DISSERTATION

RHODIUM-CATALYZED CYCLOADDITIONS BETWEEN ALKENYL ISOCYANATES AND ALKYNES: STUDY OF SCOPE, MECHANISM AND APPLICATIONS TOWARD TOTAL SYNTHESIS

Submitted by

Rebecca Ann Keller Friedman

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2010

COLORADO STATE UNIVERSITY

September 10th, 2010

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY REBECCA ANN KELLER FRIEDMAN ENTITLED RHODIUM-CATALYZED CYCLOADDITIONS: BETWEEN ALKENYL ISOCYANATES AND ALKYNES: STUDY OF SCOPE, MECHANISM AND APPLICATIONS TOWARD TOTAL SYNTHESIS BE ACCEPTED AS FULFULLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

_____
Alan Kennan

_____
Yian Shi

_____
Amy Prieto

_____
Michael McNeil

_____
Advisor: Tomislav Rovis

_____
Department Chair: Ellen R. Fisher

ABSTRACT OF DISSERTATION

RHODIUM-CATALYZED CYCLOADDITIONS BETWEEN ALKENYL ISOCYANATES AND ALKYNES: STUDY OF SCOPE, MECHANISM AND APPLICATIONS TOWARD TOTAL SYNTHESIS

Rhodium-catalyzed cycloadditions between alkenyl isocyanates and unsymmetrical, internal alkynes has been studied. A wide variety of alkynes have proven successful components in the [2+2+2] cycloaddition. Excellent yields and enantioselectivities have been achieved in the resulting indolizidinone products. Furthermore, a single regioisomer is obtained for the vast majority of alkynes subjected to reaction conditions. A logical explanation for the highly regioselective insertion for internal, unsymmetrical alkynes was provided. Small variations in the electronics and/or steric bulk of the alkyne substitution were sufficient to predictably control the insertion of the alkyne into the initial rhodacycle.

Mechanistic insight into the rhodium-catalyzed [4+2+2] cycloaddition between dienyl isocyanates and alkynes has been achieved. A series of competition and slow addition experiments, alongside analysis of enantioselectivity and product formation, provided evidence for a proposed mechanism of the [4+2+2] cycloaddition. It was determined that the diene preferentially coordinates to the rhodium, in the presence of a terminal alkyne, to provide eight-membered bicyclic azocene products.

Steps towards the total synthesis of natural product Secu'amamine A have been made. The bicyclic core of the molecule has been successfully synthesized utilizing rhodium-catalyzed [2+2+2] methodology developed within the Rovis group. Additionally, a successful, diastereoselective 1,4-reduction of the resulting vinylogous amide product and subsequent deprotection of an enyne side-chain provided an intermediate that is hypothetically two steps (an alpha-oxidation and 2+2+1 cycloaddition) away from Secu'amamine A.

Rebecca Ann Keller Friedman
Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523
Fall 2010

ACKNOWLEDGEMENTS

There are a number of people that I would like to thank for their help and support over the last five years. First, a big "Thank You!" to my advisor, Professor Tomislav Rovis. It hasn't always been an easy ride, but with your guidance and support, I have become a better chemist. I have learned more about chemistry then I ever thought possible. Thank you, Tom, for sharing your excitement for science and running a group where the standard is no less than excellent.

Thank you also, to my committee members, for taking the time to read this dissertation and sit through both my oral examination and my defense. I would especially like to thank Professor Alan Kennan for writing me reference letters and for always having an open door if questions needed to be asked.

THANK YOU! To all Rovis group members, past and present. It has definitely been an interesting environment to work in these last five years. In particular, thank you to Dr. Jennifer Moore and Dr. Jeff Johnson who showed me around the lab when I started. To my classmates, Stephen Lathrop and Harit Vora, who set a standard of research and commitment to science that I always strove to keep up with. To Dr. Robert T. Yu and Dr. Ernest Lee, who showed me the ropes on my project. To the remainder of 'Team Rhodium', Derek Dalton, Kevin Oberg, Jamie Neely and Todd Hyster for all your ideas and help over the years. Thank you to Kerem Ozboya and Claire Filloux for teaching me to really laugh out loud in lab and for proofreading this dissertation. Thanks for proofreading also go to Dr. Brian Cochran and Derek Dalton. Thank you again to Derek Dalton for helping with the diastereoselectivity models.

Thank you to all my friends near and far who have been so supportive through this entire process. I would especially like to thank Jennifer Finefield and Sarah Stevens. Your friendship and support has meant more to me than you could possibly know. Jenni, thank you for every coffee run, impromptu dinner and for being an ear when I needed someone to listen. Sarah, you are the closest thing to a sister I have outside my family. I don't think I could have made it through these last five years without your friendship (and driving ability). Thank you for spending ~1080 hours in a car with me (I did the calculations ☺). I love you both very much.

The biggest thanks go out to my family. You have always expected my best in academics, but have been supportive of any choice I made and I couldn't ask for a better combination. To my brother, Zach who can make me laugh at the drop of a hat, which was often needed throughout this process. To my mom and dad, the best parents I could have asked for. I love you both! And look Dad, it's the other bookend to your dissertation; your baby girl is a PhD!

And finally, and most importantly, I dedicate this work to my husband, Jonathan. You are my best friend and the love of my life. You have been through more with this process then anyone and have stood by me and been a rock. I could not have done this without you. There are not appropriate words to describe how much I love and thank you. Its time for that vacation!

Table of Contents

Chapter 1

Predictable Regioselective Insertion of Unsymmetrical, Internal Alkynes in Rhodium-Catalyzed [2+2+2] Cycloadditions with Alkenyl Isocyanates

1.1 Introduction

The rapid assembly of complex molecules from simple starting materials remains a prominent goal in organic synthesis. Specifically, such quick assembly of complex intermediates can provide access to a diverse range of synthetic targets. Transition-metal catalyzed cycloadditions are a powerful method to gain quick access to structures exhibiting high levels of complexity. Historically, development of transition-metal-catalyzed cycloadditions began with the formation of carbocycles, for example, [5+2] and [4+2] reactions.[1] Three component additions have also been explored, and examples include Pauson-Khand-type [2+2+1] reactions as well as [2+2+2] cyclotrimerizations.[2] Incorporation of three separate π-components provides the opportunity for many different substitutions and stereocenters to be set in a single step.

Incorporation of nitrogen into cycloaddition products allows for access to numerous heterocycles. Previous cycloadditions that incorporate nitrogen include but are not limited to, [2+1] aziridinations, 1,3-dipolar cycloadditions, and pyridine and pyridone formation.[3] Utilization of isocyanates, easily accessed *via* the Curtius rearrangment, as a π-component provides a simple way to synthesize heterocumulenes. When an isocyanate is partnered with alkynes in cycloaddition chemistry a variety of pyridone products can be formed.[4] However, related transformations that would generate nitrogen-containing heterocycles containing a carbon stereocenter had been largely ignored. When our lab

began working on this problem, we aspired to expand the scope of potential π-components to include alkenes and yield a cycloadduct with five or more contiguous stereocenters (Figure 1).

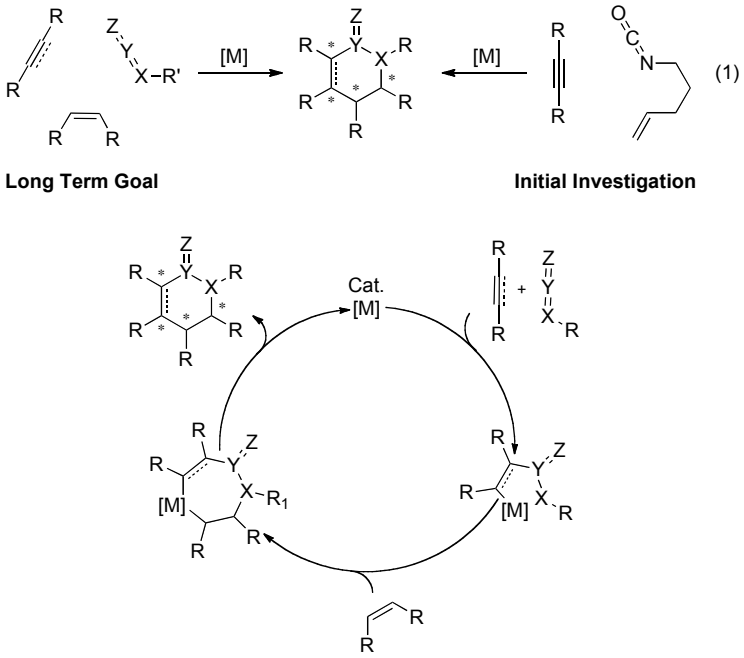
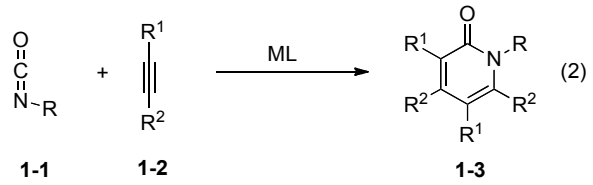


Figure 1

1.2 Background: Cycloadditions with Isocyanates

Choosing isocyanates as a π-component is an efficient way in which to incorporate nitrogen into the cycloadducts. Transition-metal-catalyzed cycloadditions, [*m*+*n*+*o*], utilizing isocyanates were first explored by Yamazaki in 1977 to form pyridones.[5]



Hoberg and coworkers[6] greatly advanced the field of transition-metal mediated cycloadditions in the 1980's. In their work, a combination of isocyanates, carbon

dioxide, alkenes and/or alkynes in nickel-mediated cycloadditions are used to obtain a variety of heterocycles (Figure 2).

Using a stoichiometric Ni(0) source, Hoberg and coworkers were able to isolate nickel metallacycles (**1-M1a and 1-M1b**). By trapping the metallacyclic intermediates with electrophiles, they were able to demonstrate the fundamental reactivity of the components and the intermediate metallacycles. Furthermore, isolation of these metallacycles provided insight into the mechanism through which similar cycloadditions could proceed. The cycloaddition occurs with oxidative cyclization of the metal, isocyanate and alkene, forming two regioisomers of the nickel metallacycle (**1-MIa**, **1-MIb**). Further research by Hoberg rendered the reaction catalytic in nickel albeit with limited scope.[6e-6f]

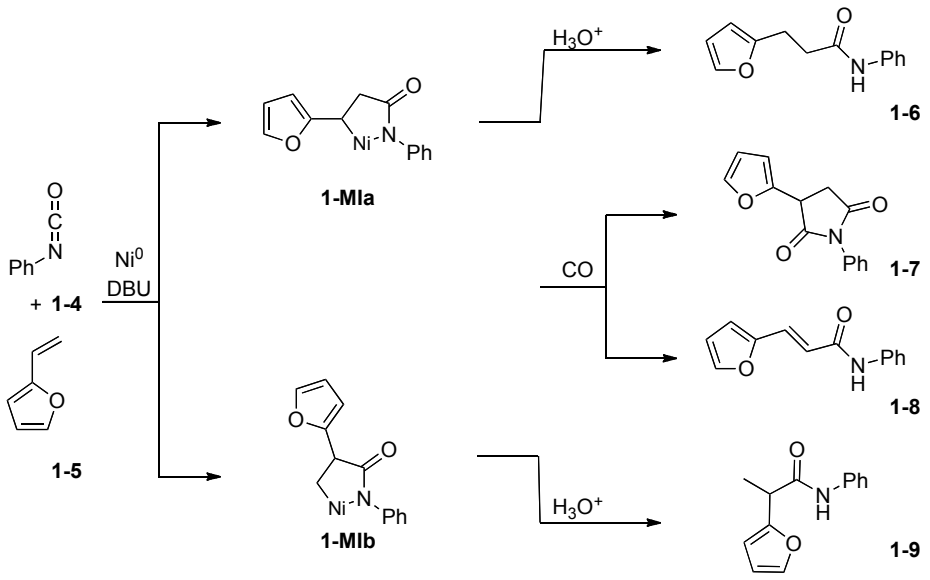
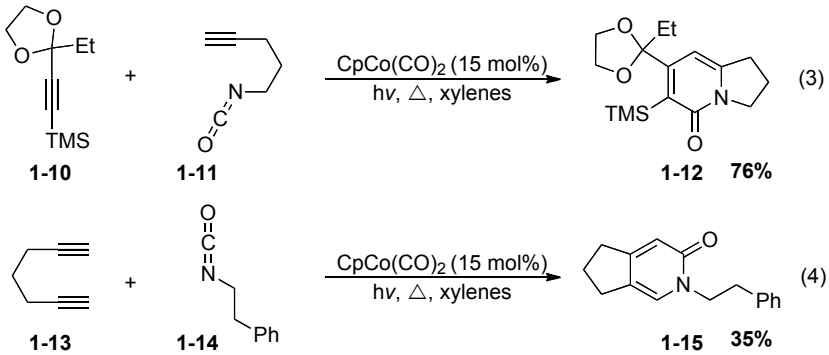


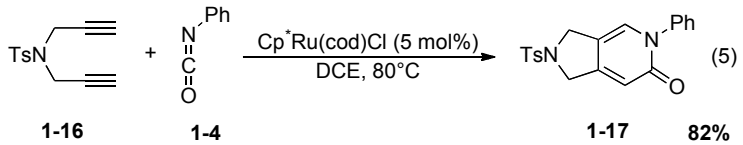
Figure 2

The use of catalytic metal in cycoladditions involving alkynes and isocyanates was thoroughly explored by Vollhardt and coworkers in the 1980s.[7] They showed that an alkyne moiety can be tethered to the isocyanate (**1-11**) or another alkyne (**1-13**) (eq. 3 and

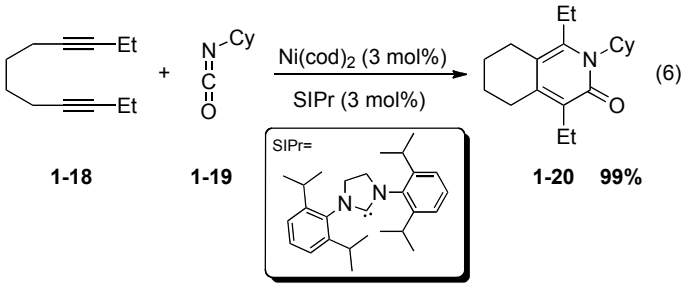
4) to provide pyridone products, with certain limitations. When the isocyanate is tethered to an alkyne, the third component of the [2+2+2] cycloaddition must be a TMS substituted alkyne (**1-10**) in order for the reaction to proceed in good yields. Moreover, harsh conditions (refluxing xylenes) are required for reactivity. When two alkynes are tethered, the [2+2+2] cycloaddition is less efficient (eq. 4).



More recently, the Itoh laboratory further developed metal-catalyzed [2+2+2] cycloadditions with the use of a ruthenium catalyst.[8] When other catalysts are used, this reaction is inefficient due to the oligomerization of the diynes. However, with the ruthenium catalyst (Cp*Ru(cod)Cl), Itoh increased the breadth of possible substrates to include diynes (eq. 5). Itoh's method utilizes a variety of 1,6 diynes and isocyanates. Expansion of the isocyanate scope was also accomplished: both aryl and alkyl isocyanates are tolerated. In more recent work[8b], the authors further expanded the scope of the reaction. It was shown that both nitriles and isothiocyanates can participate successfully in the reaction. Finally, unsymmetrical diynes can be used in reactions with good regioselectivity.

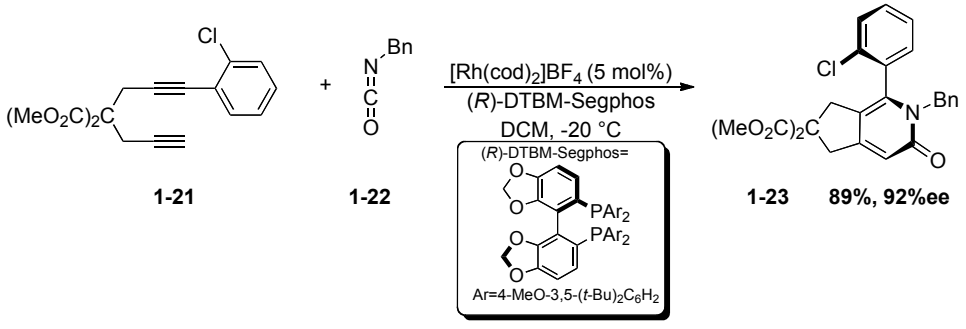


Louie and coworkers[9] explored the [2+2+2] cycloaddition reaction using diynes and nickel catalysts. A catalytic system consisting of Ni(0) and a N-heterocyclic carbene allows for a scope including both terminal and internal diynes (eq. 6). Impressively, the formation of 2-pyridones occurs at room temperature in good yields with electron-rich isocyanates.



(6)

The Tanaka laboratory investigated catalytic [2+2+2] cycloadditions with cationic rhodium and biaryl-based ligands.[10] This new catalytic system successfully produces 2-pyridones from a variety of isocyanates and alkynes in moderate to excellent yields (48-99%). With the same metal catalyst but a chiral ligand, DTBM-Segphos, the Tanaka laboratory incorporated an unsymmetrical diyne (**1-21**) to synthesize an axially chiral compound (**1-23**) in both good yields and enantioselectivity (eq. 7). This accomplishment represented the only example of an enantioselective [2+2+2] reaction incorporating an isocyanate prior to work from the Rovis group.



(7)

1.3 Rhodium-Catlyzed Cycloadditions in the Rovis Group

At the time we entered the field of [2+2+2] cycloadditions utilizing isocyanates certain benchmarks had been established. Hoberg could perform cycloadditions of alkenes and isocyanates, but only with stoichiometric amounts of nickel.[6a-c] As discussed in the previous sections, several groups could perform metal-catalyzed [2+2+2] cycloadditions with isocyanates with a variety of metals and alkynes. However, the 2-pyridones that result from the mentioned reactions possess no carbon stereocenters. We envisioned that substituting an alkyne with an alkene would allow for a stereocenter to be produced catalytically (Figure 1). This would greatly increase the synthetic utility of these reactions, allowing access to a large variety of natural products (Figure 2).

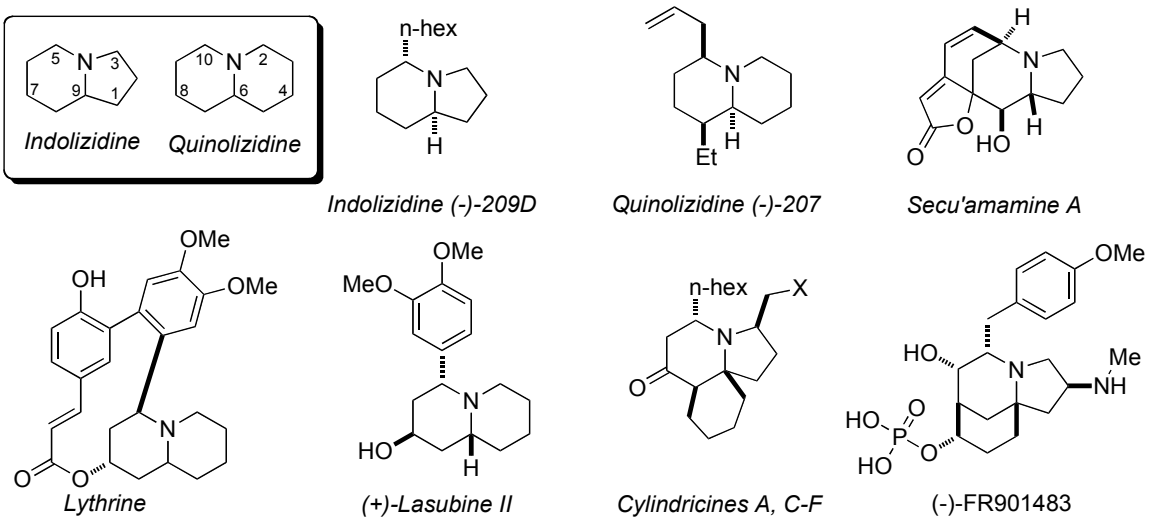


Figure 2

A major challenge accompanying the incorporation of alkenes in transition-metal catalyzed cycloadditions is the prevention of an additional equivalent of alkyne reacting with the metallacycle. Assuming that our system would proceed via metallacycles similar to those observed by Hoberg and coworkers[6] we proposed that by tethering the alkene to the isocyanate, the resulting intramolecular reaction could successfully compete with a second intermolecular alkyne insertion event. A model alkenyl isocyanate (**1-25**)

was synthesized via Curtius rearrangement of an acyl azide. This isocyanate was then tested with internal, symmetrical alkynes under a variety of catalytic conditions. A catalytic system of $[Rh(C_2H_4)_2Cl]_2$ and triarylphosphine ligands proved optimal to effect the desired transformation.

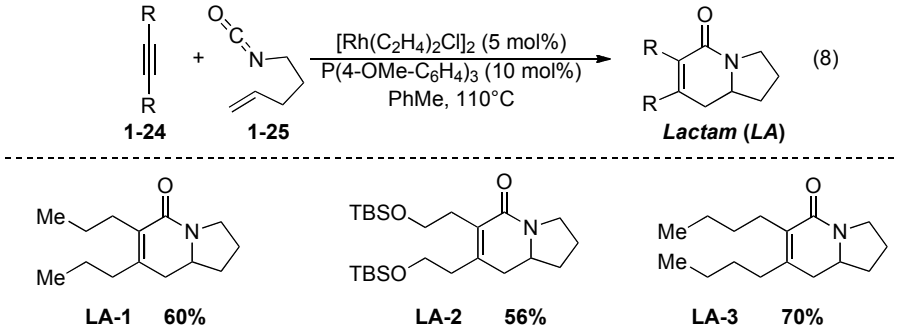


Table 1

A series of dialkylalkynes produced the expected lactam product in good yields (Table 1). However, a second product was also isolated in small amounts during these trials in trace amounts. Moreover, this heretofore, unidentified cycloadduct was the major product when diaryl alkynes were used. An X-Ray crystal structure revealed that this product was a vinylogous amide (**VA**), isomeric to lactam **LA** presumably arising from a CO-migration at some point in the catalytic cycle. This cycloadduct was also obtained in good yields for electron-rich and electron-neutral aryl substituents. The yield did decrease for more electron-poor alkynes.[11]

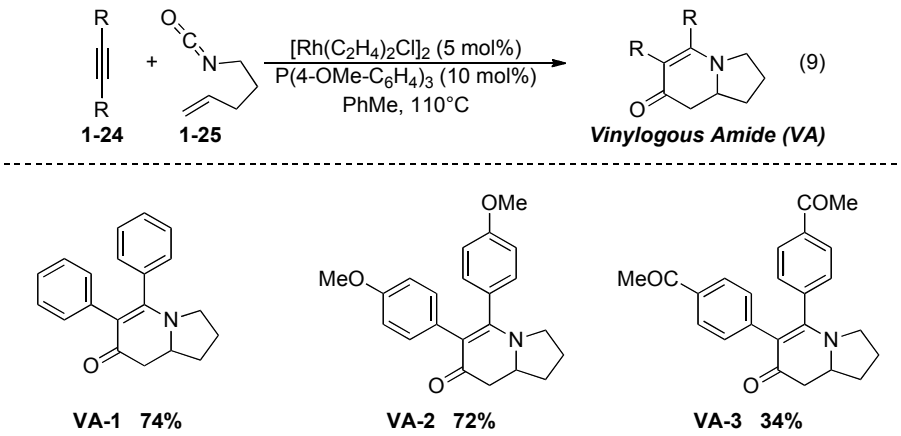


Table 2

With a basic understanding of the racemic system, R. Yu and Rovis sought to induce asymmetry. This objective would be accomplished with the use of a chiral ligand. It was found that the TADDOL-based phosphoramidites worked well as ligands in the system (**L1** and **L2**). Moreover, the introduction of phosphoramidites as ligand solved a lingering problem from the racemic reaction. Terminal alkynes participate very well with phosphoramidite ligands; in contrast, dimerization of terminal alkynes had posed a serious problem in our previous system as well as similar systems when phosphine ligands were used.[12] Alkynes still control the product selectivity (lactam (**LA**) vs. vinylogous amide (**VA**)); yields are generally good, and enantioselectivities are good to excellent in this phosphoramidite system (Table 3).

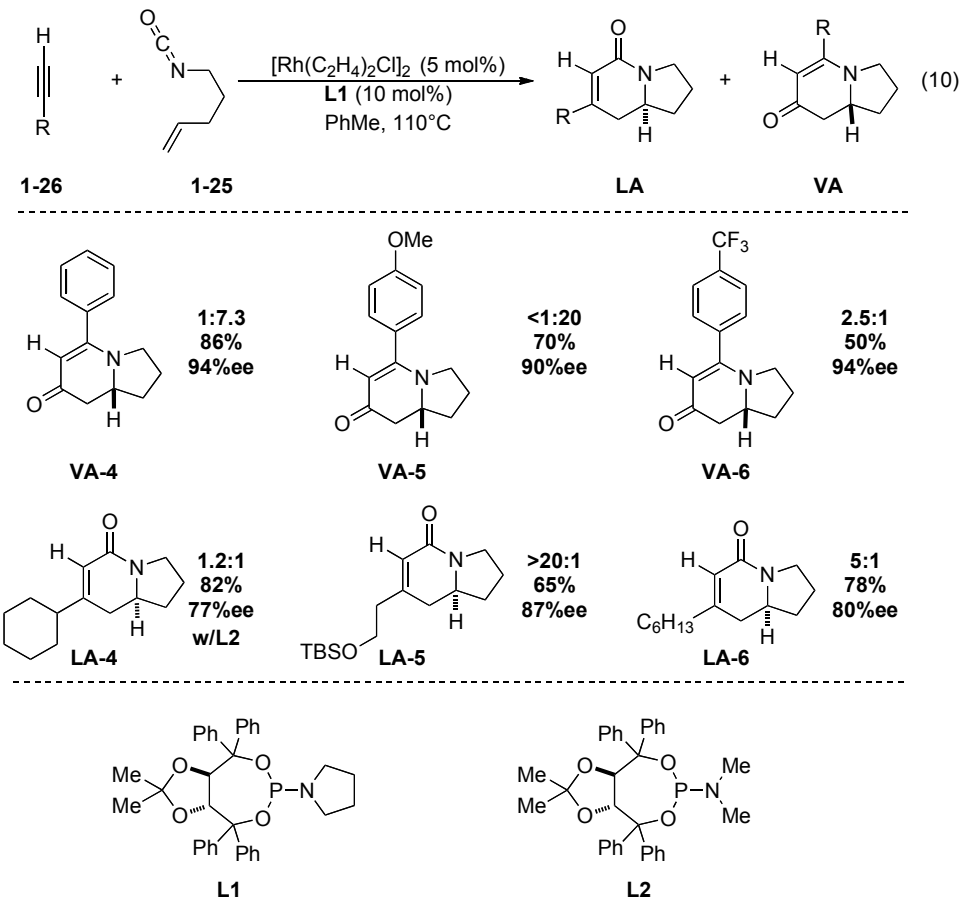


Table 3

Electronics of the alkyne, as well as sterics, affect the overall yield and product selectivity. Sterically large alkyl groups favor vinylogous amide products, while electron-deficient aryl alkynes promote formation of lactam as the major products.[13]

The reaction scope was further developed to tolerate further substitution of the alkene. Lee and Rovis showed that 1,1-disubstituted alkynes worked well with a large number of substituents. Incorporation of these substrates provides access to indolizidinone products that contain a fully substituted stereocenter (Table 4).[14] The yields and enantioselectivity of the cycloaddition are moderate to excellent and the reaction tolerates sterically large groups, such as isopropyl, on the alkene (**VA-8**). Alkyne composition still appears to control the product selectivity.

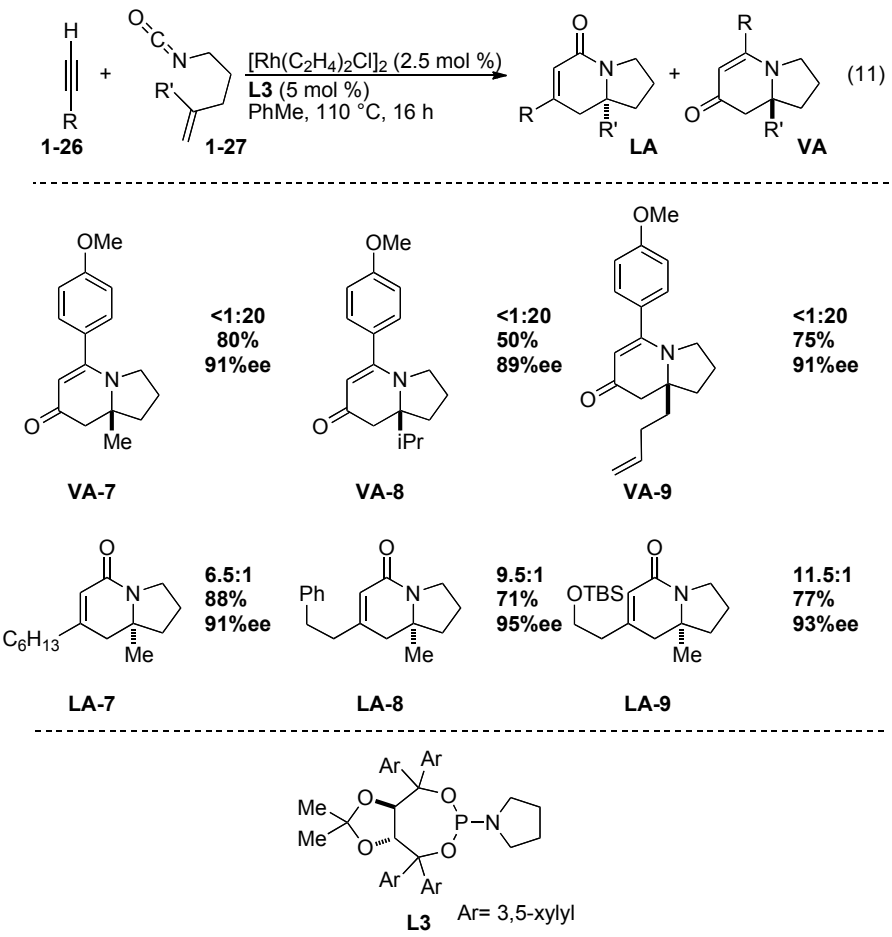


Table 4

With a substantial scope of terminal alkynes and substituted and unsubstituted alkenes established, and rendered asymmetric, a detailed mechanistic proposal can follow.[15] The mechanistic proposal suggests initial coordination of the rhodium complex to the isocyanate and the alkyne. Oxidative cyclization follows to form one of two five-membered rhodacycles.

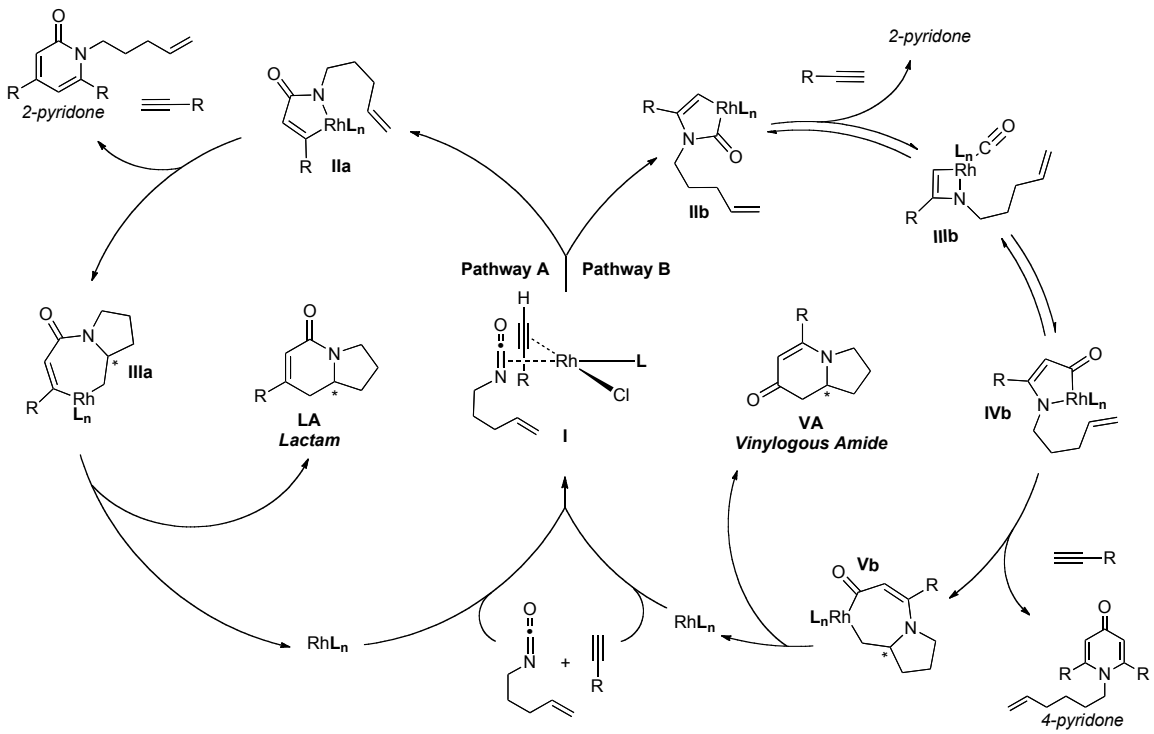


Figure 3

Insertion to form a rhodium-nitrogen bond (Pathway A) or rhodium-carbon bond (Pathway B) generates isomeric metallocycles **IIa** and **IIb**, respectively. In pathway A, the alkene can easily undergo migratory insertion, forming a seven-membered rhodacycle (**IIIa**), which upon reductive elimination, yields the lactam product (**LA**). However, in Pathway B, the alkene is not poised to insert. However, a presumed CO migration can occur, enabling a subsequent migratory insertion event to provide rhodacycle **IVb**. A final reductive elimination step reveals vinylogous amide product **VA**. Observation of both 2- and 4-pyridone side products substantiates this hypothesis.

A competition experiment between isocyanate **1-27** (R'=Me) and isocyanate **1-25** resulted in a 1:1 mixture of products, indicating that the initial, oxidative cyclization step did not include the alkene and was presumably irreversible. Moreover, this observation suggests that the 'choice' between pathway A and pathway B is determined by the

alkyne. Indeed, the lactam to vinylogous amide ratio appears to be controlled by the sterics and electronics of the alkyne.

X-ray crystal structures obtained by group members allowed for the following proposal for product selectivity.[15] The sterically large phosphoramidite controls the isocyanate and alkyne coordination to the rhodium center; one face of the rhodium square plane is hindered by the ligand, and large substituents will orient opposite the hindered face (Figure 4). This orientation allows for access to both products, depending on the rotation of the ligated alkyne and isocyanate during oxidative cyclization. If the two smaller components tilt away from the metal center, a C-C bond is formed and the lactam is ultimately obtained. Rotation in the opposite sense from the square planar intermediate results in the C-N bond formation and eventually vinylogous amide formation. Both sterics and electronics can control the cyclization.

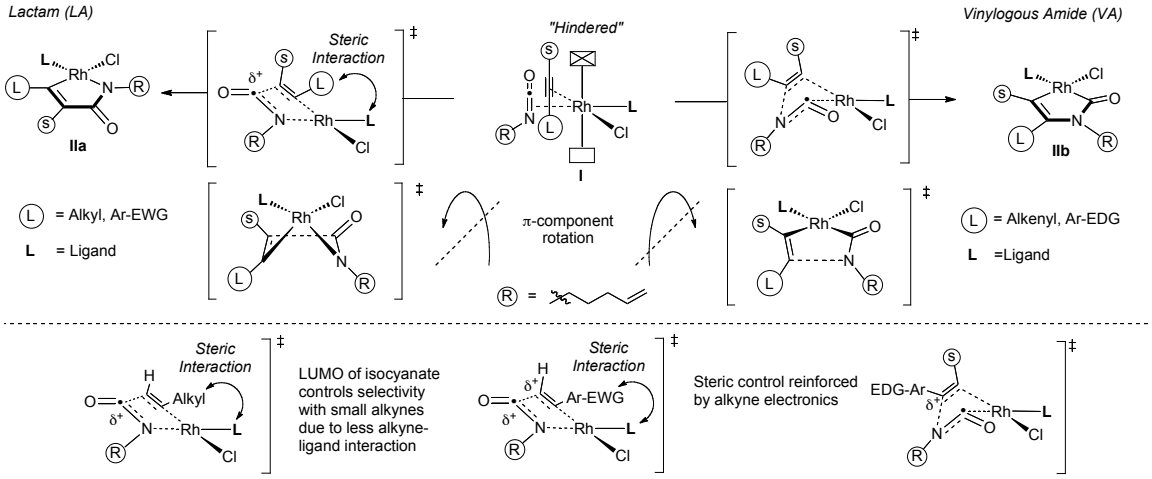


Figure 4

Both sterics and electronics can control the sense of cyclization from intermediate **I**. Lactam products, which are favored with smaller, alkyl alkynes require the larger group on the alkyne to rotate into a position proximal to the large ligand. Such rotation is

not as facile for larger alkyl or aryl alkynes, which prefer to tilt the large substituent in the opposite direction from the phosphoramidite (Pathway A, Figure 3).

Electronic preference can be partially explained by the Stockis and Hoffman model.[16] This model suggests that there exists an electronic preference for the largest LUMO coefficient of each substituent to position beta to the metal of the metallocycle. In lactam formation, the isocyanate LUMO controls this selectivity, and can either be reinforced or disfavored by the LUMO of the alkyne. Electron-deficient aryl alkynes (as well as small alkyl alkynes for steric reasons) favor lactam formation, while electron-rich (or large) alkynes favor vinylogous amide.

While alkynes had been the only variable controlling product selectivity in the initial studies, ligand design would be expected to provide another mode of regiocontrol. Initial results[13] implicated phosphoramidites on a BINOL backbone as possible candidates. Further exploration revealed two types of ligands (**L6** and **L7**) that could switch the selectivity of alkyl alkynes towards vinylogous amide, while maintaining high enantioselectivity for the desired products (Table 5).[17]

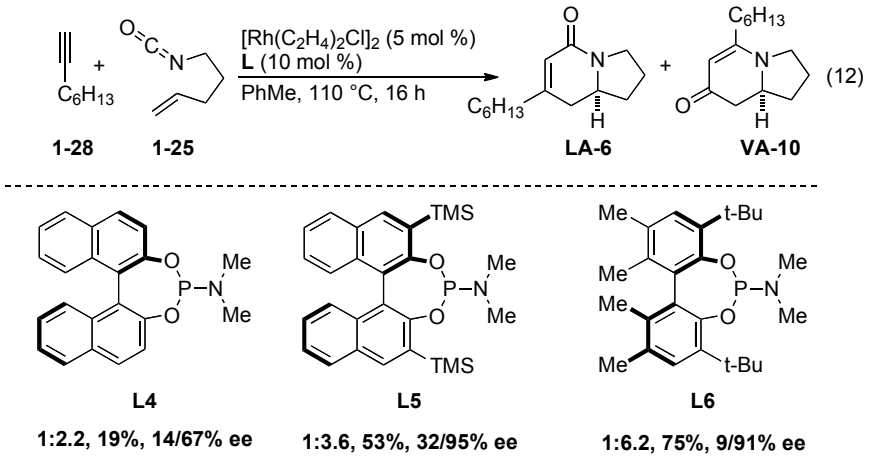


Table 5

The two most successful derivations, **L5** (GUIPHOS) and **L6**, resulted in moderate to good yields of **VA-10** and excellent enantioselectivity. The new ligand scope was expanded to include a variety of alkynes. Both ligands have substitution in the 3 and 3' positions, which appears to aid in the selectivity. Crystal structures have shown that the Rh-P bond length is shorter with the BINOL/Biaryl phosphoramidite complexes. This makes the vinylogous amide pathway preferential due to exacerbated steric interactions in the lactam pathway.[15]

Although ligand modification can promote selective vinylogous amide formation, the problem of forming lactam-type products selectively with aryl alkynes could not immediately be solved by ligand choice. However, increasing steric bulk on one of the π-components by switching the isocyanate to a carbodiimide moiety (**1-29**) does aid in this problem.[18] The carbodiimide biases oxidative cyclization towards Pathway A and metallacycle **IIa**, allowing for selective 'lactam' formation even when aryl alkynes are used as substrates. While electron-rich alkynes are able to partially override this overwhelming preference, the lactam-type product still predominates. The resulting amidine products can be modified via reduction of the imine to the amine or hydrolysis to give the lactam product.

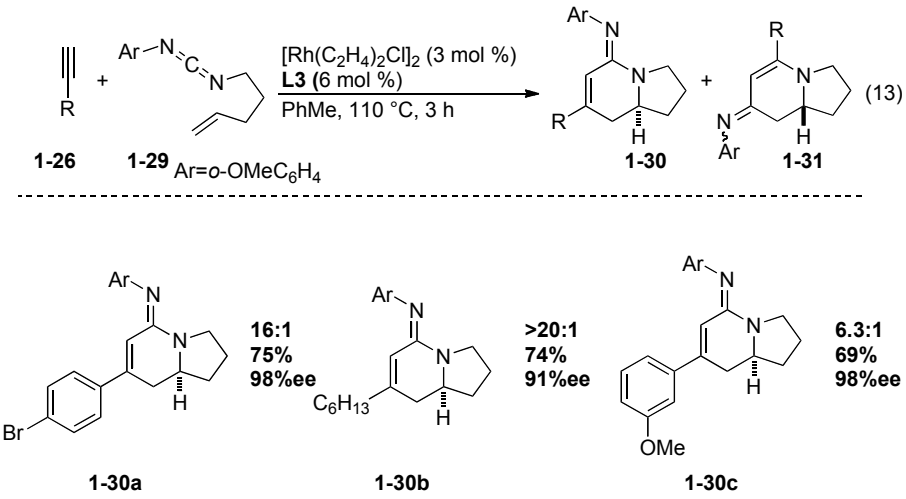


Table 6

At this point, the chemistry of terminal alkynes had been thoroughly explored in the rhodium-catalyzed cycloaddition with alkenyl isocyanates. However, the cycloaddition of symmetrical, internal alkynes had yet to be rendered asymmetric. This was successfully achieved with a variety of tolanes and GUIPHOS (**L5**) as a ligand to give a variety of vinylogous amide products. In subsequent studies of internal alkynes, we had observed that enantioselectivity depends on alkyne substitution. We hypothesized that the alkyne can coordinate to the octahedral rhodium(III) metallacycle (**IIb**) and alter the selectivity of subsequent insertions. A number of weakly coordinating, non-participating additives were tested in attempts to standardize enantioselectivity.[19] Methyl nicotinate (**1-33**) was found to be the best additive; it raises and levels enantioselectivities across a variety of substrates. We believe the methyl nicotinate binds to the octahedral rhodium and favors metallacycle **IVb2** over **IVb1** (Table 7), the other diasteromeric transition state during the olefin insertion. This removes the composition of the alkyne as a variable in the enantioselective step of the catalytic cycle.

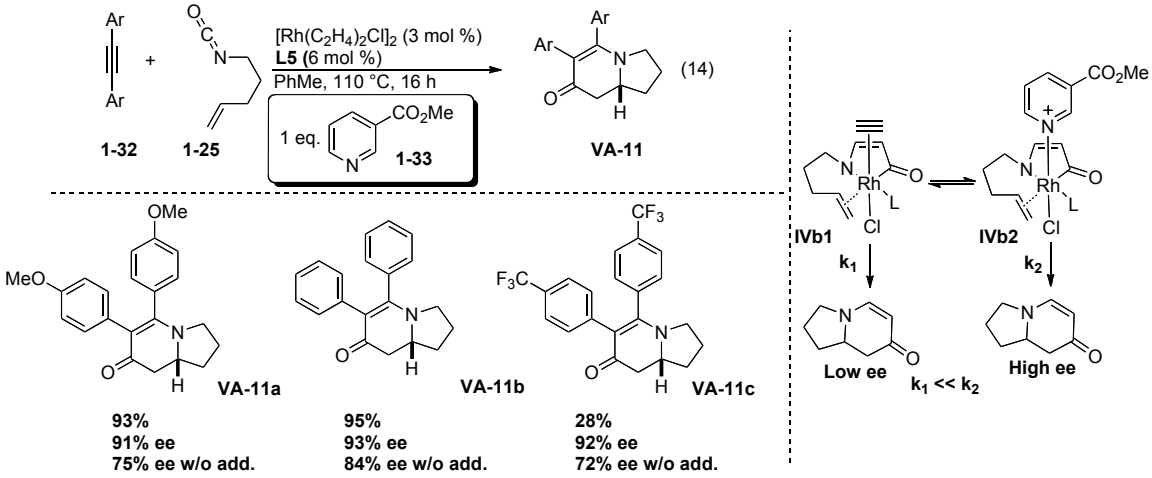


Table 7

1.4 Background: Unsymmetrical, Internal Alkynes in Cycloadditions

The investigations discussed aided in our understanding of the rhodium-catalyzed cycloaddition between alkenyl isocyanates and alkynes and this insight allowed us to tune cycloaddition conditions as necessary. It is important to emphasize that previously discussed studies focused on internal, symmetrical alkynes or terminal alkynes. Introduction of internal, unsymmetrical alkynes as cycloaddition substrates would introduce additional substituents into indolizidinone products.

A number of potential hurdles existed at the time of our investigation: first a large steric and electronic difference exists between the π-system of terminal alkynes and internal alkynes. Moreover, complications could arise if regioselectivity could not be controlled. We envisioned that internal, unsymmetrical alkynes possessing enough contrasting substituent effect (i.e. small, electron-withdrawing groups versus large electron releasing groups) might participate in a predictable, regioselective fashion. It was the hope at the beginning of this study that the parameters governing reactivity could

be elucidated and provide a guide to the incorporation of unsymmetrical alkynes in cycloaddition chemistry.

While under-explored, the use of unsymmetrical, internal alkynes in metal-catalyzed cycloadditions is not without precedent. A hurdle inherent in this transformation is regioselective insertion. A greater achievement than regioselective insertion still would be the discovery of forces controlling insertion so that predictions on modified systems could be made.

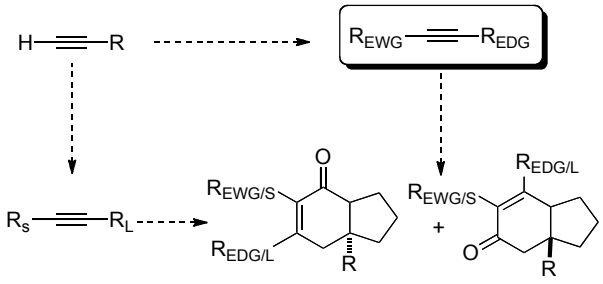


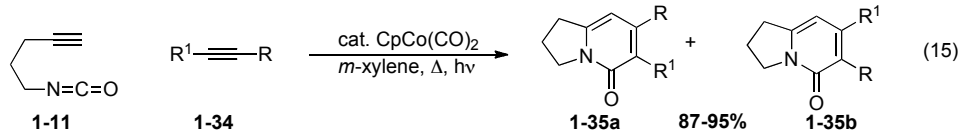
Figure 5

Several authors have pursued this problem of unsymmetrical alkyne incorporation in metal-catalyzed annulations only to obtain poor selectivites.[20] The use of internal, unsymmetrical alkynes in metal-catalyzed cycloadditions, from [4+2][21], [3+2][22], [2+2+2][23] and [2+2+1][24] has met with some success. However, the examples are generally limited to alkynes with extreme differences in either sterics or electronics[25], they have a limited scope[26] and they fail to explain the origins of selective insertion[27] which limits the general usefulness of the methodology.

Utilization of unsymmetrical, internal alkynes in metal-catalyzed [2+2+2] cycloadditions has been explored with a variety of substrates. Yamazaki used methylphenylpropiolate in his initial studies towards pyridone formation.[5] In 1983, Vollhardt and co-workers[7a] showed that unsymmetrical, internal alkynes did participate

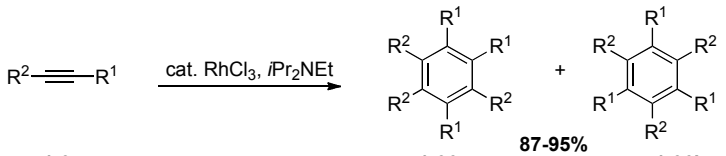
in cobalt-catalyzed [2+2+2] cycloadditions with isocyanates. A single regiosisomer is observed for trimethylsilylacetylenes. However, poor selectivity was seen for all other types of alkynes, including alkynoates. In 2007, H. Tanaka and co-workers[28] performed cyclotrimerizations utilizing unsymmetrical internal alkynes. Selectivity is attributed to alkyne electronics, but no further explanation is given. Hilt and coworkers[29] used a cobalt catalyst to cyclize two equivalents of alkyne with an alkene. They observe moderate selectivity and yields when alkyl propiolates are used. Aryl propiolates, however, are much more efficient substrates under the reaction conditions. The authors attribute selectivity to both ligand and substrate.

Vollhardt (1983):



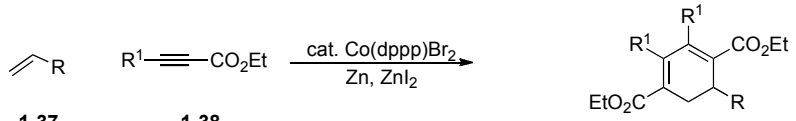
(15)

Tanaka, H. (2007):



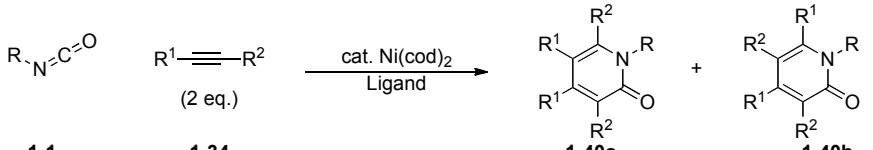
(16)

Hilt (2008):



(17)

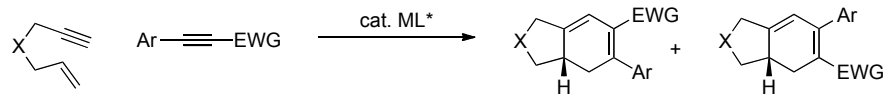
Louie (2005):



(18)

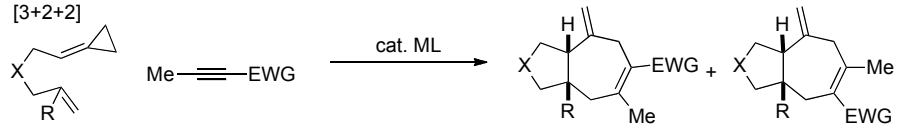
Evans (2005/2008):

[2+2+2]:



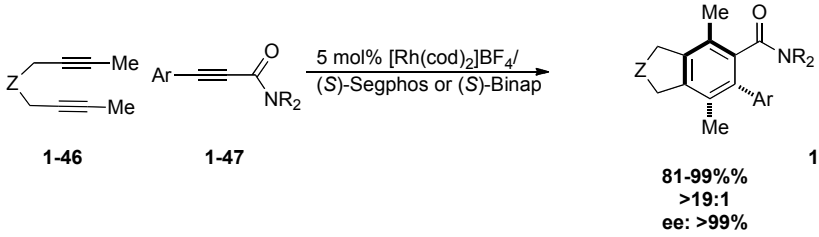
(19)

[3+2+2]



(20)

Tanaka, K. (2008)



(21)

Figure 6

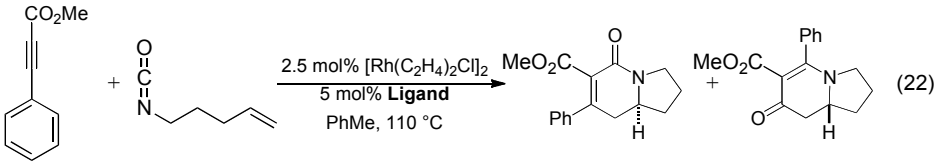
Utilizing isocyanates and diynes, Louie and coworkers[9b] developed nickel catalyzed [2+2+2] cycloadditions with unsymmetrical, internal alkynes to form a variety of pyridones. The selectivities are extremely inconsistent and the yields range from moderate to excellent. The system is highly alkyne dependent, although the steric bulk of the ligand does appear to have a role in selectivity as well. Evans and coworkers have explored [2+2+2][30a] and [3+2+2][30b] cycloadditions in an all-carbon system using unsymmetrical, internal alkynes and enynes or vinyl cyclopropanyl systems. While only aryl propiolates are represented in the scope, Evans is impressively able to show that the [2+2+2] cycloaddtion can proceed regioselectively, with excellent enantioselectivity with the appropriate catalytic system. While the [3+2+2] was rendered enantioselective with terminal alkynes, the alkyl, electron-deficient internal alkynes used were not included in the asymmetric scope, but still inserted in a regioselective fashion. Recently, the group of K. Tanaka demonstrated that the reaction of diynes and alkynamides could result in axially chiral aryl systems with excellent yields, regioselectivities and enantioselectivities.[31]

Our group, as discussed in the introduction, had already encountered the potential challenges associated with the incorporation of unsymmetrical alkynes in cycloaddition chemisty, the most significant hurdle being the absence of the inherent difference, both in sterics and electronics, present in terminal alkynes. This difference would not necessarily be present in all internal alkynes. Extending the reaction to numerous internal, unsymmetrical alkynes would represent an important advance both as a means to expand reaction scope as well as to better understand the system as a whole. Insight into the direction of internal, unsymmetrical alkynes coordination and cyclization during the

catalytic cycle has the potential to provide a template for future work with unsymmetrical, internal alkynes, ideally further than rhodium-catalyzed cycloadditions with alkynes and alkenyl isocyanates.

1.5 Initial Investigation

In preliminary studies, methylphenylpropiolate served as the alkyne of choice due to the large electronic difference between its ester and aryl functionalities. We hoped that this difference would mimic the bias present in terminal alkynes to provide good regioselectivities for the alkyne insertion. An initial ligand screen was performed on ligands that had been proven to work in previous systems. To our delight, methylphenyl propiolate inserts to give a singe regioisomer with typical reaction conditions used for terminal alkynes, phosphoramidite ligand and rhodium bisethylene dimer as precatalytic elements.



1-49 **1-25** **LA-10** **VA-12**

Product Ratio: <1 : 20

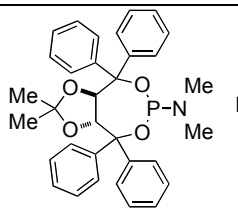
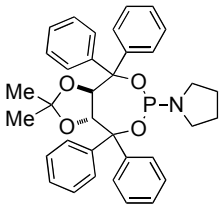
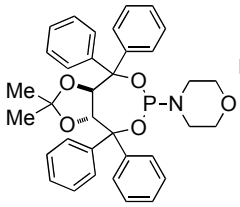
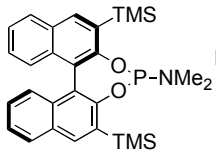
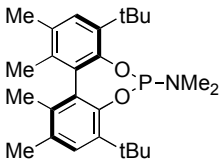
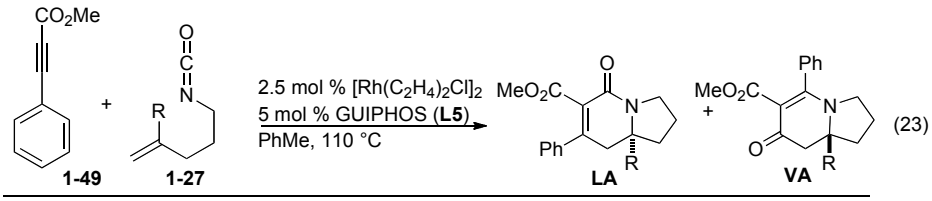
Entry	Ligand	Yield (%)	ee(%)
1	 **L2**	68	58
2	 **L1**	50	73
3	 **L7**	31	58
4	 **L5**	68	86
5	 **L6**	69	56

Table 7

With this initial result in hand, a ligand screen was performed (Table 7). As all ligands screened produced a single regioisomeric product, enantioselectivity and yield became the determining factors for which ligand to use in a subsequent alkenyl

isocyanate and alkyne scope. The best yield and best enantioselectivity came from the same ligand, GUIPHOS (**L5**), which was used in most subsequent trials.

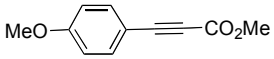
In previous work[14], we showed that 1,1-disubstituted alkenyl isocyanates participated very well with a large number of terminal alkynes. The tolerance of alkene substitutions was explored with methylphenyl propiolate (Table 8). The reactions screened all proceed with excellent yields. There was also a surprising increase in enantioselectivity when disubstituted alkenes were utilized. The composition of the substitution does not appear to matter, simply that the additional substitution is present (entries 2-4, Table 8).



(23)

Entry	R	LA: VA	yield (%)	ee (%) of VA	Product
1	H, **1-25**	< 1 : 20	86	86	**VA-12**
2	, **1-27a**	< 1 : 20	75	96	**VA-13**
3[a]	$(CH_2)_3CH_3$, **1-27b**	< 1 : 20	91	98	**VA-14**
4	Me, **1-27c**	< 1 : 20	90	98	**VA-15**

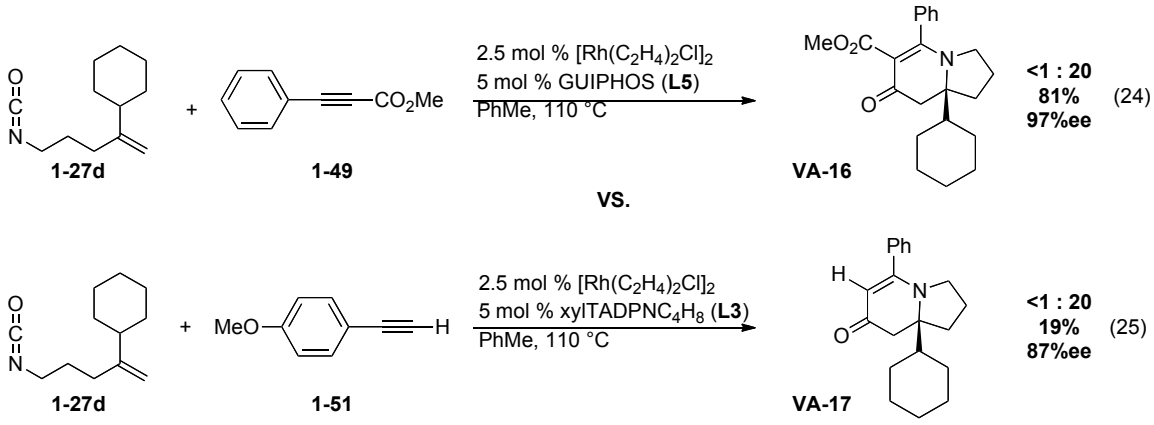
a. Alkyne **1-49a** used do to ease of separation on HPLC



1-49a

Table 8

Beyond increasing enantioselectivity relative to that obtained with monosubstituted, alkenyl isocyanate (**1-25**), the use of the unsymmetrical, internal alkyne, in conjunction with GUIPHOS (**L5**), greatly increases the efficiency of the reaction. This improvement is especially pronounced in a sterically hindered system (**eq. 24** and **25**). The previous combination of terminal alkyne with the TADDOL-phosphoramidite saw a significant decrease in yield with the sterically hindered alkyne.[14] This yield decrease was not observed for **1-27d** and **1-49**. In fact, the yields remained excellent and the enantioselectivites are also stellar.

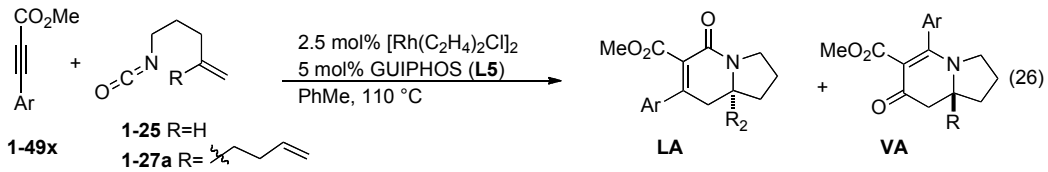


Because such a large increase in enantioselectivity was observed with 1,1-disubstituted alkenes, it was determined that it would be beneficial to run two parallel scopes when exploring the affects of internal alkynes in the reaction. Isocyanate **1-27a** was chosen due to bulk availability.

1.6 Expansion of Scope

Beginning with small changes, exploration into unsymmetrical, internal alkynes was initiated. Preliminary modifications of the alkyne probed the effects of substitution on the aryl ring (Table 9). General trends followed those observed with terminal alkynes. Yields decreased when electron-deficient aryl rings were used. With the most deficient

aryl propiolate (**1-49d**) explored, the vinylogous amide was only obtained in ~30% yield in both trials. However, the regioselective insertion remains constant; a single regioisomer is recovered. Also, product selectivity between lactam and vinylogous amide is excellent with GUIPHOS (**L5**) as a ligand, with only the vinylogous amide product observed.

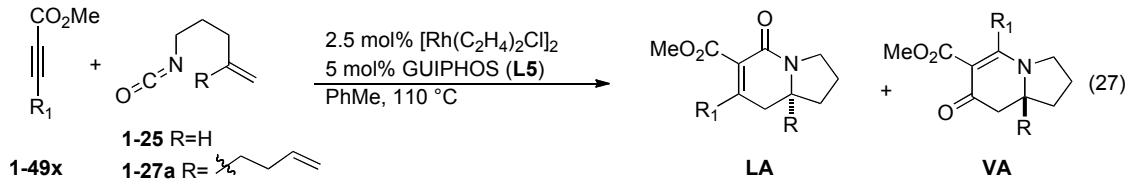


Entry	MeO_2C—≡—Ar	isocyanate	LA:VA	yield (%)	ee LA (%)	ee VA (%)	Major Product
1	MeO_2C—≡—Ph **1-49**	**1-25**	< 1 : 20	68	-	86	**VA-12**
2		**1-27a**	< 1 : 20	75	-	96	**VA-13**
3	MeO_2C—≡—OMe **1-49a**	**1-25**	< 1 : 20	80	-	70	**VA-18a**
4		**1-27a**	< 1 : 20	94	-	93	**VA-18b**
5	MeO_2C—≡—Cl **1-49b**	**1-25**	<1 : 20	83	-	77	**VA-19a**
6		**1-27a**	<1 : 20	57	-	94	**VA-19b**
7	MeO_2C—≡—Br **1-49c**	**1-25**	<1 : 20	73	-	ND	**VA-20a**
8		**1-27a**	<1 : 20	57	-	ND	**VA-20b**
9	MeO_2C—≡—CF_3 **1-49d**	**1-25**	< 1 : 20	33	-	82	**VA-21a**
10		**1-27a**	< 1 : 20	29	-	96	**VA-21b**
11	MeO_2C—≡— MeO **1-49e**	**1-25**	< 1 : 20	44	-	ND	**VA-22a**
12		**1-27a**	< 1 : 20	77	-	98	**VA-22b**

Table 9

A systematic enhancement of enantioselectivity is observed for 1,1-disubstituted alkenyl isocyanates relative to monosubstituted alkenyl isocyanates, with relative ee improvements ranging from 10% to over 20% ee. Ortho substitution is tolerated on the aryl ring of the alkyne (**1-49e**), although analysis was encumbered by presumed restricted rotation in the vinylogous amide product, creating what appears to be atropisomers.

The next incremental change we undertook was to switch the alkyne aryl group to an alkyl group, thereby probing the potential effect of sterics on alkyne insertion. Once again, a single regioisomer was obtained from incorporation for a variety of alkyl alkynes. Yields expectedly decreased when steric bulk is added to the alkyne (entries 1 and 2 vs entries 3 and 4, Table 10). Too much steric bulk (R=tBu) resulted in no reaction (Table 10).



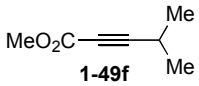
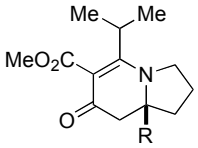
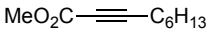
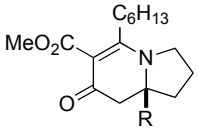
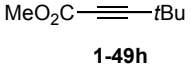
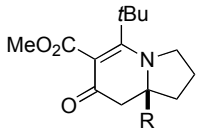
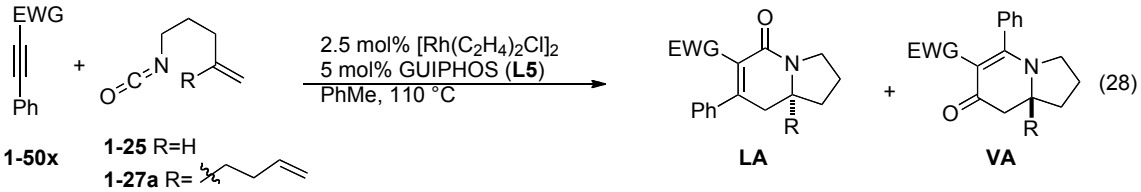
Entry	MeO_2C—≡—R	isocyanate	LA:VA	yield (%)	ee LA (%)	ee VA (%)	Major Product
1		**1-25**	<1 : 20	39	-	74	 **VA-23a**
2	**1-49f**	**1-27a**	<1 : 20	46	-	>99	**VA-23b**
3		**1-25**	1 : 7	60	62	65	 **VA-24a/LA-11a**
4	**1-49g**	**1-27a**	1 : 2.5	60	62	96	**VA-24b/LA-11b**
5		**1-25**	NR	-	-	-	 **VA-25a**
6	**1-49h**	**1-27a**	NR	-	-	-	**VA-25b**

Table 10

While regioselectivity remained excellent with respect to alkyne incorporation from aryl to alkyl substrates, a change in product selectivity was observed. When methylhexylpropiolate (**1-49g**) was used, lactam product was observed. The combined yields of lactam and vinylogous amide were moderate and superior enantioselectivity increase for the vinylogous amide product was observed. Unlike the vinylogous amide, enantioselectivity of the lactam product showed no obvious alkene dependence.

Next, we were interested in evaluating a variety of electron-withdrawing groups in the place of the alkyne methyl ester to see what electron-deficient substituents were tolerated. Both isopropyl ester and cyclohexyl ketone were successfully incorporated to form the vinylogous amide product. The yields are slightly low, presumably due to the steric bulk on the electron-withdrawing group. However, the enantioselectivities are excellent in both cases. The increase in enantioselectivity from isocyanate (**1-25**) to isocyanate (**1-27a**) can still be seen, but is not as dramatic as in the methyl ester case.



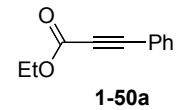
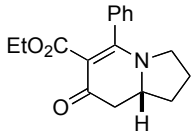
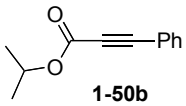
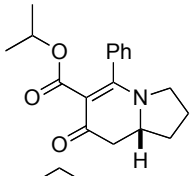
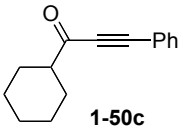
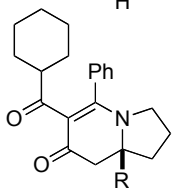
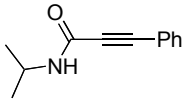
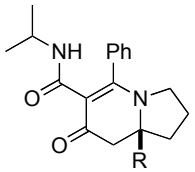
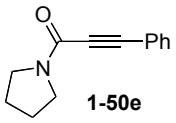
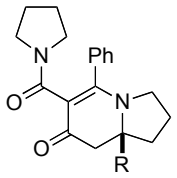
Entry	EWG—≡—Ph	isocyanate	LA:VA	yield (%)	ee LA (%)	ee VA (%)	Major Product	
1	 **1-50a**	**1-25 w/L1**	<1 : 20	41	-	72		**VA-26a**
2		**1-25 w/L5**	<1 : 20	78	-	82		
3	 **1-50b**	**1-25**	<1 : 20	62	-	73		**VA-27a**
4	 **1-50c**	**1-25**	<1 : 20	40	-	90		**VA-28a**
5		**1-27a**	<1 : 20	40	-	95		**VA-28b**
6	 **1-50d**	**1-25**	<1 : 20	91	-	11		**VA-29a**
7		**1-27a**	<1 : 20	85	-	56		**VA-29b**
8	 **1-50e**	**1-25**	NR	-	-	-		**VA-30a**
9		**1-27a**	<1 : 20	46	-	99		**VA-30b**

Table 11

Secondary amide **1-50d** also reacted in excellent yields, but enantioselectivities were poor, presumably due to coordination of the basic amide oxygen to the rhodium catalyst. When a tertiary amide was used to minimize coordination, the unsubstituted alkenyl isocyanate failed to react. The 1,1-disubstituted, however, proceeded in moderated yield (46%) and excellent enantioselectivity. This peculiar reactivity was pursued further in an effort to obtain an explanation.

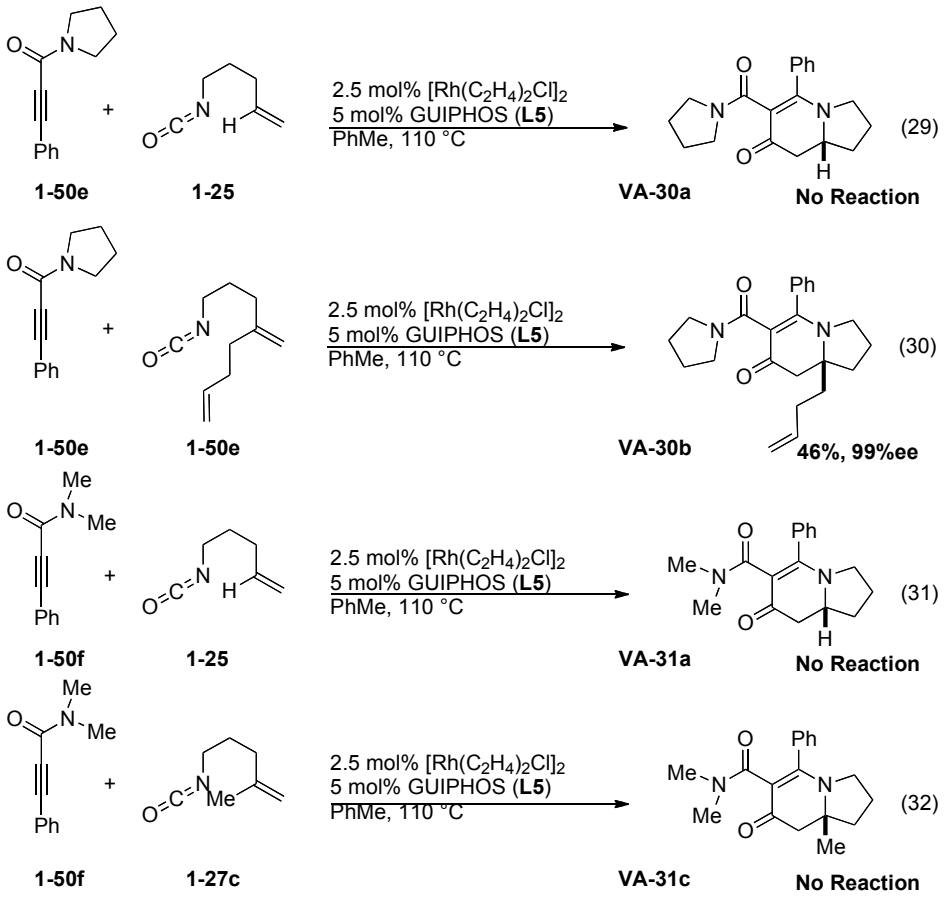
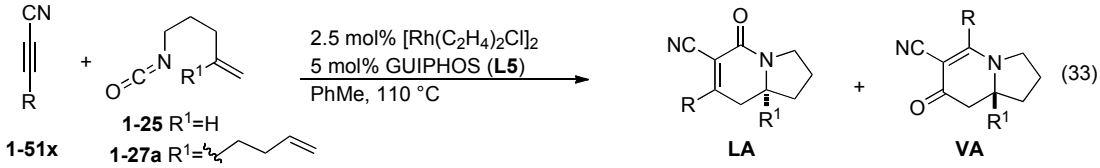


Figure 7

Initially, it was thought that amide (**1-50e**) was the culprit of the observed reactivity difference across isocyanate substrates. However, similar experiments with the corresponding dimethyl amide and the unsubstituted alkenyl isocyanate also failed. We then looked to alkenyl isocyanate substitution to explain this reactivity difference. Previous results suggested that substitution on the alkene can effect the enantioselectivity; perhaps it was this that governed reactivity of the amidoalkyne. However, a [2+2+2] cycloaddition attempted between the dimethyl amide and the methyl substituted alkene **1-27c**, failed to react as well (eq. 32). We thought that the tethered terminal olefin on isocyanate **1-27a** may play a role in modifying the rhodium coordination sphere, potentially occupying a site and displacing a competitive ligand.

The impact of this side chain must be exerted in an intramolecular fashion as an intermediate in the catalytic cycle.

After the amide study, we then explored a final type of electron-deficient alkyne, the alkynyl nitrile. We were interested in nitriles as they had the potential to elucidate the effect of substrate size on product and regioselectivity. The nitrile is much smaller than any of the carbonyls used in the study. This smaller group is more than likely responsible for the product selectivity switch towards the lactam product, not seen in most of the previous examples. The nitiriles follow the pattern of the prior trials in that only a single regioisomer of alkyne insertion is obtained. Combined yields for the nitrile cycloaddition reactions are moderate, and the enantioselectivites are extremely varied (Table 12).



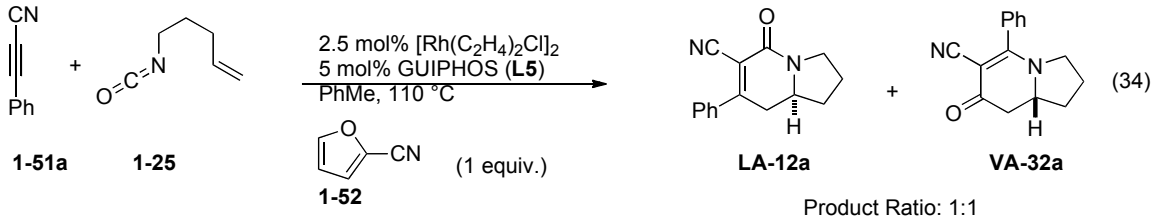
(33)

Entry	NC—≡—R	isocyanate	LA:VA	yield (%)	ee LA (%)	ee VA (%)	Major Product
1	NC—≡—Ph **1-51a**	**1-25**	1 : 1	61	48	2	**LA-12a** **VA-32a**
2	NC—≡—Ph **1-51a**	**1-27a**	1 : 1.5	61	32	87	**LA-12b** **VA-32b**
3	NC—≡—hex **1-51b**	**1-25**	> 20 : 1	31	80	-	**LA-13a**
4		**1-27a**	> 20 : 1	68	95	-	**LA-13b**

Table 12

Across the scope of electron-deficient alkynes, enantioselectivities were moderate to good, and occasionally excellent. However, a few cases produced disappointing

enantioselectivities. Concurrent work in the group had shown that non-participating additives could produce a significant increase in enantioselectivities in such cases.[19] One such additive was added to select examples to see if the enantioselectivity could be increased if necessary. The phenyl alkynyl nitrile was used as a test substrate.



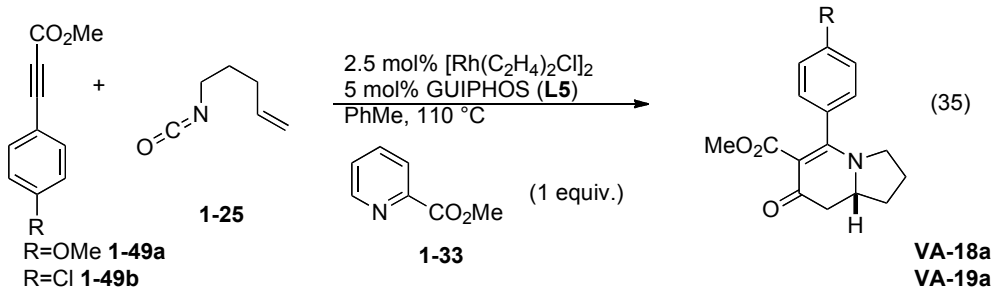
1-51a **1-25** **1-52** **LA-12a** **VA-32a**

Product Ratio: 1:1

Entry	Additive	**yield (%)**	**ee LA (%)**	**ee VA (%)**
1	Without **1-52**:	48	48	2
2	With **1-52**:	40	74	11

Table 13

An increase in the enantioselectivities in the presense of exogenous additive **1-52** is significant for lactam products, but the vinylogous amide enantioseletivity is too low to ascertain any effect. Thus, two more substrates, which produced only vinylogous amide were subjected to similar reaction conditions.



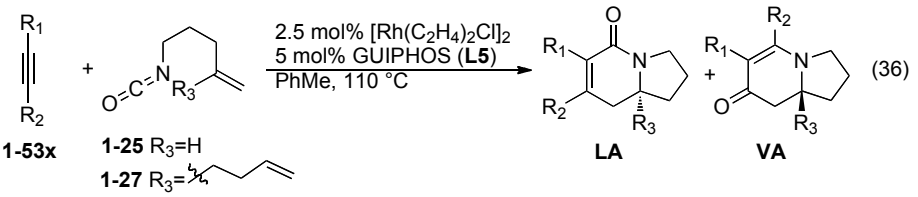
Entry	Alkyne	Additive	yield (%)	ee LA (%)	ee VA (%)
1	**1-49a**	Without **1-33**:	80	-	70
2	**1-49a**	With **1-33**:	33	-	84
3	**1-49b**	Without **1-33**:	83	-	77
4	**1-49b**	With **1-33**:	22	-	83

Table 14

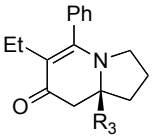
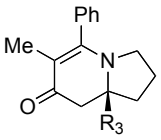
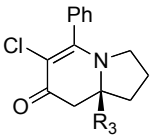
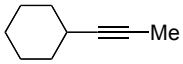
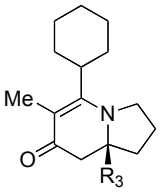
A significant increase (14%) in enantioselectivity was noted. The low yields were attributed to the hygroscopic nature of the additive. Yields certainly could be optimized if necessary. Additives remain a good solution for fixing poor enantioselectivities for internal alkynes, including electron-deficient alkynes, as shown above.

Once numerous electron-poor alkynes had been explored in our cycloaddition reaction with mono- and disubstituted alkenyl isocyanates, an effort was made to determine the minimal extent of steric and electronic difference on the alkyne necessary for regioselective insertion. Thus, we investigated alkynes that possessed subtle steric and electronic differentiation. Again, the scope was investigated in parallel for both unsubstituted and 1,1-disubstituted alkenyl isocyanates. During the investigation, it was determined that an electronic difference as small as aryl versus alkyl is enough for the reaction to proceed with regioselective insertion of the alkyne, generating a single regioisomer. The product selectivity between lactam and vinylogous amide remains high. For both phenyl butyne and phenyl propyne, enantioselectivites were moderate

(entries 1-4, Table 15). Also, the significant increase in enantioselectivity across isocyanate substrates is not observed as it is in the propiolate cases. One goal in this portion of the scope was to explore the effects of only sterics on regiocontrol. An unsymmetrical, dialkyl alkyne showed that sterics alone could control regioselectivity, with a single regioisomer of the vinylogous amide obtained, with the smaller group proximal to the carbonyl (**VA-36a**, **VA-36b**). The enantioselectivities were poor (33% and 45% ee). Using a TADDOL-based ligand (**L1**), the %ee increased slightly (56%), but the product selectivity between lactam and vinylgous amide vanished (1:1). Results with alkyne **1-53d** indicate that sterics, alongside electronics play a profound role in the outcome of the reaction.



(36)

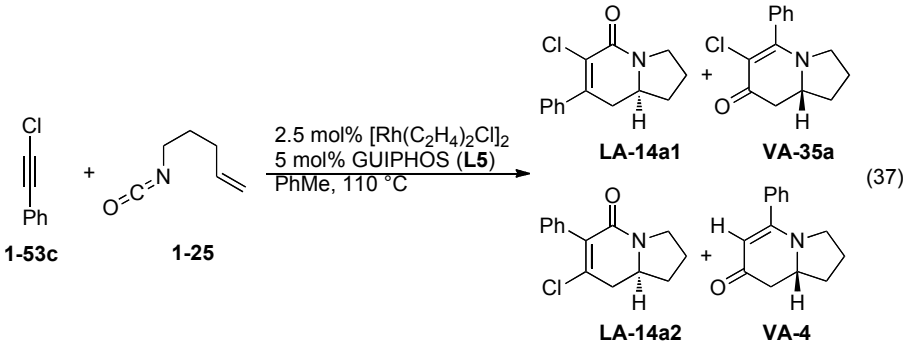
Entry	R_1—≡—R_2	isocyanate	LA:VA	yield (%)	ee LA (%)	ee VA (%)	Major Product	
1	Et—≡—Ph	**1-25**	1 : 11	84	-	76		**VA-33a**
2		**1-27a**	<1 : 20	50	-	83		**VA-33b**
	1-53a							
3	Me—≡—Ph	**1-25**	1 : 10	94	-	71		**VA-34a**
4		**1-27a**	<1 : 20	70	-	72		**VA-34b**
	1-53b							
5[a]	Cl—≡—Ph	**1-25**	1 : 5	78	12	20		**VA-35a**
6[a,b]		**1-27a**	<1 : 20	53	-	91		**VA-35b**
	1-53c							
7		**1-25**	<1 : 20	57	-	33		**VA-36a**
8		**1-27a**	<1 : 20	65	-	45		**VA-36b**
	1-53d							

a. Reaction stirred over 4Å molecular seives in order to remove water present in alkyne
b. 5% $Rh(C_2H_4)_2Cl$, 10% GUIPHOS

Table 15

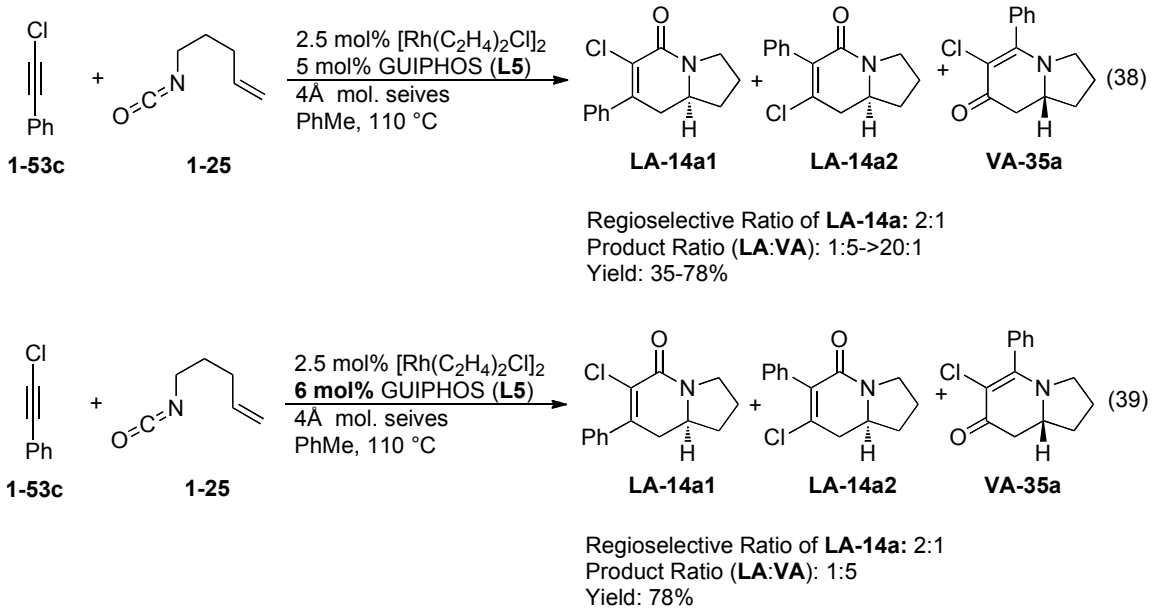
Chloro-phenylacetylene had been used successfully in ruthenium catalyzed [2+2] reactions.[32] This substrate was an attractive candidate for use in our reactions as the chlorine-carbon bond in the product would provide a functional handle for further manipulation. This alkyne showed an even larger enantioselectivity increase from mono- to disubstituted alkenyl isocyanates than the propiolate cases, enhancements ranging from 20%ee to 91%ee when a disubstituted alkenyl isocyanates is used. While the yields achieved with this system were generally moderate to good, a certain aberant behavior was observed. With a disubstituted alkenyl isocyanate (**1-27a**), the reaction proceeds

uneventfully, with excellent product, regio- and enantio- selectivity. However, with isocyanate **1-25**, the product selectivity fluctuates greatly from reaction to reaction (>20:1 to 1:5 **LA**:**VA)**. Also, a side product was recovered that appeared to be a cycloadduct arising from the terminal alkyne, phenylacetylene (**VA-4**).

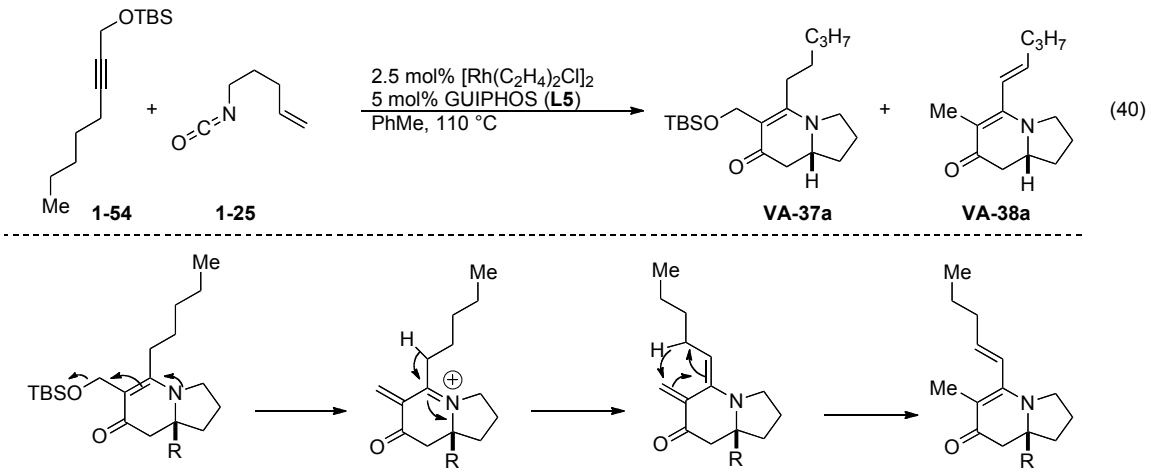


Unpredictable Yields and Product Ratios

This side product could be effectively removed by running the reaction in the presence of molecular sieves (eq. 38). Presumably alternative vinylogous amide (**VA-4**) is produced in the reaction when small amounts of water are present. Once **VA-4** had been removed, the focus shifted to erratic product selectivity. Unlike every other product obtained thus far in the scope, the lactam showed imperfect regioselectivity. In fact, **LA-14a** was recovered as an inseparable mixture of regioisomers (2:1). While a single regioisomer of **LA-14a** was never obtained, the product ratio could be maintained at 1:5 **LA**:**VA** by using a slight excess of ligand (eq. 39). Presumably, the poor regioselectivity and unpredictable product selectivity is caused by a competing, unligated cycloaddition. The unligated reaction was studied further and will be described in detail after a more thorough discussion of the unsymmetrical, internal alkyne scope.

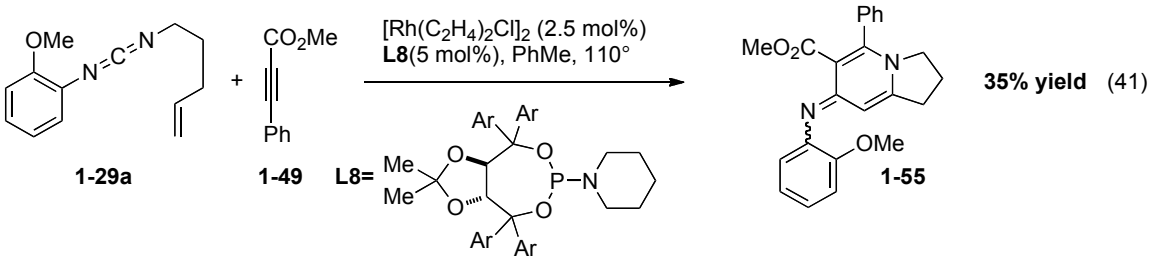


During the exploration of the aliphatic alkyne scope, protected propargyl alkynes were also explored as potential reaction components. Alkyne **1-54** was initially synthesized and utilized in a typical catalytic system, along with monosubstituted isocyanate **1-25**. Initial yields were poor, (35%) and product selectivity was only moderate (1:3 **VA-37a**: **VA-38a**). However, an interesting observation was made in the course of the studies directed at this system. While the minor product (**VA-37a**) had the expected substitution, the major product, upon collection of analytical data, did not contain the alcohol protecting group. Through further analysis of spectral data, it was determined that the vinylogous amide product can eliminate the protected alcohol and participated in a subsequent 1,5-hydrogen shift to yield vinylogous amide (**VA-38a**). This mode of reactivity, while interesting, was not pursued further and enantioselectivities were not determined.

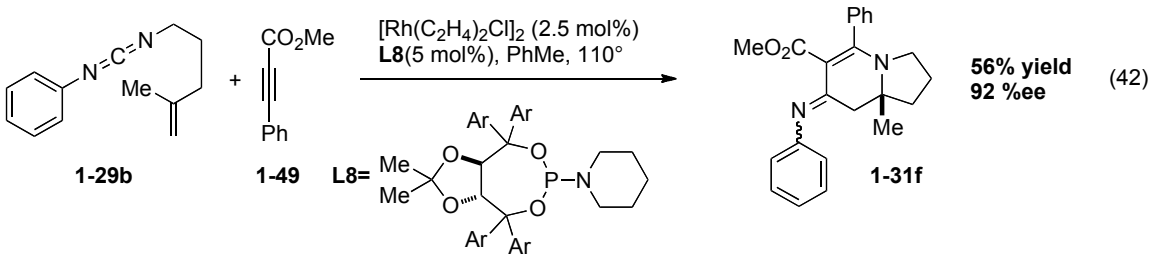


Scheme 1

To complete the breadth of the unsymmetrical, internal alkyne scope, we decided to investigate the reactivity of the alkenyl carbodiimides with internal alkynes. As mentioned earlier alkenyl carbodiimides had been shown to be reactive to give cycloadducts with terminal alkynes.[18] Unfortunately, with internal, symmetrical alkynes, carbodiimides produced unstable vinylogous amidine products, which oxidized under typical reaction conditions to eliminate the stereocenter (eq. 41).



Attempts were made to prevent the oxidation to form vinylogous amidine *(***1-55**); however, stringent air-free reaction conditions employed in an attempt to prevent the oxidation of the cycloadduct failed. This oxidation could be prevented if a substituted alkene was used instead. To prove this point, a single substrate was synthesized (eq 42), but the scope of the carbodiimides was not pursued further.



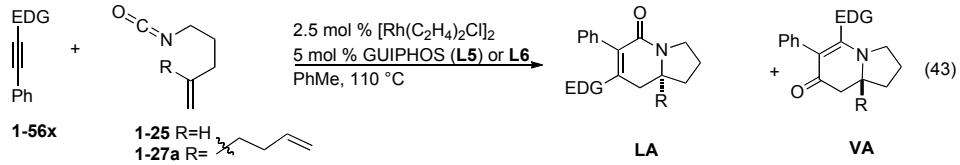
(42)

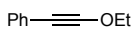
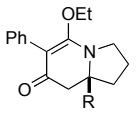
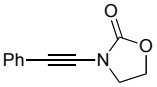
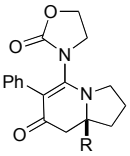
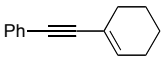
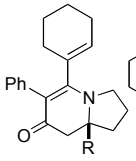
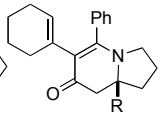
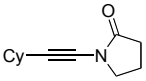
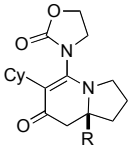
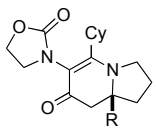
The previously explored scope made it clear that internal alkynes selectively form vinylogous amide products except in extreme cases, such as the very small and electron deficient alkynyl nitriles (**1-51a**, **1-51b**). This large influence of sterics on product selectivity is consistent with previous studies.[13-15] Larger terminal alkynes also prefer vinylogous amide products in both Rh/TADDOL systems and GUIPHOS systems.[15, 17]

1.7 Explanation of Regioselective Insertion of Unsymmetrical Alkynes

While product selectivity had been satisfactorily explained for terminal alkynes, the high regioselectivity observed with internal alkynes could not be explained by a simple steric model, as both electronics and sterics contribute significantly to regiocontrol. While significant steric disparities across alkynes contributes to regioselective cyclization of numerous polarized alkynes, so too does electronic differentiation. In all cases with internal, unsymmetrical alkynes, the stronger electron-withdrawing group is placed alpha to the nitrogen in the vinylogous amide cycloadduct. If electronics control the direction of alkyne insertion in this way, it is logical to reason that any substituent more electron-releasing than phenyl should dictate regioselectivity. Specifically, the electron-rich substituent should align distal to the carbonyl and lead to 'inversion' of regioselectivity previously seen (Tables 9-12, 15), placing the phenyl group proximal to the carbonyl.

In an effort to elucidate the degree of electronic control in the cycloaddition of unsymmetrical alkynes, we focused on incorporation of several groups (ynol ethers, ynamides and enynes) that might be expected to instigate such a reversal of regioselectivity based on electronics.



Entry[a]	EDG—≡—Ph	isocyanate	LA : VA	yield (%)	ee (%) of **LA**	ee (%) of **VA**	Major Product
1	 **1-56a**	**1-25**	1 : 4	98	-	77	 **VA-39a** **VA-39b**
2		**1-27a**	<1 : 20	98	-	97	
3	 **1-56b**	**1-25**	<1 : 20	56	-	52	 **VA-40a** **VA-40b**
4		**1-27a**	<1 : 20	91	-	85	
5	 **1-56c**	**1-25**	<1 : 20[b]	90	-	90 minor 83 major	 **VA-41a** **VA-41b**
6		**1-27a**	<1 : 20[c]	85	-	94 minor 92 major	 **VA-42a** **VA-42b**
7	 **1-56d**	**1-25**	<1 : 20[d]	90	-	ND	 **VA-43a**  **VA-44a**

a. Regiochemistry was determined by nOe spectral data.
b. Inseperable mixture of regioisomers (10:1 favoring phenyl proximal to the carbonyl, **L6** as ligand)
c. Inseperable mixture of regioisomers (10:1 favoring phenyl proximal to the carbonyl, **L6** as ligand)
d. 1:1.2 mixture of inseperable regioisomers, ratio determined by GC-MS.

Table 17

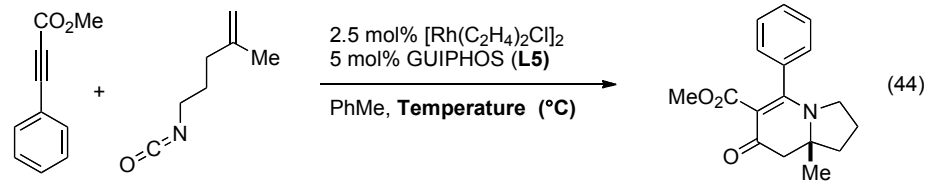
Ynol ethers and ynamides participate in the cycloaddition with a clean reversal of regioselectivity with respect to electron-deficient alkynes (**1-56**), with the phenyl group proximal to the carbonyl moiety in the vinylogous amide. Lower product selectivity observed with the ynol ether (**1-56a**) is attributed to an unligated rhodium-mediated

cycloaddition. An increase in enantioselectivity is seen in the cycloadduts produced from alkenyl isocyanate **1-27a** is used for select cases (entries 1 vs. 2 and entries 3 vs. 4, Table 17) . Yields in all examples are moderate to excellent.

In an effort to further probe the sensitivity of electronic control an alkyne was synthesized that pitted the electronics of a phenyl group against that of a vinyl group, an extremely subtle electronic difference. The product selectivity of the enyne was excellent; only vinylogous amide was seen. The regioselectivity ratio seen in vinylogous amide product with the typical ligand, GUIPHOS (**L5**), on the other hand was poor to moderate. An inseparable mixture of two regioisomers was obtained. With the monosubstiuted alkenyl isocyanate, the regioselective insertion was 5:1, and for isocyanate (**1-27a**) the ratio was 2.5:1. However, when the ligand was switched to the biphenyl-based ligand **L6**, the ratio for regioselectivity was increased to an acceptable 10:1 ratio. In this case, the phenyl group was proximal to the carbonyl group in the vinylogous amide product. Enantioselectivities of both regioisomers were excellent for both isocyanates used.

The proposed mechanism for the rhodium-catalyzed cycloaddition of alkenyl isocyanates and internal alkynes presumably follows the same mechanism as was proposed for the terminal alkynes. Experiments were conducted in order to both confirm the expected mechanism, as well as to explain the observed enhancement of enantioselectivity for disubstituted alkenyl isocyanates. Competition between substituted and unsubstituted alkenes in the presence of methylphenyl propiolate resulted in a ~1:1 mixture of products, matching previous results for terminal alkynes[15] and suggesting the alkene is not involved in the first irreversible step of the cycloaddition. However,

observation of the reaction via ^{31}P NMR indicated that while the unsubstituted alkyne did not bind to the Rh/ligand complex in the absence of alkyne **1-49**, the 1,1-disubstituted butenyl isocyanate (**1-27a**) did. It is unknown if this is the cause for the increased enantioselecitivy for cycloadducts produced with **1-25** relative to **1-27**, but it does alter the catalytic environment around the metal, which has the potential to change reactivity and selectivity. Finally, the methylphenyl propiolate (**1-49**) proved to be extremely reactive with 1,1-disubstituted alkeynl isocyanate **1-27c** with GUIPHOS as a ligand, as it reacts at much lower temperatures (25 °C) than typical reaction conditions (110 °C) (Table 18). The presence of recoverable amounts of cycloadduct from a room temperature reaction is remarkable. The reaction proceeds at good yields at temperatures as low as 60 °C. The change in enantioselectivity was unexpected and may indicate a slight change in mechanism, dependant on temperature.



(44)

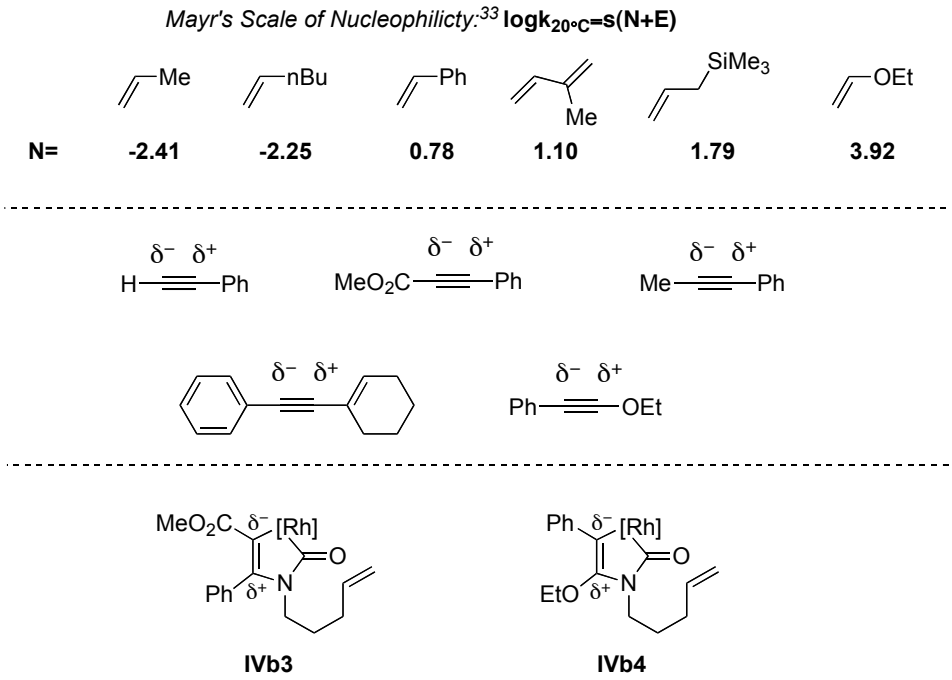
1-49 **1-27c** **VA-15**

Temperature	Yield	Enantioselectivity
23 °C	19%	95% ee
60 °C	68%	85% ee
110 °C	85%	98% ee

Table 18

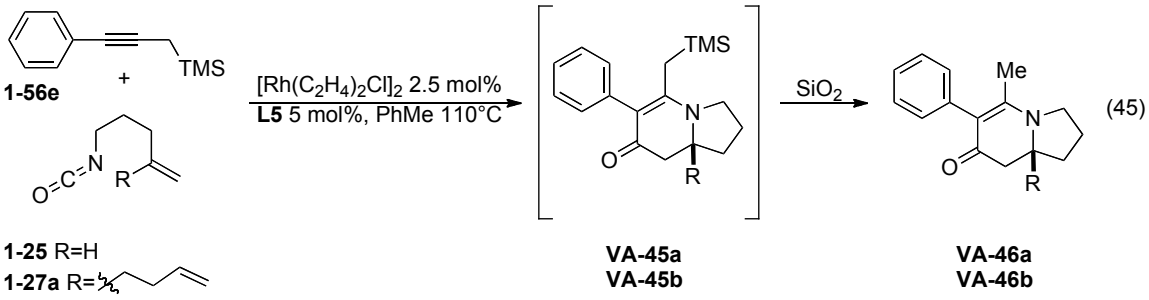
With a better understanding of reactivity, we sought to provide an explanation for the superb regioseletivity seen in these cycloadditions. The high regioseletivity of insertion can be explained and predicted by looking at the Mayr's scale of nucleophilicity.[33] Mayr's scale ranks nucleophiles according to their ability to stabilize a

positive charge. We compared Mayr's nucleophilicity values with the regioselective ratios observed for the corresponding alkynes in our cycloaddition chemistry. The larger Mayr's value present between the two substituents on the alkyne, corresponds to the substituent that inserts distally to the carbonyl group. However, sterics cannot be excluded entirely, as large groups can also coordinate away from the carbonyl. When a sterically large group is placed in competition with a strong electron-donating group, the yield is good, but the regioselective ratio for incorporation of the alkyne is 1.2:1 (entry 7 and 8, Table 19). This indicates that sterics and electronics have to cooperate for optimal regioselective insertion. However, in the absence of an overwhelming steric influence, the application of Mayr's scale of nucleophilicity provides a rationale in the form of a polarization model that explains the observed selectivities. For example, the phenyl group better stabilizes a positive charge when compared to a carbomethoxy group or an alkyl group. Regioselectivity obtained for propiolates, phenylbutyne and phenylpropyne correspond well with the Mayr's scale. The increased nucleophilicty of isoprene and ethyl vinyl ether relative to styrene results in an inversion of polarity for ynol (**1-56a**) and alkyne (**1-56c**), leading to a regioselective switch, seen in intermediates **IVb3** and **IVb4** (Scheme 2).



Scheme 2

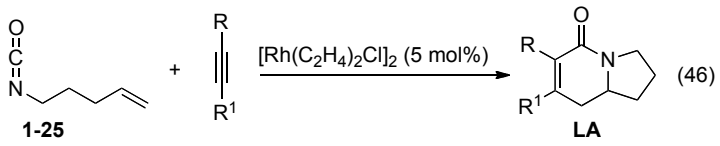
The scale shown suggests that propargyl silanes should participate with high regioselectivity, given the greater nucleophilicity of allylsilane relative to that of styrene. Alkyne **1-56e** was used in the cycloaddition and exclusively formed the vinylogous amide product, with the phenyl proximal to the carbonyl. However, the expected gamma silyl enone was not recovered. Rather, the expected product presumably undergoes a rapid protiodesilylation upon workup. The final products (**VA-46a** and **VA-46b**) are the regioisomeric analogs to the vinylogous amide formed with phenyl propyne (**VA-34a** and **VA-34b**). This use of propargyl silanes thus provides a complementary product from those obtained in the typical cycloaddition (Table 19). Attempts were made to exploit the protodesilation event to trap numerous electrophiles but without success.



	Yield (%)	ee (%)
1-25 (VA-46a)	30	75
1-27a (VA-46b)	73	92

Table 19

One final point that needed to be addressed at this point in the study was possibility of a competing, unligated reaction. A few substrates in the internal, unsymmetrical, alkyne scope that showed larger than expected amounts of lactam, with correspondingly low enantioselectivity. It was hypothesized that this selectivity was being caused by the unligated side reaction. To test this hypothesis, several unligated control expermiments were performed. Indeed, it was found that in the absense of phosphoramidite ligand, lactam product was still formed in substantial yields.



(46)

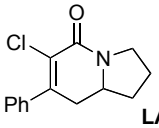
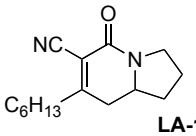
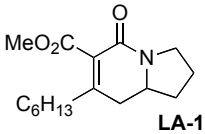
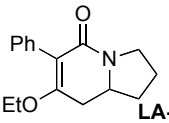
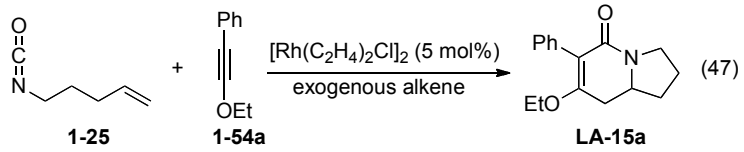
Entry	R—≡—R¹	Yield (%)	Product
1	Ph—≡—Cl **1-52c**	48	 **LA-14a**
2	C_6H_{13}—≡—CN **1-51a**	41	 **LA-13a**
3	C_6H_{13}—≡—CO_2Me **1-49g**	29	 **LA-11a**
4	EtO—≡—Ph **1-56a**	34	 **LA-15a**

Table 20

With such promising yields without the phosphoramidite, we were interested in evaluating the possibility of transferring chirality via an exogenous alkene to afford asymmetric lactam products. However, the results showed that while the cycloaddition still proceeded with the exogenous alkene present, chirality was not transferred (entry 3, Table 21).



1-25 1-54a LA-15a (47)

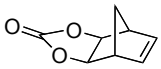
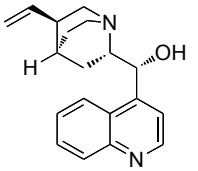
Entry	Alkene	Yield (%)
1	 1-57	31
2	 1-58	51
3	 1-59	40%, 0%ee

Table 21

To summarize this study[34], we show that unsymmetrical, internal alkynes participate successfully in good yields, enantioselectivity and most importantly, high regioselectivity in almost all products, in the rhodium-catalyzed [2+2+2] cycloaddition with alkenyl isocyanates. Of note, there is near exclusive formation of the vinylogous amide adducts in these transformations. Further, we observe extremely high regioselectivies with the vast majority of screened alkynes. Importantly, we have delineated some of the responsible factors for reguiselectivity and have a reliable model for predicting of the direction of alkyne incorporation. The synthetic utility of rhodium-catalyzed [2+2+2] cycloadditions has been increased to enable the predictable insertion of internal, unsymmetrical alkynes within indolizidine framework.

1.7 References

1. (a) Robinson, J. E. "Rhodium(I)-catalyzed [4+2] and [4+2+2] Carbocyclizations." In *Modern Rhodium-Catalyzed Organic Reactions*, P. A. Evans (Ed.), Wiley-VCH,

Weinheim (2005). (b) Wender, P. A.; Gamber, G. G.; Williams, T. J. "Rhodium(I)-catalyzed [5+2], [6+2] and [5+2+1] Cycloadditions: New Reactions for Organic Synthesis." in *Modern Rhodium-Catalyzed Organic Reactions*, P. A. Evans (Ed.), Wiley-VCH, Weinheim (2005).

2. (a) Strbing, D.; Beller, M. "Pauson-Khand Reactions." In *Transition Metals for Organic Synthesis.* M. Beller, C. Bolm (Eds.), Wiley-VCH, Weinheim (2004). (b) Brummond, K. M.; Kent, J. L. *Tetrahedron.* **2000**, *56*, 3263. (c) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830 and references therein. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (e) Malacria, M.; Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C. *Org. React.* **2007**, *68*, 1.

3. (a) Mobner, C.; Bolm, C. "Catalyzed Asymmetric Aziridinations." In *Transition Metals for Organic Synthesis.* M. Beller, C. Bolm (Eds.), Wiley-VCH, Weinheim (2004). (b) Savizky, R. M.; Austin, D. J. "Rhodium(II)-catalyzed 1,3-Dipolar Cycloaddition Reactions." In *Modern Rhodium-Catalyzed Organic Reactions*, P. A. Evans (Ed.), Wiley-VCH, Weinheim (2005). (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787. (e) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085.

4. (a) Oberg, K. M.; Lee, E. E.; Rovis, T. *Tetrahedron.* **2009**, *65*, 5056. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2309.

5. Hong, P.; Yamazaki, H. *Synthesis*. **1977**, 50. (b) Hong, P. Yamazaki, *Tetrahedron Lett.* **1977**, *15,* 1333.

6. (a) Hoberg, H.; Oster, B. W. *Synthesis.* **1982**, 324. (b) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35. (c) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.*

1983, *252*, 359. (d) Hoberg, H., Nohlen, M. *J. Orgmet. Chem.* **1991,** *412*, 225. (e) Hoberg, H., Hernandez, E. *Angew. Chem. Ed. Engl.* **1985,** *24*, 961. (f) Hoberg, H., Ballesteros, A., Sigan, A. Jegat, C. Milchereit, A. *Synthesis.* **1991,** 395.

7. (a) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991. (b) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786.

8. (a) Yamamoto, Y., Takagishi, H., Itoh, K. *Org, Lett.* **2001,** *3*, 2117. (b) Yamamoto, Y. et. al., *J. Am. Chem. Soc.* **2005,** *127,* 605.

9. (a) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (b) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098.

10. (a) Tanaka, K.; Wada, A.; Noguchi, K. *Org, Lett.* **2005,** *7*, 4737. (b) Tanaka, K.; Takahashi, Y.; Suda, T.; Hirano, M. *Synlett.* **2008**, 1724.

11. Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782.

12. (a) Albano, P.; Aresta, M. *J. Organomet. Chem.* **1980**, *190*, 243. (b) Schafer, H.; Marcy, R.; Ruping, T.; Sing, H. *J. Organomet. Chem.* **1982**, *240*, 17. (c) Ohshita, J.; Furumori, K.; Matsuguchi, A.; Ishikawa, M. *J. Org. Chem.* **1990**, *55*, 3277.

13. Yu, R. T.; Rovis, T.; *J. Am. Chem. Soc.* **2006**, *128*, 12370.

14. Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231.

15. Dalton, D. M.; Oberg, K. M.; Yu, R. T.; Lee, E. E.; Perreault, S.; Oinen, M. E.; Pease, M. L.; Malik, G.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 15717.

16. Stockis, A.; Hoffmann, R. . *J. Am. Chem. Soc.* **1980**, *102*, 2952.

17. Yu, R. T.; Lee, E. E.; Malik, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 2379.

18. Yu, R. T.; Rovis, T. . *J. Am. Chem. Soc.* **2008**, *130*, 3262.

19. Oinen, M. E.; Yu, R. T.; Rovis, T. *Org. Lett.* **2009**, *11*, 4943.

20. (a) Kajita, Y.; Matsubara, S.; Kurahashi, T. . *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 4781. (c) Rayabarapu, D. K.; Chang, K.-J.; Cheng, C.-H. *J. Org. Chem.* **2003**, *68*, 6726. (d) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (e) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. (f) Park, S. S.; Choi, J.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627. (g) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2007**, *9*, 4947.

21. Koyama, I.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 1350.

22. Man, S.; Necas, M.; Bouillon, J.-P.; Bailla, H.; Harakat, D.; Potacek, M. *Tetrahedron* **2005**, *61*, 2387.

23. (a) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474. For reviews on [2+2+2] cycloadditions forming benzenoid systems, see: Ref. 2e and (b) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508.

24. Barluenga, J.; Barrio, P.; Riesgo, L.; Lopez, L. A.; Tomas, M. *Tetrahedron* **2006**, *62,* 7547.

25. (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (b) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 4701. (c) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, *62,* 7552. (d) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 3963.

26. Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. M.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

27. (a) Gevorgyan, V.; Quan, L. G.; Yamamota, Y. *Tetrahedron Lett.* **1999**, *40*, 4089. (b) Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852. (c) Takahasi, T.; Tsai, F.-Y.;

Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

28. Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Chem. Lett.* **2007**, *36*, 998.

29. Hilt, G.; Paul, A.; Harms, K. J. *J. Org. Chem.* **2008**, *73*, 5187.

30. (a) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466. (b) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 12838.

31. Suda, T.; Noguchi, K.; Hirano, M.; Tanaka, K. *Chem.-Eur. J.* **2008**, *14*, 6593.

32. Jordan, R. W.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2006**, *71*, 5830.

33. (a) Mayr, H.; Ofial, A. R.; *J. Phys. Org. Chem.* **2008**, *21*, 584. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

34. Keller Friedman, R.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10775.

35. (a) Paquette, L. A.; Chang, J.; Liu, Z. *J. Org. Chem.* **2004**, *69*, 6441. (b) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496. (c) Hollick, J. J.; Golding, B. T.; Hardcastle, I. R.; Martin, N.; Richardson, C.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2003,** *13l* 3083. (d) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466. (e) Piers, E.; Chong, J. M.; Morton, H. E.; *Tet.* **1992**, *45,* 363. (f) Acetylenic amides were synthesized from the acid using standard peptide coupling conditions (HATU was the coupling agent of choice). (g) Braverman, S.; Cherkinsky, M.; Suresh Kumar, E. V. K.; Gottlieb, H. E. *Tet.* **2000**, *56,* 4521. (h) Yokoyama, A.; Ashida, K.; Tanaka, H. *Chem. Pharm. Bull.* **1964,** *6,* 690. (i) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. *Chem. Comm.* **2005,** 1037. (j) Sasson, Y.; Webster, O. W. *J. Chem. Soc., Chem. Commun.*, **1992,** 1200 (k) Claremon, D. A.; Phillips, B. T. *Tet. Lett.*

1988, *29,* 2155. (l) Luo, F.-T.; Wang, M.-W.; Wang, R.-T. *Org. Syn.* **1998,** *75,* 146. (m) Murray, R. E.; Zweifel, G. *Synthesis* **1980,** 150. (n) Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tet.* **2001**, *57,* 5123. (o) Wipf, P.; Coleman, C. M.; Janjic, J. M.; Iyer, P. S.; Fodor, M. D.; Shafer, Y. A.; Stephenson, C. R. J.; Kendall, C.; Day, B. W. *J. Comb. Chem.* **2005**, *7*, 322. (p) Rahman, M. T.; Fukuyama, T.; Ryu, I.; Suzuki, K.; Yonemura, K.; Hughes, P. F.; Nokihara, K. *Tet. Lett.* **2006**, *47*, 2703. (q) Denmark, S. E.; Marcin, L. R. *J. Org. Chem*. **1995**, *60,* 3221. (r) Tanaka, R.; Miller, S. I. *Tet. Lett*. **1971**, *12*, 1753. (s) Buissonneaud, D.; Cintrat, J.-C. *Tet. Lett.* **2006,** *47*, 3139. (t) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem*. **2006**, *71,* 4170.

36. Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

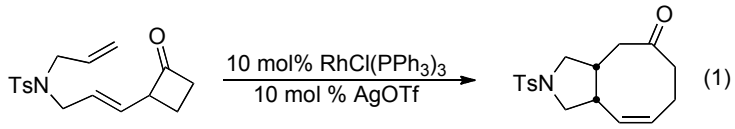
37. Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* **2007,** 2650.

Chapter 2

Rhodium-Catalyzed [4+2+2] Cycloaddition-Mechanistic Exploration Scope Expansion

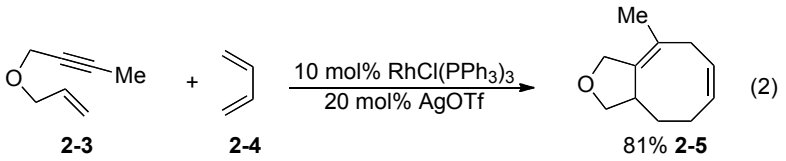
2.1 Introduction

Eight-membered rings are one of the great synthetic challenges in organic chemistry. Since the elucidation of the Taxol structure in the 1970's[1], the eight-membered ring has been a popular target for organic synthesis. They are difficult to form due to entropic effects and transannular strain at ~10 kcal/mol.[2] While ring-closing metathesis and ring expansion reactions are viable options for synthesis of said cycloadducts, transition metal-catalyzed cycloadditions have shown to be an attractive option for the synthesis of 8-membered carbocycles. Such cycloadditions include [4+4][3], [6+2][4], [5+2+1][5] and [4+2+2][6] cycloadditions. Several groups have undertaken the task of forming these mid-sized carbocycles with a variety of substrates and transition metals. Wender and coworkers[7] undertook [6+2] cycloadditions utilizing a number of different cyclobutanones (**2-1**) to successfully form a variety of [6.3.0], 8-membered carbocycles (**2-2**, eq. 1).

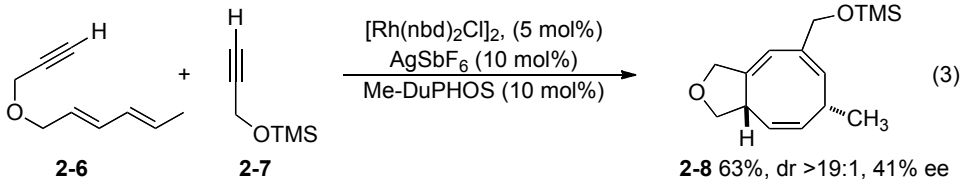


2-1 **2-2** 95% (1)

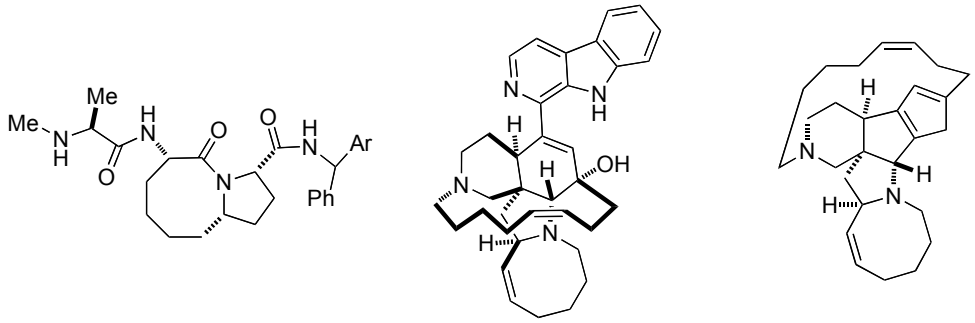
Subsequently, both Evans[8] and Gilbertson[9] began to utilize rhodium as a metal in [4+2+2] cycloadditions, again to form the eight-membered carbocycles. Evans and coworkers efficiently produced the eight-membered carbocycle by coupling an enyne to a very simple diene to form the cycloadduct in excellent yields (**2-5**, eq. 2).[8a]



Of all the current attempts, only Gilbertson has produced an enantioselective reaction. The yields and diastereoselectivities are good, but the enantioselectivities are poor and limited in examples (**2-8**, eq. 3).[9a]



The above examples exhibit concise methods to form 8-membered carbocycles, albeit with little or no enantioselectivity. However, these methods do not introduce heteroatoms into the newly formed ring. The formation of nitrogen-containing eight-membered rings (azocines) via transition-metal catalyzed cycloadditions is key to the formation of several biologically active natural products and small molecule targets (Figure 1). The manzamine alkaloids are a family that contains the [6.3.0] bicyclic azocine at its core, including Nakadomarin A and Manzamine A.[10] Also, a recently designed XIAP antagonist uses the same bicyclic azocine as a basic template.[11] Previous efforts towards such molecules tended to be rather step-intensive and relied on a ring-closing metathesis to close the eight-membered ring.[12]



XIAP Antagonist **Manzamine A** **Nakadomarin A**

Figure 1

With the success and thorough exploration of the [2+2+2] cycloaddition utilizing alkenyl isocyanates and alkynes (Section 1.3, Chapter 1), we sought to expand the methodology further to a [2+2+2] cycloaddition between alkynes and dienyl isocyanates. We also saw the potential for incorporation of both olefins, a [4+2+2] cycloaddition that would result in the production of [6.3.0] bicyclic azocines (Figure 2). The use of dienyl isocyanates may seem a logical extension of the alkenyl isocyanate scope, however, a known problem presented itself before the exploration even started. While the scope of the [2+2+2] cycloadditions had been thoroughly explored[13], a problem spot that had remained in reactivity was 1,2-substiuted alkenes, which were not reactive, unlike the 1,1-disubstituted counterparts. Presumably, the lack of reactivity was due to a lack of affinity to the metal center (Figure 2)[14]. In theory, a diene should have a better chance of incorporation than a simple 1,2-disubstituted alkene, due to conjugation.

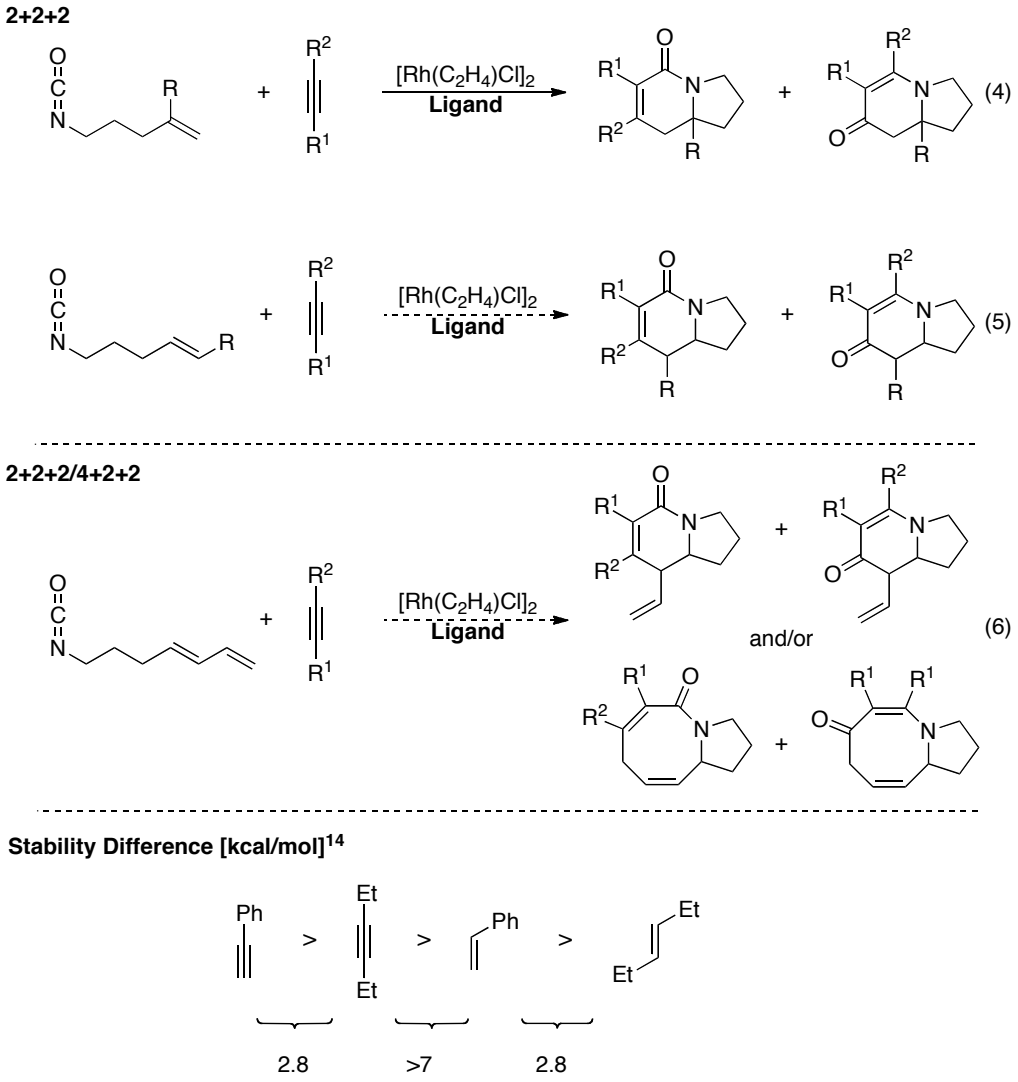
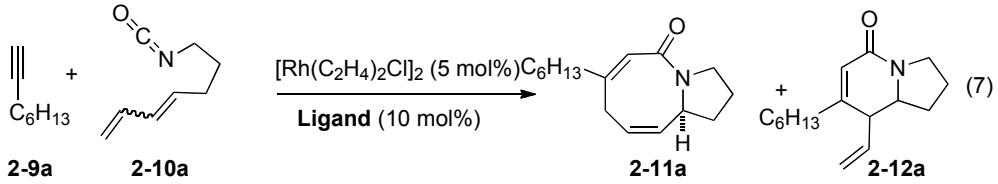


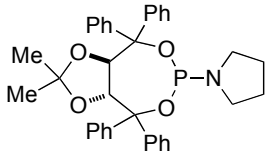
Figure 2

2.2 Previous Expansion of the Scope

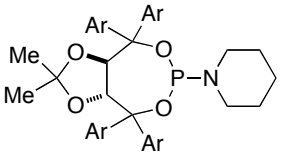
R. T. Yu found that initial results were promising, discovering that a simple dienyl isocyanate as a 1:1.4 mixture of E and Z olefin isomers, produced a mixture of [4+2+2] cycloadduct and [2+2+2] lactam product in a ratio of 4:1, preferring the azocine product (**2-11a**, eq. 7). When a single E-isomer was used, the product selectivity increased to >19:1. A brief ligand screen yielded **2-11a** in good yields and excellent enantioselectivities.



entry	E/Z ratio of **2-10a**	**L***	**2-11a : 2-12a**	yield (%) **2-11a**	*ee* (%) **2-11a**
1	1.4 : 1	**L1**	4 : 1	40	ND
2	≥19 : 1	**L1**	≥19 : 1	47	99
3	***≥19 : 1***	***L2***	***≥19 : 1***	***74***	***99***



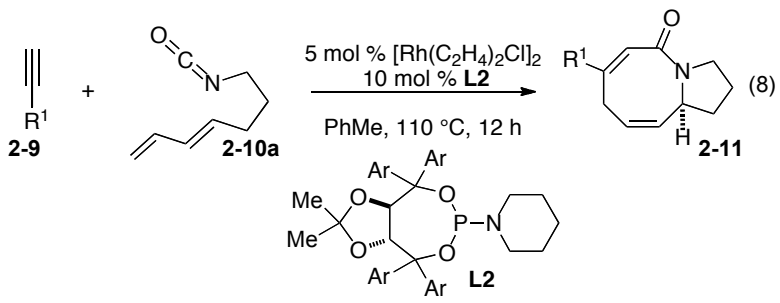
L1



L2

Table 1

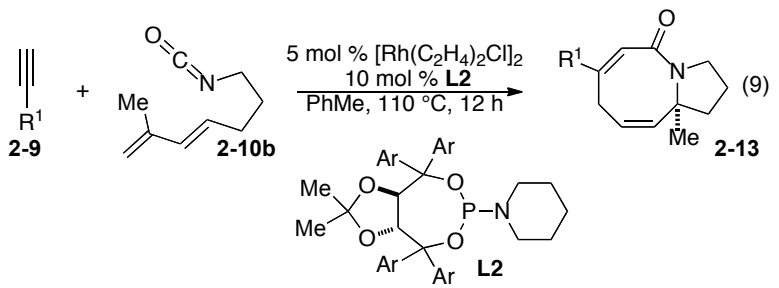
The scope was then expanded to include numerous alkynes. The lactam azocine was the only product obtained in any of these reactions. Unlike the [2+2+2] cycloaddition, in the [4+2+2] cycloaddition, no vinylogous amide product was observed (Section 1.3, Chapter 1). Alkynes that prefer the vinylogous amide pathway, such as aryl alkynes, proved less reactive in this system. Only electron-deficient aryl systems provided any product, in low yields (entry 3, Table 2). A variety of alkyl alkynes proved extremely successful in the reaction. When 1-octyne was chosen as the alkyne, the resulting yield was 74% with an excellent enantioselectivity of 99% (entry 1, Table 2). Further functionalization, including a phthalimide, silyl-proteted alcohol and benzyl group (entries 2, 4, and 5, Table 2) all proceeded with good yields (65-82%) and excellent enantioselectivity (97-99 %ee).



Entry	R^1—≡—H	yield (%)	ee 2-11 (%)	Major Product
1	C_6H_{13}—≡—H **2-9a**	74	99	**2-11a**
2	**2-9b**	65	97	**2-11b**
3	Br—≡—H **2-9c**	35	99	**2-11c**
4	TIPSO—≡—H **2-9d**	82	99	**2-11d**
5	Ph—≡—H **2-9e**	68	99	**2-11e**

Table 2

The scope was further expanded to include substitution on the diene. The resulting products contain a tri-substituted olefin. Two examples are shown in Table 3, 1-octyne and TIPS-protected propargyl alcohol. Yields are moderate (51-62%) but enantioselectivity was invariant (99 %ee) in both cases.



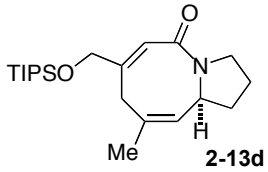
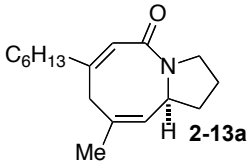
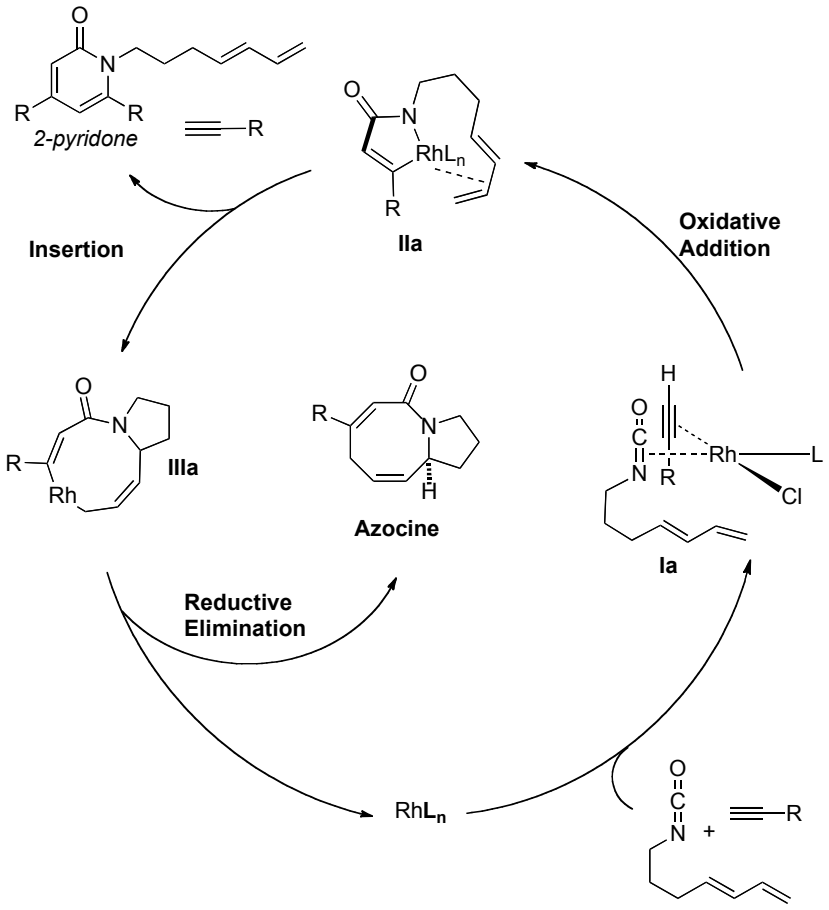
Entry	R^1—≡—H	yield (%)	ee 2-13 (%)	Major Product
1	TIPSO—≡—H **2-9d**	51	99	 **2-13d**
2	C_6H_{13}—≡—H **2-9a**	62	99	 **2-13a**

Table 3

2.3 Mechanistic Exploration of the [4+2+2] Cycloaddition

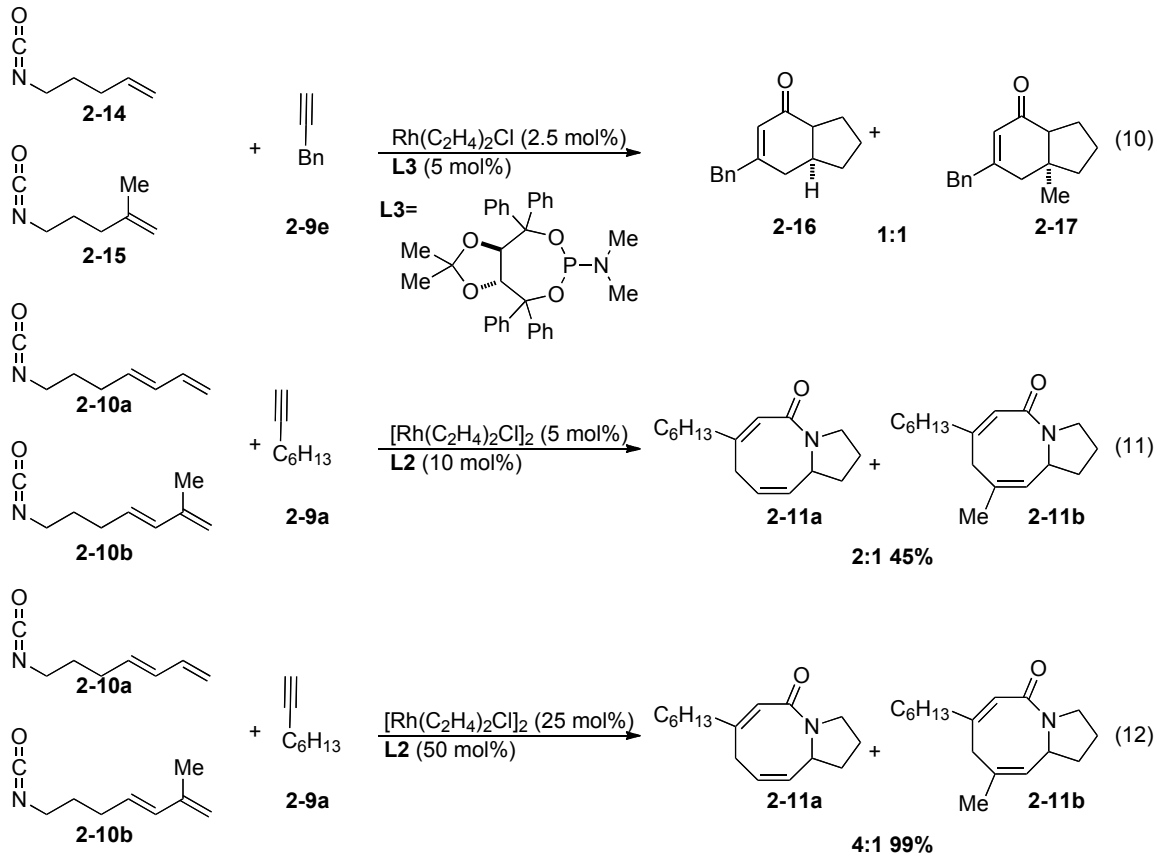
Initially, a mechanism was proposed that followed the same vein as the [2+2+2] cycloaddition, with initial coordination between the isocyanate and the alkyne (**Ia**). Oxidative addition can occur, forming the initial rhodacycle (**IIa**), followed by the migratory insertion of the diene (**IIIa**). Finally, reductive elimination yields the cycloadduct (**2-12**).



Scheme 1

While it is logical to believe that both cycloadditions would precede via the same mechanism, there were some inconsistencies that begged for further investigation. First, the enantioselectivities in the [4+2+2] reaction do not show the variability seen in the [2+2+2] cycloadditions. Also, a vinylogous amide product (eq. 4-6) is never seen, unlike the [2+2+2] cycloaddition. Alkynes, such as electron-rich aryl alkynes, that would prefer to undergo cyclization via the vinylogous-amide rhodacycle (Section 1.3, Chapter 1) do not produce product. Finally, the product ratio changes when the ratio of E/Z isomers changes, indicating that the alkene conformation has a definite influence on the catalytic cycle.

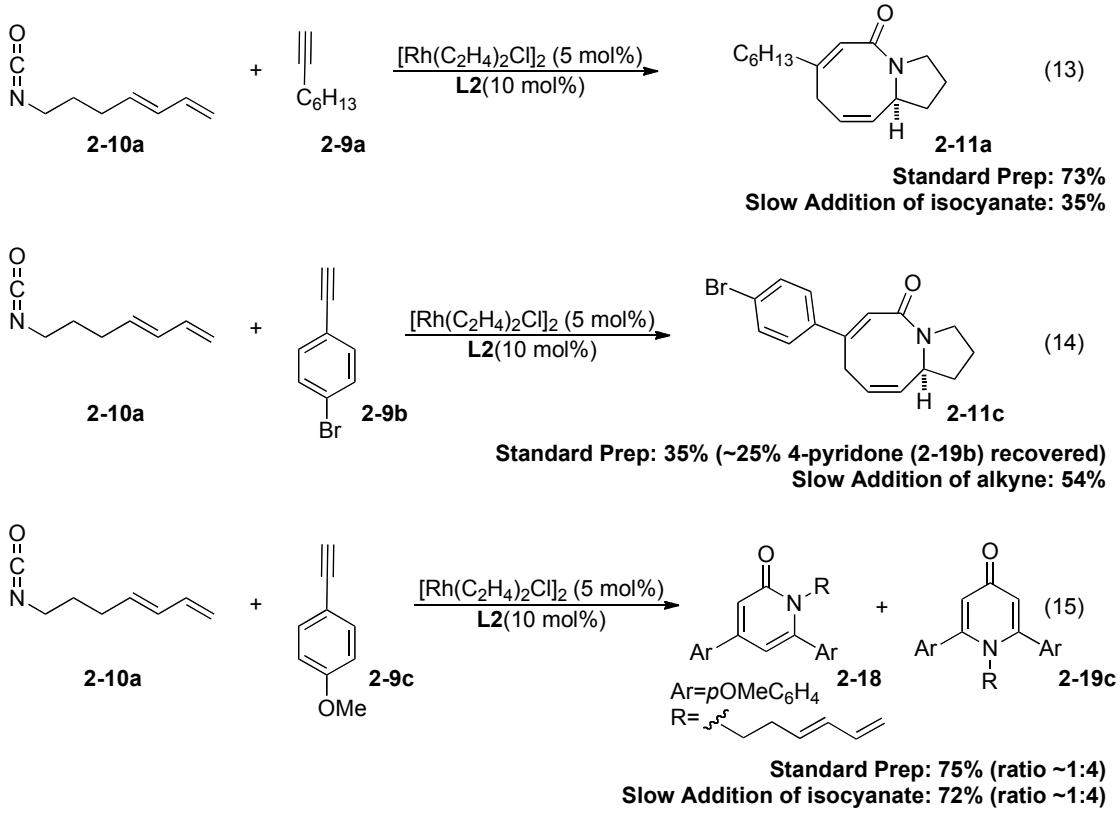
At this point, several experiments were conducted in order to investigate the initial hypothesis. With the [2+2+2] cycloaddition, a competition experiment was previously run between the parent, unsubstituted system (**2-14**) and a 1,1-substituted olefin (**2-15**).[13h] The resulting product ratio was 1:1, indicating that the alkene was not involved in the first irreversible step (eq. 10). When a similar experiment was conducted, between the unsubstituted diene (**2-10a**) and isocyanate **2-10b**, the product ratio was 2:1, favoring the unsubstituted diene. However, the recovered product of this competition experiment resulted in 45% isolated yield. When the reaction was run with higher catalyst loading, the yield is increased to 98% and the ratio also increases to 4:1 favoring the unsubstituted diene (eq. 12). These experiments show that, unlike the [2+2+2] cycloaddition, the diene in the [4+2+2] is involved in the first irreversible step. This indicates a change in the mechanism.



The next set of experiments focused on the competition between reactants present in a typical [4+2+2] reaction (eq. 13-15). Two separate reaction scenarios were considered: a coupling between alkyne (**2-9c**) and dienyl isocyanate **2-10a** that does not work well under optimized reaction conditions and one between an alkyne (**2-9a**) that worked very well and the same dienyl isocyanate (**2-10a**). If the diene and the alkyne are in competition for the binding site on rhodium, slow addition of either component should have an effect on the outcome of the reaction.

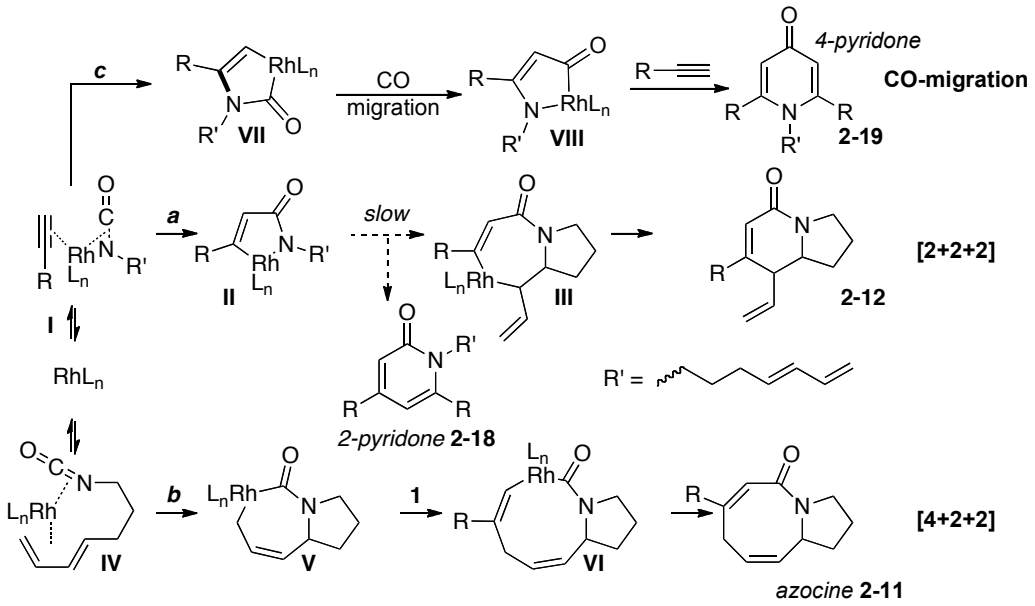
Indeed, when the dienyl isocyanate (**2-10a**) is added via slow addition to a reaction mixture containing 1-octyne (**2-9a**), rhodium and ligand (**L2**), the yield decreases from 74% to 35% (eq. 13). In contrast, when the aryl alkyne, which presumably coordinates better to rhodium, is added slowly to a reaction mixture

containing isocyanate, rhodium and ligand, the yield increases from 35% to 54% (eq. 14). In the typical reaction, there was significant recovery (25%) of 4-pyridone, a side-product of the CO-migration pathway, the first time in the [4+2+2] cycloaddition that any evidence of this pathway had been seen, indicating a competition between three potential pathways. This slow addition does not overcome the alkynes with the most affinity towards rhodium. For instance, when electron-rich alkyne **2-9f** is used in the cycloaddition, the combined yield is 75% for both 2-and 4-pyridone (eq. 15). Slow addition of the alkyne does not change the yield a significant amount.



With all the information presented, we felt that we were able to draw several conclusions and develop a new mechanistic hypothesis. The isocyanate still coordinates to rhodium initially. However, instead of alkyne binding without any hindrance, there is now a competition between diene and the alkyne for the final binding site (equilibrium

between **I** and **IV**, Scheme 2). If the alkyne binds in a stronger fashion, the rhodium inserts in what is presumed to be an irreversible fashion, forcing the reaction to follow a path where the products recovered can be the [2+2+2] lactam cycloadduct, 2-pyridone (pathway a), or if a CO-migration is able to occur, the vinylogous amide cycloadduct or 4-pyridone (pathway c). If the diene out-competes the alkyne (pathway b), it inserts irreversibly, forming the five-membered ring and a 9-membered rhodacycle (**VI**). This makes the first irreversible step and the enantioselective step likely the same. If this pathway is the outcome of the initial coordination, alkyne insertion and reductive elimination are all that remain for forming the bicyclic azocine.



Scheme 2

Examining the reactivity of the diene conformation (E vs. Z) alongside the above information corroborates this mechanistic hypothesis. First, the E to Z ratio of the diene has an effect on the product selectivity; more Z-alkene results in more [2+2+2] cycloadduct, while more E-alkene results in more [4+2+2] product. The E-alkene results in a better conformation to bind both olefins to rhodium, which would make it compete

better against the alkyne, resulting in more of the eight-membered ring. Next, the enantioselectivity is virtually invariant, indicating that there is no alkyne influence on the enantioselective step. Previously, in the study of the [2+2+2] scope, a large effect on both product selectivity and enantioselectivity was seen based on the alkyne. This influence is almost completely absent in the [4+2+2] cycloaddition. The lack of variation suggests that it is possible that the enantioselective step does not involve the alkyne, which would indicate that the stereocenter is set before the alkyne coordinates to rhodium, as seen in the [4+2+2] mechanism (Scheme 2, **V**).

The slow addition experiments (eq. 13-15) substantiate the idea that the diene and the alkyne are competing for space on the rhodium during the [4+2+2] cycloaddition. Slow addition of the alkyne allows for better binding of the diene, resulting in more [4+2+2] product (eq. 13). Slow addition of the dienyl isocyanate results in better binding of the alkyne, lowering the yield of the 8-membered azocine. Finally, the strongest piece of evidence suggesting that the diene is involved in the first irreversible step for the [4+2+2] cycloaddition comes from the competition experiments.

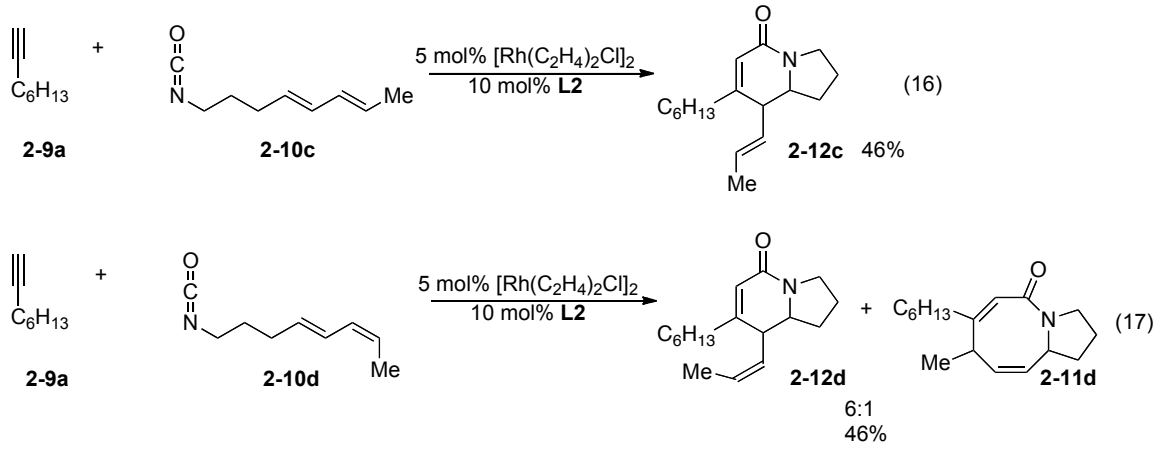
Previously, our group had determined that formation of the initial rhodacycle is the first irreversible step in the [2+2+2] cycloaddition (eq 7).[13h] The competition experiment clearly indicates that the diene is involved in the first irreversible step. The product ratio in the competition experiments (eq. 8 and 9) indicates that the unsubstituted diene is preferred to the methyl-substituted counterpart. The unsubstituted diene would bind better to rhodium that the substituted one, due to sterics. If this binding is reversible, or not involved in the first irreversible step, then this preference would not matter. However, if the binding of the diene is irreversible and in the first irreversible

step, a difference in product ratio would be seen, as suggested by standard olefin affinities to transition metals.[14] All the evidence points towards a mechanism for the rhodium catalyzed [4+2+2] cycloaddition between dienyl isocyanates and terminal alkynes that is different from the [2+2+2] cyloaddtion.[15]

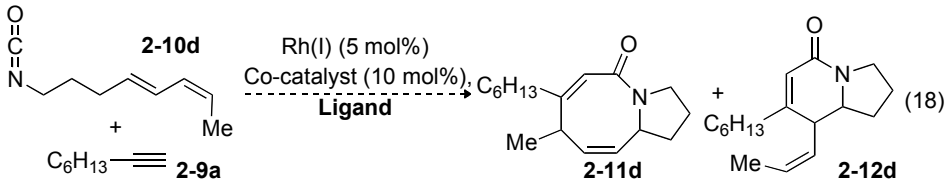
Attempts to intercept rhodacycle **VI** with alternative π-components, including ketones, isonitriles, aldehydes, and diazocarboxylates failed. Additionally, trials conducted with Ni(0) also were unsuccessful. Finally, attempts were made in order to induce reductive elimination of rhodacycle **VI** to produce a [4+2] product. Subjecting the dienyl isocyanate to reaction conditions in the absence of alkyne does not result in the desired outcome. Delayed addition of carbon monoxide or isonitrile still did not yield the desired indolizidinone.

2.4 Scope Exploration

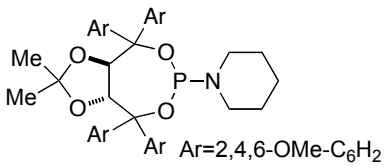
Once the mechanism had been explored, further expansion of the scope was attempted. Initial exploration by R. T. Yu[16] showed that substitution at the terminal position yielded either [2+2+2] product or a modest amount of [4+2+2] product, depending on the olefin isomer employed (eqs. 16 and 17).



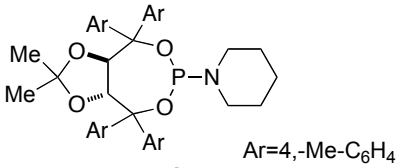
Subsequently, isocyanates **2-10c** and **2-10d** were explored further, under a variety of reaction conditions. More electron-rich TADDOL-based phosphoramidites were used, in hope of biasing the reaction towards the lactam-type product. The use of silver carbonate as a co-catalyst, in an effort to create cationic rhodium *in situ,* appeared to aid in reactivity, but proved to be an inconsistent effect, often under very similar reaction conditions. (Entries 1 and 2 in Table 4 could not be repeated on a consistent basis).



Entry	Rh	Ligand	Co-Catalyst	Result
1	$[Rh(C_2H_4)_2Cl]_2$	**L2**	Ag_2CO_3	Trace **2-11d**
2	$[Rh(C_2H_4)_2Cl]_2$	**L1**	Ag_2CO_3	1:1, 35% **2-11d**
3	$[Rh(C_2H_4)_2Cl]_2$	**L4**	None	No reaction
4	$[Rh(C_2H_4)_2Cl]_2$	**L5**	None	No reaction
5	$[Rh(CO)_2Cl]_2$	**None**	$AgSbF_5$	No reaction
6	$[Rh(CO)_2Cl]_2$	**L2**	None	No reaction
7	$[Rh(C_2H_4)_2Cl]_2$	**L2**	$ZnCl_2$	No reaction



L4

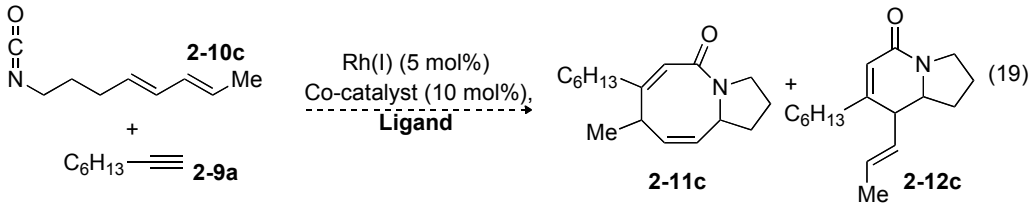


L5

Table 4

Isocyanate **2-10c** was also subjected to a variety of reaction conditions. It had been previously seen in the group that switching the halogen on the catalyst, to Br or I,

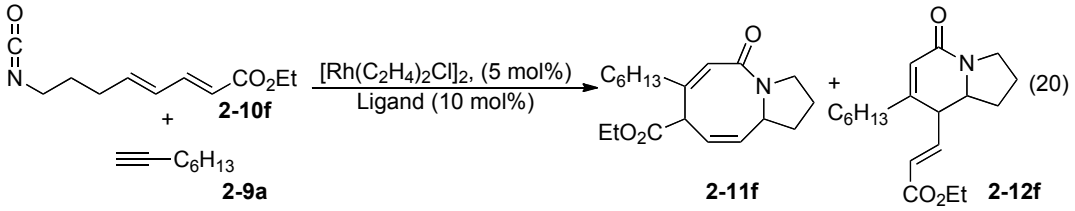
skewed the system towards lactam products.[17] However, when isocyanate **2-10c** and 1-octyne were subjected to such reaction conditions (entry 1, Table 5), the result was no reaction. The reaction does not proceed unligated, unlike the [2+2+2] cycloaddition. In fact, the E, E-diene (**2-10c**) failed to give any of the eight-membered azocine product, even when the silver carbonate was used.



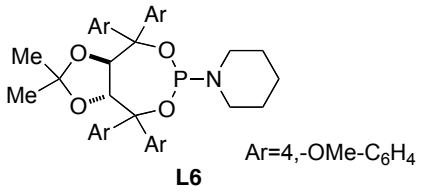
Entry	Rh	Ligand	Co-Catalyst	Result
1	$[Rh(C_2H_4)_2Br]_2$	**L2**	None	No Reaction
2	$[Rh(C_2H_4)_2Cl]_2$	**None**	None	No Reaction
3	$[Rh(C_2H_4)_2Cl]_2$	**L2**	Ag_2CO_3	<1:20, 20%

Table 5

Electronics on the alkyne were also altered, in an effort to aid in diene coordination and create cycloadducts with more variety. Initial results have shown some promise. An electron-deficient diene (**2-10f**) was synthesized successfully and subjected to the reaction conditions. A cycloadduct (**2-12f**) was obtained and initial data (ESI-MS and NMR spectroscopy) indicates that it may be the [4+2+2] product as a mixture of diastereomers (entry 2, Table 6).



Entry	Temperature	Ligand	Result
1	110	**L2**	No reaction
2	155	**L2**	>20:1, 10%
3	155, MW	**L1**	No Reaction
4	155	**L6**	No Reaction



L6

Table 6

From these results, the electronics of the diene and the ligand/co-catalyst combination appear to be the route to successful diastereoselective synthesis of [6.3.0] bicyclic azocines, but further exploration and experimentation would be necessary. In conclusion, the mechanism of the [4+2+2] cycloaddition utilizing dienyl isocyanates and alkyne has been explored, and a sufficient mechanistic hypothesis has been presented. Attempts at expansion of the diene scope have not progressed as hoped, although in the future, manipulation of the electronics of the diene should be explored.

2.5 References

1. (a) Nicolaou, K. C.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2079. (b) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15.

2. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry.* **2006**.

3. Select examples include: (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908.

4. Rigby, J. H.; Short, K. M.; Ateeq, H. S.; Henshilwood, J. A. *J. Org. Chem.* **1992**, *57*, 5290.

5. Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876.

6. (a) Varela, J. A.; Castedo, L.; Saa, C. A. *Org. Lett.* **2003***, 5*, 2841. (b) Lee, S. I.; Park, S. Y.; Chung, Y. K. *Adv. Synth. Catal.* **2006**, *348*, 2531. (c) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166. (d) Hilt, G.; Janikowski, J. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 5243.

7. Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.

8. (a) Evans, P. A.; Robinson, J. E.; Baum, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (b) Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 11150. (c) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun.* **2005**, 63.

9. (a) DeBeof, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799. (b) Gilbertson, S. R.; DeBeof, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784.

10. Examples of representative total syntheses: (a) Winkler, J. D.; Axten, J. M.; *J. Am. Chem. Soc.* **1998**, *120*, 6425. (b) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Marin, S. F.; *J. Am. Chem. Soc.* **2002**, *124*, 8584. (c) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (d) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 2876.

11. Sun, H.; Nikolovska-Coleska, Z.; Lu, J.; Meagher, J. L. Yang, C.-Y.; Qiu, S.; Tomita, Y.; Ueda, Y.; Jiang, S.; Krajewski, K.; Roller, P. P.; Stuckey, J. A.; Wang, S. *J. Am. Chem. Soc.* **2007**, *129*, 1465.

12. (a) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478. (b) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526. (c) Duggan, H. M. E.; Hitchcock, P. B.; Young, D. W. *Org. Biomol. Chem.* **2005**, *3*, 2287.

13. (a) Yu , R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782. (b) Yu , R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (c) Yu , R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 3262. (d) Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231. (e) Yu, R. T.; Lee, E. E.; Malik, G.; Rovis, T. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 2379. (f) Oberg, K. M.; Lee, E. E. *Tetrahedron* **2009**, *65*, 5056. (g) Keller Friedman, R.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10775. (h) Dalton, D. M.; Oberg, K. M.; Yu, R. T.; Lee, E. E.; Perreault, S.; Oinen, M. E.; Pease, M. L.; Malik, G.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 15717.

14. Johnson, J. B.; Rovis, T. *Angew. Chem. Int. Ed. Engl.* **2007**, *47*, 840.

15. Yu, R. T.; Keller Friedman, R.; Rovis, T.; *J. Am. Chem. Soc.* **2009**, *131*, 13250.

16. Yu, R. T. Enantioselective Rhodium-Catalyzed [2+2+2] and [4+2+2] Cycloaddition Reactions of Alkenyl Heterocumulenes: Applications to Alkaloid Synthesis. Ph.D. Dissertation, Colorado State University, Fort Collins, CO, 2008.

17. Smyth, C. Rovis, T. *Unpublished Results.*

Chapter 3

Efforts Towards the Total Synthesis of Secu'amamine A: Utilization of the Rhodium-Catalyzed [2+2+2] Cycloaddition

3.1 Introduction: Properties and Isolation

Secu'amamine A (**3-3**) is one of over twenty members of the family of *Securinega* alkaloids. Securinine (**3-1)** is the major alkaloid isolated from the leaves of the plant, *Securinega suffruticosa*.[1] Members of the family exhibit numerous biological effects, including anti-tumor, anti-malarial and central nervous system activity. Secu'amamine A is one of the newer confirmed compounds, isolated by Kobayashi and coworkers in 2003.[2] Subsequently, Secu'amamines B-G have also been isolated.[3]

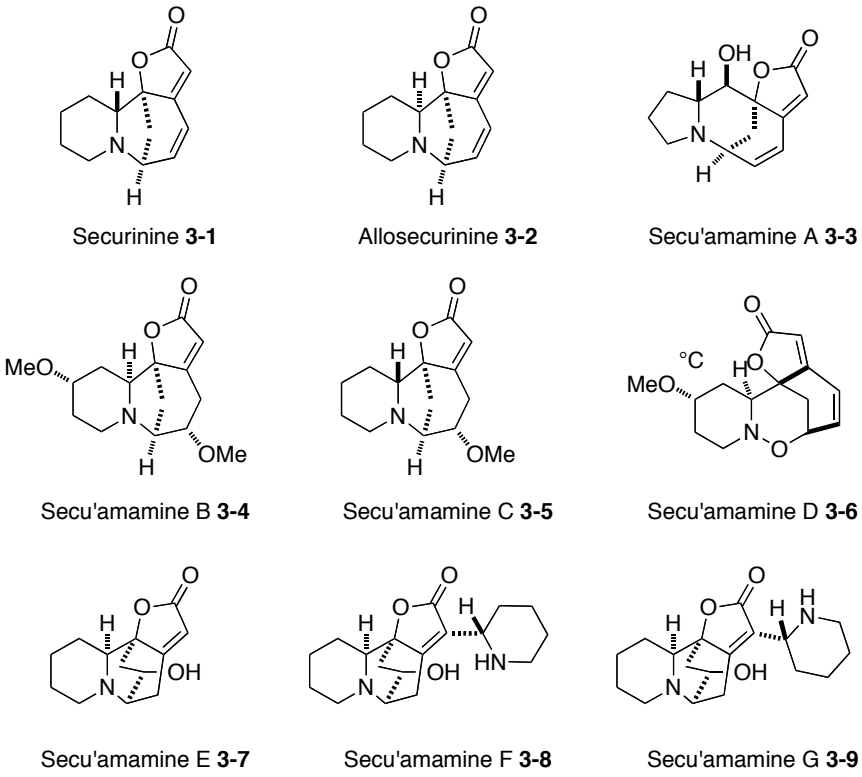
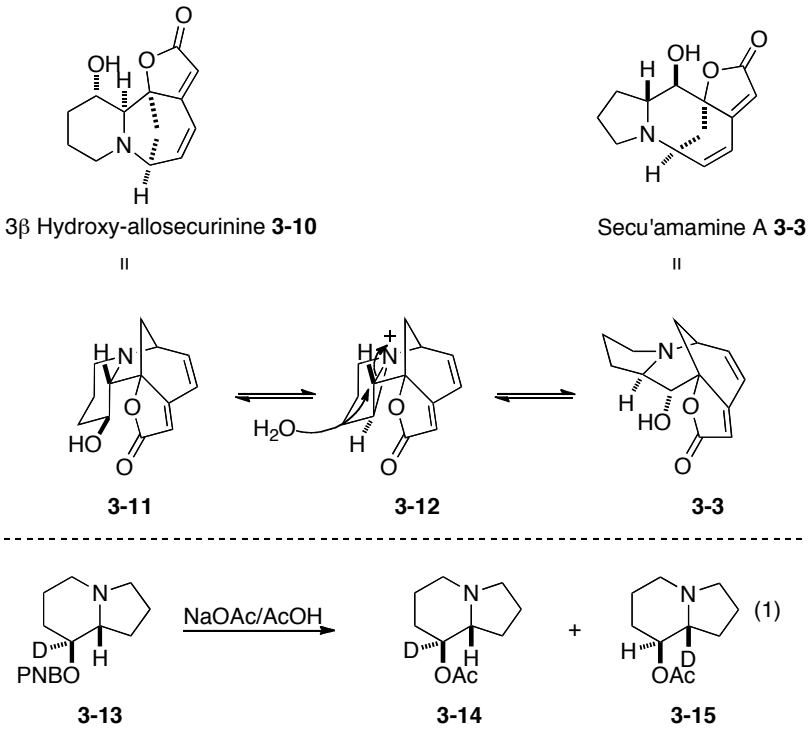


Figure 1

3.2 Introduction: Proposed Biosynthetic Pathway

Magnus and coworkers, in their efforts to pursue the total synthesis of Secu'amamine A, proposed the biological synthesis of the molecule.[4] The proposal suggests that Secu'amamine A is derived from allosecurinine, specifically, from the not-yet-isolated 3β-hydroxyallosecurine. The key step in the mechanistic proposal is the formation of a aziridinium ion (**3-12**) via the elimination of a hydroxyl group. Subsequent opening of the three-membered ring via hydrolysis results in the formation of Secu'amamine A (**3-3**). The hypothesis is not without merit, a simplified model system has illustrated that a deuterium label is scrambled, suggesting formation of the aziridinium ion (eq. 1). Magnus is currently pursing the total synthesis of Secu'amamine A via this strategy.

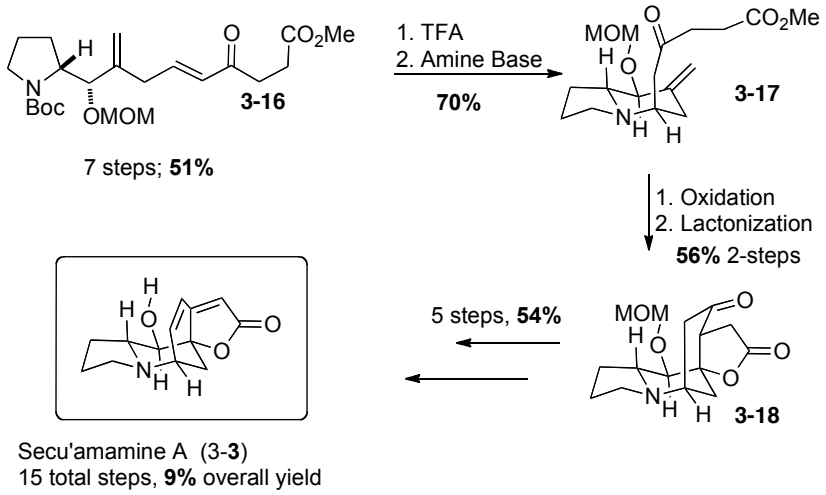


Scheme 1

3.3 Introduction: Previous Total Synthesis

To date, there has been one successful total synthesis of (-)-Secu'amamine A, by Weinreb and coworkers.[5] The key step in the synthesis is a cascade cyclization to form

the bicyclic core of Secu'amamine A. Synthesis of the precursor (**3-16**) to the cyclization includes significant functionalization of a proline-type precursor, including a Grignard addition, numerous protections and deprotections and a Horner-Wadsworth-Emmons olefination. After the key cyclization, oxidative manipulations were performed to yield the desired natural product in 15 steps and ~9% overall yield.



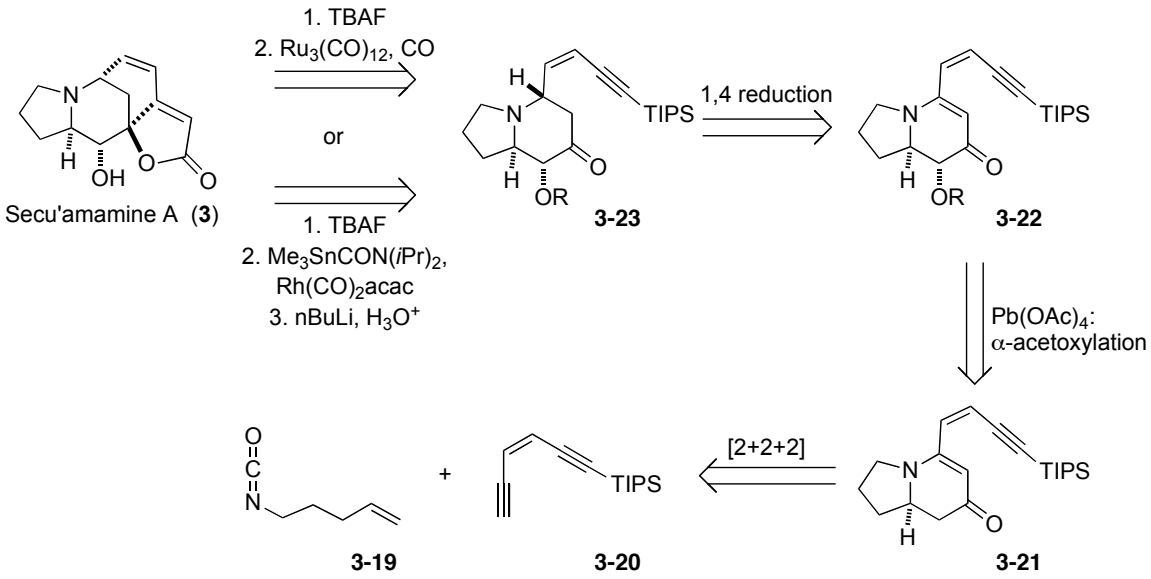
Scheme 2

3.4 Retrosynthetic Analysis

While the Weinreb synthesis was groundbreaking, there is still room for improvement. The synthesis of the Weinreb starting materials is fairly step-intensive and uses an expensive D-proline derivative as the starting material. We propose that utilizing a rhodium-catalyzed [2+2+2] cycloaddition to form the bicyclic core of Secu'amamine A (**3-3**) will significantly reduce the number of steps necessary to complete the synthesis of the natural product.

The final ring to be formed will be the unsaturated lactone. We propose to complete the molecule by using a Pauson-Khand-type cyclization, catalyzed by ruthenium. Alternatively, if the [2+2+1] cycloaddition cannot be completed successfully,

an adequate replacement would be a coupling reaction, using a vinyl tin species. Both examples are well precedented.[6] To form the bicyclic core, a [2+2+2] cycloaddition will be employed to form the vinylogous amide product (**3-21**). There are only three manipulations that need to be performed on the vinylogous amide to yield the final cyclization precursor (**3-23**). A selective α-oxidation will need to be performed, the vinylogous amide reduced to the keto-amine product and the silyl group removed from the alkyne. Literature precedent[7] suggests that the oxidation can be performed on the vinylogous amide utilizing $Pb(OAc)_4$, followed by subsequent 1,4-reduction. However, reduction of the vinylogous amide, followed by α-oxidation of the ketone is also a well-precedented possibility.[8]

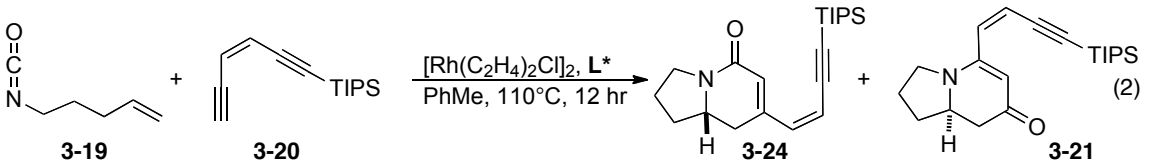


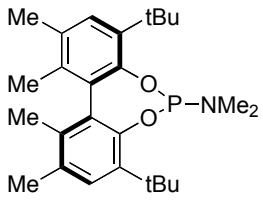
Scheme 3

3.5 Forward Synthesis

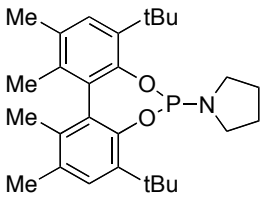
The first task to tackle on our proposed synthesis of Secu'amamine A (**3-3**) was the development of an efficient [2+2+2] cycloaddition between isocyanate **3-19** and alkyne **3-20** with acceptable yields, product selectivity and enantioselectivity. Diyne **3-20**, which

had previously been synthesized by the Molander group[9] proved to be the best option, as it provides a good framework for either option for formation of the unsaturated lactone. A variety of ligands, commonly used in our rhodium-catalyzed [2+2+2] cycloaddition methodology[10] were screened and it was found that the biphenyl and BINOL-ligands (**L1-L7**) provided adequate yields, ratios and enantioselectivities. However, the results obtained were not ideal, significant amounts of lactam product were formed, and the vinylogous amide was only synthesized with moderate enantioselectivity (<87% ee). Concurrently in the lab, a coworker, Derek Dalton, developed an electron-deficient TADDOL-based ligand, hence dubbed CKPhos (**L9**)[11], which when used in the [2+2+2] cycloaddition provides excellent selectivity towards the desired vinylogous amide product (<1:20) with excellent enantioselectivities (95% ee) as well. Thus, CKPhos (**L9**) was chosen as a ligand for the total synthesis of Secu'amamine A (**3**).

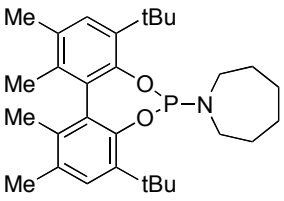




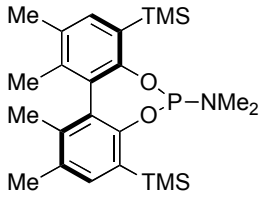
L1 1:8 95% 71%ee



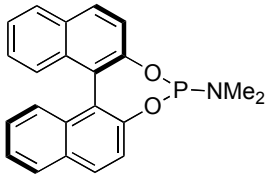
L2 1:6 55%



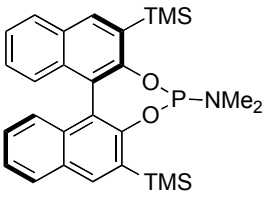
L3 No Reaction



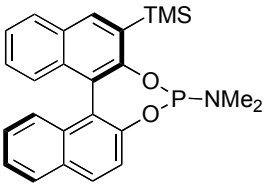
L4 1:9 79% 79%ee



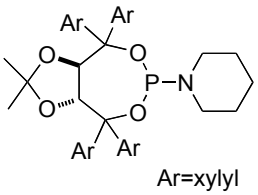
L5 No Reaction



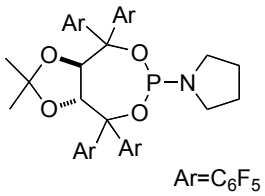
L6 1:6 66% 85%ee



L7 1:2 43% 56%ee



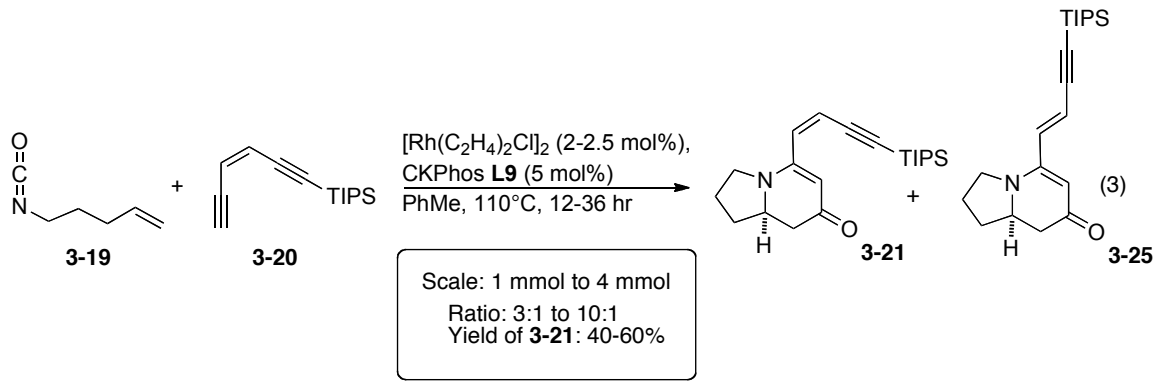
L8 >20:1 40%



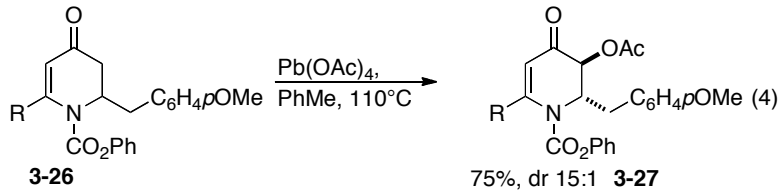
L9 <1:20 91% 95 %ee

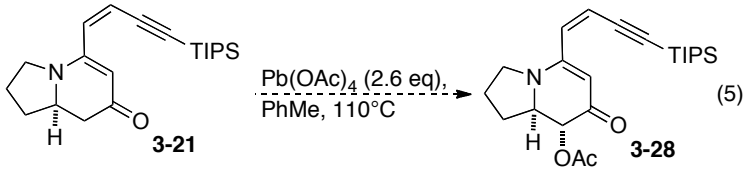
Table 1

Problems did present upon scale-up of the reaction. For unknown reasons, the cis-enyne side chain appears to isomerize under the reaction conditions to the trans-enyne side chain, giving a second vinylogous amide product (**3-25**). Efforts to eliminate this side product include running the scaled-up reaction for shorter periods of time, in more dilute conditions, and slightly deficient in rhodium pre-catalyst. While all these efforts appear to help with the ratio, none eliminate the side product entirely. However, the two isomers are readily separable and should the total synthesis be taken to completion, this reaction could certainly be optimized. Currently, large-scale yields of cis-enyne vinylogous amide **3-21** (~50% yield) are sufficient to carry on with the synthesis.



The next step of the synthesis is to install an alcohol or an acetoxy group alpha to the carbonyl of the vinylogous amide. Precedent by Comins and coworkers (eq. 4)[7] indicates that lead tetraacetate would be an ideal oxidant. Several attempts were made, variations in solvent were tried, but none were successful. Rigorous purification of $Pb(OAc)_4$ resulted in recovery of over-oxidized product, resulting in the loss of the stereocenter (Table 2, entry 5). One obvious difference between dihydropyridone (**3-27**) in the precedent and vinylogous amide (**3-21**) is the substitution at the nitrogen. An attempt to make the nitrogen more electron-deficient, by protecting it with borane, and then subjecting it to typical reaction conditions resulted in decomposition (Table 2, entry 6). Reducing both the temperature and the equivalents of oxidant only resulted in similar yields of over-oxidized product (Table 2, entry 7).





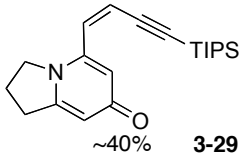
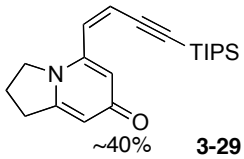
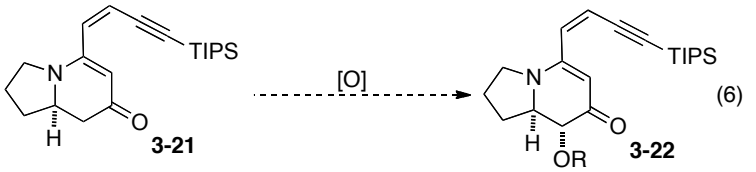
Entry	Variations	Result
1	$Pb(OAc)_4$, PhMe	Decomposition
2	$Pb(OAc)_4$, cat. AcOH	Decomposition
3	$Pb(OAc)_4$, 1 equiv. lutidine	Decomposition
4	$Pb(OAc)_4$, Benzene/AcOH (10:1)	Decomposition
5	$Pb(OAc)_4$ (recrystallized), PhMe	 ~40% **3-29**
6	$H_3B{\cdot}SMe_2$, then $Pb(OAc)_4$,	Decomposition
7	$Pb(OAc)_4$ (1.3 equiv.), 55°C	 ~40% **3-29**

Table 2

Once it was determined that $Pb(OAc)_4$ was not an appropriate oxidant for vinylogous amide **3-21**, numerous other traditional oxidative conditions were explored. Table 3 illustrates the 'best' results from each oxidation. Manganese triacetate was used as an alternative to lead tetraacetate, but the only oxidation seen was the loss of H_2 to eliminate the stereocenter (**3-29**, entry 1, Table 3). The same elimination was seen when a hypervalent iodine reagent was used as an oxidant (entry 2, Table 3). Decomposition was noted when a molybdenum oxidant (MoOPH) was used and was also seen when an oxiziridine (**30**) was used as an oxidant (entries 3 and 4, Table 3).



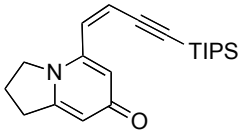
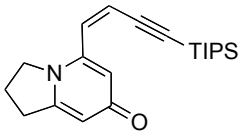
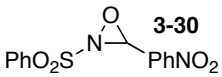
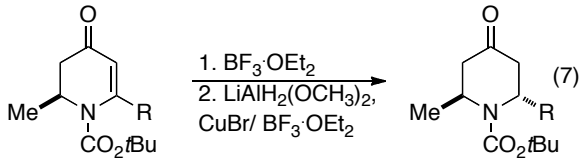
Entry	Oxidative Conditions	Result
1	$Mn(OAc)_3 \cdot 2H_2O$ (2 equiv.)	 ~30% **3-29**
2	KOH (6 equiv.) $PhI(OAc)_2$ (2 equiv.) MeOH	 ~50% **3-29**
3	Base (LDA, LiHMDS, NaHMDS) MoOPH	Decomposition
4	NaHMDS,  **3-30**	Decomposition

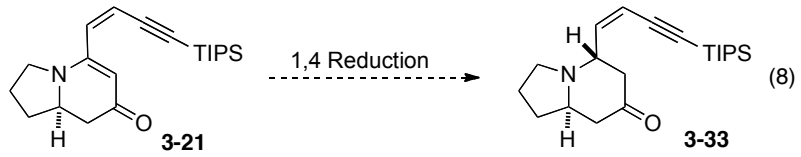
Table 3

At this point, it was determined that the oxidation would have a better chance for success if it were to take place after the 1,4-reduction. The reduction presented its own trials. Initial precedent[12] suggested that a copper-mediated hydride reduction would be necessary. However, these conditions proved unsuccessful (eq. 1, Table 4). A variety of more traditional reductants were used to reveal the keto-amine. While DIBAL did yield the reduced product, there were significant side products, believed to be indolizidine **3-34**. Attempts at optimization (decreasing equivalents of DIBAL, change in solvent, concentration, temperature) did not change the outcome of the reaction significantly (entry 3, Table 4). Red-Al produced keto-amine (**3-33**) in sufficient yields on small scale (50%), but was not robust enough to tolerate scale-up (entry 4, Table 4). Yields were erratic and no optimization technique could render a consistent outcome. Super-Hydride,

however, yielded the 1,4-reduction product in 90% yield, on scales as large as 1.0 mmol (entry 5, Tale 4). However, the reduction proved dependant on the batch of Super-Hydride used. A new bottle of Super-Hydride yielded the desired product in 60%-75% yield with the remainder of the mass balance accounted for by over-reduced amino-alcohol **3-35**. In all cases, the reduction yields a single diastereomer.



3-31 **3-32** 99% (7)



3-21 **3-33** (8)

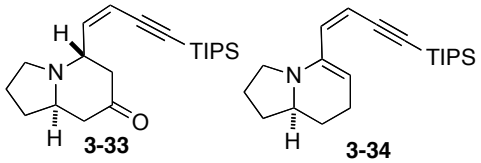
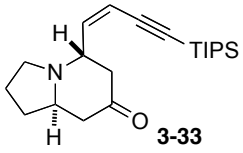
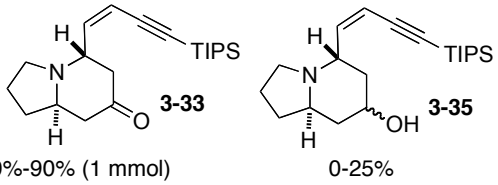
Entry	Reducing Agent	Result
1	1. $BF_3{\cdot}OEt_2$ 2. $LiAlH_2(OCH_3)_2$, CuBr/ $BF_3{\cdot}OEt_2$	No Reaction
2	L-Selectride	No Reaction
3	DIBAL (3 equiv.) 0 °C	 **3-33** **3-34** 1.5:1, 40% combined
4	Red-Al (3 equiv.), 0 °C	 **3-33** 50% (0.08 mmol)
5	Super-Hydride, (1.5 equiv.), 0 °C	 **3-33** **3-35** 60%-90% (1 mmol) 0-25%

Table 4

The diastereoselectivity was determined by substrate correlation and nOe's. A similar vinylogous amide was synthesized and reduced in an identical fashion. First, the vinylogous amide was synthesized using CKPhos as the ligand (46%). Subsequently, vinylogous amide (**3-36**) was reduced with Super-Hydride to yield **3-37**. An nOe enhancement was observed in **3-37** that was seen between the methylene protons on carbon 1 and the proton on the stereogenic carbon 6, indicating that the hydride adds onto the desired face, trans to proton on carbon 6 (Figure 2).

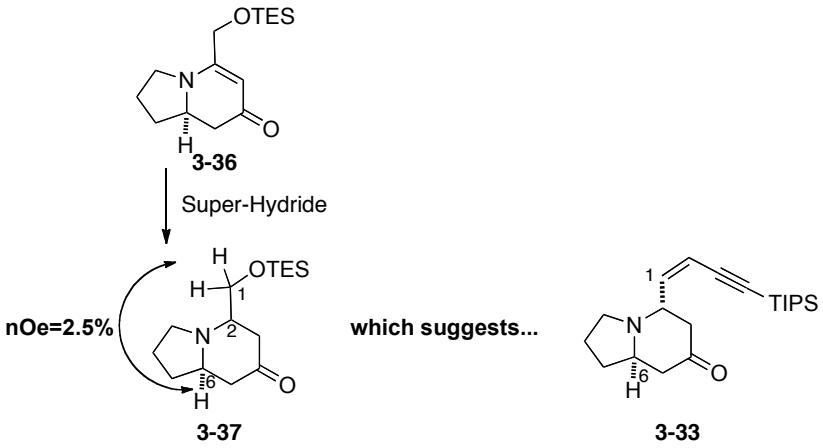


Figure 2

Model studies also suggest the addition of the hydride syn to the hydrogen on carbon-6. Assuming that a lithium enolate is formed (**3-21Li**) during the reduction, lowest energy models were computed. It appears that the six-membered ring is flat in nature, without an obvious preference of facial approach. However, if it is assumed that the boron present in the reducing coordinates to nitrogen, two possible approaches of attack can be considered (**3-21LiA** and **3-21LiB)**. We believe that addition from the top face would be preferred and we attribute this preference to torsional strain present in the transition states between boron and the axial hydrogens if attack were to occur from the bottom face (**3-21LiA**). Additionally, the calculated models show the potential for

interaction between the enyne side chain and one of the methylenes on the five-membered ring. Attack from the bottom face would presumably push this large group closer to the methylene, causing unwanted steric interactions. These models, shown in Figure 3, corroborate the experimental spectral data.

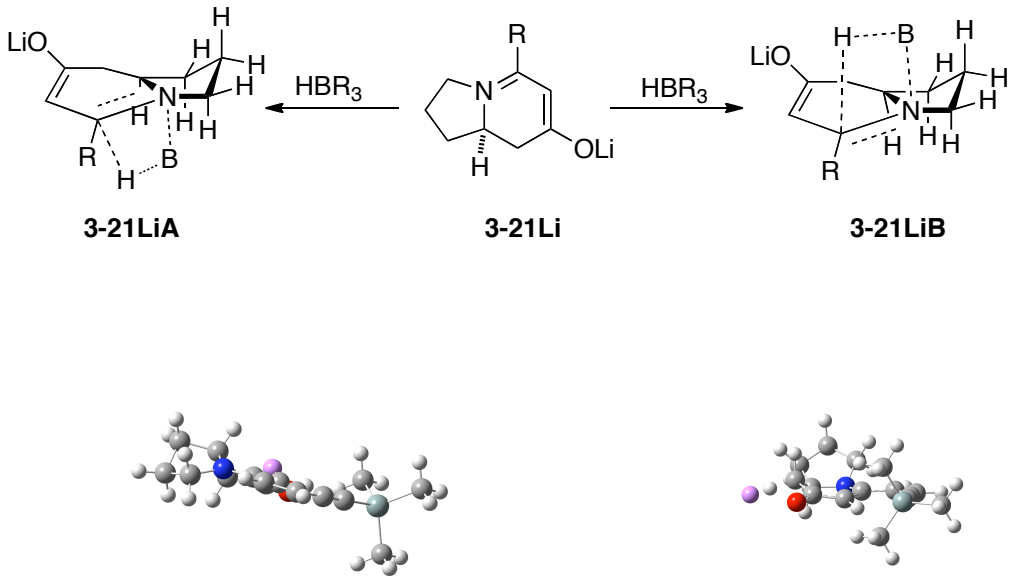
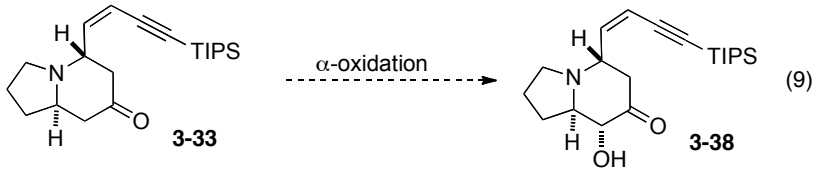


Figure 3

At this point a large effort to produce alpha-oxidized keto-amine began. A number of initial conditions were investigated, but the majority (Table 5, entries 1-4) resulted in decomposition or recovered starting material. Formation of the enolate, followed by addition of a strong oxidant, *m*CPBA, resulted in the oxidation of the amine (**3-39**) in 75% yield (Table 5, entry 5).



(9)

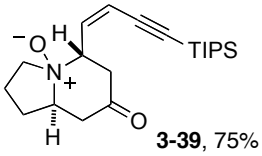
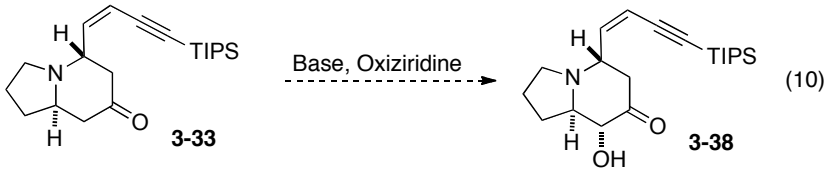
Entry	Oxidizing Conditions	Result
1	LDA/TMSCl then OsO_4/NMO H_2O/Acetone	Decomposition
2	LDA/MoOPH	Recovered SM (25%) Decomposition
3	NaHMDS/MoOPH	Recovered SM (50%) Decomposition
4	KO*t*Bu/$P(OEt)_3$, O_2	Decomposition
5	KHMDS/ 2 equiv. mCPBA	 **3-39**, 75%

Table 5

At this point, attempts at performing a successful α-oxidation became more focused, choosing two oxidants (oxiziridines and hypervalent iodide) that had proven successful with other keto-amines.[8] Initially, use of oxiziridine compounds as oxidants looked as if it may be successful, with trace amounts of product seen (Table 6, entry 2). However, after numerous attempts at optimization, the first hit could not be improved upon (Table 6, entries 3-5).



(10)

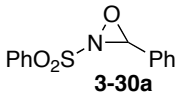
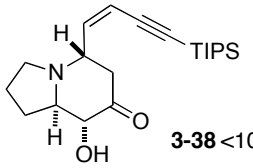
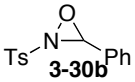
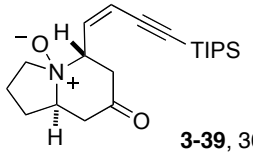
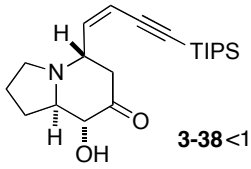
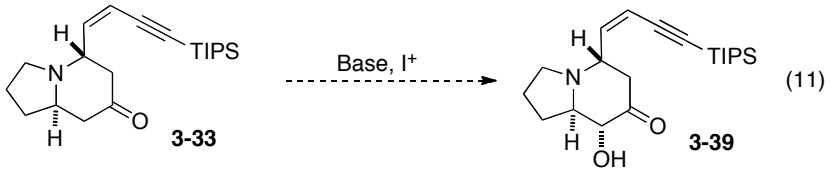
Entry	Oxidizing Conditions	Result
1	NaHMDS, (-)CSO	SM (50%)
2	KHMDS,  **3-30a**	 **3-38** <10%
3	LiHMDS/HMPA,  **3-30b**	 **3-39**, 30%
4	LiHMDS/DMPU, **3-30b**	 **3-38** <10%
5	$LiNEt_2$, **3-30b**	Decomposition

Table 6

Oxidation with hypervalent iodide sources was also attempted. A significant amount of what appeared to be the dimethyl ketal of a cycloadduct appeared to form (entry 2, Table 7). However, the confirmation of the exact structure proved difficult due to the sensitive nature of the final product. Significant analysis of the product did not give a conclusive answer. The product could not be deprotected without decomposition and slowly decomposed during analysis. However, based on the spectral data as well as the mass obtained, and in light of previous oxidation seen at the amine, **39** is the tentatively assigned structure.



(11)

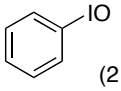
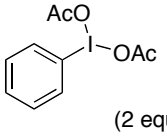
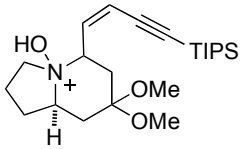
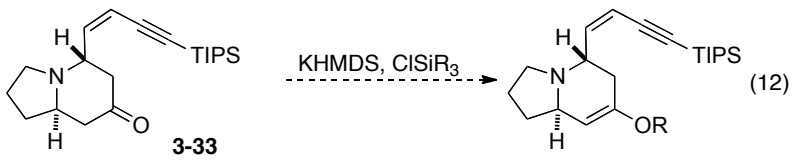
Entry	Oxidizing Conditions	Result
1	KHMDS (1.5 equiv.), BF_3OEt_2 (1 equiv.)	No Reaction
	 (2 equiv.)	
2	KOH (6 equiv.), MeOH,  (2 equiv.)	 **3-40**

Table 7

In all oxidations, one of the main roadblocks to α-oxidation appeared to be competitive oxidation of the amine. It should be noted that several protecting groups (-H, $-BH_3$, $-BF_3$, $-O^-$) were tried in attempts to avoid oxidation of the amine. None proved successful.

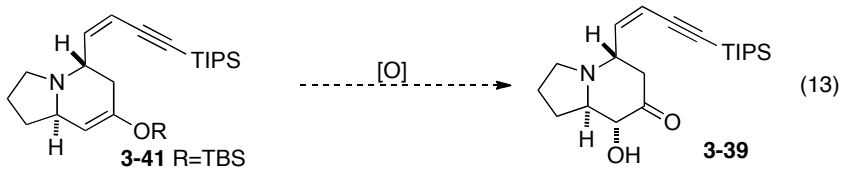
While it was not ideal to form an isolable silyl enol ether, it was necessary, to at least prove that the deprotonation could occur at the correct position. Two silyl enol ethers (**3-41** and **3-42**) were synthesized in this effort. Indeed, the deprotonation occurs on the desired side of the ketone, to produce these silyl enol ethers in good yields. The regioisomer of the silyl enol ether was based on changes in splitting in the proton NMR. These enol ethers were used in oxidation attempts that followed.



(12)

3-41 R=TBS 65%
3-42 R=TES 70%

Many attempts to oxidize TBS-silyl enol ether (**3-41**) proved unsuccessful (entries 1-3, Table 8). Attempts to epoxidize the silyl enol ether (entries 4, 5, Table 8) yield either no reaction or decomposition. The TES-silyl enol ether (**3-42**) did not prove any more reactive, which suggests that steric hindrance due to the large TBS group is not the sole reason for the lack of reactivity of **3-42**.



3-41 R=TBS **3-39** (13)

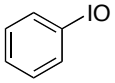
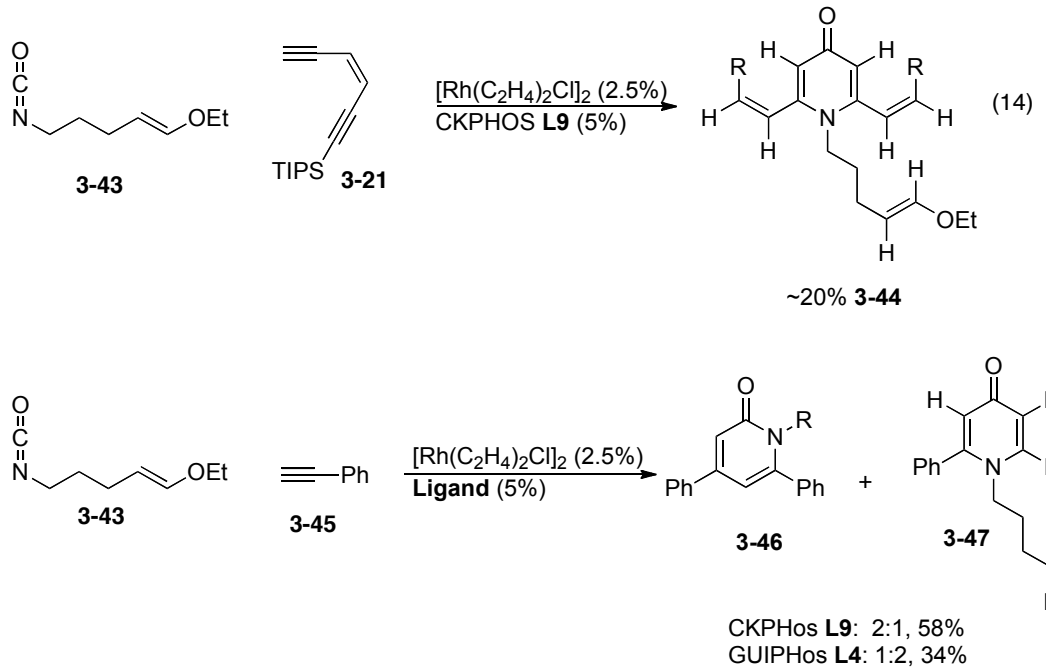
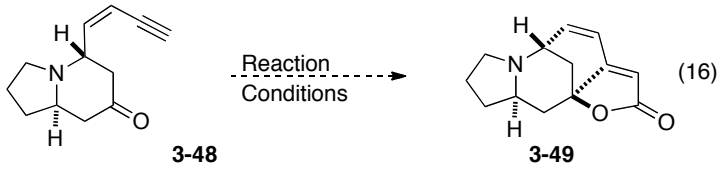
Entry	Oxidant	Result
1	mCPBA	Decomposition
2	OsO_4/NMO	Decomposition
3		No Reaction
4	H_2O_2, dichloroacetone	No Reaction
5	'In situ' DMDO: acetone, Na_2EDTA, oxone, $NaHCO_3$	Decomposition

Table 8

With the oxidation proving more difficult than we could have expected, we briefly sought a new way in which to install the necessary oxygen. We thought that perhaps the use of a 1,2-disubstituted diene (**3-43**) could insert the oxygen during the initial [2+2+2] cycloaddition. While previous results[10] indicate that the development of this reactivity may be difficult, the new ligand, CKPhos (**L9**) had shown such disparate reactivity, that an electron-rich diene, such as **3-43**, may insert. However, in a very brief study of this system, it was seen that the alkene did not insert, rather a second equivalent of alkyne did, to form both 2- and 4-pyridone (eqs. 14 and 15).



The final ring can still be formed without alpha oxidation to form deoxy-Secu'amamine A (**3-49**). In the retrosynthetic analysis, we presented two possible modes of action to close the final ring. The first method explored was the ruthenium-catalyzed Pauson-Khand type cyclization with carbon monoxide. Reaction of the substrate under the high-pressure conditions found in the precedent[6a-c] produced no product of interest (entry 1, Table 9). Changing the metal catalyst to a titanium system did not yield a successful synthesis of the final ring. Removing both the high pressure and the phosphine ligand, but keeping the ruthenium catalyst (entry 3, Table 9) resulted in presumed aromatization of the enyne, in approximately 30% yield (**3-50**).



3-48 **3-49**

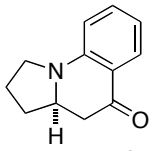
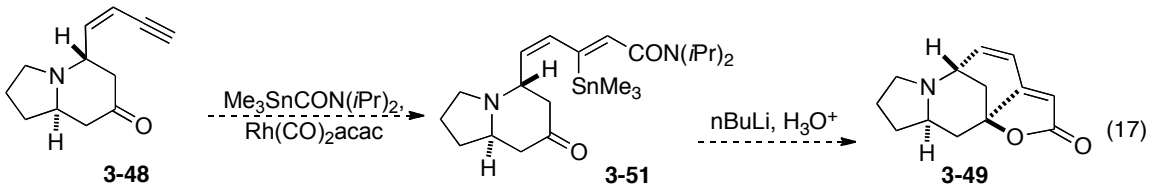
Entry	Reaction Conditions	Result
1	$Ru_3(CO)_{12}$ (10 mol%) $P(4\text{-}CF_3C_6H_4)_3$ (20 mol%) PhMe 155 °C, Fischer-Porter Tube 10 atm CO	No Reaction
2	Cp_2TiCl_2 (10 mol%) PEt_3 (20 mol%) PhMe, 180 °C ~2-5 atm CO	No Reaction
3	$Ru_3(CO)_{12}$ (20 mol%) PhMe, 110 °C 1 atm CO	 30% **3-50**

Table 9

With no initial success with the [2+2+1] cycloaddition, the coupling involving the vinyl stannane was explored. Incorporation of the trimethyl tin-diisopropyl amide onto the alkyne has proved difficult. Only starting material is recovered from attempts on **3-48** (eq 17).



3-48 **3-51** **3-49**

Efforts towards the total synthesis of Secu'amamine A include enantioselective synthesis of the bicyclic core, via a rhodium-catalyzed [2+2+2] cycloaddition between an alkenyl isocyanate and an appropriate diyne. Diastereoselective reduction with Super-Hydride follows. Investigations into both the necessary oxidation and formation of the final lactone are still in progress.

3.6 References

1. (a) Saito, S.; Kotera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y. *Tetrahedron* **1963**, *19*, 2085. (b) Snieckus, V. In *The Alkaloids*; Manske, R. H. F., Ed. The *Securinega* Alkaloids. Academic Press: New York, 1973; Vol. 14, pp. 425. (c) Beutler, J. A.; Brubaker, A. N. *Drugs Fut.* **1987**, *12*, 957.

2. Ohsaki, A.; Ishiyama, H.; Yoneda, K.; Kobayashi, J. *Tetrahedron Lett.* **2003**, *44*, 3097.

3. (a) Ohsaki, A.; Kobayashi, Y.; Yoneda, K.; Kishida, A.; Ishiyama, H. *J. Nat. Prod.* **2007**, *70*, 2003. (b) Ohsaki, A.; Nagaoka, T.; Yoneda, K.; Kishida, A. *Tetrahedron Lett.* **2009**, *50*, 6965.

4. Magnus, P.; Padilla, A. I. *Org. Lett.* **2006**, *8*, 3569.

5. Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562.

6. (a) Chatani, N.; Tobisu, M; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160. (b) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335. (c) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663. (d) Hua, R.; Onozawa, S.-Y.; Tanaka, M. *Organometallics*. **2000**, *19*, 3269.

7. Gotchev, D. B.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 9393.

8. Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Organic Reactions.* **2003**, *62*, 1.

9. Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313.

10. For reviews, see: (a) Perrault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. (b) Keller Friedman, R.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *Pure and Applied Chem.* **2010**, *82*, 1353.

11. Dalton, D. M.; Rovis, T. *Unpublished Results.*

12. Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053.

Chapter 1: Experimental

Predictable Regioselective Insertion of Unsymmetrical, Internal Alkynes in Rhodium-Catalyzed [2+2+2] Cycloadditions with Alkenyl Isocyanates

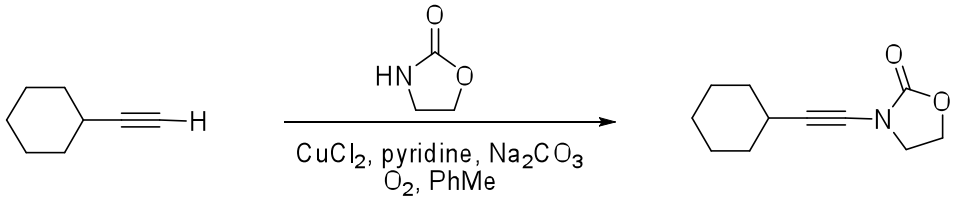
General Methods:

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and $KMnO_4$, followed by heating.

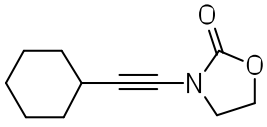
Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a SD-200 HPLC equipped with a UV-1- variable wavelength UV detector using a Chiracel OD-H, AD-H or OJ-H chiral column. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

Synthesis of Alkynes, Isocyanates and Ligands: All ligands (**L1-L7**) and isocyanates and carbodiimides (**1-25, 1-27a-c, 1-29b**) were synthesized via previous methods established within the literature.[11, 13, 14, 17, 18] Alkynes **1-49, 1-49g, 1-53a, 1-53b** were purchased from Aldrich or Alfa Aesar (**1-49g**) and used without further purification. Alkynes **1-49a-h**, **1-50a-f**, **1-51a-b**, **1-53c-d**, **1-54**, 1**-56a-c** and **1-56e** were synthesized via literature methods.[35]

Alkyne **1-56d** was synthesized using a modified method from the current literature[36] and characterization data is shown below.



Synthesis of 1-56d: A 100 mL flame-dried, round bottom flask was charged with $CuCl_2$, Na_2CO_3 and 2-oxazolidinone. The flask was then evacuated and filled with O_2. A 0.4M solution of pyridine in toluene was added to the flask. The reaction mixture was then headed to 70˚C in an oil bath. A 0.2M solution of 1-cyclohexylacetylene was added via syringe pump over a period of 4 hr. The reaction mixture was then stirred for an additional 4 hr at 70˚C. The reaction was then cooled to room temperature, concentrated under vacuum and purified via column chromatography (1:1 hexanes: ethyl acetate) to yield the product in 62% yield.

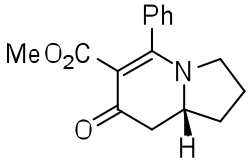


1-56d: *3-(cyclohexylethynyl)oxazolidin-2-one:* Flash Chromatography (1:1 Hexanes: EtOAc) yielded a clear oil (62%); R_f = 0.15 (1:1 Hexanes: EtOAc); IR (Thin Film) n 2930, 2853, 2279, 1977, 1782, 1486,

1409, 1219, 1122, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 4.38 (2H, t, *J* = 7.5 Hz), 3.84 (2H, t, *J* = 8.4 Hz), 2.45 (1H, m), 1.78 (2H, m), 1.67 (2H, m), 1.49-1.26 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) d 75.3, 70.5, 63.1, 47.5, 33.1, 29.1, 26.1, 25.2.

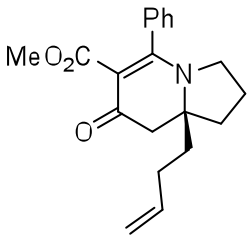
General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and internal, unsymmetrical alkynes: $[Rh(ethylene)_2Cl]_2$ was purchased from Strem Chemical, Inc. and used without further purification. An oven or flame-dried round bottom flask was charged with $[Rh(ethylene)_2Cl]_2$ (0.025 eq) and the phosphoramidite ligand **L** (0.05 eq), and was fitted with a flame-dried reflux condenser and septa in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 3.0 ml toluene was added via syringe and the resulting yellow or orange solution was stirred at ambient temperature under argon flow for 5-15 minutes. To this solution was added a solution of alkyne (1.2 eq) and isocyanate **1-25** or **1-27a-c** (0.15 mmol) in 1 ml of toluene via syringe. After an additional 1 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 12 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution, typically 1:1 hexanes:ethyl acetate to 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.

Spectral Data For [2+2+2] Cycloadducts:



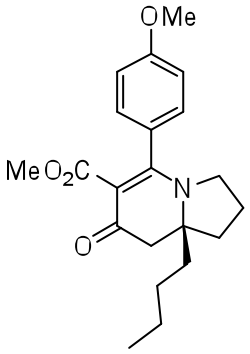
VA-12: *(R)-methyl 7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a clear oil (86%). (+) isomer: $[a]_D = 287^o$ ($CHCl_3$,

c=0.01); HPLC analysis- Chiracel OD-H column 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 17.1 minutes, Minor: 13.4 minutes, 330 nm detection light, %ee: 86%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 3058, 2940, 2873, 1701, 1629, 1521, 1445, 1312, 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.42 (2H, b, m), 7.35 (1H, b, m), 7.26 (2H, b, m), 4.07 (1H, dddd, *J* = 14.2, 7.4, 6.8, 6.8 Hz), 3.52 (1H, ddd, *J* = 11.6, 7.4, 4.8 Hz), 3.34 (3H, s), 3.12 (1H, ddd, *J* = 11.6, 8, 7 Hz), 2.55 (2H, dd, dd, *J* = overlap, cannot distinguish Hz), 2.38 (1H, m), 2.00 (1H, m), 1.89 (1H, m), 1.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.3, 167.5, 165.5, 135.9, 130.0, 129.0, 128.7, 127.7, 127.1, 104.9, 58.2, 50.6, 41.8, 32.3, 24.3; HRMS (TOF) *m/e* calcd ($M-OMe^+$) 240.1019, found 240.1024.

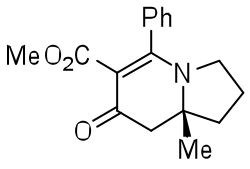


VA-13: *(R)-methyl 8a-(but-3-enyl)-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (75%). (+) isomer: $[a]_D$ = 111.0° ($CHCl_3$, c=0.009); HPLC analysis- Chiracel OJ-H column 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 8.6 minutes, Minor: 7.8 minutes, 330 nm detection light, %ee: 96%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 3058, 2919, 2848, 1737, 1624, 1511, 1440, 1327, 1240, 1184, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.41 (2H, b, m), 7.32 (1H, b, m), 7.25 (2H, b, m), 5.79 (1H, ddt, *J* = 27.2, 5.2, 4 Hz), 5.05 (1H, dd, *J* = 16.8, 1.2 Hz), 4.97 (1H, dd, *J* = 10.4 Hz), 3.46 (1H, ddd, *J* = 12, 6.8, 5.8 Hz), 3.33 (3H, s), 3.14 (1H, ddd, *J* = 11.2, 6.4, 6.2 Hz), 2.67 (1H, d, *J* = 16.0 Hz), 2.55 (1H, d, *J* = 15.6 Hz), 2.20 (2H, m), 2.04 (2H, m), 1.98-1.77 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.0, 167.4, 165.0, 137.5, 136.5, 130.2, 128.9, 128.7, 128.0, 127.2, 115.6, 104.1, 65.6,

52.2, 51.1, 45.5, 36.7, 33.2, 28.6, 23.9; HRMS (TOF) *m/e* calcd (M +Na^+) 348.1570, found 348.1554.

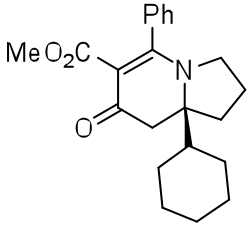


VA-14: *(R)-methyl 8a-butyl-5-(4-methoxyphenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (90%). (+) isomer: $[a]_D$ = 129.1° ($CHCl_3$, c=0.007); HPLC analysis- Chiracel OJ-H column 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 20.0 minutes, Minor: 16.9 minutes, 330 nm detection light, %ee: 98%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2960, 2879, 1721, 1629, 1511, 1445, 1337, 1301, 1250, 1158, 1066, 830, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.23 (2H, b, m), 6.91 (2H, b, m), 3.83 (3H, s), 3.48 (1H, ddd, *J* = 6, 7.2, 12 Hz), 3.40 (3H, s), 3.19 (1H, ddd, *J* = 10.8, 5.6, 5.2 Hz), 2.64 (1H, d, *J* = 16.0 Hz), 2.50 (1H, d, *J* = 15.6 Hz), 2.15 (1H, m), 1.97-1.80 (5H, m), 1.69 (1H, m), 1.46-1.18 (3H, m), 0.90 (3H, t, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 187.9, 167.6, 164.7, 160.9, 129.4, 129.1, 128.4, 114.3, 113.6, 103.7, 65.3, 55.3, 52.3, 51.0, 45.3, 36.3, 33.6, 26.2, 23.8, 23.0, 14.0; HRMS (TOF) *m/e* calcd (M +H+$^+$) 358.2010, found 358.2000.

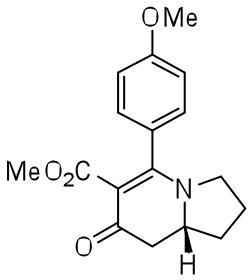


VA-15: *(R)-methyl 8a-methyl-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (65%). (+) isomer: $[a]_D$ = 137.5° ($CHCl_3$, c=0.002); HPLC analysis- Chiracel OD-H column 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 14.1 minutes, Minor: 11.1 minutes, 330 nm detection light, %ee: 97%;

R_f = 0.05 (100% EtOAc); IR (Thin Film) n 3001, 2884, 1721, 1624, 1516, 1440, 1342, 1291, 1184, 1102, 1025, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.42 (3H, b, m), 7.32 (1H, b, m), 7.26 (1H, b, m), 3.52 (1H, ddd, *J* = 11.2, 5.8, 4.8 Hz), 3.35 (3H, s), 3.10 (1H, ddd, *J* = 11.6, 7.2, 7.2 Hz), 2.71 (1H, d, *J* = 15.6 Hz), 2.48 (1H, d, *J* = 15.6 Hz), 2.09 (1H, m), 1.97-1.65 (3H, m), 1.42 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.1, 167.5, 164.5, 136.2, 130.0, 128.9, 128.6, 127.8, 127.0, 103.8, 62.8, 51.2, 51.0, 48.0, 39.8, 23.1, 21.8; HRMS (TOF) *m/e* calcd ($M+H^+$) 286.1430, found 286.1430.

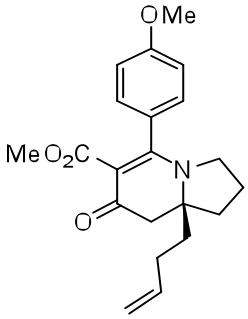


VA-16: *(R)-methyl 8a-cyclohexyl-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (80%). (+) isomer: $[a]_D$ = 116.9° (CHCl3, c=0.008); HPLC analysis- Chiracel OD-H column 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 12.9 minutes, Minor: 19.1 minutes, 330 nm detection light, %ee: 97%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 3017, 2930, 2843, 1716, 1624, 1522, 1306, 1224, 1148, 1066, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.44-7.09 (4H, b, m), 7.28 (1H, b, m), 3.35 (3H, s), 3.30 (1H, m), 3.20 (1H, m), 2.67 (2H, m), 2.22 (2H, m), 1.91-1.63 (8H, m), 1.40-.82 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.4, 165.9, 137.0, 130.5, 129.0, 128.8, 128.3, 127.7, 104.1, 68.9, 64.6, 54.4, 51.4, 44.3, 39.5, 32.9, 27.4, 27.3, 26.5, 26.4, 24.9; HRMS (TOF) *m/e* calcd ($M+H^+$) 354.2060, found 354.2060.



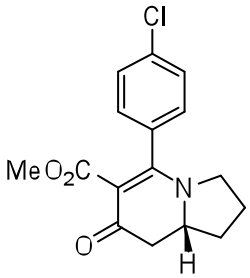
VA-18a: *(R)-methyl 5-(4-methoxyphenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography

(EtOAc) yielded a yellow oil (80%). (+) isomer: $[a]_D$ = 52.6° ($CHCl_3$, c=0.011); HPLC analysis- Chiracel AD-H column 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 18.9 minutes, Minor: 14.7 minutes, 330 nm detection light, %ee: 70%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2971, 2879, 2827, 1706, 1639, 1623, 1516, 1440, 1322, 1235, 1184, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.24 (2H, b, m), 6.92 (2H, b, m), 4.07 (1H, dddd, *J* = 7.2, 12.8, 14, 15.4 Hz), 3.83 (3H, s), 3.57 (1H, ddd, *J* = 6.2, 6.4, 11.2 Hz), 3.39 (3H, s), 3.15 (1H, ddd, *J* = 6.2, 7.6, 11.6 Hz), 2.50 (2H, m), 2.35 (1H, m), 2.04-1.71 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.3, 167.8, 165.4, 161.0, 129.3, 129.2, 127.9, 114.3, 113.9, 105.0, 57.8, 55.5, 51.3, 50.8, 41.8, 31.8, 24.3; HRMS (TOF) *m/e* calcd (M +Na^+) 324.1206, found 324.1192.

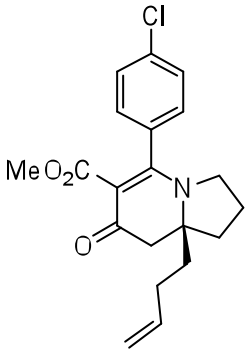


VA-18b: *(R)-methyl 8a-(but-3-enyl)-5-(4-methoxyphenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (94%). (+) isomer: $[a]_D$ = 175.9° ($CHCl_3$, c=0.008); HPLC analysis- Chiracel OJ-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 11.9 minutes, Minor: 10.0 minutes, 330 nm detection light, %ee: 93%; R_f = 0.08 (100% EtOAc); IR (Thin Film) n 3078, 2971, 2838, 1711, 1706, 1624, 1609, 1491, 1445, 1312, 1240, 1143, 1086, 1025, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 7.24 (2H, b, m), 6.91 (2H, b, m), 5.80 (1H, ddt, *J* = 17.1, 10.2, 6 Hz), 5.06 (1H, d, *J* = 17.1 Hz), 4.99 (1H, d, *J* = 9.9 Hz), 3.83 (3H, s), 3.50 (1H, m), 3.41 (3H, s), 3.21 (1H, ddd, *J* = 15.6, 11.5, 6 Hz), 2.68 (1H, d, *J* = 15.9 Hz), 2.52 (1H, d, *J* = 15.9 Hz), 2.19 (2H, m), 2.04 (2H, m), 1.73-1.99 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 187.9, 167.8, 164.9, 161.2, 137.5, 129.6, 129.4, 129.4, 129.3, 128.6,

115.6, 104.2, 65.3, 55.5, 52.5, 51.3, 45.5, 36.6, 33.4, 28.6, 24.1; HRMS (TOF) *m/e* calcd (M^+) 356.1856, found 356.1844.

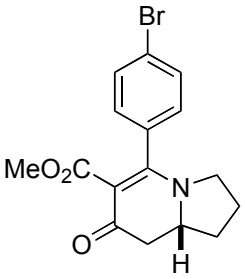


VA-19a: *(R)-methyl 5-(4-chlorophenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (83%). (+) isomer: $[a]_D$ = 303.8^o ($CHCl_3$, c=0.004); HPLC analysis- Chiracel OD-H 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 22.2 minutes, Minor: 14.5 minutes, 330 nm detection light, %ee: 77%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2986, 2955, 1721, 1634, 1516, 1434, 1301, 1194, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.40 (2H, b, m), 7.29 (1H, b, m), 7.19 (1H, b, m), 4.05 (1H, dddd, *J* = 14, 7.6, 7.4, 7.2 Hz), 3.47 (1H, ddd, *J* = 12, 7.6, 4 Hz), 3.39 (3H, s), 3.11 (1H, ddd, *J* = 11.6, 7.2, 5.6 Hz), 2.53 (2H, d, d, *J* = overlapping, cannot deconvolute Hz), 2.37 (1H, m), 2.05-1.71 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.2, 167.2, 164.4, 136.1, 134.2, 129.2, 129.1, 128.5, 104.8, 58.2, 51.3, 50.6, 41.7, 32.2, 24.2; HRMS (TOF) *m/e* calcd (M+ Na^+) 328.0711, found 328.0701.

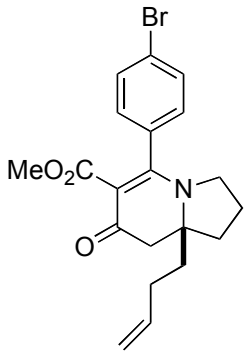


VA-19b: *(R)-methyl 8a-(but-3-enyl)-5-(4-chlorophenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (57%). (+) isomer: $[a]_D$ = 159.4^o ($CHCl_3$, c=0.01); HPLC analysis- Chiracel OD-H 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 9.5 minutes, Minor: 12.5 minutes, 330 nm detection light, %ee: 94%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2965, 2884, 1716, 1634, 1501, 1434, 1317, 1199, 1137, 1071 cm^{-1}; ^1H NMR (300

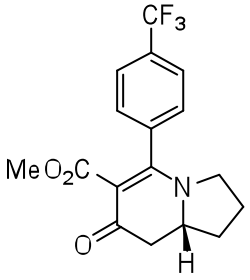
MHz, $CDCl_3$) d 7.38 (2H, b, m), 7.22 (2H, b, m), 5.77 (1H, ddt, *J* = 17.1, 10.5, 6 Hz), 5.05 (1H, dd, *J* = 17.0, 0.9 Hz), 4.99 (1H, d, *J* = 10.2 Hz), 3.47-3.39 (4H, s, m), 3.13 (1H, ddd, *J* = 11.7, 6.3, 6.2 Hz), 2.67 (1H, d, *J* = 15.9 Hz), 2.55 (1H, d, *J* = 15.9 Hz), 2.21 (2H, m), 2.09-1.74 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) d 187.9, 167.2, 163.9, 137.3, 136.3, 134.9, 129.4, 129.2, 115.7, 104.0, 65.7, 52.1, 51.2, 45.5, 36.7, 33.1, 28.5, 23.8; HRMS (TOF) *m/e* calcd (M^+) 360.1361, found 360.1351.



VA-20a: *(R)-methyl 5-(4-bromophenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (73%). (+) isomer: $[a]_D$ = 284.0° ($CHCl_3$, c=0.001); R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2943, 1714, 1630, 1525, 1314 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.58-7.56 (2H, b, m), 7.12 (1H, b, m), 7.23-7.13 (1H, b,m), 4.05 (1H, m), 3.45 (1H, ddd, 15.8, 4.0, 3.8 Hz), 3.40 (3H, s), 3.11 (1H, m), 2.60-2.50 (2H, m), 2.37 (1H, m), 1.99 (1H, m), 1.88 (1H, m), 1.76 (1H, m); NMR (100 MHz, $CDCl_3$) d 187.9, 167.0, 164.3, 134.4, 131.9, 131.9, 124.1, 104.5, 58.0, 51.1, 50.4, 41.3, 31.9, 24.0; HRMS (ESI) *m/e* calcd ($M+H^+$) 350.0386, found 340.0376.

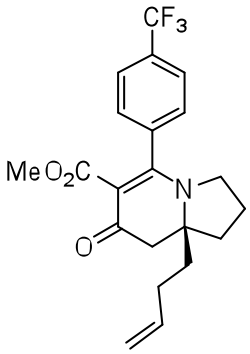


VA-20b: *(R)-methyl 5-(4-bromophenyl)-8a-(but-3-en-1-yl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (57%). (+) isomer: $[a]_D = 83.0^o$ ($CHCl_3$, c=0.003); $R_f = 0.05$ (100% EtOAc); IR (Thin Film) n 2943, 1718, 1639, 1514, 1440, 1315, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.52-7.34 (3H, b, m), 7.10-7.05 (2H, b, m), 5.71 (1H, m), 5.04 (1H, d, 17.2 Hz), 4.93 (1H, d, 10 Hz), 3.33 (3H, s), 3.07 (1H, ddd, 6.2, 6.4, 11.6 Hz), 2.60 (1H, d, 16 Hz), 2.50 (1H, d, 16 Hz), 2.18-2.11 (2H, m), 1.97-1.95 (2H, m), 1.88-1.66 (5H, m); NMR (100 MHz, $CDCl_3$) d 188.2, 167.4, 164.3, 137.5, 135.6, 132.4, 132.4, 124.9, 116.0, 104.3, 66.0 52.4, 51.5, 45.7, 37.0, 33.3, 28.8, 24.0; HRMS (ESI) *m/e* calcd ($M+H^+$) 404.0856, found 404.0851.

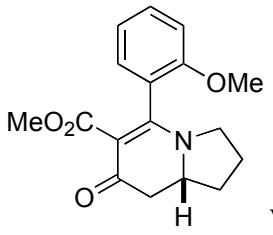


VA-21a: *(R)-methyl 7-oxo-5-(4-(trifluoromethyl)phenyl)-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (33%). (+) isomer: $[a]_D = 202.0^o$ ($CHCl_3$, c=0.007); HPLC analysis- Chiracel OD-H 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 17.9 minutes, Minor: 12.8 minutes, 330 nm detection light, %ee: 82%; $R_f = 0.05$ (100% EtOAc); IR (Thin Film) n 2960, 1711, 1624, 1516, 1424, 1317, 1173, 1117, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.07 (2H, b, t, J = 8.4 Hz), 7.49 (1H, b, d, J = 8.0 Hz), 7.39 (1H, b,d, J = 7.6 Hz), 4.07 (1H, dddd, J = 14,

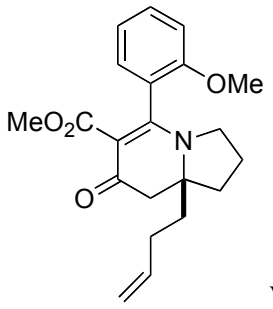
11.6, 7.6, 6.4 Hz), 3.45-3.40 (4H, s, m), 3.09 (1H, ddd, *J* = 11.6, 8.8, 6 Hz), 2.65-2.49 (2H, m), 2.41 (1H, dddd, *J* = 12.4, 6.6, 6, 3.2 Hz), 2.02 (1H, m), 1.91 (1H, m), 1.79 (1H, m); NMR (100 MHz, $CDCl_3$) d 188.1, 166.9, 164.1, 139.5, 132.0, 131.6, 128.2, 127.3, 126.0, 125.8, 104.6, 58.4, 51.3, 50.5, 41.8, 32.3, 24.2; HRMS (ESI) *m/e* calcd ($M+H^+$) 340.1155, found 340.1154.



VA-21b: *(R)-methyl 8a-(but-3-enyl)-7-oxo-5-(4-(trifluoromethyl)phenyl)-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate***:** Flash Chromatography (EtOAc) yielded a yellow oil (29%). (+) isomer: $[a]_D$ = 117.0° ($CHCl_3$, c=0.01); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 10.5 minutes, Minor: 8.9 minutes, 330 nm detection light, %ee: 96%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 3068, 2945, 2884, 1721, 1634, 1516, 1440, 1322, 1168, 1122, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.70 (2H, b, m), 7.42 (2H, b, m), 5.79 (1H, ddt, *J* = 23, 14, 8.4 Hz), 5.07 (1H, dd, *J* = 22.8, 2 Hz), 5.02 (1H, dd, *J* = 13.6, 1.6 Hz), 3.47-3.36 (4H, s, m), 3.09 (1H, ddd, *J* = 15.6, 9.6, 9.2 Hz), 2.70 (1H, d, *J* = 21.6 Hz), 2.62 (1H, d, *J* = 21.2 Hz), 2.24 (2H, m), 2.13-1.71 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 187.9, 166.9, 163.6, 140.1, 137.2, 128.4, 127.5, 126.0, 126.0, 125.8, 115.8, 104.0, 65.9, 51.9, 51.3, 45.5, 36.7, 32.9, 28.5, 23.6; HRMS (ESI) *m/e* calcd ($M+Na^+$) 416.1444, found 416.1426.

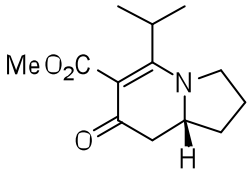


VA-22a: *(R)-methyl 5-(2-methoxyphenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (44%). (+) isomer: $[a]_D$ = 148° ($CHCl_3$, c=0.002); R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2945, 1714, 1638, 1521, 1460, 1435, 1254, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.38 (1H, dq, 1.6, 8.4 Hz), 7.09 (1H, m), 7.01-6.94 (2H, m), 4.02 (1H, m), 3.89 (2H, s), 3.81 (1H, s), 3.42 (1 H s), 3.35 (2H, s), 3.15 (1H, m), 2.58 (1H, m), 2.53 (1H, d, 8.4 Hz), 2.46 (1H, d, 15.2 Hz) 2.37 (1H, m), 2.00 (1H, m), 1.94-1.68 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.2, 167.3, 163.9, 156.0, 131.4, 128.5, 125.3, 120.8, 103.8, 56.2, 51.1, 42.0, 32.9, 23.9; (Rotomer carbons can also be seen). HRMS (ESI) *m/e* calcd ($M+H^+$) 302.1380, found 302.1387.

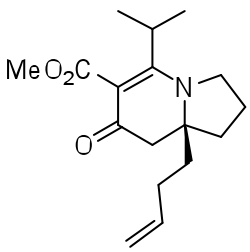


VA-22b: *(R)-methyl 8a-(but-3-en-1-yl)-5-(2-methoxyphenyl)-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (77%). (+) isomer: $[a]_D$ = 74° ($CHCl_3$, c=0.006); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH (5% diethylamine), 1.0 ml/min, Major: 24.2 minutes, Minor: 21.5 minutes, 330 nm detection light, %ee: 98%; R_f = 0.05 (100% EtOAc); R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2945, 1715, 1638, 1521, 1460, 1435, 1254, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.38 (1H, m), 7.06 (1H, m), 6.96-6.92 (2H, m), 5.78 (1H,

dddd 5.2, 6.4, 10.4, 16.8 Hz), 5.03 (1H, dd, 0.8, 17.2 Hz), 4.96 (1H, d, 10 Hz), 3.86 (2H, s), 3.76 (1H, s), 3.42 (1H, s), 3.40-3.30 (3H, s overlaps with m), 3.17 (1H, ddd, *J* = 6.2, 7.6, 12 Hz), 2.71-2.57 (2H, m), 2.31-1.63 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 187.8, 167.1, 162.8, 156.1, 137.7, 131.4, 127.8, 125.8, 121.0, 115.2, 111.3, 65.8, 56.1, 50.9, 50.2, 46.2, 36.9, 32.4, 28.4, 22.8; HRMS (ESI) *m/e* calcd ($M+H^+$) 356.1843, found 356.1856.

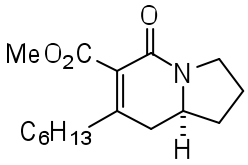


VA-23a: *(R)-methyl 5-isopropyl-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (39%). (+) isomer: $[a]_D$ = 84.2^o ($CHCl_3$, c=0.005); HPLC analysis- Chiracel OD-H 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 10.3 minutes, Minor: 8.5 minutes, 330 nm detection light, %ee: 74%; R_f = 0.10 (100% EtOAc); R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2955, 2858, 1705, 1629, 1527, 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 3.82-3.73 (4H, s, m), 3.55 (1H, ddd, *J* = 12.8, 10.8, 6.8 Hz), 2.96 (1H, ddd, *J* = 14, 10.8, 7.2 Hz), 2.46 (1H, dd, *J* = 15.8, 4 Hz), 2.33-2.25 (2H, m), 2.19 (1H, m), 1.88 (1H, m), 1.65 (2H, m), 1.32 (3H, d, *J* = 7.6 Hz), 1.23 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.6, 169.7, 169.4, 59.1, 51.9, 48.7, 41.3, 32.9, 32.0, 24.2, 19.7, 18.9; HRMS (ESI) *m/e* calcd ($M+Na^+$) 260.1257, found 260.1248.

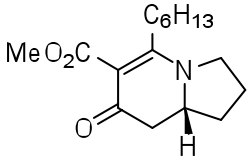


VA-23b: *(R)-methyl 8a-(but-3-enyl)-5-isopropyl-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate***:** Flash Chromatography (EtOAc) yielded a yellow oil (46%). (+) isomer:

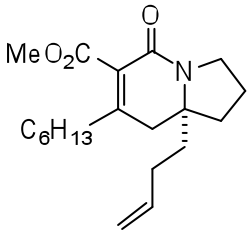
$[a]_D = 53.1^o$ ($CHCl_3$, c=0.007); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 12.6 minutes, Minor: 9.5 minutes, 330 nm detection light, %ee: 99%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 2935, 1726, 1635, 1530, 1446, 1301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.72 (1H, ddt, *J* = 17.4, 10.2, 6.3 Hz), 5.00 (1H, dd, *J* = 17.3, 1.5 Hz), 4.94 (1H, dd, *J* = 10.4, 1.2 Hz), 3.77 (3H, s), 3.65 (2H, m), 2.97 (1H, m), 2.53 (1H, d, *J* = 15.9 Hz), 2.45 (1H, d, *J* = 16.5 Hz), 2.23-1.86 (6H, m), 1.70 (2H, m), 1.49 (1H, m), 1.31 (3H, d, *J* = 7.2 Hz), 1.20 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.1, 169.3, 168.3, 137.6, 115.4, 104.4, 66.1, 51.8, 49.0, 45.1, 36.2, 32.8, 31.2, 28.7, 23.0, 19.9, 18.6; HRMS (ESI) *m/e* calcd (M^+) 292.1907, found 292.1901.



LA-11a: *(S)-methyl 7-hexyl-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (8%). (-) isomer: $[a]_D = 3.0^o$ ($CHCl_3$, c=0.003); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 9.3 minutes, Minor: 8.8 minutes, 220 nm detection light, %ee: 60%; R_f = 0.15 (100% EtOAc); IR (Thin Film) n 2955, 2858, 1731, 1655, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 3.81 (3H, s), 3.73-3.58 (2H, m), 3.45 (1H, ddd, *J* = 12.6, 10. 7.6 Hz), 2.40 (1H, dd, *J* = 17.6, 4.4 Hz), 2.32-2.15 (4H, m), 1.99 (1H, m), 1.77 (1H, m), 1.59-1.55 (4H, m), 1.29-1.24 (5H, b, m), 0.85 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.1, 161.1, 153.3, 127.4, 55.9, 52.4, 44.4, 35.0, 34.8, 33.7, 31.7, 29.3, 27.6, 23.2, 22.7, 14.3; HRMS (ESI) *m/e* calcd ($M+H^+$) 280.1907, found 280.1910.

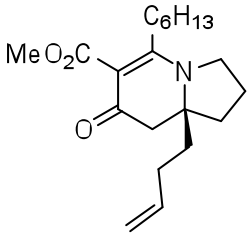


VA-24a: *(R)-methyl 5-hexyl-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (52%). (+) isomer: $[a]_D$ = 30.4° (CHCl3, c=0.01); HPLC analysis- Chiracel OD-H 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 9.1 minutes, Minor: 8.1 minutes, 330 nm detection light, %ee: 65%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2960, 2950, 2858, 1721, 1685, 1634, 1542, 1434, 1317, 1194, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 3.77-3.70 (4H, s, m), 3.53 (1H, ddd, *J* = 11, 11, 7.2 Hz), 2.69-2.53 (2H, m), 2.49 (1H, dd, *J* = 15.2, 4.4 Hz), 2.35-2.27 (2H, dd, m, *J* = 15.6 Hz), 2.13 (1H, m), 1.88 (1H, m), 1.72-1.61 (3H, m), 1.48 (1H, m), 1.41-1.27 (6H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.2, 168.4, 168.2, 103.2, 58.2, 51.6, 48.3, 41.9, 32.6, 31.6, 29.7, 28.1, 23.6, 22.7, 14.2; HRMS (ESI) *m/e* calcd ($M+H^+$) 280.1904, found 280.1907.

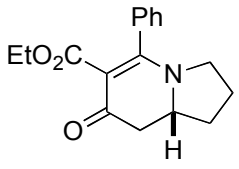


LA-11b: *(S)-methyl 8a-(but-3-enyl)-7-hexyl-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (24%). (-) isomer: $[a]_D$ = 64.0° (CHCl3, c=0.002); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 8.2 minutes, Minor: 9.4 minutes, 220 nm detection light, %ee 62%; R_f = 0.25 (100% EtOAc); IR (Thin Film) n 2945, 2863, 2356, 1737, 1650, 1614, 1429, 1276, 1219, 1096, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.73 (1H, dddd, *J* = 16.8, 10.4, 6.4, 5.2 Hz), 4.98 (1H, d, *J* = 20.8 Hz), 4.94 (1H, d, *J* = 10.4 Hz), 3.80 (3H, s), 3.64 (1H, ddd, *J* = 12.4, 8.4, 6.2 Hz), 3.48 (1H, ddd, *J* = 12.4, 7.2, 6.4 Hz), 2.48 (1H, d, *J* = 17.2 Hz), 2.34 (1H, d, *J* = 17.2 Hz), 2.28 (1H, m), 2.18 (1H, m), 2.00-

1.88 (4H, m), 1.76-1.59 (2H, m), 1.54-1.35 (4H, m), 1.32-1.18 (6H, m), 0.85 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.1, 137.8, 126.8, 115.4, 94.7, 63.1, 52.4, 44.7, 39.2, 38.3, 35.4, 34.9, 31.8, 29.8, 29.8, 29.4, 27.6, 22.8, 22.1, 14.4; HRMS (ESI) *m/e* calcd (M +H$^+$) 334.2377, found 334.2375.

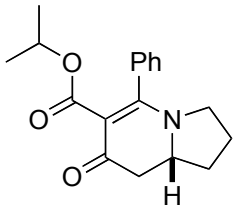


VA-24b: *(R)-methyl 8a-(but-3-enyl)-5-hexyl-7-oxo-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (38%). (+) isomer: $[a]_D$ = 31.0^o ($CHCl_3$, c=0.005); HPLC analysis- Chiracel OD-H 80:20 hexanes:irPrOH, 1.0 ml/min, Major: 10.3, Minor: 9.1, 360 nm detection light, %ee 96%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2855, 2853, 1711, 1680, 1706, 1521, 1470, 1419, 1312, 1209, 1132, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 5.70 (1H, ddt, *J* = 17, 10.4, 6.4 Hz), 4.99 (1H, dd, *J* = 17.2, 1.2 Hz), 4.94 (1H, dd, *J* = 10.6, 1.2 Hz), 3.77 (3H, s), 3.71 (1H, ddd, *J* = 18.6, 7, 4.4 Hz), 3.63 (1H, m), 2.62-2.54 (3H, d, m, *J* = 15.6 Hz), 2.45 (1H, d, *J* = 15.6 Hz), 2.22 (1H, ddd, *J* = 16, 6.6, 3.6 Hz), 2.17-1.98 (3H, m), 1.93-1.83 (2H, m), 1.76-1.66 (3H, m), 1.52-1.24 (7H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 187.9, 168.3, 167.4, 137.5, 115.5, 102.4, 65.6, 51.5, 48.5, 45.8, 36.5, 33.0, 31.6, 31.5, 29.8, 28.6, 28.1, 22.8, 22.4, 14.2; HRMS (ESI) *m/e* calcd (M +H$^+$) 334.2377, found 334.2368.

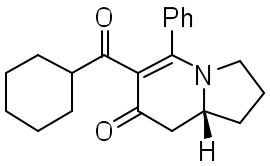


VA-26a: *(R)-ethyl 7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (78%). (+) isomer: $[a]_D$ = 246^o ($CHCl_3$, c=0.007); HPLC analysis- Chiracel OD-H 70:30 hexanes:irPrOH,

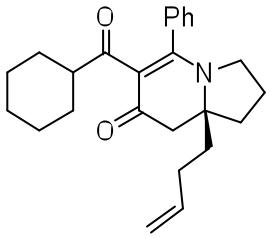
1.0 ml/min, Major: 14.7, Minor: 12.4, 330 nm detection light, %ee 82%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2978, 1713, 1630, 1525, 1451, 1312, 1182, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.39-7.25 (5H, m), 4.05 (1H, dddd, *J* = 6.8, 7.2, 7.2 14 Hz), 3.81-3.66 (2H, m), 3.49 (1H, ddd, *J*= 4.4, 8, 11.6 Hz), 3.09 (1H, ddd, *J* = 5.6, 7.6, 12 Hz), 2.56-2.44 (2H, m), 2.35 (1H, m), 1.97 (1H, m), 1.86 (1H, m), 1.73 (1H, m), 0.70 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.0, 166.5, 164.5, 135.7, 129.7, 128.6, 128.3, 127.6, 127.0, 105.0, 59.5, 57.9, 50.2, 41.3, 32.0, 24.0, 13.6; HRMS (ESI) *m/e* calcd ($M+H^+$) 286.1438, found 286.1446.



VA-27a: *(R)-isopropyl 7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (62%). (+) isomer: $[a]_D = 168^o$ ($CHCl_3$, c=0.002); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 22.0, Minor: 17.8, 330 nm detection light, %ee 73%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2976, 1709, 1628, 1579, 1451, 1367, 1182, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.42-7.31 (5H, b, m), 4.72 (1H, septet, *J* = 6.4 Hz), 4.12 (1H, m), 3.52 (1H, ddd, *J*= 4, 7.4, 11.6 Hz), 3.12 (1H, ddd, *J* = 7.2, 7.6, 11.6 Hz), 2.59 (1H, s), 2.57 (1H, d, *J*= 3.2 Hz), 2.38 (1H, m), 2.00 (1H, m), 1.91 (1H, m), 1.78 (1H, m) 0.95 (3H, d, *J* = 6.4 Hz), 0.56 (3H, d, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.0, 166.0, 164.4, 135.6, 129.7, 128.7, 128.3, 127.8, 127.3, 105.3, 66.8, 57.8, 50.3, 41.1, 31.9, 24.0, 21.6, 20.7; HRMS (ESI) *m/e* calcd ($M+H^+$) 300.1595, found 300.1594.

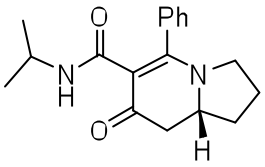


VA-28a: *(R)-6-(cyclohexanecarbonyl)-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (40%). (+) isomer: $[a]_D$ = 55.0° ($CHCl_3$, c=0.005); HPLC analysis- Chiracel OD-H 80:20 hexanes:irPrOH, 1.0 ml/min, Major: 15.3 minutes, Minor: 12.1 minutes, 360 nm detection light, %ee 90%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2930, 2853, 2366, 2320, 1690, 1614, 1516, 1322, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.65-7.27 (4H, m), 7.14 (1H, d, *J* = 6.8 Hz), 3.97 (1H, dddd, *J* = 13.8, 7.2, 7, 6.8 Hz), 3.40 (1H, ddd, *J* = 12, 7.2, 4 Hz), 3.14 (1H, ddt, *J* = 11.8, 11.6, 3.2 Hz), 3.01 (1H, ddd, *J* = 12, 8, 6 Hz), 2.55-2.43 (2H, m), 2.31 (1H, m), 1.91 (1H, m), 1.82 (1H, m), 1.79-1.51 (5H, m), 1.23-0.93 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 205.4, 189.4, 166.8, 136.2, 129.5, 128.7, 128.5, 128.1, 126.6, 113.3, 58.1, 50.5, 49.4, 42.3, 32.2, 30.1, 28.5, 26.6, 26.4, 26.0, 24.1; HRMS (TOF) *m/e* calcd (M +Na^+) 346.1782, found 346.1782.

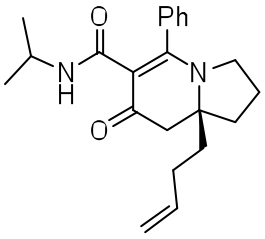


VA-28b: *(R)-8a-(but-3-enyl)-6-(cyclohexanecarbonyl)-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (40%). (+) isomer: $[a]_D$ = 136.4° ($CHCl_3$, c=0.005); HPLC analysis- Chiracel OD-H 80:20 hexanes:irPrOH, 1.0 ml/min, Major: 9.0 minutes, Minor: 8.0 minutes, 360 nm detection light, %ee 95%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 3073, 2920, 2863, 1534, 1506, 1496, 1455, 1322, 1276, 1009, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.44-7.31 (4H, m), 7.11 (1H, m), 5.78 (1H, dddd, *J* = 17, 10.4, 6, 5.2 Hz), 5.05 (1H, dd, *J* = 17.2, 1.2 Hz), 4.99 (1H, d, *J* = 10.4 Hz), 3.41 (1H, ddd, *J* = 12.4,

6.8, 6 Hz), 3.17-3.08 (2H, m), 2.74 (1H, d, *J* = 16.0 Hz), 2.52 (1H, d, *J* = 16.0 Hz), 2.22-2.17 (2H, m), 2.04-1.56 (11H, m), 1.32-1.02 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 205.0, 189.3, 166.4, 137.4, 136.9, 129.9, 128.8, 128.6, 128.3, 126.9, 115.7, 112.6, 65.6, 52.1, 49.4, 46.1, 36.6, 33.2, 30.6, 28.6, 28.1, 26.8, 26.4, 25.9, 23.7; HRMS (TOF) *m/e* calcd (M +H^+) 377.2355, found 377.2361.

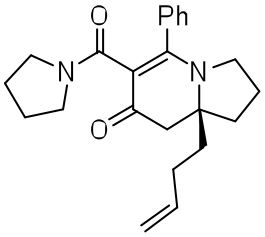


VA-29a: *(R)-N-isopropyl-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxamide:* Flash Chromatography (EtOAc) yielded a yellow oil (91%). (+) isomer: $[a]_D$ = 28.0^o ($CHCl_3$, c=0.006); HPLC analysis- Chiracel OD-H 80:20 hexanes:irPrOH, 1.0 ml/min, Major: 11.5 minutes, Minor: 12.9 minutes, 360 nm detection light, %ee 11%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 3257, 3058, 2981, 2873, 1629, 1603, 1506, 1455, 1337, 1296, 753, 718, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 8.99 (1H, b,m), 7.39 (4H, b,m), 7.17 (1H, b, m), 4.06 (1H, m), 3.96 (1H, m), 3.54 (1H, ddd, *J* = 10.8, 6.8, 6.2 Hz), 3.08 (1H, ddt, *J* = 12.4, 7.6, 7.6 Hz), 2.57 (1H, d, *J* = 4.0 Hz), 2.55 (1H, s), 2.37 (1H, ddt, *J* = 18, 12.4, 5.6 Hz), 1.96 (1H, m), 1.87 (1H, m), 1.75 (1H, m), 1.08 (6H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.7, 170.0, 165.1, 137.3, 129.4, 128.7, 128.5, 127.2, 126.3, 104.7, 57.4, 50.9, 42.5, 40.3, 31.7, 24.2, 23.4, 23.1; HRMS (ESI) *m/e* calcd (M +Na^+) 321.1573, found 321.1578.



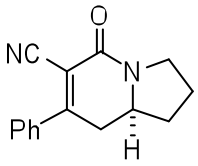
VA-29b: *(R)-8a-(but-3-enyl)-N-isopropyl-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxamide:* Flash Chromatography (EtOAc) yielded a yellow oil (91%). (+) isomer:

$[a]_D$ = 79.0^o ($CHCl_3$, c=0.007); HPLC analysis- Chiracel OD-H 80:20 hexanes:irPrOH, 1.0 ml/min, Major: 8.2 minutes, Minor: 7.2 minutes, 360 nm detection light, %ee 56%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 3268, 2971, 2950, 1639, 1598, 1486, 1440, 1291, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 8.95 (1H, b,m), 7.43 (2H, m), 7.30 (2H, m), 7.17 (1H, m), 5.79 (1H, ddt, *J* = 9.2, 5.2, 4.8 Hz), 5.06 (1H, d, *J* = 17.2 Hz), 5.01 (1H, d, *J* = 10.0 Hz), 3.96 (1H, ddd, *J* = 13.2, 6.6, 6.4 Hz), 3.40 (1H, ddd, *J* = 12.4, 6.8, 6.2 Hz), 3.12 (1H, ddt, *J* = 12, 6.4, 6.2 Hz), 2.75 (1H, d, *J* = 16.4 Hz), 2.55 (1H, d, *J* = 16.4 Hz), 2.20 (2H, m), 2.08 (2H, m), 1.93-1.80 (4H, m), 1.10 (3H, d, *J* = 6.4 Hz), 1.07 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.3, 168.1, 165.0, 137.8, 137.4, 129.6, 128.7, 128.5, 127.3, 126.7, 115.7, 103.8, 64.9, 52.4, 46.4, 40.3, 36.6, 32.4, 28.7, 23.7, 23.5, 23.1; HRMS (TOF) *m/e* calcd (M +Na^+) 375.2043, found 375.2044.

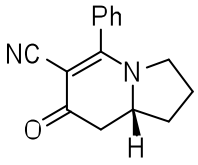


VA-30b: *(R)-8a-(but-3-enyl)-5-phenyl-6-(pyrrolidine-1-carbonyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (46%). (+) isomer: $[a]_D$ = 64.5 ($CHCl_3$, c=0.002); HPLC analysis- Chiracel OD-H 70:30 hexanes:irPrOH, 1.0 ml/min, Major: 8.4 minutes, Minor: 9.4 minutes, 360 nm detection light, %ee 99%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2971, 2914, 2341, 1762, 1629, 1557, 1465, 1431, 1306, 1212, 1147, 1082, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.40-7.37 (5H, m (b, under sharp)), 5.81 (1H, ddt, *J* = 17, 10.4, 6.4 Hz), 5.06 (1H, dd, *J* = 17.2, 1.2 Hz), 5.00 (1H, d, *J* = 10.0 Hz), 3.45-3.38 (2H, ddd; b, m, *J* = 11.2, 7.2, 5.6 Hz), 3.30 (1H, b, m), 3.13 (1H, ddd, *J* = 11.2, 8.2, 7.2 Hz), 2.89-2.66 (3H, b,m; b, d, *J* = 16.8 Hz), 2.48 (1H, d, *J* = 16.0 Hz), 2.25-2.03 (4H, b, m), 1.95-1.78 (5H, m), 1.70

(2H, b, m), 1.36 (1H, b, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 185.3, 167.0, 137.8, 134.9, 138.7, 115.5, 110.3, 65.1, 52.4, 47.5, 45.4, 45.1, 36.8, 34.0, 28.7, 25.8, 24.6; HRMS (ESI) *m/e* calcd (M +H$^+$) 365.2224, found 365.2224.

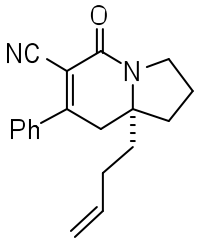


LA-12a: *(S)-5-oxo-7-phenyl-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (30%). (-) isomer: $[a]_D$ = 15.0^o ($CHCl_3$, c=0.005); HPLC analysis- Chiracel AD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 11.8 minutes, Minor: 11.3 minutes, 360 nm detection light, %ee 48%; R_f = 0.50 (100% EtOAc); IR (Thin Film) n 2981, 2904, 2223, 1650, 1445 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.60 (2H, dd, *J* = 39601.0 Hz), 7.48 (3H, m), 3.87 (1H, dddd, *J* = 10, 10, 9.4, 5.2 Hz), 3.75 (1H, ddd, *J* = 10.6, 9.6, 2 Hz), 3.58 (1H, ddd, *J* = 11, 9.8, 7.6 Hz), 3.03 (1H, dd, *J* = 17.6, 4.4 Hz), 2.73 (1H, dd, *J* = 17.6, 14 Hz), 2.32 (1H, m), 2.12 (1H, m), 1.89 (1H, m), 1.72 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 162.7, 136.3, 131.4, 129.1, 127.7, 115.3, 108.8, 55.6, 45.0, 37.2, 33.6, 29.9, 23.2; HRMS (TOF) *m/e* calcd (M +H$^+$) 239.1179, found 239.1182.

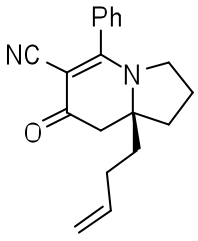


VA-32a: *(R)-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carbonitrile:* Flash Chromatography (1:1 Hexanes:EtOAc followed by MeCN) yielded a yellow oil (31%). (+) isomer: $[a]_D$ = 2^o ($CHCl_3$, c=0.006); HPLC analysis- Chiracel AD-H 85:15 hexanes:iPrOH, 1.0 ml/min, Major: 27.5 minutes, Minor: 30.0 minutes, 360 nm detection light, %ee 4%; R_f = 0.30 (100% EtOAc); IR (Thin Film) n 3073, 2981, 2858, 2208, 1654, 1547, 1455, 1296, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.62-7.58 (2H, m), 7.49-4.47 (3H, b, m), 3.87 (1H, dddd.

J=12, 9.6, 5, 4.8 Hz), 3.75 (1H, m), 3.57 (1H, m), 3.04 (1H, dd, J=17.4, 4.2), 2.73 (1H, dd, J=17.4, 13.8), 2.33 (1H, m), 2.12 (1H, m), 1.90 (1H, m), 1.81-1.60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.3, 167.1, 132.7, 131.3, 129.4, 127.8, 127.7, 127.6, 117.4, 59.0, 50.8, 40.9, 32.2, 24.2; HRMS (TOF) *m/e* calcd (M +Na^+) 238.1106, found 238.1106.

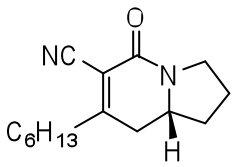


LA-12b: *(S)-8a-(but-3-enyl)-5-oxo-7-phenyl-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (20%). (-) isomer: $[a]_D$ = 13.0^o ($CHCl_3$, c=0.001); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 19.3 minutes, Minor: 20.8 minutes, 360 nm detection light, %ee 32%; R_f = 0.50 (100% EtOAc); IR (Thin Film) n 3073, 2976, 2884, 2203, 1644, 1537, 1455, 1296 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.58 (2H, b, m), 7.50 (3H, b, m), 5.73 (1H, ddt, *J* = 16.8, 10.4, 6.4 Hz), 4.97-5.04 (2H, d, d, *J* = 18.8, 10.4 Hz), 3.78 (1H, ddd, *J* = 12.4, 8.4, 6.2 Hz), 3.62 (1H, ddd, *J* = 4.8 Hz), 3.08 (1H, d, *J* = 17.6 Hz), 2.86 (1H, d, *J* = 17.6 Hz), 2.27 (1H, m), 2.05-1.99 (4H, m), 1.86-1.76 (2H, m), 1.69 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 161.6, 137.1, 131.4, 129.2, 127.6, 115.9, 94.6, 45.3, 41.5, 38.5, 35.9, 29.7, 21.9; HRMS (TOF) *m/e* calcd (M +H^+) 293.1648, found 293.1654.

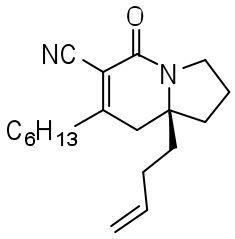


VA-32b: *(R)-8a-(but-3-enyl)-7-oxo-5-phenyl-1,2,3,7,8,8a-hexahydroindolizine-6-carbonitrile:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (41%). (+) isomer: $[a]_D$ = 72.5^o ($CHCl_3$, c=0.002); HPLC analysis- Chiracel AD-H 80:20

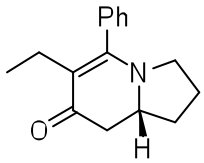
hexanes:iPrOH, 1.0 ml/min, Major: 11.7 minutes, Minor: 12.6 minutes, 360 nm detection light, %ee 87%; R_f = 0.30 (100% EtOAc); IR (Thin Film) n 3083, 2960, 2884, 2351, 1650, 1434, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.53 (4H, b, m), 7.32 (1H, b, m), 5.79 (1H, ddt, *J* = 17.2, 10.4, 6 Hz), 5.09 (1H, dd, *J* = 17.2, 1.2 Hz), 5.04 (1H, d, *J* = 10.4 Hz), 3.56 (1H, ddd, *J* = 12, 7.2, 6.2 Hz), 3.29 (1H, ddd, *J* = 12, 6.4, 6.2 Hz), 2.67 (2H, s), 2.29-2.14 (2H, m), 2.1-1.77 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.1, 170.1, 166.4, 137.0, 133.1, 131.9, 117.6, 116.2 66.8, 52.4, 45.1, 36.7, 33.5, 28.7, 23.9; HRMS (TOF) *m/e* calcd ($M+H^+$) 293.1648, found 293.1650.



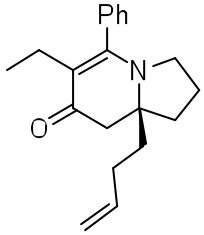
LA-13a: *(R)-7-hexyl-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (31%). (-) isomer: $[a]_D = 46.3^o$ ($CHCl_3$, c=0.004); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 10.0 minutes, Minor: 11.2 minutes, 220 nm detection light, %ee 80%; R_f = 0.70 (100% EtOAc); IR (Thin Film) n 3068, 2940, 2868, 2228, 1650, 1562, 1434, 1255, 1081, 999, 912, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 3.72-3.64 (2H, m), 3.48 (1H, ddd, *J* = 12, 7.6, 7.2 Hz), 2.64 (1H, d, *J* = 4.8 Hz), 2.60 (1H, d, *J* = 4.4 Hz), 2.56 (2H, t, *J* = 8.0 Hz), 2.34-2.22 (2H, m), 2.06 (1H, m), 1.83 (1H, m), 1.69-1.47 (3H, m), 1.39-1.25 (5H, m), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.8, 158.3, 114.4, 109.8, 55.6, 44.8, 36.8, 35.4, 33.6, 31.6, 29.1, 27.5, 23.1, 22.6, 14.2; HRMS (TOF) *m/e* calcd ($M+H^+$) 247.1805, found 247.1801.



LA-13b: *(R)-8a-(but-3-enyl)-7-hexyl-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile***:** Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (68%). (-) isomer: $[a]_D = 79.8^o$ ($CHCl_3$, c=0.006); HPLC analysis- Chiracel OD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 14.1 minutes, Minor: 20.5 minutes, 220 nm detection light, %ee 95%; $R_f = 0.60$ (100% EtOAc); IR (Thin Film) n 2966, 2884, 2223, 1660, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.72 (1H, dddd, *J* = 17, 10, 6.8, 5.2 Hz), 5.01 (1H, dd, *J* = 17.2, 1.2 Hz), 4.91 (1H, d, *J* = 10.0 Hz), 3.68 (1H, ddd, *J* = 12.4, 8.4, 6.2 Hz), 3.54 (1H, ddd, *J* = 12.4, 8.6, 5.2 Hz), 2.69 (1H, d, *J* = 18.0 Hz), 2.54 (2H, m), 2.43 (1H, d, *J* = 17.6 Hz), 2.21 (1H, ddd, *J* = 12.4, 6.4, 4 Hz), 2.04-1.92 (4H, m), 1.77-1.5 (5H, m), 1.41-1.25 (6H, m), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.4, 157.7, 137.1, 115.7, 114.4, 109.1, 63.2, 44.9, 39.6, 38.1, 37.0, 35.5, 31.7, 29.5, 29.2, 27.4, 22.7, 21.8, 14.2; HRMS (TOF) *m/e* calcd ($M+H^+$) 301.2274, found 301.2270.

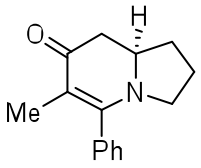


VA-33a: (*R)-6-ethyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* For all spectral data, see *JACS* **2006**, *128*, 2782. (+) isomer: $[a]_D = 102.4^o$ ($CHCl_3$, c=0.01); HPLC analysis: HPLC analysis- Chiracel AD-H 97:3 hexanes:iPrOH, 0.5 ml/min, Major: 43.3 minutes, Minor: 38.5 minutes, 330 nm detection light, %ee 76%

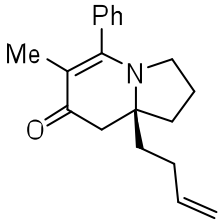


VA-33b: *(R)-8a-(but-3-enyl)-6-ethyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (50%). (+) isomer: $[a]_D = 25.6^o$

($CHCl_3$, c=0.005); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 6.5 minutes, Minor: 4.7 minutes, 360 nm detection light, %ee 83%; R_f = 0.60 (100% EtOAc); IR (Thin Film) n 2078, 2981, 2920, 1716, 1644, 1445, 1373, 1276 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.26 (3H, b, m), 7.08 (2H, b, m), 5.66 (1H, dddd, *J* = 17.2, 10.4, 6.4, 5.2 Hz), 4.90 (1H, dd, *J* = 17.2, 1.6 Hz), 4.82 (1H, dd, *J* = 10, 1.2 Hz), 3.00 (1H, ddd, *J* = 11.2, 6.4, 5.6 Hz), 2.86 (1H, ddd, *J* = 10.8, 7.2, 5.4 Hz), 2.56 (1H, d, *J* = 16.4 Hz), 2.34 (1H, d, *J* = 16.4 Hz), 2.05 (1H, m), 1.99-1.59 (9H, m), 0.65 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.5, 159.6, 138.9, 137.2, 129.8, 129.5 128.7, 115.7, 111.6, 64.7, 51.4, 46.7, 38.2, 33.8, 29.7, 24.4, 19.4, 16.0; HRMS (TOF) *m/e* calcd ($M+H^+$) 296.2009, found 296.1998.

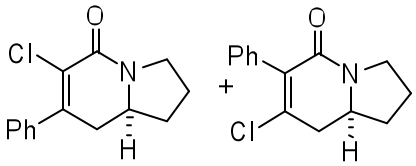


VA-34a: **(***R)-6-methyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* For all spectral data, see *JACS* **2006**, *128*, 2782. Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (94%). (+) isomer: $[a]_D$ = 181° ($CHCl_3$, c=0.003); HPLC analysis- Chiracel AD-H 99:1 hexanes:irPrOH, 1.0 ml/min, Major: 30.0 minutes, Minor: 29.0 minutes, 360 nm detection light, %ee 71%.



VA-34b: *(R)-8a-(but-3-enyl)-6-methyl-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (50%). (+) isomer: $[a]_D$ = 88.4° ($CHCl_3$, c=0.01); HPLC analysis- Chiracel OD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 10.6 minutes, Minor: 7.2 minutes, 360 nm detection

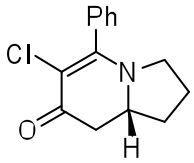
light, %ee 72%; R_f = 0.40 (100% EtOAc); IR (Thin Film) n 3078, 2981, 2920, 1731, 1614, 1527, 1450, 1301, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 7.46-7.34 (4H, b, m), 7.25-7.06 (1H, b, m), 5.80 (1H, dddd, *J* = 17.1, 13.6, 6.3, 5.1 Hz), 5.05 (1H, dd, *J* = 17.1, 1.5 Hz), 4.97 (1H, dd, *J* = 10.1, 1.2 Hz), 3.23 (1H, ddd, *J* = 10.8, 6.9, 5.9 Hz), 3.02 (1H, ddd, *J* = 10.8, 6.9, 5.6 Hz), 2.72 (1H, d, *J* = 16.2 Hz), 2.50 (1H, d, *J* = 16.2 Hz), 2.22-1.7 (8H, m), 1.99-1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) d 191.4, 159.3, 138.2, 136.6, 129.2, 128.8, 128.3, 115.1, 104.0, 64.0, 51.1, 45.5, 37.4, 33.2, 29.0, 23.9, 11.8; HRMS (TOF) *m/e* calcd ($M+H^+$) 282.1852, found 282.1839.



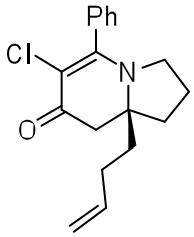
LA-14a1, LA-14a2: *Due to the HPLC results and NMR integrations, the authors believe this to be a mixture of two regioisomers.*

(S)-6-chloro-7-phenyl-2,3,8,8a-tetrahydroindolizin-5(1H)-one and (S)-7-chloro-6-phenyl-2,3,8,8a-tetrahydroindolizin-5(1H)-one: Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (16%). (-) isomer: $[a]_D = 0.4^o$ ($CHCl_3$, c=0.01); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major A: 8.8 minutes, Minor A: 9.9 minutes, 220 nm detection light, %ee 8%, Major B: 13.1 minutes, Minor B: 12.3 minutes, 220 nm detection light, %ee 20%; R_f = 0.60 (100% EtOAc); IR (Thin Film) n 3057, 2960, 2879, 1634, 1506, 1460, 1327, 1271, 1255, 1122, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.42-7.28 (7H, m), 4.01-3.88 (1H, m), 3.76-3.7 (1H, m), 3.68-3.48 (2H, m), 2.85-2.66 (3H, m), 2.31-2.23 (2H, m), 2.14-2.04 (2H, m), 1.94-1.81 (2H, m), 1.72-1.63 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 159.6, 143.9, 141.1, 138.3, 134.2,

130.2, 128.9, 128.5, 128.1, 128.0, 127.9, 55.9, 55.6, 45.5, 44.8, 40.1, 38.0, 33.5, 33.4, 23.5, 23.3; HRMS (TOF) *m/e* calcd (M +H^+) 248.0837, found 248.0836.

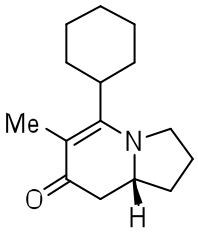


VA-35a: *(R)-6-chloro-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one***:** Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (62%). (+) isomer: $[a]_D$ = 132.5^o ($CHCl_3$, c=0.004); HPLC analysis- Chiracel AD-H 99:1 hexanes:iPrOH, 1.0 ml/min, Major: 78.7 minutes, Minor: 83.1 minutes, 360 nm detection light, %ee 20% (73% without 4Å MS); R_f = 0.40 (100% EtOAc); IR (Thin Film) n 3073, 2966, 2909, 1650, 1619, 1568, 1414, 1260, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.46 (3H, m), 7.31 (2H, b, m), 4.04 (1H, dddd, *J* = 14.8, 9.6, 5.2, 5.2 Hz), 3.32 (1H, ddd, *J* = 11.2, 7.2, 2.8 Hz), 3.15 (1H, ddd, *J* = 11.6, 10.6, 8 Hz), 2.70 (1H, dd, *J* = 16, 5.2 Hz), 2.60 (1H, t, *J* = 16.0 Hz), 2.35 (1H, m), 2.01 (1H, m), 1.93-1.73 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 184.6, 160.1, 134.2, 129.9, 129.0, 127.9, 127.8, 102.3, 58.1, 50.3, 41.6, 32.5, 24.4; HRMS (TOF) *m/e* calcd (M +H^+) 248.0864, found 248.0831.

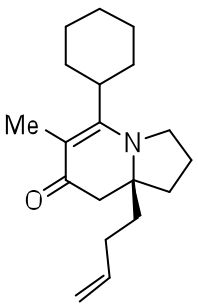


VA-35b: *(R)-8a-(but-3-enyl)-6-chloro-5-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (53%). (+) isomer: $[a]_D$ = 173.1^o ($CHCl_3$, c=0.007); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 10.5 minutes, Minor: 9.8 minutes, 360 nm detection light, %ee 91% (peaks are inverted); R_f = 0.40 (100% EtOAc); IR (Thin Film) n 2971, 2879, 1624, 1593, 1542, 1491, 1455, 1373, 1301, 1102, 1030 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) d 7.48-7.36 (5H, b, m), 5.80 (1H, dddd, *J* = 17.2, 10.4, 6, 5.2 Hz), 5.07 (1H, dd, *J* = 17.2, 1.2 Hz), 5.00 (1H, d, *J* = 10.0 Hz), 3.32 (1H, ddd, *J* = 11.6, 6.4, 5.6 Hz), 3.13 (1H, ddd, *J* = 11.6, 6.8, 5.6 Hz), 2.83 (1H, d, *J* = 16.4 Hz), 2.69 (1H, d, *J* = 16.4 Hz), 2.24-2.15 (2H, m), 2.1-1.77 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 184.3, 158.8, 137.6, 134.6, 130.2, 128.9, 128.6, 115.6, 101.8, 64.9, 51.9, 45.6, 37.0, 33.1, 28.9, 24.1; HRMS (TOF) *m/e* calcd ($M+H^+$) 302.1306, found 302.1310.

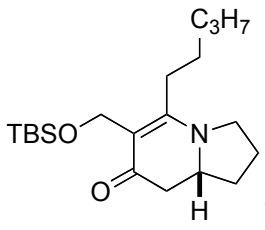


VA-36a: *(R)-5-cyclohexyl-6-methyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (57%). (+) isomer: $[a]_D = 2^o$ ($CHCl_3$, c=0.003); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 6.4 minutes, Minor: 5.9 minutes, 330 nm detection light, %ee 33%; R_f = 0.40 (100% EtOAc); IR (Thin Film) n 2935, 2884, 1731, 1634, 1522, 1434, 1271 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 3.73-3.5 (3H, m), 2.64 (1H, b, m), 2.38 (1H, dd, *J* = 15.9, 4.5 Hz), 2.29-2.14 (2H, m), 2.04 (1H, m), 1.88-1.59 (12H, s, m), 1.36-1.14 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.3, 165.2, 103.7, 64.7, 58.8, 41.7, 29.3, 29.0, 28.8, 27.3, 27.0, 26.2, 26.1, 25.8, 25.6; HRMS (TOF) *m/e* calcd ($M+H^+$) 233.1780, found 233.1782.

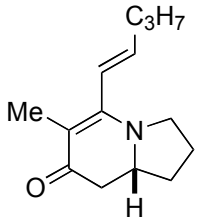


VA-36b: *(R)-8a-(but-3-enyl)-6-methyl-5-cyclohexyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (1:1 Hexanes:EtOAc) yielded a yellow oil (65%). (+) isomer: $[a]_D = 6^o$ ($CHCl_3$, c=0.003); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 7.2 minutes, Minor: 6.5 minutes,

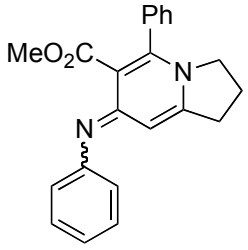
330 nm detection light, %ee 45%; R_f = 0.50 (100% EtOAc); IR (Thin Film) n 2960, 2863, 1716, 1614, 1516, 1470, 1296, 1276, 984, 907, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.71 (1H, dddd, *J* = 17.2, 10.4, 6.4, 5 Hz), 4.95 (1H, dd, *J* = 17.2, 1.2 Hz), 4.90 (1H, d, *J* = 10.4 Hz), 3.58 (2H, ddd, *J* = 21.6, 5, 3.6 Hz), 2.65 (1H, b, m), 2.49 (1H, d, *J* = 16.0 Hz), 2.36 (1H, d, *J* = 16.4 Hz), 2.12-1.98 (3H, m), 1.95 (1H, m), 1.91-1.84 (8H, m), 1.78-1.54 (6H, m), 1.33-1.15 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.0, 163.7, 138.3, 114.9, 64.7, 50.3, 45.4, 43.5, 36.5, 32.1, 29.3, 29.0, 28.7, 27.3, 26.9, 26.2, 24.0, 10.9; HRMS (TOF) *m/e* calcd ($M+H^+$) 287.2249, found 287.2253.



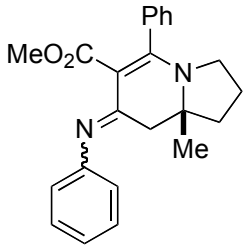
VA-37a*:* *(R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-pentyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (10%). (-) isomer: $[a]_D$ = -296° ($CHCl_3$, c=0.006) Synthesize independently using **L8** in order to characterize; R_f = 0.35 (100% EtOAc); IR (Thin Film) n 2956, 2857, 1626, 1558, 1462, 1335, 1277, 1081, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 4.48 (1H, *J*= 12 Hz), 4.30 (1H, *J*=12 Hz), 3.80 (1H, dddd, *J*= 2.4, 8.4, 8.4, 8.8 Hz), 3.66 (1H, ddd, *J* = 5.6, 10.4, 21.2 Hz), 3.52 (1H, ddd, *J*= 7.2, 8.8, 10.4 Hz), 2.43 (1H, dd, *J* = 4.4, 15.6 Hz), 2.32-2.18 (4H, m), 2.04 (1H, m), 1.83 (1H, m), 1.62 (1H, m), 1.28-1.27 (3H, m), 0.9 (9H, s) 0.11-0.99 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.0, 157.2, 109.1, 59.8, 58.1, 47.5, 42.0, 32.5, 32.1, 31.5, 26.0, 24.9, 24.1, 22.8, 18.4, 14.3, 5.2; HRMS (ESI) *m/e* calcd ($M+H^+$) 352.2666, found 352.2675.



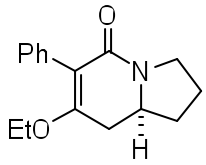
VA-38a: *(R,E)-6-methyl-5-(pent-1-en-1-yl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (25%). (-) isomer: $[a]_D$ = 92° ($CHCl_3$, c=0.006); R_f = 0.05 (100% EtOAc); IR (Thin Film) n , 2959, 2872, 1617 1534, 1460, 1374, 1282, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.92 (1H, s), 3.49 (1H, td, *J*=3.6, 9.4 Hz), 3.36 (1H, m), 3.12 (1H, t, *J* = 7.2 Hz), 2.4-2.3 (3H, m), 2.2-2.1 (3H, m), 2.1-1.9 (3H, m), 1.8 (1H, m), 1.7 (3H, s), 1.62-1.53 (2H, m), 1.46 (2H, q, *J*= 7.2Hz), 1.32-1.2 (3H, m) 0.91 (3H, t, *J*=7.6 Hz) 0.86-0.84 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.1, 157.6, 141.2, 137.9, 123.7, 115.0, 103.3, 57.5, 48.9, 48.9, 41.6, 40.1, 35.1, 32.3, 31.0, 29.3, 24.0, 21.9; HRMS (ESI) *m/e* calcd ($M+H^+$) 220.1800, found 220.1811.



1-55*: methyl 5-phenyl-7-(phenylimino)-1,2,3,7-tetrahydroindolizine-6-carboxylate*: Flash Chromatography (95:5 EtOAc:Net_3) yielded a yellow oil (35%). R_f = 0.5 (100% EtOAc); IR (Thin Film) n , 2949, 2361, 1731, 1644, 1588, 1459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.45-7.43 (5H, m), 7.30 (2H, t, *J*=7.5 Hz), 7.03-6.96 (3H, m), 6.23 (1H, b, s), 3.65 (2H, t, *J*= 6.9 Hz), 3.47 (3H, s), 2.89 (2H, t, *J*=7.5Hz), 2.10-2.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 155.5, 132.9, 129.7, 129.1, 128.7, 128.4, 122.6, 121.1, 52.5, 52.1, 30.9, 22.0; HRMS (ESI) *m/e* calcd ($M+H^+$) 345.1598, found 345.1603.

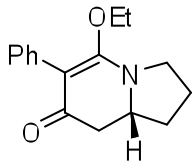


1-31f: *(R)-methyl 8a-methyl-5-phenyl-7-(phenylimino)-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylate:* Flash Chromatography (EtOAc) yielded a yellow oil (56%). (-) isomer: $[a]_D = 3^o$ (CHCl3, c=0.006); HPLC analysis- Chiracel OD-H column 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 13.1 minutes, Minor: 9.8 minutes, 330 nm detection light, %ee: 92%;R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2971, 1715, 1631, 1520, 1445, 1337, 1191, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.40-7.34 (6H, b, m), 7.26 (3H, t, *J* = 7.6 Hz), 7.01 (1H, t, *J* = 7.2 Hz), 689.00 (1H, t, *J* = 8.0 Hz), 6.81 (2H, d, *J* = 8.0 Hz), 3.46-3.40 (2H, m), 3.29 (3H, s), 3.02-2.95 (2H, m), 2.73-2.60 (3H, m), 2.24 (1H, d, *J* = 14.8 Hz), 1.94-1.77 (5H, m), 1.36 (1H, s), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 169.3, 160.4, 159.0, 156.3, 151.5, 137.0, 129.4, 129.2, 128.7, 128.6, 128.4, 126.9, 122.9, 122.7, 121.2, 104.4, 62.0, 60.7, 51.3, 50.7, 50.6, 44.9, 39.9, 39.8, 37.5, 23.3, 22.9, 22.8, 22. 6; HRMS (ESI) *m/e* calcd ($M+H^+$) 361.1911, found 361.198.

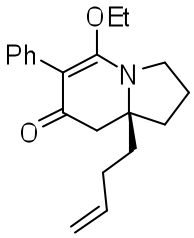


LA-15a: *(S)-7-ethoxy-6-phenyl-2,3,8,8a-tetrahydroindolizin-5(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (25%). (-) isomer: $[a]_D = 4.0^o$ ($CHCl_3$, c=0.01); HPLC analysis- Chiracel OD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 18.9 minutes, Minor: 21.1 minutes, 220 nm detection light, %ee 7%; R_f = 0.15 (100% EtOAc); IR (Thin Film) n 2986, 2935, 1737, 1537, 1475, 1450, 1317 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.29-7.24 (2H, m), 7.21-

7.18 (3H, m), 3.85-3.75 (3H, m), 3.62 (1H, ddd, *J* = 20.8, 9.2, 2 Hz), 3.54-3.44 (1H, m), 2.72 (1H, dd, *J* = 16, 4.4 Hz), 2.45 (1H, dd, *J* = 20, 14 Hz), 2.26-2.2 (1H, m), 2.06-1.99 (1H, m), 1.88-1.76 (1H, m), 1.70-1.60 (1H, m), 1.15 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 161.0, 131.1, 127.6, 126.8, 94.6, 64.9, 54.8, 33.7, 32.6, 23.3, 15.5; HRMS (ESI) *m/e* calcd (M +H^+) 258.1489, found 258.1486.

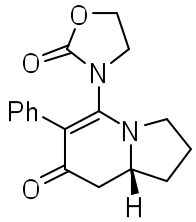


VA-39a: *(R)-5-ethoxy-6-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (73%). (+) isomer: $[a]_D$ = 176.8^o ($CHCl_3$, c=0.006); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 9.9 minutes, Minor: 12.9 minutes, 360 nm detection light, %ee 77%; R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2986, 2935, 1737, 1537, 1475, 1450, 1317 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.27-7.23 (4H, m), 7.09 (1H, m), 3.87 (1H, dddd, *J* = 15.2, 6.8, 6.8, 6.4 Hz), 3.74 (1H, ddd, *J* = 11.4, 8.6, 2.4 Hz), 3.53 (2H, q, *J* = 7.0 Hz), 3.41 (1H, ddd, *J* = 10.8, 10.2, 7.2 Hz), 2.50-2.40 (2H, dd, *J* = overlapping, could not determine J-value), 2.29 (1H, dddd, *J* = 12.4, 6.2, 6, 2.8 Hz), 2.03 (1H, m), 1.85 (1H, m), 1.66 (1H, m), 1.05 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.0, 166.5, 134.8, 130.5, 127.5, 124.9, 97.3, 68.5, 54.8, 46.1, 41.9, 32.3, 23.2, 15.1; HRMS (TOF) *m/e* calcd (M +H^+) 258.1489, found 258.1497.

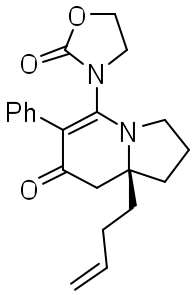


VA-39b: *(R)-8a-(but-3-enyl)-5-ethoxy-6-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (98%). (+) isomer: $[a]_D$ = 79.5^o ($CHCl_3$, c=0.01); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 5.6

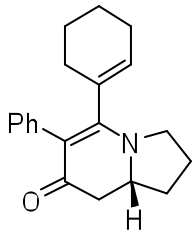
minutes, Minor: 4.9 minutes, 360 nm detection light, %ee 97%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 2986, 2924, 2868, 1757, 1629, 1562, 1460, 1419, 1322, 1219, 1127, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.3-7.25 (4H, m), 7.11 (1H, m), 5.73 (1H, dddd, *J* = 17.2, 10, 6, 5.2 Hz), 4.98 (1H, dd, *J* = 17.2, 1.2 Hz), 4.92 (1H, d, *J* = 10.0 Hz), 3.67-3.53 (4H, m), 2.66 (1H, d, *J* = 16.0 Hz), 2.50 (1H, d, *J* = 15.6 Hz), 2.19-2.08 (2H, m), 2.05-1.90 (4H, m), 1.81-1.63 (2H, m), 1.08 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.3, 166.5, 138.1, 135.3, 130.9, 128.2, 125.6, 115.2, 97.7, 68.9, 62.9, 48.1, 46.3, 37.5, 33.7, 29.1, 23.3, 15.8; HRMS (TOF) *m/e* calcd (M $+H^+$) 312.1958, found 312.1958.



VA-40a: *(R)-3-(7-oxo-6-phenyl-1,2,3,7,8,8a-hexahydroindolizin-5-yl)oxazolidin-2-one:* Flash Chromatography (EtOAc) yielded a yellow oil (56%). (+) isomer: $[a]_D$ = 296.2° ($CHCl_3$, c=0.01); HPLC analysis-Chiracel OD-H 70:30 hexanes:iPrOH, 1.0 ml/min, Major: 15.2 minutes, Minor: 13.4 minutes, 360 nm detection light, %ee 52%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 3078, 2976, 2925, 2873, 1757, 1634, 1537, 1460, 1424, 1296, 1209, 1143, 1061, 1009, 907, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.31 (2H, m), 7.19 (3H, m), 4.22-4.08 (2H, m), 3.91 (1H, ddd, *J* = 8.8, 7.2, 5.6 Hz), 3.77 (1H, ddd, *J* = 8.8, 7.2, 5.6 Hz), 3.48-3.35 (2H, m), 2.91 (1H, q, *J* = 8.8 Hz), 2.57-2.48 (2H, m), 2.34 (1H, ddt, *J* = 9.4, 6.4, 6.2 Hz), 2.16-1.95 (2H, m), 1.76 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.1, 155.7, 150.8, 134.8, 130.3, 128.8, 126.8, 106.1, 63.5, 56.5, 48.5, 44.9, 42.1, 31.9, 24.2; HRMS (TOF) *m/e* calcd (M $+H^+$) 299.1390, found 299.1380.

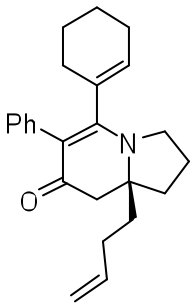


VA-40b: *(R)-3-(8a-(but-3-enyl)-7-oxo-6-phenyl-1,2,3,7,8,8a-hexahydroindolizin-5-yl)oxazolidin-2-one:* Flash Chromatography (EtOAc) yielded a yellow oil (91%). (+) isomer: $[a]_D = 154.6^o$ ($CHCl_3$, c=0.005); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major: 20.4 minutes, Minor: 14.9 minutes, 360 nm detection light, %ee 85%; R_f = 0.15 (100% EtOAc); IR (Thin Film) n 3062, 2966, 2904, 1757, 1624, 1547, 1460, 1414, 1301, 1209, 1158, 1086, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.31 (2H, m), 7.18 (3H, m), 5.77 (1H, dddd, *J* = 17.2, 10, 6.4, 5 Hz), 5.02 (1H, d, *J* = 17.2 Hz), 4.93 (1H, d, *J* = 10.0 Hz), 4.17 (1H, q), 3.94 (1H, b, q, *J* = 6.0 Hz), 3.65 (1H, b, m), 3.51 (1H, b, m), 3.36 (1H, b, q, *J* = 5.6 Hz), 2.95 (1H, b, q, *J* = 8.4 Hz), 2.77 (1H, d, *J* = 16.0 Hz), 2.51 (1H, d, *J* = 16.4 Hz), 2.24-2.1 (3H, m), 2.07-1.98 (2H, m), 1.95-1.83 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.3, 154.7, 149.6, 137.7, 134.5, 129.8, 128.5, 128.3, 126.4, 114.9, 104.6, 64.2, 63.0, 49.6, 45.8, 44.6, 36.5, 32.9, 28.3, 23.6; HRMS (TOF) *m/e* calcd ($M + H^+$) 353.1860, found 353.1856.



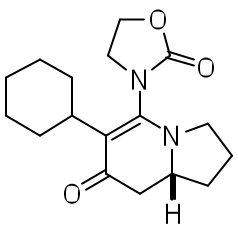
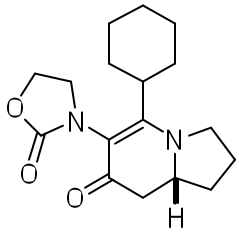
VA-41a, VA-42a: *(R)-5-cyclohexenyl-6-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one: Isolated as an inseperaable mixture of regioisomers (10:1, major product shown).* Flash Chromatography (EtOAc) yielded a yellow oil (90%). (+) isomer: $[a]_D = 64.3^o$ ($CHCl_3$, c=0.009); HPLC analysis- Chiracel OD-H 80:20 hexanes:iPrOH, 1.0 ml/min, Major A: 9.1 minutes, Minor A: 11.2 minutes, Major B: 8.2 minutes, Minor B: 7.5 minutes, 360 nm detection light (*peaks are inverted*), %ee A 83%, %ee B 90%; R_f = 0.30 (100% EtOAc); IR (Thin Film) n 2940, 2935, 1619, 1516, 1434, 1434, 1286, 758 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) d 7.32 (1H, m), 7.23-7.19 (5H, m), 7.12-7.08 (3H, m), 5.73 (1H, b, m), 5.57 (1H, b, m), 5.12 (0.4H, b,m), 4-3.91 (2H, b, m), 3.69 (1H, b, m), 3.43-3.36 (2H, b, m), 3.26 (0.4H, m), 3.07 (0.6H, m), 2.53-2.48 (3H, m), 2.35-2.26 (2H, m), 2-1.67 (14H, m), 1.55-1.10 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.4, 163.3, 136.6, 133.8, 132.0, 131.9, 131.8, 131.7, 131.2, 130.5, 130.4, 129.8, 128.6, 128.1, 127.5, 127.2, 125.6, 57.9, 57.8, 57.5, 49.7, 48.9, 42.3, 42.1, 42.0, 41.9, 41.8, 32.7, 32.6, 30.2, 28.1, 28.0, 27.4, 25.7, 25.0, 24.4, 24.3, 24.1, 24.0, 23.1; HRMS (TOF) *m/e* calcd (M $+H^+$) 294.1780, found 293.1784.

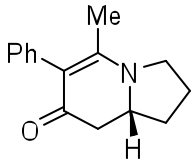


VA-41b, VA-42b: *(R)-8a-(but-3-enyl)-5-cyclohexenyl-6-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (85%). (+) isomer: $[a]_D = 189.5^o$ ($CHCl_3$, c=0.002); HPLC analysis- Chiracel OD-H 97:3 hexanes:iPrOH, 1.0 ml/min, Major A: 23.8 minutes, Minor A: 19.6 minutes, Major B: 27.8 minutes, Minor B: 12.8 minutes, 360 nm detection light (*peaks are inverted,*, %ee A 92%, %ee B 94%; R_f = 0.40 (100% EtOAc); IR (Thin Film) n 3073, 2914, 2848, 1634, 1506, 1440, 1291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.57 (0.3H, m), 7.48-7.12 (6H, m), 5.85 (1.5H, dddd; b, m, *J* = 17.2, 10.4, 6.4, 5.2 Hz), 5.56 (0.5H, b, m), 5.12-4.99 (2.3H, m), 4.79 (0.4H, m), 3.50 (1.7H, b, m), 3.35 (0.2H, ddd, *J* = 11.2, 8.6, 6.8 Hz), 3.14 (0.4H, m), 2.79 (1H, d, *J* = 16.0 Hz), 2.54-2.47 (1.1H, d, m, *J* = 15.6 Hz), 2.26-1.63 (15H, m), 1.54-1.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 190.3, 162.3, 162.2, 159.3, 138.3, 133.8, 132.7, 132.4, 131.6, 131.5, 129.8, 129.4, 129.0, 128.6, 128.4, 128.2, 128.1, 127.9, 125.5, 115.1, 114.7, 109.6, 64.1, 64.0, 51.5, 51.1, 51.0, 50.2, 46.0, 45.9, 45.8, 45.7, 45.6,

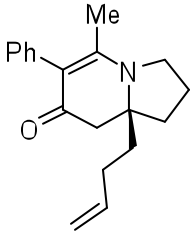
45.5, 40.4, 37.5, 37.2, 35.4, 33.5, 32.2, 31.6, 30.1, 29.4, 28.9, 28.4, 26.0, 25.8, 25.3, 24.1, 23.1, 22.5, 22.3, 22.2, 21.7; HRMS (TOF) *m/e* calcd (M +Na^+) 347.2249, found 347.2251.

VA-43a, VA-44a: *(R)-3-(6-cyclohexyl-7-oxo-1,2,3,7,8,8a-hexahydroindolizin-5-yl)oxazolidin-2-one* and *(R)-3-(5-cyclohexyl-7-oxo-1,2,3,7,8,8a-hexahydroindolizin-6-yl)oxazolidin-2-one*: The products were recovered as an inseperable mixture of the two regioisomers. The 1.2:1 ratio was determined by GC/MS, elution times were 23.74 minutes for the 'major' and 15.14 minutes for the 'minor.' Crude spectra is supplied in this supplemental data. HRMS (ESI) *m/e* calcd (M +H^+) 305.186, found 305.1863.

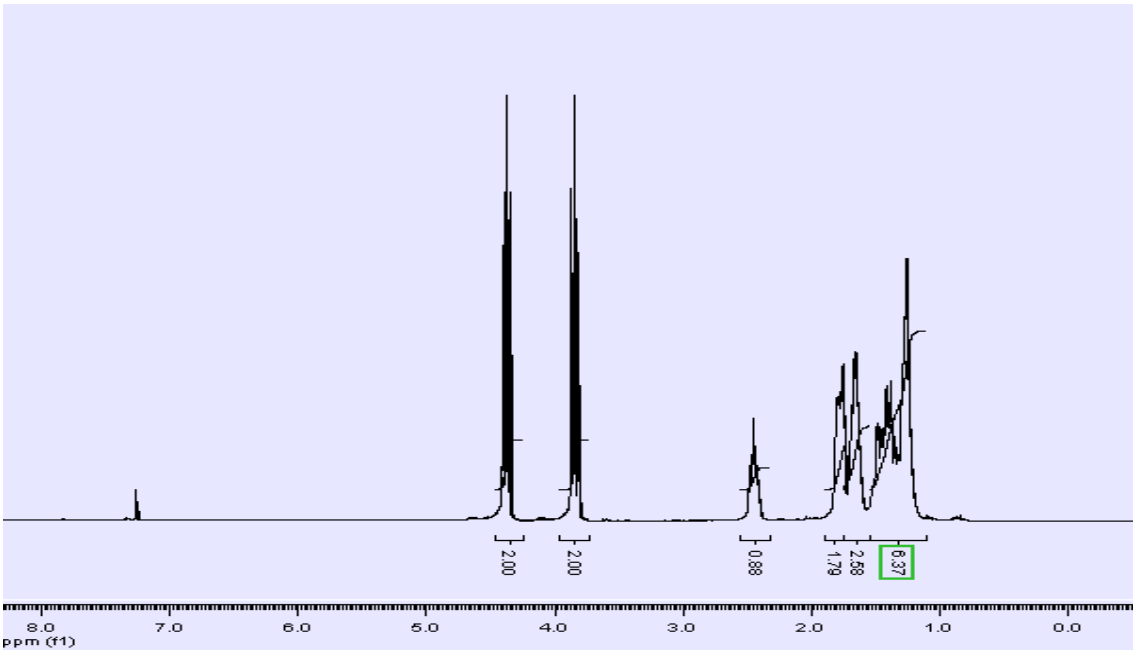


VA-46a: *(R)-5-methyl-6-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (30%). (+) isomer: $[a]_D = 29.5^o$ ($CHCl_3$, c=0.002); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 20.0 minutes, Minor: 18.1 minutes, 360 nm detection light, %ee 75%; R_f = 0.10 (100% EtOAc); IR (Thin Film) n 2950, 2853, 1619, 1532, 1301 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 7.31-7.12 (3H, m), 7.11-7.08 (2H, m), 3.81 (1H, dddd, *J* = 14.4, 14, 6.8, 6.4 Hz), 3.65-3.47 (2H, m), 2.55 (1H, dd, *J* = 15.6, 4.8 Hz), 2.45 (1H, d, *J* = 16.0 Hz), 2.31 (1H, m), 2.11 (1H, m), 1.93 (3H, s), 1.79-1.57 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 189.0, 170.2, 132.0, 128.3, 126.3, 58.2, 48.3, 42.2, 33.2, 23.9, 19.2; HRMS (TOF) *m/e* calcd (M +H^+) 227.1310, found 227.1309.

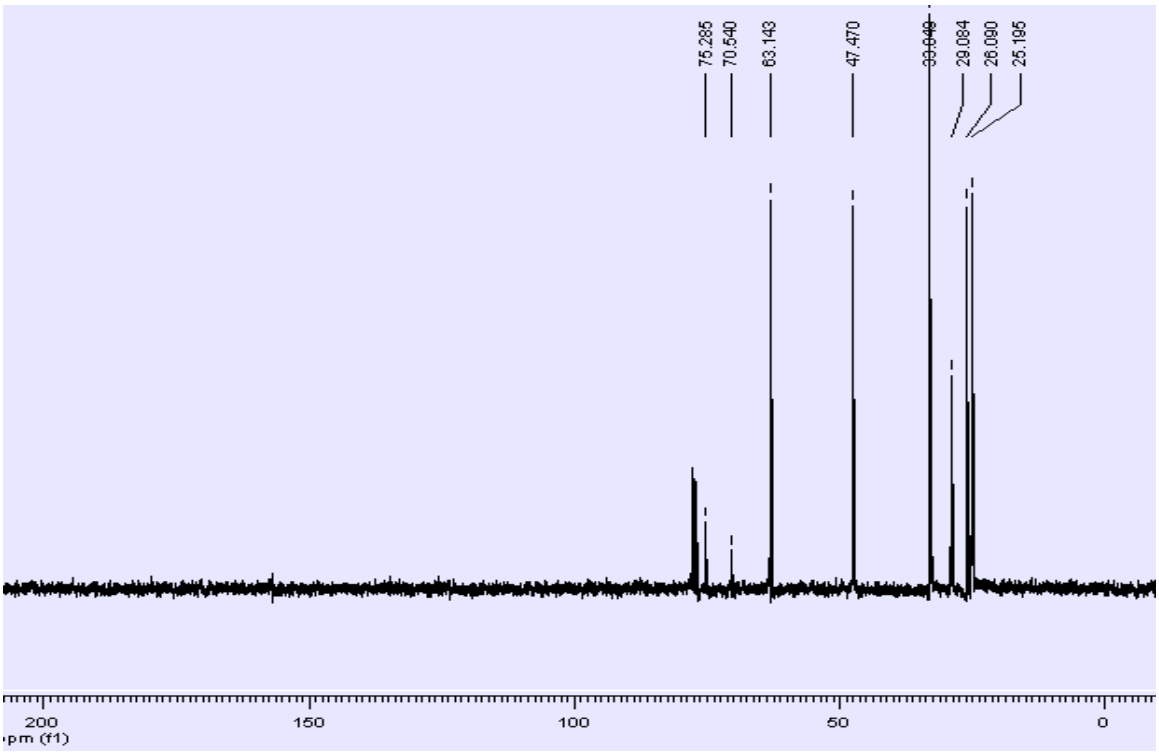


VA-46b: *(R)-8a-(but-3-enyl)-5-methyl-6-phenyl-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a yellow oil (73%). (+) isomer: $[a]_D$ = 62^o ($CHCl_3$, c=0.002); HPLC analysis- Chiracel AD-H 90:10 hexanes:iPrOH, 1.0 ml/min, Major: 25.5 minutes, Minor: 13.2 minutes, 360 nm detection light, %ee 92%; R_f = 0.15 (100% EtOAc); IR (Thin Film) n 3053, 2925, 1619, 1532, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.31 (2H, t, *J* = 7.2 Hz), 7.19 (1H, t, *J* = 5.6 Hz), 7.12 (2H, d, *J* = 6.8 Hz), 5.76 (1H, dddd, *J* = 17.2, 10.4, 6.4, 5 Hz), 5.02 (1H, dd, *J* = 17.2, 1.6 Hz), 4.95 (1H, d, *J* = 10.4 Hz), 3.67-3.56 (2H, m), 2.71-2.61 (2H, d, d, *J* = 16, 15.6 Hz), 2.25 (1H, m), 2.17 (1H, m), 2.13-1.97 (3H, m), 1.94 (3H, s), 1.82-1.53 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 188.3, 157.5, 138.5, 137.9, 132.3, 128.7, 126.6, 115.6, 111.6, 65.2, 48.9, 46.3, 37.8, 32.3, 29.5, 23.0, 20.0; HRMS (TOF) *m/e* calcd ($M+H^+$) 282.1858, found 282.1846

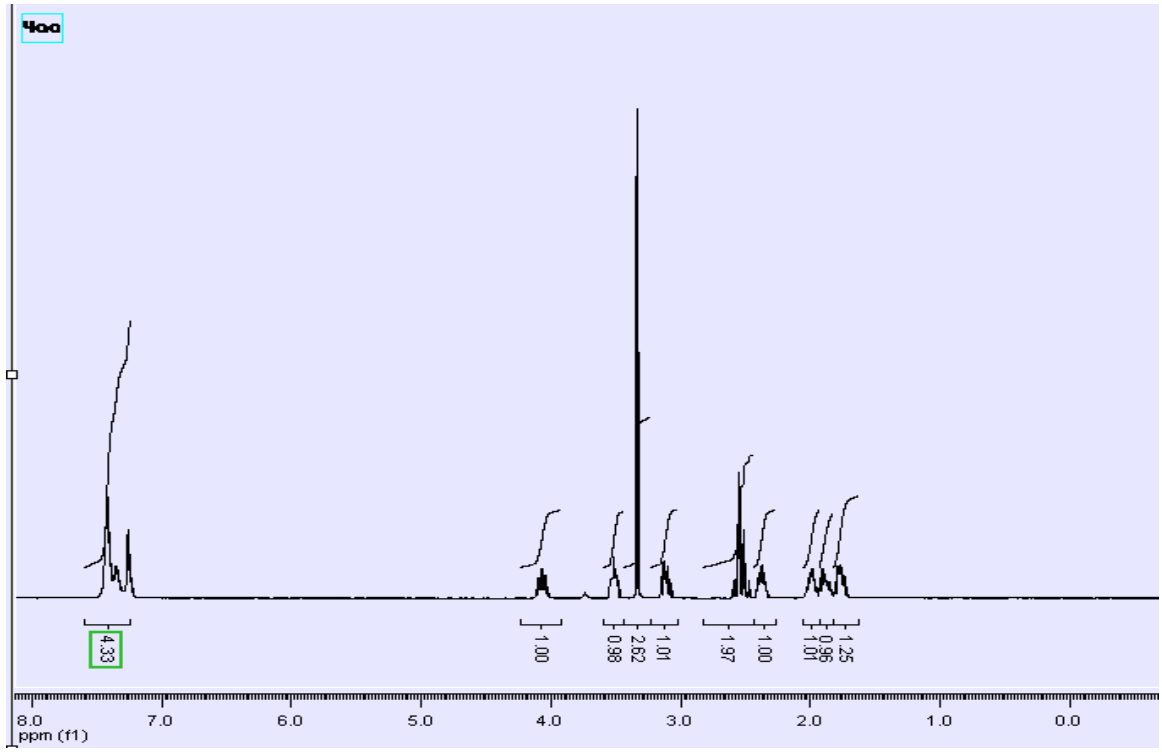
^{1}H NMR: 1-56



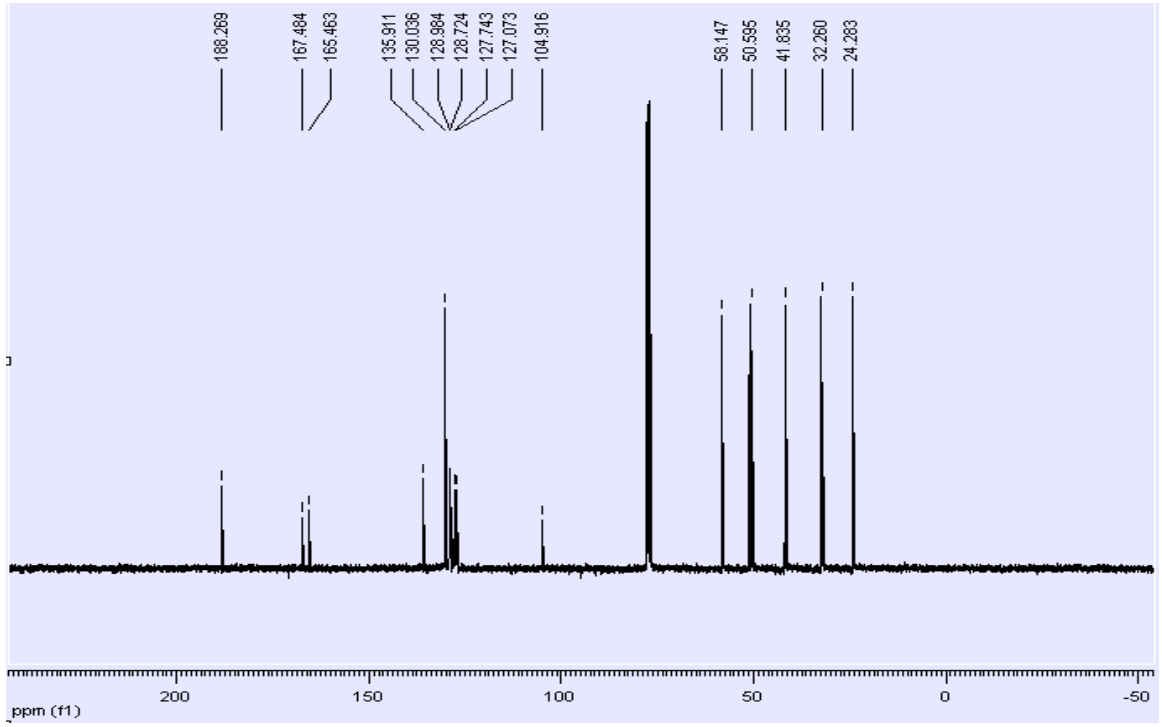
^{13}C NMR: 1-56



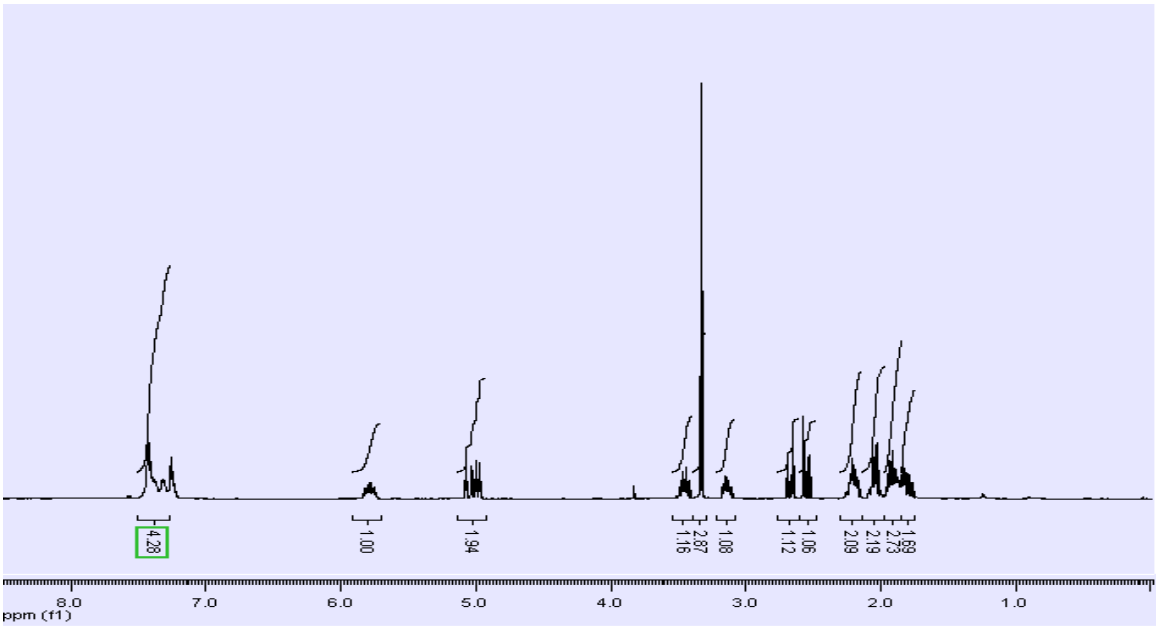
^{1}H NMR: VA-12



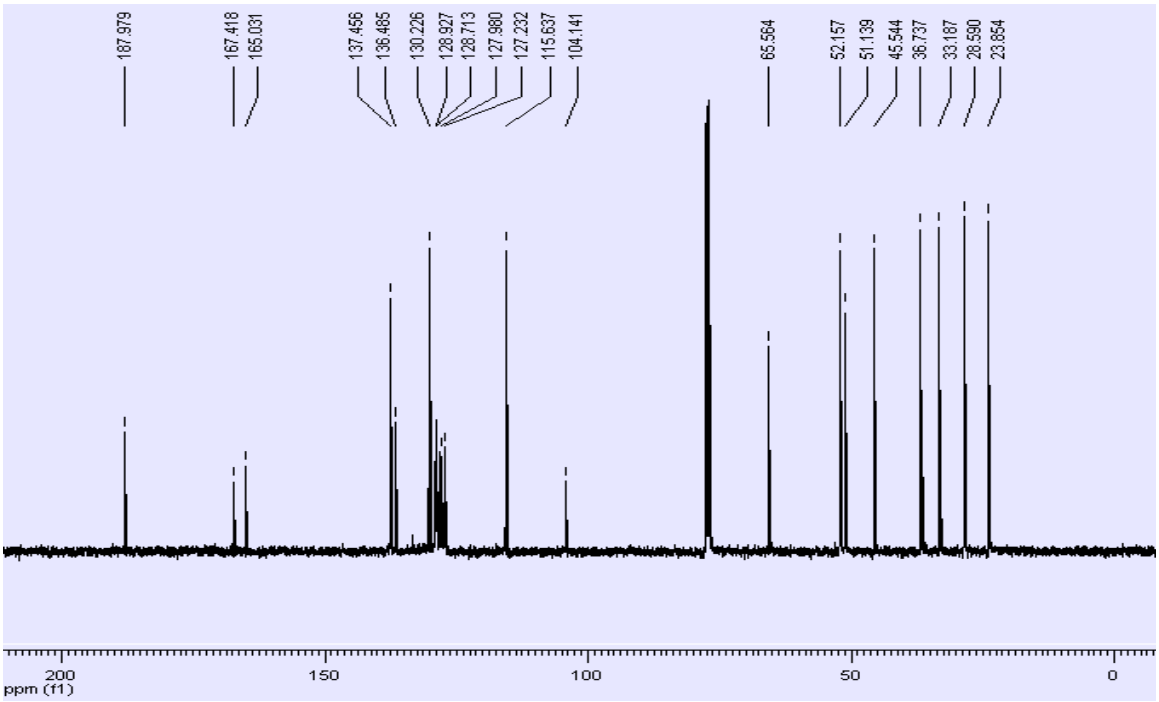
^{13}C NMR: VA-12



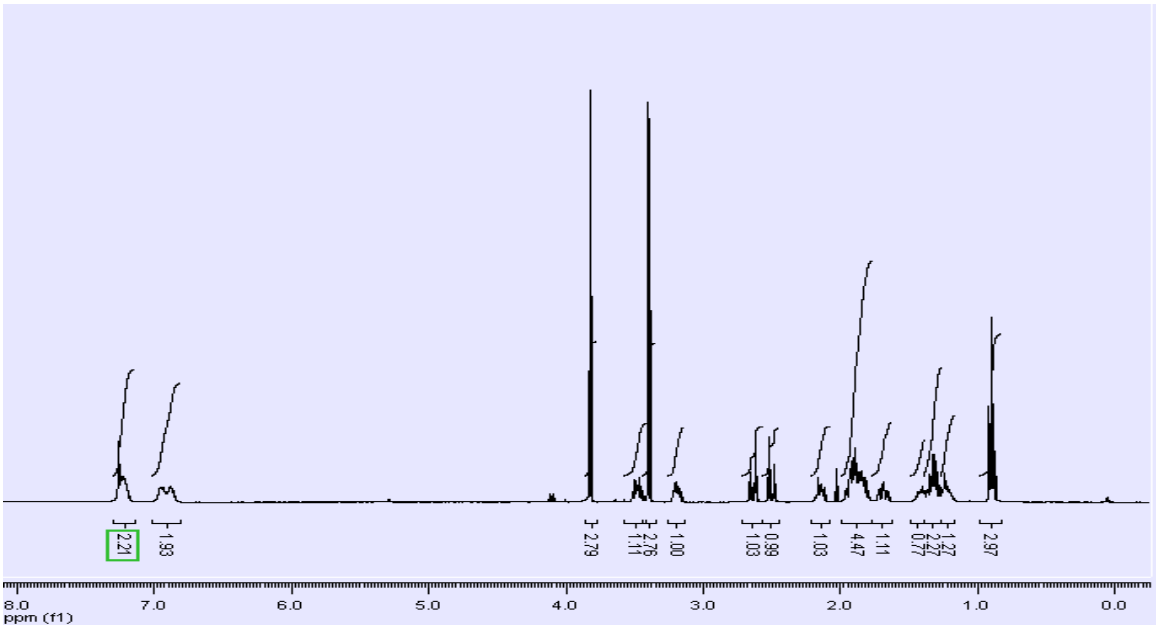
^{1}H NMR: VA-13



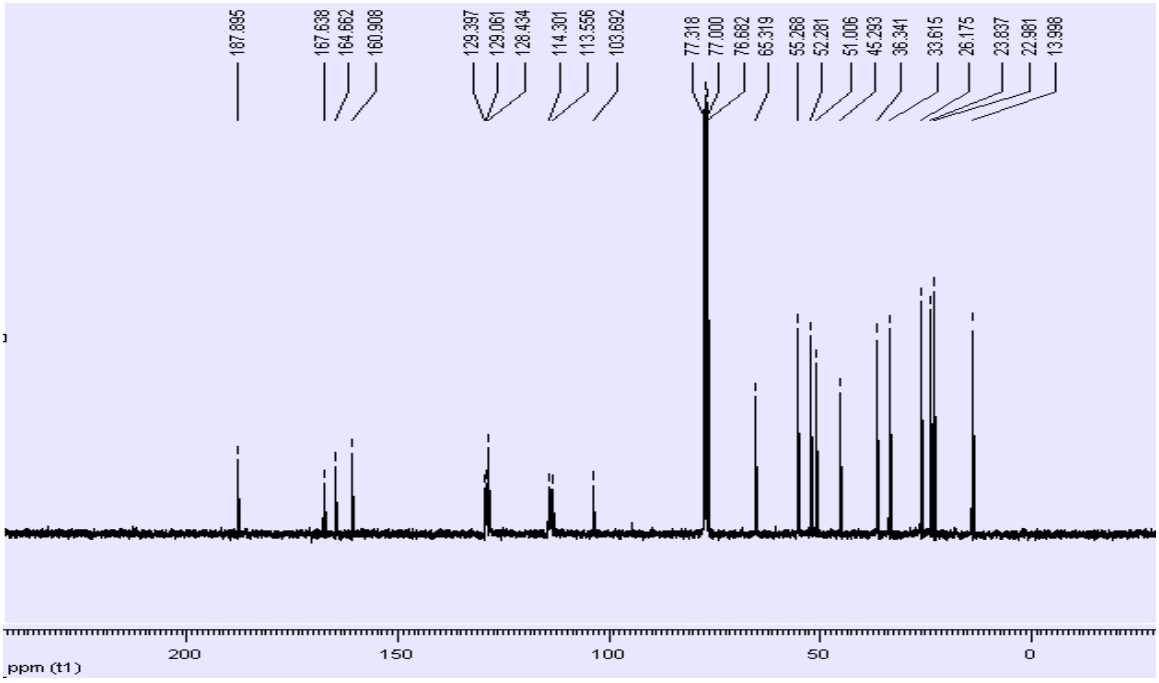
^{13}C NMR: VA-13



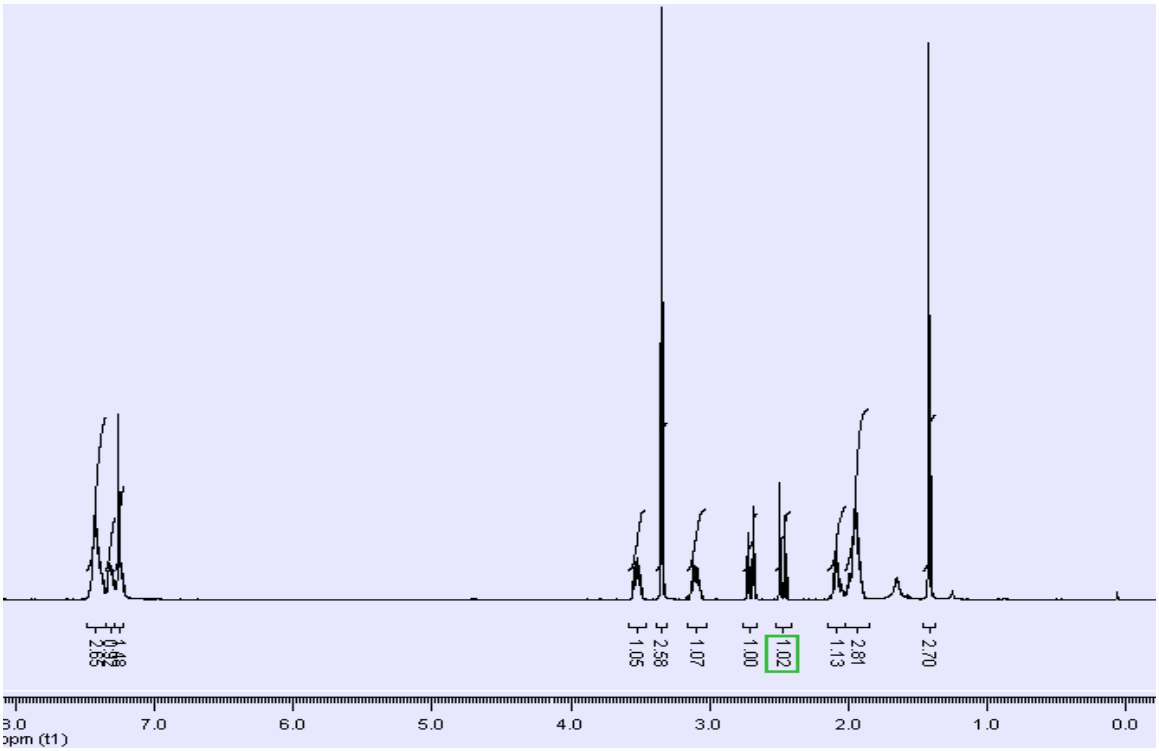
^{1}H NMR: VA-14



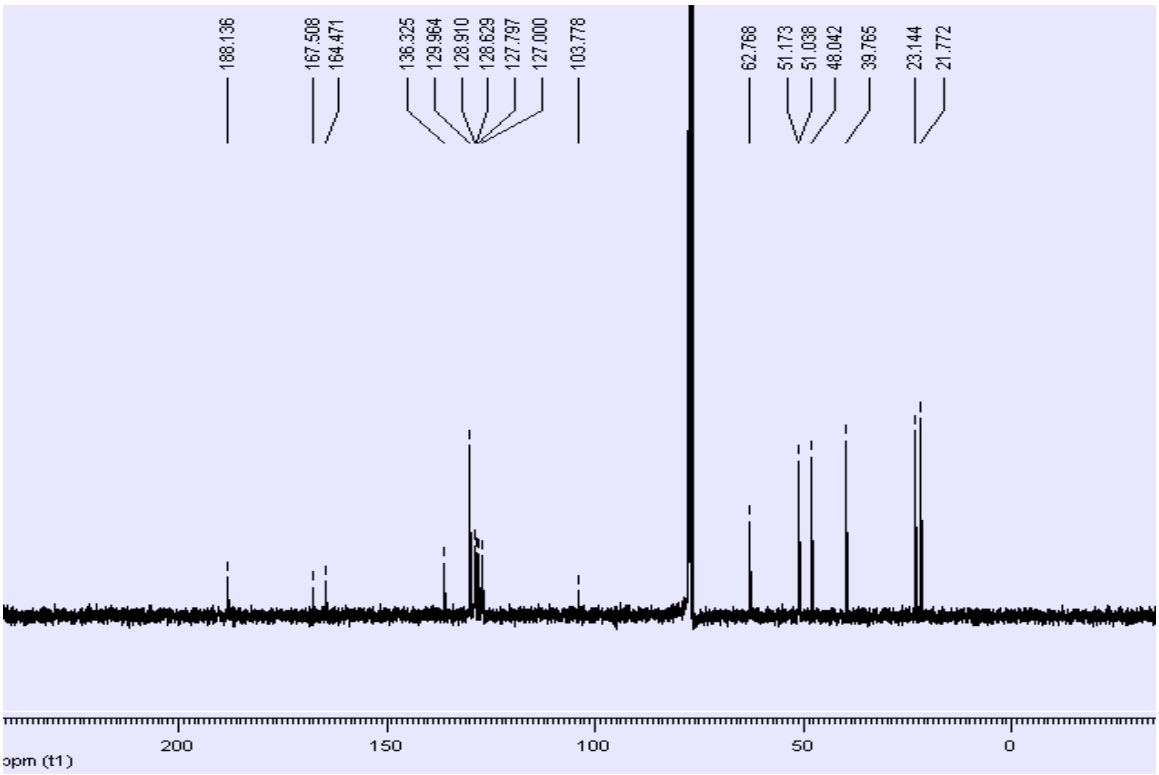
^{13}C NMR: VA-14



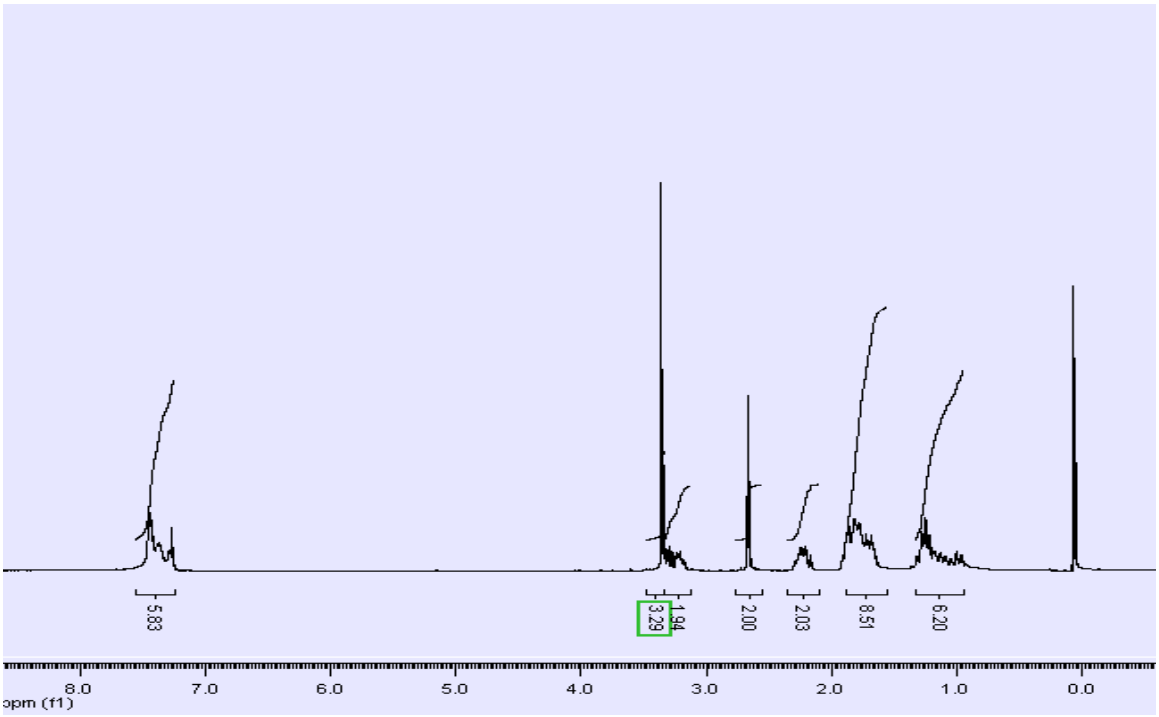
^{1}H NMR: VA-15



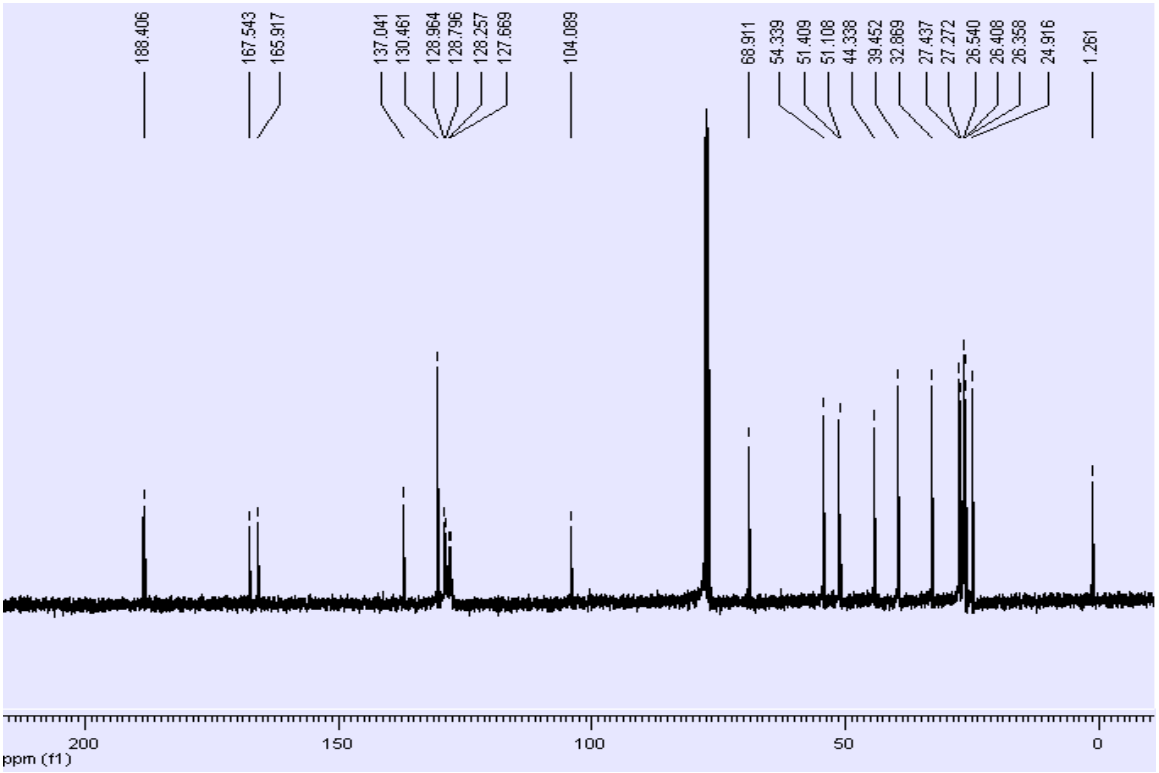
^{13}C NMR: VA-15



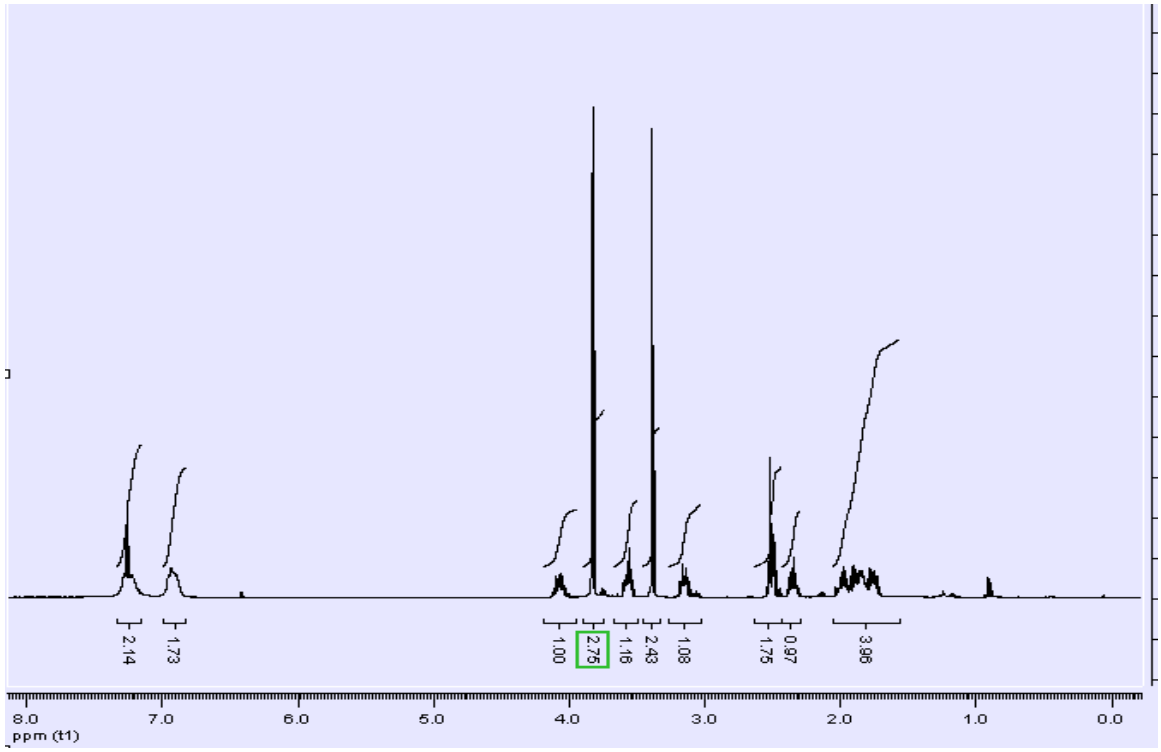
^{1}H NMR: VA-16



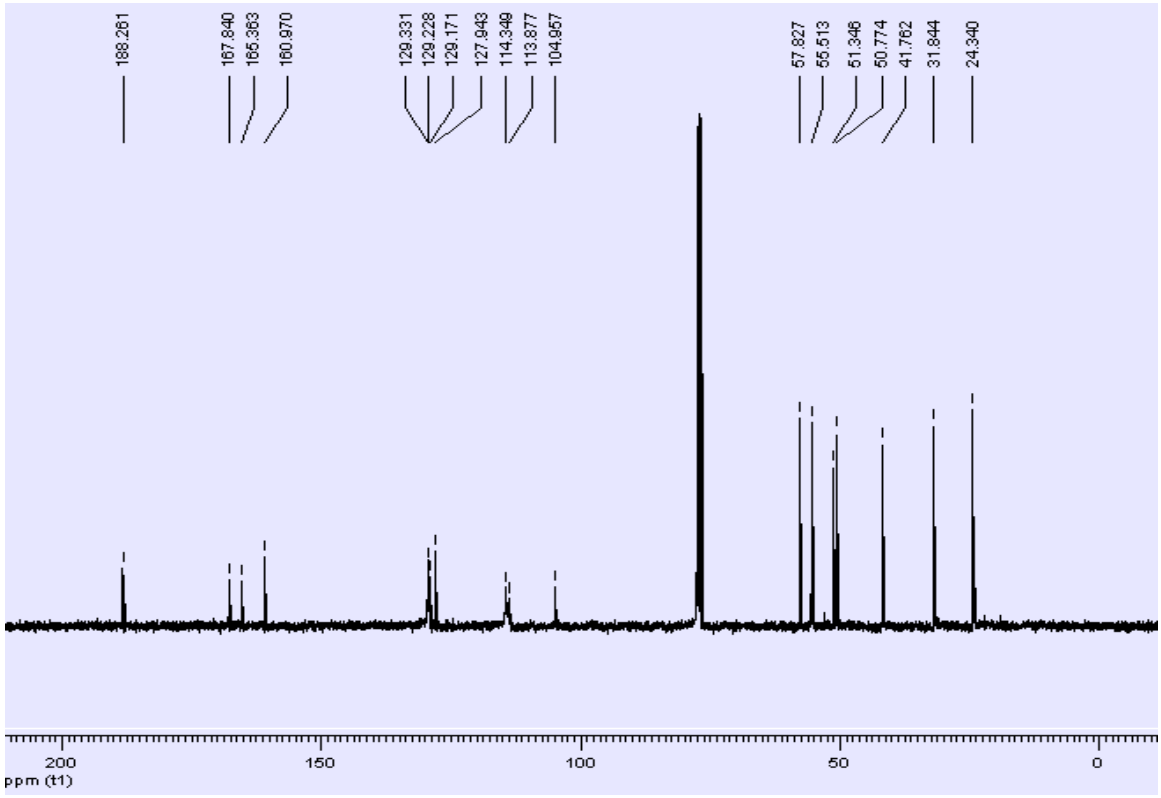
^{13}C NMR: VA-16



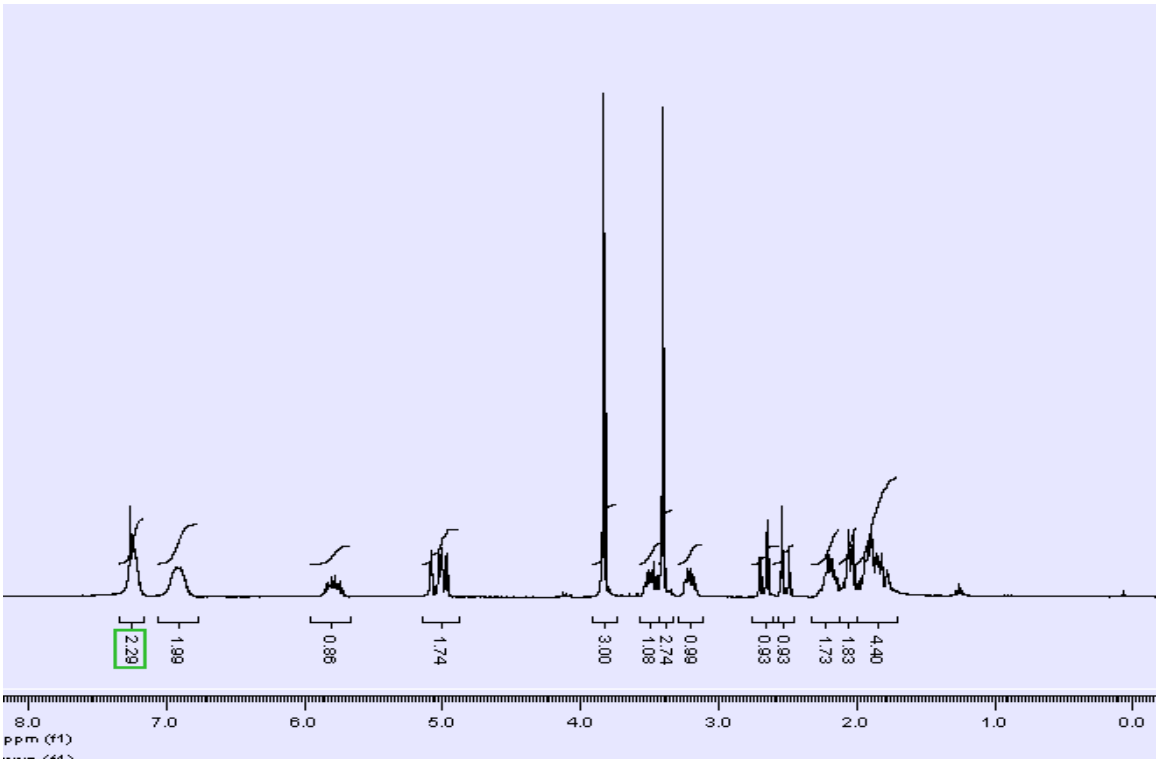
^{1}H NMR: VA-18a



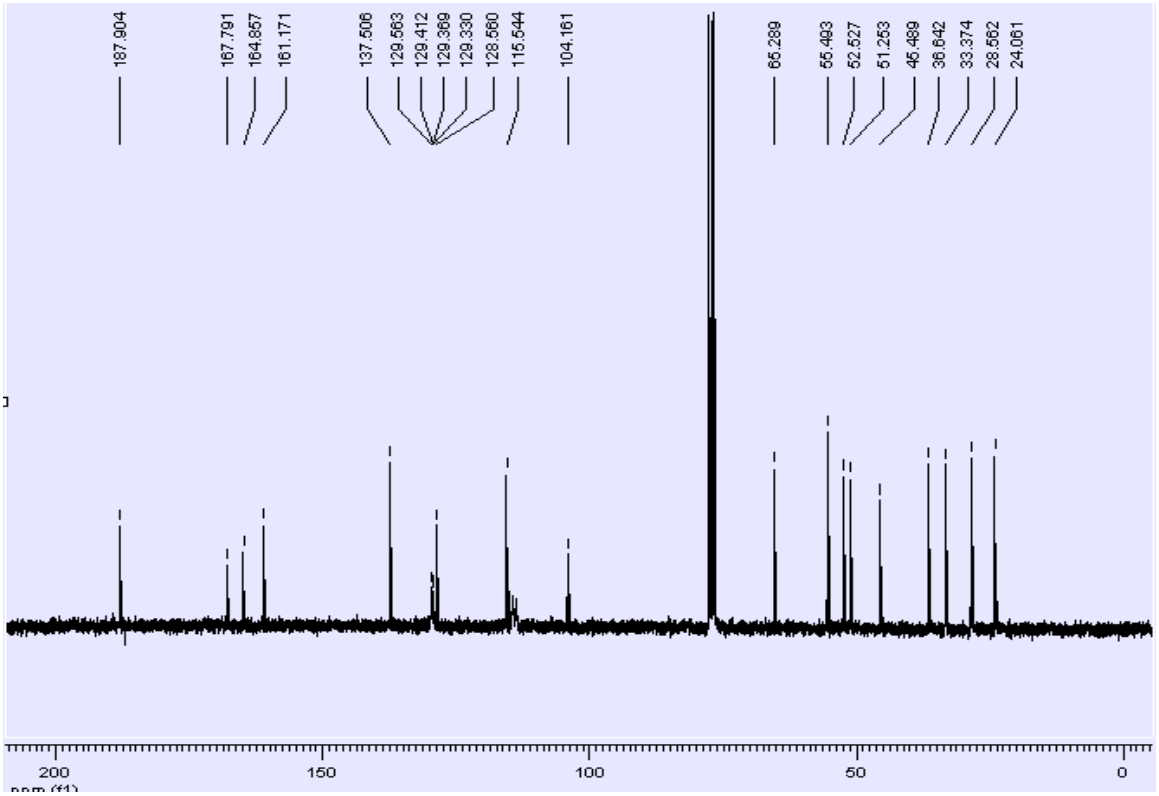
^{13}C NMR: VA-18a



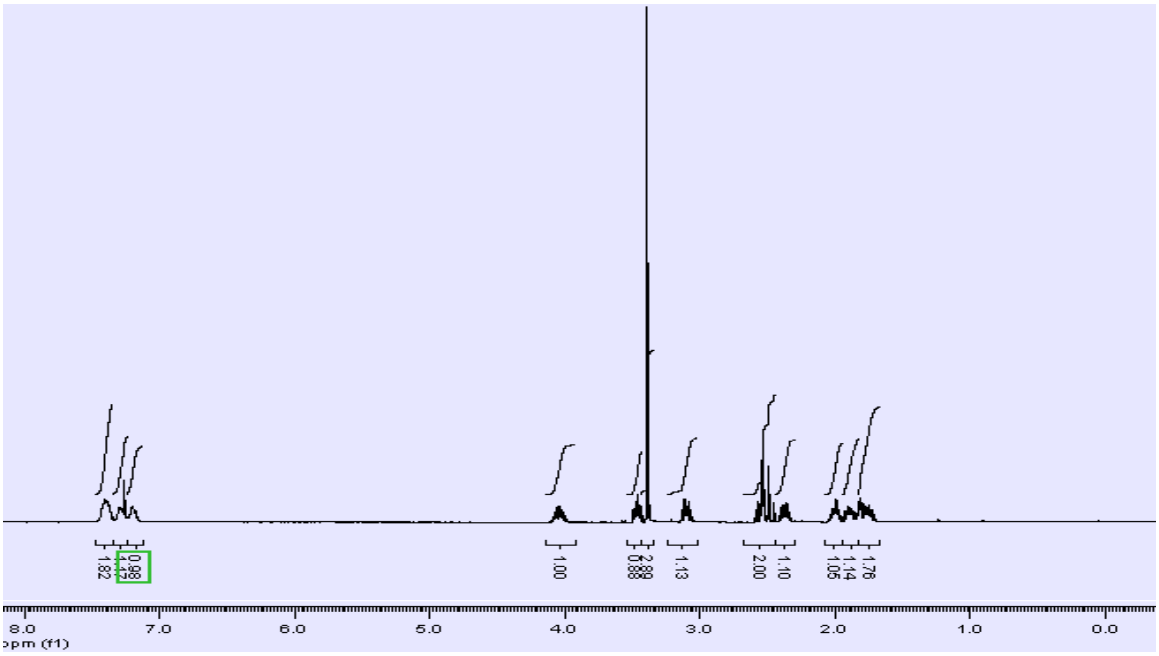
^{1}H NMR: VA-18b



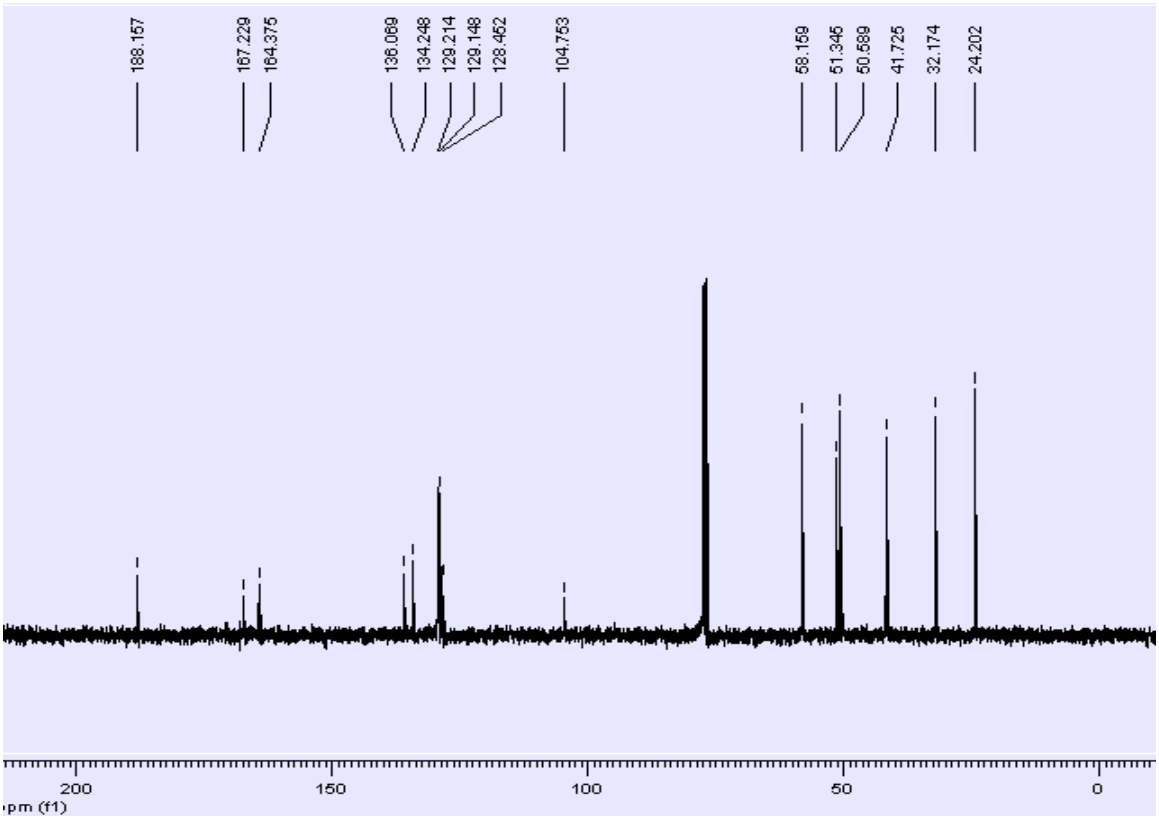
^{13}C NMR: VA-18b



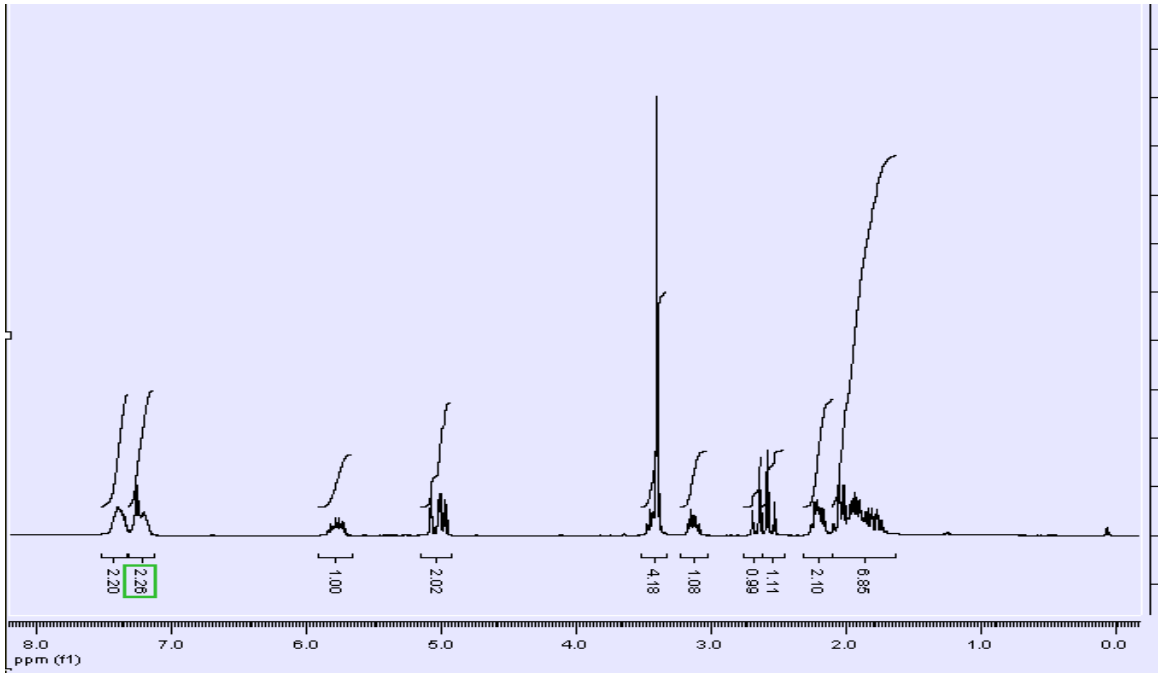
^{1}H NMR: VA-19a



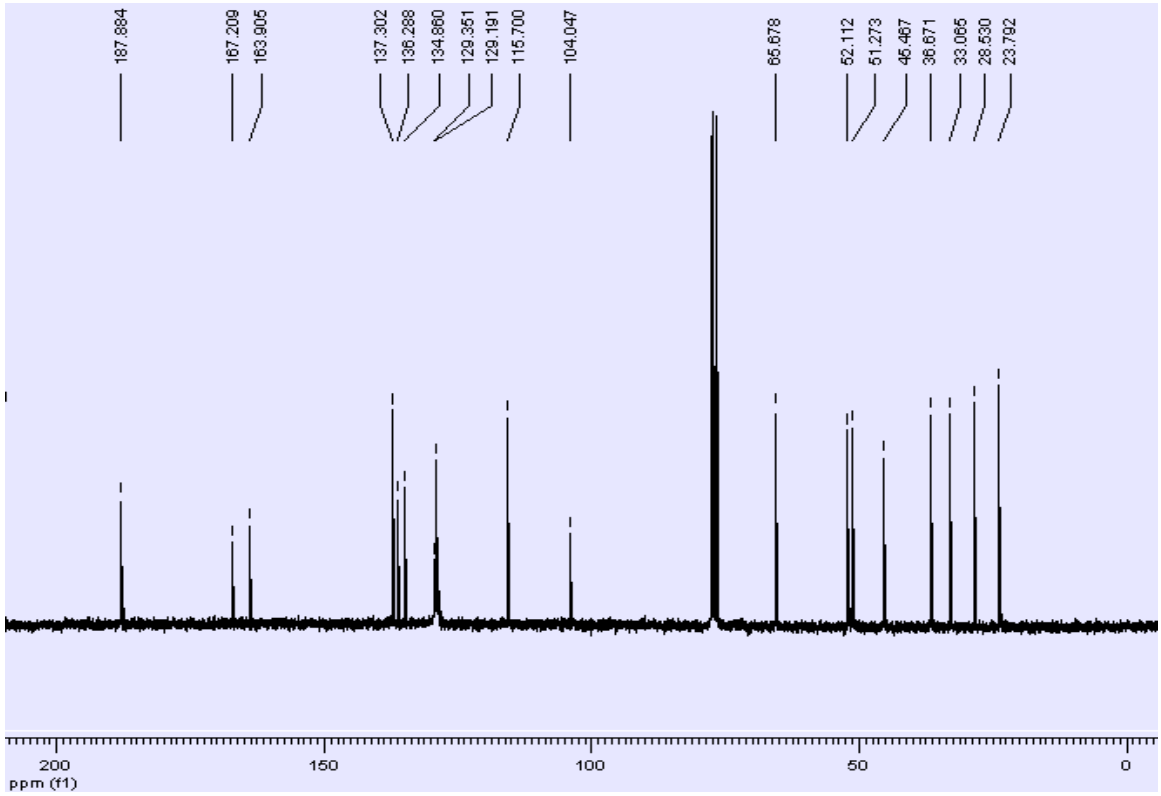
^{13}C NMR: VA-19a



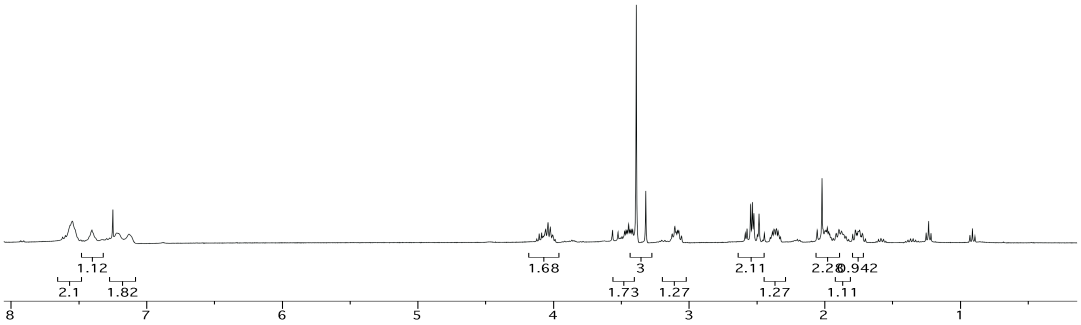
^{1}H NMR: VA-19b



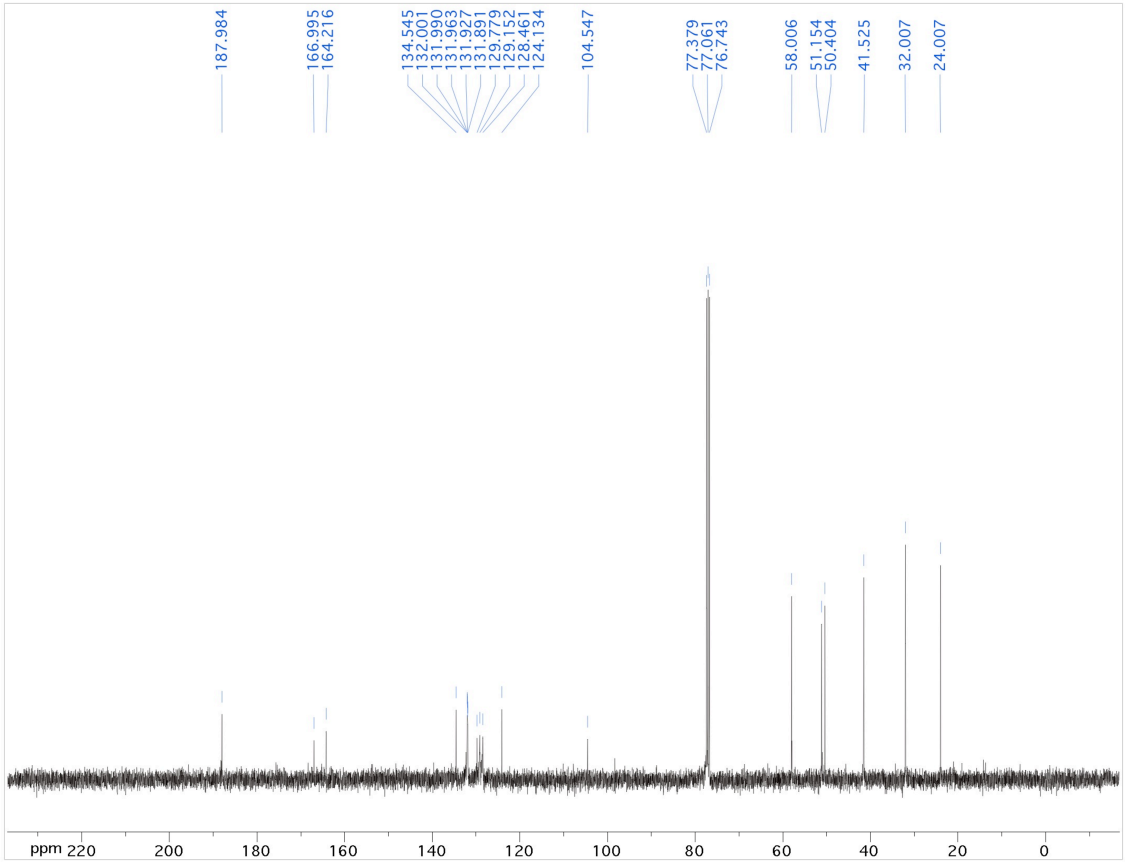
^{13}C NMR: VA-19b



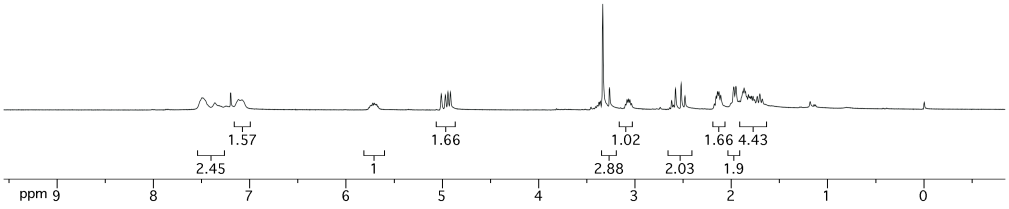
^{1}H NMR: VA-20a



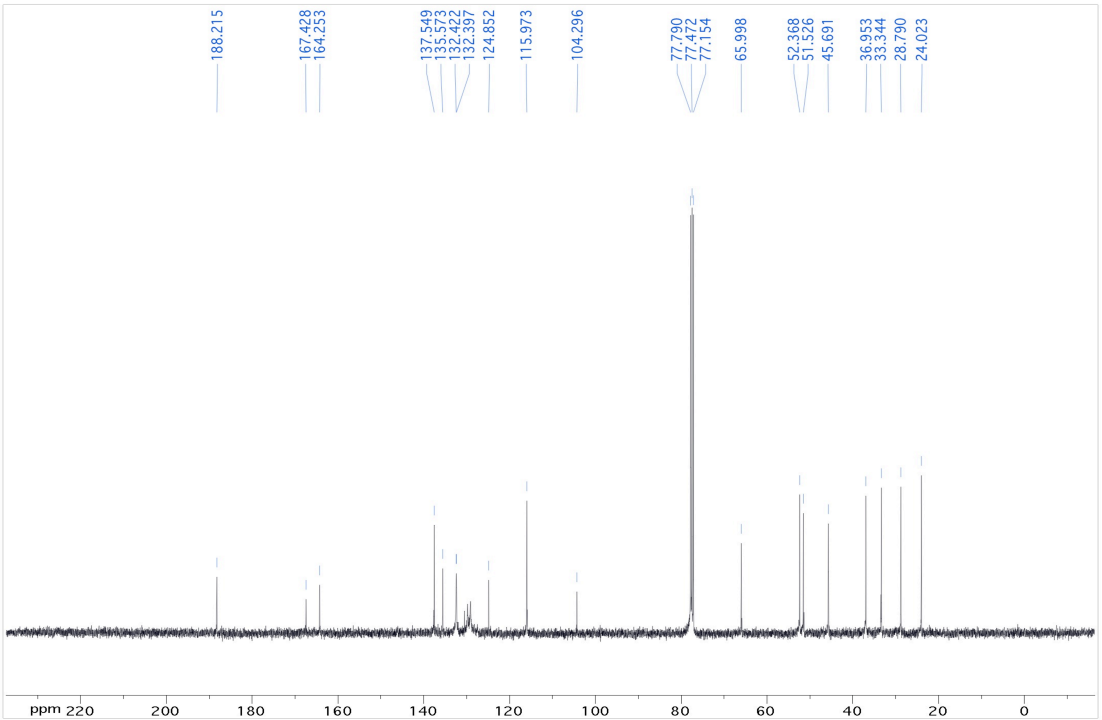
^{13}C NMR: VA-20a



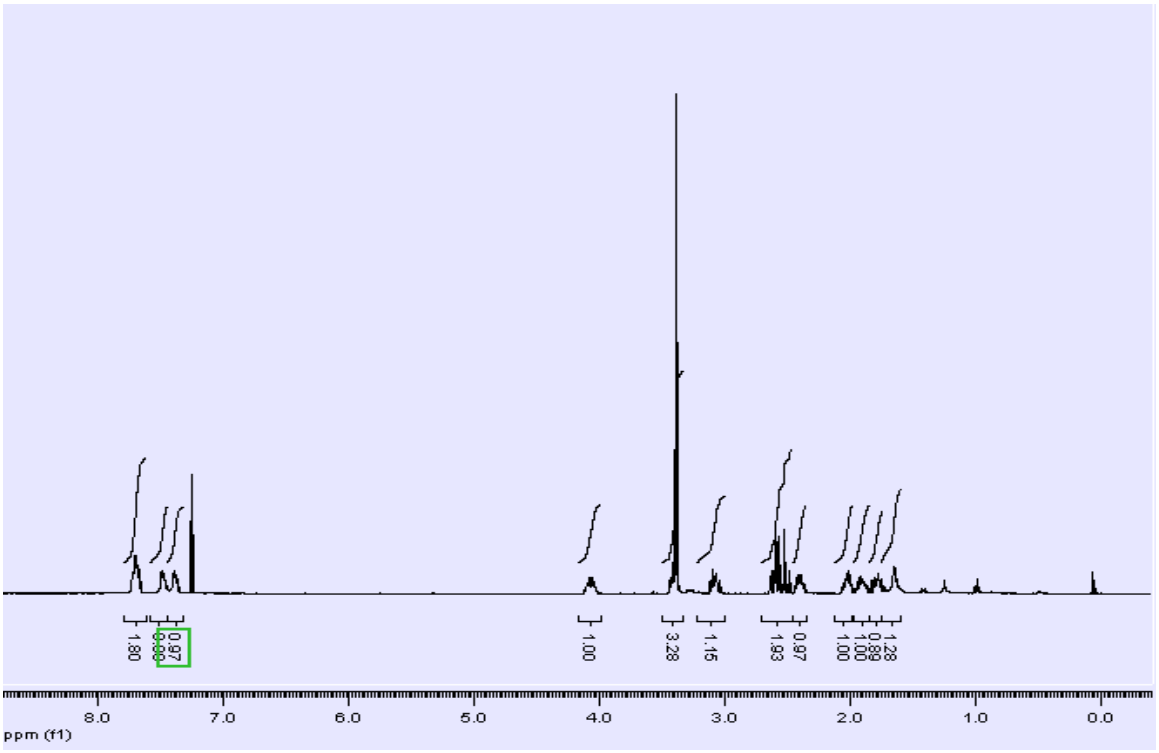
^{1}H NMR: VA-20b



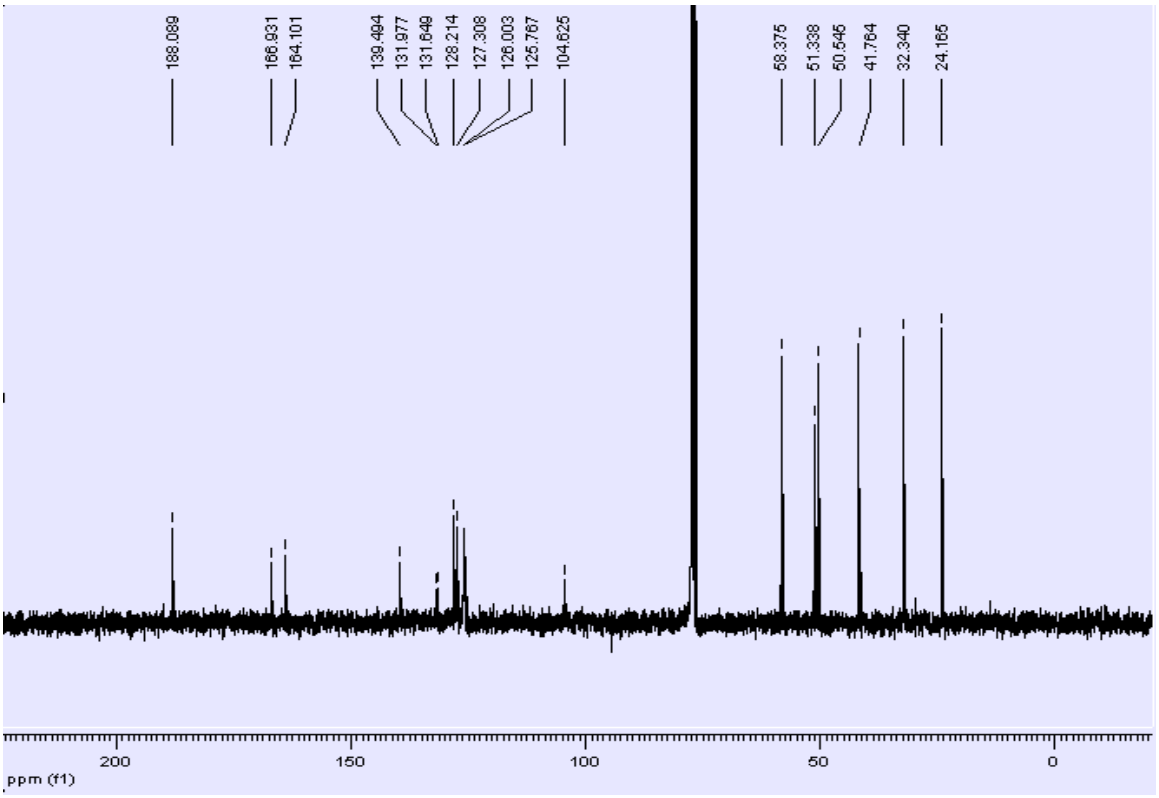
^{13}C NMR: VA-20b



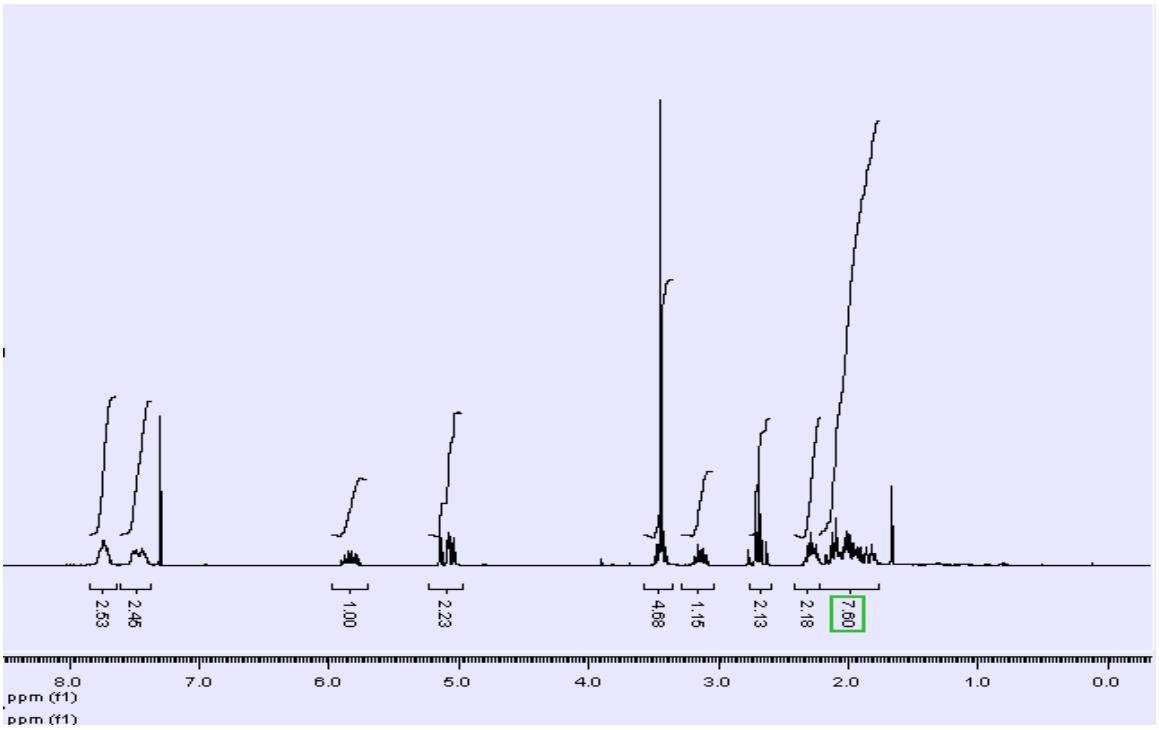
^{1}H NMR: VA-21a



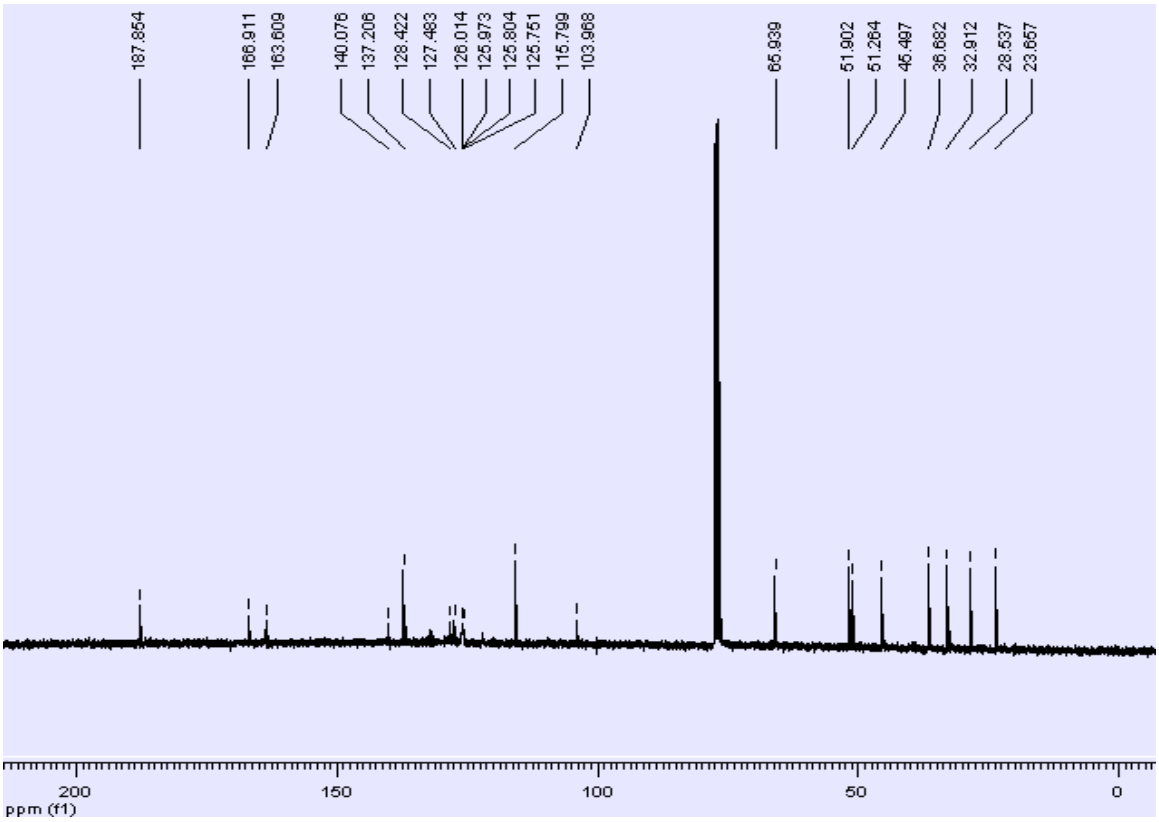
^{13}C NMR: VA-21a



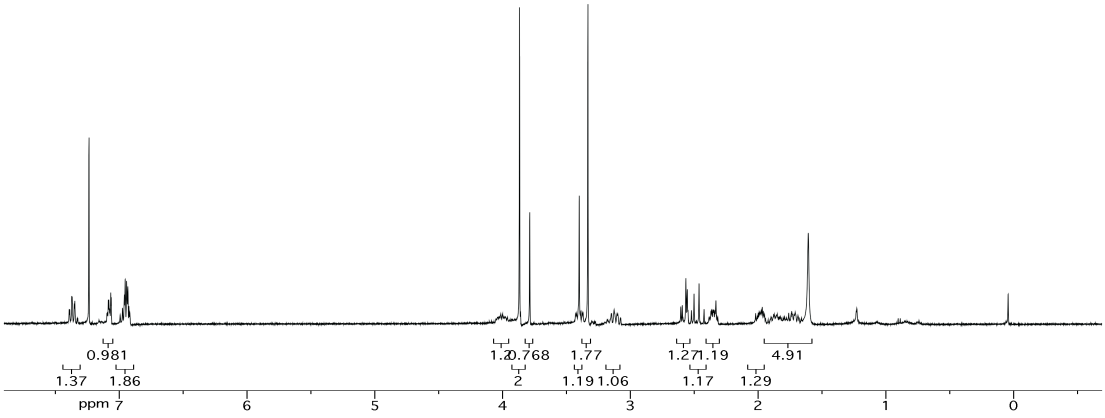
^{1}H NMR: VA-21b



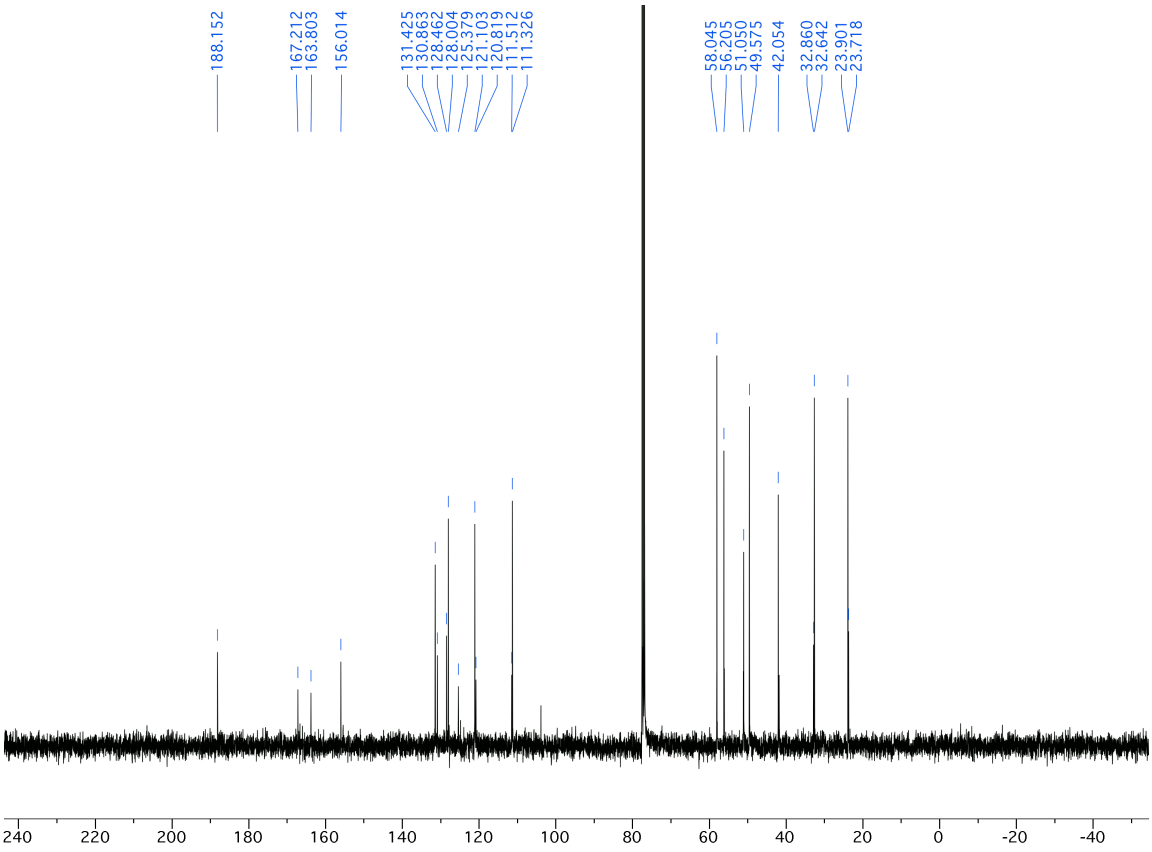
^{13}C NMR: VA-21b



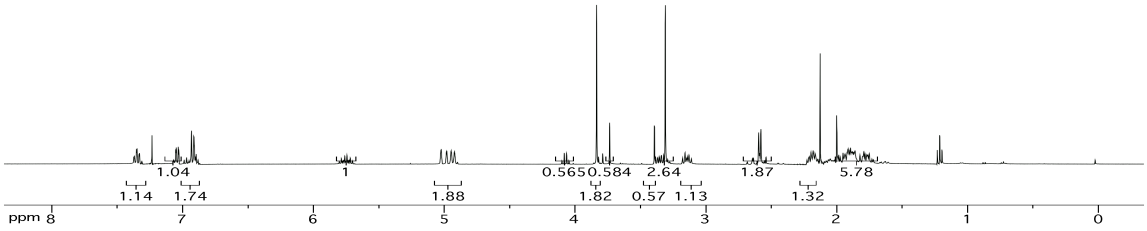
^{1}H NMR: VA-22a



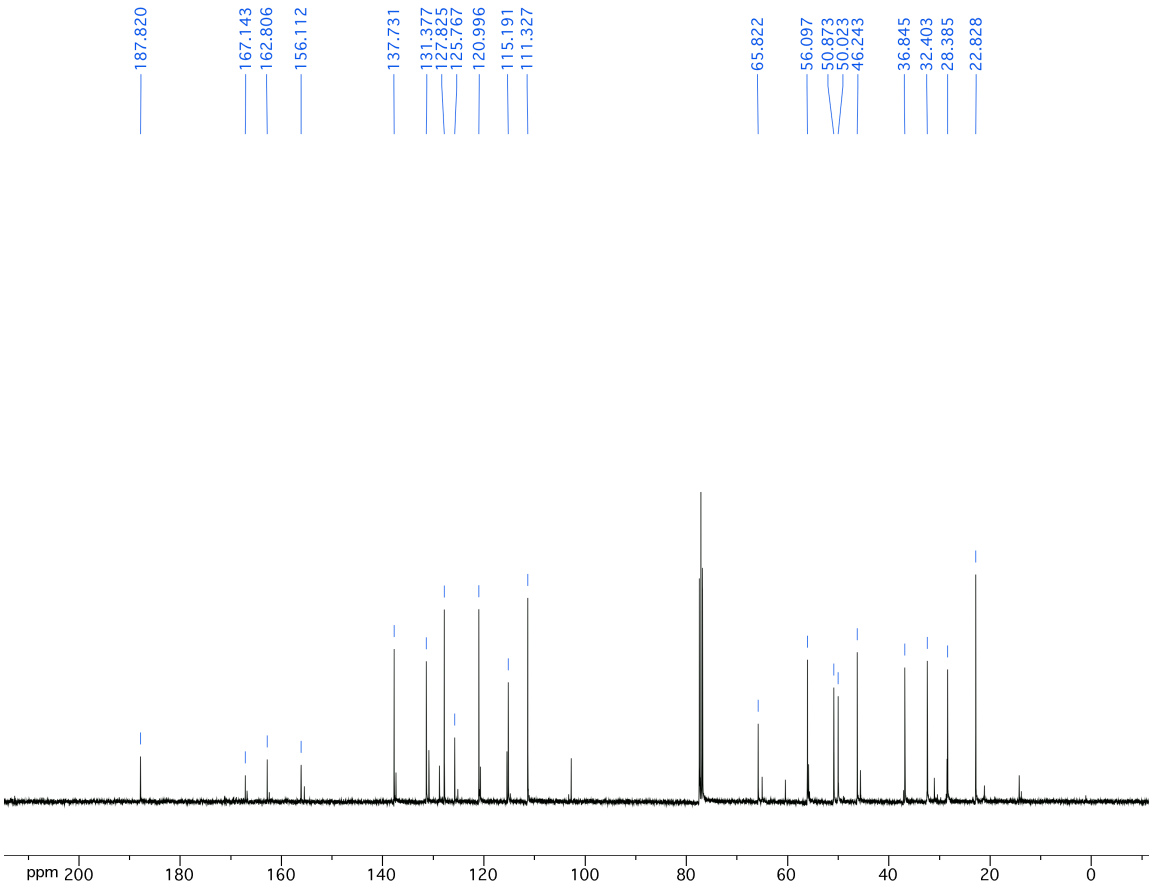
^{13}C NMR: VA-22a



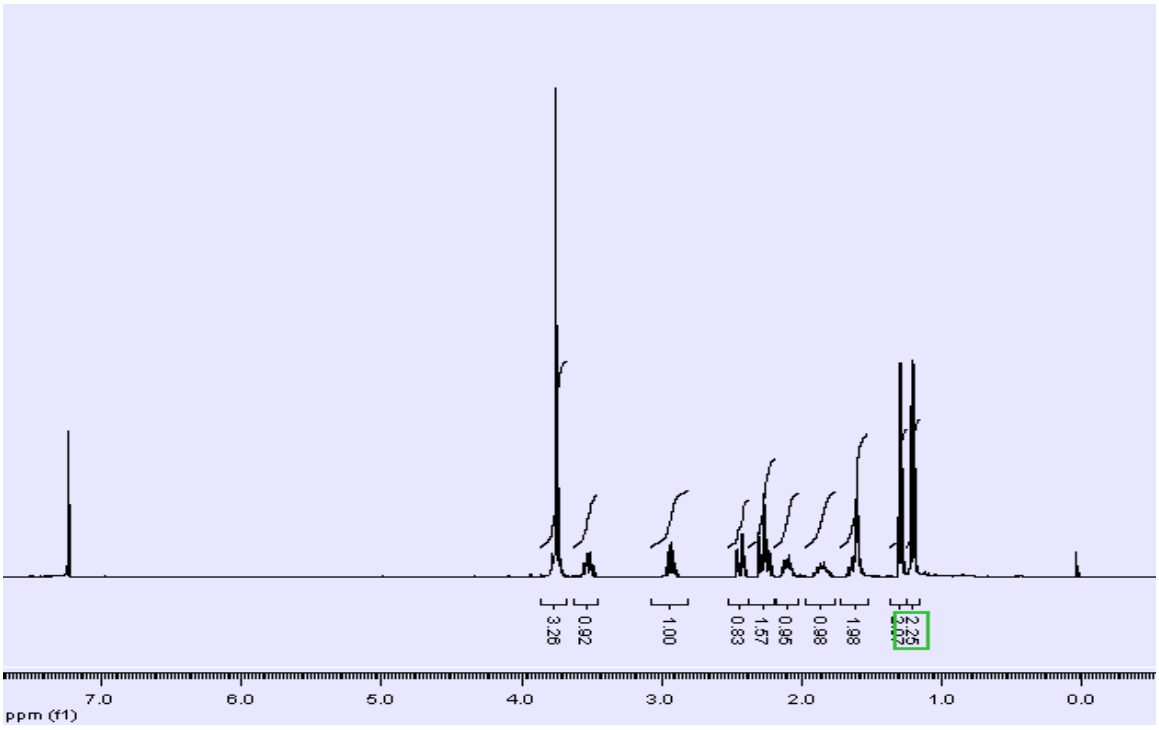
^{1}H NMR: VA-22b



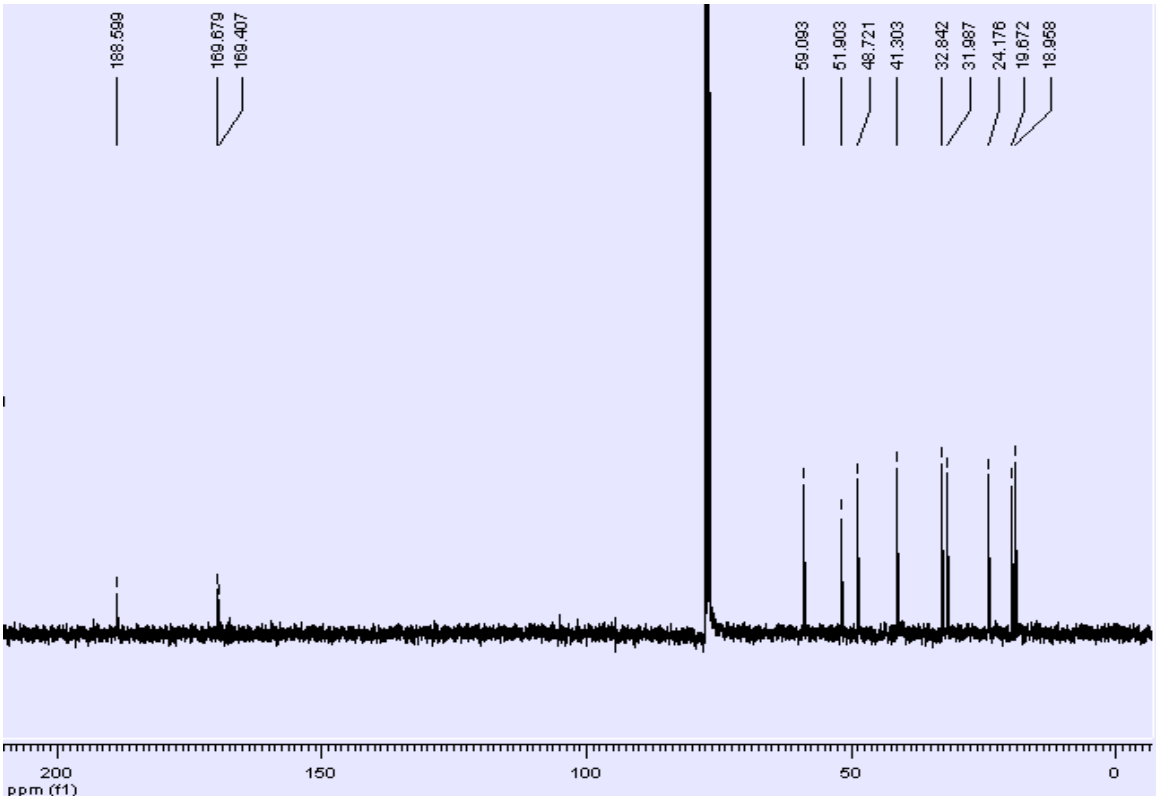
^{13}C NMR: VA-22b



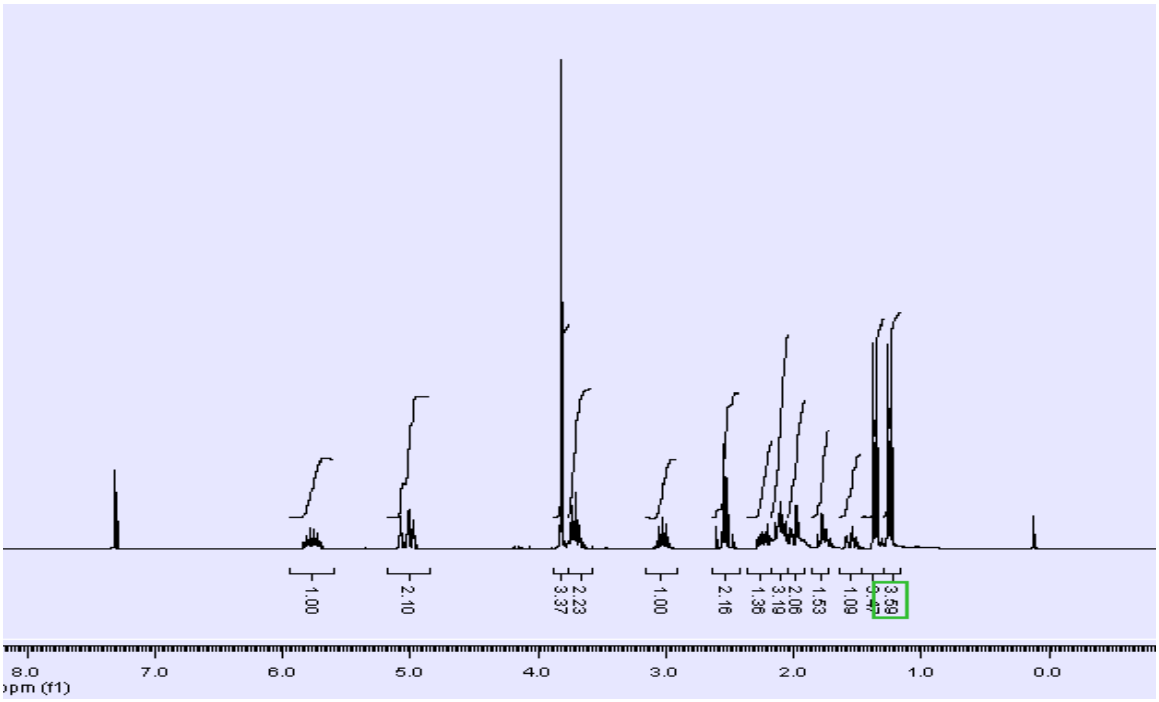
^{1}H NMR: VA-23a



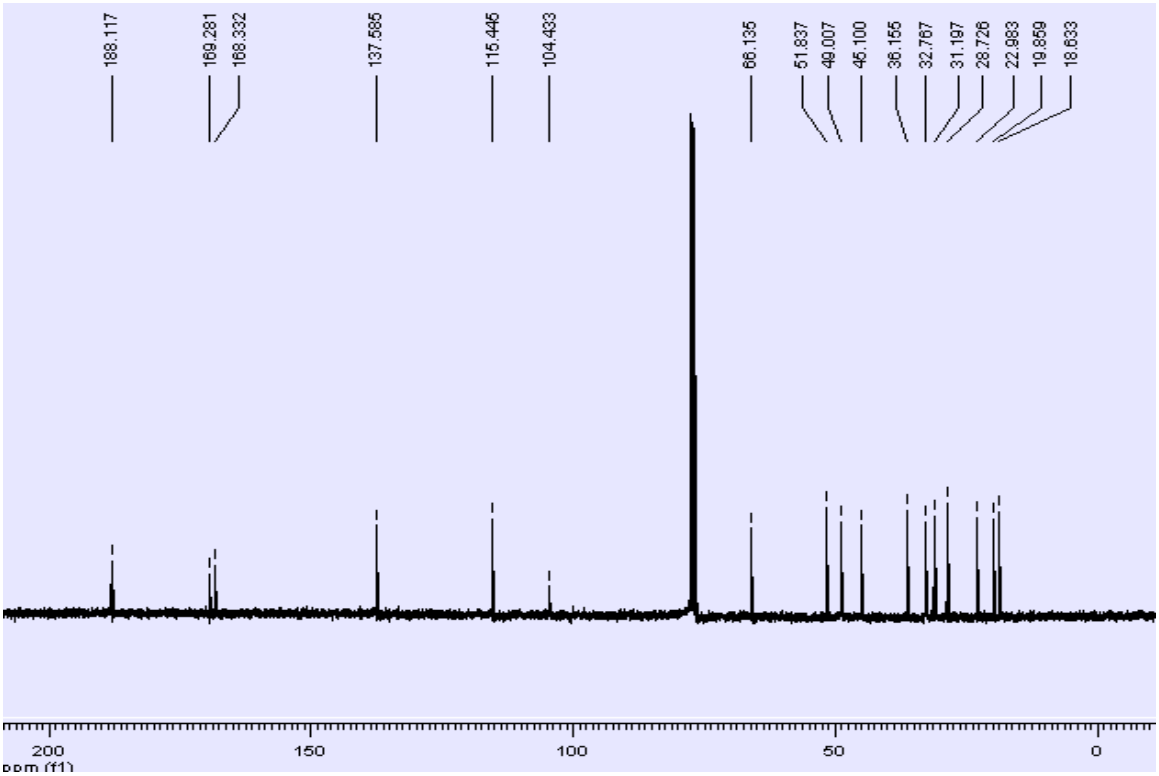
^{13}C NMR: VA-23a



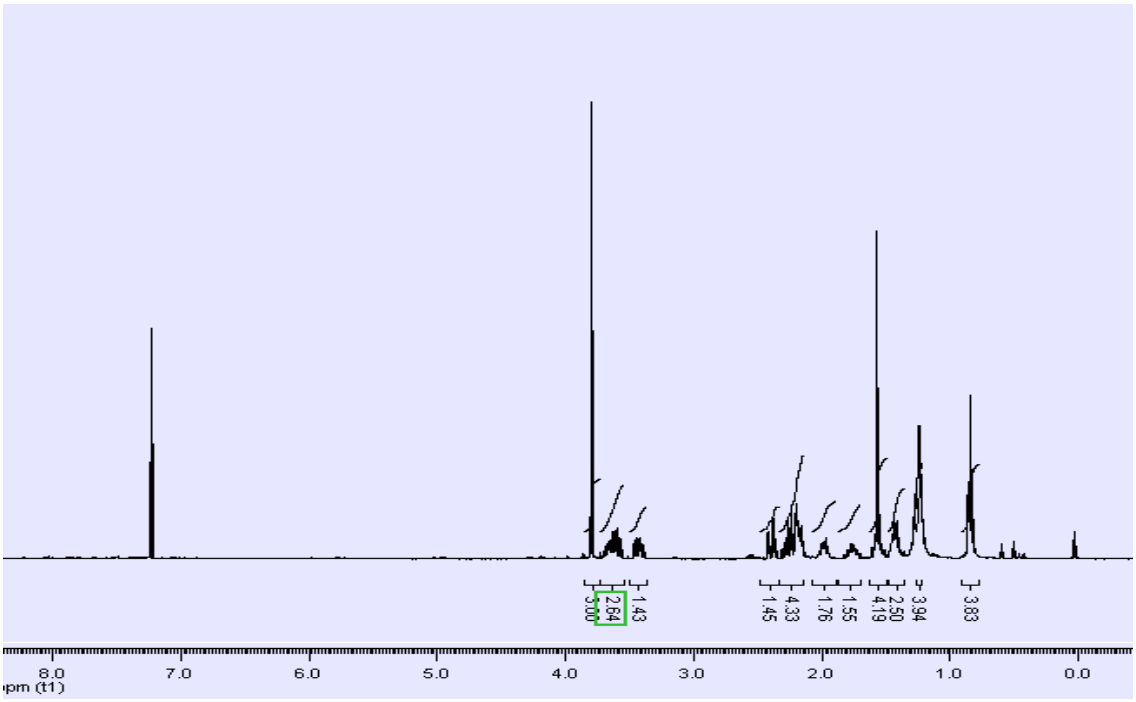
^{1}H NMR: VA-23b



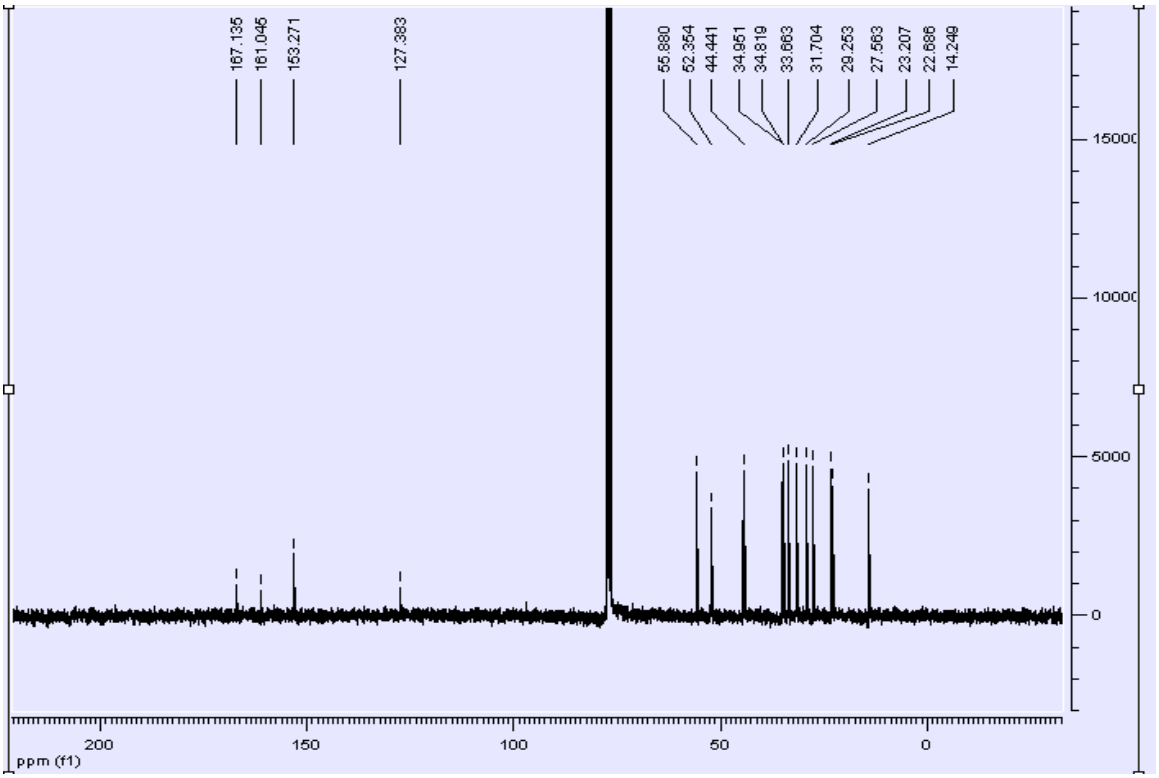
^{13}C NMR: VA-23b



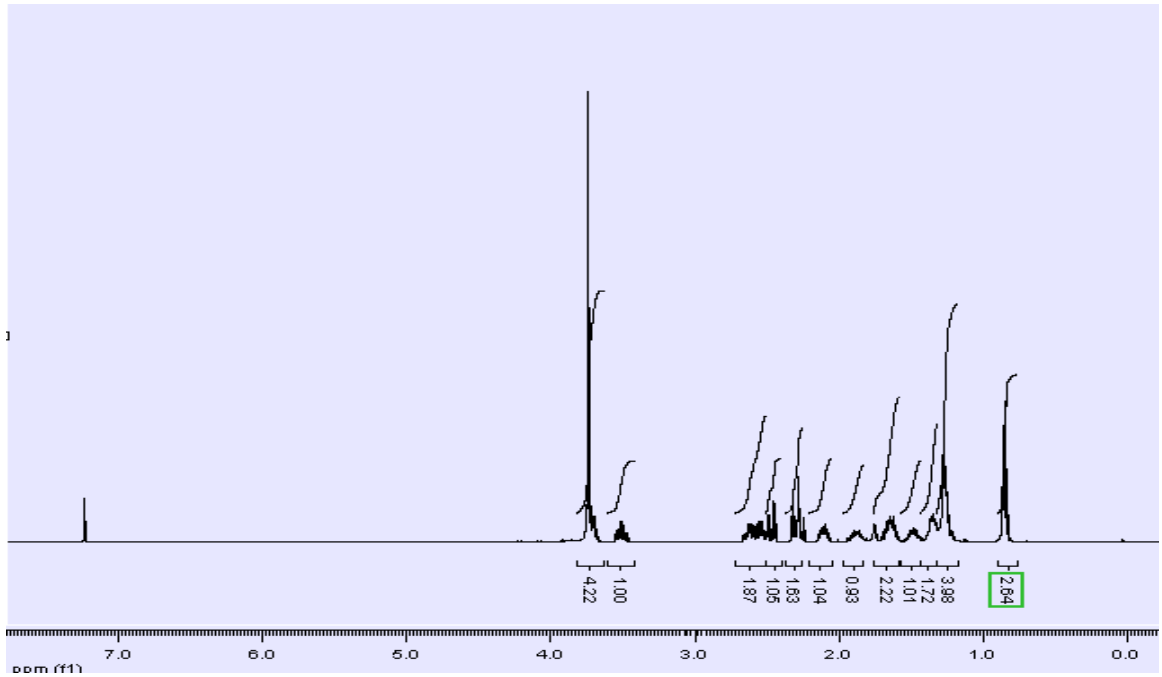
^{1}H NMR: LA-11a



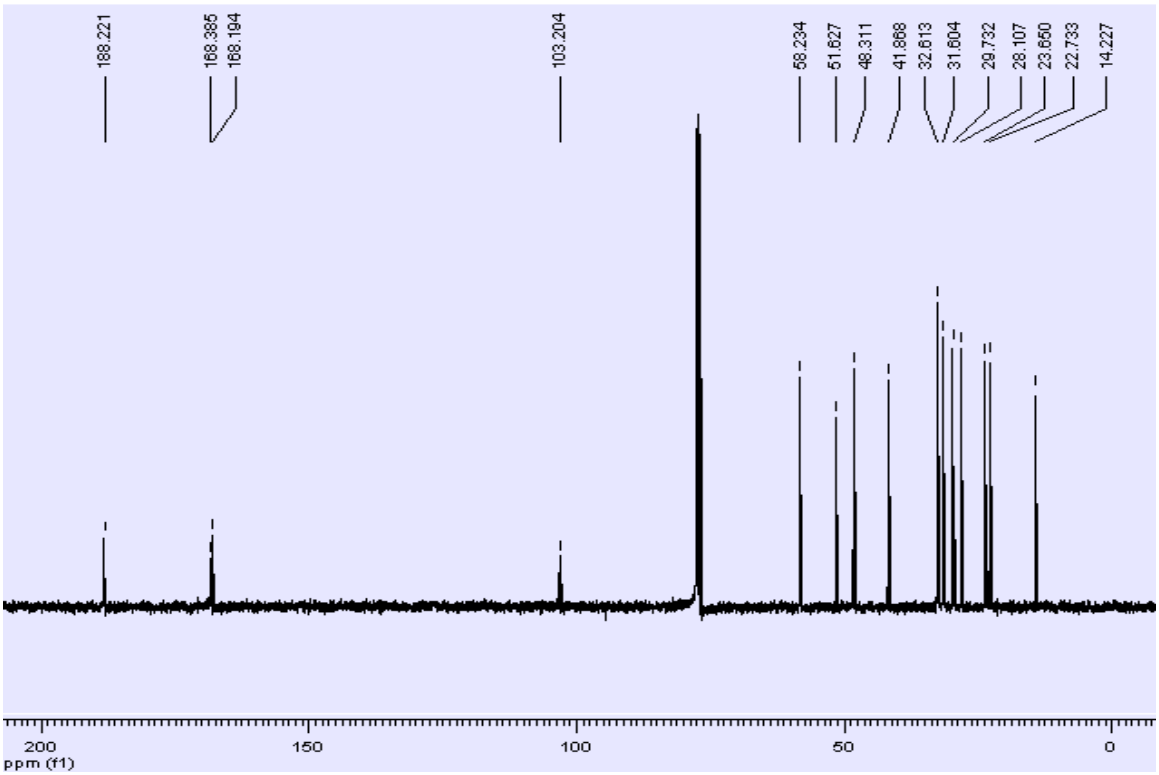
^{13}C NMR: LA-11a



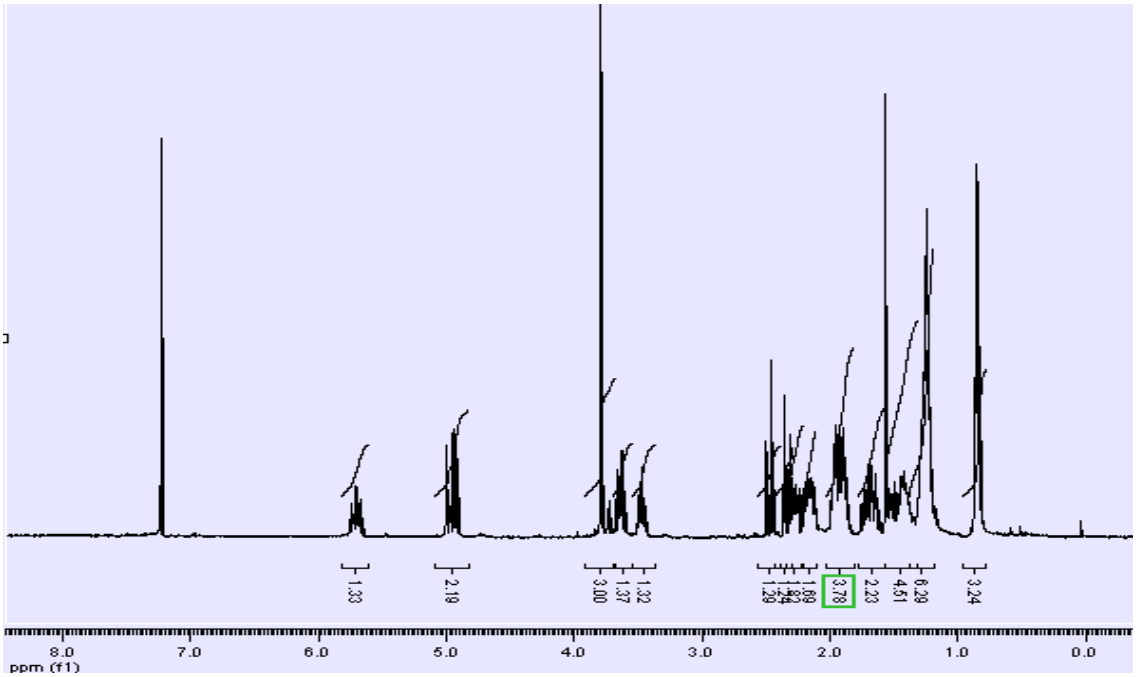
^{1}H NMR: VA-24a



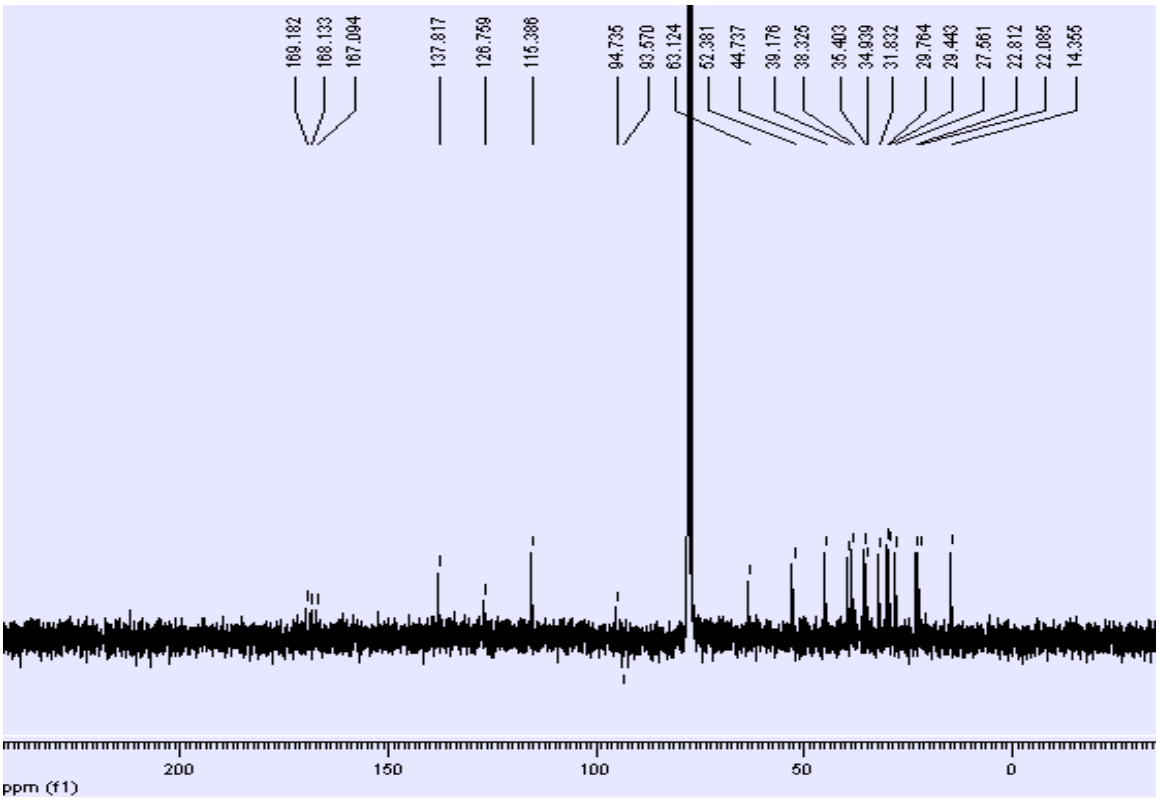
^{13}C NMR: VA-24a



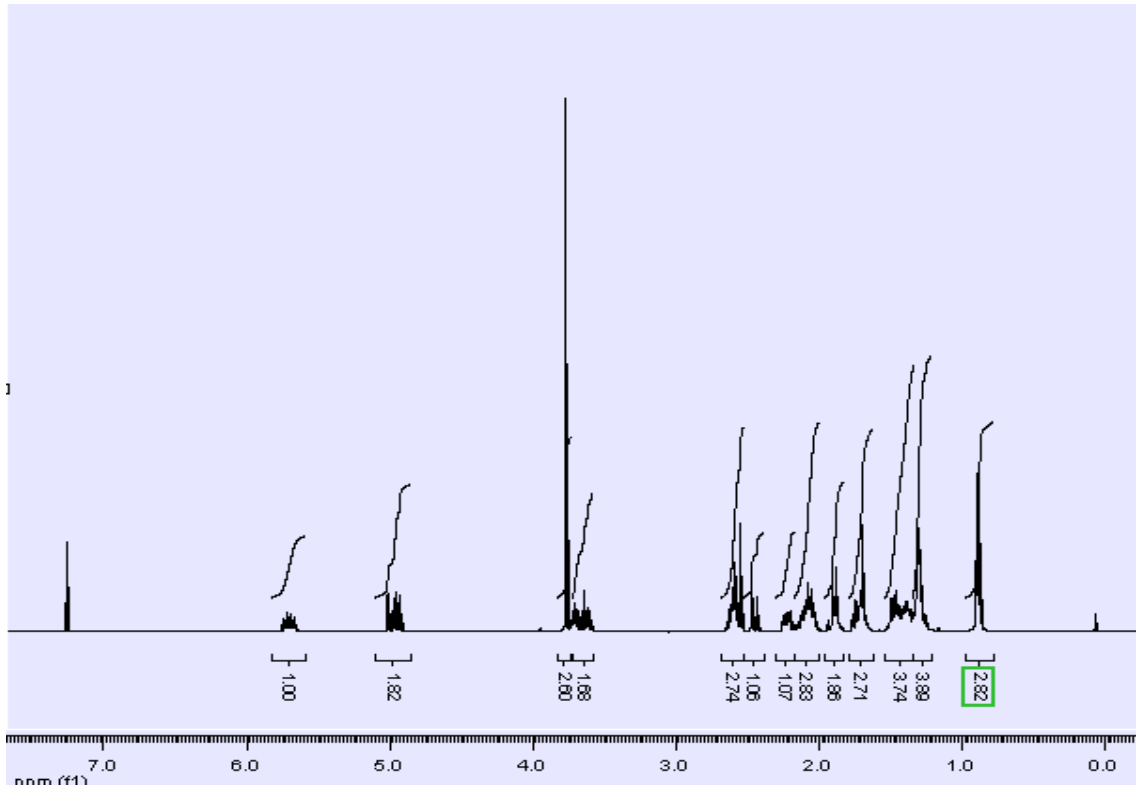
^{1}H NMR: LA-11b



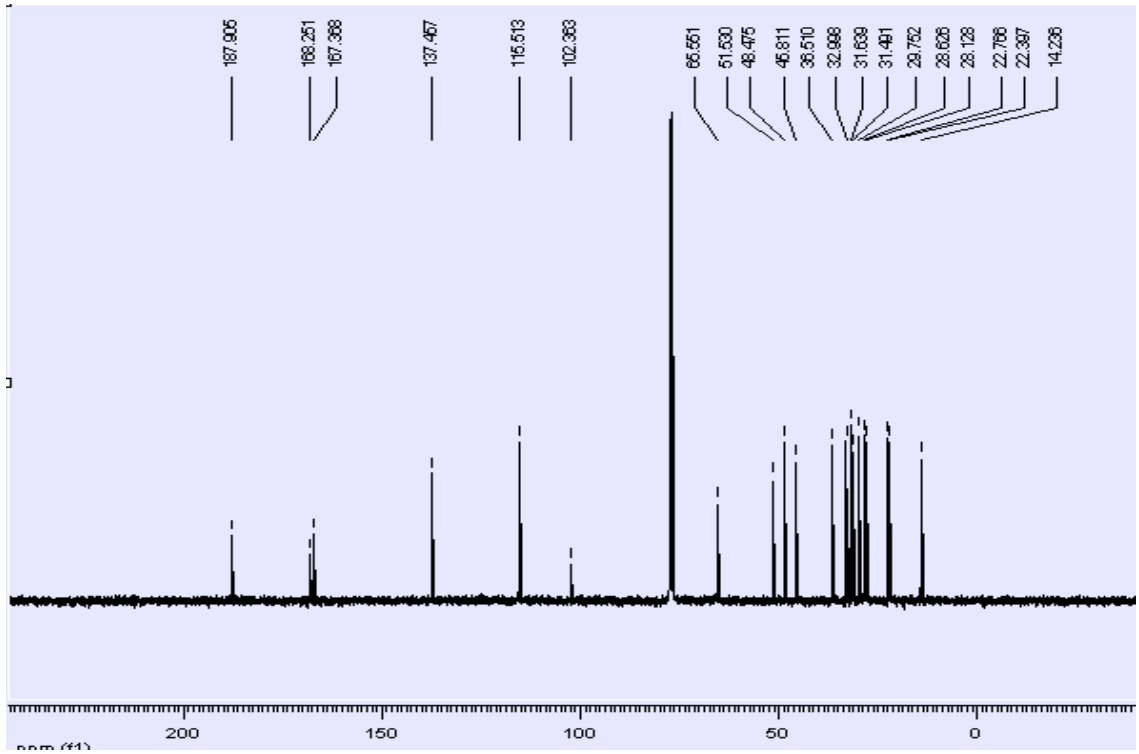
^{13}C NMR: LA-11b



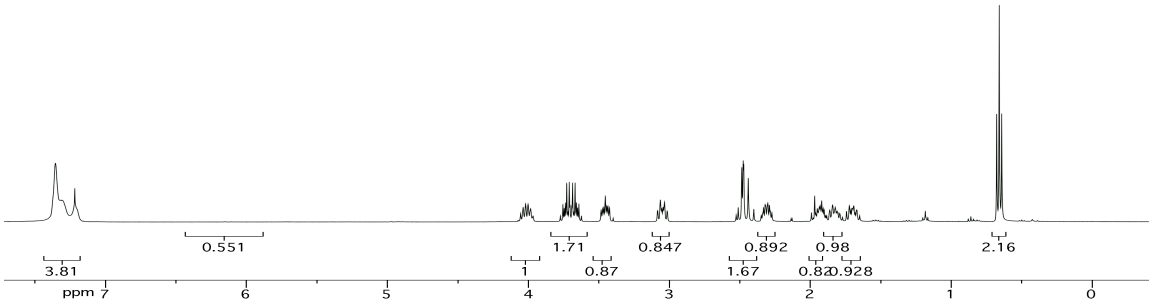
^{1}H NMR: VA-24b



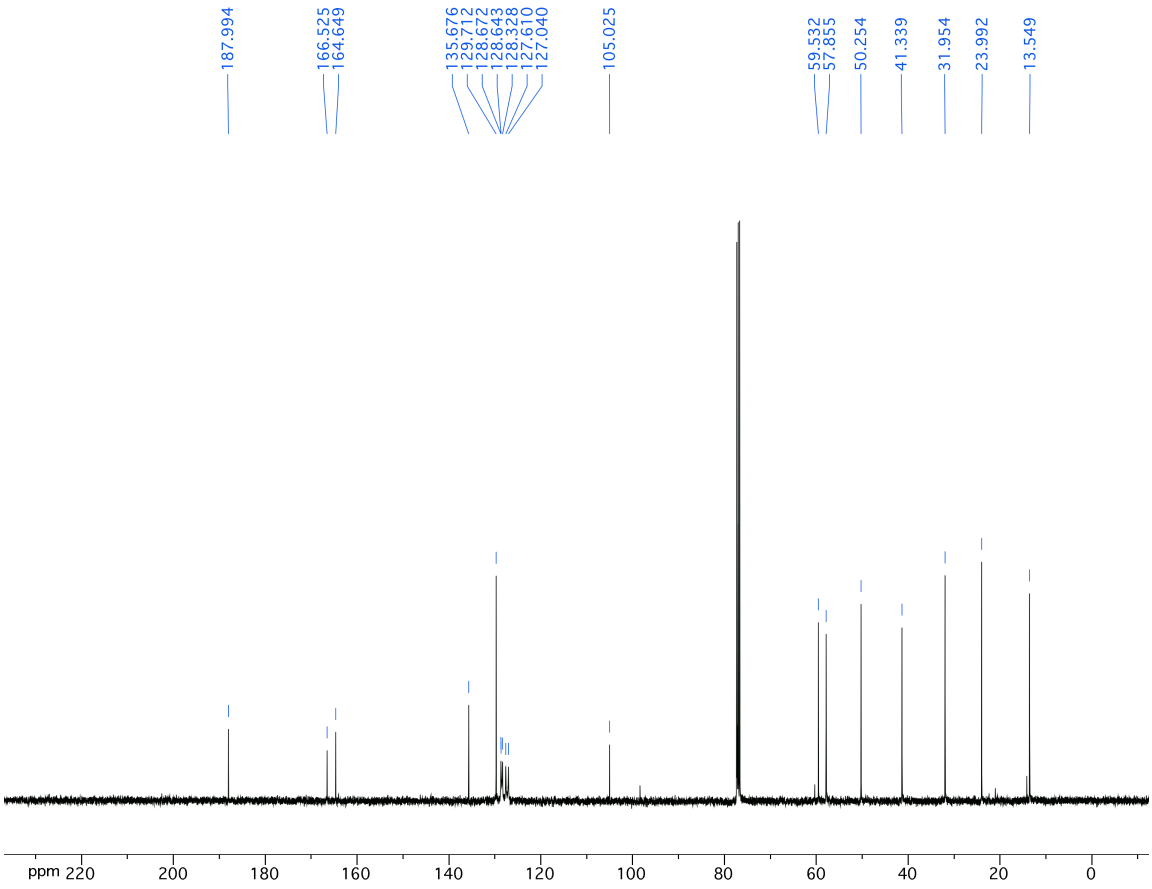
^{13}C NMR: VA-24b



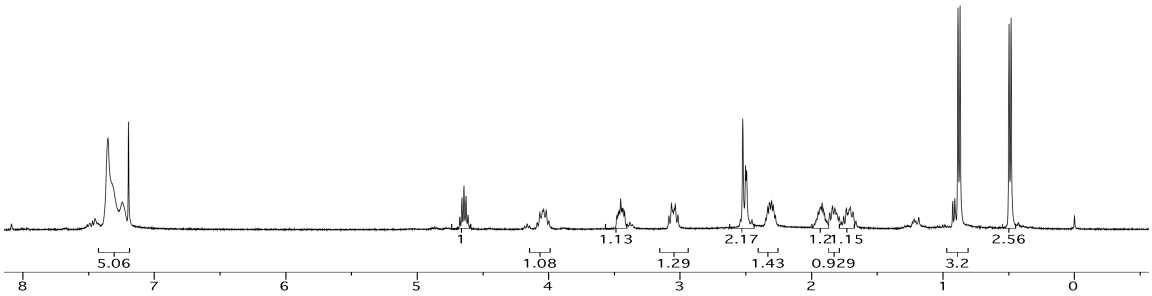
^{1}H NMR: VA-26a



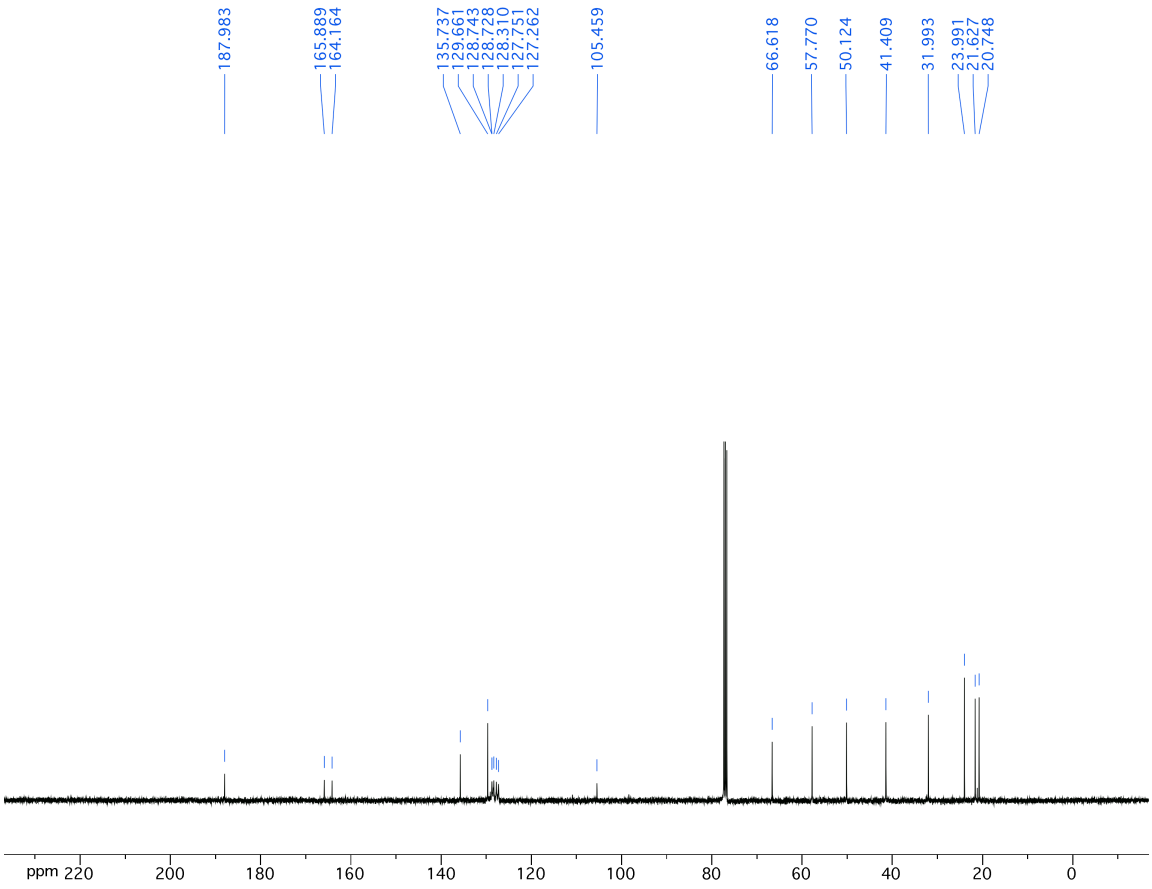
^{13}C NMR: VA-26a



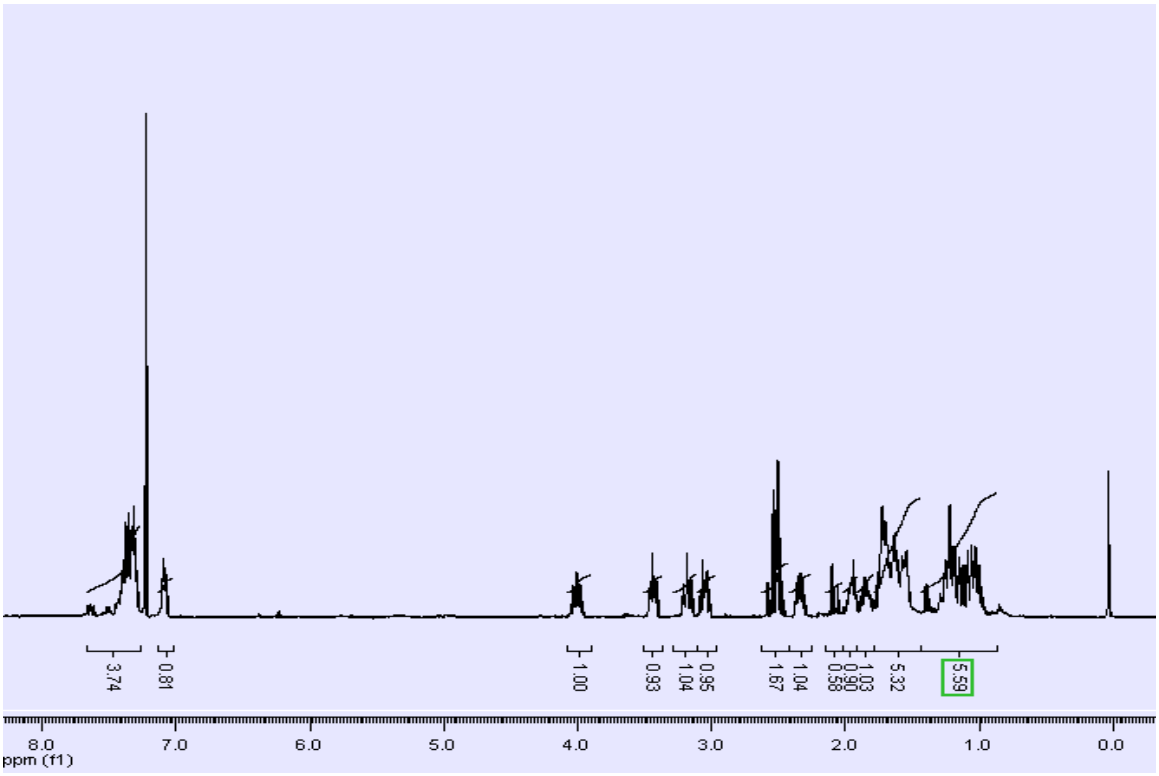
^{1}H NMR: VA-27a



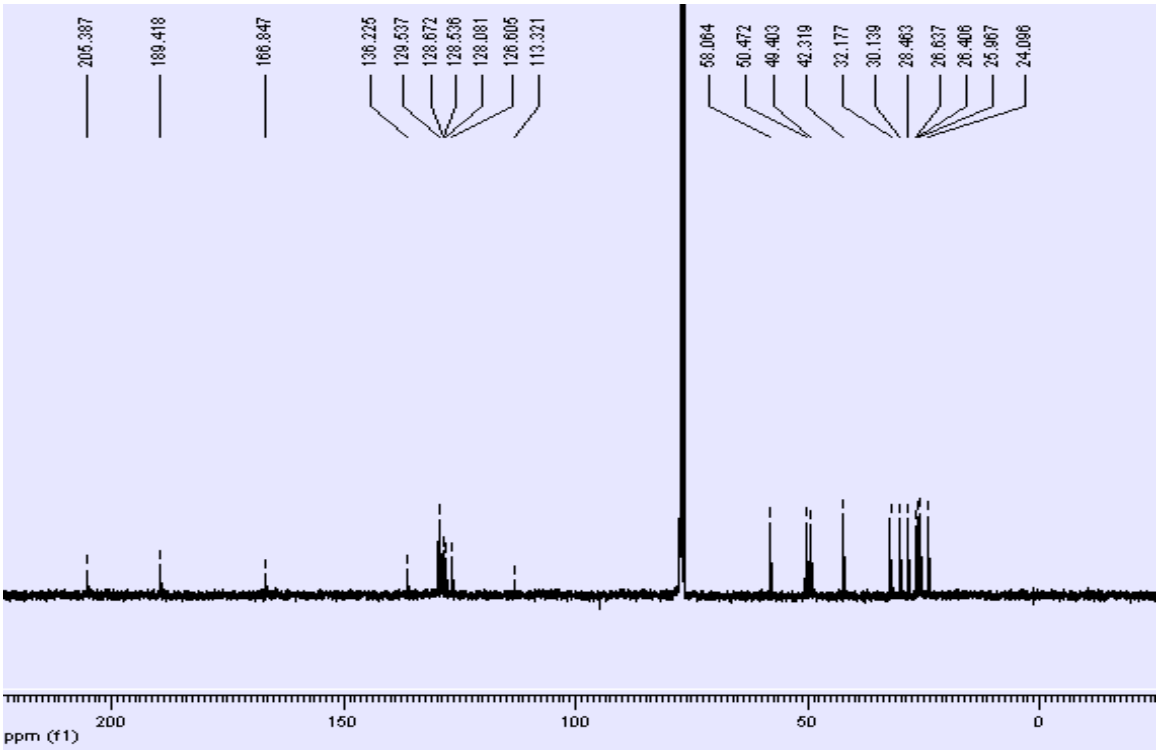
^{13}C NMR: VA-27a



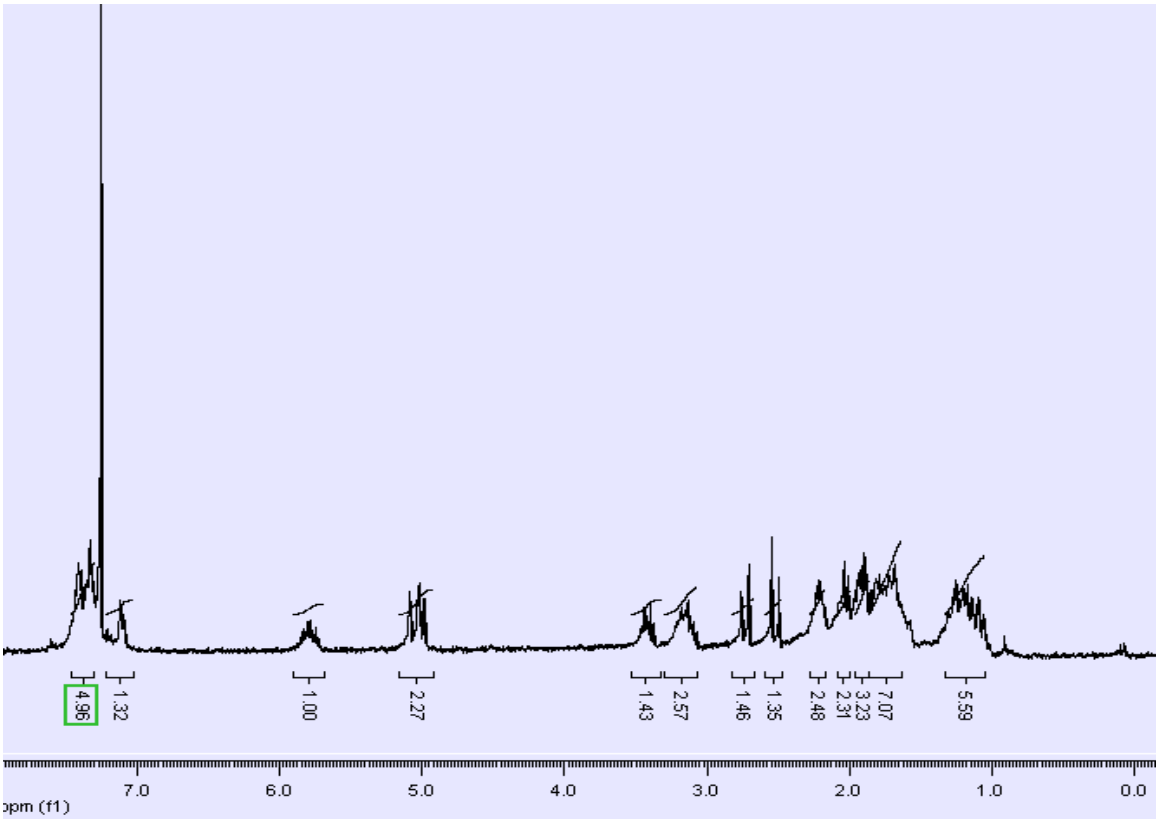
^{1}H NMR: VA-28a



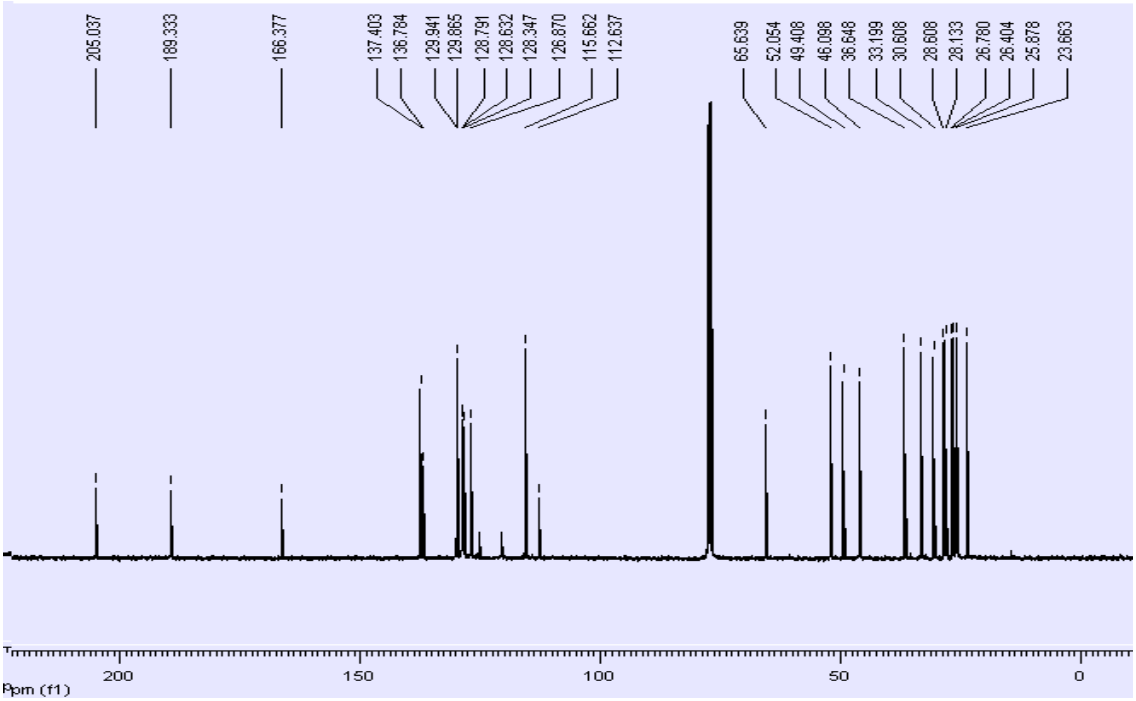
^{13}C NMR: VA-28a



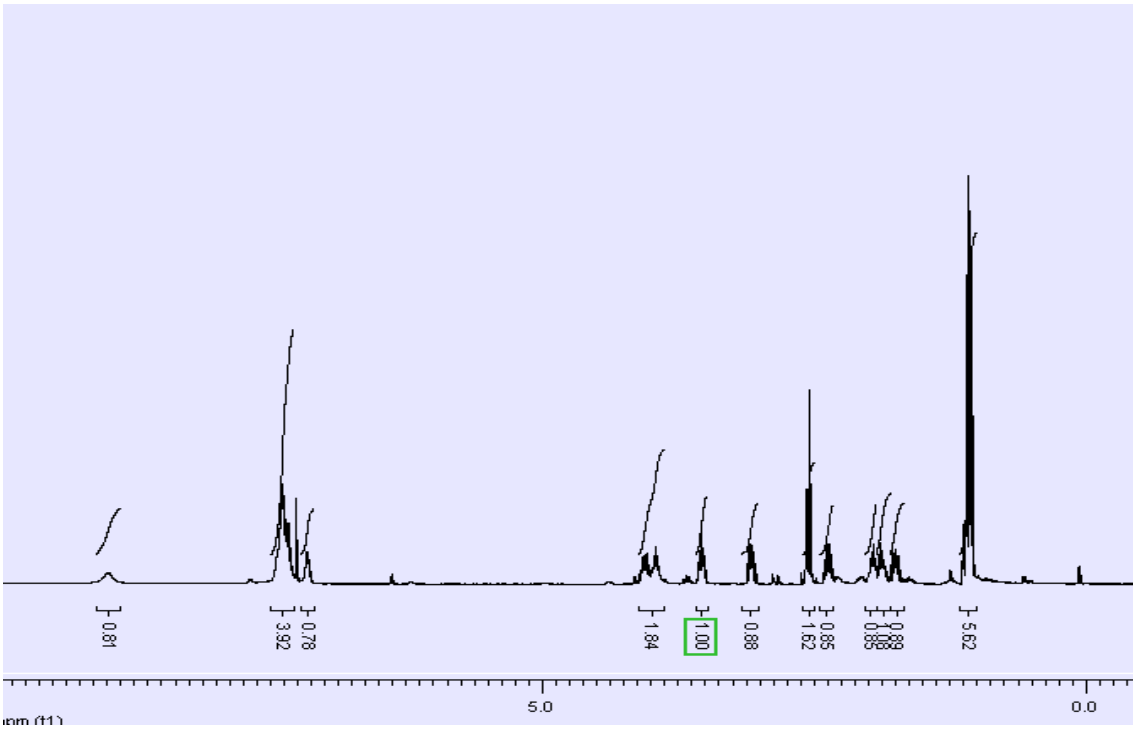
^{1}H NMR: VA-28b



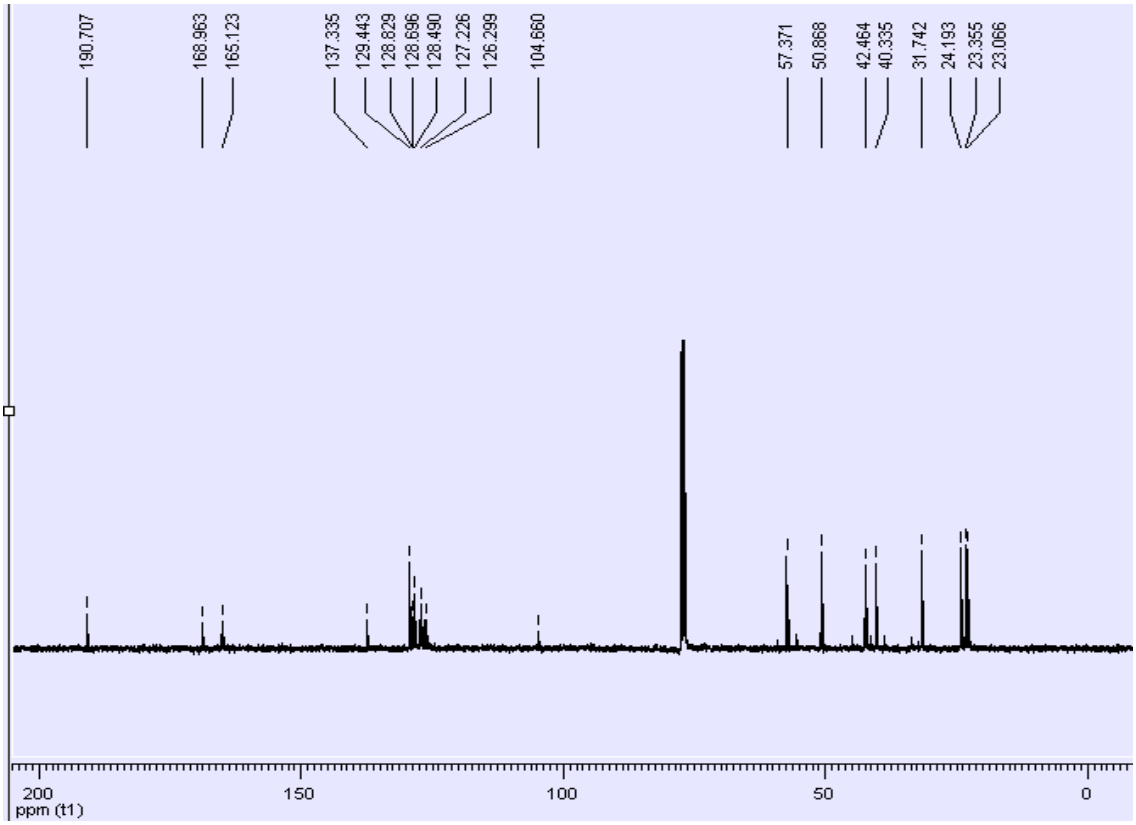
^{13}C NMR: VA-28b



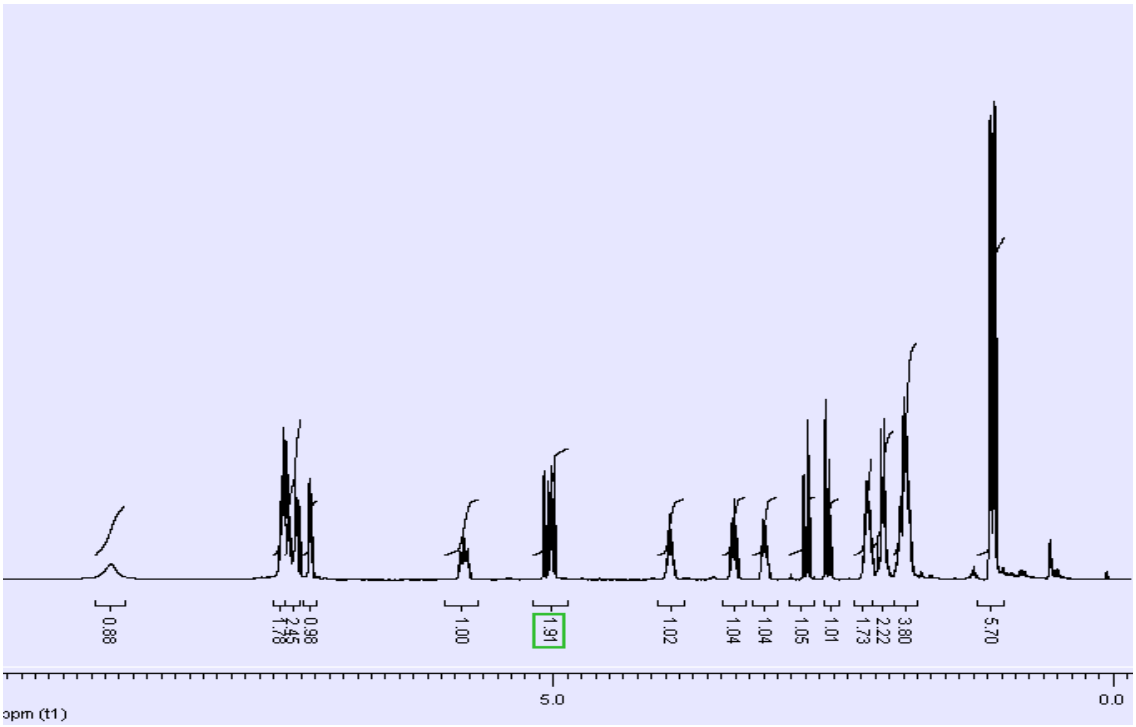
^{1}H NMR: VA-29a



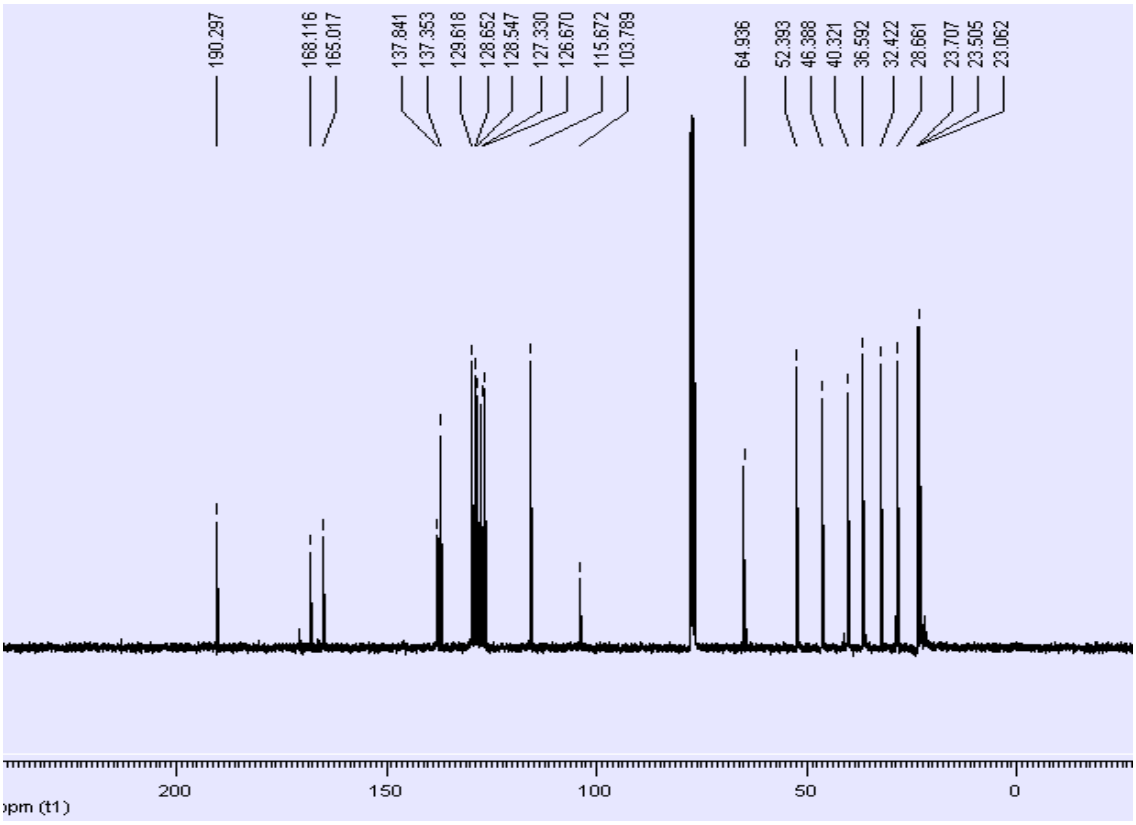
^{13}C NMR: VA-29a



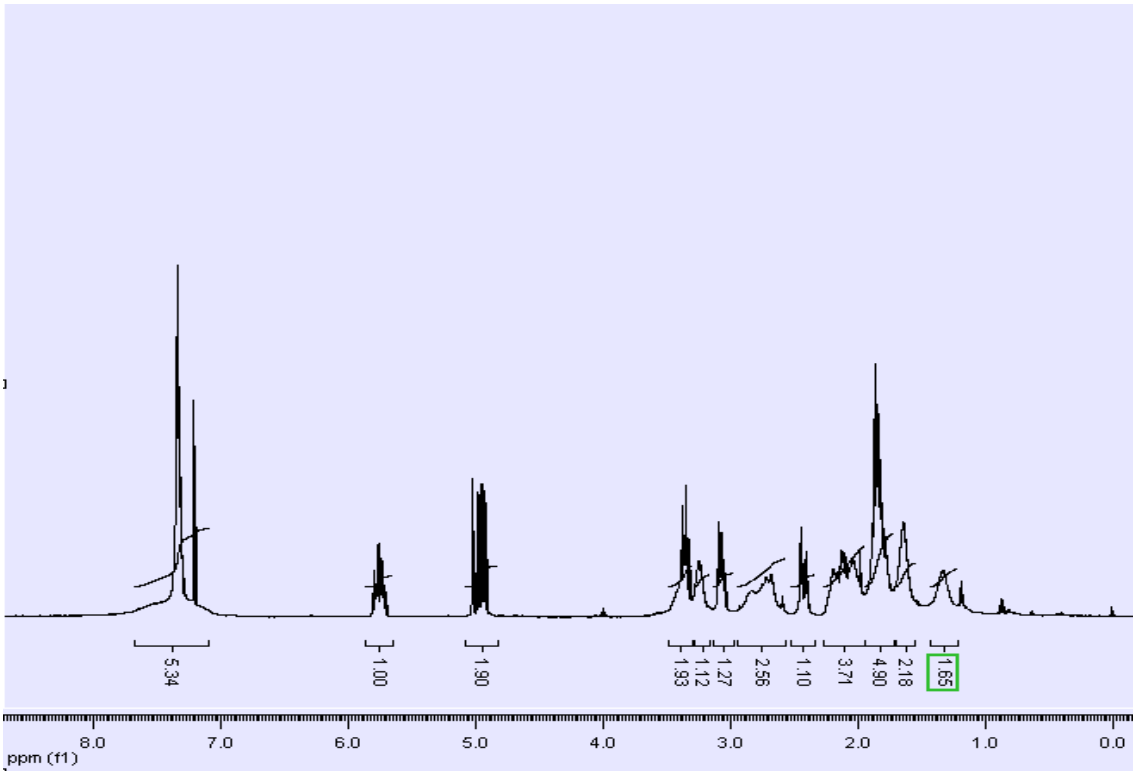
^{1}H NMR: VA-29b



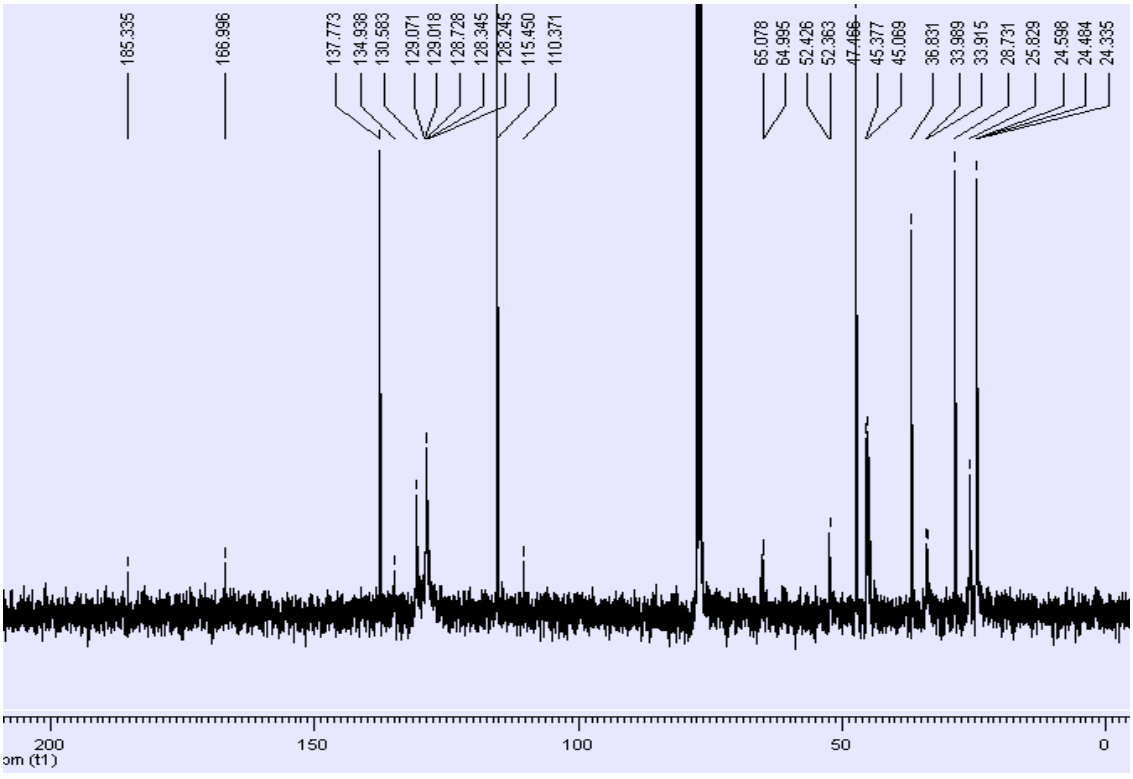
^{13}C NMR: VA-29b (move both a and b need to be moved up as well.)



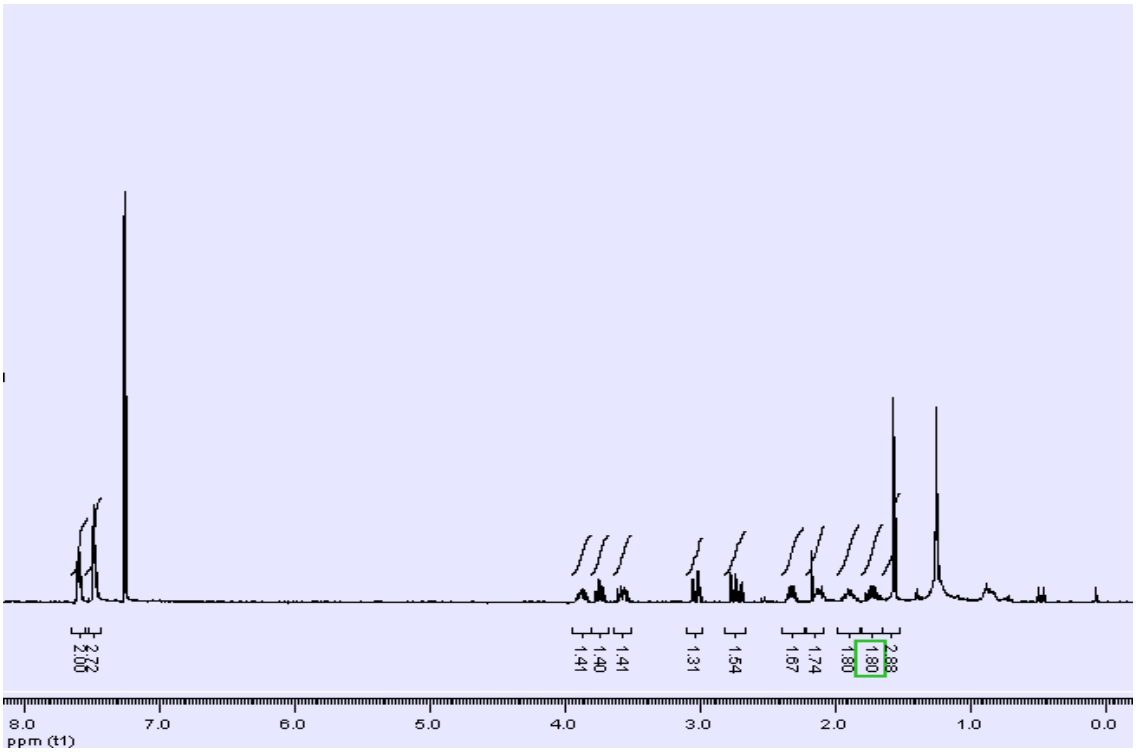
^{1}H NMR: VA-30b



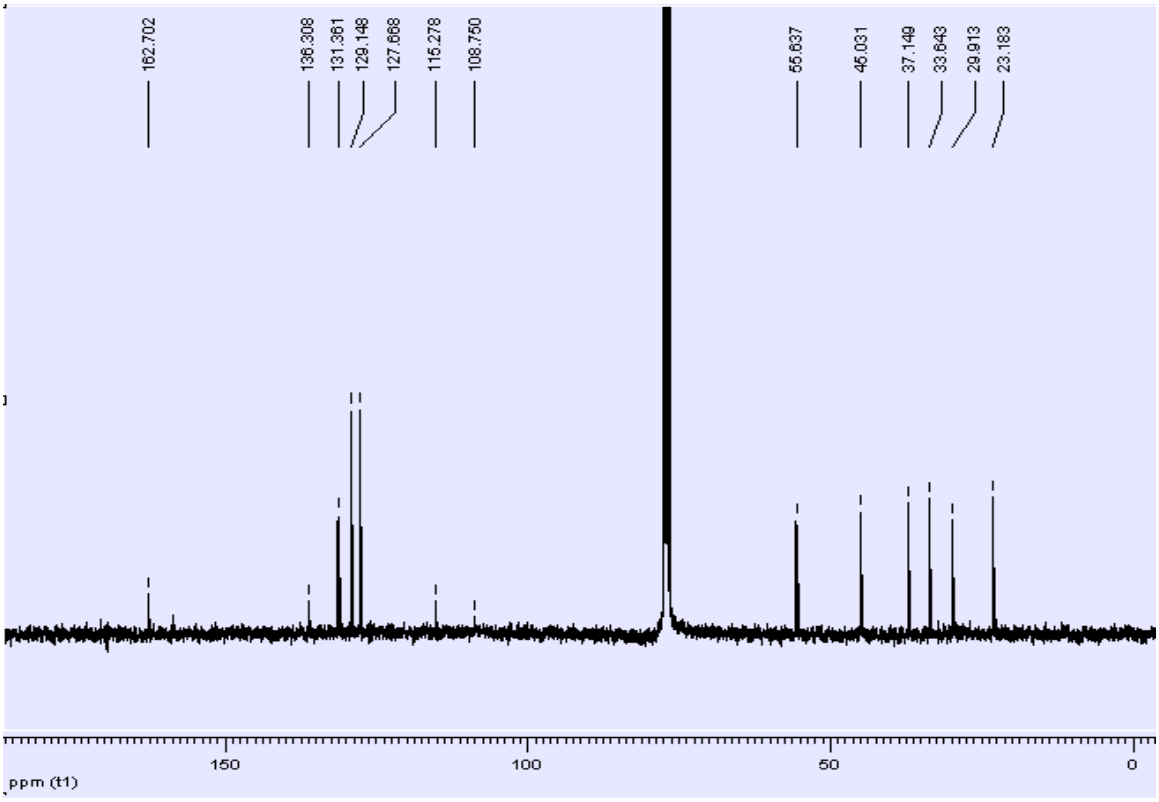
^{13}C NMR: VA-30b (make sure you put this in the correct order)



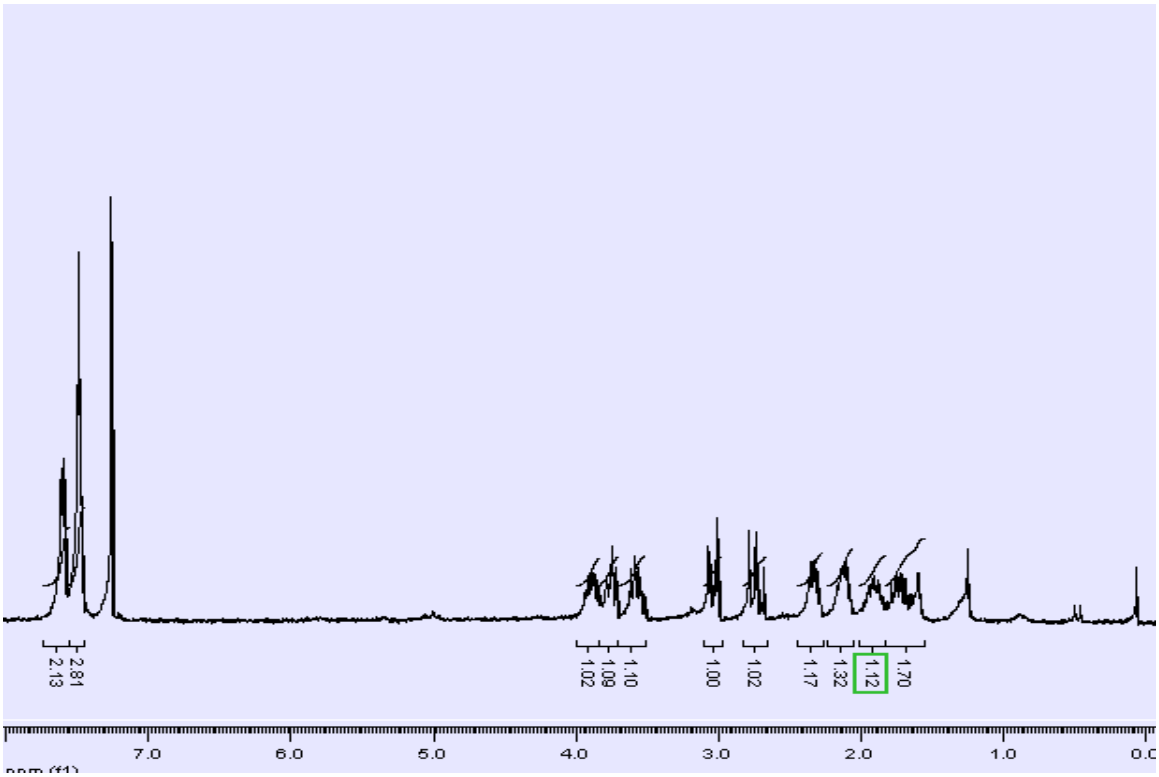
^{1}H NMR: LA-12a



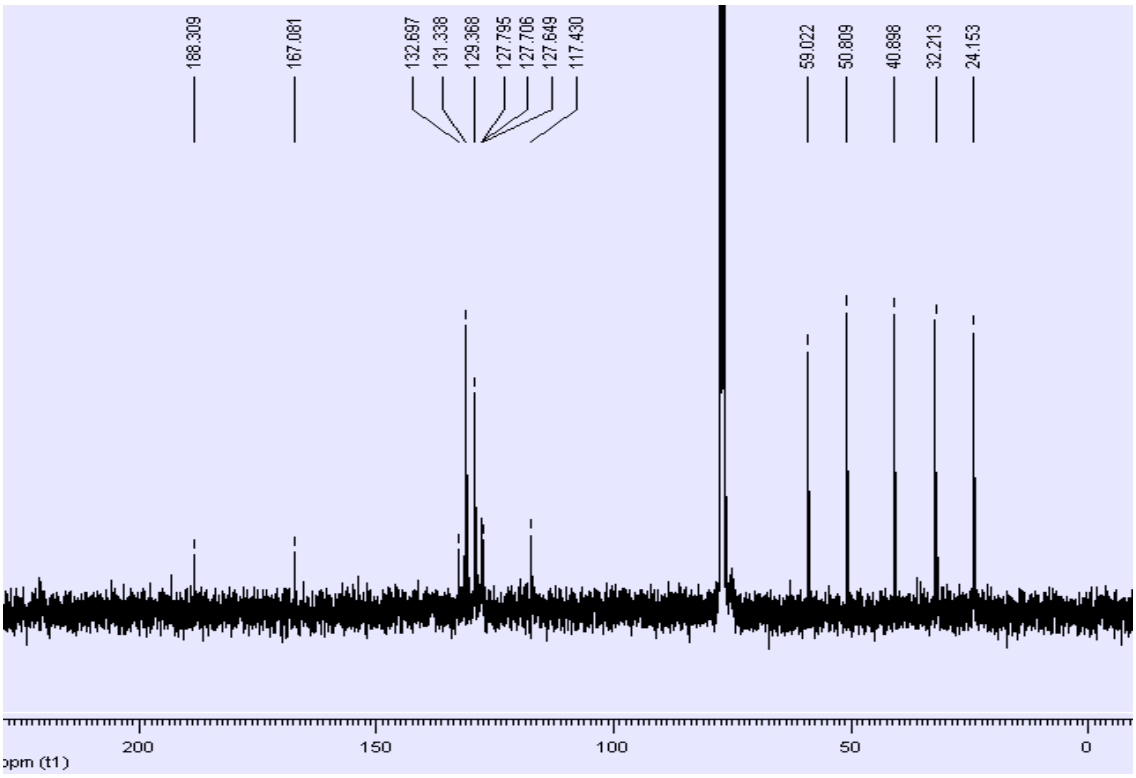
^{13}C NMR: LA-12a



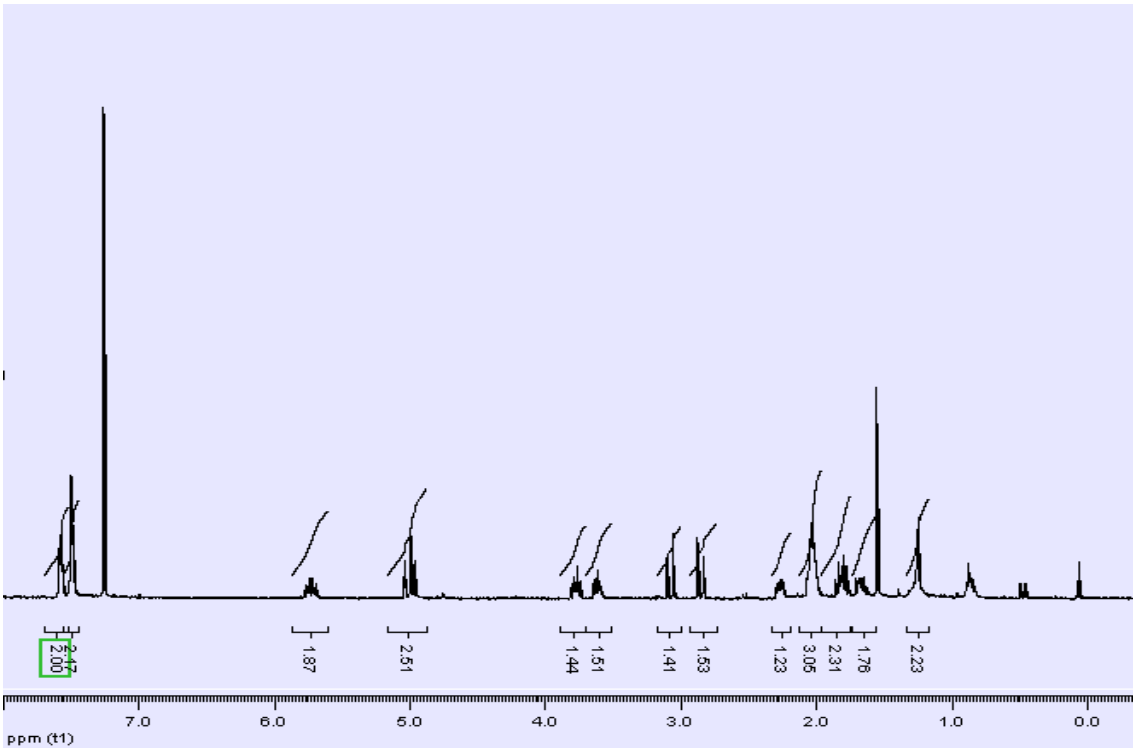
^{1}H NMR: VA-32a



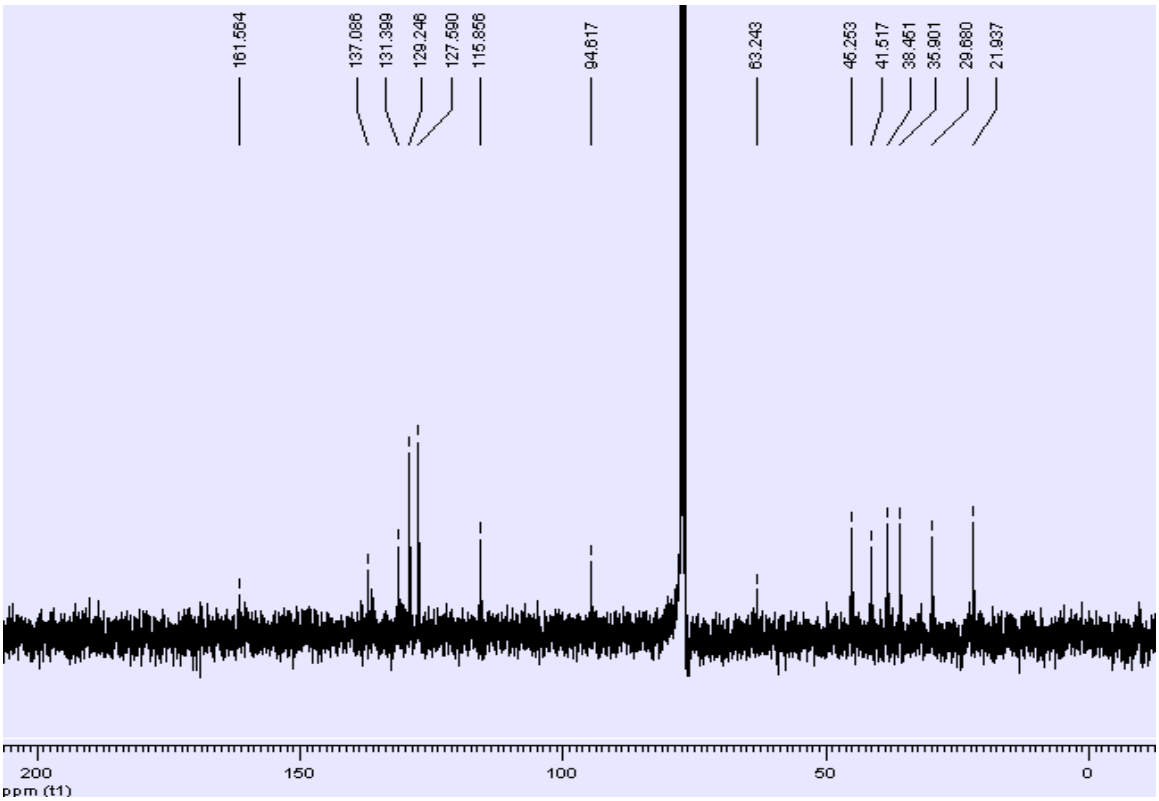
^{13}C NMR: VA-32a



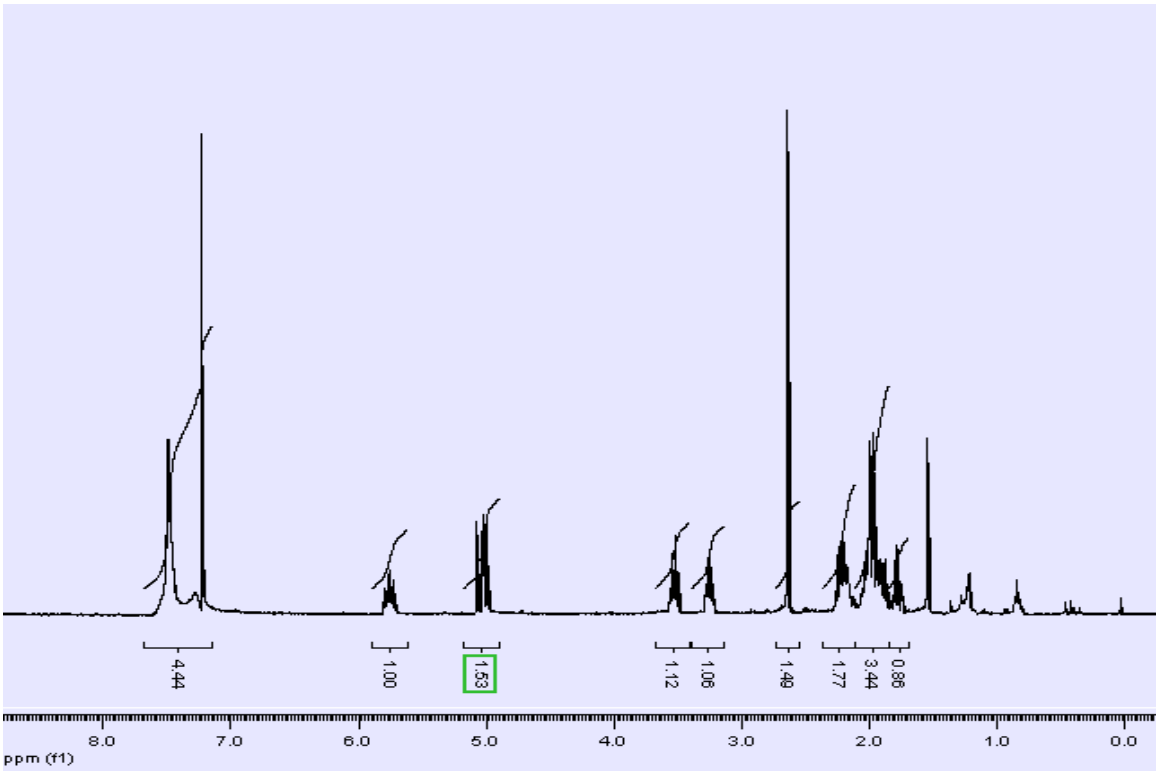
^{1}H NMR: LA-12b



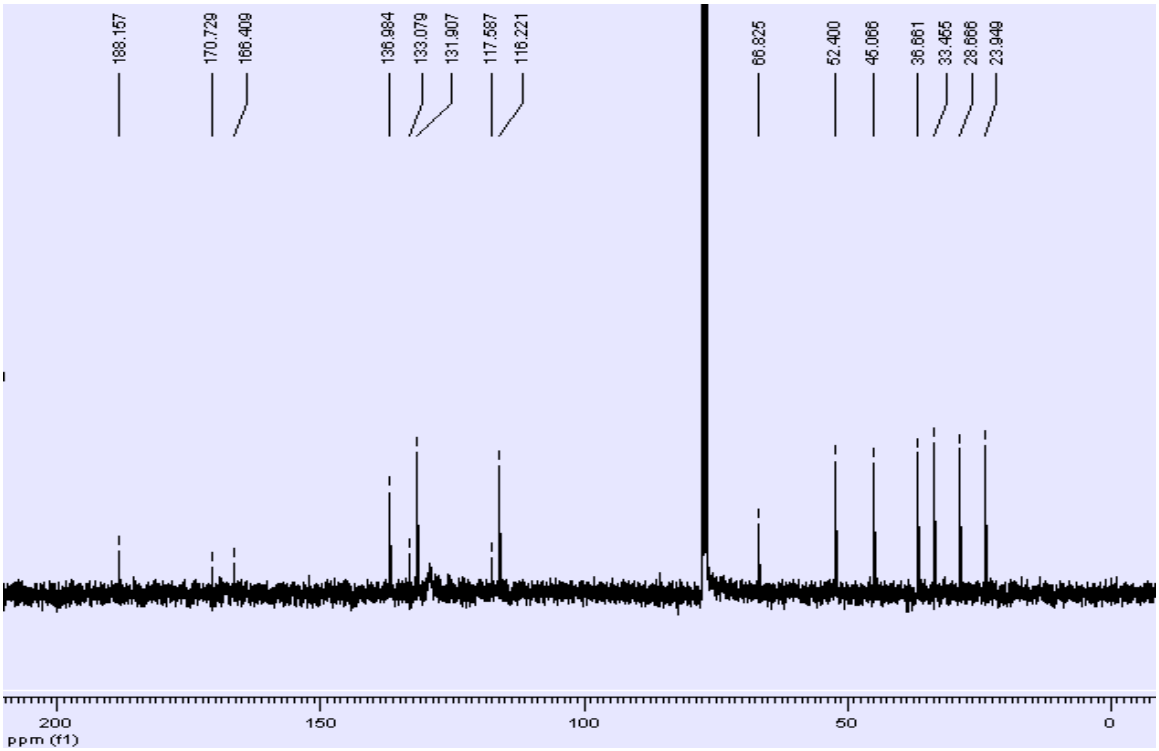
^{13}C NMR: LA-12b



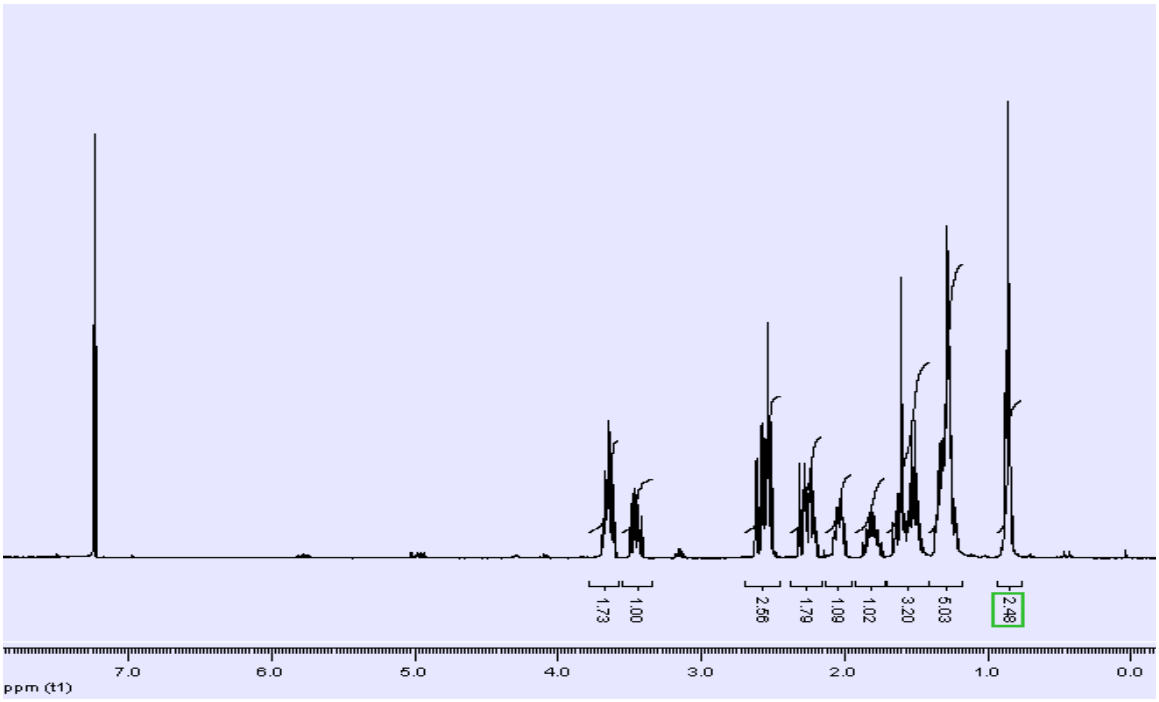
^{1}H NMR: VA-32b



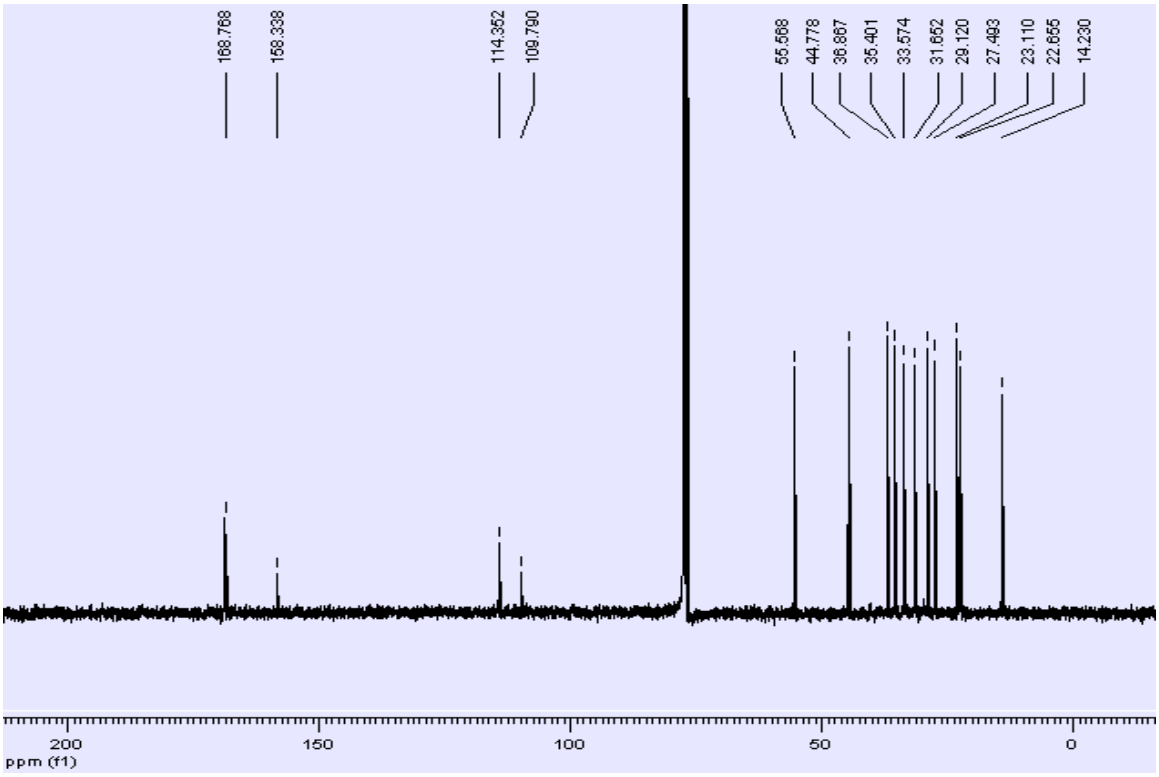
^{13}C NMR: VA-32b



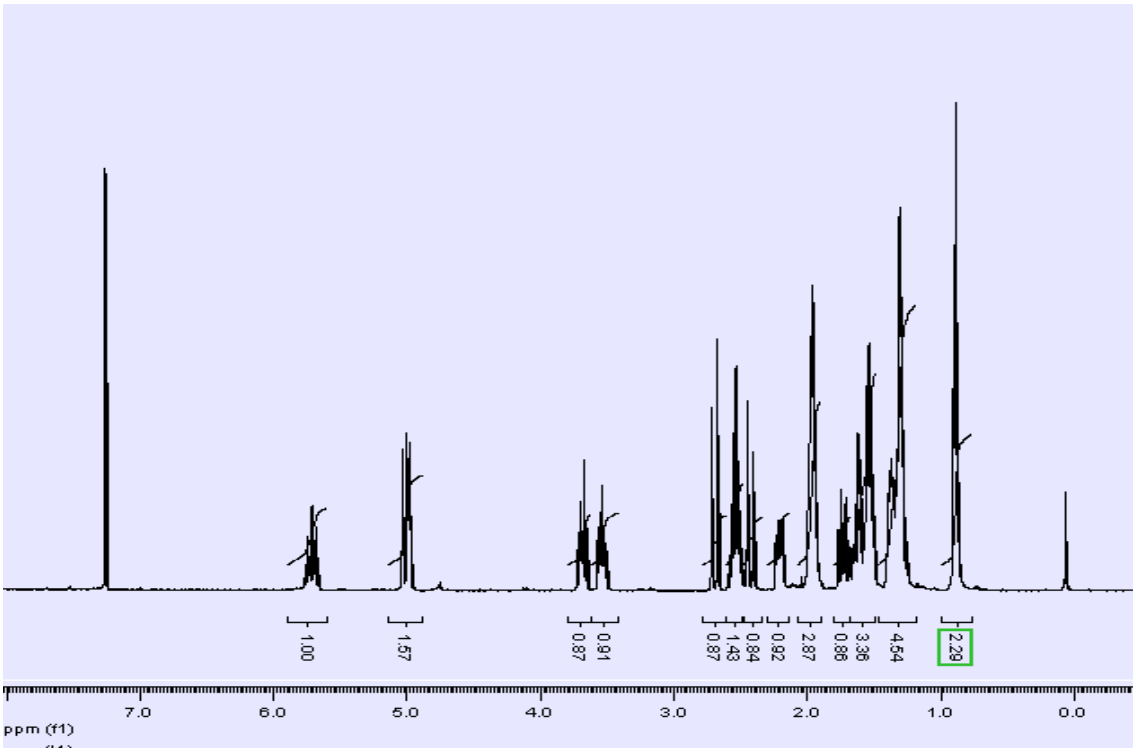
^{1}H NMR: LA-13a



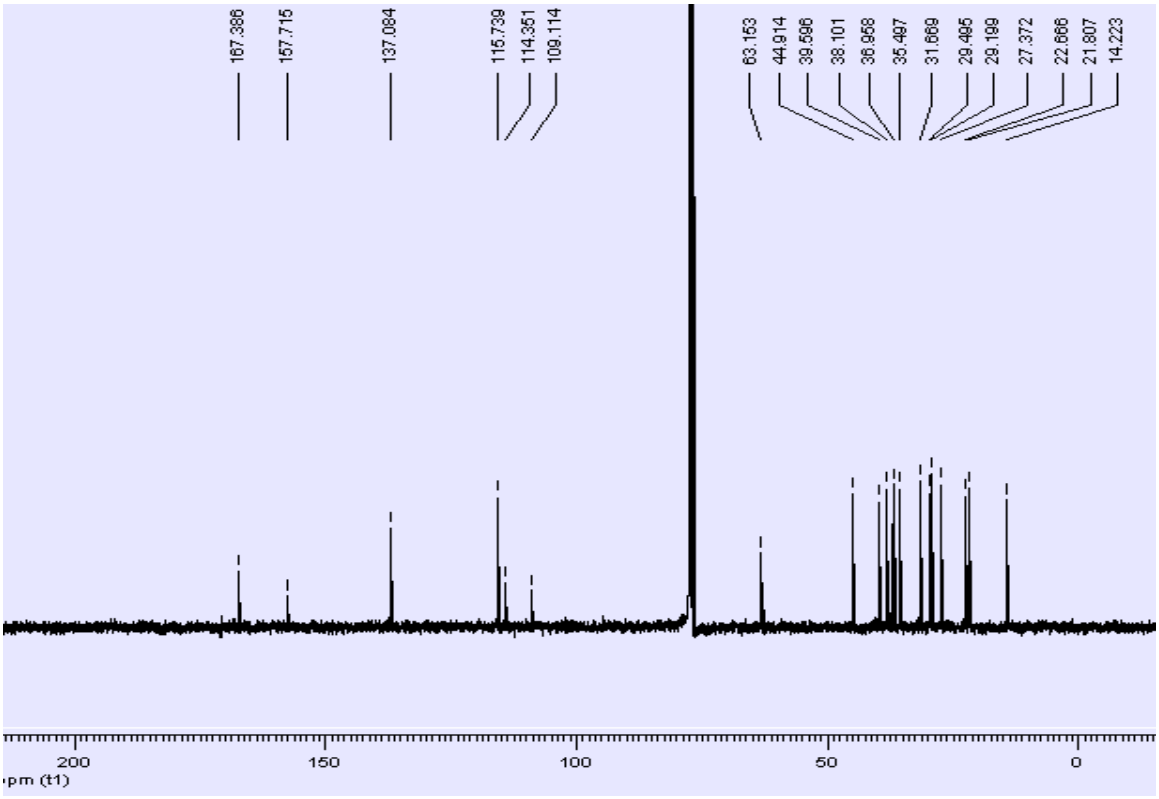
^{13}C NMR: LA-13a



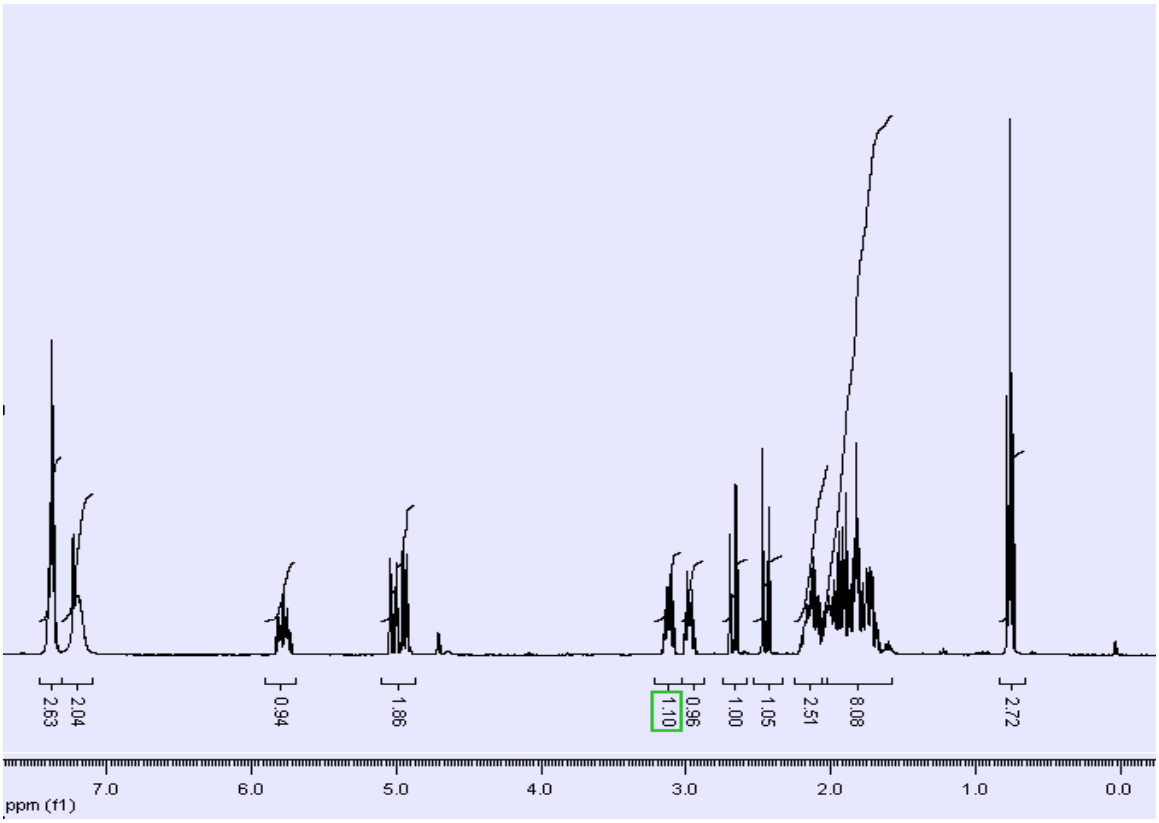
^{1}H NMR: LA-13b



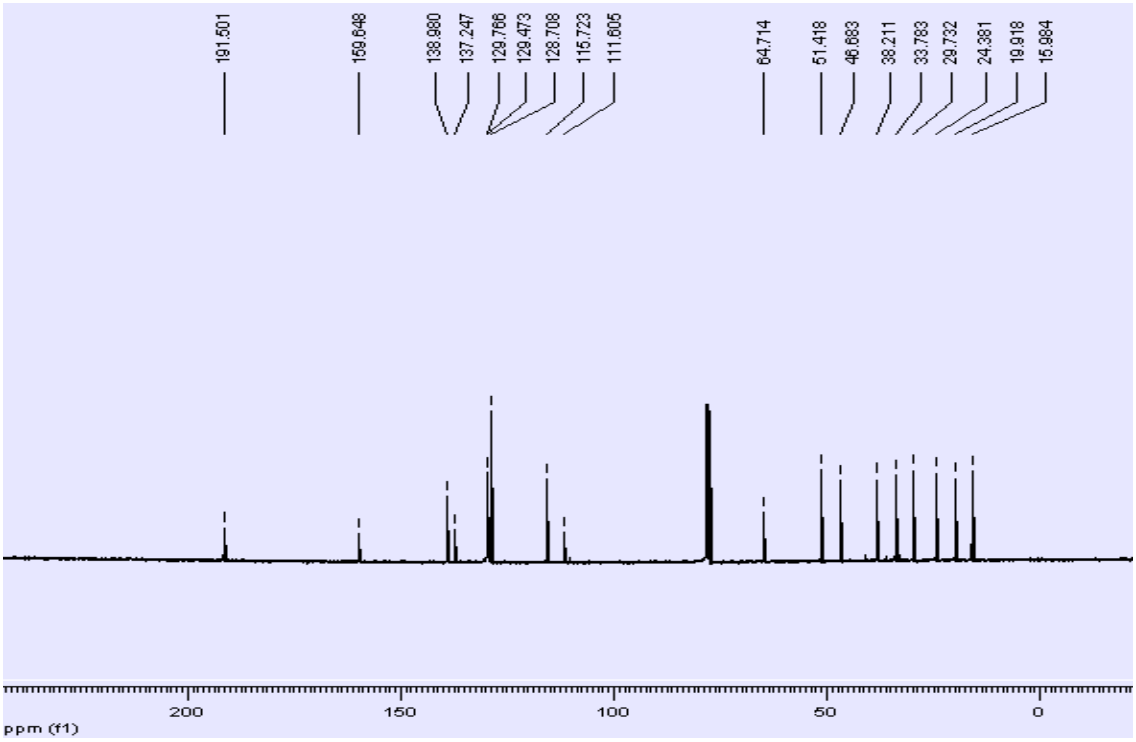
^{13}C NMR: LA-13b



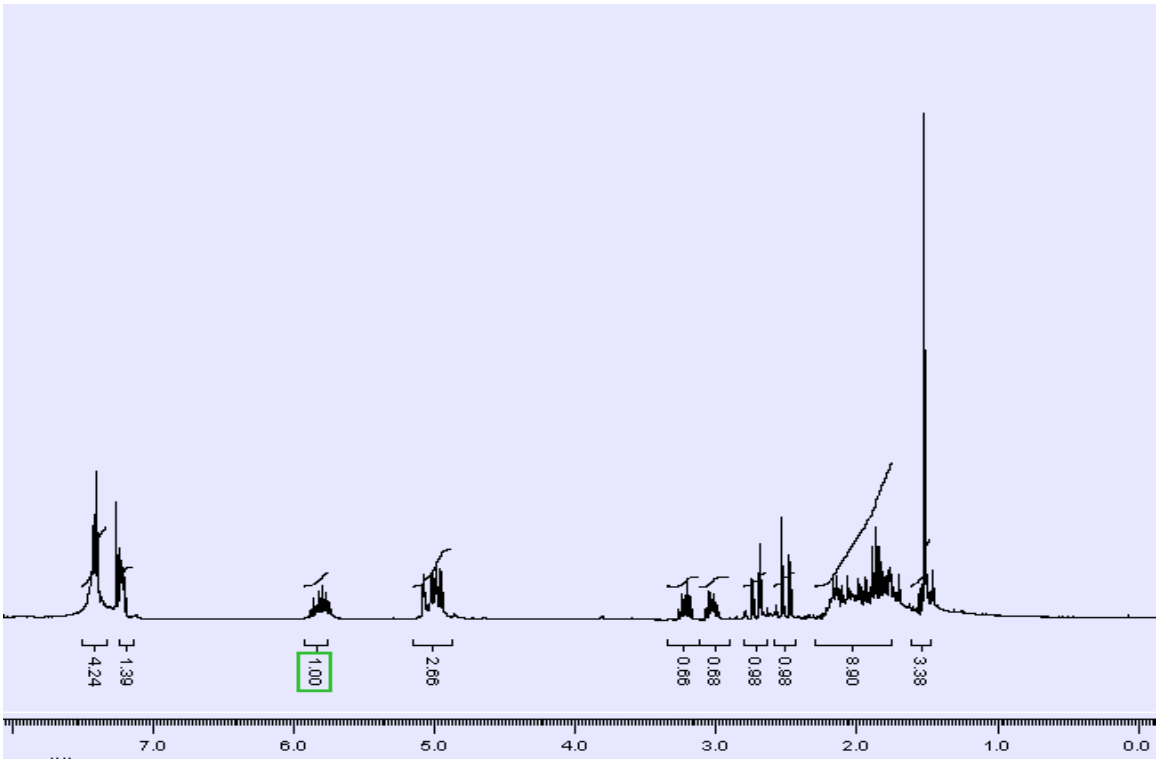
^{1}H NMR: VA-33b



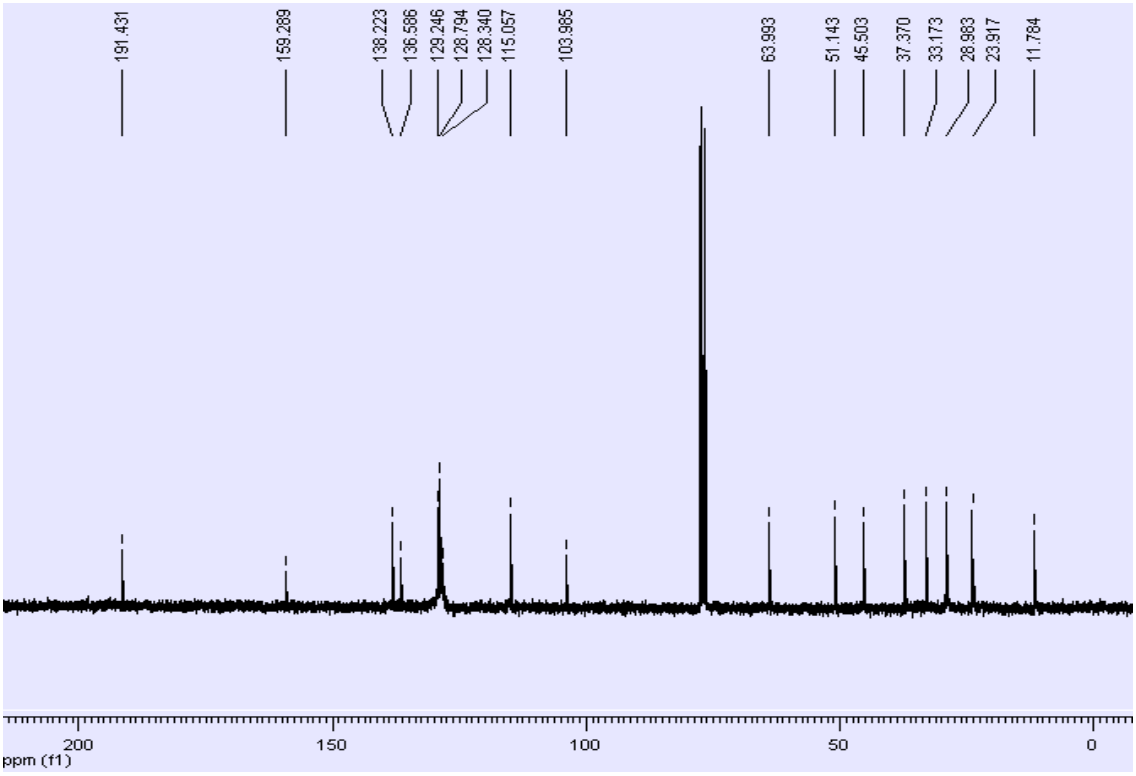
^{13}C NMR: VA-33b



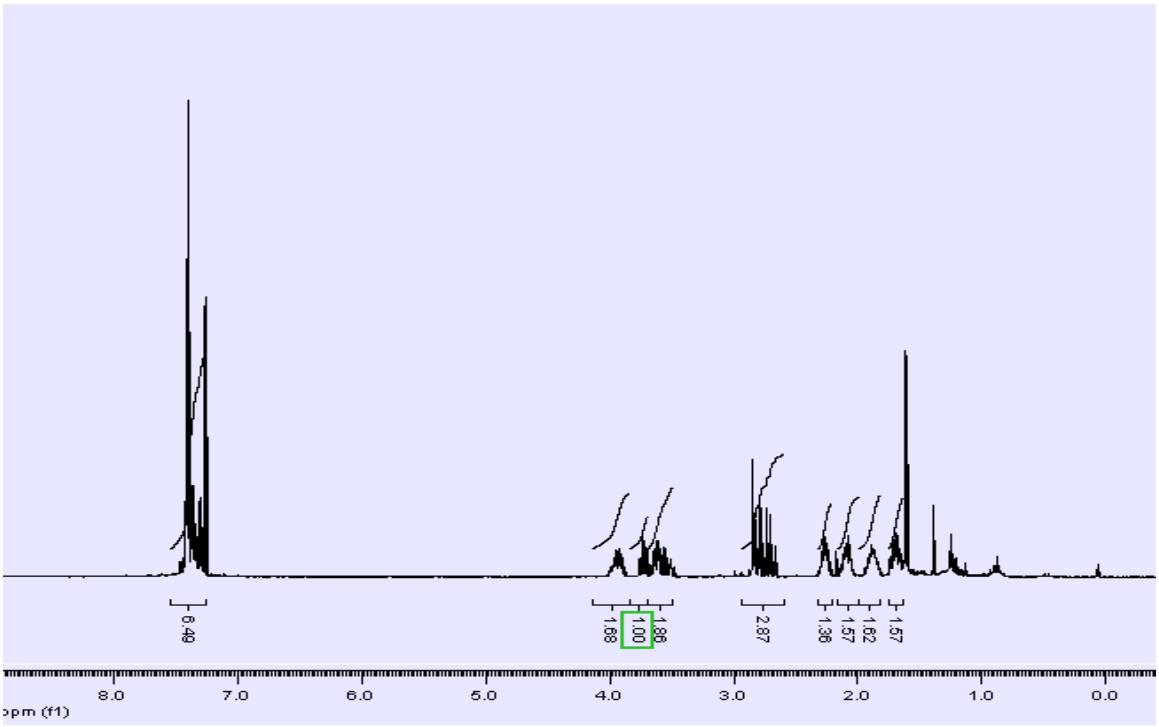
^{1}H NMR: VA-34b



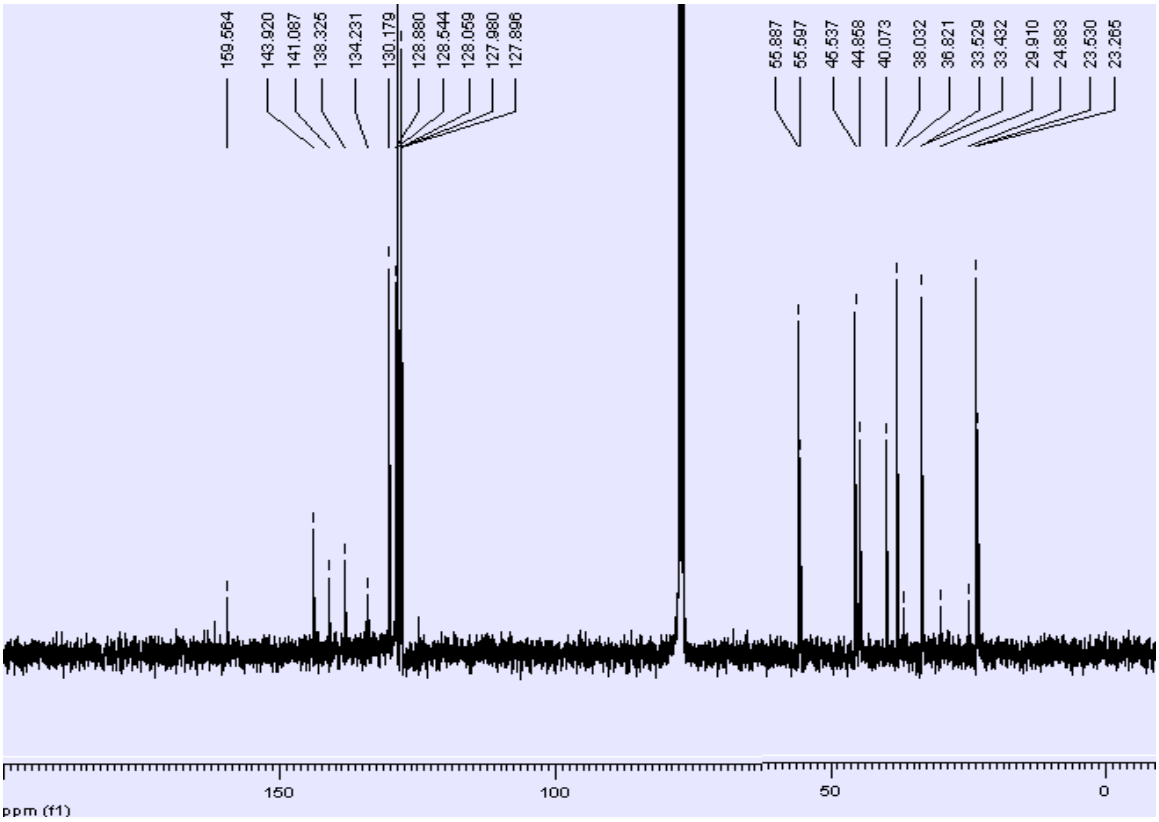
^{13}C NMR: VA-34b



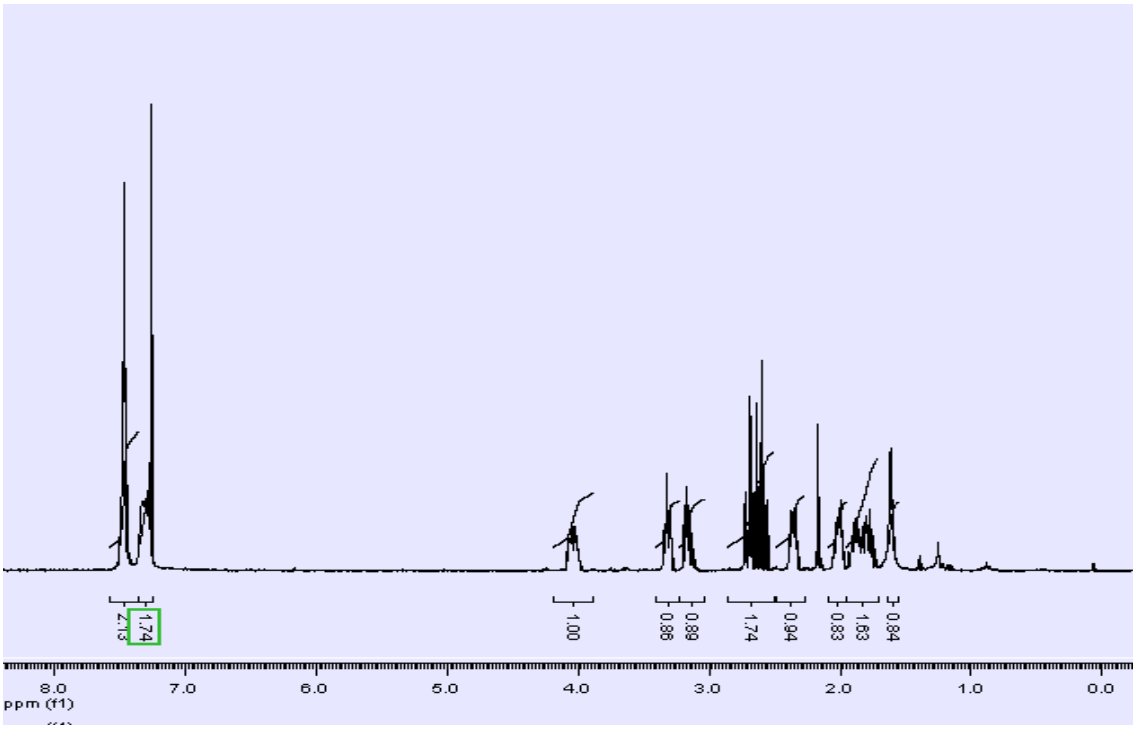
^{1}H NMR: LA-14a1, LA-14a2



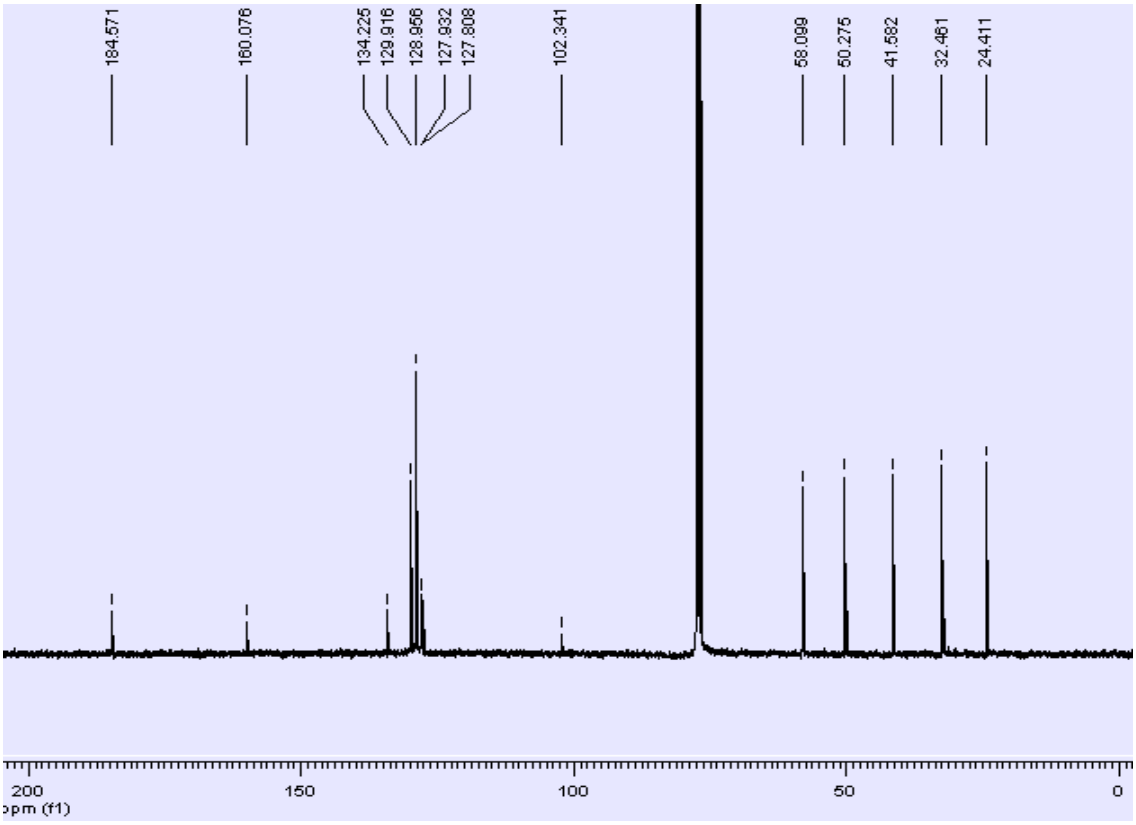
^{13}C NMR: LA-14a1, LA-14a2



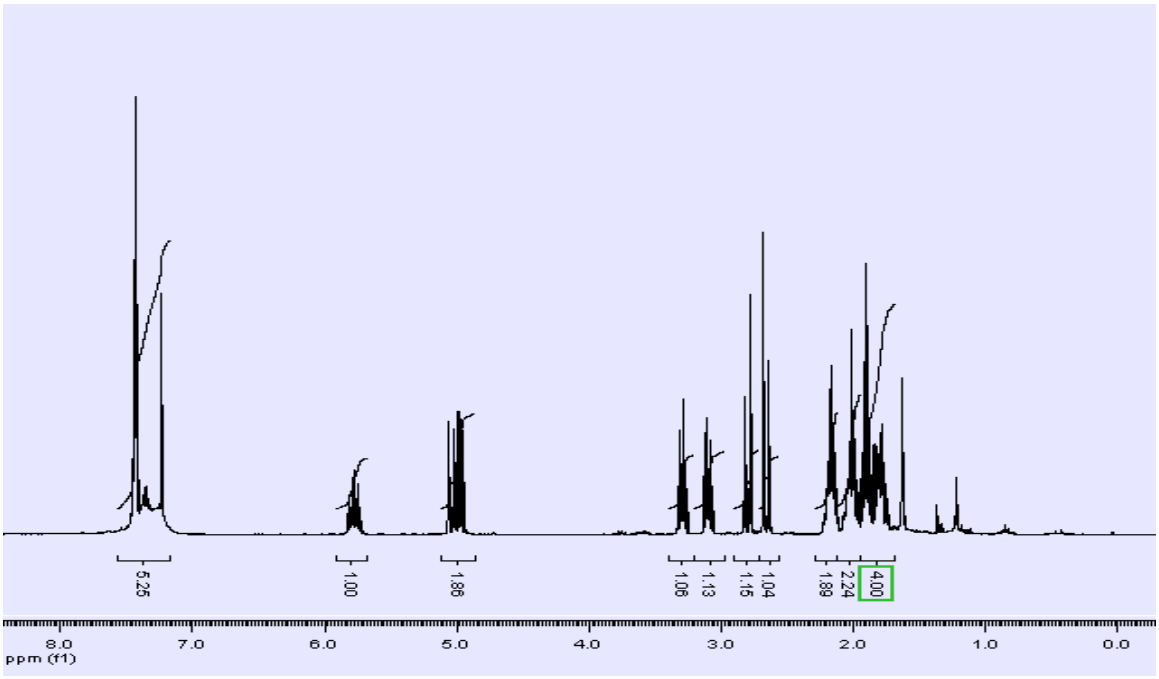
^{1}H NMR: VA-35a



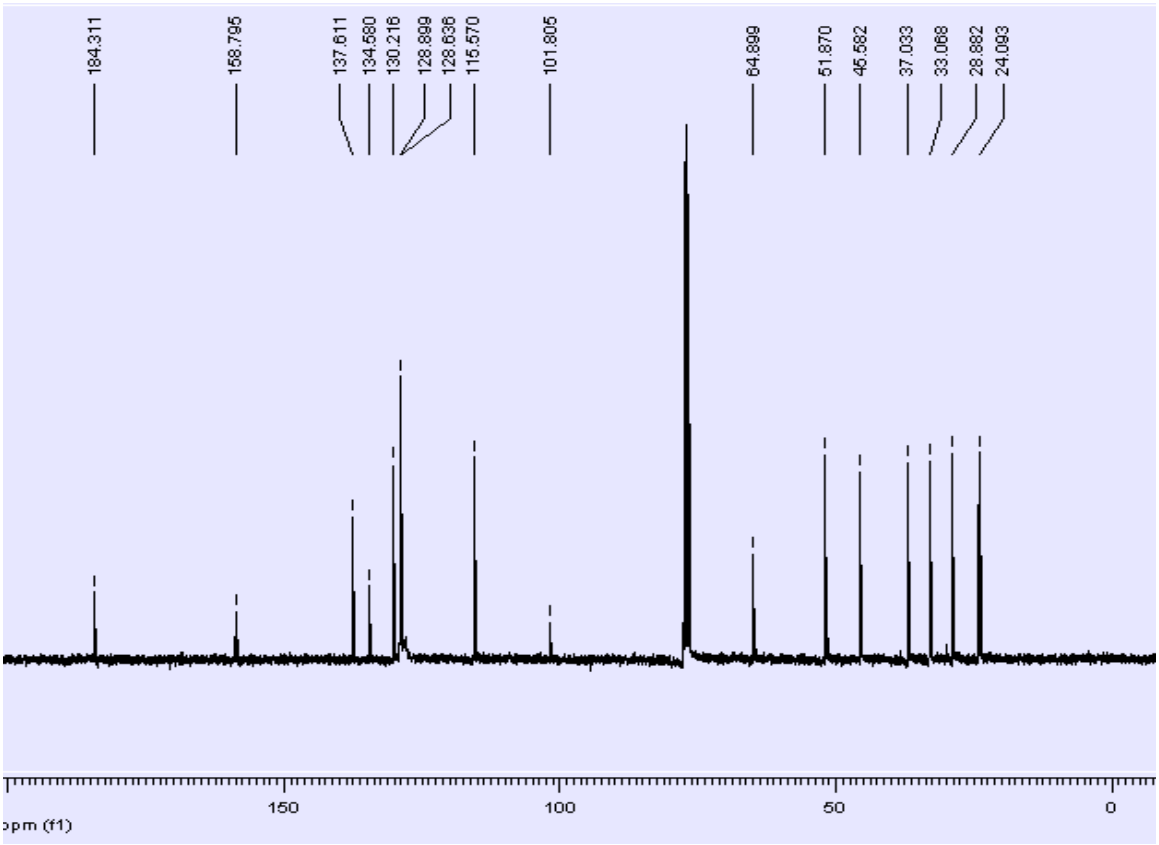
^{13}C NMR: VA-35a



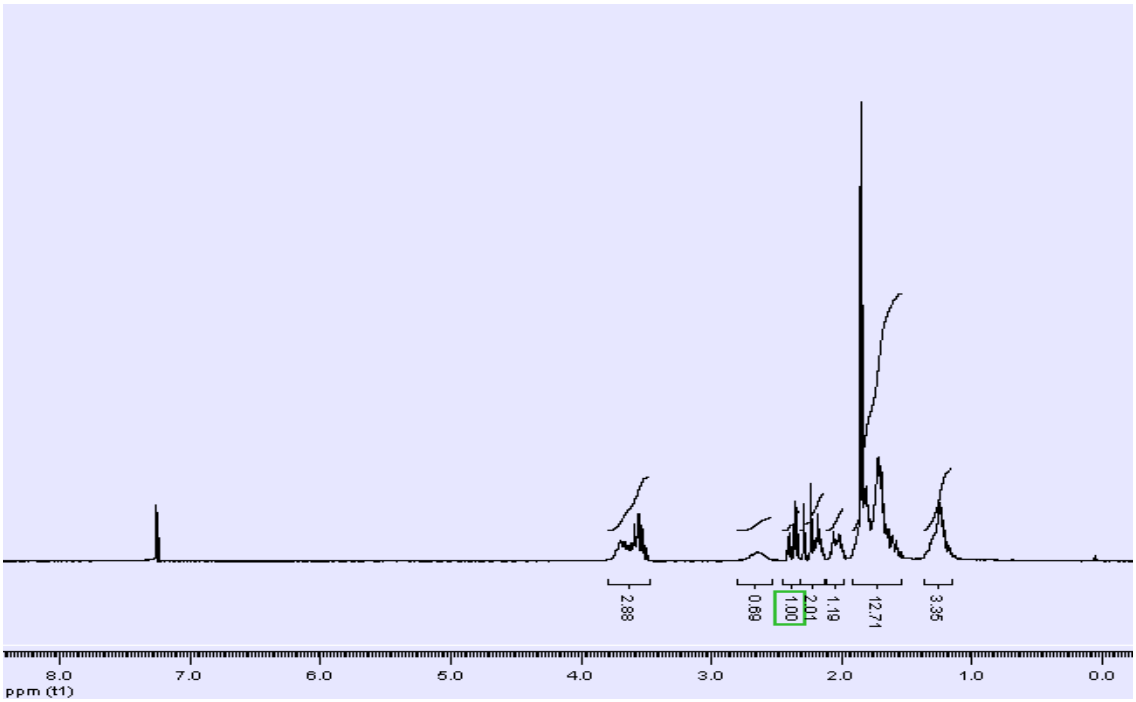
^{1}H NMR: VA-35b



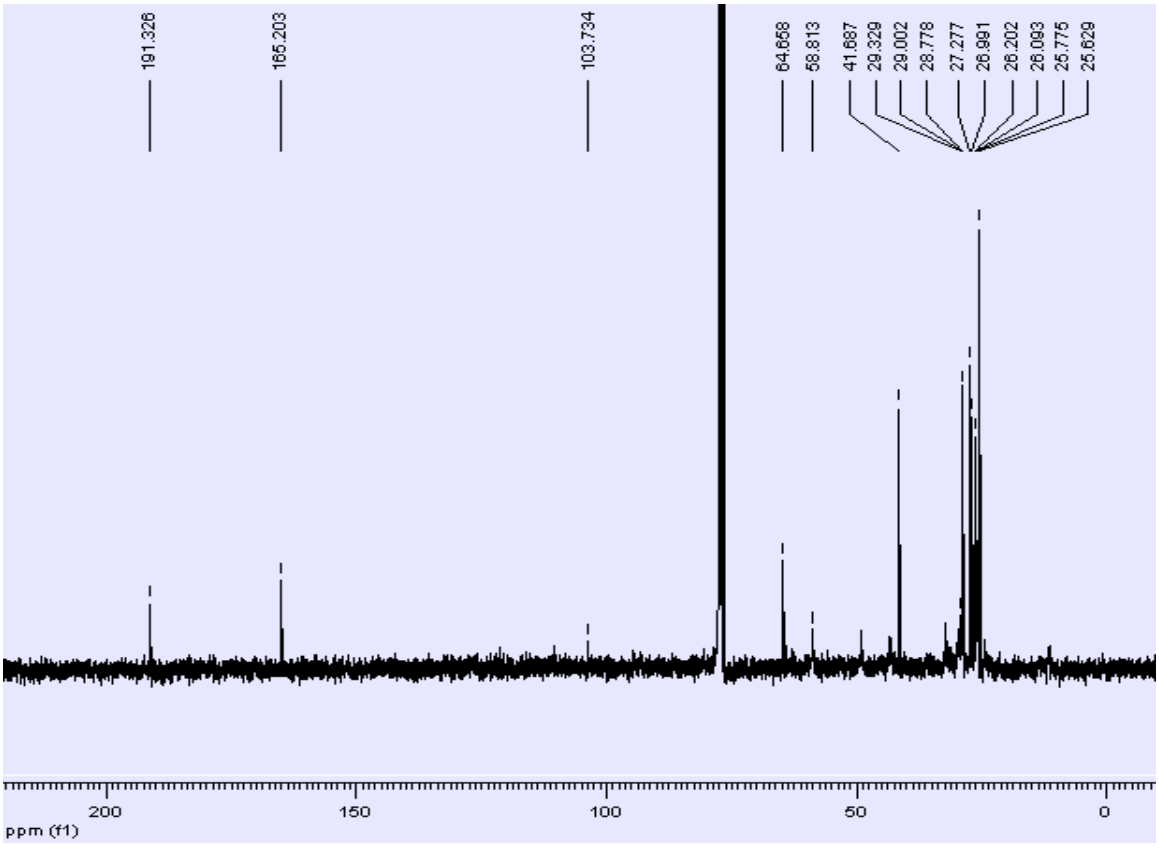
^{13}C NMR: VA-35b



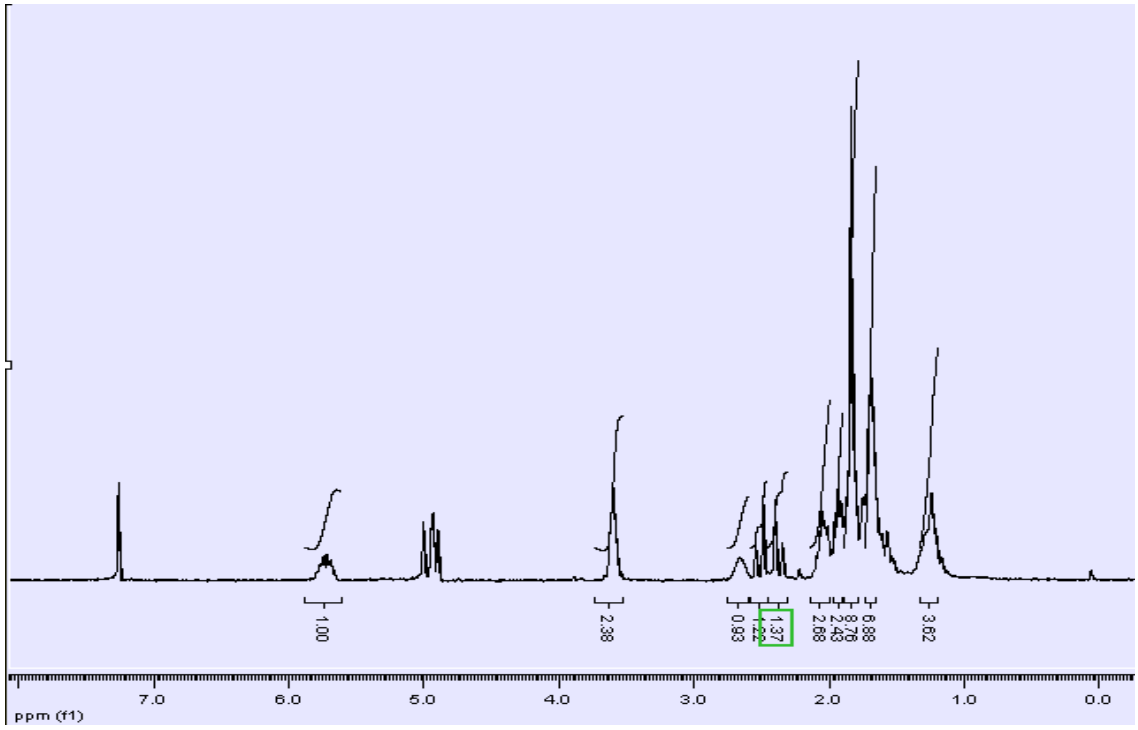
^{1}H NMR: VA-36a



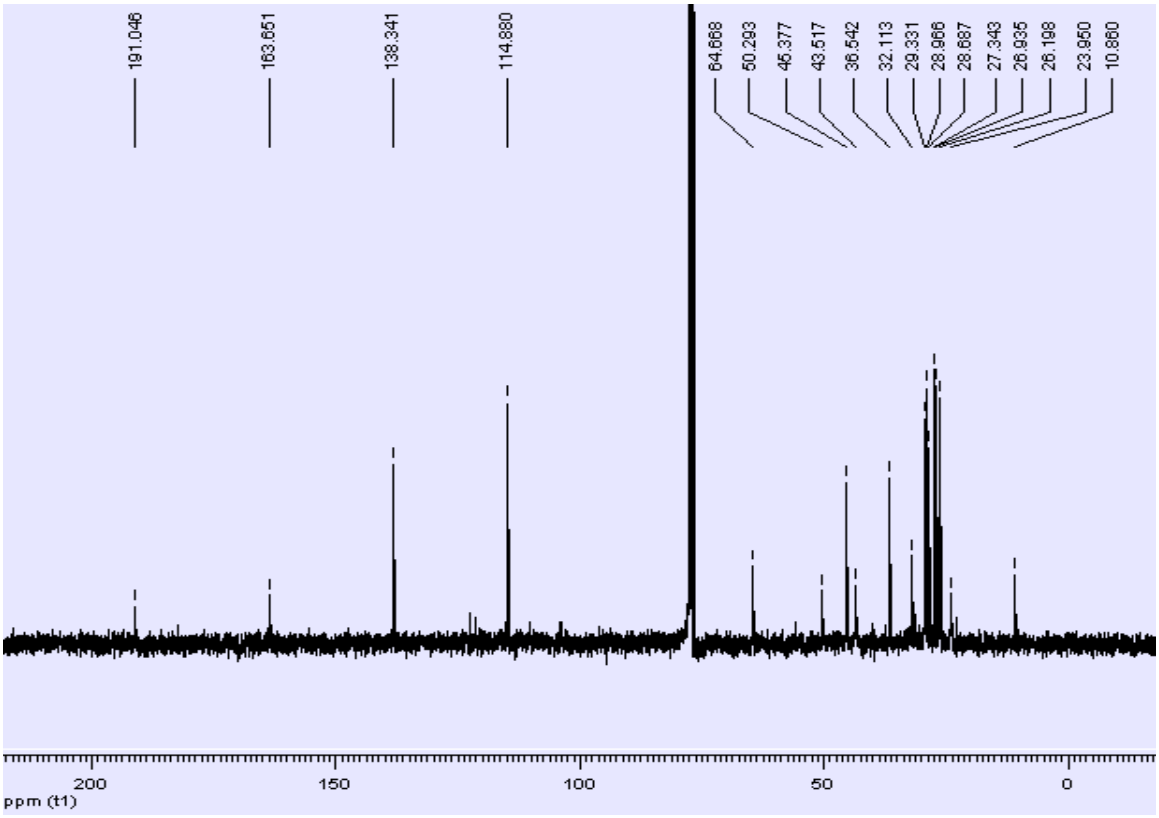
^{13}C NMR: VA-36a



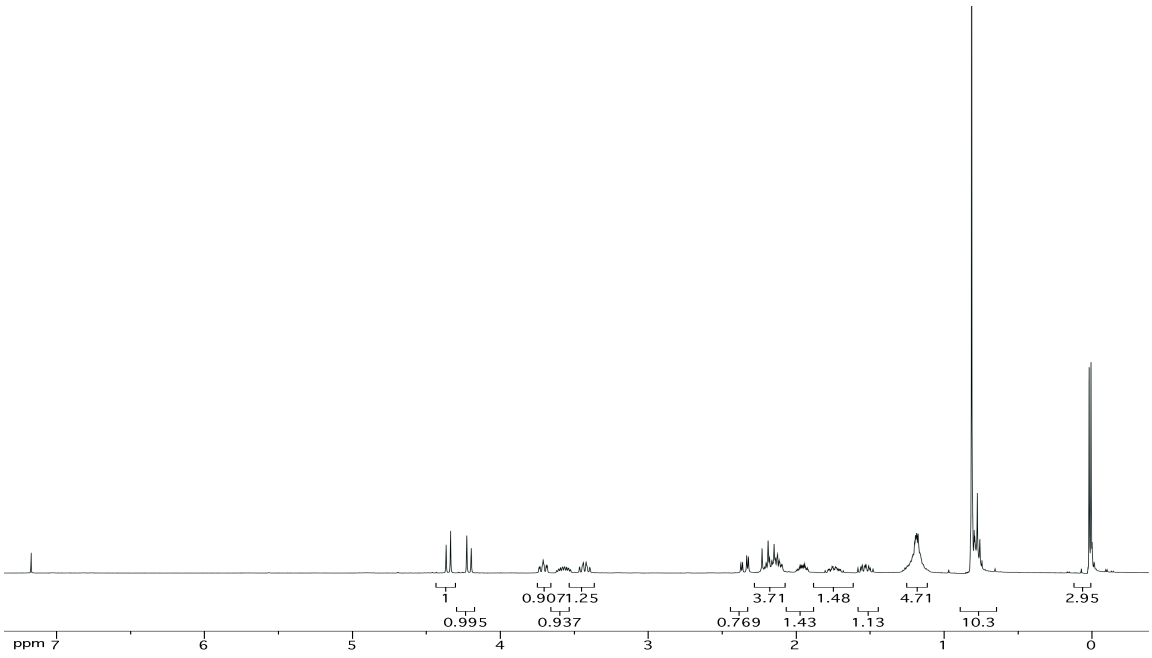
^{1}H NMR: VA-36b



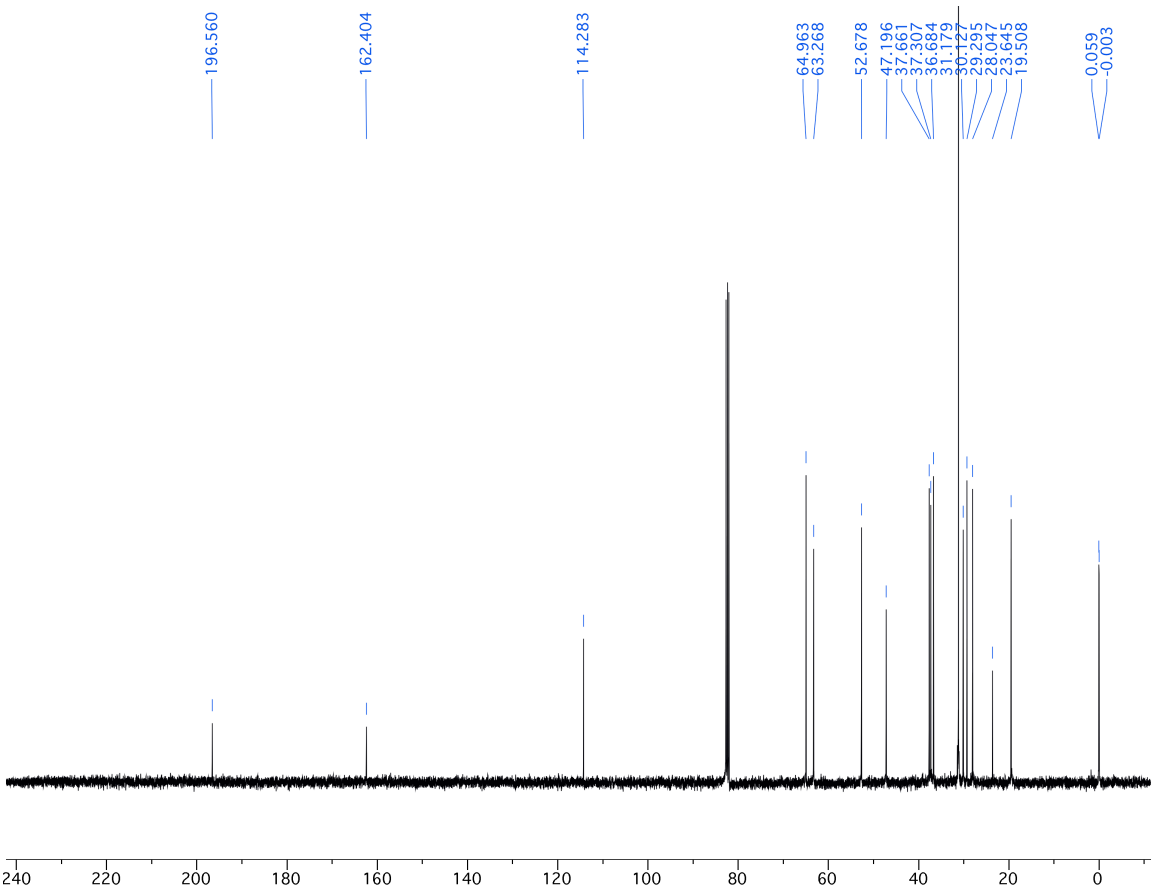
^{13}C NMR: VA-36b



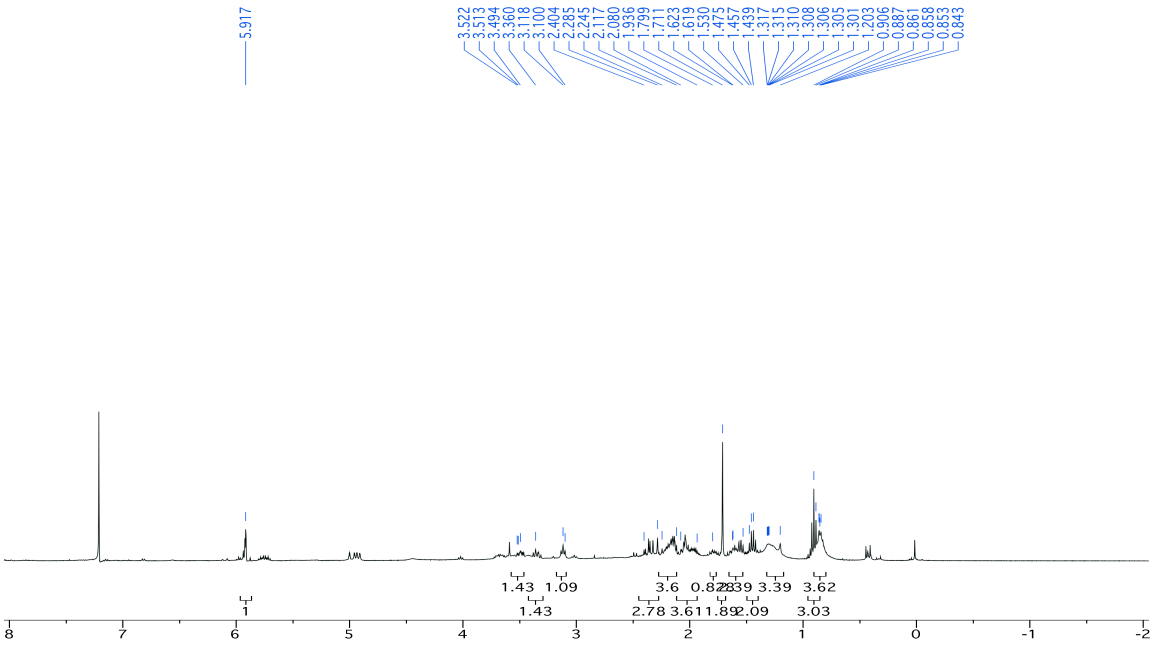
^{1}H NMR: VA-37a



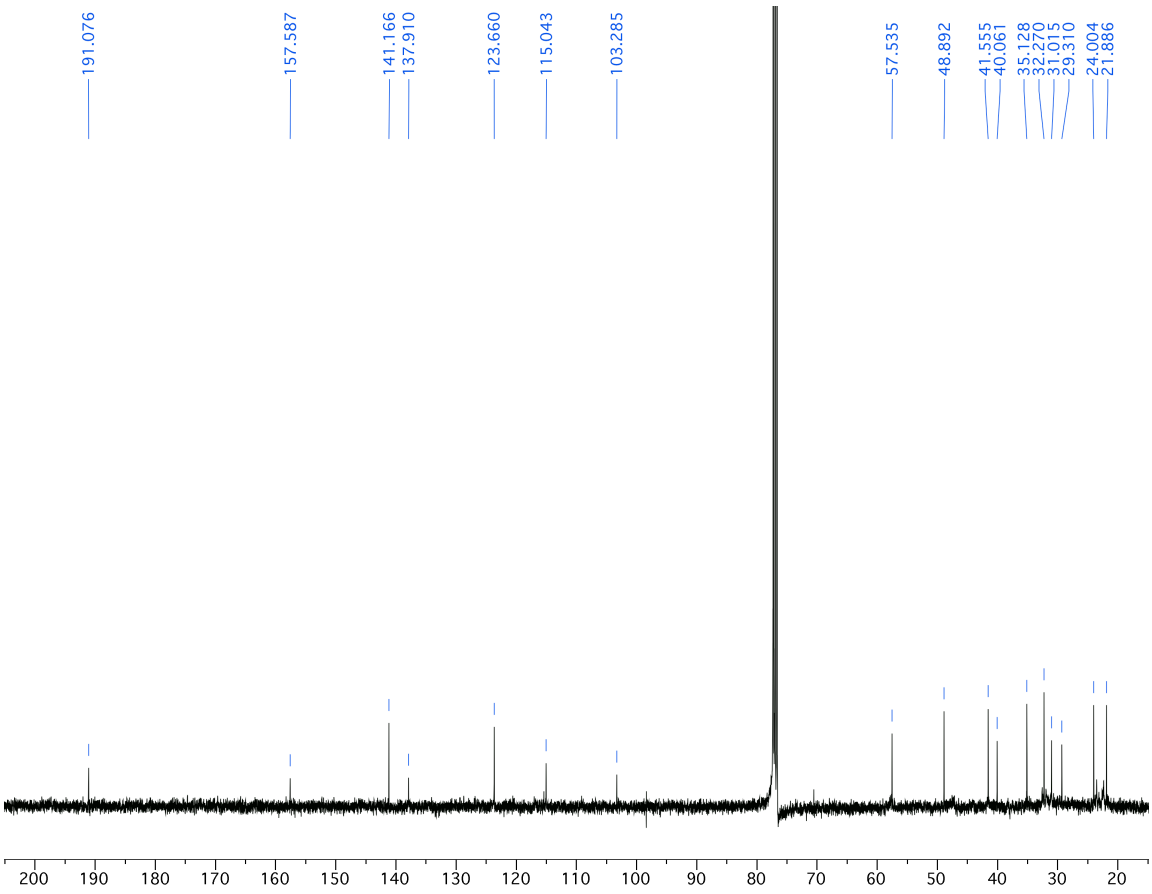
^{13}C NMR: VA-37a



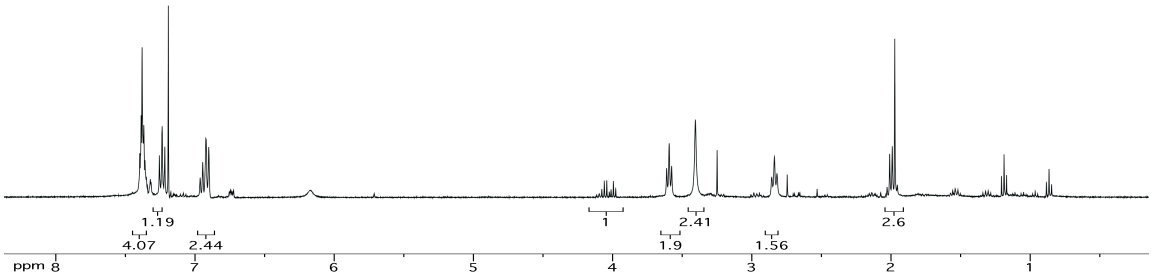
^{1}H NMR: VA-38a



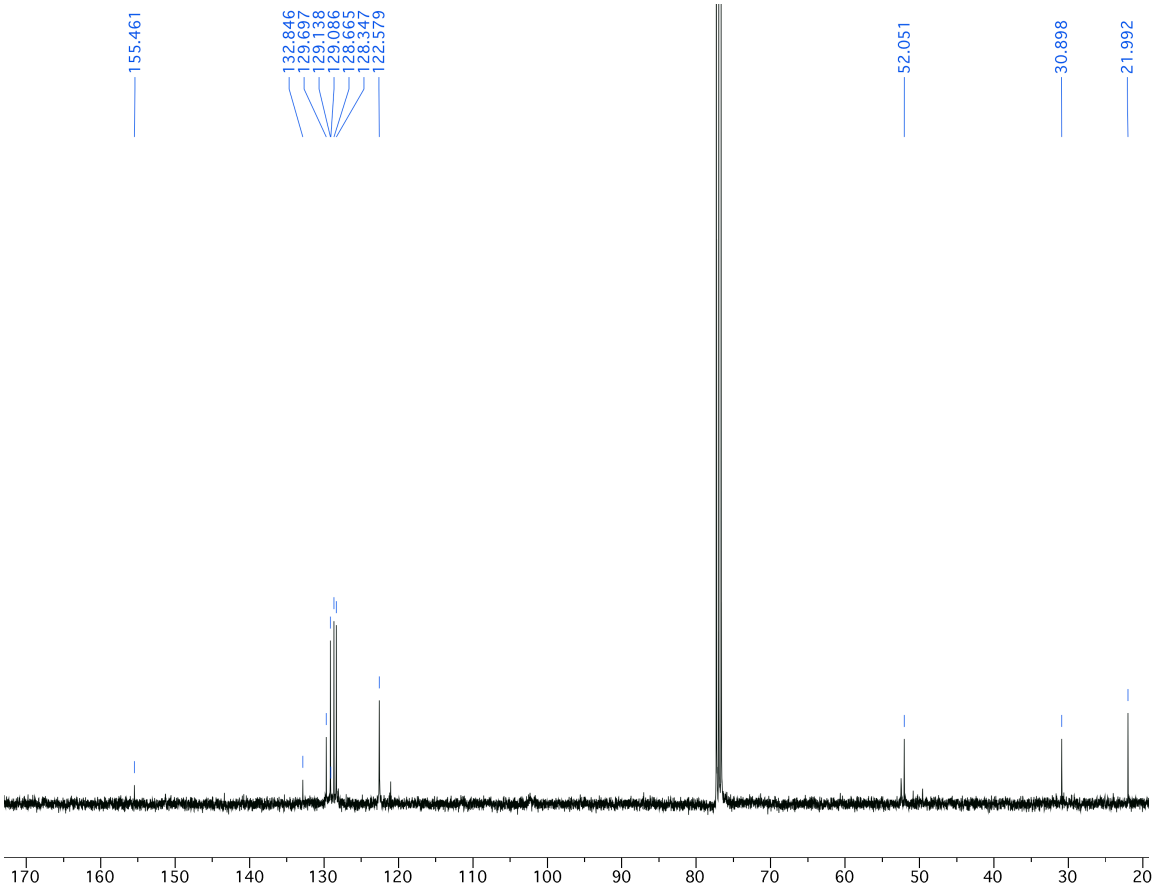
^{13}C NMR: VA-38a



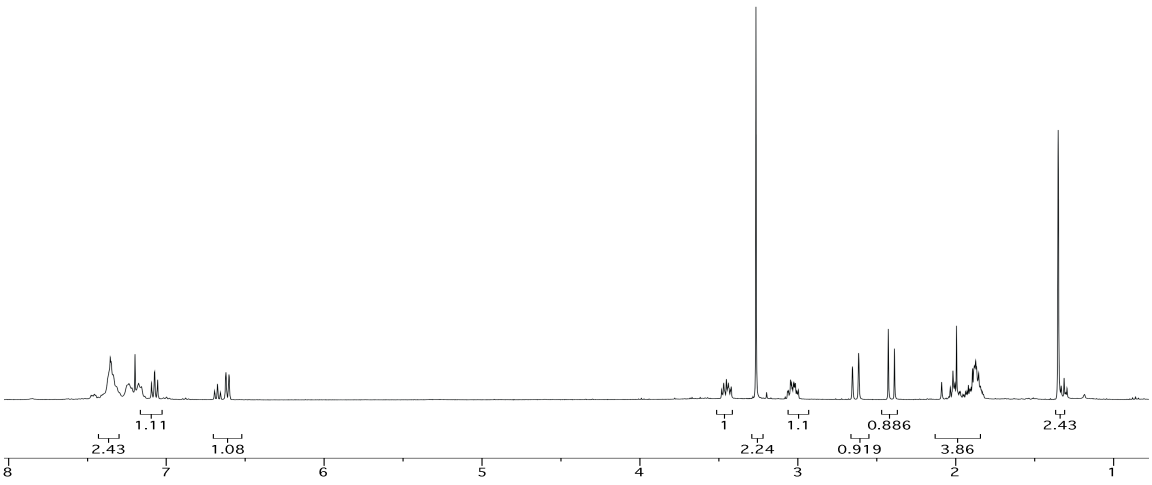
^{1}H NMR: 1-55



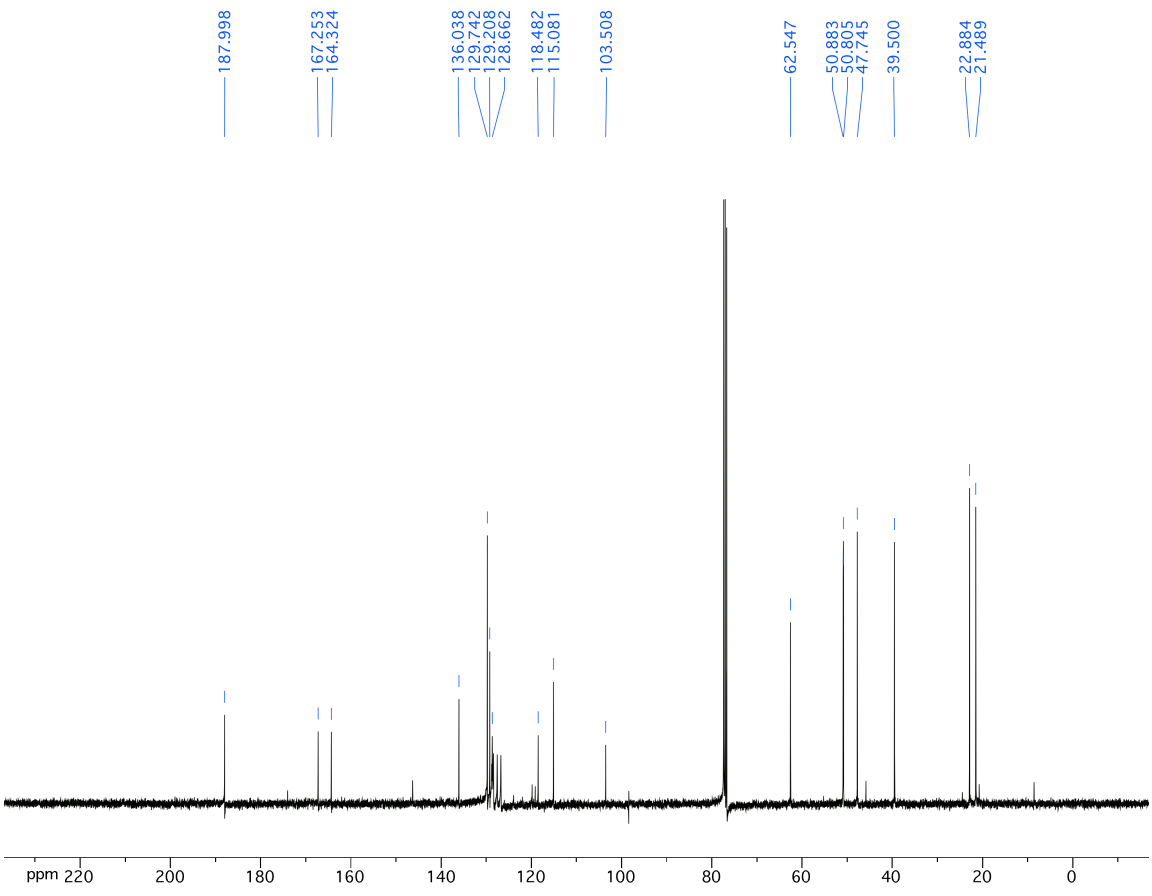
^{13}C NMR: 1-55



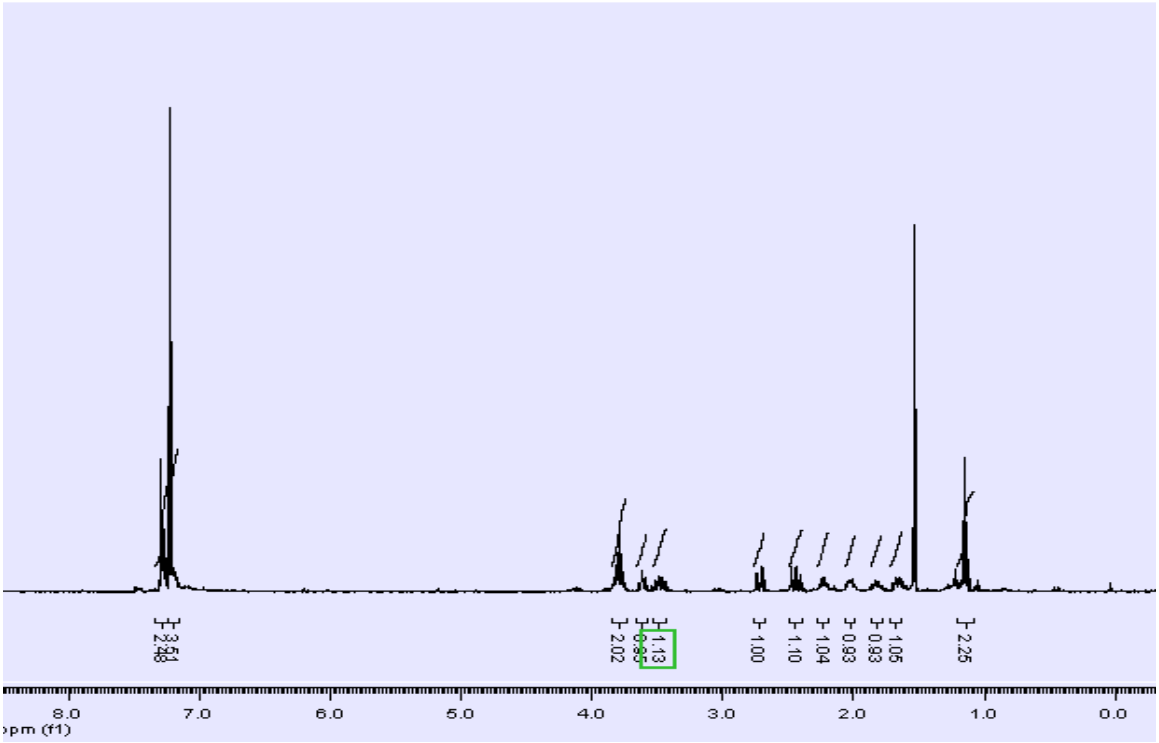
^{1}H NMR: 1-31f



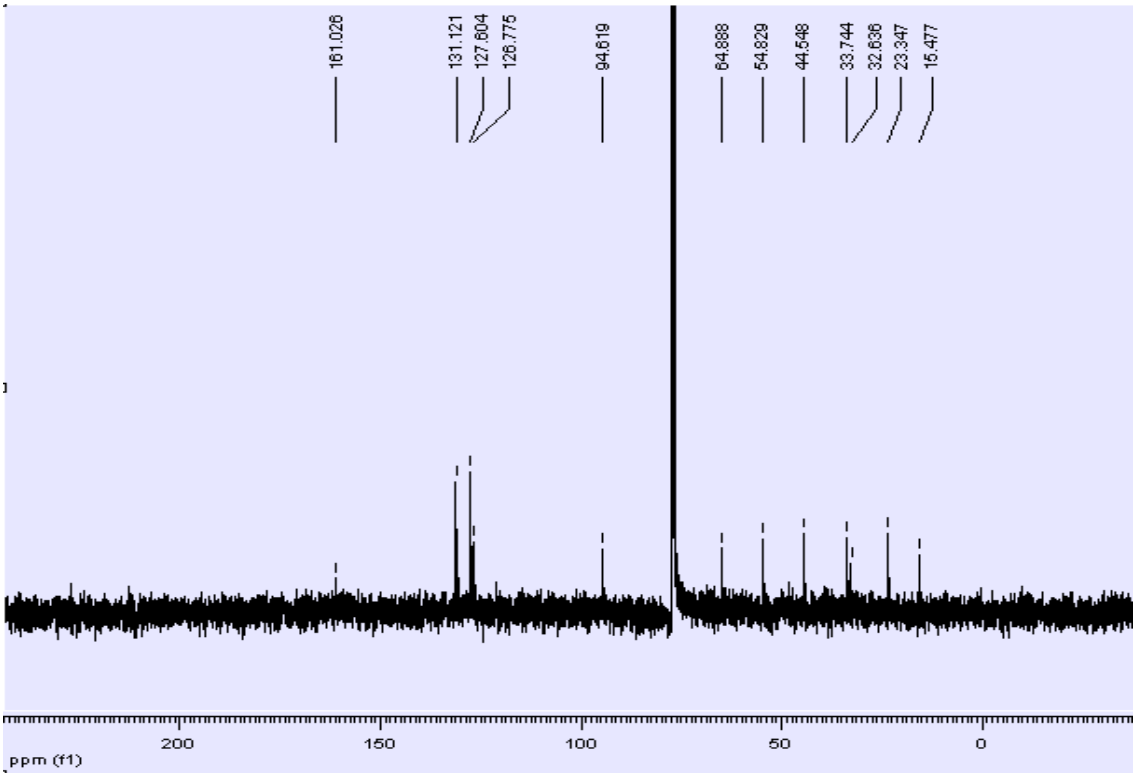
^{13}C NMR: 1-31f



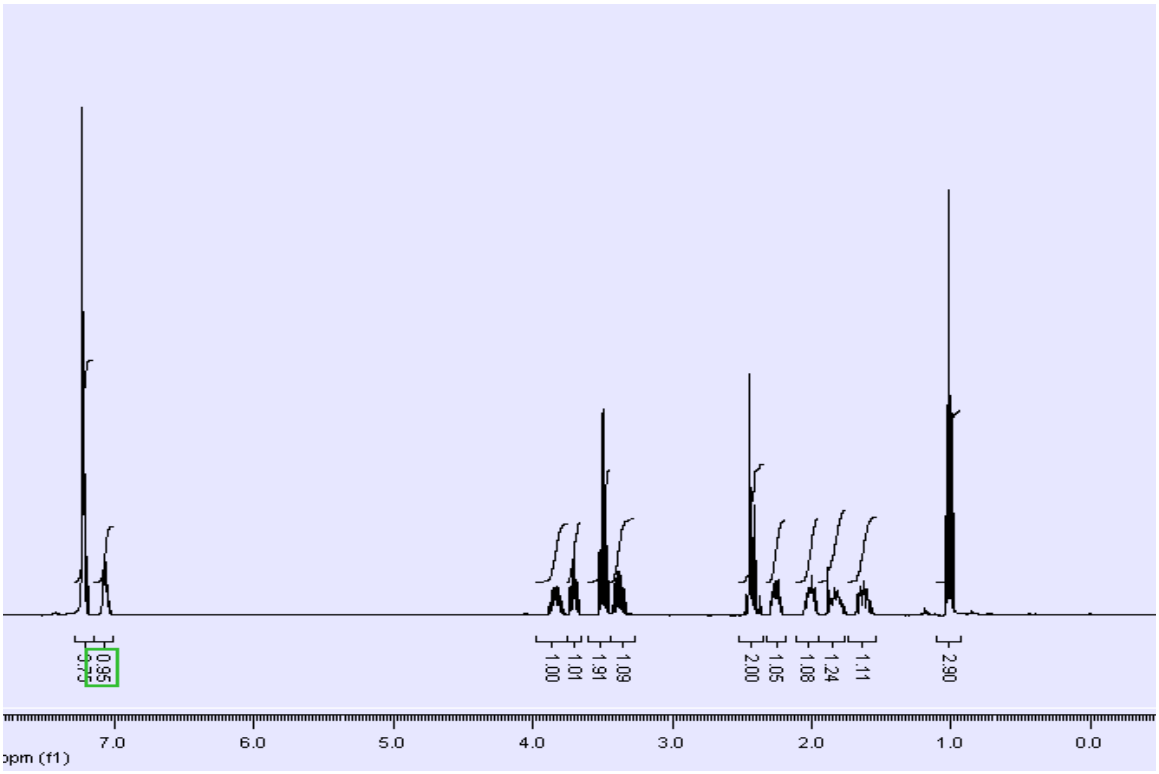
^{1}H NMR: LA-15a



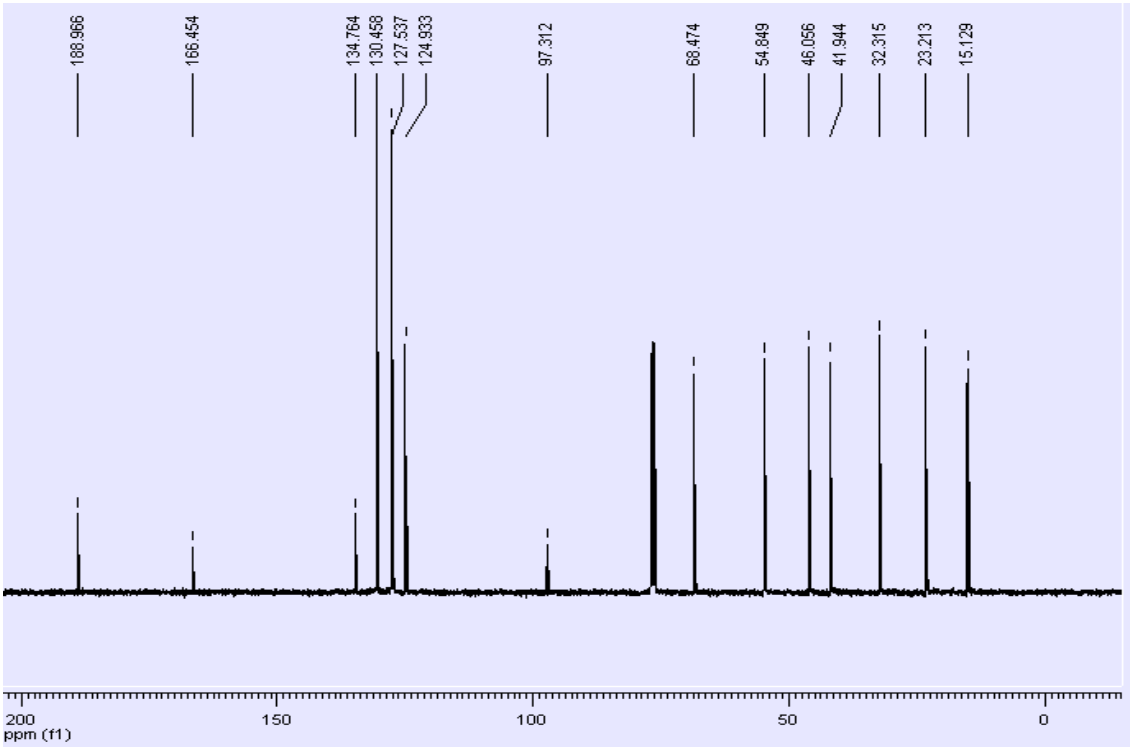
^{13}C NMR: LA-15a



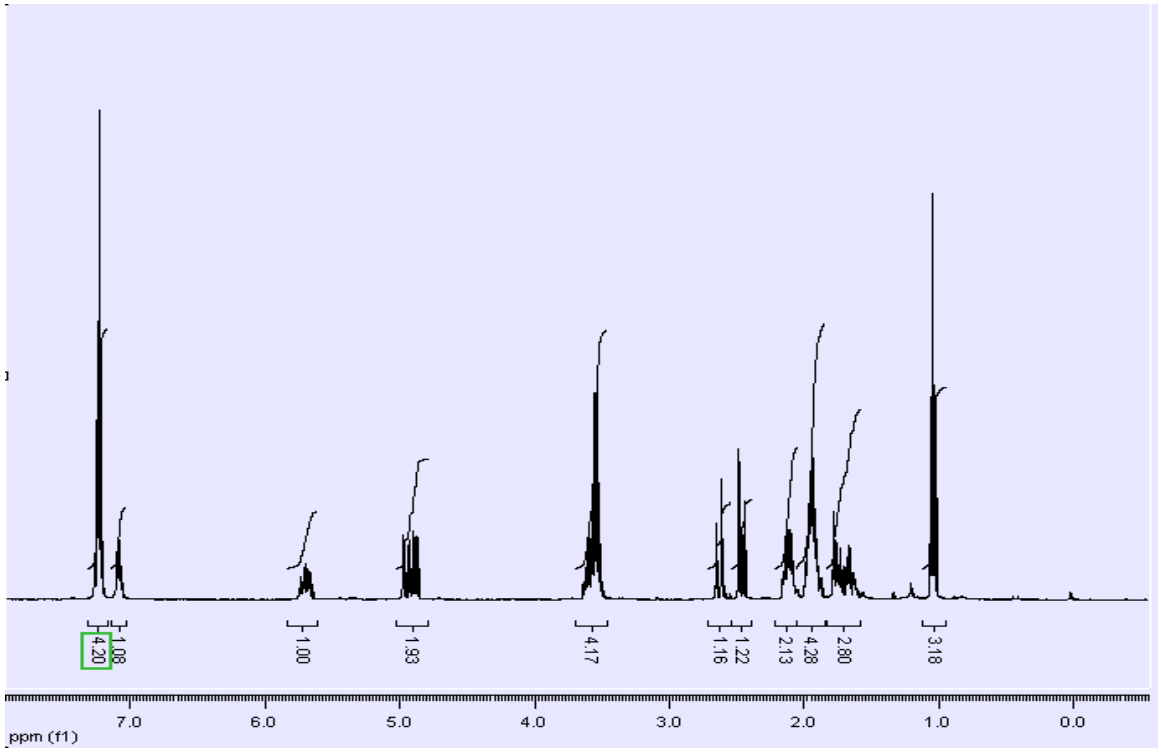
^{1}H NMR: VA-39a



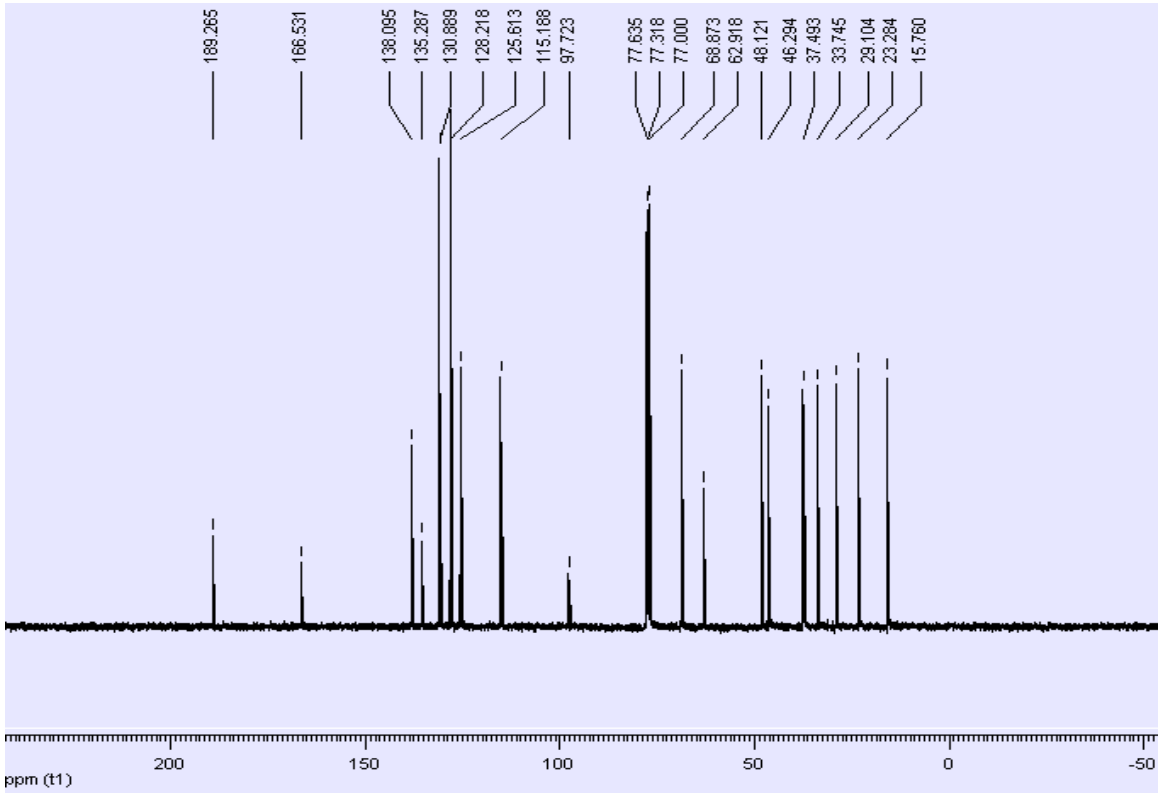
^{13}C NMR: VA-39a



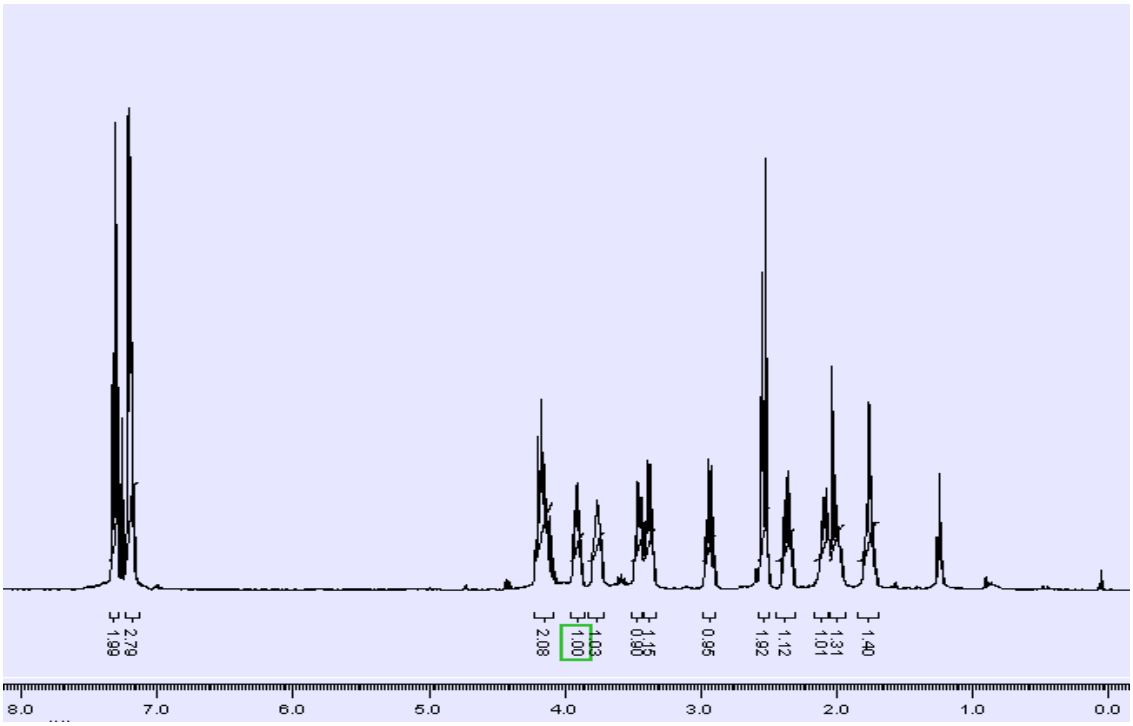
^{1}H NMR: VA-39b



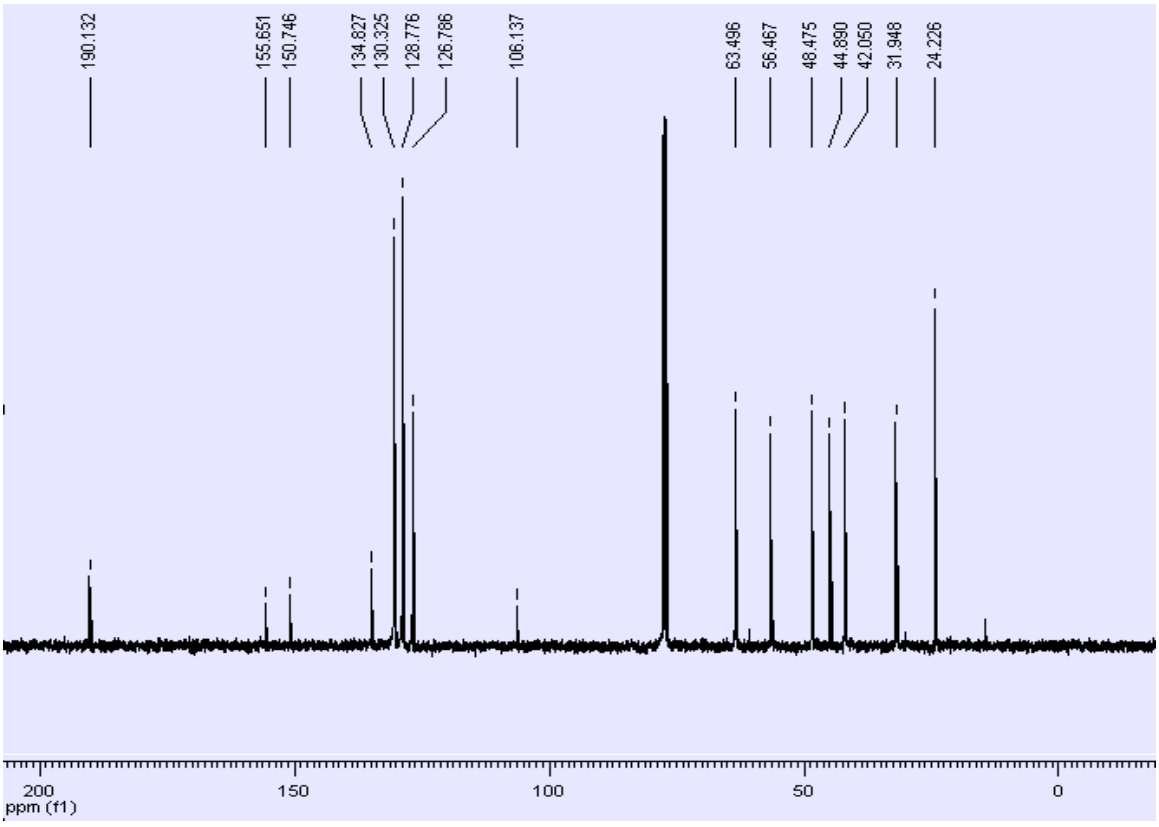
^{13}C NMR: VA-39b



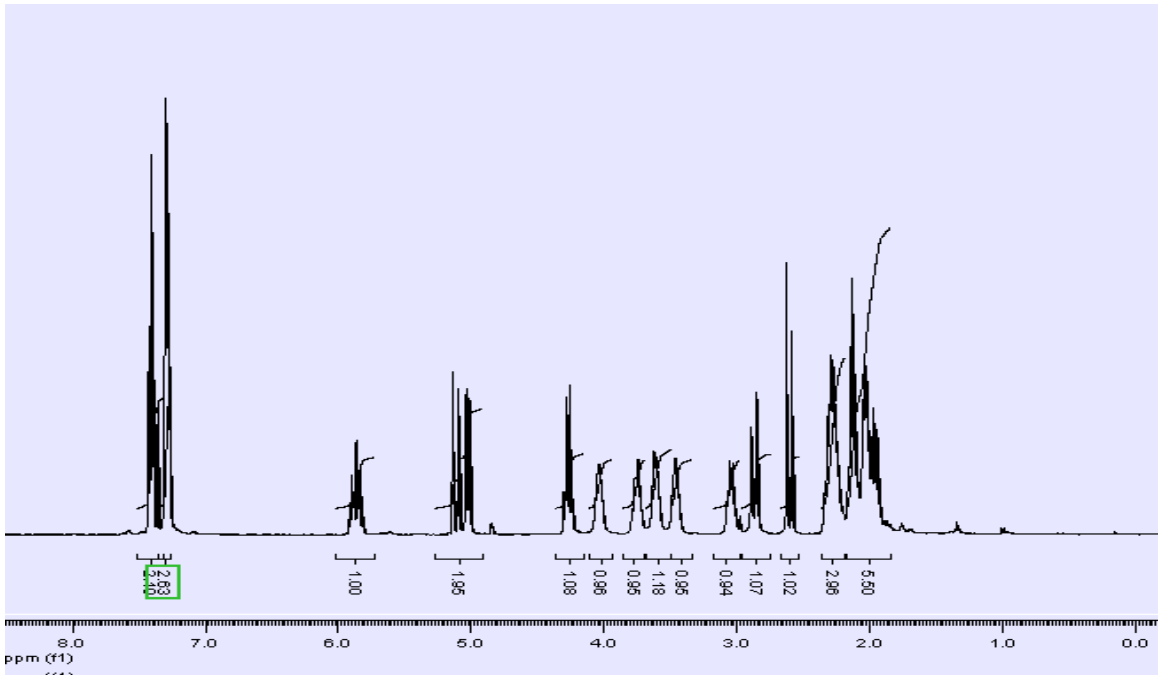
^{1}H NMR: VA-40a



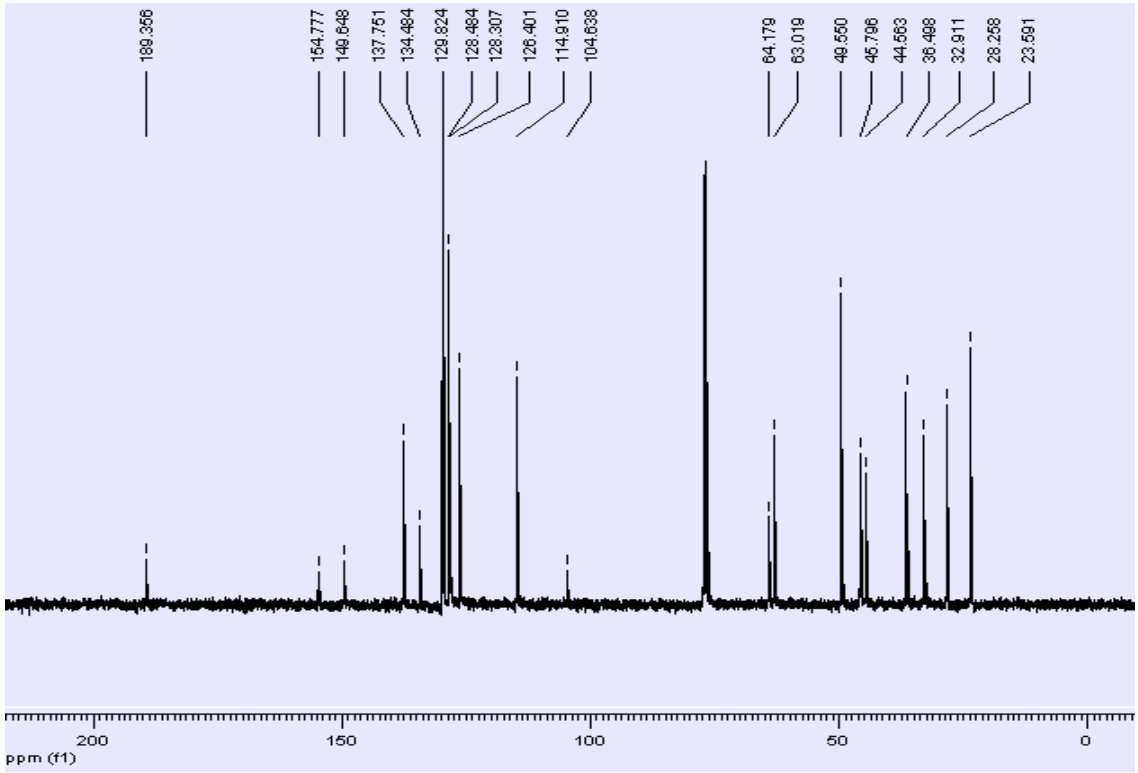
^{13}C NMR: VA-40a



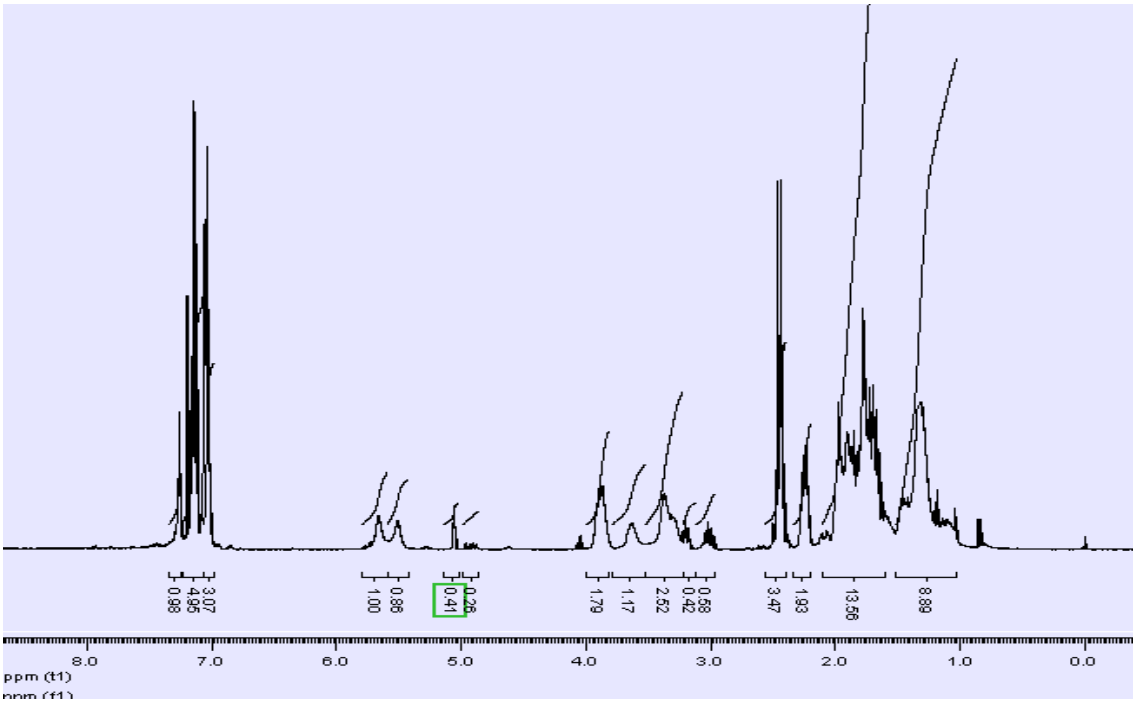
^{1}H NMR: VA-40b



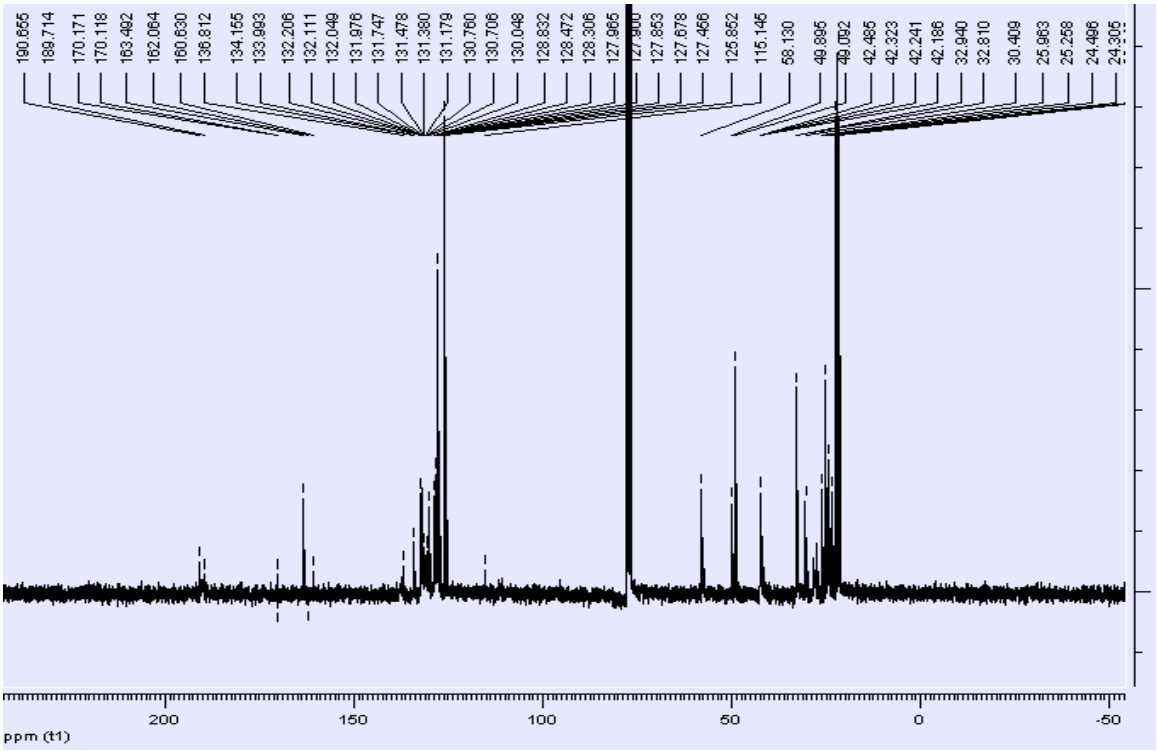
^{13}C NMR: VA-40b



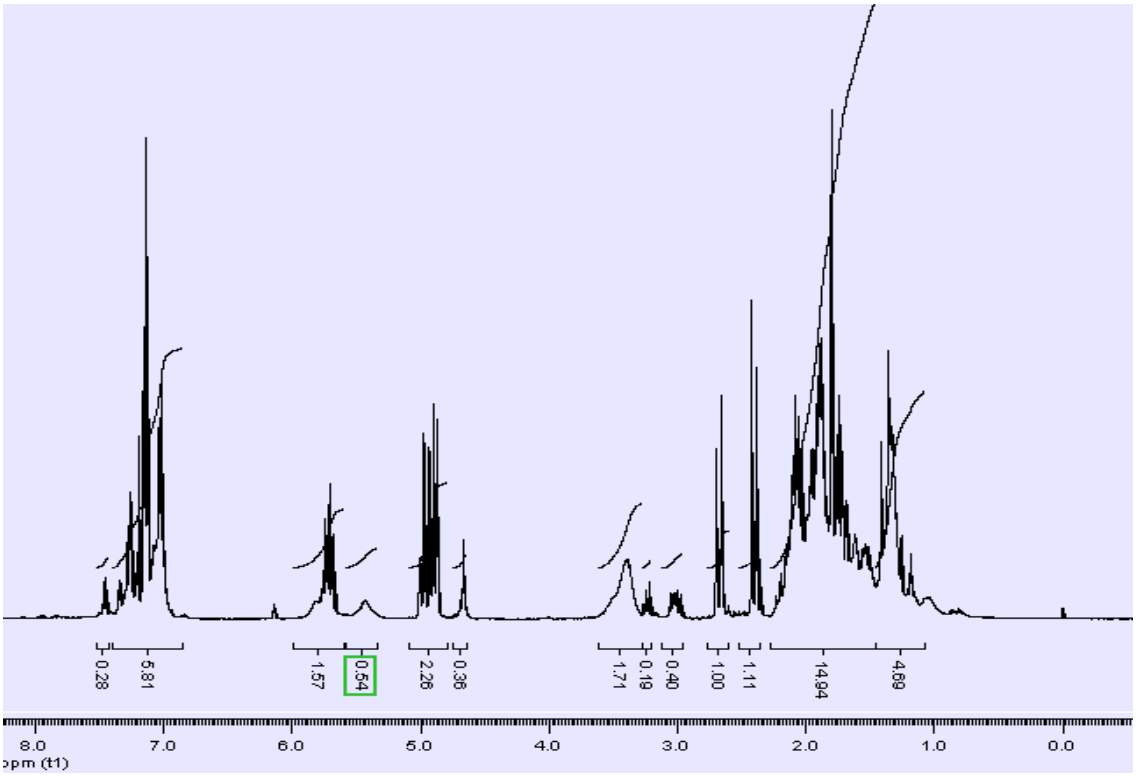
^{1}H NMR: VA-41a, VA-42a



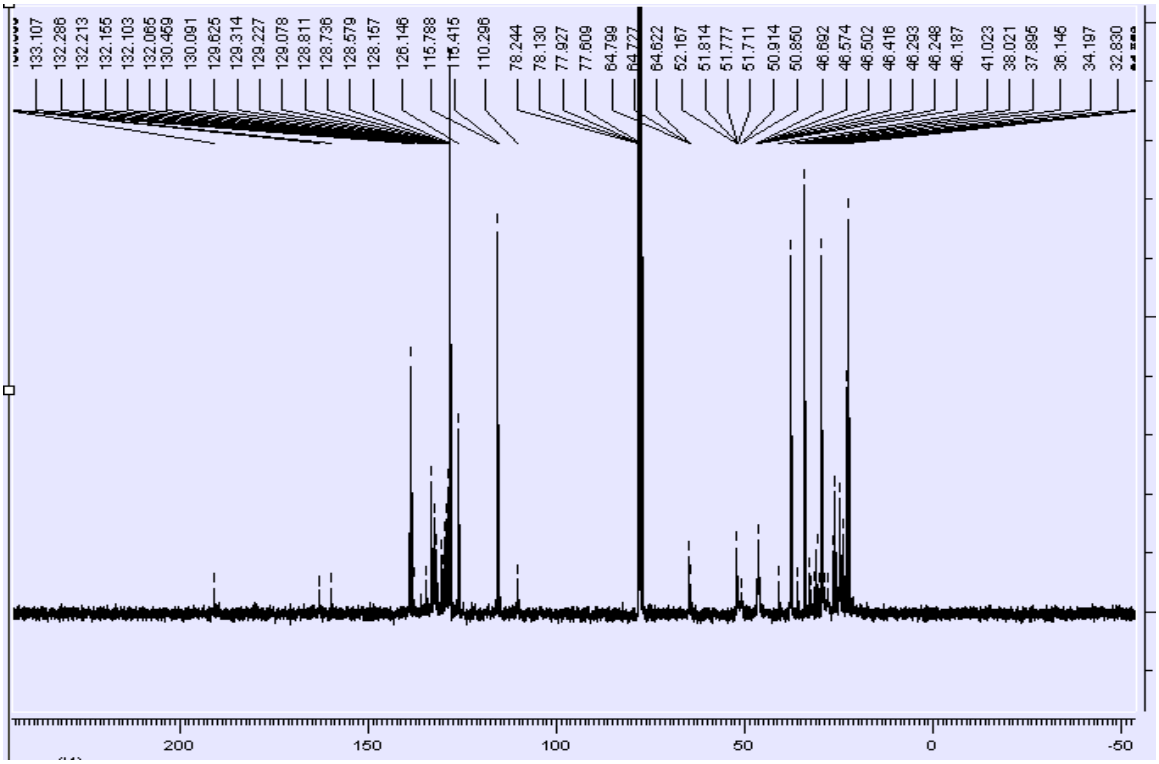
^{13}C NMR: VA-41a, VA-42a



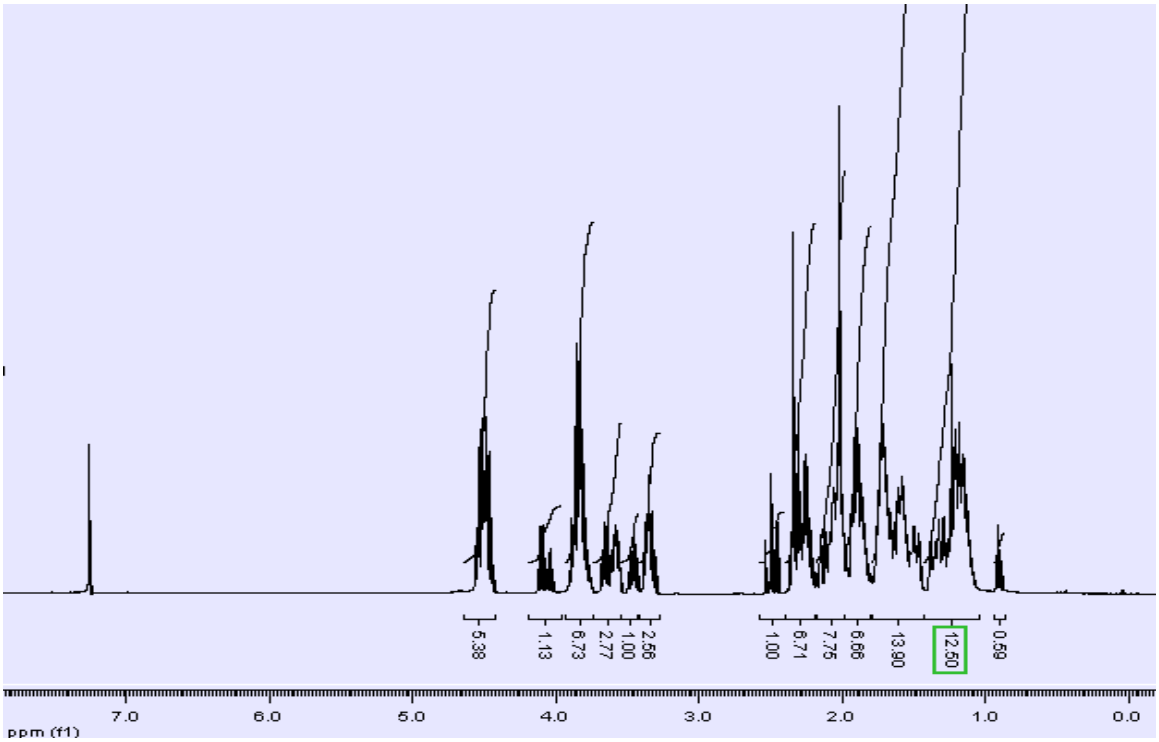
^{1}H NMR: VA-41b, VA-42b



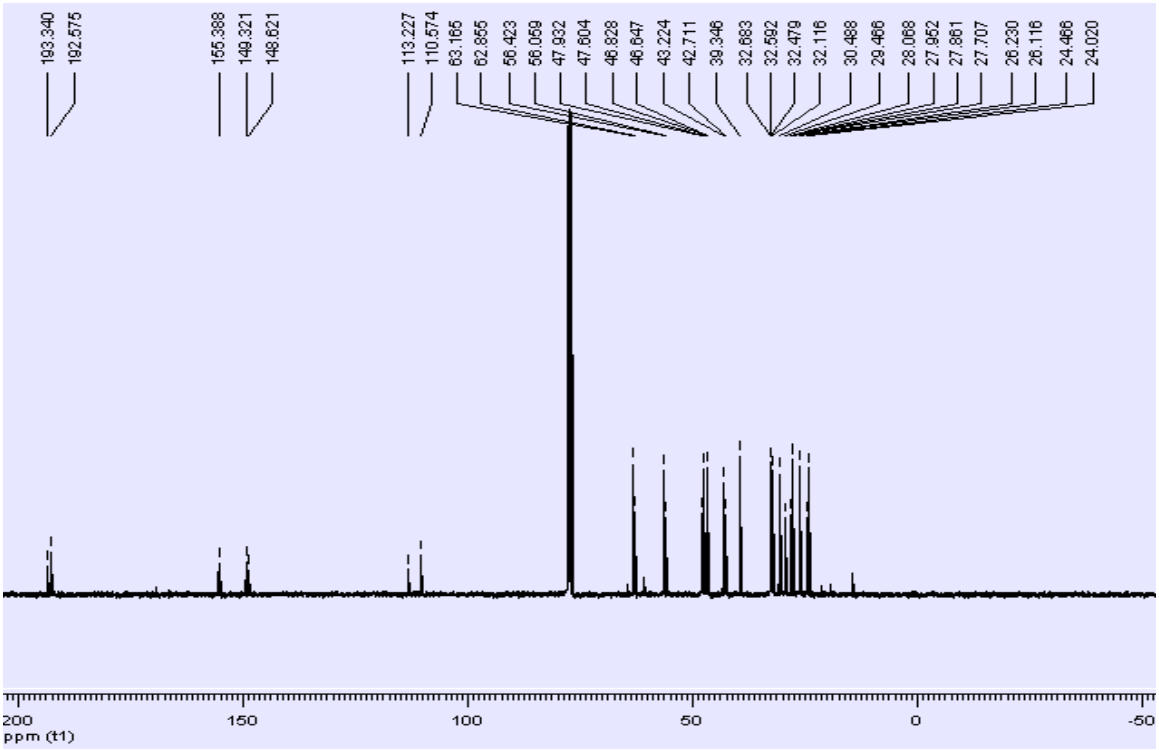
^{13}C NMR: VA-41b, VA-42b



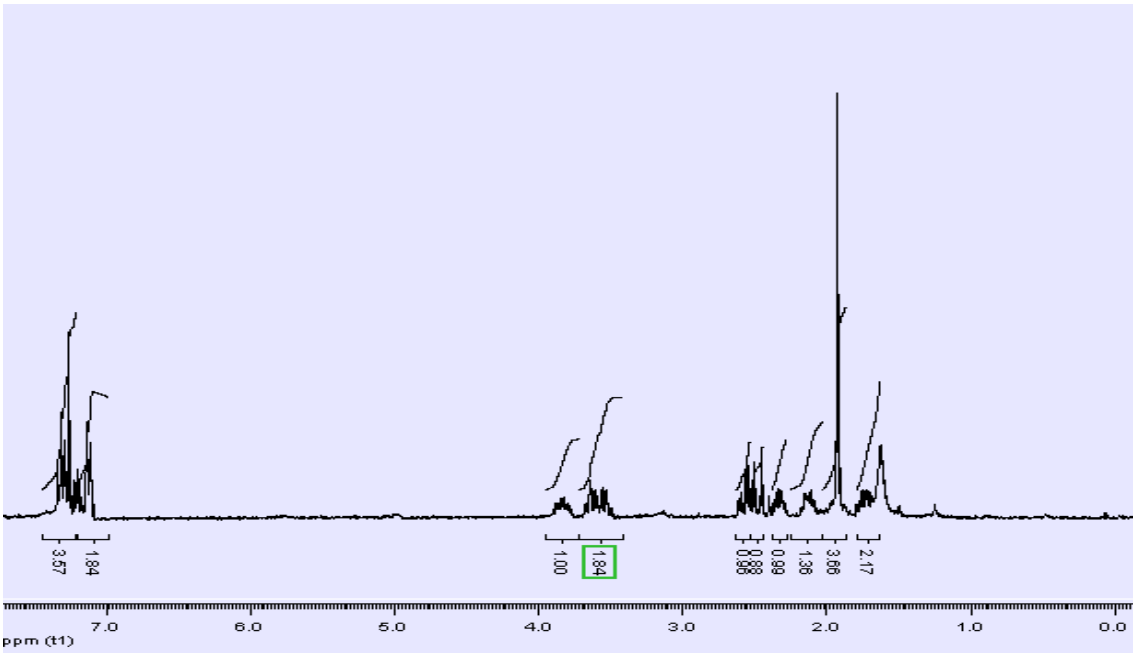
^{1}H NMR: VA-43a, VA-44a



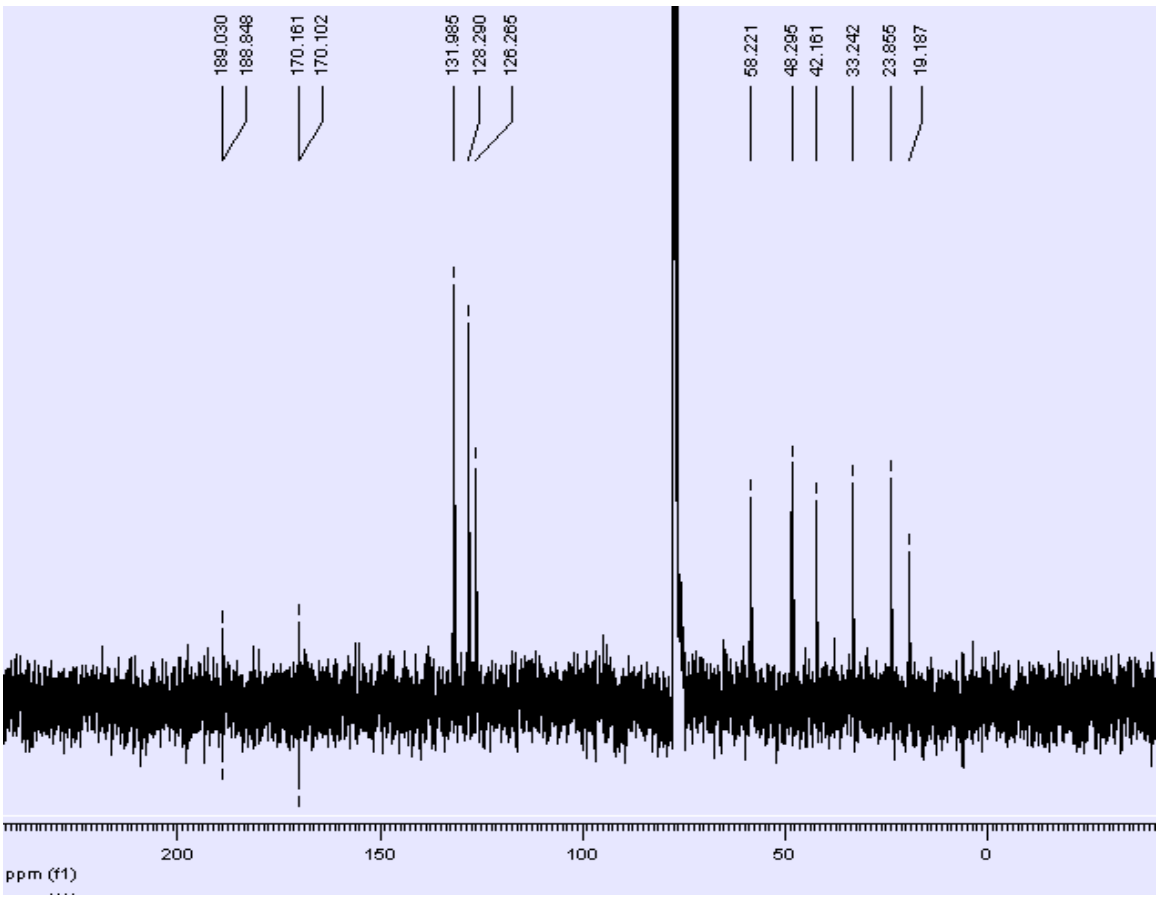
^{13}C NMR: VA-43a, VA-44a



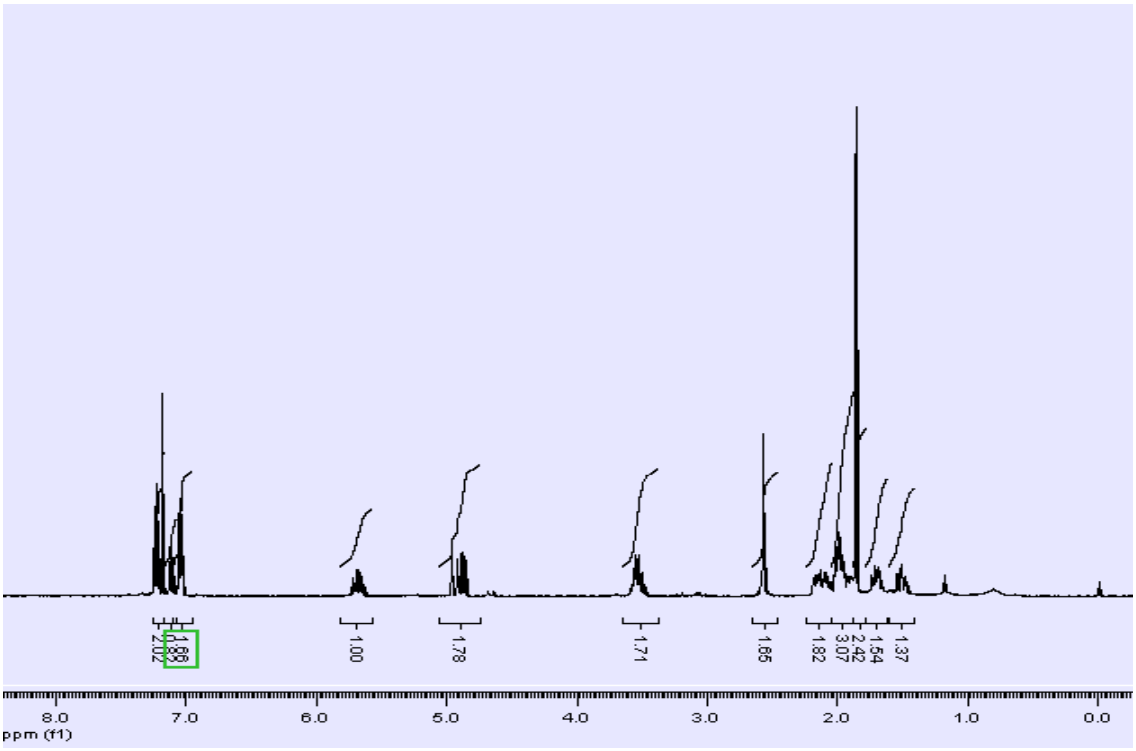
^{1}H NMR: VA-46a



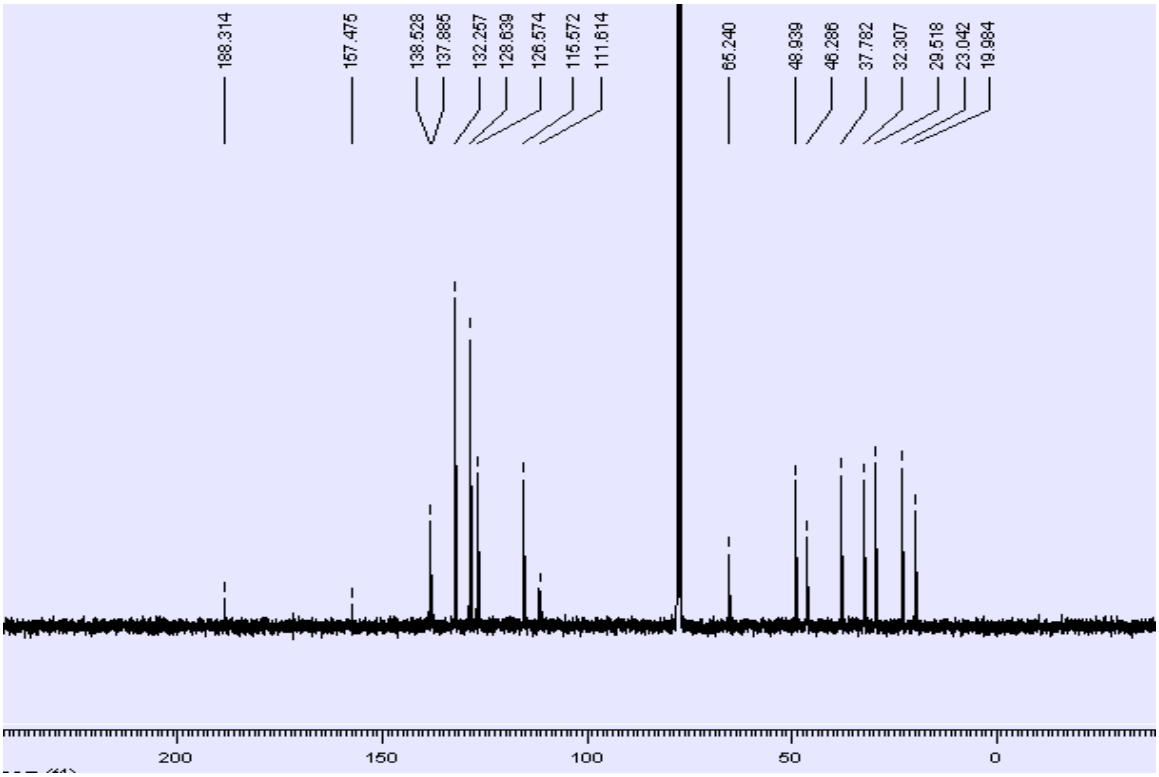
^{13}C NMR: VA-46a



^{1}H NMR: VA-46b

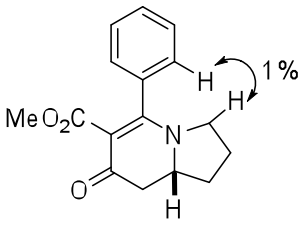


^{13}C NMR: VA-46b

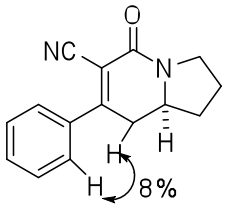


Determination of Regiochemistry:

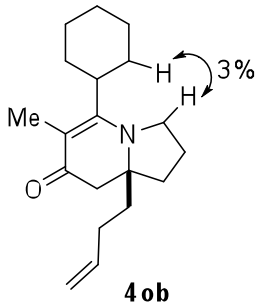
The regiochemistry was determined through Nosey1D (nOe) experiments on a Varian 400MHz NMR. The values are shown below. All other products not shown were determined via correlation to those structures that were known.



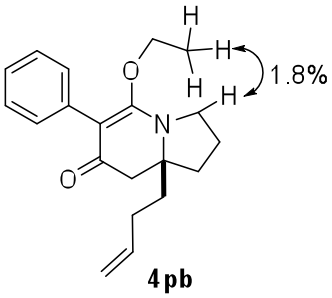
4aa



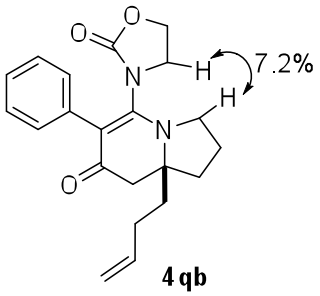
4ja



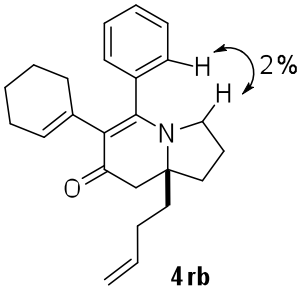
4ob



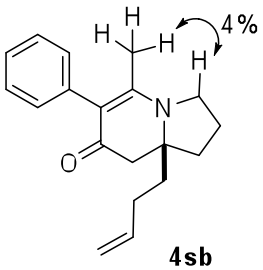
4pb



4qb



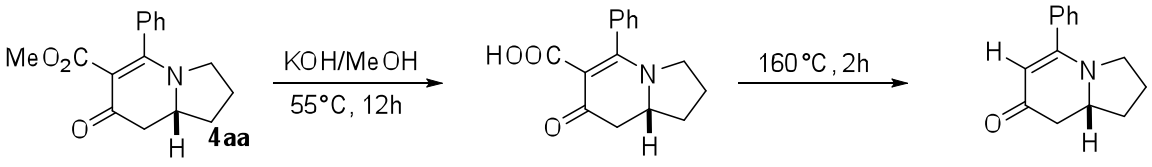
4rb



4sb

Determination of Absolute Stereochemistry:

Absolute stereochemistry was determined for **VA-12** via chemical derivitization[37] and comparison with previously synthesized compounds. All others were assigned by correlation.



The cycloadduct **VA-12** (labeled **4aa** in figure) was dissolved in methanol (0.04M) and H_2O (0.08M) and heated to 55˚C overnight. The reaction mixture was then cooled and diluted with dichloromethane, quenched with 1M HCl, extracted with dichloromethane, dried and concentrated. It was then redissolved in an excess of DCM, placed in a sealed tube and heated to 160˚C for 2h. The reaction mixture was then concentrated, purified using column chromatography (100% EtOAc) and analyzed as necessary. HPLC analysis- Chiracel OD-H column 85:15 hexanes:iPrOH, 0.6 ml/min, Major: 62.6 minutes, Minor: 60.4 minutes, 330 nm detection light, %ee: 66%. Although there was slight epimerization of the stereocenter, the major enantiomer of the final product was the same as that of the same product obtained from a [2+2+2] cycloaddition.[13]

Chapter 2 Experimental:

Rhodium-Catalyzed [4+2+2] Cycloaddition-Mechanistic Exploration Scope Expansion

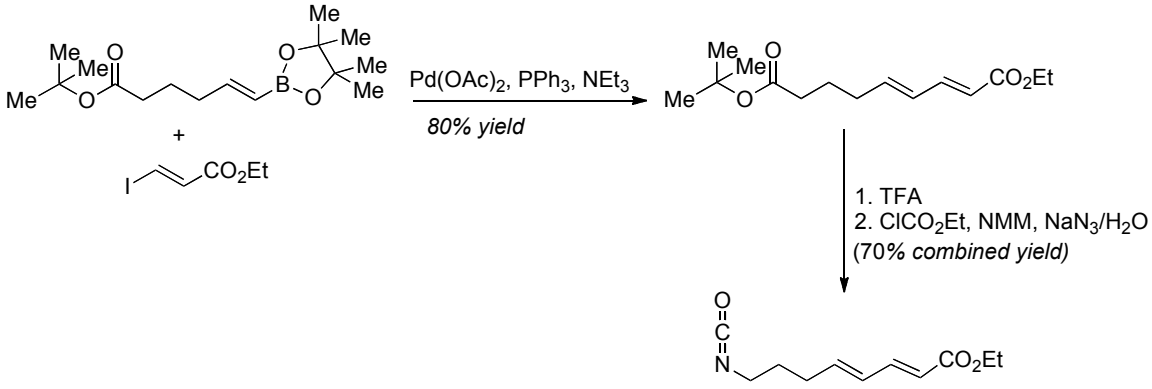
General Methods: All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and $KMnO_4$, followed by heating.

Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm.

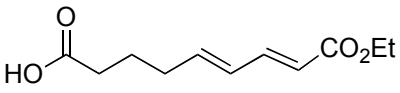
Competition and Slow Addition Experiments:

All experiments were conducted using the previously described method used for [2+2+2] cycloadditions (Chapter 1). In the competition experiments, the competing reagents were combined in solution prior to addition to the reaction mixture. In the slow addition experiments, a syringe pump was used to control the addition of the specified reagent.

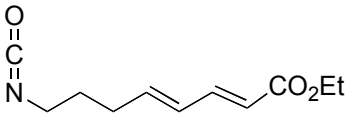
Synthesis of Isocyanate 2-10f:



The tert-butyl ester was formed via a typical Suzuki coupling in 80%. Subsequent deprotection yields the acid (characterized below). Formation of the isocyanate via a mixed anhydride followed by attack with sodium azide and a Curtius rearrangement, yields isocyanate **2-10f**.



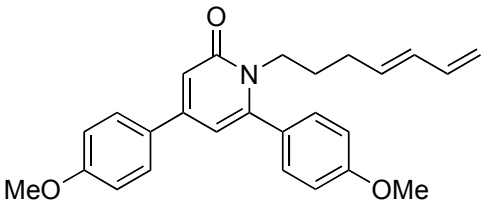
Acid 2-10f: *(5E,7E)-9-ethoxy-9-oxonona-5,7-dienoic acid* Flash Chromatography (EtOAc) yielded a clear oil (50%). R_f = 0.15 (10:1 Hexanes: EtOAc); IR (Thin Film) n 3199, 2984, 2938, 1710, 1643, 1395, 1250, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 10.24 (1H, b, s), 7.18 (1H, dd, *J* = 10.8, 15.2 Hz), 6.13 (1H, m), 6.01 (1H, m), 5.73 (1H, d, *J*=15.2 Hz), 4.13 (2H, q, *J* = 7.2 Hz), 2.30 (2H, t, *J* = 7.6 Hz), 2.17 (1H, q, *J* = 7.2 Hz), 1.72 (2H, quintet, *J*=7.2 Hz), 1.22 (3H, t, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 179.4, 167.5, 144.8, 142.8, 129.5, 120.0, 60.5, 33.4, 32.2, 23.8, 14.4; HRMS (TOF) *m/e* calcd (M^+H) 211.0976, found 211.0989.



2-10f*: (2E,4E)-ethyl 8-isocyanatoocta-2,4-dienoate*

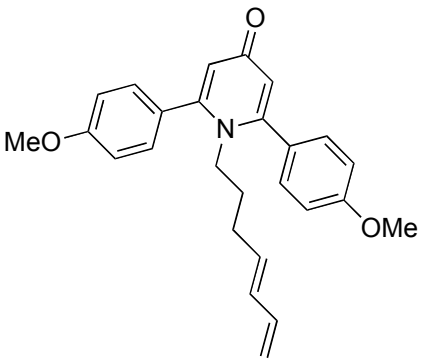
Flash Chromatography (EtOAc) yielded a clear oil (90%). R_f = 0.35 (10:1 Hexanes: EtOAc); IR (Thin Film) n 2939, 2276, 1712, 1644, 1304, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.31 (1H, m), 6.27 (1H, m), 6.11 (1H, m), 5.87 (1H, d, *J*=15.6 Hz), 4.25 (2H,

qd, *J* = 1.6, 6.8 Hz), 3.39 (2H, td, *J* = 1.6, 6.8 Hz), 2.33 (2H, q, *J* = 7.2 Hz), 1.80 (2H, quintet, *J*=6.8 Hz), 1.34 (3H, td, *J*=2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 144.2, 141.6, 129.6, 120.2, 60.2, 42.2, 30.0, 29.7, 14.3; HRMS (TOF) *m/e* calcd (M^+H) 211.1121, found 211.1125.



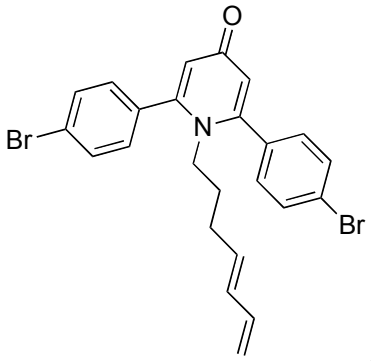
2-18: *(E)-1-(hepta-4,6-dien-1-yl)-4,6-bis(4-methoxyphenyl)pyridin-2(1H)-one(2E,4E)-ethyl 8-isocyanatoocta-2,4-dienoate*

Flash Chromatography (EtOAc) yielded a clear oil (15%). R_f = 0.35 (100% EtOAc); IR (Thin Film) n 2925, 1620, 1504, 1251, 1177, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.54 (3H, d, *J*= 8.8 Hz), 7.30 (4H, d, *J*= 8.8 Hz), 6.96 (8H, dd, *J*= 8.8, 14.4 Hz), 6.75 (1H, d, *J*=2 Hz), 6.31 (1H, d, *J* = 2.4 Hz), 6.16 (1H, ddd, *J* = 8.6, 10.4, 27.2 Hz), 5.90 (1H, dd, *J* = 10.4, 15.2 Hz), 5.41 (1H, ddd, *J*=6.8, 7.0, 15.2 Hz), 5.02 (1H, d, *J*=16.8 Hz) 4.92 (1H, d, *J*=10.4 Hz), 3.87 (6H, s), 3.84 (6H, s), 2.29-2.25 (2H, m), 1.95 (2H, q, *J*=7.2 Hz), 1.69 (3H, quintet, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 163.6, 160.7, 160.1, 149.7, 149.2, 137.0, 133.5, 131.4, 130.0, 128.0, 115.0, 114.0, 113.9, 107.6. 55.3, 44.9, 29.6, 27.9; HRMS (TOF) *m/e* calcd (M^+H) 402.2064, found 402.2065.



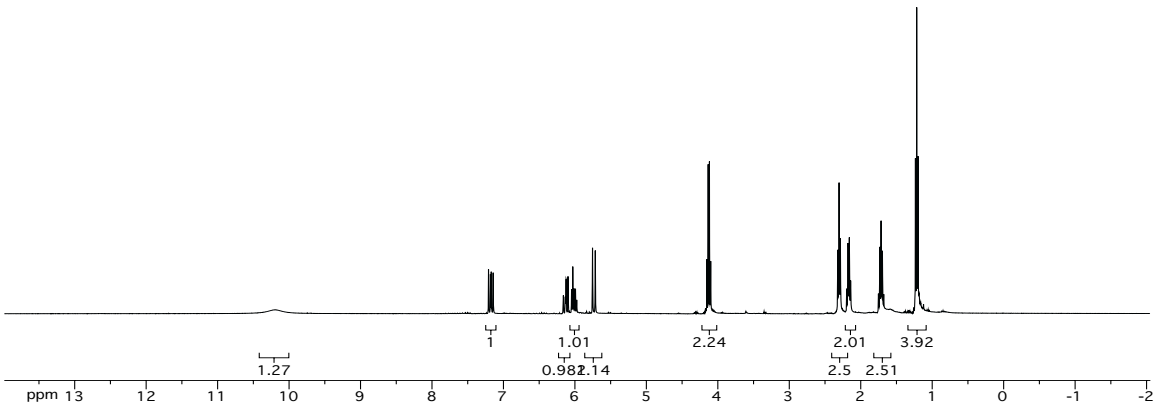
2-19c: *(E)-1-(hepta-4,6-dien-1-yl)-2,6-bis(4-methoxyphenyl)pyridin-4(1H)-one :* Flash Chromatography (EtOAc) yielded a clear oil

(60%). R_f = 0.05 (4:1 EtOAc: MeOH); IR (Thin Film) n 2935, 1646, 1608, 1509, 1293, 1178, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.33 (4H, d, *J*= 8.8 Hz), 6.98 (4H, d, *J*= 8.8 Hz), 6.37 (2H, s), 5.99 (1H, ddd, *J*=8.2, 10, 10.4 Hz), 5.65 (1H, dd, *J* = 10.4, 15.2 Hz), 4.99-4.90 (2H, m), 3.86 (3H, s), 3.82 (1H, m), 2.29-2.15 (4H, m) 1.55 (1H, q, *J*=6.8 Hz), 1.30-1.23 (3H, m; ^{13}C NMR (100 MHz, $CDCl_3$) d 178.5, 160.3, 153.1, 136.6, 132.0, 131.9, 130.0, 127.4, 120.4, 115.4, 114.3, 114.2, 55.3, 49.6, 29.1, 28.7; HRMS (TOF) *m/e* calcd (M^+H) 402.2064, found 402.2072.

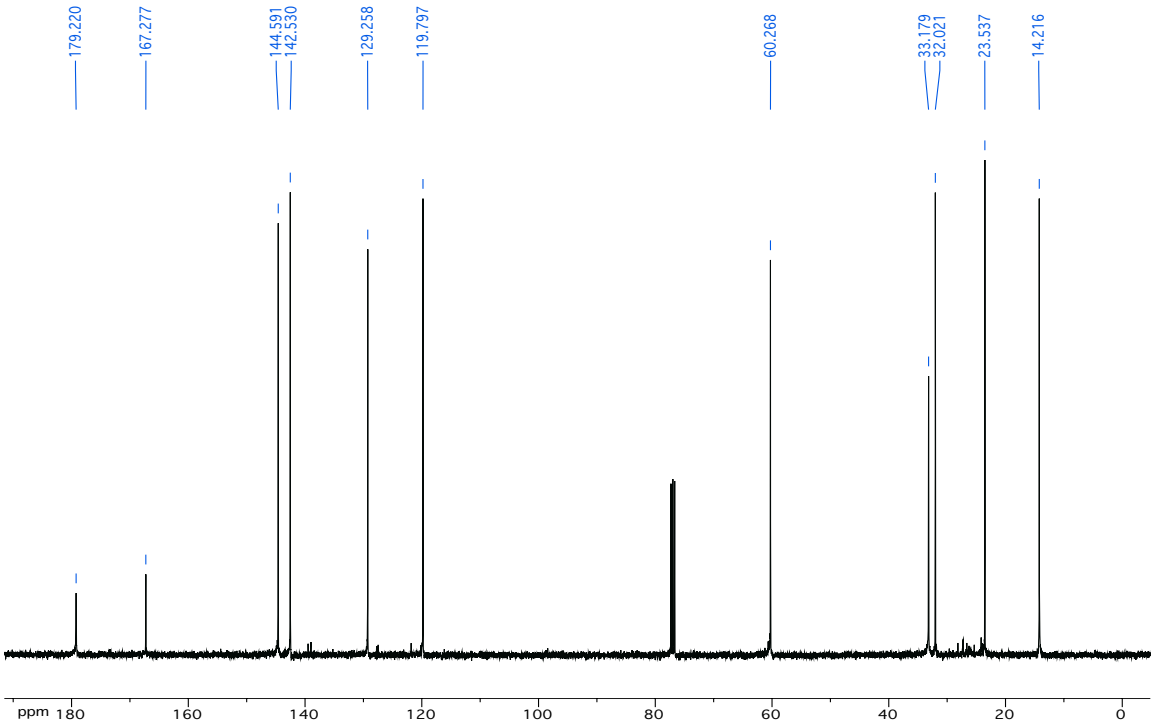


2-19b: *(E)-1-(hepta-4,6-dien-1-yl)-2,6-bis(4-methoxyphenyl)pyridin-4(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (25%). R_f = 0.05 (4:1 EtOAc: MeOH); IR (Thin Film) n 2925, 1650, 1621, 1485, 1250, 1071, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.47 (4H, d, *J*= 8.4 Hz), 7.11 (4H, d, *J*= 8.4 Hz), 6.28 (2H, s), 6.14 (2H, m), 5.17 (2H, dd, *J* = 0.8, 11.6 Hz), 5.02 (2H, d, *J*= 0.8, 18 Hz), 4.16 (3H, t, *J*=7.2 Hz), 3.18 (6H, q, *J*= 8 Hz), 2.19-2.12(11H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 160.8, 152.7, 137.4, 132.2, 131.9, 131.4, 130.3, 130.2, 129.8, 117.6, 117.1, 98.4, 48.9, 45.5, 32.7, 22.2, 21.4; HRMS (TOF) *m/e* calcd (M^+H) 498.0063, found 498.0067.

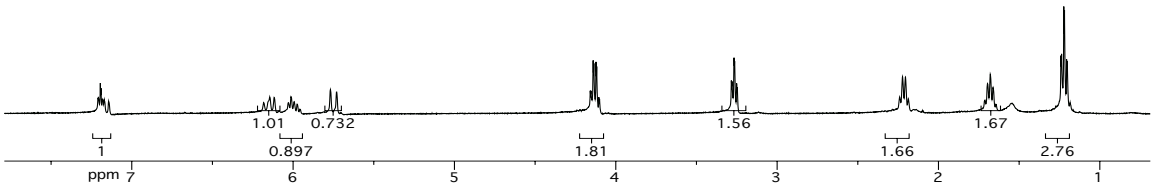
^{1}H NMR Acid 2-10f



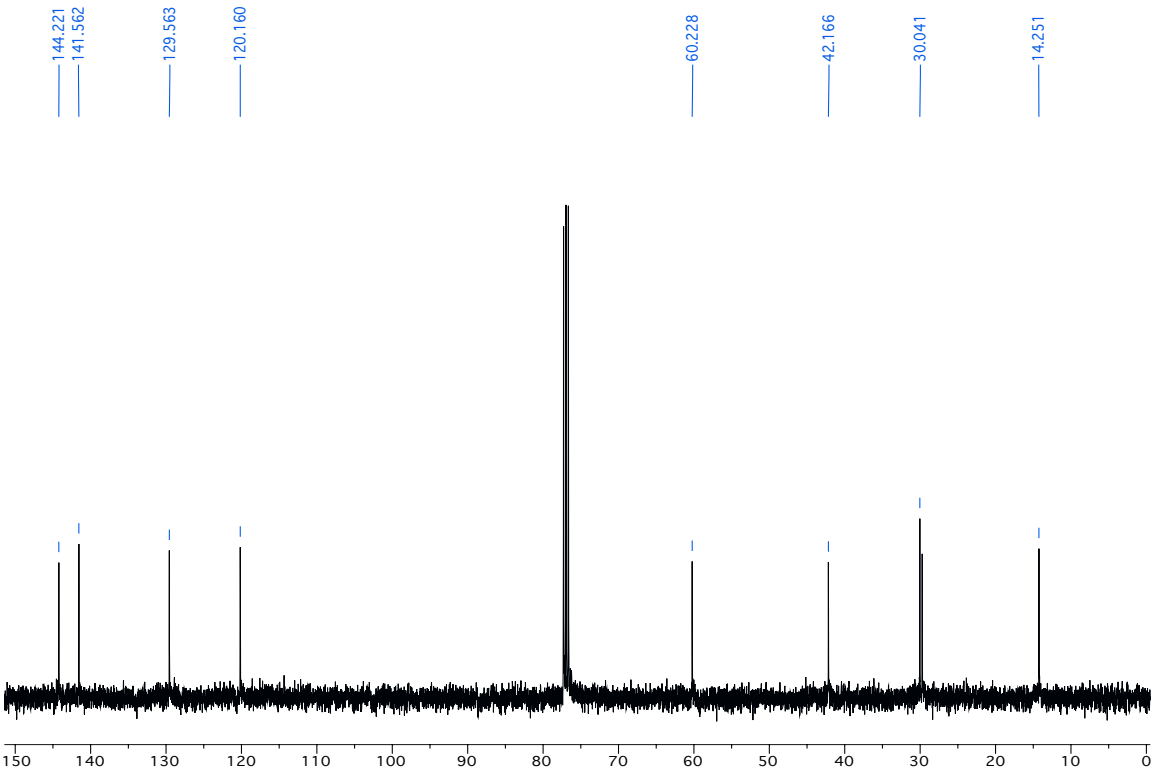
^{13}C NMR Acid 2-10f



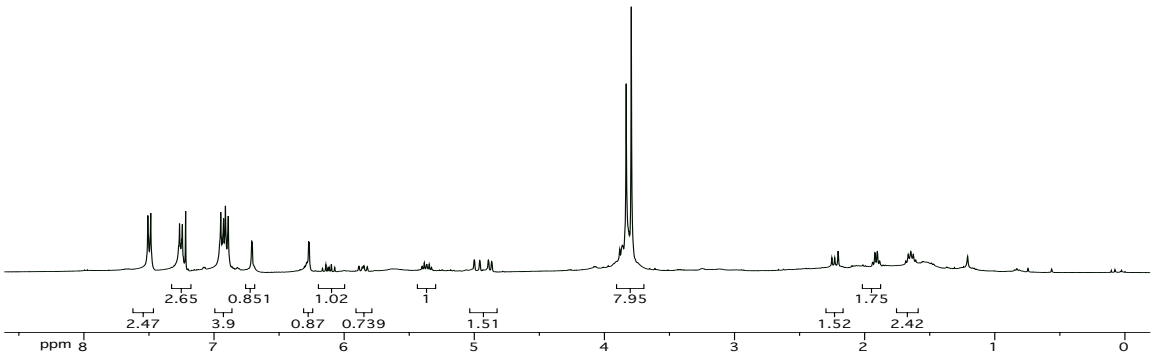
^{1}H NMR 2-10f



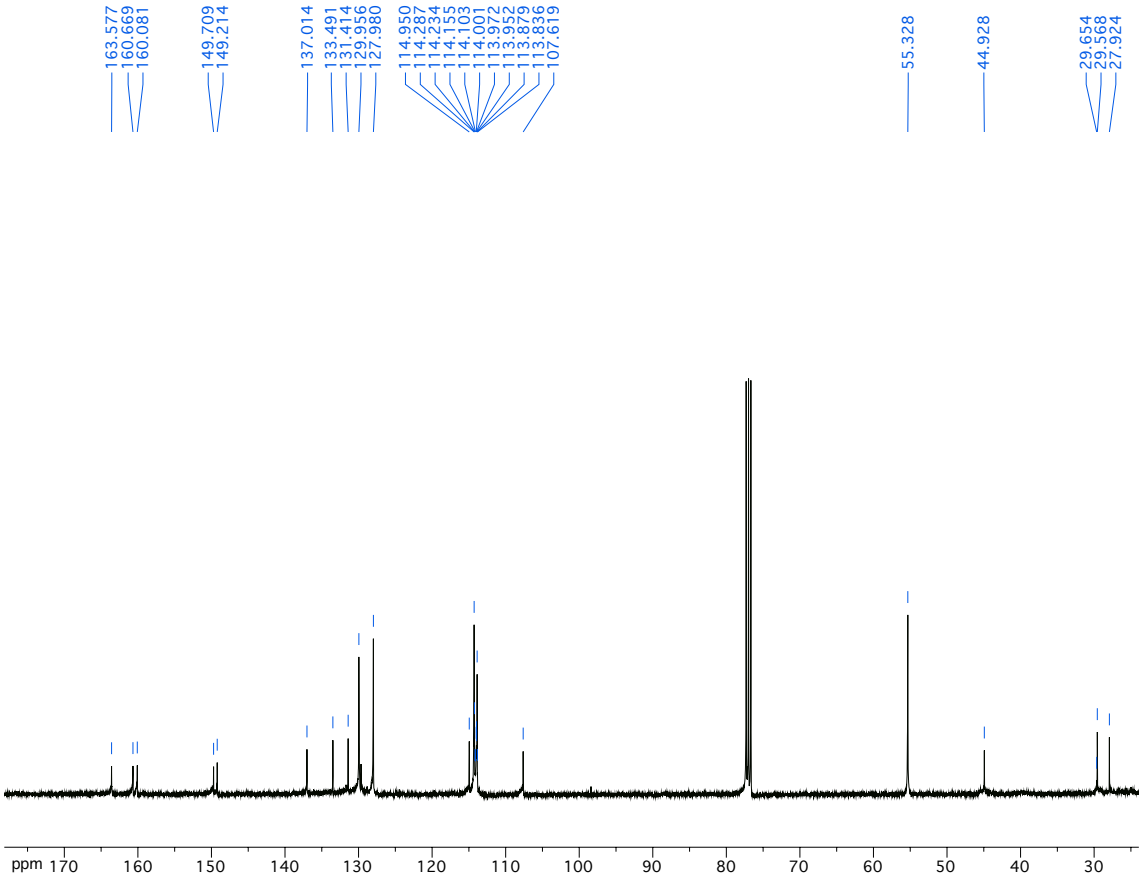
^{13}C NMR 2-10f



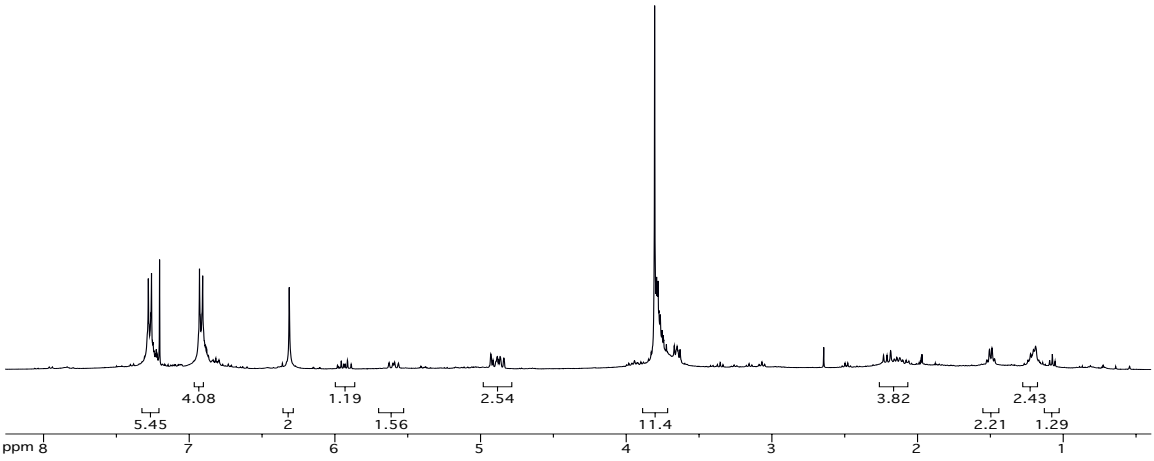
^{1}H NMR 2-18



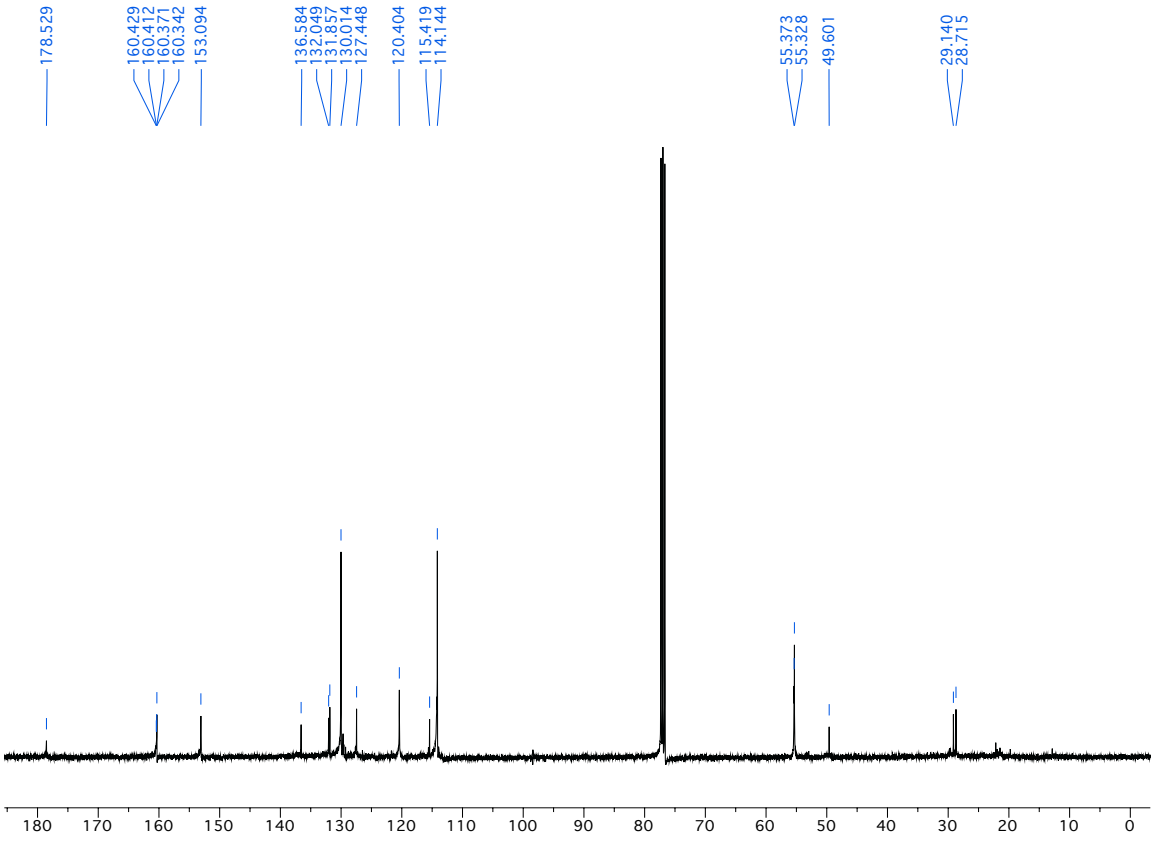
^{13}C NMR 2-18



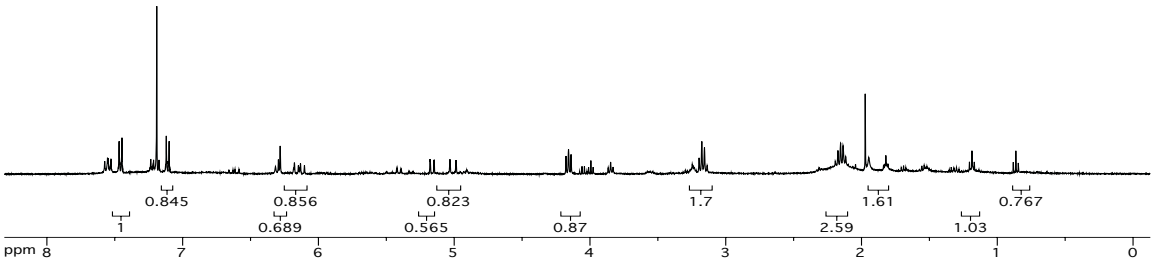
^{1}H NMR 2-19c



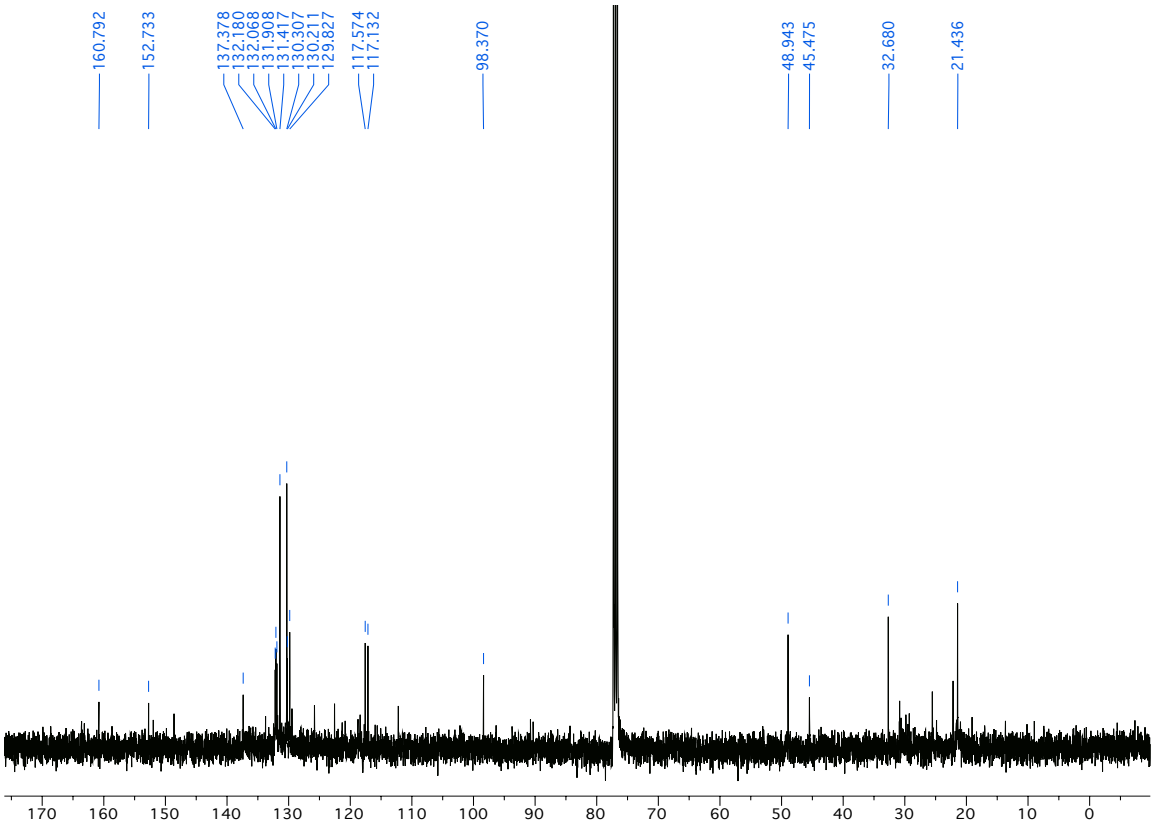
^{13}C NMR 2-19c



^{1}H NMR 2-19b



^{13}C NMR 2-19b



Chapter 3 Experimental

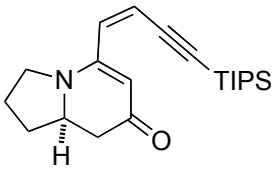
Efforts Towards the Total Synthesis of Secu'amamine A: Utilization of the Rhodium-Catalyzed [2+2+2] Cycloaddition

General Methods: All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and $KMnO_4$, followed by heating.

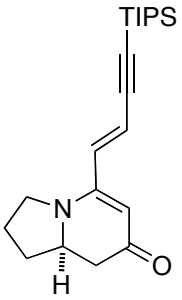
Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a SD-200 HPLC equipped with a UV-1- variable wavelength UV detector using a Chiracel OD-H, AD-H or OJ-H chiral column. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell. Models were computed using semi-empiracal, AM-1 calculation method under neutral conditions, using Gaussian to visualize.

Synthesis of 3-21: The Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and internal, unsymmetrical alkynes: $[Rh(ethylene)_2Cl]_2$ was purchased from Strem Chemical, Inc. and used without further purification. An oven or flame-dried round bottom flask was charged with $[Rh(ethylene)_2Cl]_2$ (0.025 eq) and the phosphoramidite ligand **L** (0.05 eq), and was fitted with a flame-dried reflux condenser and septa in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 3.0 ml toluene was added via syringe and the resulting yellow or orange solution was stirred at ambient temperature under argon flow for 5-15 minutes. To this solution was added a solution of alkyne **3-20** (1.2 eq) and isocyanate **3-19** (0.15 mmol) in 1 ml of toluene via syringe. After an additional 1 ml of toluene to wash down the remaining residue, the resulting solution was heated to 110 °C in an oil bath, and maintained at reflux for *ca.* 12 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution, typically 1:1 hexanes:ethyl acetate to 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product. The reaction could be successfully scaled up 3 mmol of isocyanate, with all reagent ratios kept the same. The time of the reaction was extended to 20 hr when the reaction was scaled up.

Synthesis of 3-33: Under an atmosphere of argon, 0.1g of **3-21** was dissolved in 10 mL of THF and cooled to 0 °C. 1.5 equivalents of a 1M solution of Super-H was added. The reaction was quenched after 5 minutes with Rochelle's salt and then extracted with EtOAc. The crude mixture was purified via column chromatography (100% EtOAc, .7 Rf) to yield the desired product in 60-90% yield.

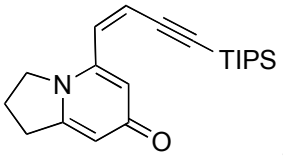


3-21: *(R,Z)-5-(4-(triisopropylsilyl)but-1-en-3-yn-1-yl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a orange solid (40-80%). (+) isomer: $[a]_D$ = 256^o ($CHCl_3$, c=0.001); HPLC analysis- Chiracel AD-H column 95:5 hexanes:iPrOH, 1.0 ml/min, Major: 19.6 minutes, Minor: 18.4 minutes, 330 nm detection light, *%*ee: 95%; R_f = 0.15 (100% EtOAc); IR (Thin Film) n 2957, 2862, 1624, 1515, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 6.26 (1H, d, *J*=12 Hz), 5.89 (1H, d, *J*=12 Hz), 5.47 (1H, s), 3.77 (1H, dddd, *J* = 5.2, 5.2, 10.4, 16 Hz), 3.54 (1H, dt *J* = 2, 9.8 Hz), 3.44 (1H, q, *J*= 10 Hz), 2.41 (1H, dd, *J* = 4.8, 15.6 Hz), 2.32-2.20 (2H, m), 2.05 (1H, m), 1.85 (1H, m), 1.66 (1H, m), 1.05 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.7, 156.0, 132.6, 115.5, 103.1, 102.1, 98.4, 58.8, 47.2, 41.5, 32.4, 23.9, 18.5, 11.1; HRMS (TOF) *m/e* calcd ($M+H^+$) 344.2404, found 344.2409.

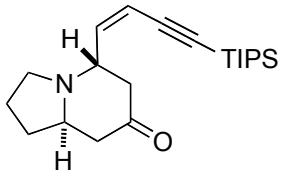


3-25: *(R,E)-5-(4-(triisopropylsilyl)but-1-en-3-yn-1-yl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one: :* Flash Chromatography (EtOAc) yielded a orange solid (40-80%). (+) isomer: $[a]_D$ = 392^o ($CHCl_3$, c=0.008); R_f = 0.10 (100% EtOAc); IR (Thin Film) n 2943, 2865, 1619, 1533, 1461, 1241, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 6.58 (1H, d, *J*=15.9 Hz), 6.30 (1H, d, *J*=15.9 Hz), 5.423 (1H, s), 3.76 (1H, m), 3.71 (1H, m), 3.46 (1H, q, m), 3.46 (1H, m), 2.47-2.31 (2H, m), 2.26 (1H, m), 2.13 (1H, m), 1.92 (1H, m), 1.66 (1H, m), 1.09 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 191.8, 156.8, 134.1,

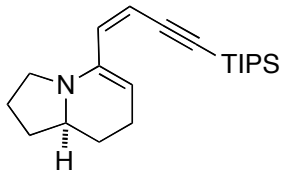
117.7, 104.2, 99.1, 94.7, 58.9, 47.4, 41.5, 32.4, 23.9, 18.5, 11.2, 11.1; HRMS (TOF) *m/e* calcd ($M+H^+$) 344.2404, found 344.241.



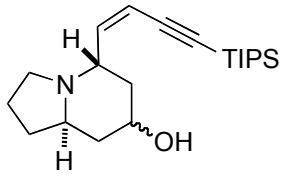
3-29: *(Z)-5-(4-(triisopropylsilyl)but-1-en-3-yn-1-yl)-2,3-dihydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a orange oil (30-50%). R_f = 0.20 (100% EtOAc); IR (Thin Film) n 2943, 2866, 1632, 1547, 1465, 1163, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 6.91 (1H, d, b, *J*=2.8 Hz), 6.45 (1H, d, *J*=15.6 Hz), 6.32 (1H, s, b), 6.03 (1H, d, *J*=16 Hz), 4.06 (2H, t, 9.6 Hz), 3.02 (2H, t, 10 Hz), 2.23 (2H, m), 1.06 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 179.4, 153.3, 143.1, 129.9, 117.3, 116.0, 112.5, 103.6, 101.7 5.2, 30.7, 21.7, 18.5, 11.1; HRMS (TOF) *m/e* calcd ($M+H^+$) 342.2248, found 344.2254.



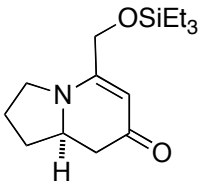
3-33: *(5S,8aR)-5-((Z)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)hexahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (40-80%). (+) isomer: $[a]_D = 38^o$ ($CHCl_3$, c=0.002); R_f = 0.70 (100% EtOAc); IR (Thin Film) n 2943, 2866, 1770, 1723, 1461, 1243 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 5.91 (1H, dd, *J*=9, 10.5 Hz), 5.65 (1H, d, *J*=10.8 Hz), 3.61 (1H, m), 3.17 (1H, dt, *J*= 1.8, 8.4 Hz), 2.54 (1H, d, *J*= 10.5 Hz), 2.42-2.27 (4H, m), 2.19 (1H, q, *J*= 12 Hz), 2.03-1.74 (3H, m), 1.55 (1H, m), 1.06 (18H, s), 1.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 207.8, 143.8, 111.6, 102.5, 98.0, 63.9, 61.2, 51.6, 47.3, 45.6, 31.2, 21.8, 18.8, 11.4; HRMS (TOF) *m/e* calcd ($M+H^+$) 346.2561, found 346.2559.



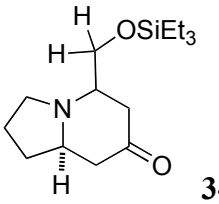
3-34: *(S,Z)-5-(4-(triisopropylsilyl)but-1-en-3-yn-1-yl)-1,2,3,7,8,8a-hexahydroindolizine:* Flash Chromatography (EtOAc) yielded a orange oil (40-80%). (+) isomer: $[a]_D$ = 1° ($CHCl_3$, c=0.002); R_f = 0.20 (100% EtOAc); IR (Thin Film) n 2943, 2866, 1461, 1073, 1017, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.88 (1H, t, *J*=10.4 Hz), 5.78 (1H, m), 5.63 (1H, d, *J*=10.8 Hz), 5.44 (1H, dd, *J*= 1.2, 9.6 Hz), 4.00 (1H, s, b), 3.21 (1H, t, b), 2.27 (1H, m), 2.17 (3H, q, *J*=9.2 Hz), 2.00 (1H, m), 1.80 (1H, m), 1.70-1.45 (3H, m), 1.07 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 128.2, 126,1, 111,2, 103.3, 63.1, 59.7, 53.2, 32.5, 30.7, 20.9, 18.8, 18.8,11.5; HRMS (TOF) *m/e* calcd ($M+H^+$) 330.2612, found 330.2617.



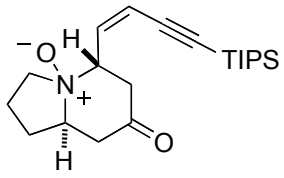
3-35: *(5S,8aR)-5-((Z)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)octahydroindolizin-7-ol:* Flash Chromatography (EtOAc) yielded a orange oil (0-25%). (+) isomer: $[a]_D$ = 17° ($CHCl_3$, c=0.001); R_f = 0.05 (100% EtOAc); IR (Thin Film) n 3357, 2943, 2866, 1614, 1542, 1462, 1242, 1168, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.89 (1H, dd, *J*=9.2, 11.2 Hz), 5.50 (1H, d, *J*= 11.2 Hz), 4.15 (1H, s, b), 3.65 (1H, dddd, *J*= 1.2, 4.8, 6, 17.2 Hz), 3.29 (1H, dt, *J*= 2.4, 10 Hz), 3.01 (1H, dt, *J*= 1.2, 9.2 Hz), 2.08 (1H, quintet, *J*= 2, 12 Hz), 2.00 (1H, q, *J*=9.2 Hz), 1.94-1.90 (2H, m), 1.82-1.59 (4H, m), 1.48-1.22 (2H, m), 1.03 (21H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 145.3, 110.3, 102.9, 98.4, 69.3, 62.6, 60.5 51.5, 40.3, 39.8, 29.8, 21.1, 18.6, 11.2; HRMS (TOF) *m/e* calcd ($M+H^+$) 348.2717, found 348.2725.



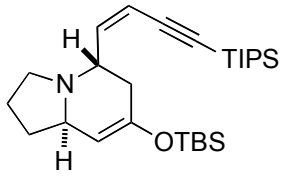
3-36: *(R)-5-(((triethylsilyl)oxy)methyl)-2,3,8,8a-tetrahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (46%). (+) isomer: $[a]_D$ = 18° ($CHCl_3$, c=0.002); R_f = 0.35 (100% EtOAc); IR (Thin Film) n 2956, 2877, 1627, 1551, 1297, 1151, 1007, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.11 (1H, s), 4.23 (2H, q, *J*= 14 Hz), 3.75 (1H, dddd, *J*= 4.4, 4.8, 5.2, 10.2 Hz), 3.62 (1H, t, *J*= 10.8 Hz), 3.41 (1H, q, *J*= 9.2 Hz), 2.41 (1H, dd, *J*= 4.8, 16 Hz), 2.30 (1H, d, *J*= 16.4 Hz), 2.24 (1H, m), 2.12 (1H, m), 1.89 (1H, m), 1.62 (1H, m), 0.94 (3H, t, *J*= 7.6 Hz) 0.61 (6H, , q, *J*= 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 145.3, 110.3, 102.9, 98.4, 69.3, 62.6, 60.5 51.5, 40.3, 39.8, 29.8, 21.1, 18.6, 11.2; HRMS (TOF) *m/e* calcd ($M+H^+$) 348.2717, found 348.2725.



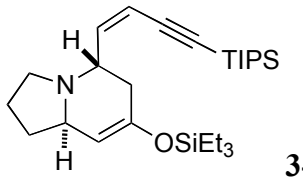
3-37: *(8aR)-5-(((triethylsilyl)oxy)methyl)hexahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (50%). (+) isomer: $[a]_D$ = 7° ($CHCl_3$, c=0.006); R_f = 0.55 (100% EtOAc); IR (Thin Film) n 2957, 2877, 2796, 1721, 1460, 1241, 1101, 745cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 3.80 (1H, dd, *J*= 4.4, 10 Hz), 3.60 (1H, dd, *J*= 6, 10 Hz), 3.27 (1H, td, *J*= 2, 8.8 Hz), 2.53-2.42 (3H, m), 2.35-2.26 (2H, m), 2.20 (1H, q, *J*= 9.2 Hz), 1.92 (1H, m), 1.82 (1H, m), 0.95 (6H, t, *J*=8 Hz), 0.59 (4H, q, *J*=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 65.5, 64.1, 62.7, 50.7, 47.0, 43.6, 30.3, 21.9, 6.7, 4.3; HRMS (TOF) *m/e* calcd ($M+H^+$ +MeOH) 316.2311, found 316.2311.



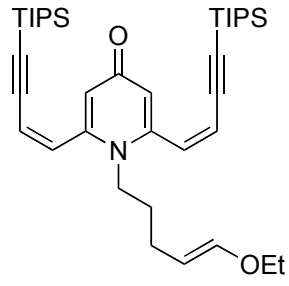
3-39: *(5S,8aR)-7-oxo-5-((Z)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)octahydro-1H-indolizine:* Flash Chromatography (EtOAc) yielded a clear oil (0-40%). (-) isomer: $[a]_D$ = 1.5° ($CHCl_3$, c=0.006); R_f = 0.05 (100% EtOAc); IR (Thin Film) n 2944, 2866, 1722, 1461, 1071, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 6.44 (1H, dd, *J*= 9.2, 10.8 Hz), 5.84 (1H, d, *J*= 10.8 Hz), 4.45 (1H, ddd, *J*= 3.6, 8.8, 12.4 Hz), 3.82 (1H, dt, *J*= 10, 11.6 Hz) 3.35 (1H, m), 3.27-3.18 (2H, m), 2.48-2.39 (2H, m), 2.31 (1H, ddd, *J*= 2, 4, 16 Hz), 2.20 (1H, m), 2.01 (1H, m), 1.94-1.89 (2H, m), 1.00 (18H, s), 0.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 203.5, 136.0, 115.7, 101.4, 99.4, 74.7, 70.4, 65.1, 40.4, 27.2, 18.6, 11.1; HRMS (TOF) *m/e* calcd ($M+H^+$ +MeOH) 362.2510, found 362.2510.



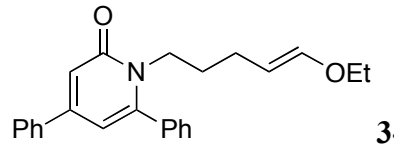
3-41: *(5S,8aR)-7-((tert-butyldimethylsilyl)oxy)-5-((Z)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)-1,2,3,5,6,8a-hexahydroindolizine:* Flash Chromatography (EtOAc) yielded a clear oil (70%). (+) isomer: $[a]_D$ = 38° ($CHCl_3$, c=0.007); R_f = 0.25 (100% EtOAc); IR (Thin Film) n 2942, 2865, 1662, 1462, 1255, 1019cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.86 (1H, dd, *J*= 9.6, 10.8 Hz), 5.58 (1H, d, *J*= 10.8 Hz), 4.61 (1H, t, *J*= 1.6 Hz), 3.98 (1H, d, b, *J*= 7.6 Hz) 3.18 (1H, td, *J*= 2, 9.2 Hz), 2.39 (1H, m), 2.22-2.09 (3H, m), 1.96 (1H, m), 1.86 (1H, m), 1.74 (1H, m), 1.49 (1H, m), 1.08 (18H, s), 1.05 (3H, s), 0.90 (9H, s), 0.13 (6H, d, *J*=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 155.1, 150.8, 114.9, 109.5, 107.8, 101.1, 82.0, 65.3, 57.1, 41.8, 35.2, 30.3, 30.3, 26.3, 26.3, 23.3; HRMS (TOF) *m/e* calcd ($M+H^+$) 460.3425, found 460.3426.



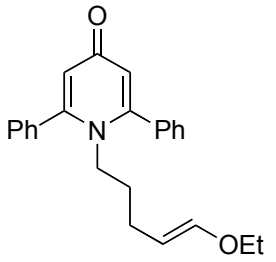
3-42: *(5S,8aR)-7-((triethylsilyl)oxy)-5-((Z)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)-1,2,3,5,6,8a-hexahydroindolizine:* Flash Chromatography (EtOAc) yielded a clear oil (70%). (+) isomer: $[a]_D$ = 40° ($CHCl_3$, c=0.003); R_f = 0.25 (100% EtOAc); IR (Thin Film) n 2.944, 2.867, 1724, 1462, 1461, 1195, 1017cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.86 (1H, dd, *J*= 9.6, 10.8 Hz), 5.58 (1H, dd, *J*= 0.4, 10.8 Hz), 4.61 (1H, t, *J*= 1.6 Hz), 3.98 (1H, d, b, *J*= 9.6 Hz) 3.17 (1H, td, *J*= 2, 9.2 Hz), 2.39 (1H, m), 2.22-2.10 (3H, m), 1.96 (1H, m), 1.84 (1H, m), 1.73 (1H, m), 1.48 (1H, m), 1.08 (18H, s), 1.05 (3H, s), 0.96 (9H, t, *J*=8 Hz), 0.66 (6H, 6, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 150.4, 146.2, 110.2, 104.3, 103.1, 96.3, 60.7, 52.5, 37.0, 30.4, 21.6, 18.6, 11.3, 6.7, 5.0; HRMS (TOF) *m/e* calcd ($M+H^+$) 460.3425, found 460.3425.



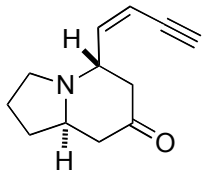
3-44: *1-((E)-5-ethoxypent-4-en-1-yl)-2,6-bis((Z)-4-(triisopropylsilyl)but-1-en-3-yn-1-yl)pyridin-4(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (20%). (+) isomer: $[a]_D$ = 40° ($CHCl_3$, c=0.003); R_f = 0.05 (4:1 EtOAc: MeOH); ^1H NMR (400 MHz, $CDCl_3$) d 6.60 (2H, s), 6.53 (2H, d, *J*= 12 Hz), 6.23 (2H, d, *J*= 12.4 Hz), 6.00 (2H, d, *J*= 11.6 Hz) 4.65 (2H, ddd, *J*= 6.4, 7.6, 12.4 Hz), 4.12 (1H, q, *J*=7.6 Hz), 3.77 (2H, d, J=10 Hz), 3.68 (2H, q, J=7.2 Hz), 1.91 (3H, q, *J*= 6.8 Hz), 1.63 (5H, m), 1.1 (9H, s), 1.03 (35H, s); HRMS (TOF) *m/e* calcd (M+) 620.433, found 620.319.



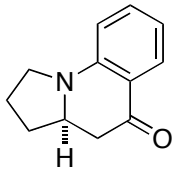
3-46: *(E)-1-(5-ethoxypent-4-en-1-yl)-4,6-diphenylpyridin-2(1H)-one:* Note: Compound decomposed from vinyl ether to aldehyde during purification for characterization: both NMR spectra and IR are that of the aldehyde, all other data is that of the ether. Flash Chromatography (EtOAc) yielded a clear oil (40%). R_f = 0.45 (100% EtOAc); IR (Thin Film) n 2936, 1721, 1651, 1572, 1537, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 9.59 (1H, s), 7.54-7.52 (2H, m), 7.44-7.43 (3H, m), 7.36-7.32 (5H, m), 6.82 (1H, d, *J*= 2 Hz), 6.33 (1H, d, *J*= 2 Hz), 3.86 (2H, t, *J*= 7.6 Hz), 2.25 (1H, td, *J*= 1.2, 7.2 Hz), 1.58 (2H, m), 1.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 150.4, 146.2, 110.2, 104.3, 103.1, 96.3, 60.7, 52.5, 37.0, 30.4, 21.6, 18.6, 11.3, 6.7, 5.0; HRMS (TOF) *m/e* calcd ($M+H^+$) 360.3425, found 360.3425.



3-47: *(E)-1-(5-ethoxypent-4-en-1-yl)-2,6-diphenylpyridin-4(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (20%). R_f = 0.05 (4:1 EtOAc: MeOH); IR (Thin Film) n 2937, 1719, 1578, 1174, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.44-7.37 (11H, m), 6.48 (2H, s), 5.79 (1H, d, *J*= 12.8 Hz), 3.94 (1H, ddd, *J*=6.4, 7.2, 12.8), 3.65 (1H, t, b, J=8 Hz), 3.35 (2H, q, J=7.2 Hz), 1.29 (2H, q, *J*= 7.2 Hz), 1.20-1.15 (2H, m), 1.11 (3H, t, *J*= 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 153.6, 146.8, 134.8, 129.6, 128.8, 128.6, 120.1, 100.6, 64.2, 50.1, 30.8, 23.4, 14.6; HRMS (TOF) *m/e* calcd ($M+H^+$) 360.1958, found 360.1965.

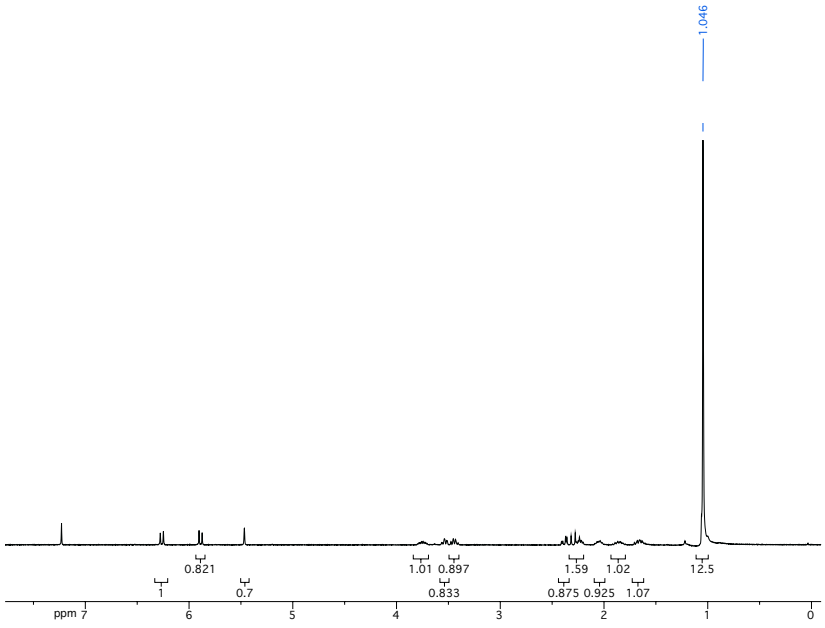


3-48: *(5S,8aR)-5-((Z)-but-1-en-3-yn-1-yl)hexahydroindolizin-7(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (60%). (+) isomer: $[a]_D$ = 275^o ($CHCl_3$, c=0.001); R_f = 0.15 (100% EtOAc); IR (Thin Film) n 2960, 2807, 1718, 1561, 1369, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.97 (1H, dt, *J*= 0.4, 12.8 Hz), 5.54 (1H, ddd, *J*=0.8, 3.2, 14.4 Hz), 3.54 (1H, dddd, J=7.6, 12.4 Hz), 3.18-3.11 (2H, m), 2.53 (1H, d, *J*= 16.4 Hz), 2.36-2.30 (3H, m), 2.18 (1H, q, *J*= 12 Hz), 1.99-1.75 (3H, m), 1.54 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 202.5, 139.6, 104.6, 78.4, 58.3, 55.5, 46.1, 41.9, 40.2; HRMS (TOF) *m/e* calcd ($M+H^+$) 190.1226, found 190.1223.

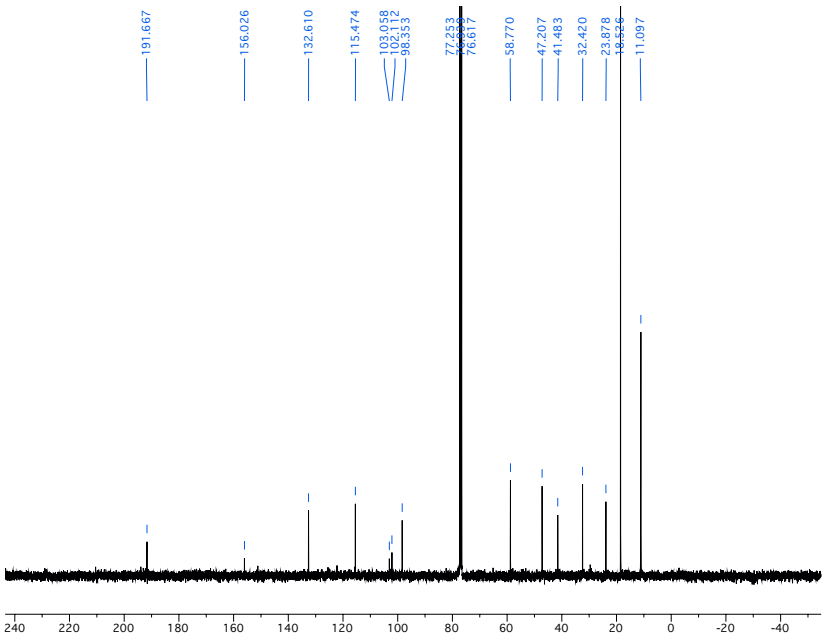


3-50: *(R)-2,3,3a,4-tetrahydropyrrolo[1,2-a]quinolin-5(1H)-one:* Flash Chromatography (EtOAc) yielded a clear oil (30%). (+) isomer: $[a]_D$ = 20^o ($CHCl_3$, c=0.001); R_f = 0.35 (100% EtOAc); IR (Thin Film) n cm^{-1} 2926, 1670, 1607, 1553, 1493, 1464; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J*= 1.6, 8 Hz), 7.37 (1H, ddd, *J*=1.6, 2.8, 7 Hz), 6.68 (1H, ddd, *J*=0.8, 7, 7.6 Hz), 6.58 (1H, *J*=8.8 Hz) 3.64 (1H, m), 3.51 (1H, m), 3.31 (1H, dt, *J*= 3.6., 10 Hz), 2.78 (1H, dd, *J*=3.2, 13.6 Hz), 2.48 (1H, t, *J*= 15.6 Hz), 2.29-2.15 (2H, m), 1.97 (1H, m), 1.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) d 135.5, 128.0, 116.0, 112.8, 58.1, 46.2, 43.7, 32.8, 23.0; HRMS (TOF) *m/e* ($M+H^+$) found 188.1173.

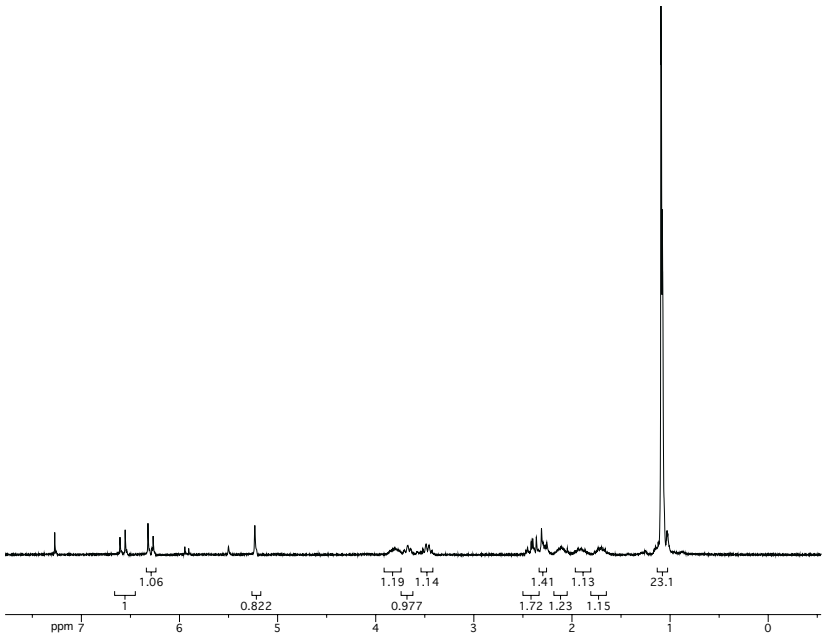
^{1}H NMR 3-21



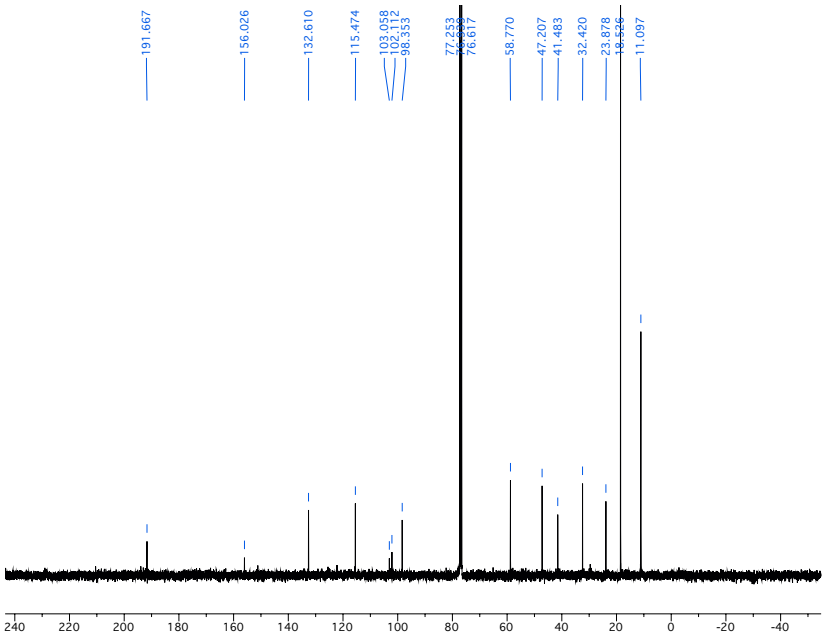
^{13}C NMR 3-21



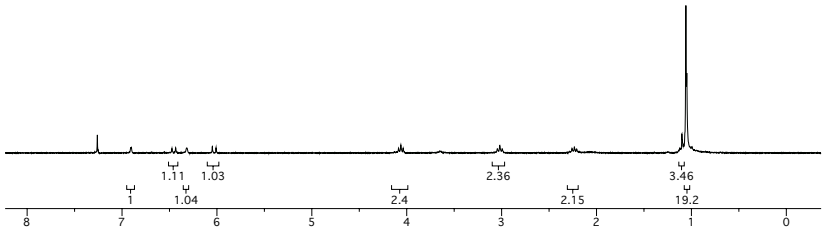
^{1}H NMR 3-25



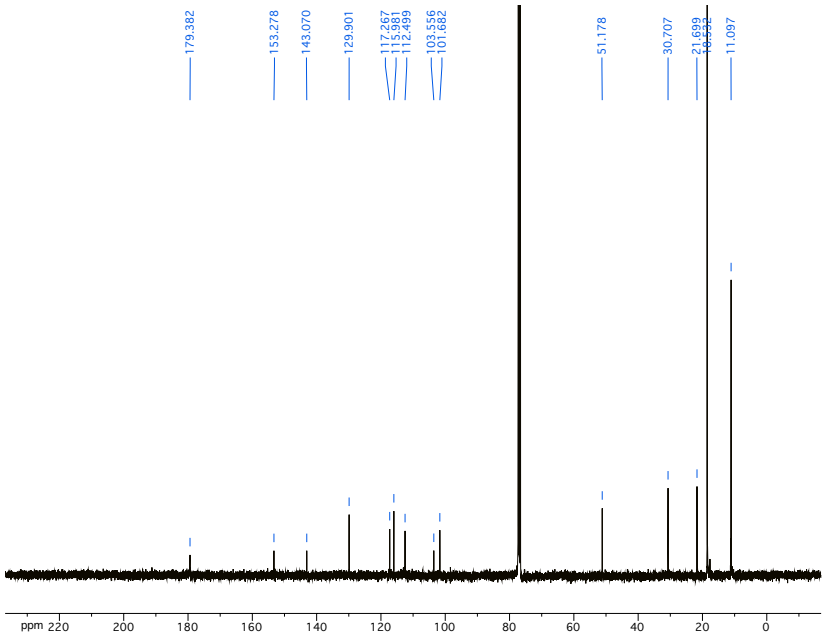
^{13}C NMR 3-25



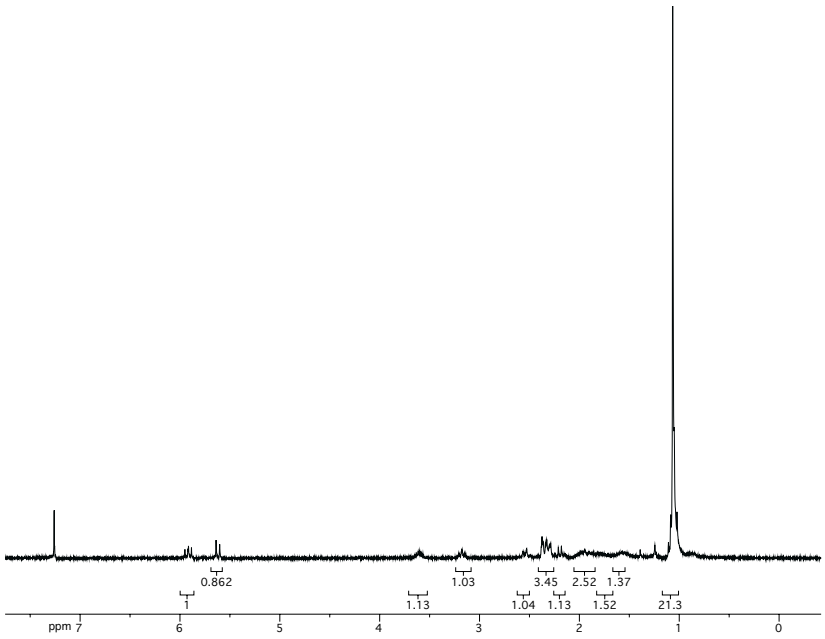
^{1}H NMR 3-29



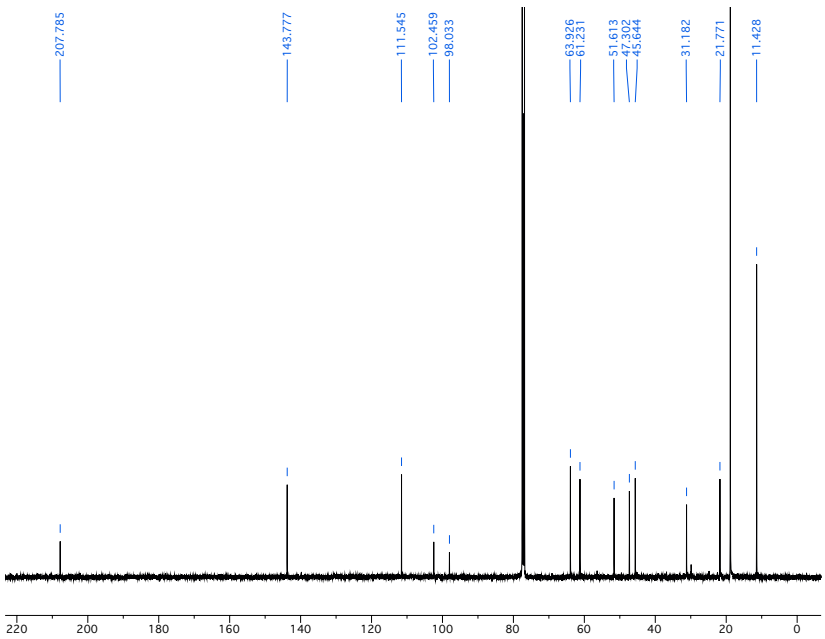
^{13}C NMR 3-29



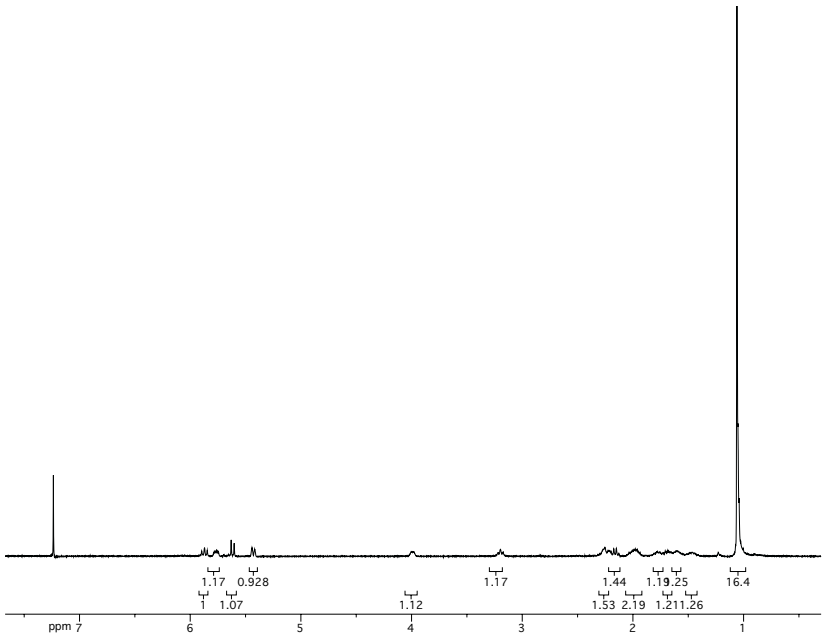
^{1}H NMR 3-33



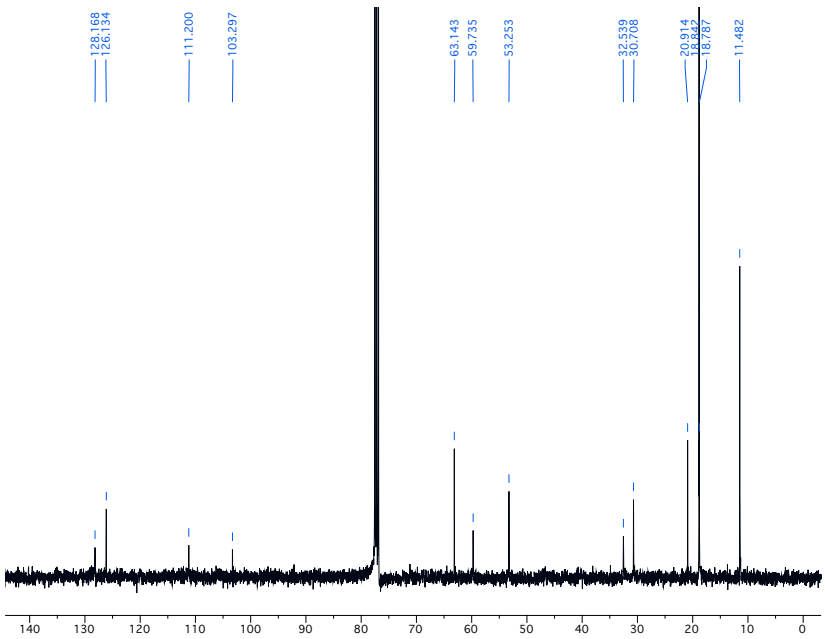
^{13}C NMR 3-33



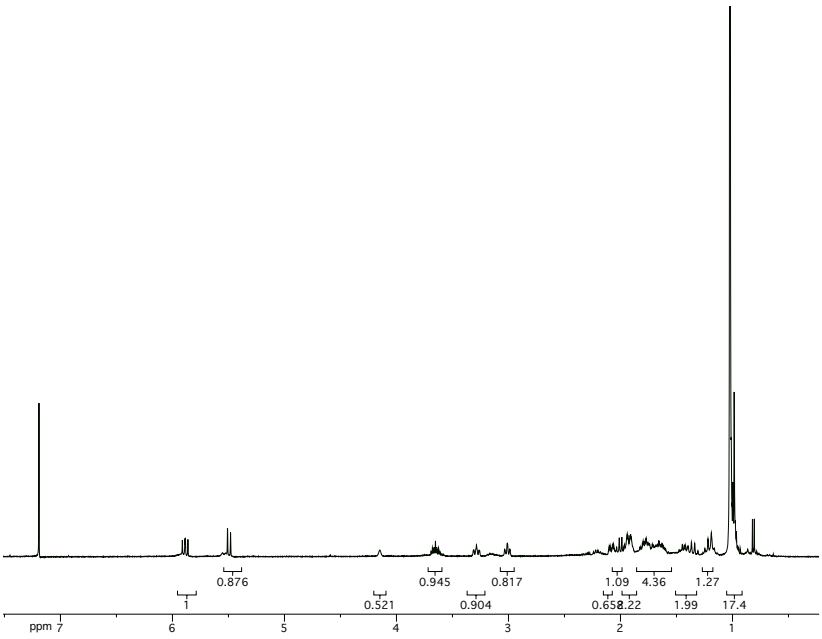
^{1}H NMR 3-34



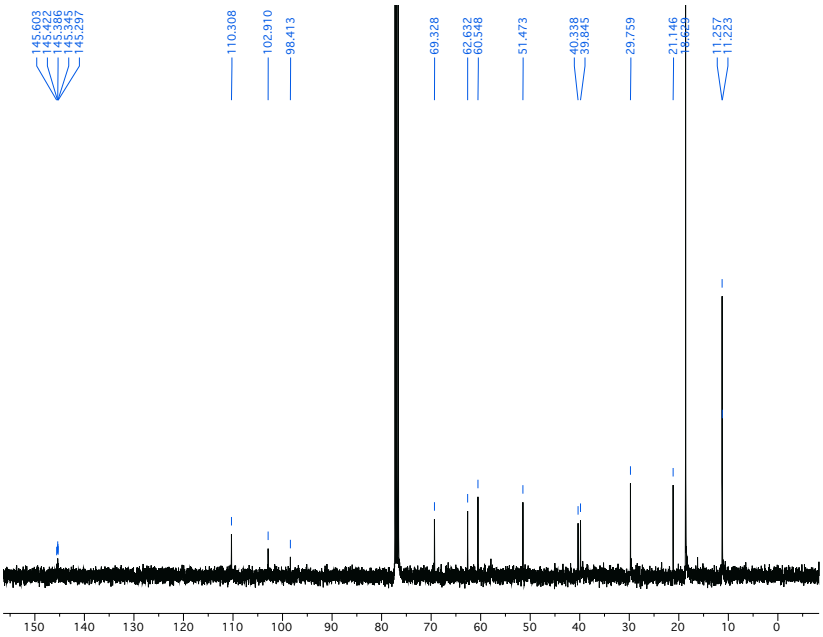
^{13}C NMR 3-34



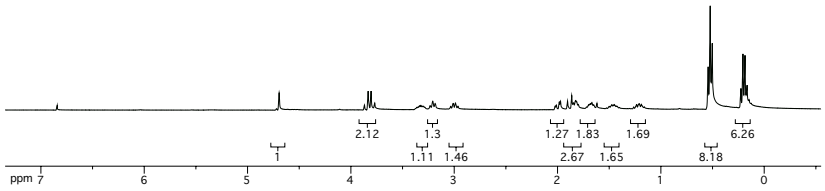
^{1}H NMR 3-35



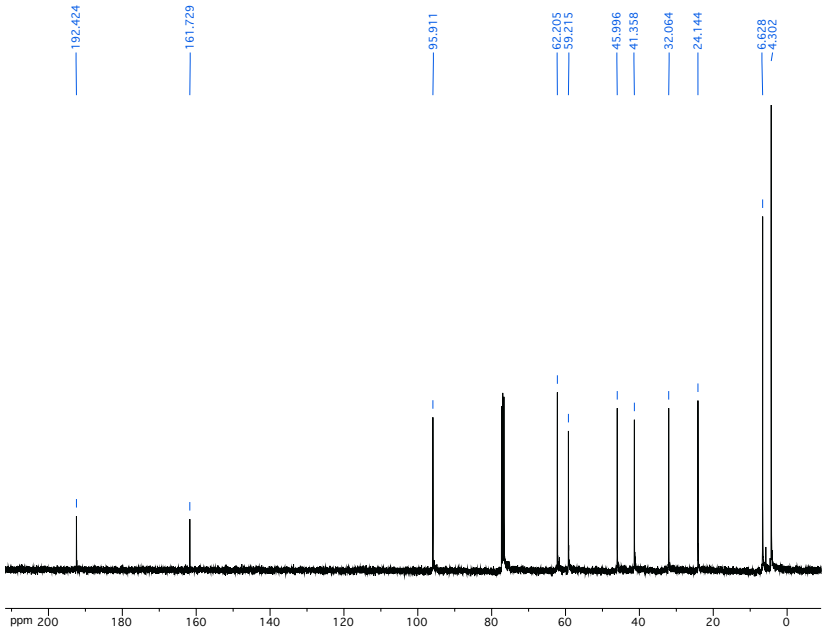
^{13}C NMR 3-35



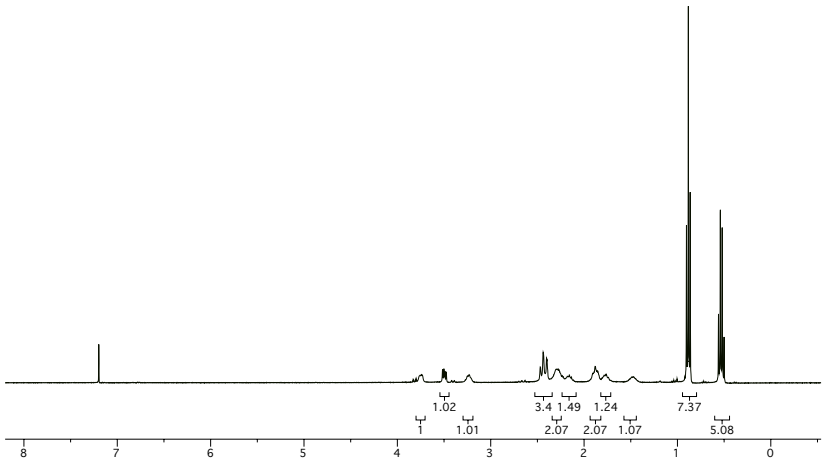
^{1}H NMR 3-36



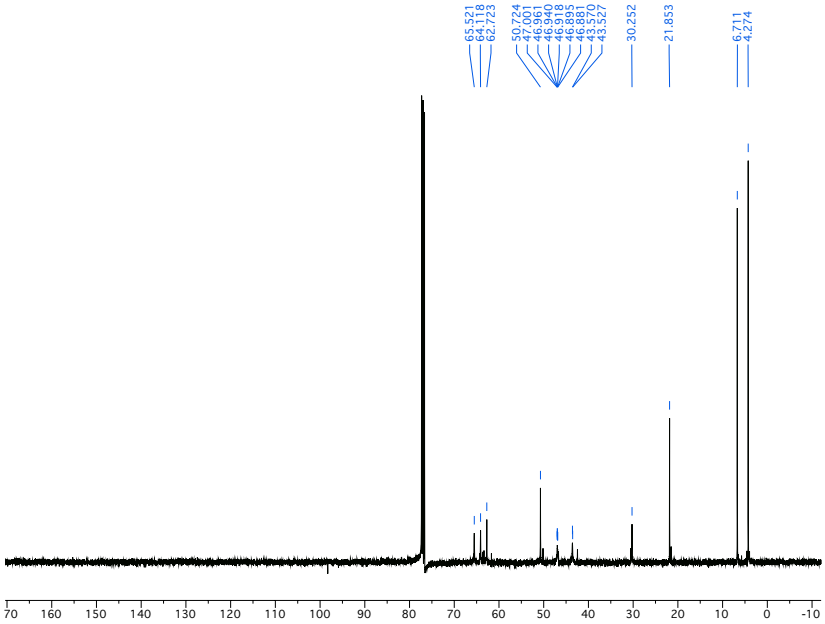
^{13}C NMR 3-36



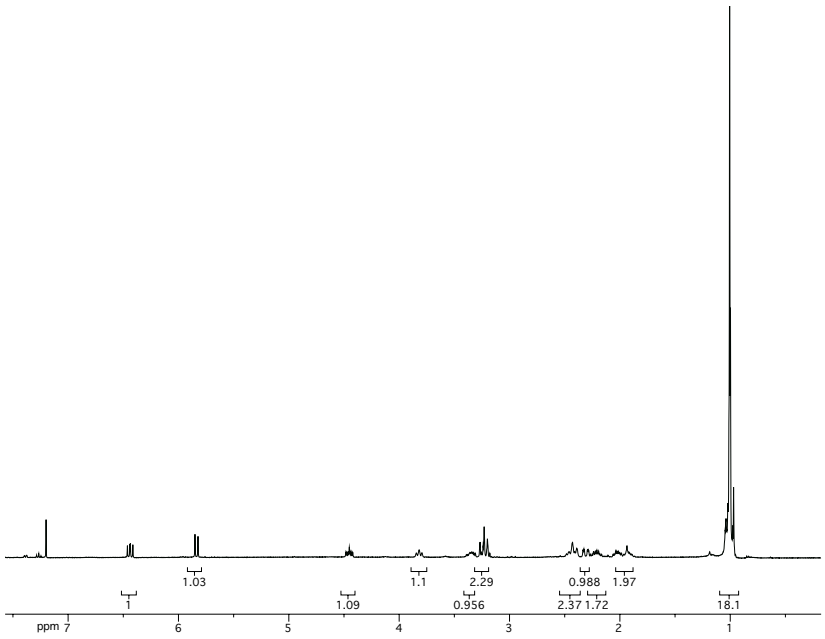
^{1}H NMR 3-37



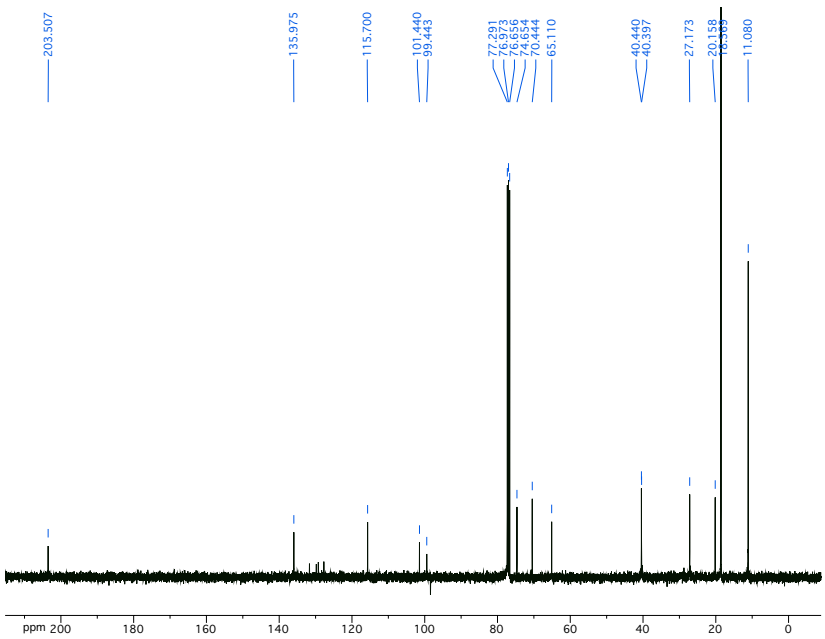
^{13}C NMR 3-37



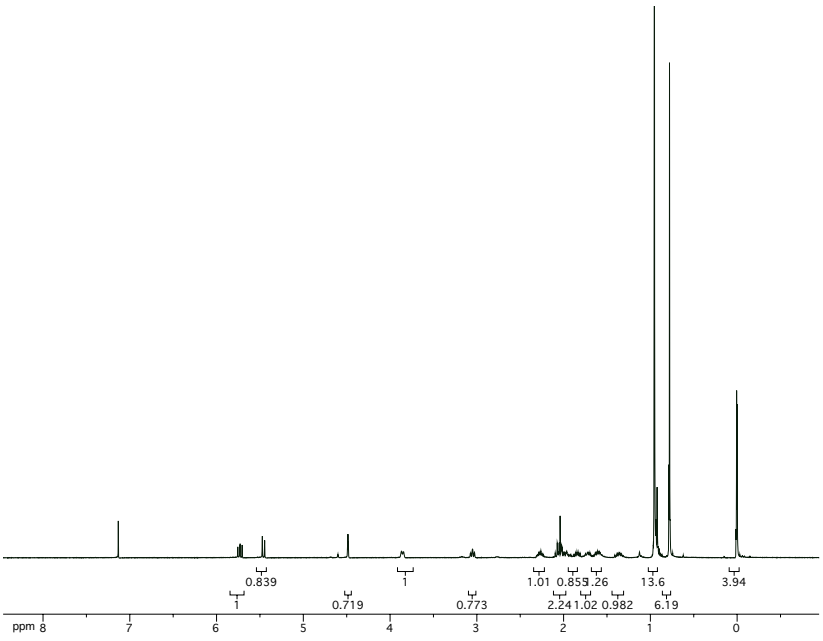
^{1}H NMR 3-39



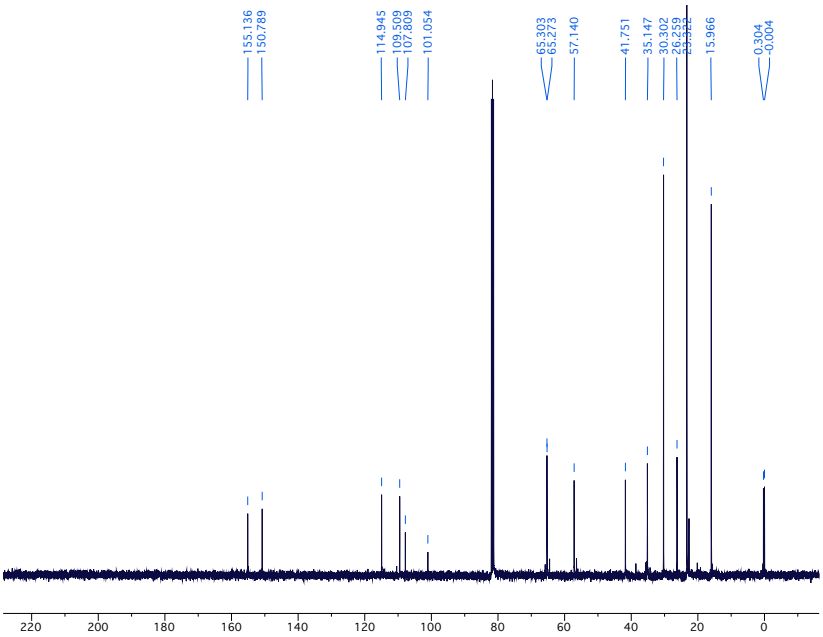
^{13}C NMR 3-39



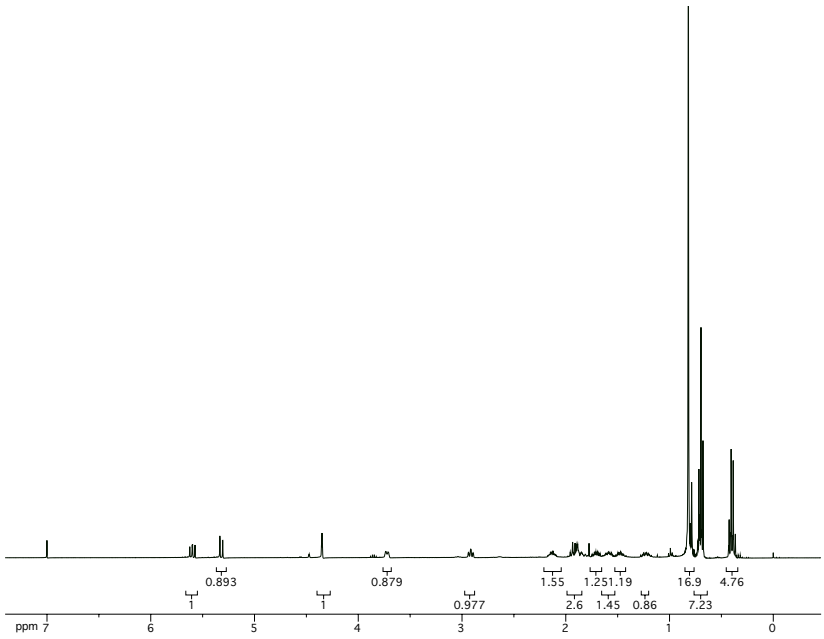
^{1}H NMR 3-41



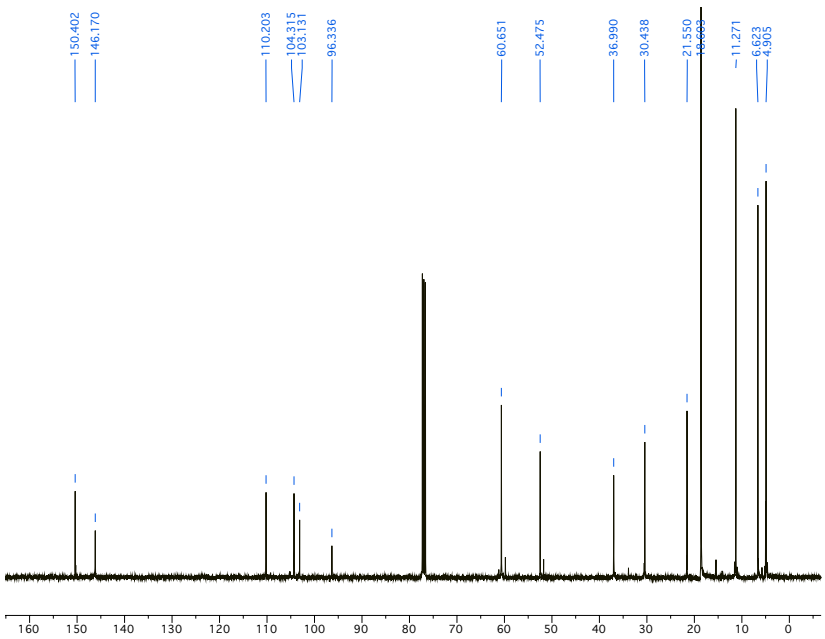
^{13}C NMR 3-41



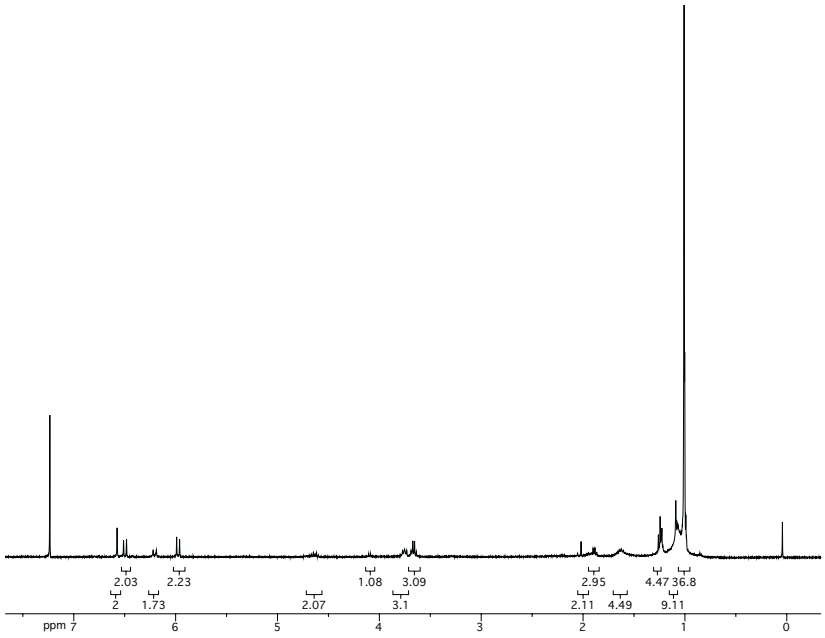
^{1}H NMR 3-42



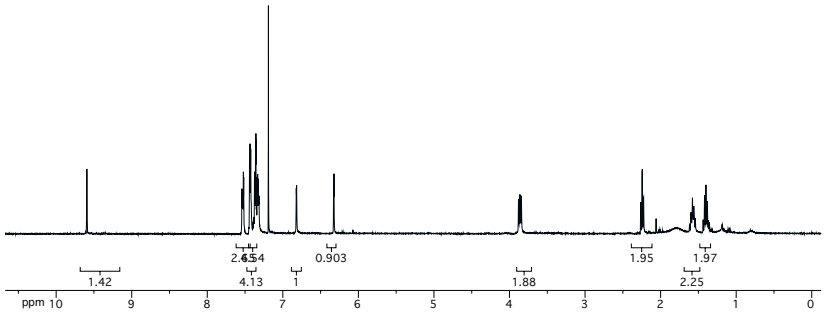
^{13}C NMR 3-42



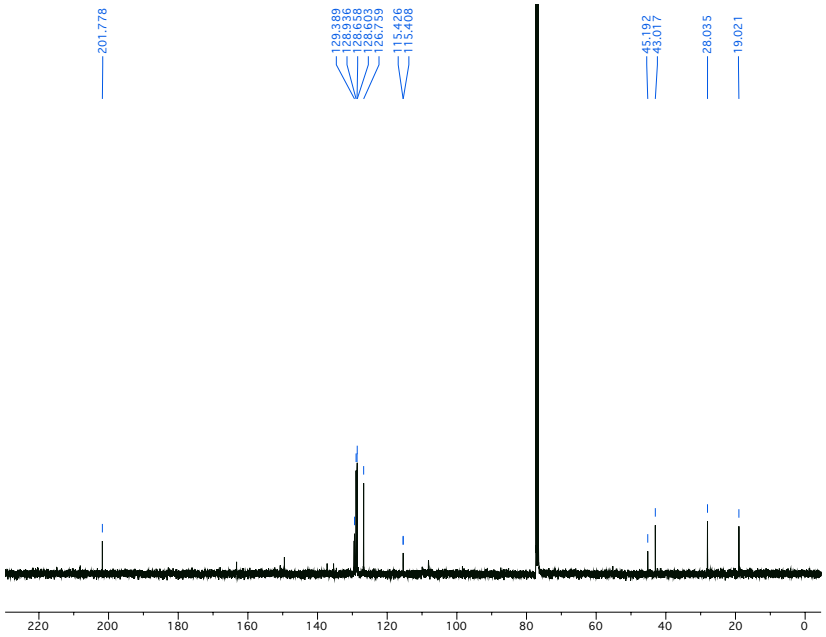
^{1}H NMR 3-44



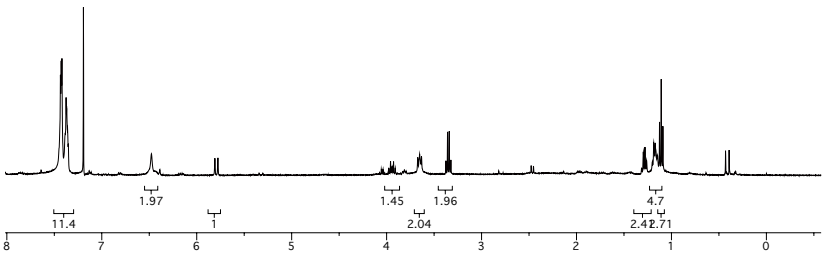
^{1}H NMR 3-46



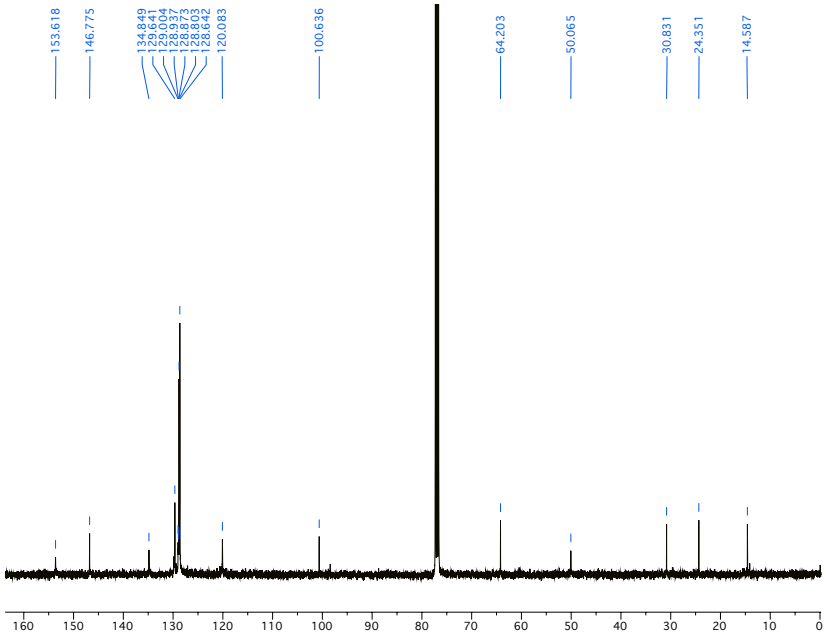
^{13}C NMR 3-46



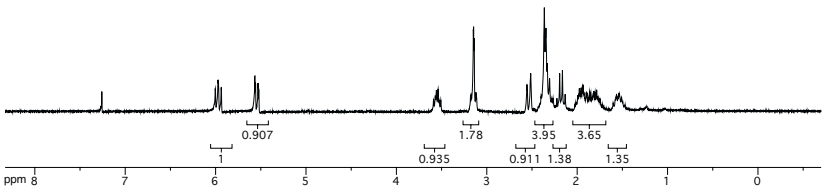
^{1}H NMR 3-47



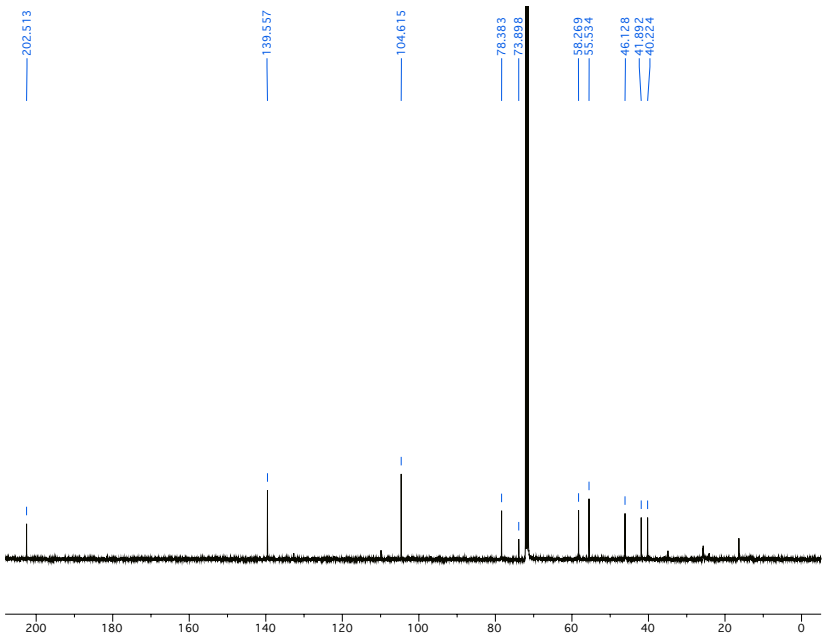
^{13}C NMR 3-47



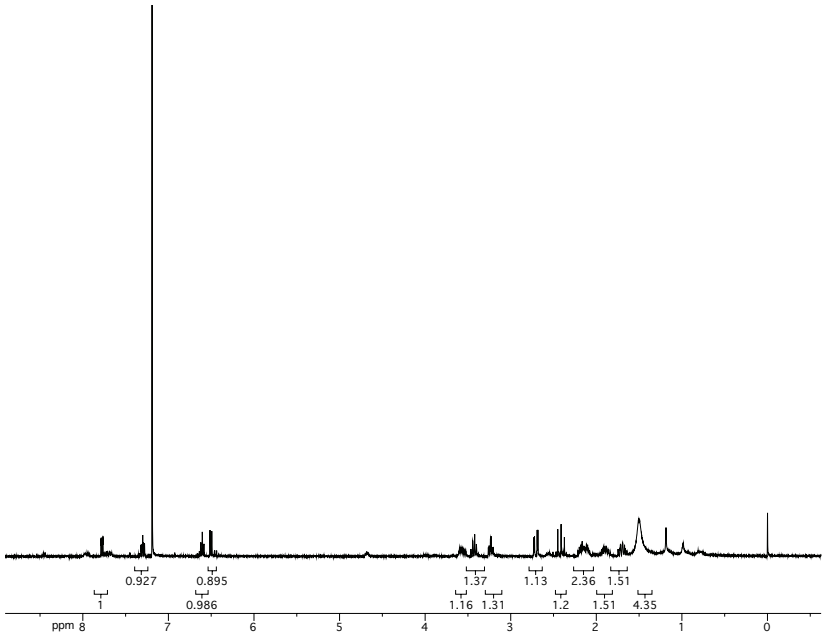
^{1}H NMR 3-48



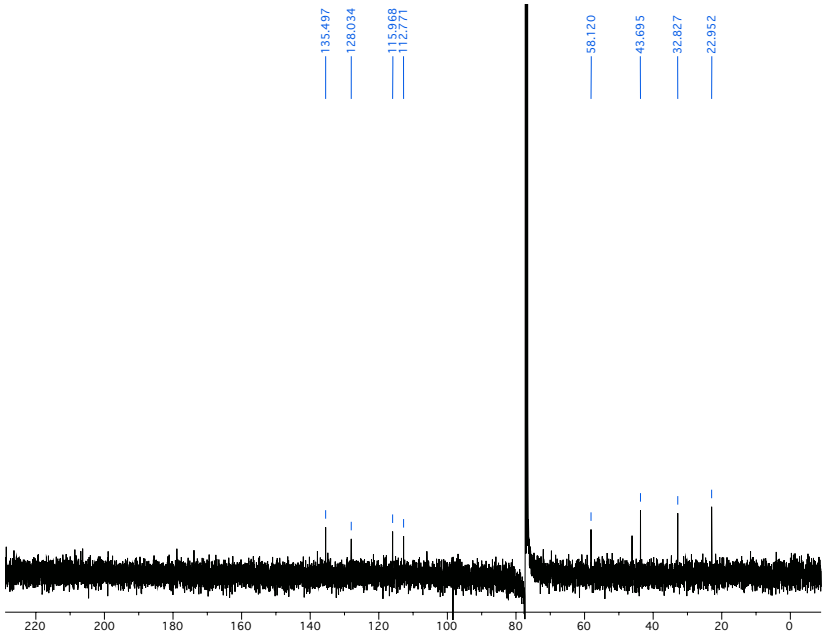
^{13}C NMR 3-48



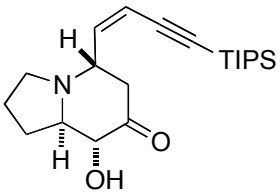
^{1}H NMR 3-50



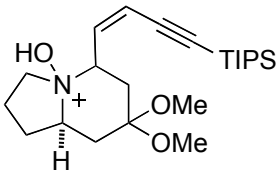
^{13}C NMR 3-50



Evidence towards **3-38** and **3-40:**



3-38: Mass of crude product indicates the presences of desired product.



3-40: IR spectra indicates absence of ketone peaks (2943, 2865, 1462 cm^{-1}). Proton NMR indicates a dimethyl acetal (see below). MS (ESI) indicates the over-oxidation of the amine.

^{1}H NMR 3-40: