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A Diversity-Oriented Synthesis Approach to Functionalized Azaheterocycles using Cyclic Alpha-Halo Eneformamides

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A DIVERSITY-ORIENTED SYNTHESIS APPROACH TO FUNCTIONALIZED AZAHETEROCYCLES USING CYCLIC ALPHA-HALO ENEFORMAMIDES

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Spencer Allen Langevin

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ABSTRACT

A DIVERSITY-ORIENTED SYNTHESIS APPROACH TO FUNCTIONALIZED AZAHETEROCYCLES USING CYCLIC ALPHA-HALO ENEFORMAMIDES

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Functionalized piperidines, azepanes, azamacrocycles, morpholines, and thiomorpholines are common structural motifs found in a wide range of pharmaceuticals such as carmegliptine, levofloxacin, thioridazine, claviciptic acid, and azithomycin. As a result, there is a strong desire to construct highly functionalized nitrogen-bearing ring scaffolds in order to construct a wide range of drug possibilities. There are several non-modular and step-uneconomical synthetic methods used in the construction of these aforementioned motifs such as ring closing metathesis, ring expansions, and intramolecular reductive amination. In this research, we present a step-economical, cost-effective, scalable, and diversity-oriented synthesis approach to highly functionalized N-heterocycles through the intermediacy of α-halo enamines/enamides. The synthetic utility of the method is exemplified through the construction of quaternary cyclic propargylic and homoallylic amines, polycyclic lactams, as well as chiral dihydro 1,4-oxazines and thiazines. Given the generality of the approach, we are confident that the synthesis and medicinal chemistry communities will undoubtedly embrace it, thus, endowing it with a practical advantage over existing methodologies.

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CHAPTER 1

INTRODUCTION

1.1 Relevance of Azaheterocycles

A heterocycle is a ring structure where at least one of the atoms that makes up the ring is something other than carbon. An azaheterocycle is a specific type of heterocycle where at least one of the atoms making up the ring is nitrogen. Synthesis of heterocycles is an extremely popular field of study amongst organic chemists for several reasons. Heterocycles are found in a wide range of pharmaceuticals, from naturally occurring compounds to fully synthetic compounds. Specifically, azaheterocycles are found to make up 59% of small molecule pharmaceuticals.[1] The remarkable number of pharmaceuticals that contain an azaheterocycle is one of the many reasons why the medicinal and synthetic communities have shown such great interest in developing drugs containing an azaheterocycle backbone.

Azaheterocycles are found in many pharmaceutical drugs and aren't limited to any one class of drug. They are found in antidepressants, antibiotics, antihistamines, HIV drugs, antineoplastic drugs and many more. Additionally, there are many different types of azaheterocycles ranging from 3 membered rings to macrocycles as large as 25-membered or more. On top of ring size, azaheterocycles can vary with respect to aromaticity, one or more additional heteroatoms, linearly or branchly fused to one or more rings. The large variety of azaheterocycles and their range of biological activity has led to a huge push to explore these rings structures as well as finding new and improved ways of synthesizing fully functionalized azaheterocycles motifs that can be tested for

biological activity and provide the foundation for larger more complex molecular architectures.

Specifically, this has led us to explore the more common azaheterocycles. In this research we are interested in exploring heterocycles commonly found in pharmaceuticals, including piperidines (the most common heterocycle found in FDA approved drugs), thiomorpholines (10th most common heterocycle), and morpholines (17th most common heterocycle).[1] A full list of the top 25 azaheterocycles found in FDA approved pharmaceuticals is shown in Figure **1-1**. We also intend to explore azaheterocycles of different ring sizes, specifically 7- and 13-membered (macrocycle).

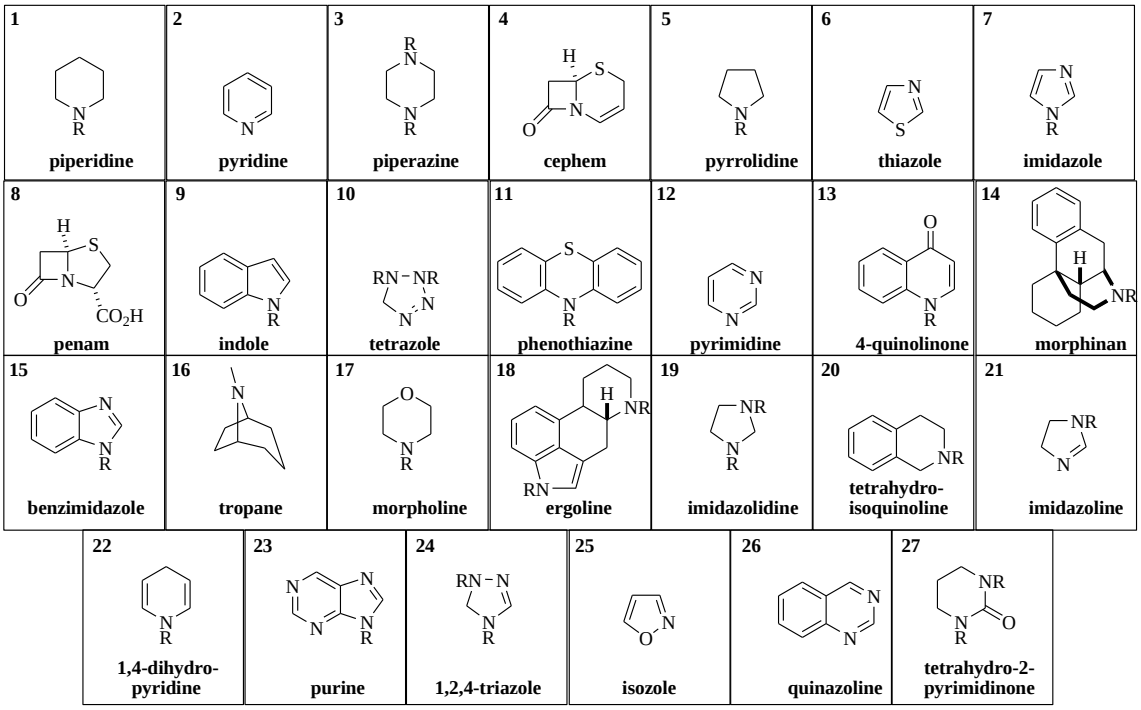
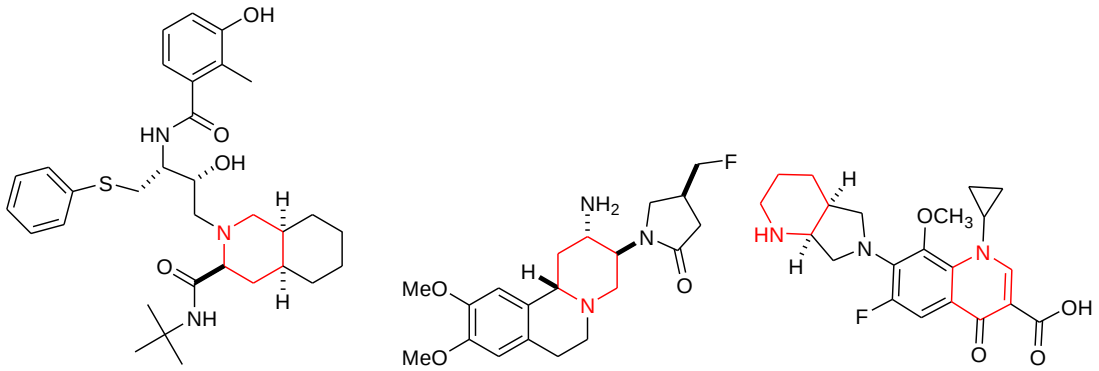


Figure 1-1 Top 27 azaheterocycle motifs in U.S. FDA approved drugs[1]

1.1.1 Relevance of piperidines

As mentioned previously, the piperidine motif is the most common azaheterocycle amongst FDA-approved drugs.[1] Fittingly, their prevalence in

pharmaceuticals with diverse biological activities endears them to the synthesis and medicinal chemistry communities. Several examples of compounds containing the piperidine motif are shown in Figure **1-2**.



Nelfinavir Carmegliptine Moxifloxacin

Figure 1-2 Examples of pharmaceuticals bearing a piperidine motif

The three examples in Figure **1-2** show the wide range of biological activity of drugs bearing a piperidine motif and showing the different ways the piperidine motif is arranged within each compound. Nelfinavir is an antiviral used in the treatment of human immunodeficiency virus (HIV). Nelfinavir made $325 million after the first year it was released, which at the time was one of the largest profits for a pharmaceutical drug in its first year.[2] Nelfinavir is a type of protease inhibitor and is used to inhibit HIV-1 and HIV-2 proteases. HIV proteases are responsible for replication of the virus as well as releasing mature viruses from the infected cell. As is the case for most HIV treatments, nelfinavir is often used in tandem with reverse transcriptase inhibitors in order to provide the most effective treatment. The piperidine moiety in nelfinavir is carbo-functionalized in three positions and has a large group coming off of nitrogen. There are three stereocenters on the piperidine skeleton. This stereochemical facet provides a great challenge for a synthetic chemist as the piperidine. Thus, the synthetic chemist will have

to append several functional handles on the piperidine skeleton while making sure chemoselectivity and stereospecificity are achievable.

Carmegliptine is a drug that is still in development but has shown great promise in the treatment of type II diabetes. Carmegliptine is a dipeptidyl peptidase IV (DPP-IV) inhibitor. DPP-IV is an enzyme that deactivates glucagon-like peptide-1 (GLP1) and glucose-dependent insulin tropic polypeptide (GIP) following food consumption. If DPP-IV is inhibited, GLP1 and GIP remain activated longer thus prolonging their anti-hyperglycemic functions.[3] Carmegliptine is a great example as it shows that the nitrogen in the piperidine motif is actually a bridge to another ring. This is typically referred to as a nitrogen bridge. This provides a challenge for synthetic chemist as creating bicycles already provides a synthetic challenge and constructing a bicycle where nitrogen is the bridge provides an even greater challenge, because when synthesizing the molecule chemo selectivity must be controlled throughout the synthesis.

Moxifloxacin (Avelox) is an antibacterial used in the treatment of several Gram-negative bacterial infections. It is used for the treatment of sinusitis, bronchitis, pneumonia, several types of skin infections, and abdominal infections. Avelox was released in 1999 and reached sales of almost $700 million by 2007. It ranks 140th of the 200 most common drugs prescribed in the United States.[4] Moxifloxacin provides several challenges to synthesize as it has three nitrogen-bearing heterocycles, two of which are piperidines and one is pyrollidine. Additionally, one of the piperidines has an unsaturation and is fused to a benzene ring thus providing even more complexity.

1.1.2 Relevance of morpholines

Morpholines are the 17th most common azaheterocyle found in FDA approved pharmaceuticals (Figure **1-1**)[1]. They are also the ranked 5th for most common 6 membered non-aromatic azaheterocycle amongst FDA approved drugs (**1-3**).

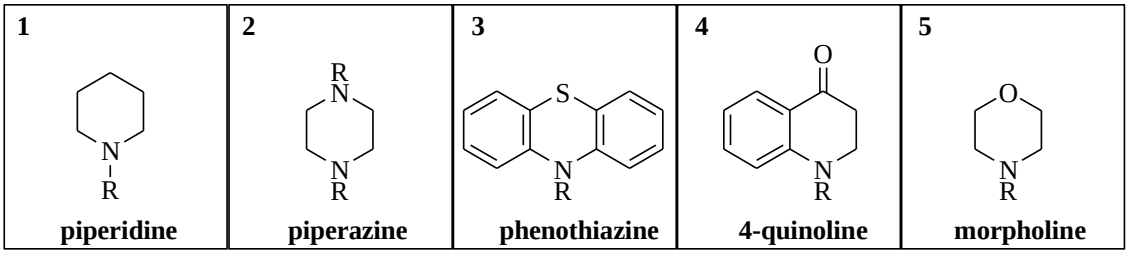


Figure 1-3 Top five six-membered nonaromatic azaheterocycles[1]

Morpholines differ from piperidines as they have two heteroatoms in the six membered ring, where the other heteroatom is oxygen in the 4 position. Having two heteroatoms increases complexity as now the positions adjacent to oxygen are more acidic than that of the positions adjacent to nitrogen. Morpholines also have a wide variety of biological activity and are wildly popular in synthetic research. Morpholine motifs are commonly found in many drug types, including antidepressants, appetite suppressants, antitumor agents, antioxidants, and antibiotics[5]. Morpholines are also found in many industrial agents that are commonly used as corrosion inhibitors, optical bleaching agents, textile dying agents, and fruit preservation agents[1]. Several examples of compounds containing morpholines are shown in Figure **1-4**.

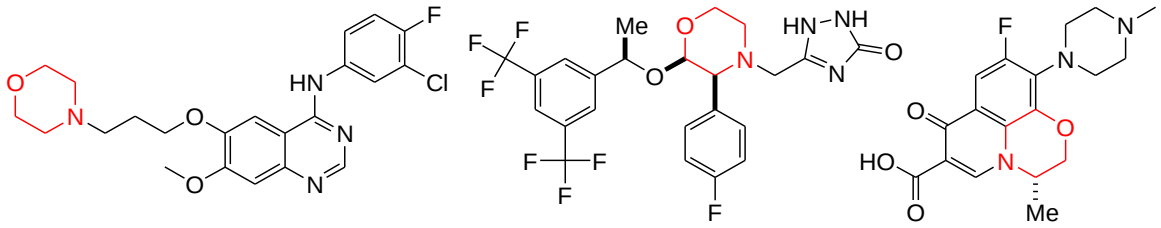


Figure 1-4 Examples of pharmaceuticals bearing a morpholine motif

Gefitinib is an epidermal growth factor receptor (EGFR) inhibitor used to treat several types of breast, lung, and other cancers. EGFR is a transmembrane protein that is activated by binding to epidermal grown factor (EGF) and transforming growth factor α (TGFα). Mutations in EGFR have been known to cause cancer, thus inhibiting this protein once mutations have occurred has been shown to reduce or minimize the growth of cancer.[6] Gefitinib has two heterocycles in the molecule, morpholine and quinazoline. Structurally, the addition of the morpholine would be the less problematic addition to this molecule, but the morpholine does play a major role in its biological activity.

Aprepitant (Emend) is used to reduce chemotherapy-induced nausea and vomiting (CINV). Aprepitant is known as an NK1 antagonist. NK1 antagonists block signals coming from NK1 receptors. NK1 receptors are what cause the impulse to vomit and thus blocking these receptors reduces nausea and vomiting.[7] Aprepitant has a morpholine motif where substituents are coming off of carbons 2 and 3. The substituent coming off of the carbon adjacent to oxygen is a trifluoromethylated phenyl and the substituent coming off the carbon adjacent to the nitrogen is fluorophenyl group. The substituent coming of nitrogen is triazolinone. It also has three chiral centers all within close proximity. Another big part of synthetic chemistry is fluorine chemistry as the addition of fluorine increases the bioavailability of a molecule.

Levofloxacin (Levaquin) is an antibiotic used to treat such bacterial infections as: sinusitis, pneumonia, urinary tract infections, chronic prostatitis, and gastroenteritis. Levofloxacin is used to treat both Gram-positive and Gram-negative bacteria. It works by inhibiting DNA gyrase and topoisomerase IV. DNA gyrase is used by bacteria to supercoil DNA so that it will fit in the cell and topoisomerase IV is used to separate DNA after it has been replicated.[8] If either mechanism is inhibited, the result is the death of the bacteria. One of the challenges here is the presence of a nitrogen bridge and three fused rings. However, the more important aspect to consider is the stereochemistry. This is because the other stereoisomer has no effect on the treatment of bacterial infections. Thus, maintaining stereochemistry is of the utmost importance.

1.1.3 Relevance of thiomorpholines

Thiomorpholines are six-membered saturated heterocycles with two heteroatoms, oxygen and sulfur. The oxygen and sulfur are on opposite (para) sides of the ring. Thiomorpholines are ranked 10th amongst FDA approved pharmaceuticals (Figure **1-1**).[1] They are also the third most common six-membered saturated heterocycle (Figure **1-3**). They are commonly found in several pharmaceuticals as well as frequently used as ligands for catalyst, or thiomorpholine derivatives themselves can be used as catalyst. Because of the wide range of uses for thiomorpholines and because of the struggle to synthesize fully functionalized thiomorpholines, they are a very popular research topic amongst organic chemists. Several compounds containing thiomorpholines are shown in Figure **1-5**.

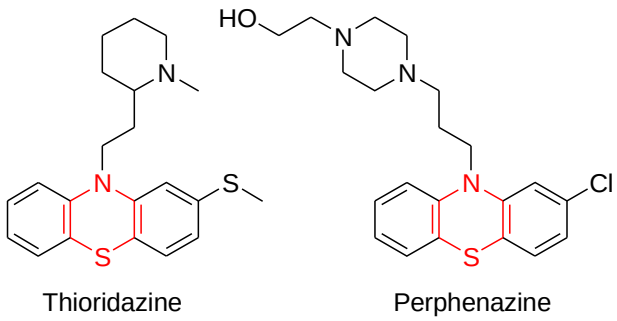


Figure 1-5 Examples of pharmaceuticals bearing a thiomorpholine motif

Thioridazine (Mellaril) is an antipsychotic drug used to treat schizophrenia. Mellaril was withdrawn in 2005 because it was causing severe cardiac arrhythmias. It is being further studied for its use as an antibiotic. Thioridazine works by inhibiting two different cytochrome p450 enzymes, CYP1A2 and CYP3A2[9]. The drug did prove effective toward the treatment of schizophrenia however due to the side effects it has been removed from the market. However, due to the success against schizophrenia, several derivatives have been made and are being tested to see if they can successfully treat schizophrenia without the unwanted side effects. Thioridazine does contain a thiolmorpholine, but more specifically when fused with two benzene rings on either side, it is referred to as a phenothiazine.

Perphenazine (Trilafon) is also an antipsychotic and has been used for many years. It is used to treat schizophrenia and bipolar disorder. Perphenazine is about five times as potent as chlorpromazine, making it a medium potency antipsychotic. Perphenazine can be taken both orally or by intramuscular injection. Perphenazine is often used in combination with fluoxetine, a type of serotonin reuptake inhibitor (SSRI).[10] Perphenazine also has a phenothiazine backbone, but it also has a piperazine motif. Piperazine in another azaheterocycle, specifically it is a six-membered ring with two nitrogens para from one another. This makes it even more interesting to synthetic

chemists and it consists of multiple azaheterocycles and piperazines are ranked third on the FDA-approved pharmaceutical lists (Figure **1-1**) and second amongst six-membered saturated azaheterocycles (Figure **1-3**).[1]

1.1.4 Relevance of azepanes and nitrogen bearing macrocycles

Azepanes are seven-membered saturated rings containing one nitrogen heteroatom. Azepanes are rarer than its five- and six-membered counterparts; however, they still make up more than 40 % of azaheterocycle pharmaceuticals with rings greater than six membered. Azepanes are ranked third for approved seven-membered azaheterocycles FDA drugs (Figure **1-6**).[1]

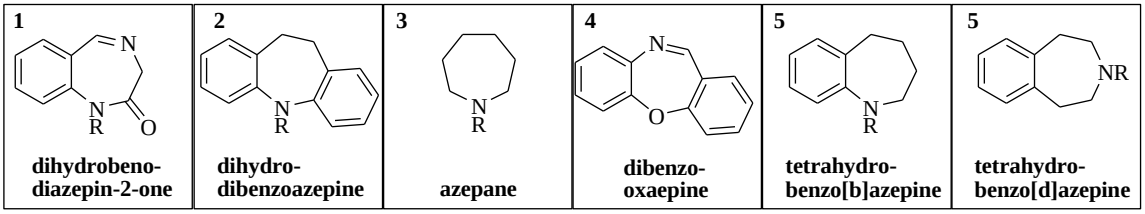


Figure 1-6 Top five seven-membered azaheterocycles FDA-approved drugs[1]

Azepanes and their derivatives have several pharmaceutical and biological applications. Additionally, recent research has shown they can be used as ligands for Diels-Alder and aza-cope rearrangements.[11] Azepane motifs are found in antibiotics, antipsychotics, anti-histamines, anticonvulsants, and many more. Azepanes have also been extracted from a wide variety of natural resources, ranging from sea sponges to fungi. Two examples of azapanes in pharmaceuticals are shown in **Figure 1-7.**

Nitrogen-bearing macrocycles are even rarer than the six- and seven-membered ring counterparts; however, they have been found in several pharmaceuticals as well as extracted from natural products. Although, research into macrocycles is still a popular

field amongst synthetic chemists because of the difficulty in making such large rings and the relatively untapped potential they may have. Depending on the source, the definition of a macrocycle is not consistent. Thus, we will consider them to be any ring greater than 10 atoms in size; however, some would argue anything 8 or more would be considered a macrocycle. Two examples of nitrogen-bearing macrocycles are shown in Figure **1-7**.

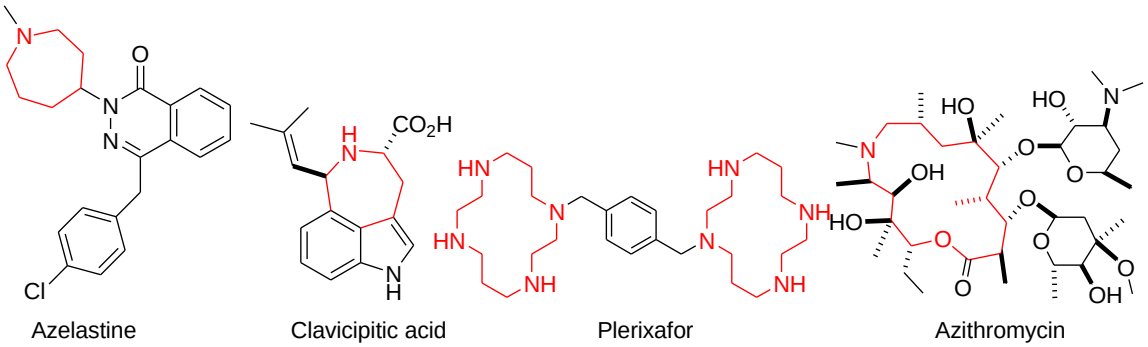


Figure 1-7 Examples of pharmaceuticals containing a azepane motif or nitrogen-bearing macrocycle

Azelastine is an antihistamine used to treat the symptoms of nasal allergies. Azelastine has many trade names and is available as a nasal spray and eye drops. Azelastine has three major effects: anti-histamine, mast-cell stabilizing,and anti-inflammatory.[12] Azelastine has two heterocycles: a phthalazinone motif (a 6-membered cyclic lactam featuring two adjacent nitrogen atoms fused to a benzene ring) and a methylated azepane coming off the lactam nitrogen.

Claviciptic acid was first synthesized in 2007 by Ku's group.[13] A more efficient synthesis was devolved by Tahara's group in 2015.[14] The overall synthesis took 10 steps. The key steps in the synthesis included asymmetric phase-transfer catalytic alkylation, and diastereoselective Pd(II)-catalyzed intramolecular aminocyclization. Claviciptic acid was isolated from ClaViceps fusiformis, which is a plant pathogen typically found on

pearl millet in Africa and India. Claviciptic acid has a very unique fused tricycle consisting of 5-, 6-, and 7-membered rings. When first isolated the compound was found as a racemic mixture. Groups such as Bartoccini[15] have synthesized both stereoisomers. Currently, studies are being done to determine any biological activity as antibiotics, antifungal, and antineoplastics.

Plerixafor (Mozobil) is an immunostimulant used to mobilize hematopoietic stem cells into the bloodstream. It is used to treat cancers such as lymphoma and multiple myeloma. It is used in combination with granulocyte colony-stimulating factor (G-CSF). G-CSF is used to move peripheral blood stem cells, which is used to generate hematopoietic stems cells used for transplantation. Unfortunately, G-CSF is not effective in 15 to 20 percent of patients, thus is used in combination with plerixafor. When used in combination with plerixafor, more stem cells are generated and can be used for transplantation.[16] Plerixafor has two 14 membered rings bearing four nitrogen atoms each. This introduces even more complexity as the compound consists of two macrocycles and has multiple heteroatoms in each.

Azithromycin is an antibiotic used to treat several types of bacterial infections such as: middle ear infections, strep throat, pneumonia, and several types of intestinal infections. It can be administered orally or intravenously. It is listed as one of the safest medicines by the World Health Organization (WHO). Azithomycin has a very broad usage and inhibits many types of Gram-positive and Gram-negative bacteria.[17] Azithomycin has a 15-membered macrocycle bearing both a nitrogen and an oxygen. It has several stereocenters, thus synthesizing this molecule can be difficult as maintaining stereochemistry as well as having a very unstable 15-membered ring proves problematic.

1.2 Diversity-oriented synthesis (DOS)

One of many challenges for an organic chemist is to construct a scheme to develop several compounds that are all structurally unique and vary in more ways than one. A true diversity oriented synthesis approach produces compounds that are different in the structural building block, stereochemistry, functional groups, and molecular framework. The simplest definition of DOS can then be explained as the thoughtful, immediate and efficient synthesis of several compounds in a specific approach to solve a complex problem.[15] The purpose behind DOS is that compounds that look structurally similar typically have similar biological activity. In a diversity oriented synthesis approach, the molecules are different enough that the biological activity of each compound can differ exponentially.

1.2.1 Merits of diversity-oriented synthesis (DOS)

As was said in the simplest definition of DOS, the end goal is to solve complex problems. Ultimately, this is driven by having a problem that has no hypothesis, meaning that we are trying to find a molecule that is biologically active but don't know where to start. In many cases there is enough known about the problem that a hypothesis can be formed and one can design a target molecule that can then be synthesized. Therein lies the difference between the hypothesis driven approach and a DOS approach. A diversity oriented approach develops a large library of structurally diverse compounds that can then be tested toward a specific problem. Once a molecule shows promise then a more detailed hypothesis-driven approach can be utilized. This is why neither a hypothesis-driven approach nor diversity oriented approach is better than the other. In most cases one drives the other.

Target-oriented synthesis (TOS) and DOS both involve complexity-generating reactions, however TOS is convergent, meaning they develop several fragments of compounds and couple them together to form one target molecule. A DOS uses multicomponent-coupling reactions and branched pathways with a forward synthetic approach to develop multiple structurally unique compounds.[15] This is best illustrated in Figure **1-8**.

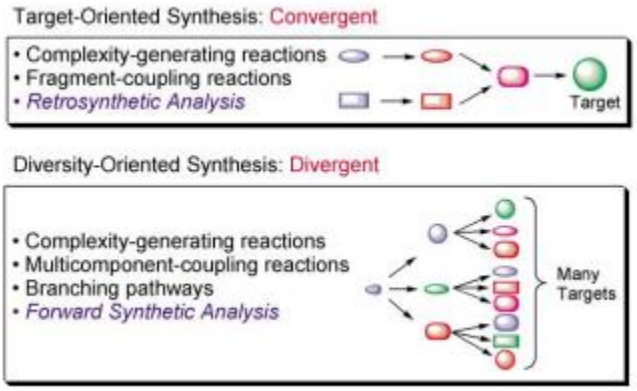


Figure 1-8 Differences between target-oriented synthesis (TOS) and diversity oriented synthesis (DOS)[15]

One of the many advantages of DOS is in drug discovery. Between the years of 1989-2002 two-thirds of FDA approved drugs were slightly modified compounds of already existing drugs.[15] Over the last several years the number of new-molecular entities (NME) has decreased. This only further illustrates the need for DOS. As previously stated, TOS is synonymous with the hypothesis-driven approach. Thus a target, or hypothesis, of a potential compound must be made then sought after. Such an approach creates a large influx in the amount of drugs that are structurally similar to drugs already on the market. In order to find new and structurally unique drugs, a DOS approach

would be desired. The use of more DOS approaches and the increasing popularity of DOS should lead to an increase in NME that hit the market.

There are two major approaches to drug discovery. The first approach looks for small molecules that produce a desired outcome. Such as developing small molecules that are toxic to bacteria. This approach has been wildly successful, and has generated such drugs as vancomycin, penicillin, streptomycin, tetracycline, erythromycin, sulfonamides, and many more. The second approach looks for a target enzyme or protein that a drug could modulate, attenuate, or inhibit its function. Both of these approaches require a large library of structurally diverse compounds in order to achieve the desired effect. DOS is perfect as it has the potential of developing a large library of compounds efficiently. Additionally, DOS provides a large variety of compounds that will allow for structure activity relationships (SAR) studies, which can aid in determining enzyme binding sites as the site in a molecule that has the largest effect on target enzymes.

The power behind a DOS approach is in very few steps a single substrate can be converted into many structurally-complex and structurally-diverse compounds. The crucial step to creating structurally-complex molecules is to use complex-generating reactions. The crucial step to generating structurally-diverse compounds is to use diverse starting materials with several branching points.

1.2.2 Challenges with diversity-oriented synthesis (DOS)

In some ways a DOS can prove to be more demanding than a TOS. In DOS, methodology has to be designed that will tolerate several different solvents, substrates, and functional groups. Another problem to avoid with the DOS approach is to maintain a systematic approach and avoid a shotgun-type approach to science, meaning aimlessly

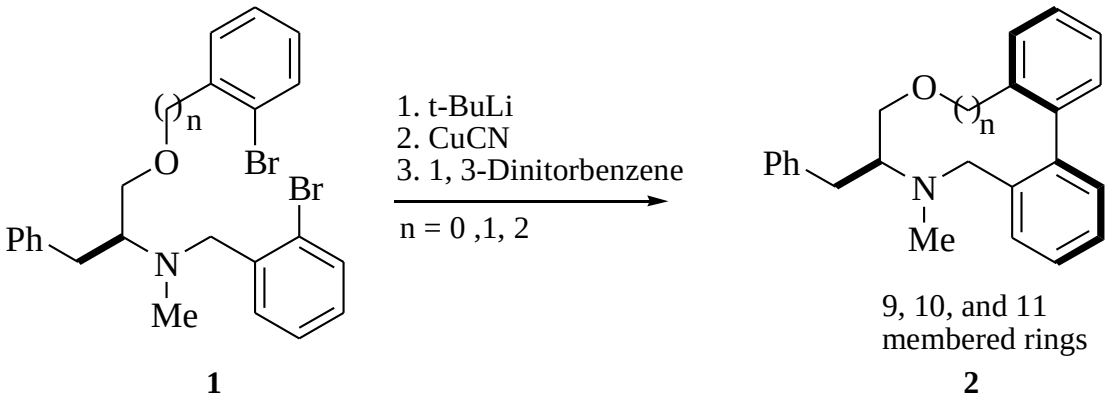
developing several compounds and just wildly testing each one for everything. This would require a large amount of man power and would not be a cost-effective strategy. There have to be some boundaries to what compounds are developed and what each one is tested for. Thus, the systematic part of a DOS needs to be a major part of the overall scheme.

The main challenge associated with a DOS is planning a systematic pathway that generates a large variety of structurally unique compounds. This requires the use of several different starting scaffolds that can then be branched in several different ways using complex reactions. This isn't as trivial as it may seem because not all starting substrates will act in a similar way. That said, trivial reactions won't provide a diverse enough library, thus complex reactions are needed. This introduces an even bigger challenge as in many cases with complex reactions, the complex reactions haven't been tested to their full potential. However, that's part of the power of a DOS, as in addition to a large library of compounds, new methodology can be discovered and then used in a TOS; an example of one approach feeding another. Ultimately both approaches have their pros and cons and DOS is becoming more and more popular through the years, but there will always be a place for TOS.

1.2.3 Commonly employed DOS approaches to N-heterocycles

One of the common ways DOS is used is to create multiple compounds that are structurally similar, however they are able to create compounds with varying ring sizes. An example of this DOS approach is by the Springs group, who constructed a pathway that used a wide range of substituted acyclic precursors **1** and was able to construct biaryl-containing medium rings efficiently and atropdiastereoselectively **2**.[16] They were

able to generate multiple ring sizes of 9-, 10-, and 11-membered heterocycles bearing both nitrogen and oxygen (Figure **1-9**). This is just one example of such a synthetic pathway. Developing DOS to construct complex molecules with varying ring sizes is an extremely challenging process that is becoming very popular amongst synthetic chemists. Although it seems trivial that a change in a ring by one atom wouldn't make much of a difference it has been shown that as ring sizes change, the biological activity of those molecules can change significantly.

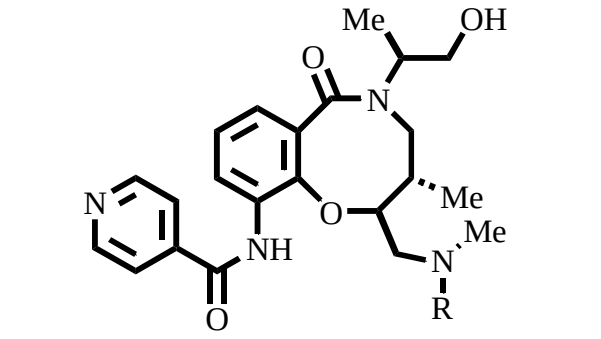


1 **2**

Figure 1-9 Example of DOS to vary ring size in a complex medium-sized oxygen- and nitrogen-bearing heterocycle[16]

Another way that DOS is used is to determine structure to activity relationships. Figure **1-10** shows how the Dandapani group was able to use DOS to construct a molecule that showed biological activity toward the treatment of parasite *Trypanosoma cruzi*, the etiological agent of Chagas disease. Because they used DOS, they were able to determine structure to activity relationships. Shown in Figure **1-10** they were able to modify the substituent coming off nitrogen. Figure **1-10** only shows a few of the many compounds they were able to generate and test against *Trypanosoma cruzi*. They were also able to change the substituent on the other nitrogen to an isopropyl group. This gave

them over 100 compounds in total. The idea being to show how subtle changes in substituents can have a huge effect on biological activity. By changing the amine substituent from phenyl to pyridine they saw a 2500 times drop in potency. Such a simple change in structure caused a huge drop. However, this shows the importance of this substituent as well as what kind of substituents are necessary for the compound to have an effect on *Trypanosoma cruzi*. This further illustrates the importance of DOS and how it can be used in SAR related studies.



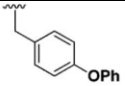
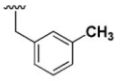
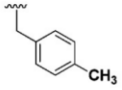
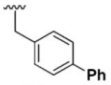
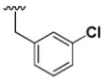
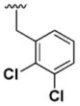
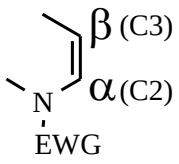
R	IC_{50} (nM)[a]	R	IC_{50} (nM)[a]
	1		56
	12		1
	>32,000		14
	165		10
	15		25

Figure 1-10 Example of how DOS can be used to determine structure-activity-relationships (SAR)

1.3 Enamides and Enecarbamates

First, we must discuss the differences between enamides and enecarbamates before we go into their importance. The difference is in the electron withdrawing group (EWG) coming off of nitrogen (Figure **1-11**).



Enamides, EWG = COR
Enecarbamates, EWG = COOR

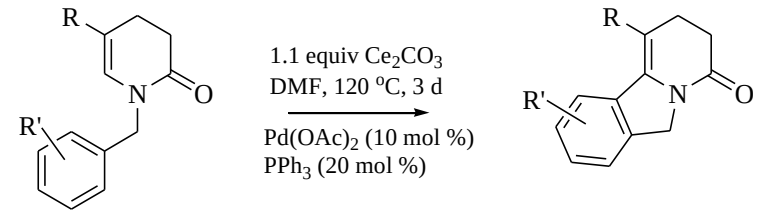
Figure 1-11 Shows the difference between an enamide and enecarbamates

In the last several years, enamides and enecarbamates have become heavily studied and have been used in a variety of ways to introduce new synthetic transformations for the synthesis of both natural products and biologically active compounds.[17] Due to the electron donating nature of nitrogen, enamides are more electron-rich than an alkene alone. Thus, this activates the C=C double bond, giving enamides and enecarbamates nucleophilic and electrophilic properties. This causes the α-carbon to be electrophilic and the β-carbon to be nucleophilic and subject to electrophilic attacks. The electrophilic nature of both the α-carbon and β-carbon can be controlled by the group attached to nitrogen. Common groups that have been explored are amides, carbamates, and sulfonamides.[18-20] Enamides and enecarbamates provide an important building block to many more complex larger nitrogen-bearing compounds. Therefore, the challenge to the synthetic community is to selectively and directly functionalize enamides and enecarbamates and to demonstrate their utility. One of the many ways that enamides and enecarbamates have been utilized is via direct metal-catalyzed functionalization of C-H bonds.[21-26] This is an effective method at directing chemical synthesis, since it avoids

the need to pre-activate substrates, which can prove to be quite costly and inefficient as it can add several synthetic steps. Over the last fifteen years, a lot of progress has been made with the use of alkenes, alkynes, arenes, and heterocycles with a large range of coupling partners. The popularity of C-H activation continues to grow and is being recognized for its large synthetic potential in the construction of new methodologies and synthetic application toward total synthesis.

1.3.1 Synthetic utility of enamides and enecarbamates- direct C2 intramolecular functionalization

In recent years, several groups have demonstrated that using intramolecular Heck coupling reactions on acyclic enamides and enecarbamates have been a means of producing azaheterocycles. Some of the important early work was done by Griggs and his group utilizing Heck coupling reactions to create a large library of azaheterocycle substrates.[27] An example of such a reaction is illustrated in Figure **1-12** where Zhang[28] and his group used an intramolecular Heck coupling reaction on *N*-acyl-2,3-dihydro-4-pyridinoneto **3** to form a tricycle with a nitrogen bridge **4**. This is just one of many examples that utilize a cyclic enamide to generate fused heterocycles.



R = hex, CH_2Ar
R' = H, OMe

3

9 examples
60-83 %

4

Figure 1-12 Example of a Heck coupling reaction with an enamide to form a tricycle

1.3.2 Synthetic utility of enamides and enecarbamates- direct C2 and C3 intermolecular functionalization

One of the major challenges with the work of enamides and enecarbamates is to control regioselectivity, in particular controlling whether the desired addition takes place at C2 or C3. This has generated a large amount of interest as many have not only tried to control which carbon the addition takes place, but also maintain stereochemistry. As discussed, one of the challenges of a DOS is to create a library of structurally unique substrates while maintaining complexity. In this case the complexity is associated with maintaining both stereo- and regio-selectivity.

Shown in Figure **1-13** is work by Gillaizeau's group,[29] Pd-catalyzed regioselective decarboxylative arylation. One of the limitations of this reaction is the need to use electron rich *ortho*-methoxy-substituted benzoic acids **6**. Additionally, only C2 activation occurred when the protecting group on nitrogen was electron withdrawing and only a single coupling event occurred (see **7)**. When there was electron rich or neutral groups on nitrogen a double coupling event occurred. The reaction is also plagued by challenges associated with double bond isomerization (see **8)**. This happens to be a common limitation with these cyclic enamide compounds, and finding ways to avoid the migration is being explored in many different ways.

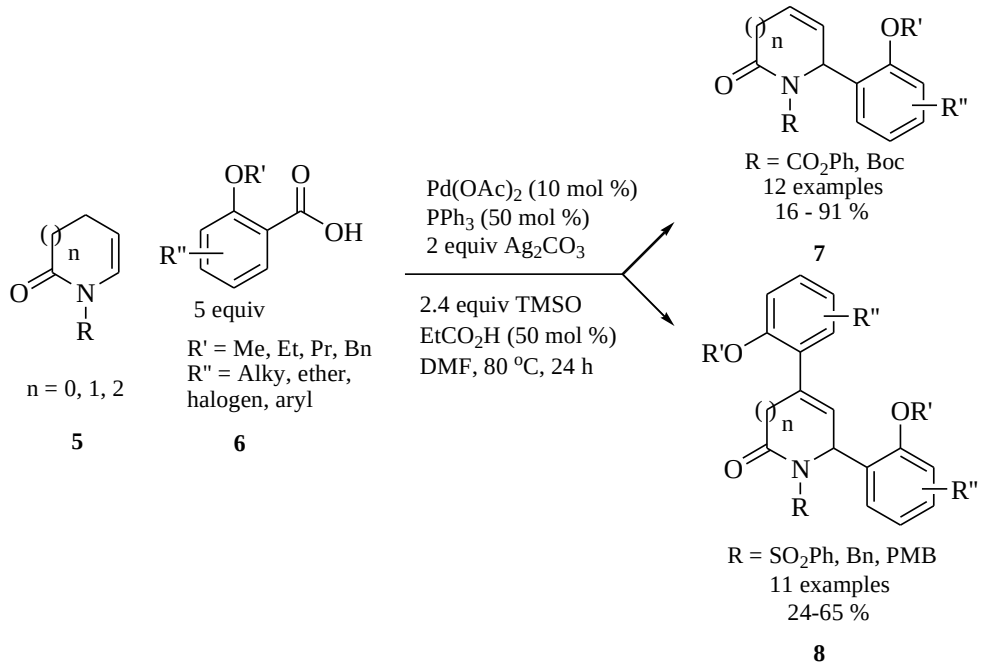
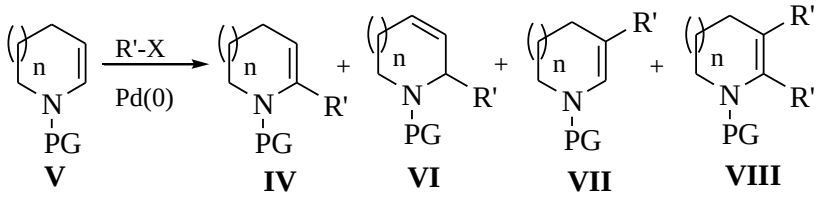


Figure 1-13 Example showing the challenges of an addition to an enamide regioselectively at carbon C2

Another challenge with enamides is to achieve C3 regioselective functionalization when the C2 position is unsubstituted. This is made all the more difficult by the fact that the C2 position is vinylic and α-amino, thus, inherently more reactive than its C3 counterpart (Figure **1-14**).

Challenges associated with the use of enamides/enecarbamates



double bond isomerization and control of regioselectivity (C2 vs C3)

Figure 1-14 Examples of the challenges of double bond isomerization and control of regioselectivity with enamides/ enecarbamates

One method of accomplishing this task has been the use of diaryliodonium salts in tandem with a copper catalyst, as eloquently demonstrated by Gillaizeau[30] (Figure **1-15**). The reactions worked well and mostly displayed regioselectivity toward the C3 position **10**. The reaction also tolerated a large variety of functional groups **9**. Unfortunately, in some cases when the diaryliodonium salt was in huge excess, (*e.g.,* 5 equiv), regioselectivity was compromised and coupling at both the C2 and C3 positions was observed. Other drawbacks of this methodology are the need for a high catalyst loading and the use of expensive reagents, thus, rendering it cost ineffective.

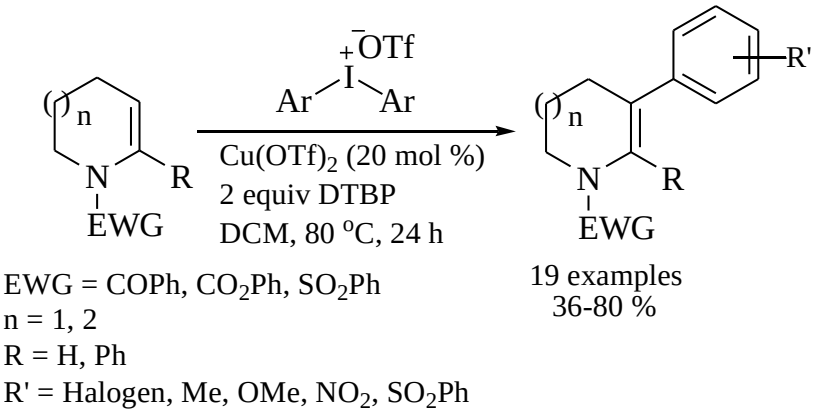


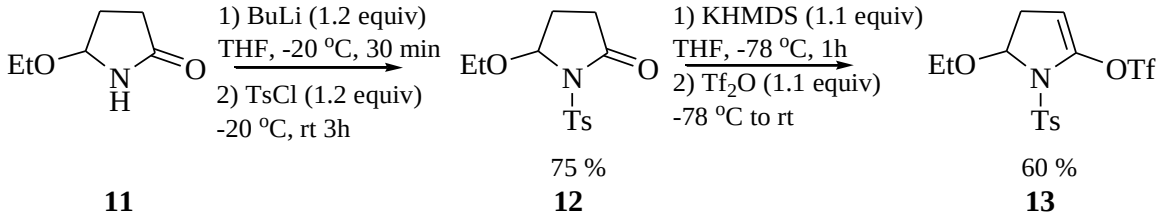
Figure 1-15 Regioselective C3 arylation of enamides

1.3.3 Challenges associated with vinyl triflates, stannanes, and phosphates

Primarily due to the aforementioned regioselectivity issues, several groups rely on the use of preactivated enamides and enecarbamates. Along these lines, enamides bearing a pendant leaving group at C2 such as a triflate, phosphate, stannane, iodide, boronate have been exploited with notoriety.

Vinyl triflates are used in a variety of coupling reactions including Stille, Heck, cuprate additions, and Nozaki-Hiyama couplings. A triflate is a powerful leaving group and has been utilized in many ways. Figure **1-16** shows Speckamp's synthesis of a vinyl

triflate **13** from an ethoxy lactam **11**. This is one of the many challenges with vinyl triflates. It takes a total of four steps to generate the vinyl triflate. Additionally, triflate reagents aren't cheap and the scheme includes harsh reaction conditions such as the use of butyl lithium. Another challenge that must be mentioned is the protecting group of nitrogen is limited in the following step (see **12)**. This limits how modular the reaction scheme can be.



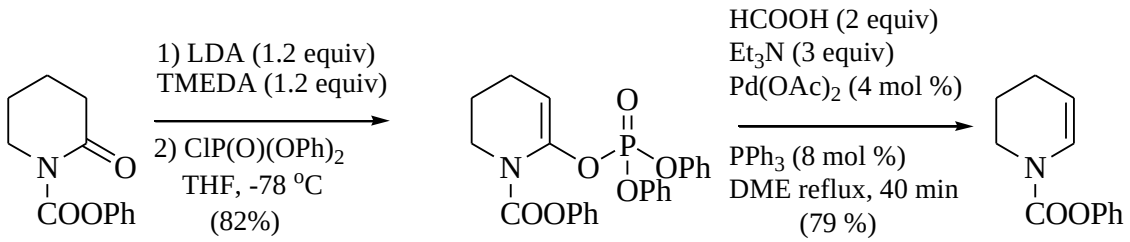
75 %

60 %

11 **12** **13**

Figure 1-16 Preparation of vinyl triflates from an ethoxy lactam

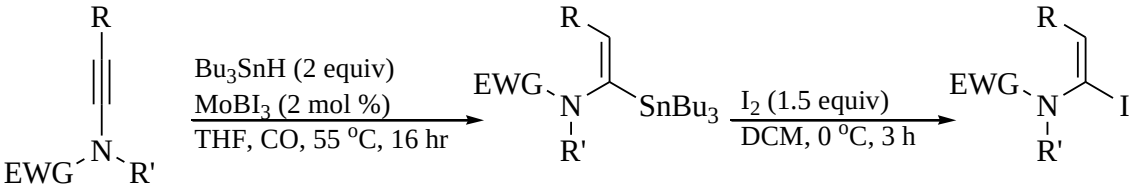
There are many challenges associated with constructing cyclic enamides and enecarbamates with the use of vinyl phosphates (Figure **1-17**). One of those challenges with vinyl phosphates is that they are not bench stable and are extremely difficult to isolate, thus once they are generated they need to be moved to the next step in the reaction. Another challenge associated with the use of vinyl phosphates is cost. The reaction scheme requires the use of expensive catalyst and lithium reagents. Additionally, once the lactam is protected with COOPh or a Boc group (see **14)**, it takes three additional steps to achieve the final desired product **14-16**. [31]



14 **15** **16**

Figure 1-17 Preparation cyclic enecarbamate utilizing vinyl phosphates

Stannanes offer another functional handle similar to that of vinyl triflates and phosphates. However, like vinyl phosphates and triflates, the use of expensive reagents as well as an expensive catalyst is necessary. Additionally, the starting alkyne **18** is not something that can be store bought, thus the reagents necessary to generate the alkyne further increases the cost and provides even more steps. Shown in Figure **1-18** Kazmaier[32] and his group generated stannanes **18** using their previously constructed catalyst. This provides additional complication, because in order to achieve good yields specific catalysts are required. Another point of interest is they do an additional reaction to replace the stanine with an iodo group (see **19)**. Mostly, because iodide is a great leaving group in its own right but can be used under more reaction conditions than its stannane precursor.



R = n-Hex, c-Pr, ph
R' = Me, Bn
EWG = Ts, Boc

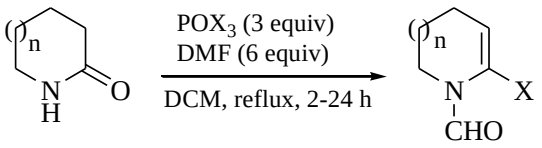
17 **18** **19**

Figure 1-18 Preparation of stannanes from substituted alkynes

Triflates, phosphates, and stannanes are all useful functional handles and have all been used in several cross-coupling reactions that generate functionalized azaheterocycles. However, we would like to find a more step-economic, cost-effective, and bench stable approach to generating an enamide bearing traceless functionality at C2.

1.3.4 Cyclic α-halo eneformamides as an alternative to triflates, phosphates, boronates and stannanes

One of the main goals of our group was to develop a substrate like that of enecarbamates and enamides but in a more step-economical, and cost effective manner. This led us to the preparation of α-halo eneformamides (Figure **1-19**).



n = 1, 2, 8 — **20**

X = Cl, Br, I — **21**

Figure 1-19 Preparation of cyclic α-halo eneformamide from lactam

Unlike that of the previous work shown with triflates, stannanes, and phosphates we were able to demonstrate the construction of the α-haloeneformamide **21** in one step through the use of a Vilsmeier-Haack reaction. Through the Vilsmeier-Haack reaction we were able to make an enamide - more specifically an eneformamide. This reaction also provides a halogen as a good leaving group coming off the C2 position. Another benefit is we have shown that this reaction can be done on several different lactam sizes, a six-, seven-, and thirteen-membered lactam (see **20)**. Additionally, the halogen can be modified depending on the type of phosphoryl reagent used. This provides a method for increasing the reactivity of the functional handle coming off the C2 position. As shown previously with the work on stannanes, it took a series of five steps to achieve what we have in one. Another benefit of this transformation is that the reaction is scalable. We have shown that this reaction can be increased to up to 100 mmol in scale. Also, this reaction does not require any use of a metal based catalyst, thus this reaction is very cost effective and the reagents used are relatively inexpensive compared to the reagents used

with triflates, stannanes, and phosphates. Another cause for excitement is that the compound is bench stable. Meaning, the compound can be held on to for long periods of time without falling apart and since the reaction is also scalable large amounts can be made and used over a long period of time. This is extremely beneficial, both from a cost effective standpoint and from a time conservation standpoint.

From a functional point of view this already functionalized precursor can be even further functionalized. The halogen connected to C2 can be used for several types of coupling reactions, such as Heck, Susuki, and Sonagashira cross-couplings to name a few. The C3 position is vinylic, and the C4 position is allylic thus, both positions can be accessed for further functionalization. Additionally, the other α-carbon can be functionalized as it is α-amino and therefore the hydrogens in that position are acidic and begging to be functionalized. Furthermore, we intend to show the extremely vast utility of this synthetic intermediate as well as show the synthetic utility of the products that are constructed from it.

1.4 Our Prior Work on Cyclic α-halo Eneformamides

1.4.1 Expedient access to α, β-difunctionalized azepenes using cyclic α-halo eneformamides

Some of the first work we did using the cyclic α-halo eneformamide was on the seven-membered variant. Having already demonstrated work showing we could effectively perform several types of coupling reactions on C2 position, we wanted to show approaches to functionalization of both the C2 and C3 positions. The first approach is to functionalize the C2 position to give **24** and then the C3 position to afford **23** and the second approach is to functionalize the C3 position to give **25** followed by

functionalizing the C2 position to afford **23**. This is illustrated in Figure **1-20.** Although it seems more likely that the bottom-up approach would be preferred because of the halogen on C2 acting as a functional handle, if the correct reaction conditions are found then direct C3 functionalization can take place followed by using coupling reactions using the halogen functional handle to functionalize C2.

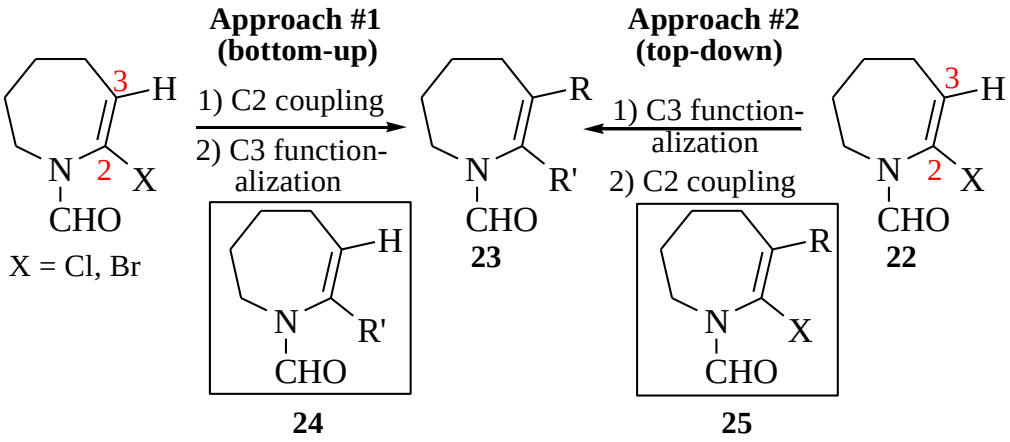


Figure 1-20 Two vicinal functionalization strategies using a cyclic α-halo eneformamide

As shown in Figure **1-21** we were able to directly and regioselectively arylate the C3 position **27** using palladium catalyzed conditions used by Gunda.[33] Consistent with what Gunda reported, the reaction depends highly on the aryl-iodo coupling partner. It was recognized that if the aryl-iodo coupling partner was electron withdrawing in nature the reaction was slow and produced low yields. Additionally, if the iodide coupling partner was ortho-substituted the reaction was slow and produced low yields. However, these conditions did allow for direct and regioselective arylation of the C3 position and didn't react with the functional handle on C2.

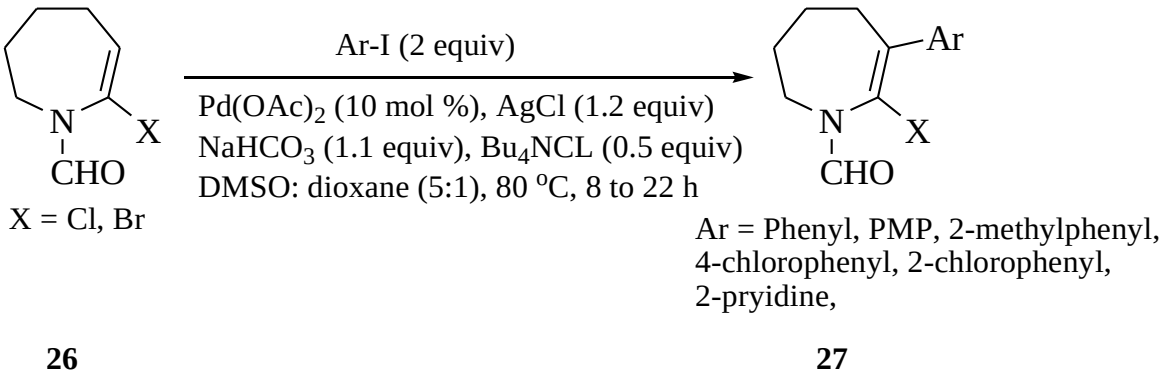


Figure 1-21 Palladium catalyzed C3 arylation of cyclic α-halo eneformamide

To illustrate the top-bottom approach after we directly functionalized the C3 position **28** we then wanted to illustrate that the subsequent functionalization of the C2 position was possible using the chloro group as a functional handle. To illustrate this we used Susuki cross-couplings with aryl boronic acids to afford the doubly substituted azepenes (see **29** and **30)**.[34] To further illustrate the substituted precursor's utility, Sonagashira cross-couplings with trimethylsilylacetylene were conducted in a catalytic amount of CuI (see **33** and **34)**. This shows two possible examples of how we were able to successfully use the top-down approach on our cyclic α-chloro eneformamides (Figure **1-22**).

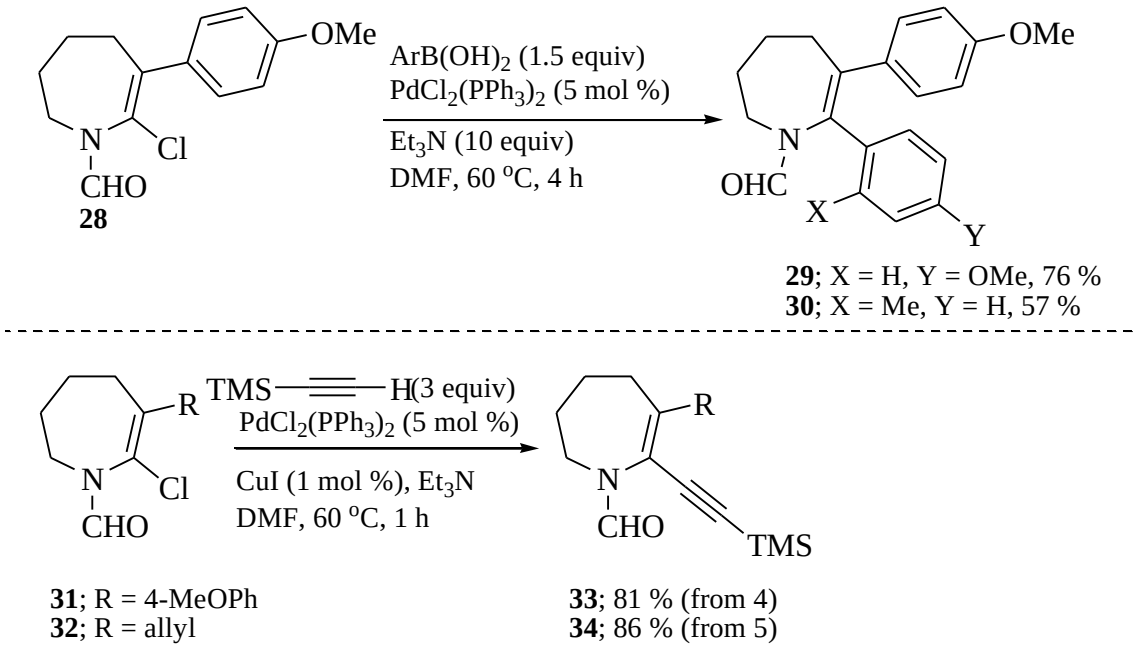
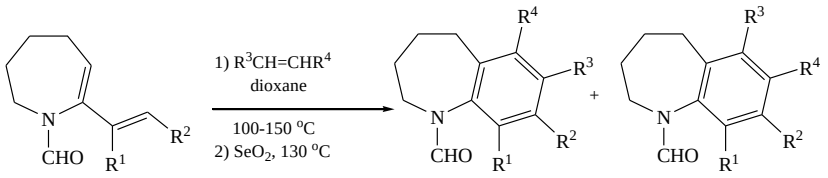


Figure 1-22 Palladium-catalyzed α-arylation and alkynylation of C2-functionalized cyclic α-chloro eneformamides

In a previous publication we showed that cyclic α-chloro eneformamides could be vinylated, alkynlated and arylated through the use of Heck, Suzuki, and Sonagashira cross-couplings.[35] We then took select examples of the α-alkenyl eneformamides **35** and used these to explore the bottom-up approach to vicinally difunctionalyzed azepenes. We took our library of newly formed dienes and explored the use of Diels-Alder / benzannulation type reaction. We took our dienes and reacted them with several asymmetrical and symmetrical dienophiles to create benzannulated azepenes (see **36** and **37)** (Figure **1-23**).



35 36 37

Entry	R^1	R^2	R^3	R^4	Ratio	% yield
1	H	Ph	CO_2Me	CO_2Me	>99 : 1	64
2	H	Ph	$R^3 + R^4 = C_2O_3$		>99 : 1	75
3	H	CO_2Me	H	CO_2Me	>99 : 1	67
4	H	CO_2Me	H	$CO_2{}^tBu$	80 : 20	73
5	H	$CO_2{}^tBu$	H	$CO_2{}^tBu$	60 : 40	77
6	OEt	H	H	$CO_2{}^tBu$	>99 : 1	80[a]
7	OEt	H	H	CONHiPr	nd	<5
8	H	Ph	H	Ph or Et	na	0[a]
9	H	$CO_2{}^tBu$	H	Ph or Et	na	0[a]
10	OEt	H	H	Ph or Et	na	0[a]

Figure 1-23 Preparation of 2-benzazepanes using α-alkenyl eneformamides

1.4.2 One-shot access to α, β-difunctionalized azepenes and dehydropiperidines by reductive cross-coupling of α-selenonyl-β-selenyl enamides with organic bromide

One of the goals in the use of our cyclic α-chloro eneformamides is to find new ways to access differentially-substituted azaheterocycles. We envisioned a route where we could take our cyclic α-chloro eneformamides and replace the bromo group with a selenonyl group **A**. This approach would then allow us to explore Denmark-motivated[36] cross-couplings and the electron withdrawing nature of the selenonyl group would afford us the opportunity to explore Comins[37] directed lithiation / trapping with electrophiles **B**,**C** (Figure **1-24**).

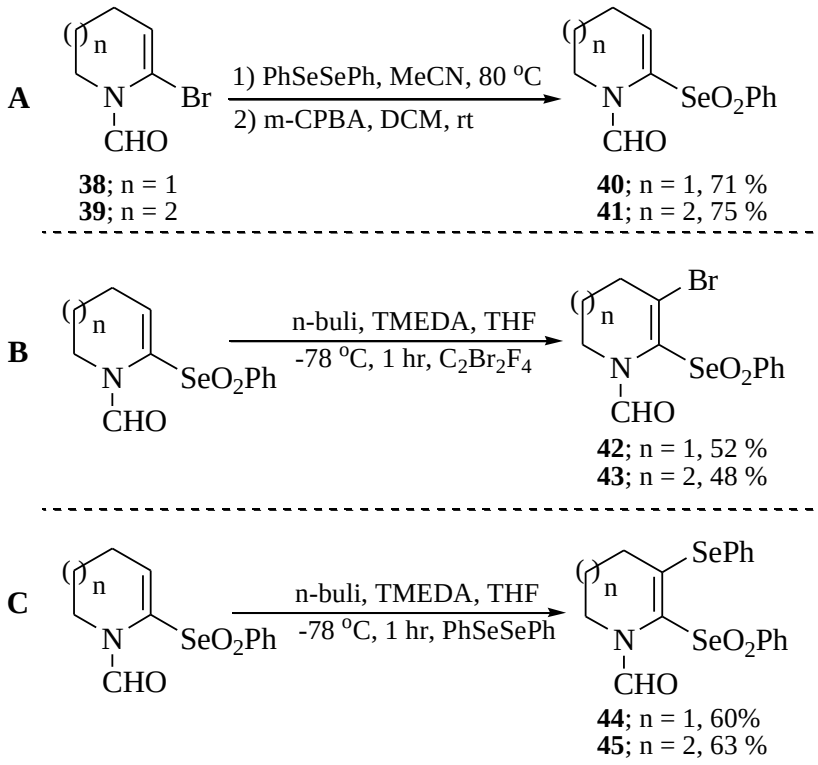


Figure 1-24 Preparation of α-selenonyl eneformamides followed by directed lithiation/trapping

Once the selenonyl group was added, Denmark-motivated cross-coupling conditions were utilized. The resulting carbofunctionalized products shown in Figure **1-25** were obtained in satisfactory yields. To show the versatility of these reaction conditions aryl, heteroaryl, alkenyl, and allyl Grignard reagents were used.

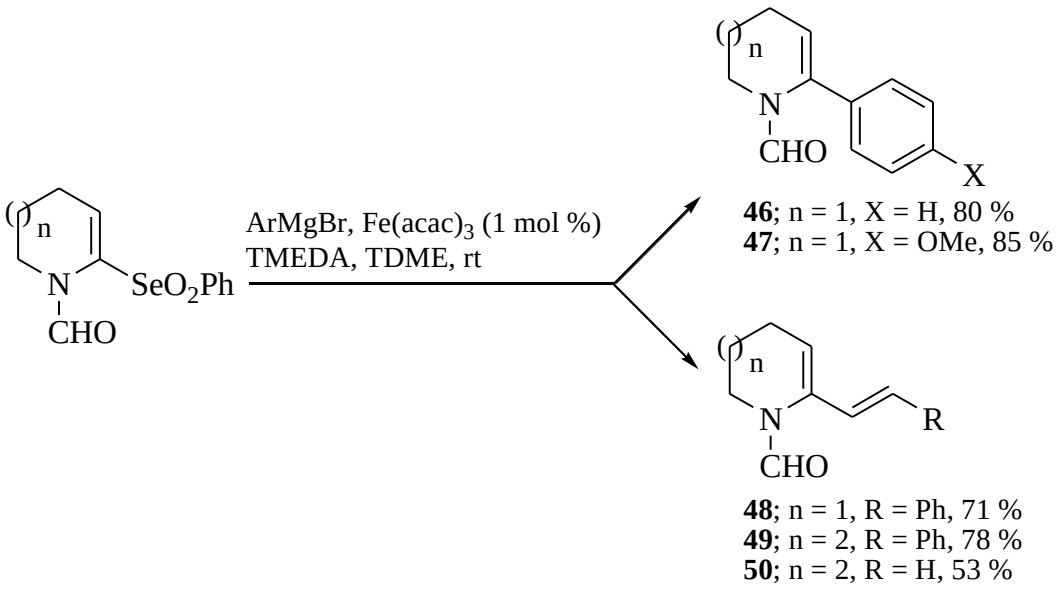
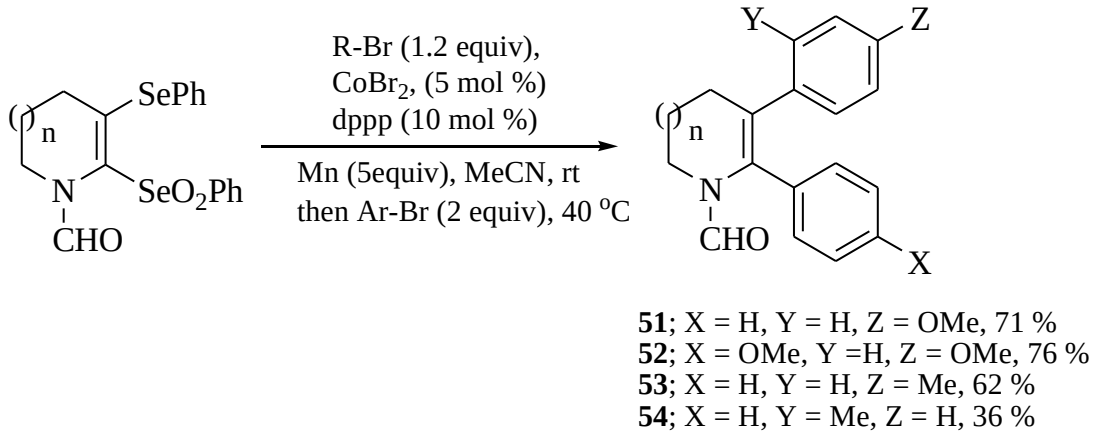


Figure 1-25 Select examples of the Denmark-motivated cross-coupling

After utilizing Comins-directing lithiation/trapping we were able to utilize the new α-selenonyl and β-selenyl functional handles to add aryl groups in a selective manner to both the C2 and C3 positions (Figure **1-26**). In order to add two different substituents this undoubtedly takes advantage of the reactivity difference between the α-selenonyl and β-selenyl requisite groups. Additionally, for the C3 functionalization to occur the reaction mixture needed to be heated to 40 °C. This strategy allowed for a wide range of aryl, allyl, alkenyl compounds to be added and allowed for quick and efficient access to bis-functionalization of the C2 and C3 positions.[38]



51; X = H, Y = H, Z = OMe, 71 %
52; X = OMe, Y =H, Z = OMe, 76 %
53; X = H, Y = H, Z = Me, 62 %
54; X = H, Y = Me, Z = H, 36 %

Figure 1- 26 Select examples of *bis*-functionalization utilizing α-selenonyl and β-selenyl requisite groups

1.5 Statement of Purpose

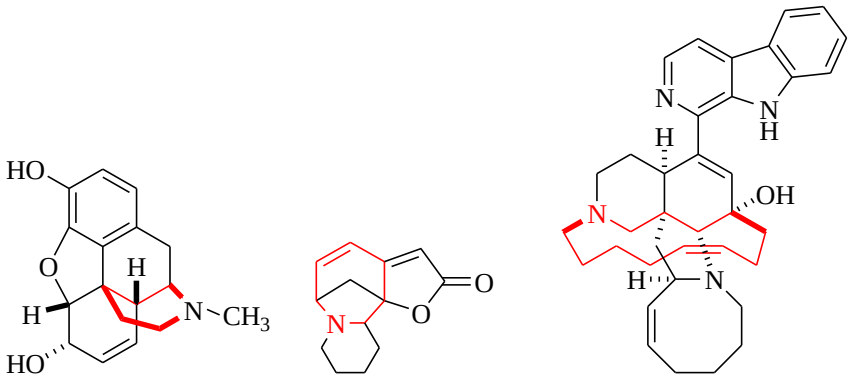
- Extension of the scope of reactivity of cyclic α-halo eneformamides to other ring sizes, especially macrocycles.
- Demonstration of the synthetic utility of α-substituted eneformamides through the preparation of quaternary propargylic and homallylic cyclic amines
- Synthesis of dihydro-1,4-oxazines, thiazines and their synthetic applications

CHAPTER 2

EXTENDING THE SCOPE OF REACTIVITY OF CYCLIC ALPHA-HALO ENEFORMAMIDES TO OTHER RING SIZES, ESPECIALLY MACROCYCLES

2.1 Introduction

As previously discussed, azaheterocycles make up the backbone of many FDA approved pharmaceuticals. Specifically, functionalized piperidines, azepanes, and aza-cyclotridecanes are found to make up the backbone of a large number of those pharmaceuticals and have been found to have a significant variety of biological activity. Shown in Figure **2-1** are select examples of pharmaceuticals or biologically active compounds containing these important structural backbones, including morphine (a well-known opiate containing a piperidine backbone), securinine (a therapeutic for primarily neurological-related diseases containing an azepane backbone), and manazamine A (a 13-membered aza-macrococyclic compound derived from sea sponges being tested for anti-cancer and anthelmintic properties).



Morphine Securinine Manzamine A

Figure 2-1 Representative piperidine, azepane, and azamacrocycle alkaloids

Commonly employed strategies to access these highly functionalized piperidines and azepanes found in these pharmaceuticals is through the use of enamides or enecarbamates. These enamide and enecarbamate precursors provide many advantages to

accessing a variety of functionalized azaheterocycles.[39-44] Specifically, the double bond corresponding to the enamide or enecarbamate on pyrollidines and piperidines has been utilized for oxidation and reduction reactions[43, 45] and has been used in carbon-carbon bond formations. The double bond has also been used in several cross-coupling reactions utilizing a functional handle at the C2 position such as vinyl triflates,[46, 47] vinyl phosphates,[31] or stannanes.[32] It has also been shown that access to C3 functionalization can be achieved through the use of Lewis acids or by the use of palladium,[29, 42] iridium,[48] or iron[44] cross-coupling strategies.

With this in mind, we recognized that these cross-coupling strategies provide the best way to access highly functionalized azaheterocycles, particularly when attempting to functionalize the C2 and C3 positons. Synthetic strategies to functionalize the C2 and C3 positions are highly sought after as they offer access to several substitution patterns found in many pharmaceuticals such as compounds in Figure **2-1**. We also wanted to seek a synthetic route that could be utilized in different ring systems. As we stated, there has been a variety of work done on 5-, 6-, and 7-membered ring systems. As a complement to the previously reported tactics, we wanted to find a synthetic strategy that could be used for a large variety of ring systems including *N*-macrocycles. We however recognize that increasing ring size can be a challenging and frustrating task given that increasing the ring size increases reactivity yet decreases stability and imposes conformational constraints.

Prior to our work, it has been shown by Occhiato, Coudert, and Sulikowski that cross-couplings can be done using vinyl triflates,[46] vinyl phosphates,[31] and α-iodo enecarbamates[49] as functional handles with the use of metalated coupling reagents

(Figure **2-2** top). However, the authors noted that these enecarbamates were not stable and thus required the use of highly reactive metalated coupling reagents.[46, 49] Since the compounds are so unstable, the reaction conditions must be chosen carefully because under many cross-coupling conditions these enecarbamate derivatives are prone to ring-opening.[46] This led us to find a more efficient bench stable methodology. Although enecarbamates and enamides are highly useful precursors for more functionalized azaheterocycles, their lack of stability and proneness to ring opening makes them less practical and less appealing as synthetic intermediates.

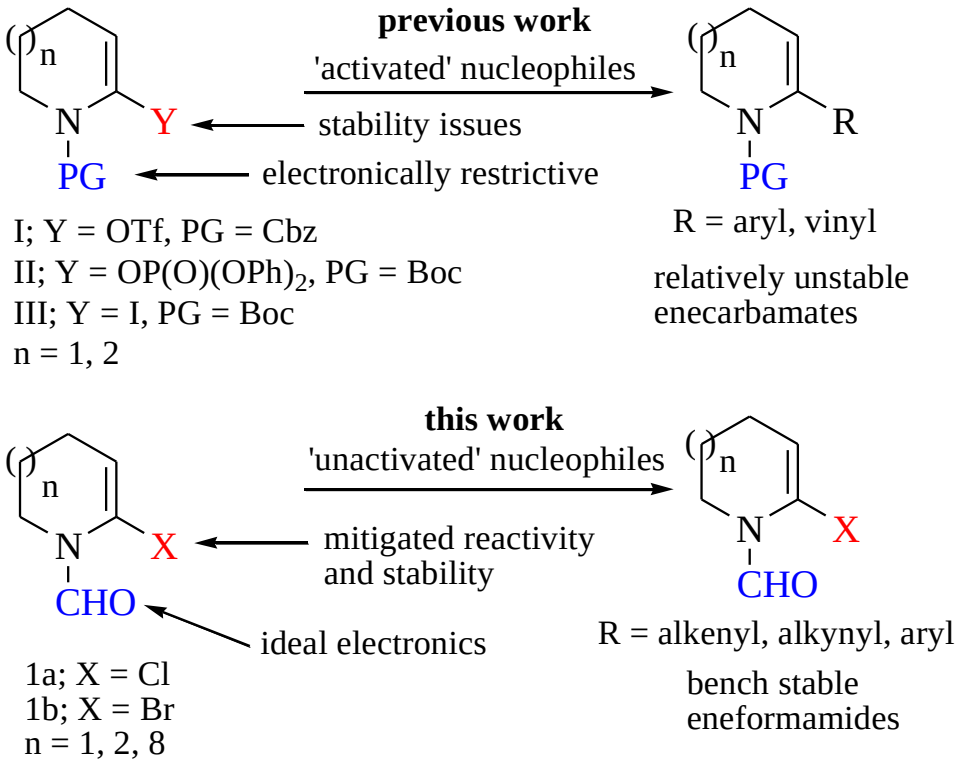


Figure 2-2 Comparison of previous C2 functionalization strategies to our work

The need for a more cost-effective, bench-stable, and modular precursor has led us to our highly coveted cyclic α-halo eneformamides. The cyclic α-halo eneformamide allows easy access to C2 and C3 functionalization to afford highly functionalized

piperidines, azepanes, and aza-macrocycles. The use of cyclic α-halo eneformamides stands above other methodologies in many ways. The cyclic α-halo eneformamides provide several advantages over the competition as they can be coupled with nonmetalated alkenes which eliminates the need to use toxic reagents such as stannanes, and eliminates the need for vinyl boronic acids/esters which are costly and unstable.

Another added advantage to the use of cyclic α-halo eneformamides is their cost-effectiveness and ability to be generated in one step from a simple lactam precursor as opposed to the several steps required by the previously employed tactics[31, 46] shown in Figure **2-2**. This allows for quick access to cyclic α-halo eneformamides where the functional handle at the C2 position and the ring size are modular. This has allowed us to access cyclic α-halo eneformamides with ring sizes of 6, 7, and 13, synthesized from valerolactam, caprolactam, and laurolactam, respectively. The unique balance of stability and reactivity has allowed us to employ a wide range of coupling strategies, such as Heck, Suzuki, and Sonagashira cross-couplings in a cost-effective, scalable, and highly modular diversity-oriented approach.

2.2 Results and Discussion

2.2.1 Synthesis of 6-, 7-, and 13-membered cyclic α-halo eneformamides

Having previously demonstrated that a Vilsmeier-Haack reaction could be used to make a 7-membered cyclic α-halo eneformamide from caprolactam[35] we decided to expand this reaction to the 6- and 13-membered rings. The 6- and 13-membered cyclic α-halo eneformamides were synthesized using the same conditions as the ones used to make the 7-membered cyclic α-halo eneformamide only using valerolactam and laurolactam respectively (Figure **2-3**). We recognize the reactivity trends between these

ring systems are very unpredictable and it turned out that extending the Vilsmeier-Haack reaction to different ring systems was a daunting task. At first glance we expected that as we increased ring size, reactivity would increase and thus reaction time would in theory decrease. However, this was not the case. Our studies have revealed that when increasing the ring size from 6 to 7, reaction times do decrease (see **2b** vs **2d**). However, when going from the 7- to the 13-membered ring system the reaction time goes from 3 hours to 3 days (see **2e**). This is probably a reflection of the conformational differences and entropic costs associated with the ring systems. The 13-membered ring is so large that the reaction probably takes more time due to steric hindrance and the need to orient itself in the proper conformation. All that said, we were able to extend the Vilsmeier-Haack reaction to both the 6- and 13-membered ring systems as well as change the functional handle at C2 to either chlorine or bromine (see **2a-d**). It is also worth mentioning that this chemistry can be further extended to attach an iodo group instead of chlorine or bromine by simply using phosphorus oxyiodide instead of its chlorine or bromine variants. This is important as it allows us to increase the reactivity of the functional handle as going from chlorine, to bromine, to iodide increases the leaving ability of the functional handle, therefore allowing for coupling with less reactive partners. The reaction is highly scalable as exemplified by the fact that we can seamlessly prepare **2e** in >100 mmol scale. Since Vilsmeier-Haack reactions with lactams of type **1** are notoriously promiscuous, from the standpoint of regioselectivity *(i.e. N- vs. C*-formylation),[50] it is quite impressive that **2a-e** are obtained in high efficiency and site selectivity. Both efficiency and selectivity are maximized when the Vilsmeier-Haack reagent is generated under refluxing conditions prior to slow introduction of **1**. In the case of laurolactam, we

have found that the reaction can be arrested at the stage where novel chloro eneformamidinium ion **A** predominates. This is noteworthy given that **A** is an acyclic diamino carbene (ADC) surrogate.

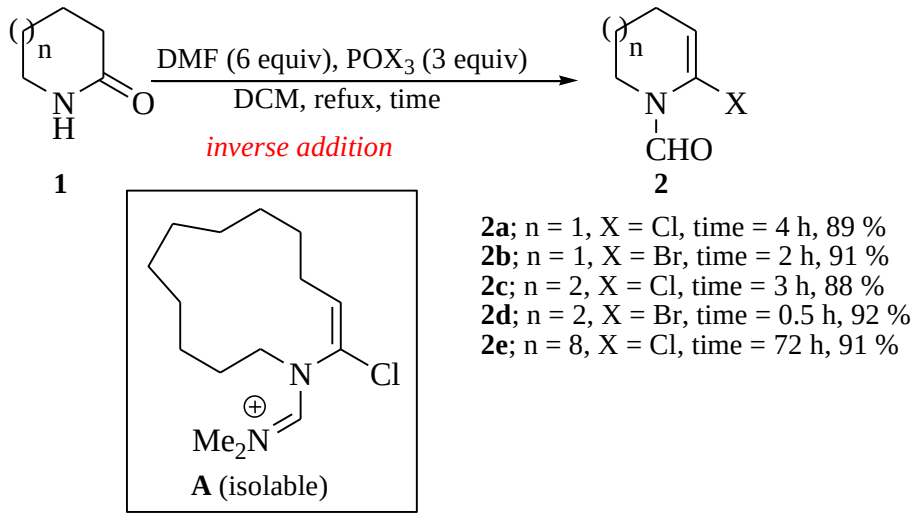


Figure 2-3 Synthesis of 6-, 7-, and 13-membered cyclic α-halo eneformamides

Transition metal-catalyzed cross-coupling reactions, especially those employing traceless activation groups (*e.g.*, cuprates) have revolutionized almost all areas of chemical synthesis.[51, 52] However, efforts toward improving cost, versatility, and operational simplicity of these methods continually necessitate the development of simple protocols that rely on feedstock organic, native functionality such as *chlorides* as requisite handles for uniting complex fragments.[53-58] Of greater appeal to the synthesis community is the prospect of utilizing these cheap and readily available organic chlorides together with unactivated nucleophiles, given that this beneficially obviates the need for preactivation.

As part of a systematic scaffolding approach aimed at exploiting the versatility of cyclic α-halo eneformamides such as **2** (Fig. **2-3**) in synthesis,[59-61] and seeking to achieve C-2 and C-3 functionalization of *N*-containing macrocycles, it was surmised that cross-

coupling reactions featuring cyclic chloro eneformamide **2e** offered a resplendent platform. Using the small, electronegative formyl group as a directing/protecting group and the chlorine atom at C-2 as a functional handle, we envisioned that **2e** would be amenable to conventional cross-coupling manifolds (*e.g.*, Sonogashira,[62] Heck,[63-65] and Suzuki[66-70]). Having collaboratively achieved partial success on the azepene[59] and dehydropiperidine[60] scaffolds, and in lieu of unsuccessful attempts to functionalize the azetidine and pyrrolidine homologues of **2e**, it became even more obvious to us that extending reactivity trends from one *N*-heterocycle to another can be quite daunting and at times foolhardy. Nevertheless, we stoically embraced the challenge of exploring the amenability of *potentially fragile* macrocyclic chloro eneformamide **2e** to C-2/C-3 functionalization protocols. Primarily due to the substantial enthalpic and entropic costs associated with the formation of large rings,[71, 72] efficient construction and functionalization of nitrogen-containing macrocycles such as azacyclotridecanes[73] have unsurprisingly posed a greater challenge to the synthesis community than have the corresponding medium ring congeners such as the azepane-,[59, 74] piperidine-,[75-86] and pyrrolidine- motifs.[87-91] Nevertheless, the architectural complexity of these functionalized large ring *N*-heterocycles and their prevalence in natural products, pharmaceuticals, materials, fragrances, ligands, and catalysts continue to inspire the development of increasingly more efficient strategies for their construction and functionalization.

We further recognized that successful implementation of our ideals would not only provide expedient access to differentially functionalized azacyclotridecanes, but increase the 3D-chemical space for the discovery of new *N*-macrocycles with medicinal value. Furthermore, these eneformamide precursors and products represent excellent

synthetic intermediates for a diverse range of transformations since they bear latent functionality at the α and β positions. For example, they may be engaged in hydrogenation,[92] cyclopropanation,[93] halogenation,[94] amination,[95] aminoxylation,[96] alkylboration,[97] hydroarylation,[98] hydroallylation,[99] oxo-amination,[100] trifluoromethylation,[101] hexannelations,[102] or allylic functionalization protocols.[103]

2.2.2 α-alkenylation of 13-membered cyclic α-chloro eneformamides

Vinylated piperidines, azepanes, and azamacrocycles are highly desired compounds because they offer the ability to be used in the construction of highly sought-after pharmaceuticals**.** Specifically, these vinylated precursors can be used as dienes in hexannelations en-route to creating fused polycyclic compounds such as those in Figure **2-1**. It has been previously reported that alkenylation of enamides at C2 can be done by using palladium-catalyzed Heck type conditions and alkenylations at C3 were possible under Fujiwara−Moritani[104, 105] type conditions. This led Sarpong and one of us[35] to optimize these conditions for the use of the 7-membered cyclic α-halo eneformamides. Using similar conditions, we have now expanded this chemistry to the 13-membered ring system (Figure **2-4**). Using these reported optimized conditions we decided to explore the limitations of the coupling partner with the 13-membered cyclic α-halo eneformamide.

We began to explore the alkene coupling partners with our cyclic α-halo eneformamide **2e** to create the diene **3a**. We explored several types of coupling partners that included electronically diverse monosubstituted acyclic alkenes. We discovered similar limitations to those experienced by Sarpong[35] and others with Heck type coupling reactions. The reaction occurs faster with better yield when the alkene coupling partner is electron rich (see **3a1-5**) compared to that of its electron poor counterpart such as **3a6**.

This is likely due to the electron withdrawing alkene affecting the oxidative-addition step in the catalytic cycle.

When allyl bromide is employed as the alkene coupling partner, the reaction proceeds with double-bond isomerization and concomitant expulsion of the bromide, thus, affording allylated eneformamide **3a7**. Other leaving group bearing allyl coupling partners such as allyl acetate fail to furnish **3a7**, thus emphasizing the importance of the bromide in generating π-allyl complexes.

To further investigate the reactivity trends from the 6- to 7- to 13-membered eneformamide we decided to see if we could couple the eneformamides together. In the case of the 6 and 7-membered rings they were both able to couple together creating a mixture of reduced and oxidized compounds (see **3a10/11** and **3b10/11**). This is due to the elimination of chlorine generating one double bond and the 1,4-elimination of palladium causing one of the eneformamides to have two double bonds (see **3a12-14**). The mixture can be converged through chemoselective hydrogenation (using H_2/Pd) for the isolated double bond in the presence of the eneformamide double bond. This facilitated characterization of the homo-coupled product of the six membered eneformamide (Sarpong[59] group had already shown the case of the 7-membered variant). Once we established that the 6 and 7 membered rings were able to successfully homo-couple and the 13-membered did not, we wanted to provide further evidence of their reactivity. To do this, we placed the 13-membered and 6-membered together and the 13-membered and 7-membered eneformamides together under the same coupling conditions and only saw homo-coupling of the 6- and 7-membered ring systems (see **3a8/9**). We then placed the 6 and 7-membered eneformamides together and saw primarly homo-

coupling of the 7-membered over the 6. This further established that the reactivity trend of the 7-membered is faster than the 6, which is faster than the 13.

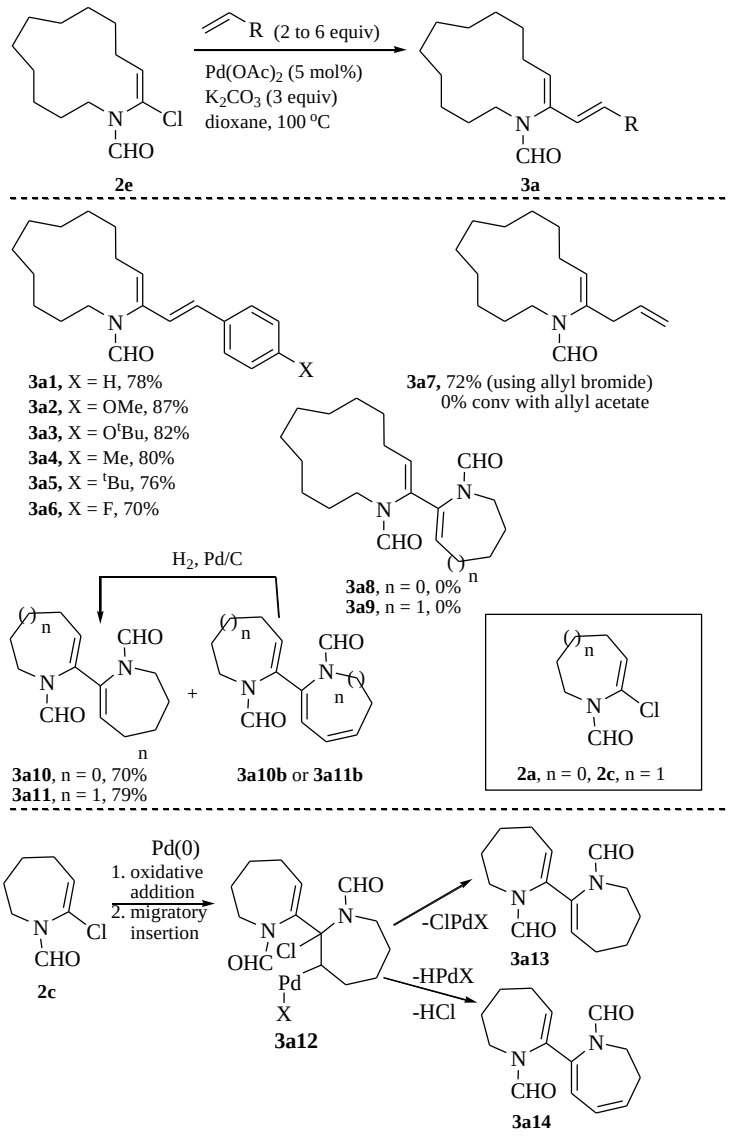


Figure 2-4 Alkenylation of macrocyclic α-chloro eneformamide **2e**

2.2.3 α-Arylation of 13 membered cyclic α-chloro eneformamides

After amply demonstrating that congruent with its azepane congener, **2e** undergoes productive Heck alkenylation, it was of interest to evaluate its performance in

Suzuki cross-coupling under conditions analogous to those popularized by Sarpong.[35] Using similar conditions, we surveyed several aryl coupling partners (Figure **2-5**). We investigated electron-rich, electron-poor, sterically demanding, and heteroaryl π-excessive and π-deficient substituents to test the limitations of the reaction conditions and the 13-membered cyclic α-halo eneformamide as opposed to its 7-membered counterpart.

Similar to the vinylation cross-couplings, we see a trend matching that of the 7-membered cyclic α-halo eneformamide. However, as was the case with the vinylations, the reaction times with the 13-membered cyclic α-halo eneformamide are significantly slower than the reaction times for the 7-membered cyclic α-halo eneformamide. The reaction proceeds much faster and more efficiently if the coupling partner is electron rich (**3b3**) as opposed to if the coupling partner is electron neutral **3b1** or electron poor **3b4**. We also tested to see if sterics would play a role by using a sterically demanding naphthyl group (**3b2**) and got relatively good yields in comparison to a smaller phenyl group **3b6**. We also compared heteroaryl π-deficient and π-excessive groups **3b5 vs. 3b6** and saw that π-excessive groups **3b5** react more efficiently and much faster than π-deficient groups **3b6**.

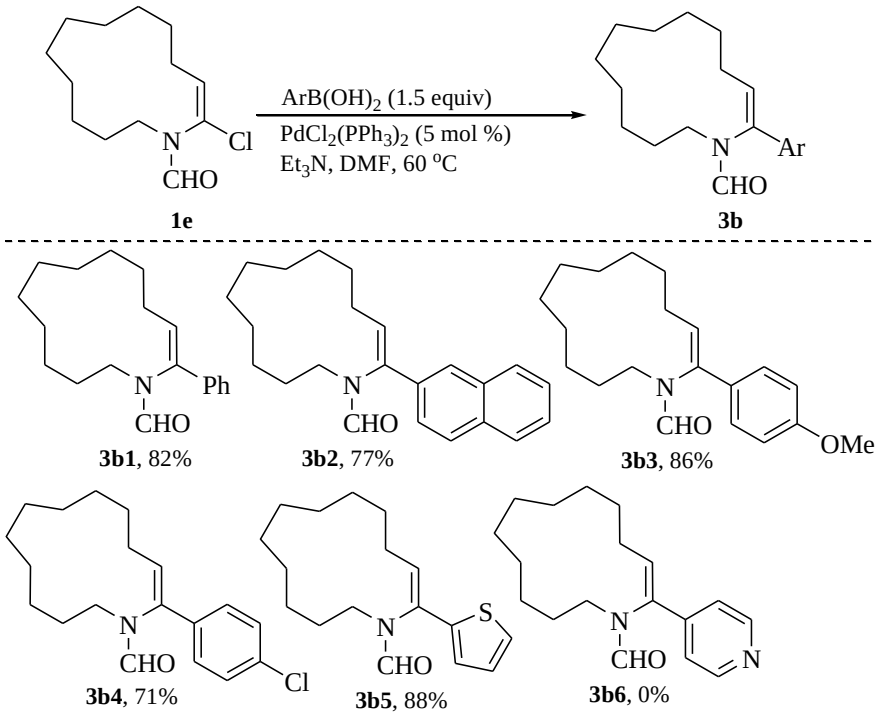


Figure 2-5 Arylation of 13-membered cyclic α-halo eneformamide **2e**

2.2.4 α-alkynylation of 6-, 7-, and 13-membered cyclic α-halo eneformamides

To further investigate the utility of our cyclic α-halo eneformamide, we investigated the possibility of synthesizing α-alkynyl azacyclotridecenes under Sonagashira cross-coupling conditions[106] (Figure **2-6**). In the event, all three cyclic α-chloro eneformamides were coupled with a variety of terminal alkyne coupling partners. Several different alkynes were used, ranging from electron rich to electron poor. To no surprise **2e** coupled slower than the 6- or 7-membered counterpart. In many cases, the 6- and 7-membered rings could undergo alkynylation at room temperature, whereas **2e** required temperatures as high as 60 °C. Electron withdrawing groups **3c21-26** were also slow to react for all ring systems and required heat of up to 40 °C. Conversely electron neutral **3c7-9, 3a13-20** and electron rich groups **3c10-12** proceeded much faster with better yields. This comes as no surprise, as with the use of palladium-catalysts, electron-

poor coupling partners have shown low reactivity and low yields for all three types of coupling reactions investigated, which corresponds to the results found by Sarpong's[35] group when they investigated the 7-membered cyclic α-halo eneformamides. Silyl-bearing acetylenes are well tolerated (see **3a4-6** and **3c1-3**). This is noteworthy since they are easily removable, thus allowing for late-stage diversification. Additionally, in the case of the tethered alkynes **3a21-26**, only the 4-, 5-, and 6-membered tethers can be purchased commercially so the use of the TMS or TIPS leaving groups afford the opportunity to attach longer tethers which can then be used to create aza-polycyclic enynes.

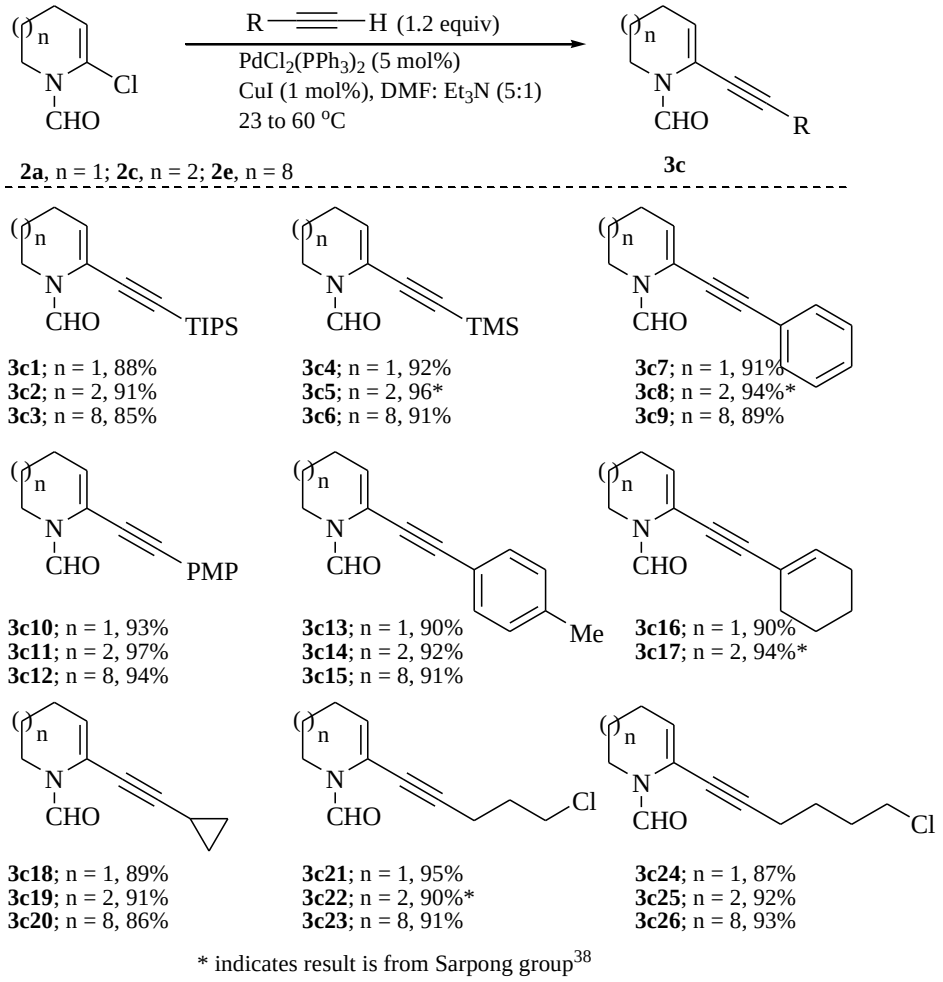


Figure 2-6 Alkynylations of 6-, 7-, and 13-membered cyclic α-chloro eneformamides

2.2.5 Oxo-halogenation of α-chloro eneformamides

The ability to achieve vicinal heterodifunctionalization of alkenes is an important yet challenging transformation that has gained an extensive amount of attention from the organic synthetic community, as it provides considerable access to a wide range of natural products and pharmaceuticals. Surprisingly, there is very little literature on methods to achieve vicinal heterodifunctionalization of vinyl chlorides. Thus, we decided to build on the lone example reported by Sarpong and one of us. Pleasingly, **2e** successfully undergoes *N*-halo succinimide-mediated oxo-iodination, oxo-bromination, and oxo-chlorination to give the vicinally heterodifunctionalized *N*-protected α-halogenated lactams depicted in .Fig. **2-7** This is noteworthy as it only takes two steps to undergo this transformation, the Vilsmeier-Haack reaction followed by oxo-halogenation versus many conventional approaches to α-halo lactams take considerably more steps and are rather inefficient.[107] Important to note, reaction times go considerably faster when using *N*-iodo succinimide compared to N-bromo succinimide compared to N-chloro succinimide. This is expected as the reactivity of the halogen increases from chloro to bromo to iodo leaving groups.

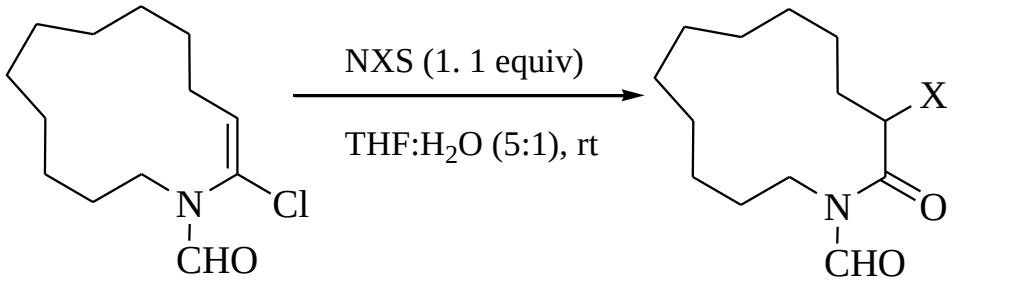


Figure 2-7. Oxo-halogenation of α-chloro eneformamide **1e**

2.3 Conclusion

In conclusion, palladium-catalyzed Heck, Suzuki, and Sonogashira cross-coupling conditions have been employed to alkenylate, arylate, and alkynylate the α-position of the lactam-derived 6, 7, and 13 membered cyclic α-halo eneformamides. Similar trends were noticed with electron poor and electron rich coupling partners for each type of coupling on each ring system. Additionally, we were able to achieve vicinal heterodifunctionalization using *N*-halo succinimide-mediated oxo-halogenation with chloride, bromide, and iodide as the halogens to construct *N*-protected α-halogenated lactams. The 13-membered cyclic α-halo eneformamides reacted slower than the 6 which was slower than the 7 showing that reactivity trends with different size ring systems can be difficult to predict. The stage has now been set for the synthesis of complex *N*-heterocycles using the current strategy, as described in the subsequent chapter.

2.4 Methods

All experiments involving palladium precatalysts were carried out under an inert atmosphere of argon or nitrogen. Et_3N, MeOH, THF, benzene, toluene, Et_2O, and acetonitrile were distilled using the Grubbs solvent system. Anhydrous DMF and 1,4-dioxane were used as purchased. Dichloromethane was distilled from $MgSO_4$. NaTFA, K_2CO_3, CuI, $NaBH_3CN$, and the boronic acids were used as purchased. The concentration of commercial *n*-BuLi (solution in hexanes) was determined prior to use by No-D NMR spectroscopy.[108] All alkenes and alkynes were newly purchased and used without further purification. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by staining with CAM, *p*-anisaldehyde,

or $KMnO_4$. Unless otherwise indicated, ^1H, ^{13}C, DEPT-135 NMR spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). [34, 38, 59, 109-112]

2.4.1 General procedure A: synthesis of 2-halo enamides

The corresponding phosphorus oxyhalide (30 mmol, 3 equiv) dissolved in CH_2Cl_2 (18 mL) was added dropwise to a solution of DMF (60 mmol, 6 equiv) in CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture (pale yellow in the case of the chloride or milky white in the case of the bromide) was refluxed for 20 min. A solution of caprolactam (10 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was stirred under reflux for the indicated time period (TLC and LC-MS monitoring was used to followed the extent of the reaction). Upon completion, the mixture was allowed to warm to room temperature and then poured into a large flask containing crushed ice. After stirring at rt for 30 min, the layers were separated. Powdered K_2CO_3 was added slowly to the mixture and the flask was swirled after each addition (***Caution***: it bubbles vigorously). The addition/swirling was continued until persistent cloudiness was observed. The neutralized/slightly basic mixture was extracted three times with CH_2Cl_2. The combined organic layer was concentrated to ~100 mL and was dried over Na_2SO_4 for 30 min. The mixture was filtered and concentrated under reduced pressure to give the desired product as an oil. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). *Caution: The 2-haloenamides are bench stable at room temperature for days but should be stored in the refrigerator either neat or as a solution in benzene.*[34, 38, 59, 109-112]

2.4.2 General procedure B: Heck coupling of 2-halo enamides with unactivated alkenes

The 2-halo enamide (1 mmol, 1.0 equiv) in DMF (2 mL, 0.50 M), $Pd(OAc)_2$ (5 mol%), additive (1 to 2.0 equiv), alkene (2 to 6 equiv) was added to an oven-dried, septum-capped vial equipped with a stir bar under a nitrogen atmosphere. The mixture was then stirred at 80 ^oC for the desired length of time (as indicated by TLC and LC-MS, usually 1 h). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~10 mL and dried for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica eluting with hexane/EtOAc. ***Note***: 1 equiv NaTFA or 2 equiv of K_2CO_3 were employed. With dioxane as the solvent, longer reaction times (monitoring by TLC and LC-MS, usually 2 h) are required. [34, 38, 59, 109-112]

To a solution of cyclic enol ether (1 equiv), palladium diacetate (0.1equiv) and silver acetate (2.5 equiv) in DMF and DMSO (10:1) at 80 °C, under open air condition was added the cycloalkene (1.5 equiv) drop wise. The mixture was allowed to stir at 80 °C for 24 h. Then the mixture was diluted with ethyl acetate (2 mL), filtered, washed with water (5 mL) and brine (5 mL). The organic layer was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc) (6:1) to afford the product as an oil. [34, 38, 59, 109-112]

2.4.3 General procedure C: Suzuki coupling of 2-halo enamides with boronic acids

The 2-halo enamide (1 mmol, 1.0 equiv) in DMF (5 mL) was added to an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar under nitrogen atmosphere. The desired boronic acid (1.2 equiv) was added followed by addition of Et_3N

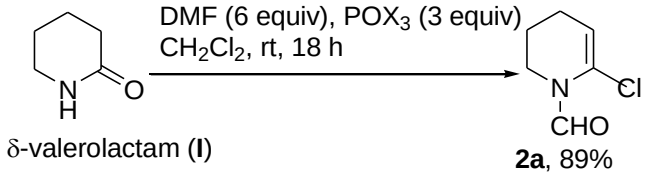
(0.7 mL, 5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) was added rapidly. The mixture was then stirred at the desired temperature for the desired length of time (as indicated by TLC and LC-MS). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~20 mL and and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc. [34, 38, 59, 109-112]

2.4.4 General procedure D: Sonogashira coupling of 2-halo enamides with terminal alkynes

The 2-halo enamide (1 mmol, 1.0 equiv) in DMF (5 mL) was added to an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar under nitrogen atmosphere. The desired alkyne (1.2 equiv) was added followed by addition of Et_3N (0.7 mL, 5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) and CuI (2 mg, 1 mol%) were added rapidly and concurrently. The mixture was then stirred at the desired temperature for the desired length of time (as indicated by TLC and LC-MS). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~20 mL and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica eluting with hexane/EtOAc. ***Note***: The coupling can be performed in the absence of CuI but longer reaction times (monitoring by TLC and LC-MS) are required. [34, 38, 59, 109-112]

2.5 Peak Assignments

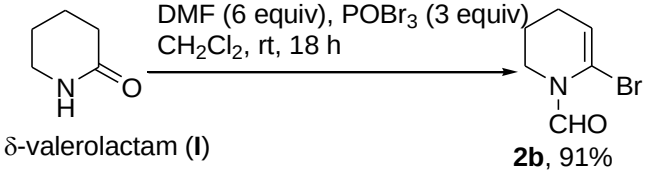
*2.5.1 Peak assignment of **2a***



δ-valerolactam (**I**) **2a**, 89%

Prepared using **General Procedure A**. Valerolactam (991.3 mg, 10 mmol), $POCl_3$ (4.6 g, 2.8 mL, 30 mmol), DMF (4.63 mL, 60 mmol), Temp = 40 ^oC, time = 4 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 1310 mg, 89%. Spectroscopic data as previously reported by us. [109]

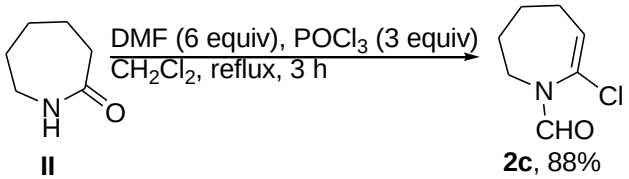
*2.5.2 Peak assignment of **2b***



δ-valerolactam (**I**) **2b**, 91%

Prepared using **General Procedure A**. Valerolactam (991.3 mg, 10 mmol), $POBr_3$ (8.6 g, 30 mmol), DMF (4.63 mL, 60 mmol), Temp = 40 ^oC, time = 2 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 1730 mg, 91%. Spectroscopic data as previously reported by us. [109]

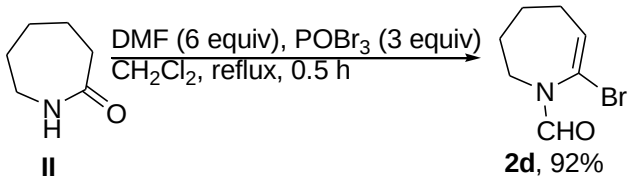
*2.5.3 Peak assignment of **2c***



II **2c**, 88%

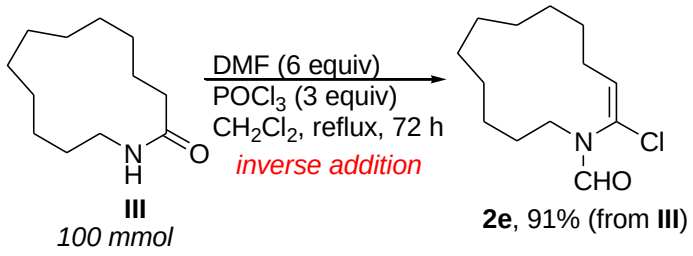
Prepared using **General Procedure A**. Caprolactam (1131.6 mg, 10 mmol), $POCl_3$ (4.6 g, 2.8 mL, 30 mmol), DMF (4.63 mL, 60 mmol), Temp = 40 ^oC, time = 3 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 1408 mg, 88%. Spectroscopic data as previously reported by us.[109]

*2.5.4 Peak assignment of **2d***



Prepared using **General Procedure A**. Caprolactam (991.3 mg, 10 mmol), $POCl_3$ (4.6 g, 2.8 mL, 30 mmol), DMF (4.63 mL, 60 mmol), Temp = 40 ^oC, time = 0.5 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 1877 mg, 92%. Spectroscopic data as previously reported by us.[109]

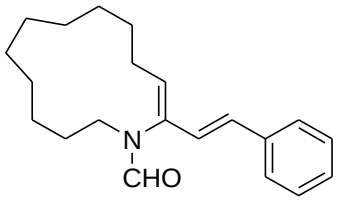
*2.5.5 Peak assignment of **2e***



Prepared using **General Procedure A**; Laurolactam **III** (11.3 g, 100 mmol), $POCl_3$ (46 g, 28 mL, 300 mmol), DMF (46.3 mL, 600 mmol), Temp = 40 ^oC, time = 72 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with

hexane/EtOAc (80:20).Yield = 22100 mg, 91%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 8.13 (s, 1H). 5.10 to 4.99 (t, 1H), 3.64 to 3.57 (t, 2H), 2.09 to 1.04 (m, 18H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.3, 130.9, 128.0, 128.0, 127.7, 127.5, 40.1, 28.1, 27.5, 26.6, 26.6, 26.5, 25.5, 25.0, 24.8, 24.2, 23.3. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{13}H_{22}ClNO$ 243.1390; found 243.1395.

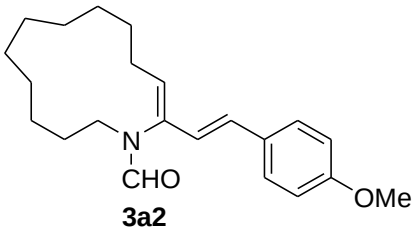
*2.5.6 Peak assignment of **3a1***



3a1

Prepared using **General Procedure B. 2e** (1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), and styrene (0.46 mL, 4 mmol, 4 equiv), (1.5 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 100 ^{o}C, time = 1 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 243 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 & 8.02 (1H, ss, major & minor rotamers)), 7.52 to 7.22 (5H, m), 6.98 to 6.94 (1H, d, major rotamer), 6.69 to 6.65 (1H, d, minor rotamer), 6.51 to 6.35 (1H, both rotamers), 5.65 to 5.61 (1H, t, both rotamers), 3.65 to 3.51 (2H, t, both rotamers), 2.42 to 2.25 (2H, t, both rotamers), 1.78 to 1.22 (16H, m, both rotamers). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 163.3, 138.4, 138.2, 137.0, 136.4, 136.3, 135.6, 134.8, 133.7, 131.3, 130.1, 129.2, 129.1, 128.8, 128.8, 128.7, 128.6, 128.3, 128.0, 127.9, 127.6, 127.0, 126.9, 126.8, 126.5, 126.5, 126.4, 120.7, 119.6, 44.4, 42.7, 26.5, 26.3, 26.1, 26.6, 26.0, 25.8, 25.8, 25.7, 25.7, 25.4, 25.1, 25.0, 24.9, 24.7, 24.2, 23.9, 23.7, 23.4. HRMS calc for $C_{21}H_{29}NO$ 311.2249, found 311.2255.

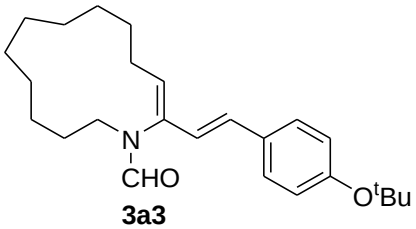
*2.5.7 Peak assignment of **3a2***



3a2

Prepared using **General Procedure B. 2e** (159.6 mg, 1.0 mmol) $Pd(OAc)_2$, (11.5 mg, 5 mol%), and 4-methoxystyrene (1.5 equiv), (1.5 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 90 ^oC, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (27:75). Yield = 297 mg, 87%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, s,s, minor & major), 7.33 to 7.31 (2H, d,d), 6.87 to 6.85 (2H, d), 6.56 to 6.46 (1H, d), 6.30 to 6.23 (1H, d), 5.62 to 5.58 (1H, t), 3.79 to 3. 58 (5H, m), 2.38 to 2.24 (2H, m), 1.63 to 1.25 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 159.8, 139.3, 138.5, 137.2, 136.2, 135.1, 134.6, 133.2, 132.5, 130.8, 130.8, 129.8, 128.1, 127.9, 127.8, 127.7, 127.3, 127.7, 127.2, 126.9, 124.9, 123.3, 119.6, 115.5, 114.2, 55.4, 55.3, 43.1, 42.7, 30.6, 29.7, 29.5, 29.4, 28.7, 28.3, 28.5, 27.4, 27.1, 26.9, 26.8, 26.7, 26.6, 26.5, 26.5, 26.3, 26.1, 26.0, 25.8, 24.6, 23.3, 23.8, 23.7, 23.2. HRMS calc for $C_{22}H_{31}NO_2$ 341.2355, found 341.2351.

*2.5.8 Peak assignment of **3a3***

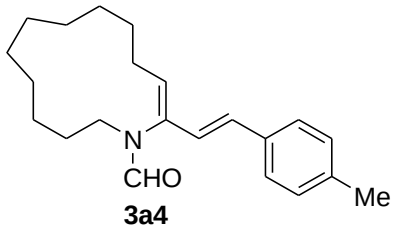


3a3

Prepared using **General Procedure B. 2e** (159.6 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), and 4-*tert*-butoxystyrene (1.5 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv),

DMF (5 mL), Temp = 100 ^{o}C, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 314.1 mg, 82%. 1H NMR (400 MHz, CDCl3) δ 8.17 (1H, s,s, minor & major), 8.21 to 7.28 (s, 1H), 7.42 to 7.28 (d, 2H), 6.82 to 6.22 (m, 1H), 3.68 to 3.37 (T, 2H), 2.61 to 2.02 (m, 2H), 2.00 to 1.02 (m, 16H). 13C NMR (101 MHz, CDCl3) δ 162.8, 158.2, 138.2, 132.5, 131.4, 130.5, 129.4, 128.9, 127.4, 126.2, 124.2, 123.1, 44.2, 42.1, 40.5, 30.6, 29.2, 28.7, 27.9, 27.4, 27.1, 26.9, 26.8, 26.7, 26.1, 25.6, 24.9, 24.7, 24.6, 24.6, 24.2, 23.9, 23.6, 23.4, 23.4. HRMS calc for $C_{25}H_{37}NO_2$ 383.2824, found 383.2827.

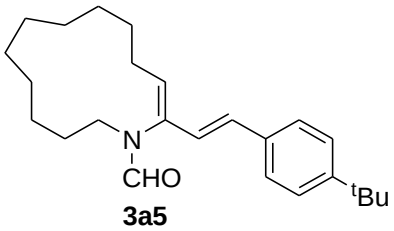
*2.5.9 Peak assignment of **3a4***



3a4

Prepared using **General Procedure B. 2e** (159.6 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), 4-methylstyrene (0.346 mL, 3 mmol, 3 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 ^{o}C, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 161.7 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28, to 8.00 (s, 1H), 7.34 to 7.10 (m, 4H), 6.96 to 6.79 (d, 1H), 6.64 to 6.30 (d, 1H), 5.69 to 5.09 (t, 1H), 3.70 to 3.36 (m, 2H), 2.62 to 1.23 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 161.9, 138.4, 138.4, 137.9, 137.1, 135.9, 133.7, 133.0, 131.2, 129.5, 129.2, 128.7, 127.1, 126.7, 124.6, 123.9, 119.7, 48.1, 44.3, 43.1, 42.8, 39.9, 39.3, 36.1, 29.7, 28.3, 27.9, 26.9, 26.8, 26.7, 25.0, 24.8, 23.9, 21.3, 21.3, 21.1. HRMS calc for $C_{22}H_{31}NO$ 325.2416, found 325.4915.

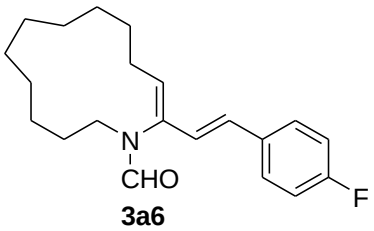
*2.5.10 Peak assignment of **3a5***



3a5

Prepared using **General Procedure B. 2e** (159.6 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), 4-*tert*-butylstyrene (0.346 mL, 3 mmol, 3 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 ^oC, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 278.9 mg, 76%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 to 8.01 (s, 1H), 7.38 to 7.26 (m, 4H), 6.95 to 6.91 (m, 1H), 6.79 to 6.34 (m, 1H), 5.69 to 5.59 (t, 1H), 3.59 to 3.02 (m, 2H), 2.59 to 1.17 (m, 27H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 151.7, 138.4, 137.1, 135.1, 133.7, 131.1, 129.1, 127.8, 125.7, 124.79, 120.5, 48.1, 44.3, 43.1, 42.7, 39.4, 34.7, 31.4, 31.3. 29.7, 28.4, 27.6, 26.8, 25.8, 24.8, 24.8, 24.7, 24.7, 24.5, 24.2, 23.9, 23.7, 23.7, 23.5. HRMS calc for $C_{25}H_{37}NO$ 367.1216, found 367.1215.

*2.5.11 Peak Assignment of **3a6***

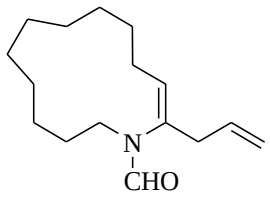


3a6

Prepared using **General Procedure B. 1a** (159.6 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), 4-fluorostyrene (0.346 mL, 3 mmol, 3 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 ^oC, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 230.3 mg,

70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 to 7.98 (s, 1H), 7.39 to 6.79 (m, 4H), 6.62 to 6.51 (d, 1H), 6.44 to 6.22 (d, 1H), 5.85 to 5.28 (t, 1H), 3.77 to 3.43 (m, 2H), 3.28 to 0.83 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 138.2, 136.8, 135.8, 134.9, 133.7, 132.1, 131.5, 130.9, 129.4, 128.0, 127.9, 126.8, 125.4, 120.5, 115.9, 48.1, 44.3, 42.7, 40.9, 39.9, 36.9, 31.5, 29.7, 28.3, 27.8, 26.9, 25.8, 25.8, 24.9, 23.9, 23.6, 23.6, 23.4. HRMS calc for $C_{15}H_{16}FNO$ 329.2216, found 329.4515.

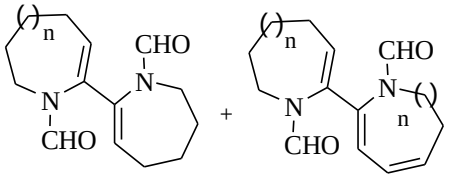
*2.5.12 Peak assignment of **3a7***



3a7, 72% (using allyl bromide)
0% conv with allyl acetate

Prepared using **General Procedure B. 2e** (159.6 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), allyl bromide (0.300 mL, 3 mmol, 3 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 ^{o}C, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 179.3 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 to 7.82 (s, 1H), 7.26 to 6.74 (m, 2H), 6.29 to 6.25 (m, 1H), 6.04 to 4.92 (t, 1H), 4.63 to 4.54 (m, 2H), 4.19 to 1.17 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 136.6, 132.9, 124.1, 117.5, 110.7, 76.7, 64.8, 43.1, 41.3, 39.9, 37.9, 36.1, 31.8, 28.2, 27.1, 26.1, 25.9, 25.3, 25.0, 24.0, 23.8, 23.7, 23.2, 23.0. HRMS calc for $C_1H_{27}NO$ 249.21, found 249.3915.

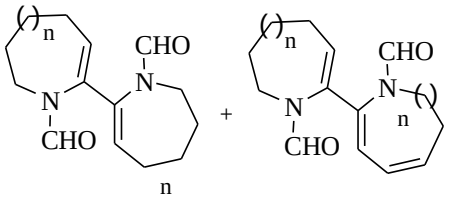
*2.5.13 Peak assignment of **3a10/3a10b***



3a10, n = 0, 70% **3a10b**

Prepared using **General Procedure B. 2a** (99.3 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), allyl bromide (0.300 mL, 3 mmol, 3 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 ^oC, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 155.7 mg, 70%. As reported by us.[109]

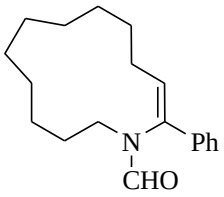
*2.5.14 Peak assignment of **3a11/3a11b***



3a11, n = 1, 79% **3a11b**

Prepared using **General Procedure B. 2a** (113.2 mg, 1.0 mmol), $Pd(OAc)_2$, (11.5 mg, 5 mol%), allyl bromide (0.300 mL, 3 mmol, 3 equiv), K_2CO_3 (138 mg, 1 mmol, 1 equiv), DMF (5 mL), Temp = 80 ^oC, time = 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 194.7 mg, 79%. As reported by us.[109]

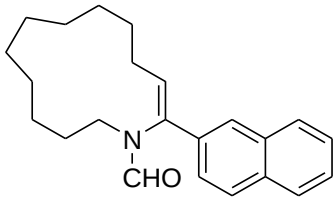
*2.5.15 Peak assignment of **3b1***



3b1, 82%

Prepared using **General Procedure C.** From **2e** (160 mg, 1.0 mmol), phenyl boronic acid (146 mg, 1.2 mmol), temp = 24 ^{o}C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 157 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.39 & 8.10 (1H, s), 7.53 to 7.22 (5H, m), 5.65 to 5.60 & 5.32 to 5.28 (1H, t, t), 3.55 to 3.23 (2H, m), 2.25 to 2.09 (2H, m), 1.70 to 1.27 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 137.5, 134.3, 129.5, 128.7, 128.5, 41.3, 28.3, 27.6, 27.5, 27.3, 27.1, 26.7, 26.4, 26.3, 26.1, 25.9, 25.7, 25.0, 24.7, 23.9, 22.9. HRMS calc for $C_{19}H_{27}NO$ 285.1154, found 285.1156.

*2.5.16 Peak assignment of **3b2***

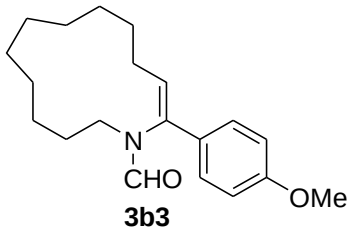


3b2

Prepared using **General Procedure C. 2e** (160 mg, 1.0 mmol), 2-naphthyl boronic acid (206 mg, 1.2 mmol) Temp = 100 ^{o}C, time = 6 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 257.9 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.53 & 8.29 (1H, s), 8.16 to 7.24 (7H, m), 5.76 to 5.67 (1H, t), 3.77 to 3.24 (2H, t), 2.25 to 2.04 (2H, m), 1.91 to 1.23 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 163.5, 162.9, 139.8,

137.6, 134.5, 133.3, 133.3, 133.1, 133.1, 131.7, 129.8, 129.4, 129.1, 128.6, 128.5, 128.5, 128.2, 128.1, 128.1, 127.9, 127.7, 127.7, 127.4, 126.7, 126.6, 126.6, 126.5, 126.4, 126.1, 126.0, 125.8, 125.8, 124.5, 122.9, 77.5, 77.2, 76.9, 44.9, 43.5, 41.5, 28.3, 28.1, 27.9, 27.8, 27.4, 27.4, 27.2, 27.0, 26.5, 26.5, 26.4, 26.0, 25.9, 25.8, 25.6, 25.2, 25.1, 24.8, 24.5, 24.4, 23.9, 23.7, 23.0, 14.3. HRMS calc for $C_{23}H_{39}NO$ 335.2210, found 335.4815.

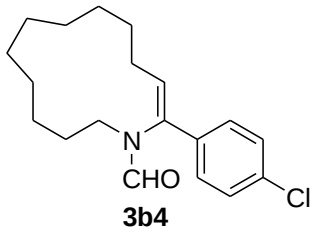
*2.5.17 Peak assignment of **3b3***



3b3

Prepared using **General Procedure C. 2e** (160 mg, 1.0 mmol), 4-methoxyphenyl boronic acid (183 mg, 1.2 mmol) Temp = 24 ^{o}C, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 203.5 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.28 & 8.17 (1H, s,s), 7.26 to 7.14 (2H, dd), 6.92 to 6.79 (2H, dd), 5.51 to 5.45 (1H, t), 3.76 (3H, s), 3.43 to 3.29 (2H, m), 2.29 to 2.06 (2H, m), 1.63 to 1.20 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 139.4, 137.2, 132.2, 130.3, 129.0, 128.7, 126.5, 116.5, 114.0, 113.8, 55.3, 47.7, 44.8, 43.2, 41.2, 40.5, 29.5, 28.3, 27.9, 26.9, 25.8, 25.8, 25.0, 24.9, 23.9, 23.6, 23.3, 22.8, 22.7. HRMS calc for $C_{20}H_{29}NO_2$ 315.2256, found 315.2255.

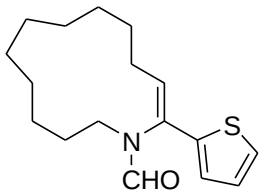
*2.5.18 Peak assignment of **3b4***



3b4

Prepared using **General Procedure C. 2e** (160 mg, 1.0 mmol), 4-chlorophenyl boronic acid (188 mg, 1.2 mmol) Temp = 24 ºC, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 165 mg, 70%. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.30 & 8.23 (1H, s,s), 7.44 to 7.11 (4H, m), 5.64 to 5.59 (1H, t), 3.54 to 3.51 (1H, m), 3.43 to 3.24 (1H, m), 2.42 to 2.05 (2H, m), 1.76 to 1.20 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 136.5, 134.8, 133.5, 132.8, 131.5, 130.9, 129.8, 128.9, 128.1, 116.8, 47.5, 46.3, 44.6, 43.3, 41.3, 40.6, 34.6, 29.7, 28.3, 27.8, 27.0, 26.4, 25.0, 24.9, 24.2, 23.9, 22.8, 22.8. HRMS calc for $C_{19}H_{26}NOCl$ 319.1759, found 319.2661.

*2.5.19 Peak assignment of **3b5***

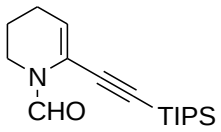


3b5

Prepared using **General Procedure C. 2e** (160 mg, 1.0 mmol), 2-thienylboronic acid (307.2 mg, 1.2 mmol) Temp = 24 ºC, time = 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 165 mg, 88%. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.33 & 8.15 (1H, s,s), 7.42 to 6.87 (3H, m), 5.87 to 5.65 (1H, t), 3.57 to 3.37 (2H, m), 2.68 to 2.03

(2H, m), 1.89 to 1.24 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 161.6, 141.5, 137.5, 134.1, 133.9, 132.2, 131.8, 131.6, 131.5, 128.4, 127.9, 127.5, 127.5, 127.3, 127.2, 126.5, 125.3, 124.9, 124.7, 124.3, 77.4, 77.1, 76.8, 48.0, 45.4, 43.9, 42.2, 28.6, 28.3, 28.3, 28.1, 27.6, 27.6, 27.5, 27.4, 27.3, 27.2, 26.7, 26.7, 26.5, 26.5, 26.4, 26.4, 26.2, 26.2, 26.1, 26.0, 25.8, 25.6, 25.5, 25.4, 25.3, 25.2, 24.9, 24.5, 24.3, 24.3, 24.1, 24.0, 23.7, 23.1. HRMS calc for $C_1H_{25}NOS$ 291.1759, found 291.4561.

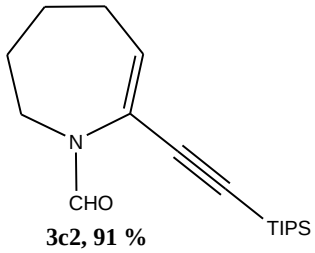
*2.5.20 Peak assignment of **3c1***



3c1, 96%

Prepared using **General Procedure D. 2a** (1.00 mmol) and triisopropyl-silylacetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 279 mg, 96%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 5.54 (t, *J* = 4.4 Hz, 1H), 3.66 – 3.58 (m, 2H), 2.17 (td, *J* = 6.3, 4.1 Hz, 2H), 1.78 (m, 4H), 1.05 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 120.8, 119.2, 98.8, 95.6, 38.9, 23.2, 20.5, 18.6, 11.4, 11.1, 10.8. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{17}H_{29}NOSi$ 291.2018; found 291.2022.

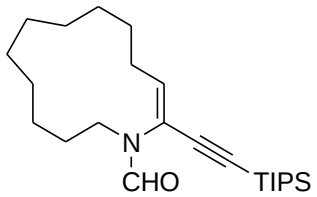
*2.5.21 Peak assignment of **3c2***



3c2, 91 %

Prepared using **General Procedure D. 2c** (1.00 mmol) and triisopropyl-silylacetylene (2 mmol, 2 equiv), Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 279 mg, 96%.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 5.84 (t, *J* = 6.1 Hz, 1H), 3.62 (t, *J* = 5.9 Hz, 2H), 2.19 (q, *J* = 5.9 Hz, 2H), 1.72 (p, *J* = 6.1 Hz, 2H), 1.58 (q, *J* = 6.1 Hz, 2H), 0.99 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.25, 129.90, 125.42, 102.79, 91.85, 44.10, 27.67, 27.50, 24.08, 18.59, 10.87. HRMS calc for $C_{18}H_{31}NOSi$ 305.1759, found 305.4561.

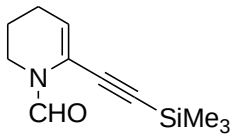
*2.5.22 Peak assignment of **3c3.***



3c3

Prepared from **General Procedure D. 2e** (1.00 mmol) and triisopropyl-silylacetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 279 mg, 96%.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 5.84 (t, *J* = 6.1 Hz, 1H), 3.62 (t, *J* = 5.9 Hz, 2H), 2.19 (q, *J* = 5.9 Hz, 2H), 1.72 (p, *J* = 6.1 Hz, 2H), 1.58 (q, *J* = 6.1 Hz, 2H), 0.99 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.25, 129.90, 125.42, 102.79, 91.85, 44.10, 43.9, 42.2, 28.6, 28.3, 28.3, 28.1, 27.6, 27. 27.2, 26.7, 26.7, 26.5, 26.5, 26.4, 26.4, 26.2, 26.2, 26.1, 26.0, 25. 24.5, 24.3, 24.3, 24.1, 24.0, 23.7, 23.1. 27.67, 27.50, 24.08, 18.59, 10.27. HRMS calc for $C_{24}H_{43}NOSi$ 389.3759, found 389.6561.

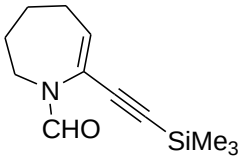
*2.5.23 Peak assignment of **3c4***



3c4, 92%

Prepared using **General Procedure D. 2a** (1.00 mmol) and trimethylsilylacetylene (2 mmol, 2 equiv), Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 190 mg, 92%. ^1H NMR (400 MHz, C_6D_6) δ 9.32 (s, 1H), 5.24 to 5.22 (t, 1H), 3.39 to 3.36 (t, 2H), 1.54 to 1.47 (m, 2H), 1.15 to 1.09 (m, 2H), 0.09 (s, 9H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.4, 121.6, 118.6, 98.9, 98.4, 39.2, 23.4, 20.8, 0.1. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{11}H_{17}NOSi$ 207.1079; found 207.1083.

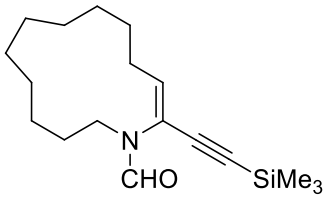
*2.5.24 Peak assignment of **3c5***



3c5, 96%

Prepared using **General Procedure D**. **2c** (1.0 mmol) and trimethylsilylacetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 212 mg, 96%. Data as previously reported by us.[59]

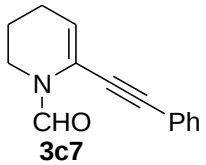
*2.5.25 Peak assignment of **3c6***



2l, 91%

Prepared using **General Procedure D. 2e** (1.0 mmol) and trimethylsilyl acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 278 mg, 91%. ^{1}H NMR (400 MHz, C_6D6, mixture of rotamers) δ 8.22 & 8.00 (1H, s, s), 5.78 5.57 (1H, t), 3.67 to 3.53 (2H, t), 2.24 to 2.19 (2H, m), 1.66 to 1.02 16H, m), 0.28 (9H, s). ^{13}C NMR (101 MHz, C_6D_6, mixture of rotamers) δ 162.0, 161.9,, 135.9, 135.5, 135.0, 134.2, 134.1, 129.2, 128.4, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.5, 127.5, 123.4, 123.3, 118.6, 101.7, 101.3, 100.8, 98.8, 93.6, 92.3, 77.0, 46.8, 42.3, 42.2, 40.7, 29.0, 28.5, 28.4, 28.3, 28.2, 28.0, 27.7, 27.7, 27.6, 27.5, 27.0, 26.8, 26.7, 26.7, 26.6, 26.5, 25.8, 25.7, 25.7, 25.3, 25.1, 24.7, 24.7, 24.5, 23.7, 23.6, 23.3, -0.4, -0.6. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{18}H_{31}NOSi$ 305.2175; found 305.2179.

*2.5.26 Peak assignment of **3c7***

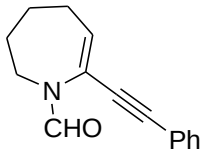


3c7

Prepared using **General Procedure D. 2a** (99.3 mg, 1.0 mmol) and phenylacetylene. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 192 mg, 91%. ^{1}H NMR (400 MHz, C_6D_6) δ

9.35 (1H), 7.28 to 7.21 (2H), 7.00 to 6.93 (3H), 5.28 to 5.25 (1H), 3.46 to 3.43 (2H), 1.60 to 1.52 (2H), 1.20 to 1.14 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.5, 132.0, 129.3, 129.0, 122.7, 121.5, 118.0, 93.39, 83.0, 39.3, 23.5, 20.8. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{14}H_{13}NO$ 211.0997; found 211.0993.

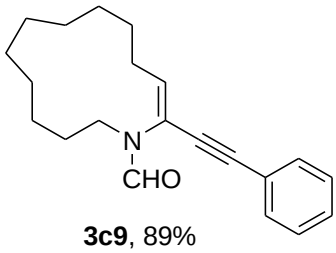
*2.5.27 Peak assignment of **3c8***



3c8, 94%

Prepared using **General Procedure D**. **2c** (113.2 mg, 1.0 mmol) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 212 mg, 94%. Data as previously reported by us.[59]

*2.5.28 Peak assignment of **3c9***

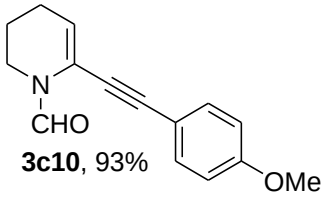


3c9, 89%

Prepared using **General Procedure D**. **2e** (1.0 mmol) and phenylacetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 275 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.29 & 8.15 (1H, s,s), 7.72 to 7.12 (5H, m), 5.88 to 5.72 (1H, m), 3.76 to 3.65 (2H, t), 2.60 to 2.14 (2H, m), 1.73 to1.04 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.5, 136.9, 135.68, 135.6, 135.3, 135.2, 135.2, 134.0, 133.1, 132.5, 132.2, 132.1, 132.0, 131.9, 131.7, 131.6, 131.59, 130.3, 129.6, 129.1, 128.8, 128.6, 128.5,

128.4, 128.3, 128.1, 127.9, 127.7, 122.3, 121.8, 95.3, 88.9, 85.4, 85.2, 42.8, 41.3, 36.5, 34.6, 31.4, 29.7, 29.2, 28.6, 28.5, 28.4, 28.2, 28.1, 28.0, 27.9, 27.6, 26.9, 26.8, 26.7, 26.5, 26.4, 26.2, 26.0, 25.9, 25.8, 25.6, 25.5, 25.5, 25.3, 25.0, 24.9, 24.8, 24.7, 24.5, 23.7, 23.6, 23.6, 23.4. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{27}NO$ 309.2093; found 309.2096.

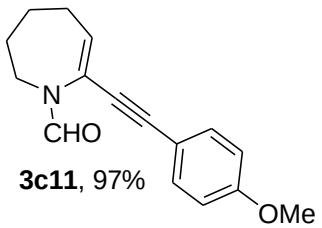
*2.5.29 Peak assignment of **3c10***



3c10, 93%

Prepared using **General Procedure D. 2a** (1.0 mmol) and *p*-methoxy-phenylacetylene (2 mmol, 2 equiv). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 224 mg, 93%. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.06 (1H, s), 7.32 (2H, d), 6.75 (2H, d), 5.59 to 5.57 (1H, t), 3.71 to 3.52 (5H, m), 2.27 to 2.18 (2H, m), 1.88 to 1.73 (2H, m). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.3, 160.2, 134.1, 133.1, 128.5, 121.0, 118.0, 114.2, 113.9, 93.0, 80.5, 55.4, 39.1, 23.4, 20.7. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{15}H_{15}NO_2$ 241.1103; found 241.1107.

*2.5.30 Peak assignment of **3c11***

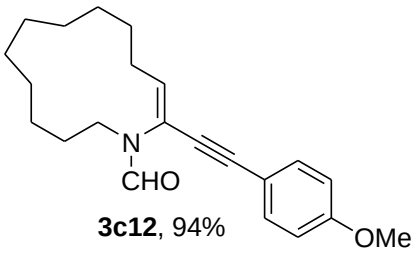


3c11, 97%

Prepared from using **General Procedure D. 2c** (1.0 mmol) and *p*-methoxyphenylacetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica

(pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 247 mg, 97%. ^1H NMR (400 MHz, Benzene-d6) δ 8.94 to 8.37 (1H, s), 7.46 to 7.00 (2H, m), 6.67 to 6.58 (2H, m), 6.06 to 5.72 (1H, t), 3.58 to 3.55 (3H, s), 1.87 to 1.83 (2H, m), 1.51 to 1.38 (2H, m), 1.30 to 1.07 (2H, m). ^{13}C NMR (101 MHz, Benzene-d6) δ 161.4, 160.2, 135.4, 128.8, 125.9, 114.4, 89.9, 85.3, 54.6, 43.9, 28.0, 27.4, 24.1. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{16}H_{17}NO_2$ 255.1259; found 255.1263.

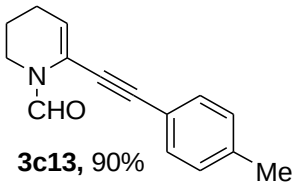
*2.5.31 Peak assignment of **3c12***



3c12, 94%

Prepared using **General Procedure D. 2e** (1.0 mmol) and *p*-methoxyphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 319 mg, 94%. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.31 & 8.13 (1H, s,s), 7.48 to 7.26 (2H, dd), 6.97 to 6.82 (2H, dd), 5.89 to 5.73 (1H, t), 3.86 to 3.66 (5H, m), 2.30 to 2.14 (2H, m), 1.73 to1.22 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.1, 160.9, 160.2, 160.1, 159.9, 139.7, 134.9, 134.8, 134.0, 133.2, 133.1, 133.1, 133.0, 132.9, 123.3, 123.3, 119.6, 114.2, 114.2, 114.1, 114.1, 114.0, 113.9, 113.8, 113.2, 95.3, 88.9, 87.9, 83.9, 81.3, 81.2, 77.5, 77.1, 76.8, 73.0, 60.4, 55.4, 55.3, 47.7, 42.7, 41.2, 29.2, 28.5, 28.5, 28.4, 28.3, 28.2, 28.1, 27.9, 27.6, 26.8, 26.8, 26.7, 26.5, 26.2, 26.0, 25.7, 25.6, 25.5, 25.2, 24.9, 24.8, 24.4, 23.7, 23.6, 23.5, 23.3, 21.1. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{22}H_{29}NO_2$ 339.2198; found 339.2193.

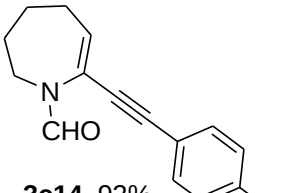
*2.5.32 Peak assignment of **3c13***



3c13, 90%

Prepared using **General Procedure D. 2a** (1.0 mmol) and *p*-methylphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 203 mg, 90%. ^1H NMR (400 MHz, Chloroform-d) δ 9.06 (1H, s), 7.32 (2H, d), 7.26 (2H, d), 5.59 to 5.57 (1H, t), 3.71 to 3.52 (2H, t), 2.34 to 2.18 (5H, m), 1.81 to 1.76 (2H, m). ^{13}C NMR (101 MHz, Chloroform-d) δ 161.2, 139.6, 133.1, 132.2, 128.6, 120.9, 118.8, 93.1, 81.1, 39.1, 23.4, 21.6, 20.7. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{15}H_{15}NO$ 225.1154; found 225.1159.

*2.5.33 Peak assignment of **3c14***

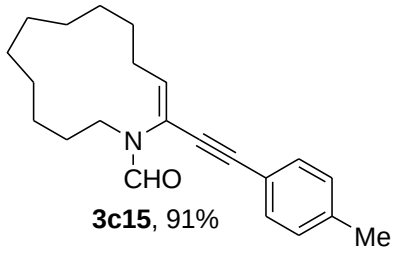


3c14, 92%

Prepared using **General Procedure D. 2c** (1.0 mmol) and *p*-methylphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 220 mg, 92%. ^1H NMR (400 MHz, Benzene-d6) δ 8.98 (1H, s), 7.89 to 7.21 (2H, d) 6.86 to 6.04 (2H, d), 5.73 to 5.70 (1H, s), 3.58 to 3.55 (2H, t), 2.03 to 1.99 (3H, s), 1.81 to 1.62 (2H, m), 1.49 to 1.37 (2H, t), 1.26 to 1.03 (2H, t). 13C NMR (101 MHz, Benzene-d6) δ 161.4, 138.8, 133.9, 129.3,

126.9, 119.5, 90.0, 86.0, 43.8, 27.9, 27.4, 24.1, 21.1. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{16}H_{17}NO$ 239.1310; found 239.1314.

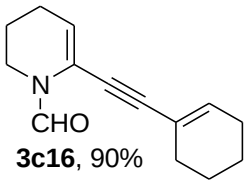
*2.5.34 Peak assignment of **3c15***



3c15, 91%

Prepared from using **General Procedure D. 2e** (1.0 mmol) and *p*-methylphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 294 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.29 & 8.05, 7.74 to 7.26 (4H, m), 5.84 to 5.76 (1H, m), 3.84 to 3.66 (2H, m), 2.47 to 2.15 (5H, m), 1.73 to 1.17 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 163.2, 162.6, 162.1, 160.9, 140.0, 139.5, 139.3, 139.0, 138.7, 135.3, 135.2, 135.2, 134.9, 134.9, 132.4, 132.2, 132.1, 131.9, 131.8, 131.5, 131.5, 131.5, 130.5, 130.3, 129.6, 129.3, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 128.2, 128.2, 128.0, 127.7, 127.7, 127.6, 123.2, 119.1, 119.1, 118.8, 114.2, 95.4, 89.1, 88.2, 84.7, 84.6, 81.9, 81.6, 77.5, 77.2, 76.8, 73.5, 55.3, 47.8, 43.3, 42.8, 41.2, 29.8, 29.2, 28.6, 28.5, 28.5, 28.4, 28.3, 28.1, 27.9, 27.7, 26.9, 26.8, 26.7, 26.5, 26.2, 26.0, 25.8, 25.6, 25.5, 25.2, 24.9, 24.8, 24.6, 24.4, 23.7, 23.6, 23.5, 23.3, 21.7, 21.6, 21.6, 21.6. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{22}H_{29}NO$ 323.2249; found 323.2252.

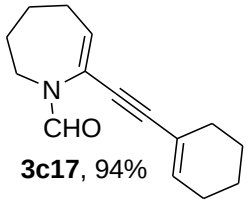
*2.5.35 Peak assignment of **3c16***



3c16, 90%

Prepared using **General Procedure D. 2a** (145 mg, 1.0 mmol) and 1-ethynylcyclohexene (0.24 mL, 2 mmol, 2 equiv). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 193 mg, 90%. ^1H NMR (400 MHz, C_6D_6) δ 9.39 (1H, s), 6.01 to 5.96 (1H, t), 5.22 to 5.20 (1H, t), 3.46 to 3.43 (2H, t), 1.99 to 1.94 (2H, m), 1.78 to 1.73 (2H, m), 1.57 to 1.46 (2H, q), 1.35 to 1.22 (4H, m), 1.17 to 1.11 (2H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 160.6, 136.6, 121.9, 120.6, 116.8, 95.3, 80.6, 39.3, 29.3, 26.2, 23.5, 22.7, 21.9, 20.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{14}H_{17}NO$ 215.1310; found 215.1313.

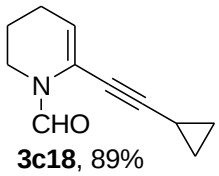
*2.5.36 Peak assignment of **3c17***



3c17, 94%

Prepared from using **General Procedure D. 2c** (160 mg, 1.0 mmol) and 1-ethynylcyclohexene (0.24 mL, 2 mmol, 2 equiv). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 215.4 mg, 94%. Data as previously reported by us.[59]

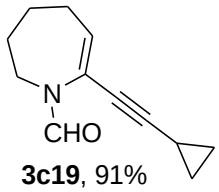
*2.5.37 Peak assignment of **3c18***



3c18, 89%

Prepared using **General Procedure D. 2a** (145 mg, 1.0 mmol) and 1-ethynylcyclopropane (2 mmol, 2 equiv). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 156 mg, 89%. 1H NMR (400 MHz, Benzene-d6) δ 9.45 to 9.12 (1H, s), 5.42 to 5.03 (1H, t), 3.64 to 3. 43 (2H, t), 1. 77 to 1.52 (2H, m), 1. 48 to 0.22 (7H, m). 13C NMR (101 MHz, Chloroform-d) δ 161.6, 121.2, 117.6, 97.8, 68.7, 39.4, 23.5, 21.1, 9.1, 0.3. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{11}H_{13}NO$ 175.0997; found 175.0993.

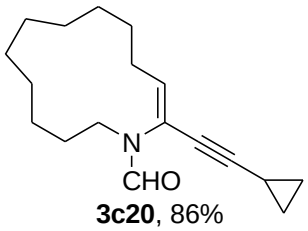
*2.5.38 Peak assignment of **3c19***



3c19, 91%

Prepared using **General Procedure D. 2c** (160 mg, 1.0 mmol) and 1-ethynylcyclopropane (2 mmol, 2 equiv). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 172 mg, 91%. 1H NMR (400 MHz, Benzene-d_6) δ 8.90 to 8.85 (1H, s), 5.60 to 5.37 (1H, t), 3.54 to 3.29 (2H, t), 2.13 to 1.92 (2H, m), 1.77 to 1.41 (2H, m), 1.24 to 1.18 (2H, m), 1.08 to 1.01 (2H, m), 0.85 to 0.26 (4H, m). 13C NMR (101 MHz, Benzene-d_6) δ 161.69, 93.78, 73.06, 43.73, 27.87, 27.13, 23.50, 8.43. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{12}H_{15}NO$ 189.1154; found 189.1151.

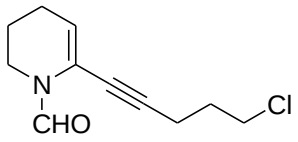
*2.5.39 Peak assignment of **3c20***



3c20, 86%

Prepared using **General Procedure D. 2e** (243 mg, 1.0 mmol) and 1-ethynylcyclopropane (2 mmol, 2 equiv). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 235 mg, 86%. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.16 & 7.96 (1H, s,s), 5.80 to 5.57 (1H, t), 3.66 to 3.41 (2H, t), 2.36 to 2.02 (2H, m), 1.73 to 0.98 (17H, m), 0.93 to 0.68 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.0, 138.8, 134.0, 123.2, 123.1, 99.9, 93.0, 77.4, 77.1, 76.8, 71.7, 68.9, 47.5, 43.1, 42.5, 40.9, 28.8, 28.5, 28.4, 28.4, 28.2, 28.0, 28.0, 27.9, 27.7, 27.6, 27.5, 26.8, 26.6, 26.6, 26.4, 26.1, 26.0, 25.9, 25.8, 25.7, 25.6, 25.4, 25.1, 24.9, 24.8, 24.6, 24.4, 23.7, 23.6, 23.5, 23.3, 9.8, 9.6, 9.3, 9.0, 8.7, 8.6, 8.5. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{18}H_{27}NO$ 273.2093; found 273.2090.

*2.5.40 Peak assignment of **3c21***

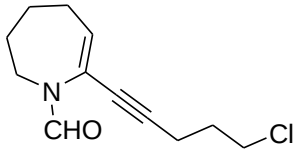


3c21, 95%

Prepared using **General Procedure D. 2a** (145 mg, 1.0 mmol) and 5-chloro-1-pentyne (0.21 mL, 2.0 mmol). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 200 mg, 95%. ^1H NMR (400 MHz, C_6D_6) δ 9.25 (1H, s), 5.14 to 5.11 (1H, t), 3.45 to 3.42 (2H, t), 3.08 to 3.05 (2H, t), 2.02 to 1.98 (2H, t), 1.57 to 1.33 (4H, m), 1.18 to 1.12 (2H, m). ^{13}C NMR (101 MHz,

C_6D_6) δ 160.5, 121.5, 116.9, 92.5, 75.2, 44.0, 39.3, 31.4, 23.4, 21.0, 16.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{11}H_{14}ClNO$ 211.0764; found 211.0769.

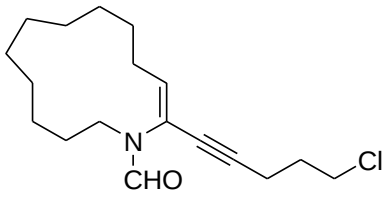
*2.5.41 Peak assignment of **3c22***



3c22, 90%

Prepared using **General Procedure D. 1b** (160 mg, 1.0 mmol) and 5-chloro-1-pentyne (0.21 mL, 2.0 mmol). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 203 mg, 90%. Data as previously reported by us.[59]

*2.5.42 Peak assignment of **3c23***

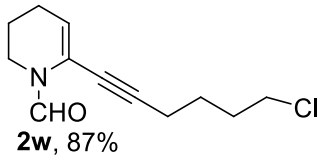


3c23, 91%

Prepared using **General Procedure D. 2e** (243 mg, 1.0 mmol) and 5-chloro-1-pentyne (0.21 mL, 2.0 mmol). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 281 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 & 7.96 (1H, s,s), 5.85 to 5.77 (1H, t), 3.77 to 3.55 (4H, m), 2.68 to 1.18 (22H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.0, 160.8, 139.2, 135.2, 122.9, 122.6, 94.4, 87.8, 86.8, 77.5, 77.5, 77.4, 77.1, 76.8, 75.0, 47.6, 43.6, 43.6, 43.4, 42.5, 41.0, 31.2, 31.1, 31.0, 28.9, 28.5, 28.4, 28.4, 28.2, 28.1, 28.0, 27.8, 27.6, 27.5, 26.8, 26.7, 26.6, 26.4, 26.3, 26.0, 25.9, 25.7, 25.5, 25.4, 25.2, 24.8, 24.8, 24.6, 24.4, 23.7, 23.6, 23.5,

23.3, 16.8, 16.6, 16.6. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{18}H_{28}ClNO$ 309.1859; found 309.1862.

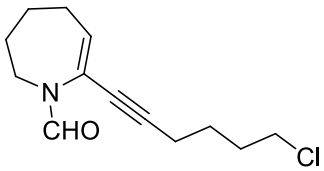
*2.5.43 Peak assignment of **3c24***



2w, 87%

Prepared from **1a** (145 mg, 1.0 mmol) and 6-chloro-1-hexyne (2.0 mmol, 2 equiv) using **General Procedure D.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 196 mg, 87%. ^{1}H NMR (400 MHz, Benzene-d6) δ 9.30 to 8.91 (1H, s), 5.22 to 4.71 (1H, t), 3.50 to 3.37 (2H, t), 3.09 to 3.06 (2H, t), 2.01 to 1.88 (2H, m), 1.70 to 1.61 (2H, m), 1.51 to 1.42 (2H, m), 1.32 to 1.20 (2H, m), 1.12 to 0.94 (4H, m). 13C NMR (101 MHz, Benzene-d6) δ 160.1, 121.1, 116.0, 108.3, 93.1, 74.4, 44.0, 38.8, 31.5, 25.4, 23.4, 20.8, 18.2. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{12}H_{16}ClNO$ 225.0920; found 225.0923.

*2.5.44 Peak assignment of **3c25***

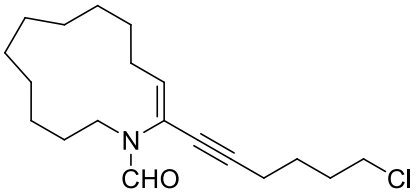


2x, 92%

Prepared from **1b** (160 mg, 1.0 mmol) and 6-chloro-1-hexyne (2.0 mmol, 2 equiv) using **General Procedure D.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 220 mg, 92%. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.56 to 8.07 (1H, s), 5.80 to 5.77 (1H, t), 3.80 to 3.41 (2H, t), 2.68 to 2.19 (4H, m), 1.93 to 1.50 (10H, m). ^{13}C NMR (101 MHz, Chloroform-d) δ 162.5,

128.8, 125.4, 89.9, 8.1, 44.5, 31.6, 28.7, 27.8, 25.6, 23.6, 18.6. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{13}H_{18}ClNO$ 239.1077; found 239.1074.

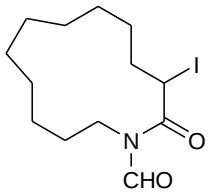
*2.5.45 Peak assignment of **3c26***



2y, 93%

Prepared from **1c** (243 mg, 1.0 mmol) and 6-chloro-1-hexyne (2.0 mmol, 2 equiv) using **General Procedure D.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 300 mg, 93%. ^{1}H NMR (400 MHz, Benzene-d6) δ 8.30 to 7.87 (1H, s), 5.53 to 5.15 (1H, t), 3.88 to 3.74 (2H, t), 3.24 to 3.06 (2H, m), 2.29 to 0.97 (24H, m). 13C NMR (101 MHz, Benzene-d6) δ 162.2, 161.1, 138.6, 138.2, 133.4, 123.5, 123.3, 95.3, 88.7, 77.7, 75.2, 44.1, 44.0, 42.3, 31.6, 28.5, 27.7, 26.7, 25.8, 25.6, 24.8, 24.5, 23.7, 23.6, 23.4, 18.4. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{19}H_{30}ClNO$ 323.2016; found 323.2020.

*2.5.46 Peak assignment of **3d1***

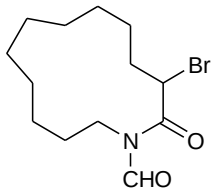


3d1

To **2e** (160 mg, 1 mmol, 1.0 equiv) dissolved in THF (5 mL) and H_2O (5 mL), was added NIS (270 mg, 1.2 mmol, 1.2 equiv) at room temperature. After complete consumption of the eneformamide (as indicated by TLC and LCMS-monitoring; <10

min), the mixture was diluted with EtOAc (20 mL) and poured into a separating funnel. It was washed with *sat*. $Na_2S_2O_3$(aq) and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product as an oil. Yield = 326.4 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (1H, s), 4.67 to 4.64 (1H, m), 4.07 to 4.00 (1H, m), 3.47 to 3.42 (1H, m), 2.45 to 2.37 (1H, m), 2.25 to 2.00 (1H, m), 1.73 to 1.17 (16H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 162.9, 77.4, 77.1, 76.8, 40.4, 36.4, 26.6, 26.6, 25.7, 25.7, 24.4, 24.2, 23.3, 18.9.

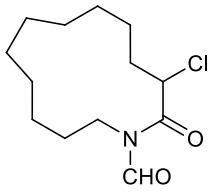
Peak assignment **3d2**



3d2

To **2e** (160 mg, 1 mmol, 1.0 equiv) dissolved in THF (5 mL) and H_2O (5 mL), was added NBS (214 mg, 1.2 mmol, 1.2 equiv) at room temperature. After complete consumption of the eneformamide (as indicated by TLC and LCMS-monitoring; <10 min), the mixture was diluted with EtOAc (20 mL) and poured into a separating funnel. It was washed with *sat*. $Na_2S_2O_3$(aq) and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product as an oil. Yield = 272.7 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 4.74 (m, 1H), 4.20 to 3.93 (m, 1H), 3.68 to 3.42 (m, 1H), 2.31 to 2.22 (m, 1H), 2.06 to 1.98 (m, 1H), 1.69 to 0.81 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 162.5, 54.0, 45.2, 40.6, 40.4, 38.7, 34.3, 31.7, 31.5, 30.4, 30.2, 29.7, 29.2, 28.9, 28.3, 28.2, 28.1, 27.5, 27.2, 26.6, 26.4, 26.1, 25.9, 25.9, 25.8, 25.6, 25.4, 25.2, 24.9, 24.7, 24.4, 24.2, 23.7, 23.7, 23.5, 23.4, 23.0.

*2.5.47 Peak assignment **3d3***



3d3

To **2e** (160 mg, 1 mmol, 1.0 equiv) dissolved in THF (5 mL) and H_2O (5 mL), was added NCS (160 mg, 1.2 mmol, 1.2 equiv) at room temperature. After complete consumption of the eneformamide (as indicated by TLC and LCMS-monitoring; <10 min), the mixture was diluted with EtOAc (20 mL) and poured into a separating funnel. It was washed with *sat*. $Na_2S_2O_3$(aq) and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product as an oil. Yield = 272.7 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 to 6.68 (s, 1H), 4.46 to 4.44 (m, 1H), 3.80 to 3.73 (m, 1H), 3.39 to 3.35 (m, 1H), 2.92 to 2.86 (m, 1H), 2.54 to 2.51 (m, 1H), 2.16 to 1.22 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 61.0, 39.7, 39.3, 34.8, 27.6, 27.2, 26.7, 26.5, 26.4, 26.3, 26.1, 25.7, 25.6, 25.5, 24.8, 24.8, 24.5, 23.9, 23.5, 22.3.

CHAPTER 3

SYNTHETIC UTILITY OF ALPHA-SUBSTITUTED ENEFORMAMIDES: PREPARATION OF QUATERNARY PROPARGYLIC AND HOMOALLYLIC CYCLIC AMINES

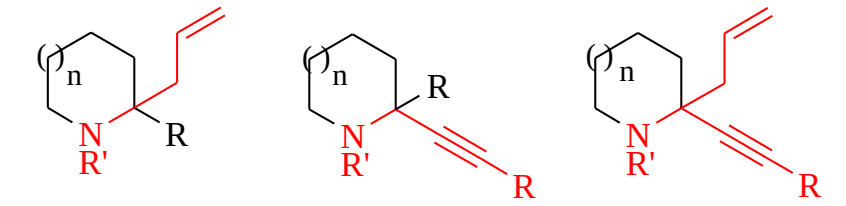
3.1 Introduction

After constructing such a large library of alkynylated and alkenylated eneformamides, we wanted to demonstrate their synthetic utility. The utility of *N*-acyl imino dienes and enamidynes has been previously explored by the likes of Toste[113] and Occhiato[114] in Conia-ene and carboauration-type reactions. We therefore sought to further examine the dynamic range of utility that such complex alkenyl and alkynyl α-eneformamides have to offer.

One of the many goals of a synthetic organic chemist is to form new carbon-carbon bonds. Generating new carbon-carbon bonds is an important synthetic process as it paves new ways to make structurally unique and biologically active molecules or pharmacophores commonly found in a large variety of pharmaceuticals. This led us to investigate nucleophilic addition to a cyclic imine with an organometallic reagent.[80, 115-124] This process generates new carbon-carbon bonds and creates a saturated[125] cyclic amine, which, as we discussed, saturated piperidines and azepanes are commonly found in a vast majority of nitrogen bearing FDA approved pharmaceuticals.

In our case, the addition of an organometallic reagent to our cyclic enamidyne would generate a cyclic α-amino propargylic quaternary stereocenter[126, 127]. Specifically, the use of an allylic organometallic nucleophile would generate a structurally complex 3-azaheterocyclic 1,5-enyne. Thus, from our large library of previously generated enamidynes, we can construct a diverse library of α-quaternary homoallylic and

propargylic 1,5-enynes (Figure **3-1**). These structurally unique quaternary homoallylic and propargylic amines offer an outstanding starting point for even more complex diversity-oriented synthesis.



homoallylic amine propargylic amine propargylic and homoallylic amine

Figure 3-1 Figure demonstrating cyclic α-quaternary homoallylic and propargylic 1, 5-enynes

We also wanted to demonstrate the utility of our newly made α-alkynyl and α-alkenyl eneformamides to construct bicycles and tricycles. As discussed in chapter one, fused heterocycles play a major role in pharmaceuticals and thus finding new and efficient ways to construct these commonly found polycyclic motifs are highly sought after amongst the organic synthetic communities.

We envisioned that our α-alkynyl eneformamides could be used to construct vinylogous lactams by wrapping the alkynyl substituent around onto an acyl group via a Knoevenagel type reaction. Vinylogous lactams are amazing substrates that are great for Diels-Alder reactions or Deslongchamps-type annulations and thus can be used to further functionalize the vinylogous lactam to afford bicyclic and tricyclic functional motifs.

We also wanted to demonstrate the utility of our α-alkenyl eneformamides as they make great dienes for Diels-Alder reactions. We envisioned the use of a cyclic diene, as that would afford us a tricycle in one step from the use of our α-alkenyl eneformamides.

This methodology opens the door to construct highly functionalized polycyclic structures with a high degree of modularity.

3.1.1 Synthetic potential of 3-azaheterocyclic-1,5-enynes

These α-quartenary homoallylic and propargylic 1, 5-enynes have a huge amount of potential synthetic utility (Figure **3-2**). We envisioned several transition metal-catalyzed processes that proceed in a regio- and stereocontrolled way such as bromoallylation[128] (see **2a/b**) or arylcyanation[129-132] (see **3a/b**). Additionally we envisioned many stereo controlled metal-catalyzed processes that form polycylic systems such as: benzannulative cycloisomerization[133] (see **4**) intramolecular hydroamination[134-141] (see **5**), and hydroaminoalkylation[142-146] (see **6a/b**).

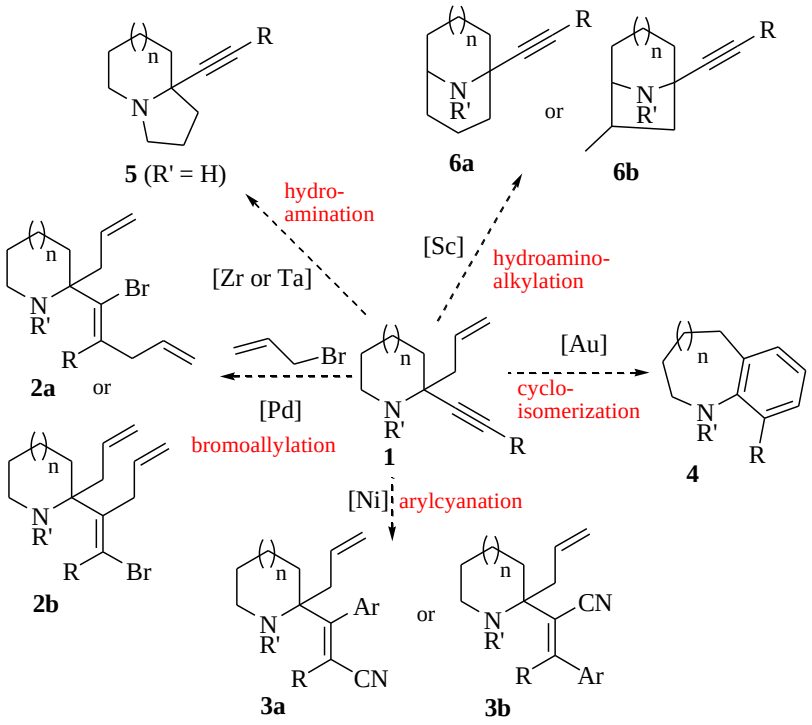


Figure 3-2 Synthetic potential of 3-azaheterocyclic-1,5-enynes of type **1**

These 3-azaheterocyclic-1,5-enynes are optically active α-quaternary propargylic and homoallylic amines and have a large amount of synthetic potential and can be used as

the precursors to a vast array of pharmaceuticals and biologically active compounds with enormous medicinal value. It has been demonstrated by many groups that these structurally unique quaternary propargylic amines can be generated from cyclic and acyclic precursors, however the α-substituents are limited to methyl and aryl groups and have been primarily on 5- and 6-membered ring systems.[127, 147, 148] Here, we demonstrate that we can generate cyclic quaternary propargylic and homoallylic amines in a cost-effective, bench stable, and modular manner

3.1.2 Possible synthetic routes to 3-azaheterocyclic-1,5-enynes

We envisioned two synthetic routes that would afford 3-azaheterocyclic 1,5-enynes such as **1** in an efficient and modular fashion (Figure **3-3**). The first approach involves taking the cyclic α-alkynyl eneformamides **8** and removing the formyl group. Following deformylation, an organometallic allyl reagent would be used to attack the cyclic alkynyl imine **7** that comes from the tautomer of the alkynyl ketimine to form **1**.

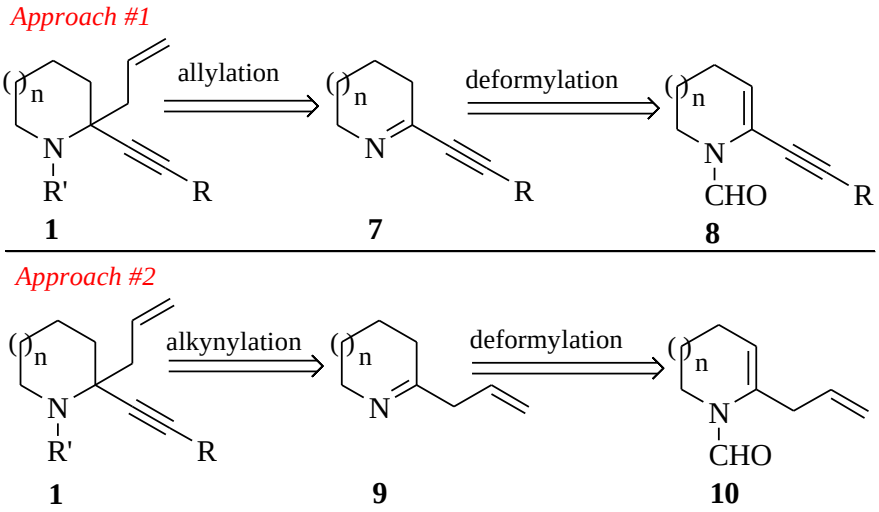


Figure 3-3 Potential synthetic routes to achieve 3-azaheterocyclic-1,5-enyne **1**

There are many potential challenges associated with the first synthetic route (Figure **3-4**). First is the reactivity of the cyclic ketimine. It is well known that cyclic

ketimines such as **7** are far less reactive then carbonyls[149] and this only adds to the challenge as the ketimine is enolizable and sterically hindered **13**. It is also recognized that ketimines are susceptible to oligomerization[150], meaning the ketimine will add to itself rather than react with another reactive nucleophile (see **12**). Another challenge presented that of chemoselectivity. It is well precedented that cyclic 1, 3-azadienes tend to undergo 1, 4 conjugate addition when reacted with allylmagnesium bromide instead of 1, 2 addition,[34] making it very challenging to predict the site selectivity of the reaction.

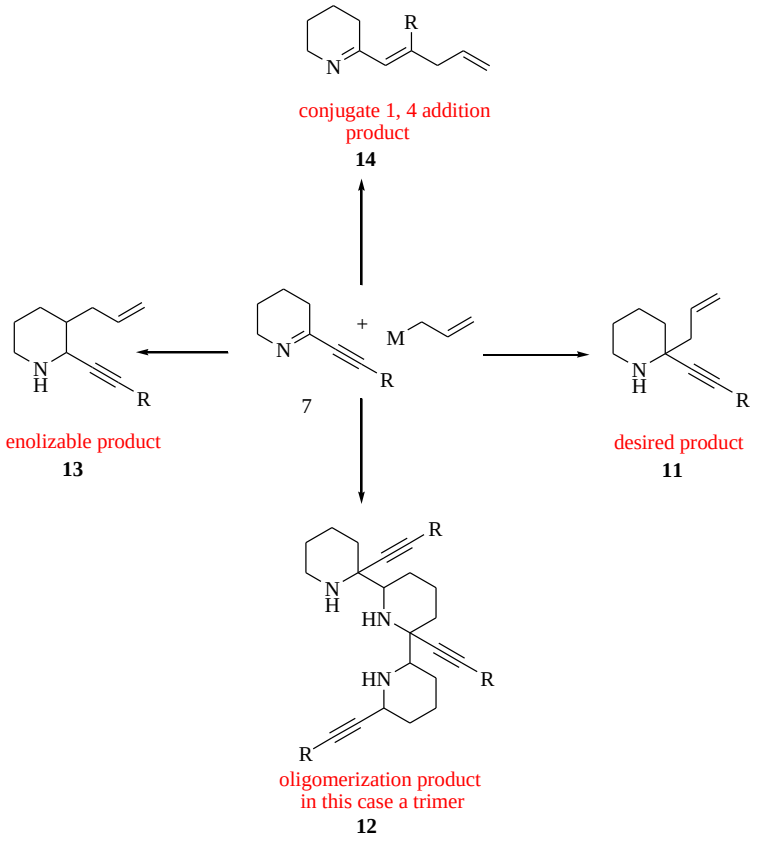


Figure 3-4 Challenges associated with first synthetic route

The second approach (Figure **3-3**) to **1** involves deformylating a skip diene **10** to make 1,4-azadiene **9** followed by subsequent addition of the alkyne using Zhang-style alkynylation[151] to make the desired 3-azaheterocyclic-1,5-enynes **1**. The main challenge with this approach has been the allylations of the cyclic α-chloro eneformamide don't

tend to proceed chemoselectively from one ring size to another. In some cases, the allylation goes to the β-position instead of the α-position.

3.2 Results and Discussion

3.2.1 Synthesis of 3-azaheterocyclic-1,5-enynes

Having already generated a large library of eneformamidynes we wanted to find conditions that would work for the first approach (Figure **3-3**). We also sought after the first approach as we were able to efficiently alkynylate all 3 ring sizes of the α-halo eneformamide. Thus, we decided to move forward with our eneformamidynes and use base-mediated conditions to remove the formyl group. This created the desired cyclic ketiminyne intermediate and subsequent allylation conditions were explored. With organometallic additions to cyclic imines in mind, we sought to find efficient conditions and a reactive partner to go from the cyclic ketiminyne intermediate **8** to the 3-azaheterocyclic-1,5-enynes **1**. To our excitement, nucleophilic addition of allylmagnesium bromide to the cyclic ketiminyne intermediate proceeds efficiently without formation of any of the aforementioned undesired oligomerization, enolizable, or 1,4-conjugate addition products (Figure **3-4**). With these conditions in hand, we deformylated a majority of our previously made eneformamidynes and took the subsequent crude cyclic ketiminyne intermediates forward with the nucleophilic addition of allylmagnesium bromide to form the desired 3-azaheterocyclic-1,5-enynes **1a-n**. Importantly, methyl-, aryl-, vinyl-, and alkynyl- Grignard reagents didn't undergo the desired transformation, which demonstrates the heightened nucleophilicity of allymagnesium bromide compared to the other possible Grignard reagents mentioned.

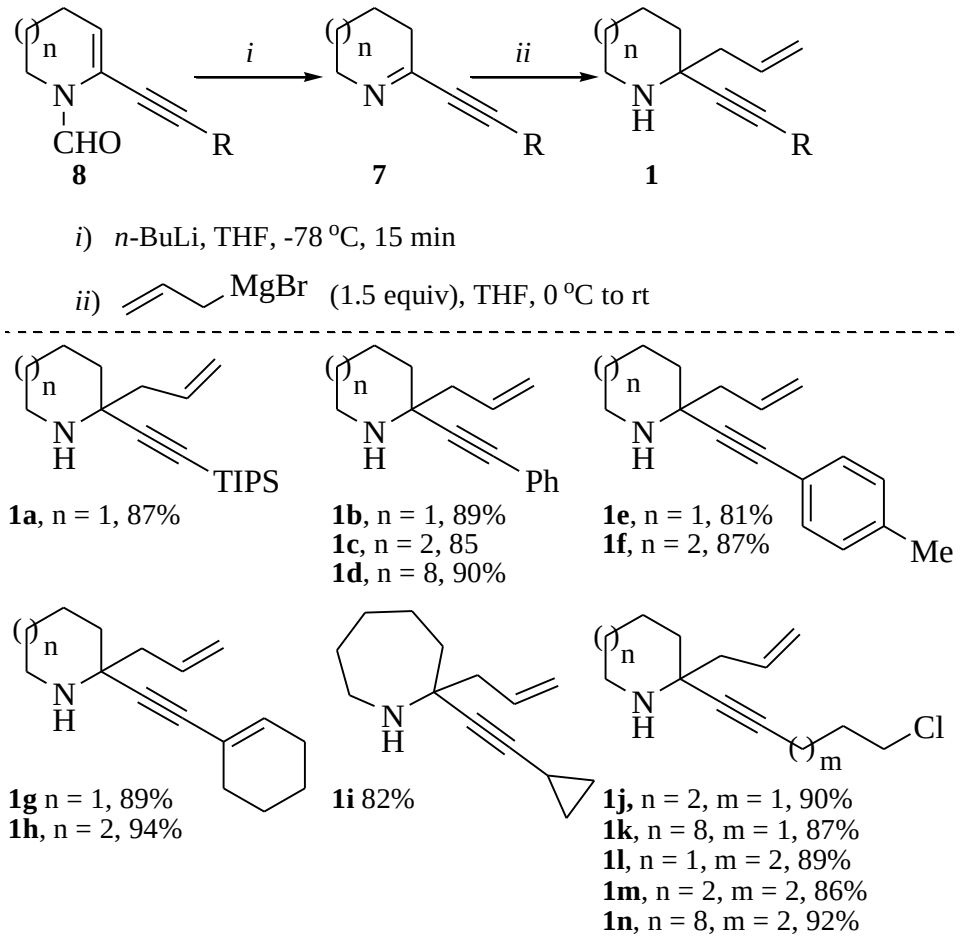


Figure 3-5 Using the first approach to synthesize 3-azaheterocyclic-1,5-enynes

Having demonstrated the efficiency of the first approach, we next desired to explore the second complementary approach. Using the allylation conditions described below, skip dienes **10a/b** were prepared. Unfortunately, the six membered cyclic α-halo eneformamide **15a** allylates at the β-position instead of the desired α-position to produce **16**. This further demonstrates that predicting the chemistry from one size heterocycle to another can be a very challenging task and should not be treated lightly. In any event, we went ahead with the skip dienes **10a/b** and deformylated with the same basic mediated conditions and alkynylated the resulting cyclic imine with zinc/BINOL-catalyzed alkynylation conditions to construct the sought after 3-azaheterocyclic-1,5-enynes **1b/c**.

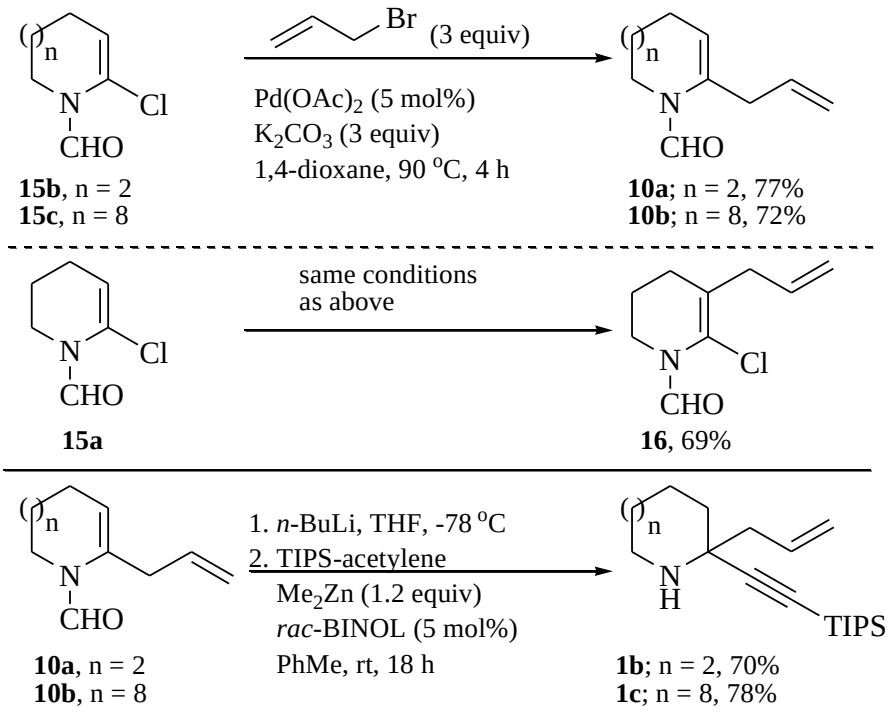


Figure 3-6 Using the second approach to synthesize 3-azaheterocyclic-1,5-enynes

3.2.2 Synthesis of aza-polycycles from α-alkynyl eneformamides

In addition to creating the highly functionalize 3-azaheterocyclic-1,5-enynes, we desired to further utilize our α-alkynyl eneformamides to construct polycyclic motifs. A quick glance at our cyclic eneformamidynes reveals that these functionalized substrates are begging to be transformed into polycyclic structures. With this in mind, we explored the idea using the TMS-bearing enamidyne. The first step was the reduction of the eneformamide double bond in the presence of an alkyne using *N*-formyl iminium reduction.[59] This was followed by desilylation (removal of the TMS group),[152] hydroboration-oxidation (conversion of the alkyne to an aldehyde),[153] deformylation (removal of protecting group on nitrogen), *N*-acylation (attaching a cyano bearing acyl group to the unveiled nitrogen), and lastly an acid-mediated Knoevenagel condensation[154] to construct the cyano-bearing α,β-unsaturated lactam **18** with relatively

high yield (Figure **3-7**). The most challenging part of this transformation was finding the optimum reaction conditions for the Knoevenagel reaction. We attempted several acid-mediated conditions such as: $TiCl_4$-Et_3N, $ZnCl_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Yb(tmhd)_3$, $MgBr_2$, and 1 N HCl. Unfortunately, none were successful in providing the desired product **18**. It was only when we used exceptionally mild conditions of extremely dilute HCl in dichloromethane (20 mM) that we were able to achieve the desired cyano-bearing α,β-unsaturated lactam **18.**

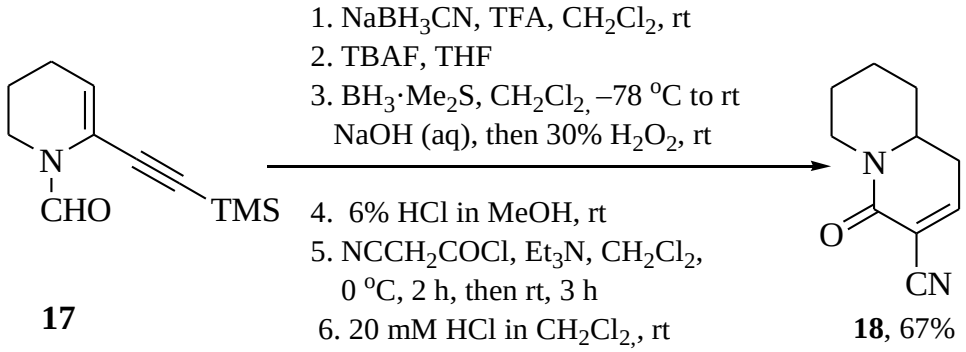
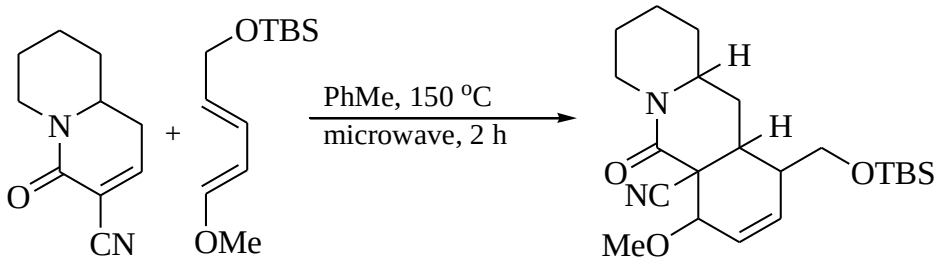


Figure 3-7 Synthesis of vinylogous lactam **18**

Once we successfully constructed cyano-bearing α,β-unsaturated lactam **18**, we evaluated its performance in a Diels-Alder reaction. Our studies have revealed that acid-labile siloxy diene **19** is a competent reactive partner for **18**, leading to the construction of highly functionalized tricycle **20**. Unfortunately, we are not able to unambiguously determine the relative configuration of the functionalized tricycle **20** at this point and further analysis is being done to ascertain the compound's relative configuration with high unambiguity.



18 **19** (2 equiv) **20**, 79%

Figure 3-8 [4 + 2] cycloaddition of diene **19** and dienophile **18**

3.2.3 Synthesis of aza-polycycles from α-alkenyl eneformamides

Having now demonstrated the synthetic utility of our α-alkynyl eneformamides, we next sought to showcase how the α-alkenyl eneformamides could be used to construct polycyclic structures. These *N*-formyl amino dienes are suitable dienes that can be used in Diels-Alder reactions. With this is mind, we were able to take α-alkenyl eneformamide **21** and react it with ester quinone **22**, in benzene, at room temperature for several hours (Figure **3-9**). Excitingly, a cycloaddition reaction proceeded stereo- and chemo-selectively to furnish a single isomer of the now fused tricycle **23** in impeccable efficiency. Additionally, we were able to acquire X-ray crystal structure of the cycloadduct, which provided unambiguous support of the relative configuration (Figure **3-9**). Although Diels-Alder reactions are known to be highly stereospecific, the *trans*-relative configuration at the ring fusion position (*i.e.*, ester and H groups) can be rationalized by invoking epimerization of the initially formed *cis*-product to the thermodynamically more favorable *trans*-adduct. One of the more amazing features of this compound is that it has four contiguous stereocenters. Pleasingly, one of the stereocenters is quartenary and another is β-amino further demonstrating the complexity of compound **23**. Additionally, the compound has both an enamide and enedione motif

which is of importance as it has been shown that there are many synthetic applications of both of these motifs, some of which we have demonstrated exhaustively.

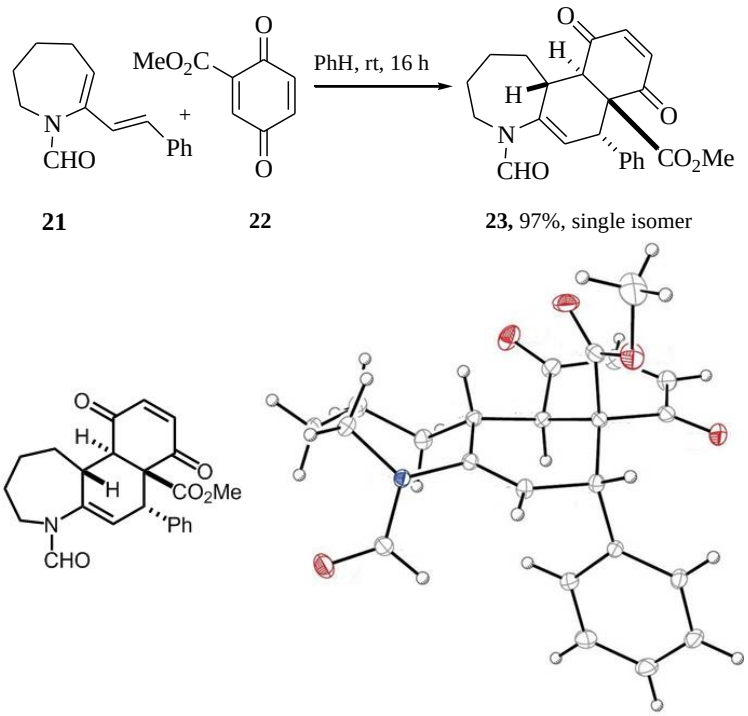


Figure 3-9 Hexannulation of *N*-formyl amino diene **21** with quinone **22**

3.3 Conclusion

In conclusion, we were able to demonstrate the synthetic utility of cyclic eneformamidynes to create novel cyclic α-quartenary homoallylic and propargylic 1,5-enynes using two different approaches. This work stands alone over existing methodologies as we were able to install quaternary centers bearing an allyl group and we were easily able to expand our methodology to three highly functionalize ring systems including a 13-membered macrocycle. We were also able to further demonstrate the utility of α-alkynyl and α-alkenyl eneformamides to construct highly functionalized tricycles featuring Knoevenagel and Diels-Alder reactions. The ability to construct fused polycyclic structures endears the current strategy to the organic synthetic communities as

polycyclic structures are found in a wide range of naturally occurring compounds and biologically active pharmaceuticals.

3.4 Methods

All experiments involving air- and moisture-sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. All alkynes, secondary amines, and electrophiles such as allyltrimethylsilane were newly purchased and used without further purification. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. All reported temperatures were internal to the reaction vessel. Unless otherwise indicated, ^{1}H, ^{13}C, and DEPT-135 spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electron spray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).[34, 38, 59, 109-112]

3.4.1 General procedure A: deformylation

A stock solution of *n*-BuLi (0.15 mL, 0.30 mmol, 2.0 M in hexanes, 1.2 equiv) was added to the crude quaternary *N*-formyl amine **12** (0.25 mmol, 1.0 equiv) dissolved in freshly distilled THF (5 mL) at –78 °C. After complete deprotection of the amine (~15 min, as indicated by TLC and GC-MS monitoring), the mixture was quenched with H_2O

and diluted with EtOAc. It was washed with *sat*. $NaHCO_3$ and then with brine. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and subjected to flash chromatography on silica. [34, 38, 59, 109-112]

3.4.2 General procedure B: Grignard addition

Allyl magnesium bromide (4.0 mL, 1.0 M solution in THF, 4 equiv) was added slowly to the crude α-alkynyl imine (1.0 mmol) dissolved in freshly distilled THF (5 mL), under nitrogen at –78 °C. The mixture was warmed slowly to room temperature. After complete consumption of the ester (as indicated by TLC and GC-MS), the mixture was cooled to 0 °C, diluted with Et_2O and quenched by slow addition of *sat.* aq NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (1:2). [34, 38, 59, 109-112]

3.4.3 General procedure C: Heck coupling of 2-halo enamides with unactivated alkenes

The 2-halo enamide (1 mmol, 1.0 equiv) in DMF (2 mL, 0.50 M), $Pd(OAc)_2$ (5 mol%), additive (1 to 2.0 equiv), alkene (2 to 6 equiv) was added to an oven-dried, septum-capped vial equipped with a stir bar, under a nitrogen atmosphere. The mixture was then stirred at 80 ^oC for the desired length of time (as indicated by TLC and LC-MS, usually 1 h). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~10 mL and dried for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica eluting with hexane/EtOAc. ***Note***: 1 equiv NaTFA or 2

equiv of K_2CO_3 were employed. With dioxane as the solvent, longer reaction times (monitoring by TLC and LC-MS, usually 2 h) are required. [34, 38, 59, 109-112]

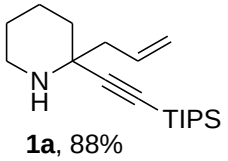
To a solution of cyclic enol ether (1equiv), at 80 °C, under open air condition was added to the cycloalkene (1.5equiv) drop wise. The mixture was allowed to stir at 80 °C for 24 h. Then the mixture was diluted with ethyl acetate (2 mL), filtered, washed with water (5 mL) and brine (5 mL). The organic layer was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc) (6:1) to afford the product as an oil. [34, 38, 59, 109-112]

3.4.4 General procedure D: N-acyl iminium reduction

To the *N*-formyl-substrate (1.0 equiv) dissolved in freshly distilled CH_2Cl_2, was added $NaBH_3CN$ (5 equiv) slowly under nitrogen at 0 °C. TFA (10 equiv) was added slowly and the mixture was stirred for 10 min at 0 °C, then for ~12 h at room temperature (monitoring by LCMS and TLC; the reduced compound is significantly more polar). Upon completion, the reaction was quenched with *sat*. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to obtain the crude product, which were purified by flash chromatography on silica eluting with hexane/EtOAc. [34, 38, 59, 109-112]

3.5 Peak Assignments

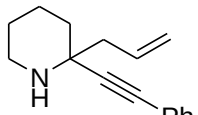
*3.5.1 Peak assignment of **1a***



1a, 88%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20 to 50:50). Yield = 67 mg, 88%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.02 – 5.84 (m, 1H), 5.20 – 4.98 (m, 2H), 3.02 (td, *J* = 12.0, 2.8 Hz, 1H), 2.86 – 2.69 (m, 1H), 2.35 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.17 (dt, *J* = 13.2, 9.5 Hz, 1H), 1.82 – 1.31 (m, 7H), 1.03 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.5, 118.8, 84.6, 73.2, 53.9, 48.0, 42.9, 37.4, 25.6, 21.6, 18.6, 18.6, 18.5, 11.5, 11.2, 11.1. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{35}NSi$ 305.2539; found 305.2544.

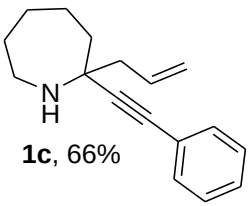
*3.5.2 Peak assignment of **1b***



1b, 87%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 49 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.66 to 6.98 (5H, m), 6.22 to 5.72 (1H, m), 5.51 to 4.88 (2H, m), 3.45 to 2.73 (2H, m), 2.51 to 0.81 (9H, m). 13C NMR (101 MHz, Chloroform-d) δ 133.6, 131.9, 128.3, 127.9, 125.6, 119.1, 92.0, 85.4, 53.9, 48.0, 43.1, 37.4, 25.7, 21.8. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{16}H_{19}N$ 225.1517; found 225.1521.

*3.5.3 Peak assignment of **1c***

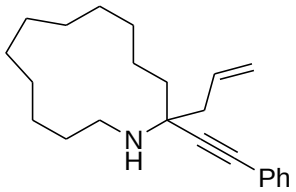


1c, 66%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield =

39.5 mg, 66%. 1H NMR (400 MHz, Chloroform-d) δ 7.88 to 6.98 (5H, m), 6.10 to 5.72 (1H, t), 5.26 to 4.95 (2H, m), 3.33 to 2.66 (2H,m), 2.48 to 0.74 (11H, m). ^{13}C NMR (101 MHz, Chloroform-d) δ 134.4, 131.9, 128.4, 128.1, 123.6, 119.9, 93.6, 84.0, 57.0, 47.9, 44.8, 42.2, 30.4, 28.0, 22.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{17}H_{21}N$ 239.1674; found 239.1678.

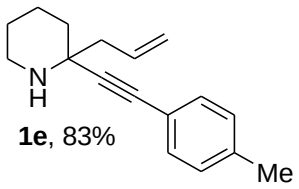
*3.5.4 Peak assignment of **1d***



1d, 74%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 39.5 mg, 74%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 to 7.10 (5H, m), 6.08 to 5.76 (1H, m), 5.41 to 4.95 (2H, m), 2.82 to 2.54 (2H, m), 2.40 to 2.14 (2H, m), 2.04 to 0.91 (21H, m). 13C NMR (101 MHz, Chloroform-d) δ 135.4, 132.1, 128.6, 128.2, 123.7, 118.4, 93.5, 84.2, 56.2, 44.7, 41.6, 37.5, 29.8, 29.2, 27.5, 27.2, 26.7, 25.8, 25.5, 24.9, 20.6. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{23}H_{33}N$ 323.2613; found 323.2610.

*3.5.5 Peak assignment of **1e***

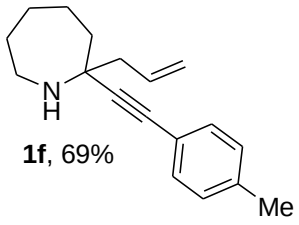


1e, 83%

Prepared from **7** (0.5 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 99 mg,

83%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.75 to 7.43 (2H, d), 7.32 to 7.07 (2H, d), 6.08 to 5.98 (1H, d), 5.22 to 4.98 (2H, m), 3.40 to 2.78 (2H, m), 2.52 to 2.01(6H, m), 1.93 to 1.74 (2H, m), 1.67 to 1.60 (2H, m), 1.51 to 1.42 (2H, m), 1.25 to 0.69 (2H, m). 13C NMR (101 MHz, Chloroform-d) δ 138.0, 133.5, 131.6, 128.5, 120.3, 119.1, 90.7, 85.8, 54.2, 47.8, 44.0, 37.2, 25.5, 21.5. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{17}H_{21}N$ 239.1674; found 239.1678.

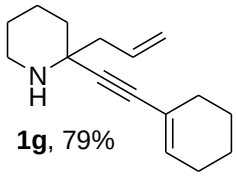
*3.5.6 Peak assignment of **1f***



1f, 69%

Prepared from **7** (0.5 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 87 mg, 69%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.68 to 7.26 (2H, d), 7.18 to 7.09 (2H, d), 6.10 to 5.76 (2H, m), 5.26 to 5.01 (2H, m), 4.10 to , 3.29 (2H m), 3.22 to 2.66 (2H, m), 2.48 to 2.43 (3H, s), 2.34 to 1.12 (8H, m). 13C NMR (101 MHz, Chloroform-d) δ 137.9, 134.6, 131.8, 129.1, 120.5, 118.3, 92.8, 84.1, 57.4, 47.9, 44.8, 42.3, 29.8, 26.1, 24.0, 22.8. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{18}H_{23}N$ 253.1830; found 253.1834.

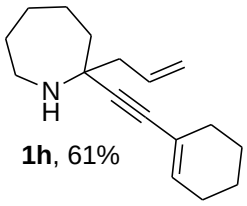
*3.5.7 Peak assignment of **1g***



1g, 79%

Prepared from **7** (0.50 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 90.5 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.03 to 5.66 (2H, m), 5.38 to 4.91 (2H, m), 3.81 to 2.70 (2H, m), 2.49 to 0.64 (17H, m). ^{13}C NMR (101 MHz, Chloroform-d) δ 134.9, 134.0, 121.3, 119.6, 88.7, 87.3, 53.8, 48.0, 44.0, 38.2, 29.7, 29.5, 23.4, 23.0. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{16}H_{23}N$ 229.1830; found 229.1830.

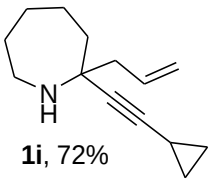
*3.5.8 Peak assignment of **1h***



1h, 61%

Prepared from **7** (0.5 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 74 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.23 to 5.80 (2H,m), 5.28 to 4.92 (2H, m), 3.03 to 2.77 (2H, m), 2.39 to 2.25 (1H, m), 2.24 to1.82 (2H, m), 1.72 to 0.82 (16H, m). 13C NMR (101 MHz, Chloroform-d) δ 138.2, 135.8,120.8, 118.6, 90.5, 85.9, 56.8, 47.9, 44.9, 42.1, 30.4, 30.0, 29.8, 29.5, 27.5, 25.9, 22.9, 22.4, 22.3. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{17}H_{25}N$ 243.1987; found 243.1984.

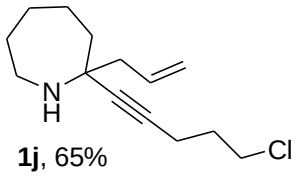
*3.5.9 Peak assignment of **1i***



1i, 72%

Prepared from **7** (0.50 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 73 mg, 72%. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.94 to 5.70 (1H, m), 5.14 to 4.86 (2H, m), 2.82 to 2.74 (2H, m), 2.72 to 2.59 (2H, m), 2.29 to 2.22 (2H, m), 2.17 to 0.57 (11H, m). 13C NMR (101 MHz, Chloroform-d) δ 134.7, 118.4, 87.0, 79.0, 56.3, 48.0, 44.9, 42.3, 30.3, 27.6, 22.8, 8.7. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{14}H_{21}N$ 203.1674; found 203.1677.

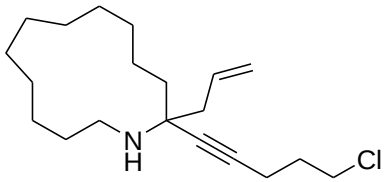
*3.5.10 Peak assignment of **1j***



1j, 65%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 39 mg, 65%. ^{1}H NMR (400 MHz, Benzene-d6) δ 6.25 to 5.99 (1H, m), 5.20 to 5.10 (2H, m), 3.52 to 3.19 (2H, t), 3.13 to 2.75 (2H, m), 2.74 to 2.46 (2H, m), 2.24 to 2.02 (2 H, t), 1.94 to 0.31 (11H, m). ^{13}C NMR (101 MHz, Benzene-d6) δ 139.1, 119.5, 83.7, 83.0, 57.9, 46.9, 43.6, 43.2, 40.0, 31.6, 30.0, 27.3, 22.7, 17.6. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{14}H_{22}ClN$ 239.1441; found 239.1445.

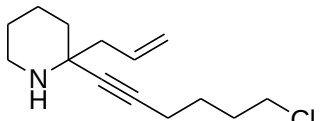
*3.5.11 Peak assignment of **1k***



1k, 71%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 57.3 mg, 71%. ^{1}H NMR (400 MHz, Benzene-d_6) δ 6.14 to 5.81 (1H, m), 5.15 to 4.95 (2H, m), 3.37 to 3.20 (2H, t), 2.84 to 0.26 (29H, m). ^{13}C NMR (101 MHz, Benzene-d_6) δ 136.5, 117.8, 87.0, 85.2, 81.6, 79.3, 55.6, 44.9, 43.0, 41.6, 38.9, 31.8, 28.8, 28.0, 26.6, 26.0, 24.8, 23.7, 21.2, 20.8, 16.1, 9.1. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{20}H_{34}ClN$ 323.2380; found 323.2384.

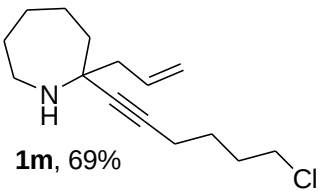
*3.5.12 Peak assignment of **1l***



1l, 77%

Prepared from **7** (0.50 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 92 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.99 to 5.75 (1H, m), 5.20 to 4.99 (2H, m), 3.77 to 3.45 (2H, m), 3.33, to 2.52 (2H, m), 2.39 to 0.82 (15H, m). 13C NMR (101 MHz, Chloroform-d) δ 133.6, 118.9, 84.6, 82.6, 53.6, 48.0, 44.7, 42.8, 37.3, 31.6, 26.2, 25.5, 21.6, 18.1. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{14}H_{22}ClN$ 239.1441; found 239.1445.

*3.5.13 Peak assignment of **1m***

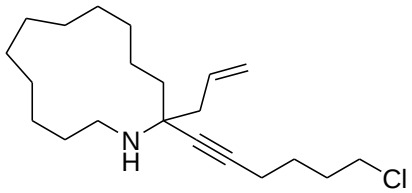


1m, 69%

Prepared from **7** (0.50 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 92

mg, 69%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (dt, *J* = 15.4, 8.1 Hz, 1H), 4.98 to 4.87 (m , 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 2.83 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.15 to 0.77 (m, 17H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 119.3, 84.4, 82.7, 56.3, 47.7, 44.5, 43.1, 42.1, 31.5, 29.6, 27.5, 25.4, 22.7, 18.4. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{15}H_{24}ClN$ 253.1597; found 253.1593.

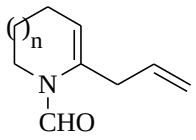
*3.5.14 Peak assignment of **1n***



1n, 74%

Prepared from **7** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 62.3 mg, 74%. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.98 to 5.67 (1H, m), 5.12 to 4.98 (2H, m), 3.71 to 3.23 (2H, t), 2.68 to 0.59 (29H, m). ^{13}C NMR (101 MHz, Chloroform-d) δ 134.9, 118.0, 87.1, 85.0, 81.7, 79.0, 55.7, 44.9, 43.9, 41.4, 37.7, 34.9, 31.9, 30.4, 29.2, 27.5, 26.8, 25.6, 24.5, 23.7, 20.6, 16.7, 8.5. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{21}H_{36}ClN$ 337.2536; found 337.2540.

*3.5.15 Peak assignment of **10a***

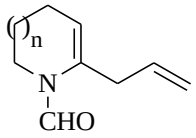


10a; n = 2, 77%

Prepared from **15b** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield =

29.1 mg, 77%. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_9H_{13}NO$ 151.0997; found 152.2056. As reported by us.[59]

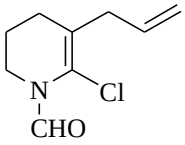
*3.5.16 Peak assignment of **10b***



10b; n = 8, 72%

Prepared from **15c** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 47.3 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 to 7.82 (s, 2H), 6.74 (m, 1H), 6.29 to 4.92 (m, 2H), 4.63 to 4.08 (t, 1H), 3.75 to 3.28 (m, 2H), 3.05 to 1.17 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 136.6, 134.1, 132.9, 129.9, 126.8, 124.1, 117.6, 117.5, 110.7, 64.8, 43.1, 41.3, 39.9, 37.9, 36.1, 31.8, 28.2, 27.9, 27.1, 26.9, 25.6, 25.5, 24.0, 24.0, 23.8, 23.7, 23.2, 23.0.

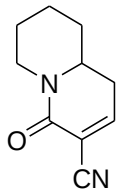
*3.5.17 Peak assignment of **16***



16, 69%

Prepared from **15a** (0.25 mmol) using General Procedures A & B. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 47.3 mg, 69%. As reported by us.[109]

*3.5.18 Peak assignment of **18***



18, 67%

***N*-formyl reduction:** Compound **17** (1 mmol) was reduced using **General Procedure D.**

Desilylation: To all of reduced **17** in THF (10.0 mL) were added CF_3CO_2H (310 mg, 2.7 mmol) and a 1.0 M solution of TBAF (4.0 mL, 4.0 mmol) in THF successively at 0 °C. The resulting reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with water, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give corresponding desilylated products.

Hydroboration-oxidation: To a solution of the crude alkynyl piperidine (1.0 equiv) in freshly distilled CH_2Cl_2 (4 mL) at –78 °C was added dropwise a 2 M solution of $BH_3{\cdot}SMe_2$ in THF (500 µL, 1 equiv). After a few minutes, the mixture was warmed to room temperature and stirring was continued for 6 h. It was then cooled to 0 °C and a few drops of 10% NaOH (aq) were added slowly followed by 0.5 mL of 30% H_2O_2. The mixture was returned to room temperature and stirred for 3 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with

brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde as an oil.

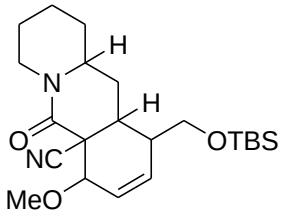
Deformylation: 6% HCl (1.5 mL) was added to the solution of *N*-formylated aldehyde (50 mg, 0.18 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 18 h. After completion of reaction (monitored by TLC), H_2O was added and the whole mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated under reduce pressure to give the free piperidinal as an oil.

Acylation: The piperidinal was dissolved in dichloromethane (5 mL) and triethylamine (1.0 mL, 7.10 mmol) was added drop-wise at 0 °C, followed by the drop-wise addition of cyanoacetylchloride (727 mg, 7.10 mmol) as a solution in dichloromethane (2 mL). The resulting red solution was stirred at the same temperature for 2 h and then warmed to room temperature for 3 h, at which time saturated aqueous $NaHCO_3$ (10 mL) was added and volatiles removed *in vacuo*. The resulting aqueous solution was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting acylated piperidinal was obtained as a red oil.

Knoevenagel condensation: To the acylated piperidinal was added a 20 mM solution of HCl/CH_2Cl_2 (prepared from AcCl/MeOH) and stirring was continued for 12 h at room temperature (TLC monitoring). The solution was diluted with DCM and transferred to a separatory funnel. Sat. aqueous NH_4Cl was added and the layers were separated. The aqueous layer was extracted with DCM and the combined layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to obtain the bicycle as an oil. ^1H NMR (400 MHz, C_6D_6) δ 6.57 to 6.54 (t, 1H), 4.42 to 4.38 (m, 1H),

2.76 to 2.67 (m, 1H), 2.28 to 2.18 (m, 2H), 1.88, to 1.80 (m, 2H), 1.55 to 0.78 (m, 5H). ^{13}C NMR (101 MHz, C_6D6) δ 159.15, 152.19, 115.27, 112.15, 53.31, 43.11, 32.60, 30.68, 24.22, 23.22. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{10}H_{12}N_2O$ 176.0950; found 176.0955.

*3.5.19 Peak assignment of **20***



20, 79%

A 10 mL microwave vial was flame-dried, evacuated and flushed with nitrogen. A solution of dienophile **18** (176 mg, 1.0 mmol) in toluene (2 mL) was added to the vial under a nitrogen atmosphere followed by a solution of diene **19**[109] (456 mg, 2 mmol) in toluene (2 mL). The mixture was heated to 150 ^{o}C under microwave irradiation for 2 h. It was then cooled to room temperature and the toluene was azeotroped off. Purification by flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20) afforded tricycle **20** in 79% yield and >95:5 dr. **Note**: It is critical to have absolutely pure starting materials as any minor impurities simply lead to decomposition of the diene.^{1}H NMR (400 MHz, Benzene-d_6) δ 5.66 (ddd, *J* = 10.4, 4.3, 2.9 Hz, 1H), 5.37 (ddt, *J* = 10.4, 2.0, 1.0 Hz, 1H), 4.89 (dp, *J* = 13.1, 1.9 Hz, 1H), 4.12 (ddt, *J* = 4.1, 1.9, 0.9 Hz, 1H), 3.45 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.31 (t, *J* = 9.8 Hz, 1H), 3.09 – 2.84 (m, 5H), 2.78 – 2.62 (m, 1H), 2.29 – 2.04 (m, 3H), 1.45 – 0.87 (m, 24H), 0.02 (s,s, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.9, 127.4, 123.7, 118.9, 76.7, 62.9, 59.1, 55.3, 49.1, 43.9, 38.0, 33.05, 31.0, 25.6, 25.3, 24.9, 23.3, 17.9, -5.7. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{22}H_{36}N_2O_3Si$ 404.2495; found 404.2491.

CHAPTER 4

SYNTHESIS OF DIHYDRO-1,4-OXAZINES, THIAZINES AND THEIR SYNTHETIC APPLICATIONS

4.1 Introduction

As part of a diversity-oriented synthesis approach to functionalized *N*,*O*- and *N*,*S*-heterocycles, it was of interest to explore the possibility of converting thiomorpholinones and morpholinones prepared using methodology developed by a fellow graduate student in our laboratories. Specifically we desired access functionalized 1, 4-oxazines and 1, 4-thiazines because they make up the backbone of a variety of pharmaceuticals making them highly sought after structural motifs within both the medicinal and synthetic organic chemistry communities. For example, 1,4-oxazines and 1,4-thiazines are found in a variety of pharmaceuticals that have been used as antibacterial, antioxidants, appetite suppressants, and antibiotics (Figure 4-1). They have also been used for other applications such as textile drying, bleaching, and fruit preservation agents. They have also been used by the organic synthetic communities as ligands as part of highly active metal based catalysts.[5, 155-158]

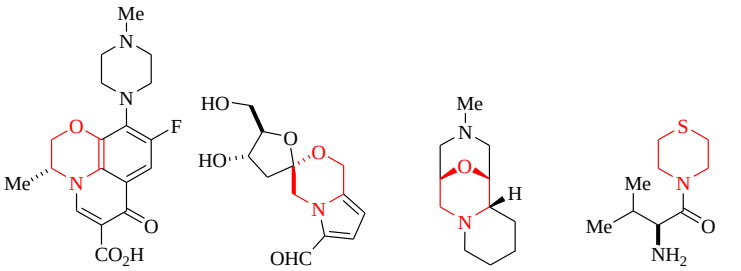


Figure 4-1 Examples of biologically active compounds featuring 1,4-oxazine and 1,4-thiazine derivatives

The popularity of finding new ways to construct unsaturated azaheterocycles containing an oxygen or sulfur has become more and more relevant as they are found in

structurally complex pharmaceutical compounds such as levofloxacin (antibacterial) [159] and acortatarin A (antioxidant).[5] This has driven the industry to find new cost-effective, efficient, and highly modular methodologies to construct these highly functionalized biologically-active motifs. These methodologies can then be used to create large diverse libraries of compounds that can be further functionalized or used in structure-activity relationship studies (SAR).[5]

In recent times, several synthetic methodologies aimed at creating 1,4-oxazines and 1,4-thiazines, many of which use a metal catalyst, have emerged such as those popularized by Katukojvala[160] (using diazoenals), Saa[161, 162] (using catalytic ruthenium carbenes derived from alkynals and alkynones), Bode[137, 163-167] (using SnAP and SLAP reagents), Tiecco[168] (using vinyl selenones), and Carreira[169, 170] (using spirocyclic 3-oxetanones) (Figure **4-2 A-C**).

From our vantage point, a diversity oriented approach to the synthesis of 1,4-oxazines and 1,4-thiazines that addresses elements such as cost-effectiveness, bench stability, and high modularity is imperative. However, it is recognized that developing such a protocol would be quite challenging as morpholines and thiomorpholines are prone to ring opening and have conformational limitations.

Our group previously reported that through the use of 1,3-azadienes of type **2** and cyclic anhydrides such as **1,** construction of highly-functionalized cyclic compounds with vicinal stereocenters with a high degree of modularity is possible through a Castagnoli-Cushman reaction (Figure **4-2D**). The combination of 1,3-azadienes with cyclic anhydrides with reduced α-C-H acidity provides a unique balance of reactivity and selectivity to form highly functionalized morpholine and

thiomorpholine bearing compounds. With these products in hand, we theorized that their amenability to chemoselective Vilsmeier-Haack functionalizations would pave the way for a DOS approach to vinylated dihydro-1,4-oxazines and thiazines such as **4**.

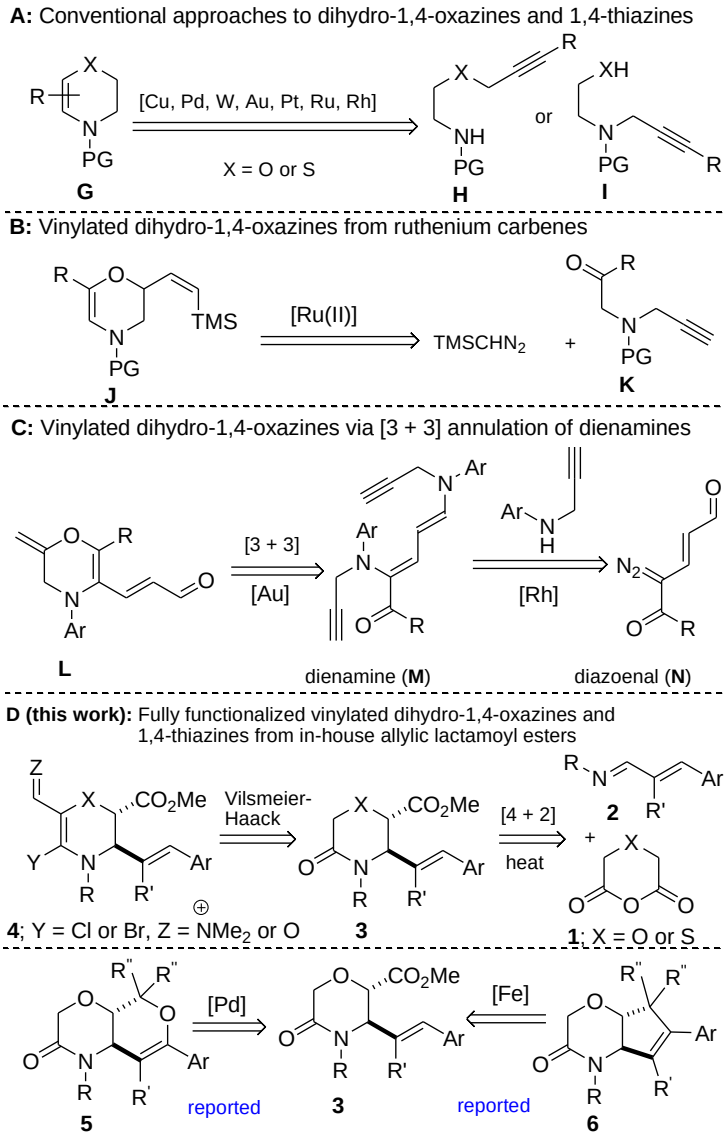


Figure 4-2 Proposed plan for accessing vinylated dihydro-1,4-oxazines and 1,4-thiazines

We were highly interested in generating these vinylated dihydro-1,4-oxazines and 1,4-thiazines because they are functionalized in all five possible positions around the ring. The Castagnoli-Cushman product **3** is already highly functionalized and the α-alkenyl motif can be used in a large variety of reactions such as hydroarylation,[98] oxoamination,[100] dioxygenation[171] trifluoro-methylation,[101] aziridination,[172] dihydropyranation **5**,[111] pentannulation **6**,[112] and boration.[97] Additionally the β-ester motif can be utilized in a wide variety of reactions such as Grignard additions, reductions, and fragment coupling protocols. The vinylated dihydro-1,4-oxazines and 1,4-thiazines **5** could also be used in a similar manner to our α-halo eneformamide as it is an α-halo enamine. Thus, the functional halogen handle can be utilized in cross-coupling strategies.

We fully recognize that there are many challenges associated with the proposed plan of studies given that morpholines and thiomorpholines are highly prone to ring opening under strong acidic and basic conditions. Thus, in order for our strategy to work, it would be absolutely imperative to find suitable conditions that negate/minimize ring-opening events. Additionally, the Vilsmeier-Haack reaction has been shown to react with esters, alkenes, electron-rich arenes, carboxylic acids, and lactams. Thus, achieving site-selective functionalization with the Vilsmeier-Haack reaction could prove to be a herculean task as our intermediate contains all of these functional groups. In this chapter, we present our thorough effort toward the assembly of a diverse library of structurally complex and fully substituted vinylated and arylated dihydro-1,4-oxazines and 1,4-thiazines. This methodology stands alone over other methodologies as these

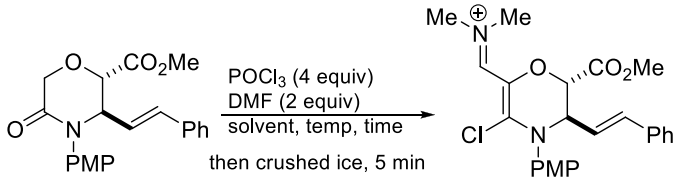
dihydro-1,4-oxazines and 1,4-thiazines can be achieved in a highly modular, cost effective, scalable manner and under mild conditions. Additionally, these highly functionalized dihydro-1,4-oxazines and 1,4-thiazines can be further functionalized by engaging them in some C-C and C-N bond forming processes, leading to the rapid assembly of molecular complexity.

4.2 Results and Discussion

4.2.1 Optimization of the Vilsmeier-Haack functionalization of allylic morpholinonate

As previously discussed, we needed to find optimum conditions for the Vilsmeier-Haack reaction to prepare vicinally functionalized alkenylated or arylated dihydro-1,4-oxazines and thiazines from lactamoyl esters of type **3**. The optimization conditions are shown in Figure **4-3**. In a similar manner to the way we generated cyclic-α-chloro eneformamides, preparation of the Vilsmeier-Haack reagent (by refluxing a solution of DMF and $POCl_3$ in dichloromethane for one hour) was first achieved followed by addition of lactamoyl ester **3a**. We allowed the reaction mixture to stir for 30 minutes at 40 °C (Figure **4-3** entry 1) and after hydrolytic workup we isolated the iminium salt **4a1** in pretty low yield. The low yield was due to the starting material **3a** not being fully consumed and the Vilsmeier-Haack reaction reacting with the alkene creating a mixture of E/Z isomers (see **7**). We then allowed the reaction to go for 2 h (Figure **4-3** entry 3) and got better yield and complete consumption of starting material (monitored by GC-MS), but the product was more of the E/Z isomers and less of the desired product. This led us to try the reaction at room temperature, and after 12 h (Figure **4-3**, entry 4) we saw complete conversion to product and no signs of the formylation of the alkene with

75% yield. Allowing the reaction to go for an extended period of time (22 h) increased the yield to 89% (Figure **4-3**, entry 5), but after allowing the reaction to go to 36 h (Figure **4-3**, entry 6), we began to see formylation of the alkene again. To further optimize the reaction, we tried to use different solvents such as 1,2-dichloroethane and chloroform at different temperatures but the reaction was quite recalcitrant (Figure **4-3**, entries 7-9) and the process was less efficient than under the dichloromethane conditions. In order to afford the chloro enamine **8** we tried the reaction without the use of dimethylformamide (DMF) and no reaction occurred. Lastly, we tried to add the $POCl_3$ and DMF to substrate **3a** directly instead of using inverse addition and we saw no conversion to product, indicating that inverse addition (adding lactam to Vilsmeier-Haack reagent) is necessary for the reaction to proceed as intended.



Entry	solvent	temperature (°C)	time (h)	yield of **4a** (%)
1	CH_2Cl_2	40	0.5	38
2	CH_2Cl_2	40	1	60
3	CH_2Cl_2	40	2	49
4	CH_2Cl_2	rt	8	75
5	CH_2Cl_2	rt	22	89
6	CH_2Cl_2	rt	36	78
7	$C_2H_4Cl_2$	rt	22	<5
8	$CHCl_3$	rt	22	20
9	$CHCl_3$	70	8	62
10[a]	CH_2Cl_2	40	18	0

a. in the absence of DMF

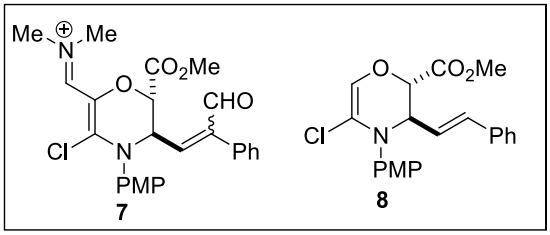


Figure 4-3 Optimization of the Vilsmeier-Haack functionalization of allylic morpholinonate **1a**

4.2.2 Synthesis of vinylated dihydro-1,4-oxazines

With optimized conditions for the Vilsmeier-Haack functionalization protocol in hand (Figure **4-3** entry 5), we began to apply these conditions to a large library of functionalized lactams **3**. We wanted to test the limitations of the Vilsmeier-Haack reaction on a library of compounds featuring different *N*-substituents and alkenyl substituents. With this in mind, we chose our *N*-substituents carefully as we knew that the *N*-substituent on morpholines can have a huge effect on biological activity. Thus, we chose a wide range of *N*-substituents, including electron-rich-, electron neutral-, and electron-poor aryl groups. We also explored the use of benzyl and alkyl *N*-substituents to further diversify the library of compounds constructed. In each case, moderate to good yields were obtained (see **4a1-4a6**).

One of the advantages of this synthetic pathway (Figure **4-4**) is our ability to isolate the iminium diene salt intermediates (**4a1 – 4a6)**. This is beneficial as the salts are more stable than their haloenal counterparts. This allows us to hold onto the compounds for longer periods of time and allow us to use them in SAR studies or for future transformations. However, we still wanted to convert the iminium salt to the haloenal as this would provide a great substrate for further functionalization. With this in mind, we ran the iminium salt compounds through flash chromatography on silica pretreated with triethylamine (**4b1-4b4**). To our satisfaction, this provided great recovery of the enal over the iminium salt. We also attempted to hydrolyze the iminium salt using a variety of conventional bases such as NaOH, KOH, NaOAc, or NH_4OAc. However, this led to low yields, loss of the starting materials (*i.e.*, **3**), and high diastereomer ratio, presumably due to epimerization.

Another benefit to this methodology is that it is highly scalable to a multi-gram scale (**4b1** and **4b4**). This transition metal-free, cost-effective, highly modular, scalable, and step-economical approach to vicinally functionalized alkenylated dihydro-1,4-oxazines and thiazines stands alone over existing methodologies.

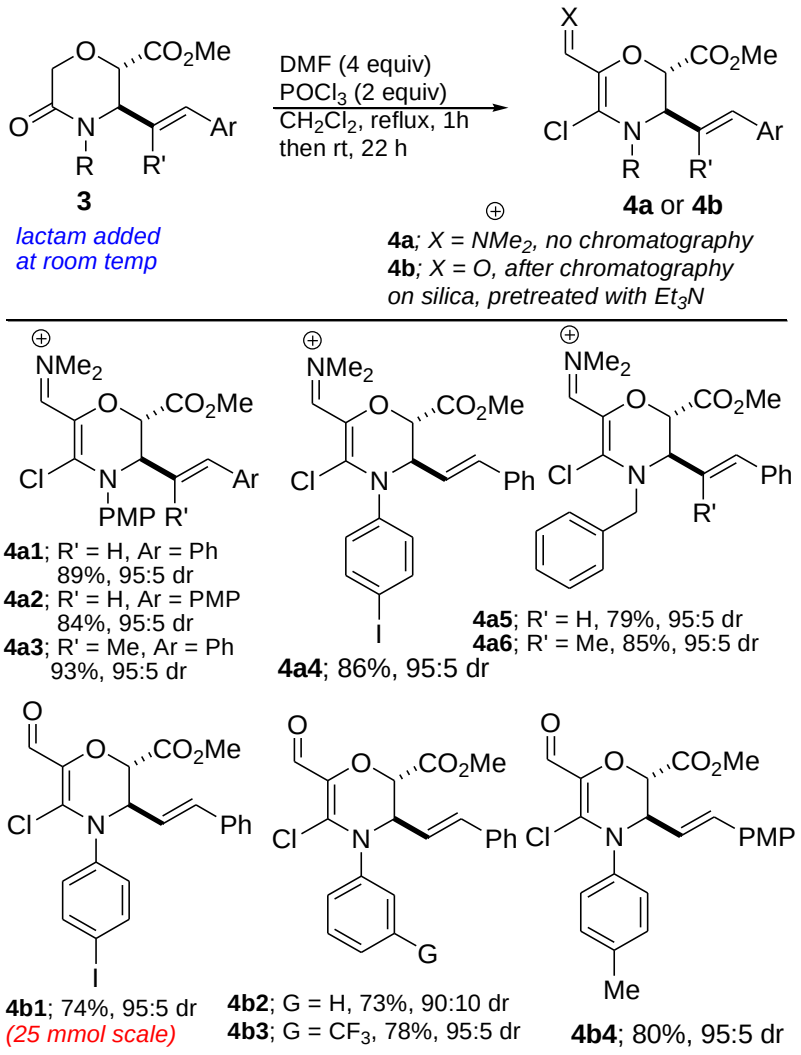


Figure 4-4 Synthesis of vinylated dihydro-1,4-oxazines

4.2.3 Synthesis of α-amino-benzylic dihydro-1,4-oxazines

We also wanted to explore this methodology on morpholinonates bearing α-amino benzylic stereocenters to construct dihydro-1,4-oxazines with similar efficiency to the vinylated products shown earlier (Figure **4-5**). We have found that in these cases, it takes

longer reaction times. Nevertheless, the reaction still proceeds with high efficacy. In the specific cases where the *N*-substituent is a *tert*-butyl group or isopropyl group the reaction is more reluctant and much higher temperatures are required (**10b1**/**10b2**). Thinking ahead, we knew we wanted to use these haloenaminals for challenging cross-coupling reactions. Thus, bromoenaminal variant **10a5** was synthesized in satisfactory and synthetically attractive yield. Although creating the bromoenaminal variant was not cost effective (1 g of $POCl_3$ costs ~\$0.045 while 1 g of $POBr_3$ costs ~\$4.6), we know that some cross-couplings, especially those featuring electron-deficient substituents, can be extremely challenging and would benefit from having a better leaving group.

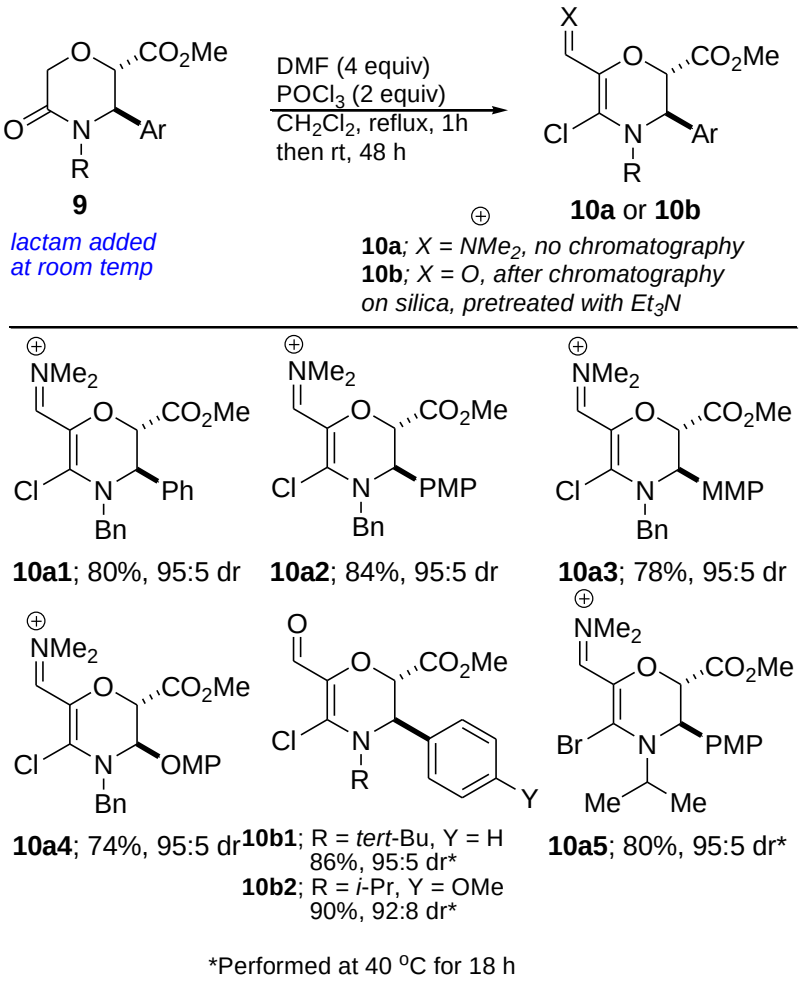


Figure 4-5 Synthesis of α-amino-benzylic dihydro-1,4-oxazines

4.2.4 Synthesis of allylic and benzylic dihydro-1,4-thiazines

As highlighted on several occasions, going from one ring system to another can be a very uphill task. In this case, we wanted to extend the synthetic methodology developed herein from morpholinates to thiomorpholinates, which are well known to ring open even under friendly reaction conditions. We were therefore very pleased to see that chemoselective vicinal difuntionalization of both allylic and benzylic thiomorpholinates (**4c1 and 12**) work with our newly found conditions (Figure **4-6**). In the case of these thiomopholinates, the reactions are much faster than with the morpholinonate counterparts. This is expected as typically sulfur-bearing heterocycles tend to be more reactive than oxygen-bearing heterocycles due to the size and electronegativity of sulfur over oxygen. Additionally, the thiomorpholinates are far more unstable than the morpholinates as they begin to decompose during the time it takes to run full NMR data analysis at room temperature. Due to the fragile nature of these compounds, yields were lower as some of the compound would decompose during the isolation and analysis steps.

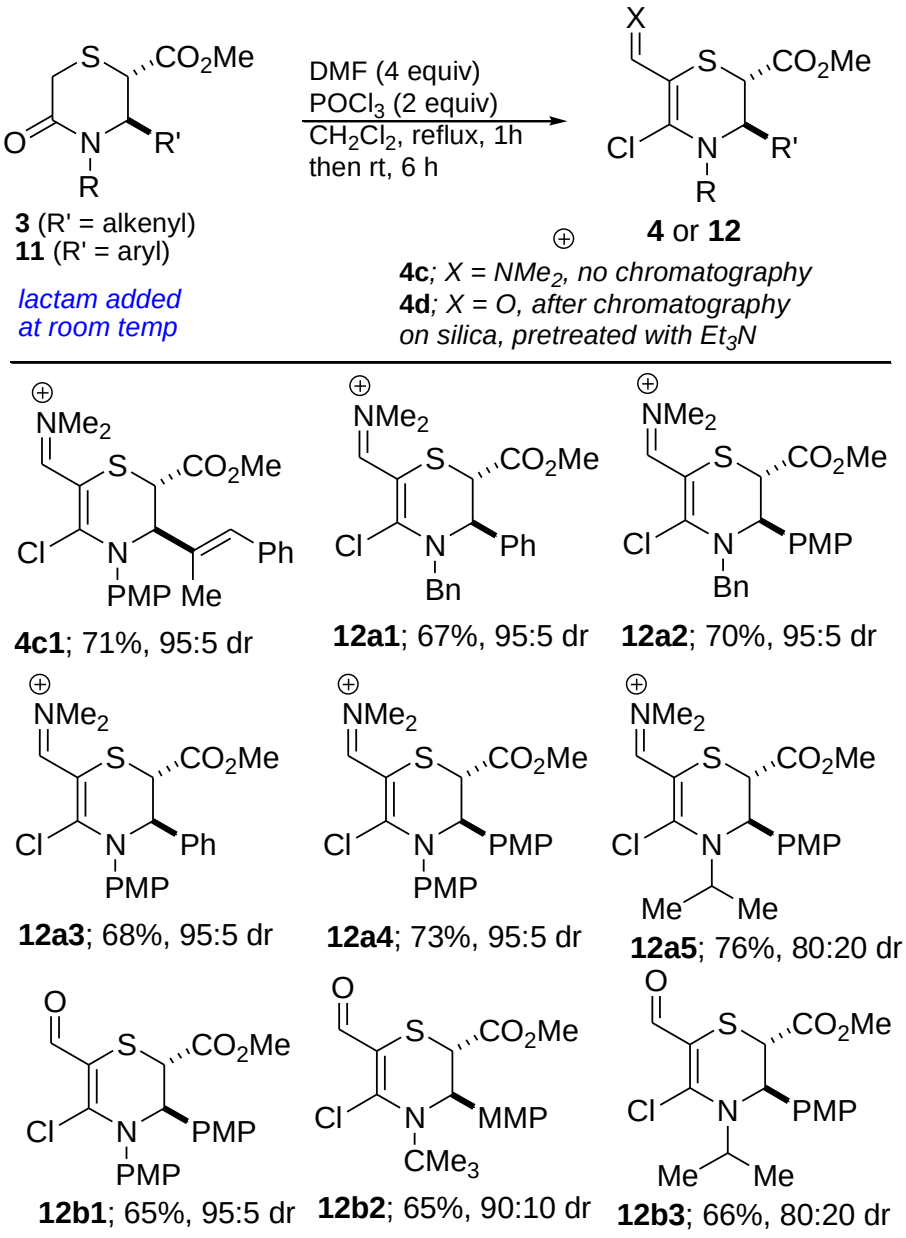


Figure 4-6 Synthesis of allylic and benzylic dihydro-1,4-thiazines

4.2.5 Sonogashira cross-coupling of iodoarylated chloro enamines or iodoarylated lactams with terminal alkynes and subsequent manipulation

Having demonstrated how we could construct a large library of vinylated and benzylic dihydro-1,4-oxazines and dihydro-1,3-thiazines, we wanted to show what we could do with them (Figure **4-7**). We wanted to illustrate their importance and to illustrate how synthetically useful these compounds are and how they can act as synthetic

precursors to even more structurally complex compounds. For example, if the *N*-substituent on these dihydro-1,4-oxazines is an iodoaryl group (**4b1)** then the iodo group and the chloro group can be used in one-pot Pd- and Cu-catalyzed Sonogashira cross-coupling reactions (Figure **4-7)**. In our case, we took the iodoarylated chloro enaminal (**4b1**) and reacted it with excess 4-ethynyltoluene to couple at both the iodo and chloro positions (**13**). To our excitement, the mild coupling conditions showed no signs of epimerization, hence, the diastereomer ratio was preserved. It is relevant that **4b1** couples efficiently at the chloro position since vinyl chlorides are rarely used in cross-couplings at room temperature. This is likely due to the slow oxidative addition step in the catalytic cycle.[173] We have also found that we can take our *N*-aryliodo lactomyl esters (**3d1 and 3d2**) and do Sonogashira type cross couplings before performing the Vilsmeier-Haack reaction (**14a-c**). Pleasingly, we find that compounds such as **14a-c** successfully undergo the Vilsmeier-Haack reaction (**15a-b**). This is exciting as this allows us to cross-couple different reagents onto the aryl-iodo position and the α-amino position. Once we couple the iodo-position on the lactamoyl ester, we performed the Vilsmeier-Haack reaction to generate the vinyl chloride and now the substrate is set up for additional cross-coupling strategies.

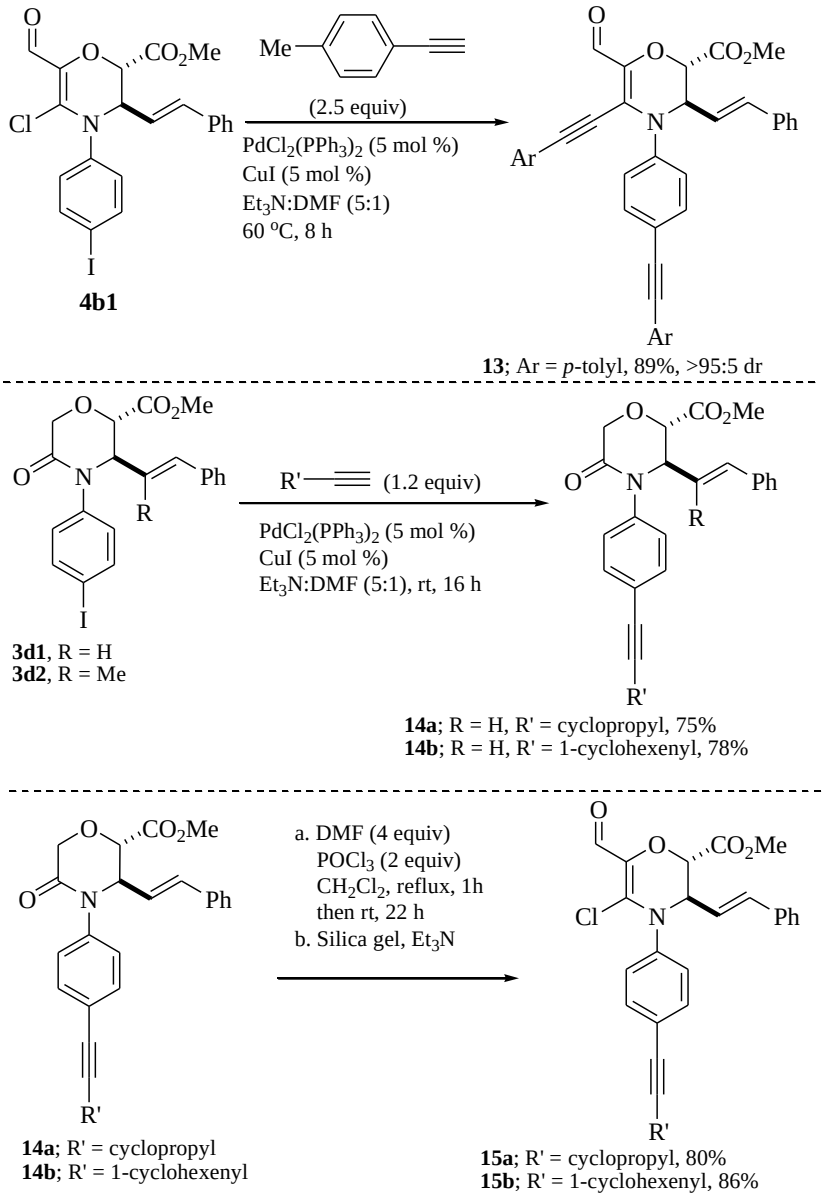


Figure 4-7 Sonogashira cross-coupling of iodoarylated chloro enamines or iodoarylated lactams with terminal alkynes and subsequent manipulation

4.2.6 Condensation of β-chloroenals with primary amines

After successfully functionalizing the vinyl chloride and iodoaryl motifs, we turned our attention to the aldehyde subunit (Figure **4-8**). Treatment of enals with primary amines is a simple way to introduce C-N bonds. Thus, we took compounds **4b2** and **15a-b** and treated them with primary amines to furnish 1,3-aziadienes such as **16a-c**.

When α-thioalkoxy-β-chloroenal **12b4** is subjected to the same reaction conditions, partial conversion to iminodiene **16d** is observed even after two weeks at room temperature. Although these are simple transformations, they are noteworthy since the azadienes may be employed as dienes or dienophiles in hexannulative-type strategies. Additionally, it is quite remarkable that we are able to isolate and store such azadienes since the fragility of imines is a common problem that plagues the synthesis community.

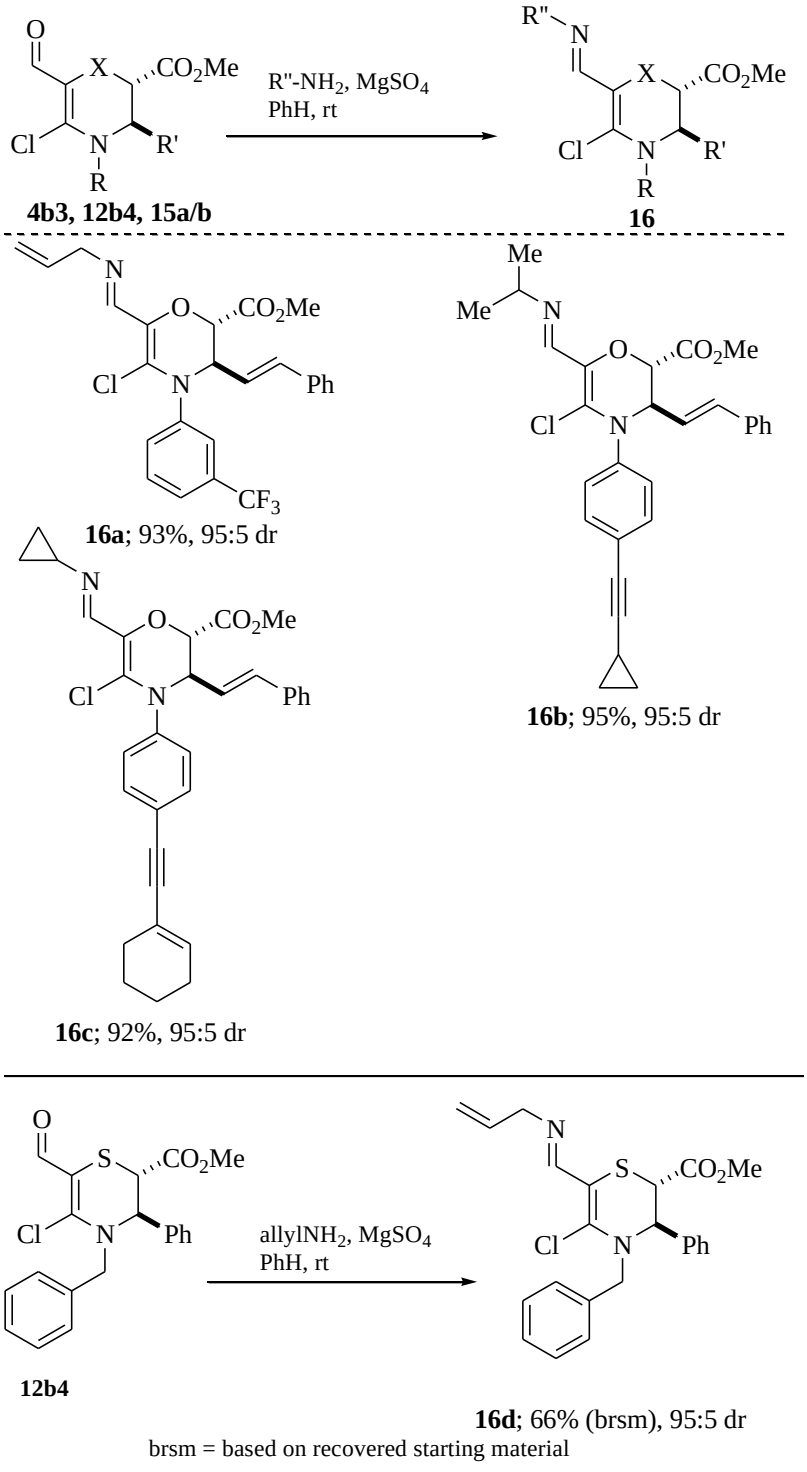


Figure 4-8 Condensation of β-chloroenals with primary amines

4.2.7 Stereoselective Wittig olefination of β-chloro enal 18 and subsequent preparation of bis-homoallylic alkenol 19

Wittig olefination of the aldehyde motif resident in **4b4** has been explored. Intrinsic to this design was the prospect of utilizing the diene product in Diels-Alder type reactions. Fortuitously, two undergraduate students in our lab have found that treatment of **4b4** with an instant ylide furnishes *E*-configured styrene derivative **17**, in excellent stereospecificity. Our group has also had resounding success with Grignard additions to lactamoyl esters of type **3**. We next attempted an addition of allylmagnesium bromide to highly functionalized dehydromorpholine **17** and were elated to obtain tertiary alkenol **18** in good yield. Additionally, no complications arising from Grignard fragment exchange or enolization were observed.

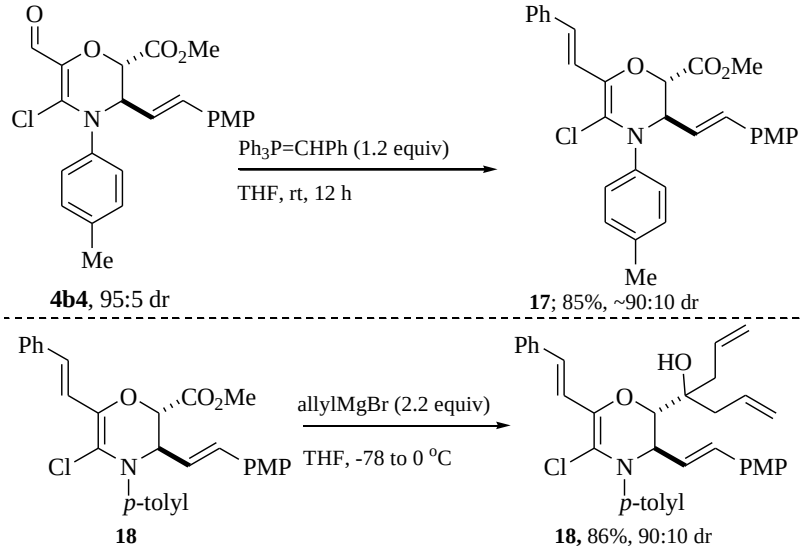


Figure 4-9 Stereoselective Wittig olefination of β-chloro enal **17** and subsequent preparation of *bis*-homoallylic alkenol **18**

4.3 Conclusion

In this chapter, we presented a cost-effective, highly modular, scalable, and DOS approach to functionalized 1,4-oxazines and 1,4-thiazines. We were able to generate

these highly functionalized 1,4-oxazines and 1,4-thiazines without the use of a transition metal-based catalyst. Since extending reactivity trends from one *N*-heterocycle to another can be a very challenging, partly due to conformational constraints and proneness to ring opening, we were quite pleased to demonstrate after rigorous optimization that these methodologies are applicable to both the morpholine and thiomorpholine heterocycles. We were also able to demonstrate the synthetic utility of these functionalized 1,4-oxazines and 1,4-thiazines by taking advantage of the chlorine leaving group, the enal motif, and the ester functional group through the use of Sonagashira cross-couplings, 1,3-azadiene formations, Wittig olefination, and Grignard additions, respectively.

4.4 Methods

All experiments involving palladium precatalysts were carried out under an inert atmosphere of argon or nitrogen. Et_3N, MeOH, THF, benzene, toluene, Et_2O, and acetonitrile were distilled using the Grubbs solvent system. Anhydrous DMF and 1,4-dioxane were used as purchased. Dichloromethane was distilled from $MgSO_4$. K_2CO_3, CuI, and the alkynes were used as purchased. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by staining with CAM, *p*-anisaldehyde, or $KMnO_4$. Unless otherwise indicated, ^1H, ^{13}C, DEPT-135 NMR spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).[34, 38, 59, 109-112]

4.4.1 General procedure A: Formation of 1,2-dihydrothiazines and –oxines

To a solution of DMF (4 mmol, 4 equiv) in CH_2Cl_2 (5 mL) at 0 ^oC was added dropwise, the corresponding phosphorus oxyhalide (2 mmol, 2 equiv) dissolved in CH_2Cl_2 (2 mL). The resulting mixture (pale yellow in the case of the chloride or milky white in the case of the bromide) was refluxed for 20 min. A solution of lactamoyl ester (1 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was stirred under reflux for the indicated time period (TLC and LC-MS monitoring was used to followed the extent of the reaction). Upon completion, the mixture was allowed to warm to room temperature and then poured into a large flask containing crushed ice. After stirring at rt for 30 min, the layers were separated. The aqueous layer was extracted once with CH_2Cl_2. The combined organic layer was concentrated to ~100 mL and was dried over Na_2SO_4 for 30 min. The mixture was filtered and concentrated under reduced pressure to give the desired product as salt. Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAC afforded the corresponding enals. *Caution: The haloenals are not very bench stable and should be stored in the refrigerator either neat or as a solution in benzene.* [34, 38, 59, 109-112]

4.4.2 General procedure B: Sonogashira coupling of dihydro-1,4-oxazines

To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added the 2-halo enamide (1 mmol, 1.0 equiv) in DMF (5 mL) under an argon or nitrogen atmosphere. The desired alkyne (1.2 equiv) was added followed by addition of Et_3N (0.7 mL, 5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%) and CuI (2 mg, 1 mol%) were added rapidly and concurrently. The mixture was then stirred at the desired temperature for the desired length of time (as indicated by

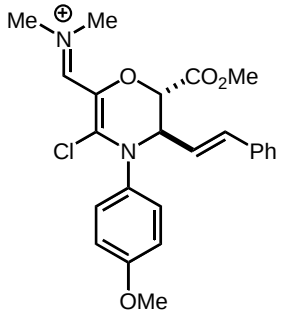
TLC and LC-MS). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~20 mL and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica eluting with hexane/EtOAc. [34, 38, 59, 109-112]

4.4.3 General procedure C: Formation of 1,3-azadienes from 1,2-dihydrothiazines and –oxines

A roundbottom flask was equipped with a stir bar, followed by the addition of the enal (1 mmol), the amine (1.5 equiv), benzene (5 mL), and anhydrous $MgSO_4$ (200 mg). The cloudy mixture was allowed to stir at room temperature with regular monitoring via Thin Layer Chromatography (TLC). After complete depletion of the amine, the mixture was filtered and concentrated under reduced pressure to attain the crude enamine, which was carried forward into the next step without further purification. Any amount of enamine not immediately used required storage in a freezer. [34, 38, 59, 109-112]

4.5 Peak Assignments

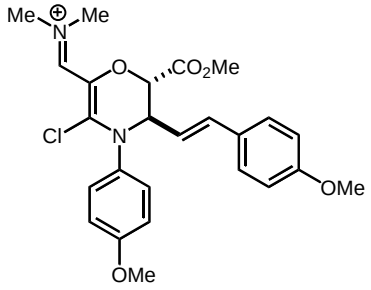
*4.5.1 Peak assignment of **4a1***



Compound **4a1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 392 mg, 89%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 - 6.69 (m, 10H), 6.32

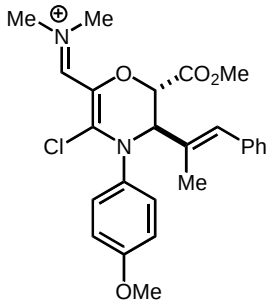
(d, *J* = 15.8 Hz, 1H), 6.14 (dd, *J* = 15.8, 8.2 Hz, 1H), 4.94 (s, 1H), 4.82 (d, *J* = 8.1 Hz, 1H), 3.69 - 3.28 (sm 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 159.9, 151.3, 144.7, 137.5, 136.1, 134.9, 129.3, 128.8, 127.7, 127.1, 124.7, 122.8, 114.8, 114.6, 74.1, 66.5, 55.6, 53.7, 50.5, 41.7.

*4.5.2 Peak assignment of **4a2***



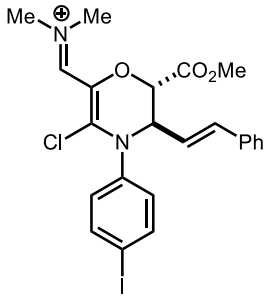
Compound **4a2:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 396 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.29 (s, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.80 (dd, *J* = 14.8, 7.7 Hz, 2H), 6.35 (d, *J* = 14.6 Hz, 2H), 5.11 (s, 1H), 4.95 - 3.60 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 160.3, 151.9, 136.6, 128.8, 134.8, 129.2, 128.0, 127.5, 123.6, 118.0, 116.0, 115.8, 74.7, 66.1, 56.3, 55.9, 53.2, 51.5, 32.2, 41.4.

Peak assignment of **4a3**



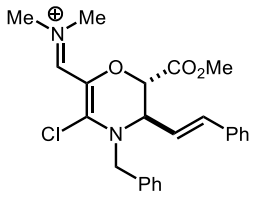
Compound **4a3:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 423 mg, 93%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (s, 1H), 7.75 – 6.98 (m, 9H), 6.94 – 6.71 (d, 2H), 6.3 (s, 1H), 4.95 (s, 1H), 4.83 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.72 (s, 6H), 2.04 – 1.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 162.6, 151.6, 146.1, 135.5, 133.8, 131.4, 130.0, 129.0, 128.8, 122.5, 115.3, 73.4, 71.6, 55.7, 55.5, 53.9, 50.5, 50.2, 41.8, 15.1.

Peak assignment of **4a4**



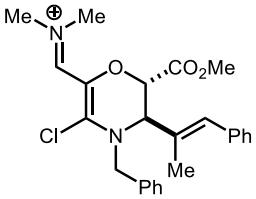
Compound **4a4:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 461 mg, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.30 – 7.16 (m, 3H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.45 (d, *J* = 15.0 Hz, 1H), 6.30 (dd, *J* = 15.5, 7.8 Hz, 1H), 5.05 (s, 1H), 4.93 (d, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 3.63 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 152.3, 143.3, 140.6, 139.0, 138.5, 136.4, 134.6, 130.3, 129.1, 128.9, 126.7, 123.1, 120.7, 95.3, 75.2, 66.0, 53.9, 50.9, 42.2.

*4.5.3 Peak assignment of **4a5***



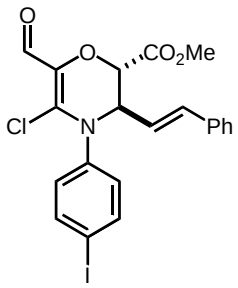
Compound **4a5:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 336 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.33 - 6.48 (m, 10H), 6.94 (dd, *J* = 15.8, 8.8 Hz, 1H), 5.22 (d, *J* = 15.5 Hz, 1H), 4.85 (s, 1H), 4.68 (d, *J* = 15.7 Hz, 1H), 4.59 (d, *J* = 9.0 Hz, 1H), 3.76 – 3.57 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 150.6, 146.6, 138.0, 134.6, 133.0, 130.2, 129.5, 129.2, 128.8, 123.1, 118.2, 74.1. 63.2, 55.9, 52.9, 50.4, 41.7.

*4.5.4 Peak assignment of **4a6***



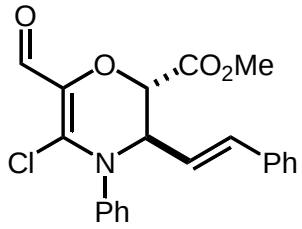
Compound **4a6:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 373 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.37 (s, 1H), 7.50 – 7.02 (m, 12H), 6.33 (s, 1H), 5.32 (d, *J* = 15.3 Hz, 1H), 4.87 (d, *J* = 5.8 Hz, 1H), 4.75 – 4.61 (m, 1H), 4.35 – 4.26 (m, 1H), 4.16 -3.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 151.4, 147.4, 135.9, 134.4, 132.8, 131.1, 130.1, 129.0, 128.2, 127.3, 122.8, 73.4, 65.1, 63.2, 60.2, 41.8, 14.2.

*4.5.5 Peak assignment of **4b1***



Compound **4b1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 376 mg, 74%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.22 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.01 (s, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.4, 167.7, 142.2, 138.5, 135.2, 134.1, 132.8, 131.5, 130.3, 128.8, 127.2, 122.4, 119.6, 91.8, 74.6, 62.6, 52.7.

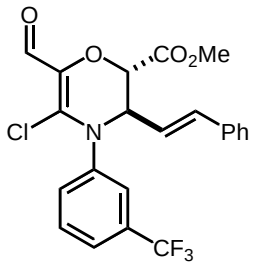
*4.5.6 Peak assignment of **4b2***



Compound **4b2:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 280 mg, 73%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.41 - 7.11 (m, 10H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.27 (dd, *J* = 15.8 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 4.74 (d, *J* = 12.8 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (101 MHz,

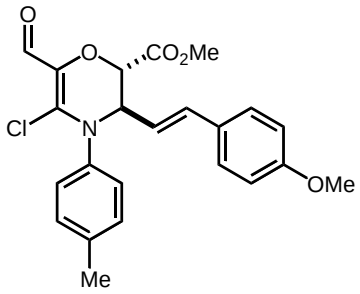
$CDCl_3$) δ 180.5, 167.9, 142.4, 135.9, 134.2, 129.7, 128.8, 127.3, 126.8, 125.7, 124.8, 122.6, 74.4, 64.2, 52.2.

*4.5.7 Peak assignment of **4b3***



Compound **4b3:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 352 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.75 (s, 1H), 7.52 (d, *J* = 4.6 Hz, 2H), 7.42 – 7.23 (m, 7H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.06 (s, 1H), 4.96 (d, *J* = 6.3 Hz, 1H), 3.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 167.6, 143.1, 135.2, 134.1, 133.4, 132.0, 131.7, 130.8, 128.8, 126.9, 124.8, 123.5, 122.1, 121.9, 119.6, 74.6, 63.8, 52.6.

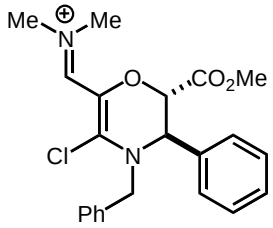
*4.5.8 Peak assignment of **4b4***



Compound **4b4:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with

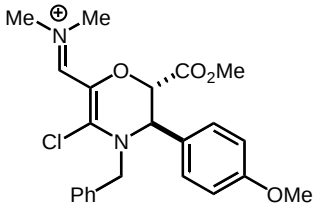
hexane/EtOAc (80:20). Yield = 342 mg, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 7.29 (d, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.88 (d, 2H), 6.80 (dd, 2H), 6.5 (d, *J* = 14.6 Hz, 1H), 6.11 (m, 1H), 4.95 - 4.60 (m, 2H), (3.84 – 3.52 (m, 6H), 2.41 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 168.3, 140.9, 138.6, 134.8, 132.8, 129.2, 128.0, 127.5, 120.6, 114.0, 74.7, 64.1, 54.3, 52.9, 21.4.

4.5.9 Peak assignment of ***10a1***



Compound **10a1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 240 mg, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (s, 1H), 7.87 - 6.96 (m, 10H), 5.25 (d, *J* = 15.4 Hz, 1H), 4.90 (d, *J* = 12.6 Hz, 1H), 4.66 (d, *J* = 15.4 Hz, 1H), 4.02 (d, *J* = 15.4 Hz, 1H), 3.56 - 3.38 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 151.3, 145.8, 134.9, 132.5, 129.7, 128.8, 128.0, 127.8, 122.2, 74.6, 63.9, 55.9, 53.1, 50.3, 41.6.

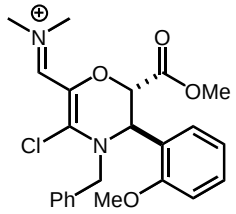
4.5.10 Peak assignment of ***10a2***



Compound **10a2:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 360 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (s, 1H), 7.60 - 6.66 (m,

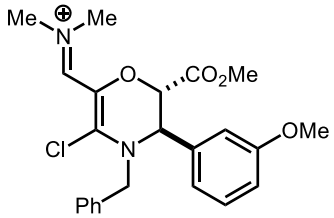
9H), 5.14 (d, *J* = 15.4 Hz, 1H), 4.67 (s, 1H), 4.57 (s, 1H), 4.17 (s, 1H), 3.67 (d, *J* = 15.4 Hz, 1H), 3.63 – 3.28 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 160.4, 151.2, 147.2, 132.7, 129.7, 128.7, 127.7. 126.8, 124.8, 114.9, 74.7, 63.4, 55.3, 54.9, 52.9, 50.1, 41.6.

*4.5.11 Peak assignment of **10a3***



Compound **10a3:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 335 mg 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 7.68 - 6.54 (m, 9H), 5.50 (d, *J* = 15.4 Hz, 1H), 4.67 (d, 1H), 4.21 -– 3.42 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 159.8, 150.8, 147.4, 132.7, 129.3, 128.2, 127.6. 126.5, 124.7, 112.9, 74.7, 58.4, 6.3, 55.9, 51.9, 50.1, 41.4.

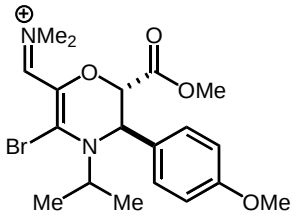
*4.5.12 Peak assignment of **10a4***



Compound **10a4:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 318 mg, 74%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 7.44 - 6.49 (m, 9H), 5.29 (d, *J* = 15.4 Hz, 1H), 4.91 (s, 1H), 4.73 (s, 1H), 4.27 (d, *J* = 15.4 Hz, 1H), 3.84

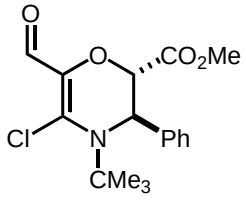
(s, 1H), 3.73 - 3.40 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 160.4, 151.4, 146.0, 138.5, 132.5, 130.9, 129.2, 128.2, 126.7, 122.2, 118.6, 114.3, 112.7, 74.7, 62.1, 55.6, 55.2, 53.1, 50.3, 41.7.

*4.5.13 Peak assignment of **10a5***



Compound **10a5:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 341 mg, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 5.20 (s, 1H), 4.64 (d, *J* = 12.1 Hz, 2H), 3.72 (s, 3H), 3.64 (d, *J* = 13.1 Hz, 6H), 3.40 (s, 3H), 1.11 (s, 3H), 0.88 (d, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 159.9, 152.5, 146.0, 128.5, 126.4, 123.9, 114.7, 75.1, 58.7, 58.7, 56.1, 53.5, 50.5, 46.0, 41.6, 22.5, 21.0.

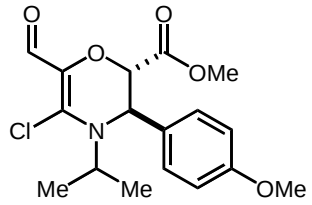
*4.5.14 Peak assignment of **10b1***



Compound **10b1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 290 mg, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.65

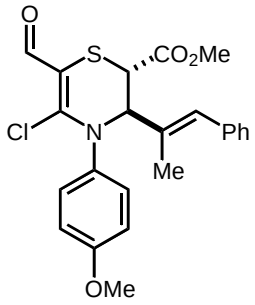
(s, 1H), 7.33 - 7.12 (m, 5H), 5.52 (d, *J* = 18.2 Hz, 1H), 4.99 (d, *J* = 18.2 Hz, 1H), 3.77 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 169.3, 137.3, 132.7, 129.4, 128.5, 128.1, 127.7, 126.0, 76.9, 61.2, 58.9, 52.8, 31.0.

4.5.15 Peak assignment of ***10b2***



Compound **10b2:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 318 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.61 (s, 1H), 7.21 (d, 2H), 6.84 (d, 2H), 5.12 (d, *J* = 18.2 Hz, 1H), 4.89 (d, *J* = 18.2 Hz, 1H), 3.58 (m, 1H), 3.85 (s, 6H), 1.04 (d, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 169.6, 160.3, 138.7, 131.4, 128.5, 114.1, 75.9, 58.2, 56.9, 53.8, 51.0, 21.3, 21.1.

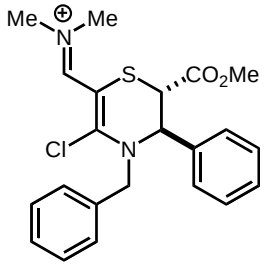
4.5.16 Peak assignment of ***4c1***



Compound **4c1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with

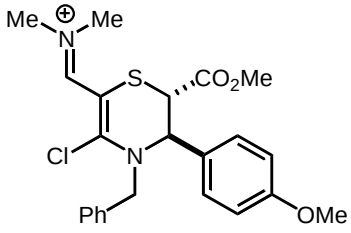
hexane/EtOAc (80:20). Yield = 314 mg, 71%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.99 (s, 1H), 7.34 (m, 7H), 7.25 (d, *J* = 7.2 Hz, 2H), 6.46 (s, 1H), 4.88 (d, 1H), 3.96 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4, 170.4, 159.2, 142.6, 137.3, 136.5, 133.3, 131.5, 129.5, 129.1, 129.1, 114.9, 102.5, 72.6, 55.5, 53.1, 40.1, 17.6.

4.5.17 Peak assignment of ***12a1***



Compound **12a1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 278 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.83 (s, 1H), 7.95 (s, 1H), 7.39 – 7.28 (m, 10 H), 5.49 – 5.30 (m, 2H), 4.44 – 4.19 (m, 1H), 3.71 – 3.32 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 162.7, 155.0, 138.9, 136.9, 136.7, 88.7, 67.5, 58.2, 53.5, 50.1, 45.8, 42.6, 30.4.

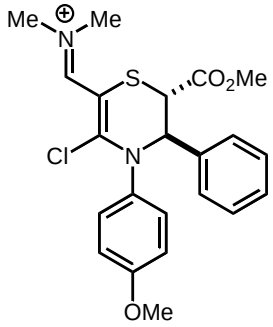
4.5.18 Peak assignment of ***12a2***



Compound **12a2:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h.

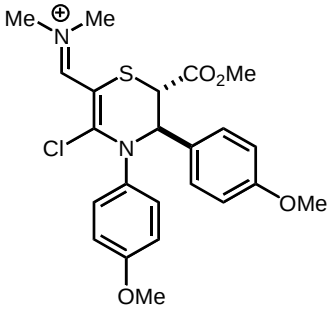
Yield = 311 mg, 70%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 7.34 –6.77 (m, 10H), 5.34 (d, *J* = 15.8 Hz, 1H), 5.26, 4.32 (d, *J* = 22.8 Hz, 1H), 4.25 (s, 1H), 3.73 - 3.31 (m, 12H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.5, 162.3, 160.6, 155.0, 134.1, 130.6, 130.2, 129.9, 114.7, 67.1, 57.9, 55.5, 53.4, 51.2, 44.3, 42.5.

*4.5.19 Peak assignment of **12a3***



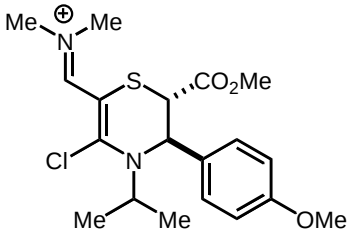
Compound **12a3:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 293 mg, 68%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 7.34 (m, 9H), 6.98 – 6.76 (m, 1H), 5.56 (s, 1H), 3.87 - 3.72 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 162.4, 160.2, 154.6, 137.3, 130.5, 129.3, 129.5, 128.5, 88.6, 72.5, 53.1, 52.3, 51.4, 42.1, 41.6.

*4.5.20 Peak assignment of **12a4***



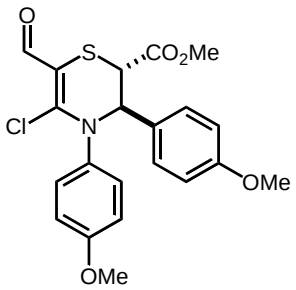
Compound **12a4:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 337 mg, 73%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 7.44 - 6.71 (m, 8H), 5.57 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.76 (s, 6H), 3.59 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 162.0, 160.3, 159.9, 154.1, 136.8, 128.9, 114.3, 88.0, 70.4, 55.6, 55.4, 53.7, 51.4, 44.1, 42.5.

*4.5.21 Peak assignment of **12a5***



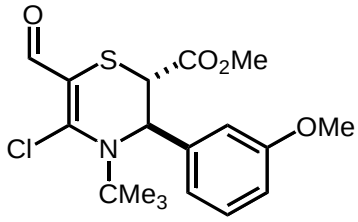
Compound **12a5:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h. Yield = 302 mg, 76%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 5.47 (s, 1H), 4.72 (dq, *J* = 13.6, 7.7, 6.9 Hz, 1H), 3.56 - 3.38 (m, 12H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.8, 162.4, 162.1, 160.0, 152.9, 131.1, 128.8, 127.4, 114.0, 87.9, 62.0, 59.7, 55.3, 53.7, 50.8, 43.9, 42.2, 21.6, 20.5.

*4.5.22 Peak assignment of **12b1***



Compound **12b1:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 281 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.90 (s, 1H), 7.24 (d, *J* = 14.3 Hz, 1H), 7.13 (dd, *J* = 16.8, 8.4 Hz, 2H), 7.01 – 6.90 (m, 2H), 6.92 – 6.73 (m, 3H), 5.34 (d, *J* = 2.1 Hz, 1H), 3.90 –3.08 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 170.0, 159.9, 159.8, 137.0, 131.2, 130.0, 129.5, 129.2, 128.9, 128.2, 127.5, 127.2, 114.8, 100.8, 67.7, 55.5, 55.5, 53.0, 43.1.

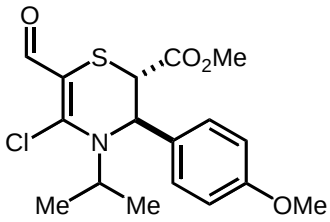
*4.5.23 Peak assignment of **12b2***



Compound **12b2:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 249 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.26 – 7.07 (m, 2H), 6.86 – 6.71 (h, *J* = 7.5, 6.6 Hz, 2H)), 5.66 (d, *J* = 4.3 Hz,

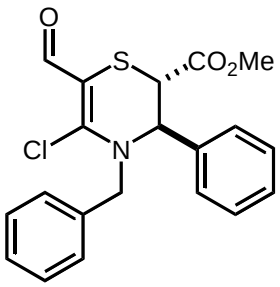
1H), 3.95 – 3.85 (d, 1H), 3.79 –3.11 (d, 6H), 1.31 (d, 9H), 1.24 – 1.14 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 170.8, 159.9, 159.7, 144.6, 140.8, 130.0, 124.8, 118.7, 112.9, 112.0, 63.5, 61.9, 55.4, 53.1, 48.3, 32.9.

*4.5.24 Peak assignment of **12b3***



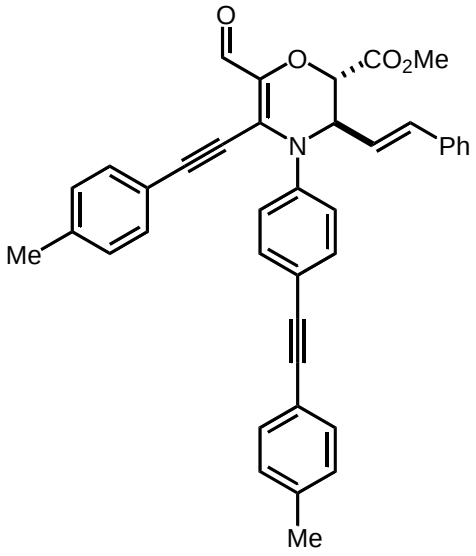
Compound **12b3:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 243 mg, 66%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (d, *J* = 15.4 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.86 – 6.73 (m, 2H), 5.29 (d, *J* = 2.7 Hz, 1H), 4.92 (p, *J* = 6.9 Hz, 1H), 3.74 (d, *J* = 8.3 Hz, 3H), 3.68 (s, 3H), 3.66 – 3.61 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.03 (dd, *J* = 20.2, 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2, 169.8, 159.6, 144.0, 133.0, 128.5, 127.4, 114.0, 100.7, 59.3, 55.3, 53.7, 53.4, 52.7, 42.1, 21.6, 20.6.

*4.5.25 Peak assignment of **12b4***



Compound **12b3:** Prepared using **General Procedure A**. **3** (1 mmol), $POCl_3$ (0.31 g, 0.2 mL, 2 mmol), DMF (0.33 mL, 4 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 317 mg, 82%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.31 – 7.02 (m, 10H), 5.25 (d, *J* = 16.0 Hz, 1H), 4.95 (s, 1H), 4.12 (d, *J* = 15.9 Hz, 1H), 3.44 (s, 3H), 2.23 (dd, *J* = 16.2, 5.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 187.2, 171.7, 150.4, 139.1, 135.7, 129.2, 128.2, 127.5, 126.9, 106.2, 63.6, 53.8, 51.8, 42.6.

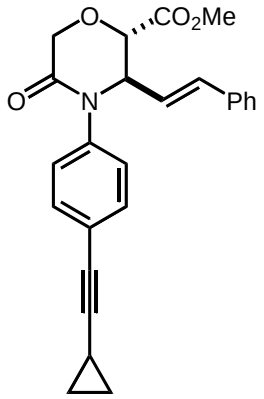
*4.5.26 Peak assignment of **13***



Compound **13:** Prepared using **General Procedure B**. **4b1** (1.0 mmol) and *p*-methylphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 514 mg, 89%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.53 - 7.12 (m, 10H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.22 (dd, *J* = 15.7, 6.8 Hz, 1H), 5.02 (m, 2H), 3.65 (s, 3H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 167.8,

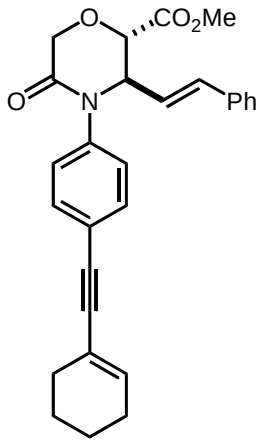
143.7, 142.2, 139.5, 138.5, 135.2, 134.1, 132.8, 129.2, 128.8, 127.2, 126.9, 125.0, 122.3, 118.8, 91.8, 81.6, 74.6, 73.5, 63.9, 52.7, 21.7.

*4.5.27 Peak assignment of **14a***



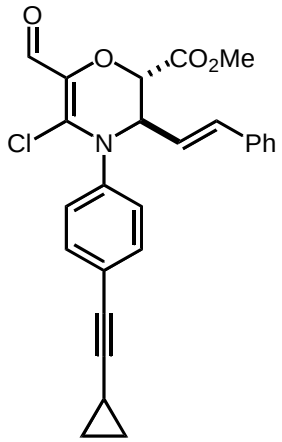
Compound **14a:** Prepared using **General Procedure B**. **3d1** (1.0 mmol) and *p*-methylphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 301 mg, 75%. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.02 (m, 9H), 6.70 – 6.21 (m, 2H), 4.84 (m, 1H), 4.68 (m, 1H), 4.62 (m, 1H), 4.51 (m, 1H), 3.95 – 3.72 (m, 3H), 1.52 (t, 1H), 0.92-0.81 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 168.3, 139.5, 142.2, 139.5, 136.4, 136.2, 134.1, 129.8, 128.2, 127.8, 124.2, 123.9, 94.8, 74.2, 73.8, 64.9, 62.7, 53.7, 9.8, 0.1.

*4.5.28 Peak assignment of **14b***



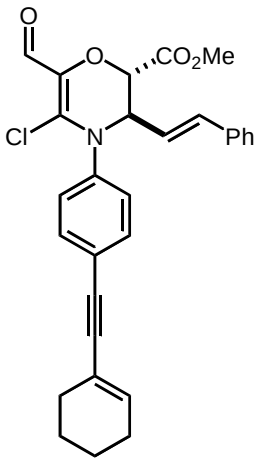
Compound **14b:** Prepared using **General Procedure B**. **3d1** (1.0 mmol) and *p*-methylphenyl-acetylene (2 mmol, 2 equiv) Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 344 mg, 78%. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 7.01 (m, 9H), 6.50 – 6.12 (m, 3H), 4.98 – 4.68 (m, 4H), 4.01 – 4.2 (s, 3H), 2.30 – 1.98 (m, 4H), 1.78 – 1.52 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 165.2, 140.2, 136.2, 136.0, 134.4, 130.2, 128.1, 127.8, 126.2, 125.8, 120.2, 92.4, 85.2, 74.6, 64.5, 64.2, 52.4, 28.4, 24.3, 23.4, 22.8.

*4.5.29 Peak assignment of **15a***



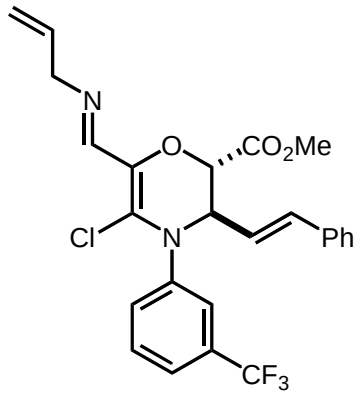
Compound **15a:** Prepared using **General Procedure A**. **14** (1 mmol), $POCl_3$ (0.46 g, 0.3 mL, 3 mmol), DMF (0.5 mL, 6 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 358 mg, 80%. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.70 – 7.21 (m, 7H), 7.22 – 7.04 (m, 2H), 6.78 – 6.52 (d, 1H), 6.41 – 6.03 (d, 1H), 5.02 – 4.88 (m, 2H), 3.87 – 3.51 (s, 3H), 1.62 – 1.42 (t, 1H), 0.98 – 0.72 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 168.8, 141.2, 138.2, 136.5, 135.4, 134.2, 133.1, 129.8, 127.2, 126.8, 125.2, 122.7, 96.1, 74.2, 63.8, 52.9, 9.7, 0.1.

*4.5.30 Peak assignment of **15b***



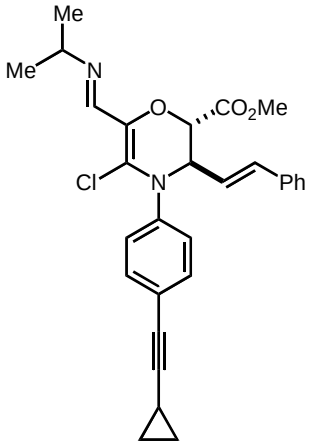
Compound **15b:** Prepared using **General Procedure A**. **14** (1 mmol), $POCl_3$ (0.46 g, 0.3 mL, 3 mmol), DMF (0.5 mL, 6 mmol), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 419 mg, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.69 – 7.41 (m, 8H), 7.20 – 7.02 (m, 2H), 6.98 – 6.48 (m, 1H), 6.41 – 6.02 (m, 2H), 5.08 – 4.75 (m, 2H), 3.76 – 3.51 (s, 3H), 2.32 – 2.01 (m, 2H), 1.89 – 1.52 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 168.2, 142.1, 136.0, 130.2, 128.1, 127.8, 126.2, 120.2, 92.2, 85.2, 74.2, 62.5, 52.4, 28.2, 24.3, 23.8, 22.8, 22.4.

*4.5.31 Peak assignment of **16a***



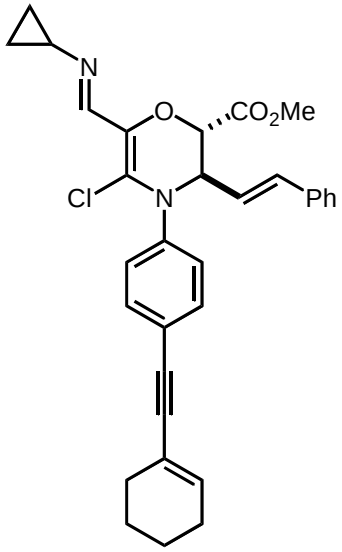
Compound **16a:** Prepared using **General Procedure C**. **4b3** (1 mmol), amine (1.5 mmol), benzene (5 mL, 5 equiv), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 455 mg, 93%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (s, 1H), 7.55 – 7.22 (m, 9H), 6.78 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 15.8, 5.1 Hz, 2H), 5.24 – 5.09 (m, 4H), 4.23 (d, *J* = 5.5 Hz, 2H), 3.83 – 3.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 152.9, 144.7, 135.6, 133.3, 132.0, 131.7, 131.0, 129.7, 128.7, 127.8, 126.9, 125.9, 123.6, 122.3, 121.1, 119.7, 116.8, 75.0, 63.9, 62.7, 52.2.

*4.5.32 Peak assignment of **16b***



Compound **16b:** Prepared using **General Procedure C**. **15** (1 mmol), amine (1.5 mmol), benzene (5 mL, 5 equiv), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 465 mg, 95%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (s, 1H), 7.90 – 6.50 (m, 9H), 6.42 – 6.04 (d, 2H), 5.10 – 4.92 (m, 2H), 4.20 – 4.98 (m, 2H), 3.98 – 3.24 (m, 4H), 2.04 – 0.92 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 150.2, 142.2, 136.2, 136.0, 130.4, 130.2, 133.1, 129.8, 128.2, 124.8, 122.2, 96.3, 74.24 63.8, 63.5, 53.2, 23.1, 9.8, 0.1.

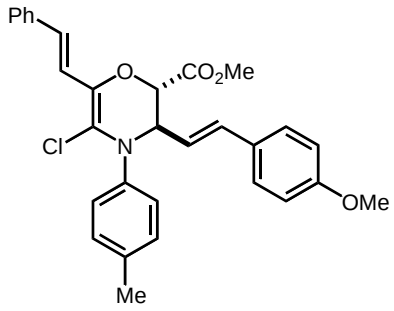
*4.5.33 Peak assignment of **16c***



Compound **16c:** Prepared using **General Procedure C**. **15** (1 mmol), amine (1.5 mmol), benzene (5 mL, 5 equiv), Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 485 mg, 92%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 7.55 – 7.24 (m, 9H), 7.10 – 6.92 (d, 2H), 6.98 – 6.48 (m, 1H), 6.47 – 6.06 (m, 2H), 5.12 – 4.68 (m, 2H), 3.88 – 3.32 (s, 3H), 3.08 – 2.94 (m, 1H), 2.32 – 2.01 (d, 2H), 1.89 – 1.52 (m,

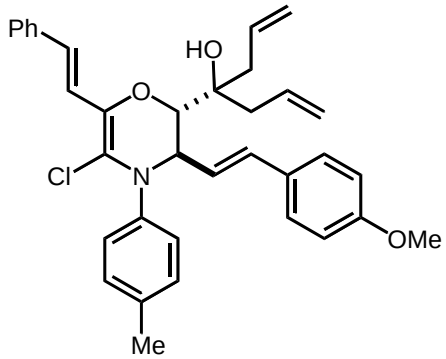
4H), 0.98-0.10 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 151.2, 142.1, 136.0, 132.4, 131.6, 130.8, 128.1, 127.8, 126.2, 120.8, 120.2, 92.4, 86.8, 74.4, 62.7, 52.4, 42.4, 28.4, 26.8, 23.8, 22.6, 22.5, 8.4, 8.3.

*4.5.34 Peak assignment of **17***



Prepared using **4b4** (1 mmol), ylide (1.2 mmol),THF (5 mL, 5 equiv), Temp = room temperature, time = 12 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 426 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 -6.88 (m, 10H), 6.80 (dd, 2H), 6.21 (m, 2H), 5.11 (m, 1H), 4.05 - 3.60 (m, 3H), (3.44 – 3.22 (m, 3H), 2.41-2.23 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 160.3, 142.9, 137.6, 136.8, 133.8, 132.2, 128.0, 127.5, 127.2, 127.1.0, 122.7, 115.1, 75.3, 55.9, 51.1, 21.3.

*4.5.35 Peak assignment of **18***



To the crude α-alkynyl imine (1.0 mmol) dissolved in freshly distilled THF (5 mL), was slowly added allyl magnesium bromide (4.0 mL, 1.0 M solution in THF, 4 equiv) under nitrogen at –78 °C. The mixture was warmed slowly to room temperature. After complete consumption of the ester (as indicated by TLC and GC-MS), the mixture was cooled to 0 °C, diluted with Et_2O and quenched by slow addition of *sat.* aq NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (1:2). Yield = 476 mg, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 -6.88 (m, 10H), 6.80 (dd, 2H), 6.21 (m, 2H), 5.11 (m, 4H), 4.35 - 4.10 (m, 1H), (3.94 – 3.72 (m, 3H), 2.41-2.23 (m, 3H), 1.95 – 1.83 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 142.9, 138.5, 137.6, 133.8, 132.2, 128.0, 127.5, 127.2, 127.1.0, 122.7, 120.1, 119.6, 115.1, 84.3, 75.9, 61.1, 56.3, 41.2, 40.1, 21.3.

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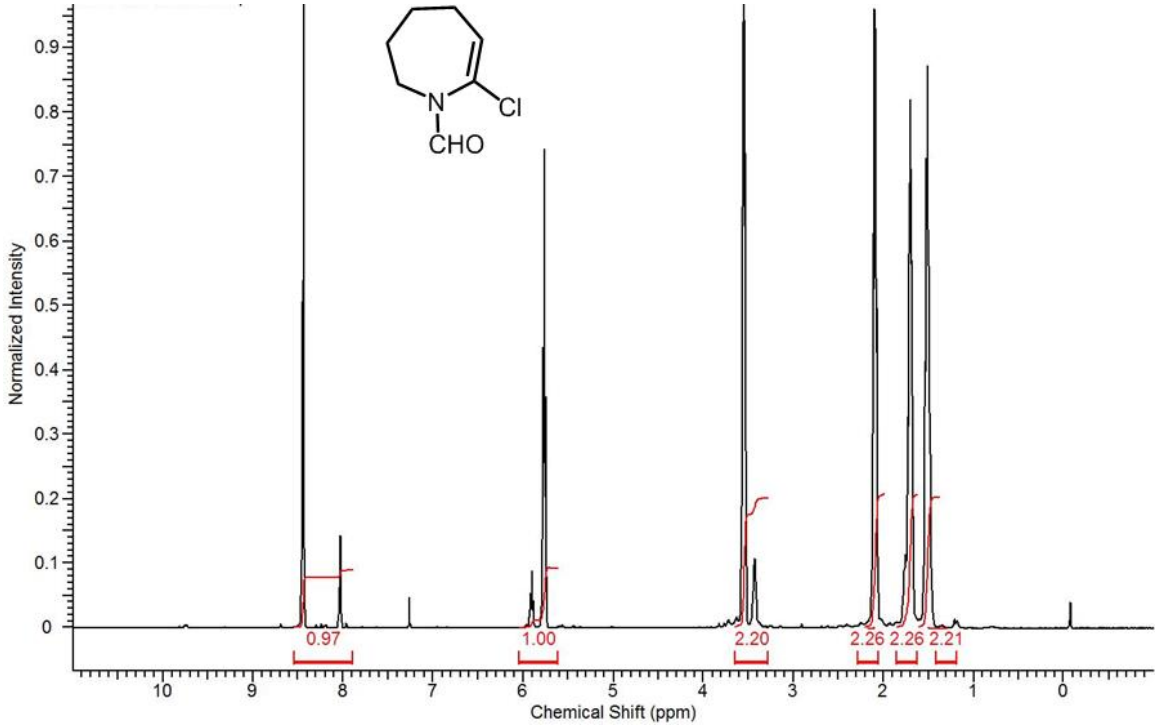
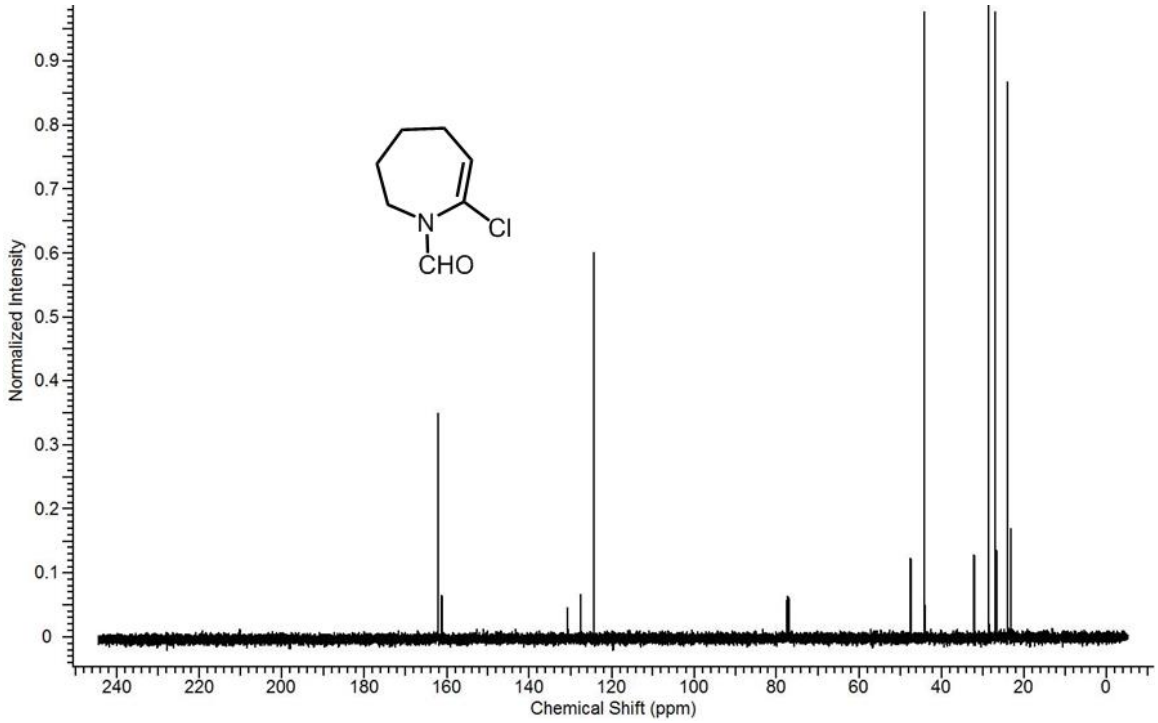
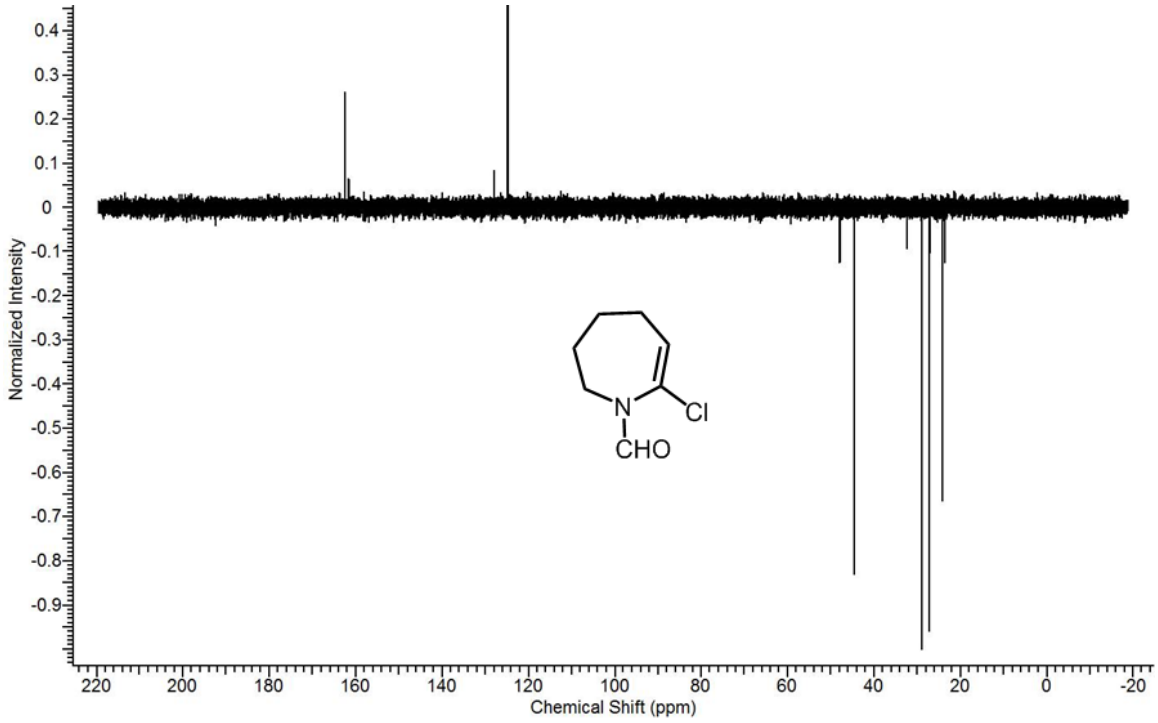


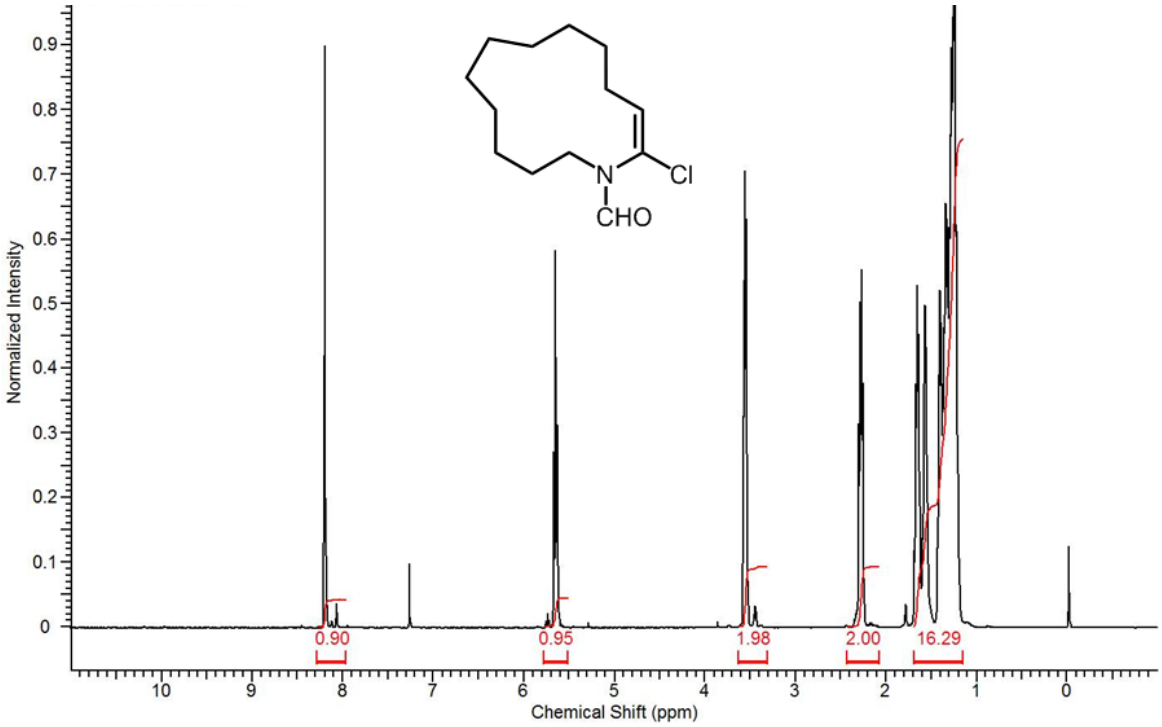
Spectra **1-1** Proton NMR spectrum of **2c.**



Spectra **1-2** Carbon NMR spectrum of **2c.**



Spectra **1-3** DEPT-135 NMR spectrum of **2c.**



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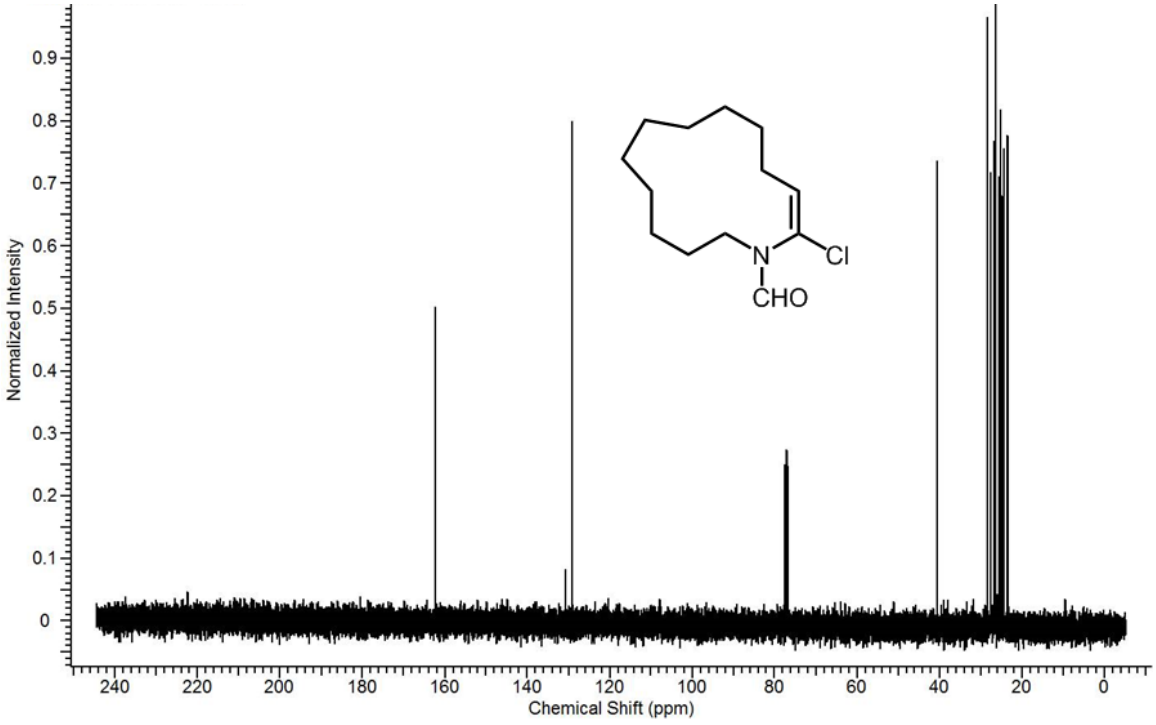
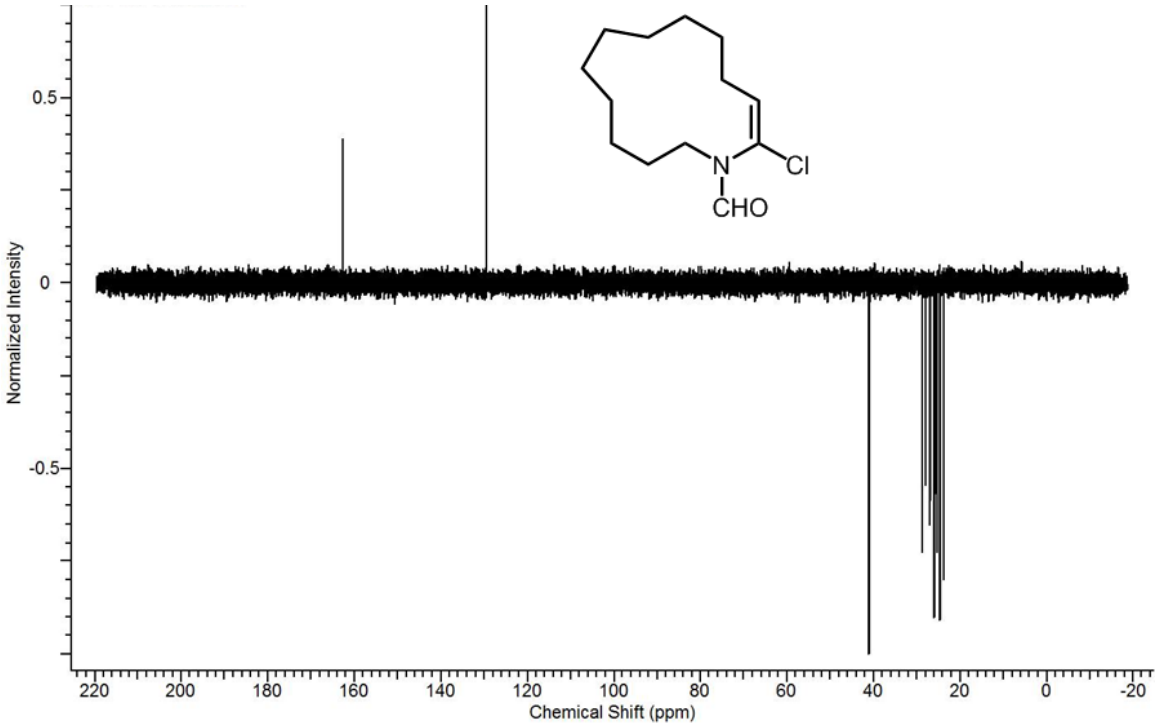
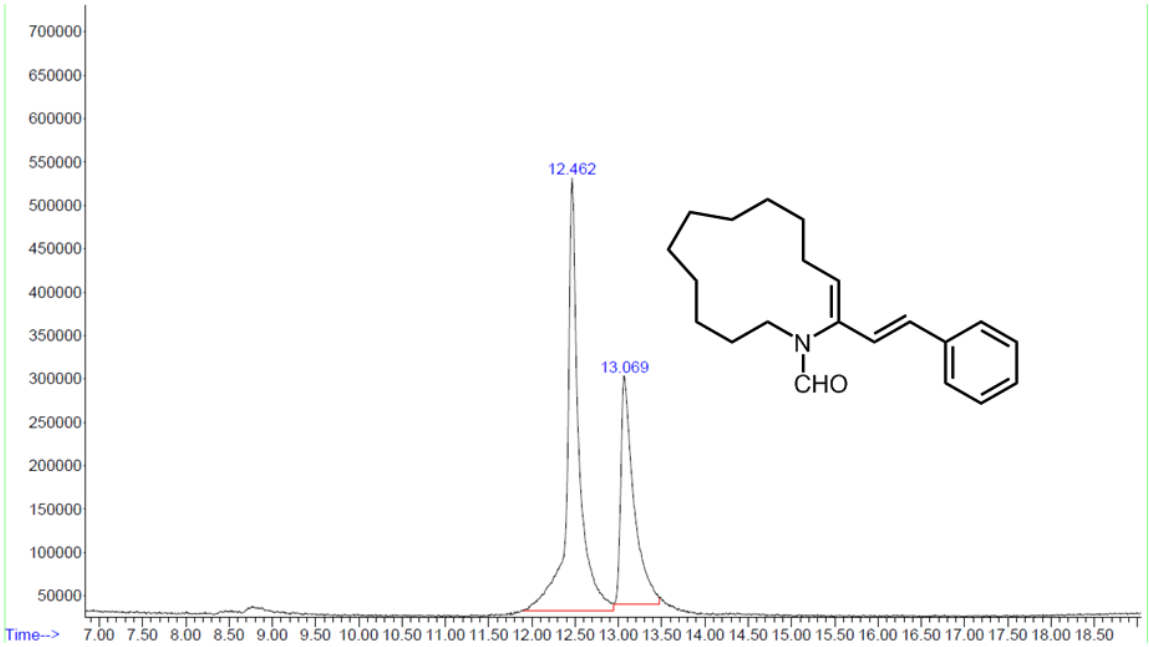


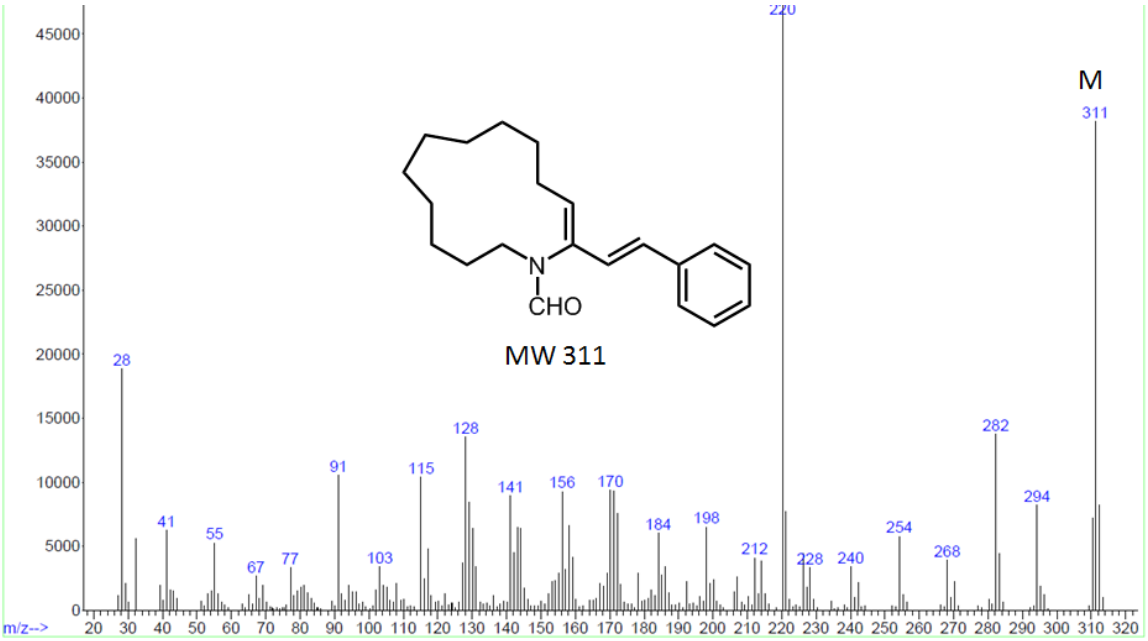
Spectra **1-5** Carbon NMR spectrum of **2e.**



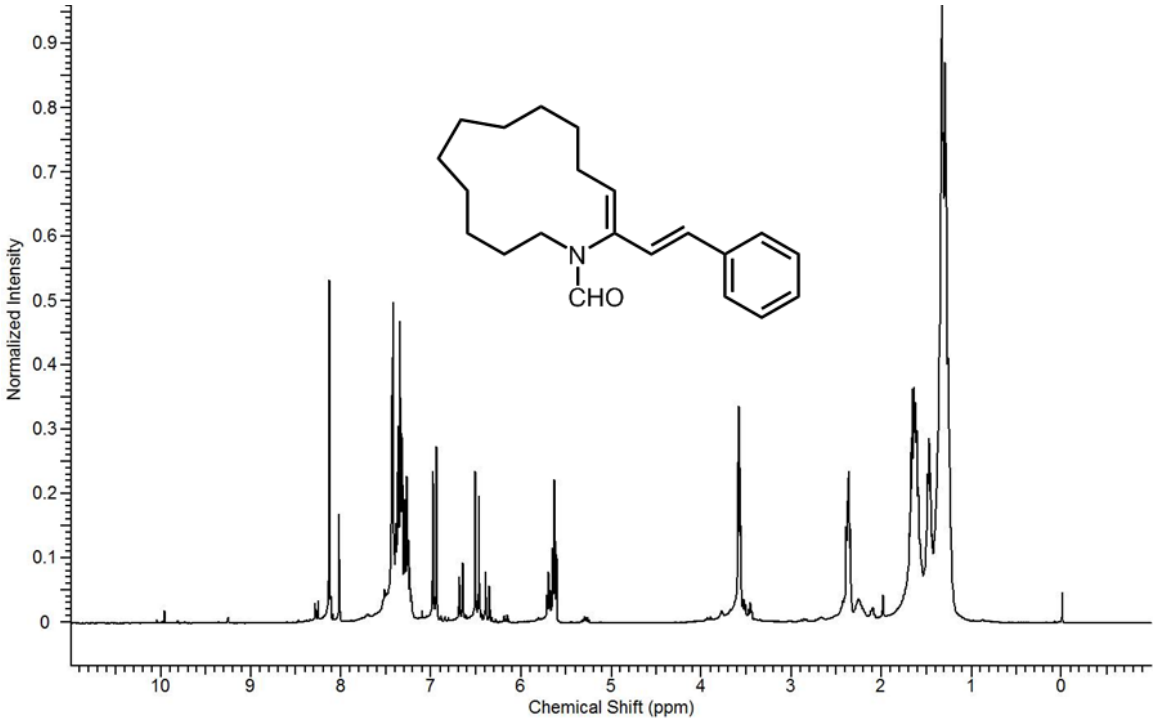
Spectra **1-6** DEPT-135 NMR spectrum of **2e.**



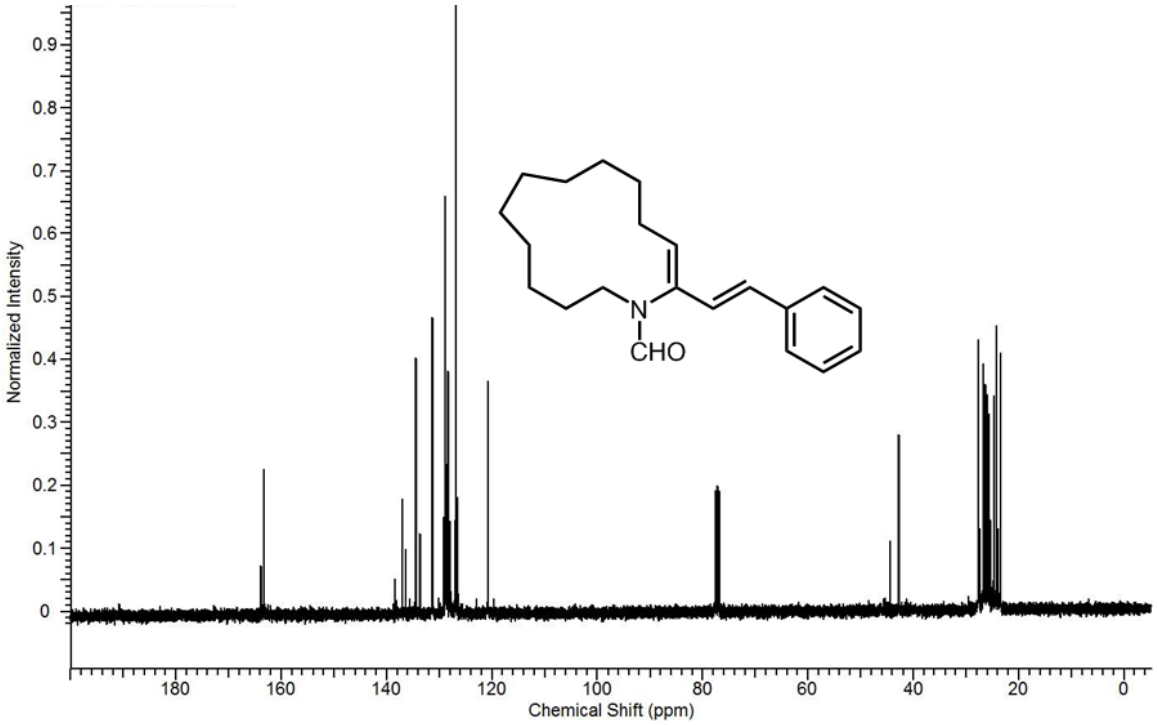
Spectra **1-7** GC spectrum of **3a1.**



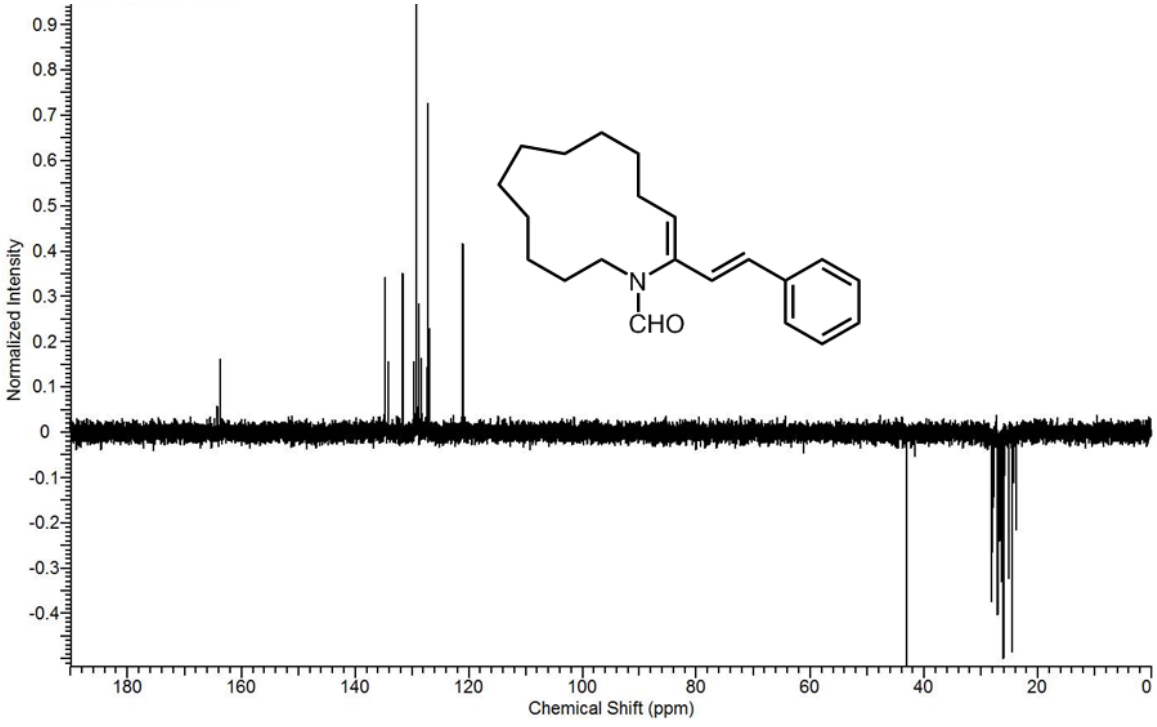
Spectra **1-8** MS spectrum of **3a1.**



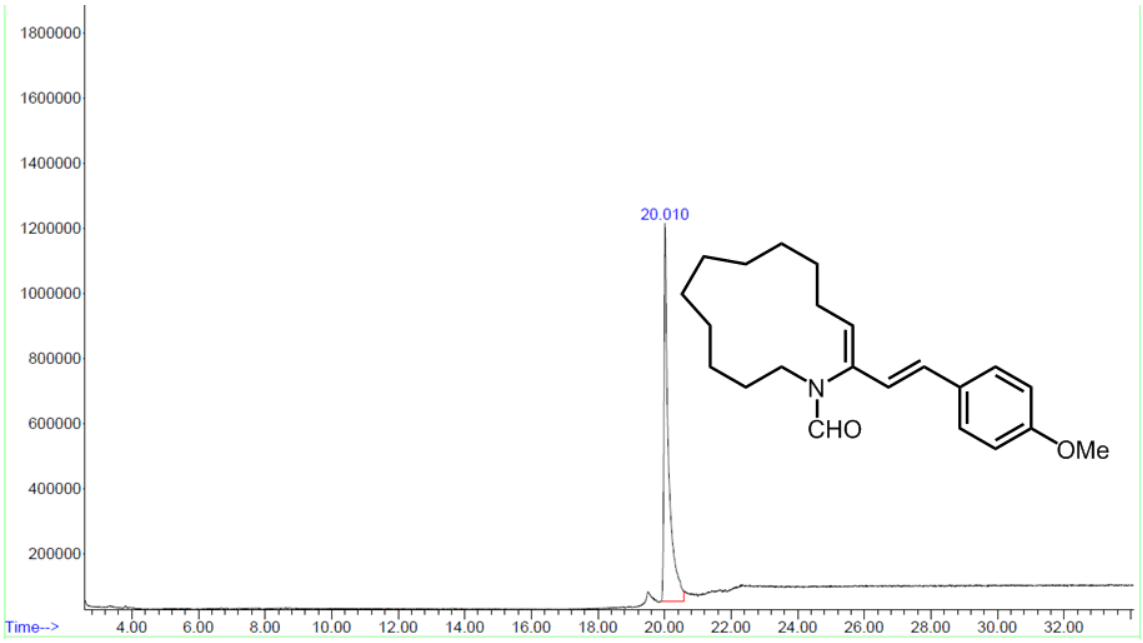
Spectra **1-9** Proton NMR spectrum of **3a1.**



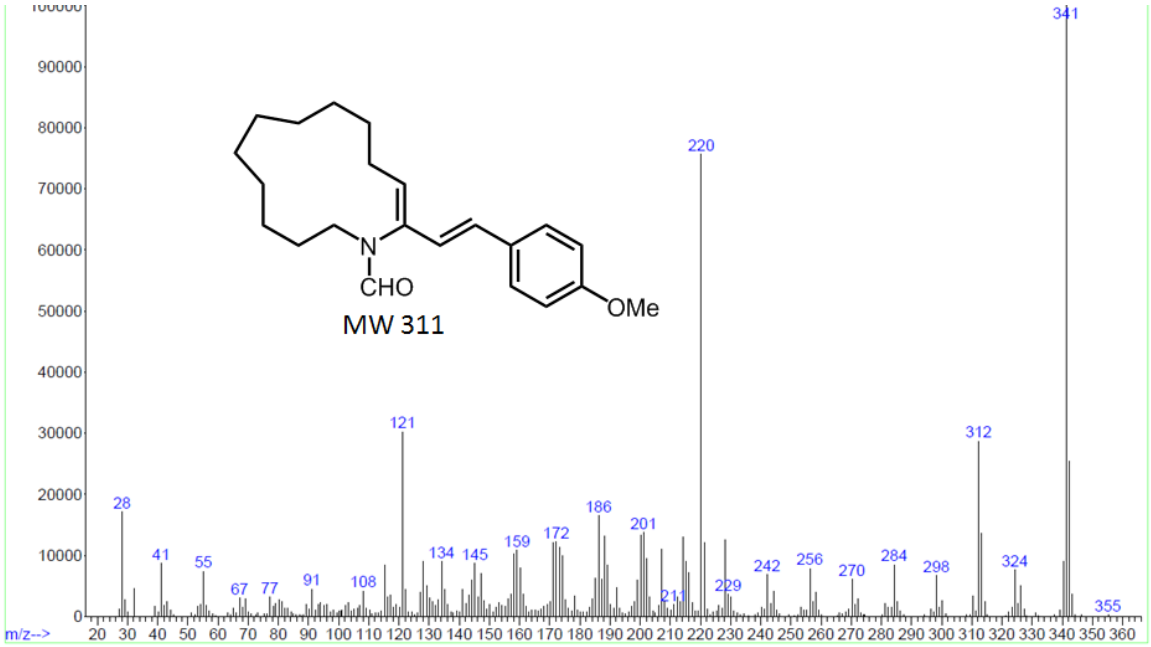
Spectra **1-10** Carbon NMR spectrum of **3a1.**



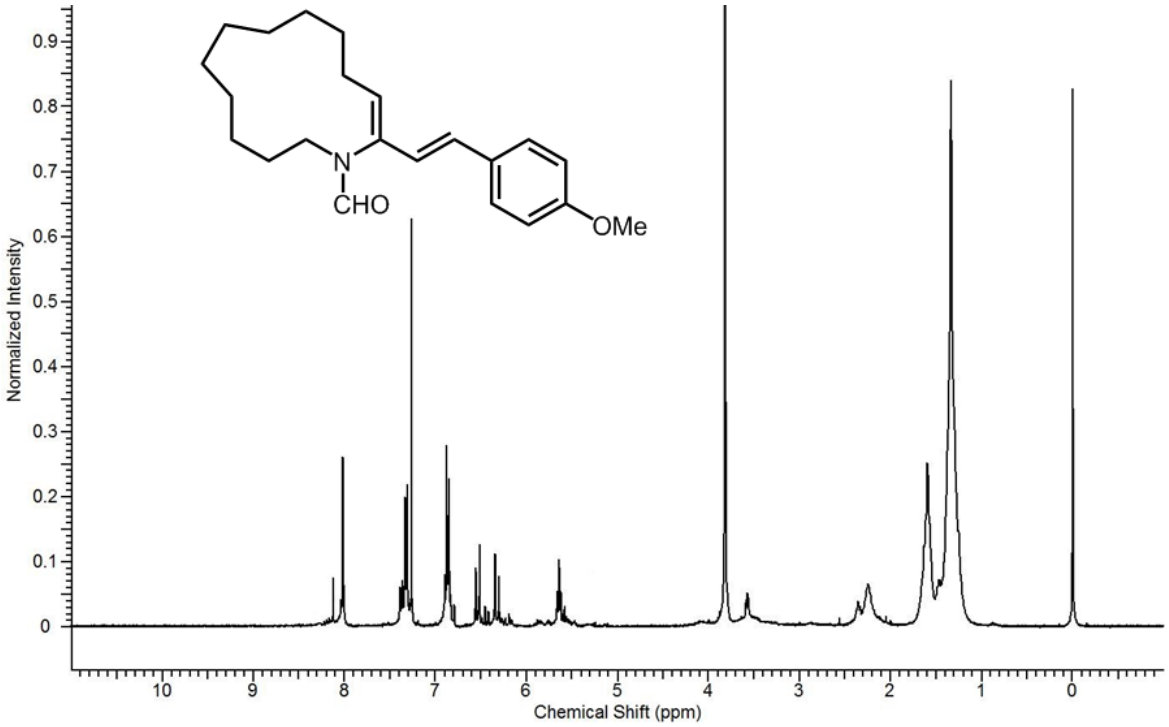
Spectra **1-11** DEPT-135 NMR spectrum of **3a1.**



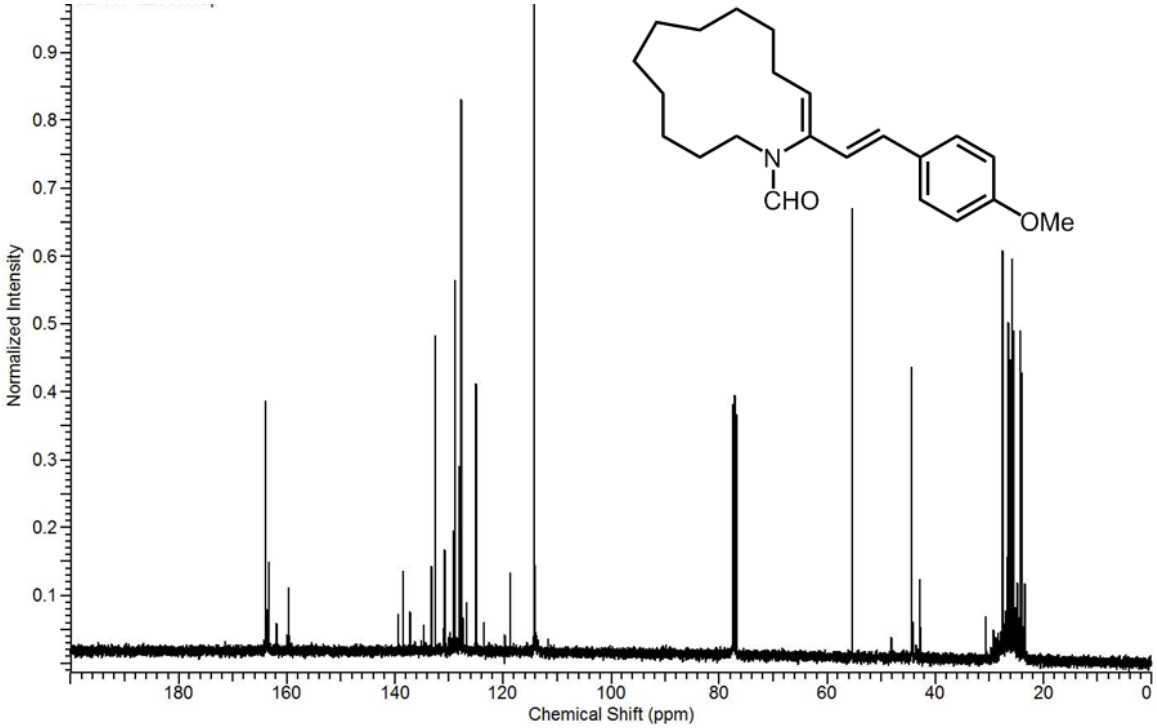
Spectra **1-12** GC spectrum of **3a2.**



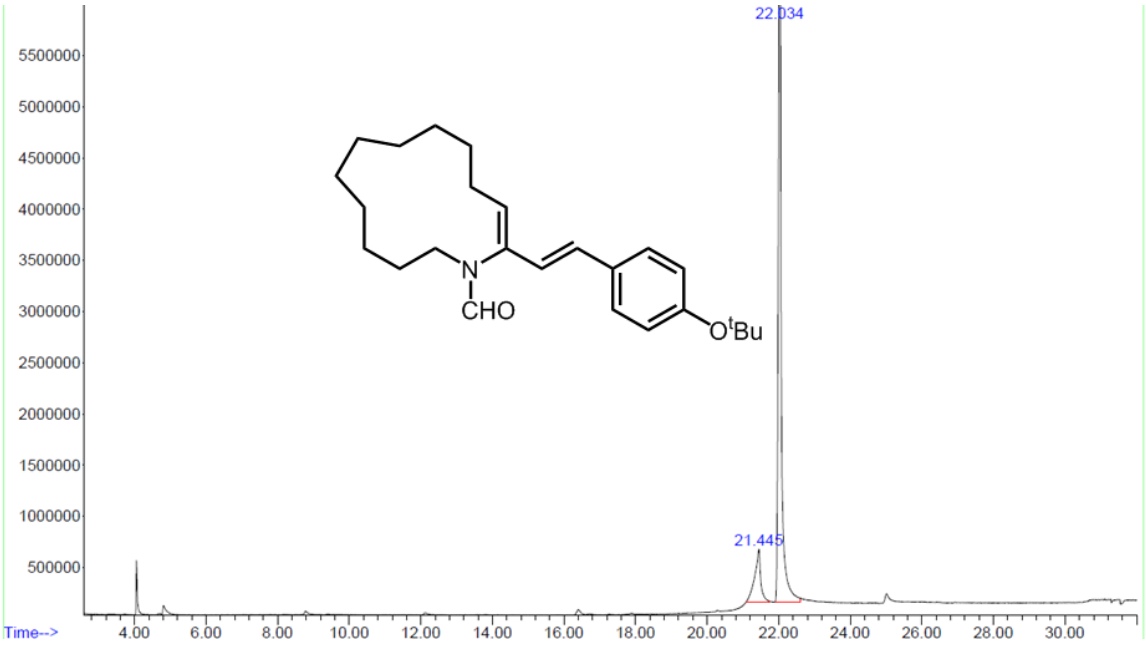
Spectra **1-13** MS spectrum of **3a2.**



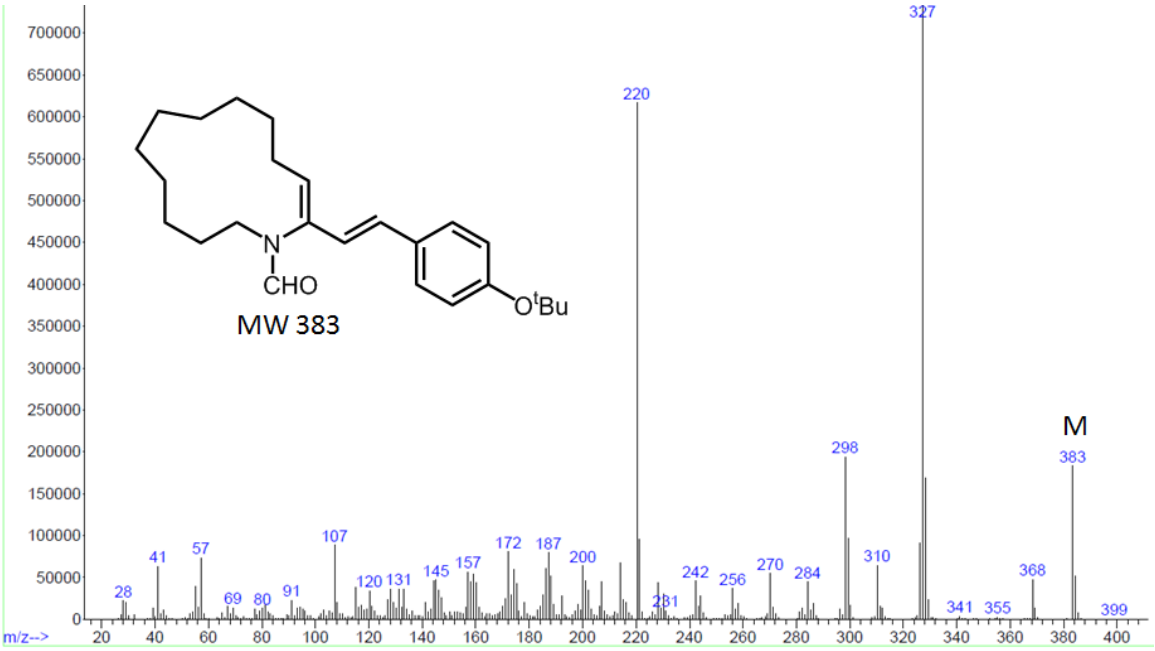
Spectra **1-14** Proton NMR spectrum of **3a2.**



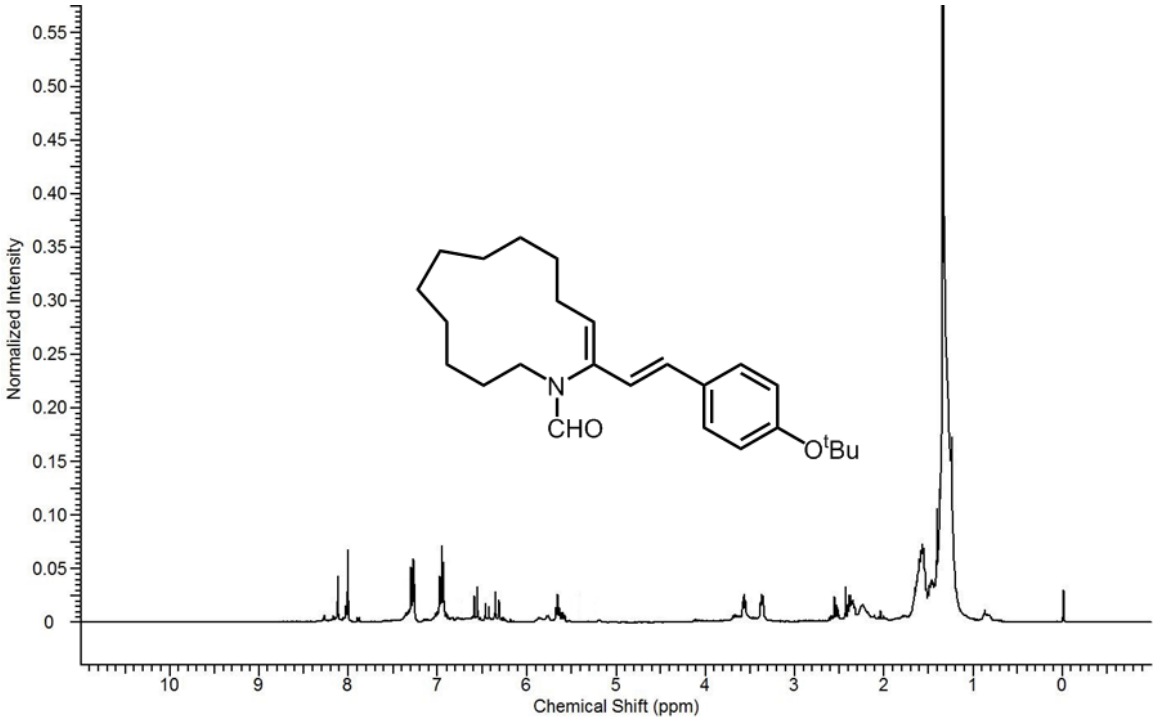
Spectra **1-15** Carbon NMR spectrum of **3a2.**



Spectra **1-16** GC spectrum of **3a3.**



Spectra **1-17** MS spectrum of **3a3.**



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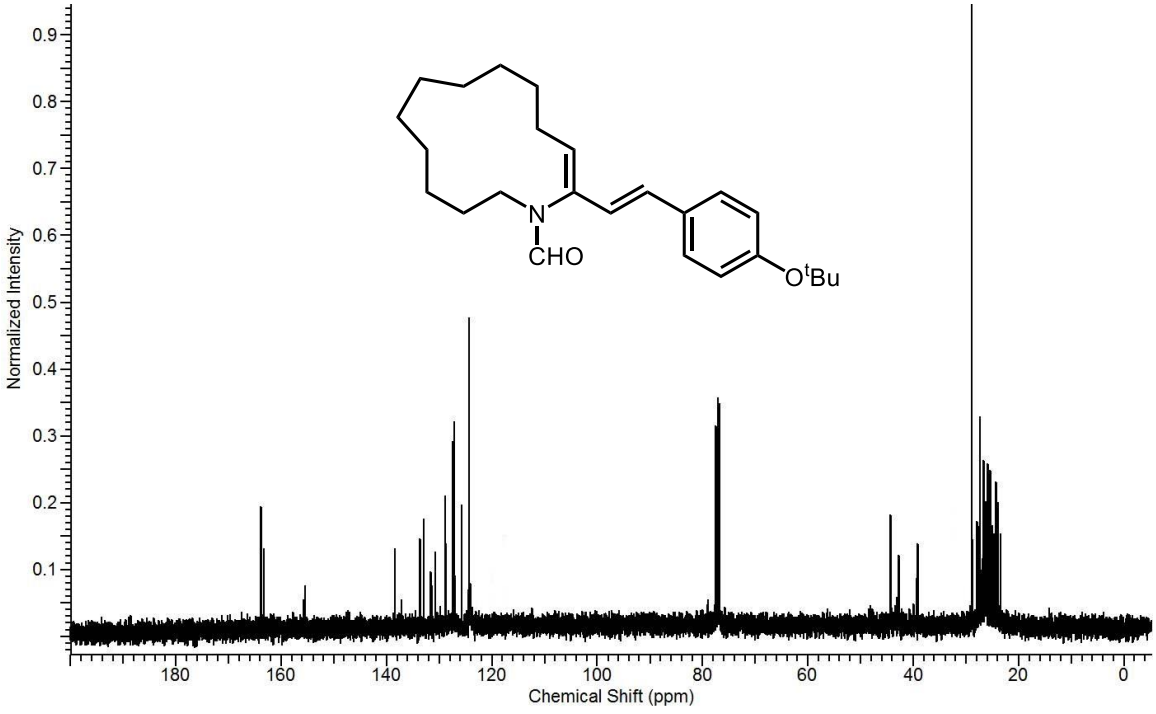
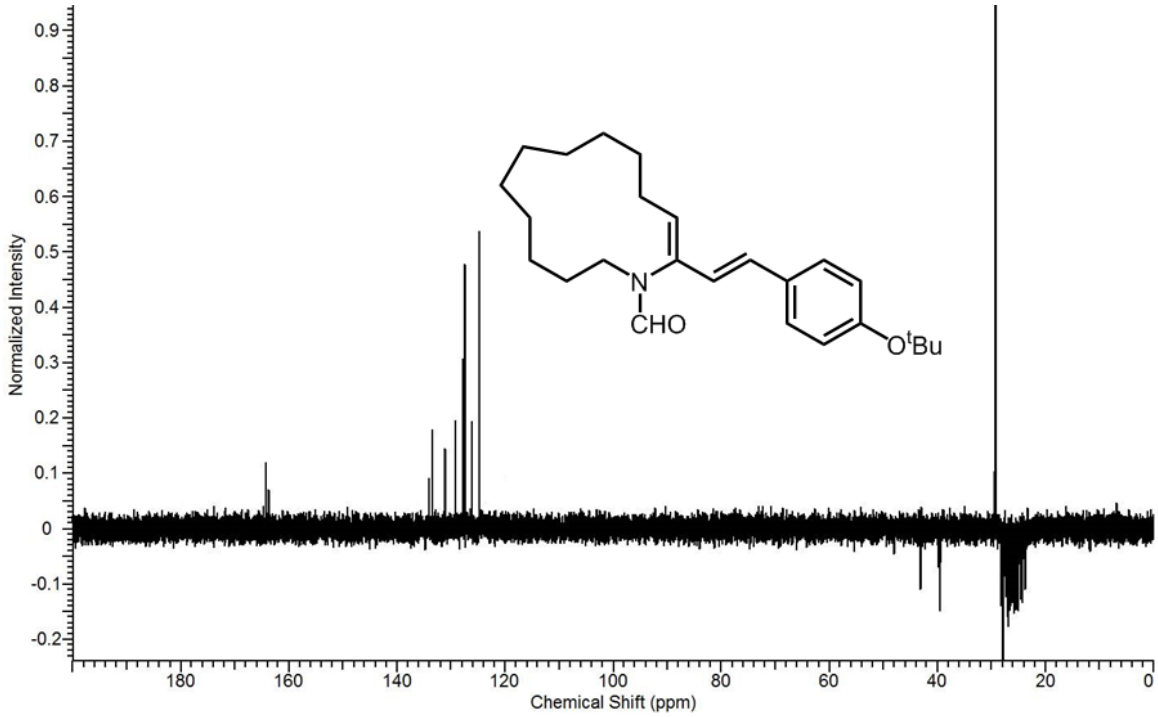
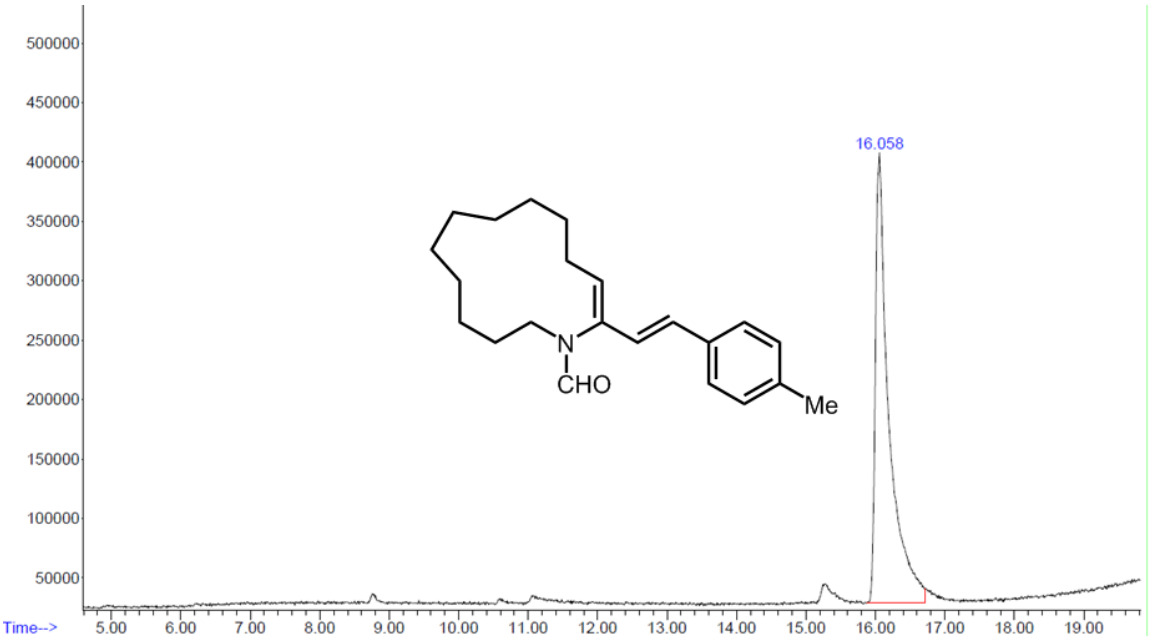


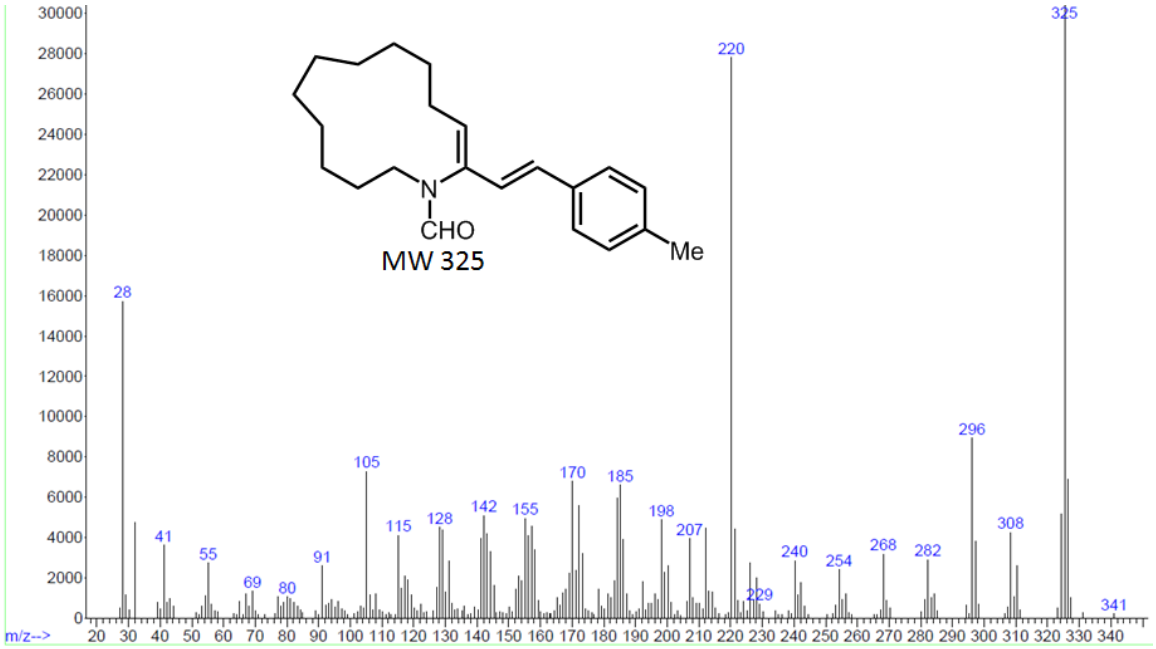
Spectra **1-19** Carbon NMR spectrum of **3a3.**



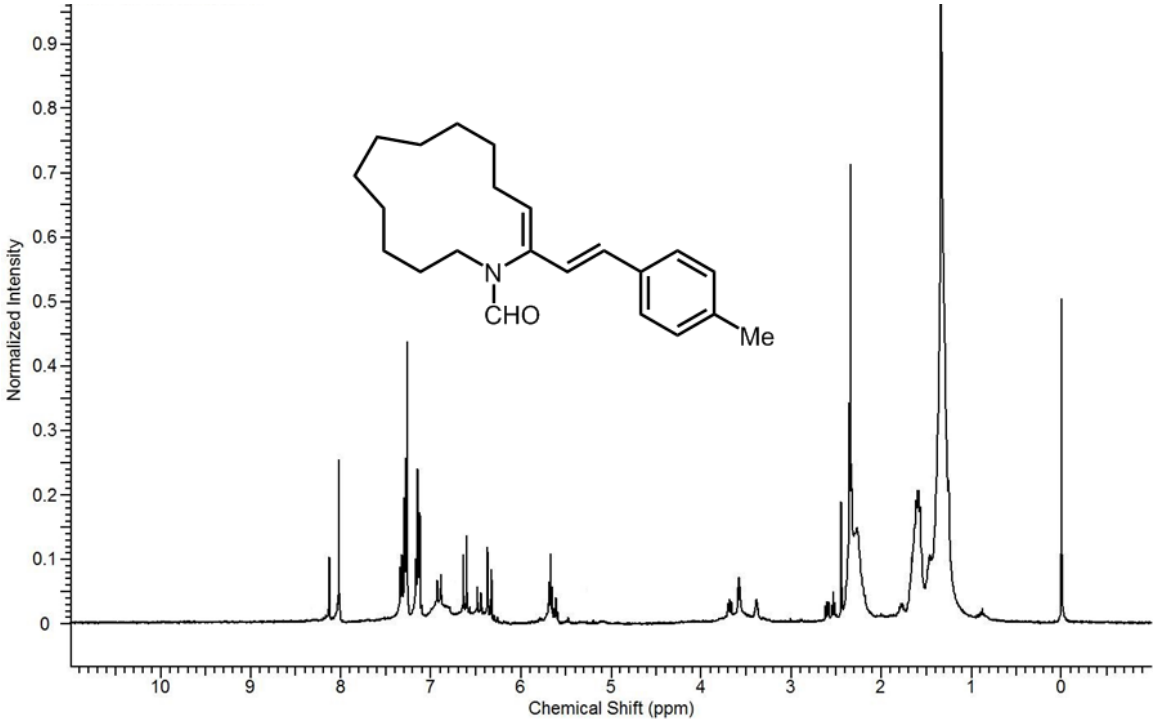
Spectra **1-20** DEPT-135 NMR spectrum of **3a3.**



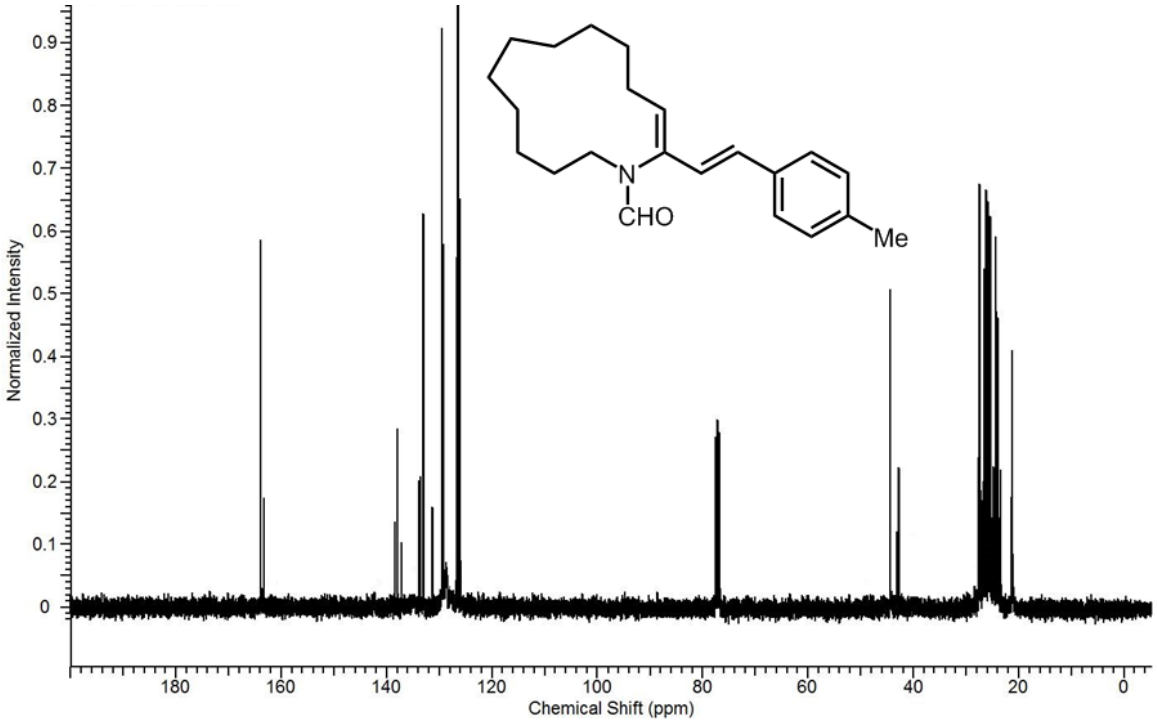
Spectra **1-21** GC spectrum of **3a4.**



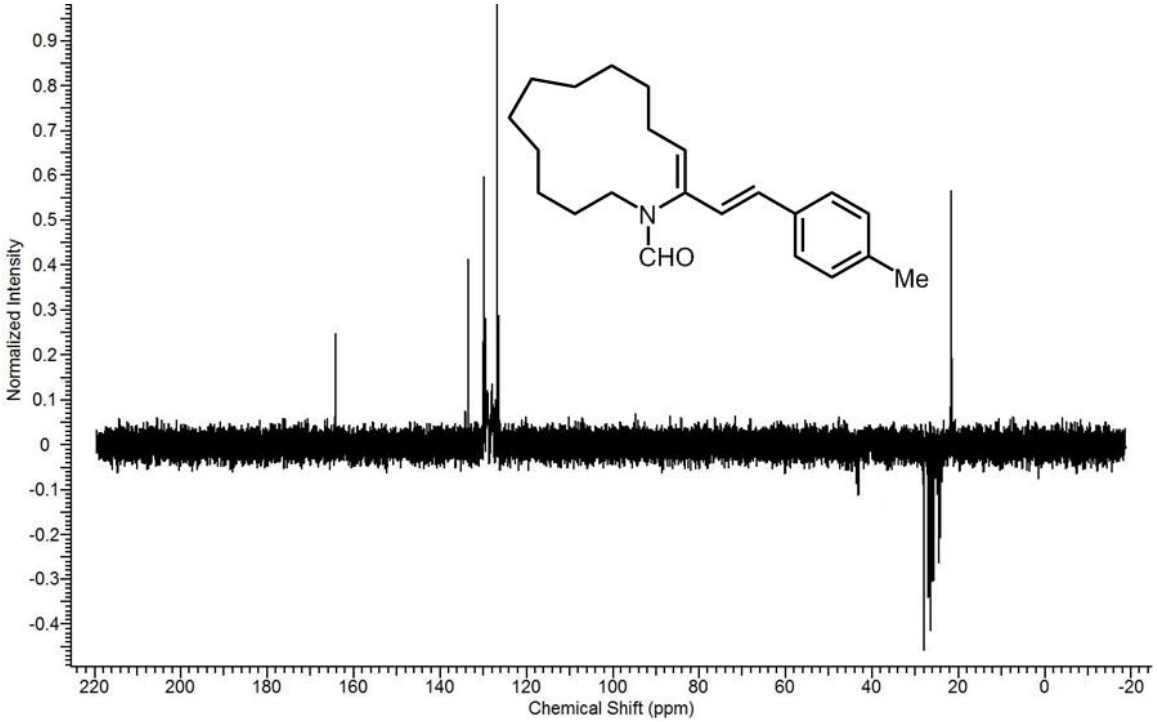
Spectra **1-22** MS spectrum of **3a4.**



Spectra **1-23** Proton NMR spectrum of **3a4.**



Spectra **1-24** Carbon NMR spectrum of **3a4.**



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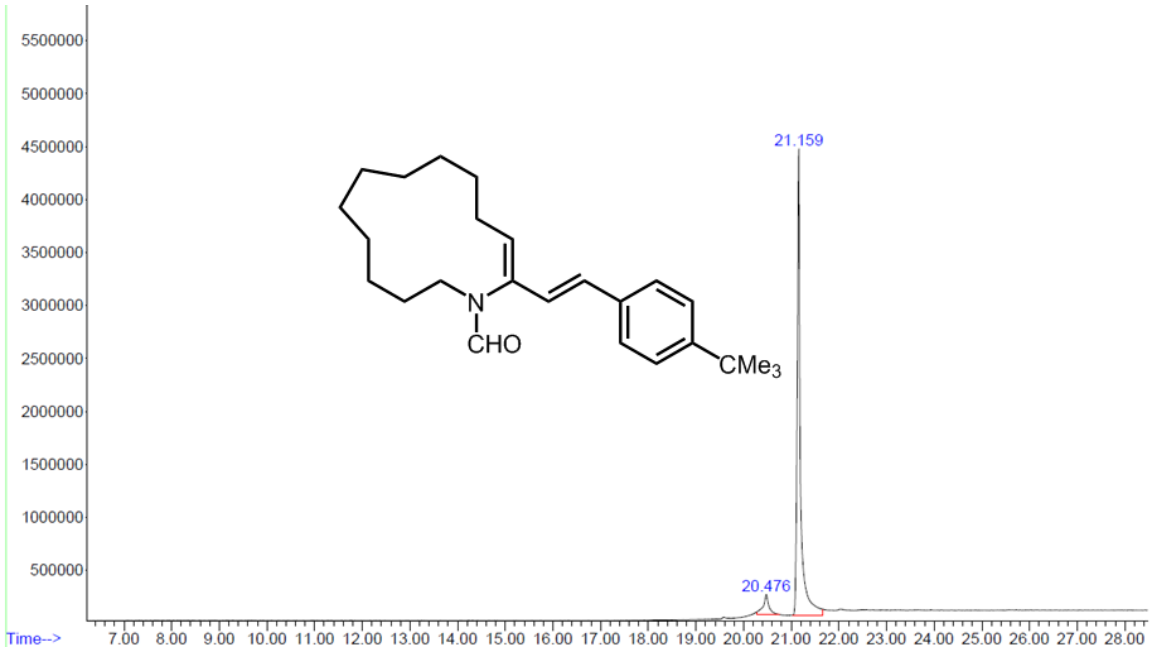
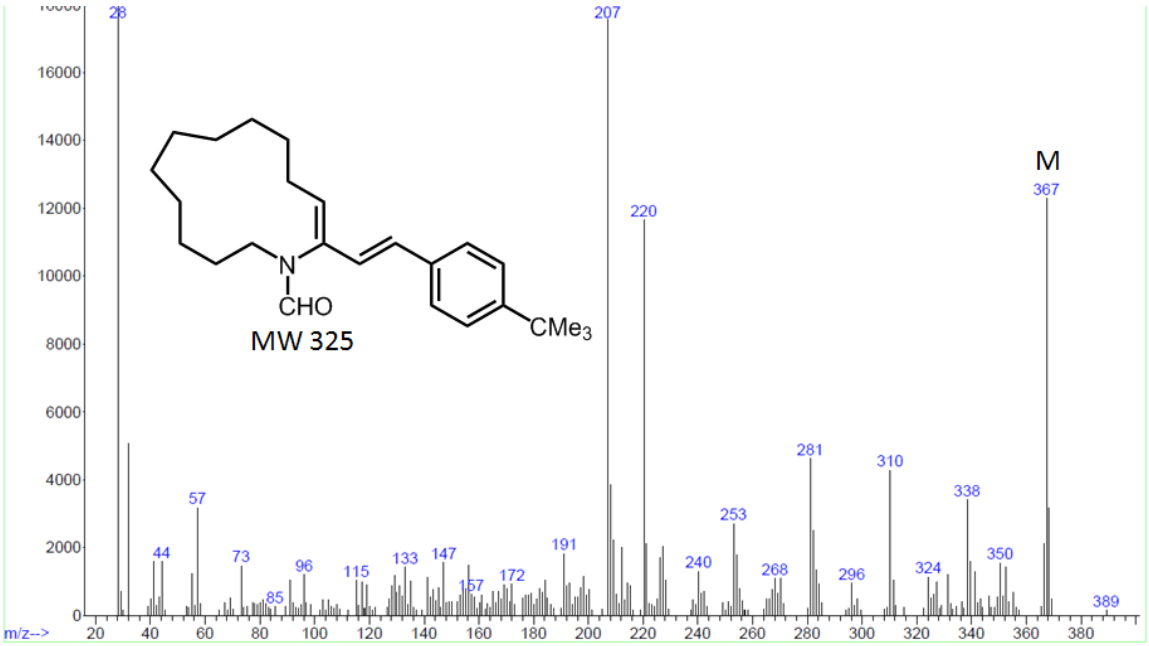
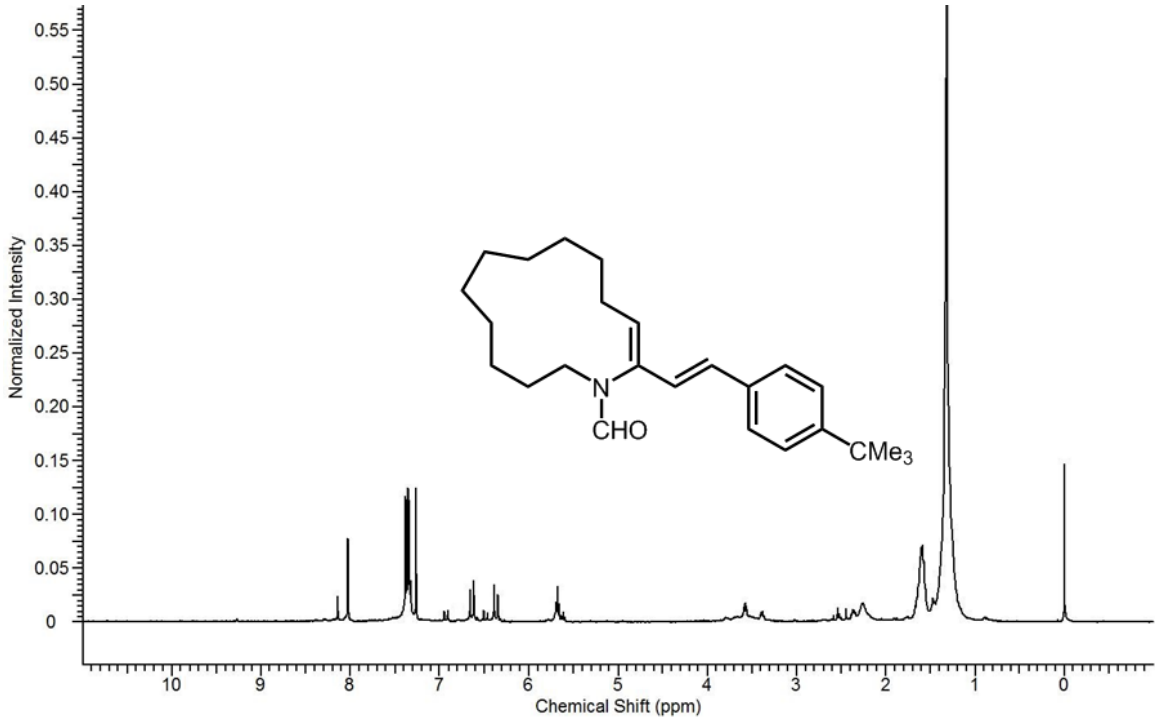


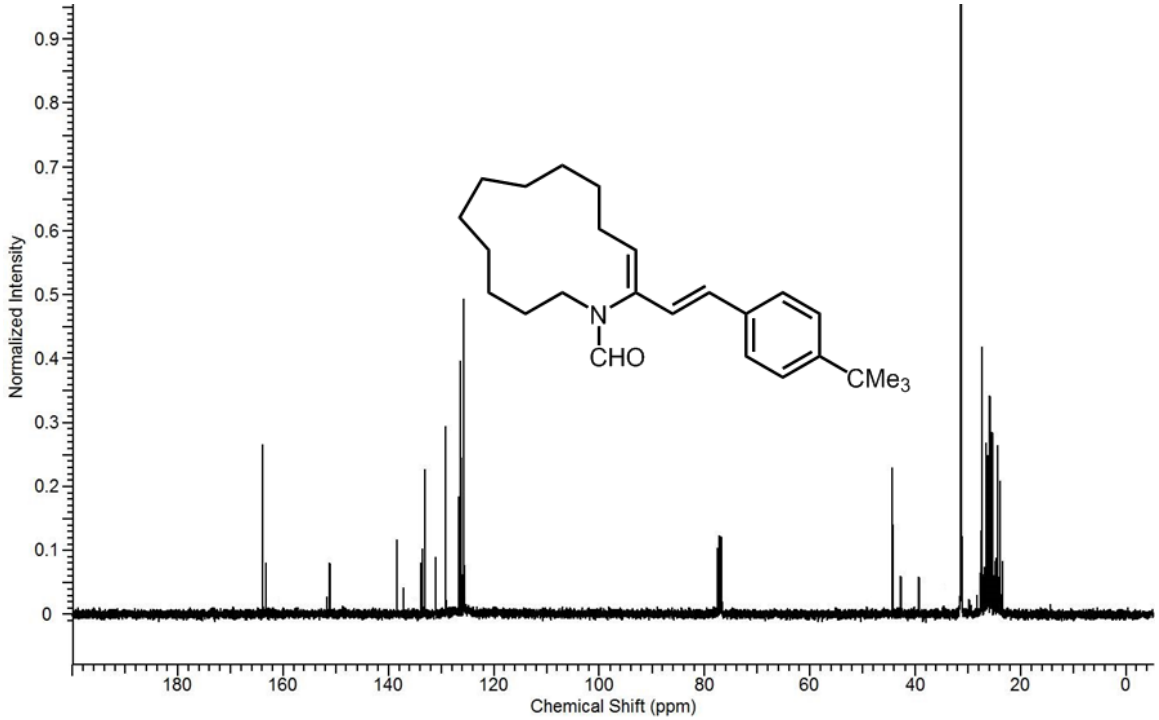
Spectra **1-26** GC spectrum of **3a5.**



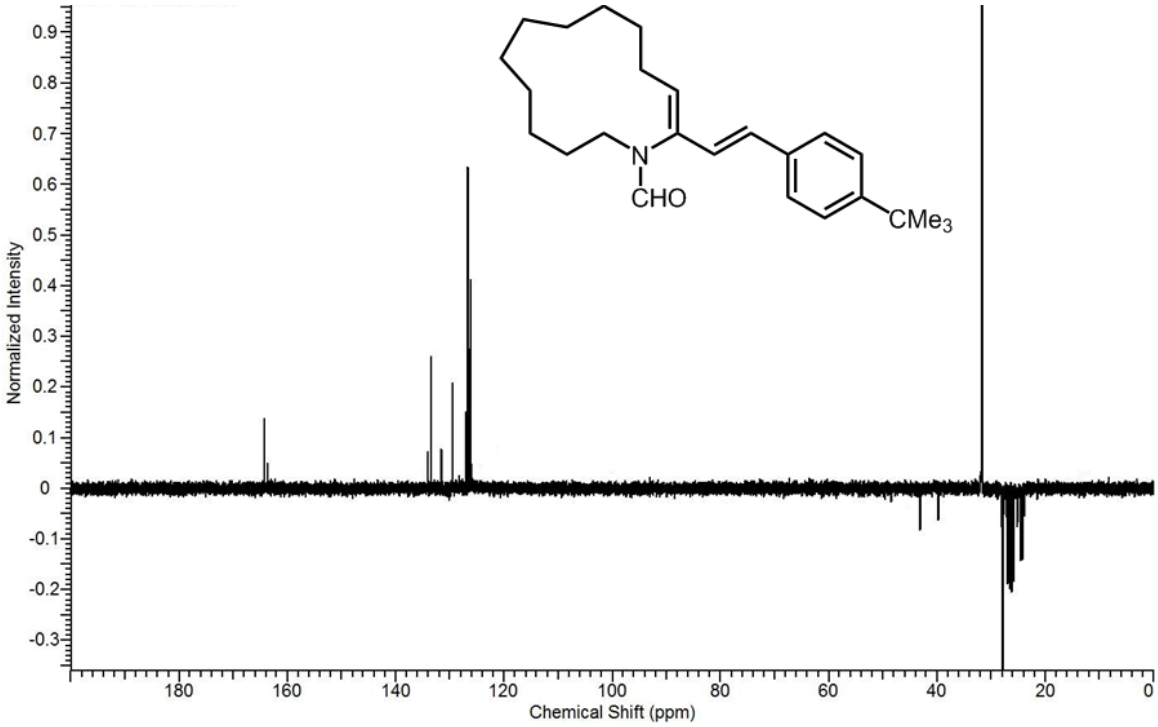
Spectra **1-27** MS spectrum of **3a5.**



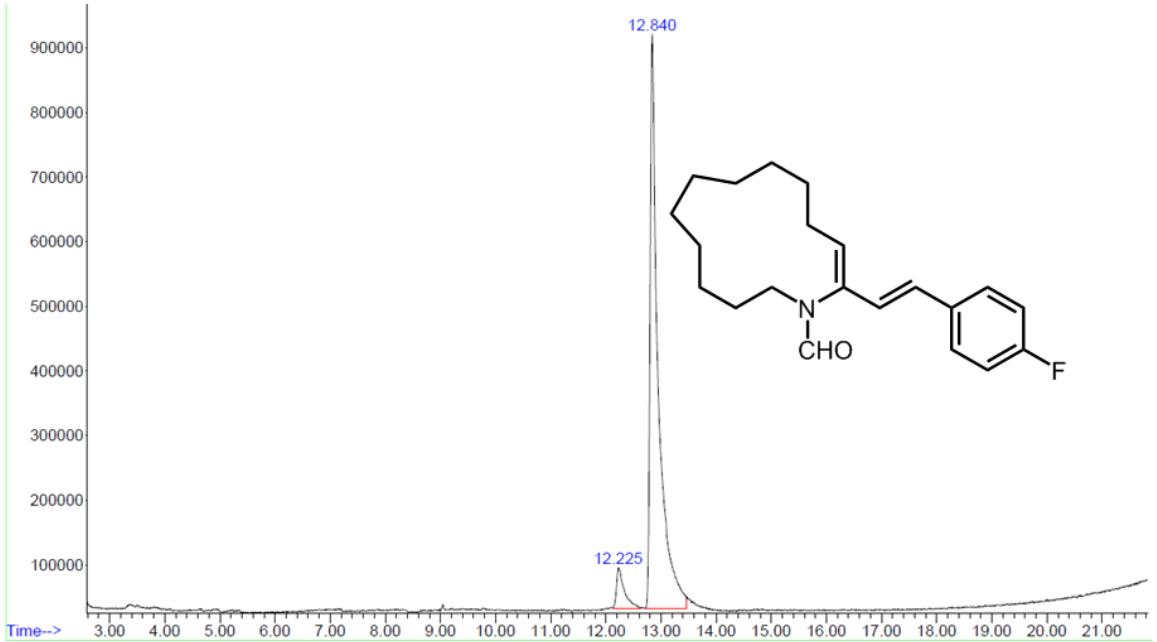
Spectra **1-28** Proton NMR spectrum of **3a5.**



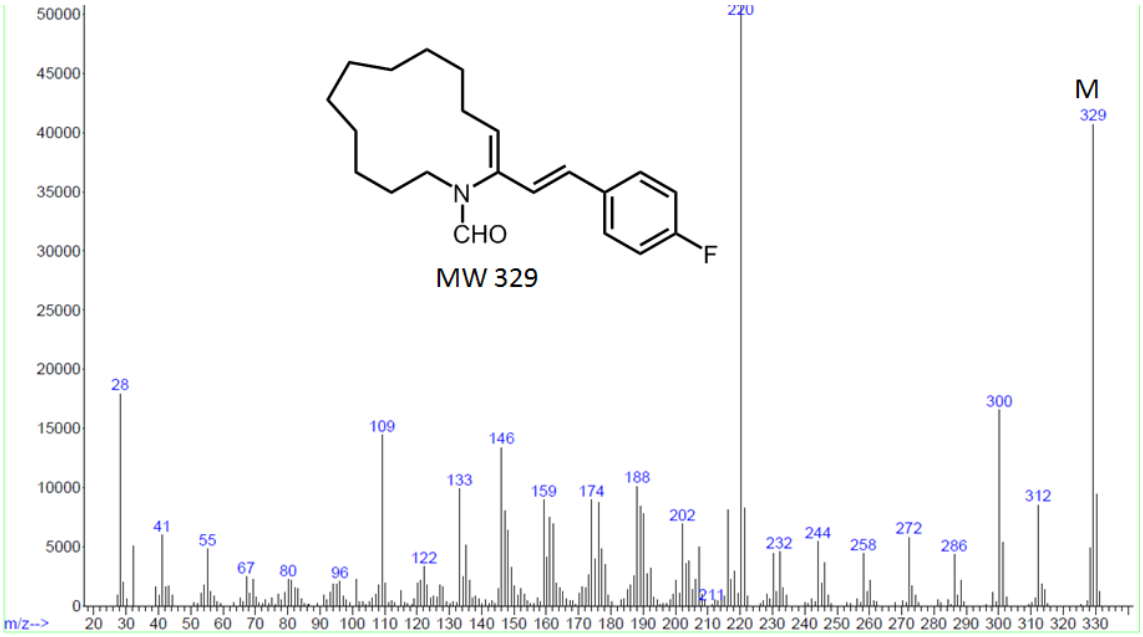
Spectra **1-29** Carbon NMR spectrum of **3a5.**



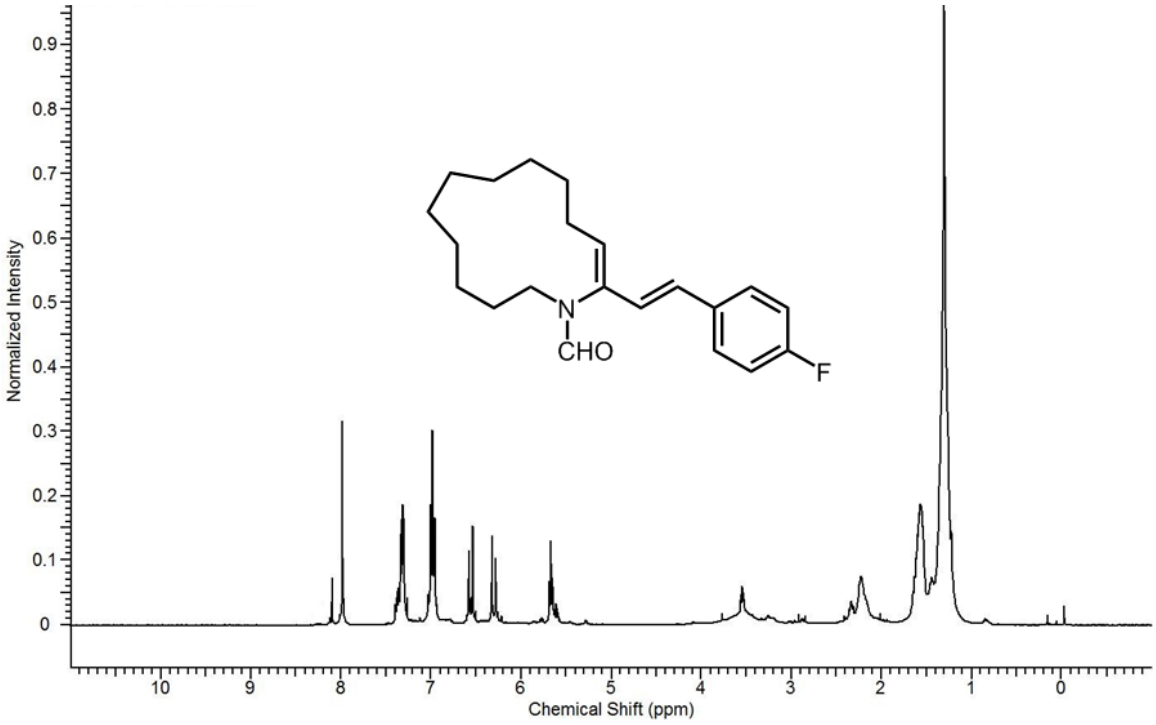
Spectra **1-30** DEPT-135 NMR spectrum of **3a5.**



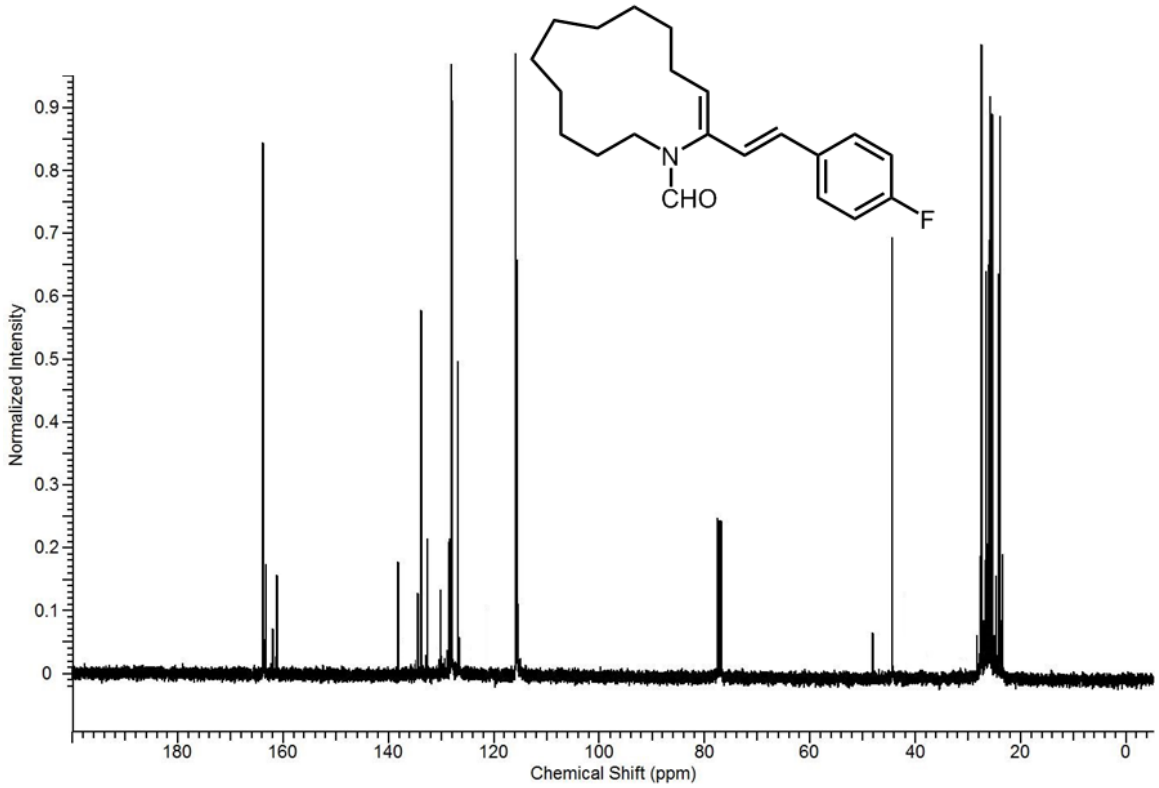
Spectra **1-31** GC spectrum of **3a6.**



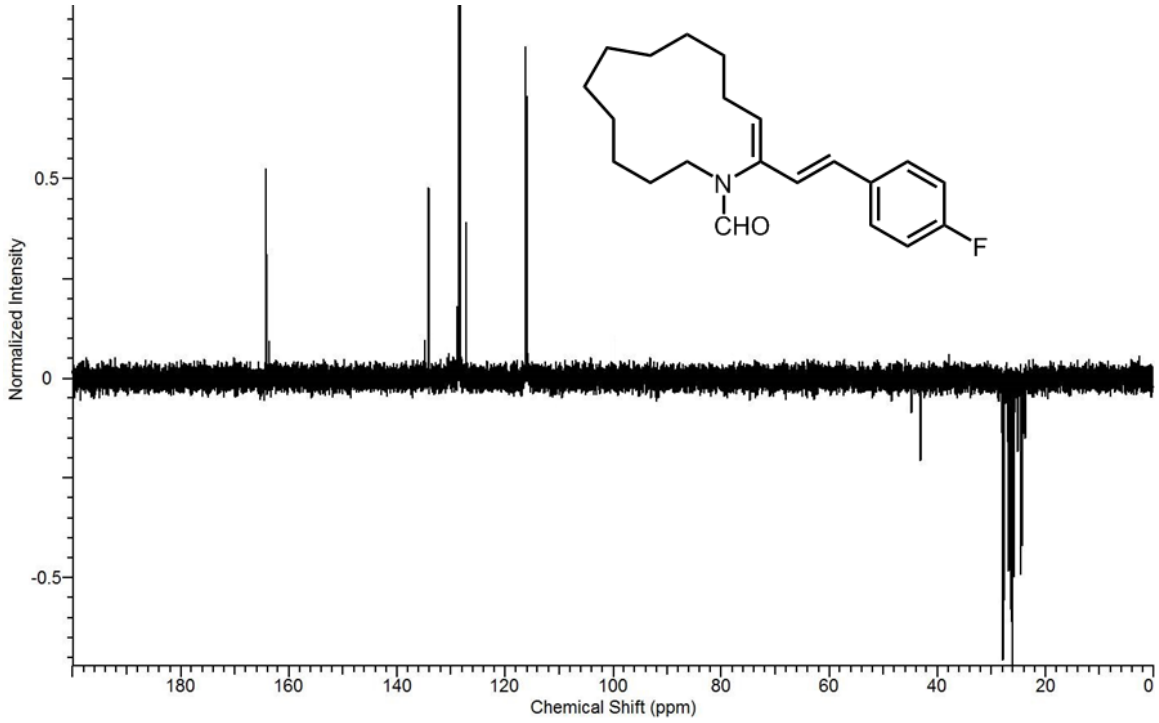
Spectra **1-32** MS spectrum of **3a6.**



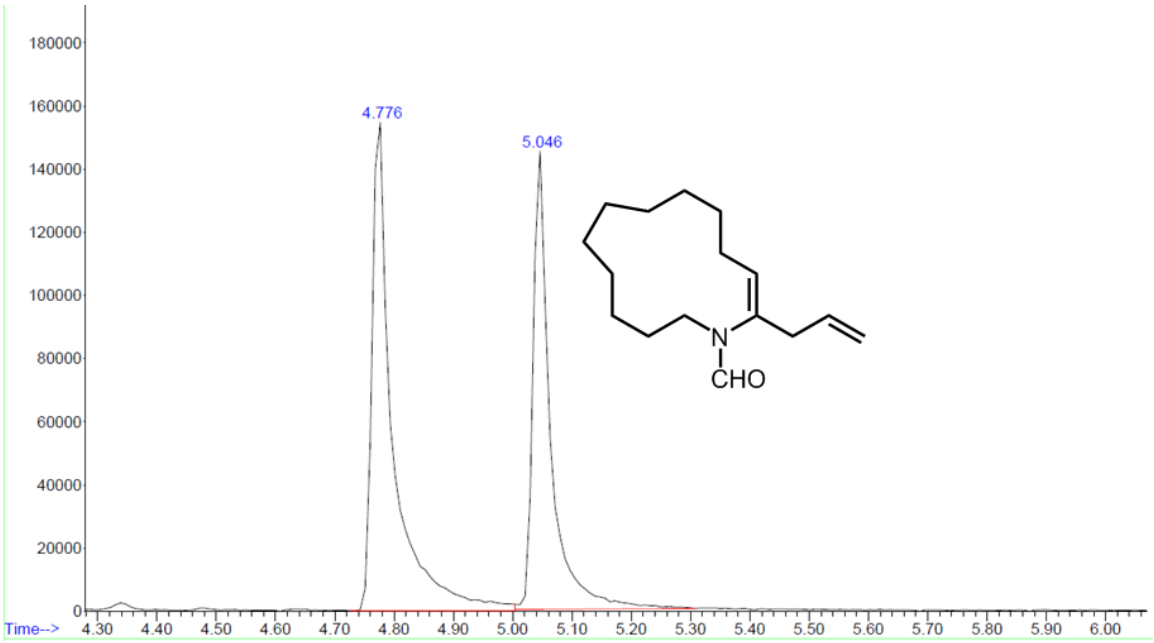
Spectra **1-33** Proton NMR spectrum of **3a6.**



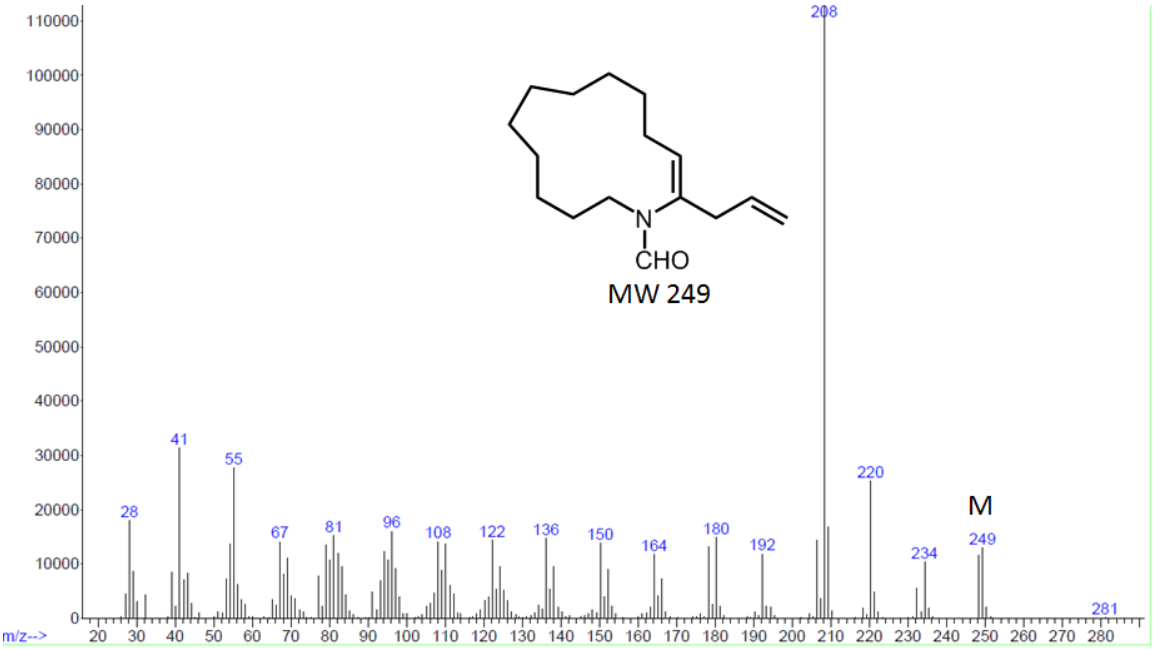
Spectra **1-34** Carbon NMR spectrum of **3a6.**



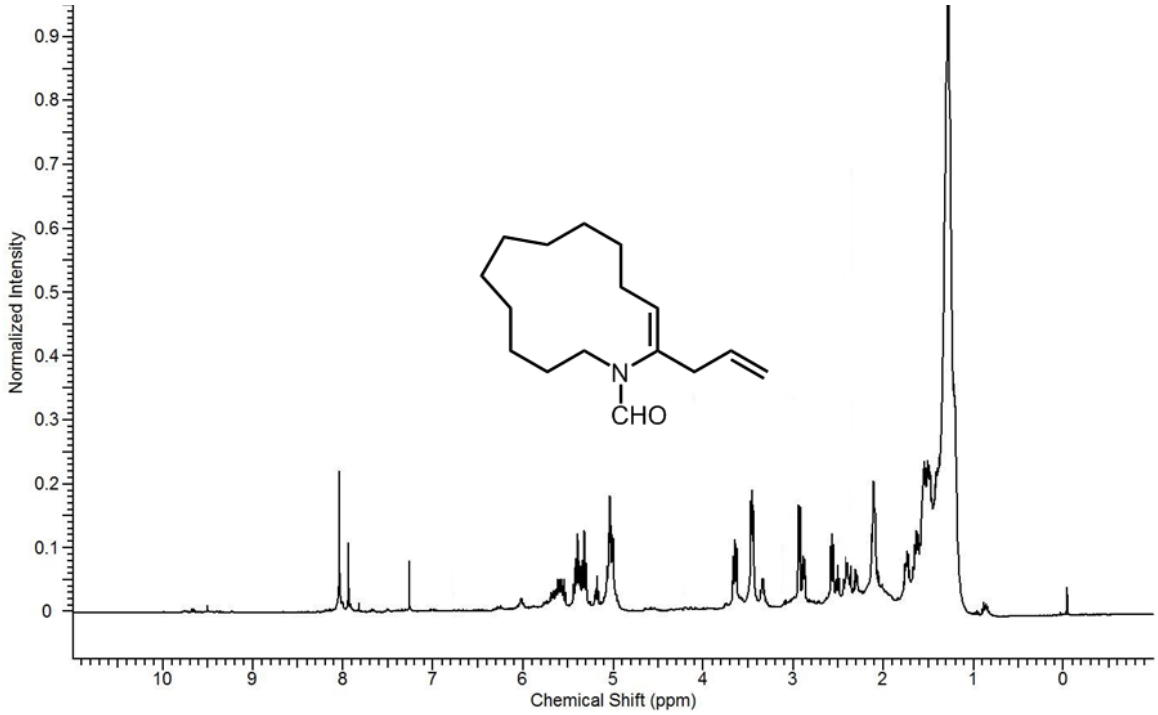
Spectra **1-35** DEPT-135 NMR spectrum of **3a6.**



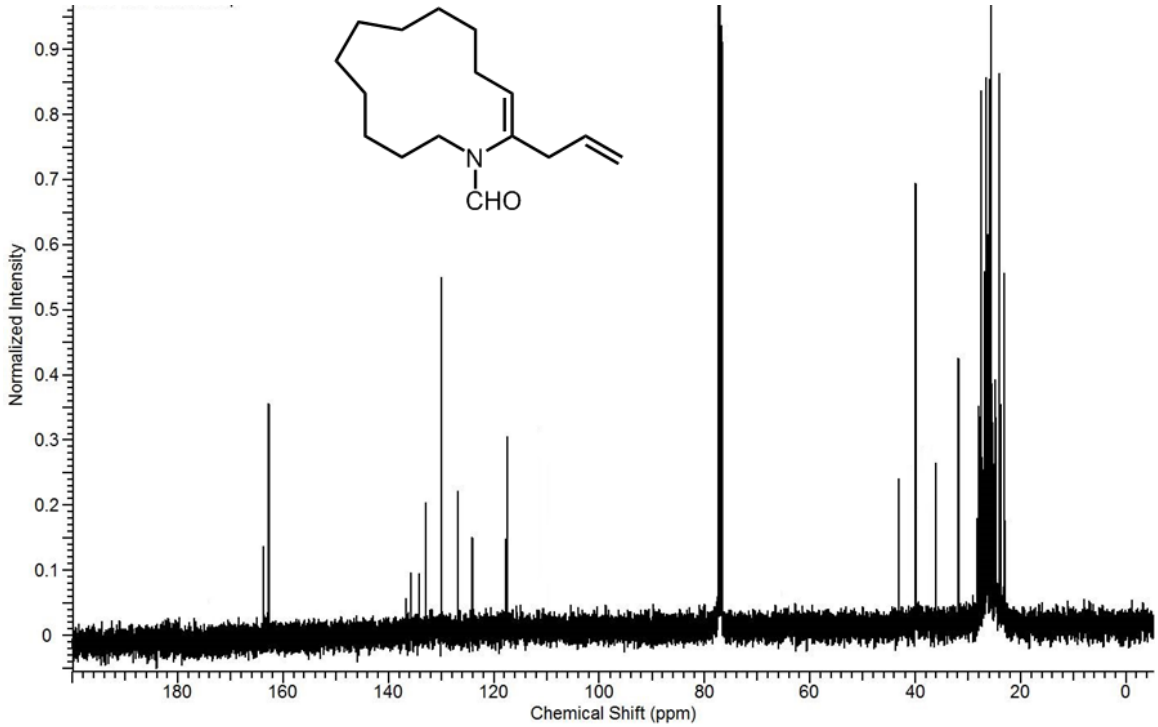
Spectra **1-36** GC spectrum of **3a7.**



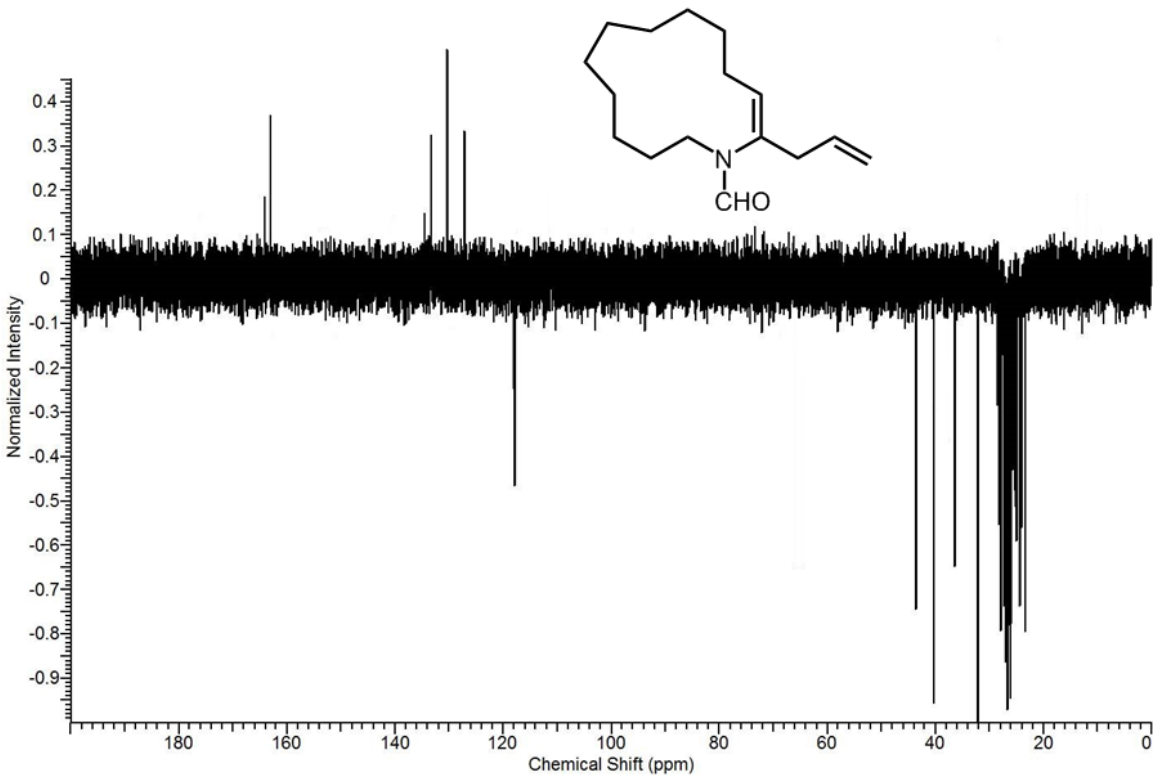
Spectra **1-37** MS spectrum of **3a7.**



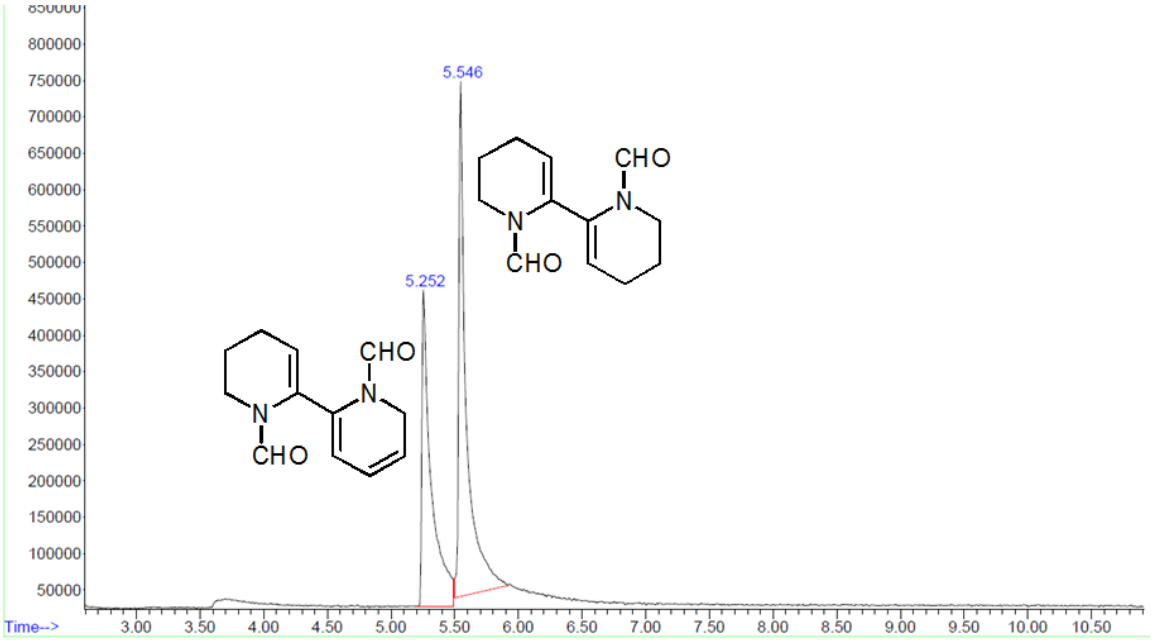
Spectra **1-38** Proton NMR spectrum of **3a7.**



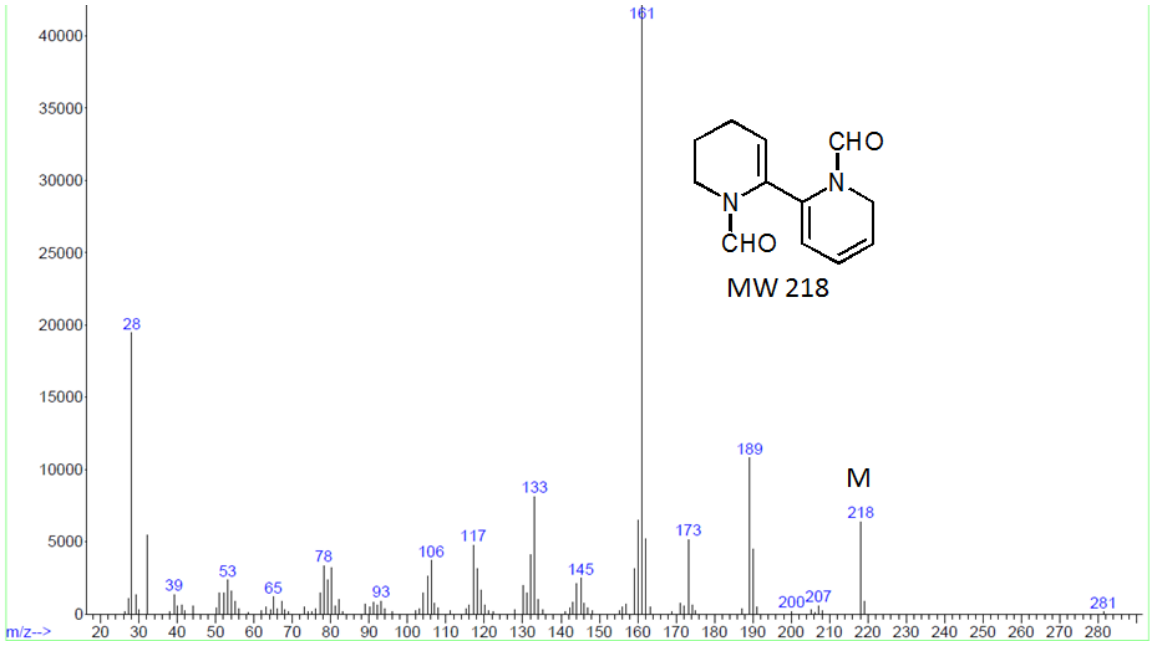
Spectra **1-39** Carbon NMR spectrum of **3a7.**



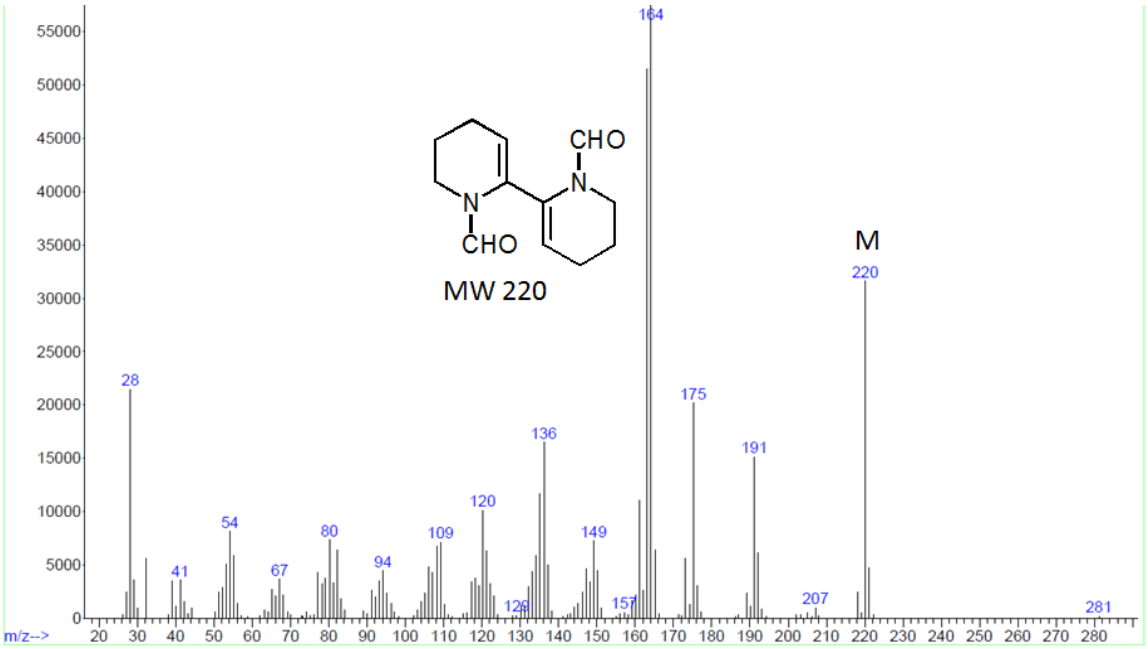
Spectra **1-40** DEPT-135 NMR spectrum of **3a7.**



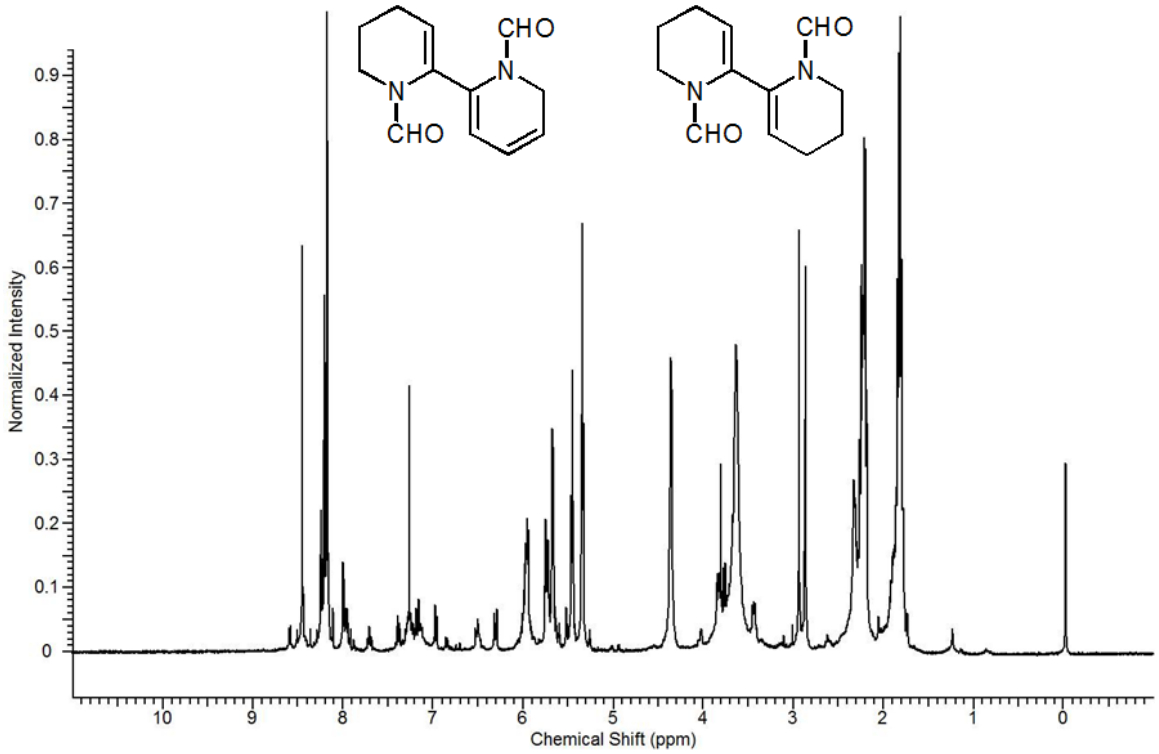
Spectra **1-41** GC spectrum of **3a10/3a10b.**



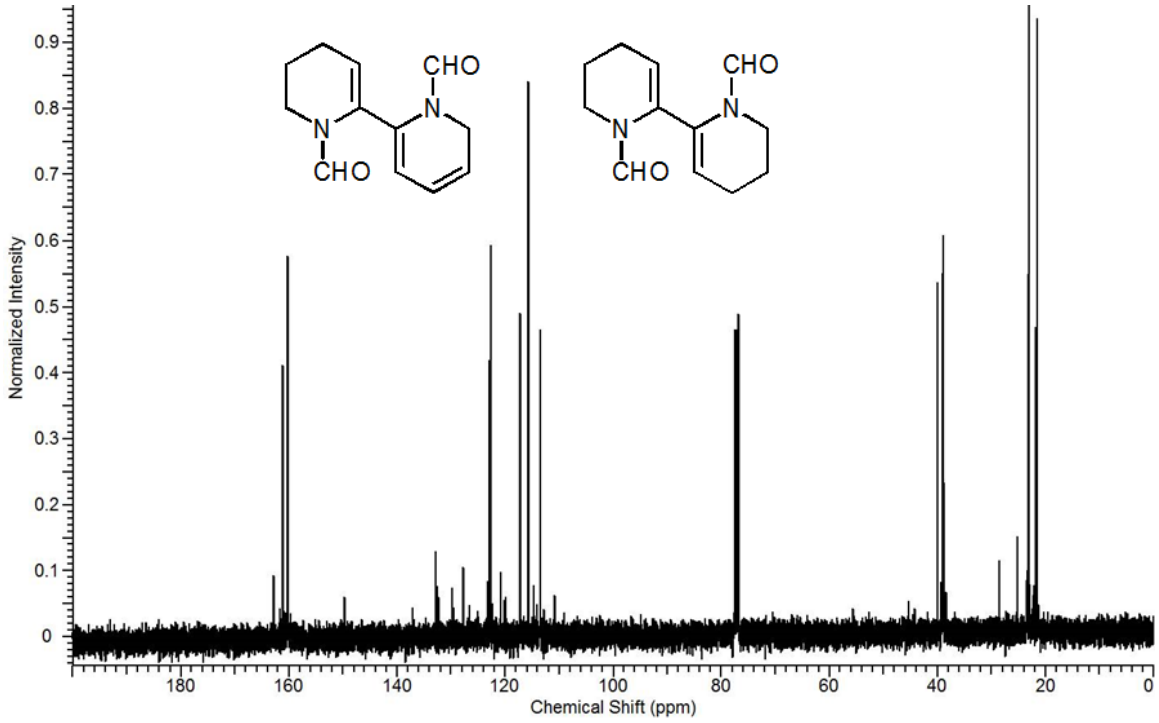
Spectra **1-42** MS spectrum of **3a10b.**



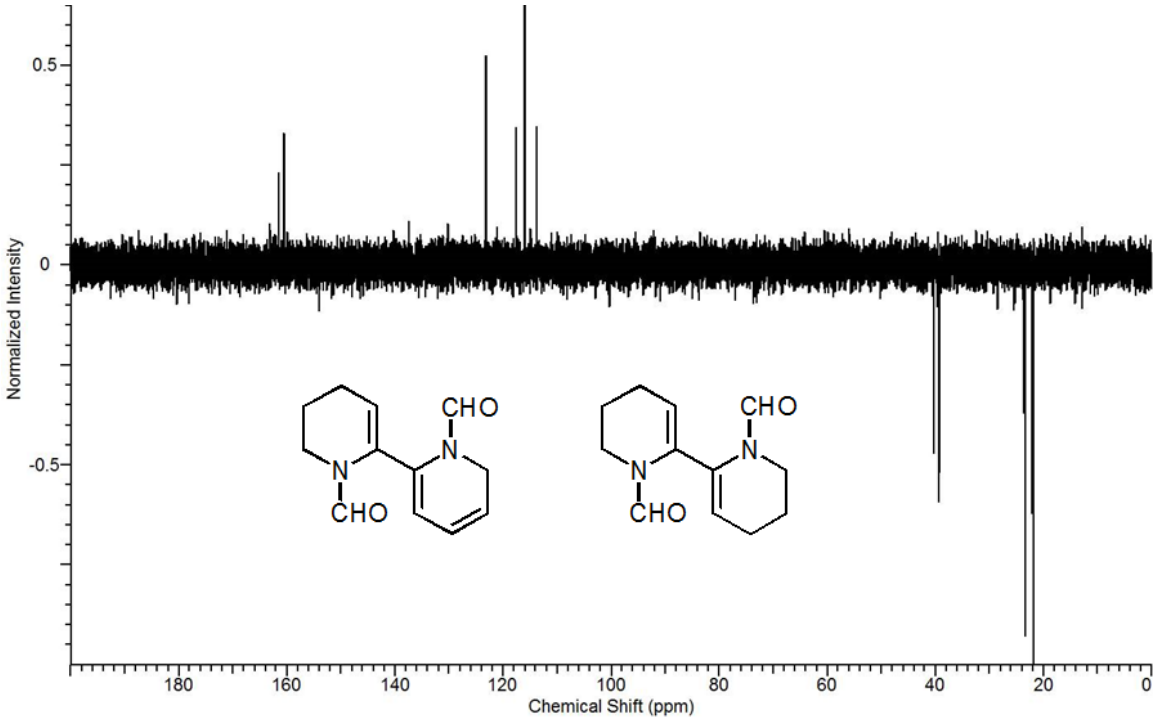
Spectra **1-43** MS spectrum of **3a10.**



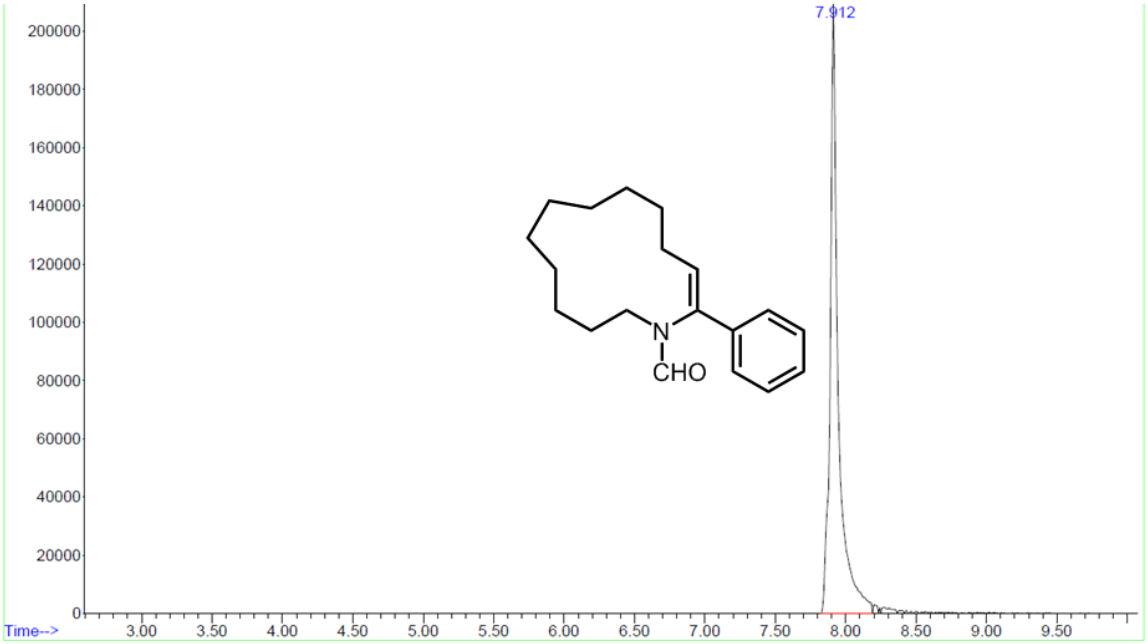
Spectra **1-44** Proton NMR spectrum of **3a10/3a10b.**



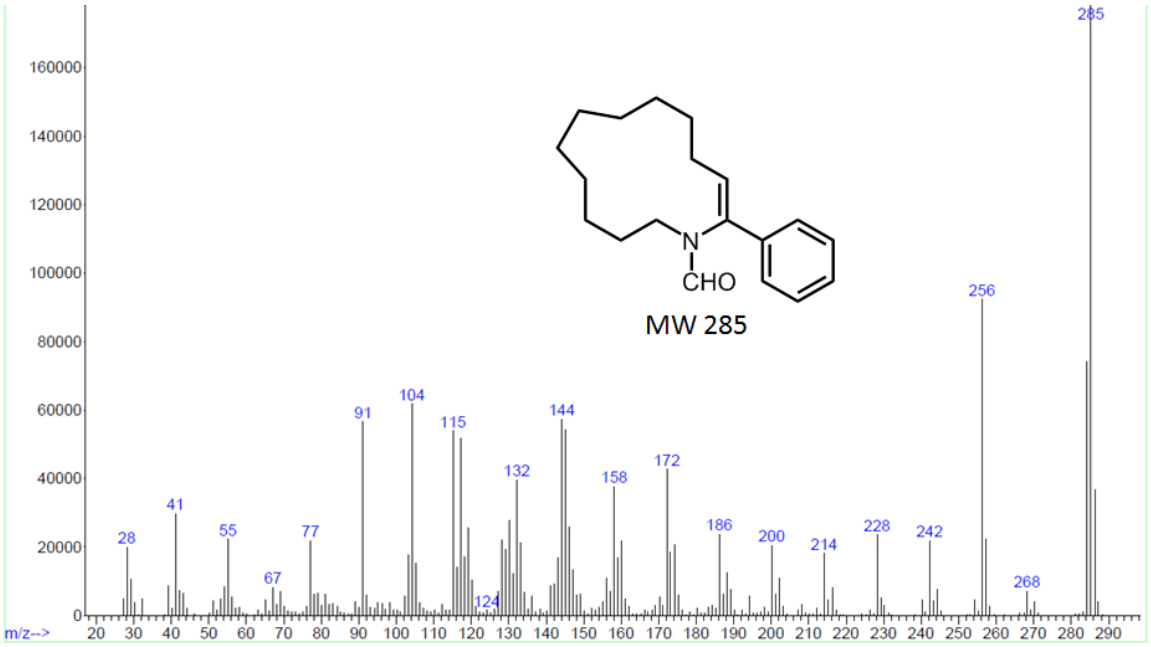
Spectra **1-45** Carbon NMR spectrum of **3a10/3a10b.**



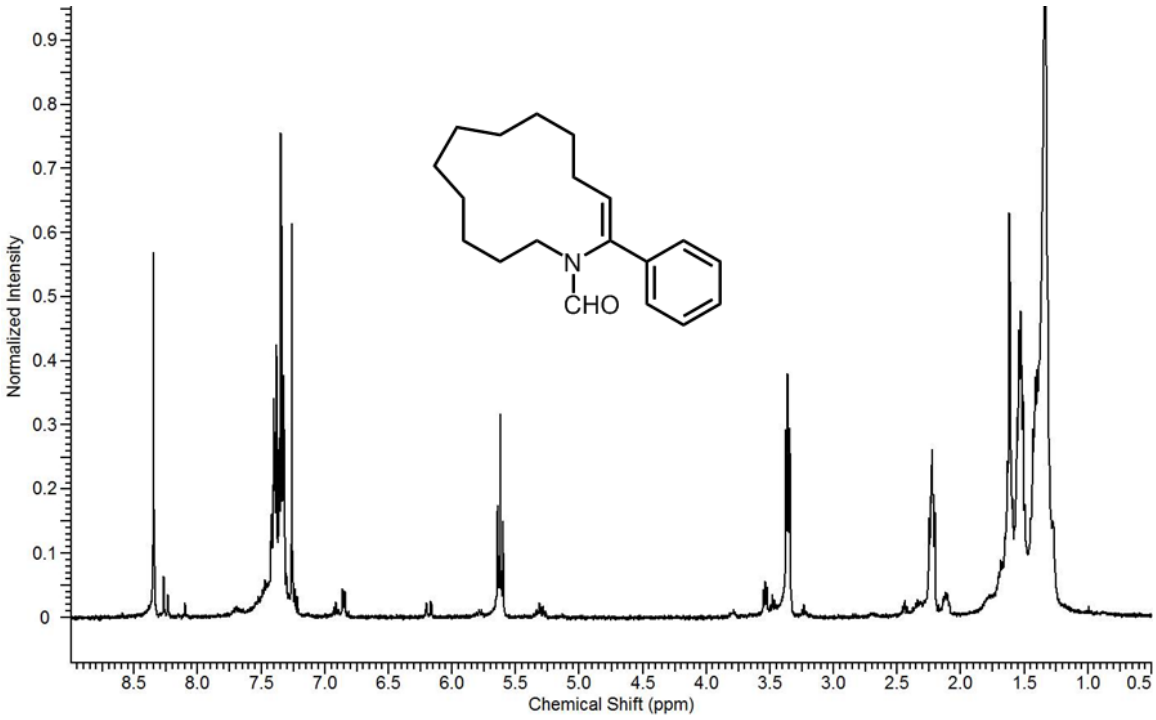
Spectra **1-46** DEPT-135 NMR spectrum of **3a10/3a10b.**



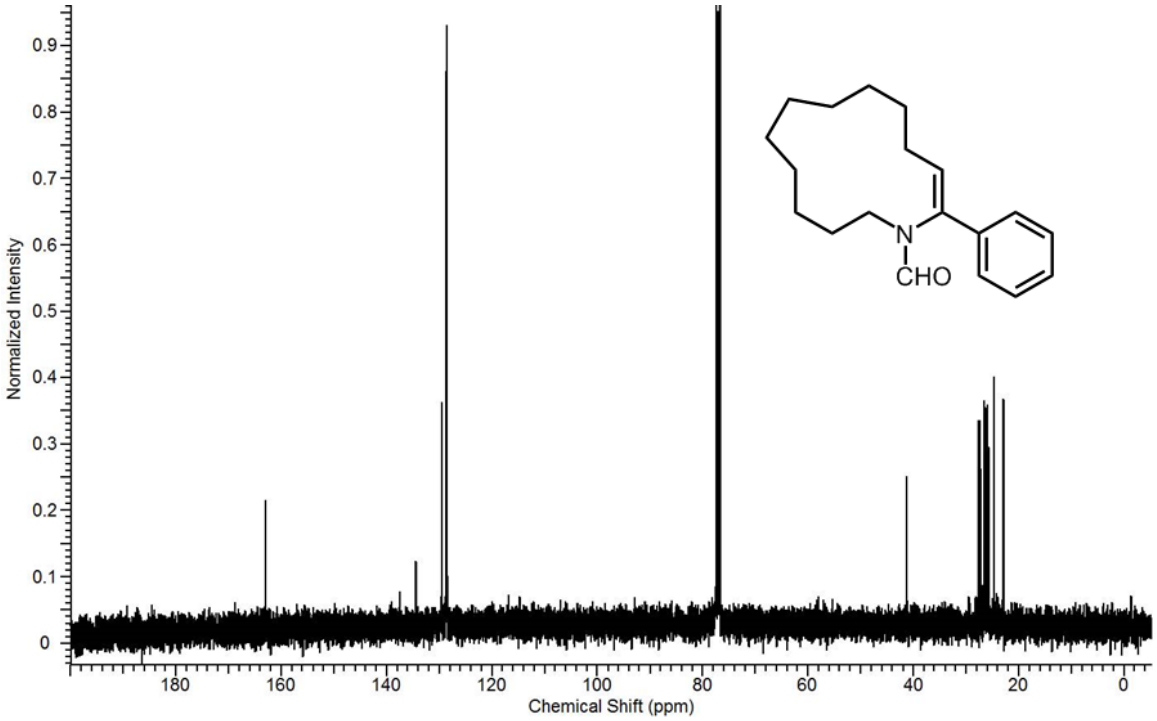
Spectra **l-47** GC spectrum of **3b1.**



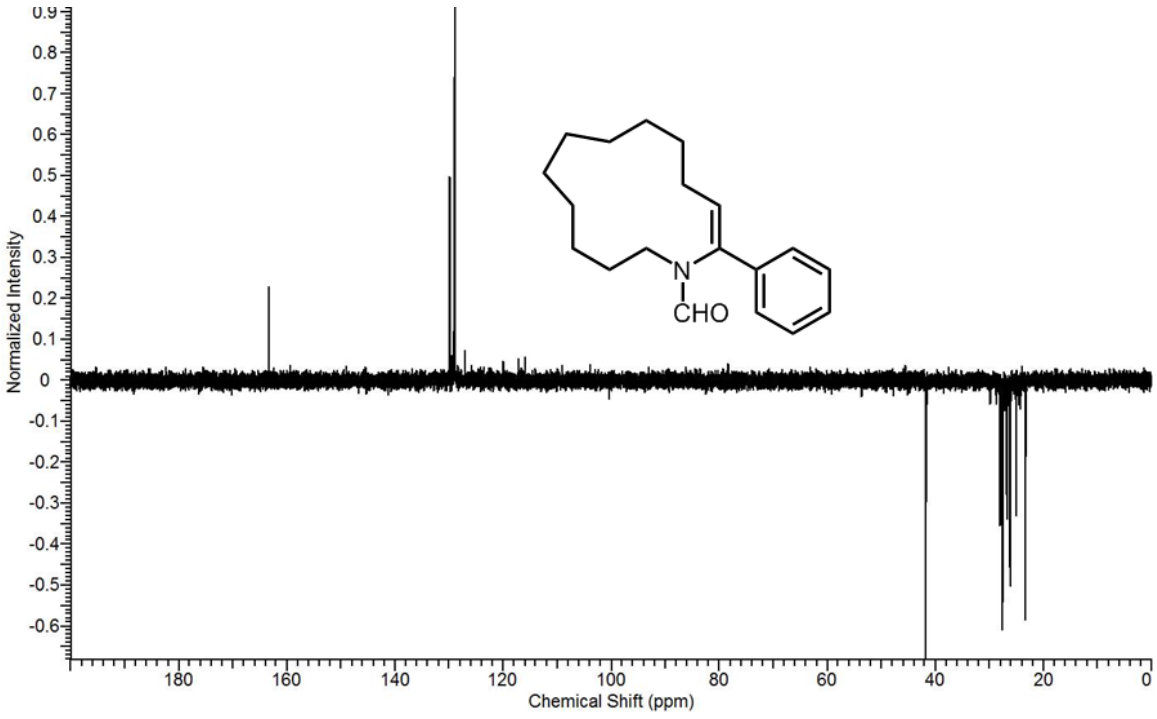
Spectra **1-48** MS spectrum of **3b1.**



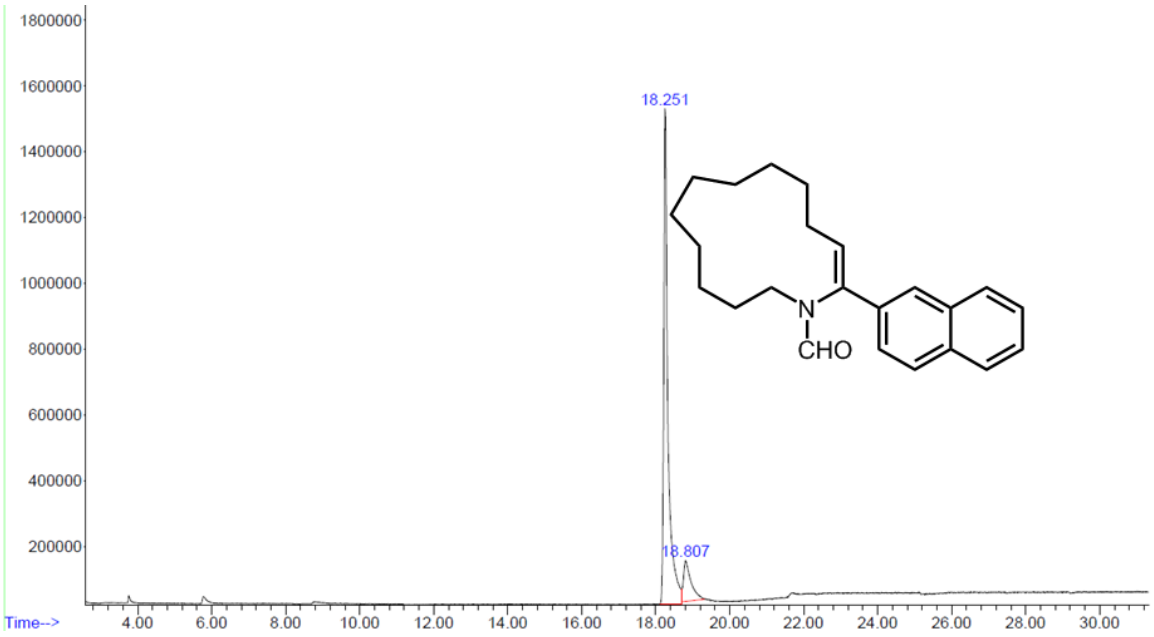
Spectra **1-49** Proton NMR spectrum of **3b1.**



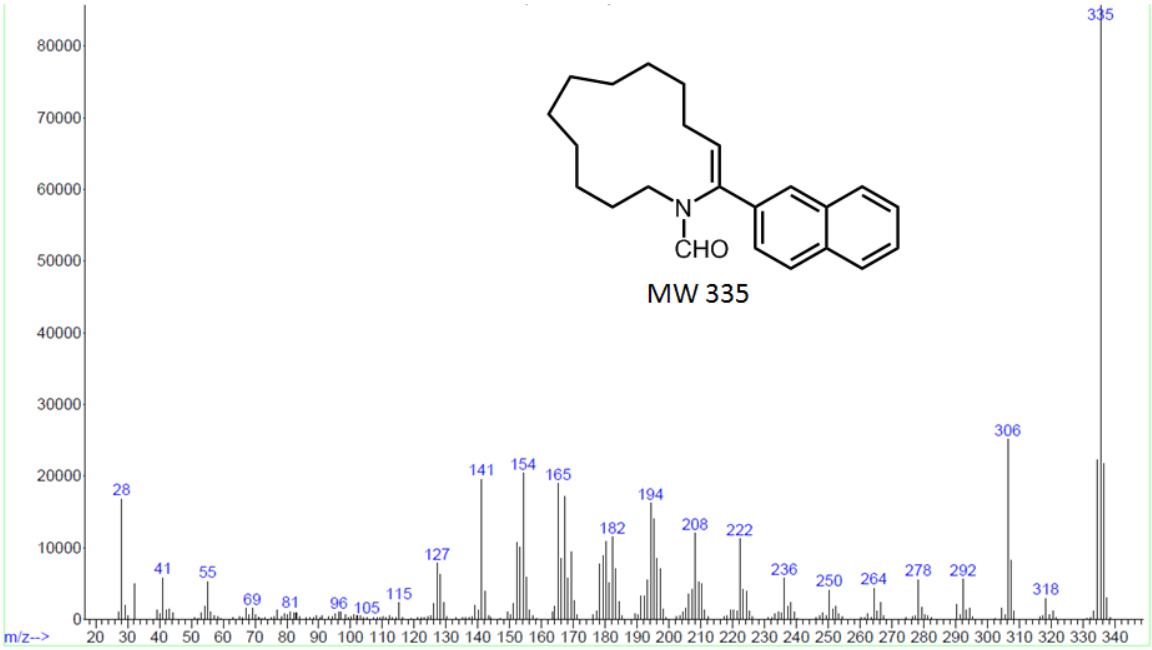
Spectra **1-50** Carbon NMR spectrum of **3b1.**



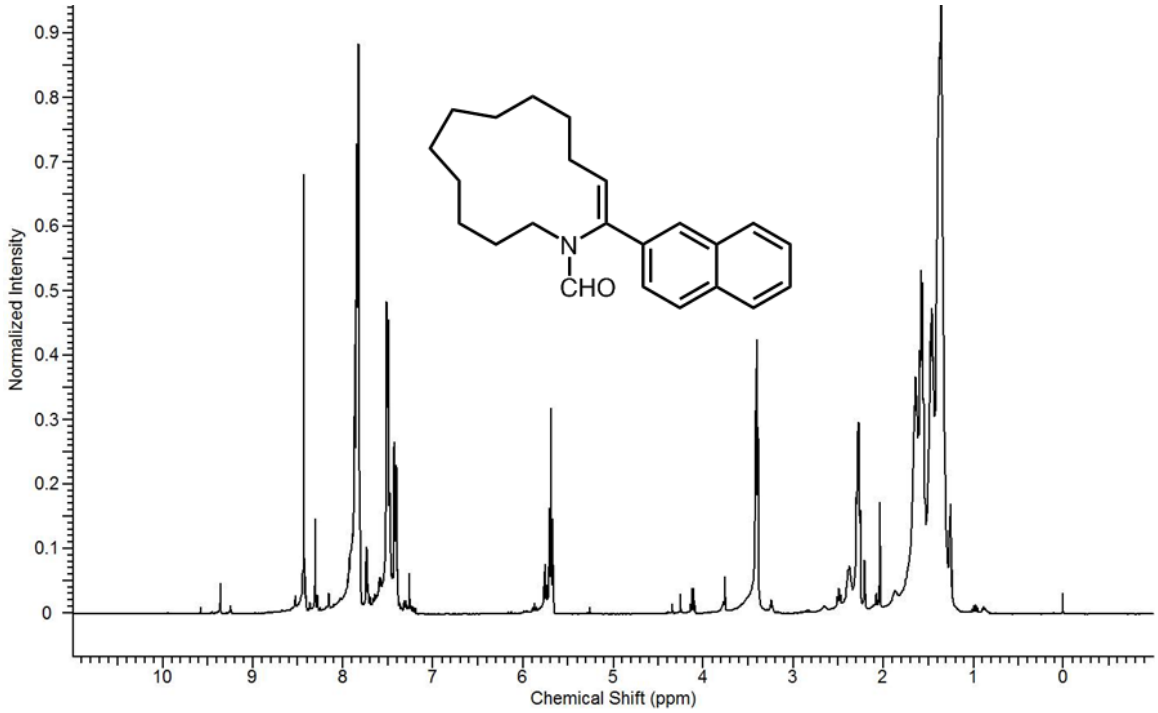
Spectra **1-51** DEPT-135 NMR spectrum of **3b1.**



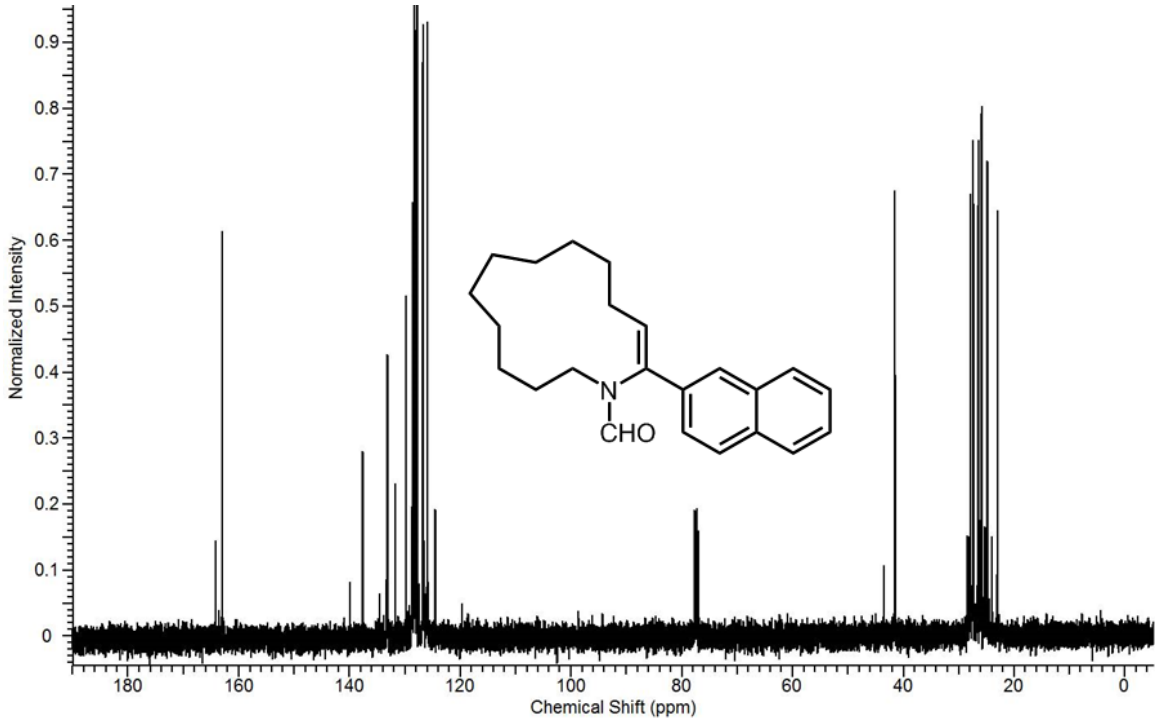
Spectra **1-52** GC spectrum of **3b2.**



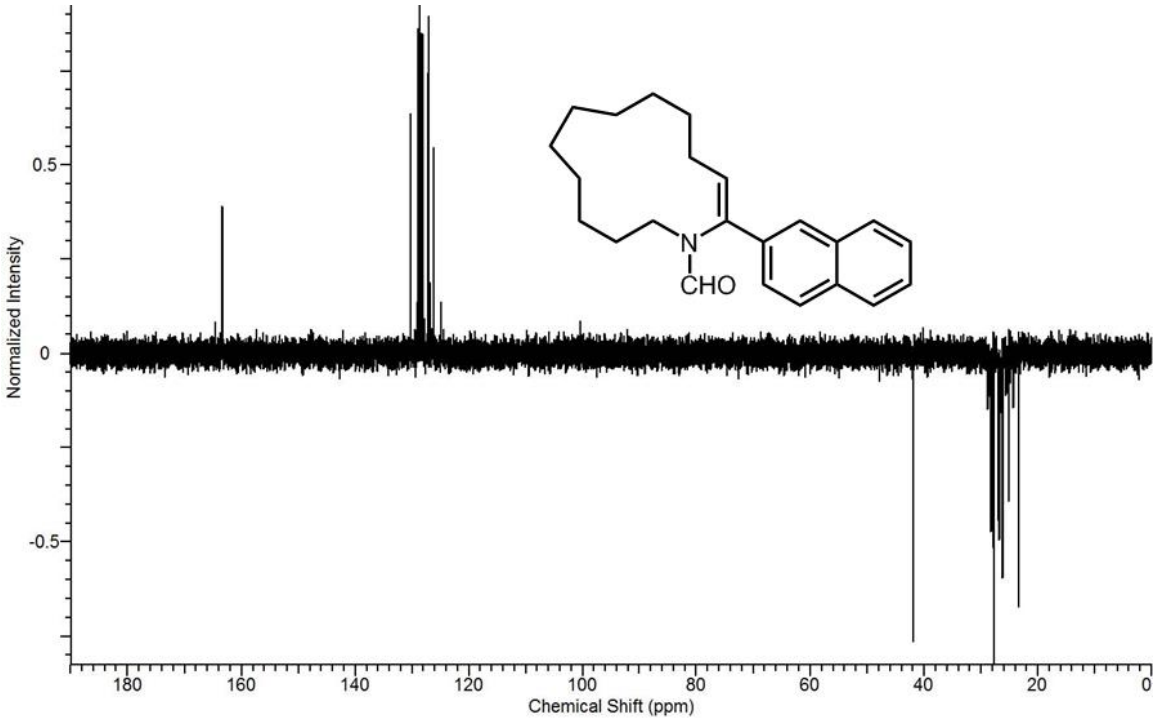
Spectra **1-53** MS spectrum of **3b2.**



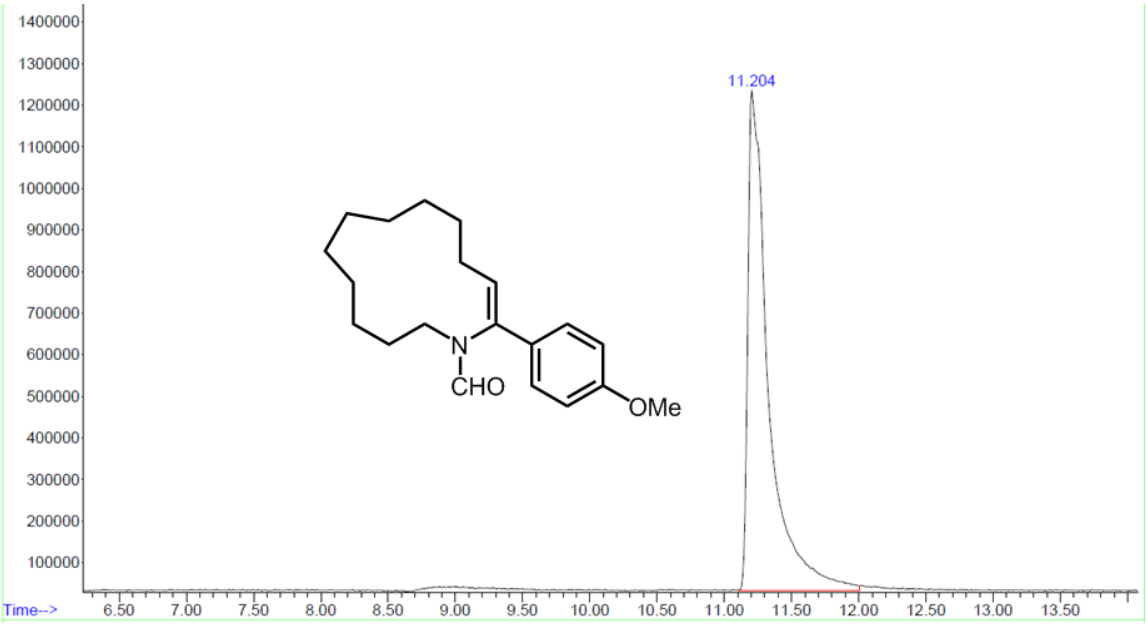
Spectra **1-54** Proton NMR spectrum of **3b2.**



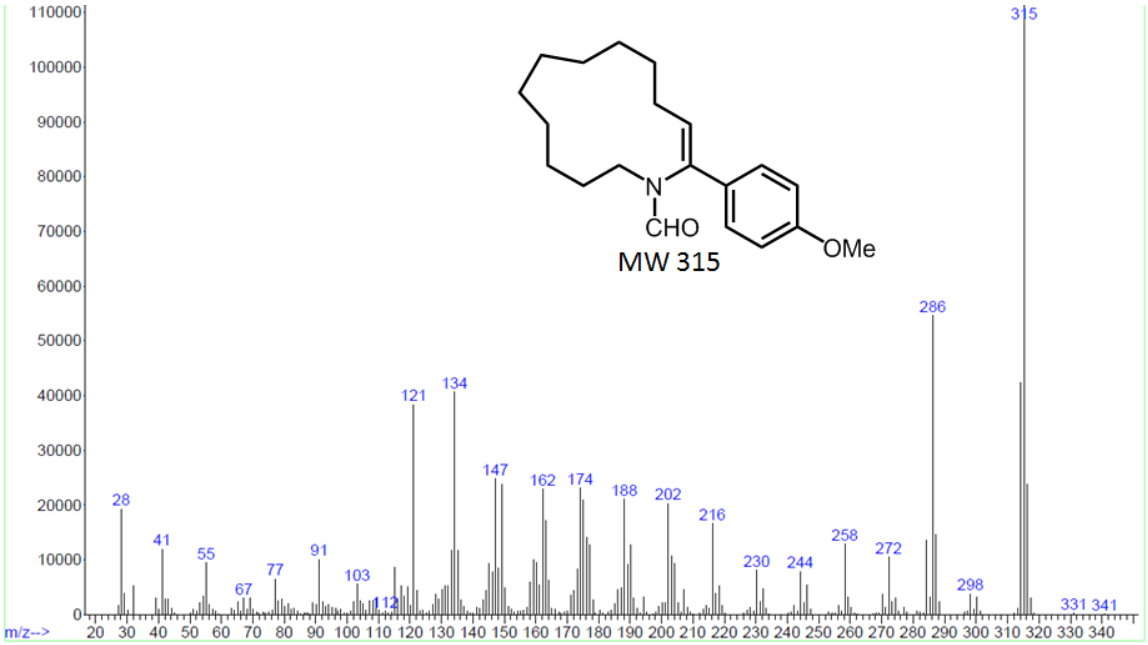
Spectra **1-55** Carbon NMR spectrum of **3b2.**



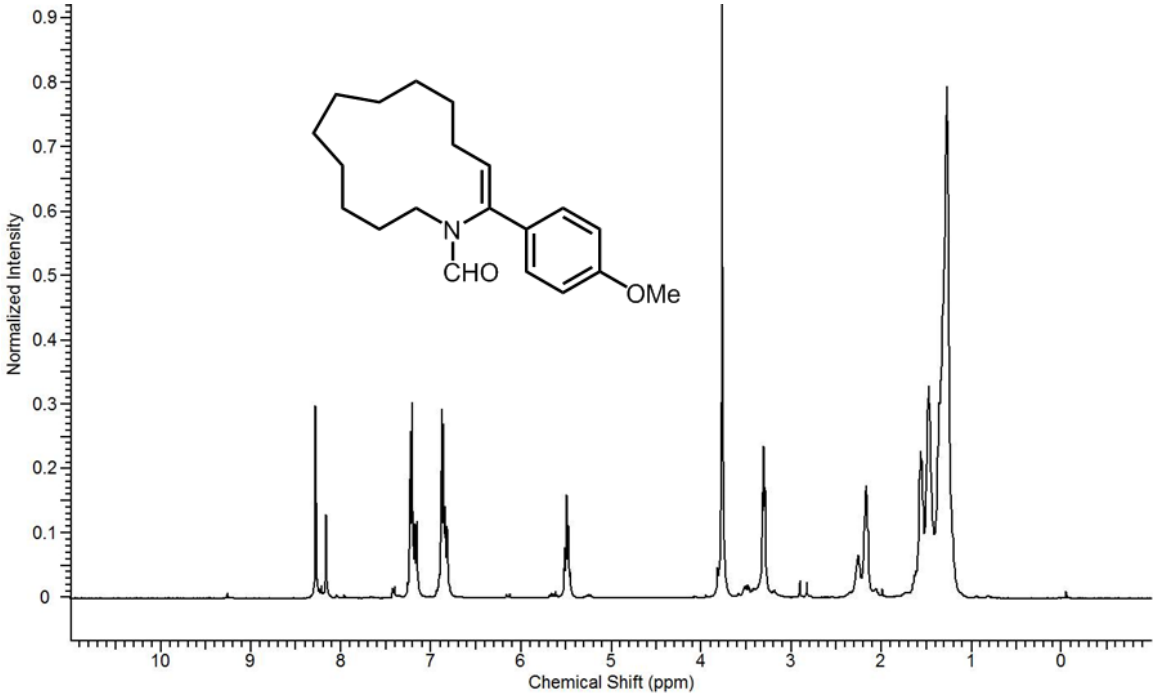
Spectra **1-56** DEPT-135 NMR spectrum of **3b2.**



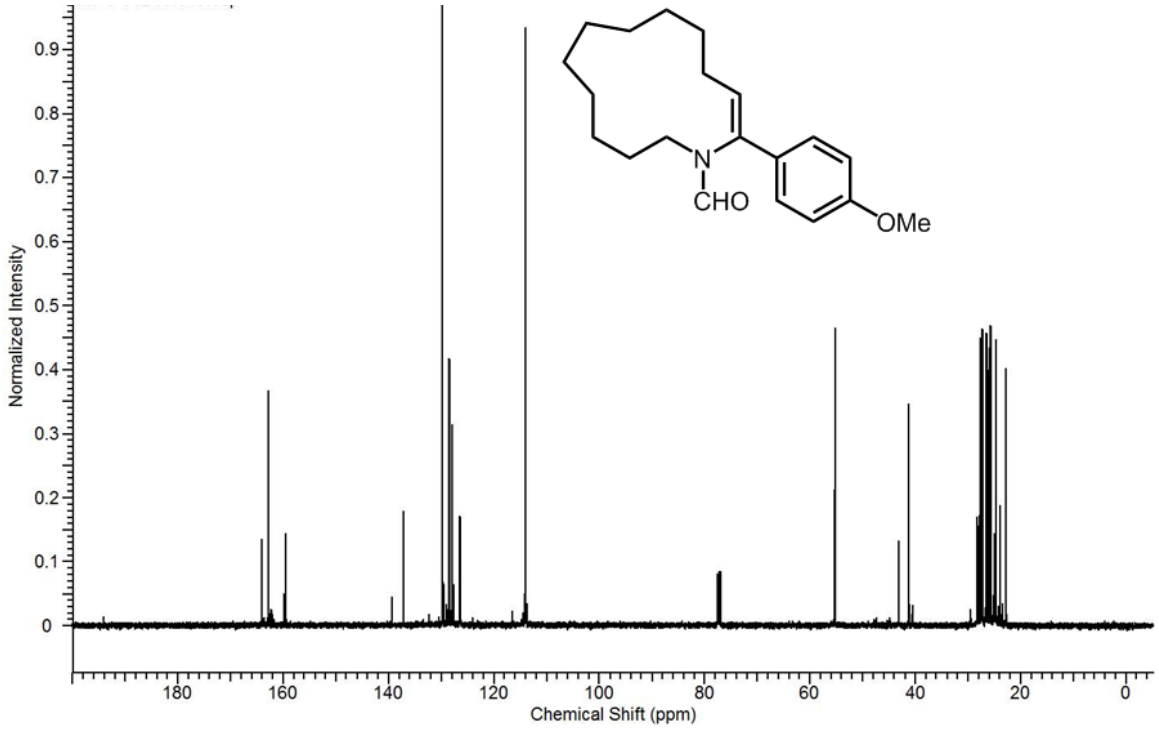
Spectra **1-57** GC spectrum of **3b3.**



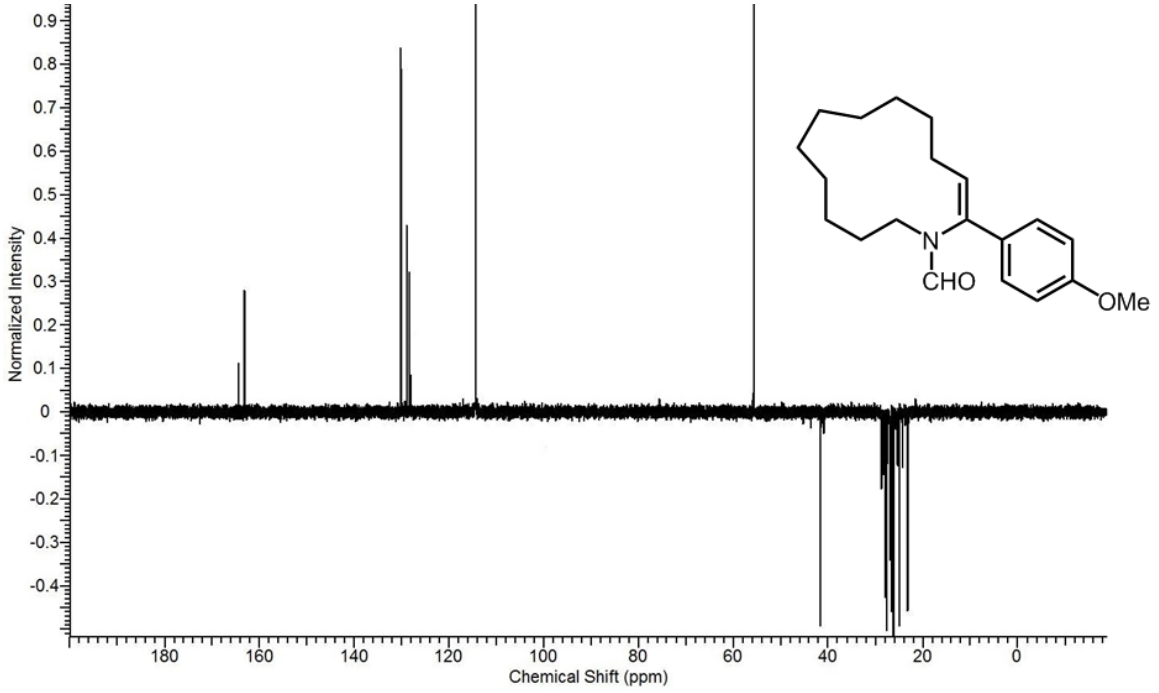
Spectra **1-58** MS spectrum of **3b3.**



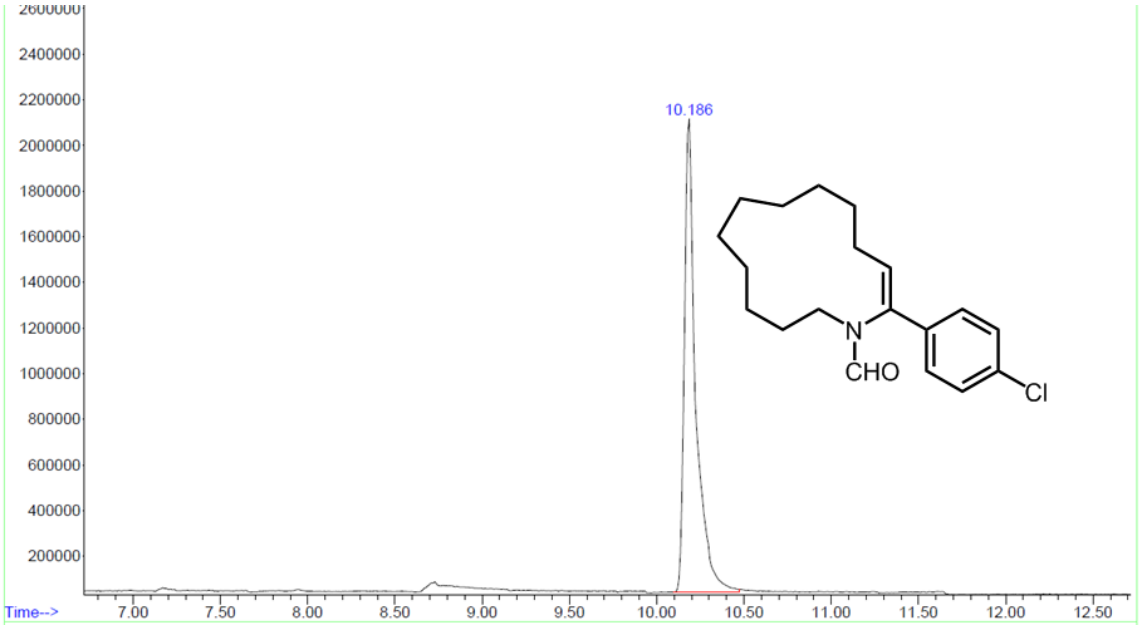
Spectra **1-59** Proton NMR spectrum of **3b3.**



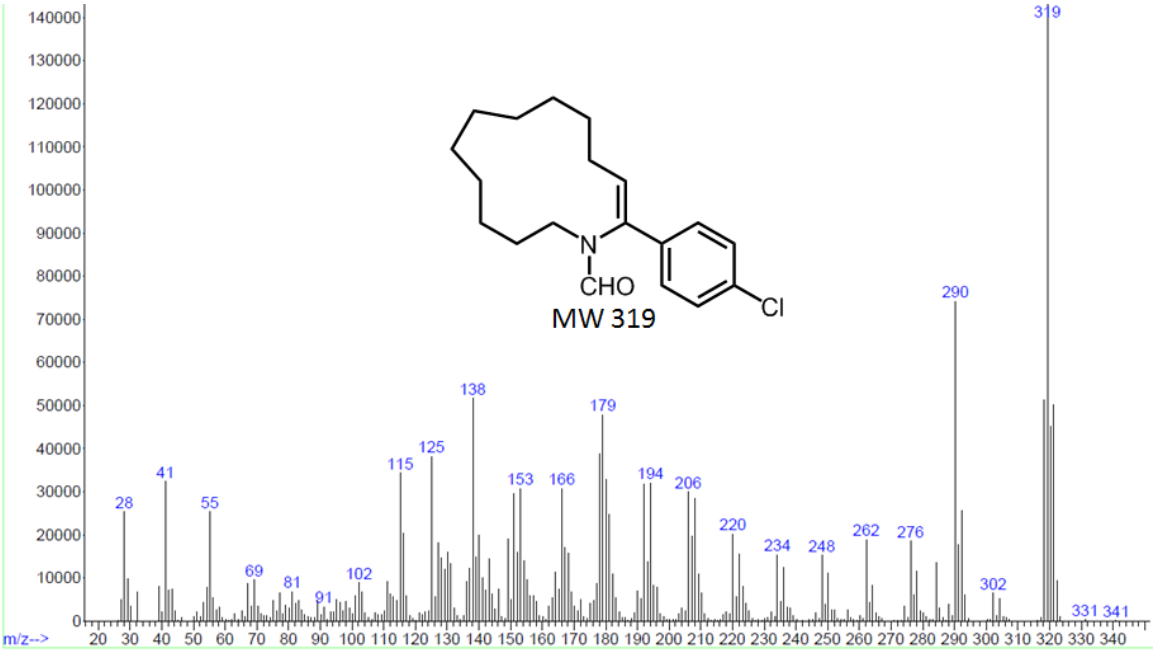
Spectra **1-60** Carbon NMR spectrum of **3b3.**



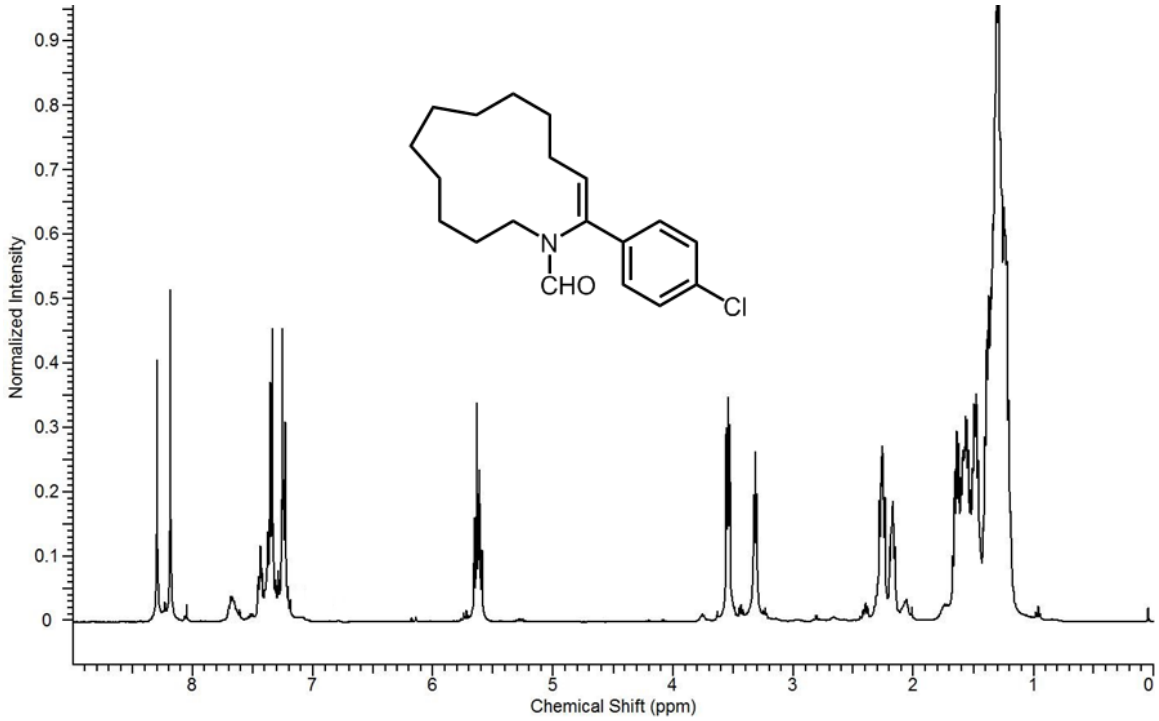
Spectra **1-61** DEPT-135 NMR spectrum of **3b3.**



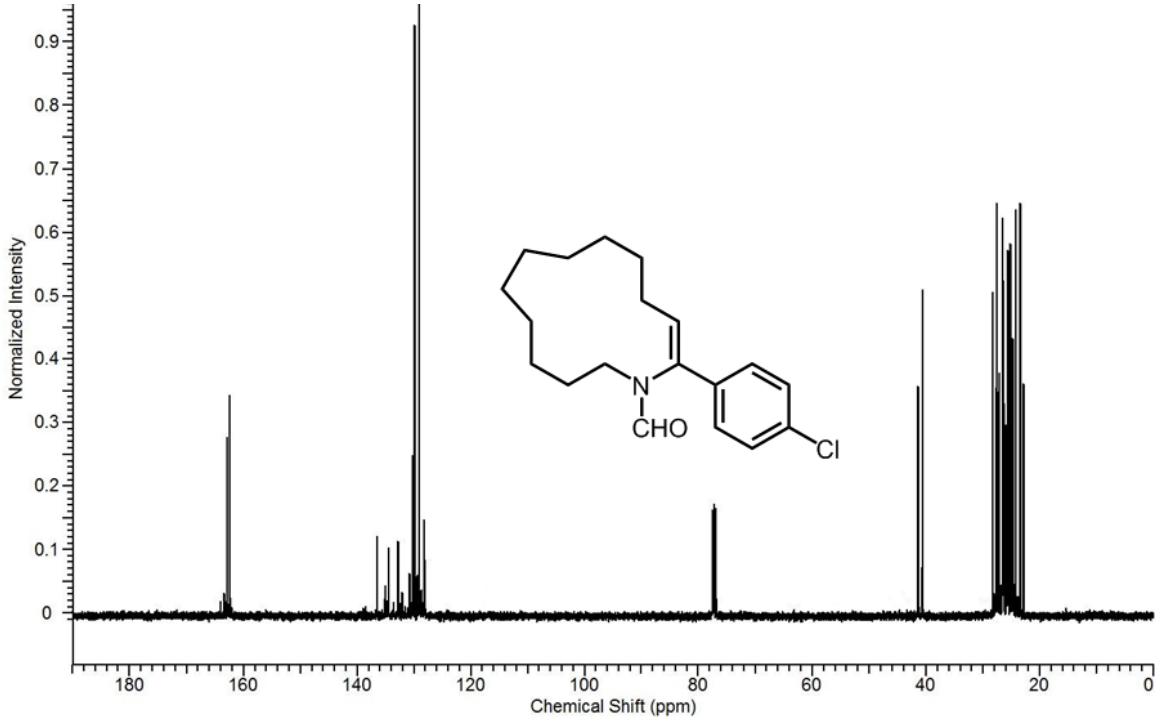
Spectra **1-62** GC spectrum of **3b4.**



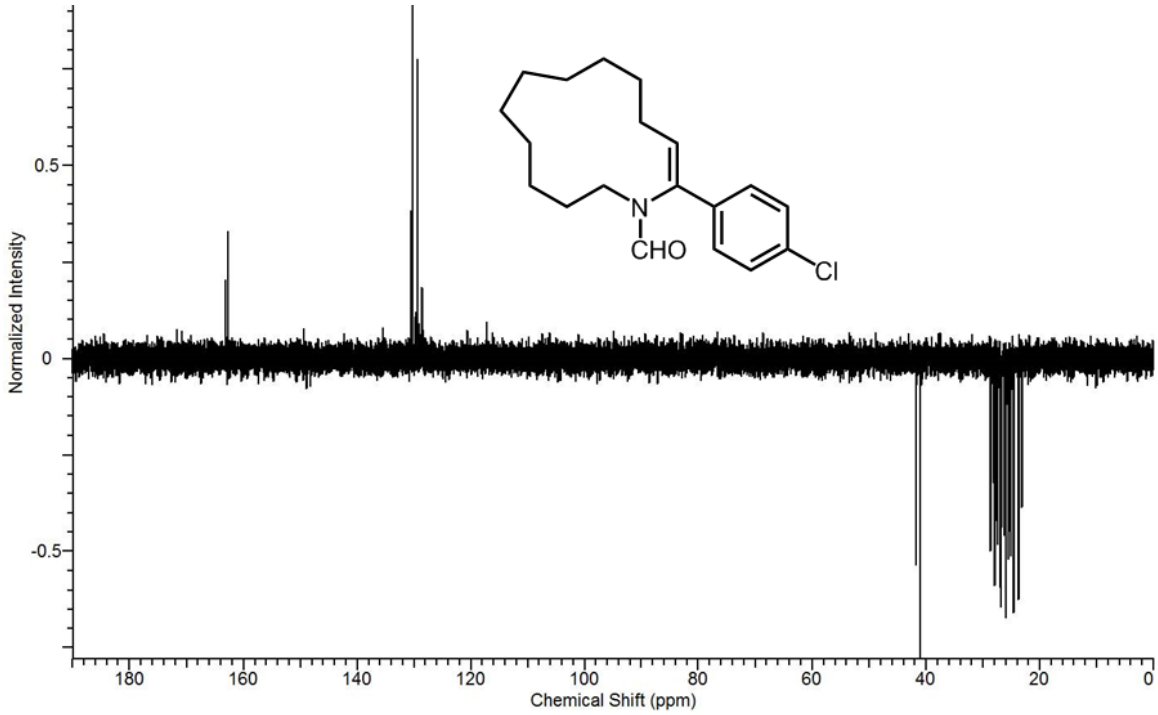
Spectra **1-63** MS spectrum of **3b4.**



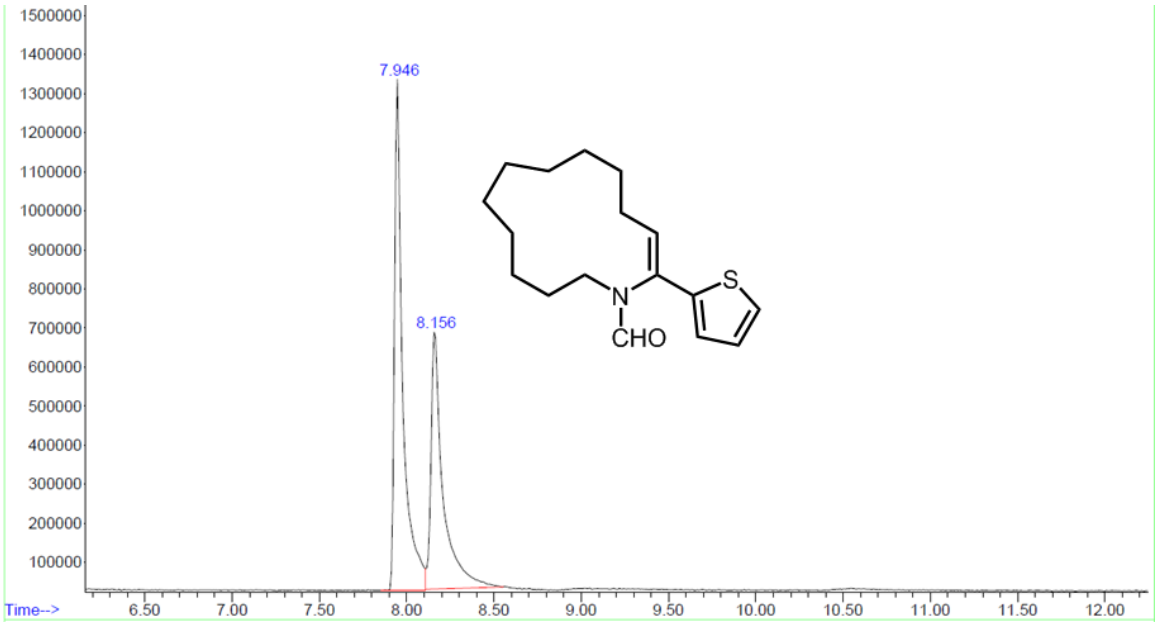
Spectra **1-64** Proton NMR spectrum of **3b4.**



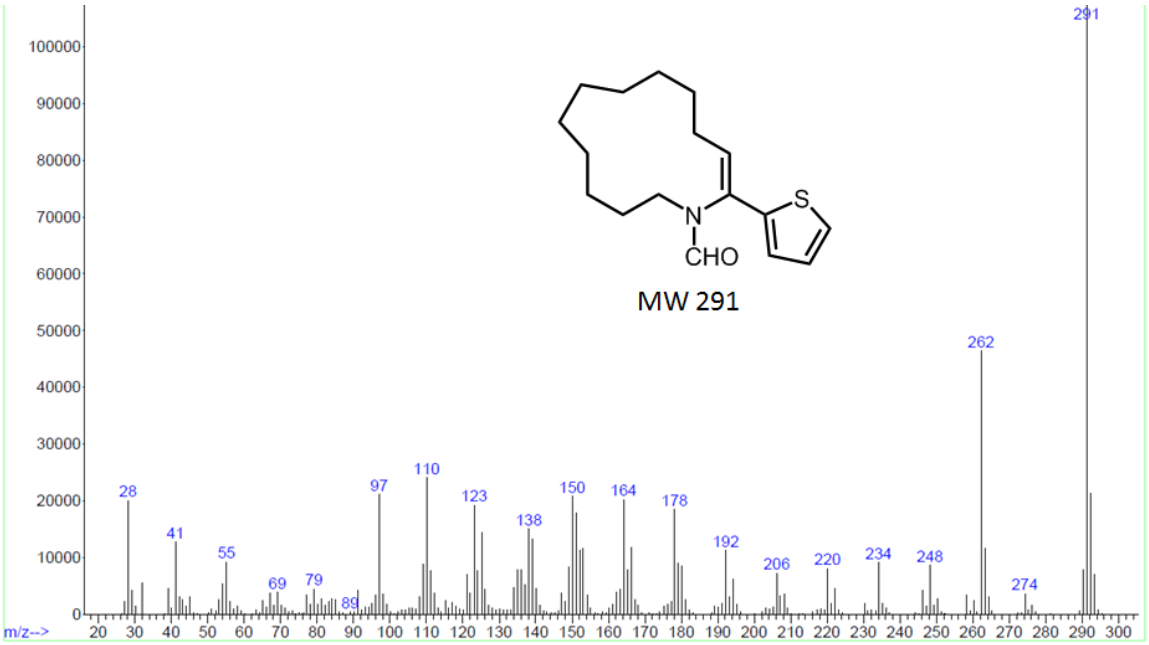
Spectra **1-65** Carbon NMR spectrum of **3b4.**



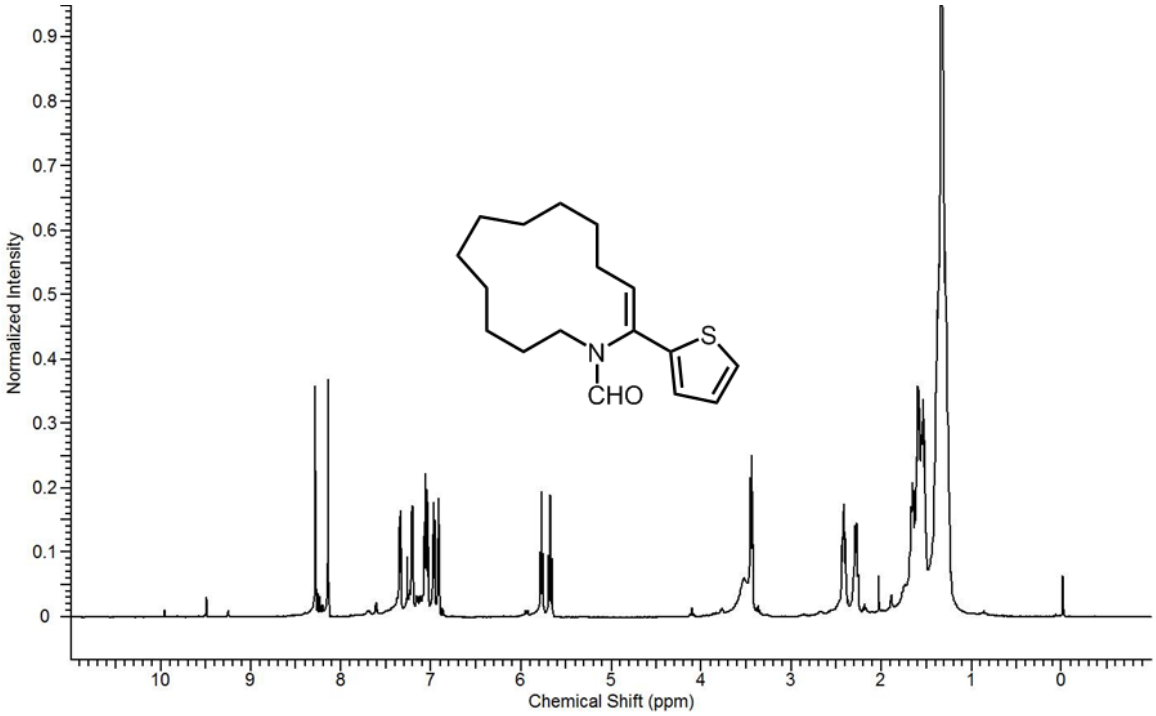
Spectra **1-66** DEPT-135 NMR spectrum of **3b4.**



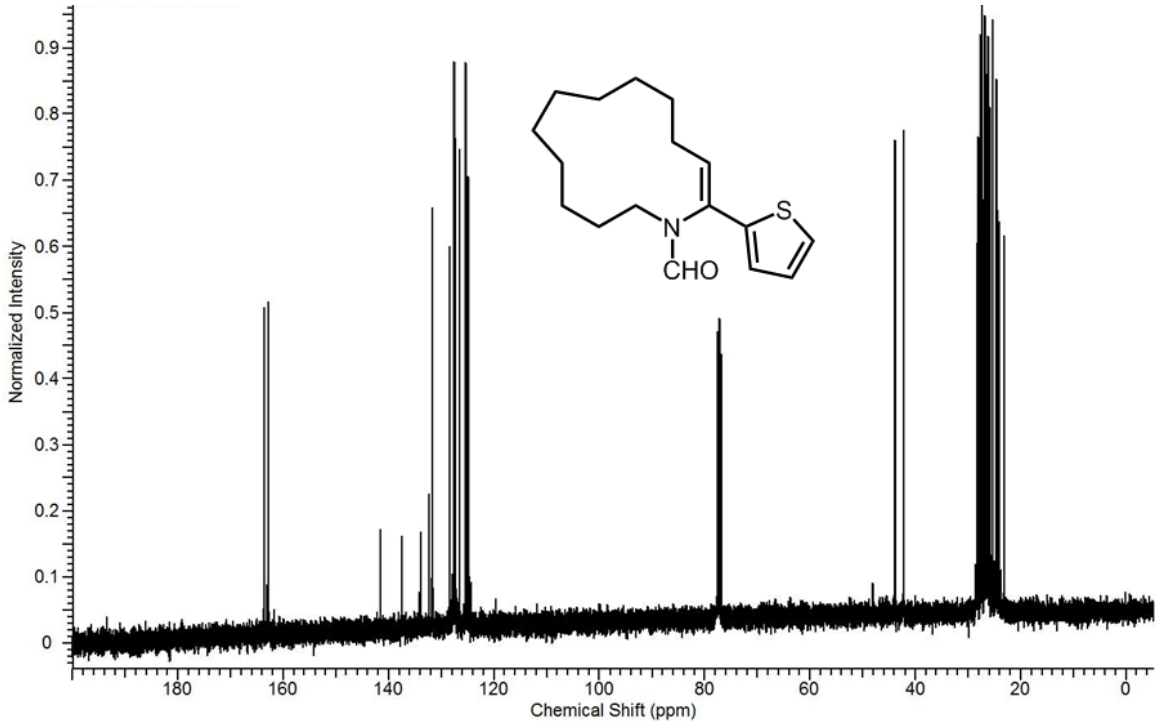
Spectra **1-67** GC spectrum of **3b5.**



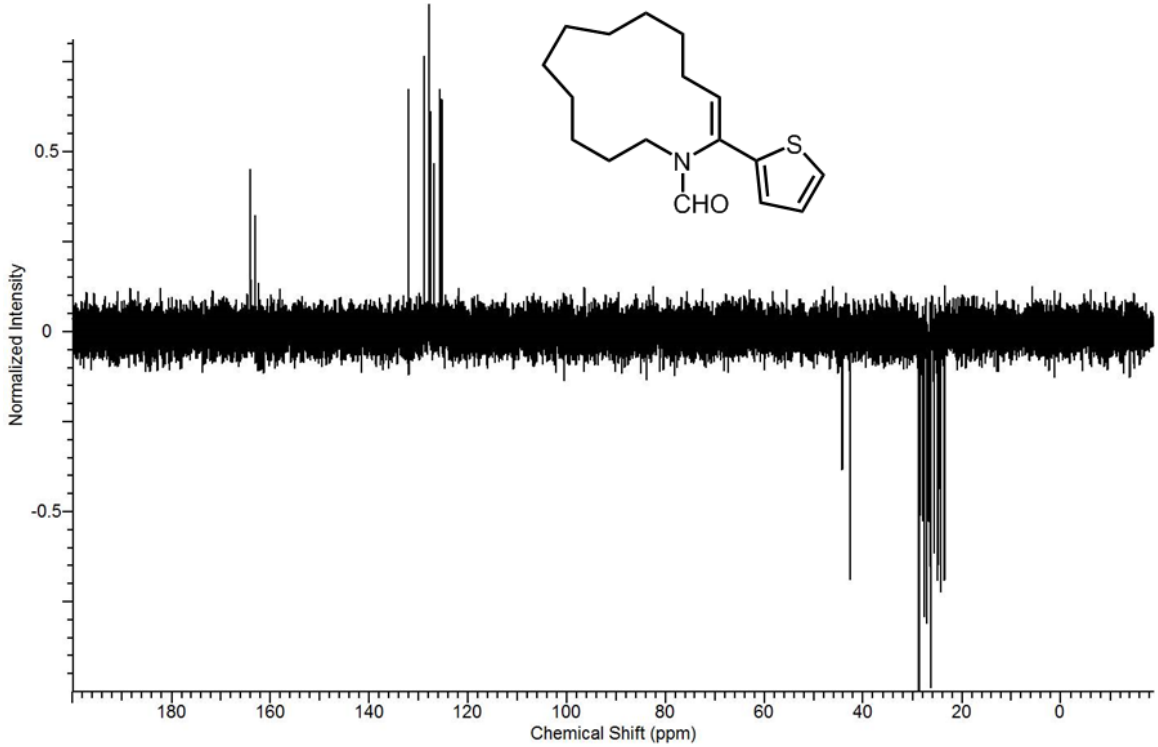
Spectra **1-68** MS spectrum of **3b5.**



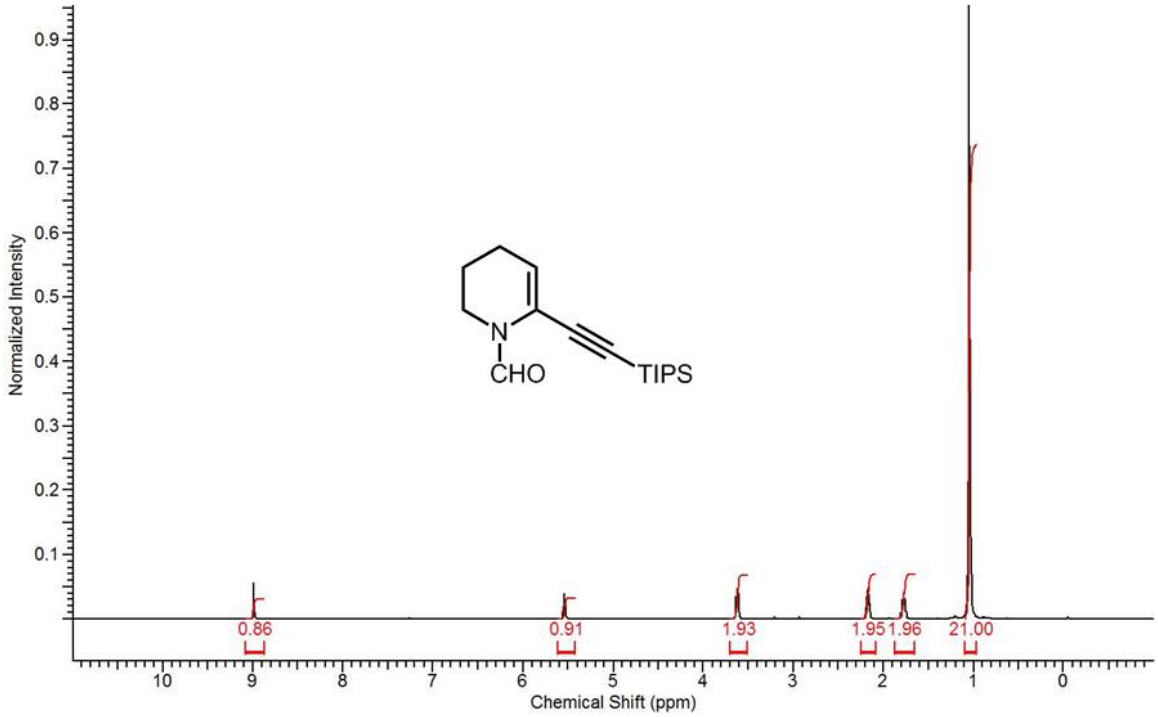
Spectra **1-69** Proton NMR spectrum of **3b5.**



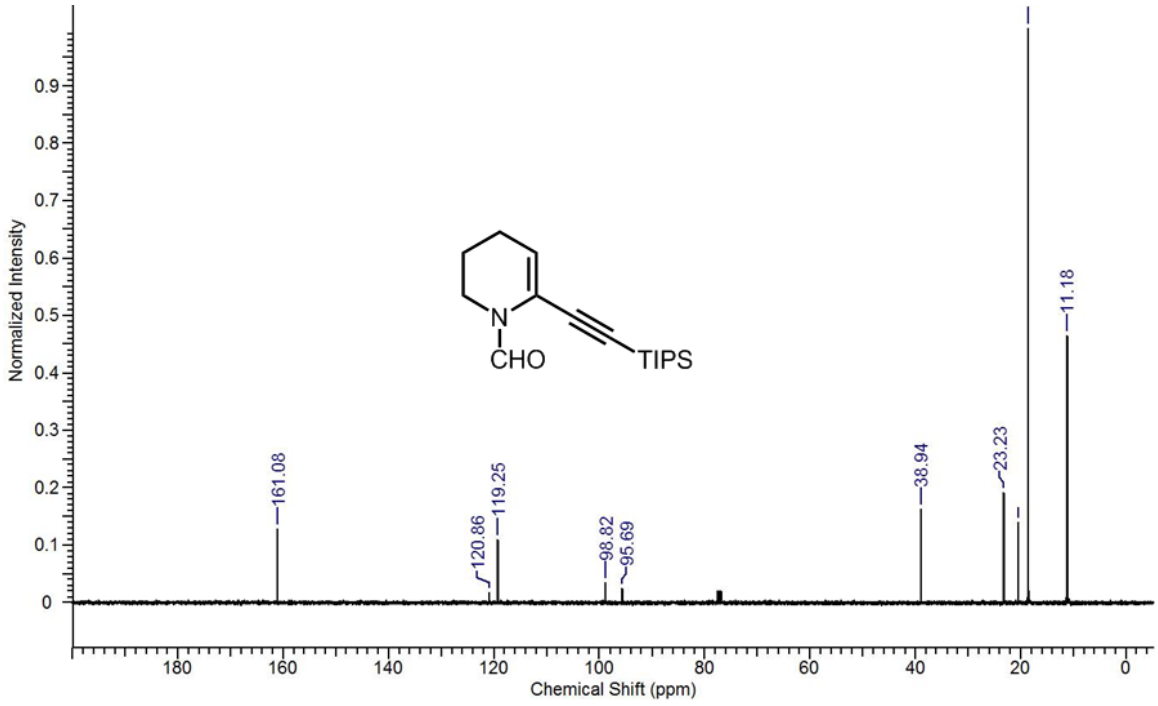
Spectra **1-70** Carbon NMR spectrum of **3b5.**



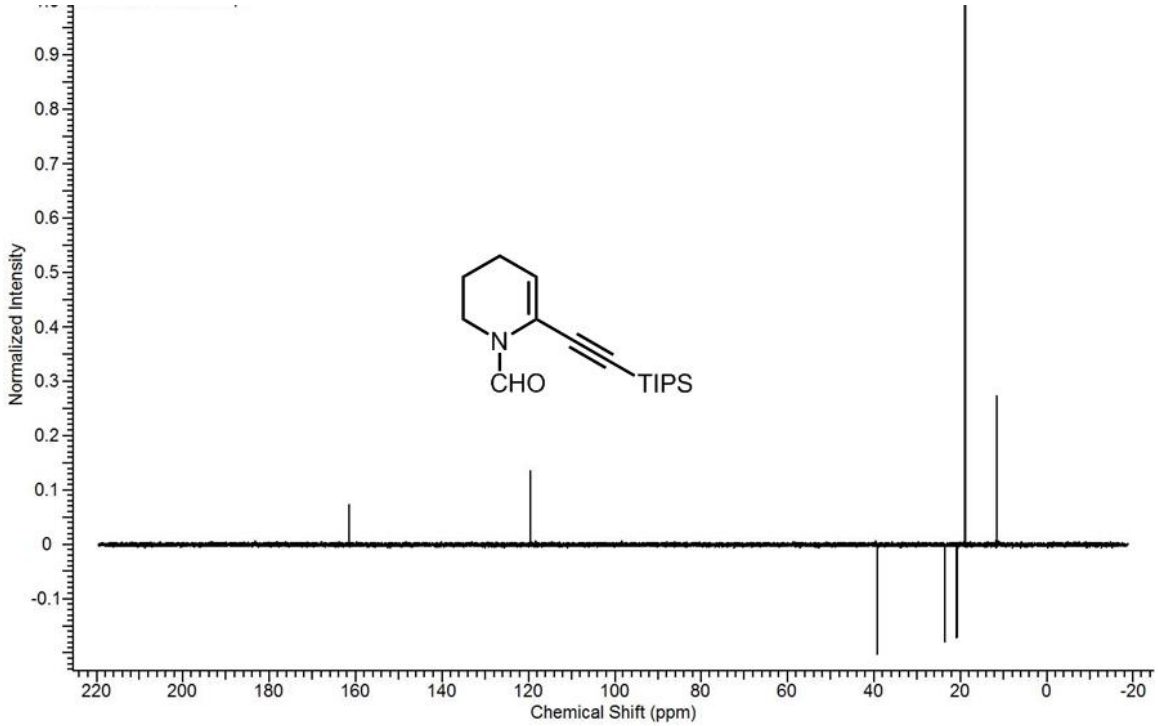
Spectra **1-71** DEPT-135 NMR spectrum of **3b5.**



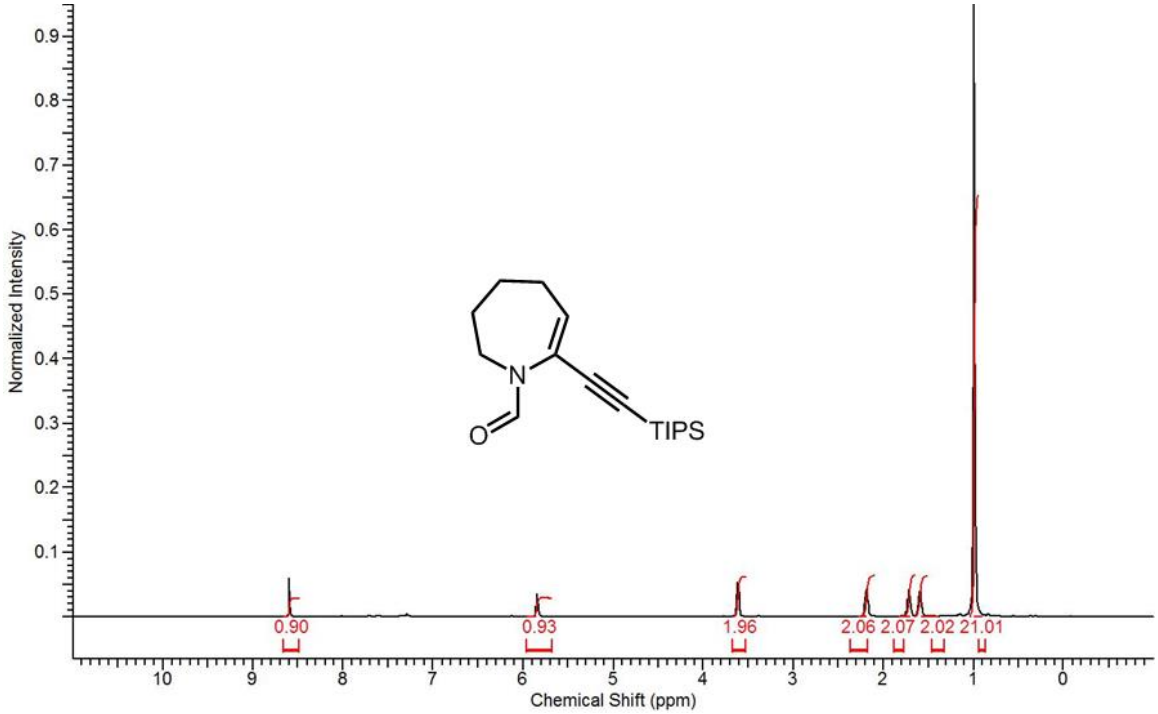
Spectra **1-72** Proton NMR spectrum of **3c1.**



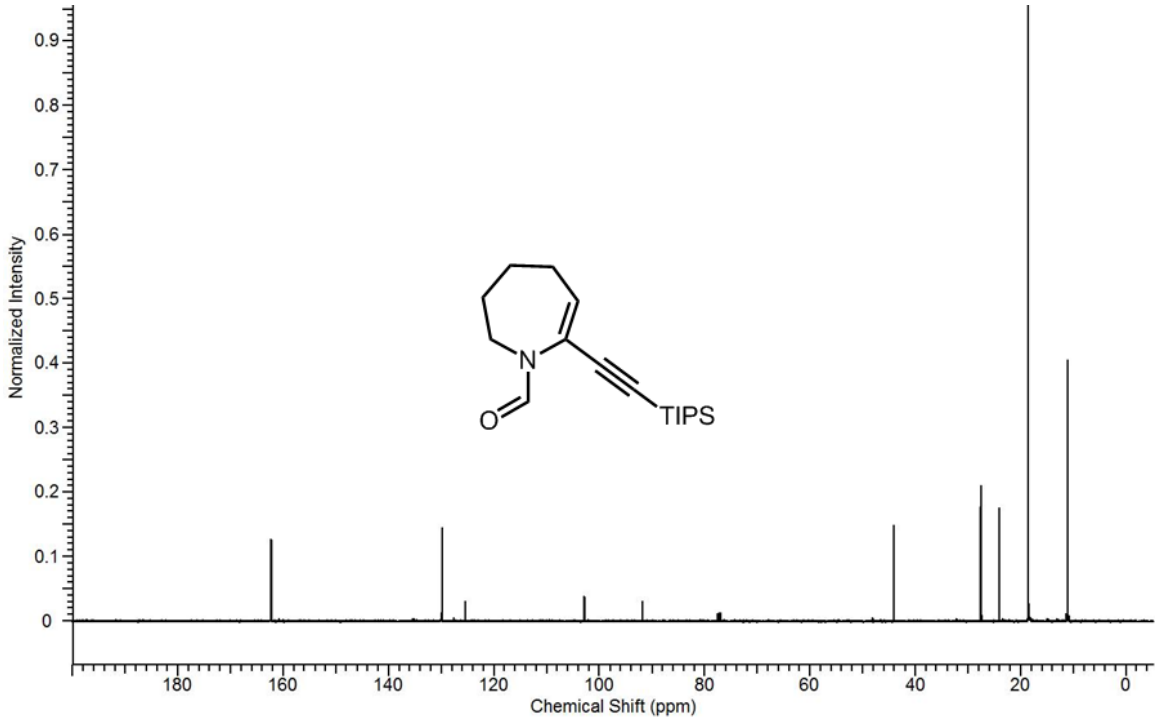
Spectra **1-73** Carbon NMR spectrum of **3c1.**



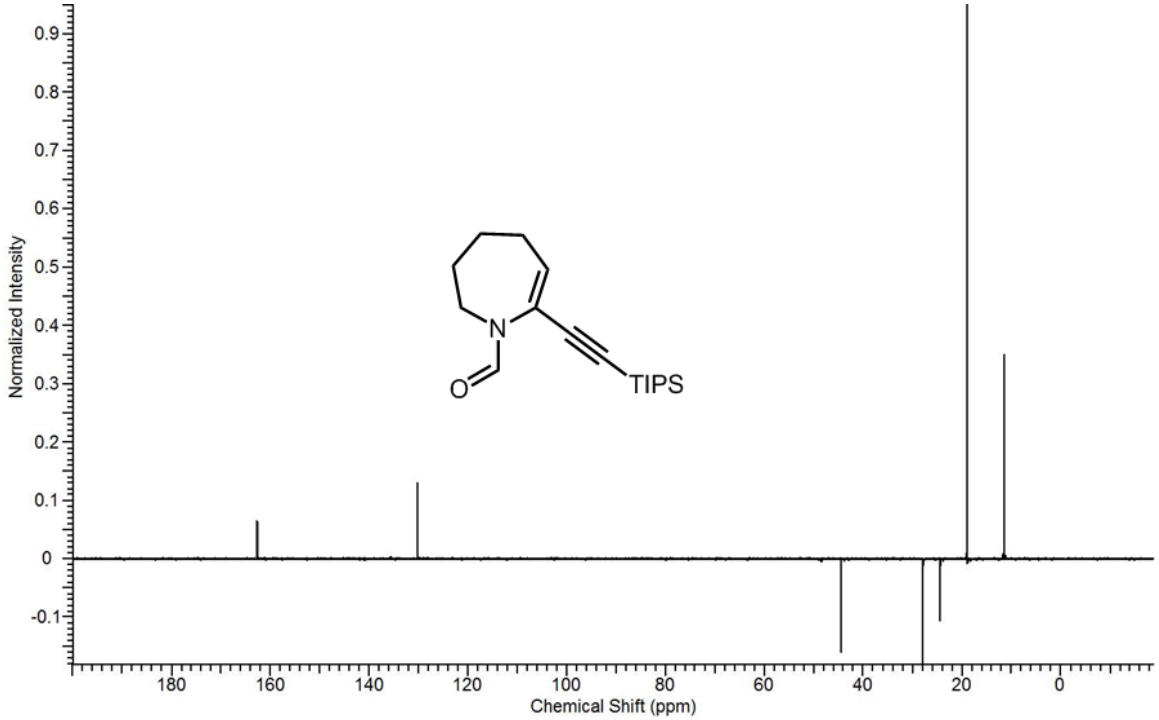
Spectra **1-74** DEPT-135 NMR spectrum of **3c1.**



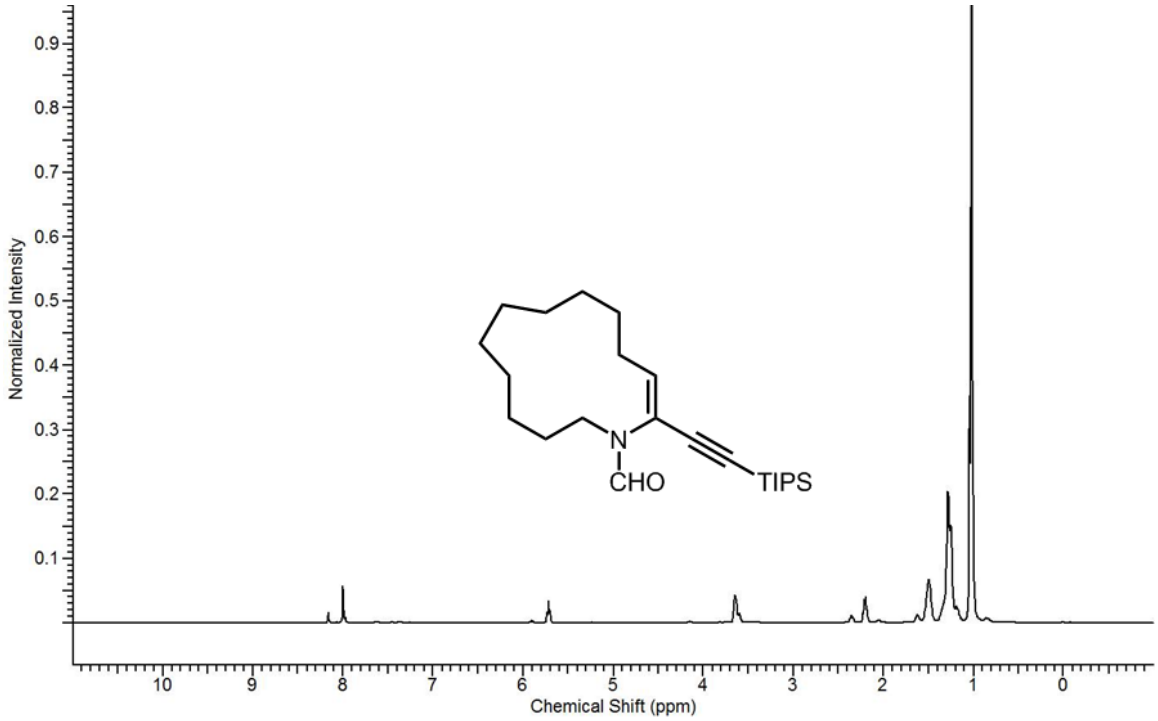
Spectra **1-75** Proton NMR spectrum of **3c2.**



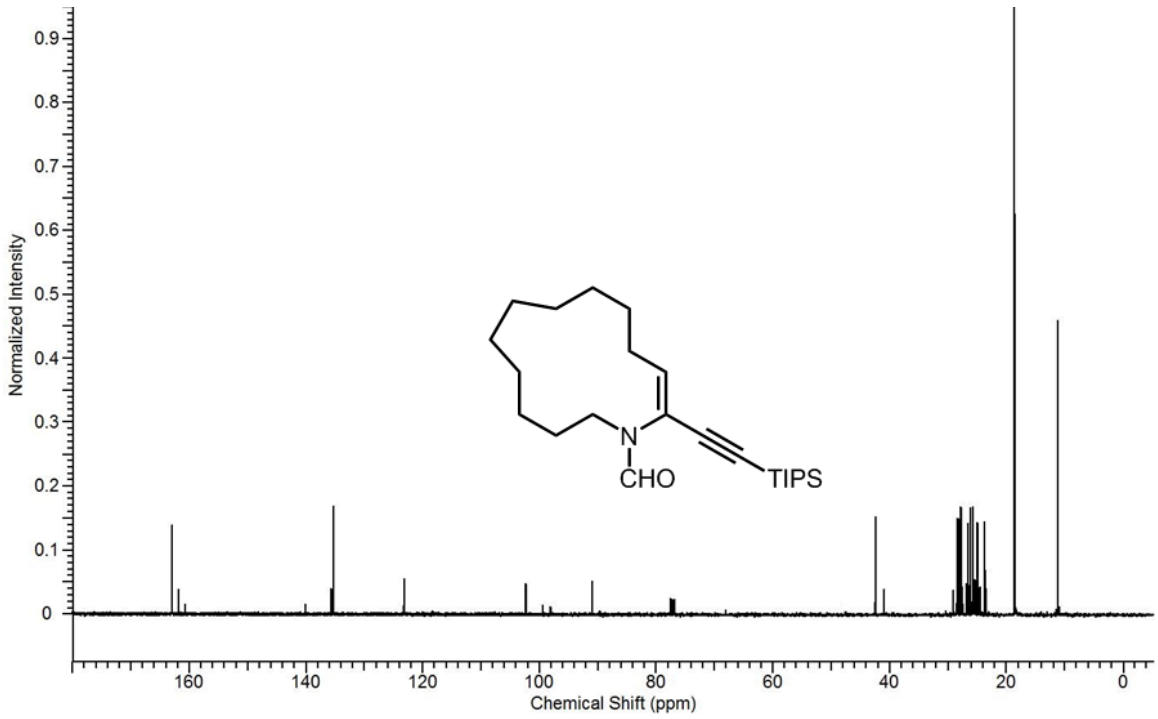
Spectra **1-76** Carbon NMR spectrum of **3c2.**



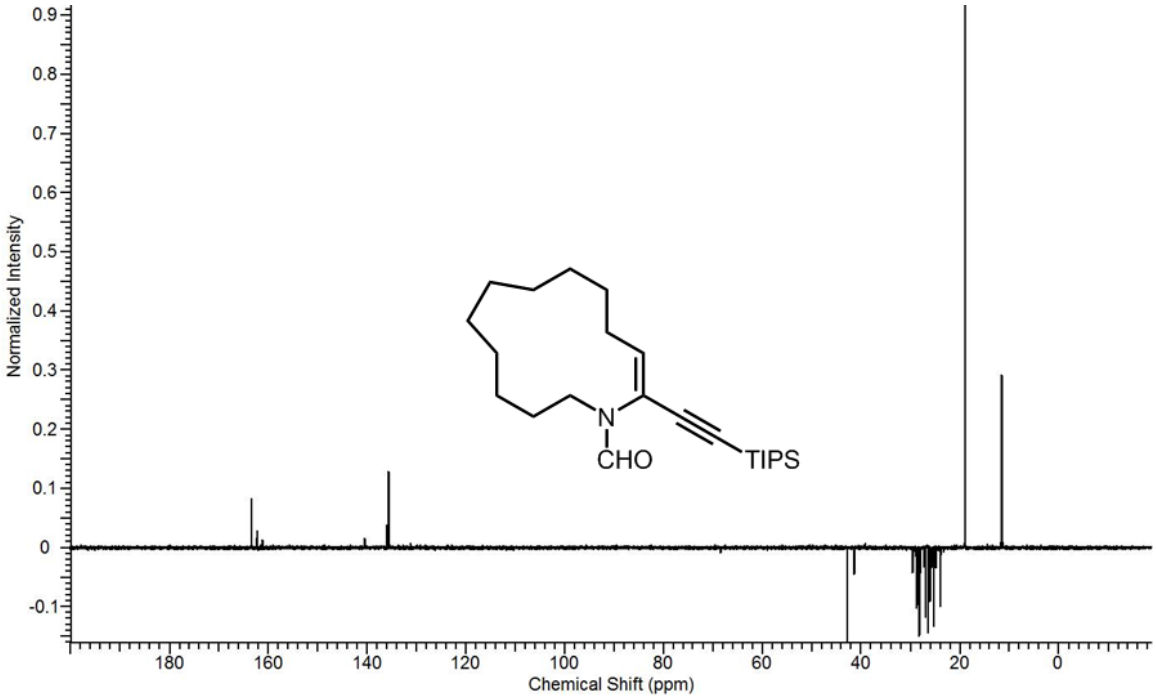
Spectra **1-77** DEPT-135 NMR spectrum of **3c2.**



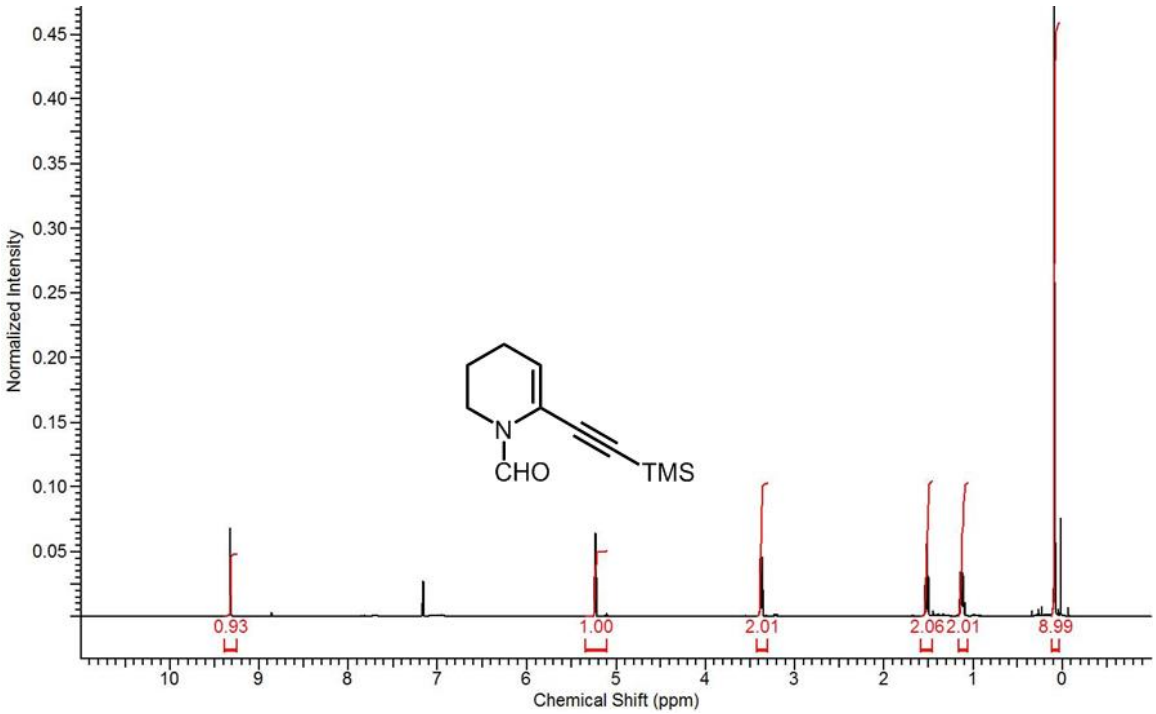
Spectra **1-78** Proton NMR spectrum of **3c3.**



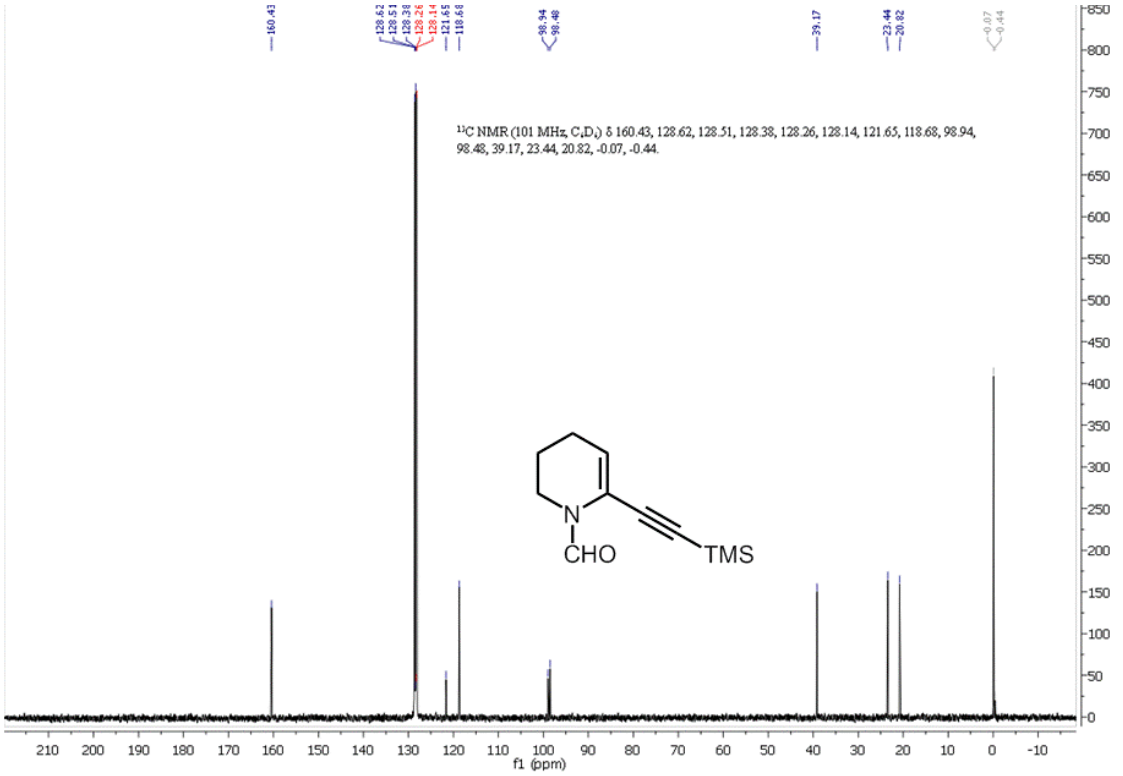
Spectra **1-79** Carbon NMR spectrum of **3c3.**



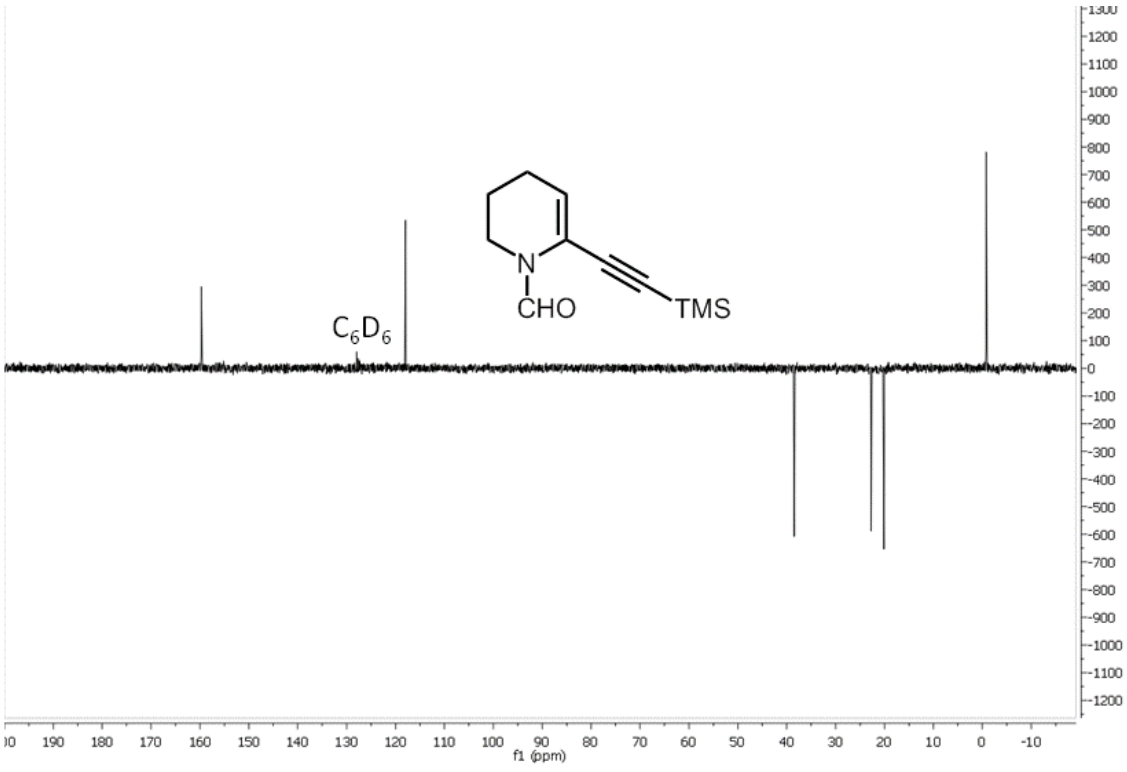
Spectra **1-80** DEPT-135 NMR spectrum of **3c3.**



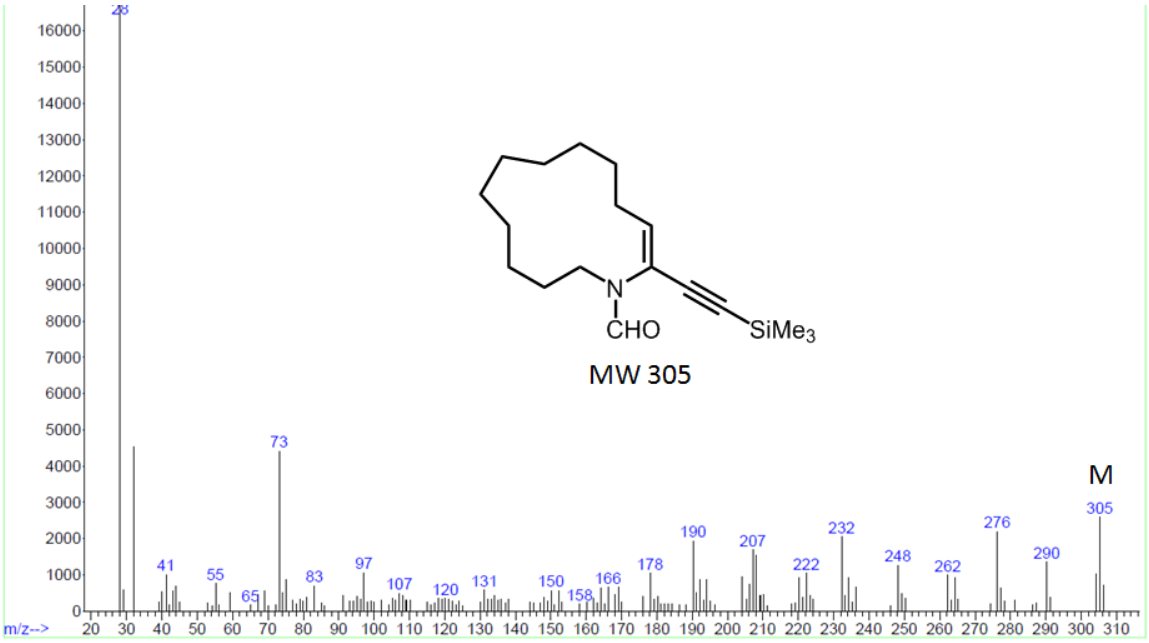
Spectra **1-81** Proton NMR spectrum of **3c4.**



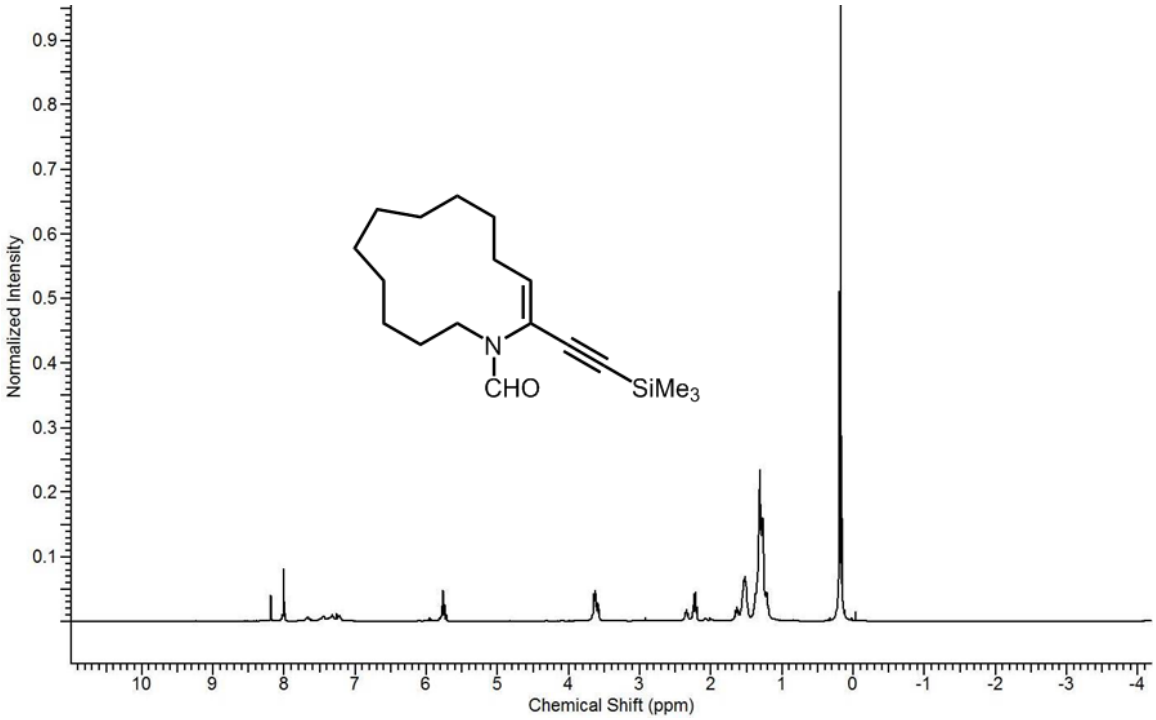
Spectra **1-82** Carbon NMR spectrum of **3c4.**



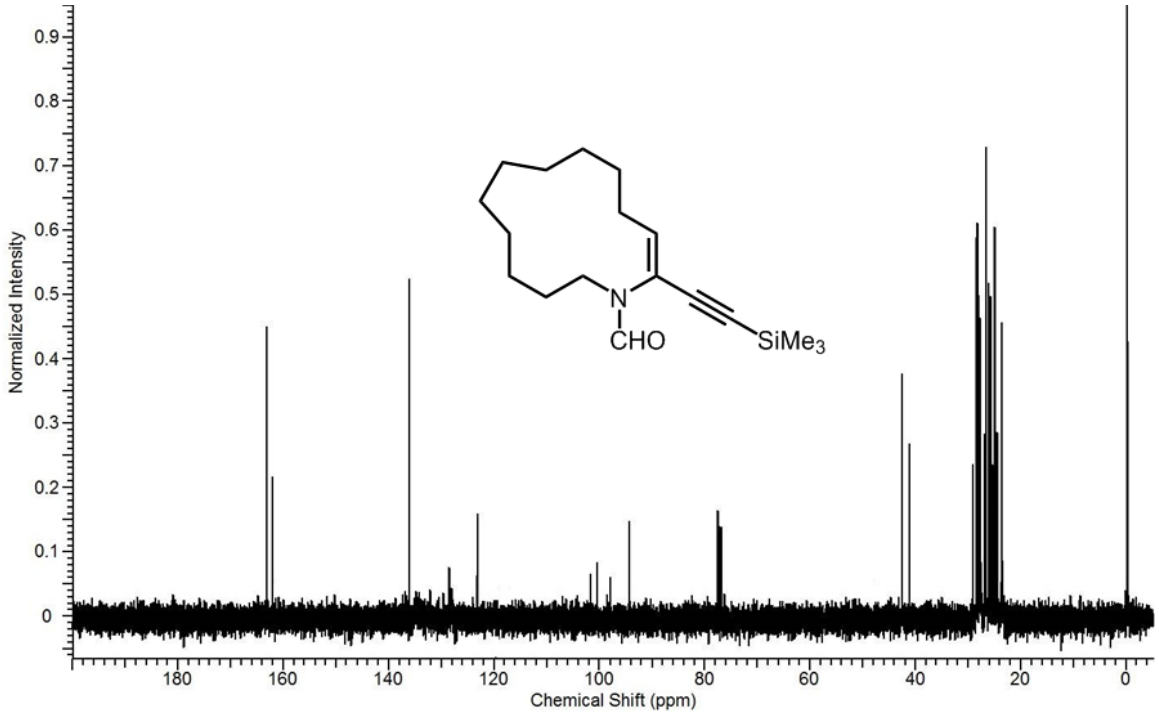
Spectra **1-83** DEPT-135 NMR spectrum of **3c4.**



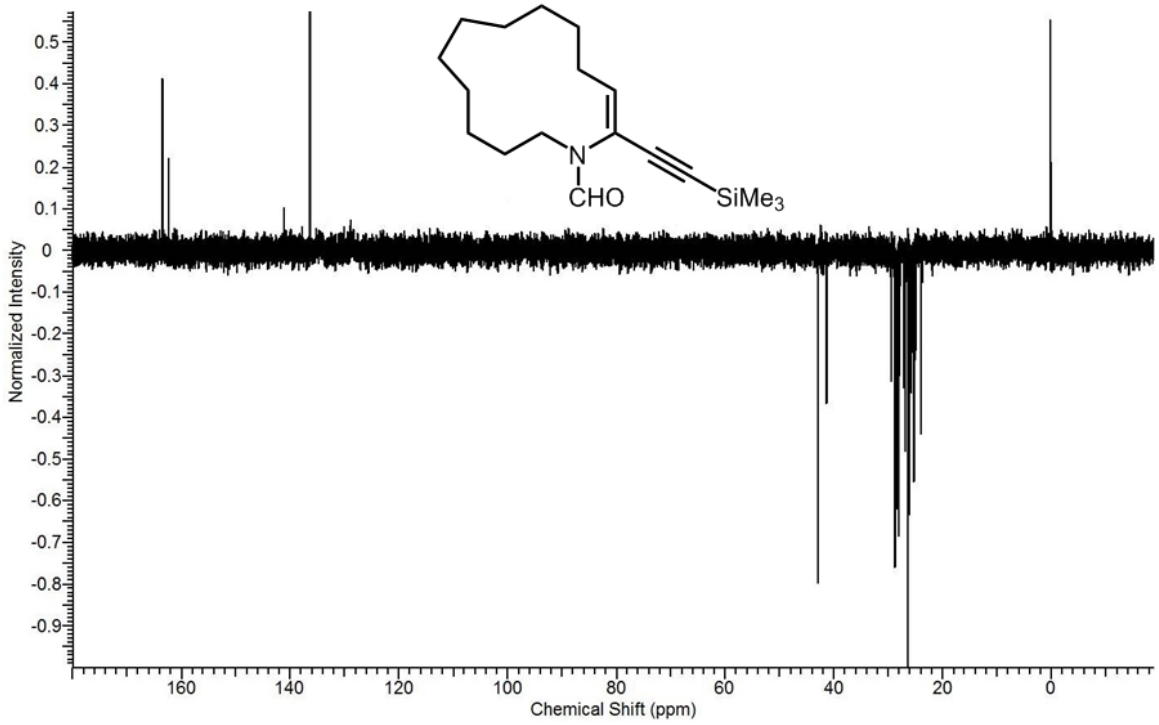
Spectra **1-84** MS spectrum of **3c6.**



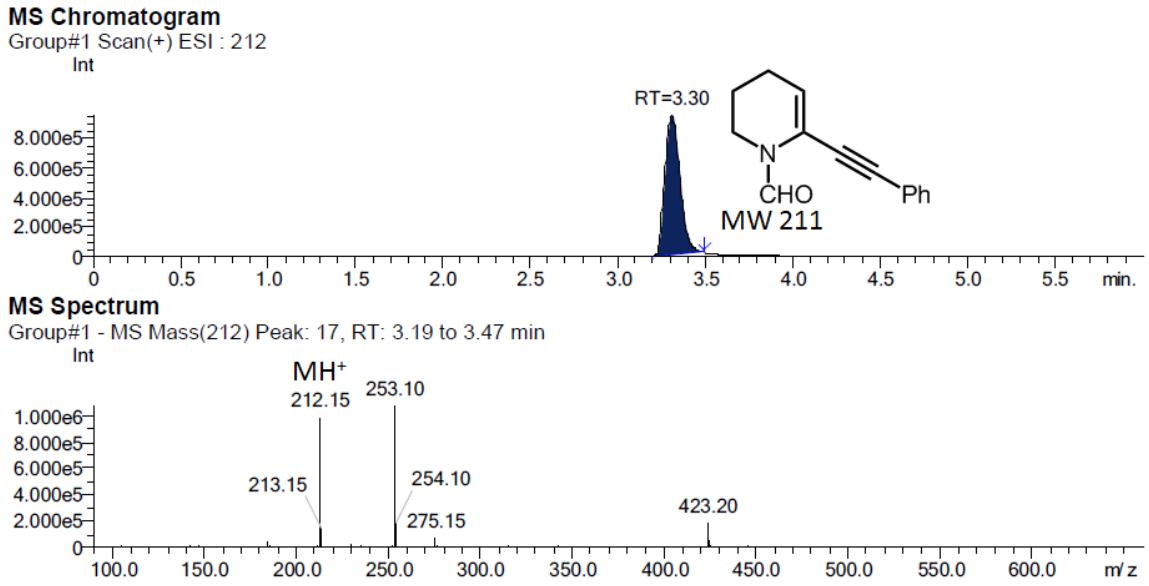
Spectra **1-85** Proton NMR spectrum of **3c6.**



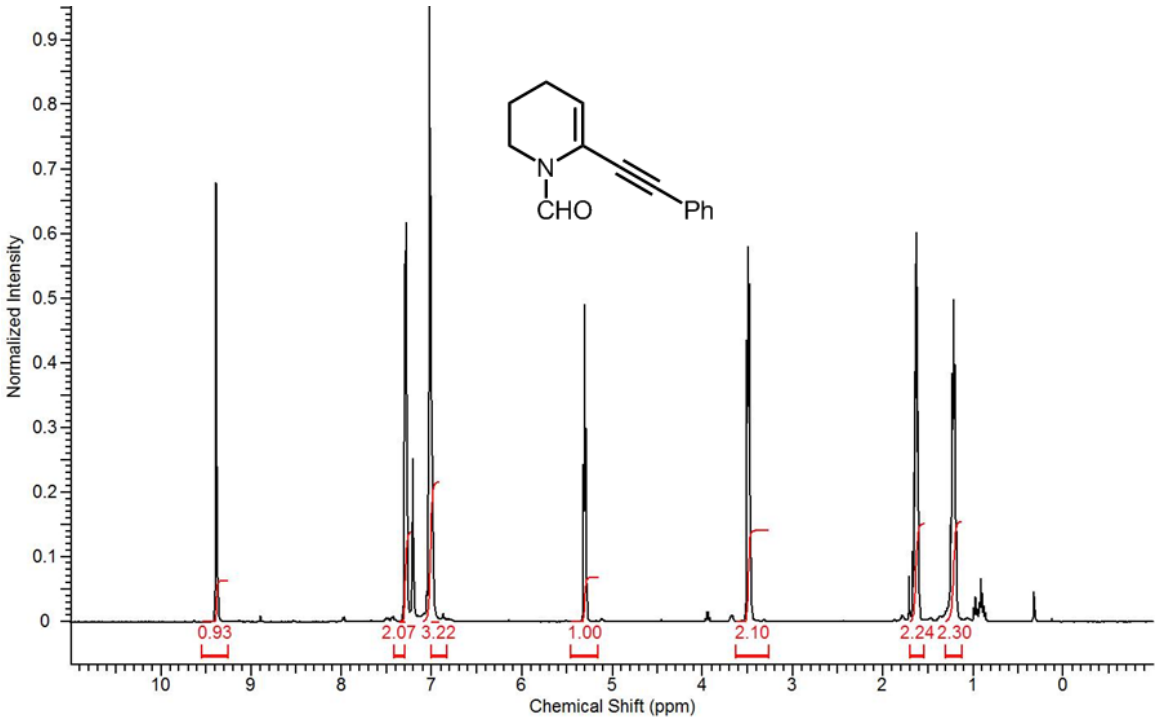
Spectra **1-86** Carbon NMR spectrum of **3c6.**



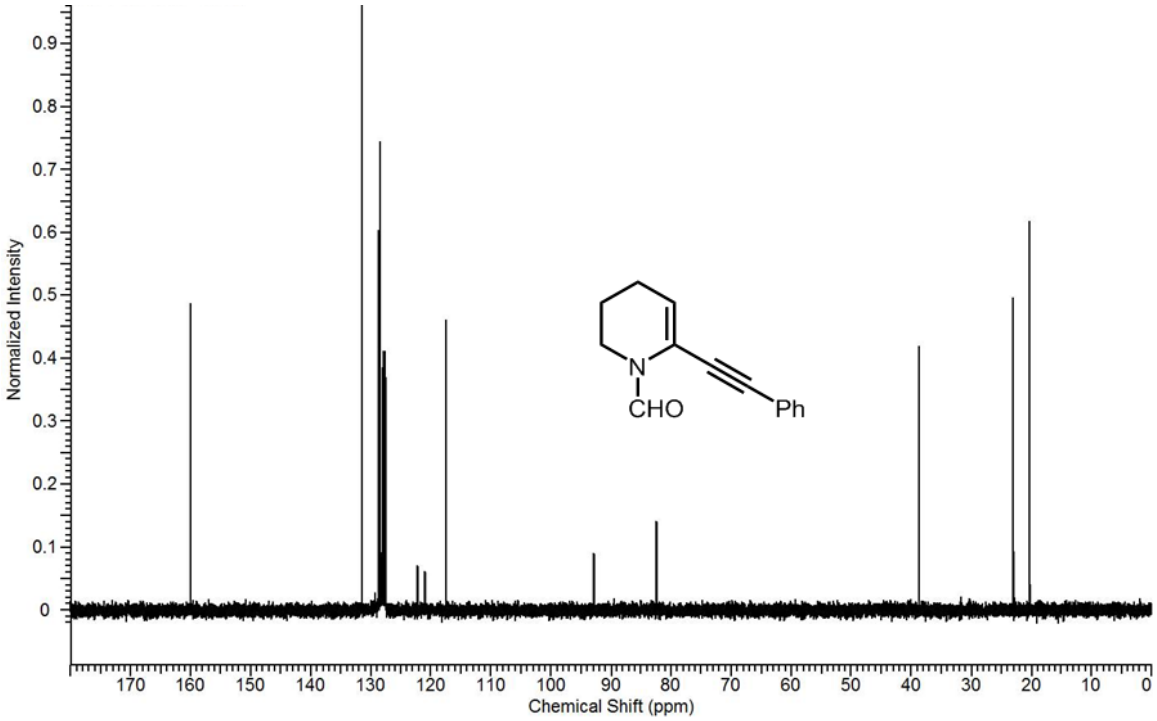
Spectra **1-87** DEPT-135 NMR spectrum of **3c6.**



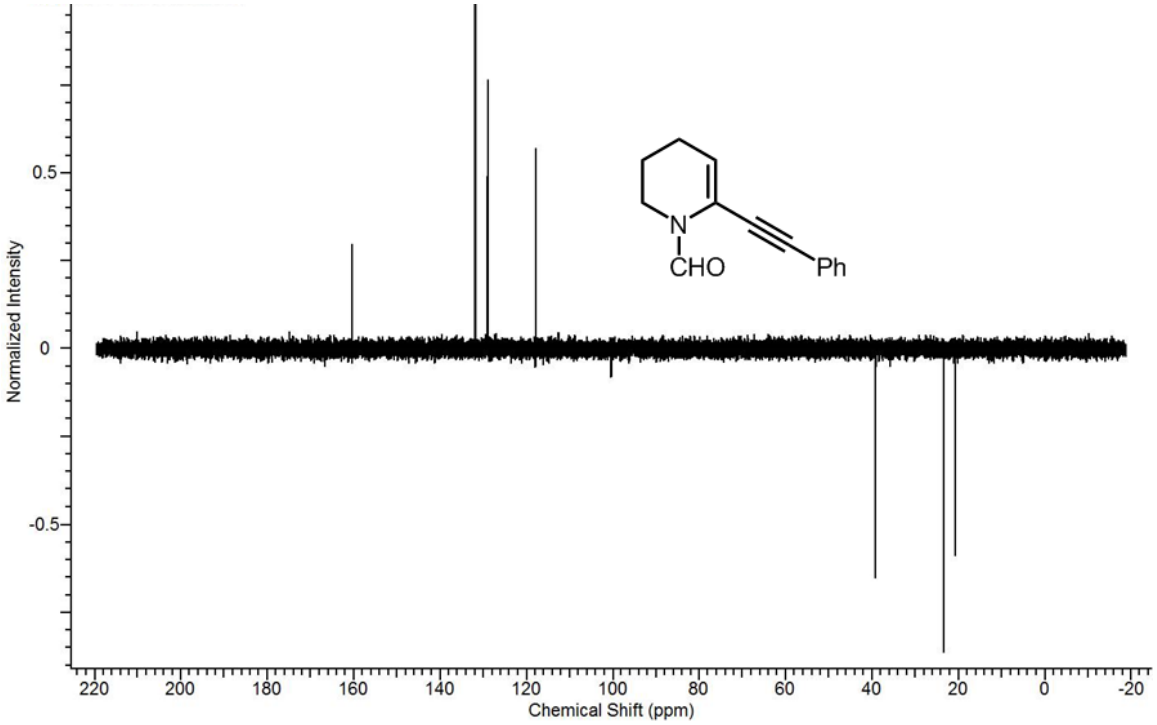
Spectra **1-88** GC-MS spectrum of **3c7.**



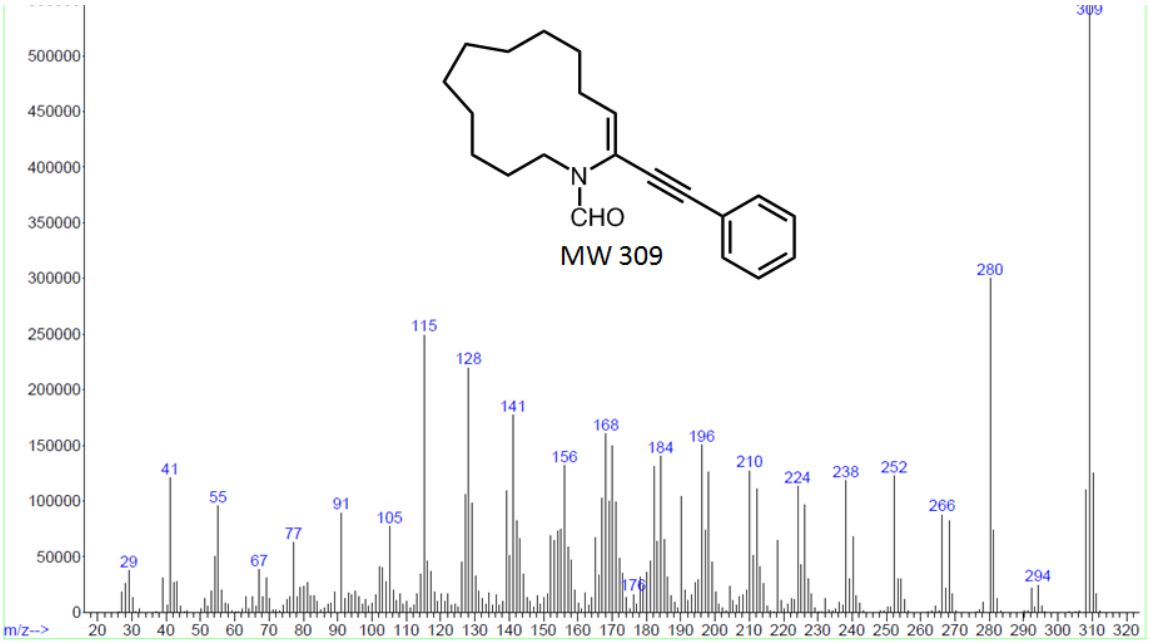
Spectra **1-89** Proton NMR spectrum of **3c7.**



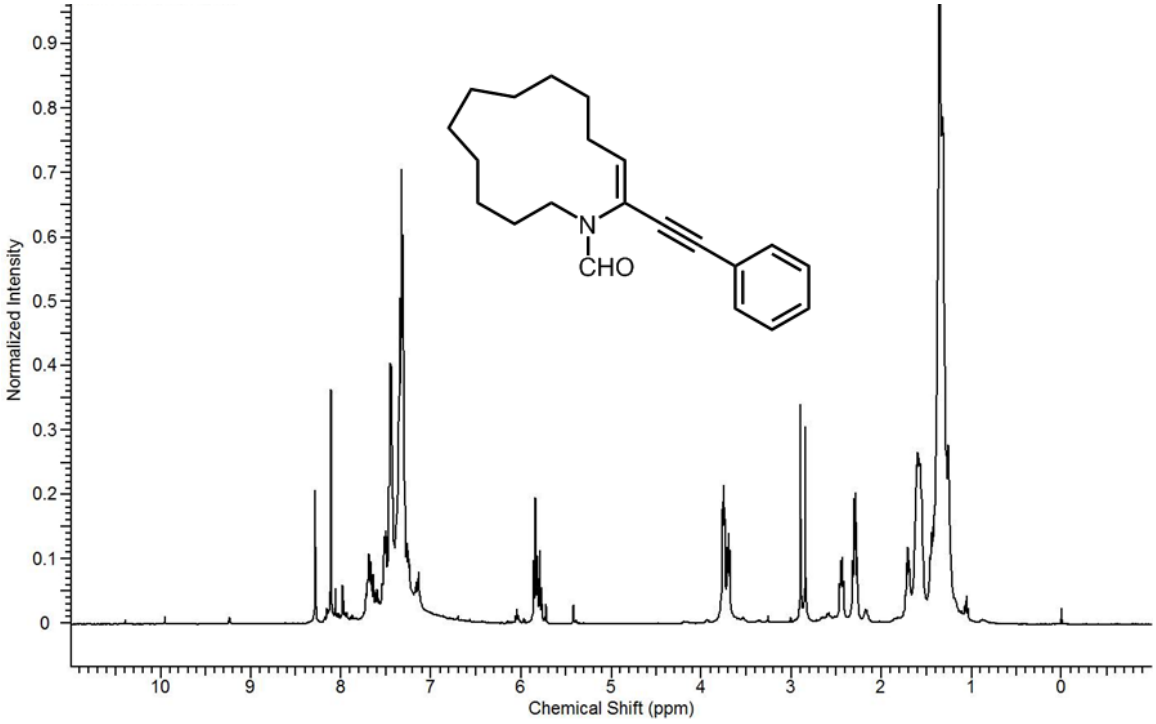
Spectra **1-90** Carbon NMR spectrum of **3c7.**



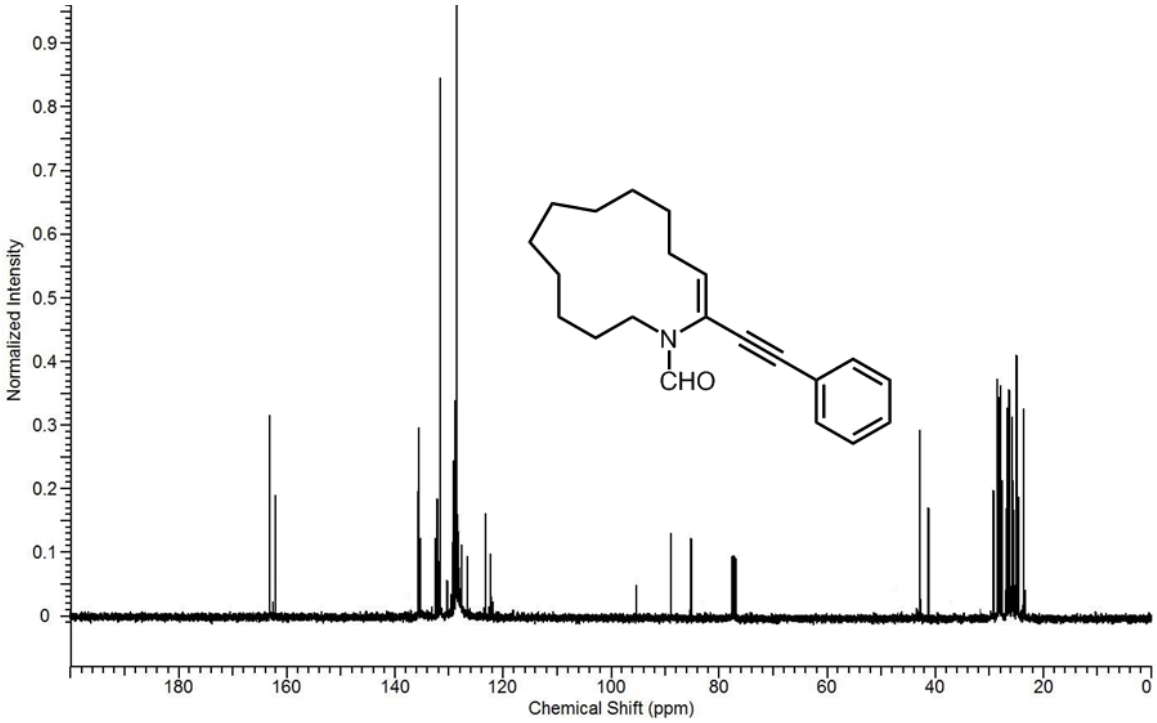
Spectra **1-91** DEPT-135 NMR spectrum of **3c7.**



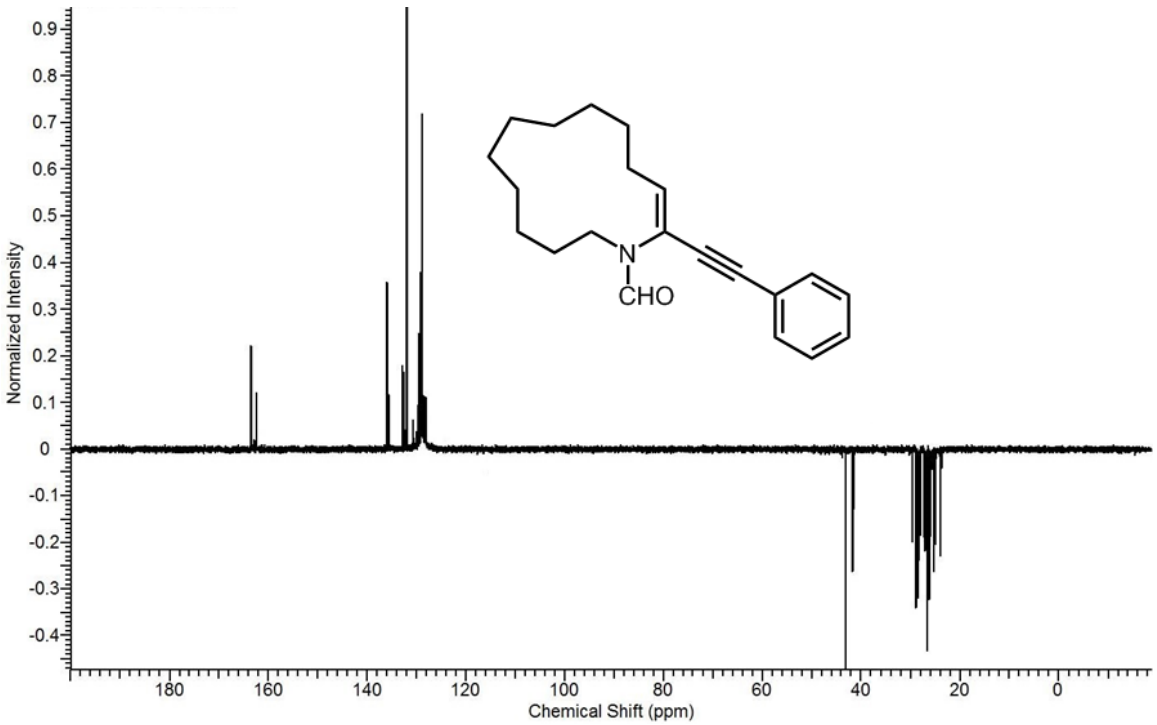
Spectra **1-92** MS spectrum of **3c9.**



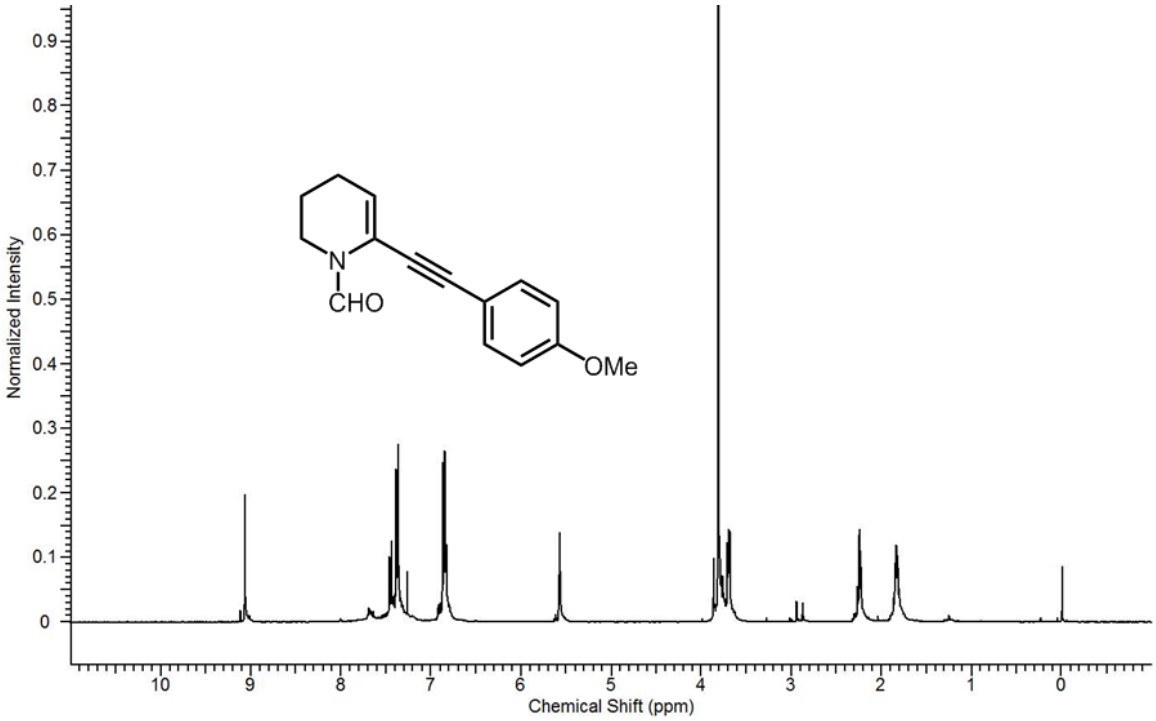
Spectra **1-93** Proton NMR spectrum of **3c9.**



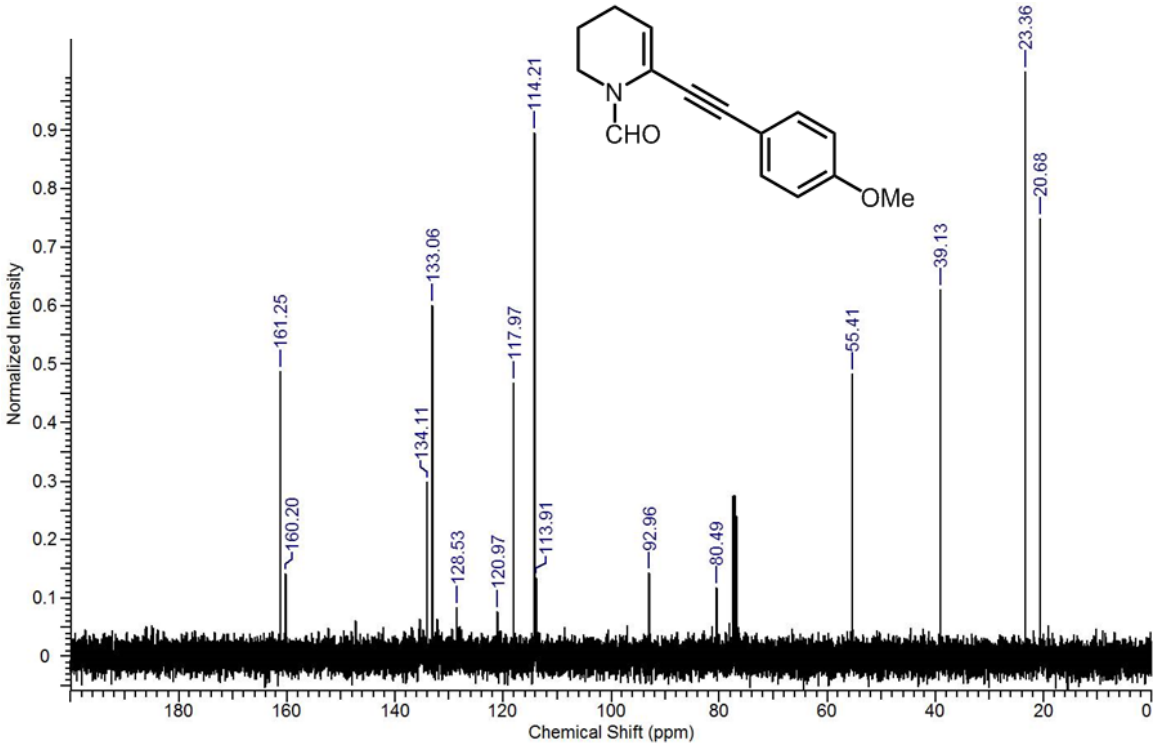
Spectra **1-94** Carbon NMR spectrum of **3c9.**



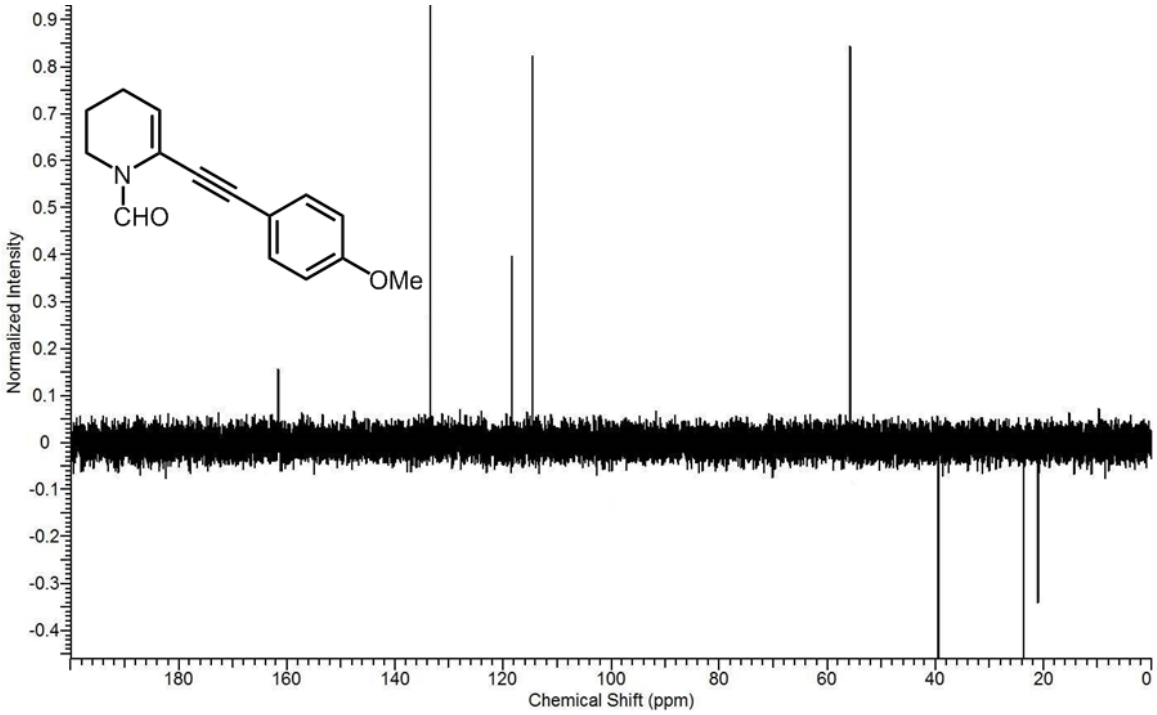
Spectra **1-95** DEPT-135 NMR spectrum of **3c9.**



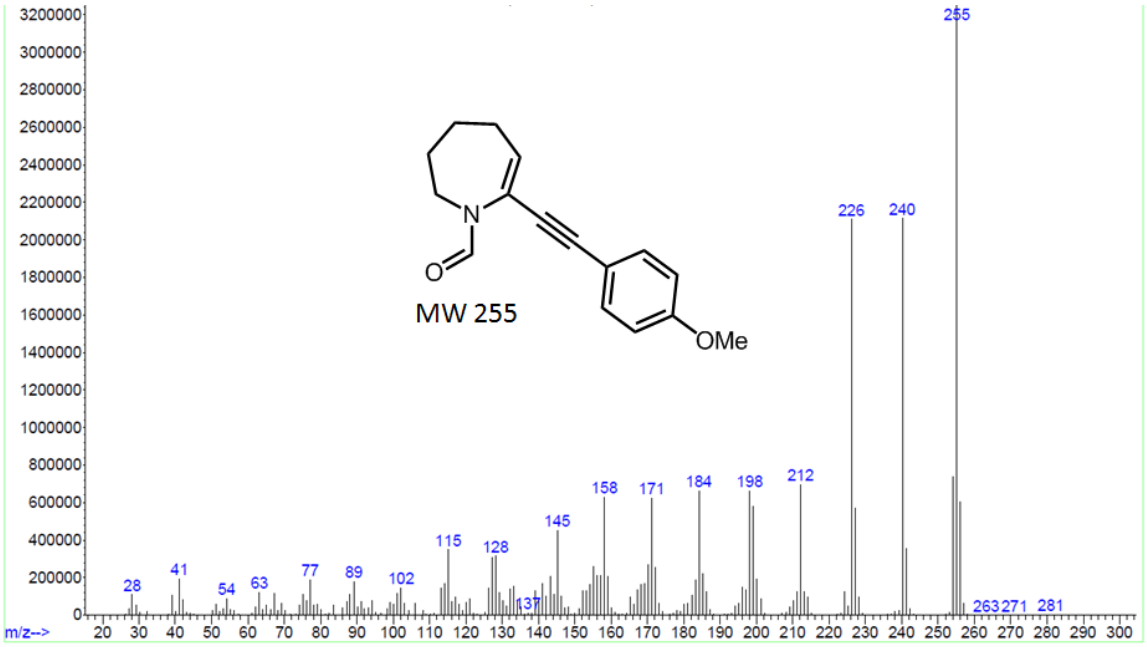
Spectra **1-96** Proton NMR spectrum of **3c10.**



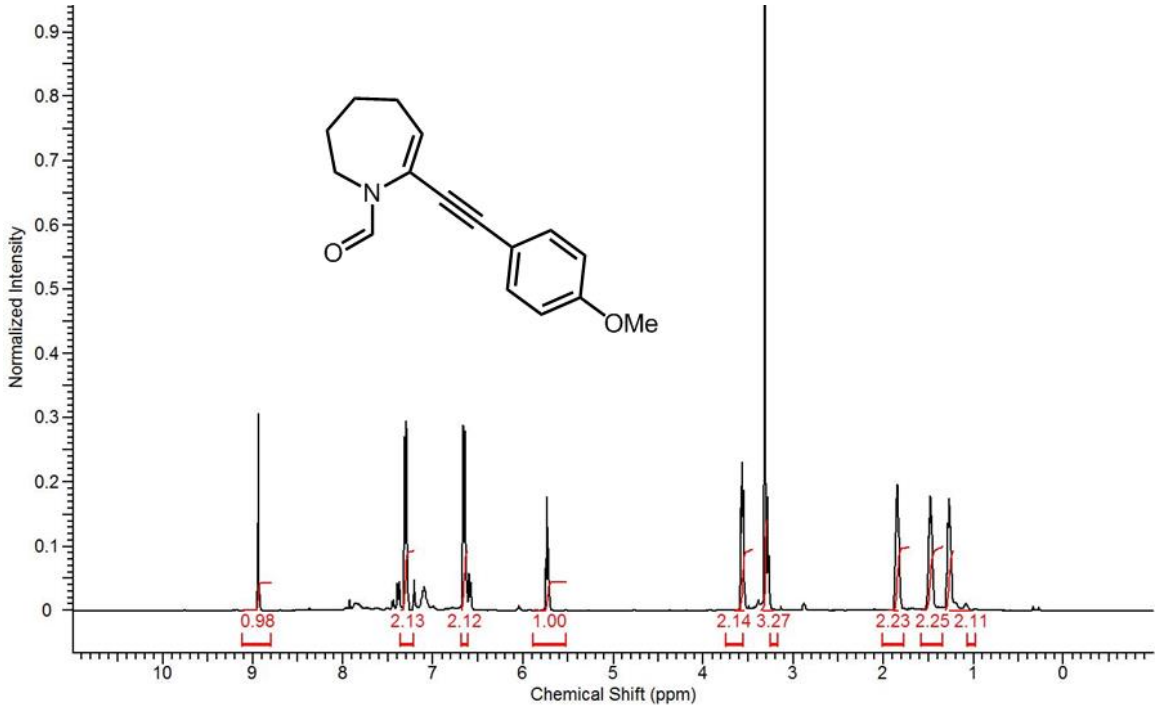
Spectra **1-97** Carbon NMR spectrum of **3c10.**



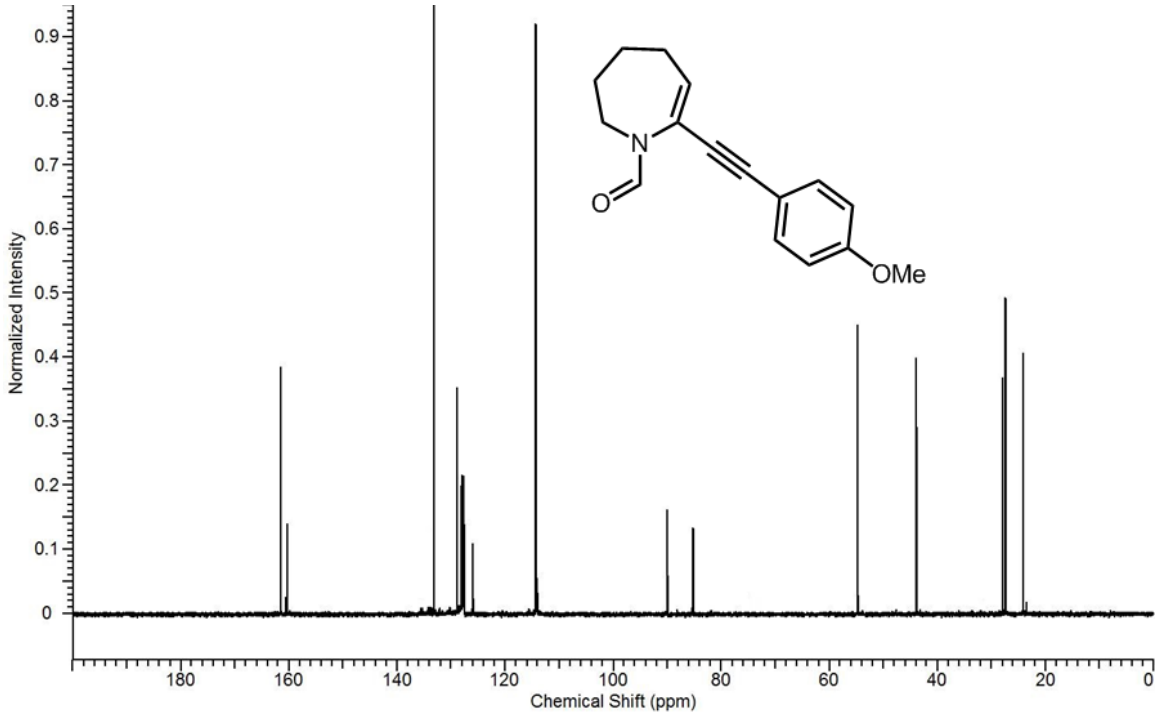
Spectra **1-98** DEPT-135 NMR spectrum of **3c10.**



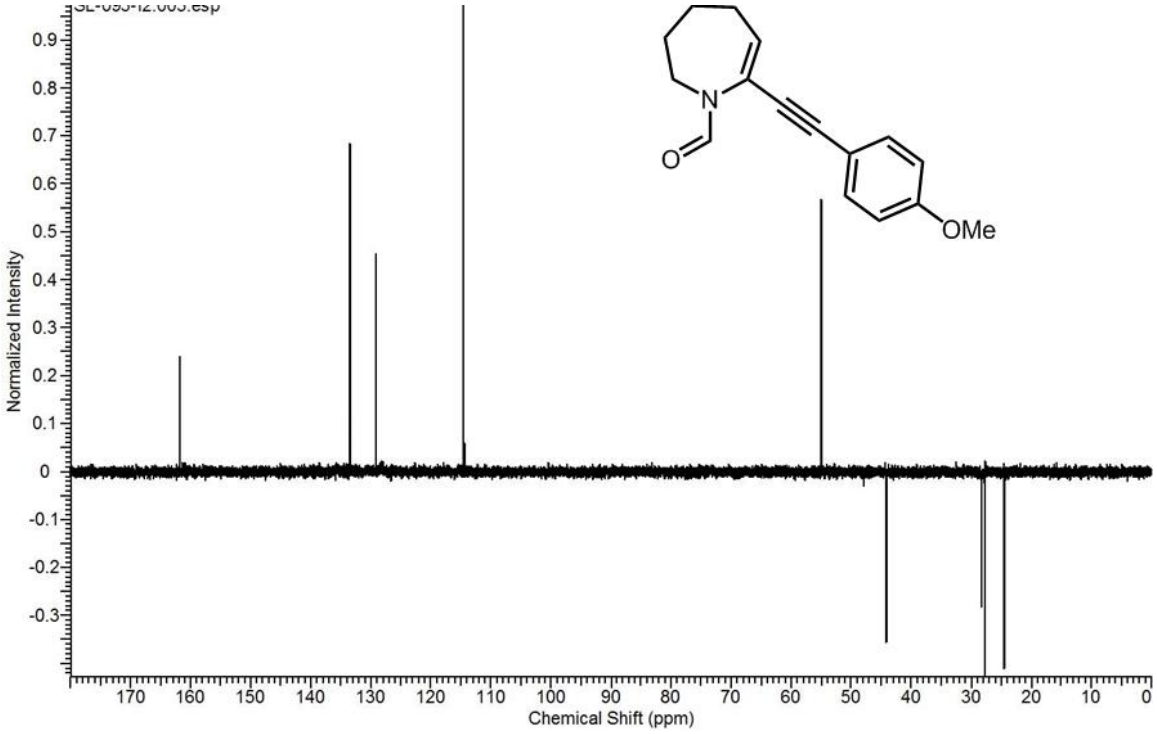
Spectra **1-99** MS spectrum of **3c11.**



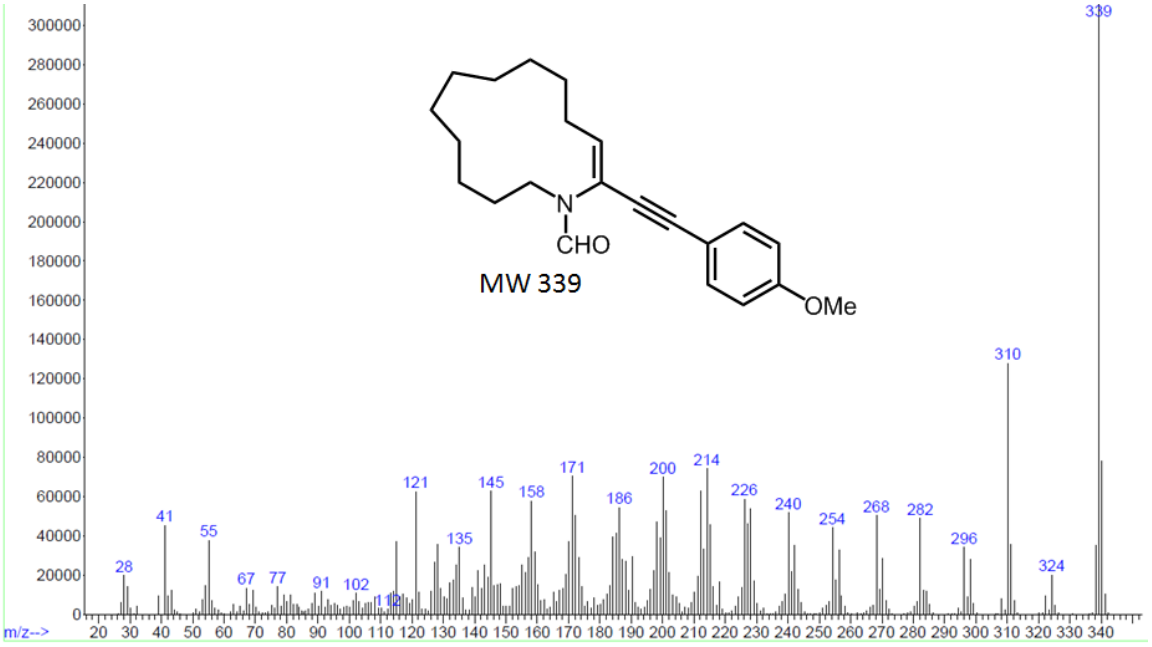
Spectra **1-100** Proton NMR spectrum of **3c11.**



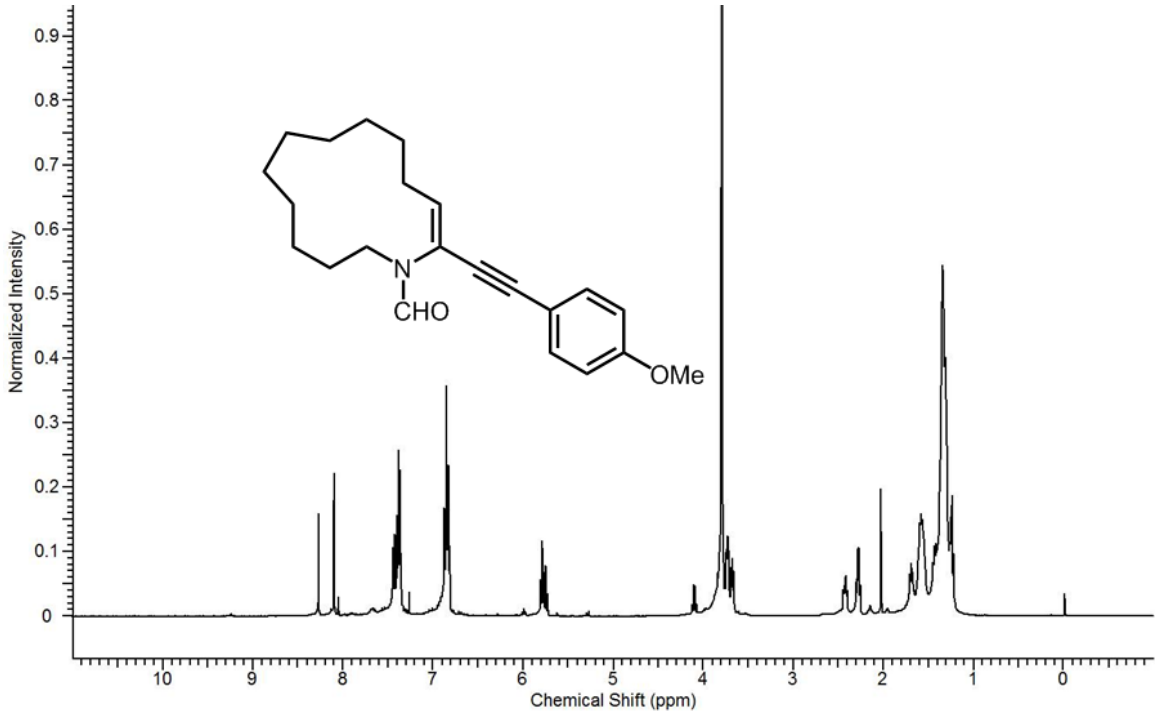
Spectra **1-101** Carbon NMR spectrum of **3c11.**



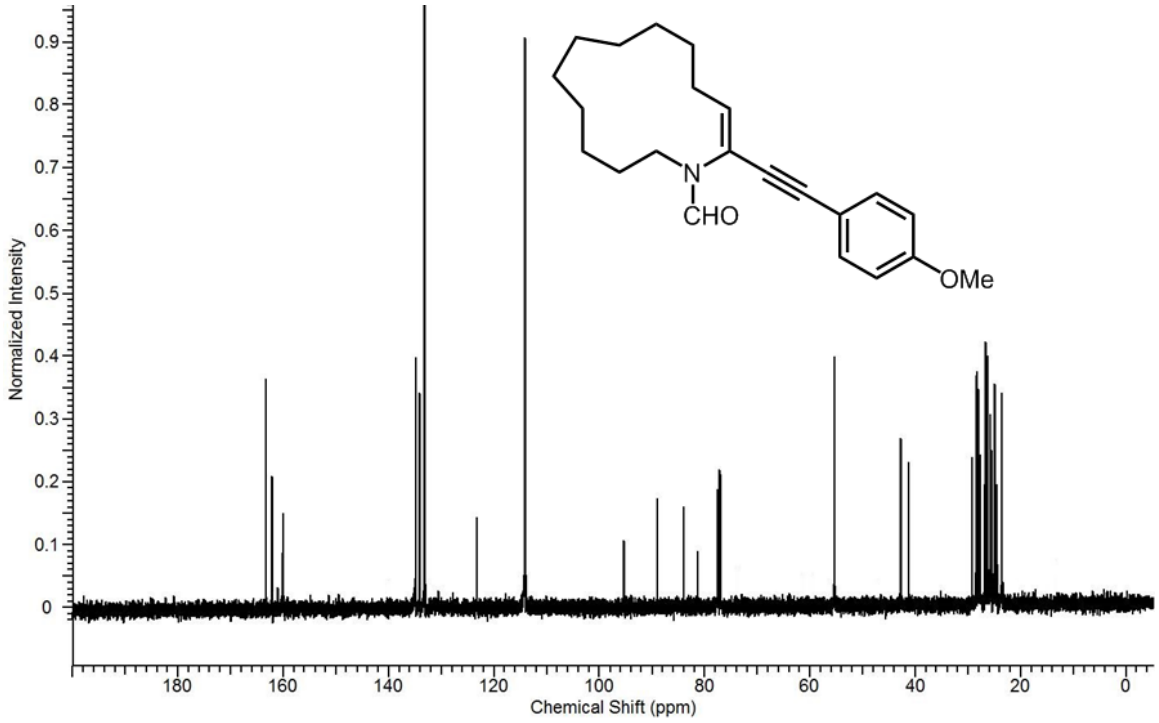
Spectra **1-102** DEPT-135 NMR spectrum of **3c11.**



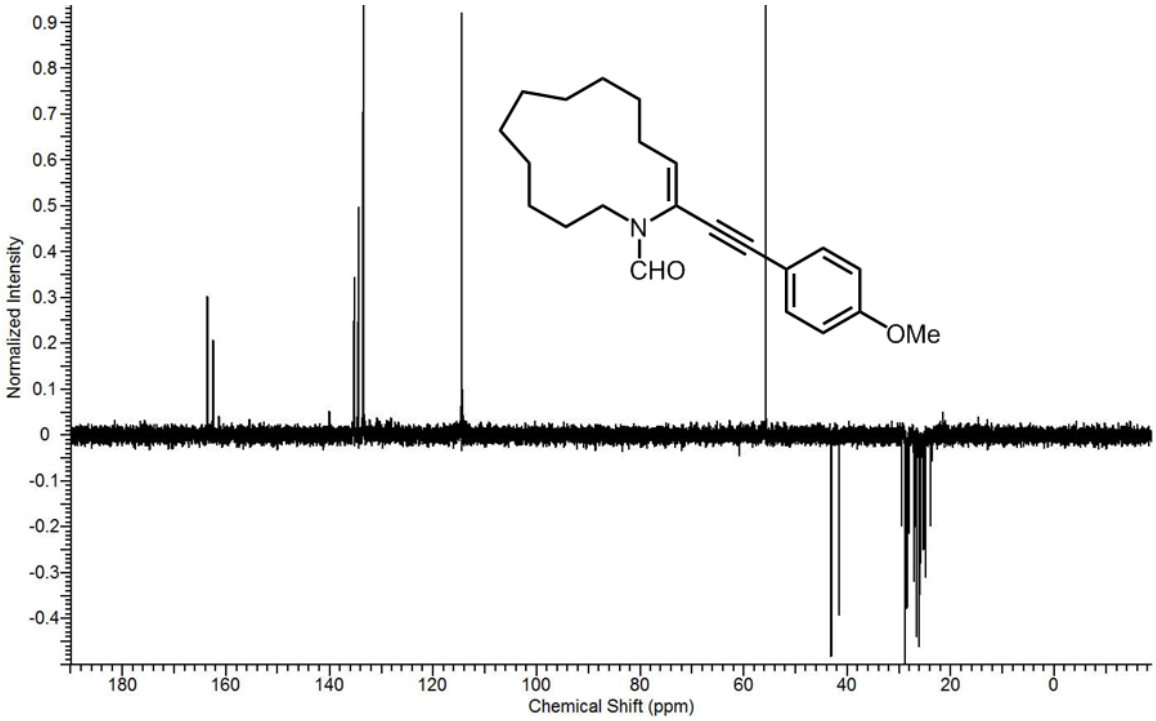
Spectra **1-103** MS spectrum of **3c12.**



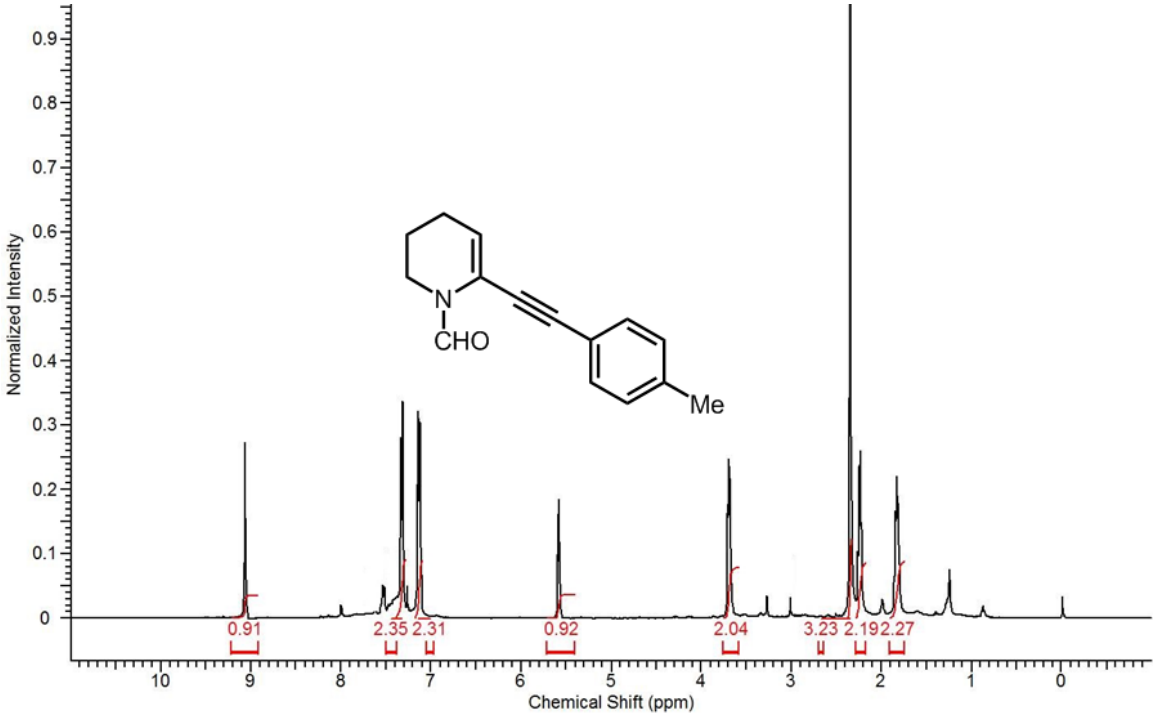
Spectra **1-104** Proton NMR spectrum of **3c12.**



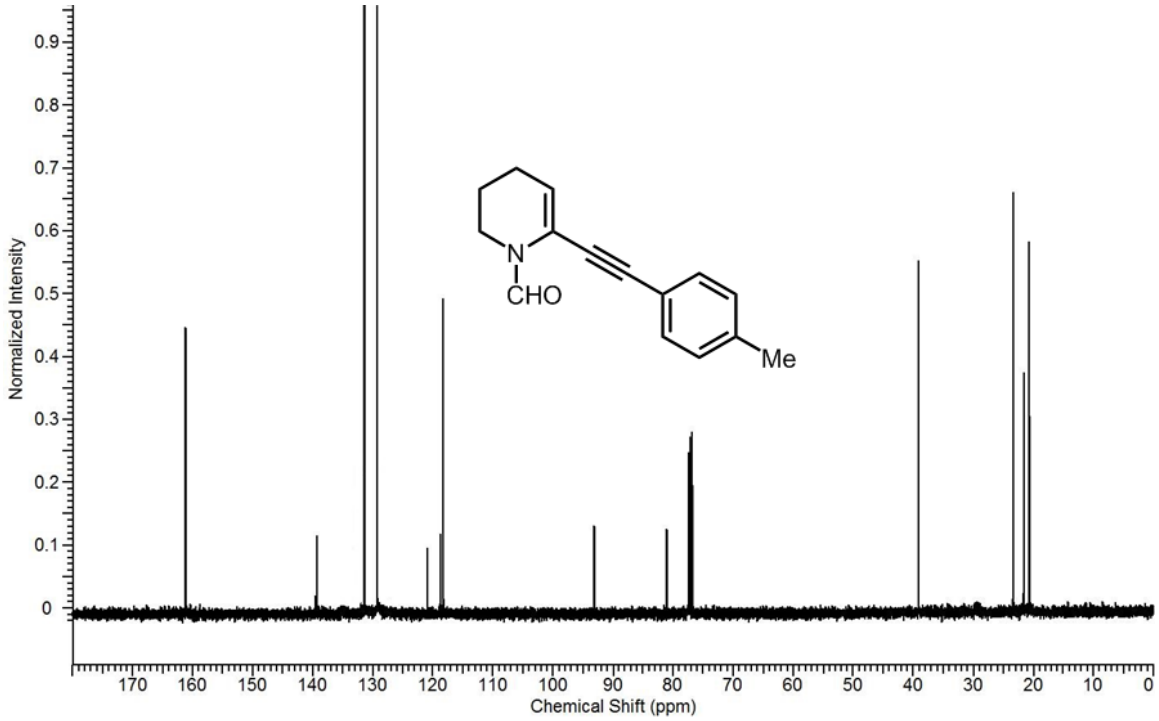
Spectra **1-105** Carbon NMR spectrum of **3c12.**



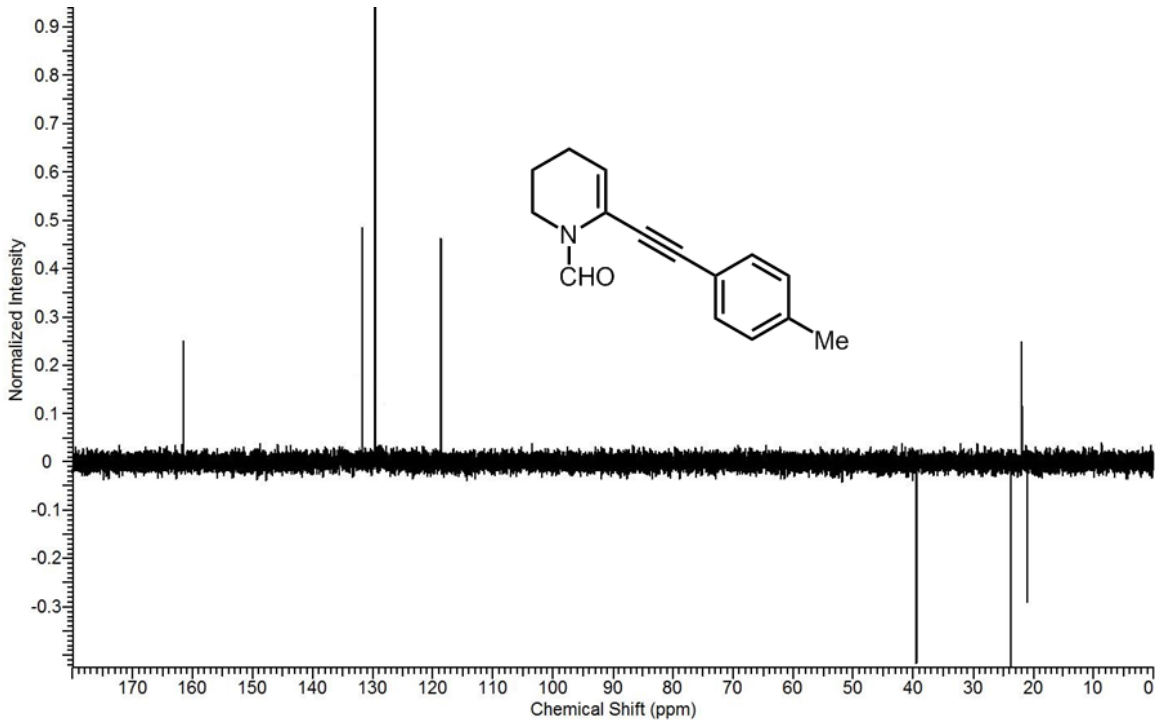
Spectra **1-106** DEPT-135 NMR spectrum of **3c12.**



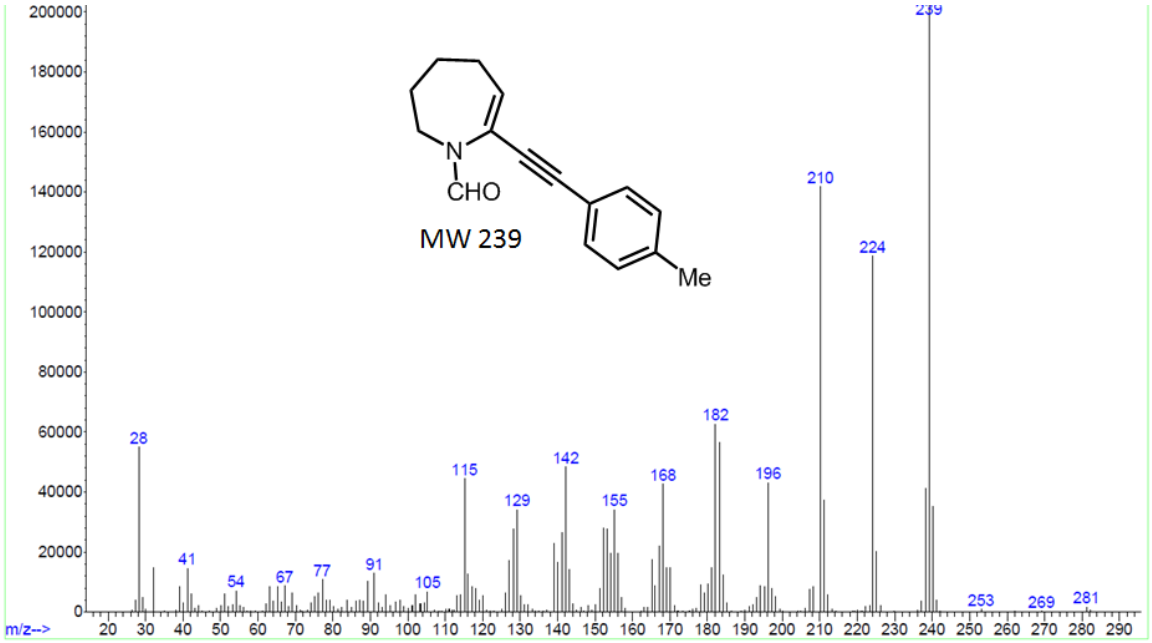
Spectra **1-107** Proton NMR spectrum of **3c13.**



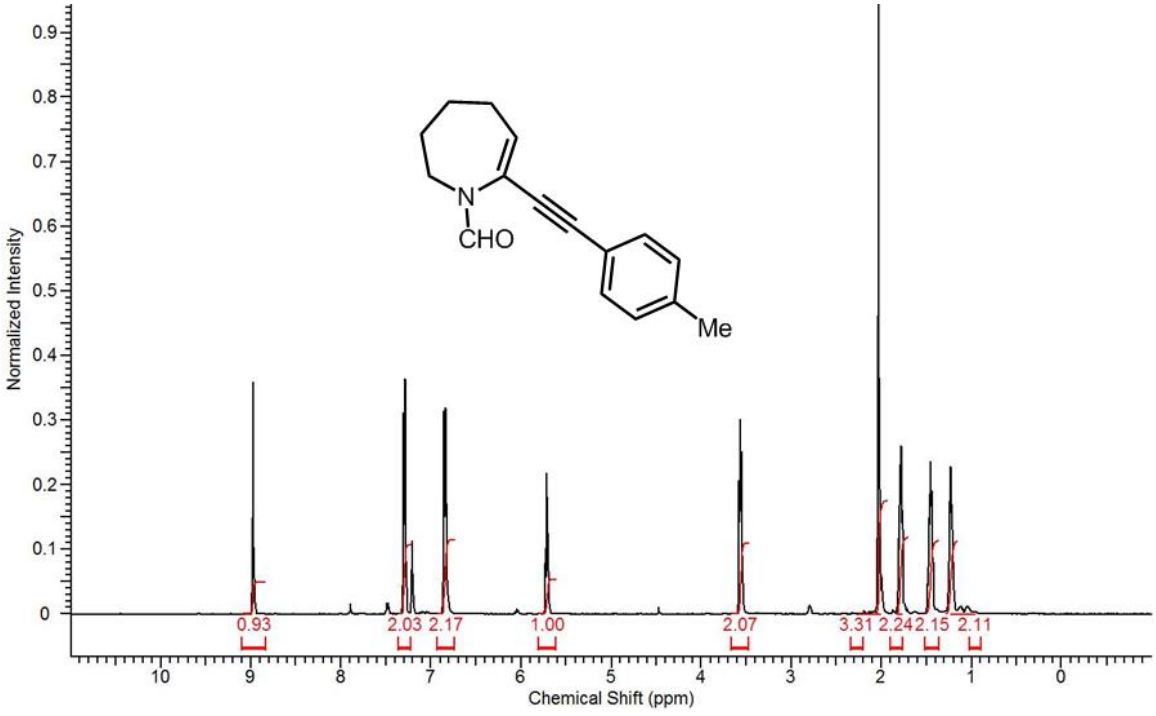
Spectra **1-108** Carbon NMR spectrum of **3c13.**



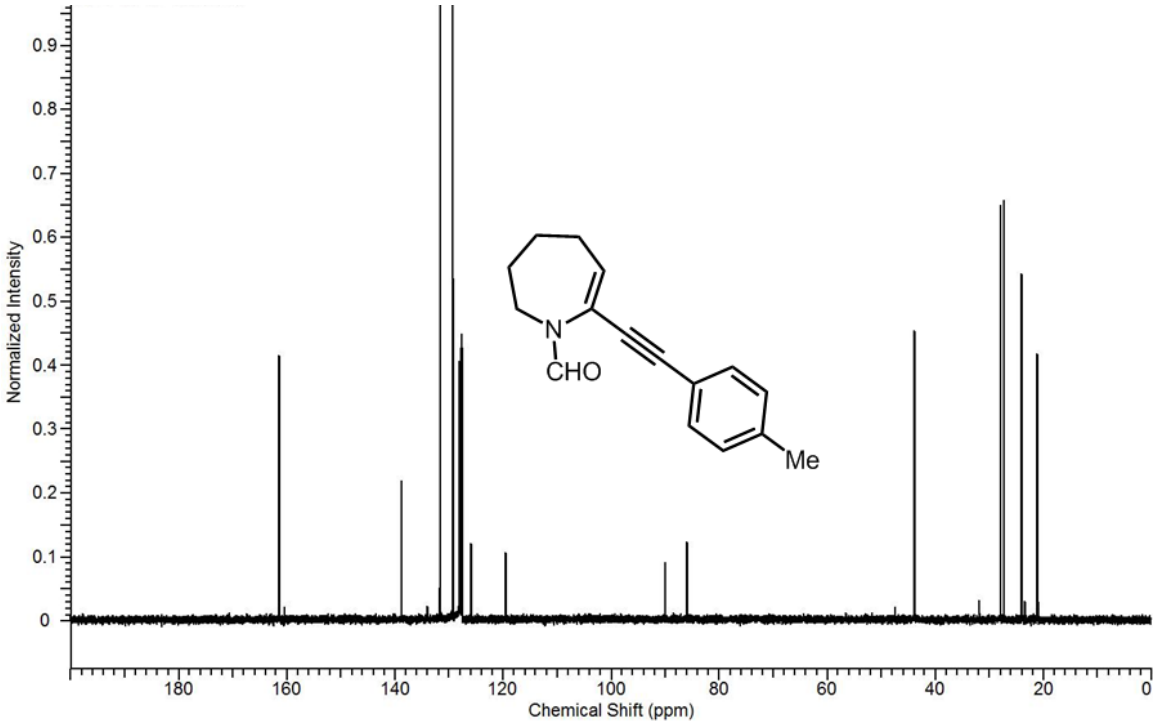
Spectra **1-109** DEPT-135 NMR spectrum of **3c13.**



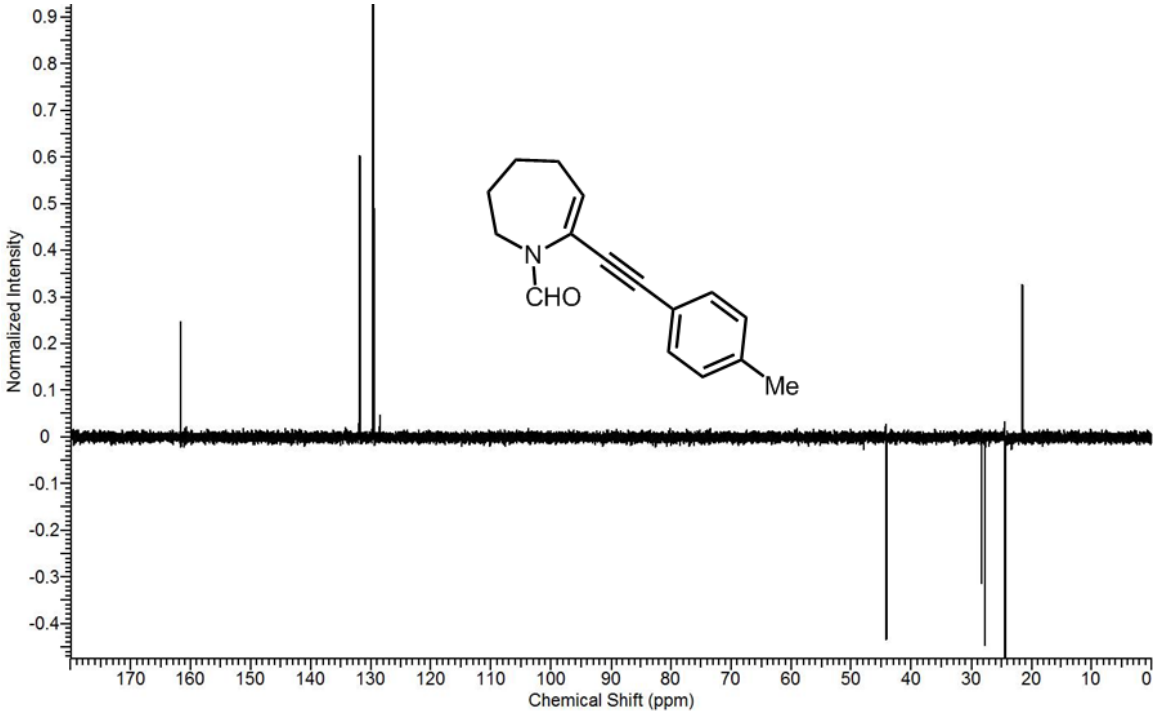
Spectra **1-110** MS spectrum of **3c14.**



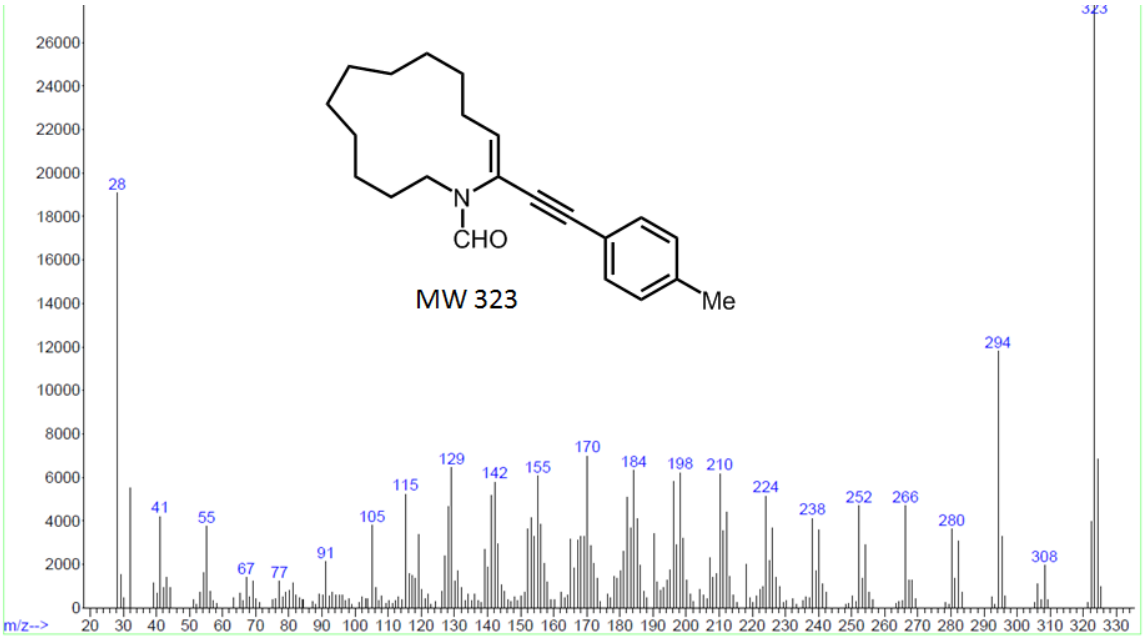
Spectra **1-111** Proton NMR spectrum of **3c14.**



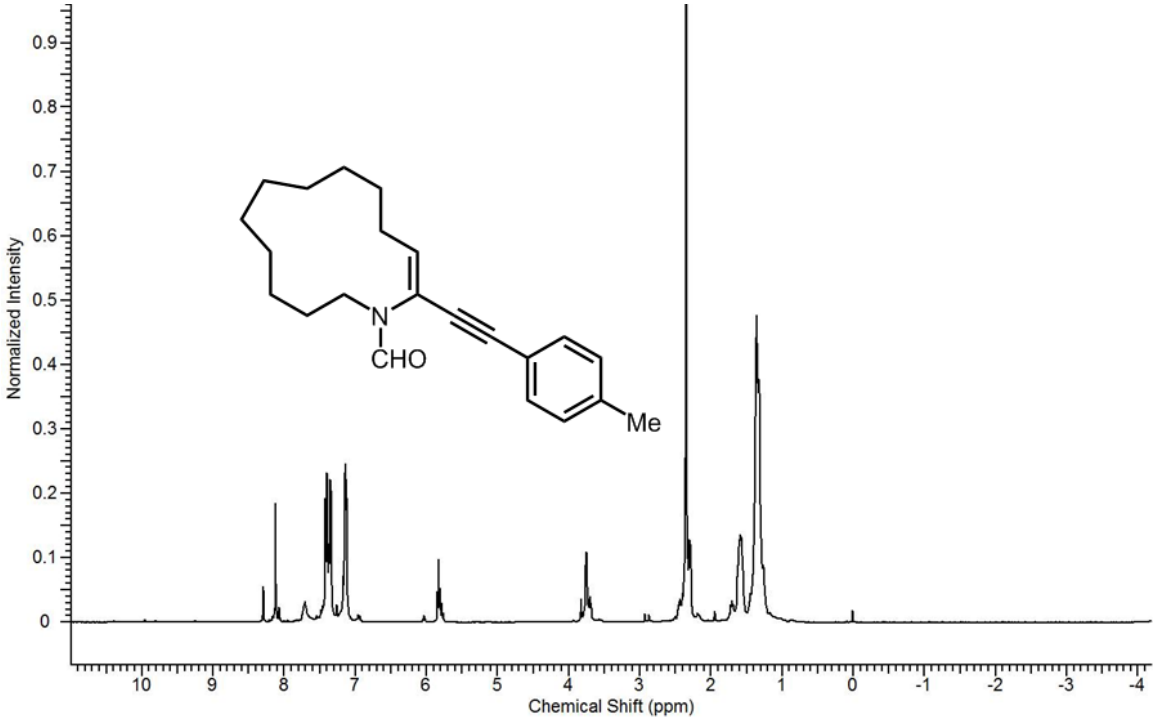
Spectra **1-112** Carbon NMR spectrum of **3c14.**



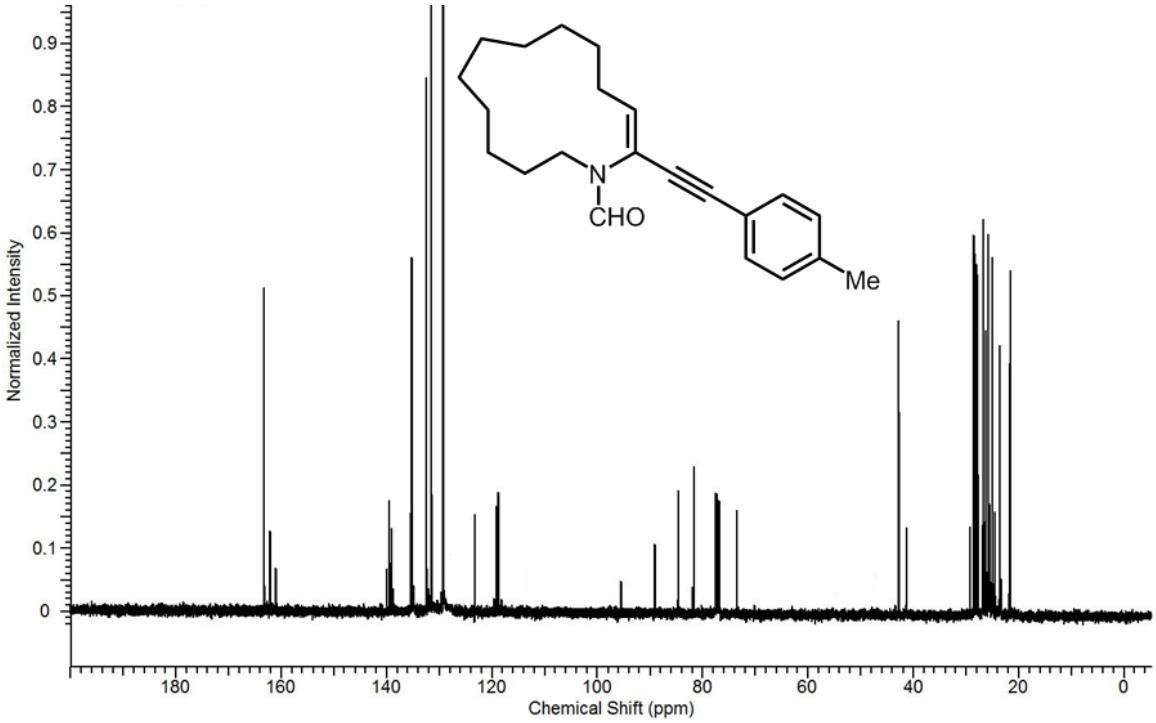
Spectra **1-113** DEPT-135 NMR spectrum of **3c14.**



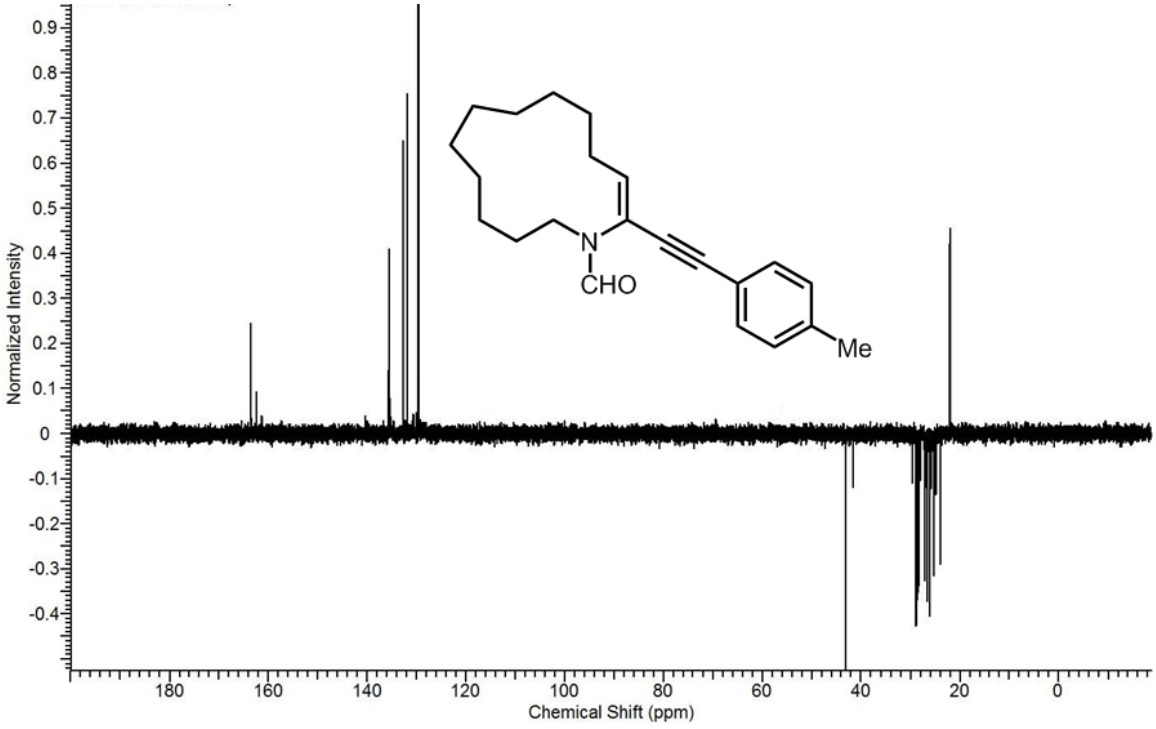
Spectra **1-114** MS spectrum of **3c15.**



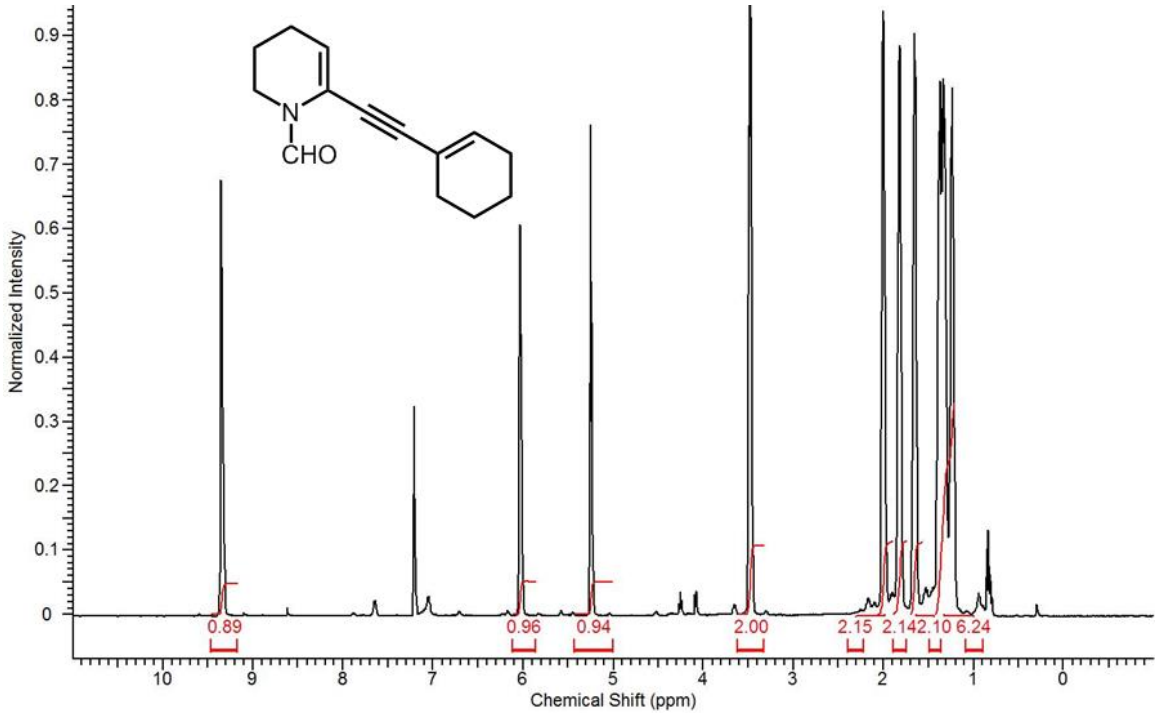
Spectra **1-115** Proton NMR spectrum of **3c15.**



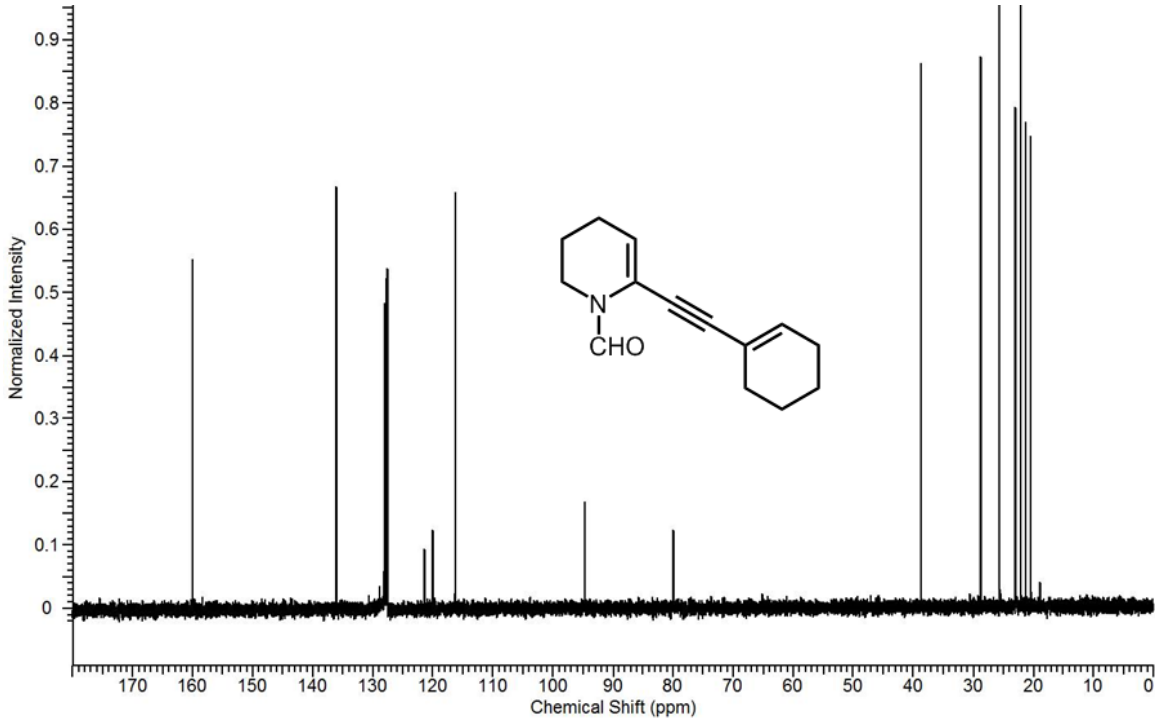
Spectra **1-116** Carbon NMR spectrum of **3c15.**



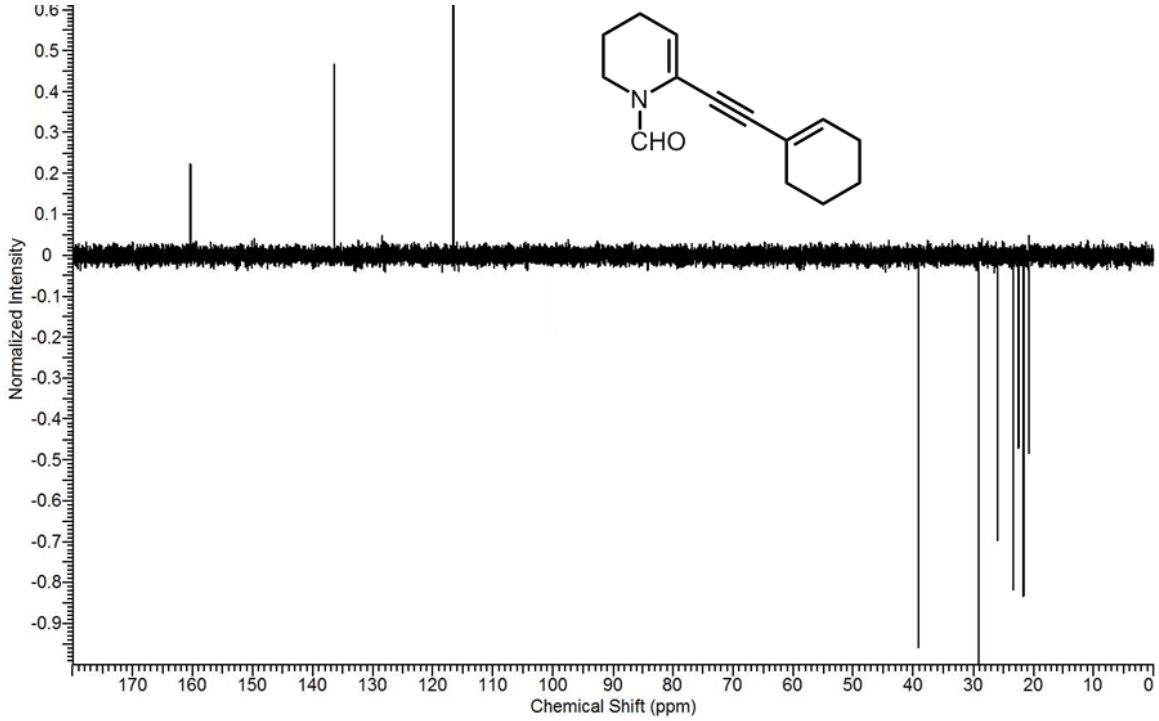
Spectra **1-117** DEPT-135 NMR spectrum of **3c15.**



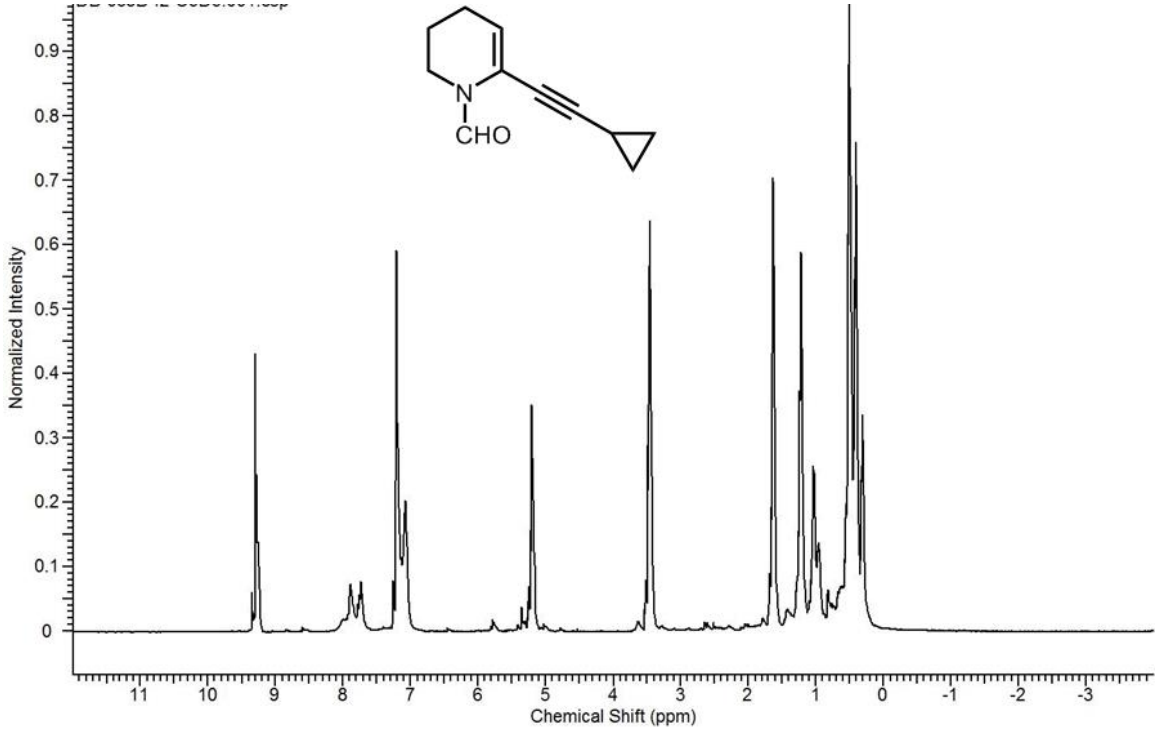
Spectra **1-118** Proton NMR spectrum of **3c16.**



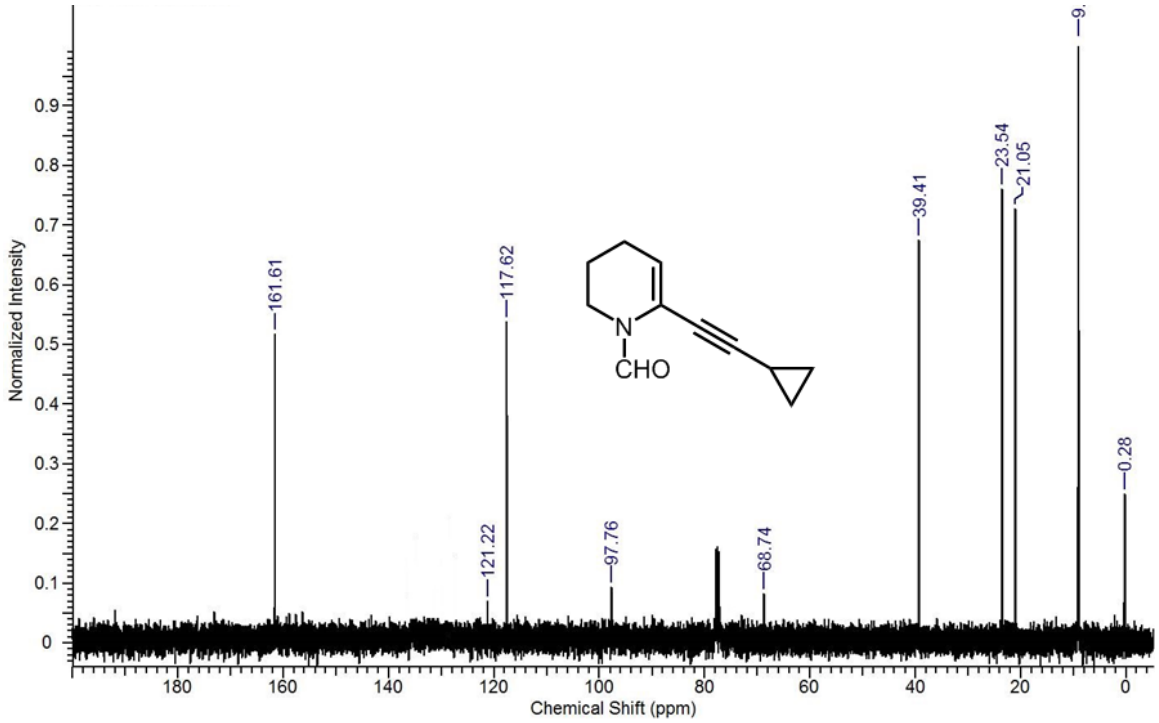
Spectra **1-119** Carbon NMR spectrum **3c16.**



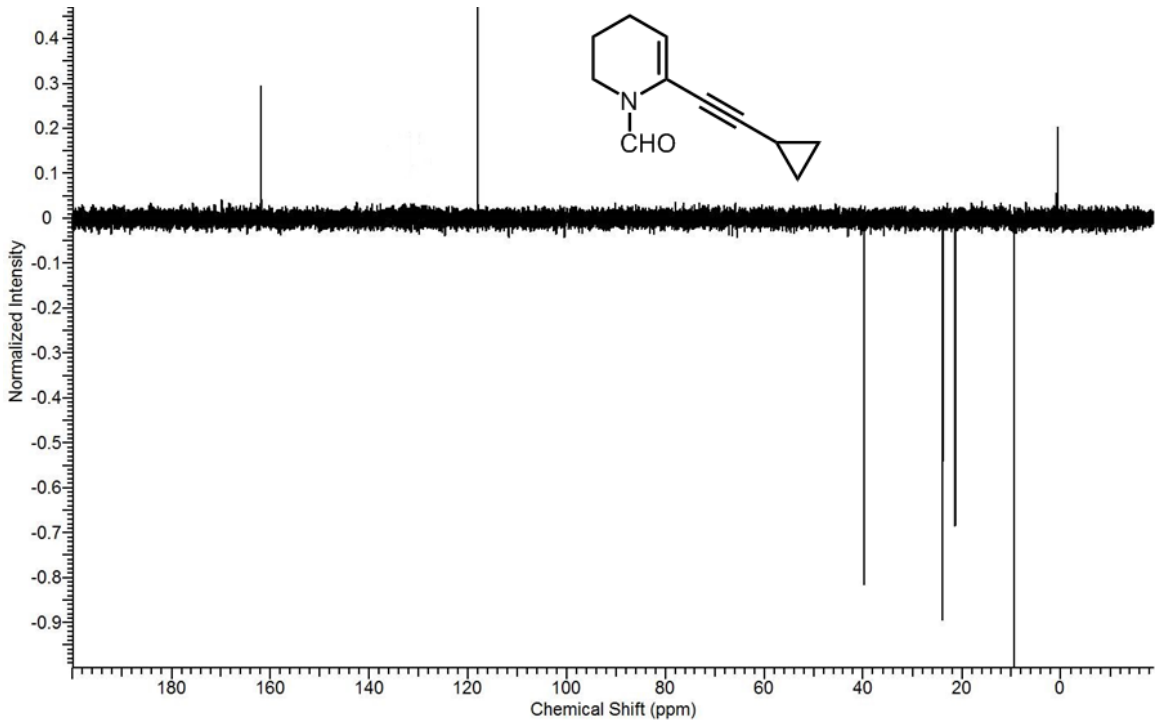
Spectra **1-120** DEPT-135 NMR spectrum **3c16.**



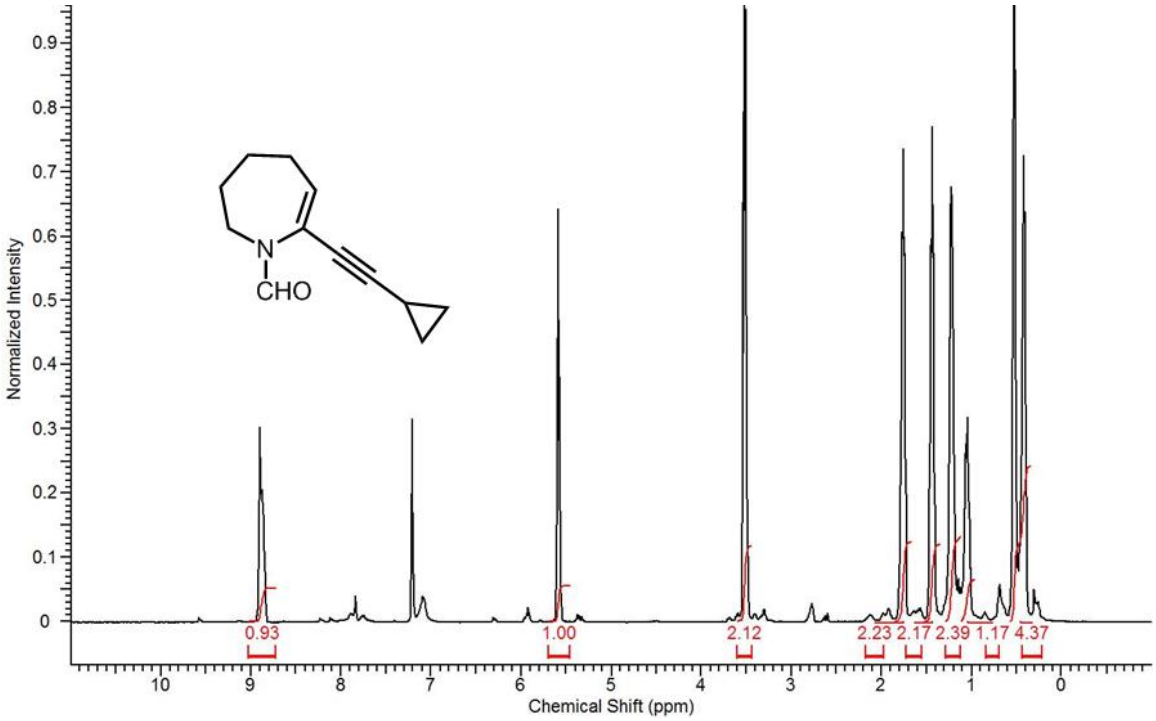
Spectra **1-121** Proton NMR spectrum of **3c18.**



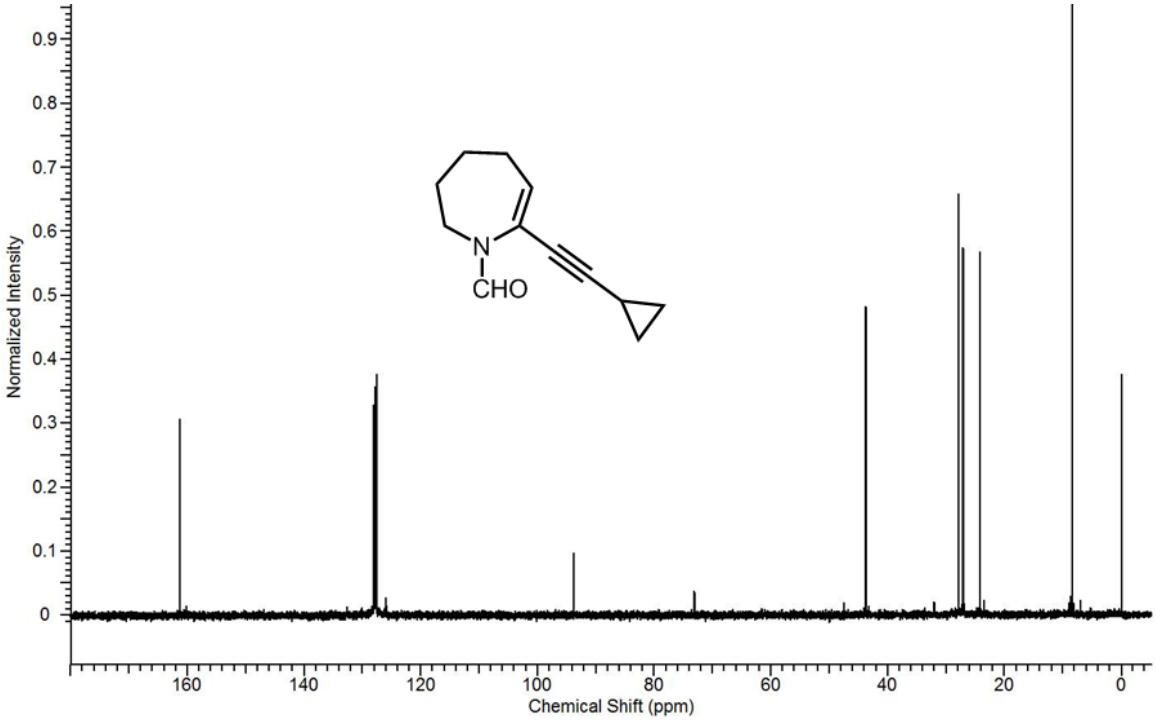
Spectra **1-122** Carbon NMR spectrum of **3c18.**



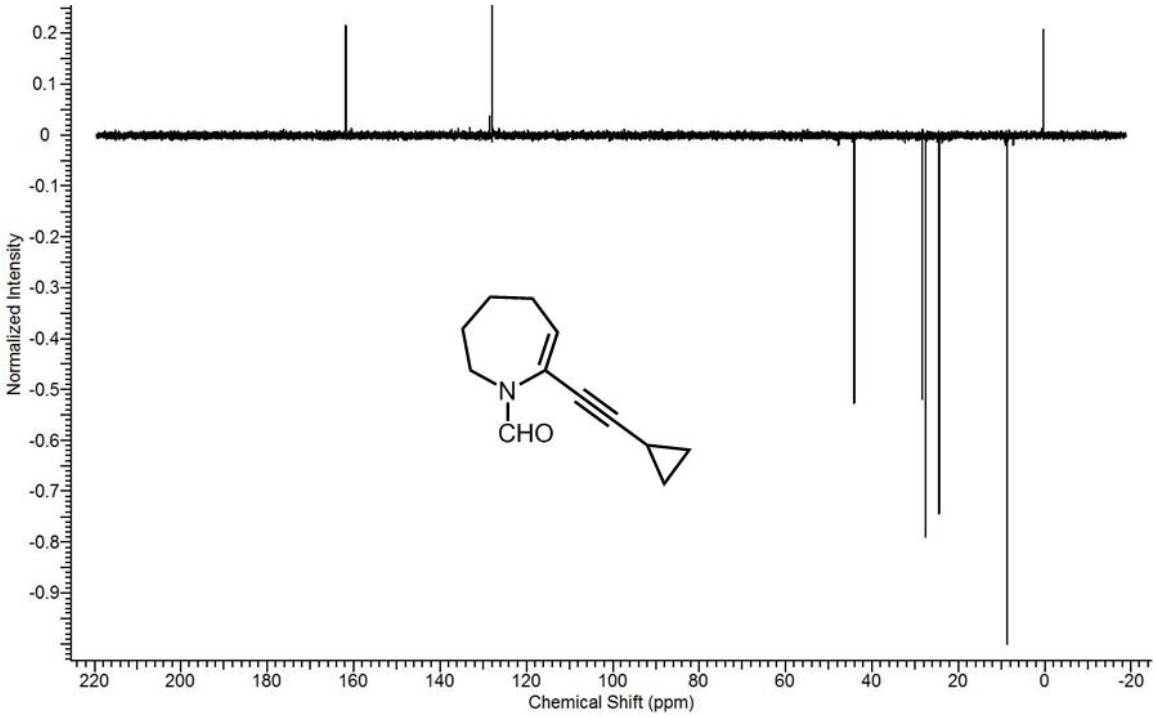
Spectra **1-123** DEPT-135 NMR spectrum of **3c18.**



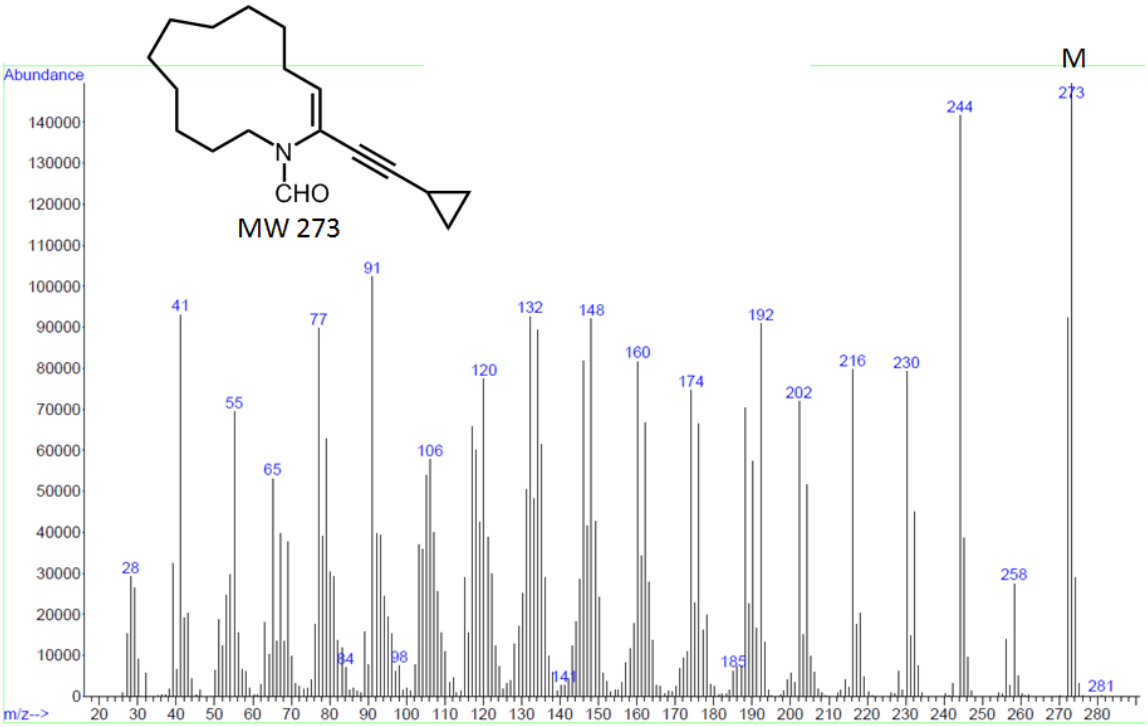
Spectra **1-124** Proton NMR spectrum of **3c19.**



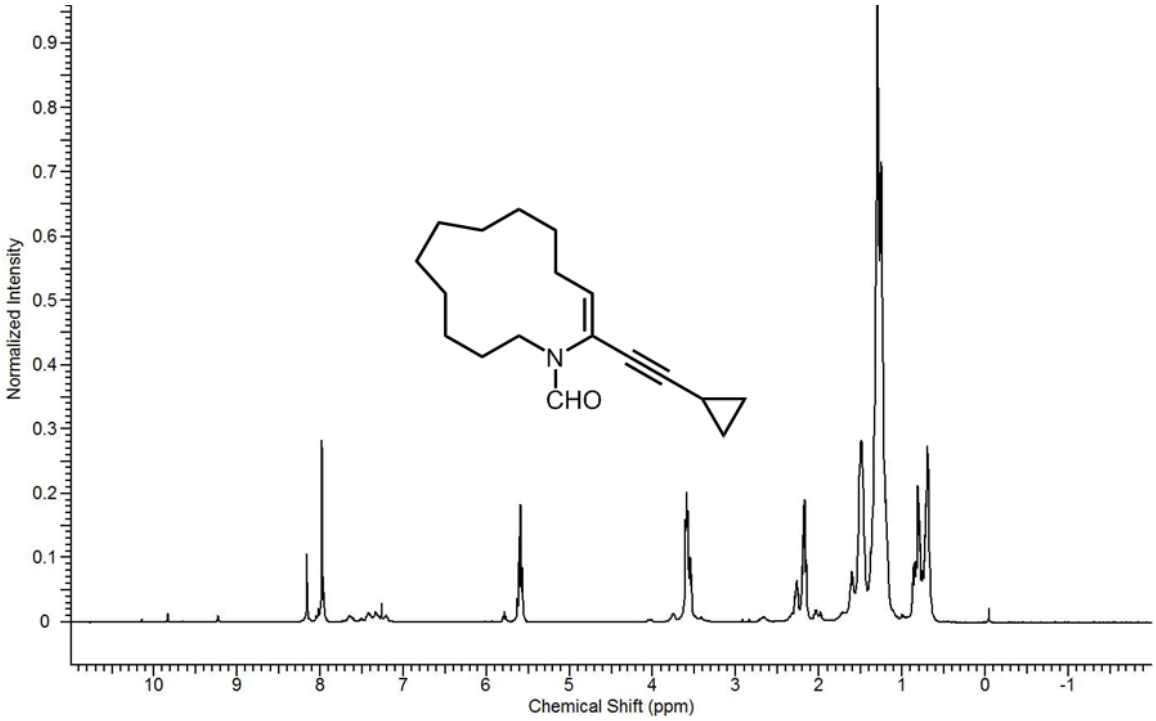
Spectra **1-125** Carbon NMR spectrum of **3c19.**



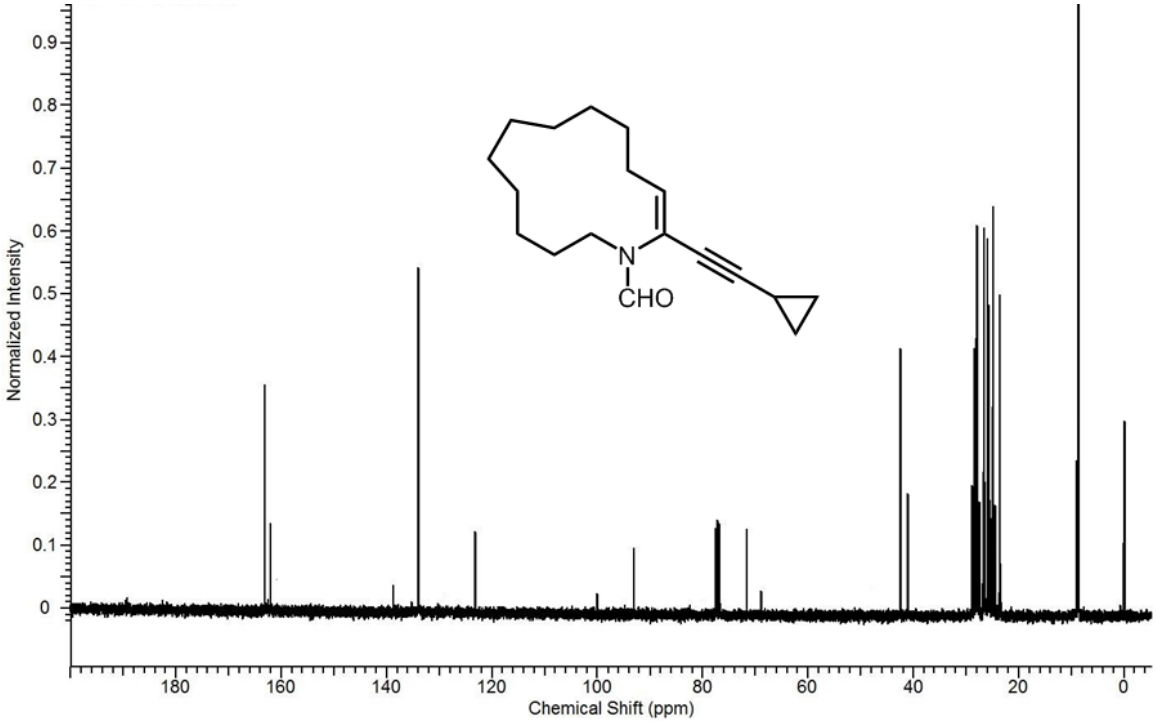
Spectra **1-126** DEPT-135 NMR spectrum of **3c19.**



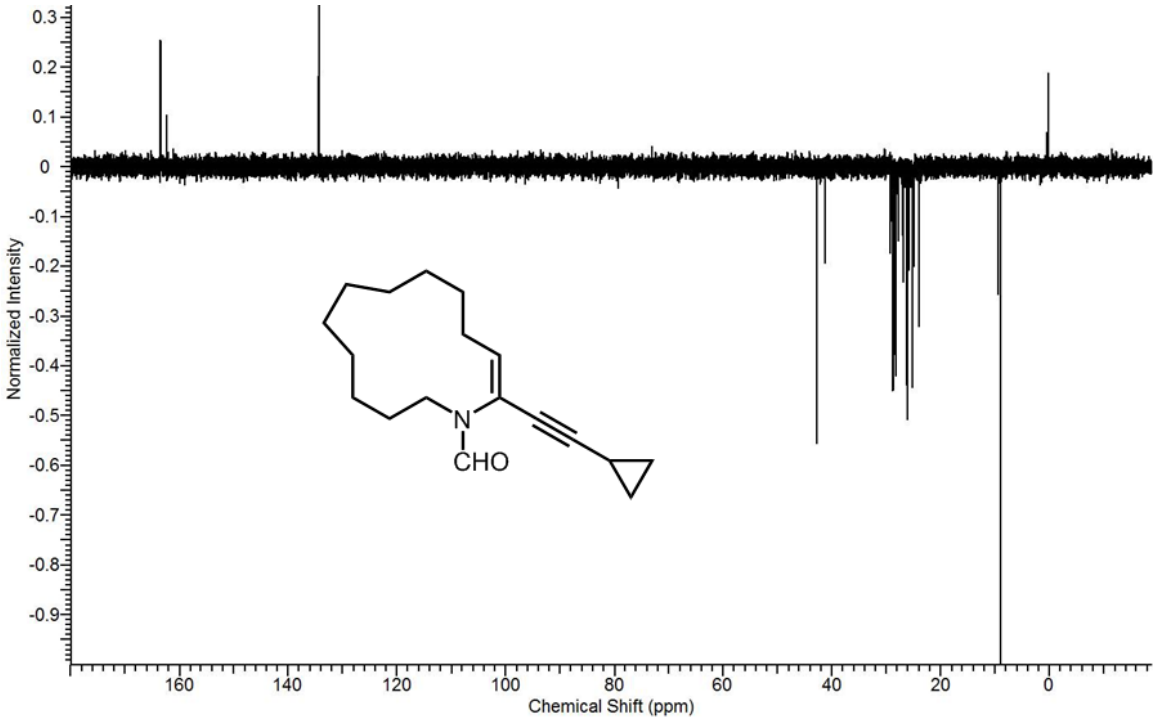
Spectra **1-127** MS spectrum of **3c20.**



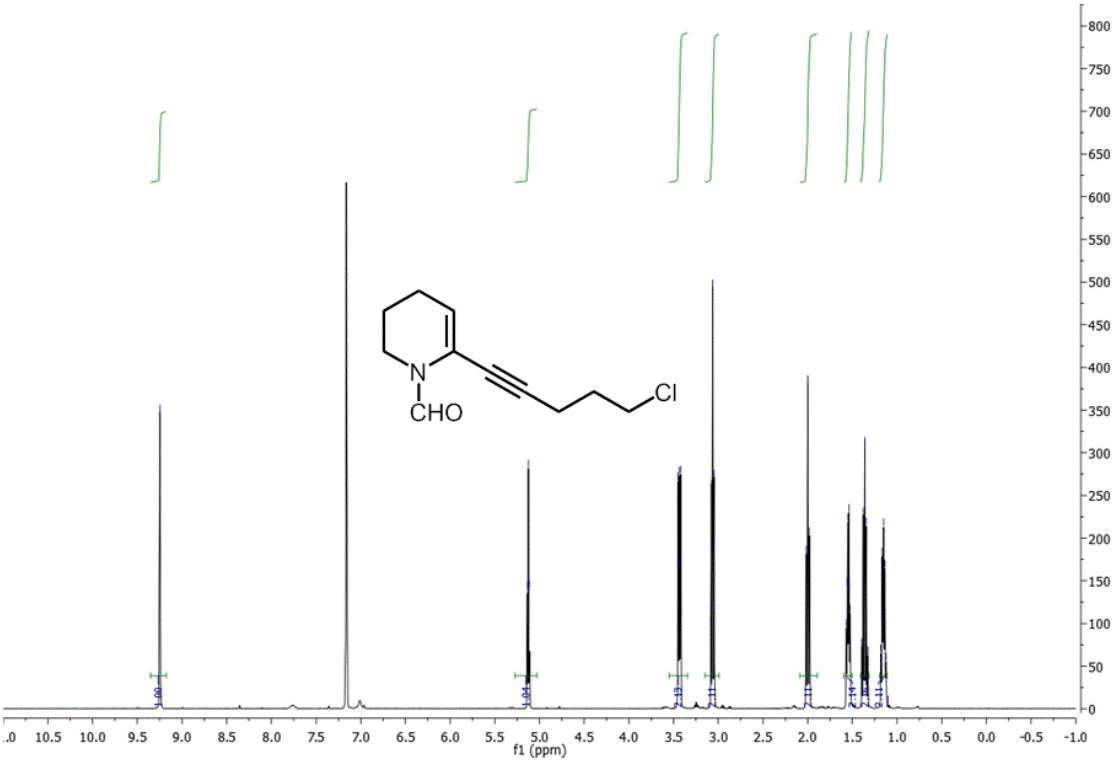
Spectra **1-128** Proton NMR spectrum of **3c20.**



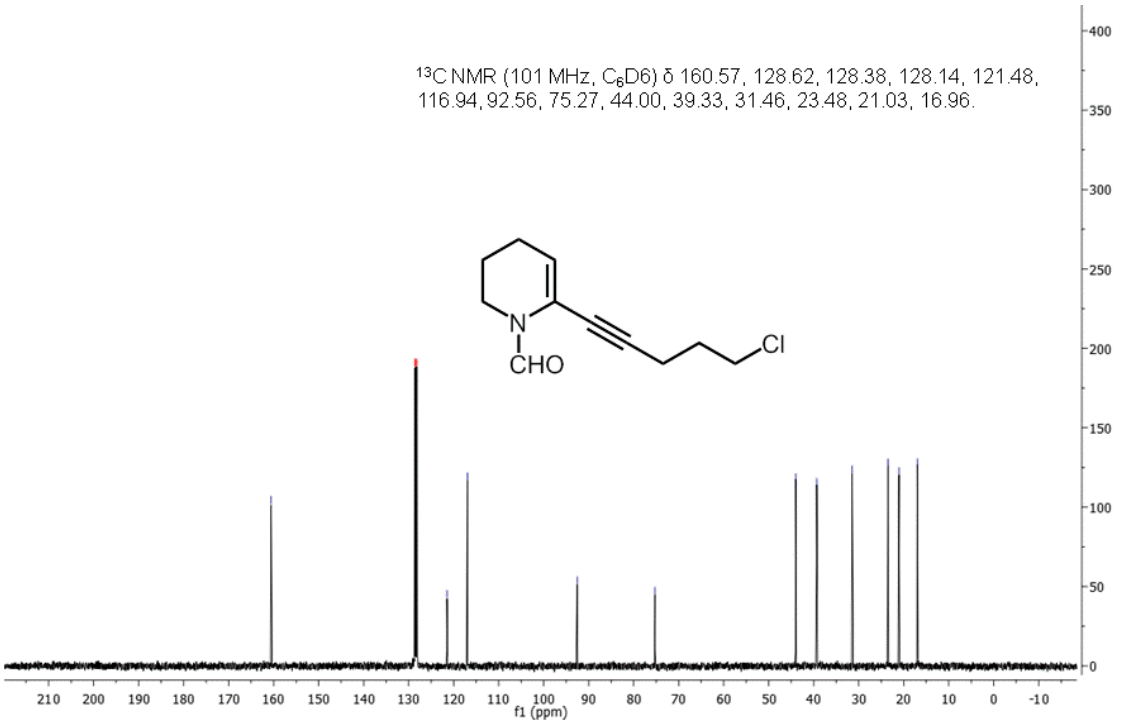
Spectra **1-129** Carbon NMR spectrum of **3c20.**



Spectra **1-130** DEPT-135 NMR spectrum of **3c20.**

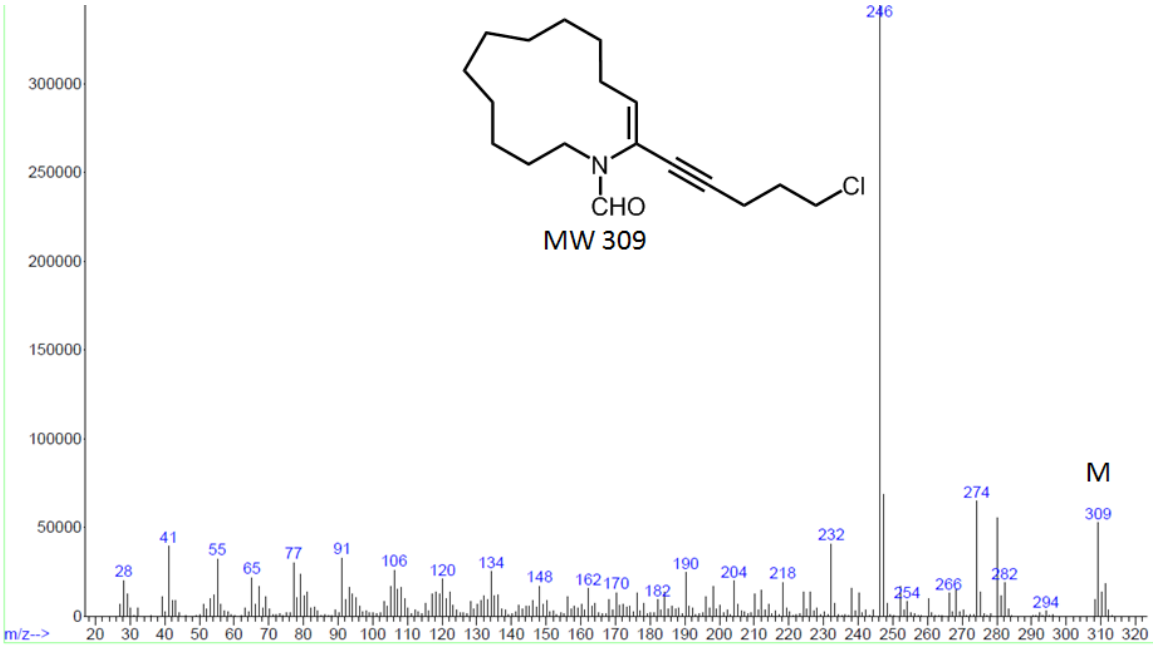


Spectra **1-131** Proton NMR spectrum of **3c21.**

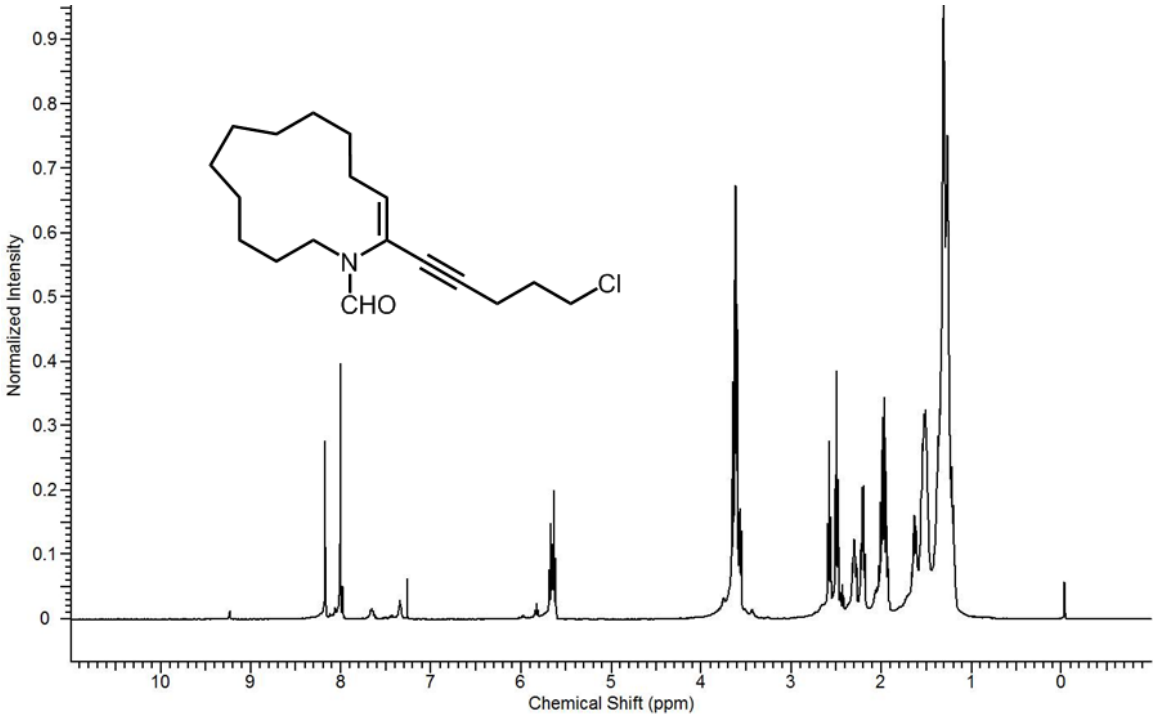


Spectra **1-132** Carbon NMR spectrum of **3c21.**

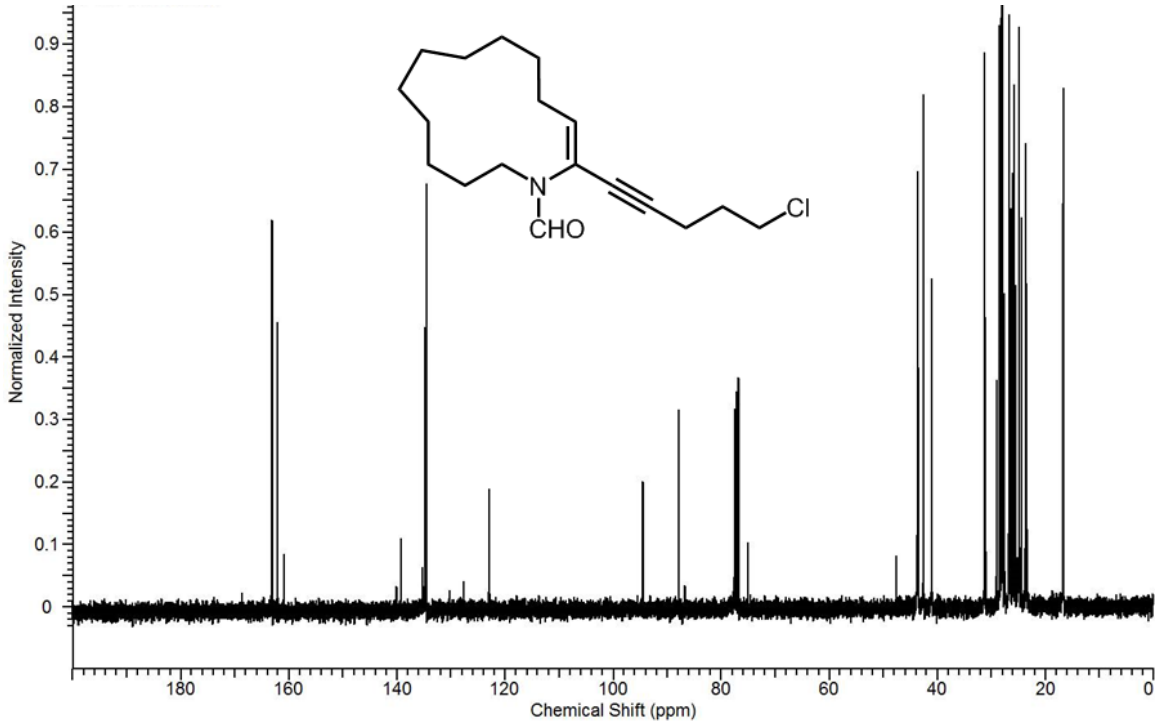
Spectra **1-133** DEPT-135 NMR spectrum of **3c21.**



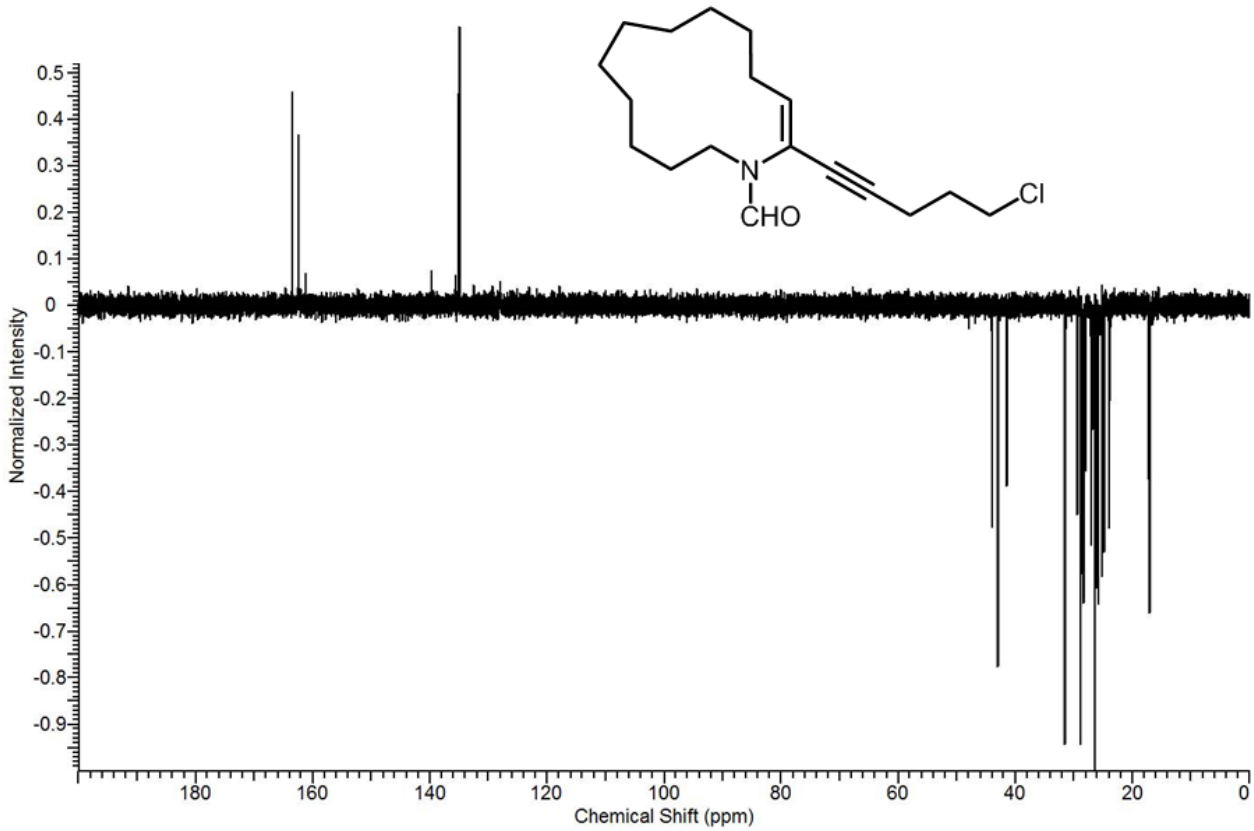
Spectra **1-134** MS spectrum of **3c23.**



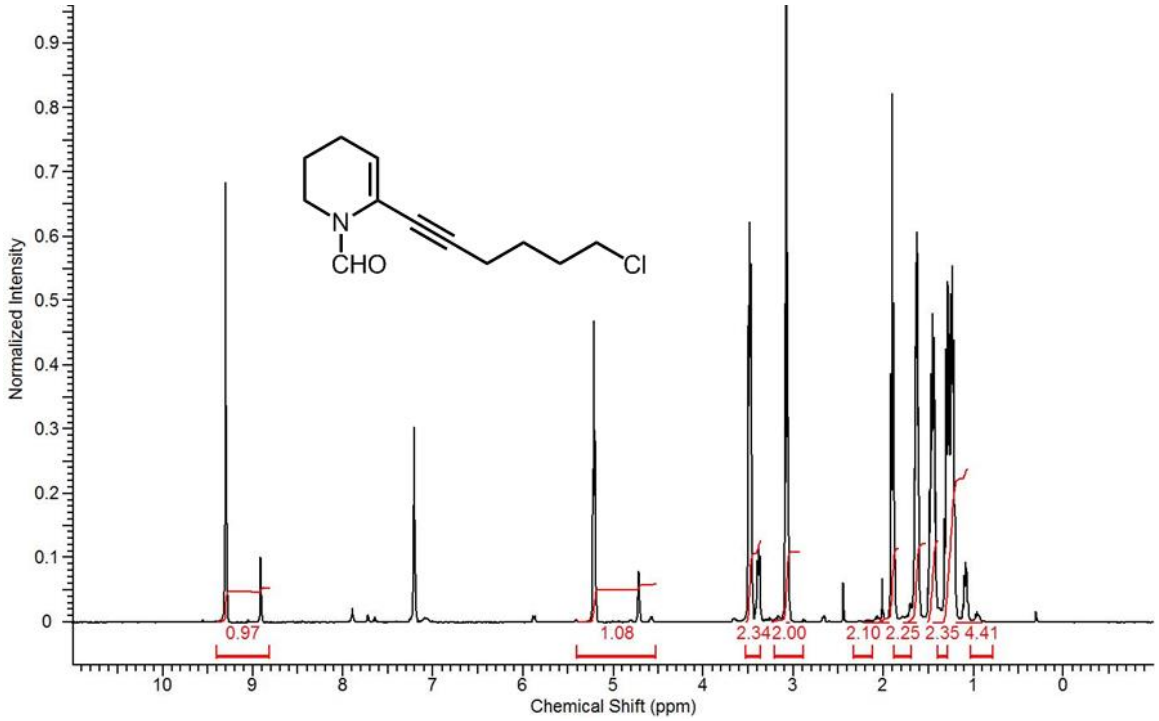
Spectra **1-135** Proton NMR spectrum of **3c23.**



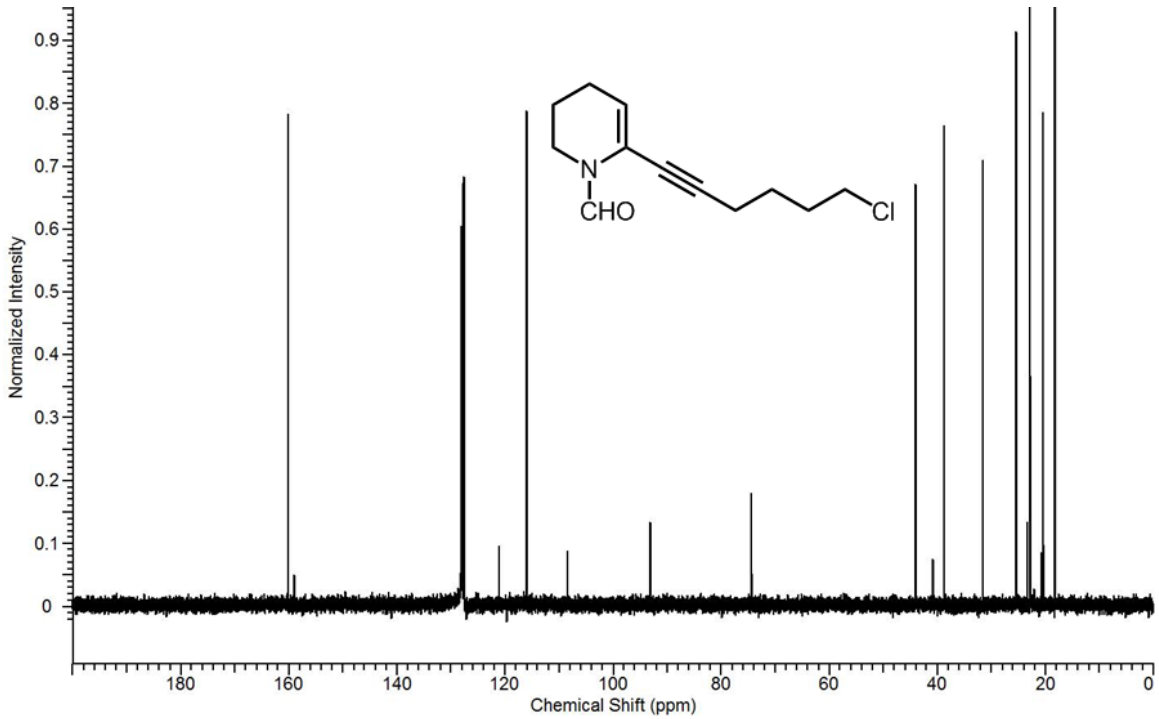
Spectra **1-136** Carbon NMR spectrum of **3c23.**



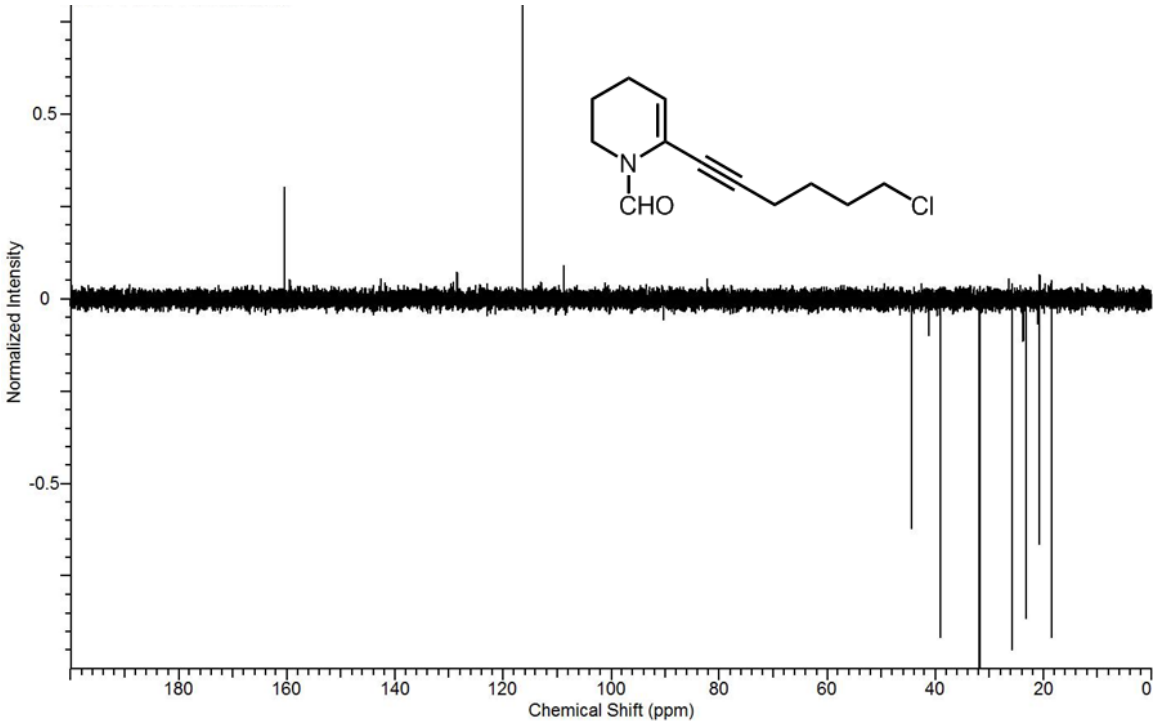
Spectra **1-137** DEPT-135 NMR spectrum of **3c23.**



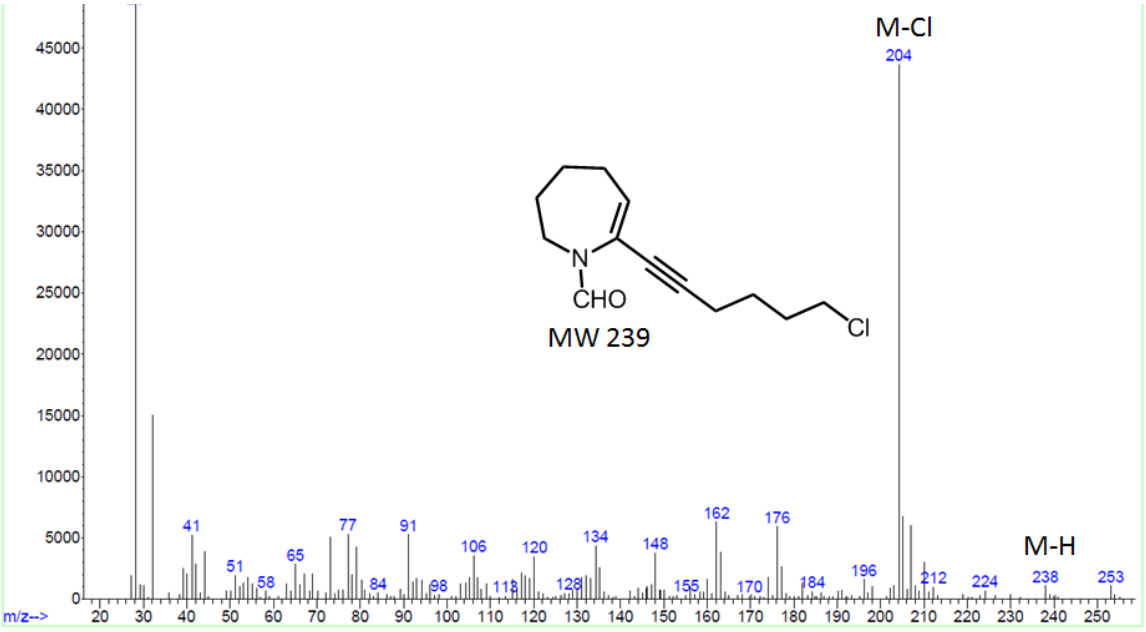
Spectra **1-138** Proton NMR spectrum of **3c24.**



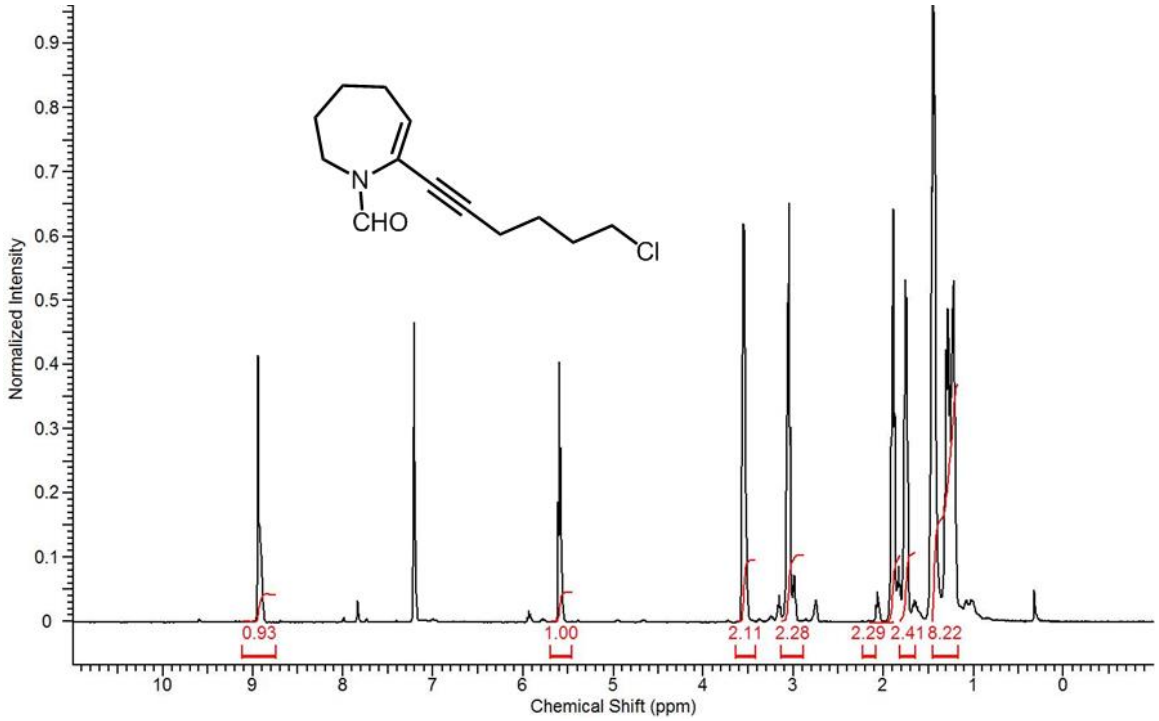
Spectra **1-139** Carbon NMR spectrum of **3c24.**



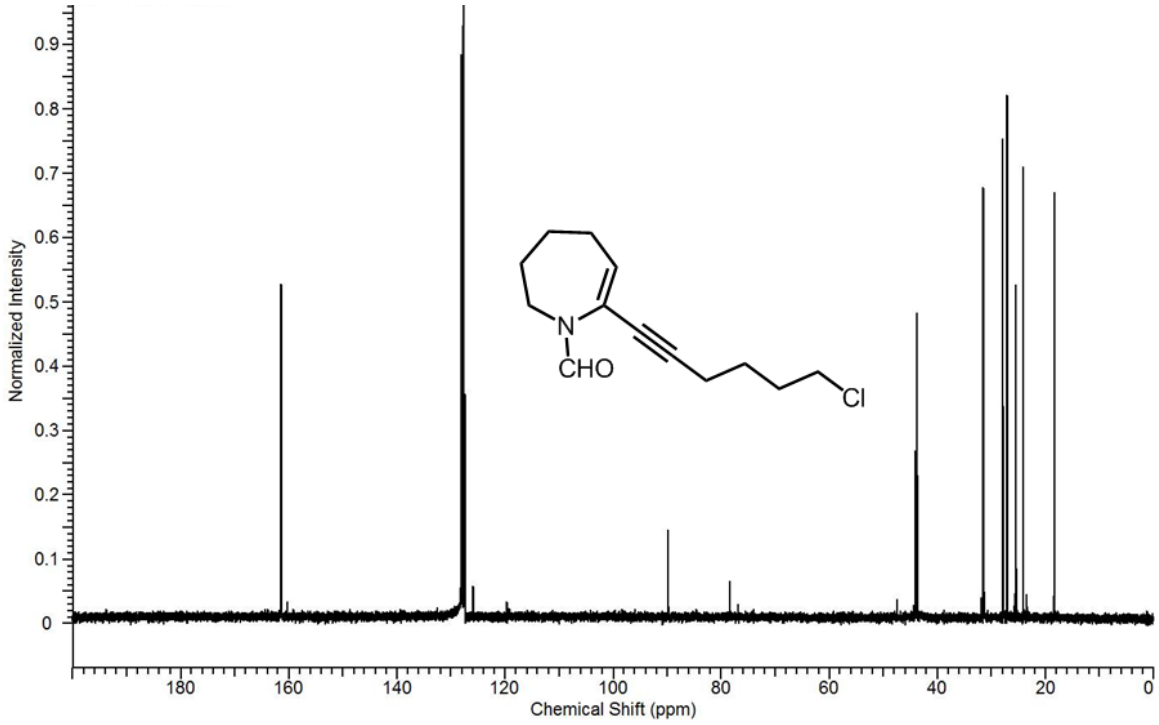
Spectra **1-140** DEPT-135 NMR spectrum of **3c24.**



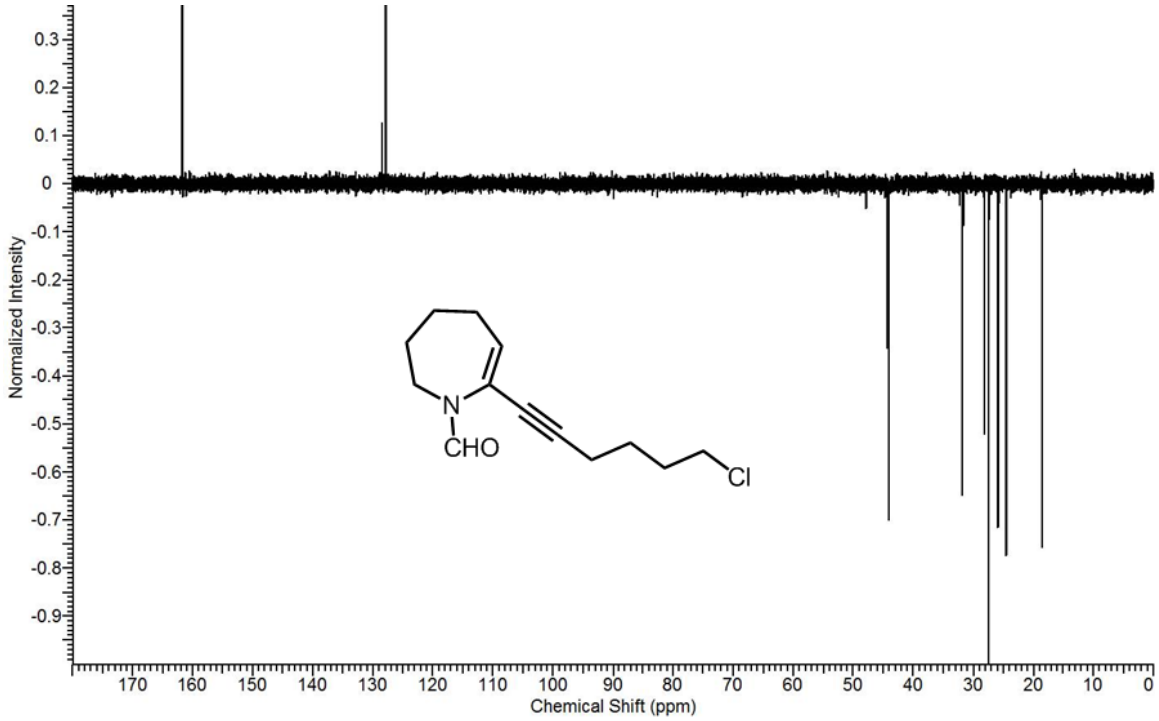
Spectra **1-141** MS spectrum of **3c25.**



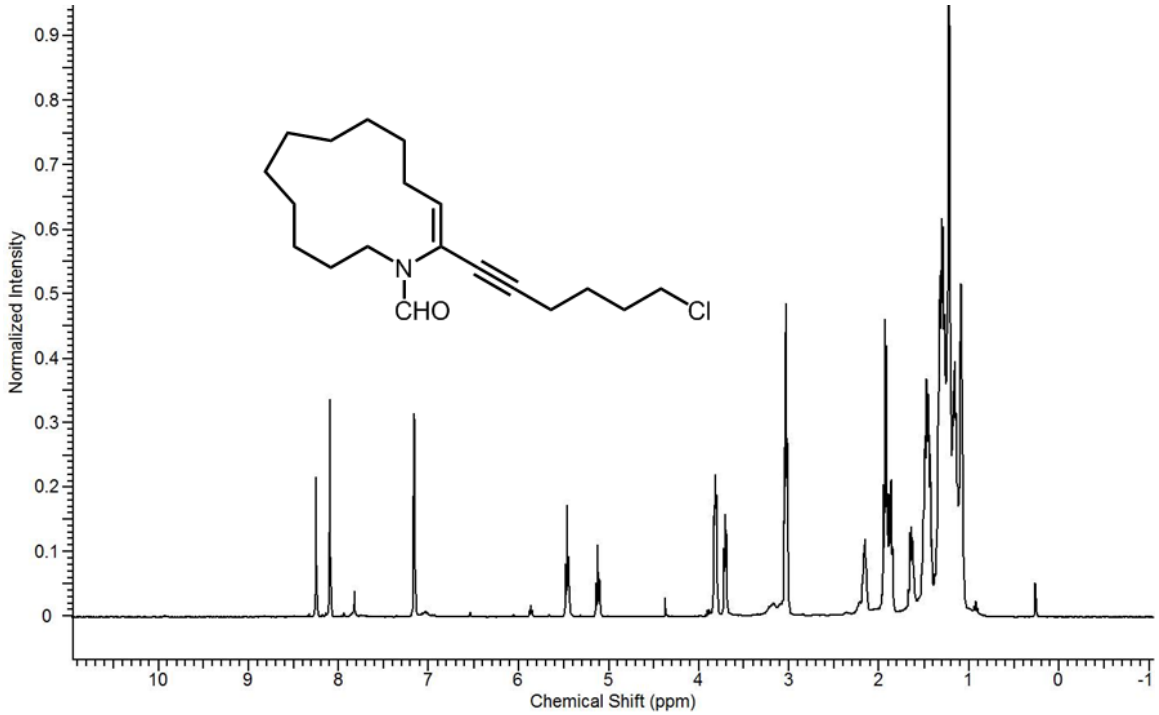
Spectra **1-142** Proton NMR spectrum of **3c25.**



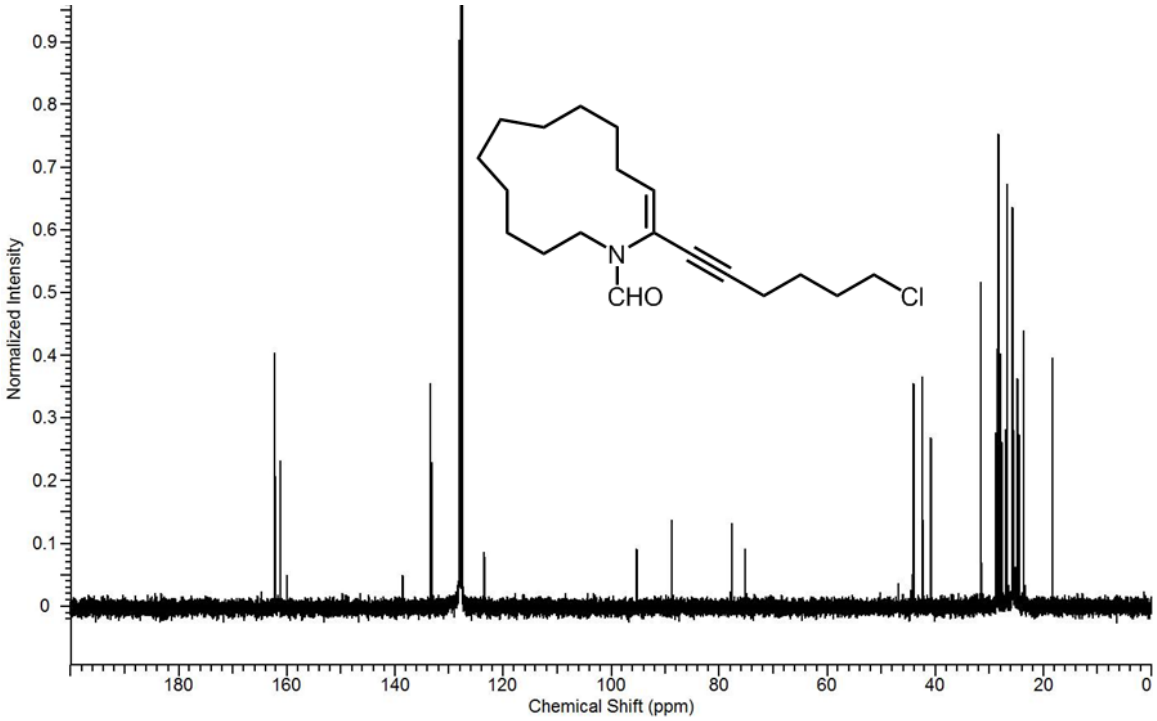
Spectra **1-143** Carbon NMR spectrum of **3c25.**



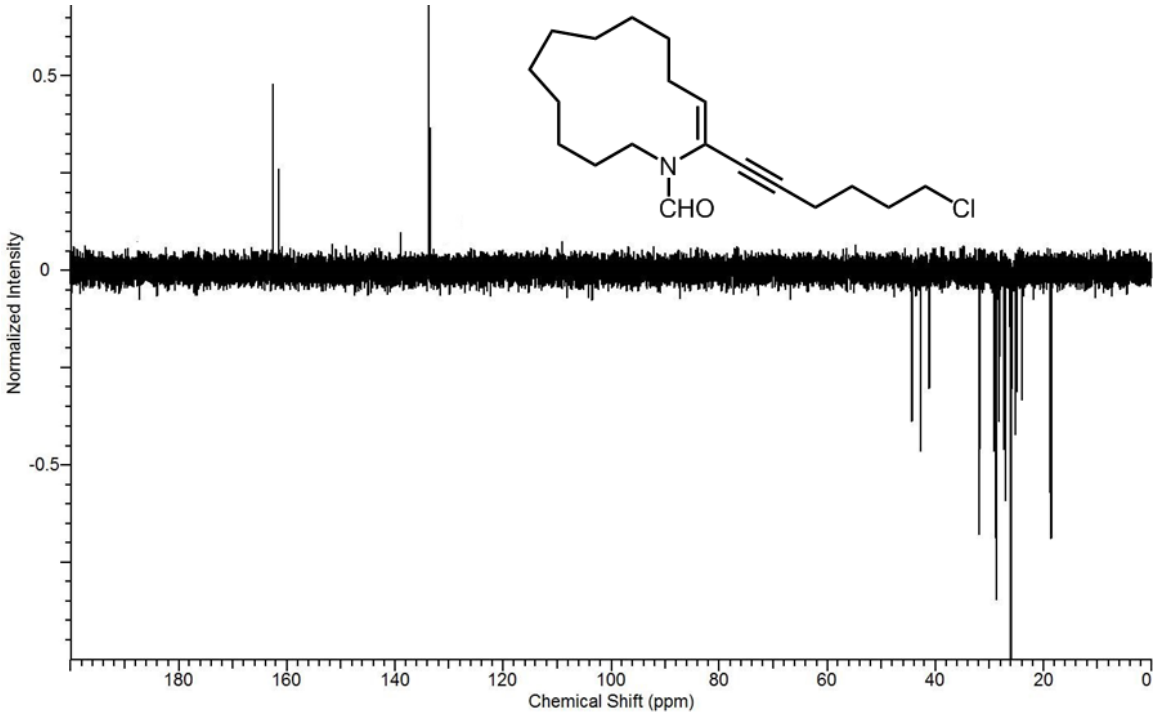
Spectra **1-144** DEPT-135 NMR spectrum of **3c25.**



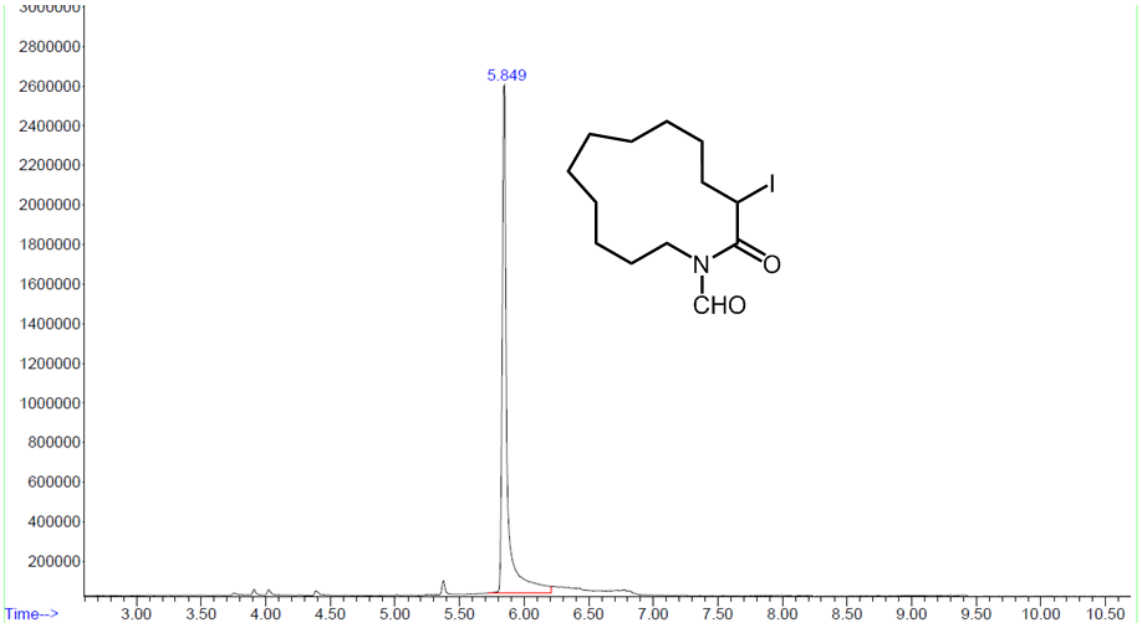
Spectra **1-145** Proton NMR spectrum of **3c26.**



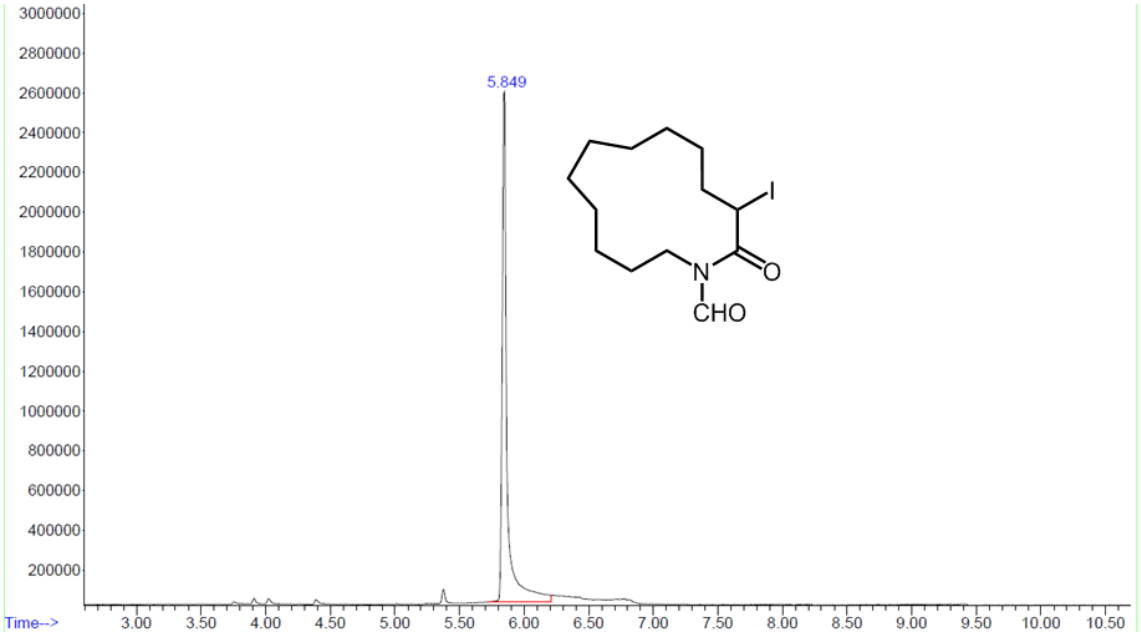
Spectra **1-146** Carbon NMR spectrum of **3c26.**



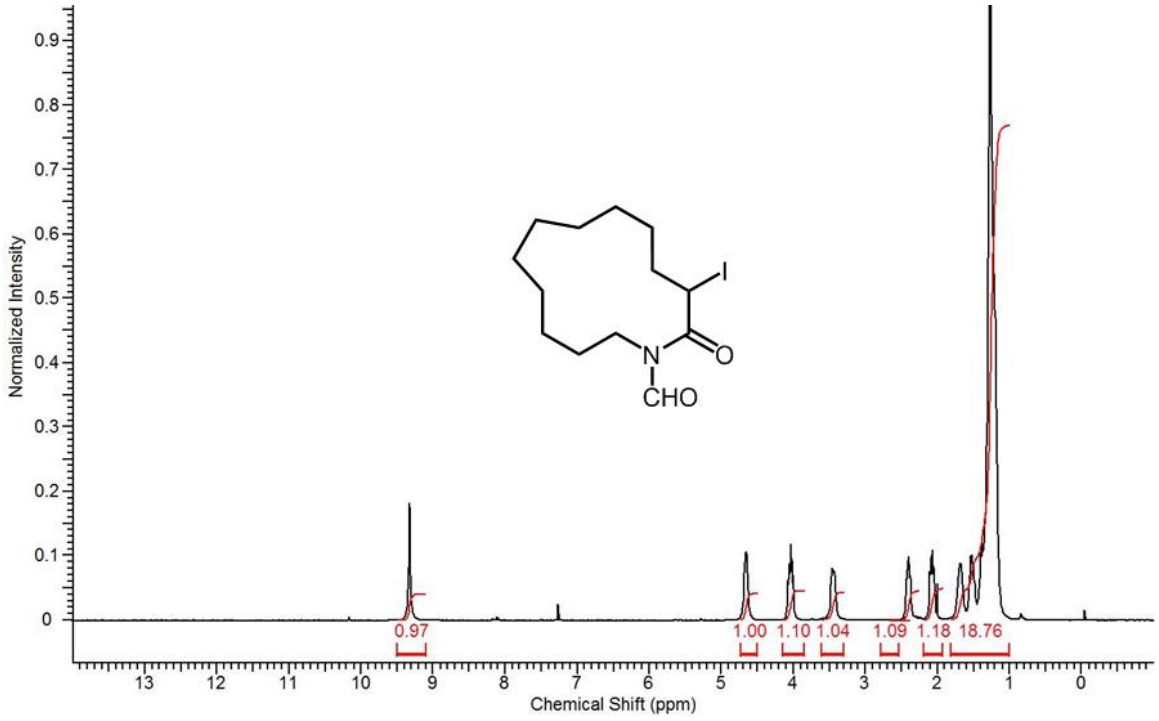
Spectra **1-147** DEPT-135 NMR spectrum of **3c26.**



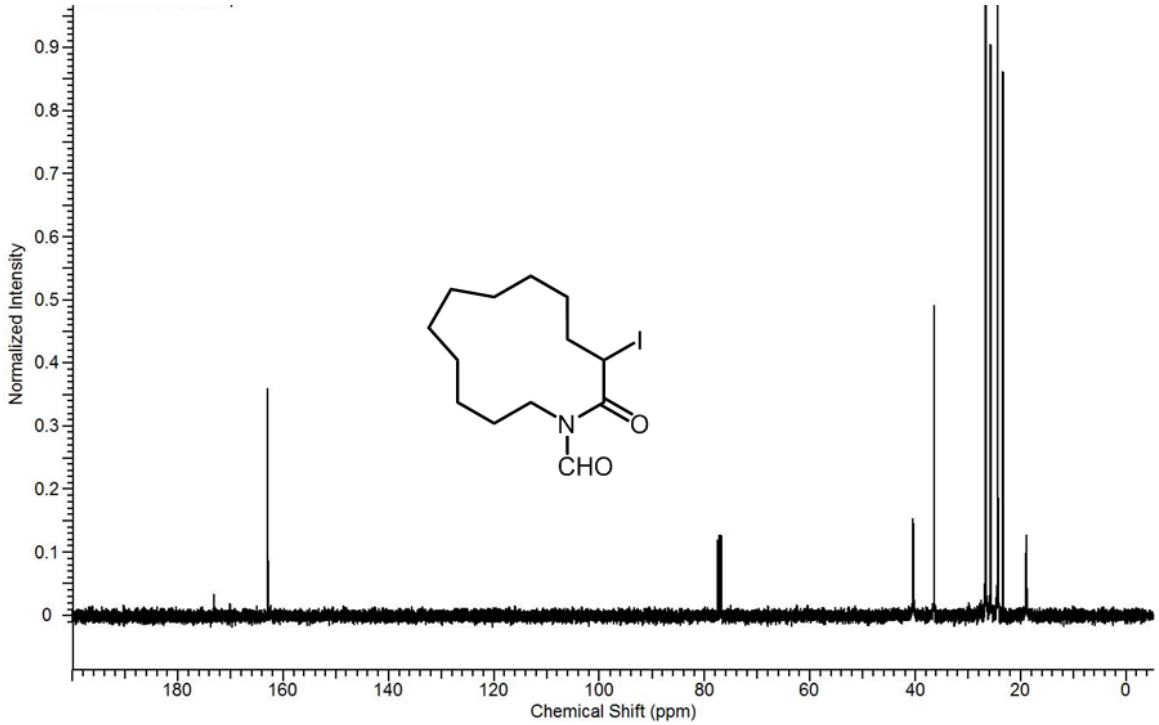
Spectra **1-148** GC spectrum of **3d1.**



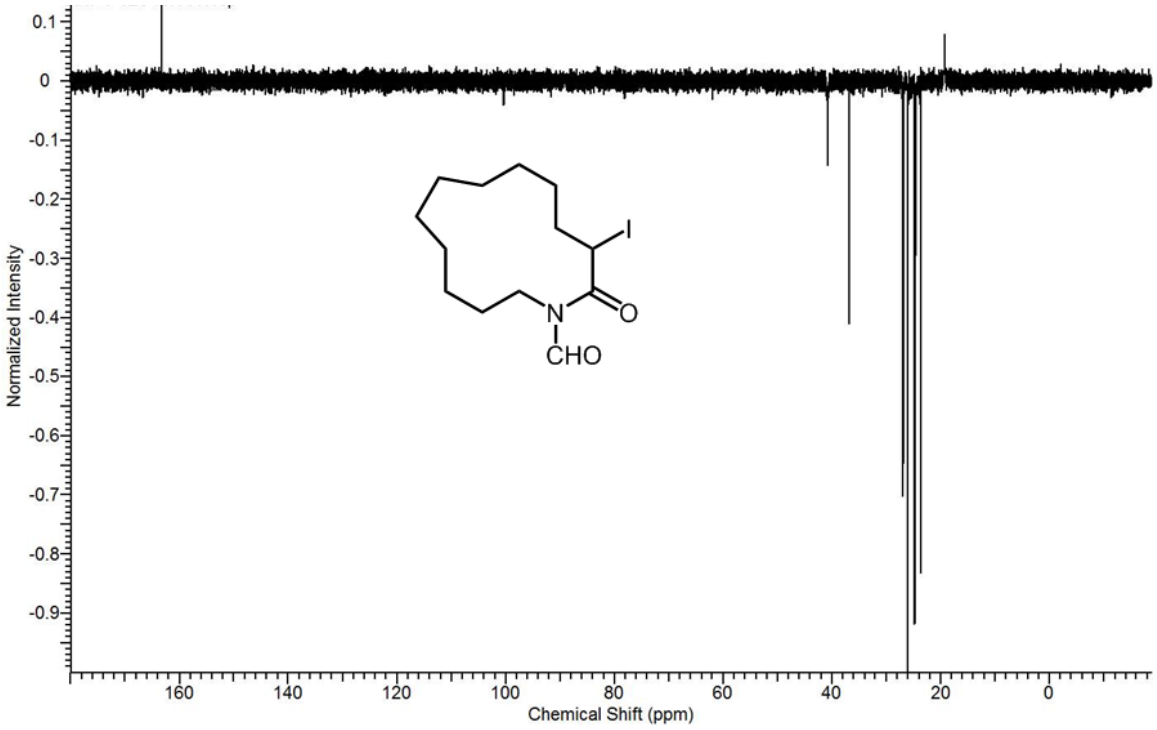
Spectra **1-149** MS spectrum of **3d1.**



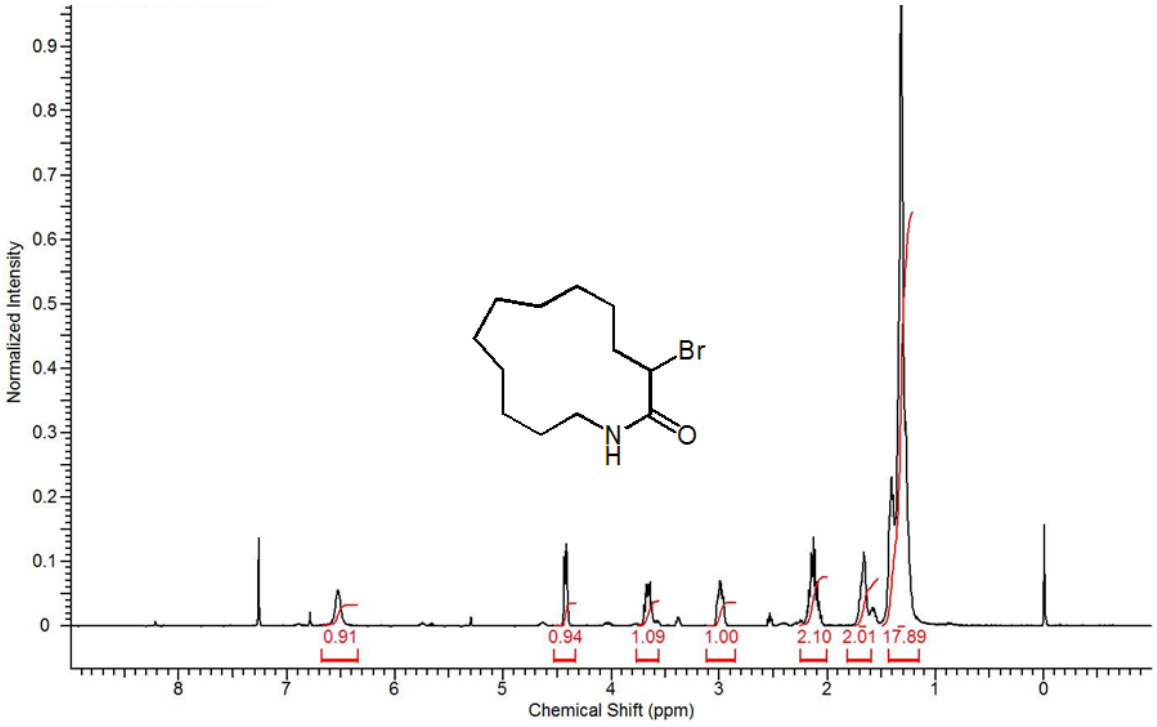
Spectra **1-150** Proton NMR spectrum of **3d1.**



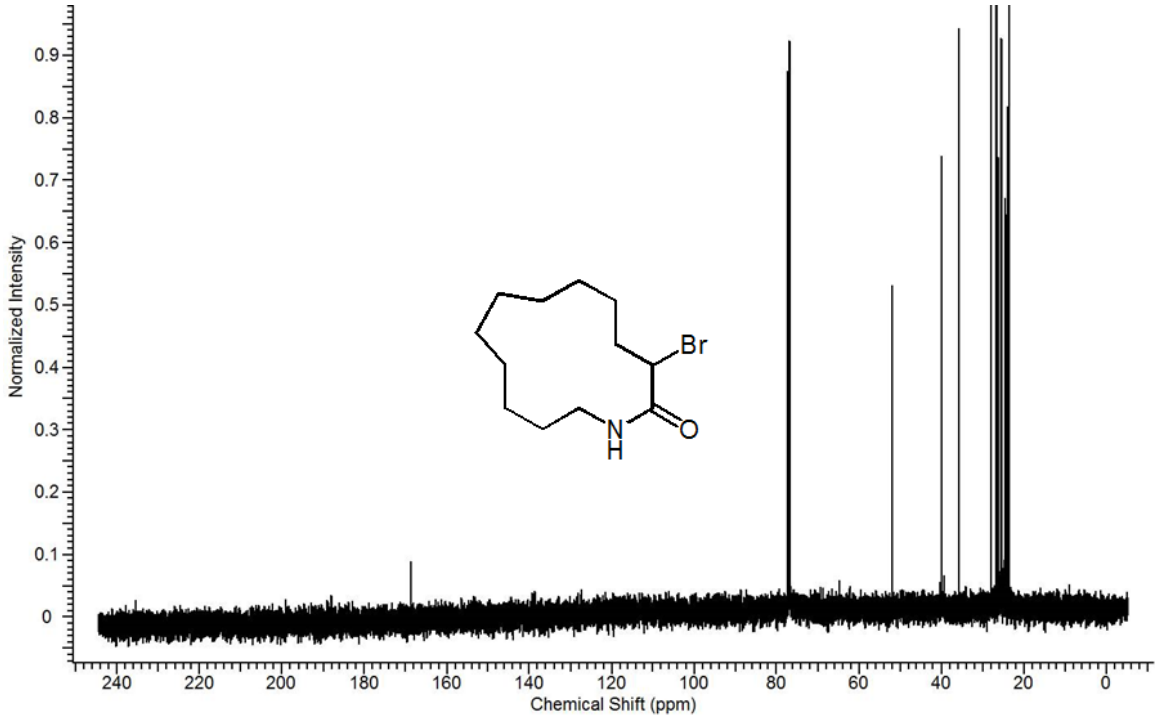
Spectra **1-151** Carbon NMR spectrum of **3d1.**



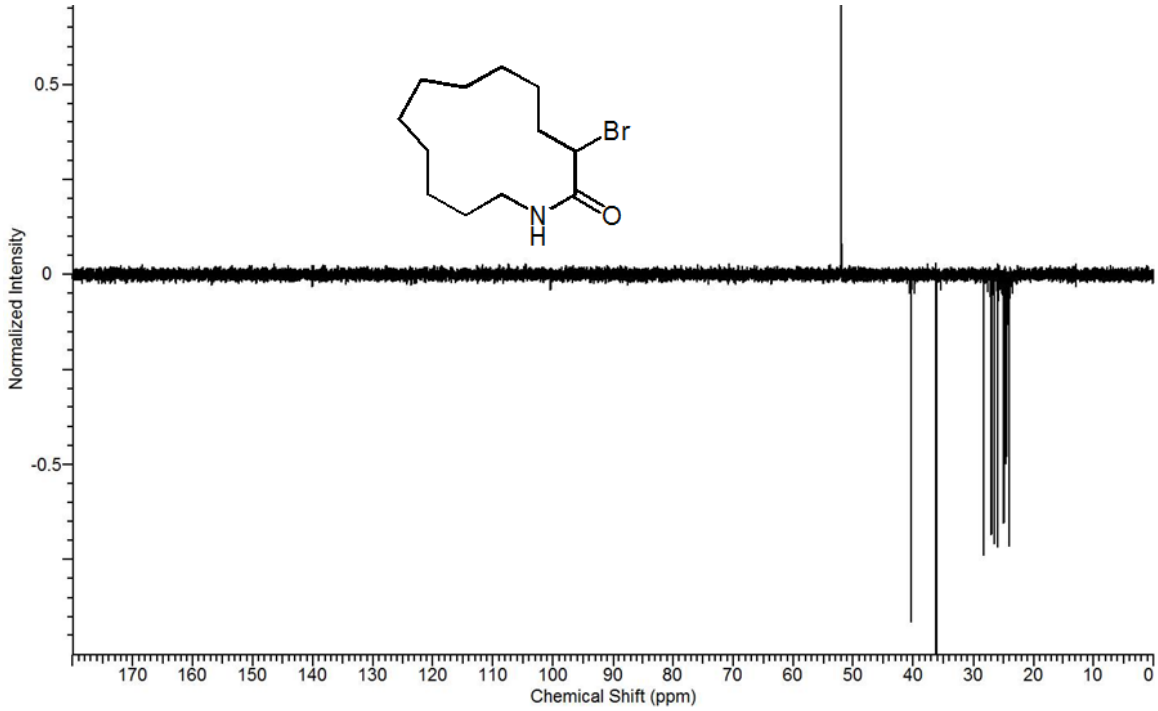
Spectra **1-152** DEPT-135 NMR spectrum of **3d1.**



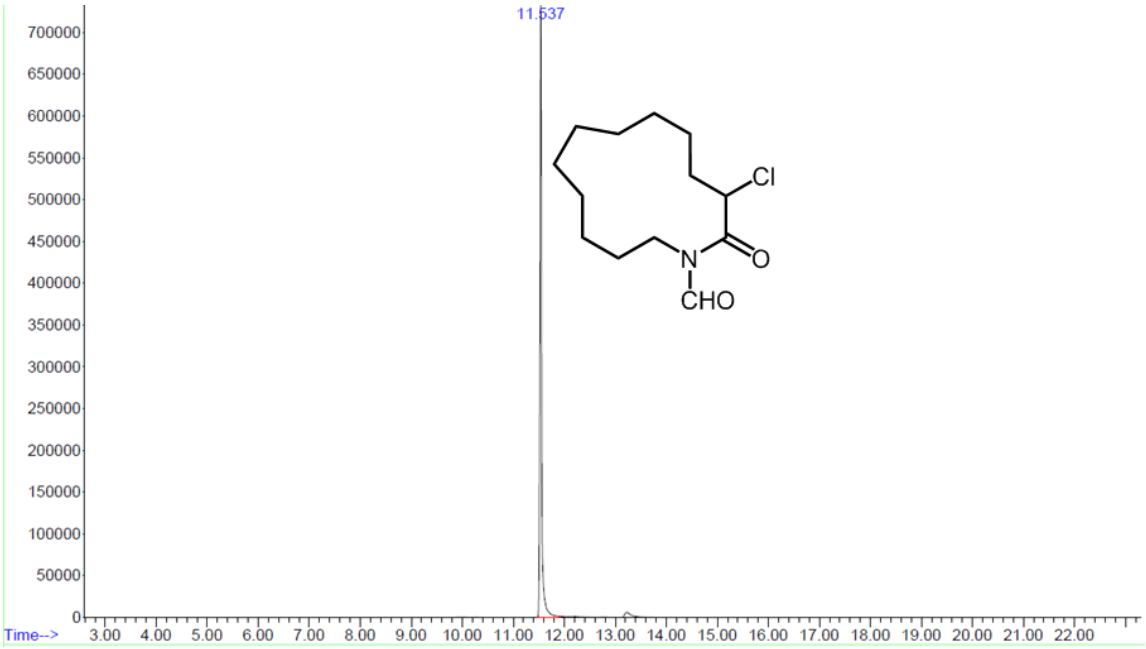
Spectra **1-153** Proton NMR spectrum of **3d2.**



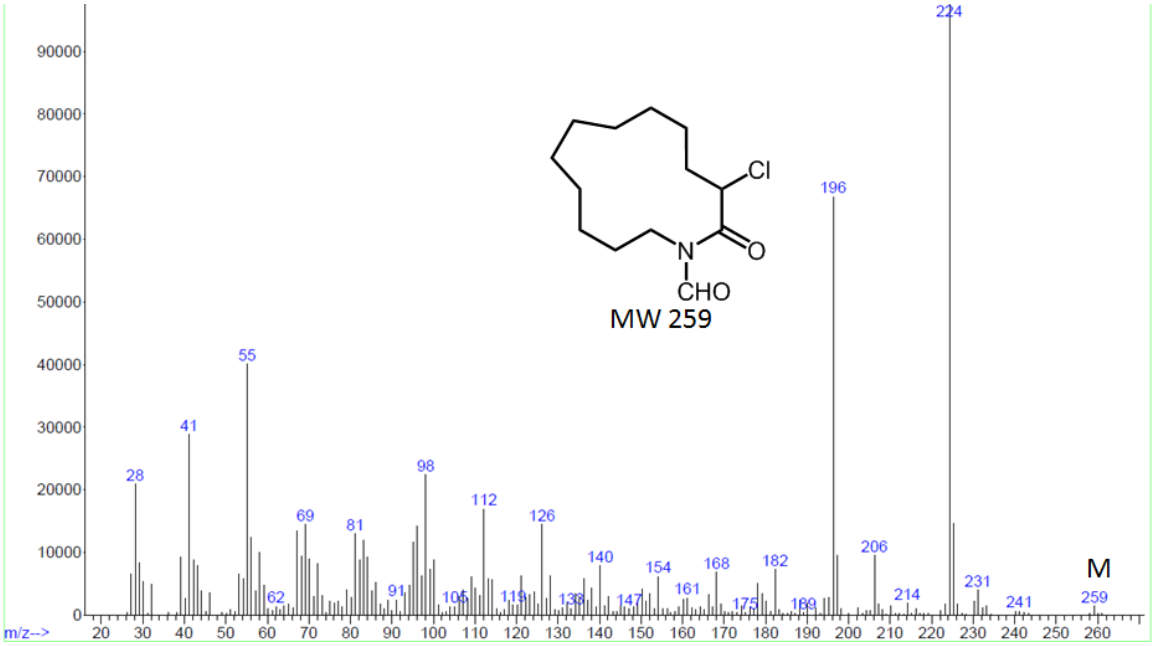
Spectra **1-154** Carbon NMRspectrum of **3d2.**



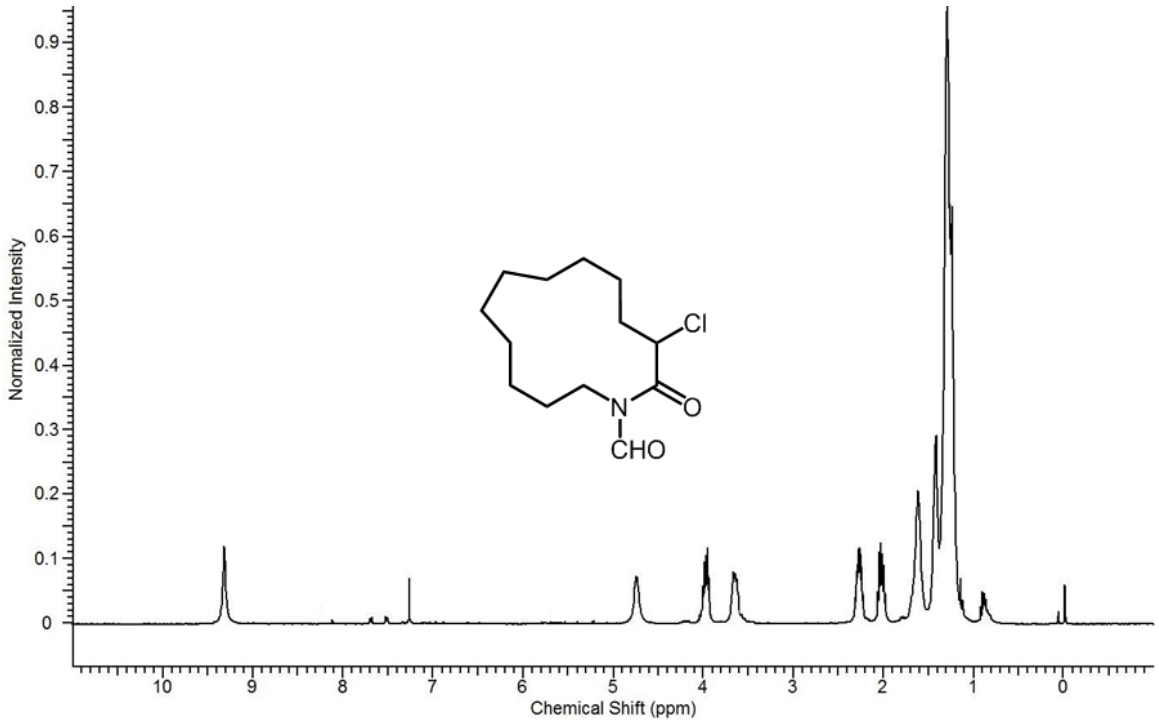
Spectra **1-155** DEPT-135 NMR spectrum of **3d2.**



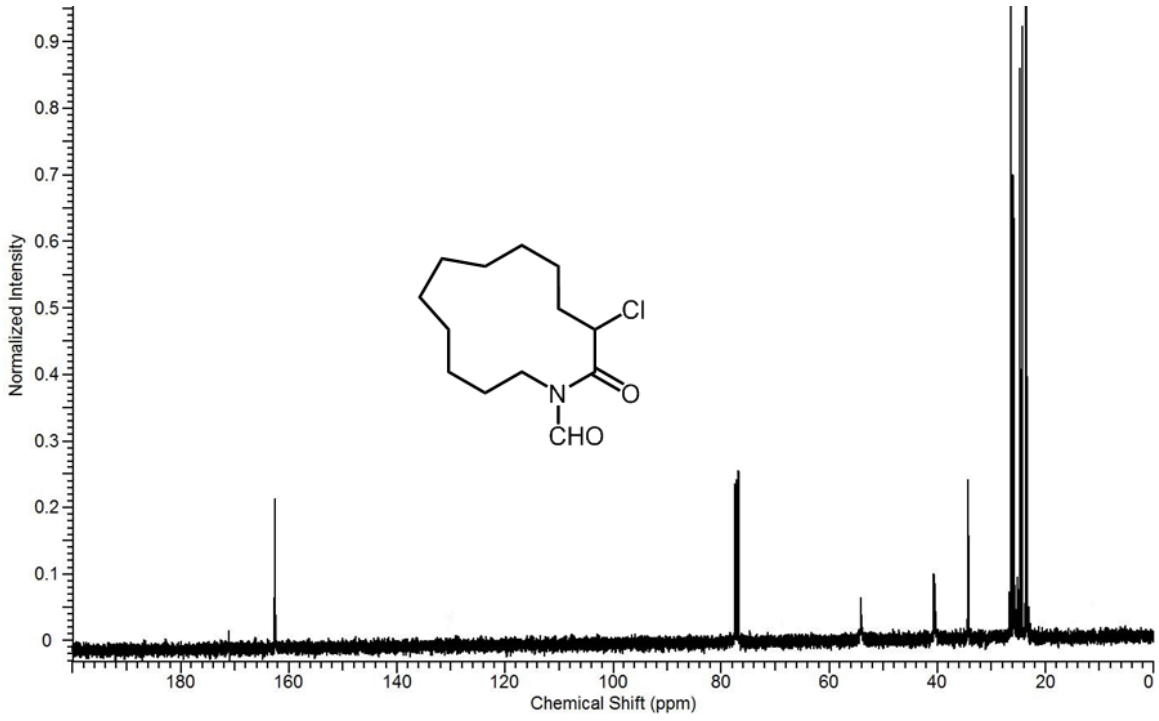
Spectra **1-156** GC spectrum of **3d3.**



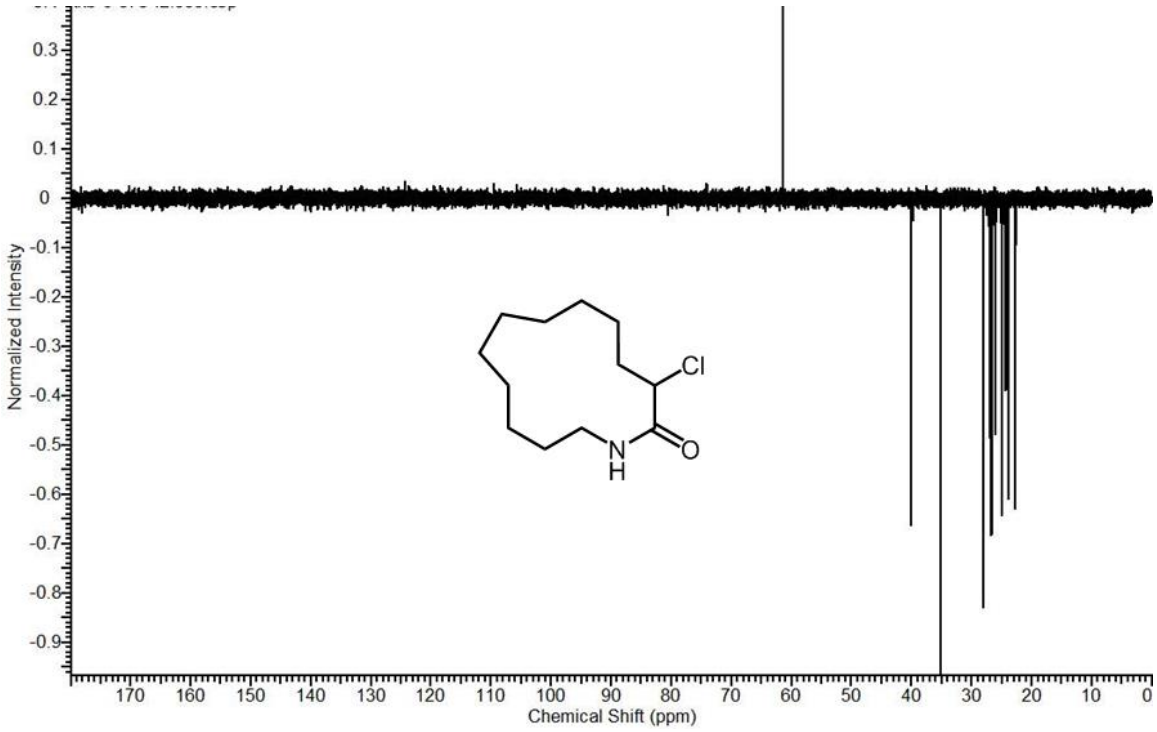
Spectra **1-157** MS spectrum of **3d3.**



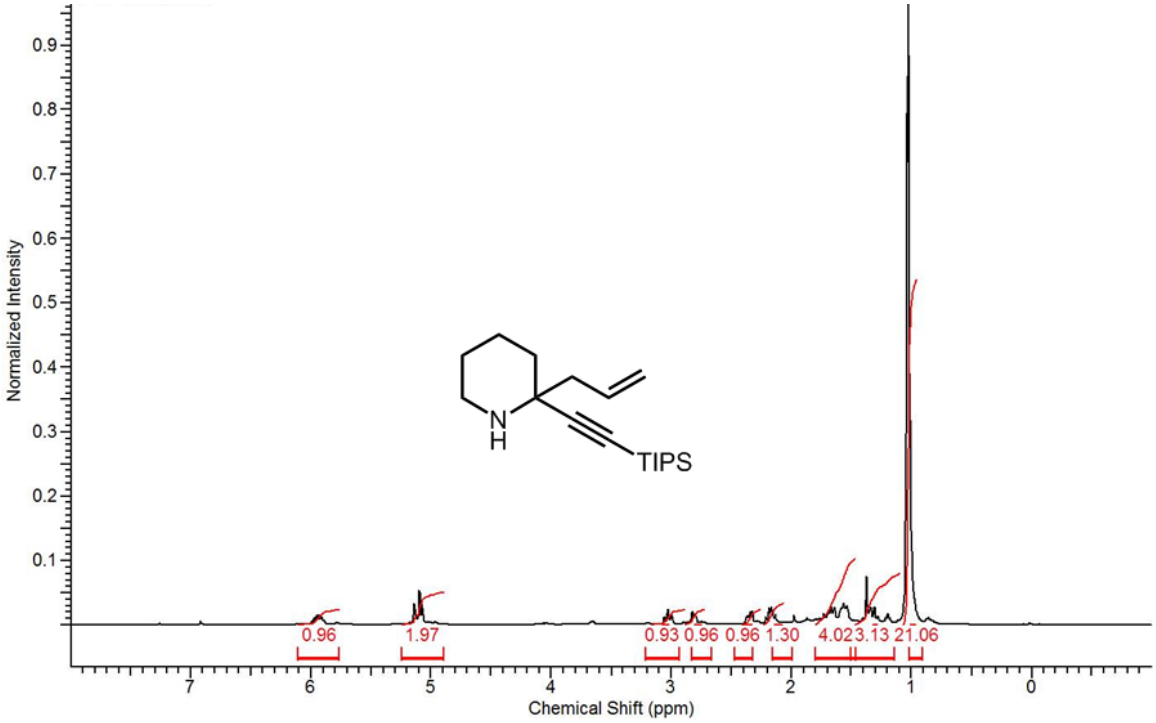
Spectra **1-158** Proton NMR spectrum of **3d3.**



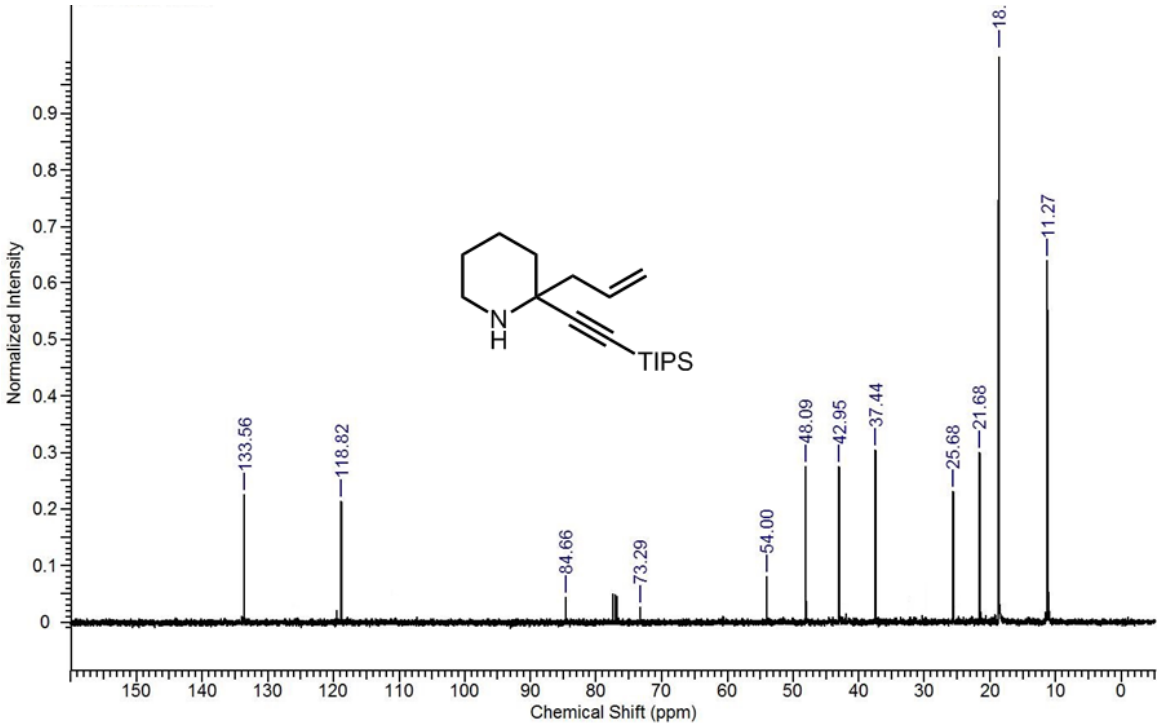
Spectra **1-159** Carbon NMR spectrum of **3d3.**



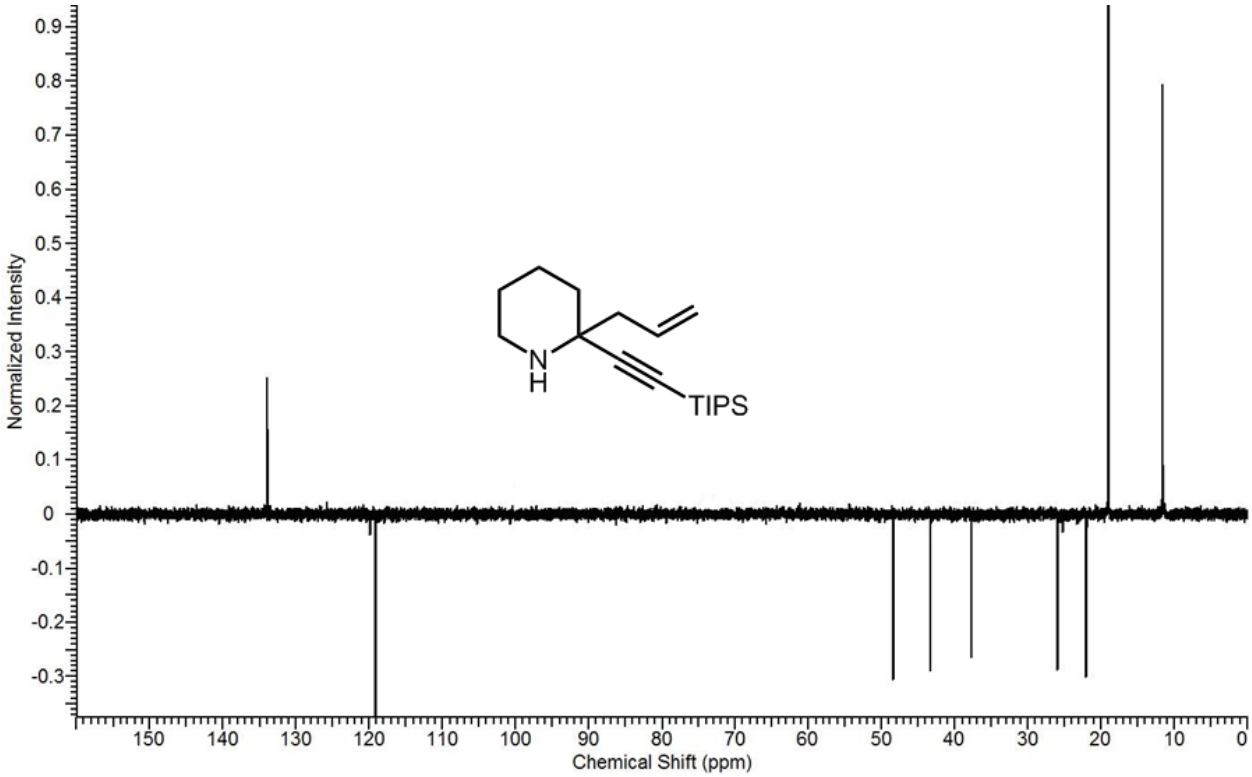
Spectra **1-160** DEPT-135 NMR spectrum of **3d3.**



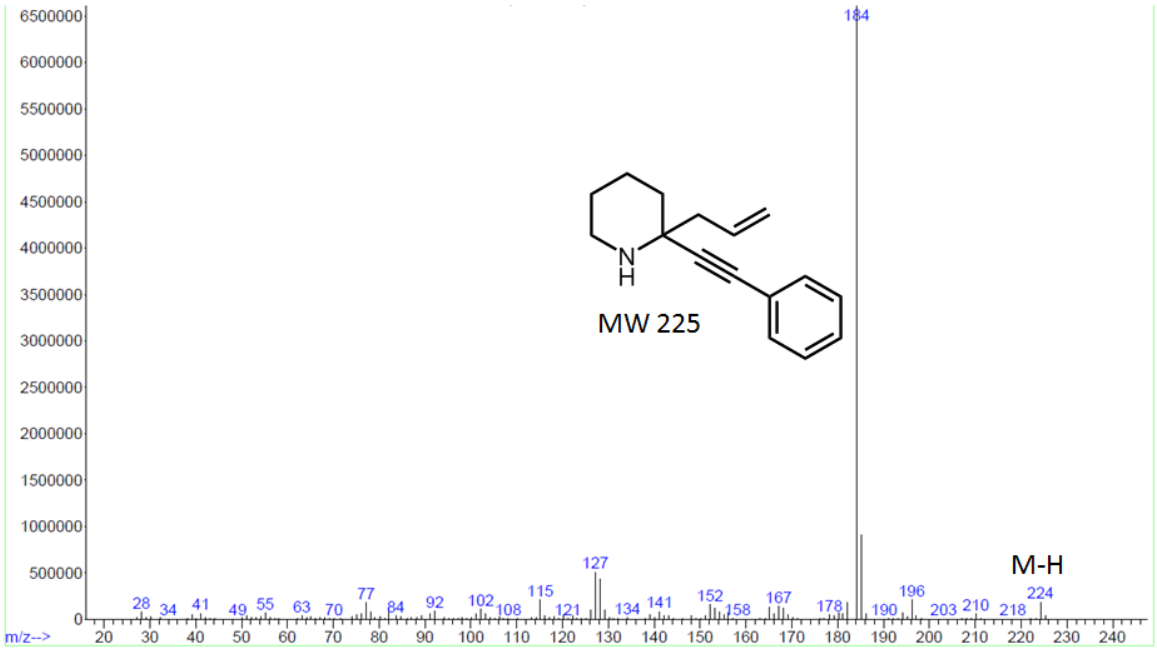
Spectra **1-1** Proton NMR spectrum of **1a.**



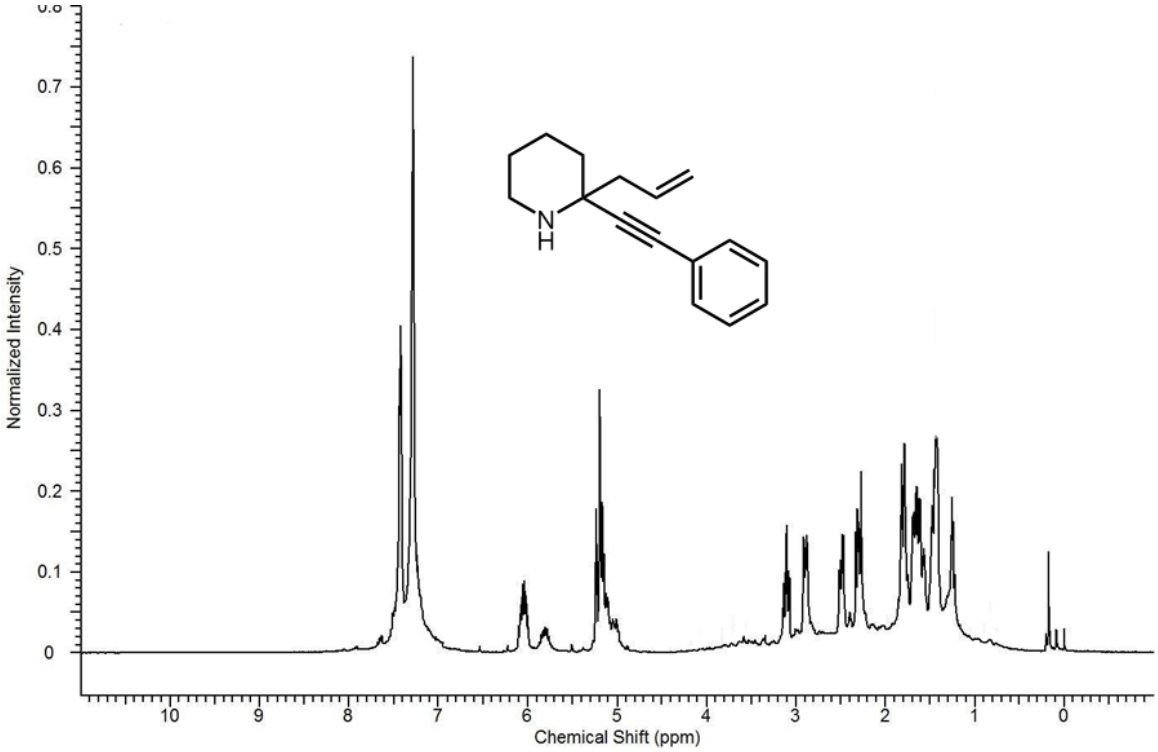
Spectra **1-2** Carbon NMR spectrum of **1a.**



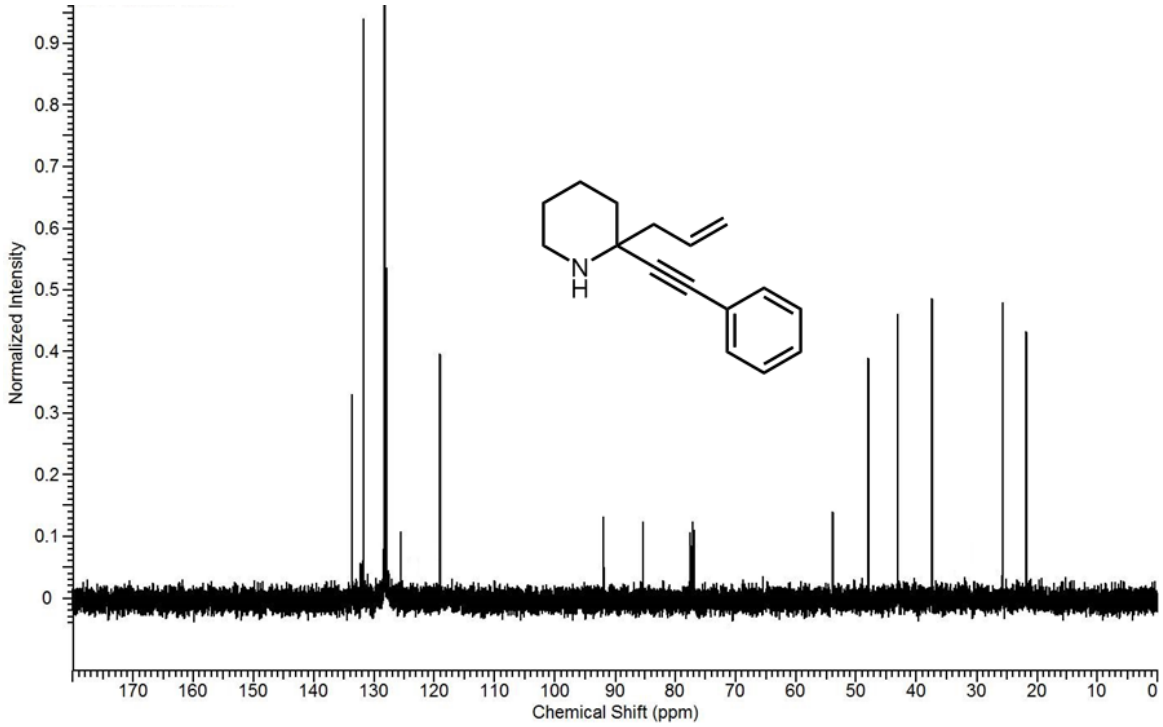
Spectra **1-3** DEPT-135 NMR spectrum of **1a.**



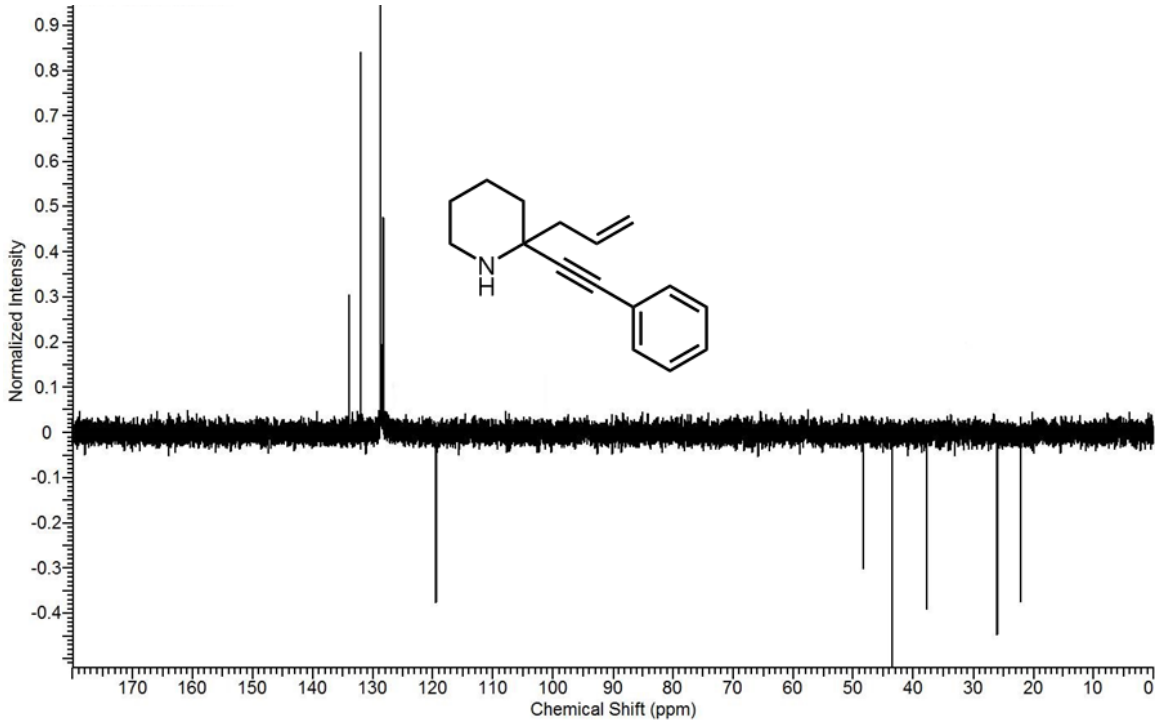
Spectra **1-4** MS spectrum of **1b.**



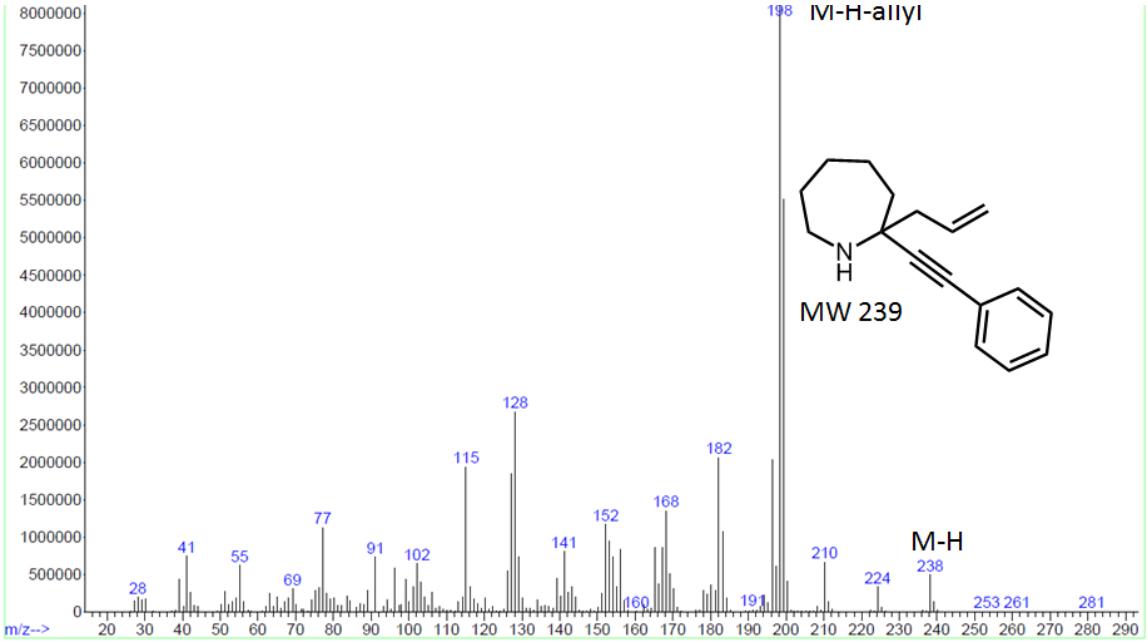
Spectra **1-5** Proton NMR spectrum of **1b.**



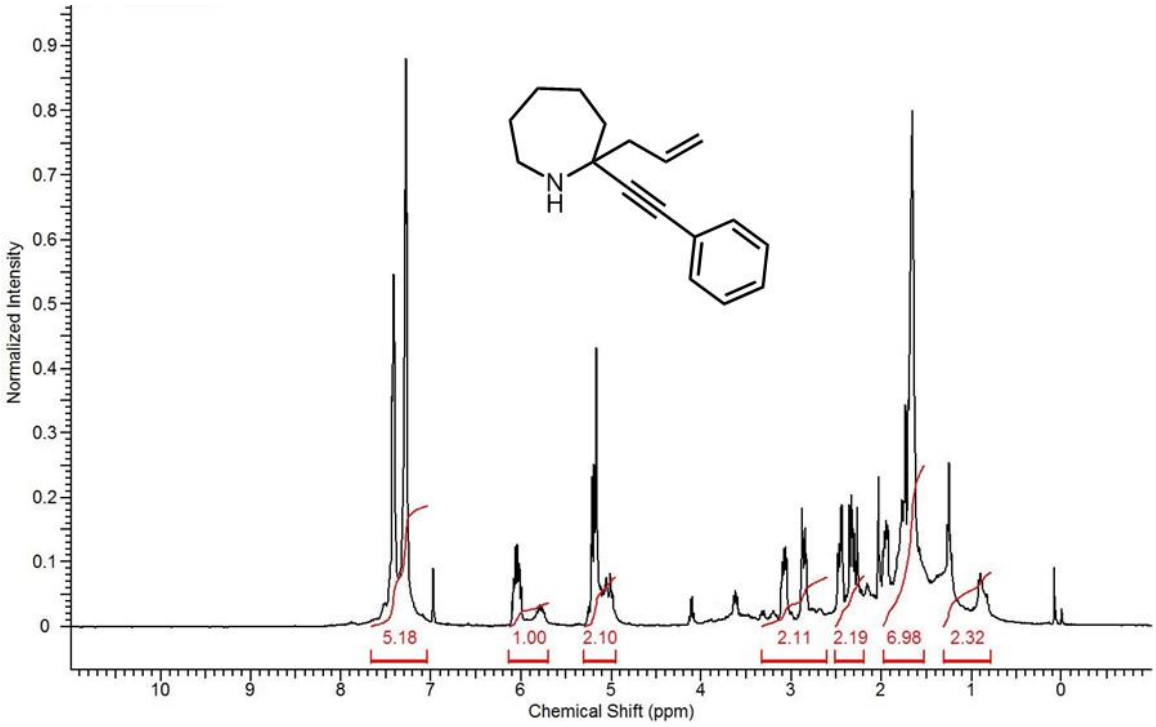
Spectra **1-6** Carbon NMR spectrum of **1b.**



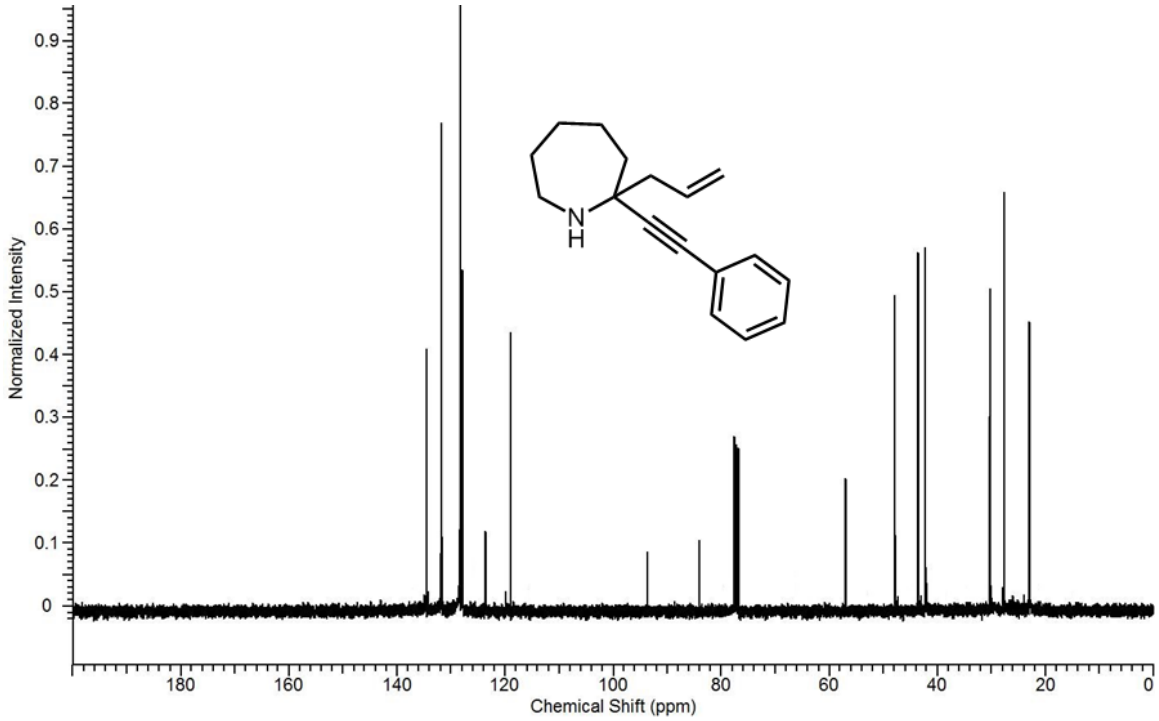
Spectra **1-7** DEPT-135 NMR spectrum of **1b.**



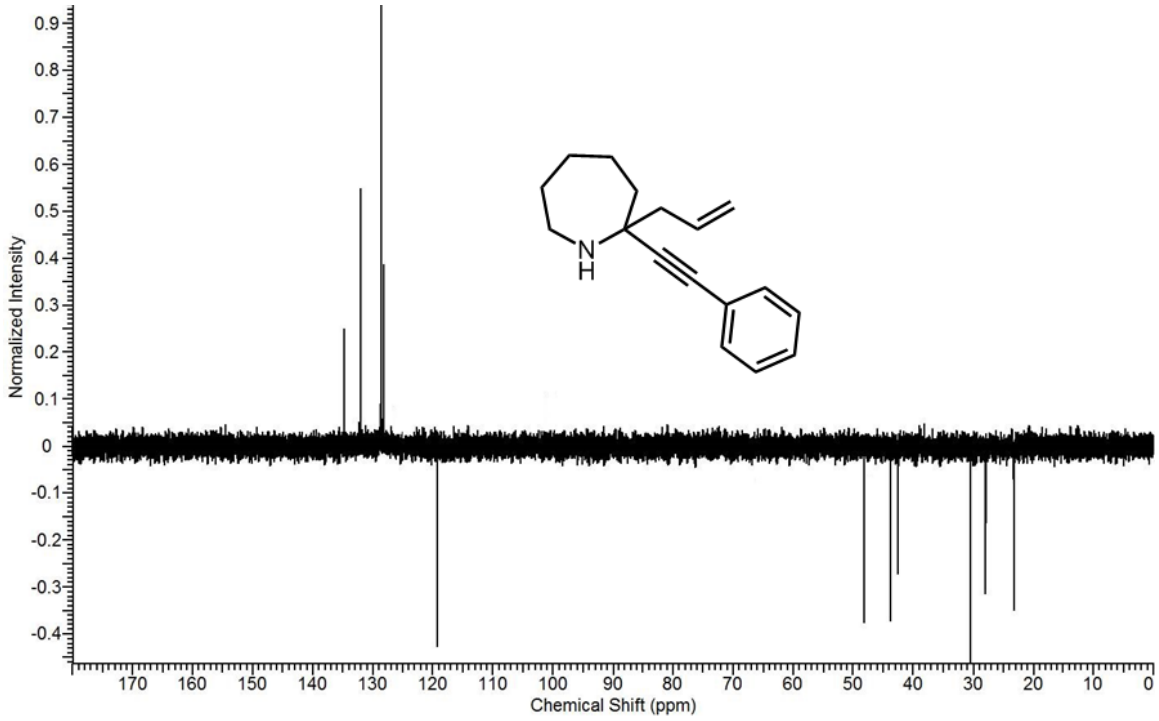
Spectra **1-8** MS spectrum of **1c.**



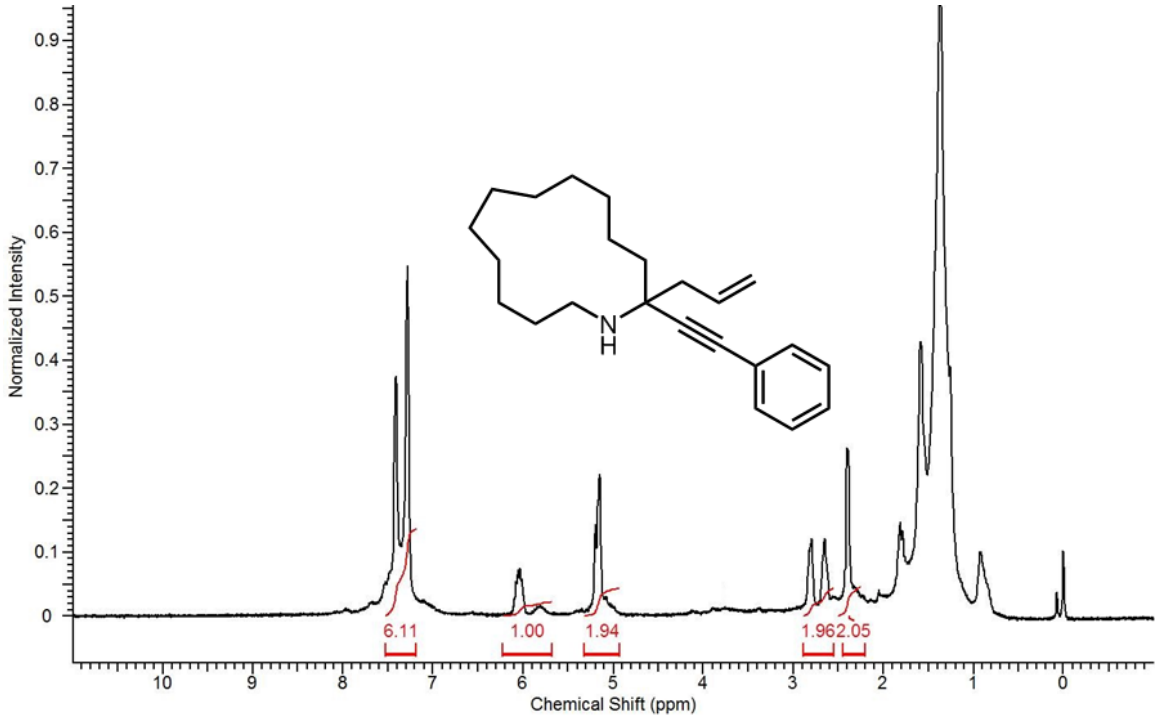
Spectra **1-9** Proton NMR spectrum of **1c.**



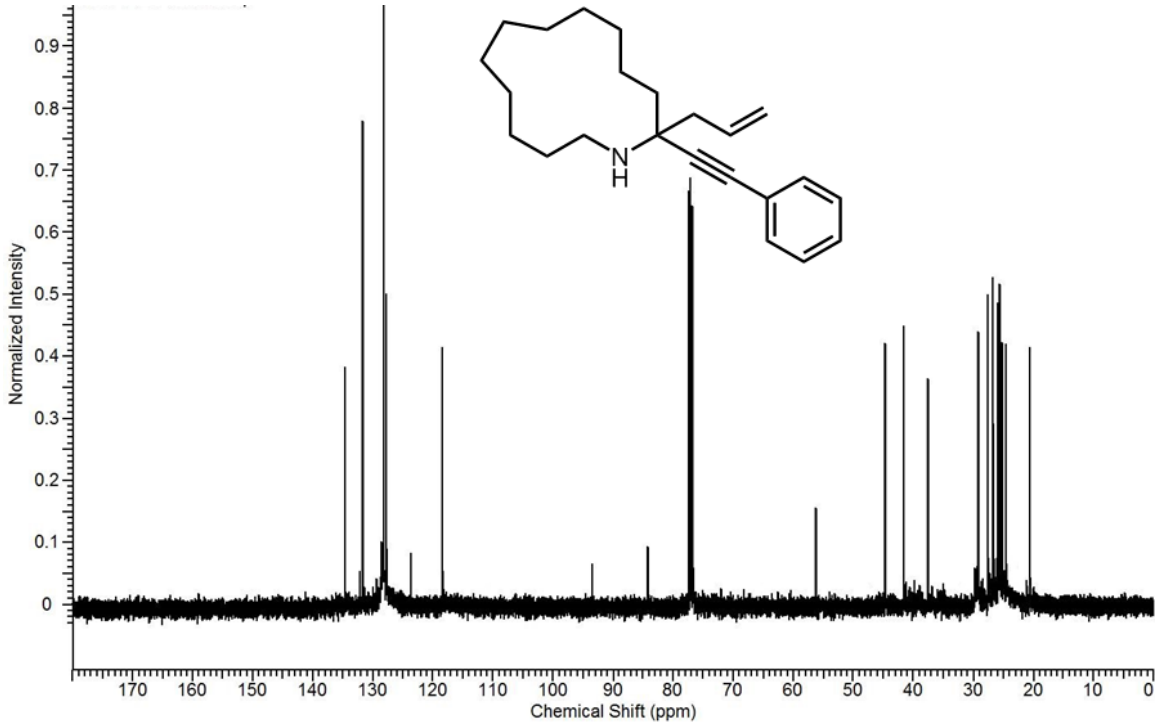
Spectra **1-10** Carbon NMR spectrum of **1c.**



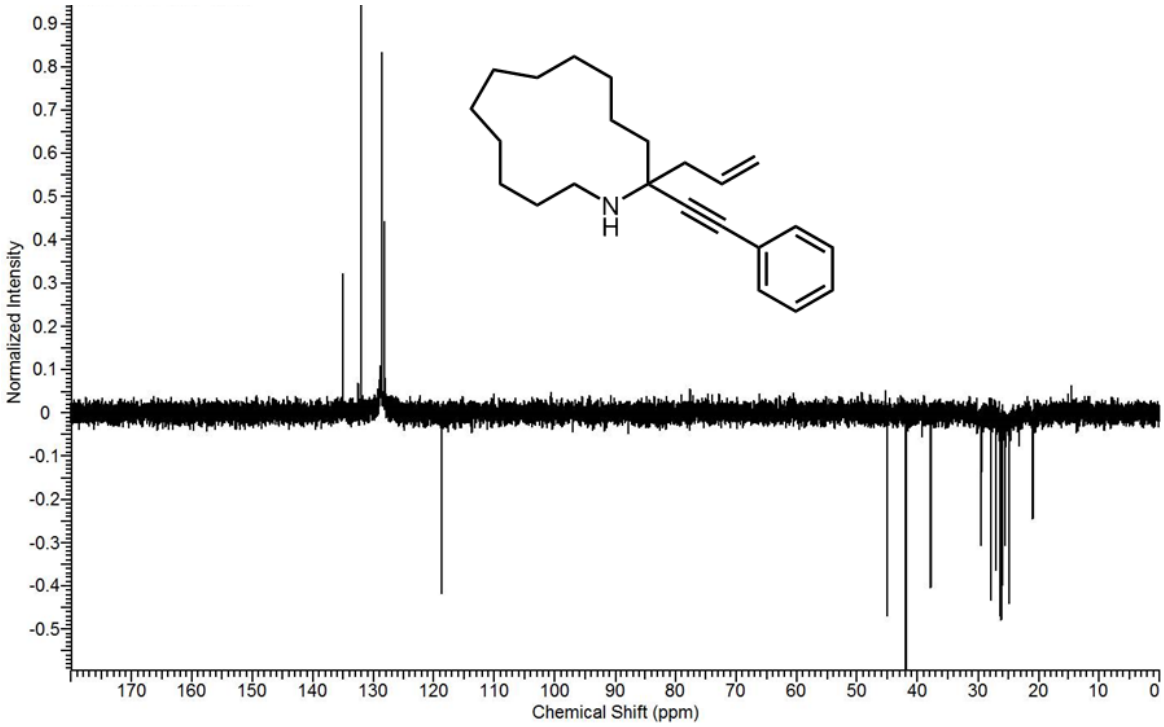
Spectra **1-11** DEPT-135 NMR spectrum of **1c.**



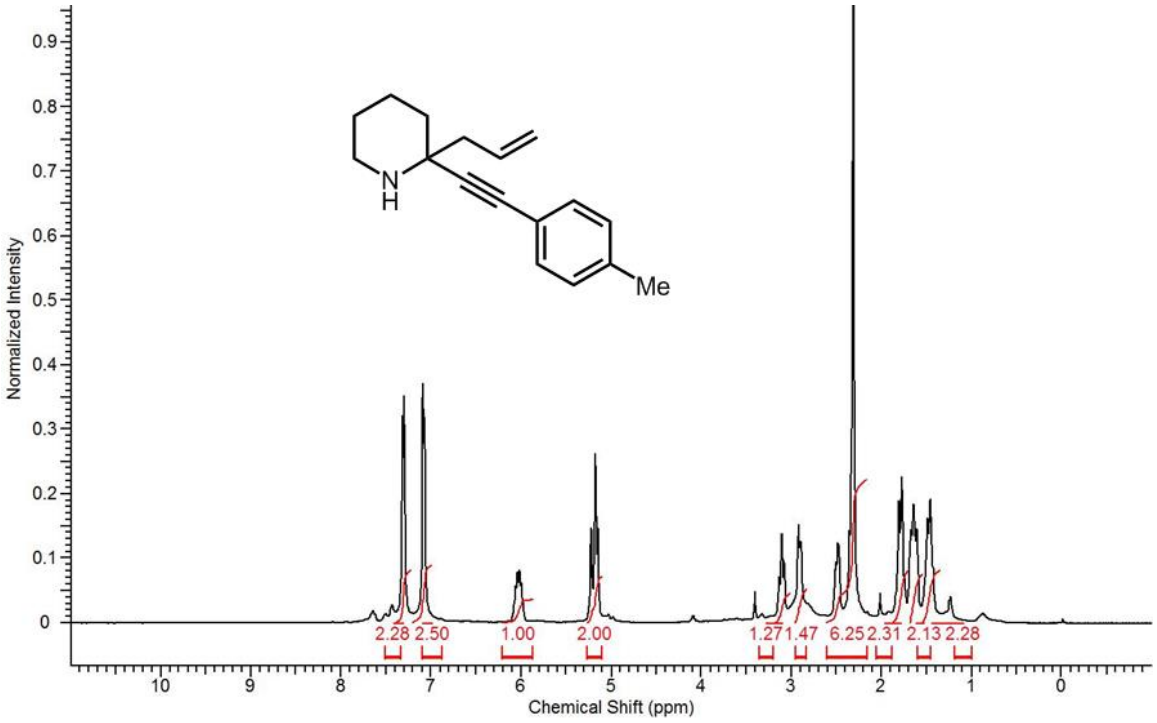
Spectra **1-12** Proton NMR spectrum of **1d.**



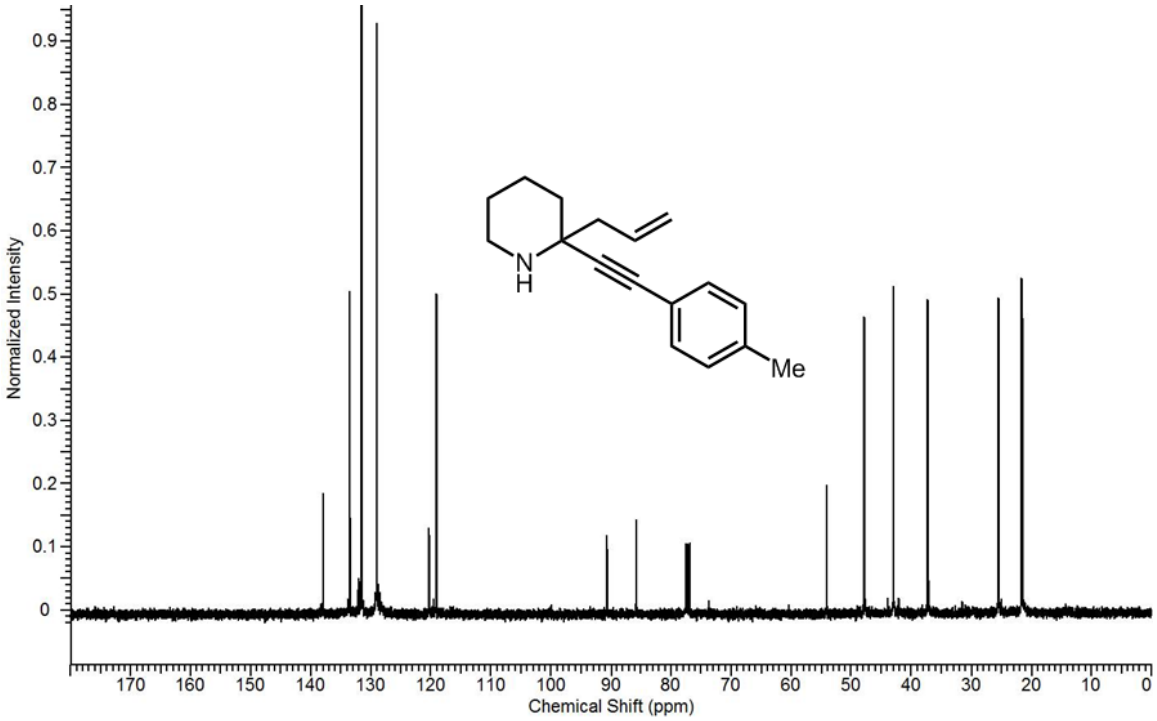
Spectra **1-13** Carbon NMR spectrum of **1d.**



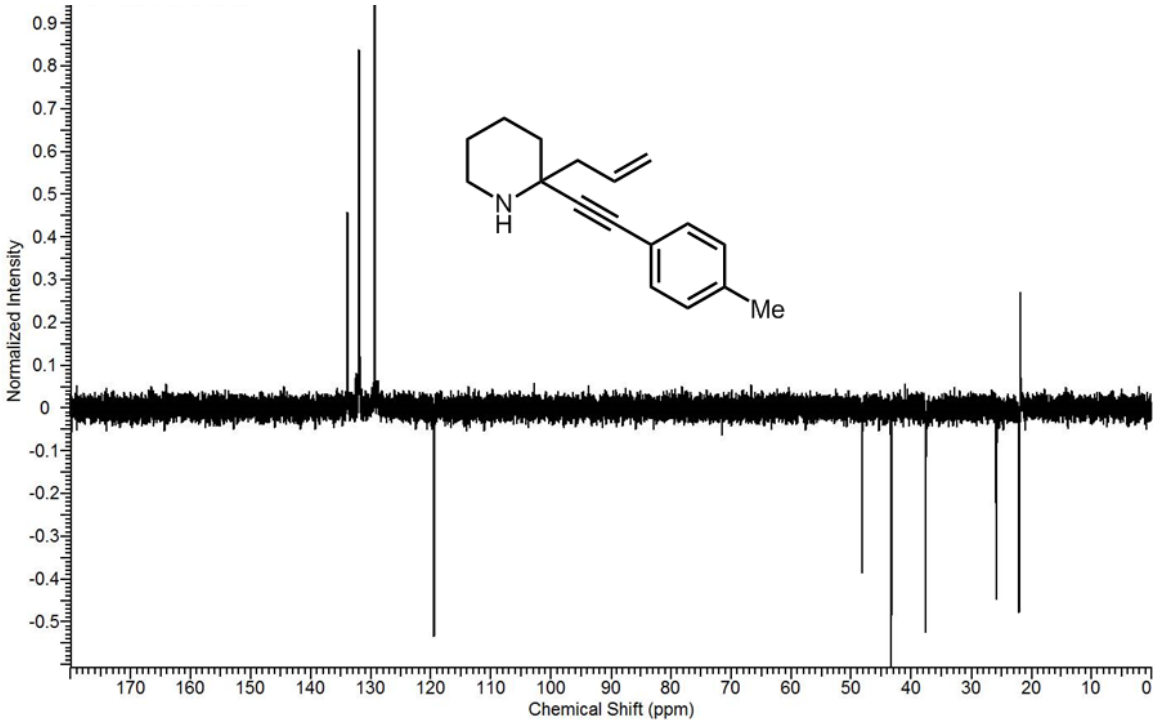
Spectra **1-14** DEPT-135 NMR spectrum of **1d.**



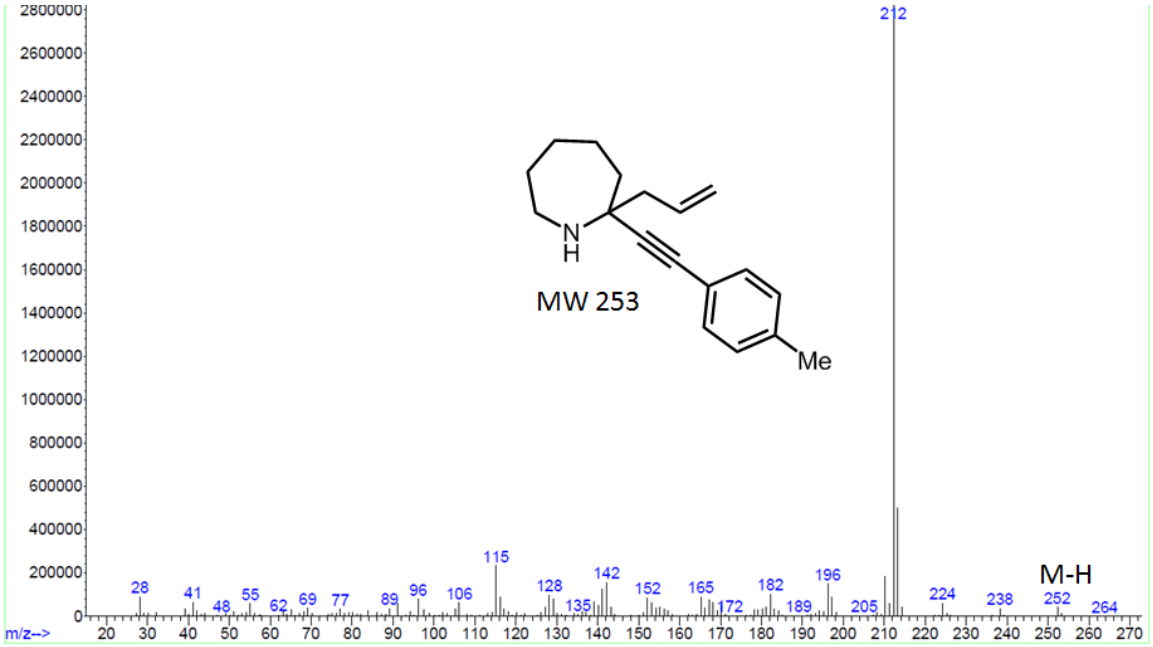
Spectra **1-15** Proton NMR spectrum of **1e.**



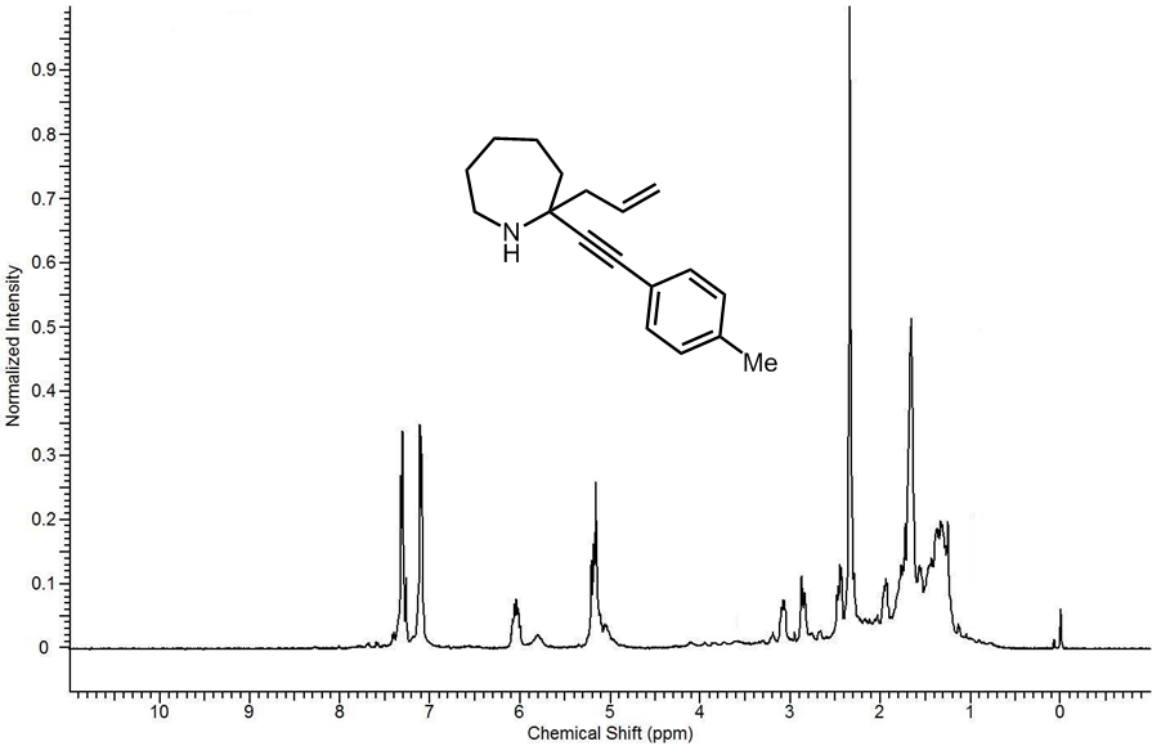
Spectra **1-16** Carbon NMR spectrum of **1e.**



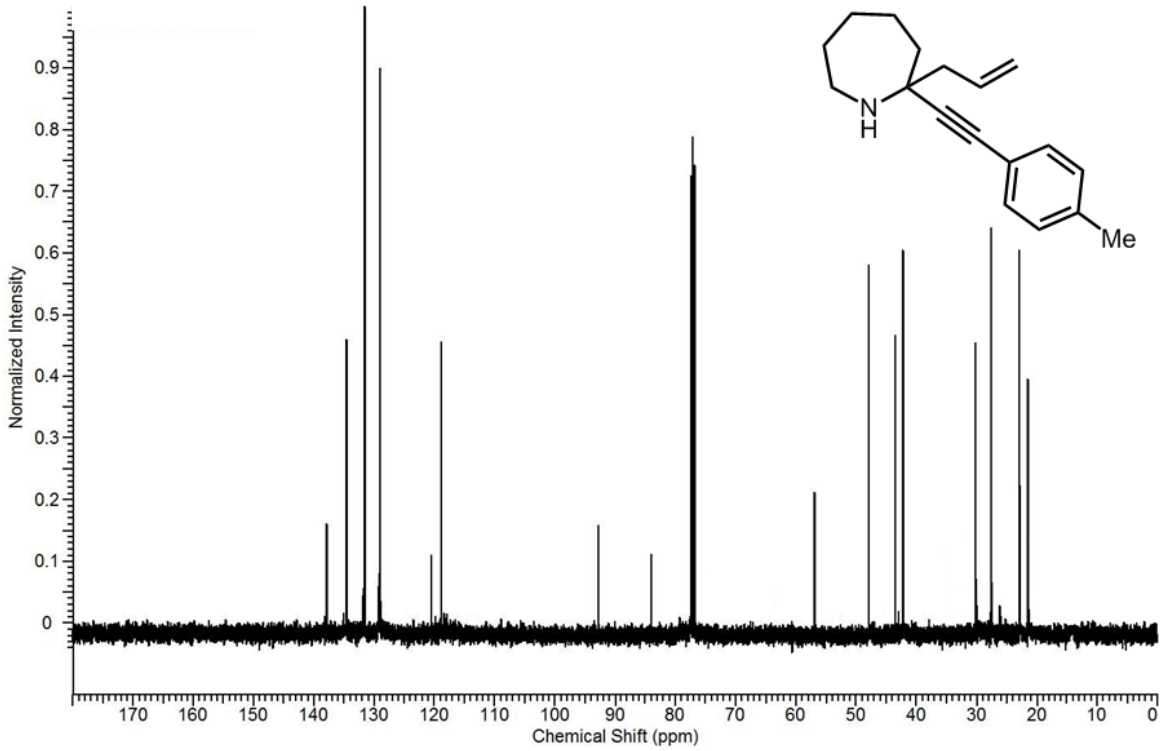
Spectra **1-17** DEPT-135 NMR spectrum of **1e.**



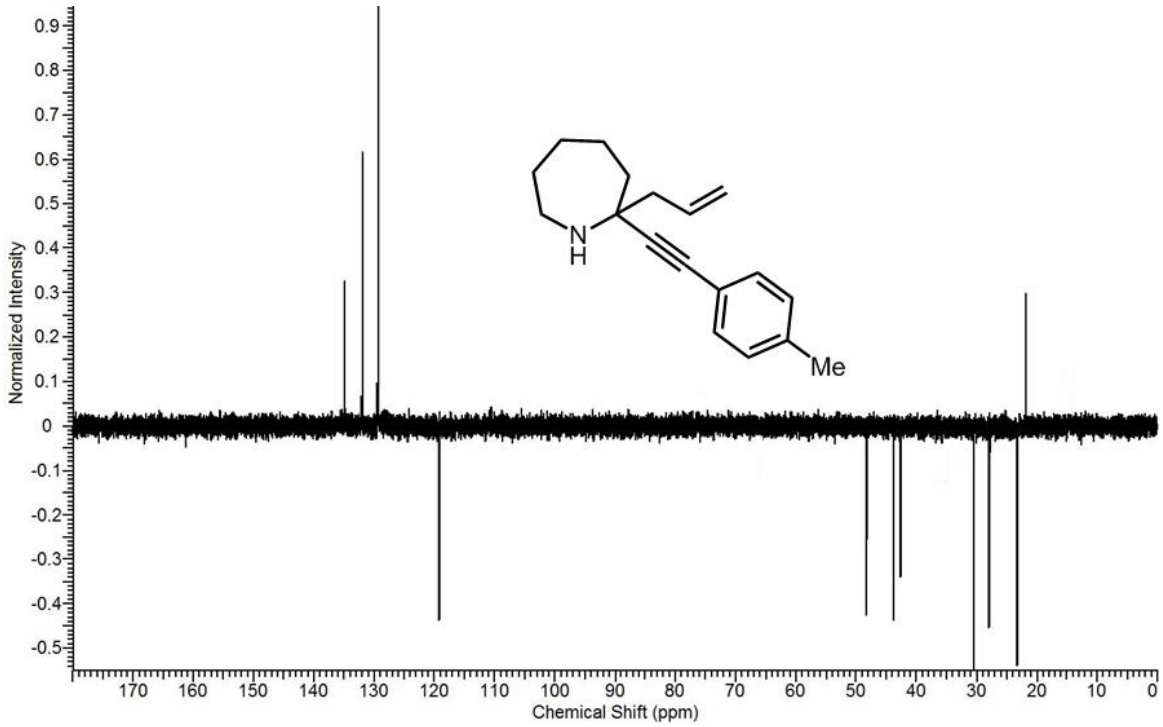
Spectra **1-18** MS spectrum of **1f.**



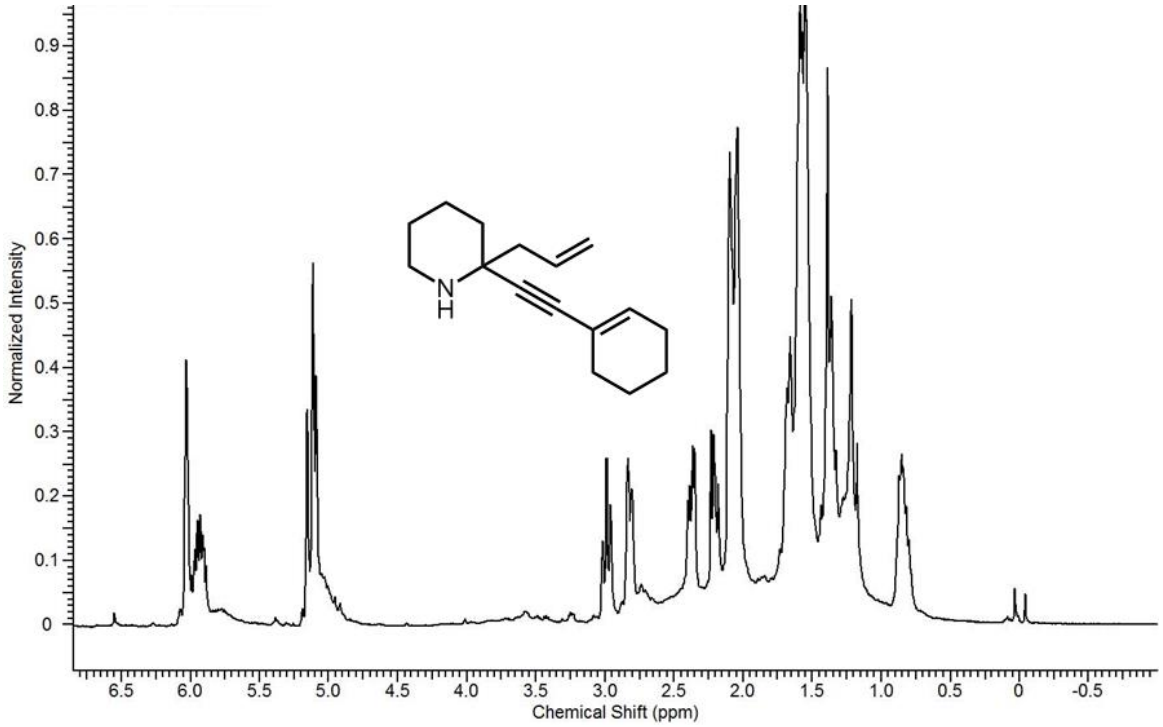
Spectra **1-19** Proton NMR spectrum of **1f.**



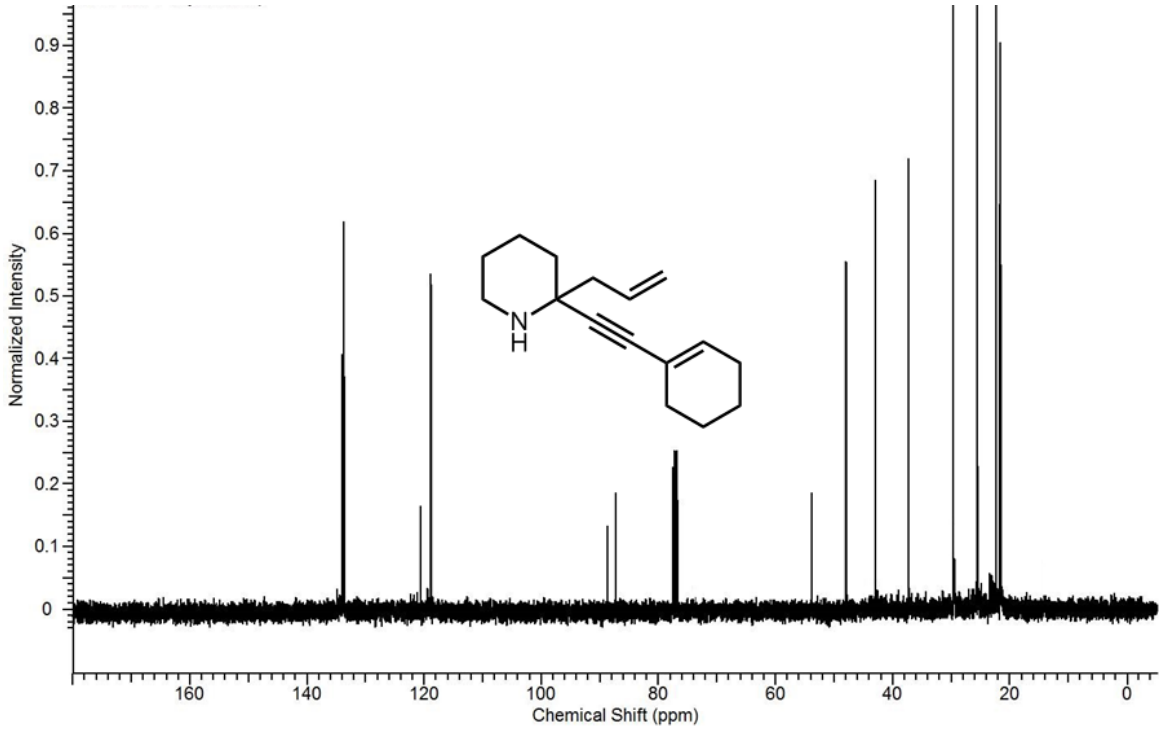
Spectra **1-20** Carbon NMR spectrum of **1f.**



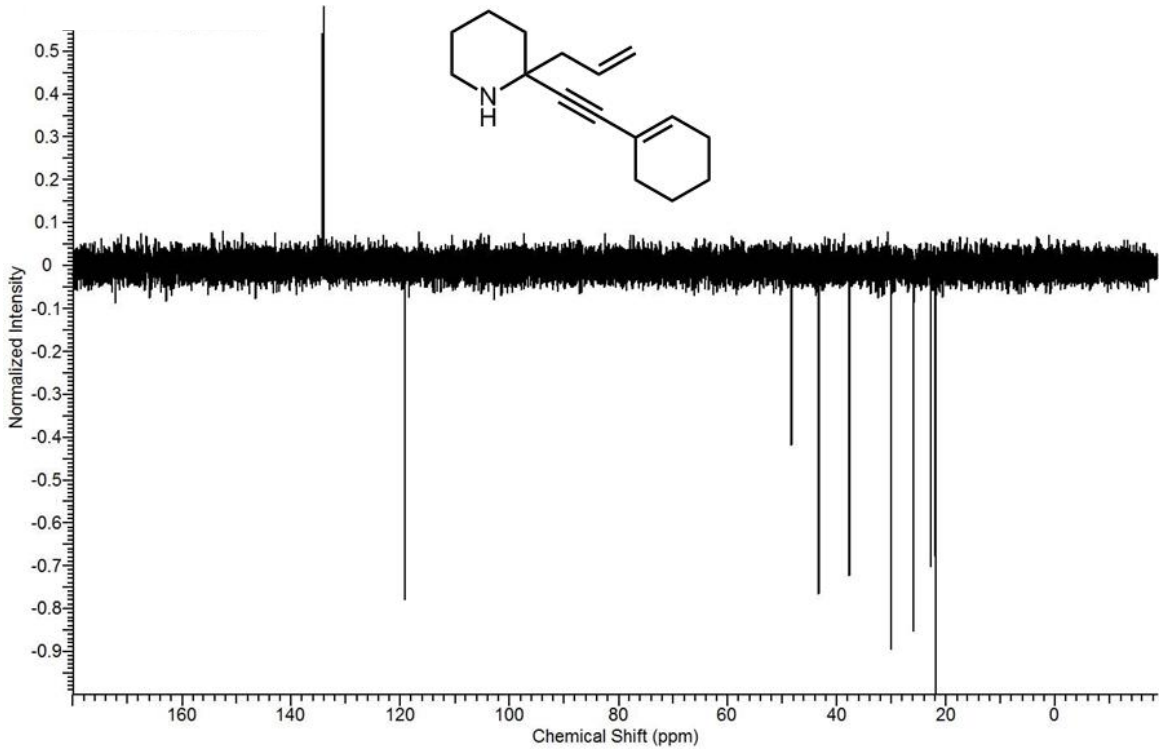
Spectra **1-21** DEPT-135 NMR spectrum of **1f.**



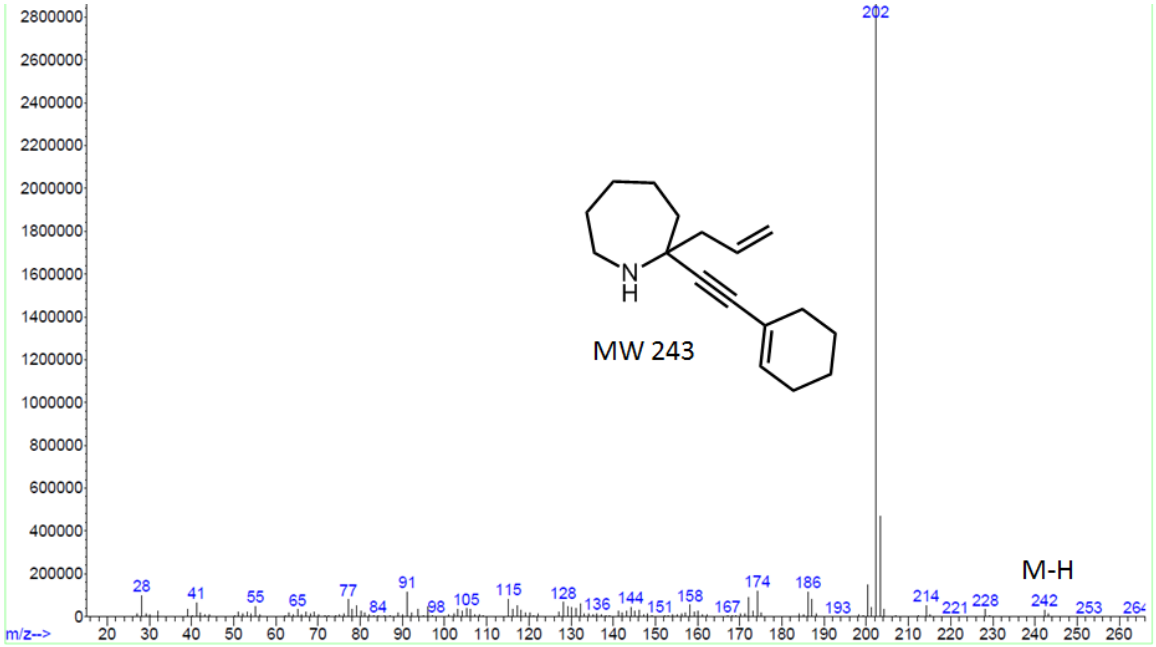
Spectra **1-22** Proton NMR spectrum of **1g.**



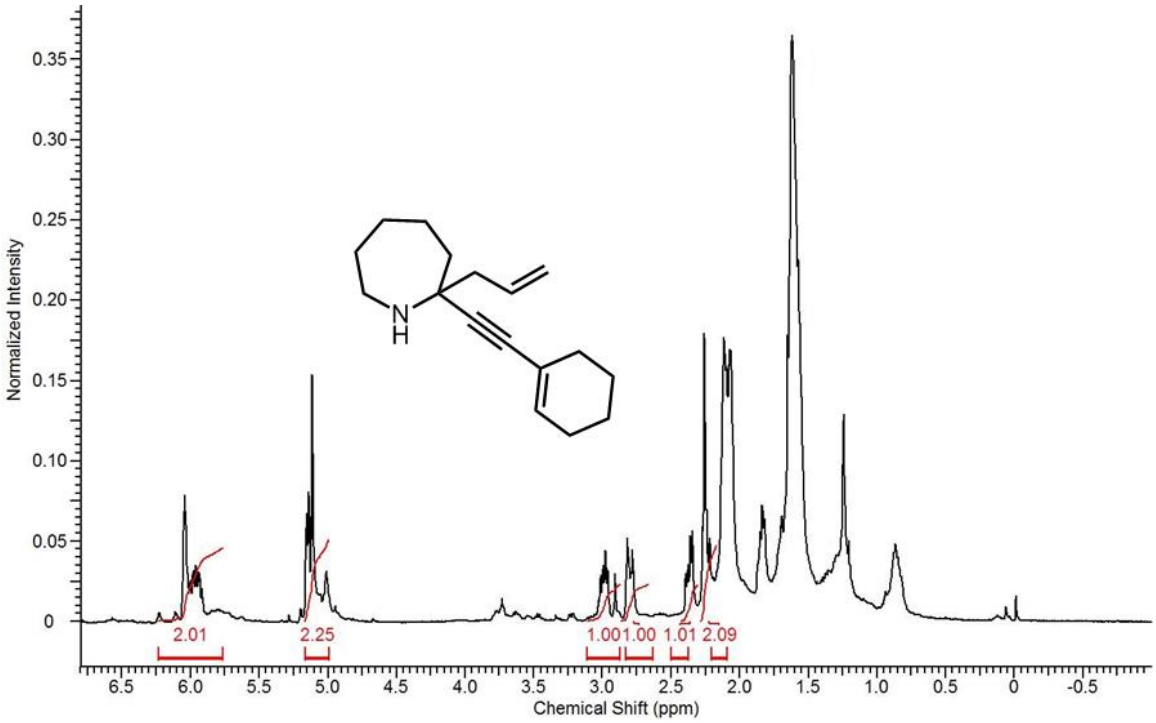
Spectra **1-23** Carbon NMR spectrum of **1g.**



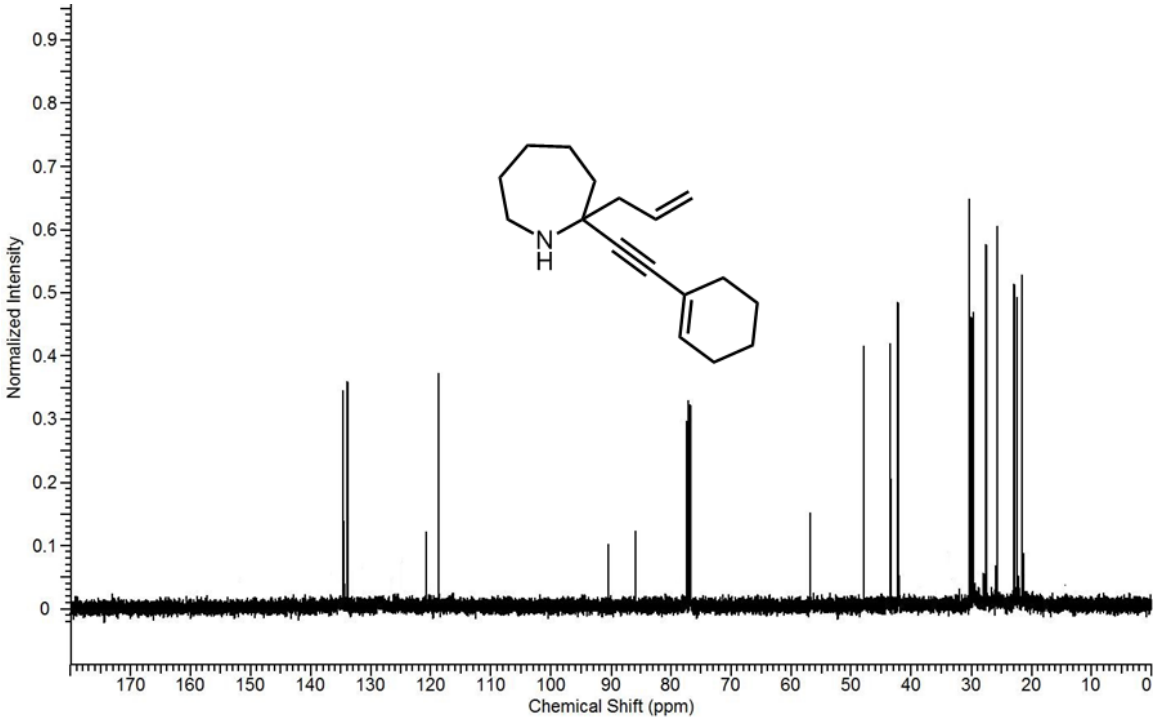
Spectra **1-24** DEPT-135 NMR spectrum of **1g.**



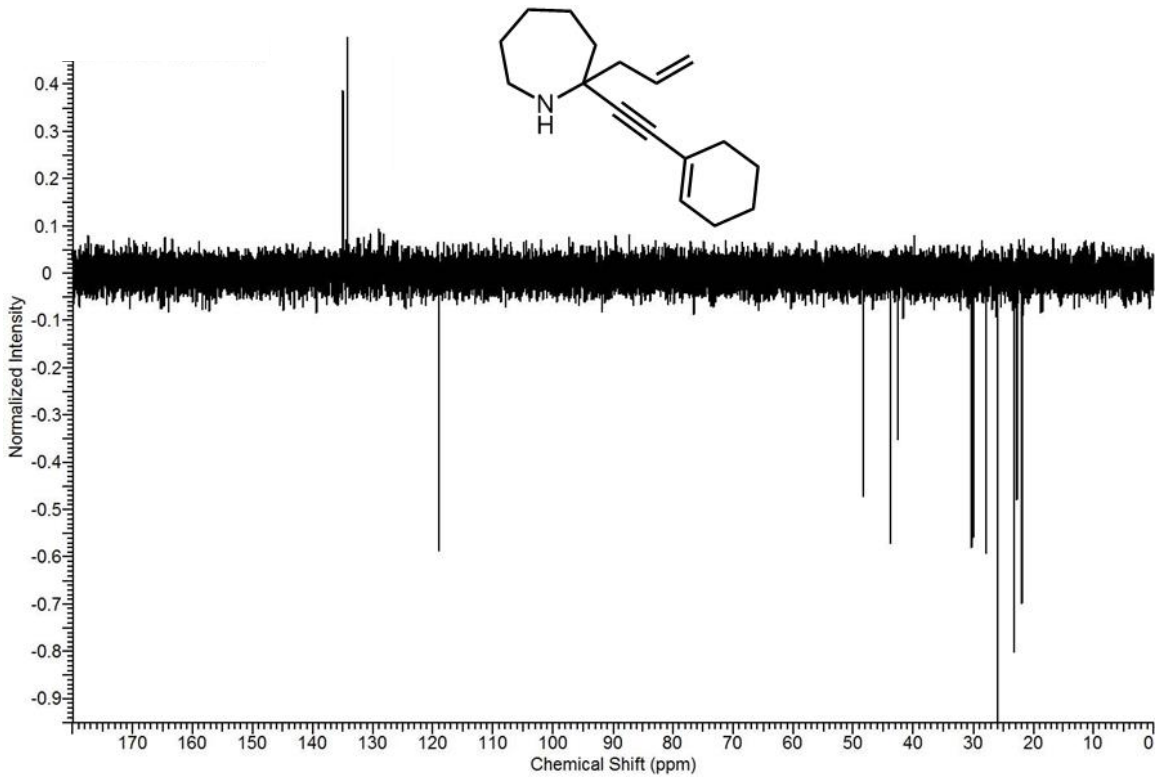
Spectra **1-25** MS spectrum of **1h.**



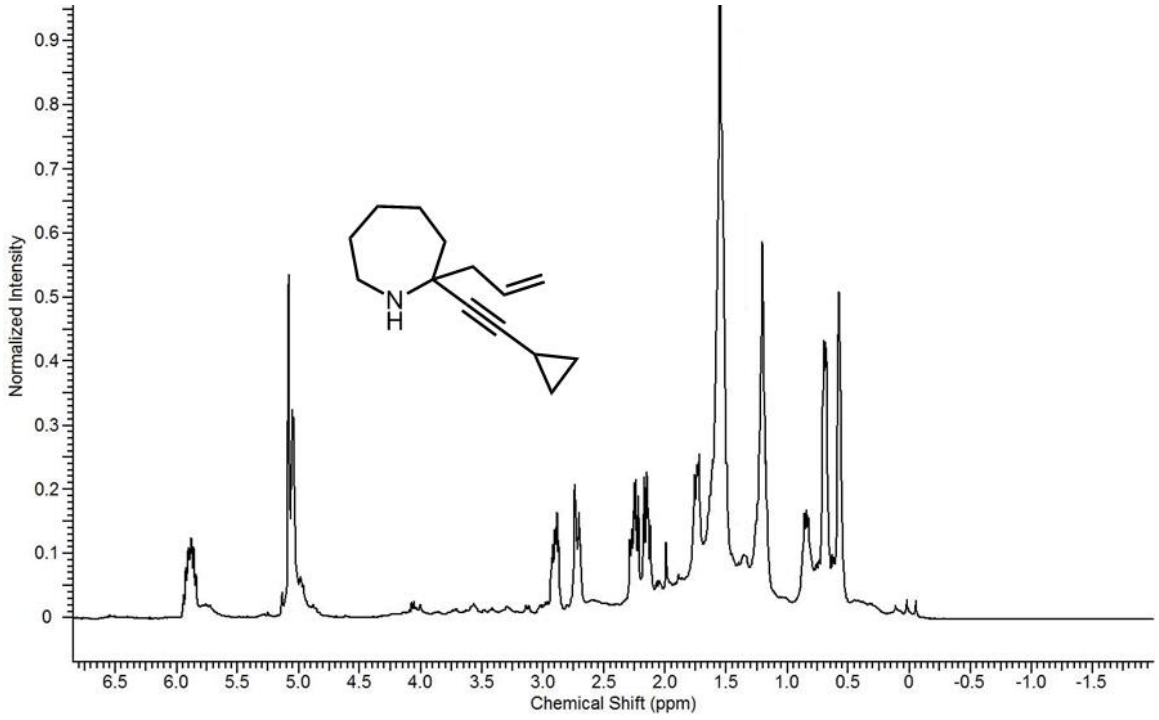
Spectra **1-26** Proton NMR spectrum of **1h.**



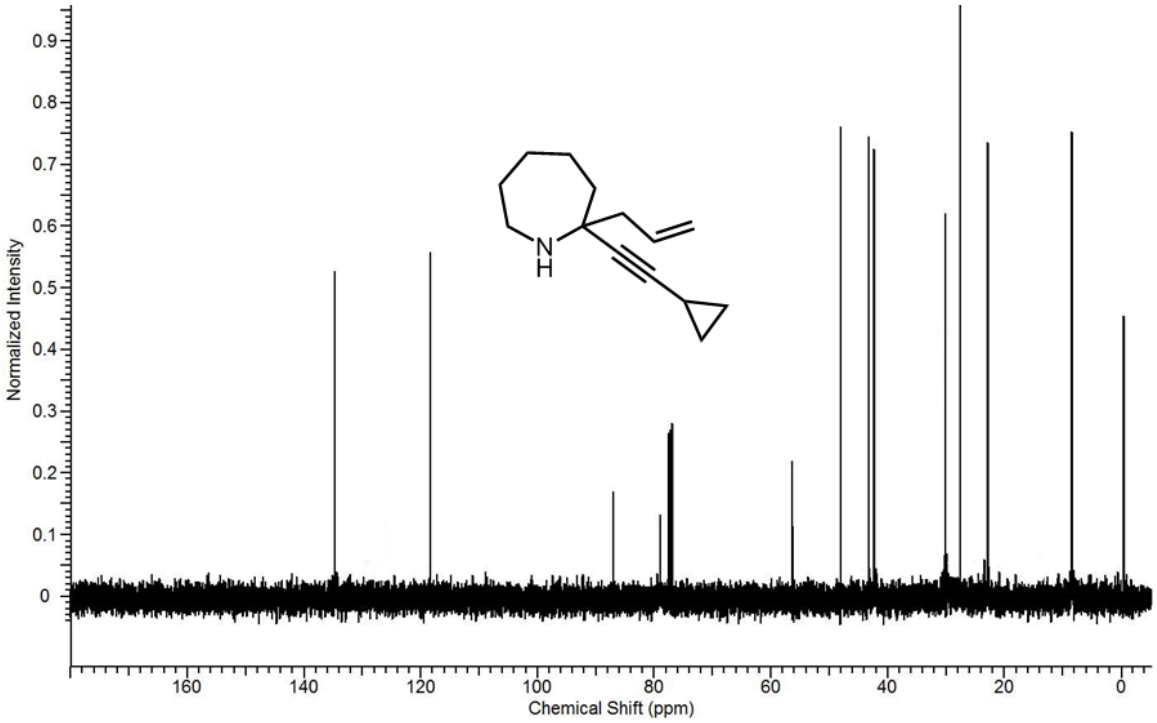
Spectra **1-27** Carbon NMR spectrum of **1h.**



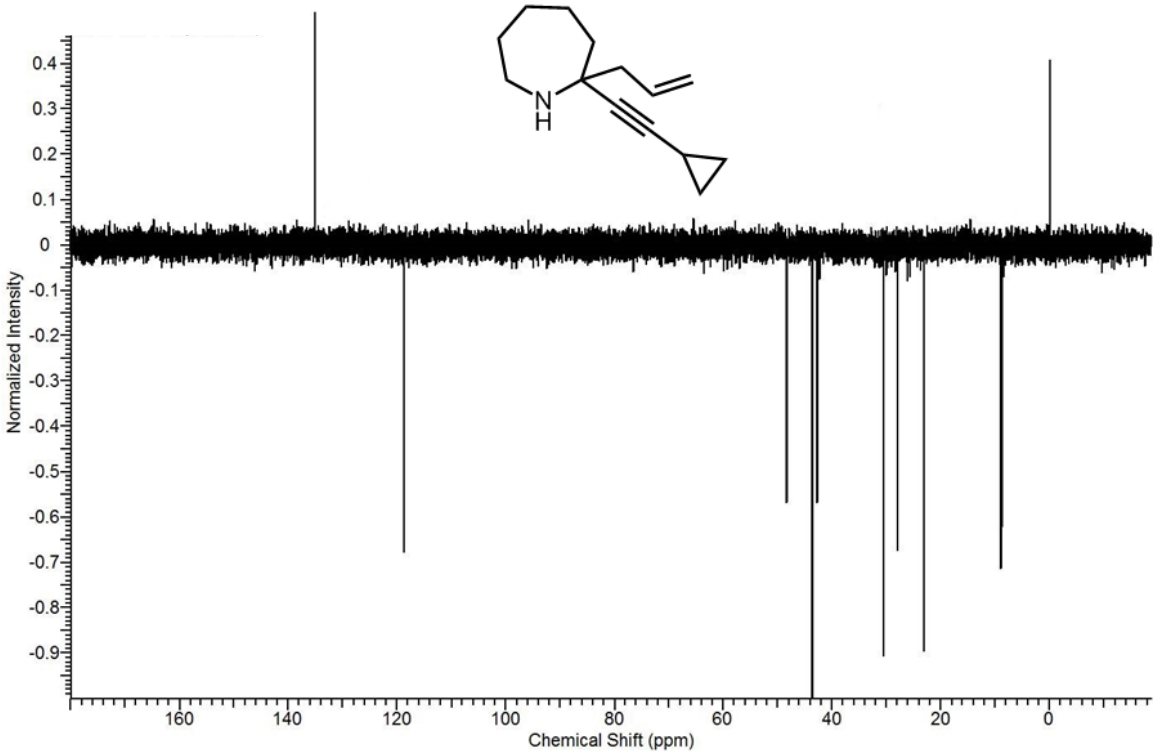
Spectra **1-28** DEPT-135 NMR spectrum of **1h.**



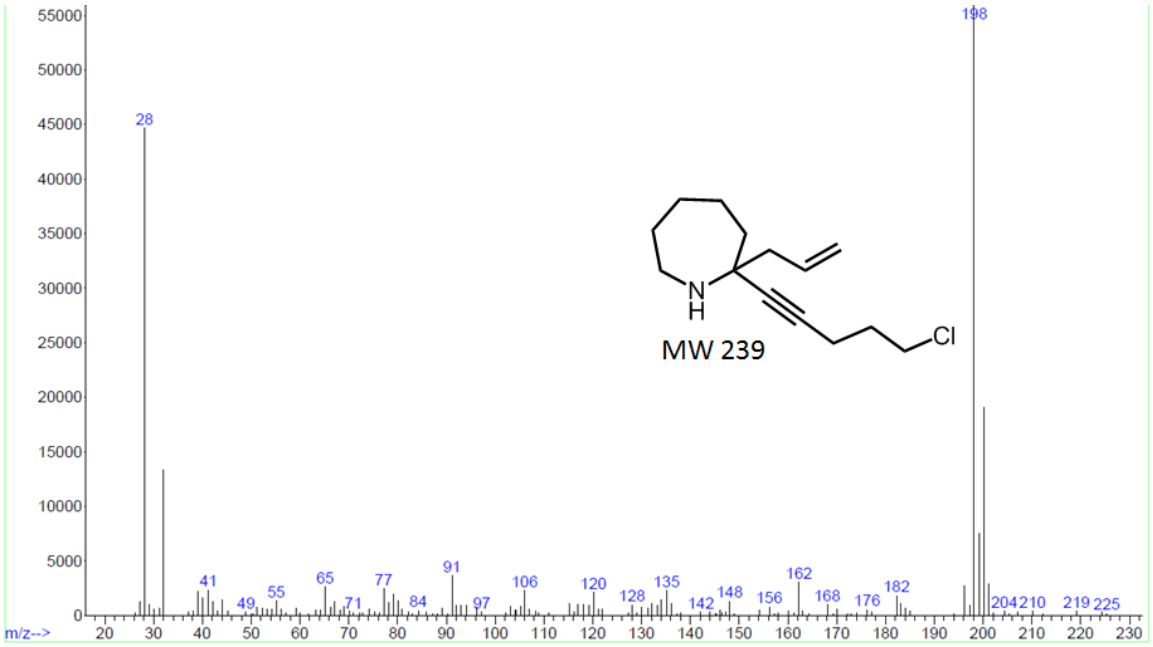
Spectra **1-29** Proton NMR spectrum of **1i.**



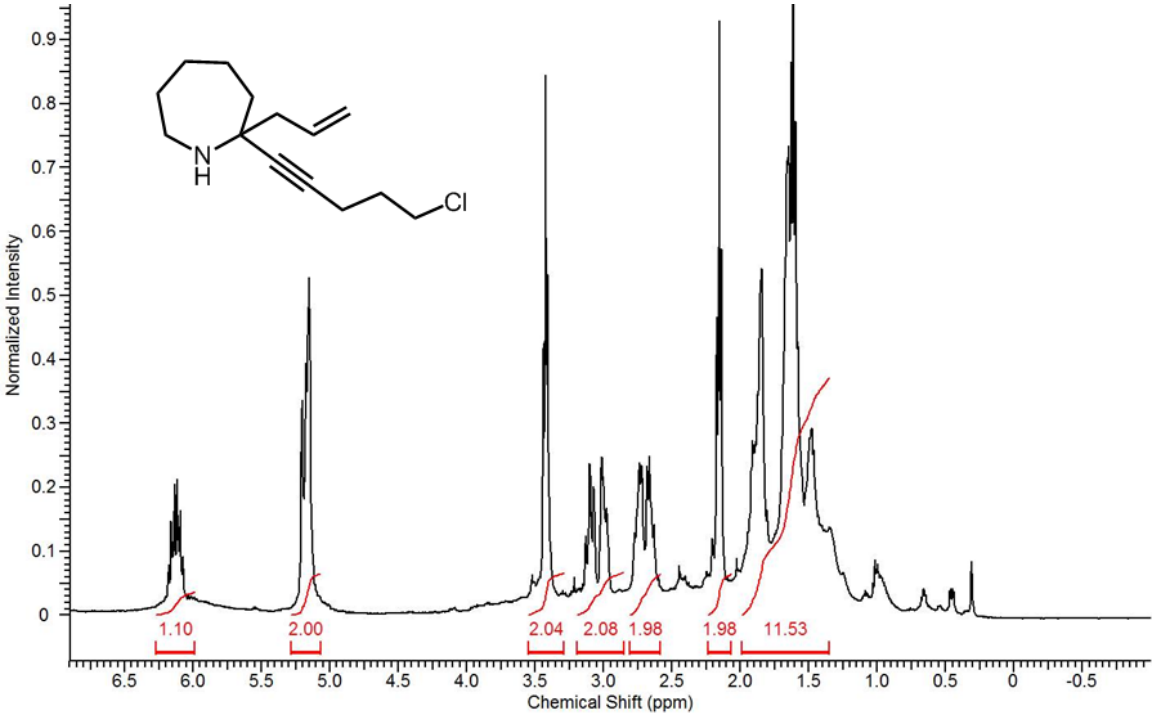
Spectra **1-30** Carbon NMR spectrum of **1i.**



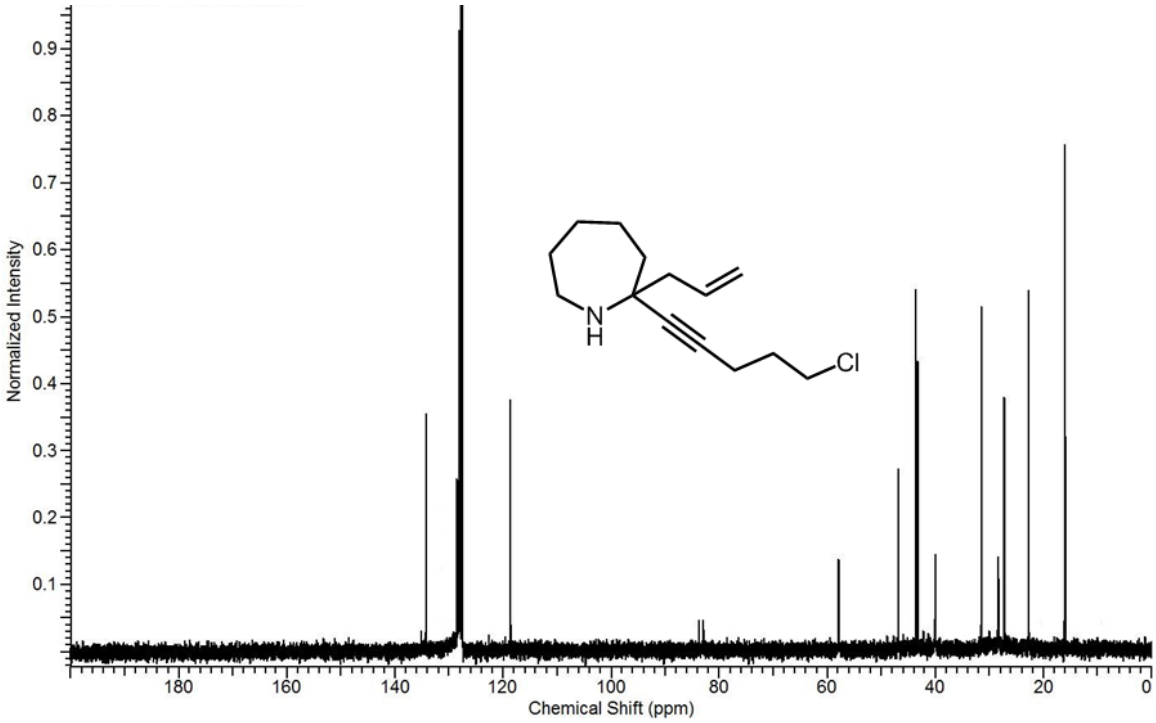
Spectra **1-31** DEPT-135 NMR spectrum of **1i.**



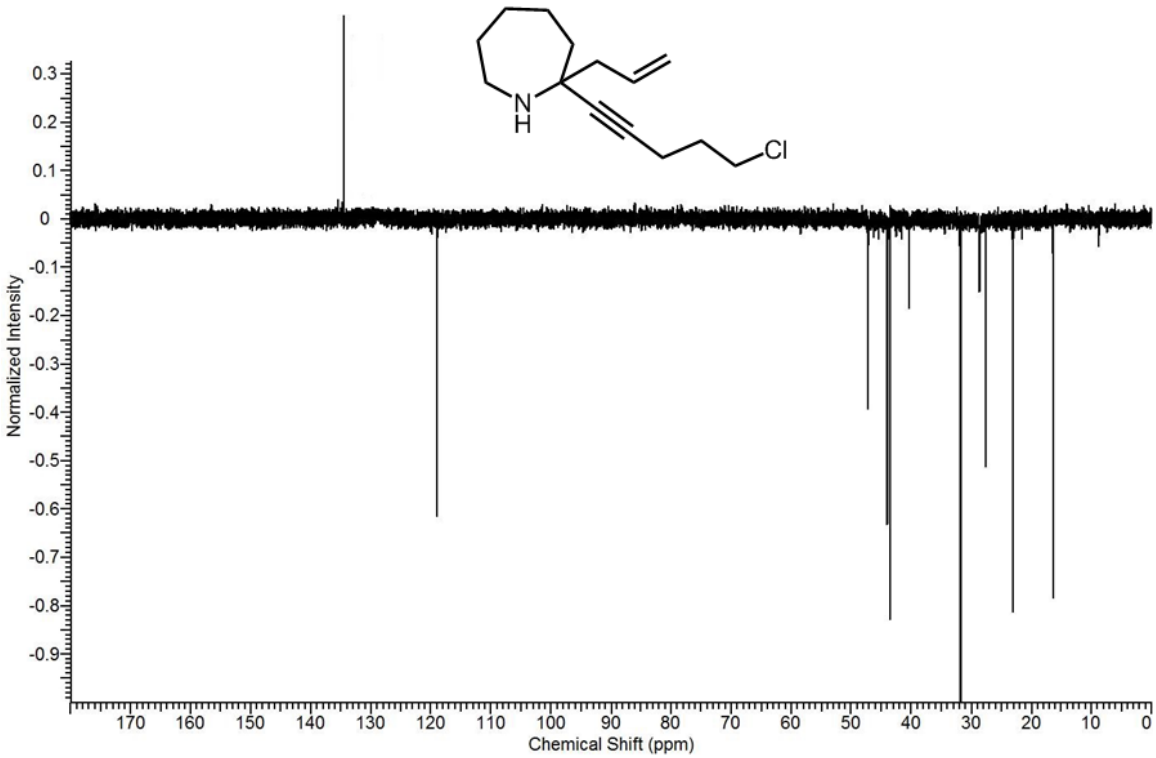
Spectra **1-32** MS spectrum of **1j.**



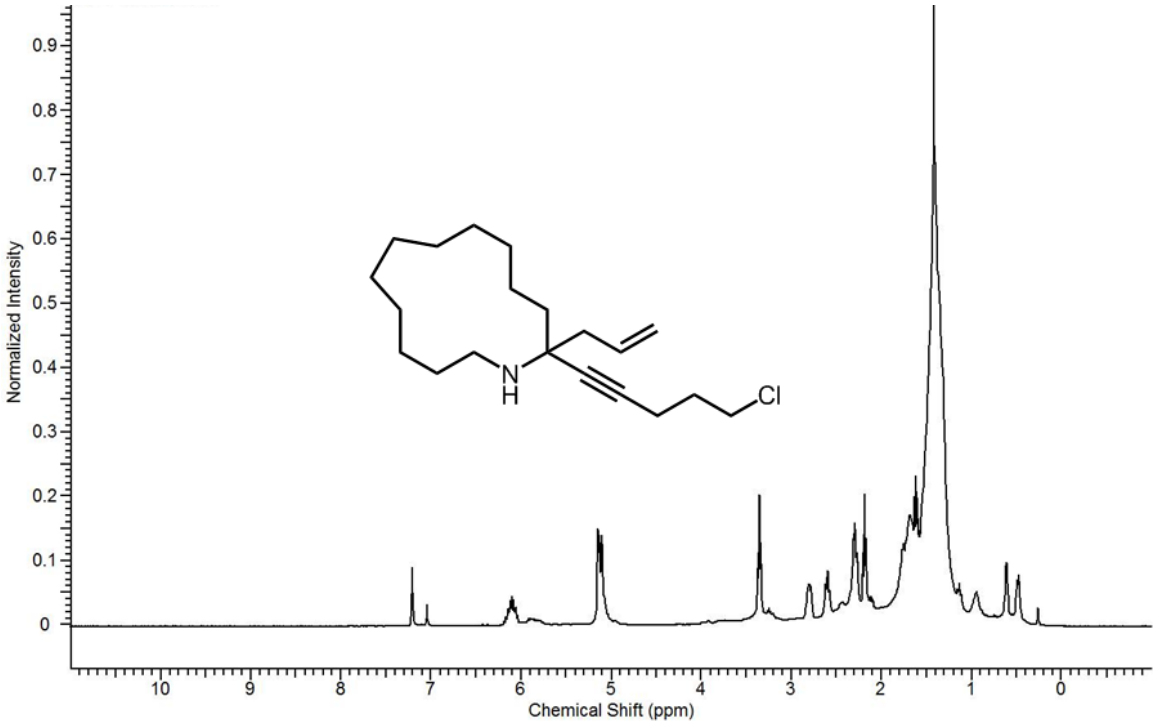
Spectra **1-33** Proton NMR spectrum of **1j.**



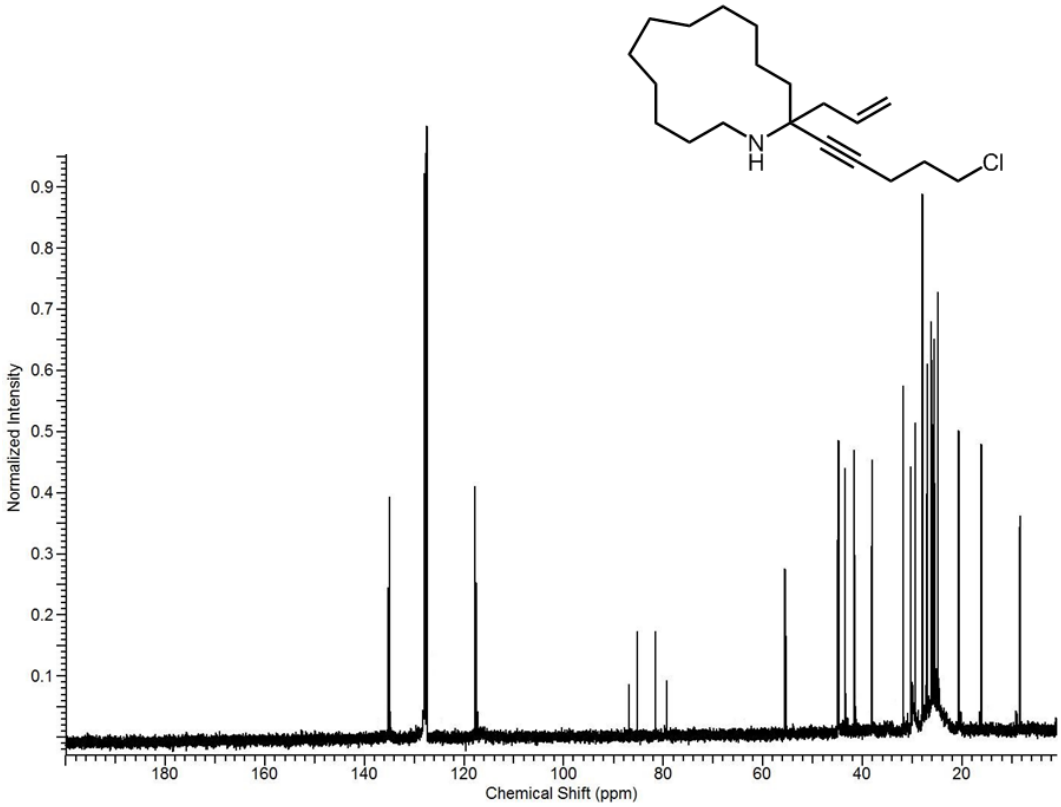
Spectra **1-34** Carbon NMR spectrum of **1j.**



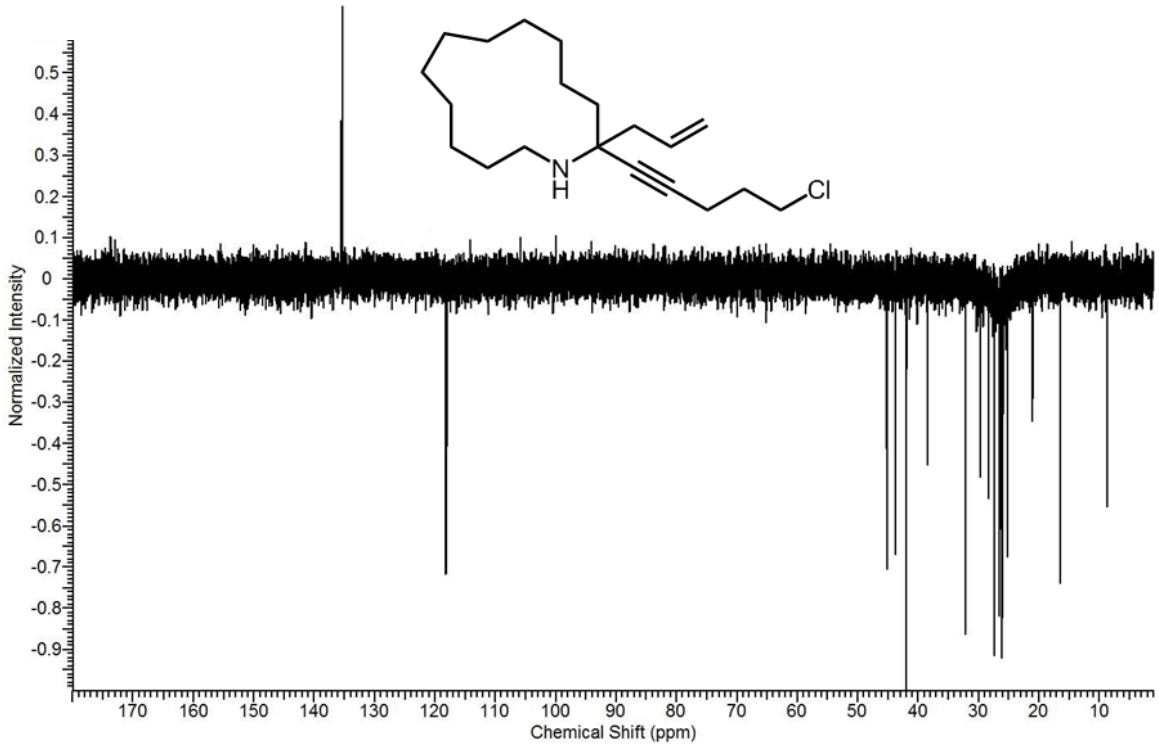
Spectra **1-35** DEPT-135 NMR spectrum of **1j.**



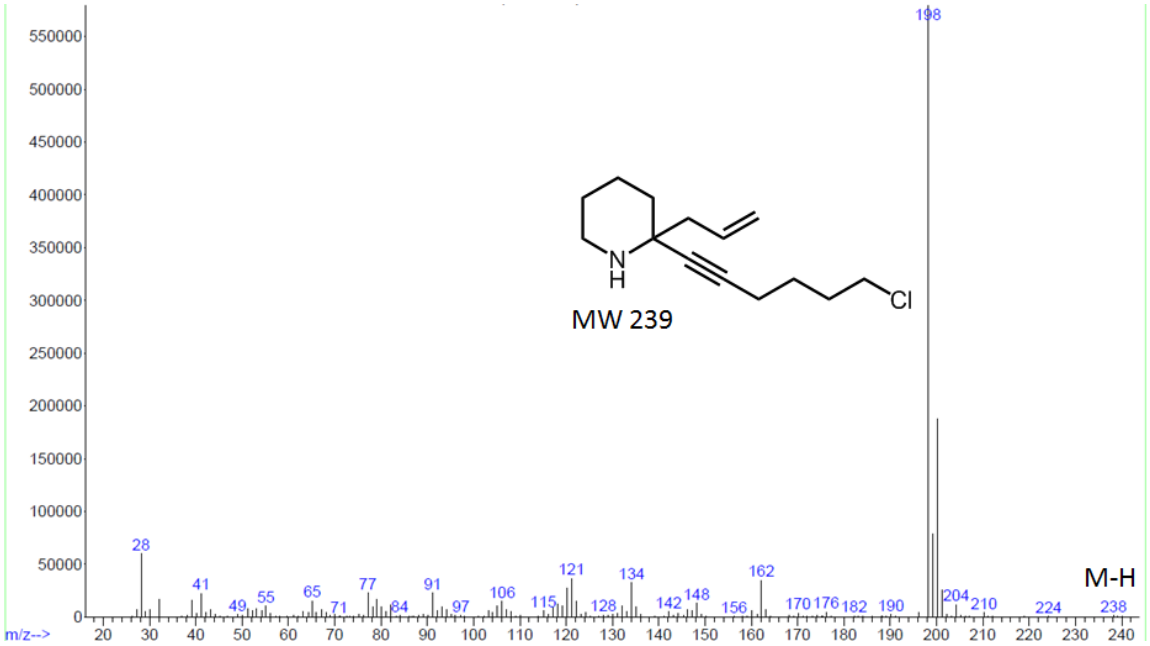
Spectra **1-36** Proton NMR spectrum of **1k.**



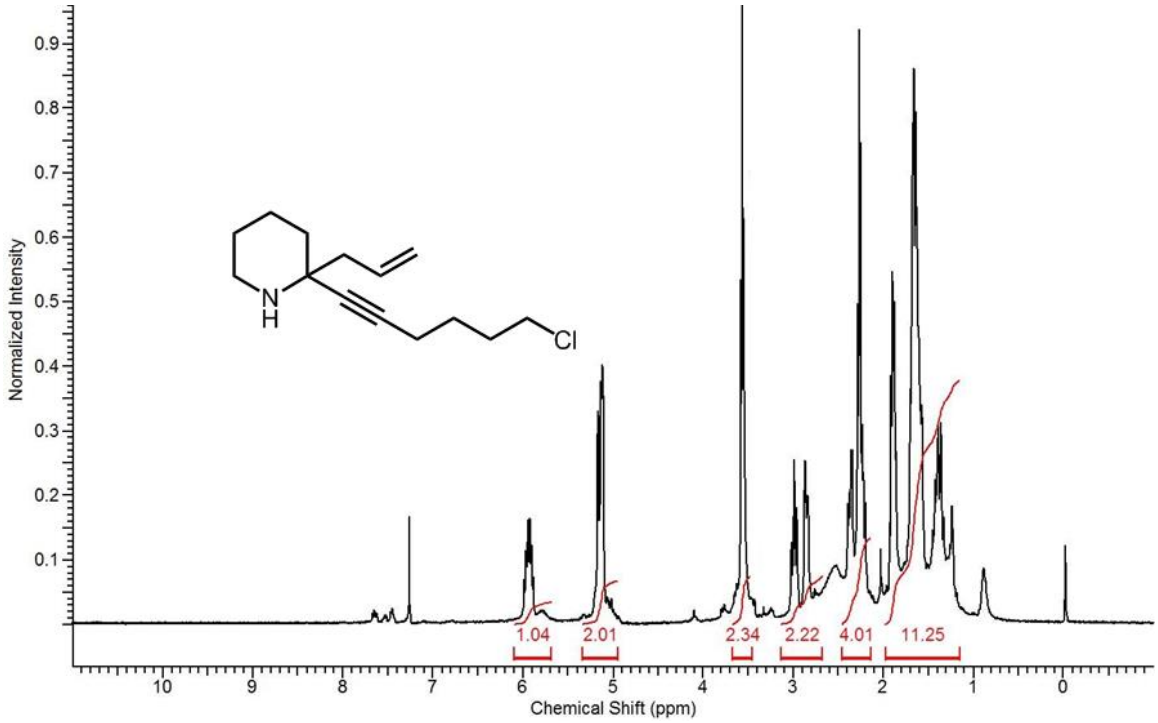
Spectra **1-37** Carbon NMR spectrum of **1k.**



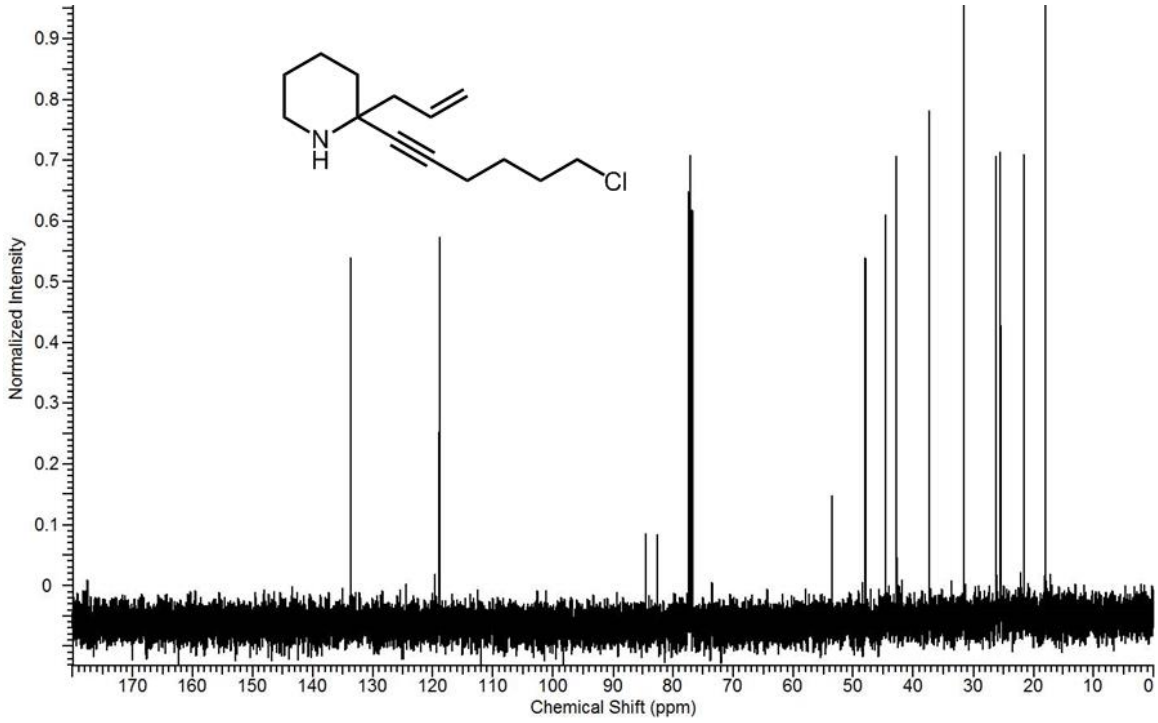
Spectra **1-38** DEPT-135 NMR spectrum of **1k.**



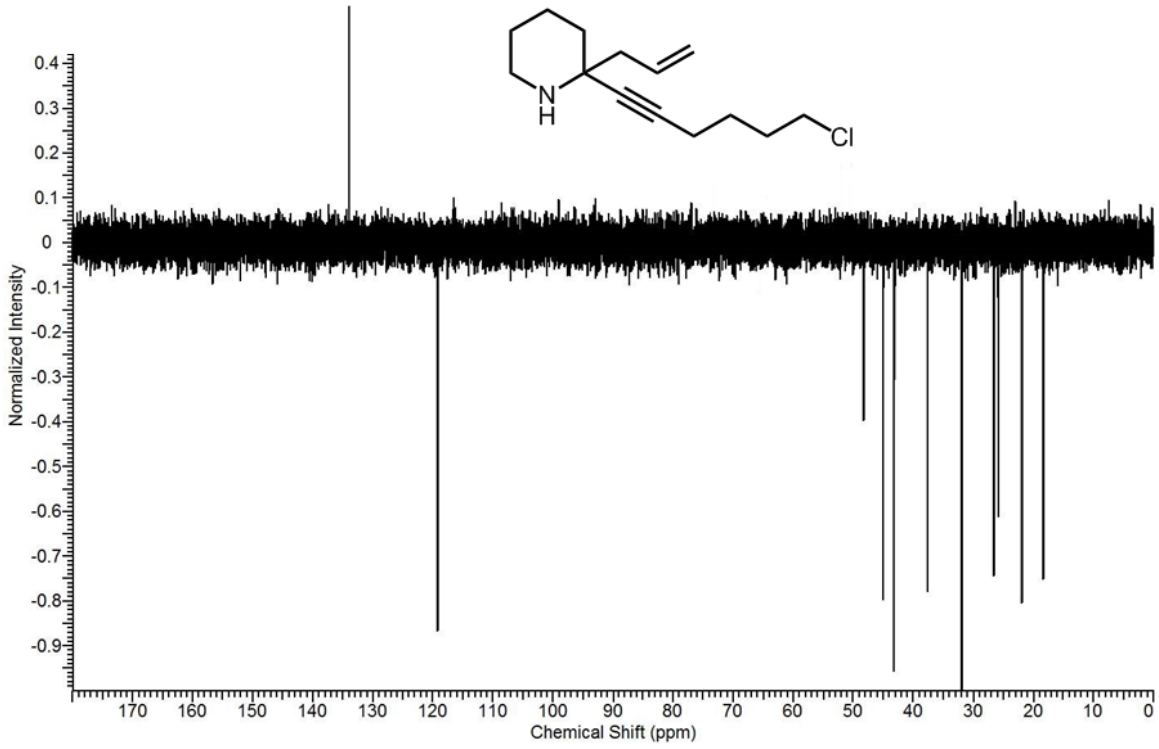
Spectra **1-39** MS spectrum of **1l.**



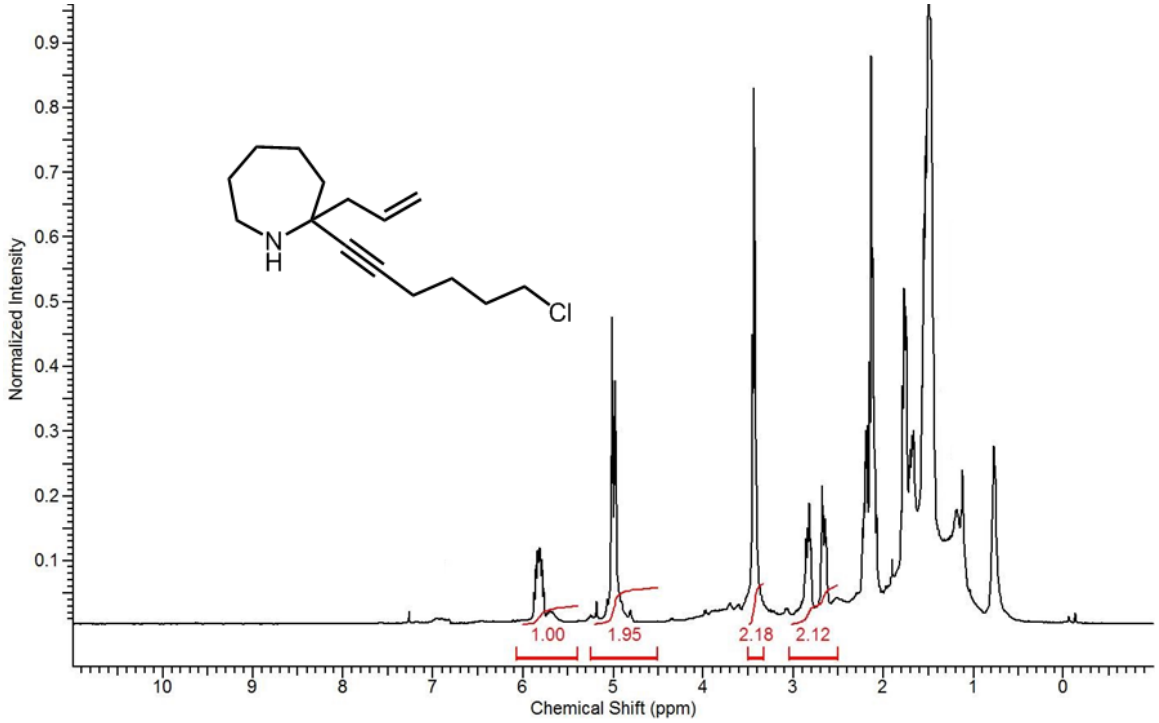
Spectra **1-40** Proton NMR spectrum of **1l.**



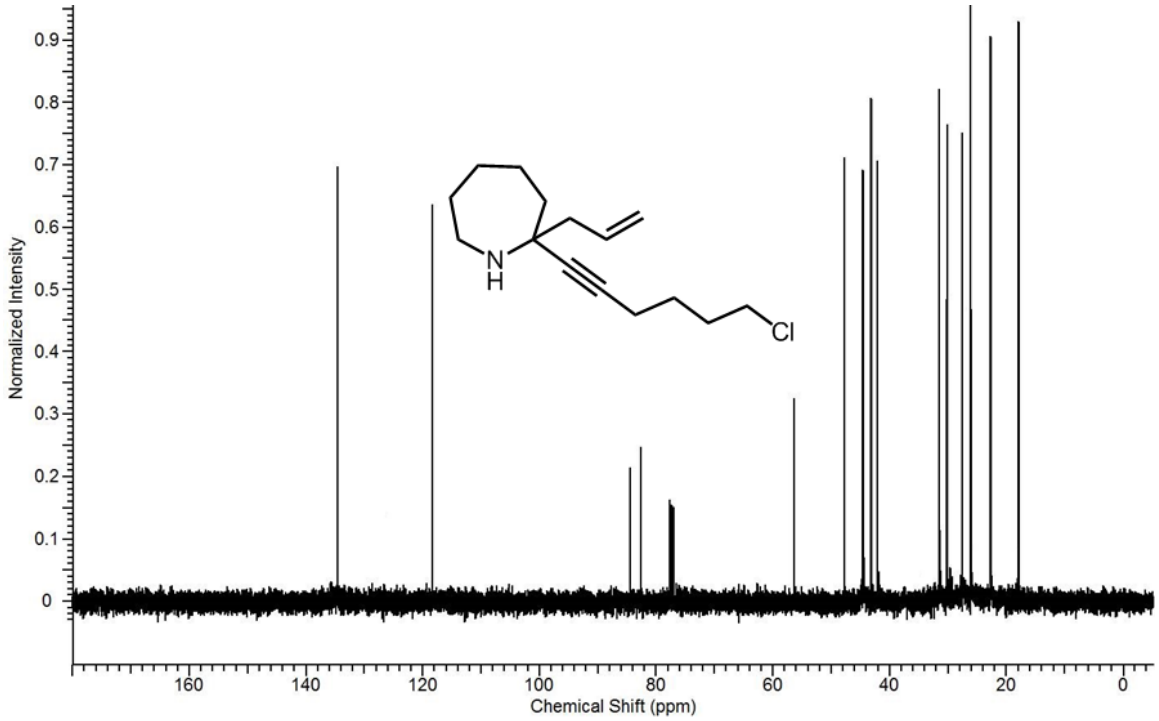
Spectra **1-41** Carbon NMR spectrum of **1l.**



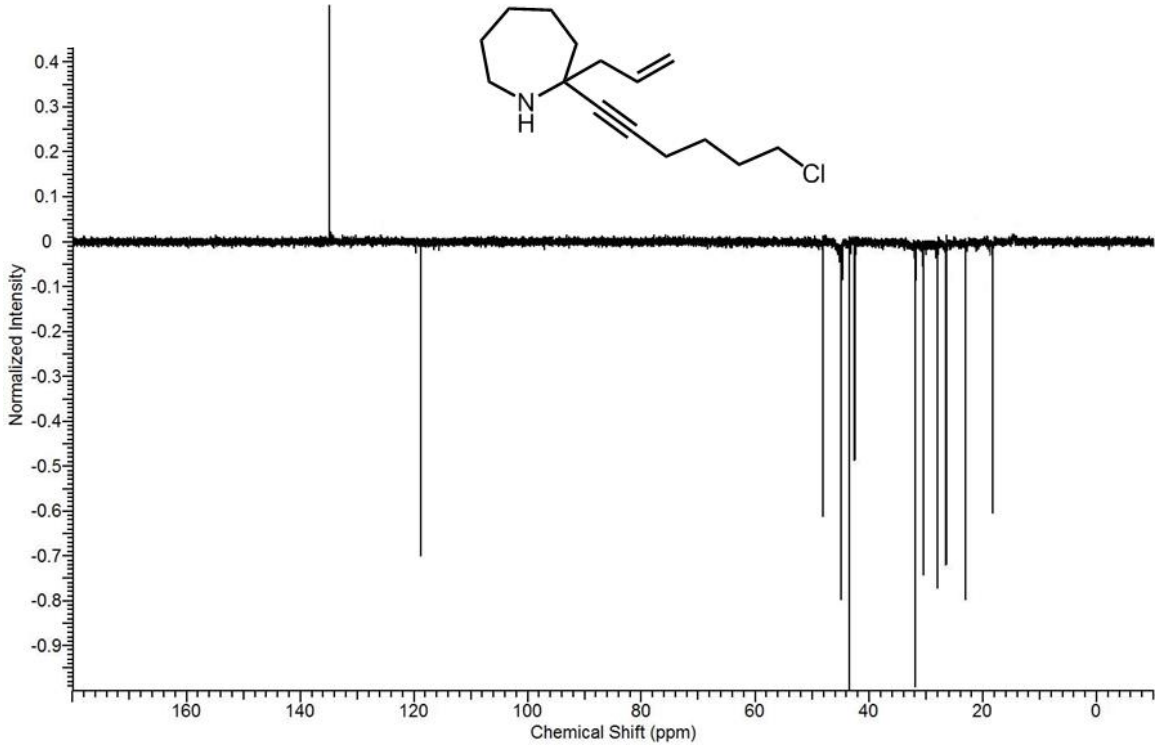
Spectra **1-42** DEPT-135 NMR spectrum of **1l.**



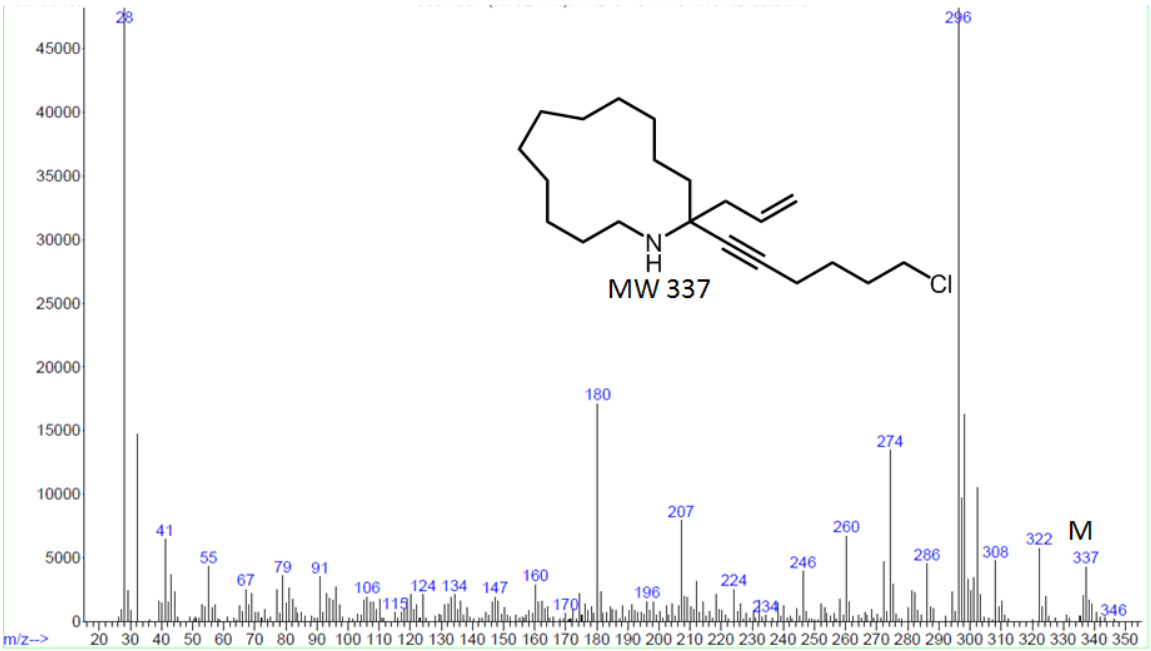
Spectra **1-43** Proton NMR spectrum of **1m.**



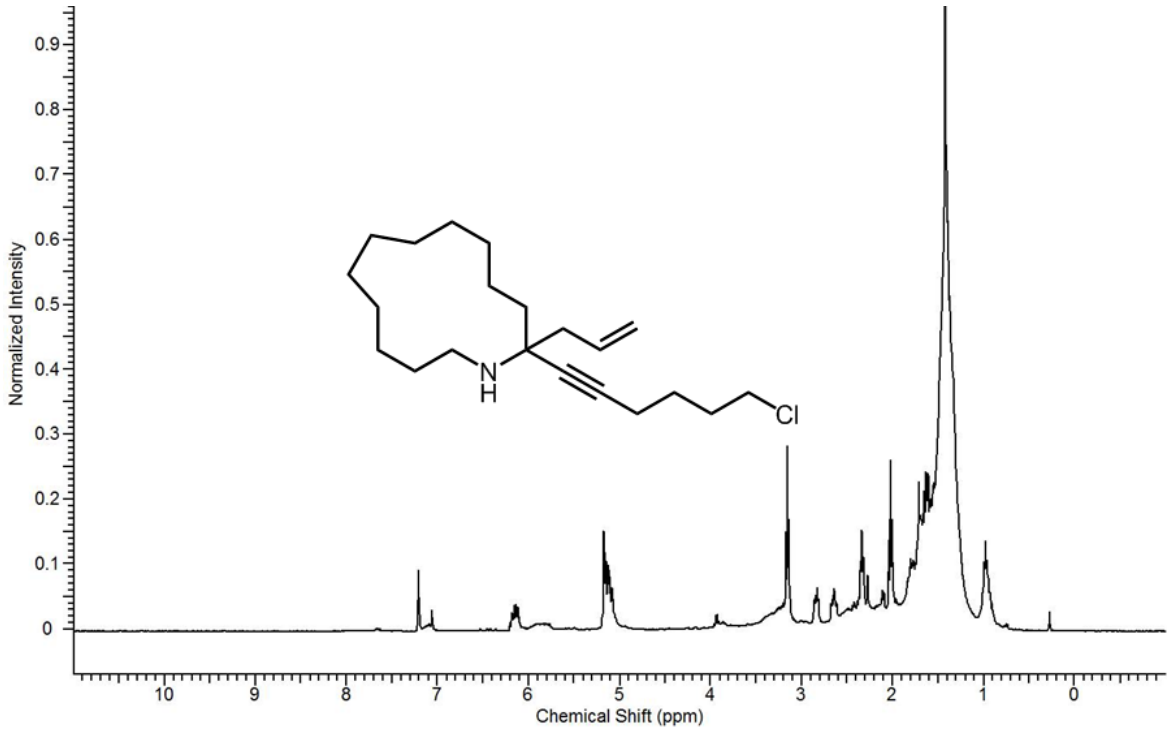
Spectra **1-44** Carbon NMR spectrum of **1m.**



Spectra **1-45** DEPT-135 NMR spectrum of **1m.**

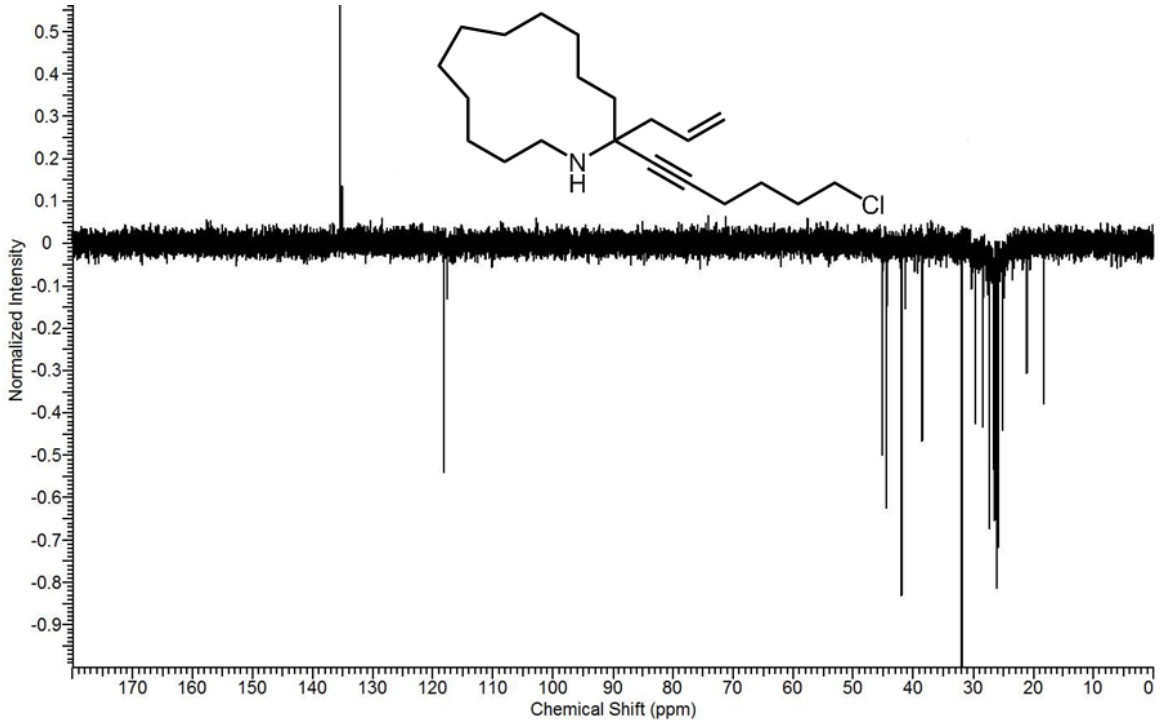


Spectra **1-46** MS spectrum of **1n.**

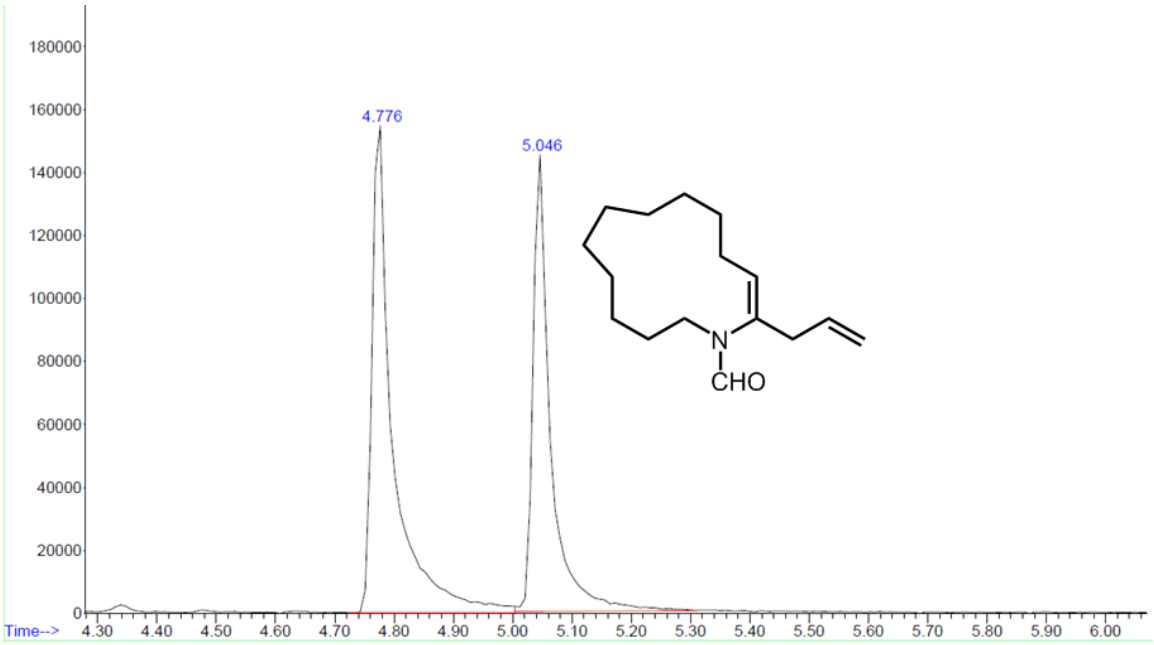


Spectra **1-47** Proton NMR spectrum of **1n.**

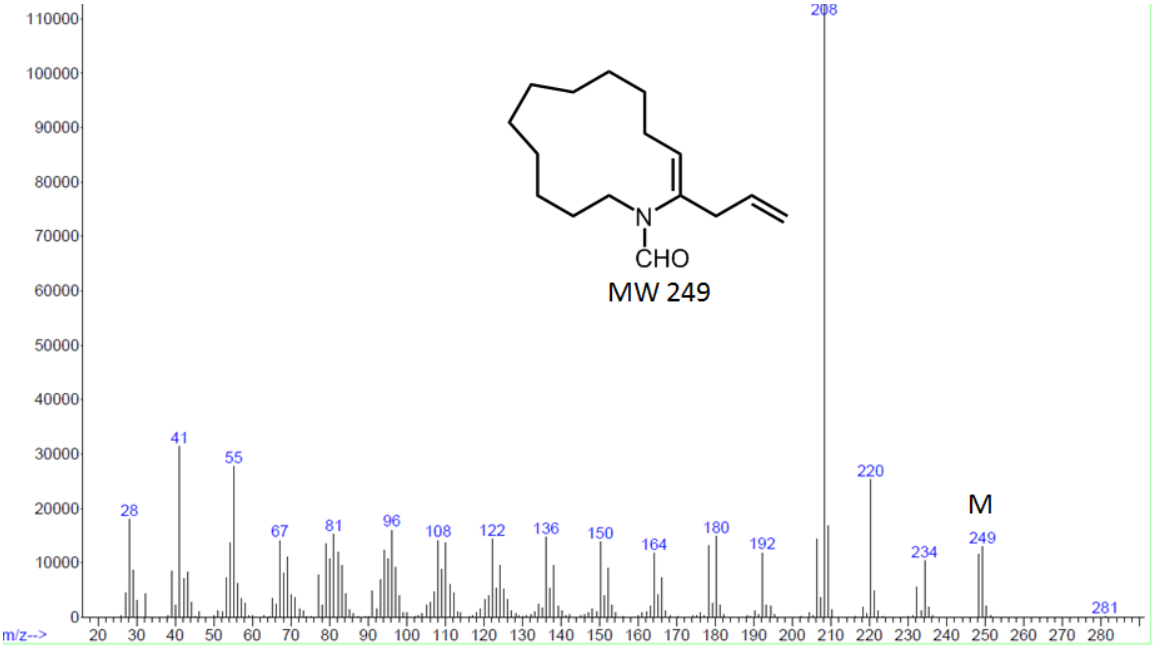
Spectra **1-48** Carbon NMR spectrum of **1n.**



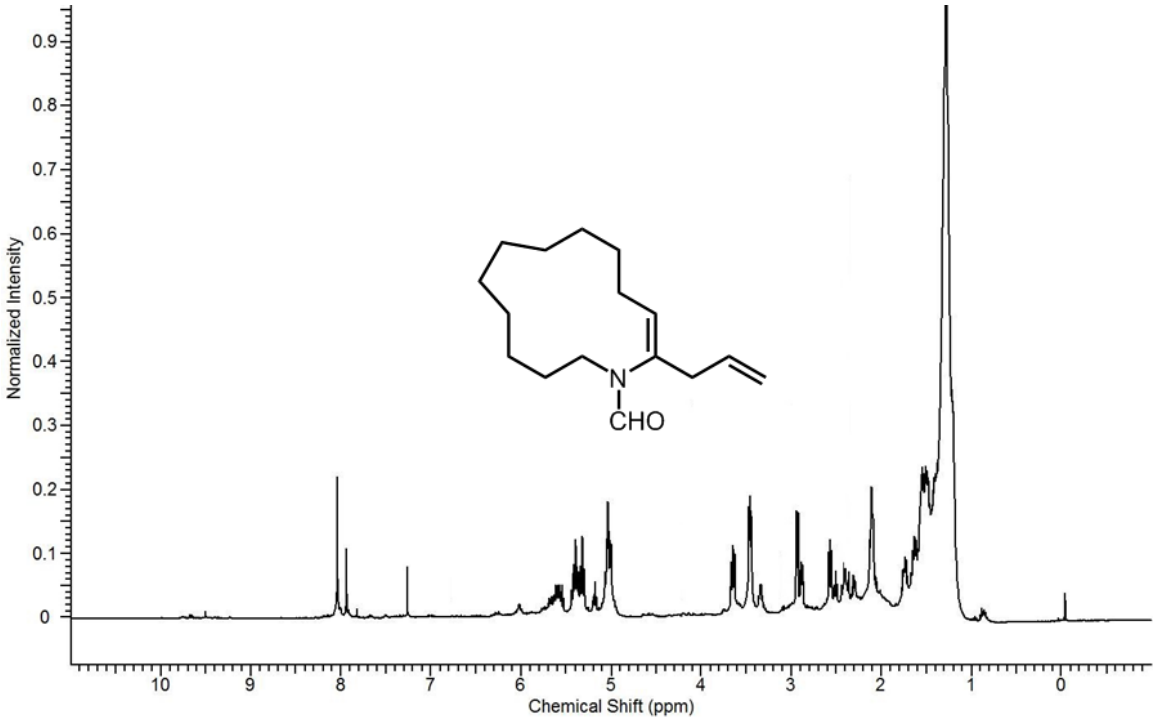
Spectra **1-49** DEPT-135 NMR spectrum of **1n.**



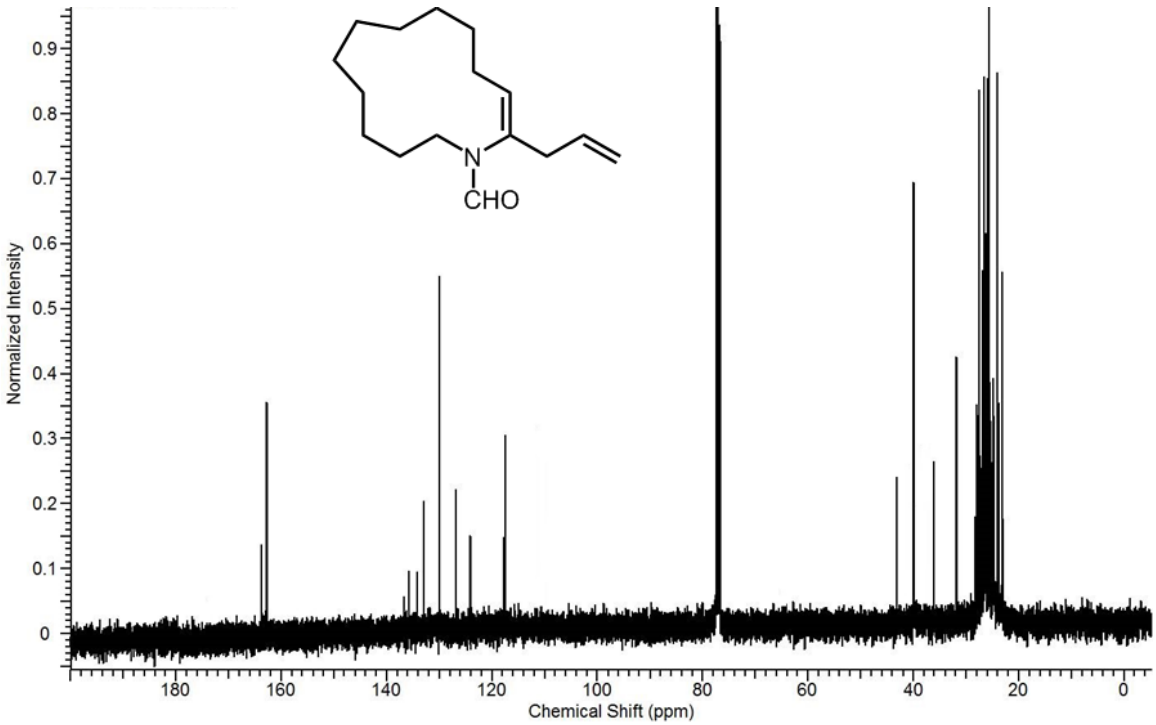
Spectra **1-50** GC spectrum of **10b.**



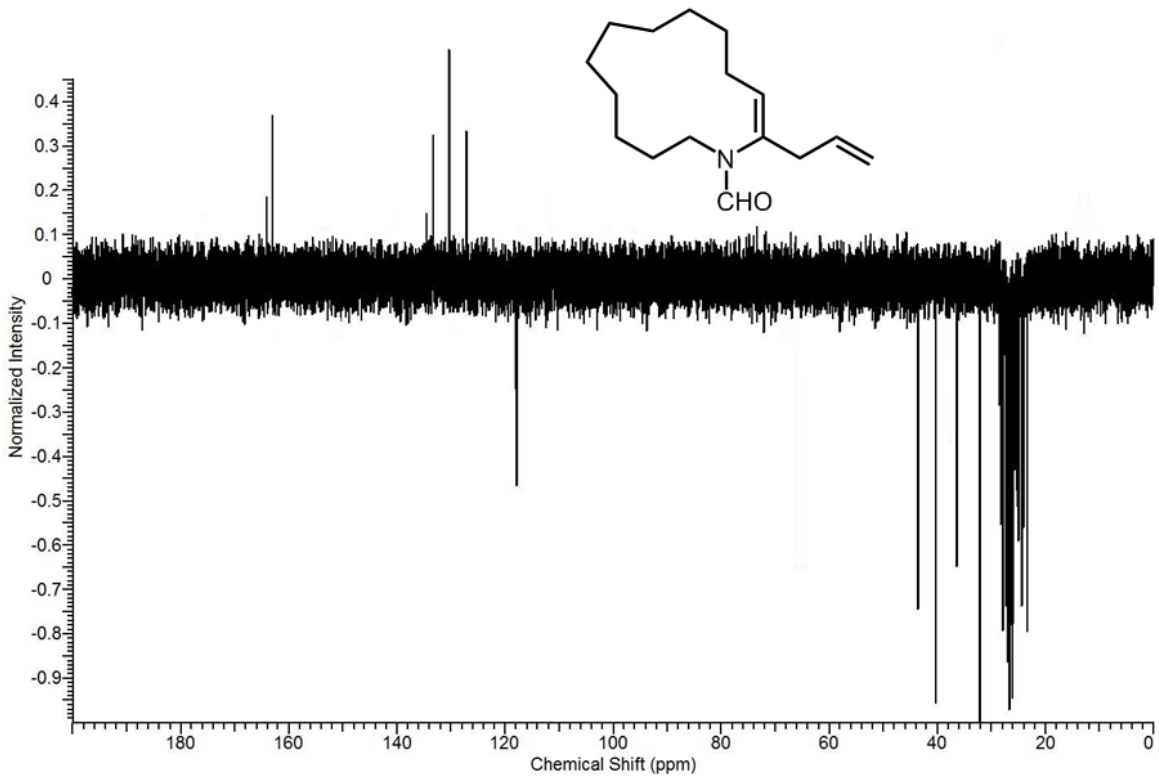
Spectra **1-51** MS spectrum of **10b.**



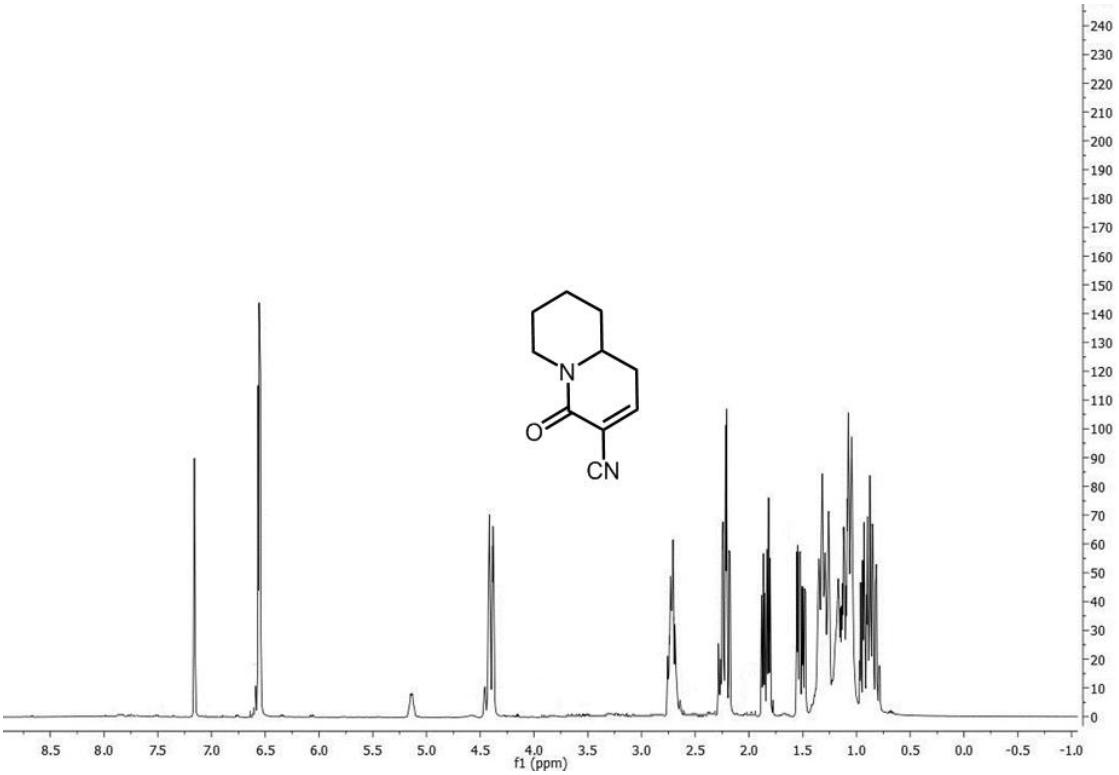
Spectra **1-52** Proton NMR spectrum of **10b.**



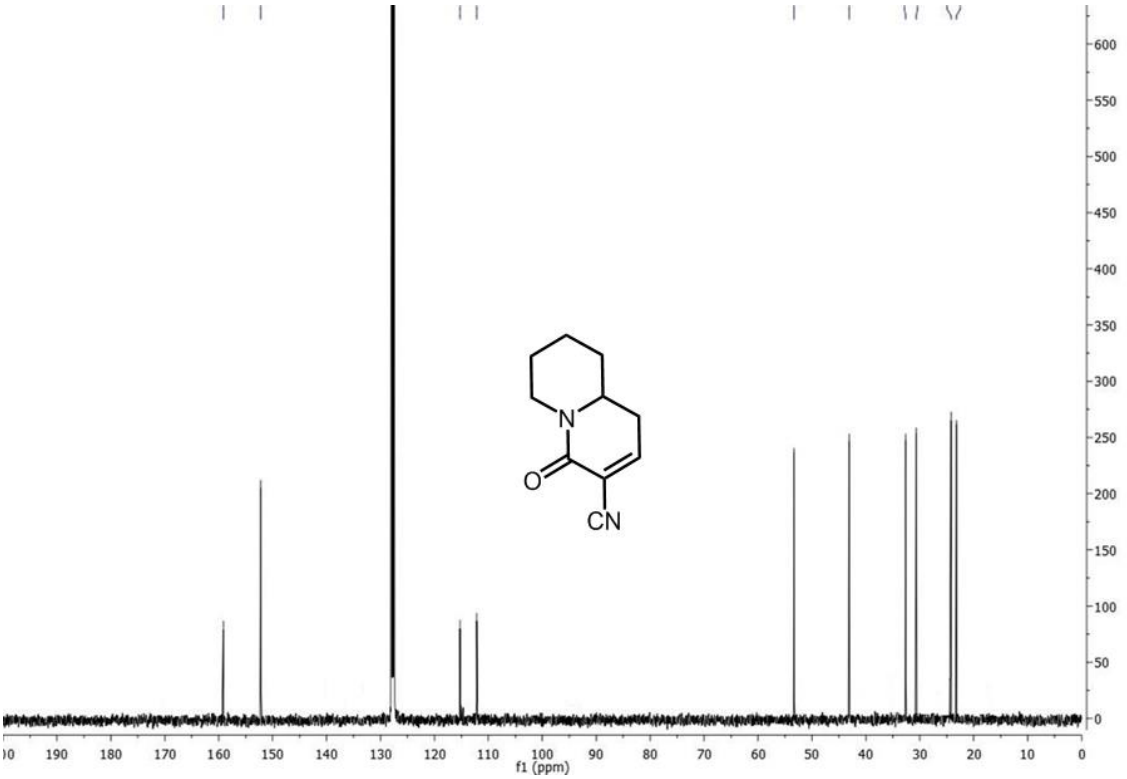
Spectra **1-53** Carbon NMR spectrum of **10b.**



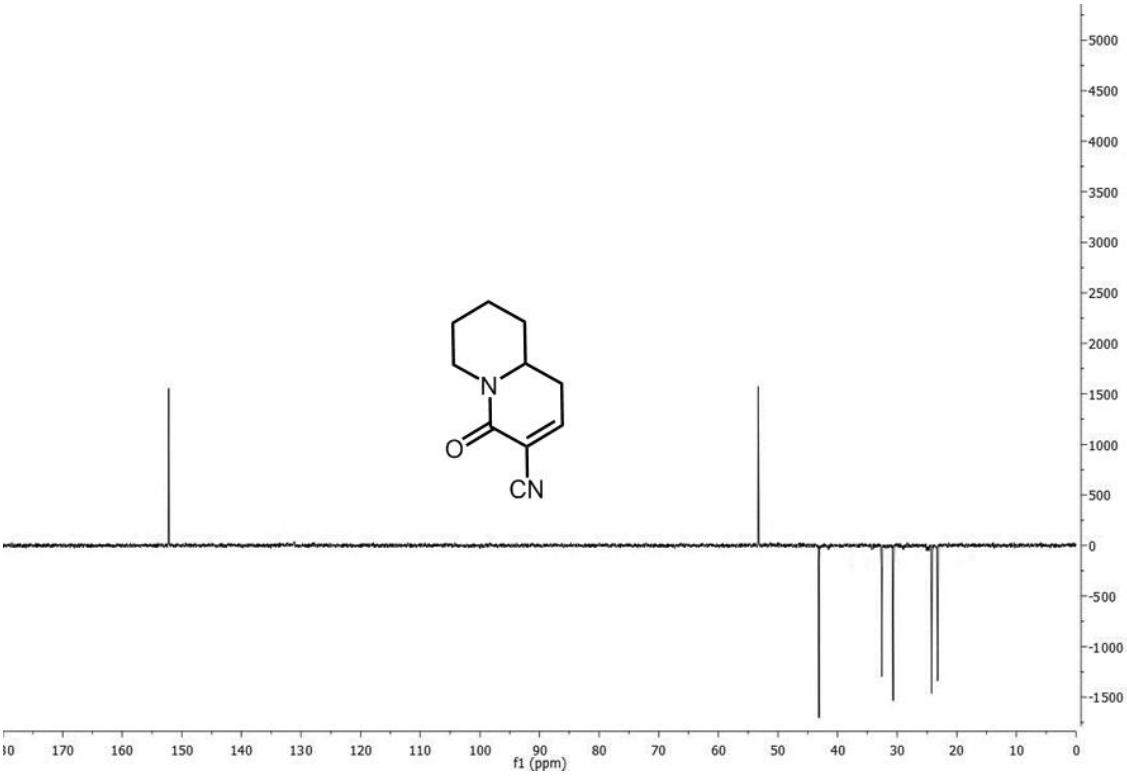
Spectra **1-54** DEPT-135 NMR spectrum of **10b.**



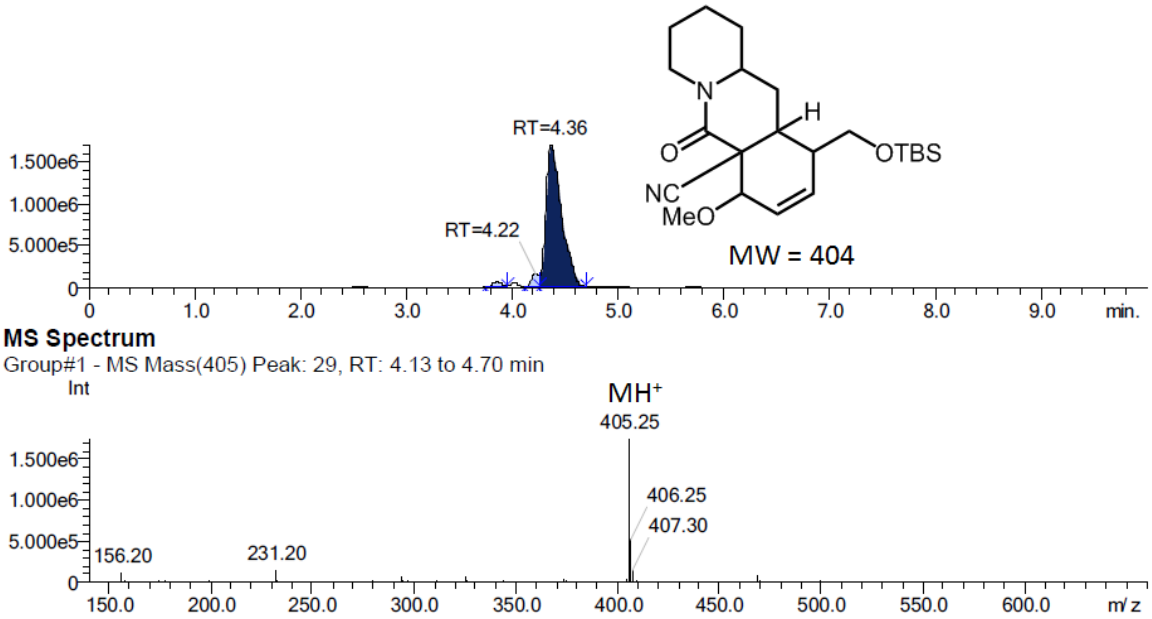
Spectra **1-55** Proton NMR spectrum of **18.**



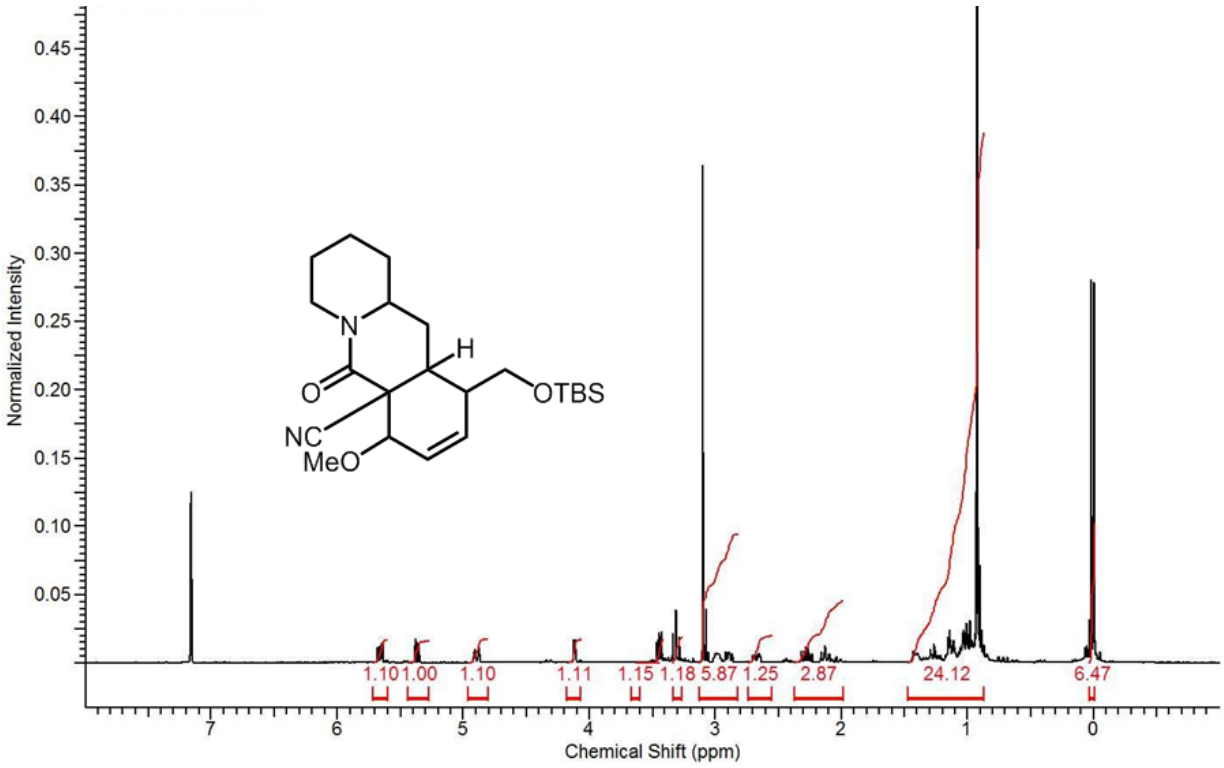
Spectra **1-56** Carbon NMR spectrum of **18.**



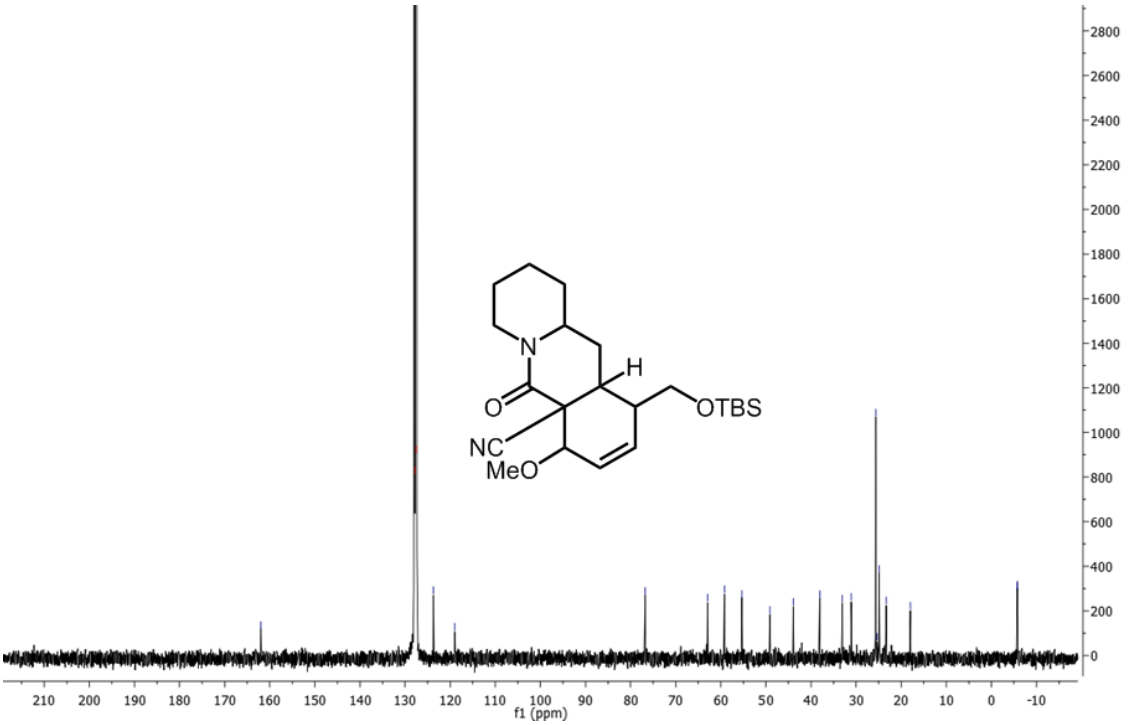
Spectra **1-57** DEPT-135 NMR spectrum of **18.**



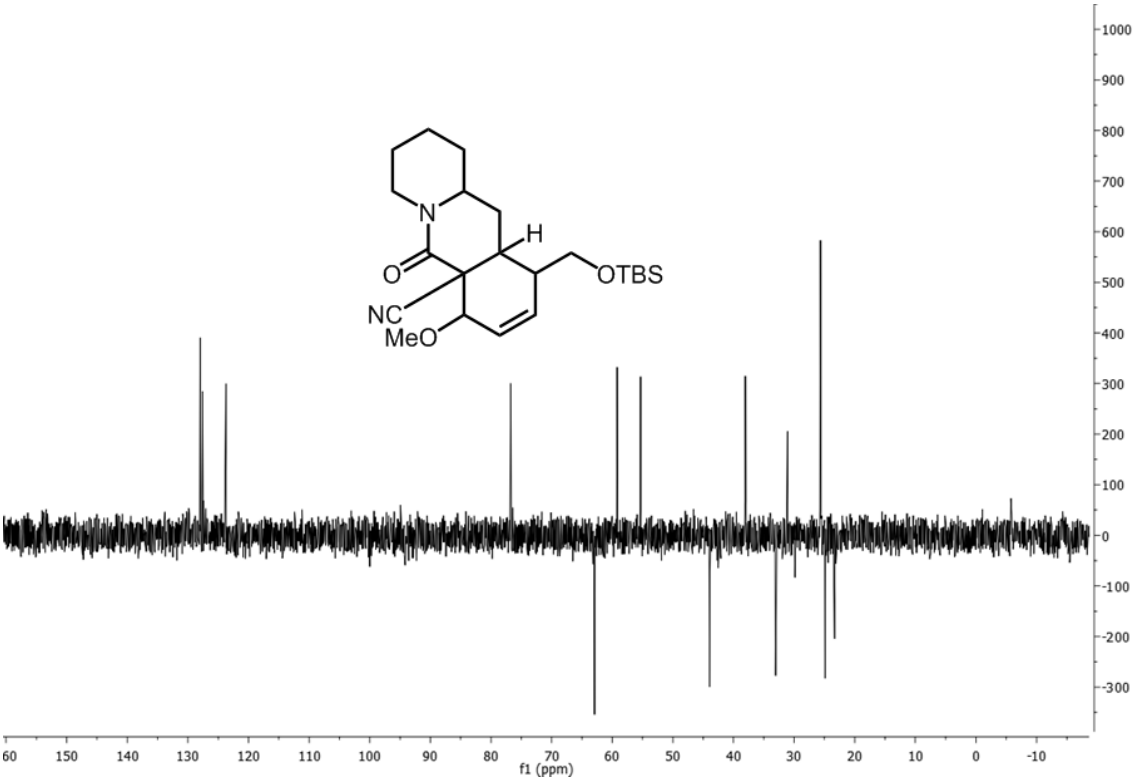
Spectra **1-58** GC-MS spectrum of **20.**



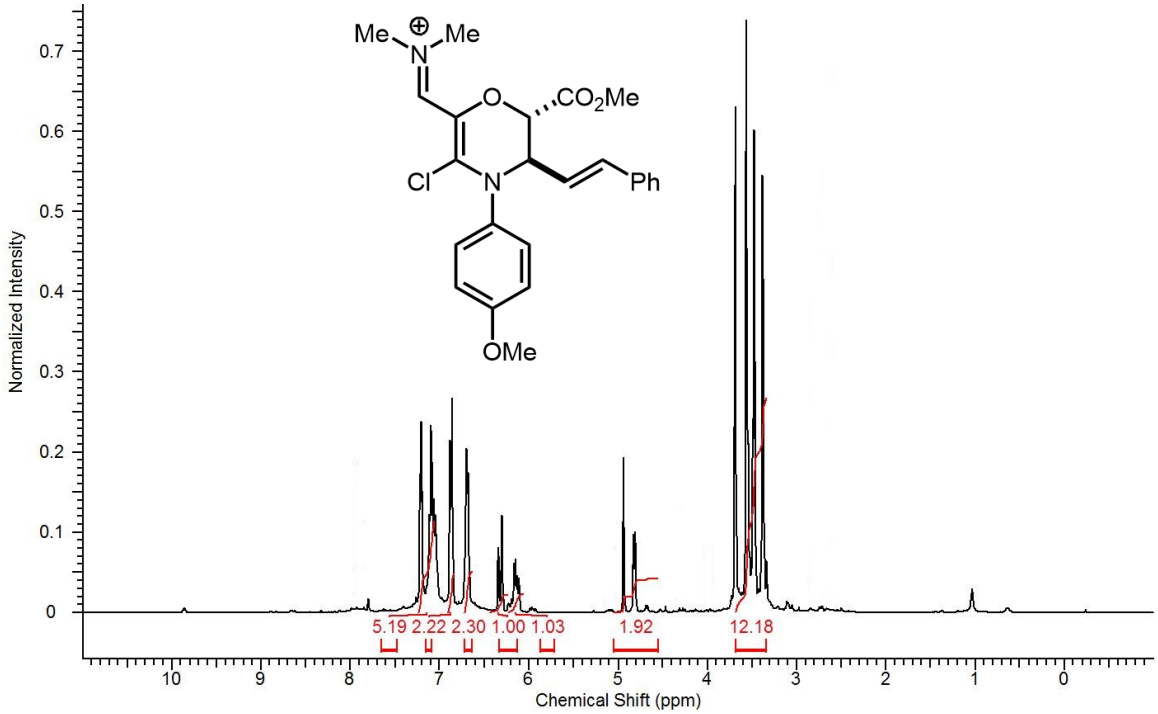
Spectra **1-59** Proton NMR spectrum of **20.**



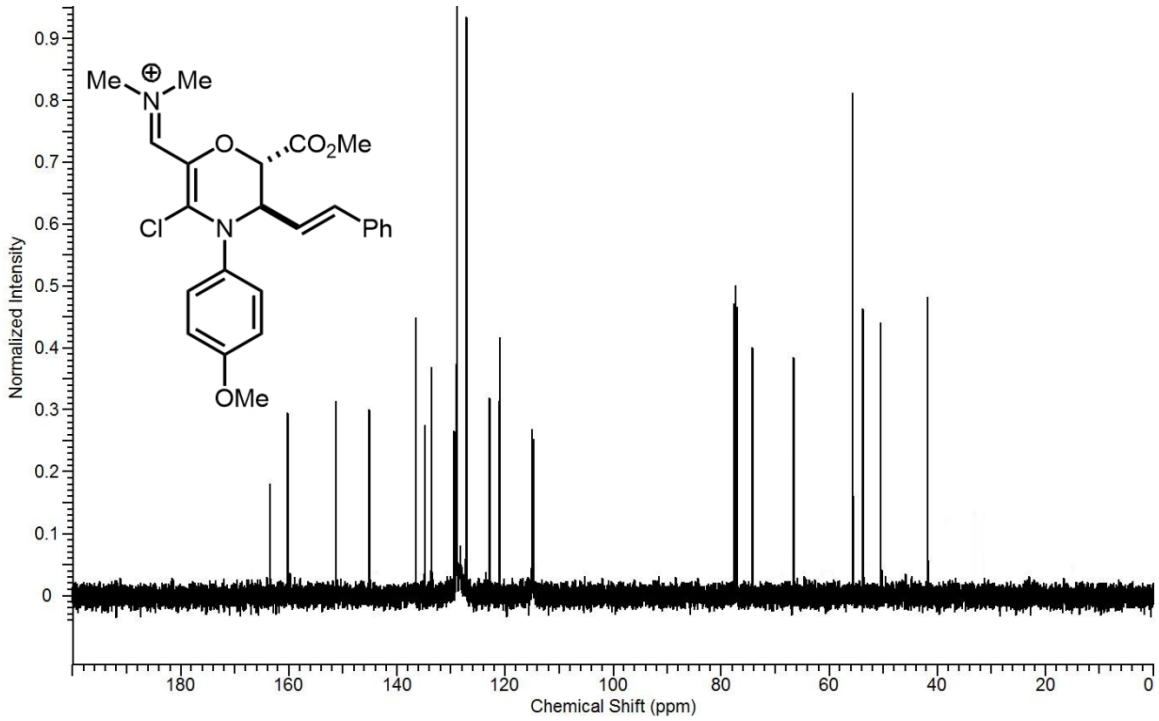
Spectra **1-60** Carbon NMR spectrum of **20.**



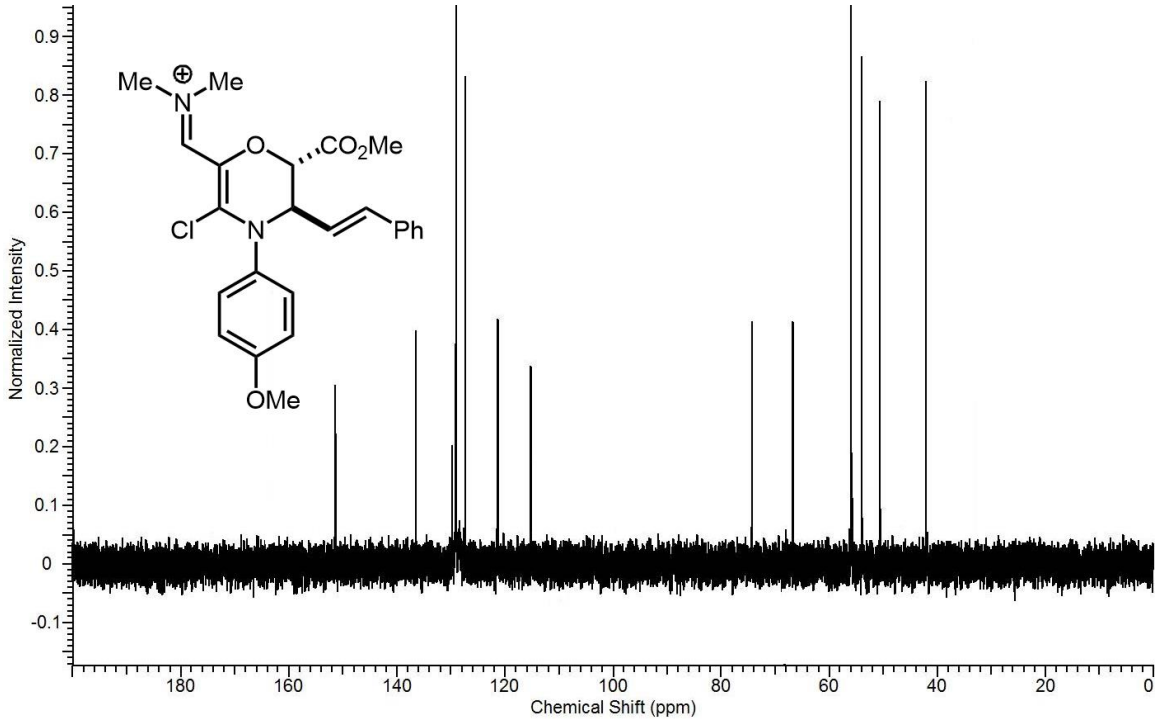
Spectra **1-61** Carbon NMR spectrum of **20.**



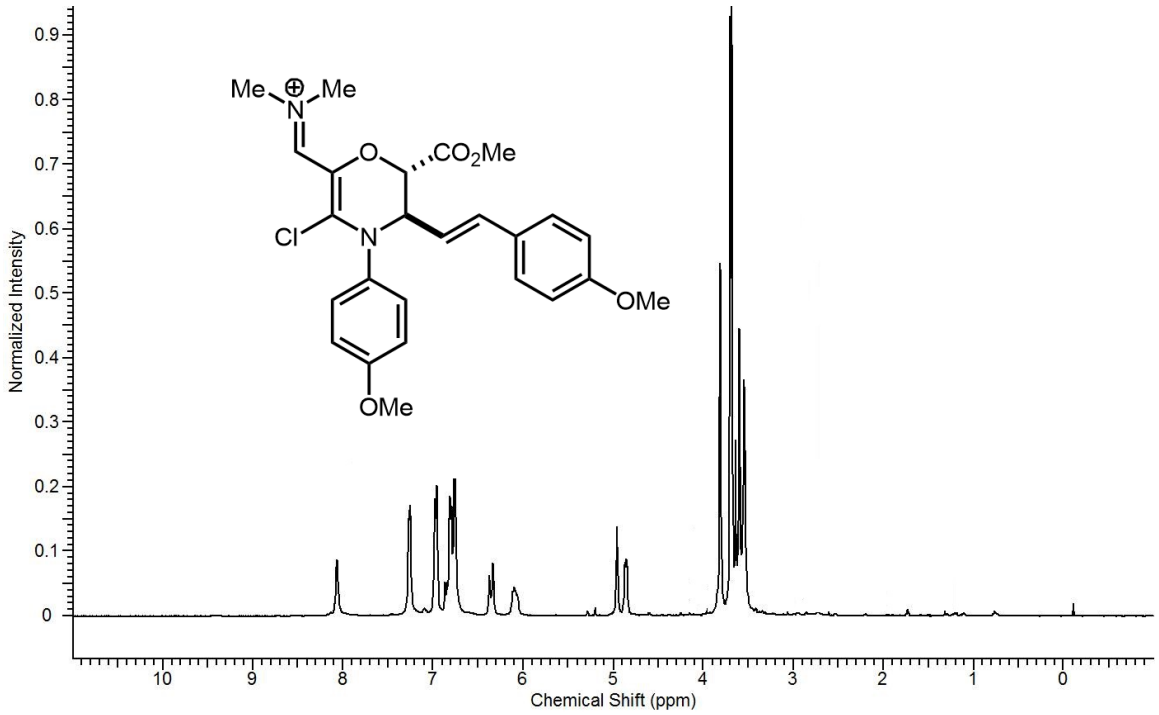
Spectra **1-1** Proton NMR spectrum of **4a1.**



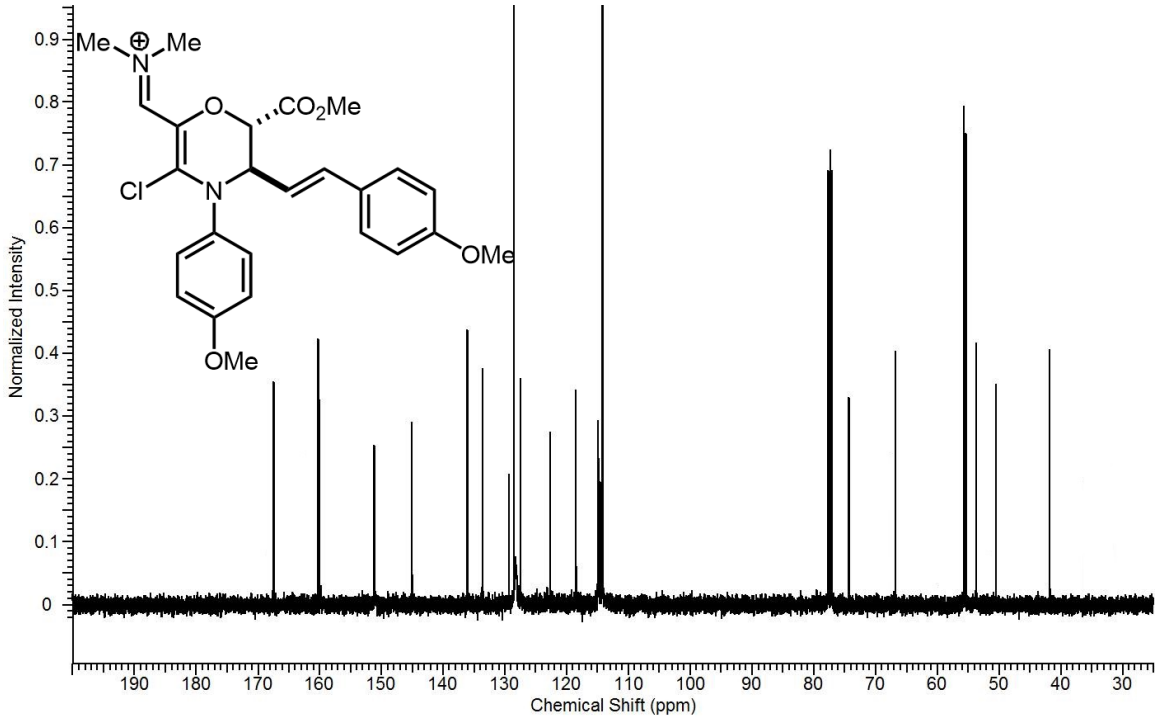
Spectra **1-2** Carbon NMR spectrum of **4a1.**



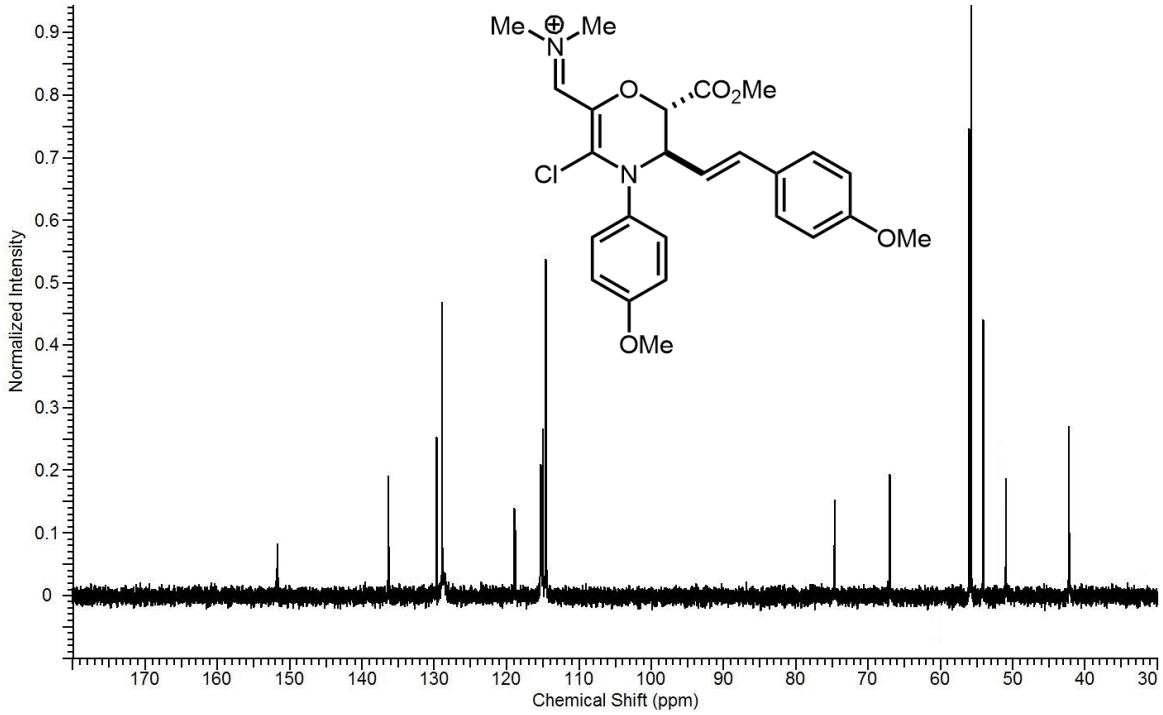
Spectra **1-3** DEPT-135 NMR spectrum of **4a1.**



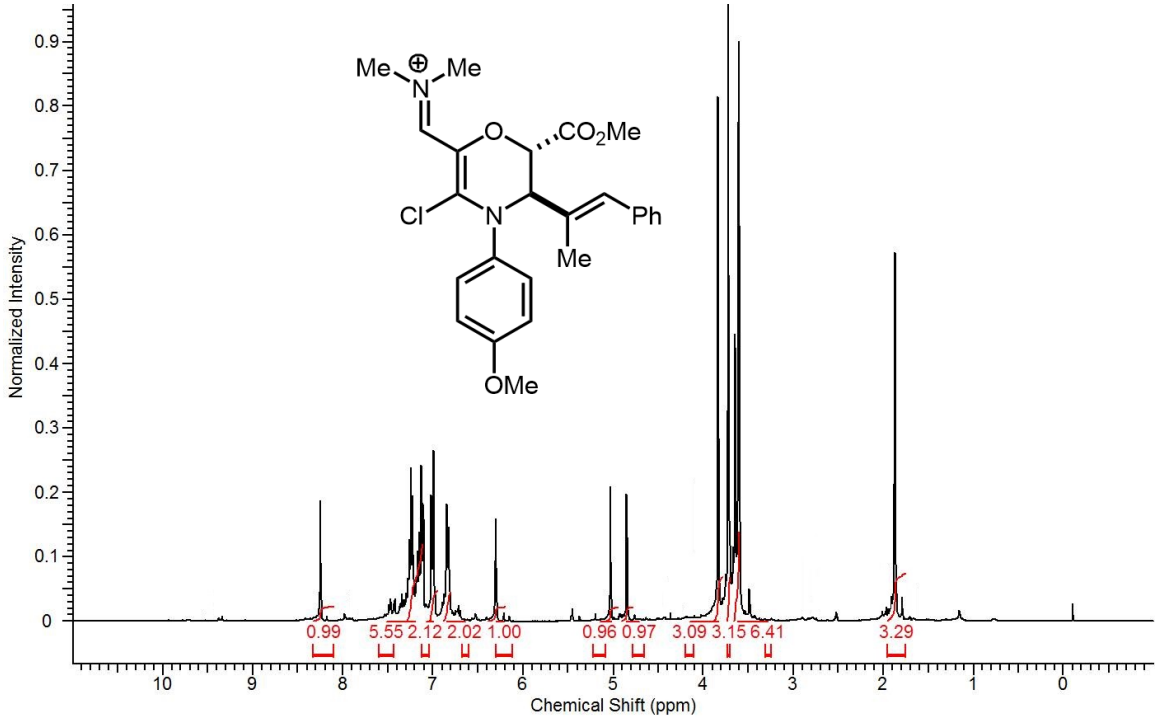
Spectra **1-4** Proton NMR spectrum of **4a2.**



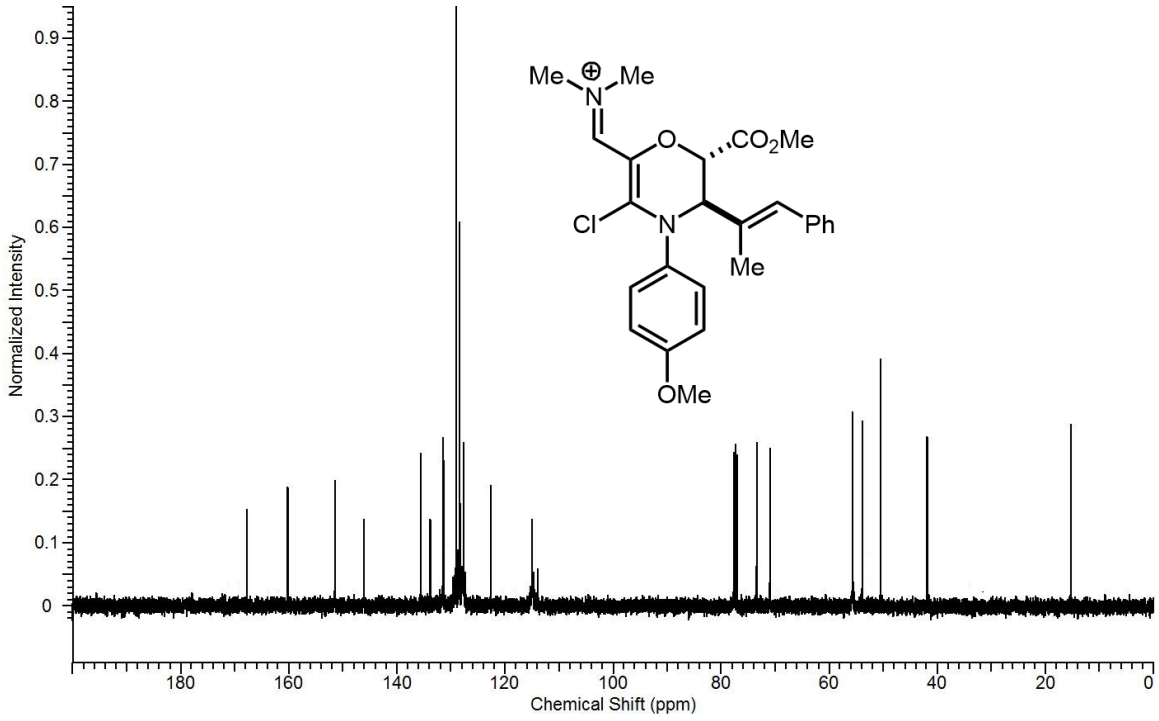
Spectra **1-5** Carbon NMR spectrum of **4a2.**



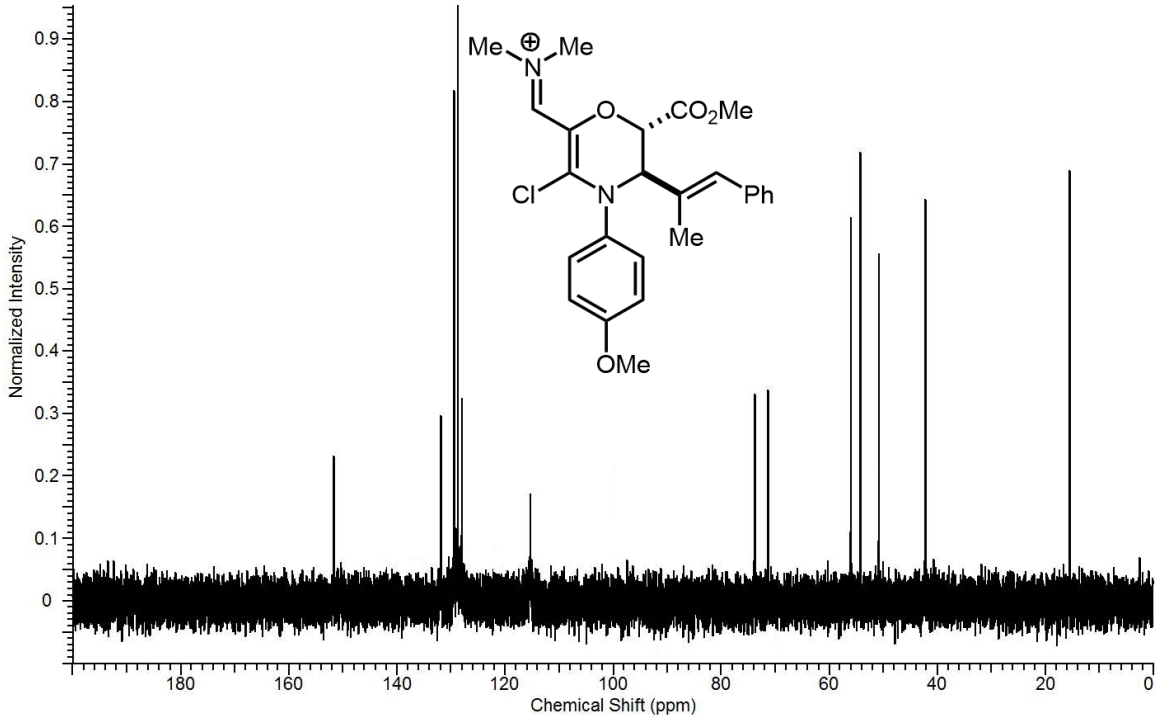
Spectra **1-6** DEPT-135 NMR spectrum of **4a2.**



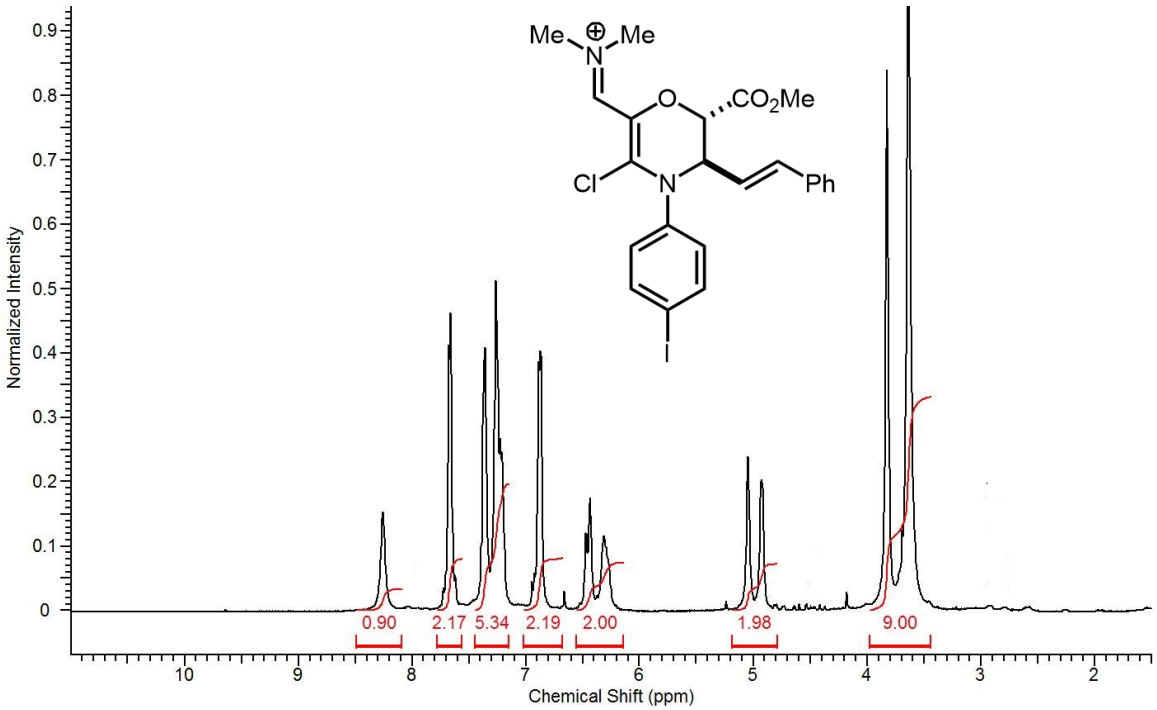
Spectra **1-7** Proton NMR spectrum of **4a3.**



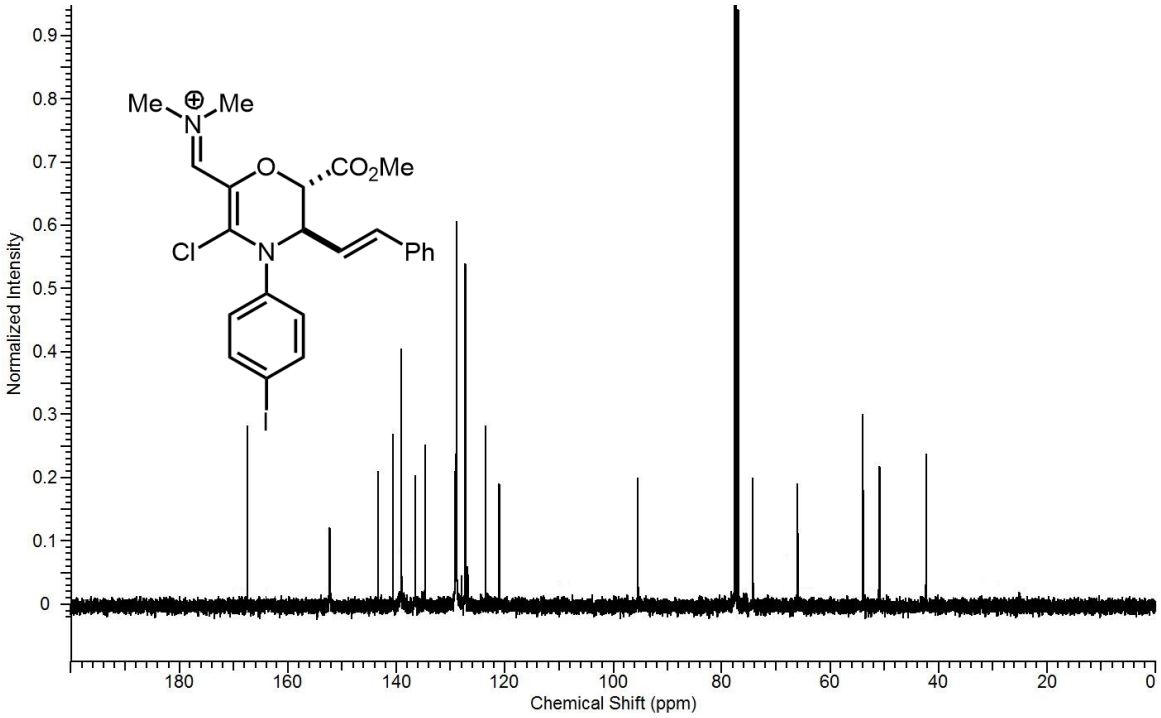
Spectra **1-8** Carbon NMR spectrum of **4a3.**



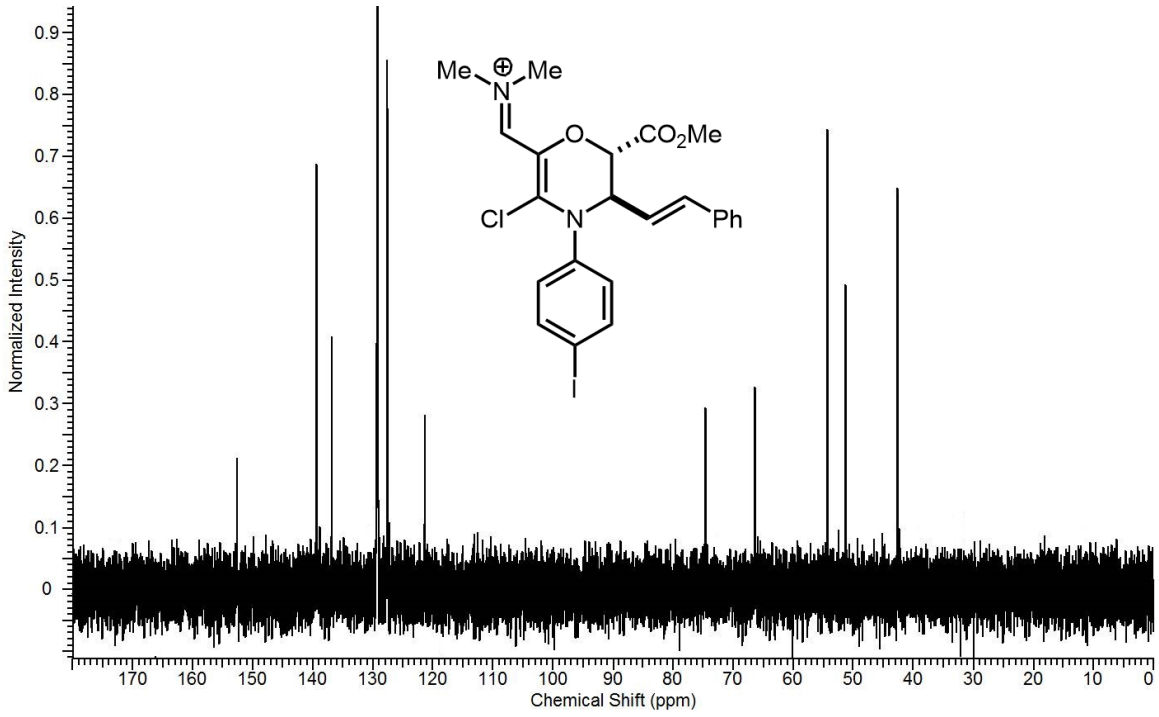
Spectra **1-9** DEPT-135 NMR spectrum of **4a3.**



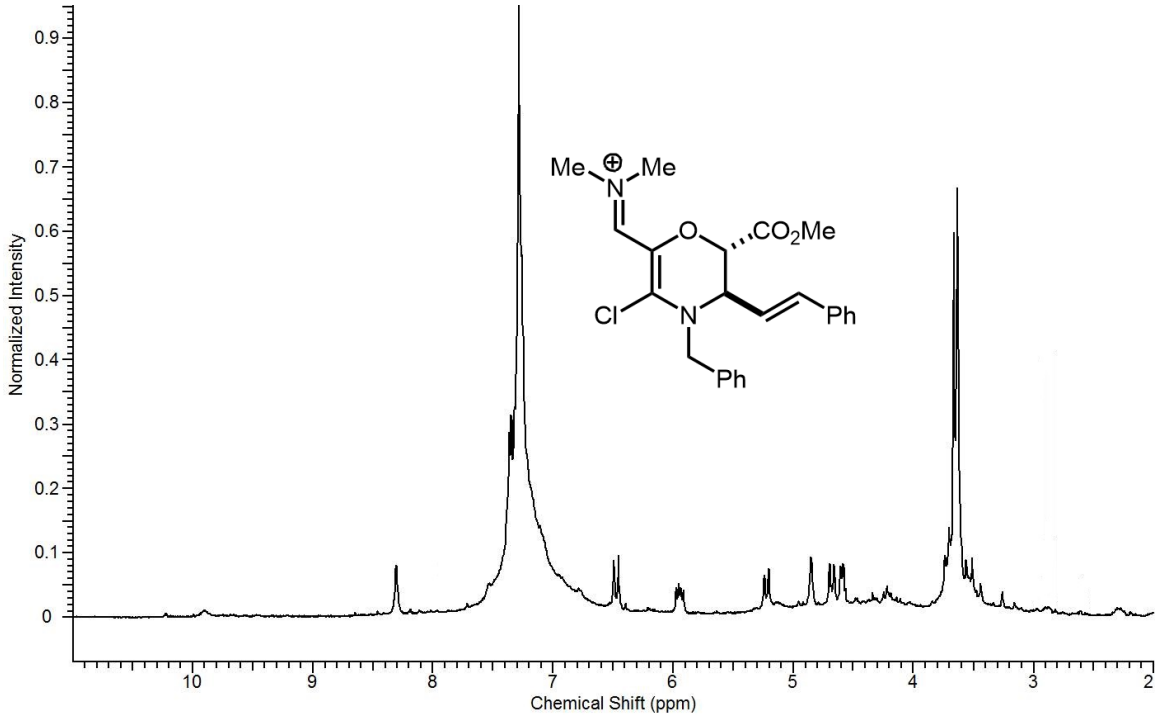
Spectra **1-10** Proton NMR spectrum of **4a4.**



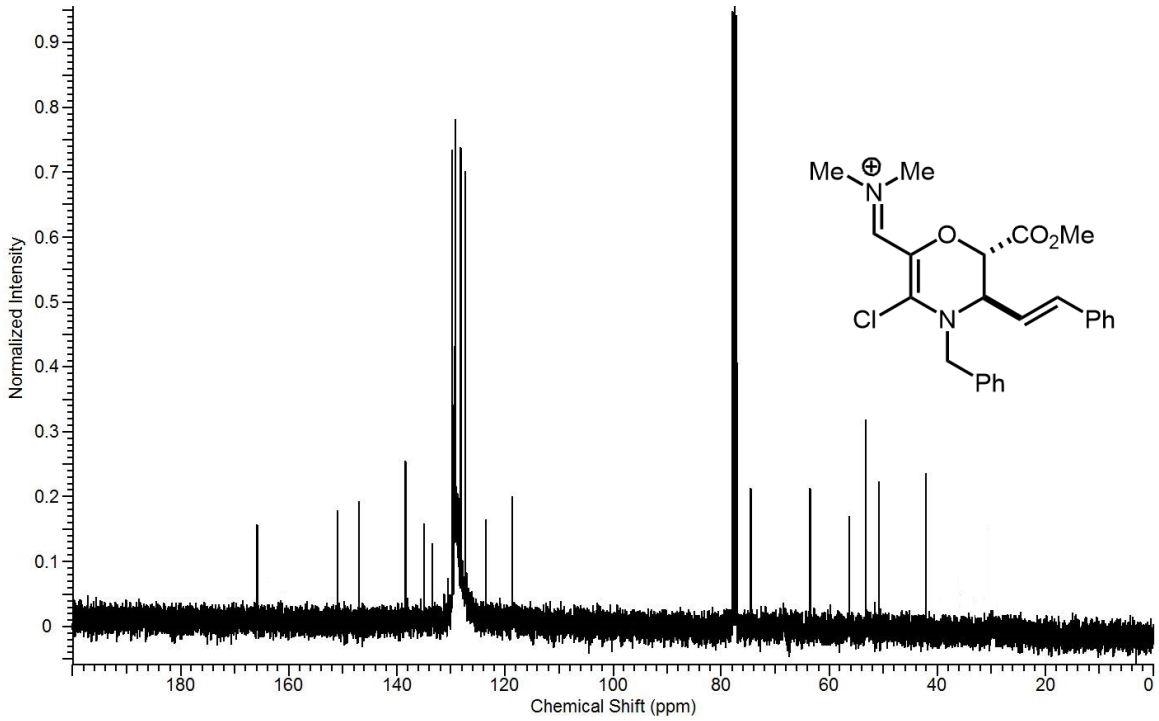
Spectra **1-11** Carbon NMR spectrum of **4a4.**



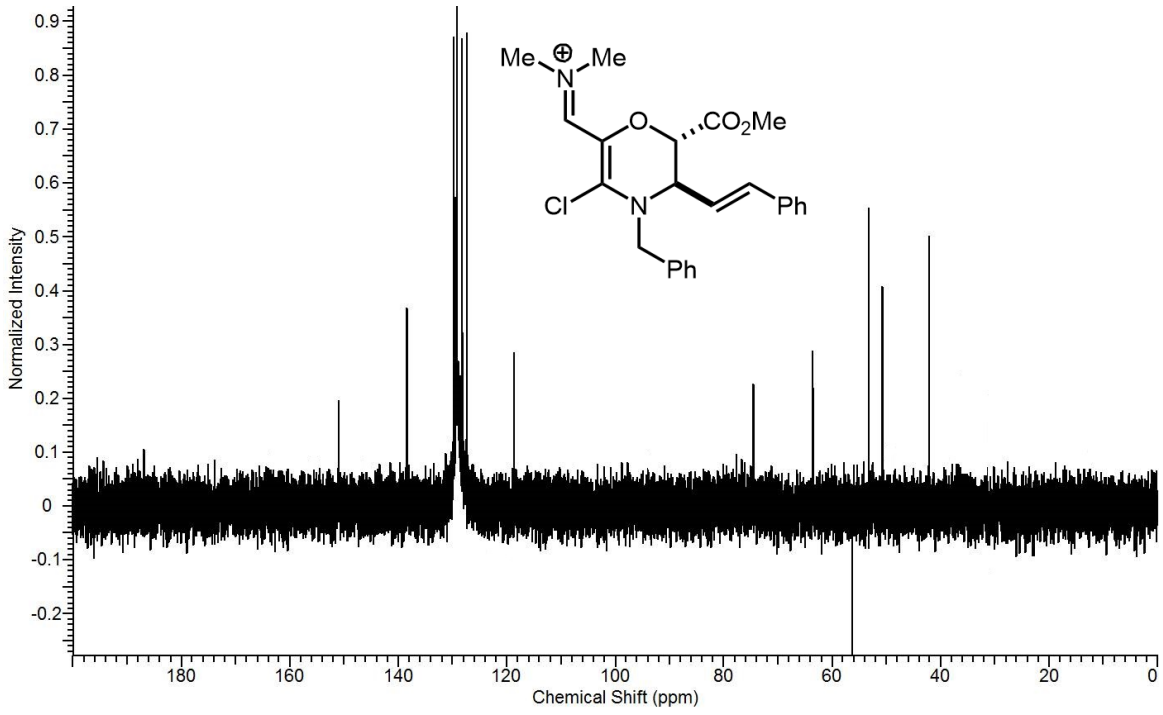
Spectra **1-12** DEPT-135 NMR spectrum of **4a4.**



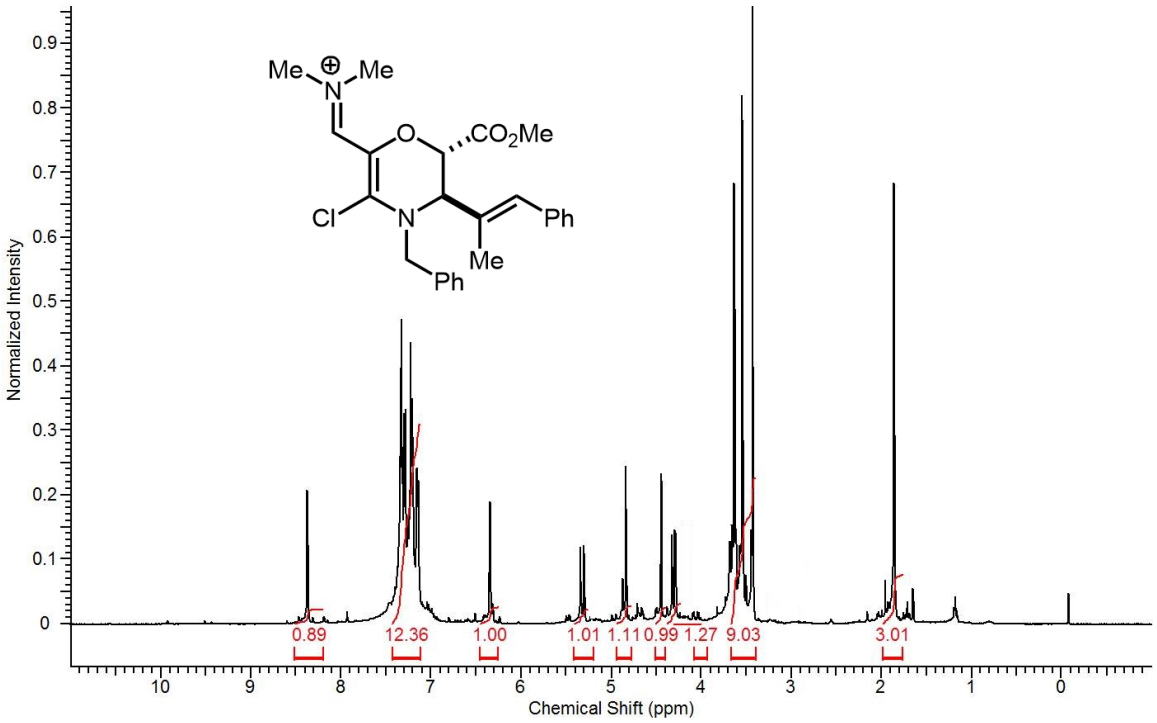
Spectra **1-13** Proton NMR spectrum of **4a5.**



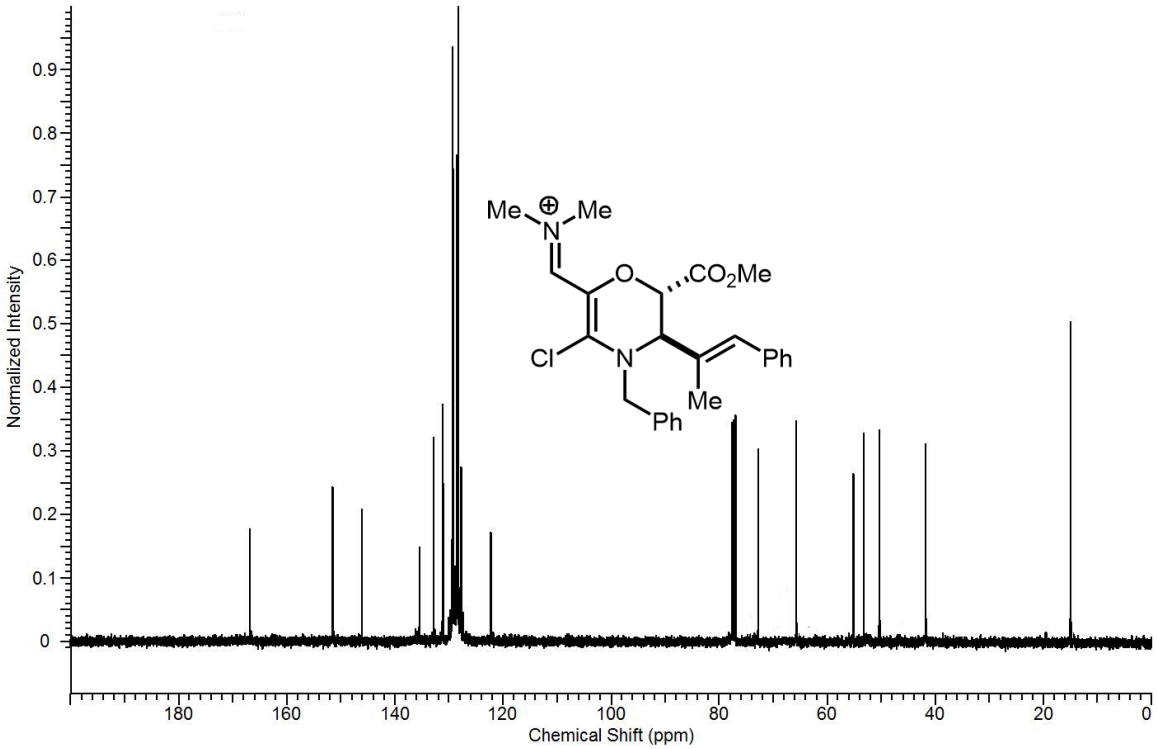
Spectra **1-14** Carbon NMR spectrum of **4a5.**



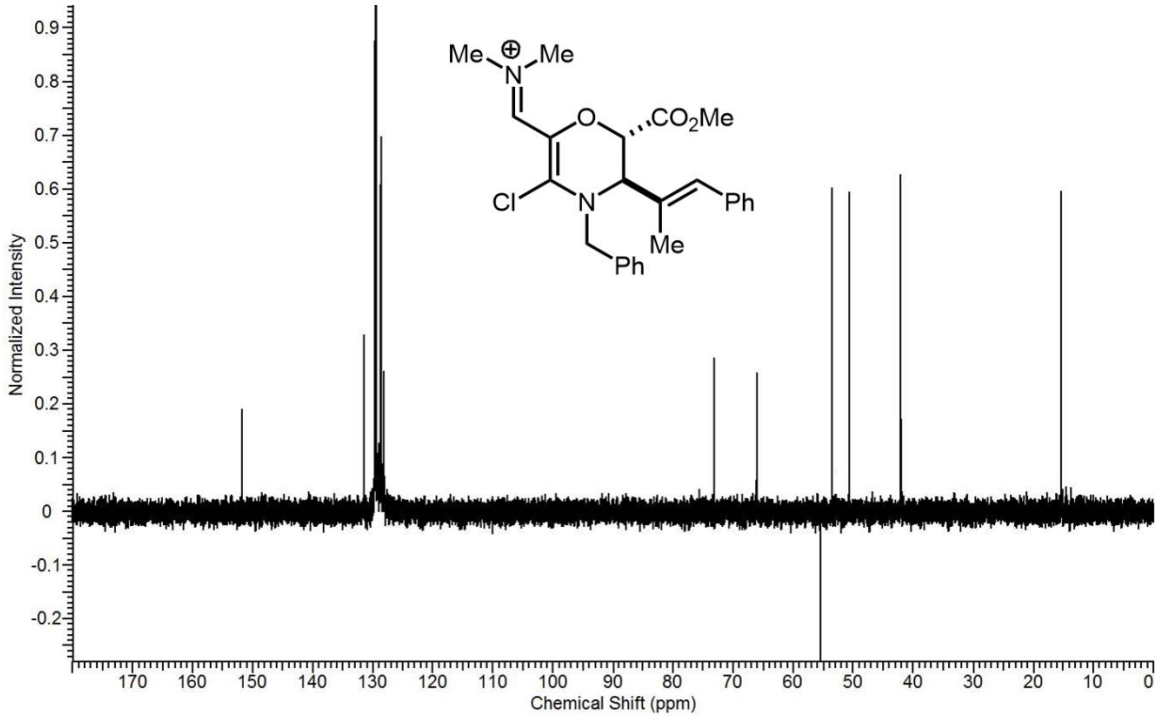
Spectra **1-15** DEPT-135 NMR spectrum of **4a5.**



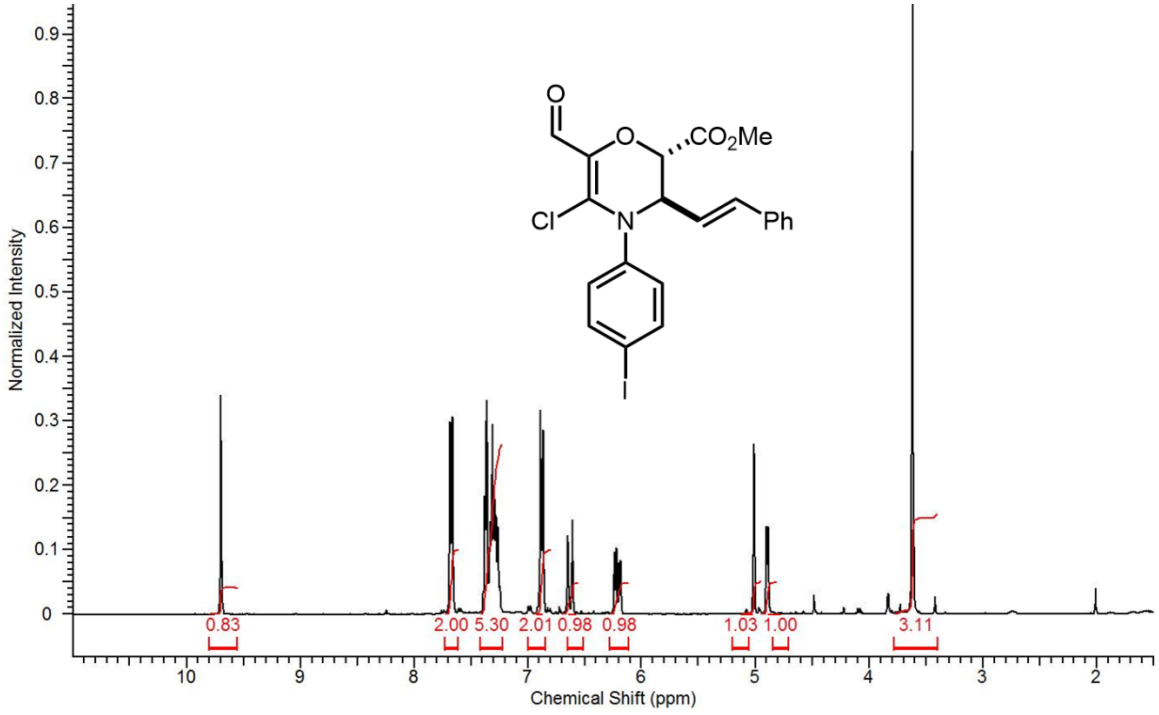
Spectra **1-16** Proton NMR spectrum of **4a6.**



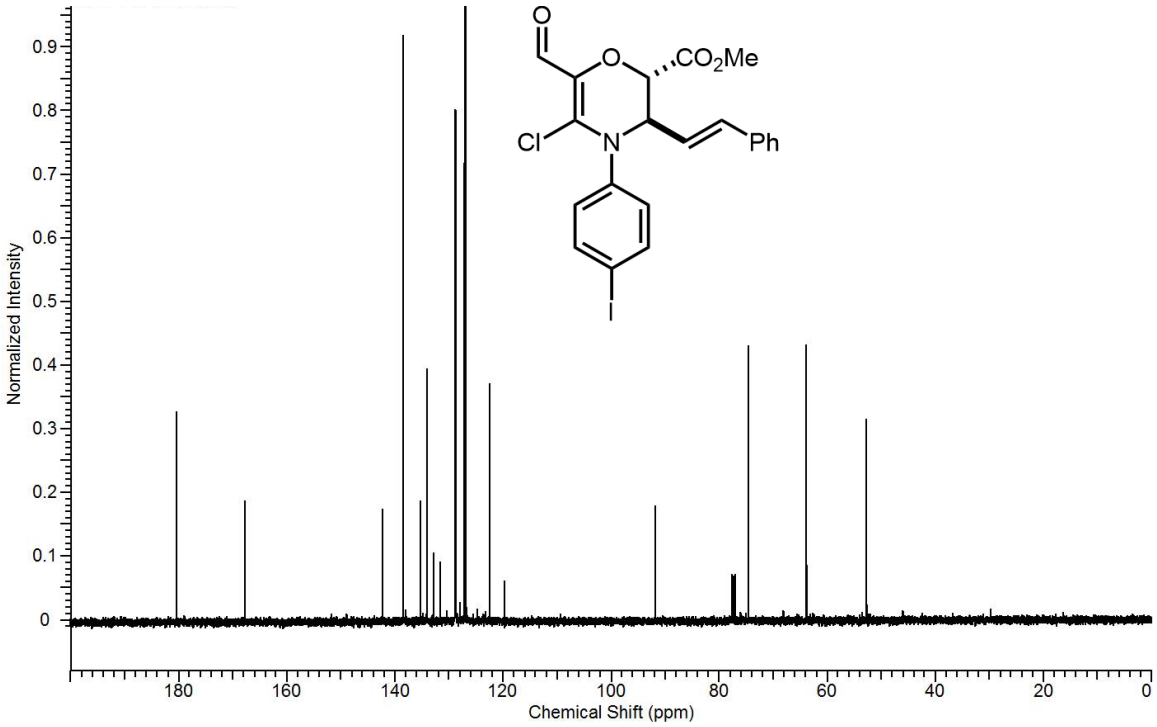
Spectra **1-17** Carbon NMR spectrum of **4a6.**



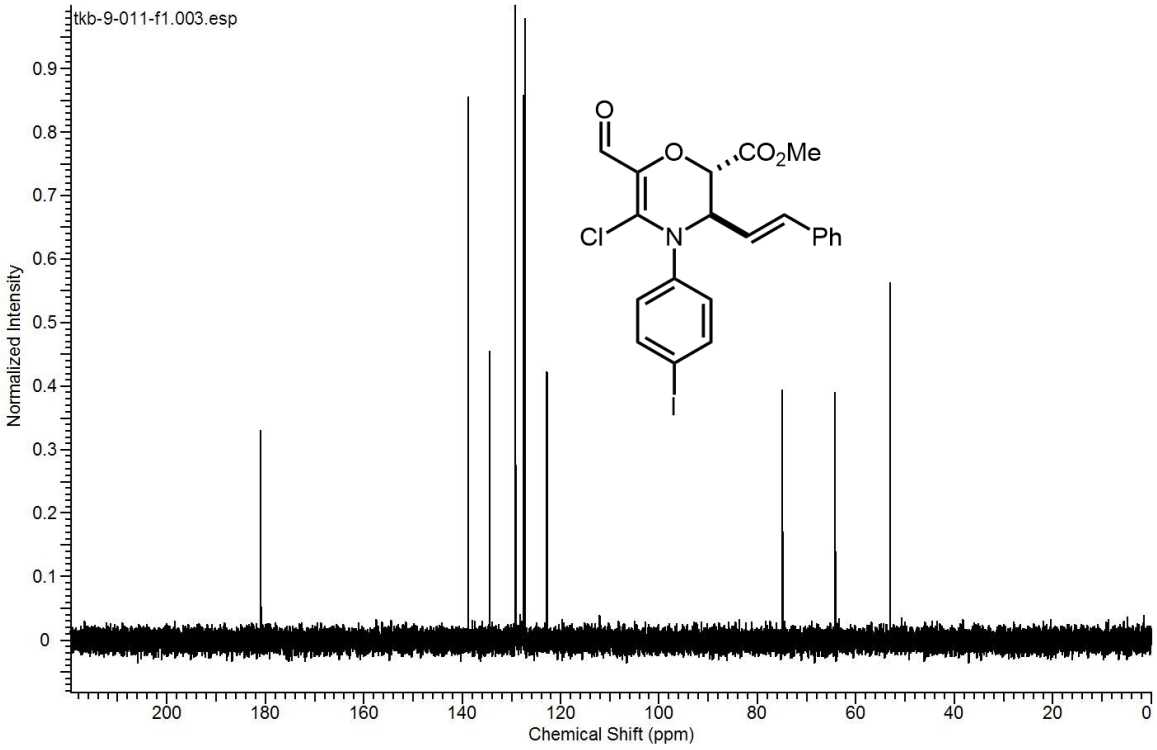
Spectra **1-18** DEPT-135 NMR spectrum of **4a6.**



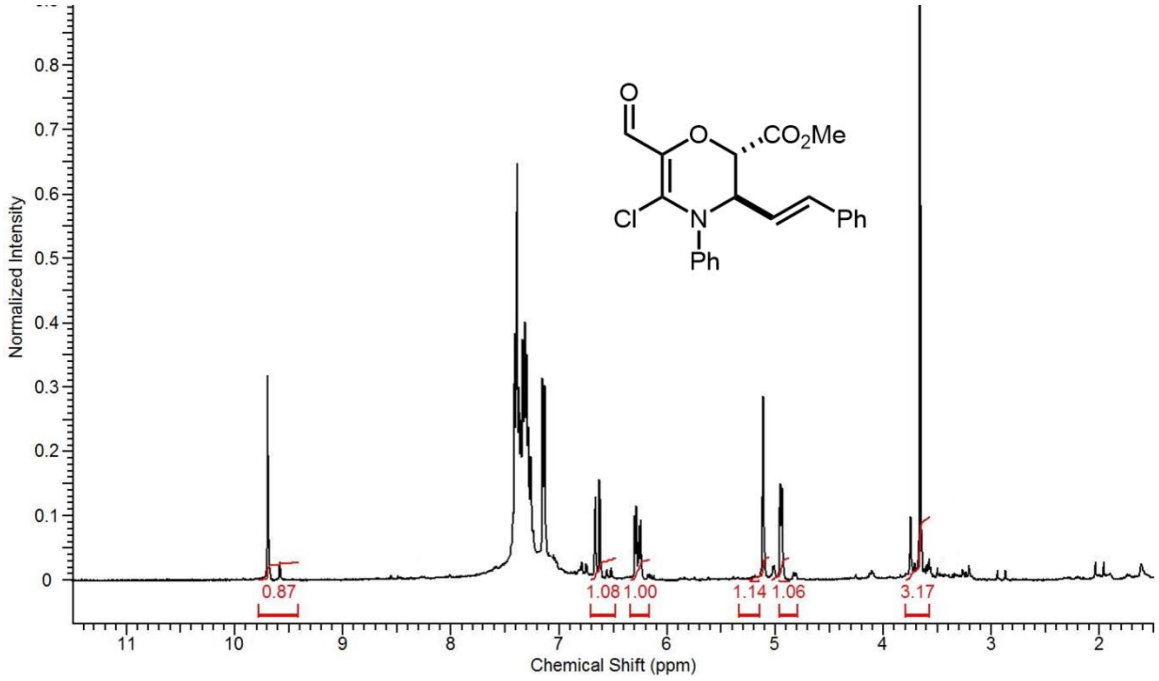
Spectra **1-19** Proton NMR spectrum of **4b1.**



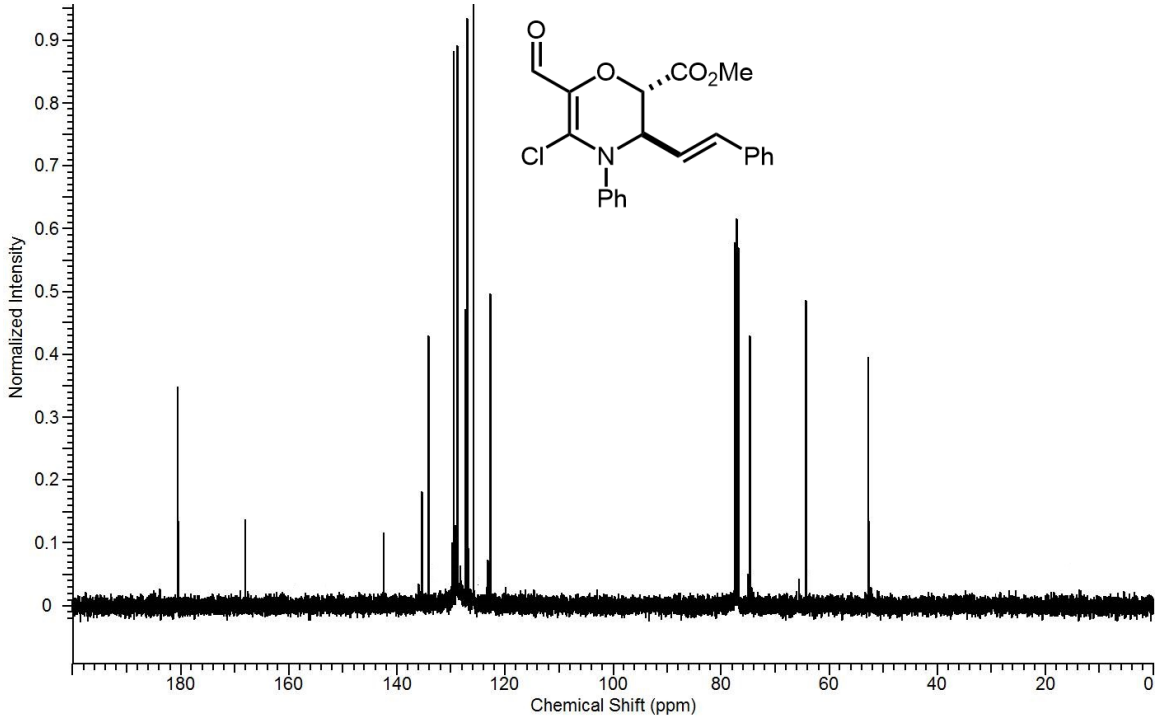
Spectra **1-20** Carbon NMR spectrum of **4b1.**



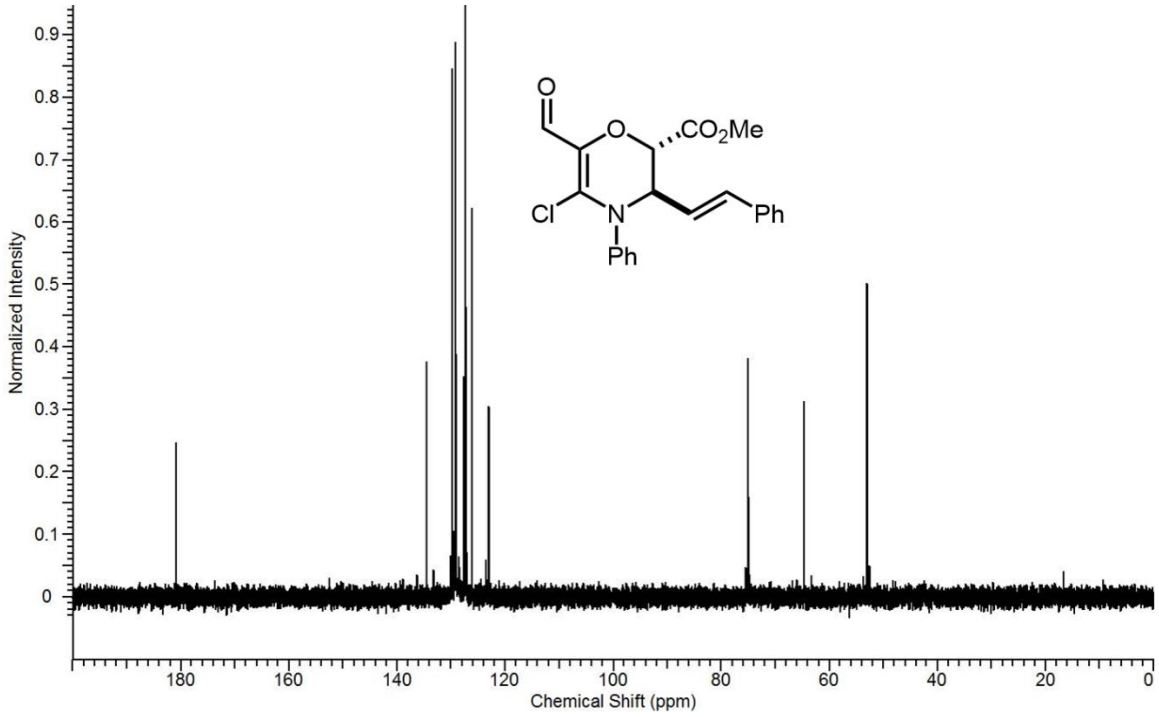
Spectra **1-21** DEPT-135 NMR spectrum of **4b1.**



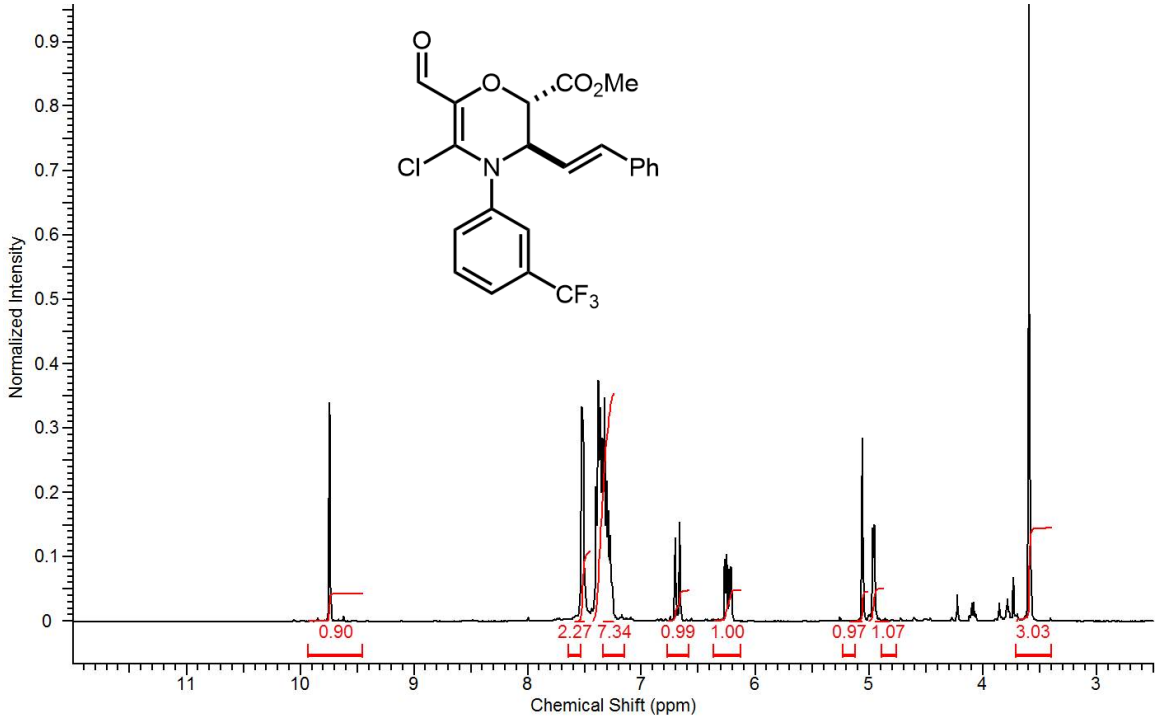
Spectra **1-22** Proton NMR spectrum of **4b2.**



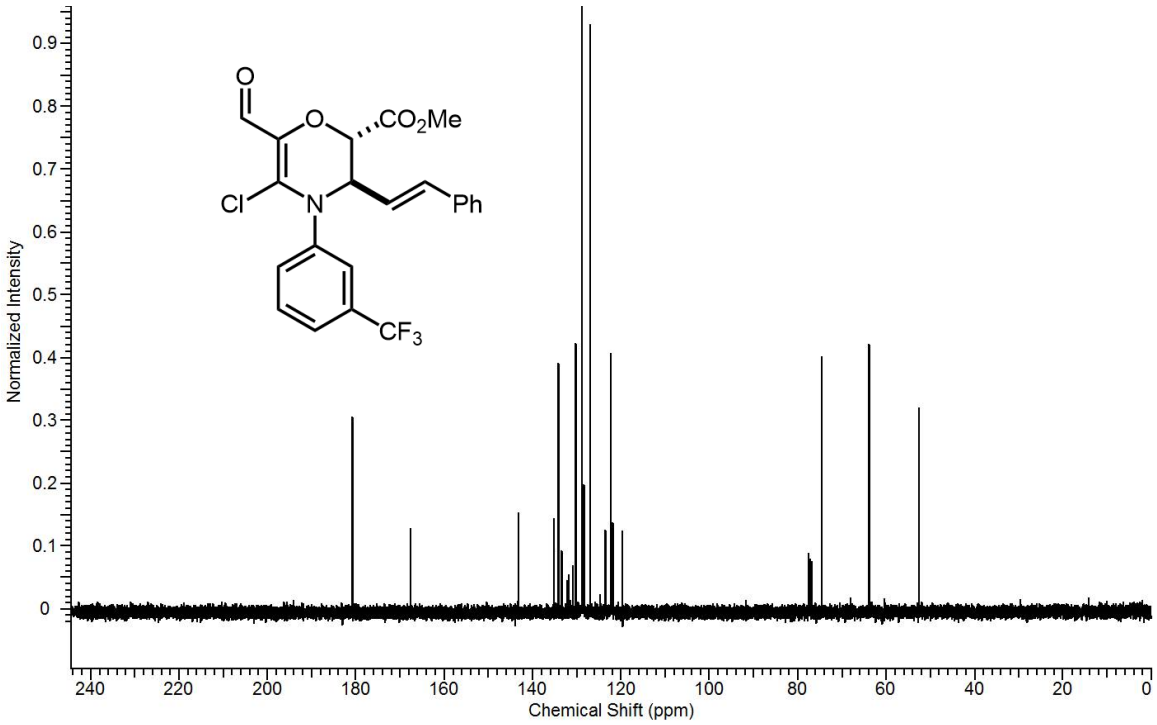
Spectra **1-23** Carbon NMR spectrum of **4b2.**



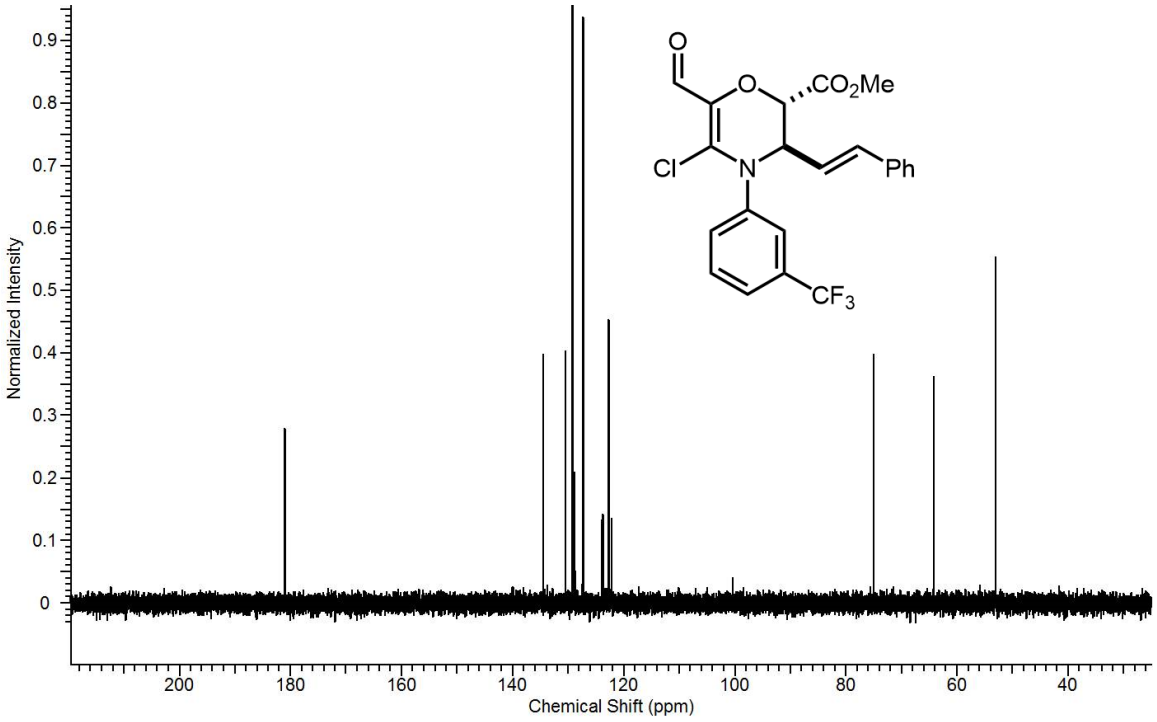
Spectra **1-24** DEPT-135 NMR spectrum of **4b2.**



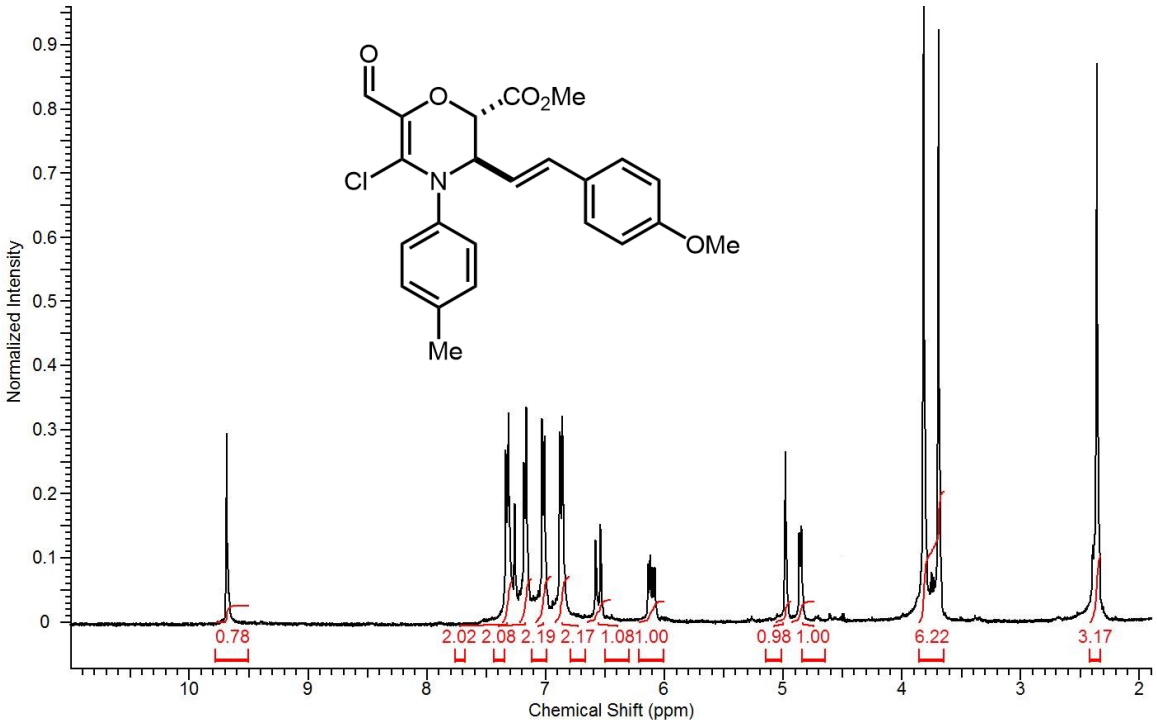
Spectra **1-25** Proton NMR spectrum of **4b3.**



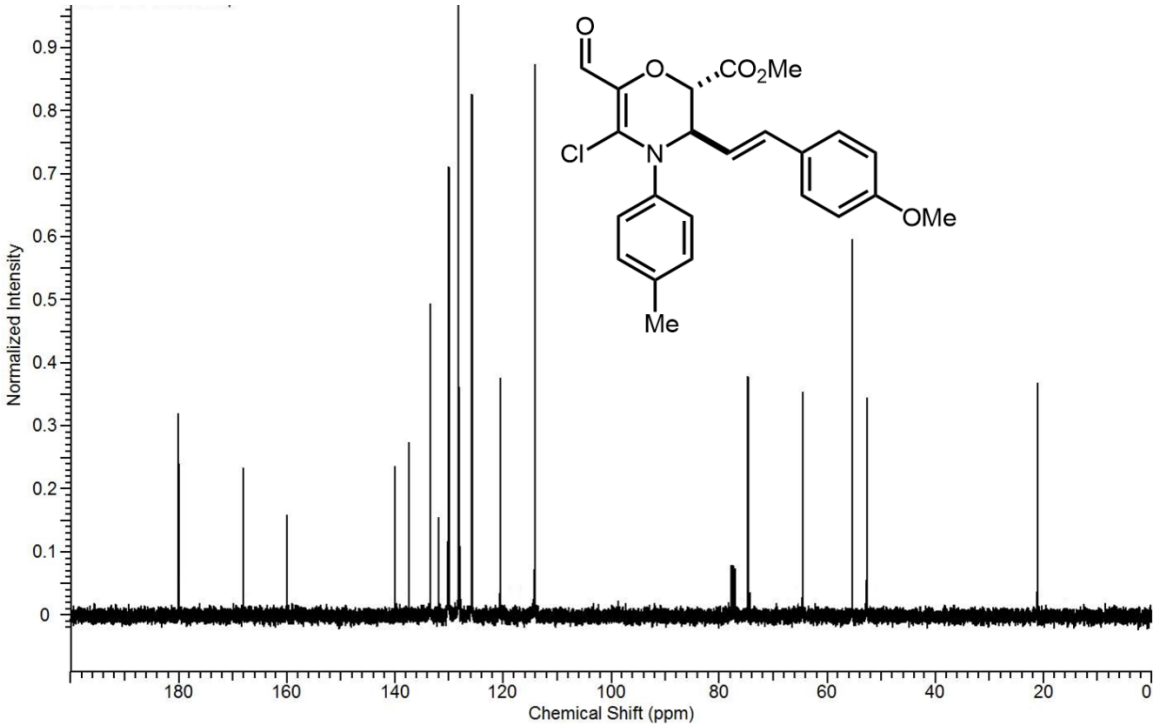
Spectra **1-26** Carbon NMR spectrum of **4b3.**



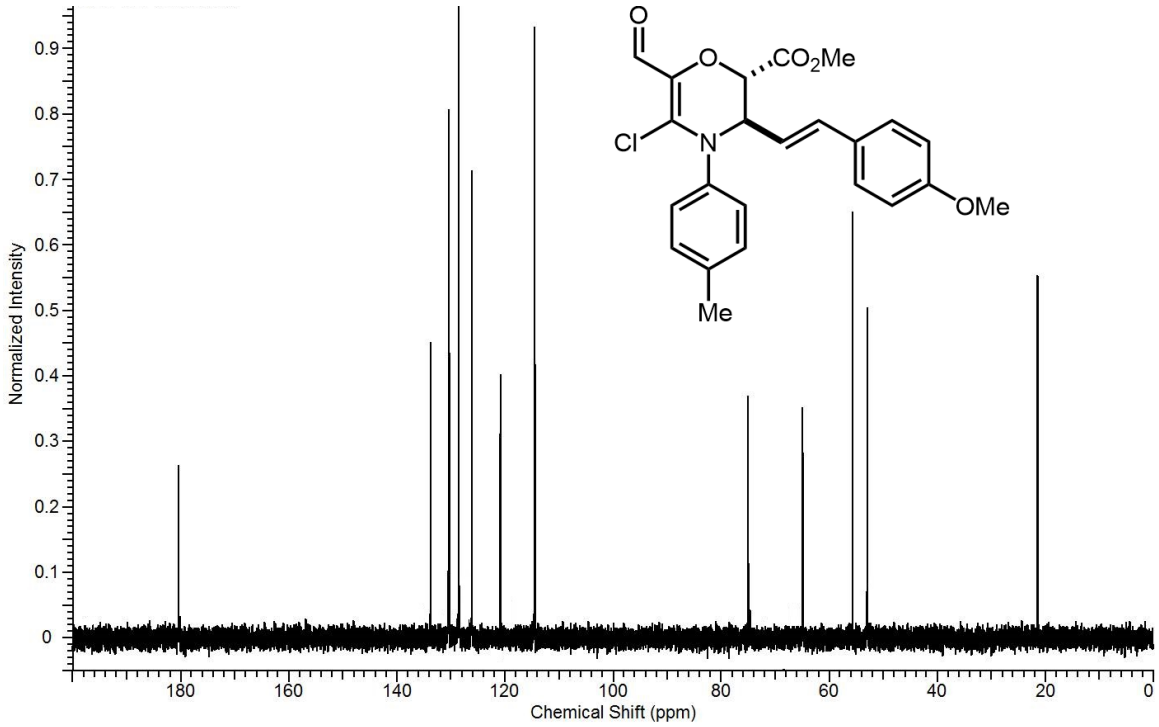
Spectra **1-27** DEPT-135 NMR spectrum of **4b3.**



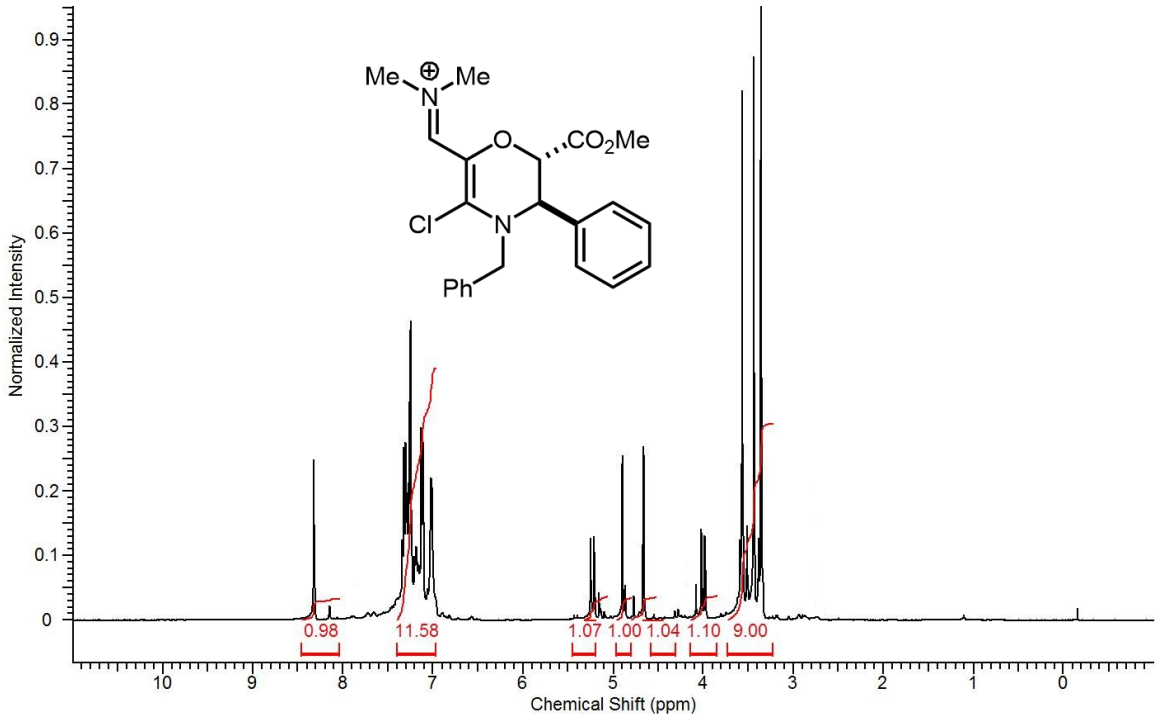
Spectra **1-28** Proton NMR spectrum of **4b4.**



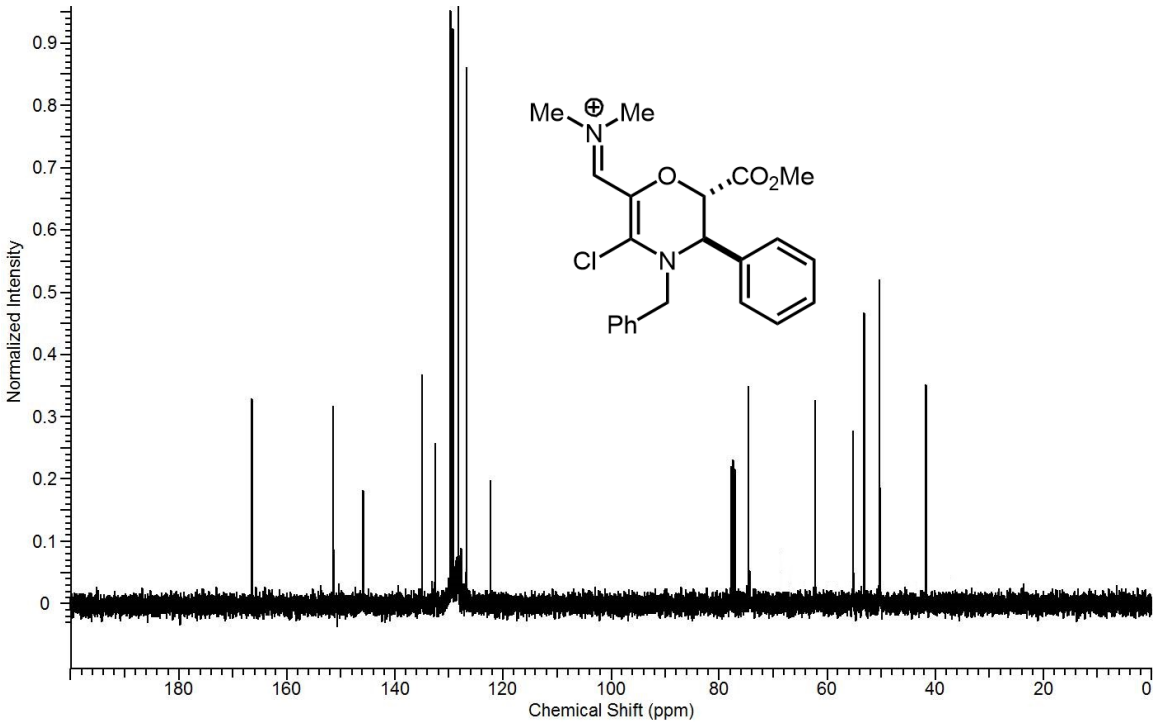
Spectra **1-29** Carbon NMR spectrum of **4b4.**



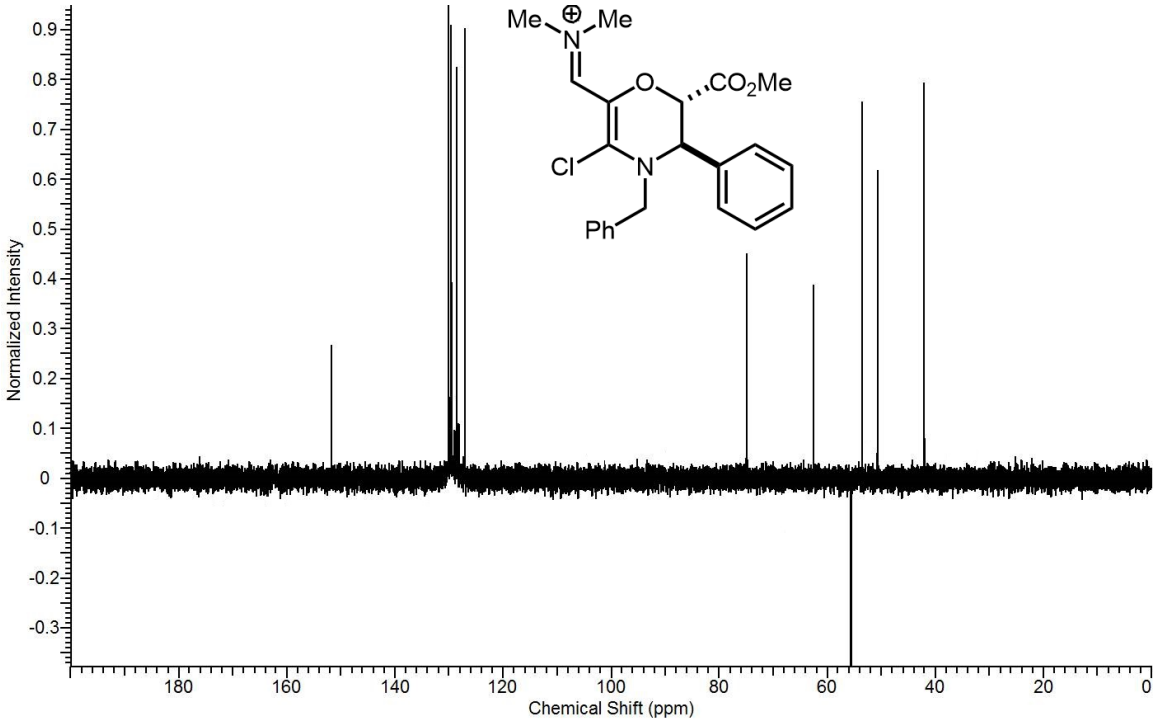
Spectra **1-30** DEPT-135 NMR spectrum of **4b4.**



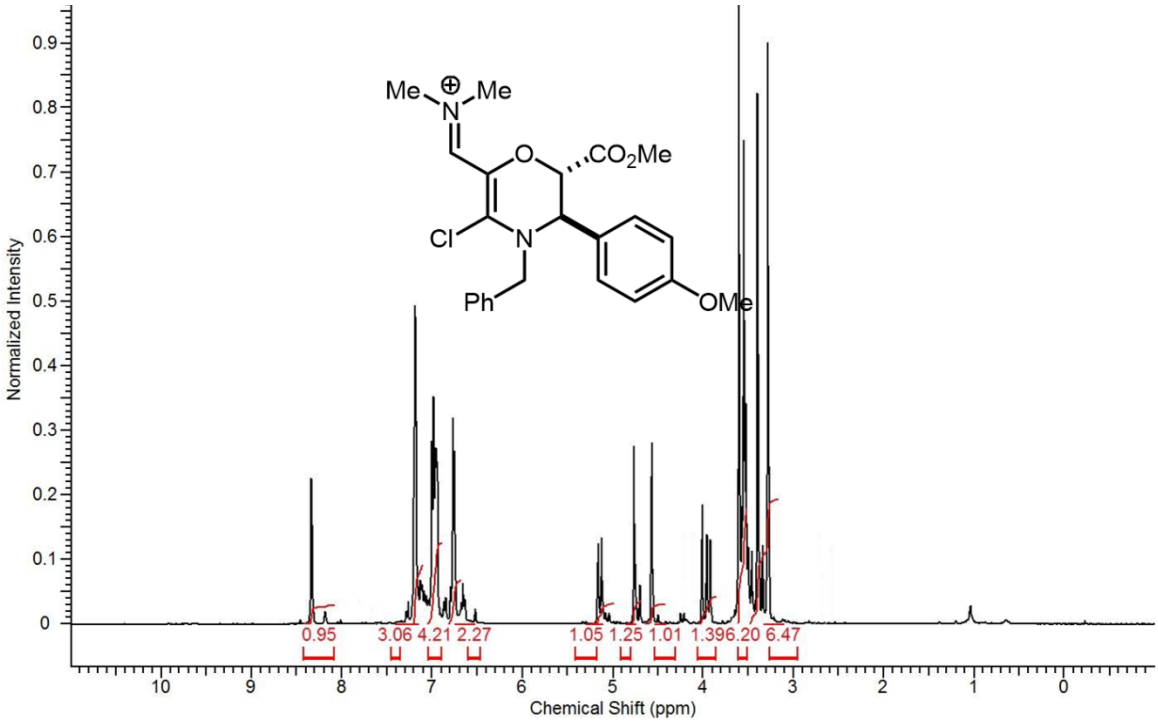
Spectra **1-31** Proton NMR spectrum of **10a1.**



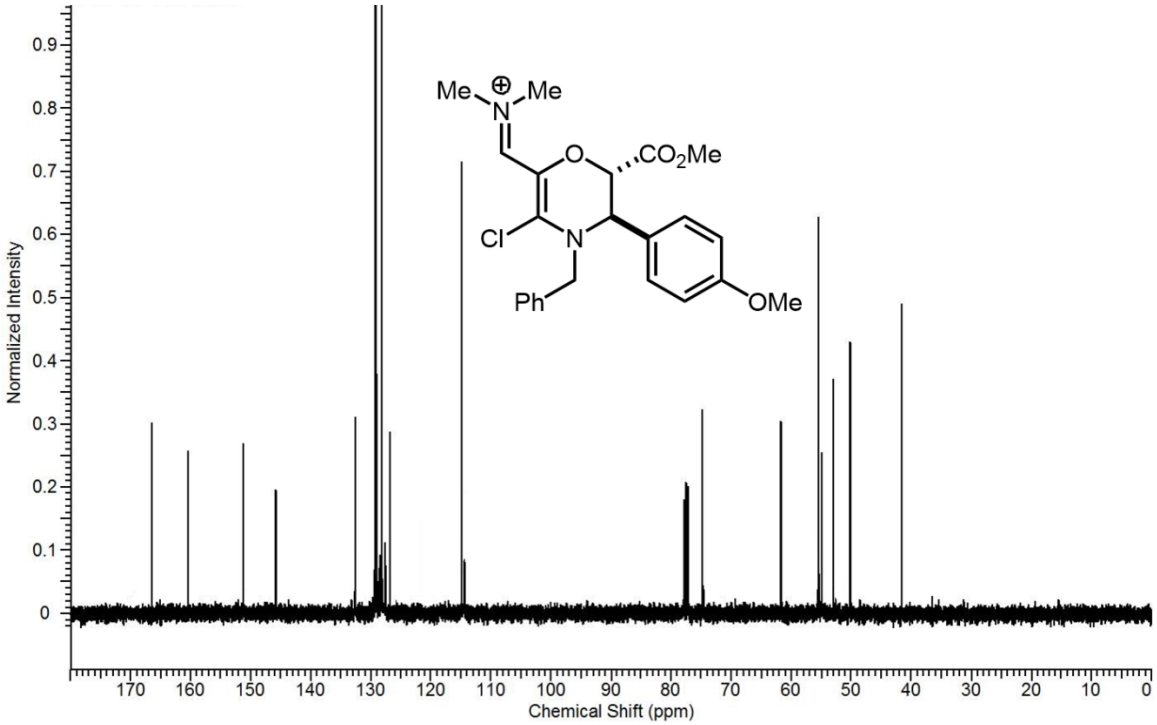
Spectra **1-32** Carbon NMR spectrum of **10a1.**



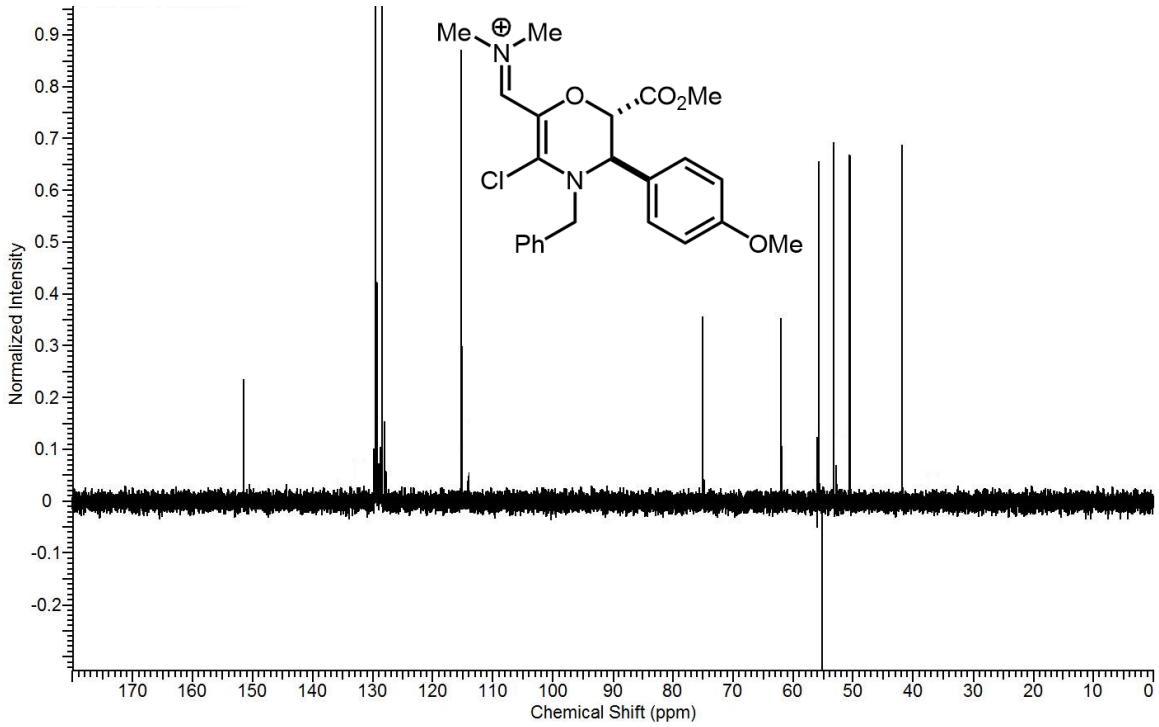
Spectra **1-33** DEPT-135 NMR spectrum of **10a1.**



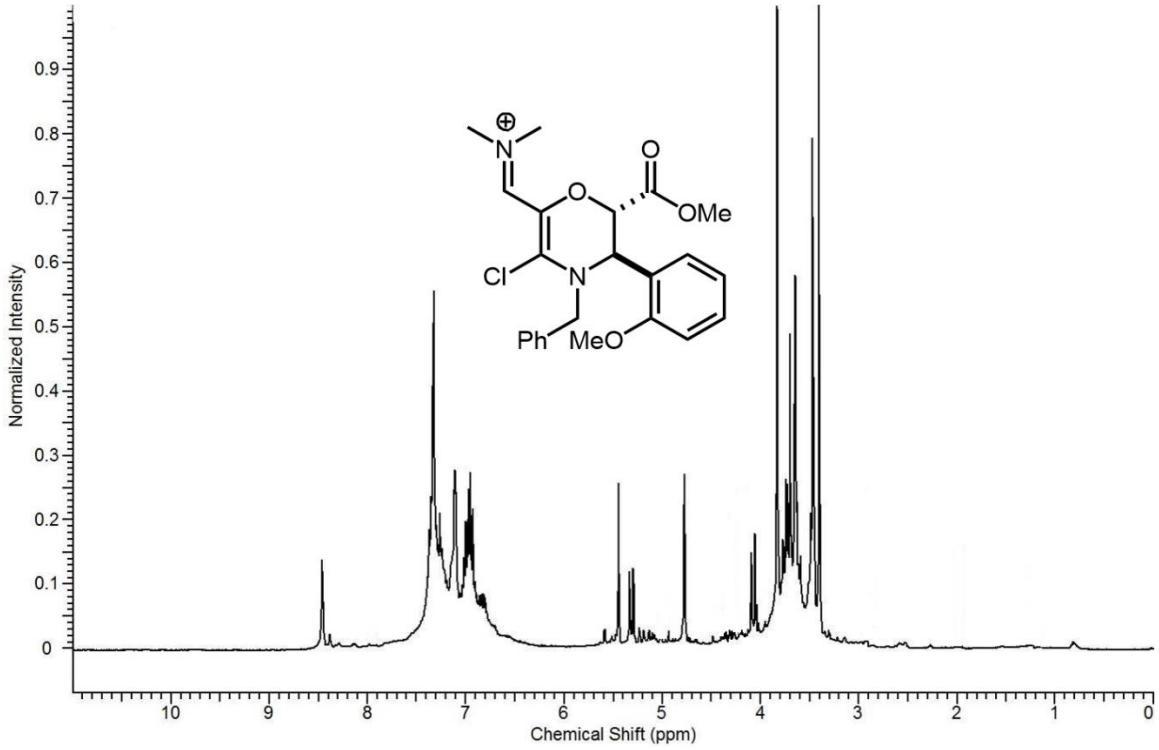
Spectra **1-34** Proton NMR spectrum of **10a2.**



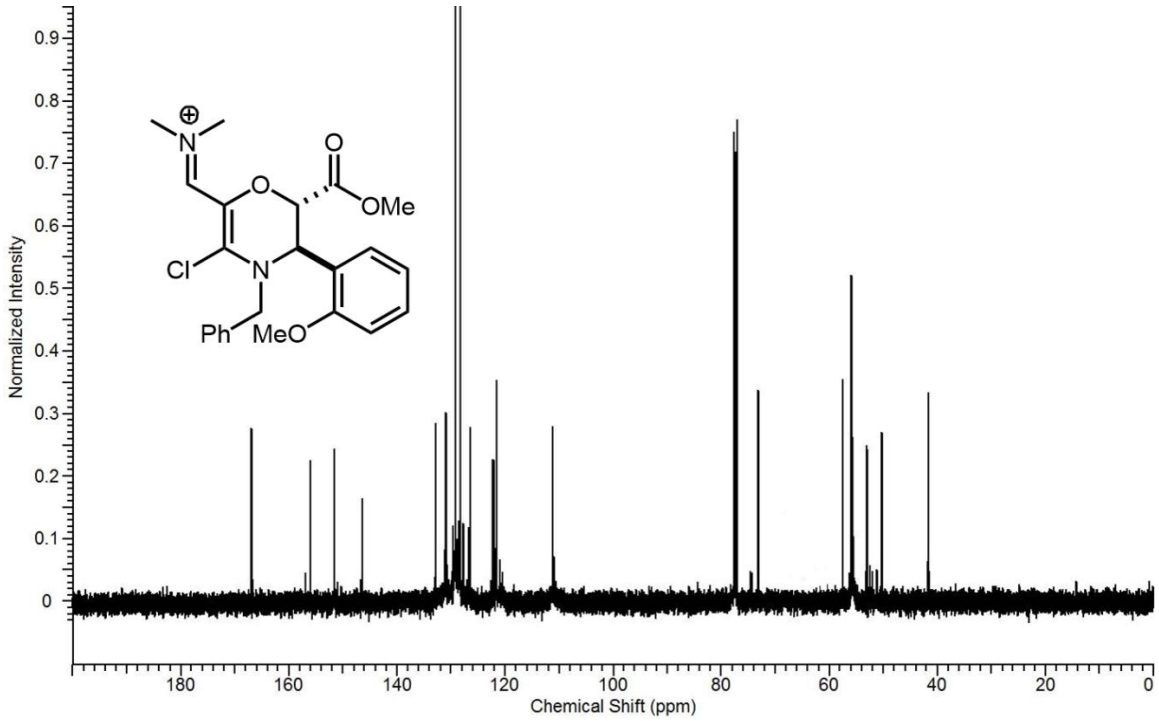
Spectra **1-35** Carbon NMR spectrum of **10a2.**



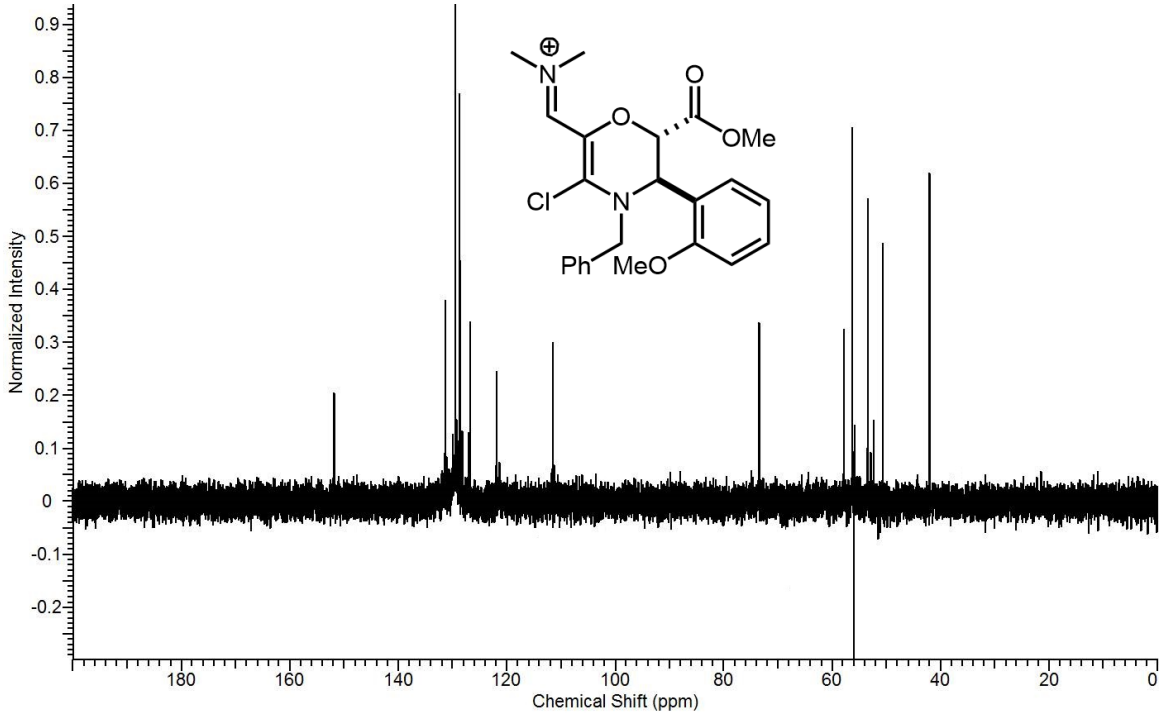
Spectra **1-36** DEPT-135 NMR spectrum of **10a2.**



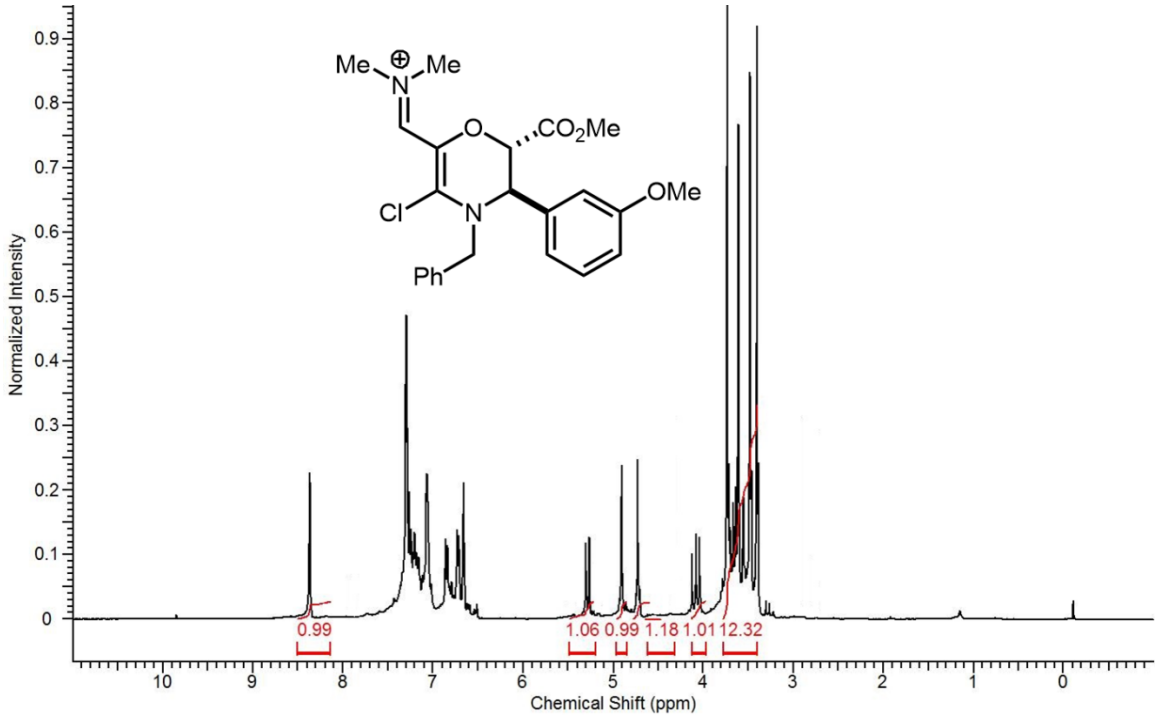
Spectra **1-37** Proton NMR spectrum of **10a3.**



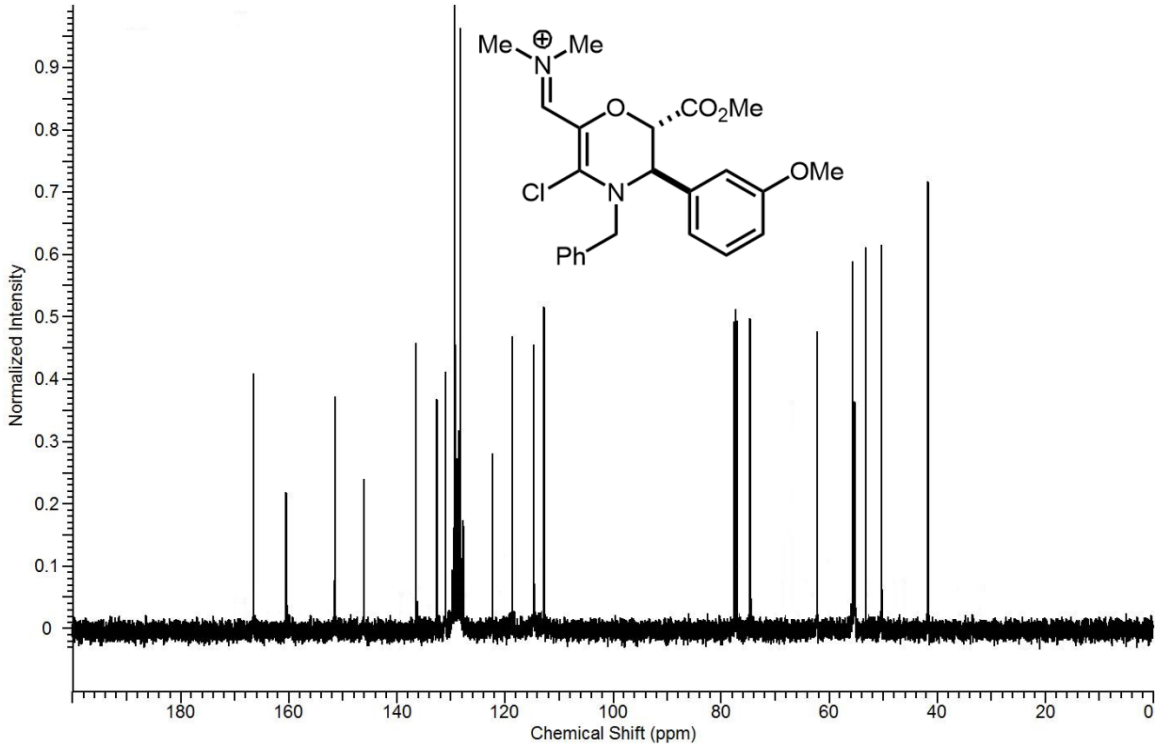
Spectra **1-38** Carbon NMR spectrum of **10a3.**



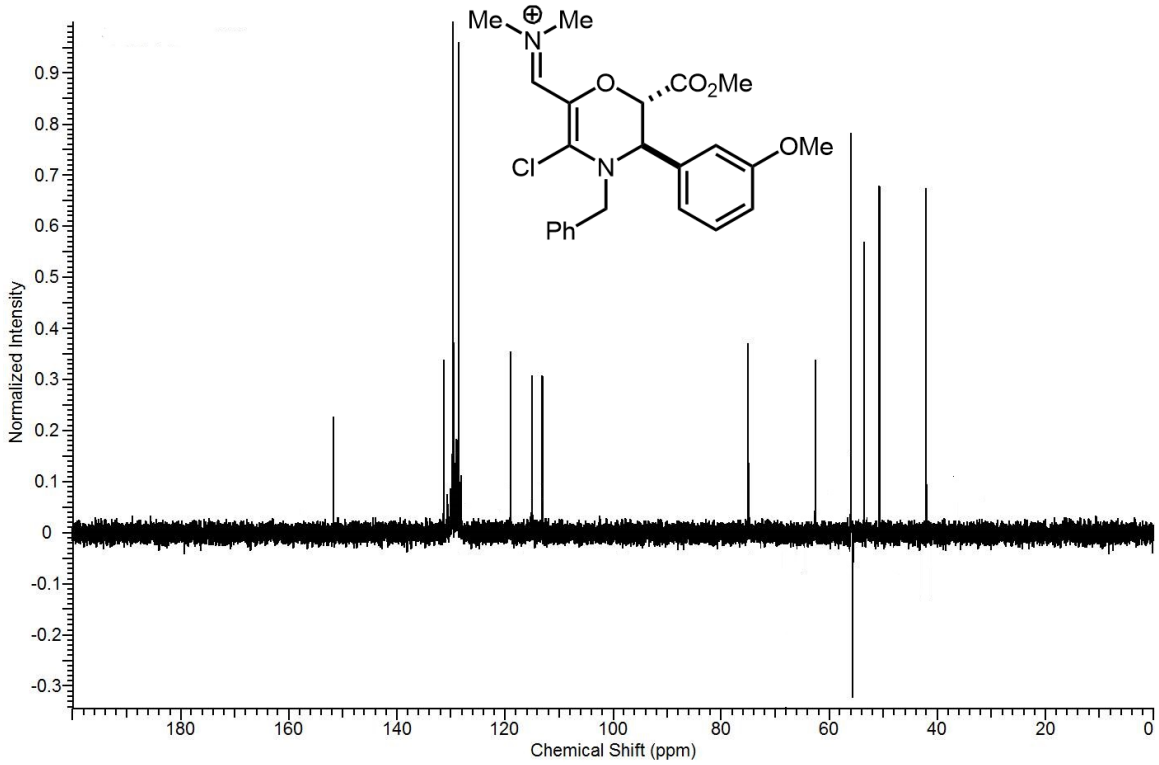
Spectra **1-39** DEPT-135 NMR spectrum of **10a3.**



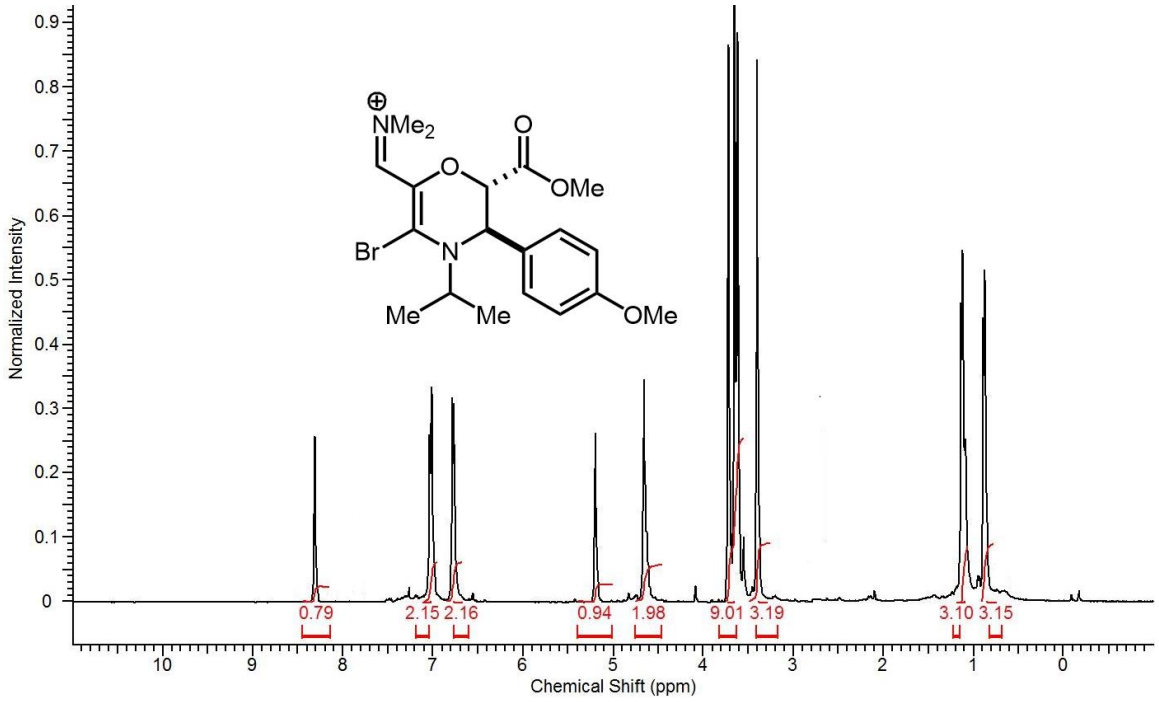
Spectra **1-40** Proton NMR spectrum of **10a4.**



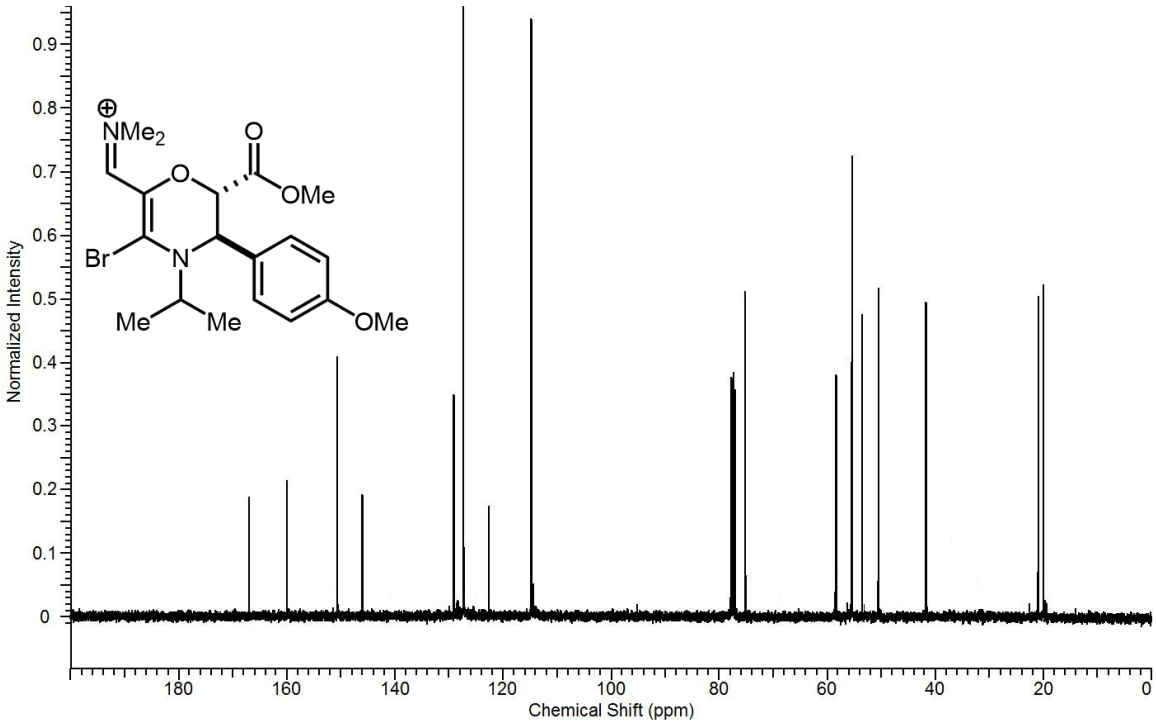
Spectra **1-41** Carbon NMR spectrum of **10a4.**



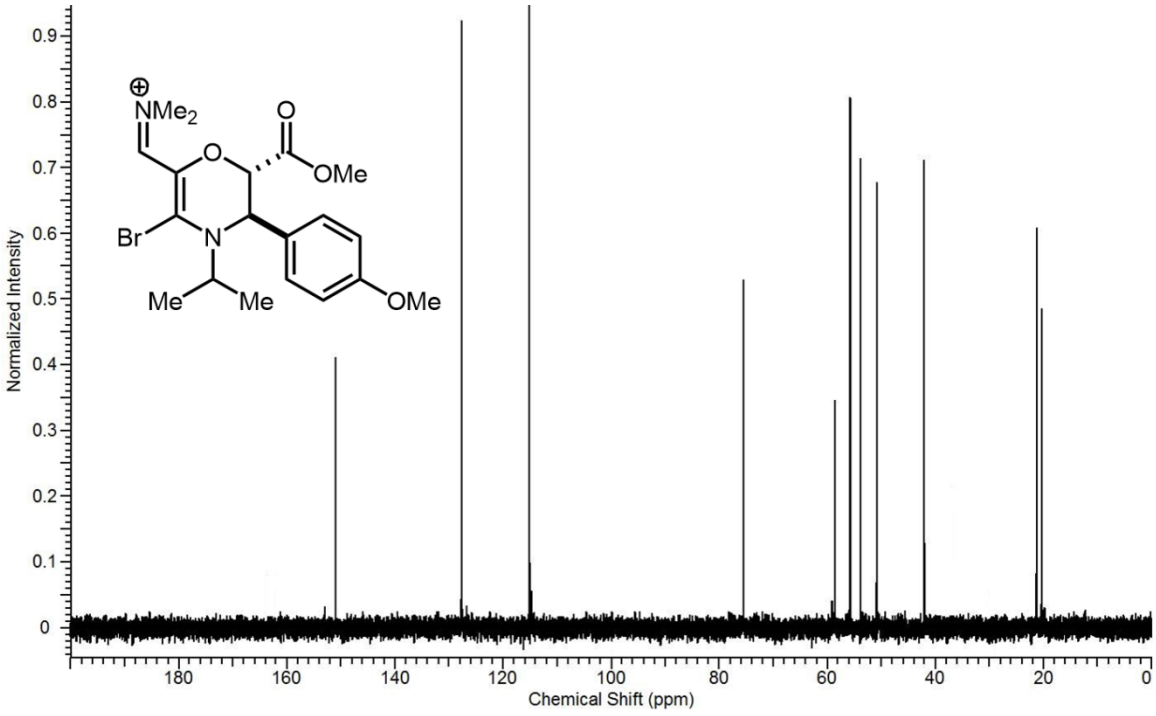
Spectra **1-42** DEPT-135 NMR spectrum of **10a4.**



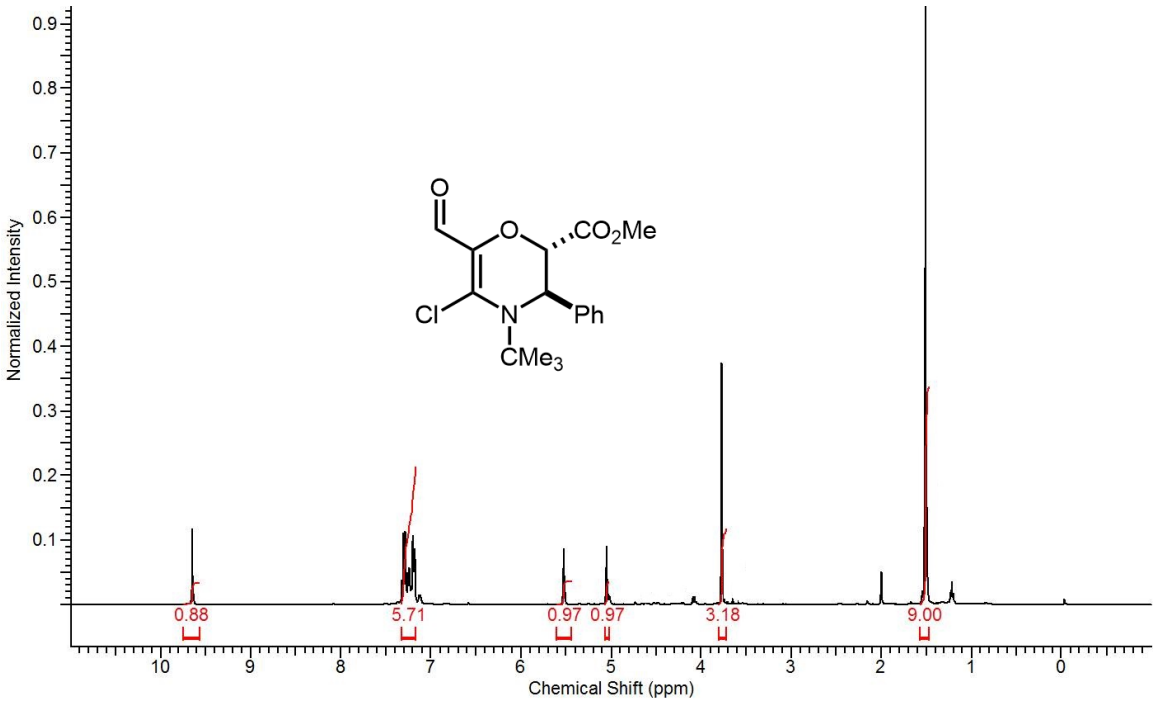
Spectra **1-43** Proton NMR spectrum of **10a5.**



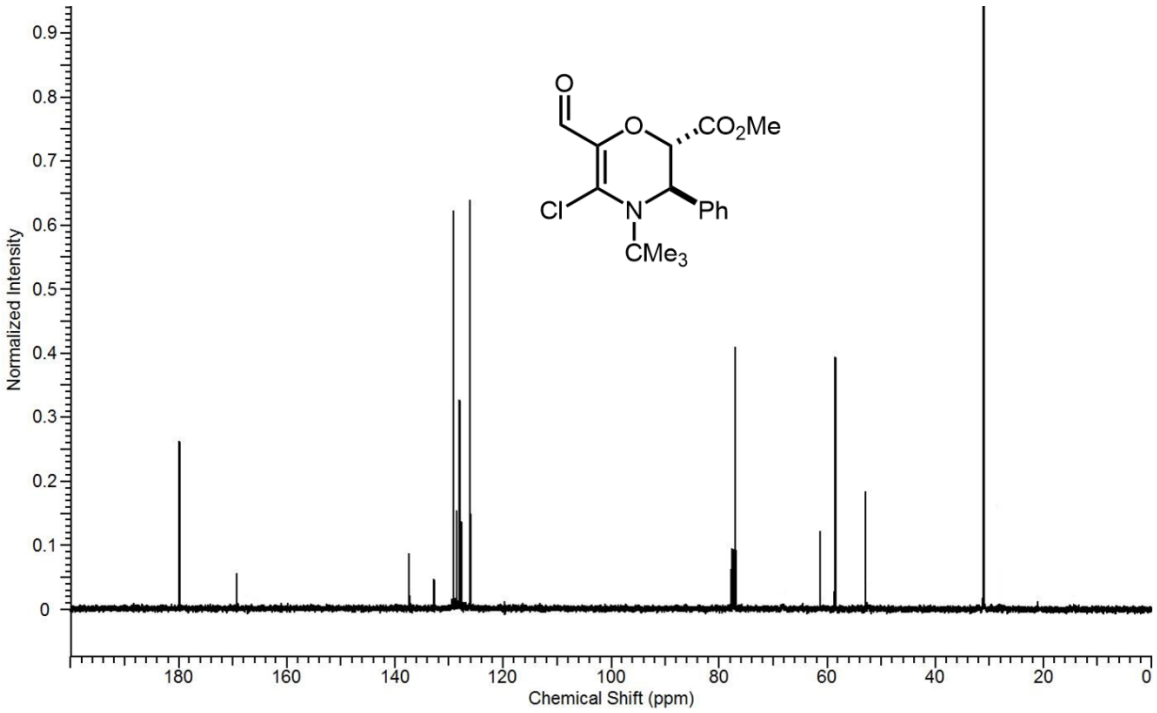
Spectra **1-44** Carbon NMR spectrum of **10a5.**



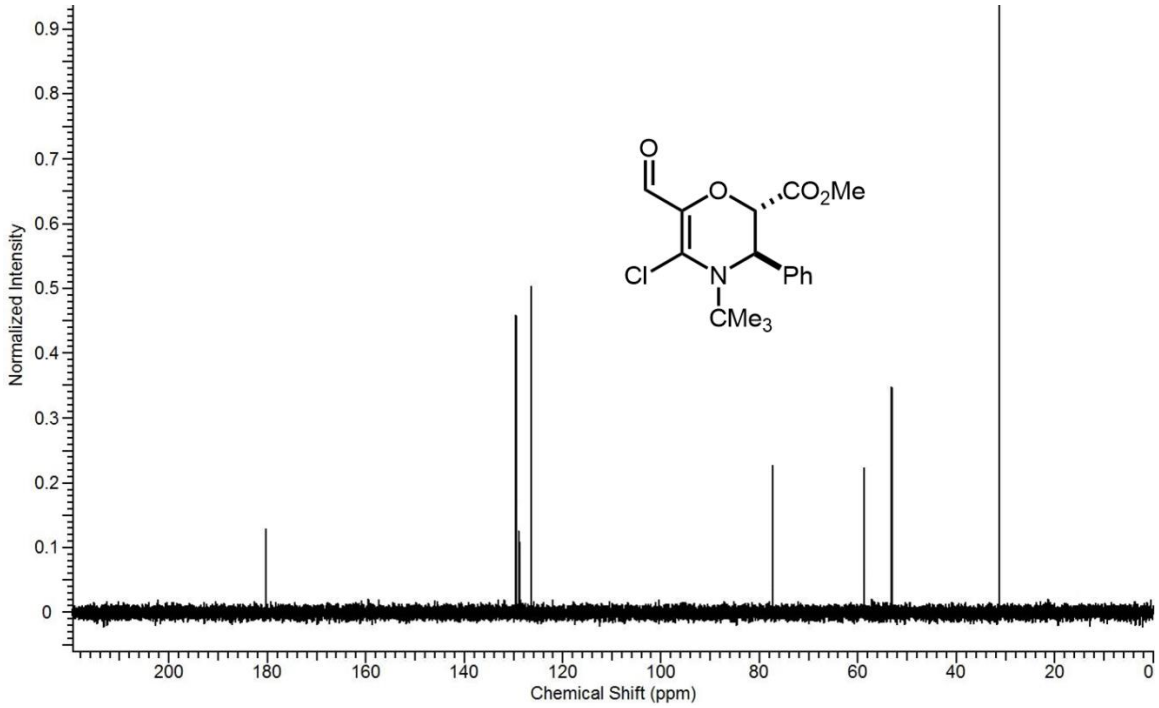
Spectra **1-45** DEPT-135 NMR spectrum of **10a5.**



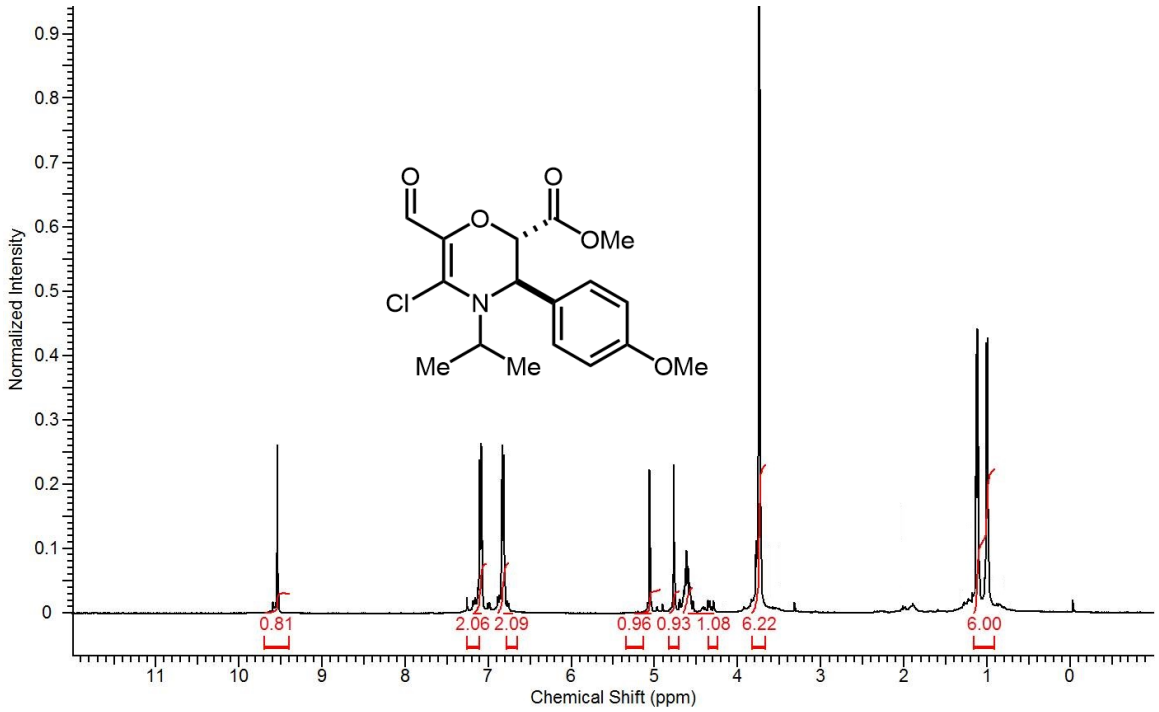
Spectra **1-46** Proton NMR spectrum of **10b1.**



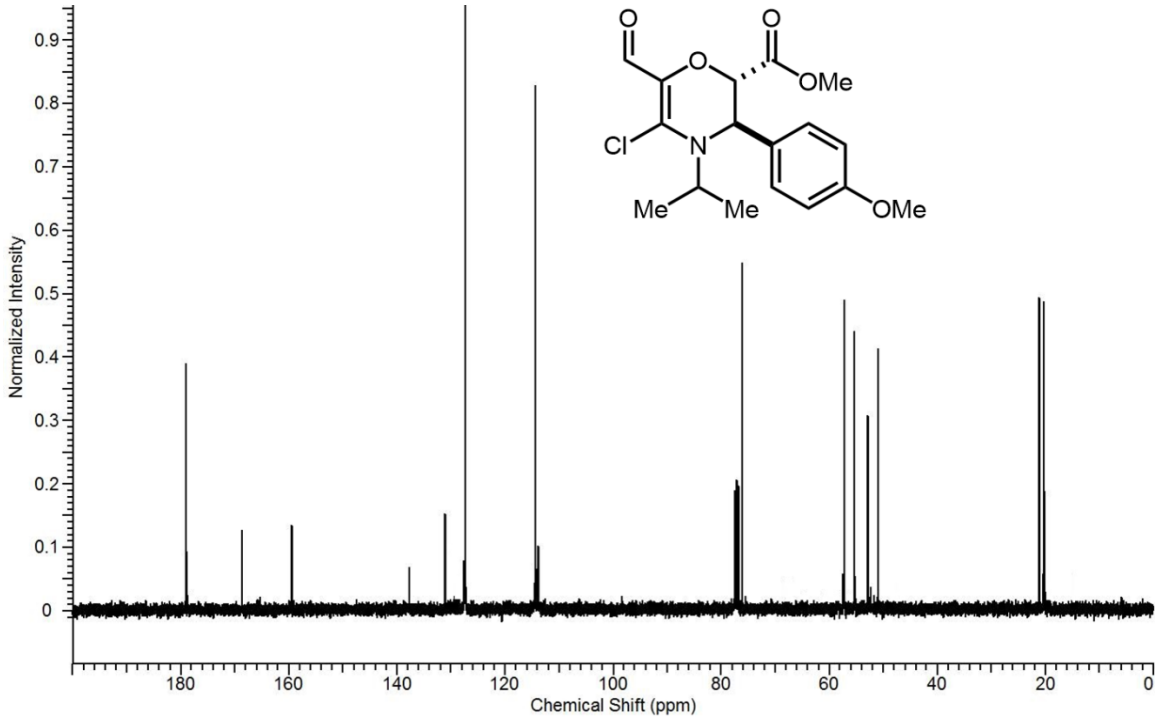
Spectra **1-47** Carbon NMR spectrum of **10b1.**



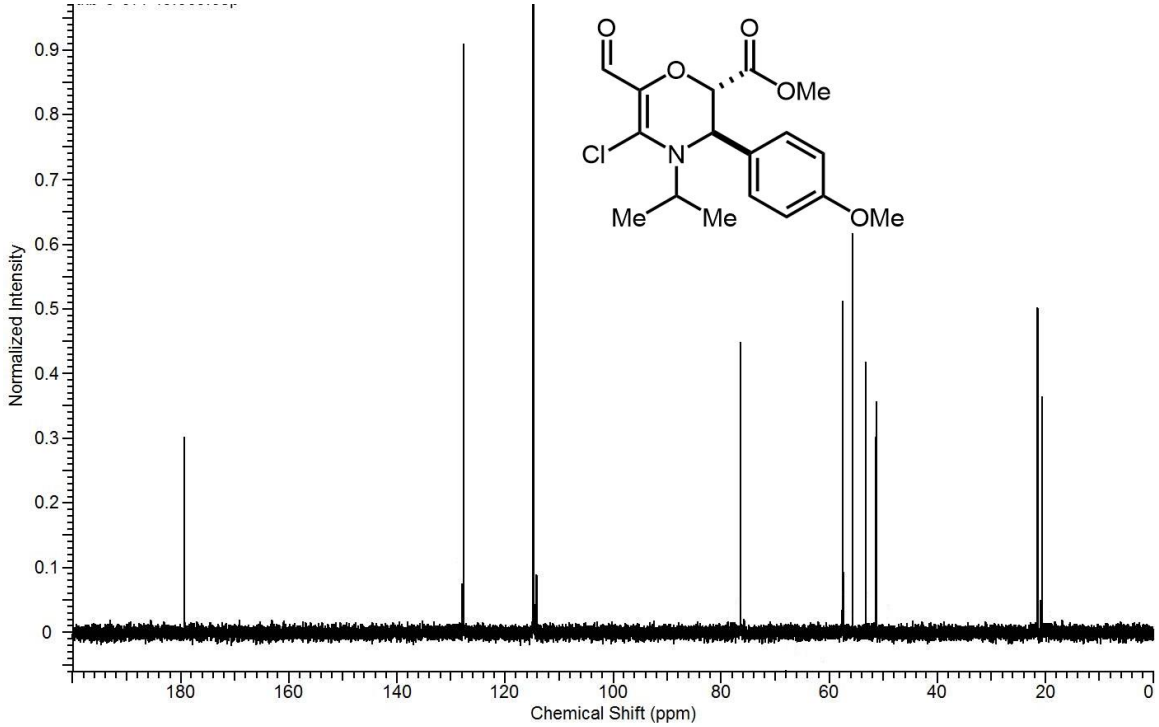
Spectra **1-48** DEPT-135 NMR spectrum of **10b1.**



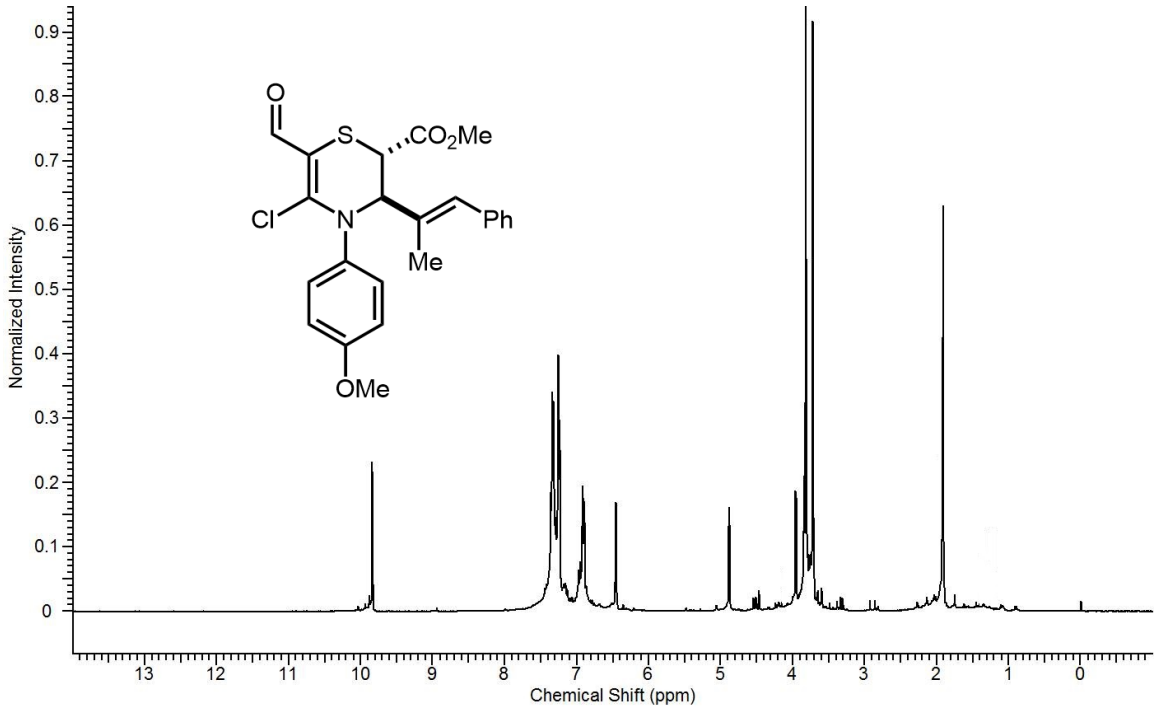
Spectra **1-49** Proton NMR spectrum of **10b2.**



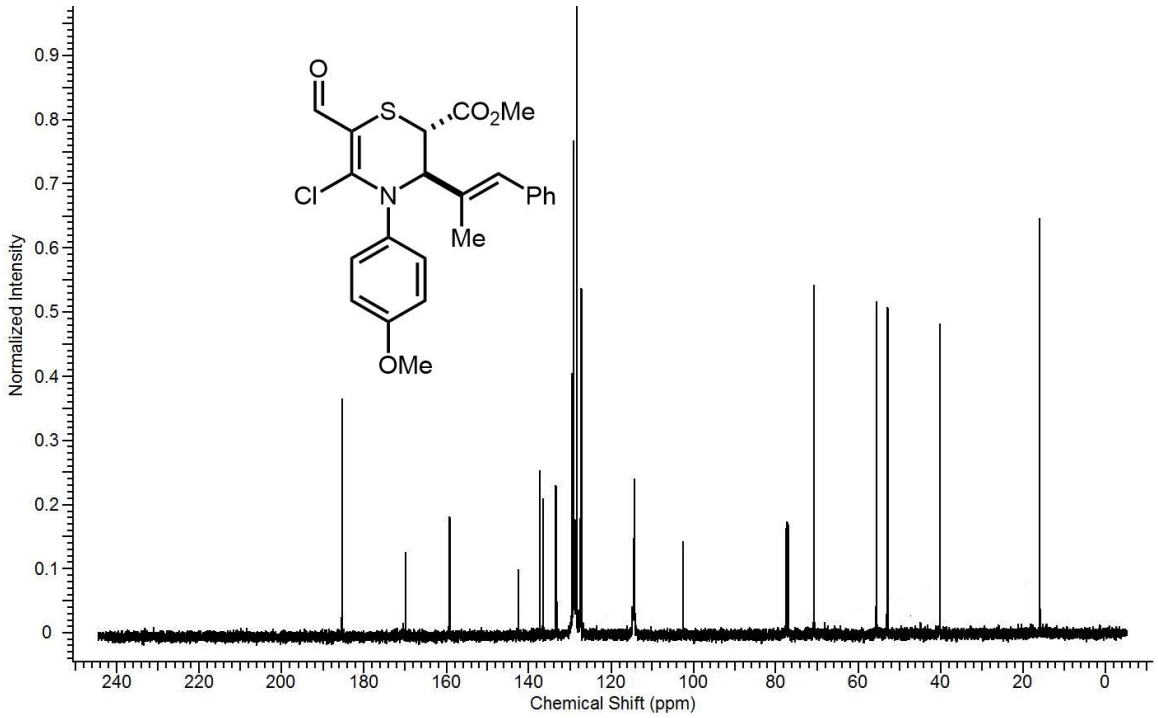
Spectra **1-50** Carbon NMR spectrum of **10b2.**



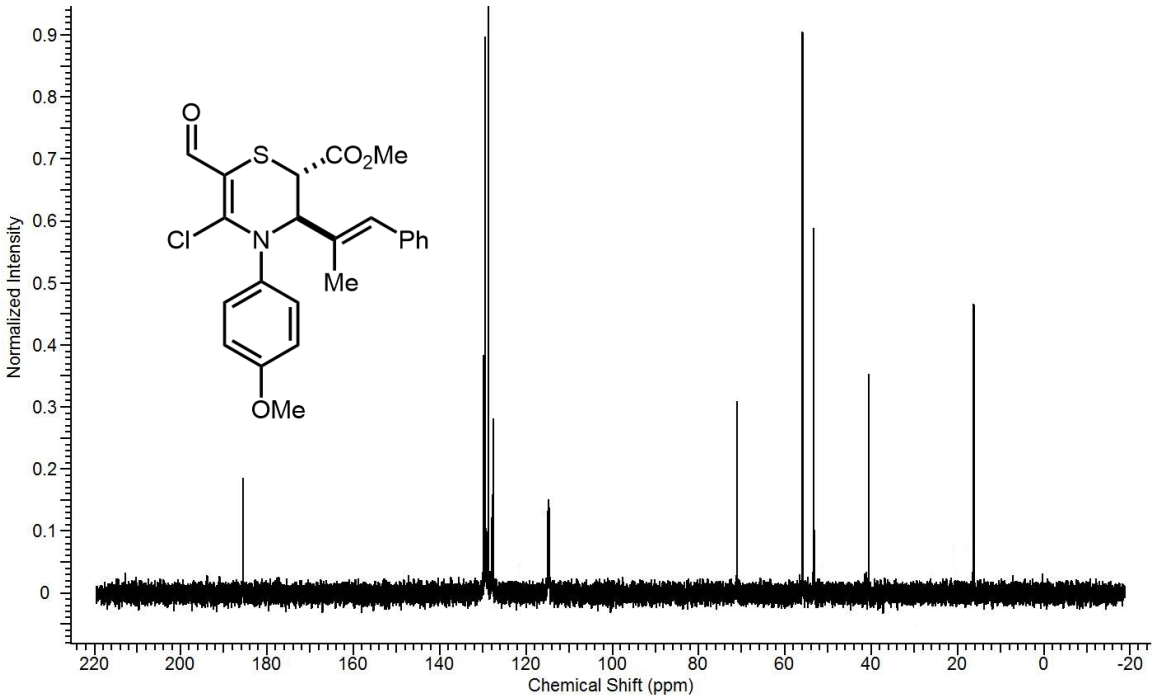
Spectra **1-51** DEPT-135 NMR spectrum of **10b2.**



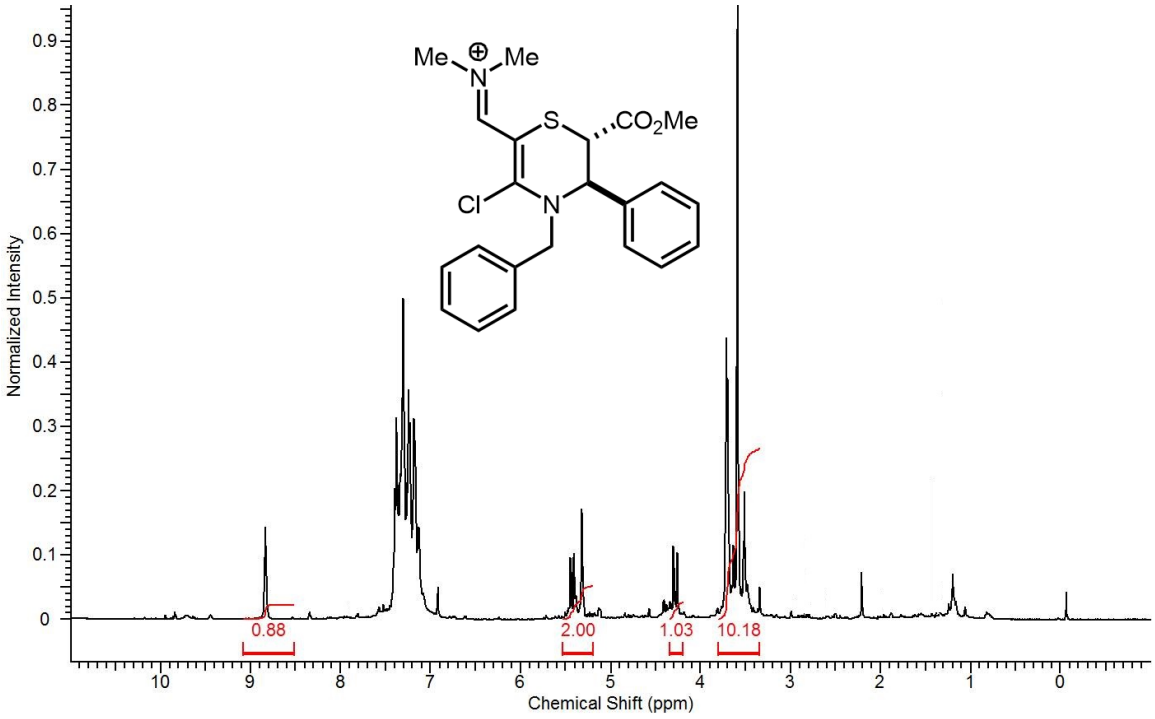
Spectra **1-52** Proton NMR spectrum of **4c1.**



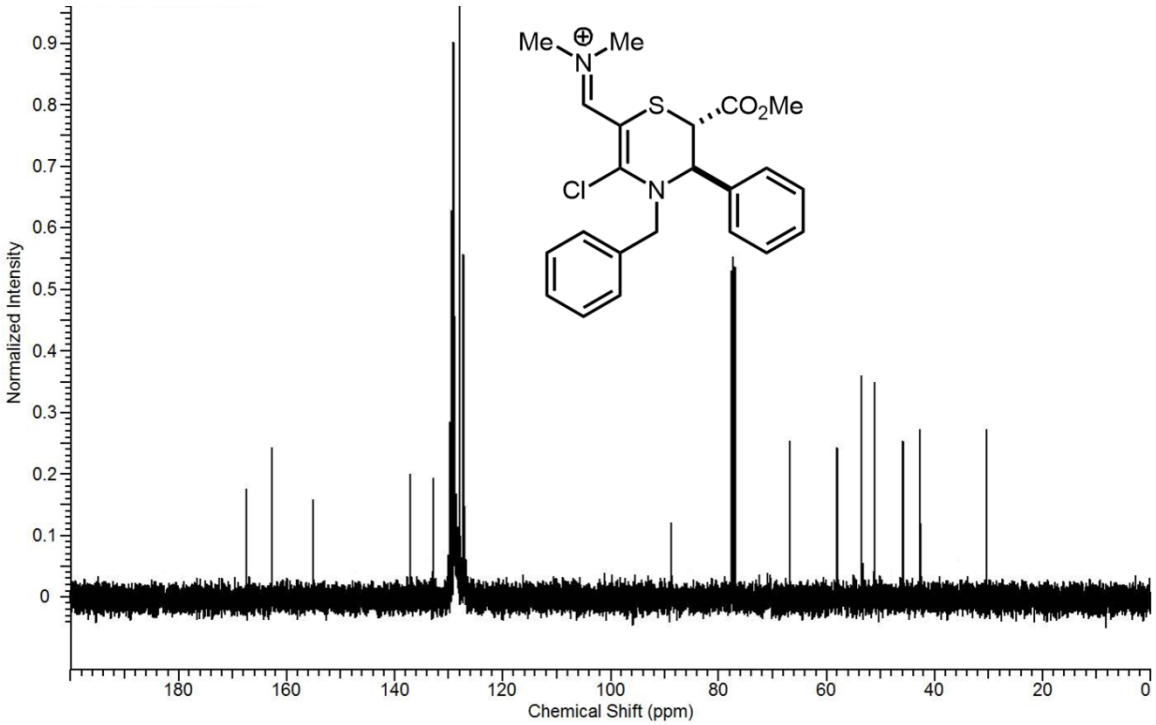
Spectra **1-53** Carbon NMR spectrum of **4c1.**



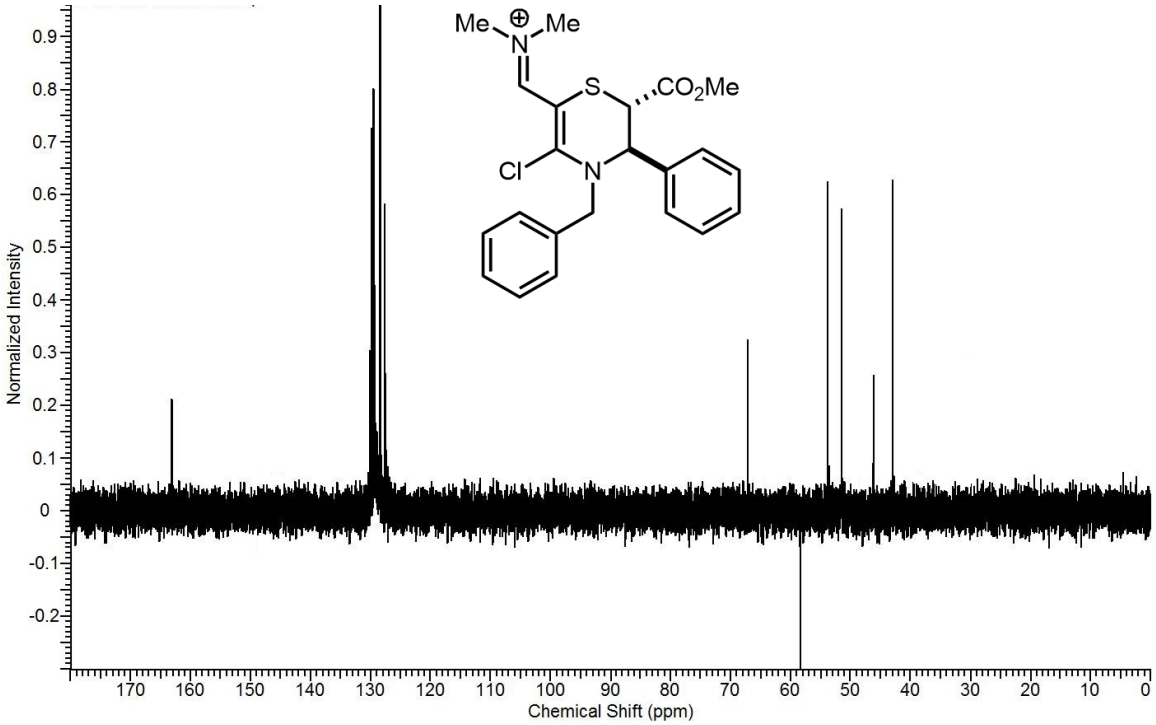
Spectra **1-54** DEPT-135 NMR spectrum of **4c1.**



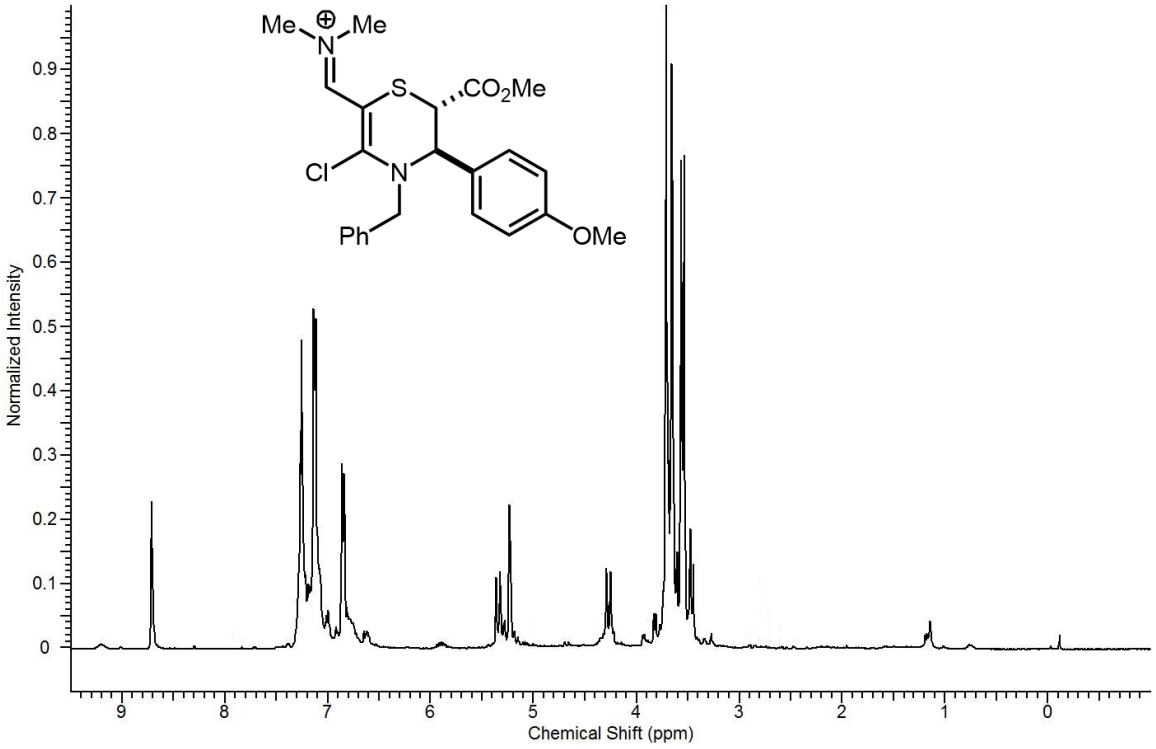
Spectra **1-55** Proton NMR spectrum of **12a1.**



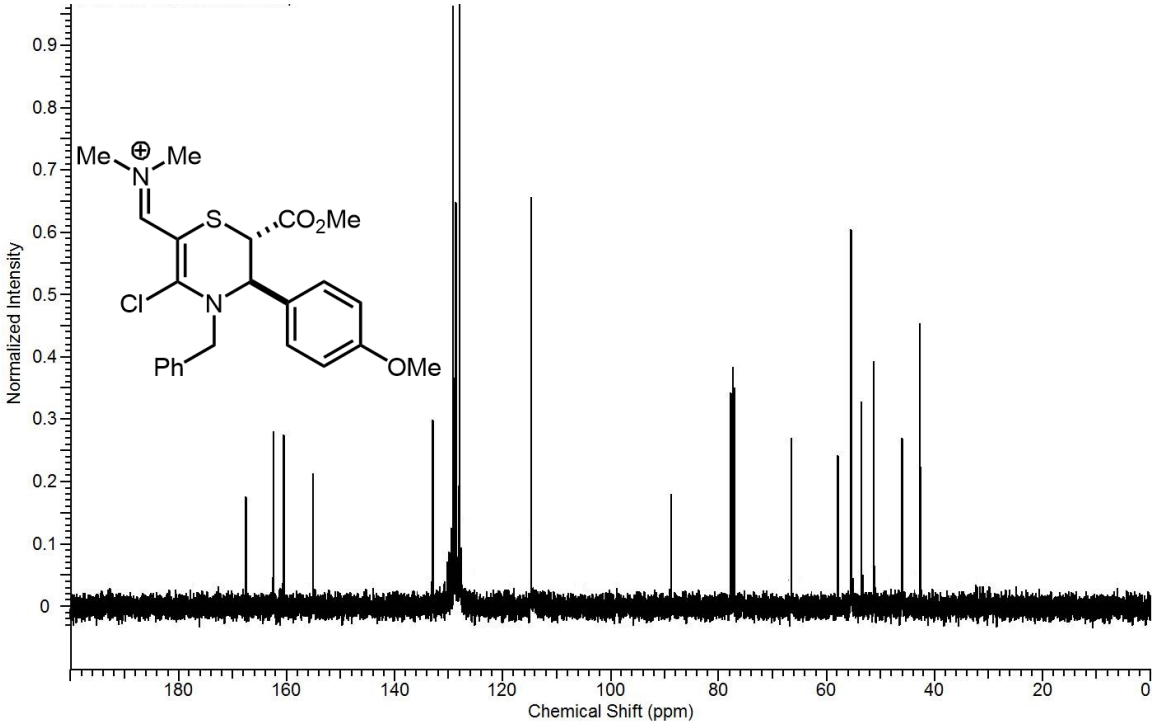
Spectra **1-56** Carbon NMR spectrum of **12a1.**



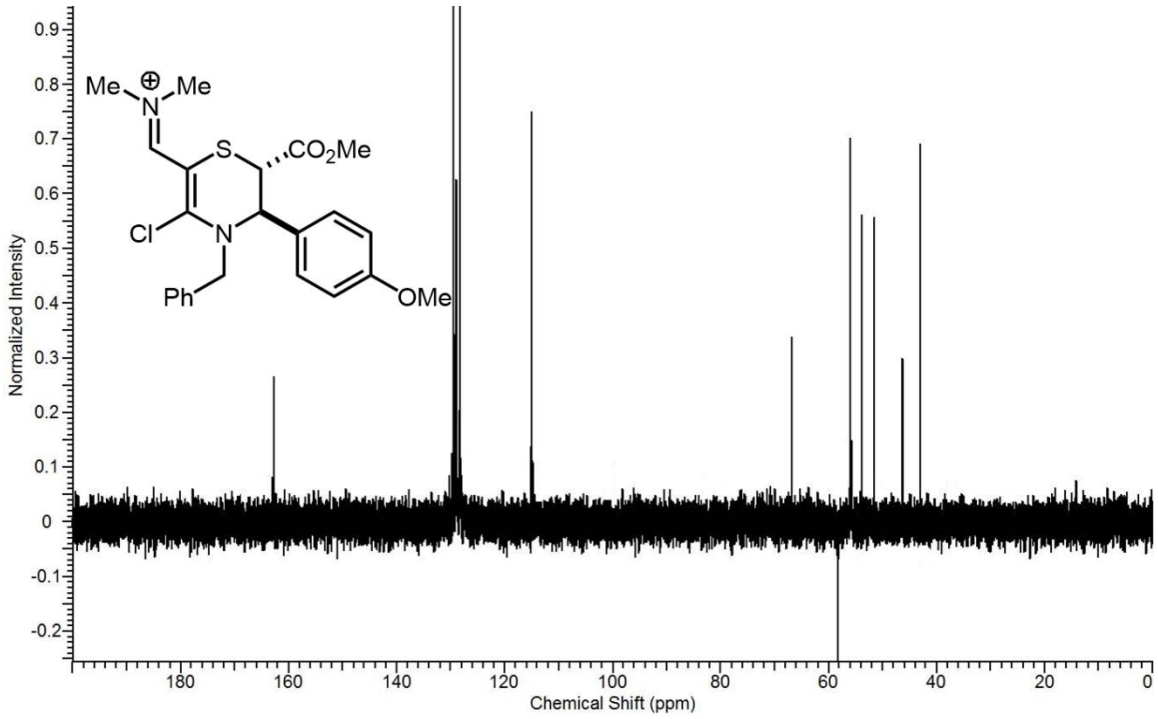
Spectra **1-57** DEPT-135 NMR spectrum of **12a1.**



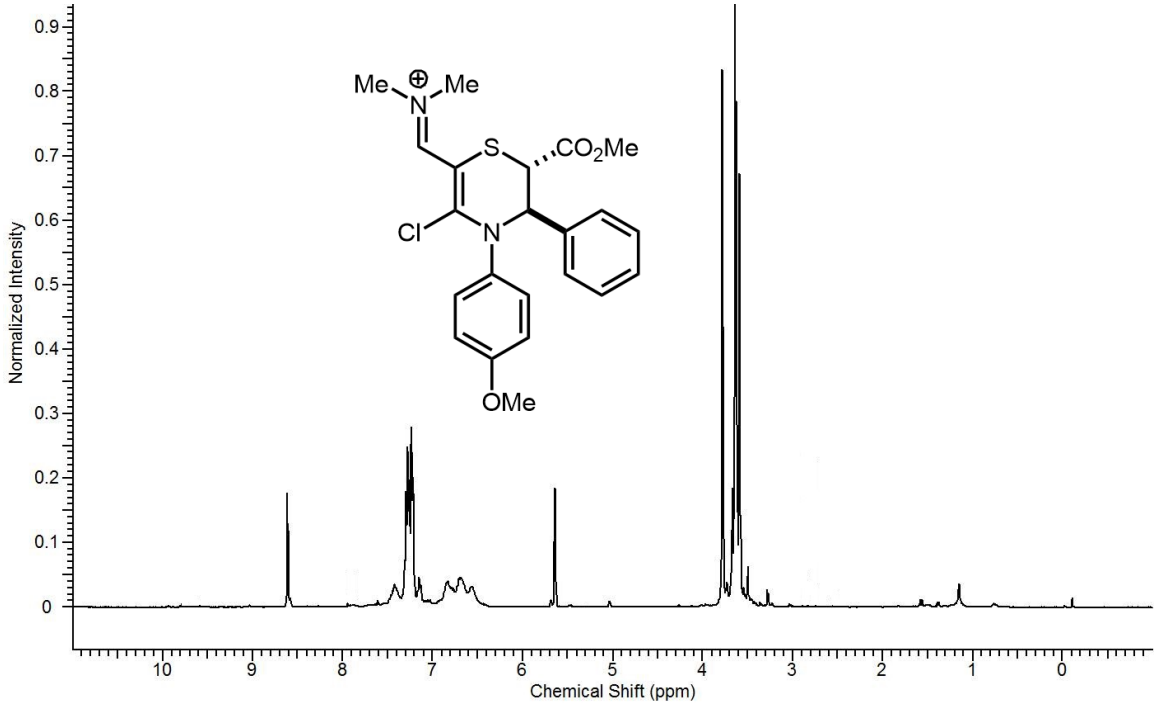
Spectra **1-58** Proton NMR spectrum of **12a2.**



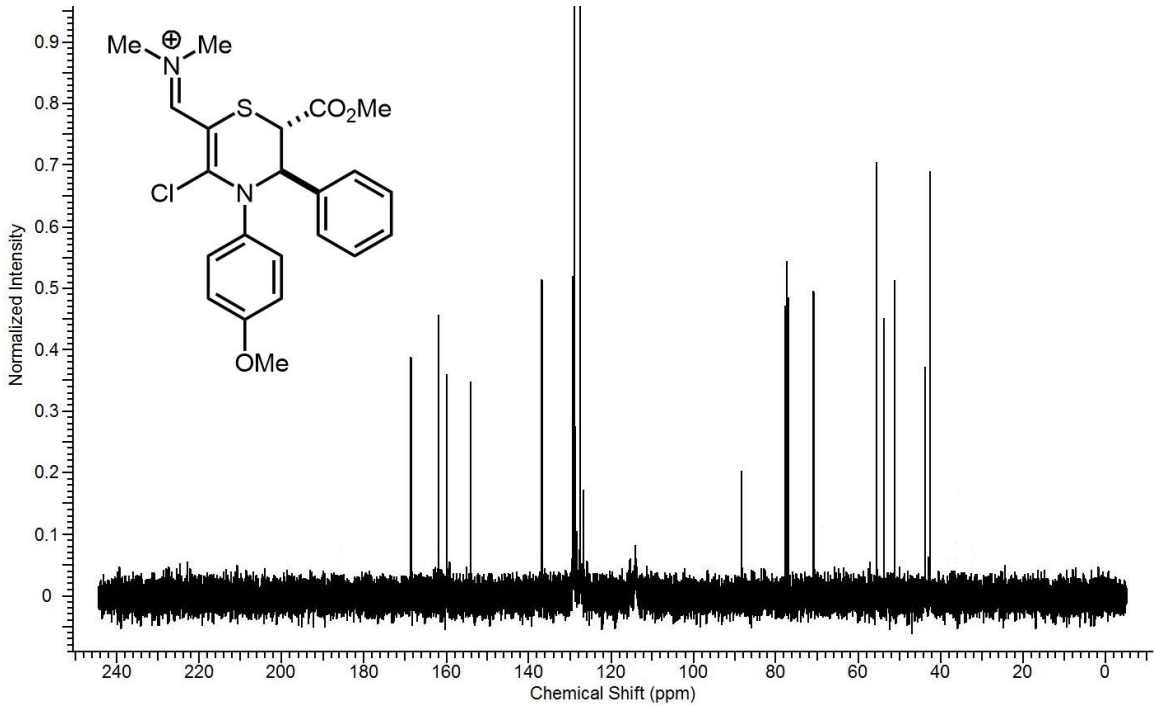
Spectra **1-59** Carbon NMR spectrum of **12a2.**



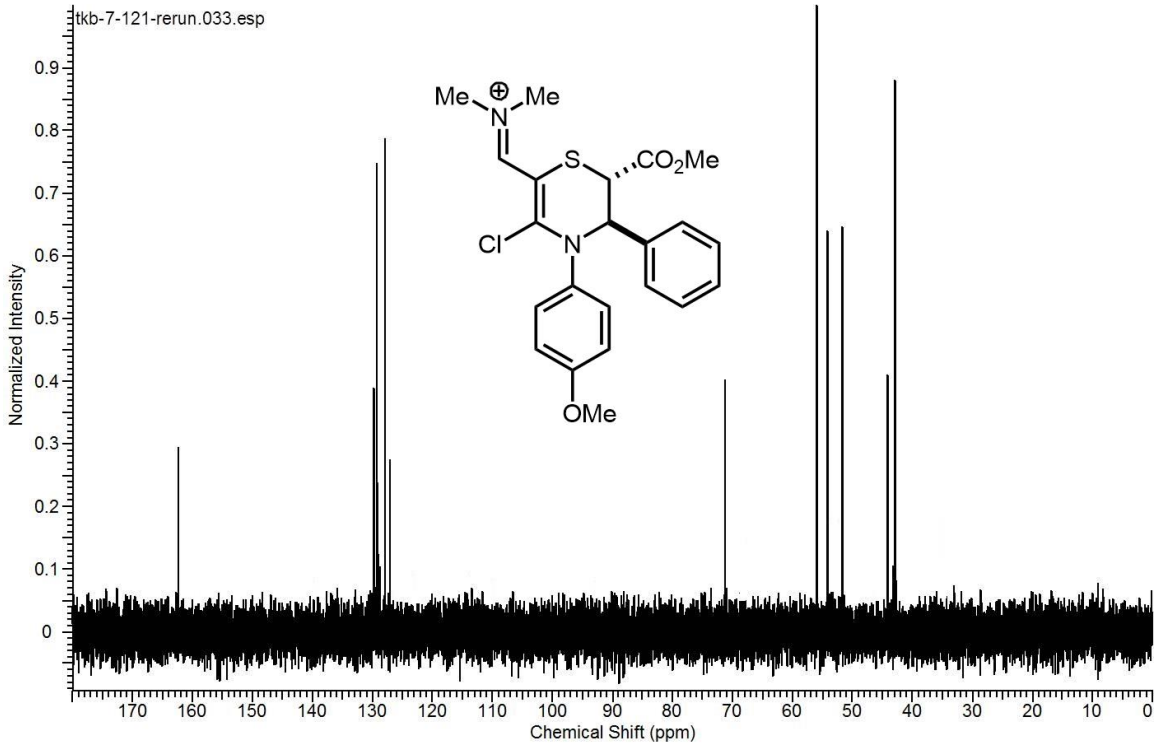
Spectra **1-60** DEPT-135 NMR spectrum of **12a2.**



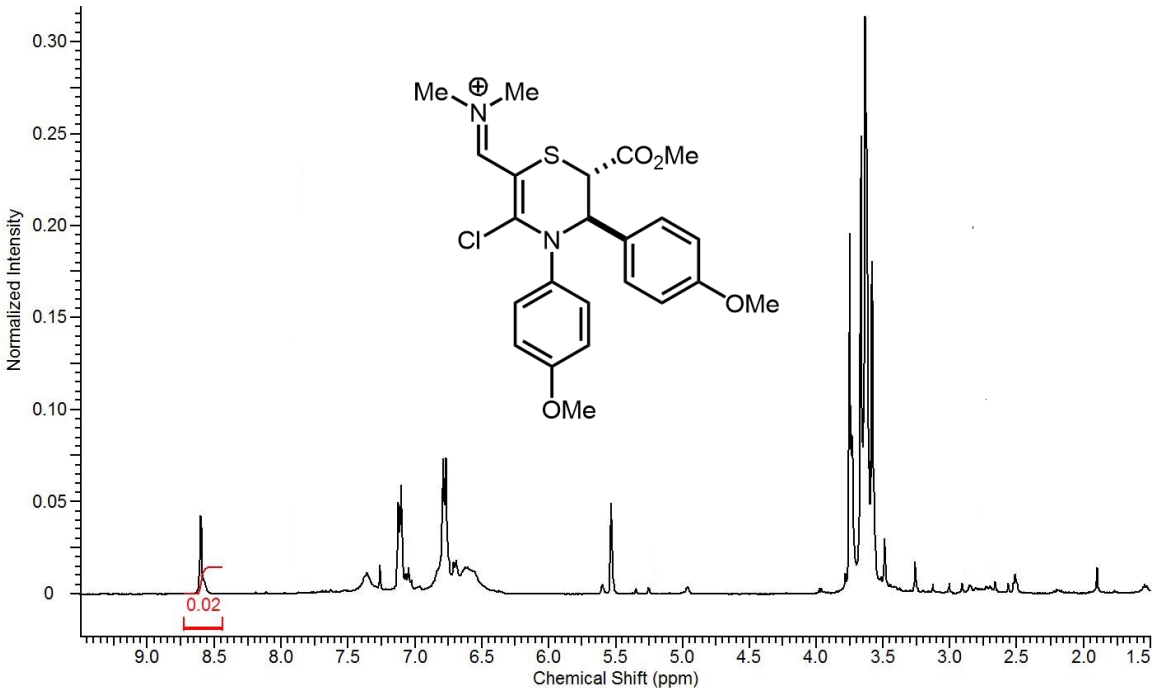
Spectra **1-61** Proton NMR spectrum of **12a3.**



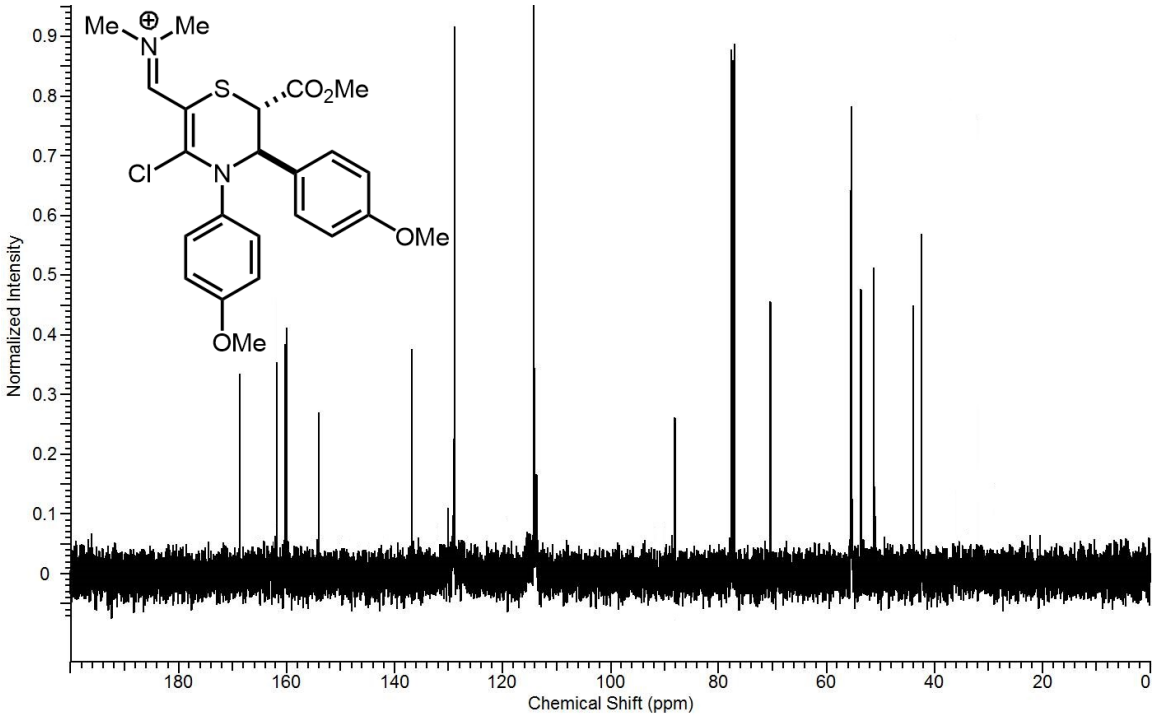
Spectra **1-62** Carbon NMR spectrum of **12a3.**



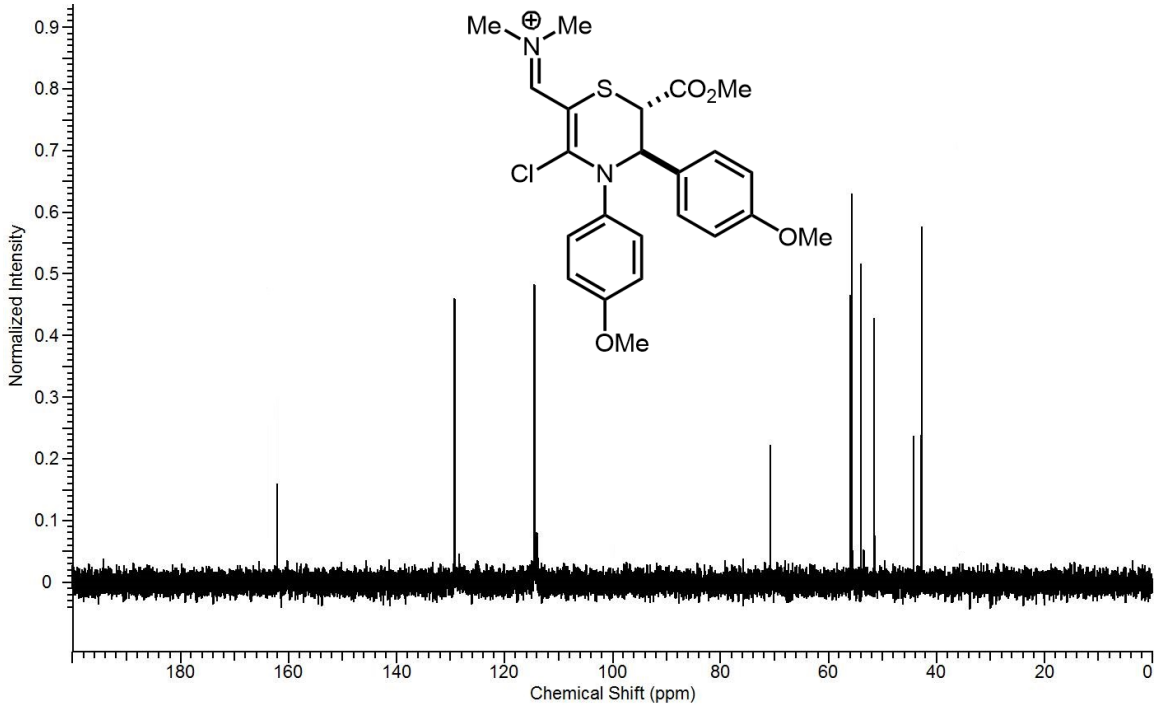
Spectra **1-63** DEPT-135 NMR spectrum of **12a3.**



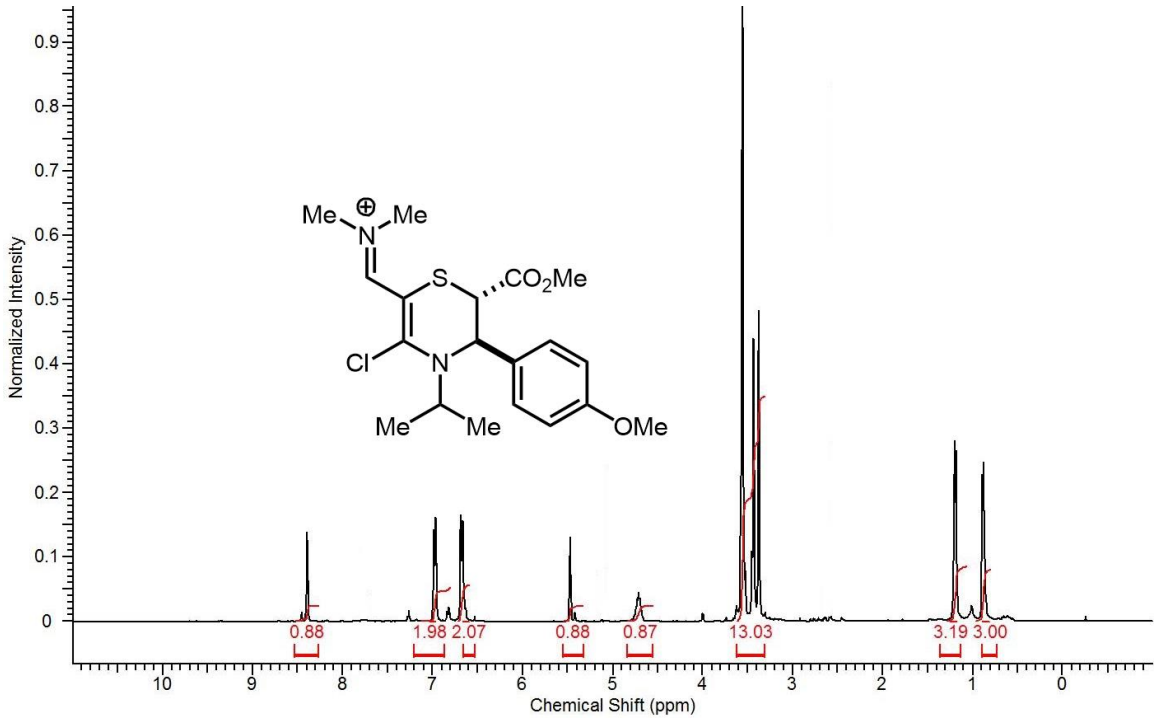
Spectra **1-64** Proton NMR spectrum of **12a4.**



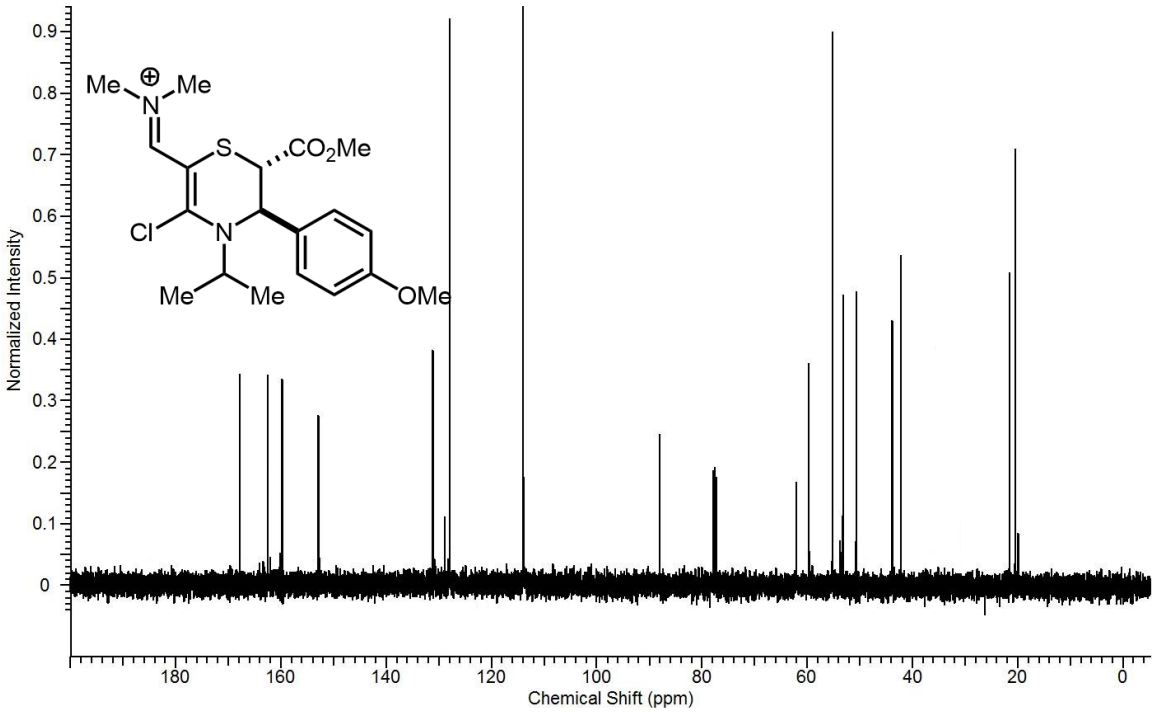
Spectra **1-65** Carbon NMR spectrum of **12a4.**



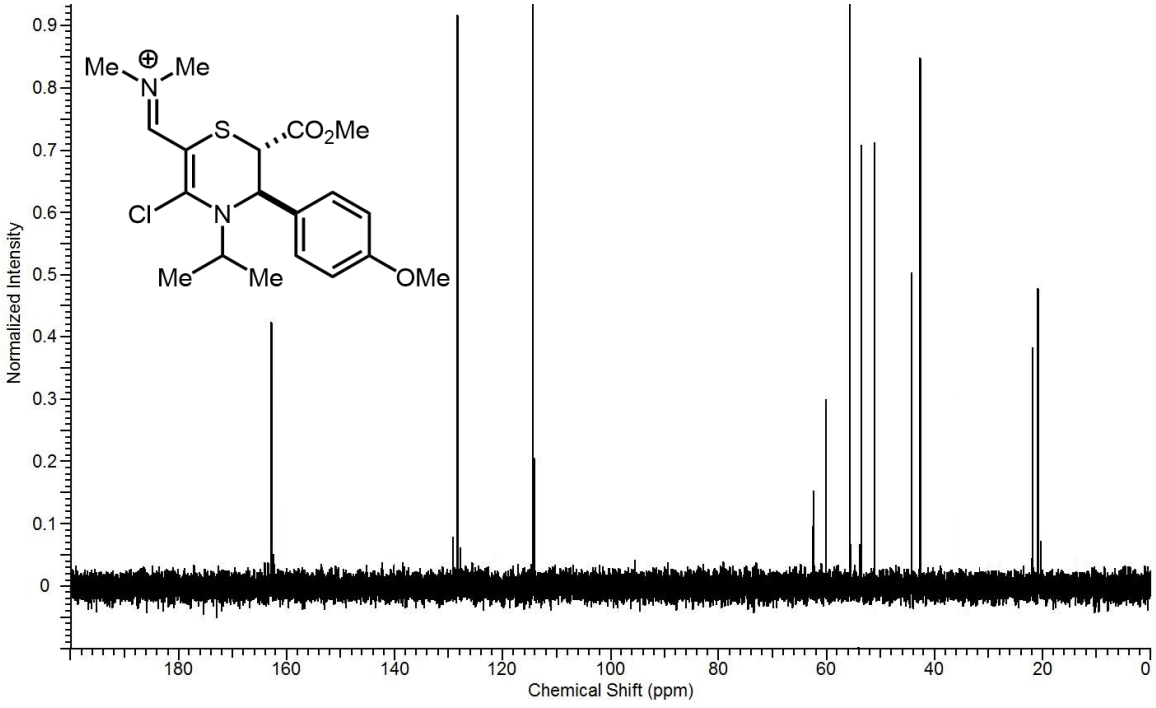
Spectra **1-66** DEPT-135 NMR spectrum of **12a4.**



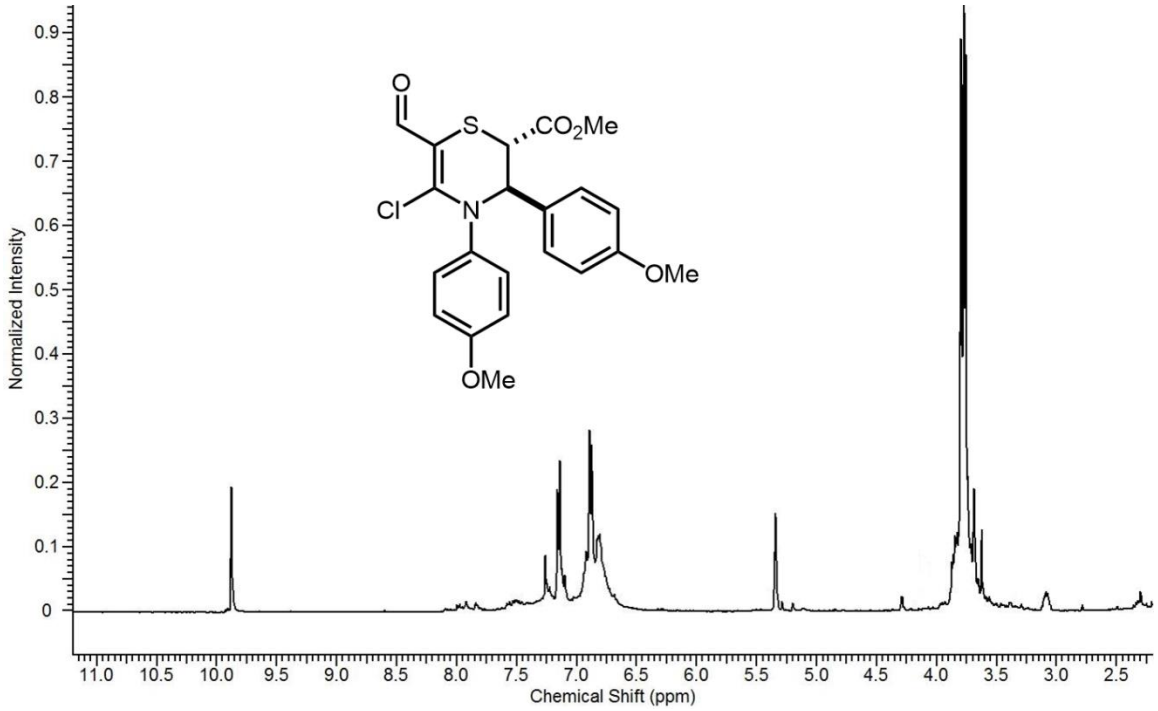
Spectra **1-67** Proton NMR spectrum of **12a5.**



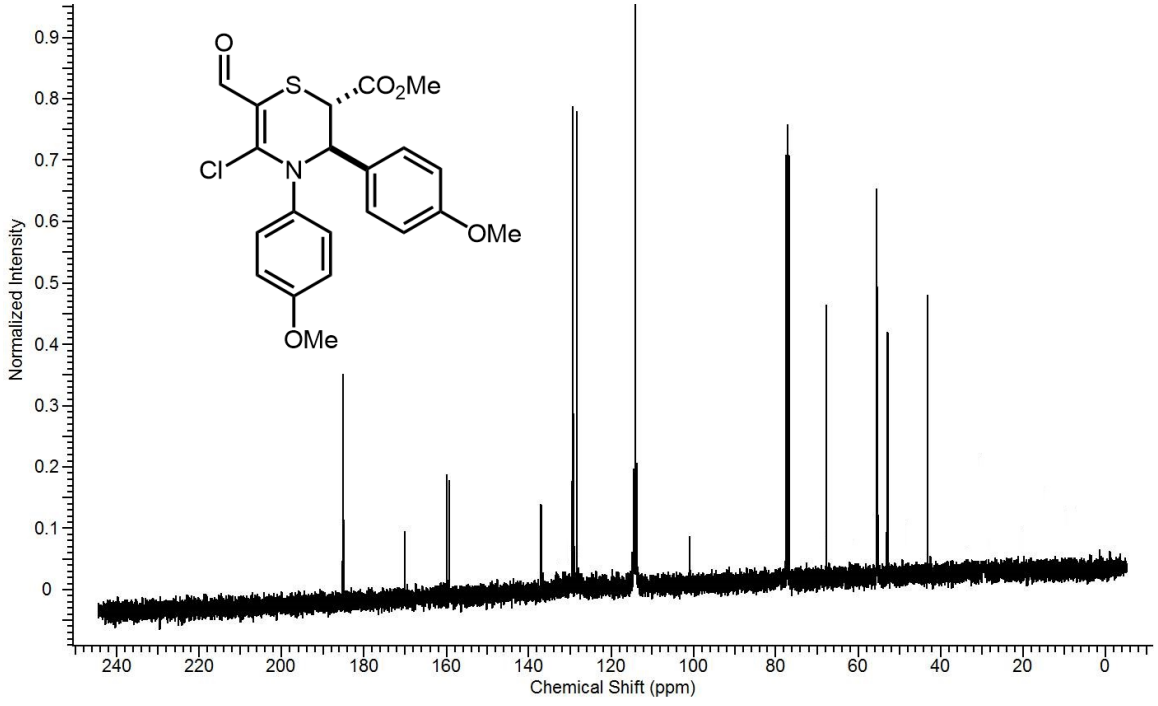
Spectra **1-68** Carbon NMR spectrum of **12a5.**



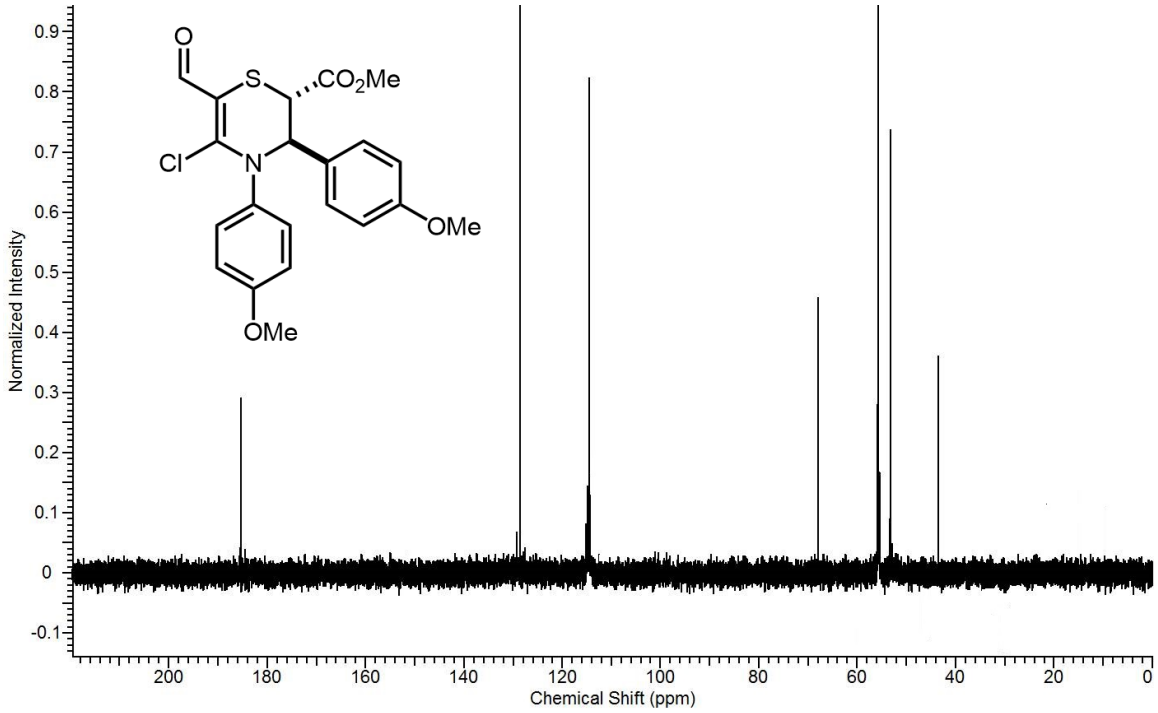
Spectra **1-69** DEPT-135 NMR spectrum of **12a5.**



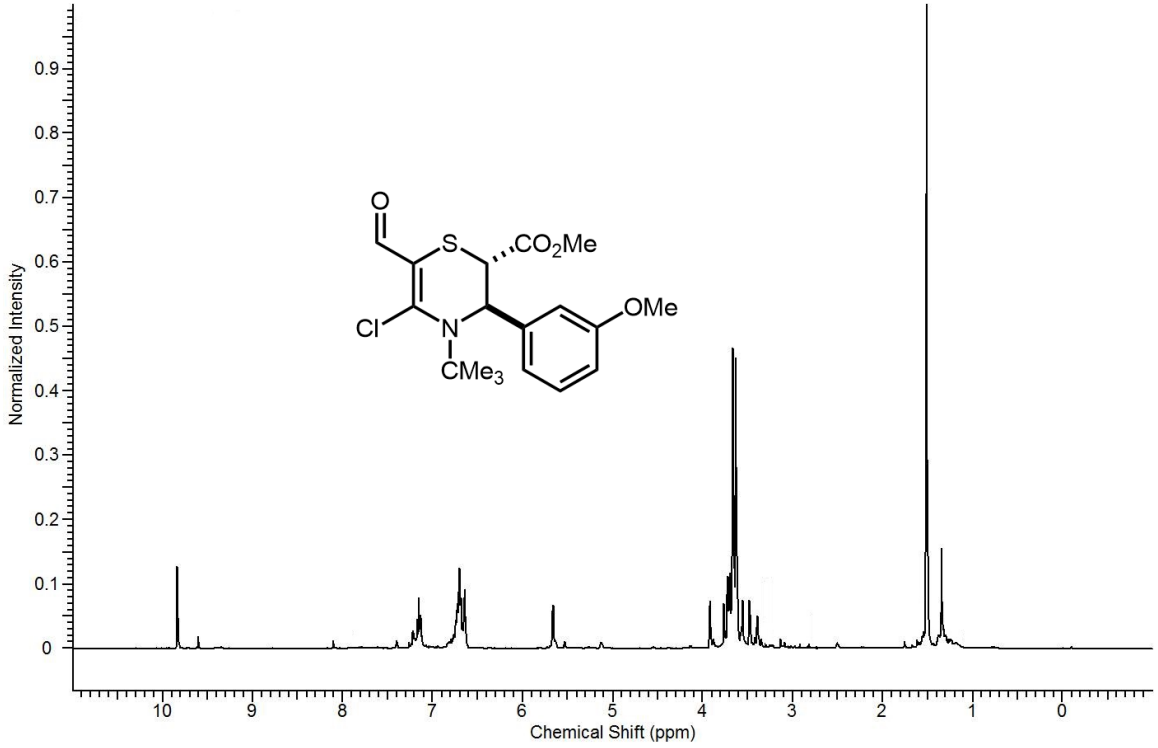
Spectra **1-70** Proton NMR spectrum of **12b1.**



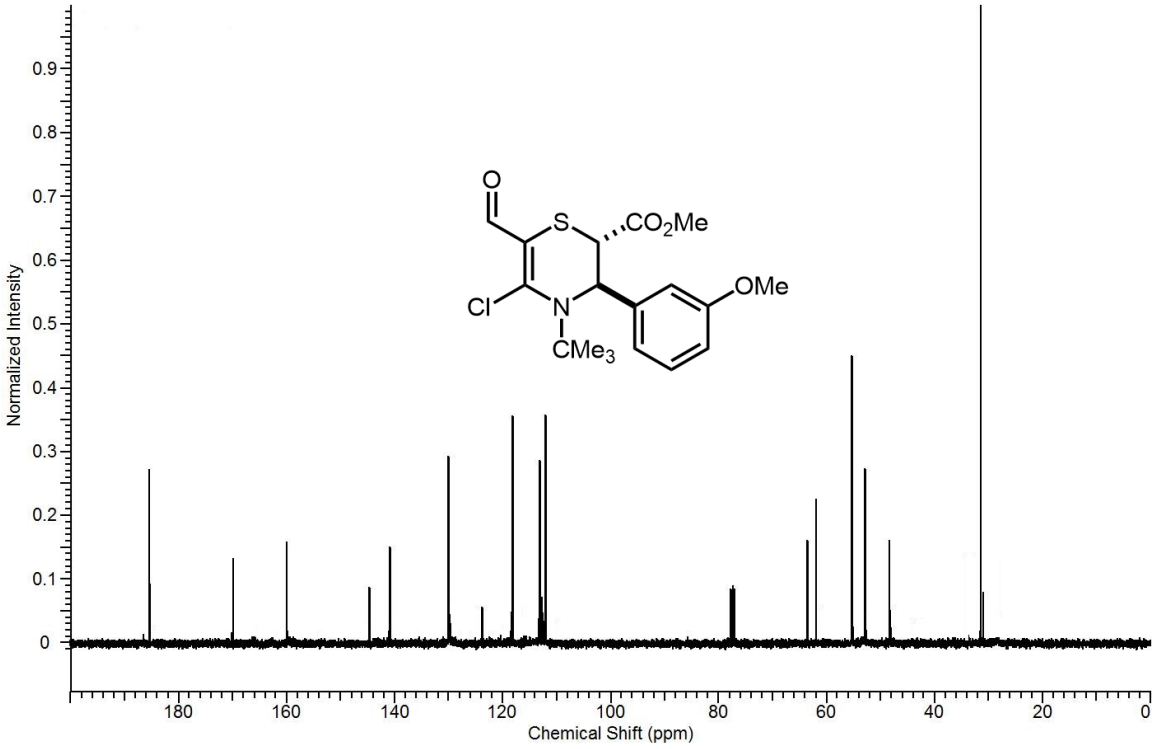
Spectra **1-71** Carbon NMR spectrum of **12b1.**



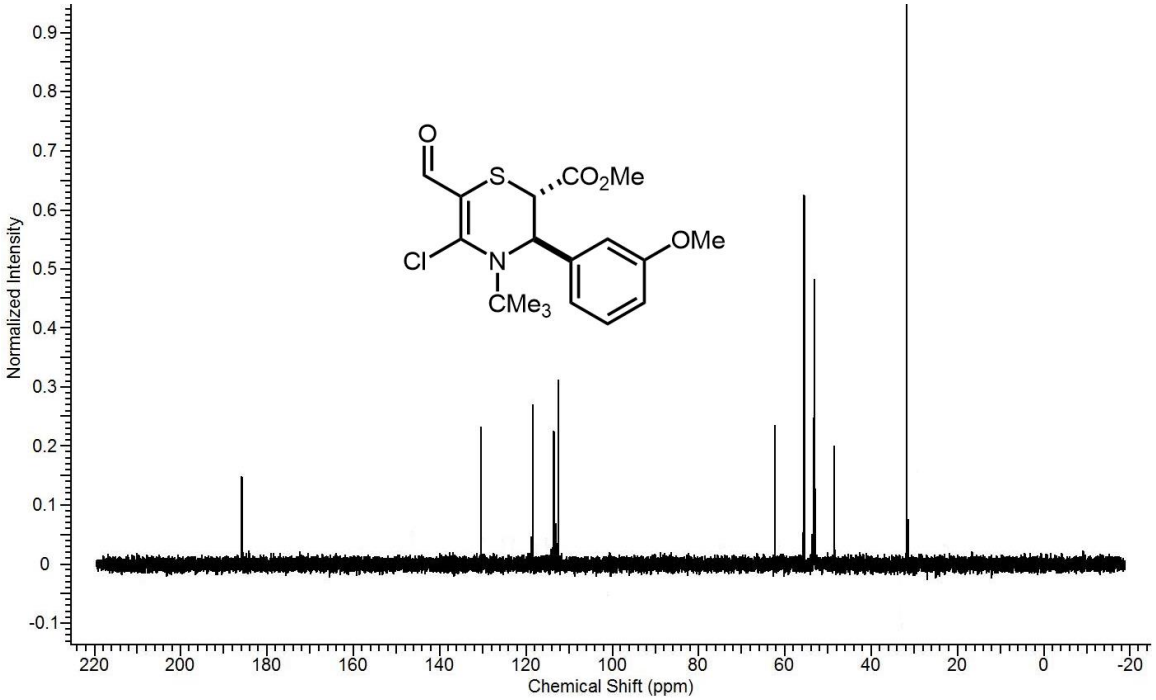
Spectra **1-72** DEPT-135 NMR spectrum of **12b1.**



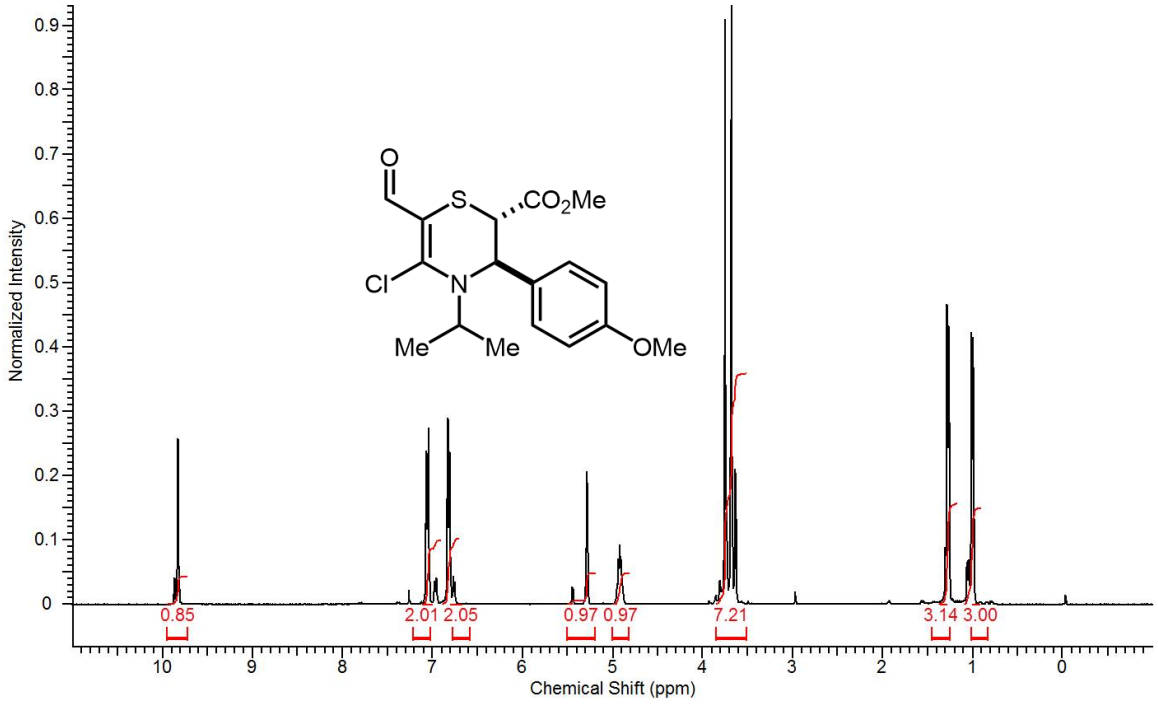
Spectra **1-73** Proton NMR spectrum of **12b2.**



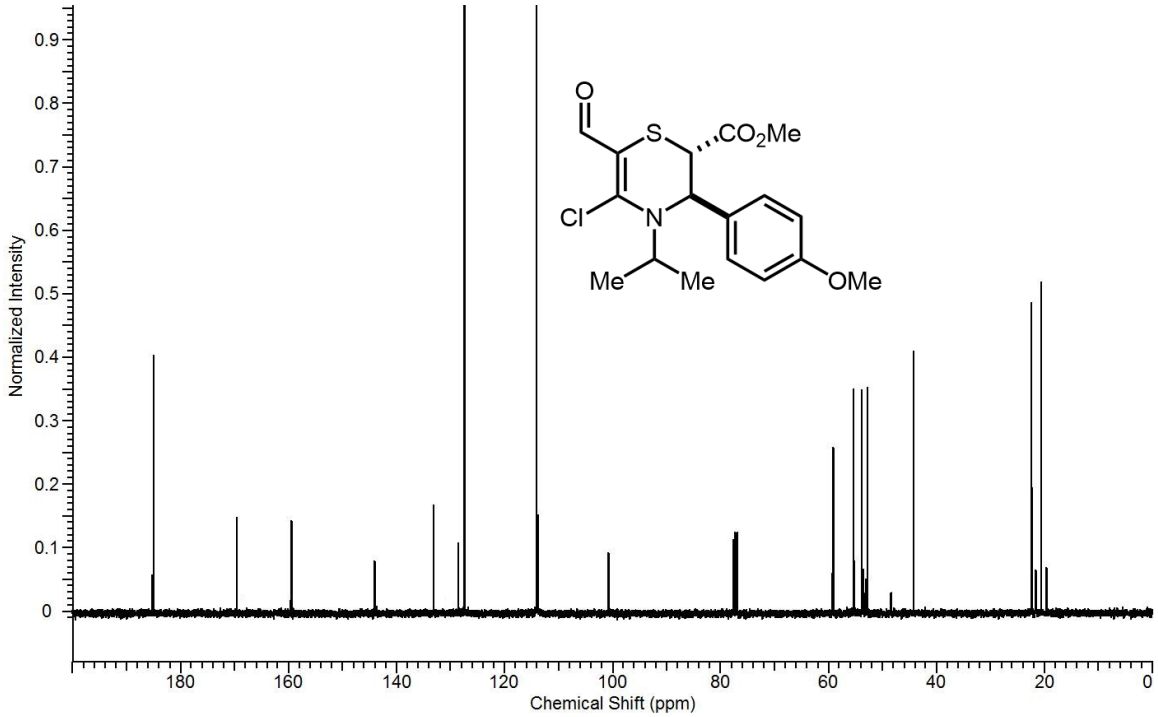
Spectra **1-74** Carbon NMR spectrum of **12b2.**



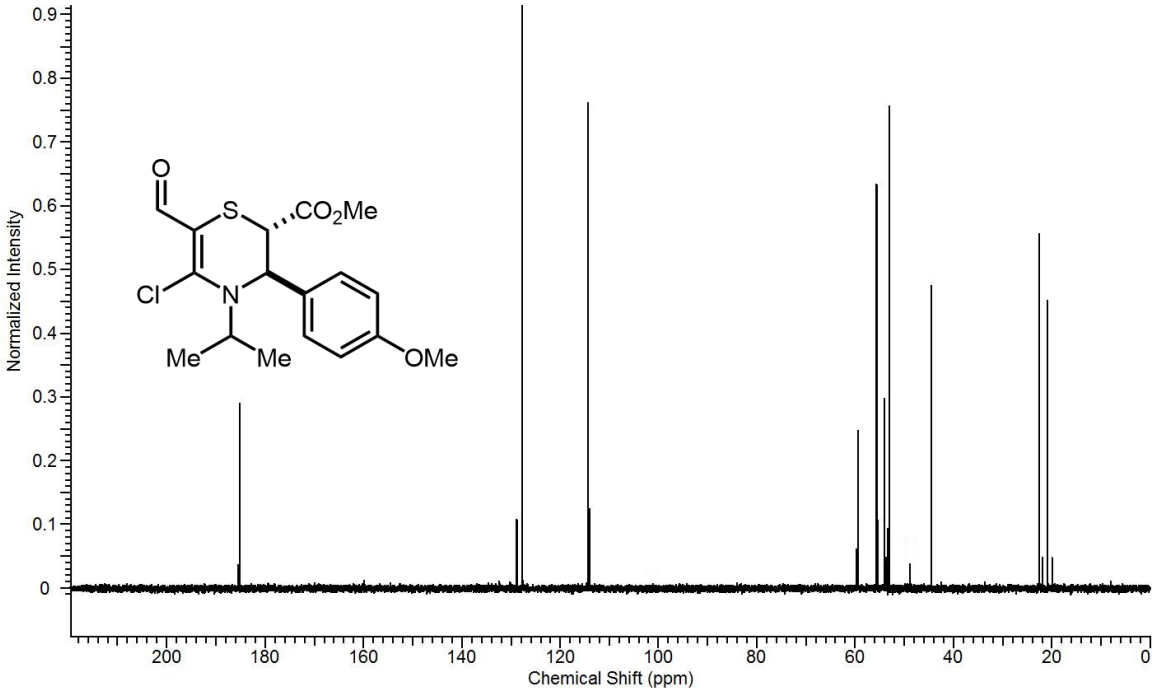
Spectra **1-75** DEPT-135 NMR spectrum of **12b2.**



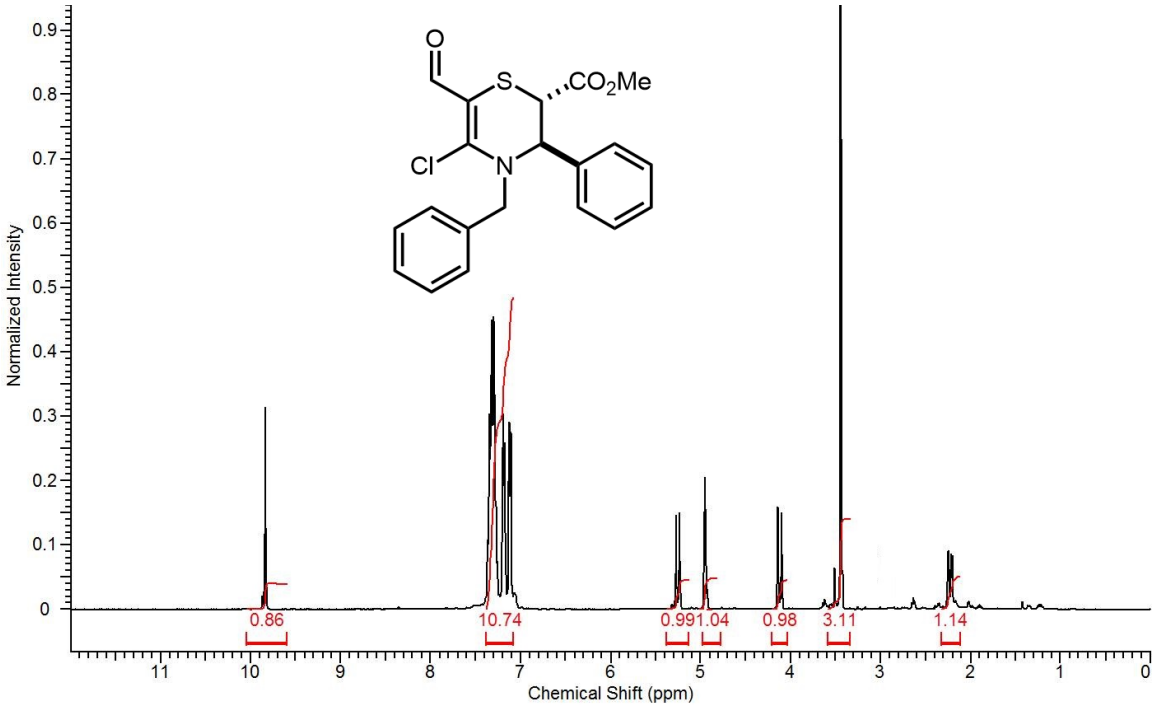
Spectra **1-76** Proton NMR spectrum of **12b3.**



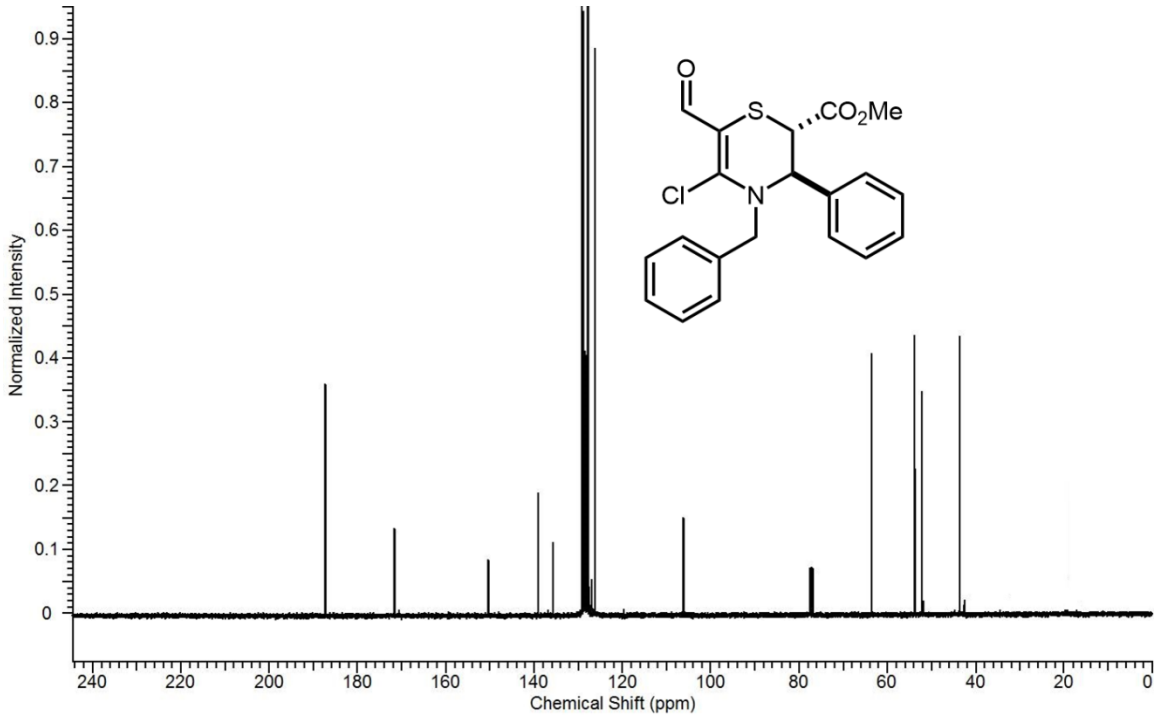
Spectra **1-77** Carbon NMR spectrum of **12b3.**



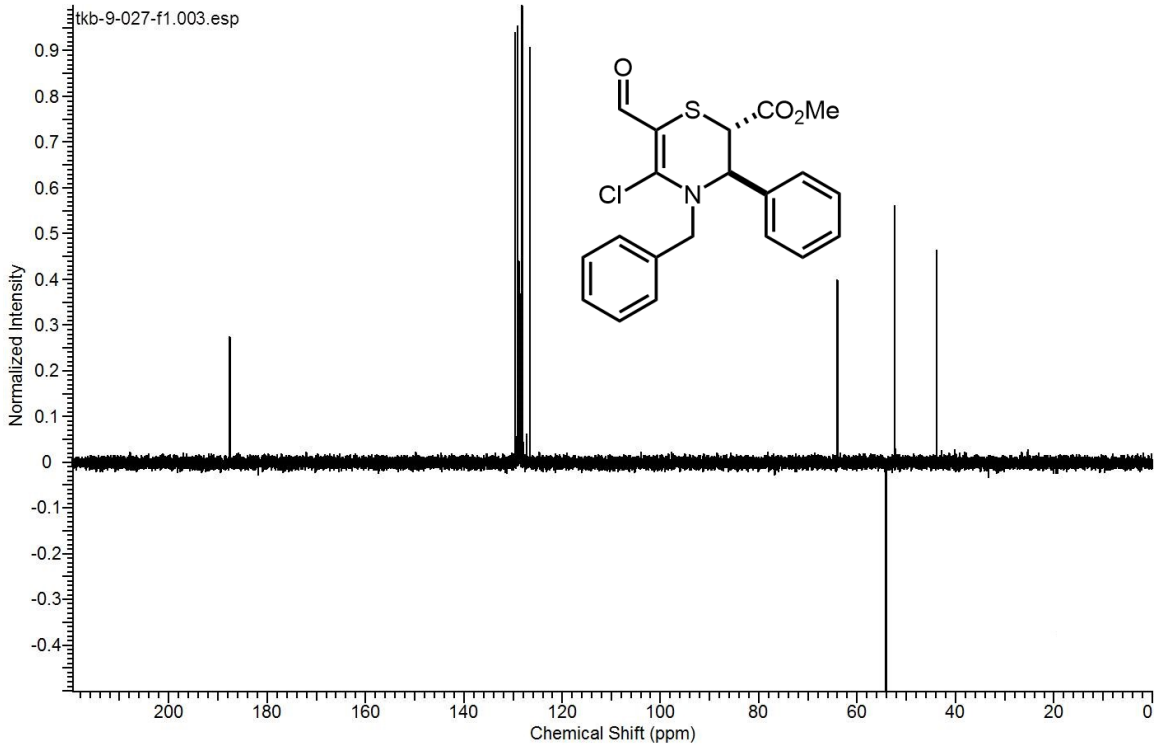
Spectra **1-78** DEPT-135 NMR spectrum of **12b3.**



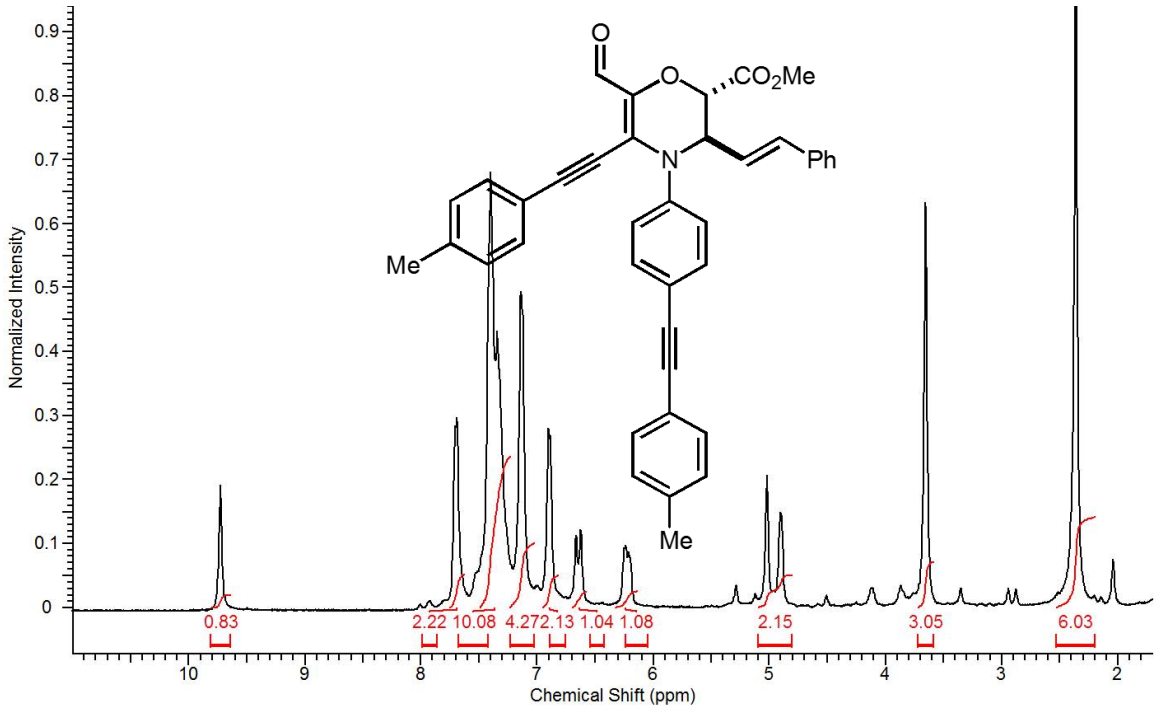
Spectra **1-79** Proton NMR spectrum of **12b4.**



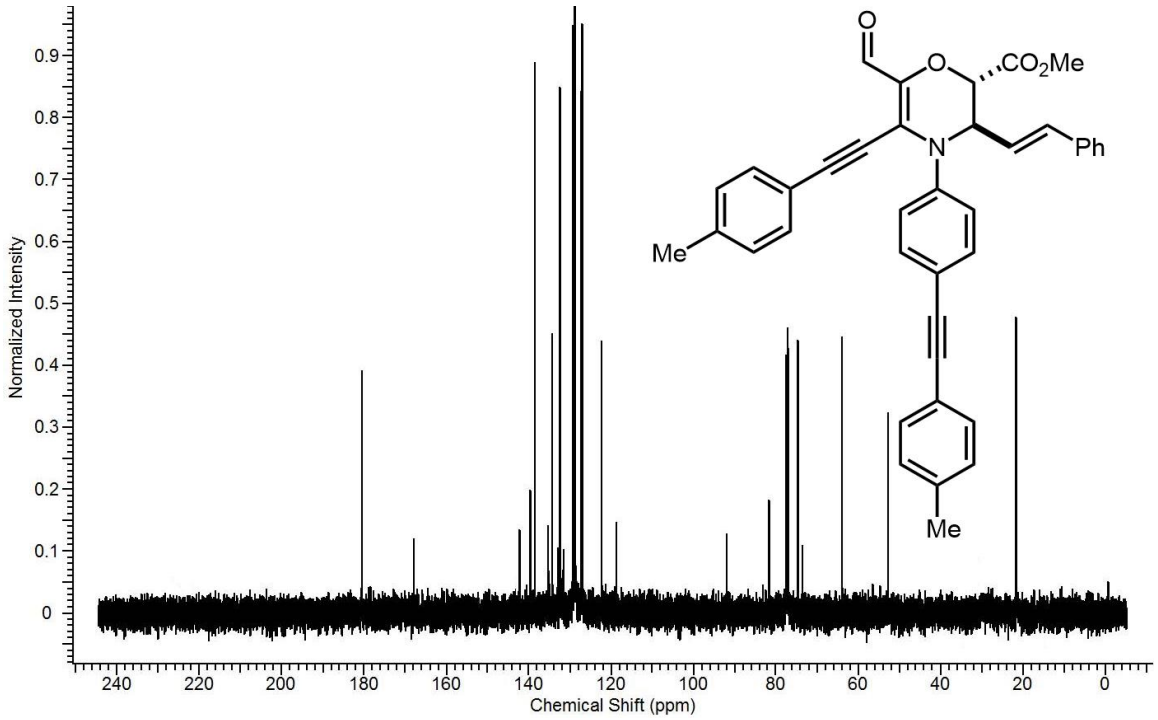
Spectra **1-80** Carbon NMR spectrum of **12b4.**



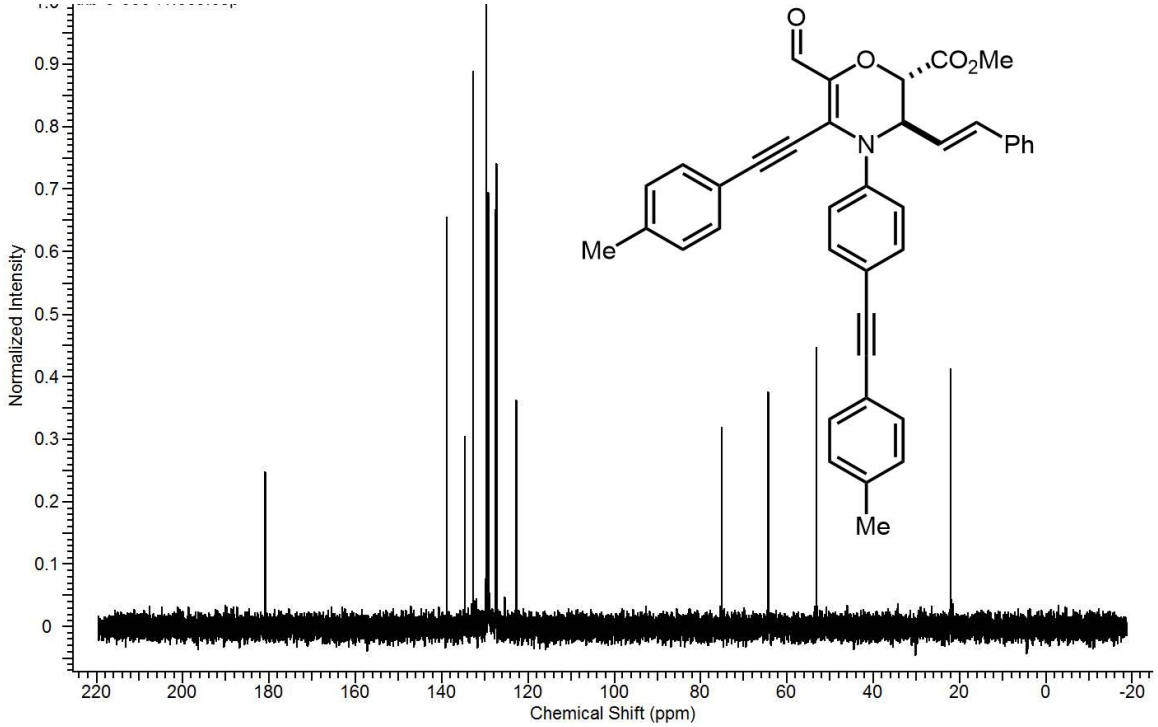
Spectra **1-81** DEPT-135 NMR spectrum of **12b4.**



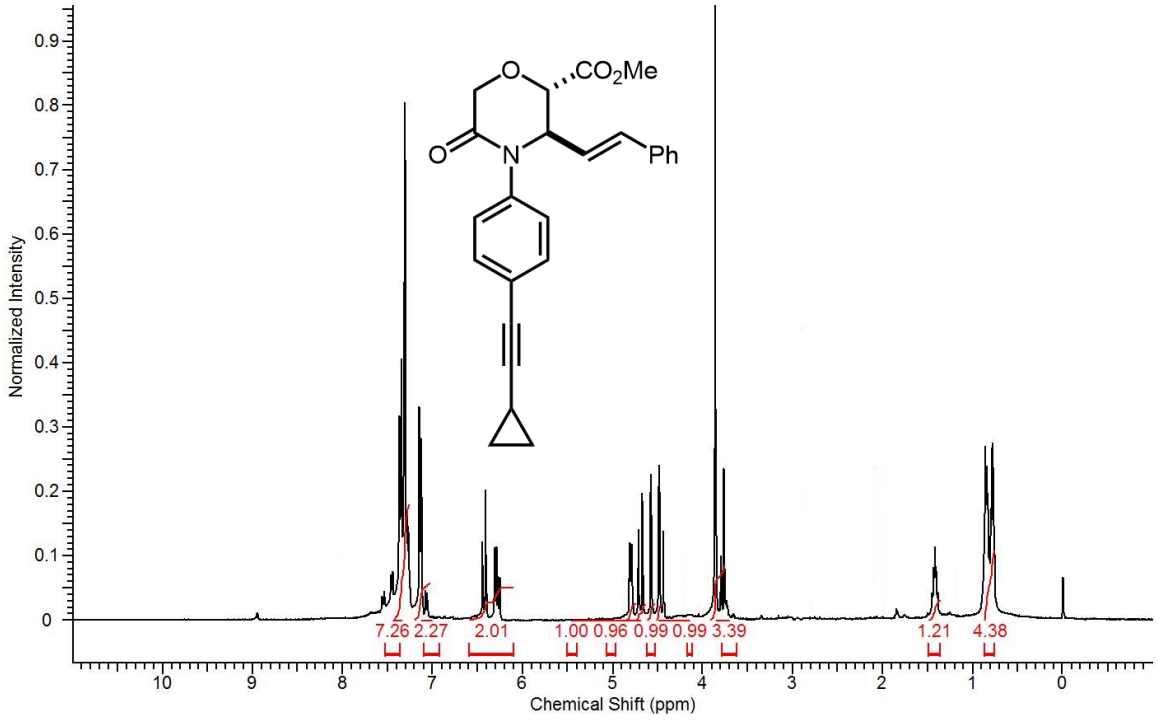
Spectra **1-82** Proton NMR spectrum of **13.**



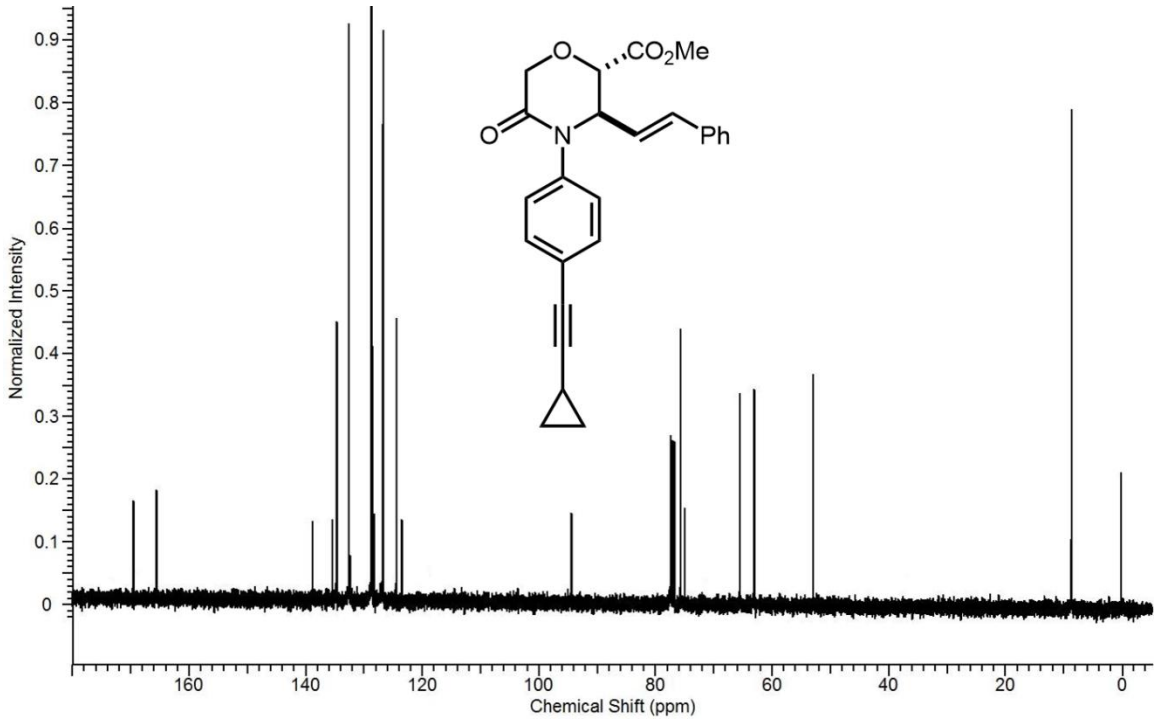
Spectra **1-83** Carbon NMR spectrum of **13.**



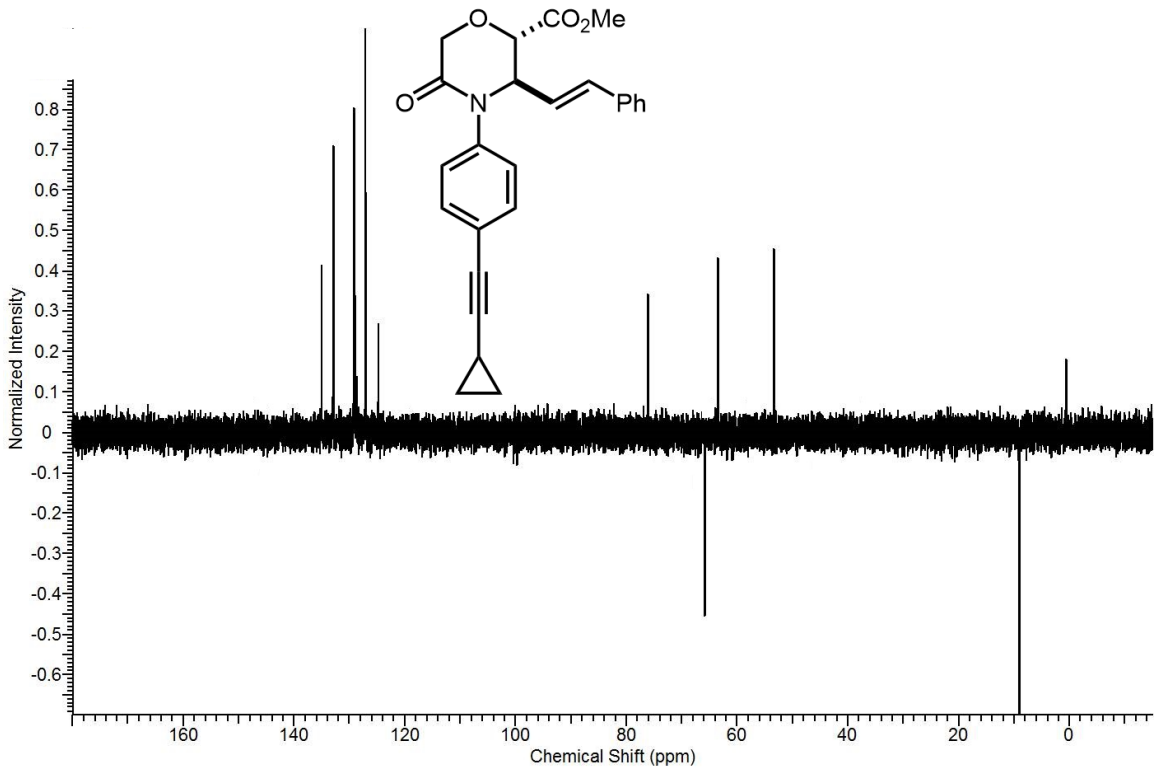
Spectra **1-84** DEPT-135 NMR spectrum of **13.**



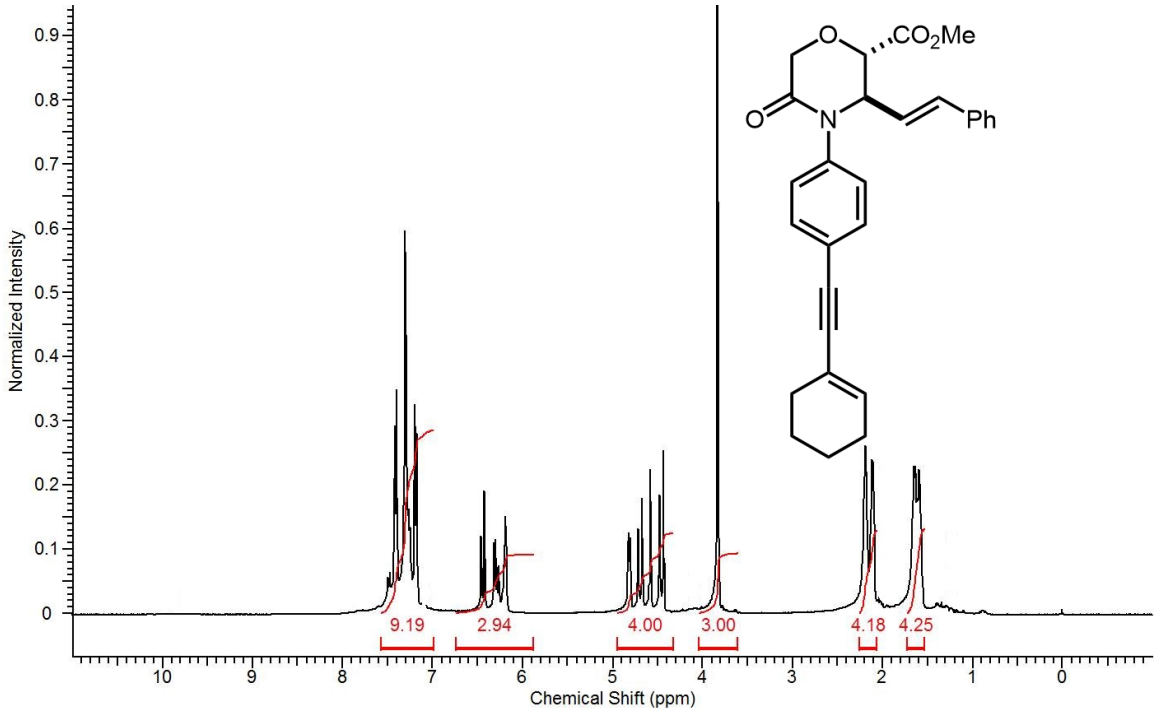
Spectra **1-85** Proton NMR spectrum of **14a.**



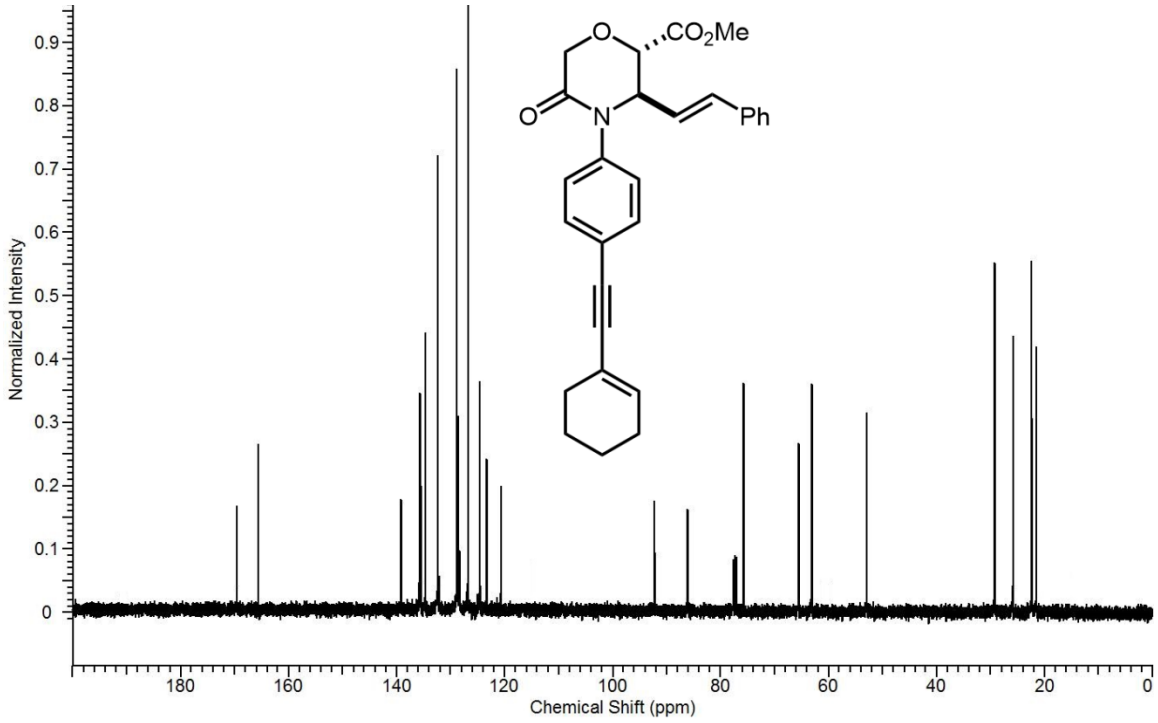
Spectra **1-86** Carbon NMR spectrum of **14a.**



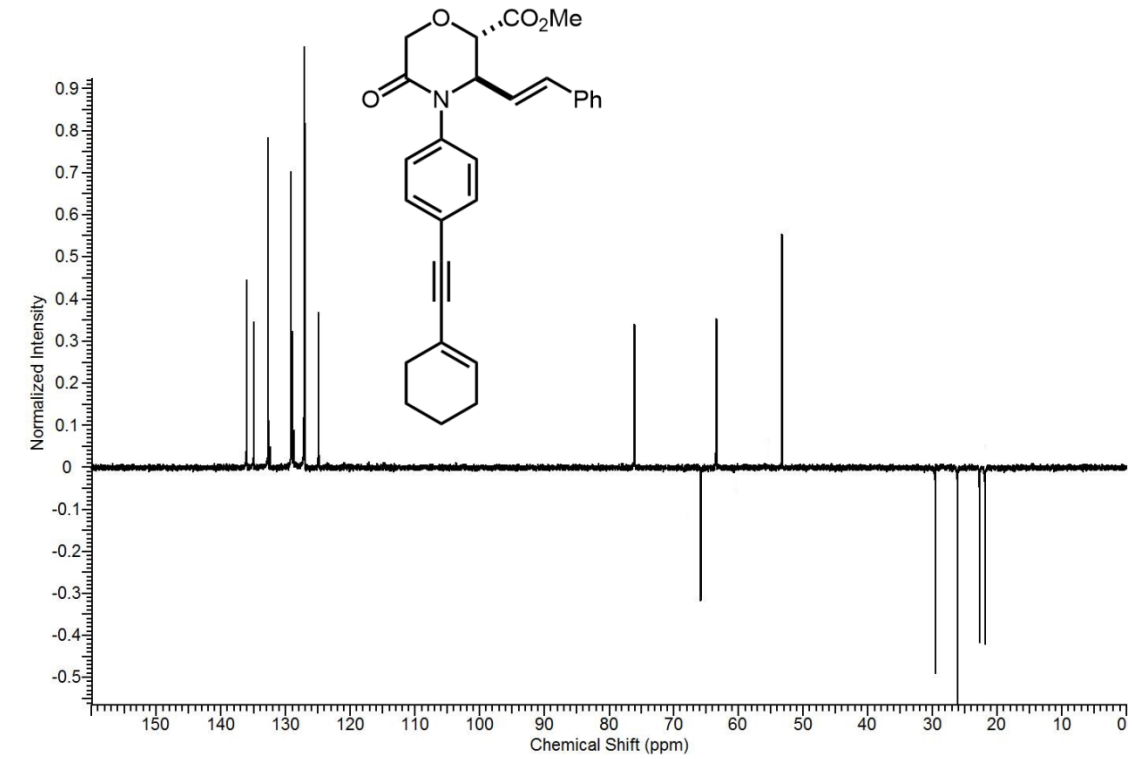
Spectra **1-87** DEPT-135 NMR spectrum of **14a.**



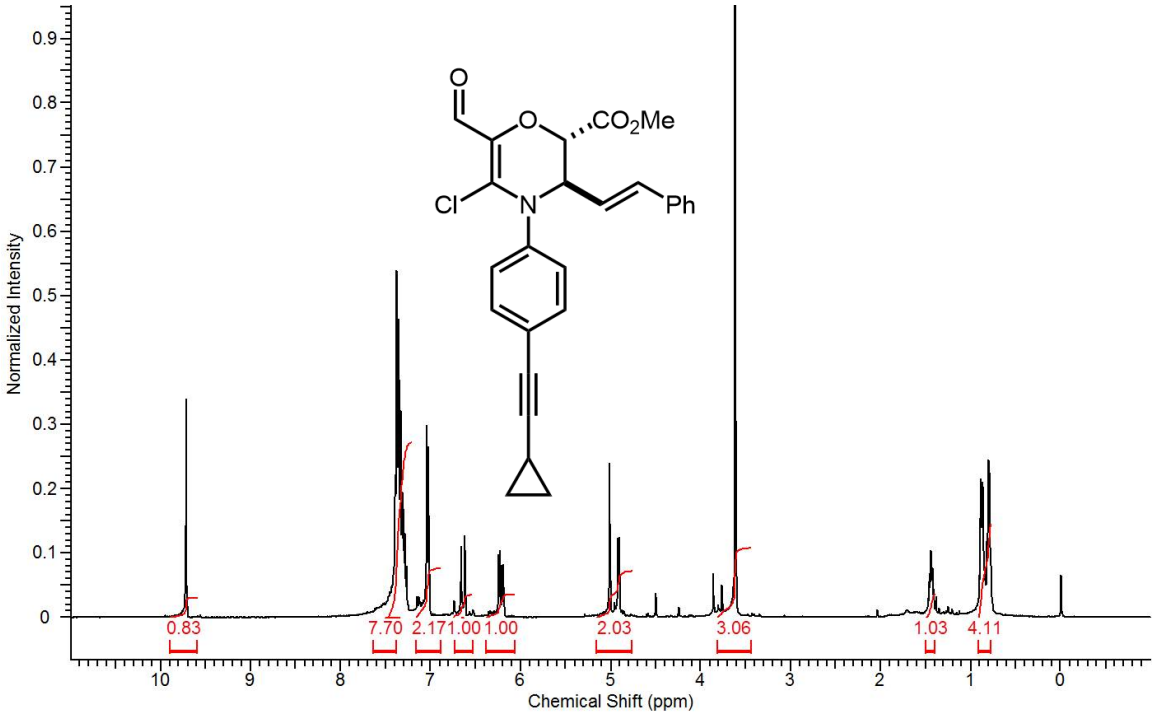
Spectra **1-88** Proton NMR spectrum of **14b.**



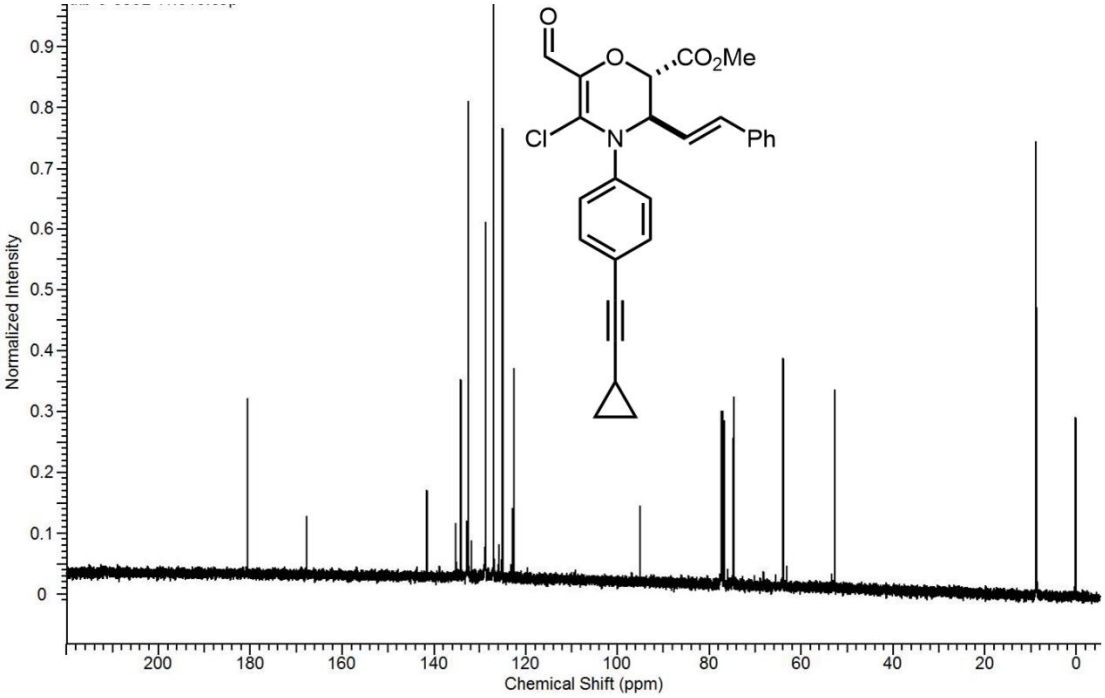
Spectra **1-89** Carbon NMR spectrum of **14b.**



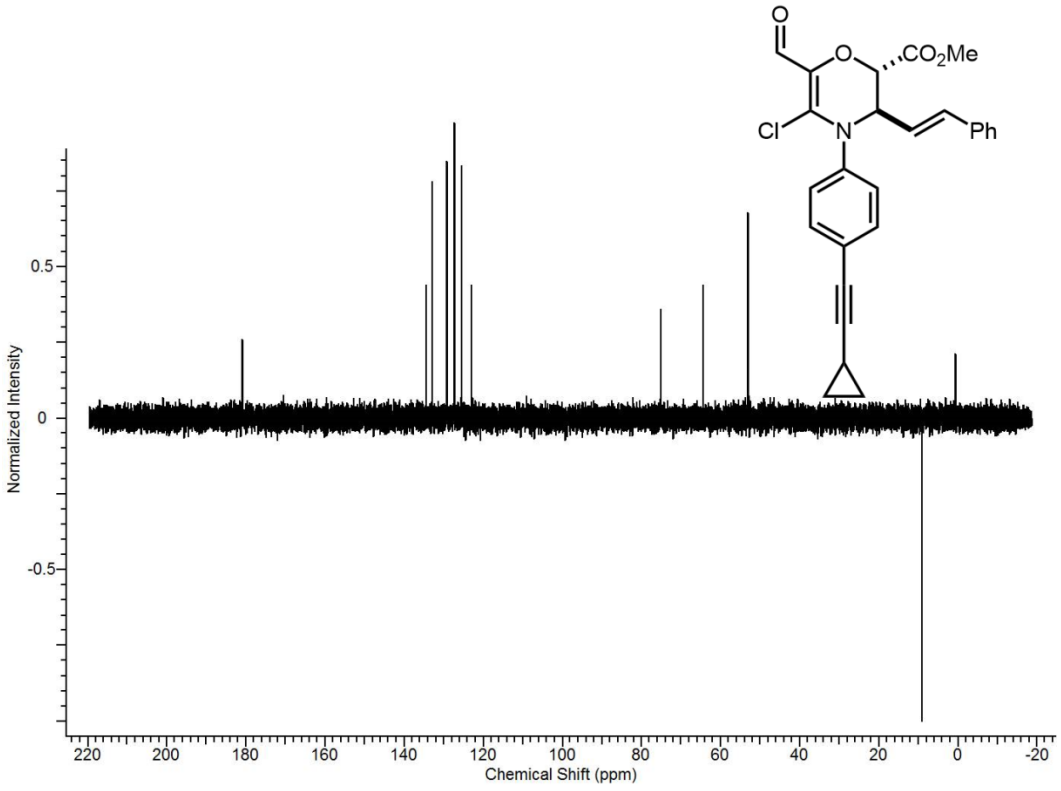
Spectra **1-90** DEPT-135 NMR spectrum of **14b.**



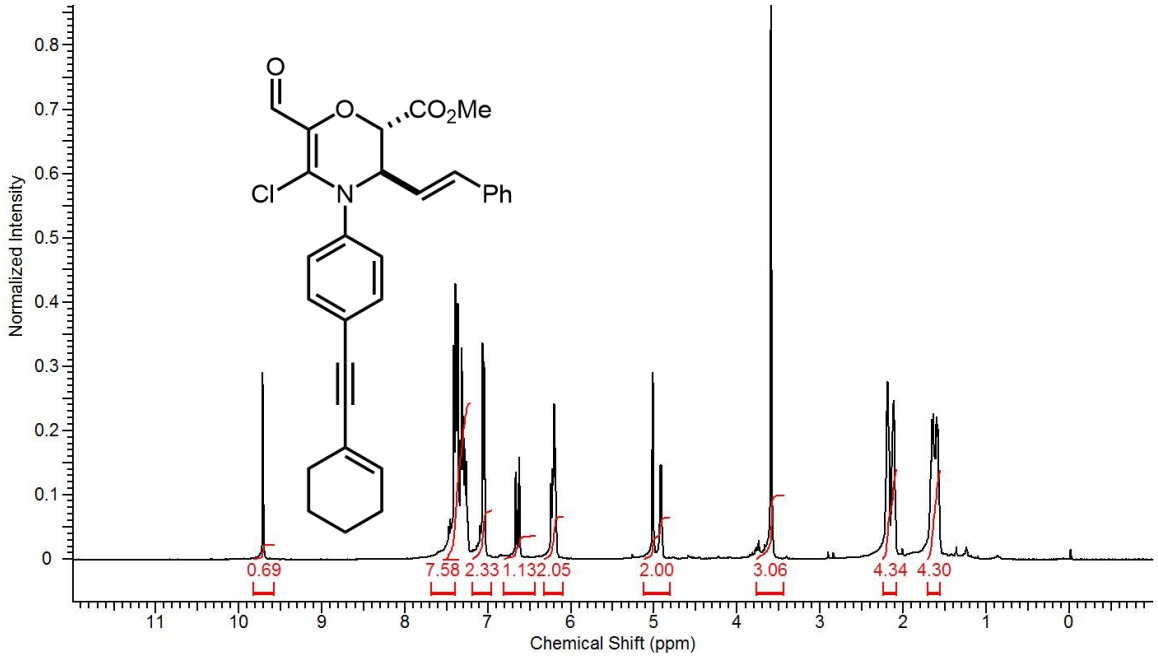
Spectra **1-91** Proton NMR spectrum of **15a.**



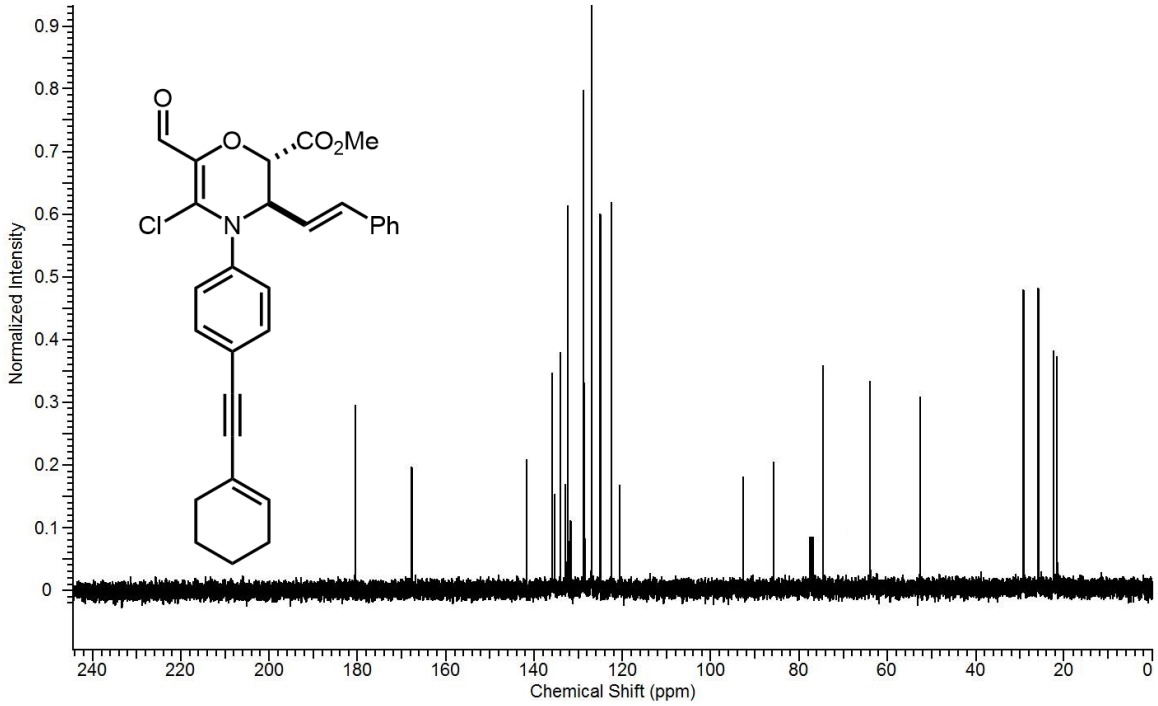
Spectra **1-92** Carbon NMR spectrum of **15a.**



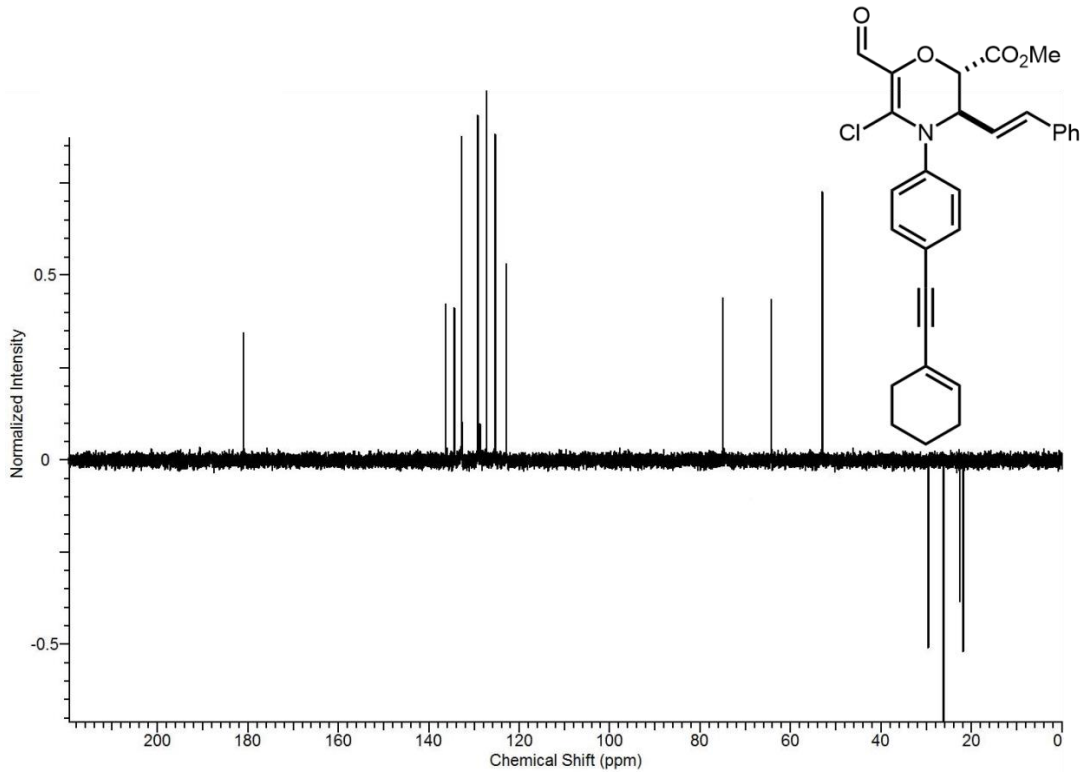
Spectra **1-93** DEPT-135 NMR spectrum of **15a.**



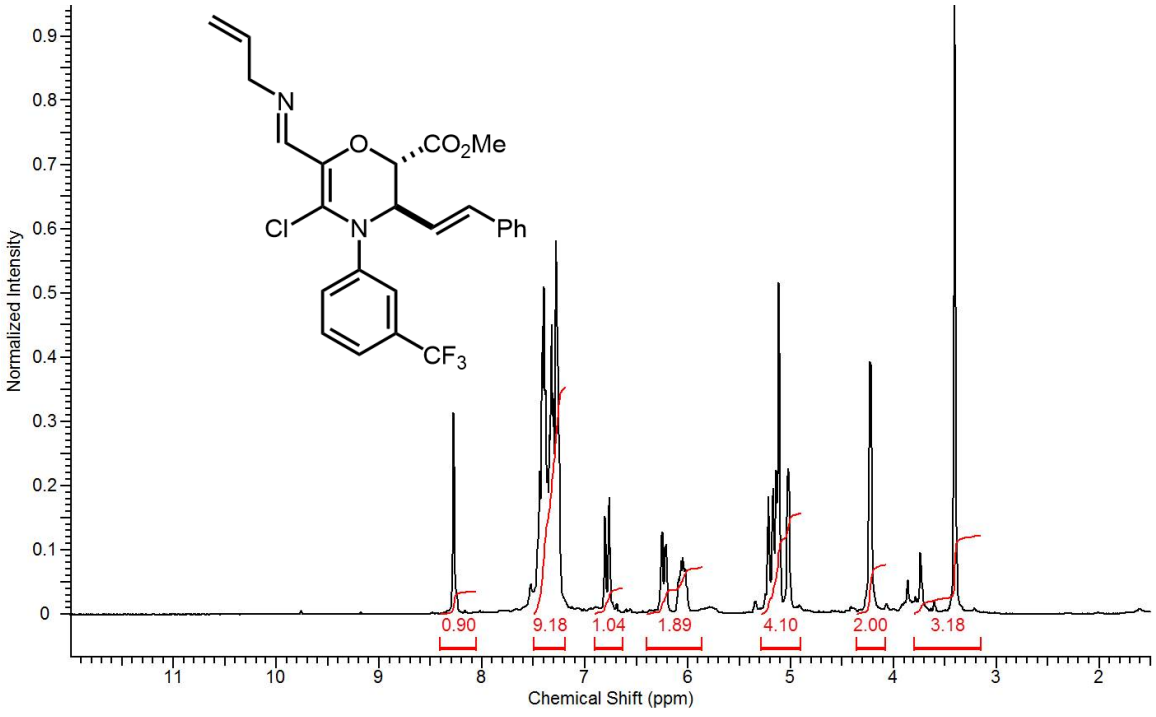
Spectra **1-94** Proton NMR spectrum of **15b.**



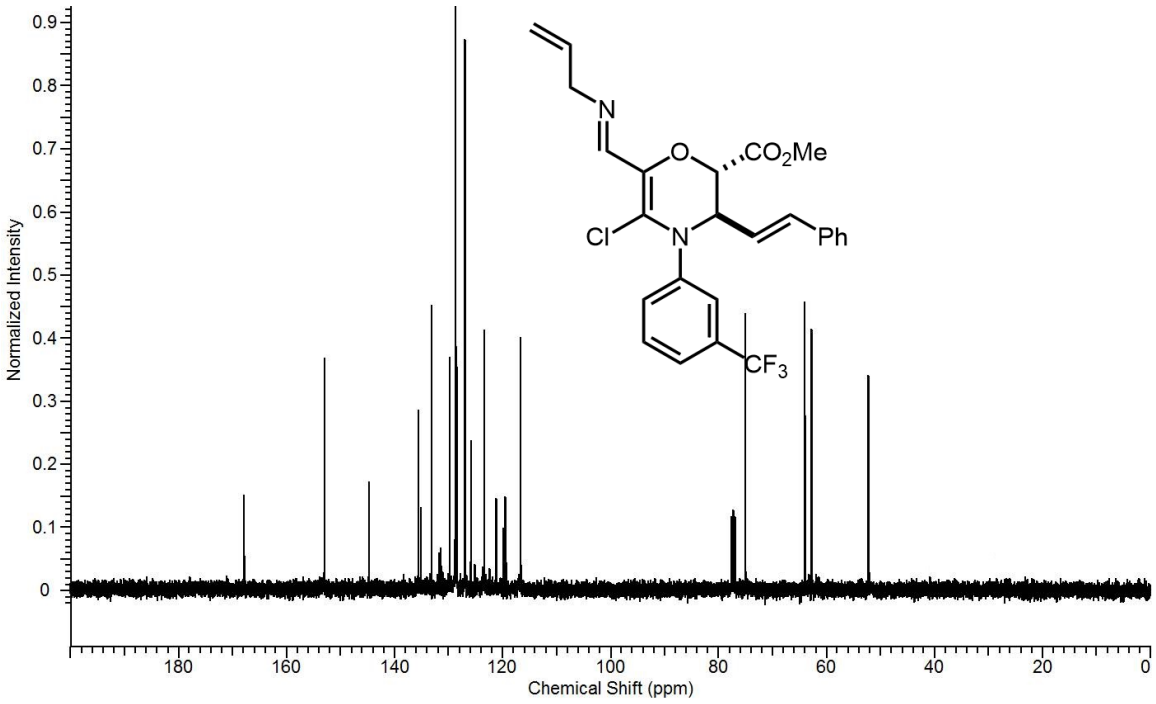
Spectra **1-95** Carbon NMR spectrum of **15b.**



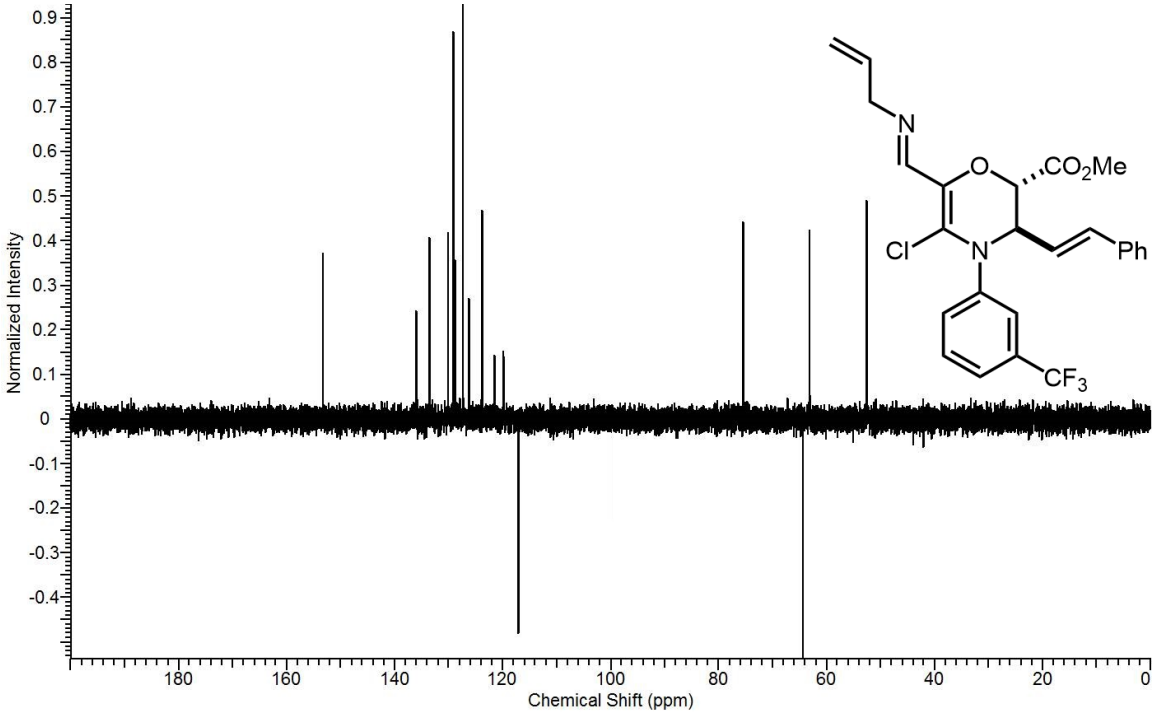
Spectra **1-96** DEPT-135 NMR spectrum of **15b.**



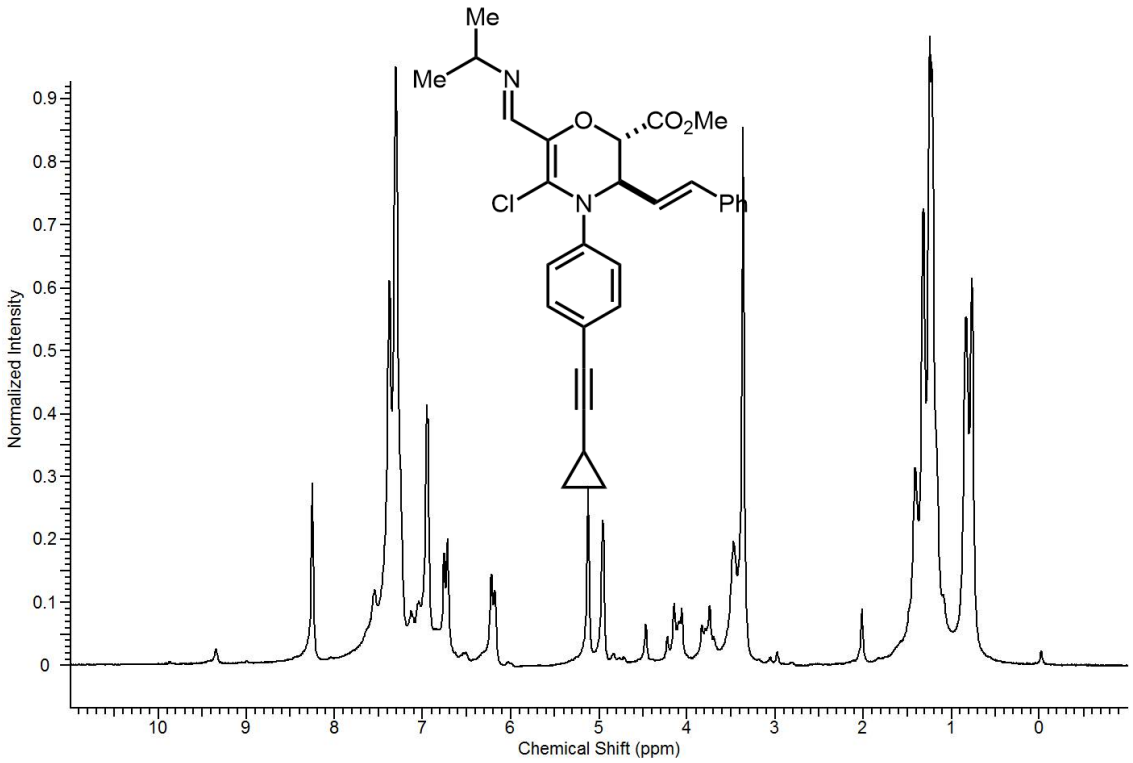
Spectra **1-97** Proton NMR spectrum of **16a.**



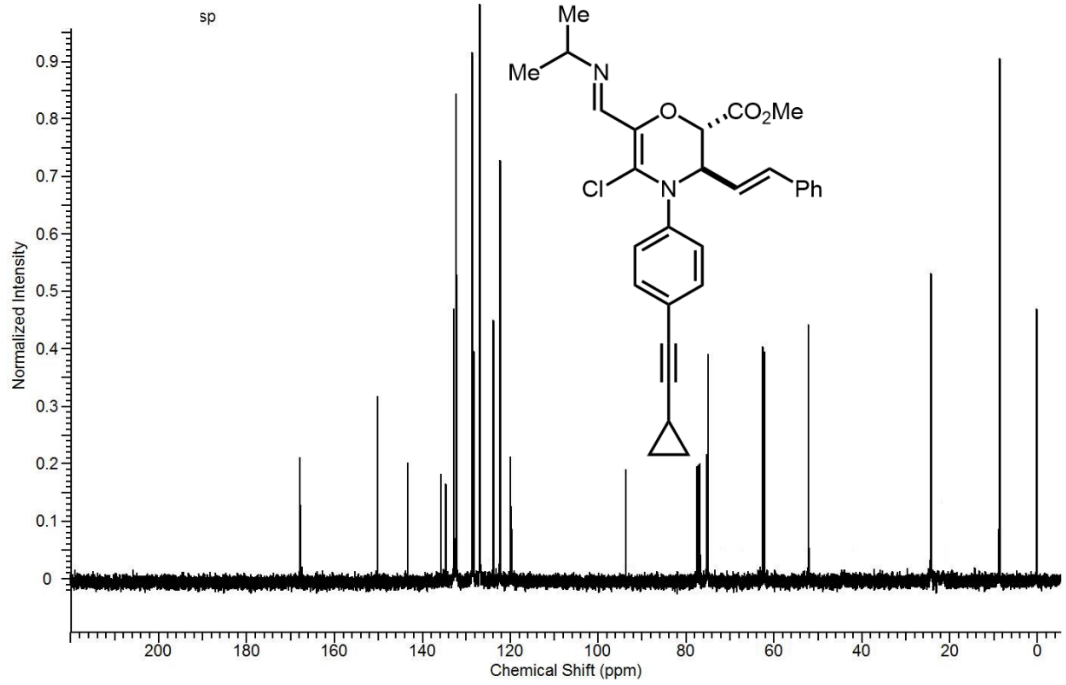
Spectra **1-98** Carbon NMR spectrum of **16a.**



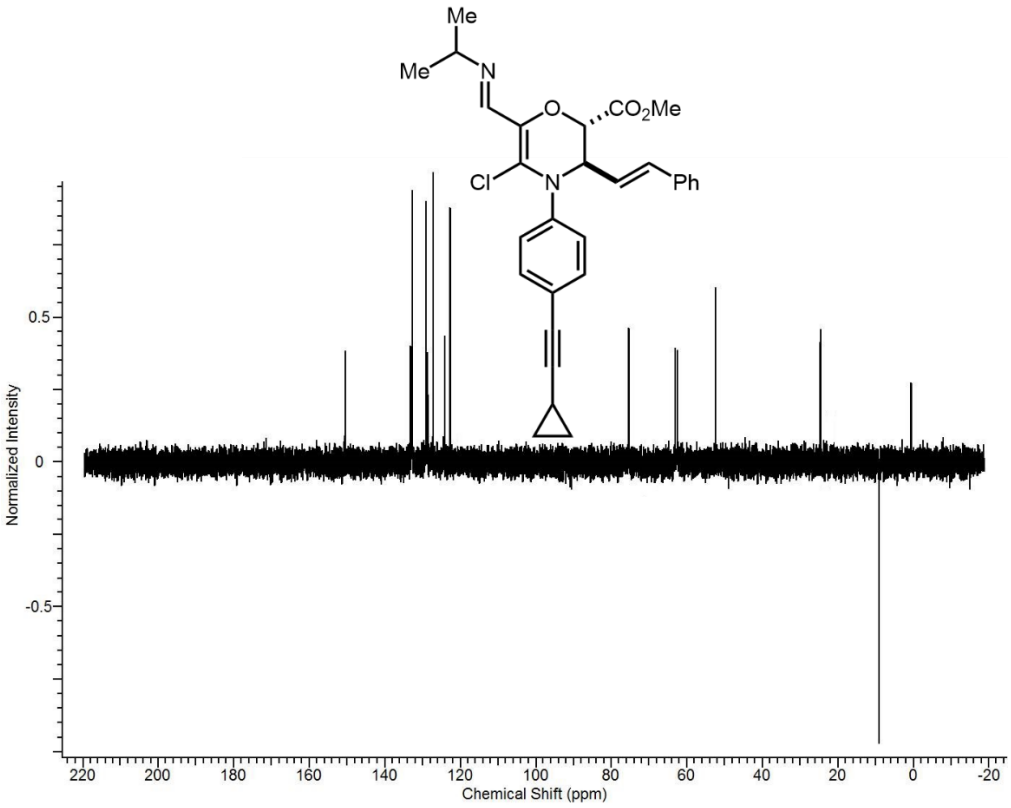
Spectra **1-99** DEPT-135 NMR spectrum of **16a.**



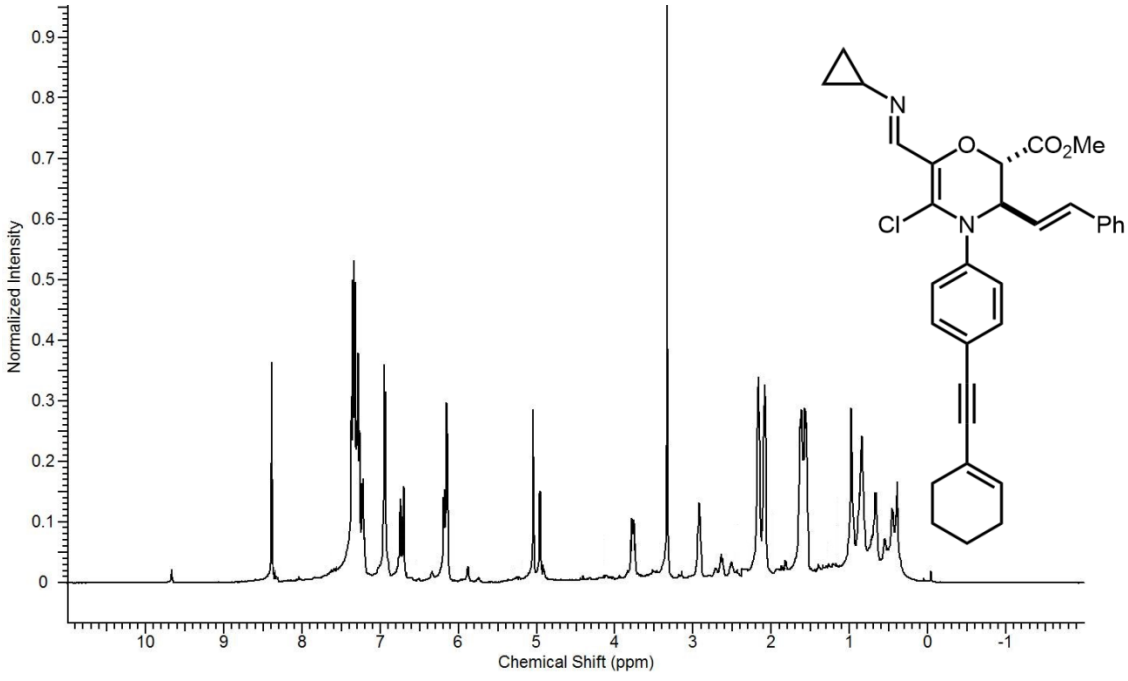
Spectra **1-100** Proton NMR spectrum of **16b.**



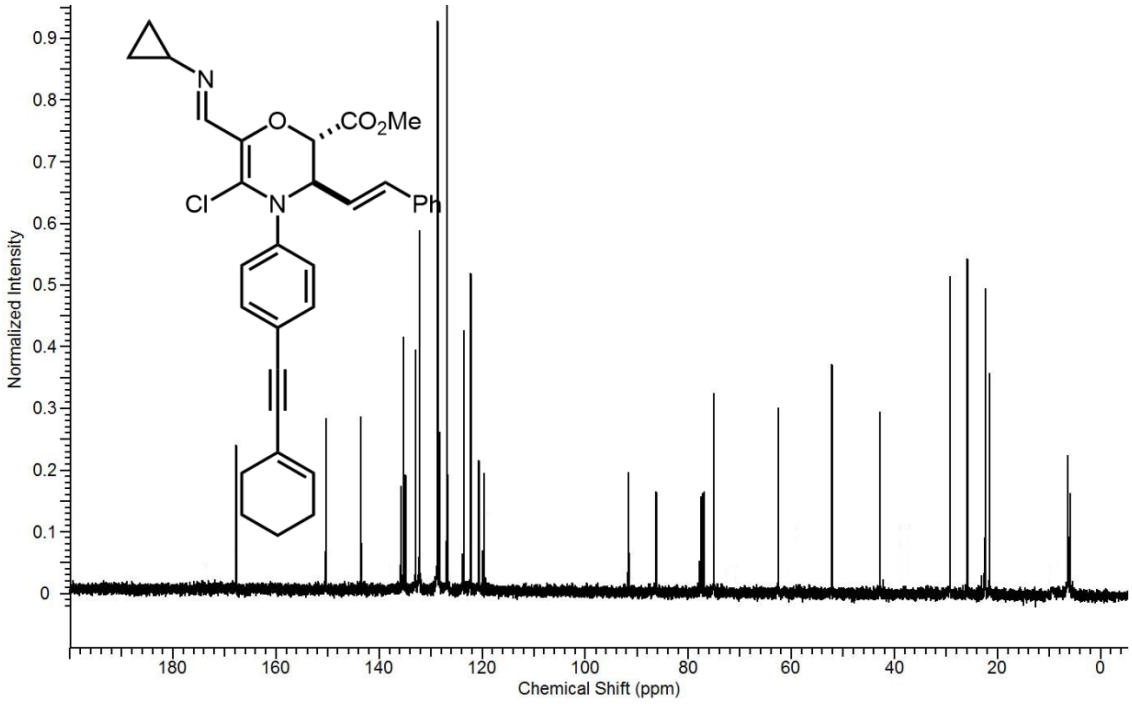
Spectra **1-101** Carbon NMR spectrum of **16b.**



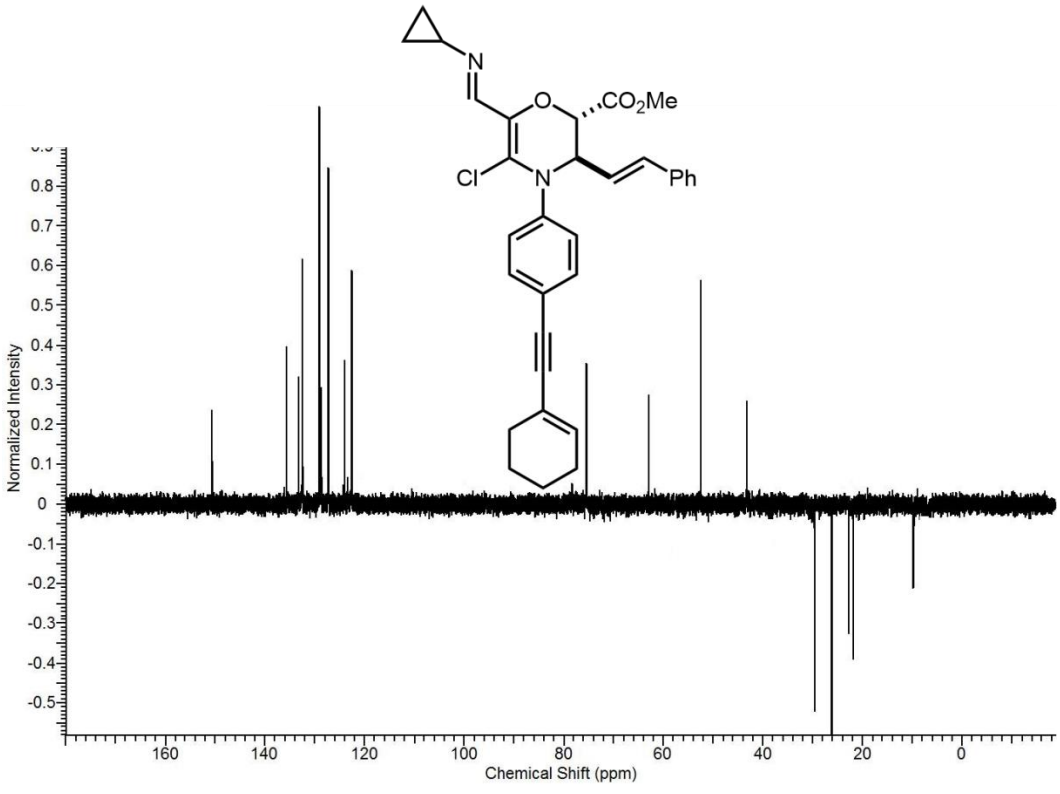
Spectra **1-102** DEPT-135 NMR spectrum of **16b.**



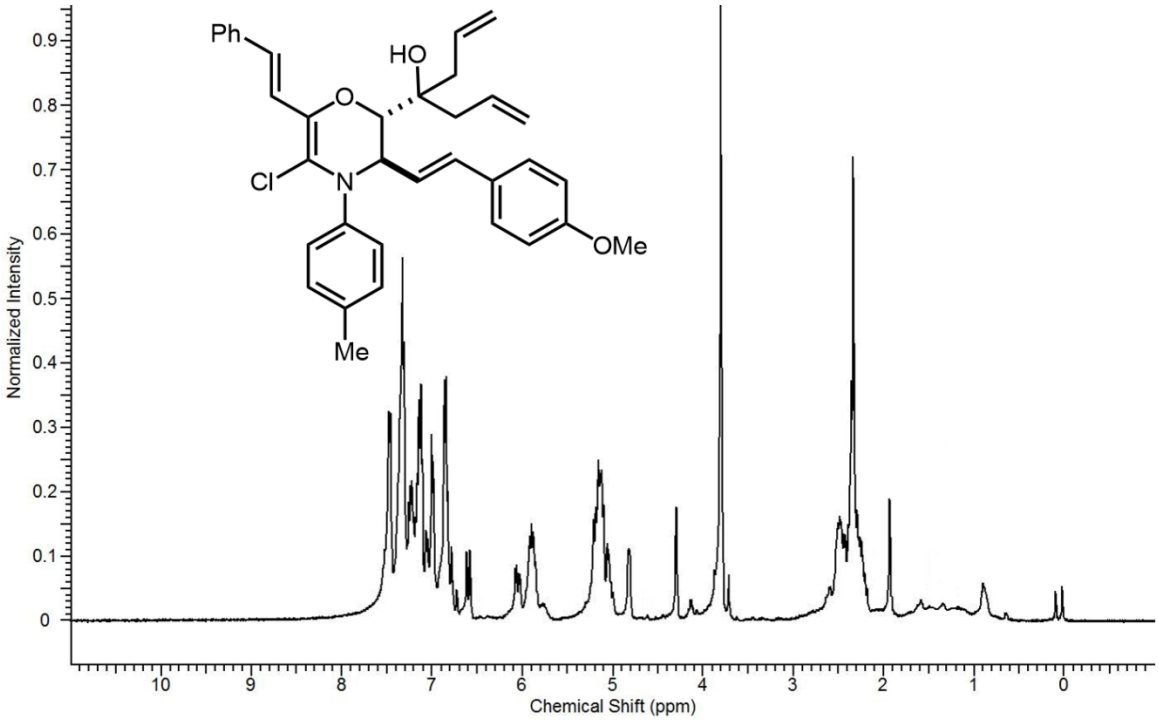
Spectra **1-103** Proton NMR spectrum of **16c.**



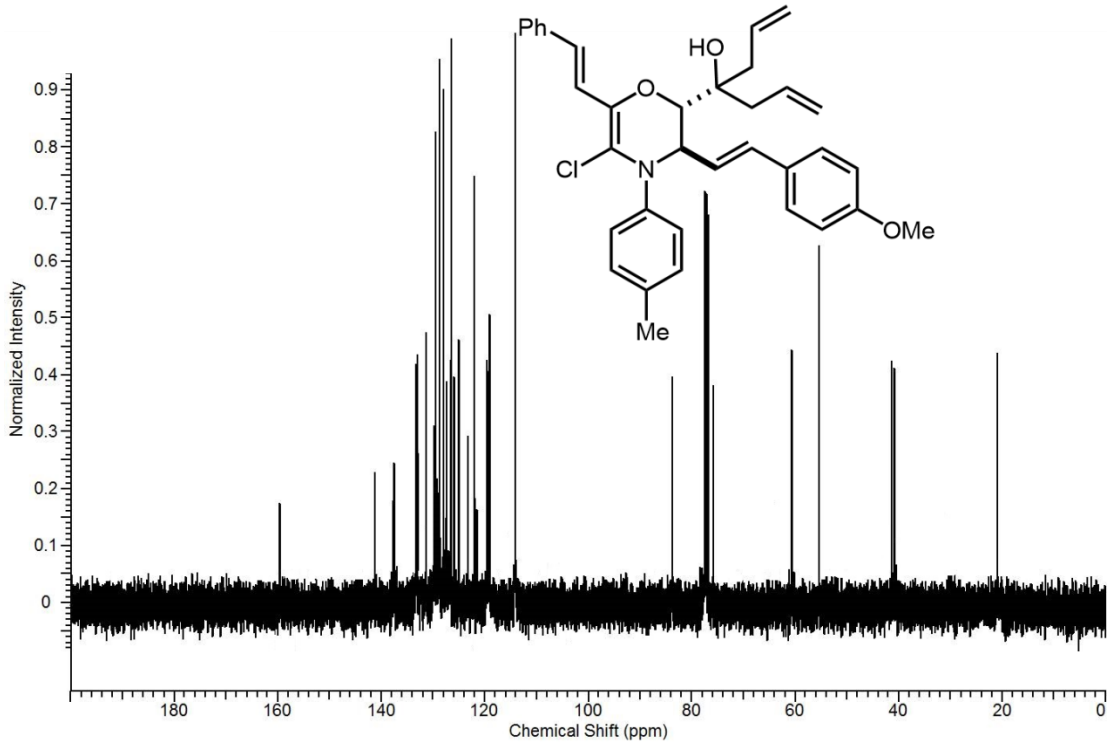
Spectra **1-104** Carbon NMR spectrum of **16c.**



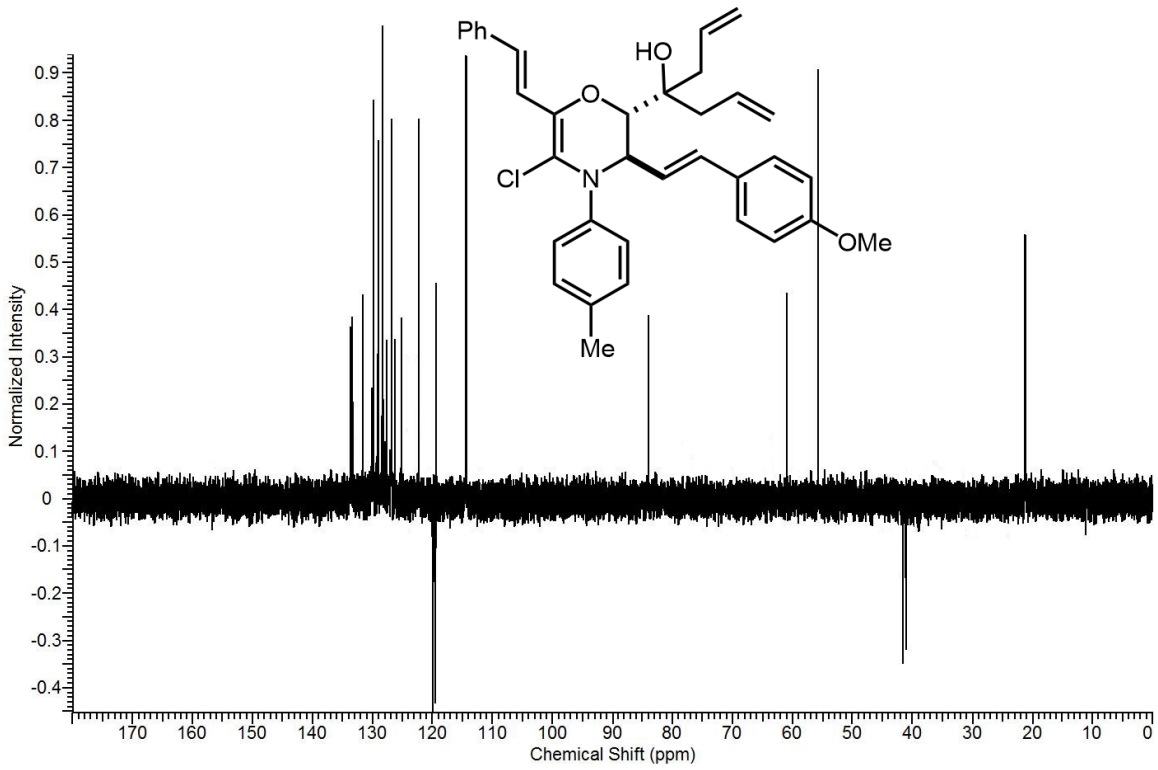
Spectra **1-105** DEPT-135 NMR spectrum of **16c.**



Spectra **1-106** Proton NMR spectrum of **18.**



Spectra **1-107** Carbon NMR spectrum of **18.**



Spectra **1-108** DEPT-135 NMR spectrum of **18.**