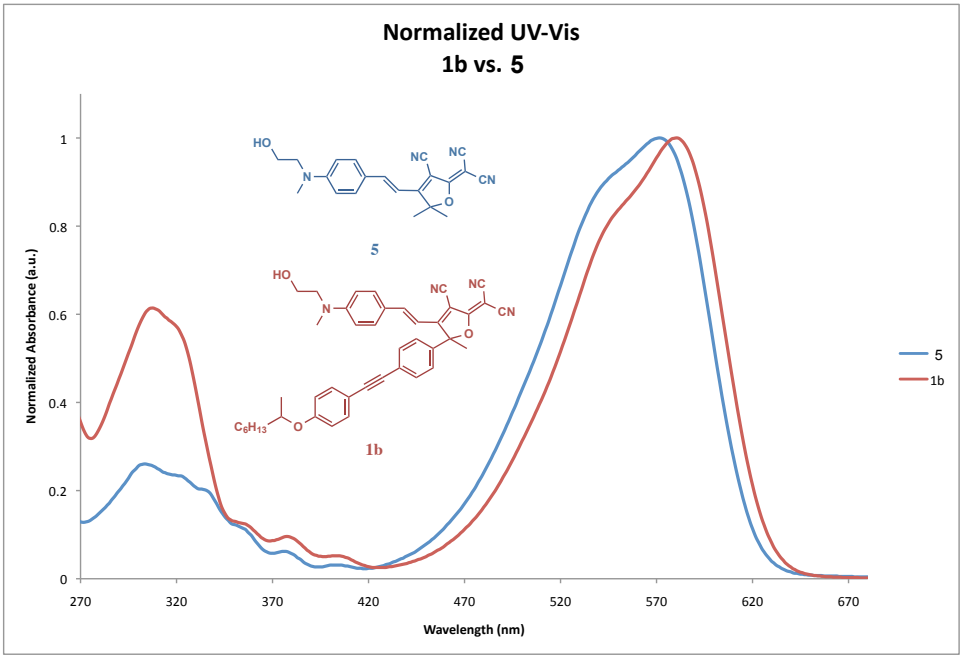


Figure 1.13. Normalized UV-Vis spectra comparing representative chromophore **1b** versus reference compound **5**

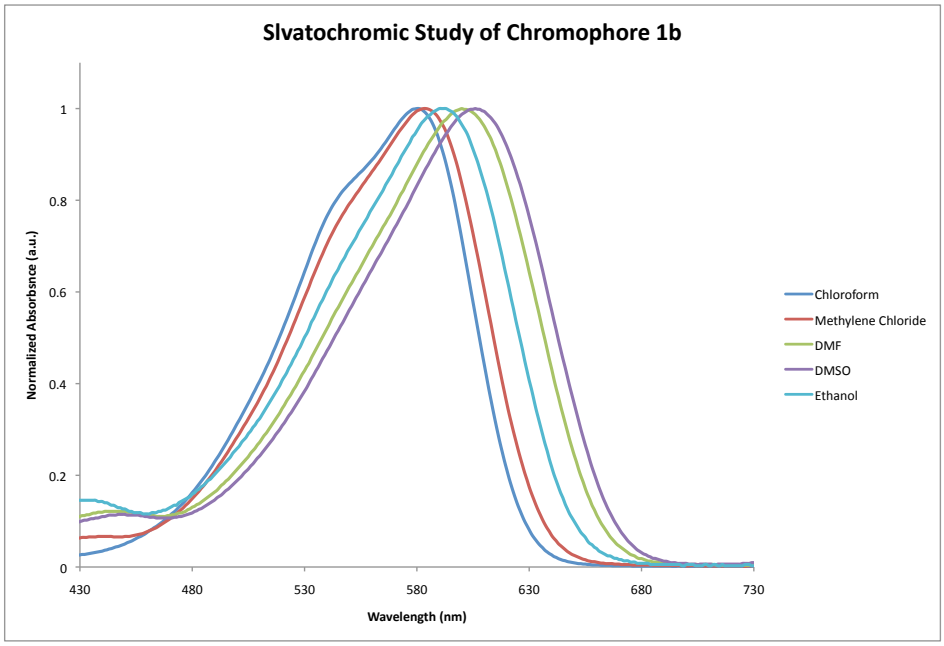


Figure 1.14. Solvatochromic study of representative chromophore **1b** showing bathochromic shift with increasing solvent dielectric constant

Positive solvatochromism, or bathochromism has been commonly considered as an indication of increased molecular hyperpolarizability, according to theoretical and experimental NLO studies.[33,34] Compound **1b** was chosen to test whether the tolane containing NLO chromophores (**1a-c**) exhibited the predicted bathochromic shifts. Through the solvatochromic study (Figure 1.14) a 25 nm red shift was observed between **1b** in chloroform and DMSO. This red shift suggests greater stabilization of the excited state with increasing dielectric constant, which in turn suggests increased molecular nonlinearity. In order to further investigate the potential hyperpolarizability of compounds **1a-c**, computational calculations were employed. Recently, theoretical calculations have not only been used to rationalize experimental results but also to predict potential in compounds. Advances in molecular orientation calculations have made it possible to calculate response properties such as optical nonlinearities. Using *p*-nitroaniline, a chromophore similar to that used by Zhang and co-workers,[8,9] and compound **5** as references, density functional theory (DFT) quantum mechanical methods were employed to determine theoretical $\beta(-2\omega;\omega,\omega)$ for each chromophore (Table 1.1). In order to save computational time, B3LYP/6-31G* method and basis set was selected using the "*polar*" function within Gaussian (G09).[35] As expected, chromophores **1a-c** showed molecular first hyperpolarizabilities much greater than that of known NLO active *para*-nitroaniline and consistent with that of reference compound **5**. As seen in Table 1.1, showed β-values ranging from 19-33 times that of *para*-nitroaniline along the dipolar axis of the chromophore.

Table 1.1. Nonlinear chromophores vs. standard **5** and *para*-nitroaniline

Compound	λ_{max}[a] (nm)	β (10^{-30} esu)	β/*p*NA-β	T_d (ºC)
1a	581	1428.5	19.1	254
1b	581	2513.5[y]	33.6	247
1c	581	2227.4	29.7	254
5	571	2276.3	30.4	274
*p*NA	---	74.9	1	---

a. All UV-Vis samples were run in chloroform

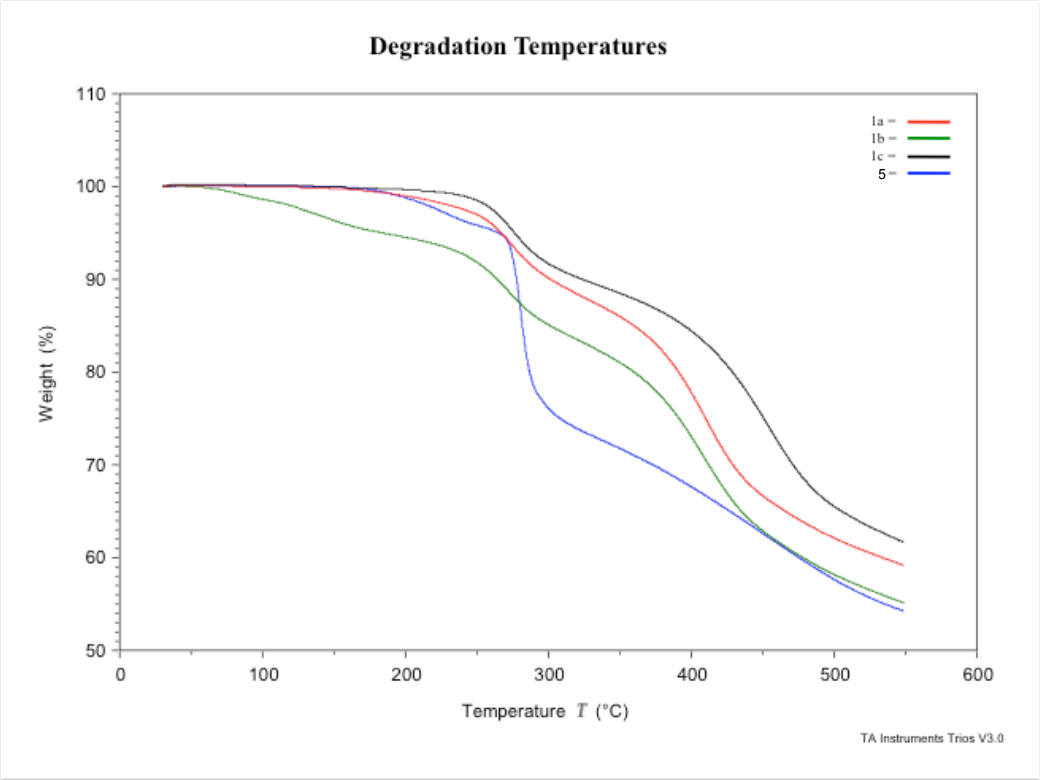


Figure 1.15. Overlain degradation temperatures of **1a-c** and **5**, analysis preformed with TGA increasing temperature 10 ºC/min.

It should also be noted that the thermal stabilities of chromophores **1a-c** as well as compound **5** were tested using thermogravimetric analysis. It can be clearly seen in Table 1.1 that the addition of the tolane lowers the degradation temperatures of compounds **1a-c** compared to the pendant-less chromophore **5**. However, all of the chromophores show

high thermal stability with onset temperatures over 240 ºC (Figure 1.15).

1.7 Conclusions

In conclusion, we set out to rationally design a molecular architecture that would allow for optimized acentric supramolecular organization. We were able to envision a construct that could facilitate a chromophore containing a large first molecular hyperpolarizability and bare the appropriate structural elements for directing order. By coupling a liquid crystal tolane to a well known NLO chromophore via strategic synthesis we were able to create an organic ferroelectric liquid crystal-like material that should intrinsically favor unidirectional chromophore order but also contains a high β chromophore along the polar axis for increased and stabilized second-order nonlinear optical potential.

With the understanding that a material must be engineered at the molecular level to achieve reproducible macroscopic electromagnetic properties, it was proposed to develop a chromophore using a bottom up approach. Utilizing this bottom up approach to constructing a unique material, we have designed and characterized a synthetic pathway to a set of novel chromophores. These chromophores have shown potential for high terminal stability as well as increased nonlinear susceptibilities.

1.8 Funding Information

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CHAPTER TWO

DESIGN AND SYNTHESIS OF PROLIGAND PYRIDINE-2,6-BIS(MONOTHIOCARBOXYLIC ACID) AND STRUCTURAL DERIVATIVES FOR USE IN ENVIRONMENTAL REMEDIATION OF CARBON TETRACHLORIDE

2.1 Abstract

Carbon tetrachloride is a carcinogenic pollutant that has contaminated groundwater beneath former grain storage and industrial sites, such as the Department of Energy's Hanford site. Current remediation of these sites involves removal and subsequent treatment, which requires handling of the hazardous material as it is transferred to another location for final destruction. Professor Thomas Lewis has previously described the use of a small molecule (pyridine-2,6-bis(monothiocarboxylic acid [PDTC]), that when complexed with copper has been shown to lead to complete dechlorination of pollutant carbon tetrachloride. The process results in conversion to non-toxic end-products (mostly CO_2) and complete removal of the problematic carbon-chlorine bonds. Synthetic chemistry can be employed to develop a series of PDTC derivatives that could increase water solubility and allow for on-site destruction of carbon tetrachloride. The current methods described in literature for the synthesis of proligand PDTC use or produces large quantities of toxic hydrogen sulfide gas. A modified procedure for large-scale production of PDTC, with minimal hydrogen sulfide production, was successfully developed. However, this method is inferior for

synthesizing more complex derivatives of PDTC (due to its length), which defines the need for a novel approach to the development of proligand derivatives. An elegant approach using a dilithiated addition into carbonyl sulfide was investigated to produce PDTC and several derivatives that could be functionalized for use in environmental remediation of carbon tetrachloride.

3.2 Introduction

Organic contaminates have become a serious issue in our environment from years of improper disposal; specifically chlorinated organic compounds present a significant risk to not only the ecosystems but also to human health. Carbon tetrachloride is a toxic, carcinogenic, and ozone-depleting compound that has been used as a solvent, industrial degassing agent, grain fumigant, fire extinguisher, and for the manufacture of nuclear weapons.[1-5] Carbon tetrachloride has been identified as a contaminant of groundwater; and in aqueous solutions, carbon tetrachloride has an estimated half-life of 7,000 years.[6] The United States Environmental Protection Agency's hazard summary of carbon tetrachloride is stated below.[7]

> "Carbon tetrachloride may be found in both ambient outdoor and indoor air. The primary effects of carbon tetrachloride in humans are on the liver, kidneys, and central nervous system (CNS). Human symptoms of acute (short-term) inhalation and oral exposures to carbon tetrachloride include headache, weakness, lethargy, nausea, and vomiting. Acute exposures to higher levels and chronic (long-term) inhalation or oral exposure to carbon tetrachloride produces liver and kidney damage in humans. Human data on the carcinogenic effects of carbon tetrachloride are limited. Studies in animals have shown that ingestion of carbon tetrachloride increases the risk of liver cancer. EPA has classified carbon tetrachloride as a Group B2, probable human carcinogen."

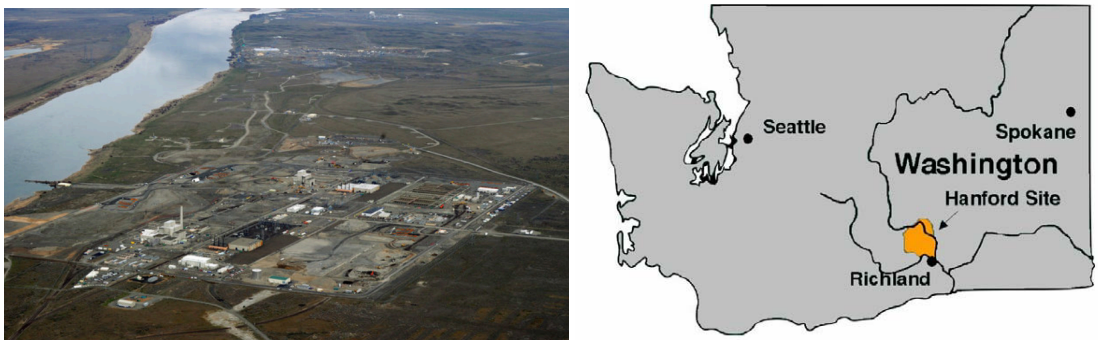


Figure 2.1. The Hanford site, located on the Columbia River in Washington State[26, 28]

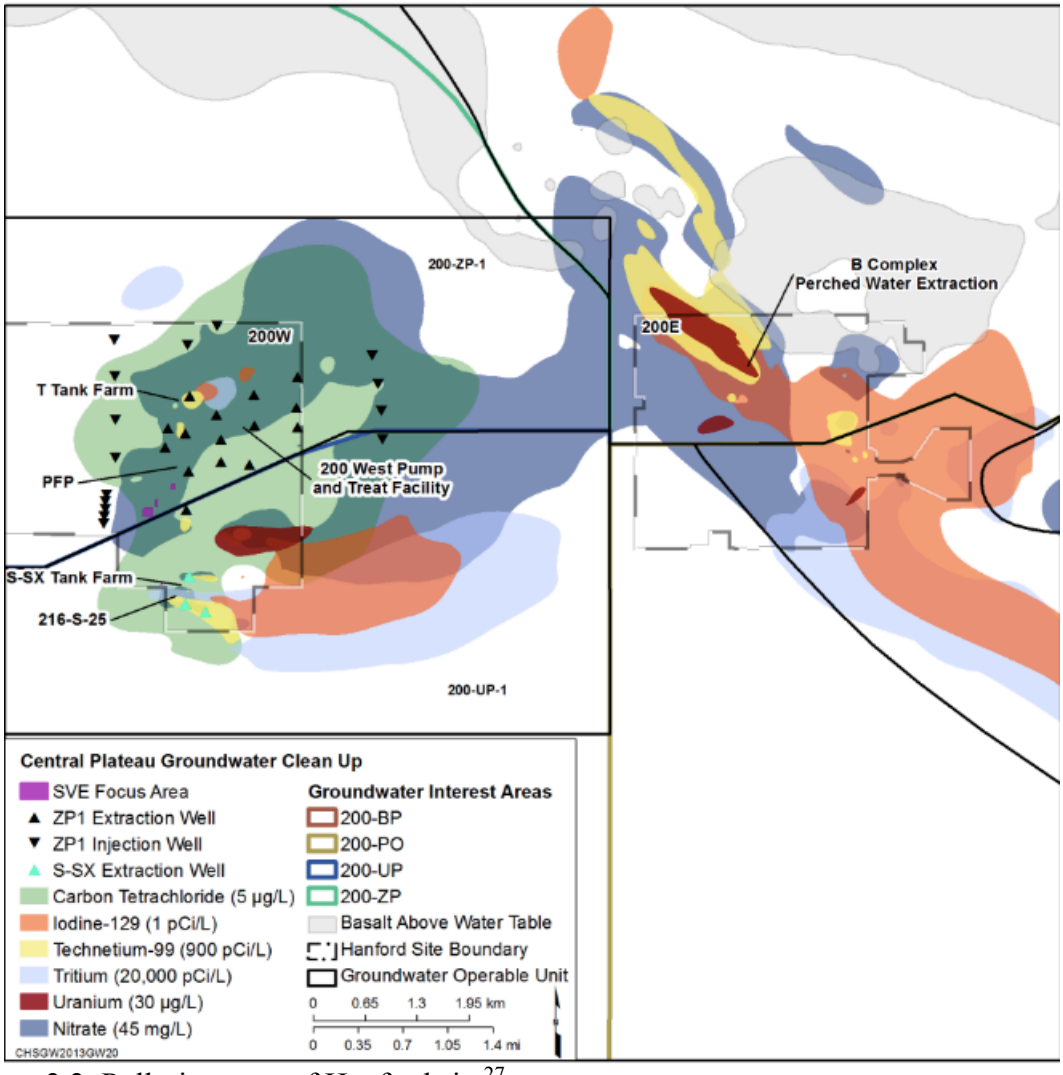


Figure 2.2. Pollution map of Hanford site[27]

Due to careless disposal over many years, carbon tetrachloride has become a priority pollutant as defined by the EPA, requiring the cleanup of contaminated sites such as the Department of Energy's Hanford site in Washington State (Figures 2.1 and 2.2). The current technologies for carbon tetrachloride destruction at the Hanford site involves removal and subsequent off-site treatment. Current projections of the cleanup timeline for carbon tetrachloride call for 125 years of continuous operation.[5]

Carbon tetrachloride has been studied for many years, in order to understand the toxicology and to identify methods for its destruction in the environment.[8,9] Several laboratories have developed methods for destroying carbon tetrachloride via a reductive pathway yielding chloroform and dichloromethane as byproducts.[10-15] However, the effective complete dichlorination of Criddle and co-workers[16] through the discovery of a pure culture, *Pseudomonas stutzeri* strain KC, that under iron limited conditions, which efficiently reduces carbon tetrachloride bypassing the radical and lesser chlorinated intermediates leading to non-toxic byproducts, largely generating carbon dioxide. The study of this process was continued by Crawford and Lewis,[1,17-19] who ultimately found that the degradation of carbon tetrachloride was due to an extracellular agent produced by the bacteria. Through electrospray tandem mass spectroscopy, NMR spectroscopy and comparison with synthetic material they identified pyridine-2,6-bis(monothiocarboxylate) [PDTC] as the active metabolite of strain KC.[18]

Subsequently, the laboratory of Lewis and Crawford tested the effect of transition metal ions on PDTC-mediated carbon tetrachloride transformation and found that of the metals screened (Fe, Co, Ni, Cu) copper was the only metal that exhibited increased

effect on the reduction of carbon tetrachloride. They formulated a potential pathway in which carbon tetrachloride is dechlorinated by Cu:PDTC by observing isolated byproducts. The mechanism, shown in Figure 2.3, requires an atom transfer and is overall a reductive pathway. Initially, one electron is transferred to carbon tetrachloride from the Cu:PDTC complex and successive chloride insertion, after which the radical $\bullet CCl_3$ is linked to form a thioester. Trichloromethanethiol is ultimately displaced by hydroxide and reduced to CO_2, CS_2 and HCl as the major byproducts, completely destroying all toxic carbon-chlorine bonds. Each Cu:PDTC can effectively reduce two equivalents of carbon tetrachloride leading to the final formation of pyridine-2,6-biscarboxylic acid.[19]

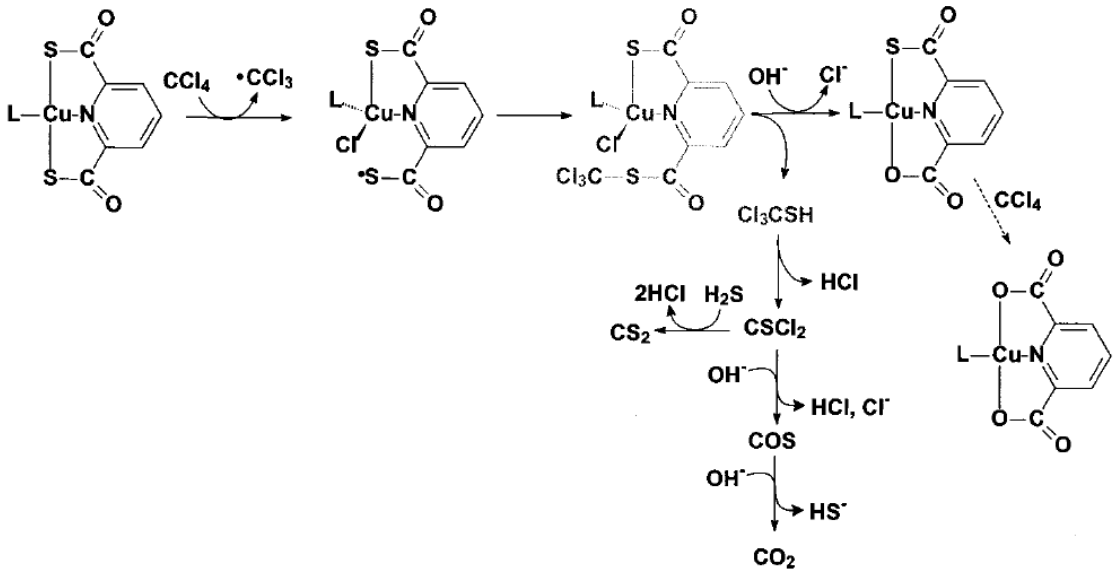
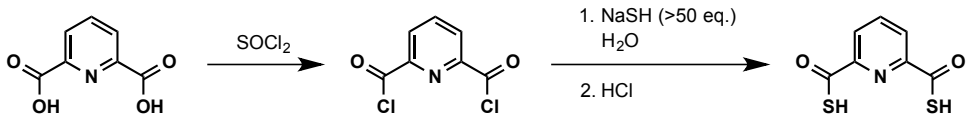


Figure 2.3. Reaction pathway explaining products of reaction between Cu(II):PDTC and carbon tetrachloride (intermediates in grey have never been identified)[19]

The incredible potential of this process led to the proposal of using synthetic pyridine-2,6-bis(monothiocarboxylic acid) as a method for environmental remediation of

carbon tetrachloride due to the destruction of all problematic carbon-chlorine bonds and conversion to non-toxic end-products. The current synthesis of PDTC was done by Crans and co-workers[20] as seen in Scheme 2.1, this process converted the dicarboxylic acid in the corresponding bis-acyl chloride which was transformed into sodium pyridine-2,6-bis(monothiocarboxylate) with excess sodium hydrosulfide. The excess hydrosulfide was neutralized with HCl and PDTC was isolated. Unfortunately, this procedure generates copious amounts of hydrogen sulfide gas and is extremely reagent inefficient.



Scheme 2.1. Crans' synthesis of PDTC

Alternatively, PDTC was constructed by bubbling hydrogen sulfide gas into a solution of the same bis-acyl chloride, again, this method uses large amounts of toxic hydrogen sulfide gas.[21]

Currently the use of Cu:PDTC yields poor solubility within solution leading to lower carbon tetrachloride destruction;[1, 17-19] whereas this method translates into higher solubility within aqueous carbon tetrachloride systems. For this reason there is a need for synthetic derivatives of PDTC, providing increased water solubility for the elimination of carbon tetrachloride in groundwater.

2.3 Results and Discussion

Initially, a series of synthetic derivatives with functionalization at the four-position of the pyridine system was envisioned. This functionalization could be altered to provide increased water solubility of the overall carbon tetrachloride degradation complex. The three compounds of interest were a carboxylic acid, primary alcohol, and polyethylene glycol at the four-position (Figure 2.4).

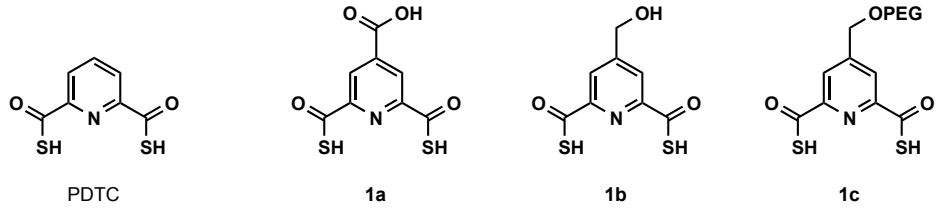
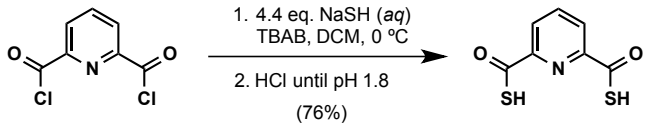


Figure 2.4. Structural derivatives of PDTC (**1a-c**)

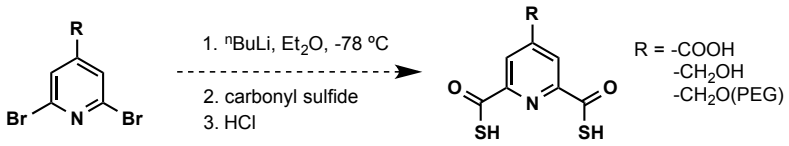
Starting directly into the derivative synthesis was not undertaken immediately, pure PDTC needed to be produced, but the current procedure for making clean reproducible PDTC needed to be optimized. To reduce the hazards and excess reagents used in the previously reported methods, pyridine-2,6-dicarbonyl dichloride of the previous method was converted to pure PDTC (Scheme 2.2) according to the optimized procedure.[29]



Scheme 2.2. Optimized conversion to PDTC

This optimized procedure[29] not only reduces the reagents used but also minimizes

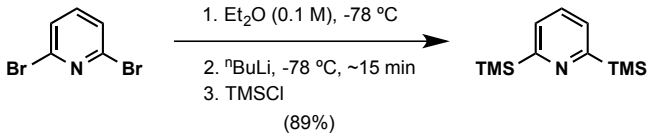
the production of harmful byproducts. Pure PDTC as well as this procedure were provided to collaborators Queen and Lewis to continue analytical experimentation. This process works well for the construction of PDTC but would prove difficult to apply to the derivative systems. Thus, Professor Livinghouse devised an elegant method for quick construction of PDTC in a single step that would facilitate functionalization at the four-position to be carried throughout the development of the desired products (**1a-c**, Fig 2.4).



Scheme 2.3. Novel approach to PDTC

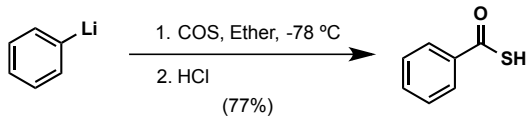
This novel procedure would go though a dilithium-halogen exchange and subsequent direct thiocarboxylation utilizing carbonyl sulfide (Scheme 2.3). To develop this process there were a few 'proof of concept' reactions that needed to be optimized. The first attempts of dilithium-halogen exchange of dibromopyridine with *n*-butyllithium resulted in a mixture of mono- and dilithiated products, observed after trapping with chlorotrimethylsilane. It was found that inverse addition of dibromopyridine, as a solid,[22] into cold (-78 ºC) diethyl ether/*n*-butyllithium mixture resulted in 100% dilithiated product. Alternately, it was discovered that at the right concentration dibromopyridine would precipitate from cold (-78 ºC) diethyl ether and direct addition of *n*-butyllithium could be done dropwise. The low solubility of dibromopyridine in diethyl ether allows for a pseudo-inversion addition process to occur, as each molecule is dilithiated as it is pulled into solution. This provides a clear point at which all lithiation has occurred through

observation; the resulting dilithiated compound is then trapped with chlorotrimethylsilane (Scheme 2.4).



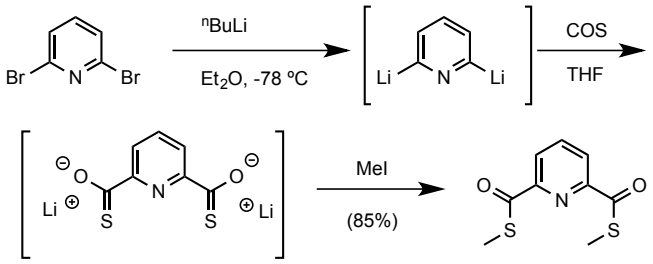
Scheme 2.4. Optimization of dilithiation procedure

Next, the direct thiocarboxylation procedure was developed. This was achieved by the reaction shown in Scheme 2.5 between phenyllithium and carbonyl sulfide.



Scheme 2.5. Testing direct thiocarboxylation conditions

Concluding the proof of concept experiments, reactions designed for construction of PDTC in a single reaction began. Early on it was discovered that direct addition of carbonyl sulfide led to isolation of undesired side products. Inverse addition of dilithiopyridine into a solution of excess carbonyl sulfide via a thin, syringe-like, cannula resulted in degradation of the lithiated pyridine. Lithiated pyridines have been shown to degrade when warmed above -30 ºC, as reported by Newkome and co-workers.[23] A thick-walled Teflon-cannula was created for a faster, more insulated transfer, which solved the issue of lithiopyridine degradation (Figure 2.5). These optimizations were determined by trapping the resulting pyridine-2,6-bis(monothiocarboxylate) with iodomethane (Scheme 2.6).



Scheme 2.6. Construction of pyridine-2,6-dithiomethylester

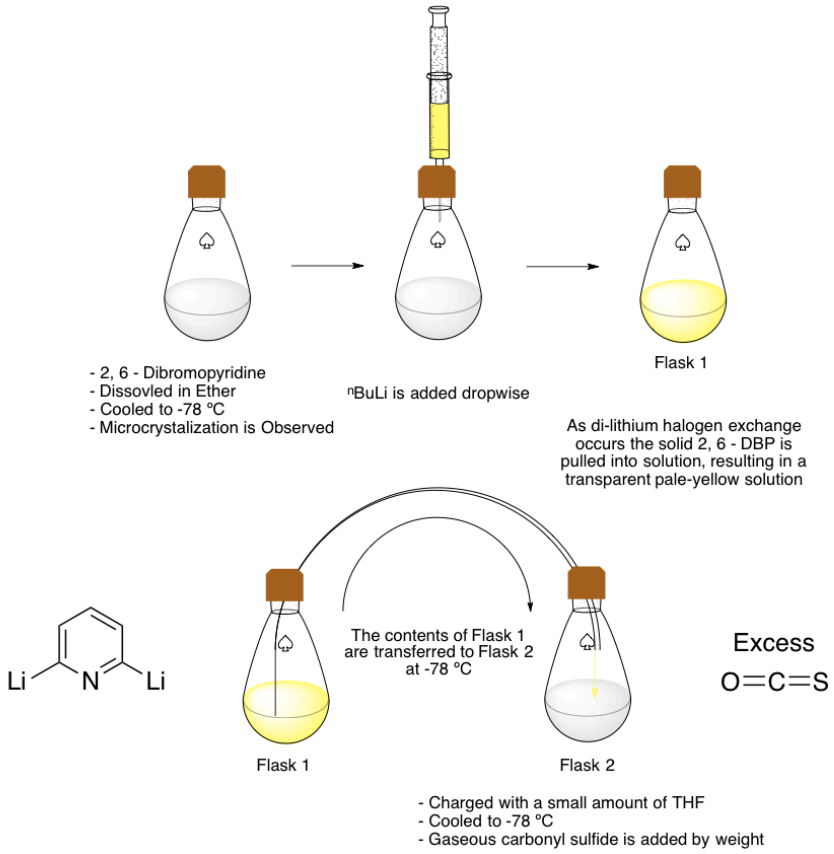
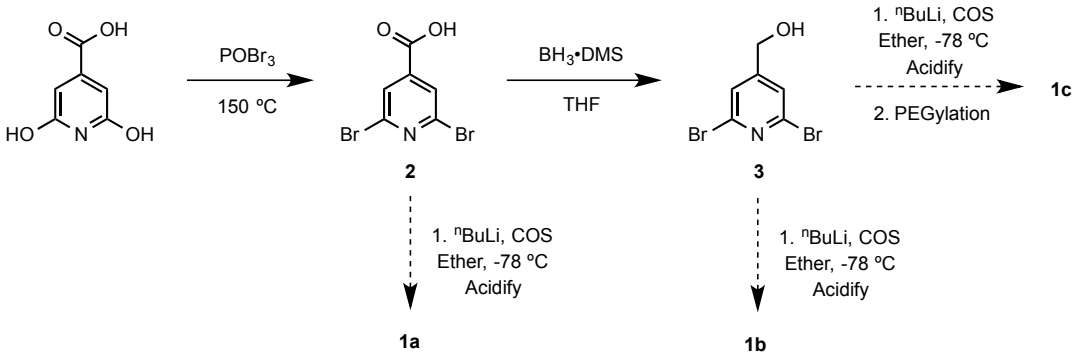


Figure 2.5. Pictorial representation of process used to successfully dilithiate and direct thiocarboxylate dibromopyridine

With the successful production of the thiomethylester, as compared to Budzikiewicz,[24] focus was shifted towards functionalized PDTC derivatives **1a-c** (Figure 2.4), which could be envisaged from citrazinic acid. Citrazinic acid or 2,6-

dihydroxypyridine-4-caboxylic acid could be readily converted into 2,6-dibromopyridine-4-carboxylic acid (**2**) using phosphorus (V) oxybromide,[25] quenching carefully with water. The dibromocarboxylic acid then could be used to provide the primary alcohol (**3**) via a borane-reduction, which would ultimately need to be protected for the subsequent dilithiated addition into carbonyl sulfide to form the bis(monothiocarboxylic acid). Upon deprotection of the OTBS group the corresponding alcohol (**1b**) could be transformed into the PEG containing **1c**.



Scheme 2.7. All derivatives possible from citrazinic acid

After **2** and **3** were made as shown above in Scheme 2.7, pursuit of the derivatives and PDTC formation utilizing the novel method developed for direct thiocarboxylation was attempted. Unfortunately, when it came time to make PDTC using the new method another issue began to unfold. The acidification step was producing decomposed product rather than pure PDTC. Many attempts were made in order to properly quench the lithium thiocarboxylates including protonation using many different acids and isolating the lithium salt before protonation. Each endeavor ultimately produced similar result: degraded PDTC or a mixture of undesired byproduct.

2.4 Conclusions

A new method was described for the formation of standard PDTC that eliminates harmful byproducts and excess toxic reagents used. Additionally, a novel route to PDTC was attempted in order to develop PDTC and structural derivatives. At this time the process still needs to be optimized to observe successful dilithium-halogen exchange and direct bisthiocarboxylation. However, the dibromide-functionalized derivates were readily constructed from citrazinic acid. Continued work on optimizing this novel procedure and design of a new route to the synthetic derivatives utilizing the dibromide intermediates are discussed in Chapter 7 of this dissertation.

2.5 Funding Information

Generous financial support from Montana Research and Economic Development Initiation is acknowledged.

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29. **Optimized Experimental Procedure for PDTC Production:** A 100-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with pyridine-2,6-dicarbonyl dichloride (1.5 g, 7.35 mmol, 1.0 equiv) and tetra-*n*-butylammonium bromide (237 mg, 0.735 mmol, 0.1 equiv). The reaction vessel was then placed under vacuum and back-filled with nitrogen (3x) followed by the addition of dry dichloromethane (30 mL). The solution was stirred and cooled to 0 ºC for the dropwise addition of sodium hydrosulfide (3.63 mL, 32.34 mmol, 4.4 equiv, sat. solution in water, 8.92M). The mixture was stirred vigorously at 0 ºC for 1 h then warmed to 23 ºC and stirring was continued overnight. The inorganic solid (NaCl) formed was dissolved using a minimal amount of degassed aqueous half brine solution and the biphasic mixture was acidified with hydrochloric acid (1M) until the aqueous layer was about pH 1.8 (pH paper). The biphasic solution was separated and the aqueous layer was extracted with dry dichloromethane (3x, under a cone of flowing nitrogen) checking the aqueous solution stayed pH 1.8 between each extraction. The organic layers were combined, washed with

degassed brine, dried over Na_2SO_4, filtered and concentrated in vacuo (back-filling with nitrogen). The solid residue was dissolved using a minimal amount of dry chloroform (passed through an alumina plug) and then pushed through a pipette plug of silica, washing with dry chloroform several times. This process should be repeated at least twice for clean PDTC. The solution was then concentrated in vacuo (back-filling with nitrogen) furnishing pyridine dithiocaboxylic acid (PDTC, 1.11 g, 76%) as an off-white solid.

CHAPTER THREE

INTRODUCTION TO METALLOAMINATION CHEMISTRY

3.1 Importance of Pyrrolidines and Piperidines

Nitrogen-containing heterocycles are an extremely important class of organic compounds. By viewing any list of Food and Drug Administration (FDA) approved pharmaceuticals, it can easily be seen that this system is a common structural motif. Of these nitrogenous heterocycles, pyrrolidines and piperidines have garnered significant research interest in the past both academically and industrially because of their prevalence within natural products and bioactive materials. In fact, a recent study showed that of 1086 totally unique small molecules approved by the FDA, that 640 contained nitrogen heterocycles.[1] Accordingly, greater than 32% of all FDA approved drugs contain a nitrogenous heterocyle within its structure (Figure 3.1).

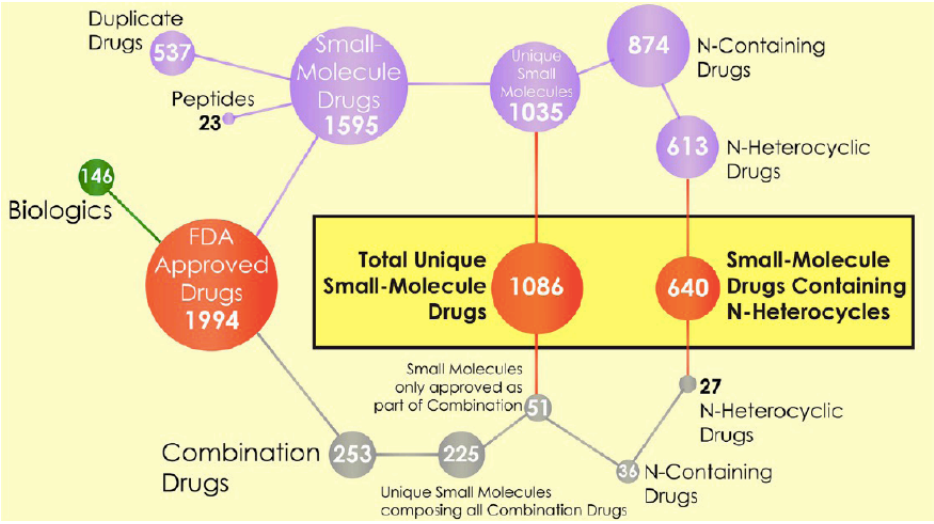


Figure 3.1. Breakdown of U. S. FDA approved drugs[1]

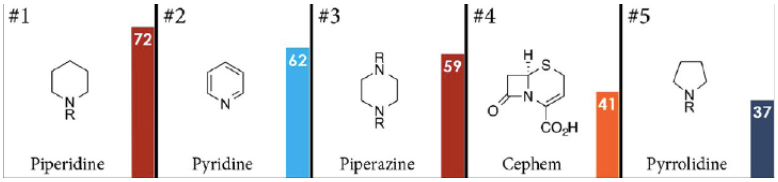


Figure 3.2. Top five most frequent nitrogen heterocycles in the U. S. FDA approved drugs[1]

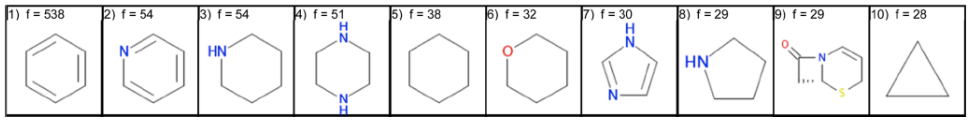


Figure 3.3. Top ten most frequently used ring systems from small molecule drugs listed in the FDA Orange Book sorted by descending frequency (f)[2]

Additionally, both the pyrrolidine and piperidine systems are among the top five most commonly occurring nitrogen heterocyles (Figure 3.2), and the top ten most commonly occurring ring systems found in medicinal drugs on the market today (Figure 3.3).[1,2] Shown in Figure 3.4 are some examples of drugs currently in use with the piperidines and pyrrolidines highlighted in red. Procylidine is an anticonvulsant medication used for epilepsy that contains a pendant pyrrolidine, while Lentiginosine consists of a fused piperidine-pyrrolidine system and is used as an amyloglucosidase inhibitor. Tiagabine contains a piperidine and is used for a variety of treatments, and lastly, morphine is a common pain medication hosting a N-methylated piperidine within its structure.

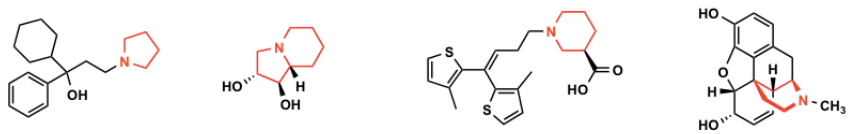


Figure 3.4. Four currently used drugs that contain either piperidine or pyrrolidine ring systems

This prevalence among FDA approved drugs has obviously led to increased interest within the field of medicinal chemistry to explore many possible routes to the formation of pyrrolidines and piperidines. Some common methods for producing these saturated nitrogenous rings are through hydroaminations and metal-mediated carboamination, also known as metalloamination reactions.

3.2 Hydroamination

The pursuit of carbon-nitrogen bond forming reactions has always been at the forefront of organic chemistry due to its various applications. Hydroamination represents a facile and highly atom economical process that consists of inter- or intramolecular addition of an amine N-H bond across a carbon-carbon region of unsaturation, such as an alkene, alkyne or allene. Many different groups have shown ingenious methods for metal mediated hydroamination processes[3,4] but the first intramolecular metal-catalyzed example of this process was shown by Marks *et. al.* in 1989.[5] In this report Marks showed the remarkably facile and regiospecific organolanthanide-catalyzed hydroamination/cyclization of N-unprotected amino olefins. The predicted catalytic cycle of this process is shown below in Figure 3.5. After Marks discovery, similar pathways were uncovered with alternative metals. In the recent review[6] the same mechanism was used to describe hydroaminations utilizing Group 3 metals and lanthanides. The catalytic activation results in the organometallic amino-olefin, subsequent olefin insertion and protonlysis leads to production of pyrrolidines and piperidines.

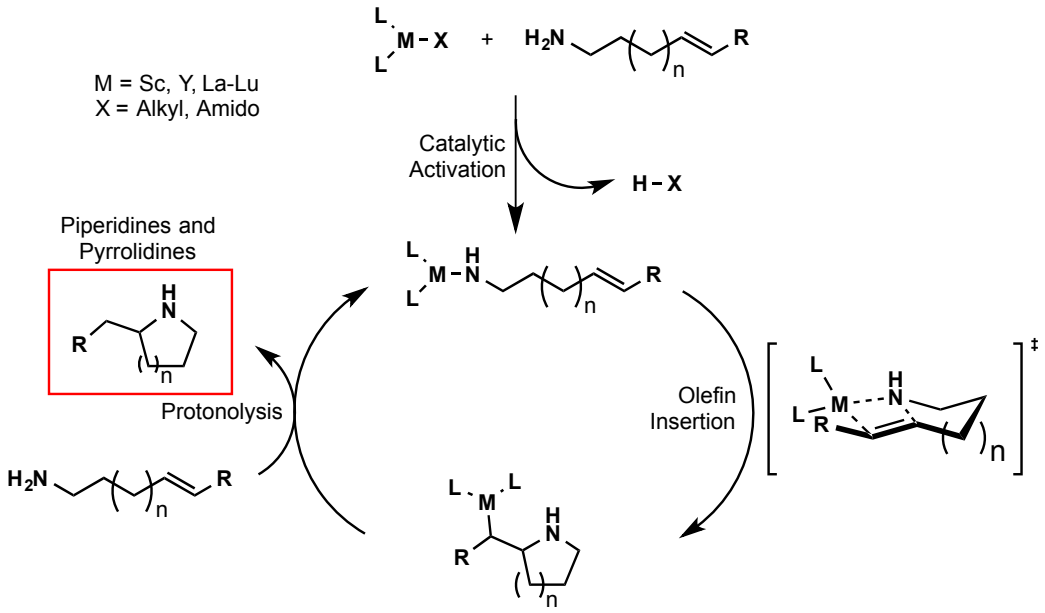


Figure 3.5. Catalytic cycle of hydroamination

Previous work of the Livinghouse lab made significant strides in the development of intramolecular alkene hydroamination methods using catalytic non-metallocene derivatives of Group 3 metals (Figure 3.6).[7] They were able to show that readily available Group 3 amides were unusually useful catalysts for facile alkene hydroamination as well as show that bis(trimethylsilyl) amides, specifically $Y[N(TMS)_2]_3$, were able to catalyze a sequential and highly stereoselective aminodiene bicyclization. The Livinghouse group went on to define neutral scandium amide complexes as useful catalyst systems for similar alkene hydroamination processes, as well as further developing yttrium complexes. It was shown that axially chiral bis-(thiolato) complexes of yttrium(III) were excellent catalysts for the asymmetric intramolecular hydroamination with increased activity towards cyclization and higher diastereoselectivities.[8-10] More recently, the Livinghouse lab developed (*R*)-*N*,*N*′-dibenzosuberyl-1,1′-binaphthyl-2,2′-diamine

proligand and observed effective enantioselective hydroamination/cyclization of aminoalkenes catalyzed by chelating diamide complexes of La(III) and Y(III).[11] Alkene hydroamination is an important and useful tool but a major shortcoming of the method can be viewed by the proton termination event following nitrogen-carbon bond formation.

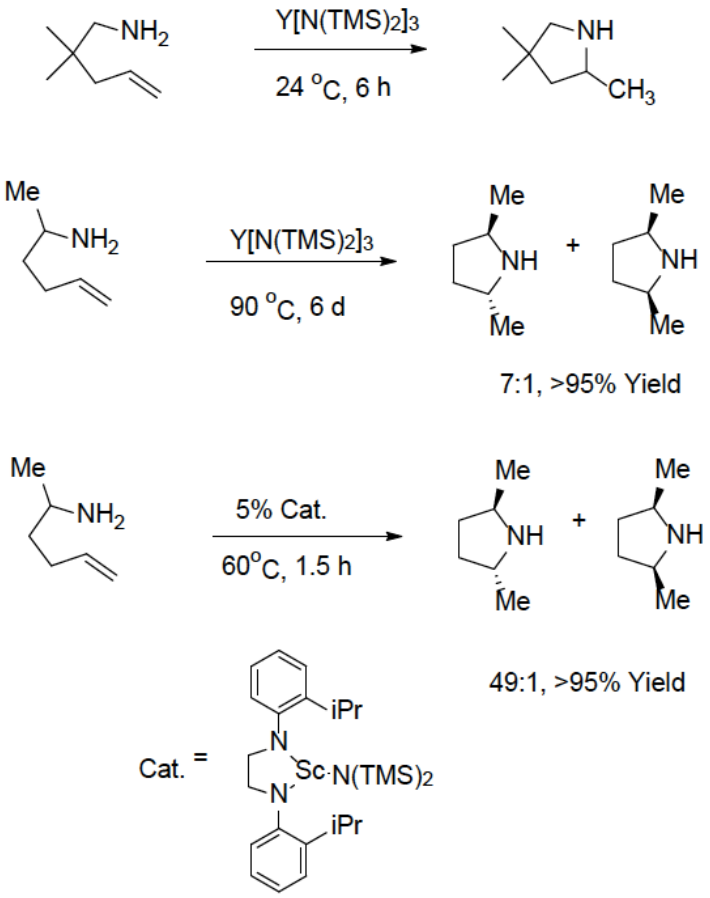


Figure 3.6. Representative early hydroamination work of Livinghouse lab[7-10,12]

3.3 Metalloamination

Metalloamination, or carboamination, reactions are tandem carbon-nitrogen bond formations with concomitant carbon-metal trapping. This process allows capture of an organometallic intermediate for further functionalization to facilitate an additional bond formation whereas hydroamination terminates with a simple protonation. This approach to heterocycles, specifically piperidines and pyrrolidines, proceeds via intramolecular insertion of a nitrogen-metal bond into a region of unsaturation forming a new carbon-nitrogen bond and carbon-metal bond, simultaneously. The superiority of this carbon-metal bond formation, over that of hydroamination's protonation event, is the ability to subsequently intercept a carbon electrophile, generating a new carbon-carbon bond. This ability to establish remarkable levels of molecular complexity in a one-pot reaction makes metalloaminations an attractive alternative for producing pyrrolidines and piperidines. Catalytic carboamination processes can proceed via two pathways. The first type begins with metal-alkene complexation followed metalloamination (C-N bond formation), resulting in an anti-addition of the electrophile (C-C bond formation), relative to the newly formed carbon-nitrogen bond. Alternatively, a metal-amide complex can form prior to metalloamination, which leads to syn-additon of the carbon electrophile, as seen in Figure 3.7.[13]

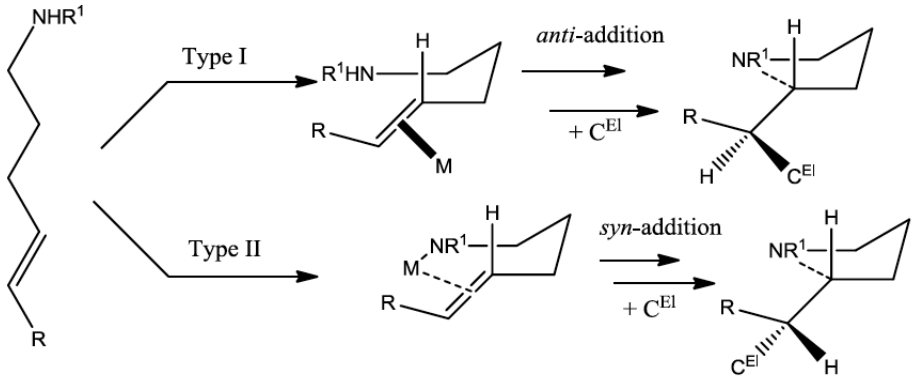
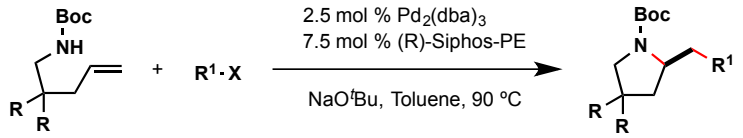


Figure 3.7. Possible mechanism of metalloamination with carbon electrophile trapping[13,14]

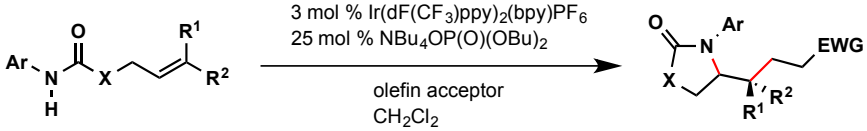
There have been reports from several laboratories that have reveled examples of carbon-nitrogen/carbon-carbon tandem bond forming reactions using catalytic Pd,[13,15-17] Cu,[18] Ir,[19] Au,[20] Rh,[21] or the stoichiometric use of Ti(IV)[22-24] or Zn(II).[25-28] A few representative examples of some current catalytic carboamination reactions are shown in Figure 3.8. Wolfe and co-workers have utilized catalytic palladium complexes to form organopalladium intermediates for the construction of pyrrolidines in good yields and enantioselectivities.[13, 15-17] Palladium is an attractive metal for catalytic metalloaminations, generating highly substituted pyrrolidines in good yields; however, the high price of palladium catalysts does pose a barrier to its applicability in large-scale industrial synthesis.

Wolfe: Palladium



61-80% yields
70-94% ee

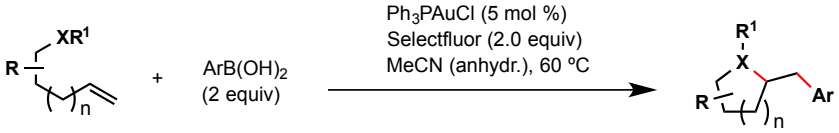
Knowles: Iridium



X = N, O

50-95% yields

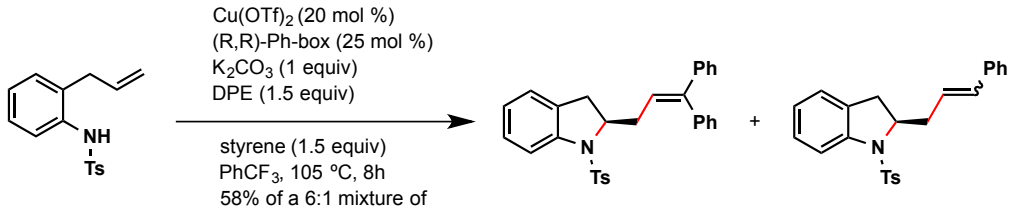
Zhang: Gold



X = N, O

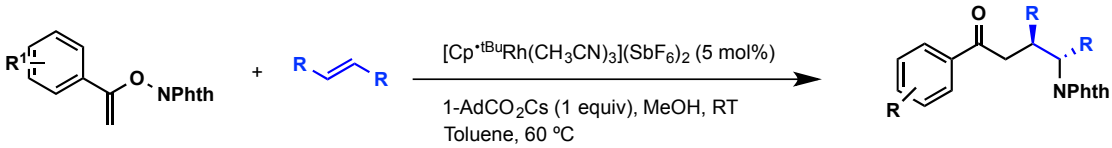
69-94% yields

Chemler: Copper



62-88% yields
good to great %ee

Rovis: Rhodium



70-80% yields

Figure 3.8. Representative catalytic carboaminations

The Knowles laboratory has developed a novel proton-coupled electron transfer based protocol for their alkene carboamination via a dual catalyst system comprised of an iridium photocatalyst and a weak phosphate base.[19] This transformation has enable construction of a variety of structurally complex heterocycles from simple amides. Zhang and co-workers described carboamination, carboalkoxylation and carbolactonization of terminal olefins via oxidative gold catalysis in order to access various substituted nitrogen and oxygen heterocycles.[20] Alternatively, a series of functionalized chiral nitrogen heterocycles such as indolines and pyrrolidines were prepared by Chemler through a copper-catalyzed enantioselective alkyl Heck-type coupling cascade procedure. This method was then utilized to devise and execute a concise synthesis to 5-HT_7 receptor antagonist.[18] The Rovis[21] Laboratory was able to perform an intermolecular carboamination using 1,2-disubstituted alkenes and a rhodium (III) catalyst system, which upon deprotection of the product can be cyclized to produce highly substituted pyrrolidines with high diastereoselectivies.

Stoichiometric metalloaminations were introduced in the early 1990's by the Livinghouse Laboratory, where they showed a novel heteroannulation procedure using Group 4 metal-imide complexes.[22] Intramolecular [2+2] cycloaddition of titanium-imide complexes was described, providing a new nitrogen-carbon bond with concurrent carbon-metal bond formation. These organotitanium intermediates could be trapped with either a carbon electrophile or a proton to produce complex products from simple amines (Figure 3.9).

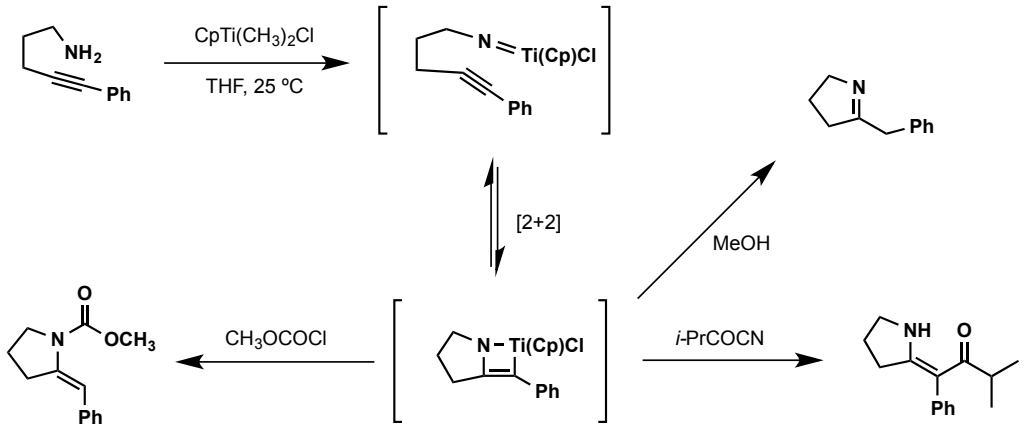


Figure 3.9. Titanium mediated metalloamination

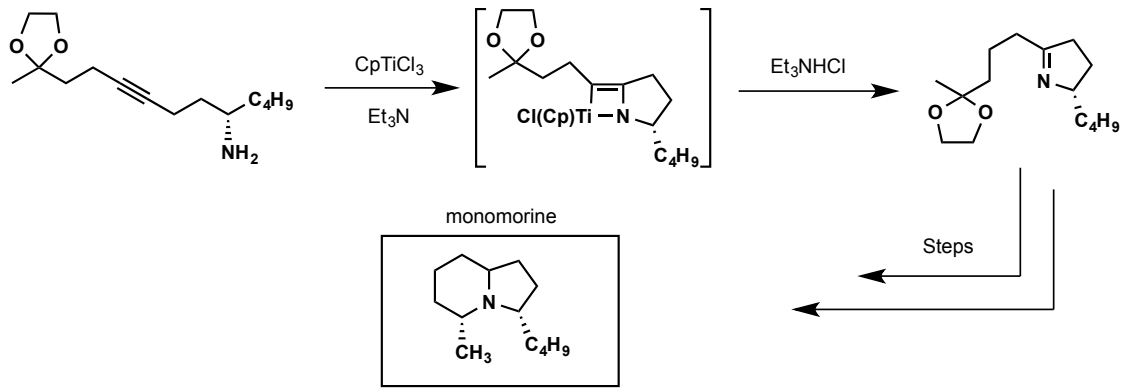


Figure 3.10. Concise total synthesis of monomorine using intramolecular [2+2] cycloaddition metalloamination[23]

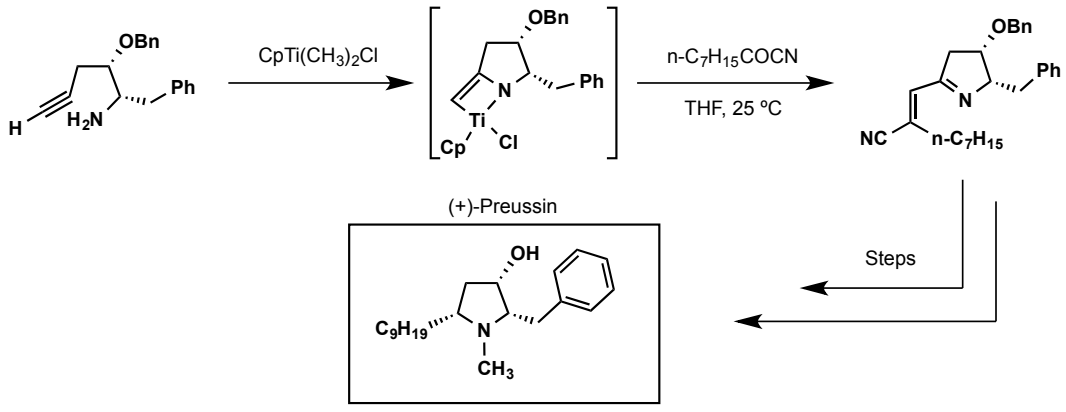


Figure 3.11. Total synthesis of (+)-preussin using intramolecular [2+2] cycloaddition metalloamination[24]

The Livinghouse group went on to utilize this novel metalloamination procedure to produce concise pathways to (±)-monomorine and (+)-preussin[23,24] as shown above in Figures 3.10 and 3.11.

Another, more recent, advancement of stoichiometric carboamination methods uses zinc as a cost-effective metal source.[25-28] The Nakamura group described a process for constructing substituted indoles and benzofurans from 1,2-phenol/analine alkynes. They showed that deprotonation of the alcohol/amine with concurrent zinc-alkyne complexation leads to cyclization, nitrogen/oxygen-carbon bond formation, and isolation of organozinc intermediate which can be transmetallated with CuCN•2LiCl, which can be intercepted by a carbon electrophile to form a new carbon-carbon bond.[25] They later went on to show that 2.05 equiv. of BuLi and $ZnCl_2$ on a terminal alkyne aniline system could effect the isolation of a dual-zinc organometallic compound which was capable of not only cyclizing to form an indole but also the formation of two new carbon-carbon bonds, as seen in Figure 3.12.[26]

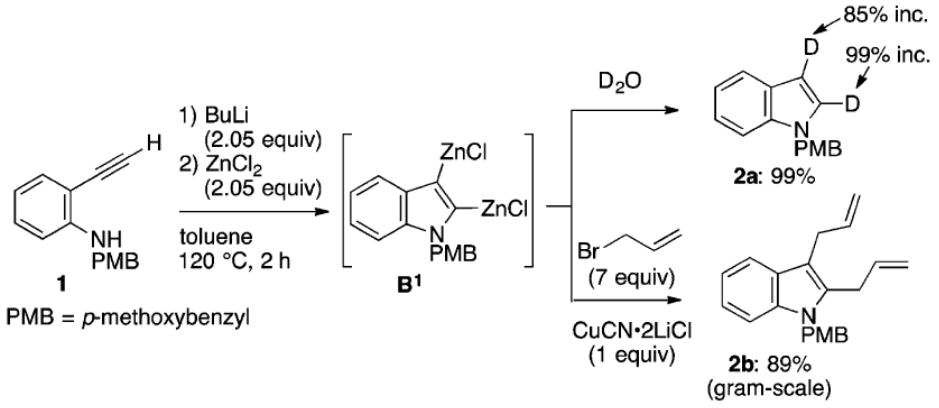


Figure 3.12. Nakamura's dual-zinc organometallic intermediate intercepting two carbon electrophiles[26]

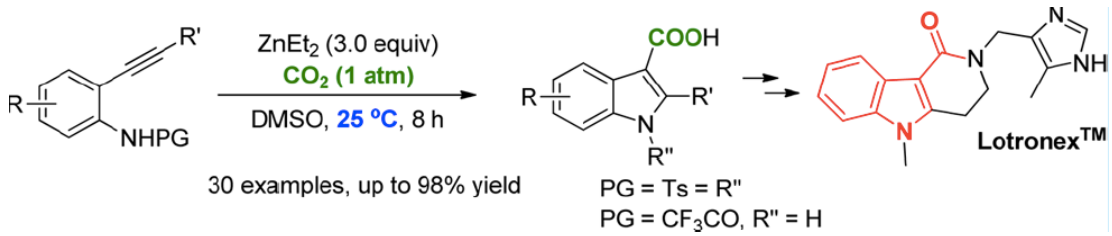


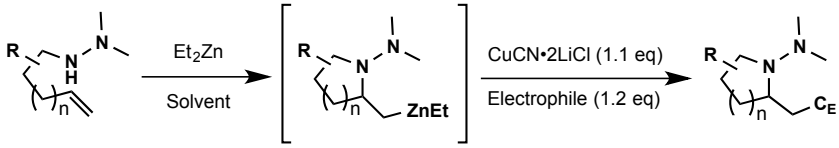
Figure 3.13. Ma's utilization of a zinc-mediated metalloamination method for the construction of Lotronex[27]

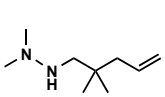
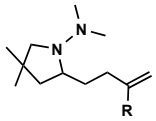
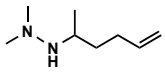
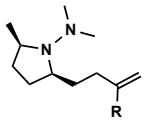
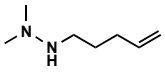
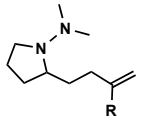
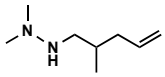
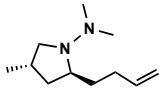
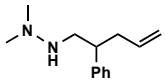
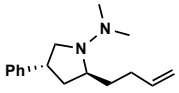
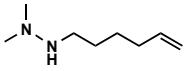
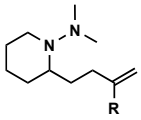
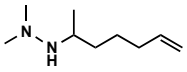
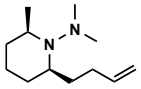
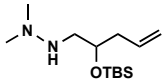
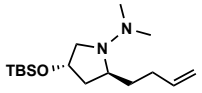
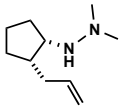
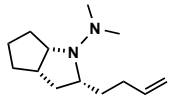
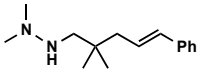
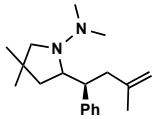
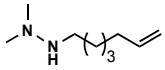
Recently, Ma and co-workers were able to use a similar procedure of direct anti-azacarboxylation 2-alkynylanilines with CO_2 mediated by excess diethylzinc to produce indole-3-carboxylic acids (Figure 3.13). To show the utility of this method they successfully synthesized Lotronex, a bioactive indole, known for its use as a competent drug for irritable bowel syndrome (IBS).[27]

Even more impressive is the recent work of the Livinghouse Lab; they report a stoichiometric zinc-mediated metalloamination/cyclization with subsequent allylation (Table 3.1).[28] This reaction was first screened on a number of nitrogen containing terminal alkenes, including a benzyl protected amine and a hydrazine. In the case of the benzyl-protected amine, only N-metallation was observed with no ring-closing carboamination occurring. However, the N,N-dimethylhydrazinoalkenes experience rapid metallation followed by ring closure, forming the nitrogen-carbon bond, and development of a new carbon-metal bond. Subsequent transmetallation furnished a copper complex, which attacks allyl bromide, the carbon electrophile, creating a new carbon-carbon bond in excellent yields. The synthetic scope of the hydrazine class was studied for a number of terminal alkenes. The reaction promoted metalloamination/cyclization on a number of starting hydrazines including those without the assistance of Thorpe-Ingold cyclization

acceleration. The Thrope-Ingold effect is defined by the repulsion of the geminal dimethyl in an open carbon chain causes an increase in the exterior angle, which in turn decreases the interior angle. This compression of the internal angle brings functional groups closer, promoting cyclization. The promoted cyclizations occur in good to excellent diastereoselectivities. Electrophilic functionalization was shown to take place with transmetallation to the copper complex, utilizing stoichiometric CuCN•2LiCl, and intercepted by either allyl bromide or methallyl chloride in excellent yields.

Table 3.1. Metalloamination/allylation of hydrazinoalkenes[28]

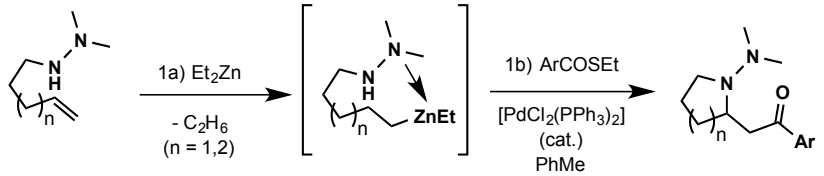


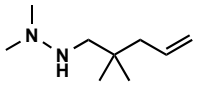
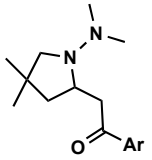
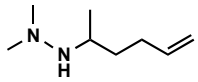
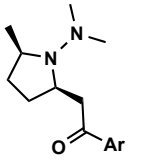
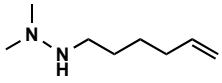
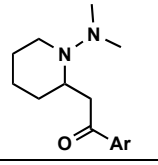
Hydrazinoalkene	Conversion [%][a]	d.r.	Product	Yield [%][f]
	>95 (18 h)[b]	---		92 (R = H) 83 (R = Me)
	>95 (6 h)[b]	>20:1 *(c/t)*		81 (R = H) 85 (R = Me)
	90 (4 h)[b]	---		80 (R = H) 76 (R = Me)
	90 (15 h)[c]	1:6 *(c/t)*		83
	90 (24 h)[d]	1:15 *(c/t)*		83
	>95 (3 h)[b]	---		93 (R = H) 88 (R = Me)
	70 (12 h)[b,e]	9:1 *(c/t)*		63
	90 (8 h)[b]	1:2 *(c/t)*		83[i]
	>95 (16 h)[b]	>20:1 *(c/t)*		87
	90 (24 h)[b]	3:1[g]		79[i]
	n. r. (3 d)[h]	---	---	---

[a] As calculated from ^{1}H NMR spectra utilizing *p*-xylene as an internal standard. [b] Reaction conducted on a 0.1 mmol scale in a 90 ºC oil bath with toluene or (trifluoromethyl)benzene as solvent. [c] Reaction conducted at 10 ºC. [d] Reaction conducted at 23 ºC. [e] Required 2 equiv of $ZnEt_2$. [f] All products were isolated as the TFA salts unless otherwise noted. [g] Stereoselectivity is unoptimized. [h] Cyclization was not observed. [i] Product isolated as the free base.

Furthermore, additional methods for the electrophilic functionalization of the carbon-zinc bond after metalloamination/cyclization have been shown to proceed. Instead of allylation, interception can take place as an acylation event according to Fukuyama's conditions[29,30] where catalytic transmetallation occurs to provide organopalladium intermediates, which rapidly acylate and recycle in a Negishi type catalytic cycle. Three substrates were cyclized and acylated according to this protocol as seen in Table 3.2 below.

Table 3.2. Metalloamination/acylation of hydrazinoalkenes[28]



Hydrazinoalkene	Conversion [%][a]	d.r.	Product	Yield [%]
	>95 (18 h)[b]	---		64
	>95 (6 h)[b]	>20:1 *(c/t)*		61
	>95 (3 h)[b]	---		61

[a] As calculated from ^{1}H NMR spectra utilizing *p*-xylene as an internal standard. [b] All reactions conducted at a 0.1 mmol scale with toluene or (trifluoromethyl)benzene as solvent. [c] Ar=4-*t*BuC_6H_4.

This diethylzinc-mediated metalloamination/cyclization with consecutive carbon electrophile interception illustrates an extremely versatile and cost-effective route for synthesizing nitrogenous heterocycles. With this novel tandem nitrogen-carbon/carbon-carbon bond forming reaction high yields and good diastereoselectivities are obtained. This method has been demonstrated to facilitate efficient construction of a wide range of pyrrolidines and piperidines.

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CHAPTER FOUR

1,2-DISUBSTITUTED ALKENES AS MIGRATORY INSERTION PARTICIPANTS IN ZINC(II) PROMOTED METALLOAMINATION/CYCLIZATIONS OF *N,N*-DIMETHYLHYDRAZINOALKENES

4.1 Contribution of Authors and Co-Authors

Manuscript in Chapter 4

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Contributions: Preformed experimental work, and assisted in editing the manuscript.

Co-Author: Ky Mickelsen

Contributions: Assisted and confirmed experimental work. Assisted in writing and editing the manuscript.

Co-Author: Sean Zabawa

Contributions: Assisted in experimental work and editing of the manuscript.

Co-Author: Bryon K. Anderson

Contributions: Assisted in experimental work and editing of the manuscript.

Co-Author: Tom Livinghouse

Contributions: Assisted with data interpretation and in writing and editing the manuscript.

4.2 Manuscript Information Page

Bryce Sunsdahl, Ky Mickelsen, Sean Zabawa, Bryon K. Anderson and Tom Livinghouse

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CHAPTER FOUR

1,2-DISUBSTITUTED ALKENES AS MIGRATORY INSERTION PARTICIPANTS IN ZINC(II) PROMOTED METALLOAMINATION/CYCLIZATIONS OF *N,N*-DIMETHYLHYDRAZINOALKENES

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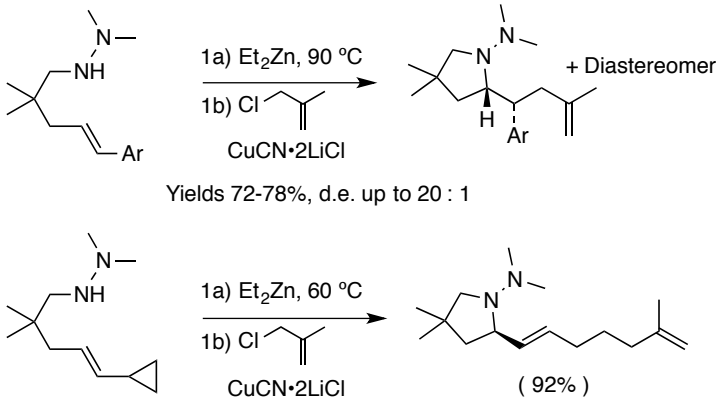


Figure 4.1. Abstract image for JOC manuscript

4.3 Abstract

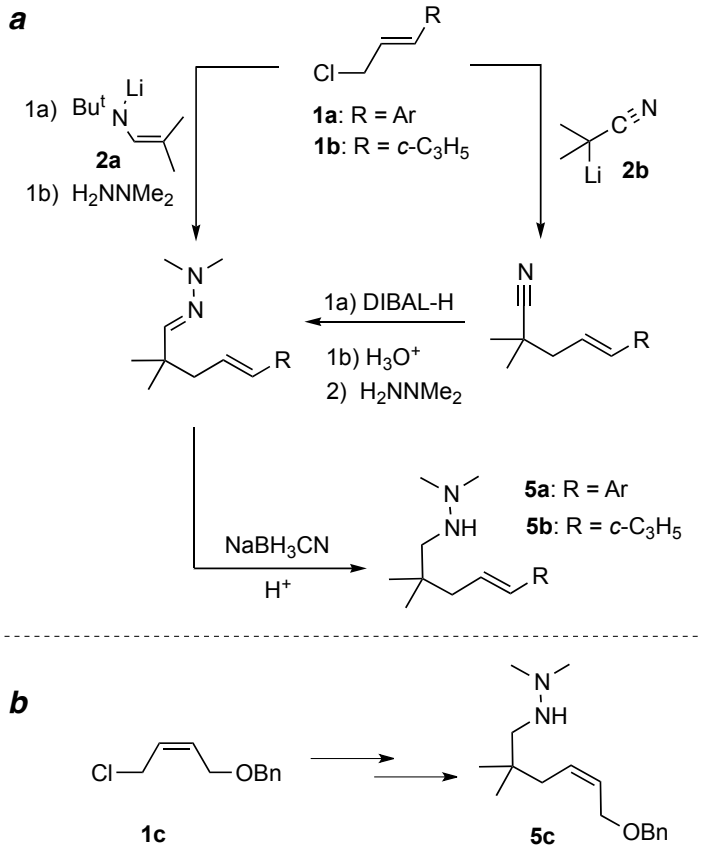
Diethylzinc mediated metalloamination/cyclization of unsaturated *N,N*-dimethylhydrazines has been extended to the use of 1,2-disubstituted alkenes as N-Zn migratory insertion acceptors. Representative 2-(aryl)ethenes and vinylcyclopropanes readily serve as reaction participants in metalloamination/cyclization-allylation cascades.

4.4 Introduction

Classical intramolecular hydroamination[1] of unsaturated carbon-carbon bonds constitutes an efficient and atom economical method for the synthesis of nitrogenous heterocycles. By definition, this process results in the simple delivery of a hydrogen atom to the terminus of the carbon-based addend. In contrast, *metalloamination*/cyclization leads to consecutive N-C/C-Metal bond formation, wherein the C-M bond can subsequently be parlayed into new functionality. Examples of the latter cascade reaction which involve the catalytic utilization of organometallic intermediates derived from Pd(II),[2-4] Cu(II),[5] Ir(III),[6] Au(I),[7] Rh(III),[8] or the stoichiometric use of Ti(IV)[9] or Zn(II)[10] intermediates have appeared.[11] The majority of *catalytic* metalloamination/cyclizations involve organometallic or free radical intermediates that are fleeting in nature, and are therefore synthetically limited in the ultimate C-M bond functionalization step. We have previously reported that *N,N*-dimethylhydrazinoalkenes bearing monosubstituted alkenes undergo facile metalloamination/cyclization mediated by diethylzinc. Subsequent allylation or acylation of the newly formed C-Zn bond, in-situ, efficiently provided the corresponding pyrrolidines or piperidines, respectively.[12] We subsequently demonstrated that suitable 1,2-disubstituted alkenes can serve as migratory insertion N-Zn acceptors in this process.

The dimethylhydrazinoalkene substrates that were used in this study were prepared in a manner analogous to the routes we reported previously.[12] Specifically, alkylation of the allylic chlorides **1a** and **1c** with the lithioimine **2a** followed by

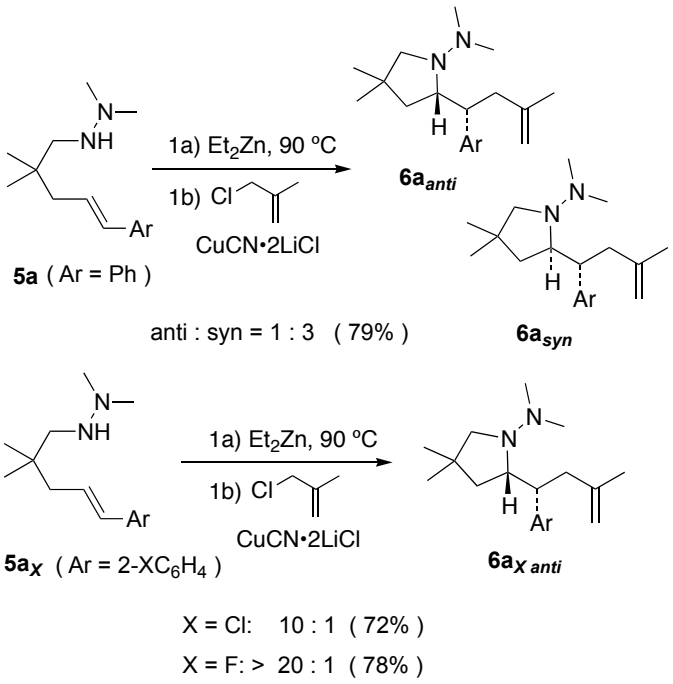
immediate hydrolysis ($H_2C_2O_4$) and dimethylhydrazone formation (Me_2NNH_2) furnished **3a** and **3c**. Alternatively, alkylation of **1b** with (lithio)-*i*-butyronitrile **2b** gave nitrile **4**, which upon reduction (DIBAL-H) and subsequent condensation of the crude aldehyde with Me_2NNH_2 provided **3b**. Reduction of the dimethylhydrazones ($NaBH_3CN$, H^+) ultimately secured the substrate dimethylhydrazinoalkenes **5a-c** (Scheme 4.1).



Scheme 4.1. Synthesis of Dimethylhydrazines

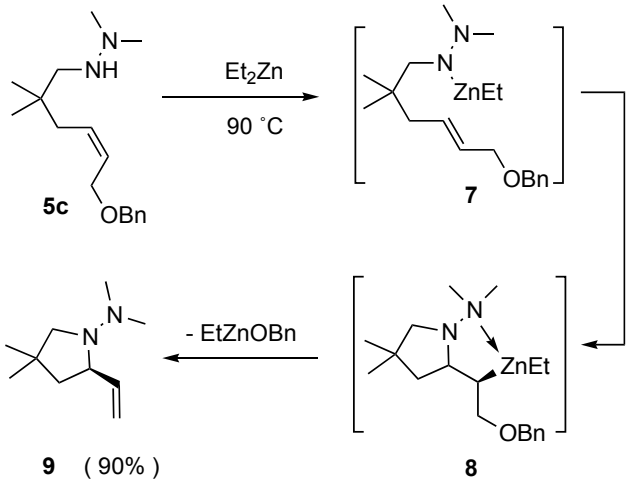
4.5 Cyclization Studies

We have previously shown that various 2-(Aryl)ethenyl substituents serve as viable participants in hydroamination/cyclizations of primary alkenes catalyzed by complexes of the group 3 metals.[13] We therefore began the present investigation by examining the metalloamination/cyclization of dimethylhydrazinoalkenes bearing this substituent type. It was readily determined that migratory insertion acceptors in this category are well suited for Zn(II) mediated metalloamination–allylation, with the stereochemical outcome being very strongly governed by the influence of the electronegativity of substituents at the 2-position. For example, allylative cyclization of the simple phenyl-bearing hydrazine **5a** [(1a) Et_2Zn (1.0 equiv), (1b) CuCN•2LiCl,[14] 1-chloro-2-methyl-2-propene (1.2 equiv)] provided the diastereomeric dimethylhydrazines $\mathbf{6a}_{a}$ and $\mathbf{6a}_{s}$ as a 1:3 mixture in 79% isolated yield. The stereochemical assignment for the major diastereomer $\mathbf{6a}_{s}$ is based on the substantial aromatic shielding effect observed for its 4β-methyl substituent (0.52 ppm) compared to the 4β-methyl (0.93 ppm) present in $\mathbf{6a}_{a}$. The corresponding 2-(chloro) derivative $\mathbf{5a_{Cl}}$ was considerably more selective in its cyclization-allylation, favoring diastereomer $\mathbf{6a_{Cl}}_{a}$ over $\mathbf{6a_{Cl}}_{s}$ (72%, de = 10:1). Moreover, analogous treatment of the 2-(fluoro) bearing substrate $\mathbf{5a_{F}}$ provided superb stereoselectivity, giving $\mathbf{6a_{F}}_{a}$ (78%, de >20:1, Scheme 4.2). The origin of this surprising stereoselectivity enhancement is under current investigation.



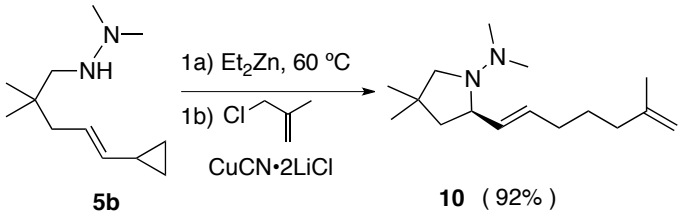
Scheme 4.2. Cyclization-Allylation of Dimethylhydrazines **5a**

In an effort to elucidate the functional group compatibility of metalloamination/cyclization, the *cis*-allylic ether bearing dimethylhydrazinoalkene **5c** was *N*-metallated with diethylzinc at 90 ºC. Under these conditions, *cis* → *trans* isomerization of the alkene occurred rapidly *prior to the metalloamination event*. In addition, β-elimination of the benzyloxy substituent proved unavoidable, leading to the direct formation of pyrrolidine **9** in 90% isolated yield after only 4 h (Scheme 4.3).



Scheme 4.3. Cyclization-Elimination of Dimethylhydrazine **5c**

The utilization of vinylcyclopropanes as cyclization participants was subsequently investigated with the expectation that cyclopropane C-C bond scission would provide a considerable driving force for ring closure. It is therefore of considerable interest that the vinylcyclopropane bearing substrate **5b** underwent *exceptionally* facile cyclization with concomitant cleavage of the cyclopropane ring to give the corresponding allylation product **10** in excellent (92%) yield (Scheme 4.4). *It should be emphasized that the vinylcyclopropane "acceptor" is by far the most reactive of the disubstituted alkenes that we have examined to date.*



Scheme 4.4. Cyclization-Allylation of Dimethylhydrazine **5b**

4.6 Conclusions

In conclusion, diethylzinc mediated metalloamination/cyclization-allylation has been extended to encompass the utilization of 1,2-disubstituted alkenes as migratory insertion participants. Highly diastereoselective (de > 20:1) C-N/C-C difunctionalization in the 2-(aryl)ethane series is observed where aryl = a 2-(fluoro)phenyl substituent. The vinylcyclopropane substituent confers high reactivity toward metalloamination with concomitant scission of the cyclopropane ring. Intramolecular metalloamination involving a 3-(benzyloxy)-1(*Z*)-propenyl substituent proceeds with initial *cis*→*trans* isomerization followed by terminal elimination of EtZnOBn.

All Experimental and Spectral Data for this Manuscript is found in the Appendix

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CHAPTER FIVE

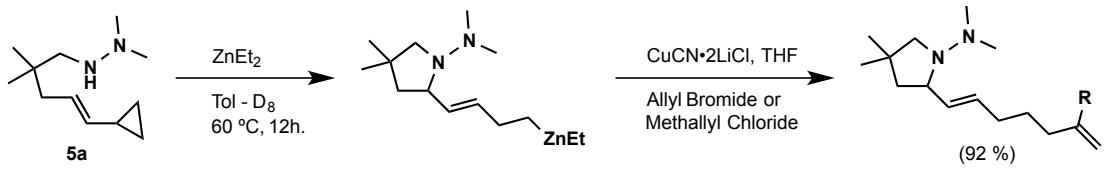
EXPLORING CYCLOPROPYL HYDRAZINOALKENES VIA ZINC(II) MEDIATED METALLOAMINATION/CYCLIZATIONS

5.1 Abstract

Expansion of the Livinghouse metalloamination/cyclization to include vinylcyclopropyl hydrazines was pursued after the successful cyclization of (*E*)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine. A computational study of this metalloamination/cyclization with concurrent cyclopropyl scission was completed in order to better understand the energy barriers associated with the progression of the reaction. Upon optimization of a successful method for developing the necessary allylic chloride needed to construct the substrates of interest, the desired vinylcyclopropyl hydrazines were synthesized. Each of the substrates was tested under several conditions with only N-metallation occurring, and though cyclization has not yet occur within this series, continued efforts will be made towards the optimization of the vinylcyclopropyl hydrazine class of molecules. The potential behind the irreversible cyclopropyl scission and development of a new region of unsaturation make this class of substrates extremely desirable.

5.2 Introduction

In the previous chapter we showed that the Zn(II) mediated metalloamination/cyclization developed in the Livinghouse Laboratory could be expanded to allow for facile cyclization of disubstituted alkenes. Of the examples shown, one was of particular interest to the Livinghouse group, namely the vinylcyclopropyl hydrazinoalkene. This specific hydrazine quickly underwent metalloamination and subsequent cyclization at a relatively low temperature in toluene. As seen in Scheme 5.1, diethylzinc facilitates cyclization with tandem irreversible cyclopropyl scission giving rise to the organozinc intermediate containing a new double bond.

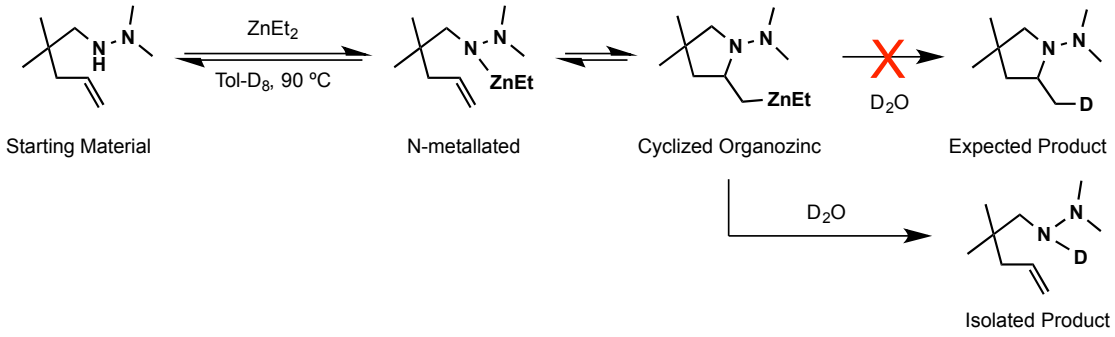


Scheme 5.1. Metalloamination/cyclization and allylation of (E)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (**5a**)

Successive alkylation with stoichiometric CuCN•2LiCl utilizing either allyl bromide or methallyl chloride leads to the respective products in excellent yields.[1]

The major allure of this substrate comes from the fact that it is the first example of an irreversible cyclization; the concurrent cyclization/ring opening of the cyclopropyl group proceeds leaving the organozinc intermediate shown in Scheme 5.1 as the only thermodynamic intermediate. Previously, the terminal hydrazinoalkenes would advance to the cyclized organozinc intermediate, but if quenched at this point with D_2O would

result in reversion to the N-metallated organozinc, affording the isolation of only starting material with no observation of the expected hydroamination product (Scheme 5.2).[2]



Scheme 5.2. Equilibrium of terminal hydrazinoalkene during metalloamination/ cyclization

In addition to providing scaffolding that allows for irreversible cyclization, the cyclopropyl scission event also leaves in its place a newly formed region of unsaturation. These two advantages could provide a pathway to cyclizing tri-substituted alkenes and add an additional reactive handle to the isolated product, giving the possibility to acquire enhanced levels of molecular complexity in a one-pot reaction.

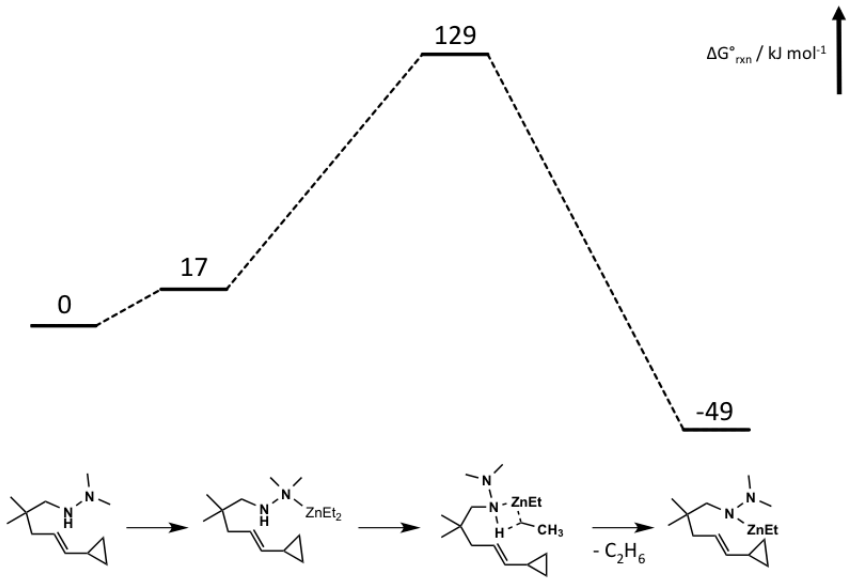
5.3 Understanding the Reaction – A Computational Experiment

In order to more fully understand the irreversible cyclization of the geminal dimethyl vinylcyclopropyl hydrazine, we studied the process via computational chemistry. This was performed with a co-worker, Tom Robinson, under the supervision of Professor Robert Szilagyi using Gaussian ’09.

Upon the introduction of diethylzinc to the geminal dimethyl starting material, immediate coordination to the external nitrogen of the hydrazine is observed, which

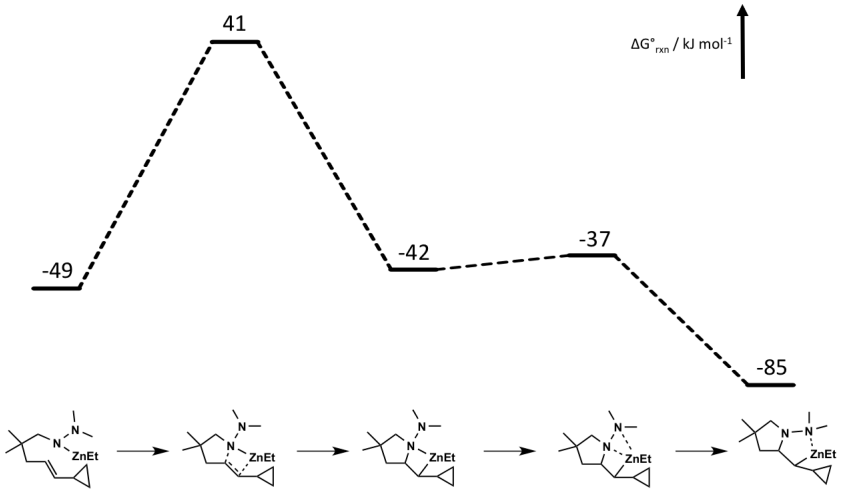
proceeds into an initial high-energy transition state. In this transition state the diethylzinc has moved onto the interior nitrogen as one to the ethyl groups coordinates to the neighboring hydrogen. This high-energy state is due to the large strain of the four-membered transition state needed in order to titrate off ethane from the reactive substrate. However, once ethane is liberated the N-metallated intermediate allows for a drop in energy creating the stable intermediate needed for cyclization (Figure 5.1).

Following the formation of the N-metallated intermediate, the zinc interacts with the pi-electrons of the olefin rendering the site more electrophilic. This high-energy transition state then falls, upon cyclization, to an unstable pseudo-five-four fused organozinc ring system which immediately expands to the lower energy intermediate with zinc reverting to coordination with the exterior nitrogen (pseudo-five-five fused ring system seen in Figure 5.2).



Potential energy surface with the lowest energy intermediates and transition states. The Gibbs free energy values (kJ/mol) were calculated at the B3LYP/6-31G(d) level of theory in PCM (solvent = toluene).

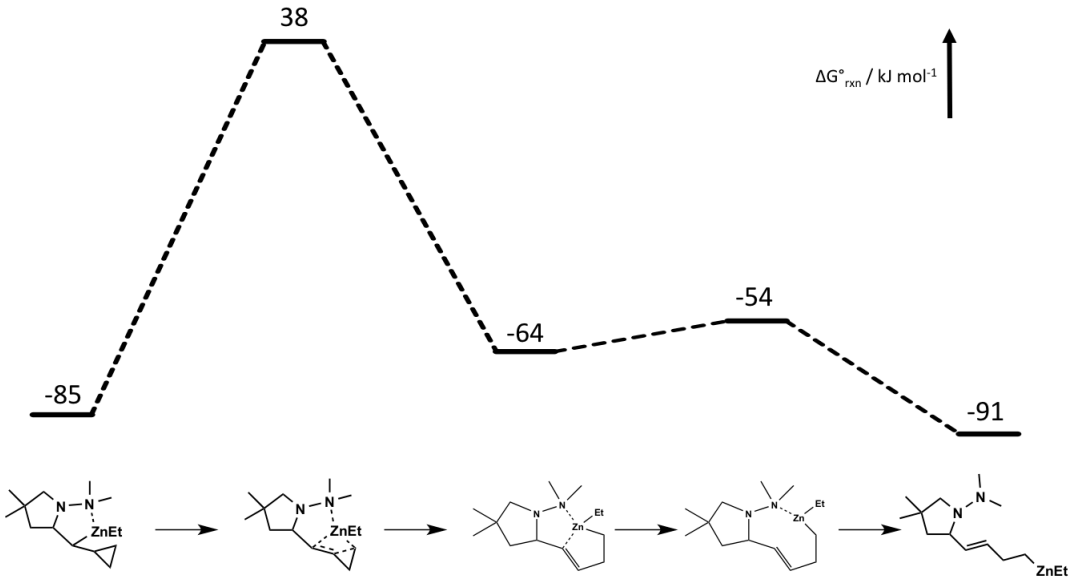
Figure 5.1. N-metallation with diethylzinc



Potential energy surface with the lowest energy intermediates and transition states. The Gibbs free energy values (kJ/mol) were calculated at the B3LYP/6-31G(d) level of theory in PCM (solvent = toluene).

Figure 5.2. N-metallated intermediate cyclization

The zinc then pulls at a hydrogen on the cyclopropane, drawing it near as the carbon-zinc bond cascades into the cyclopropane creating a new unit of internal unsaturation and simultaneous cyclopropyl scission. The resulting “tri-cyclic” intermediate (Figure 5.3) then undergoes dissociation of the zinc-carbon and zinc-nitrogen coordinations, giving rise to the experimentally observable organozinc intermediate.



Potential energy surface with the lowest energy intermediates and transition states. The Gibbs free energy values (kJ/mol) were calculated at the B3LYP/6-31G(d) level of theory in PCM (solvent = toluene).

Figure 5.3. Cyclopropyl scission and nitrogen-zinc dissociation

The potential energy diagram of the entire reaction, to the observed organozinc, can be seen in Figure 5.4 below. Connecting each of the potential energy diagrams, it is clear that there are high-energy barriers to overcome in all three major steps: metallation, cyclization and the irreversible opening of the cyclopropane ring.

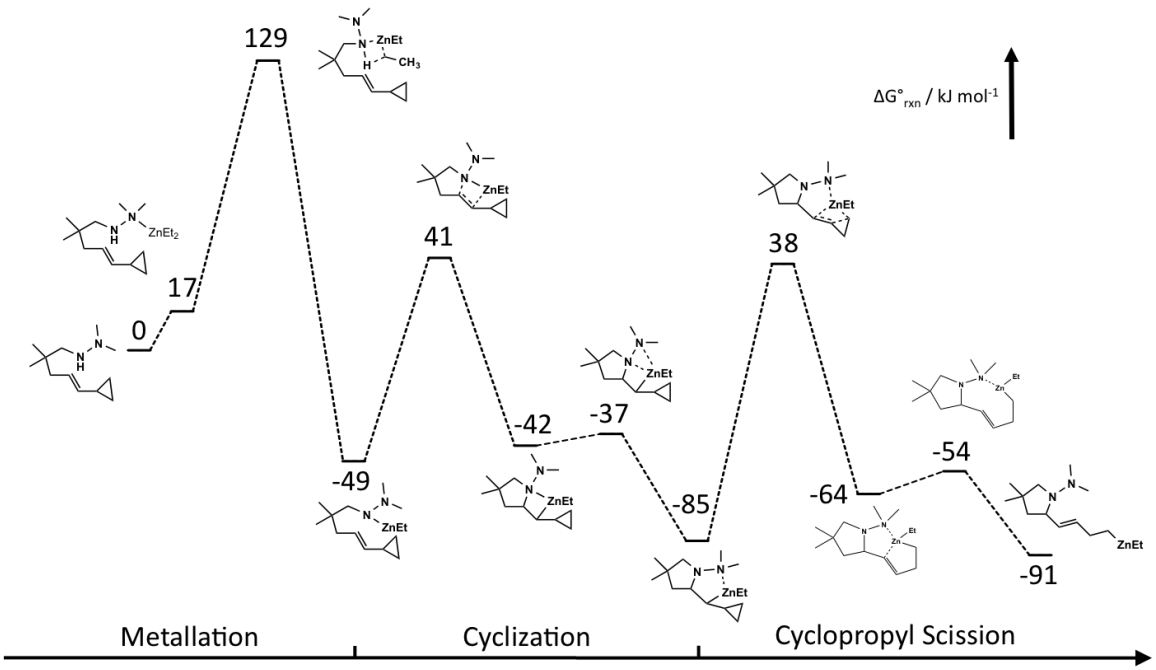


Figure 5.4. Potential energy diagram of metalloamination/cyclization (E)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine

The loss of ethane during the metallation must consume 112 KJ/mol, resulting in the ultimate production of 178 KJ/mol, leading to the favorable N-metallated intermediate. Subsequent cyclization affords a release of 36 KJ/mol, leaving the final and computationally predicted rate-determining step. The final formation of an internal olefin with simultaneous cyclopropyl ring-opening must overcome a 123 KJ/mol transition state to conclusively provide the experimentally observed organozinc intermediate in an overall exergonic (91 KJ/mol) process.

5.4 Expanding the Substrate Scope of the Cyclopropyl Hydrazinoalkenes

As shown in the previous sections, the metalloamination/cyclization and successive electrophilic functionalization of (E)-2-(5-Cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (**5a**) proceeds easily and in excellent yields. The inclusion of the vinylcyclopropyl group could lead to the cyclization onto tri-substituted alkenes via the irreversible cyclopropyl scission. Therefore, the expansion of this substrate class was of great interest.

Five initial substrates were planned that would closely emulate the original geminal dimethyl vinylcyclopropyl hydrazine. Each additional substrate would retain the same geminal dimethyl group due to the potential rate-acceleration provided via the Thorpe-Ingold effect.[3] The Thorpe-Ingold effect states (Figure 5.5) that the repulsion of the geminal dimethyl in an open carbon chain causes an increase in the angle β which in turn decreases the angle α. This compression of the internal angle α brings the X and Y groups closer, promoting cyclization.

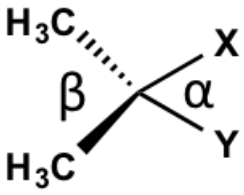


Figure 5.5. Pictorial representation of the Thorpe-Ingold effect

The initial substrates chosen are shown in Figure 5.6. The original substrate, two additional disubstituted alkenes, and 3 trisubstituted substrates were designed.

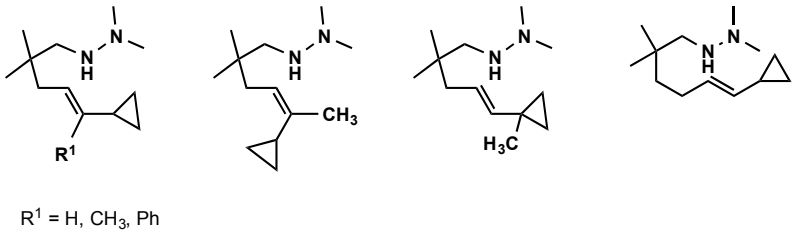
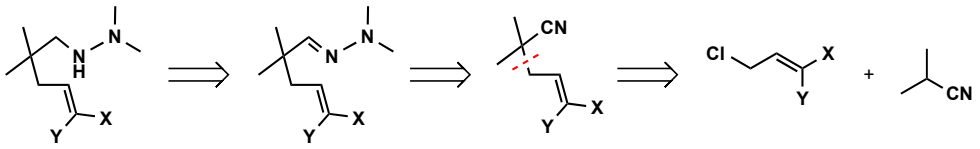


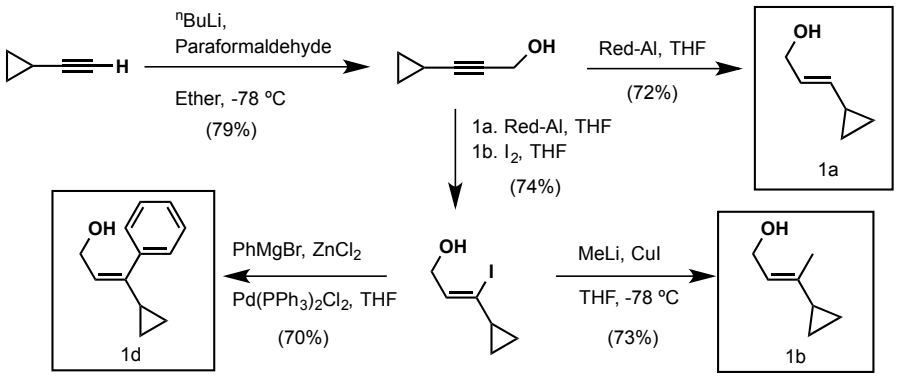
Figure 5.6. Vinylcyclopropyl hydrazine substrates, **5a-f**

Each of these substrates was envisioned to arise from their respective hydrazones, which could be envisioned from isobutyronitrile and the corresponding allylic halides (or the halide in the case of the potential six-membered ring). This disconnection would be accomplished via a retro lithiated S_N2 displacement as seen in Scheme 5.3.



Scheme 5.3. Retrosynthesis of geminal dimethyl substrates

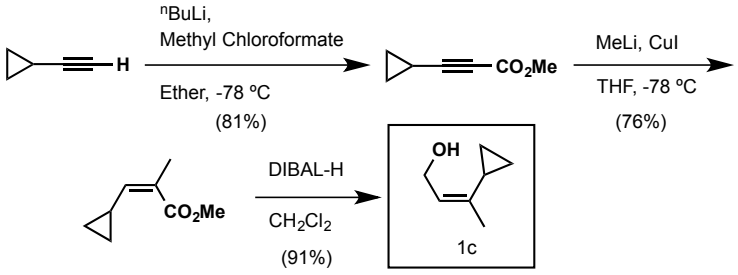
Each of the halide could be created from their corresponding alcohols, so the series of allylic alcohols necessary for these substrates was synthesized in the following manner. (Schemes 5.4 – 5.6)



Scheme 5.4. Construction of alcohols **1a, 1b, 1d**

Each of the shown vinylcyclopropanes were created through the simple deprotonation of cyclopropylacetylene and addition to paraformaldehyde resulting in 3-cyclopropyl-prop-2-yn-1-ol, which could be used to synthesize three of the desired cyclopropyl alcohols. From 3-cyclopropyl-prop-2-yn-1-ol, **1a** was easily prepared by a Red-Al reduction followed by quenching with water. The same Red-Al reduction could be utilized to construct the trisubstituted vinylhalide by trapping the aluminum intermediate with iodine. Methylated **1b** was created with use of the vinyliodide and a Gillman reagent, or alternatively **1d** could be made using a Negishi coupling.

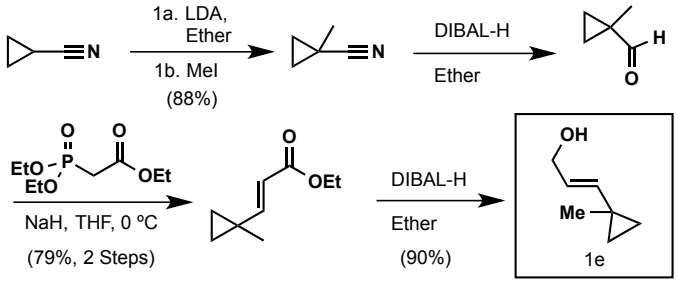
The only (Z)-alkene (**1c**), with regard to the cyclopropyl group, was designed in a similar fashion; however, lithiated cyclopropylacetylene was added to methyl chloroformate. The isolated alkyne was methylated using a similar Gillman procedure, and the corresponding methyl ester was reduced to an allylic alcohol via a DIBAL-H reduction, using excess diisobutylaluminum hydride at 0 ºC. (Scheme 5.5)



Scheme 5.5. Synthesis of (Z)-3-cyclpropyl-but-2-en-1-ol (**1c**)

The final allylic alcohol required was synthesized by the deprotonation of cyclopropyl cyanide and addition of iodomethane to allow for methylation, the cyano-group was reduced to the corresponding aldehyde via DIBAL-H reduction. The aldehyde could then undergoes a Horner-Wadsworth-Emmens reaction to create the desired (*E*)-

alkene. Finally, the ethyl ester was reduced in an analogous manner to that of the previously made **1c**.

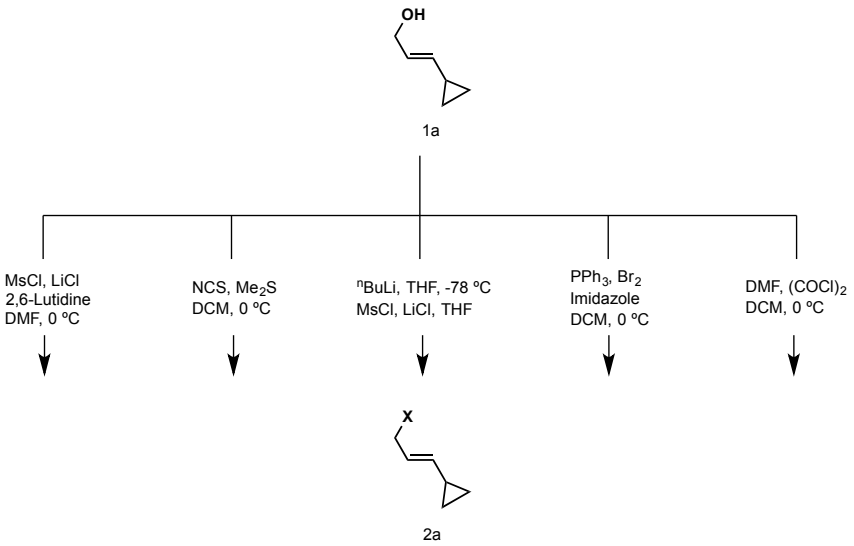


Scheme 5.6. Production of (E)-3-(1-methylcyclopropyl)-prop-2-en-1-ol (**1e**)

Once all of the necessary alcohols were constructed, the desired substrates could be made through conversion to allylic halides followed by S_N2 displacement by lithiated isobutyronitrile. Production of the allylic halides of the vinylcyclopropyl alcohols proved to be quite difficult due to their extreme reactivity and overall instability. Through a careful degradation investigation, it was found that the potential rearrangement and subsequent cyclopropyl ring opening of the reactive halides led to complete decomposition within 30 min of preparation. Thus, it was critical to carry the chlorides onto the following reaction as quickly as possible. It took time and precise study to ultimately find conditions that facilitated quick chloride formation without the production of unwanted byproducts that hindered the subsequent reaction. The classic Meyers[4] condition for allylic chloride formation was attempted, but this procedure proceeded slowly enough that by the time all starting material was consumed the product was beginning to decompose. Next, Corey's[5] conditions failed to afford full conversion of the allylic alcohol to chloride. An attempt at Trost's[6] variation of Meyers procedure led to a mixture of the (O)-mesylated intermediate and chloride that did not produce clean

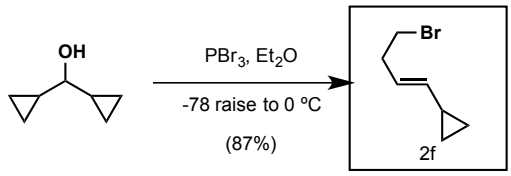
alkylation products in the following reaction. A method developed in the Wipf laboratory for constructing allylic halides, published by Ashfeld[7,8] was then attempted. This procedure made the potentially more reactive allylic bromide. However, upon work up of the second reaction the majority of the isolated product was seen to be the ring-opened diene. Finally, with the help and advice of Professor Livinghouse, a procedure was developed that solved all of the previous issues. The Vilsmeier reagent permitted instantaneous chloride formation and produced only dimethylformamide as a byproduct. This procedure allowed for extremely clean formation of the allylic chlorides and near quantative yields of the subsequent alkylation. (Scheme 5.7)

The remaining halide needed to produce all desired substrates is that of the potential six-membered product. This molecule did not suffer from the same instability that the allylic halides did due to the extended carbon chain.



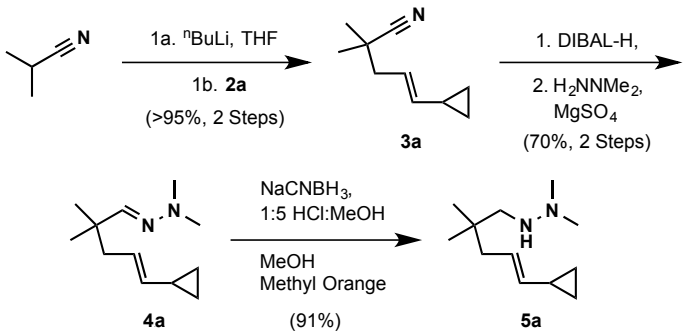
Scheme 5.7. Methods for allylic halide construction where X = Cl or Br. From left to right: Meyers conditions, Corey's procedure, Trost's variation, Ashfeld's bromide production and the conditions developed in the Livinghouse Laboratory

Compound **2f** (Scheme 5.8) was prepared with ease using dicyclopropylmethanol and phosphorous tribromide as shown below.



Scheme 5.8. Synthesis of (E)-1-bromo-4-cyclopropyl-but-3-ene (**2f**)

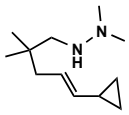
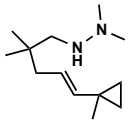
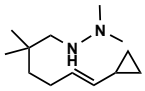
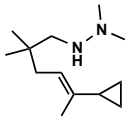
With the means to produce and carry each of the halides immediately on to the subsequent alkylation procedure, the respective cyano-compounds were produced through *n*-butyllithium deprotonation of isobutyronitrile and addition of the preformed halides as a solution in DCM/pentane. Each of these were reduced to the aldehyde and immediately condensed with *N,N*-dimethylhydrazine. Successive reduction of the hydrazones to the corresponding hydrazines was accomplishing according to a previous report from our laboratory utilizing sodium cyanoborohydride as the reducing agent.[1,2] In Scheme 5.9 below a representative synthetic pathway to hydrazine **5a** is shown and each of the other five substrates was prepared in an analogous fashion.



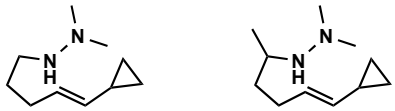
Scheme 5.9. Representative pathway to the *gem*-dimethyl vinylcyclopropyl hydrazine **5a**

With the successful synthesis of all the desired vinylcyclopropyl hydrazines (**5a-f**), it was time to begin attempts of metalloamination/cyclization allylation using the aforementioned conditions. The original substrate (*E*)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine, **5a**, was re-tested and cyclized under the previously described conditions. However, under the same conditions using the most promising substrates, seen in Table 5.1, N-metallation was achieved as determined by the appearance of ethane in the proton NMR but did not progress to cyclization and subsequent cyclopropane ring-opening. The use of an additional equivalent of diethylzinc was added and the temperature was elevated to 110 ºC for 24 h, at which point metallic zinc began to fall out of solution without the occurrence of a cyclization event.

Table 5.1. Attempted Cyclization of Vinylcyclopropyl Hydrazines

Substrate	Additive	Time	Temp	% Conv
	1.0 equiv. Et_2Zn	12 h	60 ºC	> 95%
	2.0 equiv. Et_2Zn	24 h	110 ºC	N. R.
	2.0 equiv. Et_2Zn	24 h	110 ºC	N. R.
	2.0 equiv. Et_2Zn	24 h	110 ºC	N. R.

With the hopes of cyclizing an additional substrate, two more vinylcyclopropyl hydrazines were prepared, both simple cyclopropylhydrazines (**5g** and **5h**, Figure 5.7) containing no assistance from the Thorpe-Ingold effect. In previous work, Thorpe-Ingold has played little role in rate acceleration and it was thought that these reaction conditions might allow for ring-closure of a simpler substrate. Unfortunately, these substrates also failed to continue past N-metallation.



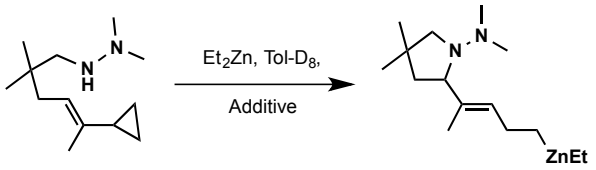
5g 5h

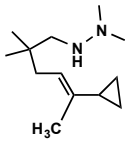
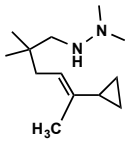
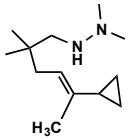
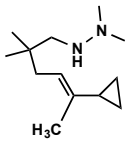
Figure 5.7. Additional vinylcyclopropyl hydrazines prepared

The work of Roesky and Blechert had previously shown increased reactivity of zinc catalysts through the addition of dimethylanilinium tetrakis(pentafluorophenyl)borate as an activator.[9] They continued on to show that this activator greatly enhanced hydroaminations when paired with diethylzinc.[10] Continued pursuit of cyclizations were made through the study of just (*E*)-2-(5-cyclopropyl-2,2,5-trimethylpent-4-en-1-yl)-1,1-dimethylhydrazine, **5b**. The work of Roesky and Blechert lead us to utilize the same borate salt as an activator to the diethylzinc in our stoichiometric metalloamination. Unfortunately Roesky and Blechert's borate activator led to no observed cyclization, even with the application of increased heat. The addition of a palladium co-catalyst was used in tandem with the zinc activator in order to attempt to pull electron density away from the alkene, which could help with lowering the activation barrier for cyclization. When these strategies failed to cyclize **5b**, we extended

the study to include the use of Toste's cationic gold (I) complex that has the potential to advantageous to a variety of metal-mediated processes.[11] These results are summarized in Table 5.2 below and show that facile N-metallation occurs with no subsequent cyclization.

Table 5.2. Further Pursuit of Cyclization



Substrate	Additive	Time	Temp	% Conv
	2 equiv. Et_2Zn	24 h	110 ºC	N. R.
	$[PhN(CH_3)_2H]^+[B(C_6F_5)_4]^-$ [a]	24 h	23 ºC - 90 ºC	N. R.
	$[PhN(CH_3)_2H]^+[B(C_6F_5)_4]^-$ [a] dppf•$PdCl_2(CH_2Cl_2)$ [a]	24 h	23 ºC - 90 ºC	N. R.
	$(PPh_3)AuCl$ [b] $AgSbF_6$ [b]	24 h	23 ºC - 90 ºC	N. R.

(a.) 10 mol% added (b.) 5 mol% added.

5.5 Conclusions

The exploration of the Livinghouse metalloamination/cyclization to include vinylcyclopropyl hydrazines was pursued after the successful cyclization of (*E*)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine, **5a**, during our initial investigation of disubstituted hydrazinoalkene.[1] The potential advantages to this particular hydrazine class came from the fact that irreversible cyclization occurred due to concurrent cyclopropyl scission. This led to the belief that a cyclopropyl series of substrates could help expand the scope of the reaction to include difficult or challenging substrates to construct, ultimately giving us access to extreme molecular complexity in a one-pot reaction. The cyclopropyl series could envision the cyclization of tri-substituted alkenes, difficult to construct macrocycles (> 6 atoms) and generate products with a remaining internal unit of unsaturation not observed in any other product produced.

The computational study of metalloamination/cyclization of (*E*)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine, **5a**, showed that cyclization and subsequent cyclopropyl scission leading to the desired organozinc intermediate, while irreversible, requires significant energy to overcome the high-energy transition states. After the optimization of a successful method for developing the necessary allylic chloride needed to construct the substrates of interest, the desired vinylcyclopropyl hydrazines were produced. Each of the substrates was tested under several conditions with only N-metallation occurring, with no continued cyclization or irreversible cyclopropane ring-opening event taking place.

Though cyclization has not yet occur within this series, continued efforts will be made towards the optimization of the vinylcyclopropyl hydrazine class of molecules. The potential behind the irreversible cyclopropyl scission and development of a new alkene make this class of substrates extremely desirable.

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CHAPTER SIX

DIETHYLZINC MEDIATED METALLOAMINATION-ALKYLATION OF *N,N*-DIMETHYLHYDRAZINOALKENES. CATALYSIS OF CARBON-ZINC ALKYLATION USING SIMPLE COPPER(I) SALTS

6.1 Contribution of Authors and Co-Authors

Manuscript in Chapter 6

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Contributions: Preformed or confirmed all experimental work. Assisted in writing and editing the manuscript.

Co-Author: Sean Zabawa

Contributions: Preformed or confirmed all experimental work. Assisted in writing and editing the manuscript.

Co-Author: Tom Livinghouse

Contributions: Assisted with data interpretation and in writing and editing the manuscript.

6.2 Manuscript Information Page

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CHAPTER SIX

DIETHYLZINC MEDIATED METALLOAMINATION-ALKYLATION OF *N,N*-DIMETHYLHYDRAZINOALKENES. CATALYSIS OF CARBON-ZINC ALKYLATION USING SIMPLE COPPER(I) SALTS

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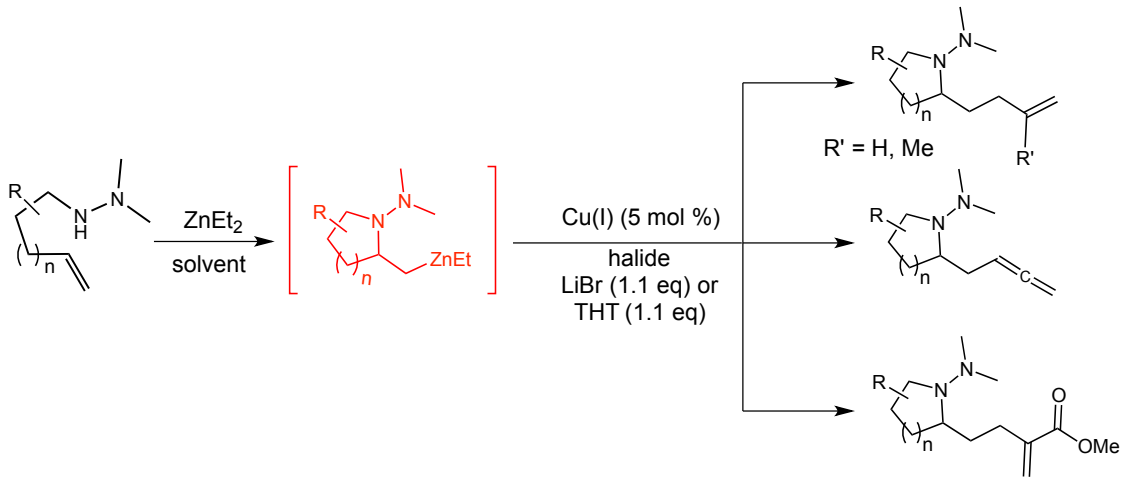


Figure 6.1. Abstract image for SYNLETT Manuscript

6.3 Abstract

Metalloamination-allylation of representative N,N-dimethylhydrazinoalkenes has been shown to be effectively catalyzed by CuBr•SMe_2, CuCN and CuI. The current method obviates the use of stoichiometric $CuCN(LiCl)_2$ as a promoter for the electrophilic functionalization event.

6.4 Introduction

Saturated N-heterocycles have come to be recognized as privileged scaffolds for drug discovery and development as a consequence of their decreased lipophilicities, improved solubility, bioavailability and pharmacokinetics.[1a,b] This class of heterocycles, many of which contain chiral centers, presents synthetic challenges that are often not well addressed by traditional synthetic methods.[1c] We have previously advanced a powerful new method for achieving N-C/C-C bond construction by way of simultaneous N-C/C-Zn metalloamination.[2a,b] Several laboratories have documented synthetically viable methods for achieving sequential N-C→C-M→C-C bond formation, with the seminal discoveries of the Bower,[3a,b] Chemler,[3c,d] Knowles[3e,f] and Wolfe[3g-j] laboratories being major advancements.[4] From a synthetic standpoint, it is significant that virtually all current procedures are limited in the final C-C bond forming step due to the fleeting nature of their requisite organometallic or free radical intermediates. By way of contrast, our work involves the intermediacy of organozinc reagents, which are comparatively robust and can be synthetically differentiated via numerous C-Zn functionalization procedures. In addition, many of the catalytic metalloamination methods for forming 5-membered rings (as well as the very few that give 6-membered rings) greatly benefit from conformational biasing effects favoring annulation. In contrast, our Zn(II) mediated annulation procedure is not reliant on conformational constraints. We have previously reported that *stoichiometric* $CuCN(LiCl)_2$[5] is an effective reagent for promoting allylations of the C-Zn

bond present in nitrogenous heterocycles of the type **2**.[2a,b] In this section we show that CuBr•SMe_2, CuCN and CuI are effective catalysts for alkylation at carbon.

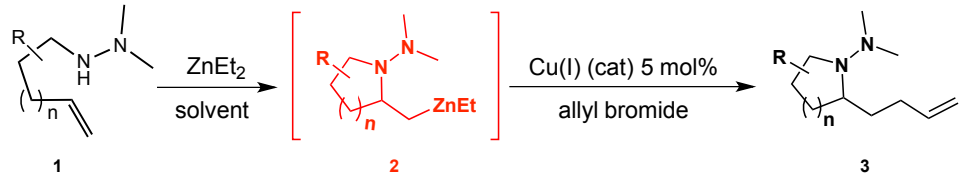
6.5 Catalyst Evaluation

The influence of aromatic solvents on the efficiency of metalloamination was initially investigated by a direct comparison of toluene to its more polar counterpart benzotrifluoride (BTF).[6] Whereas the use of each of these solvents resulted in excellent conversion (> 95%) of the N,N-dimethylhydrazinoalkene **1a** to the corresponding cyclic organozinc **2a** at 90 °C, reactions conducted in BTF proceeded more rapidly, requiring 6 h compared to 24 h when PhMe was employed. From the standpoint of economics, the use of chlorobenzene led to metalloamination in the intermediate range of 12 h. In addition, the "π-excessive" aromatic thiophene was found to offer no obvious advantages as a solvent over chlorobenzene or PhMe.

The efficacy of selected Cu(I) salts (and complexes) as allylation catalysts was then studied. From the standpoint of experimental simplicity, it is noteworthy that the "conventional" Cu(I) sources CuBr•SMe_2 CuCN and CuI proved to be excellent catalysts for the conversion of **2a** to **3a**.

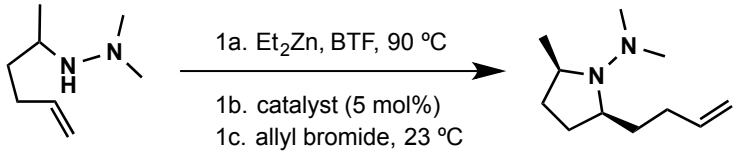
In a representative experimental procedure, exposure of **1a** (0.10 mmol) to Et_2Zn (1.0 equiv as a 2.0 M solution in BTF) in BTF (0.4 mL) at 90 °C for 6 h generated **2a** (≥ 95%, as a 20:1 *cis*/*trans* diastereomeric mixture).[7] Subsequently, tetrahydrothiophene (THT) (0.1 mL), CuBr•SMe_2 (1.02 mg, 5 mol%) and allyl bromide (4 equiv) were added in succession. Allylation was monitored by ^{1}H NMR at 23 °C for 12 h, whereupon

complete conversion to **3a** was achieved. Upon workup (*vide infra*) the pyrrolidine **3a** (95%, dr: ≥ 20:1) was furnished as a clear liquid (which could also be conveniently isolated as the trifluoroacetate salt). Although methallyl chloride had previously been found highly satisfactory as a trapping agent when *stoichiometric* $CuCN(LiCl)_2$[2a] was used as a promoter, this complex proved much less effective when used as a catalyst (5 mol%) with this less reactive chloride. In sharp contrast, the use of $CuCN(LiBr)_2$ admixed with LiBr 1 mol equiv led to rapid and highly efficient methallylation (possibly due to an internal Finkelstein activation process). Additionally, the use of THT as a Cu(I) stabilizer was determined unnecessary. *The simple substitution of LiBr (1 mol equiv) provided solutions of mixed Cu/Zn intermediates that were endowed with substantial lifetimes*. Alternative Cu(I) complexes [i.e., $CuBr•P(n\text{-}Bu)_3$, $CuBr•P(2\text{-furyl})_3$, $CuCl•(PPh_3)_2$] and CuSPh were subsequently tested and found to be inferior as catalysts, as was $AuCl•PPh_3$. The results of this study are summarized in Table 6.1. In addition, $Mo(CO)_6$ and $Mo(CO)_4$•bipy[8] were not competent as catalysts for the present transformation.



Scheme 6.1. Metalloamination-allylation of N,N-dimethyl-hydrazinoalkenes

Table 6.1. Catalyst evaluation using allyl bromide as the electrophile



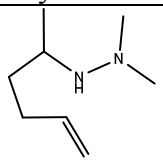
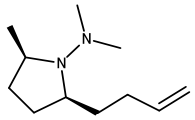
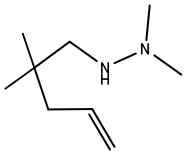
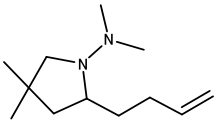
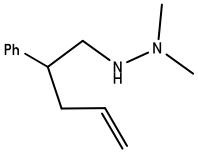
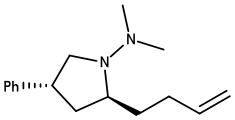
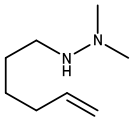
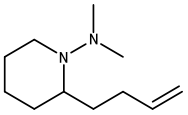
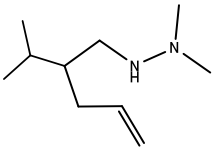
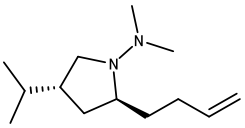
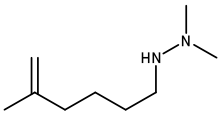
Entry	Catalyst	t_{final}	% Yield[a]
1	CuBr•DMS[c]	12 h	≥ 95
2	CuBr•DMS[b,d]	3 h	≥ 95
3	CuCN•2LiBr[b,d]	12 h	≥ 95
4	CuI[c]	15 h	≥ 95
5	CuBr•P(2-furyl)$_3$[c]	12 h	74
6	CuBr•P(*n*-Bu)$_3$[c]	12 h	70
7	CuCl•2PPh$_3$[c]	22 h	67
8	PhSCu[b,c]	10 h	65
9	AuCl•PPh$_3$[c]	22 h	25

[a] Monitored by No-D ^{1}H NMR[7] using disappearance of C-Zn methylene peak to determine completion.
[b] BTF was removed and allylation was performed in THF
[c] Reaction conducted with 1.1 eq of THT
[d] One mol equiv of LiBr was added

The synthetic scope of metalloamination/allylation was explored by subjecting additional *N*,*N*-dimethylhydrazinoalkenes (e.g., **1a**-**1d**) to an experimental protocol closely related to that described for the conversion of **1a** to **3a**. The details of this study are summarized in Table 6.2. The results presented in Table 6.2 are noteworthy, and the isolated yields are excellent in almost all cases. Significantly, the presence of Thorpe-Ingold conformational acceleration, that is of crucial importance in many hydroamination/cyclizations, is not a prerequisite for successful metalloamination/cyclization. In addition, these reactions were readily scalable (e.g.: ≥ 1 mmol). Two examples are presented in entries 1 and 4, in which simple 5- and 6-membered rings are formed efficiently *and with faster rates* than observed for **1b** (entry 2). In addition, excellent levels of diastereoselectivity are achievable. Specific cases

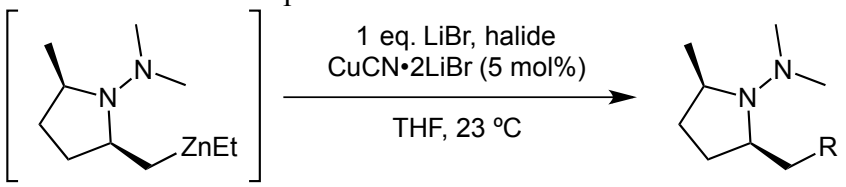
include the metalloamination/allylation of **1a** to provide pyrrolidines **3a** (*cis*/*trans* ≥ 20:1) and **1c** to give pyrrolidine **3c** (*cis/trans* = 1:15).[2a] As revealed by entry 4, facile metalloamination-allylation is also extendible to the formation of piperidines from a N,N-dimethylhydrazinoalkene that lacks conformational biasing favoring ring closure (**1d** → **3d**). It is also significant that alternative halides readily participate in the C-functionalization process. Thus, the use of propargyl bromide provided allene $\mathbf{3a_{Allene}}$ and methyl 2-(bromomethyl)acrylate furnished enoate $\mathbf{3a_{Methacrylate}}$ in highly respectable yields (Table 6.3: entries 3 and 4 respectively).

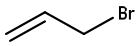
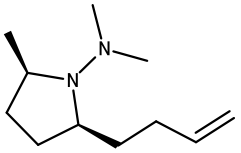
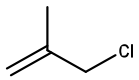
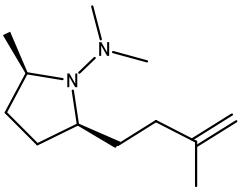
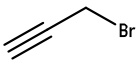
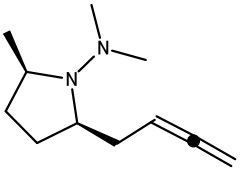
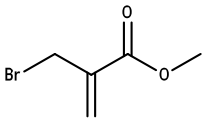
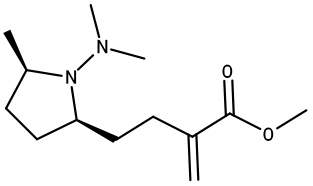
Table 6.2. Metalloamination-allylation of N,N-dimethylhydrazinoalkenes utilizing allyl bromide as the electrophile

Entry	Hydrazine	$t_{cylclize}$ [a]	$t_{allylation}$ [e,f]	d.r.[d]	Product[b]	Yield %[a,c]
1	 **1a**	6 h (90 °C)	12 h (23 °C)	20:1	 **3a**	≥ 95
2	 **1b**	18 h (90 °C)	24 h (23 °C)	--	 **3b**	≥ 95
3	 **1c**	24 h (23 °C)	22 h (23 °C)	15:1	 **3c**	90
4	 **1d**	1 h (60 °C)	8 h (23 °C)	--	 **3d**	≥ 95
5	 **1e**	24 h (23 °C)	12 h (23 °C)	6:1	 **3e**	80
6	 **1f**	--	--	--	-- **3f**	--

[a] Monitored by No-D ^{1}H NMR using BTF as the internal standard.[7]
[b] Products were isolated as TFA salts.
[c] A small quantity of the TFA salt of the starting N,N-dimethylhydrazinoalkene (**1**) was admixed with the product.
[d] Diastereomeric ratios were derived from proton NMR [3e]
[e] Monitored by the disappearance of C-Zn methylene peak to determine completion.[7]
[f] The allylation was catalyzed by CuCN•2LiBr and conducted in THF

Table 6.3. Catalytic CuCN • 2LiBr (5mol%) mediated allylation of 1-methyl-N,N,-dimethyl-4-pentene in THF with representative halides



Entry	Halides	Time	Temperature	Product[b]	% Yield[a,c]
1		12 h	23 °C	 **3a**	≥ 95
2		10 h	23 °C	 **3a-Me**	≥ 95
3		5 h	23 °C	 **3a$_{allene}$**	60
4		4 h	23 °C	 **3a$_{methacrylate}$**	65

[a] Monitored by No-D ^{1}H NMR using disappearance of C-Zn methtylene peak to determine completion.[7]

[b] Products were isolated as TFA salts subsequent to allylation in THF

[c] A small quantity of the TFA salt of the starting N,N-dimethylhydrazinoalkene (**1**) was admixed with the product.

6.6 Conclusions

In conclusion, we have shown that the readily available copper (I) derivatives $CuBr•SMe_2$, CuCN and CuI are highly effective catalysts for the allylation of zinc-bearing azacycles generated by Et_2Zn driven metalloamination/cyclization of representative N,N-dimethylhydrazinoalkenes. Metalloamination/cyclization proceeded more rapidly in benzotrifluoride (BTF) and chlorobenzene than toluene but all three solvents proved very well suited for overall cyclization-allylation. In addition, alternative attractive modes of electrophilic functionalization of the intermediate carbon-zinc bond have been revealed.

6.7 Funding Information

Generous financial support from the NIGMS (GM116949) is gratefully acknowledged.

All Experimental and Spectral Data for this Manuscript is found in the Appendix

6.8 References and Notes

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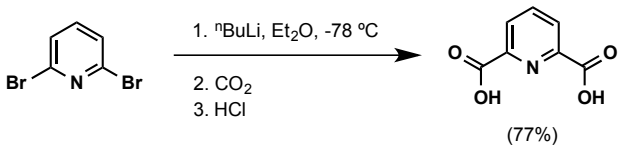
9. **General procedure for CuBr•SMe$_2$ catalyzed metalloamination-allylation**: An oven dried J. Young Tube under an argon atmosphere was charged with diethylzinc (50 μL, 2.0 M in BTF, 0.1 mmol, 1.0 equiv), BTF (0.4 mL) and the requisite N,N-dimethylhydrazinoalkene (0.1 mmol, 1.0 equiv). The tube was then placed into an oil bath (of indicated temperature) and metalloamination/cyclization was monitored using BTF as an internal standard (as evidenced by the disappearance of the olefin signals with concurrent emergence of new C-Zn methylene peaks). The temperature of the reactant mixture was subsequently returned to 23 °C for the addition of THT (0.1 mL) followed by the addition of the Cu(I) catalyst (5 mol%). Allyl bromide (4.0 equiv) was then added and its consumption, with simultaneous recession of the intermediate C-Zn methylene resonance, was monitored by No-D proton NMR. Upon completion of allylation, the reactant mixture was dispersed in diethyl ether (2 mL) and washed with 1:1 sat. NH_4Cl (aq): sat. NH_4OH (aq) (3 x 3mL). The aqueous layers were then extracted with diethyl ether (3 mL) and the combined organic layers were dried successively with brine (5 mL) and $MgSO_4$, and then filtered through a plug of silica. To the ethereal solution was added TFA (8.5 μL, 0.11 mmol, 1.1 equiv) and the mixture was concentrated *in vacuo*. The resulting salt was triturated with pentane (3 x 1 mL) and the volatiles were removed to provide the cyclization-allylation product (> 95%) as a clear viscous oil [which could also be isolated as the mono-TFA salt].

CHAPTER SEVEN

CONTINUED AND ONGOING RESEARCH

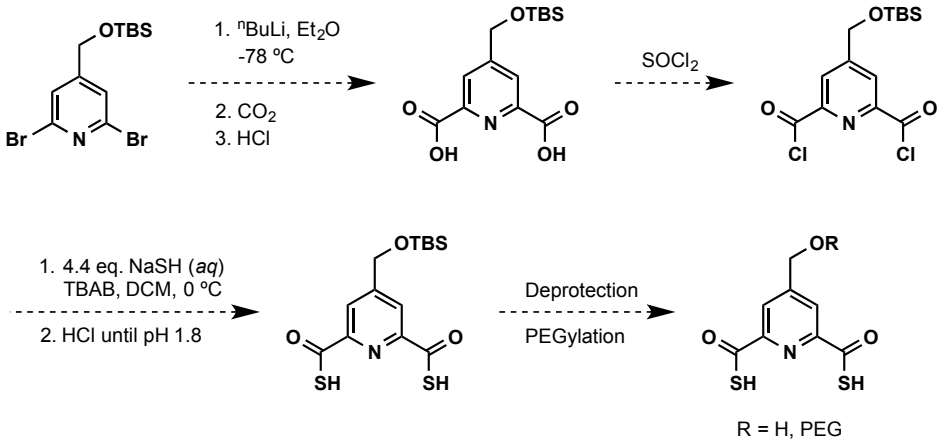
7.1 Optimization and Continued Efforts Towards PDTC Derivatives

As seen in Chapter Three of this document, a new method was developed for the safe and effective construction of pyridine-2,6-bis(monothiocarboxylic acid) [PDTC] from pyridine-2,6-dicarboxylic acid via conversion to the bis(acyl) chloride and subsequent bisthiocarboxylic acid formation with sodium bisulfide. However, development of the functionalized PDTC derivatives utilizing the novel one-step method was unable to produce PDTC or the desired structural derivatives. Continued efforts are being made within the laboratory to further develop and optimize the dilithium-halogen exchange and direct thiocarboxylation. A concurrent effort is being made to develop a new pathway to these structural derivatives by exploiting the previously optimized PDTC procedure as the final steps. Since the major issue with the novel dilithium-halogen exchange is the addition into carbonyl sulfide and isolation as the thiocarboxylic acid, the same procedure could be used to produce the far more robust dicarboxylic acid by trapping the dilithiopyridine with carbon dioxide. The 4-position functionalized 2,6-dicarboxylic acid could be carried through to the bis(acyl) chloride and subsequently isolated as the desired bisthiocarboxylic acid. Proof of concept was done as seen below in Scheme 7.1 where 2,6-dibromopyridine is dilithiated and cannulated onto carbon dioxide and acidified to generate pyridine-2,6-dicarboxylic acid, the starting material of the safe and effective procedure for producing PDTC.



Scheme 7.1. Dilithium-halogen exchange followed by direction biscarboxylation

Utilizing the dibromides synthesized from citrazinic acid, it could be envisioned that the structural derivatives of PDTC could be created using this method coupled with the previously optimized procedure. Work is currently being done to develop this procedure for the TBS-protected primary alcohol dibromide shown below in Scheme 7.2. This method could allow for the construction of two of the desired PDTC derivatives.

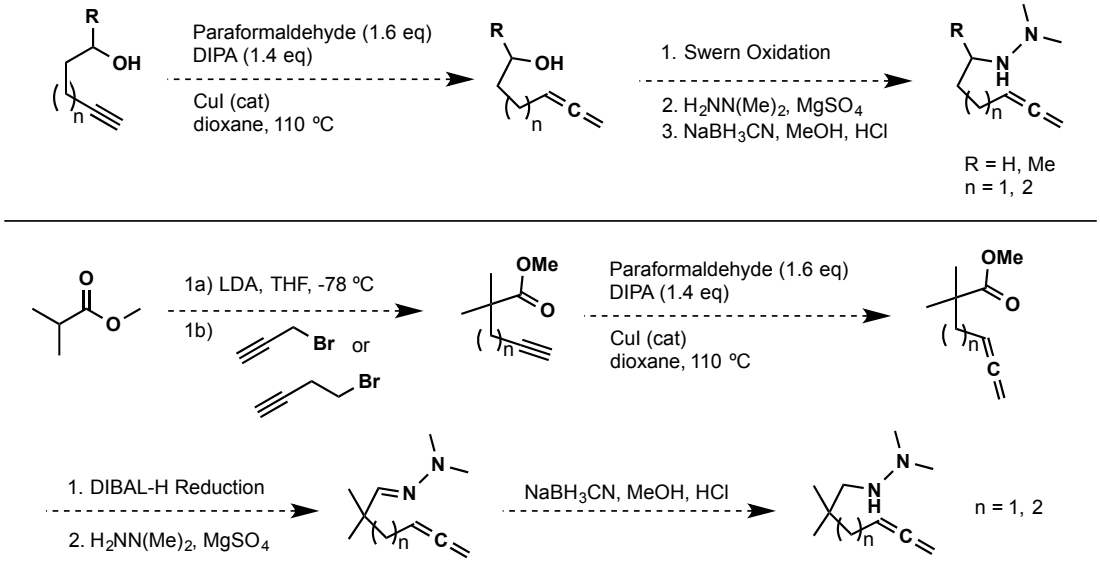


Scheme 7.2. New pathway being tested for production of PDTC derivatives

7.2 Allenes as Acceptors for Zinc-Amide Metalloamination/Cyclization

Allenes are an attractive acceptor for the zinc-mediated metalloamination/cyclization method developed in the Livinghouse laboratory. Construction of a series of allenes could prove to be a versatile addition to the substrate scope of this reaction. After cyclization/allylation the resulting product would contain

two regions of unsaturation that could be synthetic handles for further elaboration. The current hydrazinoallene scope contains two example of no substitution, two examples of 2-methyl derivatives, and two examples of geminal dimethyl hydrazinoallene, which could be synthesized by the following methods. By utilizing Ma's procedure[1] for producing allenes, the construction of the hydrazinoallenes should not prove to be problematic (Scheme 7.3).



Scheme 7.3. Potential hydrazinoallene formations

Depending on how this series performs the carboamination method we have developed, the allene acceptor could prove to give rise to diverse possibilities. With potential for cyclization of substrates with substitution at the internal carbon of the unsaturated region, which to this point has not been demonstrated.

7.3 Studies Towards Hydrazine Cleavage

Our laboratory has also been working on developing a method for the cleavage of the hydrazine bond in order to isolate pyrrolidines and piperidines from our metalloamination/cyclization and subsequent electrophilic functionalization. It is thought that making the borane complex of our cyclized hydrazines could lead to rapid cleavage of the nitrogen-nitrogen hydrazine bond. Test experiments have been initiated for isolation of the borane complexes of a similar hydrazine system, which will undergo a number of potential reductions in order to isolate the amine.

7.4 Solvation and Concentration Effects on Metalloamination/Cyclization

Solvent and reaction concentration can be large factors with regards to the efficiency and effectiveness of a reaction. Recently, it was shown (Table 7.1) conclusively that solvent does have a pronounced effect on the rate of cyclization for the Livinghouse metalloamination/cyclization conditions.[2] Studies show that increasing polarity of aromatic solvent increases the rate of cyclization. Toluene proved to be the most sluggish, chlorobenzene worked effectively and cyclization much more rapidly, while benzotrifluoride engendered the fastest rate of cyclization, finishing in nearly half the time of toluene in almost all cases.

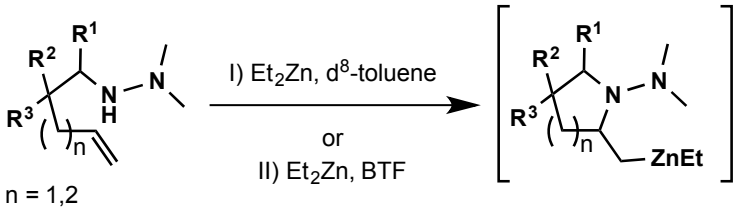
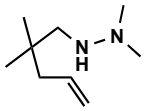
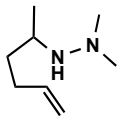
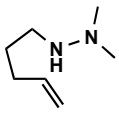
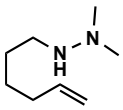
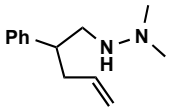
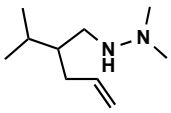


Table 7.1. Solvent effects on cyclization of hydrazinoalkenes

Entry	Solvent	Temperature	t_{50}	t_{final}	% Conversion
	Ph-Me	90 °C	7 h	30 h	95
	BTF	90 °C	3.5 h	18 h	90
	Ph-Me	90 °C	3 h	24 h	95
	BTF	90 °C	1.5 h	6 h	95
	Ph-Me	23 °C	---	14 h	75
	BTF	23 °C	---	14 h	60
	Ph-Me	90 °C	---	1.5 h	92
	BTF	60 °C	---	1 h	90
	Ph-Me	23 °C	8 h	50 h	90
	BTF	23 °C	6 h	26 h	90
	Ph-Me	35 ºC	5 h	32 h	90
	BTF	35 ºC	2.5 h	27 h	95

The effect of optimal concentration is also of interest to our laboratory and thus we set out to determine the limits of this reaction with regards to concentration. As concentration increased the rate of cyclization also increased, showing that this reaction performs most efficiently as a neat mixture of substrate and diethylzinc, with no observable degradation (Table 7.2).

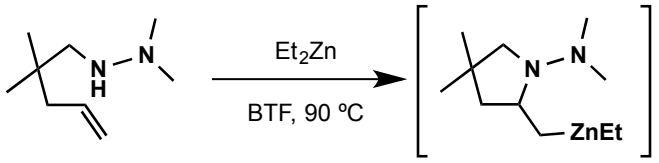


Table 7.2. Concentrative effect on the cyclization of N',N',2,2-tetramethylhydrazinopent-4-ene

Entry	Concentration (M)	t_{50}	t_{final}	% Conversion
1	0.22	3.5 h	18 h	≥ 95
2	0.55	2 h	8 h	≥ 95
3	0.87	1.5 h	6 h	≥ 95
4	1.5	0.75 h	3.5 h	≥ 95
5	neat	10 min	0.5 h	≥ 95

Notes: All entries use 1.0 equivalent of diethylzinc

It is also known that this reaction can proceed with one-half of an equivalent of diethylzinc to ultimately form the dimer-complex, ongoing studies are being done to further emphasize the preparative capabilities of this reaction. Continued research towards the efficiency and effectiveness of this metalloamination/cyclization and subsequent electrophilic functionalization could lead to industrially relevant processes for producing nitrogenous heterocycles.

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CHAPTER EIGHT

CONCLUSIONS

Throughout this dissertation the utility of organic synthesis not just for constructing molecules but also for intelligent design of necessary precursors for a given system has been shown.

When developing a novel material for increased second-order nonlinear activity, the goal was to rationally design a molecular architecture that would allow for optimized acentric supramolecular organization. A construct that could allow a chromophore containing a large first molecular hyperpolarizability and bear the appropriate structural elements for directing order was envisioned. By coupling a liquid crystal tolane to a well known NLO chromophore via strategic synthesis, an organic ferroelectric liquid crystal-like material was developed that should intrinsically favor unidirectional chromophore order while also containing a high β chromophore along the polar axis for increased and stabilized second-order nonlinear optical potential. Utilizing this bottom up approach for constructing a unique material, a synthetic pathway to a set of novel chromophores was designed and completed. These chromophores have shown potential for high terminal stability as well as increased nonlinear susceptibilities.

In environmental remediation chemistry, carbon tetrachloride is a carcinogenic pollutant that has contaminated groundwater beneath former grain storage and industrial sites, such as the Department of Energy's Hanford site. Current remediation of these sites involves removal and subsequent treatment, which requires handling of the hazardous

material as it is transferred to another location for final destruction. However, the use of a small molecule (pyridine-2,6-bis(monothiocarboxylic acid) [PDTC]), when complexed with copper has been shown to lead to complete dechlorination of pollutant carbon tetrachloride samples. The process results in conversion to nontoxic end-products (mostly CO_2) and complete removal of the problematic carbon-chlorine bonds. Synthetic chemistry was employed to develop a modified procedure for large-scale production of PDTC that eliminates harmful byproducts and excess toxic reagents used. Additionally, a novel route to PDTC was attempted in order to develop PDTC and structural derivatives for increased water solubility. Unfortunately, at this time the process still needs to be optimized to achieve successful dilithium-halogen exchange and direct bisthiocarboxylation. However, the dibromide-functionalized derivatives needed for the production of structural derivatives of PDTC were readily constructed from citrazinic acid. These molecules could allow access to two key PDTC derivatives needed for the continuation of the water-based destruction of carbon tetrachloride.

In medicinal and pharmaceutical chemistry, routes to nitrogenous heterocycles are of great importance due to their prevalence in bioactive molecules. Thus, our diethylzinc mediated metalloamination/cyclization of unsaturated *N,N*-dimethylhydrazines with subsequent electrophilic functionalization could prove to be a powerful tool for constructing pyrrolidines and piperidines. First, we extended this method to the use of 1,2-disubstituted alkenes as N-Zn migratory insertion acceptors. Both 2-(aryl)ethenes and a vinylcyclopropane readily served as reaction participants in our metalloamination/cyclization-allylation cascades. Where the vinylcyclopropane

substituent confers high reactivity toward metalloamination with concomitant scission of the cyclopropane ring. This led to the expansion of the reaction to include various vinylcyclopropyl hydrazine substrates due to the advantage of irreversible cyclization that occurred from the simultaneous cyclopropyl scission event. The cyclopropyl series showed the potential to cyclize tri-substituted alkenes, difficult to construct macrocycles (> 6 atoms) and generate products with a remaining internal unit of unsaturation not observed in any other product produced. Computational chemistry was employed to gain an understanding of the cyclopropyl series. Though cyclization did not occur within these substrates, continued efforts should be made towards the optimization of the vinylcyclopropyl hydrazine class of molecules. The potential behind the irreversible cyclopropyl scission and development of a new alkene make this class of substrates extremely desirable.

Lastly, the metalloamination-allylation of N,N-dimethylhydrazinoalkenes has been shown to be effectively catalyzed by CuBr•SMe_2, CuCN and CuI. This novel method obviates the use of stoichiometric $CuCN(LiCl)_2$ as a promoter for the electrophilic functionalization event. Metalloamination/cyclization proceeded more rapidly in benzotrifluoride (BTF) and chlorobenzene than toluene, but all three solvents proved very well suited for overall cyclization-allylation. We have shown that the readily available copper (I) derivatives, such as CuBr•SMe_2, CuCN and CuI are highly effective catalysts for the allylation of zinc-bearing azacycles generated by Et_2Zn driven metalloamination/cyclization of representative N,N-dimethylhydrazinoalkenes.

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APPENDICES

APPENDIX A

EXPERIMENTAL

CHAPTER ONE EXPERIMENTAL

Materials and Methods: All reagents and starting materials were purchased from commercial suppliers and used as received, unless otherwise stated. All reactions were carried out under nitrogen atmosphere in flame-dried glassware, unless otherwise stated. External oil bath temperatures were used to record reaction mixture temperatures. Reaction solvents tetrahydrofuran (Fisher Scientific, HPLC grade) and dichloromethane (J.T. Baker, LC grade) were dried over, and distilled from, sodium metal and calcium chloride, respectively. Solvents for filtrations, transfers, and chromatography were certified ACS grade.

(*R*)-1-bromo-4-(octan-2-yloxy)benzene[1], 1-bromo-4-(octan-2-yloxy)benzene (3b)[1], 1-bromo-4-(heptyloxy)benzene[2], (*R*)-2-methyl-4-(4-(octan-2-yloxy)phenyl)but-3-yn-2-ol[1], 2-methyl-4-(4-(octan-2-yloxy)phenyl)but-3-yn-2-ol[1], 4-(4-(heptyloxy)phenyl)-2-methylbut-3-yn-2-ol[3], (*R*)-1-ethynyl-4-(octan-2-yloxy)benzene[1], 1-ethynyl-4-(octan-2-yloxy)benzene[1], 1-ethynyl-4-(heptyloxy)benzene[3], (*E*)-2-(3-cyano-4-(4-((2-hydroxyethyl)(methyl)amino)styryl)-5,5-dimethylfuran-2(5H)-ylidene)malononitrile (**5**)[4] were prepared as previously reported. All other materials were used as received from commercial sources.

Thin layer chromatography was performed on Sorbent Technologies silica XG TLC plates. Visualization was accomplished with UV light (254 nm), and/or 2,4-dinitrophenyl hydrazine in 2 M HCl. Normal phase flash column chromatography was performed using Sorbent Technologies standard grade silica gel 60 Å, 40 – 63 μm (230 x 400 mesh), unless otherwise stated.

Both ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX500 (500 MHz, 1H; 125 MHz, 13C) or a Bruker DRX300 (300 MHz, 1H; 75MHz, 13C). Chemical shifts (δ) are reported in ppm, employing the solvent resonance as the internal standard. Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), and bs (broad singlet). Coupling constants (J) are reported in hertz (Hz). Ultraviolet-Visible (UV-Vis) spectra were recorded on a Shimadzu UV-2101PC UV-Vis scanning spectrophotometer. High resolution mass spectrometry (HRMS) was obtained by the Norte Dame Mass Spectrometry and Proteomics Facility with a Bruker micrOTOF-II.

3-Hydroxy-3-(4-iodophenyl)butan-2-one (2): A 100-mL multinecked round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar and addition funnel was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 4.86 mL (50.8 mmol, 2.5 equiv.) of ethyl vinyl ether and 20 mL of dry THF, then the mixture was cooled to -78 ºC. Once at reduced temperature, 21.39 mL (40.64 mmol, 2.0 equiv.) of 1.9 M *tert*-butyllithium in pentane was added into a sealed addition funnel and added dropwise to the reaction mixture over 30 min. The reactant mixture was then allowed to slowly warm to 0 ºC; the solution was held at 0 ºC for 30 min then cooled to -78 ºC. While the reactant mixture was cooling a 50-mL round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The 50-mL flask was then charged with 5.0 g (20.32 mmol, 1.0 equiv.) of 4'-Iodoacetophenone and 15 mL of dry THF. The resulting solution of 4'-Iodoacetophenone in THF was transferred via syringe

and added dropwise into the -78 ºC reaction mixture over 10 min. The reactant mixture was held at -78 ºC for 1 h then allowed to slowly warm to 23 ºC. The reaction was monitored by TLC and after 12 h was quenched by adding 5.0 mL of deionized water followed by 15 mL of a saturated solution of ammonium chloride in deionized water. The mixture was extracted with ethyl acetate (3 x 15 mL), and then the organic-layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude intermediate, 3-ethoxy-2-(4-iodophenyl)but-3-en-2-ol, was transferred into a 100-mL round-bottomed flask, equipped with a Teflon-coated stirring bar, and re-dispersed with 20 mL of methanol. HCl (20 mL, 3M) was added slowly to the methanol solution, an additional 20 mL of methanol was slowly added to the solution until a single-phase solution was achieved. This mixture was allowed to stir for 2 h, and then the solution was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and washed with a saturated solution of sodium bicarbonate until all residual HCl was neutralized. The organic layers were again combined and washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica (20% ethyl acetate in hexanes for elution) to afford 4.4 g (74.7%, 15.17 mmol) of a viscous, pale yellow oil. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.71 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 4.51 (s, 1H), 2.09 (s, 3H), 1.75 (s, 3H). ^{13}C-NMR (126 MHz; $CDCl_3$): δ 209.1, 141.4, 137.9, 128.1, 94.1, 79.8, 24.2, 23.5. MS (micrOTOF): (theoretical) 312.9696 (M+Na), (experimental) 312.9689.

3-Hydroxy-3-(4-((4-((*R*)-octan-2-yloxy)phenyl)ethynyl)phenyl)butan-2-one (3a): A 250-mL multinecked round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar and Liebig condenser was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 3.089 g (10.649 mmol, 1.0 equiv.) of **2**, 2.944 g (12.779 mmol, 1.2 equiv.) of (*R*)-1-ethynyl-4-(octan-2-yloxy)benzene, 0.698 g (2.662 mmol, 0.25 equiv.) of triphenylphosphine, 0.424 g (2.236 mmol, 0.21 equiv.) of copper (I) iodide, and 35 mL of freshly distilled triethylamine. The mixture was stirred and degassed for 30 min, then 0.373 g (0.532 mmol, 0.05 equiv.) of bis(triphenylphosphine)palladium (II) dichloride was added to the solution, followed by an additional 14 mL of freshly distilled triethylamine. The reactant mixture was heated to 65 ºC, after 1 h 30 mL of dry THF was added to the mixture. The reactant mixture was held at 65 ºC for 72 h, then the solution was cooled to 23 ºC and filtered through a bed of Celite. The Celite was washed with a 1:1 ethyl acetate and hexanes solution several times; the filtrate was collected and concentrated in vacuo. The crude product was purified via flash column chromatography on silica (15% ethyl acetate in hexanes for elution) to afford 4.01 g (95.9%, 10.22 mmol) of an orange-brown solid. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.51 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 4.56 (s, 1H), 4.38 (q, J = 5.9 Hz, 1H), 2.09 (s, 3H), 1.78 (s, 3H), 1.57-1.29 (m, 13H), 0.88 (s, 3H). ^{13}C-NMR (126 MHz; $CDCl_3$): δ 209.3, 158.6, 141.1, 133.2, 131.8, 126.2, 123.7, 115.9, 114.8, 90.5, 87.5, 79.9, 74.1, 36.5, 31.9, 29.4, 25.6, 24.2, 23.6, 22.7, 19.8, 14.2. MS (micrOTOF): (theoretical) 415.2244 (M+Na), (experimental) 415.2225.

Rac **3-Hydroxy-3-(4-((4-(octan-2-yloxy)phenyl)ethynyl)phenyl)butan-2-one (3b)** was synthesized (99.5% yield) employing the same procedure using 1-ethynyl-4-(octan-2-yloxy)benzene in place of (R)-1-ethynyl-4-(octan-2-yloxy)benzene.

3-(4-((4-(Heptyloxy)phenyl)ethynyl)phenyl)-3-hydroxybutan-2-one (3c): A 500-mL multinecked round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar and Liebig condenser was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 5.43 g (18.72 mmol, 1.0 equiv.) of **2**, 4.86 g (22.47 mmol, 1.2 equiv.) of 1-ethynyl-4-(heptyloxy)benzene, 1.23 g (4.68 mmol, 0.25 equiv.) of triphenylphosphine, 0.746 g (3.93 mmol, 0.21 equiv.) of copper (I) iodide, and 70 mL of freshly distilled triethylamine. The mixture was stirred and degassed for 30 min, then 0.657 g (0.936 mmol, 0.05 equiv.) of bis(triphenylphosphine)palladium (II) dichloride was added to the solution, followed by an additional 15 mL of freshly distilled triethylamine. The reaction mixture was heated to 65 ºC, after 1h 55 mL of dry THF was added to the mixture. The reaction mixture was held at 65 ºC for 72 h, then the solution was cooled to 23 ºC and filtered through a bed of Celite. The Celite was washed with a 1:1 ethyl acetate and hexanes solution several times; the filtrate was collected and concentrated in vacuo. The crude product was purified via flash column chromatography on silica (20% ethyl acetate in hexanes for elution) to afford 6.99 g (98.7%, 18.47 mmol) of a light-beige solid. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.51 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.57 (s, 1H), 3.96 (t, J = 6.5 Hz, 2H), 2.09 (s, 3H), 1.81-1.76 (m, 5H), 1.48-1.42 (m, 2H), 1.39-1.31 (m, 6H), 0.90 (t, J = 6.7 Hz, 3H). ^{13}C-NMR (126 MHz; $CDCl_3$): δ 209.3, 159.5, 141.1, 133.2, 131.8,

126.2, 123.7, 115.0, 114.7, 90.4, 87.5, 79.9, 68.2, 31.9, 29.32, 29.18, 26.1, 24.1, 23.6, 22.7, 14.2. MS (micrOTOF): (theoretical) 401.2087 (M+Na), (experimental) 401.2101.

2-(3-cyano-4,5-dimethyl-5-(4-((4-((*R*)-octan-2-yloxy)phenyl)ethynyl)phenyl)furan-2(5H)-ylidene)malononitrile (4a): A 50-mL multinecked round-bottomed flask containing 5-10 4Å molecular sieves, equipped with a Teflon-coated mechanical stirring bar and Liebig condenser was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 2.28 g (5.808 mmol, 1.0 equiv.) of **3a**, 2.30 g (34.850 mmol, 6.0 equiv.) of malononitrile and 14.5 mL of absolute ethanol. A separate 10-mL round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was charged with 46.0 mg of sodium metal and 2.0 mL of absolute ethanol. Once the sodium was completely dissolved, 1.452 mL (1.452 mmol, 0.25 equiv.) of the 1.0 M solution of sodium ethoxide in absolute ethanol was transferred into the reaction flask via syringe. The reaction mixture was heated to 85 ºC for 18 h. The solution was then cooled to 23 ºC, transferred to a 100-mL round-bottomed flask with CH_2Cl_2 (20 mL) and concentrated in vacuo. The crude product was purified via flash column chromatography on silica using methylene chloride for elution; the pure product was dissolved in chloroform, washed with water (2 x 15 mL), and brine. The organic layer was collected, dried over $MgSO_4$, and concentrated in vacuo to afford 0.913 g (32.1%, 1.865 mmol) of a pale-yellow solid. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.58 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.39 (sextet, J = 6.0 Hz, 1H), 2.23 (s, 3H), 2.02 (s, 3H), 1.77-1.29 (m, 13H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C-NMR (126 MHz; $CDCl_3$):

δ 181.7, 175.5, 159.0, 133.4, 133.0, 132.6, 126.6, 125.2, 115.9, 114.1, 110.8, 110.3, 109.0, 105.1, 101.3, 92.4, 86.6, 74.1, 59.5, 36.5, 31.9, 29.4, 25.6, 22.72, 22.55, 19.8, 14.6, 14.2. MS (micrOTOF): (theoretical) 512.2308 (M+Na), (experimental) 512.2294.

Rac-**2-(3-Cyano-4,5-dimethyl-5-(4-((4-(octan-2-yloxy)phenyl)ethynyl)phenyl)furan-2(5H)-ylidene)malononitrile (4b)** was synthesized (61.3% yield) employing the same procedure using **3b** in place of **3a**.

2-(3-Cyano-5-(4-((4-(heptyloxy)phenyl)ethynyl)phenyl)-4,5-dimthylfuran-2(5H)-ylidene)malononitrile (4c): A 100-mL multinecked round-bottomed flask containing 10-20 4Å molecular sieves, equipped with a Teflon-coated mechanical stirring bar and Liebig condenser was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 6.99 g (18.47 mmol, 1.0 equiv.) of **3c**, 7.32 g (110.82 mmol, 6.0 equiv.) of malononitrile and 46 mL of absolute ethanol. A separate 10-mL round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was charged with 0.115 g of sodium metal and 5.0 mL of absolute ethanol. Once the sodium was completely dissolved, 4.62 mL (4.62 mmol, 0.25 equiv.) of the 1.0 M solution of sodium ethoxide in absolute ethanol was transferred into the reaction flask via syringe. The reaction mixture was heated to 85 ºC for 18 h. The solution was then cooled to 23 ºC, transferred to a 100-mL round-bottomed flask with CH_2Cl_2 (20 mL) and concentrated in vacuo. The crude product was purified via flash column chromatography on silica using methylene chloride as the eluent; the pure product was dissolved in chloroform, washed

with water (2 x 20 mL), and brine. The organic layer was collected, dried over $MgSO_4$, and concentrated in vacuo to afford 1.0155 g (11.57%, 2.135 mmol) of a pale-yellow solid. ^{1}H-NMR (500 MHz; $CDCl_3$ δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 2.24 (s, 3H), 2.02 (s, 3H), 1.81-1.79 (m, 2H), 1.48-1.43 (m, 2H), 1.38-1.30 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H). ^{13}C-NMR (126 MHz; CDCl3): δ 181.6, 175.5, 159.8, 133.4, 133.0, 132.6, 126.6, 125.2, 114.8, 114.3, 110.8, 110.2, 109.0, 105.1, 101.3, 92.4, 86.6, 68.3, 31.9, 29.30, 29.17, 26.1, 22.74, 22.57, 14.6, 14.2. MS (micrOTOF): (theoretical) 498.2152 (M+Na), (experimental) 498.2177.

(*E*)-2-(3-Cyano-4-(4-((2-hydroxyethyl)(methyl)amino)styryl)-5-methyl-5-(4-((4-(R)-octan-2-yloxy)phenyl)ethynyl)phenyl)furan-2(5H)-ylidene)malononitrile (1a): A 10-mL round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 0.1638 g (0.335 mmol, 1.0 equiv.) of **4a**, 0.063 g (0.351 mmol, 1.05 equiv.) of N-methyl-N-(2-hydroxyethyl)-4-aminobenzaldehyde and 3.5 mL of absolute ethanol. The reaction mixture was heated to 40 ºC for 18 h. The reaction mixture was cooled to 23 ºC, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica (0.5% methanol in methylene chloride for elution) to afford 0.163 g (74.8%, 0.2505 mmol) of a metallic green-blue solid, blue-purple when solvated. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 15.7 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.38 (q, *J* = 6.0 Hz, 1H),

3.86 (t, *J* = 4.9 Hz, 2H), 3.63 (t, *J* = 5.2 Hz, 2H), 3.14 (s, 3H), 2.12 (s, 3H), 1.60-1.55 (m, 3H), 1.31-1.25 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H). ^{13}C-NMR (126 MHz; $CDCl_3$): δ 190.4, 176.4, 173.4, 158.9, 153.7, 149.9, 135.4, 133.4, 132.6, 132.4, 126.2, 122.2, 115.9, 114.3, 112.60, 112.50, 112.0, 111.5, 111.2, 109.2, 98.2, 92.1, 86.9, 69.0, 60.2, 54.5, 52.2, 39.5, 36.5, 31.9, 29.4, 25.6, 24.9, 22.7, 19.8, 14.2. MS (micrOTOF): (theoretical) 651.3330, (experimental) 651.3341. UV-Vis: λ_{max} = 581 nm ($CHCl_3$).

Rac-**(*E*)-2-(3-Cyano-4-(4-((2-hydroxyethyl)(methyl)amino)styryl)-5-methyl-5-(4-((4-octan-2-yloxy)phenyl)ethynyl)phenyl)furan-2(5H)-ylidene)malononitrile (1b)** was synthesized (64.9% yield) employing the same procedure using **4b** in place of **4a**.

(*E*)-2-(3-Cyano-5(4-((4-(heptyloxy)phenyl)ethynyl)phenyl)-4-(4-((2-hydroxyethyl)(methyl)amino)styryl)-5-methylfuran-2(5H)-ylidene)malononitrile (1c): A 50-mL round-bottomed flask, equipped with a Teflon-coated mechanical stirring bar was flame dried under vacuum (0.5 torr) and back-filled with dry nitrogen. The flask was then charged with 0.74 g (1.556 mmol, 1.0 equiv.) of **4c**, 0.293 g (1.634 mmol, 1.05 equiv.) of N-methyl-N-(2-hydroxyethyl)-4-aminobenzaldehyde and 15.5 mL of absolute ethanol. The reaction mixture was heated to 40 ºC for 18 h. The reaction mixture was cooled to 23 ºC, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica (0.5% methanol in methylene chloride for elution) to afford 0.706 g (71.2%, 1.109 mmol) of a metallic green-blue solid, blue-purple when solvated. ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 15.7 Hz, 1H), 6.87 (d,

J = 8.8 Hz, 2H), 6.72 (d, *J* = 15.1 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 3.96 (t, *J* = 6.6 Hz, 2H), 3.84-3.83 (m, 2H), 3.61 (t, *J* = 4.5 Hz, 2H), 3.14 (s, 3H), 2.09 (s, 3H), 1.78 (dt, *J* = 14.4, 7.0 Hz, 2H), 1.46-1.30 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (126 MHz; $CDCl_3$): δ 176.4, 173.4, 159.8, 153.6, 149.8, 135.4, 133.3, 132.6, 132.4, 126.22, 126.18, 122.3, 114.7, 114.5, 112.5, 112.0, 111.4, 109.4, 100.7, 98.8, 98.1, 92.1, 87.0, 68.3, 60.3, 54.5, 39.5, 31.9, 29.31, 29.18, 26.1, 24.9, 22.7, 14.2. MS (micrOTOF): (theoretical) 637.3173, (experimental) 637.3194. UV-Vis: λ_{max} = 581 nm ($CHCl_3$).

Output for calculated β values:[5]

Compound **1a**: First dipole hyperpolarizability, Beta (dipole orientation). ||, _|_ parallel and perpendicular components, (z) with respect to z axis, vector components x,y,z. Values do not include the 1/n! factor of 1/2. (esu units = statvolt**-1 cm**4 , SI units = C**3 m**3 J**-2)

Beta(0;0,0):

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.232544D+05	-0.200900D+03	-0.745621D+02
_|_(z)	-0.775148D+04	-0.669667D+02	-0.248540D+02
x	-0.154591D+05	-0.133555D+03	-0.495676D+02
y	-0.567396D+05	-0.490186D+03	-0.181928D+03
z	-0.116272D+06	-0.100450D+04	-0.372811D+03
||	0.260596D+05	0.225135D+03	0.835565D+02
xxx	0.646727D+04	0.558722D+02	0.207364D+02
xxy	-0.452860D+03	-0.391236D+01	-0.145203D+01
yxy	-0.260869D+04	-0.225371D+02	-0.836441D+01
yyy	-0.364098D+04	-0.314552D+02	-0.116743D+02
xxz	-0.917819D+04	-0.792925D+02	-0.294286D+02
yxz	-0.715614D+04	-0.618235D+02	-0.229452D+02
yyz	-0.830323D+04	-0.717334D+02	-0.266232D+02
zxz	-0.901162D+04	-0.778534D+02	-0.288945D+02
zyz	-0.148194D+05	-0.128028D+03	-0.475163D+02
zzz	-0.212760D+05	-0.183808D+03	-0.682184D+02

Beta(-w;w,0) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.226130D+05	-0.195359D+03	-0.725056D+02
_|_(z)	-0.778500D+04	-0.672563D+02	-0.249615D+02
x	-0.156443D+05	-0.135155D+03	-0.501614D+02
y	-0.547358D+05	-0.472875D+03	-0.175503D+03
z	-0.113065D+06	-0.976795D+03	-0.362528D+03
||	0.253176D+05	0.218724D+03	0.811773D+02
xxx	0.650108D+04	0.561643D+02	0.208448D+02
yxx	-0.387078D+03	-0.334406D+01	-0.124111D+01
yyx	-0.253205D+04	-0.218749D+02	-0.811866D+01
zxx	-0.917219D+04	-0.792406D+02	-0.294094D+02
zyx	-0.701779D+04	-0.606282D+02	-0.225016D+02
zzx	-0.858686D+04	-0.741838D+02	-0.275326D+02
xxy	-0.616468D+03	-0.532580D+01	-0.197662D+01
yxy	-0.269621D+04	-0.232932D+02	-0.864504D+01
yyy	-0.364978D+04	-0.315313D+02	-0.117025D+02
zxy	-0.723650D+04	-0.625178D+02	-0.232028D+02
zyy	-0.805996D+04	-0.696318D+02	-0.258432D+02
zzy	-0.140632D+05	-0.121495D+03	-0.450916D+02
xxz	-0.970946D+04	-0.838822D+02	-0.311320D+02
yxz	-0.748702D+04	-0.646820D+02	-0.240061D+02
yyz	-0.826465D+04	-0.714001D+02	-0.264994D+02
zxz	-0.931812D+04	-0.805013D+02	-0.298773D+02
zyz	-0.141663D+05	-0.122386D+03	-0.454224D+02
zzz	-0.202089D+05	-0.174589D+03	-0.647971D+02

Beta(-2w;w,w) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.330709D+05	-0.285707D+03	-0.106037D+03
_|_(z)	-0.112590D+05	-0.972693D+02	-0.361005D+02
x	-0.327643D+05	-0.283058D+03	-0.105054D+03
y	-0.809510D+05	-0.699353D+03	-0.259558D+03
z	-0.165355D+06	-0.142854D+04	-0.530187D+03
||	0.373999D+05	0.323106D+03	0.119917D+03
xxx	0.746373D+04	0.644808D+02	0.239314D+02
yxx	-0.930281D+03	-0.803690D+01	-0.298282D+01
zxx	-0.124965D+05	-0.107960D+03	-0.400683D+02
xyx	-0.116553D+04	-0.100693D+02	-0.373712D+01
yyx	-0.382781D+04	-0.330693D+02	-0.122734D+02
zyx	-0.106975D+05	-0.924182D+02	-0.343001D+02
xyy	-0.399253D+04	-0.344923D+02	-0.128015D+02
yyy	-0.525312D+04	-0.453828D+02	-0.168434D+02
zyy	-0.121770D+05	-0.105199D+03	-0.390437D+02
xzx	-0.126302D+05	-0.109115D+03	-0.404971D+02

yzx	-0.101484D+05	-0.876739D+02	-0.325393D+02
zzx	-0.151408D+05	-0.130805D+03	-0.485468D+02
xzy	-0.103352D+05	-0.892877D+02	-0.331382D+02
yzy	-0.113370D+05	-0.979433D+02	-0.363507D+02
zzy	-0.215916D+05	-0.186535D+03	-0.692305D+02
xzz	-0.132258D+05	-0.114261D+03	-0.424067D+02
yzz	-0.187470D+05	-0.161960D+03	-0.601098D+02
zzz	-0.309155D+05	-0.267086D+03	-0.991264D+02

Compound **1b**: First dipole hyperpolarizability, Beta (input orientation). ||, _|_ parallel and perpendicular components, (z) with respect to z axis, vector components x,y,z. Values do not include the 1/n! factor of 1/2. (esu units = statvolt**-1 cm**4 , SI units = C**3 m**3 J**-2)

Beta(0;0,0):

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.625816D+03	-0.540657D+01	-0.200659D+01
_|_(z)	-0.208605D+03	-0.180219D+01	-0.668865D+00
x	0.258597D+05	0.223408D+03	0.829157D+02
y	-0.128255D+06	-0.110802D+04	-0.411231D+03
z	-0.312908D+04	-0.270328D+02	-0.100330D+02
||	0.261747D+05	0.226129D+03	0.839254D+02
xxx	0.122763D+05	0.106058D+03	0.393623D+02
xxy	0.282934D+03	0.244433D+01	0.907190D+00
yxy	-0.329998D+04	-0.285093D+02	-0.105809D+02
yyy	-0.443543D+05	-0.383187D+03	-0.142216D+03
xxz	0.359852D+02	0.310884D+00	0.115382D+00
yxz	0.132935D+04	0.114845D+02	0.426237D+01
yyz	-0.863183D+03	-0.745723D+01	-0.276768D+01
zxz	-0.356431D+03	-0.307928D+01	-0.114285D+01
zyz	0.131975D+04	0.114016D+02	0.423158D+01
zzz	-0.215830D+03	-0.186460D+01	-0.692028D+00

Beta(-w;w,0) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.506345D+03	-0.437443D+01	-0.162353D+01
_|_(z)	-0.404237D+03	-0.349229D+01	-0.129613D+01
x	0.285364D+05	0.246532D+03	0.914979D+02
y	-0.161066D+06	-0.139148D+04	-0.516435D+03
z	-0.253173D+04	-0.218721D+02	-0.811763D+01
||	0.327187D+05	0.282664D+03	0.104908D+03
xxx	0.136718D+05	0.118114D+03	0.438368D+02

yxx	0.529983D+03	0.457864D+01	0.169932D+01
yyx	-0.415220D+04	-0.358718D+02	-0.133135D+02
zxx	-0.124216D+01	-0.107313D-01	-0.398283D-02
zyx	0.159017D+04	0.137378D+02	0.509864D+01
zzx	-0.414181D+03	-0.357820D+01	-0.132801D+01
xxy	0.346128D+03	0.299028D+01	0.110981D+01
yxy	-0.353883D+04	-0.305728D+02	-0.113468D+02
yyy	-0.556508D+05	-0.480780D+03	-0.178437D+03
zxy	0.148023D+04	0.127880D+02	0.474615D+01
zyy	-0.332604D+03	-0.287344D+01	-0.106645D+01
zzy	0.141088D+04	0.121889D+02	0.452381D+01
xxz	0.227702D+02	0.196717D+00	0.730096D-01
yxz	0.156609D+04	0.135298D+02	0.502144D+01
yyz	-0.106298D+04	-0.918334D+01	-0.340831D+01
zxz	-0.417509D+03	-0.360695D+01	-0.133869D+01
zyz	0.153491D+04	0.132605D+02	0.492149D+01
zzz	-0.274607D+03	-0.237239D+01	-0.880489D+00

Beta(-2w;w,w) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	0.263335D+03	0.227501D+01	0.844346D+00
_|_(z)	0.159897D+04	0.138138D+02	0.512687D+01
x	0.351115D+05	0.303336D+03	0.112580D+03
y	-0.290942D+06	-0.251352D+04	-0.932866D+03
z	0.131667D+04	0.113750D+02	0.422173D+01
||	0.586113D+05	0.506356D+03	0.187929D+03
xxx	0.173320D+05	0.149735D+03	0.555725D+02
yxx	0.226558D+04	0.195729D+02	0.726428D+01
zxx	-0.238182D+03	-0.205771D+01	-0.763699D+00
xyx	0.866372D+03	0.748478D+01	0.277790D+01
yyx	-0.637306D+04	-0.550583D+02	-0.204343D+02
zyx	0.215738D+04	0.186381D+02	0.691734D+01
xyy	-0.228527D+04	-0.197429D+02	-0.732739D+01
yyy	-0.100351D+06	-0.866957D+03	-0.321763D+03
zyy	0.416943D+04	0.360207D+02	0.133687D+02
xzx	-0.676349D+02	-0.584313D+00	-0.216862D+00
yzx	0.273507D+04	0.236289D+02	0.876962D+01
zzx	-0.622205D+03	-0.537536D+01	-0.199501D+01
xzy	0.196618D+04	0.169863D+02	0.630429D+01
yzy	-0.534684D+03	-0.461925D+01	-0.171439D+01
zzy	0.177498D+04	0.153344D+02	0.569123D+01
xzz	-0.608627D+03	-0.525807D+01	-0.195148D+01
yzz	0.256334D+04	0.221452D+02	0.821899D+01
zzz	-0.469980D+03	-0.406026D+01	-0.150693D+01

Compound **1c**: First dipole hyperpolarizability, Beta (input orientation). ||, _|_ parallel and perpendicular components, (z) with respect to z axis, vector components x,y,z. Values do not include the 1/n! factor of 1/2. (esu units = statvolt**-1 cm**4 , SI units = C**3 m**3 J**-2)

Beta(0;0,0):	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	0.266110D+04	0.229898D+02	0.853244D+01
_|_(z)	0.887033D+03	0.766327D+01	0.284415D+01
x	0.129256D+05	0.111667D+03	0.414441D+02
y	-0.128893D+06	-0.111354D+04	-0.413278D+03
z	0.133055D+05	0.114949D+03	0.426622D+02
||	0.260442D+05	0.225002D+03	0.835072D+02
xxx	0.111692D+05	0.964933D+02	0.358125D+02
xxy	-0.460960D+03	-0.398234D+01	-0.147800D+01
yxy	-0.688411D+04	-0.594734D+02	-0.220730D+02
yyy	-0.431315D+05	-0.372623D+03	-0.138295D+03
xxz	0.131154D+04	0.113307D+02	0.420529D+01
yxz	-0.976561D+03	-0.843673D+01	-0.313121D+01
yyz	0.313962D+04	0.271239D+02	0.100668D+02
zxz	0.234258D+02	0.202381D+00	0.751117D-01
zyz	0.628119D+03	0.542646D+01	0.201398D+01
zzz	-0.160008D+02	-0.138235D+00	-0.513044D-01

Beta(-w;w,0) w= 1550.0nm:			
	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	0.297413D+04	0.256941D+02	0.953612D+01
_|_(z)	0.119203D+04	0.102982D+02	0.382209D+01
x	0.129077D+05	0.111513D+03	0.413868D+02
y	-0.161892D+06	-0.139862D+04	-0.519084D+03
z	0.148706D+05	0.128471D+03	0.476806D+02
||	0.326170D+05	0.281786D+03	0.104582D+03
xxx	0.124369D+05	0.107445D+03	0.398772D+02
yxx	-0.328400D+03	-0.283712D+01	-0.105297D+01
yyx	-0.866174D+04	-0.748307D+02	-0.277727D+02
zxx	0.147489D+04	0.127419D+02	0.472904D+01
zyx	-0.116058D+04	-0.100265D+02	-0.372124D+01
zzx	0.237245D+02	0.204961D+00	0.760693D-01
xxy	-0.485994D+03	-0.419861D+01	-0.155827D+01
yxy	-0.789970D+04	-0.682473D+02	-0.253293D+02
yyy	-0.543125D+05	-0.469218D+03	-0.174146D+03
zxy	-0.110622D+04	-0.955688D+01	-0.354694D+01
zyy	0.328524D+04	0.283819D+02	0.105337D+02

zzy	0.694980D+03	0.600409D+01	0.222836D+01
xxz	0.147071D+04	0.127058D+02	0.471561D+01
yxz	-0.113495D+04	-0.980505D+01	-0.363905D+01
yyz	0.389140D+04	0.336187D+02	0.124772D+02
zxz	0.172292D+02	0.148847D+00	0.552431D-01
zyz	0.746659D+03	0.645055D+01	0.239406D+01
zzz	-0.391187D+01	-0.337955D-01	-0.125429D-01

Beta(-2w;w,w) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	0.385253D+04	0.332828D+02	0.123526D+2
_|_(z)	0.883120D+01	0.762947D-01	0.283160D-01
x	0.951456D+04	0.821984D+02	0.305071D+02
y	-0.292515D+06	-0.252710D+04	-0.937909D+03
z	0.192626D+05	0.166414D+03	0.617630D+02
||	0.586606D+05	0.506782D+03	0.188087D+03
xxx	0.157932D+05	0.136441D+03	0.506388D+02
yxx	0.967114D+03	0.835511D+01	0.310092D+01
zxx	0.195844D+04	0.169194D+02	0.627948D+01
xyx	-0.240061D+03	-0.207394D+01	-0.769722D+00
yyx	-0.143132D+05	-0.123655D+03	-0.458932D+02
zyx	-0.167915D+04	-0.145065D+02	-0.538395D+01
xyy	-0.924247D+04	-0.798477D+02	-0.296347D+02
yyy	-0.987459D+05	-0.853088D+03	-0.316615D+03
zyy	0.187774D+04	0.162222D+02	0.602071D+01
xzx	0.190586D+04	0.164651D+02	0.611087D+01
yzx	-0.185112D+04	-0.159922D+02	-0.593535D+01
zzx	0.695599D+01	0.600943D-01	0.223034D-01
xzy	-0.148582D+04	-0.128364D+02	-0.476409D+01
yzy	0.575636D+04	0.497304D+02	0.184570D+02
zzy	0.973012D+03	0.840606D+01	0.311983D+01
xzz	-0.102476D+02	-0.885309D-01	-0.328574D-01
yzz	0.128976D+04	0.111425D+02	0.413543D+01
zzz	0.340056D+02	0.293782D+00	0.109034D+00

Compound **5**: First dipole hyperpolarizability, Beta (dipole orientation). ||, _|_ parallel and perpendicular components, (z) with respect to z axis, vector components x,y,z. Values do not include the 1/n! factor of 1/2. (esu units = statvolt**-1 cm**4 , SI units = C**3 m**3 J**-2)

Beta(0;0,0):

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.228574D+05	-0.197470D+03	-0.732890D+02
_|_(z)	-0.761913D+04	-0.658233D+02	-0.244297D+02
x	0.275298D+05	0.237836D+03	0.882705D+02
y	-0.569250D+05	-0.491788D+03	-0.182522D+03
z	-0.114287D+06	-0.987350D+03	-0.366445D+03
||	0.261227D+05	0.225680D+03	0.837587D+02
xxx	0.169573D+03	0.146498D+01	0.543713D+00
xxy	-0.432330D+03	-0.373500D+01	-0.138621D+01
yxy	0.101980D+04	0.881028D+01	0.326985D+01
yyy	-0.234816D+04	-0.202862D+02	-0.752904D+01
xxz	-0.139888D+04	-0.120853D+02	-0.448533D+01
yxz	0.315301D+04	0.272396D+02	0.101097D+02
yyz	-0.658393D+04	-0.568800D+02	-0.211105D+02
zxz	0.798723D+04	0.690034D+02	0.256099D+02
zyz	-0.161945D+05	-0.139908D+03	-0.519255D+02
zzz	-0.301128D+05	-0.260151D+03	-0.965526D+02

Beta(-w;w,0) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.288830D+05	-0.249526D+03	-0.926093D+02
_|_(z)	-0.954096D+04	-0.824265D+02	-0.305918D+02
x	0.337475D+05	0.291552D+03	0.108207D+03
y	-0.699256D+05	-0.604103D+03	-0.224207D+03
z	-0.144415D+06	-0.124763D+04	-0.463046D+03
||	0.327928D+05	0.283304D+03	0.105145D+03
xxx	0.212510D+03	0.183592D+01	0.681383D+00
yxx	-0.530668D+03	-0.458456D+01	-0.170151D+01
yyx	0.124367D+04	0.107443D+02	0.398765D+01
zxx	-0.170728D+04	-0.147496D+02	-0.547417D+01
zyx	0.385200D+04	0.332783D+02	0.123509D+02
zzx	0.100805D+05	0.870876D+02	0.323217D+02
xxy	-0.533624D+03	-0.461009D+01	-0.171099D+01
yxy	0.124328D+04	0.107410D+02	0.398640D+01
yyy	-0.283939D+04	-0.245301D+02	-0.910411D+01
zxy	0.383999D+04	0.331745D+02	0.123124D+02

zyy	-0.806099D+04	-0.696407D+02	-0.258464D+02
zzy	-0.204936D+05	-0.177049D+03	-0.657100D+02
xxz	-0.167301D+04	-0.144535D+02	-0.536427D+01
yxz	0.374353D+04	0.323412D+02	0.120031D+02
yyz	-0.783517D+04	-0.676898D+02	-0.251224D+02
zxz	0.964960D+04	0.833651D+02	0.309401D+02
zyz	-0.196594D+05	-0.169842D+03	-0.630352D+02
zzz	-0.384567D+05	-0.332236D+03	-0.123306D+03

Beta(-2w;w,w) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.526975D+05	-0.455266D+03	-0.168967D+03
_|_(z)	-0.181283D+05	-0.156614D+03	-0.581257D+02
x	0.573511D+05	0.495469D+03	0.183888D+03
y	-0.119404D+06	-0.103155D+04	-0.382851D+03
z	-0.263488D+06	-0.227633D+04	-0.844837D+03
||	0.589821D+05	0.509559D+03	0.189118D+03
xxx	0.373999D+03	0.323106D+01	0.119918D+01
yxx	-0.890290D+03	-0.769141D+01	-0.285459D+01
zxx	-0.297045D+04	-0.256624D+02	-0.952435D+01
xyx	-0.906241D+03	-0.782922D+01	-0.290574D+01
yyx	0.206839D+04	0.178692D+02	0.663199D+01
zyx	0.671473D+04	0.580101D+02	0.215299D+02
xyy	0.206375D+04	0.178292D+02	0.661713D+01
yyy	-0.463807D+04	-0.400693D+02	-0.148713D+02
zyy	-0.142168D+05	-0.122822D+03	-0.455843D+02
xzx	-0.274192D+04	-0.236881D+02	-0.879159D+01
yzx	0.609406D+04	0.526479D+02	0.195397D+02
zzx	0.175908D+05	0.151971D+03	0.564026D+02
xzy	0.601575D+04	0.519714D+02	0.192887D+02
yzy	-0.127581D+05	-0.110220D+03	-0.409071D+02
zzy	-0.360355D+05	-0.311319D+03	-0.115543D+03
xzz	0.148469D+05	0.128265D+03	0.476045D+02
yzz	-0.307156D+05	-0.265359D+03	-0.984852D+02
zzz	-0.717668D+05	-0.620009D+03	-0.230110D+03

***para*-Nitroaniline:** First dipole hyperpolarizability, Beta (dipole orientation). ||, _|_ parallel and perpendicular components, (z) with respect to z axis, vector components x,y,z. Values do not include the 1/n! factor of 1/2. (esu units = statvolt**-1 cm**4 , SI units = C**3 m**3 J**-2)

Beta(0;0,0):

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.194795D+04	-0.168288D+02	-0.624583D+01
_|_(z)	-0.649317D+03	-0.560959D+01	-0.208194D+01
x	-0.115397D+04	-0.996937D+01	-0.370003D+01
y	-0.110623D+03	-0.955699D+00	-0.354698D+00
z	-0.973975D+04	-0.841438D+02	-0.312292D+02
||	0.196170D+04	0.169476D+02	0.628992D+01
xxx	-0.324037D+01	-0.279943D-01	-0.103898D-01
xxy	-0.453617D+01	-0.391890D-01	-0.145446D-01
yxy	0.214020D+02	0.184896D+00	0.686225D-01
yyy	0.627721D+01	0.542302D-01	0.201270D-01
xxz	-0.363821D+02	-0.314313D+00	-0.116654D+00
yxz	-0.323894D+02	-0.279819D+00	-0.103852D+00
yyz	0.298383D+03	0.257780D+01	0.956724D+00
zxz	-0.402817D+03	-0.348003D+01	-0.129158D+01
zyz	-0.386155D+02	-0.333608D+00	-0.123815D+00
zzz	-0.350858D+04	-0.303114D+02	-0.112498D+02

Beta(-w;w,0) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.173458D+04	-0.149855D+02	-0.556170D+01
_|_(z)	-0.581913D+03	-0.502728D+01	-0.186582D+01
x	-0.102938D+04	-0.889303D+01	-0.330056D+01
y	-0.986798D+02	-0.852517D+00	-0.316403D+00
z	-0.867292D+04	-0.749273D+02	-0.278085D+02
||	0.174687D+04	0.150916D+02	0.560110D+01
xxx	-0.281802D+01	-0.243455D-01	-0.903558D-02
yxx	-0.382770D+01	-0.330684D-01	-0.122730D-01
yyx	0.175371D+02	0.151507D+00	0.562303D-01
zxx	-0.319758D+02	-0.276246D+00	-0.102526D+00
zyx	-0.284558D+02	-0.245836D+00	-0.912395D-01
zzx	-0.357687D+03	-0.309014D+01	-0.114687D+01
xxy	-0.391904D+01	-0.338574D-01	-0.125659D-01
yxy	0.184899D+02	0.159738D+00	0.592852D-01
yyy	0.533006D+01	0.460476D-01	0.170901D-01
zxy	-0.284558D+02	-0.245836D+00	-0.912395D-01

zyy	0.262133D+03	0.226462D+01	0.840493D+00
zzy	-0.342891D+02	-0.296232D+00	-0.109943D+00
xxz	-0.320549D+02	-0.276930D+00	-0.102780D+00
yxz	-0.273917D+02	-0.236643D+00	-0.878276D-01
yyz	0.251056D+03	0.216892D+01	0.804975D+00
zxz	-0.358877D+03	-0.310042D+01	-0.115069D+01
zyz	-0.344032D+02	-0.297217D+00	-0.110309D+00
zzz	-0.311741D+04	-0.269320D+02	-0.999555D+01

Beta(-2w;w,w) w= 1550.0nm:

	(au)	(10**-30 esu)	(10**-50 SI)
|| (z)	-0.189002D+04	-0.163283D+02	-0.606009D+01
_|_(z)	-0.618126D+03	-0.534013D+01	-0.198194D+01
x	-0.110847D+04	-0.957633D+01	-0.355416D+01
y	-0.106262D+03	-0.918021D+00	-0.340714D+00
z	-0.945010D+04	-0.816415D+02	-0.303004D+02
||	0.190310D+04	0.164413D+02	0.610202D+01
xxx	-0.305268D+01	-0.263728D-01	-0.978799D-02
yxx	-0.365855D+01	-0.316071D-01	-0.117306D-01
zxx	-0.339968D+02	-0.293706D+00	-0.109006D+00
xyx	-0.401262D+01	-0.346659D-01	-0.128659D-01
yyx	0.170098D+02	0.146951D+00	0.545395D-01
zyx	-0.302062D+02	-0.260958D+00	-0.968521D-01
xyy	0.207032D+02	0.178860D+00	0.663821D-01
yyy	0.535060D+01	0.462250D-01	0.171560D-01
zyy	0.278204D+03	0.240346D+01	0.892022D+00
xzx	-0.349041D+02	-0.301544D+00	-0.111915D+00
yzx	-0.269334D+02	-0.232684D+00	-0.863583D-01
zzx	-0.385063D+03	-0.332664D+01	-0.123465D+01
xzy	-0.269334D+02	-0.232684D+00	-0.863583D-01
yzy	0.243470D+03	0.210339D+01	0.780653D+00
zzy	-0.369135D+02	-0.318904D+00	-0.118358D+00
xzz	-0.383910D+03	-0.331669D+01	-0.123096D+01
yzz	-0.368030D+02	-0.317949D+00	-0.118004D+00
zzz	-0.337048D+04	-0.291183D+02	-0.108070D+02

CHAPTER TWO EXPERIMENTAL

Materials and Methods: All reagents and starting materials were purchased from commercial suppliers and used as received, unless otherwise stated. All reactions were carried out under nitrogen atmosphere in flame-dried glassware, unless otherwise stated. External oil bath temperatures were used to record reaction mixture temperatures. Reaction solvents tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane, diisopropylamine, trifluoromethylbenzene and toluene were distilled from CaH_2 under nitrogen. Solvents for filtrations, transfers, and chromatography were certified ACS grade. All other materials were used as received from commercial sources. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm) or potassium permanganate staining. Flash chromatographic columns were hand-packed with silica gel 60 as a slurry in the initial elution solvent. Nuclear magnetic resonance (NMR) data were obtained at 300 MHz or 500 MHz. Infrared spectra (IR) were obtained from a FTIR-4100. High-resolution mass spectra (HRMS) were obtained from TOF instrumentation.

Optimized experimental for PDTC production: A 100-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with pyridine-2, 6-dicarbonyl dichloride (1.5 g, 7.35 mmol, 1.0 equiv) and tetra-n-butylammonium bromide (237 mg, 0.735 mmol, 0.1 equiv). The reaction vessel was then placed under vacuum and back-filled with nitrogen (3x)

followed by the addition of dry methylene chloride (30 mL). The solution was stirred and cooled to 0 ºC for the dropwise addition of sodium hydrosulfide (3.63 mL, 32.34 mmol, 4.4 equiv, sat. solution in water, 8.92M). The mixture was stirred vigorously at 0 ºC for 1h then warmed to 23 ºC and stirring continued overnight. The inorganic solid (NaCl) formed was dissolved using a minimal amount of degassed half brine solution (aq) and the biphasic mixture was acidified with hydrochloric acid (1M) until the aqueous layer was about pH 1.8 (pH paper). The biphasic solution was separated and the aqueous layer was extracted with dry/degassed methylene chloride (3 x 15 mL, under a cone of flowing nitrogen) checking the aqueous solution stayed pH 1.8 between each extraction. The organic layers were combined, washed with degassed brine, dried over Na_2SO_4, filtered and concentrated in vacuo (back-filling with nitrogen). The solid residue was dissolved using a minimal amount of dry chloroform (passed through an alumina plug) and then pushed through a pipette plug of silica, washing with dry chloroform several times. This process should be repeated at least twice for clean PDTC. The solution was then concentrated in vacuo (back-filling with nitrogen) furnishing pure pyridine dithiocaboxylic acid (PDTC) as an off-white solid. All spectral and analytical data was consistent with those previously reported for this compound.[6]

Development of the dilithiohalogen exchange by synthesis of pyridine-2,6-bis(trimethylsilane): A 5-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with 2,6-dibromopyridine (62 mg, 0.262 mmol, 1.0 equiv) and dry diethyl ether (1.0 mL). The mixture was cooled to -78 ºC, at which point microcrystallization of the starting material

was observed. To this heterogeneous solution was added *n*-butyllithium (0.17 mL, 0.537 mmol, 2.05 equiv, 3.122M solution in hexanes) dropwise over the course of 5 min. The mixture was stirred at the same temperature until a homogeneous pale-yellow solution was remained (15 min), then chlorotrimethylsilane (0.15 mL, 1.153 mmol, 4.4 equiv) was added and the solution was warmed to 23 ºC and stirred for 1h. The resulting light-brown suspension was diluted with Et_2O (5 mL) and washed with water (2 x 5 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to yield 55 mg (94%) of a light-beige solid. All spectral and analytical data was consistent with those previously reported for this compound.[7]

Construction of pyridine-2,6-bis(monothiocarboxyl)-*S*-methyl-ester using the novel dilithiohalogen exchange with direct thiocarboxylation procedure: A 5-mL round-bottomed flask (flask A), equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with 2,6-dibromopyridine (55 mg, 0.232 mmol, 1.0 equiv) and dry diethyl ether (0.93 mL). The mixture was cooled to -78 ºC, at which point microcrystallization of the starting material was observed. To this heterogeneous solution was added *n*-butyllithium (0.15 mL, 0.476 mmol, 2.05 equiv, 3.122M solution in hexanes) dropwise over the course of 5 min. The mixture was stirred at the same temperature until a homogeneous pale-yellow solution was remained (15 min). While the contents of flask A stirred, a second 25-mL round-bottomed flask (flask B) was equipped with a magnetic stirrer, flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with THF (6 mL) and cooled to -78 ºC for the gaseous addition of carbonyl sulfide. Greater than 10 equiv of carbonyl sulfide was bubbled into

the chilled THF solution, as determined by weight difference. After the 15 min of stirring for the contents of flask A was complete, a thick-walled Teflon cannula was threaded between flask A and B. The contents of flask A were quickly transferred into flask B by force-pressure cannulation. If done quick enough the resulting solution will be a light yellow-orange color, any other coloration or darkness reveals an unsuccessful addition. The solution was then slowly warmed to 23 ºC and the volatiles were removed in vacuo and the flask was recharged with nitrogen. The yellow solid was then dissolved in Et_2O (5 mL) and iodomethane (145 mg, 1.021 mmol, 4.4 equiv) was added and the solution was allowed to stir for 1h. The ethereal solution was washed with water (2 x 5 mL), the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to yield 43.2 mg (82%) of an off-white solid. All spectral and analytical data was consistent with those previously reported for this compound.[8,9]

Synthesis of the functionalized dibromides

2,6-Dibromocitracinic acid (2): A 100-mL round-bottomed flask, equipped with a magnetic stirrer and Liebig condeser, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with citrazinic acid (3.0 g, 19.34 mmol) and phosphorus oxybromide (16.63 g, 58.02 mmol, 3.0 equiv) then heated at 150 °C for 18h. After cooling to 23 ºC, the mixture was carefully quenched with DI water (10 mL), heated to reflux and cooled to 23 ºC. The resulting precipitate was filtered, washed with water and after drying, used without further purification (4.48 g, 83%). All spectral and analytical data was consistent with those previously reported for this compound.[10]

(2,6-Dibromopyridin-4-yl)methanol (3): A 50-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with 2.02 g of 2,6-dibromocitracinic acid **(2)** (7.19 mmol, 1.0 equiv) was dissolved in dry THF (22 mL) under inerst atmosphere and cooled to 0 °C. At that temperature, a solution of BH_3•DMS-complex (10.0 M in DMS, 1.08 ml, 10.79 mmol, 1.5 equiv) was added, and the mixture was stirred at 23 ºC for an additional 4h. The reaction was quenched by the addition of 5 mL THF/H_2O (1:1 v/v), the pH adjusted to 9 by saturated K_2CO_3 -solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and the solvent was removed in vacuo, yielding without further purification (2,6-dibromopyridin-4-yl)methanol as a white solid (1.84 g, 96%). All spectral and analytical data was consistent with those previously reported for this compound.[10]

2,6-Dibromopyridin-4-yl)methoxy-*tert*-butyldimethylsilyl-ether: The title compound was prepared according to the standard procedure for protecting alcohols with chloro-*tert*-butyldimethylsilane (TBDMSCl).[11] A 10-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with (2,6-dibromopyridin-4-yl)methanol (0.436 g, 1.63 mmol), TBDMSCl (0.295 g, 1.96 mmol, 1.2 equiv), imidazole (0.278 g, 4.08 mmol, 2.5 equiv) and freshly distilled dimethylformamide (0.9 mL). The reaction was allowed to stir at 23 ºC for 5h, and then the mixture was diluted with Et_2O (5 mL) and washed with DI water (3 x 5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 5 mL), the organic layers were combined, washed with brine (5 mL), dried with Na_2SO_4,

filtered, and concentrated to yield 0.62 g (*quantative*) of the title compound. **^{1}H NMR** (300 MHz; $CDCl_3$): δ 7.43 (s, 2H), 4.70 (s, 2H), 0.97 (s, 9H), 0.14 (s, 6H). **^{13}C NMR** (75 MHz; $CDCl_3$): δ 156.3, 140.7, 124.0, 62.5, 25.9, 18.4, -5.3. **HRMS** (ESI): Calcd for $C_{12}H_{19}Br_2NOSi$ $[M+H]^+$: 379.9683, found 379.9761.

CHAPTER FOUR EXPERIMENTAL

General Remarks. Materials and Methods: Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. J. Young NMR experiments were performed under an argon atmosphere, using standard Schlenk line techniques or in an argon-filled dry-box. THF and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane, diisopropylamine, trifluoromethylbenzene and toluene were distilled from CaH_2 under nitrogen. Benzene and *p*-xylene were distilled from potassium metal. All other materials were used as received from commercial sources. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm) or potassium permanganate staining. Flash chromatographic columns were hand-packed with silica gel 60 as a slurry in the initial elution solvent. Nuclear magnetic resonance (NMR) data were obtained at 300 MHz or 500 MHz. Infrared spectra (IR) were obtained from a FTIR-4100. High-resolution mass spectra (HRMS) were obtained from TOF instrumentation. Infrared spectrums were recorded neat and are reported in cm^{-1}.

(*E*)-2,2-Dimethyl-5-phenylpent-4-enal-*N*,*N*-dimethylhydrazone (3a). A 50-mL round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser and an N_2 inlet

was charged with (*E*)-2,2-dimethyl-5-phenylpent-4-enal[12] (3.66 g, 19.4 mmol) and benzene (15 mL) was subsequently added. The reactant mixture was cooled to 0 ºC and *N*,*N*-dimethylhydrazine (2.96 mL, 38.9 mmol) was added dropwise via syringe. The reactant mixture was heated to reflux for 12 h. After cooling, the resulting mixture was dried with $MgSO_4$ and filtered through a pad of Celite. The crude product was purified by bulb-to-bulb distillation (75 ºC, 0.5 torr) to afford 3.99g (89%) of the title compound as a clear oil. **^{1}H-NMR** (500 MHz, DMSO-d_6): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.63 (s, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.5, 7.7 Hz, 1H), 2.74 (s, 6H), 2.34 (d, *J* = 6.7 Hz, 2H), 1.14 (s, 6H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 146.3, 138.3, 132.6, 128.8, 127.8, 127.3, 126.4, 45.4, 43.8, 38.2, 26.5. **IR** (Film): 3025, 2957, 2906, 2864, 2820, 2782, 1598, 1495, 1468, 1444, 1019, 966, 740, 693, cm^{-1}. **HRMS** (ESI): Calcd for $C_{15}H_{22}N_2$ $[M+H]^+$: 231.1861, found 231.1883.

(*E*)-2-((E)-5-(2-Chlorophenyl)-2,2-dimethylpent-4-en-1-ylidene)-1,1-dimethylhydrazone ($3a_{cl}$). A 50-mL round-bottom flask equipped with a magnetic stirring bar and an N_2 inlet was charged with diisopropyl amine (0.981 mL, 7.00 mmol) followed by THF (10 mL). The resulting mixture was cooled to 0 ºC and *n*-butyllithium (2.21 mL, 3.10 M in hexane) was added and the solution was allowed to stir for 30 min at this temperature. A solution of *N*-(tert-butyl)-2-methylpropan-1-imine (0.890 g, 7.00 mmol) in THF (2 mL) was added dropwise via syringe and the reaction mixture was warmed to 23 ºC. After 2 h the resulting yellow solution was cooled to -78 ºC and (*E*)-1-chloro-2-(3-chloroprop-1-en-1-yl)benzene (1.40 g, 7.50 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to 23 ºC and stirred at this

temperature for 12 h. The resulting homogenous solution was diluted with ether (25 mL) and quenched with NH_4Cl (*aq*) (10 mL). The organic layer was washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude imine was immediately dissolved in THF (15 mL) and a solution of oxalic acid (1.01 g, 8.00 mmol) in H_2O (5 mL) was added at 23 ºC. The reaction mixture was allowed to stir for 2 h and subsequently diluted with diethyl ether (25 mL). The organic layer was washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude aldehyde was then dissolved in CH_2Cl_2 (10 mL) followed by *N,N*-dimethylhydrazine (0.841 g, 14.00 mmol) and $MgSO_4$. The solution was allowed to stir for 4 h, filtered through a plug of Celite and concentrated in vacuo. The crude hydrazone was purified by column chromatography on silica (5% EtOAc/Hex) to give (*E*)-2-((E)-5-(2-chlorophenyl)-2,2-dimethylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (1.13 g, 61%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.17 (td, *J* = 7.5, 1.4 Hz, 1H), 7.12 (td, *J* = 7.6, 1.8 Hz, 1H), 6.73 (d, *J* = 15.6 Hz, 1H), 6.57 (s, 1H), 6.19 (dt, *J* = 15.4, 7.6 Hz, 1H), 2.70 (s, 6H), 2.34 (dd, *J* = 7.5, 1.4 Hz, 2H), 1.10 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.5, 135.9, 132.5, 130.5, 129.5, 128.5, 127.8, 126.8, 126.6, 45.1, 43.40, 37.8, 26.2. **IR** (Film) 2948, 2734, 1566, 1457, 1434, 1251, 1025, 751 **HRMS** (ESI): Calcd for $C_{15}H_{22}ClN_2$ $[M+H]^+$: 265.1472, found: 265.1457.

(*E*)-2-((*E*)-5-(2-Fluorophenyl)-2,2-dimethylpent-4-en-1-ylidene)-1,1-dimethylhydrazone ($3a_F$). The title compound was synthesized by the general procedure for hydrazone $\mathbf{3a_{Cl}}$, utilizing *N*-(tert-butyl)-2-methylpropan-1-imine (1.00 g,

7.86 mmol) and (E)-1-(3-chloroprop-1-en-1-yl)-2-fluorobenzene (1.48 g, 8.65 mmol). The crude hydrazone was purified by column chromatography on silica (5% EtOAc/Hex) to give (*E*)-2-((*E*)-5-(2-fluorophenyl)-2,2-dimethylpent-4-en-1-ylidene)-1,1-dimethylhydrazine (1.13 g, 59%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (td, *J* = 7.7, 1.8 Hz, 1H), 7.14 (ddd, *J* = 7.3, 5.4, 1.9 Hz, 1H), 7.05 (td, *J* = 7.5, 1.2 Hz, 1H), 6.99 (ddd, *J* = 10.9, 8.1, 1.2 Hz, 1H), 6.58 (s, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.29 (dt, *J* = 16.0, 7.5 Hz, 1H), 2.70 (s, 6H), 2.33 (dd, *J* = 7.5, 1.3 Hz, 2H), 1.10 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9 (d, 1JC-F = 247.8), 145.6, 130.2, 128.1, 128.0, 127.1, 124.5, 123.9, 115.7, 115.5, 45.4, 43.4, 37.8, 26.1. **IR** (Film) 3040, 2957, 2922, 2864, 2782, 1486, 1468, 1229, 1020, 970, 753 cm^{-1} **HRMS** (ESI): Calcd for $C_{15}H_{21}FN_2$ $[M+H]^+$: 249.1768, found: 249.1746.

(*E*)-2-((*E*)-5-Cyclopropyl-2,2-dimethylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (3b). A 100-mL multinecked round-bottomed flask, equipped with a magnetic stirrer, addition funnel and rubber septum, was flame-dried under vacuum then back-filled with a nitrogen atmosphere. The flask was charged with nitrile **4** (1.0 g, 6.7 mmol) and dry CH_2Cl_2 (25 mL) then cooled to -78 ºC for the dropwise addition of DIBAL-H (13.4 mL, 13.4 mmol, 1.0 M in hexanes) via the addition funnel. The solution was allowed to stir at -78 ºC for 1 h then slowly warmed to 23 ºC over 3 h. Once the reaction was complete, the solution was chilled to 0 ºC, quenched with methanol (5 mL), diluted with Et_2O (20 mL) and 1.0 M HCl was slowly added until all the precipitate was dissolved. The biphasic solution was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$, and

concentrated in vacuo. The crude aldehyde was transferred into a 50-mL round-bottomed flask, equipped with a magnetic stirrer, and redissolved in dry CH_2Cl_2 (25 mL). A small amount of $MgSO_4$ was added to the solution prior to the dropwise addition of N,N-dimethylhydrazine (1.02 mL, 13.4 mmol) via syringe. The reaction mixture was stirred for 2 h at 23 ºC then diluted with dry Et_2O (20 mL) and filtered through a plug of Celite, washing with Et_2O (3 x 15 mL). The solution was concentrated in vacuo and purified via kugelrohr distillation (75 ºC at 1.0 torr) from CaH_2 to provide the title compound (1.20 g, 92%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.52 (s, 1H), 5.45 (dt, *J* = 14.9, 7.4 Hz, 1H), 4.98 – 4.87 (m, 1H), 2.73 – 2.60 (m, 6H), 2.11 – 1.94 (m, 2H), 1.32 (dt, *J* = 9.0, 4.5 Hz, 1H), 0.99 (d, *J* = 8.1 Hz, 6H), 0.65 – 0.57 (m, 2H), 0.30 – 0.23 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.7, 136.6, 124.0, 44.6, 43.5, 37.4, 25.7, 24.6, 13.5, 6.4. **IR** (Film) 3001, 2956, 2864, 1468, 1443, 1249, 1019, 963, 810, 587, 526 cm^{-1}. **HRMS** (ESI): Calcd for $C_{12}H_{22}N_2$ $[M+H]^+$: 195.1862, found 195.1883.

(*E*)-2-((Z)-6-(Benzyloxy)-2,2-dimethylhex-4-en-1-ylidene)-1,1-dimethylhydrazone (3c). The title compound was synthesized by the general method of hydrazone **3a$_{Cl}$** utilizing *N*-(tert-butyl)-2-methylpropan-1-imine (1.09 g, 8.60 mmol) and (Z)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene (2.29 g, 9.50 mmol) to yield (E)-2-((Z)-6-(benzyloxy)-2,2-dimethylhex-4-en-1-ylidene)-1,1-dimethylhydrazone (1.58 g, 67%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.3 Hz, 4H), 7.29 – 7.25 (m, 1H), 6.49 (s, 1H), 5.71 – 5.57 (m, 2H), 4.49 (s, 2H), 4.06 (d, *J* = 6.1 Hz, 2H), 2.67 (s, 6H), 2.13 (d, *J* = 7.3 Hz, 2H), 1.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.3, 138.4, 131.2, 129.8, 129.0, 128.3, 127.9, 127.8, 127.5, 72.2, 66.0, 43.3, 39.1, 37.6, 26.0. **IR**

(Film) 2956, 2926, 2853, 1468, 1444, 1098, 1072, 1026, 1010, 735, 698 cm^{-1}. **HRMS** (ESI): Calcd for $C_{17}H_{26}N_2O$ $[M+H]^+$: 275.2124, found 275.2115.

(*E*)-5-Cyclopropyl-2,2-dimethylpent-4-enenitrile (4). A 50-mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet was charged with diisopropylamine (0.920 g, 9.09 mmol) and THF (25 mL). The reaction mixture was cooled to 0 ºC and *n*-butyllithium (3.03 mL, 3.0M, 9.09 mmol) was added dropwise via syringe. The resulting solution was allowed to stir at this temperature for 30 min and then cooled to -78 ºC and isobutyronitrile (0.621 g, 9.00 mmol) was added dropwise via syringe and the reaction mixture was stirred for an additional 2 h at this temperature. A solution of (E)-(3-chloroprop-1-en-1-yl)cyclopropane (1.19 g, 10.2 mmol) in THF (2 mL) was added all at once and the reaction mixture was allowed to slowly warm to 23 ºC over 3 h. The reaction was quenched with aqueous NH_4Cl (5 mL) and diluted with diethyl ether (25 mL). The organic layer was washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude nitrile was purified by column chromatography on silica (5% - 15% EtOAc/Hex) to yield the title compound (1.52 g, 87%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.60 – 5.51 (m, 1H), 5.12 (ddt, *J* = 15.1, 8.6, 1.3 Hz, 1H), 2.20 (dd, *J* = 7.4, 1.2 Hz, 2H), 1.44 – 1.38 (m, 1H), 1.32 (s, 6H), 0.76 – 0.67 (m, 2H), 0.38 (dt, *J* = 6.4, 4.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.6, 125.0, 120.9, 43.8, 32.6, 26.1, 13.5, 6.7. **IR** (Film) 3005, 2987, 2933, 2234, 1662, 1468, 1459, 1021, 966. **HRMS** (ESI): Calcd for $C_{10}H_{15}N$ $[M+H]^+$: 150.1283, found 150.1289.

(*E*)-2-((*E*)-(2,2-Dimethyl-5-phenylpent-4-en-1-yl)-1,1-dimethylhydrazine (5a). A 100-mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet was charged with hydrazone **3a** (0.60g, 2.60 mmol) and methanol 30 mL was subsequently added. Sodium cyanoborohydride (0.18g, 2.87 mmol) was added in one portion and the solution was titrated with HCl:MeOH (methyl orange indicator, 20% v/v) until a light red color persisted. The reactant mixture was stirred for 30 min and the volatiles were removed in vacuo. The crude salt was neutralized with aqueous NaOH (25% w/v) to a pH of 11 and the crude product extracted with diethyl ether (3 x 10 mL). The organic layer was dried with $MgSO_4$, filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by bulb-to-bulb distillation (75-80 ºC, 0.5 torr) to afford 0.52 g (85%) of the title compound. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.43 (dt, *J* = 15.7, 7.5 Hz, 1H), 2.66 (s, 2H), 2.36 (s, 6H), 2.29 (d, *J* = 7.5 Hz, 2H), 1.78 (s, 1H), 1.07 (s, 6H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 138.6, 132.8, 128.9, 128.0, 127.3, 126.6, 59.2, 47.9, 44.3, 35.3, 26.2. **IR** (Film): 3197, 3025, 2949, 2835, 2764, 1494, 1474, 1448, 966, 692. **HRMS** (ESI): Calcd for $C_{15}H_{24}N_2$ $[M+H]^+$: 233.2018, found 233.2045.

(*E*)-2-(5-(2-Chlorophenyl)-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine ($5a_{Cl}$). The title compound was synthesized by the general reduction procedure of **5a** utilizing hydrazone **$3a_{Cl}$** (0.794 g, 3.00 mmol) and $NaBH_3CN$ (0.375 g, 6.00 mmol) to yield (E)-2-(5-(2-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.640 g, 80%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (td, *J* = 7.7, 1.8 Hz, 1H), 7.13 (tdd, *J* = 7.2, 5.1, 1.8 Hz, 1H), 7.04 (td, *J* = 7.5, 1.3 Hz, 1H), 6.98 (ddd, *J* = 10.9, 8.1, 1.3 Hz, 1H),

6.52 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.58 (s, 2H), 2.45 – 2.38 (m, 6H), 2.16 (dd, *J* = 7.6, 1.3 Hz, 2H), 1.92 (s, 1H), 0.92 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 130.5, 128.0, 127.9, 127.1, 124.3, 123.9, 115.7, 115.5, 58.7, 47.8, 44.2, 34.6, 25.8. **IR** (Film) 2950, 2832, 1489, 1223, 979, 741 cm^{-1}. **HRMS** (ESI): Calcd for $C_{15}H_{23}ClN_2$ $[M+H]^+$: 266.1550, found: 266.1562.

(*E*)-2-(5-(2-Fluorophenyl)-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine ($5a_F$). The title compound was synthesized by the general reduction procedure of **5a** utilizing hydrazone **$3a_F$** (0.751 g, 3.00 mmol) and $NaBH_3CN$ (0.375 g, 6.00 mmol) to yield (E)-2-(5-(2-fluorophenyl)-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.668 g, 89%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (td, *J* = 7.7, 1.8 Hz, 1H), 7.13 (tdd, *J* = 7.2, 5.1, 1.8 Hz, 1H), 7.04 (td, *J* = 7.5, 1.3 Hz, 1H), 6.98 (ddd, *J* = 10.9, 8.1, 1.3 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.58 (s, 2H), 2.45 – 2.38 (m, 6H), 2.16 (dd, *J* = 7.6, 1.3 Hz, 2H), 1.92 (s, 1H), 0.92 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9 (d, 1JC-F = 248.1), 130.5, 128.0, 127.9, 127.1, 124.3, 123.9, 115.7, 115.5, 58.7, 47.8, 44.2, 34.6, 25.8. **IR** (Film) 2952, 2837, 1486, 1455, 1229, 970, 753 cm^{-1}. **HRMS** (ESI): Calcd for $C_{15}H_{23}FN_2$ $[M+H]^+$: 251.1924, found: 251.1912.

(*E*)-2-(5-Cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (5b). The title compound was synthesized by the general reduction procedure of hydrazine **5a** utilizing hydrazone **3b** (0.988 g, 5.00 mmol) and $NaBH_3CN$ (0.628 g, 10.0 mmol) to yield (E)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.746 g, 76%) as a clear liquid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.45 (dt, *J* = 15.1, 7.5 Hz, 1H),

4.92 (dd, *J* = 15.1, 8.4 Hz, 1H), 2.48 (s, 2H), 2.36 (s, 6H), 1.84 (s, 2H), 1.30 (qt, *J* = 8.4, 4.8 Hz, 1H), 0.82 (s, 6H), 0.65 – 0.54 (m, 2H), 0.26 (dt, *J* = 6.3, 4.2 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.2, 124.3, 58.5, 47.7, 43.3, 34.0, 25.6, 24.6, 13.5, 6.3. **IR** (Film) **HRMS** (ESI): Calcd for $C_{12}H_{24}N_2$ $[M+H]^+$: 197.2018, found 197.2033.

(*Z*)-2-(6-(Benzyloxy)-2,2-dimethylhex-4-en-1-yl)-1,1-dimethylhydrazine (5c). The title compound was synthesized by the general reduction method of hydrazine **5a** utilizing hydrazone **3c** (1.00 g, 3.64 mmol) and $NaBH_3CN$ (0.458 g, 7.29 mmol) to yield **(**Z)-2-(6-(benzyloxy)-2,2-dimethylhex-4-en-1-yl)-1,1-dimethylhydrazine (0.916 g, 91%) as a clear oil. **^{1}H NMR** (500 MHz, DMSO) δ 7.33 (q, *J* = 3.9, 2.9 Hz, 4H), 7.26 (ddd, *J* = 7.3, 4.9, 2.3 Hz, 1H), 5.72 – 5.60 (m, 2H), 4.50 (s, 2H), 4.07 (d, *J* = 5.8 Hz, 2H), 2.51 (s, 2H), 2.38 (s, 6H), 1.99 (d, *J* = 7.0 Hz, 2H), 1.86 (s, 1H), 0.86 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.4, 130.1, 128.3, 127.9, 127.8, 127.5, 127.5, 72.2, 65.9, 58.6, 47.7, 37.7, 34.4, 25.6. **IR** (Film) 2956, 2926, 2853, 1468, 1444, 1098, 1072, 1026, 1010, 735, 698 cm^{-1} **HRMS** (ESI): Calcd for $C_{17}H_{28}N_2O$ $[M+H]^+$: 277.2281, found 277.2276.

Synthesis of Cyclic Hydrazines.

General Procedure for CuCN Mediated Allylation of Metalloamination Intermediates: In an argon-filled glove box, $ZnEt_2$ in *p*-xylene (50 μL, 2.0 M, 0.10 mmol) and toluene or (trifluoromethyl)benzene (0.5 mL) were introduced into a J. Young NMR tube equipped with a Teflon screw cap, and hydrazinoalkene (**5a-5c**) (0.10 mmol) was subsequently added. The reactant mixture was heated in a 90 ºC oil bath until metalloamination was complete (90% by ^{1}H NMR, *p*-xylene as internal standard). The

volatiles were removed in vacuo and THF (0.5 mL) was introduced to the J. Young tube in an argon-filled dry box followed by the addition of a solution of CuCN•2LiCl in THF[13] (150 μL, 1.0 M, 0.15 mmol). After 5 min, methallyl chloride (10.9 mg, 0.12 mmol)] was added and the reactant mixture was kept at 23 ºC for 2 h (or until the reaction was complete 95% ^{1}H NMR). The Teflon screw cap was removed and the reactant mixture transferred to a 10-mL test tube, diluted with diethyl ether (2.0 mL) and an aqueous solution of NH_4Cl (sat) and NH_3/H_2O (1:1 v/v, 2 mL) was subsequently added. The resulting suspension was vigorously stirred for 10 min until the aqueous layer developed a deep blue color. The organic layer was removed and washed with a second portion of NH_4Cl (sat) and NH_3/H_2O (1:1 v/v, 2 mL), followed by brine (2 mL) and dried with $MgSO_4$. The ether solution was then transferred to a 10-mL round-bottomed flask equipped with a magnetic stirring bar and a N_2 inlet and cooled to 0 ºC. Trifluoroacetic acid (13.7 mg, 0.12 mmol) was added dropwise via gas-tight syringe and the reactant mixture was allowed to stir for 1 h. The volatiles were removed in vacuo and the resultant viscous oil was triturated with pentane (3 x 1 mL) to afford the trifluoroacetate salts **6**.

***N,N*,4,4-Tetramethyl-2-(3-methyl-1-phenylbut-3-en-1-yl)pyrrolidin-1-amine (6a)**. The title compound was isolated as a clear oil (free base) 22.6 mg (79 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.27 – 7.22 (m, 2H), 7.21 – 7.17 (m, 2H), 7.17 – 7.13 (m, 1H), 4.70 – 4.61 (m, 1.5H), 3.39 (tt, *J*=8.0, 3.6, 1H), 2.97 (td, *J*=8.2, 4.3, 0.8H), 2.67 (d, *J*=14.5, 0.3H), 2.61 (d, *J*=8.0, 0.3H), 2.52 (dd, *J*=14.3, 7.8, .8H), 2.44 – 2.40 (m, 1.5H), 2.37 (s, 6H), 2.34 – 2.30 (m, 1H), 1.69 (s, 2.2H), 1.65 (s, .8H), 1.28 (dd, *J*=12.5, 8.9, 1H), 1.19 –

1.13 (m, 1H), 1.08 (s, 1H), 0.93 (s, 1H), 0.92 (s, 2H), 0.52 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 144.6, 129.9 , 128.6, 127.9, 127.0, 125.7, 125.6, 111.5, 65.6, 63.4, 53.6, 52.8, 43.3, 43.2, 40.5, 39.8, 39.6, 38.7, 38.3, 34.9, 33.5, 30.6, 29.3, 29.2, 29.0 , 22.7 , 22.3. **IR** (film): 2938, 2863, 2812, 1452, 1181, 700, cm^{-1}. **HRMS** (ESI): Calcd for $C_{19}H_{31}N_2$ $[M+H]^+$: 287.2487 , found: 287.2566.

2-(1-(2-Chlorophenyl)-3-methylbut-3-en-1-yl)-*N,N*,4,4-tetramethylpyrrolidin-1-amine ($6a_{Cl}$). The title compound was isolated as a mixture of diastereomers (1:10) (free base) 23.1 mg (72 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (ddd, *J* = 13.7, 8.2, 1.7 Hz, 2H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 7.09 – 7.00 (m, 1H), 4.49 (s, 1H), 4.39 (s, 1H), 3.59 (ddd, *J* = 11.7, 7.5, 4.0 Hz, 1H), 3.02 (dt, *J* = 14.1, 5.4 Hz, 2H), 2.58 (d, *J* = 8.5 Hz, 1H), 2.52 (d, *J* = 8.4 Hz, 1H), 2.40 (s, 1H), 2.31 (s, 6H), 1.66 (s, 3H), 1.30 – 1.26 (m, 1H), 1.25 – 1.22 (m, 1H), 1.07 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 142.1, 134.7, 129.6, 129.16 126.5, 126.1, 111.2, 64.9, 53.2, 42.9, 40.8, 39.8, 34.5, 29.3, 28.7, 22.5. **IR** (Film) 2952, 2865, 2844, 1472, 1441, 1025, 884, 750 cm^{-1}. **HRMS** (ESI): Calcd for $C_{19}H_{29}ClN_2$ $[M+H]^+$: 321.2098 found: 321.2101.

2-(1-(2-Fluorophenyl)-3-methylbut-3-en-1-yl)-,4,4- *N,N* tetramethylpyrrolidin-1-amine ($6a_F$). The title compound was isolated as a clear oil (free base) 23.7 mg (78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (td, *J* = 7.5, 1.8 Hz, 1H), 7.11 (tdd, *J* = 7.3, 5.1, 1.8 Hz, 1H), 7.01 (td, *J* = 7.5, 1.3 Hz, 1H), 6.94 (ddd, *J* = 10.9, 8.1, 1.3 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 2H), 3.50 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.10 – 2.98 (m, 1H), 2.76 (dd, *J* = 14.4, 5.8 Hz, 1H), 2.52 – 2.38 (m, 3H), 2.39 – 2.29 (m, 6H), 1.65 (s, 3H), 1.34 (dd, *J* = 12.8, 8.7

Hz, 1H), 1.27 – 1.19 (m, 1H), 0.93 (s, 3H), 0.77 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5 (d, 1JC-F = 244.1), 144.6, 131.2, 129.9, 127.1, 123.1, 115.1, 115.0, 111.3, 64.0, 53.0, 41.1, 40.4, 39.8, 34.1, 29.2, 28.9, 22.2. **IR** (Film) 3072, 2950, 2865, 2770, 1648, 1582, 1489, 1453, 1222, 886, 754 cm^{-1}. **HRMS** (ESI): Calcd for $C_{19}H_{30}FN_2$ $[M+H]^+$: 305.2394 found: 305.2357.

***N,N*,4,4-Tetramethyl-2-vinylpyrrolidin-1-amine (9)**. The title compound was isolated as a clear oil (TFA salt) 25.4 mg (90%). **1H NMR** (500 MHz, CDCl3) δ 5.84 (ddd, *J* = 17.2, 10.2, 8.4 Hz, 1H), 5.36 – 5.22 (m, 2H), 3.81 (q, *J* = 8.3 Hz, 1H), 3.16 (d, *J* = 8.8 Hz, 1H), 2.95 (s, 6H), 2.81 (d, *J* = 8.8 Hz, 1H), 1.92 (dd, *J* = 13.1, 8.0 Hz, 1H), 1.62 (dd, *J* = 13.1, 8.5 Hz, 1H), 1.16 (s, 3H), 1.13 (s, 3H). **13C NMR** (126 MHz, CDCl3) δ 136.2, 119.8, 64.9, 60.9, 45.0, 42.0, 35.0, 29.1, 28.5. **IR** (Film) 2966, 2876, 1781, 1670, 1200, 1164, 796, 704 cm-1. **HRMS** (ESI): Calcd for C10H20N2 [M+H]+: 169.1705 found: 169.1731.

(*E*)-*N,N*,4,4-Tetramethyl-2-(6-methylhepta-1,6-dien-1-yl)pyrrolidin-1-amine (10). The title compound was isolated as a clear oil (TFA salt) 33.5 mg (92%). **1H NMR** (500 MHz, CDCl3) δ 5.79 – 5.70 (m, 1H), 5.48 (dd, *J* = 15.4, 8.6 Hz, 1H), 4.70 – 4.65 (m, 1H), 4.65 – 4.60 (m, 1H), 3.83 – 3.73 (m, 1H), 3.18 (d, *J* = 9.1 Hz, 1H), 2.90 (d, *J* = 5.1 Hz, 6H), 2.79 (d, *J* = 9.1 Hz, 1H), 2.06 – 1.95 (m, 4H), 1.87 (dd, *J* = 13.1, 7.5 Hz, 1H), 1.71 – 1.66 (m, 3H), 1.66 – 1.60 (m, 2H), 1.52 – 1.45 (m, 2H), 1.16 (s, 3H), 1.13 (s, 3H). **13C NMR** (126 MHz, CDCl3) δ 145.3, 137.0, 127.2, 110.1, 64.9, 60.2, 45.1, 41.6, 37.2, 34.7, 31.6, 29.2, 28.8, 26.5, 22.2. **IR** (Film) 2966, 2936, 2873, 1780, 1670, 1652, 1463,

1202, 1168, 704 cm-1. **HRMS** (ESI): Calcd for C16H30N2 [M+H]+: 251.2120 found: 251.2163.

CHAPTER FIVE EXPERIMENTAL

Materials and Methods: Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. J. Young NMR experiments were performed under an argon atmosphere, using standard Schlenk line techniques or in an argon-filled dry-box. THF and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane, diisopropylamine, trifluoromethylbenzene and toluene were distilled from CaH_2 under nitrogen. Benzene was distilled from potassium metal. Acetaldehyde-*N*,*N*-dimethylhydrazone,[14] acetone-*N*,*N*-dimethylhydrazone,[14] (*E*)-3-cyclopropyl-prop-2-en-1-ol (**1a**),[15] (*E*)-3-cyclopropylbut-2-en-1-ol (**1b**),[15] (*Z*)-3-cyclopropylbut-2-en-1-ol (**1c**),[15] (*Z*)-3-cyclopropyl-3-phenyl-prop-2-en-1-ol (**1d**)[15] and (*E*)-3-(1-methylcyclopropyl)-prop-2-en-1-ol (**1e**)[16] were prepared as previously reported. All other materials were used as received from commercial sources. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm) or potassium permanganate staining. Flash chromatographic columns were packed with Merck silica gel 60 as a slurry in the initial elution solvent. All cyclized products isolated as the trifluoroacetic acid salt. Nuclear magnetic resonance (NMR) data were obtained from Bruker DRX-300 (300 MHz) and Bruker DRX-500 (500 MHz). Infrared spectra (IR) were obtained from JASCO FTIR-

4100. High-resolution mass spectra (HRMS) were obtained from Bruker MicroTOF with a Dart 100 – SVP 100 ion source (Ionsense Inc, Saugus, MA).

(*E*)-1-Bromo-4-cyclopropyl-but-3-ene (2f): A 10-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with dicyclopropylmethanol (0.8 g, 7.13 mmol) and dry diethyl ether (4 mL). The solution was cooled to -78 ºC for the dropwise addition of phosphorus tribromide (0.237 mL, 2.50 mmol, 0.35 equiv) and the temperature of the reaction was slowly warmed to 0 ºC and stirred for 4 h. The mixture was diluted with diethyl ether (5 mL) and washed with DI water (2 x 5 mL). The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered, concentrated and vacuum transferred to afford the title compound (1.09 g, 87%) as a light yellow oil. All spectral and analytical data was consistent with those previously reported for this compound.[17]

(*E*)-1-Chloro-3-cyclopropyl-prop-2-ene (2a): General procedure for the production of allylic chlorides using Vilsmeyer reagent. A 50-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with freshly distilled dimethylformamide (0.943 mL, 12.23 mmol, 1.2 equiv) and methylene chloride (37 mL). The solution was chilled to 0 ºC and oxalyl chloride (1.05 mL, 12.23 mmol, 1.2 equiv) was slowly added and the reaction was stirred for 10 min at 0 ºC. An ice-cold solution of (*E*)-3-cyclopropyl-prop-2-en-1-ol (1.0 g, 10.19 mmol, 1.0 equiv) in methylene chloride (2 mL) was added all at once and the mixture was again stirred for 10 min at 0 ºC. The homogeneous solution was diluted with

ice-cold pentane (10 mL) and quenched with ice-cold DI water (25 mL). The biphasic solution was separated and washed with ice-cold brine (25 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and kept at 0 ºC for the immediate use in the subsequent reaction.

(*E*)-5-Cyclopropyl-2,2-dimethylpent-4-enenitrile (3a). A 50-mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet was charged with diisopropylamine (0.920 g, 9.09 mmol) and THF (25 mL). The reactant mixture was cooled to 0 ºC and *n*-butyllithium (3.03 mL, 3.0M, 9.09 mmol) was added dropwise via syringe. The resulting solution was allowed to stir at this temperature for 30 min and then cooled to -78 ºC and isobutyronitrile (0.621 g, 9.00 mmol) was added dropwise via syringe and the reaction mixture was stirred for an additional 2 h at this temperature. A solution of (E)-1-chloro-3-cyclopropyl-prop-2-ene (1.19 g, 10.2 mmol, prepared as seen above **2a**) in dichloromethane/pentane was added all at once and the reactant mixture was allowed to slowly warm to 23 ºC over 3 h. The reaction was quenched with aqueous NH_4Cl (5 mL) and diluted with diethyl ether (25 mL). The organic layer was washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude nitrile was purified by column chromatography on silica (5% - 15% EtOAc/Hex) to yield the title compound (1.52 g, 87%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.60 – 5.51 (m, 1H), 5.12 (ddt, *J* = 15.1, 8.6, 1.3 Hz, 1H), 2.20 (dd, *J* = 7.4, 1.2 Hz, 2H), 1.44 – 1.38 (m, 1H), 1.32 (s, 6H), 0.76 – 0.67 (m, 2H), 0.38 (dt, *J* = 6.4, 4.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.6, 125.0, 120.9, 43.8, 32.6, 26.1, 13.5, 6.7. **IR** (Film) 3005, 2987, 2933, 2234,

1662, 1468, 1459, 1021, 966. **HRMS** (ESI): Calcd for $C_{10}H_{15}N$ $[M+H]^+$: 150.1283, found 150.1289.

(*E*)-2-((E)-5-Cyclopropyl-2,2-dimethylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (4a). A 100-mL multinecked round-bottomed flask, equipped with a magnetic stirrer, addition funnel and rubber septum, was flame-dried under vacuum then back-filled with a nitrogen atmosphere. The flask was charged with nitrile **3a** (1.0 g, 6.7 mmol) and dry CH_2Cl_2 (25 mL) then cooled to -78 ºC for the dropwise addition of DIBAL-H (13.4 mL, 13.4 mmol, 1.0 M in hexanes) via the addition funnel. The solution was allowed to stir at -78 ºC for 1 h then slowly warmed to 23 ºC over 3 h. Once the reaction was complete, the solution was chilled to 0 ºC, quenched with methanol (5 mL), diluted with Et_2O (20 mL) and 1.0 M HCl was slowly added until all the precipitate was dissolved. The biphasic solution was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$. The crude aldehyde was transferred into a 50-mL round-bottomed flask as a solution in dichloromethane, equipped with a magnetic stirrer. A small amount of $MgSO_4$ was added to the solution prior to the dropwise addition of N,N-dimethylhydrazine (1.02 mL, 13.4 mmol) via syringe. The reactant mixture was stirred for 2 h at 23 ºC then diluted with dry Et_2O (20 mL) and filtered through a plug of Celite, washing with Et_2O (3 x 15 mL). The solution was concentrated in vacuo and purified via kugelrohr distillation (75 ºC at 1.0 torr) from CaH_2 to provide the title compound (1.20 g, 92%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.52 (s, 1H), 5.45 (dt, J = 14.9, 7.4 Hz, 1H), 4.98 – 4.87 (m, 1H), 2.73 – 2.60 (m, 6H), 2.11 – 1.94 (m, 2H), 1.32 (dt, J = 9.0, 4.5 Hz, 1H), 0.99 (d, J = 8.1

Hz, 6H), 0.65 – 0.57 (m, 2H), 0.30 – 0.23 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.7, 136.6, 124.0, 44.6, 43.5, 37.4, 25.7, 24.6, 13.5, 6.4. **IR** (Film) 3001, 2956, 2864, 1468, 1443, 1249, 1019, 963, 810, 587, 526 cm^{-1}. **HRMS** (ESI): Calcd for $C_{12}H_{22}N_2$ $[M+H]^+$: 195.1862, found 195.1883.

(*E*)-2-(5-Cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (5a). A 100-mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet was charged with hydrazone **4a** (0.988 g, 5.00 mmol) and methanol (30 mL) was subsequently added. Sodium cyanoborohydride (0.628 g, 10.0 mmol) was added in one portion and the solution was titrated with HCl:MeOH (methyl orange indicator, 20% v/v) until a light red color persisted. The reactant mixture was stirred for 30 min and the volatiles were removed in vacuo. The crude salt was neutralized with aqueous NaOH (25% w/v) to a pH of 11 and the crude product extracted with diethyl ether (3 x 10 mL). The organic layer was dried with $MgSO_4$, filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by bulb-to-bulb distillation (75-80 ºC, 0.5 torr) to yield (E)-2-(5-cyclopropyl-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.746 g, 76%) as a clear liquid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.45 (dt, *J* = 15.1, 7.5 Hz, 1H), 4.92 (dd, *J* = 15.1, 8.4 Hz, 1H), 2.48 (s, 2H), 2.36 (s, 6H), 1.84 (s, 2H), 1.30 (qt, *J* = 8.4, 4.8 Hz, 1H), 0.82 (s, 6H), 0.65 – 0.54 (m, 2H), 0.26 (dt, *J* = 6.3, 4.2 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.2, 124.3, 58.5, 47.7, 43.3, 34.0, 25.6, 24.6, 13.5, 6.3. **IR** (Film) **HRMS** (ESI): Calcd for $C_{12}H_{24}N_2$ $[M+H]^+$: 197.2018, found 197.2033.

(*E*)-5-Cyclopropyl-2,2-dimethylhex-4-enenitrile (3b). The title compound was synthesized by the general reduction procedure of **3a** utilizing isobutyronitrile (2.06 mL, 22.98 mmol), diisopropylamine (3.54 mL, 25.27 mmol), *n*-butyllithium (9.98 mL, 25.27 mmol, 2.532 M in hexanes) and the allylic chloride (**2b**) (9.19 mmol) prepared from (*E*)-3-cyclopropylbut-2-en-1-ol (**1b**) according to the general procedure of **2a** to yield (E)-5-cyclopropyl-2,2-dimethylhex-4-enenitrile (1.494 g, 99%) as a clear oil**. ^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.31 (t, *J* = 7.4 Hz, 1H), 2.24 (d, *J* = 7.6 Hz, 2H), 1.52 (s, 3H), 1.32 (d, *J* = 17.1 Hz, 6H), 0.59-0.57 (m, 3H), 0.47 (d, *J* = 4.3 Hz, 2H). **^{13}C NMR** (126 MHz; $CDCl_3$): δ 140.8, 125.3, 116.6, 39.1, 26.4, 19.1, 14.4, 4.7. **HRMS** (ESI): Calcd for $C_{10}H_{15}N$ $[M+H]^+$: 150.1284, found 150.1301.

(*E*)-2-((*E*)-5-Cyclopropyl-2,2-dimethylhex-4-en-1-ylidene)-1,1-dimethylhydrazone (4b). The title compound was synthesized by the general reduction procedure of **4a** utilizing nitrile **3b** (1.211 g, 7.42 mmol), DIBAL-H (8.9 mL, 8.90 mmol), and *N,N*-dimethylhydrazine (1.13 mL, 14.84 mmol) to yield (E)-2-((E)-5-cyclopropyl-2,2-dimethylhex-4-en-1-ylidene)-1,1-dimethylhydrazone (1.03 g, 66%) as a clear oil. **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 6.58 (s, 1H), 5.27 (t, *J* = 7.5 Hz, 1H), 2.72 (s, 6H), 2.11 (d, *J* = 7.6 Hz, 2H), 1.51 (s, 3H), 1.43 (s, 1H), 1.06 (s, 6H), 0.57-0.54 (m, 2H), 0.44 (dd, *J* = 5.0, 1.2 Hz, 2H). **^{13}C NMR** (75 MHz; CDCl3): δ 147.0, 137.3, 119.4, 43.6, 39.7, 25.9, 19.1, 14.4, 4.4. **HRMS** (ESI): Calcd for $C_{13}H_{24}N_2$ $[M+H]^+$: 209.2019, found 209.2156.

(*E*)-2-(5-Cyclopropyl-2,2-dimethylhex-4-en-1-yl)-1,1-dimethylhydrazine (5b). The title compound was synthesized by the general reduction procedure of **5a** utilizing

hydrazone **4b** (0.88 g, 4.22 mmol) and $NaBH_3CN$ (0.292 g, 4.64 mmol) to yield (E)-2-(5-cyclopropyl-2,2-dimethylhex-4-en-1-yl)-1,1-dimethylhydrazine (0.72 g, 81%) as a clear oil. **^{1}H NMR** (300 MHz; ; C_6D_6): δ 5.60-5.54 (m, 1H), 2.68 (d, *J* = 2.5 Hz, 2H), 2.37 (dd, *J* = 5.5, 1.9 Hz, 6H), 2.19 (d, *J* = 7.8 Hz, 2H), 1.64 (s, 3H), 1.13 (d, *J* = 2.6 Hz, 1H), 1.07 (d, *J* = 2.7 Hz, 6H), 0.57 (dd, *J* = 7.1, 2.1 Hz, 4H). **^{13}C NMR** (75 MHz; C_6D_6): δ 137.0, 123.0, 120.4, 59.1, 47.8, 38.6, 26.0, 19.6, 14.7, 4.7. **HRMS** (ESI): Calcd for $C_{13}H_{26}N_2$ $[M+H]^+$: 211.2176, found 211.2157.

Compounds **3c**, **4c** and **5c** were prepared by Sean Zabawa.

Compounds **3d** and **4d** were prepared by Sean Zabawa.

(Z)-2-(5-Cyclopropyl-2,2-dimethyl-5-phenylpent-4-en-1-yl)-1,1-dimethylhydrazine (5d). The title compound was synthesized by the general reduction procedure of **5a** utilizing hydrazone **4d** (0.98 g, 3.62 mmol) and $NaBH_3CN$ (0.26 g, 4.14 mmol) to yield (Z)-2-(5-cyclopropyl-2,2-dimethyl-5-phenylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.68 g, 69%) as a clear oil. **^{1}H NMR** (500 MHz; C_6H_6): δ 7.18-7.15 (m, 4H), 7.07-7.06 (m, 1H), 5.69 (td, *J* = 7.6, 0.5 Hz, 1H), 2.47 (s, 2H), 2.18 (s, 6H), 2.02 (d, *J* = 7.6 Hz, 2H), 1.55 (dd, *J* = 7.7, 5.3 Hz, 1H), 0.88 (s, 6H), 0.74 (s, 1H), 0.51-0.48 (m, 4H). **^{13}C NMR** (126 MHz; C_6H_6): δ 143.4, 140.9, 129.6, 128.6, 126.8, 122.7, 122.3, 59.2, 47.8, 39.4, 35.0, 26.1, 19.4, 5.5. **HRMS** (ESI): Calcd for $C_{18}H_{28}N_2$ $[M+H]^+$: 273.2332, found 273.2400.

Compounds **3e** and **4e** were prepared by Sean Zabawa.

(*E*)-2-(5-(Methylcyclopropyl)-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (5e). The title compound was synthesized by the general reduction procedure of **5a** utilizing hydrazone **4e** (1.07 g, 5.13 mmol) and $NaBH_3CN$ (0.37 g, 5.90 mmol) to yield (E)-2-(5-(methylcyclopropyl)-2,2-dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.83 g, 77%) as a clear oil. **^{1}H NMR** (500 MHz; C_6H_6): δ 5.52-5.49 (m, 1H), 5.11 (d, *J* = 15.3 Hz, 1H), 2.56 (s, 2H), 2.25 (s, 6H), 2.04 (d, *J* = 7.5 Hz, 2H), 1.12 (s, 3H), 0.94 (s, 6H), 0.79 (s, 1H), 0.52-0.50 (m, 2H), 0.43 (t, *J* = 2.8 Hz, 2H). **^{13}C NMR** (126 MHz; C_6D_6): δ 140.3, 59.1, 47.8, 43.8, 34.7, 26.1, 22.1, 17.3, 15.1. **HRMS** (ESI): Calcd for $C_{13}H_{26}N_2$ $[M+H]^+$: 211.2176, found 211.2116.

(*E*)-6-Cyclopropyl-2,2-dimethylhex-5-enenitrile (3f). The title compound was synthesized by the general reduction procedure of **3a** utilizing isobutyronitrile (1.12 mL, 12.46 mmol), diisopropylamine (1.83 mL, 13.08 mmol), *n*-butyllithium (5.16 mL, 13.08 mmol, 2.532 M in hexanes) and bromide (**2f**) (1.09 g, 6.23 mmol) to yield (E)-6-cyclopropyl-2,2-dimethylhex-5-enenitrile (0.826 g, 81%) as a clear oil. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 5.49-5.46 (m, 1H), 5.02 (dd, *J* = 15.2, 8.6 Hz, 1H), 2.17 (dd, *J* = 10.6, 5.3 Hz, 2H), 1.59-1.55 (m, 2H), 1.34 (s, 6H), 1.03 (d, *J* = 6.4 Hz, 1H), 0.67-0.66 (m, 2H), 0.32 (d, *J* = 4.6 Hz, 2H). **^{13}C NMR** (75 MHz; $CDCl_3$): δ 135.1, 126.1, 125.0, 41.0, 32.2, 28.4, 26.7, 13.5, 6.4. **HRMS** (ESI): Calcd for $C_{11}H_{17}N$ $[M+H]^+$: 164.1441, found 164.1498.

(*E*)-2-((E)-6-Cyclopropyl-2,2-dimethylhex-5-en-1-ylidene)-1,1-dimethylhydrazone (4f). The title compound was synthesized by the general reduction procedure of **4a**

utilizing nitrile **3f** (0.76 g, 4.66 mmol), DIBAL-H (9.32 mL, 9.32 mmol), and *N,N*-dimethylhydrazine (0.71 mL, 9.32 mmol) to yield (E)-2-((E)-6-cyclopropyl-2,2-dimethylhex-5-en-1-ylidene)-1,1-dimethylhydrazone (0.504 g, 52%) as a clear oil. **^{1}H NMR** (500 MHz; $CDCl_3$): δ 6.50 (s, 1H), 5.47 (dt, *J* = 15.0, 6.9 Hz, 1H), 4.92 (dd, *J* = 15.2, 8.5 Hz, 1H), 2.67 (s, 6H), 1.94-1.90 (m, 2H), 1.41 (dd, *J* = 10.4, 6.5 Hz, 2H), 1.31-1.29 (m, 1H), 1.02 (s, 6H), 0.62 (dd, *J* = 8.1, 1.7 Hz, 2H), 0.28 (dd, *J* = 4.7, 1.5 Hz, 2H). **^{13}C NMR** (126 MHz; $CDCl_3$): δ 146.6, 133.5, 128.6, 43.6, 41.8, 37.2, 27.7, 26.1, 13.6, 6.4. **HRMS** (ESI): Calcd for $C_{13}H_{24}N2$ $[M+H]^+$: 209.2019, found 209.2034.

(*E*)-2-(6-Cyclopropyl-2,2-dimethylhex-5-en-1-yl)-1,1-dimethylhydrazine (5f). The title compound was synthesized by the general reduction procedure of **5a** utilizing hydrazone **4f** (0.43 g, 2.06 mmol) and $NaBH_3CN$ (0.143 g, 2.27 mmol) to yield (E)-2-(6-cyclopropyl-2,2-dimethylhex-5-en-1-yl)-1,1-dimethylhydrazine (0.398 g, 92%) as a clear oil. **^{1}H NMR** (500 MHz; C_6H_6): δ 5.56 (dt, *J* = 14.7, 7.1 Hz, 1H), 5.01 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.52 (s, 2H), 2.24 (s, 6H), 2.04-1.99 (m, 2H), 1.39 (t, *J* = 8.5 Hz, 2H), 1.28-1.27 (m, 1H), 1.12 (s, 1H), 0.91 (s, 6H), 0.54-0.50 (m, 2H), 0.29-0.26 (m, 2H). **^{13}C NMR** (126 MHz; C_6H_6): δ 133.5, 129.3, 59.2, 47.8, 40.7, 27.7, 26.5, 26.0, 14.0, 6.6. **HRMS** (ESI): Calcd for $C_{13}H_{26}N_2$ $[M+H]^+$: 211.2176, found 211.2341.

(*E*)-2-(5-Cyclopropylpent-4-en-1-yl)-1,1-dimethylhydrazine (5g). Utilizing the procedure of Corey and Enders,[14] A 50-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with diisopropylamine (3.71 g, 26.49 mmol) and THF (80 mL). The reactant

mixture was cooled to 0 ºC and *n*-butyllithium (10.26 mL, 2.532M, 25.98 mmol) was added dropwise via syringe. The resulting solution was allowed to stir at this temperature for 30 min and then cooled to -78 ºC for the quick addition of acetaldehyde-*N*,*N*-dimethylhydrazone (2.19 g, 25.48 mmol). The mixture was held at -78 ºC for 5 min then warmed to 0 ºC for 15 min, then cooled back to -78 ºC, resulting in a white suspension. To this was added a solution of (E)-1-chloro-3-cyclopropyl-prop-2-ene (10.19 mmol, prepared as seen above, **2a**) in dichloromethane/pentane was added all at once and the reaction mixture was allowed to slowly warm to 23 ºC over 3 h. The reaction was quenched with aqueous NH_4Cl (30 mL) and diluted with diethyl ether (50 mL). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, concentrated in vacuo, and vacuum transferred to yield **(**E)-2-(5-cyclopropylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (1.404 g, 82%) which was immediately used to produce the title compound by the general reduction procedure of **5a** utilizing **(**E)-2-(5-cyclopropylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (1.404 g, 8.44 mmol) just produced and $NaBH_3CN$ (0.583 g, 9.28 mmol) to yield (E)-2-(5-cyclopropylpent-4-en-1-yl)-1,1-dimethylhydrazine (1.59 g, 89%) as a clear oil. **^{1}H NMR** (300 MHz; C_6H_6): δ 5.52 (dd, *J* = 14.7, 7.3 Hz, 1H), 4.97 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.23 (s, 6H), 2.08 (dd, *J* = 14.7, 8.0 Hz, 2H), 1.59 (dd, *J* = 14.6, 7.2 Hz, 3H), 1.25 (dt, *J* = 8.5, 4.4 Hz, 1H), 0.53-0.47 (m, 2H), 0.27-0.22 (m, 2H). **^{13}C NMR** (75 MHz; C_6H_6): δ 134.2, 128.4, 48.3, 47.7, 30.7, 29.1, 14.0, 6.6. **HRMS** (ESI): Calcd for $C_{10}H_{20}N_2$ $[M+H]^+$: 169.1706, found 169.1774.

(*E*)-2-(5-Cyclopropyl-1-methylpent-4-en-1-yl)-1,1-dimethylhydrazine (5h). Utilizing the procedure of Corey and Enders,[14] A 100-mL round-bottomed flask, equipped with a magnetic stirrer, was flame-dried under vacuum, back-filled with a nitrogen atmosphere, and charged with acetone-*N*,*N*-dimethylhydrazone (1.275 g, 12.73 mmol) and dry THF (39 mL). The reaction mixture was cooled to -78 ºC and *n*-butyllithium (7.98 mL, 1.563M, 12.48 mmol) was added dropwise via syringe. The resulting solution was allowed to stir at this temperature for 30 min and then to this suspension was added a solution of (E)-1-chloro-3-cyclopropyl-prop-2-ene (5.09 mmol, prepared as seen above, **2a**) in dichloromethane/pentane was added all at once and the reactant mixture was allowed to slowly warm to 23 ºC over 3 h. The reaction was quenched with aqueous NH_4Cl (30 mL) and diluted with diethyl ether (30 mL). The organic layer was washed with brine (30 mL), dried with $MgSO_4$, concentrated in vacuo, and vacuum transferred to yield **(**E)-2-(5-cyclopropylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (0.407 g, 44%) which was immediately used to produce the title compound by the general reduction procedure of **5a** utilizing **(**E)-2-(5-cyclopropylpent-4-en-1-ylidene)-1,1-dimethylhydrazone (0.407 g, 2.26 mmol) just produced and $NaBH_3CN$ (0.156 g, 2.49 mmol) to yield (E)-2-(5-cyclopropylpent-4-en-1-yl)-1,1-dimethylhydrazine (0.34 g, 84%) as a clear oil. **^{1}H NMR** (300 MHz; C_6H_6): δ 5.53 (dt, *J* = 14.8, 7.2 Hz, 1H), 4.97 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.80 (q, *J* = 6.0 Hz, 1H), 2.24 (s, 6H), 2.14-2.01 (m, 2H), 1.69-1.61 (m, 2H), 1.42 (dd, *J* = 9.4, 6.6 Hz, 1H), 1.27-1.24 (m, 1H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.54-0.48 (m, 2H), 0.28-0.23 (m, 2H). **^{13}C NMR** (75 MHz; C_6H_6): δ 134.0, 128.5, 51.9, 48.2,

36.0, 29.3, 19.9, 14.0, 6.6. **HRMS** (ESI): Calcd for $C_{11}H_{22}N_2$ $[M+H]^+$: 183.1863, found 183.1902.

CHAPTER SIX EXPERIMENTAL

Materials and Methods: Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. J. Young NMR experiments were performed under an argon atmosphere, using standard Schlenk line techniques or in an argon-filled dry-box. THF and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane, diisopropylamine, trifluoromethylbenzene and toluene were distilled from CaH_2 under nitrogen. Benzene was distilled from potassium metal. 2,2-dimethyl-4-pentenal[18], 2,2-dimethyl-4-pentenal-*N,N*-dimethylhydrazone[19], 5-hexen-2-one-*N,N*-dimethylhydrazone,[20] 5-hexenal-*N,N*-dimethylhydrazone,[21] acetaldehyde-*N,N*-dimethylhydrazone,[14] 3-methylbutanal[22], 2-Phenylpent-4-enal-*N,N*-dimethylhydrazone[23] and acetone-*N,N*-dimethylhydrazone[14] were prepared as previously reported. All other materials were used as received from commercial sources. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm) or potassium permanganate staining. Flash chromatographic columns were packed with Merck silica gel 60 as a slurry in the initial elution solvent. All cyclized products isolated as the trifluoroacetic acid salt. Nuclear magnetic resonance (NMR) data were obtained from Bruker DRX-300 (300 MHz) and Bruker DRX-500 (500 MHz). Infrared spectra (IR) were obtained from JASCO FTIR-4100. High-resolution mass

spectra (HRMS) were obtained from Bruker MicroTOF with a Dart 100 – SVP 100 ion source (Ionsense Inc, Saugus, MA).

Synthesis of N,N-Dimethylhydrazines and N,N-Dimethylhydrazones.

2-(Hex-5-en-2-yl)-1,1-dimethylhydrazine (1a). A 500-mL oven dried round-bottomed flask equipped with a magnetic stirring bar, a N_2 atmosphere, methyl orange and $NaBH_3CN$ (1.61 g, 25.67 mmol) dissolved in MeOH (200 mL) was charged with 5-hexen-2-one-*N,N*-dimethylhydrazone (3 g, 21.39 mmol) and then degassed with N_2 (g) for 15 min with concurrent chilling to 0 °C. The yellow-orange mixture was titrated with 5:1 MeOH:HCl until the color red persisted for 30 min. The volatiles were removed in vacuo and the salts were free-based by action of a degassed 1:2 mixture of DCM and 15% NaOH (aq) (40 mL). The biphasic solution was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated in vacuo followed by distillation (0.5 torr, 23 °C) from CaH_2 to afford the title compound (2.43 g, 80%) as a colorless oil. **^{1}H-NMR** (500 MHz; C_6H_6): δ 5.81 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.06-4.96 (m, 2H), 2.77 (sextet, *J* = 6.0 Hz, 1H), 2.23 (s, 6H), 2.14-2.06 (m, 1H), 2.04-1.97 (m, 1H), 1.65-1.58 (m, 2H), 1.40 (ddt, *J* = 13.2, 9.7, 6.5 Hz, 1H), 1.01 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (126 MHz; C_6D_6): δ 139.4, 114.4, 51.9, 48.2, 35.2, 30.5, 19.7. **IR** (Film): 3184, 3078, 2977, 2946, 2842, 2809, 2766, 1641, 1478, 1450, 907, cm^{-1} **HRMS** (ESI): Calcd for $C_8H_{18}N_2$ $[M+H]^+$: 143.1548, found: 143.1495.

2-(2,2-Dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (1b). The title compound was prepared by the general procedure described for compound **1a** employing 2,2-dimethyl-4-

pentenal-*N,N*-dimethylhydrazone (2.88 g, 18.22 mmol) and $NaBH_3CN$ (1.37 g, 21.86 mmol) to furnish 2-(2,2-Dimethylpent-4-en-1-yl)-1,1-dimethylhydrazine (2.53g, 89%) as a clear liquid. **^{1}H-NMR** (600 MHz; C_6H_6): δ 5.90-5.83 (m, 1H), 5.05 (d, *J* = 12.8 Hz, 2H), 2.51 (s, 2H), 2.23 (s, 6H), 2.04 (d, *J* = 7.5 Hz, 2H), 1.62 (s, 1H), 0.91 (s, 6H). **^{13}C-NMR** (151 MHz; C_6D_6): δ 136.2, 116.9, 59.0, 47.8, 45.1, 34.4, 25.9. **IR** (Film): 3075, 2952, 2906, 2869, 2836, 2807, 2765, 1638, 1474, 1448, 912, cm^{-1} **HRMS** (ESI): Calcd for $C_9H_{20}N_2$ $[M+H]^+$: 157.1705, found: 157.1631.

1,1-Dimethyl-2-(2-phenylpent-4-en-1-yl)hydrazine (1c). The title compound was prepared by the general procedure described for compound **1a** employing 2-Phenylpent-4-enal-*N,N*-dimethylhydrazone (1.25 g, 6.31 mmol) and $NaBH_3CN$ (0.48 g, 7.57 mmol) to furnish 1,1-dimethyl-2-(2-phenylpent-4-en-1-yl)hydrazine (0.86 g, 83%) as a clear liquid. **^{1}H-NMR** (500 MHz; C_6H_6): δ 7.18-7.05 (m, 5H), 5.70 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 4.99-4.89 (m, 2H), 2.92 (t, *J* = 9.7 Hz, 2H), 2.55-2.51 (m, 1H), 2.28 (d, *J* = 15.8 Hz, 2H), 2.16 (s, 6H), 1.63 (s, 1H). **^{13}C-NMR** (126 MHz; C_6D_6): δ 144.5, 137.3, 128.7, 126.5, 116.0, 54.4, 47.6, 45.2, 39.1. **IR** (Film): 3076, 3063, 3027, 2978, 2946, 2923, 2838, 2809, 2766, 1640, 1493, 1475, 1452, 911, 700, cm^{-1}. **HRMS** (ESI): Calcd for $C_{13}H_{20}N_2$ $[M+H]^+$: 205.1705, found: 205.1720.

2-(Hex-5-en-1-yl)-1,1-dimethylhydrazine (1d). The title compound was prepared by the general procedure described for compound **1a** employing 5-Hexenal-*N,N*-dimethylhydrazone (1.00 g, 7.13 mmol) and $NaBH_3CN$ (0.54 g, 8.56 mmol) to furnish 2-(hex-5-en-1-yl)-1,1-dimethylhydrazine (0.93 g, 92%) as a clear liquid. **^{1}H-NMR** (600

MHz; C_6H_6): δ 5.77 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.03-4.96 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.24-2.22 (m, 6H), 1.99 (q, *J* = 7.1 Hz, 2H), 1.56 (s, 1H), 1.49-1.44 (m, 2H), 1.42-1.39 (m, 2H). **^{13}C-NMR** (151 MHz; C_6D_6): δ 139.2, 114.6, 48.7, 47.7, 34.2, 28.6, 27.1. **IR** (Film) 3076, 2977, 2935, 2839, 2807, 2765, 1640, 1473, 1458, 910, cm^{-1}. **HRMS** (ESI): Calcd for $C_8H_{18}N_2$ $[M+H]^+$: 143.1548, found: 143.1559.

2-Isopropylpent-4-enal-*N,N*-dimethylhydrazone. The title compound was prepared following the procedure of Corey and Enders[5]. A 250-mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet was charged with diisopropylamine (3.44 mL, 24.58 mmol) and THF (65 mL) was subsequently added. The resulting mixture was cooled to 0 °C and *n*-BuLi in hexanes (3.22 M, 7.30 mL) was added dropwise and the mixture was subsequently stirred at this temperature for 1 h. A solution of 3-methylbutanal-N,N-dimethylhydrazone (2.74 g, 21.37 mmol) in THF (10 mL) was added dropwise with stirring. After 1 h the resulting suspension was cooled to -78 °C and allyl bromide (3.10 g, 25.64 mmol) was added dropwise via syringe. The reactant mixture was stirred at this temperature for 2 h and then allowed to warm slowly to 23 °C. After 12 h the resulting mixture was poured into water/ethyl acetate (3:1, 25 mL) and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (2 x 10 mL), the combined organic layers were dried with $MgSO_4$, filtered through a plug of Celite and concentrated in vacuo. The crude compound was purified by vacuum transfer distillation (0.5 torr) to yield 2.69 g (75%) of the title compound. **^{1}H-NMR** (500 MHz; $CDCl_3$): δ 6.48 (d, *J* = 7.1 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H), 5.01-4.94 (m, 2H), 2.70 (s, 6H), 2.28-2.18 (m, 2H), 2.13 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.75 (dq, *J* = 13.4,

6.7 Hz, 1H), 0.90 (dd, *J* = 21.9, 6.8 Hz, 6H).**^{13}C-NMR** (126 MHz; $CDCl_3$): δ 141.9, 137.1, 115.8, 48.3, 43.7, 35.4, 30.6, 20.5, 19.3. **HRMS** (ESI): Calcd for $C_{10}H_{20}N_2$ $[M+H]^+$: 169.1699, found: 169.1693.

1,1-Dimethyl-2-(2-isopropylpent-4-en-1-yl)hydrazine (1e). The title compound was prepared by the general procedure described for compound **1a** employing 2-isopropylpent-4-enal-*N,N*-dimethylhydrazone (1.44 g, 8.53 mmol) and $NaBH_3CN$ (0.75 g, 11.94 mmol) to furnish 1,1-dimethyl-2-(2-isopropylpent-4-en-1-yl)hydrazine (1.27g, 88%) as a clear liquid. **^{1}H-NMR** (600 MHz; C_6H_6): δ 5.84 (dq, *J* = 17.0, 8.5 Hz, 1H), 5.05 (dd, *J* = 28.6, 13.6 Hz, 2H), 2.64 (ddd, *J* = 59.4, 11.8, 6.4 Hz, 2H), 2.24 (s, 6H), 2.13 (t, *J* = 6.8 Hz, 2H), 1.88 (dq, *J* = 12.7, 6.3 Hz, 1H), 1.55 (d, *J* = 21.4 Hz, 1H), 1.52 (q, *J* = 5.8 Hz, 1H), 0.88 (d, *J* = 7.0 Hz, 6H). **^{13}C-NMR** (151 MHz; C_6D_6): δ 138.9, 115.4, 49.5, 47.7, 43.2, 34.4, 28.7, 19.74, 19.54. . **HRMS** (ESI): Calcd for $C_{10}H_{22}N_2$ $[M+H]^+$: 171.1856, found: 171.1854.

5-Methylhex-5-enal-N,N-dimethylhydrazone. A 100-mL round-bottomed flask with magnetic stirrer, was flame-dried under vacuum and back-filled with a nitrogen atmosphere, then charged with ethyl-5-methyl-5-hexenoate (1.5 g, 9.60 mmol) and dry DCM (30 mL). The solution was cooled to -78 ºC before the dropwise addition of diisobutylaluminium hydride (10.37 mL, 1.01 M in hexanes). The mixture was stirred at this temperature for 1 h, and then excess DIBAL-H was quenched by the addition of 1.0 M HCl (*aq)* (10 mL). Dichloromethane (30 mL) was added and the solution was warmed to 23 ºC and the biphasic mixture was separated. The organic layer was washed with 1.0

M HCl (*aq)* (15 mL), the aqueous layers were combined and extracted with DCM (2 x 15 mL). All organic layers were combined and pushed through a plug of Celite, washing with DCM (2 x 10 mL). The DCM solution containing 5-methylhex-5-enal was transferred to a 250-mL round-bottomed flask, equipped with a magnetic stirrer and dried with $MgSO_4$ before the addition of N,N-dimethylhydrazine (1.15 g, 19.2 mmol). This mixture was stirred for 4 h at 23 ºC, filtered, concentrated in vacuo, and purified by vacuum transfer distillation (0.5 torr) to yield 1.22 g of the title compound as a colorless oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 6.66 (t, *J* = 5.5 Hz, 1H), 4.69 (d, *J* = 17.0 Hz, 2H), 2.72 (s, 6H), 2.22 (q, *J* = 7.0 Hz, 2H), 2.04 (t, *J* = 7.5 Hz, 2H), 1.71 (s, 3H), 1.61 (quintet, *J* = 7.7 Hz, 2H). **^{13}C-NMR** (151 MHz; $CDCl_3$): δ 145.7, 139.5, 110.2, 43.5, 37.4, 32.8, 25.9, 22.5. . **HRMS** (ESI): Calcd for $C_9H_{18}N_2$ $[M+H]^+$: 155.1543, found: 155.1540.

1,1-Dimethyl-2-(5-methylhex-5-en-1-yl)hydrazine (1f). The title compound was prepared by the general procedure described for compound **1a** employing 5-methylhex-5-enal-N,N-dimethylhydrazone (1.0 g, 6.48 mmol) and $NaBH_3CN$ (0.53 g, 8.43 mmol) to furnish 1,1-Dimethyl-2-(5-methylhex-5-en-1-yl)hydrazine (0.74 g, 74%) as a clear liquid. **^{1}H-NMR** (600 MHz; C_6H_6): δ 4.80 (q, *J* = 1.1 Hz, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.24 (s, 6H), 1.98 (t, *J* = 7.1 Hz, 2H), 1.64 (s, 3H), 1.49-1.47 (m, 4H). **^{13}C-NMR** (151 MHz; C_6D_6): δ 145.9, 110.3, 48.8, 47.7, 38.2, 28.8, 25.8, 22.5. **HRMS** (ESI): Calcd for $C_9H_{20}N_2$ $[M+H]^+$: 157.1699, found: 157.1696.

Synthesis of Cyclic Hydrazines.

General Procedure for CuBr•SMe_2 Catalyzed Allylation of Metalloamination Intermediates: An oven-dried J. Young Tube was blanketed with an argon atmosphere and charged with diethyl zinc (50 μL, 2.0 M in BTF, 0.1 mmol, 1.0 equiv), BTF (0.4 mL) and the requisite N,N-dimethylhydrazinoalkene (0.1 mmol, 1.0 equiv). The tube was then placed into an oil bath (of indicated temperature) and metalloamination/cyclization was monitored using BTF as an internal standard (as evidenced by the disappearance of the olefin signals with concurrent emergence of new C-Zn methylene peaks). The temperature of the reactant mixture was subsequently returned to 23 °C for the addition of THT (0.1 mL) followed by the addition of the Cu (I) catalyst (5 mol%). Allyl bromide (4.0 equiv) was then added and its consumption, with simultaneous recession of the intermediate C-Zn methylene resonance, was monitored by No-D proton NMR. Upon completion of allylation, the reactant mixture was dispersed in diethyl ether (2 mL) and washed with 1:1 sat. NH_4Cl (aq): sat. NH_4OH (aq) (3 x 3mL). The aqueous layers were then extracted with diethyl ether (3 mL) and the combined organic layers were dried successively with brine (5 mL) and $MgSO_4$, and then filtered through a plug of silica. To the ethereal solution was added TFA (8.5 μL, 0.11 mmol, 1.1 equiv) and the mixture was concentrated in vacuo. The resulting salt was triturated with pentane (3 x 1 mL) and the volatiles were removed to provide the cyclization-allylation product (> 95%) as a clear viscous oil.

2-(But-3-en-1-yl)-*N*,*N*,5-trimethylpyrrolidine-1-amine (3a). Cyclization was completed after 6 h at 90 °C, allylation was accomplished in 12 h at 23 °C. The title compound was isolated as a light yellow oil. 29.0 mg (98%). **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 5.77 (tdd, *J* = 11.7, 11.0, 5.4 Hz, 1H), 5.06-5.00 (m, 2H), 3.55 (dq, *J* = 13.4, 6.7 Hz, 1H), 3.40-3.34 (m, 1H), 2.88 (s, 6H), 2.20-2.15 (m, 1H), 1.99 (dtt, *J* = 32.5, 11.1, 5.6 Hz, 4H), 1.82 (td, *J* = 11.8, 5.9 Hz, 3H), 1.42 (d, *J* = 6.4 Hz, 3H). **^{13}C-NMR** (151 MHz; $CDCl_3$): δ 161.0, 160.8, 136.9, 116.1, 63.7, 59.0, 41.4, 32.2, 30.5, 29.7, 27.2, 19.2. **IR** (Film): 3360 (b), 2927, 2611 (b), 1738, 1672, 1465, 1409, 1199, 1134, 798, 719, cm^{-1}. **HRMS** (ESI): Calcd for $C_{11}H_{22}N_2$ $[M+H]^+$: 183.1861, found: 183.1734.

2-(But-3-en-1-yl)-*N*,*N*,4,4-tetramethylpyrrolidin-1-amine (3b). Cyclization was completed after 18 h at 90 °C, allylation was accomplished in 24 h at 23 °C. The title compound was isolated as a light yellow oil, which slowly solidified upon storage. 30.8 mg (95%) **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 5.78-5.71 (m, 1H), 5.07-5.02 (m, 2H), 3.41 (dt, *J* = 10.3, 6.6 Hz, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 2.94 (d, *J* = 10.8 Hz, 1H), 2.71 (s, 6H), 2.20 (td, *J* = 11.3, 5.3 Hz, 1H), 2.15-2.09 (m, 1H), 2.01 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.92 (dd, *J* = 13.2, 6.7 Hz, 1H), 1.78 (dddd, *J* = 13.1, 10.2, 7.9, 5.3 Hz, 1H), 1.75-1.70 (m, 1H), 1.19 (d, *J* = 27.8 Hz, 6H). **^{13}C-NMR** (151 MHz; $CDCl_3$): δ 161.2, 161.0, 160.7, 160.4, 136.6, 116.3, 55.6, 42.8, 40.7, 35.3, 30.4, 29.2, 28.5. **IR** (Film): 3448 (b), 2968, 2875, 1674, 1463, 1409, 1197, 1132, cm^{-1}. **HRMS** (ESI): Calcd for $C_{12}H_{24}N_2$ $[M+H]^+$: 197.2018, found: 197.2058.

2-(But-3-en-1-yl)-*N*,*N*-dimethyl-4-phenylpyrrolidin-1-amine (3c). Cyclization was completed after 24 h at 23 °C, allylation was accomplished in 22 h at 23 °C The title compound was isolated as the trifluoroacetic acid salt (12.9 mg). When the reaction was conducted at 23 ºC the *cis/trans* selectivity increased to 15:1. The title compound was isolated as light yellow oil (33.5 mg, 90%). Spectral information of *cis* diastereomer. **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 7.34-7.24 (m, 5H), 5.84-5.69 (m, 1H), 5.09-5.01 (m, 2H), 3.73-3.67 (m, 1H), 3.54 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.38 (dd, *J* = 17.8, 9.2 Hz, 1H), 2.76 (s, 6H), 2.45 (td, *J* = 16.1, 6.5 Hz, 3H), 2.25 (dd, *J* = 12.8, 5.2 Hz, 2H), 2.08 (td, *J* = 14.0, 7.2 Hz, 3H).**^{13}C-NMR** (75 MHz; $CDCl_3$): δ 161.4, 161.0, 138.7, 136.7, 129.1, 127.8, 127.5, 116.3, 66.2, 49.9, 42.5, 40.9, 37.9, 30.6, 29.5. **IR** (Film): 2978, 2584 (b), 1734, 1671, 1457, 1196, 1140, 720, 701, cm^{-1}. **HRMS** (ESI): Calcd for $C_{16}H_{24}N_2$ $[M+H]^+$: 245.2018, found: 245.1904.

2-(But-3-en-1-yl)-*N*,*N*-dimethylpiperidin-1-amine (3d). Cyclization was completed after 0.5 h at 60 °C, allylation was accomplished in 8 h at 35 °C. The title compound was isolated as a light yellow oil. 28.4 mg (96%). **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 5.77-5.70 (m, 1H), 5.07-5.02 (m, 2H), 3.64 (d, *J* = 10.6 Hz, 1H), 2.95 (t, *J* = 10.2 Hz, 1H), 2.74 (t, *J* = 11.2 Hz, 1H), 2.66 (s, 6H), 2.39-2.34 (m, 1H), 2.23 (ddt, *J* = 14.3, 9.2, 5.0 Hz, 1H), 2.18-2.11 (m, 1H), 2.04-1.98 (m, 2H), 1.96-1.89 (m, 2H), 1.87 (t, *J* = 11.5 Hz, 1H), 1.80-1.74 (m, 1H), 1.32 (dddt, *J* = 17.4, 13.1, 8.9, 4.2 Hz, 1H). **^{13}C-NMR** (75 MHz; CDCl3): δ 136.8, 116.2, 63.8, 39.2, 29.7, 28.5, 28.3, 22.66, 22.49. **IR** (Film): 2956, 2566 (b), 1779, 1669, 1461, 1170, 797 cm^{-1}. **HRMS** (ESI): Calcd for $C_{11}H_{22}N_2$ $[M+H]^+$: 183.1861, found: 183.1733.

2-(But-3-en-1-yl)-*N*,*N*-dimethyl-4-isopropylpyrrolidin-1-amine (3e). Cyclization was completed after 24 h at 23 °C, allylation was accomplished in 12 h at 23 °C. The title compound was isolated as a light yellow oil. 25.6 mg (80%). **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 5.79-5.68 (m, 1H), 5.08-5.00 (m, 2H), 3.39 (d, J = 9.6 Hz, 3H), 2.66 (s, 6H), 2.41 (td, J = 13.9, 7.4 Hz, 1H), 2.26-2.07 (m, 3H), 2.10-1.78 (m, 3H), 1.67-1.49 (m, 2H), 0.92 (d, J = 6.6 Hz, 6H).**^{13}C-NMR** (75 MHz; $CDCl_3$): δ 161.3, 160.8, 136.7, 116.3, 66.4, 47.4, 44.2, 40.7, 34.1, 32.0, 30.6, 29.1, 21.5, 20.7. **HRMS** (ESI): Calcd for $C_{13}H_{27}N_2$ $[M+H]^+$: 211.2169, found: 211.2171.

***N*,*N*,2-Trimethyl-5-(3-methylbut-3-en-1-yl)pyrrolidin-1-amine (3a-Me)**. An oven-dried J. Young Tube was blanketed with an argon atmosphere and charged with diethyl zinc (50 μL, 2.0 M in BTF, 0.1 mmol, 1.0 equiv), BTF (0.4 mL) and the requisite N,N-dimethylhydrazinoalkene (0.1 mmol, 1.0 equiv). The tube was then placed into an oil bath (of indicated temperature) and metalloamination/cyclization was monitored using BTF as an internal standard (as evidenced by the disappearance of the olefin signals with concurrent emergence of new C-Zn methylene peaks). The temperature of the reactant mixture was subsequently returned to 23 °C followed removal of volatiles and solvation in THF (0.4 mL). CuCN•2LiBr (5 mol%, 1 M in THF) along with LiBr (1.0 equiv) was added. Methallyl chloride (4.0 equiv) was then added and its consumption, with simultaneous recession of the intermediate C-Zn methylene resonance, was monitored by No-D proton NMR. Upon completion of allylation, the reactant mixture was dispersed in diethyl ether (2 mL) and washed with 1:1 sat. NH_4Cl (aq): sat. NH_4OH (aq) (3 x 3mL).

The aqueous layers were then extracted with diethyl ether (3 mL) and the combined organic layers were dried successively with brine (5 mL) and $MgSO_4$, and then filtered through a plug of silica. To the ethereal solution was added TFA (8.5 μL, 0.11 mmol, 1.1 equiv) and the mixture was concentrated in vacuo. The resulting salt was triturated with pentane (3 x 1 mL) and the volatiles were removed to provide the cyclization-allylation product 29.8 mg (> 95%) as a clear viscous oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 4.72 (d, *J* = 40.1 Hz, 2H), 3.58 (q, *J* = 6.5 Hz, 1H), 3.38-3.36 (m, 1H), 2.88 (s, 6H), 2.10-2.00 (m, 5H), 1.83 (td, *J* = 9.4, 5.2 Hz, 3H), 1.72 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (126 MHz; $CDCl_3$): δ 161.3, 161.0, 144.1, 111.3, 63.8, 58.8, 41.5, 34.5, 31.0, 29.9, 27.3, 22.2, 19.5. **HRMS** (ESI): Calcd for $C_{12}H_{24}N_2$ [M+H]+: 197.2018, found: 197.1886.

***N*,*N*,2-Trimethyl-5-(but-2,3-dien-1-yl)pyrrolidin-1-amine (3a-Al).** Cyclization was completed after 6 h at 90 °C, alkylation was accomplished following the procedure of **3a-Me** utilizing 4.0 equiv of propargyl bromide in 6 h at 23 °C. The title compound was isolated as a light yellow oil. 17.1 mg (60% yield). **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 5.14-5.09 (m, 1H), 4.75 (dd, *J* = 3.7, 1.5 Hz, 2H), 3.58-3.55 (m, 1H), 3.51-3.50 (m, 1H), 3.03-2.88 (m, 6H), 2.57-2.51 (m, 1H), 2.36-2.32 (m, 1H), 2.09-2.00 (m, 2H), 1.87-1.83 (m, 1H), 1.79-1.76 (m, 1H), 1.40 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (75 MHz; $CDCl_3$): δ 209.5, 162.1, 161.6, 86.0, 75.6, 62.3, 58.3, 41.6, 33.6, 30.8, 29.9, 28.2. **HRMS** (ESI): Calcd for $C_{13}H_{25}N_2O_2$ [M+H]+: 181.1699, found: 181.1691.

***N*,*N*,2-Trimethyl-5-(3-methacrylatebut-3-en-1-yl)pyrrolidin-1-amine (3a-Ac).** Cyclization was completed after 6 h at 90 °C, alkylation was accomplished following the

procedure of **3a-Me** utilizing only 1.0 equiv of methyl-2-(bromomethyl)acylate in 6 h at 23 °C. The title compound was isolated as a light yellow oil 22.8 mg (65% yield). **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 6.17 (d, *J* = 1.1 Hz, 1H), 5.61 (d, *J* = 1.1 Hz, 1H), 3.74 (s, 3H), 3.53 (dq, *J* = 13.1, 6.3 Hz, 1H), 3.38 (s, 1H), 2.88 (s, 6H), 2.39-2.24 (m, 2H), 2.04-1.96 (m, 3H), 1.87-1.77 (m, 3H), 1.38 (d, *J* = 6.2 Hz, 3H). **^{13}C-NMR** (75 MHz; $CDCl_3$): δ 167.6, 139.4, 125.9, 62.9, 57.9, 52.0, 41.4, 33.2, 30.5, 29.8, 28.8, 27.9. **HRMS** (ESI): Calcd for $C_{13}H_{25}N_2O_2$ [M+H]+: 241.1911, found: 241.1908.

Representative Preparative Scale Reactions.

2-(But-3-en-1-yl)-*N*,*N*,5-trimethylpyrrolidine-1-amine (3a). In an argon-filled glove box, a 10-mL Schlenk flask equipped with a magnetic stirring bar was charged with $ZnEt_2$ in BTF (0.50 mL, 2.0 M, 1.0 mmol), BTF (4 mL) and 2-(Hex-5-en-2-yl)-1,1-dimethylhydrazine (142 mg, 1.0 mmol). The reactant mixture was removed from the dry box, fitted with an N_2 inlet and placed in a 90 °C oil bath for 8 h. The temperature of the reaction was returned to 23 °C for the addition of THT (1.0 mL), CuI (10.0 mg, 5 mol%) and allyl bromide (0.3 mL, 3.5 mmol) in succession. After immersion in a 35 °C oil bath for 5 hours the reactant mixture was diluted with Et_2O (15 mL), and an aqueous solution of NH_4Cl (sat) and NH_3 /H_2O (1:1 v/v, 10 mL) was subsequently added. The resulting suspension was vigorously stirred for 10 min until the aqueous layer developed a deep blue color. The flasks contents were poured into a separatory funnel and the biphasic solution was separated. The organic layer was washed with a second portion of NH_4Cl and NH_3 /H_2O (1:1 v/v, 10 mL), followed by brine (NaCl, 15 mL) and dried with $MgSO_4$.

The resulting ethereal solution was transferred to a 50-mL round-bottomed flask equipped with a magnetic stirring bar and an N_2 inlet. The reactant mixture was cooled to 0 °C and acidified with trifluoroacetic acid (125 mg, 1.1 mmol). The volatiles were removed in vacuo and the resultant oil was triturated with pentane (3 x 2 mL) to furnish 0.277 g (93.7%) of the title compound as a light yellow oil. Spectral data was identical with that previously reported (vide supra).

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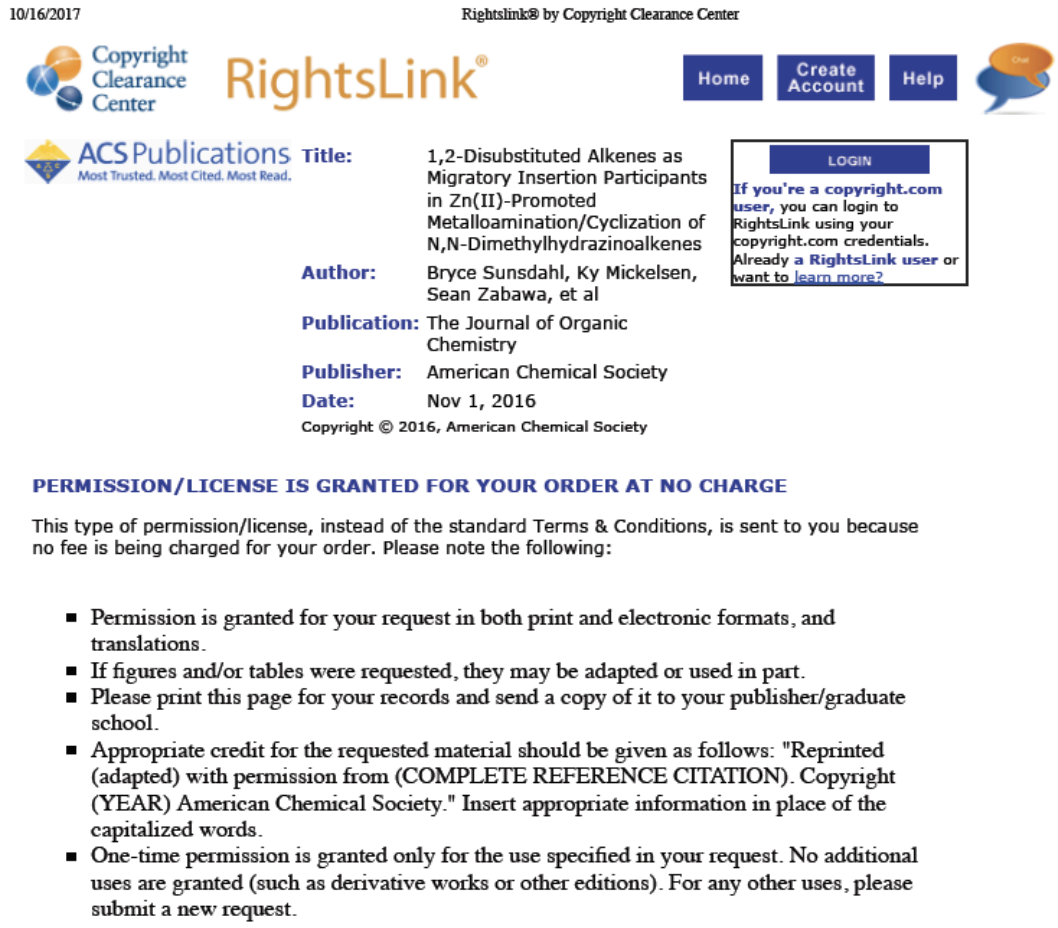
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APPENDIX B

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Title: 1,2-Disubstituted Alkenes as Migratory Insertion Participants in Zn(II)-Promoted Metalloamination/Cyclization of N,N-Dimethylhydrazinoalkenes

Author: Bryce Sunsdahl, Ky Mickelsen, Sean Zabawa, et al

Publication: The Journal of Organic Chemistry

Publisher: American Chemical Society

Date: Nov 1, 2016

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Title: Diethylzinc-Mediated Metalloamination–Alkylation of N,N-Dimethylhydrazinoalkenes. Catalysis of C–Zn Alkylation Using Simple Cu(I) Salts

Author: Ky Mickelsen, Sean Zabawa, Tom Livinghouse

Publication: Synlett

Publisher: Thieme

Date: Oct 12, 2017

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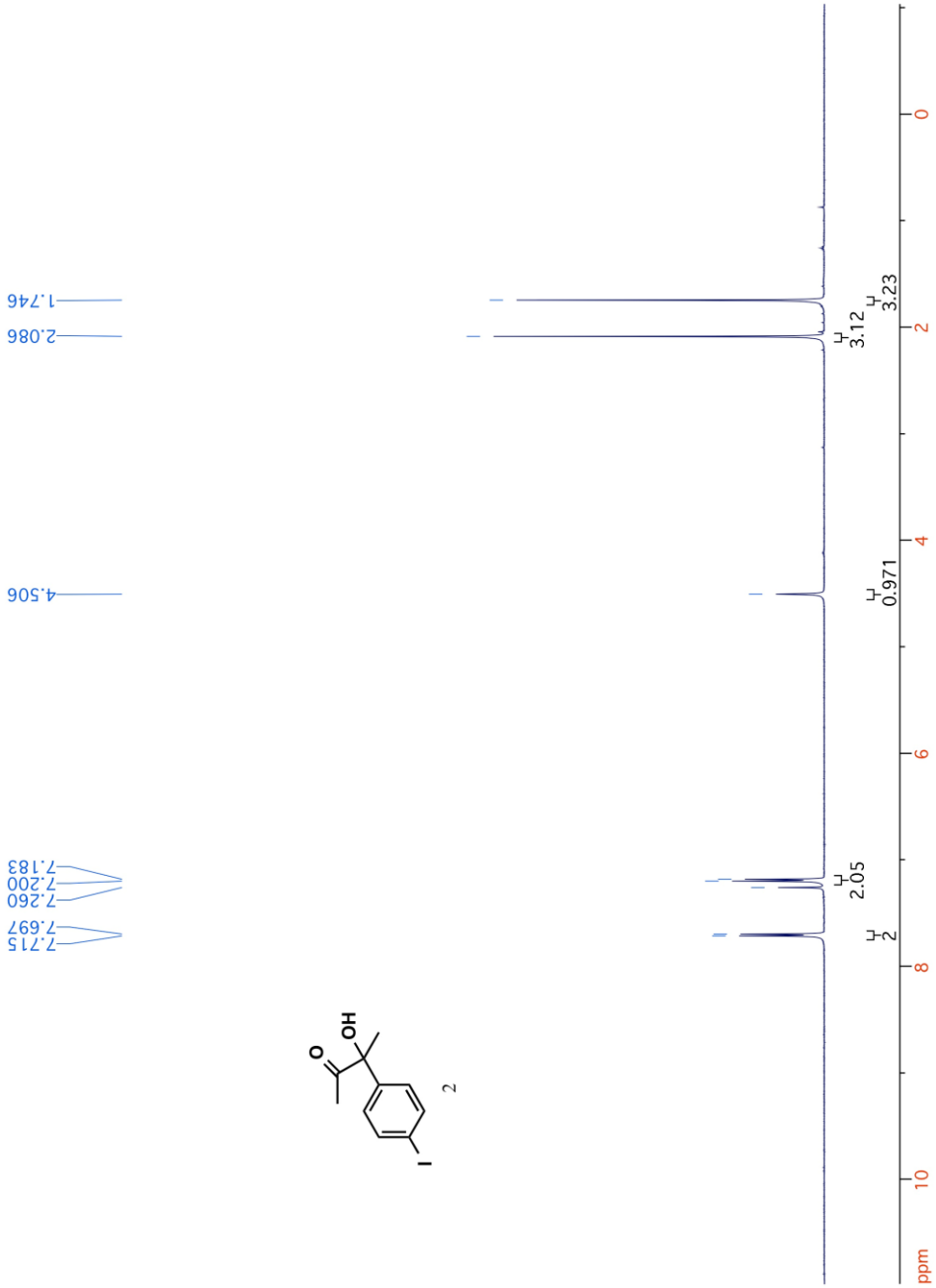
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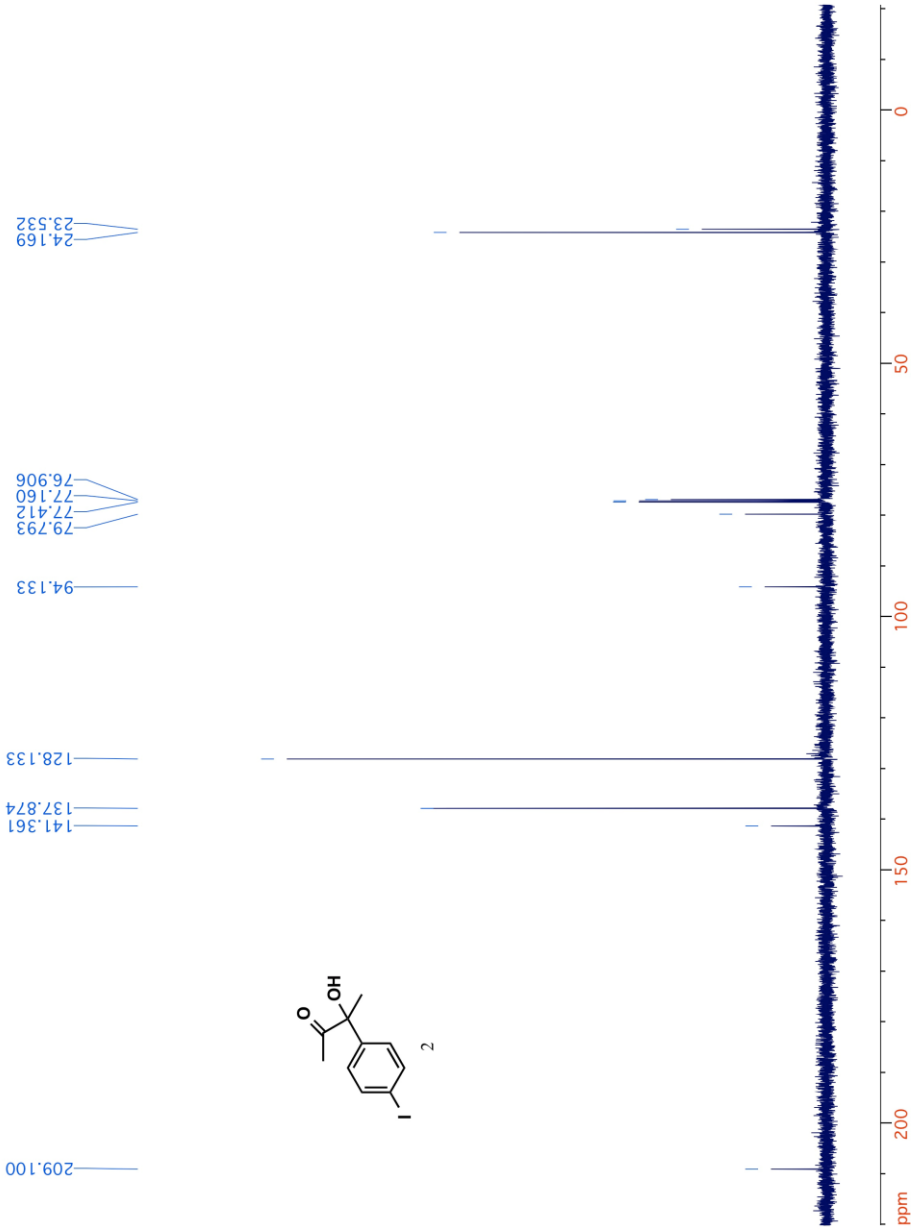
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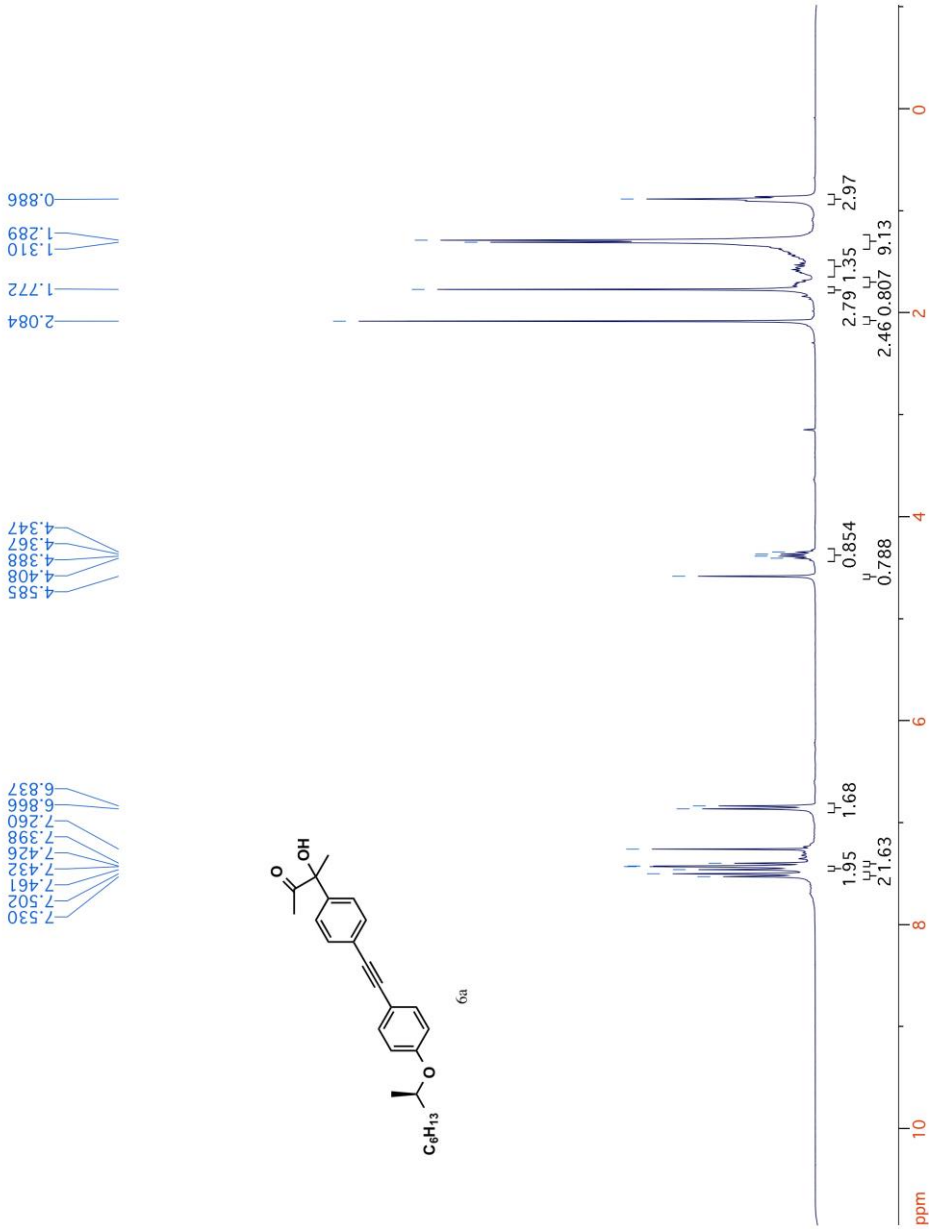
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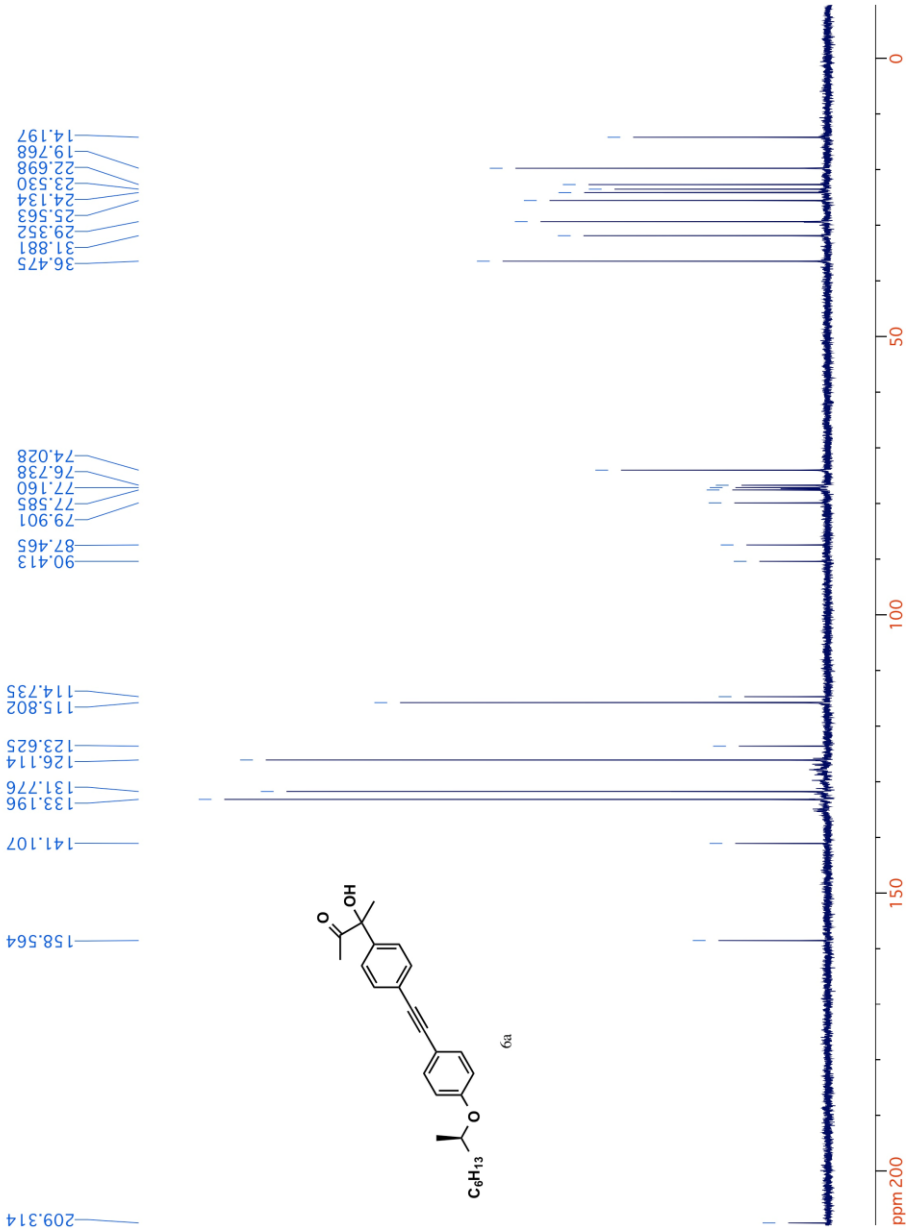
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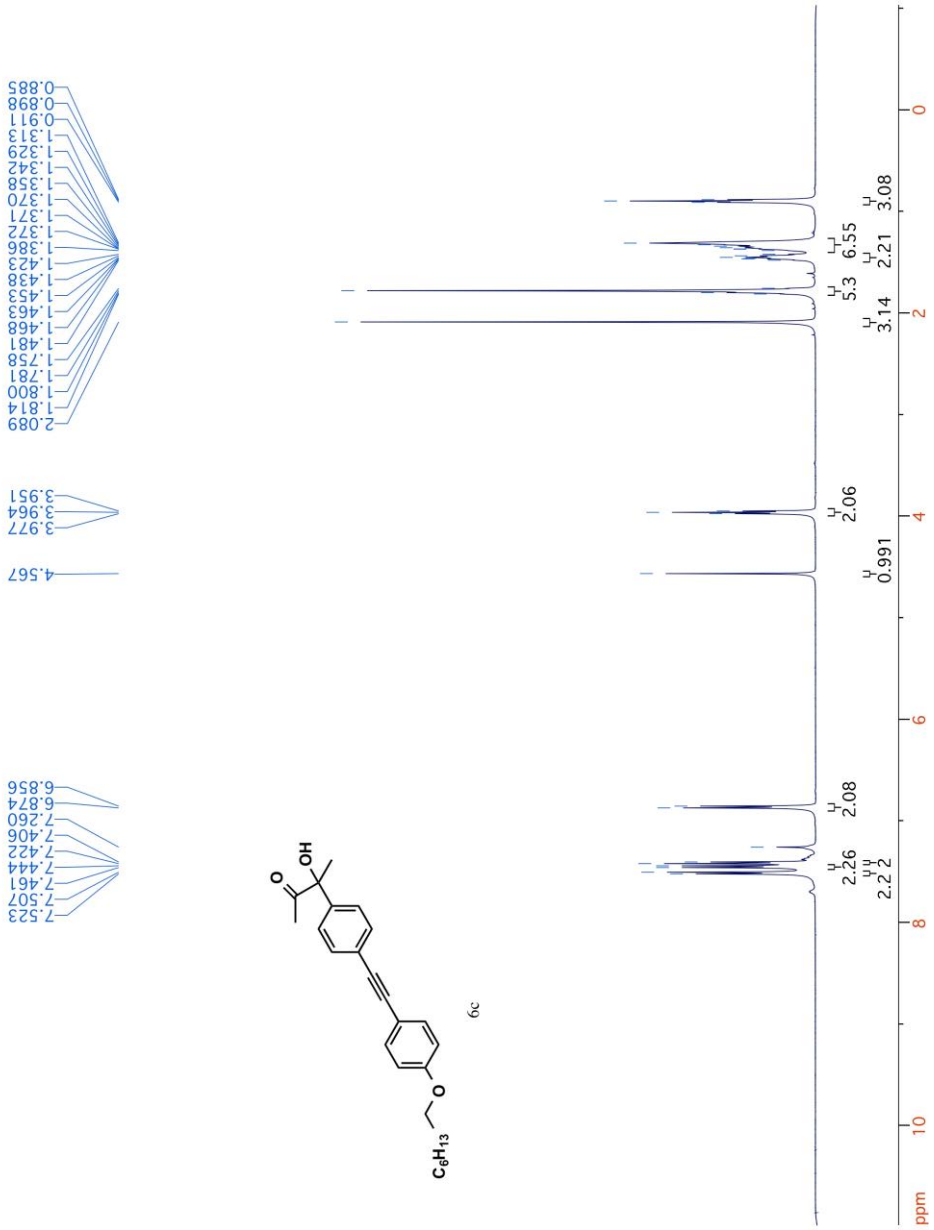
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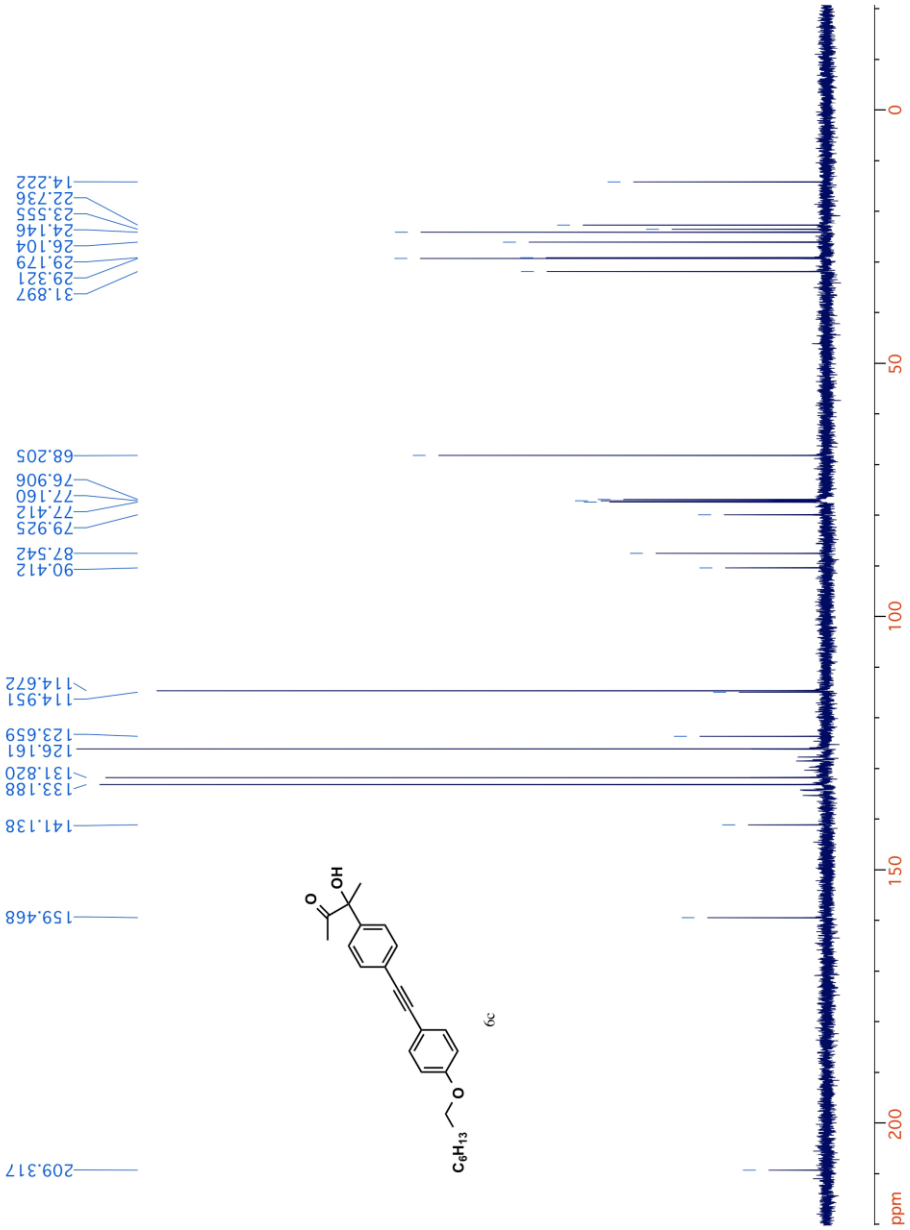


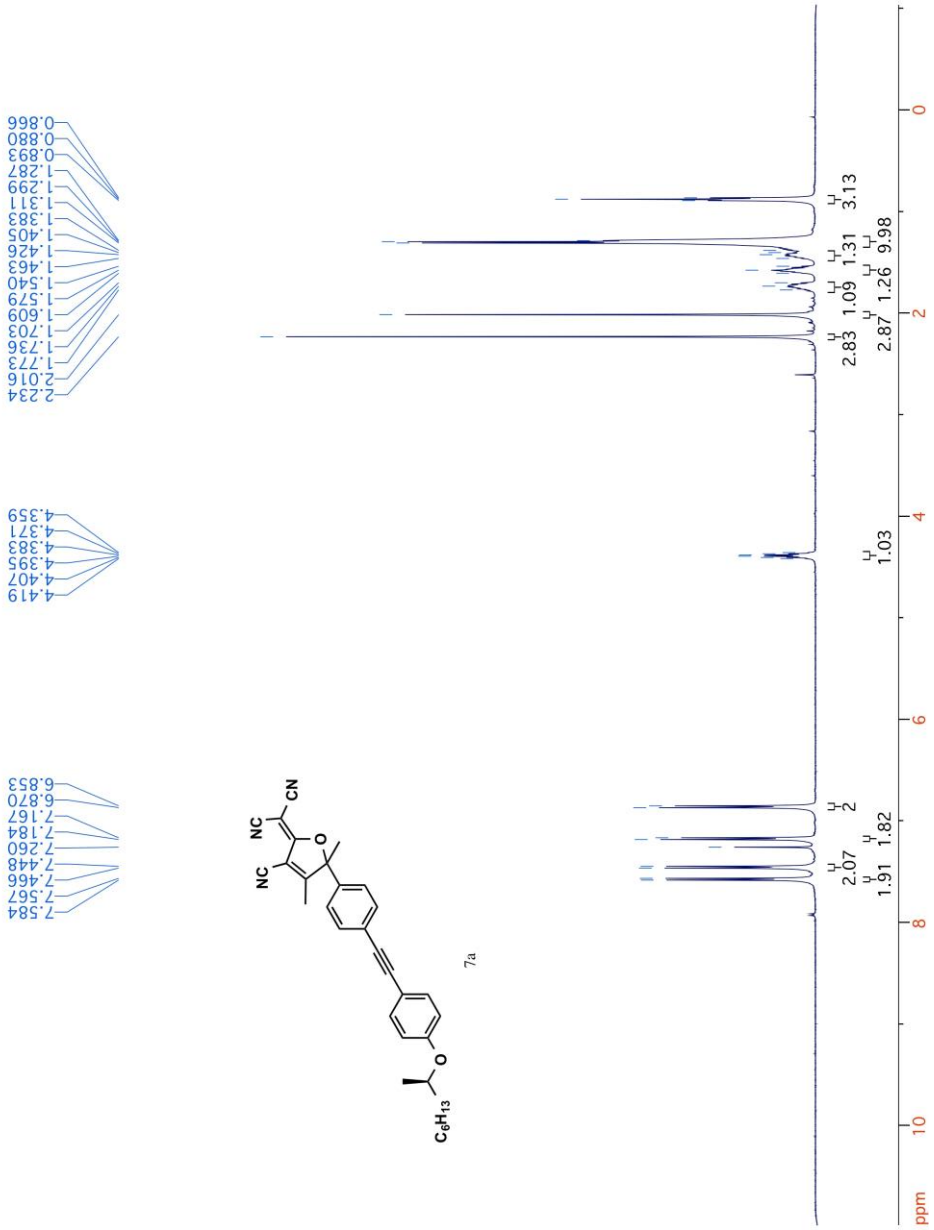

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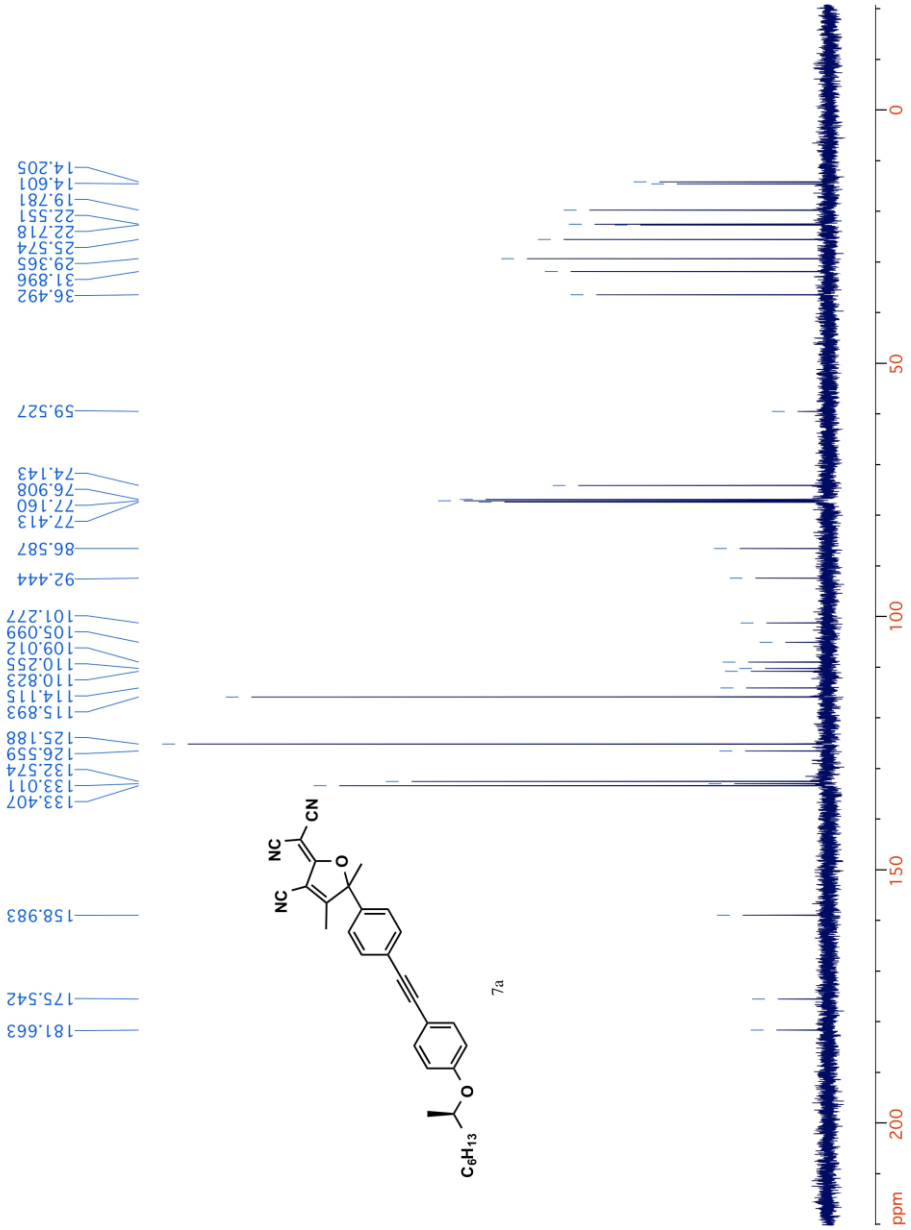

7.530
7.502
7.461
7.432
7.426
7.398
7.260
6.866
6.837
4.585
4.408
4.388
4.367
4.347
2.084
1.772
1.310
1.289
0.886
OH
O
O
C6H13
6a
1.95
21.63
1.68
0.854
0.788
2.79
1.35
2.46
0.807
9.13
2.97
ppm

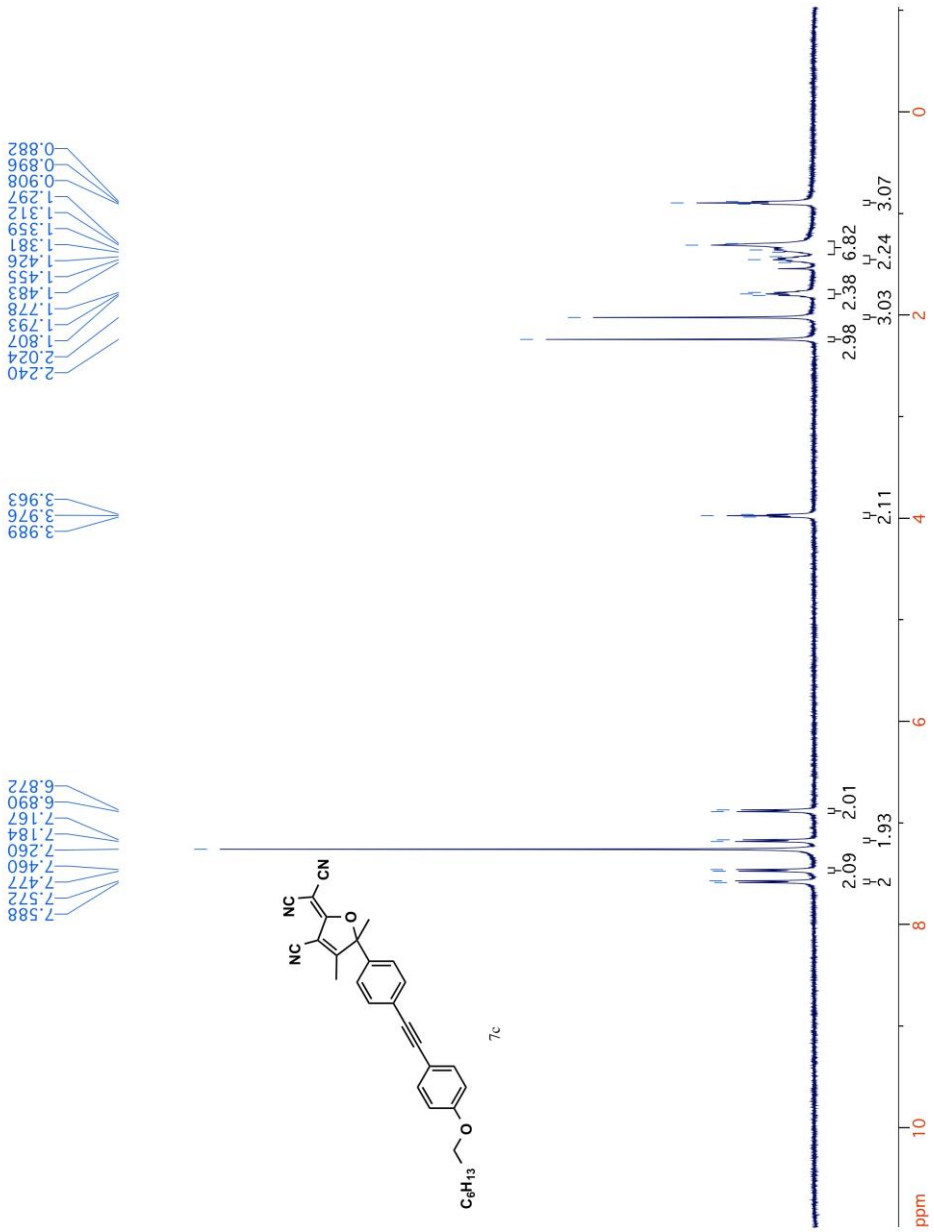

209.314
158.564
141.107
133.196
131.776
126.114
123.625
115.802
114.735
90.413
87.465
79.901
77.585
77.160
76.738
74.028
36.475
31.881
29.352
25.563
24.134
23.530
22.698
19.768
14.197
OH
O
O
C6H13
6a
ppm 200
150
100
50
0

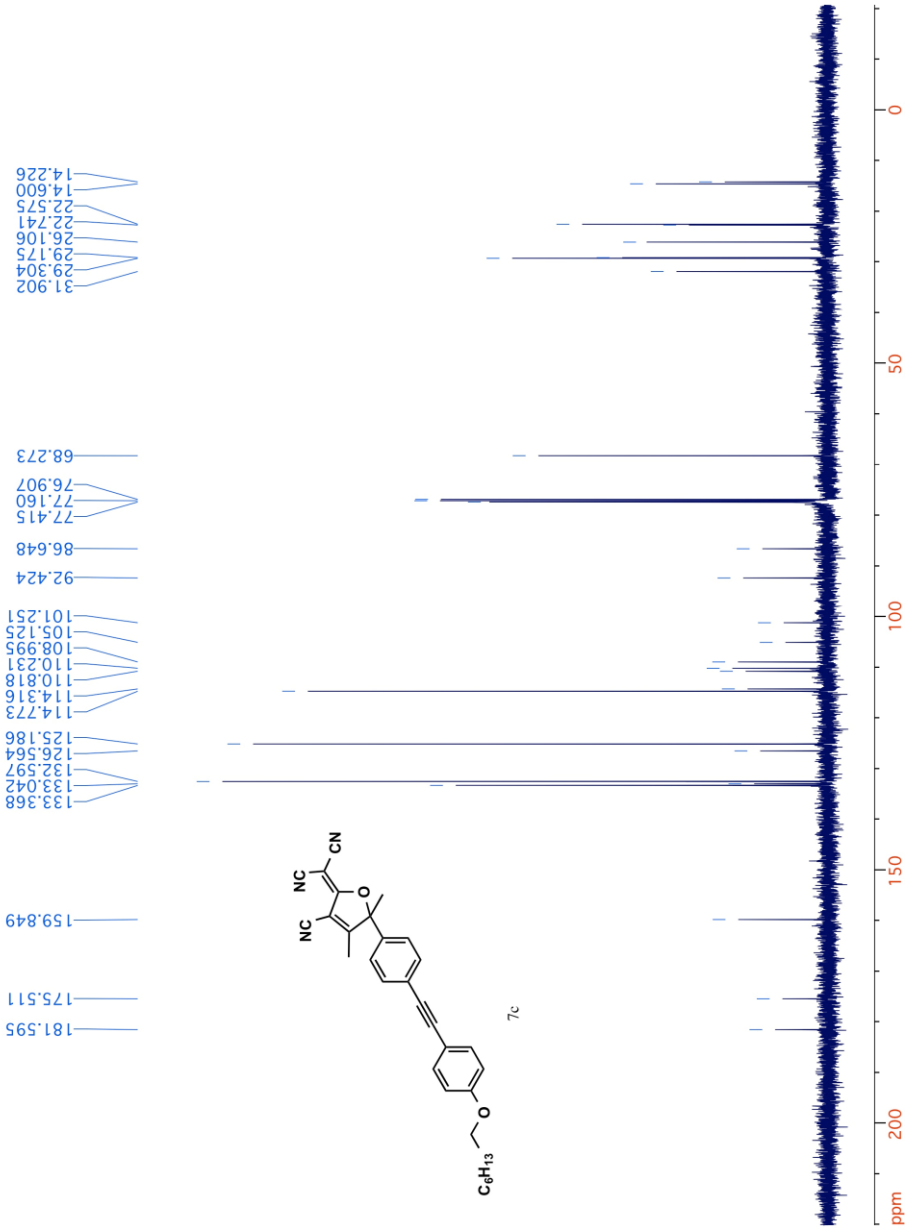

7.523
7.507
7.461
7.444
7.422
7.406
7.260
6.874
6.856
3.977
3.964
3.951
4.567
2.089
1.814
1.800
1.781
1.758
1.481
1.468
1.463
1.453
1.438
1.423
1.386
1.372
1.371
1.370
1.358
1.342
1.329
1.313
0.911
0.898
0.885
OH
O
O
C6H13
6c
2.26
2.22
2.08
0.991
2.06
3.14
5.3
2.21
6.55
3.08
ppm
0
2
4
6
8
10

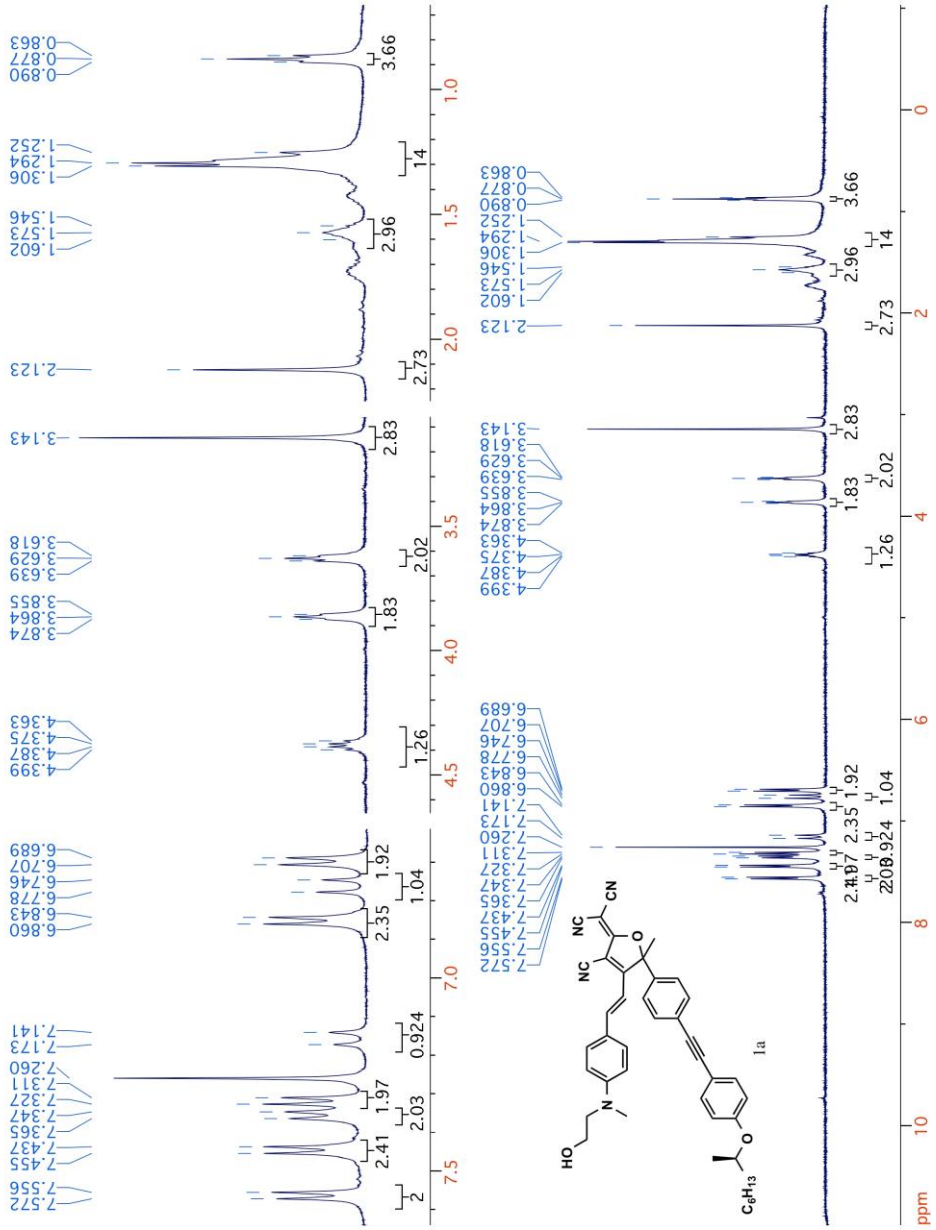

209.317
159.468
141.138
133.188
131.820
126.161
123.659
114.951
114.672
90.412
87.542
79.925
77.412
77.160
76.906
68.205
31.897
29.321
29.179
26.104
24.146
23.555
22.736
14.222
OH
O
O
C_6H_{13}
ppm
0
50
100
150
200

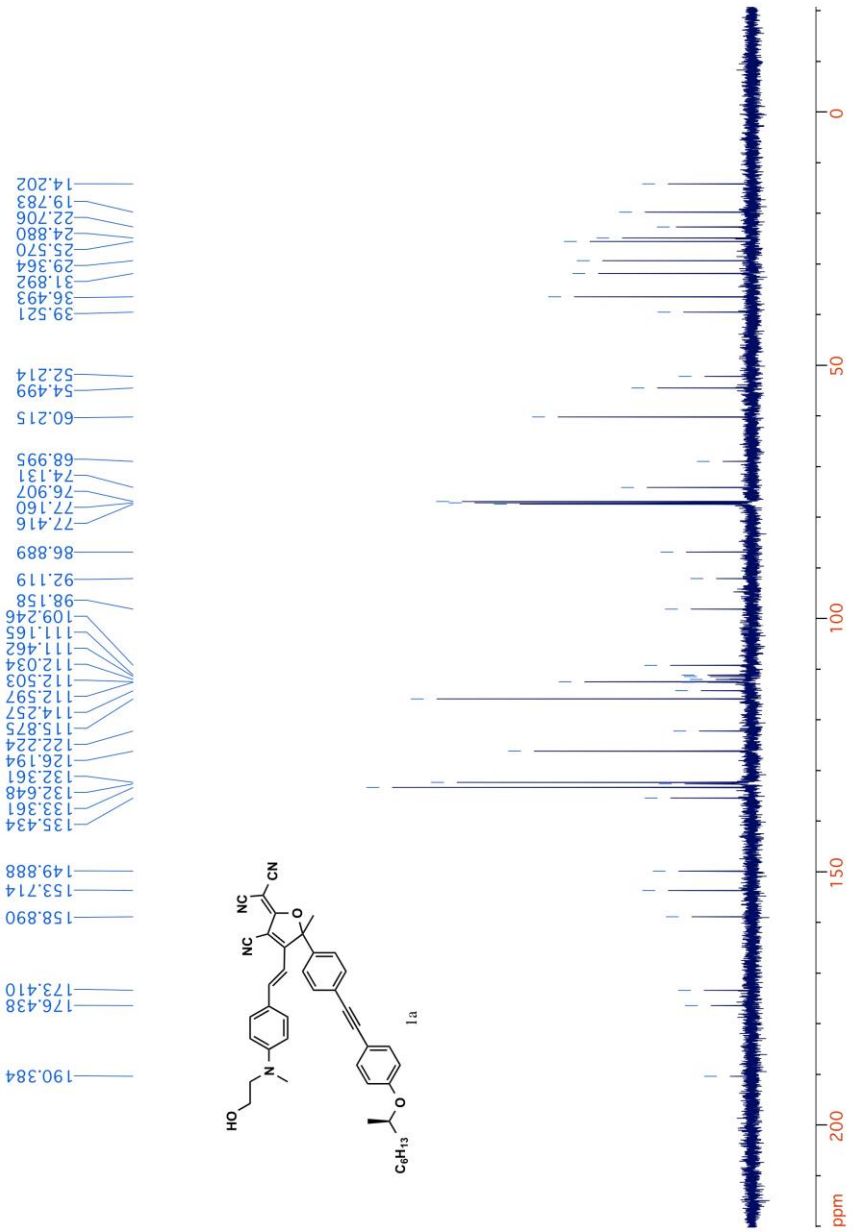

0.866
0.880
0.893
1.287
1.299
1.311
1.383
1.405
1.426
1.463
1.540
1.579
1.609
1.703
1.736
1.773
2.016
2.234
4.359
4.371
4.383
4.395
4.407
4.419
6.853
6.870
7.167
7.184
7.260
7.448
7.466
7.567
7.584
NC
CN
NC
O
O
C6H13
7a
2.83
1.09
1.31
3.13
2.87
1.26
9.98
1.03
2.07
1.91
1.82
2
ppm

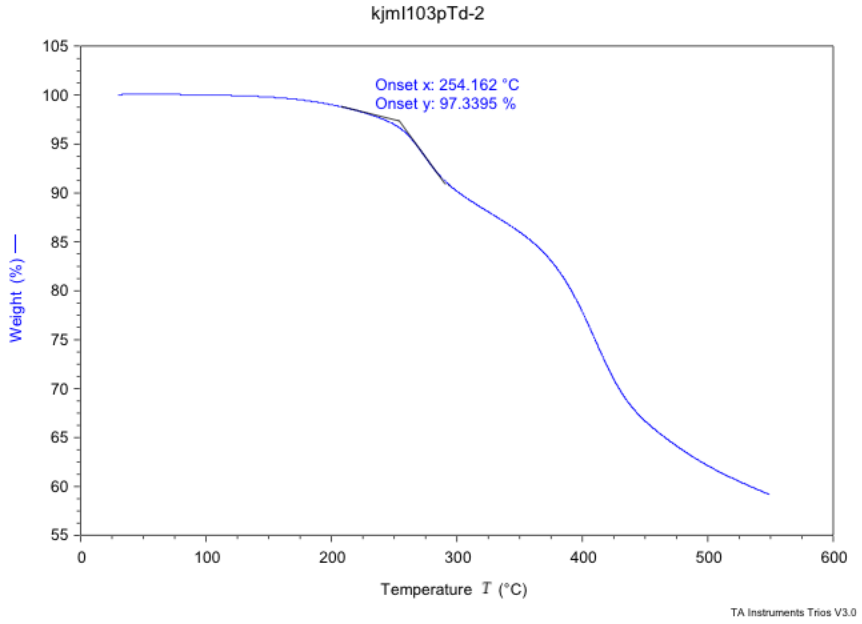

181.663
175.542
158.983
133.407
133.011
132.574
126.559
125.188
115.893
114.115
110.823
110.255
109.012
105.099
101.277
92.444
86.587
77.413
77.160
76.908
74.143
59.527
36.492
31.896
29.365
25.574
22.718
22.551
19.781
14.601
14.205
NC
CN
NC
O
O
C6H13
7a
0
50
100
150
200
ppm

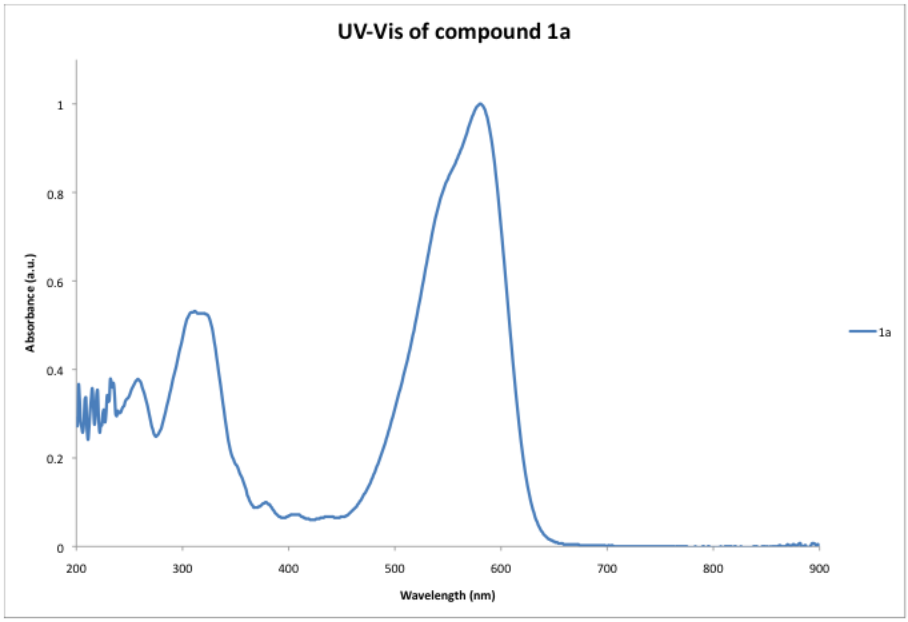

7.588
7.572
7.477
7.460
7.260
7.184
7.167
6.890
6.872
3.989
3.976
3.963
2.240
2.024
1.807
1.793
1.778
1.483
1.455
1.426
1.381
1.359
1.312
1.297
0.908
0.896
0.882
NC
CN
NC
O
O
C6H13
7c
2.09
2.01
1.93
2
2.11
2.98
2.38
3.03
6.82
2.24
3.07
ppm
10
8
6
4
2
0

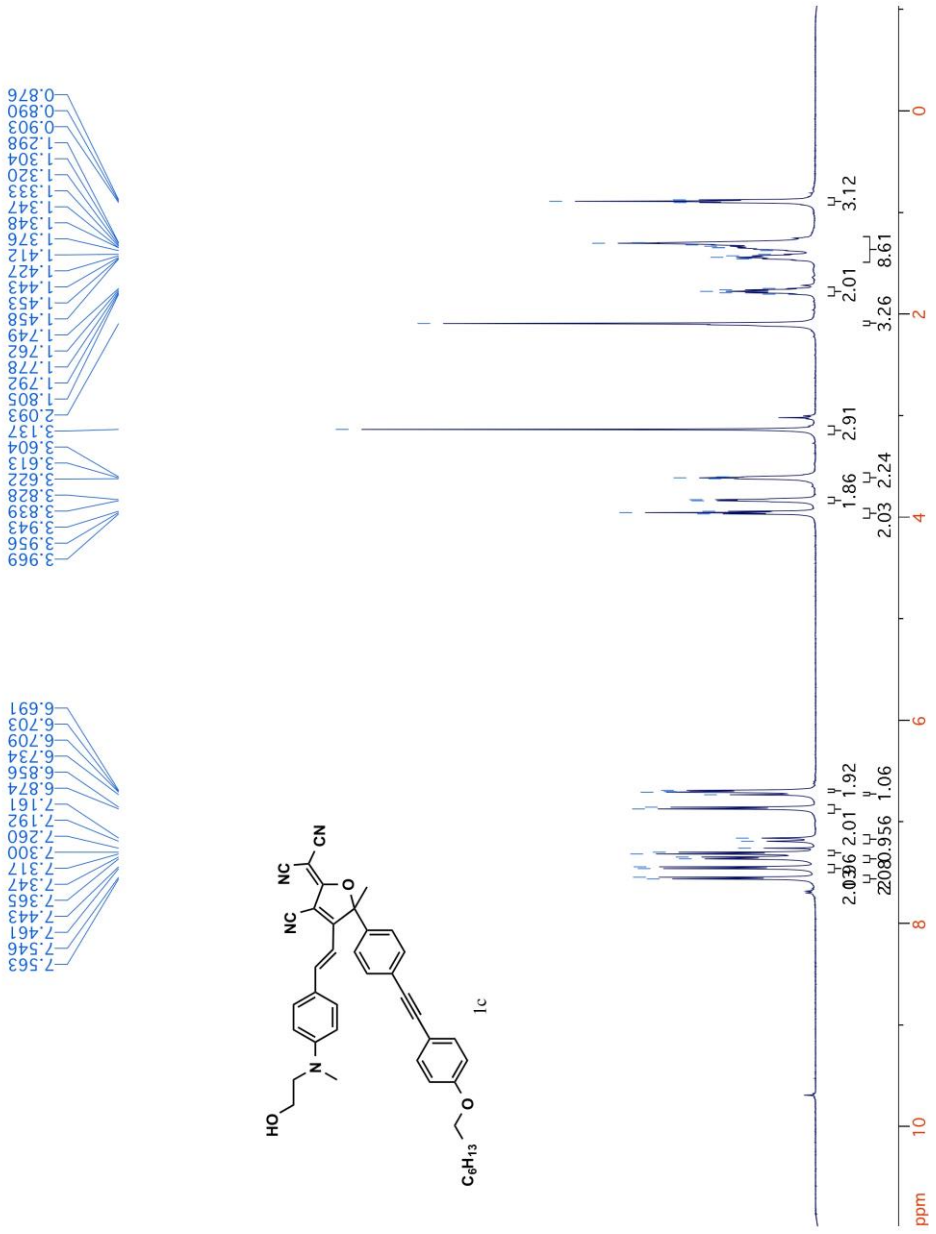

14.226
14.600
22.575
22.741
26.106
29.175
29.304
31.902
68.273
76.907
77.160
77.415
86.648
92.424
101.251
105.125
108.995
110.231
110.818
114.316
114.773
125.186
126.564
132.597
133.042
133.368
159.849
175.511
181.595
NC
CN
O
O
C_6H_{13}
7c
0
50
100
150
200
ppm

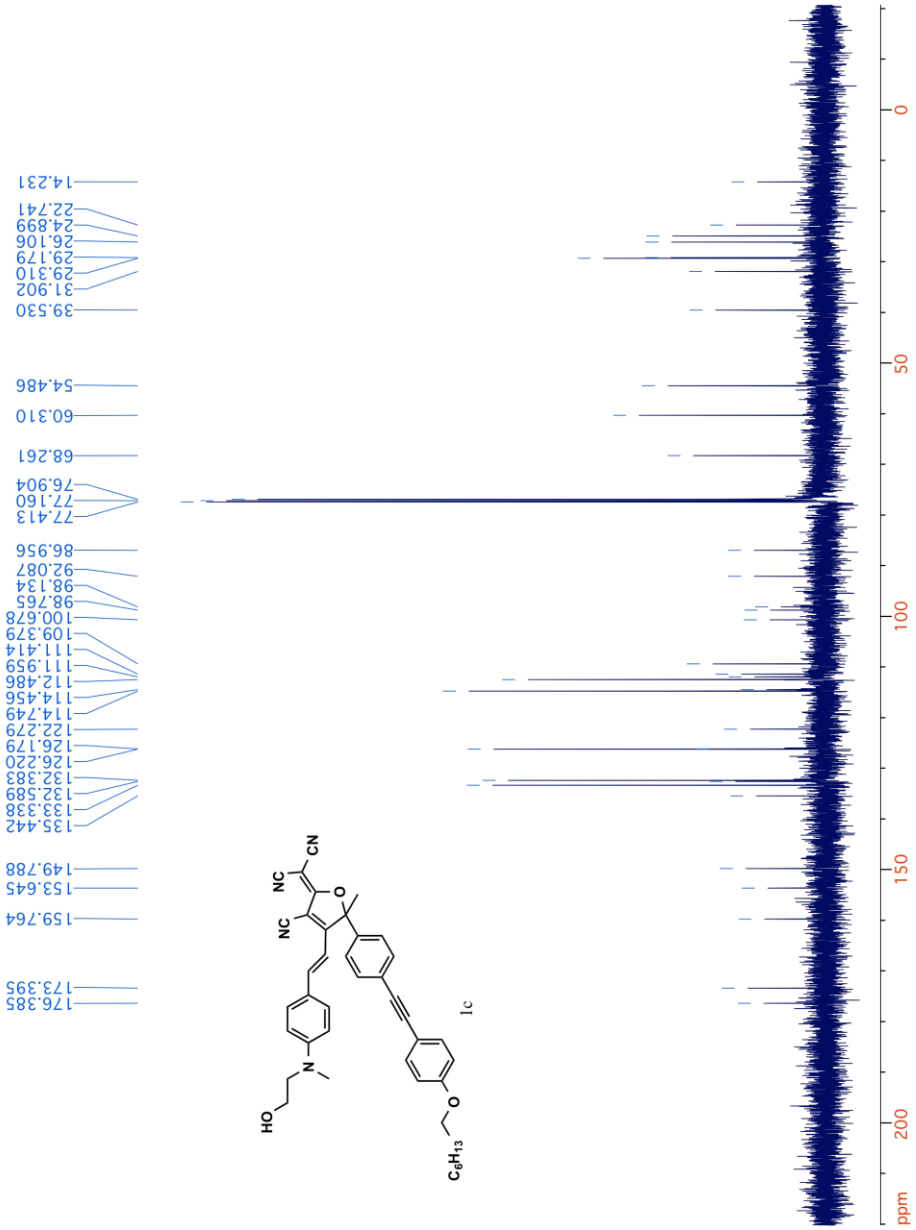

NC
CN
NC
O
N
HO
O
C_6H_{13}
1a
ppm

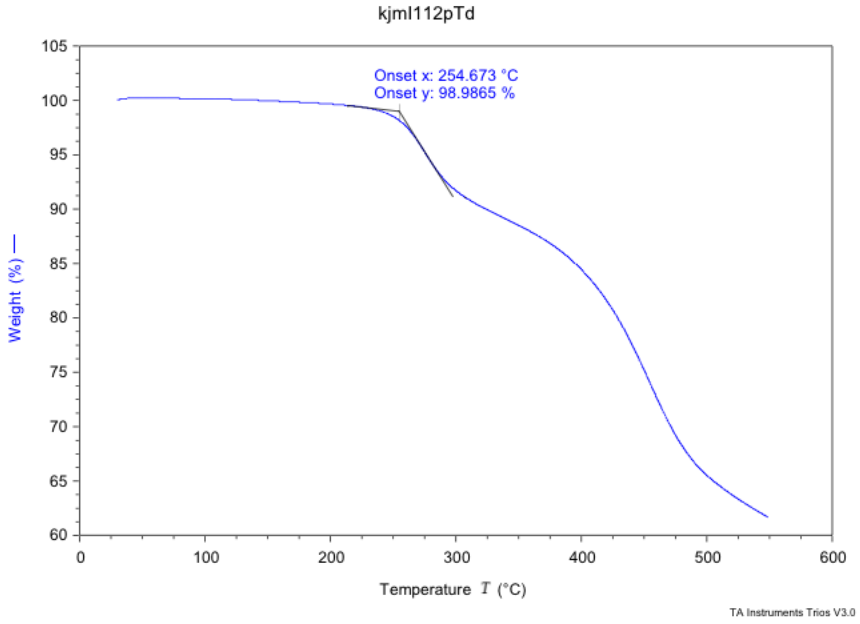

14.202
19.783
22.706
24.880
25.570
29.364
31.892
36.493
39.521
52.214
54.499
60.215
68.995
74.131
76.907
77.160
77.416
86.889
92.119
98.158
109.246
111.165
111.462
112.034
112.503
112.597
114.257
115.875
122.224
126.194
132.361
132.648
133.361
135.434
149.888
153.714
158.890
173.410
176.438
190.384
NC
CN
NC
O
N
HO
O
C_6H_{13}
1a
0
50
100
150
200
ppm

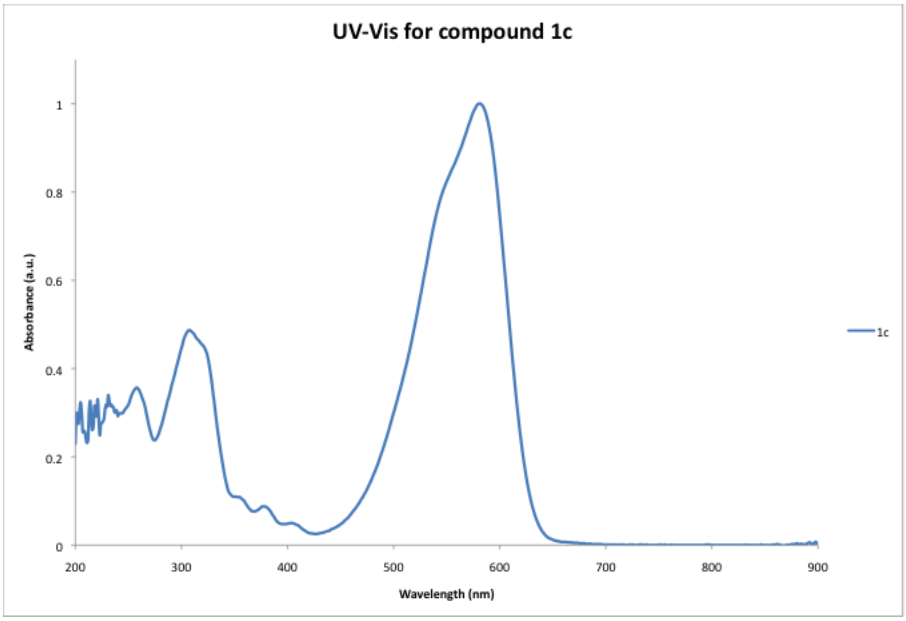

kjml103pTd-2
Onset x: 254.162 °C
Onset y: 97.3395 %
Weight (%)
Temperature T (°C)
TA Instruments Trios V3.0


UV-Vis of compound 1a
Absorbance (a.u.)
Wavelength (nm)
1a

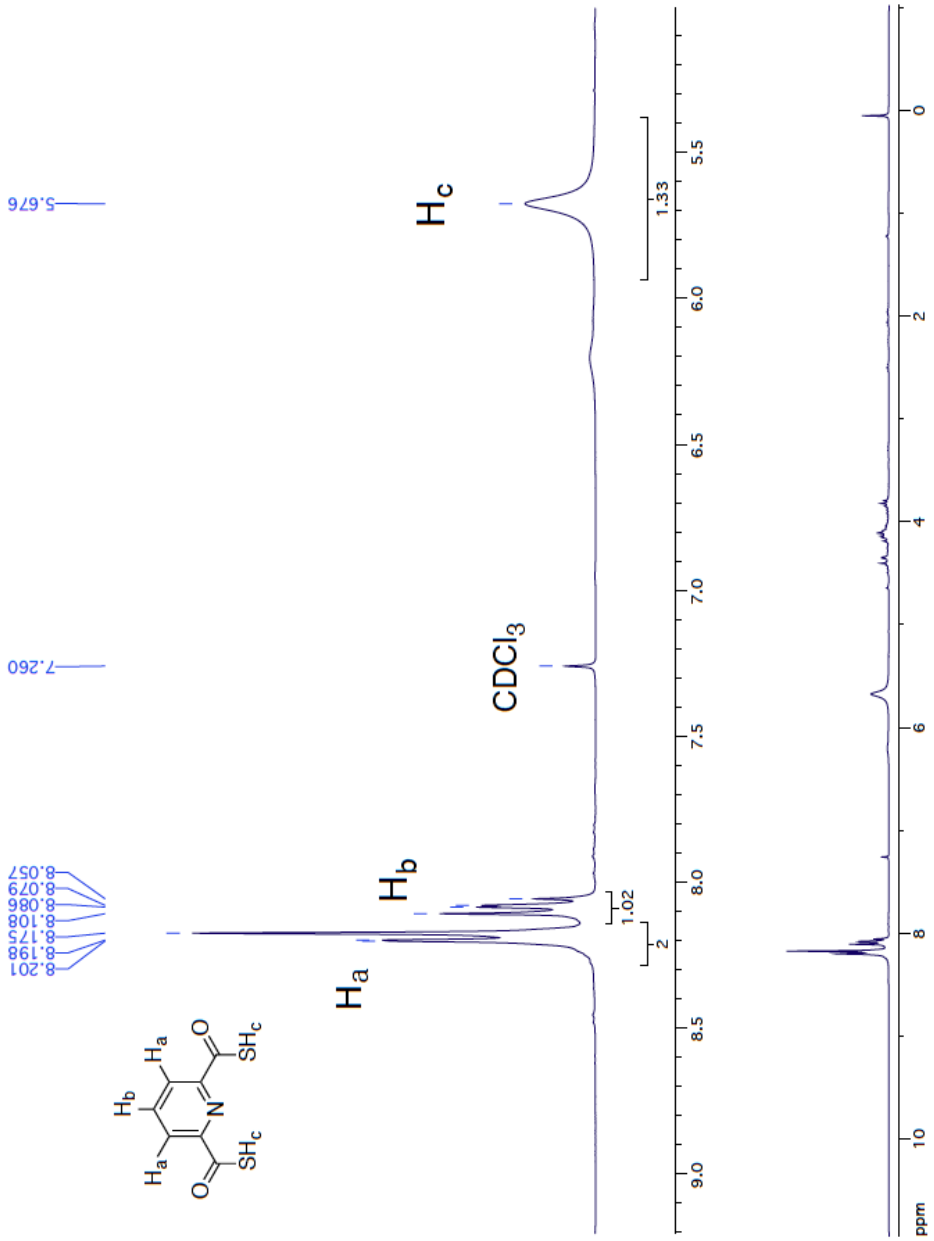

0.876
0.890
0.903
1.298
1.304
1.320
1.333
1.347
1.348
1.376
1.412
1.427
1.443
1.453
1.458
1.749
1.762
1.778
1.792
1.805
2.093
3.137
3.604
3.613
3.622
3.828
3.839
3.943
3.956
3.969
6.691
6.703
6.709
6.734
6.856
6.874
7.161
7.192
7.260
7.300
7.317
7.347
7.365
7.443
7.461
7.546
7.563
NC
NC
CN
O
N
HO
O
C6H13
Ic
2.00
2.01
1.92
1.06
0.956
2.03
1.86
2.24
2.91
3.26
2.01
8.61
3.12
ppm
0
2
4
6
8
10

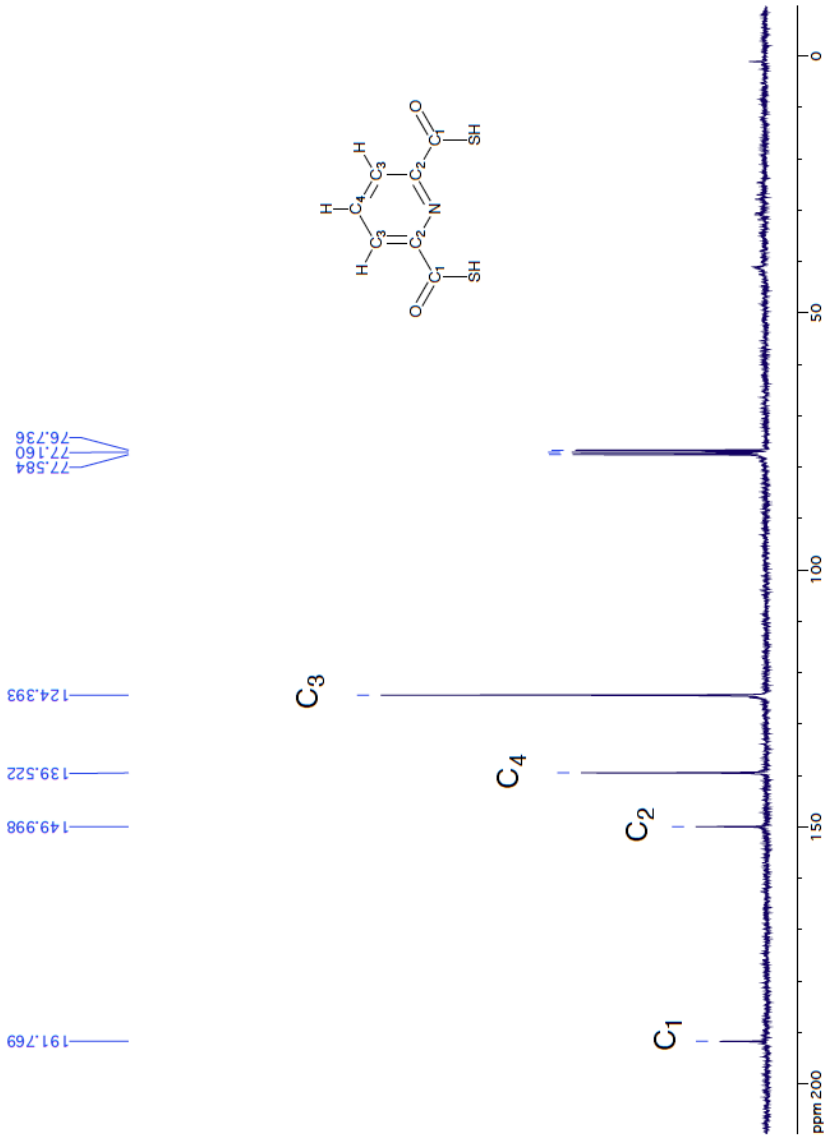

14.231
22.741
24.899
26.106
29.179
29.310
31.902
39.530
54.486
60.310
68.261
76.904
77.160
77.413
86.956
92.087
98.134
98.765
100.678
109.379
111.414
111.959
112.486
114.456
114.749
122.279
126.179
126.220
132.383
132.589
133.338
135.442
149.788
153.645
159.764
173.395
176.385
NC
CN
NC
O
N
HO
O
C6H13
1c
0
50
100
150
200
ppm

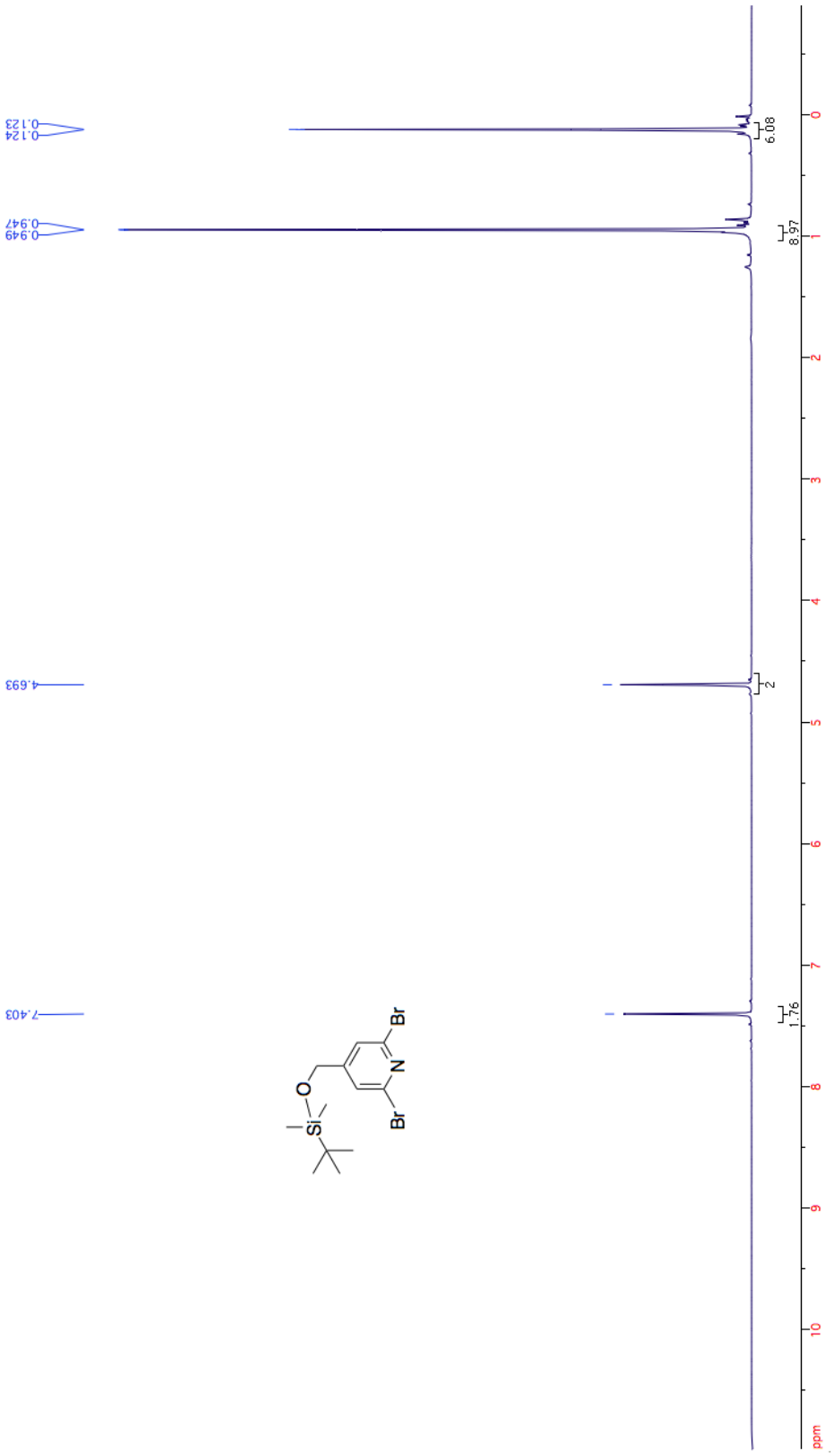

kjml112pTd
Onset x: 254.673 °C
Onset y: 98.9865 %
Weight (%)
Temperature T (°C)
TA Instruments Trios V3.0

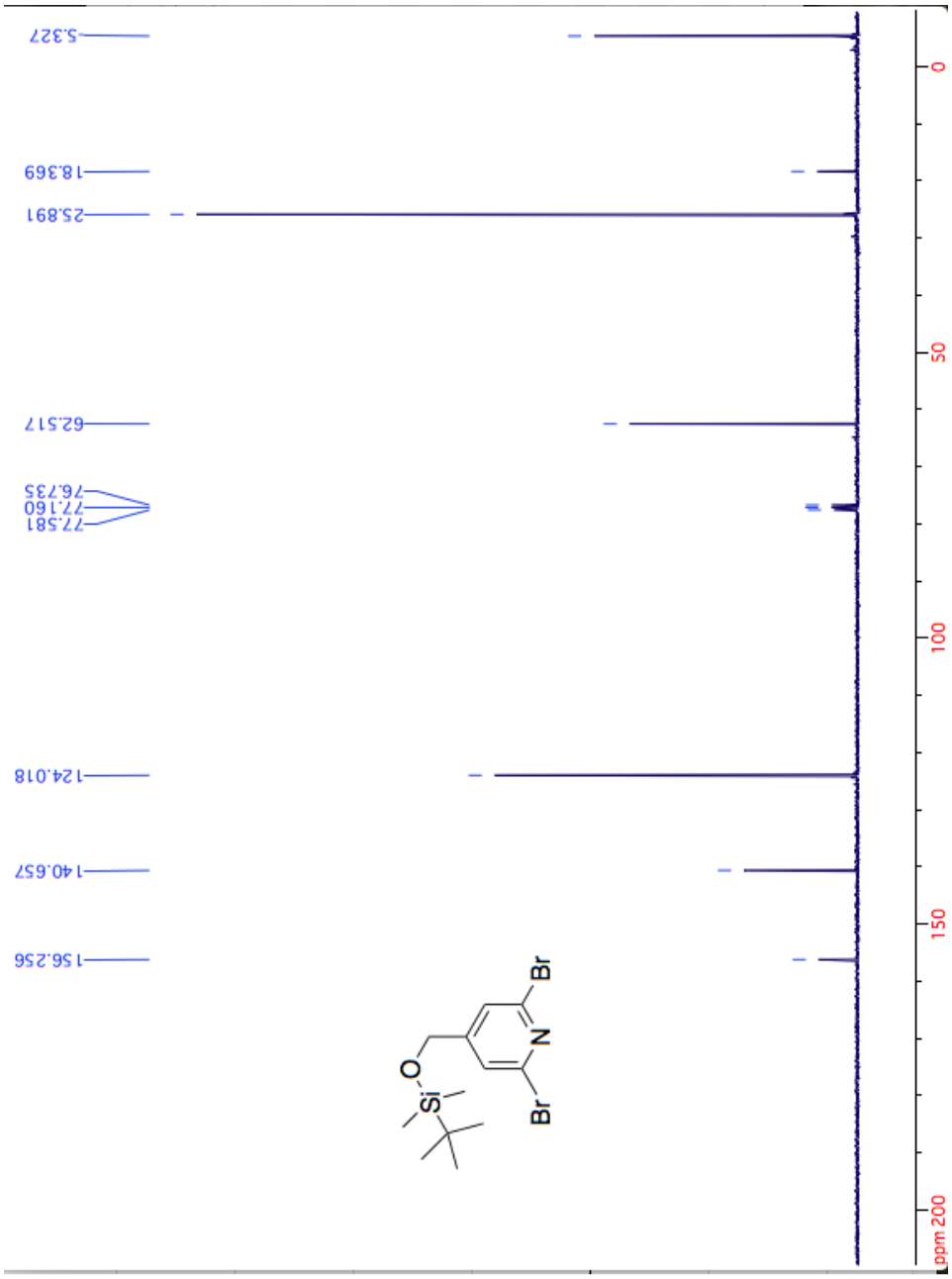

UV-Vis for compound 1c
Absorbance (a.u.)
Wavelength (nm)
1c

Chapter Two Spectral Data

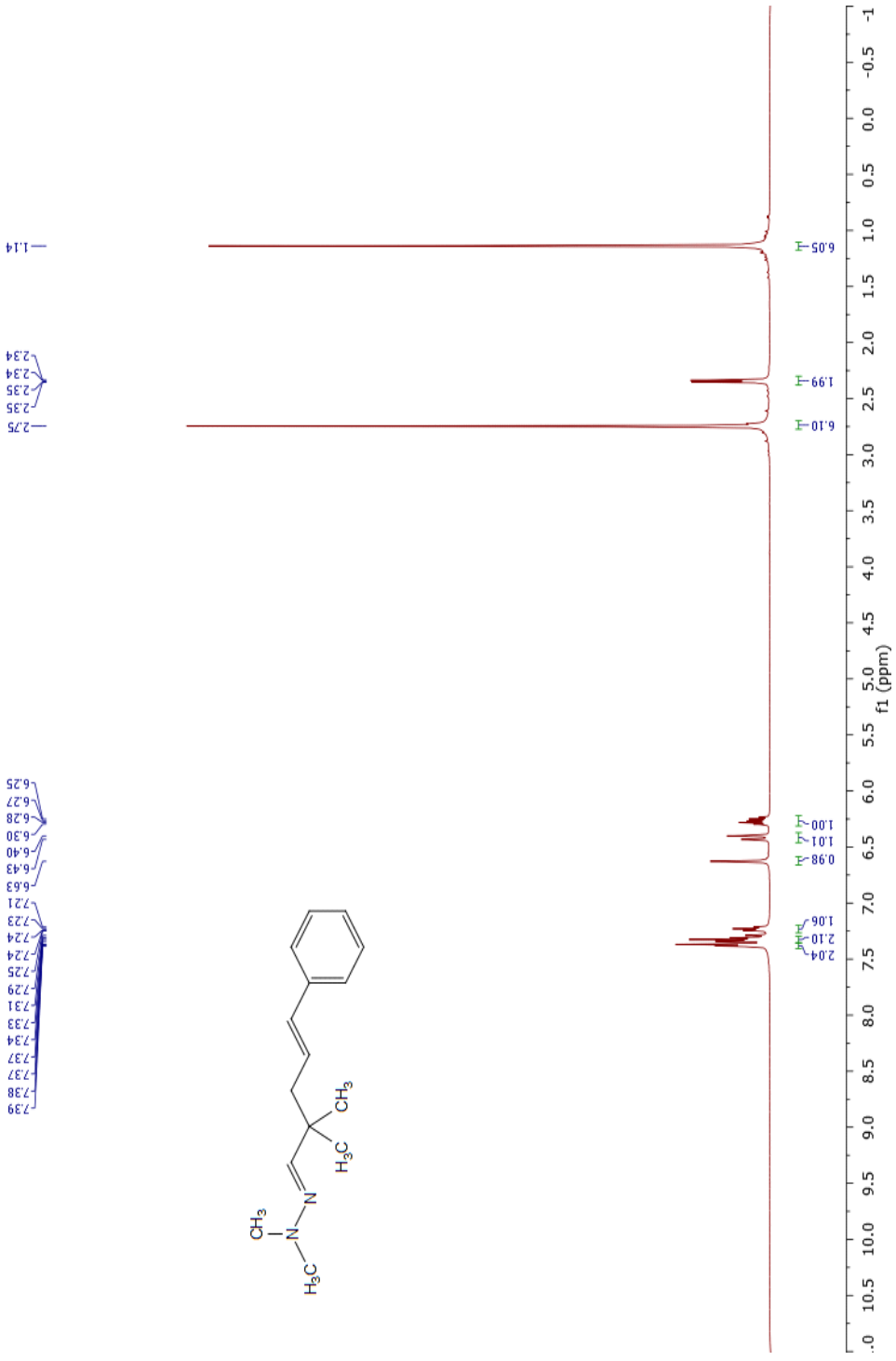


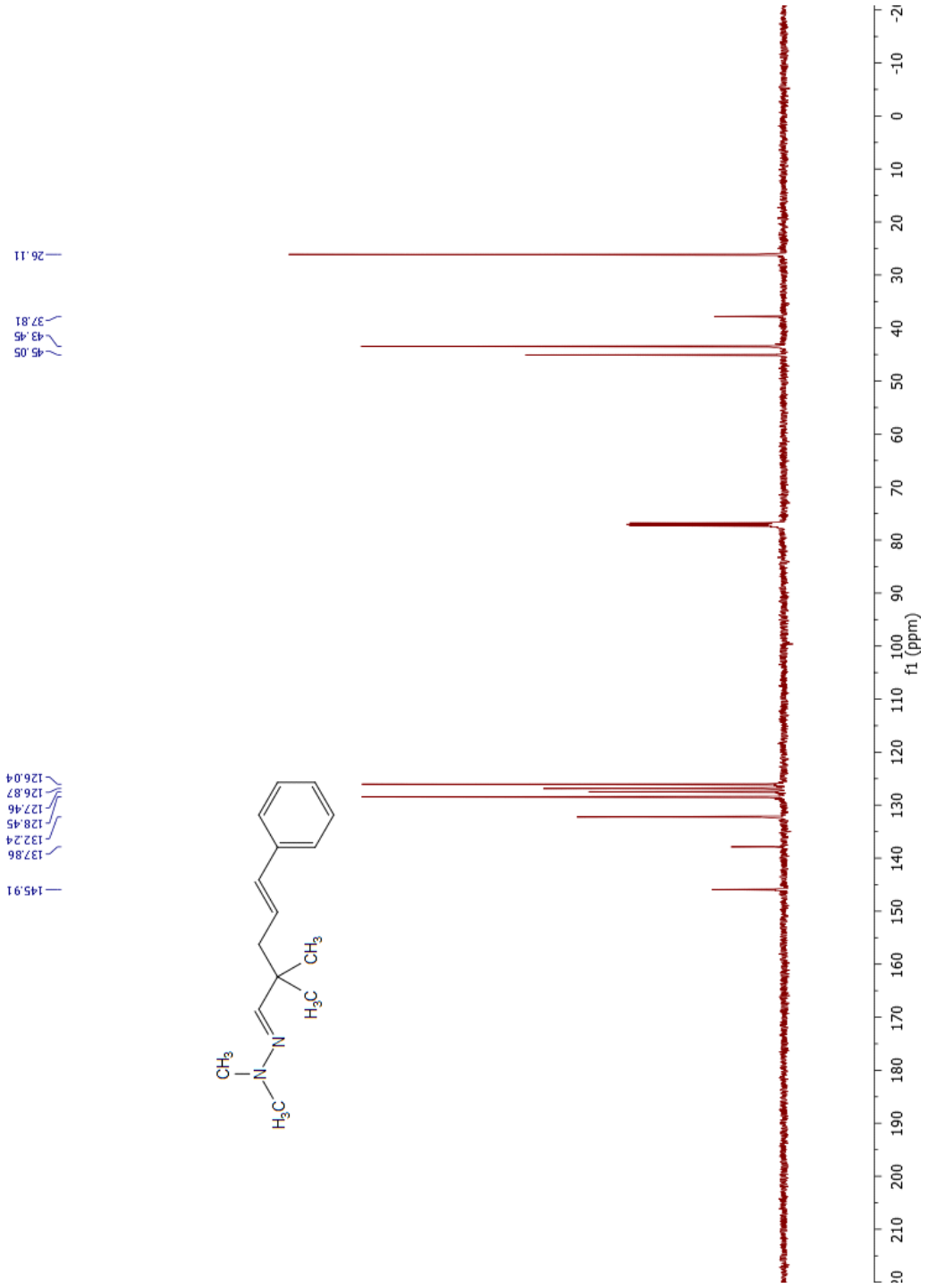

191.769
149.998
139.522
124.393
77.584
77.160
76.736
C1
C2
C4
C3
ppm 200
150
100
50
0

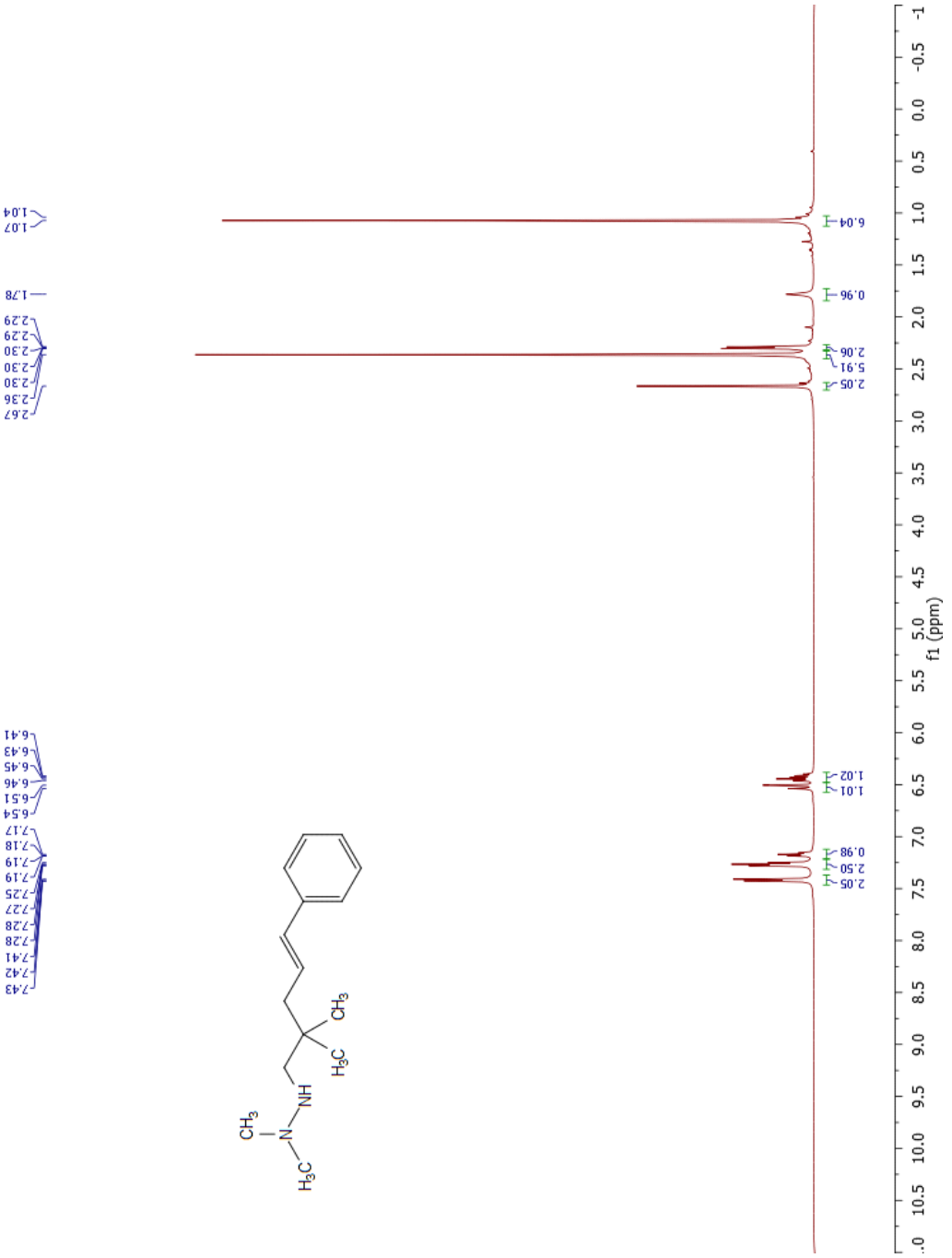

0.123
0.124
0.947
0.949
4.693
7.403
6.08
8.97
2
1.76
Br
N
Br
O
Si
ppm

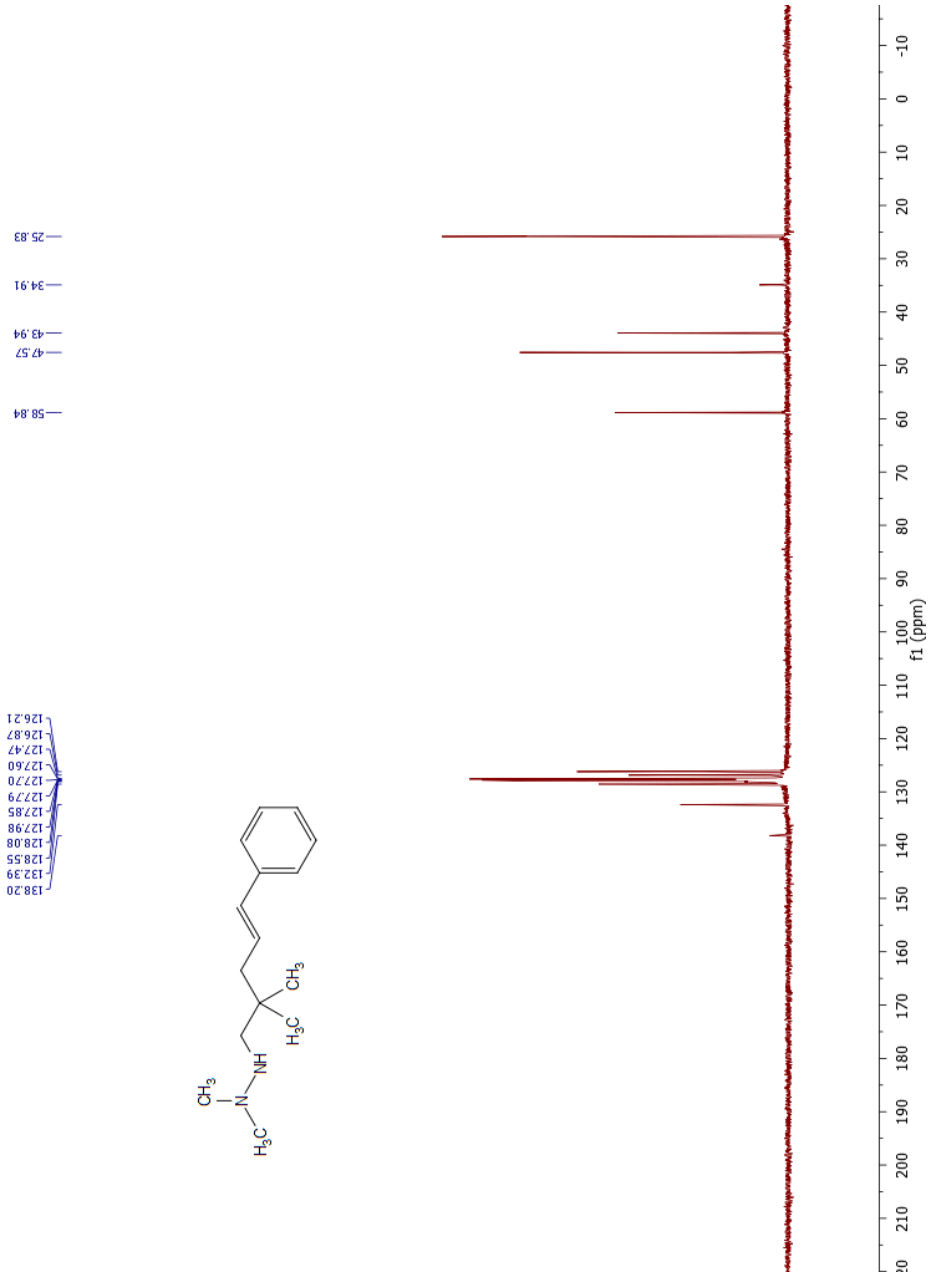

5.327
18.369
25.891
62.517
76.735
77.160
77.581
124.018
140.657
156.256
Br
N
Br
O
Si
0
50
100
150
200
ppm

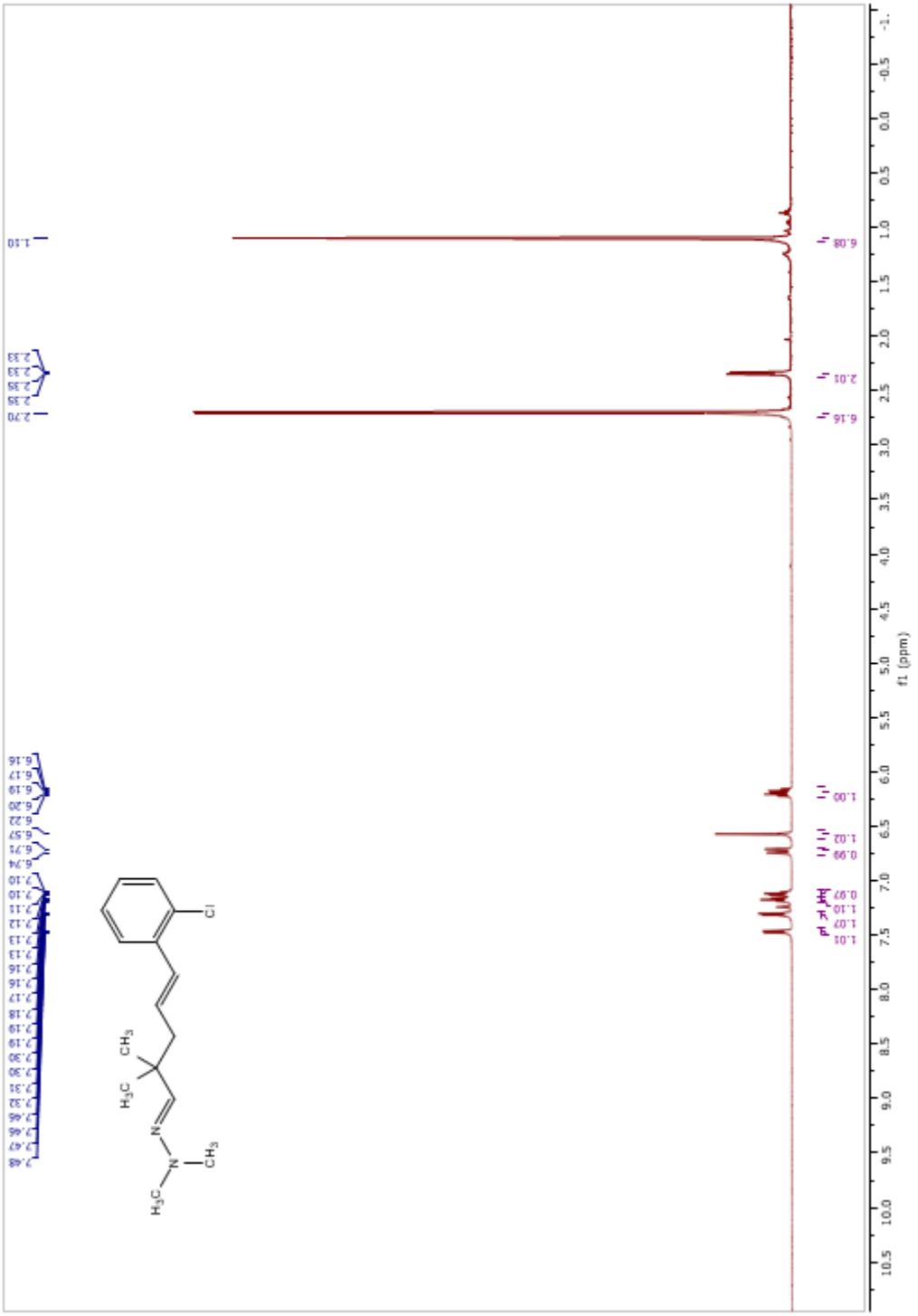
Chapter Four Spectral Data

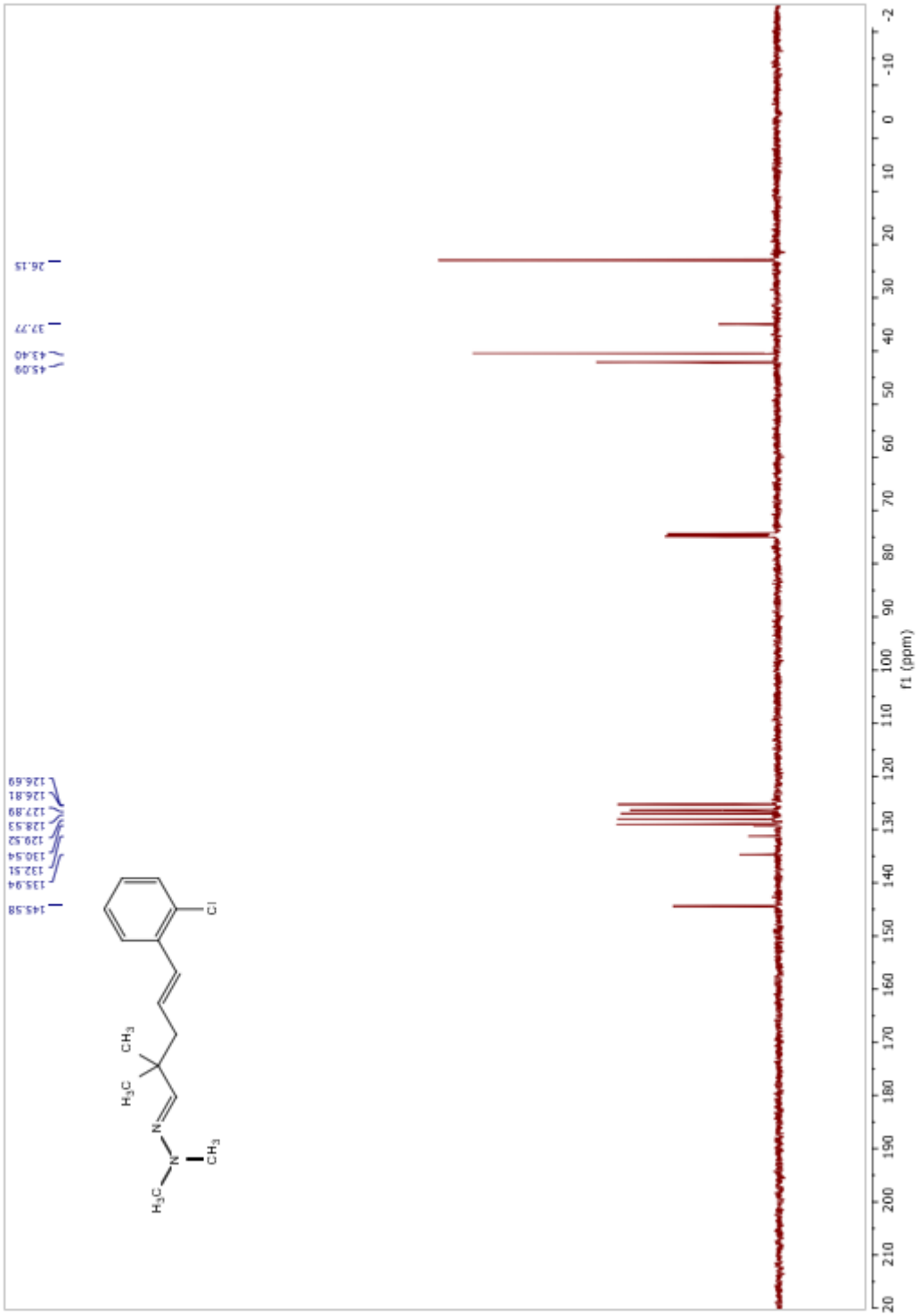


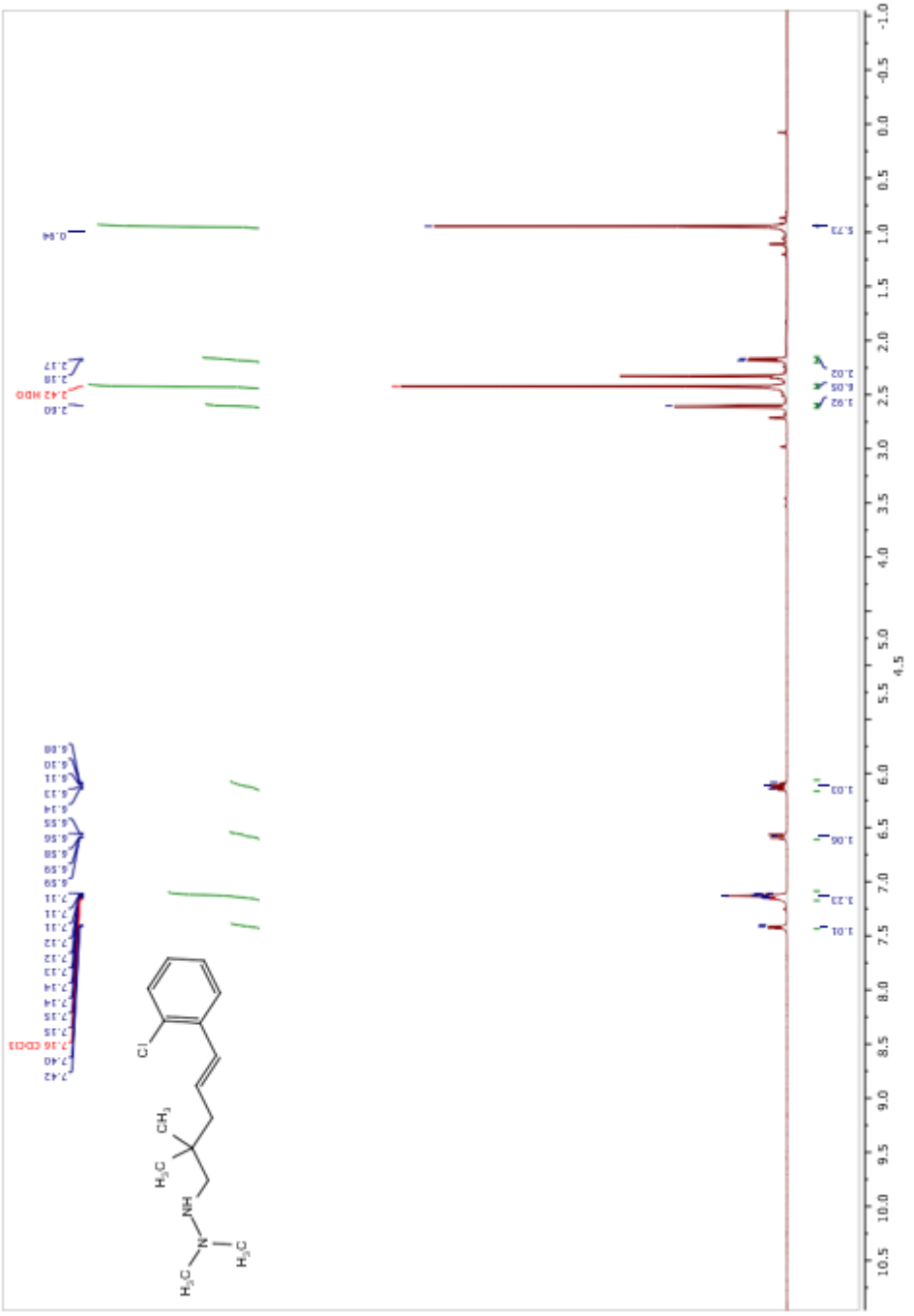

145.91
137.86
132.24
128.45
127.46
126.87
126.04
45.05
43.45
37.81
26.11
CH3
N
N
H3C
H3C
CH3
f1 (ppm)

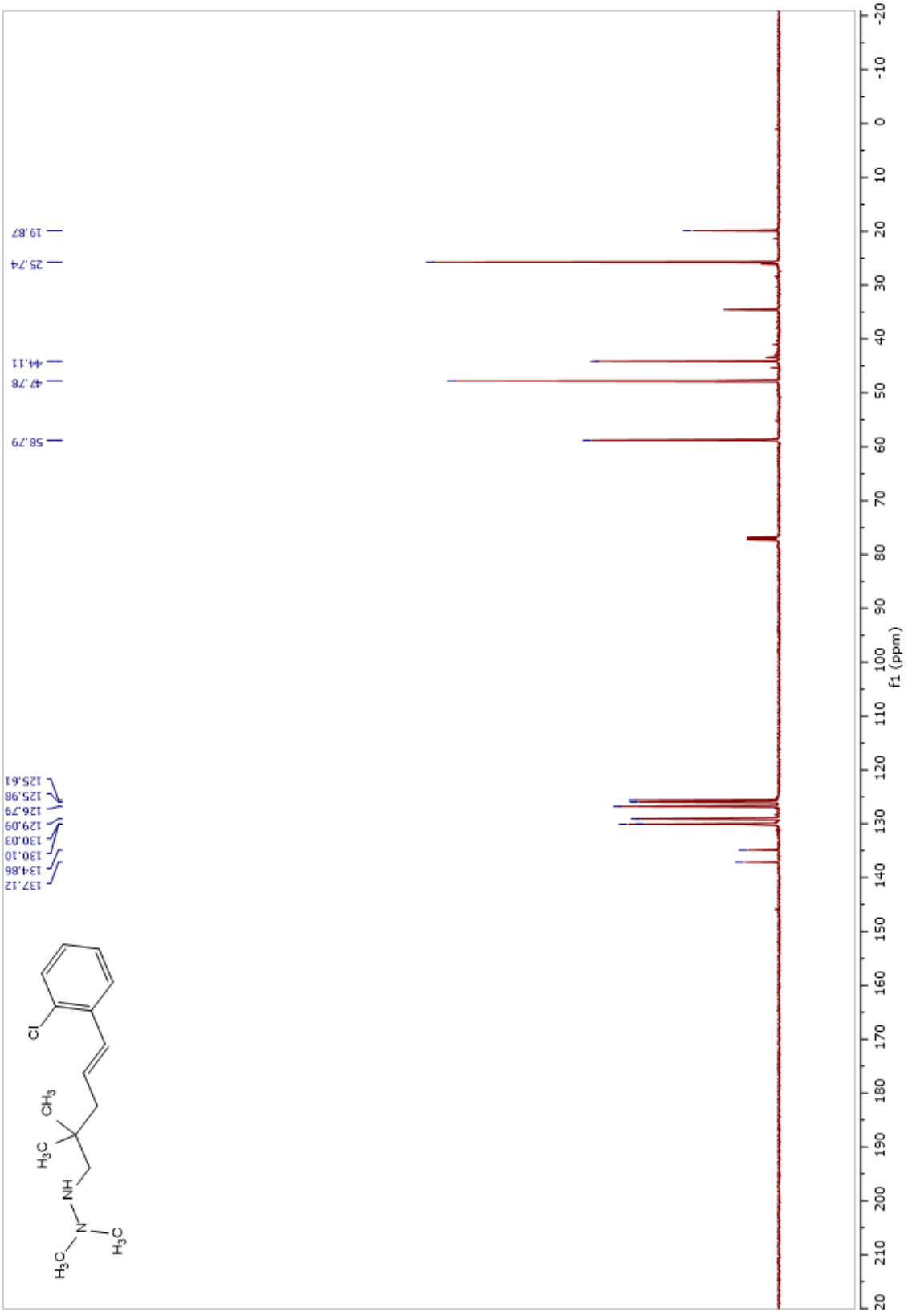

f1 (ppm)
6.04
0.96
2.06
5.91
2.05
1.01
1.02
0.98
2.50
2.05
1.04
1.07
1.78
2.67
2.36
2.30
2.30
2.30
2.29
2.29
6.41
6.43
6.45
6.46
6.51
6.54
7.17
7.18
7.19
7.19
7.25
7.27
7.28
7.28
7.41
7.42
7.43
CH3
N
H3C
NH
H3C
CH3

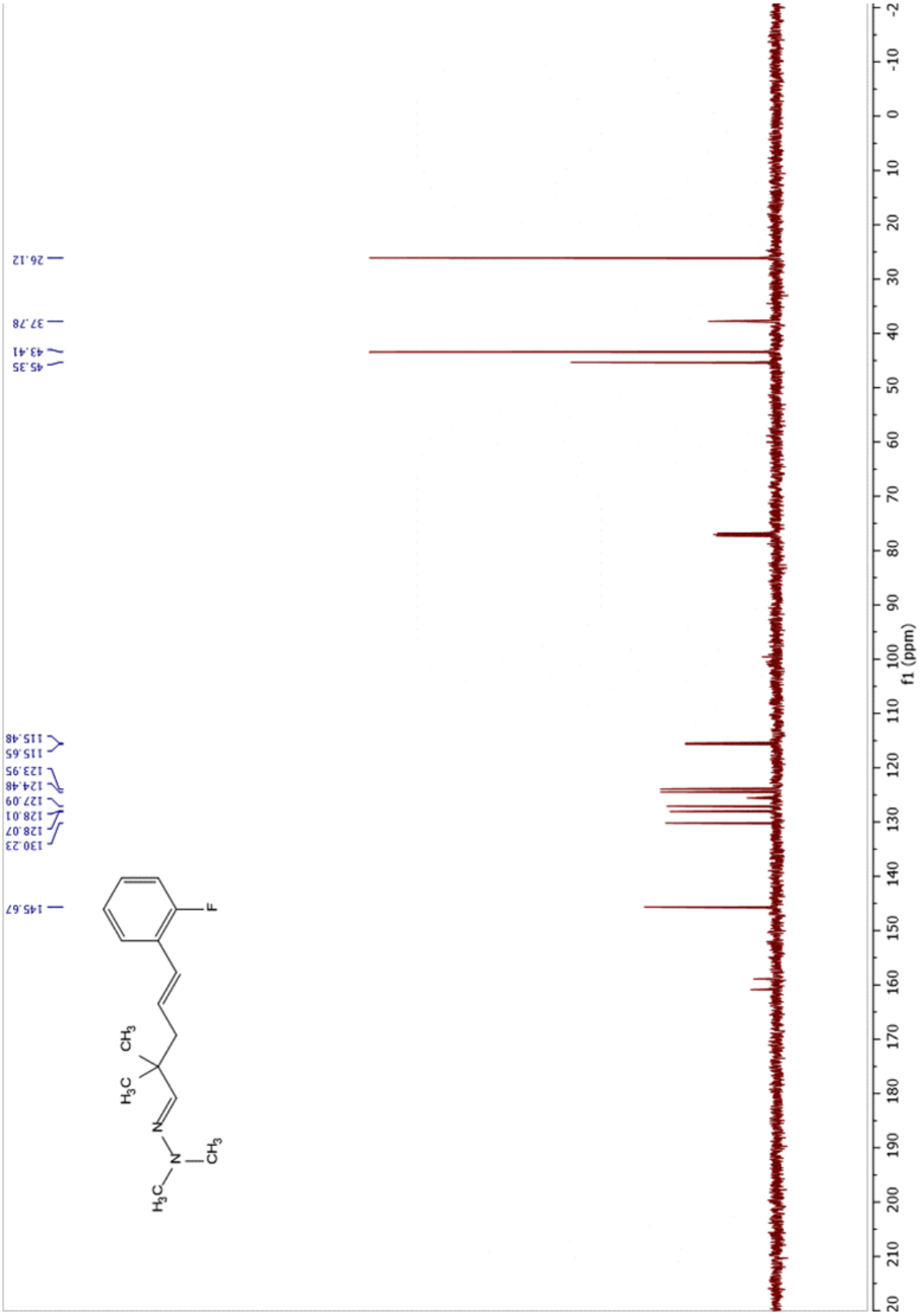

25.83
34.91
43.94
47.57
58.84
126.21
126.87
127.47
127.60
127.70
127.79
127.85
127.98
128.08
128.55
132.39
138.20
CH3
N
NH
H3C
H3C
CH3
f1 (ppm)

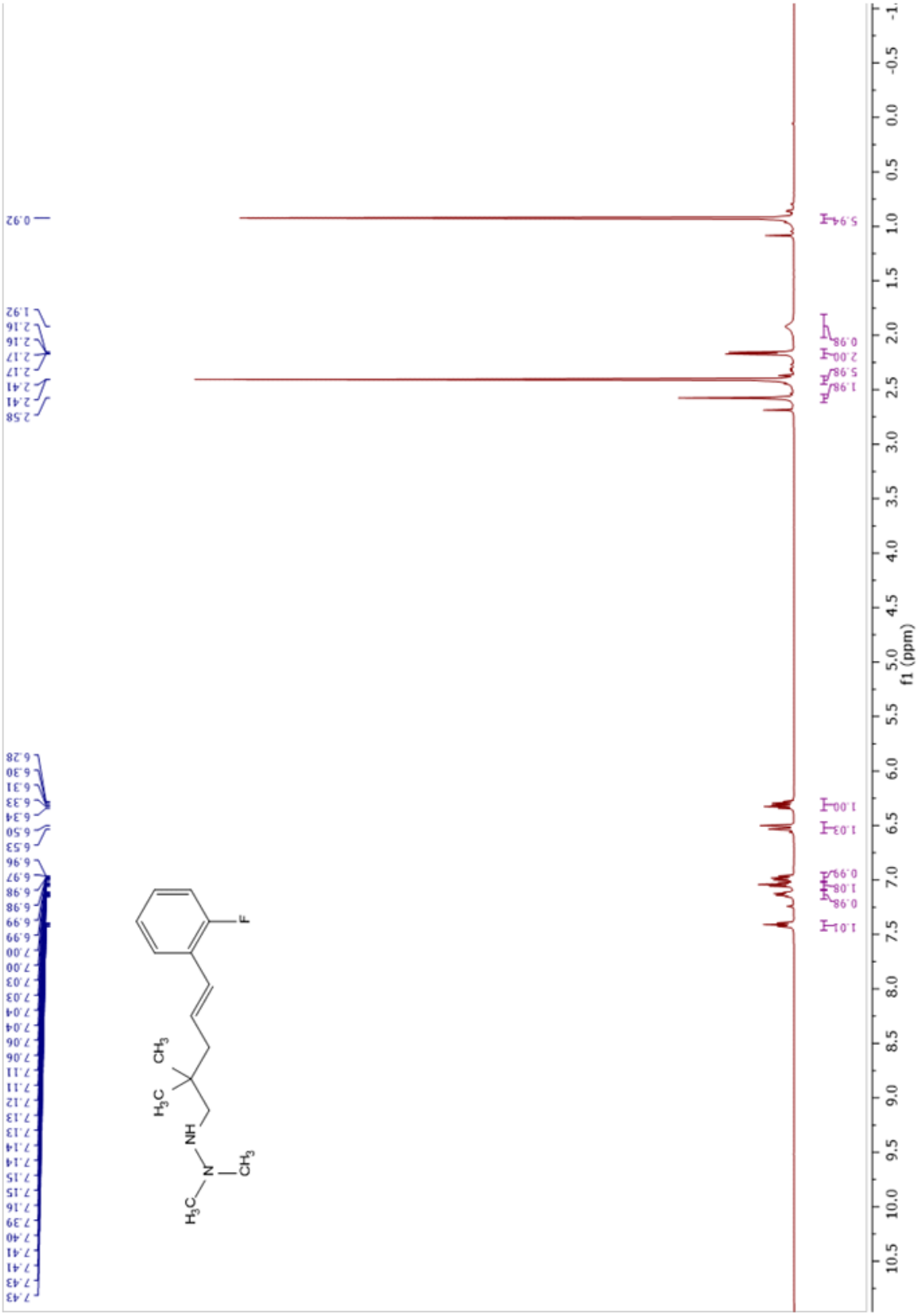

Cl
CH3
H3C
N
N
CH3
H3C
f1 (ppm)

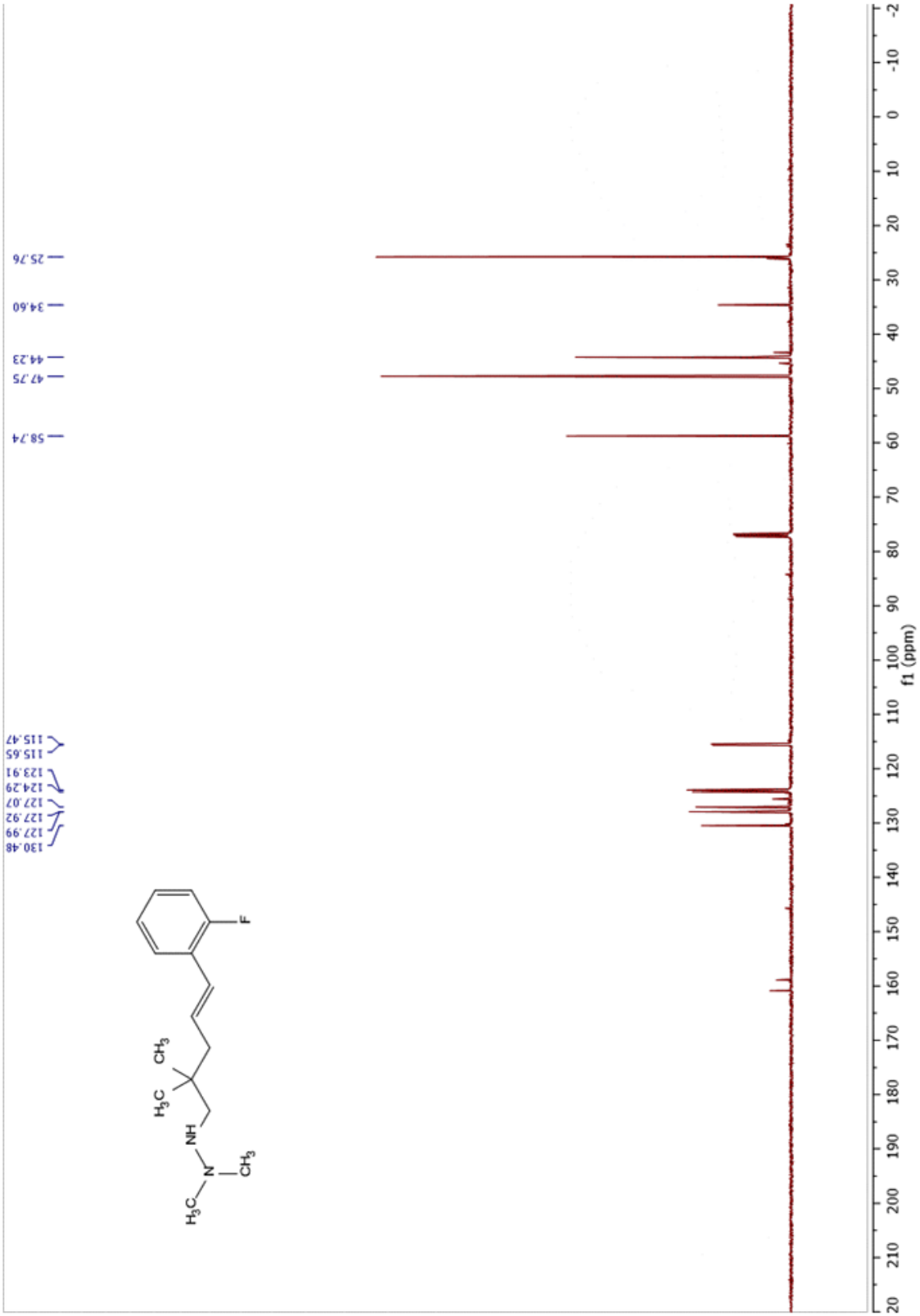

26.15
37.77
43.40
45.09
126.69
126.81
127.89
128.53
129.52
130.54
132.51
135.94
145.58
Cl
CH3
H3C
N
N
CH3
H3C
f1 (ppm)

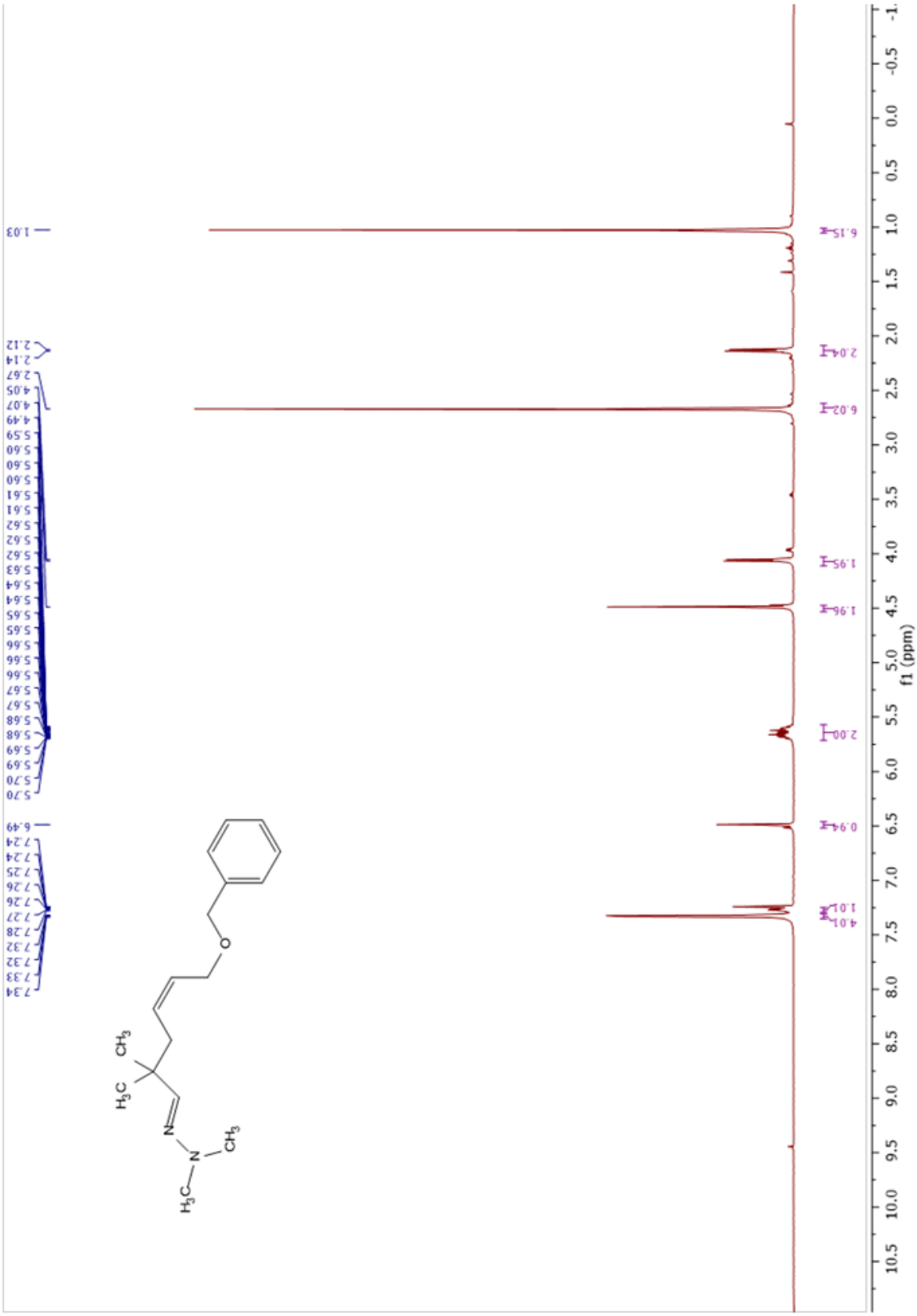

Cl
CH3
H3C
NH
N
H3C
H3C

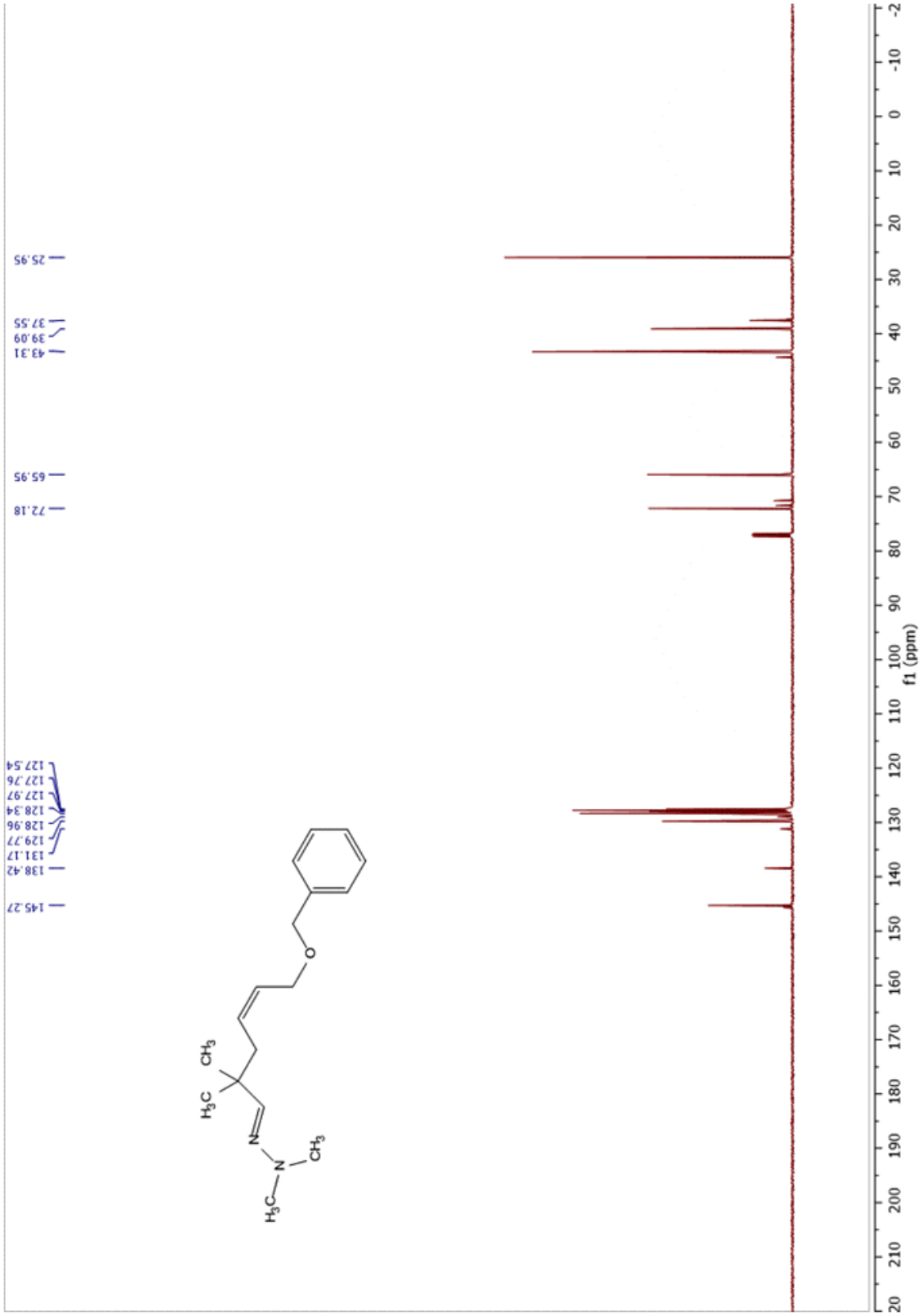

19.87
25.74
44.11
47.78
58.79
125.61
125.98
126.79
129.09
130.03
130.10
134.86
137.12
Cl
CH3
H3C
NH
N
H3C
H3C
f1 (ppm)

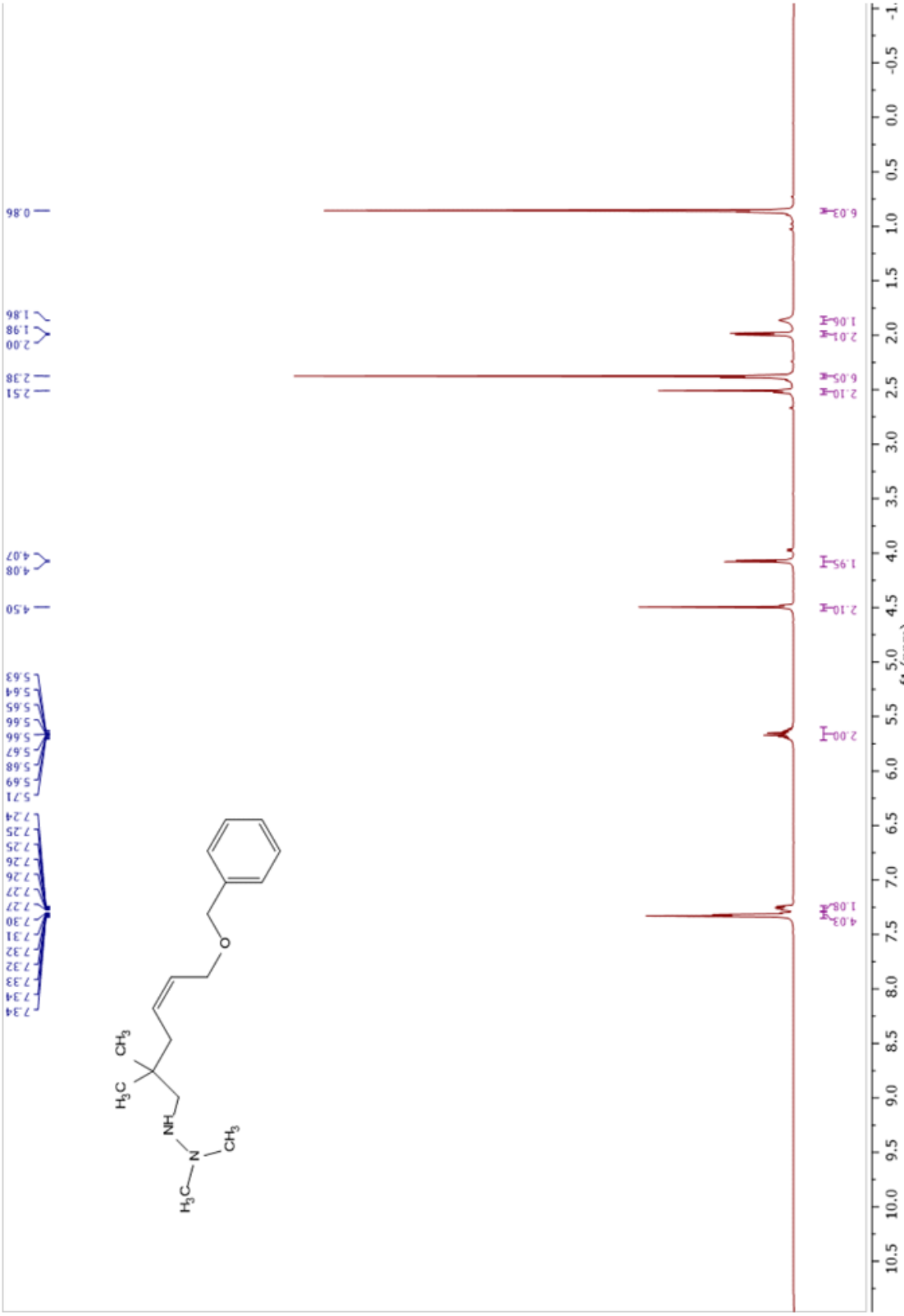

26.12
37.78
43.41
45.35
115.48
115.65
123.95
124.48
127.09
128.01
128.07
130.23
145.67
F
CH3
H3C
N
N
CH3
H3C
f1 (ppm)

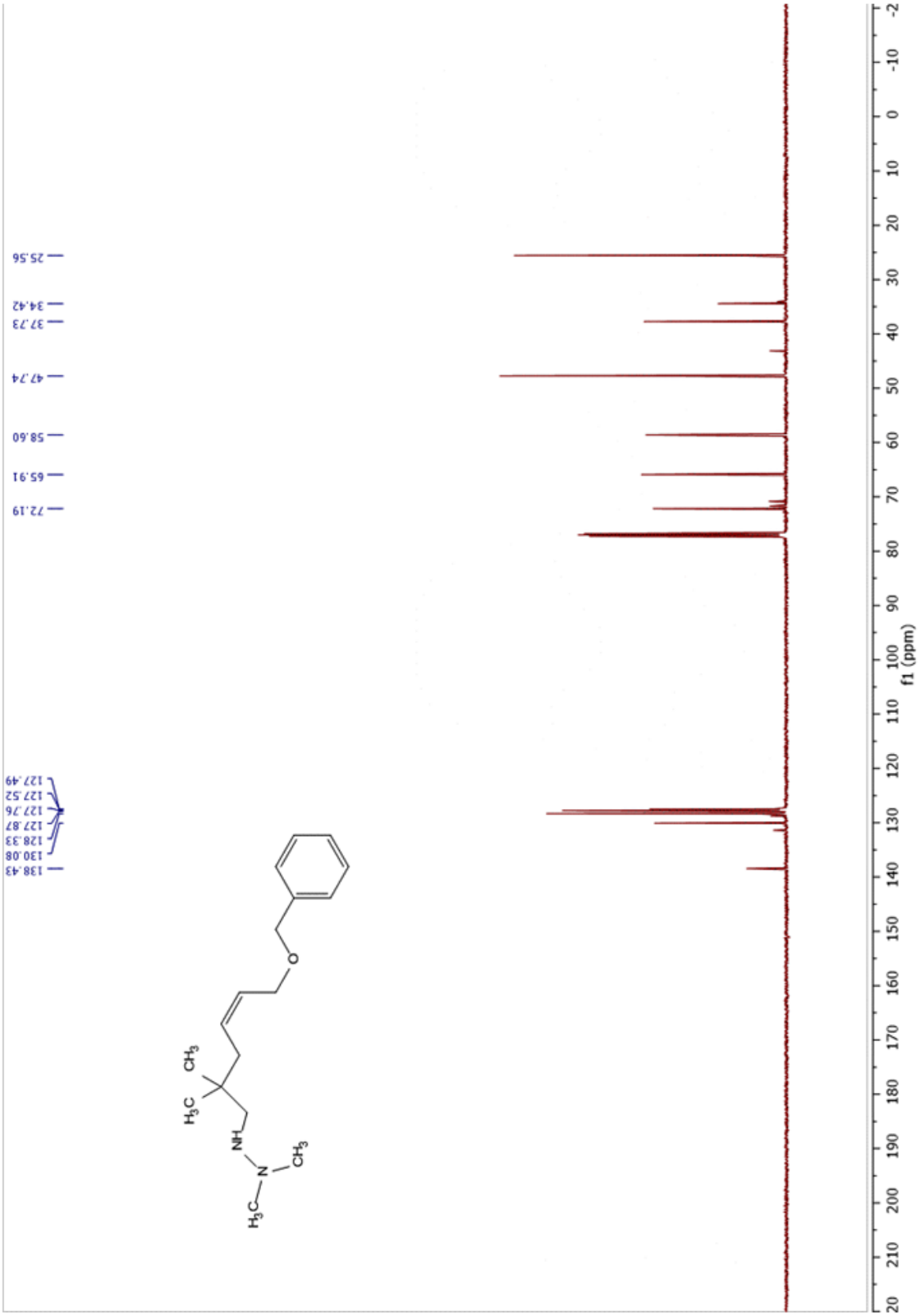

F
H3C
CH3
NH
N
CH3
H3C
f1 (ppm)

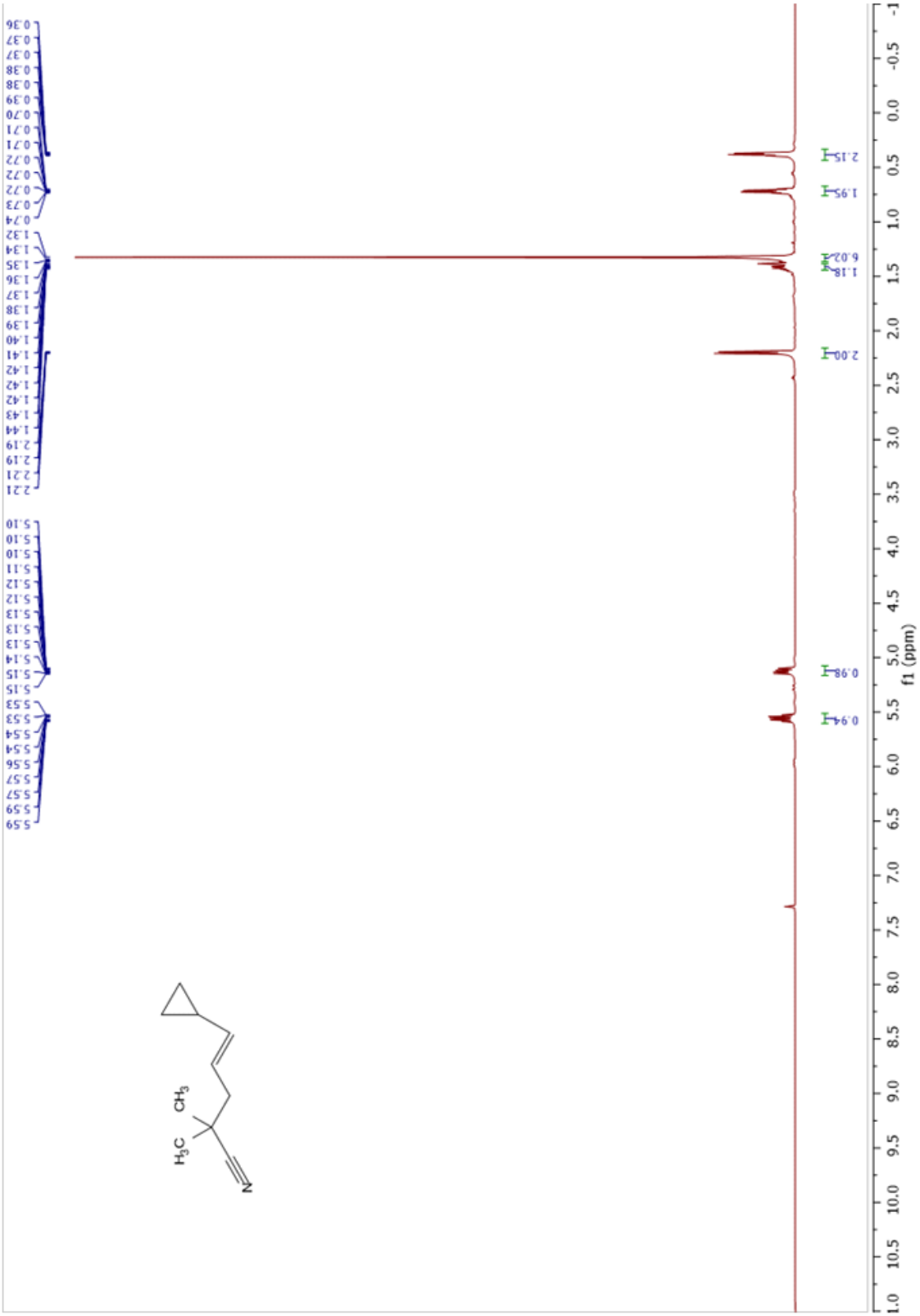

25.76
34.60
44.23
47.75
58.74
115.47
115.65
123.91
124.29
127.07
127.92
127.99
130.48
F
CH3
H3C
NH
N
CH3
H3C
f1 (ppm)

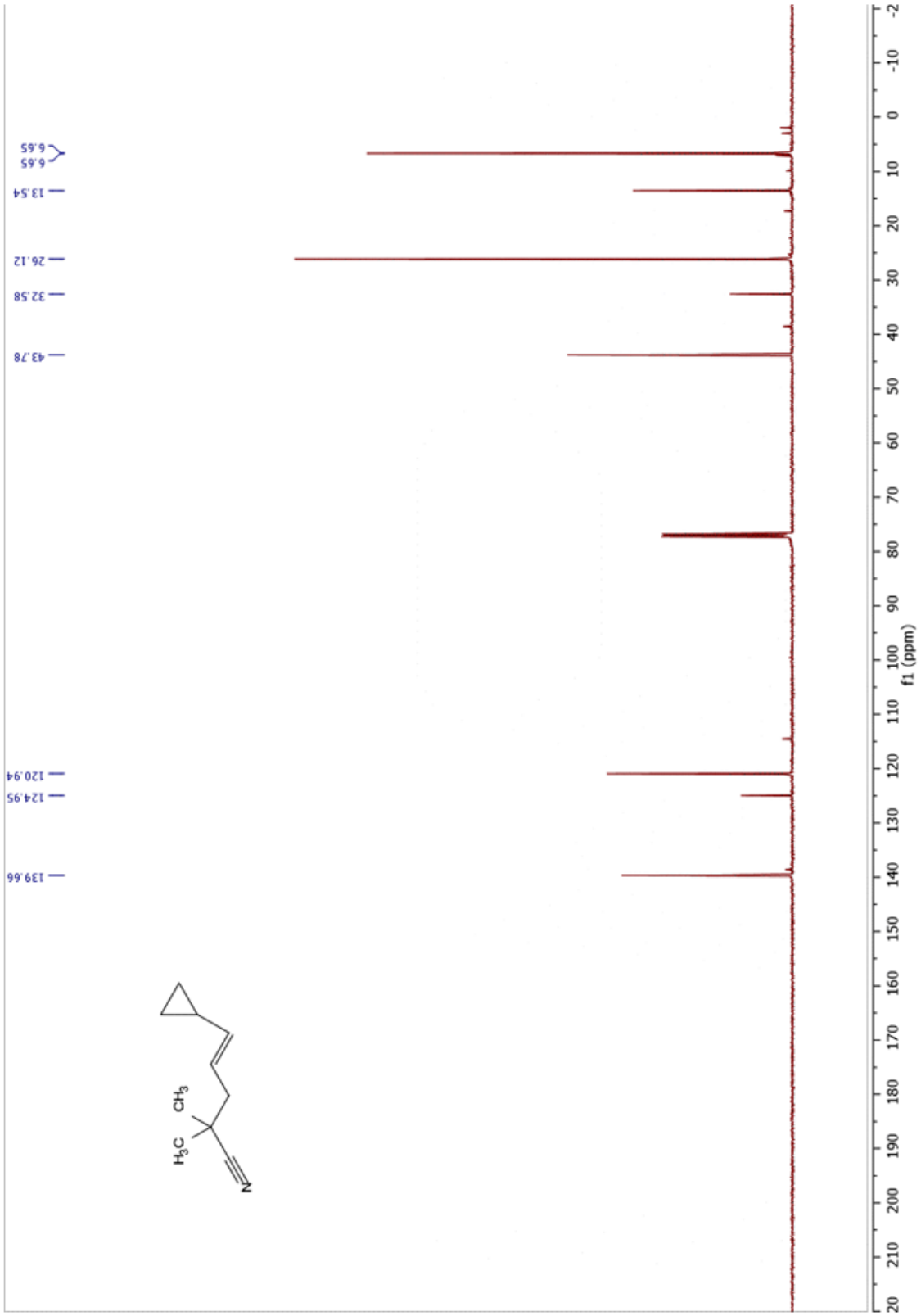

f1 (ppm)
6.15
2.04
6.02
1.95
1.96
2.00
0.94
4.01
1.03
2.12
2.14
2.67
4.05
4.07
4.49
5.59
5.60
5.60
5.60
5.61
5.61
5.62
5.62
5.62
5.63
5.64
5.64
5.65
5.65
5.66
5.66
5.66
5.67
5.67
5.68
5.68
5.69
5.69
5.70
5.70
6.49
7.24
7.24
7.25
7.26
7.26
7.27
7.28
7.32
7.32
7.33
7.34
O
N
N
CH3
H3C
H3C
CH3

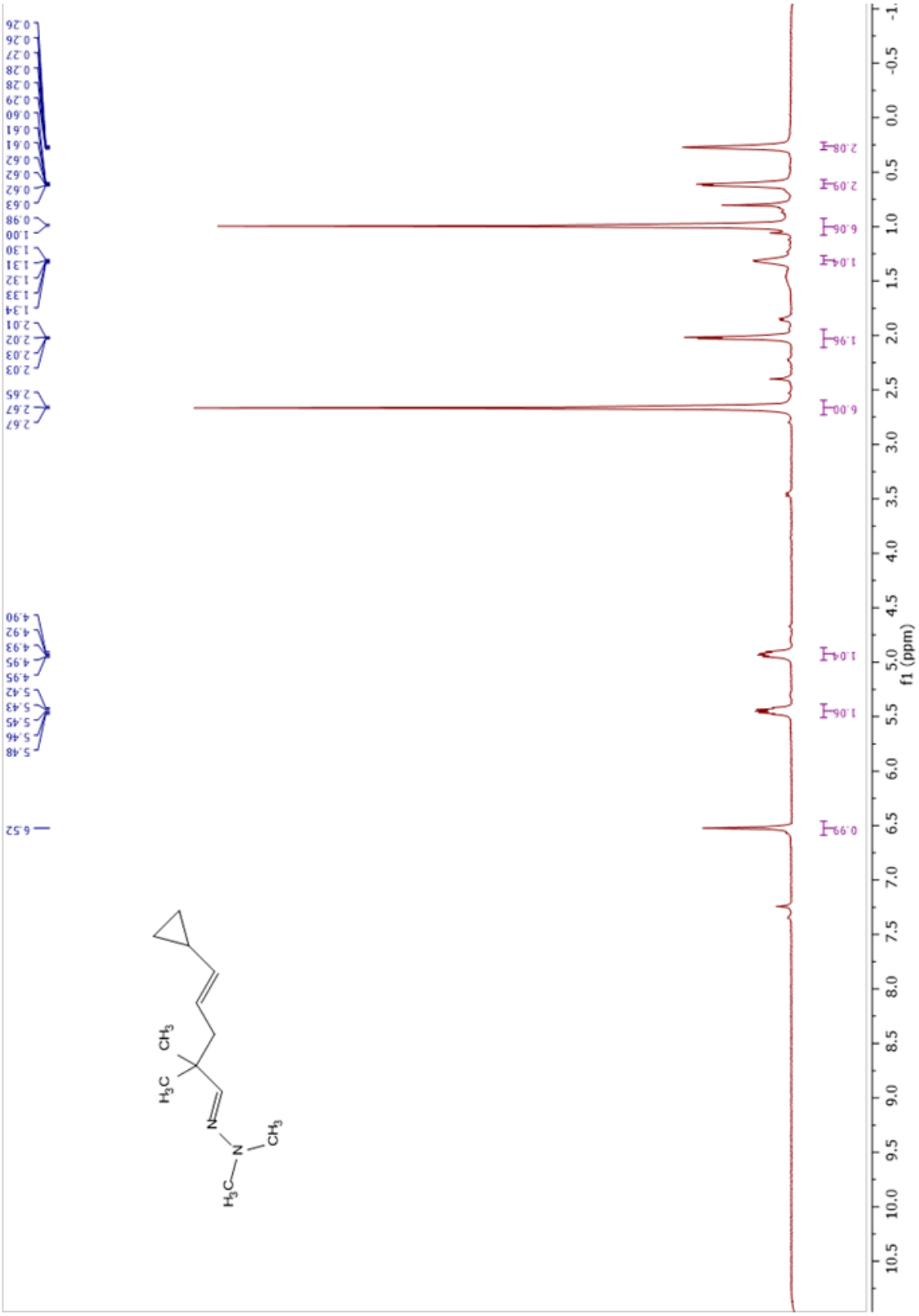

25.95
37.55
39.09
43.31
65.95
72.18
127.54
127.76
127.97
128.34
128.96
129.77
131.17
138.42
145.27
f1 (ppm)

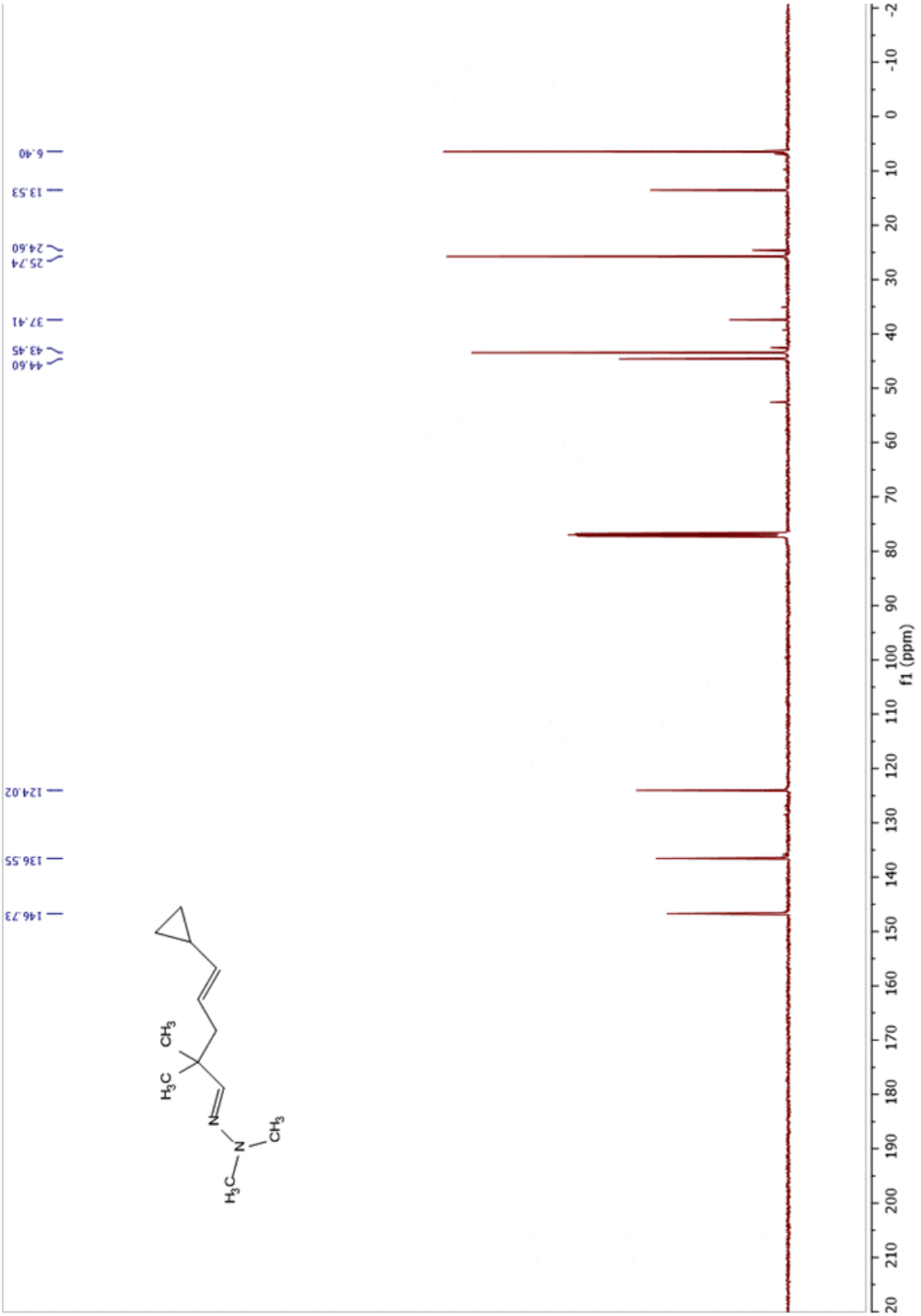

f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.
0.86
1.86
1.98
2.00
2.38
2.51
4.07
4.08
4.50
5.63
5.64
5.65
5.66
5.67
5.68
5.69
5.71
7.24
7.25
7.25
7.26
7.26
7.27
7.27
7.30
7.31
7.32
7.32
7.33
7.34
7.34
6.03
1.06
2.01
6.05
2.10
1.95
2.10
2.00
4.03
1.08
O
NH
N
CH3
H3C
CH3
H3C

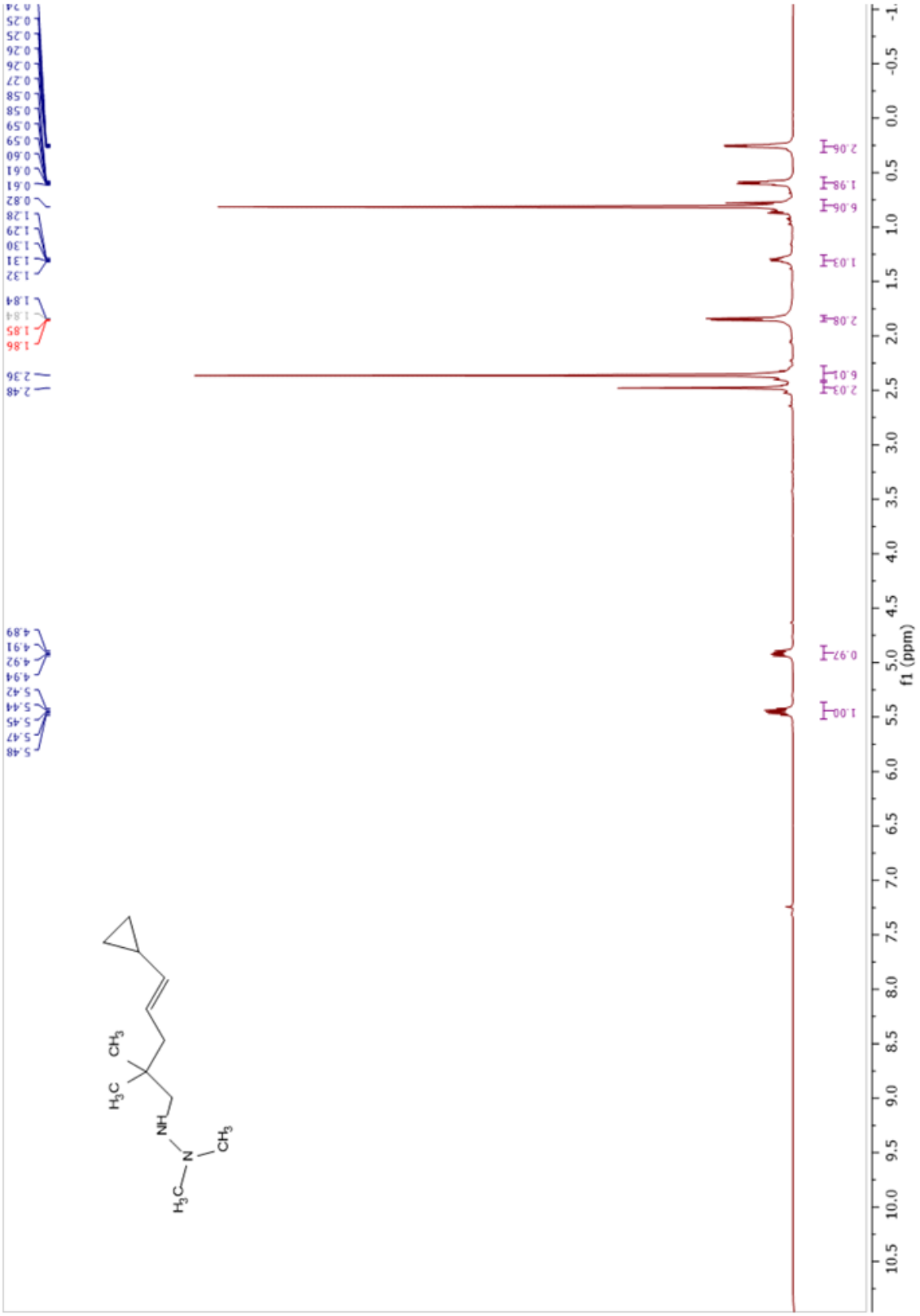

25.56
34.42
37.73
47.74
58.60
65.91
72.19
127.49
127.52
127.76
127.87
128.33
130.08
138.43
f1 (ppm)

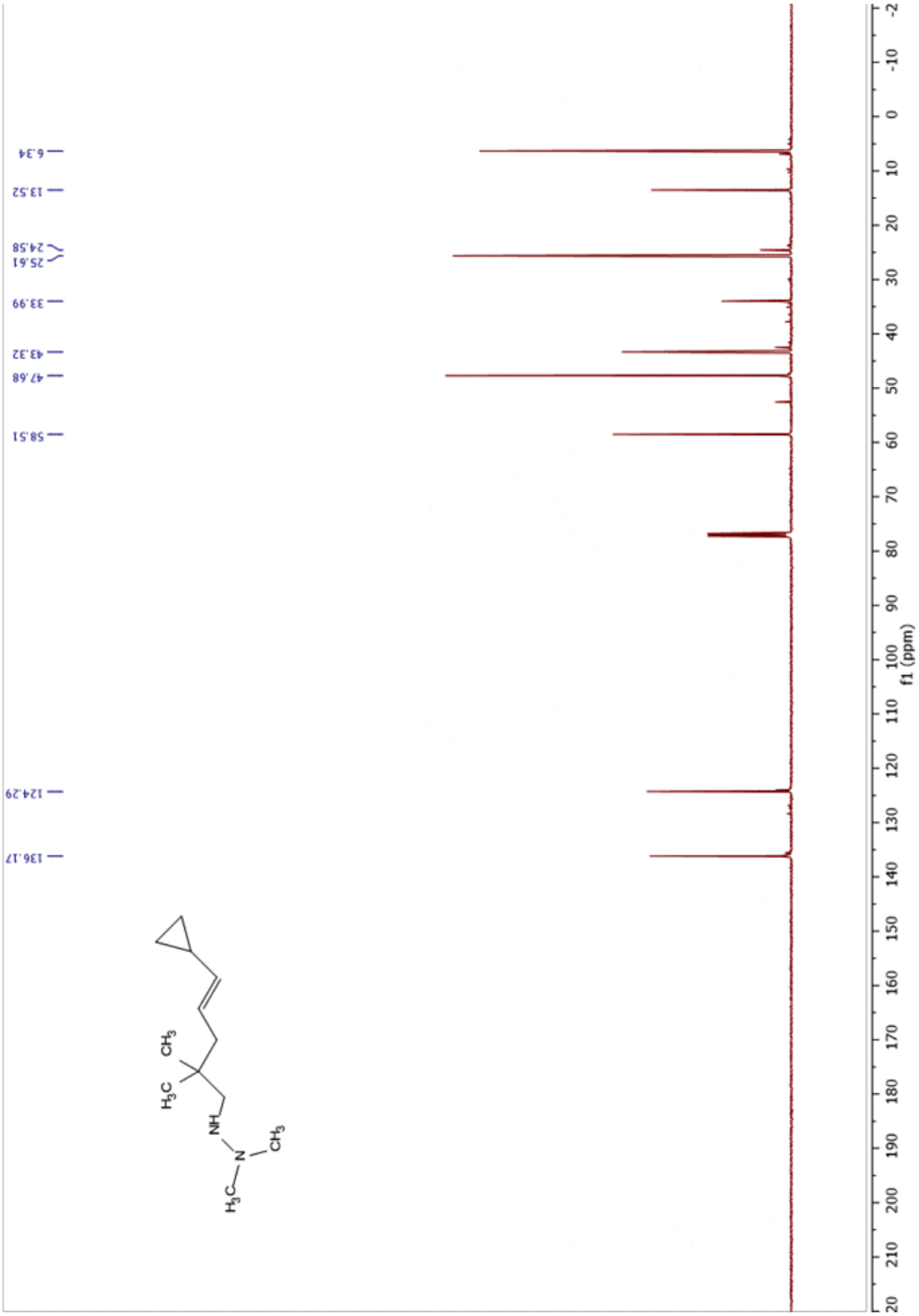

f1 (ppm)
2.15
1.95
6.02
2.00
0.98
0.94
H3C
CH3
N

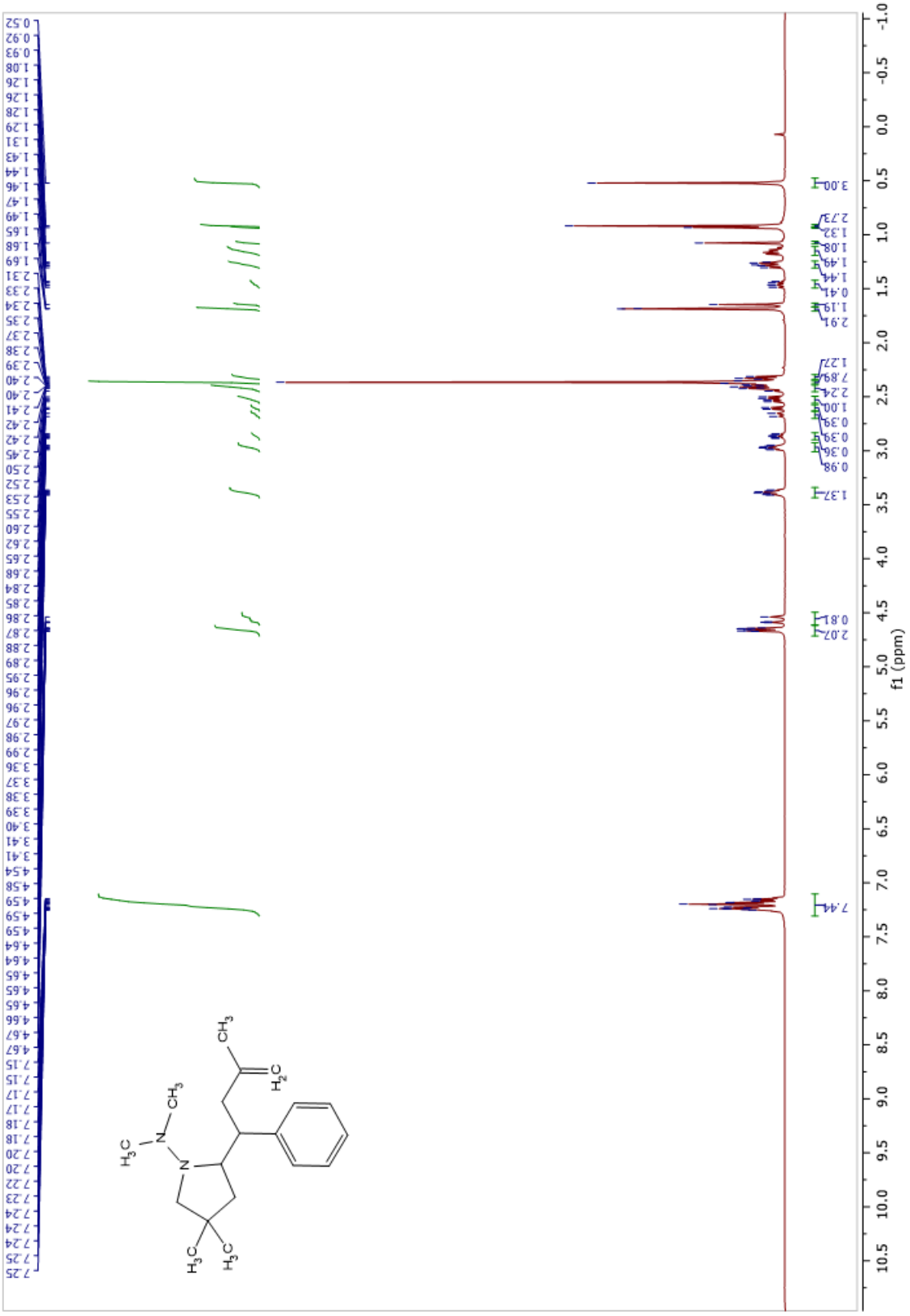

6.65
6.65
13.54
26.12
32.58
43.78
120.94
124.95
139.66
CH3
H3C
N
f1 (ppm)

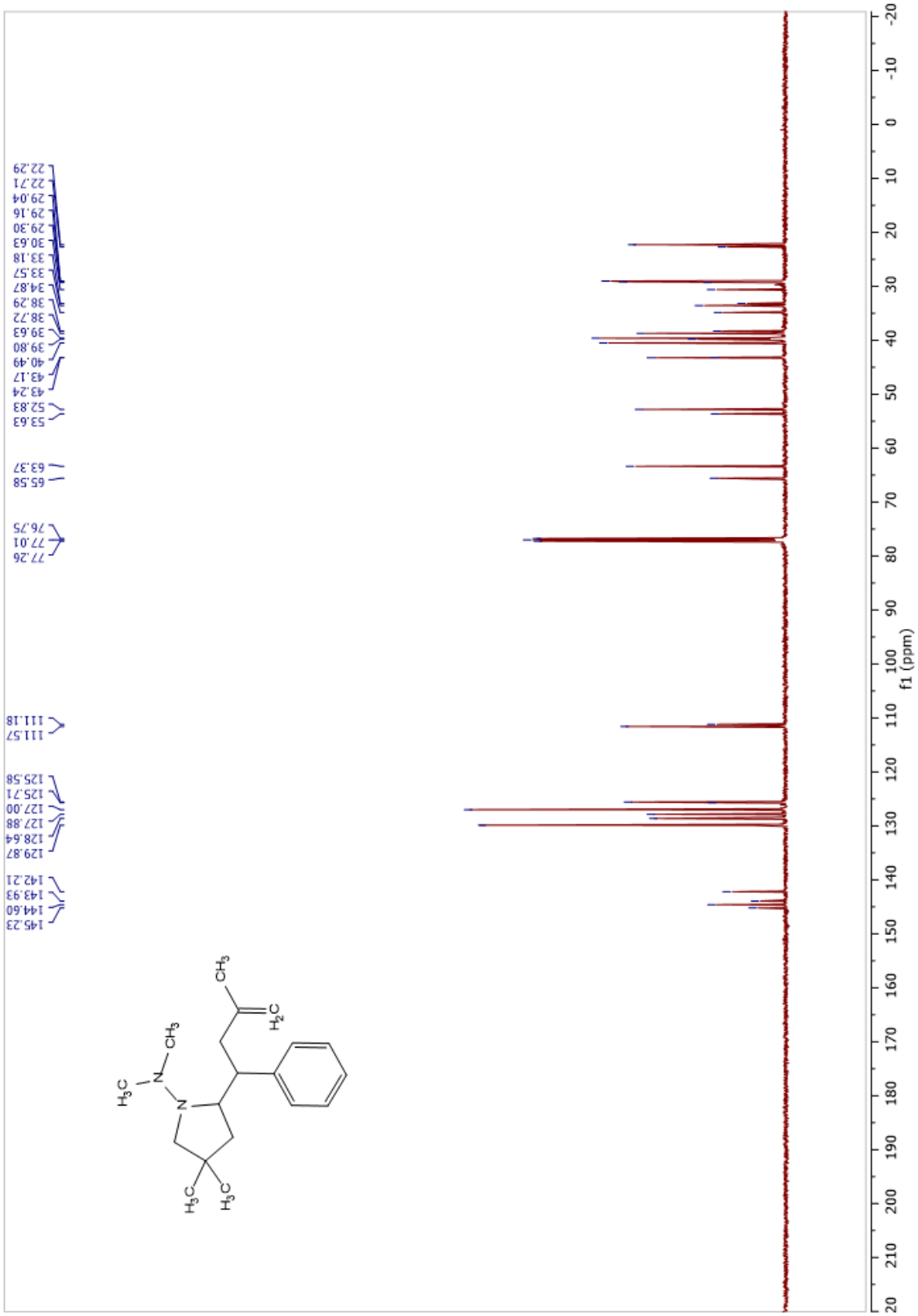

f1 (ppm)
2.08
2.09
6.06
1.04
1.96
6.00
1.04
1.06
0.99
6.52
4.90
4.92
4.93
4.95
4.95
5.42
5.43
5.45
5.46
5.48
2.65
2.67
2.67
2.01
2.02
2.03
2.03
1.30
1.31
1.32
1.33
1.34
1.00
0.98
0.63
0.62
0.62
0.62
0.61
0.61
0.60
0.29
0.28
0.28
0.27
0.26
0.26
CH3
H3C
N
N
CH3
H3C

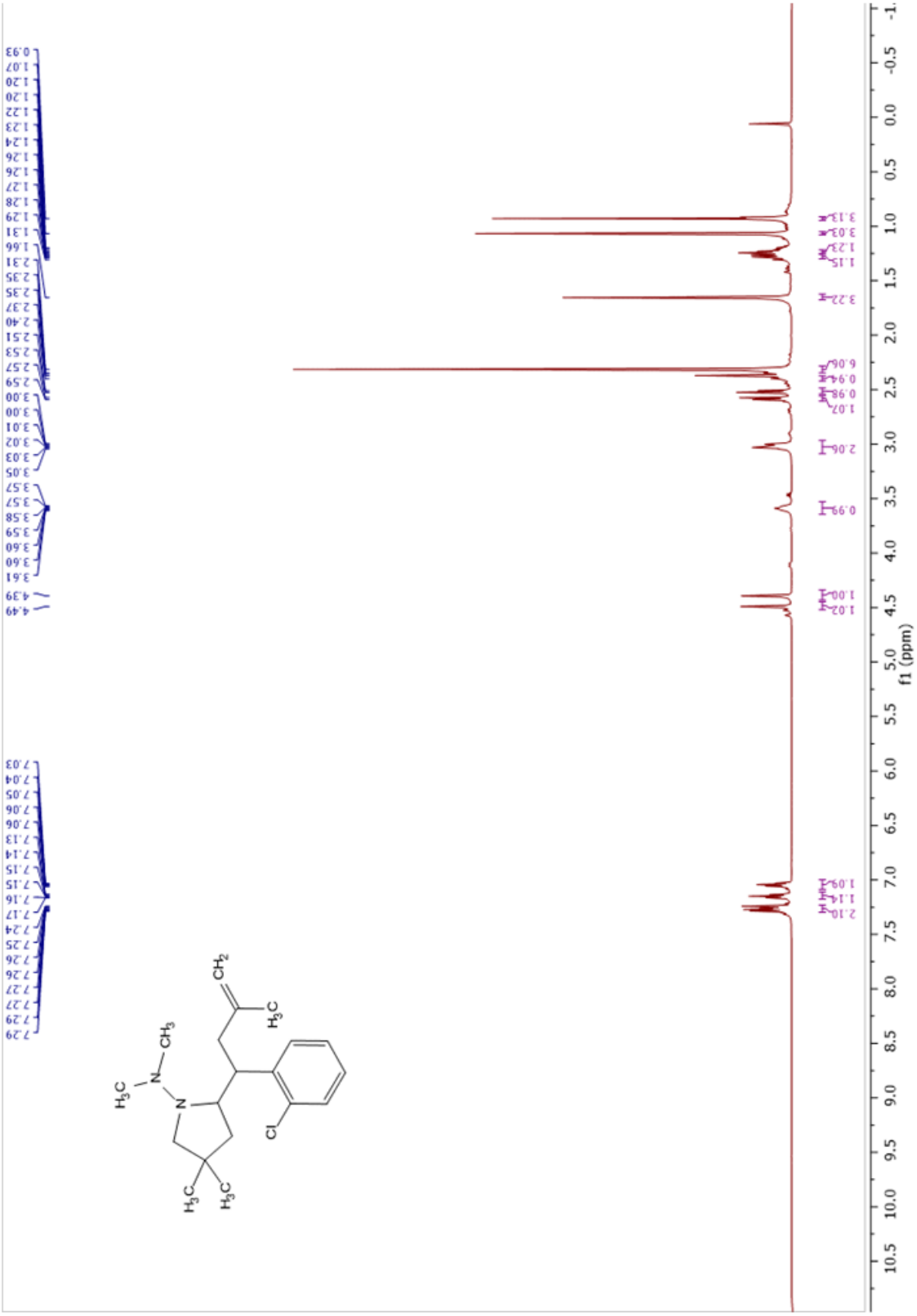

6.40
13.53
24.60
25.74
37.41
43.45
44.60
124.02
136.55
146.73
f1 (ppm)

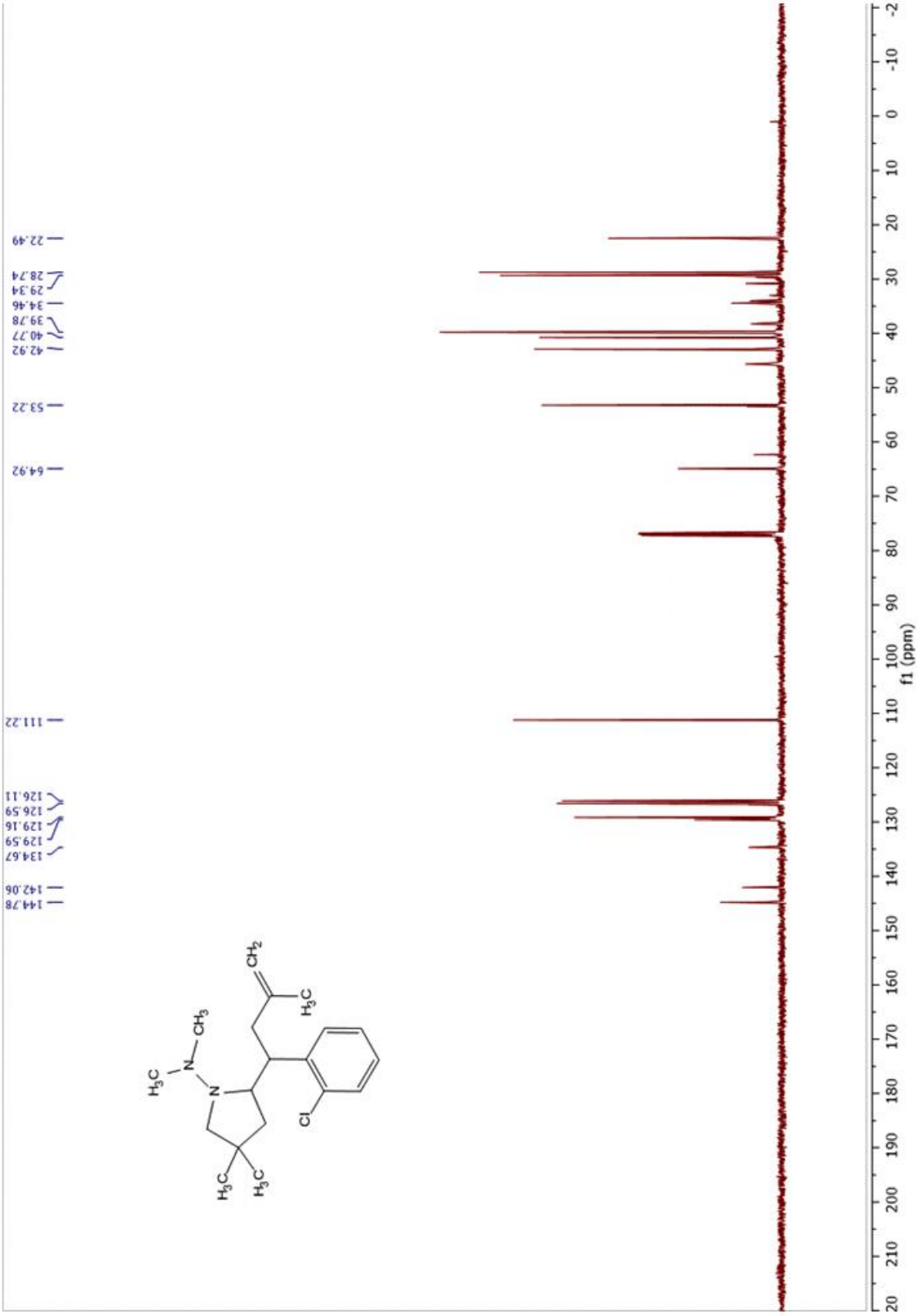

f1 (ppm)
2.06
1.98
6.06
1.03
2.08
6.01
2.03
0.97
1.00
H3C
CH3
NH
N
CH3
H3C

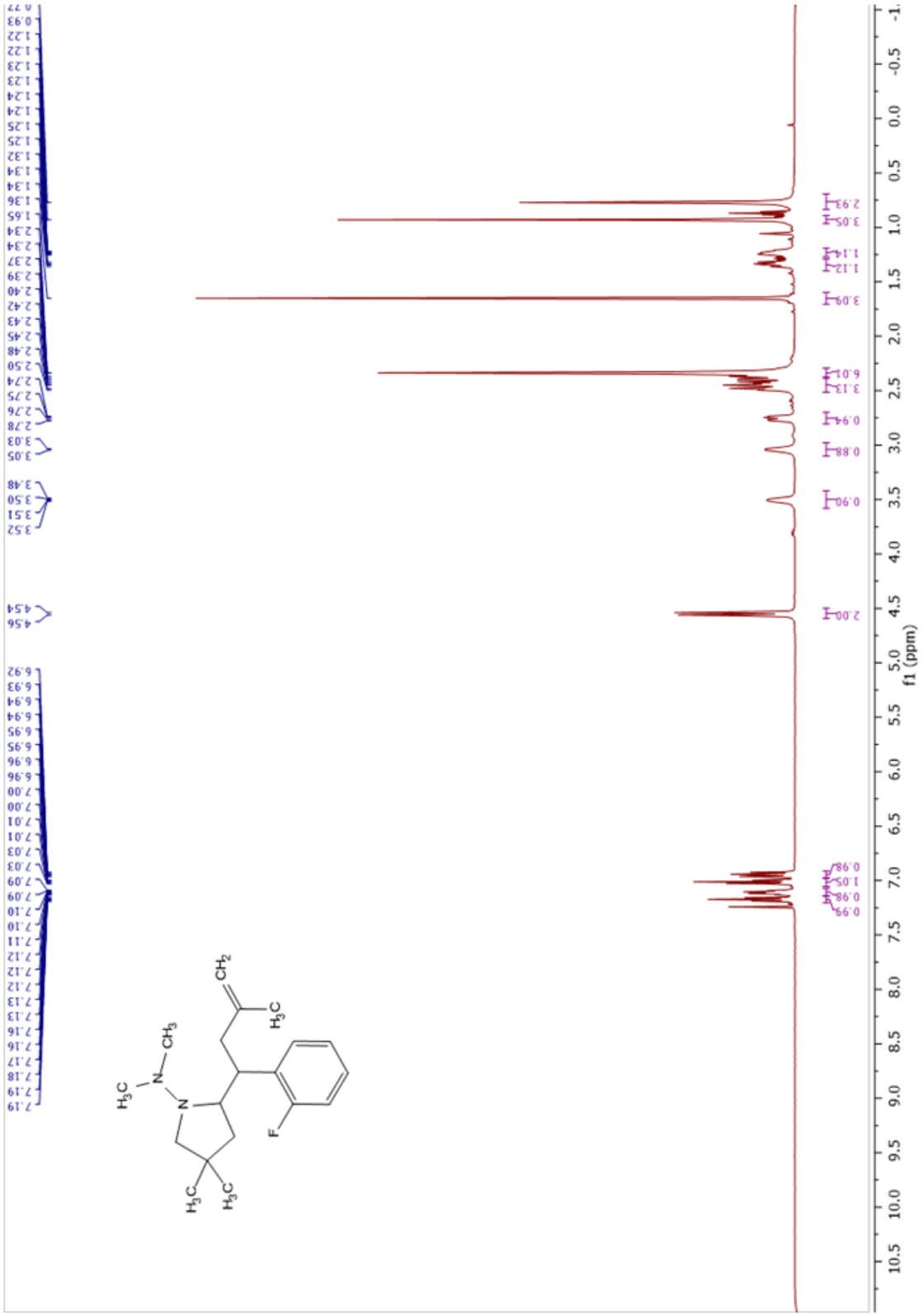

136.17
124.29
58.51
47.68
43.32
33.99
25.61
24.58
13.52
6.34
f1 (ppm)
NH
N
CH3
H3C

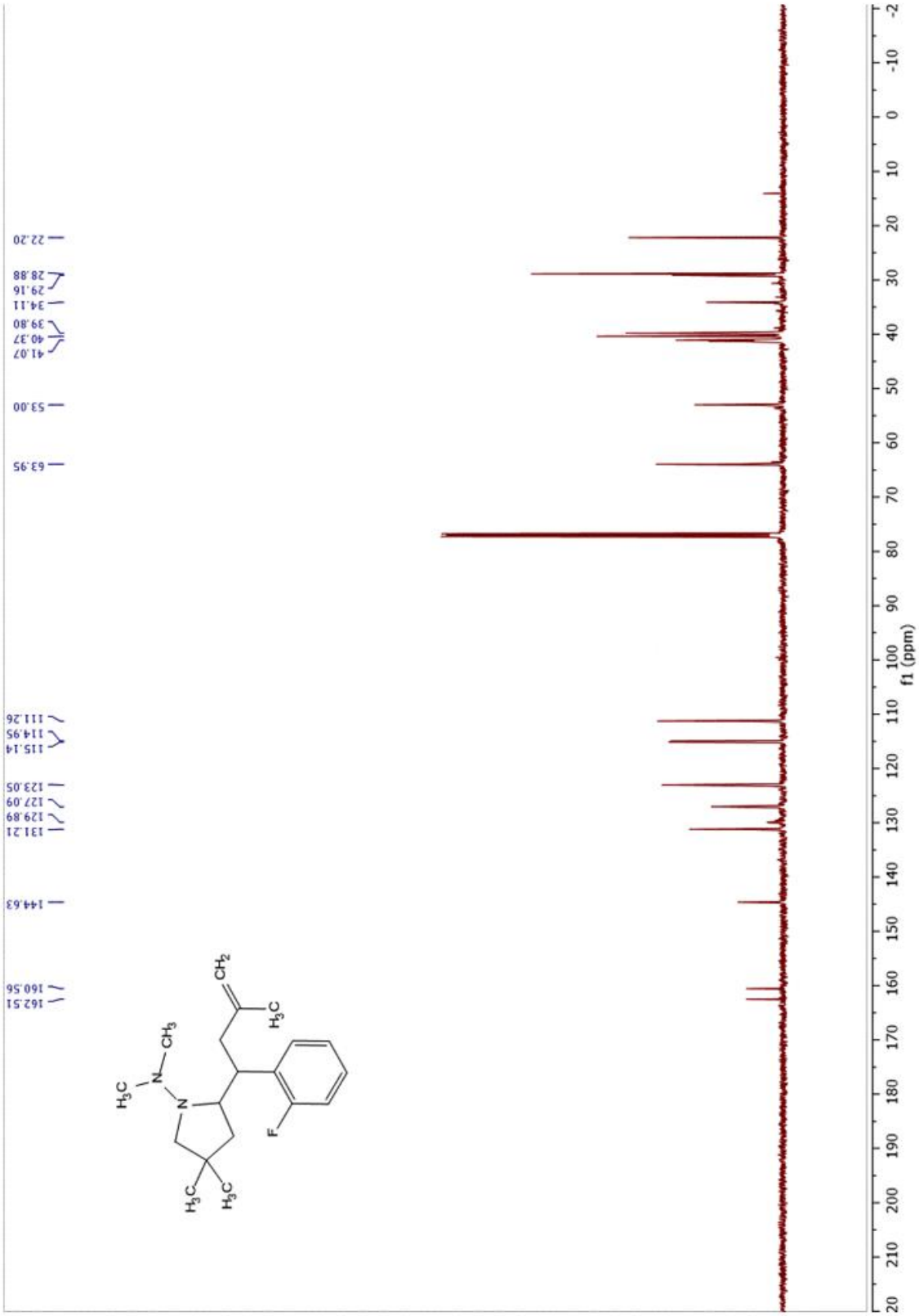

f1 (ppm)
3.00
2.73
1.37
0.81
7.44
2.07

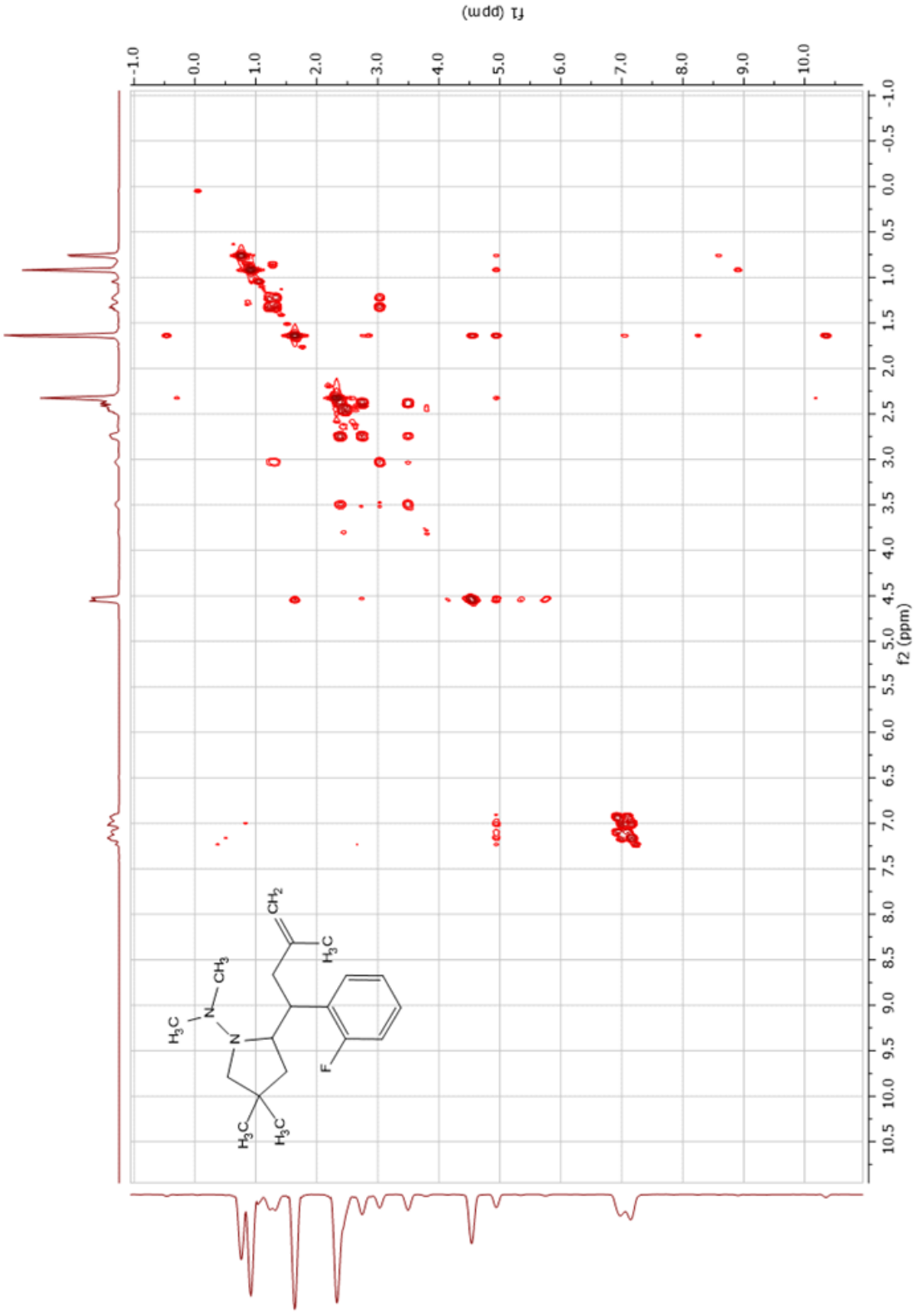

145.23
144.60
143.93
142.21
129.87
128.64
127.88
127.00
125.71
125.58
111.57
111.18
77.26
77.01
76.75
65.58
63.37
53.63
52.83
43.24
43.17
40.49
39.80
39.63
38.72
38.29
34.87
33.57
33.18
30.63
29.30
29.16
29.04
22.71
22.29
f1 (ppm)

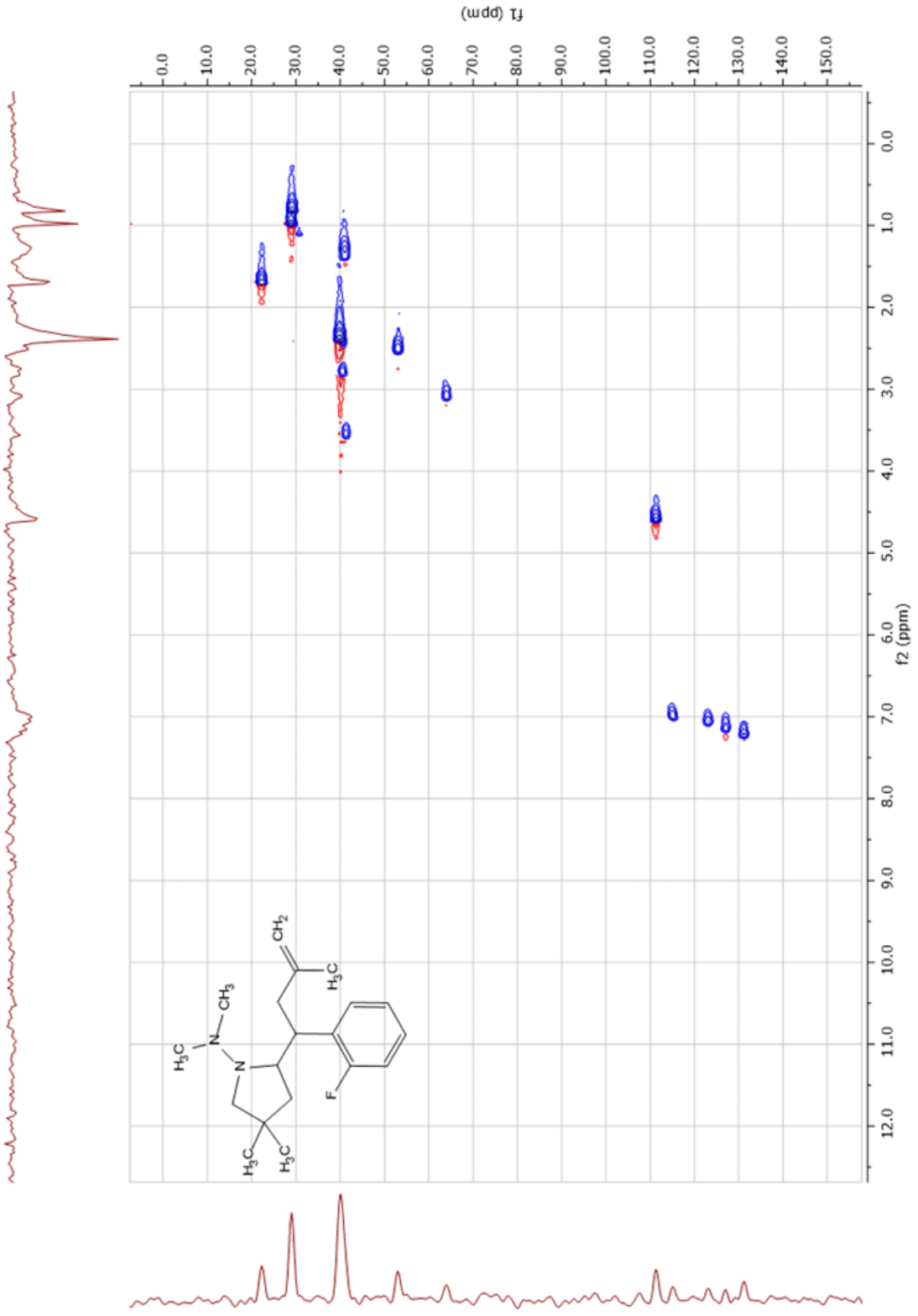

f1 (ppm)

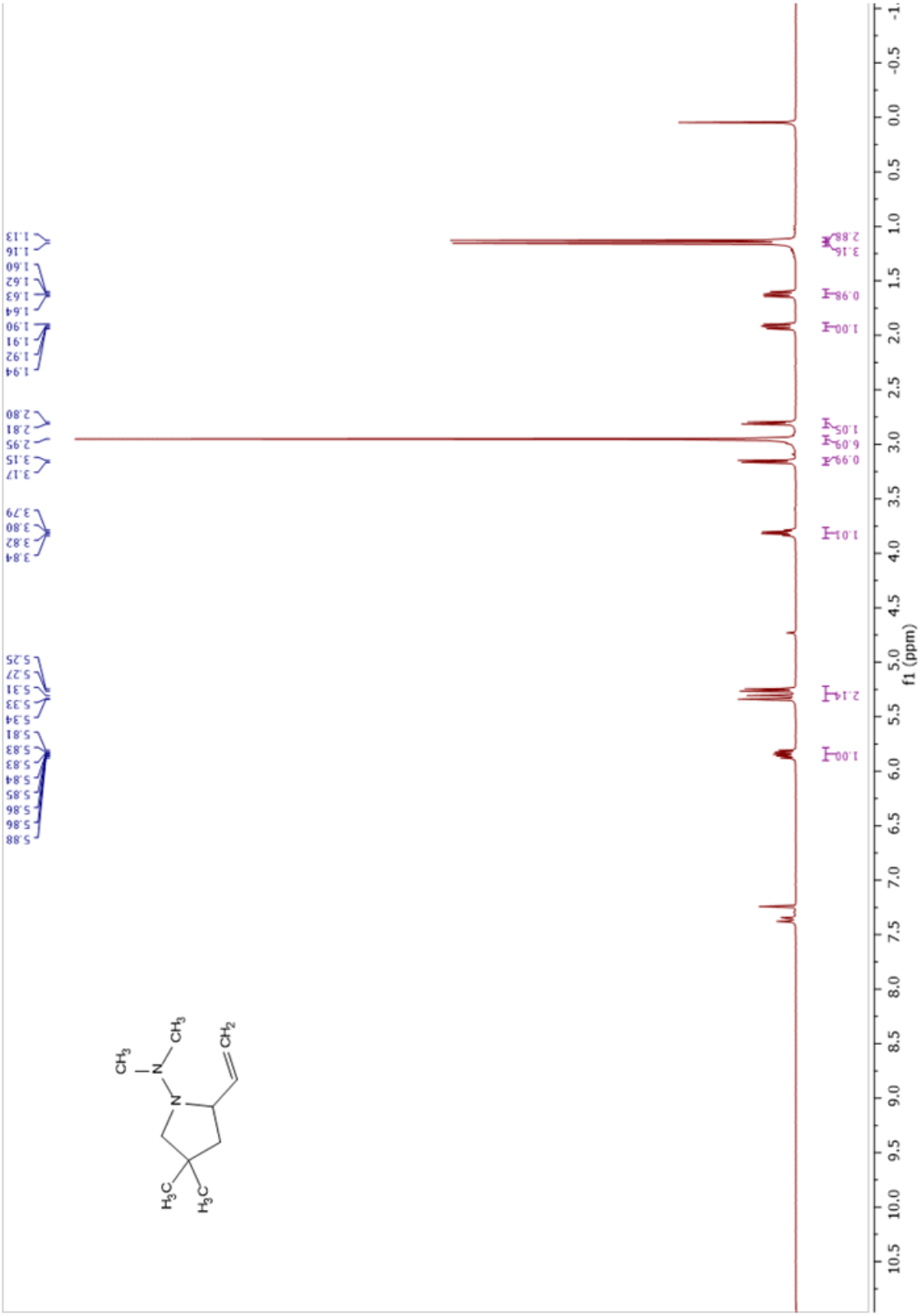

22.49
28.74
29.34
34.46
39.78
40.77
42.92
53.22
64.92
111.22
126.11
126.59
129.16
129.59
134.67
142.06
144.78
f1 (ppm)

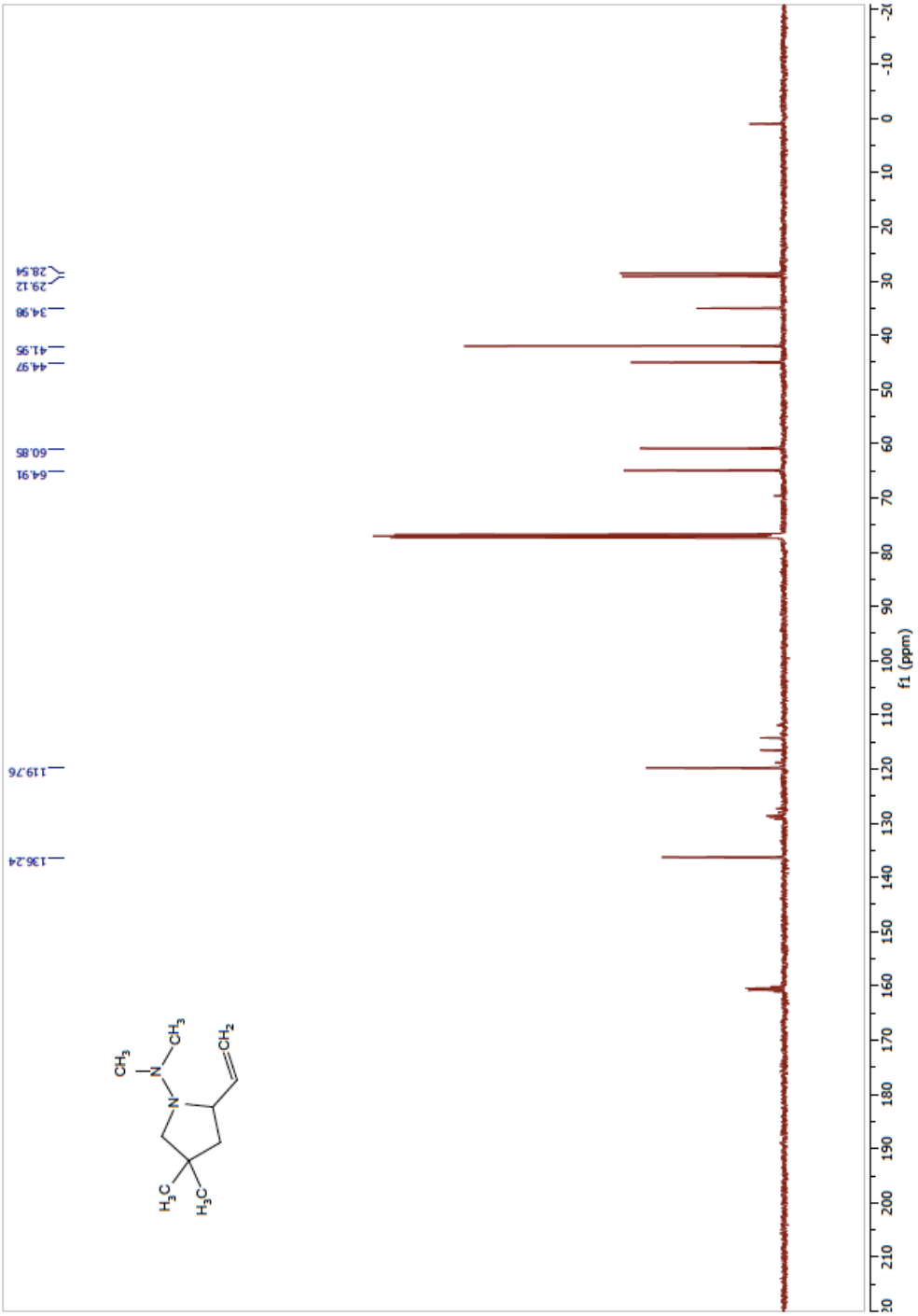

f1 (ppm)
F
CH2
H3C
CH3
N
N
H3C
H3C
H3C

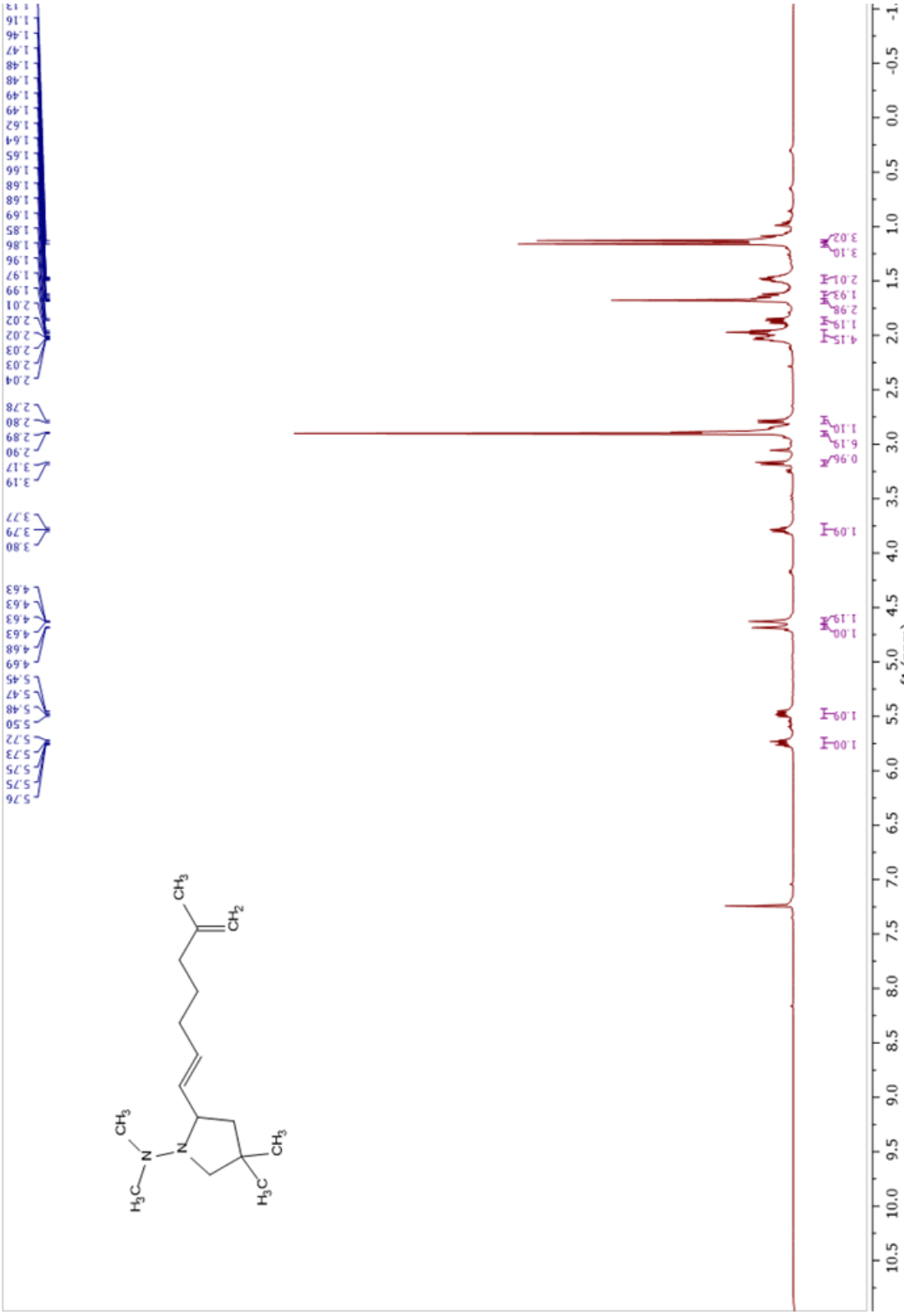

22.20
28.88
29.16
34.11
39.80
40.37
41.07
53.00
63.95
111.26
114.95
115.14
123.05
127.09
129.89
131.21
144.63
160.56
162.51
f1 (ppm)

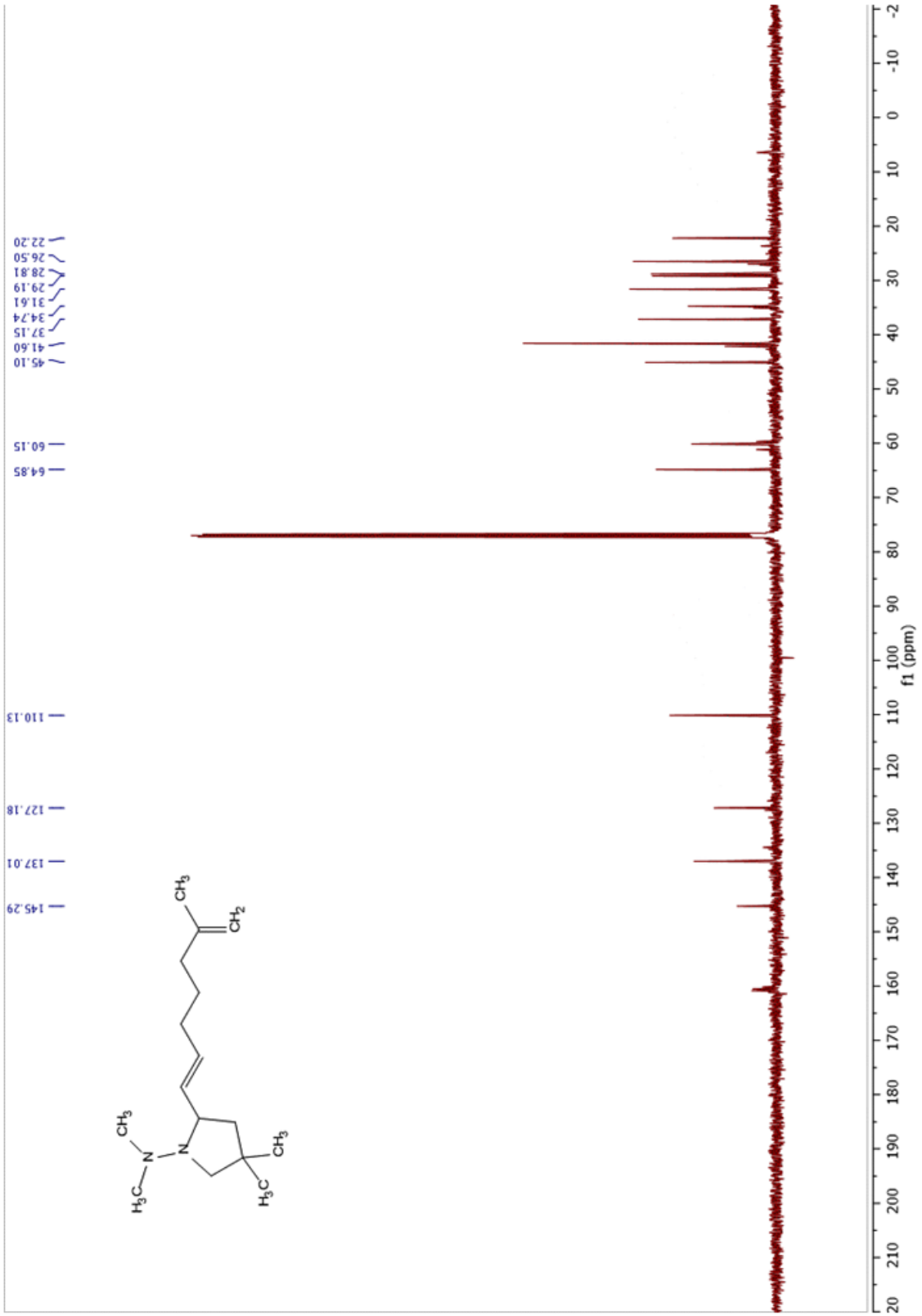

f1 (ppm)
f2 (ppm)
CH2
H3C
CH3
H3C
N
N
F
H3C
H3C


f1 (ppm)
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
f2 (ppm)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
CH2
H3C
CH3
N
N
H3C
H3C
H3C
F

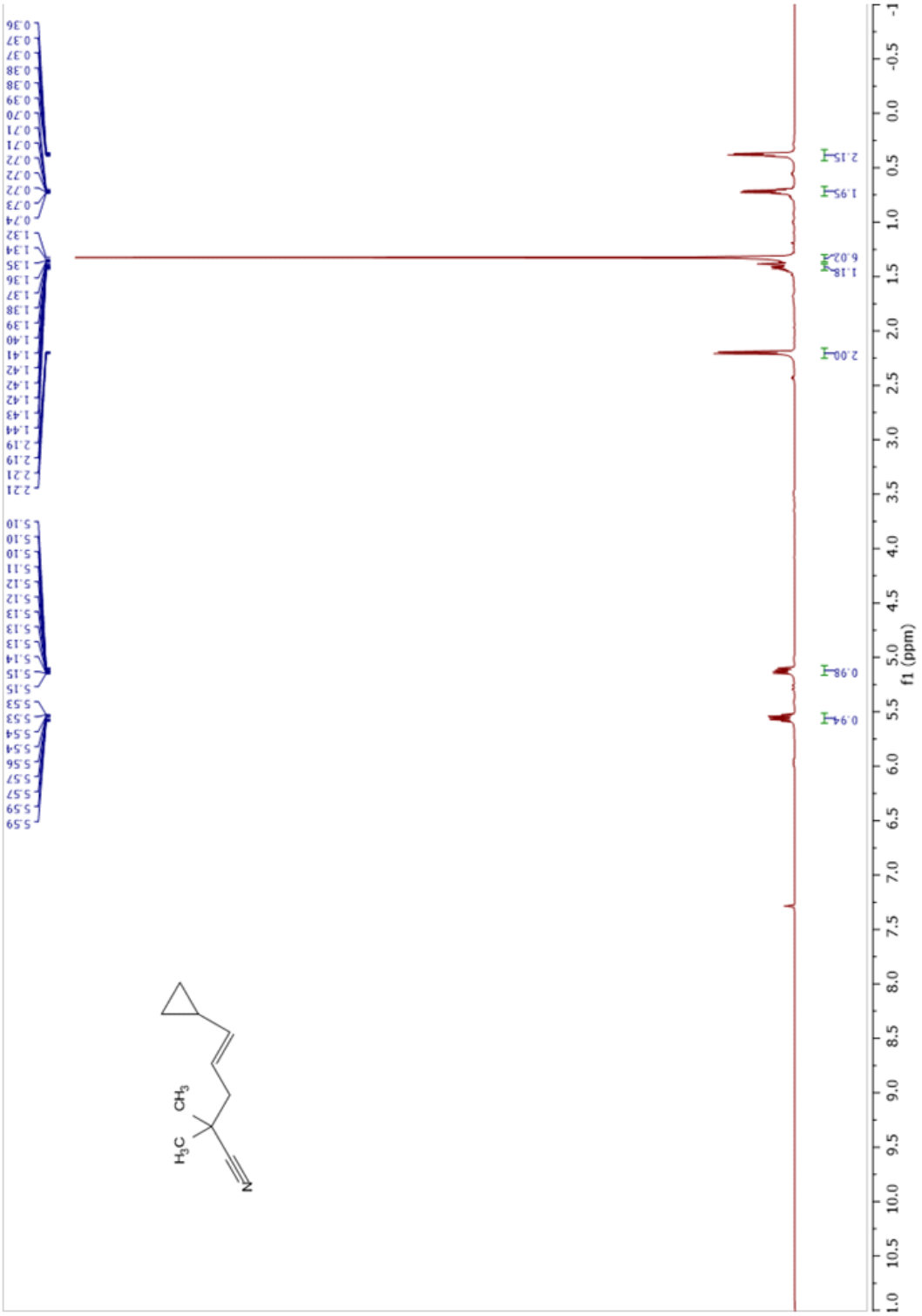

f1 (ppm)

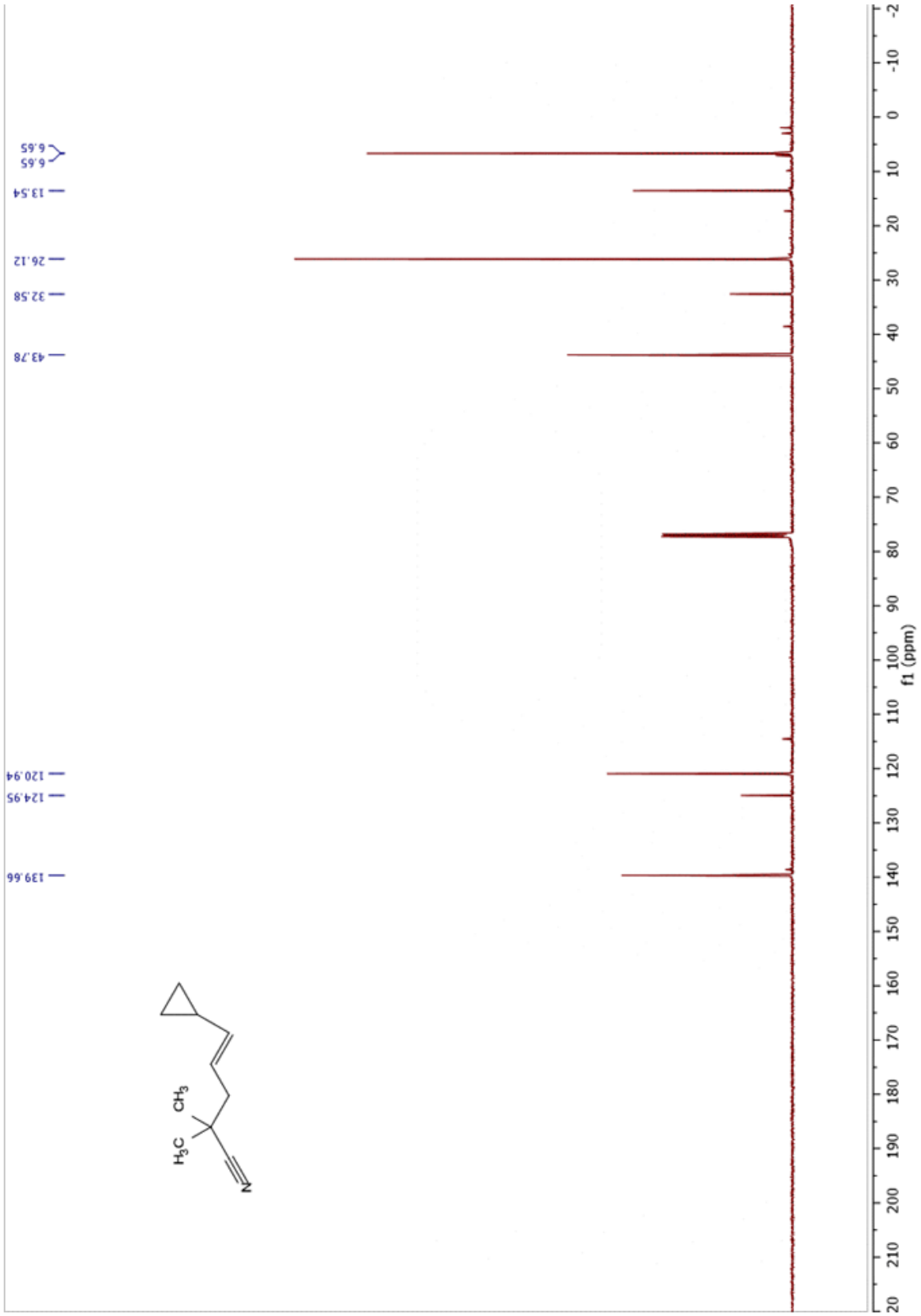

136.24
119.76
64.91
60.85
44.97
41.95
34.98
29.12
28.54
f1 (ppm)
CH3
N
CH3
N
CH2
H3C
H3C

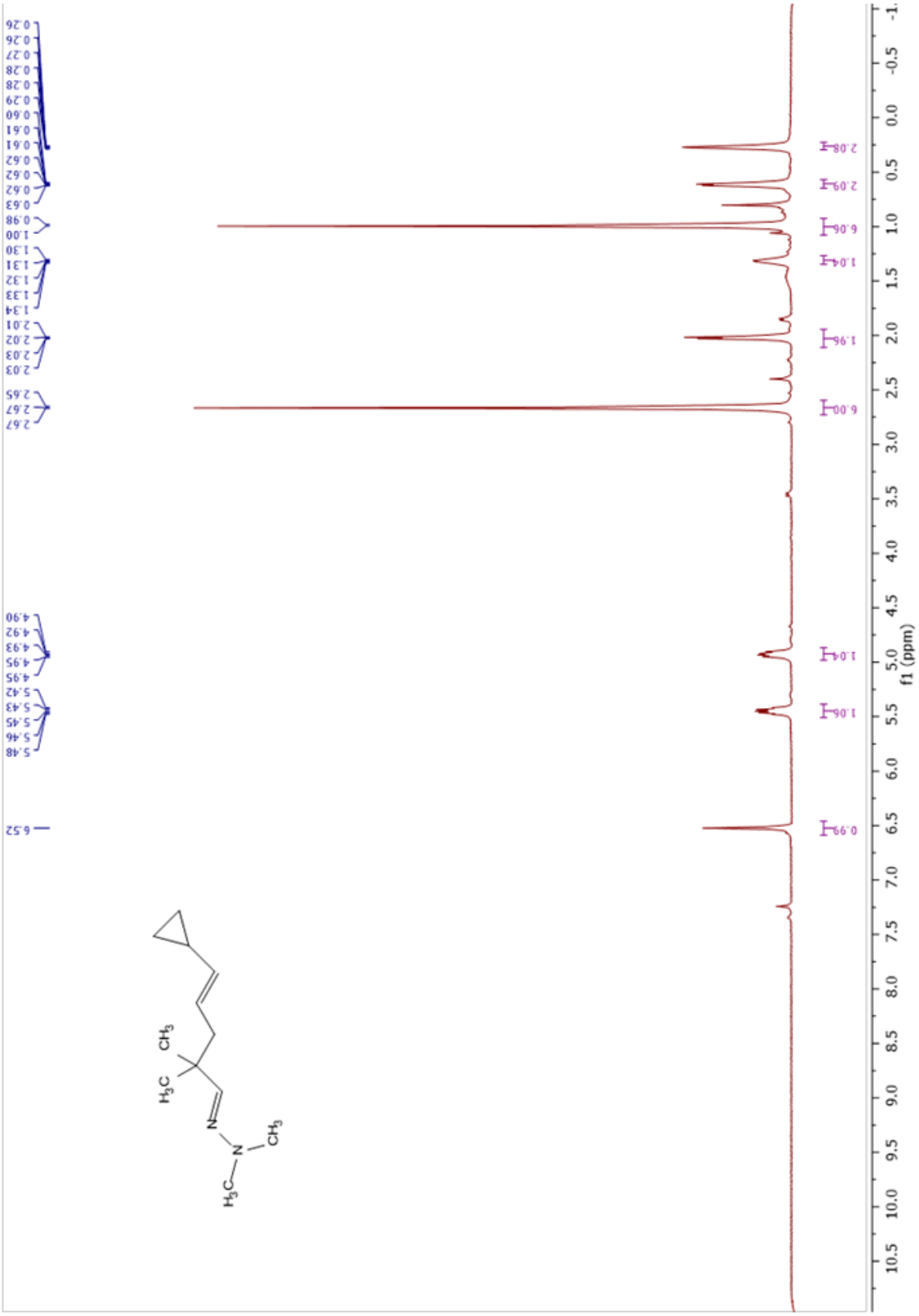

f1 (ppm)

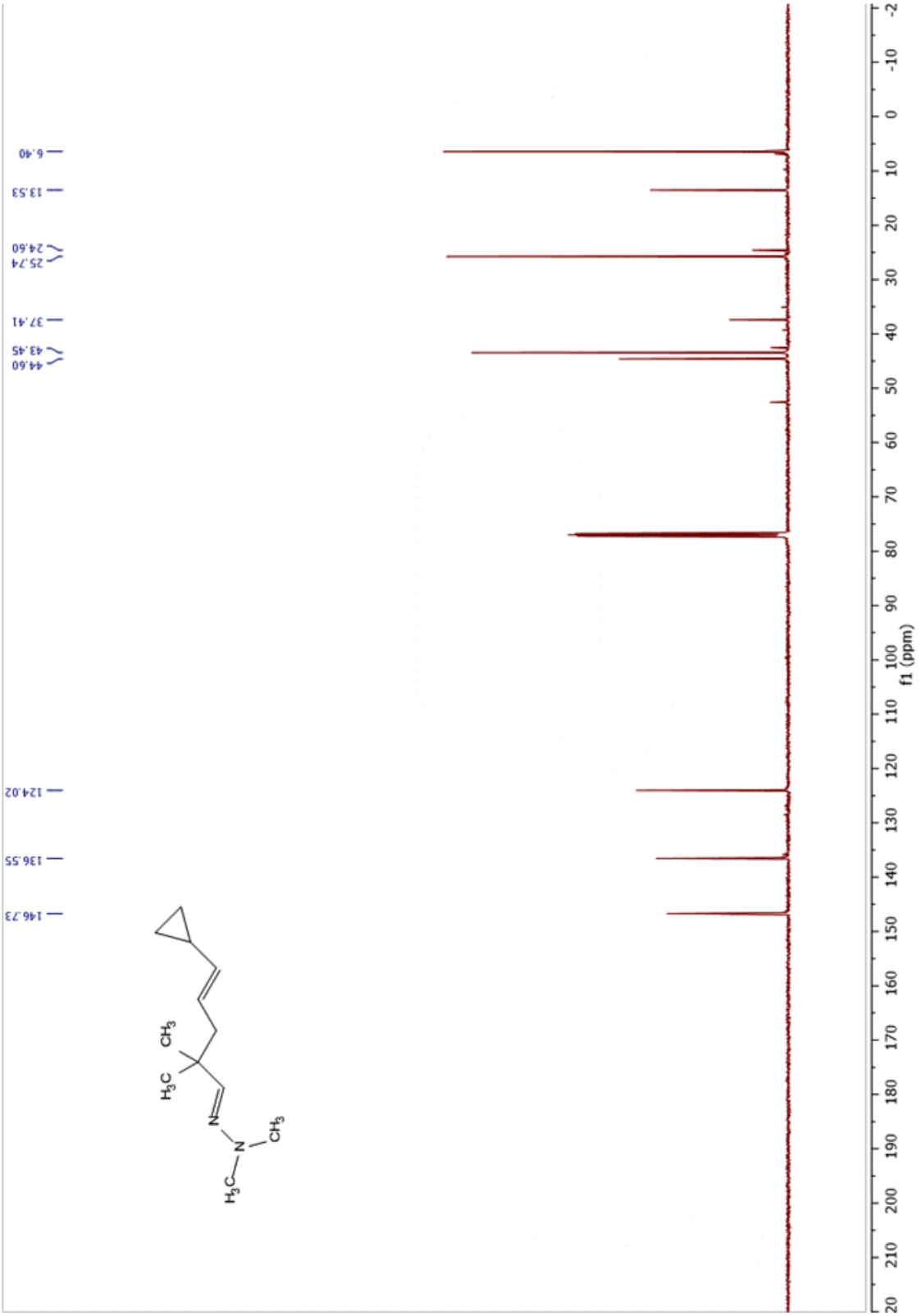

145.29
137.01
127.18
110.13
64.85
60.15
45.10
41.60
37.15
34.74
31.61
29.19
28.81
26.50
22.20
f1 (ppm)

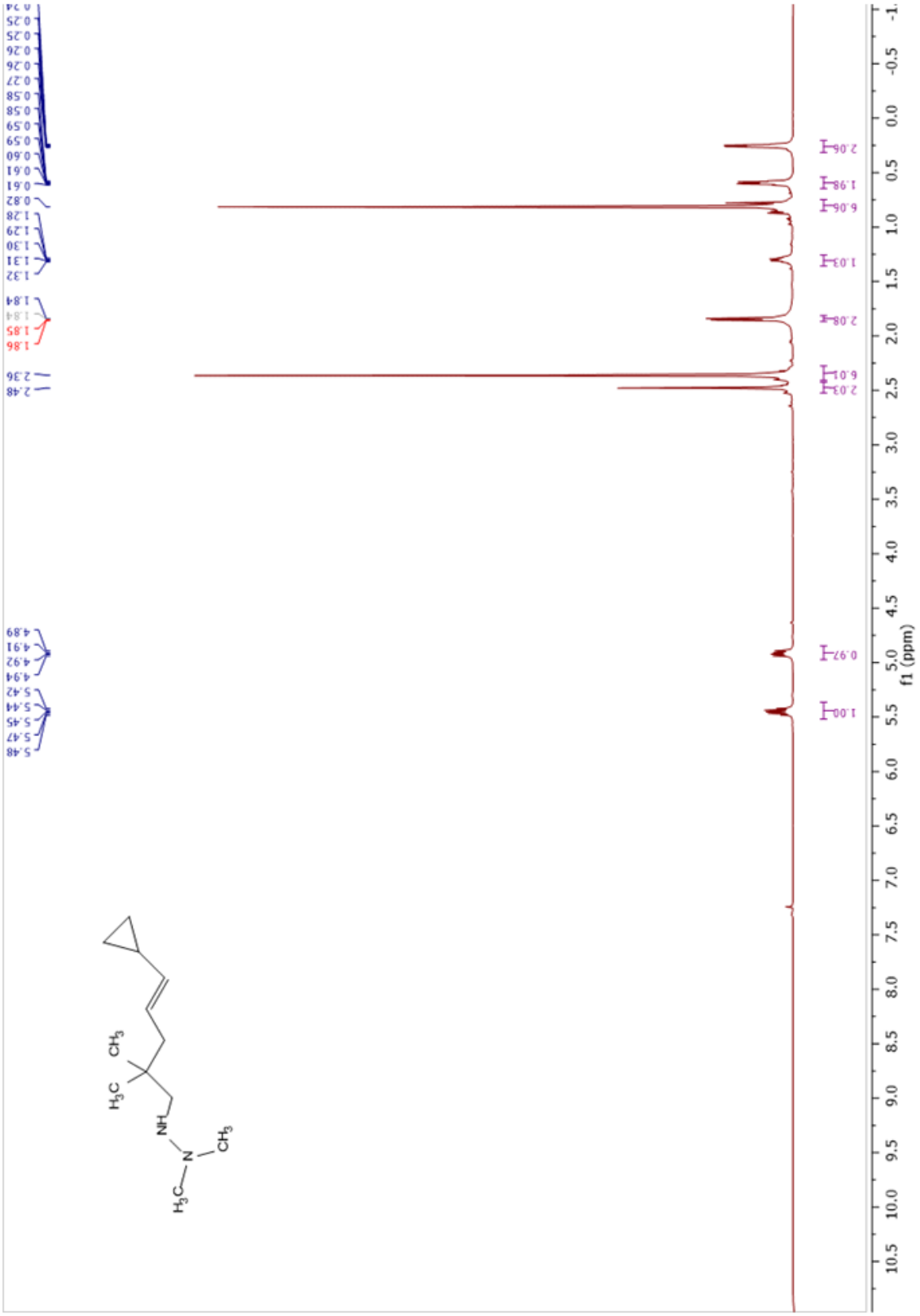
Chapter Five Spectral Data

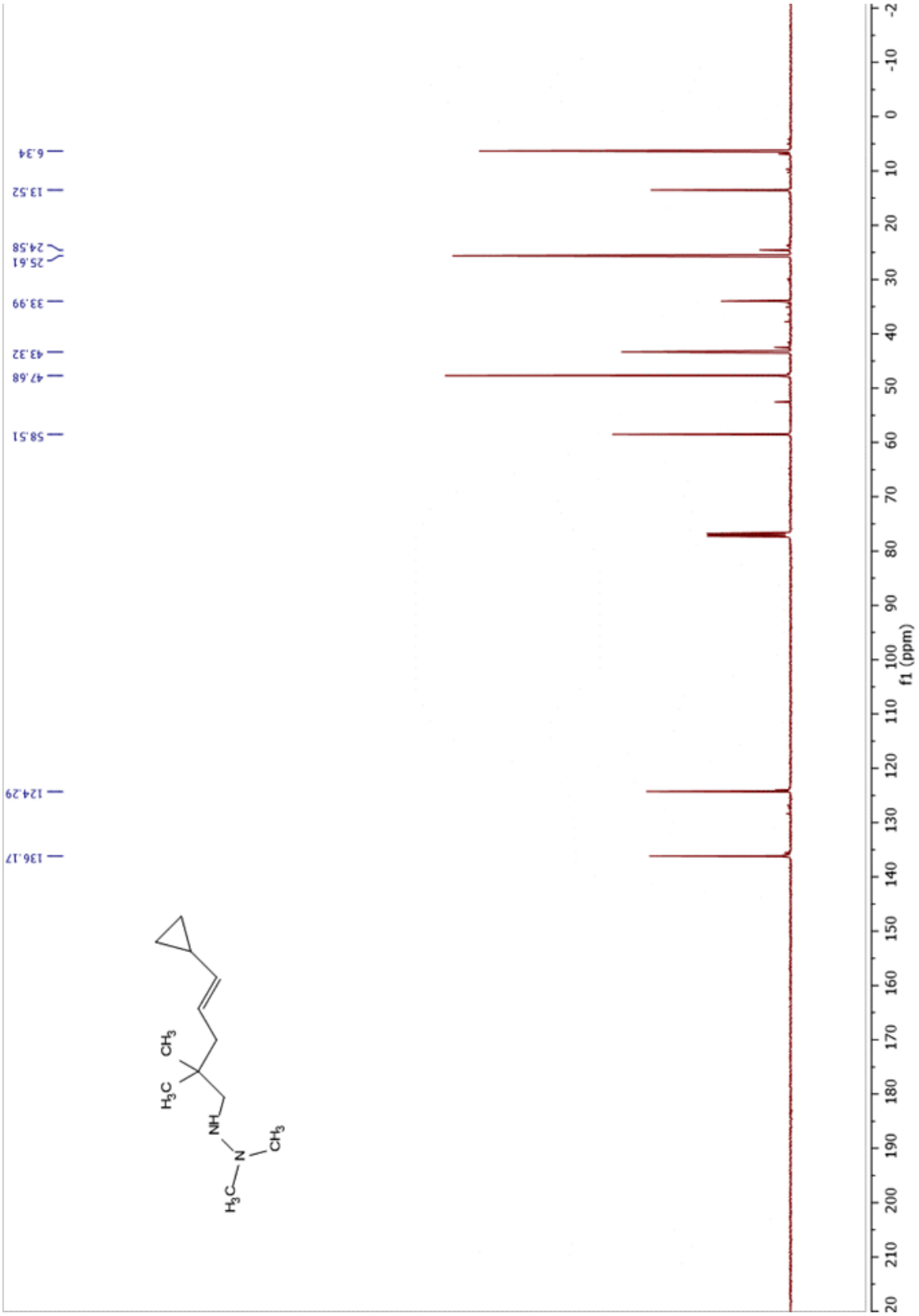


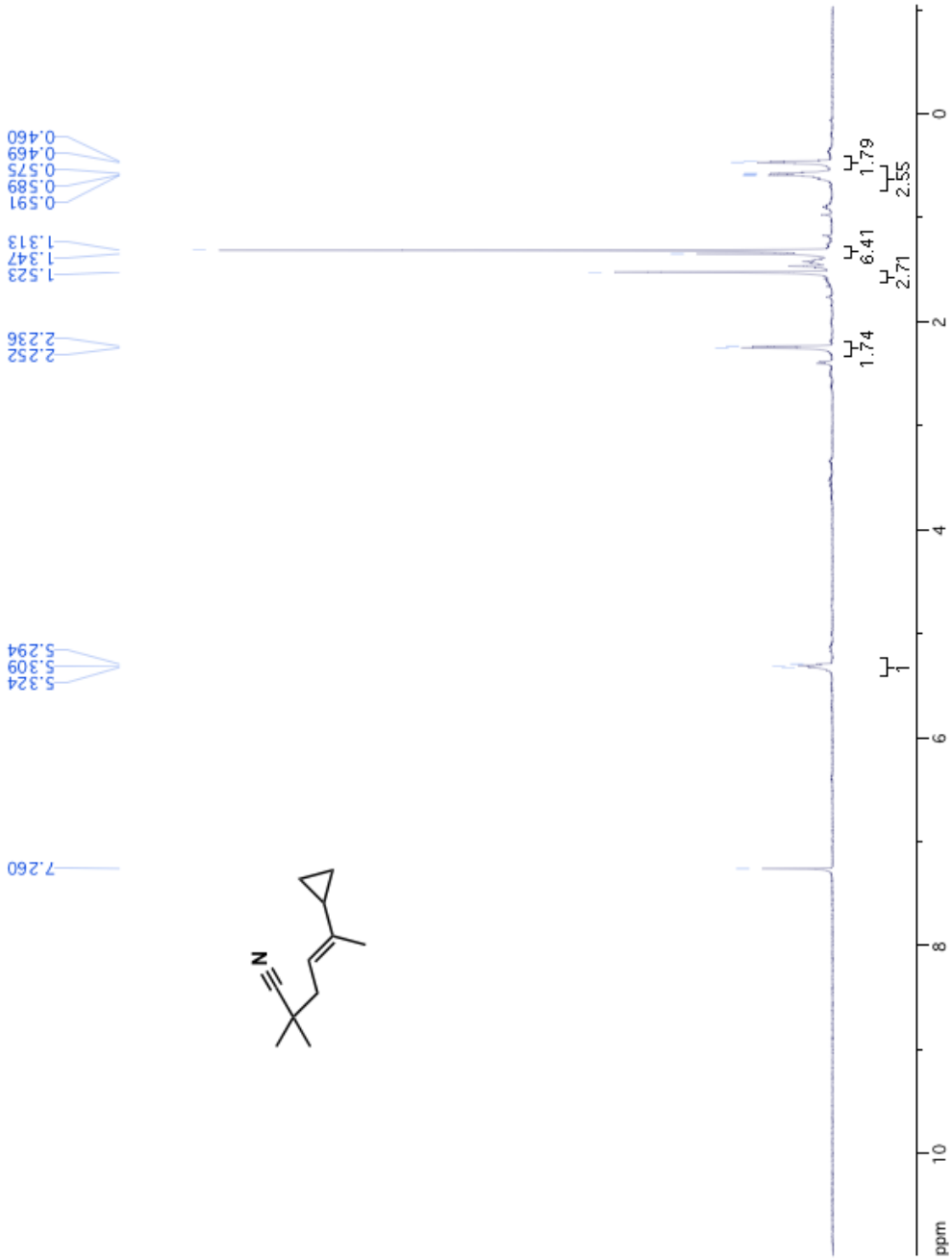

6.65
6.65
13.54
26.12
32.58
43.78
120.94
124.95
139.66
CH3
H3C
N
f1 (ppm)

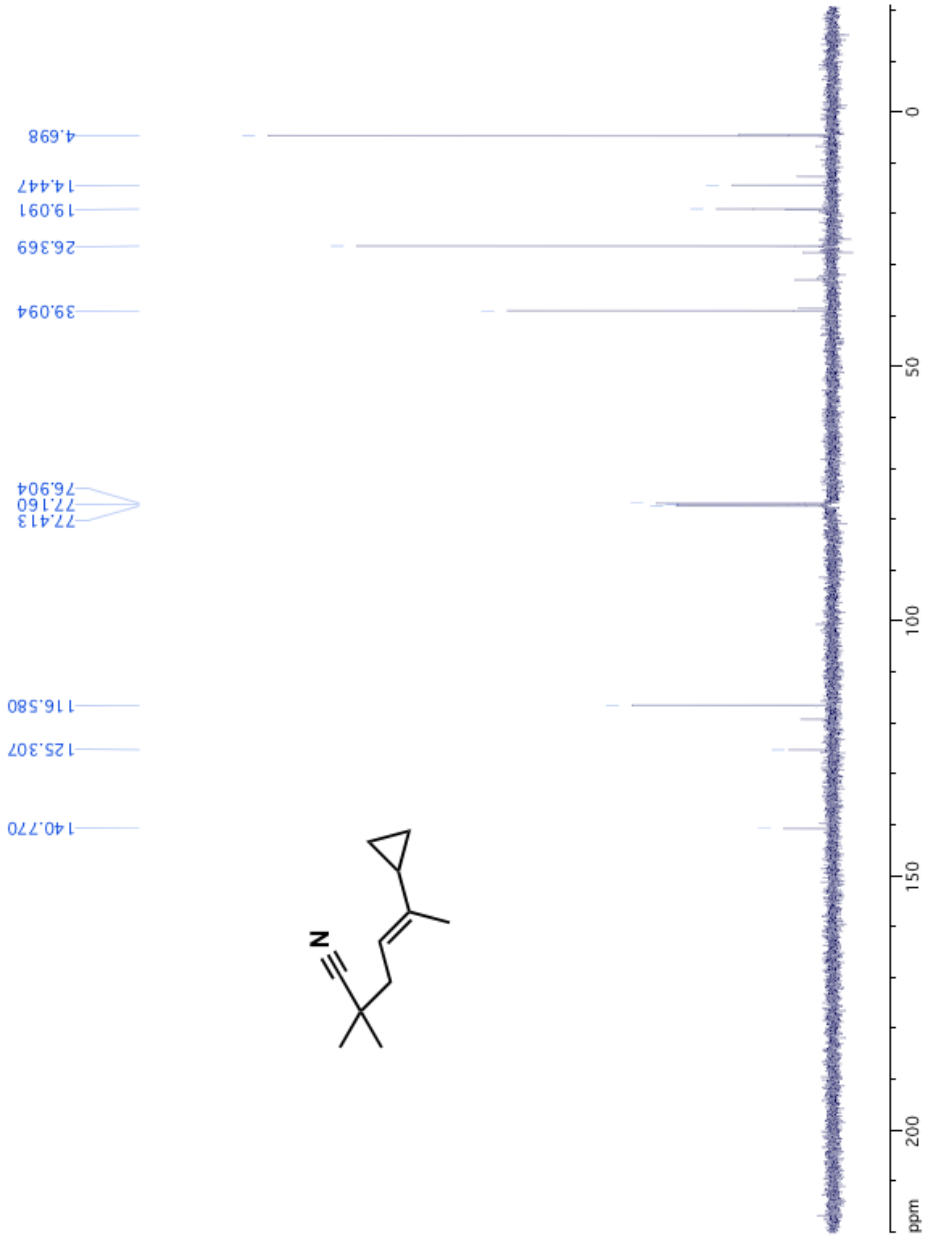

f1 (ppm)
H3C
CH3
N
N
CH3
H3C

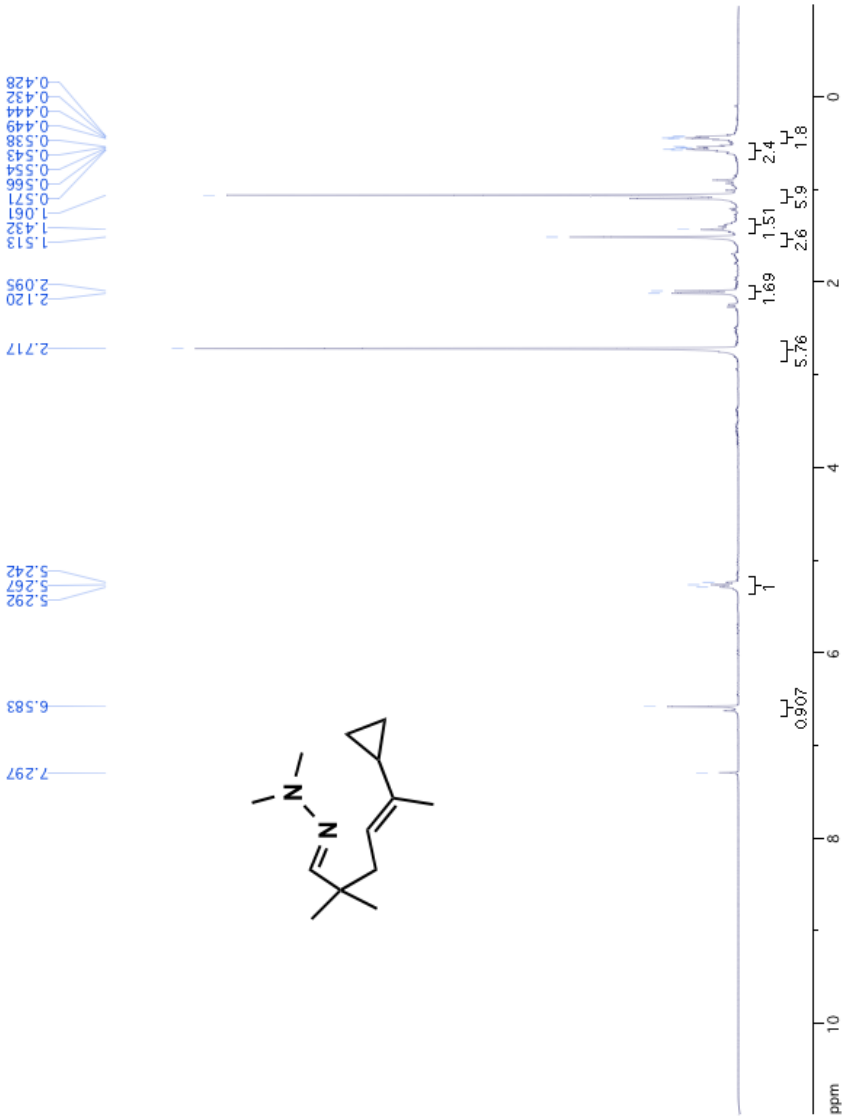

6.40
13.53
24.60
25.74
37.41
43.45
44.60
124.02
136.55
146.73
f1 (ppm)

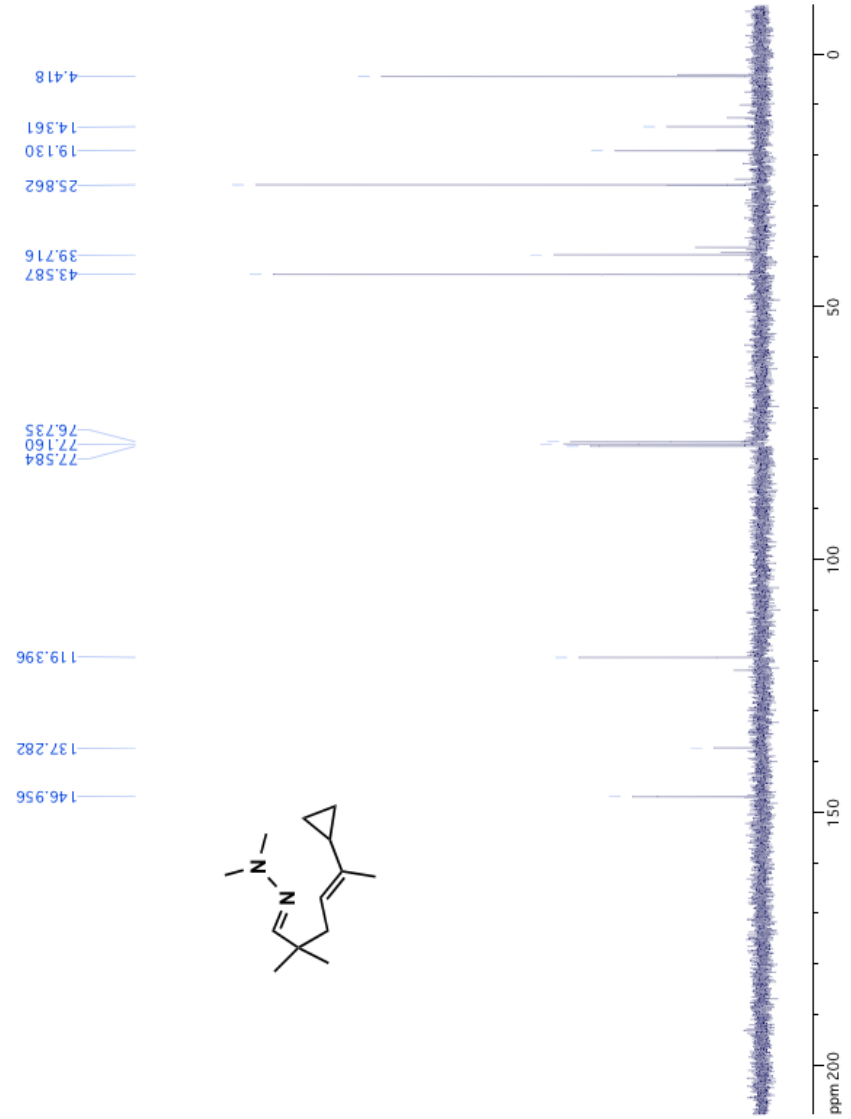

f1 (ppm)
2.06
1.98
6.06
1.03
2.08
6.01
2.03
0.97
1.00
NH
N
CH3
H3C
CH3
H3C

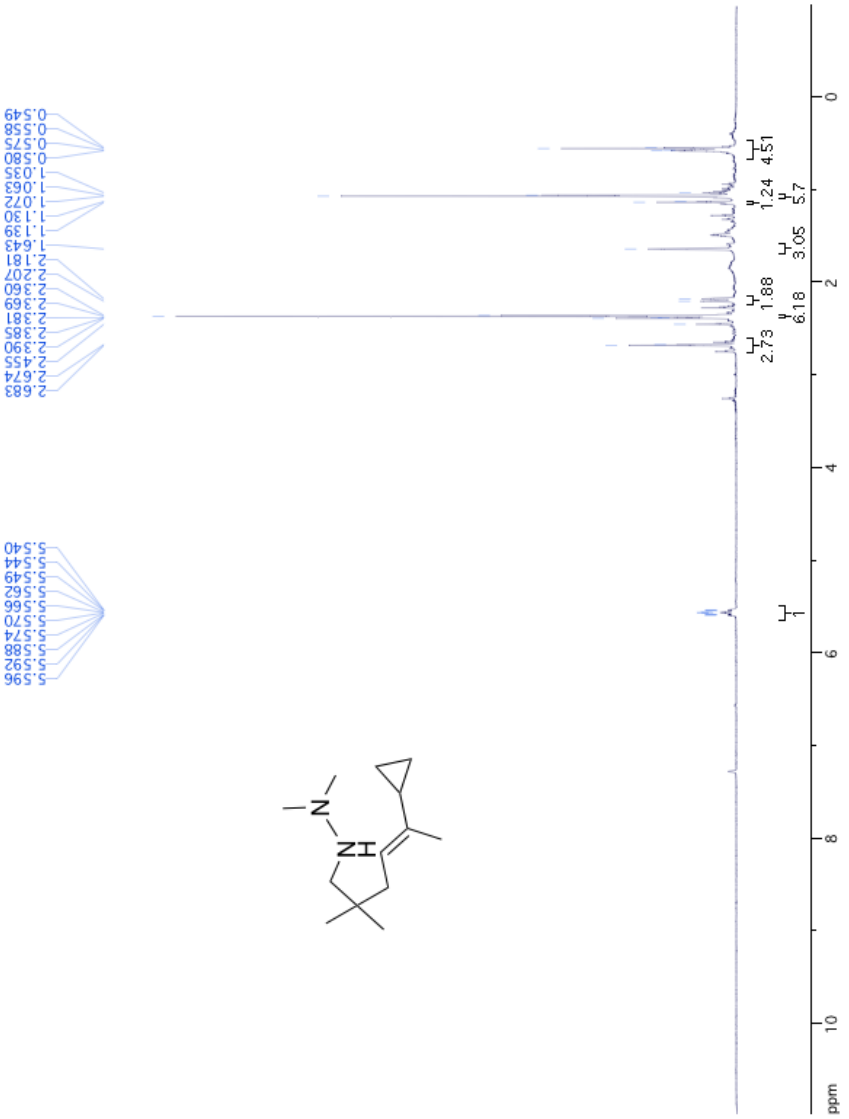

136.17
124.29
58.51
47.68
43.32
33.99
25.61
24.58
13.52
6.34
f1 (ppm)
NH
N
CH3
H3C
CH3
H3C

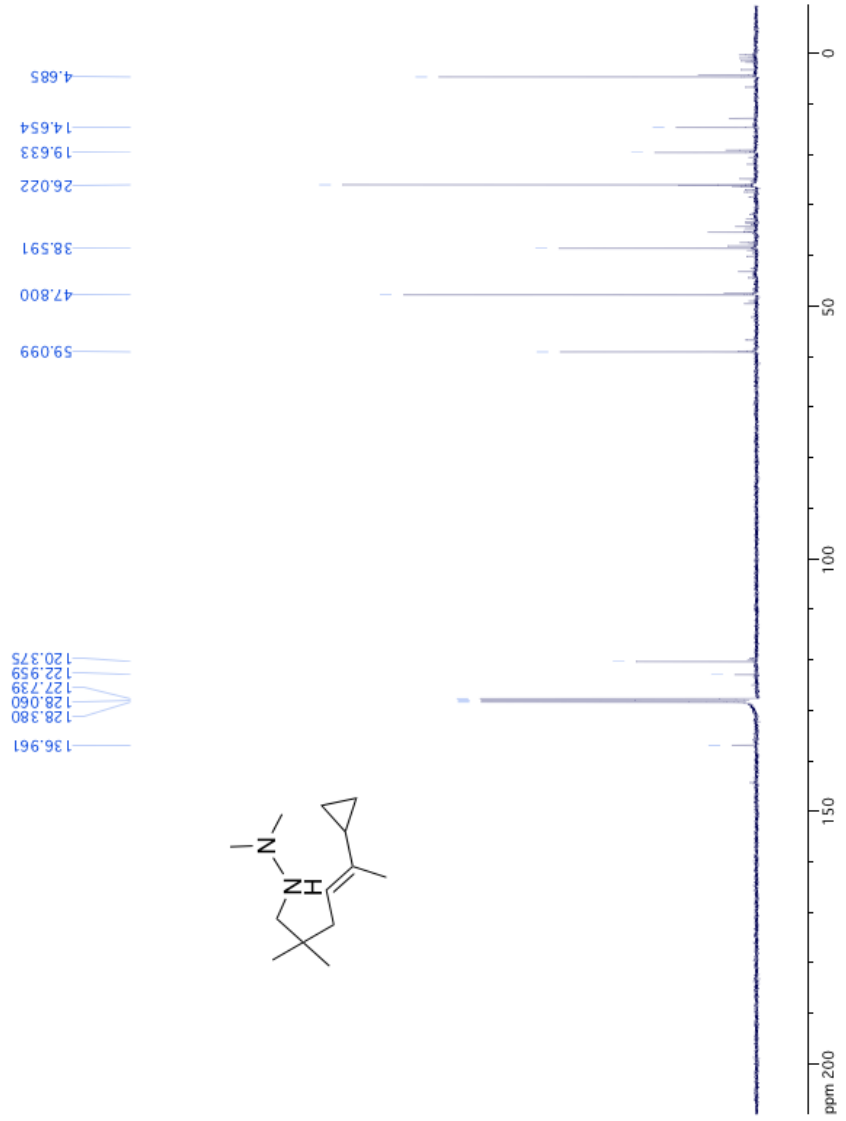

7.260
5.324
5.309
5.294
2.252
2.236
1.523
1.347
1.313
0.591
0.589
0.575
0.469
0.460
1
1.74
6.41
2.71
1.79
2.55
N
ppm

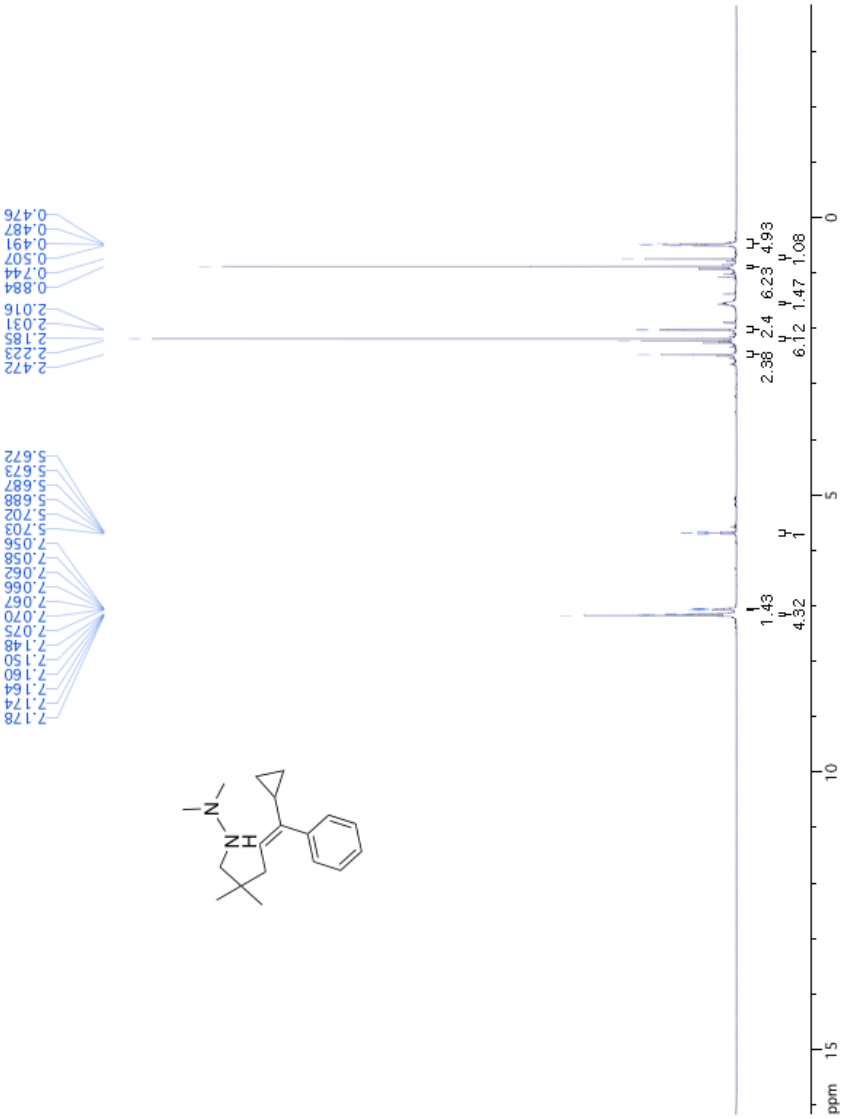

4.698
14.447
19.091
26.369
39.094
76.904
77.160
77.413
116.580
125.307
140.770
N
0
50
100
150
200
ppm

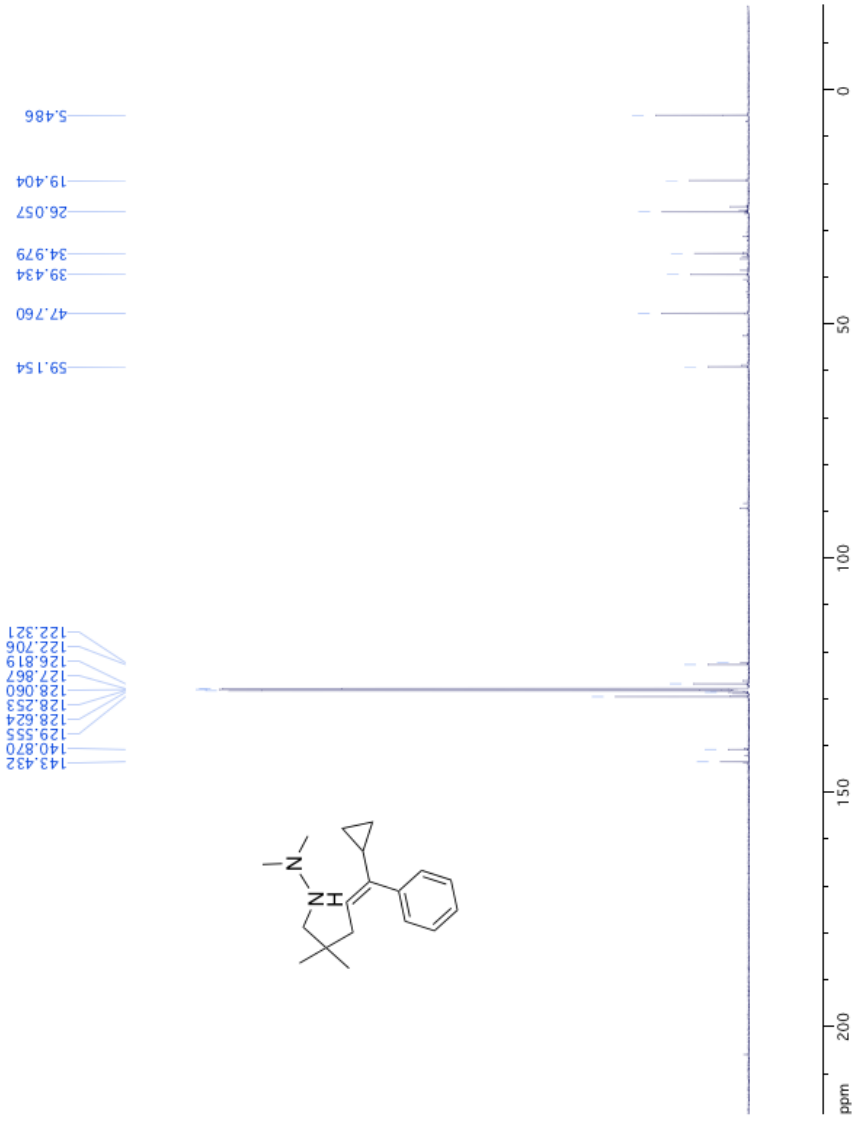

0.428
0.432
0.444
0.449
0.538
0.543
0.554
0.566
0.571
1.061
1.432
1.513
2.095
2.120
2.717
5.242
5.267
5.292
6.583
7.297
0.907
1
5.76
1.89
2.6
1.51
5.9
2.4
1.8
ppm
0
2
4
6
8
10
N
N

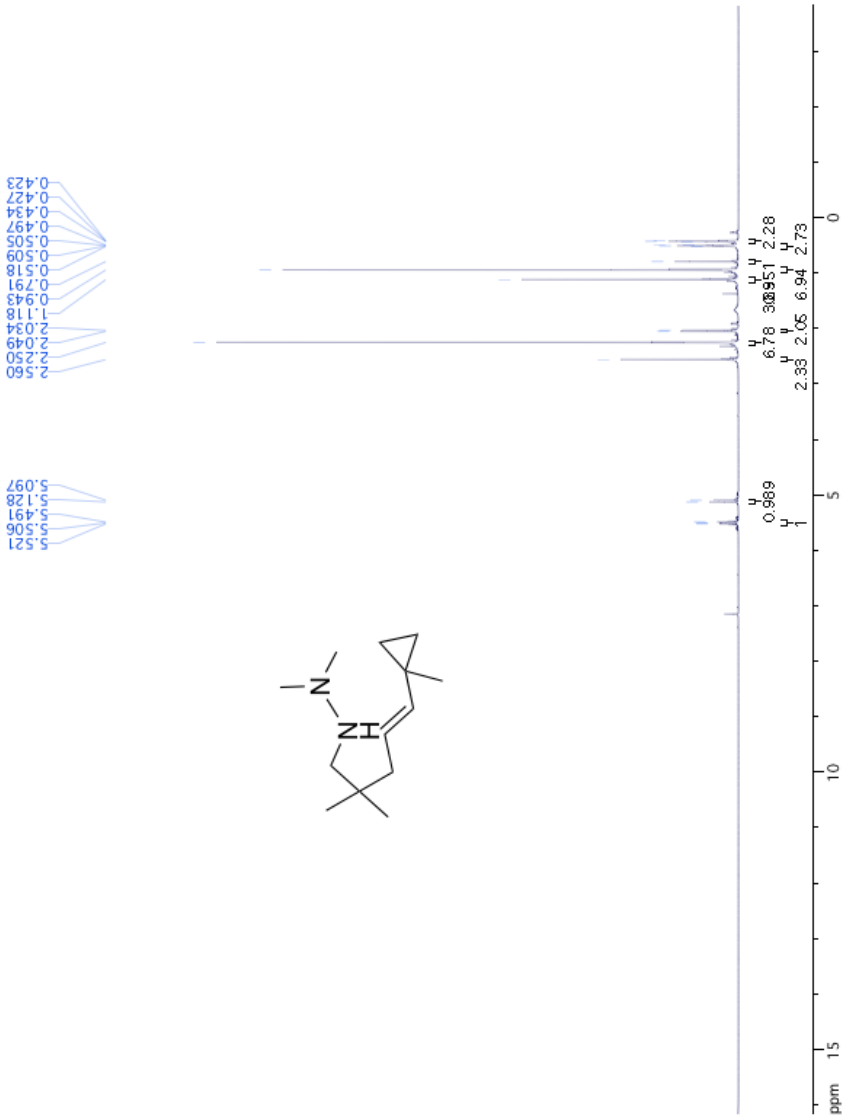

4.418
14.361
19.130
25.862
39.716
43.587
76.735
77.160
77.584
119.396
137.282
146.956
0
50
100
150
ppm 200

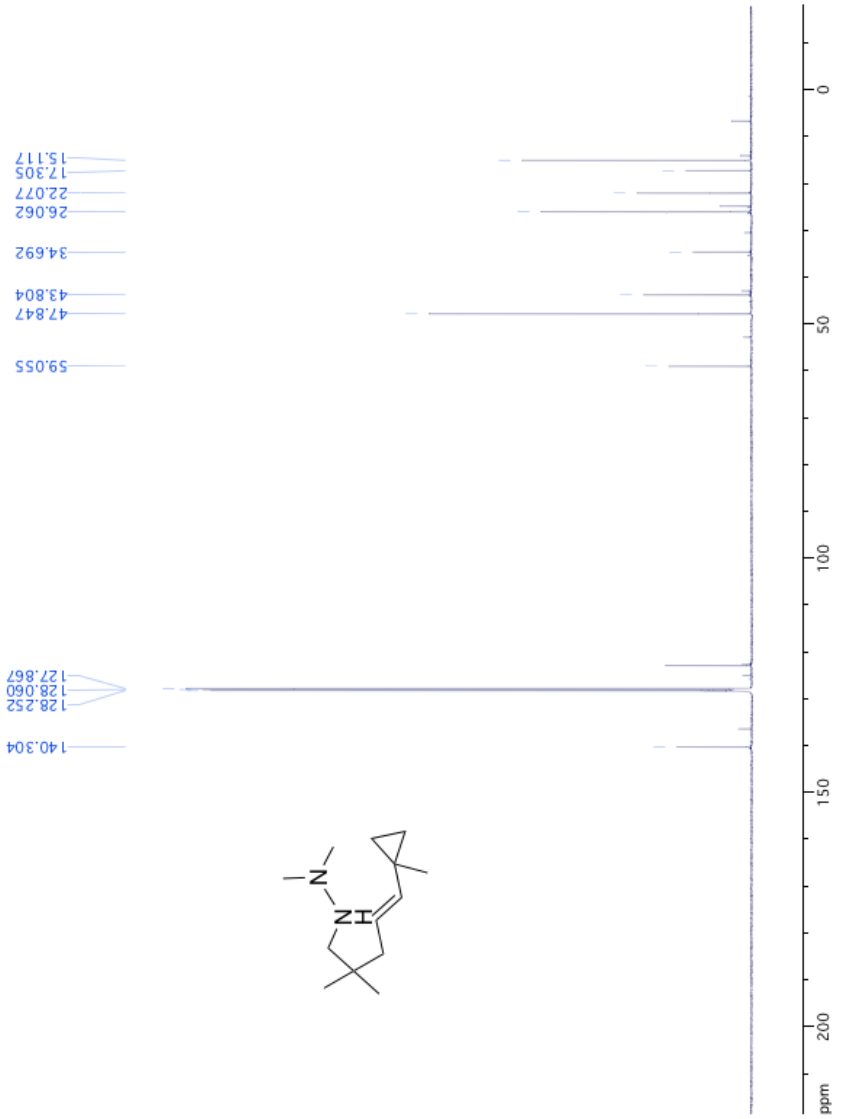

5.596
5.592
5.588
5.574
5.570
5.566
5.562
5.549
5.544
5.540
2.683
2.674
2.655
2.390
2.385
2.381
2.369
2.360
2.207
2.181
1.643
1.139
1.130
1.072
1.063
1.035
0.580
0.575
0.558
0.549
1
2.73
1.88
6.18
3.05
1.24
5.7
4.51
ppm
0
2
4
6
8
10
N
NH

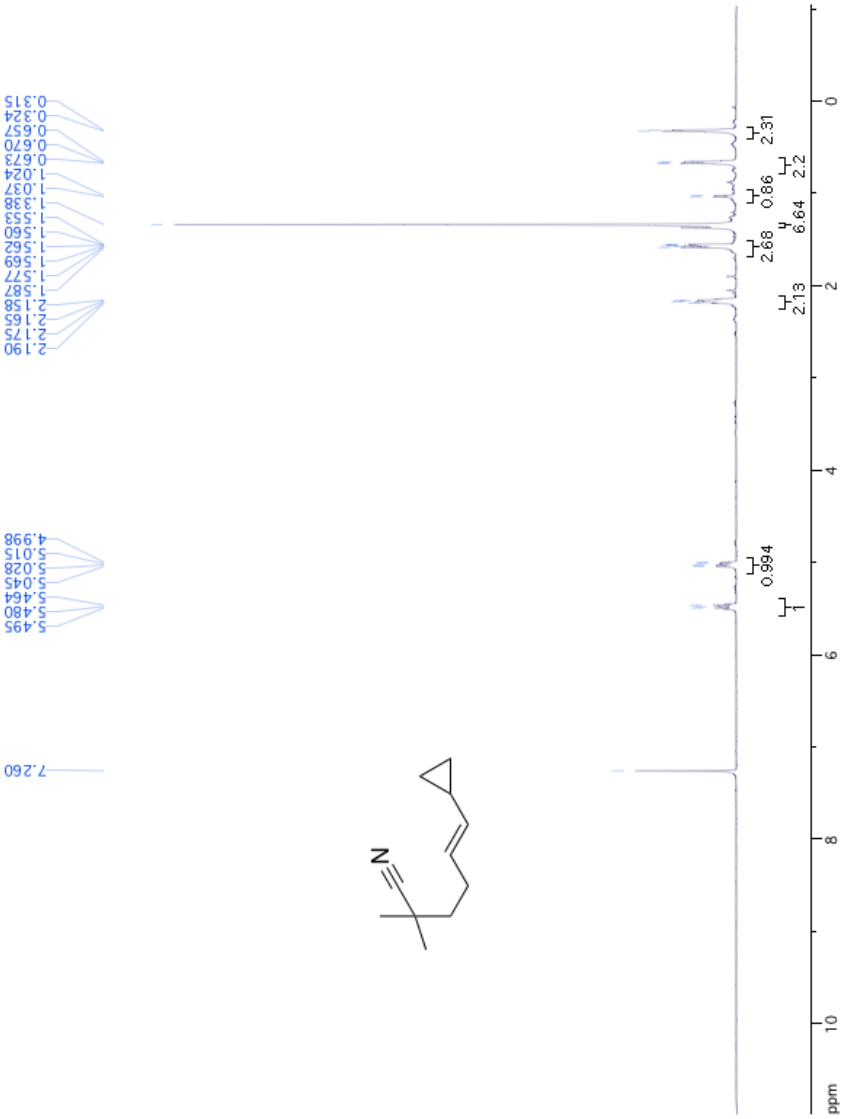

4.685
14.654
19.633
26.022
38.591
47.800
59.099
120.375
122.959
127.739
128.060
128.380
136.961
0
50
100
150
ppm 200

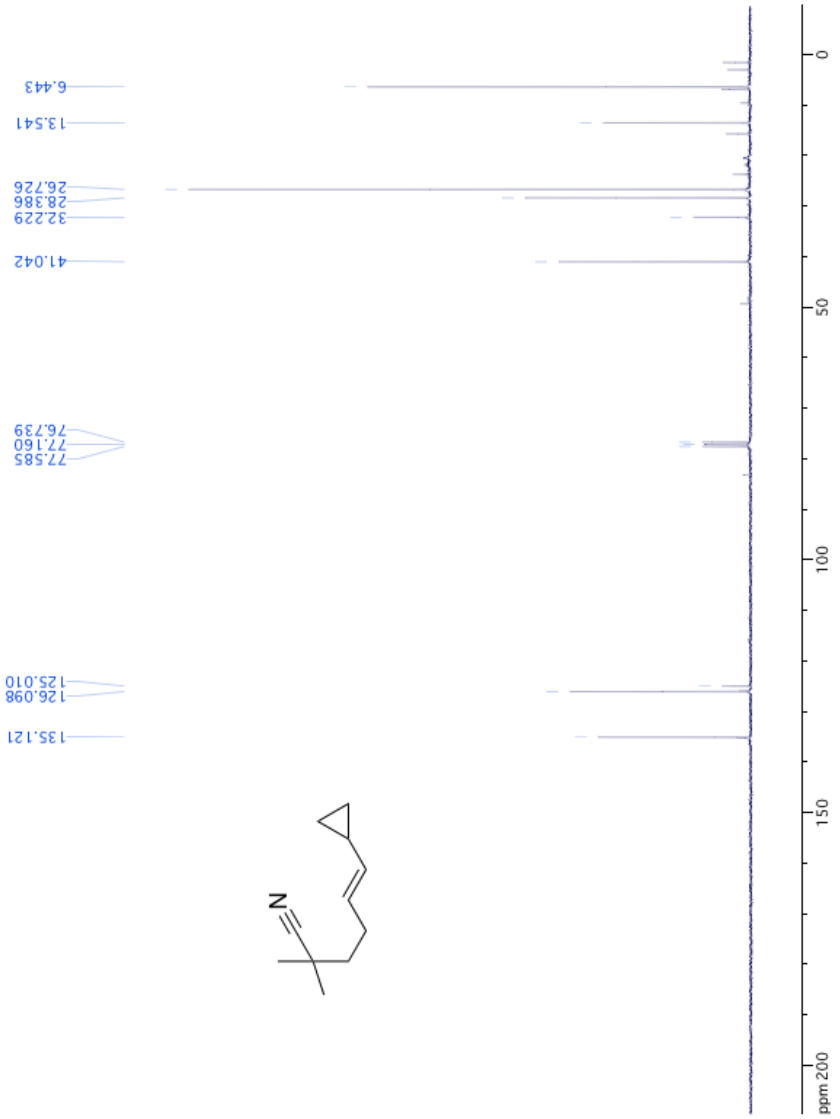

0.476
0.487
0.491
0.507
0.744
0.884
2.016
2.031
2.185
2.223
2.472
5.672
5.673
5.687
5.688
5.702
5.703
7.056
7.058
7.062
7.066
7.067
7.070
7.075
7.148
7.150
7.160
7.164
7.174
7.178
1.43
4.32
1
2.38
2.4
6.12
6.23
1.47
4.93
1.08
ppm
15
10
5
0

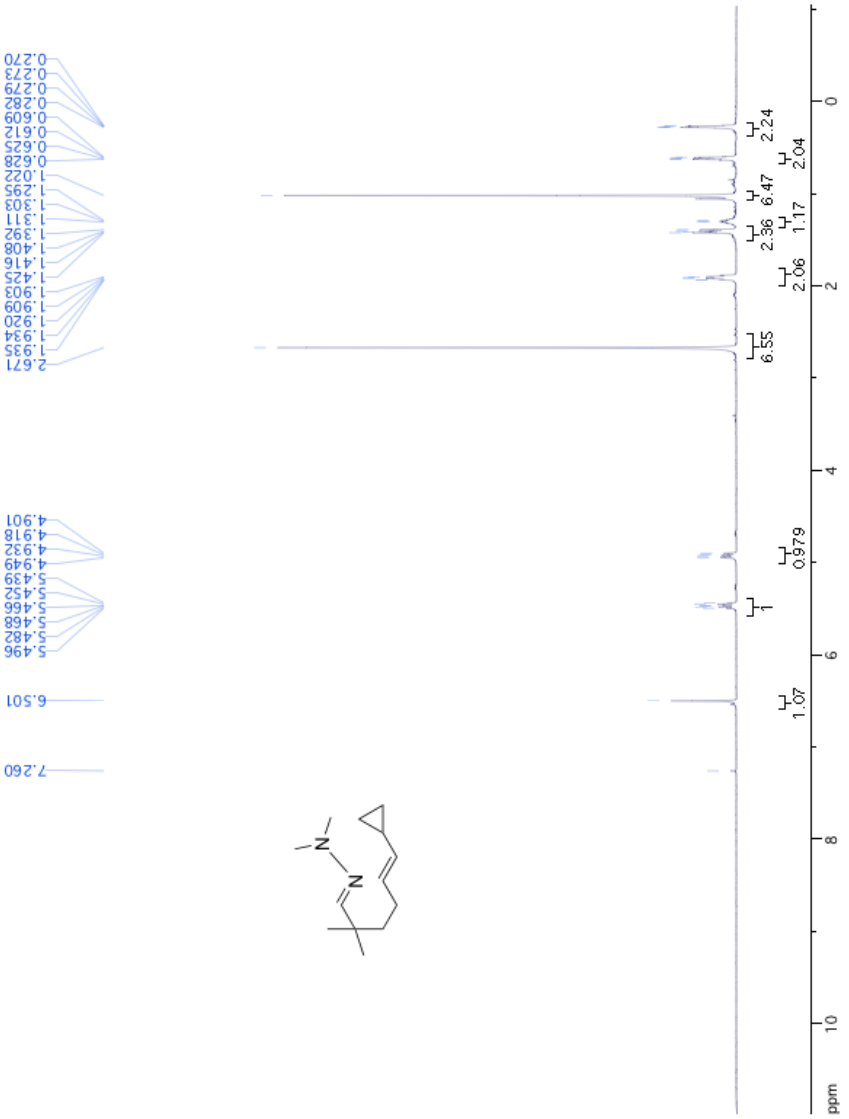

5.486
19.404
26.057
34.979
39.434
47.760
59.154
122.321
122.706
126.819
127.867
128.060
128.253
128.624
129.555
140.870
143.432
0
50
100
150
200
ppm

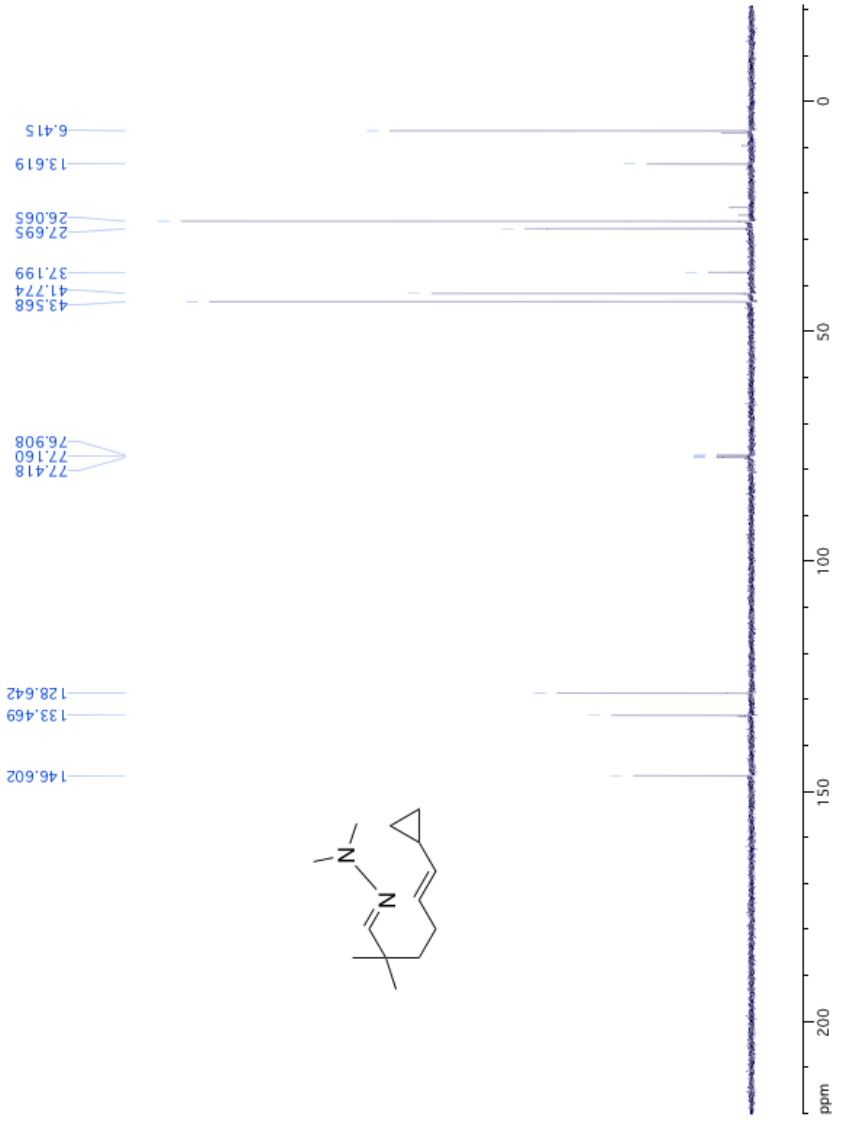

0.423
0.427
0.434
0.497
0.505
0.509
0.518
0.791
0.943
1.118
2.034
2.049
2.250
2.560
5.097
5.128
5.491
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2.73
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10
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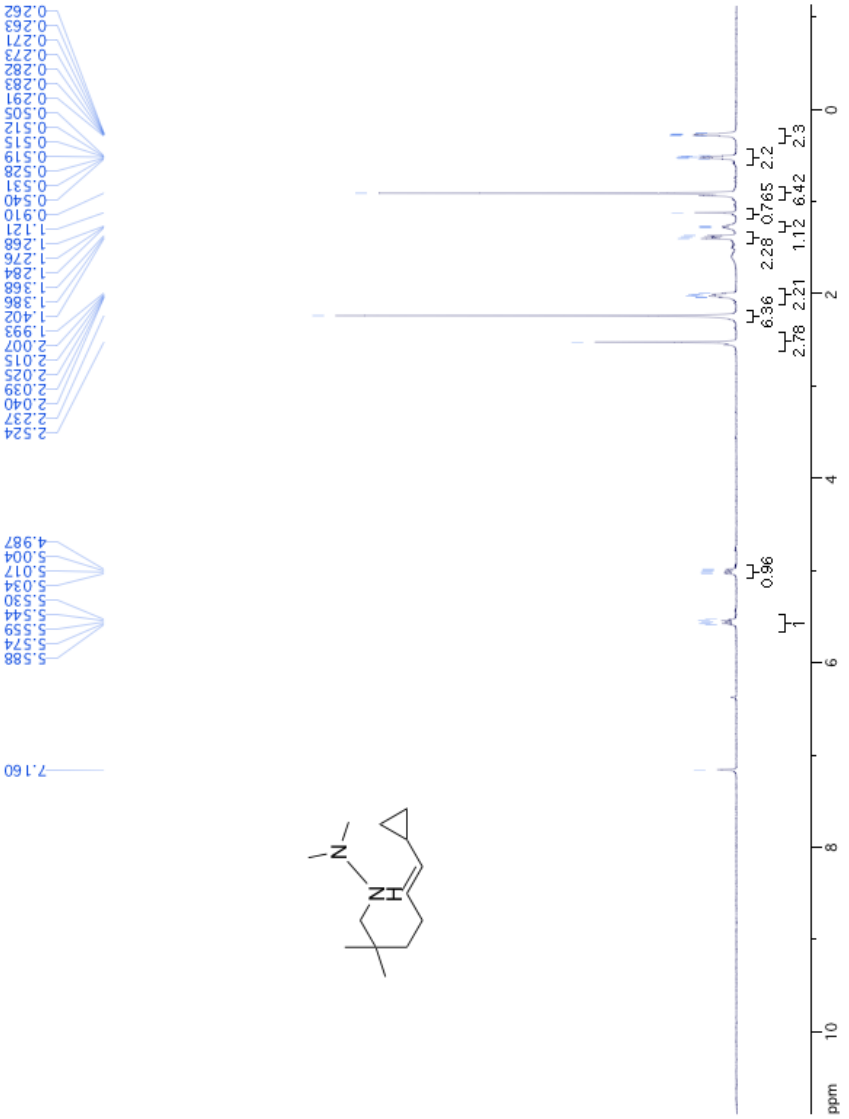

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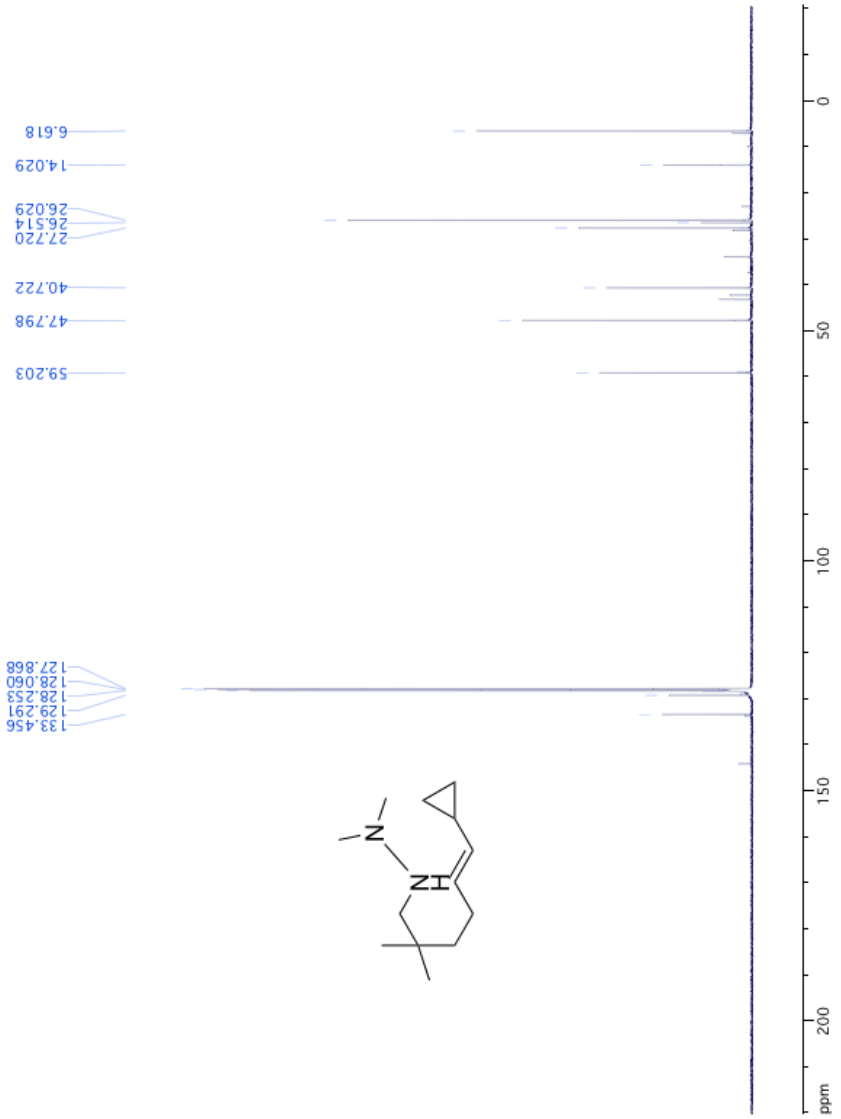

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5.028
5.015
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2.165
2.158
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1.577
1.569
1.562
1.560
1.553
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1.037
1.024
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0.670
0.657
0.324
0.315
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8
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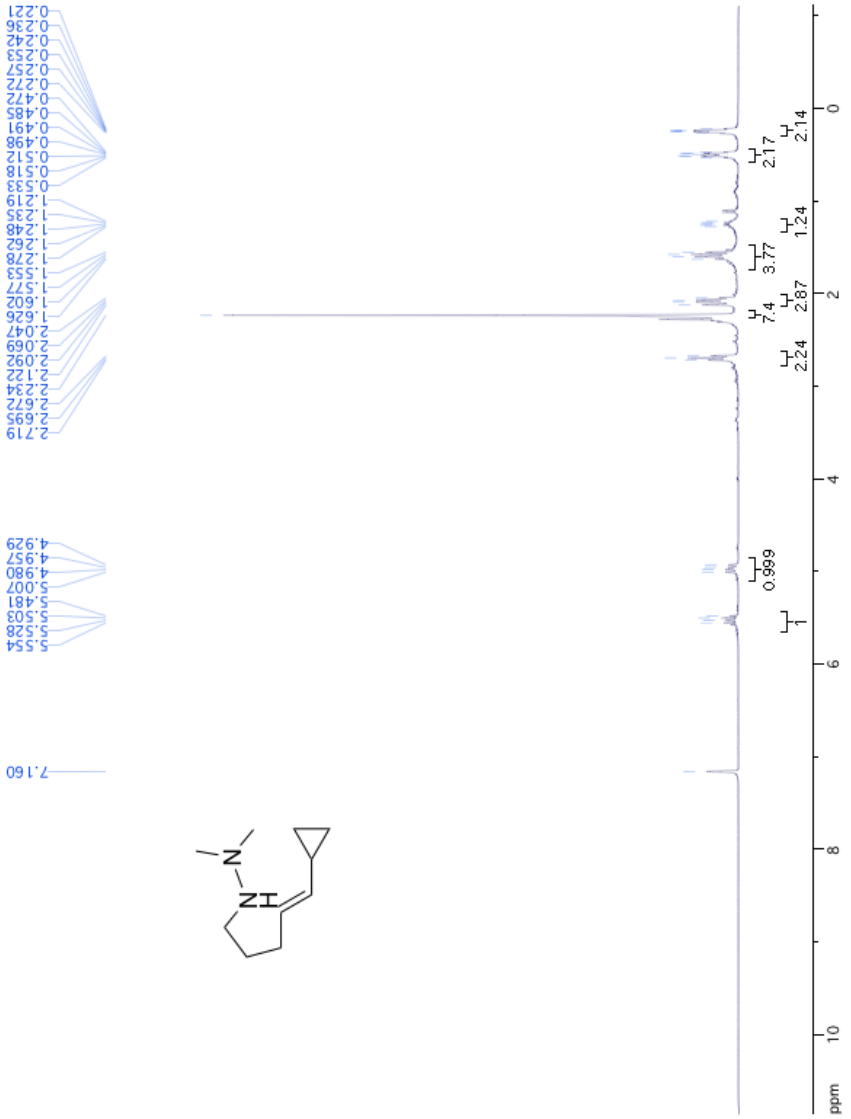

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26.726
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77.585
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ppm 200

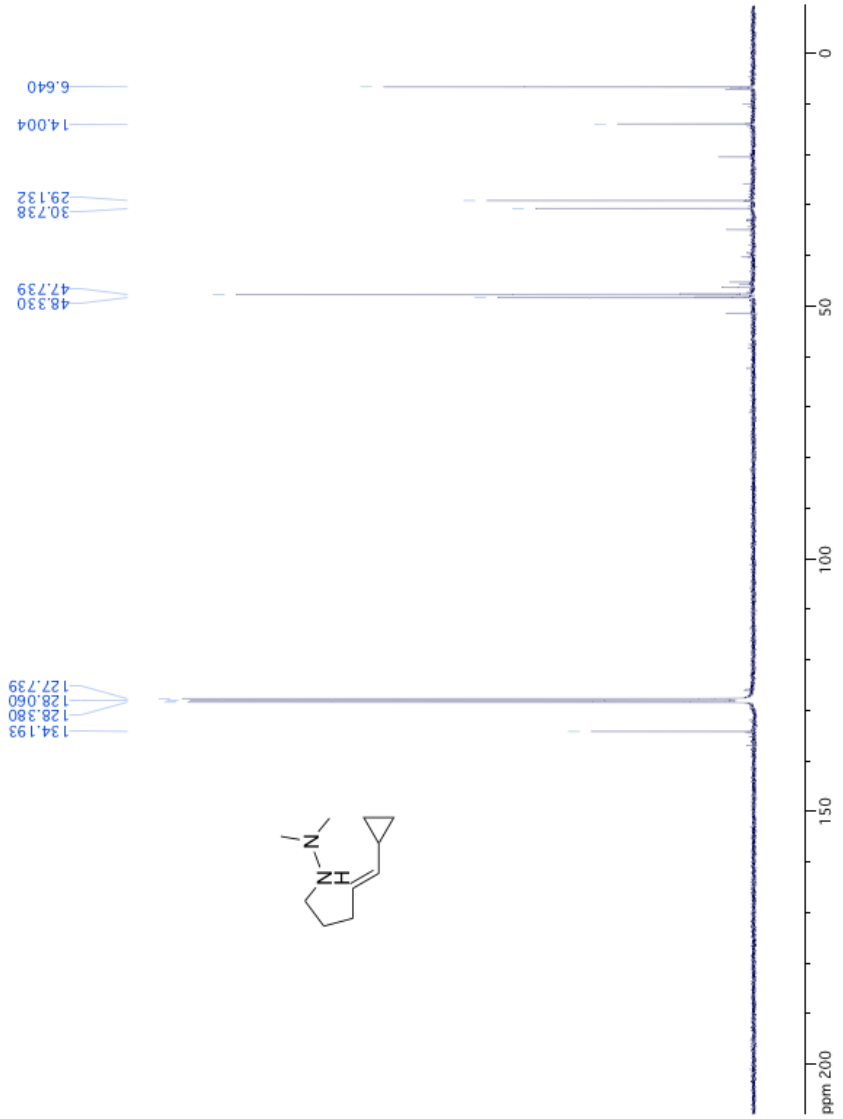

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5.466
5.452
5.439
4.949
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4.918
4.901
2.671
1.935
1.934
1.920
1.909
1.903
1.425
1.416
1.408
1.392
1.311
1.303
1.295
1.022
0.628
0.625
0.612
0.609
0.282
0.279
0.273
0.270
1.07
1
0.979
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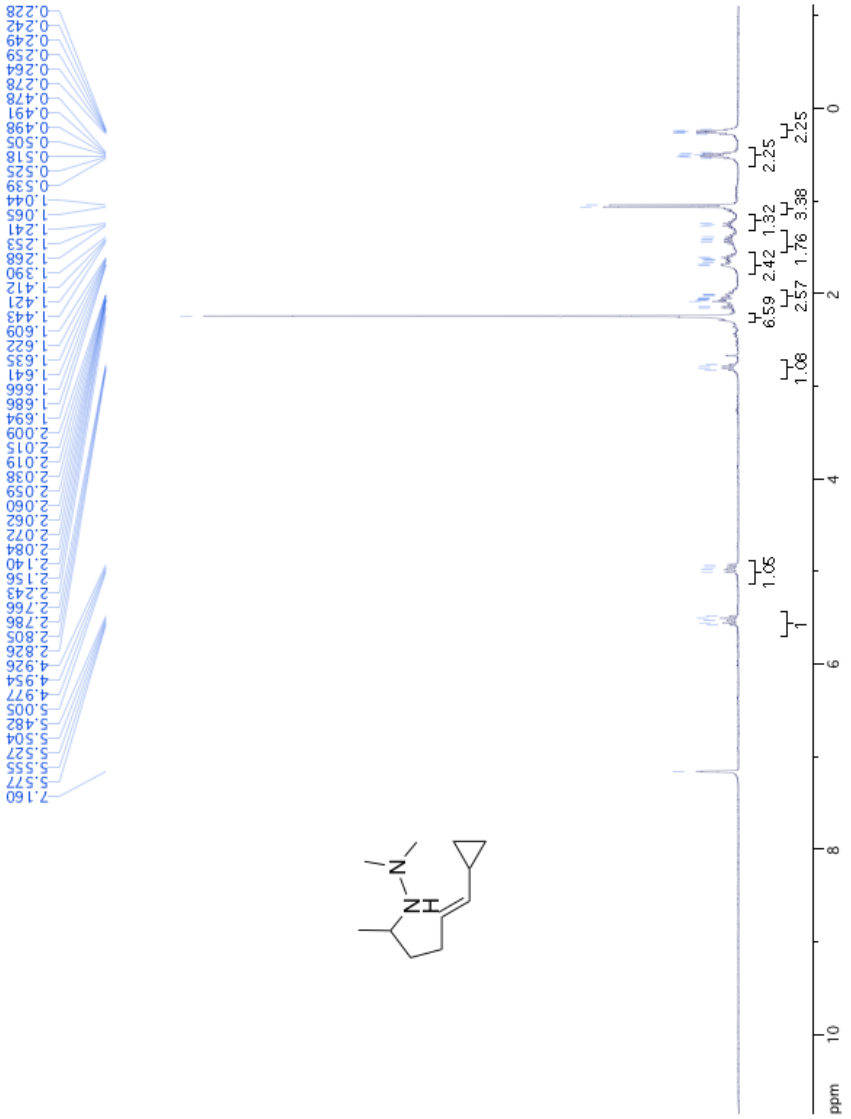

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26.065
27.695
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41.774
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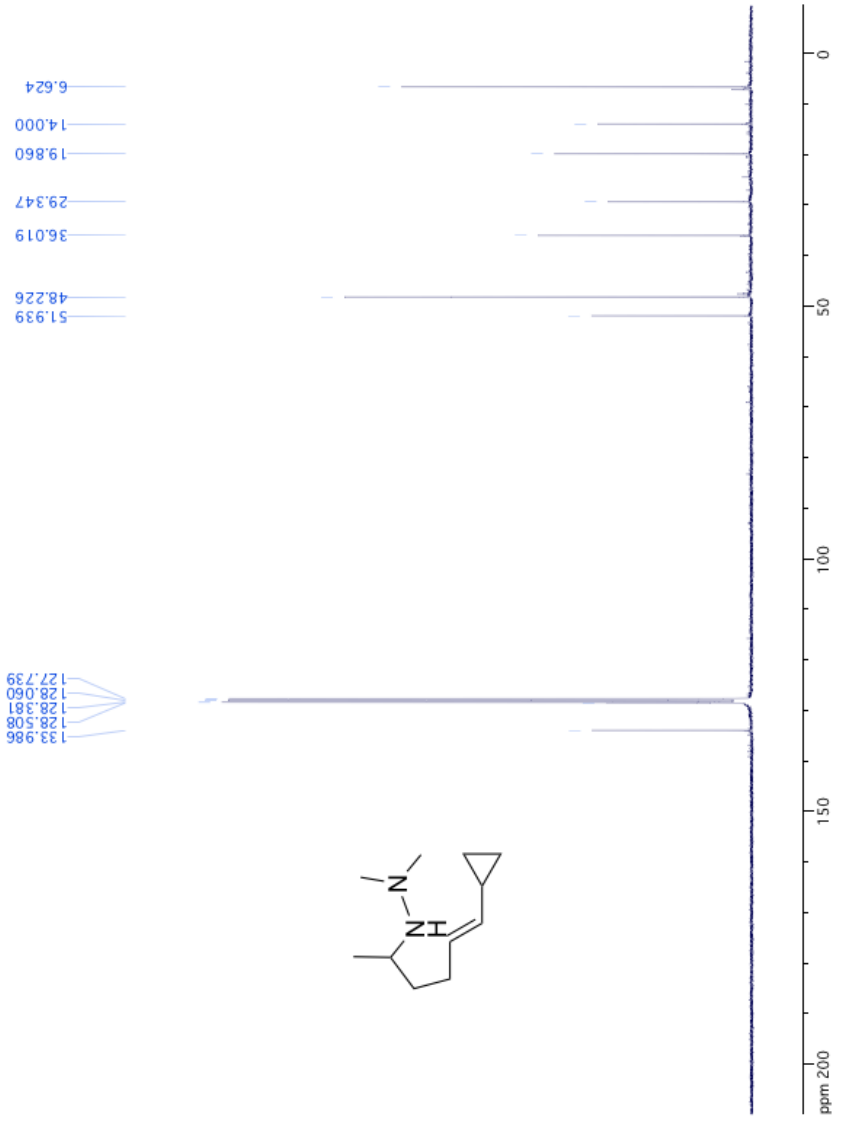

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5.574
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5.544
5.530
5.034
5.017
5.004
4.987
2.524
2.237
2.040
2.039
2.025
2.015
2.007
1.993
1.402
1.386
1.368
1.284
1.276
1.268
1.121
0.910
0.540
0.531
0.528
0.519
0.515
0.512
0.505
0.291
0.283
0.282
0.273
0.271
0.263
0.262
0.96
6.36
2.21
2.78
2.28
0.765
1.12
6.42
2.2
2.3
ppm


6.618
14.029
26.029
26.514
27.720
40.722
47.798
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127.868
128.060
128.253
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200
ppm
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NH

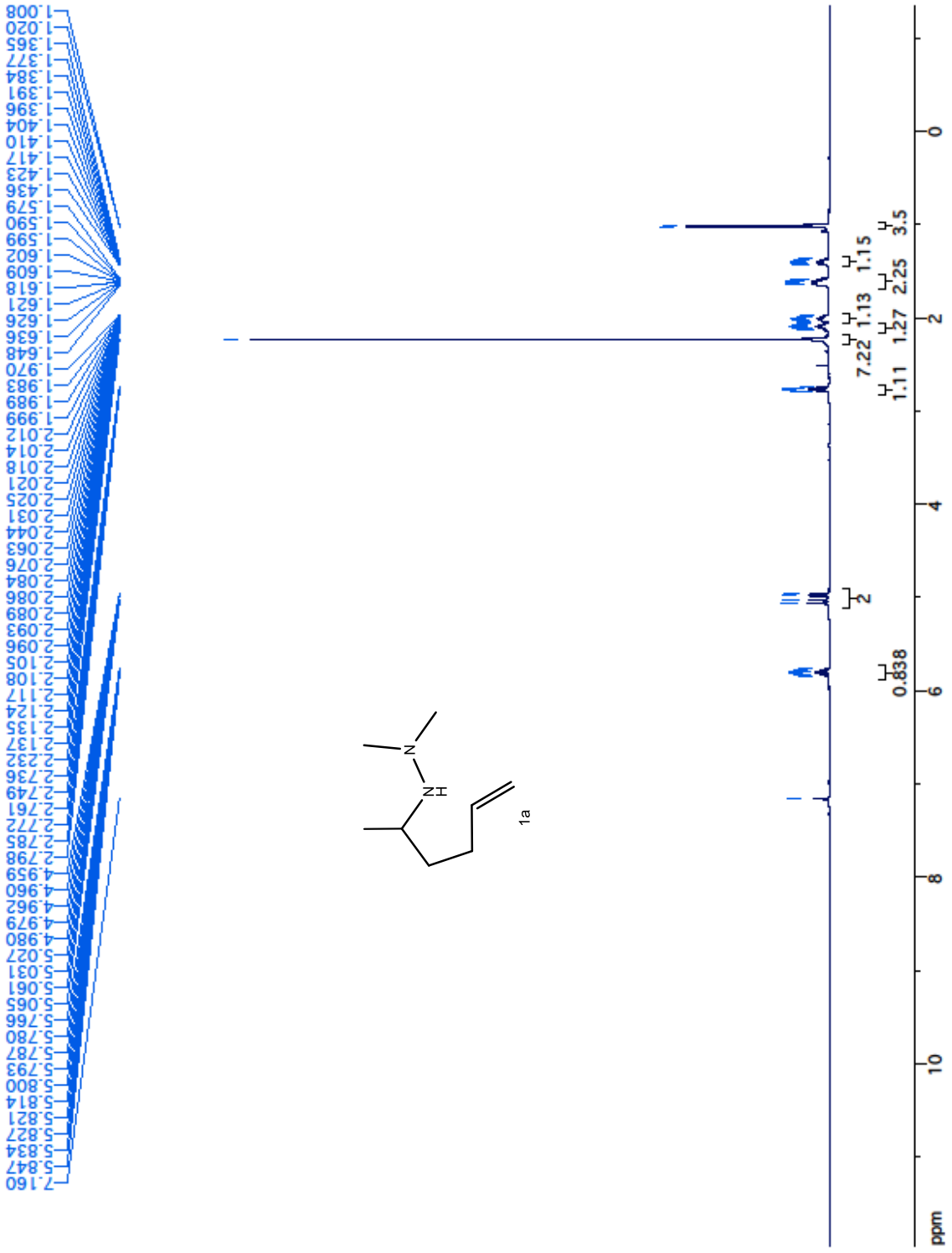

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0.236
0.242
0.253
0.257
0.272
0.472
0.485
0.491
0.498
0.512
0.518
0.533
1.219
1.235
1.248
1.262
1.278
1.553
1.577
1.602
1.626
2.047
2.069
2.092
2.122
2.234
2.672
2.695
2.719
4.929
4.957
4.980
5.007
5.481
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0.999
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3.77
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2.14
ppm

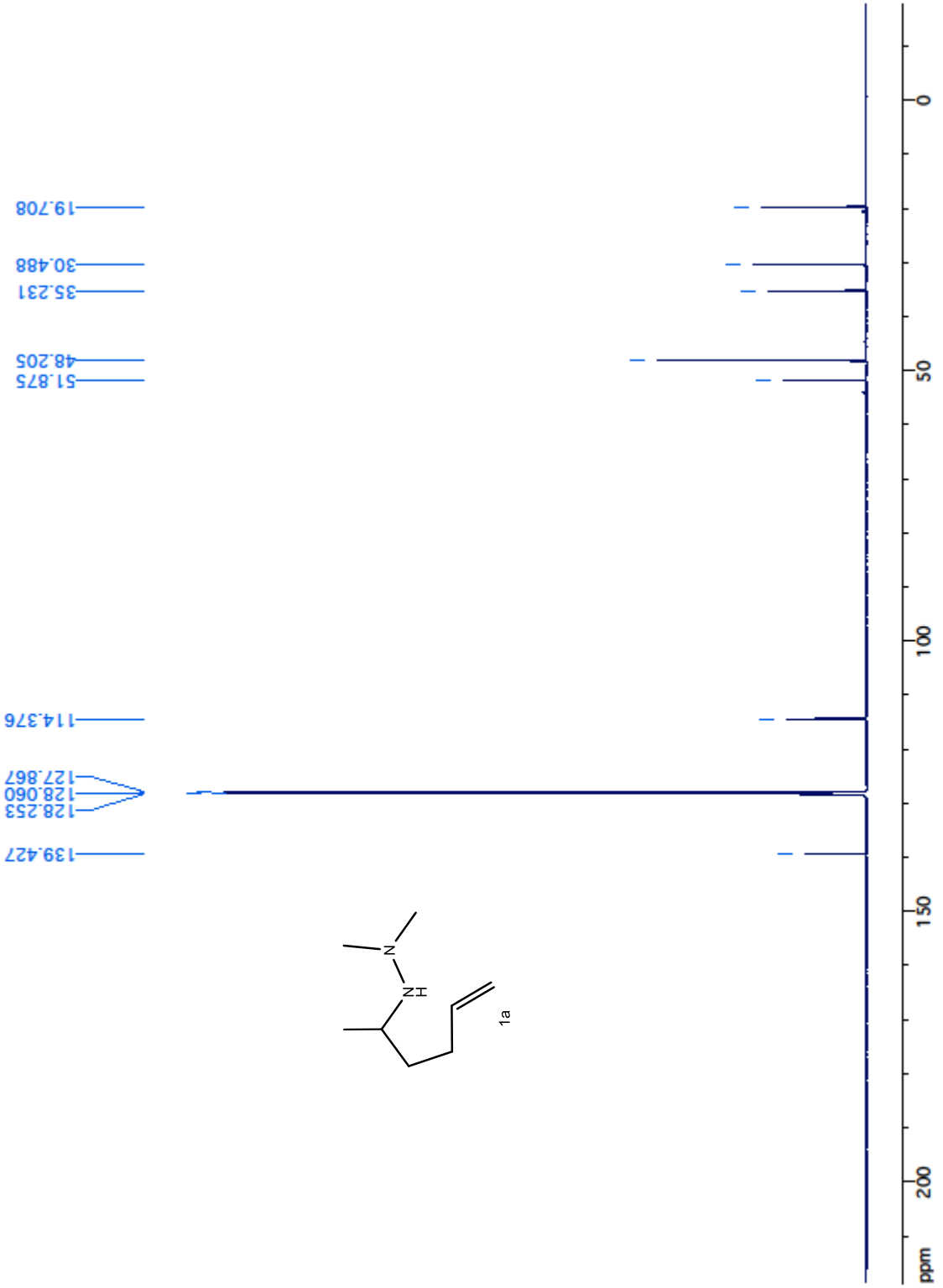

6.640
14.004
29.132
30.738
47.739
48.330
127.739
128.060
128.380
134.193
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100
150
ppm 200

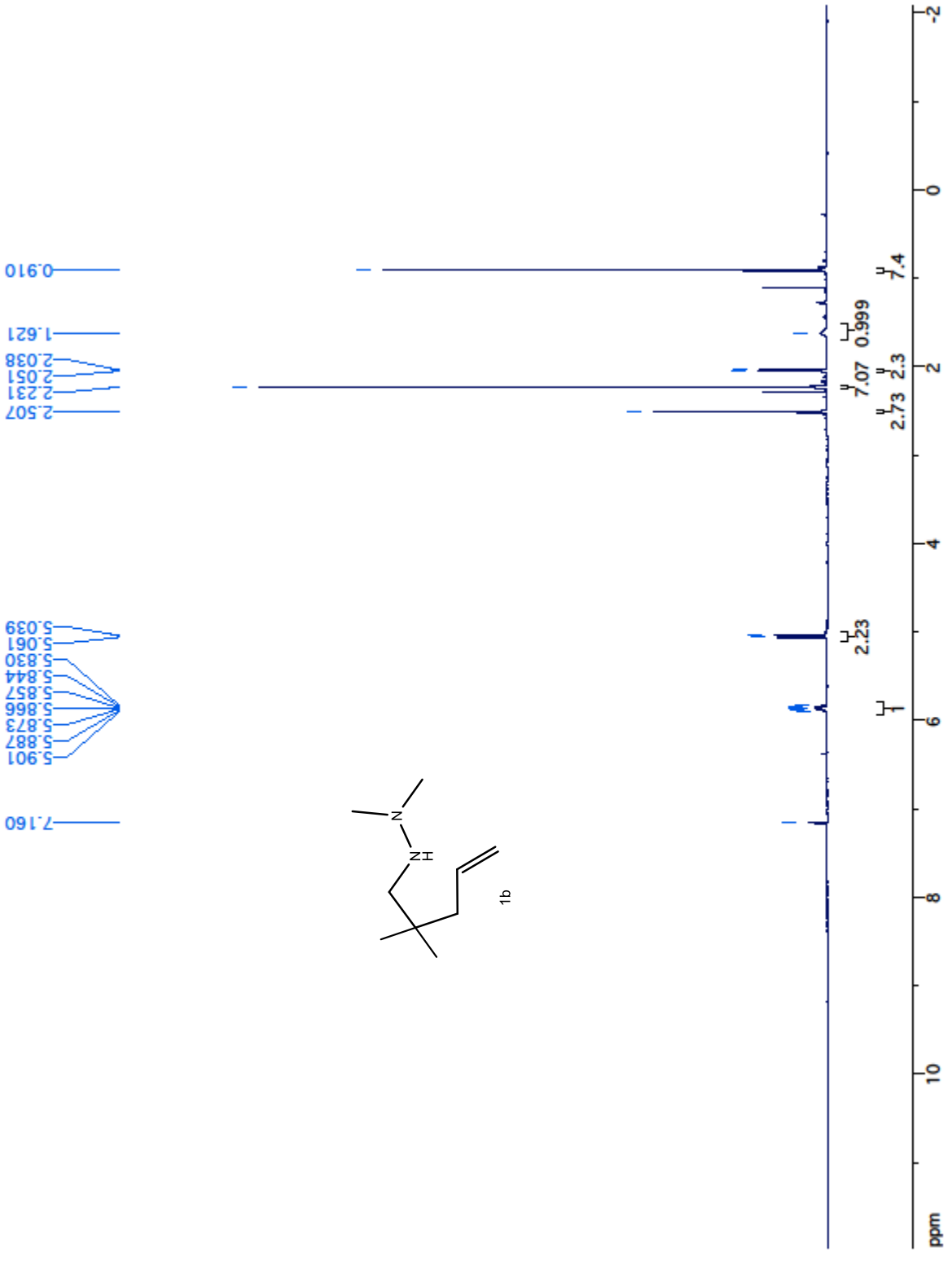

0.228
0.242
0.249
0.259
0.264
0.278
0.478
0.491
0.498
0.505
0.518
0.525
0.539
1.044
1.065
1.241
1.253
1.268
1.390
1.412
1.421
1.443
1.609
1.622
1.635
1.641
1.666
1.686
1.694
2.009
2.015
2.019
2.038
2.059
2.060
2.062
2.072
2.084
2.140
2.156
2.243
2.766
2.786
2.805
2.826
4.926
4.954
4.977
5.005
5.482
5.504
5.527
5.555
5.577
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1.08
6.59
2.57
2.42
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1.32
3.38
2.25
2.25
ppm

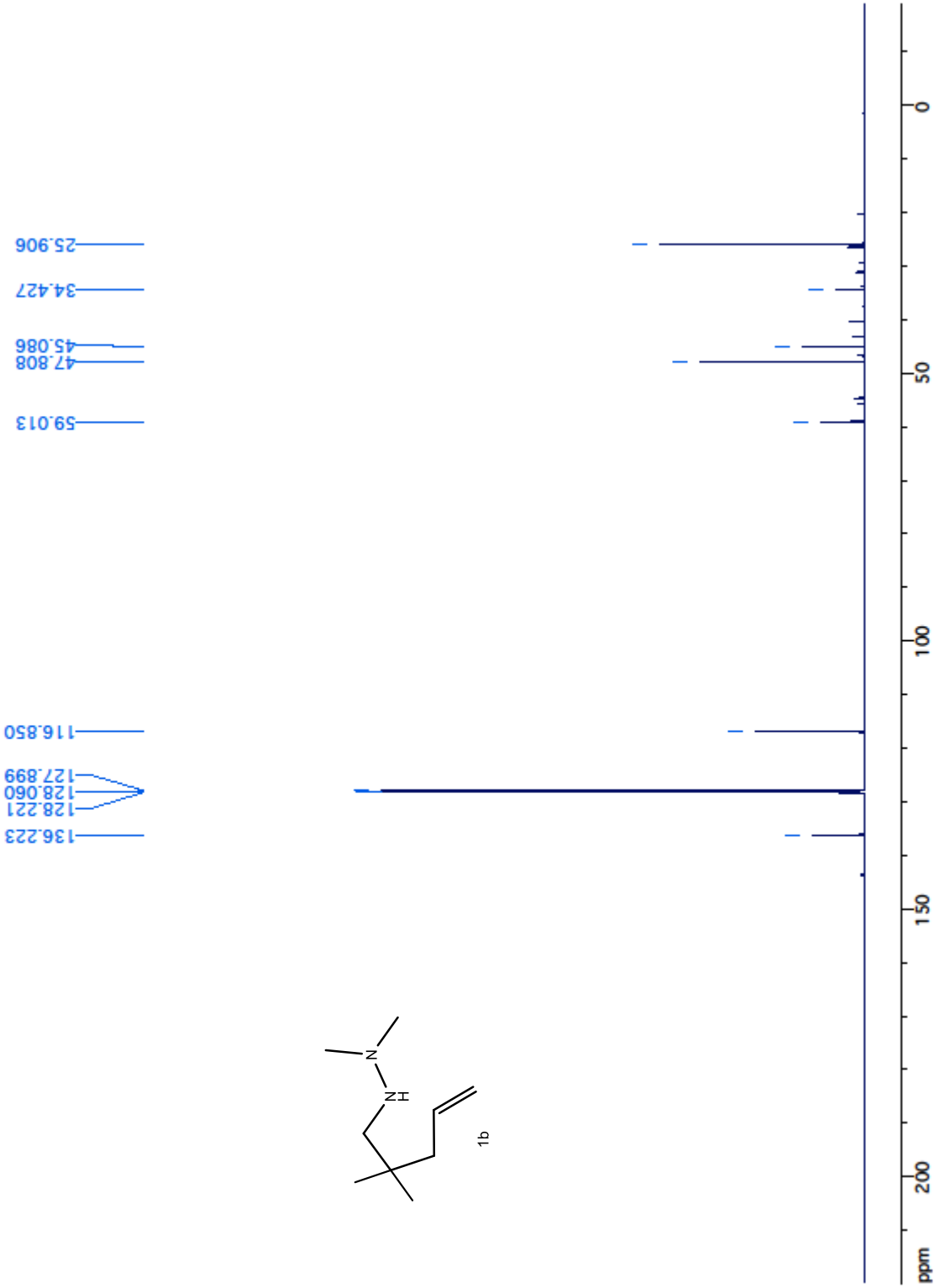

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36.019
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127.739
128.060
128.381
128.508
133.986
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150
ppm 200

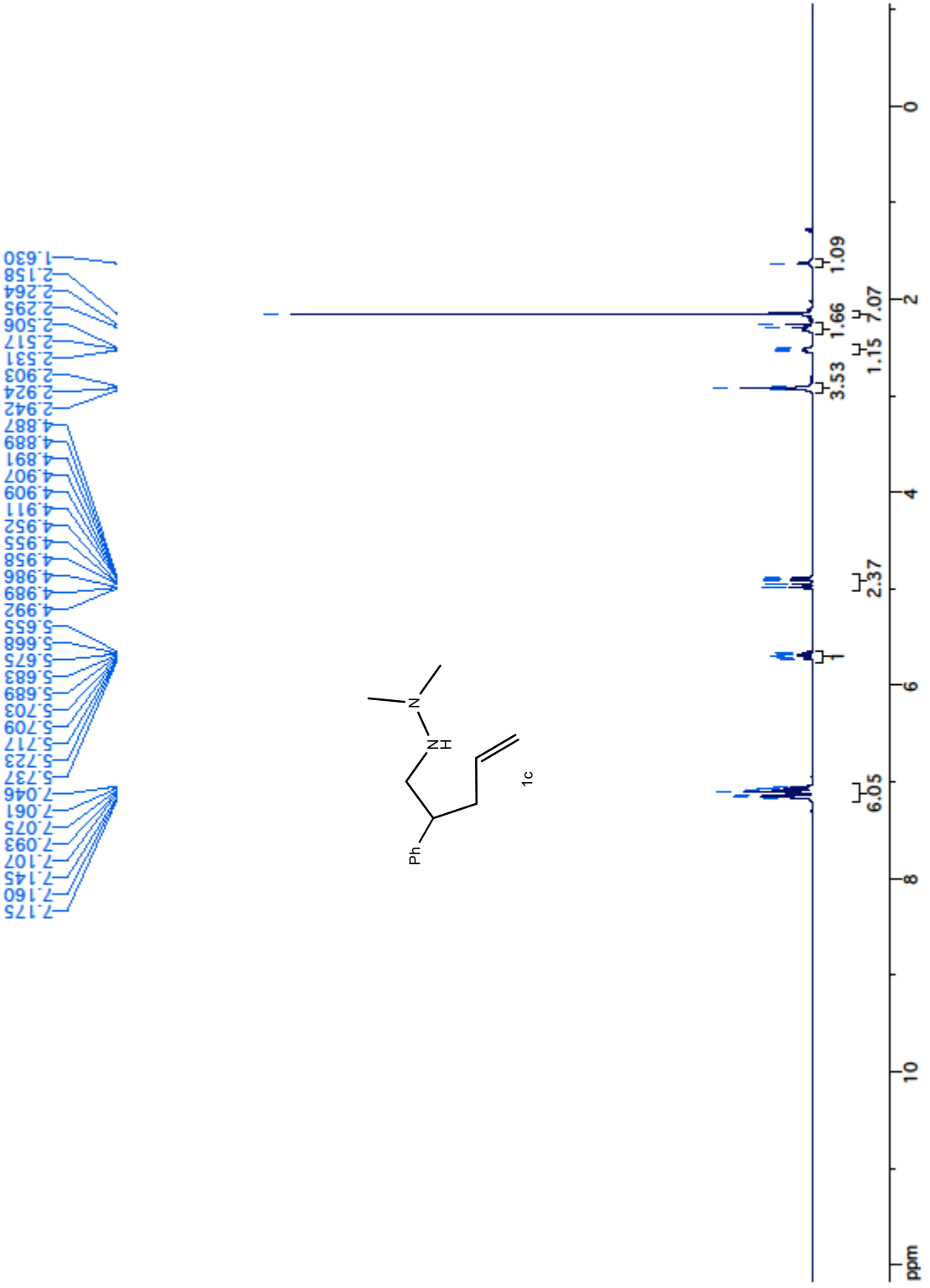
Chapter Six Spectral Data

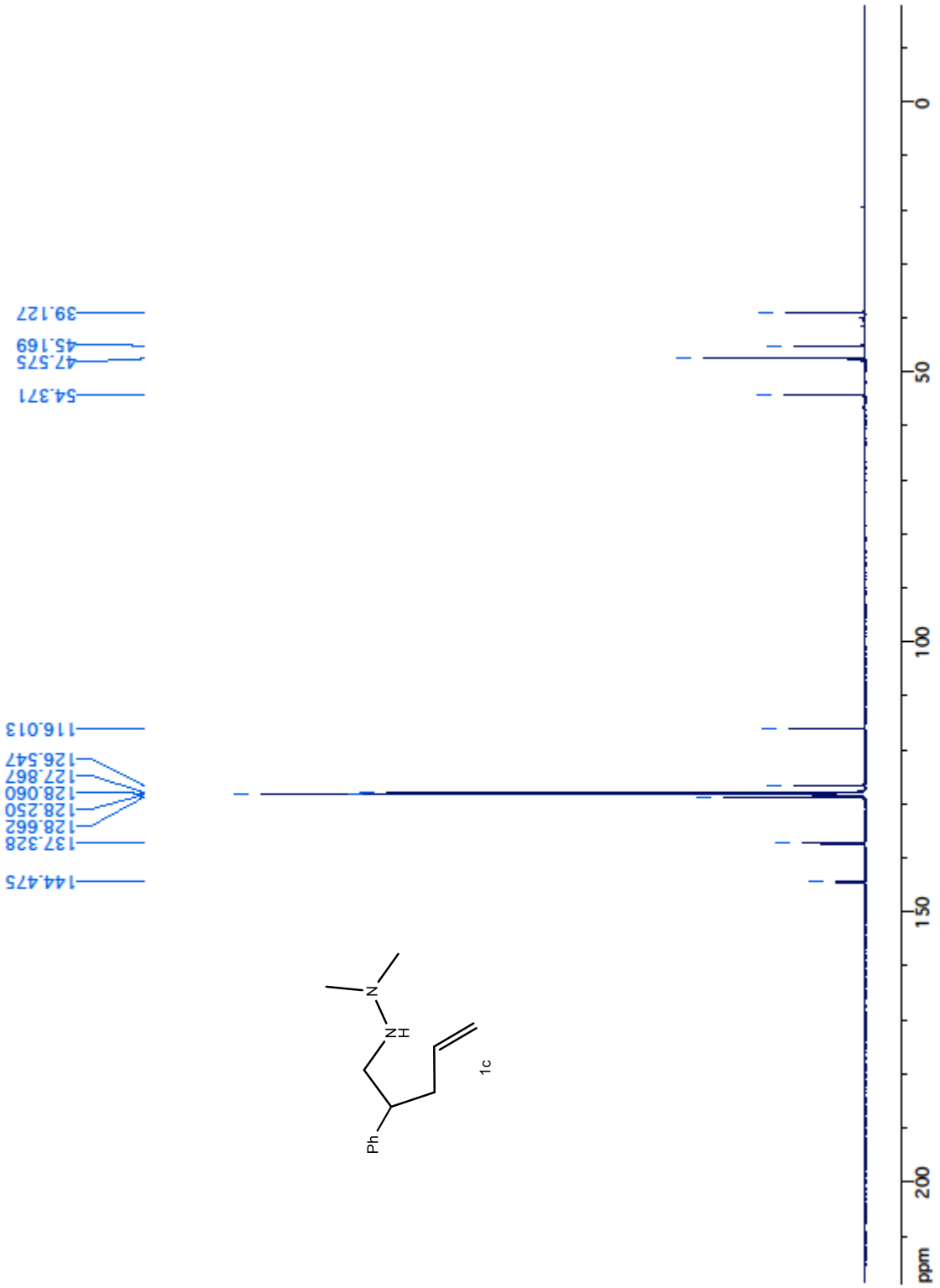


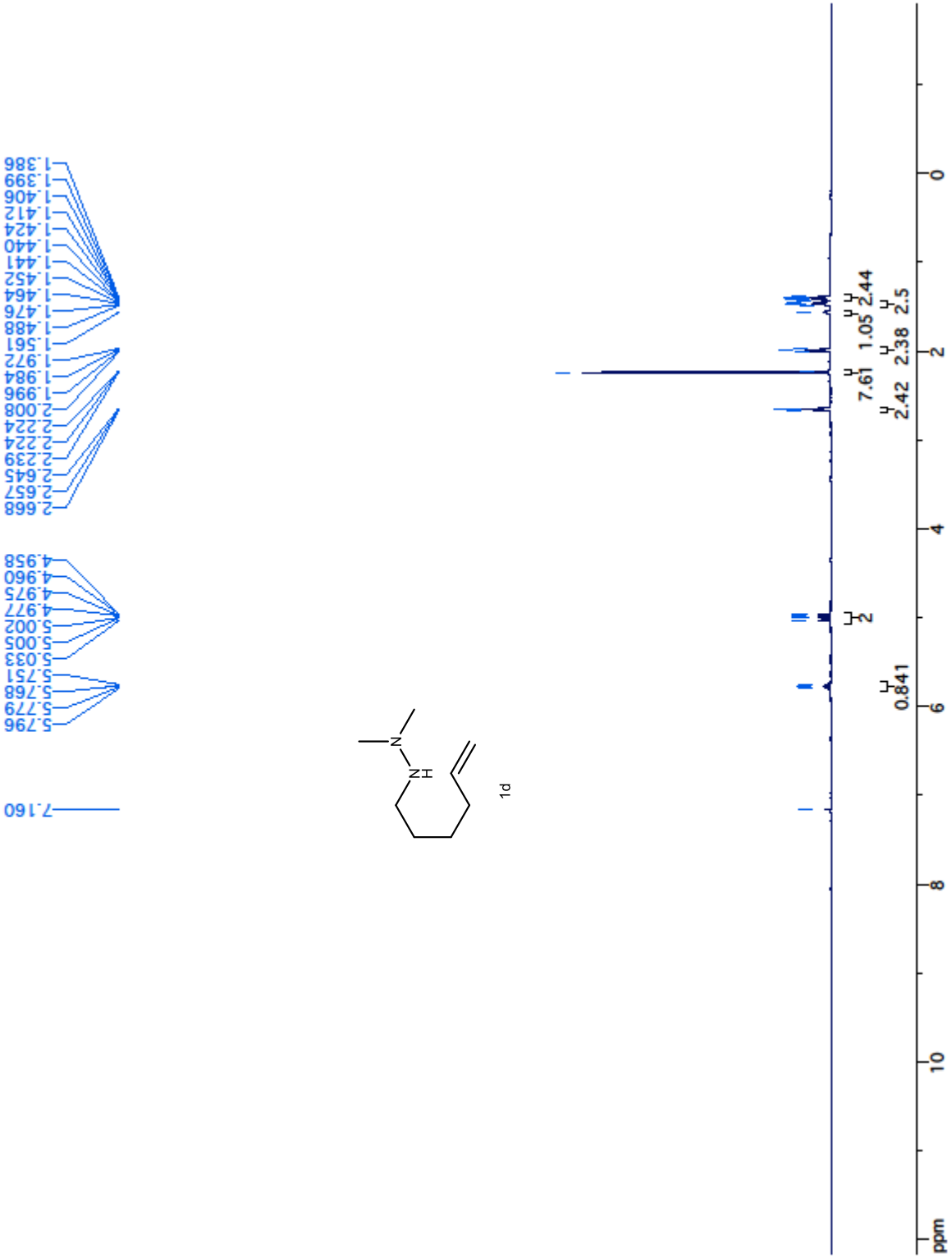

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127.867
128.060
128.253
139.427
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100
150
200
ppm

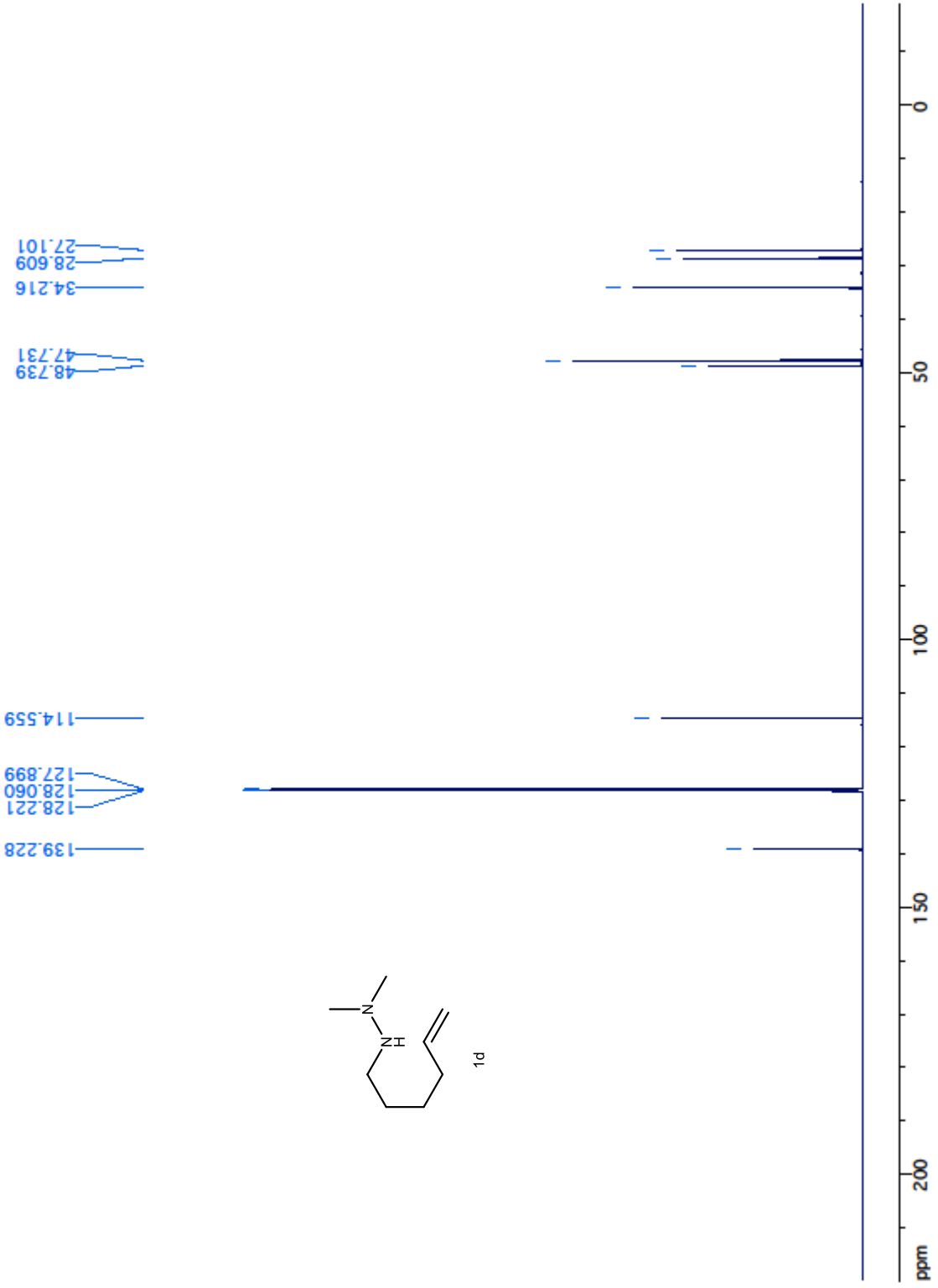

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1.621
2.038
2.051
2.231
2.507
5.039
5.061
5.830
5.844
5.857
5.866
5.873
5.887
5.901
7.160
1b
ppm

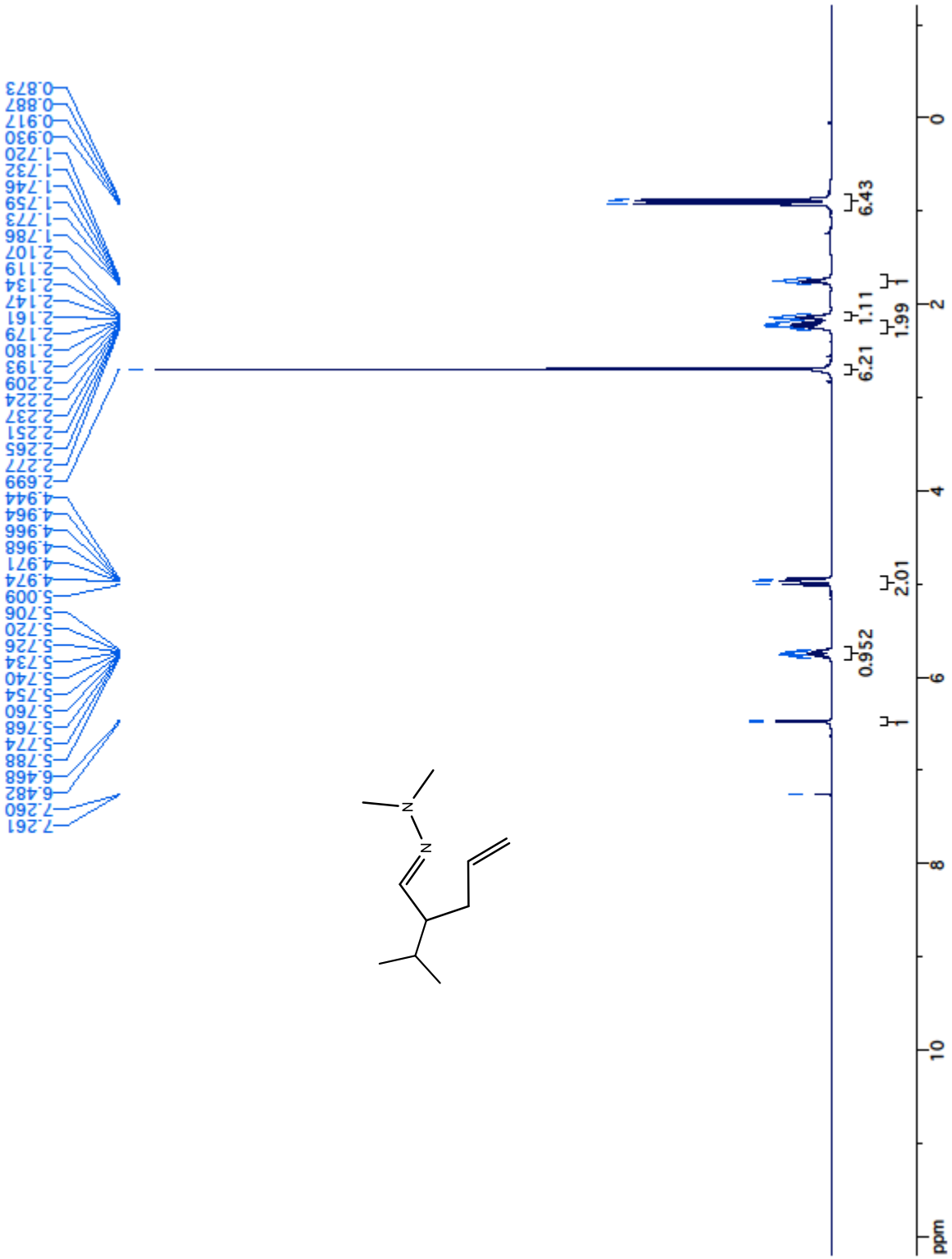

25.906
34.427
45.086
47.808
59.013
116.850
127.899
128.060
128.221
136.223
0
50
100
150
200
ppm
N
HN
1b

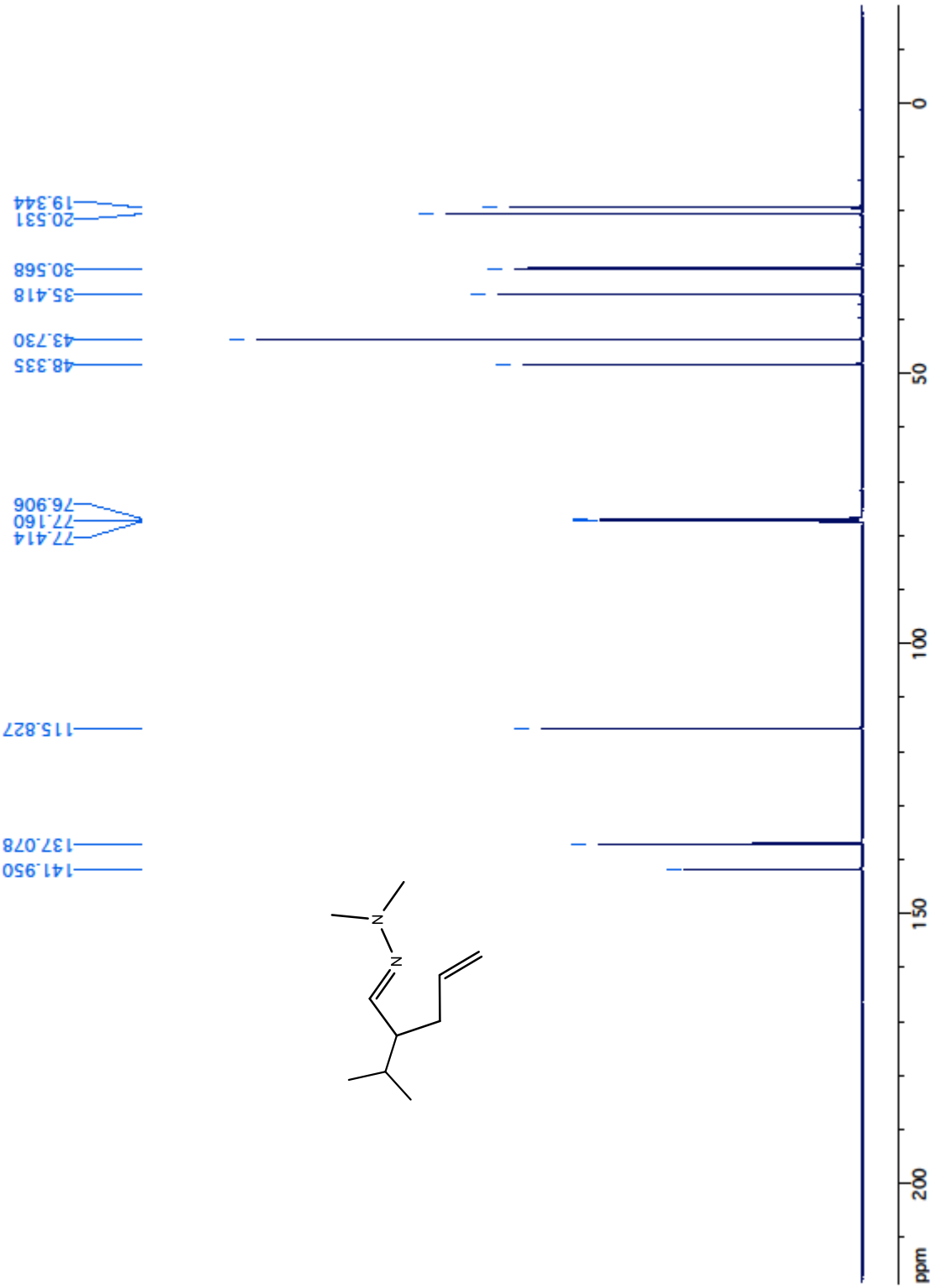

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2.158
2.264
2.295
2.506
2.517
2.531
2.903
2.924
2.942
4.887
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4.891
4.907
4.909
4.911
4.952
4.955
4.958
4.986
4.989
4.992
5.655
5.668
5.675
5.683
5.689
5.703
5.709
5.717
5.723
5.737
7.046
7.061
7.075
7.093
7.107
7.145
7.160
7.175
Ph
N
NH
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7.07
3.53
1.15
2.37
1
6.05
ppm
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2
4
6
8
10

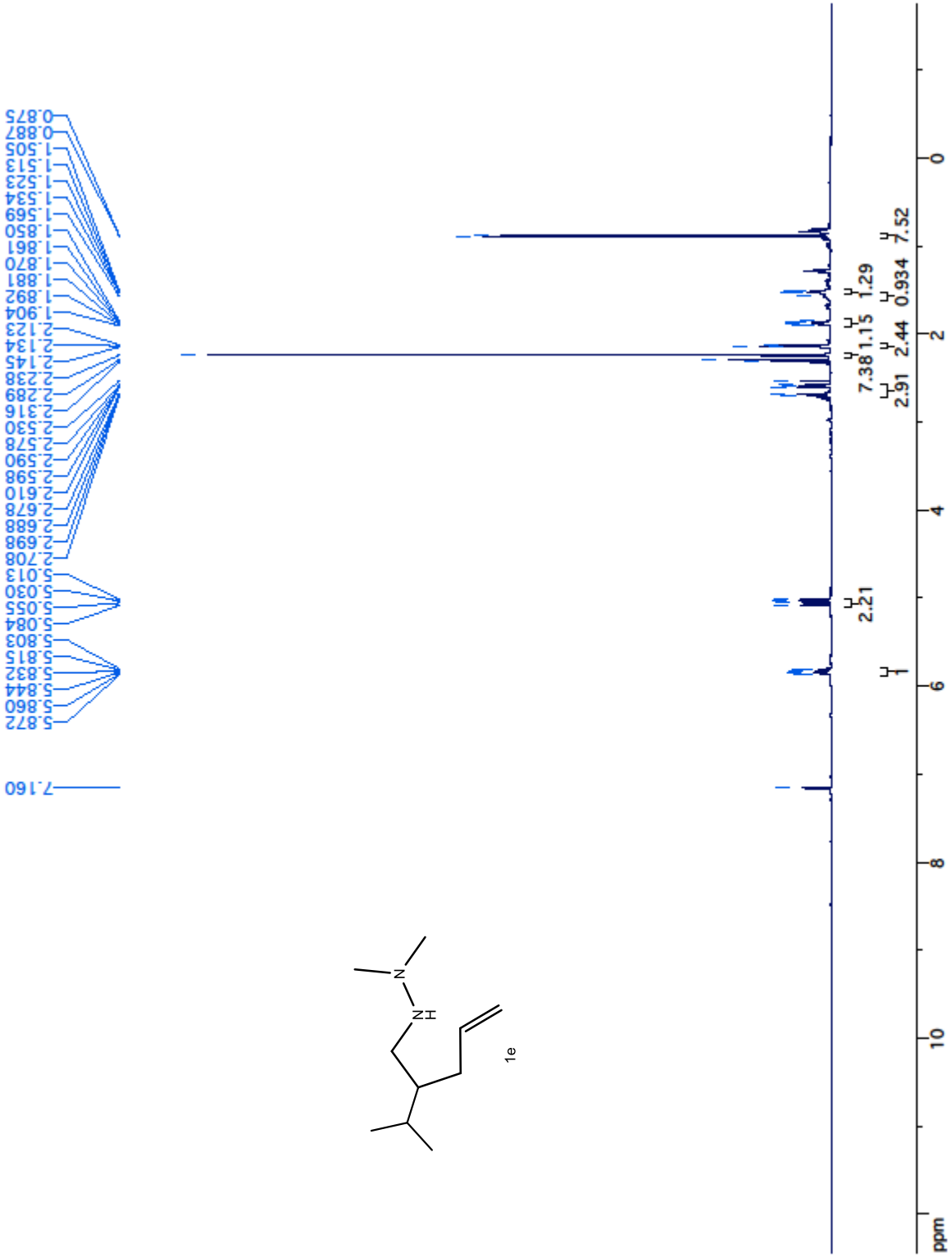

39.127
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47.575
54.371
116.013
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128.662
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144.475
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Ph
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200
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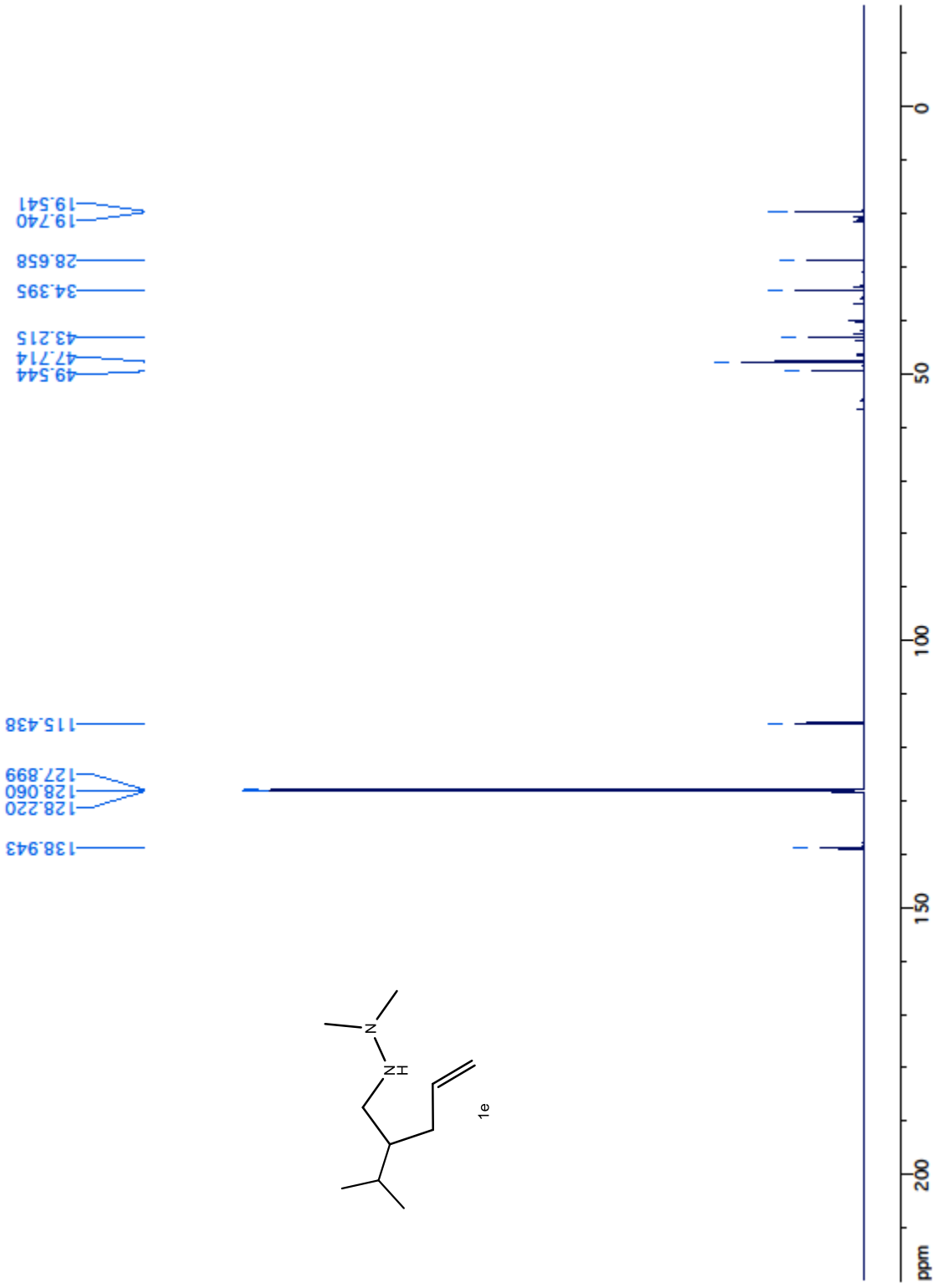

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5.033
5.005
5.002
4.977
4.975
4.960
4.958
2.668
2.657
2.645
2.239
2.224
2.224
2.008
1.996
1.984
1.972
1.561
1.488
1.476
1.464
1.452
1.441
1.440
1.424
1.412
1.406
1.399
1.386
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2.42
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2.38
2.44
2.5

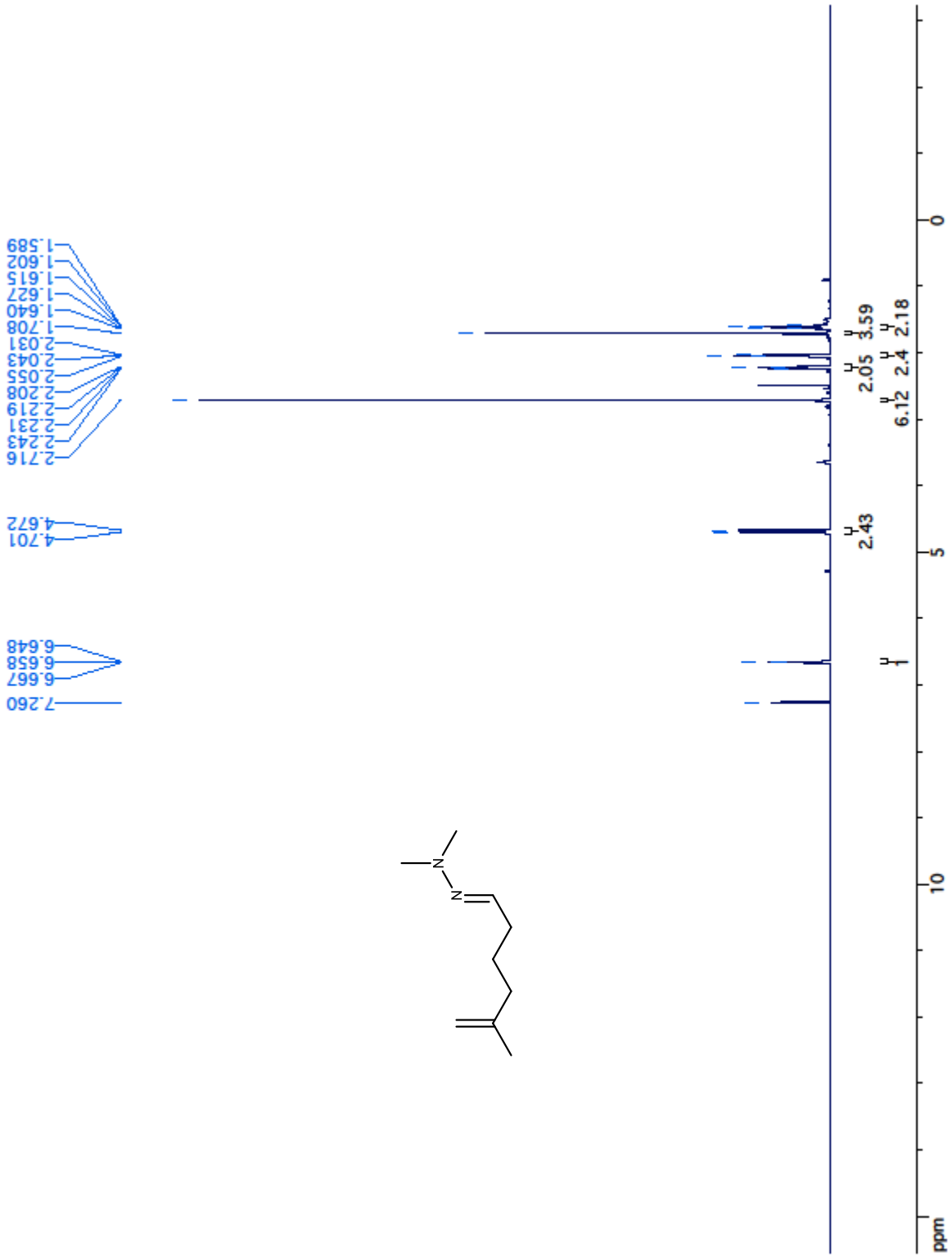

27.101
28.609
34.216
47.731
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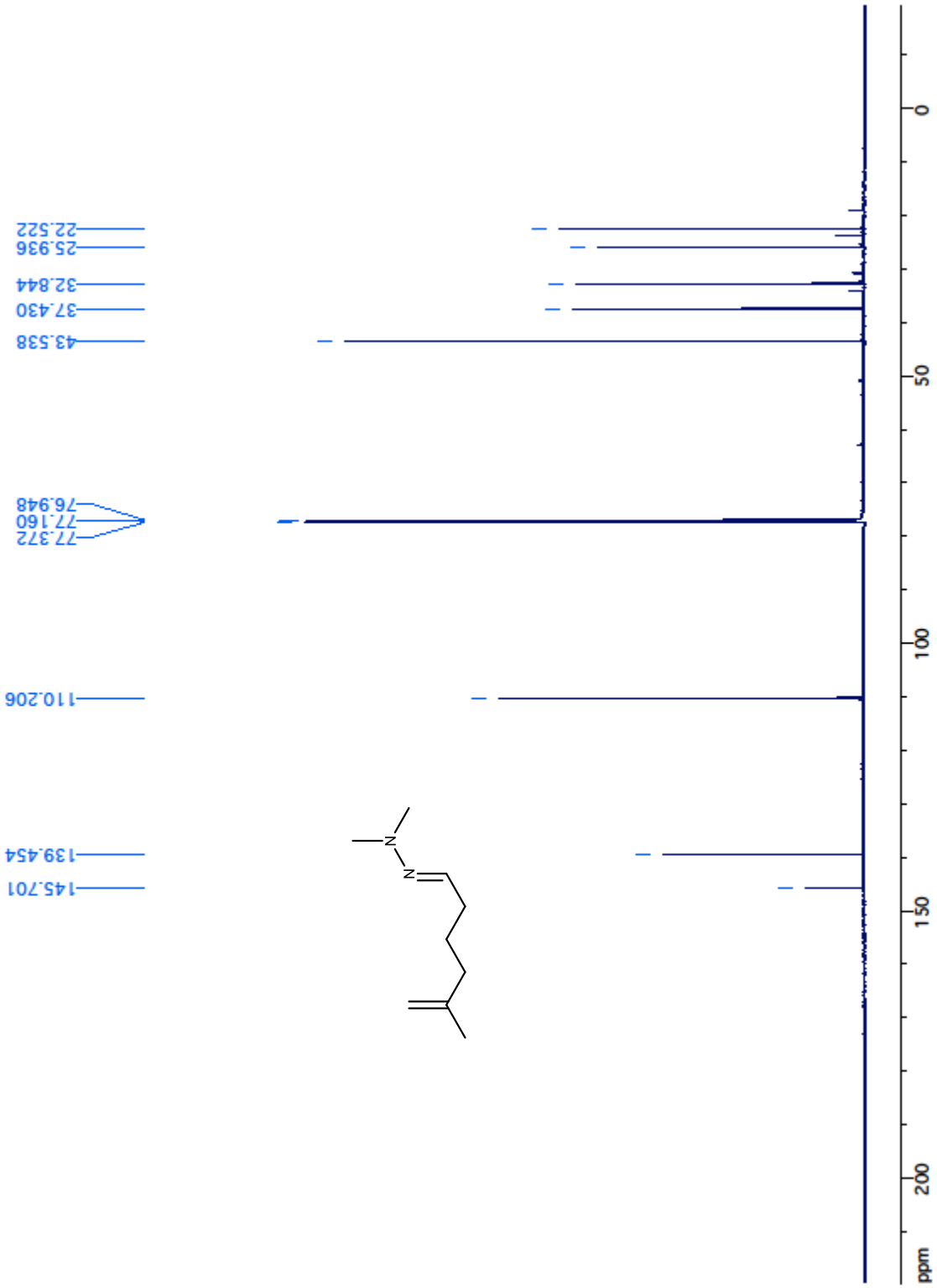

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2.134
2.147
2.161
2.179
2.180
2.193
2.209
2.224
2.237
2.251
2.265
2.277
2.699
4.944
4.964
4.966
4.968
4.971
4.974
5.009
5.706
5.720
5.726
5.734
5.740
5.754
5.760
5.768
5.774
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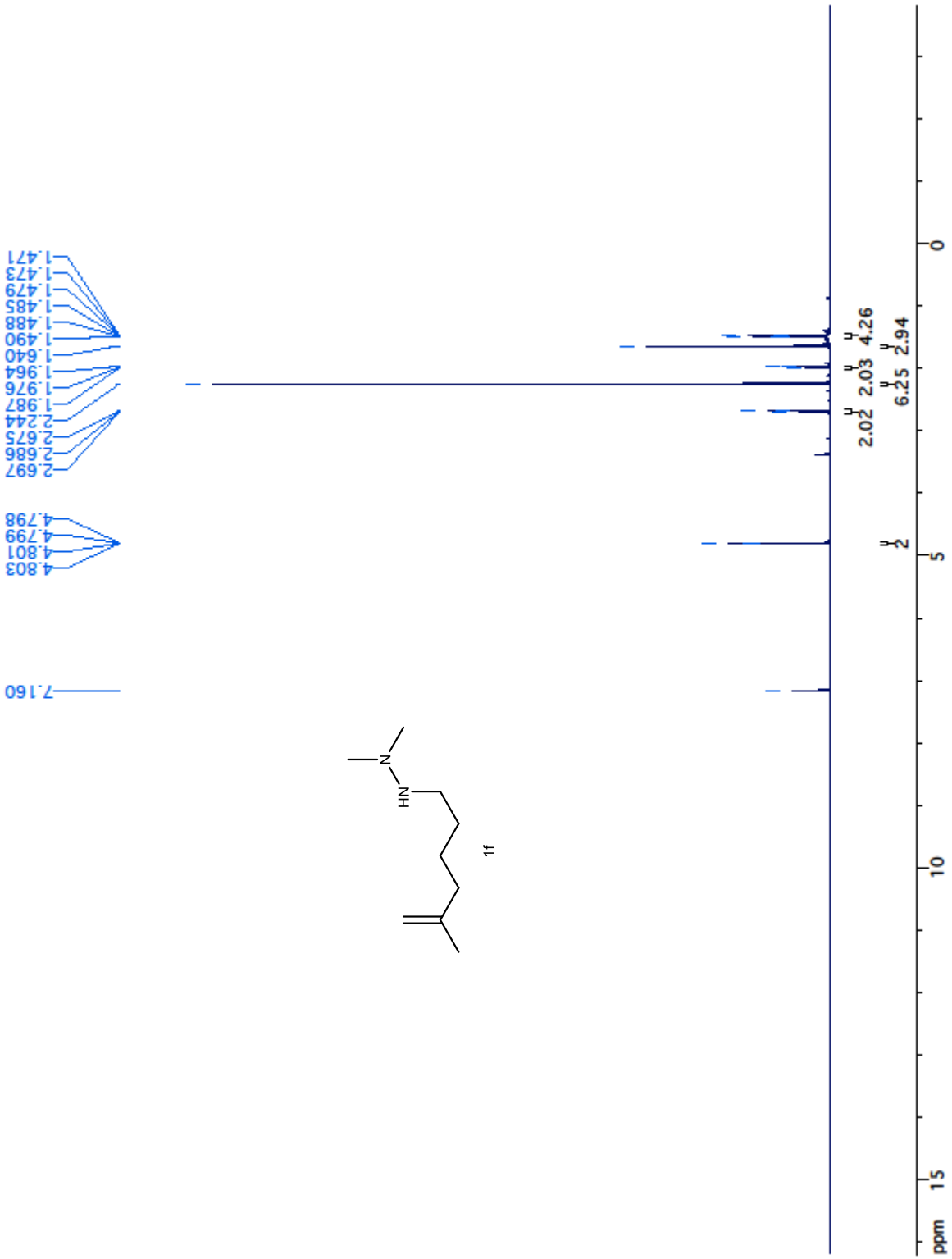

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35.418
43.730
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77.160
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200
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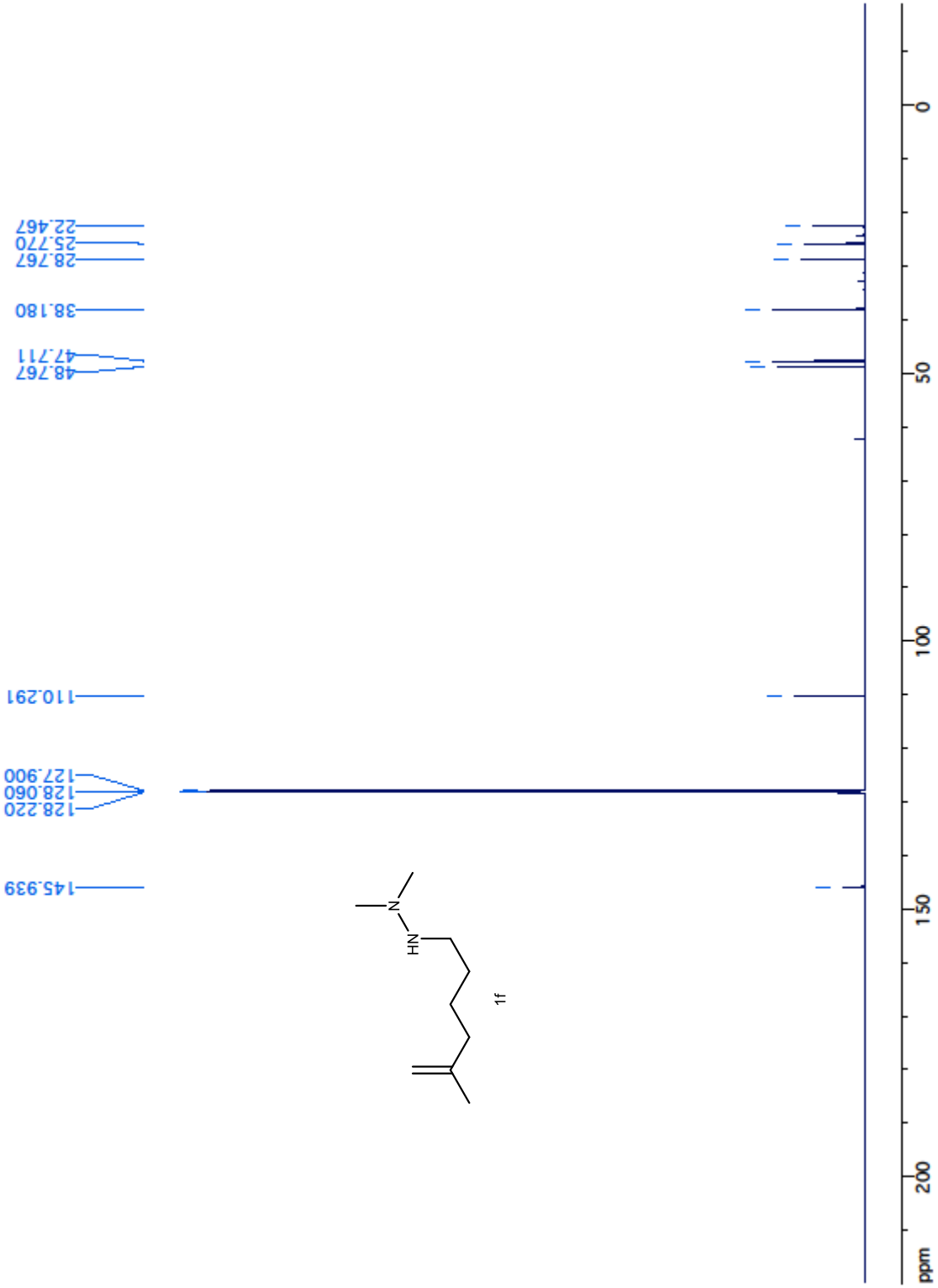

0.875
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1.523
1.534
1.569
1.850
1.861
1.870
1.881
1.892
1.904
2.123
2.134
2.145
2.238
2.289
2.316
2.530
2.578
2.590
2.598
2.610
2.678
2.688
2.698
2.708
5.013
5.030
5.055
5.084
5.803
5.815
5.832
5.844
5.860
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1
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7.52
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1e

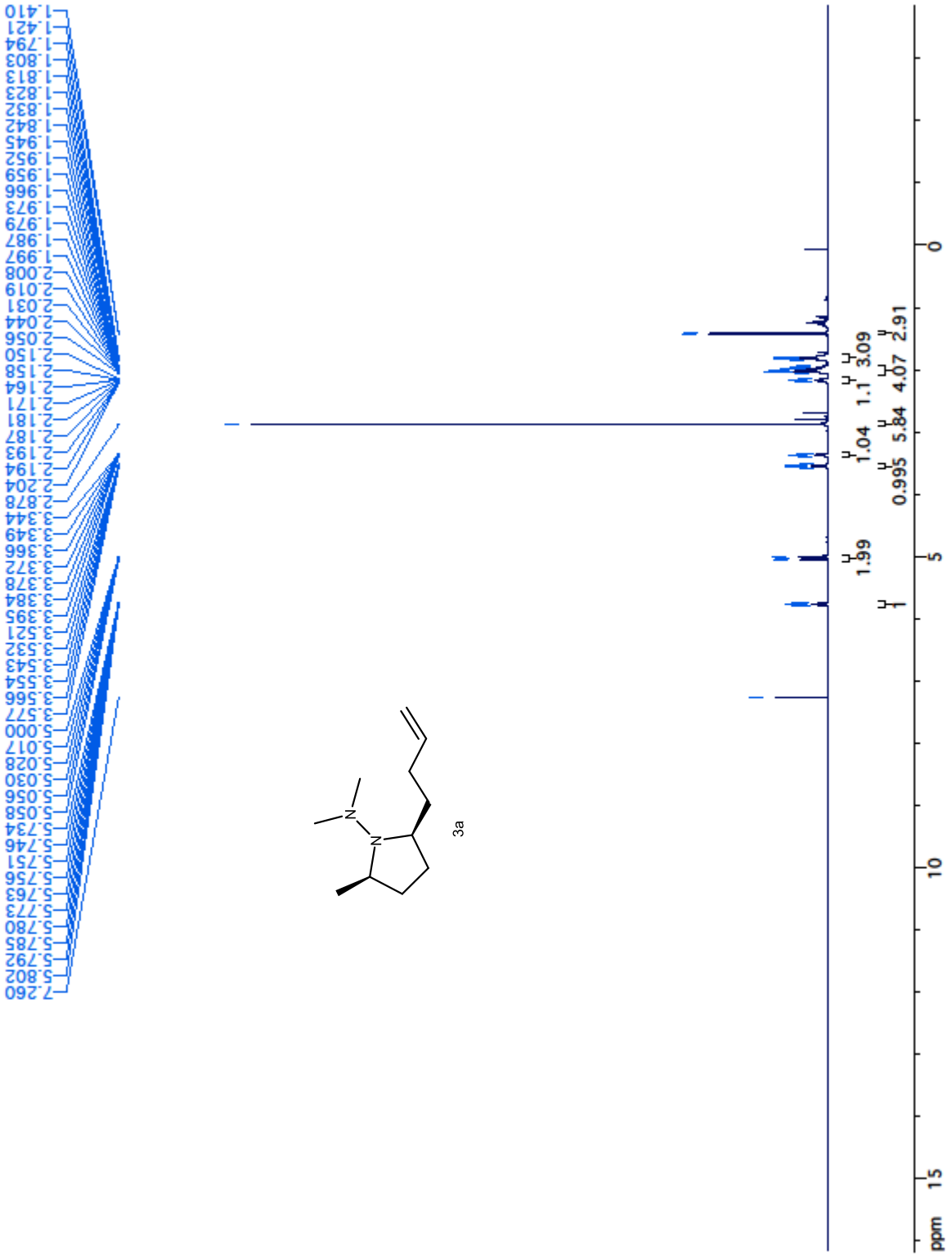

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HN
1e

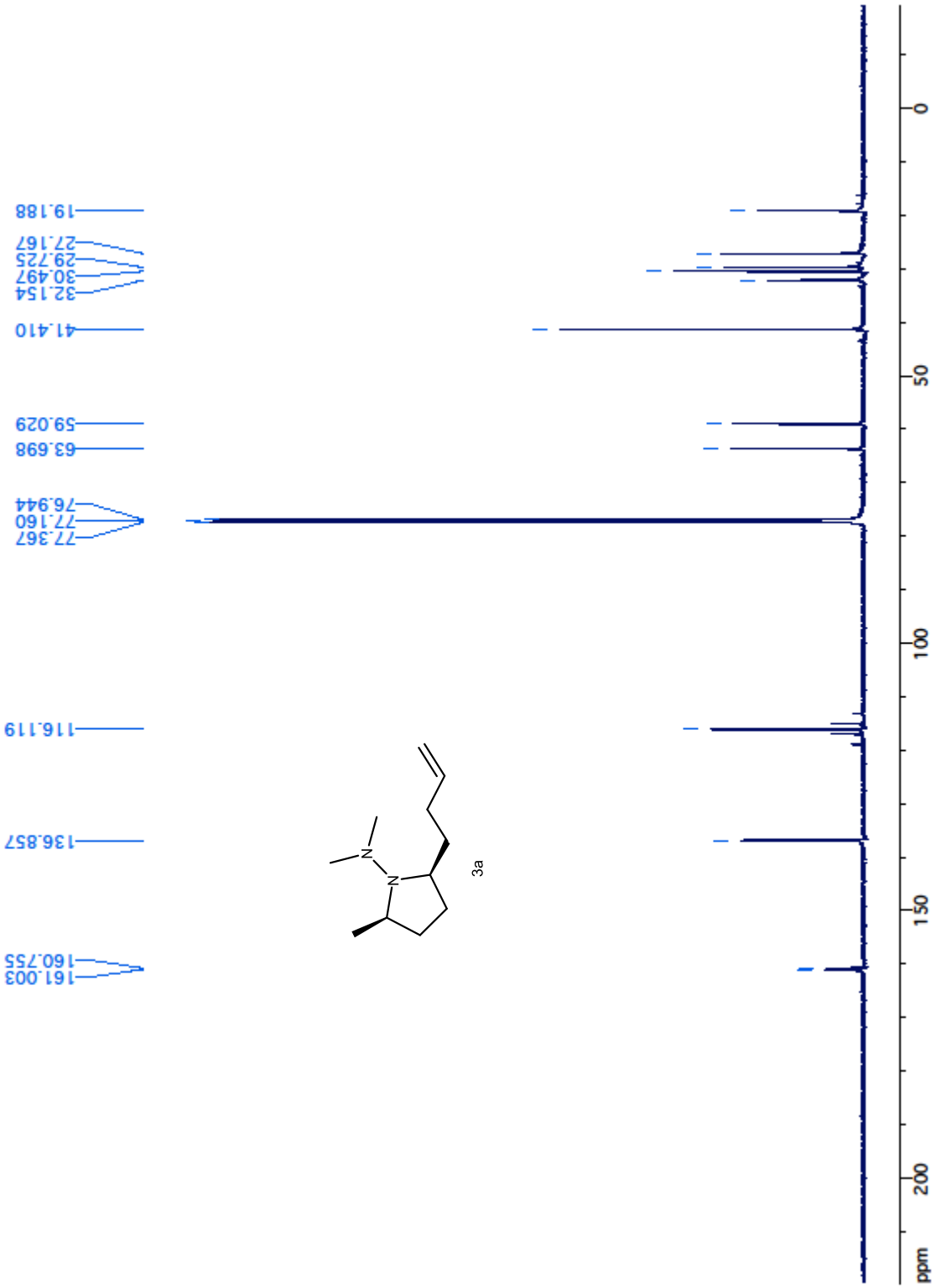

1.589
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1.627
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1.708
2.031
2.043
2.055
2.208
2.219
2.231
2.243
2.716
4.672
4.701
6.648
6.658
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2.43
1
6.12
2.4
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3.59
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ppm
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5
10

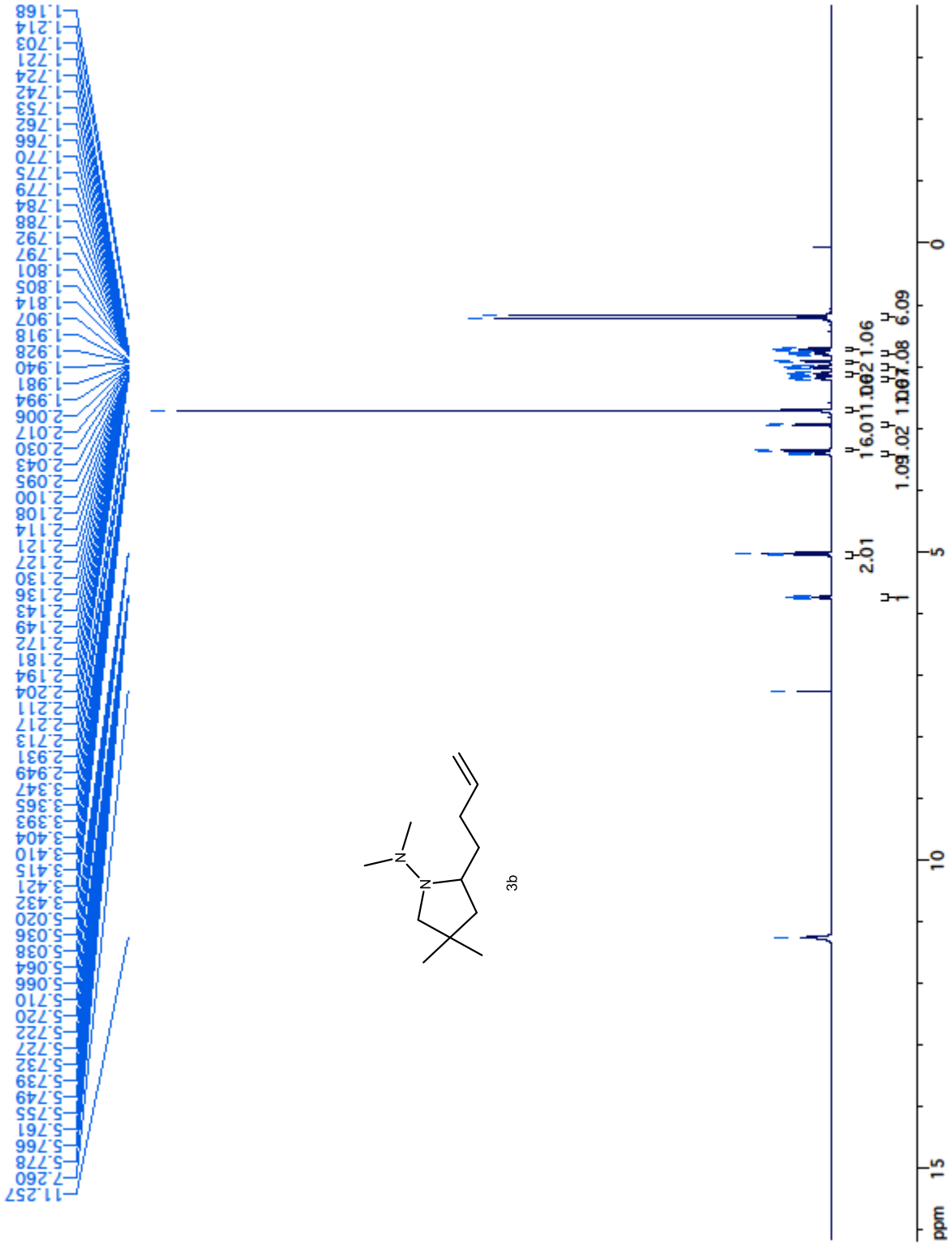

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37.430
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200
ppm

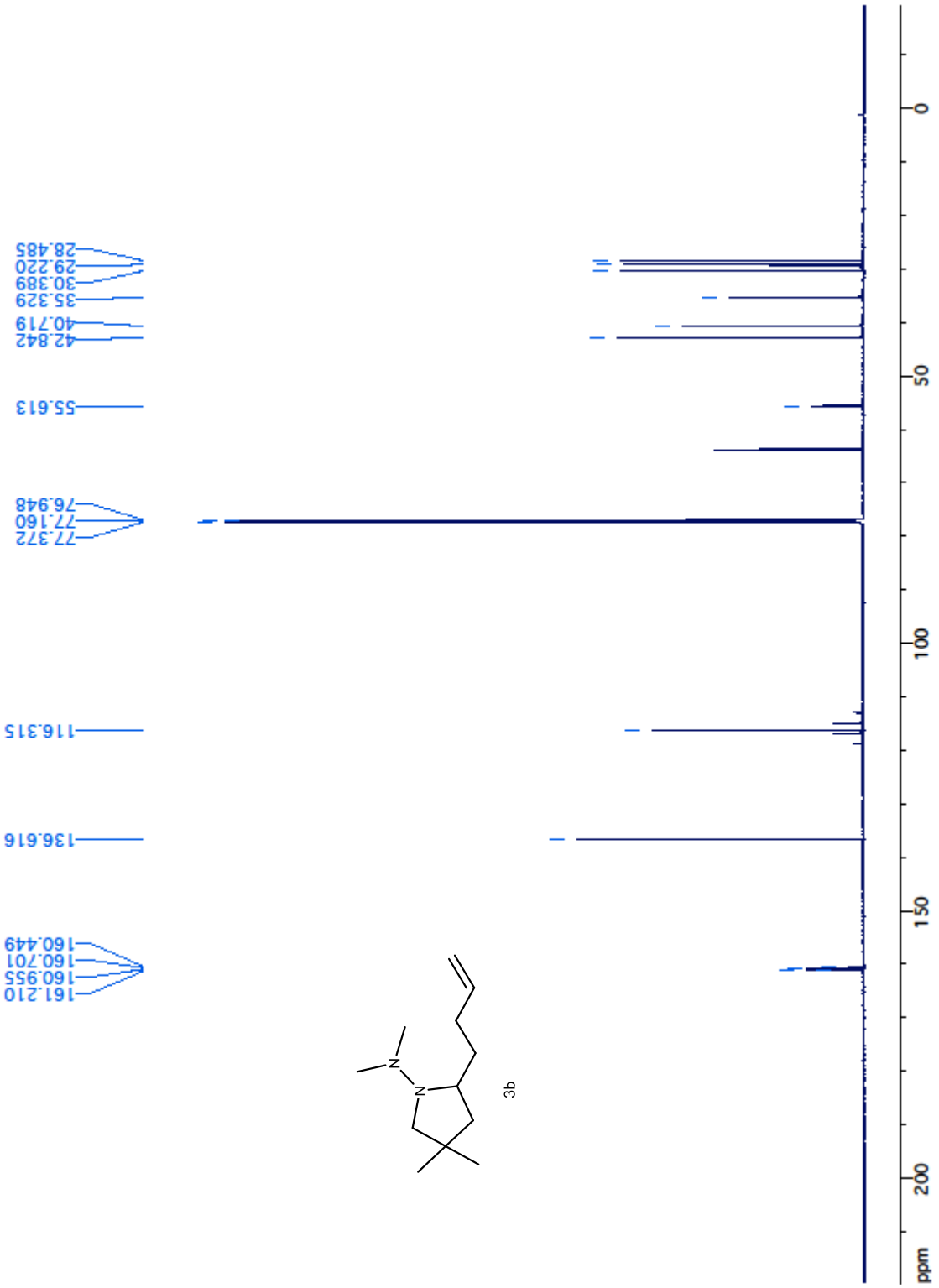

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2.675
2.244
1.987
1.976
1.964
1.640
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1.479
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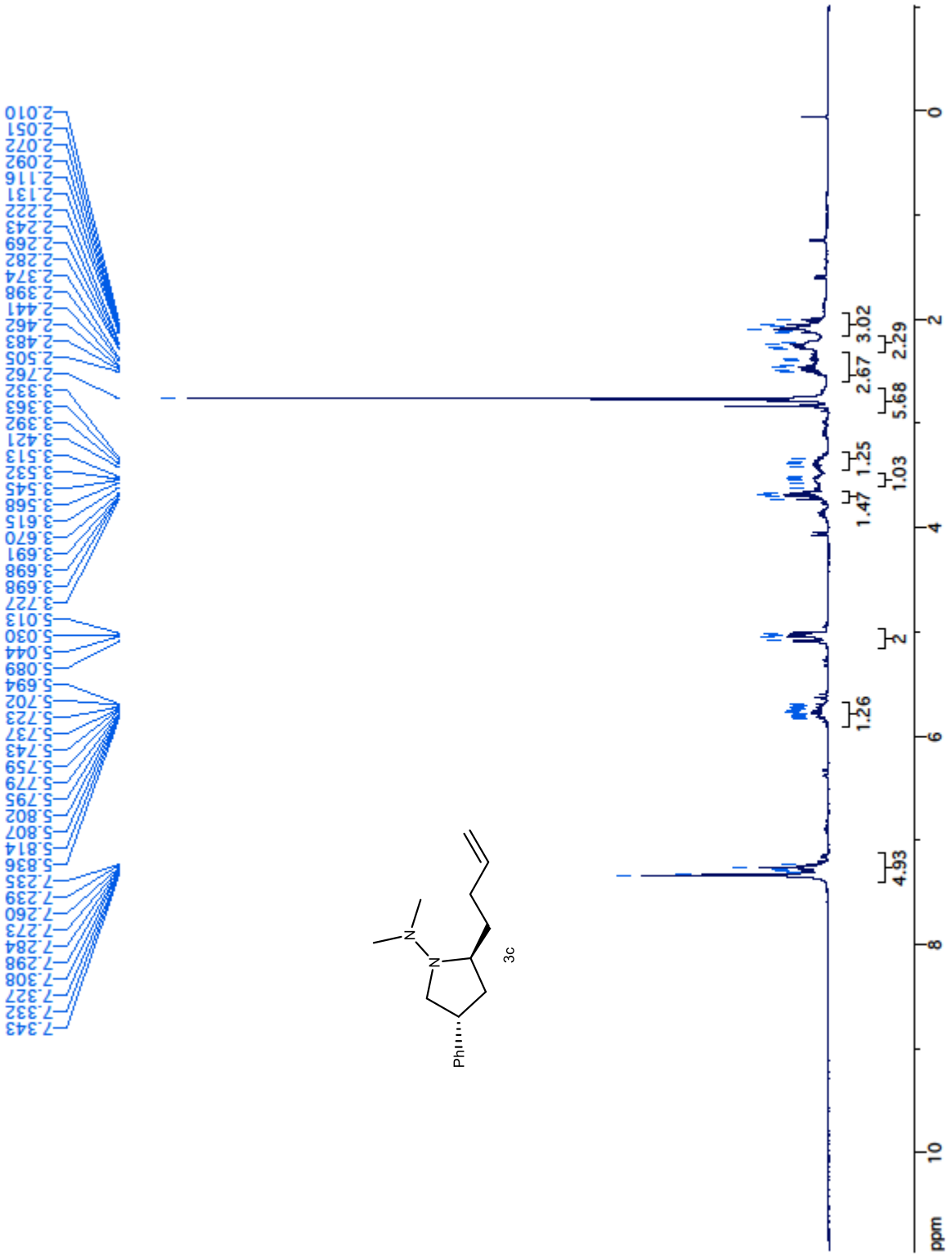

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47.711
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200
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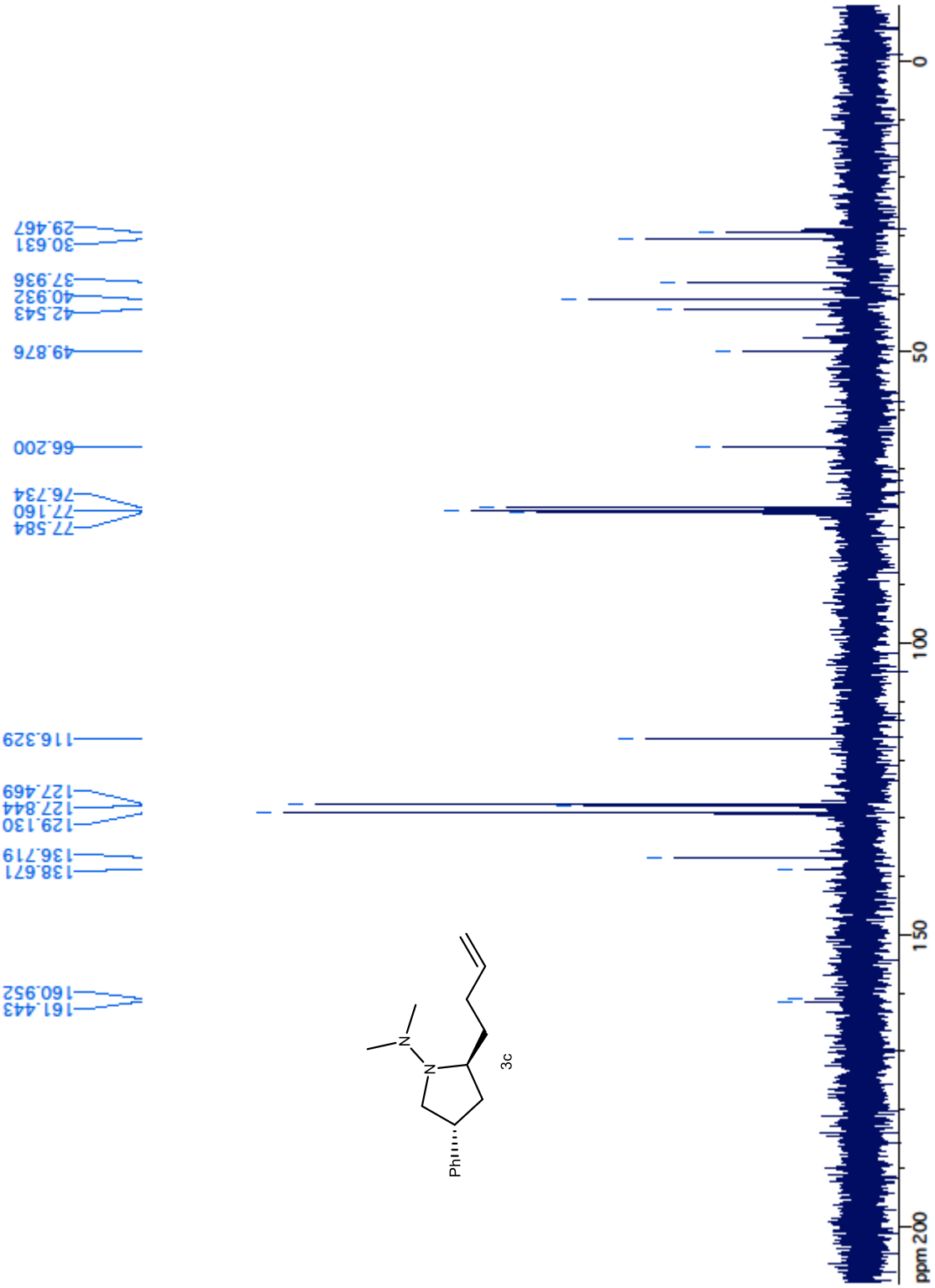

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5.056
5.030
5.028
5.017
5.000
3.577
3.566
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3.543
3.532
3.521
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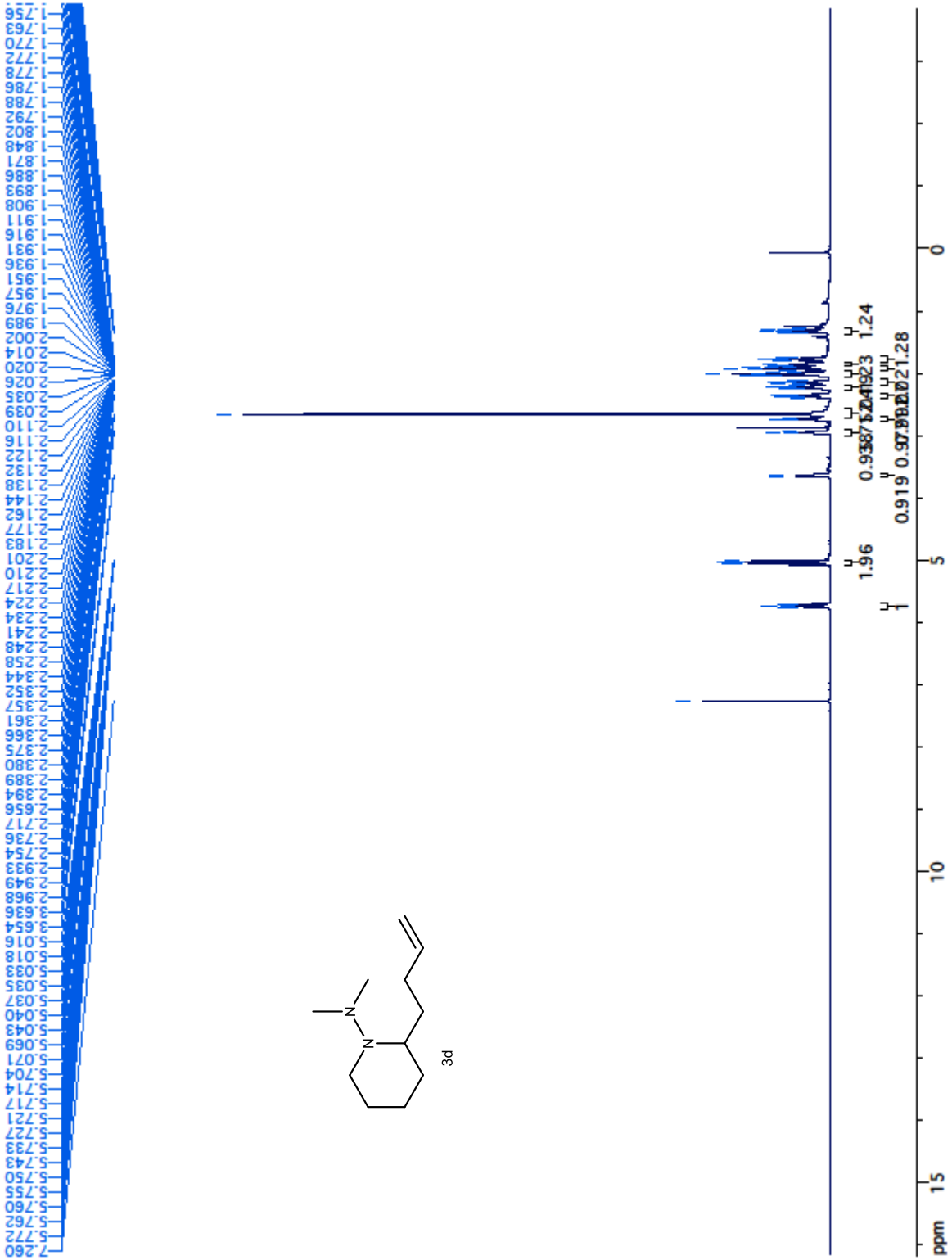

19.188
27.167
29.725
30.497
32.154
41.410
59.029
63.698
76.944
77.160
77.367
116.119
136.857
160.755
161.003
3a
0
50
100
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200
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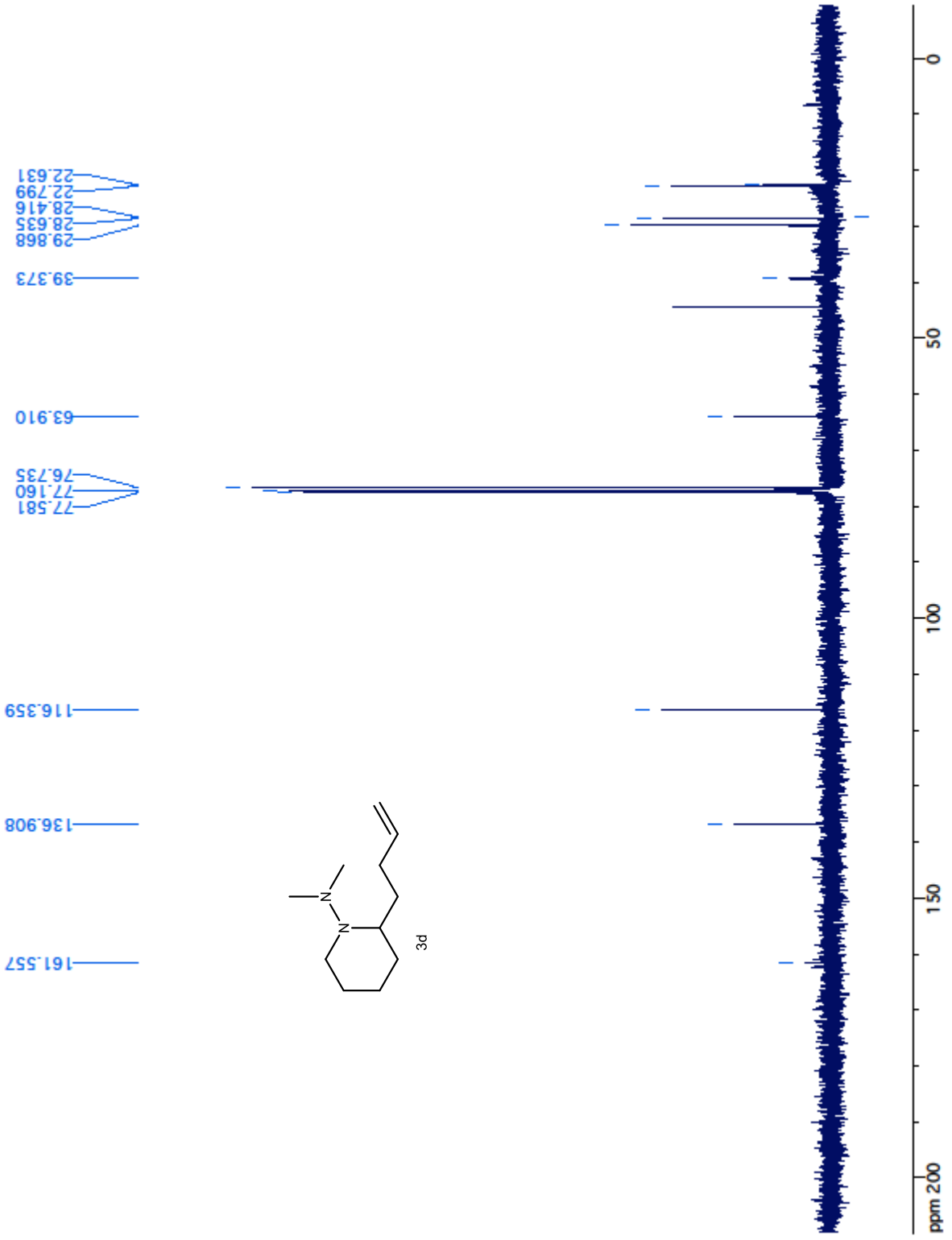

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6.09
1.09
1.02
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7.260
5.778
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5.761
5.755
5.749
5.739
5.732
5.727
5.722
5.720
5.710
5.066
5.064
5.038
5.036
5.020
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3.421
3.415
3.410
3.404
3.393
3.365
3.347
2.949
2.931
2.713
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2.204
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2.181
2.172
2.149
2.143
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2.130
2.127
2.121
2.114
2.108
2.100
2.095
2.043
2.030
2.017
2.006
1.994
1.981
1.940
1.928
1.918
1.907
1.814
1.805
1.801
1.797
1.792
1.788
1.784
1.779
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1.753
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1.168

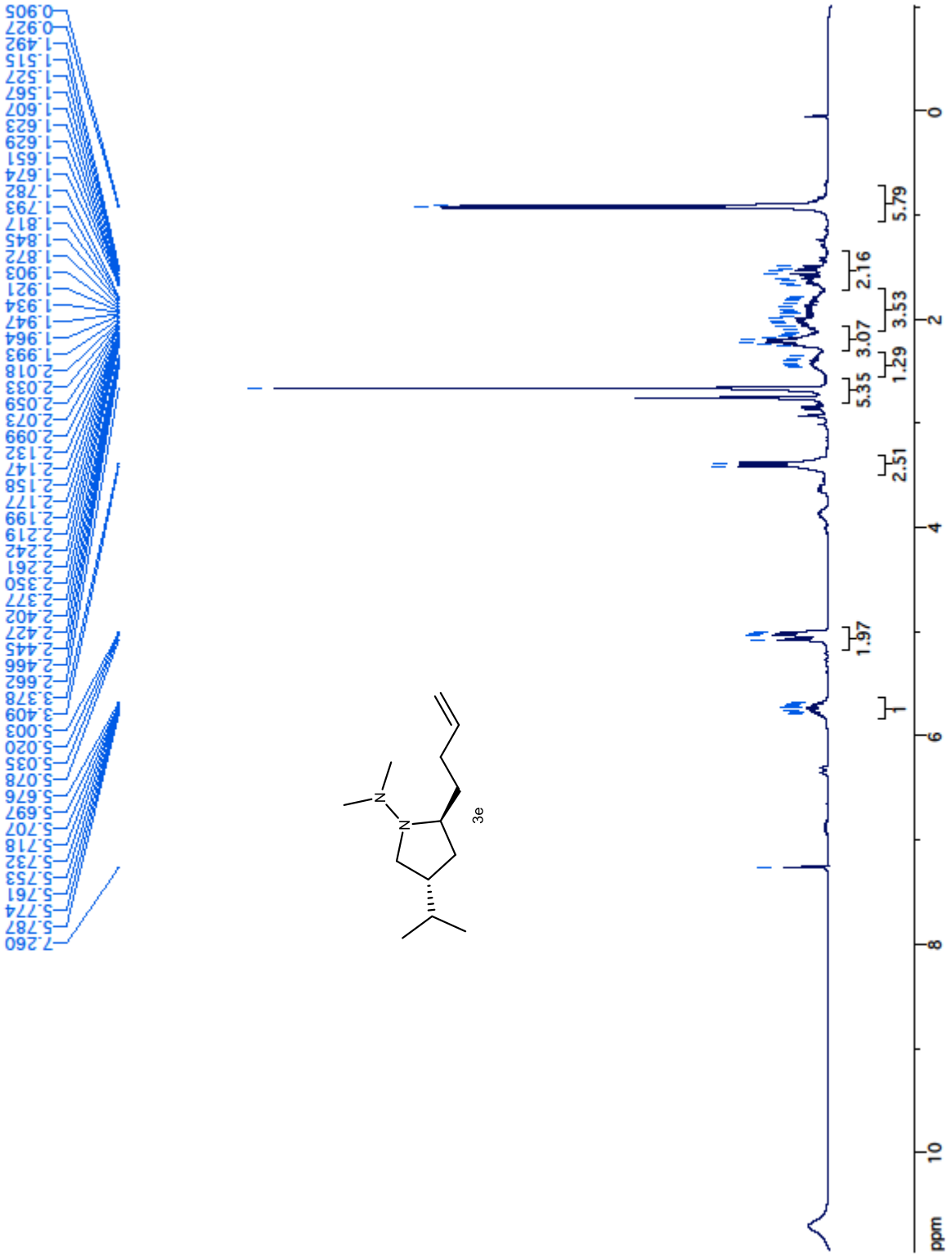

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160.701
160.449
136.616
116.315
77.372
77.160
76.948
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40.719
35.329
30.389
29.220
28.485
0
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100
150
200
ppm
3b

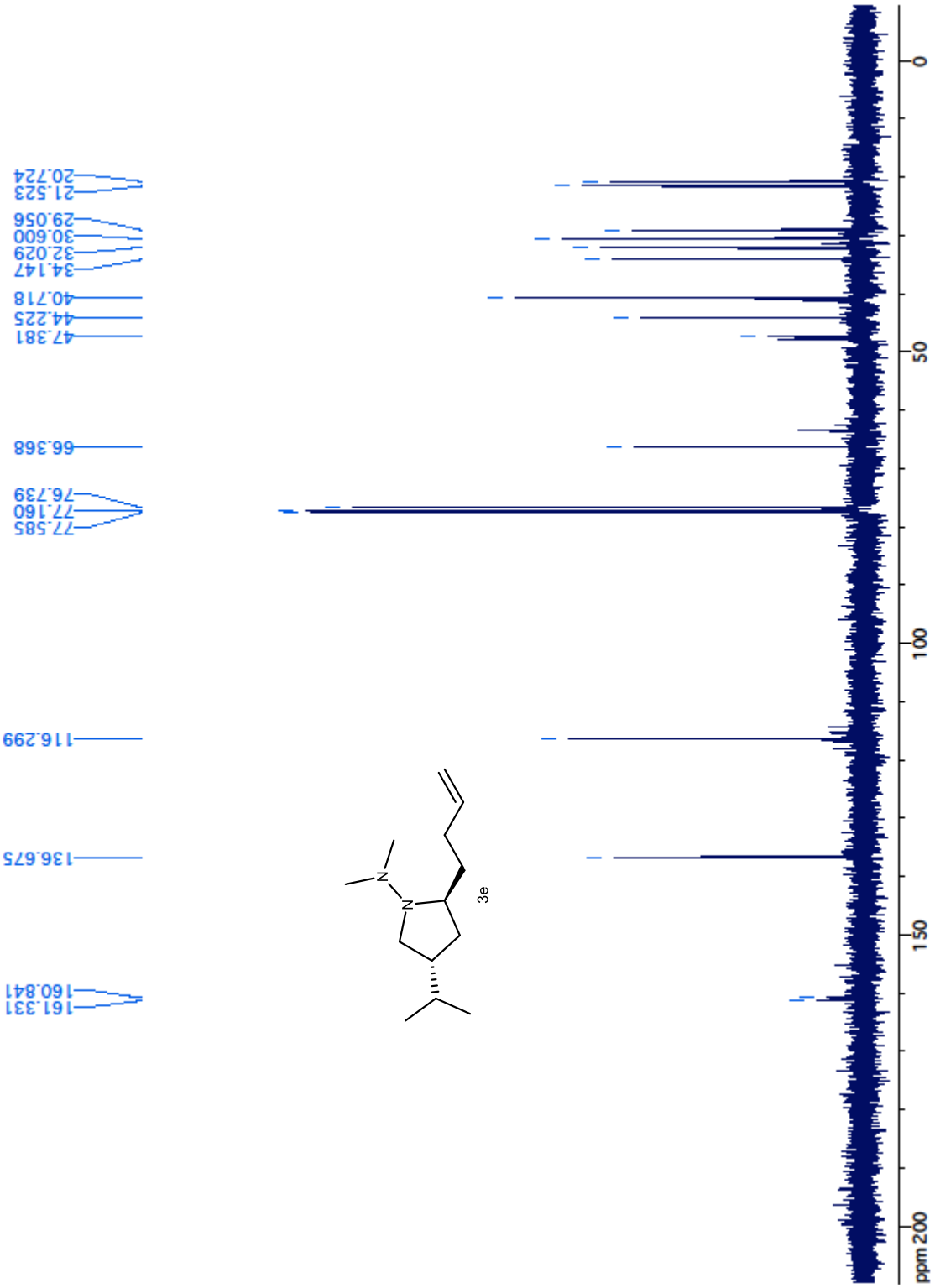

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2.072
2.092
2.116
2.131
2.222
2.243
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2.398
2.441
2.462
2.483
2.505
2.762
3.332
3.363
3.392
3.421
3.513
3.532
3.545
3.568
3.615
3.670
3.691
3.698
3.698
3.727
5.013
5.030
5.044
5.089
5.694
5.702
5.723
5.737
5.743
5.759
5.779
5.795
5.802
5.807
5.814
5.836
7.235
7.239
7.260
7.273
7.284
7.298
7.308
7.327
7.332
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2
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ppm
Ph
3c

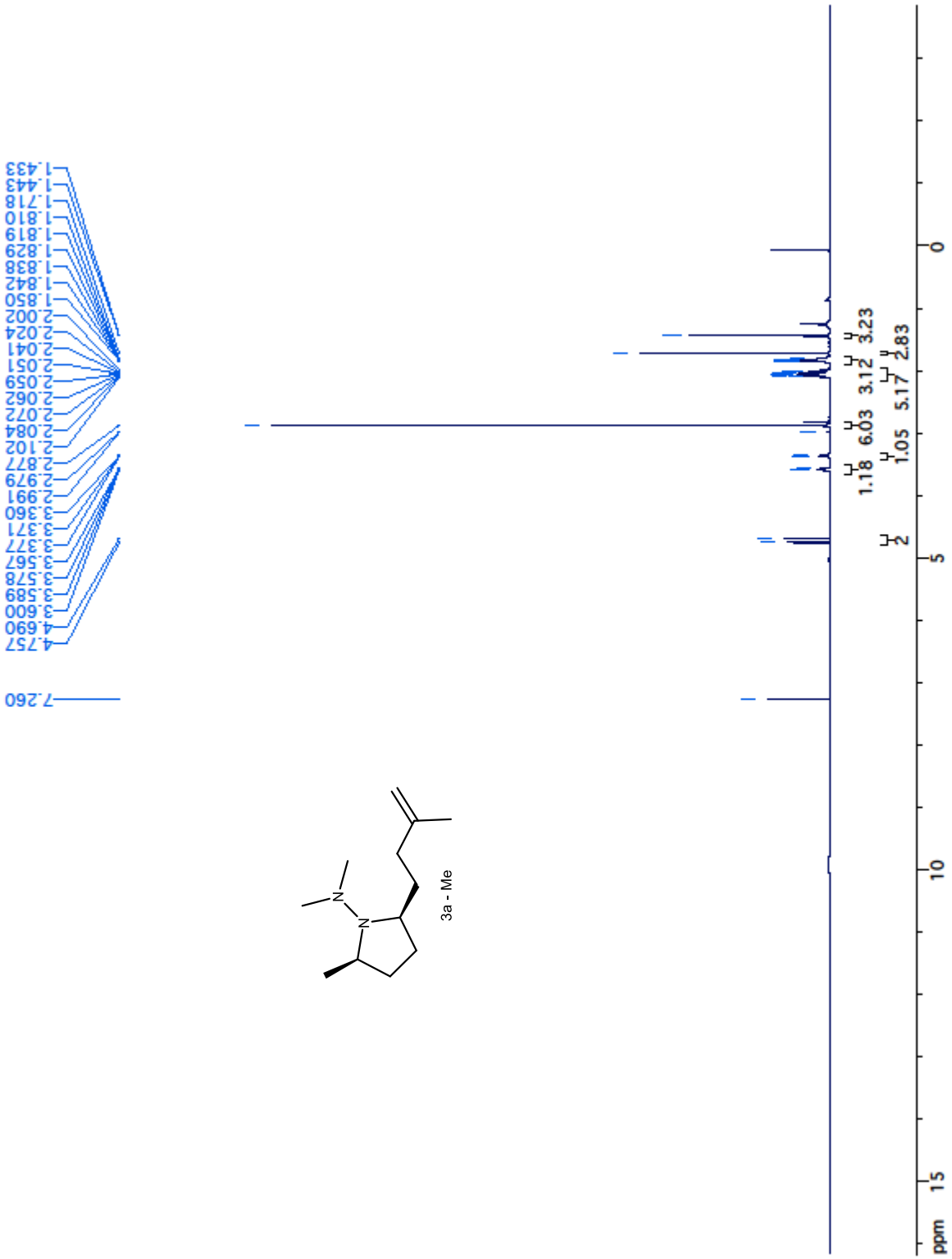

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127.469
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136.719
138.671
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161.443
ppm 200
150
100
50
0
N
N
Ph
3c

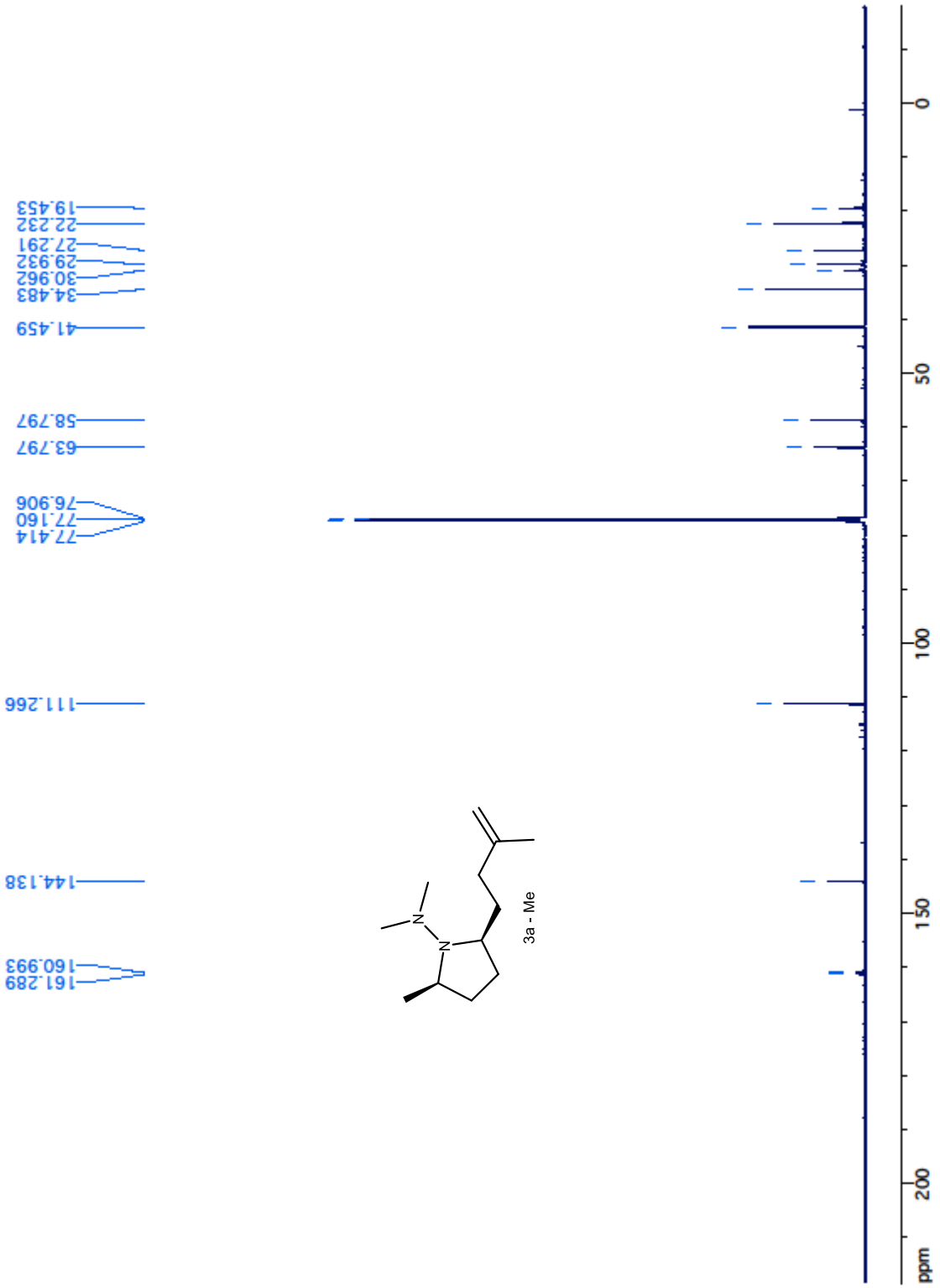

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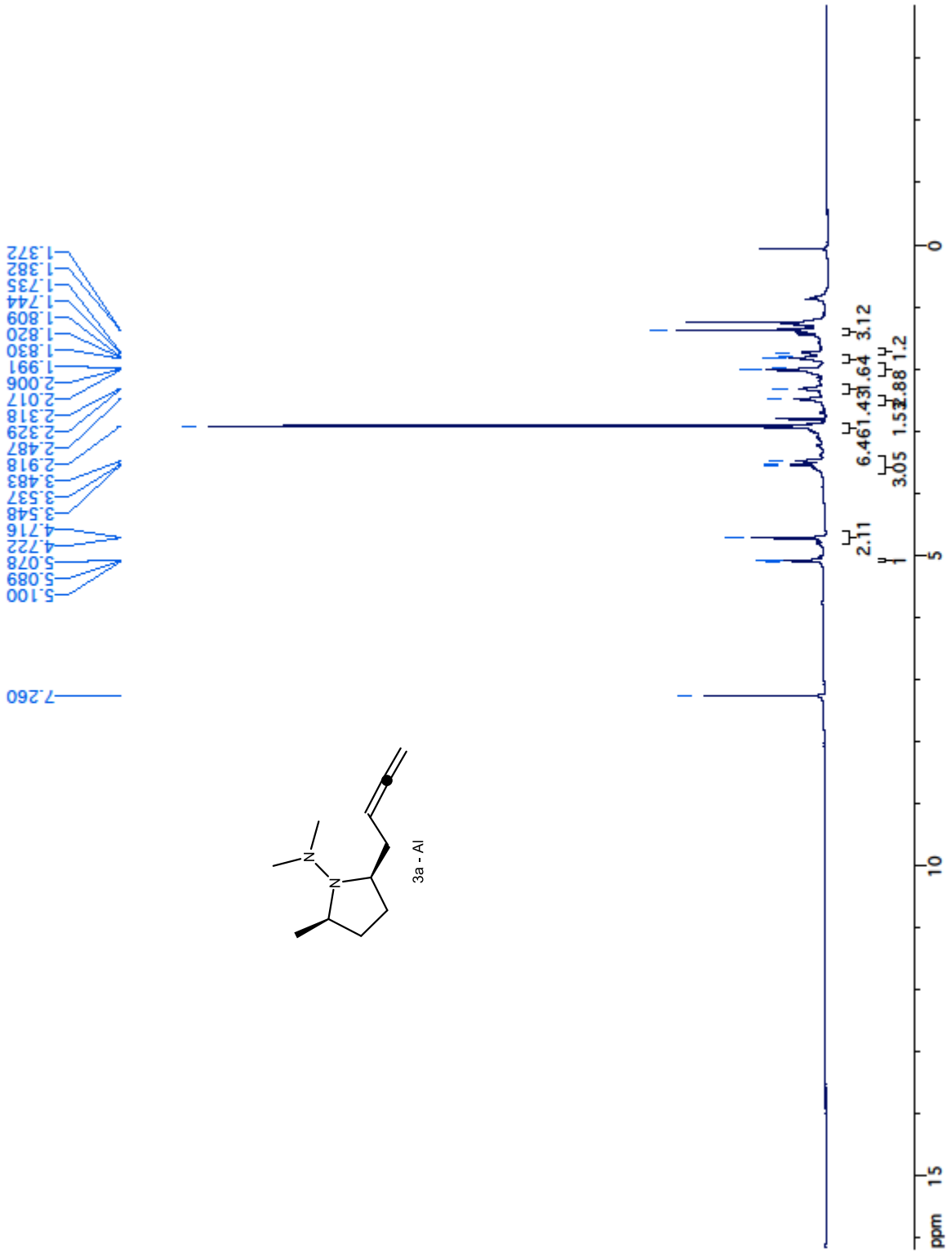

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28.635
29.868
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76.735
77.160
77.581
116.359
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161.557
3d
0
50
100
150
ppm 200

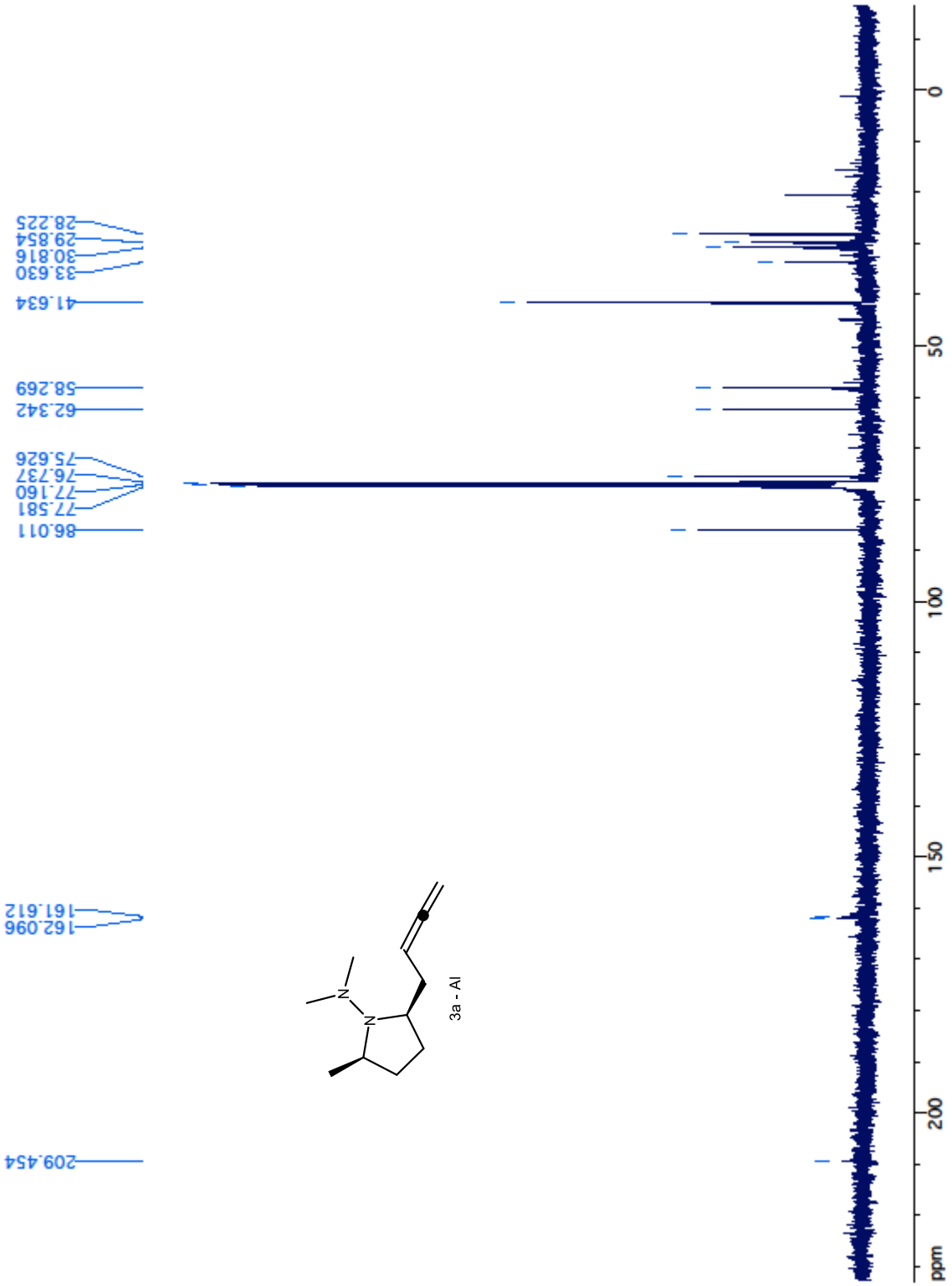

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1.629
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1.782
1.793
1.817
1.845
1.872
1.903
1.921
1.934
1.947
1.964
1.993
2.018
2.033
2.059
2.073
2.099
2.132
2.147
2.158
2.177
2.199
2.219
2.242
2.261
2.350
2.377
2.402
2.427
2.445
2.466
2.662
3.378
3.409
5.003
5.020
5.035
5.078
5.676
5.697
5.707
5.718
5.732
5.753
5.761
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3e
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3.07
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2.16
5.79
ppm

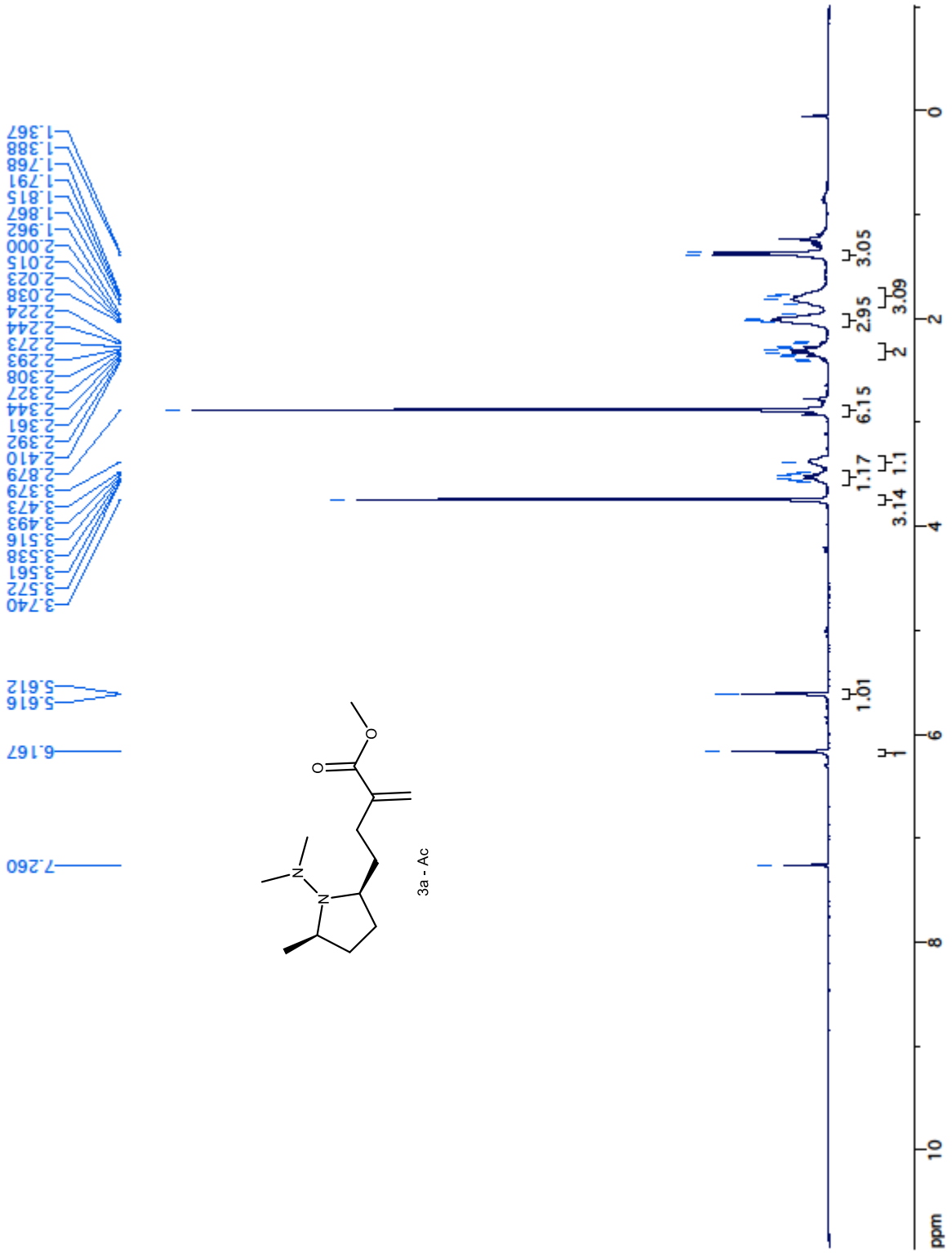

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44.225
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77.585
116.299
136.675
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3e
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100
150
200
ppm

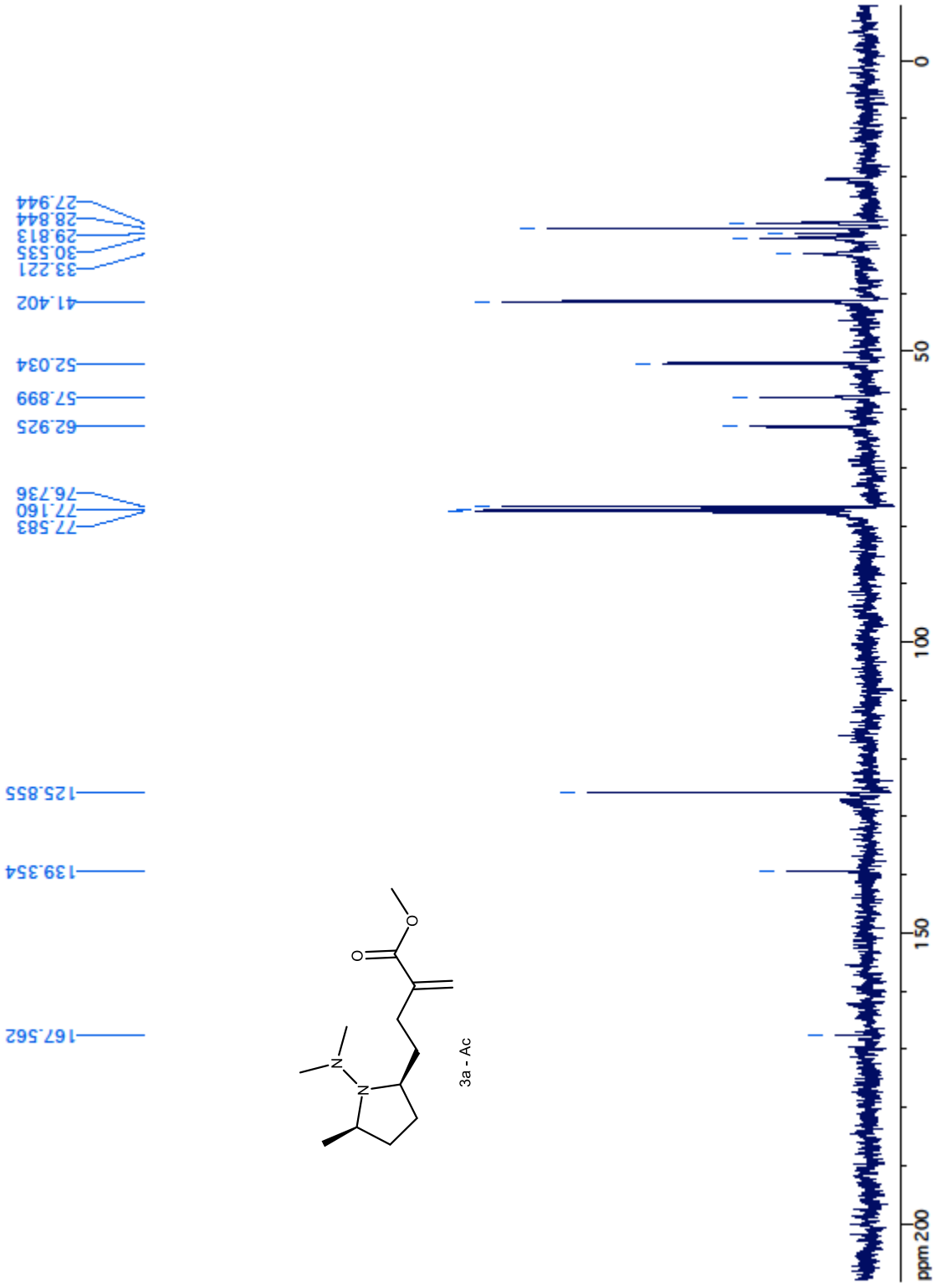

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3.600
3.589
3.578
3.567
3.377
3.371
3.360
2.991
2.979
2.877
2.102
2.084
2.072
2.062
2.059
2.051
2.041
2.024
2.002
1.850
1.842
1.838
1.829
1.819
1.810
1.718
1.443
1.433
1.18
6.03
1.05
5.17
3.12
2.83
3.23
3a - Me
ppm


19.453
22.232
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29.932
30.962
34.483
41.459
58.797
63.797
76.906
77.160
77.414
111.266
144.138
160.993
161.289
3a - Me
0
50
100
150
200
ppm


7.260
5.100
5.089
5.078
4.722
4.716
3.548
3.537
3.483
2.918
2.487
2.329
2.318
2.017
2.006
1.991
1.830
1.820
1.809
1.744
1.735
1.382
1.372
2.11
3.05
6.46
1.53
1.43
3.88
1.64
1.2
3.12
3a - Al
ppm
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10
5
0


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86.011
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77.160
76.737
75.626
62.342
58.269
41.634
33.630
30.816
29.854
28.225
0
50
100
150
200
ppm
3a - Al


3a - Ac
ppm


27.944
28.844
29.813
30.535
33.221
41.402
52.034
57.899
62.925
76.736
77.160
77.583
125.855
139.354
167.562
3a - Ac
0
50
100
150
ppm 200