

DISSERTATION

THE FORMATION AND REACTIVITY OF α,β -UNSATURATED PLATINUM CARBENES:
NEW APPROACHES TO HETEROCYCLE SYNTHESIS

Submitted by

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In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Summer 2014

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ABSTRACT

THE FORMATION AND REACTIVITY OF α,β -UNSATURATED PLATINUM CARBENES: NEW APPROACHES TO HETEROCYCLE SYNTHESIS

The use of transition metal carbenes in organic synthesis has enabled chemists to promote an incredible variety of bond-forming reactions. These intermediates are traditionally accessed via the decomposition of diazo species. Alternative methods for accessing metal carbene intermediates from functional groups beyond diazo species could present many practical advantages and would complement the existing methods.

Presented herein are our efforts to develop a novel method of carbene generation from the reactions of alkynes and π -acidic transition metals, and their use in the synthesis of different heterocycles. Our initial investigations focused on the ability to generate substituted furan products from the intramolecular addition of alcohols into alkynes containing propargylic methyl ethers.

We then extended this reaction manifold to the synthesis of complementary positional isomers of isoxazoles, adding both propargylic *N*-hydroxycarbamates and propargylic *N*-Boc amino ethers into the activated alkyne. Key to this transformation was the inclusion of Brønsted acids to facilitate activation and elimination of the methyl ether leaving group.

While studying the synthesis of furans and isoxazoles it was observed that the nature of the carbene could be modulated, leading to selective silicon or hydrogen migration. Also observed

was the addition of nucleophiles into the β -position of the carbene species. This last mode of reactivity led to the discovery of a new way to synthesize vicinal bisheterocycles using alkyne activation conditions.

ACKNOWLEDGMENTS

I sit here trying to breakdown the writer's block that has caused me to put off this last, though arguably the most important, piece of my dissertation. Graduate school has presented many challenges over the past six years. The obvious ones were visible from the beginning, but many more surfaced throughout my time at Colorado State. Each was either overcome, or negligently cast aside, to be dealt with another day. What allowed me to keep going was knowing that no matter what happened, I had an amazing group of colleagues and friends to bolster my spirits and keep me pushing through.

I owe a tremendous amount of gratitude to my advisor, Professor Eric Ferreira. You have been the single most influential person in my maturation as a scientist. Your patience, and willingness to let me work independently on my projects were greatly appreciated, and allowed me to become a much more confident researcher. I admire your humble excitement towards your research program, and your dedication to do your best in every aspect of your profession. Thank you so much for everything you have done for me. I want to thank my doctoral committee (Professor's Tomislav Rovic, Alan Kennan, Michael Elliott and Dean Crick) for helpful discussions about my research and this dissertation. A special thanks goes to Alan Kennan for taking a chance, and granting me the opportunity to teach several lectures in the department.

I also need to thank the countless individuals I have worked with over the years. My colleagues at Theravance, most notably Dr. Seok-ki Choi, Paul Fatheree and Dr. Dan Marquess each gave me remarkable freedoms to develop and pursue my own ideas in lab, giving me the confidence I

needed to be successful during my PhD studies. I want to Professor Bakthan Singaram for allowing me to work in his group as an undergraduate, and for tolerating my flightiness as a researcher. Lastly, I have to thank Dr. Gary Fisher for initiating my enthusiasm for organic chemistry, and for creating the opportunity to get my green hands into a research lab.

I owe each of my colleagues in the Ferreira group a sincere thank you (and probably an apology for something) for being awesome friends/supporters. First, I have to thank Eric Newcomb (lil Mike) for wading through chapters of this dissertation, your enthusiasm for research, patience ☺, and being an awesome friend. You've been a constant voice of reason when I've struggled and are always willing to help out. Doug, your dedication to doing what's right and humility about your accomplishments was appreciated, as were the bottles of home brew you left on my desk. Erin, your work ethic, ability to keep trying, and conviction to be true to yourself are admirable, and motivated me to keep on pushing on. I reckon it would be a crime to not give a special shout out to my D-wing buddies Brian and Curtis. Much of what went on in there is hard to, and probably shouldn't be, repeated. Brian, I'm sure my daily rants were exactly what you wanted to hear at the time, but you humored me nonetheless. I will be forever impressed by your willingness to do whatever was needed to keep your project advancing, even if it meant battling endless and tedious separations. Curtis, for your meticulous execution of experiments, enthusiasm for organic preparations, and ability to draw an analogy to whatever I was doing to being "cat-like." I want to thank Tarik for being my TA of the year and for rapidly expanding the scope of our project. Suzie, your ability to run countless experiments and still maintain a spotless hood is incredible and speaks to your abilities as an experimentalist. Lastly, I want to

thank the younger students Francisco and Phil for being proud members of the group and helping me to feel...old I guess.

There are many other friends that have helped me technically and emotionally throughout grad school. Dr. Derek Dalton for being a great role model in lab, Dr. Nick Barczak for always being honest and excitable about the littlest things, and Claire Filloux for reminding me to always be true to myself.

To my family, for always being there for me. My parents taught me to always believe in myself and to take pride in everything that I do. I want to thank each of my siblings; Kathy, Carol, Karen and Michael, for being amazing role models and always cheering me up whenever the opportunity presented itself. Much of what I have achieved is due to always wanting to follow your leads.

Lastly, I owe everything I have to my wife Arren. You have inspired me in so many ways, and have always been supportive of me. I know I wouldn't have made it this far if it wasn't for your unconditional love and willingness to accept the many challenges the past few years have presented.

DEDICATION

To Arren and my family

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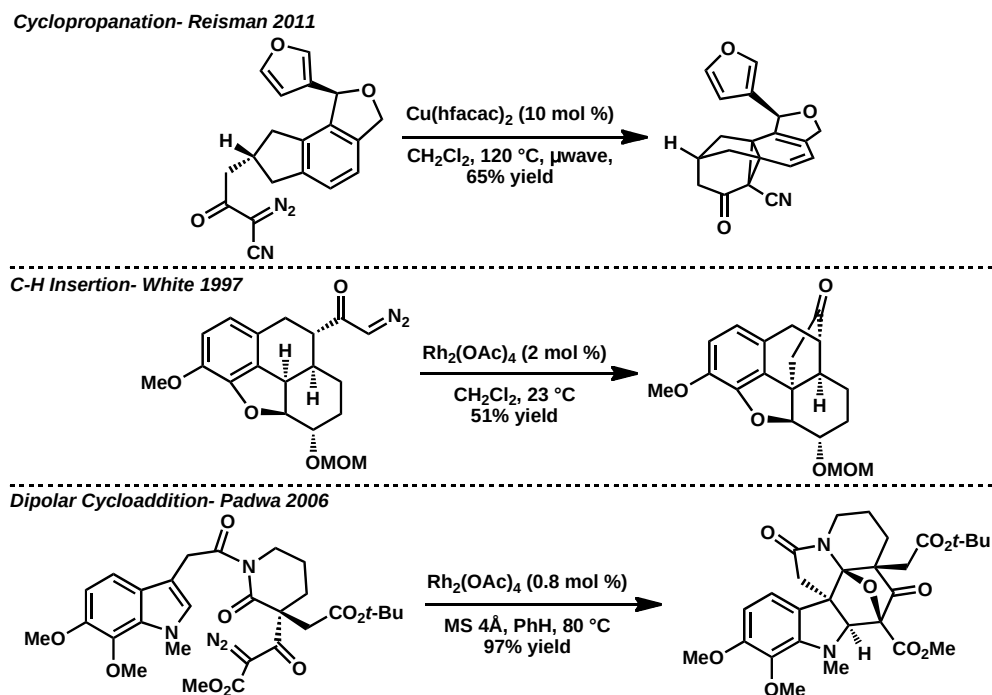
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CHAPTER ONE

The Use of Metal Carbenes as Powerful Bond Forming Intermediates

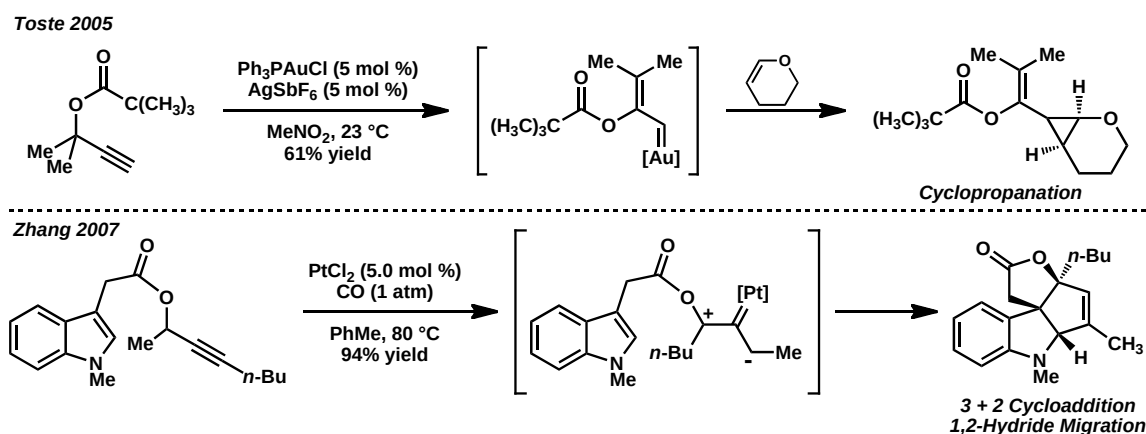
1.1 The Use of Metal Carbenes in Organic Synthesis

The unique reactivity of metal carbenes and their ability to form a variety of carbon-carbon and carbon-heteroatom bonds has been known for over a century.¹ This chemistry remained largely overlooked until the 1970's, when Kochi reported on the mechanism of Cu(I/II) catalyzed diazo decomposition, and Teyssié reported the use of Rh(II) acetate as an excellent catalyst for diazo decomposition.² Since then, the application of this reactivity has, in many ways, revolutionized the rapid generation of molecular complexity.³ Once generated, metal-carbenes can undergo a variety of bond forming reactions that are otherwise difficult to mimic using more traditional synthetic approaches. A highlight of some of the more common reactions is provided in Scheme 1.1.1, and includes cyclopropanations, C-H insertions, and dipolar cycloadditions.⁴



Scheme 1.1.1. Reactions of Metal Carbenes.

One limitation to the approaches used to generate Rh/Cu carbenes is the use of diazo species as precursors. Alternative methods for accessing metal carbene intermediates from functional groups beyond diazo species could present many practical advantages, and would complement the existing methods. Recent developments in alkyne activation chemistry have demonstrated that the use of alkynophilic metals such as gold or platinum can generate the respective metal carbenes from alkynes. Once generated, these intermediates undergo analogous reactions as their Rh/Cu counterparts like cyclopropanations, cycloadditions and bond migrations to generate more complex molecular structures (Scheme 1.1.2.).⁵

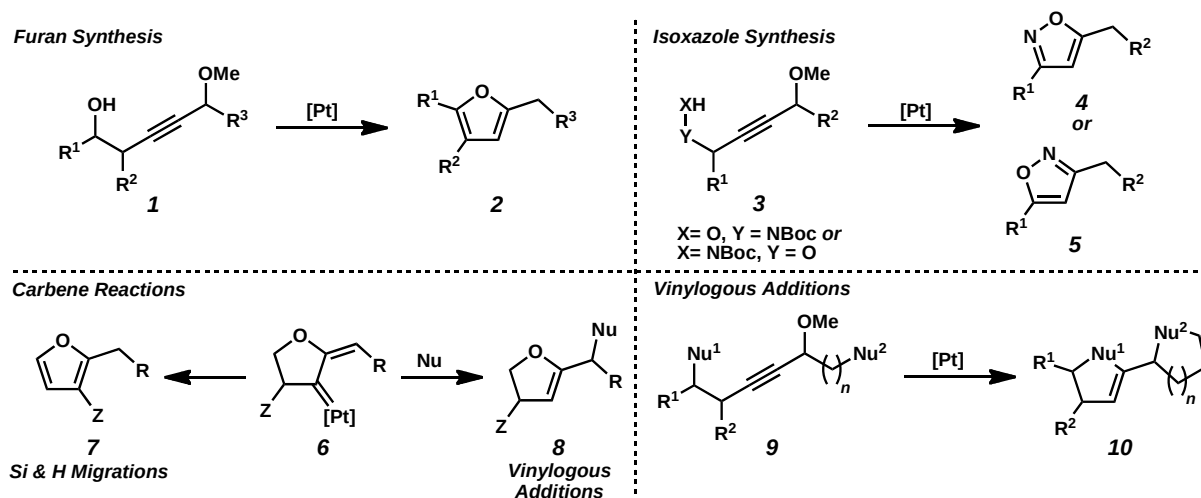


Scheme 1.1.2. Carbene Generation Using Gold and Platinum Catalysis.

1.2 New Method for Generating Platinum Carbenes

The research presented herein describes our efforts to develop a novel method of carbene generation from the reactions of alkynes and π -acidic transition metals, and their use in the synthesis of different heterocycles. Our initial investigations focused on the ability to generate substituted furan products from the intramolecular addition of alcohols into alkynes containing propargylic methyl ethers (Scheme 1.2.1).⁶ Our failure to demonstrate an acid promoted elimination/isomerization mechanism led us to believe that a carbene intermediate was forming

during the reaction. We then extended this reaction manifold to the synthesis of complementary positional isomers of isoxazoles, adding both propargylic *N*-hydroxycarbamates and propargylic *N*-Boc amino ethers into the activated alkyne.⁷ While we were pursuing these two projects we began to look for evidence that supported the formation of a carbene intermediate. The result was demonstrating the ability to selectively migrate silicon or hydrogen groups into the carbene, as well as inducing nucleophilic additions into the β -position (vinylogous addition) of the carbene species. This last mode of reactivity led to the discovery of a new way to synthesize vicinal bisheterocycles using alkyne activation conditions.⁸



Scheme 1.2.1. Heterocycle Synthesis via α,β -Unsaturated Platinum Carbenes.

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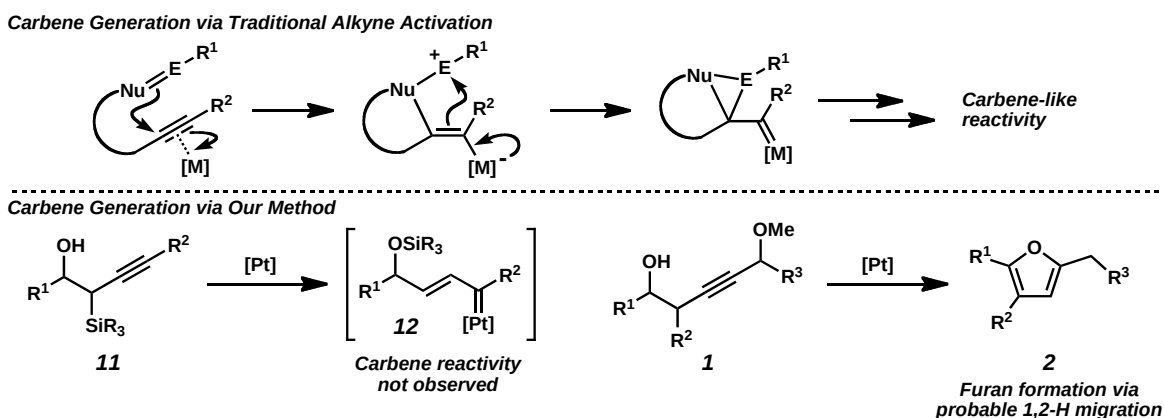
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CHAPTER TWO

Synthesis of Polysubstituted Furans via 1,2-Hydride Migrations into Platinum Carbenes

2.1 Introduction

The use of transition metal carbenes in organic synthesis has enabled chemists to promote an incredible variety of bond forming reactions.⁹ These reactive intermediates are traditionally generated by exposing diazo ylides to Cu(I) or Rh(II) catalysts.¹⁰ Recently chemists have taken advantage of the π -acidic character of gold and platinum salts to generate the corresponding gold/platinum carbenes via reactions with alkynes.¹¹ For the majority of these reactions the activated alkyne is attacked by a pendant nucleophile, resulting in the formation of a new electrophilic atom- traditionally in the form of a carbocation-like species (Scheme 2.1.1). Our initial strategy, where the electrophilic and nucleophilic atoms were on the same side of the alkyne, failed to produce carbene-like transformations. Changing our scaffold to place the electrophile on the opposite side of the alkyne as the nucleophile enabled the formation of furan products via a putative platinum carbene.¹² These reactions proceeded in good to excellent yields and demonstrated tolerance to a variety of functional groups.



Scheme 2.1.1. Approaches to Carbene Generation via Platinum Catalysis.

2.2 Alkynophilicity

2.2.1 Metal-Alkene/Alkyne Bonding Interactions

Transition metals have been known to form strong interactions with the π -systems of alkenes and alkynes for over a century. The preparation and characterization of $\text{K}^+[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_3]^- \cdot \text{H}_2\text{O}$, known as Zeise's salt, was disclosed in 1827, and it is one of the earliest examples of a transition metal complex that contains ethylene as one of its ligands.¹³ Analysis of the x-ray structure shows the coordinated ethylene ligand binds perpendicularly to the plane formed by the metal center and the three chloride ligands, with an equal bond length between the metal and the two carbons of ethylene (Figure 2.2.1).¹⁴ The Dewar-Chatt-Duncanson model best describes the binding interactions in most metal-alkene/alkyne complexes.¹⁵ Two interactions account for the majority of the bonding interactions between the two species. One interaction involves the donation of a pair of bonding π -electrons on the alkene/alkyne into an empty hybrid orbital on the metal (σ -donation). The effect of this donation is a loss of electron density around the alkene/alkyne ligand, and a buildup of electron density around the metal. A second bonding interaction occurs as electrons in a filled hybrid d -orbital on the metal donate into the empty π^* of the alkene/alkyne. This back donation is strongest for electron rich metals like $\text{Ni}(0)$, $\text{Pd}(0)$ and $\text{Pt}(0)$, with these metals binding more strongly to electron deficient π -systems, while electrophilic metals like $\text{Pd}(\text{II})$ and $\text{Pt}(\text{II})$ bind more strongly to electron rich π -systems.¹⁶

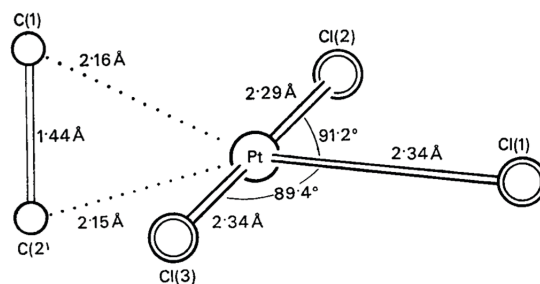


Figure 2.2.1. Ethylene Bonding and Corresponding Bond Lengths/Angles in Zeise's Salt.

Though Chatt and Duncanson used the structure of Zeise's salt to illustrate the binding interactions between the alkene and the platinum metal, it was later shown that platinum(II) does not back-donate into the π -system as significantly as it was believed to.¹⁷ Instead, the stability of the bound ethylene in Zeise's salt and related compounds is due to the strong σ -donation of the alkene ligand into the metal. This is also true for cationic gold complexes. Frenking and Rayón performed energy partitioning analysis on cationic gold (Au^+) ethylene and acetylene complexes and calculated the percent contribution to the overall ΔE_{orb} term that the four orbital interactions between the metal and ligand make (Figure 2.2.2).¹⁸ The strongest contributor to the orbital term for both ethylene (67.0%) and acetylene (64.6%) complexes was the σ -donation from the π -system to the metal, with the π -back donation only contributing 25.5% and 27.1% of the covalent bonding interactions respectively. Comparatively, the σ -donation from acetylene into Au^+ is significantly stronger (-63.1 kcal/mol) than Ag^+ (-25.6 kcal/mol). One effect of these bonding interactions is the shifting of electron density away from the π -system of the ligand, and thus increasing the electrophilicity of the ligand. The greater ability of Au^+ to accept electron donation from alkynes than Ag^+ correlates well with experimental observations that Au^+ is a better catalyst for promoting nucleophilic addition into π -systems. Preference in the activation of alkynes over alkenes is not a result of alkynes binding the metals more strongly than alkenes

(the opposite is true), but is a result of alkynes being intrinsically more electrophilic than alkenes.¹⁹ Lastly, the induced electrophilicity of the ligand increases further as the bonding shifts from a symmetrical η^2 coordination to an unsymmetrical η^1 coordination, with this slippage immediately preceding nucleophilic addition into the ligand.²⁰

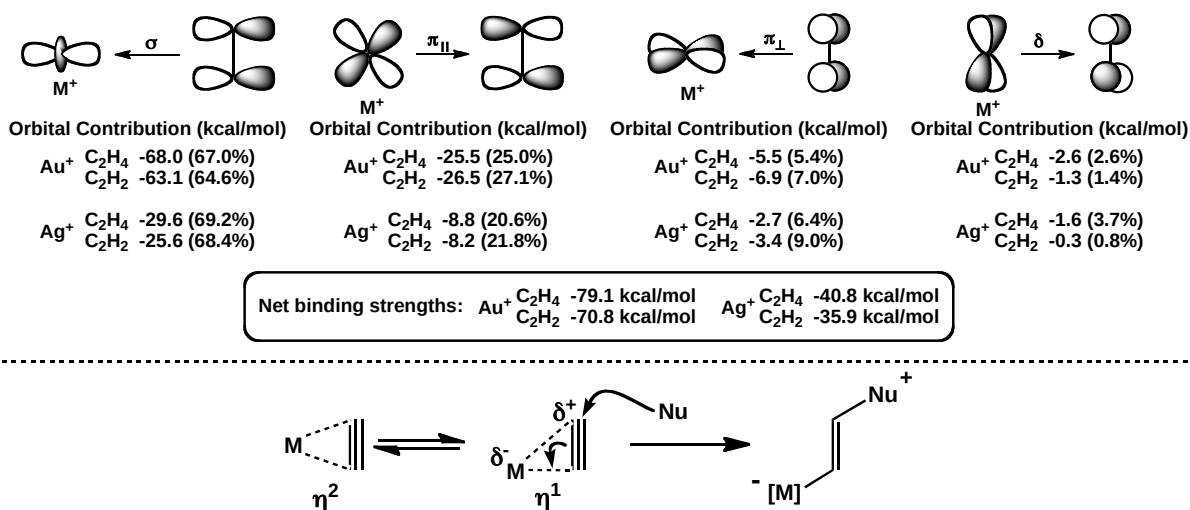


Figure 2.2.2. Bonding Interactions in Au⁺/Ag⁺ π -Systems.

2.2.2 Relativistic Effects in Gold and Platinum Catalysis

The binding interaction between electron deficient metals and π -systems described above does not fully explain why gold and platinum salts are the catalysts of choice for alkyne activation chemistry. Another important consideration is that the nature of the bonding between these metals and their respective ligands is strongly influenced by relativistic effects.²¹ The basic theory of relativity states that as the speed of an object approaches the speed of light, its mass approaches infinity. As the radial velocity of electrons increases in heavier atoms, the mass of the electrons becomes more significant, and the Bohr radius of the electron becomes smaller. One result of this effect is that heavier atoms like gold and platinum experience very strong contractions of their respective 6s orbitals, with the net result being an overall shortening and

strengthening of the metal ligand bonds (Figure 2.2.3).²² This effect is strongest for elements in the 6th row of the periodic table, requiring that any accurate treatments on the bonding environments in these metals must account for relativistic influences. Calculations on the bond dissociation energies of a number of metal-carbene complexes performed by Koch and Schwarz reflect the increasing significance of relativistic effects on bonding as one moves down the periodic table.²³ In general, correcting the bonding in both Ni (6.5 kcal/mol) and Pd (14.7 kcal/mol) carbene complexes results in a modest change in the overall bond strengths. Accounting for relativistic effects in Pt results in a calculated bond dissociation energy that is 53.5 kcal/mol higher than when relativistic effects are not considered. The bond dissociation energy for Au (65.5 kcal/mol) increases even more than Pt, with the relativistic bonding accounting for 72% of the total bond energy. This contraction of the *s* and *p*-orbitals results in shielding the nuclear attraction felt by electrons in the *d* and *f* orbitals, causing a net expansion of these orbitals. This expansion contributes to the apparent “softness” of Pt and Au, making interactions with soft nucleophiles like π -systems more favorable.²⁴

Carbene Complex	Nonrelativistic (nr) BDE (kcal/mol)	Quasirelativistic (qr) BDE (kcal/mol)	ΔE (qr vs nr)
NiCH ₂ ⁺	81.6	88.1	6.5
PdCH ₂ ⁺	68.5	83.2	14.7
PtCH ₂ ⁺	66.2	119.7	53.5
AuCH ₂ ⁺	25.4	90.9	65.5

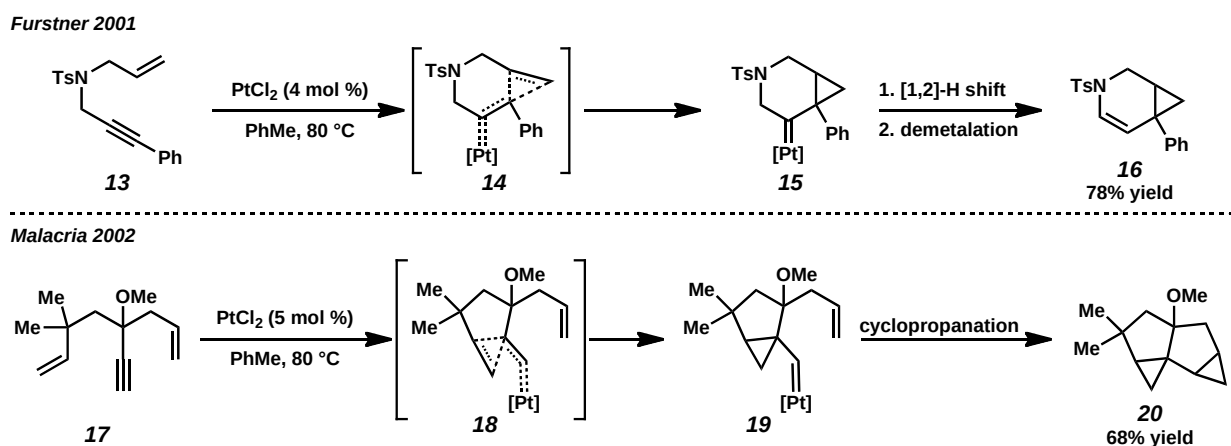
Figure 2.2.3. Relativistic Contributions to Binding in Metal-Carbene Complexes.

2.3 Using a Brook Rearrangement to Access Metal Carbenes

2.3.1 New Method for Carbene Generation

Alkyne activation chemistry has been used to form metal carbenes from a variety of substrates. The vast majority of these reactions rely on the nucleophilic attack of a π -system into an

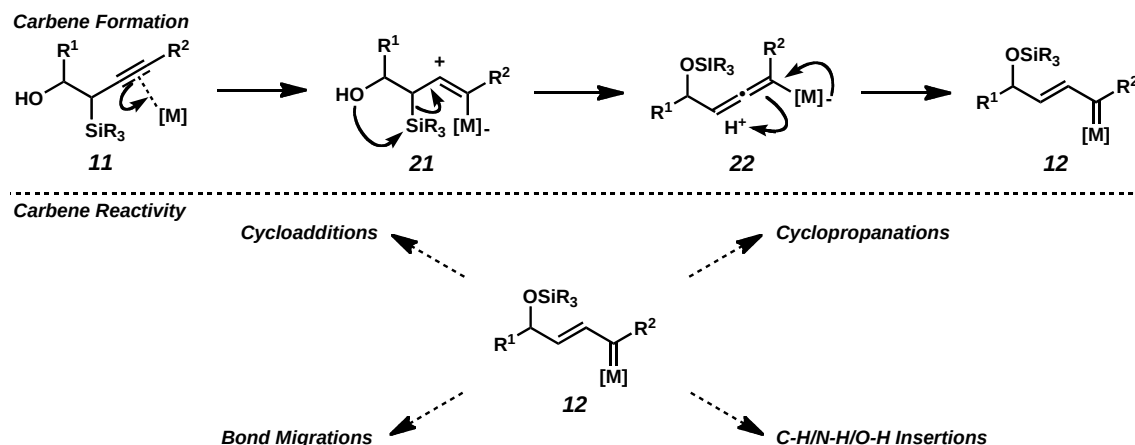
activated alkyne, forming a new electrophilic atom, which can then undergo subsequent bond formation. Reports by Fürstner and Malacria illustrate this reactivity, where an alkene reacts with an activated alkyne to form a cyclopropane and a platinum carbene (Scheme 2.3.1, **15** & **19**).²⁵ The carbene can then undergo a [1,2]-hydride migration or react with an additional nucleophile to form the observed products. One issue with this mode of reactivity is it results in cyclopropane formation and limits the application of this reactivity in broader contexts. Our plan was to develop a new method for generating the metal carbene that would allow for a broader product base.



Scheme 2.3.1. Traditional Carbene Generation Using Platinum Catalysis.

Our initial hypothesis was that an electron rich bond could be used as the nucleophile instead, donating the two bonding electrons to form an allenyl metal species. The use of a Brook rearrangement in concert with alkyne activation chemistry could be used to generate an α,β -unsaturated metal carbene (Scheme 2.3.2).²⁶ Coordination of the alkyne by an electrophilic metal would pull electron density away from the alkyne, creating an electron deficient carbon β to the carbon-silicon bond. This electron deficiency would initiate a [1,3]-Brook rearrangement (**21**), leading to the formation of the allenyl metal species (**22**), which upon protonation would

generate the desired metal carbene (**12**).²⁷ Once formed, the metal carbene could undergo subsequent reactions to generate a variety of products. The advantage of this approach is that the products of the reactions would contain only a silyl ether as a result of the reaction, a functional group that can be easily manipulated.

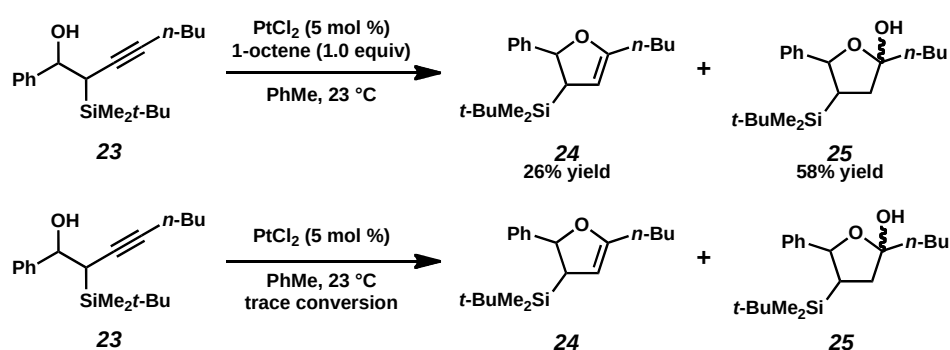


Scheme 2.3.2 Proposed Method for Carbene Generation.

2.3.2 Initial Reactions of β -hydroxypropargylsilanes

Our investigation began with exposure of propargylsilane **23** to conditions that are typically used in Pt(II) catalysis.²⁸ We included alkenes as a trap for the Pt-carbene, hoping to induce cyclopropanation of the π -system. Exposure of **23** to 5.0 mol % of PtCl₂ in toluene at elevated temperatures in the presence of 1-octene led to the formation of a complex mixture of products. Performing the reaction at ambient temperature in the presence of 1-octene followed by an aqueous workup resulted in a mixture of dihydropyran **24** in 26% yield and its hydrate **25** in 58% yield as the major species (Scheme 2.3.3). Analysis of the crude ¹H NMR indicated no incorporation of 1-octene into any of the reaction products. Running the reaction in the presence of 1-hexene or styrene resulted in identical reactivity compared to when 1-octene was used, confirming that the olefin was not being consumed in the reaction. Exposure of **23** to PtCl₂ in

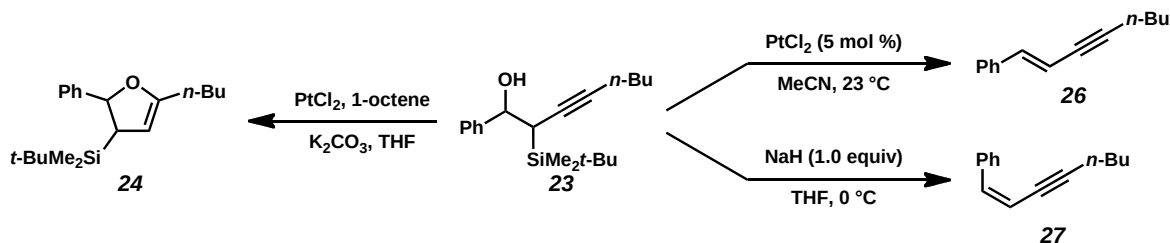
toluene in the absence of 1-octene revealed a surprising dependence on the alkene; after stirring for 48 h at ambient temperature, only trace conversion of the starting material was observed. This sluggish reactivity suggested that, while not being incorporated into the substrate being studied, the olefin activated the catalyst and accelerated the rate of the reaction.²⁹ Other solvents were screened as well and afforded similar results. At this point it was evident that the favored process was a hydroalkoxylation of the activated alkyne to form vinyl ethers or acetals,³⁰ and not the desired interaction between oxygen and silicon.



Scheme 2.3.3. Reactivity of β -Hydroxy Propargylsilane **23**.

The experiments described above indicated that the primary mode of reactivity for this system was addition of the hydroxyl nucleophile into the activated alkyne. This observed reactivity was contrary to our hypothesis, which required the alcohol to add into the silicon group to initiate the desired Brook rearrangement. One way to presumably promote this interaction is to generate small concentrations of the alkoxide by exposing the substrate to weakly basic conditions. Exposure of **23** to K_2CO_3 in THF in the presence of PtCl_2 led to formation of the observed dihydrofuran product **24** (Scheme 2.3.4). Performing the reaction in MeCN resulted in the formation of enyne **26**, the product of an acid-promoted Peterson elimination.³¹ Strongly basic conditions in the absence of PtCl_2 also favored the Peterson elimination, with the *cis*-olefin **27**

being formed exclusively. These last two experiments provided strong evidence that the preferred flow of the C-Si electrons in the β -hydroxy propargyl silane systems was away from the alkyne, not into the π -system like we envisioned. We then sought a new model system, realizing that this scaffold was not going to yield the desired carbene intermediates we hoped to form.

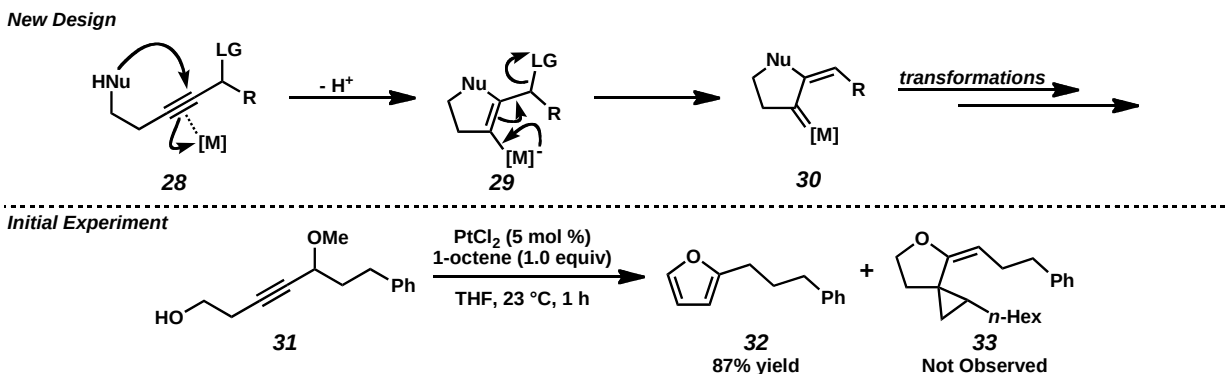


Scheme 2.3.4. Preferred Reactivity of β -Hydroxy Propargylsilane **23**.

2.3.3 Design of a New Scaffold

The challenges that the β -hydroxy propargylsilane substrates presented forced us to reconsider the design of our scaffold. We envisioned a system where the electrophilic group was placed on the propargylic position on the opposite side of the alkyne as the attacking nucleophile (Scheme 2.3.5). Our hope was that the placement of these two components on opposite sides of the alkyne would prevent the nucleophile from interacting with the planned electrophilic group until after the metal had activated the alkyne. Compound **28** served as a model to test our new approach. In this system, a 5-*endo-dig* cyclization would occur upon activation of the alkyne, leading to the formation of vinyl metal species **29**. At this point the metal can donate into the π -system, extrude the leaving group, and form the α,β -unsaturated carbene (**30**). The inclusion of an appropriate nucleophile would then enable us to trap the carbene species. With these design elements in mind, we synthesized propargylic methyl ether **31** and exposed it to PtCl_2 in the presence of 1-octene, which we hoped would trap the carbene as cyclopropane **33**. Isolated from

this reaction was furan **32**, with no formation of cyclopropane **33** observed. The isolation of the furan product in high yield intrigued us, and we set out to further explore this new transformation. While there are numerous methods to synthesize furans via acid/base chemistry or transition metal catalysis, what piqued our interest in this result was what it could tell us about the nature of the intermediates involved.



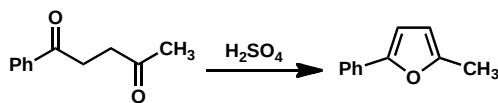
Scheme 2.3.5. Formation of Furan **32** via Platinum Catalysis.

2.4 Background: The Synthesis of Furans

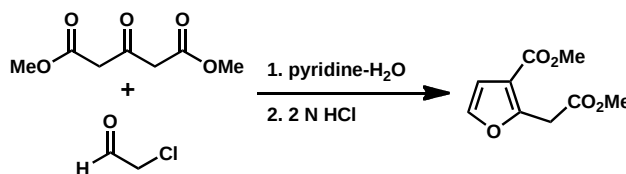
2.4.1 Classic Approaches to Furan Synthesis

Chemistry centered on the formation of furans has been known for over a century, with two of the classic and still synthetically useful ways to construct furans, the Paal-Knorr and Feist-Bénary furan syntheses, being the first methods that were developed for generating this heterocycle (Scheme 2.4.1).³² These two reactions can be remarkably efficient, but they also require the use of strong acids or bases, a feature that limits the scope in each case. Recent developments in π -activation chemistry have led to a significant increase in methods aimed at creating furans from linear precursors.³³ These methods all rely on the nucleophilic addition of an alcohol or carbonyl oxygen onto an activated alkyne or allene using late transition metals such as Ag(I), Pt(II), or Au(I/III) salts.

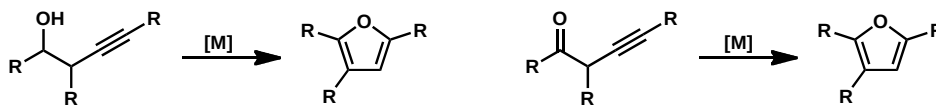
Paal-Knorr Furan Synthesis



Feist-Bénary Furan Synthesis- Tada 1994



Furan Synthesis via π -Activation

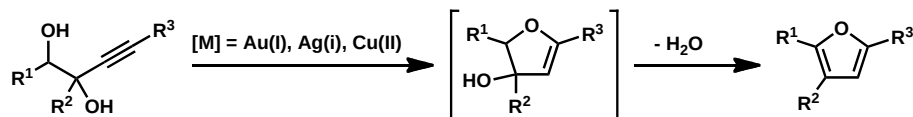


Scheme 2.4.1. Approaches to Furan Synthesis.

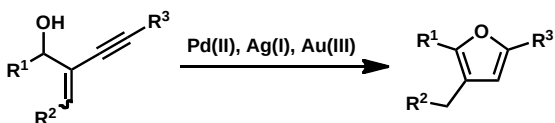
2.4.2 Furan Synthesis via π -Activation

Several methods to synthesize furans from homopropargylic oxygen nucleophiles via π -activation chemistry have been reported, all of which rely on the initial addition of an oxygen nucleophile into the activated alkyne to form the corresponding dihydrofuran intermediate. One approach within in this reaction class is the combined cyclization-dehydration sequence of vicinal propargylic diols (Scheme 2.4.2).³⁴ This reaction can be promoted using a variety of alkynophilic metals including Ag(I), Au(I), and Cu(II) and generally proceeds in high yields. Cycloisomerizations involving alkynyl allylic alcohols have also been reported using Ag(I), Pd(II) or Au(III) catalysts.³⁵ These reactions initially form a dihydrofuran intermediate with an exocyclic alkene in the 4-position. These intermediates then rapidly isomerize to the aromatic system. Alkynyl epoxides can also undergo cycloisomerization processes to form substituted furans.³⁶ In these reactions the addition of the epoxide oxygen into the activated alkyne generates a carbocation at the 4-position of the dihydrofuran ring. Deprotonation α to the carbocation produces the observed furans.

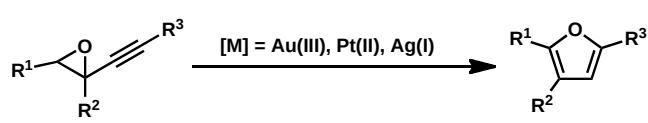
Cyclization-Dehydration Strategy



Alkynyl Allylic Alcohols Strategy



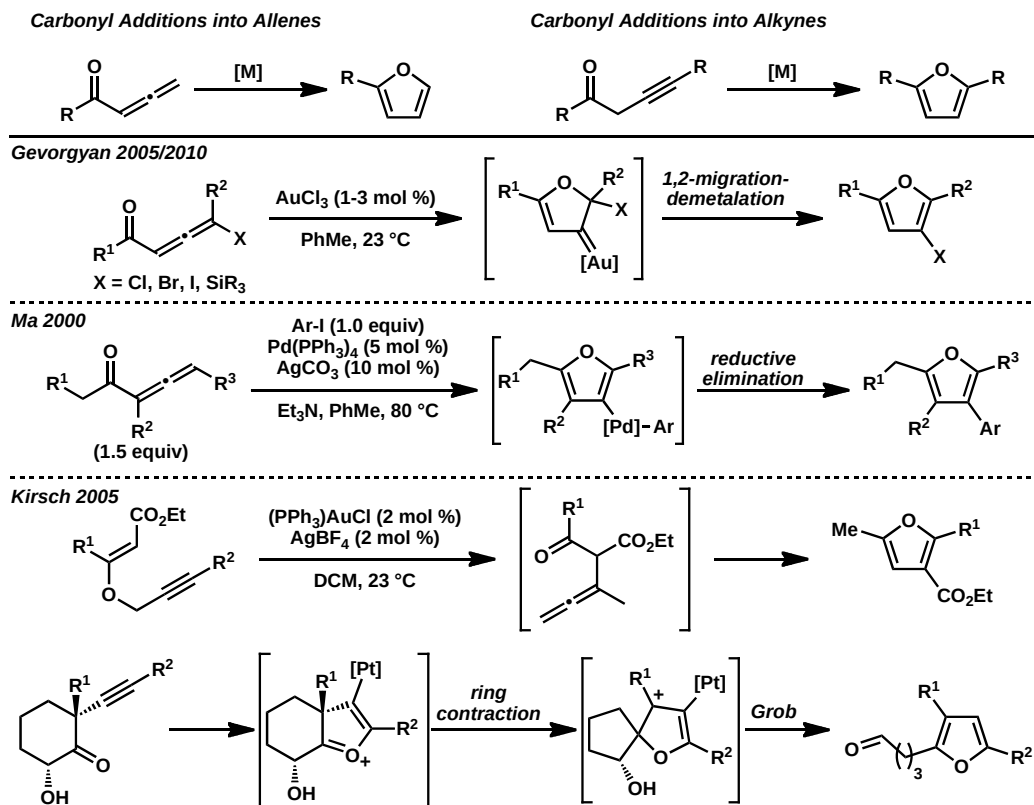
Alkynyl Epoxide Strategy



Scheme 2.4.2. Synthesis of Furans Using Oxygen Nucleophiles.

Additional strategies for furan synthesis have relied on the ability of carbonyl groups to add into activated alkynes or allenes. Gevorgyan has shown that Au(III) will initiate a 5-*endo-trig* cyclization of allenyl ketones to form the corresponding Au carbene (Scheme 2.4.3).³⁷ This intermediate undergoes 1,2-halo/silyl migration followed by demetalation to form the furan products. Similar additions of carbonyls into allenes have been reported using Ag(I), Rh(I), Pt(II) or Au(III) based catalysts by Marshall, Hashmi, Ma, and Che, respectively.³⁸ Ma's approach, which uses a Pd(II) catalyst generated from the oxidative addition of aryl iodides, enables the synthesis of 3-arylated furans: a substitution pattern that is difficult to introduce via standard π -activation of alkynes. Alkynyl ketones can also be used as precursors to substituted furans.³⁹ This chemistry relies on the metal catalyzed isomerization to the corresponding allenones, which then react to form substituted furans. Kirsch demonstrated a unique method to form furans via π -activation chemistry. This method uses a Au(I) catalyzed propargyl-Claisen reaction of propargyl vinyl ethers to form an intermediate allene, which subsequently reacts with the newly formed carbonyl to generate the furan products.⁴⁰ Skipped ynones have also been used to generate furans using π -activation.⁴¹ The generation of oxocarbenium intermediates can lead to either immediate deprotonation to form the heterocycle or a carbocation rearrangement

followed by a fragmentation leading to the formation of the furan ring as shown by Kirsch. These examples all highlight the various methods that have been developed to generate furans from an assortment of diverse starting materials. Our approach would not only complement this existing body of research, but would also enable us to explore the possibility of Pt-carbene formation and subsequent exploitation.



Scheme 2.4.3. Furan Synthesis via Carbonyl Additions into π -Systems.

2.5 The Synthesis of Furans from Propargylic Methyl Ethers

2.5.1 Reaction Optimization

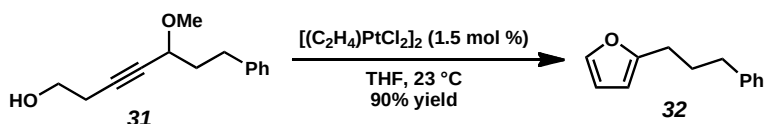
The formation of furan **32** in high yield when exposed to a platinum catalyst led us to study the reaction more closely. Removing the 1-octene from the reaction conditions resulted in much slower reaction times and variable yields (Table 2.5.1, entry 1). We speculated that the alkene

must have been influencing the metal in a way that was not required for the observed reactivity to occur. Other ligands were examined as well, with CO, Et₃N, pyridine and PPh₃ all performing worse than the ligandless conditions when used in equal amounts to PtCl₂ (Table 2.5.1 entries 3, 5 and 7). The use of superstoichiometric (20 equivalents with respect to platinum) Et₃N, pyridine and PPh₃ resulted in no conversion of alcohol **31** to furan **32** (Table 2.5.1 entries 4, 6 and 8). The latter results helped us to identify potential functional group limitations of the reaction, as strongly σ -coordinating functional groups like amines would deactivate the catalyst by saturating the potential sites for alkyne coordination.⁴² The enhancement of reactivity that was observed with 1-octene was also observed with several other alkenes (Table 2.5.1, entries 9-20).^{43,44} In each case the use of 1.0 equivalent of the alkene led to faster reaction times and higher yields. This effect was most pronounced with the use of 1,5-cyclooctadiene (Table 2.5.1, entries 17, 18), which induced much slower reactivity when 0.05 equivalents (1 equivalent with respect to Pt) than when no ligand was included (Table 2.5.1 entry 1). Increasing to 1.0 equivalent of 1,5-cyclooctadiene led to results that were similar to those observed with the use of 1-octene (Table 2.5.1 entry 14). Our initial hypothesis was that the olefin ligands were helping to solubilize the PtCl₂ by breaking up the polymeric structure of the catalyst.⁴⁵ The use of a readily soluble platinum source like Zeise's dimer (Scheme 2.5.1) produced the best result, forming furan **32** in 90% yield in only 5 minutes.

Table 2.5.1. Ligand Optimization for the Platinum Catalyzed Furan Formation.

Entry	Ligand	Equiv	Time (h)	Yield (%) ^a
1	none	N/A	7-20	83
2	CO	1.0 atm	24	0 ^b
3	Et ₃ N	0.05	72	3 ^b
4		1.0	72	0 ^b
5	pyridine	0.05	72	20 ^b
6		1.0	72	0 ^b
7	PPh ₃	0.05	4	65
8		1.0	30	0 ^b
9	methyl acrylate	0.05	14	63
10		1.0	7.5	90
11	ethyl vinyl ether	0.05	8	75
12		1.0	1.5	82
13	1-octene	0.05	3	83
14		1.0	1	87
15		0.05	66	32
16		1.0	48	25
17		0.05	66	31
18		1.0	1	86
19		0.05	24	54
20		1.0	2.5	91

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Reaction did not go to completion. ^c Used instead of PtCl₂.



Scheme 2.5.1. Zeise's Dimer as the Catalyst.

2.5.2 Effects of Alkene Binding on Platinum(II) Catalysts

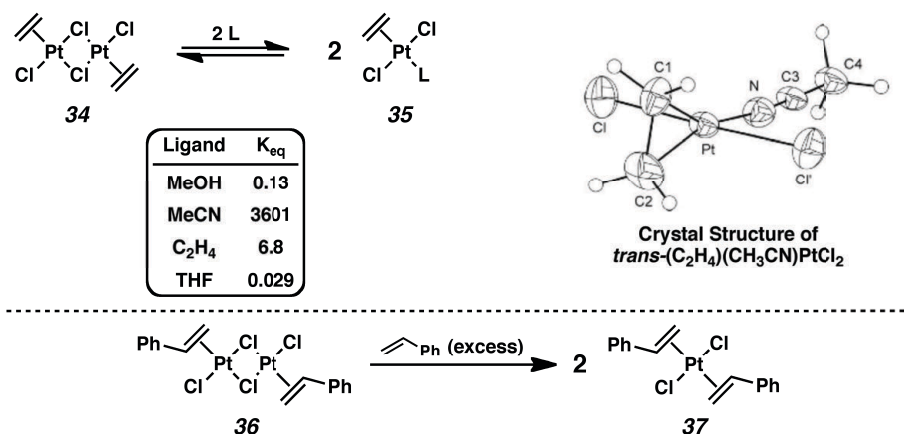
The observation of a noticeable increase in the rate of the above reactions led us to investigate the potential role the alkene has on the nature of the platinum catalyst. The variability in reactivity of the various Pt(II) olefin complexes indicates the mode of activation extends beyond simply solubilization of the metal. As discussed earlier, alkene/alkyne coordination is the result

of both donation of electrons from the C-C π -bond into empty d -orbitals on the metal, and the back-donation from the filled metal d -orbitals into the π^* of the alkene or alkyne. In Pt(II) systems this back-donation is minor, and the major bonding interaction is due to the σ -donation of the olefin. The inclusion of monodentate olefins produced an increase in the rate of consumption of the starting material, and also higher yields of the furan product (**32**, Table 2.5.1). Electron rich olefins like ethyl vinyl ether and 1-octene were better activators than the sterically more encumbered β -pinene, or electron deficient methyl acrylate. The two bidentate olefins that were examined, norbornadiene and 1,5-cyclooctadiene, strongly inhibited the reaction at low concentrations. It is possible that at low concentrations both COD and NBD undergo bidentate coordination to the platinum center, making it less likely to coordinate & activate the alkyne of the substrate.^{46,47}

In addition to describing the relative binding strengths of the olefins to platinum, it is also important to discuss the influences coordinated alkenes have on ligand substitutions around the metal center. Several reports detail the ligand exchange reactions of Pt(II) salts, using Zeise's dimer ($[(C_2H_4)PtCl_2]_2$) or Zeise's salt ($K[(C_2H_4)PtCl_3 \cdot H_2O]$) as the platinum source, both of which are much more soluble than $PtCl_2$ in organic solvents.⁴⁸ The synthesis of $PtCl_2(MeCN)_2$ is accomplished by refluxing $PtCl_2$ in MeCN for 12 hours, suggesting the dissolution of the $PtCl_2$ polymer in organic solvents is not facile, supporting our belief that the slow reaction times that are observed in the absence of added alkene are due to solubility issues.

It has also been shown by Otto and coworkers that Zeise's dimer (**34**) will rapidly cleave via bridge-splitting to form the corresponding *trans*-monomeric complexes (**35**) (Scheme 2.5.2).⁴⁹

This bridge splitting has also been observed when dimeric [(styrene)PtCl₂]₂ (**36**) is exposed to excess styrene, forming the monomeric (styrene)₂PtCl₂ complex (**37**).⁵⁰ Monomeric mixed (olefin)(alkyne)PtCl₂ complexes can also be prepared by exposing Zeise's dimer to various alkynes.⁵¹ These monomeric platinum-olefin complexes can then rapidly undergo ligand exchange reactions (such as alkyne coordination and activation) due to the strong *trans*-influence of the olefin ligand.⁵² This effect is strongest for olefins that experience greater back-bonding from the metal, as they are able to stabilize the buildup of electron density around the metal in the transition state. The dramatic increase in reactivity observed for Zeise's dimer compared to PtCl₂-olefin systems in our system is due to many of the effects described above. Being readily soluble in THF introduces more platinum into the reaction, and the ability to form mononuclear diolefin/alkyne complexes of the type **37** would lead to a highly electrophilic platinum center, which would be better at promoting alkyne activation reactions.



Scheme 2.5.2. Ligand Exchange Reactions of Zeise's Dimer.

2.5.3 Effect of the Propargylic Leaving Group

Once we had identified reaction conditions that favored formation of the furan product, we then sought to evaluate the role of the propargylic leaving group. Several substrates were synthesized

with a variety of leaving groups in the propargylic position (Table 2.5.2). In each case the starting material was completely consumed in 15 minutes, indicating the rate of the reaction was not dependent on the dissociative ability of the leaving group. What was instead observed was a noticeable decrease in yields that is consistent with the pKa's of the corresponding acids. Our hypothesis was that the methyl ethers were forming methoxide as the byproduct of this reaction. Correspondingly when the dissociating group is a chloride (Table 2.5.2, entry 1), HCl is the byproduct of the reaction. The formation of a strong acid could potentially decompose the product, resulting in decreased yields of the reaction. Sulfonate ester leaving groups provided higher yields (Table 2.5.2, Entries 2 and 3) than when the chloride was used, but were still lower than the methyl ether. Propargylic acetate **42** produced a minimal amount of the desired furan, most likely due to competing known rearrangements of propargylic carboxylates.⁵³ We synthesized lactone **43** (which is too geometrically constrained to participate in competing acyloxy migrations) as a way to test carboxylate leaving groups (Table 2.5.2, entry 5). The expected furan (**44**) was produced in only 23% yield after treatment with TMSCHN₂. The use of more basic leaving groups like alcohols and ethers (Table 2.5.2, Entries 6 and 7) proved optimal, with the ethereal leaving group forming the desired furan **32** in 90% isolated yield in only 15 minutes at room temperature. These two groups also contain Lewis basic oxygen atoms which potentially enhance the deprotonation of the attacking nucleophile via proton bridging; this will be discussed in more detail in section 2.5.5.

Table 2.5.2. Evaluation of the Propargylic Leaving Group.

Entry	Substrate	Product	Time (min)	Conversion (%)	Yield (%) ^a
1			15	100	5
2			15	100	37
3			15	100	61
4			15	100	9
5			15	100	23 ^{b,c}
6			15	100	84
7			15	100	90 ^b

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Isolated yield. ^c After treatment with TMSCHN₃.

2.5.4 Synthesis of Furans from Propargylic Methyl Ethers

Having established an optimal catalyst and leaving group, we began our investigation to the generality of this reaction. A variety of substrates bearing different functional groups were synthesized and exposed to the cyclization conditions (Table 2.5.3). Several acid sensitive functional groups tolerated the reaction including silyl ethers, esters, carboxylic acids, carbamates, alkenes and acetals. Particularly noteworthy is the isolation of furan **51**, in which the double bond was not isomerized into conjugation, a testament to the mildness of the reaction

conditions. The furan product arising from propargylic ether **54** was not stable and would decompose upon standing. To avoid this the carboxylic acid was converted to the methyl ester using TMSCHN₂, producing furan **44** in 66% yield.

Table 2.5.3. Functional Group Compatibility.

Entry	Substrate	Product	Time (min)	Isol. Yield (%)
1			5	90
2			10	75
3			10	80
4			10	86
5			20	89
6			15	66 ^a
7			20	90
8			10	80

^a After treatment with TMSCHN₂.

Several polysubstituted furans were also synthesized using this method. In general substrates bearing secondary hydroxyl nucleophiles were much slower to react than those with primary hydroxyl nucleophiles, requiring longer reaction times or higher temperatures to go to

completion. One exception to this was allylic alcohol **64**, which cyclized to the furan product in 15 min at room temperature. The increased reactivity of this substrate relative to its saturated analog suggests the alkene helps to activate the catalyst by making it more electrophilic or by coordinating the metal and directing it to the alkyne. Cyclohexanols also reacted to give trisubstituted furans. Both the *trans*- (**66**) and *cis*- (**68**) substrates (Table 2.5.4, entries 5 and 6) reacted with similar times and yields indicating the orientation of the nucleophile and electrophile in cyclic systems has little effect on the reactivity of the substrates. Finally, tertiary ether **69** was also shown to be very reactive towards cyclization, with the increased substitution around the ethereal leaving group having no effect on the time of the reaction.

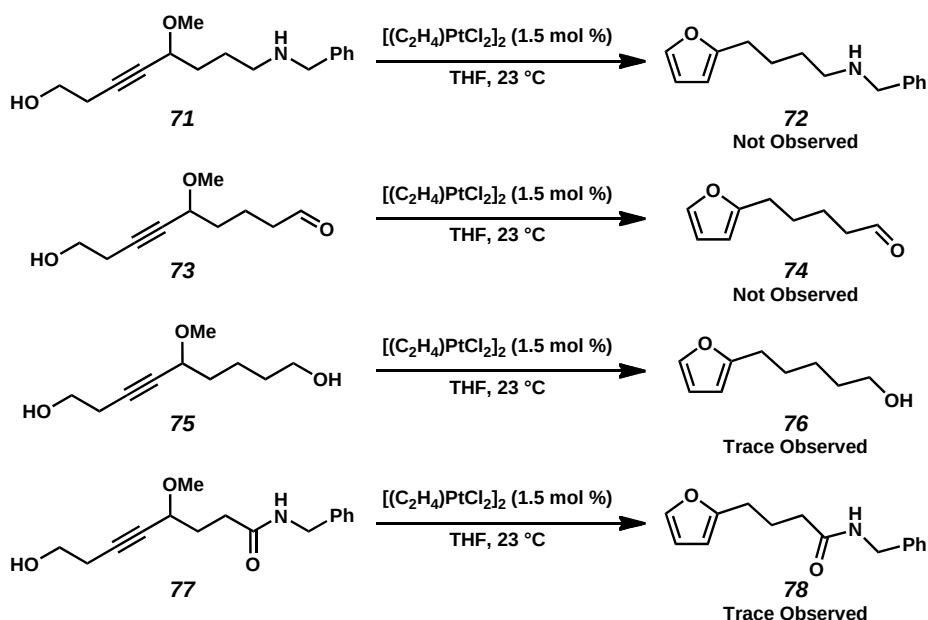
Table 2.5.4. Synthesis of Di- and Trisubstituted Furans.

Entry	Substrate	Product	Time (h)	Isol. Yield (%)
1			0.5	79
2			0.75	74
3			0.33 ^a	93
4			0.25	78
5			22	80
6			20	84
7			0.33	77

^a Reaction run at 50 °C.

Several substrates were not compatible with the reaction conditions. Compounds containing free alcohols, aldehydes, amides and amines all failed to form the desired furans (Scheme 2.5.3). Amine **71** most likely poisons the platinum catalyst by coordination and deactivation of the metal, while aldehyde **73** could potentially react via intramolecular aldol reactions under the Lewis acidic conditions. Alcohol **75** and amide **77** both reacted under the conditions, but analysis of the crude ¹H NMR's for these substrates indicated only trace amounts of the furan

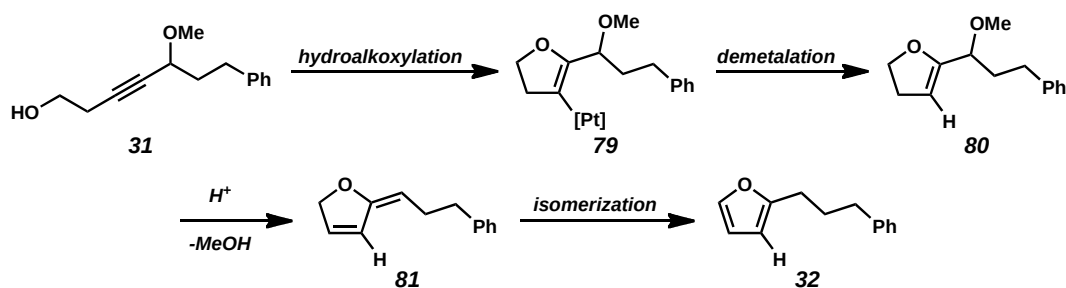
products (**76** and **78**) formed. It is now known that these substrates were most likely reacting via a different pathway, which will be discussed in Chapter 5.



Scheme 2.5.3. Failed Furan Syntheses.

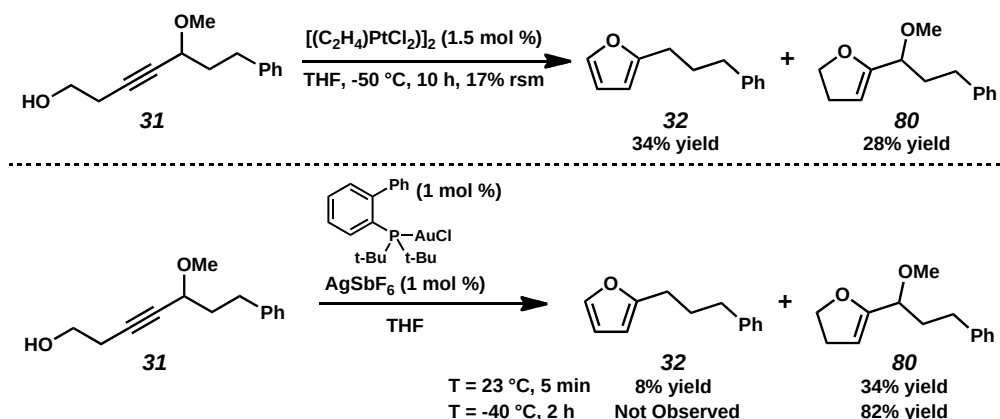
2.5.5 Examination of an Acid Catalyzed Aromatization Mechanism

Our initial hypothesis for the formation of furan products was that the platinum metal was able to extrude the propargylic leaving group, resulting in the formation of an α,β -unsaturated platinum carbene. A second hypothesis was that the platinum initiated a hydroalkoxylation of the alkyne, which upon demetalation resulted in dihydrofuran **80** (Scheme 2.5.4). At this point either adventitious acid or the metal could promote an elimination of MeOH to form diene **81**, which upon isomerization would generate the observed furan **32**. The intramolecular addition of heteroatom nucleophiles onto alkynes using gold or platinum salts is well known.³⁰ If this mechanism were operative, then exposing the intermediate dihydrofuran **80** to the reaction conditions or to any acid source should form the furan product.



Scheme 2.5.4. Acid Catalyzed Formation of Furan **32**.

If dihydrofuran **80** was an intermediate in this reaction, then the acid promoted elimination of methanol/isomerization (**80**→**32**) would have to be very fast compared to the hydroalkoxylation/demetalation event (**31**→**80**), since no intermediate products were ever observed while running these reactions under the optimized conditions. The only instances where dihydrofuran **80** was observed was when the reaction was conducted at low temperatures, or when cationic gold(I) salts were used (Scheme 2.5.5). Exposure of alcohol **31** to Zeise's dimer at -50 °C resulted in a very slow conversion to both the furan product **32** and dihydrofuran **80**. Similar results were obtained with the use of the cationic Au(I) JohnPhos complex. It is worth noting the differences in reactivity between the cationic Au(I) catalyst and Zeise's dimer at room temperature, with the former producing only minimal amounts of furan **32**. This could be due to differences in the abilities of the metals to generate adventitious H^+ under the reaction conditions, or differences in the amount of back donation of the metals into the π -systems, with gold being unable to extrude the methyl ether.



Scheme 2.5.5. Formation of Hydroalkoxylation Products.

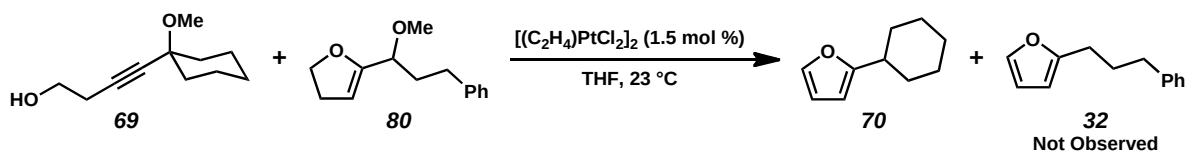
If dihydrofuran **80** was an intermediate product during the acid promoted formation of furans, then exposing it to a variety of Brønsted or Lewis acids should promote the elimination/isomerization to the heterocycle. Exposure of dihydrofuran **80** to weak acids like SiO_2 , NH_4Cl , and AcOH resulted in minimal conversion of the starting material, and no formation of the expected furan product **32** (Table 2.5.5, entries 1-3). Stronger acids like TFA, HCl , and sulfonic acids resulted in rapid decomposition of the vinyl ether starting material, and no observed formation of the furan product (Table 2.5.5, entries 4-7). Zeise's dimer was also unable to promote the elimination/isomerization to the furan product, with each of the reactions forming undetermined decomposition side products (Table 2.5.5, entries 8-12).

Table 2.5.5. Acid Promoted Furan Formation.

Entry	Catalyst	Equiv	Time	Conversion (%) ^a	Yield 32 (%) ^a
1	silica gel	1.0	72 h	67	0
2	NH ₄ Cl	1.0	72 h	25	0
3	AcOH	1.0	72 h	37	0
4	CF ₃ CO ₂ H	1.0	10 min	100	0
5	HCl	1.0	10 min	100	0
6	TsOH	1.0	10 min	100	0
7	CSA	0.05	10 min	100	0
8	[(C ₂ H ₄)PtCl ₂] ₂	0.005	72 h	84	0
9	[(C ₂ H ₄)PtCl ₂] ₂ ^b	0.005	72 h	86	0
10	[(C ₂ H ₄)PtCl ₂] ₂	0.05	10 min	100	0
11	[(C ₂ H ₄)PtCl ₂] ₂ ^b	0.05	22 h	100	0
12	[(C ₂ H ₄)PtCl ₂] ₂ ^c	0.05	10 min	100	0

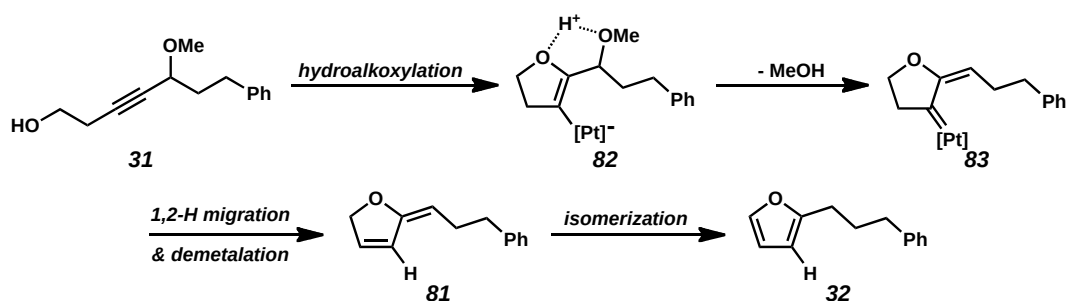
^a Determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Run with 1.1 equiv 2,6-di-*tert*-butylpyridine. ^c Run with 0.05 equiv CSA in reaction.

We suspected that Zeise's dimer could be acting as a precatalyst, with the active catalyst being generated *in situ* in the presence of the alkyne. To test this we combined dihydrofuran **80** and alcohol **69** in the same vial and exposed the mixture to Zeise's dimer (Scheme 2.5.6). After 10 minutes both of the starting materials had been consumed, with only furan **70** observed in the crude ¹H NMR. These experiments demonstrated that the hydroalkoxylation-acid mediated elimination/isomerization pathway is not operative for the conversion of alcohol **31** to furan **32**, and that another mechanistic explanation must be responsible for this platinum catalyzed transformation.



Scheme 2.5.6. Generation of a Catalytically Active Platinum Species.

A second mechanistic hypothesis for the generation of furans from propargylic methyl ethers is one where vinyl metal species **82** forms. Back-donation from the metal center into the π -system eliminates MeOH, forming the α,β -unsaturated platinum carbene (**83**). (Scheme 2.5.7). The carbene would then undergo a 1,2-hydride migration-demetalation to form diene **81**, which would rapidly isomerize to form the aromatic heterocycle. If this mechanism is operative, it would explain why we were unable to convert dihydrofuran **80** to furan **32**, as the dihydrofuran is never an intermediate in this pathway. We then set out to confirm the formation of the platinum carbene by evaluating the migratory aptitudes of hydrogen vs. silicon into α -carbenes, the results of which are described in Chapter 4.



Scheme 2.5.7. Furan Formation by a Proposed Platinum Carbene.

2.6 Conclusion

Our efforts to generate platinum carbenes from two different scaffolds have been described. Our initial hypothesis that β -hydroxypropargylsilanes could serve as precursors was found to be incorrect, as competing known processes prevented the carbene from forming. The use of propargylic methyl ethers led to the discovery of a novel method for synthesizing substituted furans. This reaction was strongly influenced by the use of bystander olefins, which activated the platinum catalyst, leading to faster reaction times and higher yields. Overall this reaction demonstrated good functional group compatibility, and in general produced the heterocycle in

good to excellent yields without affecting acid labile functional groups. Attempts to demonstrate an acid-catalyzed isomerization as part of the mechanism failed, leading us to believe a second pathway where a platinum carbene is a key intermediate was possible.

2.7 Experimental Section

2.7.1 Materials and Methods

Reactions were performed under an ambient atmosphere unless otherwise noted. Tetrahydrofuran, ether, dichloromethane and toluene were purified by passing through activated alumina columns. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products, (West Columbia, SC), Strem (Newburyport, MA) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 μm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde or KMnO_4 solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz), or a Varian 400 MR (at 400 MHz) and are reported relative to SiMe_4 (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) and are reported relative to SiMe_4 (δ 0.0). All IR spectra were obtained on NaCl plates (film) with a Bruker Tensor 27. All gas chromatography was performed on a Varian CP-3800 gas chromatograph. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.

2.7.2 Platinum Catalyzed Furan Synthesis

Table 2.5.3 (*reproduced*):

Entry	Substrate	Product	Time (min)	Isol. Yield (%)
1			5	90
2			10	75
3			10	80
4			10	86
5			20	89
6			15	66 ^a
7			20	90
8			10	80

^a After treatment with TMSCHN₂.

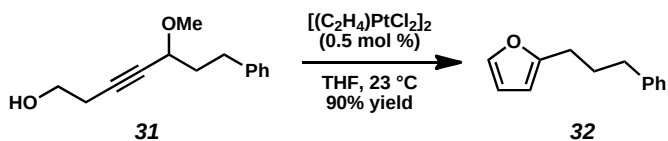


Table 2.5.3, Entry 1. According to the general procedure, homopropargylic alcohol **31** (218 mg, 1.00 mmol) and $[(C_2H_4)PtCl_2]_2$ (2.9 mg, 0.00500 mmol) were stirred in THF (10.0 mL, 0.10 M) under an ambient atmosphere at room temperature for 5 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL).

The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford furan **32** (168 mg, 90% yield, R_f = 0.29 in 19:1 hexanes/EtOAc) as a colorless oil.

Furan 32: Spectroscopic data matched that previously reported.⁵⁴

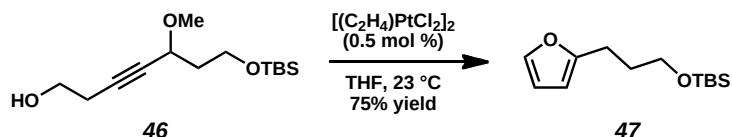


Table 2.5.3, Entry 2. According to the general procedure, homopropargylic alcohol **46** (235 mg, 0.862 mmol) and $[(C_2H_4)PtCl_2]_2$ (7.6 mg, 0.0129 mmol) were stirred in THF (8.60 mL, 0.10 M) under an ambient atmosphere at room temperature for 10 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford furan **47** (156 mg, 75% yield, R_f = 0.58 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 47: ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 2.0 Hz, 1H), 6.27 (dd, J = 3.1, 2.0 Hz, 1H), 5.98 (d, J = 3.1 Hz, 1H), 3.65 (t, J = 6.2 Hz, 2H), 2.69 (quint, J = 7.4 Hz, 2H), 1.85 (t, J = 7.4 Hz, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 141.1, 110.4, 105.1, 62.6, 31.4, 26.3, 24.7, 18.7, -5.0; IR (film) 2956, 1805, 1472, 1104, 837 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ $[C_{13}H_{24}O_2Si + H]^+$: 241.1618, found 241.1623.

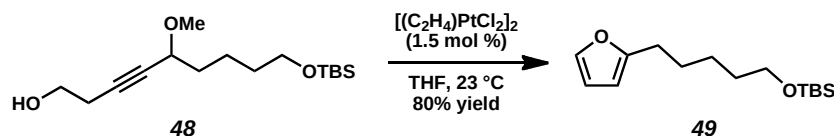


Table 2.5.3, Entry 3. According to the general procedure, homopropargylic alcohol **48** (210 mg, 0.700 mmol) and $[(C_2H_4)PtCl_2]_2$ (6.2 mg, 0.0105 mmol) were stirred in THF (7.00 mL, 0.10 M) under an ambient atmosphere at room temperature for 10 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford furan **49** (151 mg, 80% yield, R_f = 0.61 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 49: ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 1.6 Hz, 1H), 6.27 (dd, J = 2.7, 2.0 Hz, 1H), 5.97 (d, J = 3.1 Hz, 1H), 3.60 (t, J = 6.3 Hz, 2H), 2.62 (t, J = 7.4 Hz, 2H), 1.65 (quint, J = 7.4 Hz, 2H), 1.54 (quint, J = 6.4 Hz, 2H), 1.42-1.34 (comp m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 110.4, 105.0, 63.5, 32.9, 28.3, 28.2, 26.3, 25.8, 18.7, -4.9; IR (film) 2932, 1805, 1463, 1104, 836 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{15}H_{28}O_2Si + H$] $^+$: 269.1931, found 269.1941.

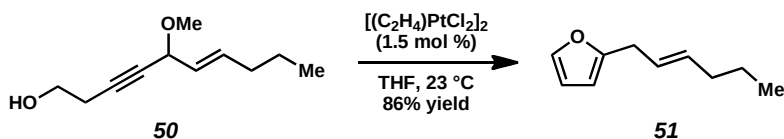


Table 2.5.3, Entry 4. According to the general procedure, homopropargylic alcohol **50** (182 mg, 1.00 mmol) and $[(C_2H_4)PtCl_2]_2$ (8.8 mg, 0.0150 mmol) were stirred in THF (10.0 mL, 0.10 M) under an ambient atmosphere at room temperature for 10 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm, silica basified with Et_3N prior to loading), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary

evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, silica basified with Et₃N prior to loading) to afford furan **51** (129 mg, 86% yield, *R*_f = 0.78 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 51: ¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, *J* = 2.0, 0.8 Hz, 1H), 6.28 (dd, *J* = 3.1, 2.0 Hz, 1H), 5.99 (dq, *J* = 3.1, 0.8 Hz, 1H), 5.59-5.50 (m, 2H), 3.33 (m, 2H), 2.04-1.98 (m, 2H), 1.41 (sextet, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 141.4, 133.3, 125.6, 110.5, 105.4, 34.9, 31.8, 22.8, 14.0; IR (film) 2960, 2874, 1596, 1506, 968 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₀H₁₄O + H]⁺: 151.1117, found 151.1111.

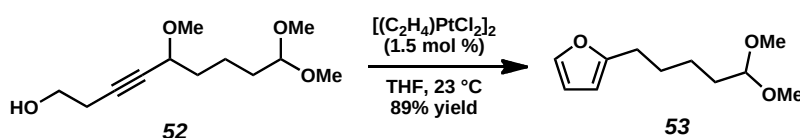


Table 2.5.3, Entry 5. According to the general procedure, homopropargylic alcohol **52** (115 mg, 0.500 mmol) and [(C₂H₄)PtCl₂]₂ (4.4 mg, 0.00750 mmol) were stirred in THF (5.00 mL, 0.10 M) under an ambient atmosphere at room temperature for 20 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm, silica basified with Et₃N prior to loading), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/Et₂O eluent, silica basified with Et₃N prior to loading) to afford furan **53** (88.0 mg, 89% yield, *R*_f = 0.56 in 4:1 hexanes/EtOAc) as a colorless oil.

Furan 53: ¹H NMR (400 MHz, CDCl₃) δ 7.29 (dd, *J* = 1.8, 1.1 Hz, 1H), 6.27 (dd, *J* = 3.1, 2.0 Hz, 1H), 5.97 (m, 1H), 4.35 (t, *J* = 4.7 Hz, 1H), 3.31 (s, 6H), 2.63 (t, 7.8 Hz, 2H), 1.68-1.60 (m, 2H), 1.44-1.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 141.1, 110.9, 105.0, 104.8, 53.0,

32.6, 28.2, 24.5; IR (film) 2948, 1727, 1596, 1386, 1192, 730 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₁H₁₈O₃ + H]⁺: 199.1329, found 199.1324.

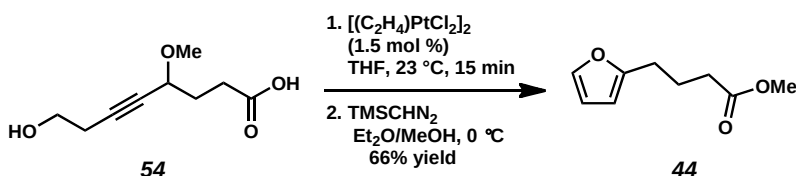


Table 2.5.3, Entry 6. According to the general procedure, homopropargylic alcohol **54** (93.1 mg, 0.500 mmol) and [(C₂H₄)PtCl₂]₂ (4.4 mg, 0.00750 mmol) were stirred in THF (5.00 mL, 0.10 M) under an ambient atmosphere at room temperature for 15 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with CH₂Cl₂/MeOH (49:1, 20 mL). The solvent was removed by rotary evaporation and the resulting oil was redissolved in 4:1 Et₂O/MeOH and cooled to 0° C under an argon atmosphere. Trimethylsilyl diazomethane (0.300 mL, 2.0 M in hexanes, 0.600 mmol) was added dropwise and the reaction was stirred for 1 h at 0 °C. The solvent was then removed by rotary evaporation, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford furan **44** (55.8 mg, 66% yield, R_f = 0.68 in 1:1 hexanes/EtOAc) as a colorless oil.

Furan 44: Spectroscopic data matched that previously reported.⁵⁵

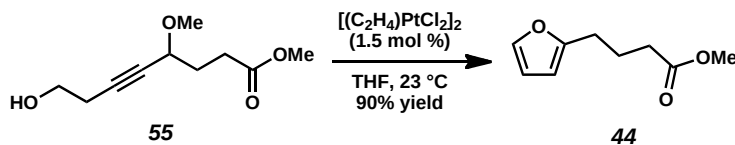


Table 2.5.3, Entry 7. According to the general procedure, homopropargylic alcohol **55** (100 mg, 0.500 mmol) and [(C₂H₄)PtCl₂]₂ (4.4 mg, 0.00750 mmol) were stirred in THF (5.00 mL, 0.10 M) under an ambient atmosphere at room temperature for 20 min. Upon completion, the

reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc (20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford furan **44** (75.6 mg, 90% yield, R_f = 0.68 in 1:1 hexanes/EtOAc) as a colorless oil.

Furan 44: Spectroscopic data matched that previously reported.⁵⁵

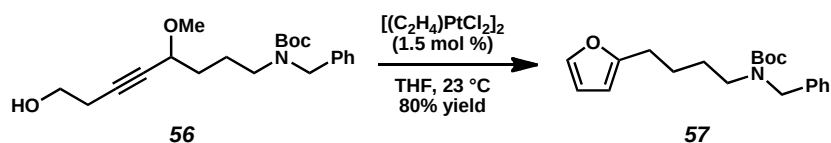


Table 2.5.3, Entry 8. According to the general procedure, homopropargylic alcohol **56** (108 mg, 0.300 mmol) and $[(C_2H_4)PtCl_2]_2$ (2.6 mg, 0.00450 mmol) were stirred in THF (3.00 mL, 0.10 M) under an ambient atmosphere at room temperature for 10 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford furan **57** (79.0 mg, 80% yield, R_f = 0.40 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 57: Line broadening in ^1H NMR due to the presence of rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (comp m, 3H), 7.25-7.18 (comp m, 3H), 6.26 (app. s, 1H), 5.94 (d, J = 2.7 Hz, 1H), 4.41 (br s, 2H), 3.23 (br s, 1H), 3.14 (br s, 1H), 2.61 (t, J = 6.3 Hz, 2H), 1.65-1.52 (comp m, 4H), 1.46 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 156.3, 141.1, 138.9, 128.8, 128.0, 127.4, 110.4, 105.1, 79.9, 50.7, 50.2, 46.6, 28.8, 28.0, 25.6; IR (film) 3030, 1950, 1696, 1597, 1365, 881 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + Na)^+$ $[C_{20}H_{27}NO_3 + Na]^+$: 352.1833, found 352.1880.

Table 2.5.4 (*reproduced*):

Entry	Substrate	Product	Time (h)	Isol. Yield (%)
1	 58	 59	0.5	79
2	 60	 61	0.75	74
3	 62	 63	0.33 ^a	93
4	 64	 65	0.25	78
5	 66	 67	22	80
6	 68	 67	20	84
7	 69	 70	0.33	77

^a Reaction run at 50 °C.

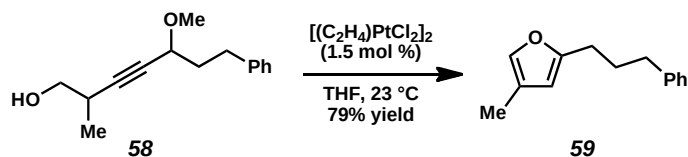


Table 2.5.4, Entry 1. According to the general procedure, homopropargylic alcohol **58** (232 mg, 1.00 mmol) and $[(C_2H_4)PtCl_2]_2$ (8.8 mg, 0.0150 mmol) were stirred in THF (10.0 mL, 0.10 M) under an ambient atmosphere at room temperature for 30 min. Upon completion, the

reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/Et₂O eluent) to afford furan **59** (158 mg, 79% yield, *R_f* = 0.67 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 59: ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 7.07 (s, 1H), 5.88, (s, 1H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.00 (s, 3H), 1.96 (quint, *J* = 7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 156.4, 142.4, 137.7, 128.8, 128.7, 126.1, 120.7, 108.1, 35.6, 30.0, 27.9, 10.2; IR (film) 2940, 1945, 1798, 1454, 1114, 744 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₄H₁₆O + H]⁺: 201.1274, found 201.1276.

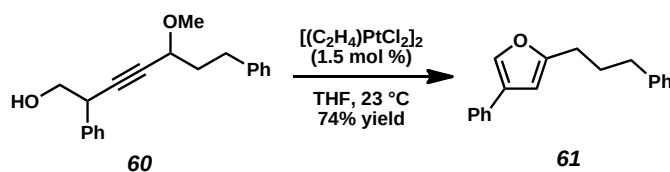


Table 2.5.4, Entry 2. According to the general procedure, homopropargylic alcohol **60** (0.237 mg, 0.805 mmol) and [(C₂H₄)PtCl₂]₂ (7.1 mg, 0.0120 mmol) were stirred in THF (8.05 mL, 0.10 M) under an ambient atmosphere at room temperature for 45 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford furan **61** (156 mg, 74% yield, *R_f* = 0.76 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 61: ¹H NMR (400 MHz, CDCl₃) δ 7.61 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32-7.28 (comp m, 2H), 7.24-7.18 (comp m, 4H), 6.33 (s, 1H), 2.70 (app. q, *J* = 7.0 Hz, 4H), 2.03 (quint, *J* = 7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.5, 142.2, 137.0, 133.2, 129.1, 128.8, 128.7, 127.3, 127.1, 126.2, 126.0, 35.6, 29.9, 27.9; IR (film) 3028, 2938, 1946,

1602, 1496, 1124 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₉H₁₈O + H]⁺: 263.1430, found 263.1435.

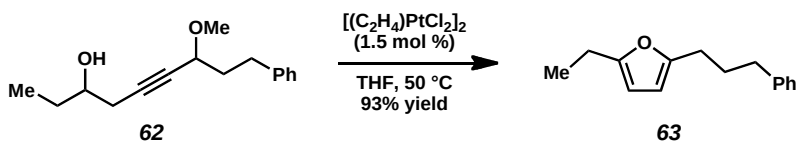


Table 2.5.4, Entry 3. According to the general procedure, homopropargylic alcohol **62** (246 mg, 1.00 mmol) was stirred in THF (10.0 mL, 0.10 M) under an ambient atmosphere. $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (8.8 mg, 0.0150 mmol) was added, and the reaction was placed in a preheated oil bath at 50 °C for 20 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford furan **63** (199 mg, 93% yield, R_f = 0.63 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 63: ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.26 (comp m, 2H), 7.22-7.16 (comp m, 3H), 5.87 (app. s, 1H), 5.86 (app. s, 1H), 2.67 (t, J = 7.4 Hz, 2H), 2.60 (q, J = 7.4 Hz, 2H), 1.96 (quint, J = 7.8 Hz, 2H), 1.21 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.4, 154.4, 142.5, 128.8, 128.6, 126.1, 105.5, 104.5, 98.8, 35.7, 30.1, 27.9, 21.7, 12.6; IR (film) 3027, 2938, 1944, 1567, 1454, 776 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₅H₁₈O + H]⁺: 215.1430, found 215.1436.

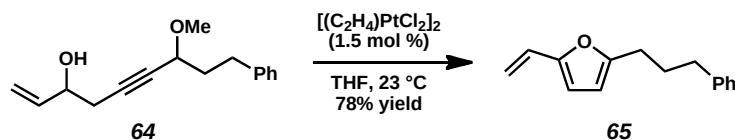


Table 2.5.4, Entry 4. According to the general procedure, homopropargylic alcohol **64** (244 mg, 1.00 mmol) and $[(C_2H_4)PtCl_2]_2$ (8.8 mg, 0.0150 mmol) were stirred in THF (10.0 mL, 0.10 M) under an ambient atmosphere at room temperature for 15 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford furan **65** (165 mg, 78% yield, R_f = 0.60 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 65: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (comp m, 2H), 7.23-7.18 (comp m, 3H), 6.45 (dd, J = 18.4, 11.4 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 5.99 (d, J = 3.2 Hz, 1H), 5.58 (d, J = 17.6 Hz, 1H), 5.08 (d, J = 11.4 Hz, 1H), 2.69 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.00 (quint, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 152.0, 142.3, 128.9, 128.7, 126.2, 125.5, 111.0, 109.3, 107.1, 35.6, 30.0, 27.0; IR (film) 3027, 2939, 1946, 1640, 1528, 1454, 785 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{15}H_{16}O + H$] $^+$: 213.1274, found 213.1278.

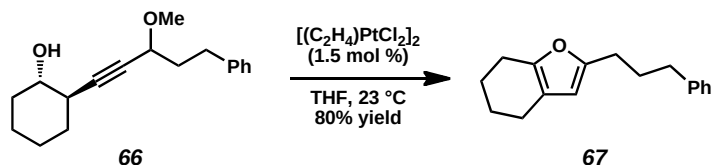


Table 2.5.4, Entry 5. According to the general procedure, homopropargylic alcohol **66** (272 mg, 1.00 mmol) and $[(C_2H_4)PtCl_2]_2$ (8.8 mg, 0.0150 mmol) were stirred in THF (10.0 mL, 0.10 M) under an ambient atmosphere at room temperature for 22 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL).

The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford furan **67** (192 mg, 80% yield, R_f = 0.58 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 67: Spectroscopic data matched that previously reported in the literature.⁵⁶ HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₇H₂₀O + H]⁺: 241.1587, found 241.1589.

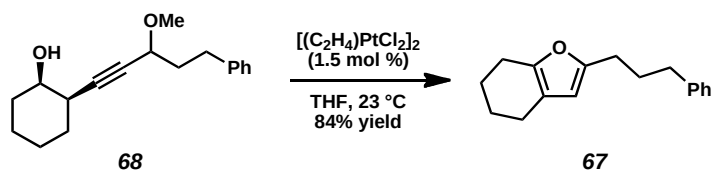


Table 2.5.4, Entry 6. According to the general procedure, homopropargylic alcohol **68** (267 mg, 0.980 mmol) and [(C₂H₄)PtCl₂]₂ (8.6 mg, 0.0147 mmol) were stirred in THF (9.80 mL, 0.10 M) under an ambient atmosphere at room temperature for 20 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford furan **67** (197 mg, 84% yield, R_f = 0.58 in 9:1 hexanes/EtOAc) as a colorless oil.

Furan 67: Spectroscopic data matched that previously reported in the literature.⁵⁶ HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₇H₂₀O + H]⁺: 241.1587, found 241.1589.

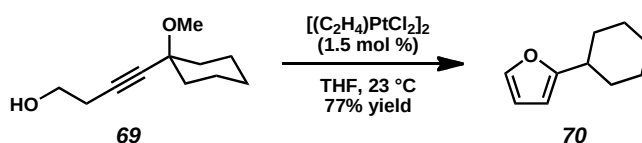


Table 2.5.4, Entry 7. According to the general procedure, homopropargylic alcohol **69** (91.1 mg, 0.500 mmol) and [(C₂H₄)PtCl₂]₂ (4.4 mg, 0.00750 mmol) were stirred in THF (5.00 mL,

0.10 M) under an ambient atmosphere at room temperature for 10 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford furan **70** (58.0 mg, 77% yield, R_f = 0.81 in 9:1 hexanes/EtOAc) as a pale yellow oil.

Furan 70: ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, J = 2.0, 0.8 Hz, 1H), 6.28 (dd, J = 3.1, 2.0 Hz, 1H), 5.95 (dt, J = 3.1, 0.8 Hz, 1H), 2.62 (m, 1H), 2.06-1.99 (m, 2H), 1.83-1.74 (m, 2H), 1.74-1.67 (m, 1H), 1.42-1.33 (m, 4H), 1.30-1.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.4, 140.7, 110.2, 102.9, 37.6, 31.9, 26.5, 26.3; IR (film) 3116, 2934, 2855, 1506, 1449, 1011 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{10}\text{H}_{14}\text{O} + \text{H}$] $^+$: 151.1117, found 151.1123.

2.7.3 Optimization of Pt-Catalyst Conditions

Table 2.5.1 (reproduced):

Entry	Ligand	Equiv	Time (h)	Yield (%) ^a
1	none	N/A	7-20	83
2	CO	1.0 atm	24	0 ^b
3	Et ₃ N	0.05	72	3 ^b
4		1.0	72	0 ^b
5	pyridine	0.05	72	20 ^b
6		1.0	72	0 ^b
7	PPh ₃	0.05	4	65
8		1.0	30	0 ^b
9	methyl acrylate	0.05	14	63
10		1.0	7.5	90
11	ethyl vinyl ether	0.05	8	75
12		1.0	1.5	82
13	1-octene	0.05	3	83
14		1.0	1	87
15		0.05	66	32
16		1.0	48	25
17		0.05	66	31
18		1.0	1	86
19		0.05	24	54
20		1.0	2.5	91

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Reaction did not go to completion. ^c Used instead of PtCl₂.

Table 2.5.1, entry 1. To a solution of alcohol **31** (21.8 mg, 0.100 mmol) in THF (1.00 mL, 0.1 M) under an ambient atmosphere was added a standard solution of 4,4'-di-*t*-butylbiphenyl (80.0 μ L, 0.125 M in THF, 0.0100 mmol). To this was added PtCl₂ (1.3 mg, 0.00500 mmol) and the reaction was stirred at room temperature. Upon completion, as determined by TLC, the reaction was filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with hexanes/EtOAc (1:1, 4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

GC Conditions: Column- Agilent Technologies CP-Sil 8 CB (15 x 0.25)

Method: 100 °C for 18 min., warm to 180 °C over 4 min., 180 °C for 20 min. Furan R_f = 20.1 min., standard R_f = 31.8 min. Furan integrations multiplied by 1.86 to correct for the response differences.

Table 2.5.1, entry 2. To a solution of alcohol **31** (21.8 mg, 0.100 mmol) in THF (1.00 mL, 0.1 M), under ambient atmosphere, was added a standard solution of 4,4'-di-*t*-butylbiphenyl (80.0 μ L, 0.125 M in THF, 0.0100 mmol). To this was added PtCl₂ (1.3 mg, 0.00500 mmol). A stream of CO gas was then bubbled through the solution for 10 min at which time a balloon was added and the reaction was stirred at room temperature under a CO atmosphere. No reaction was detected by TLC after stirring for 24 h.

Table 2.5.1, entries 3, 5, 7, 9, 11, 13, 15, 17, 19. To a solution of alcohol **31** (21.8 mg, 0.100 mmol) in THF (1.00 mL, 0.1 M), under ambient atmosphere, was added a standard solution of 4,4'-di-*t*-butylbiphenyl (80.0 μ L, 0.125 M in THF, 0.0100 mmol). To this was added a solution of each ligand tested (0.00500 mmol, 10% by volume in THF). PtCl₂ (1.3 mg, 0.00500 mmol) was then added and the reaction was stirred at room temperature. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with hexanes/EtOAc (1:1, 4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 2.5.1, entries 4, 6, 8, 10, 12, 14, 16, 18, 20. To a solution of alcohol **31** (21.8 mg, 0.100 mmol) in THF (1.00 mL, 0.1 M), under ambient atmosphere, was added a standard solution of 4,4'-di-*t*-butylbiphenyl (80.0 μ L, 0.125 M in THF, 0.0100 mmol). To this was added each

ligand tested (0.100 mmol). PtCl_2 (1.3 mg, 0.00500 mmol) was then added and the reaction was stirred at room temperature. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with hexanes/EtOAc (1:1, 4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield. Entries 4, 6, and 8 did not produce any furan product by TLC and were not injected onto the GC to determine yield.

2.7.4 Propargylic Leaving Group Optimization

Table 2.5.2 (*reproduced*):

Reaction scheme showing the conversion of a propargylic alcohol (38) to a furan product (32) using $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (1.5 mol %) in THF at 23 °C under ambient air.

Entry	Substrate	Product	Time (min)	Conversion (%)	Yield (%) ^a
1			15	100	5
2			15	100	37
3			15	100	61
4			15	100	9
5			15	100	23 ^{b,c}
6			15	100	84
7			15	100	90 ^b

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Isolated yield. ^c After treatment with TMSCHN_2 .

General procedure. To a solution of substrate (0.0500 mmol) in THF (0.500 mL, 0.10 M), under ambient atmosphere, was added a standard solution of 4,4'-di-*tert*-butyl biphenyl (40.0 μ L, 0.125 M in THF, 0.00500 mmol). To this was added $[(C_2H_4)PtCl_2]_2$ (40.0 μ L, 0.0188 M in THF, 0.00750 mmol) and the reactions were stirred at room temperature. Upon consumption of starting material as determined by TLC, the reactions were quenched with Et_3N (14.0 μ L, 0.100 mmol) and filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with hexanes/ $EtOAc$ (1:1, 4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yields.

GC Conditions: Column- Agilent Technologies CP-Sil 8 CB (15 x 0.25), 1.0 mL/min carrier gas
Method: 100 °C for 18 min., warm to 180 °C over 4 min., 180 °C for 20 min. Furan R_f = 20.1 min, standard R_f = 31.8 min. Furan integrations multiplied by 1.86 to correct for the response differences.

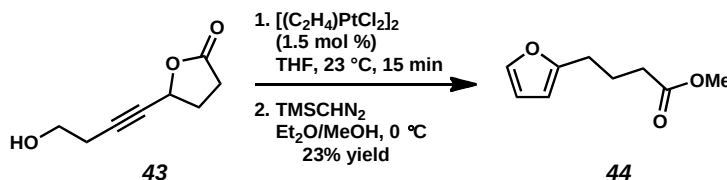
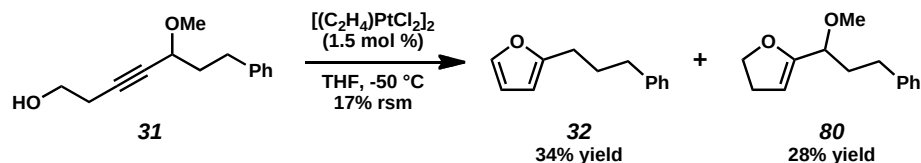


Table 2.5.2, Entry 5. According to the general procedure, lactone **43** (86.1 mg, 0.559 mmol) and $[(C_2H_4)PtCl_2]_2$ (4.9 mg, 0.00838 mmol) were stirred in THF (5.59 mL, 0.10 M) under ambient atmosphere at room temperature for 15 min. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with $CH_2Cl_2/MeOH$ (49:1, 10 mL). The solvent was removed by rotary evaporation and the resulting oil was redissolved in $Et_2O/MeOH$ (4:1, 5.59 mL) and cooled to 0° C under an argon atmosphere. Trimethylsilyldiazomethane (1.12 mL, 2.0 M in hexanes, 2.24 mmol) was added dropwise and the reaction was stirred for 1 h at 0° C. The solvent was then removed by rotary evaporation, and the residue was purified by

flash chromatography (4:1 hexanes/EtOAc eluent) affording furan **44** (21.6 mg, 23% yield, R_f = 0.68 in 1:1 hexanes/EtOAc) as a colorless oil.

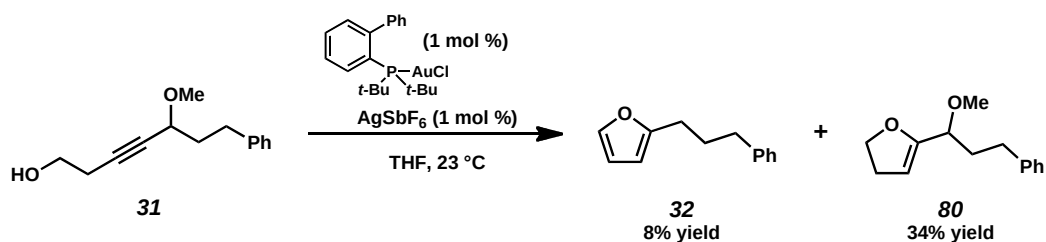
Furan 44: Spectroscopic data matched that previously reported.⁵⁵

2.7.5 Hydroalkoxylation Experiments

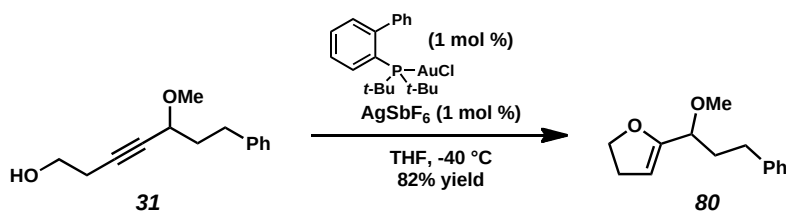


Homopropargylic alcohol **31** (21.8 mg, 0.100 mmol) was stirred in THF (1.00 mL, 0.10 M) under an ambient atmosphere at $-50\text{ }^\circ\text{C}$. $[(C_2H_4)PtCl_2]_2$ (0.9 mg, 0.0015 mmol) was added, and the reaction was maintained at $-50\text{ }^\circ\text{C}$ for 10 h. The reaction was quenched with Et_3N (approx. 75 μL) and filtered through a plug of silica gel (0.5 x 1 cm), washing with EtOAc/hexanes (1:1, 5 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/ Et_2O eluent) to afford furan **32** (6.4 mg, 34% yield), vinyl ether **80** (6.2 mg, 28% yield, R_f = 0.39 in 9:1 hexanes/EtOAc), and alcohol **31** (3.8 mg, 17% recovered) as colorless oils.

Vinyl ether 80: ^1H NMR (400 MHz, C_6D_6) δ 7.14-7.09 (comp m, 4H), 7.07-7.02 (m, 1H), 4.69 (t, J = 2.0 Hz, 1H), 4.03 (td, J = 9.4, 1.6 Hz, 2H), 3.69-3.64 (m, 1H), 3.21 (s, 3H), 2.82-2.66 (comp m, 2H), 2.24 (t, J = 9.4 Hz, 2H), 2.21-2.03 (comp m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 157.6, 141.8, 128.2, 128.0, 125.4, 96.1, 75.9, 69.3, 56.0, 34.8, 31.4, 29.3; IR (film) 2926, 1662, 1496, 1197, 1107, 932 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(M + H)^+$ [$C_{14}H_{18}O_2 + H$] $^+$: 219.1385, found 219.1379.



To a flask containing $(t\text{-Bu})_2((o\text{-Ph})\text{C}_6\text{H}_4)\text{AuCl}$ (1.6 mg, 0.00300 mmol) and AgSbF_6 (1.0 mg, 0.00300 mmol) under an argon atmosphere was added THF (1.0 mL) and the mixture was stirred at room temperature for 10 min. A solution of homopropargylic alcohol **31** (65.4 mg, 0.300 mmol) in THF (2.00 mL, 0.10 M reaction concentration) was added dropwise. After 5 min the reaction was quenched with Et_3N (approx. 75 μL) and filtered through a plug of silica gel (0.5 x 1 cm), washing with EtOAc /hexanes (1:1, 5 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/ Et_2O eluent) to afford furan **32** (4.4 mg, 8% yield), and vinyl ether **80** (22.3 mg, 34% yield).



To a flask containing $(t\text{-Bu})_2((o\text{-Ph})\text{C}_6\text{H}_4)\text{AuCl}$ (10.6 mg, 0.0200 mmol) and AgSbF_6 (6.8 mg, 0.0200 mmol) under an argon atmosphere was added THF (15 mL) and the mixture was stirred at room temperature for 10 min. The solution was cooled to -40 °C and a solution of homopropargylic alcohol **31** (436 mg, 2.00 mmol) in THF (5.00 mL, 0.10 M reaction concentration) was added dropwise. After 2 h the reaction was quenched with Et_3N (approx. 150 μL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc /hexanes (1:1, 10 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash

chromatography (19:1 hexanes/Et₂O eluent) to afford vinyl ether **80** (356 mg, 82% yield) as a colorless oil.

2.7.6 Analysis of the Hydroalkoxylation Product as a Potential Intermediate

Table 2.5.5 (*reproduced*):

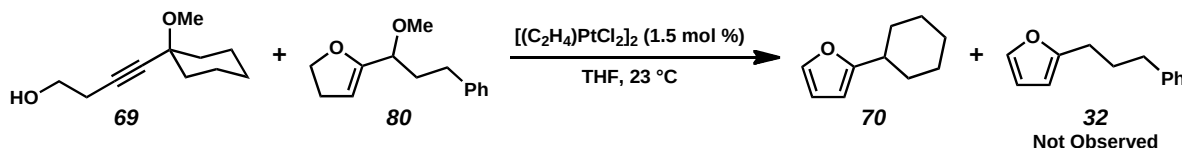
Reaction scheme: **80** $\xrightarrow[\text{THF, 23 } ^\circ\text{C}]{\text{catalyst}}$ **32**

Entry	Catalyst	Equiv	Time	Conversion (%) ^a	Yield 32 (%) ^a
1	silica gel	1.0	72 h	67	0
2	NH ₄ Cl	1.0	72 h	25	0
3	AcOH	1.0	72 h	37	0
4	CF ₃ CO ₂ H	1.0	10 min	100	0
5	HCl	1.0	10 min	100	0
6	TsOH	1.0	10 min	100	0
7	CSA	0.05	10 min	100	0
8	[(C ₂ H ₄)PtCl ₂] ₂	0.005	72 h	84	0
9	[(C ₂ H ₄)PtCl ₂] ₂ ^b	0.005	72 h	86	0
10	[(C ₂ H ₄)PtCl ₂] ₂	0.05	10 min	100	0
11	[(C ₂ H ₄)PtCl ₂] ₂ ^b	0.05	22 h	100	0
12	[(C ₂ H ₄)PtCl ₂] ₂ ^c	0.05	10 min	100	0

^a Determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Run with 1.1 equiv 2,6-di-*tert*-butylpyridine. ^c Run with 0.05 equiv CSA in reaction.

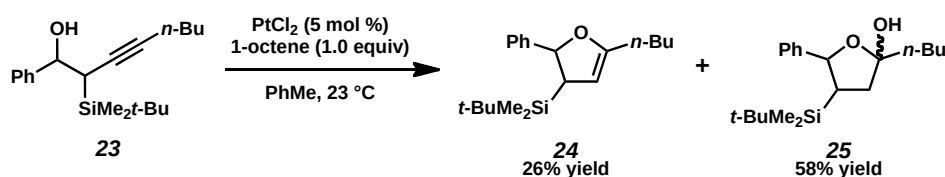
General procedure. To a solution of vinyl ether **80** (0.0400 mmol) in THF (0.400 mL, 0.10 M), under ambient atmosphere, was added a standard solution of 4,4'-di-*tert*-butyl biphenyl (32.0 μ L, 0.125 M in THF, 0.00400 mmol). To this was added the acid or [(C₂H₄)PtCl₂]₂ in the requisite amount and the reactions were stirred at room temperature. Upon consumption of starting material as determined by TLC, the reactions were quenched with Et₃N (14.0 μ L, 0.100 mmol) and filtered through a plug of SiO₂ (0.5 x 0.5 cm), washing with hexanes/EtOAc (1:1, 2.0 mL). The resulting filtrate was injected directly onto a GC to determine the conversions/yields. GC Conditions: Column- Agilent Technologies CP-Sil 8 CB (15 x 0.25), 1.0 mL/min carrier gas

Method: 100 °C for 18 min., warm to 180 °C over 4 min., 180 °C for 20 min. Furan R_F = 20.1 min, standard R_F = 31.8 min. The dihydrofuran integration values were multiplied by 1.84 to correct for the response differences. The furan integration values were multiplied by 1.86 to correct for the response differences.



To a solution of alcohol **69** (0.0400 mmol) and vinyl ether **80** (0.0400 mmol) in THF (0.400 mL, 0.10 M), under ambient atmosphere, was added $[(C_2H_4)PtCl_2]_2$ (0.000600 mmol) and the reaction was stirred at room temperature. Upon consumption of starting material as determined by TLC, the reaction was quenched with Et_3N (14.0 μ L, 0.100 mmol) and filtered through a plug of SiO_2 (0.5 x 0.5 cm), washing with hexanes/EtOAc (1:1, 2.0 mL). The solvent was removed by rotary evaporation and the crude residue was analyzed by ^1H NMR.

2.7.7 Early Experiments



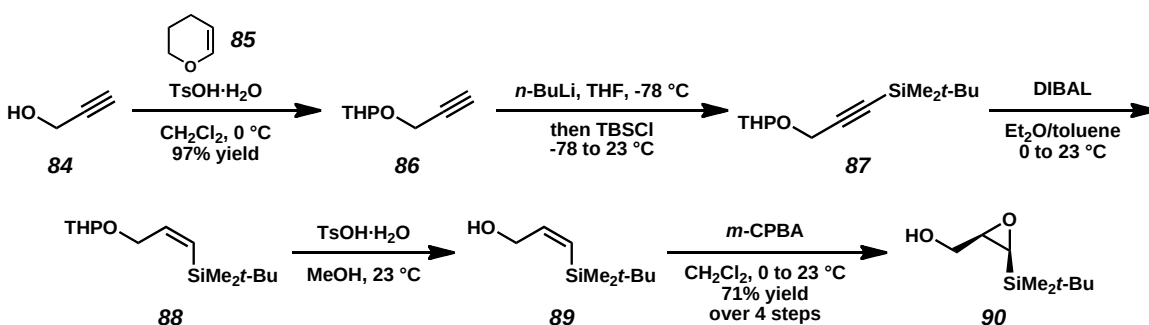
A solution of alcohol **23** (0.126 g, 0.400 mmol) in PhMe (2.00 mL, 0.2 M) was degassed with argon via bubbling for 10 min. 1-octene (0.125 mL, 0.800 mmol) was added followed by $PtCl_2$ (5.3 mg, 0.0200 mmol) and the reaction was stirred at 23 °C for 16 h. Upon completion, the reaction was filtered through a SiO_2 plug (0.5 x 3.0 cm), washing with EtOAc (5.0 mL). The solvent was removed by rotary evaporation and the recovered residue was purified by flash

chromatography (9:1 hexanes/EtOAc eluent) to afford dihydrofuran **24** (33.0 mg, 26% yield, R_f = 0.68 in 9:1 hexanes/EtOAc) and hemiacetal **25** (77.0 mg, 2:1 mixture of diastereomers, 58% yield, R_f = 0.12 in 9:1 hexanes/EtOAc) as colorless oils.

Dihydrofuran 24: ^1H NMR (300 MHz, CDCl_3) δ 7.62-7.59 (m, 1H), 7.48-7.42 (m, 1H), 7.40-7.24 (comp m, 3H), 5.40 (d, J = 7.2 Hz, 1H), 4.54-4.52 (m, 1H), 2.40-2.34 (m, 1H), 2.19 (app. t, J = 7.2 Hz, 2H), 1.61-1.26 (comp m, 4H), 0.96-0.88 (comp m, 9H), 0.83-0.74 (comp m, 3H) 0.03- -0.04 (comp m, 6H).

Hemiacetal 25: ^1H NMR (300 MHz, CDCl_3) δ 7.54-7.51 (m, 1.3H), 7.43-7.40 (m, 0.7H), 7.24-7.07 (comp m, 3H), 5.40 (d, J = 10.8 Hz, 0.3H), 4.92 (d, J = 10.5 Hz, 0.7H), 2.34-2.14 (comp m, 2H), 2.09 (br s, 1H), 1.86-1.66 (comp m, 2H), 1.56-1.39 (comp m, 2H), 1.36-1.21 (comp m, 2H), 0.93-0.85 (comp m, 3H), 0.79 (s, 3H), 0.76 (s, 6H), 0.06 (s, 1H), -0.08 (s, 2H), -0.27 (s, 1H), -0.30 (s, 2H).

2.7.8 Substrate Synthesis



To a solution of propargyl alcohol (**84**, 8.86 mL, 150 mmol) in CH_2Cl_2 (300 mL, 0.5 M) at 0°C was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.300 g, 1.50 mmol), followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 14.3 mL, 158 mmol). After stirring at 0°C for 5 min the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NaHCO_3 (100 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL), and the

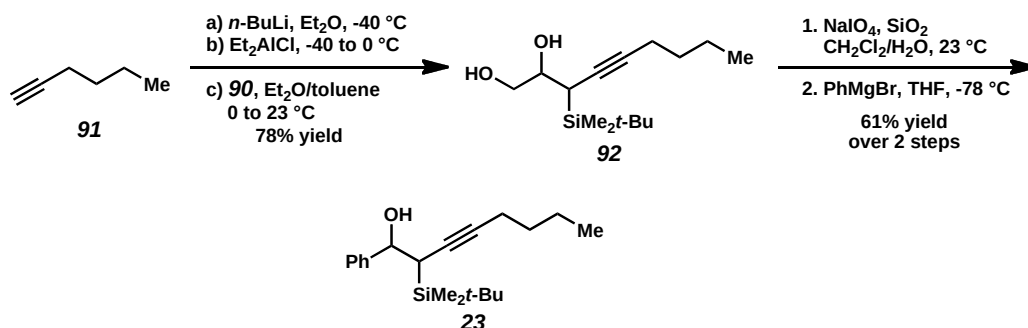
combined organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, affording acetal **86** (20.5 g, 97% yield, $R_f = 0.28$ in 9:1 hexanes/EtOAc) as a yellow oil.

To a solution of acetal **86** (5.60 g, 40.0 mmol) in THF (40.0 mL, 1.00 M) at -78°C under argon was added *n*-BuLi (16.8 mL, 2.5 M in hexanes, 42.0 mmol), and the resulting solution was stirred for 30 min at -78°C . A solution of TBSCl (6.33 g, 42.0 mmol) in THF (10.0 mL, 4.2 M) was then added, and the reaction was stirred at -78°C for 1 h, then warmed to room temperature and stirred for 3 h. The reaction was quenched with water (50 mL) and stirred for 15 min. The mixture was diluted with Et_2O (100 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (50 mL), and the combined organic phases were washed with brine (50 mL) and dried over MgSO_4 . The solution was concentrated in vacuo, affording the crude silane (**87**, 10.1 g, $R_f = 0.52$ in 9:1 hexanes/EtOAc) as a yellow oil.

To a solution of crude silane **87** (10.1 g) dissolved in diethyl ether (20.0 mL, 2.00 M) at 0°C under argon was added DIBAL-H (44.0 mL, 1.0 M in toluene, 44.0 mmol). The reaction was warmed to room temperature and stirred for 20 h. The reaction was poured into 1.0 N HCl (100 mL) cooled to 0°C in ice and stirred until the solution became clear. The layers were separated, and the aqueous phase was extracted with Et_2O (50 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed via rotary evaporation, affording crude alkene **88** (9.90 g, $R_f = 0.53$ in 9:1 hexanes:EtOAc) as a pale yellow oil.

To a solution of crude alkene **88** (9.90 g) dissolved in MeOH (80.0 mL, 0.50 M) was added TsOH•H₂O (76.0 mg, 0.0400 mmol), and the reaction was stirred at room temperature for 4 h. The reaction was quenched with sat. aq. NaHCO₃ (100 mL), and the resulting mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation, affording crude alcohol **89** (6.71 g, *R_f* = 0.48 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of crude alcohol **89** (6.71 g) in CH₂Cl₂ (160 mL, 0.25 M) at 0 °C was added *m*CPBA (13.4 g, 77% by wt., 60.0 mmol), and the reaction was slowly warmed to room temperature and stirred for 3 h. The reaction was quenched with sat. aq. Na₂S₂O₃ (100 mL) and stirred for 30 min. Sat. aq. NaHCO₃ (150 mL) was then added, and the solution was stirred for an additional 30 min. The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (100 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The recovered residue was purified by flash chromatography (9:1 → 1:1 hexanes/EtOAc eluent), affording epoxide **90** (5.37 g, 71% yield over 4 steps, *R_f* = 0.38 in 2:1 hexanes/EtOAc) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 3.87 (dd, *J* = 12.0, 2.9 Hz, 2H), 3.51 (d, *J* = 11.7 Hz, 1H), 3.48 (d, *J* = 11.7 Hz, 1H), 3.37 (m, 1H), 2.41 (d, *J* = 5.1 Hz, 1H), 0.96 (s, 9H), 0.08 (app. d, 6H).

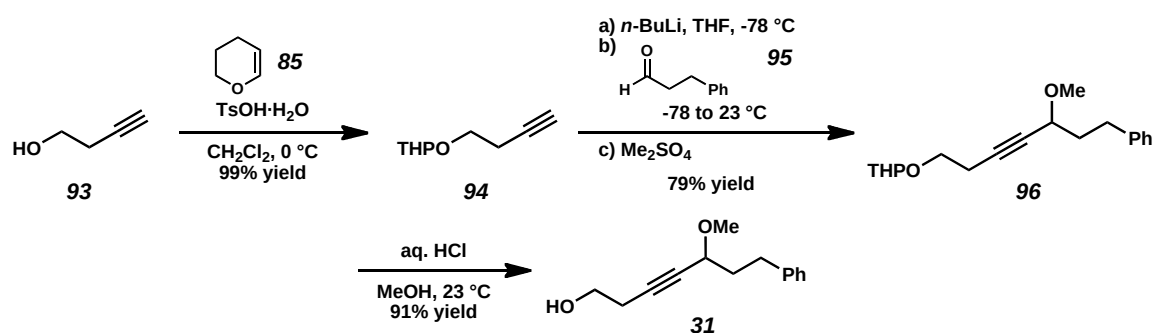


To a solution of 1-hexyne (**91**, 5.43 mL, 48.3 mmol) in Et₂O (12.0 mL, 4.0 M) at -40 °C under argon was added *n*-BuLi (19.3 mL, 2.5 M in hexanes, 48.3 mmol), and the reaction was stirred for 30 min. To this solution was added Et₂AlCl (26.8 mL, 1.8 M solution in toluene, 48.3 mmol) dropwise, and the resulting solution was stirred at -40 °C for 15 minutes, and then was warmed to 0 °C and stirred for 15 min. The reaction was cooled to -40° C, and a solution of epoxide **90** (3.03 g, 16.1 mmol) in toluene (100.0 mL, 0.16 M) was added over 10 min. The reaction was slowly warmed to room temperature and stirred for 18 h. The reaction was cooled to 0 °C, and water was cautiously added. Once gas evolution ceased, the mixture was diluted with 1 N HCl (100 mL) and stirred for 30 min. The phases were separated, and the aqueous phase was extracted with Et₂O (100 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The recovered oil was purified by flash chromatography (4:1 → 1:1 hexanes/EtOAc eluent), affording glycol **92** (3.39 g, 78% yield, *R*_f = 0.40 in 2:1 hexanes/EtOAc) as a colorless oil.

To a suspension of silica gel (10.0 g) stirred vigorously in CH₂Cl₂ (80 mL, 0.060 M) was added a solution of NaIO₄ (1.39 g, 6.50 mmol) in water (10.0 mL, 0.65 M), and the mixture was stirred until a fine dispersion was formed. To this was added a solution of glycol **92** (1.35 g, 5.00 mmol) in CH₂Cl₂ (10.0 mL, 0.50 M), and the reaction was stirred at room temperature for 1 h.

The reaction was then filtered, and the solid was washed with CH₂Cl₂ (50 mL). The filtrate was concentrated in vacuo, and half of the recovered clear oil was dissolved in Et₂O (12.0 mL, 0.20 M) and cooled to -78 °C under argon. Phenylmagnesium bromide (1.25 mL, 3.0 M in Et₂O, 3.75 mmol) was added, and the reaction was stirred at -78 °C 1 h. The reaction was quenched with 1 N HCl (10 mL) and warmed to room temperature. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were dried over MgSO₄ and concentrated in vacuo. The recovered oil was purified by flash chromatography (9:1 → 3:1 hexanes/EtOAc eluent), affording alcohol **23** (0.481 g, 61% yield (based on 2.5 mmol of glycol) over 2 steps, *R*_f = 0.42 in 9:1 hexanes/EtOAc) as a colorless oil.

β-Hydroxypropargylsilane 23: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.25 (comp m, 5H), 4.81 (dd, *J* = 8.4, 3.3 Hz, 1H), 2.61 (d, *J* = 8.4 Hz, 1H), 2.26 (m, 1H), 2.17 (td, *J* = 6.6, 2.2 Hz, 2H), 1.50-1.25 (comp m, 4H), 0.97 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.14 (s, 3H), 0.04 (s, 3H).



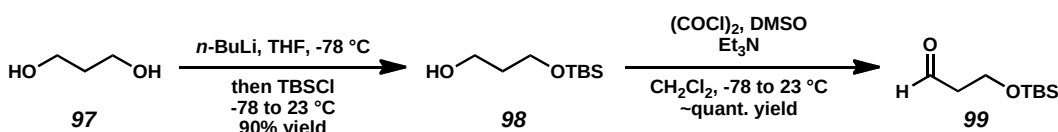
To a solution of 3-butyn-1-ol (**93**, 7.57 mL, 100 mmol) in CH₂Cl₂ (100 mL, 1.0 M) at 0 °C was added TsOH·H₂O (0.190 g, 1.00 mmol) followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 9.52 mL, 105 mmol). After stirring at 0 °C for 5 min, the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated NaHCO₃ (50 mL),

and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (50 mL), and the combined organic layers were dried over MgSO₄ and concentrated in vacuo, affording acetal **94** (15.3 g, 99% yield, R_f = 0.31 in 9:1 hexanes/EtOAc) as pale yellow oil.

To a solution of acetal **94** (1.54 g, 10.0 mmol) in THF (40.0 mL, 0.25 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min at -78 °C. Hydrocinnamaldehyde (**95**, 1.32 mL, 10.0 mmol) was then added, and the reaction was stirred at -78° C for 1 h, then warmed to room temperature and stirred for 2 h. Me₂SO₄ (0.945 mL, 13.0 mmol) was added, and the reaction was stirred for 12 h at room temperature. The reaction mixture was quenched with 1 M NaOH (20 mL) and stirred for 15 min. The mixture was then diluted with Et₂O (40 mL) and the layers were separated. The aqueous phase was extracted with Et₂O (20 mL) and the combined organic phases were washed with brine (40 mL) and dried over MgSO₄. The solution was concentrated in vacuo, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **96** (2.39 g, 79% yield, R_f = 0.64 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **96** (2.39 g, 7.90 mmol) in MeOH (80.0 mL, 0.10 M) was added 3 N HCl (approx. 125 µL), and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) to afford alcohol **31** (1.57 g, 91% yield, R_f = 0.25 in 2:1 hexanes/EtOAc) as a colorless oil.

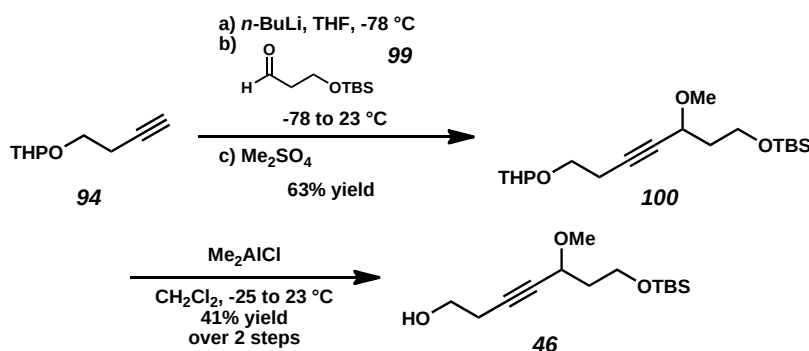
Homopropargylic alcohol 31: ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.25 (comp m, 2H), 7.20-7.18 (comp m, 3H), 3.90 (t, $J = 6.2$ Hz, 1H), 3.72 (t, $J = 6.2$ Hz, 2H), 3.39 (s, 3H), 2.76 (t, $J = 7.0$ Hz, 2H), 2.52 (td, $J = 6.2, 1.6$ Hz, 2H), 2.08-1.92 (comp m, 2H), 1.91-1.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 128.8, 128.7, 126.2, 83.4, 81.1, 70.8, 61.4, 56.7, 37.7, 31.8, 23.5; IR (film) 3385, 2934, 2228, 1603, 1338, 750 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{NH}_4)^+$ [$\text{C}_{14}\text{H}_{18}\text{O}_2 + \text{NH}_4$] $^+$: 236.1645, found 236.1642.



To a solution of 1,3-propanediol (**97**, 1.44 mL, 20.0 mmol) in THF (40.0 mL, 0.50 M) at -78°C under argon was added $n\text{-BuLi}$ (8.00 mL, 2.5 M in hexanes, 20.0 mmol), and the resulting solution was stirred for 30 min at -78°C . A solution of TBSCl (3.01 g, 20.0 mmol) in THF (2.00 mL) was added rapidly, and the resulting mixture was stirred at -78°C for 10 min, and then warmed to room temperature and stirred for 3 h. The reaction was diluted with water (50 mL) and extracted with Et_2O (50 mL). The aqueous phase was extracted with Et_2O (50 mL) and the combined organic layers were washed with brine and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording silyl ether **98** (3.43 g, 90% yield, $R_f = 0.40$ in 4:1 hexanes/ EtOAc) as a clear oil.

To a solution of oxalyl chloride (1.00 mL, 16.5 mmol) in CH_2Cl_2 (100 mL, 0.17 M) at -78°C under argon was added DMSO (2.34 mL, 33.0 mmol) dropwise. The solution was stirred at -78°C for 10 min. A solution of alcohol **98** (2.85 g, 15.0 mmol) in CH_2Cl_2 (7.50 mL) was then added slowly, and the reaction was stirred at -78°C for 1 h. Et_3N (10.5 mL, 75.0 mmol) was

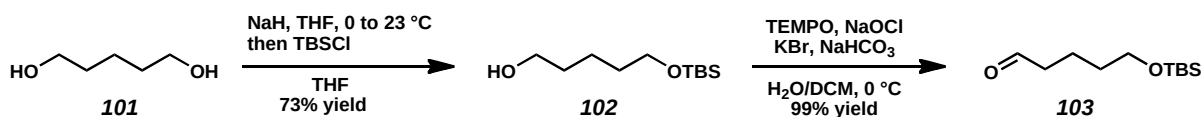
then added, and the reaction mixture was maintained at -78 °C for 10 min before being warmed to room temperature and stirred for 30 min. The reaction was then quenched with water (100 mL), and the phases were separated. The organic layer was washed sequentially with 1 N HCl (100 mL), sat. aq. NaHCO₃ (100 mL), and brine (100 mL), and was dried over MgSO₄. The solvent was removed via rotary evaporation, affording aldehyde **99** (2.79 g crude) as an amber oil.



To a solution of alkyne **94** (2.31 g, 15.0 mmol) in THF (45.0 mL, 0.33 M) at -78° C under argon was added *n*-BuLi (6.00 mL, 2.5 M in hexanes, 15.0 mmol), and the resulting solution was stirred for 30 minutes at -78 °C. Aldehyde **99** (assume 15.0 mmol) was then added, and the reaction was stirred at -78 °C for 2 h. Me₂SO₄ (1.70 mL, 18.0 mmol) was added, and the reaction was warmed to room temperature and stirred for 14 h. The reaction was quenched with 1 M NaOH (30 mL) and stirred for 15 min. The reaction was diluted with Et₂O (50 mL), and the layers were separated. The aqueous was extracted with Et₂O (50 mL), and the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **100** (3.37 g, 63% yield over 2 steps, *R*_f = 0.51 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **100** (0.748 g, 2.10 mmol) in CH₂Cl₂ (21.0 mL, 0.10 M) at -25 °C under argon was added Me₂AlCl (4.20 mL, 1.0 M in hexanes, 4.20 mmol). The reaction was maintained at -25 °C for 20 min, then warmed to room temperature and stirred for 3 h. The reaction was slowly quenched with sat. aq. NaHCO₃ (10 mL), and the resulting mixture was extracted with Et₂O (2 x 20 mL). The combined organic phases were dried over MgSO₄, and the solution was concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), affording alcohol **46** (0.237 g, 41% yield, *R_f* = 0.21 in 4:1 hexanes/EtOAc) as a colorless oil.

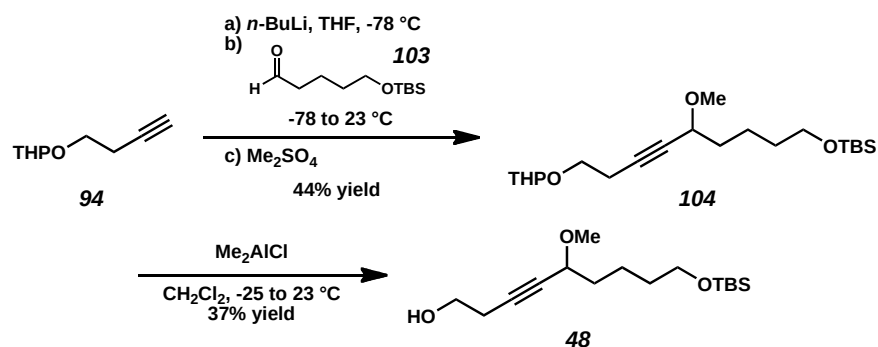
Homopropargylic alcohol 46: ¹H NMR (400 MHz, CDCl₃) δ 4.12 (m, 1H), 3.76-3.71 (comp m, 4H), 3.39 (s, 3H), 2.51 (td, *J* = 6.3, 2.0 Hz, 2H), 1.98-1.79 (comp m, 2H), 1.69 (s, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 83.0, 81.4, 68.5, 61.5, 59.5, 56.8, 39.3, 26.3, 23.5, 18.7, -5.0; IR (film) 3372, 2932, 2361, 1467, 1104, 837 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₄H₂₈O₃Si + H]⁺: 273.1880, found 273.1886.



To a solution of 1,5-pentanediol (**101**, 5.41 g, 52.0 mmol) in THF (346 mL, 0.15 M) at 0 °C was added NaH (1.60 g, 60% dispersion in mineral oil, 40.0 mmol). The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 2 h. TBSCl (6.03 g, 40.0 mmol) was then added and the solution was stirred at ambient temperature for 12 h. The reaction mixture was poured into water (300 mL) and extracted with Et₂O (2 x 200 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The

resulting residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent), producing alcohol **102** (6.39 g, 73% yield, R_f = 0.27 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **102** (4.06 g, 18.6 mmol) in CH_2Cl_2 (46.0 mL, 0.4 M) at 0 °C was added TEMPO (29.0 mg, 0.186 mmol). A solution of KBr (2.43 g, 20.5 mmol) in 5% aq. NaHCO_3 (93.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (11.8 mL, 10% aq., 19.0 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with H_2O (50 mL) and brine (50 mL). The organic phase was dried over MgSO_4 , and the solvent was removed by rotary evaporation, affording aldehyde **103** (3.98 g, 99% yield, R_f = 0.64 in 4:1 hexanes/EtOAc) as a colorless oil.⁵⁷

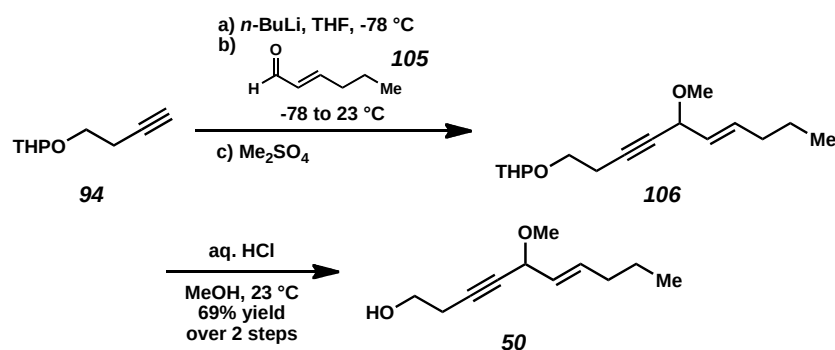


To a solution of alkyne **94** (1.62 g, 10.5 mmol) in THF (31.5 mL, 0.33 M) at -78 °C under argon was added $n\text{-BuLi}$ (4.20 mL, 2.5 M in hexanes, 10.5 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (2.28 g, 10.5 mmol) was then added, and the reaction was stirred at -78 °C for 2 h. Me_2SO_4 (1.19 mL, 12.6 mmol) was added, and the reaction was warmed to room temperature and stirred for 12 h. The reaction was quenched with 1 M NaOH

(30 mL) and stirred for 15 min. The reaction was diluted with Et₂O (30 mL), and the layers were separated. The aqueous was extracted with Et₂O (30 mL), and the combined organic layers were washed with brine (30 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **104** (1.77 g, 44% yield, *R_f* = 0.55 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **104** (0.845 g, 2.20 mmol) in CH₂Cl₂ (20.0 mL, 0.10 M) at -25 °C under argon was added Me₂AlCl (4.20 mL, 1.0 M in hexanes, 4.40 mmol). The reaction was maintained at -25 °C for 20 min, then warmed to room temperature and stirred for 3 h. The reaction was slowly quenched with sat. aq. NaHCO₃ (10 mL) and the resulting mixture was extracted with Et₂O (2 x 20 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), affording alcohol **48** (0.247 g, 37% yield, *R_f* = 0.24 in 4:1 hexanes/EtOAc) as a colorless oil.

Homopropargylic alcohol 48: ¹H NMR (400 MHz, CDCl₃) δ 3.93 (tt, *J* = 6.2, 2.0 Hz, 1H), 3.72 (t, *J* = 6.3 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.38 (s, 3H), 2.51 (td, *J* = 6.3, 2.0 Hz, 2H), 1.75-1.65 (comp m, 3H), 1.56-1.43 (comp m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 83.0, 81.4, 71.7, 63.4, 61.5, 56.7, 35.9, 32.9, 26.3, 23.5, 22.0, 18.7, -4.9; IR (film) 3385, 2934, 2236, 1779, 1255, 837 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₆H₃₂O₃Si + H]⁺: 301.2193, found 301.2204.

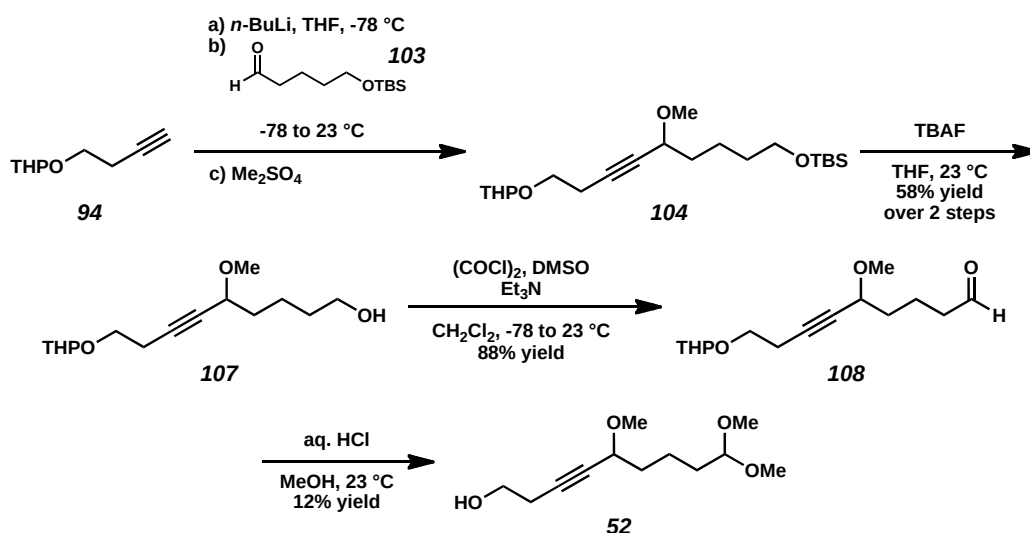


To a solution of alkyne **94** (1.54 g, 10.0 mmol) in THF (40.0 mL, 0.25 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min at -78 °C. *Trans*-2-hexenal (**105**, 1.16 mL, 10.0 mmol) was then added, and the reaction was stirred at -78 °C for 1 h, then warmed to room temperature and stirred for 2 h. Me₂SO₄ (1.04 mL, 11.0 mmol) was added, and the resulting mixture was stirred for 15 h at room temperature. The reaction was quenched with 1 M NaOH (20 mL) and stirred for 15 min. The mixture was then diluted with Et₂O (40 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solution was concentrated in vacuo, and the resulting crude ether (**106**, 2.65 g, *R*_f = 0.53 in 4:1 hexanes/EtOAc) was used immediately in the subsequent transformation.

To a solution of crude ether **106** (2.65 g, 10.0 mmol) in MeOH (100 mL, 0.10 M) at 23 °C was added 1 N HCl (approx. 75 μL), and the reaction mixture was stirred for 3 h. The reaction was then quenched with sat. aq. NaHCO₃ (50 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (9:1 →

2:1 hexanes/EtOAc eluent) to afford alcohol **50** (1.25 g, 69% yield over 2 steps, R_f = 0.33 in 2:1 hexanes/EtOAc) as a pale yellow oil.

Homopropargylic alcohol 50: ^1H NMR (400 MHz, CDCl_3) δ 5.88-5.81 (m, 1H), 5.52-5.46 (m, 1H), 4.42 (d, J = 5.5 Hz, 1H), 3.72 (t, J = 6.3 Hz, 2H), 3.34 (s, 3H), 2.53 (td, J = 6.2, 1.5 Hz, 2H), 2.10-2.01 (comp m, 2H), 1.95 (s, 1H), 1.42 (sextet, J = 7.4 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.5, 127.5, 84.2, 79.9, 71.9, 61.4, 55.7, 34.4, 23.6, 22.4, 14.0; IR (film) 3422, 2959, 2242, 1669, 1464 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{11}\text{H}_{18}\text{O}_2 + \text{H}$] $^+$: 183.1380, found 183.1382.



To a solution of alkyne **94** (2.65 g, 17.2 mmol) in THF (50.0 mL, 0.34 M) at -78°C under argon was added $n\text{-BuLi}$ (6.90 mL, 2.5 M in hexanes, 17.2 mmol), and the resulting solution was stirred for 30 min at -78°C . A solution of aldehyde **103** (3.72 g, 17.2 mmol) in THF (5.00 mL) was then added, and the reaction mixture was stirred at -78°C for 2 h. Me_2SO_4 (2.11 mL, 22.4 mmol) was added, and the reaction was stirred for 10 h at room temperature. The reaction was then quenched with 1 M NaOH (40 mL) and stirred for 15 min. The mixture was diluted with Et_2O (50 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (40

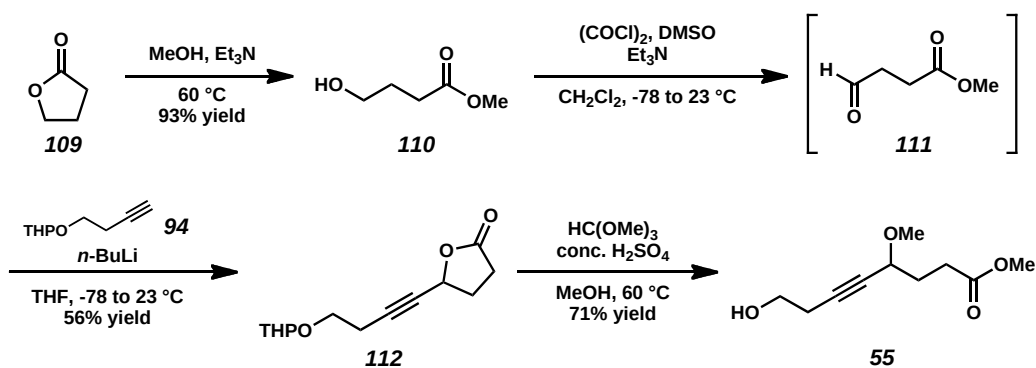
mL), and the combined organic phases were washed with brine (50 mL) and dried over MgSO₄. The solution was concentrated in vacuo, and the resulting crude ether (**104**, 6.90 g) was used immediately in the subsequent reaction without further purification.

To a solution of crude ether **104** (assume 17.2 mmol) in THF (50.0 mL, 0.34 M) at 23 °C was added TBAF (20.6 mL, 1.0 M in THF, 20.6 mmol), and the resulting mixture was stirred for 3 h. The reaction mixture was then diluted with Et₂O (50 mL) and washed with water (50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄, and concentrated in vacuo. The crude oil was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent), affording alcohol **107** (2.72 g, 58% yield over 2 steps, *R_f* = 0.18 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of oxalyl chloride (0.700 mL, 8.00 mmol) in CH₂Cl₂ (12.0 mL, 0.66 M) at -78 °C under argon was added DMSO (1.14 mL, 16.0 mmol) dropwise. The solution was stirred at -78 °C for 5 min. A solution of alcohol **107** (2.16 g, 8.00 mmol) in CH₂Cl₂ (4.0 mL) was then added slowly, and the reaction was stirred for 15 min. Et₃N (5.60 mL, 40.0 mmol) was then added, and the reaction was maintained at -78 °C for 15 min, and then warmed to room temperature and stirred for 30 min. The reaction was quenched with water (20 mL), and the phases were separated. The organic layer was washed sequentially with 1 N HCl (20 mL), sat. aq. NaHCO₃ (20 mL), and brine (20 mL), and then dried over MgSO₄. The solvent was removed via rotary evaporation, affording aldehyde **108** (1.89 g, 88% yield, *R_f* = 0.36 in 4:1 hexanes/EtOAc) as a pale yellow oil. The aldehyde was used immediately in the subsequent transformation without further purification.

To a solution of aldehyde **108** (1.89 g, 7.00 mmol) in MeOH (70.0 mL, 0.10 M) at 23 °C was added 3 N HCl (approx. 50 μ L), and the reaction was stirred for 3 h. The reaction was then quenched with sat. aq. NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, and the solution was concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 $\rightarrow$ 1:1 hexanes/EtOAc eluent, the silica was neutralized with Et₃N prior to loading), affording alcohol **52** (0.186 g, 12% yield with 0.529 g (41% yield) of the aldehyde recovered, R_f = 0.30 in 1:1 hexanes/EtOAc) as a colorless oil.

Homopropargylic alcohol 52: ¹H NMR (400 MHz, CDCl₃) δ 4.36 (t, J = 5.5 Hz, 1H), 3.93 (tt, J = 6.3, 2.0 Hz, 1H), 3.72 (app. q, J = 6.2 Hz, 2H), 3.38 (s, 3H), 3.31 (s, 6H), 2.50 (td, J = 6.3, 2.0 Hz, 2H), 1.95 (t, J = 6.3 Hz, 1H), 1.75-1.60 (comp m, 4H), 1.54-1.47 (comp m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 104.7, 83.3, 81.1, 71.6, 61.5, 56.7, 53.0 35.8, 32.5, 23.5, 20.8; IR (film) 3452, 2940, 2234, 1738, 1463, 951 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₁₂H₂₂O₄ + Na]⁺: 253.1410, found 253.1413.



To a solution of lactone **109** (0.760 mL, 10.0 mmol) in MeOH (50.0 mL, 0.20 M) was added Et₃N (8.40 mL, 60.0 mmol), and the reaction was heated to 60 °C and stirred for 15 h. The reaction was then cooled, diluted with hexanes (50 mL) and concentrated in vacuo. The residual

MeOH was removed azeotropically with hexanes (2 x 20 mL), affording alcohol **110** (1.10 g, 93% yield, R_f = 0.52 in 2:1 EtOAc/hexanes) as an amber oil.

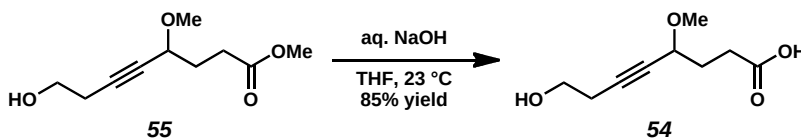
To a solution of oxalyl chloride (4.38 mL, 50.0 mmol) in CH_2Cl_2 (75.0 mL, 0.66 M) at -78°C under argon was added DMSO (7.10 mL, 100 mmol) dropwise. The solution was stirred at -78°C for 5 min, and then a solution of alcohol **110** (5.80 g, 50.0 mmol) in CH_2Cl_2 (20.0 mL) was added slowly, and the reaction was stirred for 15 min. Et_3N (35.1 mL, 250 mmol) was then added, and the reaction was maintained at -78°C for 15 min before being warmed to room temperature and stirred for 10 min. The reaction was quenched with water (100 mL), stirred for 20 min, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic layers were washed sequentially with 1 N HCl (50 mL), sat. aq. NaHCO_3 (50 mL), and brine (50 mL). The solution was dried over MgSO_4 , and the solvent was removed via rotary evaporation, affording aldehyde **111** (3.50 g, 61% yield) as a pale yellow oil. The aldehyde was used immediately in the subsequent transformation without further purification. ^1H NMR (300 MHz, CDCl_3) δ 9.81 (s, 1H), 3.69 (s, 3H), 2.81 (t, J = 6.2 Hz, 2H), 2.62 (t, J = 6.6 Hz, 2H).

To a solution of alkyne **94** (3.70 g, 24.0 mmol) in THF (160 mL, 0.15 M) at -78°C under argon was added $n\text{-BuLi}$ (9.60 mL, 2.5 M in hexanes, 24.0 mmol), and the resulting solution was stirred for 30 min at -78°C . A solution of aldehyde **111** (2.70 g, 24.0 mmol) in THF (5.00 mL) was then added, and the reaction was stirred at -78°C for 1 h, and then it was warmed to room temperature and stirred for 16 h. The reaction was quenched with water (40 mL) and stirred for 15 min. The mixture was diluted with Et_2O (100 mL), and the layers were separated. The

aqueous phase was extracted with 50 mL Et₂O, and the combined organic layers were washed with brine and dried over MgSO₄. The solution was concentrated in vacuo, and the resulting crude oil was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent), affording lactone **112** (3.11 g, 56% yield, *R_f* = 0.45 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of lactone **112** (0.803 g, 3.40 mmol) in MeOH (20.0 mL, 0.17 M) at 23 °C was added trimethyl orthoformate (0.743 mL, 6.80 mmol) followed by H₂SO₄ (approx. 25 μL, 98%). The reaction was heated to 60 °C and stirred for 12 h, and then it was cooled to room temperature. The reaction was quenched with sat. aq. NaHCO₃ (20 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude oil was purified by flash chromatography (9:1 → 3:2 hexanes/EtOAc eluent), affording alcohol **55** (0.480 g, 71% yield, *R_f* = 0.31 in 1:1 hexanes/EtOAc) as a colorless oil.

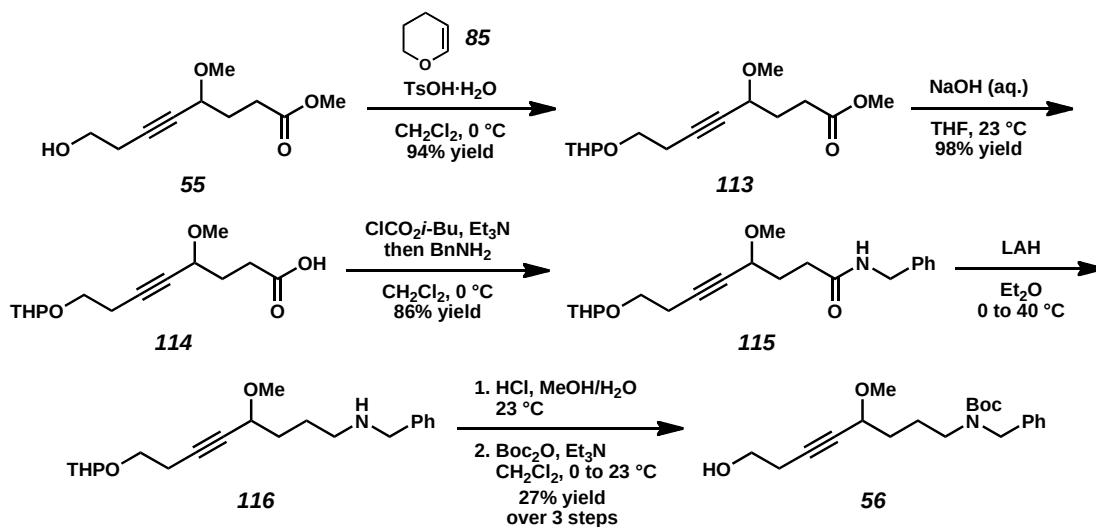
Homopropargylic alcohol 55: ¹H NMR (400 MHz, CDCl₃) δ 4.01 (tt, *J* = 6.0, 2.0 Hz, 1H), 3.71 (app. q, *J* = 6.2 Hz, 2H), 3.68 (s, 3H), 3.37 (s, 3H), 2.51-2.46 (comp m, 4H), 2.04-1.99 (comp m, 2H), 1.93 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 83.9, 80.3, 70.5, 61.4, 56.8, 52.0, 31.0, 30.1, 23.5; IR (film) 3468, 2951, 2248, 1790, 1184, 925 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₀H₁₆O₄ + H]⁺: 201.1121, found 201.1115.



To a solution of ester **55** (0.400 g, 2.00 mmol) in THF (10.0 mL, 0.20 M) at room temperature was added a 1 M solution of NaOH (6.00 mL, 6.00 mmol), and the resulting solution was stirred

for 6 h. The THF was then removed via rotary evaporation, and the remaining solution was acidified to pH $\sim$ 2.0 with 3 N HCl. The solution was then saturated with NaCl and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The resulting oil was purified by flash chromatography (99:1 CH₂Cl₂/MeOH eluent), affording acid **54** (0.316 g, 85% yield, R_f = 0.34 in 9:1 CH₂Cl₂/MeOH) as a colorless oil.

Homopropargylic alcohol 54: ¹H NMR (400 MHz, CDCl₃) δ 4.04 (tt, J = 6.2, 1.6 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 3.39 (s, 3H), 2.58-2.49 (comp m, 4H), 2.05 (q, J = 7.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 178.7, 84.2, 80.1, 70.5, 61.4, 56.8, 30.7, 30.0, 23.3; IR (film) 3265, 2234, 1716, 1102 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₉H₁₄O₄ + H]⁺: 187.0965, found 187.0964.



To a solution of alcohol **55** (1.09 g, 5.44 mmol) dissolved in CH₂Cl₂ (11.0 mL, 0.50 M) at 0 °C was added TsOH·H₂O (10.3 mg, 0.0544 mmol). To this mixture was added 3,4-dihydro-2H-pyran (**85**, 0.520 mL, 5.70 mmol), and the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NaHCO₃ (10 mL), and the phases were

separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, affording acetal **113** (1.45 g, 94% yield, $R_f = 0.71$ in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **113** (1.45 g, 5.10 mmol) in THF (25.0 mL, 0.2 M) was added a 1 M solution of NaOH (15.3 mL, 15.3 mmol), and the reaction was stirred for 20 h at room temperature. The reaction was acidified to pH $\sim$ 2 with 3 N HCl, and the mixture was saturated with NaCl. The solution was then extracted with CH_2Cl_2 (4 x 15 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed by rotary evaporation, affording acid **114** (1.35 g, 98% yield, $R_f = 0.47$ in 1:1 hexanes/EtOAc w/ 10% AcOH) as a colorless oil.

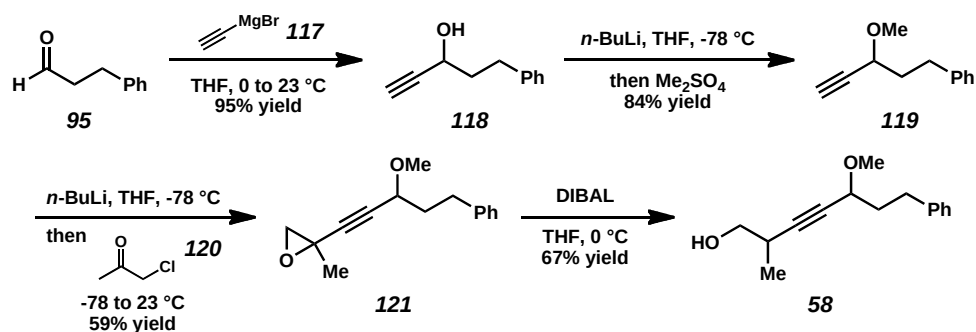
To a solution of acid **114** (1.35 g, 5.00 mmol) in CH_2Cl_2 (25.0 mL, 0.2 M) at 0 °C was added isobutyl chloroformate (0.654 mL, 5.00 mmol) followed by Et_3N (1.05 mL, 7.50 mmol). After 20 min, benzylamine (0.655 mL, 6.00 mmol) was added, and the reaction was warmed to room temperature. After 16 h the reaction was quenched with 1 N HCl (20 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (25 mL), and the combined organic phases were washed with sat. aq. NaHCO_3 (25 mL), dried over MgSO_4 , and concentrated in vacuo. The recovered residue was purified by flash chromatography (4:1 $\rightarrow$ 1:1 hexanes/EtOAc eluent), affording amide **115** (1.54 g, 86% yield, $R_f = 0.48$ in 1:2 hexanes/EtOAc) as a colorless oil.

To a suspension of LiAlH_4 (0.215 g, 5.69 mmol) in Et_2O (10.0 mL) at 0 °C was added a solution of amide **115** (0.511 g, 1.42 mmol) in Et_2O (5.00 mL). The reaction was heated to 40 °C for 4 h,

then cooled to 0 °C and quenched with H₂O (2.00 mL) and 1 M NaOH (4.00 mL). The suspension was filtered, and the filtrate was washed with Et₂O (10 mL). The filtrate was concentrated in vacuo, affording crude amine **116** (0.436 g, R_f = 0.15 in 9:1 CH₂Cl₂/MeOH plate neutralized with Et₃N prior to loading) as a colorless oil.

To a solution of crude amine **116** (0.436 g) in MeOH (20.0 mL, 0.070 M) was added 3 N HCl (0.500 mL, 1.50 mmol), and the reaction was stirred at room temperature for 6 h. The reaction was concentrated in vacuo and MeOH was removed azeotropically with PhMe (3 x 10 mL), producing a white semisolid. The residue was dissolved into CH₂Cl₂ (10.0 mL, 0.14 M), cooled to 0 °C, and neutralized with Et₃N (0.590 mL, 0.421 mmol). Di-*tert*-butyl dicarbonate (0.371 g, 1.70 mmol) was then added and the reaction was warmed to room temperature and stirred for 12 h. The reaction was quenched with sat. aq. NH₄Cl (15 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed via rotary evaporation, and the recovered oil was purified by flash chromatography (4:1 → 3:2 hexanes/EtOAc eluent), affording alcohol **56** (0.136 mg, 27% yield over 3 steps, R_f = 0.66 in 1:2 hexanes/EtOAc) as a colorless oil.

Homopropargylic alcohol 56: Line broadening in ¹H NMR due to presence of rotamers. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.29 (comp m, 2H), 7.25-7.19 (comp m, 3H), 4.43 (br s, 2H), 3.93 (br s, 1H), 3.72 (app. q, J = 6.3 Hz, 2H), 3.36 (s, 3H), 3.29-3.13 (br m, 2H), 2.49 (td, J = 6.2, 1.9 Hz, 2H), 1.64 (br m, 4H), 1.52-1.41 (br m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 191.8, 129.3, 128.8, 128.6, 127.4, 80.1, 71.4, 61.4, 56.7, 46.5, 33.0, 28.8, 23.5; IR (film) 3452, 2934, 2232, 1952, 1697, 1455, 879 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₂₁H₃₁NO₄ + H]⁺: 362.2326, found 362.2323.



To a solution of ethynylmagnesium bromide (**117**, 63.0 mL, 0.5 M in THF, 31.5 mmol) at 0 °C was added aldehyde **95** (3.97 mL, 30.0 mmol), and the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with 1 N HCl (40 mL) and extracted with Et₂O (2 x 50 mL). The combined organic layers were dried over MgSO₄, and the solution was concentrated in vacuo, affording alcohol **118** (4.58 g, 95% yield, *R_f* = 0.56 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **118** (4.58 g, 28.6 mmol) in THF (85.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (11.4 mL, 2.5 M in hexanes, 28.6 mmol), and the resulting solution was stirred for 30 min at -78 °C. Me₂SO₄ (2.97 mL, 31.5 mmol) was added, and the reaction was warmed to room temperature and stirred for 12 h. The reaction was quenched with 1 M NaOH (15 mL) and stirred for 15 min. The mixture was diluted with Et₂O (80 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (50 mL), and the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solution was concentrated in vacuo, and the resulting crude oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **119** (4.16 g, 84% yield, *R_f* = 0.44 in 9:1 hexanes/EtOAc) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.33-7.27 (comp m, 2H), 7.24-7.20 (comp m, 3H), 3.92 (td, *J* =

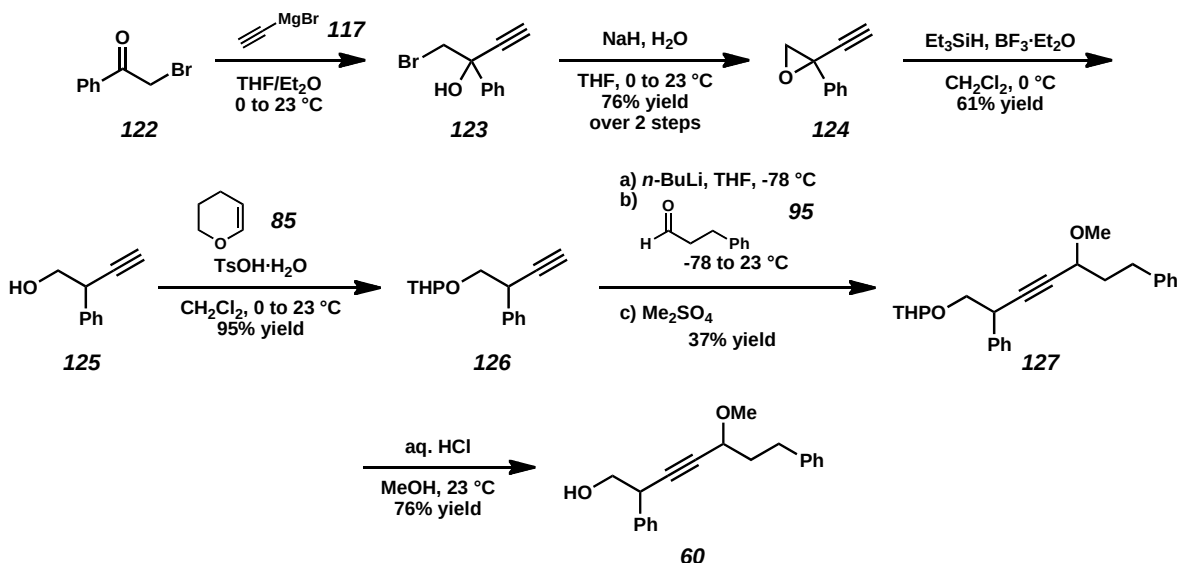
6.6, 2.0 Hz, 1H), 3.43 (s, 3H), 2.80 (t, $J = 7.3$ Hz, 2H), 2.49 (d, $J = 2.2$ Hz, 1H), 2.10-2.00 (comp m, 2H).

To a solution of ether **119** (1.74 g, 10.0 mmol) dissolved in THF (50.0 mL, 0.20 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min at -78 °C. Chloroacetone (**120**, 0.796 mL, 10.0 mmol) was then added, and the reaction was stirred at -78 °C for 1 h, then warmed to room temperature and stirred for 14 h. The reaction was quenched with water (50 mL), diluted with Et₂O (50 mL), and the layers were separated. The organic phase was washed with brine (50 mL), dried over MgSO₄, and concentrated in vacuo. The crude oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording epoxide **121** (1.36 g, 59% yield, $R_f = 0.56$ in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of epoxide **121** (1.09 g, 4.72 mmol) in THF (5.70 mL, 0.82 M) at 0 °C under argon was added DIBAL-H (5.70 mL, 1.0 M in hexanes, 5.70 mmol), and the reaction was warmed to room temperature and stirred for 4 h. The reaction was quenched with water (5 mL) and diluted with Et₂O (20 mL). The mixture was then washed with 1 N HCl (20 mL), then brine (20 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude oil was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent), affording alcohol **58** (0.740 g, 67% yield, $R_f = 0.36$ in 2:1 hexanes:EtOAc) as a pale yellow oil.

Homopropargylic alcohol 58: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 3.92 (td, $J = 6.7, 1.6$ Hz, 1H), 3.60-3.53 (comp m, 2H), 3.39 (s, 3H), 2.79-2.71 (comp m, 2H), 2.07-1.93 (comp m, 2H), 1.73 (s, 1H),

1.19 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 128.9, 128.7, 126.3, 88.3, 81.1, 70.8, 67.2, 56.6, 37.8, 31.8, 29.9, 17.5; IR (film) 3418, 2935, 2733, 1948, 1455, 1105 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{15}\text{H}_{20}\text{O}_2 + \text{H}$] $^+$: 233.1536, found 233.1536.



To a solution of ethynylmagnesium bromide (**117**, 63.0 mL, 0.5 M in THF, 31.5 mmol) at 0 °C was added a solution of 2-bromoacetophenone (**122**, 5.97 g, 30.0 mmol) in Et_2O (40.0 mL, 0.78 M) dropwise via addition funnel. The reaction was then warmed to room temperature and stirred for 1.5 h. The reaction was quenched with water (30 mL) and diluted with Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (30 mL). The combined organic phases were washed sequentially with 1 N HCl (40 mL), saturated NaHCO_3 (40 mL), and brine (40 mL), and then dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude alcohol **123** (8.13 g, $R_f = 0.37$ in 4:1 hexanes/ EtOAc) as a brown oil.

To a solution of crude alcohol **123** (8.13 g) in THF (200 mL, 0.15 M) at 0 °C was slowly added NaH (1.44 g, 60% dispersion on mineral oil, 36.0 mmol), followed by water (0.540 mL, 30.0 mmol). Once gas evolution ceased, the reaction was warmed to room temperature and stirred for 30 min. The reaction was quenched with saturated NH₄Cl (100 mL), and the organic solvent was removed via rotary evaporation. The aqueous mixture was extracted with Et₂O (2 x 50 mL), and the combined organic phases were dried over MgSO₄ and concentrated in vacuo. The recovered oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording epoxide **124** (3.27 g, 76% yield over 2 steps, R_f = 0.51 in 4:1 hexanes/EtOAc) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.53-7.48 (comp m, 2H), 7.40-7.32 (comp m, 3H), 3.43 (d, J = 5.9 Hz, 1H), 3.03 (d, J = 5.9 Hz, 1H), 2.53 (s, 1H).

To a solution of epoxide **124** (3.00 g, 20.8 mmol) in CH₂Cl₂ (200 mL, 0.10 M) at 0 °C was added Et₃SiH (4.48 mL, 31.2 mmol). BF₃•Et₂O (2.57 mL, 20.8 mmol) was then added, and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with saturated NaHCO₃ (100 mL). The layers were separated, and the aqueous phase was extracted with CH₂Cl₂ (50 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The recovered oil was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent), affording alcohol **125** (2.16 g, 71% yield, R_f = 0.21 in 4:1 hexanes/EtOAc) as a brown oil.

To a solution of alcohol **125** (2.16 g, 14.7 mmol) in CH₂Cl₂ (30.0 mL, 0.50 M) at 0 °C was added TsOH•H₂O (28.0 mg, 0.147 mmol) followed by 3,4-dihydro-2*H*-pyran (**85**, 1.24 mL, 15.5 mmol). The reaction was warmed to room temperature and stirred for 1 h. The reaction was

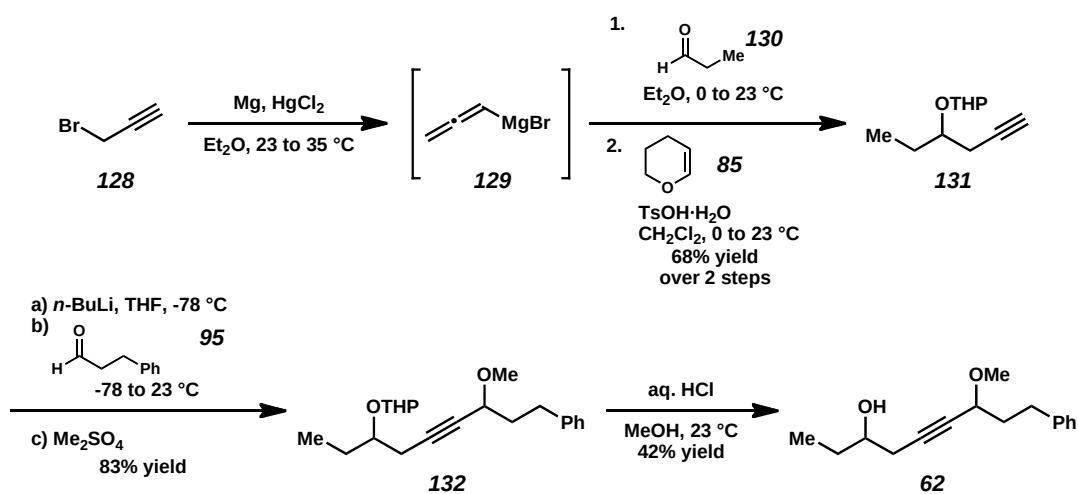
quenched with saturated NaHCO_3 (30 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (30 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, affording acetal **126** (3.27 g, 97% yield, R_f = 0.48 in 4:1 hexanes/EtOAc) as a brown oil.

To a solution of acetal **126** (0.897 g, 3.90 mmol) in THF (20.0 mL, 0.20 M) at -78°C under argon was added *n*-BuLi (1.56 mL, 2.5 M in hexanes, 3.90 mmol), and the resulting solution was stirred for 30 min at -78°C . Hydrocinnamaldehyde (**95**, 0.515 mL, 3.90 mmol) was then added, and the reaction was stirred at -78°C for 1 h, then warmed to room temperature and stirred for 2 h. Me_2SO_4 (0.455 mL, 4.70 mmol) was added, and the reaction was stirred for 10 h at room temperature. The reaction was quenched with 1 M NaOH (10 mL), and was stirred for 15 min. The mixture was diluted with Et_2O (20 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **127** (0.541 g, 37% yield, R_f = 0.48 in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of ether **127** (0.541 g, 1.44 mmol) in MeOH (10.0 mL, 0.14 M) was added 3 N HCl (approx. 25 μL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with saturated NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered oil was purified by flash chromatography (6:1 $\rightarrow$ 3:1

hexanes/EtOAc eluent), affording alcohol **60** (0.321 g, 76% yield, $R_f = 0.45$ in 2:1 hexanes/EtOAc) as a pale yellow oil.

Homopropargylic alcohol 60: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.35 (comp m, 4H), 7.33-7.28 (comp m, 3H), 7.24-7.20 (comp m, 3H), 4.03 (t, $J = 6.6$ Hz, 1H), 3.93 (td, $J = 6.7, 1.6$ Hz, 1H), 3.78 (t, $J = 6.6$ Hz, 2H), 3.45 (s, 3H), 3.44 (s, 3H), 2.82 (t, $J = 7.4$ Hz, 2H), 2.15-2.00 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.7, 138.3, 138.2, 129.0, 128.8, 128.7, 128.2, 127.8, 126.3, 85.5, 83.5, 70.84, 70.82, 68.0, 56.7, 41.7, 37.8, 37.7, 31.83, 31.81; IR (film) 3424, 2933, 2233, 1949, 1494, 1101, 751 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+ [\text{C}_{20}\text{H}_{22}\text{O}_2 + \text{H}]^+$: 295.1693, found 295.1695.



To a suspension of Mg turnings (2.88 g, 120 mmol) and HgCl_2 (10.0 mg, .0370 mmol) in Et_2O (36.0 mL) was added a solution of propargyl bromide (**128**, 13.4 mL, 80% wt. in PhMe, 120 mmol) in Et_2O (110 mL, 0.92 M) dropwise via an addition funnel. Once the reaction began to reflux, it was cooled to room temperature in a water bath and stirred until the magnesium was consumed. The Grignard was used immediately as an approximately 0.75 M solution.

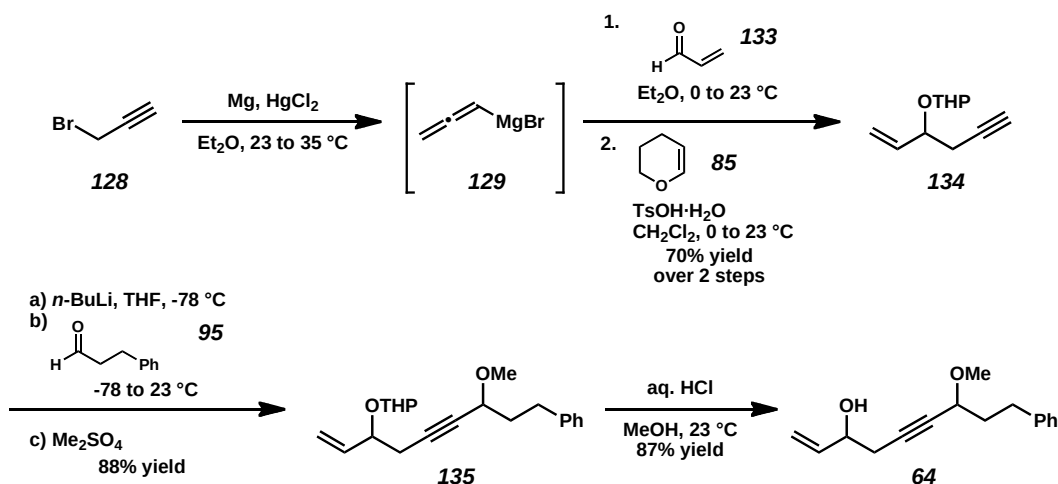
To the Grignard solution prepared above (28.8 mL, 0.75 M in Et₂O, 21.6 mmol) at 0 °C was added freshly distilled propionaldehyde (**130**, 1.30 mL, 18.0 mmol), and the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with water (20 mL), and the phases were separated. The organic phase was washed with 1 N HCl (20 mL), then brine (20 mL), dried over MgSO₄, and concentrated in vacuo. The recovered oil was dissolved in CH₂Cl₂ (36.0 mL, 0.50 M) and cooled to 0 °C. TsOH•H₂O (34.0 mg, 0.180 mmol) was added, followed by 3,4-dihydro-2H-pyran (**85**, 1.71 mL, 18.9 mmol), and the reaction was warmed to room temperature. After stirring for 20 h the reaction was quenched with sat. aq. NaHCO₃ (20 mL), and the phases were separated. The organic layer was dried over MgSO₄ and concentrated in vacuo. The recovered oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording acetal **131** (2.23 g, 68% yield, *R_f* = 0.42 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **131** (1.88 g, 10.3 mmol) in THF (30.9 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.13 mL, 2.5 M in hexanes, 10.3 mmol), and the resulting solution was stirred for 30 min at -78 °C. Hydrocinnamaldehyde (**95**, 1.36 mL, 10.3 mmol) was then added, and the reaction was stirred at -78 °C for 1 h, then warmed to room temperature and stirred for 2 h. Me₂SO₄ (1.17 mL, 12.4 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 1 M NaOH (20 mL) and stirred for 15 min. The mixture was diluted with Et₂O (40 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (30 mL), and the combined organic phases were washed with brine (30 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **132** (2.83 g, 83% yield, *R_f* = 0.55 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of ether **132** (2.83 g, 8.56 mmol) in MeOH (85.0 mL, 0.10 M) was added 3 N HCl (approx. 150 μ L), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The recovered oil was purified by flash chromatography (9:1 $\rightarrow$ 4:1 hexanes/EtOAc eluent) to afford alcohol **62** (0.887 g, 42% yield, R_f = 0.20 in 4:1 hexanes/EtOAc) as a clear oil.

Homopropargylic alcohol 62: Characterized as an approximately 2:1 mixture of diastereomers.

¹H NMR (400 MHz, CDCl₃) δ 7.31-7.26 (comp m, 2H), 7.22-7.17 (comp m, 3H), 3.92 (app. t, J = 6.3 Hz, 1H), 3.76-3.65 (m, 1H), 3.40 (s, 3H), 2.77 (t, J = 7.4 Hz, 2H), 2.52 (dd, J = 5.1, 2.0 Hz, 1H), 2.47 (dd, J = 5.1, 2.0 Hz, 1H), 2.42 (d, J = 5.5 Hz, 1H), 2.37 (d, J = 5.8 Hz, 1H), 2.07-1.94 (comp m, 2H), 1.85 (m, 1H), 1.63-1.52 (comp m, 2H), 0.97 (t, J = 7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 141.8, 128.8, 128.7, 126.3, 83.1, 81.7, 71.8, 70.9, 56.7, 37.8, 31.8, 29.5, 27.6, 10.2; IR (film) 3424, 2933, 2228, 1948, 1496, 1102 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₆H₂₂O₂ + H]⁺: 247.1693, found 247.1696.



To a suspension of Mg turnings (2.88 g, 120 mmol) and HgCl_2 (10.0 mg, 0.0370 mmol) in Et_2O (36.0 mL) was added a solution of bromide **128** (13.4 mL, 80% wt. in PhMe , 120 mmol) in Et_2O (110 mL, 0.92 M) dropwise via an addition funnel. Once the reaction began to reflux, it was cooled to room temperature in a water bath and stirred until the magnesium was consumed. The Grignard was used immediately as an approximately 0.75 M solution.

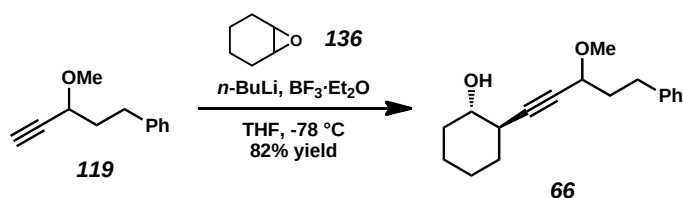
To the Grignard solution prepared above (28.8 mL, 0.75 M in Et_2O , 21.6 mmol) at $0\text{ }^\circ\text{C}$ was added freshly distilled acrolein (**133**, 1.20 mL, 18.0 mmol), and the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with water (20 mL), and the layers were separated. The organic layer was washed with 1 N HCl (30 mL), then brine (30 mL), dried over MgSO_4 , and concentrated in vacuo. The recovered oil was dissolved in CH_2Cl_2 (36.0 mL, 0.50 M) and cooled to $0\text{ }^\circ\text{C}$. $\text{TsOH}\cdot\text{H}_2\text{O}$ (34.0 mg, 0.180 mmol) was added followed by 3,4-dihydro-2H-pyran (**85**, 1.71 mL, 18.9 mmol), and the reaction was warmed to room temperature. After stirring for 22 h the reaction was quenched with sat. aq. NaHCO_3 (20 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. The recovered oil

was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording acetal **134** (2.26 g, 70% yield, R_f = 0.42 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **134** (2.14 g, 11.8 mmol) in THF (35.4 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.72 mL, 2.5 M in hexanes, 11.8 mmol), and the resulting solution was stirred for 30 min at -78 °C. Hydrocinnamaldehyde (**95**, 1.56 mL, 11.8 mmol) was then added, and the reaction was stirred at -78° C for 1 h, then warmed to room temperature and stirred for 2 h. Me₂SO₄ (1.33 mL, 14.2 mmol) was added, and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 1 M NaOH (20 mL) and stirred for 15 min. The mixture was then diluted with Et₂O (40 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (30 mL), and the combined organic phases were washed with brine (30 mL), dried over MgSO₄, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **135** (3.40 g, 88% yield, R_f = 0.55 in 4:1 hexanes/EtOAc) as a colorless oil.

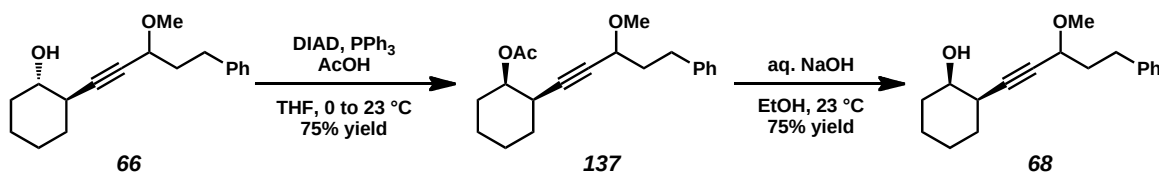
To a solution of ether **135** (3.40 g, 10.3 mmol) in MeOH (100 mL, 0.10 M) was added 3 N HCl (approx. 150 µL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) to afford alcohol **64** (2.21 g, 87% yield, R_f = 0.20 in 4:1 hexanes/EtOAc) as a colorless oil.

Homopropargylic alcohol 64: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 5.95 (ddd, J = 16.9, 10.7, 5.7 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.20 (d, J = 9.8 Hz, 1H), 4.33-4.25 (m, 1H), 3.92 (t, J = 6.5 Hz, 1H), 3.39 (s, 3H), 2.77 (t, J = 7.4 Hz, 2H), 2.57-2.47 (comp m, 2H), 2.06-1.94 (comp m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 139.4, 128.8, 128.7, 126.3, 116.2, 110.4, 82.4, 81.9, 71.34, 71.31, 70.8, 56.7, 37.7, 31.8, 28.1; IR (film) 3423, 3027, 2229, 1949, 1603, 1496 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{16}\text{H}_{20}\text{O}_2 + \text{H}$] $^+$: 245.1536, found 245.1541.



Following the procedure of Yamaguchi,⁵⁸ to a solution of alkyne **119** (1.05 g, 6.00 mmol) in THF (36.0 mL, 0.17 M) at -78°C under argon was added $n\text{-BuLi}$ (2.40 mL, 2.5 M in hexanes, 6.00 mmol), and the reaction was stirred for 30 min. $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.900 mL, 7.20 mmol) was added, and the reaction was stirred for 5 min. Cyclohexene oxide (**136**, 0.730 mL, 7.20 mmol) was then added, and the reaction was stirred at -78°C for 4 h. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and warmed to room temperature. The mixture was then diluted with Et_2O (30 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic layers were washed with brine (30 mL), dried over MgSO_4 , and concentrated in vacuo. The recovered residue was purified by flash chromatography (9:1 $\rightarrow$ 4:1 hexanes/ EtOAc eluent), affording alcohol **66** (1.34 g, 82% yield, R_f = 0.32 in 4:1 hexanes/ EtOAc) as a colorless oil.

Homopropargylic alcohol 66: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.26 (comp m, 2H), 7.21-7.18 (comp m, 3H), 3.94 (td, $J = 6.6, 1.4$ Hz, 1H), 3.59-3.56 (m, 1H), 3.46 (m, 1H), 3.39 (s, 3H), 2.77-2.75 (comp m 2H), 2.18 (s, 1H), 2.09-1.94 (comp m, 4H), 1.80-1.74 (comp m, 1H) 1.70-1.64 (m, 1H), 1.46-1.33 (comp m, 2H), 1.31-1.17 (comp m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 128.9, 128.7, 126.3, 88.0, 81.3, 73.9, 70.8, 56.6, 39.3, 37.8, 33.4, 31.9, 31.4, 25.1, 24.5; IR (film) 3431, 3027, 2934, 2228, 1946, 1603 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{18}\text{H}_{24}\text{O}_2 + \text{H}$] $^+$: 273.1849, found 273.1846.

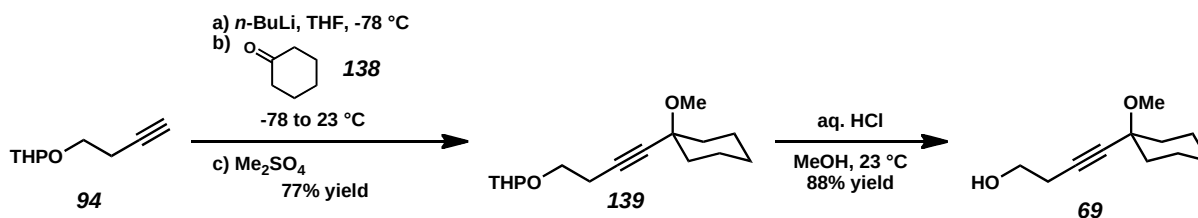


To a solution of alcohol **66** (0.967 g, 3.55 mmol) in THF (22.0 mL, 0.16 M) at 0 °C was added PPh_3 (2.79 g, 10.7 mmol). To this was added diisopropyl azodicarboxylate (2.06 mL, 10.7 mmol), followed by AcOH (0.612 mL, 10.7 mmol), causing a white precipitate to form. After 5 min the reaction was warmed to room temperature and stirred for 20 h. The reaction was diluted with Et_2O (30 mL), and the mixture was washed with sat. aq. NaHCO_3 (30 mL), then brine (30 mL). The solution was dried over MgSO_4 and concentrated in vacuo, and the recovered slurry was purified by flash chromatography (9:1 $\rightarrow$ 4:1 hexanes/ EtOAc eluent), affording acetate **137** (0.834 g, 75% yield, $R_f = 0.55$ in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of acetate **137** (0.471 g, 1.50 mmol) in EtOH (15.0 mL, 0.10 M) was added 1 M NaOH (6.00 mL, 6.00 mmol), and the reaction was stirred at room temperature for 8 h. The reaction was extracted with Et_2O (2 x 20 mL), and the combined organic phases were dried over MgSO_4 and concentrated in vacuo. The recovered oil was purified by flash chromatography (6:1

hexanes:EtOAc eluent), affording alcohol **68** (0.308 g, 75% yield, $R_f = 0.32$ in 4:1 hexanes/EtOAc) as a colorless oil.

Homopropargylic alcohol 68: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.22-7.19 (comp m, 3H), 3.96 (td, $J = 6.6, 1.6$ Hz, 1H), 3.70-3.64 (m, 1H), 2.93-2.88 (m, 1H), 2.81-2.77 (comp m, 2H), 2.11-1.94 (comp m, 2H), 1.90-1.82 (m, 1H), 1.79 (dd, $J = 7.4, 1.2$ Hz, 1H), 1.70-1.66 (comp m, 3H), 1.62-1.51 (comp m, 2H), 1.44-1.37 (m, 1H), 1.35-1.24 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 128.9, 128.7, 126.3, 86.5, 83.1, 70.8, 70.2, 56.7, 37.9, 36.3, 31.9, 31.8, 29.3, 23.2, 22.6; IR (film) 3441, 2935, 2858, 2234, 1946, 1603 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{18}\text{H}_{24}\text{O}_2 + \text{H}$] $^+$: 273.1849, found 273.1843.

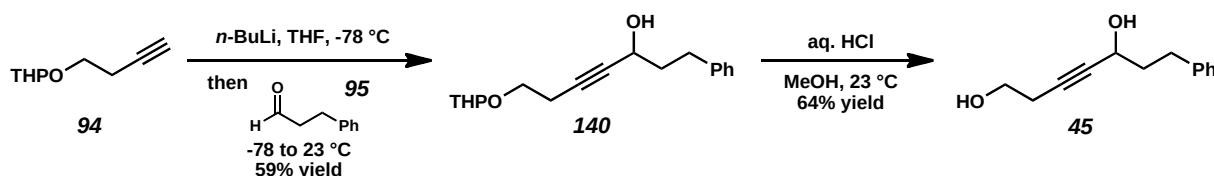


To a solution of acetal **94** (0.771 g, 5.00 mmol) in THF (20.0 mL, 0.25 M) at -78°C under argon was added $n\text{-BuLi}$ (2.00 mL, 2.5 M in hexanes, 5.00 mmol), and the resulting solution was stirred for 30 min at -78°C . Cyclohexanone (**138**, 0.518 mL, 5.00 mmol) was then added, and the reaction was stirred at -78°C for 1 h, then warmed to room temperature and stirred for 2 h. Me_2SO_4 (0.714 mL, 7.50 mmol) was added, and the reaction was stirred for 20 h at room temperature. The reaction was quenched with 1 M NaOH (10 mL) and stirred for 15 min. The mixture was then diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic layers were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, and the resulting

crude oil was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), affording ether **139** (1.03 g, 77% yield, R_f = 0.53 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **139** (1.03 g, 3.85 mmol) in MeOH (50.0 mL, 0.080 M) was added 3 N HCl (approx. 75 μ L), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with sat. aq. NaHCO₃ (50 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (4:1 → 2:1 hexanes/EtOAc eluent) to afford alcohol **69** (0.616 g, 88% yield, R_f = 0.15 in 4:1 hexanes/EtOAc) as colorless oil.

Homopropargylic alcohol 69: ¹H NMR (400 MHz, CDCl₃) δ 3.72 (app. q, J = 6.3 Hz, 2H), 3.34 (s, 3H), 2.52 (t, J = 6.6 Hz, 2H), 1.89-1.82 (comp m, 2H), 1.80-1.77 (m, 1H), 1.68-1.60 (comp m, 2H), 1.60-1.45 (comp m, 5H), 1.30-1.25 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 83.7, 82.8, 74.3, 61.6, 50.9, 37.2, 25.8, 23.5, 23.2; IR (film) 3385, 2937, 2824, 2233, 1448 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₁H₁₈O₂ + H]⁺: 183.1380, found 183.1380.

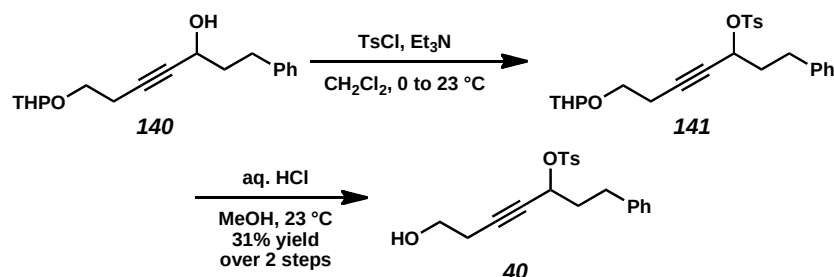


To a solution of acetal **94** (4.62 g, 30.0 mmol) in THF (90.0 mL, 0.3 M) at -78 °C under argon was added *n*-BuLi (12.0 mL, 2.5 M in hexanes, 30.0 mmol), and the resulting solution was stirred for 30 min at -78 °C. Hydrocinnamaldehyde (**95**, 3.96 mL, 30.0 mmol) was then added, and the reaction was stirred at -78 °C for 1 h, then warmed to room temperature and stirred for 2

h. The reaction was quenched with water (50 mL) and stirred for 5 min. The reaction was diluted with Et₂O (100 mL) and the phases were separated. The aqueous phase was extracted with Et₂O (50 mL), and the combined organic phases were washed with brine (50 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting crude oil was purified by flash chromatography (4:1 → 2:1 hexanes/EtOAc eluent), affording alcohol **140** (5.13 g, 59% yield, R_f = 0.28 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **140** (0.288 g, 1.00 mmol) in MeOH (10.0 mL, 0.10 M) was added 3 N HCl (approx. 25 μ L), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with sat. aq. NaHCO₃ (10 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed in vacuo. The resulting oil was purified by flash chromatography (4:1 → 1:1 hexanes/EtOAc eluent) to afford diol **45** (0.131 g, 64% yield, R_f = 0.28 in 1:2 hexanes/EtOAc) as colorless oil.

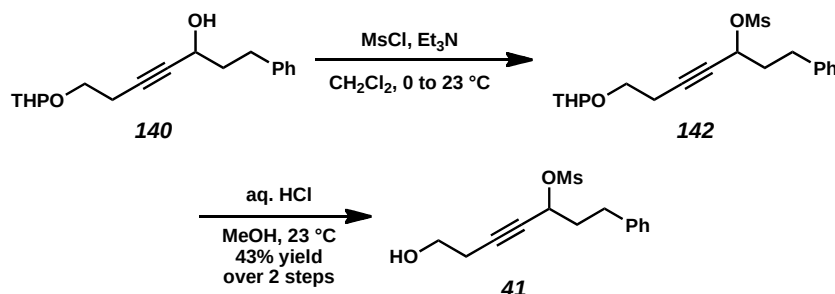
Propargylic alcohol 45: ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.26 (comp m, 2H), 7.23-7.17 (comp m, 3H), 4.37 (m, 1H), 3.72 (app. q, J = 5.9 Hz, 2H), 2.79 (t, J = 7.8 Hz, 2H), 2.50 (tt, J = 6.2, 2.0 Hz, 2H), 2.01 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 141.6, 128.82, 127.77, 126.3, 83.4, 82.7, 62.2, 61.4, 39.8, 31.8, 23.4; IR (film) 3426, 2231, 1603, 1496, 1046 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₃H₁₆O₂ + H]⁺: 205.1223, found 205.1221.



To a solution of alcohol **140** (0.576 g, 2.00 mmol) in CH_2Cl_2 (6.00 mL, 0.33 M) at 0 °C was added Et_3N (0.562 mL, 4.00 mmol) followed by TsCl (0.495 g, 2.60 mmol), and the reaction was warmed to room temperature. After 6 h the reaction was diluted with Et_2O (20 mL) and washed with sat. aq. NaHCO_3 (10 mL). The aqueous phase was extracted with Et_2O (10 mL), and the combined organic phases were washed sequentially with 1 N HCl (15 mL), sat. aq. NaHCO_3 (15 mL), and brine (15 mL). The organic phase was dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered crude tosylate **141** (0.741 g, $R_f = 0.37$ in 2:1 hexanes/ EtOAc) was immediately dissolved into MeOH (20.0 mL, 0.1 M). To this solution was added 3 N HCl (approx. 25 μL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with Et_3N (approx. 25 μL). The solution was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered residue was purified by flash chromatography (6:1 $\rightarrow$ 3:2 hexanes/ EtOAc eluent), affording alcohol **40** (0.218 g, 31% yield over 2 steps, $R_f = 0.26$ in 2:1 hexanes/ EtOAc) as a colorless oil.

Propargylic tosylate 40: ^1H NMR (400 MHz, CDCl_3) δ 7.83-7.79 (comp m, 2H), 7.36-7.31 (comp m, 2H), 7.29-7.25 (comp m, 2H), 7.22-7.17 (m, 1H), 7.14-7.10 (comp m, 2H), 5.05 (tt, $J = 6.3, 2.0$ Hz, 1H), 3.58 (t, $J = 5.8$ Hz, 2H), 2.78-2.66 (comp m, 2H), 2.45 (s, 3H), 2.33 (td, $J = 6.3, 2.0$ Hz, 2H), 2.18-2.03 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 140.5, 134.4, 130.0, 128.9, 128.7, 128.4, 126.6, 98.7, 86.7, 78.0, 71.6, 61.0, 37.8, 31.2, 23.4, 22.0; IR (film) 3741,

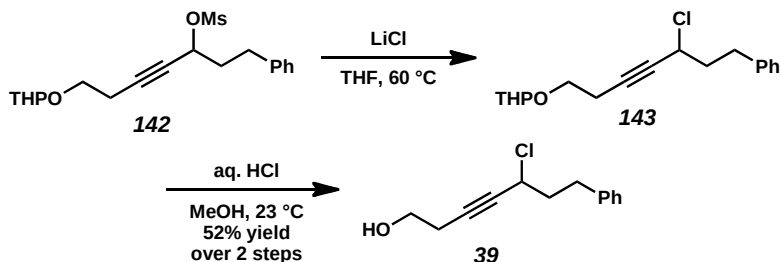
2243, 1599, 1454, 1175 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for $(M + \text{Na})^+ [\text{C}_{20}\text{H}_{22}\text{O}_4\text{S} + \text{Na}]^+$: 381.1131, found 381.1122.



To a solution of alcohol **140** (0.576 g, 2.00 mmol) in CH₂Cl₂ (6.00 mL, 0.33 M) at 0 °C was added Et₃N (0.562 mL, 4.00 mmol) followed by MsCl (0.202 mL, 2.60 mmol), and the reaction was warmed to room temperature. After 30 min the reaction was diluted with Et₂O (20 mL) and washed with sat. aq. NaHCO₃ (10 mL). The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed sequentially with 1 N HCl (15 mL), sat. aq. NaHCO₃ (15 mL) and brine (15 mL). The organic phase was dried over MgSO₄, and the solvent was removed via rotary evaporation. The recovered crude mesylate (**142**, 0.683 g, R_f = 0.28 in 2:1 hexanes/EtOAc) was immediately dissolved into MeOH (20.0 mL, 0.1 M). To this solution was added 3 N HCl (approx. 25 μL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with Et₃N (approx. 50 μL), diluted with water (20 mL), and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The recovered residue was purified by flash chromatography (6:1 $\rightarrow$ 2:3 hexanes/EtOAc eluent), affording alcohol **41** (0.240 g, 43% yield over 2 steps, R_f = 0.37 in 1:2 hexanes/EtOAc) as a colorless oil.

Propargylic mesylate 41: ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.27 (comp m, 2H), 7.23-7.19 (comp m, 3H), 5.19-5.15 (m, 1H), 3.76 (t, J = 6.2 Hz, 2H), 3.11 (s, 3H), 2.84-2.75 (comp m, 2H),

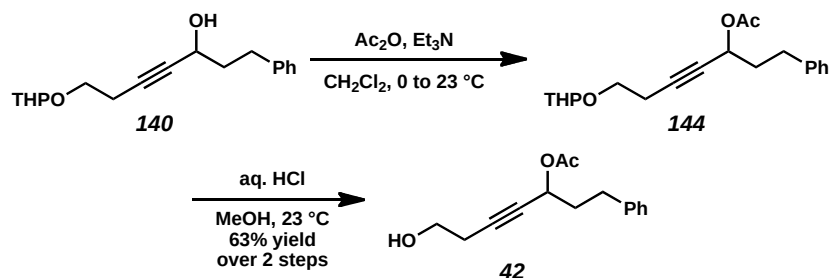
2.53 (td, $J = 6.3, 2.0$ Hz, 2H), 2.25-2.14 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.4, 128.9, 128.8, 126.7, 87.5, 78.0, 71.6, 61.1, 39.5, 37.7, 31.3, 23.3; IR (film) 3534, 2242, 1603, 1359, 1173 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+ [\text{C}_{14}\text{H}_{18}\text{O}_4\text{S} + \text{Na}]^+$: 305.0818, found 305.0826.



To a solution of mesylate **142** (0.732 g, 2.00 mmol) in THF (50.0 mL, 0.040 M) was added anhydrous LiCl (3.38 g, 80.0 mmol), and the reaction was heated to 60 °C for 18 h. The solvent was removed in vacuo, and the residue was diluted with Et_2O (30 mL) and filtered. The filtrate was washed with water (10 mL), dried over MgSO_4 , and concentrated in vacuo, producing crude chloride **143** (0.539 g, $R_f = 0.70$ in 2:1 hexanes/ EtOAc) as a colorless oil. The recovered material was immediately dissolved in MeOH (20.0 mL, 0.10 M). To this was added 3 N HCl (approx. 25 μL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with Et_3N (approx. 25 μL), diluted with water (20 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered residue was purified by flash chromatography (6:1 to 3:2 hexanes/ EtOAc eluent), affording chloride **39** (0.232 g, 52% yield over 2 steps, $R_f = 0.32$ in 2:1 hexanes/ EtOAc) as a colorless oil.

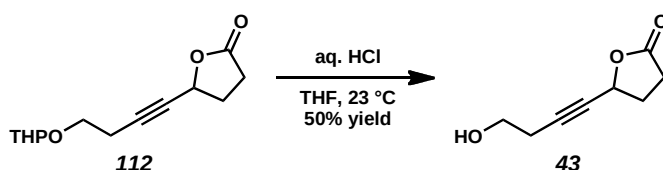
Propargylic chloride 39: ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (comp m, 2H), 7.24-7.19 (comp m, 3H), 4.50 (tt, $J = 6.6, 2.0$ Hz, 1H), 3.74 (t, $J = 6.3$ Hz, 2H), 2.86 (t, $J = 7.8$ Hz, 2H),

2.53 (td, $J = 6.3, 2.0$ Hz, 2H), 2.27-2.22 (comp m, 2H), 1.83-1.72 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.5, 128.88, 128.87, 126.6, 84.3, 80.7, 61.2, 48.6, 41.2, 32.7, 23.5; IR (film) cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{13}\text{H}_{15}\text{ClO} + \text{H}$] $^+$: 240.1150 found 240.1155.



To a solution of alcohol **140** (0.576 g, 2.00 mmol) in CH_2Cl_2 (6.00 mL, 0.33 M) at 0 °C was added Et_3N (0.562 mL, 4.00 mmol) followed by Ac_2O (0.246 mL, 2.60 mmol), and the reaction was warmed to room temperature. After 6 h the reaction was diluted with Et_2O (20 mL) and washed with sat. aq. NaHCO_3 (10 mL). The aqueous phase was extracted with Et_2O (10 mL), and the combined organic phases were washed sequentially with 1 N HCl (15 mL), sat. aq. NaHCO_3 (15 mL), and brine (15 mL). The organic phase was dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered crude acetate **144** (0.619 g, $R_f = 0.40$ in 2:1 hexanes/ EtOAc) was immediately dissolved in MeOH (20.0 mL, 0.1 M). To this solution was added of 3 N HCl (approx. 25 μL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with Et_3N (approx. 25 μL), diluted with water (20 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered residue was purified by flash chromatography (6:1 $\rightarrow$ 3:2 hexanes/ EtOAc eluent), affording alcohol **42** (0.309 g, 63% yield over 2 steps, $R_f = 0.29$ in 2:1 hexanes/ EtOAc) as a colorless oil.

Propargylic acetate 42: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.26 (comp m, 2H), 7.22-7.17 (comp m, 3H), 5.34 (tt, $J = 6.3, 1.9$ Hz, 1H), 3.73 (app. q, $J = 6.3$ Hz, 2H), 2.76 (t, $J = 7.8$ Hz, 2H), 2.50 (td, $J = 6.3, 2.0$ Hz, 2H), 2.13-2.03 (comp m, 2H), 2.07 (s, 3H), 1.90-1.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 141.1, 128.8, 128.7, 126.5, 83.4, 79.9, 64.3, 61.2, 36.7, 31.7, 23.5, 21.4; IR (film) 3457, 2242, 1740, 1497, 1241 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{15}\text{H}_{18}\text{O}_3 + \text{H}$] $^+$: 247.1329, found 247.1327.



To a solution of lactone **112** (0.357 g, 1.50 mmol) in THF (5.00 mL, 0.30 M) was added 1 N HCl (5.00 mL, 5.00 mmol), and the reaction was stirred at room temperature for 2 h. The reaction was neutralized with sat. aq. NaHCO_3 (10 mL), and the suspension was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed via rotary evaporation. The recovered oil was purified by flash chromatography (3:2 $\rightarrow$ 1:3 hexanes/EtOAc eluent), affording alcohol **43** (0.116 g, 50% yield, $R_f = 0.19$ in 1:2 hexanes/EtOAc) as a colorless oil.

Propargylic lactone 43: ^1H NMR (400 MHz, CDCl_3) 5.13 (t, $J = 6.3$ Hz, 1H), 3.76-3.71 (comp m, 2H), 2.71-2.59 (m, 1H), 2.54-2.48 (comp m, 4H), 2.31-2.23 (m, 1H), 2.10-1.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.4, 85.6, 78.6, 69.7, 61.1, 30.3, 28.2, 23.4; IR (film) 3423, 2246, 1782, 1186 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_8\text{H}_{10}\text{O}_3 + \text{H}$] $^+$: 155.0703, found 155.0704.

CHAPTER TWO NOTES AND REFERENCES

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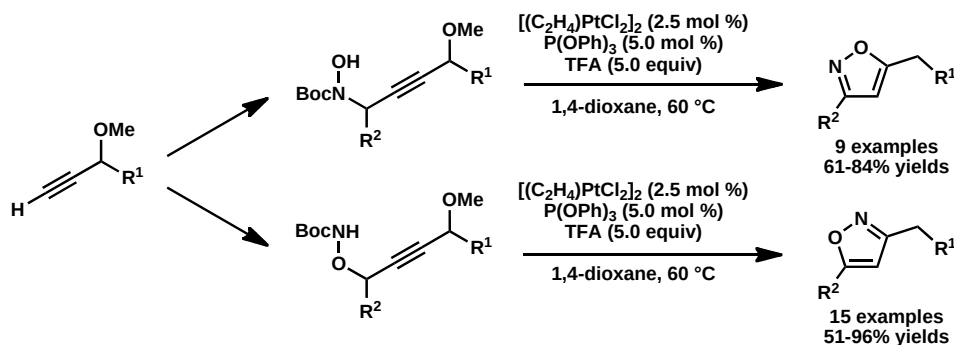
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CHAPTER THREE

Synthesis of Complementary Positional Isomers of Isoxazoles

3.1 Introduction

Our success at synthesizing furans from the nucleophilic addition of alcohols into alkynes bearing propargylic methyl ethers led us to identify other classes of heterocycles that could be formed via this method. We identified isoxazoles as attractive targets for their prevalence in medicinal chemistry,⁵⁹ applications as synthetic intermediates,⁶⁰ and providing an opportunity to synthesize both isoxazole isomers from a common intermediate. Described herein is our effort toward identifying competent substrates for the proposed 5-*endo-dig* cyclizations, development of an active catalyst/ligand system, and the requirement for a Brønsted acid additive to facilitate the reaction. As illustrated in Scheme 3.1.1, we were able to extend this method of heterocycle synthesis to the construction of a variety of 3,5-disubstituted isoxazoles in good to excellent yields.⁶¹ We were then able to demonstrate the utility of this method to the construction of an antirhinovirus pharmaceutical and its positional isomer in two steps from the same terminal alkyne precursor.



Scheme 3.1.1. The Synthesis of Isomeric Isoxazoles from a Common Intermediate.

3.2 Background

3.2.1 Isoxazoles as Synthetically Useful Heterocycles

Isoxazoles are synthetically important heterocycles because of the ease with which the ring can be converted to a variety of functional groups. This reactivity is due to the presence of the relatively weak (54 kcal/mol) nitrogen-oxygen single bond, and its poor aromatic character.⁶² Many of the common transformations of this heterocycle manipulate the N-O bond, or the fixed imine properties of the heterocycle, leading to the formation of a variety of carbonyl containing compounds (Figure 3.2.1). The reaction between 3-unsubstituted isoxazoles and variety of alkoxide bases will form the corresponding α -cyanocarbonyl compounds in generally good yields.⁶³ Reduction of the N-O bond to form the corresponding β -enaminoketones can be accomplished by using SmI_2 ,⁶⁴ or hydrogenolysis using platinum⁶⁵ or Raney nickel⁶⁶ as the catalyst. Alkylation of the nitrogen atom with Meerwein's salt followed by treatment with sodium hypochlorite produces α -hydroxy- β -diketones.⁶⁷ Thermolysis of a variety of substituted isoxazoles results in cleavage of the N-O bond, followed by rearrangement to form substituted azirines.⁶⁸ The coupling of these fundamental transformations of the isoxazole ring with subsequent synthetic manipulations enables the synthesis of a variety of substituted heterocyclic ring systems.⁶⁹

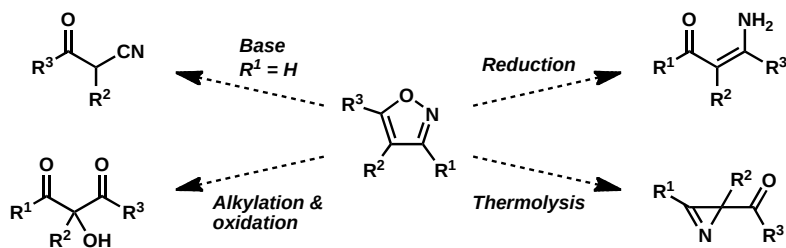
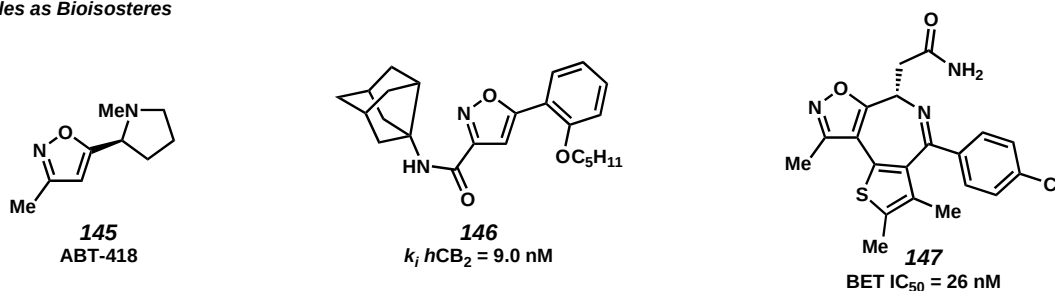


Figure 3.2.1. Common Transformations of Isoxazoles.

3.2.2 Isoxazoles as Medicinally Important Heterocycles

The isoxazole ring has demonstrated utility in a variety of medicinal and agrochemical contexts (Figure 3.2.2). The stability of the isoxazole ring, along with its Lewis basic sites, allows it to be used in place of a variety of different heterocycles. Isoxazole **145** has been evaluated as a potential treatment for Alzheimer's disease due to its nanomolar binding efficiency to neuronal nicotinic acetylcholine receptors (nAChR) and its efficacy in cognitive performance tests in mice.⁷⁰ These studies demonstrated the use of the isoxazole ring as a competent isostere for the pyridine ring, allowing ABT-418 to bind to the $\alpha 4\beta 2$ nAChR in a manner that is similar to the way nicotine binds to these receptors. The use of isoxazoles as isosteres of other heterocycles was extended to a class of compounds that were recently reported to have *in vivo* anti-inflammatory activities against mouse colitis models.⁷¹ Compound **146** used an isoxazole in place of a pyrazole ring; the result was a CB₂ receptor agonist with a binding affinity of 9.0 nM. Finally the structure of the potent BET inhibitor **147** used an isoxazole ring in place of a triazole to mimic binding interactions with an asparagine residue at the active site of the protein.⁷²

Isoxazoles as Bioisosteres



Isoxazoles as Prodrugs

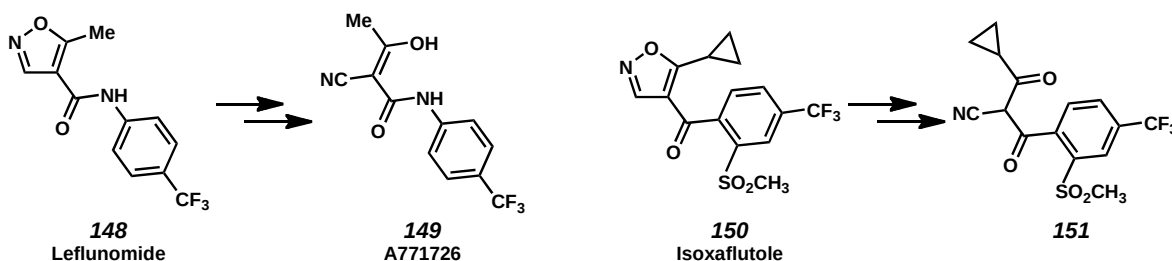


Figure 3.2.2. Medicinally Active Isoxazoles.

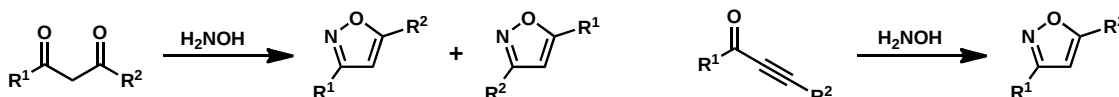
Isoxazoles are also attractive heterocycles for drug discovery due to their ability to be metabolized *in vivo* to more active compounds (Figure 3.2.2). The immunosuppressive agent Leflunomide (**148**) is actually a prodrug, showing little activity until it is metabolized *in vivo* to the active compound A771726 (**149**).⁷³ The presence of the isoxazole is necessary in this case, as it serves as a precursor for the biologically active α -cyanocarbonyl, a reaction that is not possible when other heterocycles are used. Similarly, the bleaching herbicide Isoxaflutole (**150**) is converted in plants to the active diketonitrile (**151**); which is responsible for inhibiting *p*-hydroxyphenylpyruvate dioxygenase (HPPD) and causing plant death.^{74, 75} The specific binding ability/reactivity of the isoxazole ring in these examples highlights its importance as a useful heterocycle in a variety of biologically active compounds.

3.2.3 Current Strategies in Isoxazole Synthesis

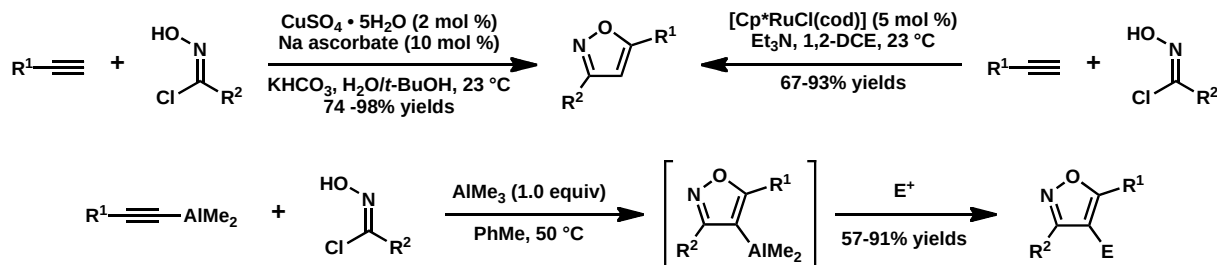
The earliest synthesis of isoxazoles was reported by Claisen in 1888 and involved the condensation and cyclization of hydroxylamine onto 1,3-diketones (Scheme 3.2.1).⁷⁶ This method has many drawbacks, with the primary issue being the formation of a mixture of isomeric isoxazole products.⁷⁷ The regioselectivity issues can be avoided by condensing hydroxylamine onto ynones, leading to the synthesis of a single 3,5-disubstituted isoxazole product.⁷⁸ Enones also participate in this mode of reactivity, reacting with hydroxylamine to produce 5-hydroxy-2-isoxazolines. The hydroxy-isoxazolines can subsequently be dehydrated to the corresponding isoxazoles.⁷⁹ Nitrile oxides can also react with both alkenes and alkynes to form the corresponding isoxazolines/isoxazoles respectively, though these reactions require elevated temperatures to be successful.⁸⁰ The sluggish reactivity of alkynes toward this cycloaddition is problematic, but has been overcome with the use of a Cu(I) or Ru(II) catalyst

system to form 3,5-disubstituted isoxazoles under mild conditions (Scheme 3.2.1).⁸¹ While these cycloaddition strategies give single isoxazole isomers when terminal alkynes are used, they still produce mixtures of both isoxazole products when internal alkynes are used as the coupling partner. Single isomers of trisubstituted isoxazoles can be accessed via the cycloaddition of aluminum acetylides and nitrones.⁸² The initial cyclization forms aluminated isoxazoles, which can subsequently react with a variety of electrophiles like H^+ , NCS, NIS or isocyanates to produce the desired isoxazole in good overall yields.

Hydroxylamine Condensation Approaches



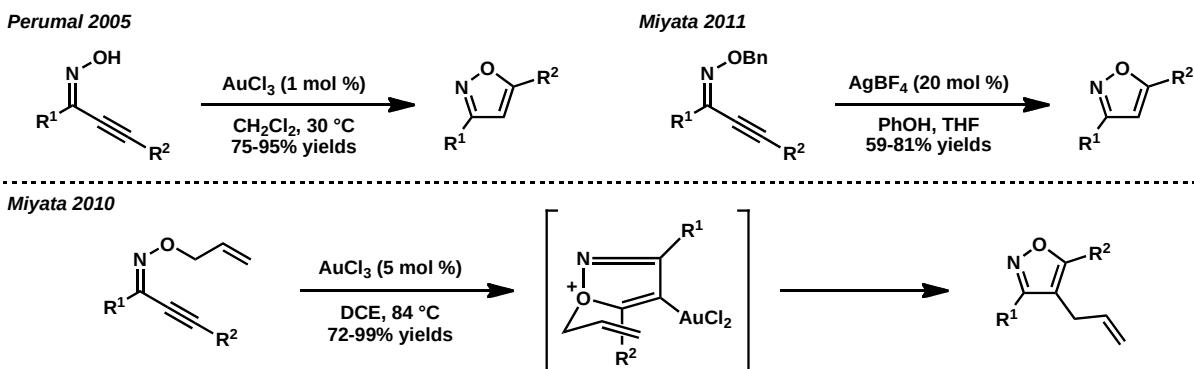
Metal Promoted [3 + 2] Cycloadditions



Scheme 3.2.1. Isoxazole Synthesis Using Intermolecular Couplings.

An additional strategy toward the construction of the isoxazole ring utilizes alkyne activation chemistry to create the carbon-heteroatom bond. Within this mode of reactivity are two approaches. The first uses alkynyl oximes/oxime ethers as the nucleophile, and a π -acidic metal like Ag(I) or Au(III) to form 3,5-disubstituted isoxazoles in good yields (Scheme 3.2.2).⁸³ Electrophilic halogen sources like ICl are also effective, converting the alkynyl *O*-methyl oximes into synthetically useful 4-iodoisoxazoles.⁸⁴ Both the benzyl and methyl oxime ethers cleave and are trapped by exogenous nucleophiles under the reaction conditions. Alternatively, Miyata and coworkers have shown that when alkynyl *O*-allyl oximes are exposed to alkyne activation

conditions, the allyl group is transferred to the 4-position of the isoxazole ring to produce trisubstituted isoxazoles.⁸⁵ In these reactions the cyclization event forms a vinyl gold species, which readily undergoes the allyl transfer through a 6-membered transition state. Protodemetalation then forms the 4-allylated isoxazole.

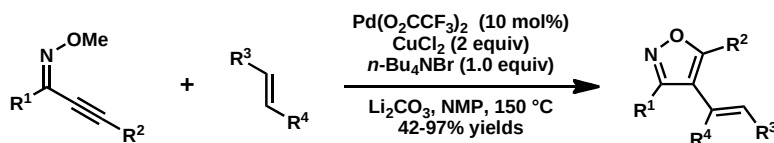


Scheme 3.2.2. Isoxazole Formation via Alkynyl Oximes/Oxime Ethers.

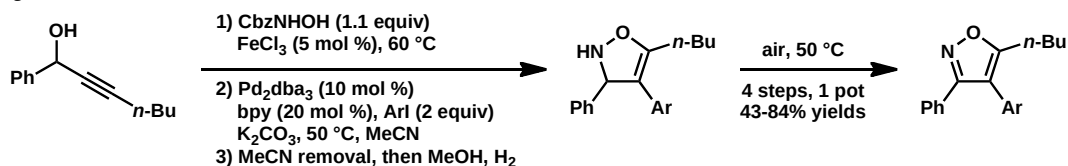
Several recent reports use Pd(II) to activate the alkyne to form a vinyl-palladium species (Scheme 3.2.3). The main advantage of these methods is their ability to form trisubstituted isoxazoles, which are difficult to make via traditional alkyne activation approaches using gold or platinum salts. Chen demonstrated in 2012 that alkynyl *O*-methyl oximes can add into alkynes activated by Pd(II); the resulting vinyl palladium species can then undergo a Heck coupling with a variety of olefins to produce trisubstituted isoxazoles.⁸⁶ Campagne and coworkers have also demonstrated a one pot, multistep approach that uses Fe(III) to substitute propargyl alcohols with *N*-Cbz hydroxylamine.⁸⁷ The resulting propargyl *N*-hydroxycarbamate then adds into the activated alkyne via Pd(II) catalysis (formed from the oxidative addition of the Ar-I bond). Hydrogenolysis of the Cbz-group forms the isoxazoline, which is readily oxidized to the isoxazole by ambient air. All of these approaches have established synthetic utility, and allow for the rapid construction of the isoxazole ring. We hoped to complement this existing body of

research by developing a method that could access both positional isomers of substituted isoxazoles from a common intermediate.

Chen 2012



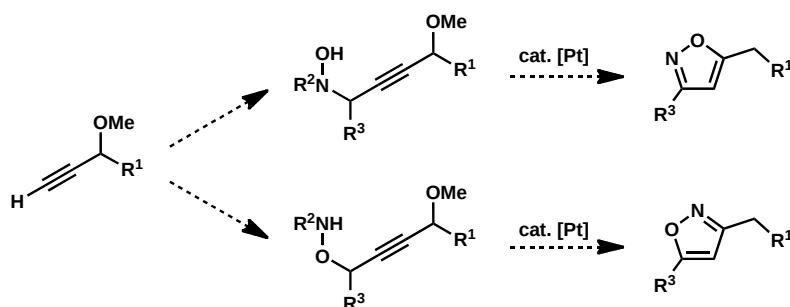
Campagne 2011



Scheme 3.2.3. Palladium(II) Catalyzed Syntheses of Trisubstituted Isoxazoles.

3.2.4 Our Proposed Synthesis of Isoxazoles

We believed the reaction pathway that was used to make substituted furans could be extended to the synthesis of isoxazoles, where both propargylic *N*-hydroxylamines or carbamoyl ethers could be used under similar alkyne activation conditions to generate complementary positional isomers of isoxazoles. To accomplish this we would need to develop a way to synthesize precursors to both of the desired isoxazole isomers from an advanced intermediate (Scheme 3.2.4). Several issues would need to be addressed for this approach to be successful: (1) we would need to identify a reliable route to synthesize the desired starting materials (2) demonstrate that the nitrogen/oxygen based nucleophiles are compatible with the alkyne activation conditions (3) find an R^3 group that would readily cleave under the reaction conditions to produce the isoxazole. With these concerns in mind we began our efforts to extend our furan method to the synthesis of isoxazoles.

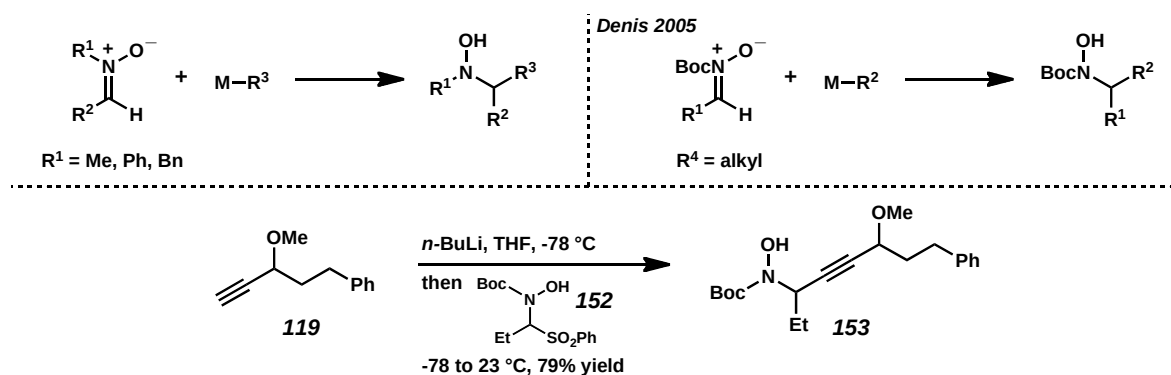


Scheme 3.2.4. Proposed Method Towards the Synthesis of Isoxazoles.

3.3 Synthesis of Isoxazoles from Propargylic *N*-hydroxycarbamates

3.3.1 Identification and Synthesis of the Model Substrate

Our first task in developing a successful method for the synthesis of isoxazoles was to identify an appropriate substrate on which to base our optimization studies. The principal requirement was the propargyl hydroxylamine motif in the structure, with the methyl ether on the opposite side of the alkyne. These substrates could be easily accessed by the addition of an acetylide anion into a nitron (Scheme 3.3.1).⁸⁸ One concern with this substrate class was the presence of a Lewis basic nitrogen atom in the structure, a functional group that was not compatible with the platinum catalysts used in our synthesis of furans.⁸⁹ We also feared that an alkyl group would not readily ionize off of the nitrogen atom, preventing the aromatic isoxazole from forming. A more attractive option would be to use an *N*-hydroxy-*t*-butylcarbamate as the nucleophilic species, which can be easily synthesized from the corresponding *N*-Boc nitron.⁹⁰ Exposure of alkyne **119** to *n*-BuLi at -78 °C, followed by addition of 0.5 equivalents of *N*-Boc nitron precursor **152** produced the desired *N*-hydroxycarbamate **153** in 79% yield (Scheme 3.3.1). With a reliable route to our desired substrate, we then focused our attention on evaluating its competency in the desired cyclization reaction.

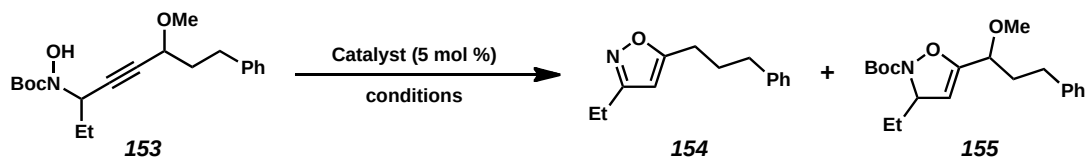


Scheme 3.3.1. Synthesis of Propargylic *N*-Hydroxylamines.

3.3.2 Optimization of Reaction Conditions

With our test substrate in hand we began our investigation of conditions that would generate the desired isoxazole from *N*-hydroxycarbamate **153**. Our initial conditions using Zeise's dimer that were effective for the synthesis of furans provided minimal reactivity with **153**. Even at elevated temperatures only modest conversions to isoxazole **154** and isoxazoline **155** were observed (Table 3.3.1, Entry 1). Several solvents were examined (Table 3.3.1, Entries 2-8), with acetonitrile producing the desired isoxazole (**154**) in 44% yield. Other Pt(II) salts were examined as well (Table 3.3.1, Entries 9-13), each performing much more poorly than Zeise's dimer. The use of carbophilic metals other than platinum was also unsuccessful (Table 3.3.1, Entries 14-18), with the major product isolated from the reactions being undesired isoxazoline **155**. These experiments made it clear that the conditions that generated the furan products would not translate to the current system, and that there must be something unique about the *N*-hydroxycarbamate that is preventing the desired reactivity.

Table 3.3.1. Catalyst Evaluation.

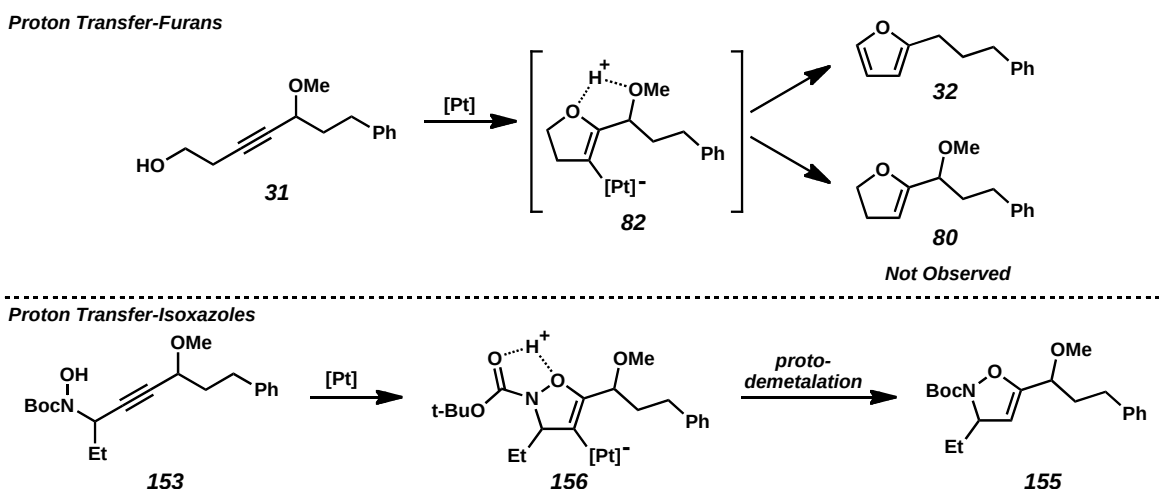


Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield 154 (%) ^a	Yield 155 (%) ^a
1	[(C ₂ H ₄)PtCl ₂] ₂ ^b	THF	70	18	15	7
2	[(C ₂ H ₄)PtCl ₂] ₂ ^b	1,4-dioxane	70	18	22	12
3	[(C ₂ H ₄)PtCl ₂] ₂ ^b	CH ₂ Cl ₂	70	66	9 ^c	0 ^c
4	[(C ₂ H ₄)PtCl ₂] ₂ ^b	ClCH ₂ CH ₂ Cl	70	66	23 ^c	14 ^c
5	[(C ₂ H ₄)PtCl ₂] ₂ ^b	PhCH ₃	70	18	18	12
6	[(C ₂ H ₄)PtCl ₂] ₂ ^b	PhH	70	66	21 ^c	18 ^c
7	[(C ₂ H ₄)PtCl ₂] ₂ ^b	CH ₃ CN	70	66	44 ^c	17 ^c
8	[(C ₂ H ₄)PtCl ₂] ₂ ^b	PhCH ₃	60	16	22	9
9	PtCl ₂ /1-octene ^d	PhCH ₃	60	16	35	9
10	K ₂ PtCl ₄	PhCH ₃	60	48	0	0
11	(PPh ₃) ₂ PtCl ₂	PhCH ₃	60	48	0	0
12	(PhCN) ₂ PtCl ₂	PhCH ₃	60	48	0	0
13	(PPh ₃) ₂ PtHCl	PhCH ₃	60	48	0	0
14	Pd(OAc) ₂	PhCH ₃	60	16	0	18
15	Pd(OCOCF ₃) ₂	PhCH ₃	60	16	0	36
16	PPh ₃ AuCl/AgSbF ₆ ^e	CH ₂ Cl ₂	-10	0.5	0	44
17	IPrAuCl/AgSbF ₆ ^e	CH ₂ Cl ₂	-10→23	3.0	3	50
18	<i>o</i> -biphenyl(<i>t</i> -Bu) ₂ PAuCl/AgSbF ₆ ^e	CH ₂ Cl ₂	-10	0.5	2	73

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Used 2.5 mol % catalyst. ^c Reaction did not go to completion. ^d Used 1.0 equiv 1-octene as an additive. ^e Used 5 mol % AgSbF₆.

At this point it was evident that one issue that could be hindering the desired reaction was extrusion of the methyl ether and not the nucleophilicity of the *N*-hydroxycarbamates. During our development of the furan chemistry we had never observed the hydroalkoxylation product (**80**) when using Pt(II) catalysts under the standard conditions (Scheme 3.3.2). Our rationalization for why the methyl ethers were ideal leaving groups was due to their inability to ionize until the hydroalkoxylation event occurred, requiring a proton transfer between the hydroxyl group and the methyl ether to activate the ethereal leaving group. The alcohols used in

the furan chemistry did not have any Lewis basic residues that could disrupt the proton transfer event, whereas the *N*-hydroxycarbamate (**153**) contains a carbonyl that could compete with the methyl ether during the proton transfer step (**156**). We rationalized that the carbonyl group was preventing the activation of the methyl ether, resulting in the competitive formation of the hydroalkoxylation product. With this in mind we sought conditions that could restore the desired reactivity.

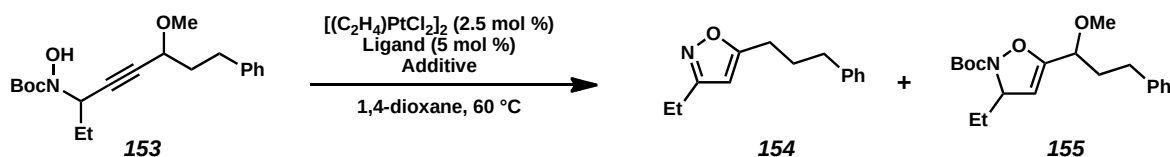


Scheme 3.3.2. Activation of the Methyl Ether via Proton Transfer.

Our efforts to promote the desired reactivity focused on restoring the proton transfer event to activate the methyl ether, as well as using electron-donating ligands to increase the back-donation of the Pt(II) catalyst, both of which should facilitate the desired reactivity by enhancing extrusion of the methyl ether.⁹¹ Exposure of **153** to Zeise's dimer and acetic acid (Table 3.3.2, Entry 1) resulted in a 39% yield of the desired isoxazole **154**, 17% higher than when acetic acid was not added to the reaction. The addition of 5.0 mol % triphenylphosphine increased the yield to 48%, indicating that the more electron rich the Pt(II) catalyst is, the more readily it can back-donate into the π -system of the substrate. At this point we examined a few different Brønsted

acids (Table 3.3.2, Entries 3-6) in the reaction. Ammonium formate inhibited the reaction, most likely due to the over-coordination of the Pt(II) center with excess amine ligands, preventing the activation of the alkyne.⁹² The use of a strong acid like *p*-toluenesulfonic acid resulted in only decomposition products, but the use of trifluoroacetic acid produced the desired isoxazole in 81% yield. The use of Na₂CO₃ severely impaired the reaction, producing minimal conversion after 60 h. Lowering the trifluoroacetic acid loading to five equivalents in the presence of triphenylphosphine increased the yield of the desired isoxazole to 96%. Other phosphine ligands were also tested (Table 3.3.2, Entries 9-12), with triphenylphosphite producing isoxazole **154** in 96% yield. The more strongly donating trialkyl phosphines inhibited the reaction, most likely due to making the Pt(II) center too electron rich to fully engage the π -system of the alkyne. Overall the results of these experiments corroborated our two suspicions about what was preventing the desired reactivity: the proton transfer event was being disrupted by the presence of an additional Lewis basic site and the Pt catalyst needed to be more electron rich to facilitate extrusion of the activated methyl ether. Under the optimized reaction conditions both the triphenylphosphine and trifluoroacetic acid act synergistically to produce the isoxazole in high yield.

Table 3.3.2. Effect of Phosphine Ligands and Additives.



Entry	Ligand	Additive (equiv)	Time (h)	Yield 154 (%) ^a	Yield 155 (%) ^a
1	-	AcOH (10)	32	39	11
2	PPh ₃	AcOH (10)	21	48	14
3	PPh ₃	(NH ₄)HCO ₂ (10)	70	0	0
4	PPh ₃	H ₃ PO ₄ (10)	70	76	11
5	PPh ₃	TFA (10)	16	81	1
6	PPh ₃	TsOH (2)	17	0	0
7	PPh ₃	Na ₂ CO ₃ (1)	60	6	< 1
8	PPh ₃	TFA (5)	16	96	1
9	PCy ₃ ^b	TFA (5)	70	57	3
10	P(<i>n</i> -Bu) ₃ ^b	TFA (5)	70	49	4
11	P(<i>t</i> -Bu) ₂ (<i>o</i> -biphenyl) ^b	TFA (5)	70	47	2
12	P(OPh) ₃	TFA (5)	16	96	1

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Performed under an argon atmosphere.

3.3.3 Effect of the Nitrogen Protecting Group

With optimized conditions in hand, we then investigated what effect the nitrogen protecting group had on the reaction. Several carbamates were synthesized and exposed to the reaction conditions (Table 3.3.3, entries 1-6). The *t*-butyl carbamate (Table 3.3.3, entry 6) produced the desired isoxazole **154** with the highest yield and also the shortest reaction time. The success of acid stable carbamates like methyl and ethyl carbamate, and the acetamide substrate (Table 3.3.3, entries 1, 2, 7) were surprising, as it was originally hypothesized that these groups would not readily cleave under the reaction conditions. The free hydroxylamine (Table 3.3.3, entry 8) performed poorly in this reaction, producing the desired isoxazole **154** in only 7% yield. This result gave us some early insight to the mechanism of this reaction, indicating the cyclization

event occurs before removal of the carbamate protecting group. A more thorough explanation of the mechanism of this reaction is presented in Section 3.3.6.

Table 3.3.3. Nitrogen Protecting Group Evaluation.

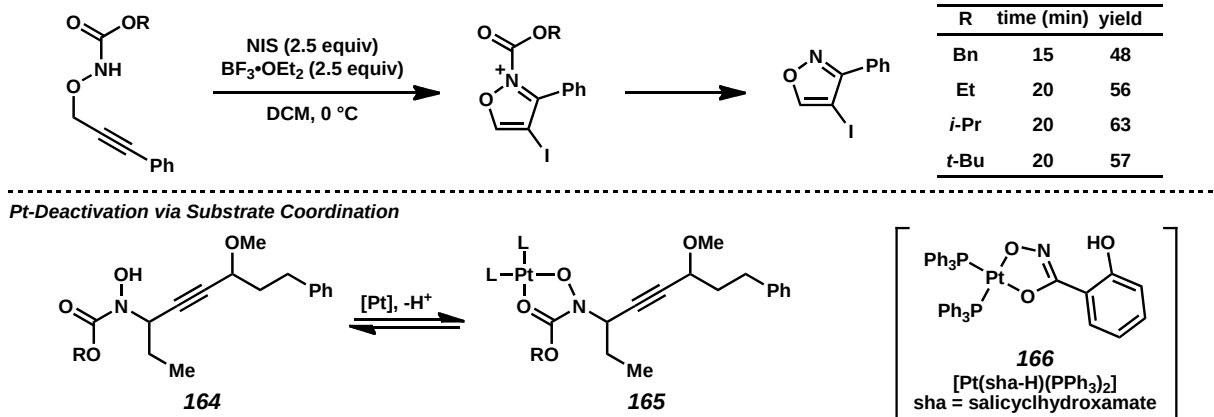
Entry	Substrate	Time (h)	Yield (%) ^a	Entry	Substrate	Time (h)	Yield (%) ^a
1		96	71	5		96	53
2		96	59	6		17	96
3		72	72	7		20	64
4		42	48	8		6	7

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard.

Also surprising was the effect the carbamate groups had on the rate of consumption of the starting material, with bulkier groups converting the starting material with much shorter reaction times. The oxidative cyclization developed by Wada and coworkers also examined the effect that the carbamate protecting group on nitrogen had on the formation of isoxazoles (Scheme 3.3.3).⁹³ They observed that the isopropyl carbamate produced the desired isoxazole in slightly higher yields than the ethyl, benzyl or *t*-butyl carbamates, yet the different protecting groups did not affect the reaction times to the same extent as what we had observed in our system. One hypothesis to explain the carbamate effect on the rate of ring closure is that the less sterically hindered carbonyls more easily coordinate the platinum catalyst under the reaction conditions to

form a complex like **165** (Scheme 3.3.3). Hydroxamic acids have been shown to coordinate to platinum centers via a bidentate coordination between the hydroxyl and carbonyl oxygen atoms, with complex $[\text{Pt}(\text{sha-H})(\text{PPh}_3)_2]$ (**166**) being representative.⁹⁴ The resulting complex (**165**) would be less likely to coordinate and activate alkynes due to the presence of the strongly bound bidentate ligand. Increasing the bulk of the R group on the carbamate oxygen disfavors this type of coordination around the platinum center, and facilitates the desired reactivity. It is suspected the presence of the allyl group in carbamate **159** provides additional activation of the platinum catalyst, which offsets this effect to a small extent.⁹⁵ The variable yields of the desired isoxazole product (**154**) generated by the different *N*-protecting groups is most likely due to complications with the cleavage of this group.

Wada 2011



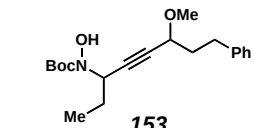
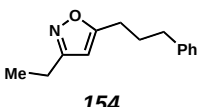
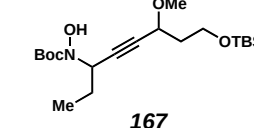
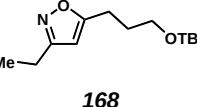
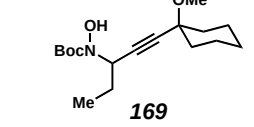
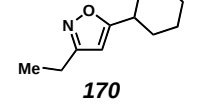
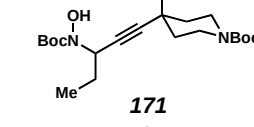
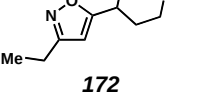
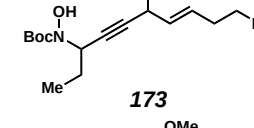
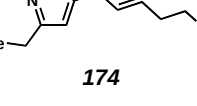
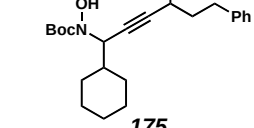
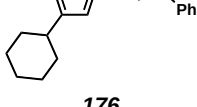
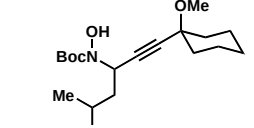
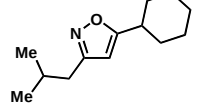
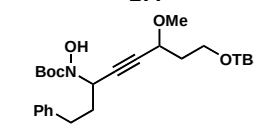
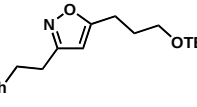
Scheme 3.3.3. Substrate Coordination as an Explanation for Reaction Rates.

3.3.4 Synthesis of Isoxazoles from Propargylic *N*-Hydroxycarbamates

Having established the optimized cyclization conditions, a number of isoxazoles were synthesized using this method (Table 3.3.4).⁹⁶ An array of 3,5-disubstituted isoxazoles can be accessed from their corresponding *N*-hydroxycarbamates in good overall yield. Particularly noteworthy is isoxazole **172**, which features a separate Boc carbamate that is not cleaved under

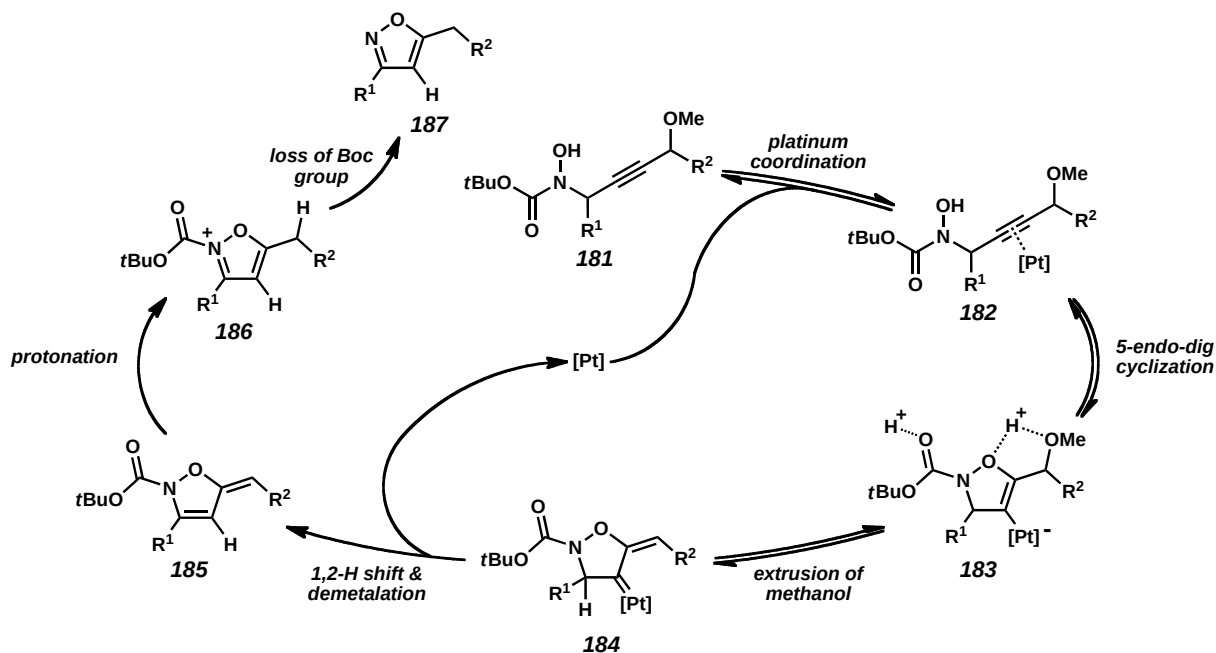
the reaction conditions, and isoxazole **174**, which contains an alkene that did not isomerize into conjugation with the heterocyclic ring under the reaction conditions. Other acid labile functional groups like silyl ethers were also tolerant of the reaction conditions. These examples highlight the fact that the reaction conditions are still quite mild, despite the inclusion of 5.0 equivalents of trifluoroacetic acid.

Table 3.3.4. Synthesis of Isoxazoles from *N*-Hydroxycarbamates.

$ \begin{array}{c} \text{BocN} \begin{array}{c} \text{OH} \\ \\ \text{CH}(\text{R}^1) \end{array} \text{---} \text{C} \equiv \text{C} \text{---} \text{CH}(\text{OMe})\text{R}^2 \\ \xrightarrow[\text{1,4-dioxane, 60 }^\circ\text{C}]{\begin{array}{c} [(\text{C}_2\text{H}_5)_4\text{PtCl}_2]_2 \text{ (2.5 mol \%)} \\ \text{P}(\text{OPh})_3 \text{ (5 mol \%)} \\ \text{TFA (5.0 equiv)} \end{array}} \\ \text{Product: } \begin{array}{c} \text{N} \text{---} \text{O} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \quad \\ \text{R}^1 \quad \text{CH}_2\text{R}^2 \end{array} \end{array} $				
Entry	Substrate	Product	Time (h)	Isol. Yield (%)
1	 153	 154	12	84
2	 167	 168	1	79
3	 169	 170	12	70
4	 171	 172	40	71
5	 173	 174	7	61
6	 175	 176	4	68
7	 177	 178	16	63
8	 179	 180	16	63

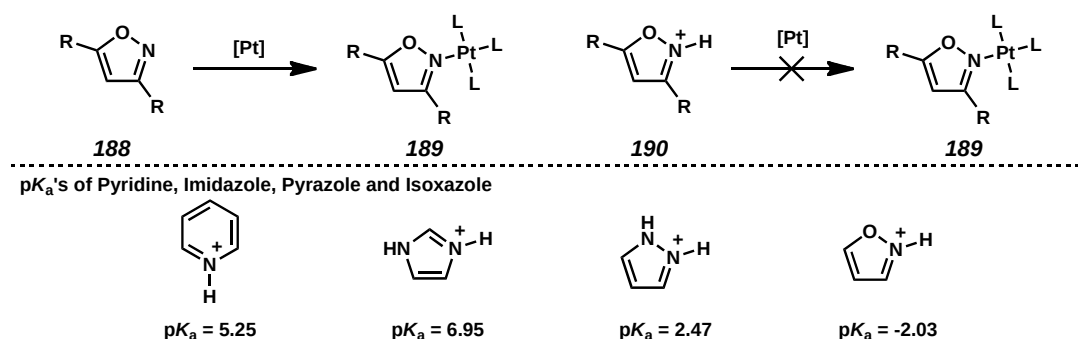
3.3.5 Mechanistic Proposal for the Formation of Isoxazoles from *N*-hydroxycarbamates

The mechanistic picture for the formation of isoxazoles is similar to that proposed for the formation of furans in Chapter 2, with a few important differences. Scheme 3.3.4 illustrates the general mechanism that we believe to be operative in this reaction. Coordination of the alkyne π -bond to the platinum catalyst initiates the 5-*endo-dig* cyclization, leading to vinyl-metal intermediate **183**. The inclusion of a Brønsted acid restores the proton transfer from the hydroxyl nucleophile to the oxygen atom of the methyl ether. This activates the ether, allowing back-donation from the platinum center to extrude methanol and form the α,β -unsaturated platinum carbene **184** (evidence in support of the formation of carbene **184** is discussed in Chapter 4). A 1,2-hydride shift followed by demetalation produces diene **185**, which readily isomerizes via protonation of the exocyclic alkene to form aromatic *N*-Boc iminium **186**. The loss of the Boc-protecting group from the iminium then generates the isoxazole product.



Scheme 3.3.4. Potential Mechanism for the Formation of Isoxazoles.

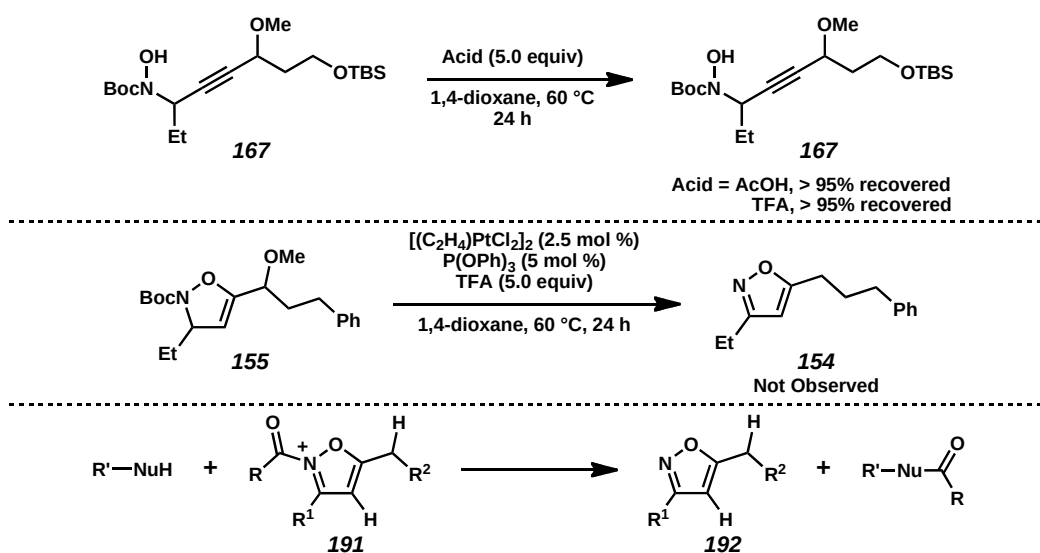
It is possible that coordination of the isoxazole product to platinum (**189**) would deactivate the platinum catalyst in a manner that is similar to the effect added pyridine had on the reactions to form furans (Scheme 3.3.5).⁹⁷ The addition of a Brønsted acid would protonate the isoxazole nitrogen atom, preventing product coordination and deactivation of the catalyst. One problem with this hypothesis is that isoxazoles are very nonbasic when compared to other nitrogen containing heterocycles like pyridine, imidazole and pyrazole, with the pK_a of isoxazole being measured at -2.03.⁹⁸ It is possible that the added trifluoroacetic acid ($pK_a = 0.23$) protonates the isoxazole nitrogen (**190**) preventing coordination to platinum, but the differences in pK_a 's indicates this equilibrium would favor the unprotonated isoxazole. The inclusion of acetic acid ($pK_a = 4.76$) also helped promote the desired reaction, and it is highly unlikely that protonation of the isoxazole occurred when acetic acid was added to the reaction. This points to the role of the acid additive as being more than just a means to prevent the isoxazole products from poisoning the catalyst, and gives credence to the hypothesis that the acid helps to activate the methyl ether.



Scheme 3.3.5. Product Inhibition of the Platinum Catalyst.

Cleavage of the nitrogen-protecting group as the last step of the reaction is supported by several observations. As mentioned earlier, the free hydroxylamine was not reactive under the

conditions, producing the desired isoxazole in only 7% yield (See Table 3.3.1). Exposure of *N*-hydroxycarbamate **167** to a solution of either TFA or AcOH in 1,4-dioxane at 60 °C for 24 h resulted in no conversion to the free hydroxylamine **163** (Scheme 3.3.6). Exposure of isoxazoline **155** to the reaction conditions also did not produce isoxazole **154**, eliminating the possibility of a hydroalkoylation event, followed by an acid catalyzed elimination-deprotection-isomerization sequence. These results, coupled with the fact that several acid-stable carbamates and an acetamide were all successful in this reaction (see Table 3.3.1), points to the formation of a more activated nitrogen species that renders the protecting group much more labile. While the acid-labile Boc group likely decomposes to form CO₂ and isobutylene, the acid-stable protecting groups must cleave with the assistance of an attacking nucleophile. The aromatic iminium **191** is consistent with this hypothesis, as it could transfer the protecting acyl group readily to a variety of nucleophiles (most likely methanol) in a manner similar to the way acyl dimethylaminopyridiniums react.⁹⁹ These insights helped us to gain a better understanding of the reaction and implicated that this transformation could be extended to substrates that would lead to complementary isoxazole products.

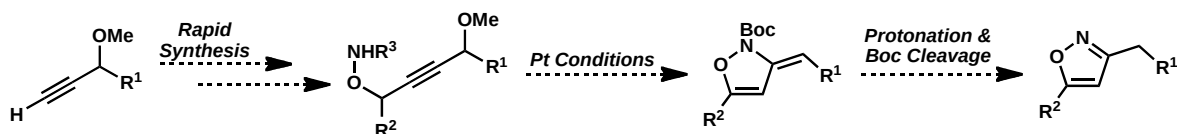


Scheme 3.3.6. Cleavage of the Nitrogen Protecting Group.

3.4 Synthesis of Isoxazoles from Propargylic *N*-Boc Amino Ethers

3.4.1 Identification and Synthesis of the Model Substrate

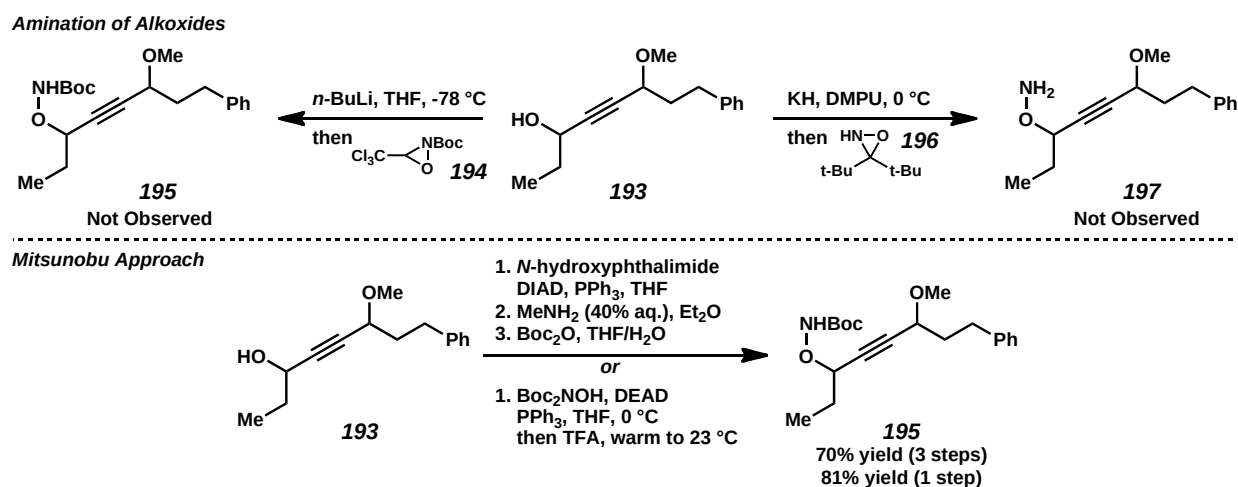
Having established a method for converting propargylic *N*-hydroxycarbamates to isoxazoles, we turned our focus on extending this method to the synthesis of isoxazoles from propargylic amino ethers. This would require a protected nitrogen atom adding into the activated alkyne to initiate the reaction, followed by extrusion of the activated methyl ether, 1,2-hydride shift, and subsequent isomerization to the aromatic heterocycle (Scheme 3.4.1). Among the questions we had concerning this substrate class were: (1) could we synthesize the target substrates rapidly from an advanced intermediate (2) would the aminoethers be compatible with the desired reaction/would the conditions developed for the *N*-hydroxy carbamates work for this substrate class? If we could successfully address these two concerns, it would enable a facile synthesis of complementary positional isomers of the isoxazoles produced from the *N*-hydroxycarbamate substrates.



Scheme 3.4.1. Isoxazoles from Propargylic Amino Ethers.

We decided to use *N*-Boc amino ethers as our nitrogen based nucleophiles, as we had already demonstrated the controlled cleavage of the carbamate upon aromatization of the heterocycle. Synthetically we could access these substrates by the amination of propargylic alcohols followed by Boc protection. Propargylic alcohol **193** was easily synthesized from the addition of the lithium acetylide of alkyne **119** into propionaldehyde. Efforts to directly aminate the hydroxyl group using oxaziridines **194**¹⁰⁰ or **196**¹⁰¹ failed to generate the desired amination products

(Scheme 3.4.2). A lengthy synthesis of **195** using a Mitsunobu reaction with *N*-hydroxyphthalimide followed by deprotection and Boc protection produced the desired *N*-Boc amino ether **195** in 70% yield over the three steps. While this synthesis was reliable, an alternate procedure using Boc_2NOH ¹⁰² as the nucleophile in a Mitsunobu reaction followed by removal of one of the Boc groups *in situ* produced the desired *N*-Boc amino ether **195** in 81% yield in one step. This later synthesis enabled the rapid construction of our desired isoxazole precursor via a route that is more closely aligned with our initial goal of producing the isoxazole substrates rapidly from an advanced alkyne intermediate.



Scheme 3.4.2. Synthesis of *N*-Boc Amino Ethers.

3.4.2 Synthesis of Isoxazoles from Propargylic *N*-Boc Amino Ethers

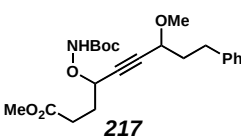
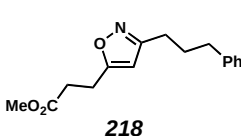
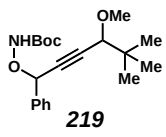
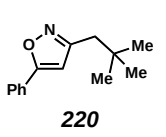
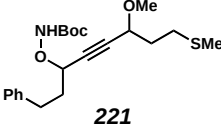
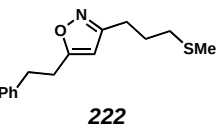
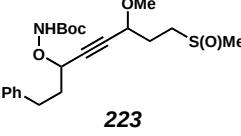
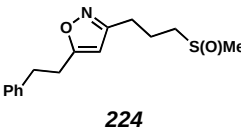
Exposure of **195** to the previously developed reaction conditions resulted in the formation of the desired isoxazole **198** in 93% yield. Using these conditions we were able to synthesize a number of substituted isoxazole products (Table 3.4.1). Of note are the six isoxazoles (Table 3.4.1, entries 1-6), which are the direct complements of the heterocycles formed from the *N*-hydroxycarbamates (Table 3.3.4, entries 1-6), with each compound originating from common

propargylic ether starting materials. Acid labile groups were stable to the reaction conditions, with Boc carbamates and silyl ethers being compatible with the transformation (Table 3.4.1, entries 2, 4). Additional functional groups like carboxylic acids, esters, thioethers and sulfoxides were unaffected by the reaction conditions, producing the isoxazole in good yields (Table 3.4.1, entries 10, 11, 13, 14). This substrate class converted to the desired isoxazoles with much shorter reaction times and in higher yields than the *N*-hydroxycarbamates. The increased reactivity of the amino ethers compared to the hydroxycarbamates could be due to decreased allylic strain in the substrates, allowing for a more reactive conformation of the substrate, as well as differences in the inherent nucleophilicity of the nitrogen vs. the oxygen nucleophiles.

Table 3.4.1. Synthesis of Isoxazoles from Propargylic *N*-Boc Amino Ethers.

$ \begin{array}{c} \text{NH-Boc} \\ \\ \text{O} \\ \\ \text{R}^1 - \text{CH}_2 - \text{C} \equiv \text{C} - \text{CH}(\text{OMe}) - \text{R}^2 \\ \xrightarrow[\text{1,4-dioxane, 60 } ^\circ\text{C}]{\begin{array}{c} [(\text{C}_2\text{H}_5)_4\text{PtCl}_2]_2 \text{ (2.5 mol \%)} \\ \text{P(OPh)}_3 \text{ (5 mol \%)} \\ \text{TFA (5.0 equiv)} \end{array}} \\ \text{Product: Isoxazole ring with R}^1 \text{ and R}^2 \text{ substituents} \end{array} $				
Entry	Substrate	Product	Time (h)	Isol. Yield (%)
1	 195	 198	4	93
2	 199	 200	1.5	96
3	 201	 202	1.5	86
4	 203	 204	1.5	93
5	 205	 206	0.25	88
6	 207	 208	0.25	96
7	 209	 210	0.25	89
8	 211	 212	0.25	83
9	 213	 214	0.5	87
10	 215	 216	2	52

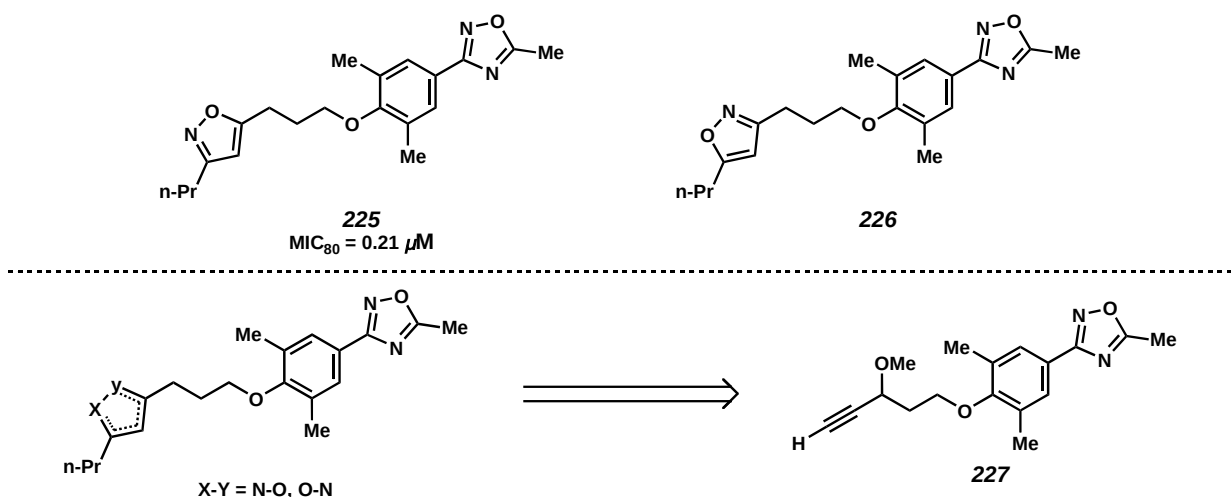
Table 3.4.1. Continued.

11	 217	 218	0.5	71
12	 219	 220	0.5	75
13	 221	 222	96	51
14	 223	 224	2	71

3.5 Application of Isoxazole Method

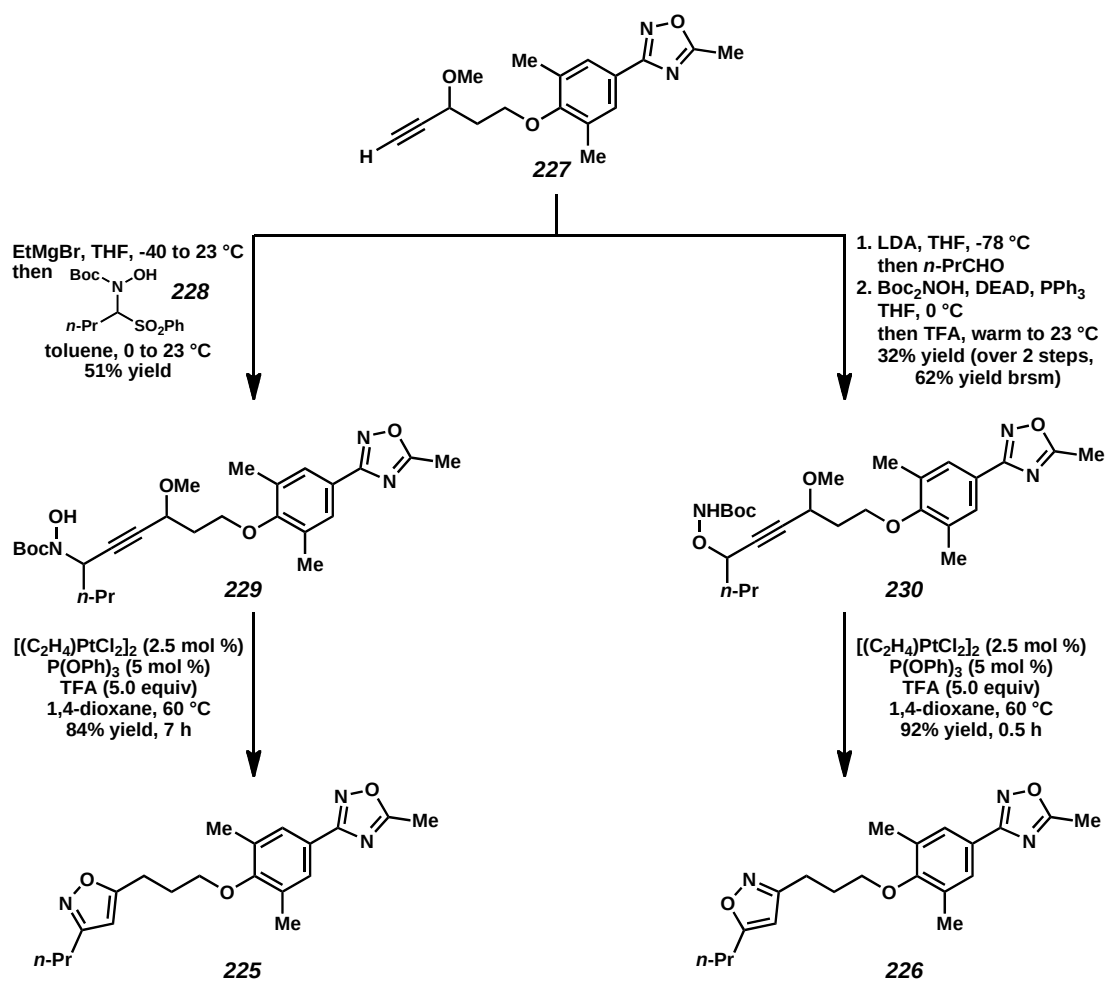
3.5.1 Synthesis of Complementary Antirhinovirus Compounds

The most attractive feature of our approach to isoxazole synthesis is the ease with which one can access both positional isomers of the heterocycle. While several of our substrates demonstrated this potential, we sought a more functionally diverse intermediate to use as the branch point in an isoxazole synthesis. Ideally our targets could highlight the potential of our method in a medicinal chemistry context. Isoxazole **225** (Scheme 3.5.1) was an ideal substrate, as it had demonstrated antirhinovirus activity with an MIC₈₀ value of 0.21 μM , could be synthesized from terminal alkyne **227**, and its positional isomer (**226**) was not studied.^{103,104} Several studies have demonstrated the effect that the positioning of nitrogen and oxygen atoms in the isoxazole ring can have pronounced influences on the activity of the parent compound.¹⁰⁵ We hoped to apply our method to access both positional isomers of isoxazole **225** as a way to highlight the general utility of our process.



Scheme 3.5.1. General Utility of Our Method.

Deprotonation of propargylic ether **227** with ethyl magnesium bromide followed by exposure to *N*-Boc nitron precursor **228** produced the desired *N*-hydroxy carbamate (**229**) in 51% yield (Scheme 3.5.2). Use of a Grignard reagent was critical, as lithium acetylides generated from LDA or *n*-BuLi did not add into the nitron. Synthesis of the *N*-Boc amino ether was accomplished using the Mitsunobu protocol described earlier, producing the desired amino ether (**230**) in 32% yield (62% brsm) over the two steps. Exposure of *N*-hydroxy carbamate **229** and *N*-Boc amino ether **230** to the Pt-catalyzed conditions produced the desired isoxazoles in 84% and 92% yields respectively. In each case, the oxadiazole ring was not affected by the acidic conditions, nor did it appear to hinder the reactivity of the Pt(II) catalyst. The success of these two reactions validated our approach to the synthesis of complementary positional isomers, and demonstrated its potential utility.

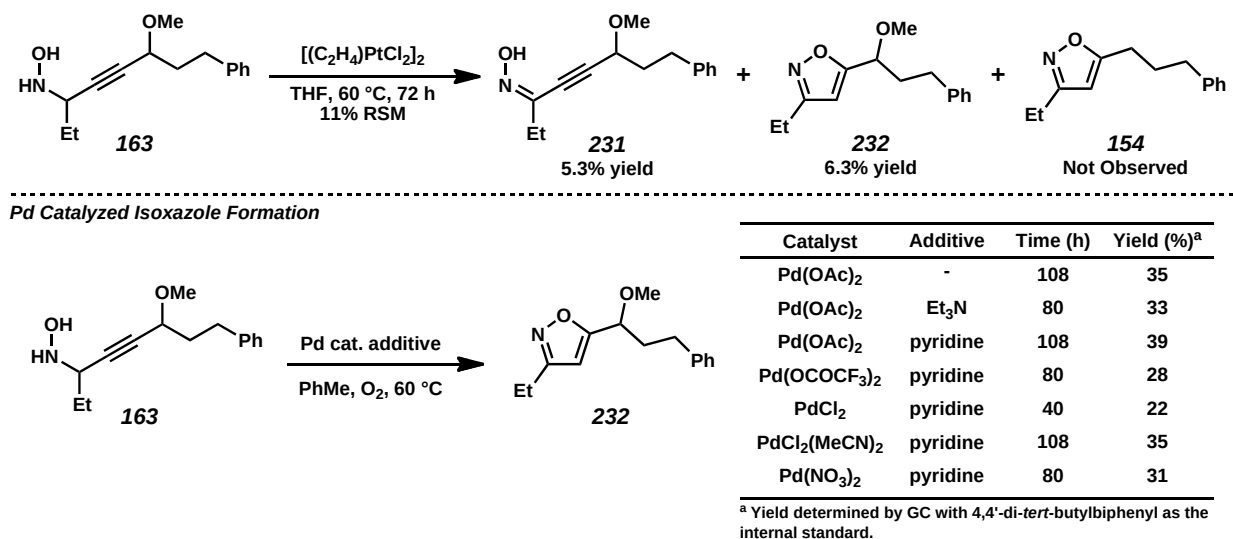


Scheme 3.5.2. Synthesis of Antirhinovirus Compounds.

3.6 Synthesis of Isoxazoles from Hydroxylamines

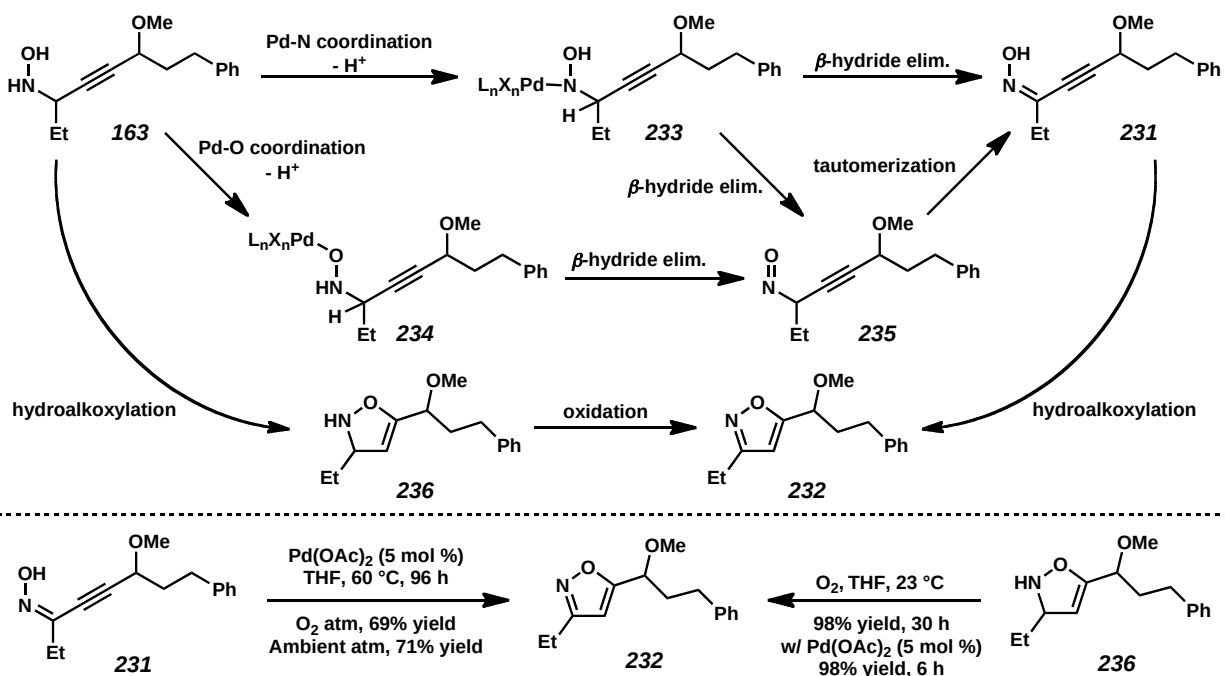
3.6.1 Evaluation of an Aerobic Oxidation of Hydroxylamines

We made an interesting observation during our evaluation of reaction conditions to promote the formation of isoxazoles from protected hydroxylamines. As discussed above (Table 3.3.3), when free hydroxylamine **163** was exposed to the reaction conditions only minimal conversion to the expected isoxazole product **154** was observed. Our initial hypothesis was that the acidic reaction conditions were protonating the nitrogen atom, resulting in a decreased nucleophilicity of the hydroxyl group. Exposing hydroxylamine **163** to Zeise's dimer in THF at 60 °C resulted in a complex mixture of products, with < 5% of desired isoxazole **154** forming (Scheme 3.6.1). Two products that were isolated from this reaction were oxime **231** and isoxazole **232**, both of which contained the propargylic methyl ether. The formation of oxime **231** led us to believe a metal catalyzed aerobic oxidation of hydroxylamine **163** was occurring, a reaction that would be much more facile using Pd(II) catalysis.¹⁰⁶ Exposing hydroxylamine **163** to a variety of Pd(II) salts/amine ligand combinations resulted in modest yields of isoxazole **232**. In general the major issue with this reaction was the slow conversion of oxime **231** to isoxazole **232**.



Scheme 3.6.1. Palladium(II) Catalyzed Isoxazole Formation.

Mechanistically we envisioned this reaction proceeding through three different pathways (Scheme 3.6.2). The first involves Pd(II) coordination & deprotonation at oxygen followed by β -hydride elimination to produce oxime **231**. An analogous pathway where Pd(II) coordination & deprotonation at nitrogen, followed by β -hydride elimination would produce nitroso **235**, which could tautomerize to oxime **231**. Hydroalkoxylation of the alkyne by the oxime would lead to the formation of the desired isoxazole. A third pathway involves hydroalkoxylation to produce isoxazoline **236**, which could then be oxidized to afford the desired isoxazole. Exposure of oxime **231** to Pd(OAc)₂ resulted in good yields of isoxazole **232**, with similarly long reaction times required regardless of the atmosphere of the reaction. Exposure of isoxazoline **236** to an oxygen atmosphere resulted in nearly quantitative conversion to isoxazole **232** after 30 h. This reaction was even faster when run in the presence of Pd(OAc)₂, forming isoxazole **232** in 98% yield after only 6 h. Based on these experiments we reasoned that both the oxidation and hydroalkoxylation events were slow on these substrates and that the air oxidation of isoxazoline **236** was a possible route to isoxazole formation. While these results are preliminary, they demonstrate potential as a way to study aerobic oxidation processes in the context of isoxazole synthesis.



Scheme 3.6.2. Potential Mechanisms for the Palladium(II) Catalyzed Isoxazole Formation.

3.7 Conclusion

We have developed a novel approach to isoxazole synthesis that enables the formation of complementary positional isomers from an advanced alkyne intermediate. Our optimization efforts provided insights into the potential mechanism for the transformation. The addition of trifluoroacetic acid imparted additional activation of the propargylic methyl ether, enabling formation of the desired isoxazoles. Also demonstrated was the effect of phosphine ligation on the platinum catalyst, with slightly donating phosphines enhancing the back-donation of the metal into the π -system, as evidenced by higher yields of the isoxazole product. The cyclization reactions all proceeded efficiently and showed a tolerance to a variety of different functional groups, a testament to the mildness of the reaction conditions. Finally our ability to synthesize the more functionalized isoxazoles (225 and 226) using our approach highlights the broader utility of our method.

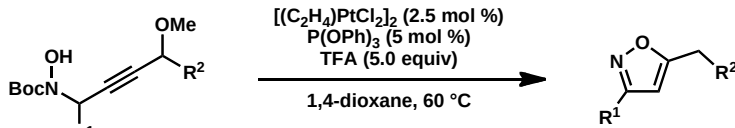
3.8 Experimental Section

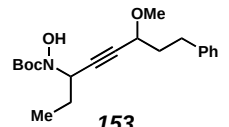
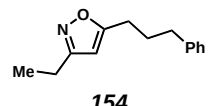
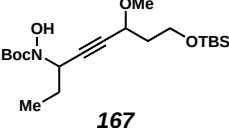
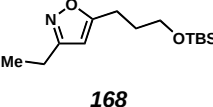
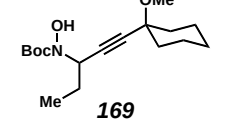
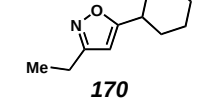
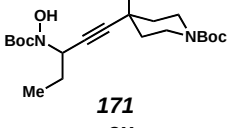
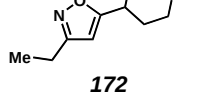
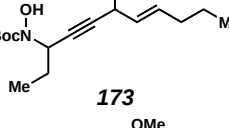
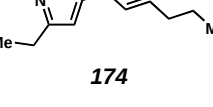
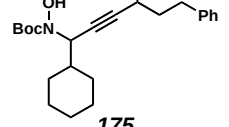
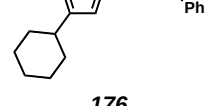
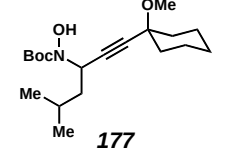
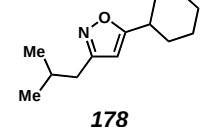
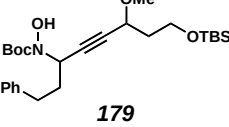
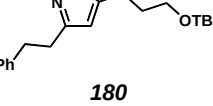
3.8.1 Materials and Methods

Reactions were performed under an ambient atmosphere unless otherwise noted. Tetrahydrofuran, ether, dichloromethane and toluene were purified by passing through activated alumina columns. 1,4-dioxane was distilled over sodium/benzophenone. Triphenylphosphite was purified by passing through an alumina column under an argon atmosphere. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products, (West Columbia, SC), Strem (Newburyport, MA) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 μm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde or KMnO_4 solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on a Varian 400 MR (at 400 MHz), and are reported relative to SiMe_4 (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) and are reported relative to SiMe_4 (δ 0.0). All IR spectra were obtained on NaCl plates (film) with a Bruker Tensor 27. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.

3.8.2 Platinum Catalyzed Isoxazole Synthesis: *N*-Hydroxycarbamates

Table 3.3.4. (reproduced)



Entry	Substrate	Product	Time (h)	Isol. Yield (%)
1	 153	 154	12	84
2	 167	 168	1	79
3	 169	 170	12	70
4	 171	 172	40	71
5	 173	 174	7	61
6	 175	 176	4	68
7	 177	 178	16	63
8	 179	 180	16	63

General procedure for the platinum catalyzed isoxazole synthesis. To a solution of triphenylphosphite (5.0 mol %) in 1,4-dioxane (1/3 of total reaction volume) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (2.5 mol %). After 15 min, trifluoroacetic acid (5.00 equiv) was added and the mixture was stirred for 1 min. The resulting solution was then added to a solution of the *N*-hydroxycarbamates in 1,4-dioxane (2/3 of total reaction volume, 0.10 M in substrate–final concentration), and the mixture was heated at 60 °C in a sealed vial. Upon completion, as determined by TLC, the reaction was quenched with Et_3N (0.500 mL), and filtered through a plug of silica gel. The plug was washed with additional solvent (2x reaction volume). The solvent was then removed via rotary evaporation, and the crude isoxazole was purified by silica gel flash chromatography.

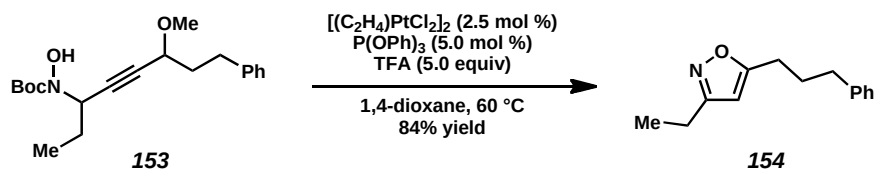


Table 3.3.4, Entry 1. According to the general procedure, to a solution of triphenylphosphite (39.3 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μ L, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **153** (0.104 g, 0.300 mmol) in 1,4-dioxane (1.87 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 12 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1

hexanes/EtOAc eluent) to afford isoxazole **154** (54.1 mg, 84% yield, R_f = 0.54 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 154: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 5.83 (s, 1H), 2.69 (comp m, 6H), 2.02 (quintet, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.0, 165.3, 141.4, 128.59, 128.57, 126.2, 100.3, 35.2, 29.2, 26.3, 19.7, 12.8; IR (film) 2936, 2360, 1602, 1455, 1368, 1159, 746 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{14}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 216.1383, found 216.1372.

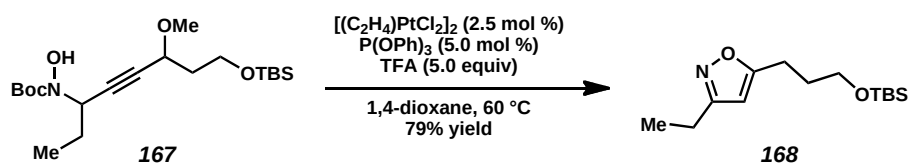


Table 3.3.4, Entry 2. According to the general procedure, to a solution of triphenylphosphite (39.3 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere, was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μL , 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **167** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **168** (63.7 mg, 79% yield, R_f = 0.62 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 168: ^1H NMR (400 MHz, CDCl_3) δ 5.83 (s, 1H), 3.65 (t, J = 6.0 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 2.65 (q, J = 7.6 Hz, 2H), 1.92-1.85 (m, 3H), 1.25 (t, J = 7.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 165.3, 100.3, 61.9, 30.7, 26.1, 23.4, 19.7, 18.4, 12.8, -5.2; IR (film) 2956, 1604, 1255, 1104, 836 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for ($\text{M} + \text{H}$) $^+$ [$\text{C}_{14}\text{H}_{27}\text{NO}_2\text{Si} + \text{H}$] $^+$: 270.1884, found 270.1892.

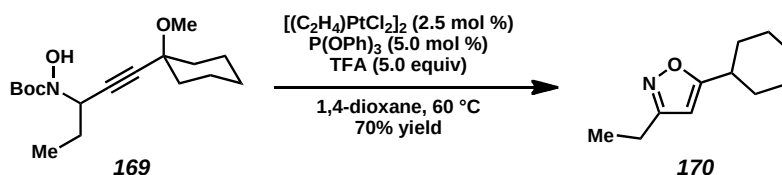


Table 3.3.4, Entry 3. According to the general procedure, to a solution of triphenylphosphite (65.6 μL , 10% (v/v) in 1,4-dioxane, 0.0250 mmol) in 1,4-dioxane (1.50 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (7.3 mg, 0.0125 mmol). After 15 min, trifluoroacetic acid (0.186 mL, 2.00 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **169** (0.156 g, 0.500 mmol) in 1,4-dioxane (3.50 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 12 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (8.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) to afford isoxazole **170** (62.8 mg, 70% yield, R_f = 0.64 in 4:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 170: ^1H NMR (400 MHz, CDCl_3) δ 5.78 (s, 1H), 2.71 (ddd, J = 14.6, 7.2, 3.7 Hz, 1H), 2.64 (q, J = 7.6 Hz, 2H), 2.04-2.00 (comp m, 2H), 1.79 (comp m, 2H), 1.70 (m, 1H), 1.46-1.31

(comp m, 5H), 1.24 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.6, 165.0, 98.3, 36.5, 31.3, 26.0, 25.8, 19.8, 12.8; IR (film) 2933, 1680, 1597, 1450, 981, 801 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{11}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 180.1383, found 180.1377.

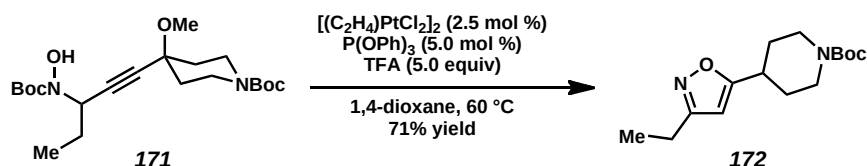


Table 3.3.4, Entry 4. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **171** (0.124 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a TeflonTM cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 40 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/ EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **172** (68.4 mg, 71% yield, $R_f = 0.40$ in 2:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 172: ^1H NMR (400 MHz, CDCl_3) δ 5.81 (app d, $J = 0.7$ Hz, 1H), 4.12 (comp m, 2H), 2.92-2.82 (comp m, 3H), 2.64 (q, $J = 7.6$ Hz, 2H), 2.00-1.95 (m, 2H), 1.65-1.53 (m, 2H), 1.44 (s, 9H), 1.24 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.5, 165.2, 154.8, 98.9, 79.8, 43.44, 43.40, 34.7, 30.2, 28.5, 19.7, 12.7; IR (film) 2976, 1695, 1599, 1423, 1169, 770 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_3 + \text{Na}$] $^+$: 303.1679, found 303.1685.

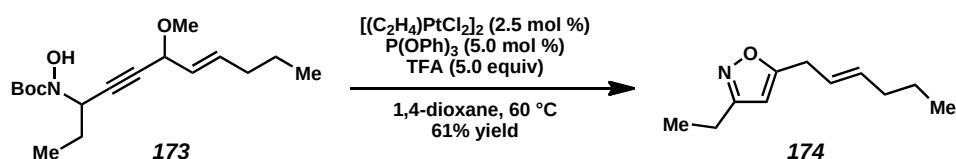


Table 3.3.4, Entry 5. According to the general procedure, to a solution of triphenylphosphite (39.4 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **173** (93.4 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 7 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **174** (32.7 mg, 61% yield, R_f = 0.60 in 4:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 174: ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.68-5.61 (m, 1H), 5.57-5.50 (m, 1H), 3.42 (dt, J = 6.5, 1.0 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 2.07-2.01 (m, 2H), 1.43 (sextet, J = 7.4 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 165.4, 134.6, 123.5, 100.5, 34.7, 30.4, 22.5, 19.8, 13.8, 12.9; IR (film) 2965, 1700, 1460, 1251, 966 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{11}H_{17}NO + H$] $^+$: 180.1383, found 180.1374.

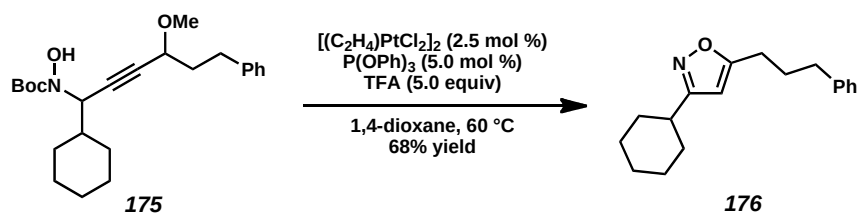


Table 3.3.4, Entry 6. According to the general procedure, to a solution of triphenylphosphite (39.4 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **175** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 4 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **176** (55.0 mg, 68% yield, R_f = 0.62 in 4:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 176: ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (comp m, 2H), 7.22-7.18 (comp m, 3H), 5.82 (s, 1H), 2.72 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.02 (sextet, J = 7.6 Hz, 2H), 1.97-1.95 (comp m, 2H), 1.83-1.79 (comp m, 2H), 1.75-1.71 (m, 1H), 1.48-1.33 (comp m, 5H), 1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.5, 141.4, 128.6, 126.1, 99.19, 99.17, 36.0, 35.3, 32.2, 29.2, 26.3, 26.1, 26.0; IR (film) 2929, 1602, 1450, 902, 700 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(M + H)^+$ [$C_{18}H_{23}NO + H$] $^+$: 270.1852, found 270.1850.

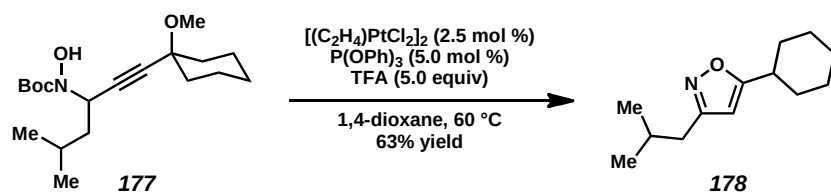


Table 3.3.4, Entry 7. According to the general procedure, to a solution of triphenylphosphite (39.4 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **177** (0.102 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 16 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **178** (39.1 mg, 63% yield, R_f = 0.61 in 4:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 178: ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 2.72 (ddd, J = 8.2, 6.5, 6.3 Hz, 1H), 2.48 (d, J = 7.2 Hz, 2H), 2.04-2.02 (m, 2H), 1.94 (dt, J = 13.6, 6.8 Hz, 1H), 1.79 (dt, J = 8.3, 3.8 Hz, 2H), 1.73-1.69 (m, 1H), 1.49-1.23 (m, 5H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 163.0, 99.0, 36.4, 35.2, 31.3, 28.1, 26.0, 25.8, 22.6; IR (film) 2932, 1597, 1450, 1170, 1022, 792 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{13}H_{21}NO + H$] $^+$: 208.1696, found 208.1696.

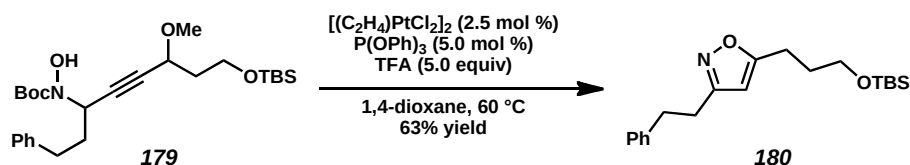


Table 3.3.4, Entry 8. According to the general procedure, to a solution of triphenylphosphite (39.3 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μ L, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **179** (0.142 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 16 h. Upon completion, the reaction was quenched with Et_3N (0.50 mL), and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **180** (64.7 mg, 63% yield, R_f = 0.62 in 4:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 180: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 5.76 (s, 1H), 3.65 (t, J = 6.0 Hz, 2H), 3.00-2.92 (m, 4H), 2.79 (t, J = 7.6 Hz, 2H), 1.91-1.84 (m, 2H), 0.91-0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.3, 140.9, 128.6, 128.5, 126.4, 100.7, 61.9, 34.6, 30.6, 28.1, 26.1, 23.3, 18.4, -5.2; IR (film) 2930, 1710, 1603, 1256, 1104, 837 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{20}H_{31}NO_2Si + H$] $^+$: 346.2197, found 346.2200.

3.8.3 Platinum Catalyzed Isoxazole Synthesis: *N*-Boc Amino Ethers

Table 3.4.1. (reproduced)

Entry	Substrate	Product	Time (h)	Isol. Yield (%)
1	 195	 198	4	93
2	 199	 200	1.5	96
3	 201	 202	1.5	86
4	 203	 204	1.5	93
5	 205	 206	0.25	88
6	 207	 208	0.25	96
7	 209	 210	0.25	89
8	 211	 212	0.25	83
9	 213	 214	0.5	87

Table 3.4.1. Continued.

10			2	52
11			0.5	71
12			0.5	75
13			96	51
14			2	71

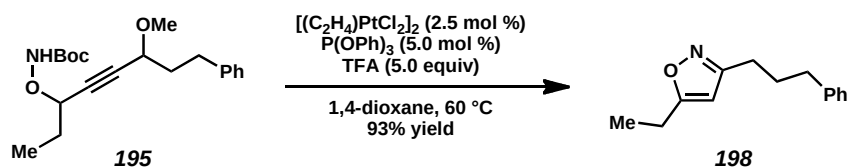


Table 3.4.1, Entry 1. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **195** (0.104 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 4 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation,

and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazole **198** (59.8 mg, 93% yield, R_f = 0.57 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 198: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.26 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.81 (s, 1H), 2.76-2.64 (m, 6H), 1.99 (quintet, J = 7.7 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 163.8, 141.8, 128.6, 128.5, 126.0, 99.8, 35.4, 30.1, 25.8, 20.3, 11.9; IR (film) 2977, 1603, 1454, 1345, 700 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{14}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 216.1383, found 216.1377.

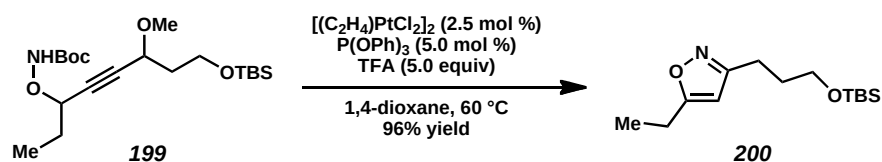


Table 3.4.1, Entry 2. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **199** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **200** (77.8 mg, 96% yield, R_f = 0.63 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 200: ^1H NMR (400 MHz, CDCl_3) δ 5.82 (s, 1H), 3.67 (t, J = 6.2 Hz, 2H), 2.75-2.67 (comp m, 4H), 1.90-1.83 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 163.9, 100.0, 62.4, 31.5, 26.1, 22.8, 20.3, 18.5, 11.9, -5.2; IR (film) 2955, 1604, 1255, 1104, 837 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{14}\text{H}_{27}\text{NO}_2\text{Si} + \text{H}$] $^+$: 270.1184, found 270.1189.

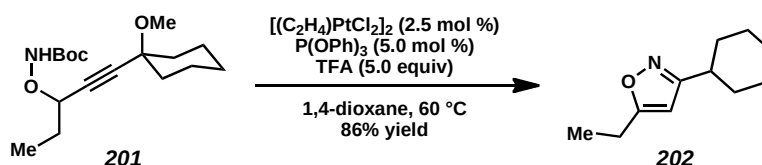


Table 3.4.1, Entry 3. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **201** (93.4 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon $^{\text{TM}}$ cap, placed in an aluminum block that was preheated to 60 $^{\circ}\text{C}$, and stirred for 1.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) to afford isoxazole **202** (46.5 mg, 86% yield, R_f = 0.62 in 4:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 202: ^1H NMR (400 MHz, CDCl_3) δ 5.83 (s, 1H), 2.76-2.68 (m, 1H), 2.73 (q, J = 7.6 Hz, 2H) 1.98-1.95 (comp m, 2H), 1.82-1.78 (comp m, 2H), 1.76-1.71 (m, 1H), 1.50-1.36 (comp m, 5H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 168.5, 98.4, 36.1, 32.2,

26.15, 26.06, 20.4, 11.9; IR (film) 2977, 1602, 1449, 1139, 813 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₅H₁₆O + H]⁺: 180.1383, found 180.1385.

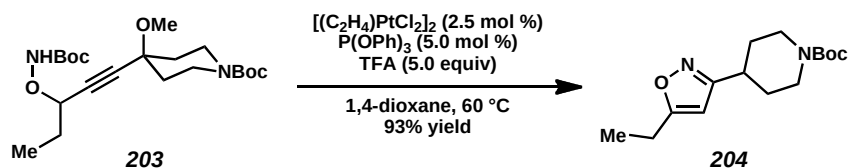


Table 3.4.1, Entry 4. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added [(C₂H₄)PtCl₂]₂ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **203** (0.124 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 1.5 h. The reaction was quenched with Et₃N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et₂O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent, SiO₂ neutralized with Et₃N) to afford isoxazole **204** (78.0 mg, 93% yield, R_f = 0.28 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazole 204: ¹H NMR (400 MHz, CDCl₃) δ 5.84 (s, 1H), 4.16 (d, J = 13.3 Hz, 2H), 2.88 (tt, J = 13.0, 3.2 Hz, 3H), 2.75 (q, J = 7.6 Hz, 2H), 1.95-1.91 (comp m, 2H), 1.64 (qd, J = 12.4, 4.0 Hz, 2H), 1.48 (s, 9H), 1.29 (td, J = 7.6, 1.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 166.9, 154.9, 98.3, 79.7, 43.7, 34.3, 31.0, 28.6, 20.4, 11.8; IR (film) 2977, 1694, 1422, 1170, 770 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₅H₂₈N₂O₃ + H]⁺: 303.1679, found 303.1678.

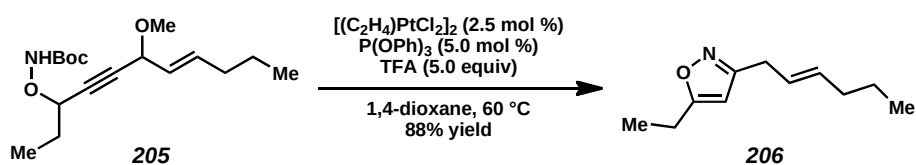


Table 3.4.1, Entry 5. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **205** (93.4 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **206** (47.2 mg, 88% yield, R_f = 0.58 in 4:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 206: ^1H NMR (400 MHz, CDCl_3) δ 5.82 (s, 1H), 5.63-5.48 (comp m, 2H), 3.34-3.32 (comp m, 2H), 2.76-2.70 (qd, J = 7.3, 0.8 Hz, 2H), 2.03-1.98 (comp m, 2H), 1.39 (sextet, J = 7.4 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 163.1, 133.7, 125.2, 100.0, 34.7, 29.7, 22.5, 20.4, 13.8, 11.9; IR (film) 2961, 1603, 1422, 1222, 968 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{11}\text{H}_{17}\text{NO} + \text{H}$] $^+$: 180.1383, found 180.1380.

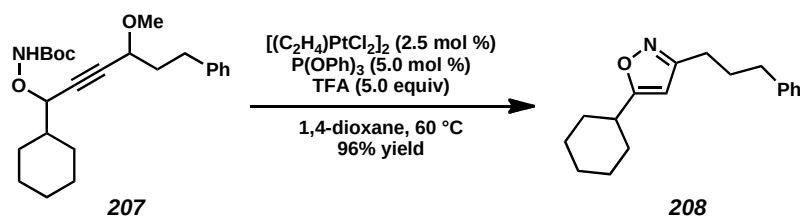


Table 3.4.1, Entry 6. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **207** (0.120 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a TeflonTM cap, placed in an aluminum block that was preheated to 60 $^\circ\text{C}$, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) to afford isoxazole **208** (77.7 mg, 96% yield, R_f = 0.61 in 4:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 208: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.77 (s, 1H), 2.70 (comp m, 5H), 2.05-1.95 (comp m, 4H), 1.82-1.78 (comp m, 2H), 1.74-1.70 (m, 1H), 1.49-1.32 (comp m, 4H), 1.26 (dtd, J = 14.7, 7.2, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.7, 163.5, 141.8, 128.6, 128.5, 126.0, 98.6, 36.4, 35.5, 31.3, 30.1, 26.0, 25.82, 25.80; IR (film) 2932, 1597, 1451, 1351, 1029, 747 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ $[\text{C}_{18}\text{H}_{23}\text{NO} + \text{H}]^+$: 270.1852, found 270.1844.

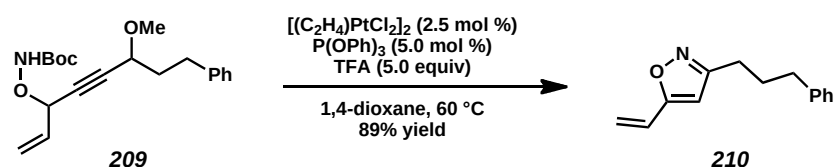


Table 3.4.1, Entry 7. According to the general procedure, to a solution of triphenylphosphite (39.4 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **209** (0.103 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **210** (57.0 mg, 89% yield, R_f = 0.57 in 4:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 210: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (comp m, 2H), 7.21-7.18 (comp m, 3H), 6.58 (dd, J = 17.7, 11.3 Hz, 1H), 6.05 (s, 1H), 5.98 (dd, J = 17.7, 0.8 Hz, 1H), 5.53 (dd, J = 11.3, 0.9 Hz, 1H), 2.70 (t, J = 5.1 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.04-1.97 (quintet, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 164.0, 141.6, 128.6, 128.5, 126.1, 122.6, 120.3, 101.3, 35.4, 30.0, 25.7; IR (film) 2938, 1566, 1424, 1278, 983 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for $(M + H)^+$ [$C_{14}H_{15}NO + H$]⁺: 214.1226, found 214.1235.

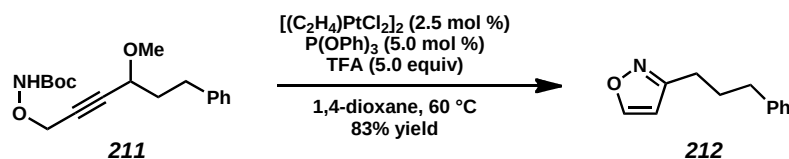


Table 3.4.1, Entry 8. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **211** (95.8 mg, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 $^\circ\text{C}$, and stirred for 0.25 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) to afford isoxazole **212** (46.4 mg, 83% yield, R_f = 0.59 in 4:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 212: ^1H NMR (400 MHz, CDCl_3) δ 8.32-8.31 (m, 1H), 7.31-7.27 (comp m, 2H), 7.21-7.18 (comp m, 3H), 6.19 (d, J = 1.7 Hz, 1H), 2.74 (t, J = 7.7 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H), 2.02 (quintet, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.7, 158.3, 141.6, 128.61, 128.55, 126.1, 104.1, 35.4, 30.0, 25.5; IR (film) 2938, 1950, 1566, 1418, 1118, 875 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{12}\text{H}_{13}\text{NO} + \text{H}$] $^+$: 188.1070, found 188.1069.

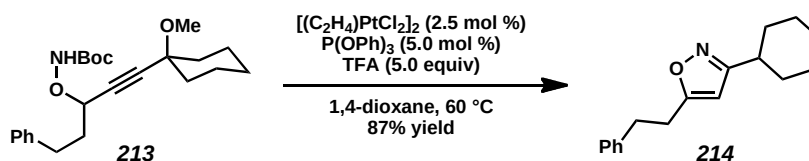


Table 3.4.1, Entry 9. According to the general procedure, to a solution of triphenylphosphite (4.5 mg, 0.0150 mmol) in 1,4-dioxane (0.870 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.2 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.107 mL, 1.43 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **213** (0.111 g, 0.287 mmol) in 1,4-dioxane (2.00 mL, 0.10 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) to afford isoxazole **214** (66.6 mg, 87% yield, $R_f = 0.59$ in 4:1 hexanes/ EtOAc) as an off-white solid.

Isoxazole 214: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.23-7.17 (comp m, 3H), 5.78 (s, 1H), 3.00 (app. s, 4H), 2.70 (tt, $J = 11.3, 3.6$ Hz, 1H), 1.95-1.93 (comp m, 2H), 1.85-1.78 (comp m, 2H), 1.75-1.68 (m, 1H), 1.47-1.32 (comp m, 4H), 1.30-1.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 168.5, 140.4, 128.6, 128.4, 126.5, 99.54, 99.52, 36.0, 33.8, 32.2, 28.8, 26.12, 26.05; IR (film) 3113, 2927, 1601, 1450, 1002, 894 cm^{-1} ; HRMS (ESI^+) m/z calc'd for ($\text{M} + \text{H}$) $^+$ [$\text{C}_{17}\text{H}_{21}\text{NO} + \text{H}$] $^+$: 256.1696, found 256.1698.

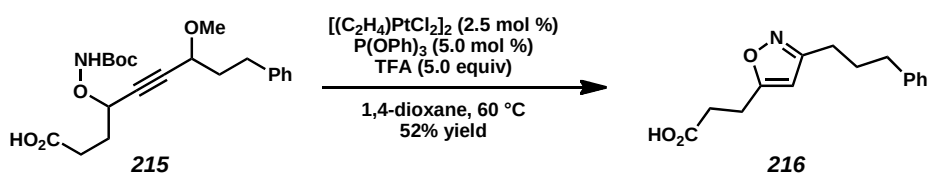


Table 3.4.1, Entry 10. According to the general procedure, to a solution of triphenylphosphite (31.7 μL , 10% (v/v) in 1,4-dioxane, 0.0121 mmol) in 1,4-dioxane (0.800 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (3.6 mg, 0.00605 mmol). After 15 min, trifluoroacetic acid (0.103 mL, 1.39 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **215** (94.8 mg, 0.242 mmol) in 1,4-dioxane (1.60 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 $^\circ\text{C}$, and stirred for 2 h. The reaction was filtered through a plug of silica gel (0.5 x 2 cm, SiO_2 acidified w/ 0.5% $\text{AcOH}:\text{Et}_2\text{O}$), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (1:1 hexanes/ Et_2O w/ 0.5% AcOH as eluent) to afford isoxazole **216** (32.7 mg, 52% yield, R_f = 0.29 in 1:2 hexanes/ Et_2O w/ 1% AcOH) as a white solid.

Isoxazole 216: ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.88 (s, 1H), 3.05 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.67 (app q, J = 7.5 Hz, 4H), 1.98 (quintet, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 170.9, 164.0, 141.6, 128.6, 128.5, 126.1, 101.2, 35.4, 31.6, 29.9, 25.7, 22.0; IR (film) cm^{-1} ; HRMS (ESI^+) m/z calc'd for ($\text{M} + \text{H}$)⁺ [$\text{C}_{15}\text{H}_{17}\text{NO}_3 + \text{H}$]⁺: 260.1281, found 260.1292.

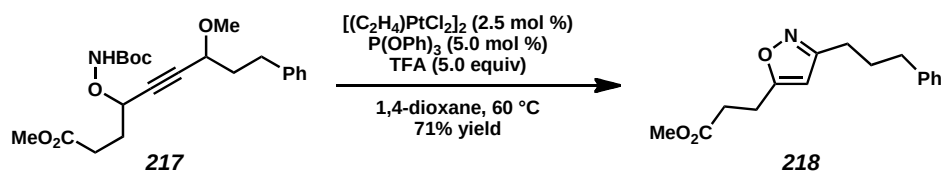


Table 3.4.1, Entry 11. According to the general procedure, to a solution of triphenylphosphite (36.5 μ L, 10% (v/v) in 1,4-dioxane, 0.0139 mmol) in 1,4-dioxane (0.780 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.1 mg, 0.00695 mmol). After 15 min, trifluoroacetic acid (0.103 mL, 1.39 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **217** (0.112 g, 0.278 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 $^\circ$ C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **218** (53.7 mg, 71% yield, R_f = 0.50 in 2:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 218: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.86 (s, 1H), 3.70 (s, 3H), 3.05 (t, J = 7.5 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.68-2.63 (comp m, 4H), 1.98 (quintet, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.1, 163.9, 141.6, 128.6, 128.5, 126.0, 101.0, 52.0, 35.4, 31.7, 29.9, 25.7, 22.2; IR (film) 2950, 1738, 1603, 1496, 1198 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{16}H_{19}NO_3 + H$] $^+$: 274.1438, found 274.1439.

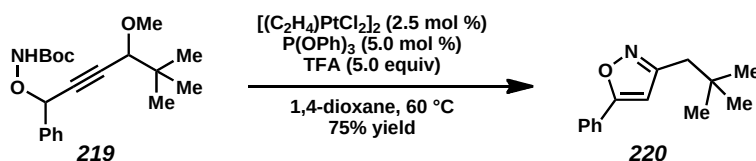


Table 3.4.1, Entry 12. According to the general procedure, to a solution of triphenylphosphite (39.4 μ L, 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **219** (0.104 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **220** (48.1 mg, 75% yield, R_f = 0.67 in 2:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 220: ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.76 (comp m, 2H), 7.47-7.36 (comp m, 3H), 6.36 (s, 1H), 2.60 (s, 2H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.4, 130.0, 129.0, 127.8, 125.8, 100.9, 40.2, 31.2, 29.7; IR (film) 2959, 1955, 1615, 1575, 1451, 1101, 948 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(M + H)^+$ [$C_{14}H_{17}NO + H$] $^+$: 216.1383, found 216.1381.

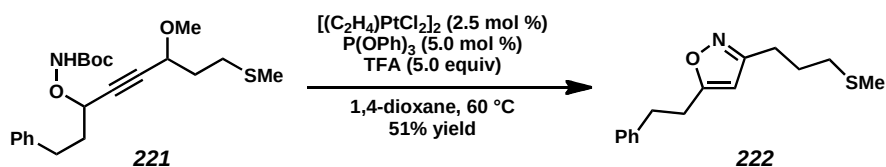


Table 3.4.1, Entry 13. According to the general procedure, to a solution of triphenylphosphite (39.4 μL , 10% (v/v) in 1,4-dioxane, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **221** (0.118 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon[™] cap, placed in an aluminum block that was preheated to 60 $^\circ\text{C}$, and stirred for 96 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent, SiO_2 neutralized with Et_3N) to afford isoxazole **222** (39.7 mg, 51% yield, R_f = 0.51 in 4:1 hexanes/ EtOAc) as a colorless oil.

Isoxazole 222: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.24-7.16 (comp m, 3H), 5.77 (s, 1H), 3.05-2.97 (comp m, 4H), 2.73 (t, J = 7.5 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.10 (s, 3H), 1.98-1.90 (quintet, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 163.3, 140.3, 128.7, 128.4, 126.6, 101.1, 33.7, 33.6, 28.7, 27.7, 25.2, 15.6; IR (film) 3280, 2931, 1748, 1604, 1455, 1017 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(M + H)^+$ [$\text{C}_{15}\text{H}_{19}\text{NOS} + \text{H}$] $^+$: 262.1260, found 262.1254.

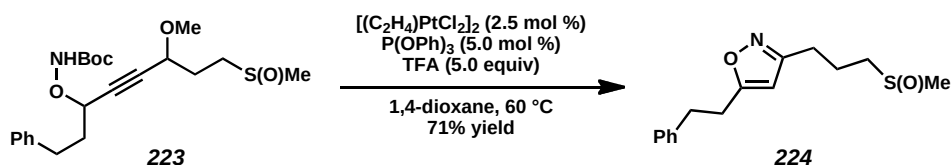
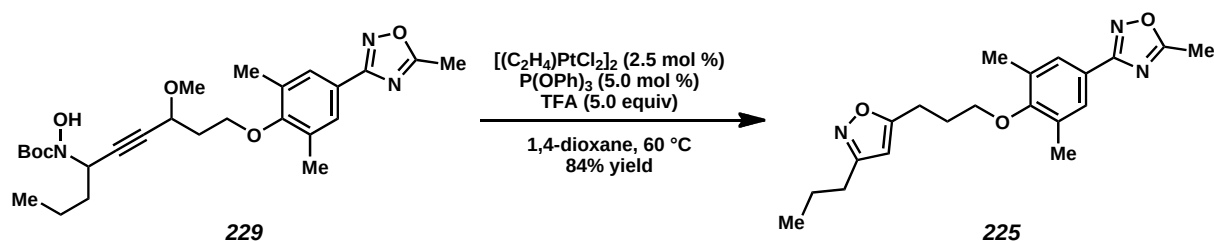


Table 3.4.1, Entry 14. According to the general procedure, to a solution of triphenylphosphite (4.6 mg, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (0.112 mL, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **223** (0.123 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 2 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (0→10% MeOH/EtOAc eluent) to afford isoxazole **224** (59.1 mg, 71% yield, R_f = 0.50 in 2:1 hexanes/EtOAc) as an off-white solid.

Isoxazole 224: ^1H NMR (400 MHz, CD_2Cl_2) δ 7.28 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 8.1 Hz, 3H), 5.84 (s, 1H), 3.04-2.97 (comp m, 4H), 2.77 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 2.50 (s, 3H), 2.08 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 162.8, 140.7, 128.8, 128.6, 126.7, 101.1, 39.1, 33.8, 28.8, 25.4, 21.6; IR (film) 3178, 2933, 2349, 1739, 1368, 1106, 753 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{15}H_{19}NO_2S + H$] $^+$: 278.1209, found 278.1212.

3.8.4 Platinum Catalyzed Isoxazole Synthesis: Antirhinovirus Analogues

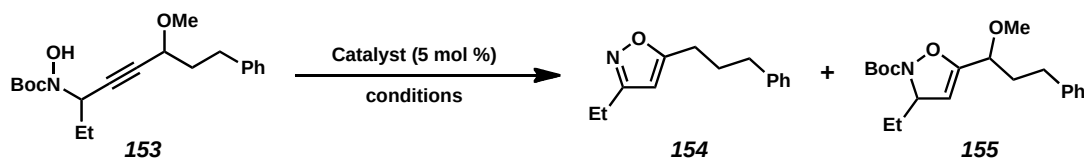


According to the general procedure, to a solution of triphenylphosphite (2.0 mg, 0.00654 mmol) in 1,4-dioxane (0.300 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (1.9 mg, 0.00327 mmol). After 15 min, trifluoroacetic acid (48.7 μ L, 0.654 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of *N*-hydroxycarbamate **229** (63.7 mg, 0.131 mmol) in 1,4-dioxane (1.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 7 h. The reaction was quenched with Et_3N (0.250 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (4.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/ Et_2O eluent) to afford isoxazole **225** (39.0 mg, 84% yield, R_f = 0.47 in 4:1 hexanes/ $EtOAc$) as a colorless oil.

Isoxazole 225: Spectroscopic data matched that previously reported.¹⁰⁷ ^1H NMR (400 MHz; $CDCl_3$): δ 7.72 (s, 2H), 5.89 (s, 1H), 3.85 (t, J = 6.1 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.63 (s, 3H), 2.61 (t, J = 8.0 Hz, 2H), 2.30 (s, 6H), 2.21 (comp m, 2H), 1.68 (sextet, J = 7.5 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 172.3, 168.2, 164.1, 158.4, 131.7, 128.1, 122.2, 100.8, 70.8, 28.4, 28.1, 23.6, 21.8, 16.4, 13.9, 12.5.

3.8.5 Optimization of Pt-Catalyst Conditions

Table 3.3.1. (reproduced)



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield 154 (%) ^a	Yield 155 (%) ^a
1	$[(C_2H_4)PtCl_2]_2$ ^b	THF	70	18	15	7
2	$[(C_2H_4)PtCl_2]_2$ ^b	1,4-dioxane	70	18	22	12
3	$[(C_2H_4)PtCl_2]_2$ ^b	CH ₂ Cl ₂	70	66	9 ^c	0 ^c
4	$[(C_2H_4)PtCl_2]_2$ ^b	ClCH ₂ CH ₂ Cl	70	66	23 ^c	14 ^c
5	$[(C_2H_4)PtCl_2]_2$ ^b	PhCH ₃	70	18	18	12
6	$[(C_2H_4)PtCl_2]_2$ ^b	PhH	70	66	21 ^c	18 ^c
7	$[(C_2H_4)PtCl_2]_2$ ^b	CH ₃ CN	70	66	44 ^c	17 ^c
8	$[(C_2H_4)PtCl_2]_2$ ^b	PhCH ₃	60	16	22	9
9	PtCl ₂ /1-octene ^d	PhCH ₃	60	16	35	9
10	K ₂ PtCl ₄	PhCH ₃	60	48	0	0
11	(PPh ₃) ₂ PtCl ₂	PhCH ₃	60	48	0	0
12	(PhCN) ₂ PtCl ₂	PhCH ₃	60	48	0	0
13	(PPh ₃) ₂ PtHCl	PhCH ₃	60	48	0	0
14	Pd(OAc) ₂	PhCH ₃	60	16	0	18
15	Pd(OCOCF ₃) ₂	PhCH ₃	60	16	0	36
16	PPh ₃ AuCl/AgSbF ₆ ^e	CH ₂ Cl ₂	-10	0.5	0	44
17	IPrAuCl/AgSbF ₆ ^e	CH ₂ Cl ₂	-10→23	3.0	3	50
18	<i>o</i> -biphenyl(<i>t</i> -Bu) ₂ PAuCl/AgSbF ₆ ^e	CH ₂ Cl ₂	-10	0.5	2	73

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Used 2.5 mol % catalyst. ^c Reaction did not go to completion. ^d Used 1.0 equiv 1-octene as an additive. ^e Used 5 mol % AgSbF₆.

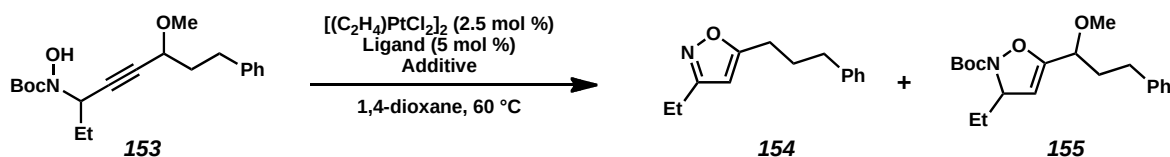
Table 3.3.1, entries 1-7: A solution of *N*-hydroxycarbamate **153** (0.121 g, 0.350 mmol) and 4,4'-di-*t*-butylbiphenyl (23.1 mg, 0.0875 mmol) in CH₂Cl₂ (7.00 mL, 0.1 M) was prepared under ambient atmosphere. The solution was transferred to separate vials and the solvent was then removed by rotary evaporation. The resulting residue was dissolved in the desired solvent (0.500 mL, 0.10 M). The resulting solutions were added to vials containing $[(C_2H_4)PtCl_2]_2$ (0.7 mg, 0.00125 mmol), and the reactions were placed in an aluminum block preheated to 70 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0

cm), washing with Et₂O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 3.3.1, entries 8-15: A solution of *N*-hydroxycarbamate **153** (83.2 mg, 0.240 mmol) and 4,4'-di-*t*-butylbiphenyl (16.0 mg, 0.0600 mmol) in PhMe (2.40 mL, 0.1 M) was prepared under ambient atmosphere. The solution (0.300 mL, 0.300 mmol) was transferred to separate vials, the desired catalyst (5.0 mol %) was added, and the reactions were placed in an aluminum block preheated to 60 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 3.3.1, entries 16-18: To a solution of the gold catalyst (5.0 mol %) and AgSbF₆ (5.0 mol %) in CH₂Cl₂ (0.100 mL) cooled to -10 °C under argon was added a solution of *N*-hydroxycarbamate **153** (10.4 mg, 0.0300 mmol) and 4,4'-di-*t*-butylbiphenyl (2.0 mg, 0.00750 mmol) in CH₂Cl₂ (0.200 mL, 0.10 M final concentration). The reactions were stirred at -10 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield. Entry 17 was warmed to 23 °C after 30 min.

Table 3.3.2. (reproduced)



Entry	Ligand	Additive (equiv)	Time (h)	Yield 154 (%) ^a	Yield 155 (%) ^a
1	-	AcOH (10)	32	39	11
2	PPh ₃	AcOH (10)	21	48	14
3	PPh ₃	(NH ₄)HCO ₂ (10)	70	0	0
4	PPh ₃	H ₃ PO ₄ (10)	70	76	11
5	PPh ₃	TFA (10)	16	81	1
6	PPh ₃	TsOH (2)	17	0	0
7	PPh ₃	Na ₂ CO ₃ (1)	60	6	< 1
8	PPh ₃	TFA (5)	16	96	1
9	PCy ₃ ^b	TFA (5)	70	57	3
10	P(<i>n</i> -Bu) ₃ ^b	TFA (5)	70	49	4
11	P(<i>t</i> -Bu) ₂ (<i>o</i> -biphenyl) ^b	TFA (5)	70	47	2
12	P(OPh) ₃	TFA (5)	16	96	1

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Performed under an argon atmosphere.

Table 3.3.2, entries 1-6: A solution of *N*-hydroxycarbamate **153** (62.4 mg, 0.180 mmol) and 4,4'-di-*t*-butylbiphenyl (12.0 mg, 0.0450 mmol) in 1,4-dioxane (1.20 mL, 0.1 M) was prepared under ambient atmosphere. The solution (0.200 mL, 0.0300 mmol) was transferred to separate vials, and the desired additive was added. To this was added 0.100 mL of a solution of $[(C_2H_4)PtCl_2]_2$ (2.4 mg, 0.00450 mmol) and PPh₃ (2.4 mg, 0.00900 mmol) in 1,4-dioxane (0.600 mL). The reactions were sealed and placed in an aluminum block that was preheated to 60 °C. Upon completion, as determined by TLC, the acidic reactions were quenched with Et₃N (0.250 mL), filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (4.0 mL). Basic reactions were plugged directly through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

Table 3.3.2, entries 7-11: A solution of *N*-hydroxycarbamate **153** (52.0 mg, 0.150 mmol) and 4,4'-di-*t*-butylbiphenyl (10.0 mg, 0.0375 mmol) in 1,4-dioxane (1.00 mL, 0.66 M) was prepared under ambient atmosphere. The solution (0.200 mL, 0.0300 mmol) was transferred to separate vials containing a solution of $[(C_2H_4)PtCl_2]_2$ (0.4 mg, 0.000750 mmol), and the desired ligand (0.00150 mol) in 1,4-dioxane (0.100 mL). TFA (11.2 μ L, 0.150 mmol) was immediately added, and the reactions were placed in an aluminum block that was preheated to 60 °C. Upon completion, as determined by TLC, the reactions were quenched with Et_3N (0.250 mL), and filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with Et_2O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield. Entries 9, 10 and 11 were run under an argon atmosphere.

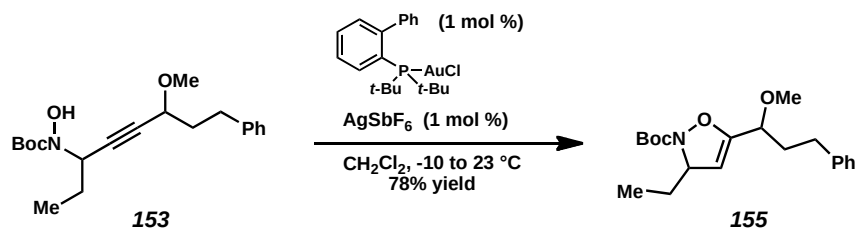
Table 3.3.3. (reproduced)

Entry	Substrate	Time (h)	Yield (%) ^a	Entry	Substrate	Time (h)	Yield (%) ^a
1		96	71	5		96	53
2		96	59	6		17	96
3		72	72	7		20	64
4		42	48	8		6	7

^a Yield determined by GC with 4,4'-di-*tert*-butylbiphenyl as the internal standard.

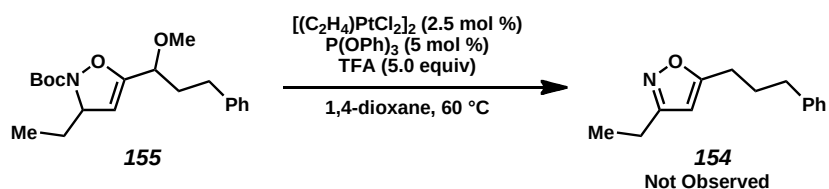
General Procedure: To 1,4-dioxane (1/3 of reaction volume) was added triphenylphosphine (5.0 mol %) followed by the addition of $[(C_2H_4)PtCl_2]_2$ (2.5 mol %). After 15 min, trifluoroacetic acid (5.00 equiv) was added and the mixture was stirred for 1 min. The resulting solution was then added to a solution of the *N*-hydroxycarbamates/amide/amine (0.0300 mmol) and 4,4'-*tert*-butylbiphenyl (0.00750 mmol) in 1,4-dioxane (2/3 of reaction volume, 0.10 M final concentration), and the mixture was heated at 60 °C in a sealed vial. Upon completion, as determined by TLC, the reaction was quenched with Et_3N (0.100 mL), and filtered through a plug of silica gel. The plug was washed with Et_2O (2x reaction volume), and the resulting solution was injected directly onto a GC to determine yields.

3.8.6 Hydroalkoxylation Experiments



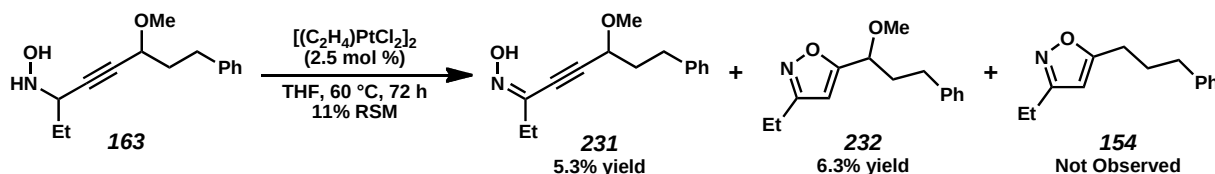
To a solution of *o*-biphenyl(*t*-Bu) $_2$ PAuCl (4.2 mg, 0.00800 mmol) and AgSbF₆ (2.7 mg, 0.00800 mmol) in CH₂Cl₂ (0.400 mL) at -10 °C under argon was added a solution of *N*-hydroxycarbamate **153** (0.278 g, 0.800 mmol) in CH₂Cl₂ (0.400 mL, 0.10 M final concentration). The reaction was stirred at -10 °C for 2 h, then warmed to 23 °C and stirred for an additional 2 h. The reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (4.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford isoxazoline **155** (0.218 g, 78% yield, R_f = 0.60 in 4:1 hexanes/EtOAc) as a colorless oil.

Isoxazoline 155: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (comp m, 2H), 7.20-7.16 (comp m, 3H), 4.91 (m, 1H), 4.85 (td, $J = 5.7, 2.3$ Hz, 1H), 3.80 (t, $J = 6.6$ Hz, 1H), 3.39 (s, 1.5H), 3.36 (s, 1.5H), 2.79-2.65 (comp m, 2H), 2.08-1.97 (comp m, 2H), 1.66-1.56 (comp m, 2H), 1.50 (app. d, $J = 0.8$ Hz, 9H), 0.95 (comp m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 157.6, 154.9, 154.2, 141.5, 128.64, 128.62, 128.5, 126.0, 98.5, 98.2, 82.4, 82.3, 74.8, 74.6, 67.0, 66.9, 57.4, 57.1, 35.5, 35.1, 31.52, 31.47, 29.19, 29.17, 28.3, 9.4, 9.3; IR (film) 2972, 1741, 1496, 1456, 1369, 1165, 749 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for ($\text{M} + \text{H}$) $^+$ [$\text{C}_{20}\text{H}_{29}\text{NO}_4 + \text{H}$] $^+$: 348.2175, found 348.2140 (did not pass).



According to the general procedure, to a solution of triphenylphosphite (19.7 μL , 10% solution in 1,4-dioxane, 0.00750 mmol) in 1,4-dioxane (0.500 mL) under an ambient atmosphere was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (2.2 mg, 0.00375 mmol). After 15 min, trifluoroacetic acid (56.0 μL , 0.750 mmol) was added and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of isoxazoline **155** (52.1 mg, 0.150 mmol) in 1,4-dioxane (1.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a TeflonTM cap and placed in an aluminum block that was preheated to 60 °C. After 24 h the reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). ^1H NMR and GC analysis indicated isoxazole **154** did not form.

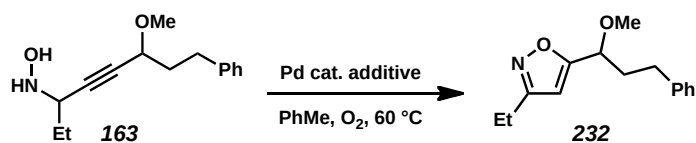
3.8.7 Synthesis of Isoxazoles from Hydroxylamines



Hydroxylamine **163** (49.4 mg, 0.200 mmol) and $[(C_2H_4)PtCl_2]_2$ (2.9 mg, 0.005 mmol) were stirred in THF (2.00 mL, 0.10 M) under an ambient atmosphere at 60 °C for 72 h. The reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford oxime **231** (2.6 mg, 5.3% yield, R_f = 0.38 in 4:1 hexanes/EtOAc), isoxazole **232** (3.1 mg, 6.3% yield, R_f = 0.64 in 4:1 hexanes/EtOAc) and hydroxylamine **163** (5.4 mg, 11% yield) as colorless oils.

Oxime 231: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 4.07 (t, J = 6.6 Hz, 1H), 3.43 (s, 3H), 2.80 (t, J = 7.8 Hz, 2H), 2.49 (q, J = 7.8 Hz, 2H), 2.16-2.00 (comp m, 2H), 1.16 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 141.3, 128.7, 128.6, 126.2, 90.5, 81.1, 70.7, 56.8, 37.1, 31.5, 22.0, 10.4.

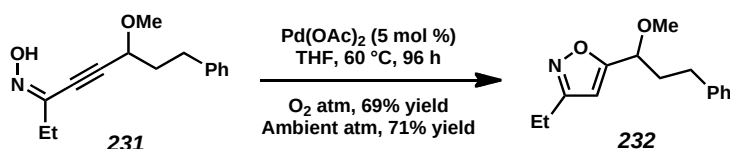
Isoxazole 232: ^1H NMR (400 MHz, $CDCl_3$) 7.33-7.26 (comp m, 2H), 7.25-7.12 (comp m, 3H), 6.06 (s, 1H), 4.28 (dd, J = 7.7, 5.5 Hz, 1H), 3.34 (s, 3H), 2.75-2.65 (comp m, 4H), 2.25-2.02 (comp m, 2H), 1.28 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.2, 141.2, 128.63, 128.60, 126.2, 100.9, 75.1, 57.6, 36.3, 31.4, 19.7, 12.7.



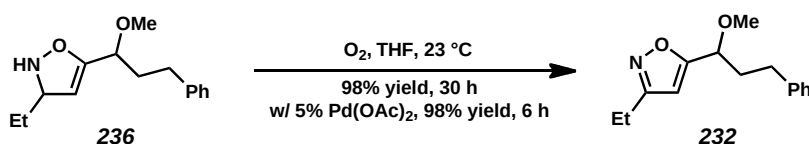
Catalyst	Additive	Time (h)	Yield (%) ^a
Pd(OAc) ₂	-	108	35
Pd(OAc) ₂	Et ₃ N	80	33
Pd(OAc) ₂	pyridine	108	39
Pd(OCOCF ₃) ₂	pyridine	80	28
PdCl ₂	pyridine	40	22
PdCl ₂ (MeCN) ₂	pyridine	108	35
Pd(NO ₃) ₂	pyridine	80	31

^a Yield determined by GC with 4,4'-*tert*-butylbiphenyl as the internal standard.

General Procedure: A solution of hydroxylamine **163** (7.4 mg, 0.0300 mmol) and 4,4'-*di-t*-butylbiphenyl (2.0 mg, 0.00750 mmol) in PhMe (0.2 mL, 0.15 M) was prepared under ambient atmosphere. The resulting solution was added to separate vials containing the desired catalyst (5.0 mol %) and ligand (10.0 mol %), and the reactions were placed in an aluminum block preheated to 60 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

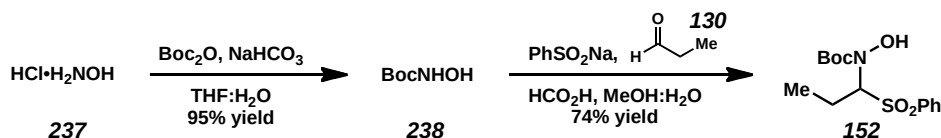


Oxime **231** (12.1 mg, 0.0494 mmol) and 4,4'-*di-t*-butylbiphenyl (3.3 mg, 0.0123 mmol) were stirred in THF (0.494 mL, 0.10 M). Pd(OAc)₂ (0.5 mg, 0.00247 mmol) was added and the resulting solution was stirred under an ambient atmosphere (or degassed with O₂ via bubbling) at 23 °C for 96 h. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (4.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.



Isoxazoline **236** (14.1 mg, 0.0569 mmol) and 4,4'-di-*t*-butylbiphenyl (3.8 mg, 0.0142 mmol) were stirred in PhCH₃ (0.500 mL, 0.11 M). Pd(OAc)₂ (0.6 mg, 0.00284 mmol) was added (if used) and the resulting solutions were degassed with O₂ via bubbling and stirred at 23 °C. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO₂ (0.5 x 2.0 cm), washing with Et₂O (2.0 mL). The resulting filtrate was injected directly onto a GC to determine the yield.

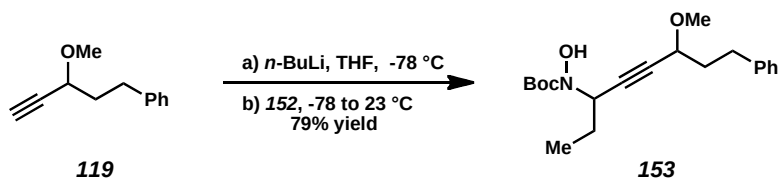
3.8.8 Substrate Synthesis



To a solution of NH₂OH·HCl (**237**, 5.21 g, 75.0 mmol) in THF:H₂O (1:1, 166 mL, 0.45 M) at 0 °C was added NaHCO₃ (12.6 g, 150 mmol), and the solution was stirred for 5 min. Boc₂O (16.4 g, 75.0 mmol) was added and the reaction was stirred at 0 °C for 2 h. The reaction was diluted with EtOAc (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL), and the combined organic phases were washed sequentially with sat. aq. NaHCO₃ (150 mL), H₂O (150 mL), brine (150 mL), dried over MgSO₄. The solvent was removed by rotary evaporation affording carbamate **238** (9.46 g, 95% yield) as a white solid.

Following the procedure of Denis,⁸⁹ to a solution of sodium benzenesulfinate (1.54 g, 9.40 mmol) in MeOH:H₂O (1:2, 11.1 mL, 0.85 M) was added carbamate **238** (0.500 g, 3.76 mmol), propionaldehyde (**130**, 0.539 mL, 7.52 mmol), and formic acid (0.327 mL, 7.52 mmol). The

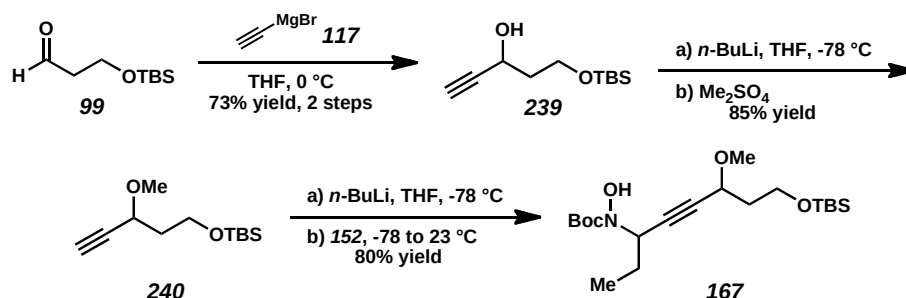
reaction was stirred at room temperature for 16 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The solid was dried under reduced pressure affording *N*-hydroxycarbamate **152** (0.879 g, 74% yield) as a white solid.



To a solution of alkyne **119** (3.96 g, 22.8 mmol) in THF (25.4 mL, 0.90 M) at $-78\text{ }^\circ\text{C}$ under argon was added *n*-BuLi (9.12 mL, 2.5 M in hexanes, 22.8 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **152** (3.61 g, 11.4 mmol) in THF (25.4 mL, 0.45 M) was added dropwise, and the reaction was stirred at $-78\text{ }^\circ\text{C}$ for 2 h, then warmed to $23\text{ }^\circ\text{C}$ and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted with Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic phases were washed with brine (50 mL) and dried over MgSO_4 . The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/ EtOAc eluent) affording *N*-hydroxycarbamate **153** (3.13 g, 79% yield, $R_f = 0.43$ in 4:1 hexanes/ EtOAc) as an amber oil.

***N*-Hydroxycarbamate 153:** Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 7.30-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 4.64 (td, $J = 8.0, 0.8$ Hz, 1H), 3.94 (td, $J = 6.8, 1.6$ Hz, 1H), 3.38 (app. d, $J = 2.8$ Hz, 3H), 2.77 (t, $J = 7.9$ Hz, 2H), 2.07-1.95 (comp m, 2H), 1.94-1.80 (comp m, 2H), 1.51 (s, 9H), 1.02 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.6, 141.5, 128.7, 128.5, 126.1, 83.2, 82.9, 70.5, 70.4, 56.5, 54.2, 37.41, 37.35, 31.58, 31.56, 28.4, 28.2, 26.42, 26.40, 10.9; IR (film) 3281, 2976, 1699, 1369,

1106, 701 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for $(\text{M} + \text{Na})^+ [\text{C}_{20}\text{H}_{29}\text{NO}_4 + \text{Na}]^+$: 370.1997, found 370.2002.



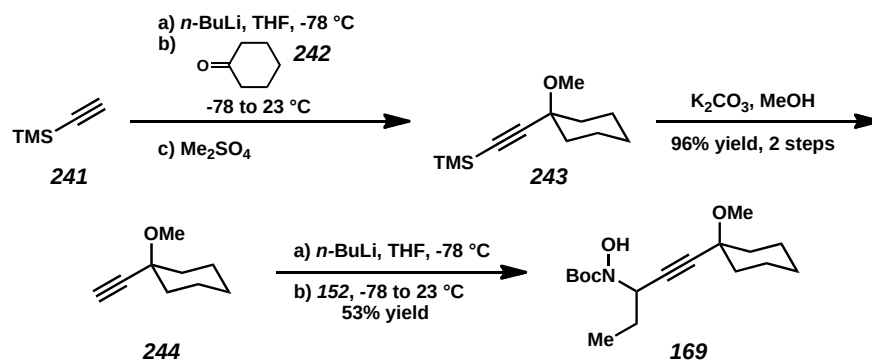
To a solution of ethynylmagnesium chloride (**117**, 100 mL, 0.50 M in THF, 50.0 mmol) at 0 °C was added a solution of aldehyde **99** (9.40 g, 50.0 mmol) in Et₂O (10 mL) and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. NH₄Cl (50 mL), and diluted with hexanes (100 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted with Et₂O (50 mL). The organic layers were combined, washed with brine (100 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude material was purified by flash chromatography (19:1→9:1 hexanes/EtOAc eluent) affording alcohol **239** (7.84 g, 73% yield over 2 steps, R_f = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **239** (7.25 g, 33.9 mmol) in THF (100 mL, 0.34 M) at -78 °C under argon was added *n*-BuLi (14.4 mL, 2.35 M in hexanes, 33.9 mmol) and the reaction was stirred for 30 min. Me₂SO₄ (3.22 mL, 33.9 mmol) was then added and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with water (100 mL), and diluted with hexanes (100 mL). The layers were separated and the aqueous phase was extracted with Et₂O (50 mL). The organic phases were combined, washed with brine (50 mL), dried over MgSO₄ and the solvent was removed by rotary evaporation. The crude material was purified by flash

chromatography (19:1 hexanes/EtOAc eluent) affording alkyne **240** (6.61 g, 85% yield, R_f = 0.73 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alkyne **240** (0.912 g, 4.00 mmol) in THF (6.0 mL, 0.67 M) at -78 °C under argon was added *n*-BuLi (1.70 mL, 2.35 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **152** (0.630 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) was added dropwise and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 4 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL) and dried over MgSO_4 . The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **167** (0.645 g, 80% yield, R_f = 0.36 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 167:** Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 5.95 (br s, 1H), 4.62 (td, J = 7.7, 1.5 Hz, 1H), 4.17-4.13 (m, 1H), 3.78-3.68 (comp m, 2H), 3.37 (d, J = 3.0 Hz, 3H), 2.75 (q, J = 7.4 Hz, 2H), 1.97-1.79 (comp m, 4H), 1.50 (s, 9H), 0.99 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.5, 82.9, 82.8, 68.1, 59.2, 56.5, 54.1, 39.00, 38.96, 28.4, 28.2, 26.36, 26.35, 26.1, 18.5, 10.9, -5.2; IR (film) 3264, 2932, 1700, 1463, 1109, 835 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{20}\text{H}_{39}\text{NO}_5\text{Si} + \text{Na}$] $^+$: 424.2490, found 424.2497.

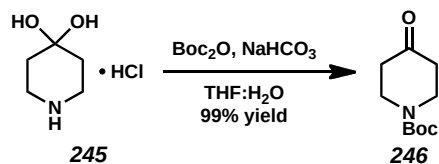


To a solution of ethynyltrimethylsilane (**241**, 7.07 mL, 50.0 mmol) in THF (150 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (20.0 mL, 2.5 M in hexanes, 50.0 mmol), and the resulting solution was stirred for 30 min. Cyclohexanone (**242**, 5.18 mL, 50.0 mmol) was added and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 2 h. Me₂SO₄ (5.71 mL, 60.0 mmol) was added and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH₄OH (75 mL), stirring for 15 min. The mixture was diluted with Et₂O (100 mL) and the layers were separated. The aqueous phase was extracted with Et₂O (50 mL) and the combined organic phases were dried over MgSO₄. The solvent was removed by rotary evaporation affording ether **243** (10.5 g crude, *R_f* = 0.73 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **243** (10.5 g crude, assumed 50.0 mmol) in MeOH (300 mL, 0.15 M) at 23 °C was added K₂CO₃ (8.28 g, 60.0 mmol), and the reaction was stirred for 15 h. The reaction was diluted with brine (300 mL), and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording alkyne **244** (6.60 g, 96% yield over 2 steps, *R_f* = 0.68 in 4:1 hexanes/EtOAc) as a colorless oil.

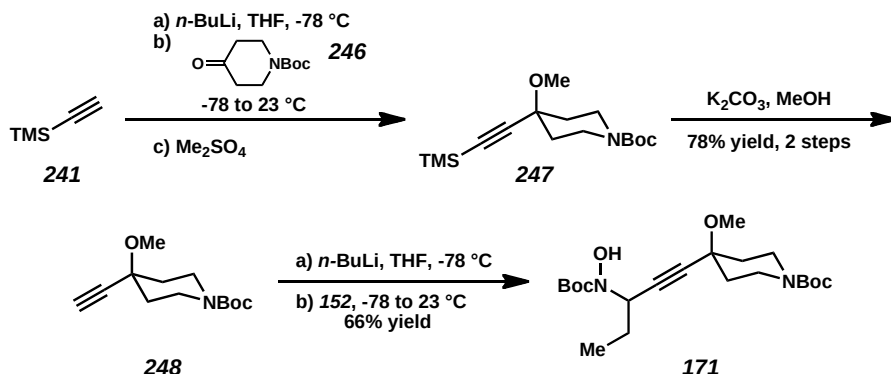
To a solution of alkyne **244** (0.552 g, 4.00 mmol) in THF (4.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **152** (0.630 g, 2.00 mmol) in THF (4.00 mL, 0.50 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (10 mL). The combined organic phases were washed with brine (10 mL), and dried over MgSO₄. The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **169** (0.329 g, 53% yield, *R*_f = 0.37 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 169:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 5.93 (br s, 1H), 4.61 (t, *J* = 7.7 Hz, 1H), 3.34 (s, 3H), 1.90-1.80 (comp m, 4H), 1.63 (comp m, 2H), 1.55-1.51 (comp m, 2H), 1.50 (s, 9H), 1.49-1.45 (comp m, 3H), 1.30-1.24 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 85.2, 83.1, 82.7, 74.2, 54.3, 50.8, 37.0, 36.9, 28.4, 26.5, 25.6, 23.05, 23.02, 11.0; IR (film) 3281, 2937, 1700, 1368, 1170, 926 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₁₇H₂₉NO₄ + Na]⁺: 334.1989, found 334.1972.



To a solution of 4-piperidone monohydrate hydrochloride (**245**, 7.68 g, 50.0 mmol) in THF:H₂O (1:1, 100 mL, 0.50 M) at 23 °C was added NaHCO₃ (8.40 g, 100 mmol), and the solution was stirred for 15 min. Boc₂O (13.1 g, 60.0 mmol) was added, and the reaction was stirred for 12 h. The reaction was diluted with Et₂O (50 mL), and washed with 5% aq. KHSO₄ (100 mL). The

aqueous layer was extracted with Et₂O (50 mL), and the combined organic layers were washed sequentially with 5% KHSO₄ (50 mL), H₂O (50 mL), and brine (50 mL). The organic material was dried over MgSO₄, and the solvent was removed by rotary evaporation affording ketone **246** (10.0 g, 99% yield, *R_f* = 0.51 in 1:1 hexanes/EtOAc) as a white solid.



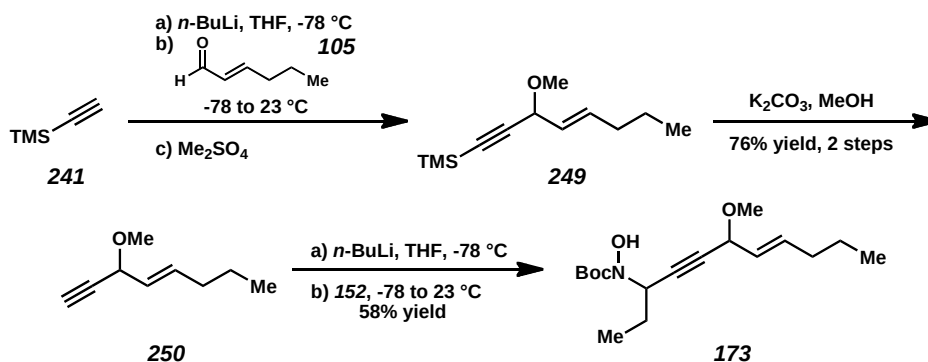
To a solution of ethynyltrimethylsilane (**241**, 1.44 mL, 10.2 mmol) in THF (30 mL, 0.34 M) at -78 °C under argon was added *n*-BuLi (4.08 mL, 2.5 M in hexanes, 10.2 mmol), and the resulting solution was stirred for 30 min. A solution of ketone **246** (2.04 g, 10.2 mmol) in THF (10 mL, 1.0 M) was added, and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 4 h. Me₂SO₄ (1.07 mL, 11.3 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH₄OH (20 mL), stirring for 15 min. The mixture was diluted with Et₂O (30 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (15 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed by rotary evaporation affording ether **247** (3.15 g crude, *R_f* = 0.59 in 4:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ether **247** (3.15 g crude, assumed 10.2 mmol) in MeOH (68 mL, 0.15 M) at 23 °C was added K₂CO₃ (1.68 g, 12.2 mmol), and the reaction was stirred for 5 h. The reaction was

diluted with brine (50 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1→6:1 hexanes/EtOAc eluent) affording alkyne **248** (1.90 g, 78% yield over 2 steps, *R_f* = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alkyne **248** (0.956 g, 4.00 mmol) in THF (4.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **152** (0.630 g, 2.00 mmol) in THF (4.00 mL, 0.50 M) was added dropwise and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 12 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (10 mL). The combined organic phases were washed with brine (10 mL), and dried over MgSO₄. The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording hydroxycarbamate **171** (0.540 g, 66% yield, *R_f* = 0.41 in 2:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 171:** ¹H NMR (400 MHz, CDCl₃) δ 4.61 (t, *J* = 7.7 Hz, 1H), 3.73 (dt, *J* = 13.7, 4.7 Hz, 2H), 3.34 (s, 3H), 3.25-3.18 (comp m, 2H), 1.88-1.82 (comp m, 4H), 1.64 (ddd, *J* = 13.2, 9.5, 3.8 Hz, 2H), 1.49 (s, 9H), 1.44 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 154.8, 84.6, 83.3, 82.9, 79.8, 72.6, 54.0, 51.0, 38.9, 36.3, 28.6, 28.4, 26.4, 10.9; IR (film) 3286, 2976, 1714, 1456, 768 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₁H₃₆N₂O₆ + Na]⁺: 435.2466, found 435.2443.

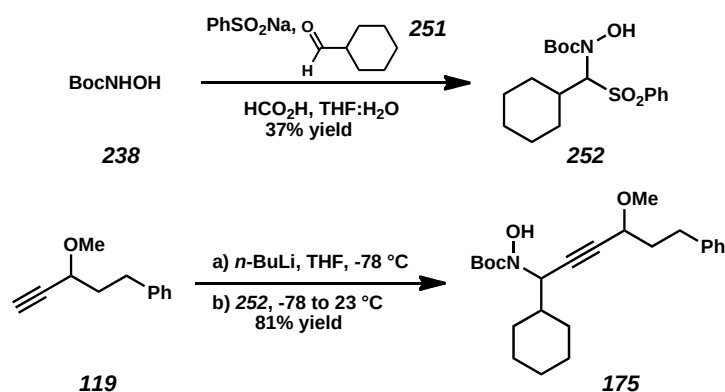


To a solution of ethynyltrimethylsilane (**241**, 1.41 mL, 10.0 mmol) in THF (30.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min. *Trans*-2-hexenal (**105**, 1.16 mL, 10.0 mmol) was added and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me_2SO_4 (1.04 mL, 11.0 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH_4OH (20 mL), stirring for 15 min. The mixture was diluted with Et_2O (30 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (15 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed by rotary evaporation affording ether **249** (2.21 g crude, $R_f = 0.74$ in 4:1 hexanes/ EtOAc) as a pale yellow oil.

To a solution of ether **249** (2.21 g crude, assumed 10.0 mmol) in MeOH (40.0 mL, 0.25 M) at 23 °C was added K_2CO_3 (1.65 g, 12.0 mmol), and the reaction was stirred for 16 h. The reaction was diluted with brine (50 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) affording alkyne **250** (1.04 g, 76% yield over 2 steps, $R_f = 0.69$ in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of alkyne **250** (0.544 g, 3.97 mmol) in THF (12.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (1.59 mL, 2.50 M in hexanes, 3.97 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **152** (0.624 g, 1.98 mmol) in THF (12.0 mL, 0.17 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 15 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **173** (0.357 g, 58% yield, *R*_f = 0.23 in 4:1 hexanes/EtOAc) as an amber oil.

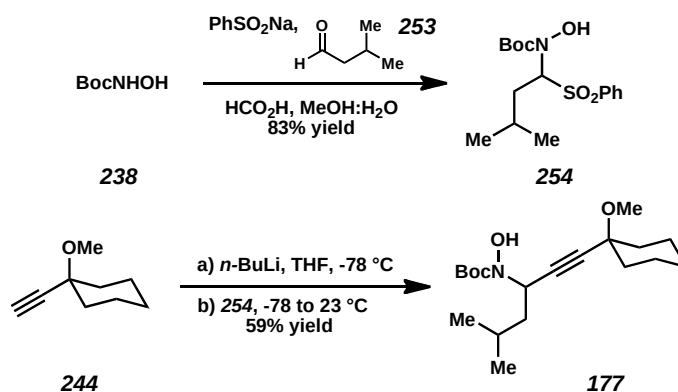
***N*-Hydroxycarbamate 173:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 5.98 (br s, 1H), 5.87 (dtd, *J* = 15.2, 6.9, 1.2 Hz, 1H), 5.52-5.46 (m, 1H), 4.65 (td, *J* = 7.7, 1.4 Hz, 1H), 4.49 (dd, *J* = 6.3, 1.0 Hz, 1H), 3.34 (d, *J* = 1.4 Hz, 3H), 2.07-2.01 (comp m, 2H), 1.93-1.80 (comp m, 2H), 1.48-1.47 (comp m, 9H), 1.41 (q, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.5, 135.4, 126.9, 84.2, 84.1, 82.8, 81.5, 81.4, 71.4, 55.44, 55.42, 54.1, 34.2, 28.4, 26.3, 22.2, 13.8, 10.9; IR (film) 2962, 1996, 1703, 1603, 1165, 968 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M - H)⁺ [C₁₇H₂₉NO₄ - H]⁺: 310.2024, found 310.2019.



To a solution of sodium benzenesulfinate (3.09 g, 18.8 mmol) in THF:H₂O (1:1, 22.0 mL, 0.85 M) was added carbamate **238** (1.00 g, 7.52 mmol), cyclohexanecarboxaldehyde (**251**, 1.82 mL, 15.0 mmol) and formic acid (0.983 mL, 22.6 mmol). The reaction was stirred at room temperature for 16 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The solid was dried under reduced pressure affording hydroxycarbamate **252** (1.02 g, 37% yield) as a white solid.

To a solution of alkyne **119** (0.523 g, 3.00 mmol) in THF (3.00 mL, 1.0 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **252** (0.553 g, 1.50 mmol) in THF (3.00 mL, 0.50 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 15 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (10 mL). The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **175** (0.618 g, 81% yield, R_f = 0.40 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 175:** ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (m, 2H), 7.19 (comp m, 3H), 6.13 (br s, 1H), 4.43 (d, J = 9.9 Hz, 1H), 3.95 (t, J = 6.2 Hz, 1H), 3.39 (d, J = 3.2 Hz, 3H), 2.77 (t, J = 7.8 Hz, 2H), 2.09-1.94 (comp m, 2H), 1.92-1.65 (comp m, 5H), 1.50 (s, 9H), 1.34-1.12 (comp m, 4H), 1.09-0.91 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.50, 157.47, 141.5, 128.7, 128.5, 126.1, 83.44, 83.38, 82.7, 82.6, 70.51, 70.47, 57.8, 56.6, 40.1, 40.0, 37.5, 37.4, 31.62, 31.58, 30.5, 29.7, 28.4, 26.4, 26.0, 25.8; IR (film) cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{Na})^+ [\text{C}_{24}\text{H}_{35}\text{NO}_4 + \text{Na}]^+$: 424.2464, found 424.2453.

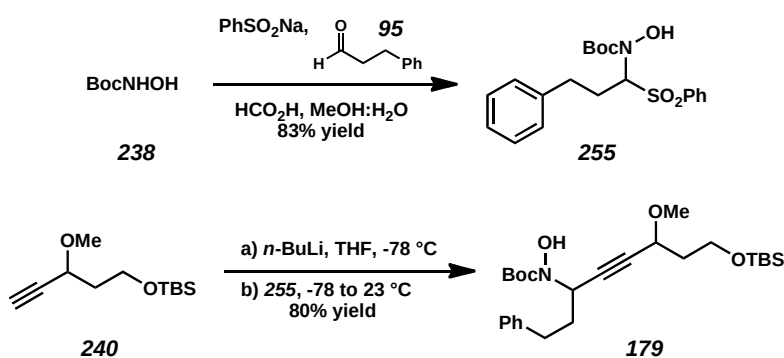


To a solution of sodium benzenesulfinate (3.09 g, 18.8 mmol) in $\text{MeOH}:\text{H}_2\text{O}$ (1:2, 22.5 mL, 0.84 M) was added carbamate **238** (1.00 g, 7.52 mmol), isovalerylaldehyde (**253**, 1.63 mL, 15.0 mmol) and formic acid (0.983 mL, 22.6 mmol). The reaction was stirred at room temperature for 18 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The recovered solid was dried under reduced pressure affording *N*-hydroxycarbamate **254** (2.13 g, 83% yield) as a white solid.

To a solution of alkyne **244** (0.552 g, 4.00 mmol) in THF (4.00 mL, 1.0 M) at $-78\text{ }^\circ\text{C}$ under argon was added $n\text{-BuLi}$ (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **254** (0.684 g, 2.00 mmol) in THF (6.00 mL, 0.33

M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **177** (0.397 g, 59% yield, *R*_f = 0.43 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 177:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 4.78 (t, *J* = 7.5 Hz, 1H), 3.34 (s, 3H), 1.89-1.86 (comp m, 2H), 1.79-1.70 (comp m, 3H), 1.68-1.59 (comp m, 3H), 1.52-1.48 (comp m, 14H), 0.94 (dd, *J* = 6.1, 3.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 85.1, 83.3, 82.8, 74.2, 51.23, 51.15, 50.84, 50.80, 41.6, 37.0, 36.9, 28.4, 25.6, 25.0, 23.05, 23.03, 22.44, 22.39; IR (film) 3280, 2937, 1699, 1454, 1170, 1094, 925 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₁₉H₃₃NO₄ + Na]⁺: 362.2302, found 362.2302.

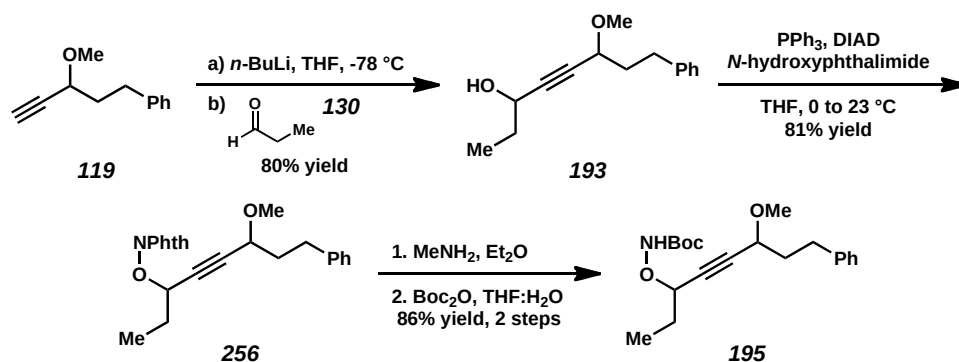


To a solution of sodium benzenesulfinate (3.09 g, 18.8 mmol) in MeOH:H₂O (1:2, 22.5 mL, 0.84 M) was added carbamate **238** (1.00 g, 7.52 mmol), hydrocinnamaldehyde (**95**, 1.98 mL, 15.0 mmol) and formic acid (0.983 mL, 22.6 mmol). The reaction was stirred at room temperature for

14 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 25 mL). The recovered solid was dried under reduced pressure affording *N*-hydroxycarbamate **255** (2.45 g, 83% yield) as a white solid.

To a solution of alkyne **240** (0.912 g, 4.00 mmol) in THF (6.00 mL, 0.67 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. A solution of *N*-hydroxycarbamate **255** (0.780 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then warmed to 23 °C and stirred for 14 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **179** (0.472 g, 50% yield, *R*_f = 0.36 in 4:1 hexanes/EtOAc) as an amber oil.

***N*-Hydroxycarbamate 179:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.27 (comp m, 3H), 7.25-7.20 (comp m, 2H), 4.67 (t, *J* = 7.7 Hz, 1H), 4.16 (td, *J* = 7.2, 1.9 Hz, 1H), 3.78-3.68 (comp m, 2H), 3.38 (d, *J* = 3.8 Hz, 3H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.25-2.05 (comp m, 2H), 1.98-1.80 (comp m, 2H), 1.48 (s, 1H), 1.47 (s, 8H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 141.1, 128.6, 126.2, 83.4, 83.3, 82.9, 82.69, 82.65, 68.1, 68.0, 59.1, 56.6, 56.5, 51.9, 51.8, 39.01, 38.98, 34.4, 32.2, 28.34, 28.29, 26.1, 26.0, 18.5, -5.20, -5.25; IR (film) 3264, 2931, 1699, 1456, 1106, 835 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₆H₄₃NO₅Si + Na]⁺: 500.2803, found 500.2823.



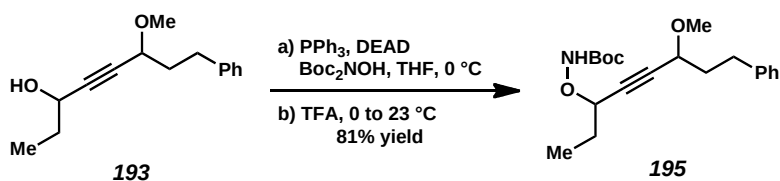
To a solution of alkyne **119** (0.870 g, 5.00 mmol) in THF (15.0 mL, 0.33 M) at $-78\text{ }^{\circ}\text{C}$ under argon was added $n\text{-BuLi}$ (2.12 mL, 2.35 M in hexanes, 5.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**130**, 0.361 mL, 5.00 mmol) was added dropwise, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (15 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic phases were washed with brine (15 mL), dried over MgSO_4 , and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (4:1 hexanes/ EtOAc eluent) affording alcohol **193** (0.933 g, 80% yield, $R_f = 0.20$ in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of PPh_3 (0.485 g, 1.85 mmol) in THF (10.0 mL, 0.19 M) at $0\text{ }^{\circ}\text{C}$ under argon was added DIAD (0.313 mL, 1.62 mmol) dropwise. After 10 min a solution of alcohol **193** (0.359 g, 1.54 mmol) in THF (3.00 mL, 0.50 M) was added. After 5 min $N\text{-hydroxyphthalimide}$ (0.264 g, 1.62 mmol) was added, and the reaction was warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered

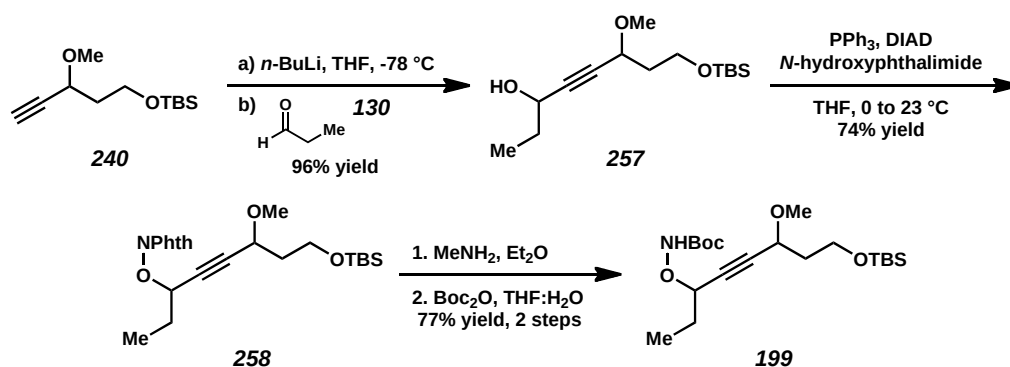
residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **256** (0.468 g, 81% yield, R_f = 0.26 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **256** (0.468 g, 1.24 mmol) in Et₂O (5.0 mL, 0.25 M) at 23 °C was added MeNH₂ (0.228 mL, 40% solution in H₂O, 2.61 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (5.0 mL). The filtrate was concentrated in vacuo and redissolved in THF:H₂O (5:1, 6.20 mL, 0.20 M). Boc₂O (0.270 g, 1.24 mmol) was added and the reaction was stirred for 16 h. The reaction was diluted with Et₂O (5 mL) and sat. aq. NaHCO₃ (5 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (5 mL). The combined organic layers were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (19:1→9:1 hexanes/EtOAc eluent) affording amino ether **195** (0.350 g, 86% yield over 2 steps, R_f = 0.47 in 4:1 hexanes/EtOAc) as a colorless oil.

Amino ether 195: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.27 (comp m, 2H), 7.23-7.16 (comp m, 3H), 4.55-4.52 (m, 1H), 3.98 (t, J = 6.4 Hz, 1H), 3.41 (d, J = 0.9 Hz, 3H), 2.79 (t, J = 7.4 Hz, 2H), 2.12-1.96 (comp m, 2H), 1.89-1.72 (comp m, 2H), 1.48 (s, 9H), 1.06 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 141.4, 128.7, 128.6, 126.1, 85.4, 85.3, 83.93, 83.90, 82.0, 70.44, 70.42, 56.62, 56.61, 37.33, 37.28, 31.58, 31.57, 28.4, 27.1, 9.7; IR (film) 3285, 2977, 1747, 1455, 1104, 700 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + NH₄)⁺ [C₂₀H₂₉NO₄ + NH₄]⁺: 365.2435, found 365.2434.



To a solution of alcohol **193** (0.116 g, 0.500 mmol) in THF (1.00 mL, 0.50 M) under argon was added PPh_3 (0.157 g, 0.600 mmol) and Boc_2NOH (0.140 g, 0.600 mmol).⁹⁸ The resulting solution was cooled to 0 °C, and a solution of DEAD (0.0941 mL, 0.600 mmol) in THF (0.200 mL) was added dropwise over 40 min. The reaction was stirred at 0 °C for 8 h. TFA (0.900 mL) was then added dropwise, and the reaction was warmed to 23 °C, and stirred until the reaction was complete by TLC. The reaction was poured into sat. aq. Na_2CO_3 (15.0 mL) and stirred for 10 min. The mixture was diluted with Et_2O (5.0 mL), and the phases were separated. The aq. phase was extracted with Et_2O (5.0 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation and the recovered oil was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) producing amino ether **195** (0.140 g, 81% yield) as a colorless oil.



To a solution of alkyne **240** (0.684 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added $n\text{-BuLi}$ (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**130**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction

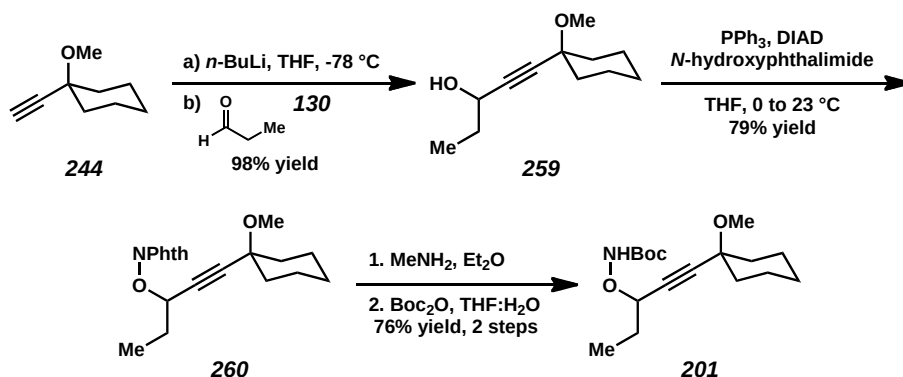
was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The phases were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation affording alcohol **257** (0.820 g, 96% crude yield, *R_f* = 0.39 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh₃ (0.903 g, 3.44 mmol) in THF (17.2 mL, 0.20 M) at 0 °C under argon was added DIAD (0.583 mL, 3.01 mmol) dropwise. After 10 min a solution of alcohol **257** (0.820 g, 2.87 mmol) in THF (5.7 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.490 g, 3.01 mmol) was added, and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO₃ (30 mL), and diluted with Et₂O (15 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (15 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording phthalimide **258** (0.920 g, 74% yield, *R_f* = 0.40 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **258** (0.920 g, 2.13 mmol) in Et₂O (10.6 mL, 0.25 M) at 23 °C was added MeNH₂ (0.390 mL, 40% solution in H₂O, 4.48 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (10.0 mL). The filtrate was concentrated in vacuo and redissolved in THF:H₂O (4:1, 12.5 mL, 0.20 M). Boc₂O (0.464 g, 2.13 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et₂O (10 mL), sat. aq. NaHCO₃ (10 mL) and the layers were separated. The aqueous layer

was extracted with Et₂O (10 mL), and the combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (19:1→9:1 hexanes/EtOAc eluent) affording amino ether **199** (0.659 g, 77% yield over 2 steps, *R_f* = 0.51 in 4:1 hexanes/EtOAc) as a colorless oil.

Amino ether 199: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 2.6 Hz, 1H), 4.53-4.49 (m, 1H), 4.19 (ddd, *J* = 7.5, 6.1, 1.4 Hz, 1H), 3.80-3.69 (comp m, 2H), 3.40 (s, 3H), 1.99-1.72 (comp m, 4H), 1.48 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 156.51, 156.49, 85.6, 85.5, 83.62, 83.58, 81.9, 68.1, 59.1, 56.68, 56.66, 38.9, 28.4, 27.1, 26.1, 18.5, 9.7, -5.2; IR (film) 3282, 2932, 1750, 1472, 1251, 813 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₀H₃₉NO₅Si + Na]⁺: 424.2490, found 424.2481.



To a solution of alkyne **244** (0.414 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**130**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic

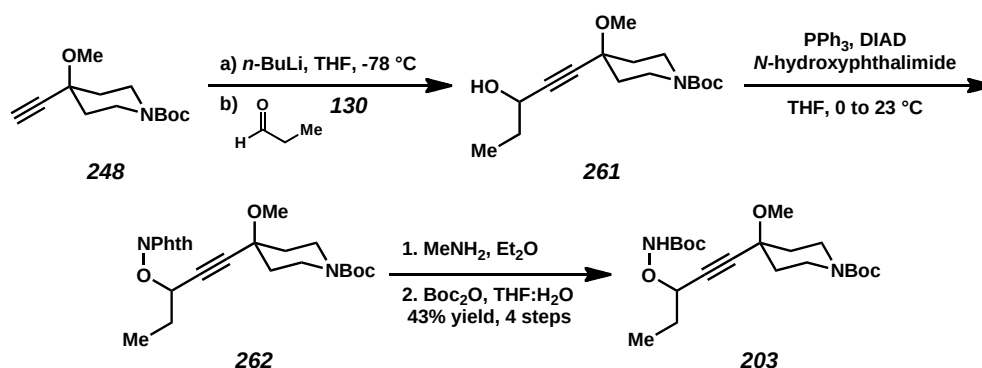
phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed by rotary evaporation affording alcohol **259** (0.577 g, 98% crude yield, R_f = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh₃ (0.926 g, 3.53 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.597 mL, 3.08 mmol) dropwise. After 10 min a solution of alcohol **259** (0.577 g, 2.94 mmol) in THF (6.00 mL, 0.48 M) was added. After 5 min *N*-hydroxyphthalimide (0.502 g, 3.08 mmol) was added, the reaction was warmed to 23 °C, and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO₃ (30 mL), and diluted with Et₂O (15 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (15 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford phthalimide **260** (0.796 g, 79% yield, R_f = 0.34 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **260** (0.796 g, 2.33 mmol) in Et₂O (12.0 mL, 0.20 M) at 23 °C was added MeNH₂ (0.428 mL, 40% solution in H₂O, 4.90 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H₂O (3:1, 15.0 mL, 0.20 M). Boc₂O (0.508 g, 2.33 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et₂O (10 mL), and sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (10 mL). The combined organic layers were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash

chromatography (9:1 hexanes/EtOAc eluent) affording amino ether **201** (0.557 g, 76% yield over 2 steps, $R_f = 0.45$ in 4:1 hexanes/EtOAc) as a colorless oil.

Amino ether 201: ^1H NMR (400 MHz, CDCl_3) δ 7.20 (s, 1H), 4.54 (t, $J = 6.4$ Hz, 1H), 3.36 (s, 3H), 1.92-1.87 (comp m, 2H), 1.86-1.71 (comp m, 2H), 1.68-1.62 (comp m, 2H), 1.60-1.52 (comp m, 4H), 1.48 (s, 9H), 1.33-1.24 (m, 2H), 1.04 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.5, 87.9, 83.6, 81.9, 77.1, 74.1, 50.9, 36.85, 36.82, 28.4, 27.2, 25.6, 23.0, 9.7; IR (film) 3265, 2937, 1996, 1747, 1169, 926 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{17}\text{H}_{29}\text{NO}_4 + \text{Na}$] $^+$: 334.1989, found 334.1989.



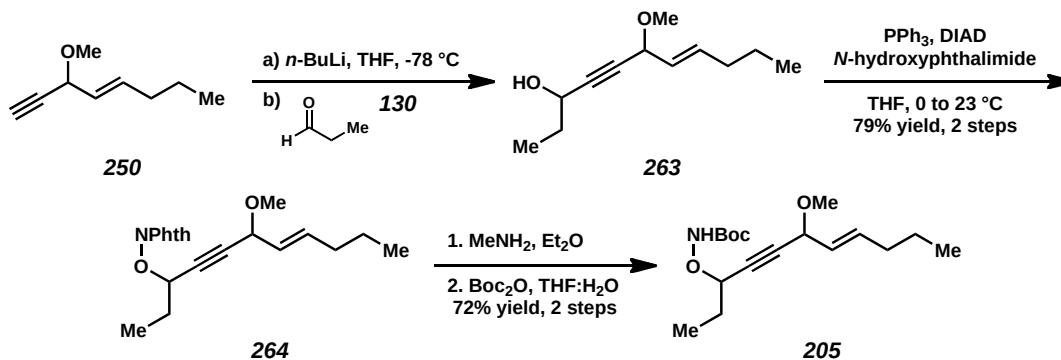
To a solution of alkyne **248** (0.717 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at $-78\text{ }^\circ\text{C}$ under argon was added $n\text{-BuLi}$ (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**130**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction was stirred at $-78\text{ }^\circ\text{C}$ for 10 min, then warmed to $23\text{ }^\circ\text{C}$ and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO_4 . The solvent was removed by rotary evaporation affording alcohol **261** (0.914 g crude, $R_f = 0.10$ in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of crude alcohol **261** (0.914 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/ EtOAc eluent) affording phthalimide **262** (1.17 g, R_f = 0.42 in 2:1 hexanes/ EtOAc) as a yellow oil that was carried on with a small amount of the hydrazine byproduct.

To a solution of phthalimide **262** (1.17 g, 2.64 mmol) in Et_2O (13.0 mL, 0.20 M) at 23 °C was added MeNH_2 (0.483 mL, 40% solution in H_2O , 5.54 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF: H_2O (4:1, 15.0 mL, 0.20 M). Boc_2O (0.576 g, 2.64 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. NaHCO_3 (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/ EtOAc eluent) affording amino ether **203** (0.539 g, 43% yield over 4 steps, R_f = 0.25 in 4:1 hexanes/ EtOAc) as a pale yellow oil.

Amino ether 203: ^1H NMR (400 MHz, CDCl_3) δ 7.17 (s, 1H), 4.52 (t, J = 6.5 Hz, 1H), 3.71 (dt, J = 14.3, 5.0 Hz, 2H), 3.36 (s, 3H), 3.25 (ddd, J = 13.3, 9.5, 3.6 Hz, 2H), 1.91-1.65 (m, 6H), 1.47

(s, 9H), 1.44 (s, 9H), 1.03 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.6, 154.8, 86.0, 84.9, 82.0, 79.8, 77.0, 72.5, 51.11, 51.09, 40.7, 36.1, 28.6, 28.4, 9.7; IR (film) 3265, 2976, 1747, 1698, 1165, 771 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_6 + \text{Na}$] $^+$: 435.2466, found 435.2465.



To a solution of alkyne **250** (0.414 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at $-78\text{ }^\circ\text{C}$ under argon was added $n\text{-BuLi}$ (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Propionaldehyde (**130**, 0.220 mL, 3.30 mmol) was added dropwise, and the reaction was stirred at $-78\text{ }^\circ\text{C}$ for 10 min, then warmed to $23\text{ }^\circ\text{C}$ and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO_4 . The solvent was removed by rotary evaporation affording alcohol **263** (0.585 g crude, $R_f = 0.31$ in 4:1 hexanes/ EtOAc) as a colorless oil.

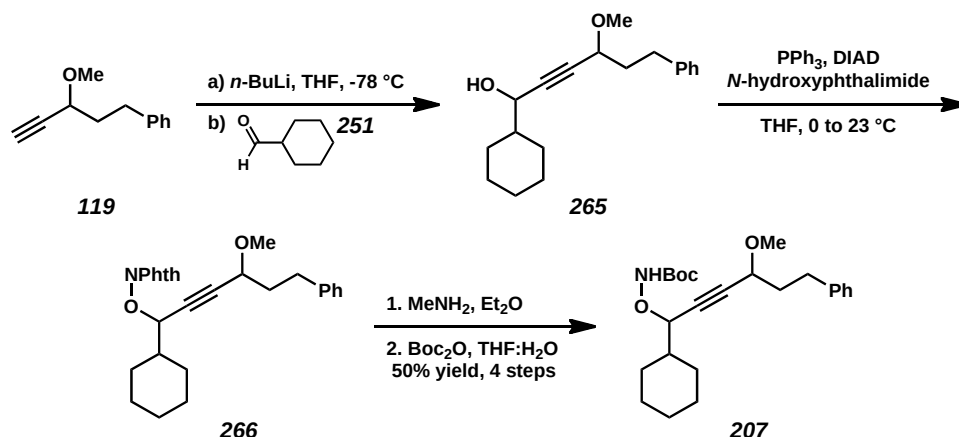
To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at $0\text{ }^\circ\text{C}$ under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of crude alcohol **263** (0.585 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min N -

hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. NaHCO₃ (30 mL), and diluted with Et₂O (15 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (15 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **264** (0.808 g, 79% yield over 2 steps, *R_f* = 0.34 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **264** (0.808 g, 2.37 mmol) in Et₂O (12.0 mL, 0.20 M) at 23 °C was added MeNH₂ (0.434 mL, 40% solution in H₂O, 4.98 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H₂O (4:1, 12.0 mL, 0.20 M). Boc₂O (0.517 g, 2.37 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et₂O (10 mL), and sat. aq. NaHCO₃ (10 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (10 mL). The combined organic phases were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording amino ether **205** (0.534 g, 72% yield over 2 steps, *R_f* = 0.50 in 4:1 hexanes/EtOAc) as a pale yellow oil.

Amino ether 205: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.22 (br s, 1H), 5.87 (dt, *J* = 15.2, 6.9 Hz, 1H), 5.50 (ddd, *J* = 15.3, 6.4, 1.3 Hz, 1H), 4.53-4.49 (comp m, 2H), 3.35 (d, *J* = 0.8 Hz, 3H), 2.06-2.01 (comp m, 2H), 1.86-1.72 (comp m, 2H), 1.46 (s, 9H), 1.41 (q, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 135.62, 135.57, 126.84, 126.80, 84.72, 84.69, 84.04, 84.01, 81.9, 71.5,

55.57, 55.55, 34.2, 28.4, 27.0, 22.2, 13.8, 9.7; IR (film) 3282, 2970, 1722, 1461, 1392, 1164, 969 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for $(\text{M} + \text{Na})^+$ $[\text{C}_{17}\text{H}_{29}\text{NO}_4 + \text{Na}]^+$: 334.1989, found 334.1984.



To a solution of alkyne **119** (0.522 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Cyclohexanecarboxaldehyde (**251**, 0.363 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , and the solvent was removed by rotary evaporation affording alcohol **265** (0.923 g crude, R_f = 0.40 in 4:1 hexanes/ EtOAc) as a colorless oil.

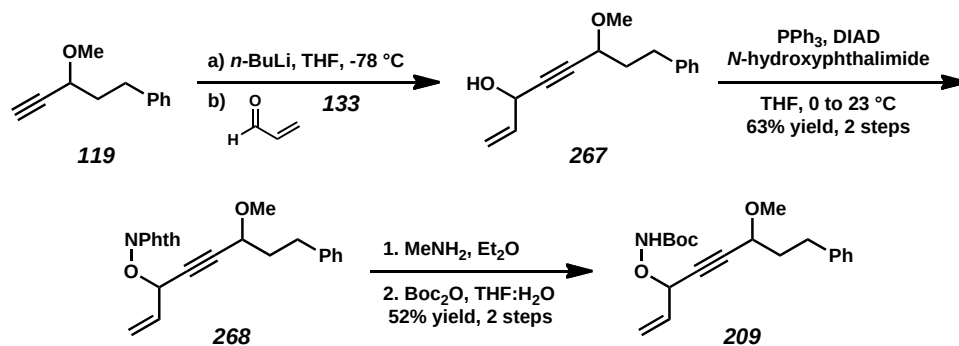
To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of crude alcohol **265** (0.585 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and

stirred for 18 h. The reaction was quenched with sat. aq. NaHCO_3 (30 mL) and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/ EtOAc eluent) affording phthalimide **266** (1.43 g, $R_f = 0.34$ in 4:1 hexanes/ EtOAc) as a pale yellow oil that contained the hydrazine byproduct.

To a solution of phthalimide **266** (1.43 g, assumed 3.00 mmol) in Et_2O (12.0 mL, 0.25 M) at 23 °C was added MeNH_2 (0.550 mL, 40% solution in H_2O , 6.30 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in $\text{THF}:\text{H}_2\text{O}$ (4:1, 15.0 mL, 0.20 M). Boc_2O (0.654 g, 3.00 mmol) was added, and the reaction was stirred for 12 h. The reaction was diluted with Et_2O (10 mL), sat. aq. NaHCO_3 (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL), and the combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) affording amino ether **207** (0.607 g, 50% yield over 4 steps, $R_f = 0.51$ in 4:1 hexanes/ EtOAc) as a colorless oil.

Amino ether 207: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.25 (comp m, 2H), 7.20-7.16 (comp m, 4H), 4.38 (ddd, $J = 5.9, 3.2, 1.4$ Hz, 1H), 3.99-3.95 (m, 1H), 3.40 (d, $J = 1.6$ Hz, 3H), 2.78 (t, $J = 7.8$ Hz, 2H), 2.11-1.95 (comp m, 2H), 1.90-1.87 (comp m, 2H), 1.75-1.70 (comp m, 2H), 1.67-1.62 (m, 1H), 1.46 (d, $J = 0.6$ Hz, 9H), 1.30-1.09 (comp m, 5H), 0.96-0.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.4, 141.5, 128.7, 128.6, 126.1, 86.1, 86.0, 83.1, 81.9, 80.64, 80.61, 70.49, 70.47, 56.7, 56.6, 41.18, 41.15, 37.43, 37.36,

31.63, 31.61, 29.2, 29.1, 28.37, 28.35, 26.47, 26.45, 26.0, 25.9; IR (film) 3282, 2979, 1946, 1748, 1453, 1166, 753 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₂₄H₃₅NO₄ + Na]⁺: 424.2458, found 424.2462.



To a solution of alkyne **119** (0.696 g, 4.00 mmol) in THF (12.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (1.60 mL, 2.50 M in hexanes, 4.00 mmol), and the reaction was stirred for 30 min. Acrolein (**133**, 0.267 mL, 4.00 mmol) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 1 h. The reaction was quenched with sat. aq. NH₄Cl (12 mL), and diluted with Et₂O (12 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (12 mL). The combined organic layers were washed with brine (12 mL), and dried over MgSO₄. The solvent was removed by rotary evaporation affording alcohol **267** (0.842 g crude, R_f = 0.22 in 4:1 hexanes/EtOAc) as a colorless oil.

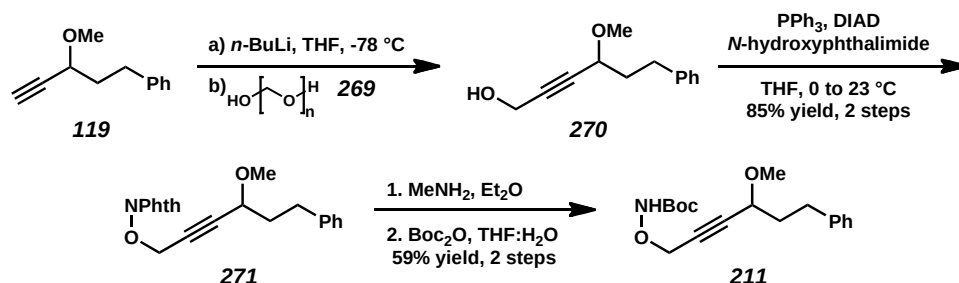
To a solution of PPh₃ (1.26 g, 4.80 mmol) in THF (26.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.813 mL, 4.20 mmol) dropwise. After 10 min a solution of crude alcohol **267** (0.842 g, assumed 4.00 mmol) in THF (8.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.685 g, 4.20 mmol) was added, and the reaction was warmed to 23 °C,

and stirred for 18 h. The reaction was quenched with sat. aq. NaHCO_3 (40 mL), and diluted with Et_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/ EtOAc eluent) affording phthalimide **268** (0.942 g, 63% yield over 2 steps, R_f = 0.54 in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of phthalimide **268** (0.942 g, 2.51 mmol) in Et_2O (12.5 mL, 0.20 M) at 23 °C was added MeNH_2 (0.410 mL, 40% solution in H_2O , 5.27 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in $\text{THF}:\text{H}_2\text{O}$ (4:1, 15.0 mL, 0.20 M). Boc_2O (0.547 g, 2.51 mmol) was added and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (10 mL), and sat. aq. NaHCO_3 (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over MgSO_4 , and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) affording amino ether **209** (0.452 g, 52% yield over 2 steps, R_f = 0.44 in 4:1 hexanes/ EtOAc) as a colorless oil.

Amino ether 209: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.21-7.18 (comp m, 4H), 5.99 (ddd, J = 16.8, 10.4, 6.2 Hz, 1H), 5.58 (dt, J = 17.1, 1.2 Hz, 1H), 5.38 (dd, J = 10.2, 0.5 Hz, 1H), 5.08 (ddd, J = 5.9, 2.7, 1.4 Hz, 1H), 4.02-3.98 (m, 1H), 3.42 (d, J = 1.3 Hz, 3H), 2.81-2.77 (comp m, 2H), 2.14-1.97 (comp m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.5, 141.4, 132.8, 128.7, 128.6, 126.1, 120.72, 120.67, 87.22, 87.18, 82.1, 81.67, 81.65, 76.2, 70.4, 56.7, 37.24, 37.20, 31.5, 28.3; IR (film)

3283, 2933, 1746, 1603, 1455, 1103, 701 cm^{-1} ; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₂₀H₂₇NO₄ + Na]⁺: 368.1832, found 368.1821.



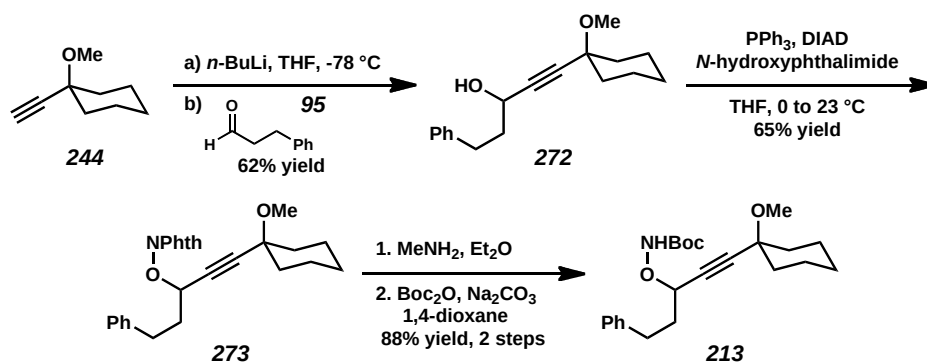
To a solution of alkyne **119** (0.522 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at $-78\text{ }^{\circ}\text{C}$ under argon was added $n\text{-BuLi}$ (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Paraformaldehyde (**269**, 94.5 mg, 3.15 mmol) was added, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 12 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO_4 . The solvent was removed by rotary evaporation affording alcohol **270** (0.647 g crude, $R_f = 0.42$ in 2:1 hexanes/ EtOAc) as a colorless oil.

To a solution of PPh_3 (0.943 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at $0\text{ }^{\circ}\text{C}$ under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **270** (0.647 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min N -hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 20 h. The reaction was quenched with sat. aq. NaHCO_3 (30 mL), and diluted with Et_2O (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (20 mL). The combined

organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) affording phthalimide **271** (0.886 g, 85% yield over 2 steps, $R_f = 0.42$ in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **271** (0.886 g, 2.53 mmol) in Et_2O (12.0 mL, 0.20 M) at 23 °C was added MeNH_2 (0.465 mL, 40% solution in H_2O , 5.33 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in 1,4-dioxane (10.0 mL, 0.25 M). Na_2CO_3 (0.268 g, 2.53 mmol) was added, followed by Boc_2O (0.551 g, 2.53 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et_2O (20 mL), and sat. aq. NaHCO_3 (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over MgSO_4 , and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording amino ether **211** (0.478 g, 59% yield over 2 steps, $R_f = 0.41$ in 4:1 hexanes/EtOAc) as a colorless oil.

Amino ether 211: ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.22 (comp m, 2H), 7.16-7.12 (comp m, 3H), 4.50 (d, $J = 1.6$ Hz, 2H), 3.94-3.89 (m, 1H), 3.36 (s, 3H), 2.74 (td, $J = 7.8, 1.8$ Hz, 2H), 2.07-1.91 (comp m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.5, 141.4, 128.7, 128.6, 126.1, 86.4, 82.3, 80.7, 70.4, 64.2, 56.7, 37.1, 31.5, 28.3; IR (film) 3279, 2933, 1950, 1745, 1368, 1103, 701 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{NH}_4)^+ [\text{C}_{18}\text{H}_{25}\text{NO}_4 + \text{NH}_4]^+$: 337.2122, found 337.2125.



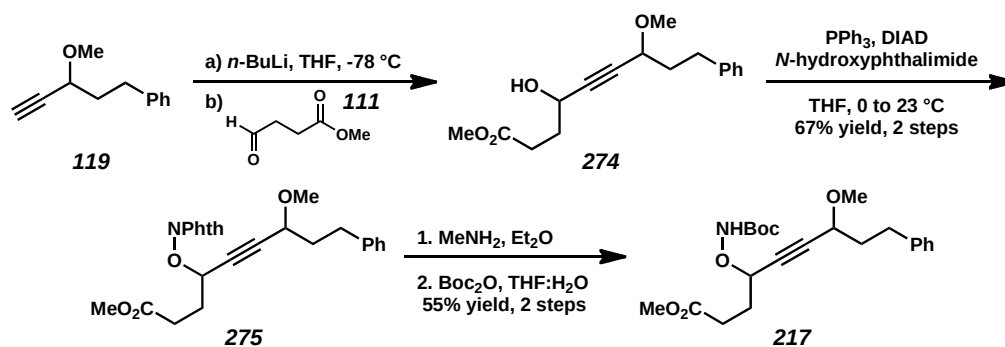
To a solution of alkyne **244** (0.414 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at $-78\text{ }^{\circ}\text{C}$ under argon was added $n\text{-BuLi}$ (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Hydrocinnamaldehyde (**95**, 0.395 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO_4 . The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (4:1 hexanes/ EtOAc eluent), affording alcohol **272** (0.503 g, 62% yield, $R_f = 0.31$ in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of PPh_3 (0.582 g, 2.22 mmol) in THF (12.0 mL, 0.18 M) at $0\text{ }^{\circ}\text{C}$ under argon was added DIAD (0.376 mL, 1.94 mmol) dropwise. After 10 min a solution of alcohol **272** (0.503 g, 1.85 mmol) in THF (3.60 mL, 0.50 M) was added. After 5 min $N\text{-hydroxyphthalimide}$ (0.316 g, 1.94 mmol) was added, and the reaction was slowly warmed to $23\text{ }^{\circ}\text{C}$, and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (20 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The

recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording phthalimide **273** (0.504 g, 65% yield, R_f = 0.51 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **273** (0.504 g, 1.21 mmol) in Et₂O (6.00 mL, 0.20 M) at 23 °C was added MeNH₂ (0.222 mL, 40% solution in H₂O, 2.54 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (5.0 mL). The filtrate was concentrated in vacuo, and redissolved in 1,4-dioxane (4.80 mL, 0.25 M). Na₂CO₃ (0.128 g, 1.21 mmol) was added, followed by Boc₂O (0.264 g, 1.21 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et₂O (10 mL), and sat. aq. NaHCO₃ (10 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (10 mL). The combined organic phases were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording amino ether **213** (0.411 g, 88% yield over 2 steps, R_f = 0.38 in 4:1 hexanes/EtOAc) as a colorless oil.

Amino ether 213: ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.27 (comp m, 2H), 7.22-7.17 (comp m, 4H), 4.61 (t, J = 6.5 Hz, 1H), 3.38 (s, 3H), 2.85 (td, J = 8.0, 2.0 Hz, 2H), 2.19-2.00 (comp m, 2H), 1.94-1.90 (comp m, 2H), 1.70-1.50 (comp m, 7H), 1.48 (s, 9H), 1.35-1.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 141.3, 128.6, 126.2, 88.3, 83.5, 82.0, 75.3, 74.1, 51.0, 50.9, 36.84, 36.81, 35.8, 31.6, 28.4, 28.3, 25.6, 23.0; IR (film) 3265, 2936, 1748, 1164, 700 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₂₃H₃₃NO₄ + Na]⁺: 410.2302, found 410.2295.



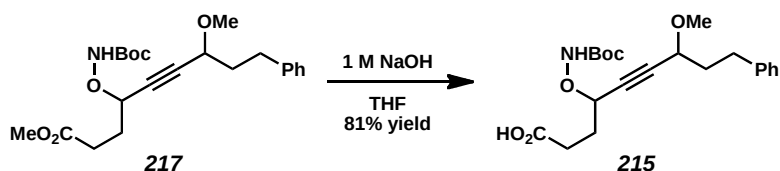
To a solution of alkyne **119** (0.522 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Methyl 4-oxobutanoate (**111**, 0.314 mL, 3.00 mmol) was added and the reaction was stirred at -78 °C for 30 min. The reaction was quenched with sat. aq. NH₄Cl (10 mL) and warmed to 23 °C. The reaction was diluted with Et₂O (10 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (10 mL), and the combined organic layers were washed with brine (10 mL), and dried over MgSO₄. The solvent was removed by rotary evaporation affording alcohol **274** (0.960 g crude, *R*_f = 0.35 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh₃ (0.943 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **274** (0.960 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. NaHCO₃ (30 mL), and diluted with Et₂O (20 mL). The layers were separated and the aqueous phase was extracted with Et₂O (20 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1→2:1 hexanes/EtOAc eluent)

affording phthalimide **275** (1.07 g, 67% yield over 2 steps, $R_f = 0.34$ in 2:1 hexanes/EtOAc) as a colorless oil.

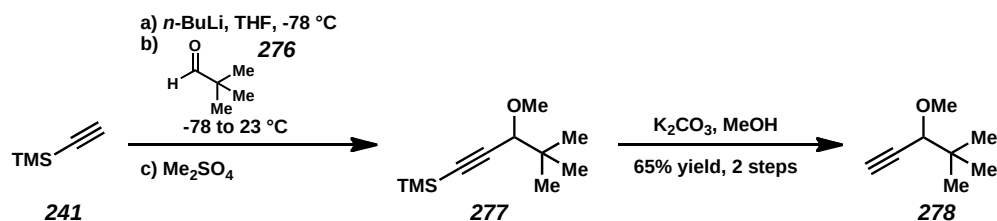
To a solution of phthalimide **275** (1.07 g, 2.01 mmol) in Et₂O (10.0 mL, 0.20 M) at 23 °C was added MeNH₂ (0.368 mL, 40% solution in H₂O, 4.22 mmol) and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H₂O (4:1, 10.0 mL, 0.20 M). Boc₂O (0.438 g, 2.01 mmol) was added and the reaction was stirred for 12 h. The reaction was diluted with Et₂O (10 mL), and sat. aq. NaHCO₃ (20 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (10 mL). The combined organic phases were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording amino ether **217** (0.448 g, 55% yield over 2 steps, $R_f = 0.50$ in 2:1 hexanes/EtOAc) as a colorless oil.

Amino ether 217: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.27 (comp m, 2H), 7.21-7.16 (comp m, 3H), 4.66-4.63 (m, 1H), 3.97-3.94 (m, 1H), 3.68 (s, 3H), 3.40 (s, 3H), 2.79-2.75 (m, 2H), 2.58 (td, $J = 7.5, 3.0$ Hz, 2H), 2.14-2.09 (m, 2H), 2.08-1.96 (m, 2H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 156.5, 141.3, 128.7, 128.6, 126.1, 85.9, 83.0, 82.1, 74.72, 74.70, 70.3, 56.7, 51.9, 37.23, 37.19, 31.5, 29.6, 28.8, 28.3; IR (film) 3300, 2980, 1740, 1440, 1168, 1104, 701 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₂₂H₃₁NO₆ + Na]⁺: 428.2044, found 428.2048.



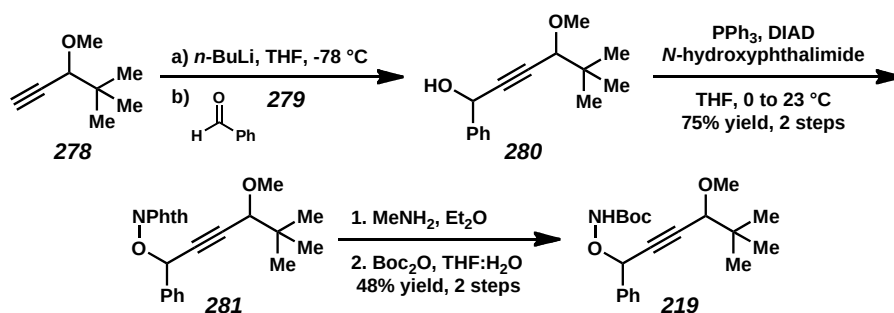
To a solution of amino ether **217** (0.206 g, 0.509 mmol) in THF (2.50 mL, 0.2 M) at 23 °C was added NaOH (2.50 mL, 1.0 M in H₂O, 2.50 mmol), and the reaction was stirred for 16 h. The THF was removed by rotary evaporation and the resulting aqueous solution was acidified to pH ~ 2.0 with 10% aq. HCl. The solution was then saturated with NaCl, and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude material was purified by flash chromatography (1:1 hexanes/Et₂O with 1% AcOH) affording amino ether **215** (0.156 g, 81% yield, *R_f* = 0.43 in 2:1 Et₂O/hexanes with 1% AcOH) as a colorless oil.

Amino ether 215: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 1H), 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 4.65 (ddd, *J* = 7.3, 5.1, 1.8 Hz, 1H), 3.98-3.94 (m, 1H), 3.40 (s, 3H), 2.79-2.75 (comp m, 2H), 2.65-2.61 (comp m, 2H), 2.14-2.08 (comp m, 2H), 2.06-1.94 (comp m, 2H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 178.1, 156.8, 141.3, 128.7, 128.63, 128.57, 128.5, 126.1, 86.03, 86.02, 82.94, 82.92, 82.4, 74.62, 74.60, 70.4, 56.7, 37.2, 37.1, 31.5, 29.6, 28.7, 28.3; IR (film) 3258, 2980, 1714, 1250, 1164, 1105 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₁H₂₉NO₆ + Na]⁺: 414.1887, found 414.1889.



To a solution of ethynyltrimethylsilane (**241**, 1.41 mL, 10.0 mmol) in THF (30.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.00 mL, 2.5 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min. Pivaldehyde (**276**, 1.10 mL, 10.0 mmol) was added, and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me₂SO₄ (1.04 mL, 11.0 mmol) was added, and the reaction was stirred for 16 h. The reaction was quenched with 10% aq. NH₄OH (20 mL), stirring for 15 min. The mixture was diluted with Et₂O (30 mL) and the layers were separated. The aqueous phase was extracted with Et₂O (15 mL) and the combined organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation affording ether **277** (1.95 g crude) as a pale yellow oil.

To a solution of ether **277** (2.21 g crude, assumed 10.0 mmol) in MeOH (40.0 mL, 0.25 M) at 23 °C was added K₂CO₃ (1.65 g, 12.0 mmol) and the reaction was stirred for 16 h. The reaction was diluted with brine (50 mL), and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (9:1 pentane/Et₂O eluent) affording alkyne **278** (0.817 g, 65% yield over 2 steps) as a volatile, colorless oil.

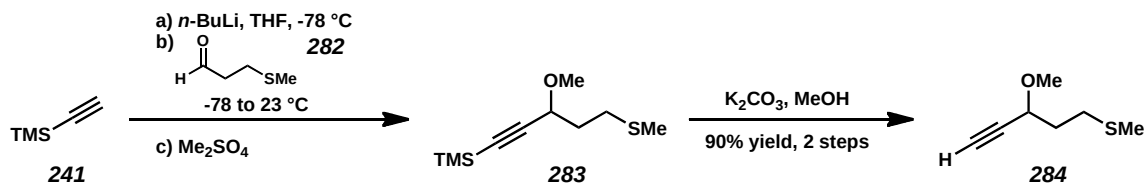


To a solution of alkyne **278** (0.378 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at $-78\text{ }^{\circ}\text{C}$ under argon was added $n\text{-BuLi}$ (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Benzaldehyde (**279**, 0.305 mL, 3.00 mmol) was added dropwise, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO_4 . The solvent was removed by rotary evaporation affording alcohol **280** (0.695 g, 99% crude yield, $R_f = 0.46$ in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of PPh_3 (0.944 g, 3.60 mmol) in THF (20.0 mL, 0.218 M) at $0\text{ }^{\circ}\text{C}$ under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **280** (0.695 g, 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min N -hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (30 mL), and diluted with Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) affording phthalimide **281** (0.850 g, 75% yield, $R_f = 0.36$ in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of phthalimide **281** (0.850 g, 2.25 mmol) in Et₂O (11.2 mL, 0.20 M) at 23 °C was added MeNH₂ (0.413 mL, 40% solution in H₂O, 4.73 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in THF:H₂O (3:1, 14.0 mL, 0.16 M). Boc₂O (0.491 g, 2.25 mmol) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et₂O (10 mL), and sat. aq. NaHCO₃ (10 mL). The layers were separated and the aqueous phase was extracted with Et₂O (10 mL). The combined organic phases were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording amino ether **219** (0.378 g, 48% yield over 2 steps, *R_f* = 0.43 in 4:1 hexanes/EtOAc) as a pale yellow oil.

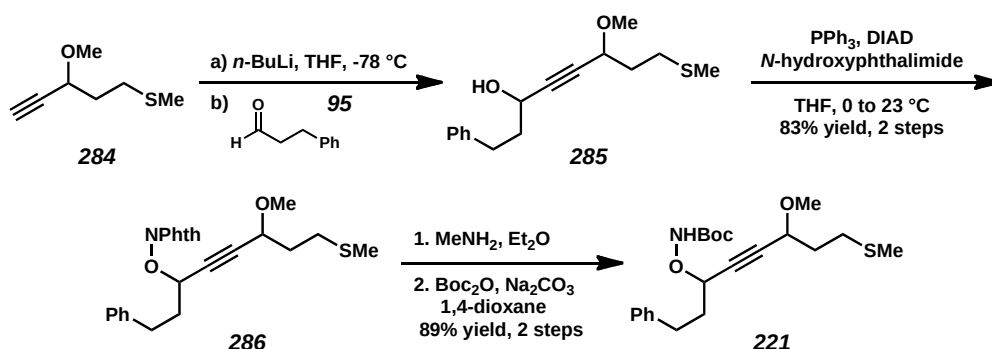
Amino ether 219: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.60 (m, 2H), 7.41-7.36 (m, 3H), 7.19 (s, 1H), 5.66 (t, *J* = 1.8 Hz, 1H), 3.66 (d, *J* = 1.5 Hz, 1H), 3.45 (d, *J* = 1.8 Hz, 3H), 1.48 (s, 9H), 1.02 (d, *J* = 1.8 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 156.4, 136.1, 136.0, 129.3, 128.8, 128.7, 128.6, 87.0, 86.9, 82.80, 82.76, 82.1, 80.9, 57.8, 35.8, 28.4, 26.0; IR (film) 3285, 2977, 1723, 1367, 1098 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₀H₂₉NO₄ + Na]⁺: 370.1989, found 370.1981.



To a solution of ethynyltrimethylsilane (**241**, 2.82 mL, 20.0 mmol) in THF (50.0 mL, 0.40 M) at -78 °C under argon was added *n*-BuLi (8.00 mL, 2.5 M in hexanes, 20.0 mmol), and the resulting solution was stirred for 30 min. 3-(Methylthio)propionaldehyde (**282**, 2.00 mL, 20.0 mmol) was

added, and the reaction was stirred for 30 min at -78 °C, then warmed to room temperature and stirred for 30 min. Me₂SO₄ (2.09 mL, 22.0 mmol) was added, and the reaction was stirred for 14 h. The reaction was quenched with 10% aq. NH₄OH (20 mL), stirring for 15 min. The mixture was diluted with Et₂O (50 mL), and the layers were separated. The aqueous phase was extracted with Et₂O (25 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed by rotary evaporation affording ether **283** (4.27 g crude, *R_f* = 0.58 in 9:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ether **283** (4.27 g crude, assumed 20.0 mmol) in MeOH (100 mL, 0.20 M) at 23 °C was added K₂CO₃ (2.76 g, 22.0 mmol), and the reaction was stirred for 5 h. The reaction was diluted with brine (100 mL), and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The crude residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording alkyne **284** (2.55 g, 90% yield over 2 steps, *R_f* = 0.50 in 9:1 hexanes/EtOAc) as a colorless oil.



To a solution of alkyne **284** (0.427 g, 3.00 mmol) in THF (10.0 mL, 0.30 M) at -78 °C under argon was added *n*-BuLi (1.29 mL, 2.32 M in hexanes, 3.00 mmol), and the reaction was stirred for 30 min. Hydrocinnamaldehyde (**95**, 0.395 mL, 3.00 mmol) was added dropwise, and the

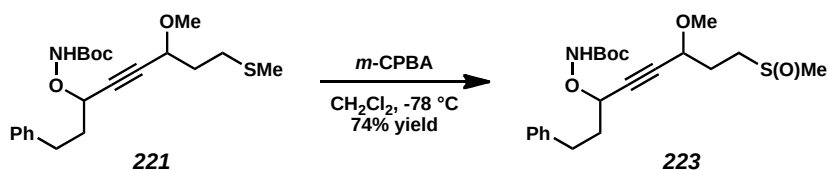
reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO₄. The solvent was removed by rotary evaporation affording alcohol **285** (0.836 g crude, *R_f* = 0.50 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh₃ (0.943 g, 3.60 mmol) in THF (20.0 mL, 0.18 M) at 0 °C under argon was added DIAD (0.610 mL, 3.15 mmol) dropwise. After 10 min a solution of alcohol **285** (0.836 g, assumed 3.00 mmol) in THF (6.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.514 g, 3.15 mmol) was added, and the reaction was warmed to 23 °C and stirred for 20 h. The reaction was quenched with sat. aq. NaHCO₃ (30 mL), and diluted with Et₂O (20 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (20 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **286** (1.05 g, 83% yield over 2 steps, *R_f* = 0.56 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **286** (1.05 g, 2.49 mmol) in Et₂O (12.5 mL, 0.20 M) at 23 °C was added MeNH₂ (0.456 mL, 40% solution in H₂O, 5.23 mmol), and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et₂O (10.0 mL). The filtrate was concentrated in vacuo, and redissolved in 1,4-dioxane (10.0 mL, 0.25 M). Na₂CO₃ (0.264 g, 2.49 mmol) was added, followed by Boc₂O (0.543 g, 2.49 mmol), and the reaction was

stirred for 14 h. The reaction was diluted with Et₂O (20 mL) and sat. aq. NaHCO₃ (20 mL). The layers were separated, and the aqueous phase was extracted with Et₂O (10 mL). The combined organic phases were dried over MgSO₄, and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording amino ether **221** (0.877 g, 89% yield over 2 steps, *R*_f = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

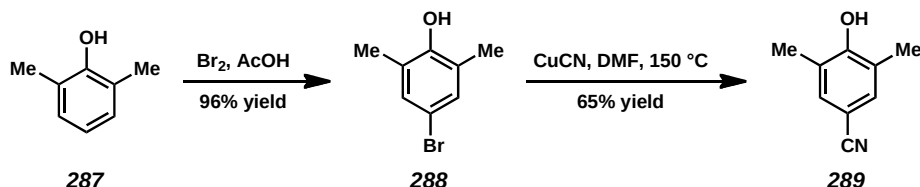
Amino ether 221: ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.27 (comp m, 2H), 7.22-7.17 (comp m, 3H), 4.58 (tt, *J* = 6.5, 1.8 Hz, 1H), 4.18 (ddd, *J* = 7.0, 5.9, 1.2 Hz, 1H), 3.42 (d, *J* = 0.5 Hz, 3H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.19-2.12 (m, 1H), 2.11 (s, 3H), 2.08-1.93 (comp m, 3H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 141.1, 128.5, 126.1, 85.15, 85.10, 83.99, 83.95, 81.9, 75.1, 69.8, 56.70, 56.65, 35.5, 35.1, 31.5, 29.9, 28.3, 15.6; IR (film) 3280, 2931, 1748, 1604, 1368, 1247, 1103 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₂₁H₃₁NO₄S + H]⁺: 394.2047, found 394.2043.



To a solution of carbamoyl ether **221** (0.393 g, 1.00 mmol) in DCM (5.00 mL, 0.2 M), cooled at -78 °C under an argon atmosphere, was added *m*-CPBA (0.224 g, 77% max wt, 1.00 mmol). The reaction was stirred for 1 h, quenched with sat. aq. Na₂S₂O₃ (5.0 mL), and was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with CH₂Cl₂ (5.0 mL). The combined organic layers were combined and washed with sat. aq. NaHCO₃ (20 mL), dried over MgSO₄, and the solvent removed by rotary evaporation. The crude oil was purified by

flash chromatography (0→5% MeOH/EtOAc) affording amino ether **223** (0.301 g, 74% yield, R_f = 0.48 in 1:19 MeOH/EtOAc) as a colorless oil.

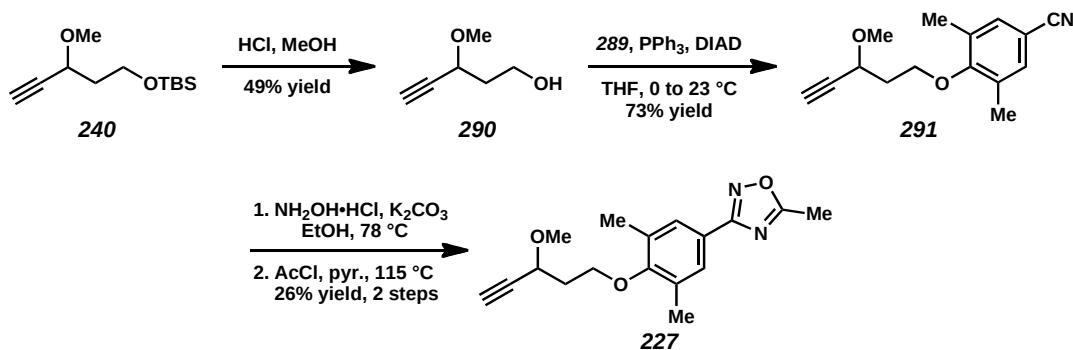
Amino ether 223: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.26 (comp m, 2H), 7.21-7.16 (comp m, 3H), 4.57-4.54 (m, 1H), 4.23-4.18 (m, 1H), 3.41 (dd, J = 1.3, 0.9 Hz, 3H), 2.98-2.87 (comp m, 2H), 2.86-2.80 (comp m, 2H), 2.61-2.58 (comp m, 3H), 2.26-2.17 (comp m, 2H), 2.17-2.09 (m, 1H), 2.07-1.98 (m, 1H), 1.47 (d, J = 1.0 Hz, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.6, 141.12, 141.09, 128.6, 126.2, 85.12, 85.10, 85.0, 84.9, 84.13, 84.08, 84.0, 81.8, 75.1, 69.7, 56.8, 50.0, 38.8, 35.4 31.5, 28.4; IR (film) 3178, 2933, 2349, 1739, 1368, 1106, 753 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{21}\text{H}_{31}\text{NO}_5\text{S} + \text{Na}$] 432.1815, found 432.1811.



To a solution of phenol **287** (0.892 g, 7.30 mmol) in acetic acid (5.00 mL, 1.5 M) at $0\text{ }^\circ\text{C}$ was added a solution of Br_2 (0.373 mL, 7.30 mmol) in acetic acid (5.00 mL, 1.5 M). The reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 20 min. The reaction was poured into NaHCO_3 (100 mL, 1% aq.) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over MgSO_4 . The solvent was removed by rotary evaporation affording bromide **288** (1.40g, 96% yield, R_f = 0.26 in 9:1 hexanes/EtOAc) as an off-white solid.

A solution of bromide **288** (1.40 g, 7.00 mmol) in DMF (5.50 mL, 1.3 M) was degassed with argon via bubbling for 15 min. CuCN (0.721 g, 8.05 mmol) was added and the reaction was

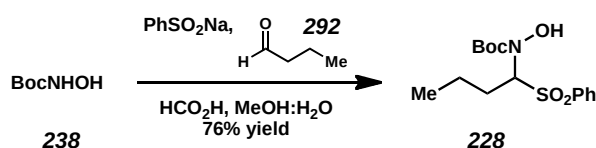
heated at 150 °C for 6 h. The reaction mixture was cooled to room temperature and then poured into a mixture of FeCl₃ (1.60 g), concentrated HCl (0.70 ml) and water (5 ml). The resulting slurry was filtered, washed with water (5 ml) and EtOH (20 ml), and the EtOH was removed by rotary evaporation. To the aqueous mixture was added NaOH (50 ml, 1.0 M), and the resulting mixture was stirred at 50 °C for 30 min. The solid was filtered and washed with water (20 ml). 1 M HCl was added to the filtrate until the pH ~ 4. The precipitate was extracted with EtOAc (2 x 20 mL), and the combined organic layers were washed with brine, and dried over MgSO₄. The solvent was removed by rotary evaporation affording nitrile **289** (0.665 g, 65% yield, *R*_f = 0.50 in 2:1 hexanes/EtOAc) as a yellow solid.



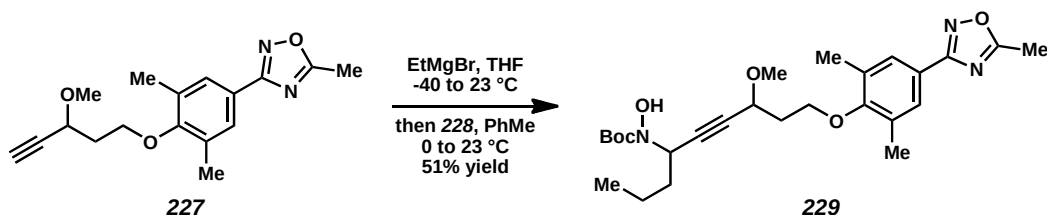
To a solution of alkyne **240** (0.922 g, 4.05 mmol) in MeOH (20.0 mL, 0.2 M) was added HCl (0.500 mL, 10% aq.) and the reaction was stirred at 23 °C for 4 h. The reaction was poured into water (100 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) affording alcohol **290** (0.227 g, 49% yield, *R*_f = 0.38 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **290** (0.492 g, 4.32 mmol), PPh_3 (1.36 g, 5.18 mmol) and nitrile **289** (0.665 g, 4.52 mmol) in THF (29.0 mL, 0.15 M) at 0 °C, was added DIAD (0.919 mL, 4.75 mmol). The reaction was stirred at 0 °C for 30 min., then warmed to 23 °C and stirred for 10 h. The solvent was removed via rotary evaporation, and the residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording ether **291** (0.765 g, 73% yield, R_f = 0.48 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **291** (0.765 g, 3.15 mmol) in absolute EtOH (9.30 mL, 0.34 M) was added K_2CO_3 (2.17 g, 15.7 mmol) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (**237**, 1.09 g, 15.7 mmol). The reaction was heated at 85 °C for 17 h, then filtered. The filter cake was washed with warm absolute EtOH (10 mL), and the combined filtrates were concentrated under reduced pressure producing the crude amidoxime (0.851 g, R_F = 0.59 in 2:1 EtOAc/hexanes) as an amber oil. The crude amidoxime (0.851 g, assumed 3.15 mmol) was dissolved in pyridine (0.97 mL, 3.2 M), and acetyl chloride (0.448 mL, 6.30 mmol) was added dropwise until the pyridine began to reflux. The reaction was heated at 115 °C for 1 h, then cooled to 23 °C and diluted with Et_2O (20 mL). The solution was washed with water (20 mL), brine (20 mL), and dried over MgSO_4 . The solvent was removed by rotary evaporation and the recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc) affording oxadiazole **227** (0.249 g, 26% yield over 2 steps, R_f = 0.37 in 4:1 hexanes/EtOAc) as a colorless oil.

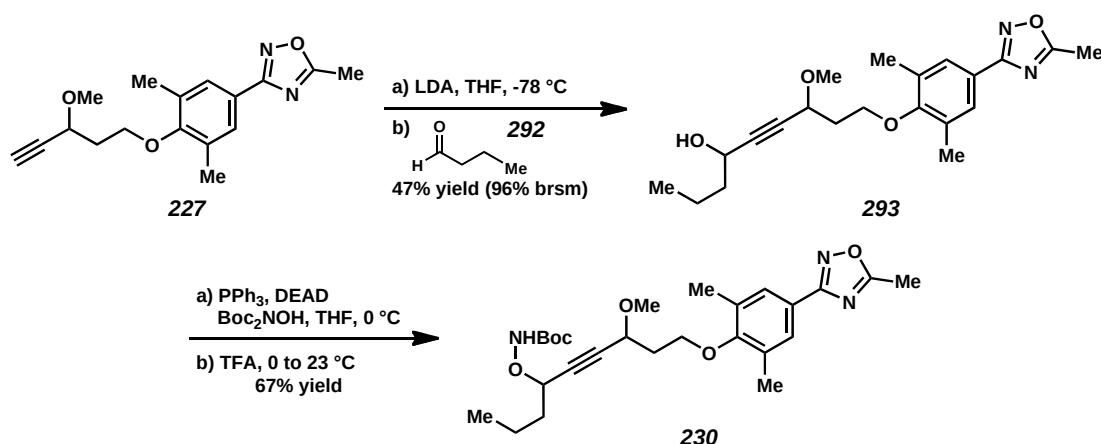


To a solution of sodium benzenesulfinate (1.54 g, 9.40 mmol) in MeOH:H₂O (1:2, 11.3 mL, 0.84 M) was added carbamate **238** (0.500 g, 3.76 mmol), butyraldehyde (**292**, 0.678 mL, 7.52 mmol) and formic acid (0.327 mL, 7.52 mmol). The reaction was stirred at room temperature for 20 h, and then filtered. The recovered precipitate was suspended in water and filtered, washing with pentane (2 x 15 mL). The recovered solid was dried under reduced pressure affording *N*-hydroxycarbamate **228** (0.945 g, 76% yield) as a white solid.



To a solution of alkyne **227** (180.0 mg, 0.600 mmol) in THF (0.600 mL, 1.0 M), cooled to -40 °C under argon was added ethylmagnesium bromide (0.200 mL, 0.600 mmol, 3.0 M solution in Et₂O) and the reaction was stirred at -40 °C for 15 min, then warmed to 23 °C. The magnesium acetylide was then added to a solution of *N*-hydroxycarbamate **228** (98.7 mg, 0.300 mmol) in toluene (3.00 mL, 0.1 M) at 0 °C. The reaction was warmed to 23 °C and stirred for 1 h. HCl (5.0 mL, 0.5 N) was added and the mixture was extracted with Et₂O (2 x 10 mL). The combine organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording *N*-hydroxycarbamate **229** (73.9 mg, 51% yield, *R*_f = 0.21 in 4:1 hexanes/EtOAc) as a colorless oil.

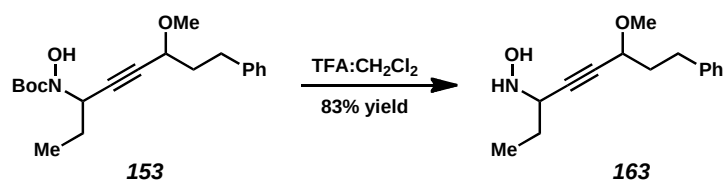
N-hydroxycarbamate 229: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz; CDCl_3): δ 7.72 (s, 2H), 4.74 (td, J = 7.7, 1.1 Hz, 1H), 4.39-4.35 (m, 1H), 3.95-3.91 (comp m, 2H), 3.45-3.41 (m, 3H), 2.63 (s, 3H), 2.33 (s, 6H), 2.23-2.15 (comp m, 2H), 1.88-1.75 (comp m, 2H), 1.47 (s, 9H), 1.46-1.39 (comp m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.5, 168.3, 158.4, 157.4, 157.3, 131.9, 128.1, 122.2, 83.61, 83.59, 82.8, 82.40, 82.38, 68.1, 56.7, 52.1, 36.6, 34.9, 28.3, 19.4, 16.3, 13.6, 12.5; IR (film) 3283, 2963, 1700, 1353, 1207, 1114. HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{26}\text{H}_{37}\text{N}_3\text{O}_6 + \text{Na}$] $^+$: 510.2575, found 510.2584.



To a solution of alkyne **227** (150 mg, 0.500 mmol) in THF (2.50 mL, 0.2 M) at $-78\text{ }^\circ\text{C}$ under argon was added LDA (0.500 mL, 1.0 M in THF, 0.500 mmol), and the reaction was stirred at $-78\text{ }^\circ\text{C}$ for 10 min., then warmed to $23\text{ }^\circ\text{C}$ for 15 min. The reaction was then cooled to $-78\text{ }^\circ\text{C}$, and butyraldehyde (**292**, 49.6 μL , 0.550 mmol) was added. The reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (5.0 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/ EtOAc eluent) affording alkyne **227** (74.0 mg, 49% recovery), and alcohol **293** (87.0 mg, 47% yield, R_f = 0.34 in 2:1 hexanes/ EtOAc) as colorless oils.

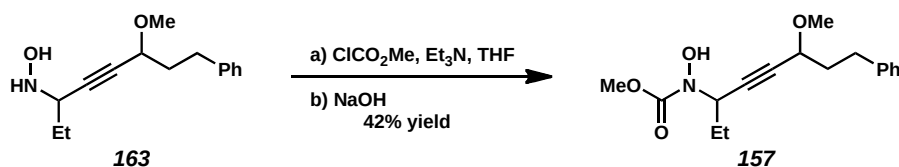
To a solution of alcohol **293** (87.0 mg, 0.234 mmol) in THF (0.468 mL, 0.50 M) under argon was added PPh₃ (73.6 mg, 0.281 mmol) and Boc₂NOH (65.5 mg, 0.281 mmol). The resulting solution was cooled to 0 °C, and a solution of DEAD (44.0 μL, 0.281 mmol) in THF (0.100 mL) was added dropwise over 30 min. The reaction was stirred at 0 °C for 14 h. TFA (0.700 mL) was then added dropwise, and the reaction was warmed to 23 °C, and stirred until the reaction was complete by TLC. The reaction was poured into sat. aq. Na₂CO₃ (5.0 mL) and stirred for 10 min. The mixture was diluted with Et₂O (5.0 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (5.0 mL), and the combined organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation and the recovered oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording amino ether **230** (76.1 mg, 67% yield, *R_f* = 0.38) as a colorless oil.

Amino ether 230: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (s, 2H), 7.27 (s, 1H), 4.57 (t, *J* = 6.5 Hz, 1H), 4.41 (t, *J* = 6.7 Hz, 1H), 3.97-3.91 (comp m, 2H), 3.45 (s, 3H), 2.63 (d, *J* = 0.8 Hz, 3H), 2.32 (s, 6H), 2.23-2.19 (comp m, 2H), 1.83-1.66 (comp m, 2H), 1.57-1.50 (comp m, 2H), 1.46 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 188.5, 176.4, 168.3, 158.3, 156.5, 131.9, 128.1, 122.2, 84.9, 84.4, 82.0, 75.8, 75.7, 68.12, 68.10, 68.0, 56.8, 36.6, 35.8, 28.3, 18.7, 16.3, 13.9, 12.5; IR (film) 3282, 2964, 2251, 1748, 1584, 1353, 1107. HRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₆H₃₇N₃O₆ + Na]⁺: 510.2575, found 510.2590.



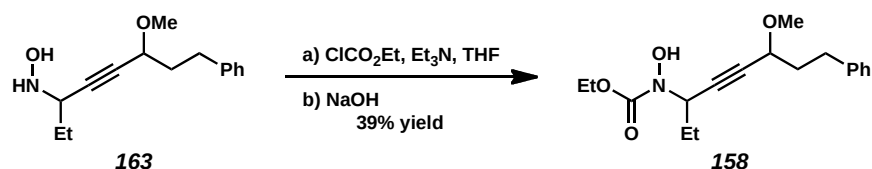
To carbamate **153** (1.39 g, 4.00 mmol) was added a CH₂Cl₂:TFA (3:1, 40.0 mL, 0.10 M) mixture, and the reaction was stirred at 23 °C for 2 h. The solvent was removed by rotary evaporation, and the residue was dissolved in CH₂Cl₂ (20 mL). The solution was washed with sat. aq. NaHCO₃ (40 mL), and the phases separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were dried over MgSO₄, and the solvent removed by rotary evaporation. The crude residue was purified by flash chromatography (2:1→1:1 hexanes/EtOAc eluent) affording *N*-hydroxylamine **163** (0.821 g, 83% yield, *R*_f = 0.35 in 1:1 hexanes/EtOAc) as a colorless oil.

***N*-Hydroxylamine 163:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.50 (br s, 1H), 3.96 (td, *J* = 6.5, 1.5 Hz, 1H), 3.77-3.73 (m, 1H), 3.41 (s, 3H), 2.78 (td, *J* = 7.8, 2.6 Hz, 2H), 2.11-1.95 (comp m, 2H), 1.84-1.73 (m, 1H), 1.70-1.59 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 141.5, 128.7, 128.5, 126.1, 98.8, 84.9, 83.49, 83.45, 70.51, 70.49, 56.55, 56.54, 56.3, 37.43, 37.40, 31.58, 31.57, 25.6, 10.4; IR (film) 3258, 2935, 1947, 1603, 1105, 749 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₅H₂₁NO₂ + Na]⁺: 248.1645, found 248.1646.



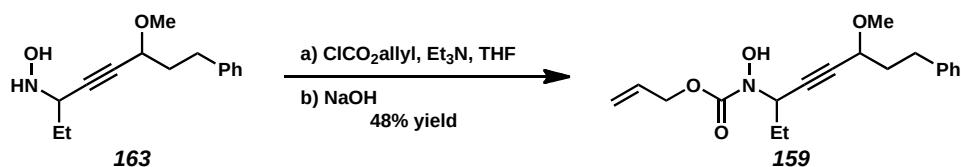
To a solution of *N*-hydroxylamine **163** (98.8 mg, 0.400 mmol) and Et_3N (84.0 μL , 0.600 mmol) in THF (0.800 mL, 0.5 M) cooled at $-10\text{ }^\circ\text{C}$, was added methyl chloroformate (33.9 μL , 0.440 mmol), and the reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 3 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 20 h. The reaction was diluted with Et_2O (5.0 mL), and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 $\rightarrow$ 2:1 hexanes/ EtOAc eluent) affording *N*-hydroxycarbamate **157** (51.7 mg, 42% yield, $R_f = 0.29$ in 2:1 hexanes/ EtOAc) as a colorless oil.

***N*-Hydroxycarbamate 157**: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.26 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.93 (br s, 1H), 4.75 (t, $J = 7.7\text{ Hz}$, 1H), 3.94 (td, $J = 6.6, 1.6\text{ Hz}$, 1H), 3.80 (s, 3H), 3.38 (d, $J = 2.3\text{ Hz}$, 3H), 2.78-2.74 (comp m, 2H), 2.09-1.95 (comp m, 2H), 1.92-1.84 (comp m, 2H), 1.01 (t, $J = 7.4\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.7, 158.11, 158.09, 141.5, 128.7, 128.6, 126.1, 83.19, 83.17, 82.93, 82.90, 70.45, 70.43, 56.5, 53.8, 37.31, 37.28, 31.6, 31.5, 26.32, 26.28, 10.8; IR (film) 3300, 2936, 1951, 1745, 1603, 1455, 752 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+ [\text{C}_{17}\text{H}_{23}\text{NO}_4 + \text{Na}]^+$: 328.1519, found 328.1514.



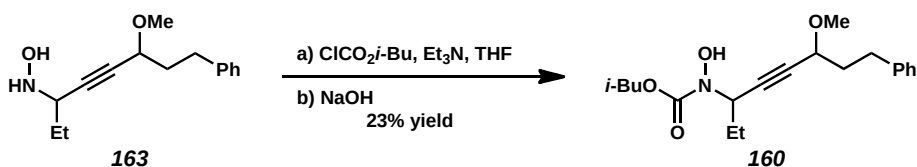
To a solution of *N*-hydroxylamine **163** (0.135 g, 0.540 mmol) and Et_3N (113 μL , 0.810 mmol) in THF (1.00 mL, 0.54 M) cooled at 0 °C, was added ethyl chloroformate (57.0 μL , 0.601 mmol), and the reaction was warmed to 23 °C and stirred for 1 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 16 h. The reaction was diluted with Et_2O (5.0 mL), and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (4:1→2:1 hexanes/ EtOAc eluent) affording *N*-hydroxycarbamate **158** (67.4 mg, 37% yield, R_f = 0.15 in 4:1 hexanes/ EtOAc) as a colorless oil.

***N*-Hydroxycarbamate 158:** Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.20-7.17 (comp m, 3H), 5.99 (br s, 1H), 4.75 (td, J = 7.7, 1.0 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.94 (td, J = 6.6, 1.6 Hz, 1H), 3.39 (d, J = 2.5 Hz, 3H), 2.76 (t, J = 7.6 Hz, 2H), 2.09-1.94 (comp m, 2H), 1.92-1.84 (comp m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.71, 189.69, 157.88, 157.85, 141.5, 128.7, 128.5, 126.1, 83.1, 83.0, 70.5, 70.4, 63.0, 56.5, 53.8, 37.33, 37.29, 31.6, 31.5, 26.33, 26.29, 14.7, 10.8; IR (film) 3304, 2936, 1949, 1699, 1455, 752 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{18}\text{H}_{25}\text{NO}_4 + \text{Na}$] $^+$: 342.1676, found 342.1674.



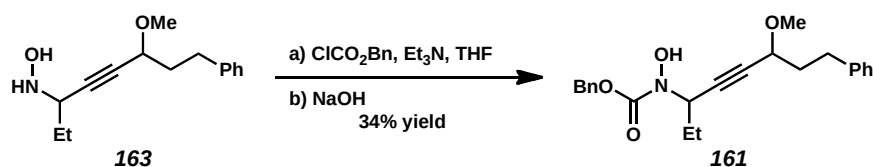
To a solution of *N*-hydroxylamine **163** (98.8 mg, 0.400 mmol) and Et_3N (84.0 μL , 0.600 mmol) in THF (0.800 mL, 0.50 M) cooled at $-10\text{ }^\circ\text{C}$, was added allyl chloroformate (47.0 μL , 0.440 mmol), and the reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 3 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (5.0 mL) and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (4:1 $\rightarrow$ 2:1 hexanes/ EtOAc eluent) affording *N*-hydroxycarbamate **159** (63.2 mg, 48% yield, R_f = 0.22 in 4:1 hexanes/ EtOAc) as a colorless oil.

***N*-hydroxycarbamate 159:** Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (comp m, 2H), 7.21-7.17 (comp m, 3H), 5.94 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.4, 1.2 Hz, 1H), 4.79-4.75 (m, 1H), 4.68 (dq, J = 5.7, 1.4 Hz, 2H), 3.94 (td, J = 6.5, 1.5 Hz, 1H), 3.38 (d, J = 2.4 Hz, 3H), 2.76 (t, J = 7.7 Hz, 2H), 2.09-1.94 (comp m, 2H), 1.93-1.84 (comp m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.7, 141.5, 132.1, 128.7, 128.6, 126.1, 118.7, 83.3, 82.88, 82.86, 70.5, 70.4, 67.4, 56.6, 53.9, 53.8, 37.32, 37.29, 31.6, 31.5, 26.34, 26.31, 10.8; IR (film) 3306, 2936, 1950, 1706, 1100, 752 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{19}\text{H}_{25}\text{NO}_4 + \text{Na}$] $^+$: 354.1676, found 354.1678.



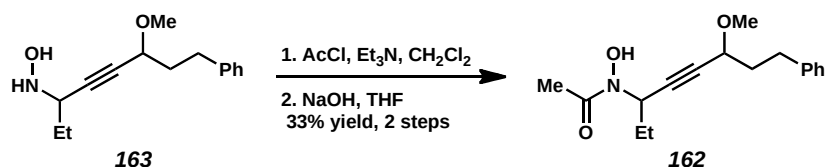
To a solution of *N*-hydroxylamine **163** (98.8 mg, 0.400 mmol) and Et_3N (84.0 μL , 0.600 mmol) in THF (0.800 mL, 0.50 M) cooled at $-10\text{ }^\circ\text{C}$, was added isobutyl chloroformate (57.0 μL , 0.440 mmol), and the reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 3 h. NaOH (1.00 mL, 5% aq.) was added, and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (5.0 mL) and H_2O (5.0 mL) and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1→2:1 hexanes/ EtOAc eluent) affording *N*-hydroxycarbamate **160** (32.2 mg, 23% yield, $R_f = 0.27$ in 4:1 hexanes/ EtOAc) as a colorless oil.

***N*-hydroxycarbamate 160:** Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (comp m, 2H), 7.20-7.16 (m, 3H), 5.77 (br s, 1H), 4.73 (t, $J = 7.6\text{ Hz}$, 1H), 4.02-3.92 (comp m, 3H), 3.38 (d, $J = 2.6\text{ Hz}$, 3H), 2.76 (t, $J = 7.8\text{ Hz}$, 2H), 2.07-1.93 (comp m, 3H), 1.93-1.83 (comp m, 2H), 1.02 (t, $J = 7.4\text{ Hz}$, 3H), 0.95 (d, $J = 6.7\text{ Hz}$, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.7, 158.1, 141.5, 128.7, 128.6, 126.1, 83.00, 82.98, 73.0, 70.44, 70.43, 56.5, 53.9, 37.4, 37.3, 31.6, 31.5, 28.1, 26.4, 26.3, 19.10, 19.08, 10.9; IR (film) 3300, 2964, 1947, 1703, 1456, 1104, 751 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{20}\text{H}_{29}\text{NO}_4 + \text{Na}$] $^+$: 370.1989, found 370.1996.



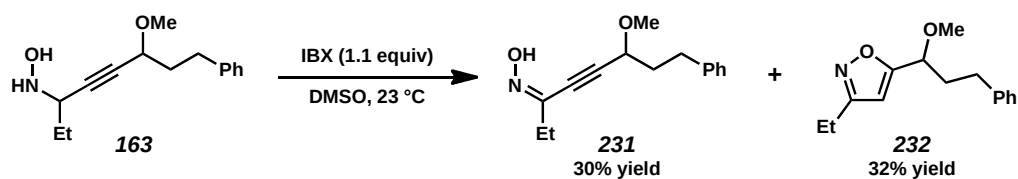
To a solution of *N*-hydroxylamine **163** (46.4 mg, 0.188 mmol) and Et_3N (66.9 μL , 0.470 mmol) in THF (0.400 mL, 0.47 M) cooled at $-10\text{ }^\circ\text{C}$, was added benzyl chloroformate (40.2 μL , 0.282 mmol), and the reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 3 h. NaOH (0.50 mL, 5% aq.) was added, and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (5.0 mL) and H_2O (5.0 mL), and the layers were separated. The aqueous layer was extracted with additional Et_2O (5.0 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (4:1 $\rightarrow$ 2:1 hexanes/ EtOAc eluent) affording *N*-hydroxycarbamate **161** (24.2 mg, 34% yield, R_f = 0.41 in 4:1 hexanes/ EtOAc) as a colorless oil.

***N*-hydroxycarbamate 161:** Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.26 (comp m, 7H), 7.21-7.17 (comp m, 3H), 6.16 (br s, 1H), 5.21 (s, 2H), 4.80-4.76 (m, 1H), 4.70 (s, 1H), 3.92 (td, J = 6.5, 1.4 Hz, 1H), 3.35 (d, J = 2.6 Hz, 2H), 2.77-2.73 (comp m, 2H), 2.06-1.94 (comp m, 2H), 1.92-1.82 (comp m, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.5, 141.4, 135.8, 128.71, 128.65, 128.54, 128.49, 128.3, 127.8, 127.1, 126.1, 83.10, 83.07, 83.00, 82.97, 70.43, 70.41, 68.5, 65.5, 56.5, 53.8, 37.3, 37.2, 31.5, 26.29, 26.27, 10.8; IR (film) 3288, 2936, 1952, 1704, 1455, 1103, 750 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{NH}_4)^+ [\text{C}_{23}\text{H}_{27}\text{NO}_4 + \text{NH}_4]^+$: 399.2278, found 399.2280.

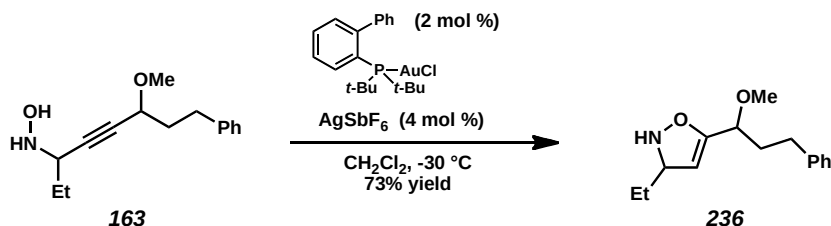


To a solution of *N*-hydroxylamine **163** (90.7 mg, 0.367 mmol) and Et₃N (0.141 mL, 1.10 mmol) cooled at 0 °C was added AcCl (65.5 μ L, 0.918 mmol), and the reaction was warmed to 23 °C and stirred for 2 h. The reaction was diluted with CH₂Cl₂ (2.0 mL) and H₂O (2.0 mL), and the layers were separated. The aqueous was extracted with CH₂Cl₂ (2.0 mL), and the combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was dissolved in THF (1.50 mL, 0.25 M). To this was added NaOH (0.75 mL, 1.0 M aq.) and the reaction was stirred at 23 °C for 5 h. The reaction was quenched with HCl (0.50 mL, 1.0 N aq.) and diluted with Et₂O (2.0 mL). The layers were separated and the aqueous layer was extracted with additional Et₂O (2.0 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) affording *N*-hydroxyamide **162** (34.8 mg, 33% yield 2 steps, *R*_f = 0.30 in 1:1 hexanes/EtOAc) as a colorless oil.

***N*-hydroxyamide 162:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.27 (comp m, 2H), 7.21-7.18 (comp m, 3H), 5.30 (s, 1H), 4.54 (br s, 1H), 3.96-3.92 (m, 1H), 3.39 (d, *J* = 1.6 Hz, 3H), 2.78-2.74 (comp m, 2H), 2.18 (s, 3H), 2.10-1.93 (comp m, 2H), 1.85 (br s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 141.4, 128.64, 128.57, 126.1, 70.4, 56.60, 56.58, 37.2, 31.5, 10.8; IR (film) 3164, 2934, 1619, 1496, 1174, 1104, 749 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₇H₂₃NO₃ + H]⁺: 290.1751, found 290.1747.



A solution of 2-iodoxybenzoic acid (123 mg, 0.440 mmol) in DMSO (0.600 mL, 0.7 M) was stirred at 23 °C for 25 min. To this was added a solution of *N*-hydroxylamine **163** (98.8 mg, 0.400 mmol) in DMSO (0.600 mL, 0.66 M) and the reaction was stirred at 23 °C for 1.5 h. The reaction was diluted with EtOAc (10 mL) and NaOH (5.0 mL, 1.0 M). The layers were separated and the aqueous layer was extracted with additional EtOAc (5.0 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording oxime **231** (29.0 mg, 30% yield) and isoxazole **232** (31.6 mg, 32% yield) as colorless oils.



To a solution of *o*-biphenyl(*t*-Bu)₂PAuCl (4.2 mg, 0.00800 mmol) and AgSbF₆ (5.5 mg, 0.0160 mmol) in CH₂Cl₂ (2.00 mL) at -30 °C under argon was added a solution of hydroxylamine **163** (98.8 mg, 0.400 mmol) in CH₂Cl₂ (2.00 mL, 0.10 M final concentration). The reaction was stirred at -30 °C for 1.5 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with Et₂O (8.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford isoxazoline **236** (72.1 mg, 73% yield, *R*_f = 0.58 in 1:1 hexanes/EtOAc) as a colorless oil.

Isoxazoline 236: Characterized as a 1:1 mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.26 (comp m, 2H), 7.22-7.15 (comp m, 3H), 5.00 (dd, $J = 9.0, 1.6$ Hz, 1H), 4.18-4.06 (m, 1H), 3.78 (t, $J = 6.2$ Hz, 1H), 3.36 (s, 1.5H), 3.34 (s, 1.5H), 2.78-2.63 (comp m, 2H), 2.08-1.92 (comp m, 2H), 1.63-1.42 (comp m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.7, 141.6, 128.7, 128.6, 128.5, 126.0, 100.4, 100.1, 98.7, 75.1, 75.0, 57.3, 57.1, 35.1, 35.0, 31.7, 31.6, 31.4, 10.2.

CHAPTER THREE NOTES AND REFERENCES

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- ⁹⁵ See Chapter 2.5.3 for a more detailed discussion of alkene activation of Pt(II) salts.
- ⁹⁶ Variable yields using triphenylphosphine were observed upon scale up of the reaction to form isoxazole **154**; the use of triphenylphosphite produced more consistent results.
- ⁹⁷ See Chapter 2.5.1 for a relevant discussion.
- ⁹⁸ The decrease in basicity of the isoxazole nitrogen is believed to be due to the large destabilization of the π -bonding that occurs upon protonation of the heterocycle. For a more detailed discussion see: Olivella, S.; Vilarrasa, J. *J. Heterocyclic Chem.* **1981**, *18*, 1189-1196.
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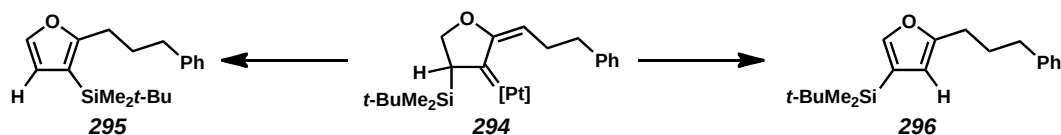
CHAPTER FOUR

Support for the Formation of α,β -Unsaturated Platinum Carbenes

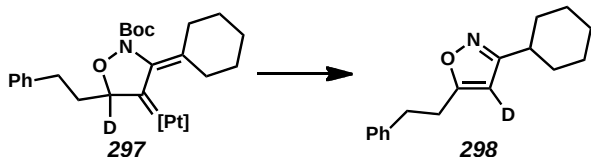
4.1 Introduction

The mechanistic discussion for the platinum catalyzed conversion of propargylic methyl ethers to furans (Chapter 2) and isoxazoles (Chapter 3) has thus far been limited to the activation of the leaving group. Several experiments indicated that the formation of these heterocycles was more complicated than a hydroalkoxylation event, followed by an acid mediated elimination and isomerization. A second mechanistic hypothesis involves the formation of an α,β -unsaturated platinum carbene, followed by a 1,2-hydride migration and isomerization to form the two heterocycles. This chapter highlights reactivity that is consistent with the formation of an intermediate carbene species: chiefly the observation of 1,2-atom migrations and vinylogous additions (Scheme 4.1.1).¹⁰⁸

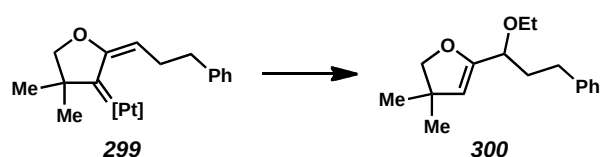
1,2-H/Si Migration



1,2-D Migration



Vinylogous Addition



Scheme 4.1.1. Reactions of Platinum Carbenes.

4.2 Metal Carbenes as Reaction Intermediates

4.2.1 Bonding in Metal Carbene Complexes

Alkynes can undergo a variety of unique transformations when exposed to gold or platinum catalysts. Many of the products isolated from these reactions, e.g., cyclopropanes, imply the formation of a gold or platinum carbene as a key intermediate. This has led to a heated debate concerning the intermediates involved in these reactions, focusing on whether they are metal carbenes or metalated carbocations.¹⁰⁹ One way to characterize the nature of these gold/platinum species is to make an analogy to the accepted bonding in rhodium carbenes. Initially two bonding environments were proposed, one being a metal carbene, and the other a metal stabilized carbocation (Figure 4.2.1). The bonding in metal carbenes consists of nearly equal ligand(carbon)-to-metal σ -donation and metal-to-ligand(carbon) π -donation, while metal stabilized carbocations are characterized primarily by only ligand to metal σ -donation. Padwa and Snyder have modeled the rhodium species generated from the decomposition of diazo compounds and found that the rhodium-carbon bond is a single bond, with equal “half bond” contributions from the ligand-metal σ -bond and the metal to ligand π -bond.¹¹⁰ This finding is consistent with the formation of a rhodium carbene and best explains the reactivity of this species.

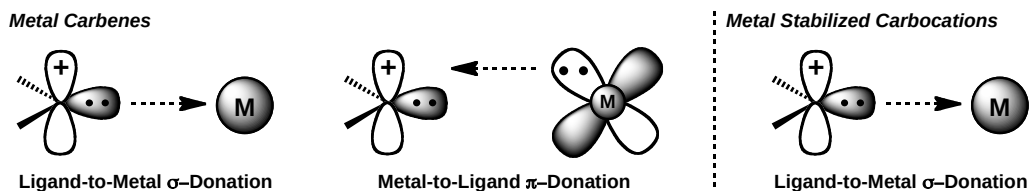
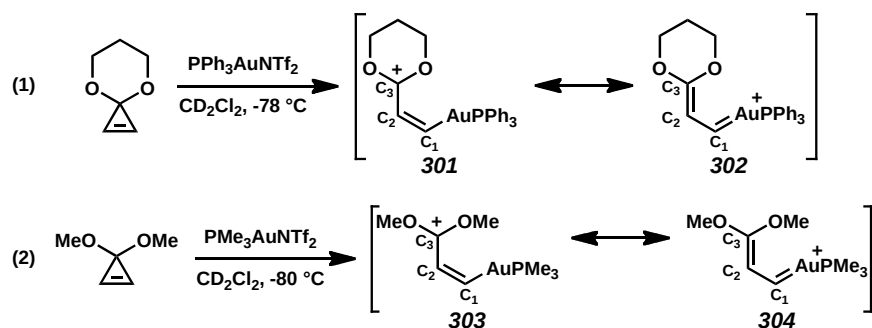


Figure 4.2.1. Bonding in Metal Carbene Complexes.

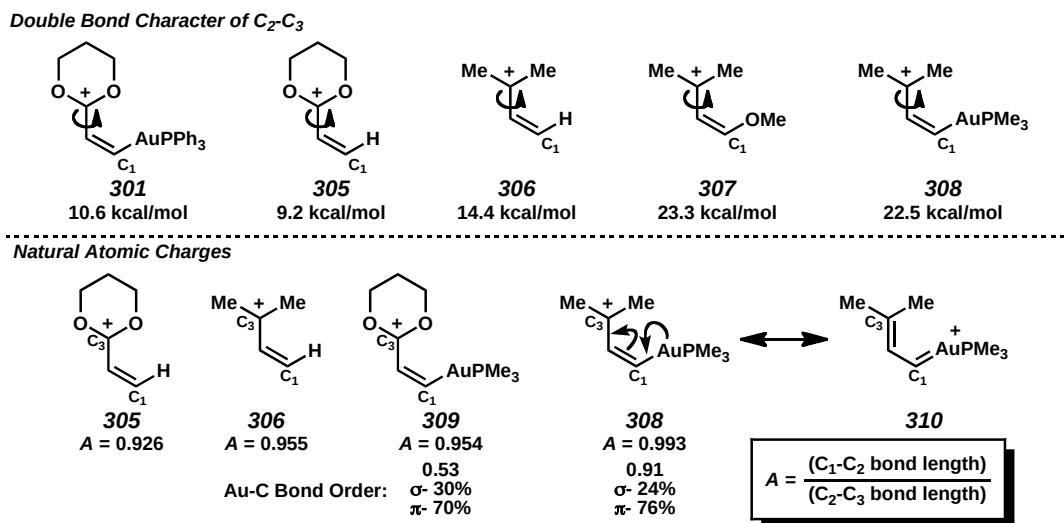
The metalated intermediates in gold and platinum catalysis have been primarily described as metal stabilized carbocations, with several experiments supporting this argument. Fürstner demonstrated that the rearrangement of cyclopropene acetals using cationic gold complexes led to the formation of organogold species **301** (Scheme 4.2.1).¹¹¹ Analysis of the ^1H NMR at -78°C revealed that the two CH_2 groups of the acetal appear as a single signal, indicative of a rapid rotation around the $\text{C}_2\text{-C}_3$ bonds, while the J -couplings showed the presence of a Z -alkene between $\text{C}_1\text{-C}_2$. This indicates the structure of gold species resembles cation **301**, where no π -donation from the gold occurs. The use of the strongly donating trimethylphosphine ligand did little to increase the π -donation from the metal. Line broadening observed in the ^1H NMR of **303** indicated a very slight barrier to rotation around the $\text{C}_2\text{-C}_3$ bond of *ca.* 11.0 kcal/mol, consistent with the single bond character between these atoms in gold species **303**. Both of these experiments suggest that the bonding in these systems resembles a gold stabilized cation (**301/303**), and not a gold carbene (**302/304**).



Scheme 4.2.1. Cation Stabilization by Gold(I).

One problem with the experiment described above is that the stabilization of the carbocation by the acetal can greatly overshadow any electron donation from gold. Using acetal **301** as their starting point, Toste and Goddard were able to develop a model to determine the stabilization of

carbocations via electron donation from gold in a variety of different organogold species.¹¹² They confirmed the lack of any significant stabilization by gold in carbocation **301**, measuring the barrier to rotation about the C₂-C₃ bond to be 10.6 kcal/mol, only 1.4 kcal/mol more than the H-substituted cation (**305**) (Scheme 4.2.2). Exchanging the acetal oxygens for methyl groups resulted in an increase in the rotational barrier around the C₂-C₃ bond to 14.4 kcal/mol in the C₁-H (**306**) substituted carbocation. The substitution of hydrogen for a methoxy group (**307**) resulted in a barrier of rotation around the C₂-C₃ bond of 23.3 kcal/mol, a value that is only 0.8 kcal/mol higher than the rotational barrier for the gold substituted carbocation **308** (22.5 kcal/mol). These last calculations provide strong evidence that the π -back-bonding in gold can stabilize carbocations to the same extent as the strongly donating methoxy group. Finally, the gold-carbon natural bond order was calculated for complexes **308** and **309**. In both cases the bond order was less than 1 (0.53 for **309**, 0.91 for **308**) consisting of both σ and π -bonding interactions, with the π -donation from gold being the major contributor. The presence of these interactions in the gold carbenes again draws parallels to the double “half bond” character of rhodium carbenes described above. While these calculations do not indicate the gold carbene is the predominant structure of these species, it does provide evidence that the true nature of the carbon-gold bond lies between the two extremes represented by resonance forms **308** and **310**, and provides a fair analogy to the accepted bonding present in rhodium carbenes. These findings inform our understanding of the intermediates formed in gold/platinum catalyzed processes, and explains why transformations reminiscent of carbene reactivity occur with both metals.



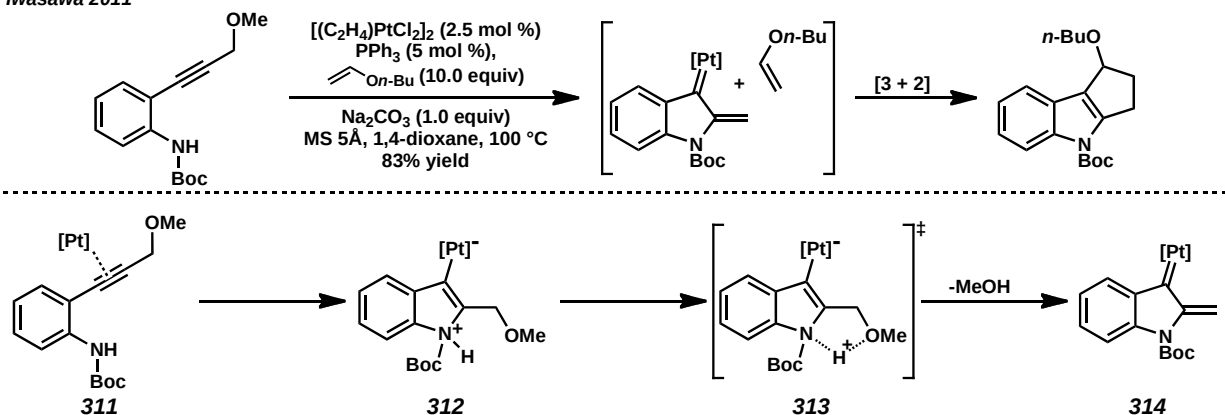
Scheme 4.2.2. Bonding in Gold(I) Carbenes.

4.3 Evidence to Support Formation of α,β -Unsaturated Platinum Carbenes

4.3.1 Generating Platinum Carbenes from Propargylic Methyl Ethers

During our investigations described in Chapter 2, a similar method for the generation of platinum carbenes was reported.¹¹³ Iwasawa demonstrated that exposing *N*-Boc anilines containing propargylic methyl ethers to Zeise's dimer at elevated temperatures resulted in a 5-*endo-dig* cyclization, followed by the extrusion of methanol to form unsaturated platinum carbene **314** (Scheme 4.3.1). This species could then undergo a [3+2] cycloaddition with vinyl ethers to form a variety of polycyclic products. Zhang and coworkers recently modeled the proposed reaction pathway, finding that the extrusion of methanol to form carbene **314** represents the rate-determining step of the reaction.¹¹⁴ The platinum carbene (**314**) was also found to be more stable than the immediate product of the 5-*endo-dig* cyclization (**312**), highlighting the stability gained by forming the platinum carbene.

Iwasawa 2011

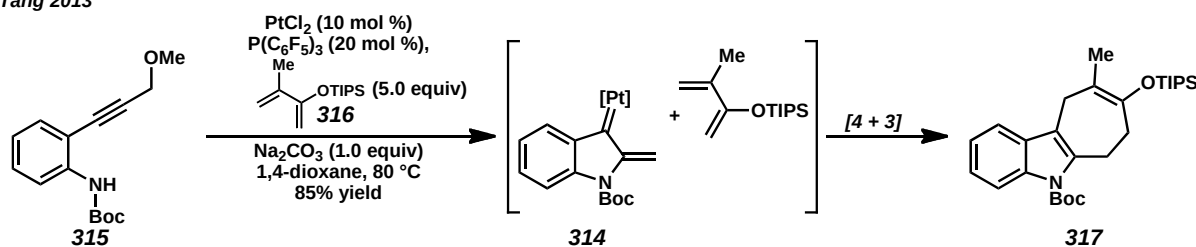


Scheme 4.3.1. [3 + 2] Cycloadditions of Unsaturated Platinum Carbenes.

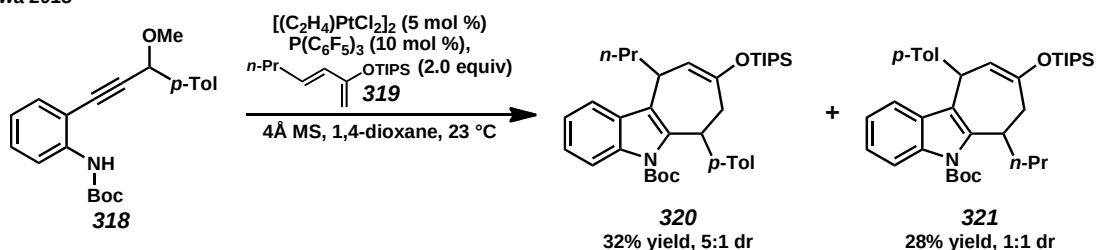
Tang extended this method of platinum carbene generation to achieve formal [4+3] cycloadditions between the unsaturated platinum carbene and electron rich dienes (Scheme 4.3.2).¹¹⁵ The substrate scope for this reaction was complemented by a later report by Iwasawa, who generated similar annulated indole products via a formal [4 + 3] cycloaddition between an unsaturated platinum carbene and siloxydienes.¹¹⁶ Both of these reactions involve the formation of these unsaturated platinum carbenes as the key step. Once generated, the reaction can proceed through two different pathways to form the observed cycloadduct (Scheme 4.3.2, eqs. 1 & 2). The first involves a vinylogous addition of the silyl enol ether (**316**) into the β -position of the unsaturated platinum carbene to form indole metal species **322**. Addition of the indole metal species into the stabilized carbocation closes the cycloheptene ring (**323**), which can then undergo deplatination to form the annulated indole (**317**). A second mechanistic proposal was offered by Iwasawa, suggesting the reaction proceeds via a [4 + 2] cycloaddition on the unsaturated carbene, followed by a ring expansion to form the metalated cycloheptene (**317**), which can then deplatinate to form the observed product. Evidence supporting the second pathway is based on the observation that propargylic methyl ether **318** reacts with siloxydiene

319 to form two isomeric cycloadducts. Indole **320** is the result of a 1,2-shift of the *n*-propyl substituted carbon, while indole **321** arises as a result of the 1,2-shift of the *p*-tolyl substituted carbon. Both mechanisms support the hypothesis that propargylic methyl ethers can act as precursors to unsaturated platinum carbenes.

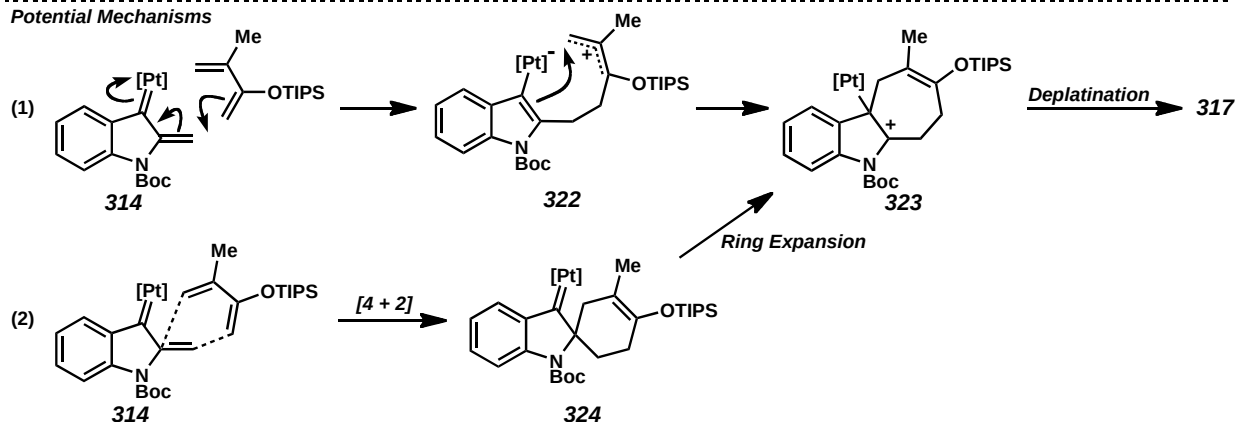
Tang 2013



Iwasawa 2013



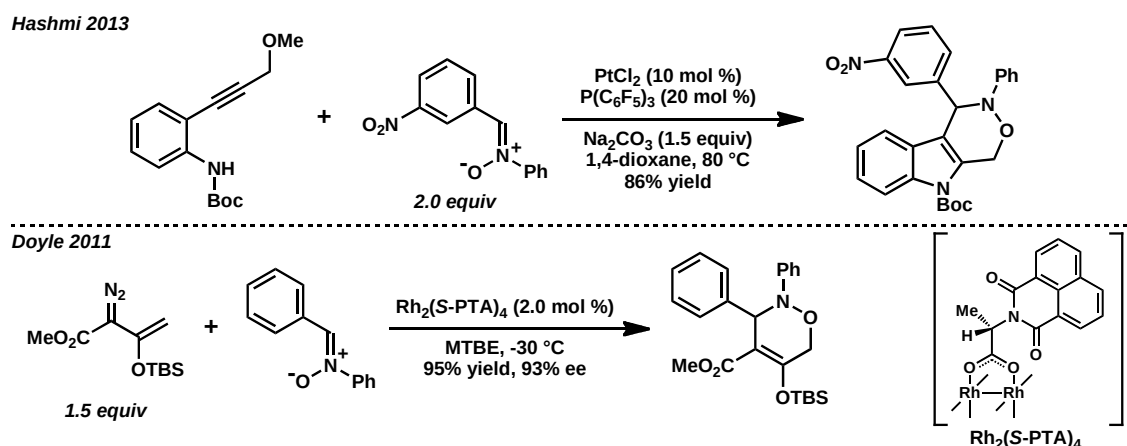
Potential Mechanisms



Scheme 4.3.2. Formal [4 + 3] Cycloadditions of Unsaturated Platinum Carbenes.

A final example by Hashmi uses the same method of platinum carbene generation as Iwasawa and Tang.¹¹⁷ In this case the unsaturated carbene undergoes a formal [3 + 3] cycloaddition to form a variety of 1,2-oxazinoindole products (Scheme 4.3.3). This chemistry provides a salient analogy to known reactions of rhodium carbenes. Doyle has shown that exposing

vinyl diazoacetates to $\text{Rh}_2(\text{S-PTA})_4$ results in formation of the unsaturated rhodium carbene, which subsequently reacts with nitrones through a formal [3 + 3] cycloaddition to form 1,2-oxazines in high yield and high enantioselectivity.¹¹⁸ This last example highlights the fact that the unsaturated platinum carbenes generated by exposing propargylic methyl ethers can undergo the same types of reactions as the more common rhodium carbenes. Each of these examples applies the same method of generating unsaturated platinum carbenes that we have used in our studies. What follows are our own observations that are consistent with carbene formation and how these findings helped us to develop new reactions via this unique intermediate.



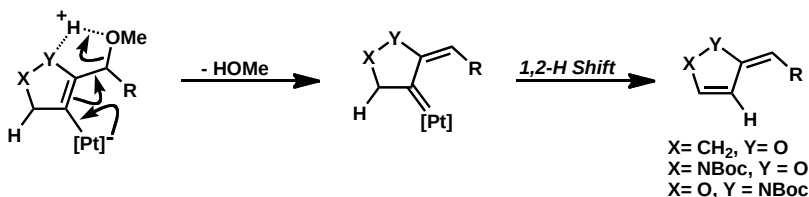
Scheme 4.3.3. Analogous Reactions of Unsaturated Platinum and Rhodium Carbenes.

4.3.2 1,2-Hydride Migrations into Metal Carbenes

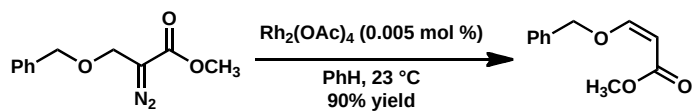
Our efforts at this point focused on experiments designed to provide a better understanding of the intermediates formed during the synthesis of furans and isoxazoles. One proposal was that a platinum carbene forms and undergoes a 1,2-hydride shift, reactivity that has been well established in rhodium, gold and platinum carbenes. Both Ganem and Taber have shown that 1,2-hydride migrations occur in rhodium carbenes to form the corresponding *cis*-alkenes (Scheme 4.3.4).¹¹⁹ Toste has demonstrated that pyrroles can be synthesized via 1,2-hydride

migrations into a gold carbene, which was formed by the back-donation from the gold to extrude a leaving group.¹²⁰ Our research group has also shown that both hydrogen and alkyl groups can migrate into adjacent platinum carbenes.¹²¹ With these examples in mind, we set out to look more closely at the nature of the intermediates in our furan and isoxazole syntheses.

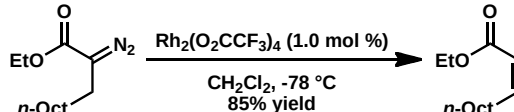
Proposed 1,2-H Shift



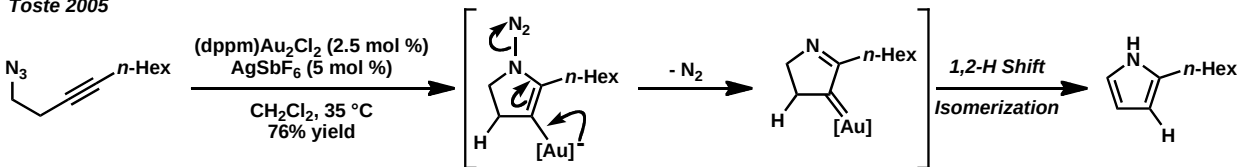
Ganem 1981



Taber 1995



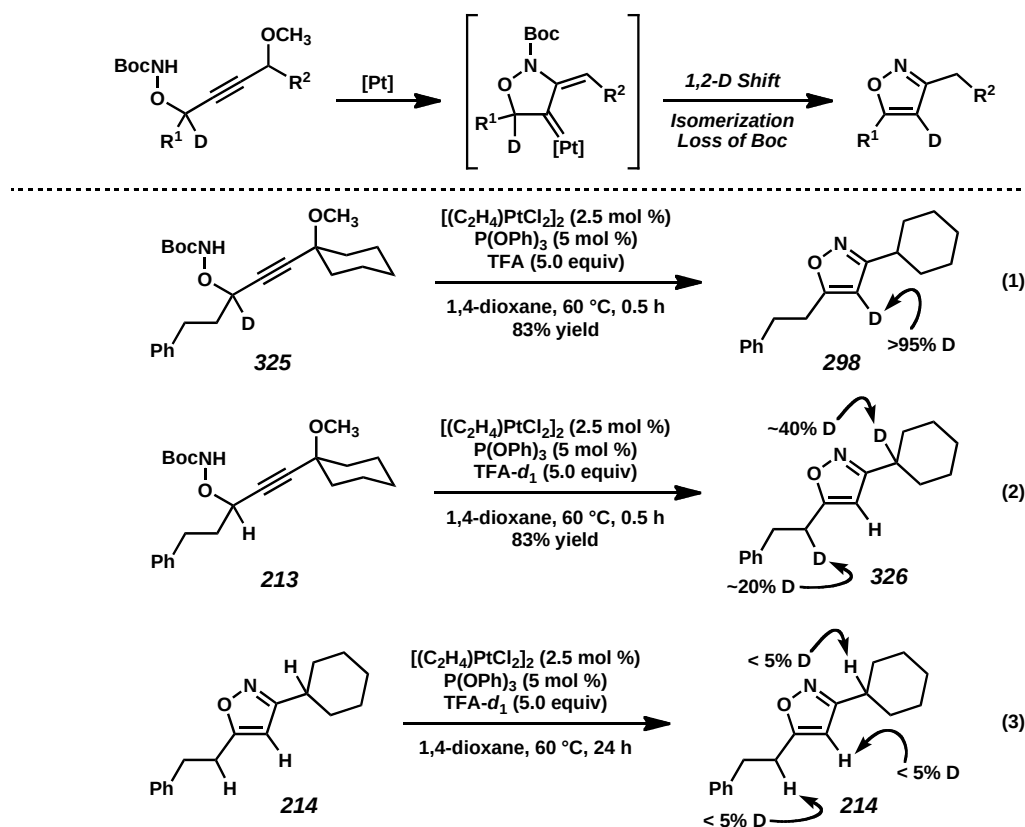
Toste 2005



Scheme 4.3.4. Hydride Migrations into Metal Carbenes.

Our synthesis of the *N*-Boc amino ethers described earlier provided us with an opportunity to incorporate a deuterium atom at the propargylic position. Upon carbene formation, the requisite 1,2-deuteride migration would place deuterium at the 4-position of the corresponding isoxazole (Scheme 4.3.5). Any loss in deuterium enrichment in the isoxazole product would inform us of potential competing acid catalyzed elimination/isomerization pathways. We first exposed deuterium labeled *N*-Boc amino ether **325** to the cyclization conditions using protic TFA as the acid source (Scheme 4.3.5, eq. 1). Isoxazole **298** was isolated with >95% deuterium incorporation at the 4-position, providing strong evidence that a 1,2-deuteride shift had occurred into an adjacent Pt carbene. Subjecting the non-deuterium labeled *N*-Boc amino ether analog

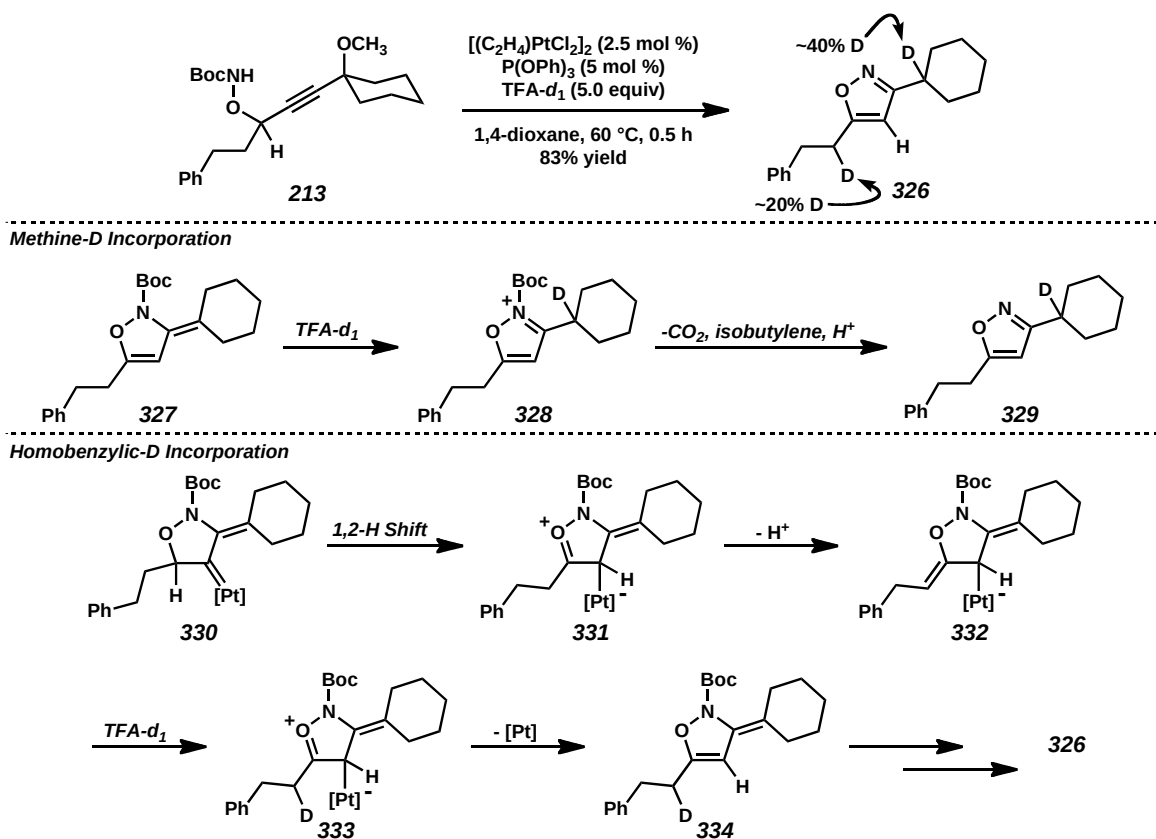
213 to the reaction conditions using TFA-*d*₁ as the acid source produced isoxazole **326** with no deuterium incorporation at the 4-position (Scheme 4.3.5, eq. 2). Instead, the isolated isoxazole showed *ca.* 40% deuterium incorporation at the methine position, and *ca.* 20% deuterium at the homobenzylic position. Exposing isoxazole **214** to the reaction conditions where TFA-*d*₁ was used as the acid source resulted in no deuterium incorporation at either position (Scheme 4.3.5, Eq 3), confirming that deuterium incorporation occurred during the formation of the isoxazole.



Scheme 4.3.5. Deuterium Labeling Experiments.

Deuterium incorporation at the two positions in isoxazole **326** is easily rationalized by our proposed mechanism (Scheme 4.3.6). Incorporation of deuterium at the methine position when the TFA-*d*₁ experiment was performed was expected, as this position is protonated during formation of iminium **328** and subsequent isomerization to the heterocycle. The low deuterium

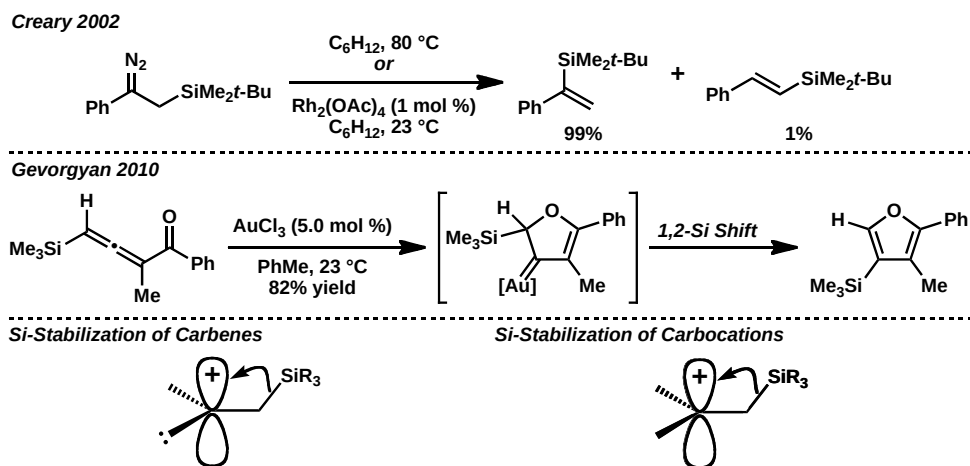
incorporation suggests that the extruded methanol could also serve as a proton source during the isomerization.¹²² The observation of deuterium incorporation at the homobenzylic position was unforeseen, and provides insight to the asynchronous nature of the 1,2-H migration. Once the alkyl metal species (**331**) forms, the resulting oxocarbenium can eliminate H⁺ leading to vinyl ether **332**. Protonation of vinyl ether **332** with TFA-*d*₁ reforms the oxocarbenium, which can then demetalate to form the deuterated vinyl ether (**334**). This deprotonation-protonation event can only occur if the demetalation is sufficiently slow, a fact that seems to be the case for this substrate class. Each of these deuterium studies provided strong evidence to support the formation of a platinum carbene as a key intermediate in these reactions.



Scheme 4.3.6. Deuterium Incorporation with TFA-*d*₁.

4.3.3 Selective H/Si Migrations into Pt Carbenes

A variety of non-hydrogen groups have been shown to migrate into adjacent metal carbenes, with 1,2-silicon migrations occurring in both rhodium and gold carbenes (Scheme 4.3.7). Creary has shown that silicon groups will migrate into adjacent carbenes with high selectivity over competing 1,2-H shifts.¹²³ This preference was observed in carbenes generated via thermal or $\text{Rh}_2(\text{OAc})_4$ mediated decomposition of diazo species. Gevorgyan recently reported on the selective 1,2-Si shifts into gold carbenes as a way to generate diversely functionalized furans.¹²⁴ Calculations performed on this system revealed that the 1,2-Si shift is 12.5 kcal/mol lower in energy than the corresponding 1,2-H shift. One explanation for this preference for silicon migration is that the electron rich C–Si bond can better stabilize the electrophilic carbenes through hyperconjugation, much like β -silicon groups can stabilize carbocations.¹²⁵



Scheme 4.3.7. Silicon Migrations in Rhodium Carbenes.

We decided to test the migratory aptitude of silicon groups into the proposed platinum carbene. Exposing propargylsilane **335** to Zeise's dimer in THF resulted in formation of both the 1,2-Si (**295**) and 1,2-H (**296**) migration products in a 1:3 ratio (Table 4.3.1, entry 1). Switching the solvent to toluene slightly favored 1,2-Si migration (Table 4.3.1, entry 2). Using PtCl_2 and 1-

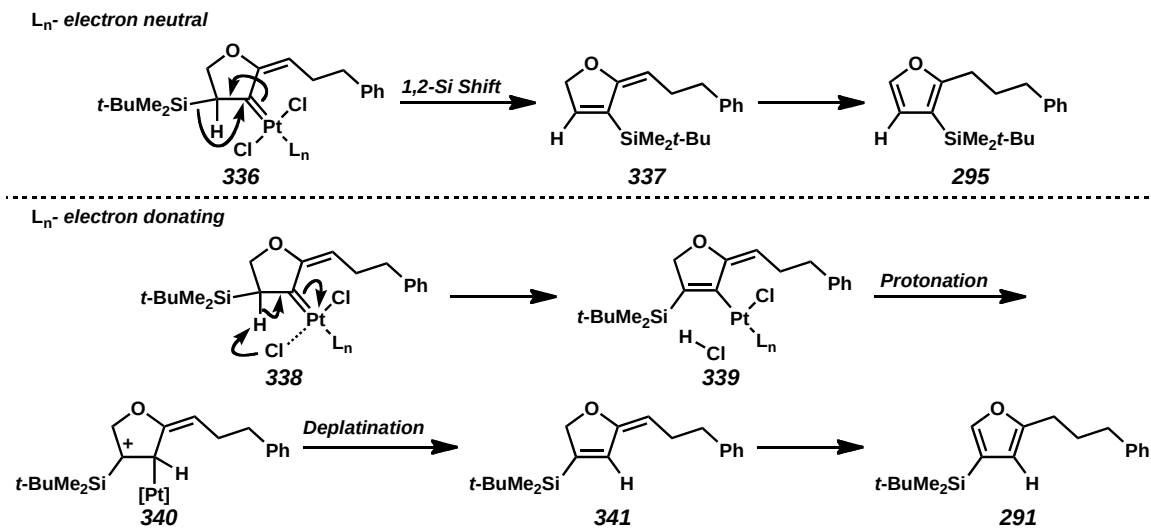
octene led to a slight increase in the preference for silyl migration, but more importantly it reduced the amount of protodesilylation that was observed with Zeise's dimer. The most dramatic change to the selectivity of this reaction occurred upon heating, which greatly favored furan **295** (Table 4.3.1, entries 5, 6 and 9). Using the conditions described in entry 6 resulted in a 92% yield of the two silylfurans as a 16:1 mixture, favoring the 1,2-Si migration product (**295**). Switching to strongly donating solvents like THF reversed the selectivity to favoring 1,2-H migration (Table 4.3.1, entries 7, 8). The inclusion of olefin ligands accelerated the reaction, and resulted in a notable increase in the selectivity for furan **296** (Table 4.3.1, entries 11, 12). Under the optimal conditions we were able to isolate the silylfurans in 83% yield as an 8.5:1 mixture, favoring the 1,2-H migration product (**296**).

Table 4.3.1. Optimization of the 1,2-H vs. 1,2-Si Migrations.

Entry	Catalyst ^a	Solvent	Temp (°C)	Additive (equiv)	Time	Ratio (295 : 296) ^b
1	[(C ₂ H ₄)PtCl ₂] ₂	THF	23	-	30 min	1 : 3.0 ^c
2	[(C ₂ H ₄)PtCl ₂] ₂	PhCH ₃	23	-	1 h	1.5 : 1 ^c
3	PtCl ₂	PhCH ₃	23	1-octene (1.0)	2 h	2.5 : 1
4	PtCl ₂	PhCH ₃	23	1-octene (5.0)	1.5 h	3.6 : 1
5	PtCl ₂	PhCH ₃	60	1-octene (5.0)	10 min	10 : 1
6	PtCl ₂	PhCH ₃	100	1-octene (5.0)	5 min	16 : 1 92% yield ^d
7	PtCl ₂	THF	23	-	70 h	1 : 3.0 ^c
8	PtCl ₂	THF	50	-	5 h	1 : 2.1 ^c
9	PtCl ₂	1,4-dioxane	100	-	5 min	6.0 : 1 ^c
10	PtCl ₂	THF	23	PPh ₃ (0.05)	24 h	1 : 2.0 ^c
11	PtCl ₂	THF	23	1-octene (1.0)	2 h	1 : 9.4 ^c
12	PtCl ₂	THF	23	ethyl vinyl ether (1.0)	8 h	1 : 8.5 ^c 83% yield ^d

^a [(C₂H₄)PtCl₂]₂ (1.5 mol %) or PtCl₂ (5 mol %). ^b Determined by ¹H NMR. ^c 10-20% of desilylated furan 32 observed in ¹H NMR. ^d Isolated yield.

The selectivity observed in the Si vs. H-migration is presumably based on the differential bonding environments around the carbene. The conditions that favored 1,2-Si migration were those that employed elevated temperatures. It is postulated that elevated temperatures enhance the carbene character of the platinum species, favoring the silicon migration pathway (Scheme 4.3.8). The nature of the carbene changes when a strongly donating solvent like THF is used. In this case the more electron rich carbene dissociates a chloride ligand, facilitating an intermolecular deprotonation to form the vinyl platinum species (**339**), which can then undergo protodeplatination to give the formal 1,2-H migration product. This hypothesis is supported by calculations that were performed by Gevorgyan and Li, which demonstrated that ligand dissociation from a gold carbene can promote this type of intramolecular deprotonation.¹²⁶

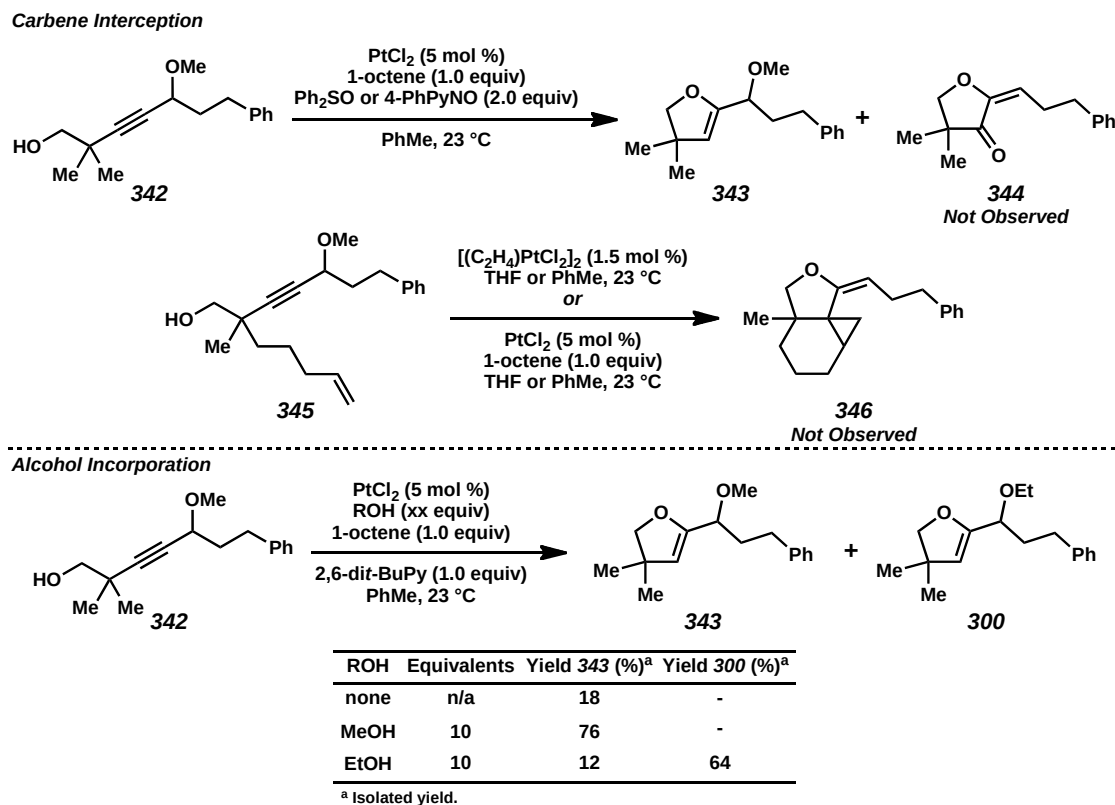


Scheme 4.3.8. Rationale for the Selectivity in 1,2-Si vs. 1,2-H Shifts.

4.3.4 Additional Reactions of α,β -Unsaturated Platinum Carbenes

Confident that we were forming the unsaturated platinum carbene, we set out to investigate alternative reaction pathways of this intermediate. We installed the geminal methyl groups in propargylic ether **342** with the expectation that doing so would block any 1,2 shift, and thus

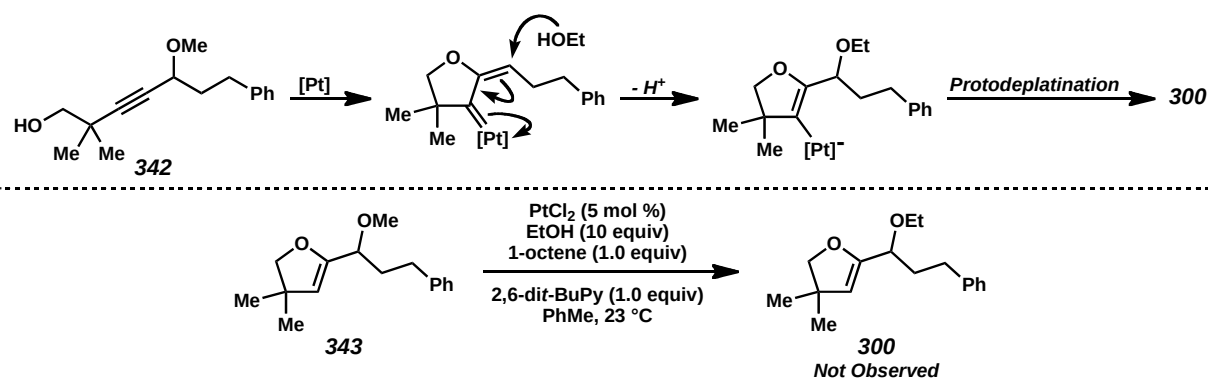
extend the lifetime of the carbene intermediate. Hoping to promote a carbene oxidation, we included known oxygen transfer reagents like *N*-oxides and sulfoxides (Scheme 4.3.9).¹²⁷ Exposing alkyne **342** to catalytic Zesie's dimer resulted in a complex mixture of products, with no observable carbene oxidation (**344**). Efforts to produce an intramolecular cyclopropanation with alkene **345** were unsuccessful. One byproduct that was identified from the attempted carbene oxidations was dihydrofuran **343**. We wondered if the extruded methanol was adding back into the β -position of the unsaturated carbene. Exposing alkyne **342** to PtCl_2 in the presence of a base resulted in an 18% yield of methyl ether **343**. The inclusion of 10.0 equivalents of methanol increased the yield to 76%, suggesting that the increased concentration of methanol was favoring vinylogous addition. In the presence of 10.0 equivalents of ethanol, the corresponding ethyl ether (**300**) was isolated in 64% yield, with the methyl ether (**343**) being recovered in 12% yield. This last observation confirmed the β -position of the unsaturated carbene as a potential site for nucleophilic addition, and prompted us to look at this reactivity more closely.



Scheme 4.3.9. Additional Reactions of Platinum Carbenes.

The incorporation of ethanol at the vinylogous position represents a significant departure from the traditional reactivity of alkynes in the presence of π -acidic metals and excess alcohols.¹²⁸ Our hypothesis was that blocking the 1,2-H shift enabled the platinum carbene to undergo nucleophilic additions at the β -position (Scheme 4.3.10). This readily explained why the methyl ether **343** was formed in higher yield when additional methanol was added to the reaction, and also accounted for the incorporation of ethanol to form ethyl ether **347**. We ruled out the possibility of alcohol exchange occurring as a simple platinum catalyzed substitution process. Exposing dihydrofuran **343** to the reaction conditions used for ethanol incorporation resulted in no formation of ethyl ether **347** after 14 h. This implicated that the platinum carbene was

undergoing a new mode of reactivity, leading us to explore the vinylogous addition of nucleophiles to the unsaturated platinum carbene in a broader context.



Scheme 4.3.10. Proposed Mechanism for Ethanol Incorporation.

4.4 Conclusion

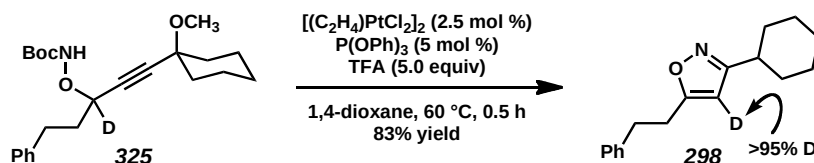
The results described above provided us with greater confidence that the operative reaction pathway in both the furan and isoxazole syntheses involved the formation of an unsaturated platinum carbene, and gave us insight into several interesting aspects of this chemistry. Our observation of a 1,2-deuteride migration presented strong evidence to support the involvement of a platinum carbene; as did our ability to selectively migrate silicon groups into the carbene. Exposing unlabeled carbamoyl ethers to conditions that promote isoxazole formation created an opportunity to indirectly assess the rate of deplatination. Lastly, the observation that alcohols could add vinylogously into the unsaturated platinum carbene presented a unique mode of reactivity for these intermediates, and spurred our investigation into a new method for synthesizing vicinal bisheterocycles, which will be discussed in Chapter 5.

4.5 Experimental Section

4.5.1 Materials and Methods

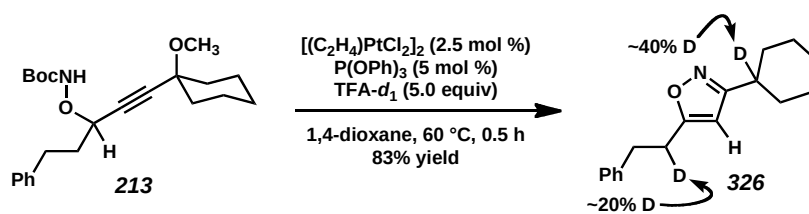
Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, ether, dichloromethane and toluene were purified by passing through activated alumina columns. 1,4-dioxane was distilled over sodium/benzophenone. Triphenylphosphite was purified by passing through an alumina column under an argon atmosphere. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products, (West Columbia, SC), Strem (Newburyport, MA) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 μm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde or KMnO_4 solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on a Varian 400 MR (at 400 MHz), and are reported relative to SiMe_4 (δ 0.00). ^2H NMR spectra were acquired on a Varian 400 MR (at 400 MHz) and are reported relative to SiMe_4 (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) and are reported relative to SiMe_4 (δ 0.0). All IR spectra were obtained on NaCl plates (film) with a Bruker Tensor 27. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.

4.5.2 Deuterium Labeling Studies



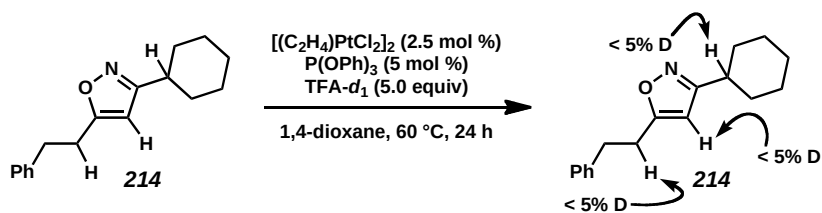
Scheme 4.3.5, eq. 1. According to the general procedure, to a solution of triphenylphosphite (4.6 mg, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid (112 μ L, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **325** (0.116 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **298** (64.3 mg, 84% yield, R_f = 0.59 in 4:1 hexanes/ $EtOAc$) as a pale yellow solid.

Isoxazole 298: ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (comp m, 2H), 7.23-7.17 (comp m, 3H), 3.01 (comp m, 4H), 2.73-2.66 (m, 1H), 1.95-1.93 (comp m, 2H), 1.82-1.78 (comp m, 2H), 1.75-1.69 (m, 1H), 1.47-1.32 (comp m, 5H), 1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.5, 140.4, 128.6, 128.4, 126.5, 36.0, 33.8, 32.2, 28.8, 26.1, 26.0; IR (film) 2927, 1582, 1496, 1070, 699 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{17}H_{20}DNO + H$] $^+$: 257.1759, found 257.1765.



Scheme 4.3.5, eq. 2. According to the general procedure, to a solution of triphenylphosphite (4.6 mg, 0.0150 mmol) in 1,4-dioxane (1.00 mL) under an ambient atmosphere was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol). After 15 min, trifluoroacetic acid- d_1 (112 μ L, 1.50 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of amino ether **213** (0.116 g, 0.300 mmol) in 1,4-dioxane (2.00 mL, 0.1 M final concentration in 1,4-dioxane) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 0.5 h. The reaction was quenched with Et_3N (0.500 mL) and filtered through a plug of silica gel (0.5 x 2 cm), washing with Et_2O (6.0 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (9:1 hexanes/ $EtOAc$ eluent) to afford isoxazole **326** (63.8 mg, 83% yield, R_f = 0.59 in 4:1 hexanes/ $EtOAc$) as a pale yellow solid.

Isoxazole 326: See spectroscopic information for ^1H and ^2H NMR's.

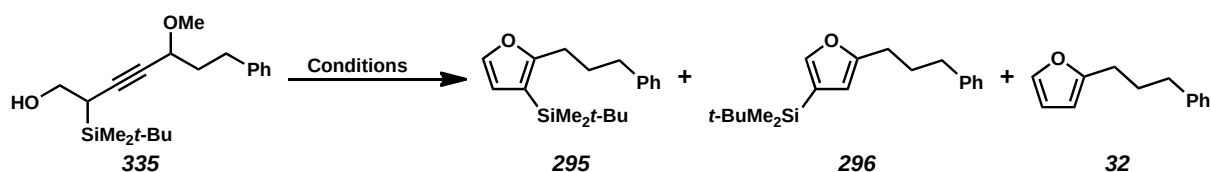


Scheme 4.3.5, eq. 3. To a solution of triphenylphosphite (1.6 mg, 0.00500 mmol) in 1,4-dioxane (0.330 mL) was added $[(C_2H_4)PtCl_2]_2$ (1.5 mg, 0.00250 mmol). After 15 min, trifluoroacetic acid- d_1 (38.3 μ L, 0.500 mmol) was added, and the resulting solution was stirred for 1 min. The catalyst mixture was then added to a solution of isoxazole **214** (25.5 mg, 0.100 mmol) in 1,4-

dioxane (0.660 mL, 0.1 M final concentration) in a 2-dram vial. The vial was sealed with a Teflon™ cap, placed in an aluminum block that was preheated to 60 °C, and stirred for 24 h. The reaction was diluted with Et₂O (2.0 mL) and washed with saturated NaHCO₃ solution (5.0 mL). The aqueous layer was extracted with Et₂O (2.0 mL), and the combined organic layers were dried over MgSO₄, filtered and the solvent removed by rotary evaporation. Deuterium incorporation in the product was not observed.

4.5.3 1,2-H vs. 1,2-Si Migrations

Table 4.3.1 (reproduced):



Entry	Catalyst ^a	Solvent	Temp (°C)	Additive (equiv)	Time	Ratio (295 : 296) ^b
1	$[(C_2H_4)PtCl_2]_2$	THF	23	-	30 min	1 : 3.0 ^c
2	$[(C_2H_4)PtCl_2]_2$	PhCH ₃	23	-	1 h	1.5 : 1 ^c
3	PtCl ₂	PhCH ₃	23	1-octene (1.0)	2 h	2.5 : 1
4	PtCl ₂	PhCH ₃	23	1-octene (5.0)	1.5 h	3.6 : 1
5	PtCl ₂	PhCH ₃	60	1-octene (5.0)	10 min	10 : 1
6	PtCl ₂	PhCH ₃	100	1-octene (5.0)	5 min	16 : 1 92% yield ^d
7	PtCl ₂	THF	23	-	70 h	1 : 3.0 ^c
8	PtCl ₂	THF	50	-	5 h	1 : 2.1 ^c
9	PtCl ₂	1,4-dioxane	100	-	5 min	6.0 : 1 ^c
10	PtCl ₂	THF	23	PPh ₃ (0.05)	24 h	1 : 2.0 ^c
11	PtCl ₂	THF	23	1-octene (1.0)	2 h	1 : 9.4 ^c
12	PtCl ₂	THF	23	ethyl vinyl ether (1.0)	8 h	1 : 8.5 ^c 83% yield ^d

^a $[(C_2H_4)PtCl_2]_2$ (1.5 mol %) or PtCl₂ (5 mol %). ^b Determined by ¹H NMR. ^c 10-20% of desilylated furan 32 observed in ¹H NMR. ^d Isolated yield.

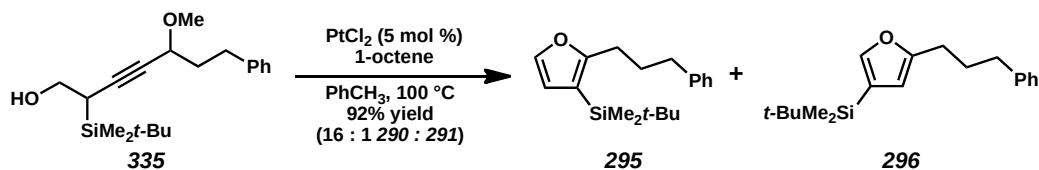


Table 4.3.1, Entry 6. Homopropargylic alcohol 335 (99.6 mg, 0.300 mmol) and 1-octene (235 μ L, 1.50 mmol) were stirred in PhMe (3.00 mL, 0.10 M) under an ambient atmosphere at 100 °C. PtCl₂ (4.0 mg, 0.0150 mmol) was added and the reaction was stirred for 5 min. Upon completion, the reaction was cooled to room temperature, filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc

eluent) to afford a 16:1 mixture of furans **295** and **296** (82.8 mg, 92% yield overall, $R_f = 0.48$ in 19:1 hexanes/EtOAc), which could not be further separated, as a colorless oil.

Furan 295: ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, $J = 2.0$ Hz, 1H), 7.31-7.26 (comp m, 2H), 7.21-7.16 (comp m, 3H), 6.25 (d, $J = 1.8$ Hz, 1H), 2.70-2.65 (comp m, 4H), 2.02-1.94 (m, 2H), 0.86 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.5, 142.3, 140.6, 128.8, 128.6, 126.1, 115.7, 109.9, 36.0, 31.2, 29.0, 26.8, 26.7, -4.7; IR (film) 2954, 2856, 1941, 1510, 1251 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{19}\text{H}_{28}\text{OSi} + \text{H}$] $^+$: 301.1982, found 301.1979.

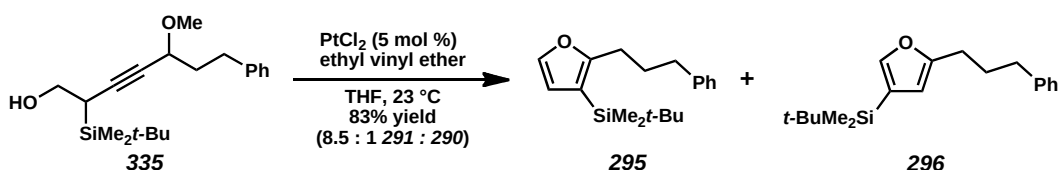
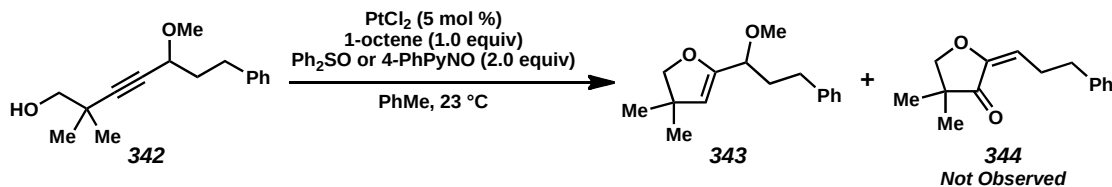


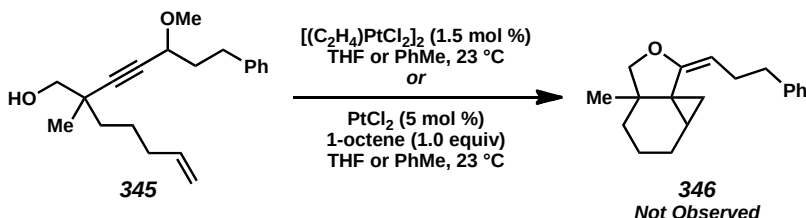
Table 4.3.1, Entry 12. Homopropargylic alcohol **335** (90.0 mg, 0.271 mmol), ethyl vinyl ether (27.1 μL , 0.271 mmol), and PtCl_2 (3.6 mg, 0.0135 mmol) were stirred in THF (2.70 mL, 0.10 M) under an ambient atmosphere at room temperature for 8 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:1, 20 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford a 8.5:1 mixture of furans **296** and **295** (67.4 mg, 83% yield overall, $R_f = 0.48$ in 19:1 hexanes/EtOAc), which could not be further separated, as a colorless oil.

Furan 296: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.26 (comp m, 2H), 7.22-7.17 (comp m, 4H), 5.97 (s, 1H), 2.66 (app. td, $J = 7.4, 3.5$ Hz, 4H), 1.99 (quint, $J = 7.8$ Hz, 2H), 0.90 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.6, 146.5, 142.4, 128.8, 128.7, 126.2, 109.6, 35.7, 30.0, 27.7, 26.7, 16.9, -5.2; IR (film) 3028, 2856, 1941, 1516, 1260 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{19}\text{H}_{28}\text{OSi} + \text{H}$] $^+$: 301.1982, found 301.1989.

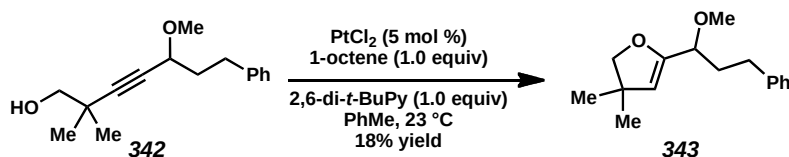
4.5.4 Additional Reactions of α,β -Unsaturated Platinum Carbenes



General Procedure: To a solution of alcohol **342** (0.0500 mmol) in PhMe (0.50 mL, 0.1 M) under ambient atmosphere was added diphenylsulfoxide or 4-phenylpyridine-*N*-oxide (0.100 mmol). 1-octene (0.0500 mmol) was then added followed by PtCl_2 (0.00250 mmol), and the reaction was stirred at room temperature. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with hexanes/EtOAc (1:1, 4.0 mL). The solvent was removed by rotary evaporation and the crude residue was analyzed by ^1H NMR.

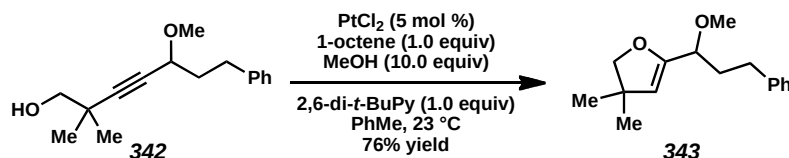


General Procedure: To a solution of alcohol **345** (14.3 mg, 0.0500 mmol) in solvent (0.500 mL, 0.1 M) under ambient atmosphere was added 1-octene (0.0500 mmol) followed by PtCl_2 (0.00250 mmol) or Zeise's dimer (0.00125 mmol), and the reaction was stirred at room temperature. Upon completion, as determined by TLC, the reactions were filtered through a plug of SiO_2 (0.5 x 2.0 cm), washing with hexanes/EtOAc (1:1, 4.0 mL). The solvent was removed by rotary evaporation and the crude residue was analyzed by ^1H NMR.



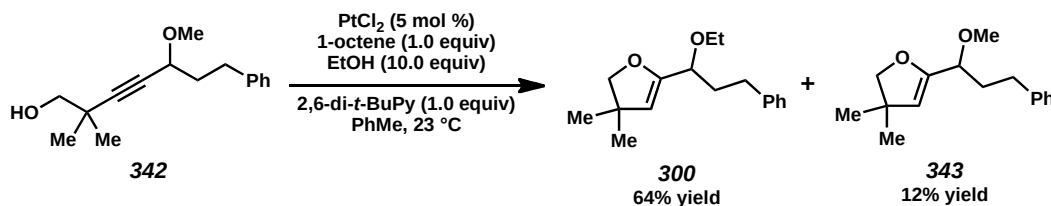
To a solution of alcohol **342** (49.2 mg, 0.200 mmol) in PhMe (2.00 mL, 0.10 M) was added 1-octene (31.5 μL , 0.200 mmol) and 2,6-di-*t*-butylpyridine (44.2 μL , 0.200 mmol). PtCl_2 (2.7 mg, 0.0100 mmol) was then added, and the reaction was stirred under an ambient temperature at room temperature for 26 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm, neutralized with Et_3N prior to loading), washing with EtOAc/hexanes (1:2, 10 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (hexanes $\rightarrow$ 19:1 hexanes/ Et_2O) to afford ether **343** (8.7 mg, 18% yield, R_f = 0.31 in 9:1 hexanes/ Et_2O eluent) as a colorless oil.

Ether 343: ^1H NMR (400 MHz, C_6D_6) δ 7.17 (s, 4H), 7.10-7.05 (m, 1H), 4.66 (s, 1H), 3.84 (s, 2H), 3.67 (dd, J = 7.0, 5.9 Hz, 1H), 3.24 (s, 3H), 2.85-2.69 (comp m, 2H), 2.25-2.06 (comp m, 2H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 156.8, 142.8, 129.2, 129.0, 126.4, 109.5, 83.1, 76.8, 56.9, 43.7, 35.8, 32.4, 28.2, 28.1; IR (film) 3027, 1663, 1460, 1108, 700 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{16}\text{H}_{22}\text{O}_2 + \text{H}$] $^+$: 247.1698, found 247.1697.



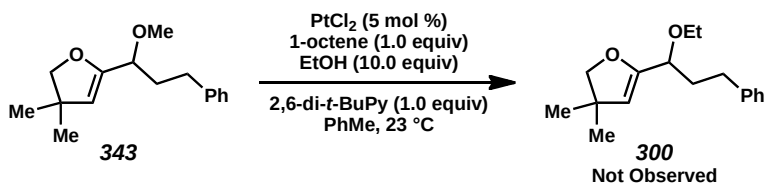
To a solution of alcohol **342** (49.2 mg, 0.200 mmol) in PhMe (2.00 mL, 0.10 M) was added 1-octene (31.5 μL , 0.200 mmol), 2,6-di-*t*-butylpyridine (44.2 μL , 0.200 mmol) and MeOH (80.9 μL , 2.00 mmol). PtCl_2 (2.7 mg, 0.0100 mmol) was then added, and the reaction was stirred under an ambient atmosphere at room temperature for 2 h. Upon completion, the reaction was

filtered through a plug of silica gel (0.5 x 2 cm, neutralized with Et₃N prior to loading), washing with EtOAc/hexanes (1:2, 10 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (hexanes → 19:1 hexanes/Et₂O eluent) to afford ether **343** (37.3 mg, 76% yield, *R_f* = 0.31 in 9:1 hexanes/Et₂O) as a colorless oil.



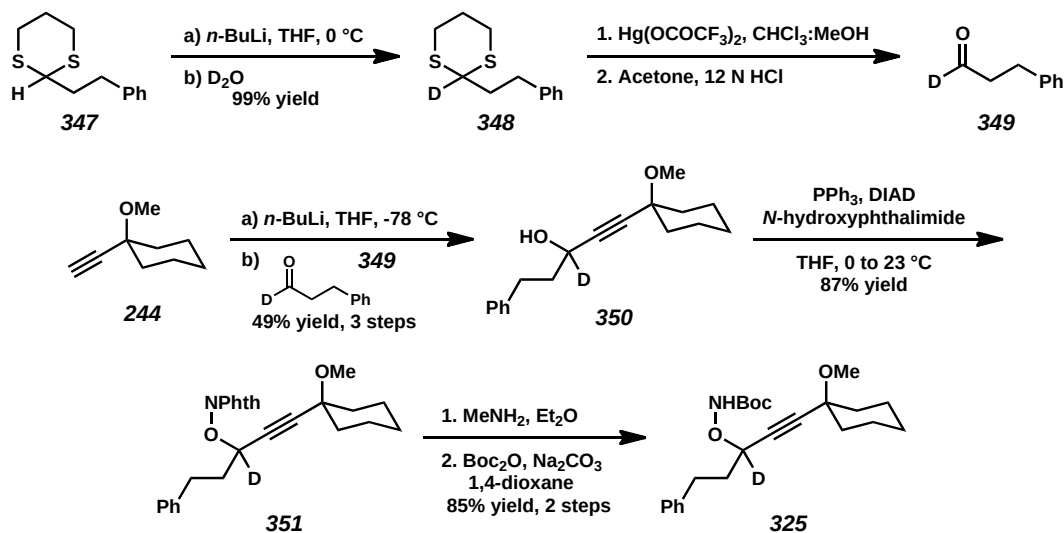
To a solution of alcohol **342** (73.8 mg, 0.300 mmol) in PhMe (3.00 mL, 0.10 M) was added 1-octene (47.0 μ L, 0.300 mmol), 2,6-di-*t*-butylpyridine (66.3 μ L, 0.300 mmol) and EtOH (175 μ L, 3.00 mmol). PtCl₂ (4.0 mg, 0.0150 mmol) was then added, and the reaction was stirred under an ambient atmosphere at room temperature for 2 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2 cm, neutralized with Et₃N prior to loading), washing with EtOAc/hexanes (1:2, 10 mL). The solvent was removed by rotary evaporation, and the resulting oil was purified by flash chromatography (hexanes → 19:1 hexanes/Et₂O eluent) to afford ether **300** (49.7 mg, 64% yield, *R_f* = 0.37 in 9:1 hexanes/Et₂O) and ether **343** (8.7 mg, 12% yield, *R_f* = 0.31 in 9:1 hexanes/Et₂O) as colorless oils.

Ether 300: ¹H NMR (400 MHz, C₆D₆) δ 7.17 (s, 4H), 7.10-7.05 (m, 1H), 4.69 (s, 1H), 3.86 (s, 2H), 3.80 (dd, *J* = 7.0, 5.5 Hz, 1H), 3.64 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.88-2.70 (comp m, 2H), 2.25-2.08 (comp m, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 157.8, 143.1, 129.5, 129.2, 126.6, 109.1, 83.4, 75.5, 65.2, 43.4, 36.3, 32.7, 28.5, 28.4, 16.3; IR (film) 3027, 1663, 1458, 1105, 699 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₇H₂₄O₂ + H]⁺: 261.1848, found 261.1847.



To a solution of ether **343** (9.7 mg, 0.0394 mmol) in PhMe (0.394 mL, 0.10 M) was added 1-octene (6.22 μL , 0.0394 mmol) and EtOH (22.9 μL , 0.394 mmol). PtCl_2 (0.5 mg, 0.00197 mmol) was then added, and the reaction was stirred under an ambient temperature at room temperature for 14 h. The reaction was filtered through a plug of silica gel (0.5 x 2 cm), washing with EtOAc/hexanes (1:2, 10 mL). The solvent was removed by rotary evaporation, and the resulting oil was analyzed by NMR. No formation of ether **300** was detected in the crude spectrum.

4.5.5 Substrate Synthesis



To a solution of dithiane **347**¹²⁹ (3.36 g, 15.0 mmol) in THF (30.0 mL, 0.5 M) at -30 °C under argon was added *n*-BuLi (7.20 mL, 2.50 M in hexanes, 18.0 mmol), and the reaction was stirred at -30 °C for 2 h. D_2O (0.540 mL, >99.9% D, 30.0 mmol) was added, and the reaction was warmed to 23 °C, and stirred for an additional 15 min. The reaction was diluted with hexanes

(30 mL) and washed with H₂O (30 mL). The aqueous phase was extracted with Et₂O (30 mL), and the combined organic layers were dried over MgSO₄, and the solvent removed by rotary evaporation affording deuterated dithiane **348** (3.35 g, 99% yield, >98% D incorporation, *R_f* = 0.64 in 1:1 hexanes/CH₂Cl₂) as a colorless oil.

To a solution of dithiane **348** (0.450 g, 2.00 mmol) in CHCl₃:MeOH (100:1, 40.4 mL, 0.05 M) was added Hg(OCOCF₃)₂ (1.28 g, 3.00 mmol), and the reaction was stirred for 12 h. Celite (2.0 g) was added, and the reaction was filtered, washing with CHCl₃ (10 mL). The solvent was removed in vacuo, and the recovered residue was dissolved into acetone (15.0 mL, 0.13 M). To this was added HCl (10.0 mL, 12.0 N) and the reaction was stirred for 40 min. The acetone was removed in vacuo, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5.0 mL). The combined organic layers were dried over MgSO₄, and the solvent removed by rotary evaporation, affording aldehyde **349** (0.378 g crude, *R_f* = 0.58 in 1:1 hexanes/CH₂Cl₂ eluent) as a colorless oil.

To a solution of alkyne **244** (0.276 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the reaction was stirred for 30 min. Aldehyde **349** (0.378 g, assumed 2.00 mmol) in THF (2.00 mL, 1.0 M) was added dropwise, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with sat. aq. NH₄Cl (10 mL), and diluted with Et₂O (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO₄. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (4:1

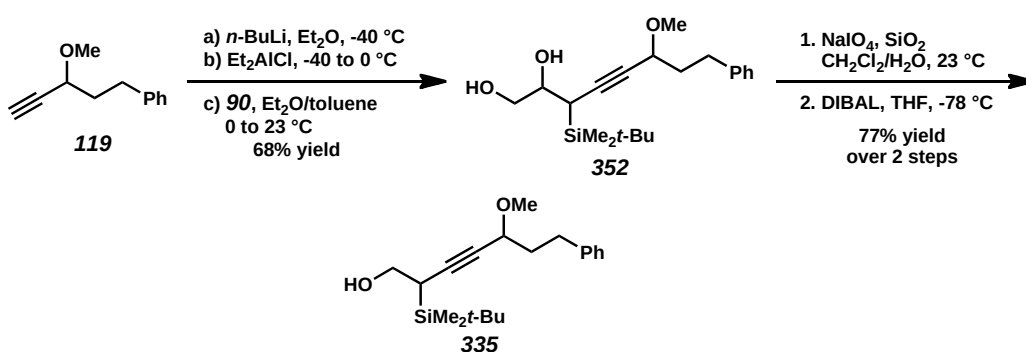
hexanes/EtOAc eluent), affording alcohol **350** (0.270 g, 49% yield over 3 steps, $R_F = 0.31$ in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of PPh_3 (0.309 g, 1.18 mmol) in THF (8.00 mL, 0.15 M) at 0 °C under argon was added DIAD (0.201 mL, 1.04 mmol) dropwise. After 10 min a solution of alcohol **350** (0.270 g, 0.987 mmol) in THF (2.00 mL, 0.50 M) was added. After 5 min *N*-hydroxyphthalimide (0.169 g, 1.04 mmol) was added and the reaction was warmed to 23 °C, and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (20 mL) and diluted with Et_2O (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The recovered residue was purified by flash chromatography (9:1→4:1 hexanes/EtOAc eluent) affording phthalimide **351** (0.360 g, 87% yield, $R_f = 0.51$ in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **351** (0.360 g, 0.860 mmol) in Et_2O (4.30 mL, 0.20 M) at 23 °C was added MeNH_2 (0.158 mL, 40% solution in H_2O , 1.81 mmol) and the reaction was stirred for 1 h. The reaction was cooled to 0 °C and filtered, washing with additional Et_2O (5.0 mL). The filtrate was concentrated in vacuo, and dissolved in 1,4-dioxane (3.50 mL, 0.25 M). Na_2CO_3 (91.2 mg, 0.860 mmol) was added, followed by Boc_2O (0.182 g, 0.860 mmol), and the reaction was stirred for 14 h. The reaction was diluted with Et_2O (5.0 mL) and sat. aq. NaHCO_3 (5.0 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (5.0 mL). The combined organic phases were dried over MgSO_4 and the solvent removed by rotary evaporation. The recovered residue was purified by flash chromatography (4:1 hexanes/EtOAc

eluent) affording amino ether **325** (0.285 g, 85% yield over 2 steps, R_f = 0.38 in 4:1 hexanes/EtOAc) as a colorless oil.

Amino ether 325: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (comp m, 2H), 7.22-7.19 (comp m, 4H), 3.38 (s, 3H), 2.85 (ddd, J = 9.0, 7.0, 1.9 Hz, 2H), 2.18-2.00 (comp m, 2H), 1.94-1.90 (comp m, 2H), 1.70-1.50 (m, 7H), 1.48 (s, 9H), 1.35-1.26 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.5, 141.4, 128.6, 126.2, 88.2, 83.5, 82.0, 74.1, 51.0, 50.9, 36.84, 36.82, 35.6, 31.6, 28.4, 28.30, 28.26, 25.6, 23.0; IR (film) 3262, 2936, 1747, 1454, 1247, 1093 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+ [\text{C}_{23}\text{H}_{32}\text{DNO}_4 + \text{Na}]^+$: 411.2365, found 411.2353.



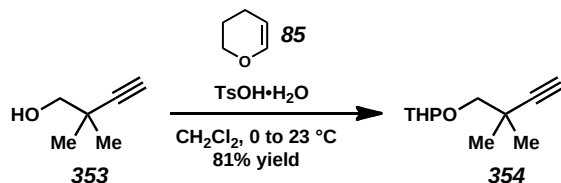
To a solution of alkyne **119** (5.22 g, 30.0 mmol) in Et_2O (20.0 mL, 0.67 M) at $-40\text{ }^\circ\text{C}$ under argon was added $n\text{-BuLi}$ (12.0 mL, 2.5 M in hexanes, 30.0 mmol), and the reaction was stirred for 30 min. To this solution was added Et_2AlCl (30.0 mL, 1.0 M in hexanes, 30.0 mmol) dropwise, and the resulting solution was stirred at $-40\text{ }^\circ\text{C}$ for 15 min, and then was warmed to $0\text{ }^\circ\text{C}$ and stirred for 15 min. The reaction was cooled to $-40\text{ }^\circ\text{C}$, and a solution of epoxide **90** (1.88 g, 10.0 mmol) in toluene (60.0 mL, 0.17 M) was added over 10 min. The reaction was slowly warmed to room temperature and stirred for 16 h. The reaction was cooled to $0\text{ }^\circ\text{C}$, and water was cautiously added. Once gas evolution ceased, the mixture was diluted with 1 N HCl (50

mL) and stirred for 30 min. The phases were separated, and the aqueous phase was extracted with Et₂O (50 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The recovered oil was purified by flash chromatography (4:1 → 1:1 hexanes/EtOAc eluent), affording glycol **352** (2.47 g, 68% yield, *R_f* = 0.20 in 2:1 hexanes/EtOAc) as a colorless oil.

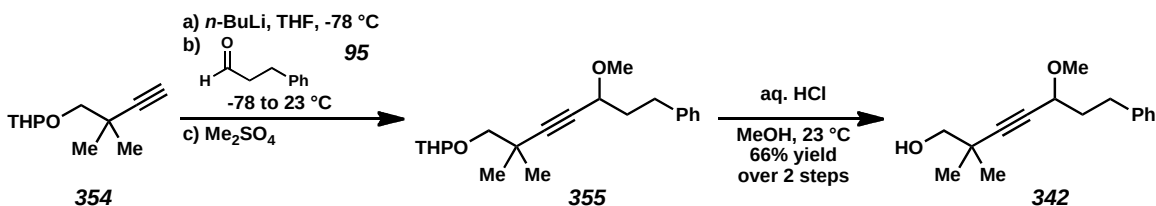
To a suspension of silica gel (9.00 g) stirred vigorously in CH₂Cl₂ (80 mL, 0.060 M) was added a solution of NaIO₄ (1.30 g, 6.40 mmol) in water (9.00 mL, 0.70 M), and the mixture was stirred until a fine dispersion was formed. To this was added a solution of glycol **352** (1.80 g, 4.97 mmol) in CH₂Cl₂ (10.0 mL, 0.50 M), and the reaction was stirred at room temperature for 1 h. The reaction was then filtered, and the solid was washed with CH₂Cl₂ (50 mL). The filtrate was concentrated in vacuo, and the recovered clear oil was immediately dissolved in THF (25.0 mL, 0.20 M) and cooled to -78 °C under argon. DIBAL-H (6.00 mL, 1.0 M solution in hexanes, 6.00 mmol) was added, and the reaction was stirred at -78 °C for 25 min. The reaction was quenched with 1 N HCl (50 mL) and warmed to room temperature. The mixture was diluted with Et₂O (25 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were dried over MgSO₄ and concentrated in vacuo. The recovered oil was purified by flash chromatography (9:1 → 3:1 hexanes/EtOAc eluent), affording alcohol **335** (1.28 g, 77% yield over 2 steps, *R_f* = 0.34 in 4:1 hexanes/EtOAc) as a colorless oil.

β-Hydroxypropargylsilane 335: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.26 (comp m, 2H), 7.21-7.17 (comp m, 3H), 3.95 (td, *J* = 6.2, 2.0 Hz, 1H), 3.76 (d, *J* = 4.3 Hz, 1H), 3.74 (d, *J* = 4.6 Hz, 1H), 3.67 (app. t, *J* = 9.8 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.77 (t, *J* = 8.2 Hz, 2H), 2.26-2.22 (m, 1H), 2.02-1.94 (comp m, 3H), 0.97 (s, 9H), 0.13

(s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.9, 128.8, 128.7, 126.2, 86.5, 82.2, 71.10, 71.08, 63.34, 63.30, 56.61, 56.58, 38.07, 38.05, 31.9, 27.2, 23.15, 23.12, 18.1, 17.7, -6.34, -6.30, -6.7; IR (film) 3455, 2216, 1727, 1251, 1103 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{NH}_4)^+ [\text{C}_{20}\text{H}_{32}\text{O}_2\text{Si} + \text{NH}_4]^+$: 350.2510, found 350.2503.



To a solution of alcohol **353**¹³⁰ (5.64 g, 57.5 mmol) in CH_2Cl_2 (57.5 mL, 1.0 M) at 0 °C was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.109 g, 0.575 mmol), followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 5.12 mL, 60.3 mmol). After stirring at 0 °C for 5 min the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. aq. NaHCO_3 (50 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, and the recovered residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **354**¹³¹ (8.53 g, 81% yield, R_f = 0.54 in 9:1 hexanes/EtOAc) as a colorless oil.

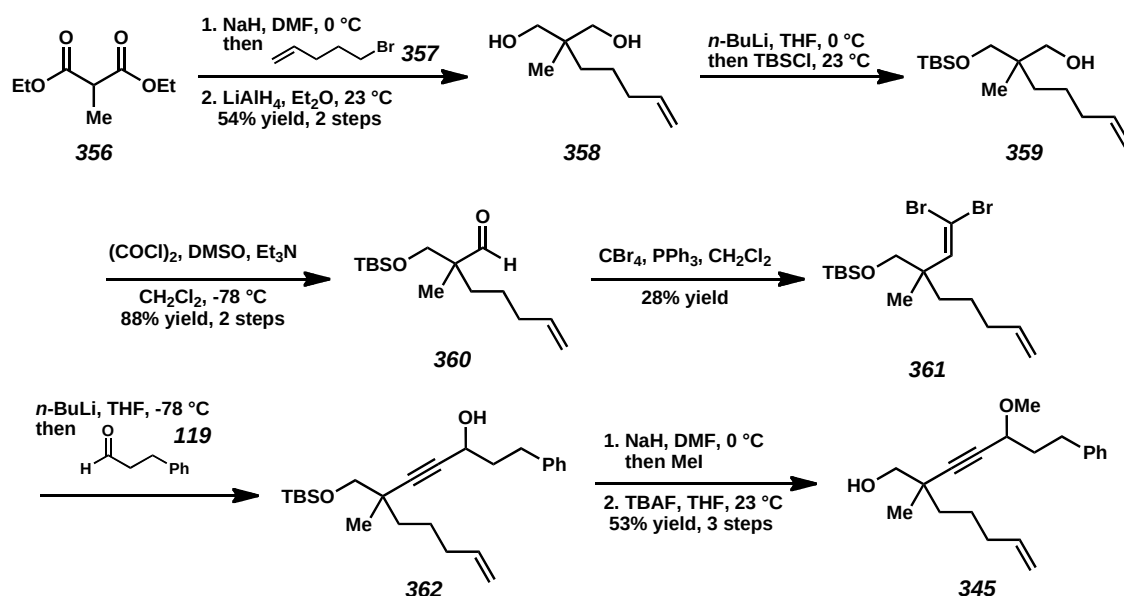


To a solution of alkyne **354** (0.273 g, 1.50 mmol) in THF (6.0 mL, 0.25 M) at -78 °C under argon was added $n\text{-BuLi}$ (0.600 mL, 2.5 M in hexanes, 1.50 mmol), and the resulting solution

was stirred for 30 min at -78 °C. Hydrocinnamaldehyde (**95**, 0.198 mL, 1.50 mmol) was then added, and the reaction was stirred at -78° C for 1 h, then warmed to room temperature and stirred for 2 h. Me₂SO₄ (0.285 mL, 3.00 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction mixture was quenched with 1 M NaOH (10 mL) and stirred for 15 min. The mixture was then diluted with Et₂O (10 mL) and the layers were separated. The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solution was concentrated in vacuo, affording crude ether **355** (0.497 g, *R*_f = 0.54 in 4:1 hexanes/EtOAc) as an amber colorless oil.

To a solution of crude ether **355** (0.497 g, approx. 1.50 mmol) in MeOH (15.0 mL, 0.10 M) was added 3 N HCl (approx. 50 µL), and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. aq. NaHCO₃ (15 mL), and the resulting suspension was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) to afford alcohol **342** (0.242 g, 66% yield over 2 steps, *R*_f = 0.27 in 4:1 hexanes/EtOAc) as a colorless oil.

Homopropargylic alcohol 342: ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.26 (comp m, 3H), 7.22-7.18 (comp m, 2H), 3.92 (t, *J* = 6.6 Hz, 1H), 3.41 (app. d, *J* = 7.0 Hz, 2H), 3.38 (s, 3H), 2.80-2.73 (comp m, 2H), 2.09-1.91 (comp m, 2H), 1.75 (t, *J* = 6.6 Hz, 1H), 1.23 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 141.8, 128.8, 128.7, 126.3, 91.6, 80.6, 71.9, 70.7, 56.5, 37.8, 34.7, 31.9, 25.9; IR (film) 3444, 3027, 2233, 1947, 1603, 700 cm⁻¹; HRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₆H₂₂O₂ + H]⁺: 247.1693, found 247.1692.



To a solution of diethyl methylmalonate (**356**, 3.48 g, 20.0 mmol) in DMF (40.0 mL, 0.5 M) at 0 °C under argon was added NaH (0.80 g, 60% dispersion in mineral oil, 20.0 mmol), and the resulting solution was warmed to 23 °C and stirred for 1 h. 1-bromo-4-pentene (**357**, 2.36 mL, 20.0 mmol) was added, and the reaction was heated at 80 °C for 20 h. The reaction was cooled to 23 °C, quenched with H₂O (40 mL), and the resulting suspension was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with LiCl (20 mL, 10% aq.), dried over MgSO₄, and the solvent was removed via rotary evaporation to afford the crude diester (5.09 g, *R*_F = 0.68 in 4:1 hexanes/EtOAc) as an amber oil. The diester was immediately dissolved in Et₂O (20.0 mL, 1.0 M) and added to a solution of LiAlH₄ (3.04 g, 80.0 mmol) in Et₂O (80.0 mL, 1.0 M) at 0 °C. The reaction was warmed to 23 °C and stirred for 4 h. The reaction was quenched with sequential additions of H₂O (2.9 mL), NaOH (5.0 mL, 15% aq.) and H₂O (8.75 mL). The resulting slurry was filtered, and washed with Et₂O (50 mL). The solvent was removed via rotary evaporation and the resulting oil was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford diol **358** (1.75 g, 54% yield over 2 steps, *R*_f = 0.47 in 1:2 hexanes/EtOAc) as a colorless oil.

To a solution of diol **358** (1.71 g, 10.8 mmol) in THF (43.2 mL, 0.25 M) at 0 °C was added *n*-BuLi (4.34 mL, 2.5 M in hexanes, 10.8 mmol) and the reaction was stirred for 30 min. TBSCl (1.63 g, 10.8 mmol) was added and the reaction was stirred for 2 h. Upon completion, the reaction was quenched with H₂O (40 mL) and the resulting solution was extracted with Et₂O (3 x 15 mL). The combined organics were dried over MgSO₄ and the solvent was removed by rotary evaporation to afford crude alcohol **359** (3.21 g, *R*_f = 0.65 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of oxalyl chloride (1.04 mL, 11.9 mmol) in CH₂Cl₂ (54.0 mL, 0.22 M) at -78 °C under argon was added DMSO (1.70 mL, 23.8 mmol) dropwise. The solution was stirred at -78 °C for 10 min. A solution of alcohol **359** (2.85 g, 15.0 mmol) in CH₂Cl₂ (7.50 mL) was then added slowly, and the reaction was stirred at -78 °C for 1 h. Et₃N (7.6 mL, 54.0 mmol) was then added, and the reaction mixture was maintained at -78 °C for 10 min before being warmed to room temperature and stirred for 10 min. The reaction was then quenched with water (100 mL), and the phases were separated. The organic layer was washed sequentially with 1 N HCl (50 mL), sat. aq. NaHCO₃ (50 mL), and brine (50 mL), and was dried over MgSO₄. The solvent was removed via rotary evaporation. The crude residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford aldehyde **360** (2.57 g, 88% yield over 2 steps, *R*_f = 0.45 in 19:1 hexanes/EtOAc) as a colorless oil.

To a solution of CBr₄ (6.30 g, 19.0 mmol) in CH₂Cl₂ (90.0 mL, 0.21 M) at 0 °C was added PPh₃ (9.96 g, 38.0 mmol) and the solution was stirred for 15 min. Aldehyde **360** (2.57 g, 9.50 mmol) was added and the reaction was warmed to 23 °C and stirred for 18 h. The reaction was

quenched with H₂O (80 mL) and the resulting solution was extracted with CH₂Cl₂ (2 x 25 mL). The combined organics were dried over MgSO₄, and the solvent was removed by rotary evaporation. The resulting slurry was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford dibromoolefin **361** (1.12 g, 28% yield, R_f = 0.77 in 19:1 hexanes/EtOAc) as a yellow oil.

To a solution of dibromoolefin **361** (0.848 g, 2.00 mmol) in THF (20.0 mL, 0.1 M) at -78 °C was added *n*-BuLi (1.6 mL, 2.5 M in hexanes, 4.00 mmol) and the reaction was stirred for 2 h. Hydrocinnamaldehyde (**119**, 0.264 mL, 2.00 mmol) was added and the reaction was warmed to 23 °C and stirred for 3 h. Upon completion, the reaction was quenched with H₂O (20 mL) and the resulting solution was extracted with Et₂O (3 x 15 mL). The combined organics were dried over MgSO₄, and the solvent was removed by rotary evaporation to afford crude alcohol **362** (0.795 g, R_f = 0.61 in 4:1 hexanes/EtOAc) as an amber oil.

To a solution of alcohol **362** (0.795 g, 2.00 mmol) in DMF (10.0 mL, 0.2 M) at 0 °C under argon was added NaH (0.080 g, 60% dispersion on mineral oil, 2.00 mmol), and the resulting solution was warmed to 23 °C and stirred for 2 h. Iodomethane (0.149 mL, 2.40 mmol) was added and the reaction was stirred for 24 h. The reaction was quenched with H₂O (40 mL), and the resulting suspension was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with LiCl (10 mL, 10% aq.), dried over MgSO₄, and the solvent was removed via rotary evaporation. The crude residue was dissolved in THF (10.0 mL, 0.2 M) and stirred at 23 °C. TBAF (2.40 mL, 1.0 M in THF, 2.40 mmol) was added and the reaction was stirred for 2 h. The solvent was removed by rotary evaporation and the recovered residue was purified by flash

chromatography (9:1 hexanes/EtOAc eluent) to afford alcohol **345** (0.404 g, 53% yield over 2 steps, R_f = 0.68 in 4:1 hexanes/EtOAc) as a colorless oil.

Alcohol 345: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.26 (comp m, 2H), 7.22-7.17 (comp m, 3H), 5.88-5.75 (m, 1H), 5.02 (dd, J = 17.2, 1.6 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 3.93 (t, J = 6.2 Hz, 1H), 3.45 (q, J = 10.6 Hz, 2H), 3.38 (s, 3H), 2.76 (t, J = 7.8 Hz, 2H), 2.12-1.91 (comp m, 4H), 1.68 (s, 1H), 1.60-1.52 (comp m, 3H), 1.41-1.32 (m, 1H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.6, 138.7, 128.6, 128.5, 126.1, 114.9, 90.3, 81.6, 70.6, 70.5, 56.4, 38.4, 37.7, 37.44, 37.43, 34.2, 31.7, 24.4, 23.5.

CHAPTER FOUR NOTES AND REFERENCES

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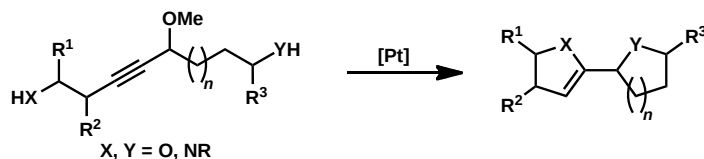
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CHAPTER FIVE

Synthesis of Vicinal Bisheterocycles from Propargylic Methyl Ethers

5.1 Introduction

The discovery of vinylogous additions of alcohols into unsaturated platinum carbenes prompted us to explore ways to extend this reactivity toward the formation of more complex molecular structures. We envisioned the use of substrates containing two nucleophilic atoms positioned on opposite sides of the alkyne, enabling us to close two ring systems during the reaction. The products of these reactions would be vicinal bisheterocycles, a structural element that is prevalent in a variety of natural products and pharmaceuticals. This manifold would allow us to examine any effect that the nucleophilic groups, ring sizes, and substitution might have on the outcomes of the reaction. Described herein is our development of this unique reactivity, where we induce a novel, double cyclization event to generate a variety of vicinal bisheterocycles in excellent yields, regioselectivities, and diastereoselectivities (Scheme 5.1.1).¹³² Also described are results that indicate non-heteroatom nucleophiles can add vinylogously into the unsaturated platinum carbene, expanding the scope of this reactivity to include enols and nontraditional hydride sources as competent nucleophiles.



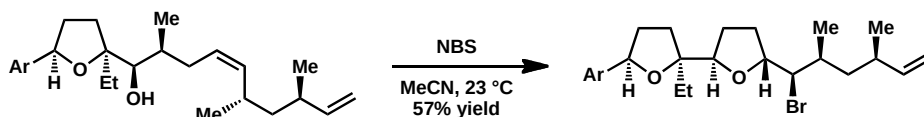
Scheme 5.1.1. Synthesis of Vicinal Bisheterocycles.

5.2 Background

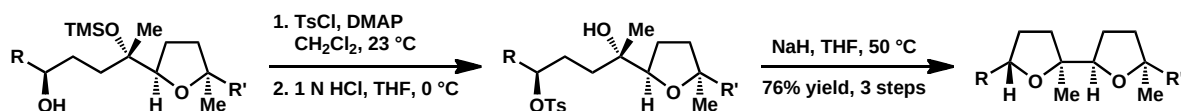
5.2.1 Traditional Syntheses of Vicinal Bisheterocycles

Vicinal bisheterocycles are a structural motif present in many biologically active natural products, with the polyether ionophores monensin and ionomycin being representative of these compounds. Efforts to synthesize these types of natural products have led to many reliable methods to install bistetrahydrofurans and bistetrahydropyrans.¹³³ Unfortunately, most of these approaches rely on the stepwise closure of each ring system. Examples of this strategy include the additions of hydroxyl nucleophiles onto activated alkenes like in Kishi's monensin synthesis, or involve intramolecular S_N2 displacements similar to the one used by Lautens in his synthesis of ionomycin (Scheme 5.2.1).¹³⁴ While these approaches are successful, a more attractive option would be one that enables two or more heterocycles to be formed during a single operation.

Kishi 1979



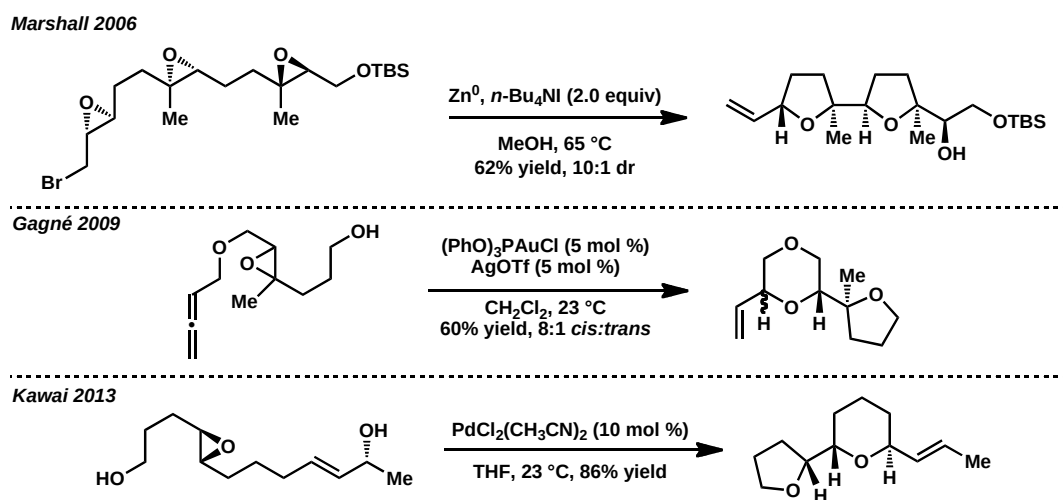
Lautens 2002



Scheme 5.2.1. Stepwise Approaches to Bistetrahydrofurans.

Alternative approaches to the formation of vicinal bisheterocycles as a single, polycyclization event promoted by a Lewis acid have also been developed.¹³⁵ Marshall has shown that terminal epoxy halides will react with zinc powder to form intermediate allylic zinc alkoxides.¹³⁶ These reactive species can then undergo a Lewis acid catalyzed epoxide-opening cascade to form the bisheterocycles. Employing this method toward the synthesis of the C₁₇-C₃₂ fragment of Ionomycin resulted in formation of the bistetrahydrofuran motif in a 62% yield and 10:1

diastereomeric ratio (Scheme 5.2.2). Acid mediated epoxide opening cascades have also been used to close both bistetrahydrofuran and bistetrahydropyran systems, though this process will favor formation of the smaller tetrahydrofuran ring over the tetrahydropyran in cases where both could form.¹³⁷ Recently Gagné reported a gold(I) catalyzed cascade of allenyl epoxides to generate a variety of vicinal bisheterocycles.¹³⁸ Kawai has synthesized vicinal tetrahydrofuran-tetrahydropyran ring systems using $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ to promote the addition of epoxides into activated allylic alcohols.¹³⁹ These reactions proceeded with high stereospecificities and in generally high yields.

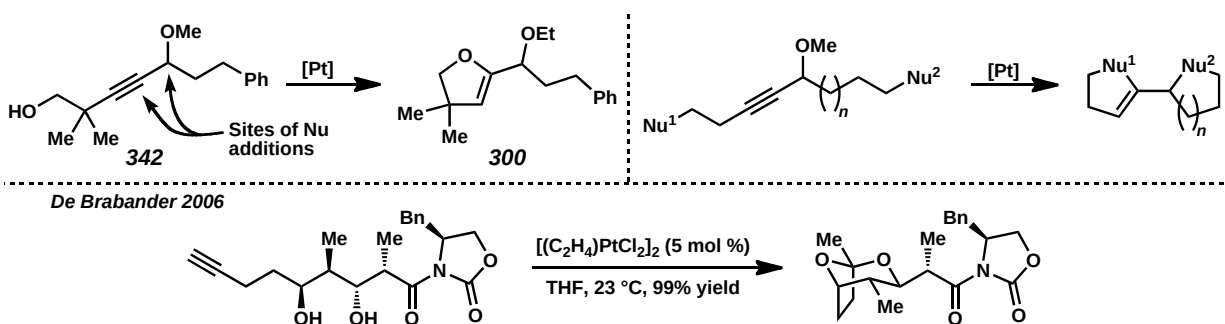


Scheme 5.2.2. Vicinal Double Heterocyclization Cascades.

5.2.2 Vicinal Bisheterocyclizations via Alkyne Activation

The platinum catalyzed formation of ethyl ether **300** from propargylic methyl ether **342** via an unsaturated platinum carbene demonstrated two sites for nucleophilic additions in these systems. We were intrigued by the possibility of intercepting this carbene with a tethered nucleophile to form vicinal bisheterocycles (Scheme 5.2.3). In order for this proposal to be successful we would have to overcome the traditional reactivity of geminal addition observed for alkynes

bearing two heteroatom nucleophiles.¹⁴⁰ A relevant example of this type of reactivity is the spiroketalization promoted by Zeise's dimer in De Brabander's synthesis of Saliniketal B.¹⁴¹ Our investigation into this type of cyclization event would also provide us with an opportunity to both study the types of nucleophiles that would be competent in this reaction and determine if the vinylogous addition of the second nucleophile could outcompete the 1,2-H migration that had been observed in both the furan and isoxazole syntheses. With these questions in mind we began our investigation into the intramolecular vinylogous addition of nucleophiles into unsaturated platinum carbenes to generate vicinal bisheterocycles.



Scheme 5.2.3. Proposed Double Heterocyclization.

5.3 Platinum Catalyzed Synthesis of Vicinal Bisheterocycles: Blocked 1,2-H Migration

5.3.1 Reaction Optimization

We began our optimization studies using diol **363** as our test substrate. It was believed that the inclusion of the propargylic geminal dimethyl substitution would enable the carbene to persist by blocking any potential hydrogen shift, and allowing the addition of the second hydroxyl nucleophile. Exposing diol **363** to the catalytic conditions we had developed to synthesize furans resulted in rapid consumption of the starting material (Table 5.3.1, entry 1). Although we did not observe the expected diether (**364**), we were nevertheless pleased to observe the formation of methyl acetal **365**. This result confirmed our belief that the pendant primary alcohol could

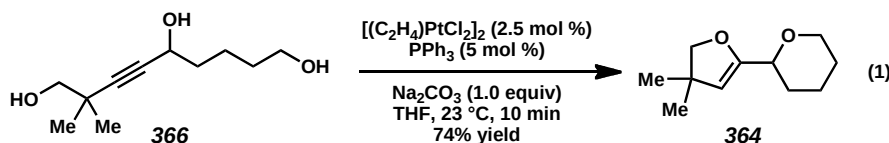
intercept the putative carbene via a vinylogous addition mechanism. We rationalized that the acetal was forming due to the mildly acidic reaction conditions engaging the enol ether. The use of pyridine bases to scrub adventitious acid resulted in variable reactivity (Table 5.3.1, entries 2, 3). The moderately coordinating 2,6-lutidine inhibited the reaction, and non-coordinating 2,6-di-*t*-butyl pyridine formed the desired bisheterocycle (**364**) in 77% yield. Various inorganic bases were also examined (Table 5.3.1, entries 4-11), leading to the formation of the desired product (**364**) in generally good yields. Other platinum sources were tested and proved to be inferior to Zeise's dimer (Table 5.3.1, entries 12, 13), producing minimal reactivity even in the presence of 1-octene. We found the inclusion of phosphines generally provided an increase in yield, with PPh₃ providing the desired bisether in 90% isolated yield (Table 5.3.1, entries 15-19). Exposing a propargylic alcohol (**366**) instead of the methyl ether to the optimized reaction conditions resulted in formation of the bisheterocycle in a diminished yield (74%), but also highlighted the versatility of this reaction (eq 1).

Table 5.3.1. Optimization of the Platinum Catalyzed Double Heterocyclization.

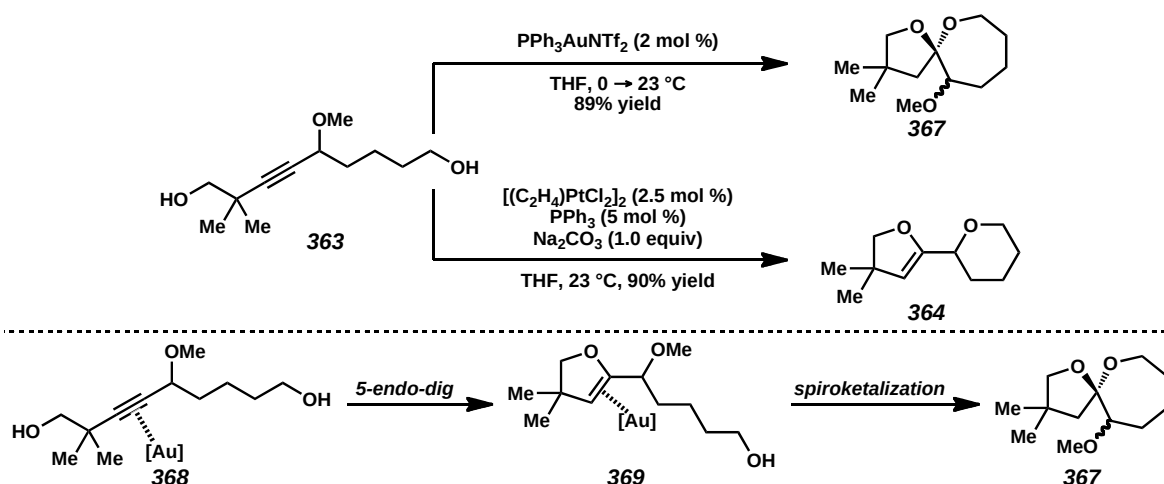
Entry	Catalyst	Ligand	Solvent	Base	Time	Yield (364:365) ^a
1	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	-	10 min	0:83 ^b
2	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	2,6-lutidine	144 h	4:0 ^c
3	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	2,6-di- <i>t</i> -Butylpyridine	10 min	77:0
4	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NaHCO ₃	10 min	57:24
5	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NH ₄ OAc	10 min	74:0
6	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NaOPiv	4 h	69:0
7	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	K ₂ CO ₃	10 min	76:0
8	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NaOAc	10 min	76:0
9	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	Cs ₂ CO ₃	20 h	76:0
10	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	K ₃ PO ₄	20 h	71:0
11	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	Na ₂ CO ₃	10 min	76:0
12	PtCl ₂ ^d	PPh ₃	THF	Na ₂ CO ₃	72 h	14:0 ^c
13	PtCl ₂ ^d	1-octene (1.0 equiv)	THF	Na ₂ CO ₃	72 h	12:0 ^c
14	[(C ₂ H ₄)PtCl ₂] ₂	-	1,4-dioxane	Na ₂ CO ₃	10 min	78:0
15	[(C ₂ H ₄)PtCl ₂] ₂	PPh ₃	1,4-dioxane	Na ₂ CO ₃	10 min	77:0
16	[(C ₂ H ₄)PtCl ₂] ₂	P(OPh) ₃	THF	Na ₂ CO ₃	10 min	65:26
17	[(C ₂ H ₄)PtCl ₂] ₂	PCy ₃	THF	Na ₂ CO ₃	10 min	84:0
18	[(C ₂ H ₄)PtCl ₂] ₂	PPh ₃	THF	Na ₂ CO ₃	10 min	90:0 ^b

^a Yield determined by ¹H NMR using 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Isolated yield.

^c Reaction did not go to completion. ^d 5 mol %.



The use of cationic gold in the double cyclization afforded the traditional product seen in these types of reactions; producing spiroketal **367** instead of the vicinal bisheterocycle (**364**) that forms under platinum catalyzed conditions (Scheme 5.3.1). Formation of the spiroketal is most likely a consequence of gold being unable to extrude the propargylic leaving group, resulting in vinyl ether formation (**369**) and subsequent ketalization. This result highlights the privileged reactivity that platinum exerts over gold in these cyclizations, implicating that platinum is a stronger π -donator than gold.¹⁴²



Scheme 5.3.1. Divergent Reactivity of $\text{Ph}_3\text{PAuNTf}_2$.

5.3.2 Scope of the Double Heterocyclizations

With optimized conditions in hand, we evaluated the scope of the double cyclizations. As depicted in Table 5.3.2, a variety of bicyclic systems can be formed with both oxygen and nitrogen based nucleophiles participating in the ring closures. With respect to bisethers, the second cyclization can be induced to form 5-, 6-, and 7-membered rings. The formation of oxepane **373** (Table 5.3.2, entry 3) is particularly notable, as the synthesis of oxepanes from linear alcohols via C–O bond formation is a traditionally challenging reaction.¹⁴³ The ease with which this ring formation occurs (10 min, 23 °C), with little entropic biasing, is reflective of the highly electrophilic reactivity of this carbene intermediate. Phenols also react to form the corresponding benzofuran products (Table 5.3.2, entry 4). Secondary hydroxyl nucleophiles generated tetrahydrofurans with modest diastereoselectivity, although a β -disubstituted carbene species was intercepted with slightly improved stereocontrol (Table 5.3.2, entries 5, 6). Six-membered ring formation with secondary hydroxyl nucleophiles resulted in the generation of *cis*-2,6-disubstituted tetrahydropyrans with excellent diastereoselectivity (Table 5.3.2, entries 7-9).

The observed selectivity is likely due to the more pronounced energy barriers observed in the closure of six vs. five membered ring systems. More remote stereocenters also encouraged reasonable levels of diastereoselection during the C–O bond formation (Table 5.3.2, entries 10, 11).¹⁴⁴

In addition to ethereal compounds, an array of nitrogen-based heterocycles can be formed via this transformation. Amides, carbamates, and sulfonamides are all competent *N*-nucleophiles toward the formation of functionalized piperidines (Table 5.3.2, entries 12-14). Additionally, indoles **397** and **399** were produced, where an *N*-Boc-aniline serves as the initial nucleophilic species for the 5-*endo* cyclization. Similar tetrahydropyran diastereoselectivities were observed when incorporating *N*-nucleophiles. Interestingly, the reaction times were only affected when the nature of the nucleophile participating in the initial ring closure was changed.

Table 5.3.2. Platinum Catalyzed Double Heterocyclizations.

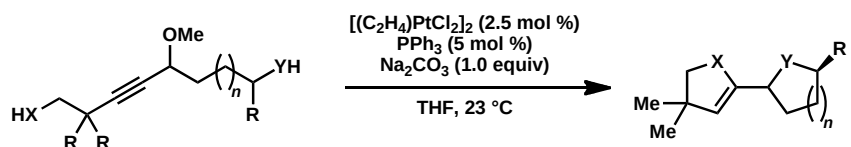
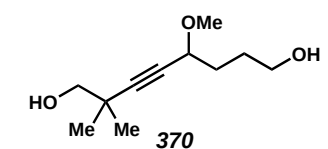
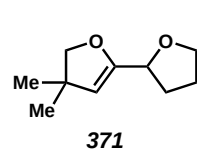
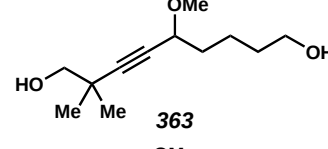
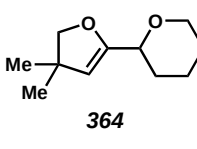
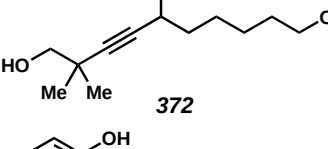
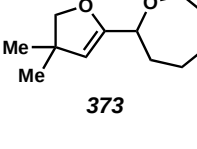
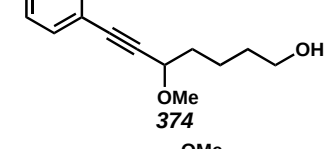
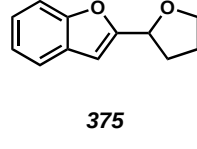
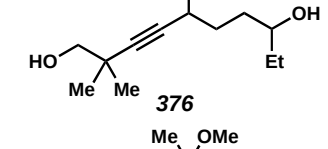
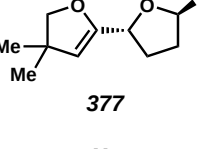
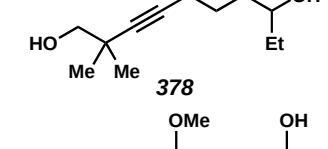
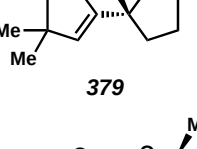
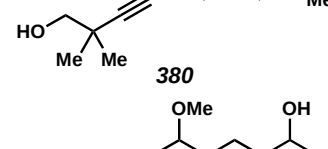
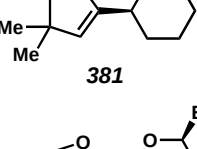
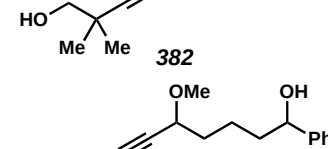
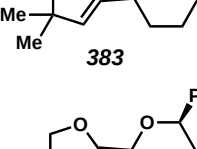
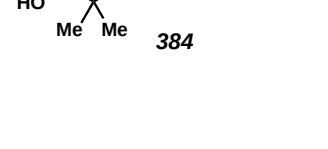
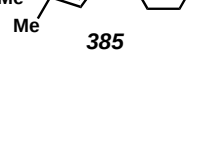
 $[(C_2H_4)_2PtCl_2]_2$ (2.5 mol %) PPh_3 (5 mol %) Na_2CO_3 (1.0 equiv) THF, 23 °C					
Entry	Substrate	Product	Time	Isol. Yield (%)	dr ^a
Diethers					
1	 370	 371	10 min	90	-
2	 363	 364	10 min	90	-
3	 372	 373	10 min	81 ^b	-
4	 374	 375	30 min	83 ^c	-
5	 376	 377	10 min	83	3 : 2
6	 378	 379	70 h	72	3 : 1
7	 380	 381	10 min	82	>19 : 1
8	 382	 383	10 min	84	17 : 1
9	 384	 385	10 min	80	>19 : 1

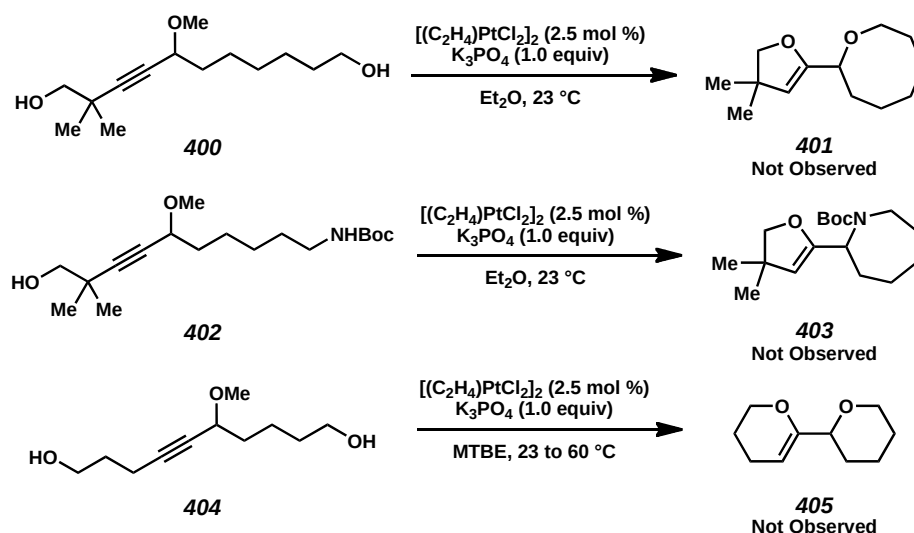
Table 5.3.2. Continued.

10			48 h	72	4 : 1
11			44 h	71	5 : 1
<i>Nitrogen Heterocycles</i>					
12			10 min	86	-
13			10 min	89	-
14			46 h	83	-
15			1.5 h	85 ^c	-
16			90 min	59 ^c	15 : 1

^a Determined by ¹H NMR. ^b Reaction performed without PPh₃ in Et₂O using K₃PO₄ as the base. ^c Reaction performed without PPh₃ or Na₂CO₃ in 1,4-dioxane.

Select alkyne substrates reflect some of the current limitations of this chemistry (Scheme 5.3.2). Both alkynes **400** and **402** did not form the expected bicyclic compounds. Presumably, the ring sizes of the oxocane and the azepane were too difficult to form via this method. The failure of diol **404** was also notable. This process would require initiation by a 6-*endo* cyclization of the

initial alcohol to allow for the formation of the unsaturated platinum carbene. It is possible that a competitive 5-*exo* cyclization onto the coordinated alkyne may be disrupting this process.

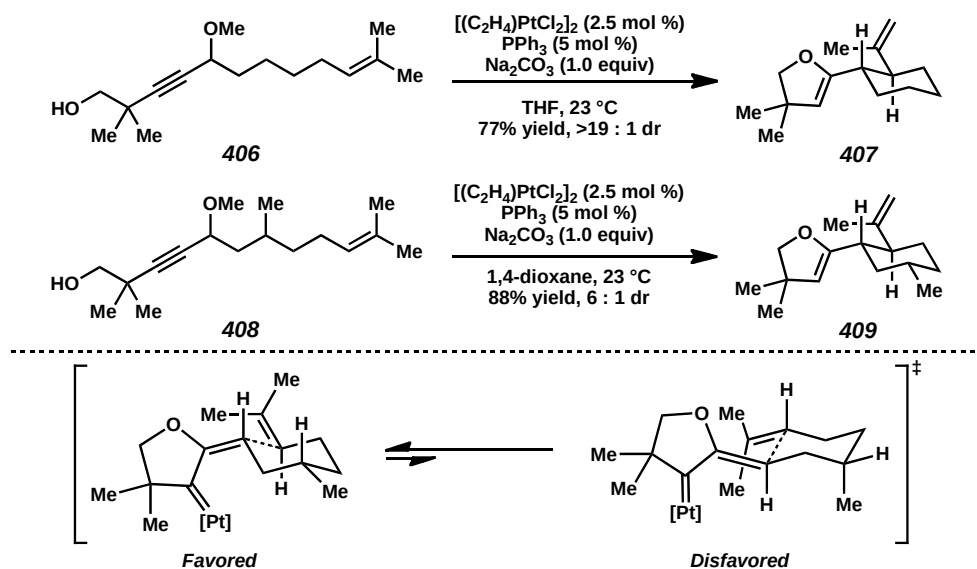


Scheme 5.3.2. Failed Double Heterocyclizations.

5.3.3 Carbon Nucleophiles

The success of relatively non-nucleophilic groups like sulfonamides to participate in the vinylogous addition led us to explore the potential for using carbon nucleophiles. Vinyl ethers have been shown to react with unsaturated platinum carbenes, resulting in formal [3 + 2] and [4 + 3] cycloadditions.¹⁴⁵ We wondered if tethered alkenes could avoid potential cycloadditions, and instead participate in the vinylogous addition to form carbocycles. Exposing alkene **406** to the reaction conditions resulted in formation of carbocycle **407** in 77% yield and >19:1 diastereoselectivity favoring the *trans* stereoisomer (Scheme 5.3.3). Remote stereocenters can also influence the diastereoselectivity of the ring closure. Subjecting alkene **408** to Zeise's dimer resulted in the formation of carbocycle **409** in 88% yield and 6:1 dr. The diastereoselectivity in this last example can be rationalized as the result of a chair-like transition state during the vinylogous addition. The favored conformation is one where the methyl group is equatorial, free

rotation around the two π -systems allows the ring closure to occur, resulting in the two hydrogen atoms being *trans* to each other. This reactivity apparently supersedes the formation of cycloadducts that form with more electron rich alkenes, differentiating our vinylogous additions from this chemistry.



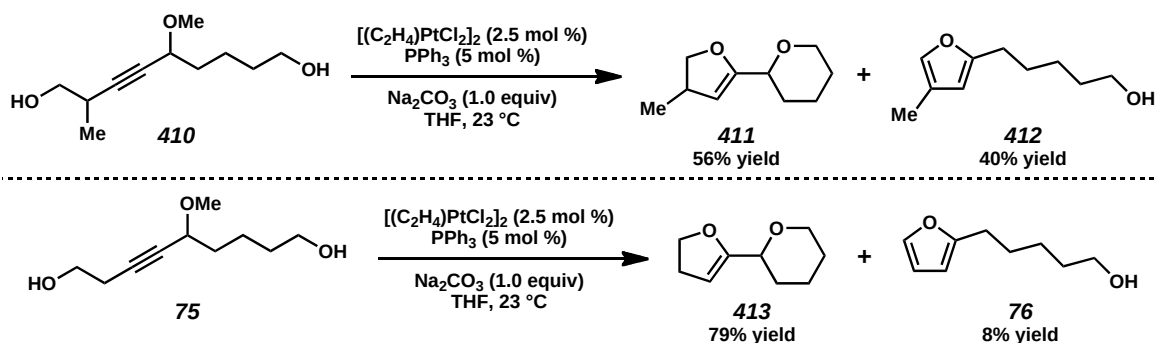
Scheme 5.3.3. Formation of Carbocycles.

5.4 Competing 1,2-H Migrations

5.4.1 Reaction Optimization

The success of the bisheterocyclizations described above prompted us to find ways to extend the versatility of this reaction. Our inclusion of groups to block any competing 1,2-H shifts allowed the vinylogous addition to be the favored process but also could limit the broader application of this method. Our fears that removing these blocking groups would restore the 1,2-H migration as the dominant pathway were well reasoned, as every substrate we had tested to date that allowed for this migration had done precisely that.¹⁴⁶ With this concern in mind, we synthesized diols **410** and **75** and exposed them to the optimized conditions for the bisheterocyclization

reaction (Scheme 5.4.1). Diol **410**, with a single methyl group in the propargylic position, gave a mixture of bisheterocycle **411** and furan **412** in 56% and 40% yields, respectively, with formation of the bisheterocycle proceeding via the desired vinylogous addition pathway, and the furan arising from undesired 1,2-H migration. Exposing diol **75** to the same conditions generated bisheterocycle **413** and furan **76** in 79% and 8% yields respectively, indicating that substitution at the propargylic position enhances the 1,2-H migration. These results were promising, and encouraged us to develop conditions that would favor vinylogous addition over the 1,2-H shift.



Scheme 5.4.1. Selectivity in 1,2-H Shifts vs. Vinylogous Addition.

The increased competition between 1,2-H migration and vinylogous addition observed as a result of methyl substitution at the propargylic position led us to select this substrate for our optimization studies (Table 5.4.1). Based on our studies of the selective 1,2-H vs. 1,2-Si migrations we concluded that strongly donating solvents and ligands favor 1,2-H migrations via a chloride dissociation-deprotonation mechanism.¹⁴⁷ Removing the phosphine ligand reduced the yields of both bisheterocycle **411** and furan **412**, and led to the observation of the hydroalkoxylation product alcohol **414** (Table 5.4.1, entry 2). At this point it became evident that conditions that limit the 1,2-H migration pathway also promote the formation of

hydroalkoxylation products, both of which compete with the desired vinylogous addition. Screening less Lewis basic solvents in the absence of a phosphine ligand produced variable results (Table 5.4.1, entries 3-6), with 1,4-dioxane reducing the amount of furan formation but increasing the yield of alcohol **414**. Less polar solvents nearly eliminated the 1,2-H migration pathway, but also led to decomposition of the dihydrofuran rings in **411** and **414** as the methyl acetals. Using different bases in toluene provided improvements to the yield, with more soluble bases eliminating formation of the methyl acetal (Table 5.4.1, entries 7-14). While modest improvements were observed by manipulating the reaction in toluene (Table 5.4.1, entries 15-19), it wasn't until methyl *t*-butyl ether (MTBE) was used as the solvent that the selectivity began to markedly favor the vinylogous addition pathway (Table 5.4.1, entries 21-25). We found that using MTBE as the solvent, PPh₃ as the ligand and K₃PO₄ as the base provided the optimal conditions, forming bisheterocycle **411** in 66% yield by ¹H NMR, with only 6% and 3% yields of the furan and alcohol side products respectively.

Table 5.4.1. Conditions Optimization for Formation of Bisheterocycle **411**.

Reaction scheme showing the cyclization of compound **410** to form bisheterocycle **411**. Compound **410** is a diol with an internal alkyne and a methyl group. Reagents: $[(C_2H_4)PtCl_2]_2$ (2.5 mol %), ligand (5 mol %), Base (1.0 equiv), Solvent. Products **411**, **412**, and **414** are shown below.

Entry	Ligand	Solvent	Temp (°C)	Base	Time (min)	Yield (411 : 412 : 414) ^a
1	PPh ₃	THF	23	Na ₂ CO ₃	10	56:40 ^b
2	-	THF	23	Na ₂ CO ₃	10	40:22:5
3	-	1,4-dioxane	23	Na ₂ CO ₃	10	42:10:13
4	-	Et ₂ O	23	Na ₂ CO ₃	10	0:1:0 ^c
5	-	PhMe	23	Na ₂ CO ₃	10	0:1:0 ^c
6	-	PhH	23	Na ₂ CO ₃	10	0:1:0 ^c
7	-	PhMe	23	2,6-di- <i>t</i> -Butylpyridine	10	33:3:11
8	-	PhMe	23	sodium tartrate	10	0:1:0 ^c
9	-	PhMe	23	K ₂ CO ₃	10	0:1:0 ^c
10	-	PhMe	23	NaOAc	10	0:1:0 ^c
11	-	PhMe	23	K ₃ PO ₄	10	0:1:0 ^c
12	-	PhMe	23	NaOPiv	10	52:3:17
13	-	PhMe	23	NaOBz	10	51:1:14
14	-	PhMe	23	Cs ₂ CO ₃	10	50:2:13
15	PPh ₃	PhMe	23	Cs ₂ CO ₃	4 h	44:1:12
16	PPh ₃	PhMe	60	Cs ₂ CO ₃	10	56:4:9 ^d
17	-	PhMe	60	Cs ₂ CO ₃	10	59:4:9 ^d
18	-	PhMe	60	Cs ₂ CO ₃	10	53:4:9
19	PPh ₃	Et ₂ O	23	K ₃ PO ₄	16 h	46:5:3
20	PPh ₃	MTBE:PhMe (1:1)	23	K ₃ PO ₄	10	54:4:6
21	PCy ₃	MTBE	23	K ₃ PO ₄	10	49:16:7
22	P(OPh) ₃	MTBE	23	K ₃ PO ₄	10	0:15:0 ^c
23	PPh ₃	MTBE	55	K ₃ PO ₄	10	59:13:3
24	PPh ₃	MTBE	23	K ₃ PO ₄	10	66:6:3

^a Yield determined by ¹H NMR using 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Isolated yield. ^c Only methyl acetal observed by TLC and ¹H NMR. ^d Used 5Å MS.

5.4.2 Double Cyclizations, Avoiding the 1,2-H Shift

Table 5.4.2 describes our extension of the double heterocyclization reaction to include substrates where the 1,2-H shift can be competitive. A variety of polyethers were formed in good yields overall. Primary and secondary alcohols can be used as nucleophiles, with the secondary hydroxyl nucleophiles requiring longer reaction times for the initial cyclization. High

diastereoselectivities were also achieved during the closure of 2,6-disubstituted tetrahydropyrans. Finally, bridging bicycle **420** was synthesized as a highlight of how this method can be used to generate molecular complexity via this unconventional bond forming strategy.

Table 5.4.2. Platinum Catalyzed Double Heterocyclizations: Avoiding 1,2-H Shifts.

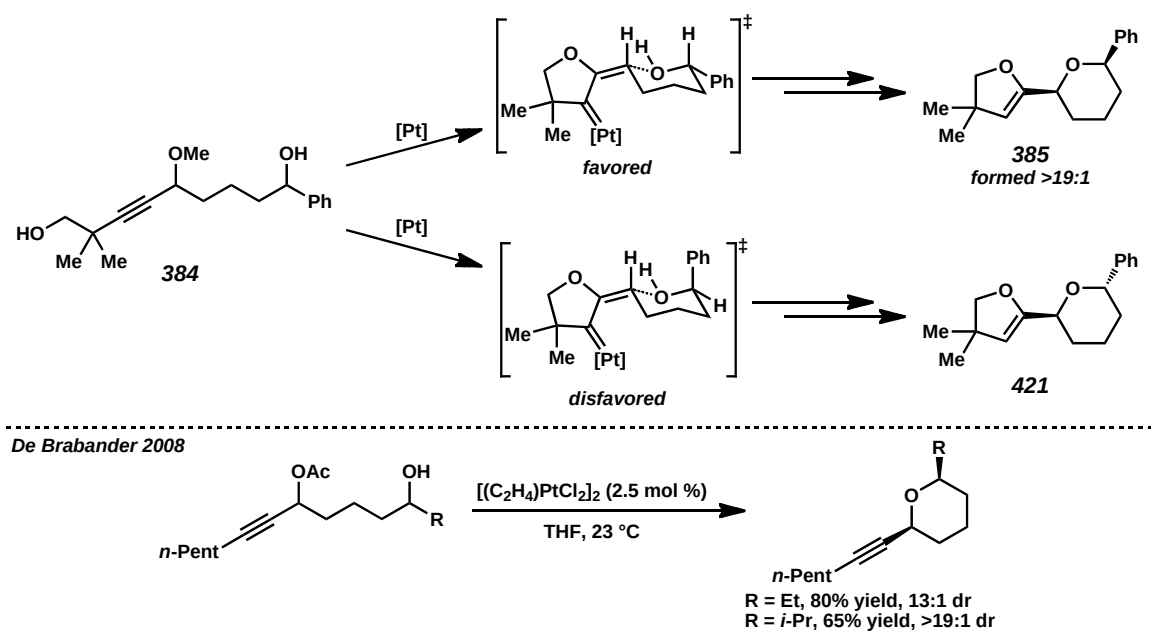
Entry	Substrate	Product	Time	Isol. Yield (%)	dr ^a
1	 410	 411	10 min	76	~ 1 : 1
2	 75	 413	10 min	85	-
3	 415	 416	10 min	81	10 : 1
4	 417	 418	14 h	74	~ 1 : 1
5	 419	 420	10 min	90	-

^a Determined by ¹H NMR.

5.4.3 Reexamining the Mechanism for Vinylogous Additions

The ability to achieve high diastereoselectivities in the 1,6-disubstituted tetrahydropyrans products is one aspect of this double cyclization that informs our understanding of the transition states of the second ring closure event. Using diol **384** as a model, we believe the closure of the

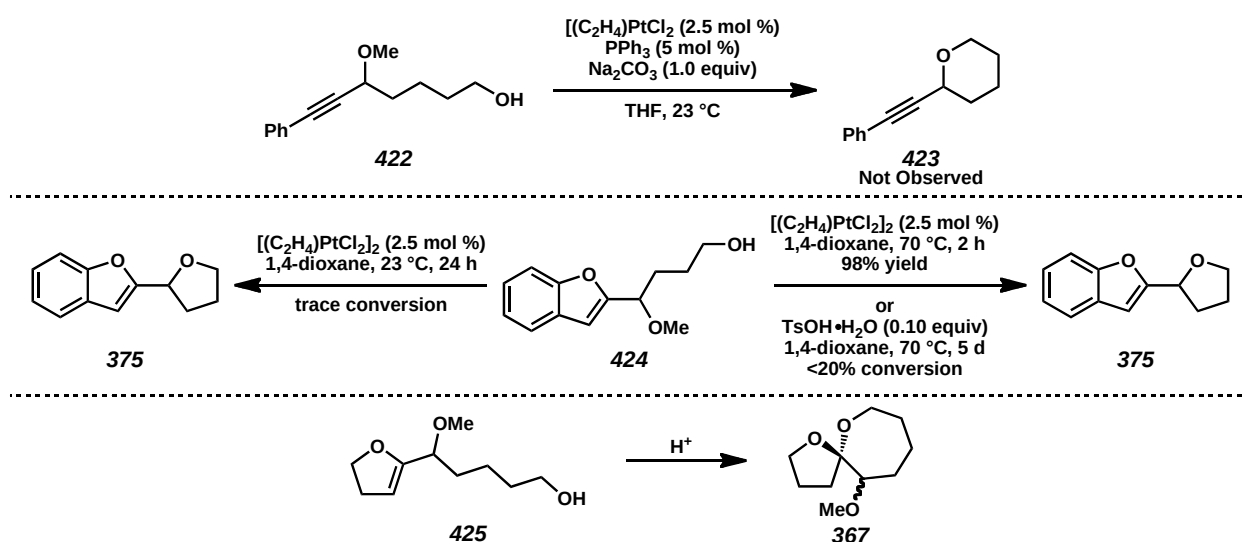
tetrahydropyran occurs through a chair-like transition state, where both the unsaturated platinum carbene and the phenyl group are in a pseudo equatorial position (Scheme 5.4.2). Addition of the hydroxyl nucleophile then proceeds via an S_N2' like addition of the hydroxyl group onto the alkene. Similar diastereoselectivities and transition states were reported by De Brabander while studying the cycloetherification reactions of ω -hydroxy propargylic esters, which also favored the formation of *cis*-2,6-disubstituted tetrahydropyrans.¹⁴⁸ Also noted in De Brabander's work was the ability of remote stereocenters to influence the diastereoselectivity of the ring closure, an observation that is consistent with the diastereoselectivity observed during the closure of carbocycle **409** (Scheme 5.3.3).



Scheme 5.4.2. Diastereoselectivity in the Closure of Tetrahydropyrans.

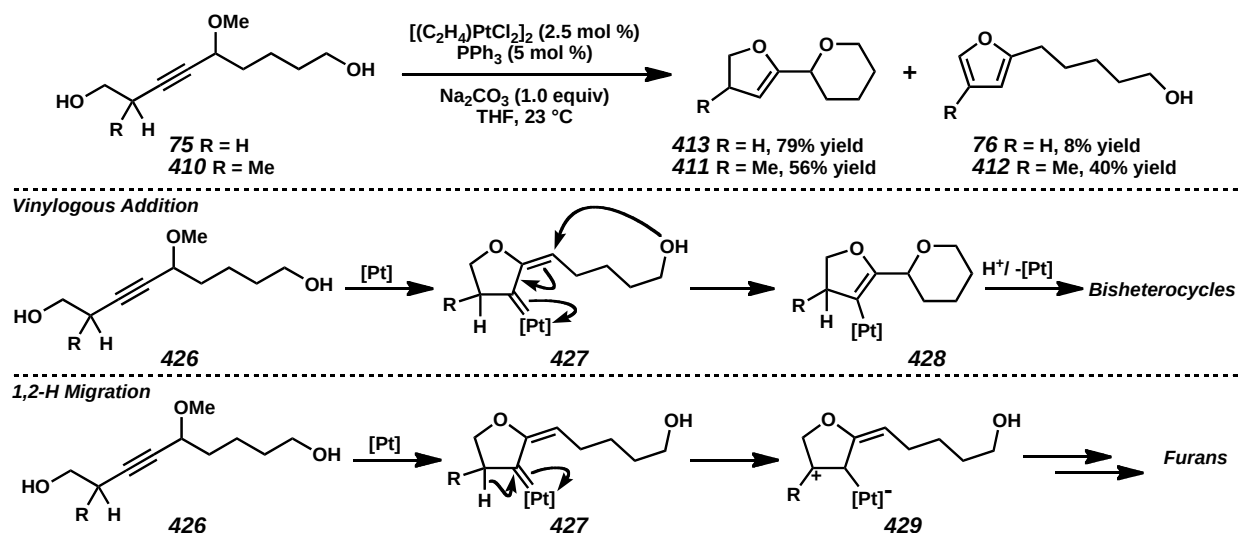
A second concern was the possibility that a simple propargylic ionization mechanism was operative under the reaction conditions.¹⁴⁹ To test this possibility we subjected alcohol **422** to the reaction conditions (Scheme 5.4.3). After 24 h no ring closure had occurred to form

tetrahydropyran **423**, supporting our belief that the second nucleophilic addition was occurring into an unsaturated platinum carbene. This observation did not hold true for aromatic systems. When benzofuran **424** was exposed to Zeise's dimer at 23 °C the expected bisheterocycle was formed in trace amounts after 24 h. This sharply contrasted the reactivity of phenol **374** (See Table 5.3.2, entry 4), which converted to bisheterocycle **375** after 10 min. Upon heating to 70 °C, the conversion of benzofuran **424** to the bisheterocycle (**375**) was remarkably efficient, proceeding in 98% yield after 2 hours. Exposing benzofuran **424** to 0.10 equiv of *p*-toluenesulfonic acid at 70 °C also promoted the closure of the tetrahydrofuran ring, though this process was considerably slower than when Zeise's dimer was used.¹⁵⁰ These last experiments highlight a fundamental difference in reactivity between the aromatic substrates and the dihydrofurans, with the tetrahydrofuran closure in the benzofurans proceeding through both an unsaturated carbene or acid catalyzed ionization of the furfurylic ether.¹⁵¹ It is unlikely that dihydrofurans are intermediates in the aliphatic substrates, as these would probably close to form ketals like **367**, as was seen when $\text{PPh}_3\text{AuNTf}_2$ was used as the catalyst (See Scheme 5.3.1).



Scheme 5.4.3. Mechanistic Considerations.

Another interesting observation that came out of these studies was the different selectivities of 1,2-H migration (as determined by formation of furans) compared to vinylogous addition (as determined by formation of bisheterocycles) in substrates bearing propargylic hydrogens (Scheme 5.4.4). Vinylogous addition was the more favored process in diol **75**, where the propargylic position was a simple CH₂ group. The inclusion of a propargylic methyl group in diol **410** led to an increased preference for 1,2-H migration, suggesting that substitution at the propargylic position enhances the migratory aptitude of the hydrogen atom. This observation is easily rationalized when comparing the mechanisms of the two competing processes. Once the unsaturated platinum carbene (**427**) forms, the reaction can either proceed through vinylogous addition of the pendant hydroxyl group to form the bisheterocycles, or undergo a 1,2-H migration leading to furan products. As discussed earlier, the 1,2-H migration is likely an asynchronous process,¹⁵² causing positive charge to develop at the propargylic position as the hydrogen migrates to the platinum carbene. The inclusion of electron donating groups (i.e. methyl) will stabilize the positive charge, and promote the 1,2-H migration more than groups like H or electron deficient groups. This enhancement of 1,2-H migrations by electron donating groups is also observed in singlet and rhodium carbenes, and it provides additional, clear evidence to support the formation of a platinum carbene during these reactions.¹⁵³

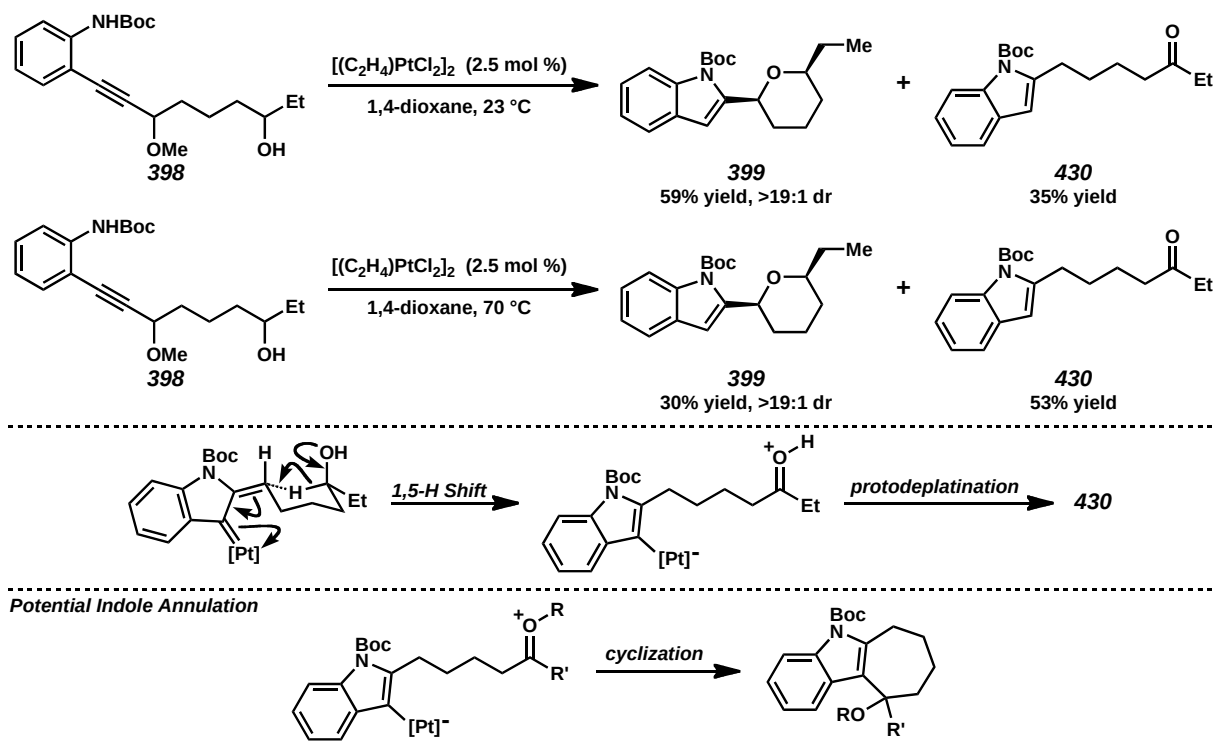


Scheme 5.4.4. Influence of Bystander Groups on 1,2-H Migrations.

5.5 Future Directions in Vinylogous Additions

5.5.1 1,5-Hydride Migrations

The ability to form the bisheterocycles described above relies on the inherent electrophilicity of the β -carbon of the unsaturated platinum carbene. This enables a variety of oxygen, nitrogen and carbon based nucleophiles to add into this position with relative ease. We observed a curious result while examining the scope of the double cyclizations (Scheme 5.5.1). When aniline **398** was exposed to Zeise's dimer and heated at 23 °C, the expected bisheterocycle (**399**) was formed in 59% yield. Also isolated from this reaction was ketone **430**, which formed in 35% yield. Elevating the temperature favored formation of the ketone over the bisheterocycle, producing each in 53% and 30% yields respectively. Our current hypothesis is that the ketone forms as the result of a 1,5-H migration into the unsaturated carbenes.¹⁵⁴ In this case, donation by the alcohol oxygen facilitates the H-migration by stabilizing the developing positive charge. This 1,5-H migration could enable the synthesis of annulated indoles via formation of an oxocarbenium, followed by nucleophilic attack by the metalated indole to close the cycloheptane ring.

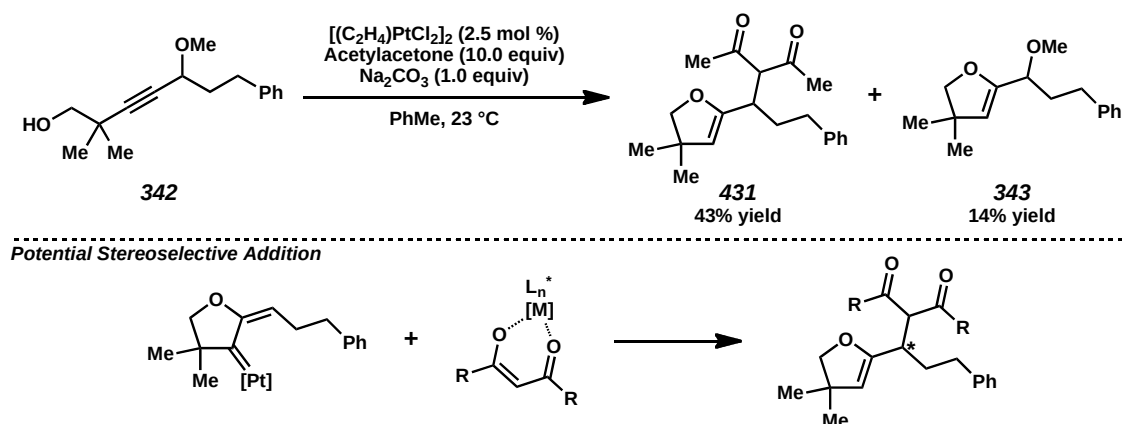


Scheme 5.5.1. 1,5-H Migrations into Unsaturated Platinum Carbenes.

5.5.2 Intermolecular Enol Ether Additions

The unsaturated carbenes that we have described thus far have primarily been used to create new carbon-heteroatom and carbon-carbon bonds via intramolecular pathways. Intermolecular C-C bond forming reactions have also been observed with this system. Exposure of alcohol **342** to Zeise's dimer in the presence of acetylacetone resulted in the isolation of vinyl ether **431** (Scheme 5.5.2). We suspect the enol ether adds into the unsaturated carbene in a vinylogous fashion to afford the product. If this mechanism is indeed operative, then we can apply conditions that activate 1,3-dicarbonyls to our system to potentially render this addition more efficient, as well as stereoselective.¹⁵⁵ The demonstration of 1,5-H migrations and enol ether additions under unoptimized conditions hints at some of the other reaction pathways that

unsaturated platinum carbenes can proceed through; highlighting their potential as useful intermediates in the construction of more complex molecules.



Scheme 5.5.2. Vinylogous Enol Addition.

5.6 Conclusion

This chapter described our early investigations into the vinylogous additions of nucleophiles into unsaturated platinum carbenes. A variety of substituted bisheterocycles were constructed using a variety of heteroatom and carbon nucleophiles. Rigorous examination of the reaction conditions enabled us to identify conditions that favored vinylogous addition over the competing 1,2-H migration pathway, allowing us to broaden the scope of this reaction. The ring closures were highly diastereoselective toward the formation of a variety of disubstituted tetrahydropyrans. Also described are early results that extend the reactivity of unsaturated platinum carbenes towards the addition of hydrides and enols.

5.7 Experimental Section

5.7.1 Materials and Methods

Reactions were performed under ambient atmosphere unless otherwise noted. Tetrahydrofuran, ether, dichloromethane and toluene were purified by passing through activated alumina columns, 1,4-dioxane was distilled over sodium/benzophenone. All other solvents used were ACS grade, and all other reagents were used as received unless otherwise noted. Zeise's Dimer, $[(C_2H_4)PtCl_2]_2$, was purchased from Strem Chemical Company. All other commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products, (West Columbia, SC), Strem (Newburyport, MA) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 μm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde or $KMnO_4$ stain solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on a Varian 400 MR (at 400 MHz), and are reported relative to $SiMe_4$ (δ 0.00). VT ^1H NMR spectra were acquired on a Varian 300 MR (at 300 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). IR spectra were obtained on NaCl plates (film) with a Bruker Tensor 27 Ft-IR or as a film on a Nicolet iS50 FT-IR. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS, low resolution mass spectrometry data were acquired on an Agilent 6100 Single Quad LC/MS.

Table 5.3.2. (Reproduced)

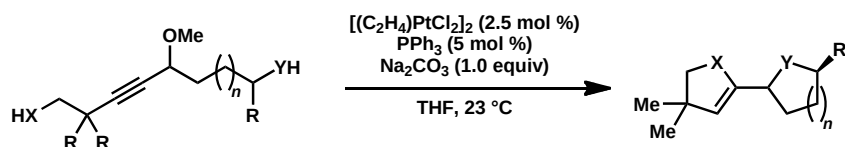
284

Table 5.3.2. *Continued.*

9			10 min	80	>19 : 1
10			48 h	72	4 : 1
11			44 h	71	5 : 1

Nitrogen Heterocycles

12			10 min	86	-
13			10 min	89	-
14			46 h	83	-
15			1.5 h	85 ^c	-
16			90 min	59 ^c	15 : 1

^a Determined by ¹H NMR. ^b Reaction performed without PPh₃ in Et₂O using K₃PO₄ as the base. ^c Reaction performed without PPh₃ or Na₂CO₃ in 1,4-dioxane.

General procedure for the platinum-catalyzed double heterocyclizations. To a solution of triphenylphosphine (5 mol %) in THF (1/3 total reaction volume) was added $[(C_2H_4)PtCl_2]_2$ (2.5 mol %). After 15 min this solution was added to a prestirred solution of the substrate (1.0 equiv) and Na_2CO_3 (1.0 equiv) in THF (2/3 reaction volume, 0.1 M in substrate final concentration). The reaction was stirred at 23 °C and monitored by TLC. Upon completion, Et_3N (100 μ L) was added, and the solution was filtered through a SiO_2 (neutralized with 1% Et_3N) plug, washing with Et_2O (2x reaction volume). The solvent was then removed by rotary evaporation, and the resulting residue was purified by flash chromatography on SiO_2 (neutralized with 1% Et_3N).

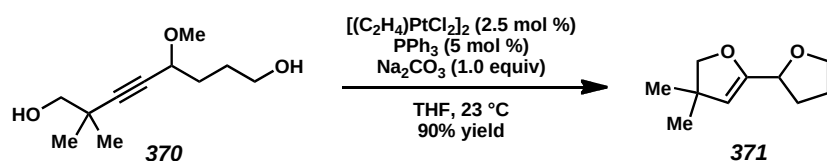


Table 5.3.2, Entry 1. According to the general procedure, to a solution of triphenylphosphine (6.6 mg, 0.0250 mmol) in THF (2.50 mL) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (7.3 mg, 0.0125 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **370** (100 mg, 0.500 mmol) and Na_2CO_3 (106 mg, 0.500 mmol) in THF (2.50 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μ L) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with Et_3N) affording diether **371** (75.8 mg, 90% yield, R_f = 0.58 in 9:1 hexanes/ $EtOAc$) as a colorless oil.

Diether 371: ^1H NMR (400 MHz, C_6D_6) δ 4.80 (s, 1H), 4.50 (t, J = 6.8 Hz, 1H), 3.88 (s, 2H), 3.84 (dt, J = 8.0, 6.4 Hz, 1H), 3.65-3.59 (m, 1H), 1.92-1.84 (m, 1H), 1.82-1.62 (comp m, 2H),

1.51-1.41 (m, 1H), 0.97 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.4, 106.9, 83.1, 74.6, 68.4, 42.8, 30.3, 27.90, 27.87, 26.0; IR (film) 2958, 1670, 1461, 1198, 1078, 995 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+ [\text{C}_{10}\text{H}_{16}\text{O}_2 + \text{H}]^+$: 169.1, found 169.1.

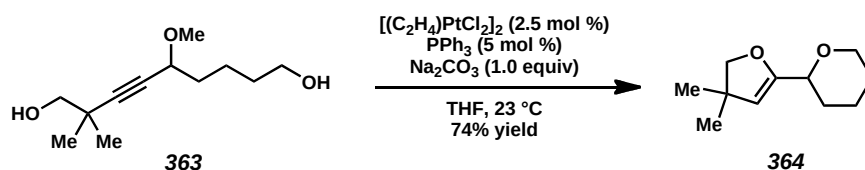


Table 5.3.2, Entry 2. According to the general procedure, to a solution of triphenylphosphine (6.6 mg, 0.0250 mmol) in THF (2.50 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (7.3 mg, 0.0125 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **363** (107 mg, 0.500 mmol) and Na_2CO_3 (53.0 mg, 0.500 mmol) in THF (2.50 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **364** (81.9 mg, 90% yield, R_f = 0.57 in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 364: ^1H NMR (400 MHz, C_6D_6) δ 4.91 (d, J = 1.1 Hz, 1H), 3.92-3.87 (m, 2H), 3.89 (s, 1H), 3.22 (td, J = 11.7, 2.4 Hz, 1H), 1.85-1.78 (m, 1H), 1.63-1.51 (m, 2H), 1.47-1.35 (m, 1H), 1.18-1.14 (m, 1H), 1.13-1.06 (m, 1H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.3, 106.1, 82.9, 74.2, 68.3, 42.9, 30.4, 28.0, 27.9, 26.3, 23.4; IR (film) 2954, 1672, 1461, 1197, 1095, 895 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+ [\text{C}_{11}\text{H}_{18}\text{O}_2 + \text{H}]^+$: 183.1, found 183.1.

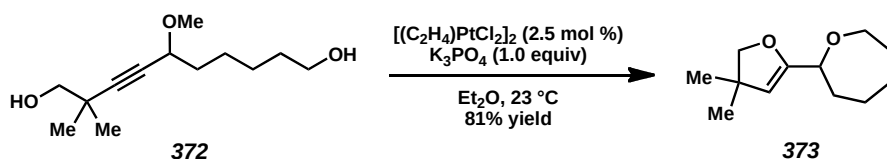


Table 5.3.2, Entry 3. To a solution of diol **372** (91.2 mg, 0.400 mmol) and K_3PO_4 (84.8 mg, 0.400 mmol) in Et_2O (4.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **373** (63.2 mg, 81% yield, $R_f = 0.62$ in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 373: ^1H NMR (400 MHz, C_6D_6) δ 4.88 (d, $J = 1.2$ Hz, 1H), 4.17 (qd, $J = 4.4, 1.2$ Hz, 1H), 3.90 (s, 2H), 3.81-3.75 (m, 1H), 3.49-3.43 (m, 1H), 1.98-1.91 (m, 1H), 1.86-1.77 (m, 1H), 1.68-1.61 (m, 1H), 1.57-1.50 (m, 1H), 1.45-1.33 (m, 4H), 1.00 (d, $J = 0.9$ Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.0, 106.4, 83.0, 75.1, 67.8, 42.8, 33.7, 31.6, 28.0, 27.9, 27.8, 25.7; IR (film) 2927, 2360, 1668, 1460, 1121, 1030, 995 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{12}\text{H}_{20}\text{O}_2 + \text{Na}$] $^+$: 219.2, found 219.1.

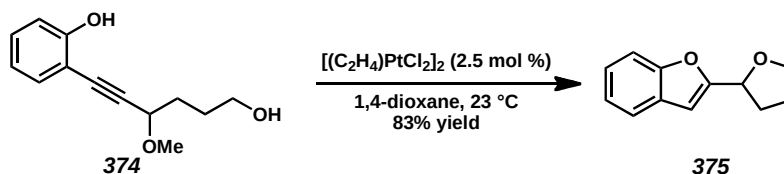


Table 5.3.2, Entry 4. To a solution of phenol **374** (114 mg, 0.518 mmol) in 1,4-dioxane (5.18 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (7.6 mg, 0.0130 mmol), and the resulting solution was stirred at 23 °C for 30 min. Upon completion, the reaction was filtered through a plug of silica

gel (0.5 x 2.0 cm), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording benzofuran **375** (80.2 mg, 83% yield, *R*_f = 0.40 in 9:1 hexanes/EtOAc) as a pale brown oil.

Benzofuran 375: ¹H NMR (400 MHz, C₆D₆) δ 7.38-7.34 (comp m, 2H), 7.10-7.02 (comp m, 2H), 6.45 (t, *J* = 0.9 Hz, 1H), 4.90 (t, *J* = 6.8 Hz, 1H), 3.85-3.80 (m, 1H), 3.63 (td, *J* = 7.6, 6.0 Hz, 1H), 1.94-1.76 (comp m, 2H), 1.68-1.57 (m, 1H), 1.50-1.40 (m, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 159.5, 155.6, 128.9, 124.2, 123.0, 121.2, 111.5, 103.0, 74.6, 68.5, 31.1, 26.0; IR (film) 2978, 1453, 1253, 1169, 1053, 751 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₂H₁₂O₂ + H]⁺: 189.0, found 188.9.

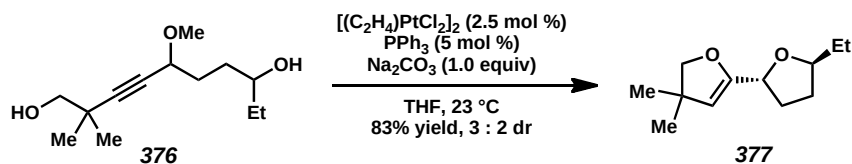


Table 5.3.2, Entry 5. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in THF (2.00 mL) at 23 °C was added [(C₂H₄)PtCl₂]₂ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **376** (91.2 mg, 0.400 mmol) and Na₂CO₃ (42.4 mg, 0.400 mmol) in THF (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et₃N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂ neutralized with 1% Et₃N) affording diether **377** (65.4 mg, 83% yield, 3:2 dr, *R*_f = 0.58 in 9:1 hexanes/EtOAc) as a colorless oil.

Diether 377: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, C_6D_6) δ 4.84 (s, 0.4H), 4.78 (s, 0.6H), 4.60 (t, J = 6.9 Hz, 0.6H), 4.49 (dd, J = 7.6, 6.0 Hz, 0.4H), 4.00 (quintet, J = 6.8 Hz, 0.6H), 3.88 (s, 2H), 3.69-3.61 (m, 0.4H), 2.02-1.76 (comp m, 2.5H), 1.76-1.64 (m, 0.4H), 1.65-1.54 (m, 1H), 1.50-1.32 (comp m, 1.5H), 1.27-1.18 (m, 0.6H), 0.97 (s, 6H), 0.93 (t, J = 7.6 Hz, 1.2H), 0.89 (t, J = 7.6 Hz, 1.8H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.8, 107.0, 106.7, 83.14, 83.13, 81.7, 81.0, 74.8, 74.4, 42.8, 31.6, 31.0, 30.6, 30.5, 29.2, 29.1, 27.92, 27.90, 27.8, 10.9, 10.7; IR (film) 2931, 1462, 1336, 1060, 966 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{12}\text{H}_{20}\text{O}_2 + \text{H}$] $^+$: 197.1, found 197.1.

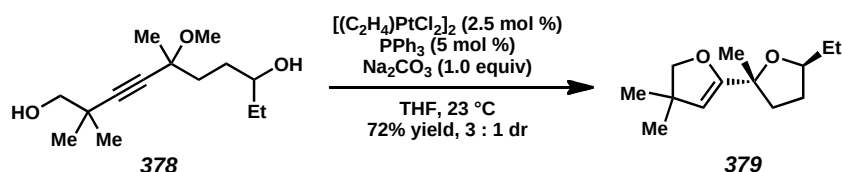


Table 5.3.2, Entry 6. According to the general procedure, to a solution of triphenylphosphine (3.9 mg, 0.0150 mmol) in THF (1.50 mL) at 23 $^\circ\text{C}$ was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **378** (72.7 mg, 0.300 mmol) and Na_2CO_3 (31.8 mg, 0.300 mmol) in THF (1.50 mL, 0.1 M final concentration). The reaction was stirred at 23 $^\circ\text{C}$ for 70 h. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **379** (45.3 mg, 72% yield, 3:1 dr, R_f = 0.59 in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 379: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, C_6D_6) δ 4.89 (s, 0.25H), 4.81 (s, 0.75H), 4.02 (quintet, $J = 6.6$ Hz, 0.75H), 3.88 (s, 2H), 3.85-3.76 (m, 0.25H), 2.26-2.19 (m, 1H), 1.87-1.53 (comp m, 4H), 1.52 (s, 3H), 1.48-1.26 (comp m, 2H), 0.98 (s, 6H), 0.97-0.89 (comp m, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 162.5, 161.9, 105.7, 105.1, 83.3, 83.2, 83.1, 81.2, 81.1, 80.3, 42.8, 37.4, 36.4, 32.0, 31.6, 31.3, 30.5, 29.6, 27.93, 27.90, 27.88, 26.8, 26.3, 11.0, 10.6; IR (film) 2960, 1663, 1461, 1363, 1113, 1073, 980 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{13}\text{H}_{22}\text{O}_2 + \text{H}$] $^+$: 211.1, found 211.0.

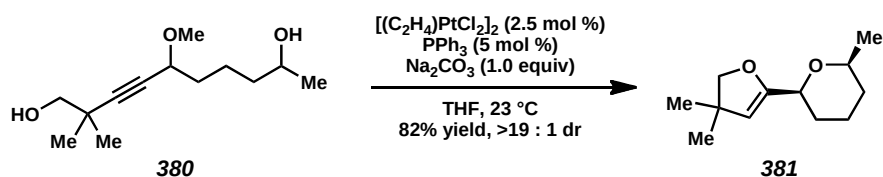


Table 5.3.2, Entry 7. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in THF (2.00 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **380** (91.2 mg, 0.400 mmol) and Na_2CO_3 (42.0 mg, 0.400 mmol) in THF (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **381** (64.5 mg, 82% yield, >19:1 dr, $R_f = 0.50$ in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 381: ^1H NMR (400 MHz, C_6D_6) δ 4.94 (d, $J = 1.2$ Hz, 1H), 3.99-3.96 (m, 1H), 3.92 (s, 2H), 3.32-3.24 (m, 1H), 1.88-1.82 (m, 1H), 1.62-1.55 (comp m, 2H), 1.53-1.49 (m, 1H), 1.28-

1.20 (comp m, 2H), 1.18 (d, $J = 6.4$ Hz, 3H), 1.01 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.4, 106.0, 82.9, 74.3, 74.2, 42.8, 33.4, 29.9, 27.99, 27.97, 23.8, 22.5; IR (film) 3369, 2931, 2232, 1461, 1336, 1055 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{12}\text{H}_{20}\text{O}_2 + \text{H}$] $^+$: 197.1536, found 197.1530.

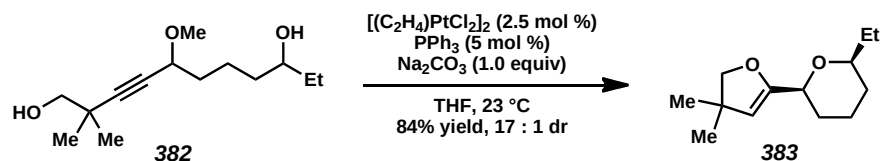


Table 5.3.2, Entry 8. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in THF (2.00 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **382** (96.9 mg, 0.400 mmol) and Na_2CO_3 (42.0 mg, 0.400 mmol) in THF (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μL) was added, and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **383** (70.9 mg, 84% yield, 17:1 dr, $R_f = 0.54$ in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 383: ^1H NMR (400 MHz, C_6D_6) δ 4.92 (d, $J = 1.2$ Hz, 1H), 3.96 (ddd, $J = 11.2, 2.4, 1.2$ Hz, 1H), 3.90 (s, 2H), 3.07 (dddd, $J = 10.8, 7.1, 5.2, 1.2$ Hz, 1H), 1.88-1.83 (m, 1H), 1.65-1.56 (comp m, 2H), 1.55-1.48 (m, 1H), 1.45-1.34 (m, 1H), 1.31-1.20 (m, 2H), 1.16-1.05 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.94 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.5, 105.9, 82.9, 79.4, 74.3, 42.8, 31.2, 30.3, 29.8, 28.1, 28.0, 23.7, 10.2; IR (film) 2936, 1673, 1461, 1199, 1097, 1004 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{13}\text{H}_{22}\text{O}_2 + \text{H}$] $^+$: 211.1693, found 211.1690.

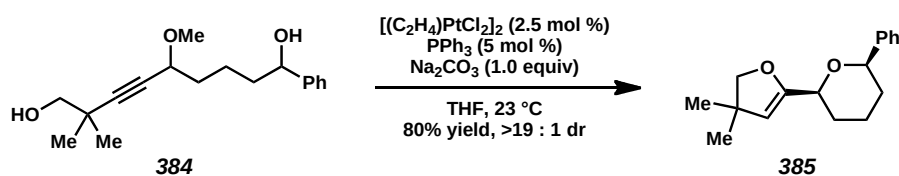


Table 5.3.2, Entry 9. According to the general procedure, to a solution of triphenylphosphine (3.5 mg, 0.0133 mmol) in THF (1.33 mL) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (3.9 mg, 0.00665 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **384** (77.2 mg, 0.266 mmol) and Na_2CO_3 (28.2 mg, 0.266 mmol) in THF (1.33 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μ L) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with 1% Et_3N) affording diether **385** (54.7 mg, 80% yield, > 19:1 dr, R_f = 0.49 in 9:1 hexanes/ $EtOAc$) as a colorless oil.

Diether 385: ^1H NMR (400 MHz, C_6D_6) δ 7.42-7.40 (comp m, 2H), 7.22-7.19 (comp m, 2H), 7.13-7.08 (m, 1H), 4.97 (d, J = 1.2 Hz, 1H), 4.23 (dd, J = 10.8, 2.4 Hz, 1H), 4.09 (ddd, J = 11.2, 2.4, 1.2 Hz, 1H), 3.93 (s, 2H), 1.93-1.87 (m, 1H), 1.64-1.53 (comp m, 3H), 1.48-1.30 (comp m, 2H), 1.02 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.2, 144.0, 128.4, 127.4, 126.2, 106.1, 83.0, 80.0, 74.7, 42.9, 34.3, 29.9, 28.03, 27.96, 24.0; IR (film) 2953, 1673, 1496, 1192, 1096, 1046, 751 cm^{-1} ; HRMS (ESI $^+$) m/z calc'd for $(M + H)^+$ [$C_{17}H_{22}O_2 + H$] $^+$: 259.1693, found 259.1692.

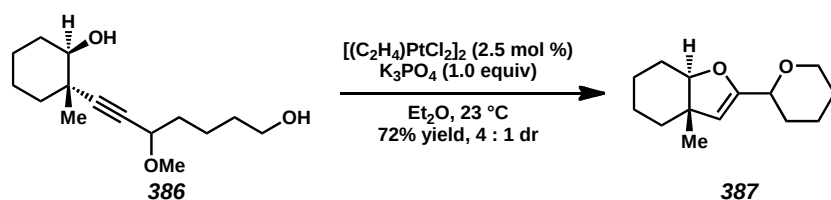


Table 5.3.2, Entry 10. To a solution of diol **386** (102 mg, 0.400 mmol) and K_3PO_4 (84.8 mg, 0.400 mmol) in Et_2O (4.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (9.4 mg, 0.0160 mmol), and the resulting solution was stirred at 23 °C for 48 h. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **387** (64.3 mg, 72% yield, 4:1 dr, R_f = 0.39 in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 387: ^1H NMR (400 MHz, C_6D_6 , major diastereomer only) δ 5.31 (s, 1H), 3.94-3.88 (comp m, 2H), 3.67 (dd, J = 12.8, 3.6 Hz, 1H), 3.23 (td, J = 11.6, 2.4 Hz, 1H), 1.90-1.79 (comp m, 2H), 1.75-1.62 (comp m, 2H), 1.60-1.48 (comp m, 3H), 1.46-1.36 (comp m, 2H), 1.29-1.17 (comp m, 3H), 1.15-1.06 (comp m, 2H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.4, 110.7, 90.4, 74.7, 68.3, 44.5, 34.8, 30.6, 26.3, 25.0, 24.5, 23.5, 21.3, 17.7; IR (film) 2933, 1639, 1442, 1200, 1085, 1046, 902 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{14}\text{H}_{22}\text{O}_2 + \text{Na}$] $^+$: 255.2, found 255.2.

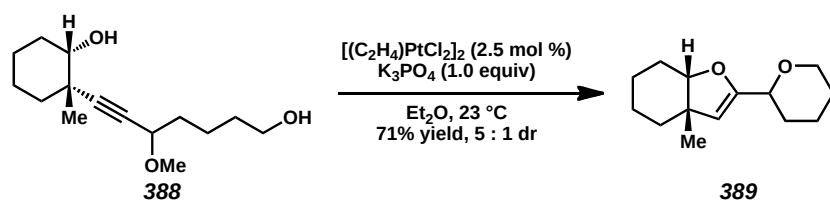


Table 5.3.2, Entry 11. To a solution of diol **388** (102 mg, 0.400 mmol) and K_3PO_4 (84.8 mg, 0.400 mmol) in Et_2O (4.00 mL, 0.1 M) was added $[(C_2H_4)PtCl_2]_2$ (9.4 mg, 0.0160 mmol), and the resulting solution was stirred at 23 °C for 44 h. Upon completion, Et_3N (100 μ L) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with 1% Et_3N) affording diether **389** (63.1 mg, 71% yield, 5:1 dr, R_f = 0.37 in 9:1 hexanes/ $EtOAc$) as a colorless oil.

Diether 389: ^1H NMR (400 MHz, C_6D_6 , major diastereomer only) δ 5.30 (s, 1H), 3.94-3.88 (comp m, 2H), 3.66 (dd, J = 12.8, 3.5 Hz, 1H), 3.23 (td, J = 11.6, 2.4 Hz, 1H), 1.90-1.78 (comp m, 2H), 1.75-1.62 (comp m, 2H), 1.59-1.47 (comp m, 3H), 1.46-1.36 (comp m, 2H), 1.28-1.17 (comp m, 3H), 1.14-1.07 (comp m, 2H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.4, 110.7, 90.4, 74.7, 68.4, 44.5, 34.8, 30.6, 26.3, 25.0, 24.5, 23.5, 21.3, 17.7; IR (film) 2933, 1639, 1453, 1371, 1200, 1085, 1038, 902 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(M + H)^+$ [$C_{14}H_{22}O_2 + H$] $^+$: 223.1, found 223.0.

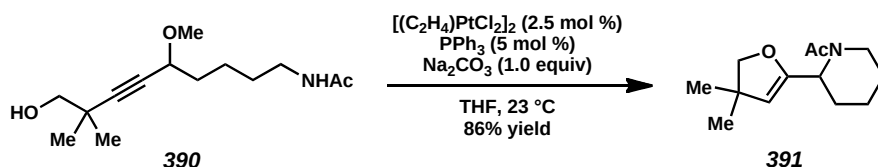


Table 5.3.2, Entry 12. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in THF (2.00 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of acetamide **390** (102 mg, 0.400 mmol) and Na_2CO_3 (42.4 mg, 0.400 mmol) in THF (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (2:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording piperidine **391** (76.4 mg, 86% yield, $R_f = 0.30$ in 1:1 hexanes/ EtOAc) as a colorless oil.

Piperidine 391: ^1H NMR (300 MHz, C_6D_6 , 70 °C, rotamers coalesced at elevated temperature) δ 4.48 (d, $J = 1.4$ Hz, 1H), 3.79 (s, 2H), 2.82 (s, 1H), 1.93-1.92 (m, 1H), 1.88 (s, 3H), 1.63 (s, 1H), 1.45-1.30 (comp m, 5H), 1.20-1.10 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6 , 23 °C, appears as mixture of rotamers) δ 191.7, 169.3, 154.6, 108.9, 108.2, 82.8, 52.0, 46.4, 43.24, 43.15, 38.1, 28.1, 27.8, 27.6, 27.1, 26.79, 26.75, 26.2, 25.4, 21.6, 21.3, 20.6, 20.4; IR (film) 2937, 1641, 1419, 1271, 1139, 993 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ $[\text{C}_{13}\text{H}_{21}\text{NO}_2 + \text{H}]^+$: 224.1, found 224.2.

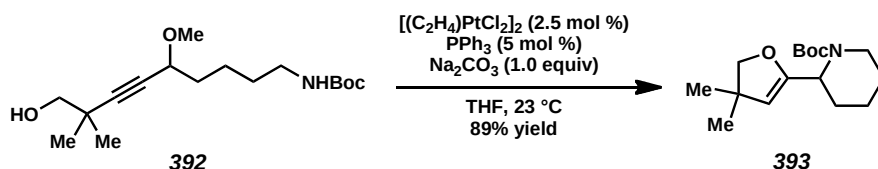


Table 5.3.2, Entry 13. According to the general procedure, to a solution of triphenylphosphine (3.9 mg, 0.0150 mmol) in THF (1.50 mL) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of carbamate **392** (93.7 mg, 0.300 mmol) and Na_2CO_3 (31.8 mg, 0.300 mmol) in THF (1.50 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μ L) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with 1% Et_3N) affording piperidine **393** (74.7 mg, 89% yield, R_f = 0.53 in 9:1 hexanes/ $EtOAc$) as a colorless oil.

Piperidine 393: ^1H NMR (300 MHz, C_6D_6 , 70 °C, rotamers coalesced at elevated temperature) δ 5.08 (br s, 1H), 4.56 (s, 1H), 4.15 (app. d, J = 13.2 Hz, 1H), 3.82 (s, 2H), 2.97 (td, J = 12.6, 3.3 Hz, 1H), 1.98-1.94 (m, 1H), 1.48 (s, 9H), 1.47-1.22 (comp m, 5H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 155.7, 108.1, 82.7, 79.0, 49.8 (broadened), 43.2, 40.7 (broadened), 28.5, 28.0, 27.8, 26.9, 25.7, 20.3; IR (film) 2934, 1694, 1404, 1248, 1161, 999 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(M + Na)^+$ [$C_{16}H_{27}NO_3 + Na$] $^+$: 304.2, found 304.2.

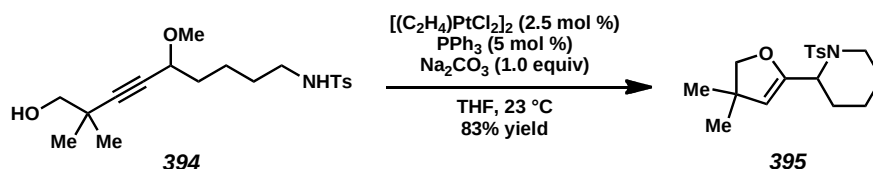


Table 5.3.2, Entry 14. According to the general procedure, to a solution of triphenylphosphine (3.9 mg, 0.0150 mmol) in THF (1.50 mL) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of sulfonamide **394** (110 mg, 0.300 mmol) and Na_2CO_3 (31.8 mg, 0.300 mmol) in THF (1.50 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 46 h. Upon completion, Et_3N (100 μ L) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ $EtOAc$ eluent, SiO_2 neutralized with 1% Et_3N) affording piperidine **395** (82.9 mg, 83% yield, R_f = 0.37 in 9:1 hexanes/ $EtOAc$) as a colorless oil.

Piperidine 395: ^1H NMR (400 MHz, C_6D_6) δ 7.78 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 8.2 Hz, 2H), 5.03 (m, 1H), 4.50 (d, J = 1.4 Hz, 1H), 3.85-3.80 (m, 1H), 3.66 (ABq, J = 8.4 Hz, $\Delta\nu$ = 31.7 Hz, 2H), 3.13-3.06 (m, 1H), 1.92 (s, 3H), 1.89-1.85 (m, 1H), 1.42-1.37 (comp m, 2H), 1.23-1.13 (comp m, 3H), 0.86 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 154.6, 142.3, 139.7, 129.5, 127.7, 109.5, 82.7, 51.1, 43.0, 42.3, 27.73, 27.71, 27.5, 25.2, 21.1, 20.0; IR (film) 3527, 2955, 1707, 1336, 1153, 1038, 733 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(M + H)^+$ [$C_{18}H_{25}NO_3S + H$] $^+$: 336.1, found 336.1.

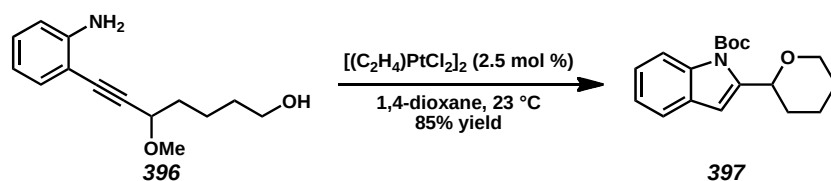


Table 5.3.2, Entry 15. To a solution of aniline **396** (100 mg, 0.300 mmol) in 1,4-dioxane (3.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was stirred at 23 °C for 1.5 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent) affording indole **397** (77.1 mg, 85% yield, R_f = 0.45 in 9:1 hexanes/ EtOAc) as a colorless oil.

Indole 397: ^1H NMR (400 MHz, CDCl_3) δ 8.08-8.06 (m, 1H), 7.50 (m, 1H), 7.27-7.17 (comp m, 2H), 6.68 (s, 1H), 5.08-5.05 (m, 1H), 4.15-4.11 (m, 1H), 3.71-3.65 (m, 1H), 2.15 (m, 1H), 1.97-1.93 (m, 1H), 1.74-1.71 (m, 1H), 1.70 (s, 9H), 1.66-1.54 (comp m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.4, 143.0, 136.7, 129.3, 123.9, 122.7, 120.6, 115.7, 106.5, 84.0, 74.4, 69.2, 32.8, 28.4, 26.2, 23.8; IR (film) 2933, 1729, 1453, 1326, 1159, 1077, 742 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ $[\text{C}_{18}\text{H}_{23}\text{NO}_3 + \text{H}]^+$: 324.1, found 323.9.

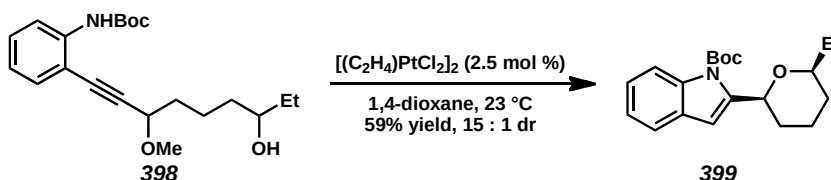
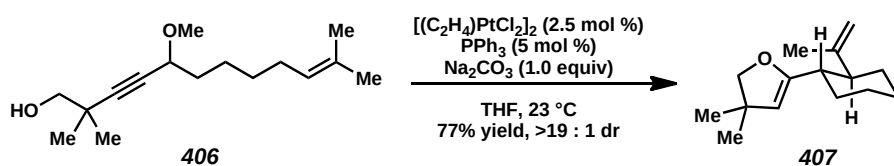


Table 5.3.2, Entry 16. To a solution of aniline **398** (72.2 mg, 0.200 mmol) in 1,4-dioxane (2.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (2.9 mg, 0.00500 mmol), and the resulting solution was stirred at 23 °C for 1.5 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm), washing with Et_2O (6 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent)

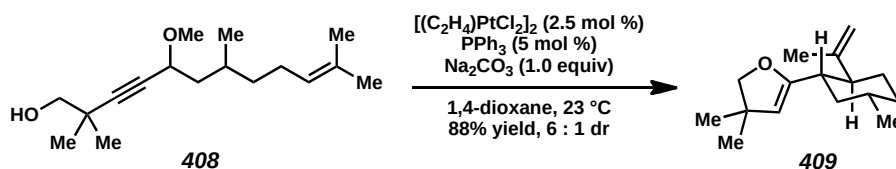
affording indole **399** (38.6 mg, 59% yield, 15:1 dr, R_f = 0.55 in 9:1 hexanes/EtOAc) as a colorless oil.

Indole 399: ^1H NMR (400 MHz, CDCl_3) δ 8.08-8.05 (m, 1H), 7.50-7.48 (m, 1H), 7.24-7.16 (comp m, 2H), 6.69 (t, J = 0.8 Hz, 1H), 5.10 (ddd, J = 10.8, 1.6, 0.8 Hz, 1H), 3.50-3.43 (m, 1H), 2.14-2.09 (m, 1H), 1.99-1.92 (m, 1H), 1.69 (s, 9H), 1.67-1.46 (comp m, 4H), 1.34-1.24 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.4, 143.1, 136.9, 129.4, 123.8, 122.7, 120.6, 115.7, 106.7, 83.9, 79.8, 73.9, 32.0, 31.2, 29.6, 28.4, 24.0, 10.2; IR (film) 2933, 1729, 1453, 1326, 1159, 1077, 742 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{20}\text{H}_{27}\text{NO}_3 + \text{Na}$] $^+$: 352.1, found 351.9.



Scheme 5.3.3. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in THF (2.00 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.00100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of alkene **406** (101 mg, 0.400 mmol) and Na_2CO_3 (42.4 mg, 0.400 mmol) in THF (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording cyclohexane **407** (68.0 mg, 77% yield, > 19:1 dr, R_f = 0.68 in 9:1 hexanes/EtOAc on basic TLC plate) as a pale yellow oil.

Cyclohexane 407: ^1H NMR (400 MHz, C_6D_6) δ 4.87 (m, 1H), 4.81 (m, 1H), 4.43 (s, 1H), 3.83 (s, 2H), 2.28 (td, $J = 11.6, 3.2$ Hz, 1H), 2.09 (td, $J = 11.6, 3.2$ Hz, 1H), 1.96-1.89 (m, 1H), 1.70 (s, 3H), 1.67-1.52 (comp m, 4H), 1.25-1.05 (comp m, 3H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.5, 149.0, 110.8, 105.7, 82.4, 49.8, 42.9, 41.1, 32.6, 31.7, 28.2, 28.1, 26.6, 26.4, 19.2; IR (film) 2929, 2361, 1662, 1449, 1002, 884 cm^{-1} ; LRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{15}\text{H}_{24}\text{O} + \text{H}$] $^+$: 221.2, found 221.2.



Scheme 5.3.3. According to the general procedure, to a solution of triphenylphosphine (1.3 mg, 0.00500 mmol) in 1,4-dioxane (0.500 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (1.5 mg, 0.00250 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of alkene **408** (26.6 mg, 0.100 mmol) and Na_2CO_3 (10.6 mg, 0.100 mmol) in 1,4-dioxane (0.500 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 30 min. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (4 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording cyclohexane **409** (20.7 mg, 88% yield, 6:1 dr, $R_f = 0.71$ in 9:1 hexanes/ EtOAc) as a pale yellow oil.

Cyclohexane 409: ^1H NMR (300 MHz, C_6D_6) δ 4.98 (m, 1H), 4.93 (m, 1H), 4.53 (s, 1H), 3.94 (s, 2H), 2.45-2.12 (comp m, 2H), 2.05-1.89 (comp m, 1H), 1.80 (s, 3H), 1.79-1.60 (comp m, 3H), 1.47-1.23 (comp m, 2H), 1.12 (s, 6H), 1.00-0.90 (comp m, 4H).

5.7.3 Double Cyclizations - Avoiding the 1,2-H Shift

Table 5.4.2. (Reproduced)

Entry	Substrate	Product	Time	Isol. Yield (%)	dr ^a
1			10 min	76	~ 1 : 1
2			10 min	85	-
3			10 min	81	10 : 1
4			14 h	74	~ 1 : 1
5			10 min	90	-

^a Determined by ¹H NMR.

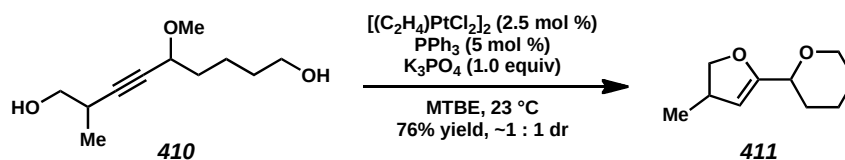


Table 5.4.2, Entry 1. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in MTBE (2.00 mL) at 23 °C was added [(C₂H₄)PtCl₂]₂ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **410** (80.0 mg, 0.400 mmol) and K₃PO₄ (84.8 mg, 0.400 mmol) in

MTBE (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et₃N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂ neutralized with 1% Et₃N) affording diether **411** (50.8 mg, 76% yield, ~1:1 dr, *R_f* = 0.45 in 9:1 hexanes/EtOAc) as a colorless oil.

Diether 411: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, C₆D₆) δ 4.98-4.95 (m, 1H), 4.25-4.20 (m, 1H), 3.93-3.87 (comp m, 2H), 3.76-3.71 (m, 1H), 3.22 (td, *J* = 11.6, 2.4 Hz, 1H), 2.84-2.74 (m, 1H), 1.87-1.80 (m, 1H), 1.64-1.52 (comp m, 2H), 1.41 (qt, *J* = 12.4, 4.0 Hz, 1H), 1.23 (tt, *J* = 12.4, 4.0 Hz, 1H), 1.12-1.05 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 159.4, 128.1, 100.8, 100.7, 77.3, 77.2, 74.2, 74.1, 68.38, 68.35, 37.43, 37.40, 30.6, 30.4, 26.3, 23.5, 23.4, 20.7; IR (film) 2953, 1670, 1452, 1201, 1094, 1005, 895 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₀H₁₆O₂ + H]⁺: 169.1, found 169.0.

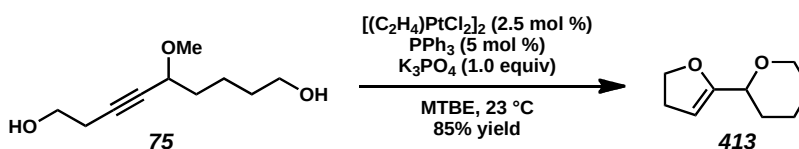


Table 5.4.2, Entry 2. According to the general procedure, to a solution of triphenylphosphine (6.6 mg, 0.0250 mmol) in MTBE (2.50 mL) at 23 °C was added [(C₂H₄)PtCl₂]₂ (7.3 mg, 0.0125 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **75** (93.0 mg, 0.500 mmol) and K₃PO₄ (106 mg, 0.500 mmol) in MTBE (2.50 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et₃N (100 μL) was added, and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent

was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂ neutralized with 1% Et₃N) affording diether **413** (65.5 mg, 85% yield, *R*_f = 0.39 in 9:1 hexanes/EtOAc) as a colorless oil.

Diether 413: ¹H NMR (400 MHz, C₆D₆) δ 4.97 (ddd, *J* = 3.6, 2.4, 1.2 Hz, 1H), 4.08 (t, *J* = 9.6 Hz, 2H), 3.94-3.87 (comp m, 2H), 3.22 (td, *J* = 11.6, 2.4 Hz, 1H), 2.33-2.27 (comp m, 2H), 1.86-1.80 (m, 1H), 1.65-1.52 (comp m, 2H), 1.41 (qt, *J* = 12.4, 4.0 Hz, 1H), 1.24-1.15 (m, 1H), 1.13-1.06 (m, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 159.9, 94.0, 74.2, 70.0, 68.4, 30.5, 30.1, 26.3, 23.4; IR (film) 2936, 1672, 1202, 1163, 1094, 898 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₉H₁₄O₂ + H]⁺: 155.1, found 155.0.

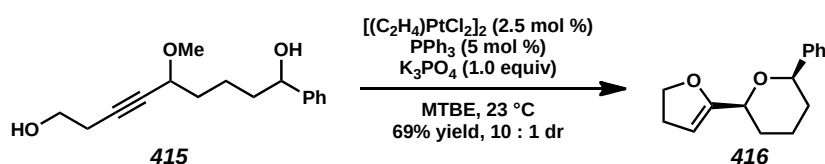


Table 5.4.2, Entry 3. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in MTBE (2.00 mL) at 23 °C was added [(C₂H₄)PtCl₂]₂ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **415** (105 mg, 0.400 mmol) and K₃PO₄ (84.8 mg, 0.400 mmol) in MTBE (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et₃N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂ neutralized with 1% Et₃N) affording diether **416** (74.5 mg, 81% yield, 10:1 dr, *R*_f = 0.47 in 9:1 hexanes/EtOAc) as a colorless oil.

Diether 416: ^1H NMR (400 MHz, C_6D_6) δ 7.42-7.40 (comp m, 2H), 7.22-7.19 (comp m, 2H), 7.13-7.09 (m, 1H), 4.99-4.98 (m, 1H), 4.23 (dd, $J = 10.8, 2.4$ Hz, 1H), 4.11 (t, $J = 9.6$ Hz, 3H), 2.35-2.30 (comp m, 2H), 1.89-1.84 (m, 1H), 1.67-1.53 (comp m, 3H), 1.47-1.30 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.7, 144.0, 128.4, 127.3, 126.2, 94.3, 80.0, 74.7, 70.1, 34.2, 30.1, 29.9, 24.0; IR (film) 2937, 1673, 1451, 1176, 1095, 1043, 931 cm^{-1} ; LRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{15}\text{H}_{18}\text{O}_2 + \text{H}$] $^+$: 253.1, found 253.1.

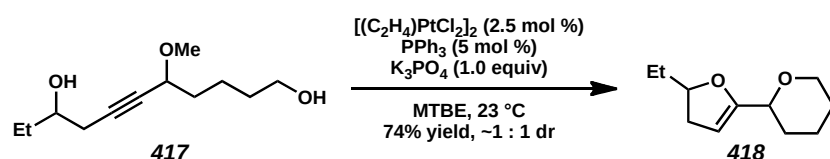


Table 5.4.2, Entry 4. To a solution of diol **417** (85.6 mg, 0.400 mmol) and K_3PO_4 (84.8 mg, 0.400 mmol) in MTBE (4.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred at 23 °C for 14 h. Upon completion, Et_3N (100 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et_3N), washing with Et_2O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent, SiO_2 neutralized with 1% Et_3N) affording diether **418** (54.1 mg, 74% yield, ~1:1 dr, $R_f = 0.47$ in 9:1 hexanes/ EtOAc) as a colorless oil.

Diether 418: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, C_6D_6) δ 4.92-4.90 (m, 1H), 4.42-4.34 (m, 1H), 3.93-3.87 (comp m, 2H), 3.22 (td, $J = 12.0, 2.4$ Hz, 1H), 2.54-2.47 (m, 1H), 2.15-2.07 (m, 1H), 1.87-1.80 (m, 1H), 1.68-1.52 (comp m, 3H), 1.47-1.36 (comp m, 2H), 1.20 (tt, $J = 12.4, 4.0$ Hz, 1H), 1.12-1.06 (m, 1H), 0.88 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.7, 158.6, 92.9, 82.8, 82.6, 73.9, 73.8, 67.93, 67.90, 34.83, 34.80, 30.1,

30.0, 29.0, 28.9, 25.9, 23.1, 23.0, 9.30, 9.25; IR (film) 2935, 1672, 1463, 1204, 1165, 1095, 901 cm^{-1} ; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₁H₁₈O₂ + H]⁺: 183.1, found 183.0.

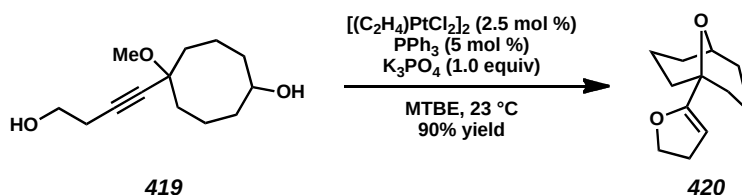
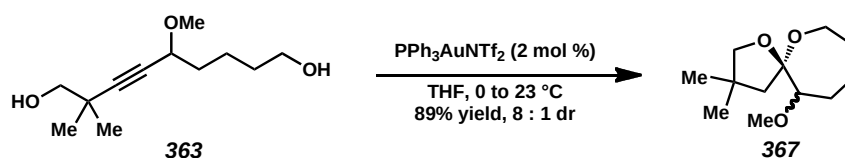


Table 5.4.2, Entry 5. According to the general procedure, to a solution of triphenylphosphine (5.2 mg, 0.0200 mmol) in MTBE (2.00 mL) at 23 °C was added [(C₂H₄)PtCl₂]₂ (5.8 mg, 0.0100 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **419** (90.4 mg, 0.400 mmol) and K₃PO₄ (84.8 mg, 0.400 mmol) in MTBE (2.00 mL, 0.1 M final concentration). The reaction was stirred at 23 °C for 10 min. Upon completion, Et₃N (100 μ L) was added and the reaction mixture was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂ neutralized with 1% Et₃N) affording diether **420** (69.9 mg, 90% yield, R_f = 0.47 in 9:1 hexanes/EtOAc) as a colorless oil.

Diether 420: ¹H NMR (400 MHz, C₆D₆) δ 5.02 (t, J = 2.4 Hz, 1H), 4.10 (app. t, J = 9.2 Hz, 3H), 2.32 (td, J = 9.2, 2.4 Hz, 2H), 2.05-1.91 (comp m, 4H), 1.89-1.77 (comp m, 4H), 1.51-1.42 (comp m, 2H), 1.25-1.20 (comp m, 2H); ¹³C NMR (100 MHz, C₆D₆) δ 165.6, 90.8, 70.3, 69.8, 67.9, 33.4, 30.0, 29.3, 19.4; IR (film) 2929, 1668, 1245, 1207, 1060, 1037, 888 cm^{-1} ; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₂H₁₈O₂ + H]⁺: 195.2, found 195.1.

5.7.4 Miscellaneous Experiments



Scheme 5.3.1: To a solution of diol **363** (42.8 mg, 0.200 mmol) in THF (2.00 mL, 0.1 M) cooled to 0 °C was added $\text{PPh}_3\text{AuNTf}_2$ (2.9 mg, 0.00400 mmol). The resulting solution was stirred at 0 °C for 1 h, then warmed to 23 °C and stirred for 1 h. Upon completion, the reaction mixture was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et_3N), washing with Et_2O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent) affording acetal **367** (38.0 mg, 89% yield, 8:1 dr, $R_f = 0.53$, $R_f = 0.45$ in 9:1 hexanes/ EtOAc) as a colorless oil.

Acetal 367: Major diastereomer. ^1H NMR (400 MHz, C_6D_6) δ 3.81-3.70 (comp m, 2H), 3.61-3.55 (comp m, 2H), 3.38-3.35 (m, 1H), 3.26 (s, 3H), 3.21 (s, 0.37H, minor diastereomer), 2.40 (d, $J = 12.8$ Hz, 1H), 1.75 (t, $J = 12.8$ Hz, 1H), 1.74-1.60 (comp m, 3H), 1.58-1.52 (m, 1H), 1.31-1.26 (m, 1H), 1.20-1.12 (m, 1H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 113.3, 85.9, 79.3, 62.4, 57.9, 47.5, 39.0, 30.3, 30.0, 28.4, 27.1, 26.4; IR (film) 2933, 1446, 1277, 1171, 1108, 1050 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{12}\text{H}_{22}\text{O}_3 + \text{H}$] $^+$: 215.1642, found 215.1648.

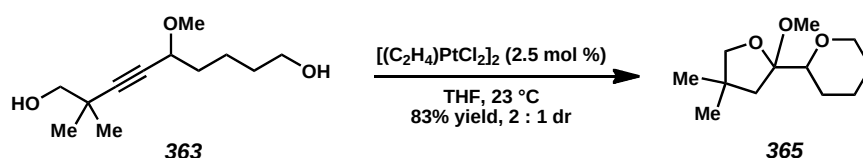
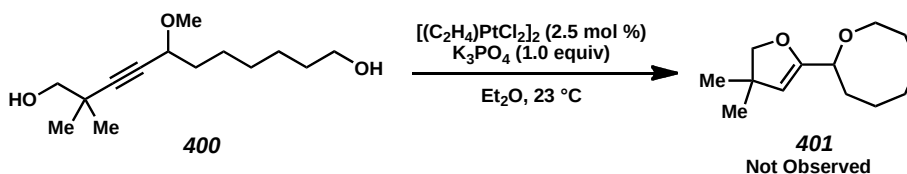


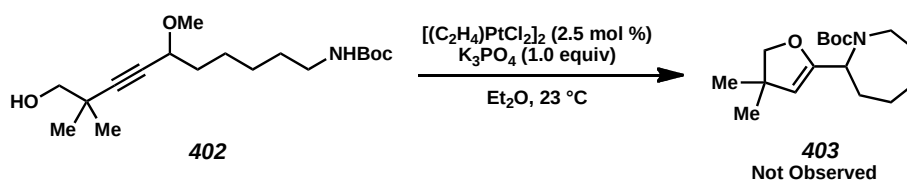
Table 5.3.1, Entry 1. To a solution of diol **363** (42.8 mg, 0.200 mmol) in THF (2.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (2.9 mg, 0.00500 mmol). The reaction mixture was stirred at 23 °C for

10 min. Upon completion, Et₃N (100 μ L) was added and the reaction was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (5 mL). The solvent was removed by rotary evaporation, and the recovered residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂ neutralized with 1% Et₃N) affording acetal **365** (35.4 mg, 83% yield, 2:1 dr, R_f = 0.37, R_f = 0.31 in 9:1 hexanes/EtOAc) as a colorless oil.

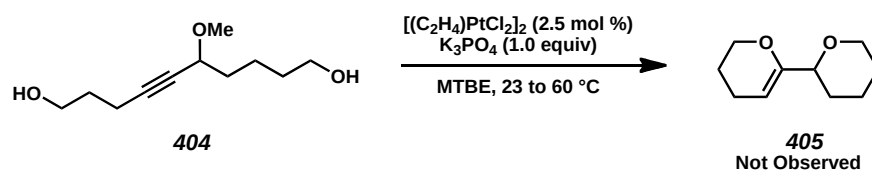
Acetal 365: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, C₆D₆) δ 3.92-3.87 (m, 1H), 3.69-3.65 (comp m, 1.66H), 3.65-3.56 (m, 1H), 3.51-3.49 (m, 0.33H), 3.34 (s, 1H), 3.27-3.23 (m, 0.33H), 3.21 (s, 2H), 3.18-3.14 (m, 0.33H), 2.28 (d, J = 12.8 Hz, 0.66H), 1.98 (ABq, J = 13.3 Hz, $\Delta\nu$ = 38.0 Hz, 1H), 1.78-1.59 (comp m, 3H), 1.47-1.17 (comp m, 3.66H), 1.12 (s, 2H), 1.09 (s, 2H), 1.06 (s, 1H), 0.97 (s, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 111.3, 111.0, 80.6, 80.2, 77.8, 77.5, 68.8, 68.6, 48.4, 48.3, 48.1, 46.6, 38.7, 38.3, 28.7, 28.1, 27.5, 27.3, 27.2, 27.0, 26.5, 26.4, 23.7; IR (film) 2955, 1465, 1206, 1090, 1044, 901 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₁₂H₂₂O₃ + Na]⁺: 237.1467, found 237.1461.



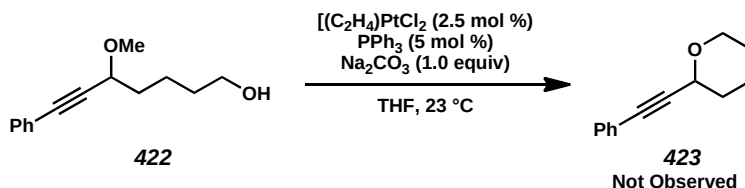
Scheme 5.3.2. To a solution of diol **400** (96.9 mg, 0.400 mmol) and K₃PO₄ (84.8 mg, 0.400 mmol) in Et₂O (4.00 mL, 0.1 M) was added [(C₂H₄)PtCl₂]₂ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred at 23 °C for 24 h, at which time no conversion to oxocane **401** was observed. Other reaction conditions were tried as well with minimal conversion of the diol. Bisheterocycle **401** was never observed.



Scheme 5.3.2. To a solution of carbamate **402** (98.1 mg, 0.300 mmol) and K_3PO_4 (63.6 mg, 0.300 mmol) in Et_2O (3.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was stirred at 23 °C for 40 h, at which time no conversion to azepane was observed. Other reaction conditions were tried as well, and compound **403** was never observed.

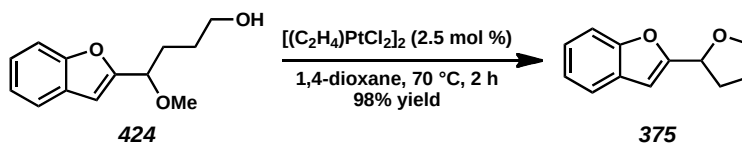


Scheme 5.3.2. To a solution of diol **404** (80.0 mg, 0.400 mmol) and K_3PO_4 (84.8 mg, 0.400 mmol) in MTBE (4.00 mL, 0.1 M) was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (5.9 mg, 0.0100 mmol), and the resulting solution was stirred at 23 °C for 96 h, at which time no conversion of starting material was observed. The reaction was heated to 60 °C for 24 h with no formation of diether **405** observed. Other reaction conditions were tried as well, and compound **405** was never observed.

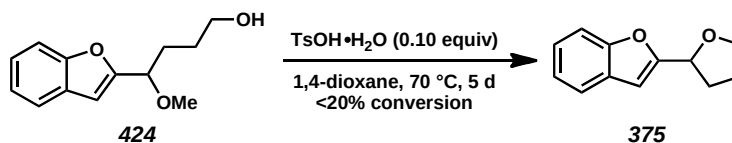


Scheme 5.4.3. To a solution of triphenylphosphine (1.3 mg, 0.00500 mmol) in THF (0.500 mL) at 23 °C was added $[(\text{C}_2\text{H}_4)\text{PtCl}_2]_2$ (1.5 mg, 0.00250 mmol) and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of alcohol **422** (21.8 mg, 0.100 mmol) and Na_2CO_3 (10.6 mg, 0.100 mmol) in THF (0.500 mL, 0.1 M final

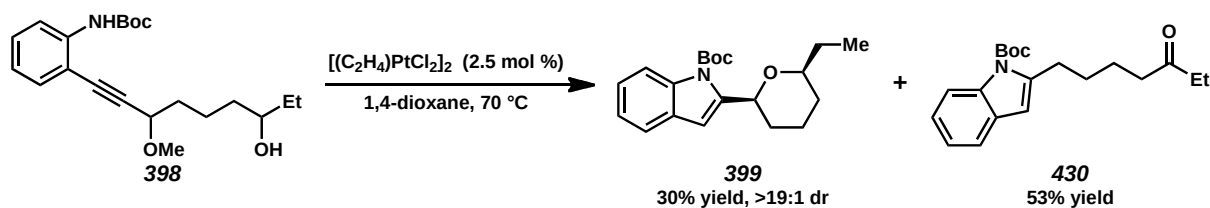
concentration). The reaction was stirred at 23 °C for 24 h. During this time minimal reaction progress was observed by TLC. Et₃N (100 μL) was added and the solution was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation. The known ether (**423**)¹⁵⁶ was not observed in the ¹H NMR of the recovered crude residue. Greater than 90% of alcohol **422** was recovered.



Scheme 5.4.3. To a solution of benzofuran **424** (66.0 mg, 0.300 mmol) in 1,4-dioxane (3.00 mL, 0.1 M) was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was heated to 70 °C for 1 h. Upon completion, the reaction was cooled to ambient temperature, and the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm, neutralized with 1% Et₃N), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent, SiO₂) affording bisheterocycle **375** (55.5 mg, 98% yield, R_f = 0.40 in 9:1 hexanes/EtOAc) as a pale brown oil.

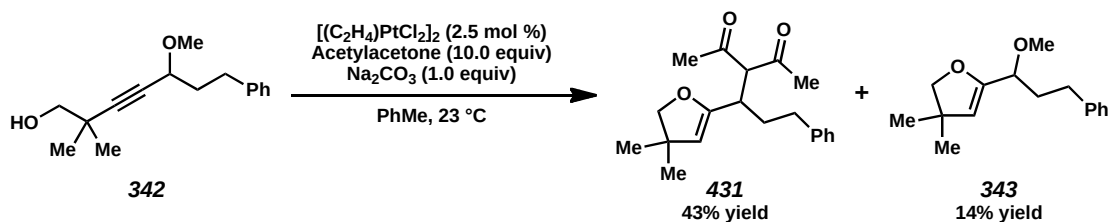


Scheme 5.4.3. To a solution of benzofuran **424** (11.0 mg, 0.0500 mmol) in 1,4-dioxane (0.500 mL, 0.1 M) was added *p*-toluenesulfonic acid (1.0 mg, 0.00500 mmol), and the resulting solution was heated to 70 °C and monitored by TLC. After 5 d some conversion to Benzofuran **375**, had occurred, but considerable starting material remained.



Scheme 5.5.1. To a solution of aniline **398** (108 mg, 0.300 mmol) in 1,4-dioxane (3.00 mL, 0.1 M) heated at 70 °C was added $[(C_2H_4)PtCl_2]_2$ (4.4 mg, 0.00750 mmol), and the resulting solution was stirred for 1 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2.0 cm), washing with Et₂O (8 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) affording indole **399** (30.1 mg, 30% yield >19:1 dr, R_f = 0.55 in 9:1 hexanes/EtOAc) as a colorless oil and indole **430** (52.0 mg, 53% yield, dr, R_f = 0.35 in 9:1 hexanes/EtOAc).

Indole 430: ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 8.2 Hz, 1H), 7.46-7.42 (m, 1H), 7.25-7.15 (comp m, 2H), 6.35 (s, 1H), 3.01 (t, J = 6.6 Hz, 2H), 2.46 (t, J = 6.7 Hz, 2H), 2.43 (q, J = 7.4 Hz, 2H), 1.70 (comp m, 4H), 1.69 (s, 9H), 1.09 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 211.7, 150.7, 142.0, 136.7, 129.4, 123.3, 122.7, 119.8, 115.7, 107.3, 83.8, 42.3, 36.1, 30.1, 28.6, 28.4, 23.7, 8.0.



Scheme 5.5.2. To a solution of alcohol **342** (49.2 mg, 0.200 mmol) in toluene (2.00 mL, 0.1 M) was added acetylacetone (0.205 mL, 2.00 mmol) and Na₂CO₃ (21.2 mg, 0.200 mmol). Zeise's dimer ($[(C_2H_4)PtCl_2]_2$, 2.9 mg, 0.0050 mmol) was added, and the resulting solution was stirred at 23 °C for 1 h. Upon completion, the reaction was filtered through a plug of silica gel (0.5 x 2.0

cm), washing with Et₂O (10 mL). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording diketone **431** (27.2 mg, 43% yield, R_f = 0.29 in 9:1 hexanes/EtOAc) as a colorless oil.

Diketone 431: ¹H NMR (400 MHz, C₆D₆) δ 7.27-7.17 (comp m, 3H), 7.13-7.05 (comp m, 2H), 4.46 (s, 1H), 3.90 (d, J = 11.0 Hz, 1H), 3.74 (q, J = 8.2 Hz, 2H), 3.20 (td, J = 11.0, 3.9 Hz, 1H), 2.71-2.66 (m, 1H), 2.59-2.48 (m, 1H), 1.91 (s, 3H), 1.74 (s, 3H), 1.80-1.64 (comp m, 2H), 0.93 (s, 3H), 0.90 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 202.3, 201.8, 155.7, 142.4, 129.14, 129.10, 126.6, 110.3, 82.9, 72.8, 43.3, 39.0, 34.1, 32.9, 29.9, 29.0, 28.1, 28.0; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₂₀H₂₆O₃ + H]⁺: 315.2, found 315.2.

5.7.5 Reaction Optimization

Table 5.3.1. (Reproduced)

Reaction scheme showing the conversion of diol **363** to products **364** and **365** using a catalyst, ligand, base, and solvent at 23 °C.

Entry	Catalyst	Ligand	Solvent	Base	Time	Yield (364:365) ^a
1	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	-	10 min	0:83 ^b
2	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	2,6-lutidine	144 h	4:0 ^c
3	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	2,6-di- <i>t</i> -Butylpyridine	10 min	77:0
4	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NaHCO ₃	10 min	57:24
5	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NH ₄ OAc	10 min	74:0
6	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NaOPiv	4 h	69:0
7	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	K ₂ CO ₃	10 min	76:0
8	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	NaOAc	10 min	76:0
9	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	CS ₂ CO ₃	20 h	76:0
10	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	K ₃ PO ₄	20 h	71:0
11	[(C ₂ H ₄)PtCl ₂] ₂	-	THF	Na ₂ CO ₃	10 min	76:0
12	PtCl ₂ ^d	PPh ₃	THF	Na ₂ CO ₃	72 h	14:0 ^c
13	PtCl ₂ ^d	1-octene (1.0 equiv)	THF	Na ₂ CO ₃	72 h	12:0 ^c
14	[(C ₂ H ₄)PtCl ₂] ₂	-	1,4-dioxane	Na ₂ CO ₃	10 min	78:0
15	[(C ₂ H ₄)PtCl ₂] ₂	PPh ₃	1,4-dioxane	Na ₂ CO ₃	10 min	77:0
16	[(C ₂ H ₄)PtCl ₂] ₂	P(OPh) ₃	THF	Na ₂ CO ₃	10 min	65:26
17	[(C ₂ H ₄)PtCl ₂] ₂	PCy ₃	THF	Na ₂ CO ₃	10 min	84:0
18	[(C ₂ H ₄)PtCl ₂] ₂	PPh ₃	THF	Na ₂ CO ₃	10 min	90:0 ^b

^a Yield determined by ¹H NMR using 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Isolated yield.

^c Reaction did not go to completion. ^d 5 mol %.

General Procedures:

Table 5.3.1, entries 2-11, 14: To a solution of diol **363** (8.5 mg, 0.0400 mmol) and 4,4'-di-*tert*-butylbiphenyl (2.6 mg, 0.0100 mmol) in THF or 1,4-dioxane (0.400 mL, 0.1M) was added the desired base (0.0400 mmol), and the mixture was stirred at 23 °C for 10 min. [(C₂H₄)PtCl₂]₂ (0.6 mg, 0.00100 mmol) was then added, and the resulting solution was stirred at ambient temperature and monitored by TLC. Upon completion, Et₃N (25 µL) was added and the reaction was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ¹H NMR.

Table 5.3.1, entry 13: To a solution of diol **363** (8.5 mg, 0.0400 mmol), 4,4'-di-*tert*-butylbiphenyl (2.6 mg, 0.0100 mmol), Na₂CO₃ (4.2 mg, 0.0400 mmol) and 1-octene (6.3 μL, 0.0400 mmol) in THF (0.400 mL, 0.1 M) was added PtCl₂ (0.5 mg, 0.00200 mmol). The resulting solution was stirred at 23 °C and monitored by TLC. After 72 h, Et₃N (25 μL) was added and the reaction was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ¹H NMR.

Table 5.3.1 entries 12, 15-18: To a solution of phosphine (0.00300 mmol) in THF or 1,4-dioxane (0.300 mL) at 23 °C was added [(C₂H₄)PtCl₂]₂ (0.9 mg, 0.00150 mmol) or PtCl₂ (0.8 mg, 0.00300 mmol) and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **363** (12.8 mg, 0.0600 mmol), Na₂CO₃ (6.4 mg, 0.0600 mmol) and 4,4'-di-*tert*-butylbiphenyl (4.0 mg, 0.0150 mmol) in THF or 1,4-dioxane (0.300 mL, 0.1 M final concentration). The reaction mixture was stirred at ambient temperature and monitored by TLC. Upon completion, Et₃N (25 μL) was added and the solution was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ¹H NMR.

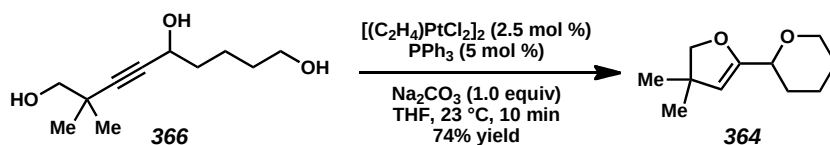


Table 4, entry 19: To a solution of triphenylphosphine (0.7 mg, 0.00250 mmol) in THF (0.250 mL) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (0.7 mg, 0.00125 mmol), and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of triol **366** (10.0 mg, 0.0500 mmol), Na_2CO_3 (5.3 mg, 0.0500 mmol) and 4,4'-di-*tert*-butylbiphenyl (6.6 mg, 0.0250 mmol) in THF (0.250 mL, 0.1 M final concentration). The reaction mixture was stirred at ambient temperature for 10 min. Upon completion, Et_3N (25 μ L) was added, and the solution was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et_3N), washing with Et_2O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ^1H NMR.

Table 5.4.1. (Reproduced)

Reaction scheme showing the cyclization of diol **410** to products **411**, **412**, and **414**. Reagents: $[(C_2H_4)PtCl_2]_2$ (2.5 mol %), ligand (5 mol %), Base (1.0 equiv), Solvent.

Entry	Ligand	Solvent	Temp (°C)	Base	Time (min)	Yield (411 : 412 : 414) ^a
1	PPh ₃	THF	23	Na ₂ CO ₃	10	56:40 ^b
2	-	THF	23	Na ₂ CO ₃	10	40:22:5
3	-	1,4-dioxane	23	Na ₂ CO ₃	10	42:10:13
4	-	Et ₂ O	23	Na ₂ CO ₃	10	0:1:0 ^c
5	-	PhMe	23	Na ₂ CO ₃	10	0:1:0 ^c
6	-	PhH	23	Na ₂ CO ₃	10	0:1:0 ^c
7	-	PhMe	23	2,6-di- <i>t</i> -Butylpyridine	10	33:3:11
8	-	PhMe	23	sodium tartrate	10	0:1:0 ^c
9	-	PhMe	23	K ₂ CO ₃	10	0:1:0 ^c
10	-	PhMe	23	NaOAc	10	0:1:0 ^c
11	-	PhMe	23	K ₃ PO ₄	10	0:1:0 ^c
12	-	PhMe	23	NaOPiv	10	52:3:17
13	-	PhMe	23	NaOBz	10	51:1:14
14	-	PhMe	23	Cs ₂ CO ₃	10	50:2:13
15	PPh ₃	PhMe	23	Cs ₂ CO ₃	4 h	44:1:12
16	PPh ₃	PhMe	60	Cs ₂ CO ₃	10	56:4:9 ^d
17	-	PhMe	60	Cs ₂ CO ₃	10	59:4:9 ^d
18	-	PhMe	60	Cs ₂ CO ₃	10	53:4:9
19	PPh ₃	Et ₂ O	23	K ₃ PO ₄	16 h	46:5:3
20	PPh ₃	MTBE:PhMe (1:1)	23	K ₃ PO ₄	10	54:4:6
21	PCy ₃	MTBE	23	K ₃ PO ₄	10	49:16:7
22	P(OPh) ₃	MTBE	23	K ₃ PO ₄	10	0:15:0 ^c
23	PPh ₃	MTBE	55	K ₃ PO ₄	10	59:13:3
24	PPh ₃	MTBE	23	K ₃ PO ₄	10	66:6:3

^a Yield determined by ¹H NMR using 4,4'-di-*tert*-butylbiphenyl as the internal standard. ^b Isolated yield. ^c Only methyl acetal observed by TLC and ¹H NMR. ^d Used 5 Å MS.

General Procedures:

Table 5, entries 2-15, 19, 20: To a solution of diol **410** (10.0 mg, 0.0500 mmol) and 4,4'-di-*tert*-butylbiphenyl (3.3 mg, 0.0125 mmol) in the desired solvent (0.500 mL, 0.1 M) was added the desired base (0.0500 mmol), and the mixture was stirred at 23 °C for 10 min. $[(C_2H_4)PtCl_2]_2$ (0.6 mg, 0.00100 mmol) was then added and the resulting solution was stirred at the desired temperature and monitored by TLC. Upon completion, Et₃N (25 µL) was added and the reaction

was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ¹H NMR.

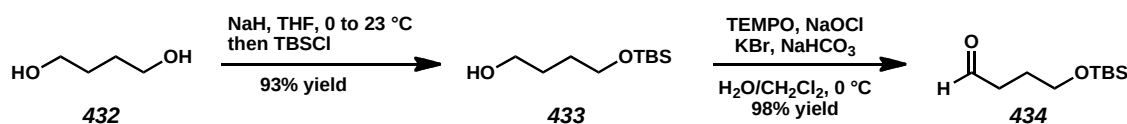
Table 5, entries 16-18, 21-26: To a solution of phosphine (0.00250 mmol) in the desired solvent (0.250 mL) under an ambient atmosphere was added [(C₂H₄)PtCl₂]₂ (0.7 mg, 0.00125 mmol) and the resulting solution was stirred for 15 min. The catalyst mixture was then added to a prestirred solution of diol **410** (10.0 mg, 0.0500 mmol), base (0.0500 mmol) and 4,4'-di-*tert*-butylbiphenyl (3.3 mg, 0.0125 mmol) in the desired solvent (0.250 mL, 0.1 M final concentration). The reaction mixture was stirred at the desired temperature and monitored by TLC. Upon completion, Et₃N (25 μL) was added and the solution was filtered through a plug of silica gel (0.5 x 1.0 cm, neutralized with 1% Et₃N), washing with Et₂O (5 mL). The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ¹H NMR.

Furan 412: ¹H NMR (400 MHz, CDCl₃) δ 7.05 (s, 1H), 5.84 (s, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 1.98 (s, 3H), 1.69-1.56 (comp m, 5H), 1.44-1.36 (comp m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 156.4, 137.4, 120.6, 107.7, 63.0, 32.6, 28.1, 27.0, 25.4, 10.0; IR (film) 3356, 2938, 1618, 1552, 1118, 1051 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₀H₁₆O₂ + H]⁺: 169.1, found 169.2.

Vinyl ether 414: Characterized as a 3:1 mixture of diastereomers. ¹H NMR (400 MHz, C₆D₆) δ 4.75 (d, *J* = 2.4 Hz, 0.25H), 4.73 (d, *J* = 2.4 Hz, 0.75H), 4.20 (t, *J* = 9.2, Hz, 1.5H), 4.18 (t, *J* = 9.2 Hz, 0.5H), 3.73-3.65 (comp m, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 3.25 (s, 2.25H), 3.24 (s, 0.75H), 2.79-2.69 (m, 1H), 1.89-1.75 (comp m, 2H), 1.59-1.48 (m, 1H), 1.46-1.36 (comp m, 3H), 0.86

(d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 157.7, 103.6, 103.5, 77.7, 77.6, 77.2, 77.1, 62.6, 56.74, 56.70, 37.4, 37.3, 33.5, 33.0, 22.22, 22.17, 20.9, 20.8; IR (film) 2422, 2938, 1996, 1662, 1453, 1091 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} - \text{OCH}_3)^+$ [$\text{C}_{11}\text{H}_{20}\text{O}_3 - \text{OCH}_3$] $^+$: 169.1, found 169.2.

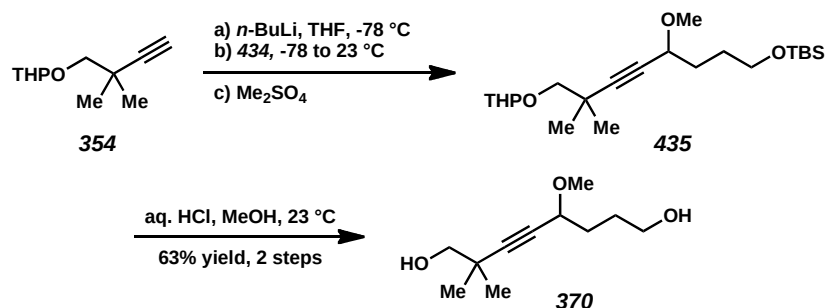
5.7.6 Substrate Synthesis



To a solution of 1,4-butanediol (**432**, 3.96 g, 44.0 mmol) in THF (220 mL, 0.2 M) at 0 °C was added NaH (1.60 g, 60% dispersion in mineral oil, 40.0 mmol). The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 2 h. TBSCl (6.03 g, 40.0 mmol) was then added and the solution was stirred at 23 °C for 14 h. The reaction mixture was poured into water (200 mL) and extracted with Et₂O (2 x 200 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent), affording alcohol **433** (7.56 g, 93% yield, $R_f = 0.20$ in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **433** (3.06 g, 15.0 mmol) in CH₂Cl₂ (37.5 mL, 0.4 M) at 0 °C was added TEMPO (23.4 mg, 0.150 mmol). A solution of KBr (1.96 g, 16.5 mmol) in 5% aq. NaHCO₃ (75.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (9.76 mL, 10% aq., 15.8 mmol) was added dropwise and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (20 mL) was added, and

the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 25 mL), and the combined organic phases were washed with H₂O (50 mL) and brine (50 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **434**¹⁵⁷ (3.02 g, 98% yield, *R*_f = 0.71 in 4:1 hexanes/EtOAc) as a pale yellow oil.

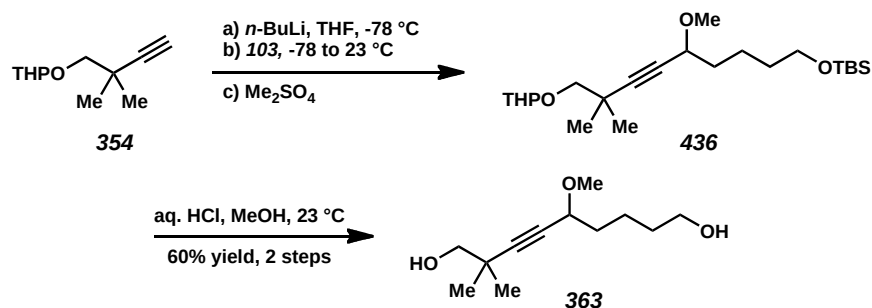


To a solution of acetal **354** (0.472 g, 2.59 mmol) in THF (7.78 mL, 0.33 M) at -78° C under argon was added *n*-BuLi (1.12 mL, 2.32 M in hexanes, 2.59 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **434** (0.524 g, 2.59 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.297 mL, 3.11 mmol) was added, and the reaction was stirred for 12 h at 23 °C. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (15 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (15 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **435** (0.967 g, *R*_f = 0.62 in 4:1 hexanes/EtOAc) as an amber oil.

To a solution of crude ether **435** (0.967 g, assumed 2.59 mmol) in MeOH (25.9 mL, 0.1 M) was added 10% aq. HCl (approx. 75 μL), and the reaction was stirred at 23 °C for 4 h. The reaction was quenched with Et₃N (approx 75 μL), and the solvent was removed via rotary evaporation.

The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:2 hexanes/EtOAc eluent) affording diol **370** (0.325 g, 63% yield over 2 steps, R_f = 0.34 in 1:2 hexanes/EtOAc) as a colorless oil.

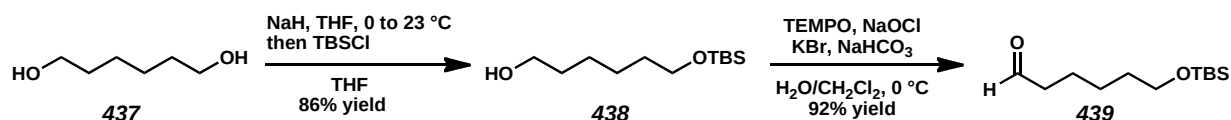
Diol 370: ^1H NMR (400 MHz, CDCl_3) δ 4.01 (t, J = 5.5 Hz, 1H), 3.67-3.64 (comp m, 2H), 3.40 (s, 2H), 3.38 (s, 3H), 2.32 (s, 2H), 1.82-1.63 (comp m, 4H), 1.20 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 92.0, 79.9, 71.8, 71.3, 62.6, 56.4, 34.4, 32.7, 28.6, 25.6; IR (film) 3385, 2934, 2236, 1448, 1336, 1055 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{11}\text{H}_{20}\text{O}_3 + \text{H}$] $^+$: 201.1, found 201.1.



To a solution of acetal **354** (1.46 g, 8.00 mmol) in THF (24.0 mL, 0.33 M) at -78°C under argon was added $n\text{-BuLi}$ (3.45 mL, 2.32 M in hexanes, 8.00 mmol), and the resulting solution was stirred for 30 min at -78°C . Aldehyde **103** (1.72 g, 8.00 mmol) was then added, and the reaction was stirred at -78°C for 10 min, then warmed to room temperature and stirred for 15 min. Me_2SO_4 (0.989 mL, 10.4 mmol) was added, and the reaction was stirred for 14 h at 23°C . The reaction was quenched with 10% aq. NH_4OH (20 mL) and stirred for 15 min. The mixture was diluted with Et_2O (30 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **436** (3.28 g, R_f = 0.72 in 4:1 hexanes/EtOAc) as an amber oil.

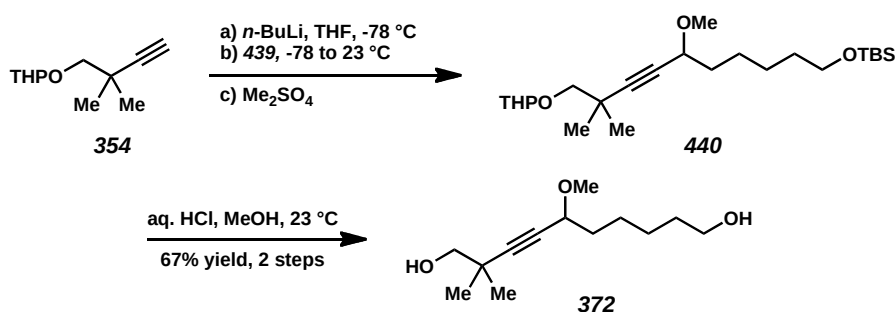
To a solution of crude ether **436** (3.28 g, assumed 8.00 mmol) in MeOH (80.0 mL, 0.1 M) was added 10% aq. HCl (approx. 125 μ L), and the reaction was stirred at 23 °C for 3 h. The reaction was quenched with Et₃N (approx. 125 μ L), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:2 hexanes/EtOAc eluent) affording diol **363** (1.02 g, 60% yield over 2 steps, R_f = 0.23 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 363: ¹H NMR (400 MHz, CDCl₃) δ 3.95 (t, J = 6.4 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.40 (s, 2H), 3.37 (s, 3H), 1.95 (br s, 2H), 1.78-1.65 (comp m, 2H), 1.64-1.49 (comp m, 4H), 1.21 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 91.3, 80.3, 71.7, 71.4, 62.8, 56.4, 35.5, 34.4, 32.3, 25.67, 25.65, 21.6; IR (film) 3383, 2936, 2234, 1461, 1338, 1058 cm⁻¹; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₂H₂₂O₃ + H]⁺: 215.2, found 215.1.



To a solution of 1,6-hexanediol (**437**, 5.91 g, 50.0 mmol) in THF (200 mL, 0.25 M) at 0 °C was added NaH (1.20 g, 50.0 mmol). The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 3 h. TBSCl (7.53 g, 50.0 mmol) was then added and the solution was stirred at 23 °C for 16 h. The reaction mixture was poured into water (200 mL) and extracted with Et₂O (2 x 200 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation, affording alcohol **438** (9.97 g, 86% yield, R_f = 0.38 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **438** (2.55 g, 11.0 mmol) in CH₂Cl₂ (25.0 mL, 0.4 M) at 0 °C was added TEMPO (17.7 mg, 0.110 mmol). A solution of KBr (1.44 g, 12.1 mmol) in 5% aq. NaHCO₃ (60.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (6.95 mL, 10% aq., 11.3 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (15 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 25 mL), and the combined organic phases were washed with H₂O (50 mL) and brine (50 mL). The organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation, affording aldehyde **439**¹⁵⁸ (2.32 g, 92% yield, *R*_f = 0.64 in 4:1 hexanes/EtOAc) as a colorless oil.

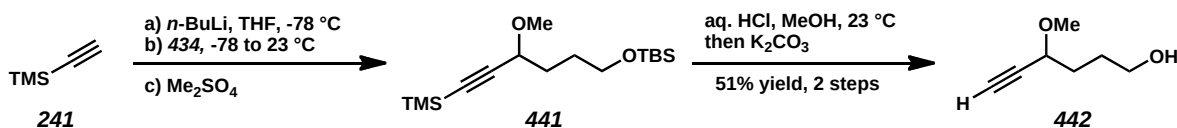


To a solution of acetal **354** (1.82 g, 10.0 mmol) in THF (30.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (4.31 mL, 2.32 M in hexanes, 10.0 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **439** (2.30 g, 10.0 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (1.14 mL, 12.0 mmol) was added, and the reaction was stirred at 23 °C for 16 h. The reaction was quenched with 10% aq. NH₄OH (30 mL) and stirred for 15 min. The mixture was diluted with Et₂O (30 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (30 mL), and the combined organic phases were washed with brine (30 mL) and dried over MgSO₄.

The solvent was removed via rotary evaporation, affording crude ether **440** (4.62 g, $R_f = 0.57$ in 9:1 hexanes/EtOAc) as an amber oil.

To a solution of crude ether **440** (4.62 g, assumed 10.0 mmol) in MeOH (100 mL, 0.1 M) was added 10% aq. HCl (approx. 150 μ L), and the reaction was stirred at 23 °C for 6 h. The reaction was quenched with Et₃N (approx. 150 μ L), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:2 hexanes/EtOAc eluent) affording diol **372** (1.50 g, 67% yield over 2 steps, $R_f = 0.28$ in 1:2 hexanes/EtOAc) as a colorless oil.

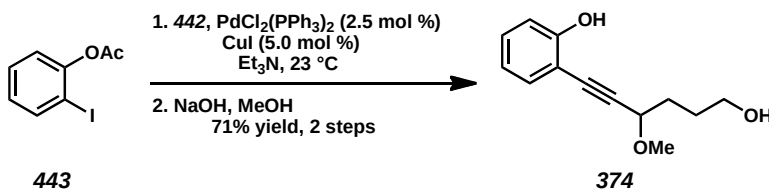
Diol 372: ¹H NMR (400 MHz, CDCl₃) δ 3.94 (app. td, $J = 6.5, 1.3$ Hz, 1H), 3.64 (app. td, $J = 6.5, 2.3$ Hz, 2H), 3.39 (app. d, $J = 1.3$ Hz, 2H), 3.36 (app. d, $J = 1.3$ Hz, 3H), 1.84-1.71 (comp m, 2H), 1.71-1.64 (comp m, 2H), 1.61-1.56 (comp m, 2H), 1.47-1.37 (comp m, 4H), 1.21 (app. d, $J = 1.5$ Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 91.2, 80.4, 71.7, 71.4, 62.9, 56.3, 35.8, 34.4, 32.7, 25.64, 25.57, 25.2; IR (film) 3365, 2932, 2232, 1463, 1336, 1053 cm⁻¹; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₃H₂₄O₃ + Na]⁺: 251.2, found 251.2.



To a solution of trimethylsilylacetylene (**241**, 0.848 mL, 6.00 mmol) in THF (18.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (2.59 mL, 2.32 M in hexanes, 6.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **434** (1.21 g, 6.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.742 mL, 7.80 mmol) was added, and the reaction was stirred for 16 h at 23 °C.

The reaction was quenched with 10% aq. NH_4OH (20 mL) and stirred for 15 min. The mixture was diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic phases were washed with brine (30 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **441** (2.06 g, $R_f = 0.76$ in 4:1 hexanes/ EtOAc) as an amber oil.

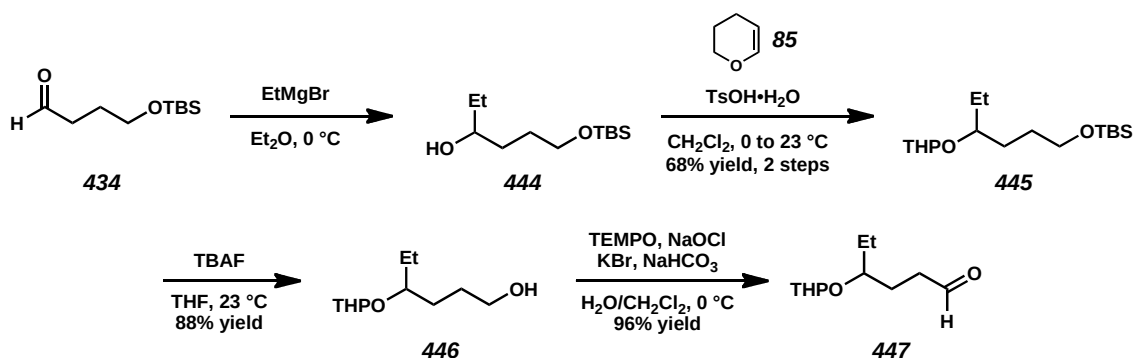
To a solution of crude ether **441** (2.06 g, assumed 6.00 mmol) in MeOH (60.0 mL, 0.1 M) was added 10% aq HCl (approx. 75 μL), and the reaction was stirred at 23 °C for 1 h, at which time TLC indicated complete consumption of the starting material. K_2CO_3 (0.993 g, 7.20 mmol) was then added and the reaction mixture was stirred at 23 °C for 15 h. The solution was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over MgSO_4 and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:1 hexanes/ EtOAc eluent) affording alkyne **442** (0.395 g, 51% yield over 2 steps, $R_f = 0.40$ in 1:1 hexanes/ EtOAc) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 4.01 (td, $J = 6.0, 1.6$ Hz, 1H), 3.71-3.63 (comp m, 2H), 3.42 (s, 3H), 2.46 (d, $J = 1.6$ Hz, 1H), 1.88-1.67 (comp m, 5H).



A solution of 2-iodophenyl acetate¹⁵⁹ (**443**, 0.262 g, 1.00 mmol) and alkyne **442** (0.153 g, 1.20 mmol) in Et_3N (3.00 mL, 0.3 M) was degassed with argon via bubbling for 15 min. CuI (9.5 mg, 0.0500 mmol) was added followed by $\text{PdCl}_2(\text{PPh}_3)_2$ (17.5 mg, 0.0250 mmol), and the mixture

was stirred at 23 °C for 4 h. Upon completion, the reaction mixture was filtered through a SiO₂ plug (0.5 x 3.0 cm), washing with EtOAc (20 mL). The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in MeOH (5.00 mL, 0.2 M). 5 M NaOH (2.00 mL, 10.0 mmol) was added and the resulting solution was stirred at 23 °C for 12 h. The solution was acidified to pH ~3 with HCl (3.50 mL, 10% aq.) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine (20 mL), and dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (4:1→1:2 hexanes/EtOAc eluent) affording phenol **374** (0.155 g, 71% yield over 2 steps, *R*_f = 0.35 in 1:1 hexanes/EtOAc) as a colorless oil.

Phenol 374: ¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.27-7.22 (m, 1H), 6.94 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.86 (m, 1H), 6.48 (br s, 1H), 4.31 (t, *J* = 5.4 Hz, 1H), 3.78-3.69 (comp m, 2H), 3.49 (s, 3H), 2.37 (br s, 1H), 1.99-1.94 (comp m, 2H), 1.93-1.86 (m, 1H), 1.84-1.74 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 157.5, 131.9, 130.7, 120.3, 115.3, 108.9, 94.4, 81.5, 71.8, 62.6, 57.0, 32.6, 28.5; IR (film) 3314, 2937, 1602, 1486, 1448, 1291, 1062 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₃H₁₆O₃ + H]⁺: 221.1, found 221.1.



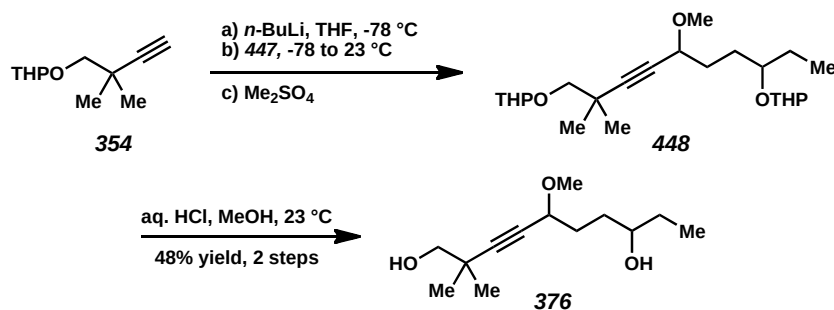
To a solution of aldehyde **434** (3.03 g, 15.0 mmol) in Et₂O (45.0 mL, 0.33 M) cooled to 0 °C was added EtMgBr (5.50 mL, 3.00 M in Et₂O, 16.5 mmol) dropwise. The reaction mixture was

stirred at 0 °C for 30 min, then was quenched with H₂O (10 mL). The mixture was poured into 1 N HCl (30 mL) and extracted with Et₂O (2 x 20 mL). The combined organic phases were washed with H₂O (30 mL), brine (30 mL) and dried over MgSO₄. The solvent was removed by rotary evaporation, affording alcohol **444** (3.05 g crude, R_f = 0.51 in 4:1 hexanes/EtOAc) as a pale orange oil.

To a solution of crude alcohol **444** (3.05 g, 13.1 mmol) in CH₂Cl₂ (26.2 mL, 0.5 M) at 0 °C was added TsOH•H₂O (24.9 mg, 0.131 mmol), followed by slow addition of 3,4-dihydro-2*H*-pyran (**85**, 1.40 mL, 16.5 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 14 h. The reaction was quenched with sat. aq. NaHCO₃ (30 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (30 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **445** (3.23 g, 68% yield over 2 steps, R_f = 0.51 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **445** (3.23 g, 10.2 mmol) in THF (10.2 mL, 1.0 M) at 23 °C was added TBAF (25.5 mL, 1.0 M in THF, 25.5 mmol) dropwise over 5 min, and the reaction mixture was stirred for 5 h. The reaction mixture was poured into H₂O (50 mL) and extracted with Et₂O (2 x 20 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording alcohol **446** (1.81 g, 88% yield, R_f = 0.37 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **446** (1.21 g, 6.00 mmol) in CH₂Cl₂ (15.0 mL, 0.4 M) at 0 °C was added TEMPO (9.4 mg, 0.0600 mmol). A solution of KBr (0.785 g, 6.60 mmol) in 5% aq. NaHCO₃ (30.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (3.72 mL, 10% aq., 6.00 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (10 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 25 mL), and the combined organic phases were washed with H₂O (50 mL) and brine (50 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **447** (1.15 g, 96% yield, *R*_f = 0.75 in 1:1 hexanes/EtOAc) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 9.80 (s, 0.5H), 9.77 (s, 0.5H), 4.63-4.55 (m, 1H), 3.94-3.82 (m, 1H), 3.71-3.54 (m, 1H), 3.53-3.41 (m, 1H), 2.60 (t, *J* = 7.1 Hz, 1H), 2.47 (t, *J* = 7.1 Hz, 1H), 1.97-1.62 (comp m, 4H), 1.61-1.42 (comp m, 6H), 0.93 (t, *J* = 7.4 Hz, 1.5H), 0.89 (t, *J* = 7.7 Hz, 1.5H).

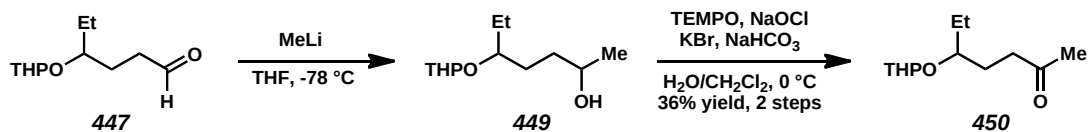


To a solution of acetal **354** (0.364 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.862 mL, 2.32 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **447** (0.400 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.247 mL, 2.60 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture

was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **448** (0.864 g, *R_f* = 0.47 in 9:1 hexanes/EtOAc) as an amber oil.

To a solution of crude ether **448** (0.864 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 6 h. The reaction was quenched with Et₃N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 → 1:2 hexanes/EtOAc eluent) affording diol **376** (0.219 g, 48% yield over 2 steps, *R_f* = 0.58 in 1:2 hexanes/EtOAc) as a colorless oil.

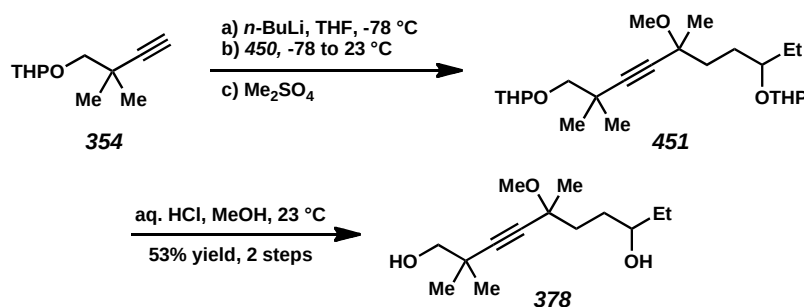
Diol 376: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 4.01 (td, *J* = 5.6, 2.8 Hz, 1H), 3.60-3.51 (m, 1H), 3.40 (s, 2H), 3.37 (app. d, *J* = 2.0 Hz, 3H), 2.22 (comp m, 2H), 1.86-1.79 (comp m, 2H), 1.74-1.63 (m, 1H), 1.61-1.44 (comp m, 3H), 1.21 (s, 6H), 0.94 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 92.2, 91.7, 80.1, 79.9, 73.0, 72.9, 71.84, 71.77, 71.5, 71.4, 56.5, 56.4, 34.5, 34.4, 32.6, 32.3, 32.1, 30.4, 30.3, 25.61, 25.55, 10.2, 10.1; IR (film) 3381, 2931, 1462, 1336, 1060, 966 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₃H₂₄O₃ + H]⁺: 229.2, found 229.2.



To a solution of aldehyde **447** (0.749 g, 3.74 mmol) in THF (18.7 mL, 0.2 M) cooled to -78 °C was added MeLi (2.80 mL, 1.6 M in Et₂O, 4.49 mmol) dropwise. The reaction mixture was

stirred at -78 °C for 10 min, then was warmed to 23 °C and quenched with H₂O (20 mL). The solution was extracted with Et₂O (2 x 20 mL), and the combined organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation, affording alcohol **449** (0.763 g crude, *R_f* = 0.42 in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of crude alcohol **449** (0.763 g, assumed 3.74 mmol) in CH₂Cl₂ (9.30 mL, 0.4 M) at 0 °C was added TEMPO (5.8 mg, 0.0374 mmol). A solution of KBr (0.489 g, 4.11 mmol) in 5% aq. NaHCO₃ (18.7 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (2.31 mL, 10% aq., 3.74 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (10 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were washed with H₂O (20 mL) and brine (20 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), affording ketone **450** (0.285 g, 36% yield over 2 steps, *R_f* = 0.38 in 4:1 hexanes/EtOAc) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 4.63-4.57 (m, 0.5H), 4.56-4.50 (m, 0.5H), 3.96-3.83 (m, 1H), 3.62-3.53 (m, 1H), 3.50-3.41 (m, 1H), 2.65-2.56 (m, 1H), 2.46 (t, *J* = 7.4 Hz, 1H), 2.15 (s, 3H), 1.92-1.62 (comp m, 4H), 1.62-1.42 (comp m, 6H), 0.98-0.83 (comp m, 3H).

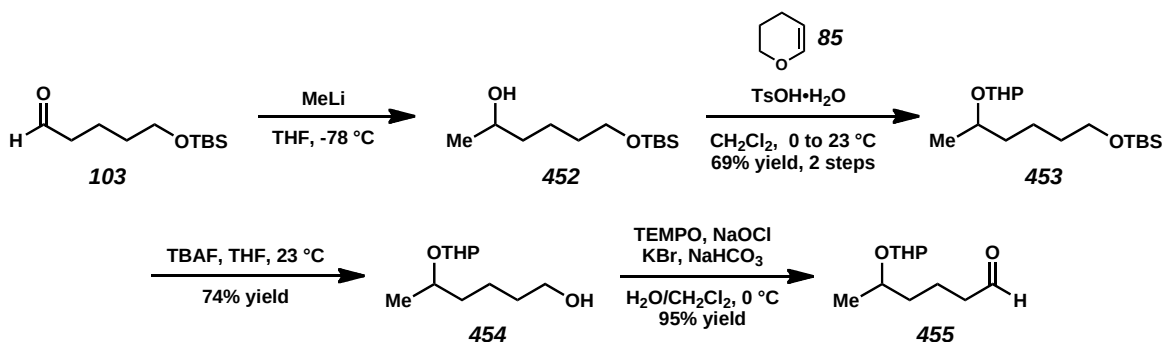


To a solution of acetal **354** (0.231 g, 1.27 mmol) in THF (3.81 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.547 mL, 2.32 M in hexanes, 1.27 mmol), and the resulting solution was stirred for 30 min at -78 °C. Ketone **450** (0.272 g, 1.27 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.157 mL, 1.65 mmol) was added, and the reaction was stirred for 18 h at 23 °C. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **451** (0.561 g, *R*_f = 0.53 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of crude ether **451** (0.561 g, assumed 1.27 mmol) in MeOH (12.7 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 8 h. The reaction was quenched with Et₃N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 → 1:1 hexanes/EtOAc eluent) affording diol **378** (0.162 g, 53% yield over 2 steps, *R*_f = 0.21 in 1:1 hexanes/EtOAc) as a colorless oil.

Diol 378: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 3.60-3.50 (m, 1H), 3.39 (s, 3H), 3.33 (d, *J* = 2.8 Hz, 2H), 2.25 (br s, 2H), 1.87-1.69 (comp m, 2H), 1.67-

1.59 (m, 1H), 1.57-1.45 (comp m, 3H), 1.38 (s, 3H), 1.20 (s, 6H), 0.94 (app. td, $J = 7.2, 0.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 91.7, 91.0, 82.4, 82.2, 74.0, 73.8, 73.5, 72.9, 71.9, 71.8, 51.3, 38.7, 37.7, 34.5, 34.4, 32.3, 31.9, 30.4, 30.3, 26.0, 25.9, 25.7, 25.63, 25.61, 25.59, 10.20, 10.18; IR (film) 3369, 2933, 2234, 1461, 1302, 1061 cm^{-1} ; LRMS (ESI^+) m/z calc'd for ($\text{M} + \text{Na}$) $^+$ [$\text{C}_{14}\text{H}_{26}\text{O}_3 + \text{Na}$] $^+$: 265.2, found 265.1.



To a solution of aldehyde **103** (2.23 g, 10.3 mmol) in THF (30.9 mL, 0.33 M) cooled to -78 °C was added MeLi (7.76 mL, 1.6 M in Et_2O , 12.4 mmol) dropwise. The reaction mixture was stirred at -78 °C for 10 min, then was warmed to 23 °C and quenched with H_2O (20 mL). The solution was extracted with Et_2O (2 x 20 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation, affording alcohol **452** (2.27 g crude, $R_f = 0.37$ in 4:1 hexanes/ EtOAc) as a yellow oil.

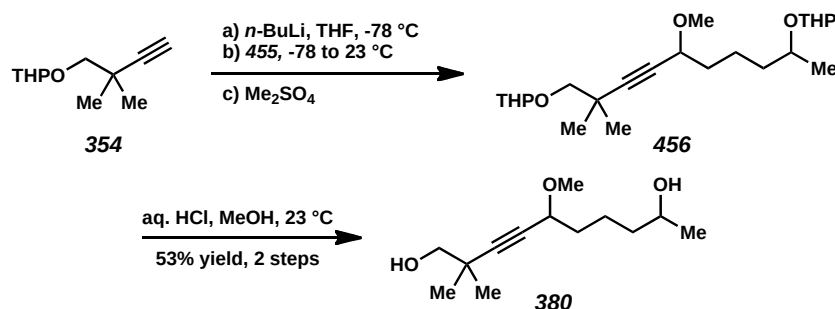
To a solution of crude alcohol **452** (2.27 g, 9.78 mmol) in CH_2Cl_2 (19.5 mL, 0.5 M) at 0 °C was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (39.3 mg, 0.206 mmol), followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 0.919 mL, 10.8 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (30 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (30 mL), and the combined

organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **453** (2.24 g, 69% yield over 2 steps, $R_f = 0.56$ in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **453** (2.24 g, 7.09 mmol) in THF (21.2 mL, 0.33 M) at 23 °C was added TBAF (10.6 mL, 1.0 M in THF, 10.6 mmol) dropwise over 5 min, and the reaction mixture was stirred for 20 h. The reaction mixture was poured into H_2O (50 mL) and extracted with Et_2O (2 x 20 mL). The combined organic phases were dried over MgSO_4 and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording alcohol **454** (1.06 g, 74% yield, $R_f = 0.38$ in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **454** (0.424 g, 2.20 mmol) in CH_2Cl_2 (5.50 mL, 0.4 M) at 0 °C was added TEMPO (3.4 mg, 0.0220 mmol). A solution of KBr (0.288 g, 2.42 mmol) in 5% aq. NaHCO_3 (11.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (1.43 mL, 10% aq., 2.31 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic phases were washed with H_2O (10 mL) and brine (10 mL). The organic phase was dried over MgSO_4 , and the solvent was removed by rotary evaporation, affording aldehyde **455** (0.419 g, 95% yield, $R_f = 0.39$ in 4:1 hexanes/EtOAc) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 9.79-9.76 (m, 1H), 4.71-4.65 (m, 0.5H), 4.64-4.60

(m, 0.5H), 3.99-3.58 (comp m, 3H), 3.54-3.43 (m, 1H), 2.52-2.40 (comp m, 2H), 1.96-1.76 (comp m, 2H), 1.75-1.63 (comp m, 2H), 1.61-1.42 (comp m, 5H), 1.25-1.10 (comp m, 3H).

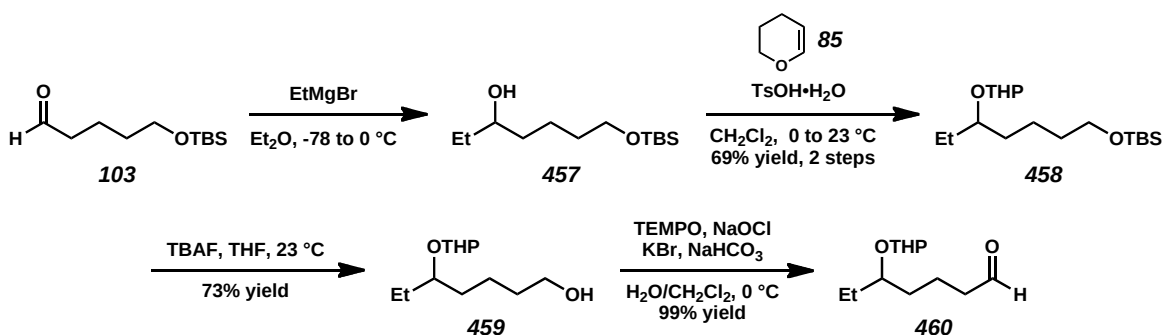


To a solution of acetal **354** (0.364 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.862 mL, 2.32 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **455** (0.400 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me_2SO_4 (0.247 mL, 2.60 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 10% aq. NH_4OH (10 mL) and stirred for 15 min. The mixture was diluted with Et_2O (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **456** (0.831 g, R_f = 0.22 in 9:1 hexanes/ EtOAc) as an amber oil.

To a solution of ether **456** (0.864 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 6 h. The reaction was quenched with Et_3N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:2 hexanes/ EtOAc eluent)

affording diol **380** (0.243 g, 53% yield over 2 steps, $R_f = 0.35$ in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 380: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 3.94 (t, $J = 6.4$ Hz, 1H), 3.80 (sextet, $J = 6.0$ Hz, 1H), 3.39 (s, 2H), 3.36 (s, 3H), 1.78-1.62 (comp m, 4H), 1.60-1.41 (comp m, 4H), 1.20 (s, 6H), 1.18 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 91.4, 91.3, 80.33, 80.27, 71.8, 71.4, 68.0, 56.39, 56.37, 38.9, 38.8, 35.7, 35.6, 34.4, 30.7, 25.6, 23.7, 23.6, 21.64, 21.56; IR (film) 3369, 2931, 2232, 1461, 1336, 1055 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+ [\text{C}_{13}\text{H}_{24}\text{O}_3 + \text{Na}]^+$: 251.1618, found 251.1621.



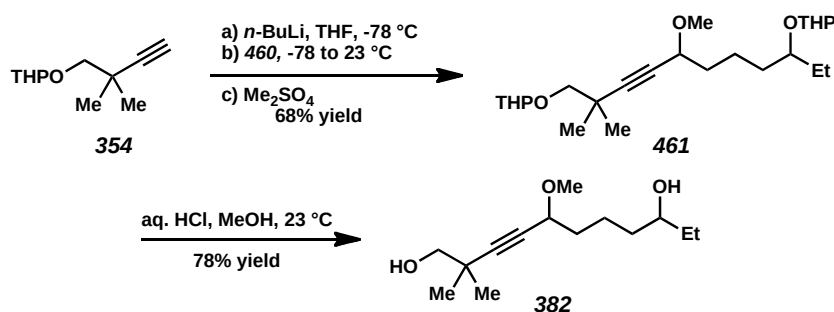
To a solution of aldehyde **103** (0.562 g, 2.60 mmol) in Et_2O (13.0 mL, 0.2 M) cooled to -78 $^{\circ}\text{C}$ was added EtMgBr (0.953 mL, 3.0 M in Et_2O , 2.86 mmol) dropwise. The reaction mixture was stirred at -78 $^{\circ}\text{C}$ for 10 min, then was warmed to 23 $^{\circ}\text{C}$ and quenched with H_2O (20 mL). The mixture was diluted with 1 N HCl (20 mL) and the solution was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary evaporation, affording alcohol **457** (0.529 g crude, $R_f = 0.43$ in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of crude alcohol **457** (0.529 g, 2.15 mmol) in CH₂Cl₂ (6.45 mL, 0.33 M) at 0 °C was added TsOH•H₂O (4.9 mg, 0.0260 mmol), followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 0.231 mL, 0.231 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 20 h. The reaction was quenched with sat. aq. NaHCO₃ (10 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (10 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **458** (0.596 g, 69% yield over 2 steps, *R_f* = 0.54 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **458** (0.596 g, 1.81 mmol) in THF (9.00 mL, 0.2 M) at 23 °C was added TBAF (2.90 mL, 1.0 M in THF, 2.90 mmol) dropwise over 5 min, and the reaction mixture was stirred for 28 h. The reaction mixture was poured into H₂O (15 mL) and extracted with Et₂O (2 x 20 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent), affording alcohol **459** (0.284 g, 73% yield, *R_f* = 0.20 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **459** (0.284 g, 1.31 mmol) in CH₂Cl₂ (3.25 mL, 0.4 M) at 0 °C was added TEMPO (2.0 mg, 0.0131 mmol). A solution of KBr (0.171 g, 1.44 mmol) in 5% aq. NaHCO₃ (5.50 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (0.831 mL, 10% aq., 0.131 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (5

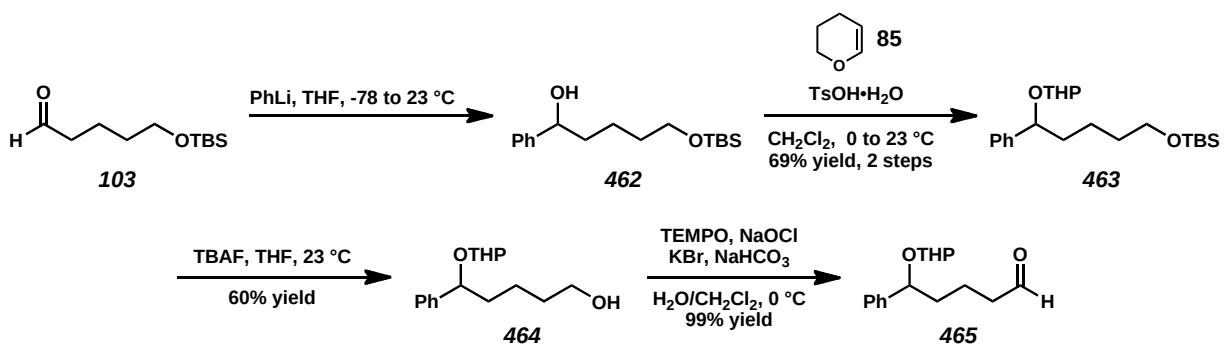
mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were washed with H₂O (10 mL) and brine (10 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **460** (0.277 g, 99% yield, *R*_f = 0.57 in 2:1 hexanes/EtOAc) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 9.76 (s, 1H), 4.67-4.58 (m, 1H), 3.97-3.83 (m, 1H), 3.68-3.42 (comp m, 2H), 2.51-2.38 (comp m, 2H), 1.91-1.41 (comp m, 12H), 0.93 (t, *J* = 7.4 Hz, 1.5H), 0.86 (t, *J* = 7.4 Hz, 1.5H).



To a solution of acetal **354** (0.239 g, 1.31 mmol) in THF (4.00 mL, 0.3 M) at -78 °C under argon was added *n*-BuLi (0.564 mL, 2.32 M in hexanes, 1.31 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **460** (0.277 g, 1.31 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.162 mL, 1.70 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation and the resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **461** (0.363 g, 68% yield, *R*_f = 0.28 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of crude ether **461** (0.363 g, 0.885 mmol) in MeOH (8.85 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μ L), and the reaction was stirred at 23 °C for 15 h. The reaction was quenched with Et₃N (approx. 50 μ L), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:2 hexanes/EtOAc eluent) affording diol **382** (0.168 g, 78% yield, R_f = 0.35 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 382: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 3.95 (t, J = 6.4 Hz, 1H), 3.61-3.50 (m, 1H), 3.39 (s, 2H), 3.37 (s, 3H), 2.06-1.98 (m, 2H), 1.75-1.66 (comp m, 2H), 1.65-1.56 (m, 1H), 1.54-1.41 (comp m, 5H), 1.20 (s, 6H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 91.4, 91.3, 80.3, 80.2, 73.2, 71.7, 71.4, 56.38, 56.36, 36.5, 36.4, 35.7, 35.6, 34.4, 30.4, 30.3, 25.7, 25.6, 21.6, 21.4, 10.0; IR (film) 3366, 2934, 2362, 1462, 1337, 1104, 1059 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₁₄H₂₆O₃ + Na]⁺: 265.1774, found 265.1777.



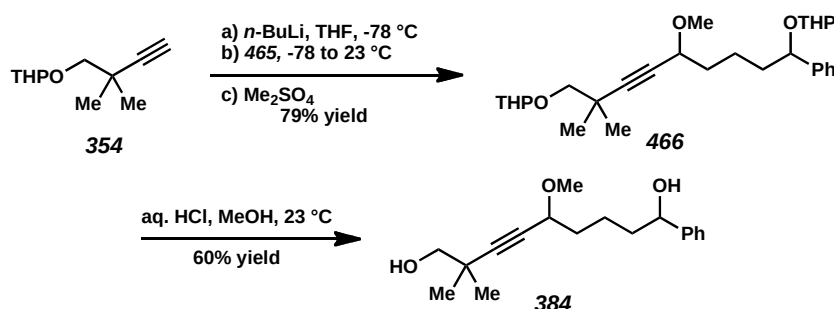
To a solution of aldehyde **103** (0.562 g, 2.60 mmol) in THF (13.0 mL, 0.2 M) cooled to -78 °C was added PhLi (1.59 mL, 1.8 M in dibutyl ether, 2.86 mmol) dropwise. The reaction mixture was stirred at -78 °C for 10 min, then was warmed to 23 °C and quenched with H₂O (20 mL). The solution was extracted with Et₂O (2 x 10 mL), and the combined organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation, affording alcohol **462** (0.791 g crude, R_f = 0.51 in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of alcohol **462** (0.791 g, assumed 2.60 mmol) in CH₂Cl₂ (8.67 mL, 0.33 M) at 0 °C was added TsOH•H₂O (4.9 mg, 0.0260 mmol), followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 0.231 mL, 2.73 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO₃ (20 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (10 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **463** (0.508 g, 52% yield over 2 steps, *R_f* = 0.54 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of acetal **463** (0.508 g, 1.34 mmol) in THF (6.70 mL, 0.2 M) at 23 °C was added TBAF (2.14 mL, 1.0 M in THF, 2.14 mmol) dropwise over 5 min, and the reaction mixture was stirred for 22 h. The reaction mixture was poured into H₂O (20 mL) and extracted with Et₂O (2 x 10 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording alcohol **464** (0.211 g, 60% yield, *R_f* = 0.19 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **464** (0.211 g, 0.798 mmol) in CH₂Cl₂ (2.00 mL, 0.4 M) at 0 °C was added TEMPO (1.2 mg, 0.00798 mmol). A solution of KBr (0.104 g, 0.878 mmol) in 5% aq. NaHCO₃ (4.00 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (0.504 mL, 10% aq., 0.814 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (5

mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were washed with H₂O (10 mL) and brine (10 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **465** (0.207 g, 99% yield, *R*_f = 0.53 in 2:1 hexanes/EtOAc) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 9.77-9.68 (m, 1H), 7.41-7.27 (comp m, 5H), 4.83-4.81 (m, 0.3H), 4.67-4.65 (m, 0.7H), 4.62-4.54 (m, 0.3H), 4.43-4.33 (m, 0.7H), 3.97-3.84 (m, 0.7H), 3.57-3.42 (m, 1H), 3.32-3.22 (m, 0.3H), 2.52-2.34 (comp m, 2H), 1.95-1.38 (comp m, 10H).

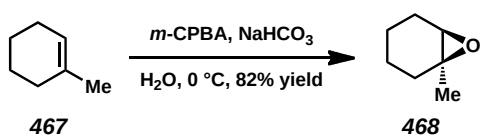


To a solution of acetal **354** (0.145 g, 0.798 mmol) in THF (2.00 mL, 0.4 M) at -78 °C under argon was added *n*-BuLi (0.343 mL, 2.32 M in hexanes, 0.343 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **465** (0.207 g, 0.798 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.0986 mL, 1.03 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (5 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (5 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation and the resulting residue was

purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ether **466** (0.287 g, 79% yield, R_f = 0.22 in 9:1 hexanes/EtOAc) as a colorless oil.

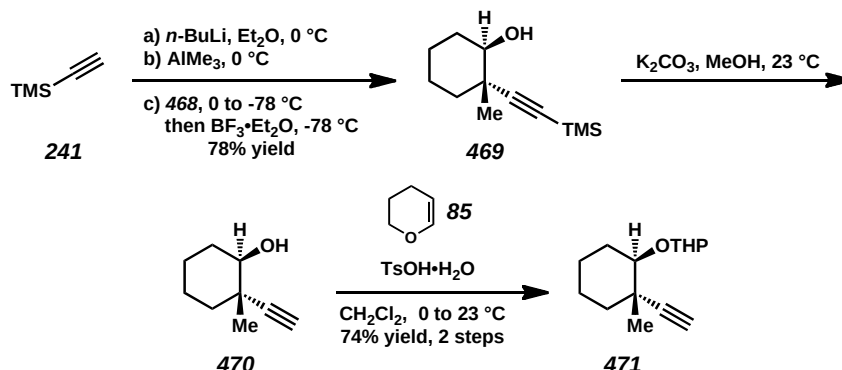
To a solution of crude ether **466** (0.287 g, 0.627 mmol) in MeOH (6.27 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μ L), and the reaction was stirred at 23 °C for 15 h. The reaction was quenched with Et₃N (approx. 50 μ L), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:2 hexanes/EtOAc eluent) affording diol **384** (0.110 g, 60% yield, R_f = 0.49 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 384: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.32 (comp m, 4H), 7.30-7.27 (m, 1H), 4.68 (dd, J = 6.4, 2.0 Hz, 1H), 3.93 (td, J = 6.4, 1.8 Hz, 1H), 3.37 (app. d, J = 4.4 Hz, 2H), 3.35 (s, 3H), 2.07-2.01 (m, 2H), 1.89-1.78 (m, 1H), 1.77-1.64 (comp m, 3H), 1.63-1.51 (m, 1H), 1.50-1.41 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 145.0, 144.9, 128.6, 127.7, 126.00, 125.98, 91.4, 91.3, 80.3, 80.2, 74.6, 74.5, 71.8, 71.7, 71.3, 56.41, 56.36, 38.7, 35.6, 35.5, 34.4, 25.6, 21.8, 21.6; IR (film) 3386, 2936, 2232, 1453, 1337, 1060 cm⁻¹; HRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₁₈H₂₆O₃ + Na]⁺: 313.1774, found 313.1776.



According to the procedure of Fringuelli,¹⁶⁰ to a solution of 1-methylcyclohexene (**467**, 5.93 mL, 75% reported purity, 37.5 mmol) in 0.3 M aq. NaHCO₃ (300 mL, 0.125 M) at 0 °C was added *m*-CPBA (10.6 g, 81% wt., 50.0 mmol). The reaction mixture was stirred at 0 °C for 2 h. The mixture was then poured into pentane (100 mL), and the phases were separated. The aqueous

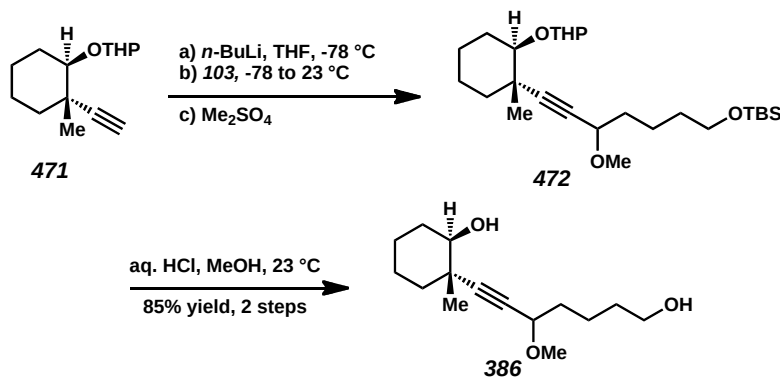
phase was extracted with pentane (50 mL) and the combined organic layers were washed with sat. aq. NaHCO₃ (50 mL), brine (50 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording epoxide **468** (3.45 g, 82% yield, *R_f* = 0.74 in 4:1 hexanes/EtOAc) as a colorless liquid.



According to the procedure of Pagenkopf,¹⁶¹ to a solution of trimethylsilylacetylene (**241**, 3.72 mL, 26.3 mmol) in Et₂O (100 mL, 0.26 M) cooled to 0 °C was added *n*-BuLi (11.3 mL, 2.32 M in hexanes, 26.3 mmol), and the mixture was stirred for 5 min. Trimethylaluminum (0.550 mL, 2.00 M in toluene, 26.3 mmol) was added and the reaction mixture was warmed to 23 °C and stirred for 15 min. Epoxide **468** (2.80 g, 25.0 mmol) was added and the reaction mixture was cooled to -78 °C. BF₃•Et₂O (5.16 mL, 41.8 mmol) was added dropwise and the reaction was stirred at -78 °C for 2 h. The reaction was quenched with MeOH (2 mL), and warmed to 23 °C. The mixture was poured into H₂O (100 mL) and the phases were separated. The aqueous phase was extracted with Et₂O (50 mL), and the combined organic layers were washed with H₂O (50 mL), brine (50 mL) and dried over MgSO₄. The solvent was removed by rotary evaporation and the resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording alcohol **469** (4.12 g, 78% yield, *R_f* = 0.60 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **469** (4.12 g, 19.6 mmol) in MeOH (130 mL, 0.15 M) was added K₂CO₃ (2.98 g, 21.6 mmol) and the reaction mixture was stirred at 23 °C for 12 h. The solution was poured into H₂O (200 mL), and extracted with CH₂Cl₂ (3 x 40 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed via rotary evaporation, affording crude alkyne **470** (2.44 g, *R*_f = 0.58 in 4:1 hexanes/EtOAc) as a yellow oil.

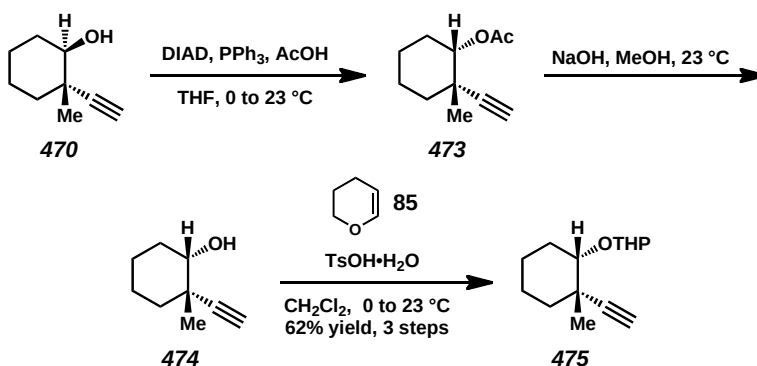
To a solution of crude alkyne **470** (2.44 g, assumed 19.6 mmol) in CH₂Cl₂ (78.4 mL, 0.25 M) at 0 °C was added TsOH•H₂O (37.4 mg, 0.392 mmol), followed by slow addition of 3,4-dihydro-2*H*-pyran (**85**, 1.75 mL, 20.6 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 18 h. The reaction was quenched with sat. aq. NaHCO₃ (60 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (30 mL), and the combined organic phases were dried over MgSO₄. The solvent was removed via rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **471** (3.23 g, 74% yield over 2 steps, *R*_f = 0.65 in 9:1 hexanes/EtOAc) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 4.77-4.70 (m, 1H), 3.99-3.86 (m, 1H), 3.74-3.69 (m, 0.5H), 3.62-3.57 (m, 0.5H), 3.54-3.44 (m, 1H), 2.15 (app. d, *J* = 6.6 Hz, 1H), 1.95-1.46 (comp m, 12H), 1.45-1.32 (comp m, 2H), 1.30 (s, 1.5H), 1.19 (s, 1.5H).



To a solution of acetal **471** (0.444 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (0.432 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.247 mL, 2.60 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (5 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (5 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **472** (0.968 g, *R*_f = 0.69 in 4:1 hexanes/EtOAc) as an amber oil.

To a solution of crude ether **472** (0.968 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 3 h. The reaction was quenched with Et₃N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 → 1:2 hexanes/EtOAc eluent) affording diol **386** (0.431 g, 85% yield over 2 steps, *R*_f = 0.42 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 386: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 3.98-3.95 (m, 1H), 3.68-3.63 (comp m, 3H), 3.37 (s, 3H), 1.92-1.85 (m, 1H), 1.73-1.69 (comp m, 4H), 1.62-1.50 (comp m, 8H), 1.47-1.35 (m, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 98.7, 92.8, 80.4, 74.4, 71.4, 62.9, 56.3, 37.2, 35.62, 35.60, 35.2, 35.1, 32.5, 32.4, 29.3, 21.9, 21.8, 21.69, 21.67; IR (film) 3379, 2930, 2233, 1446, 1337, 1069, 996 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+ [\text{C}_{15}\text{H}_{26}\text{O}_3 + \text{H}]^+$: 255.2, found 255.2.

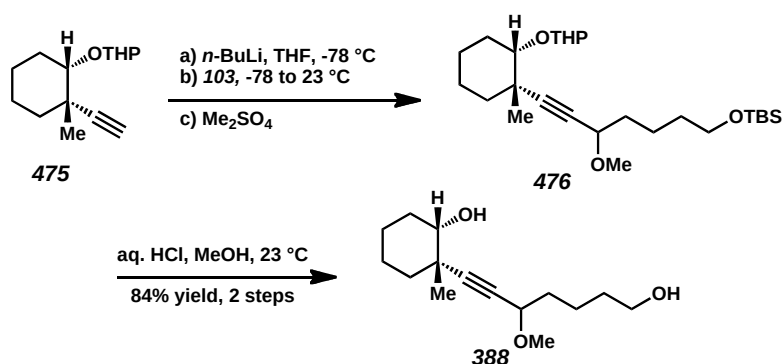


To a solution of alcohol **470** (0.911 g, 6.60 mmol) in THF (33.0 mL, 0.2 M) cooled at 0 °C was added PPh_3 (2.08 g, 7.92 mmol) and AcOH (0.453 mL, 7.92 mmol). DIAD (1.57 mL, 7.92 mmol) was added dropwise and the resulting solution was slowly warmed to 23 °C and stirred for 14 h. The solvent was removed by rotary evaporation and the recovered residue was purified by flash chromatography (9:1 $\rightarrow$ 4:1 hexanes/EtOAc eluent), affording ester **473** (1.61 g, contaminated with diisopropyl hydrazide, R_f = 0.40 in 4:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of ester **473** (1.61g, assumed 6.60 mmol) in MeOH (20.0 mL, 0.33 M) was added 5 M NaOH (7.00 mL, 35.0 mmol) and the reaction mixture was stirred at 23 °C for 4 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over MgSO_4 , and the solvent was removed by rotary

evaporation, affording crude alcohol **474** (1.28 g, $R_f = 0.55$ in 2:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of crude alkyne **474** (1.28 g, assumed 6.60 mmol) in CH_2Cl_2 (13.2 mL, 0.5 M) at 0 °C was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (12.6 mg, 0.0660 mmol), followed by slow addition of 3,4-dihydro-2*H*-pyran (**85**, 0.560 mL, 6.60 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 2 h. The reaction was quenched with sat. aq. NaHCO_3 (20 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, and the resulting oil was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording acetal **475** (0.903 g, 62% yield over 3 steps, $R_f = 0.49$ in 9:1 hexanes/EtOAc) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 4.77-4.70 (m, 1H), 3.99-3.86 (m, 1H), 3.75-3.69 (m, 0.5H), 3.60 (dd, $J = 6.0, 3.0$ Hz, 0.5H), 3.54-3.43 (m, 1H), 2.14 (app. d, $J = 6.3$ Hz, 1H), 1.96-1.44 (comp m, 12H), 1.44-1.33 (comp m, 2H), 1.30 (s, 1.5H), 1.20 (s, 1.5H).

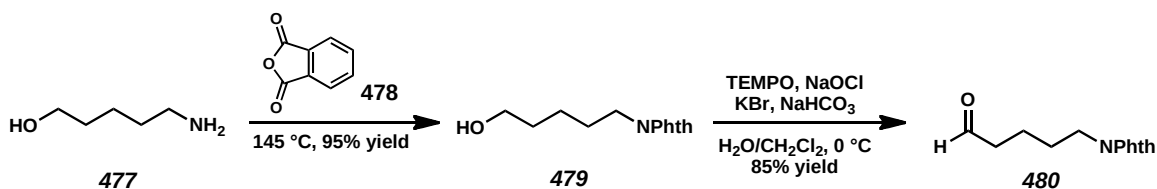


To a solution of acetal **475** (0.444 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at $-78\text{ }^\circ\text{C}$ under argon was added $n\text{-BuLi}$ (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at $-78\text{ }^\circ\text{C}$. Aldehyde **103** (0.432 g, 2.00 mmol) was then added, and the

reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.247 mL, 2.60 mmol) was added, and the reaction was stirred for 14 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (5 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (5 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **476** (0.983 g, *R_f* = 0.73 in 4:1 hexanes/EtOAc) as an amber oil.

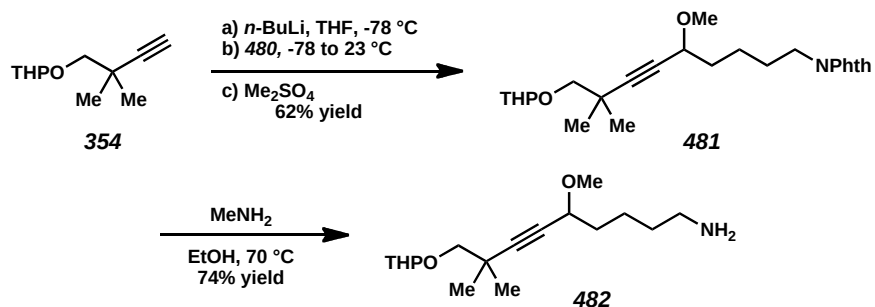
To a solution of crude ether **476** (0.983 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 µL), and the reaction was stirred at 23 °C for 3 h. The reaction was quenched with Et₃N (approx. 50 µL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 → 1:2 hexanes/EtOAc eluent) affording diol **388** (0.426 g, 84% yield over 2 steps, *R_f* = 0.40 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 388: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 3.96 (t, *J* = 6.4 Hz, 1H), 3.68-3.63 (comp m, 3H), 3.37 (s, 3H), 1.93-1.85 (m, 1H), 1.73-1.67 (comp m, 5H), 1.62-1.51 (comp m, 8H), 1.47-1.35 (comp m, 2H), 1.21 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 92.8, 80.4, 74.4, 71.4, 62.8, 56.3, 37.2, 35.61, 35.59, 35.2, 35.1, 32.44, 32.42, 29.3, 21.9, 21.8, 21.68, 21.65; IR (film) 3356, 2930, 2234, 1446, 1337, 1071 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₅H₂₆O₃ + H]⁺: 255.2, found 255.0.



To 5-aminopentan-1-ol (**477**, 1.62 g, 15.8 mmol) was added phthalic anhydride (**478**, 2.22 g, 15.0 mmol) and the mixture was heated to 145 °C for 16 h. The reaction mixture was cooled to 23 °C, diluted with EtOAc (60 mL), and washed sequentially with sat. aq. NaHCO₃ (40 mL), 1 M KHSO₄ (40 mL) and brine (40 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording phthalimide **479** (3.31 g, 95% yield, R_f = 0.24 in 1:1 hexanes/EtOAc) as a colorless oil.

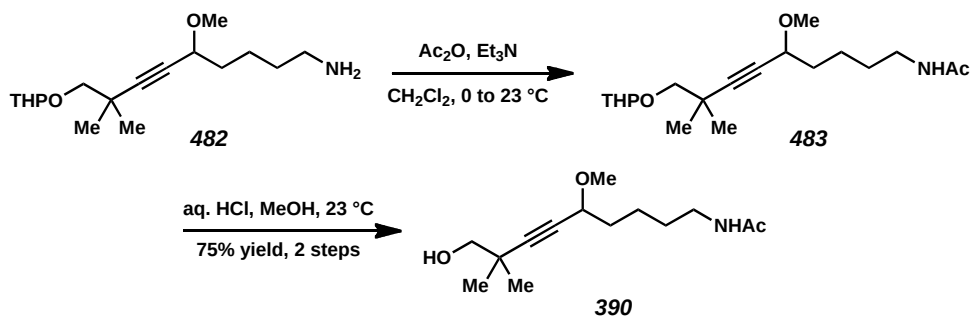
To a solution of phthalimide **479** (1.86 g, 8.00 mmol) in CH₂Cl₂ (20.0 mL, 0.4 M) at 0 °C was added TEMPO (12.5 mg, 0.0800 mmol). A solution of KBr (1.05 g, 8.80 mmol) in 5% aq. NaHCO₃ (40.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (4.96 mL, 10% aq., 8.00 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (15 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organic phases were washed with H₂O (30 mL) and brine (30 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **480**¹⁶² (1.56 g, 85% yield, R_f = 0.55 in 1:1 hexanes/EtOAc) as a colorless oil.



To a solution of acetal **354** (1.22 g, 6.71 mmol) in THF (20.1 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (2.89 mL, 2.32 M in hexanes, 6.71 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **480** (1.55 g, 6.71 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.832 mL, 8.72 mmol) was added, and the reaction was stirred for 16 h at 23 °C. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (20 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were washed with brine (40 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, and the recovered residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording phthalimide **481** (1.76 g, 62% yield, *R*_f = 0.73 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of phthalimide **481** (1.76 g, 4.12 mmol) in EtOH (20.6 mL, 0.2 M) was added MeNH₂ (0.899 mL, 40% wt in H₂O, 10.3 mmol), and the resulting reaction solution was heated to 70 °C for 3 h. The reaction was cooled to 23 °C and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (19:1 CH₂Cl₂/MeOH → 9:1:1 CH₂Cl₂/MeOH/Et₃N eluent), affording amine **482** (0.905 g, 74% yield, *R*_f = 0.27 in 9:1 CH₂Cl₂/MeOH w/ 2% Et₃N) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 4.68-4.62 (m, 1H), 3.96-3.81 (comp m, 2H), 3.60-3.56 (m, 1H), 3.55-3.46 (m, 1H), 3.34 (s, 3H), 3.24-3.19 (m,

1H), 2.82-2.70 (comp m, 2H), 1.91-1.77 (m, 1H), 1.75-1.39 (comp m, 11H), 1.23 (s, 3H), 1.22 (s, 3H).

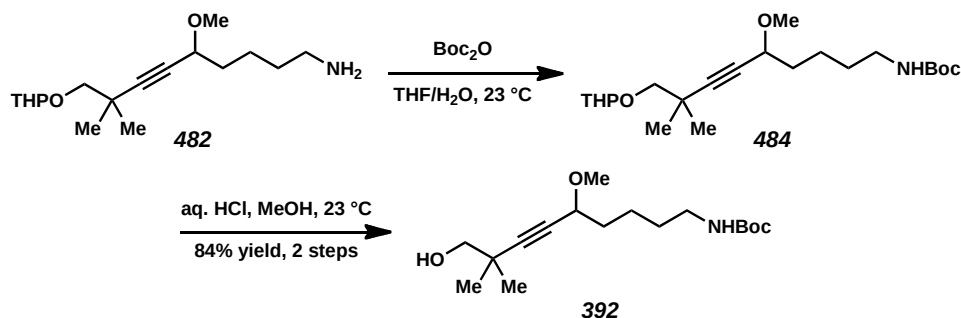


To a solution of amine **482** (0.300 g, 1.01 mmol) in CH_2Cl_2 (2.00 mL, 0.5 M) cooled at 0 °C was added Et_3N (0.309 mL, 2.22 mmol) followed by Ac_2O (0.105 mL, 1.11 mmol). The reaction mixture was stirred for 12 h at 23 °C and was then quenched with H_2O (5.0 mL). The mixture was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation, affording acetamide **483** (0.320 g crude, R_f = 0.59 in 9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) as a colorless oil.

To a solution of acetamide **483** (0.320 g, assumed 1.01 mmol) in MeOH (10.0 mL, 0.1 M) was added 10% aq. HCl (approx. 25 μL), and the resulting solution was stirred at 23 °C for 6 h. Upon completion, Et_3N (approx. 25 μL) was added and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (19:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ eluent), affording acetamide **390** (0.192 g, 75% yield over 2 steps, R_f = 0.36 in 9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) as a colorless oil.

Acetamide 390: ^1H NMR (400 MHz, CDCl_3) δ 5.77 (br s, 1H), 3.94 (t, J = 6.4 Hz, 1H), 3.40 (s, 2H), 3.36 (s, 3H), 3.25 (q, J = 6.4 Hz, 2H), 2.32 (br s, 1H), 1.98 (s, 3H), 1.74-1.64 (comp m, 2H), 1.57-1.43 (comp m, 4H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 91.5, 80.1,

71.7, 71.2, 56.4, 39.7, 35.4, 34.4, 29.4, 25.68, 25.65, 23.4, 22.7; IR (film) 3294, 2932, 1736, 1651, 1554, 1293, 1058 cm^{-1} ; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₄H₂₅NO₃ + H]⁺: 256.2, found 256.2.

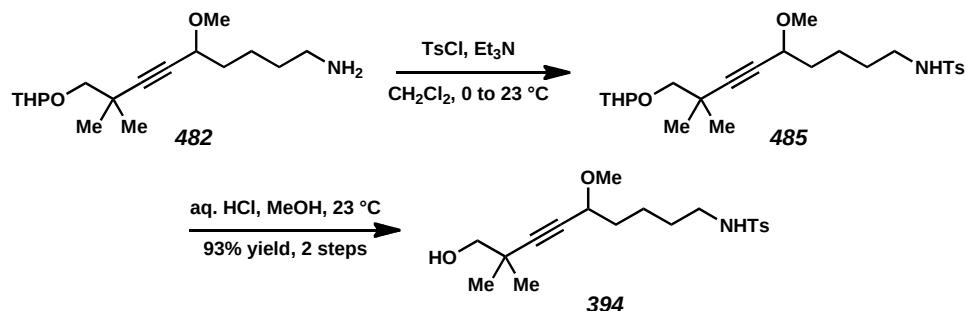


To a solution of amine **482** (0.300 g, 1.01 mmol) in THF/H₂O (5:1, 5.00 mL, 0.2 M) was added Boc₂O (0.231 g, 1.06 mmol), and the mixture was stirred at 23 °C for 14 h. The reaction was diluted with Et₂O (10 mL), and washed with H₂O (10 mL). The aqueous phase was extracted with Et₂O (10 mL), and the combined organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation, affording carbamate **484** (0.405 g, R_f = 0.85 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of carbamate **484** (0.405 g, assumed 1.01 mmol) in MeOH (10.0 mL, 0.1 M) was added 10% aq. HCl (approx. 25 μL), and the resulting solution was stirred at 23 °C for 4 h. Upon completion, Et₃N (approx. 25 μL) was added and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording carbamate **392** (0.263 g, 84% yield over 2 steps, R_f = 0.40 in 1:1 hexanes/EtOAc) as a colorless oil.

Carbamate 392: ¹H NMR (400 MHz, CDCl₃) δ 4.55 (br s, 1H), 3.93 (t, J = 6.4 Hz, 1H), 3.39 (s, 2H), 3.35 (s, 3H), 3.10 (t, J = 6.8 Hz, 2H), 1.93 (br s, 1H), 1.74-1.58 (comp m, 2H), 1.52-1.46

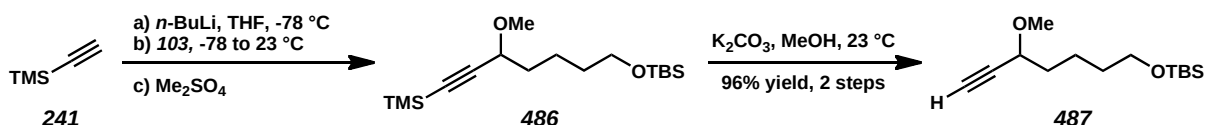
(comp m, 4H), 1.43 (s, 9H), 1.20 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.2, 91.3, 80.3, 71.7, 71.2, 56.3, 40.7, 35.5, 34.4, 29.8, 28.6, 25.67, 25.66, 22.6; IR (film) 3356, 2933, 1687, 1521, 1365, 1272, 1166 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{17}\text{H}_{31}\text{NO}_4 + \text{Na}$] $^+$: 336.2, found 336.2.



To a solution of amine **482** (0.300 g, 1.01 mmol) in CH_2Cl_2 (2.00 mL, 0.5 M) cooled to 0 °C was added Et_3N (0.295 mL, 2.12 mmol) followed by *p*-toluenesulfonyl chloride (0.202 g, 1.06 mmol). The reaction mixture was stirred for 15 h at ambient temperature and was then quenched with H_2O (5.0 mL). The mixture was extracted with CH_2Cl_2 (2 x 5 mL), and the combined organic layers were dried over MgSO_4 . The solvent was removed by rotary evaporation, affording sulfonamide **485** (0.449 g crude, R_f = 0.71 in 1:1 hexanes/ EtOAc) as a yellow oil.

To a solution of sulfonamide **485** (0.449 g, assumed 1.01 mmol) in MeOH (10.0 mL, 0.1 M) was added 10% aq. HCl (approx. 25 μL), and the resulting solution was stirred at 23 °C for 6 h. Upon completion, Et_3N (approx. 25 μL) was added and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (4:1 $\rightarrow$ 1:1 hexanes/ EtOAc eluent), affording sulfonamide **394** (0.344 g, 93% yield over 2 steps, R_f = 0.33 in 1:1 hexanes/ EtOAc) as a colorless oil.

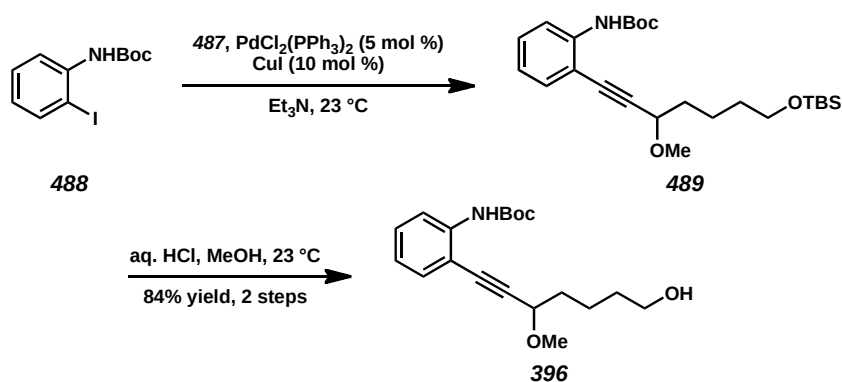
Sulfonamide 394: ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 3.90 (t, J = 6.4 Hz, 1H), 3.42 (s, 2H), 3.35 (s, 3H), 2.94 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H), 1.88 (br s, 1H), 1.67-1.56 (comp m, 2H), 1.53-1.41 (comp m, 4H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.5, 137.1, 129.8, 127.2, 91.6, 79.9, 71.7, 71.1, 56.4, 43.0, 35.1, 34.3, 29.2, 25.68, 25.66, 22.3, 21.7; IR (film) 3490, 3279, 2933, 1733, 1325, 1156, 815 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{19}\text{H}_{29}\text{NO}_4\text{S} + \text{H}$] $^+$: 368.2, found 368.2.



To a solution of trimethylsilylacetylene (**241**, 1.13 mL, 8.00 mmol) in THF (24.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (3.20 mL, 2.50 M in hexanes, 8.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (1.73 g, 8.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me_2SO_4 (0.989 mL, 10.4 mmol) was added, and the reaction was stirred for 20 h at 23 °C. The reaction was quenched with 10% NH_4OH (20 mL) and stirred for 15 min. The mixture was diluted with Et_2O (25 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (25 mL), and the combined organic phases were washed with brine (30 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **486** (3.15 g, R_f = 0.62 in 9:1 hexanes/ EtOAc) as a colorless oil.

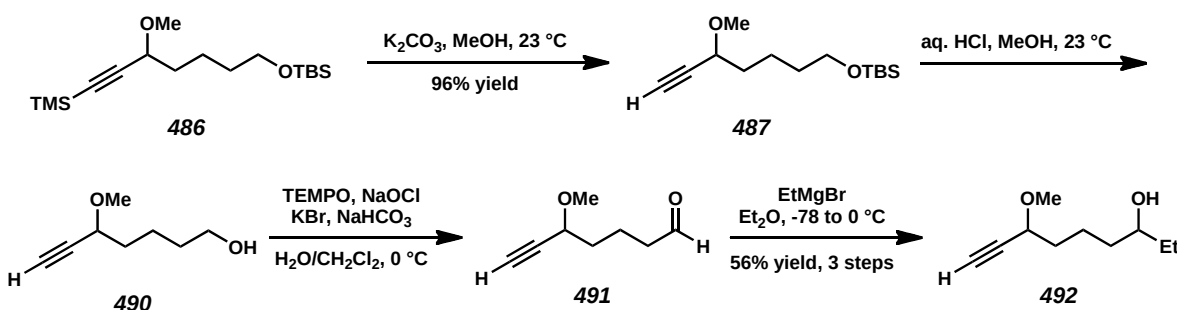
To a solution of crude ether **486** (3.15 g, assumed 8.00 mmol) in MeOH (80.0 mL, 0.1 M) was added K_2CO_3 (1.21 g, 8.80 mmol), and the reaction mixture was stirred at 23 °C for 16 h. The reaction solution was poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The

combined organic phases were dried over MgSO_4 and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording alkyne **487** (1.96 g, 96% yield over 2 steps, R_f = 0.56 in 9:1 hexanes/EtOAc) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 3.93 (td, J = 6.3, 1.9 Hz, 1H), 3.61 (t, J = 6.0 Hz, 2H), 3.41 (s, 3H), 2.42 (d, J = 1.9 Hz, 1H), 1.78-1.64 (m, 2H), 1.60-1.43 (comp m, 4H), 0.89 (s, 9H), 0.04 (s, 6H).



A solution of *N*-Boc-aniline **488**¹⁶³ (0.319 g, 1.00 mmol) and alkyne **487** (0.281 g, 1.10 mmol) in Et_3N (3.00 mL, 0.33 M) was degassed with argon via bubbling for 15 min. CuI (19.0 mg, 0.100 mmol) was added followed by $\text{PdCl}_2(\text{PPh}_3)_2$ (35.1 mg, 0.0500 mmol) and the mixture was stirred at 23°C for 6 h. Upon completion the reaction mixture was filtered through a SiO_2 plug (0.5 x 3.0 cm), washing with EtOAc (10 mL). The filtrate was concentrated under reduced pressure, and the recovered crude silyl ether **489** was dissolved in MeOH (10.0 mL, 0.1 M). To this solution was added 10% aq. HCl (approx. 25 μL), and the resulting reaction mixture was stirred at 23°C for 2 h. The reaction was quenched with Et_3N (approx. 25 μL) and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording *N*-Boc-aniline **396** (0.280 g, 84% yield over 2 steps, R_f = 0.33 in 2:1 hexanes/EtOAc) as a pale brown oil.

N-Boc-aniline 396: ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 7.6, 1.6 Hz, 1H), 7.32-7.28 (m, 1H), 7.24 (br s, 1H), 6.95 (td, J = 7.6, 1.2 Hz, 1H), 4.25 (t, J = 6.4 Hz, 1H), 3.69 (t, J = 6.2 Hz, 2H), 3.49 (s, 3H), 1.93-1.83 (comp m, 2H), 1.69-1.59 (m, 4H), 1.55 (br s, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.5, 139.7, 131.9, 129.9, 122.2, 117.8, 110.8, 95.0, 81.6, 81.0, 71.9, 62.8, 56.8, 35.4, 32.5, 28.4, 21.8; IR (film) 3403, 2933, 1733, 1516, 1447, 1154, 754 cm^{-1} ; LRMS (ESI $^+$) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{19}\text{H}_{27}\text{NO}_4 + \text{Na}$] $^+$: 356.2, found 356.9.



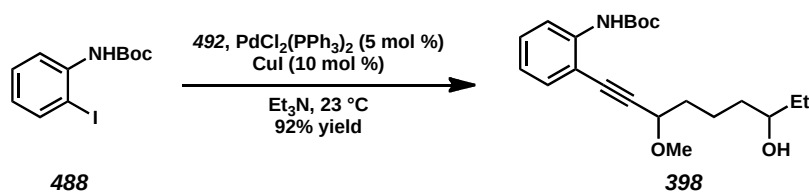
To a solution of ether **486** (2.62 g, assumed 8.00 mmol) in MeOH (80.0 mL, 0.1 M) was added K_2CO_3 (1.21 g, 8.80 mmol) and the reaction mixture was stirred at 23 °C for 15 h. The solution was poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over MgSO_4 and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording alkyne **487** (1.96 g, 96% yield, R_f = 0.56 in 9:1 hexanes/EtOAc) as colorless oil.

To a solution of alkyne **487** (0.768 g, 3.00 mmol) in MeOH (30.0 mL, 0.1 M) was added 10% aq. HCl (approx. 150 μL), and the reaction was stirred at 23 °C for 2 h. The reaction mixture was poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic

phases were dried over MgSO_4 and the solvent was removed via rotary evaporation, affording alcohol **490** (0.443 g crude, $R_f = 0.38$ in 1:1 hexanes/EtOAc) as colorless oil.

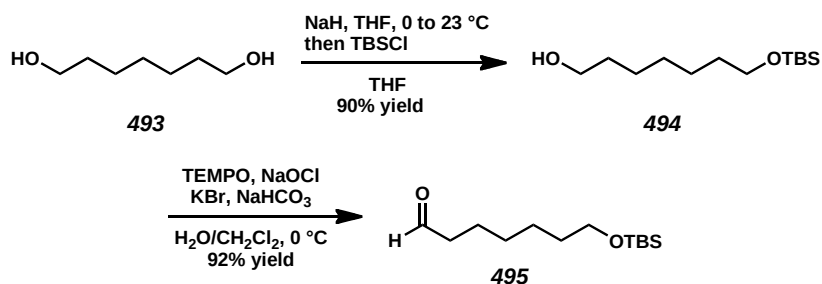
To a solution of alcohol **490** (0.443 g, assumed 3.00 mmol) in CH_2Cl_2 (7.50 mL, 0.4 M) at 0 °C was added TEMPO (4.7 mg, 0.0300 mmol). A solution of KBr (0.393 g, 3.30 mmol) in 5% aq. NaHCO_3 (15.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (1.85 mL, 10% aq., 3.00 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over MgSO_4 , and the solvent was removed by rotary evaporation, affording aldehyde **491** (0.441 g crude, 99% yield, $R_f = 0.50$ in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of aldehyde **491** (0.441 g, assumed 3.00 mmol) in Et_2O (15.0 mL, 0.2 M) cooled to -78 °C was added EtMgBr (1.33 mL, 3.0 M in Et_2O , 4.00 mmol) dropwise. The reaction mixture was stirred at -78 °C for 10 min, then was warmed to 23 °C and quenched with H_2O (20 mL). The mixture was diluted with 1 N HCl (20 mL) and the solution was extracted with Et_2O (2 x 20 mL). The combined organic phases were dried over MgSO_4 , and the solvent was removed by rotary evaporation. The resulting oil was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording alkyne **492** (0.281 g, $R_f = 0.42$ in 2:1 hexanes/EtOAc) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 3.98-3.90 (m, 1H), 3.59-3.47 (m, 1H), 3.41 (s, 3H), 2.44 (d, $J = 1.9$ Hz, 1H), 1.81-1.59 (comp m, 3H), 1.57-1.37 (comp m, 6H), 0.94 (t, $J = 7.4$ Hz, 3H).



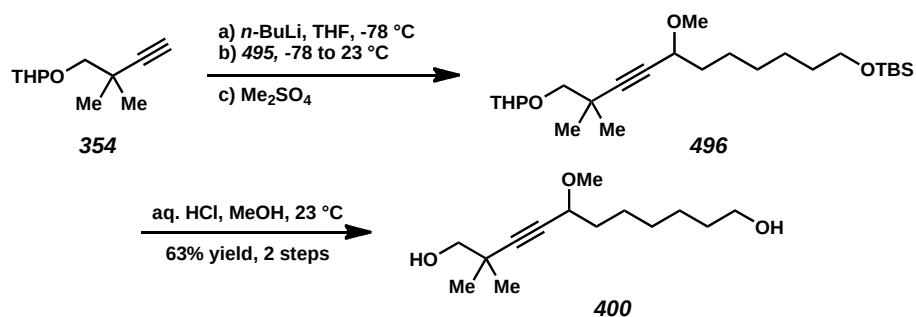
A solution of *N*-Boc-aniline² **488** (0.421 g, 1.32 mmol) and alkyne **492** (0.281 g, 1.65 mmol) in Et₃N (5.00 mL, 0.33 M) was degassed with argon via bubbling for 15 min. CuI (25.1 mg, 0.132 mmol) was added followed by PdCl₂(PPh₃)₂ (46.3 mg, 0.0660 mmol) and the mixture was stirred at 23 °C for 16 h. Upon completion, the reaction mixture was filtered through a SiO₂ plug (0.5 x 3.0 cm), washing with EtOAc (10 mL). The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording *N*-Boc-aniline **398** (0.439 g, 92% yield, *R*_f = 0.43 in 2:1 hexanes/EtOAc) as a pale brown oil.

***N*-Boc-aniline 398:** Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.32-7.28 (m, 1H), 7.24 (br s, 1H), 6.95 (td, *J* = 7.6, 1.2 Hz, 1H), 4.26 (td, *J* = 6.4, 1.2 Hz, 1H), 3.60-3.54 (m, 1H), 3.50 (s, 3H), 1.92-1.81 (m, 2H), 1.75-1.65 (m, 1H), 1.63-1.40 (comp m, 5H) 1.53 (s, 9H), 1.33-1.24 (m, 1H), 0.95 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 139.8, 131.9, 129.9, 122.2, 117.8, 110.8, 95.1, 81.6, 80.0, 73.2, 73.1, 71.9, 56.80, 56.79, 36.66, 36.65, 35.8, 35.7, 30.40, 30.37, 28.5, 21.7, 10.1; IR (film) 3403, 2932, 1734, 1517, 1448, 1155 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + Na)⁺ [C₂₁H₃₁NO₄ + Na]⁺: 384.2, found 383.9.



To a solution of 1,7-heptanediol (**493**, 1.98 g, 15.0 mmol) in THF (45.0 mL, 0.33 M) at 0 °C was added NaH (0.600 g, 60% dispersion in mineral oil, 15.0 mmol). The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 1 h. TBSCl (2.26 g, 15.0 mmol) was then added and the solution was stirred at ambient temperature for 10 h. The reaction mixture was poured into water (100 mL) and extracted with Et₂O (2 x 50 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation, affording alcohol **494** (3.33 g, 90% yield, R_f = 0.36 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **494** (0.738 g, 3.00 mmol) in CH₂Cl₂ (6.00 mL, 0.5 M) at 0 °C was added TEMPO (4.7 mg, 0.0300 mmol). A solution of KBr (0.393 g, 3.30 mmol) in 5% aq. NaHCO₃ (12.0 mL, 0.25 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (1.95 mL, 10% aq., 3.15 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (5 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were washed with H₂O (10 mL) and brine (10 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **495**¹⁶⁴ (3.98 g, 99% yield, R_f = 0.64 in 4:1 hexanes/EtOAc) as a colorless oil.

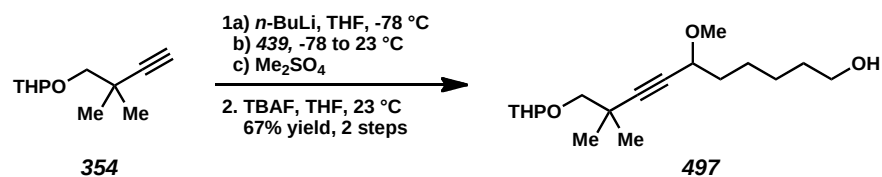


To a solution of acetal **354** (0.364 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **495** (0.488 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.247 mL, 2.60 mmol) was added, and the reaction was stirred at 23 °C for 18 h. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **496** (0.939 g, *R*_f = 0.71 in 4:1 hexanes/EtOAc) as an amber oil.

To a solution of crude ether **496** (0.939 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 2 h. The reaction was quenched with Et₃N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording diol **400** (0.305 g, 63% yield over 2 steps, *R*_f = 0.30 in 1:2 hexanes/EtOAc) as a colorless oil.

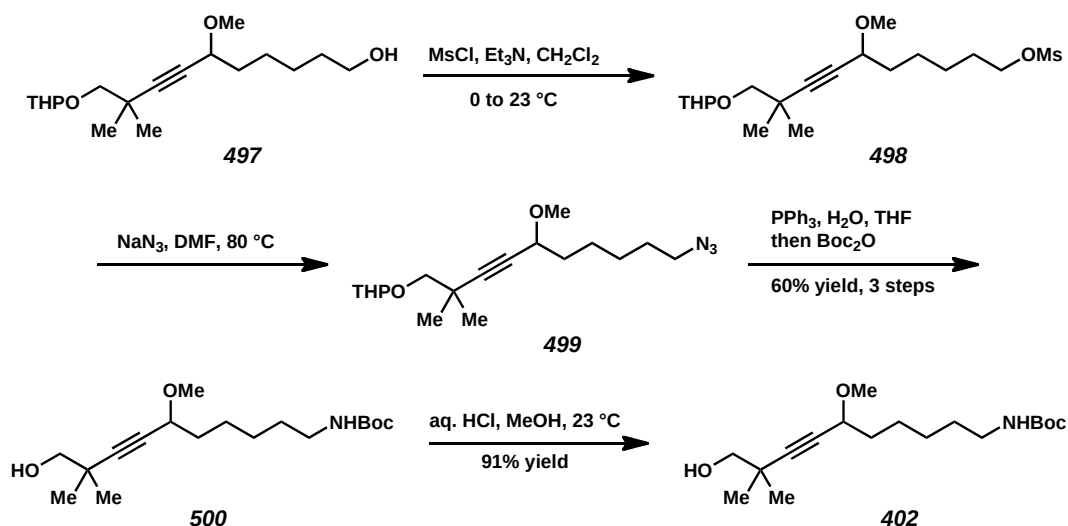
Diol 400: ¹H NMR (400 MHz, CDCl₃) δ 3.93 (t, *J* = 6.4 Hz, 1H), 3.63 (t, *J* = 6.8 Hz, 2H), 3.39 (s, 2H), 3.36 (s, 3H), 1.71-1.61 (comp m, 4H), 1.60-1.53 (comp m, 2H), 1.47-1.40 (comp m, 2H),

1.39-1.32 (comp m, 4H), 1.21 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 91.1, 80.6, 71.7, 71.4, 63.1, 56.3, 35.8, 34.4, 32.7, 29.2, 25.72, 25.65, 25.3; IR (film) 3337, 2932, 2251, 1721, 1053, 905 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{14}\text{H}_{26}\text{O}_3 + \text{Na}$] $^+$: 265.2, found 265.1.



To a solution of acetal **354** (0.662 g, 3.63 mmol) in THF (12.1 mL, 0.30 M) at -78°C under argon was added $n\text{-BuLi}$ (1.45 mL, 2.50 M in hexanes, 3.63 mmol), and the resulting solution was stirred for 30 min at -78°C . Aldehyde **439** (0.837 g, 3.63 mmol) was then added, and the reaction was stirred at -78°C for 10 min, then warmed to 23°C and stirred for 15 min. Me_2SO_4 (0.449 mL, 4.71 mmol) was added, and the reaction was stirred for 16 h at room temperature. The reaction was quenched with 10% aq. NH_4OH (15 mL) and stirred for 15 min. The mixture was diluted with Et_2O (30 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (15 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation affording the crude ether (1.58 g, $R_f = 0.69$ in 4:1 hexanes/ EtOAc) as a colorless oil. The crude residue (1.58 g, assumed 3.63 mmol) was dissolved in THF (3.63 mL, 1.0 M) and stirred at 23°C . TBAF (9.07 mL, 1.0 M in THF, 9.07 mmol) was added dropwise over 2 min, and the reaction mixture was stirred for 2 h. The reaction mixture was poured into H_2O (20 mL) and extracted with Et_2O (2 x 15 mL). The combined organic phases were dried over MgSO_4 and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/ EtOAc

eluent), affording alcohol **497** (0.759 g, 67% yield over 2 steps, $R_f = 0.20$ in 2:1 hexanes/EtOAc) as a colorless oil.



To a solution of alcohol **497** (0.669 g, 2.14 mmol) in CH_2Cl_2 (6.50 mL, 0.33 M) at $0\text{ }^\circ\text{C}$ was added Et_3N (0.595 mL, 4.28 mmol). Methanesulfonyl chloride (0.214 mL, 2.79 mmol) was added dropwise and the reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for 10 min. The resulting solution was diluted with H_2O (15 mL) and Et_2O (30 mL). The phases were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were washed sequentially with 1 N aq. HCl (15 mL), sat. aq. NaHCO_3 (15 mL), H_2O (15 mL) and brine (15 mL), and then dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude mesylate **498** (0.773 g, $R_f = 0.70$ in 1:1 hexanes/EtOAc) as a colorless oil.

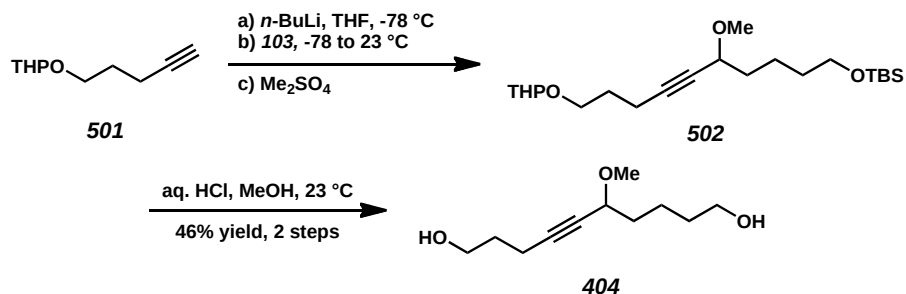
To a solution of crude mesylate **498** (0.773 g, assumed 2.14 mmol) in DMF (3.60 mL, 0.60 M) was added NaN_3 (0.209 g, 3.21 mmol) and the mixture was heated to $80\text{ }^\circ\text{C}$ for 1 h. The solution was cooled to $23\text{ }^\circ\text{C}$ and poured into EtOAc (30 mL). The organic phase was washed sequentially with 10% aq. LiCl (20 mL), H_2O (20 mL), and brine (20 mL), and then dried over

MgSO₄. The solvent was removed via rotary evaporation, affording crude azide **499** (0.605 g, R_f = 0.64 in 4:1 hexanes/EtOAc) as a pale amber oil.

To a solution of azide **499** (0.605 g, assumed 2.14 mmol) in THF was added PPh₃ (1.40 g, 5.30 mmol) followed by H₂O (0.250 mL) and the reaction was stirred at 23 °C for 3 h. Boc₂O (0.700 g, 0.321 mmol) was then added and the reaction was stirred at 23 °C for 6 h. The solvent was removed by rotary evaporation and the crude residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording carbamate **500** (0.528 g, 60% yield over 3 steps, R_f = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of carbamate **500** (0.528 g, 1.28 mmol) in MeOH (12.8 mL, 0.1 M) was added 10% aq. HCl (approx. 50 µL), and the reaction was stirred at 23 °C for 2 h. The reaction was quenched with Et₃N (approx. 50 µL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) affording alcohol **402** (0.381 g, 91% yield, R_f = 0.63 in 1:1 hexanes/EtOAc) as a colorless oil.

Alcohol 402: ¹H NMR (400 MHz, CDCl₃) δ 3.92 (t, J = 6.4 Hz, 1H), 3.40 (d, J = 6.8 Hz, 2H), 3.36 (s, 3H), 3.10 (q, J = 6.4 Hz, 2H), 1.93 (t, J = 6.8 Hz, 1H), 1.72-1.59 (comp m, 3H), 1.51-1.40 (comp m, 12H), 1.37-1.31 (comp m, 2H), 1.21 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 156.1, 91.2, 80.4, 71.7, 71.3, 56.3, 40.6, 35.8, 34.4, 30.1, 28.6, 26.6, 25.68, 25.66, 25.0; IR (film) 3352, 2931, 1687, 1522, 1365, 1167 cm⁻¹; LRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₁₈H₃₃NO₄ + Na]⁺: 350.2, found 350.4.

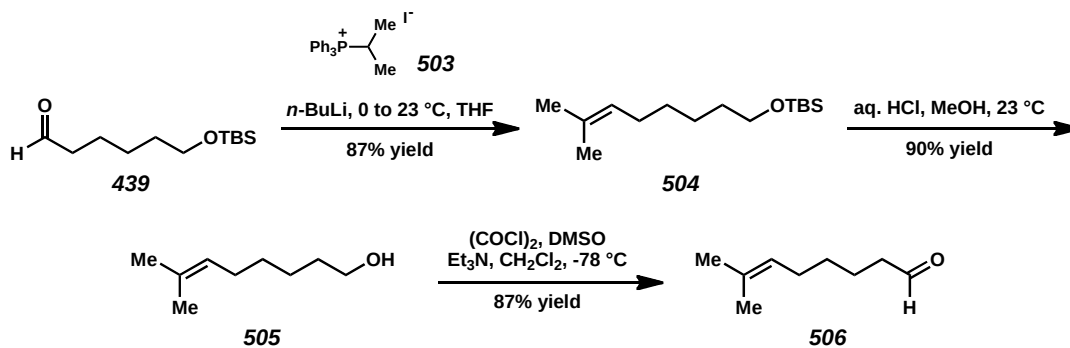


To a solution of acetal **501** (0.504 g, 3.00 mmol) in THF (9.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (1.20 mL, 2.50 M in hexanes, 3.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (0.512 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.371 mL, 3.90 mmol) was added, and the reaction was stirred for 15 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (20 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation and the resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording ether **502** (0.931 g, 78% yield, *R*_f = 0.63 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **502** (0.931 g, 2.34 mmol) in MeOH (23.4 mL, 0.1 M) was added 10% aq. HCl (approx. 75 μL), and the reaction was stirred at 23 °C for 5 h. The reaction was quenched with Et₃N (approx. 75 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (2:1 → 1:5 hexanes/EtOAc eluent) affording diol **404** (0.276 g, 59% yield, *R*_f = 0.18 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 404: ¹H NMR (400 MHz, CDCl₃) δ 3.99 (tt, *J* = 8.4, 2.8 Hz, 1H), 3.53-3.47 (comp m, 2H), 3.43 (s, 3H), 3.42-3.35 (comp m, 2H), 2.24 (td, *J* = 9.2, 2.4 Hz, 2H), 1.91-1.83 (comp m, 2H),

1.70-1.53 (comp m, 4H), 1.50-1.40 (comp m, 2H), 1.04-0.94 (m, 1H), 0.84-0.76 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 85.9, 79.5, 71.5, 62.7, 61.6, 56.4, 35.6, 32.4, 31.4, 21.6, 15.4; IR (film) 3340, 2935, 2231, 1433, 1136, 1056 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{Na})^+$ [$\text{C}_{11}\text{H}_{20}\text{O}_3 + \text{Na}$] $^+$: 223.1, found 223.3.

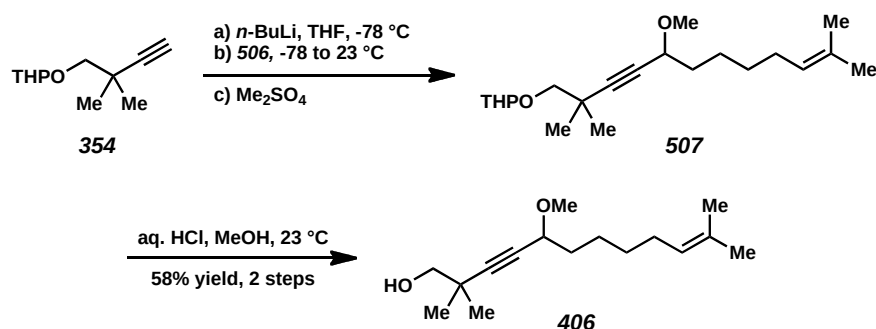


To a solution of isopropyltriphenylphosphonium iodide (**503**, 16.2 g, 37.5 mmol) in THF (150 mL, 0.25 M) at 0 °C under argon was added $n\text{-BuLi}$ (15.0 mL, 2.50 M in hexanes, 37.5 mmol), and the resulting solution was stirred for 30 min at 0 °C. Aldehyde **439** (5.46 g, 23.7 mmol) in THF (10.0 mL) was added rapidly and the resulting mixture was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 1 h. The reaction was quenched with H_2O (50 mL) and sat. aq. NH_4Cl (50 mL). The resulting mixture was extracted with hexanes (2 x 100 mL). The combined organic phases were dried over MgSO_4 and filtered. The solvent was removed via rotary evaporation and the recovered residue was purified by flash chromatography (19:1 hexanes/ EtOAc eluent), affording alkene **504** (5.28 g, 87% yield, R_f = 0.47 in 19:1 hexanes/ EtOAc) as a colorless oil.

To a solution of alkene **504** (5.28 g, 20.6 mmol) in MeOH (103 mL, 0.2 M) was added 10% aq. HCl (0.500 mL), and the reaction was stirred at 23 °C for 30 min. The reaction was quenched

with Et₃N (0.500 mL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) affording alcohol **505** (2.63 g, 90% yield, *R*_f = 0.33 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of oxalyl chloride (1.33 mL, 15.7 mmol) in CH₂Cl₂ (65.0 mL, 0.24 M) at -78 °C under argon was added DMSO (2.23 mL, 31.4 mmol) dropwise, and the resulting solution was stirred at -78 °C for 15 min. Alcohol **505** (1.86 g, 13.1 mmol) in CH₂Cl₂ (10 mL) was added and the resulting solution was stirred at -78 °C for 30 min. Et₃N (9.13 mL, 65.5 mmol) was then added and the solution was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 30 min. The reaction was quenched with H₂O (100 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (50 mL), and the combined organic layers were washed with H₂O (100 mL), then brine (100 mL), and dried over MgSO₄. The solvent was removed via rotary evaporation and the recovered residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording aldehyde **506**¹⁶⁵ (1.60 g, 87% yield, *R*_f = 0.66 in 4:1 hexanes/EtOAc) as an amber oil.

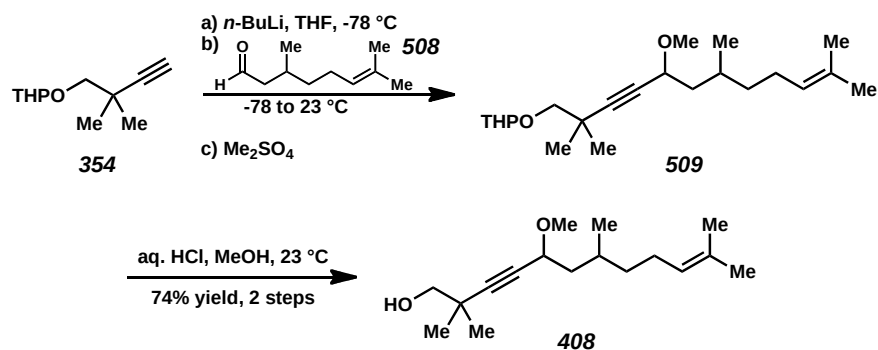


To a solution of acetal **354** (0.364 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the resulting solution

was stirred for 30 min at -78 °C. Aldehyde **506** (0.280 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.247 mL, 2.60 mmol) was added, and the reaction was stirred at 23 °C for 15 h. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (10 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (10 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **507** (0.684 g, *R_f* = 0.82 in 4:1 hexanes/EtOAc) as an amber oil.

To a solution of crude ether **507** (0.684 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 µL), and the reaction was stirred at 23 °C for 2 h. The reaction was quenched with Et₃N (approx. 50 µL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording alcohol **406** (0.295 g, 58% yield over 2 steps, *R_f* = 0.33 in 4:1 hexanes/EtOAc) as a colorless oil.

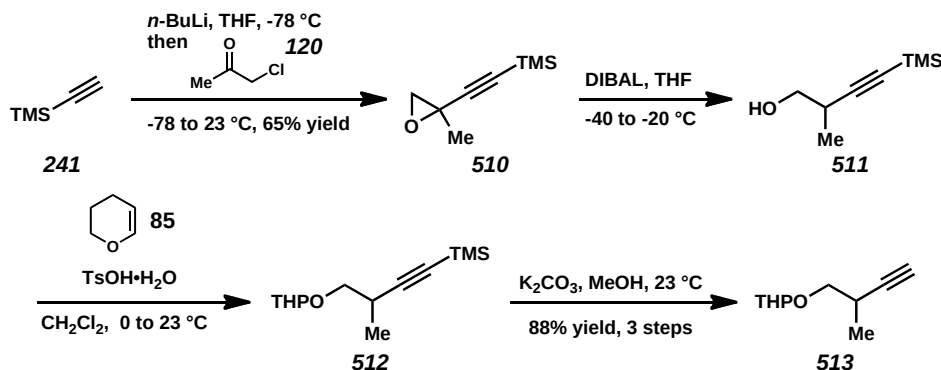
Alcohol 406: ¹H NMR (400 MHz, CDCl₃) δ 5.10 (tt, *J* = 6.8, 1.2 Hz, 1H), 3.93 (t, *J* = 6.4 Hz, 1H), 3.40 (d, *J* = 6.8 Hz, 2H), 3.37 (s, 3H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.77 (t, *J* = 6.8 Hz, 1H), 1.73-1.62 (comp m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.46-1.30 (comp m, 4H), 1.21 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 131.6, 124.7, 91.0, 80.7, 71.8, 71.5, 56.3, 35.9, 34.5, 29.7, 28.0, 25.9, 25.7, 25.1, 17.8; IR (film) 3444, 2931, 1459, 1337, 1106, 1057 cm⁻¹; LRMS (ESI⁺) *m/z* calc'd for (M + H)⁺ [C₁₆H₂₈O₂ + H]⁺: 253.2, found 253.1.



To a solution of acetal **354** (0.546 g, 3.00 mmol) in THF (9.00 mL, 0.33 M) at $-78\text{ }^{\circ}\text{C}$ under argon was added $n\text{-BuLi}$ (1.30 mL, 2.32 M in hexanes, 3.00 mmol), and the resulting solution was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$. ($\pm$)-Citronellal (**508**, 0.544 mL, 3.00 mmol) was then added, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then warmed to $23\text{ }^{\circ}\text{C}$ and stirred for 15 min. Me_2SO_4 (0.343 mL, 3.60 mmol) was added, and the reaction was stirred at $23\text{ }^{\circ}\text{C}$ for 18 h. The reaction was quenched with 10% aq. NH_4OH (10 mL) and stirred for 15 min. The mixture was diluted with Et_2O (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **509** (1.15 g crude, $R_f = 0.80$ in 4:1 hexanes/ EtOAc) as an amber oil.

To a solution of crude ether **509** (1.15 g, assumed 3.00 mmol) in MeOH (30.0 mL, 0.1 M) was added 10% aq. HCl (approx. 100 μL), and the reaction was stirred at $23\text{ }^{\circ}\text{C}$ for 2 h. The reaction was quenched with Et_3N (approx. 100 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (9:1 hexanes/ EtOAc eluent) affording alcohol **408** (0.594 g, 74% yield over 2 steps, $R_f = 0.43$ in 4:1 hexanes/ EtOAc) as a colorless oil.

Alcohol 408: Characterized as a 1:1 mixture of diastereomers. ^1H NMR (300 MHz, C_6D_6) δ 5.29 (m, 1H), 4.13 (m, 1H), 3.39 (s, 2H), 3.38 (s, 3H), 2.20-2.08 (comp m, 2H), 2.06-1.82 (comp m, 2H), 1.79 (s, 1.5H), 1.77 (s, 1.5H), 1.65 (s, 3H), 1.56-1.41 (comp m, 2H), 1.38-1.27 (m, 1H), 1.23 (s, 6H), 1.00 (d, $J = 6.3$ Hz, 3H).



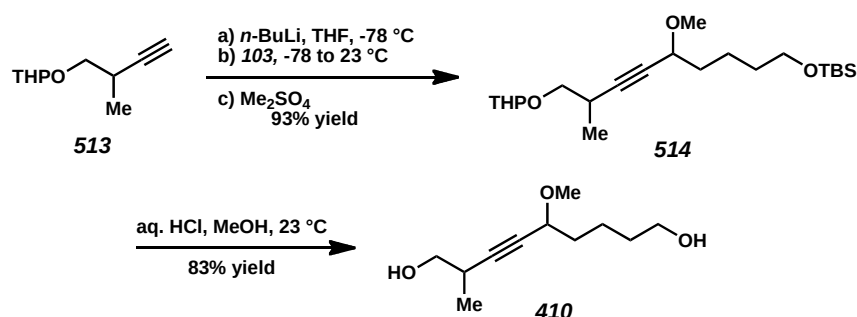
To a solution of trimethylsilylacetylene (**241**, 5.64 mL, 40.0 mmol) in THF (200 mL, 0.2 M) cooled to -78°C under argon was added $n\text{-BuLi}$ (16.0 mL, 40.0 mmol), and the resulting solution was stirred for 30 min. Chloroacetone (**120**, 3.29 mL, 40.0 mmol) was added and the reaction mixture was warmed to 23°C and stirred for 28 h. The solvent was removed by rotary evaporation and the resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording epoxide **510** (4.03 g, 65% yield, $R_f = 0.71$ in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of epoxide **510** (4.03 g, 26.1 mmol) in THF (26.1 mL, 1.0 M) cooled to -40°C under argon was added DIBAL (31.3 mL, 1.0 M in hexanes, 31.3 mmol). The reaction mixture was stirred for 1 h at -40°C . The reaction was quenched with water (25 mL) and diluted with 1 N HCl (50 mL). The mixture was extracted with Et_2O (2 x 40 mL), and the combined organic layers were washed with H_2O (50 mL), then brine (50 mL), and dried over MgSO_4 . The solvent

was removed by rotary evaporation, affording crude alcohol **511** (4.13 g, $R_f = 0.36$ in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **511** (4.13 g, assumed 26.1 mmol) in CH_2Cl_2 (52.2 mL, 0.5 M) at 0 °C was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (49.8 mg, 0.261 mmol), followed by slow addition of 3,4-dihydro-2H-pyran (**85**, 2.31 mL, 27.4 mmol). After stirring at 0 °C for 5 min the reaction was warmed to 23 °C and stirred for 4 h. The reaction was quenched with sat. aq. NaHCO_3 (50 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL), and the combined organic phases were dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude acetal **512** (6.40 g crude, $R_f = 0.53$ in 9:1 hexanes/EtOAc) as a colorless oil.

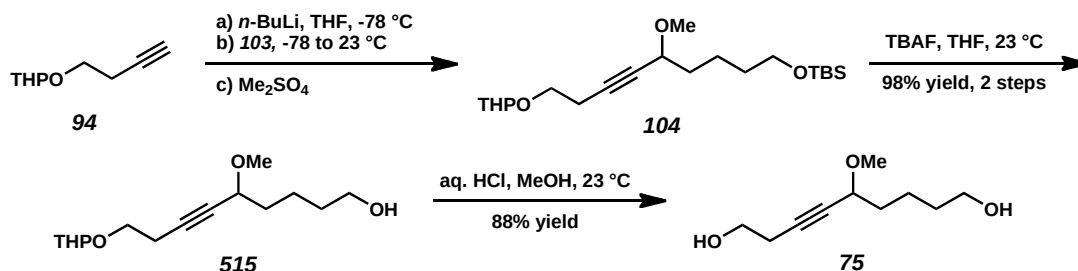
To a solution of crude acetal **512** (6.40 g, assumed 26.1 mmol) in MeOH (174 mL, 0.15 M) was added K_2CO_3 (4.32 g, 31.3 mmol) and the reaction mixture was stirred at 23 °C for 16 h. The solution was poured into H_2O (200 mL), and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried over MgSO_4 and the solvent was removed via rotary evaporation. The resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent) affording alkyne **513** (3.86 g, 88% yield over 3 steps, $R_f = 0.46$ in 9:1 hexanes/EtOAc) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 4.68-4.61 (m, 1H), 3.95-3.82 (m, 1H), 3.80-3.74 (m, 0.5H), 3.66-3.58 (m, 0.5H), 3.56-3.44 (comp m, 1.5H), 3.37-3.29 (m, 0.5H), 2.73 (sextet of doublets, $J = 6.9, 1.9$ Hz, 1H), 2.05 (t, $J = 1.9$ Hz, 1H), 1.90-1.46 (comp m, 6H), 1.22 (d, $J = 6.9$ Hz, 3H).



To a solution of acetal **513** (1.01 g, 6.00 mmol) in THF (18.0 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (2.40 mL, 2.50 M in hexanes, 6.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (1.30 g, 6.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.685 mL, 7.20 mmol) was added, and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (20 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation and the resulting residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent), affording ether **514** (2.21 g, 93% yield, *R*_f = 0.41 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of crude ether **514** (1.59 g, assumed 4.00 mmol) in MeOH (40.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 2 h. The reaction was quenched with Et₃N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (4:1 → 1:2 hexanes/EtOAc eluent) affording diol **410** (0.668 g, 83% yield, *R*_f = 0.22 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 410: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 3.94 (td, J = 6.4, 2.0 Hz, 1H), 3.62 (t, J = 6.4 Hz, 2H), 3.57-3.49 (comp m, 2H), 3.36 (s, 3H), 2.73-2.64 (m, 1H), 2.27 (s, 2H), 1.77-1.63 (comp m, 2H), 1.61-1.48 (comp m, 4H), 1.16 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 88.21, 88.18, 80.5, 71.4, 66.9, 62.6, 56.4, 35.4, 32.3, 29.6, 21.6, 17.2; IR (film) 3349, 2934, 1455, 1336, 1044 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{11}\text{H}_{20}\text{O}_3 + \text{H}$] $^+$: 201.1, found 201.0.

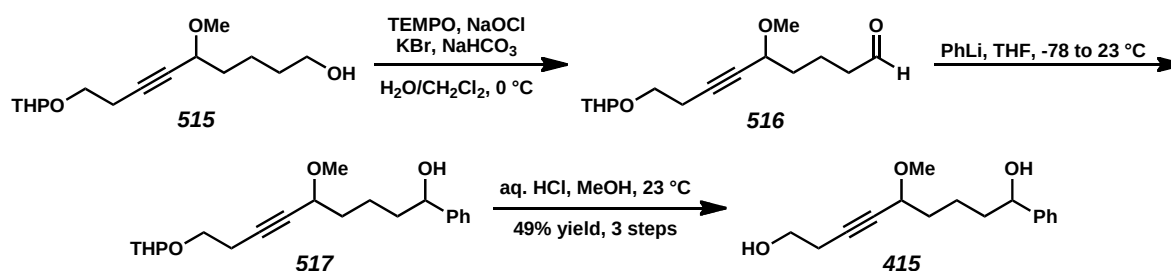


To a solution of acetal **94**¹⁶⁶ (0.770 g, 5.00 mmol) in THF (15.0 mL, 0.33 M) at $-78\text{ }^\circ\text{C}$ under argon was added $n\text{-BuLi}$ (2.00 mL, 2.50 M in hexanes, 5.00 mmol), and the resulting solution was stirred for 30 min at $-78\text{ }^\circ\text{C}$. Aldehyde **103** (1.08 g, 5.00 mmol) was then added, and the reaction was stirred at $-78\text{ }^\circ\text{C}$ for 10 min, then warmed to $23\text{ }^\circ\text{C}$ and stirred for 15 min. Me_2SO_4 (0.618 mL, 6.50 mmol) was added, and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 10% aq. NH_4OH (10 mL) and stirred for 15 min. The mixture was diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **104** (1.99 g, R_f = 0.67 in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of crude ether **104** (1.99 g, assumed 5.00 mmol) in THF (5.00 mL, 1.0 M) at 23 °C was added TBAF (15.0 mL, 1.0 M in THF, 15.0 mmol) dropwise over 5 min, and the reaction mixture was stirred for 2 h. The reaction mixture was poured into H₂O (20 mL) and extracted with Et₂O (2 x 15 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed by rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent), affording alcohol **515** (1.33 g, 98% yield, R_f = 0.39 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **515** (0.946, 3.50 mmol) in MeOH (35.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μ L), and the reaction was stirred at 23 °C for 2 h. The reaction was quenched with Et₃N (approx. 50 μ L), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (2:1 $\rightarrow$ 1:4 hexanes/EtOAc eluent) affording diol **75** (0.574 g, 88% yield, R_f = 0.12 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 75: ¹H NMR (400 MHz, CDCl₃) δ 3.94 (tt, J = 6.4, 2.0 Hz, 1H), 3.73-3.70 (t, J = 6.0 Hz, 2H), 3.66-3.63 (t, J = 6.0 Hz, 2H), 3.38 (s, 3H), 2.50 (td, J = 6.0, 2.0 Hz, 2H), 2.01-1.86 (br s, 2H), 1.77-1.66 (comp m, 2H), 1.63-1.48 (comp m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 83.2, 80.8, 71.5, 62.7, 61.2, 56.5, 35.4, 32.4, 23.3, 21.6; IR (film) 3348, 2937, 1457, 1338, 1107, 1046 cm⁻¹; LRMS (ESI⁺) m/z calc'd for (M + H)⁺ [C₁₀H₁₈O₃ + H]⁺: 187.1, found 187.0.

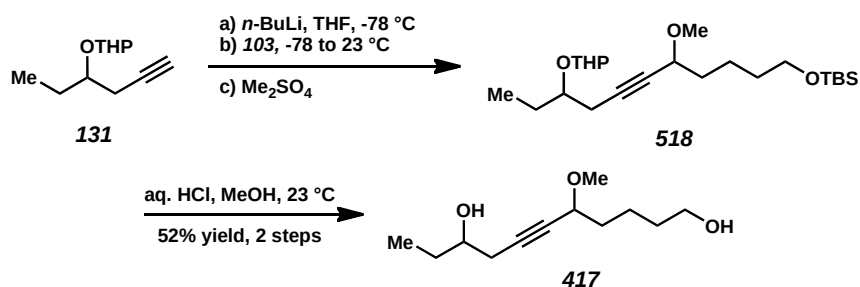


To a solution of alcohol **515** (0.531 g, 1.97 mmol) in CH₂Cl₂ (5.00 mL, 0.4 M) at 0 °C was added TEMPO (3.07 mg, 0.0197 mmol). A solution of KBr (0.257 g, 2.16 mmol) in 5% aq. NaHCO₃ (10.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (1.47 mL, 13% aq., 3.10 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (10 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were washed with H₂O (20 mL) and brine (20 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation, affording aldehyde **516** (0.462 g crude, *R_f* = 0.67 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of crude aldehyde **516** (0.462 g, 1.72 mmol) in THF (8.60 mL, 0.2 M) cooled to -78 °C was added PhLi (1.00 mL, 1.8 M in dibutyl ether, 1.80 mmol) dropwise. The reaction mixture was stirred at -78 °C for 10 min, then was warmed to 23 °C and quenched with H₂O (10 mL). The solution was extracted with Et₂O (2 x 10 mL), and the combined organic layers were dried over MgSO₄. The solvent was removed by rotary evaporation, affording alcohol **517** (0.637 g crude, *R_f* = 0.60 in 1:1 hexanes/EtOAc) as a brown oil.

To a solution of crude alcohol **517** (0.637 g, assumed 1.72 mmol) in MeOH (17.2 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μ L), and the reaction was stirred at 23 °C for 1 h. The reaction was quenched with Et₃N (approx. 50 μ L), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (2:1 $\rightarrow$ 1:2 hexanes/EtOAc eluent) affording diol **415** (0.251 g, 49% yield over 3 steps, R_f = 0.35 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 415: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (comp m, 3H), 7.29-7.25 (comp m, 2H), 4.68 (t, J = 6.4 Hz, 1H), 3.94-3.90 (m, 1H), 3.73-3.66 (comp m, 2H), 3.36 (s, 3H), 2.50-2.45 (comp m, 2H), 2.14-1.96 (comp m, 2H), 1.87-1.79 (m, 1H), 1.78-1.66 (comp m, 3H), 1.64-1.54 (m, 1H), 1.53-1.41 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 144.90, 144.85, 128.6, 127.7, 126.00, 125.97, 83.3, 83.2, 80.9, 80.8, 74.5, 71.5, 71.4, 61.2, 56.5, 38.8, 35.54, 35.46, 23.29, 23.26, 21.81, 21.75; IR (film) 3368, 2937, 1453, 1337, 1103, 1048, 701 cm⁻¹; LRMS (ESI⁺) m/z calc'd for (M + Na)⁺ [C₁₆H₂₂O₃ + Na]⁺: 285.2, found 285.0.

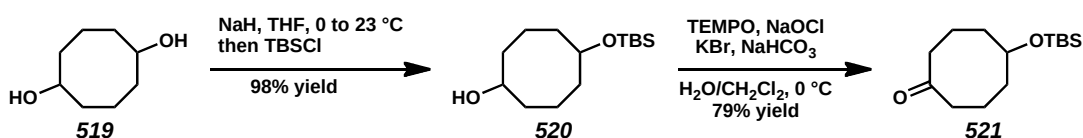


To a solution of acetal **131** (0.364 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (0.432 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄

(0.247 mL, 2.60 mmol) was added, and the reaction was stirred for 18 h at room temperature. The reaction was quenched with 10% aq. NH_4OH (10 mL) and stirred for 15 min. The mixture was diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **518** (0.939 g, $R_f = 0.78$ in 4:1 hexanes/ EtOAc) as a colorless oil.

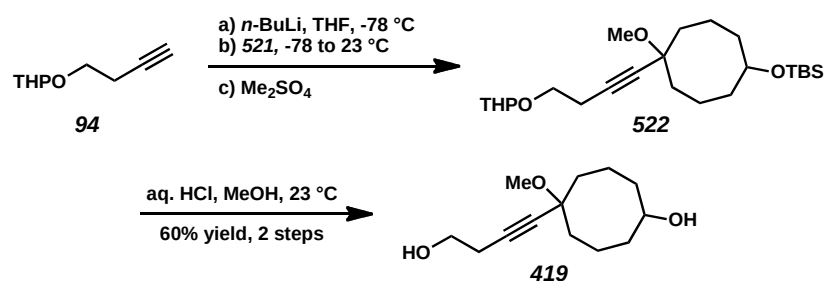
To a solution of crude ether **518** (0.939 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 5 h. The reaction was quenched with Et_3N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (2:1 $\rightarrow$ 1:2 hexanes/ EtOAc eluent) affording diol **417** (0.224 g, 52% yield over 2 steps, $R_f = 0.24$ in 1:2 hexanes/ EtOAc) as a colorless oil.

Diol 417: Characterized as a mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) δ 3.95 (td, $J = 6.4, 1.2$ Hz, 1H), 3.70-3.63 (comp m, 3H), 3.38 (s, 3H), 2.50-2.44 (m, 1H), 2.39-2.33 (m, 1H), 1.89-1.84 (comp m, 2H), 1.77-1.65 (comp m, 2H), 1.63-1.49 (comp m, 5H), 1.47-1.29 (m, 1H), 0.98-0.94 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 82.88, 82.86, 81.4, 71.6, 71.5, 62.7, 56.5, 37.4, 37.1, 35.5, 32.7, 32.4, 29.3, 28.0, 27.3, 22.9, 22.0, 21.6, 14.2, 10.1; IR (film) 3358, 2933, 2237, 1461, 1332, 1107, 978 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{12}\text{H}_{22}\text{O}_3 + \text{H}$] $^+$: 215.2, found 215.0.



To a solution of 1,5-cyclooctanediol (**519**, 2.16 g, 15.0 mmol) in THF (75.0 mL, 0.2 M) at 0 °C was added NaH (0.360 g, 15.0 mmol, washed with hexanes to remove mineral oil). The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 °C and stirred for 2 h. TBSCl (2.26 g, 15.0 mmol) was then added and the solution was stirred at ambient temperature for 18 h. The reaction mixture was poured into water (100 mL) and extracted with Et₂O (2 x 75 mL). The combined organic phases were dried over MgSO₄, and the solvent was removed by rotary evaporation, affording alcohol **520** (3.83 g, 98% yield, R_f = 0.27 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of alcohol **520** (2.58 g, 10.0 mmol) in CH₂Cl₂ (25.0 mL, 0.4 M) at 0 °C was added TEMPO (15.6 mg, 0.100 mmol). A solution of KBr (1.30 g, 11.0 mmol) in 5% aq. NaHCO₃ (50.0 mL, 0.2 M) was then added to the organic phase, and the mixture was stirred vigorously at 0 °C. NaOCl (6.82 mL, 10% aq., 11.0 mmol) was added dropwise, and the reaction mixture was stirred for 15 min. Upon completion, a saturated solution of Na₂S₂O₃ (20 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organic phases were washed with H₂O (30 mL) and brine (30 mL). The organic phase was dried over MgSO₄, and the solvent was removed by rotary evaporation. The resulting oil was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording ketone **521**¹⁶⁷ (2.02 g, 79% yield, R_f = 0.55 in 4:1 hexanes/EtOAc) as a colorless oil.

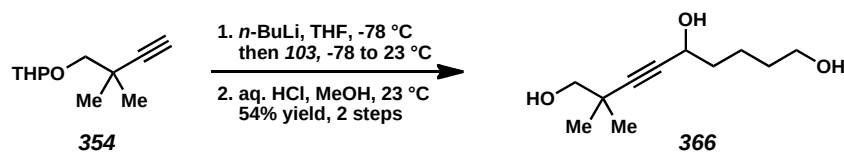


To a solution of acetal **94** (0.308 g, 2.00 mmol) in THF (6.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.800 mL, 2.50 M in hexanes, 2.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Ketone **521** (0.512 g, 2.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me₂SO₄ (0.247 mL, 2.60 mmol) was added, and the reaction was stirred for 18 h at room temperature. The reaction was quenched with 10% aq. NH₄OH (10 mL) and stirred for 15 min. The mixture was diluted with Et₂O (20 mL), and the phases were separated. The aqueous phase was extracted with Et₂O (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO₄. The solvent was removed via rotary evaporation, affording crude ether **522** (0.882 g, *R*_f = 0.71 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of ether **522** (0.882 g, assumed 2.00 mmol) in MeOH (20.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 5 h. The reaction was quenched with Et₃N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (2:1 → 1:2 hexanes/EtOAc eluent) affording diol **419** (0.273 g, 60% yield over 2 steps, *R*_f = 0.15 in 1:2 hexanes/EtOAc) as a colorless oil.

Diol 419: Characterized as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 3.88-3.79 (m, 1H), 3.72 (t, *J* = 6.4 Hz, 0.33H), 3.70 (t, *J* = 6.4 Hz, 0.66H), 3.30 (s, 2H), 3.28 (s, 1H), 2.51

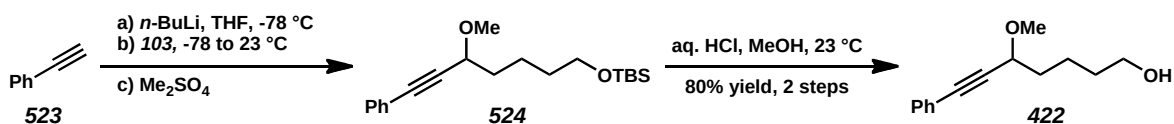
(t, $J = 6.4$ Hz, 0.7H), 2.50 (t, $J = 6.4$ Hz, 1.3H), 1.96-1.86 (comp m, 6H), 1.85-1.77 (comp m, 2H), 1.75-1.58 (comp m, 3H), 1.56-1.47 (comp m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 84.4, 83.3, 82.8, 81.9, 71.5, 71.3, 61.37, 61.35, 51.1, 50.9, 37.8, 37.6, 35.8, 35.4, 23.2, 18.90, 18.85; IR (film) 3359, 2934, 1446, 1051, 959 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{13}\text{H}_{22}\text{O}_3 + \text{H}$] $^+$: 227.2, found 227.0.



To a solution of acetal **354** (0.182 g, 1.00 mmol) in THF (3.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.431 mL, 2.32 M in hexanes, 1.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (0.216 g, 1.00 mmol) was then added and the reaction was stirred at -78 °C for 10 min, then warmed to room temperature and stirred for 15 min. The reaction was quenched with H_2O (5 mL), diluted with Et_2O (5 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (5 mL), and the combined organic phases were washed with brine (10 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation and the recovered residue was dissolved in MeOH (10.0 mL, 0.1 M). 10% aq. HCl (approx. 50 μL) was added, and the reaction was stirred at 23 °C for 7 h. The reaction was quenched with Et_3N (approx 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (1:1 $\rightarrow$ 0:1 hexanes/ EtOAc eluent) affording triol **366** (0.108 g, 54% yield over 2 steps, $R_f = 0.10$ in 1:4 hexanes/ EtOAc) as a colorless oil.

Triol 366: ^1H NMR (400 MHz, CDCl_3) δ 4.38 (t, $J = 6.4$ Hz, 1H), 3.65 (app. t, $J = 6.0$ Hz, 3H), 3.39 (s, 2H), 1.73-1.66 (comp m, 2H), 1.63-1.55 (comp m, 3H), 1.54-1.42 (comp m, 3H), 1.18 (s,

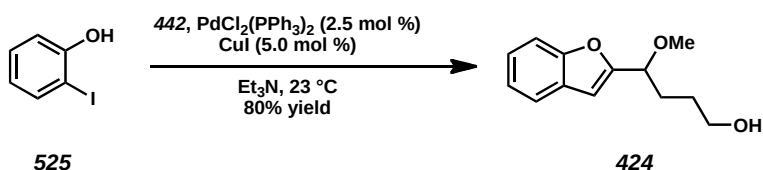
6H); ^{13}C NMR (100 MHz, CDCl_3) δ 90.3, 82.4, 71.7, 62.5, 62.2, 37.5, 34.2, 32.1, 25.7, 25.6, 21.4; IR (film) 3332, 2937, 1657, 1480, 1056 cm^{-1} ; LRMS (ESI $^+$) m/z calc'd for $(\text{M} - \text{OH})^+$ [$\text{C}_{11}\text{H}_{20}\text{O}_3 - \text{OH}$] $^+$: 183.1, found 183.2.



To a solution of phenylacetylene (**523**, 0.109 mL, 1.00 mmol) in THF (3.00 mL, 0.33 M) at -78 °C under argon was added *n*-BuLi (0.400 mL, 2.50 M in hexanes, 1.00 mmol), and the resulting solution was stirred for 30 min at -78 °C. Aldehyde **103** (0.216 g, 1.00 mmol) was then added, and the reaction was stirred at -78 °C for 10 min, then warmed to 23 °C and stirred for 15 min. Me_2SO_4 (0.114 mL, 1.20 mmol) was added, and the reaction was stirred for 15 h at room temperature. The reaction was quenched with 10% aq. NH_4OH (5 mL) and stirred for 15 min. The mixture was diluted with Et_2O (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL), and the combined organic phases were washed with brine (20 mL) and dried over MgSO_4 . The solvent was removed via rotary evaporation, affording crude ether **524** (0.348 g, R_f = 0.82 in 4:1 hexanes/ EtOAc) as a colorless oil.

To a solution of crude ether **524** (0.173 g, assumed 1.00 mmol) in MeOH (10.0 mL, 0.1 M) was added 10% aq. HCl (approx. 50 μL), and the reaction was stirred at 23 °C for 1 h. The reaction was quenched with Et_3N (approx. 50 μL), and the solvent was removed via rotary evaporation. The resulting residue was purified by flash chromatography (2:1 hexanes/ EtOAc eluent) affording alcohol **422** (0.174 g, 80% yield over 2 steps, R_f = 0.58 in 1:1 hexanes/ EtOAc) as a colorless oil.

Alcohol 422: ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.43 (comp m, 2H), 7.33-7.29 (comp m, 3H), 4.18 (t, J = 6.4 Hz, 1H), 3.68 (t, J = 6.0 Hz, 2H), 3.47 (s, 3H), 1.87-1.80 (comp m, 2H), 1.67-1.56 (comp m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 131.9, 128.5, 128.4, 122.9, 88.0, 86.1, 71.8, 62.9, 56.7, 35.5, 32.6, 21.7; IR (film) 3376, 2935, 1489, 1337, 1071, 756 cm^{-1} ; LRMS (ESI^+) m/z calc'd for $(\text{M} + \text{H})^+$ [$\text{C}_{14}\text{H}_{18}\text{O}_2 + \text{H}$] $^+$: 219.1, found 219.0.



To a solution of 2-iodophenol (**525**, 0.220 g, 1.00 mmol) and alkyne **442** (0.153 g, 1.20 mmol) in 1,4-dioxane (0.500 mL, 2.0 M) at 23 °C was added Et_3N (0.500 mL, 1.0 M final concentration), and the resulting solution was degassed with argon via bubbling for 15 min. CuI (19.0 mg, 0.100 mmol) was added followed by $\text{PdCl}_2(\text{PPh}_3)_2$ (35.0 mg, 0.0500 mmol), and the mixture was stirred at 23 °C for 3 h. Upon completion, the reaction mixture was filtered through a SiO_2 plug (0.5 x 3.0 cm), washing with EtOAc (10 mL). The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (4:1 hexanes/ EtOAc eluent) affording benzofuran **424** (0.176 g, 80% yield, R_F = 0.39 in 1:1 hexanes/ EtOAc) as a pale brown oil.

Benzofuran 424: ^1H NMR (400 MHz, CDCl_3) δ 7.55 (ddd, J = 7.6, 1.2, 0.4 Hz, 1H), 7.49-7.46 (m, 1H), 7.29-7.20 (comp m, 2H), 6.67-6.66 (m, 1H), 4.35 (dd, J = 7.6, 6.0 Hz, 1H), 3.67 (t, J = 6.4 Hz, 2H), 3.35 (s, 3H), 2.11-1.94 (comp m, 3H), 1.77-1.62 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 154.9, 127.9, 124.1, 122.7, 120.9, 111.3, 104.6, 76.7, 62.6, 56.9, 30.9,

28.9; IR (film) 3388, 2934, 1473, 1252, 1110, 1061, 933 cm^{-1} ; HRMS (ESI^+) m/z calc'd for $(\text{M} - \text{OMe})^+$ [$\text{C}_{13}\text{H}_{16}\text{O}_3 - \text{OMe}]^+$: 189.1, found 189.0.

CHAPTER FIVE NOTES AND REFERENCES

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- ¹⁴² The calculated bond dissociation energy for PtCH_2^+ is 119.7 kcal/mol while AuCH_2^+ is 90.9 kcal/mol, indicating the combination of σ and π -donation is stronger in platinum. See: Heinemann, C.; Hertwig, R. H.; Wesendrup, R.; Koch, W.; Schwarz, H. *J. Am. Chem. Soc.* **1995**, *117*, 495-500.
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¹⁵⁰ Exposure to *p*-toluenesulfonic acid resulted in slow conversion to the bisheterocycle, with considerable starting material remaining after 5 d.

¹⁵¹ Another possibility is that benzofuran reenters the catalytic cycle via metalation with platinum at the 3-position.

¹⁵² See Chapter 4.3.2 for relevant discussions.

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APPENDIX ONE

Spectra Relevant to Chapter Two

Synthesis of Polysubstituted Furans via 1,2-Hydride Migrations into Platinum Carbenes

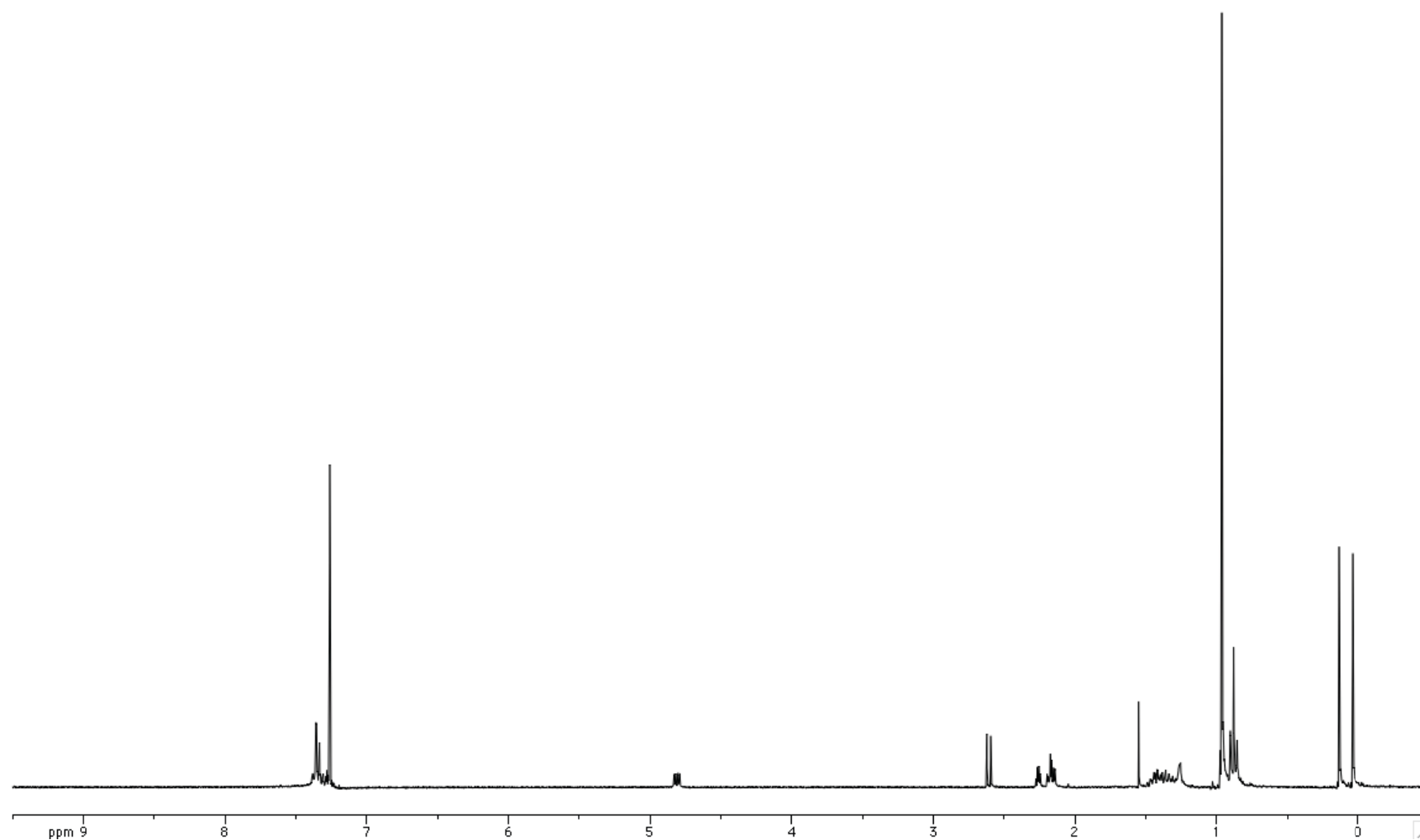
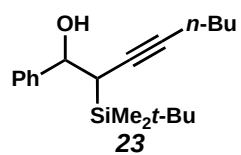
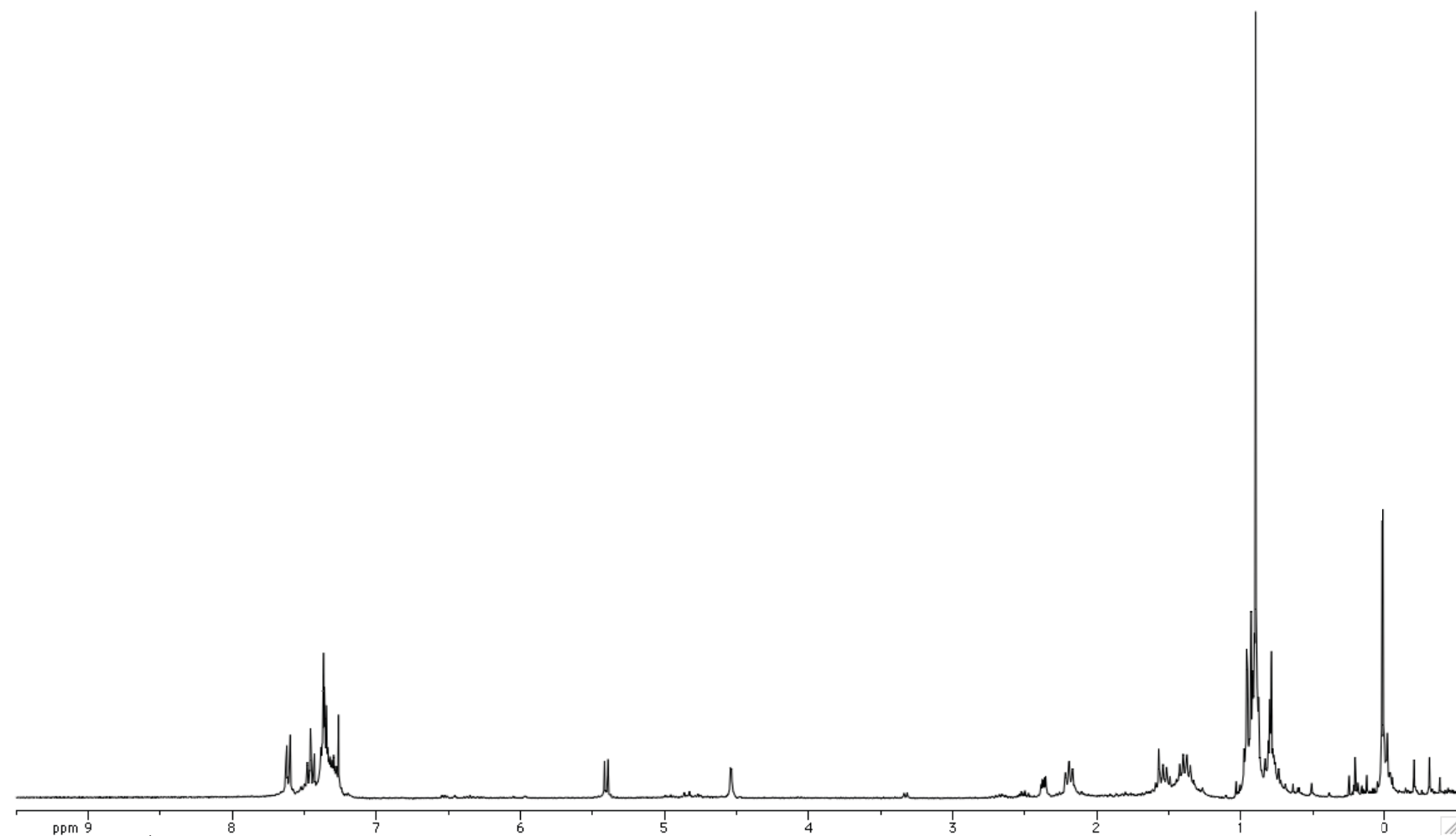


Figure A1.1 ^1H NMR (300 MHz, CDCl_3) of compound **23**



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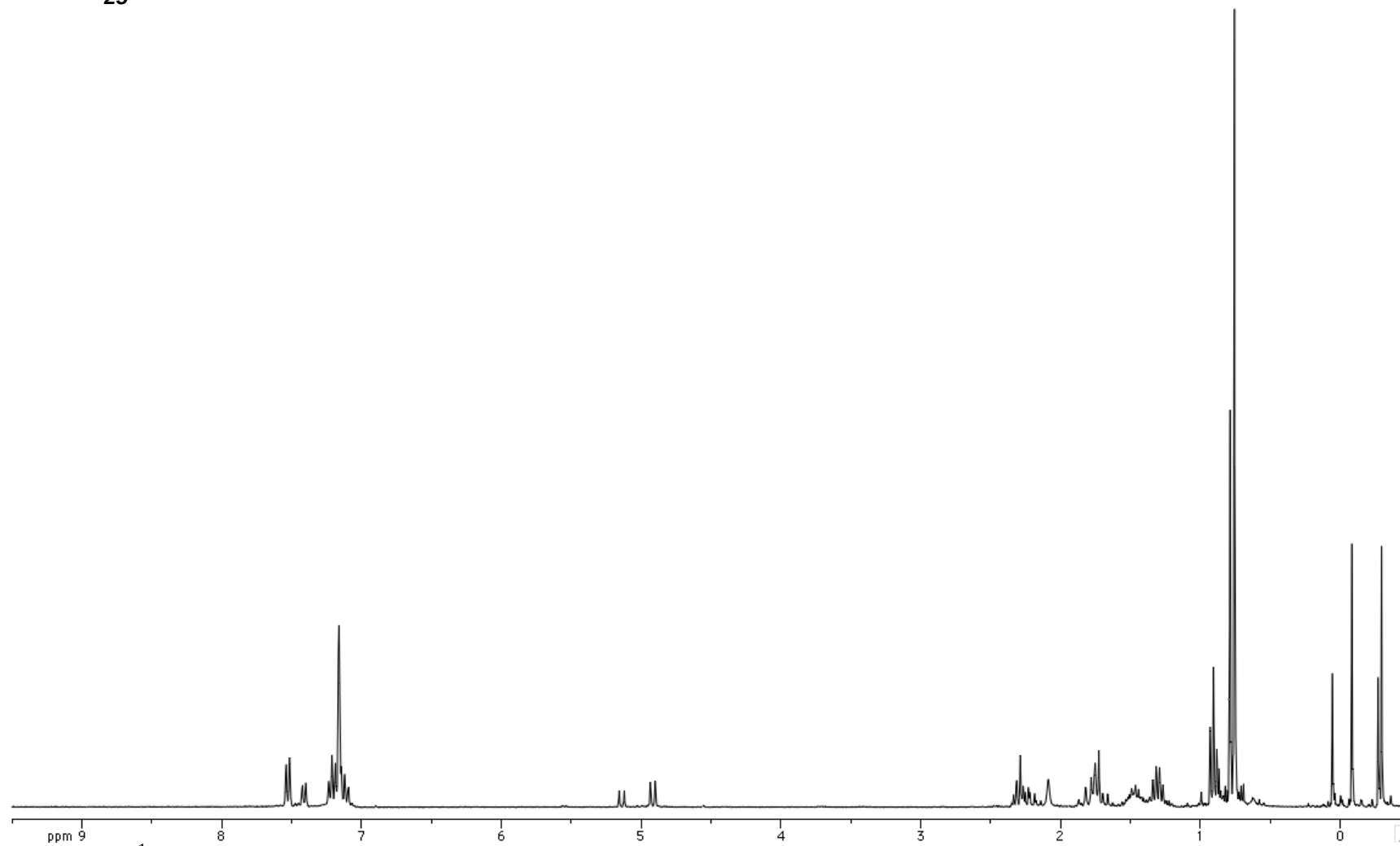
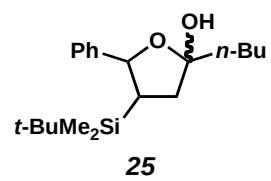


Figure A1.3 ^1H NMR (300 MHz, C_6D_6) of compound **25**

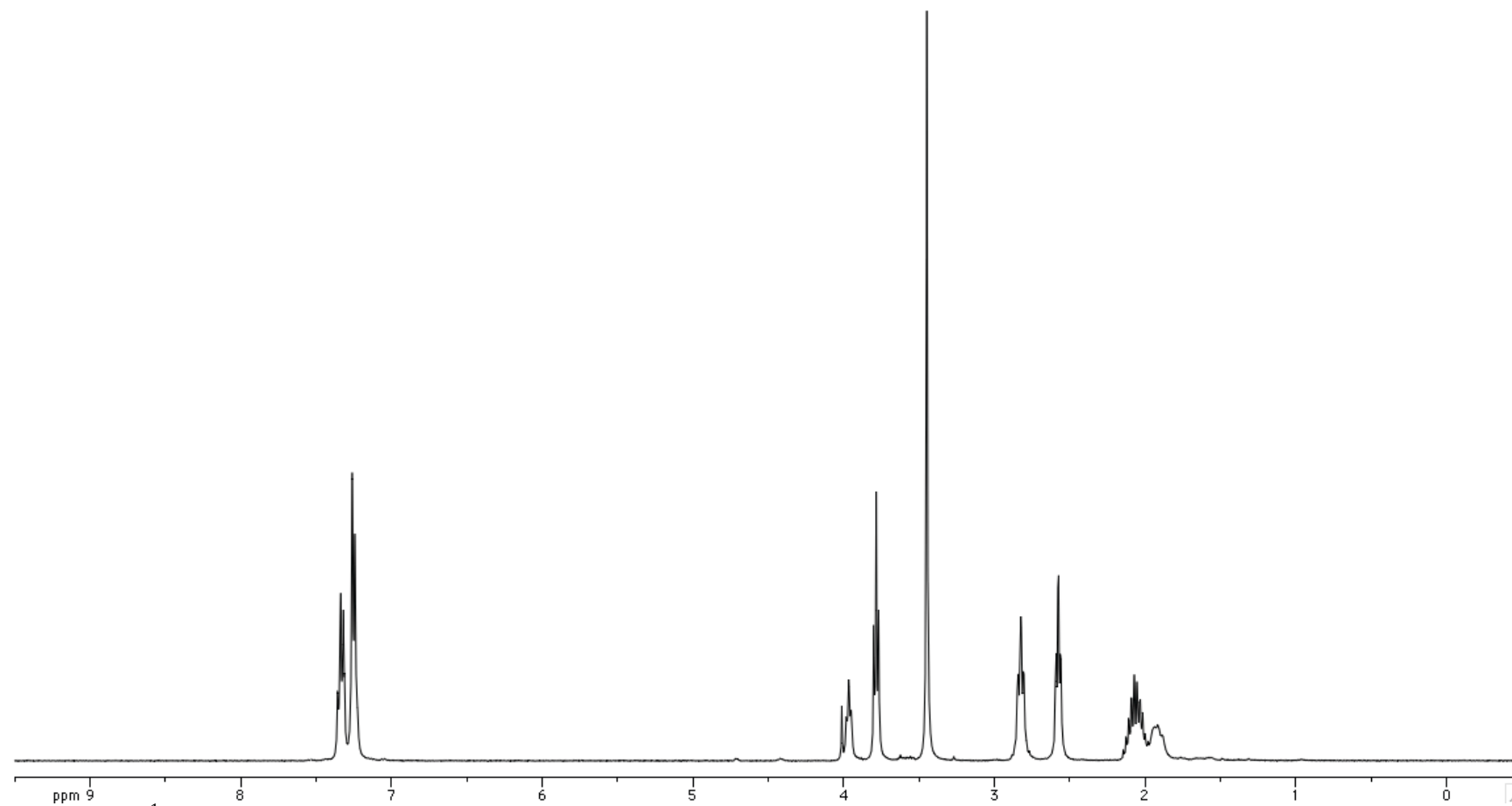
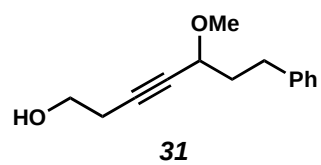
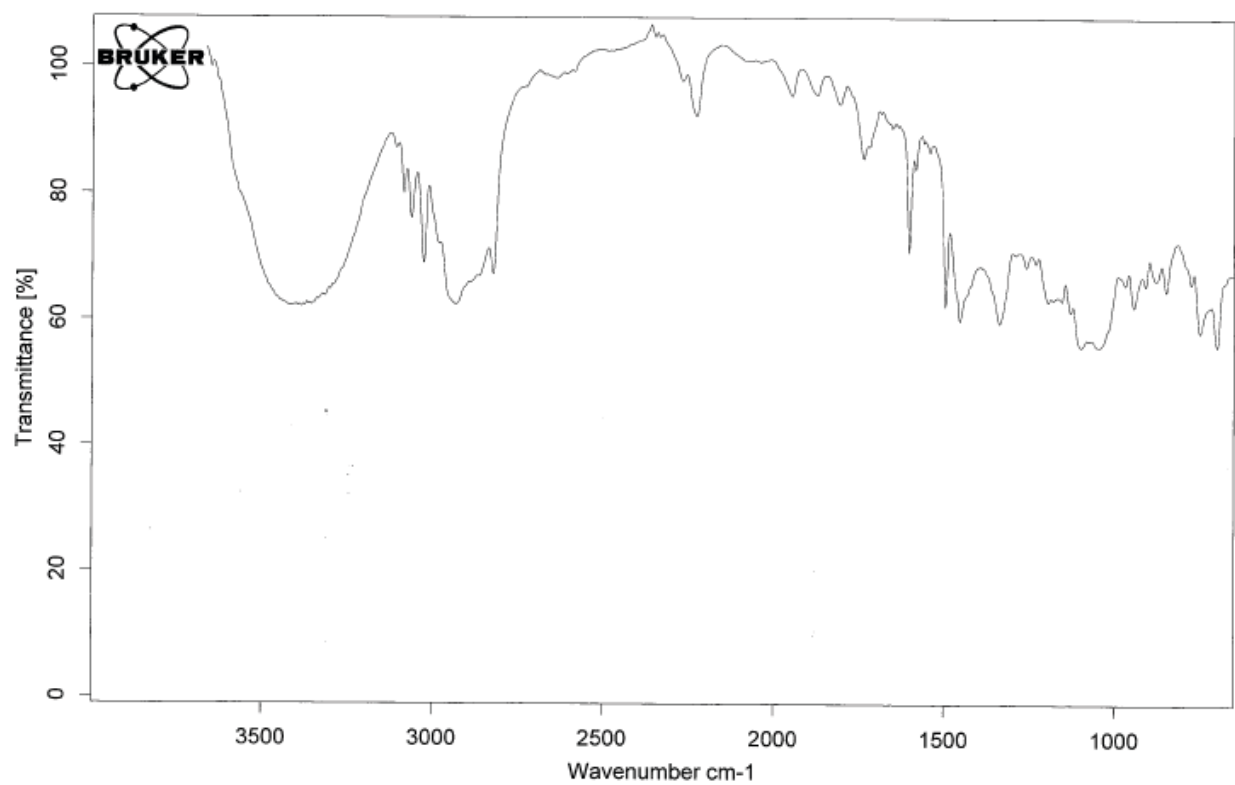
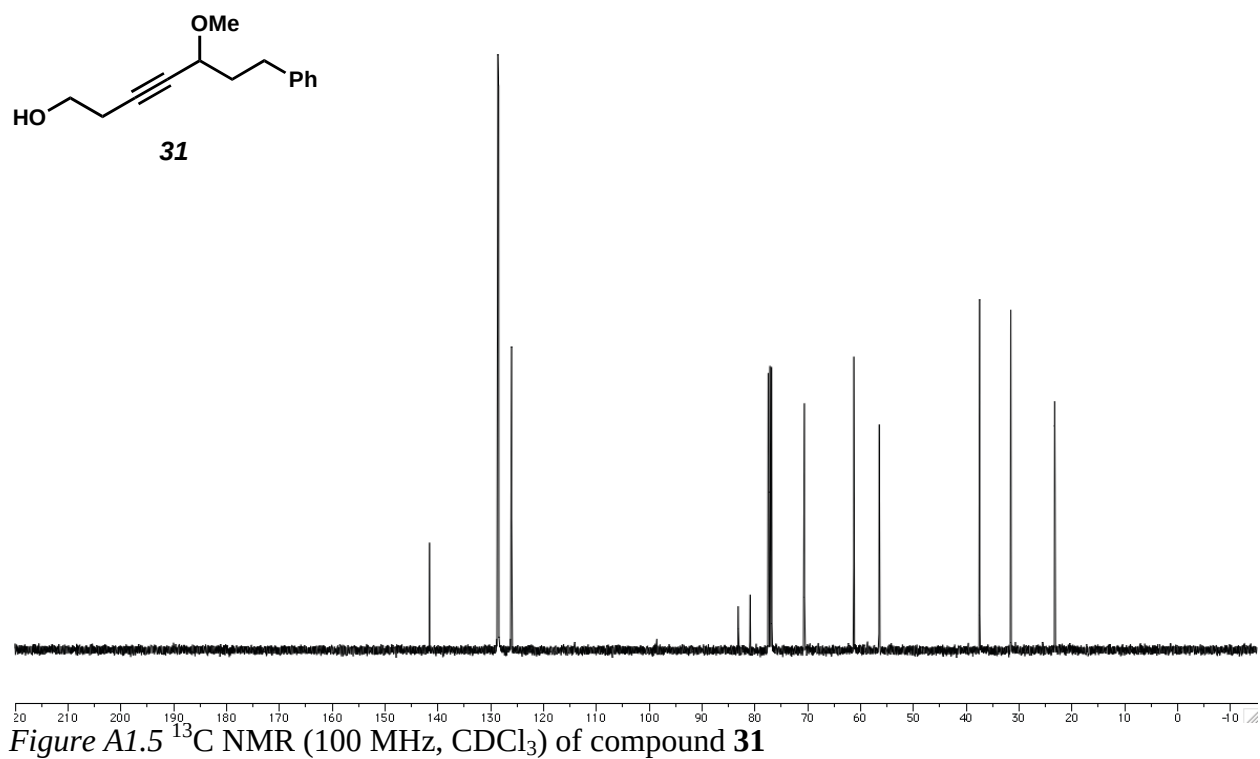


Figure A1.4 ^1H NMR (400 MHz, CDCl_3) of compound **31**



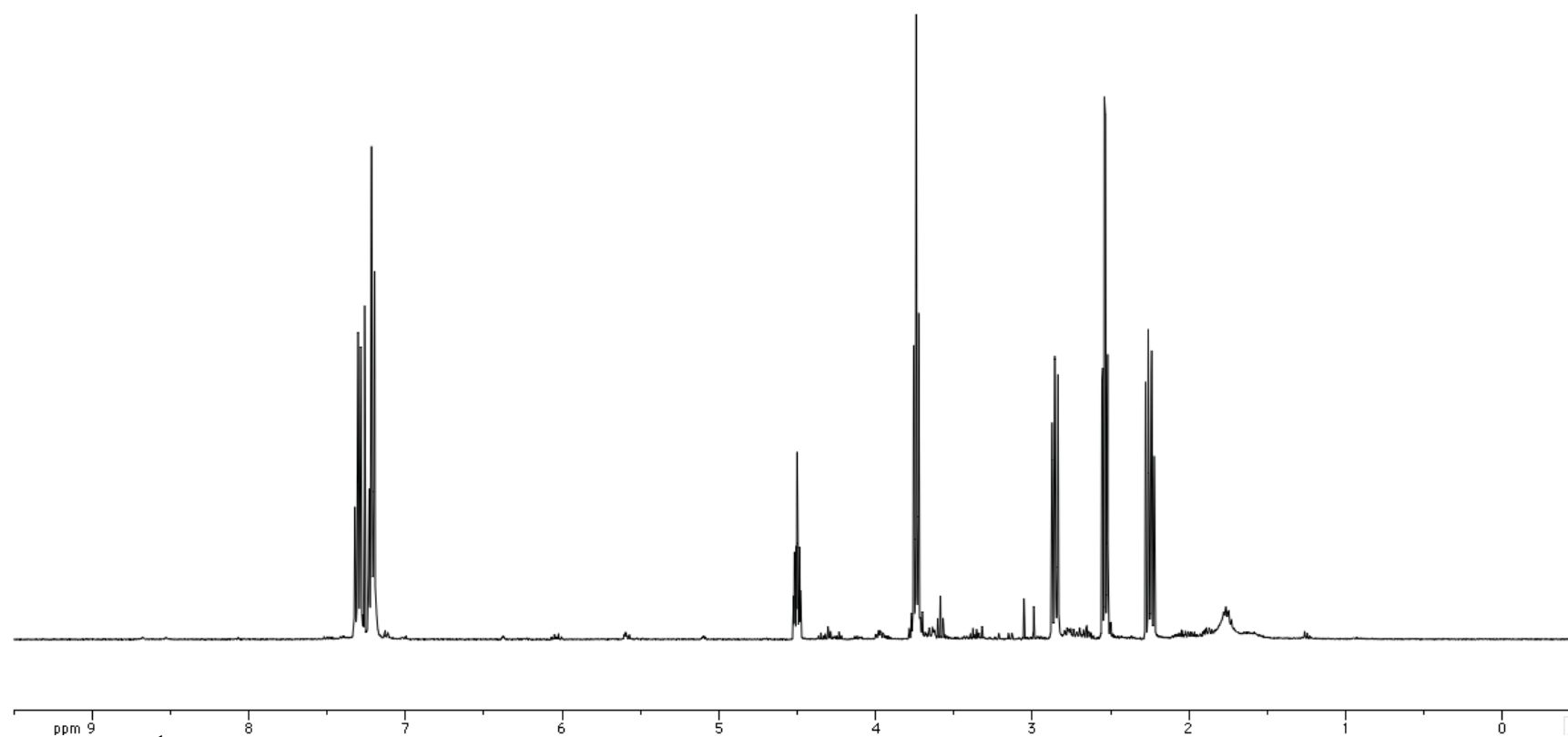
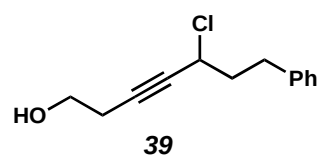
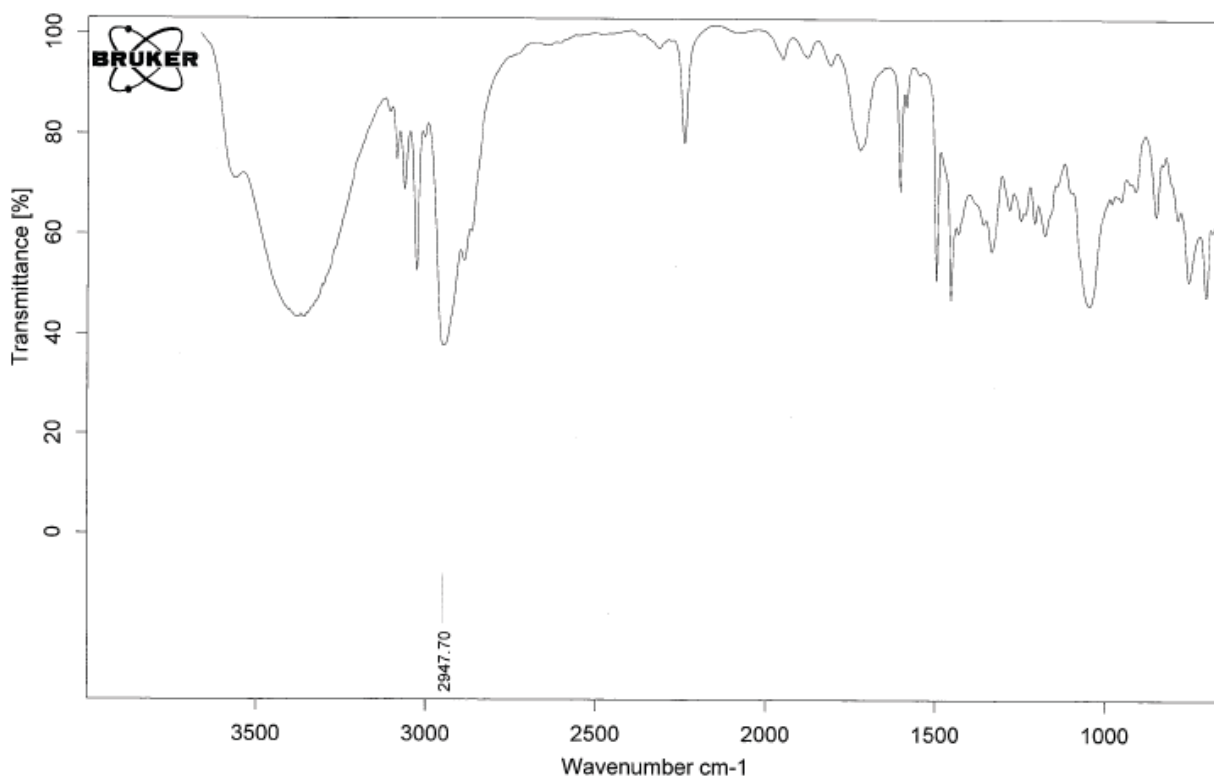
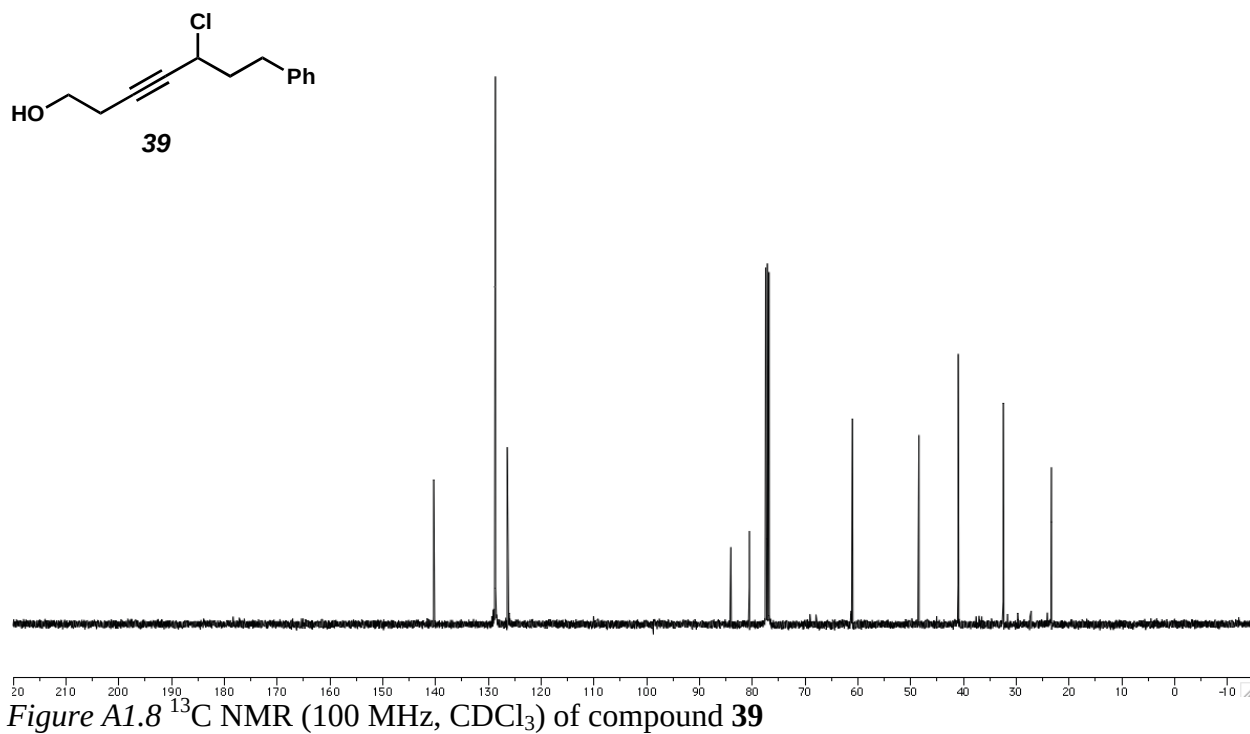


Figure A1.7 ^1H NMR (400 MHz, CDCl_3) of compound **39**



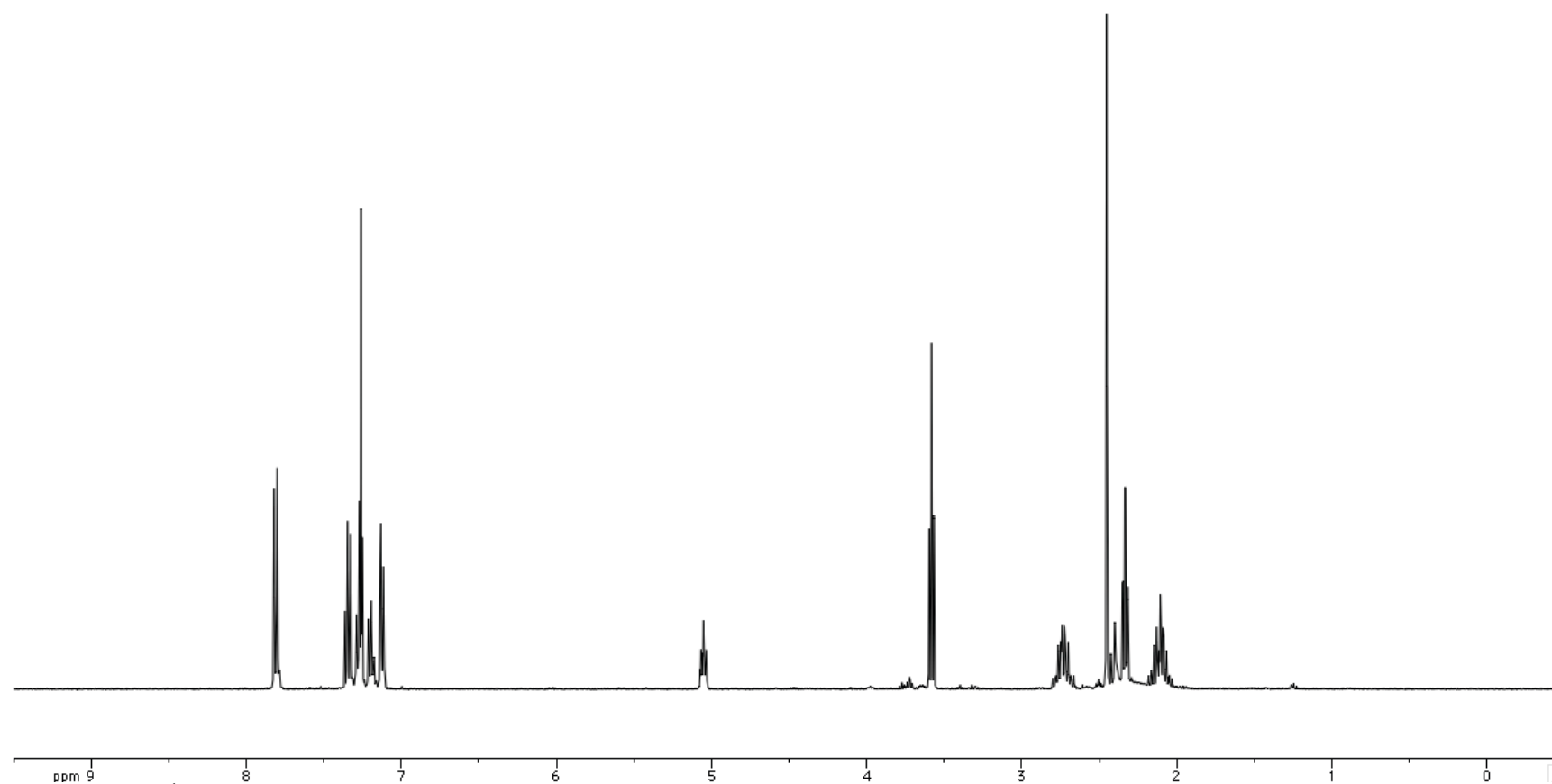
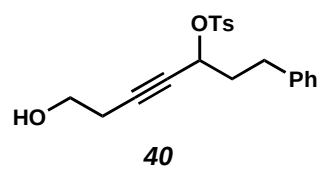


Figure A1.10 ¹H NMR (400 MHz, CDCl₃) of compound **40**

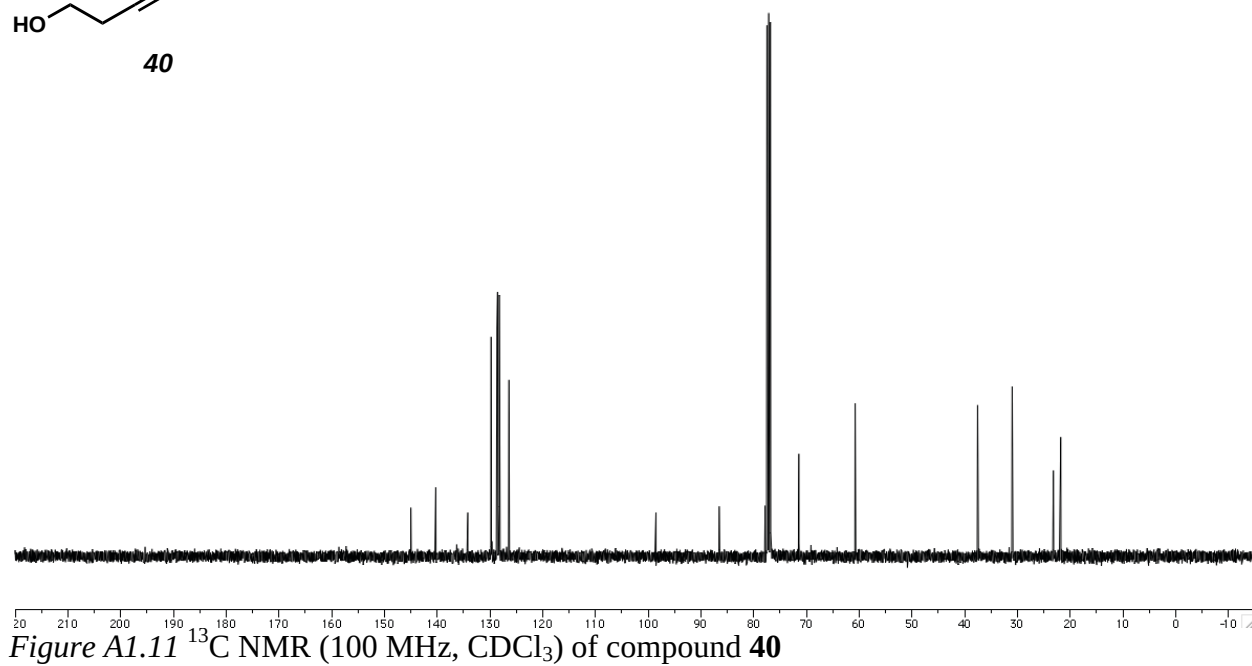
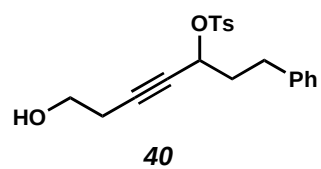


Figure A1.11 ¹³C NMR (100 MHz, CDCl₃) of compound **40**

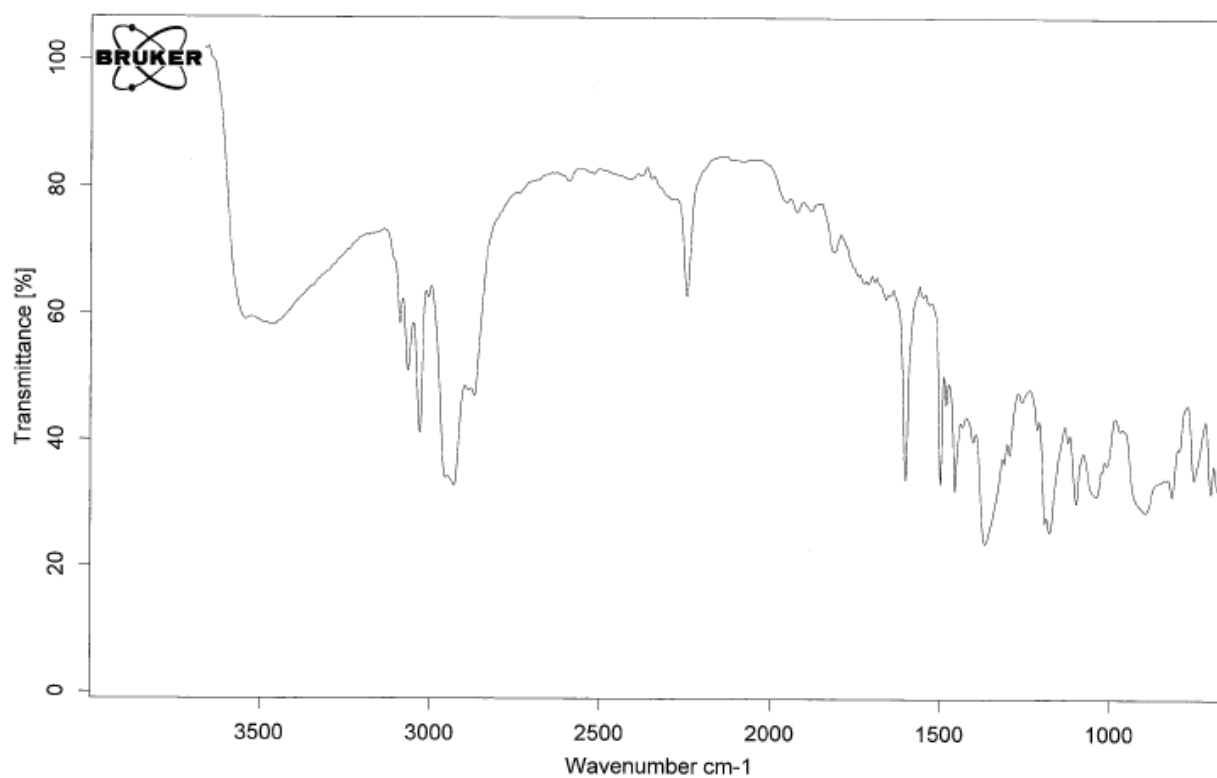


Figure A1.12 Infrared spectrum (thin film) of compound **40**

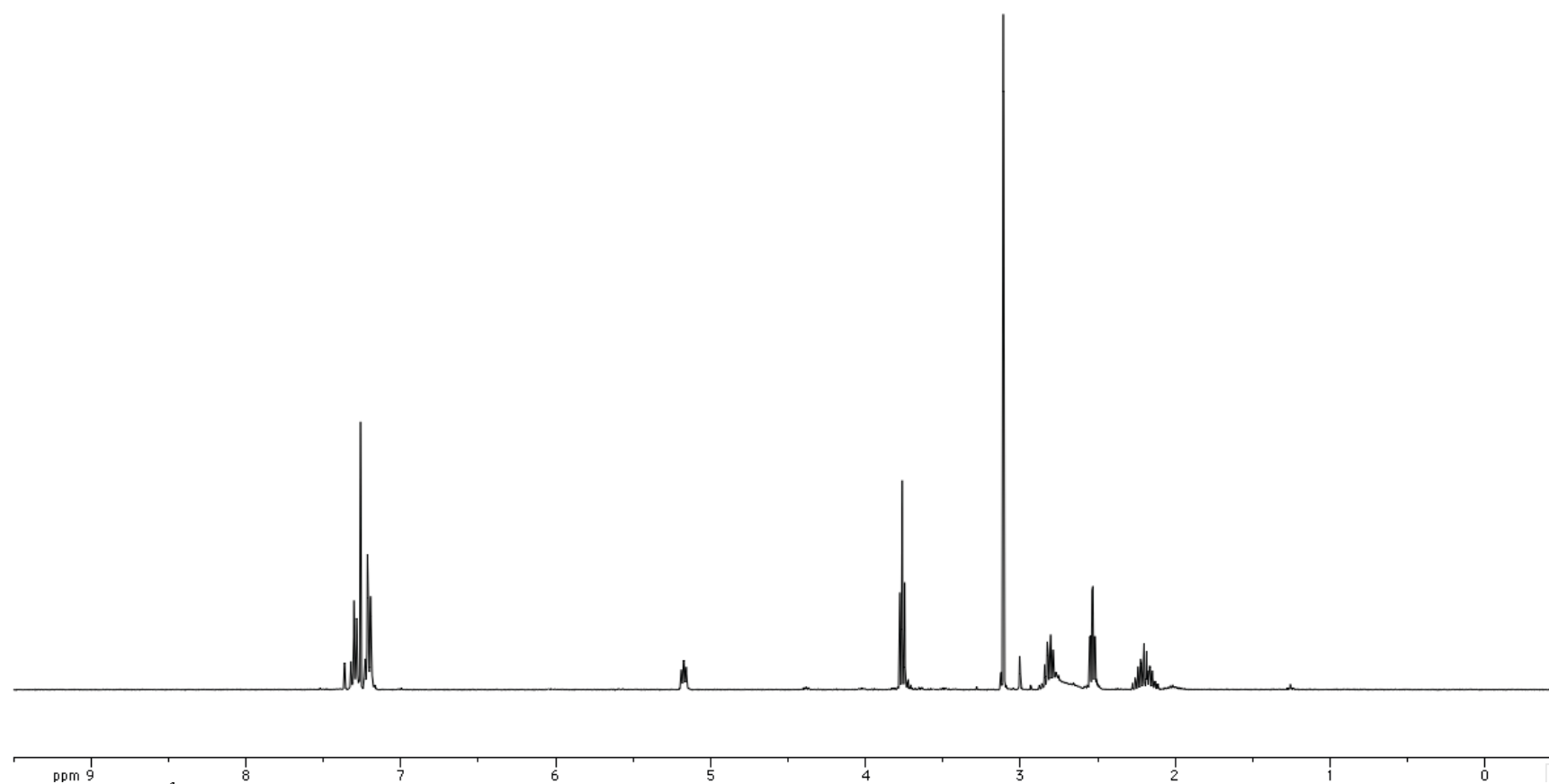
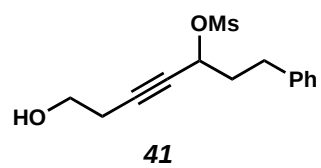
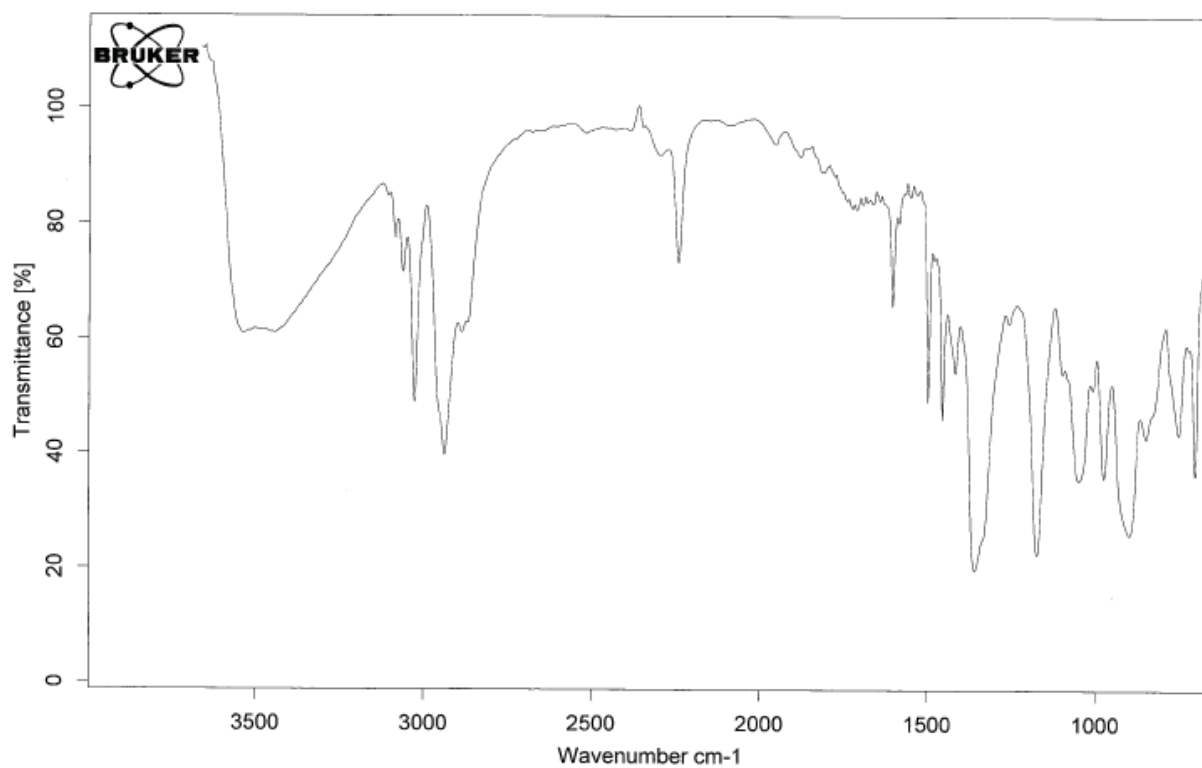
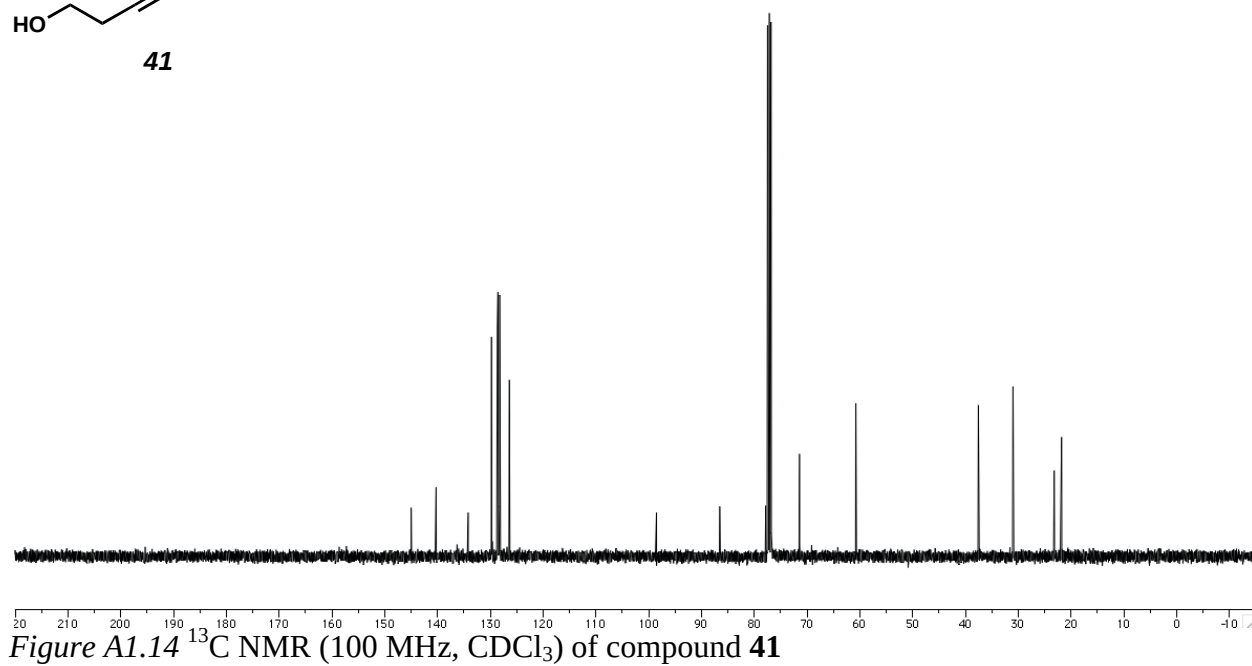
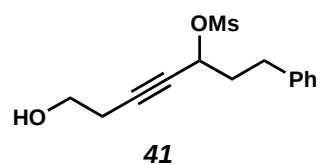


Figure A1.13 ^1H NMR (400 MHz, CDCl_3) of compound **41**



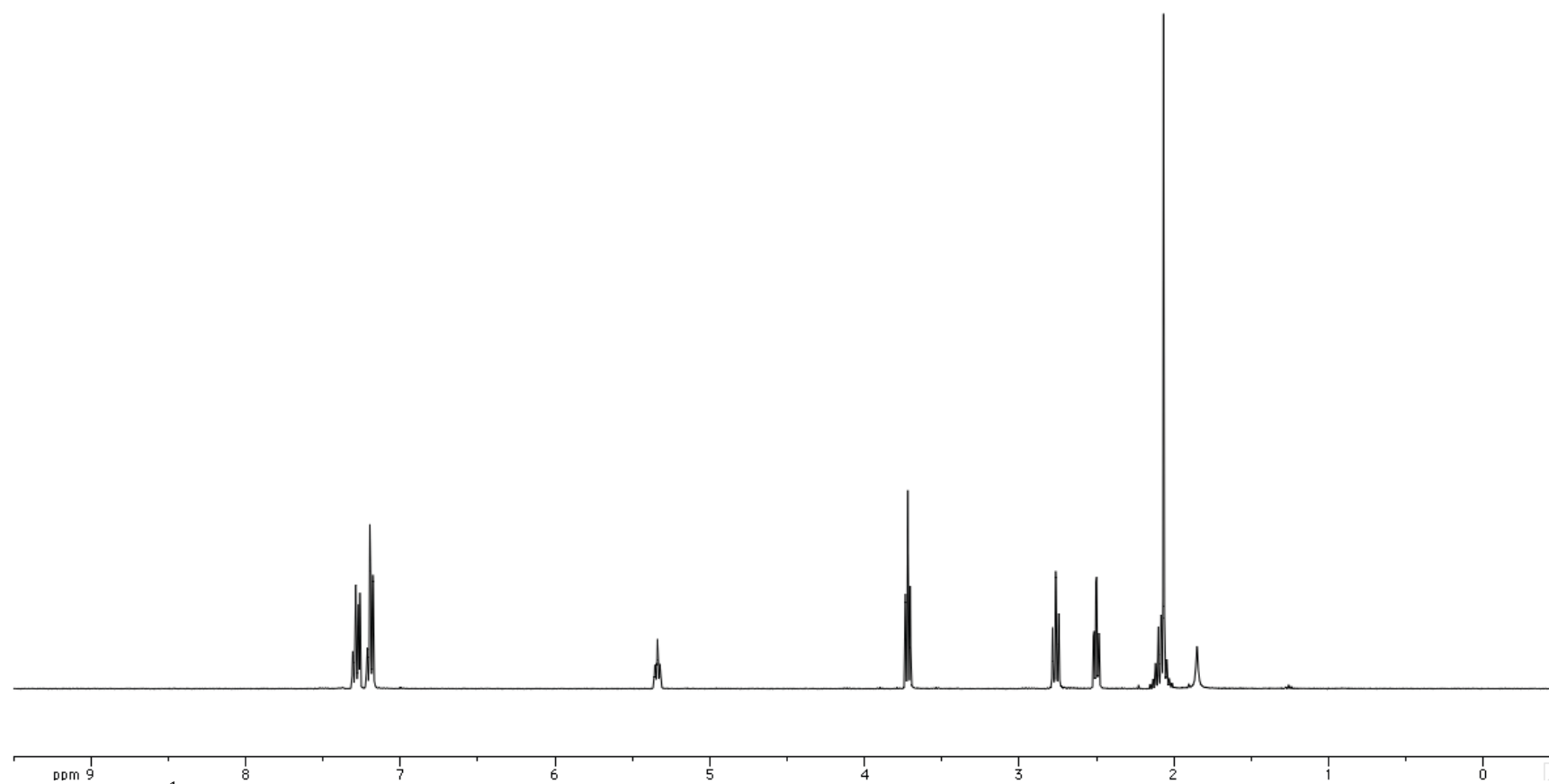
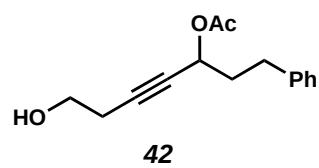


Figure A1.16 ^1H NMR (400 MHz, CDCl_3) of compound **42**

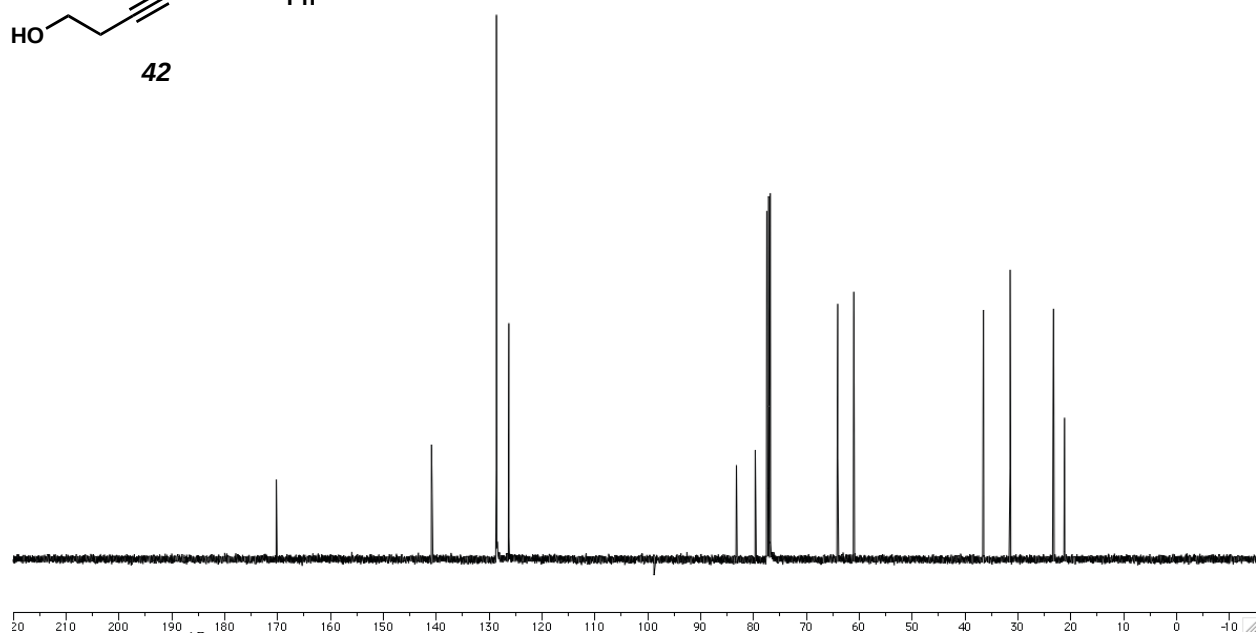
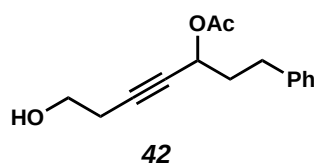


Figure A1.17 ¹³C NMR (100 MHz, CDCl₃) of compound **42**

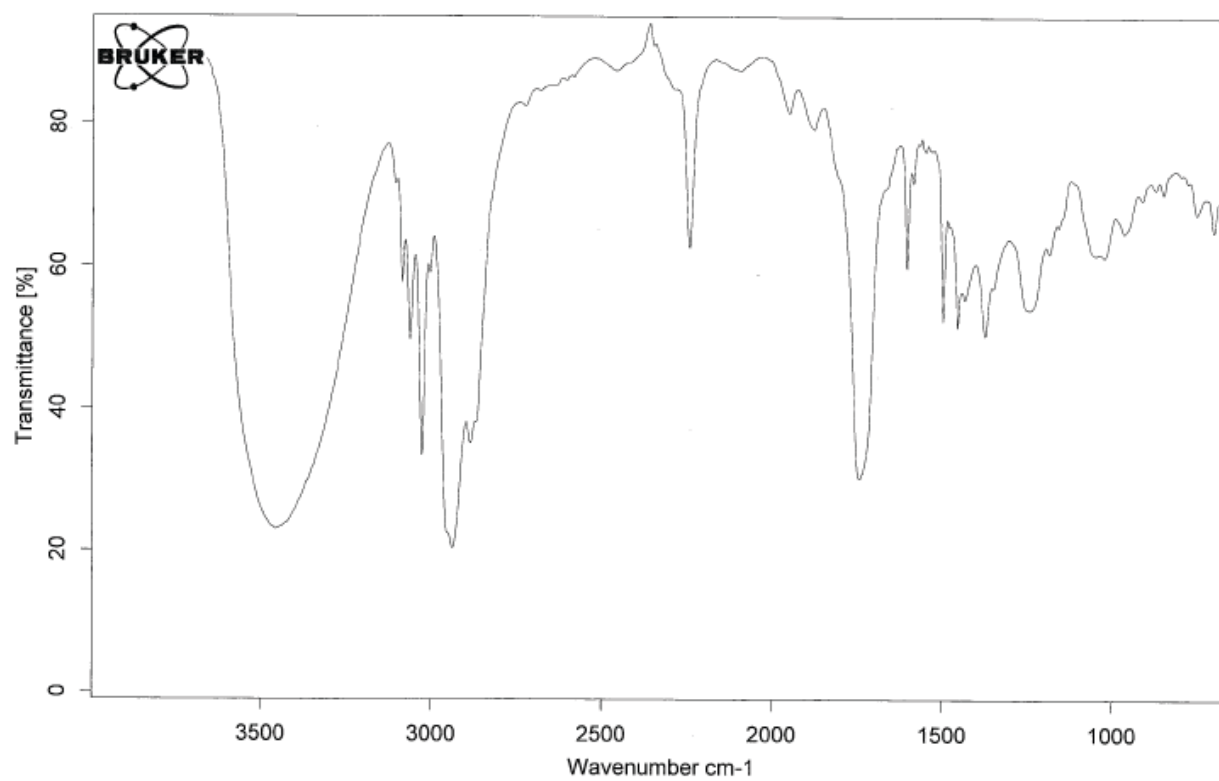


Figure A1.18 Infrared spectrum (thin film) of compound **42**

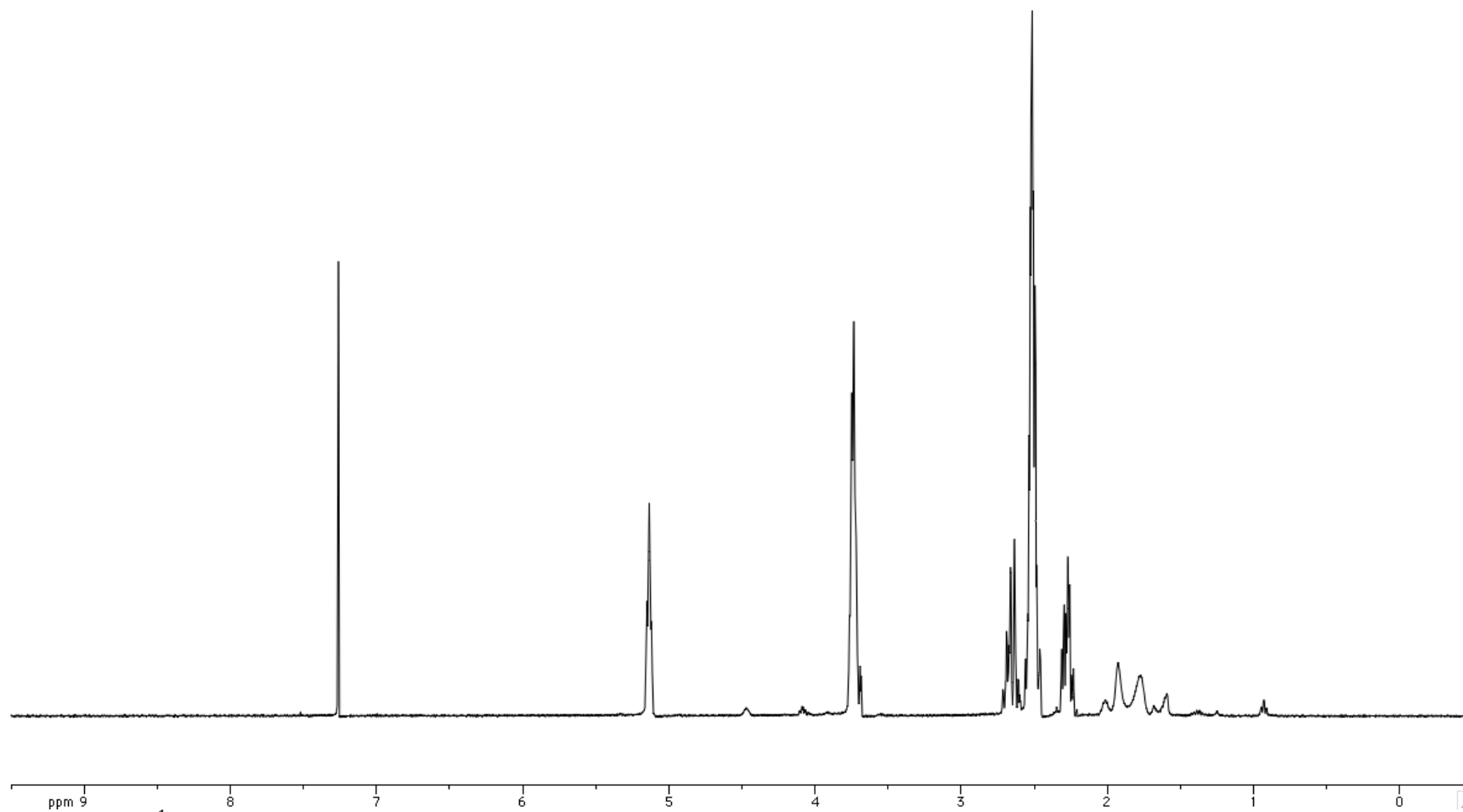
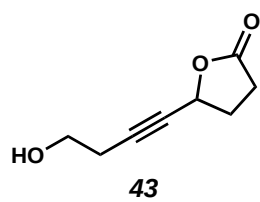


Figure A1.19 ^1H NMR (400 MHz, CDCl_3) of compound **43**

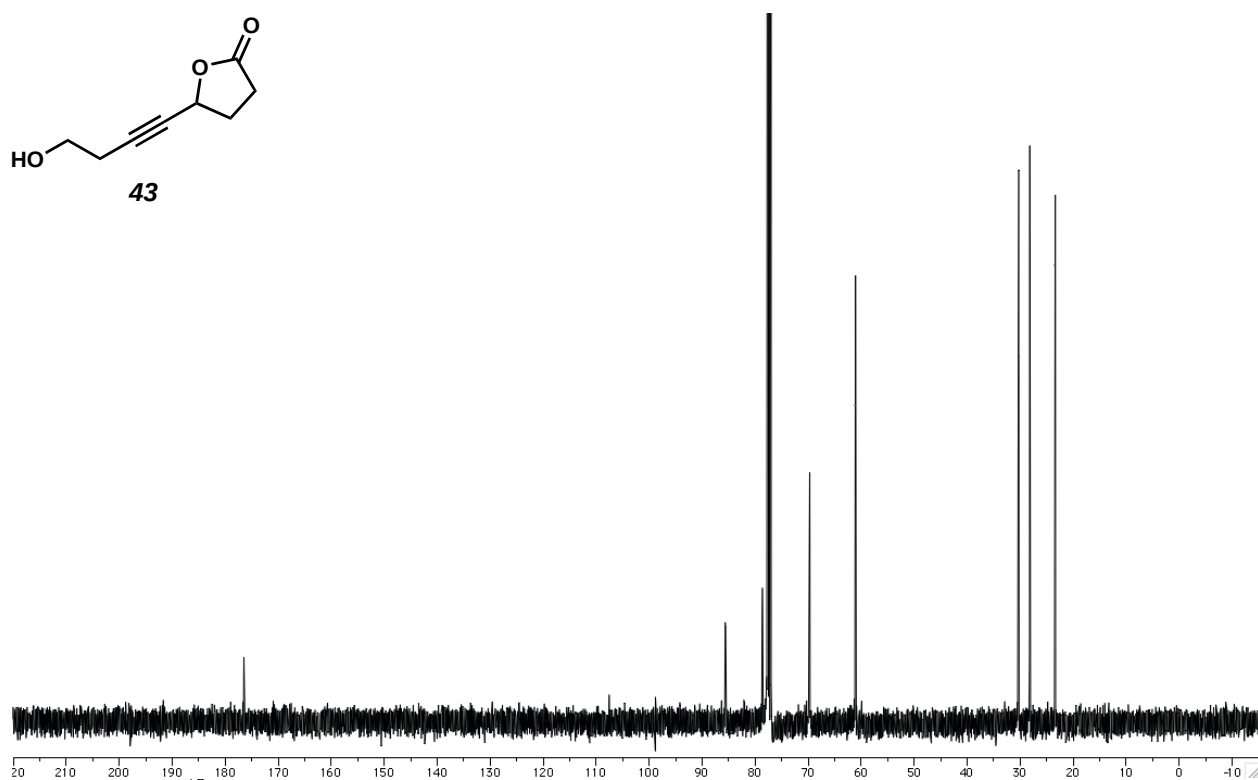
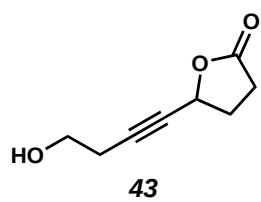


Figure A1.20 ^{13}C NMR (100 MHz, CDCl_3) of compound **43**

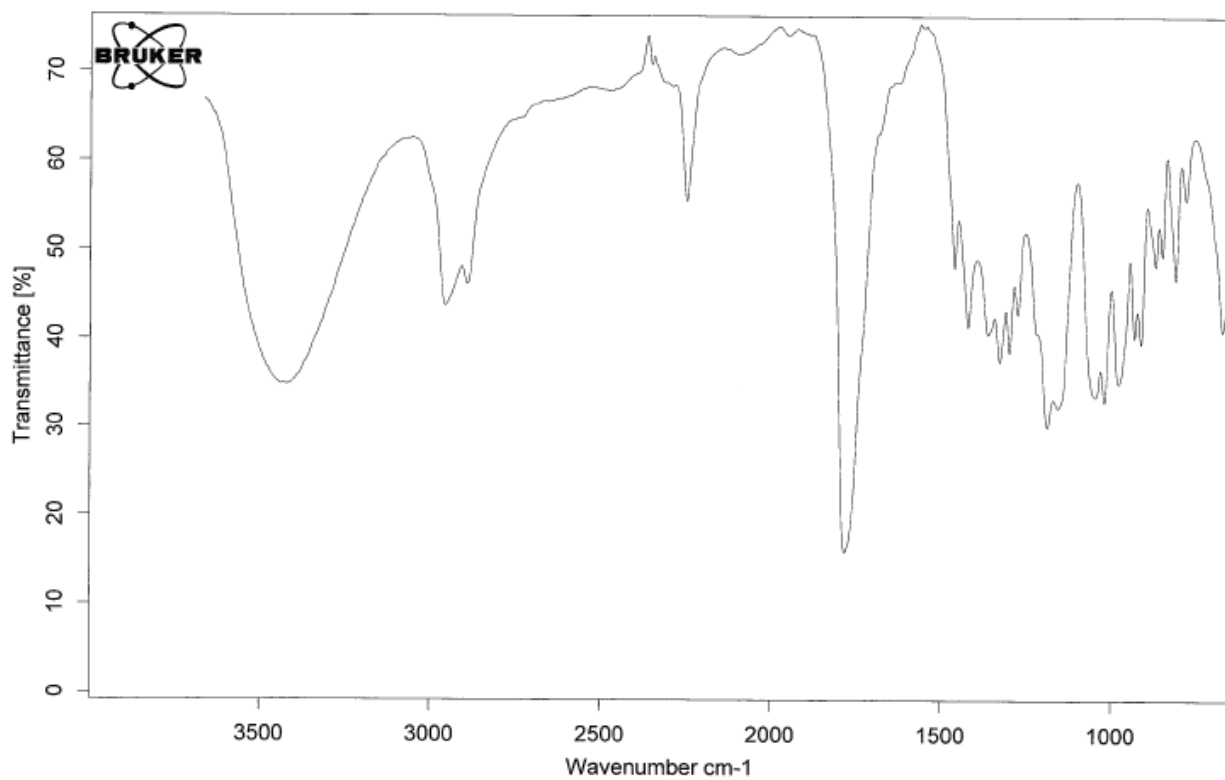


Figure A1.21 Infrared spectrum (thin film) of compound **43**

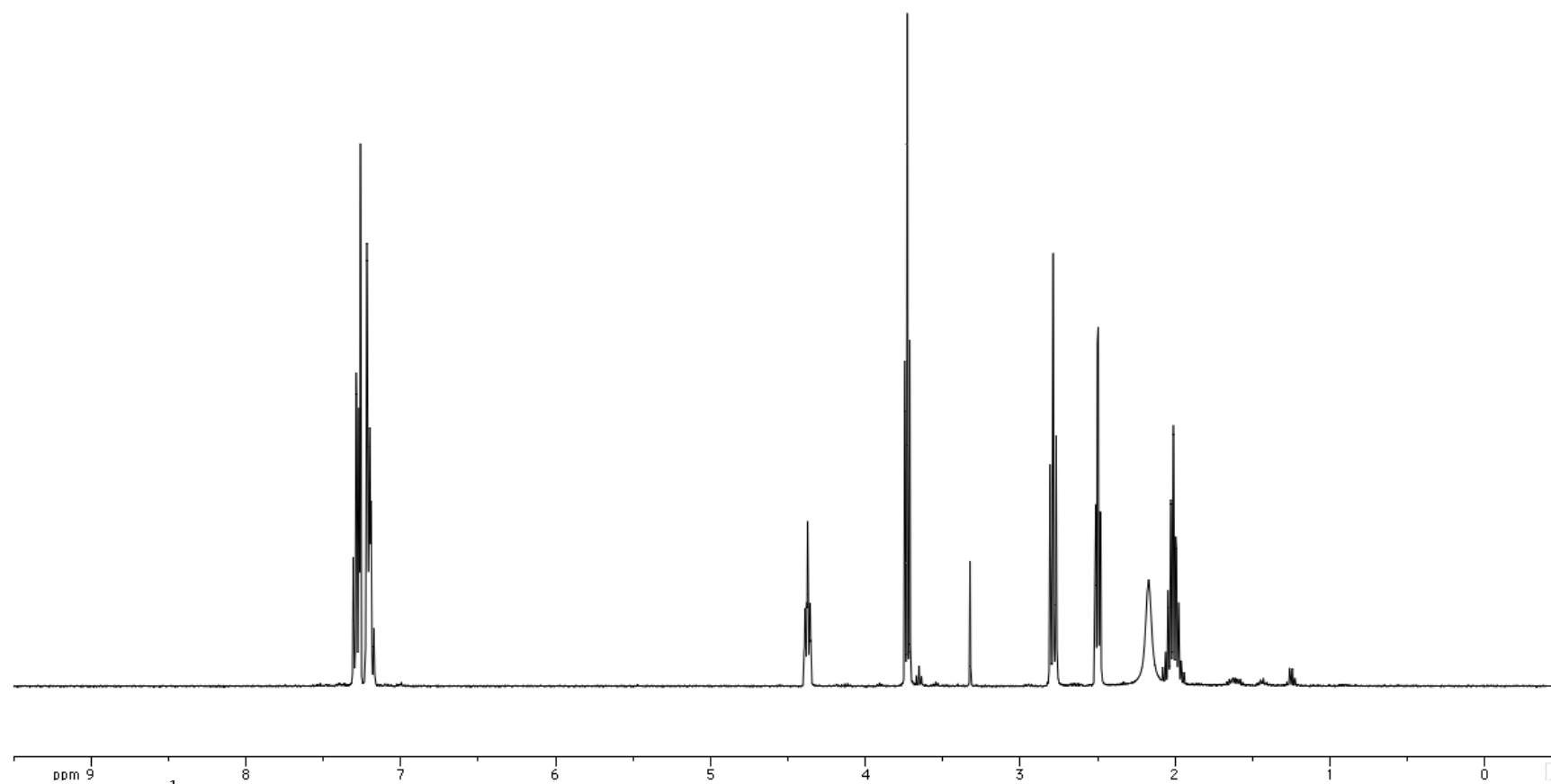
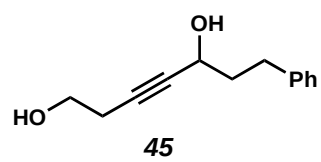


Figure A1.22 ^1H NMR (400 MHz, CDCl_3) of compound **45**

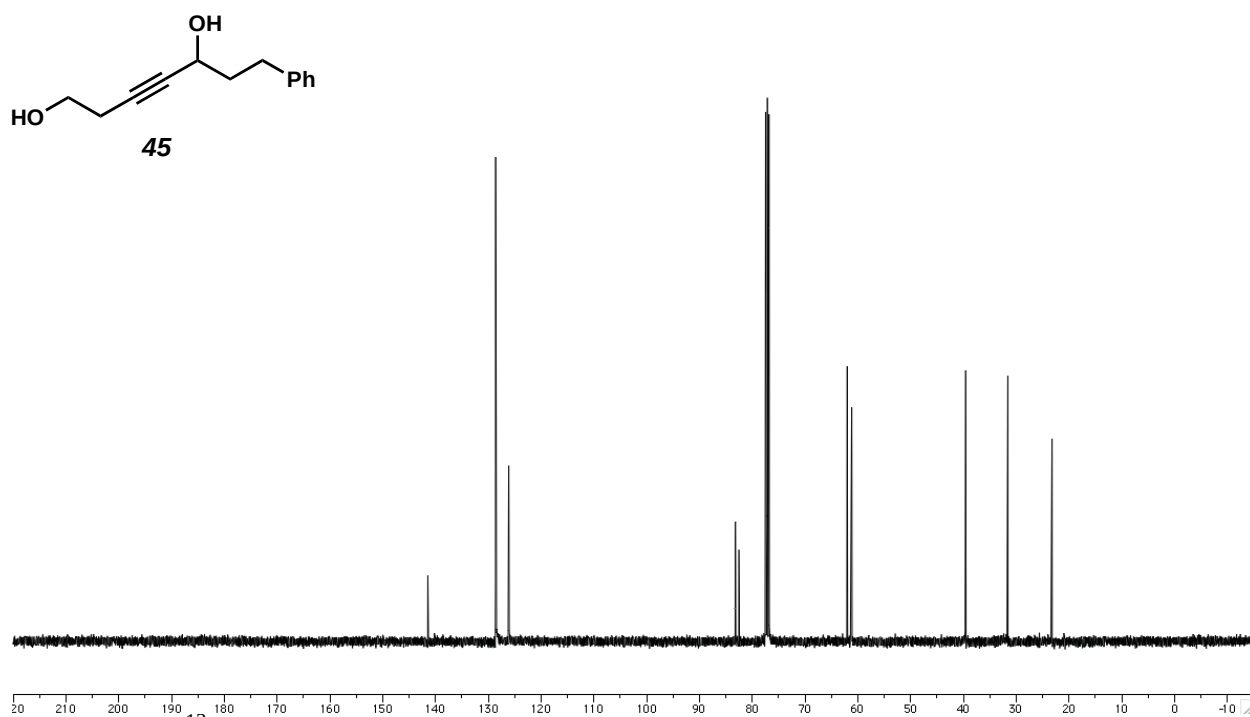


Figure A1.23 ^{13}C NMR (100 MHz, CDCl_3) of compound **45**

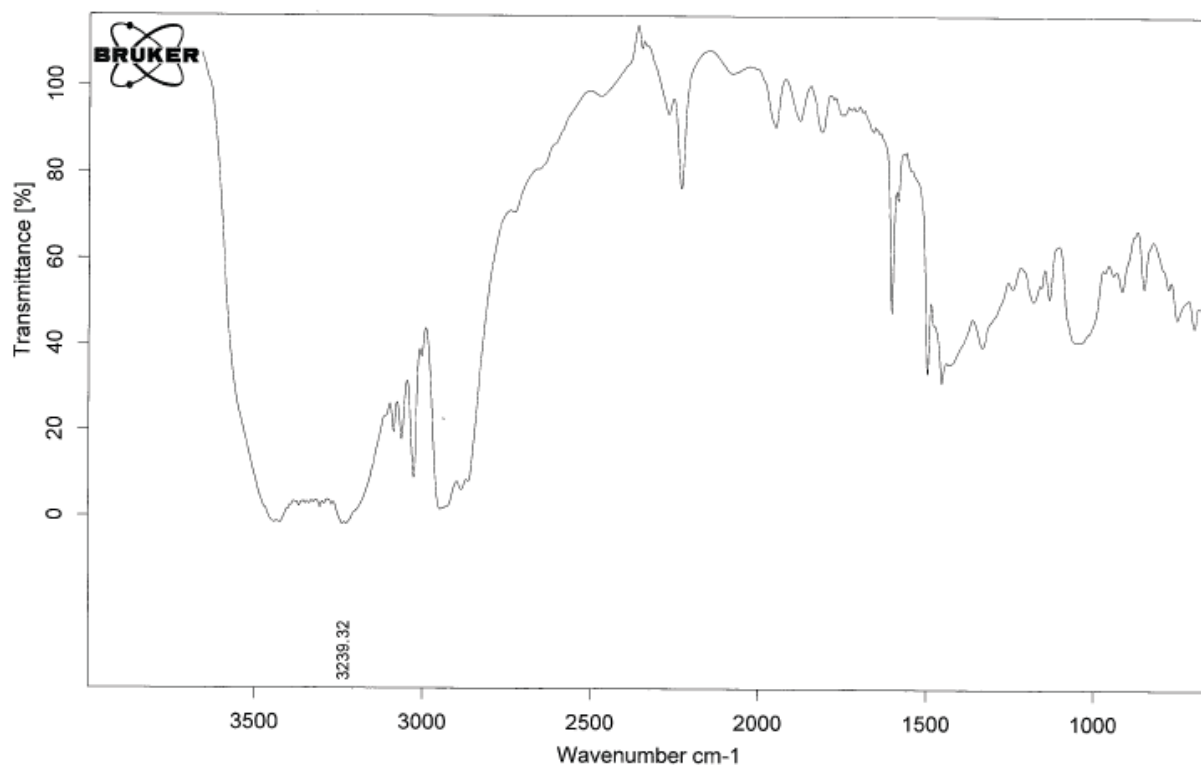


Figure A1.24 Infrared spectrum (thin film) of compound **45**

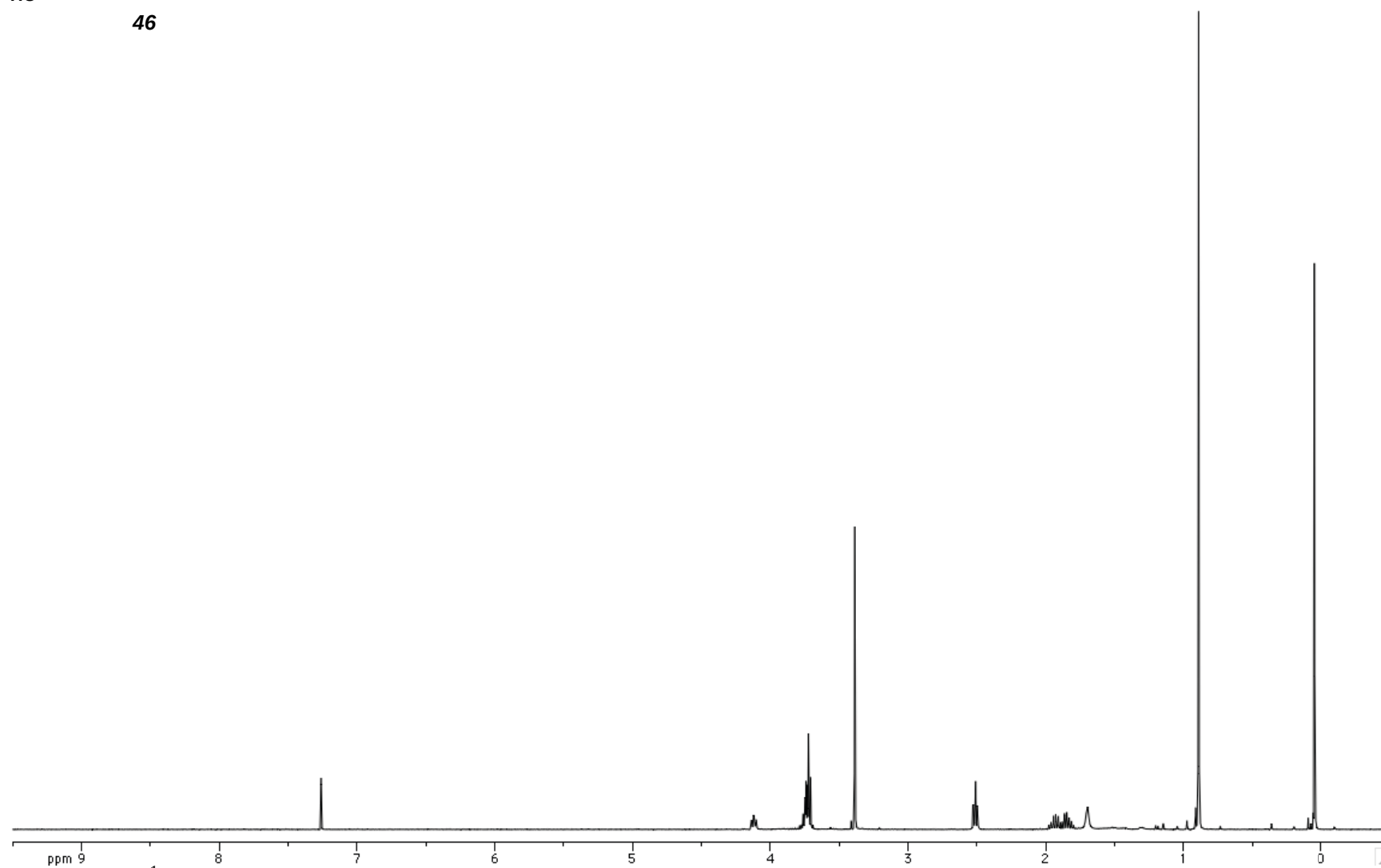
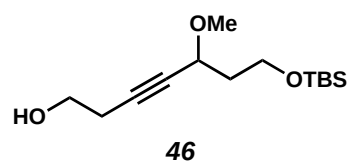


Figure A1.25 ^1H NMR (400 MHz, CDCl_3) of compound **46**

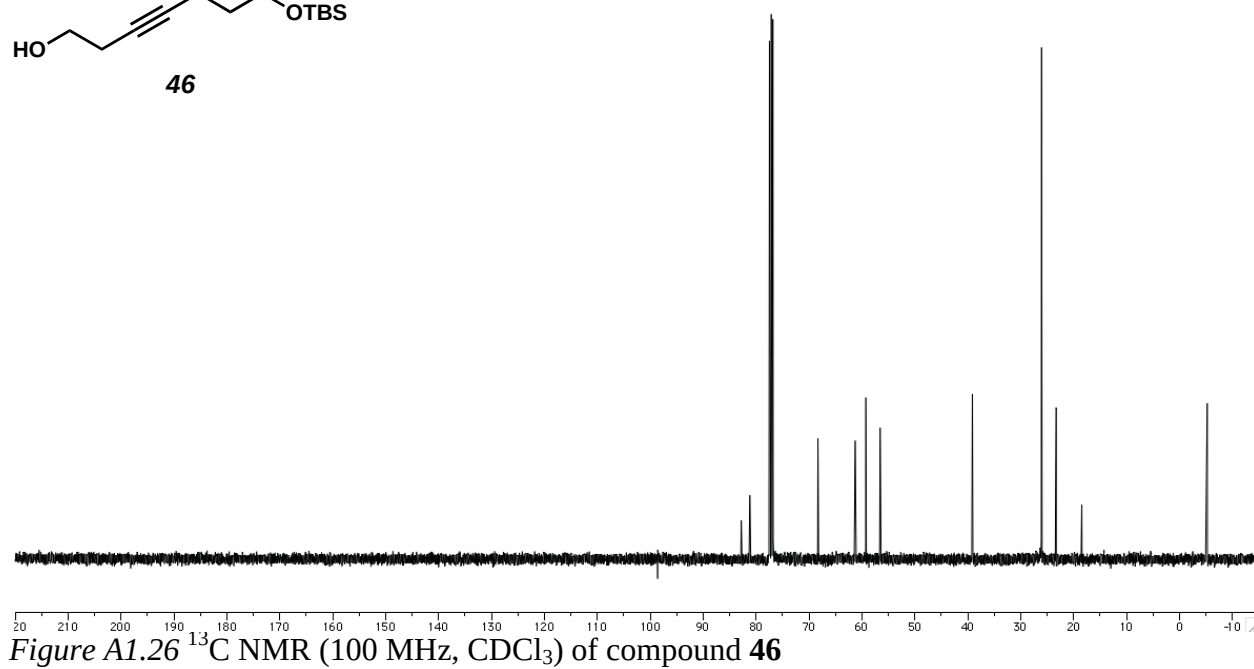
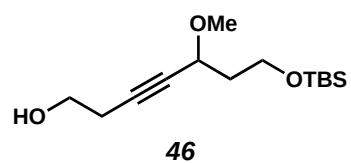


Figure A1.26 ¹³C NMR (100 MHz, CDCl₃) of compound **46**

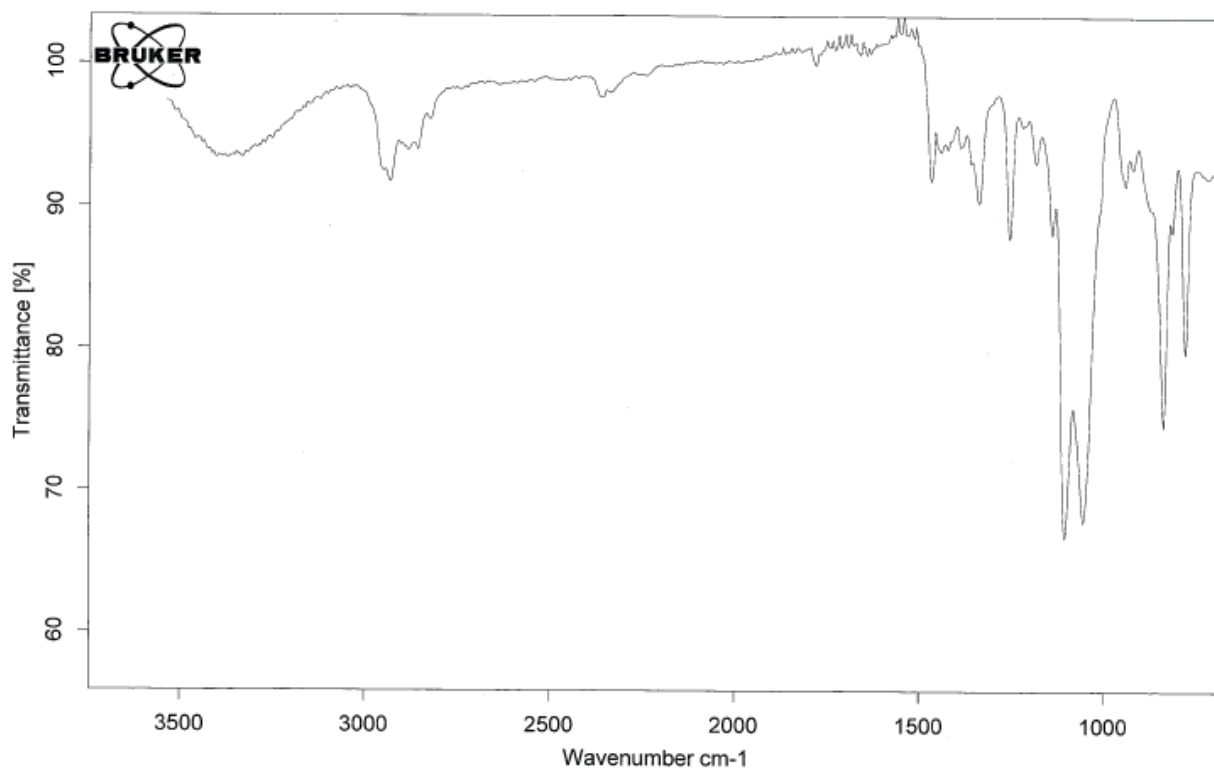
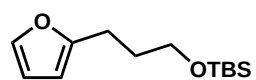


Figure A1.27 Infrared spectrum (thin film) of compound **46**



47

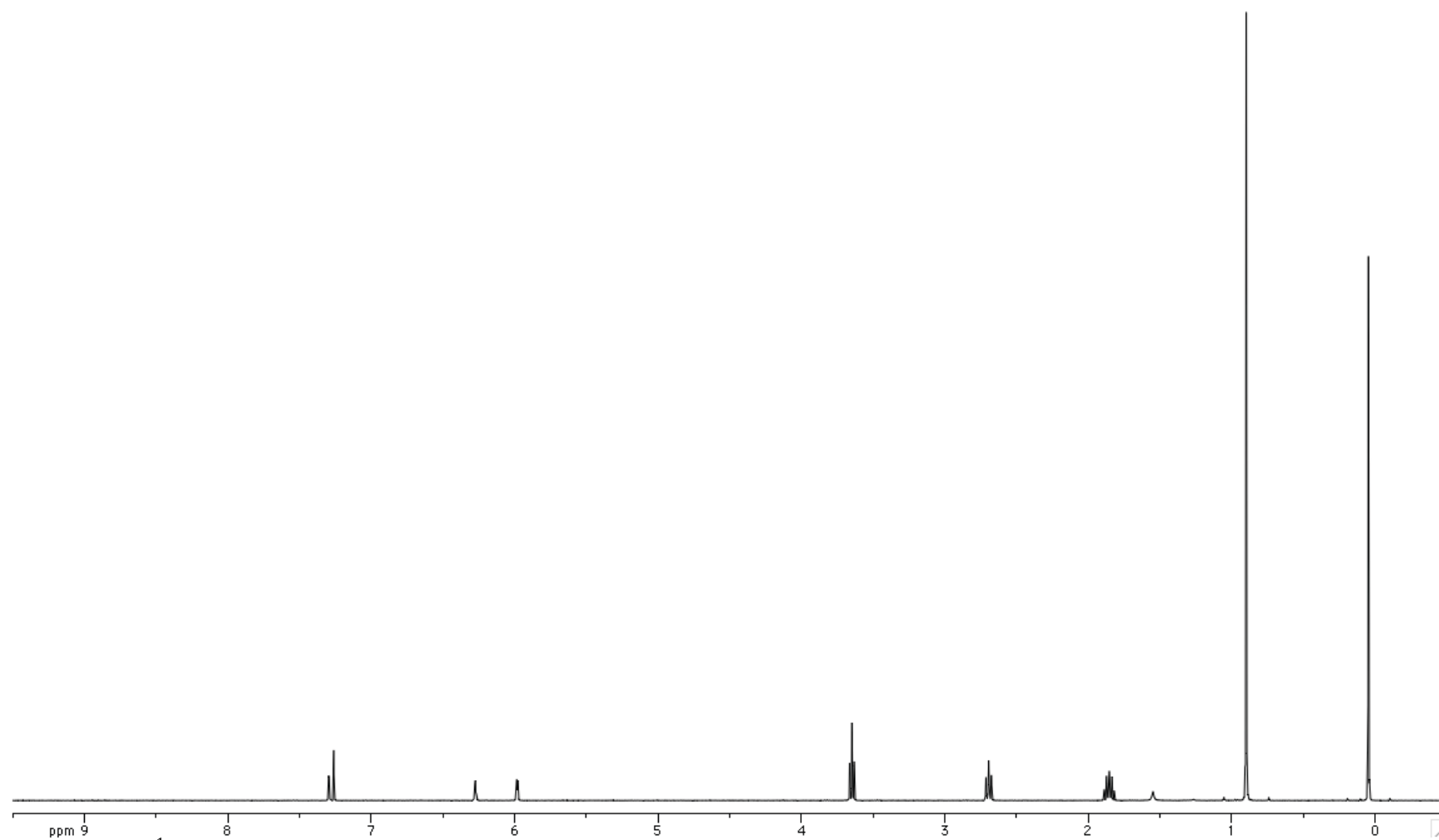
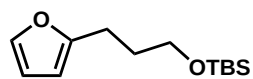


Figure A1.28 ^1H NMR (400 MHz, CDCl_3) of compound 47



47

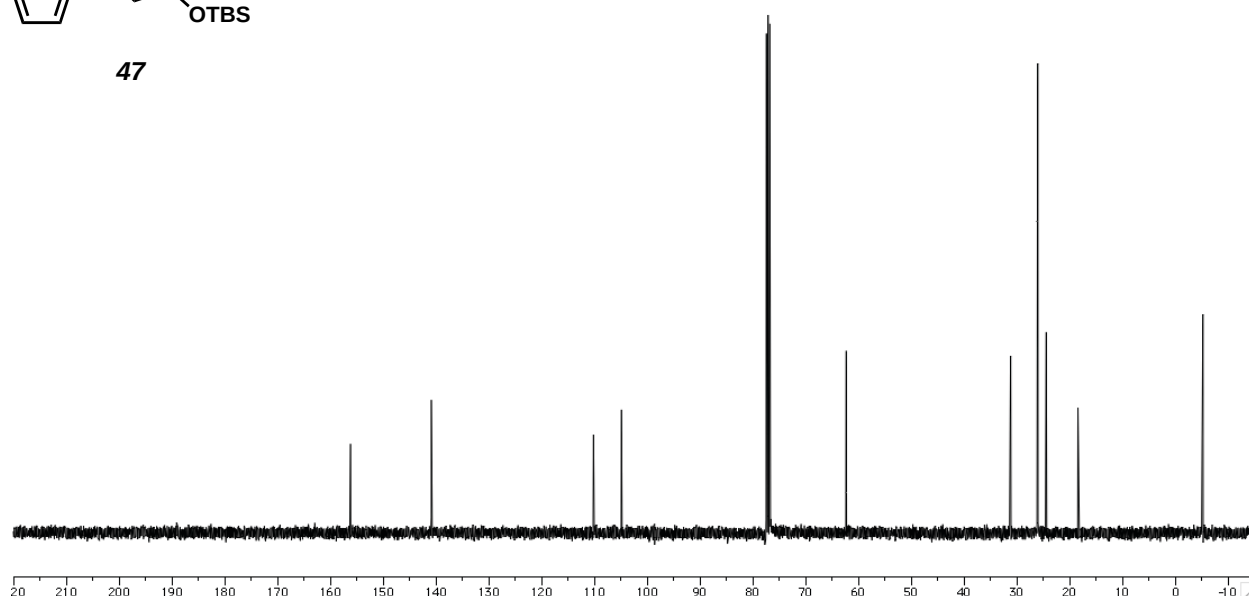


Figure A1.29 ^{13}C NMR (100 MHz, CDCl_3) of compound **47**

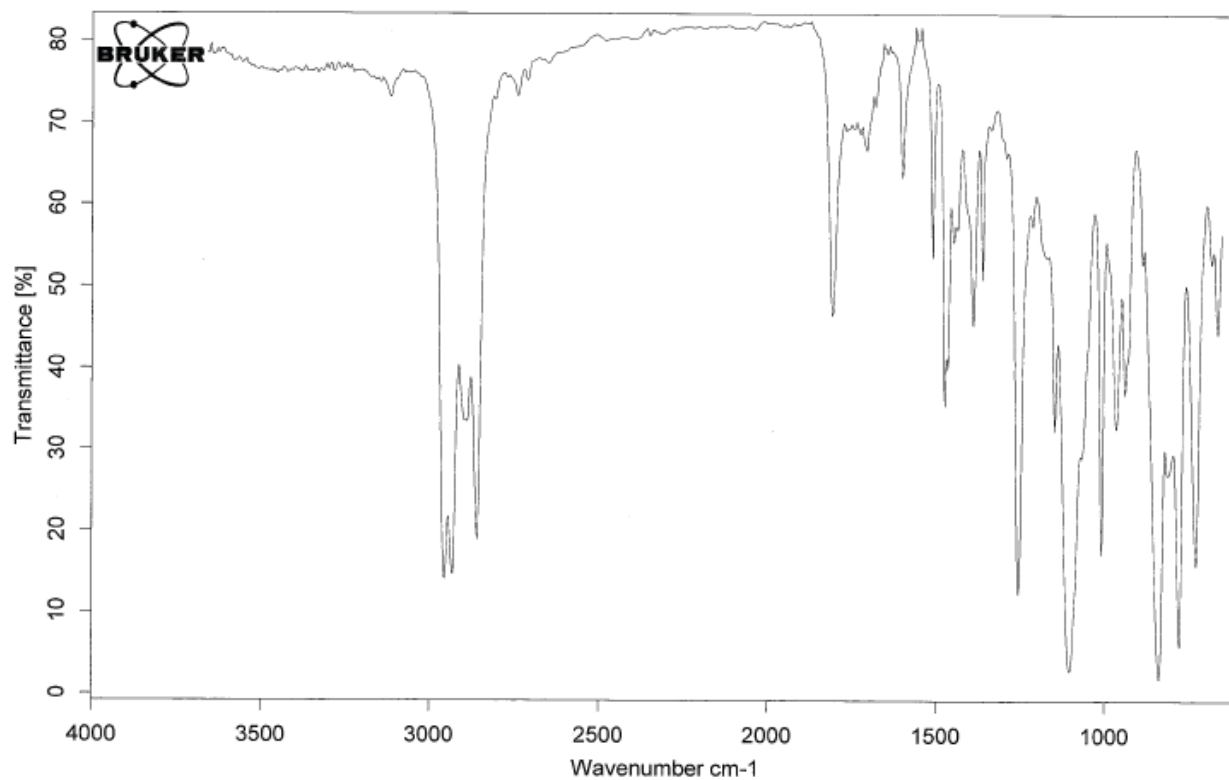


Figure A1.30 Infrared spectrum (thin film) of compound **47**

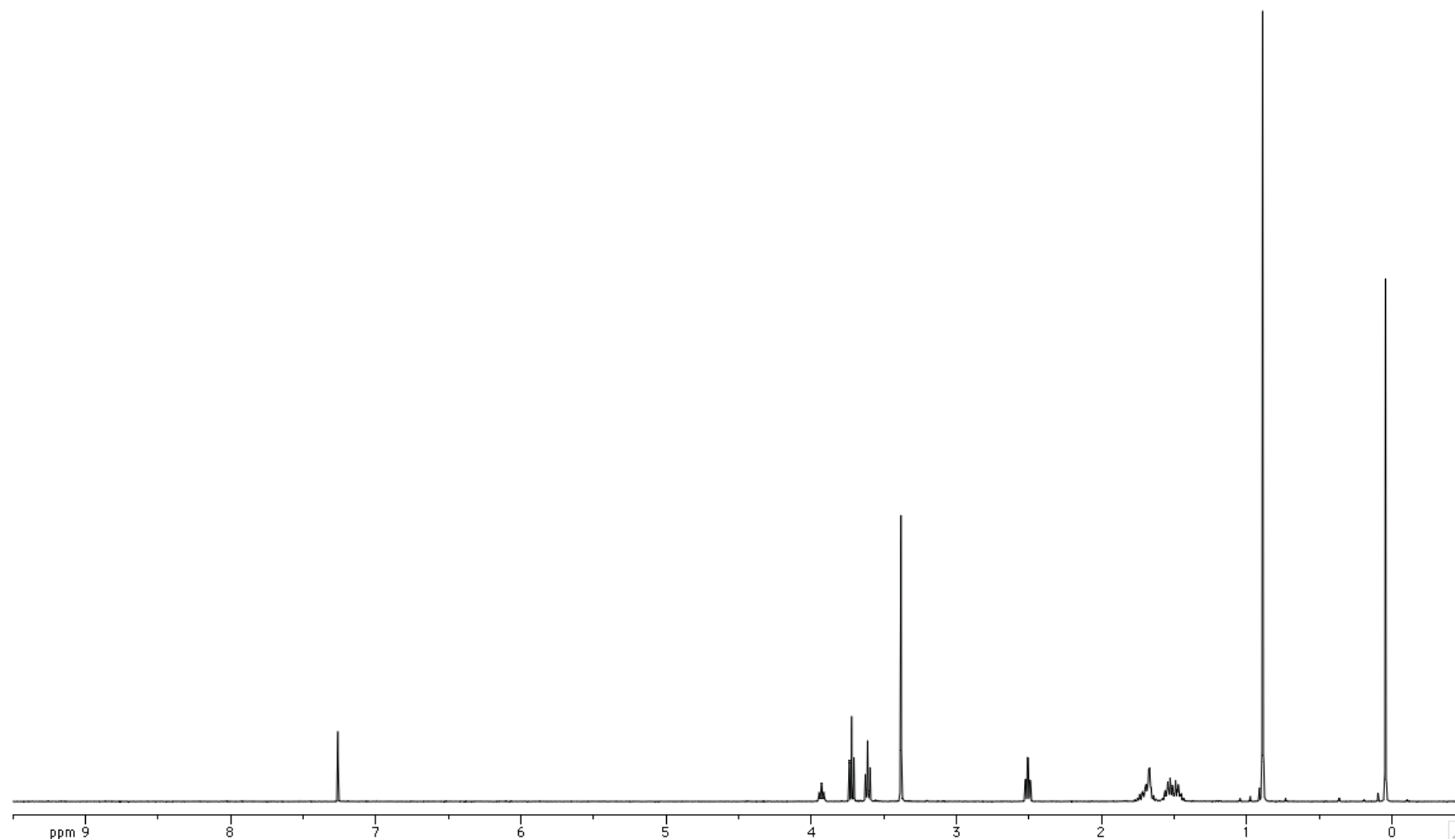
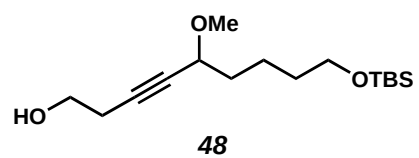


Figure A1.31 ^1H NMR (400 MHz, CDCl_3) of compound **48**

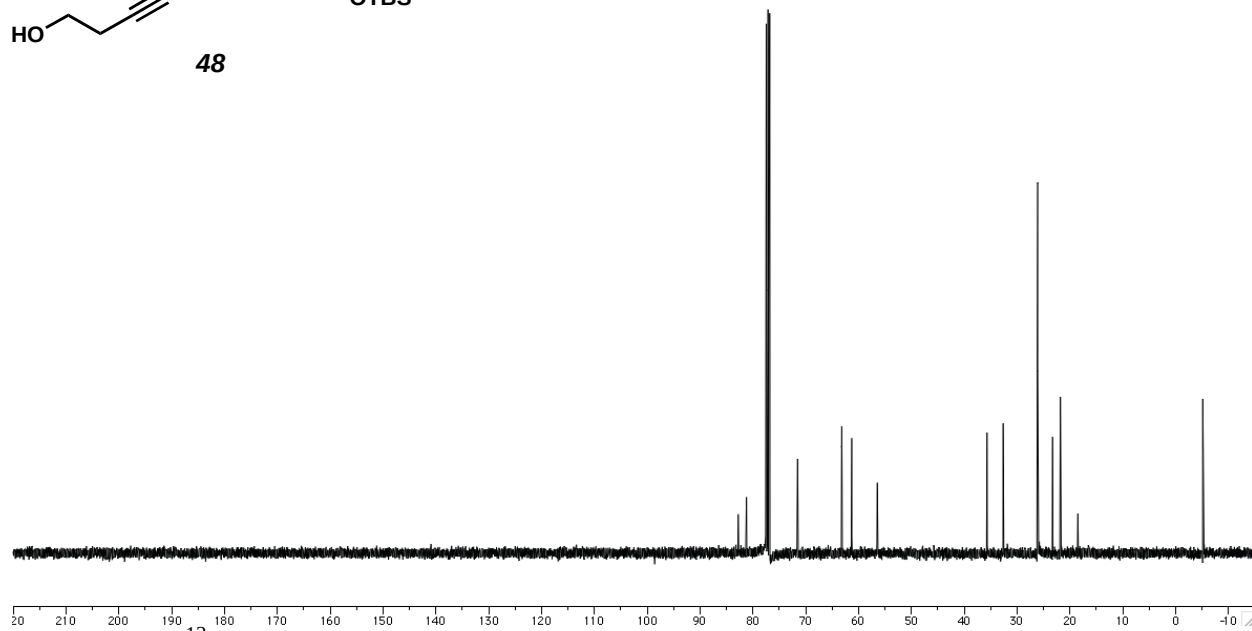
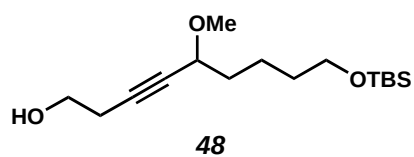


Figure A1.32 ^{13}C NMR (100 MHz, CDCl_3) of compound **48**

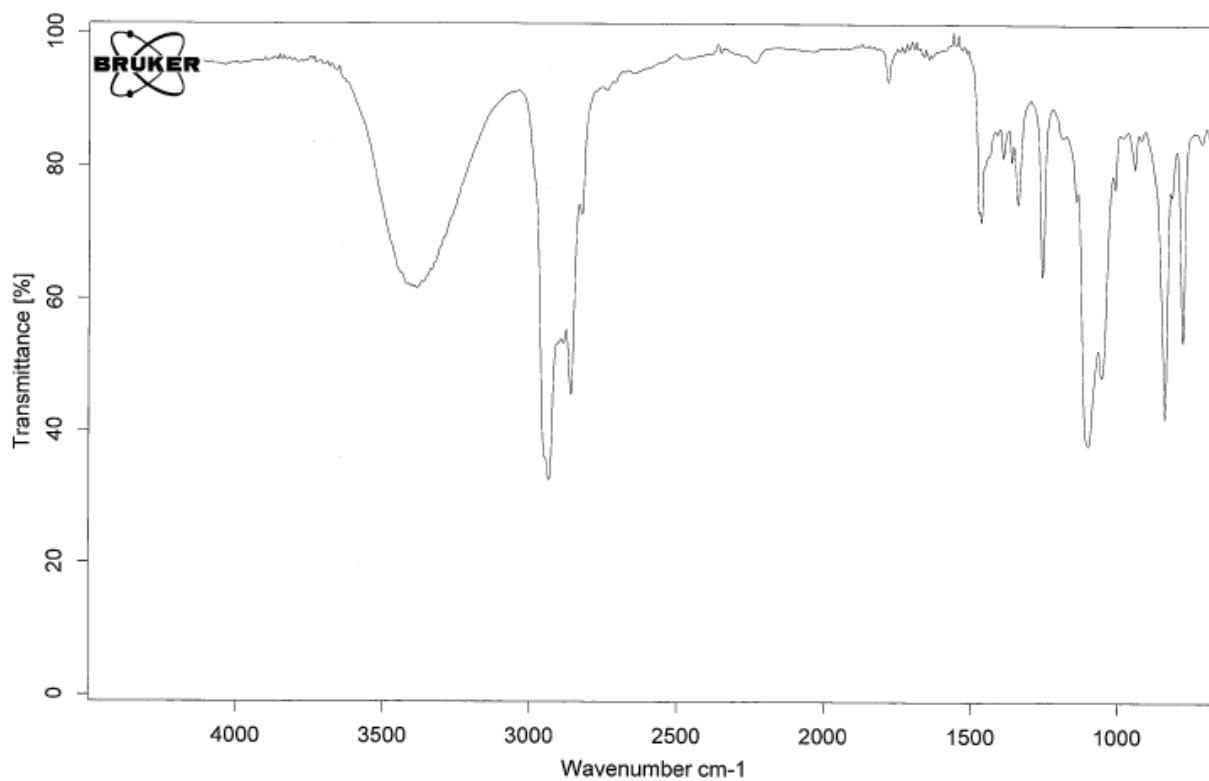


Figure A1.33 Infrared spectrum (thin film) of compound **48**

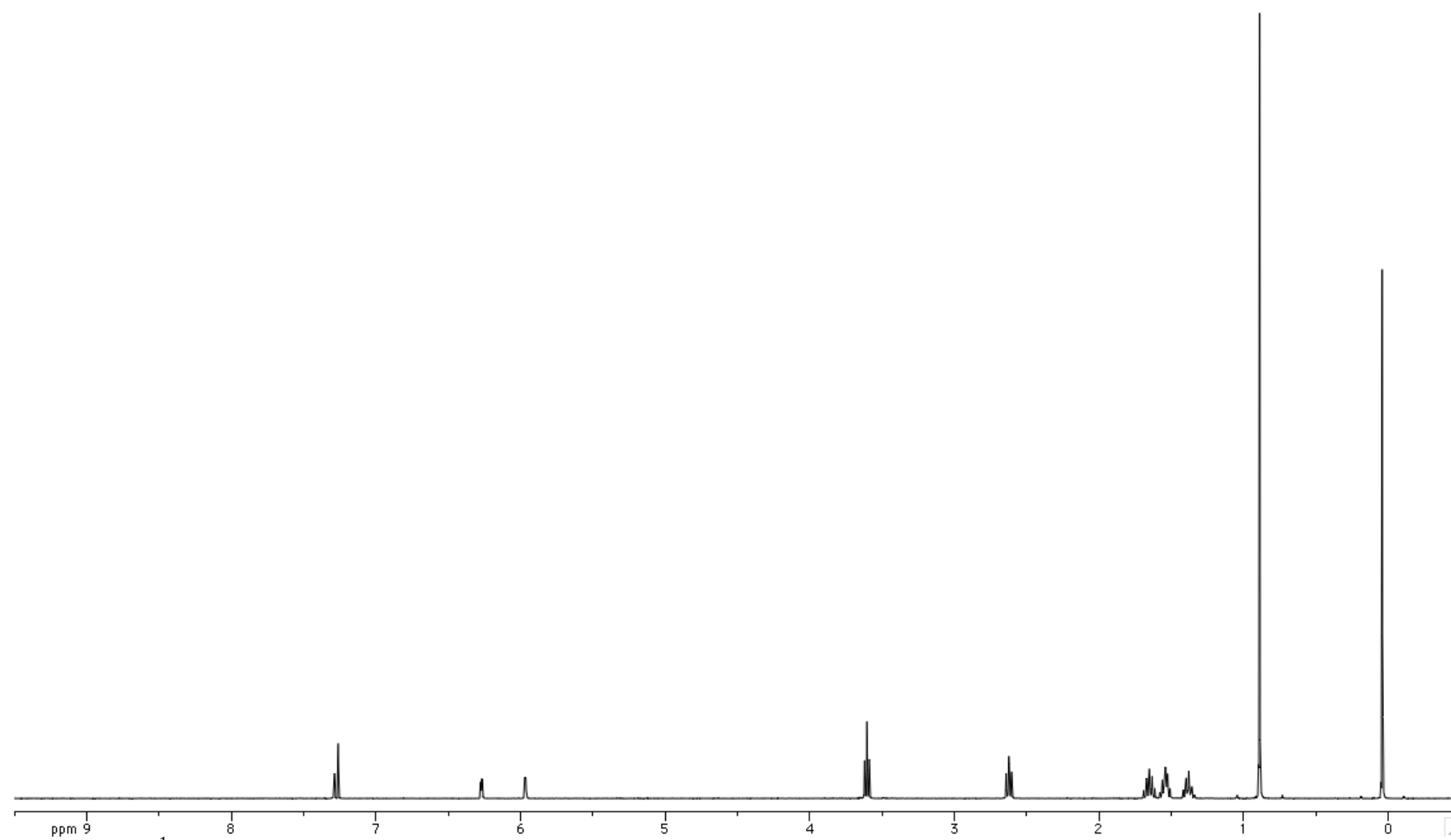
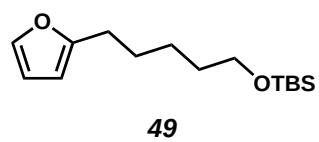
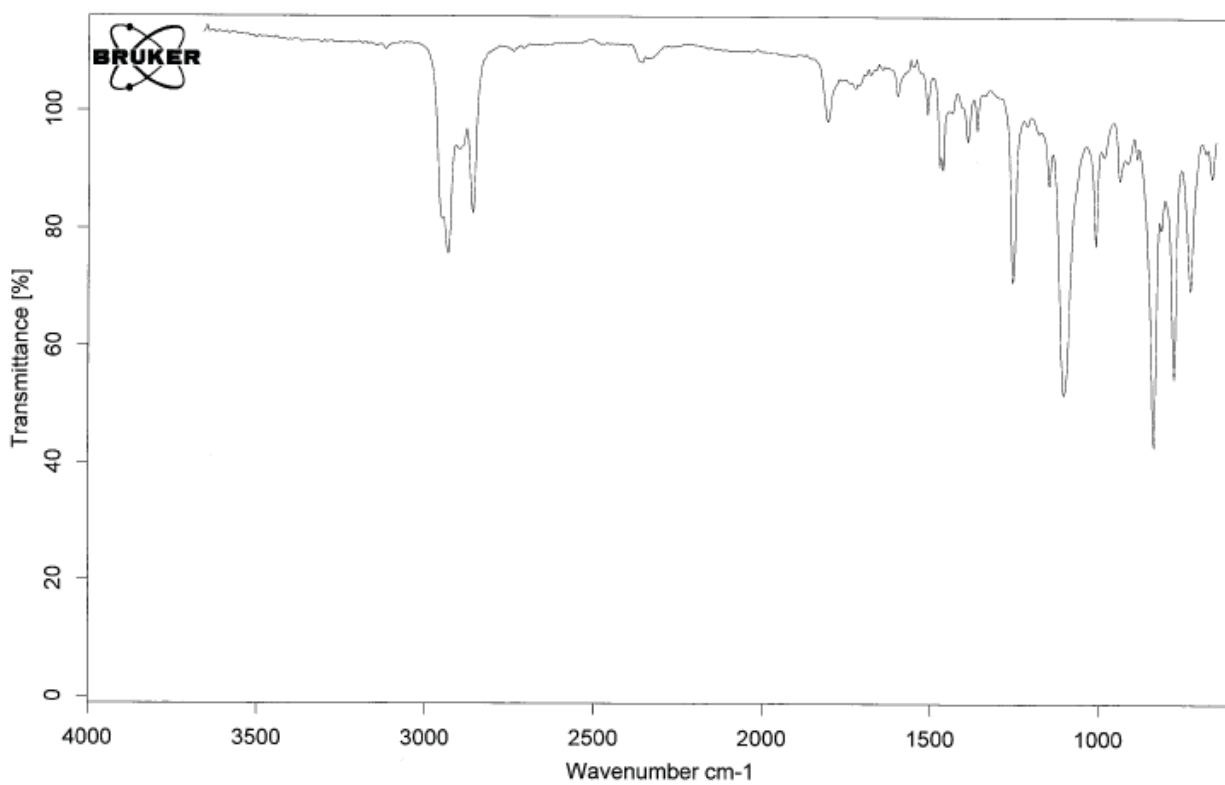
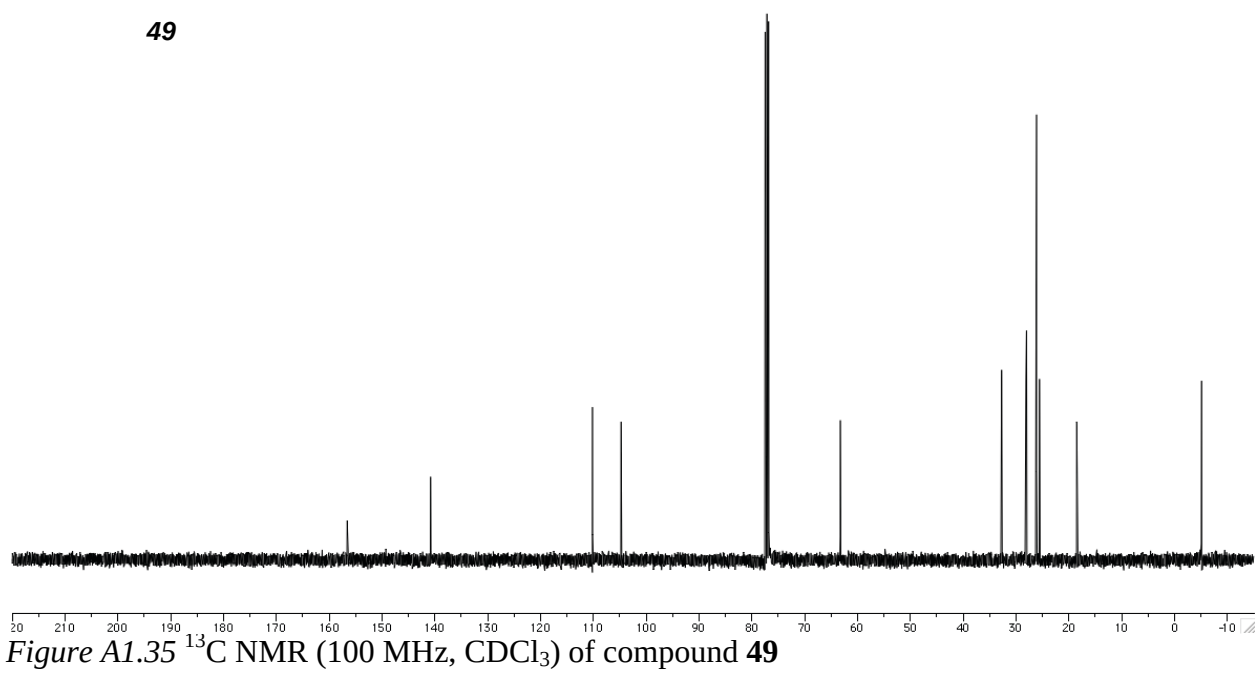
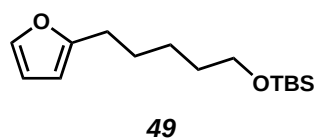


Figure A1.34 ^1H NMR (400 MHz, CDCl_3) of compound **49**



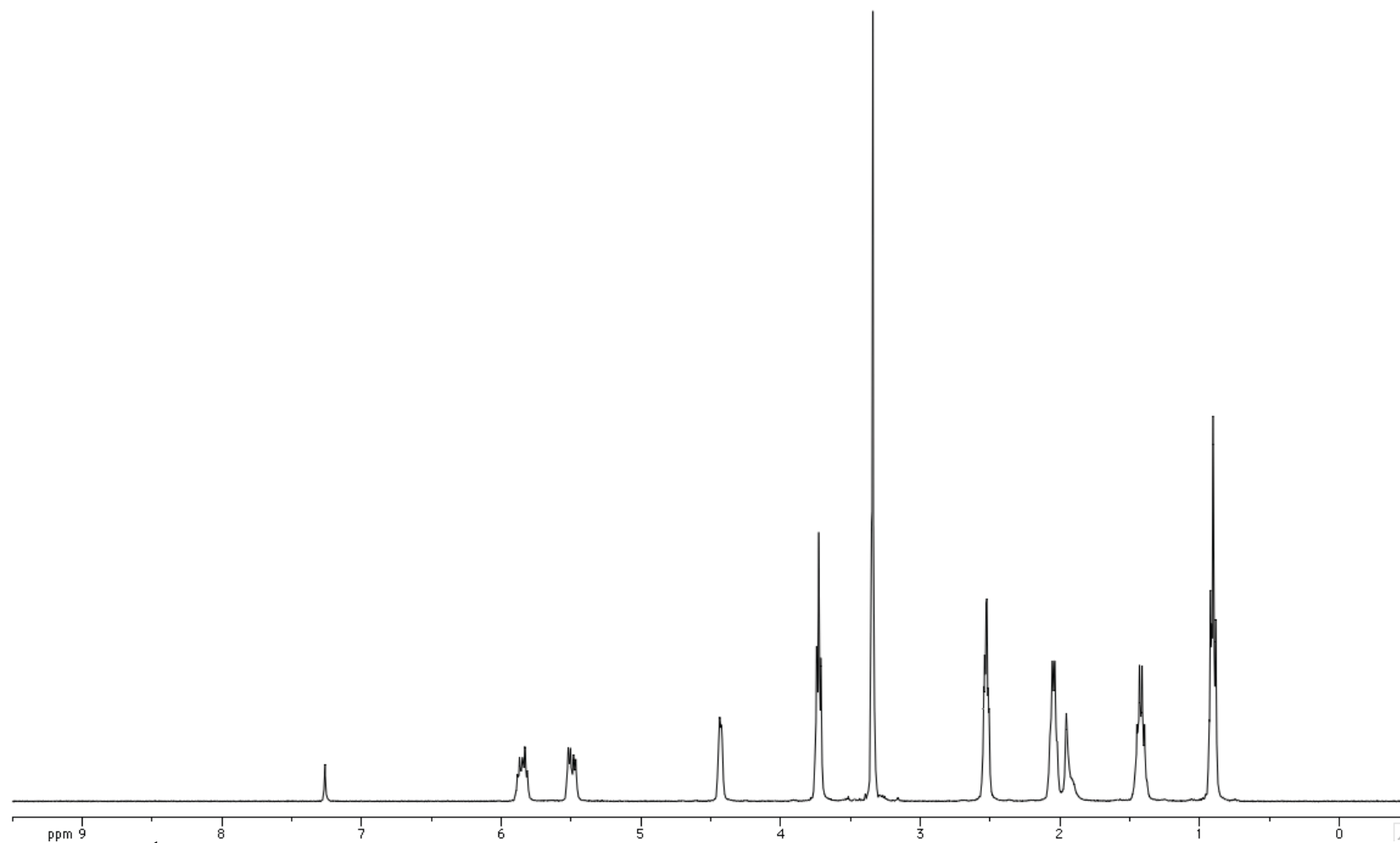
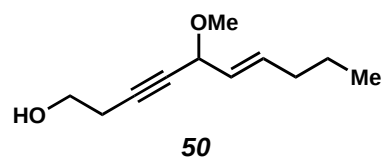


Figure A1.37 ^1H NMR (400 MHz, CDCl_3) of compound **50**

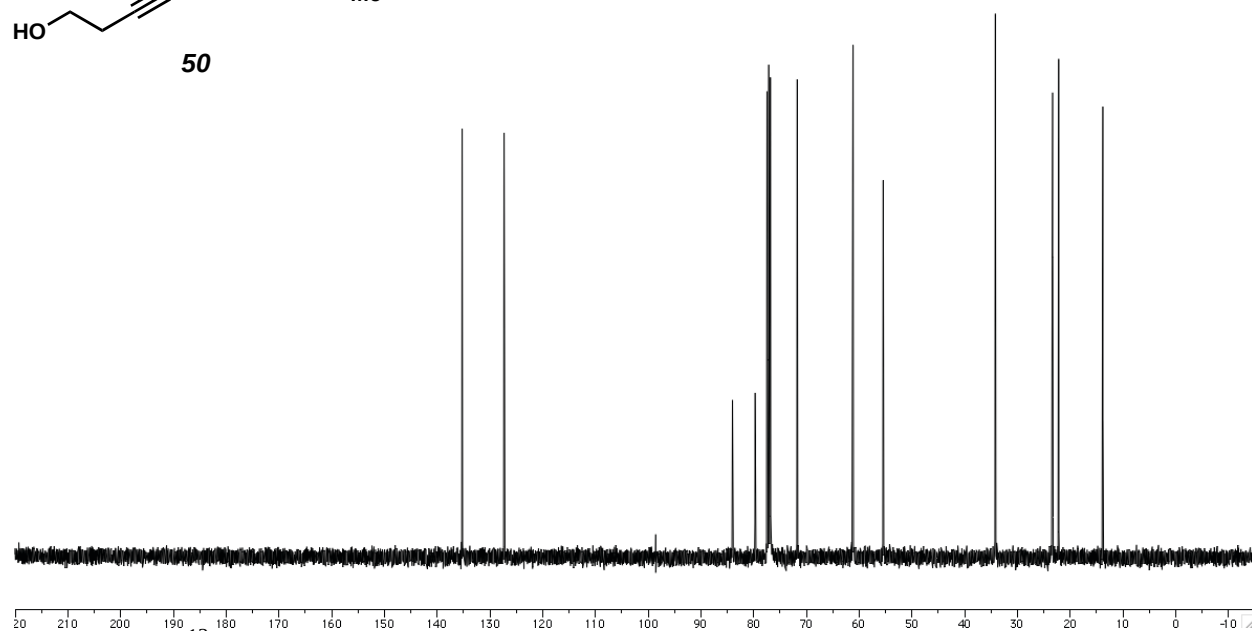
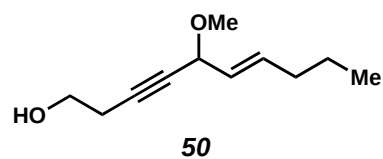


Figure A1.38 ^{13}C NMR (100 MHz, CDCl_3) of compound **50**

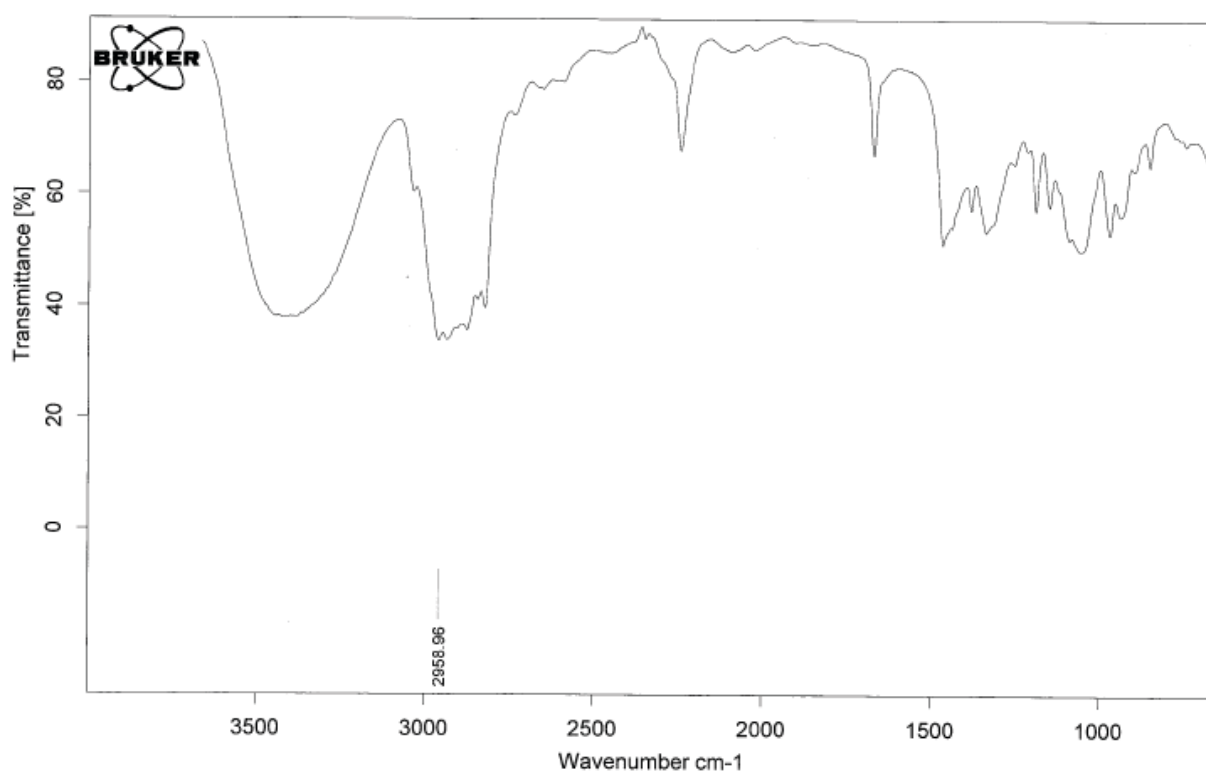


Figure A1.39 Infrared spectrum (thin film) of compound **50**

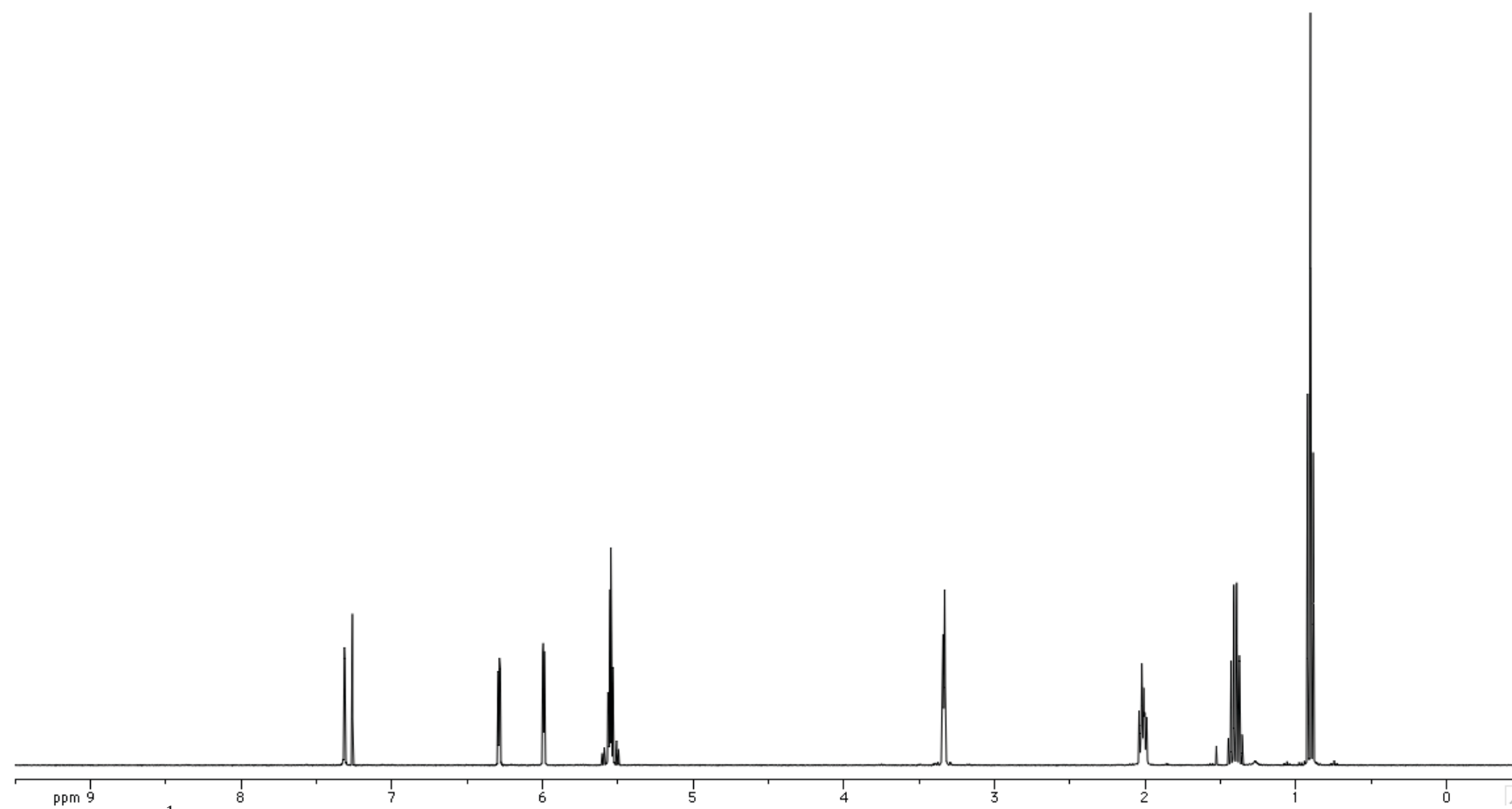
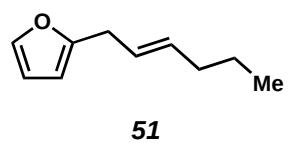


Figure A1.40 ^1H NMR (400 MHz, CDCl_3) of compound **51**

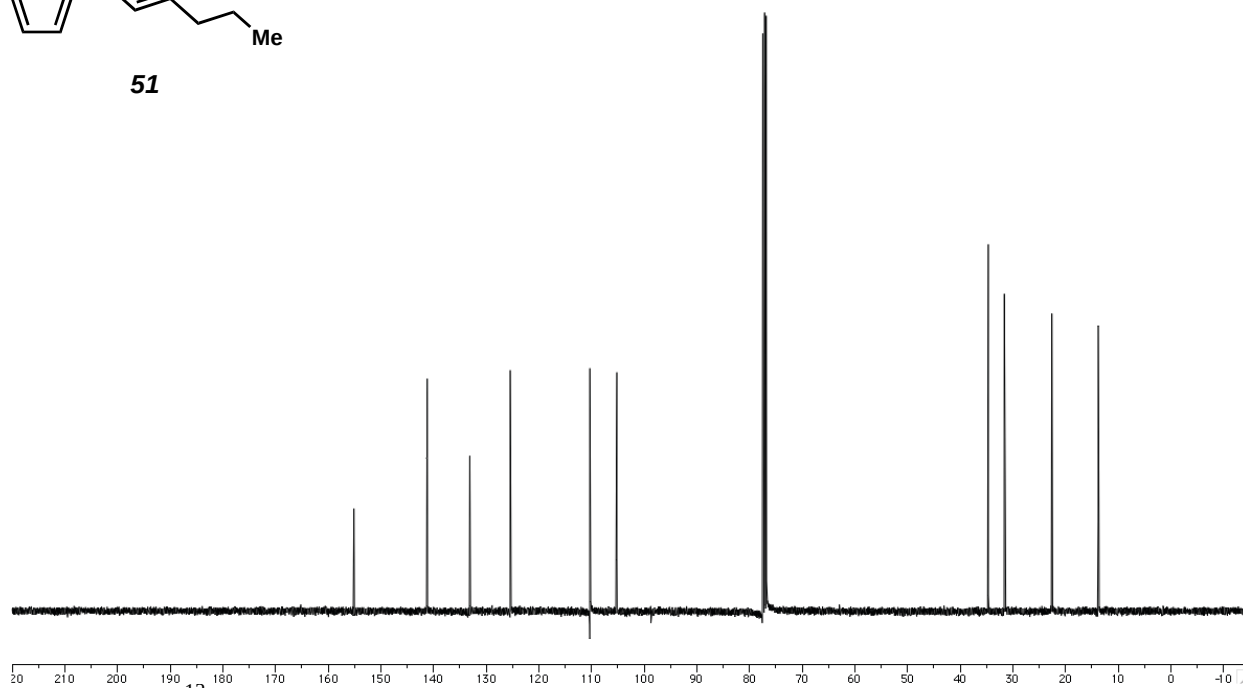
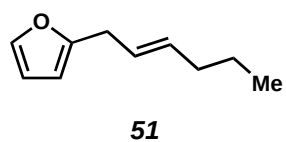


Figure A1.41 ^{13}C NMR (100 MHz, CDCl_3) of compound **51**

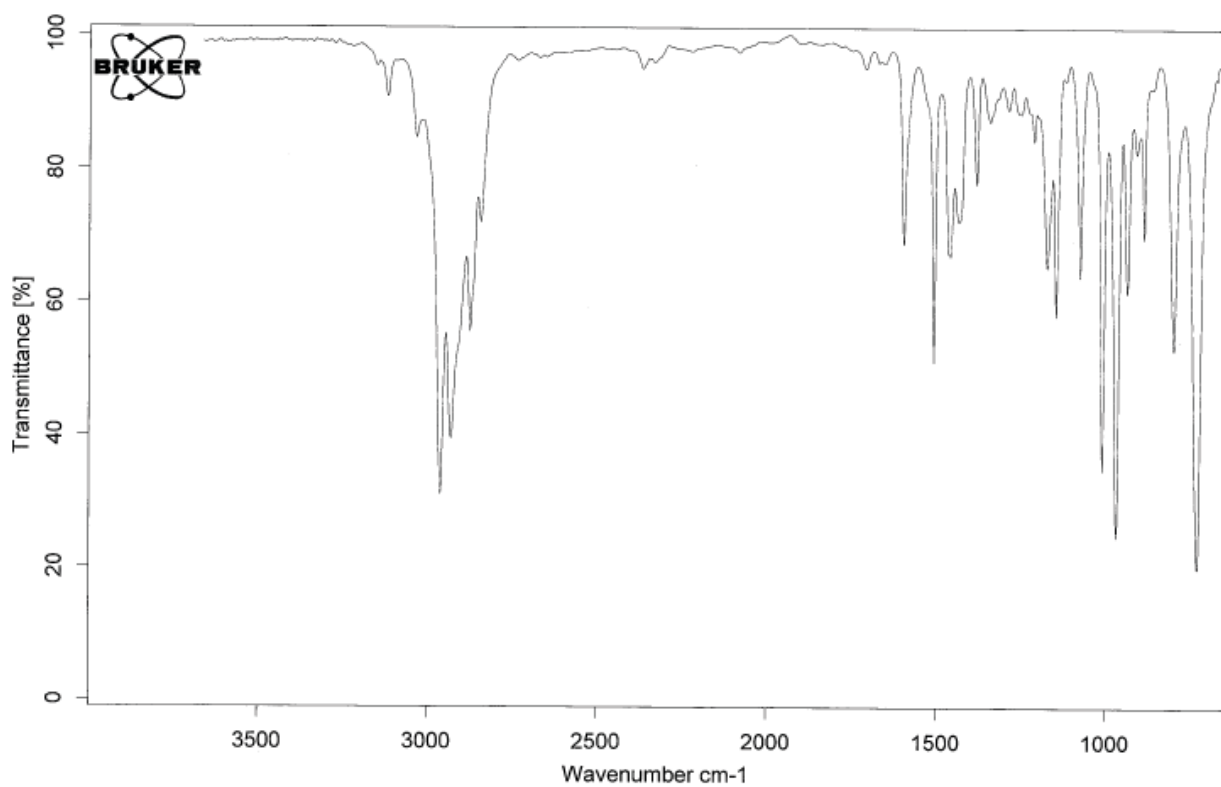


Figure A1.42 Infrared spectrum (thin film) of compound **51**

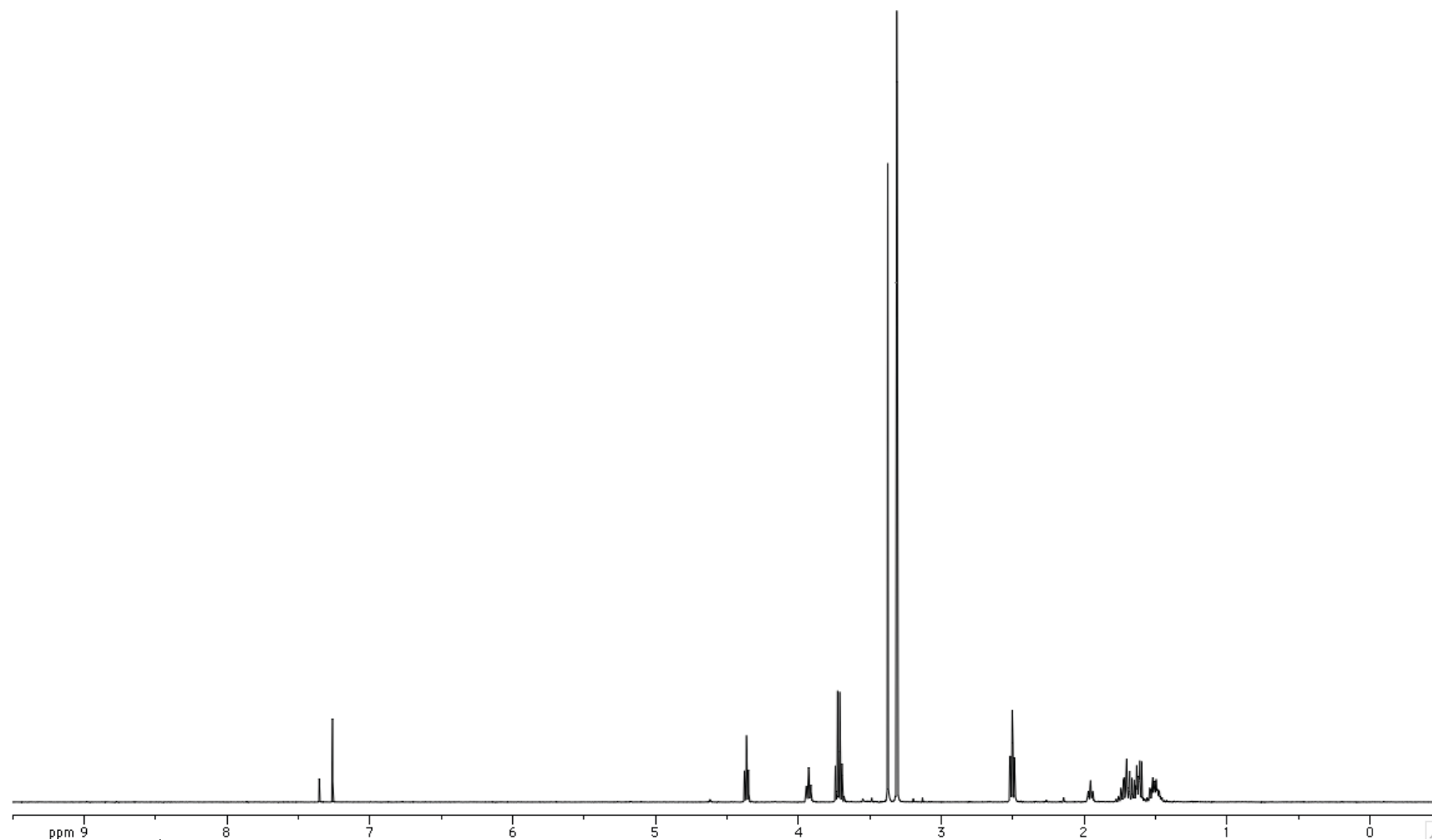
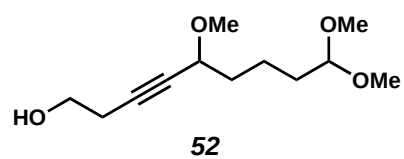
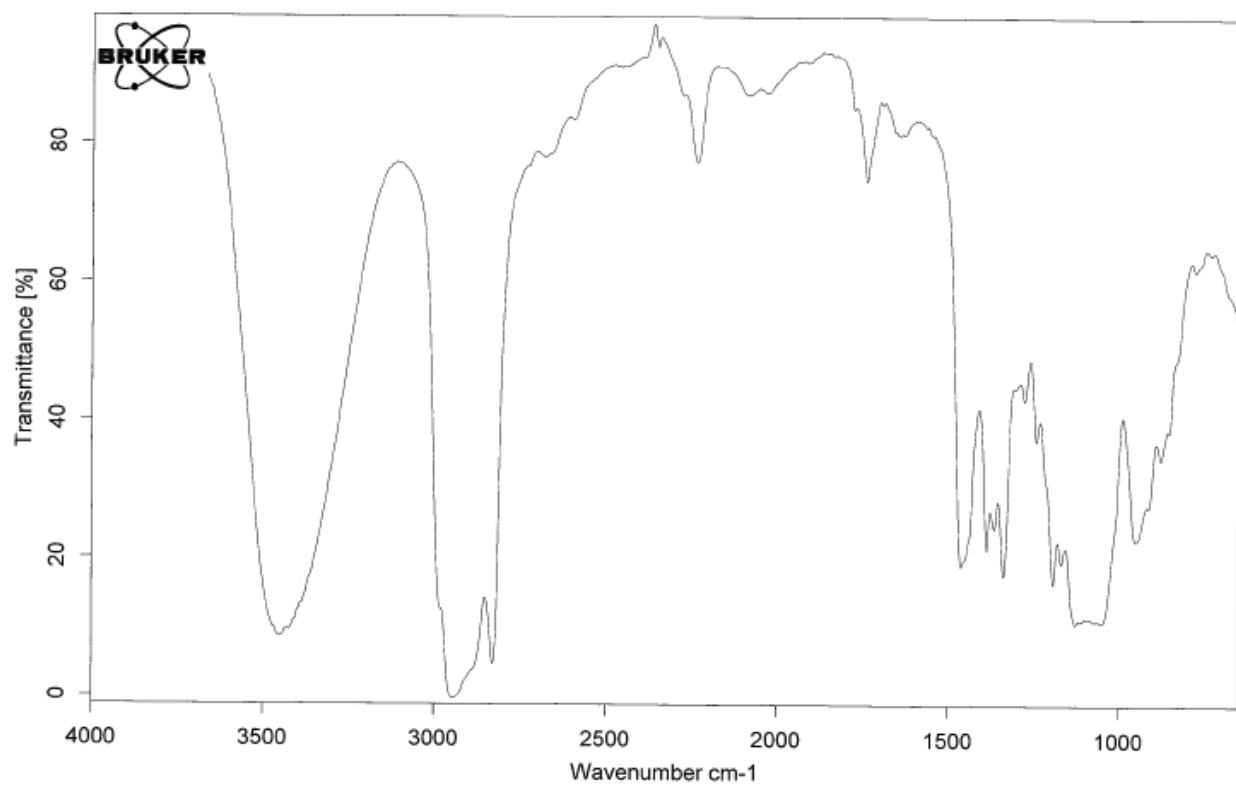
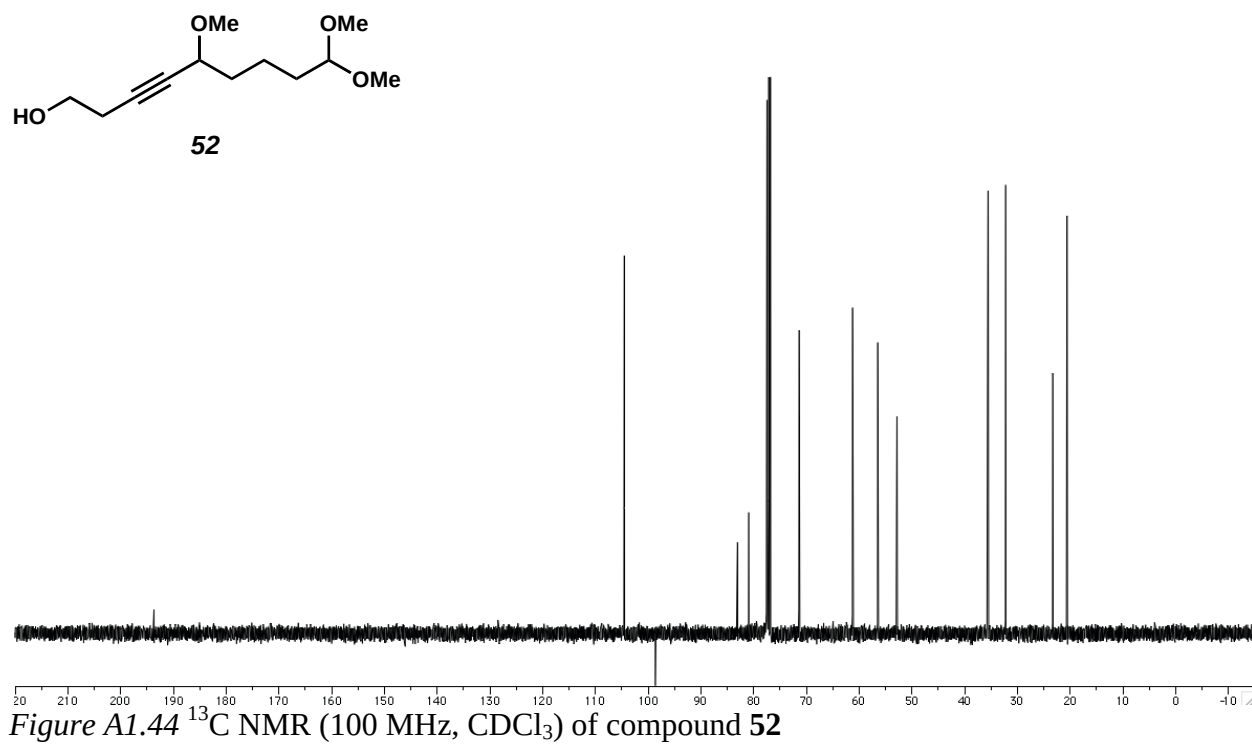


Figure A1.43 ^1H NMR (400 MHz, CDCl_3) of compound **52**



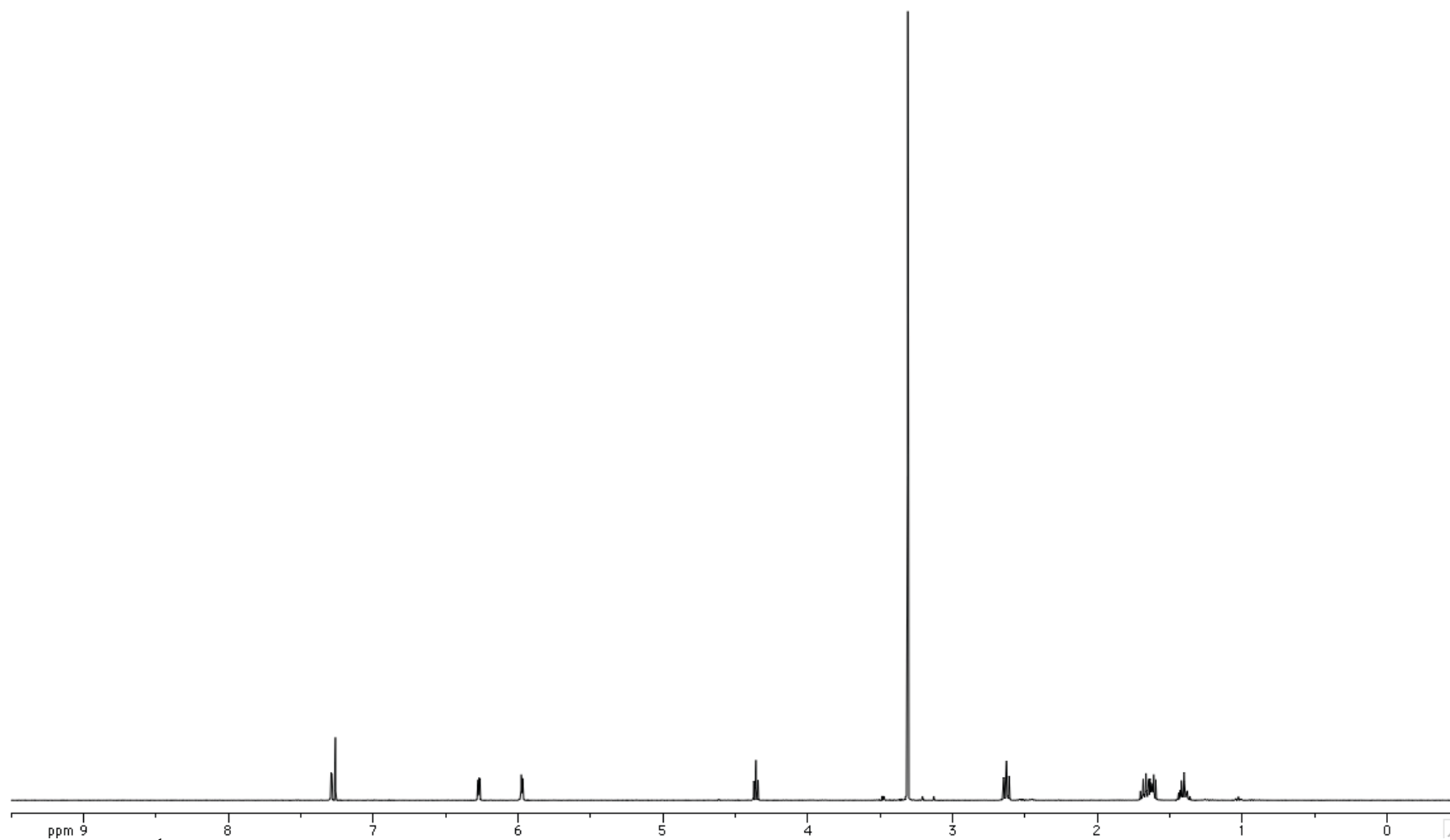
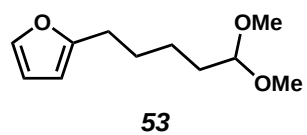


Figure A1.46 ^1H NMR (400 MHz, CDCl_3) of compound **53**

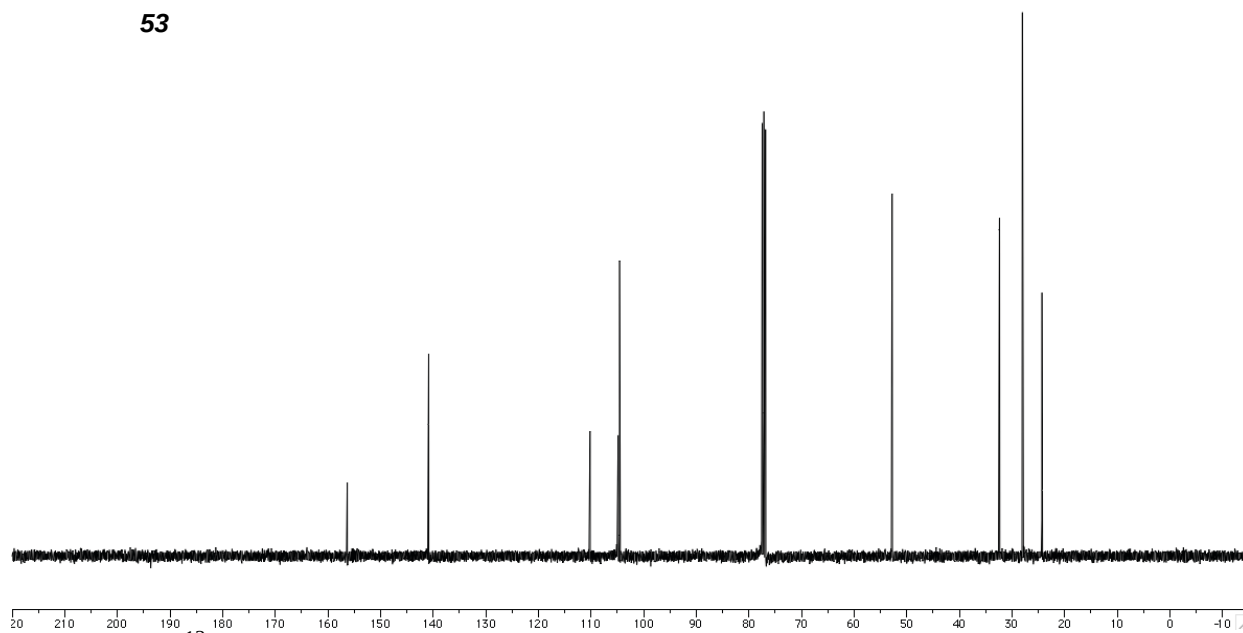
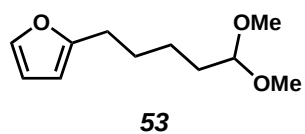


Figure A1.47 ^{13}C NMR (100 MHz, CDCl_3) of compound 53

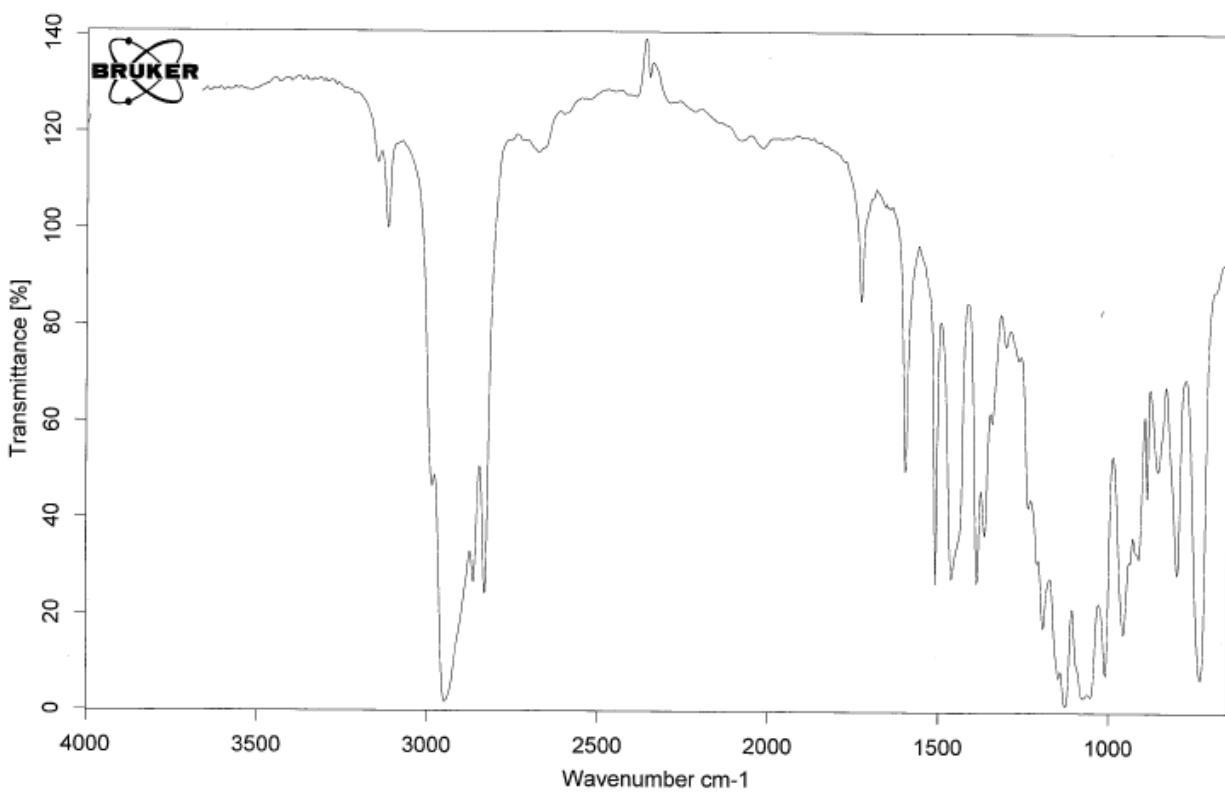


Figure A1.48 Infrared spectrum (thin film) of compound 53

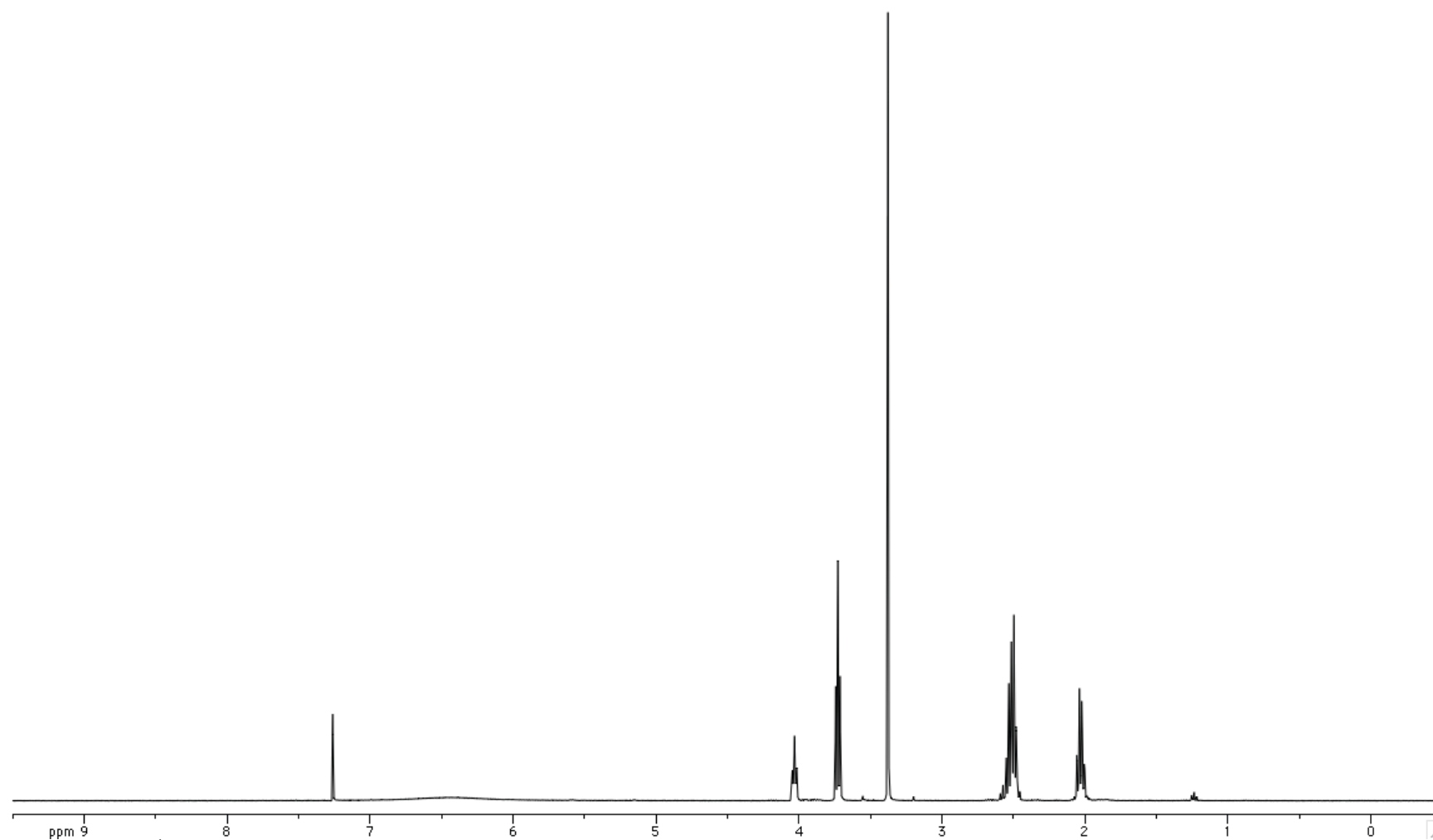
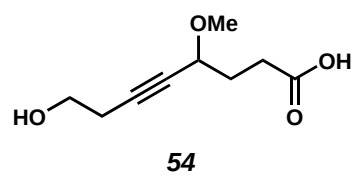


Figure A1.49 ¹H NMR (400 MHz, CDCl₃) of compound **54**

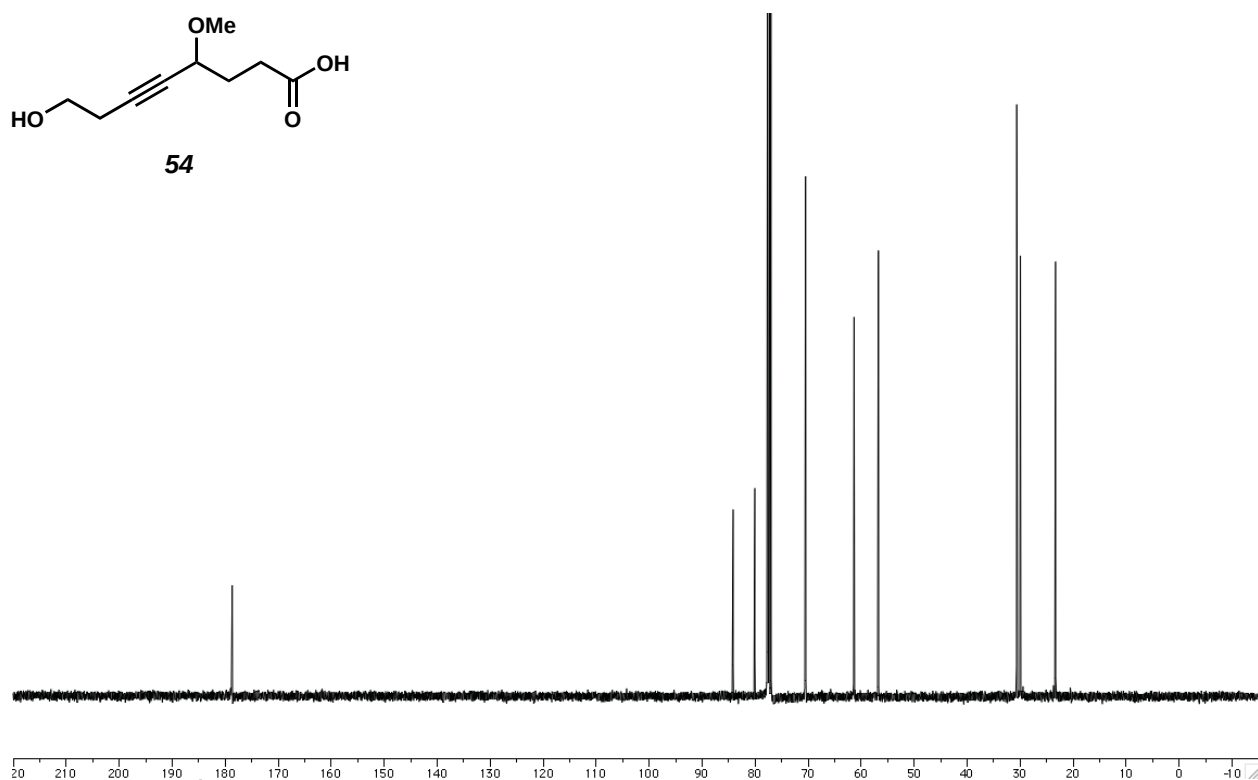
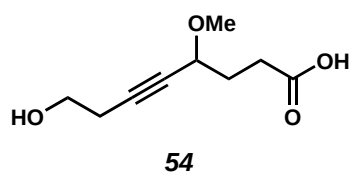


Figure A1.50 ^{13}C NMR (100 MHz, CDCl_3) of compound **54**

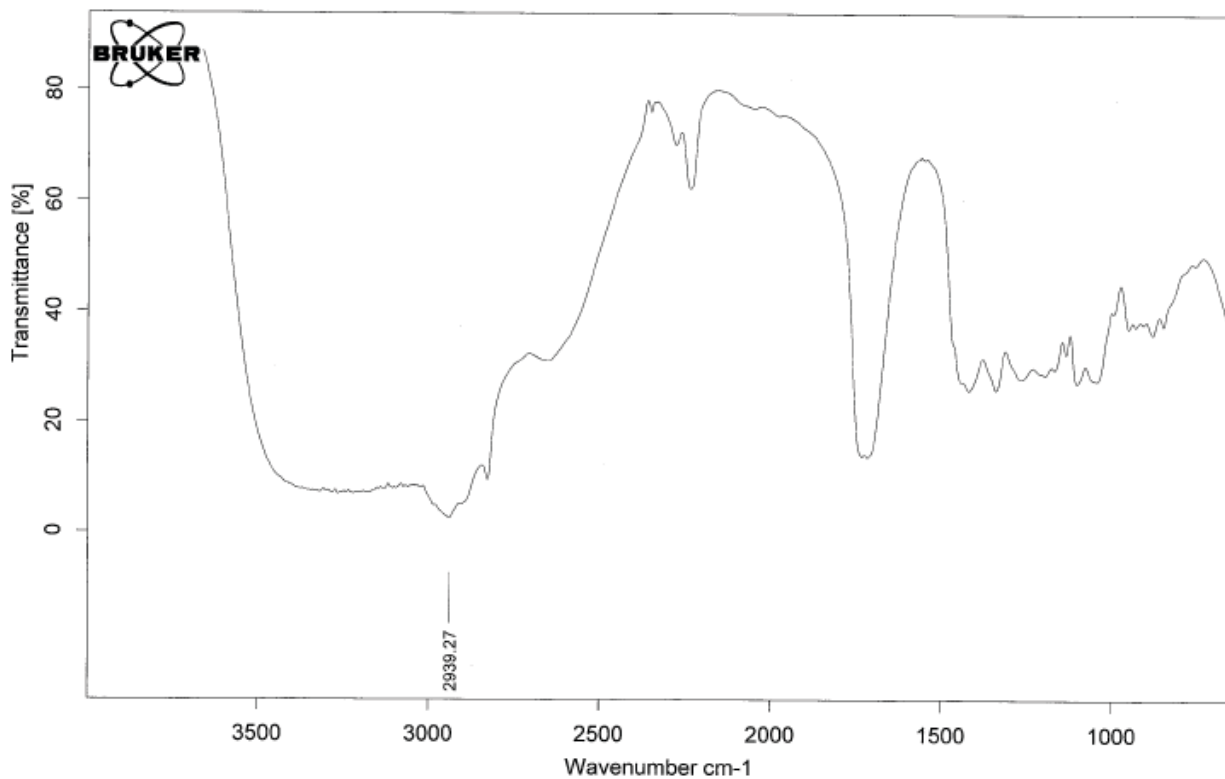


Figure A1.51 Infrared spectrum (thin film) of compound **54**

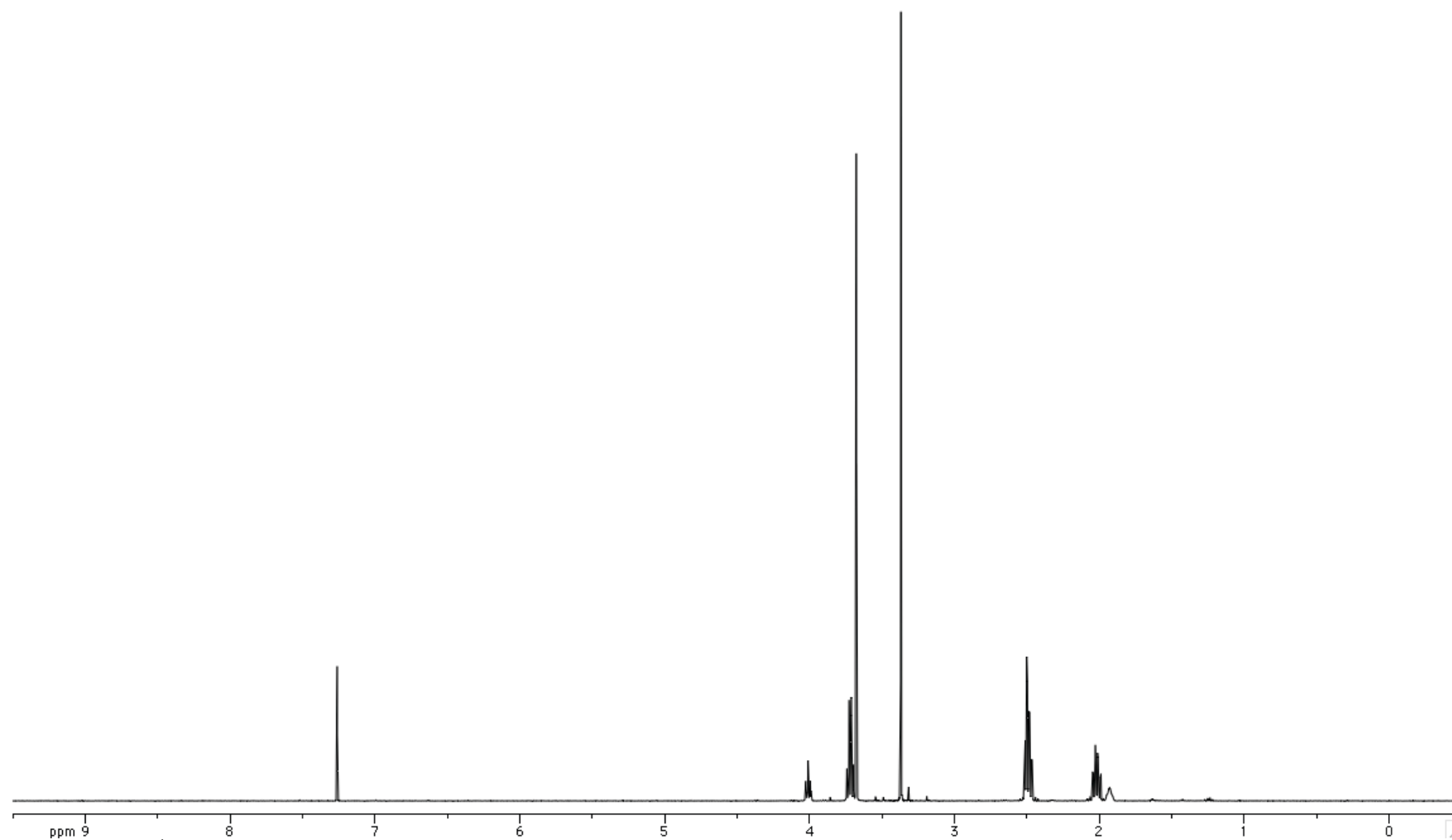
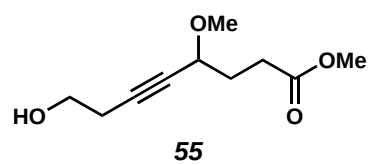


Figure A1.52 ^1H NMR (400 MHz, CDCl_3) of compound **55**

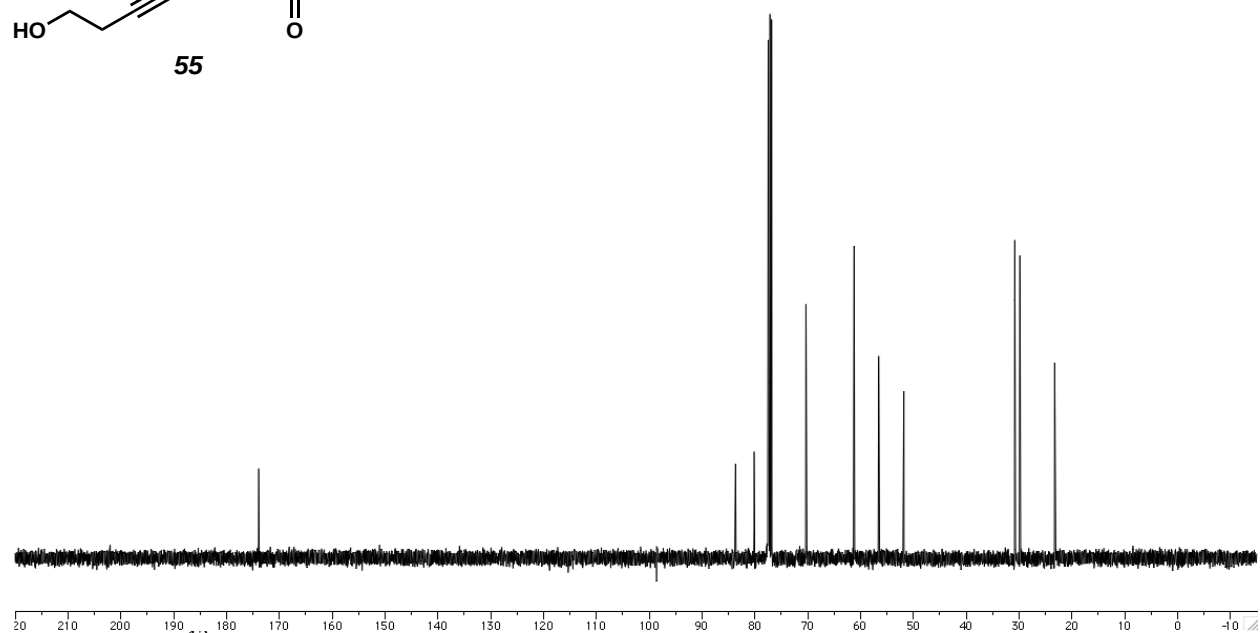
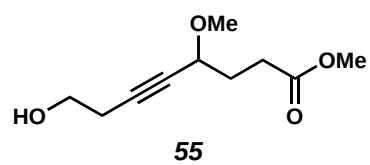


Figure A1.53 ¹³C NMR (100 MHz, CDCl₃) of compound 55

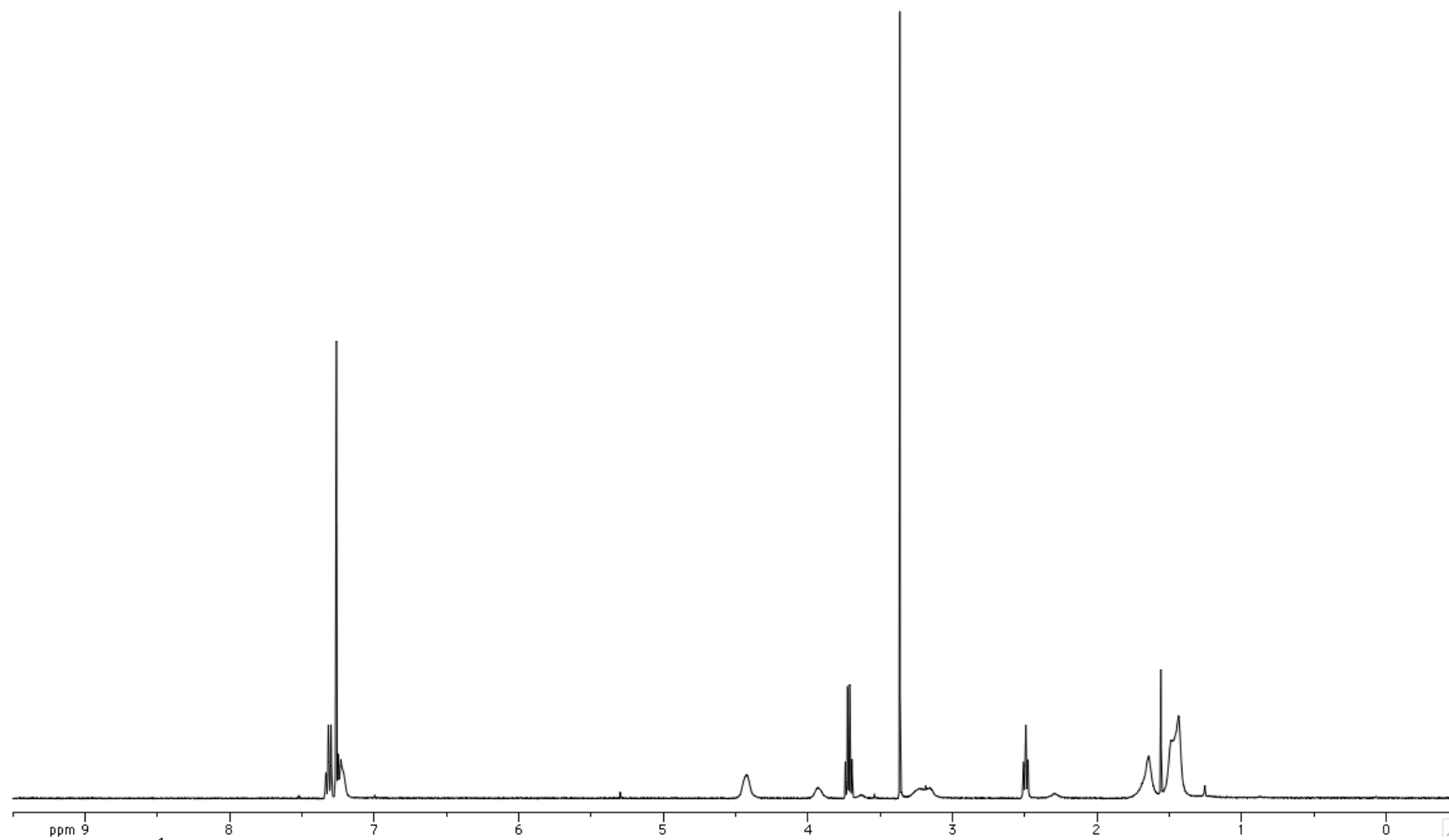
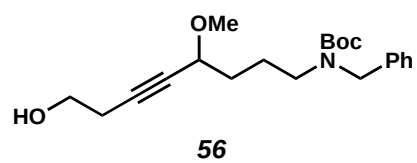


Figure A1.54 ^1H NMR (400 MHz, CDCl_3) of compound **56**

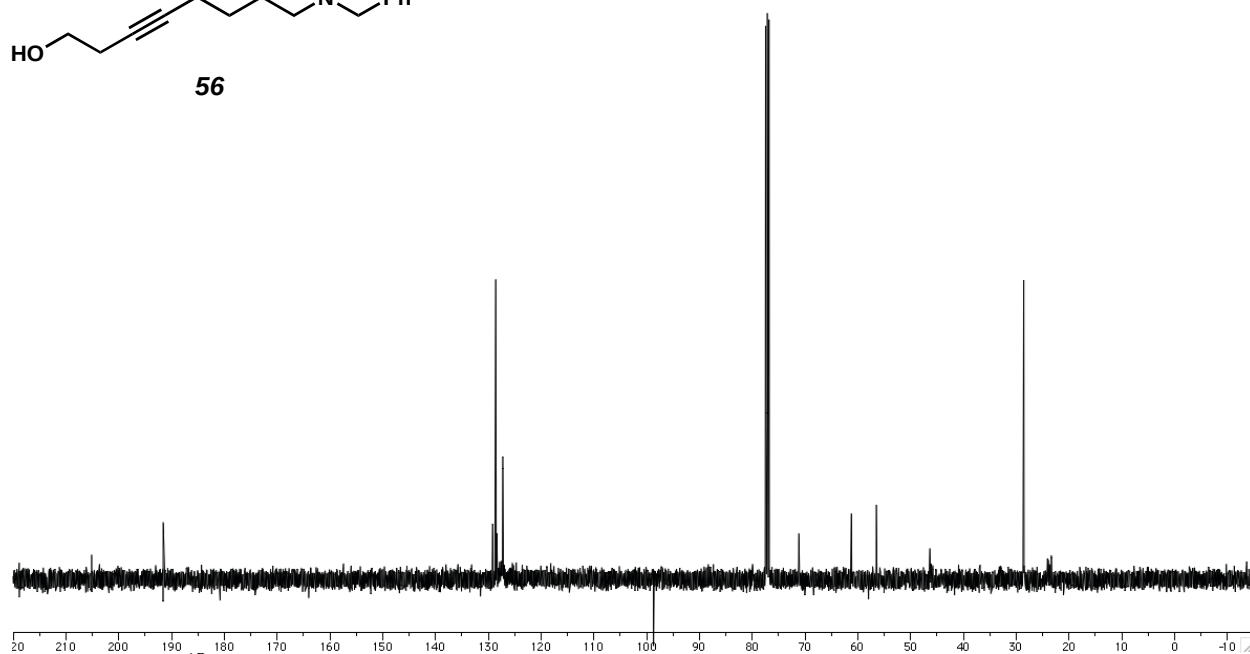
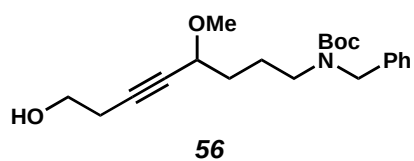


Figure A1.55 ¹³C NMR (100 MHz, CDCl₃) of compound **56**

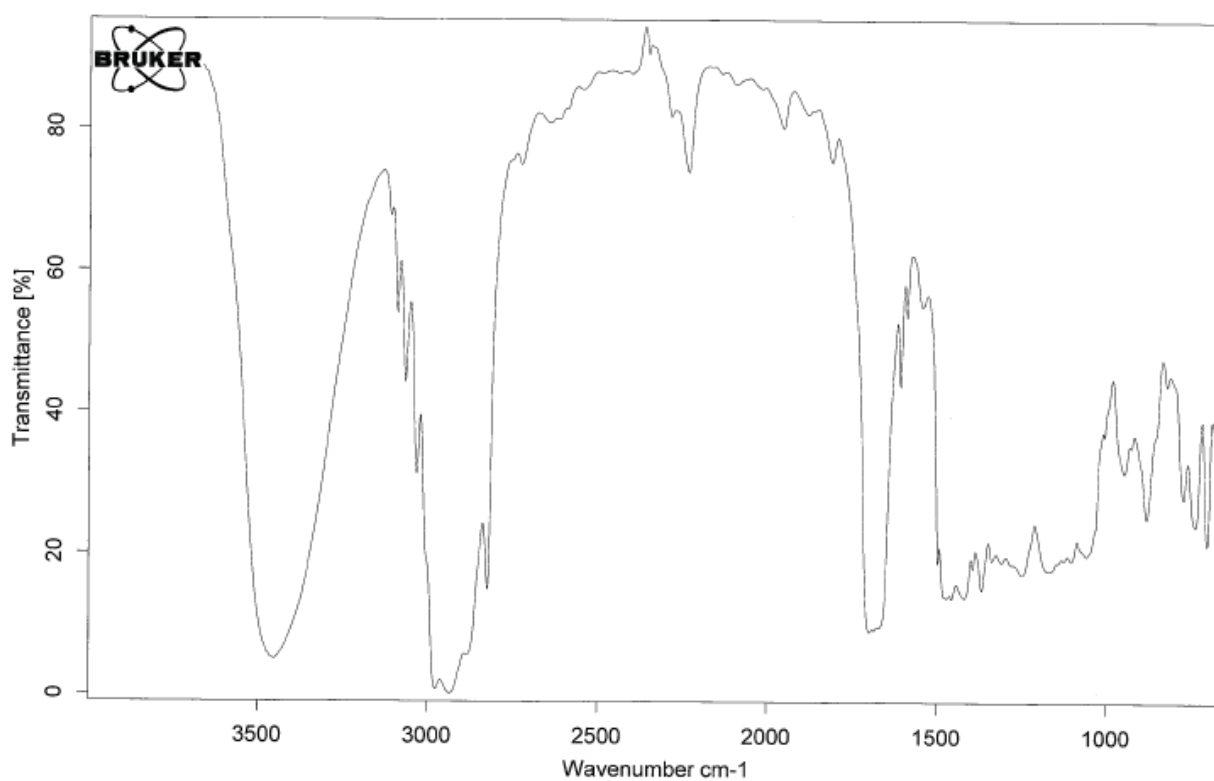
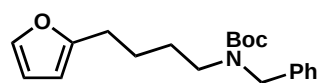


Figure A1.56 Infrared spectrum (thin film) of compound **56**



57

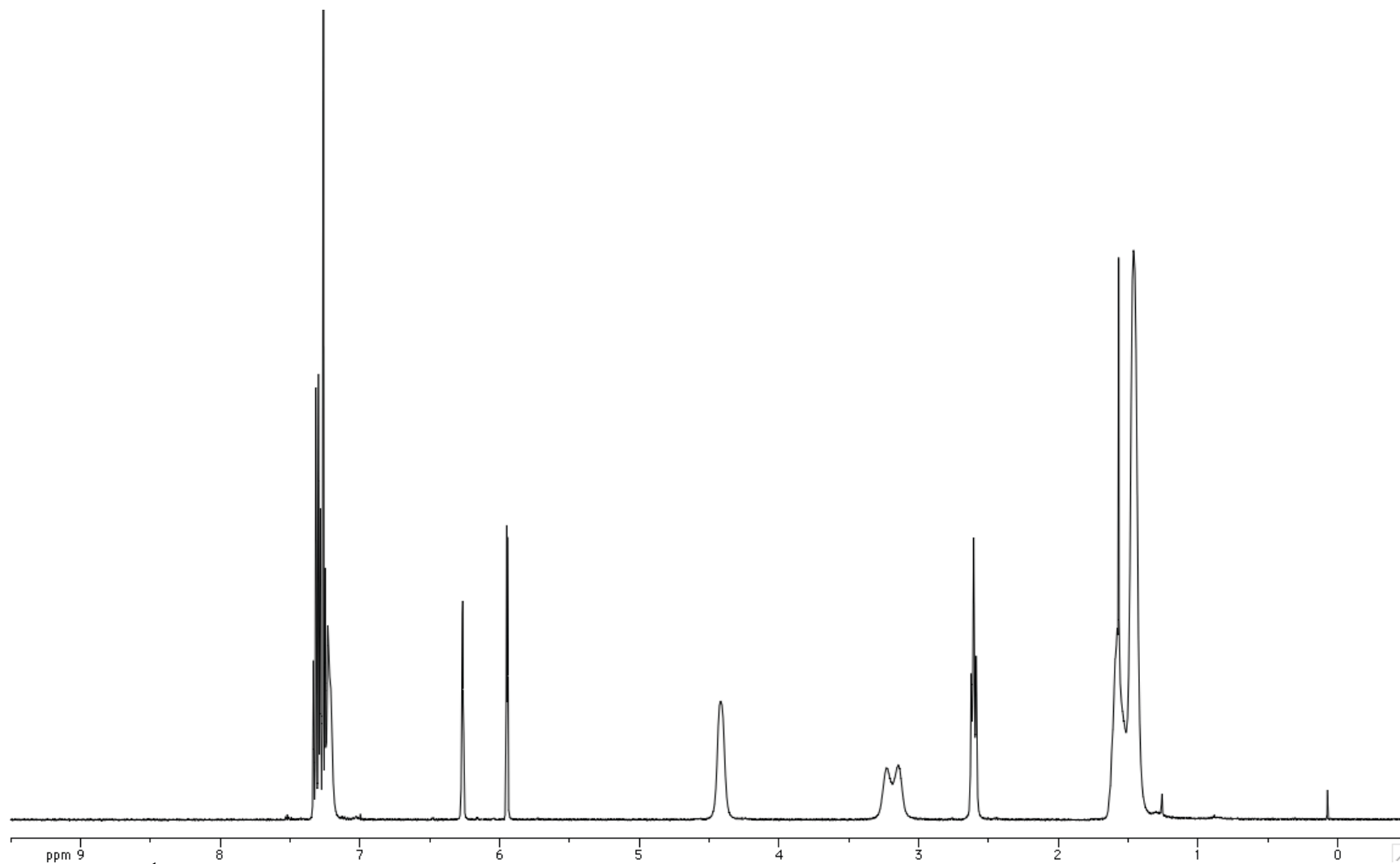


Figure A1.57 ^1H NMR (400 MHz, CDCl_3) of compound 57

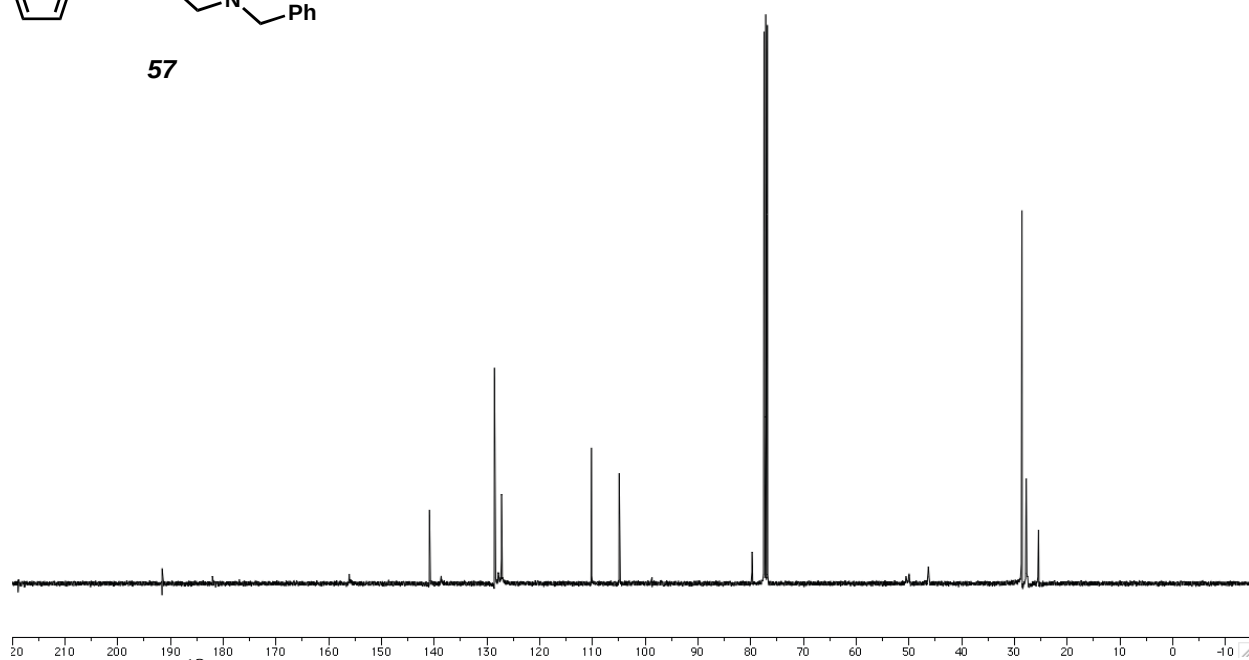
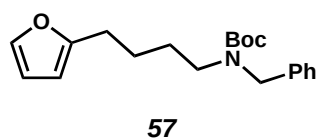


Figure A1.58 ^{13}C NMR (100 MHz, CDCl_3) of compound **57**

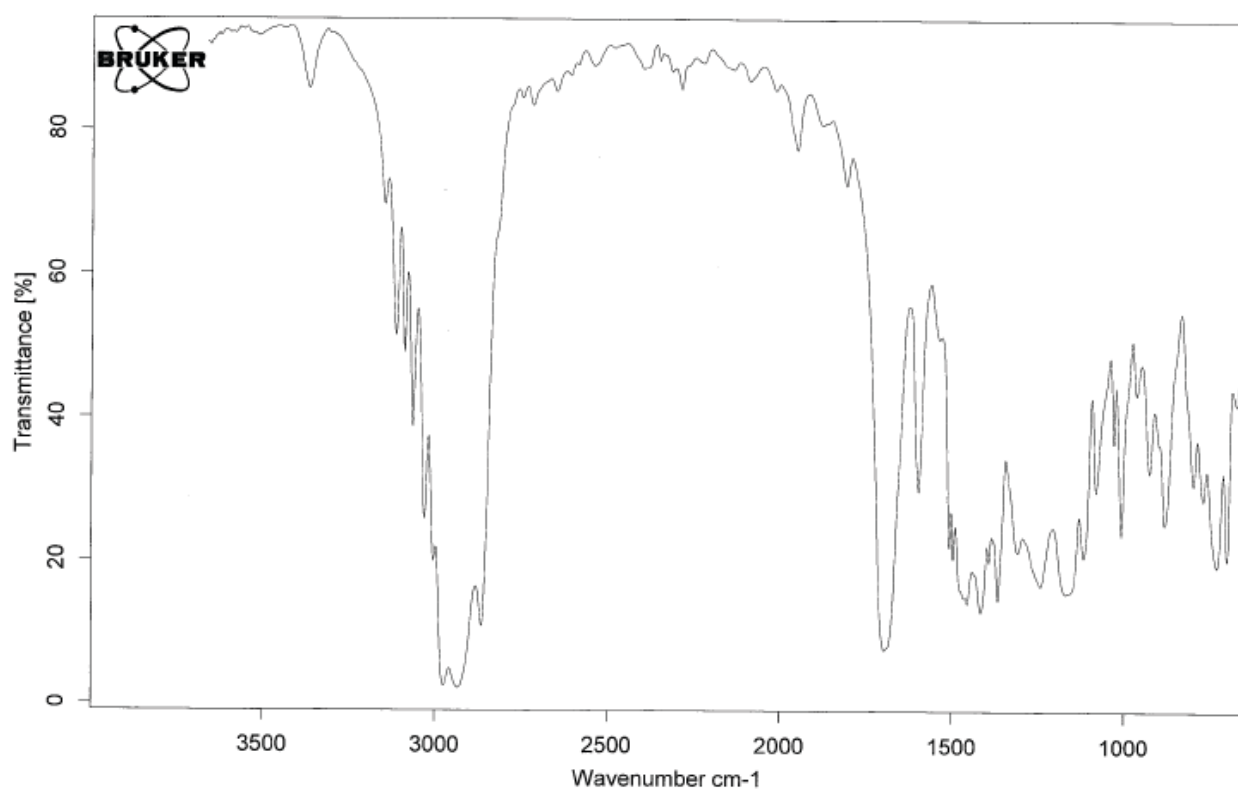


Figure A1.59 Infrared spectrum (thin film) of compound **57**

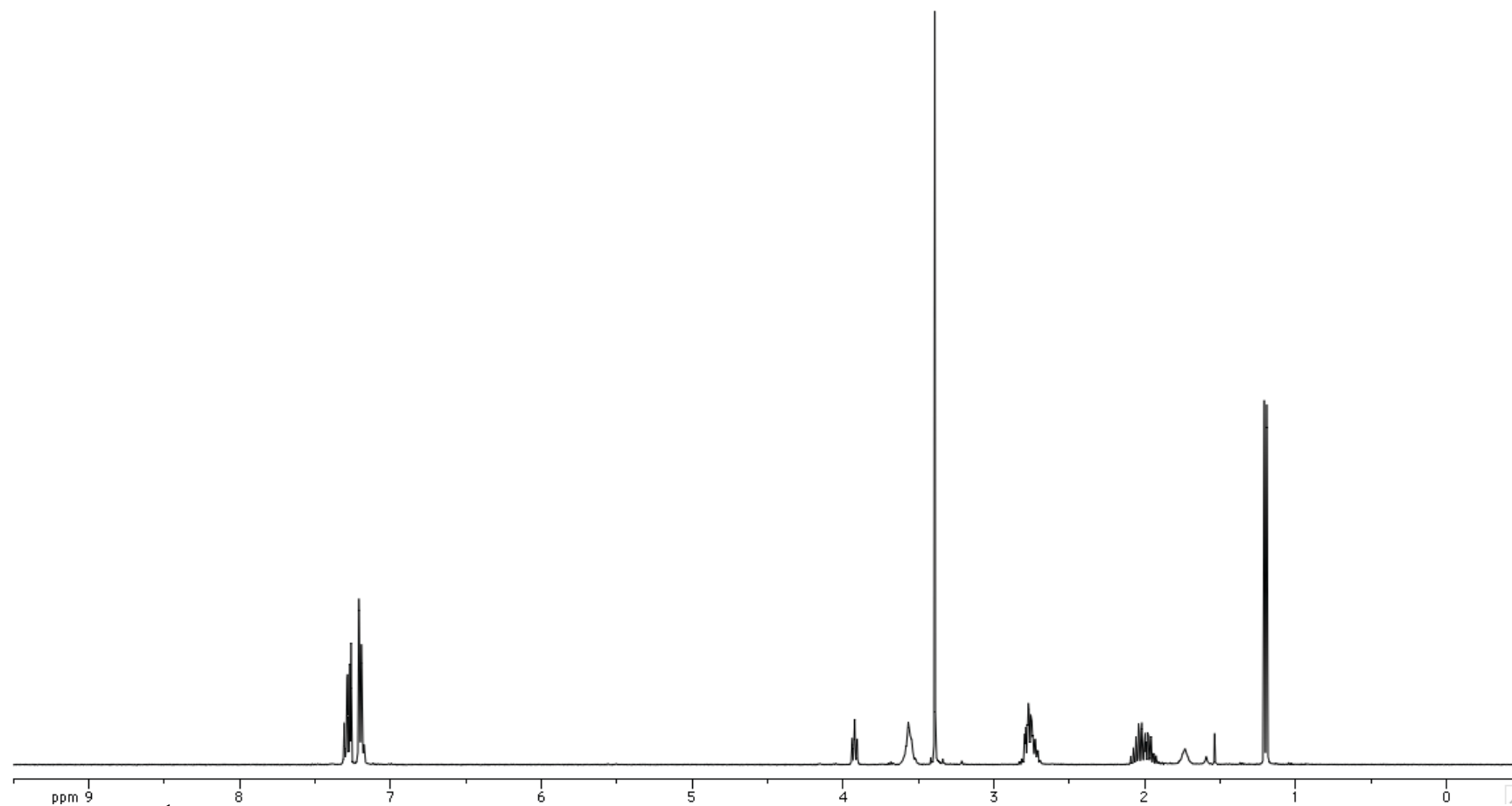
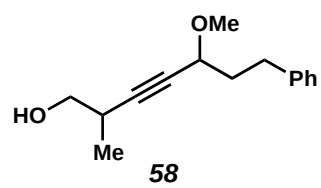
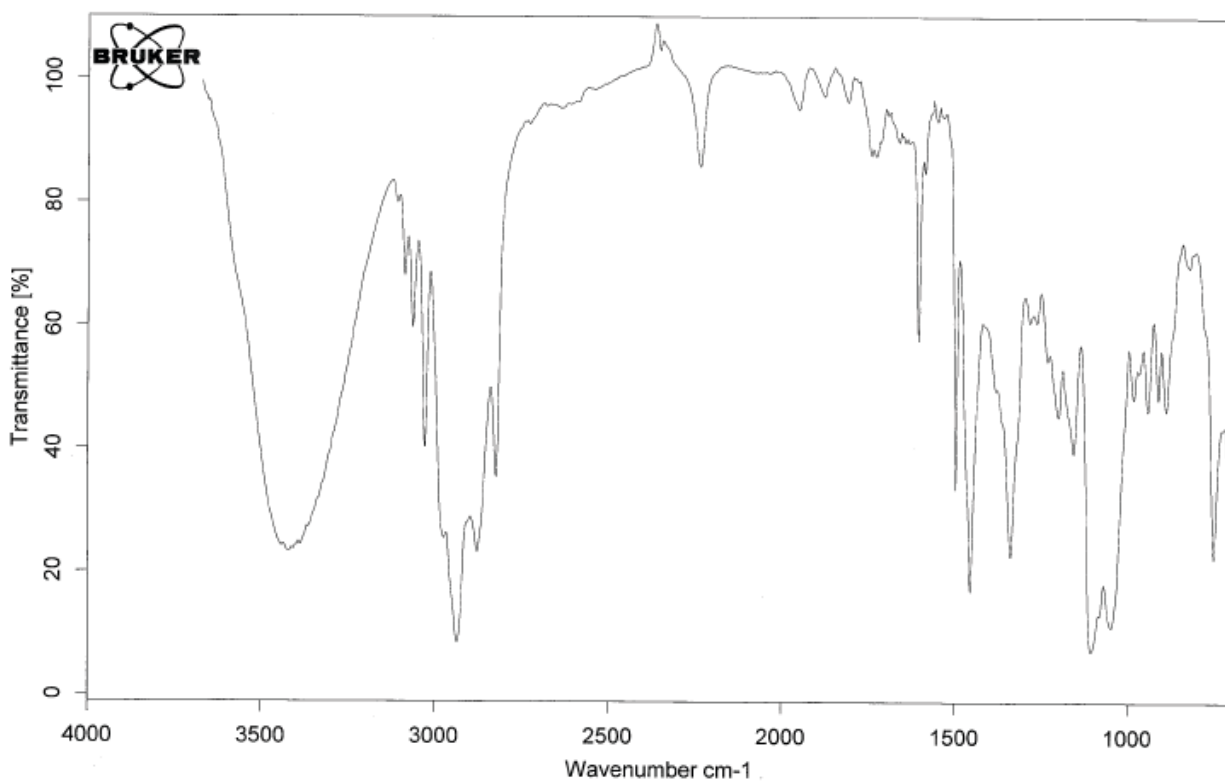
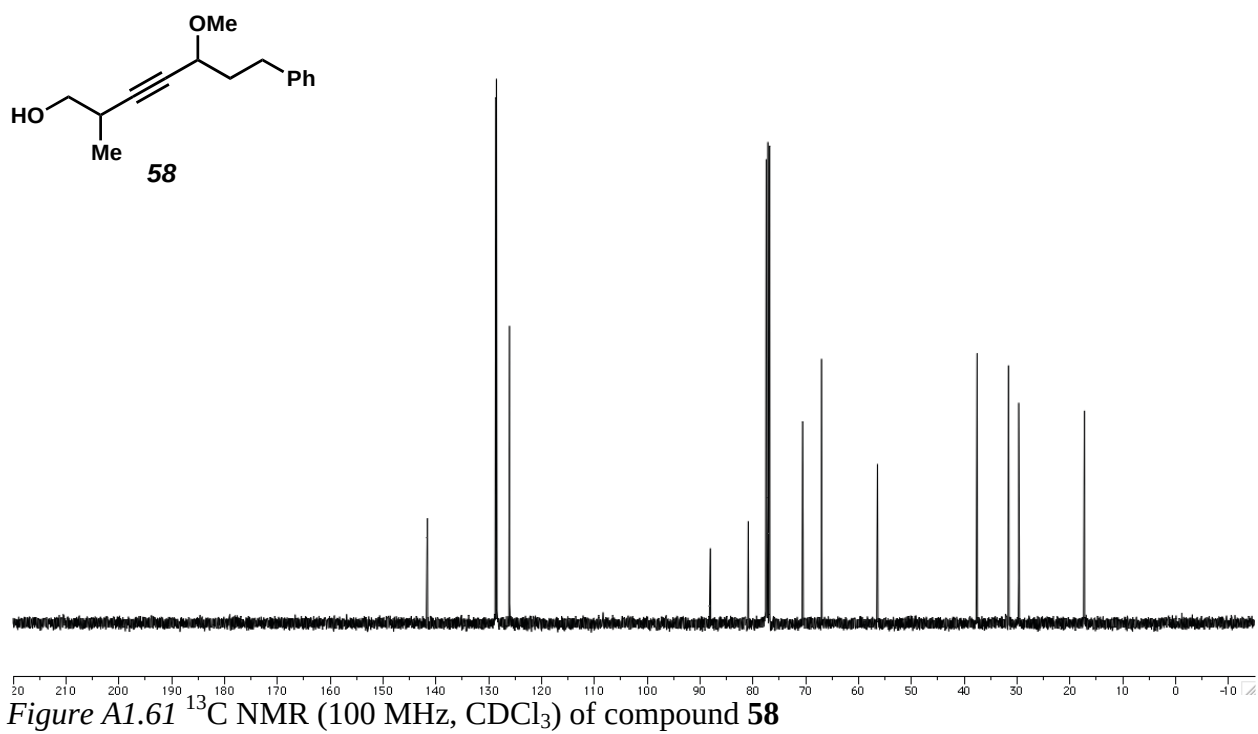


Figure A1.60 ^1H NMR (400 MHz, CDCl_3) of compound **58**



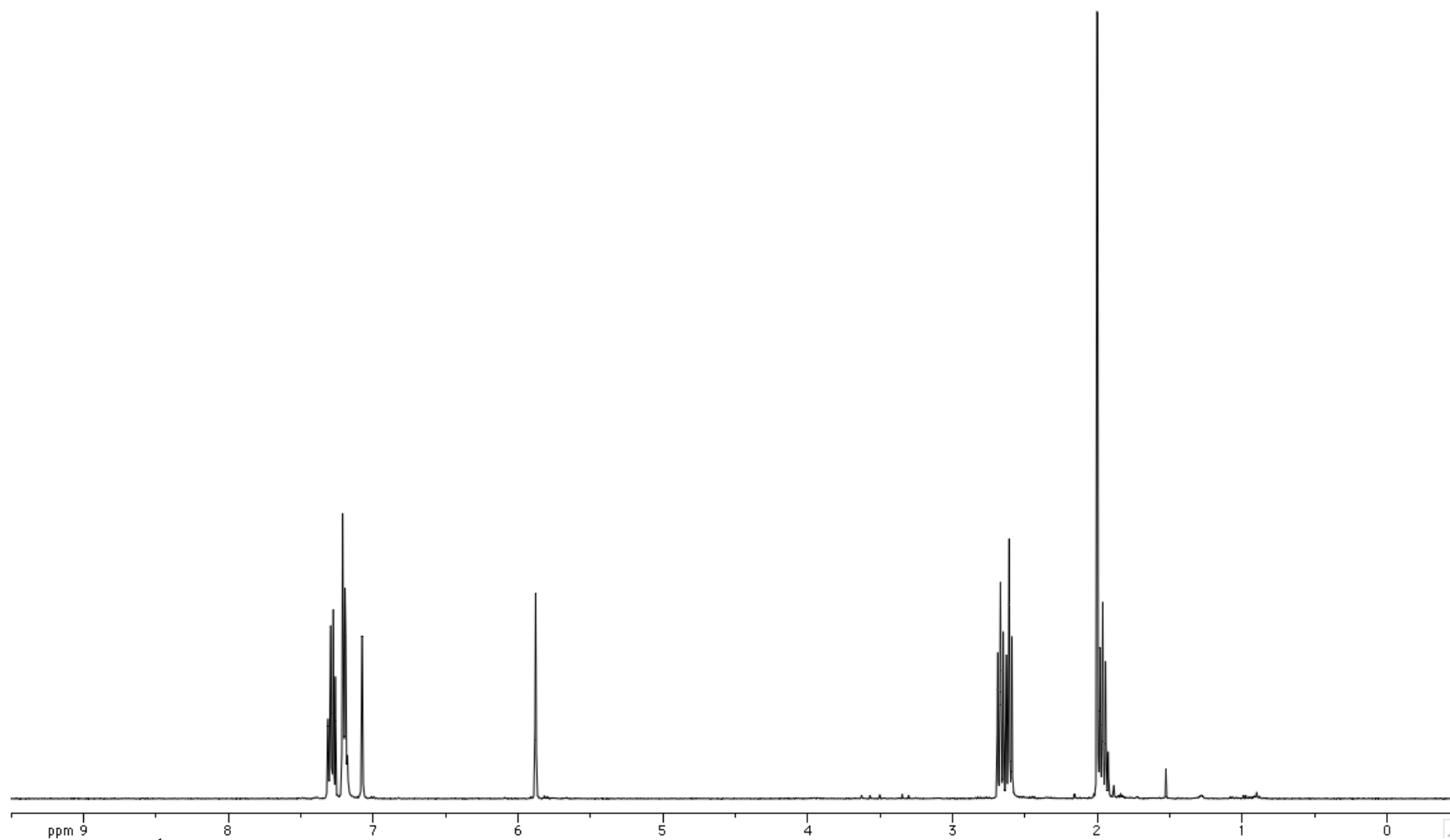
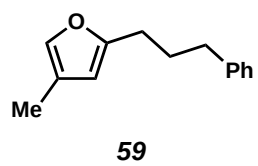
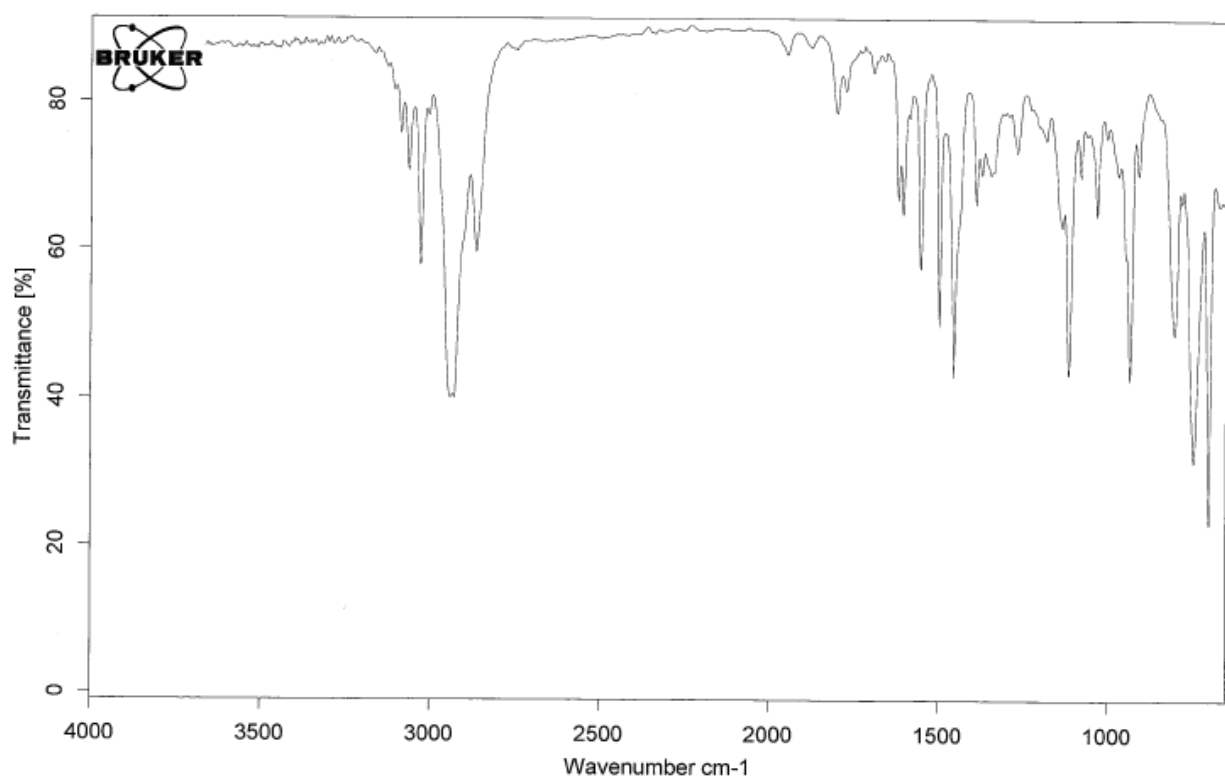
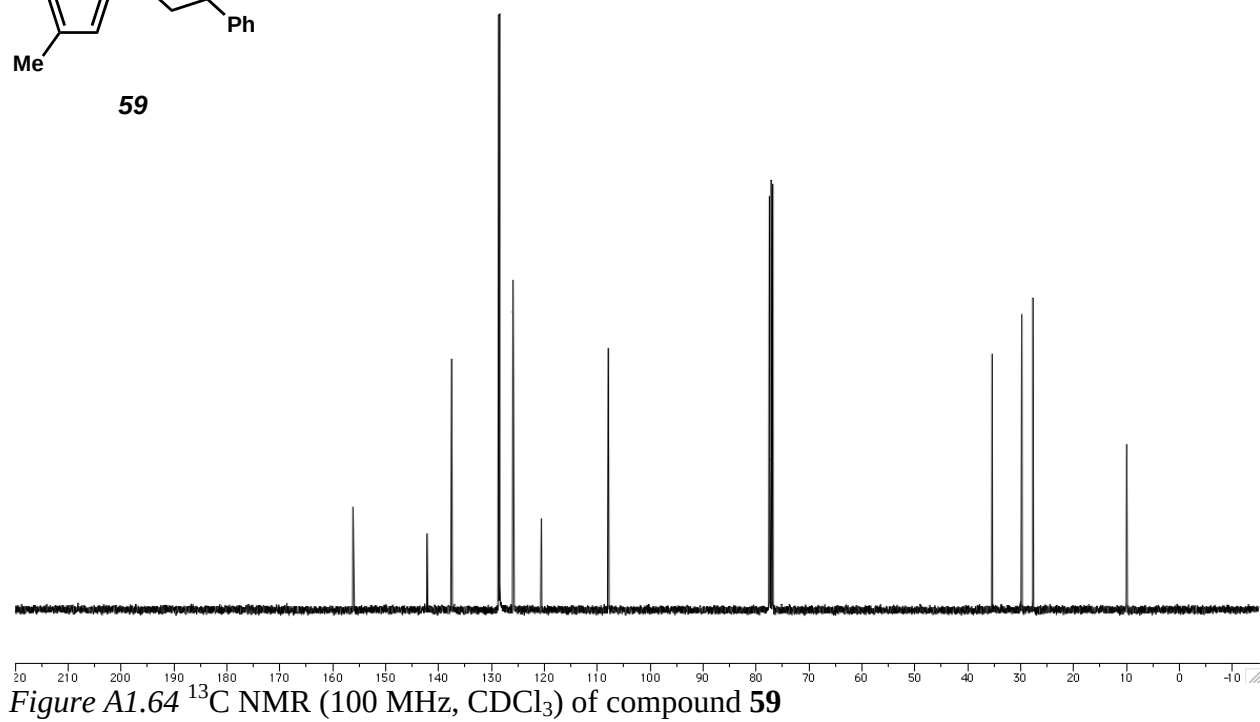
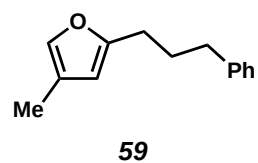


Figure A1.63 ^1H NMR (400 MHz, CDCl_3) of compound 59



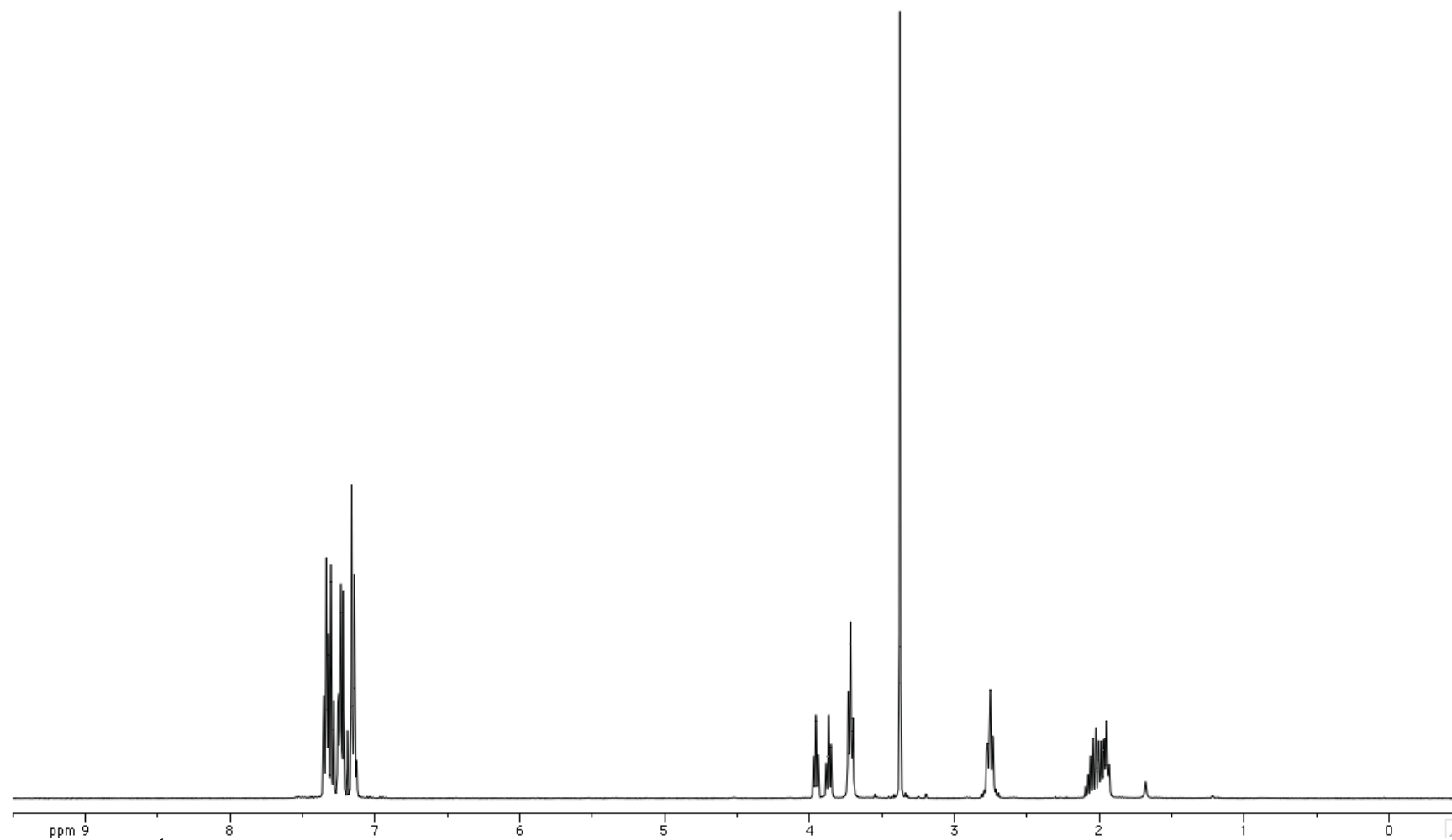
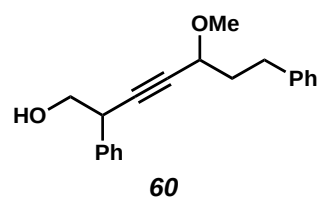


Figure A1.66 ^1H NMR (400 MHz, C_6D_6) of compound **60**

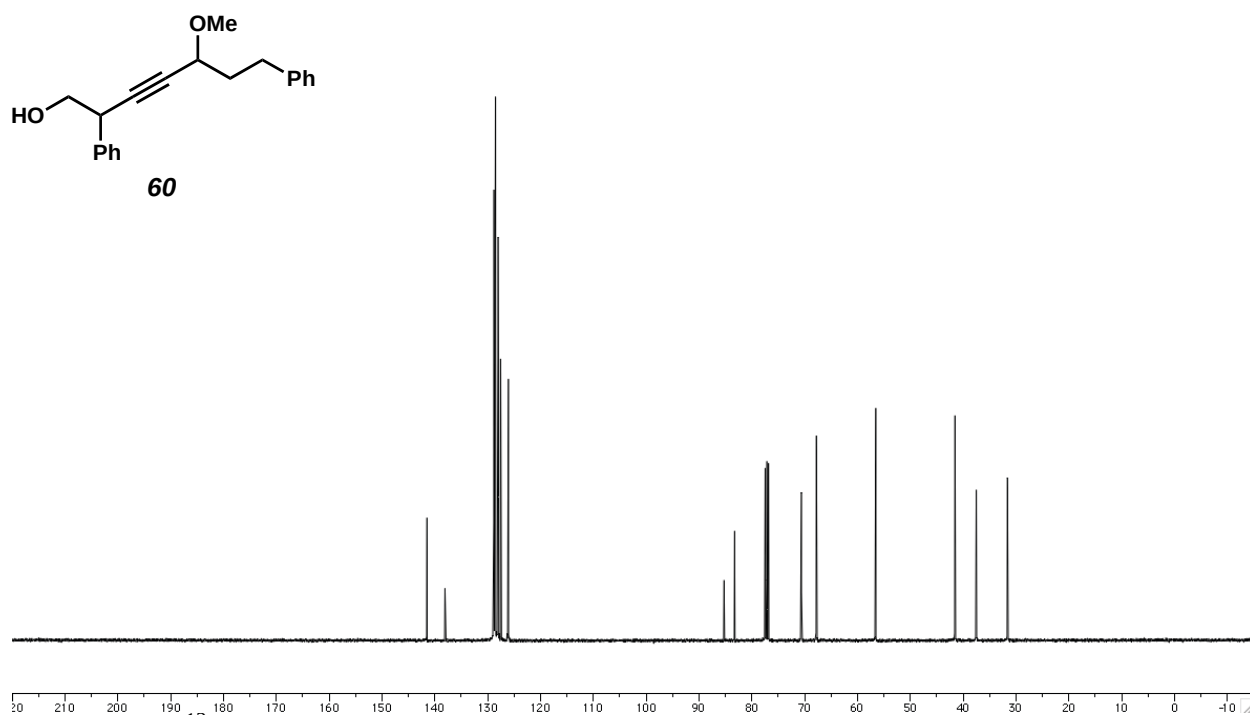


Figure A1.67 ^{13}C NMR (100 MHz, C_6D_6) of compound **60**

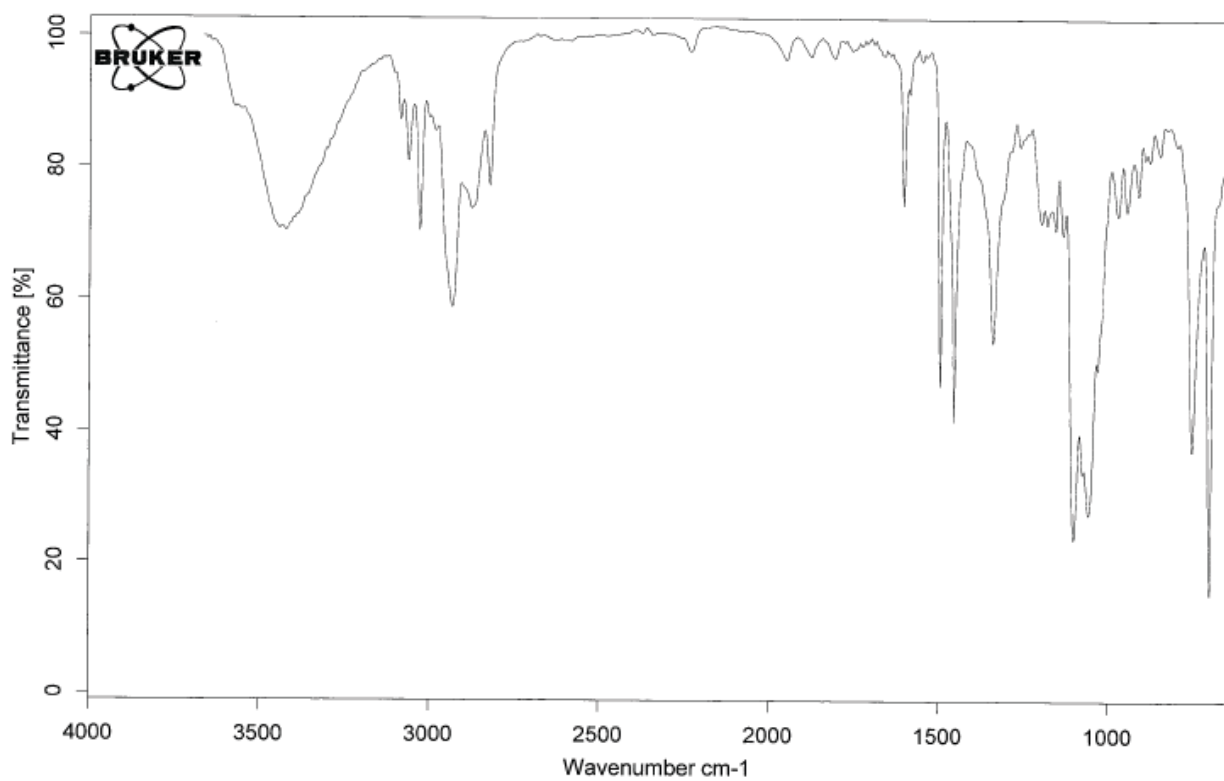
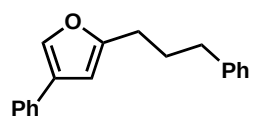


Figure A1.68 Infrared spectrum (thin film) of compound **60**



61

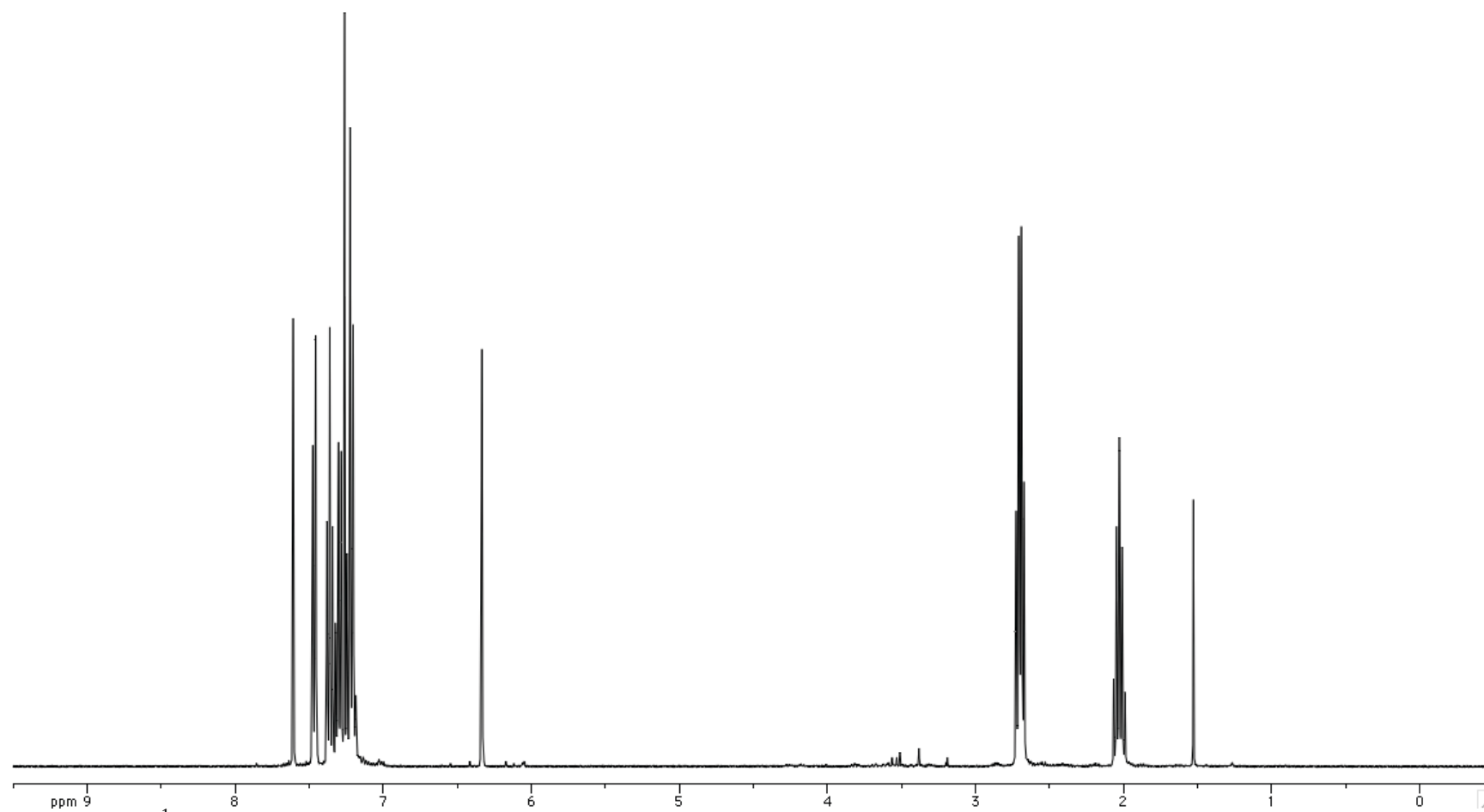


Figure A1.69 ^1H NMR (400 MHz, CDCl_3) of compound **61**

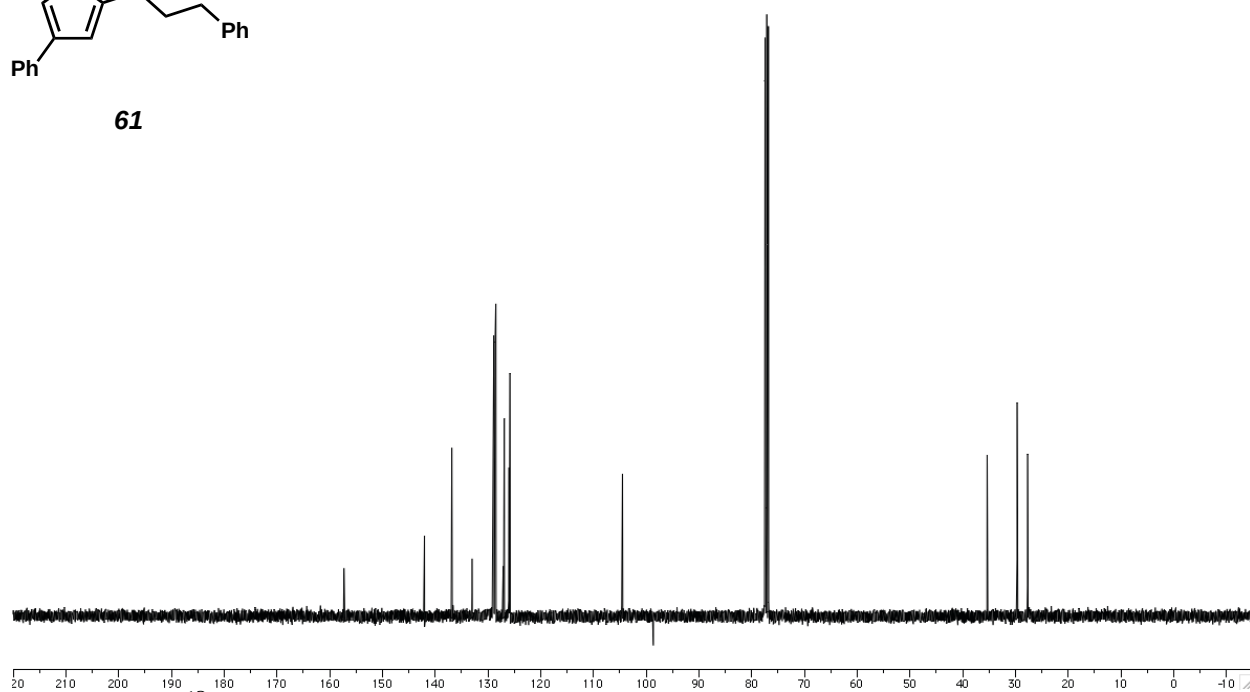
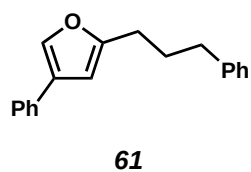


Figure A1.70 ^{13}C NMR (100 MHz, CDCl_3) of compound **61**

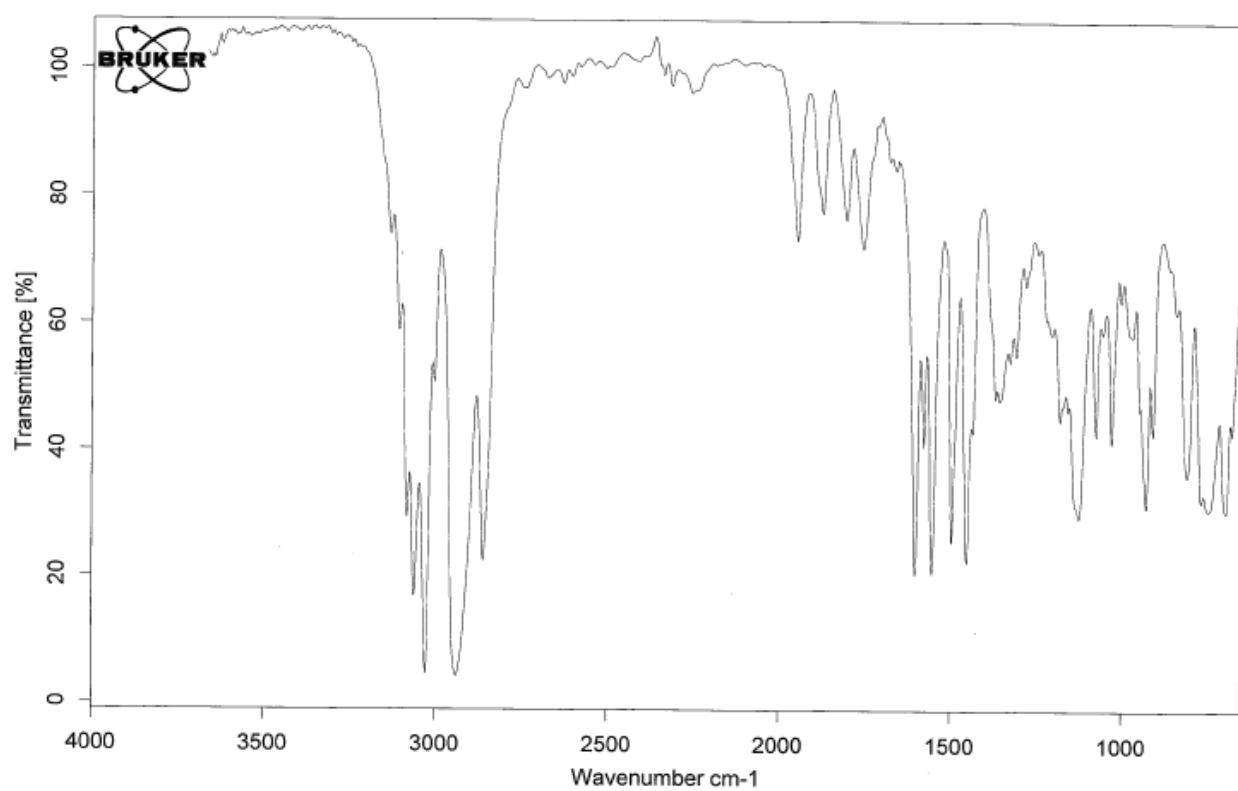


Figure A1.71 Infrared spectrum (thin film) of compound **61**

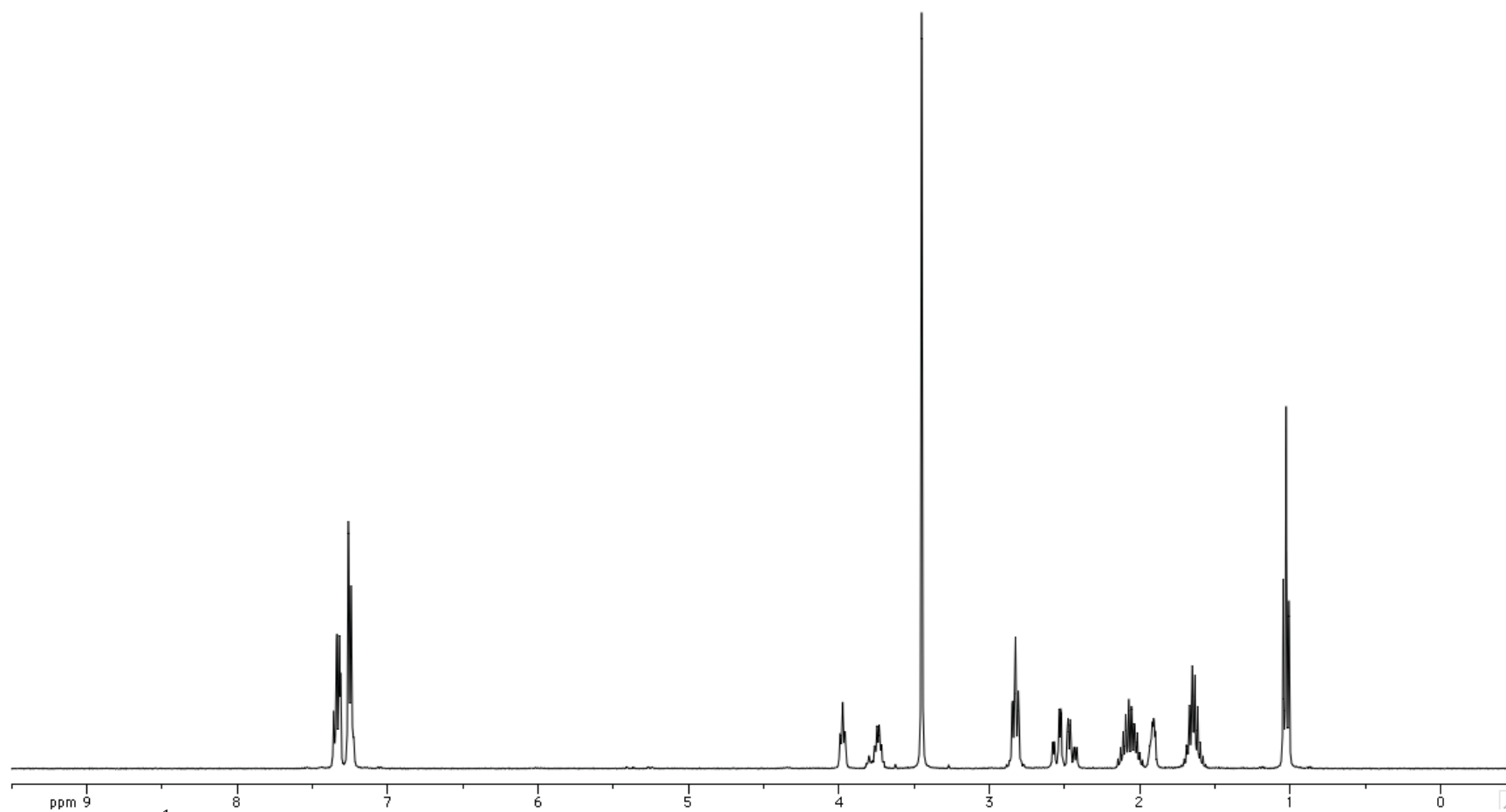
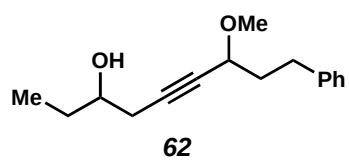


Figure A1.72 ^1H NMR (400 MHz, CDCl_3) of compound **62**

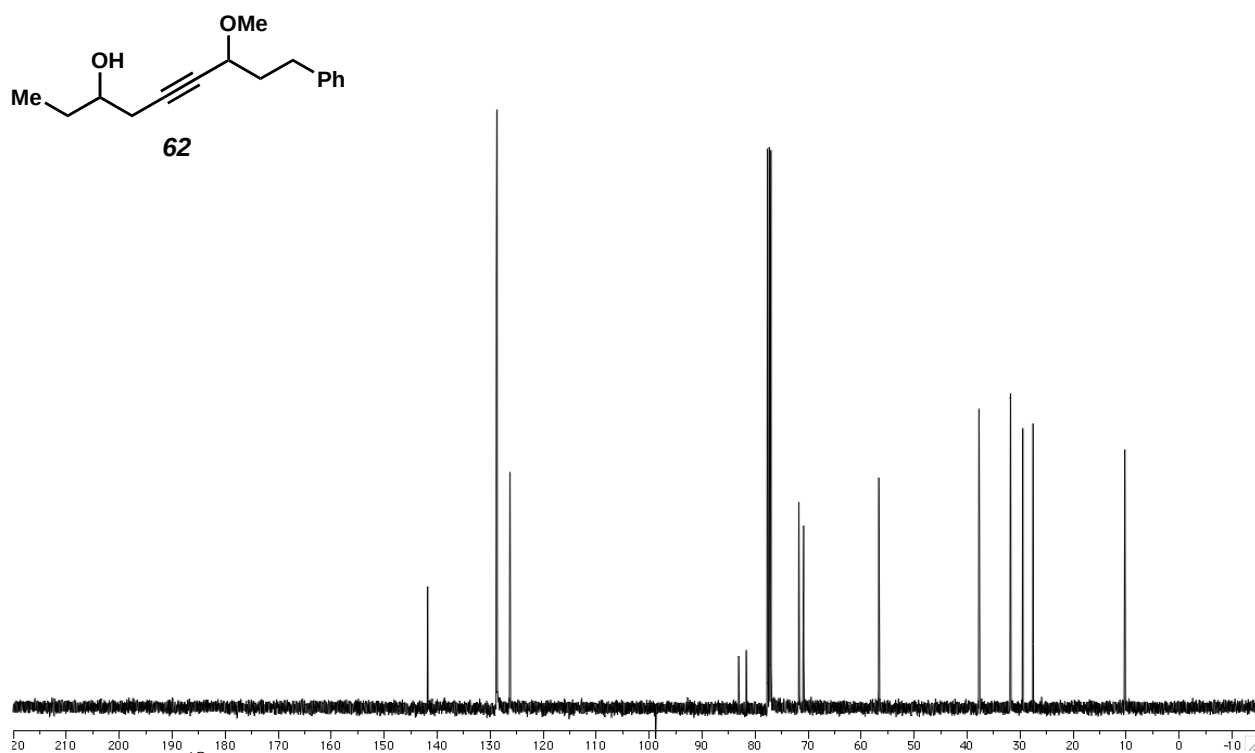


Figure A1.73 ^{13}C NMR (100 MHz, CDCl_3) of compound **62**

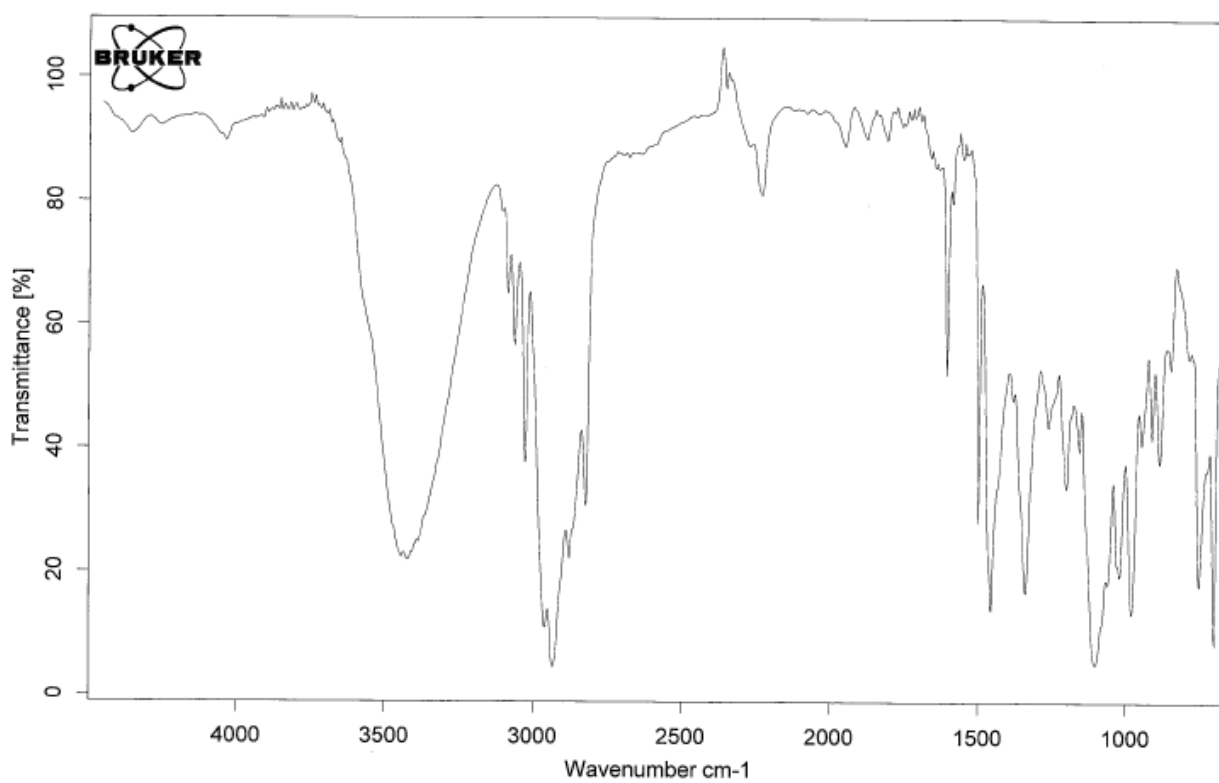


Figure A1.74 Infrared spectrum (thin film) of compound **62**

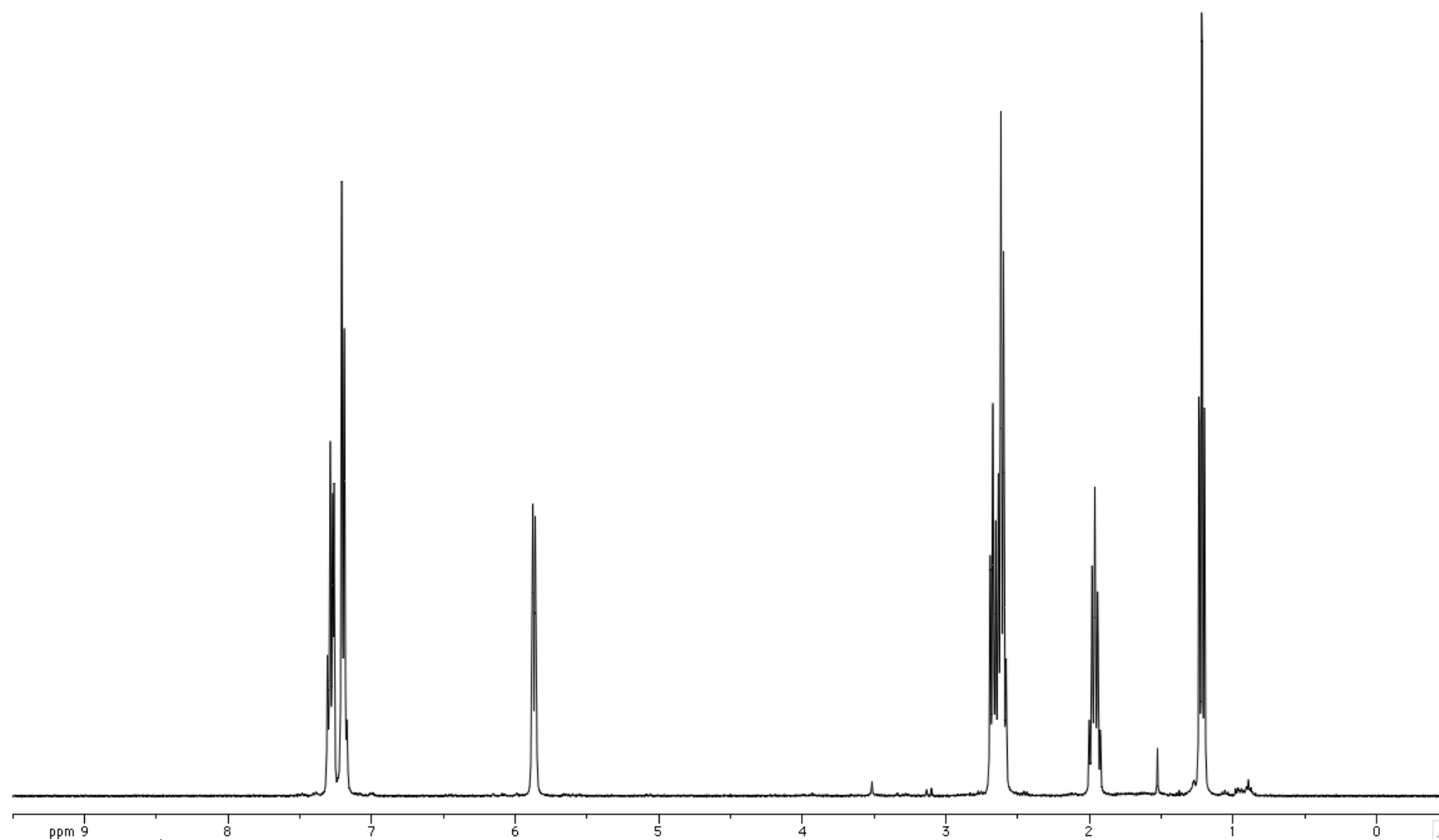
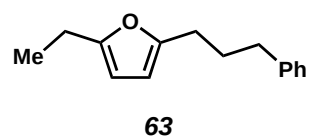


Figure A1.75 ^1H NMR (400 MHz, CDCl_3) of compound **63**

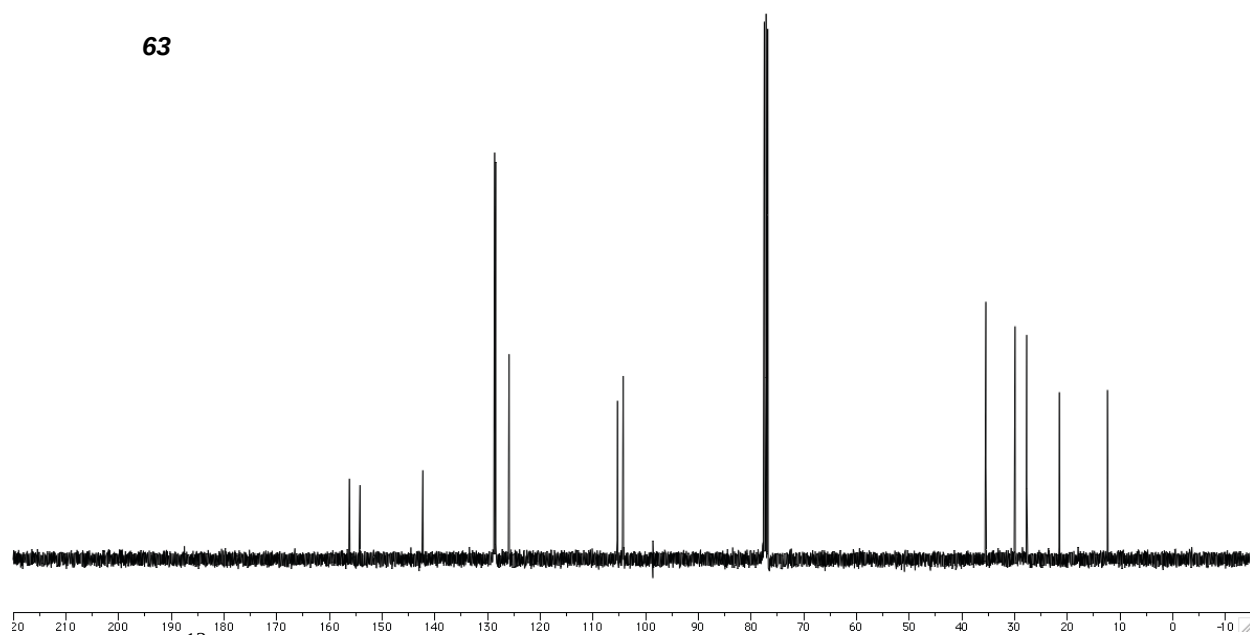
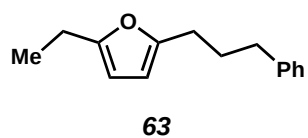


Figure A1.76 ^{13}C NMR (100 MHz, CDCl_3) of compound **63**

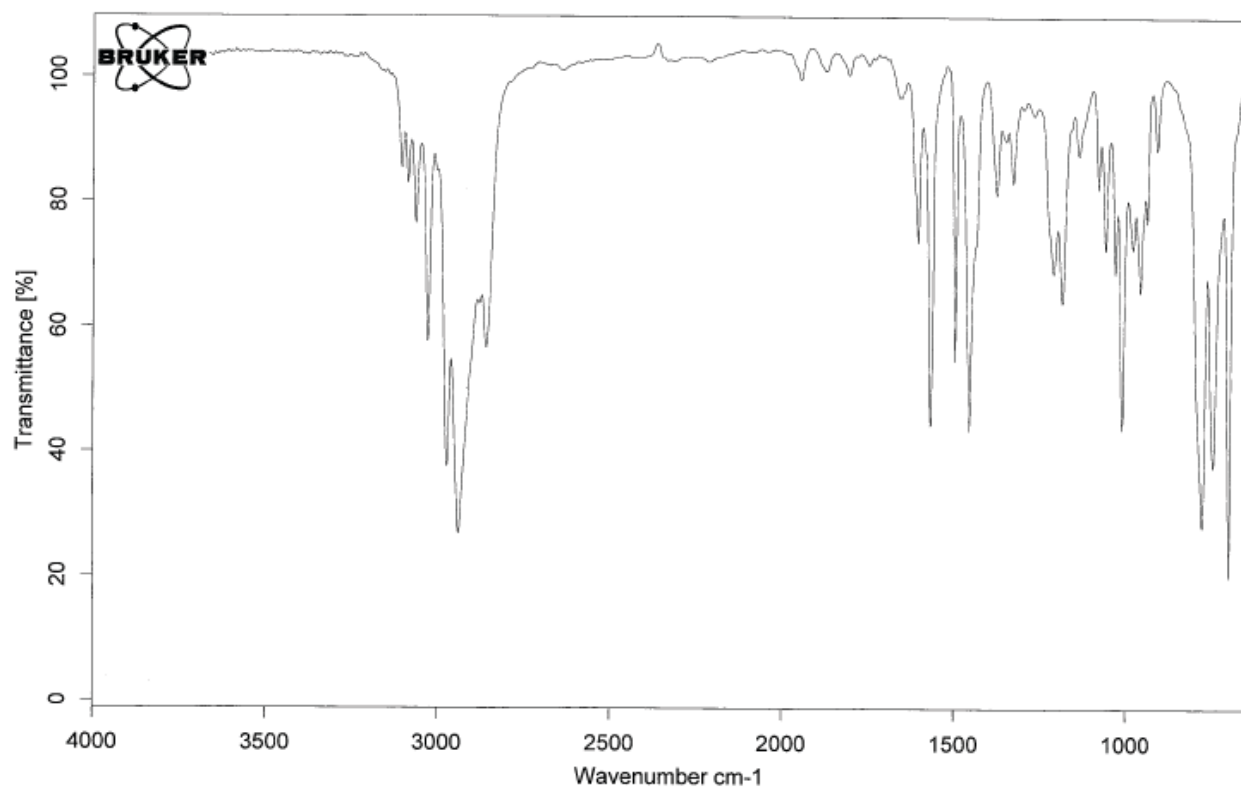


Figure A1.77 Infrared spectrum (thin film) of compound **63**

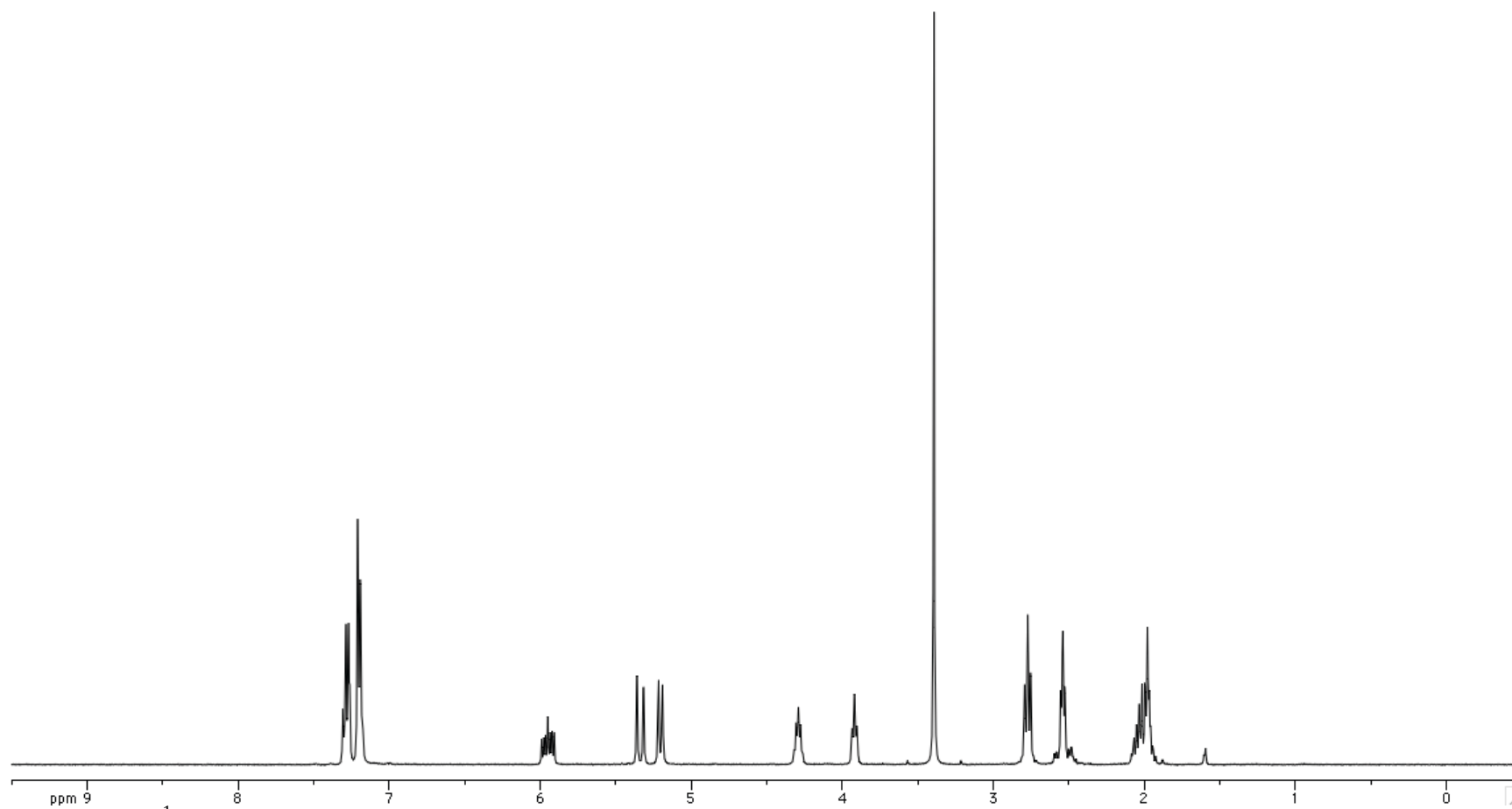
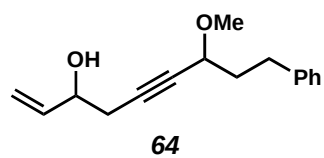


Figure A1.78 ¹H NMR (400 MHz, CDCl₃) of compound **64**

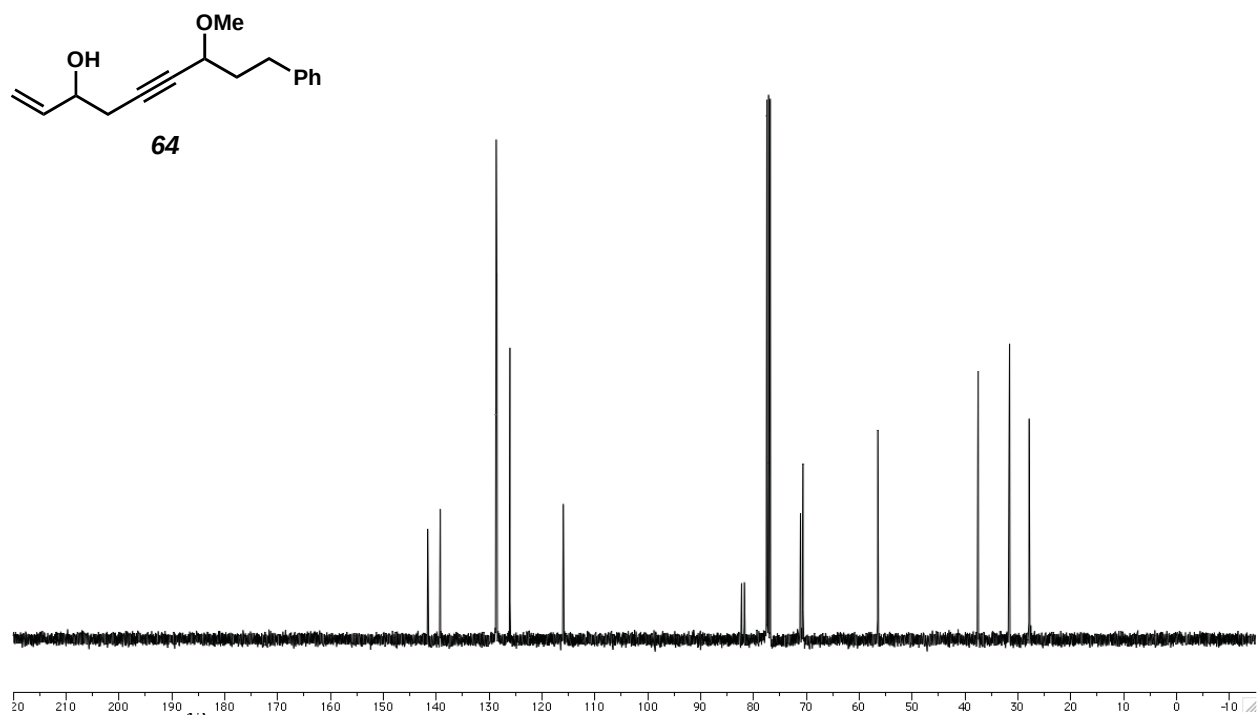


Figure A1.79 ^{13}C NMR (100 MHz, CDCl_3) of compound **64**

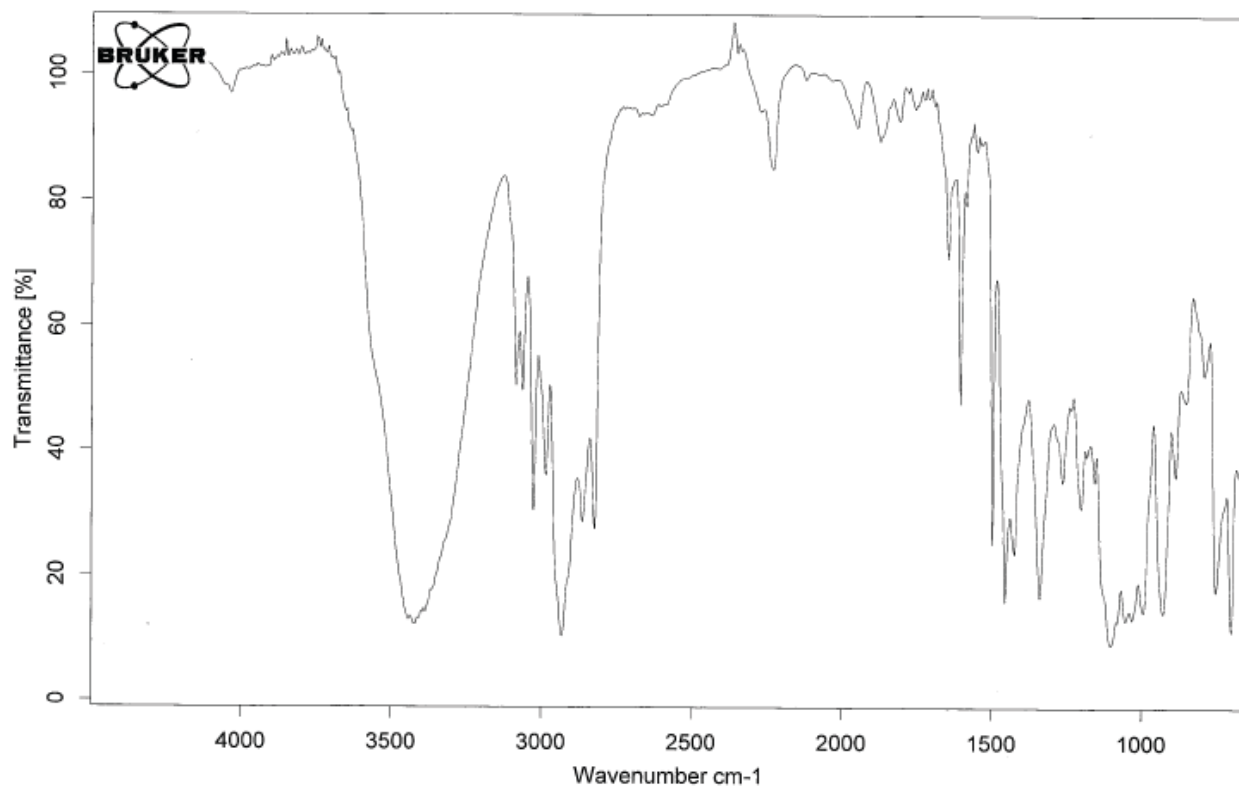


Figure A1.80 Infrared spectrum (thin film) of compound **64**

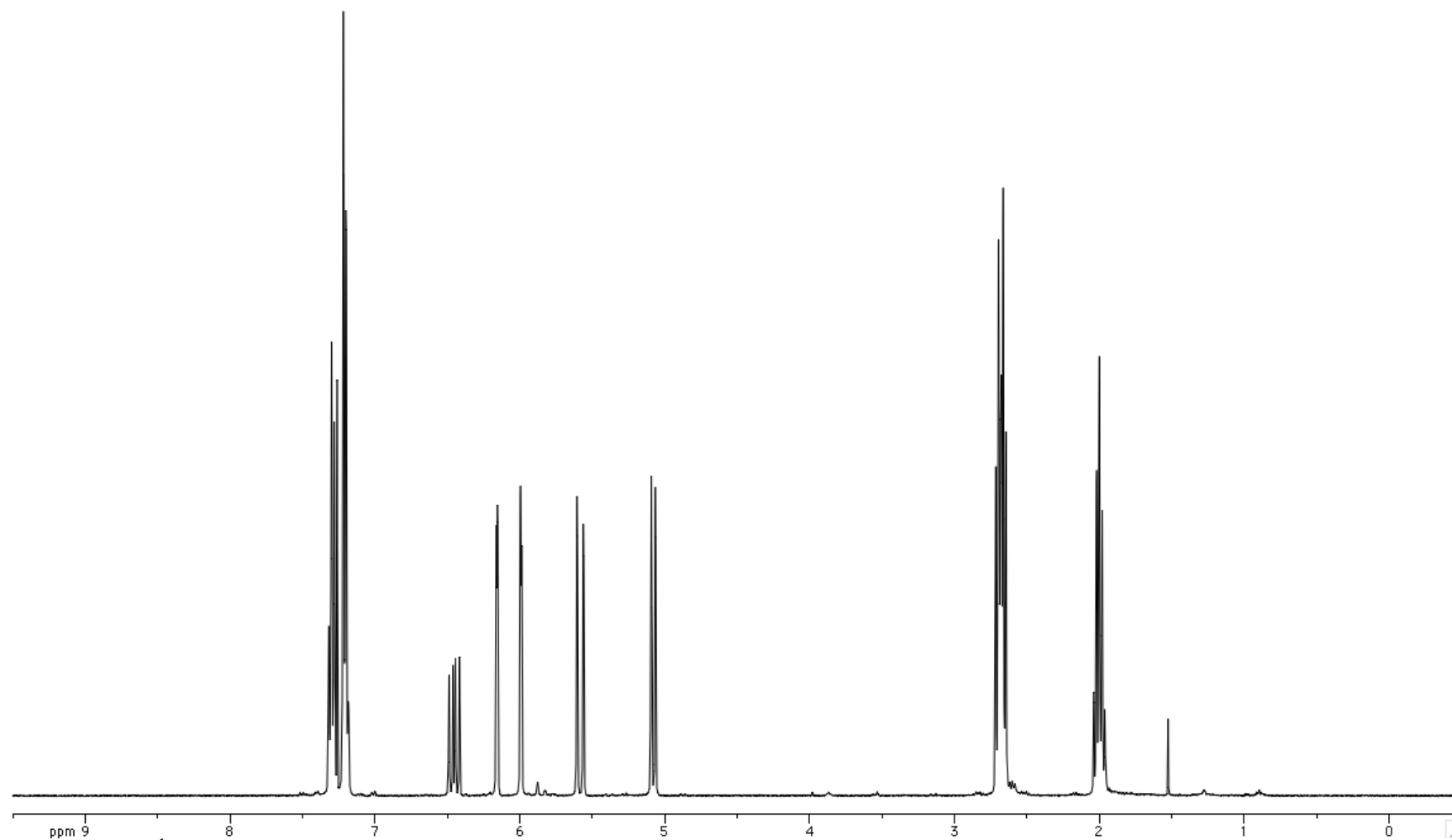
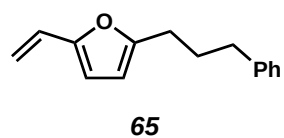
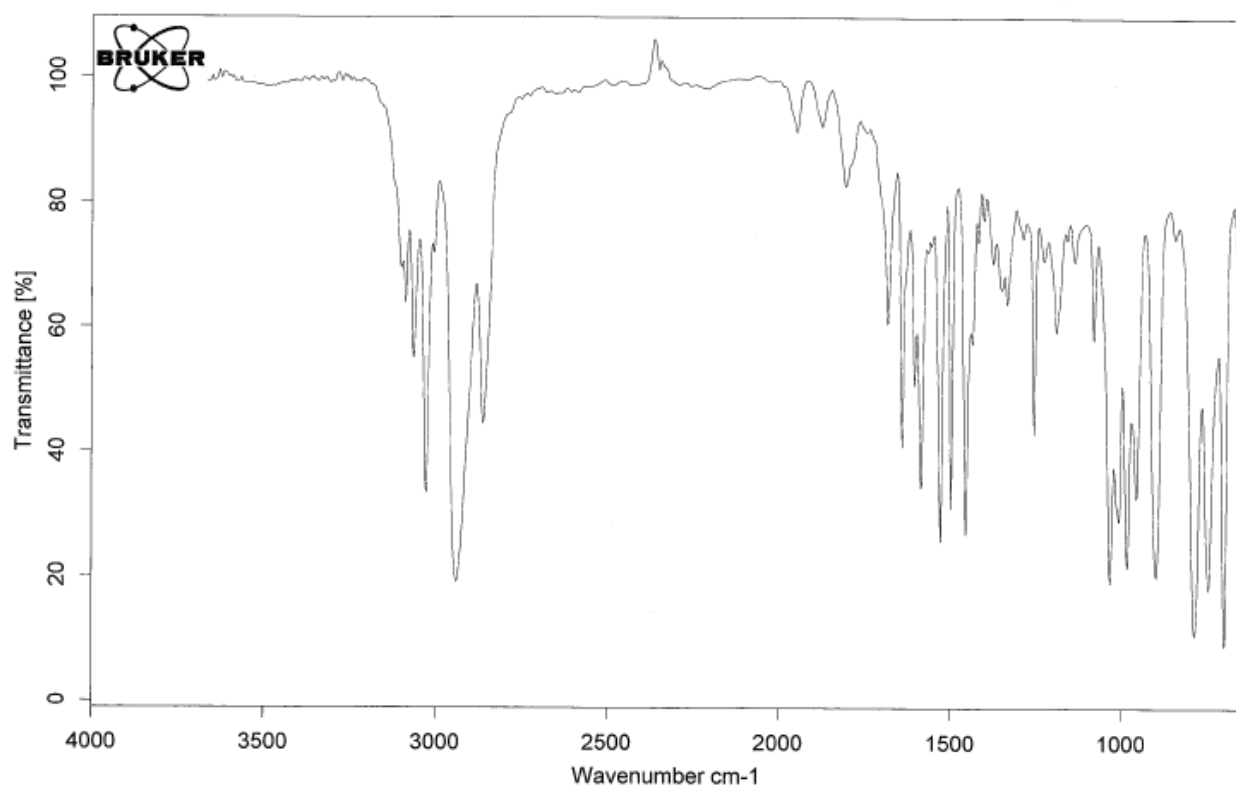
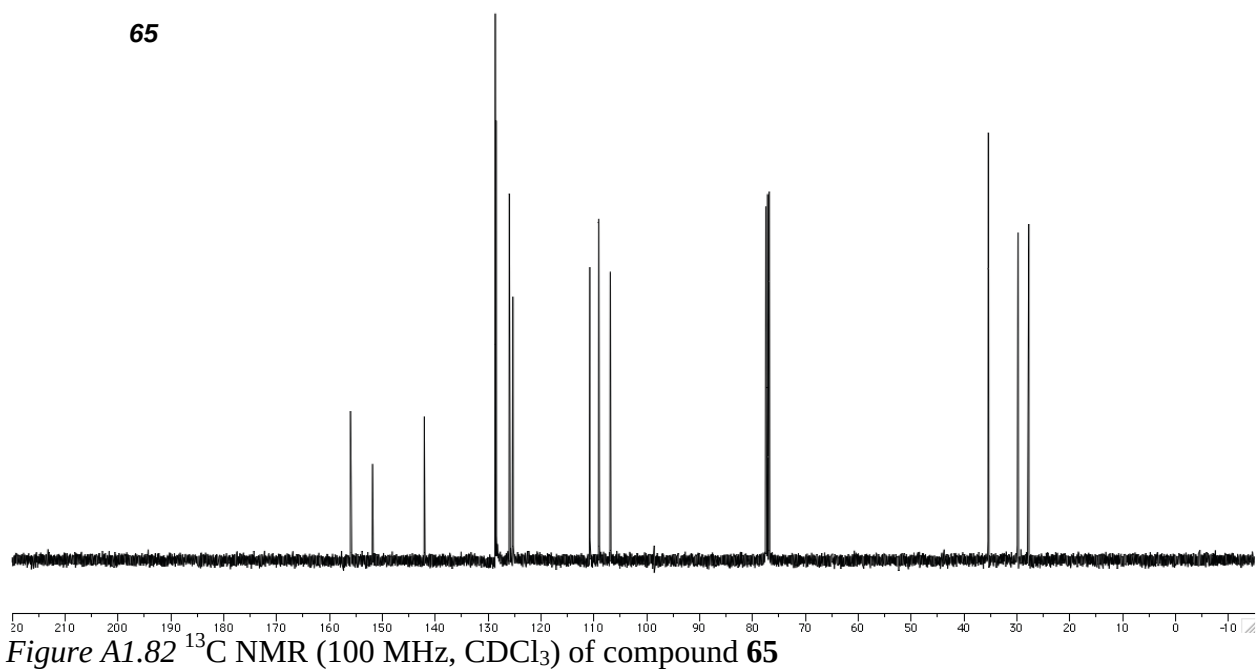
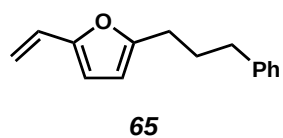


Figure A1.81 ^1H NMR (400 MHz, CDCl_3) of compound **65**



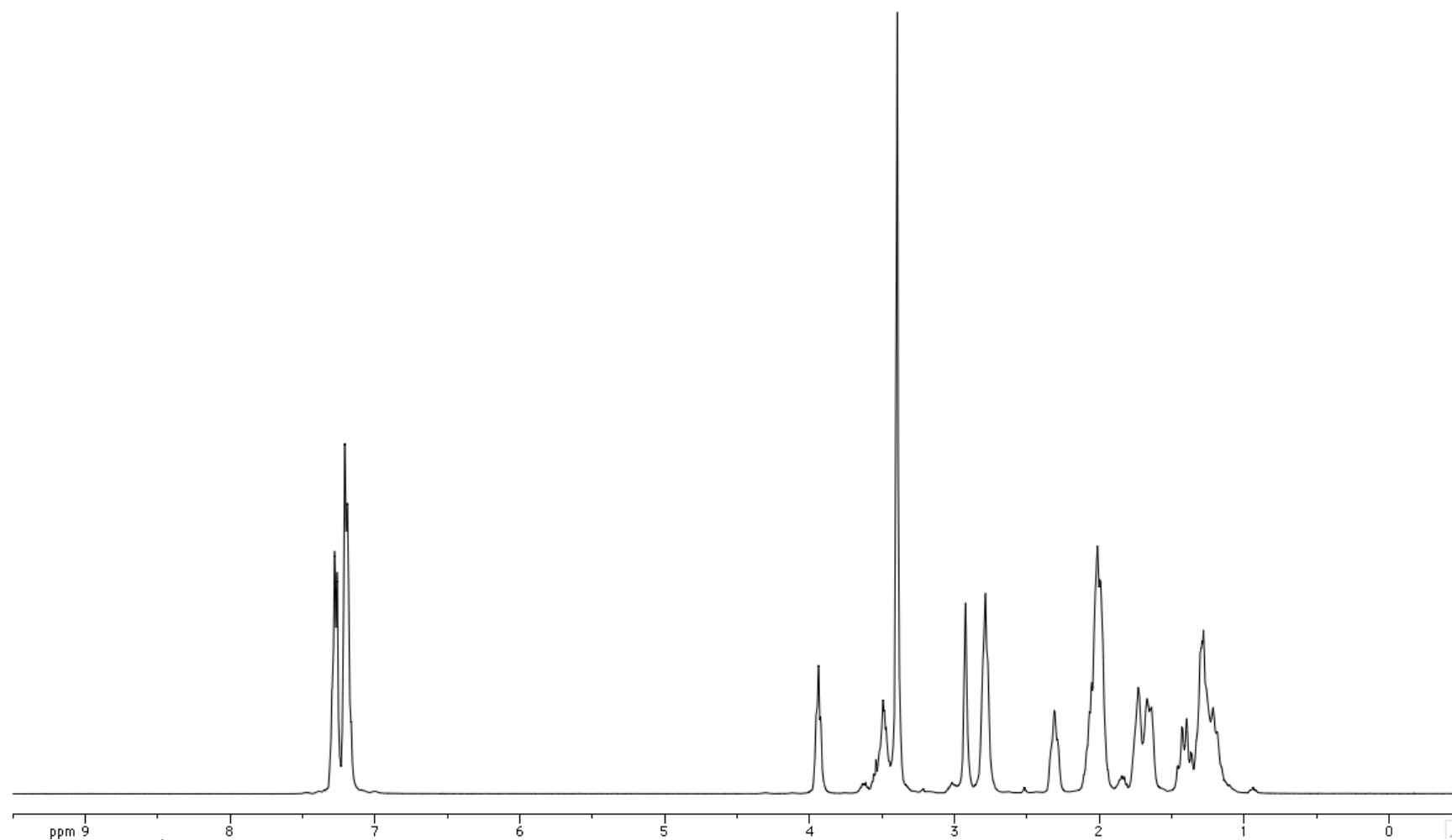
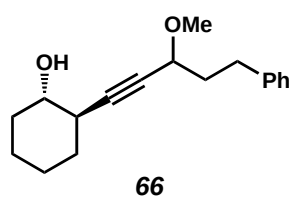
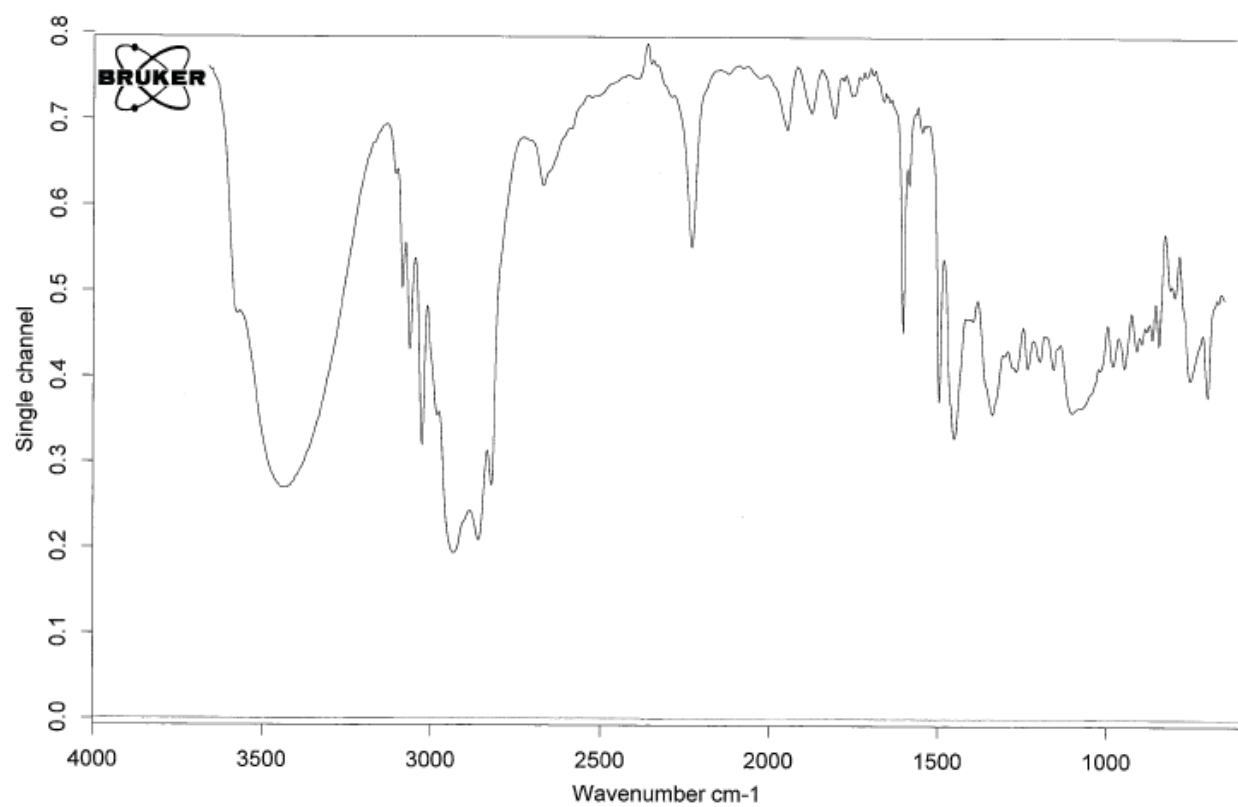
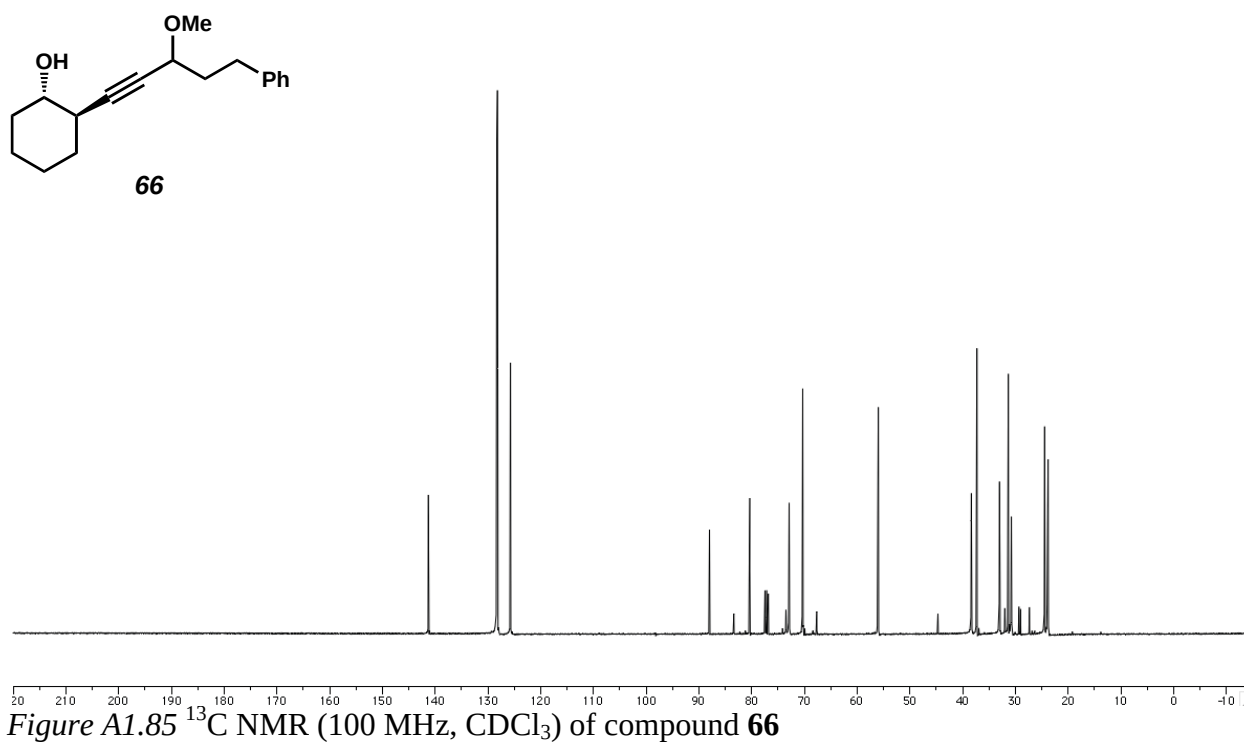
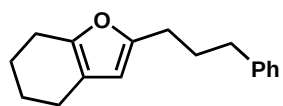


Figure A1.84 ^1H NMR (400 MHz, CDCl_3) of compound **66**





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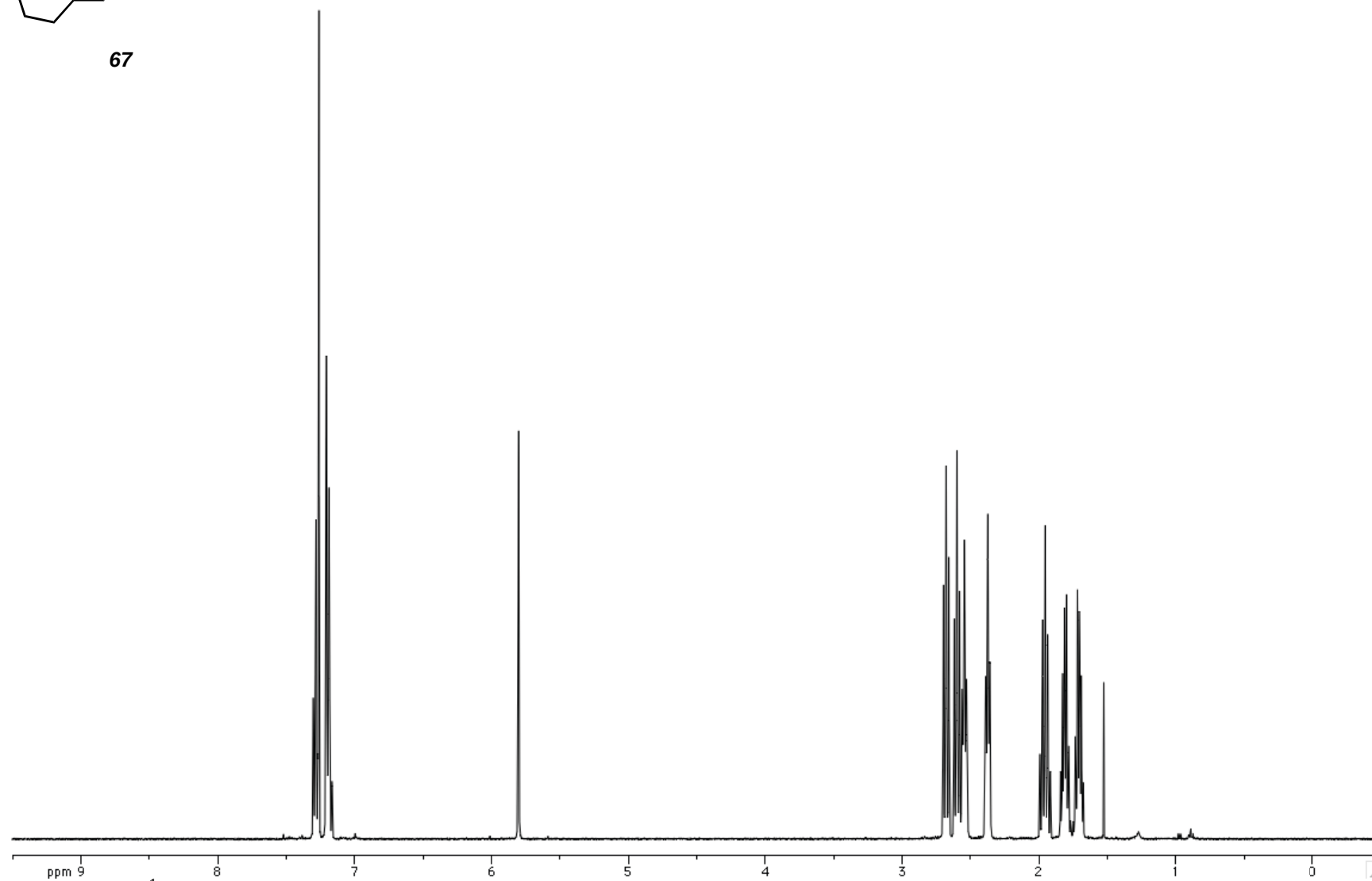


Figure A1.87 ^1H NMR (400 MHz, CDCl_3) of compound **67**

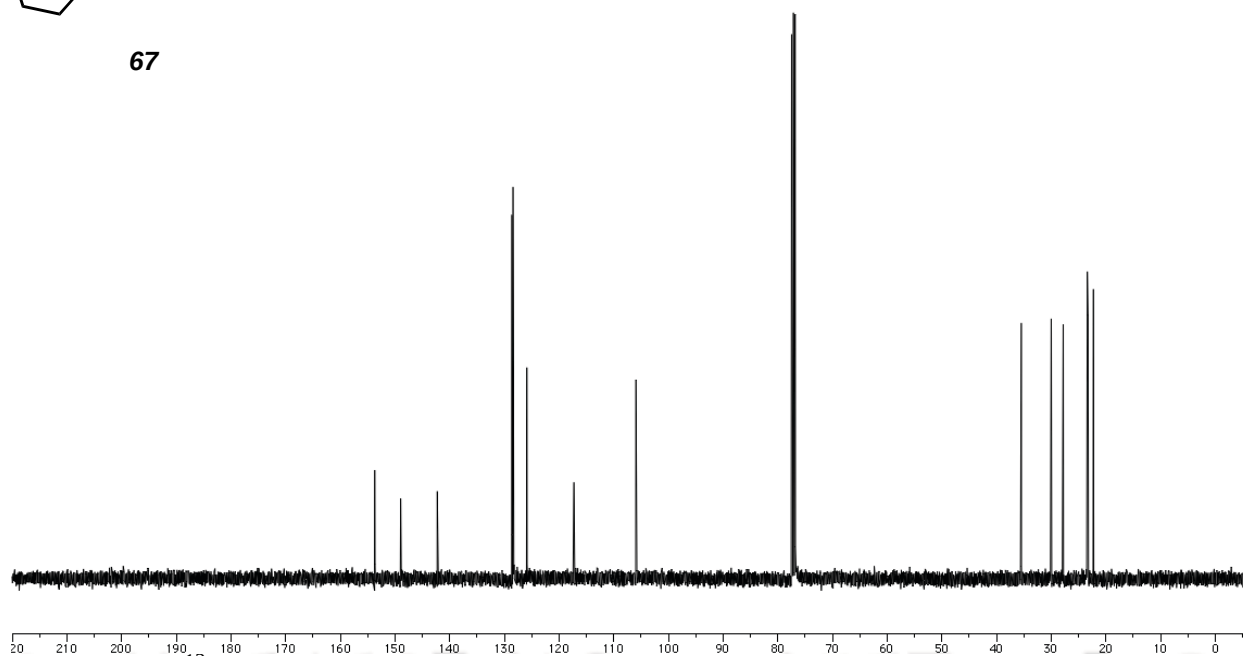
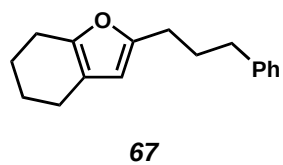


Figure A1.88 ^{13}C NMR (100 MHz, CDCl_3) of compound **67**

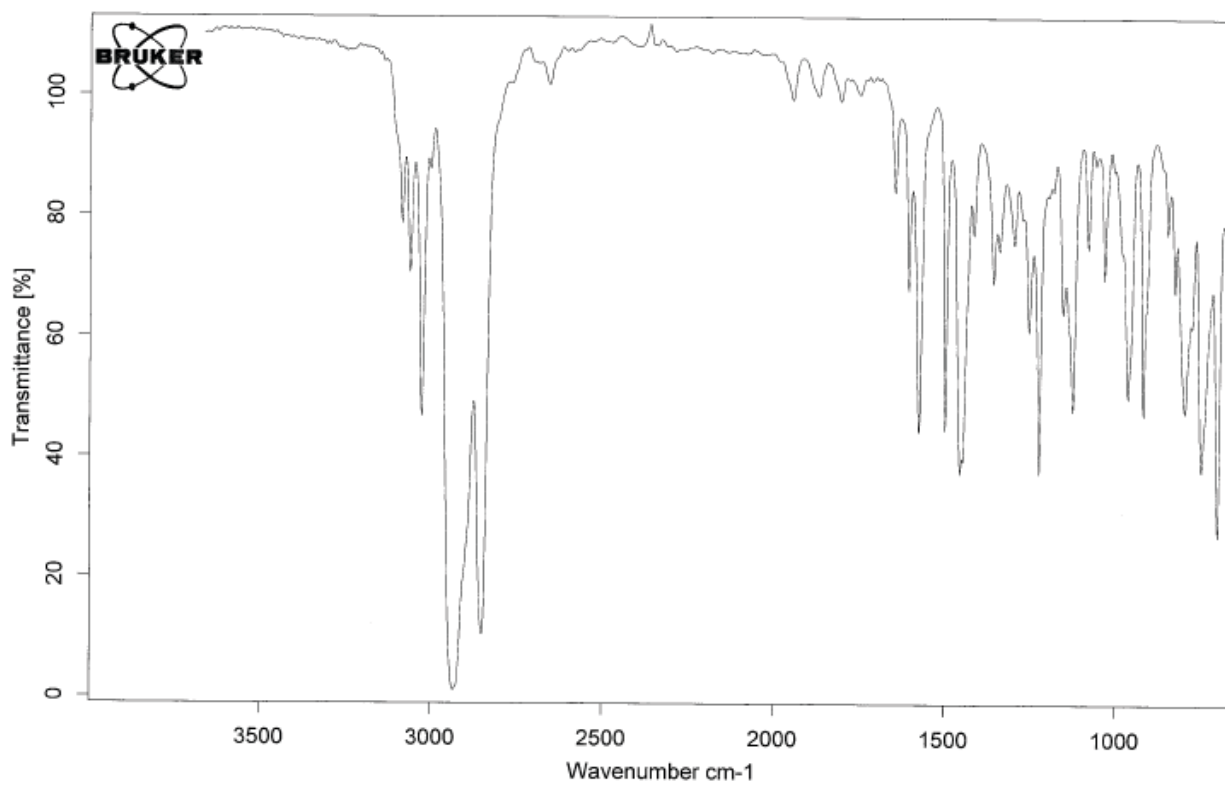


Figure A1.89 Infrared spectrum (thin film) of compound **67**

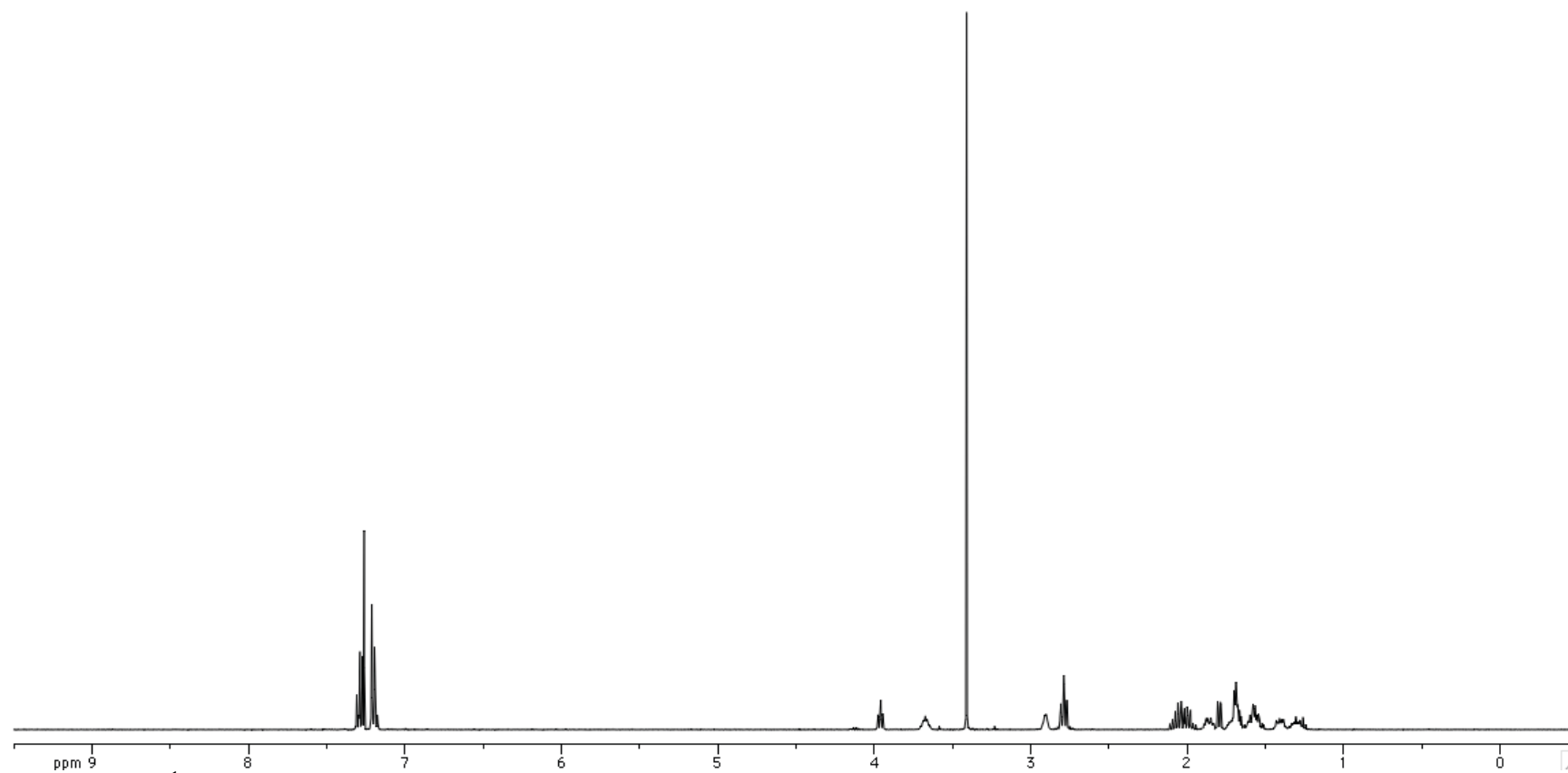
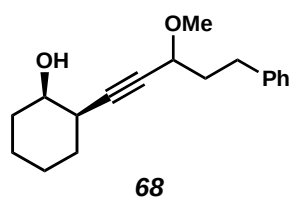


Figure A1.90 ^1H NMR (400 MHz, CDCl_3) of compound **68**

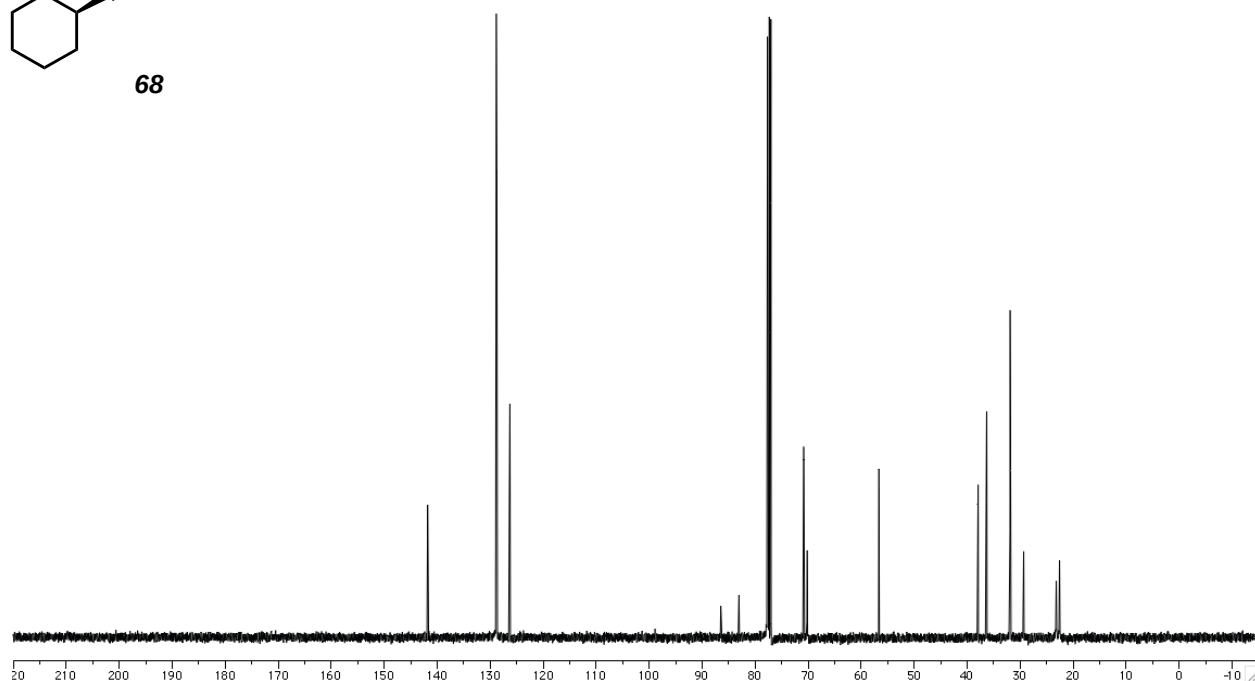
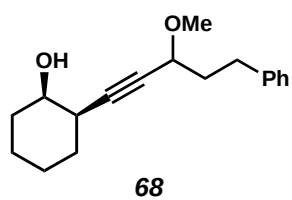


Figure A1.91 ¹³C NMR (100 MHz, CDCl₃) of compound **68**

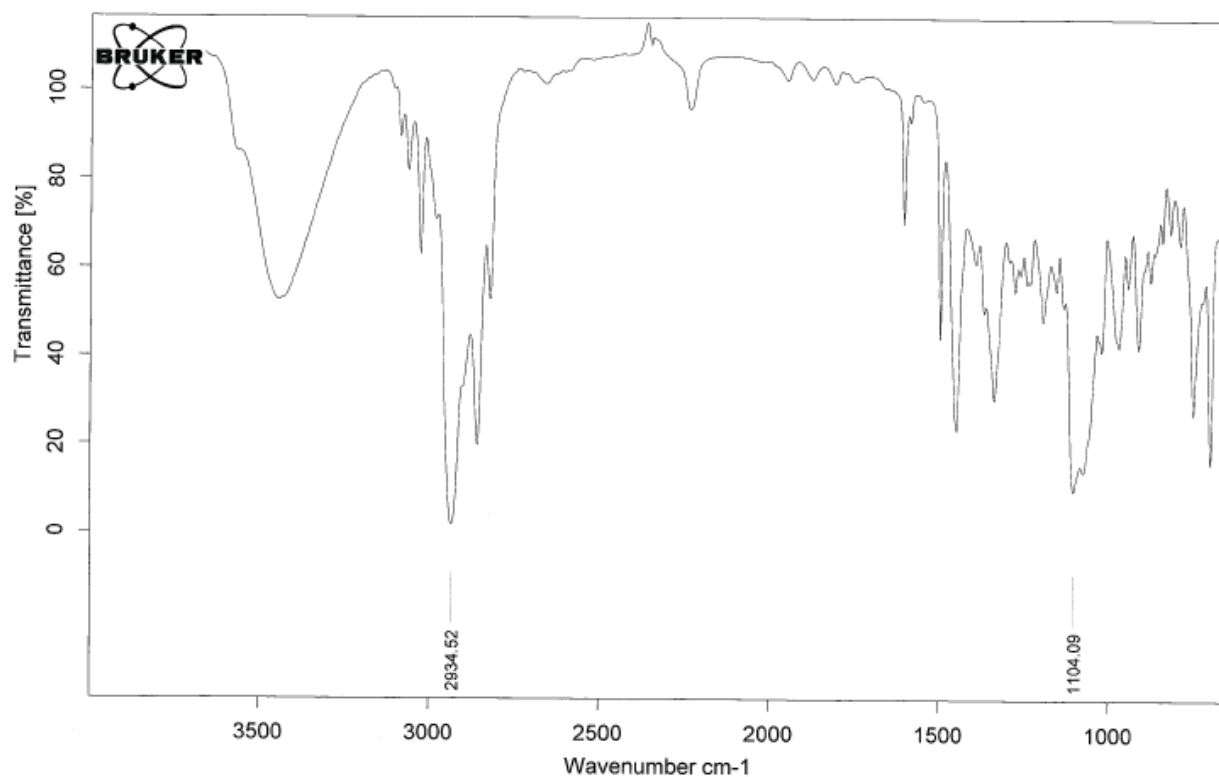


Figure A1.92 Infrared spectrum (thin film) of compound **68**

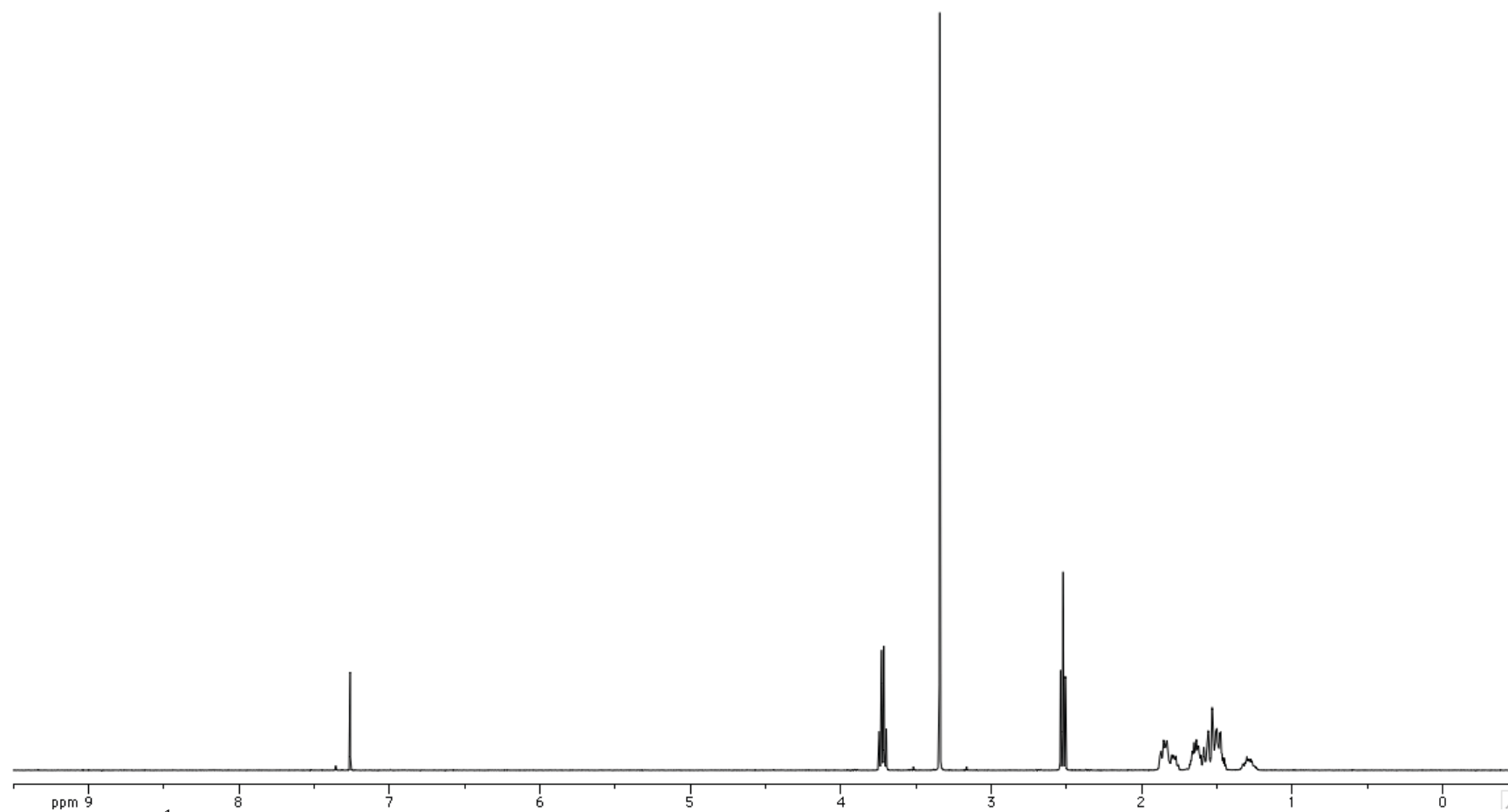
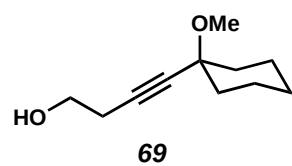


Figure A1.93 ^1H NMR (400 MHz, CDCl_3) of compound **69**

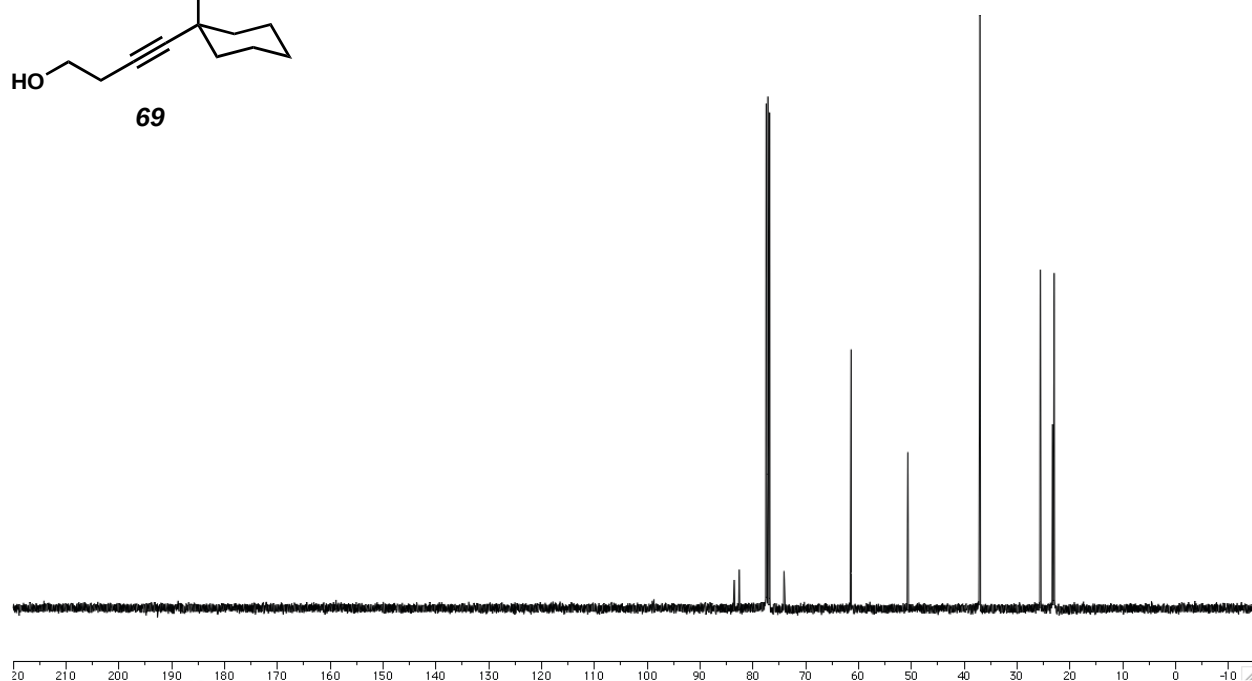
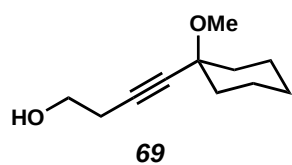


Figure A1.94 ^{13}C NMR (100 MHz, CDCl_3) of compound **69**

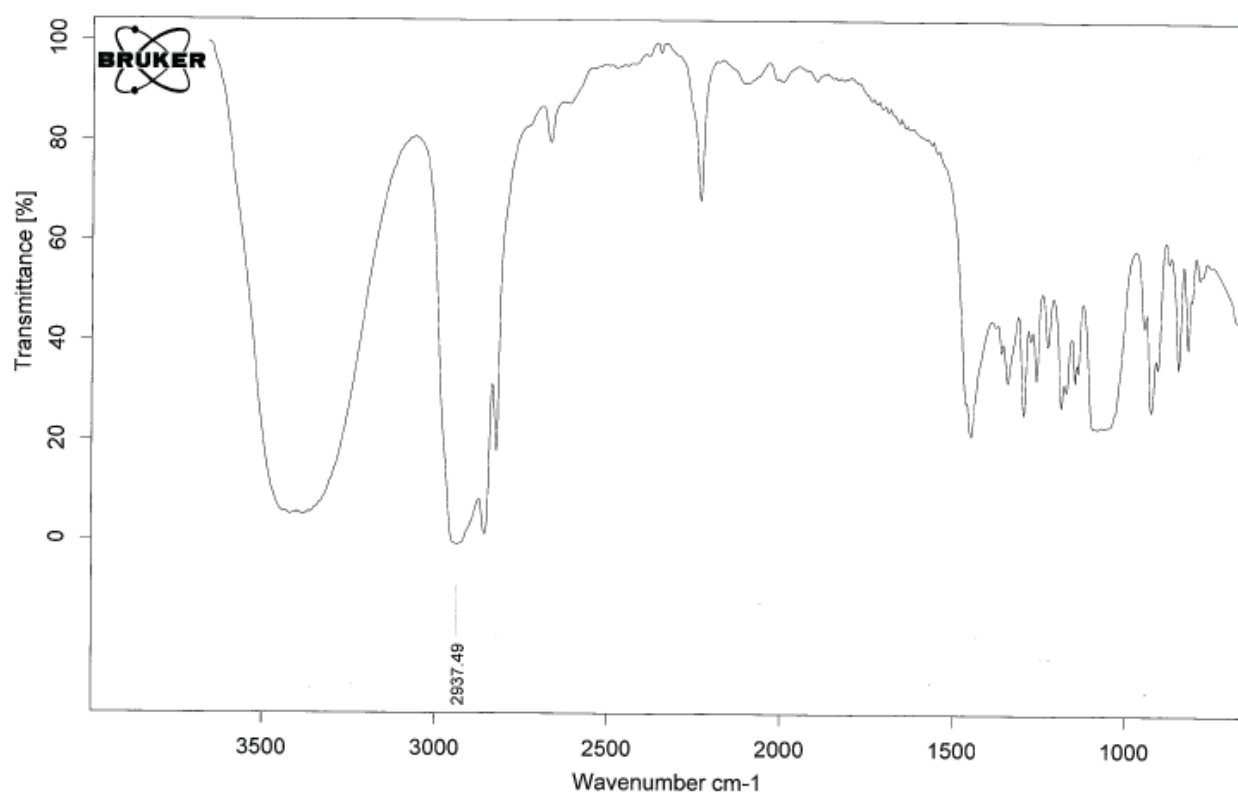
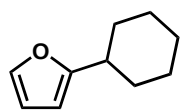


Figure A1.95 Infrared spectrum (thin film) of compound **69**



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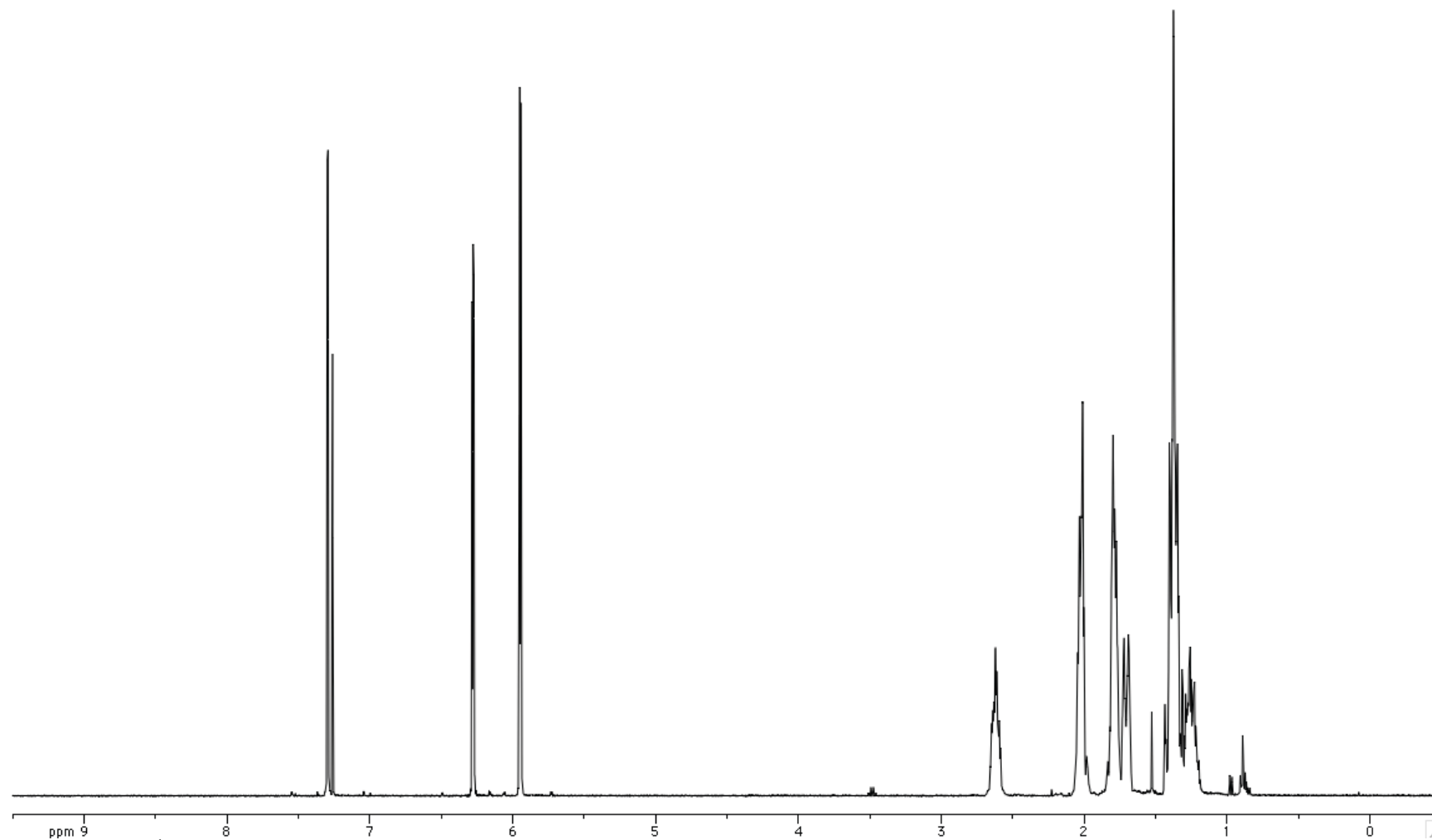
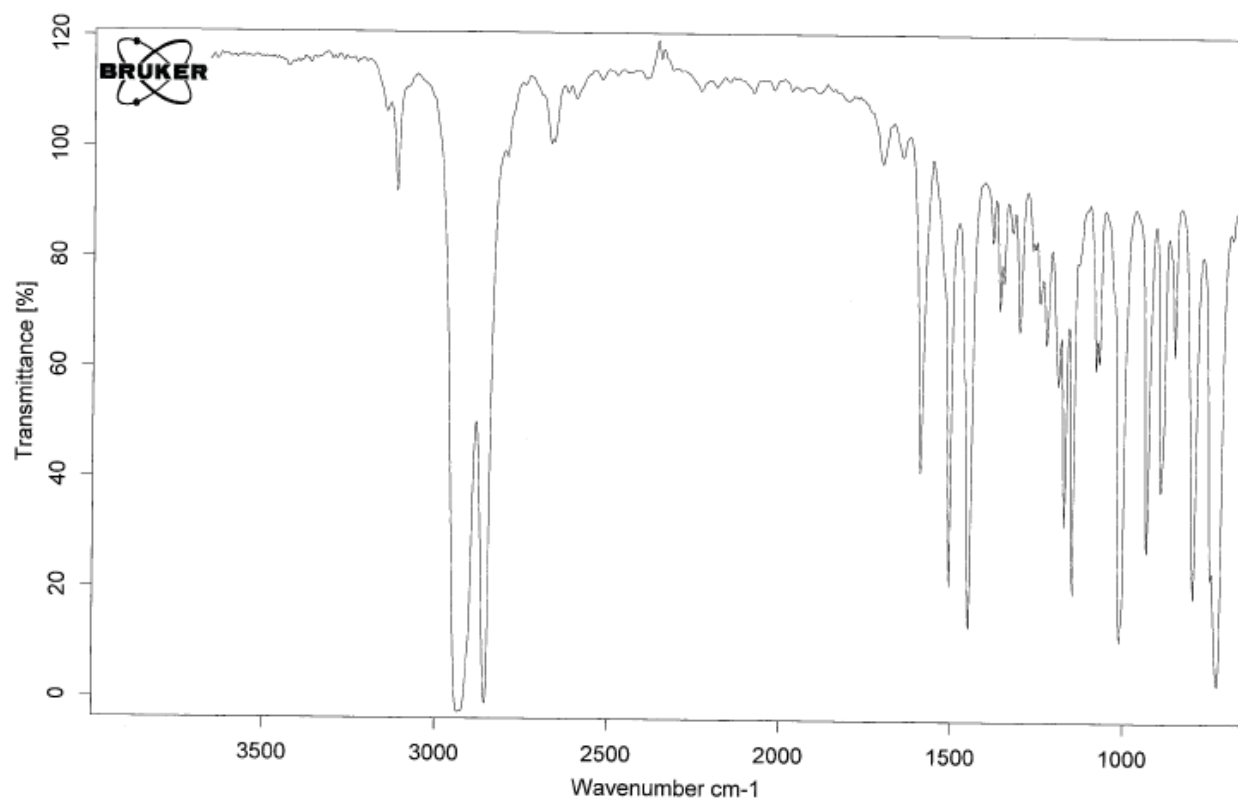
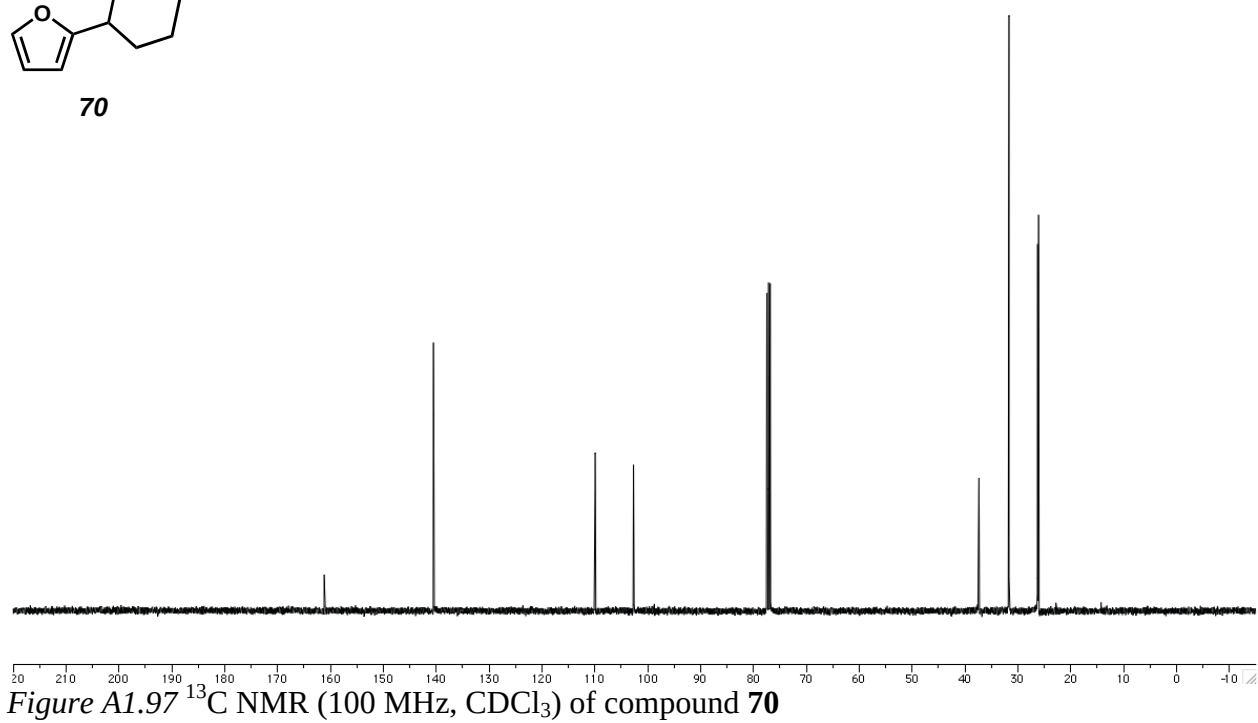
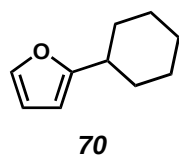


Figure A1.96 ^1H NMR (400 MHz, CDCl_3) of compound **70**



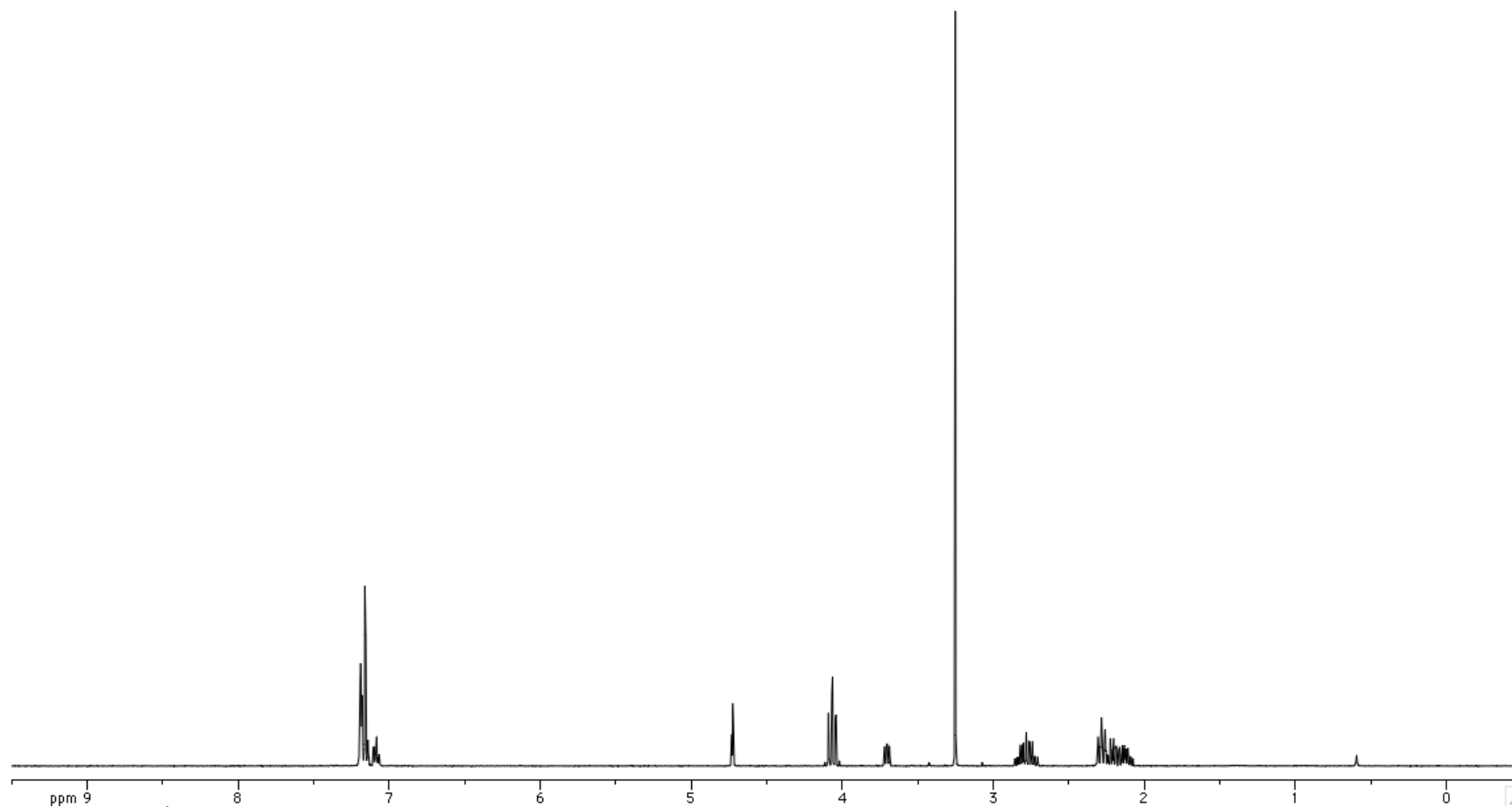
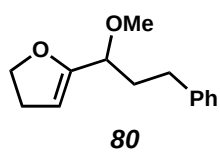
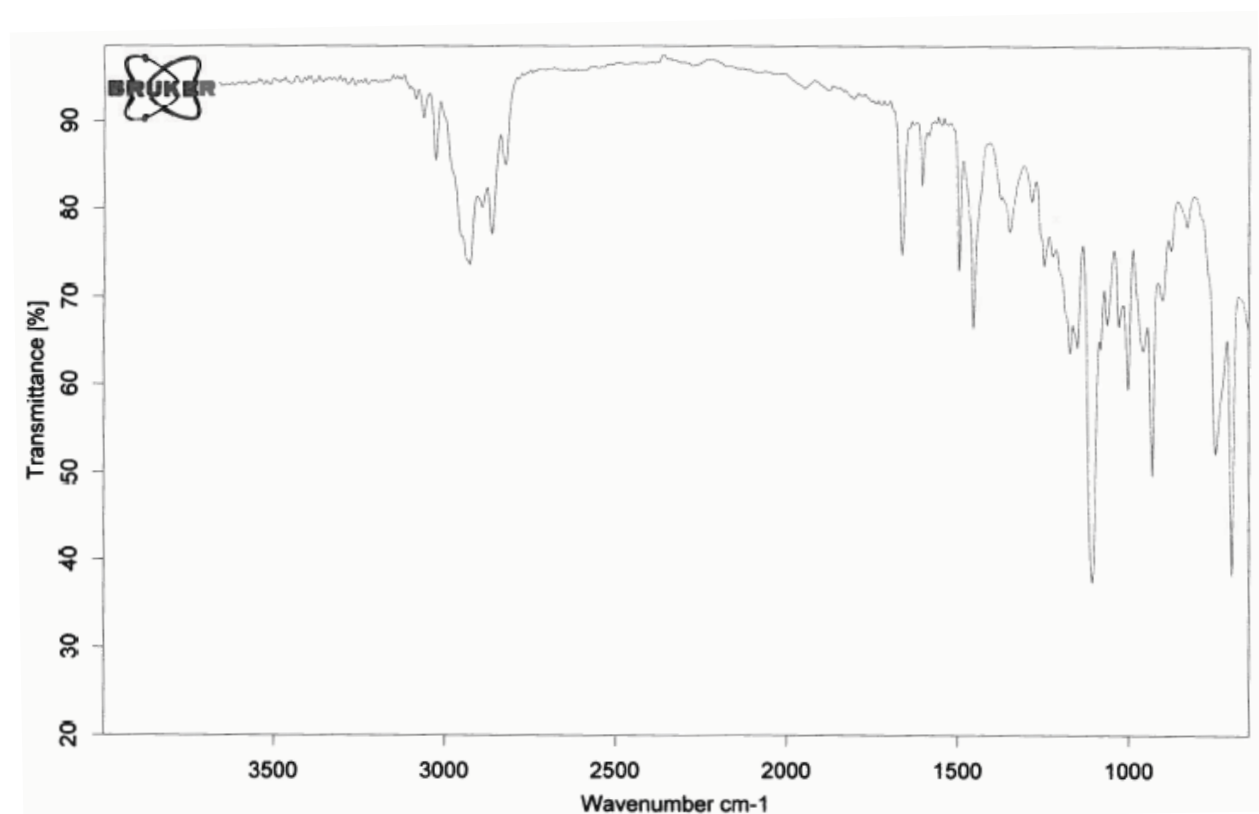
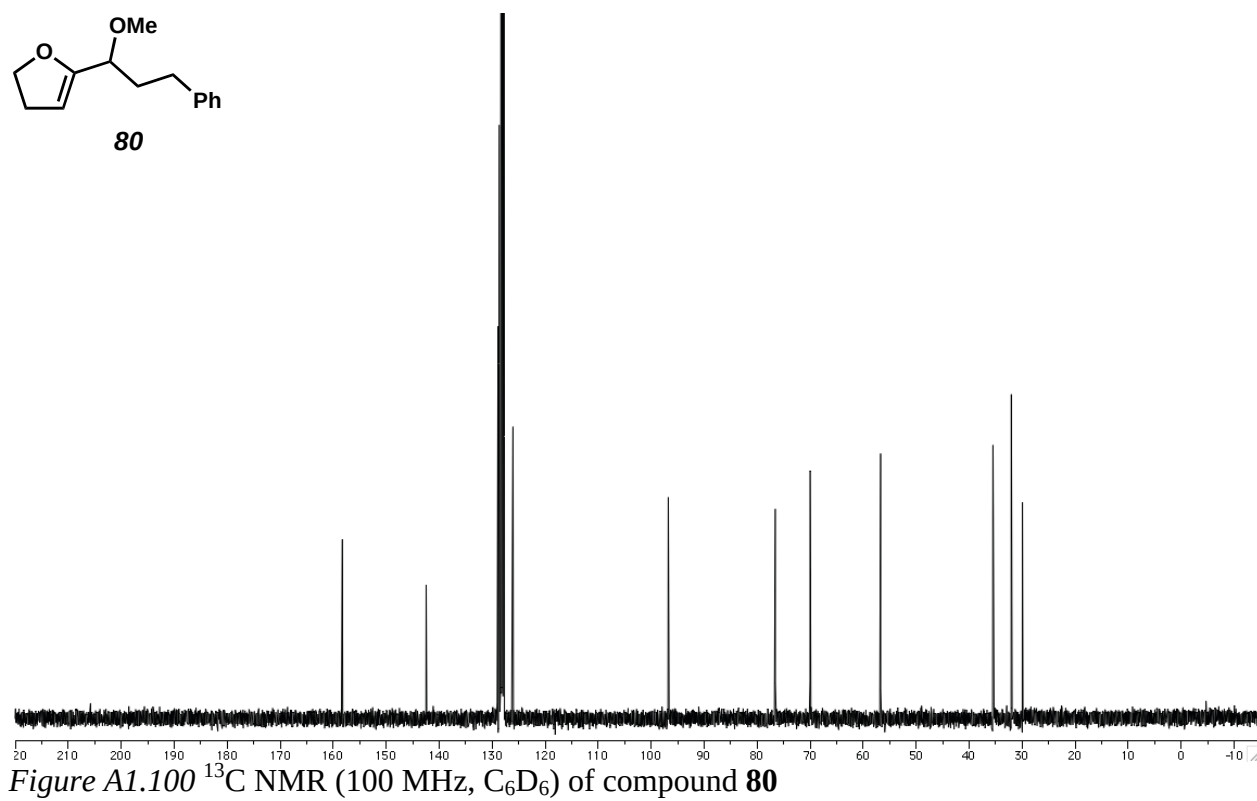
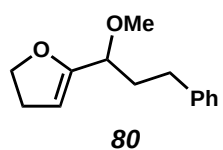


Figure A1.99 ^1H NMR (400 MHz, C_6D_6) of compound **80**



APPENDIX TWO

Spectra Relevant to Chapter Three

Synthesis of Complementary Positional Isomers of Isoxazoles

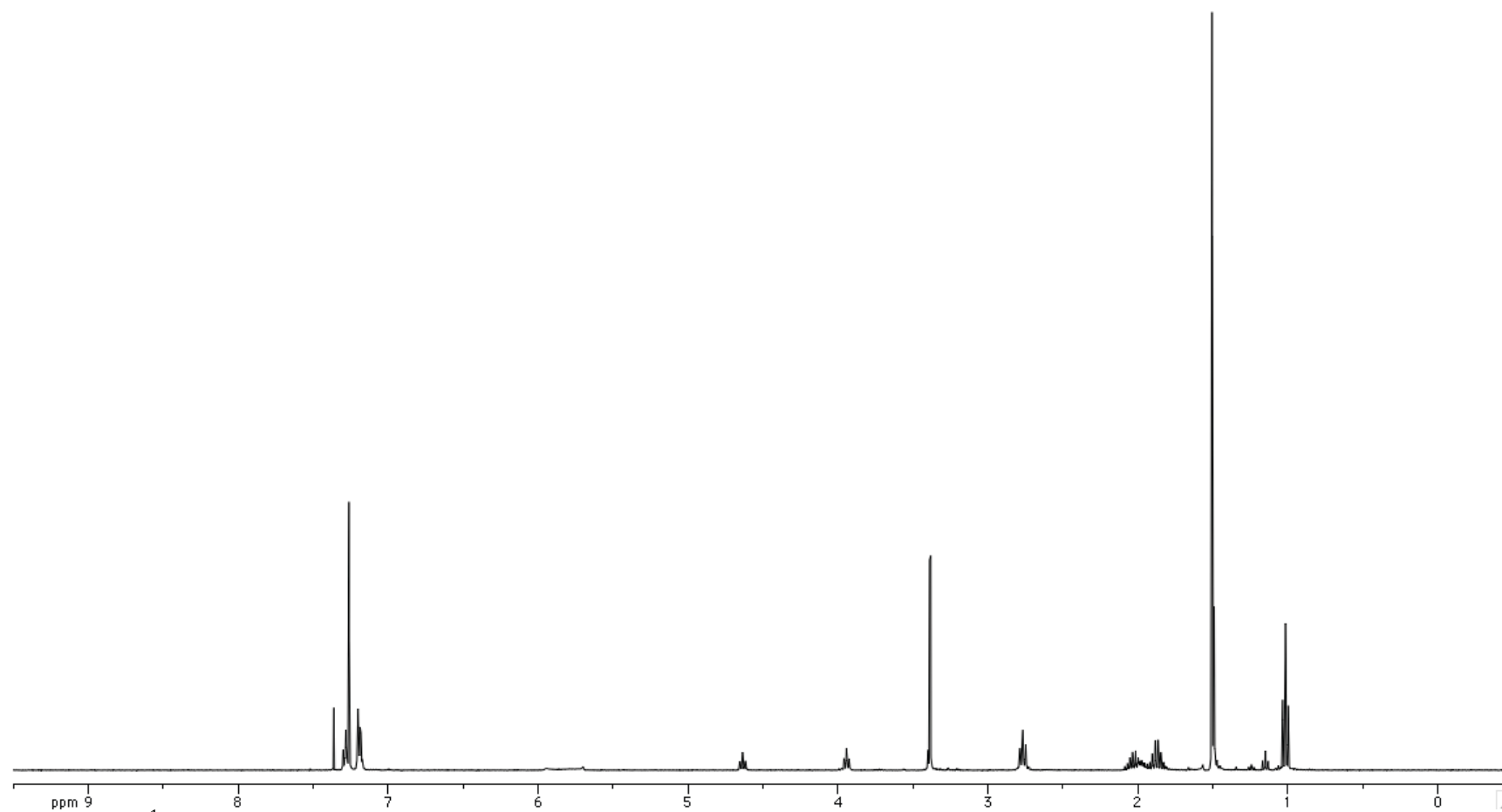
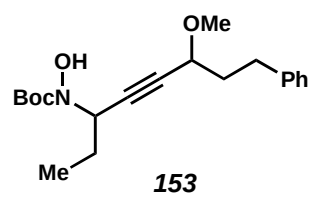
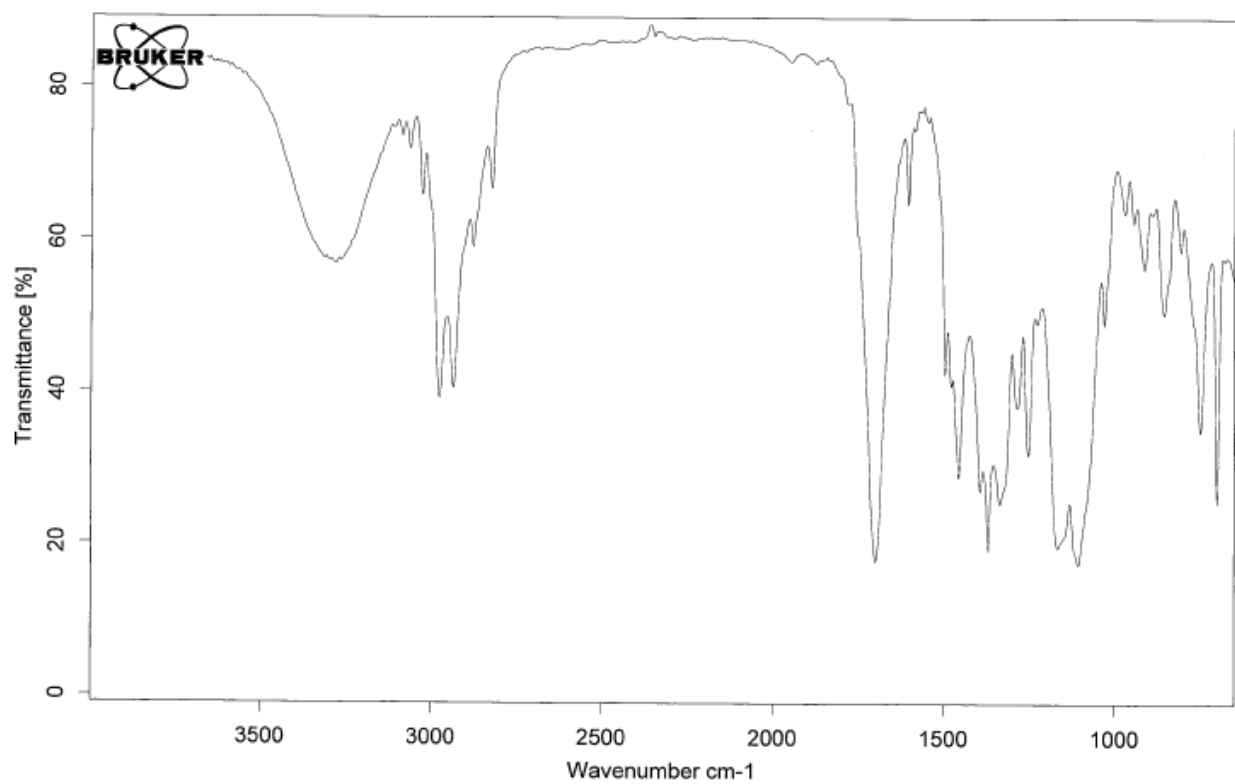
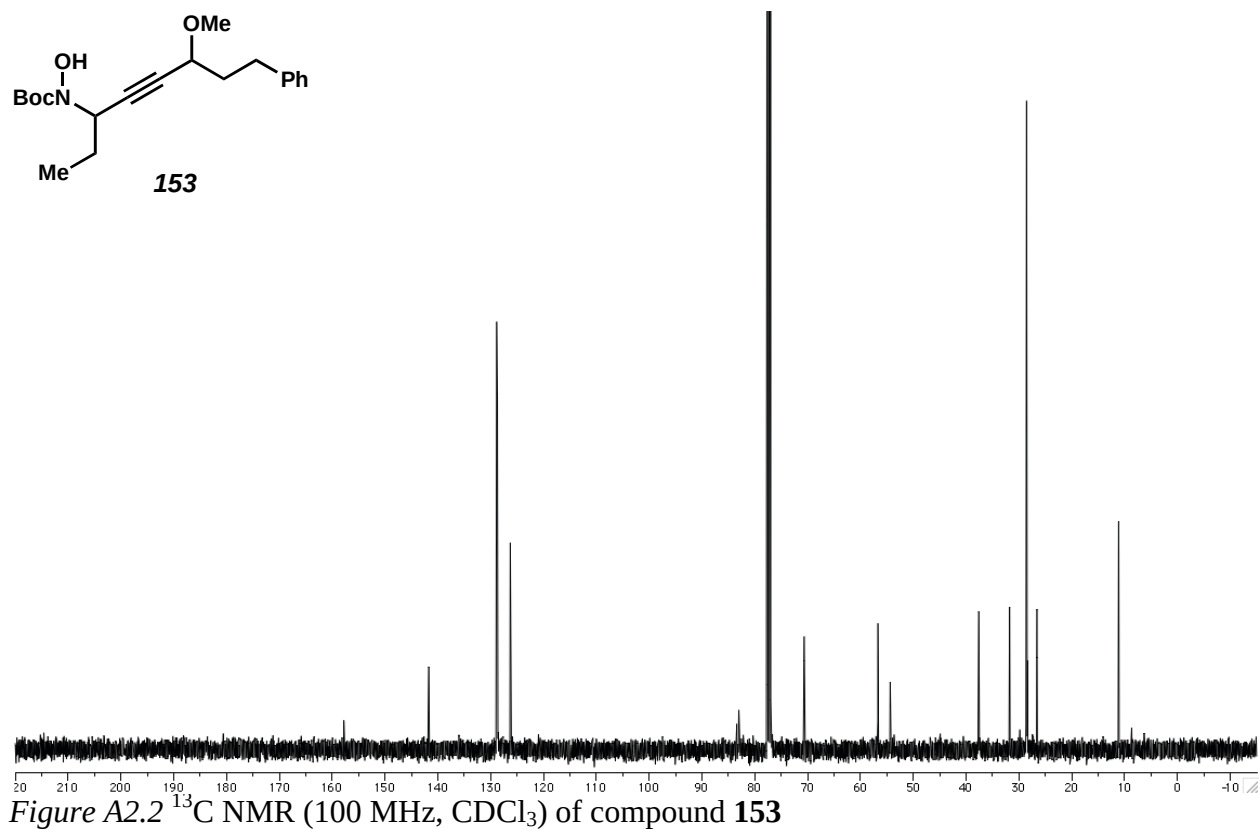


Figure A2.1 ^1H NMR (400 MHz, CDCl_3) of compound **153**



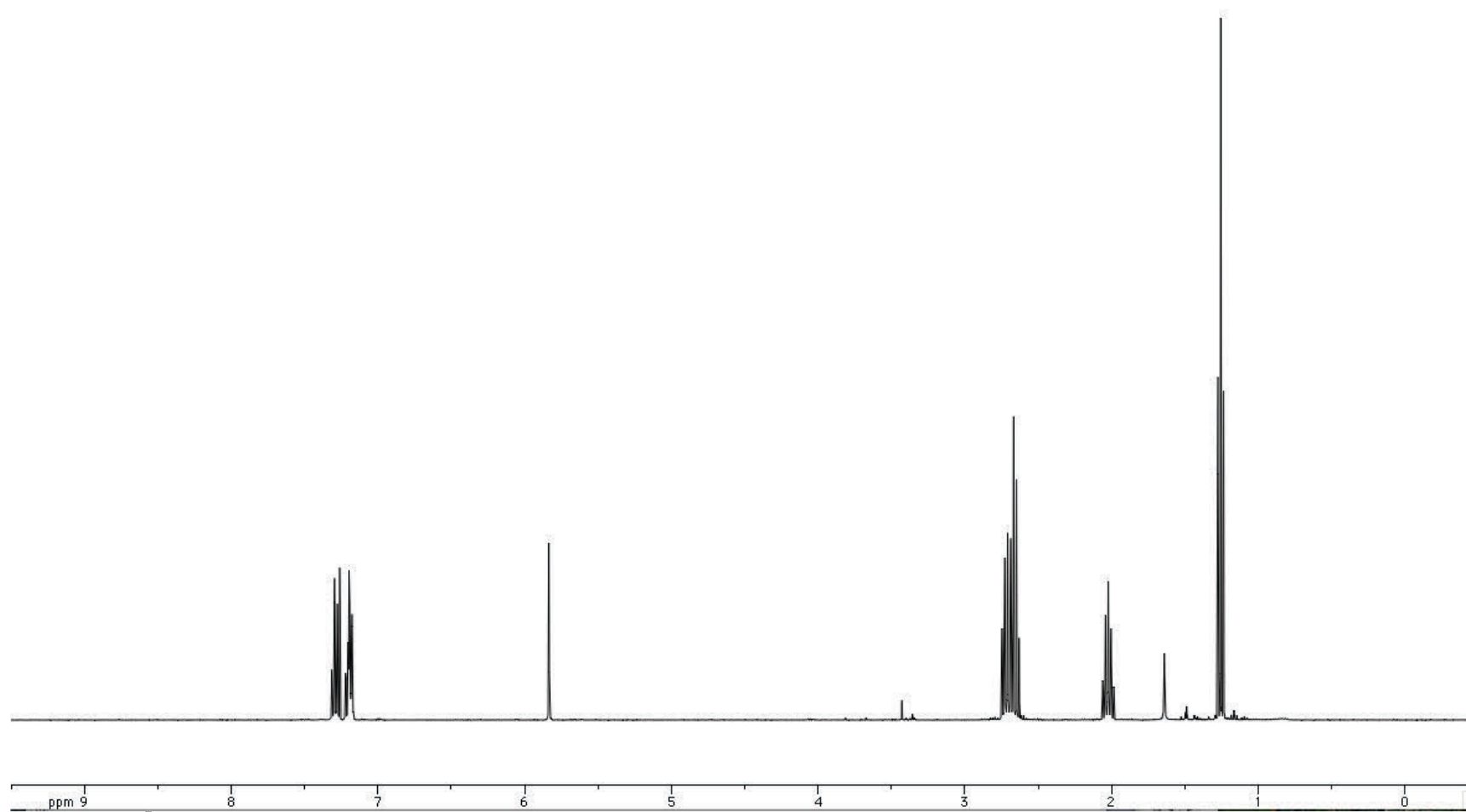
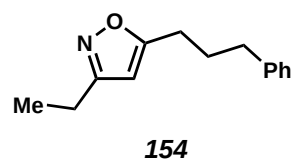
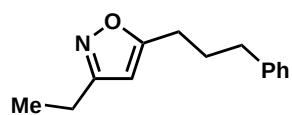


Figure A2.4 ^1H NMR (400 MHz, CDCl_3) of compound **154**



154

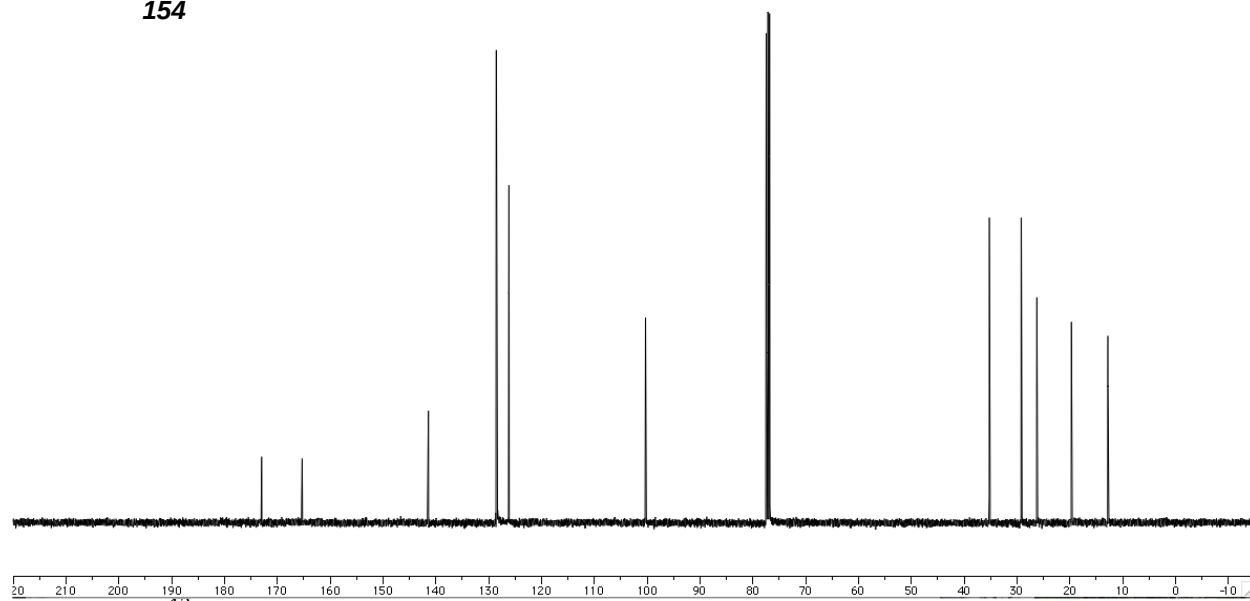


Figure A2.5 ^{13}C NMR (100 MHz, CDCl_3) of compound **154**

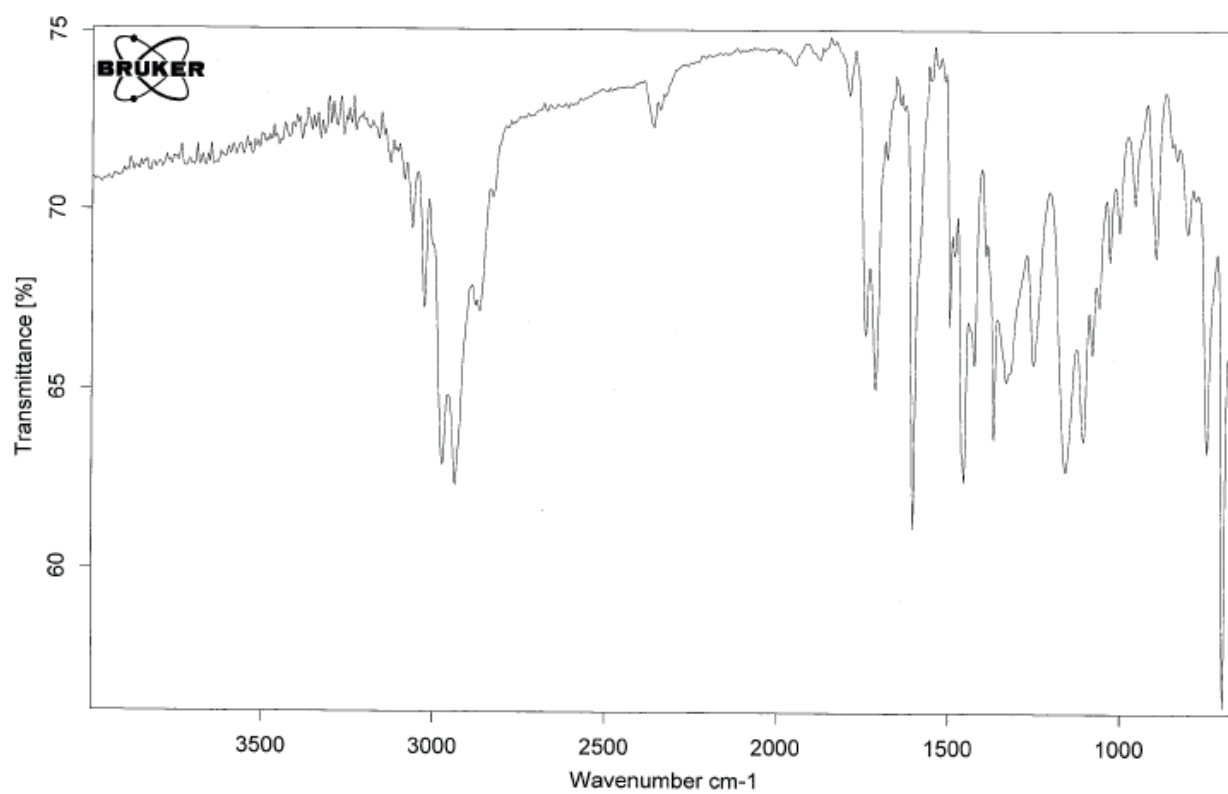


Figure A2.6 Infrared spectrum (thin film) of compound **154**

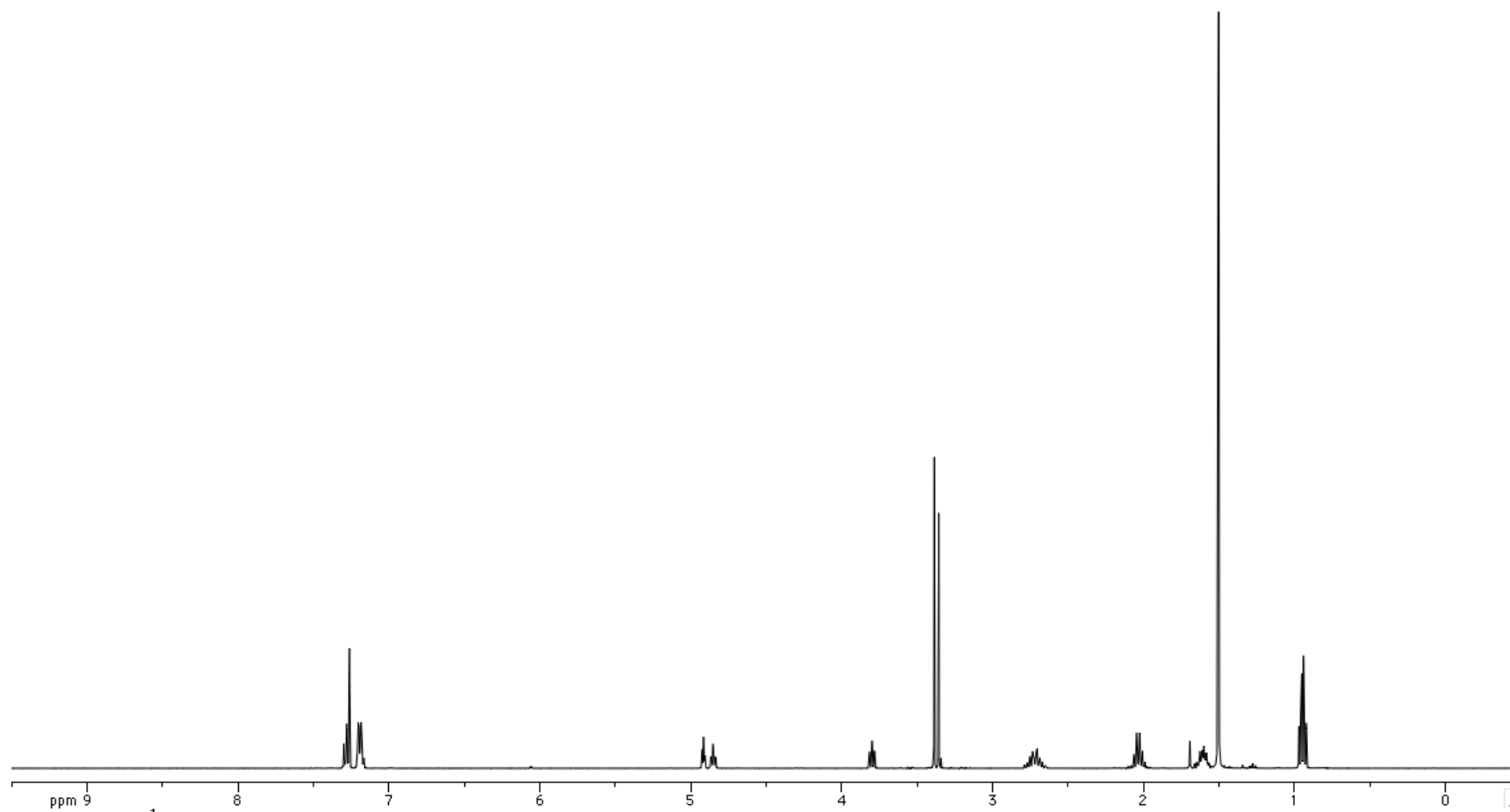
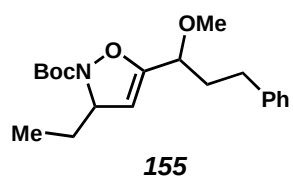
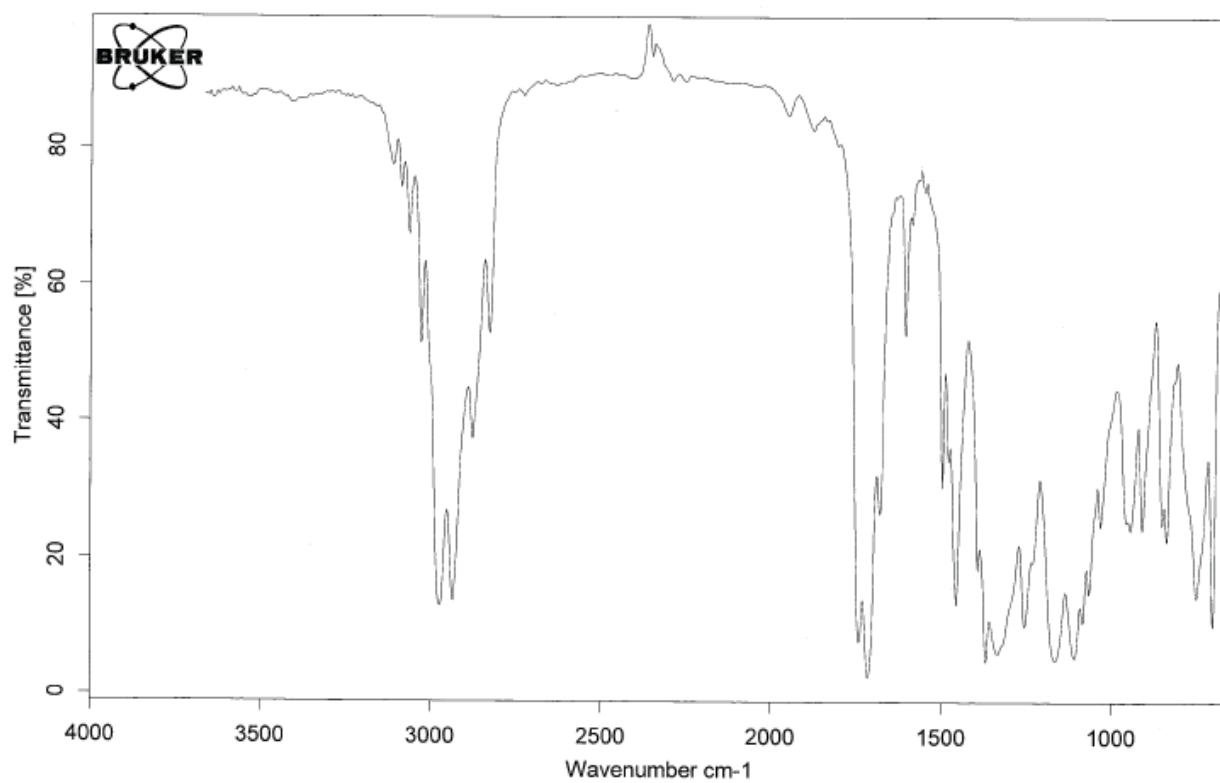
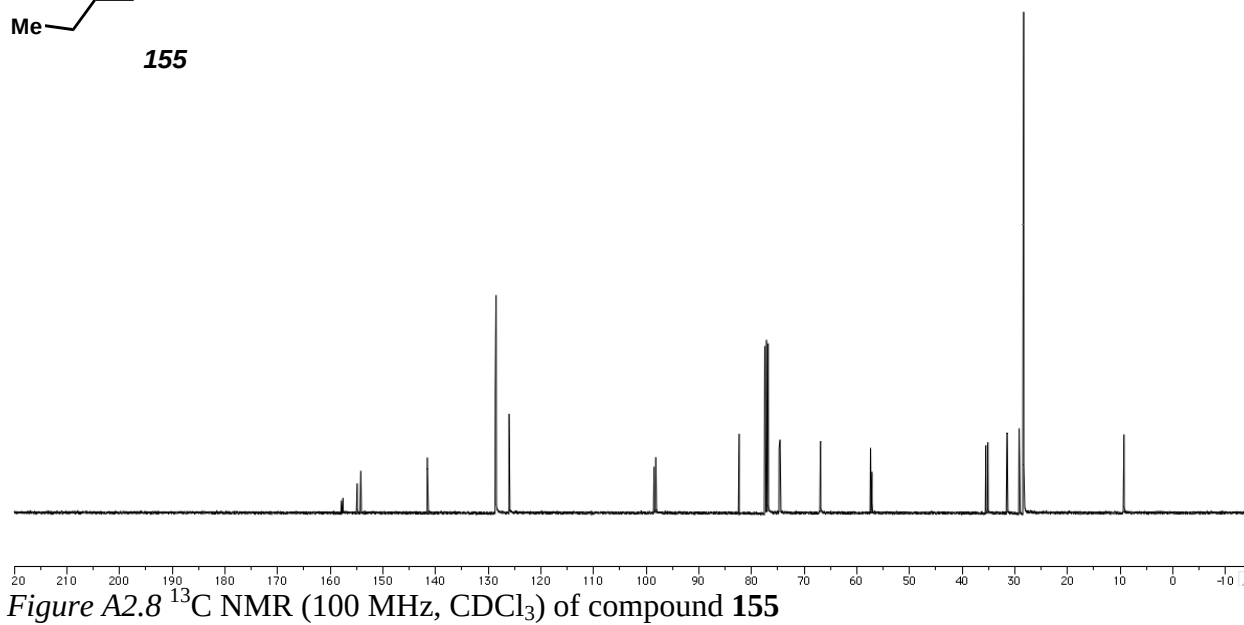
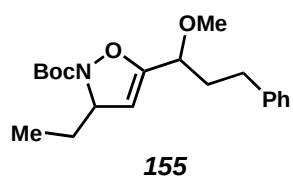


Figure A2.7 ^1H NMR (400 MHz, CDCl_3) of compound **155**



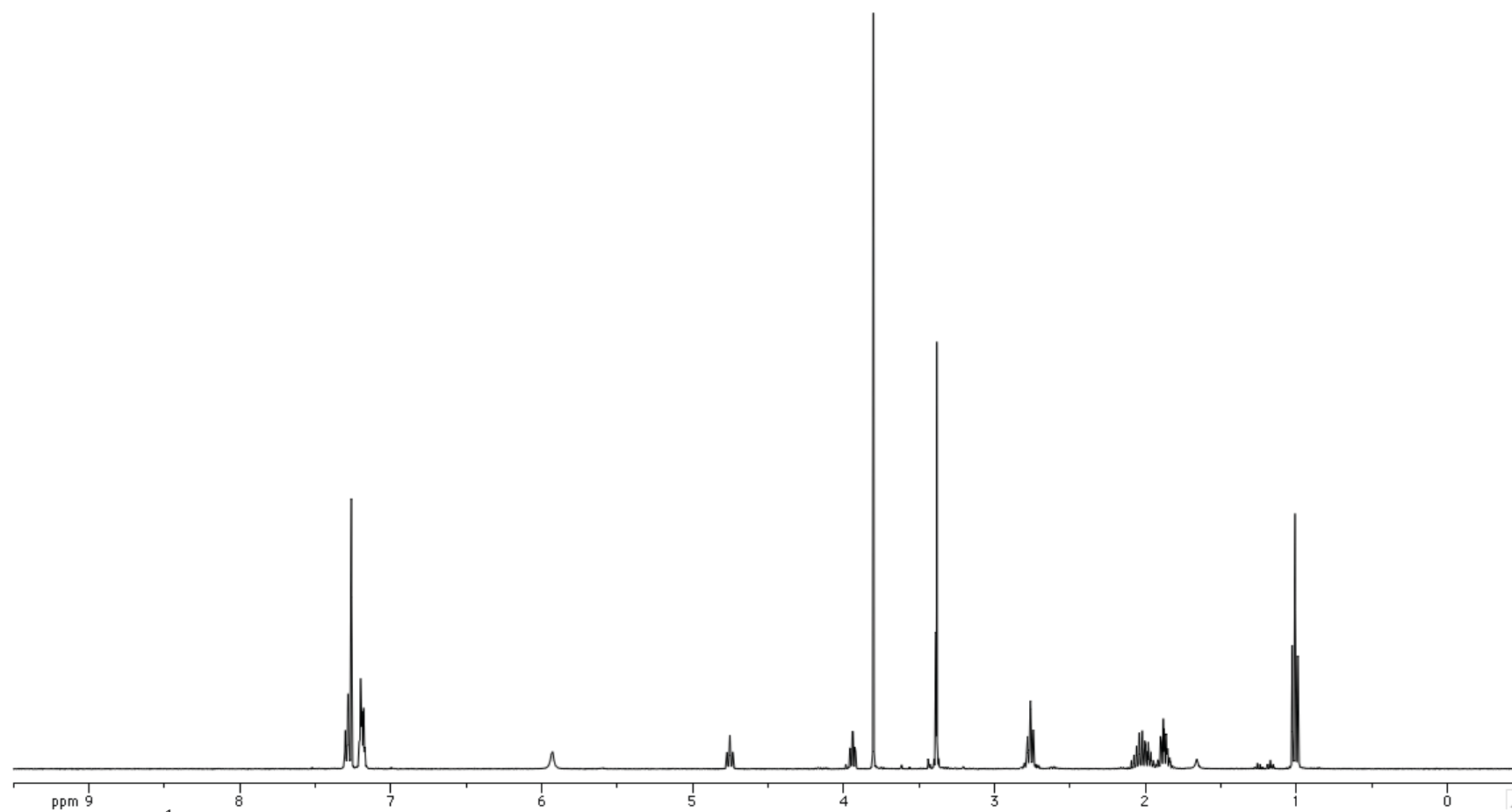
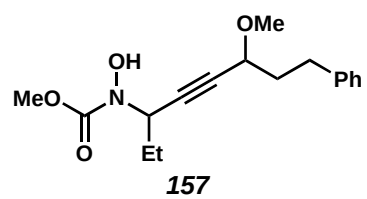


Figure A2.10 ^1H NMR (400 MHz, CDCl_3) of compound **157**

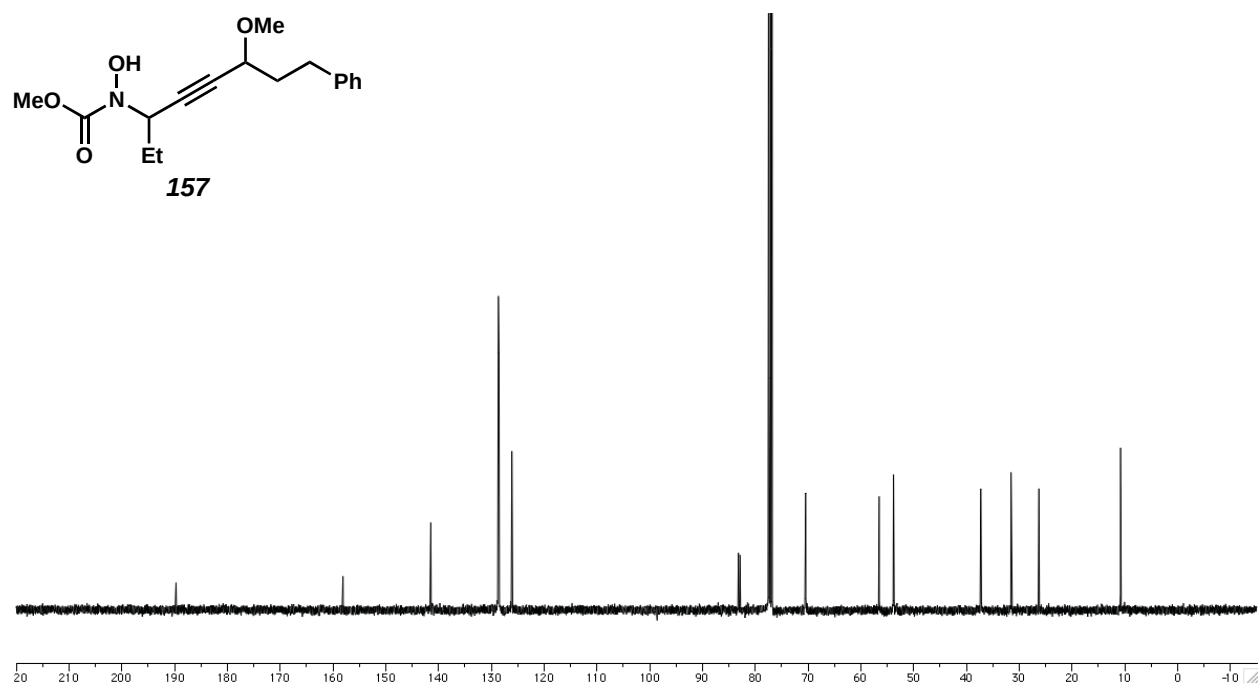


Figure A2.11 ¹³C NMR (100 MHz, CDCl₃) of compound **157**

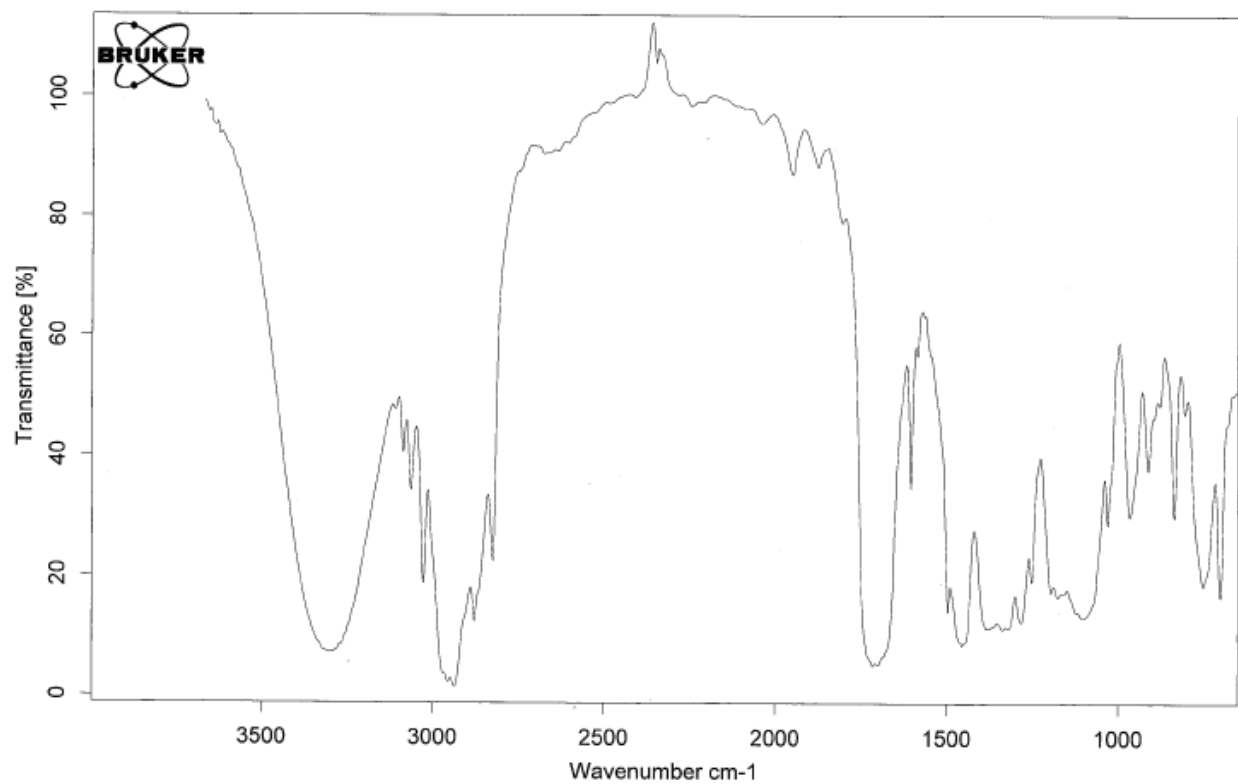


Figure A2.12 Infrared spectrum (thin film) of compound **157**

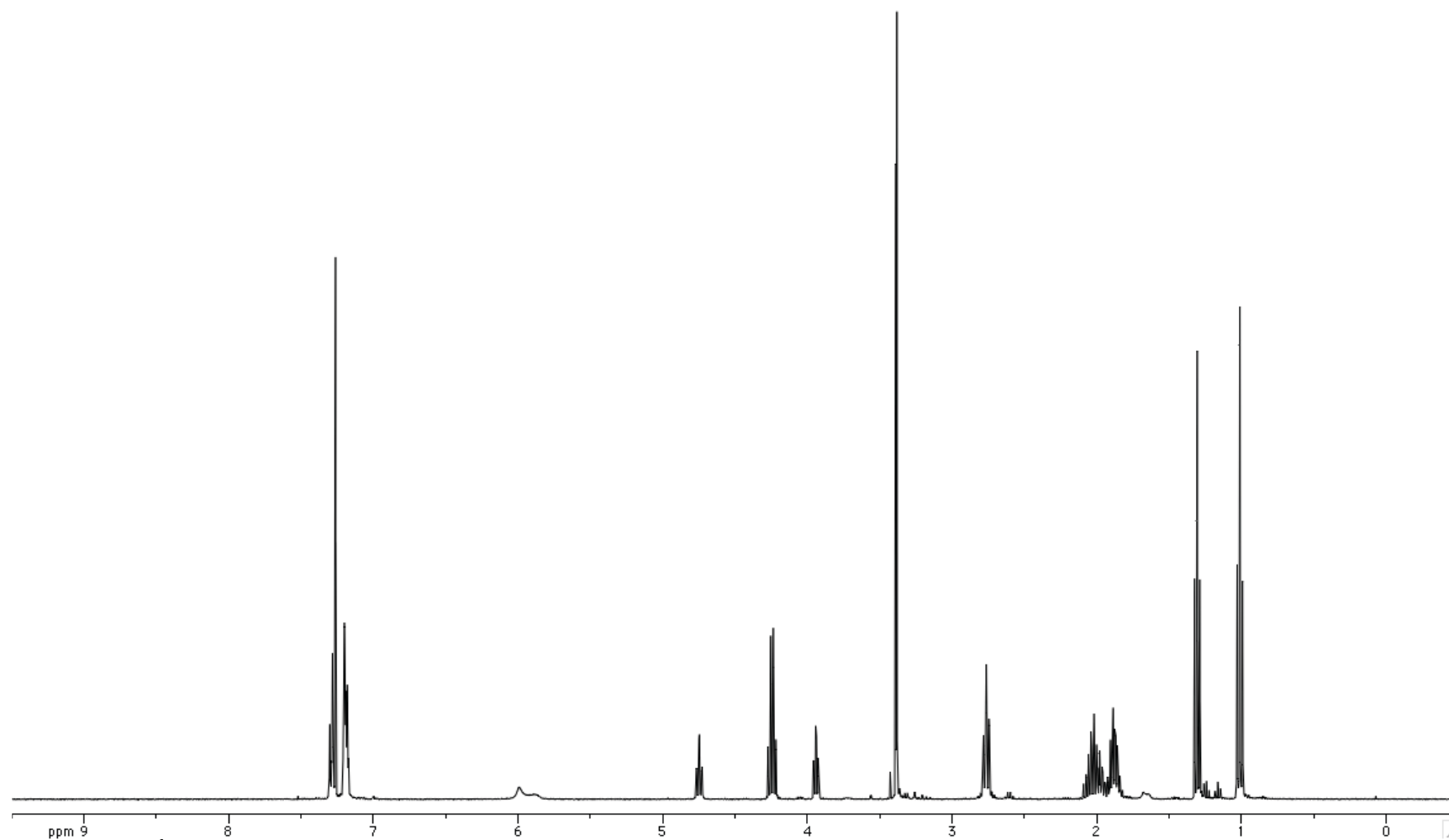
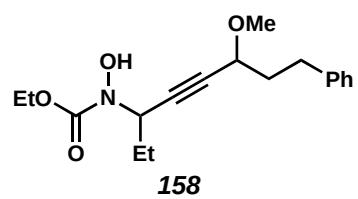
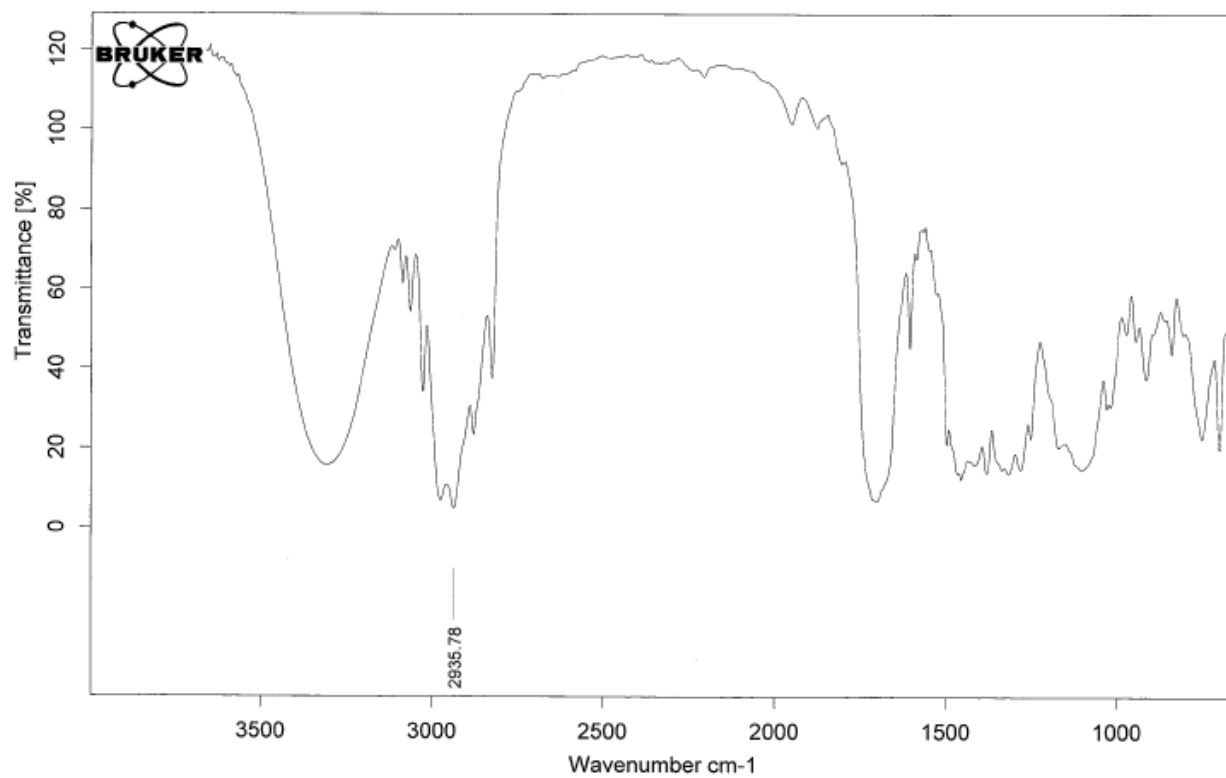
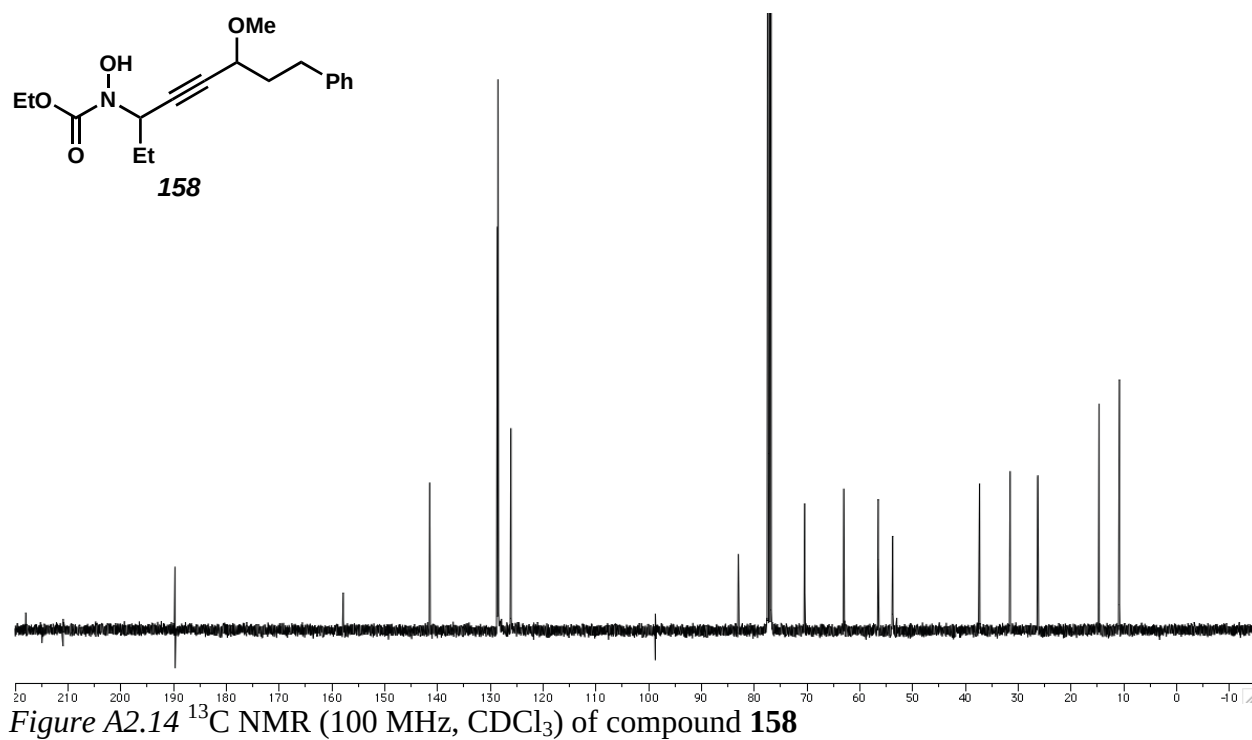


Figure A2.13 ^1H NMR (400 MHz, CDCl_3) of compound **158**



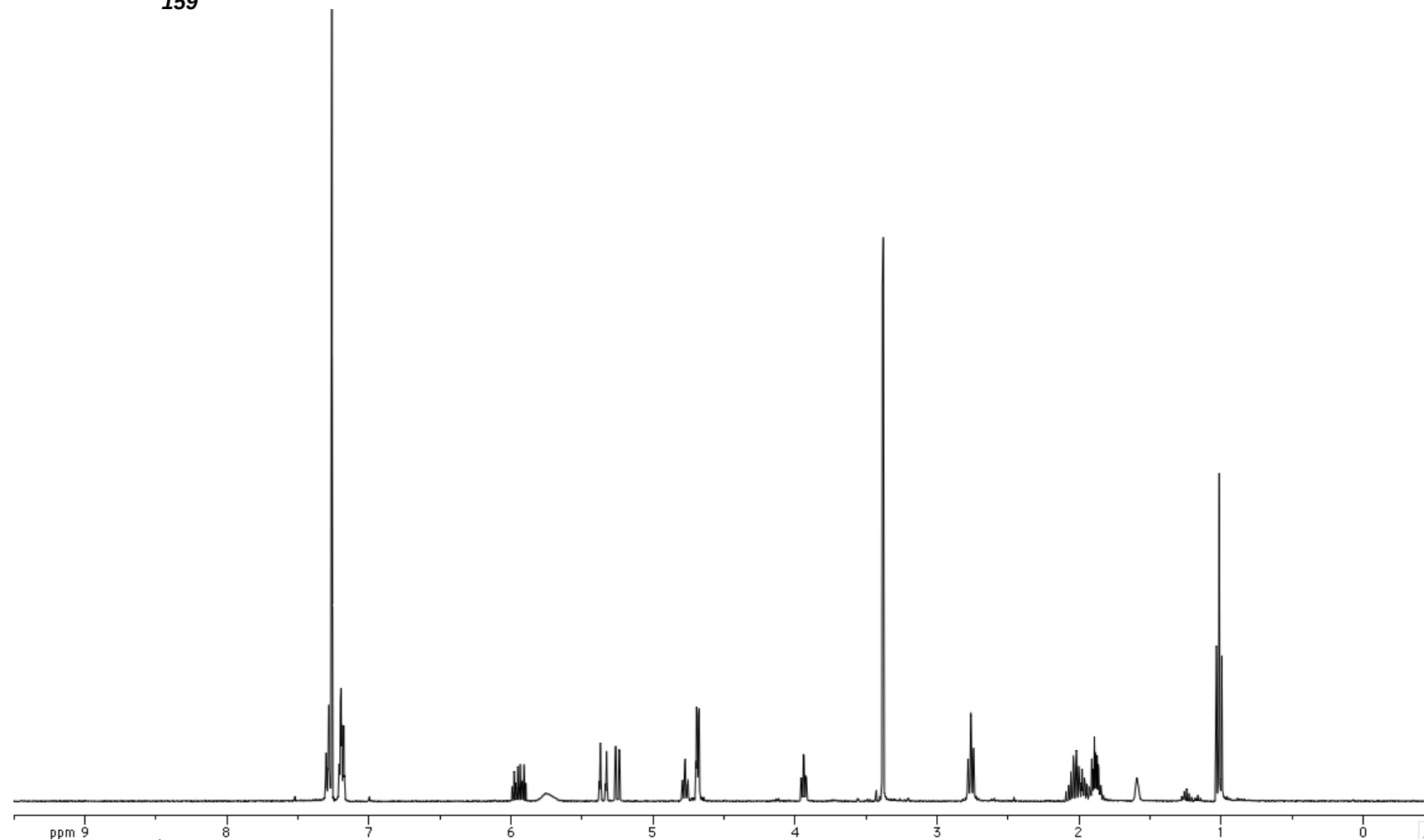
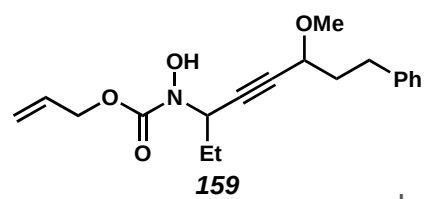
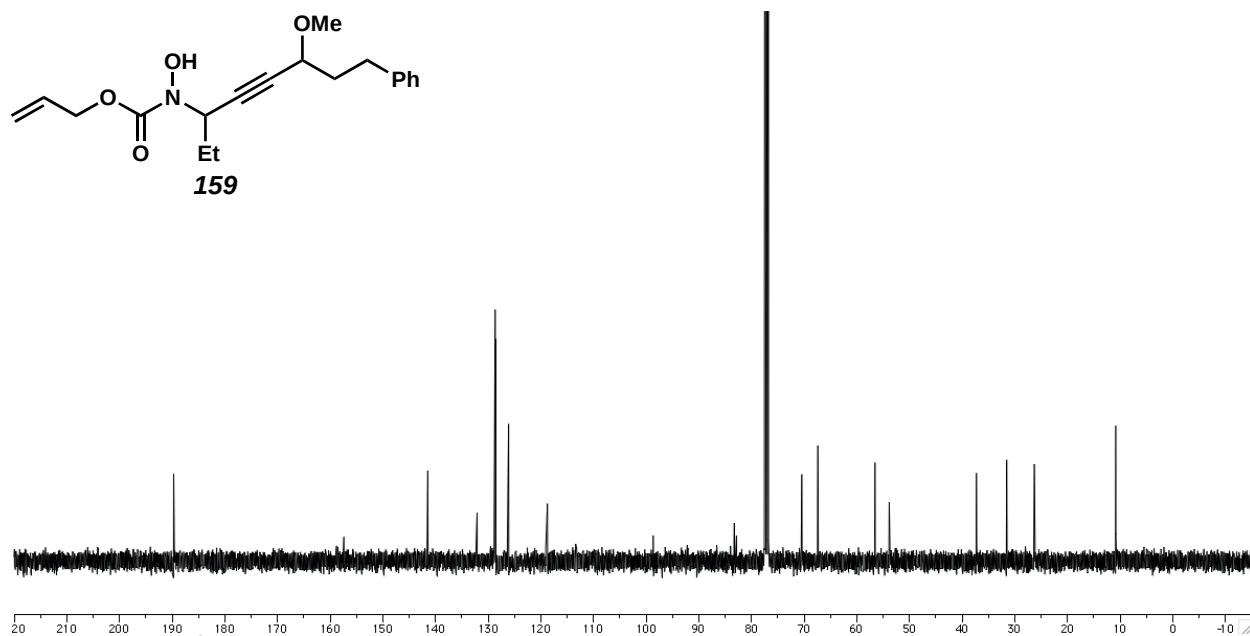


Figure A2.16 ^1H NMR (400 MHz, CDCl_3) of compound **159**



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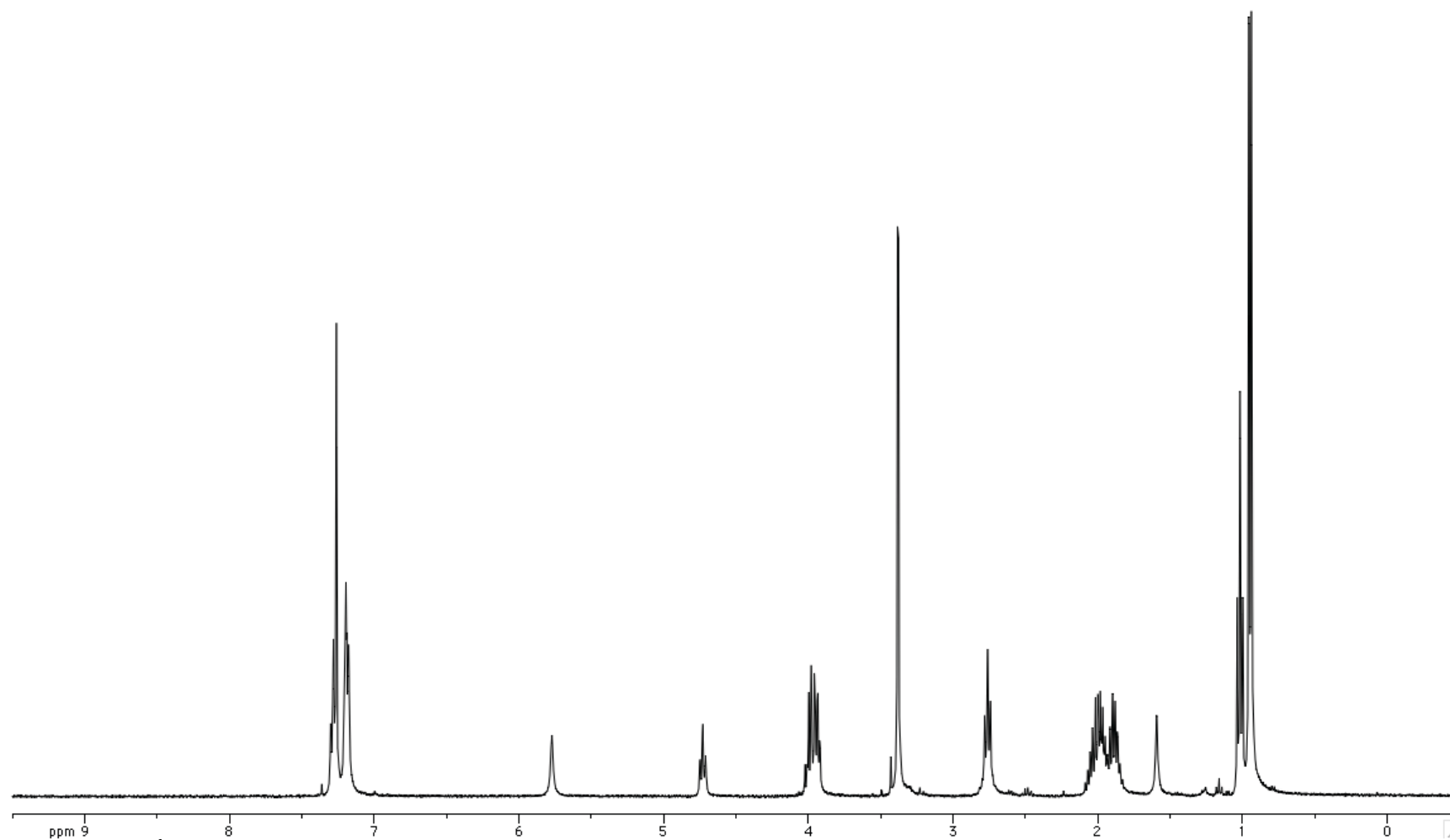
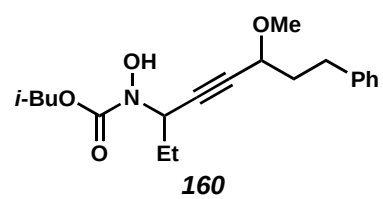


Figure A2.19 ^1H NMR (400 MHz, CDCl_3) of compound **160**

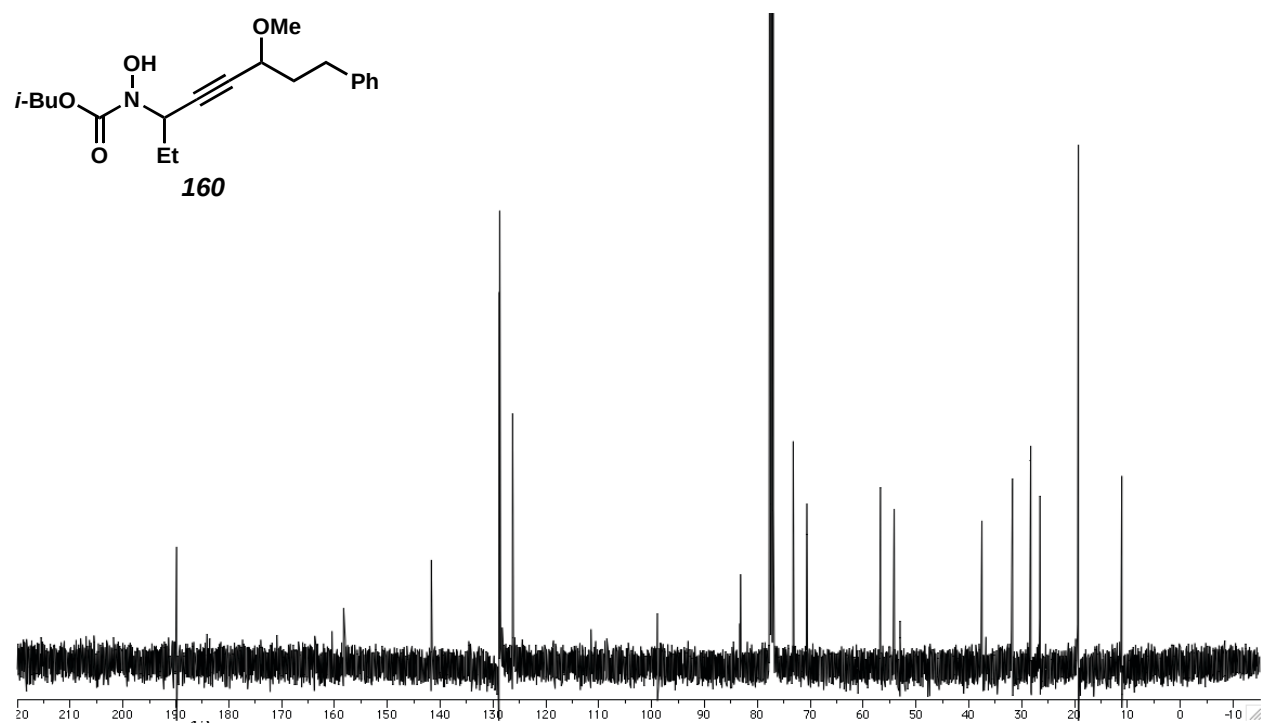


Figure A2.20 ¹³C NMR (100 MHz, CDCl₃) of compound **160**

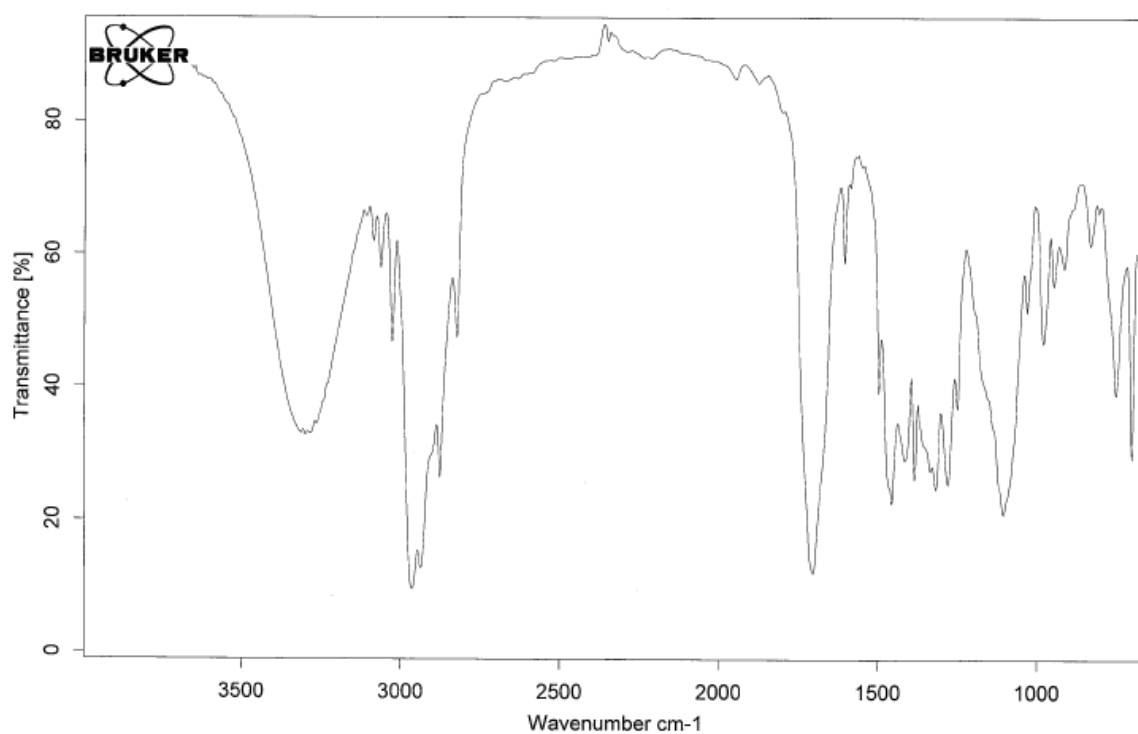


Figure A2.21 Infrared spectrum (thin film) of compound **160**

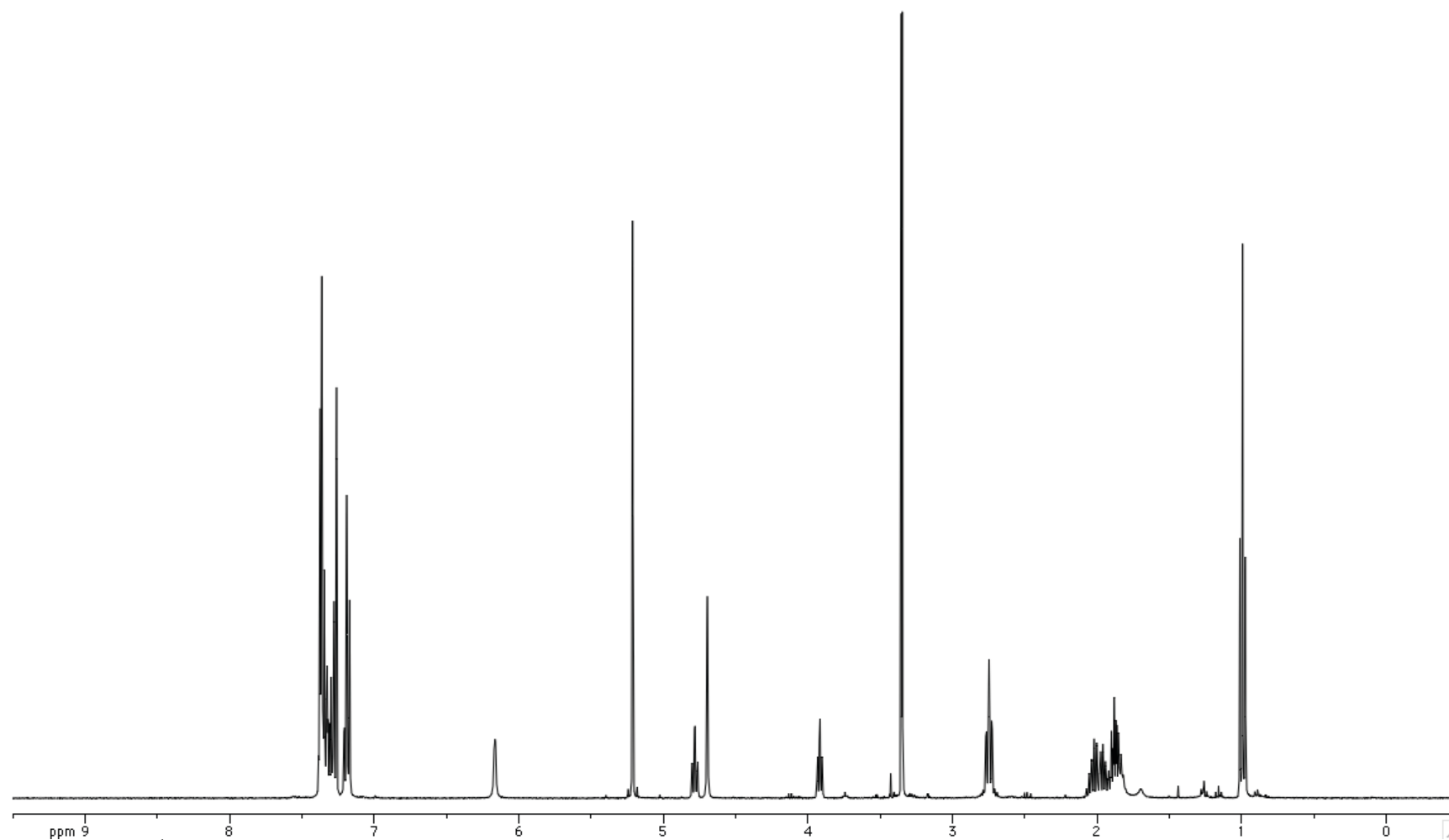
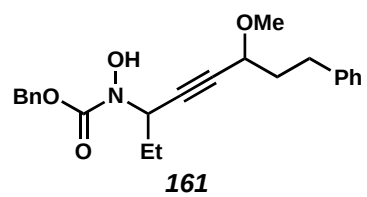
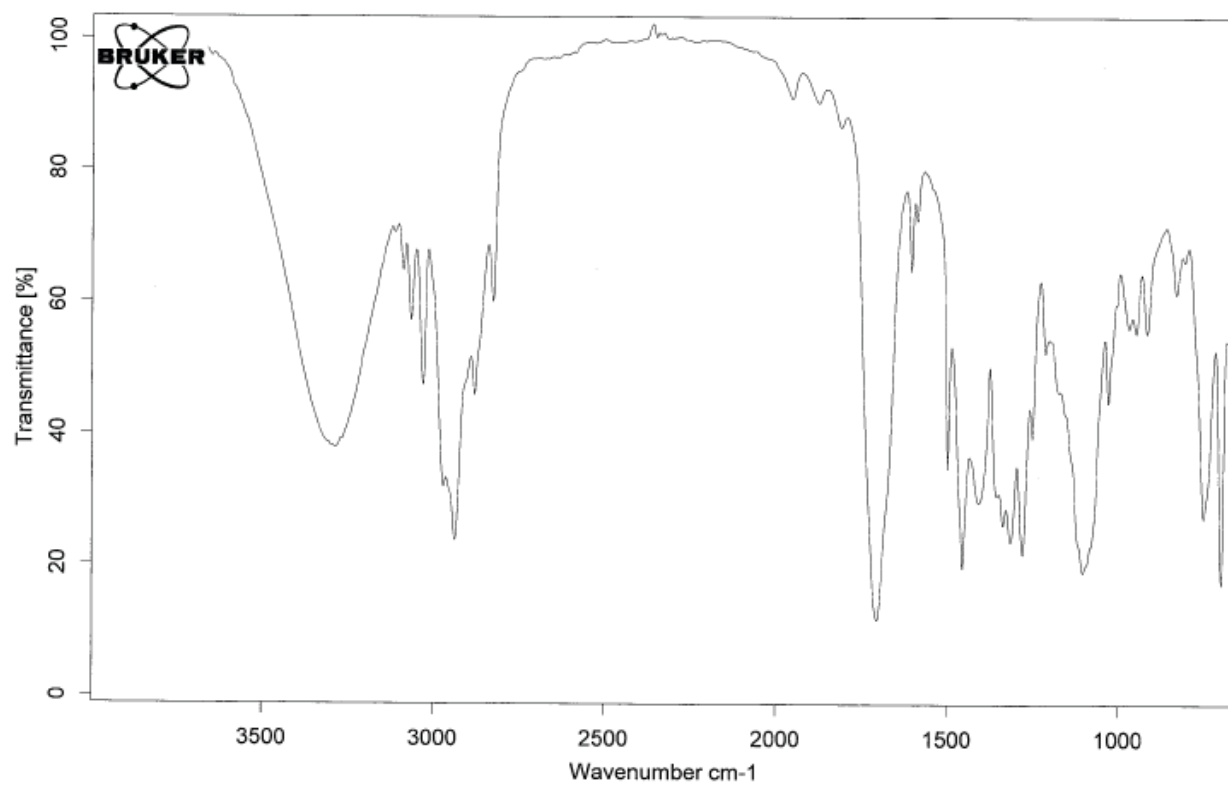
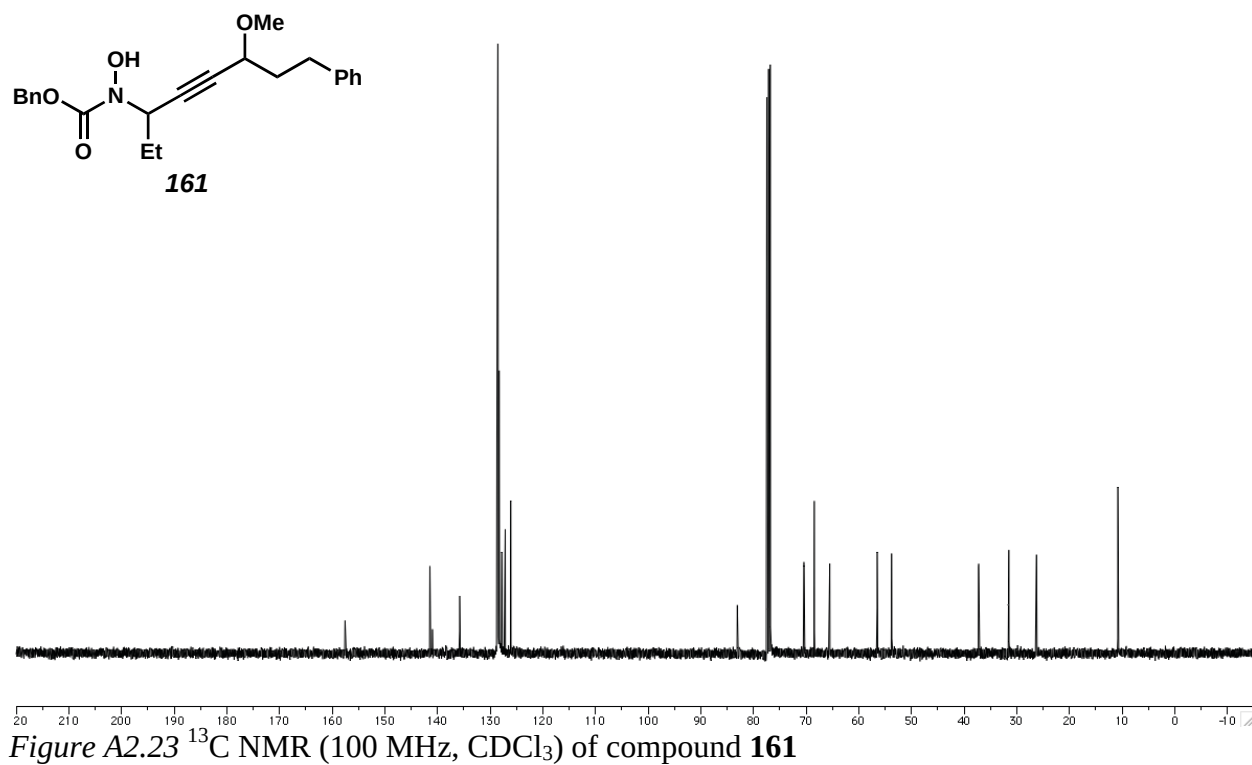


Figure A2.22 ^1H NMR (400 MHz, CDCl_3) of compound **161**



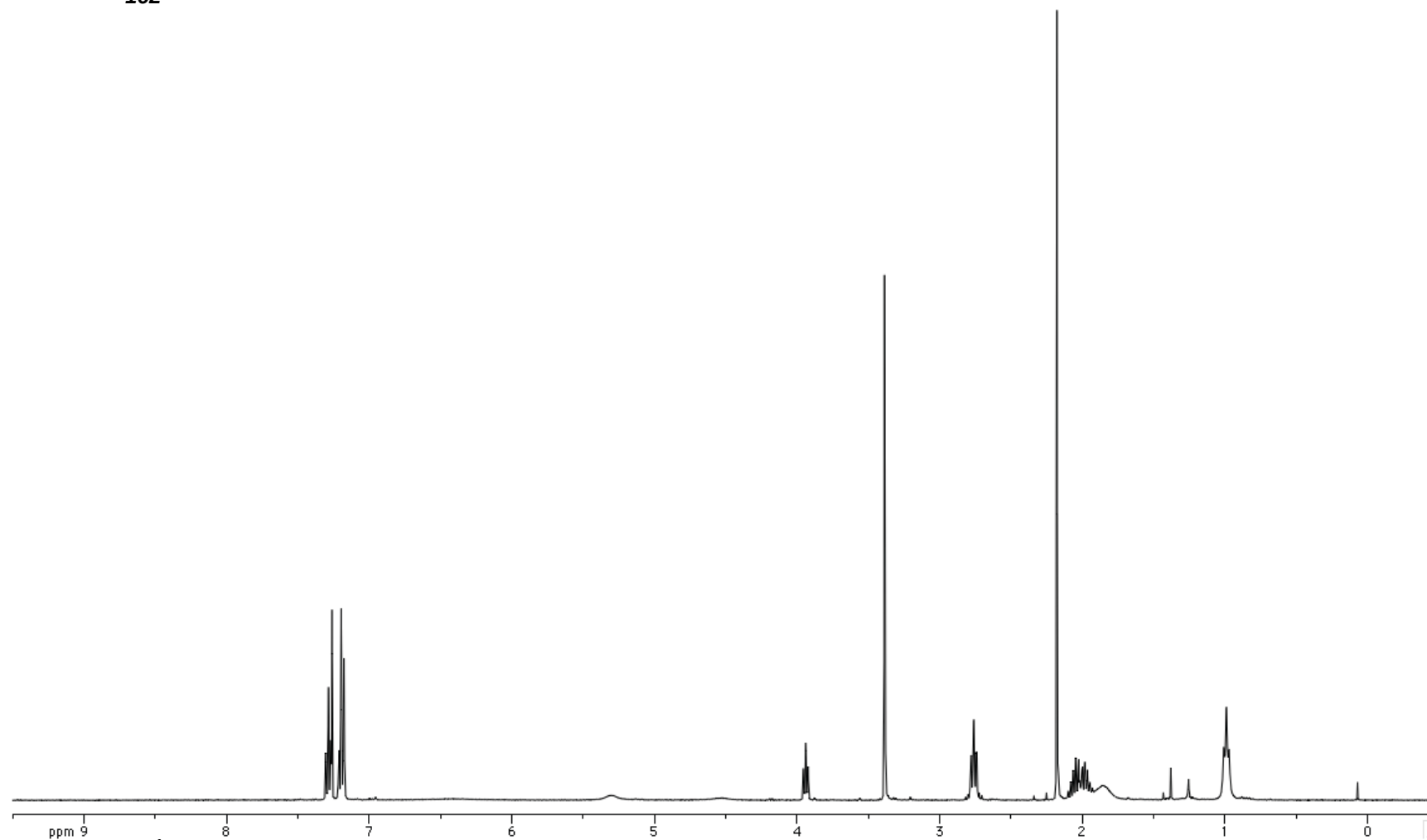
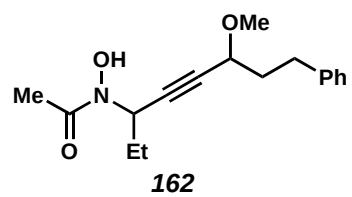
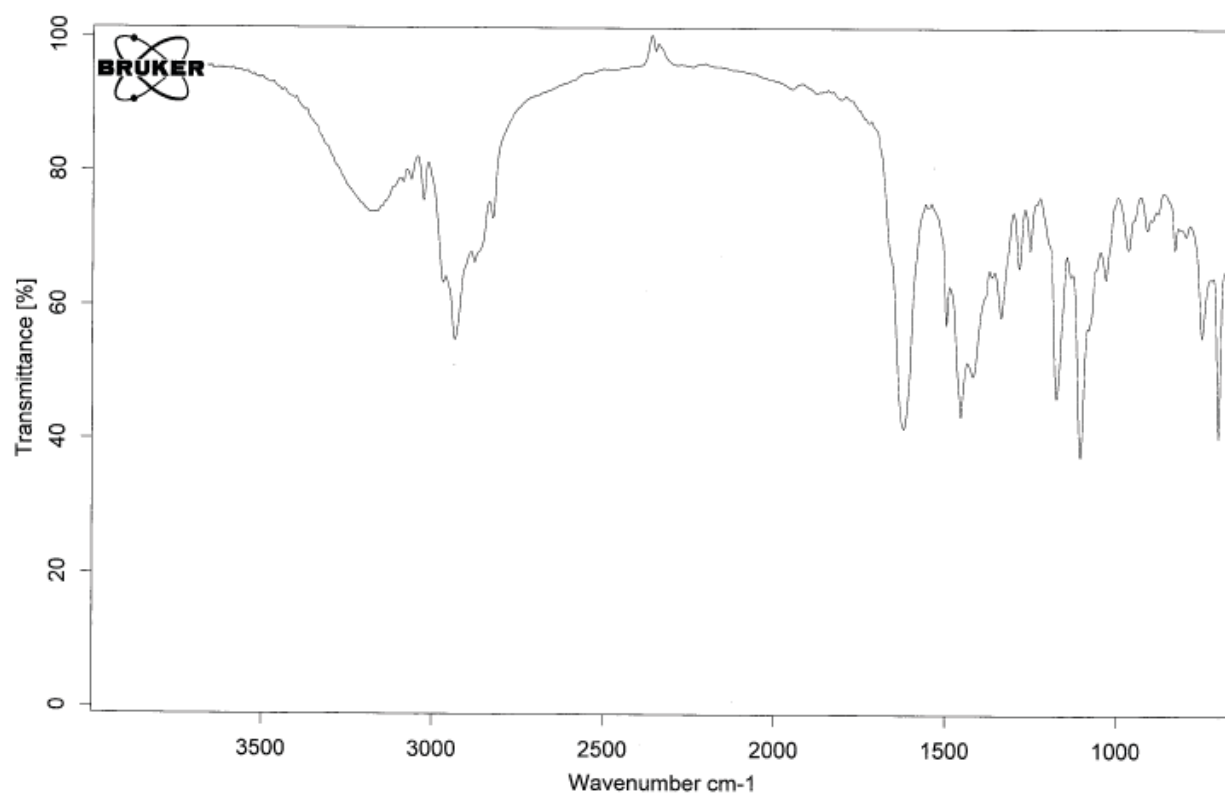
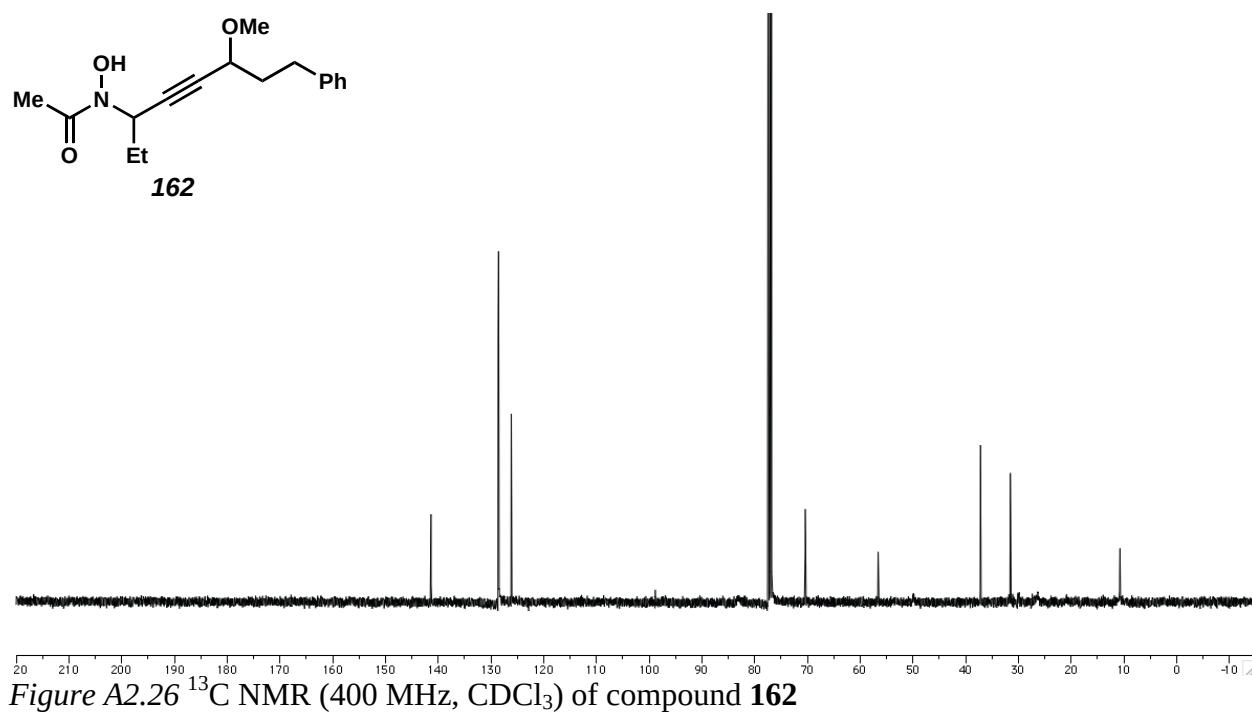


Figure A2.25 ^1H NMR (400 MHz, CDCl_3) of compound **162**



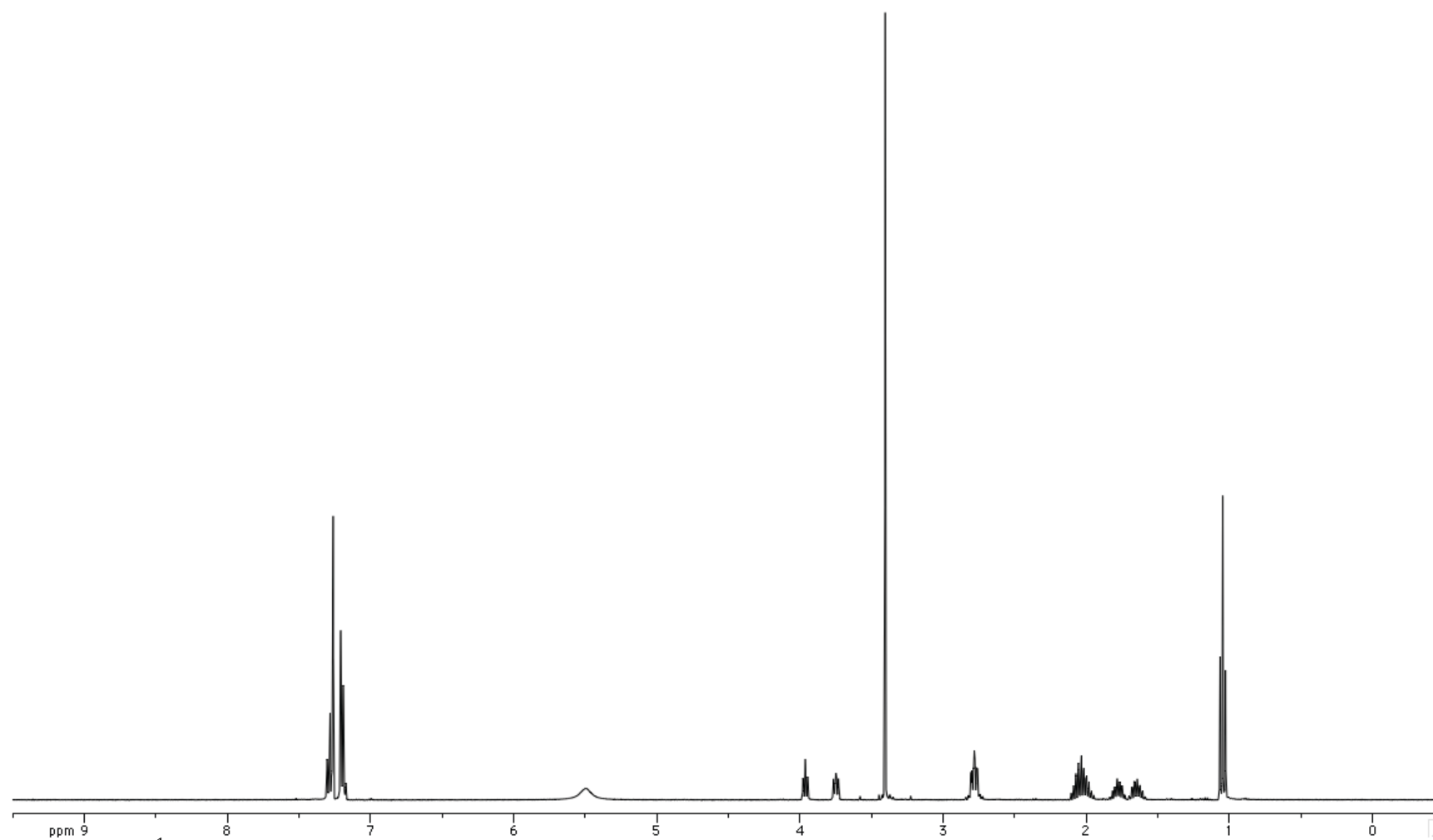
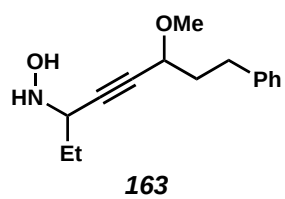
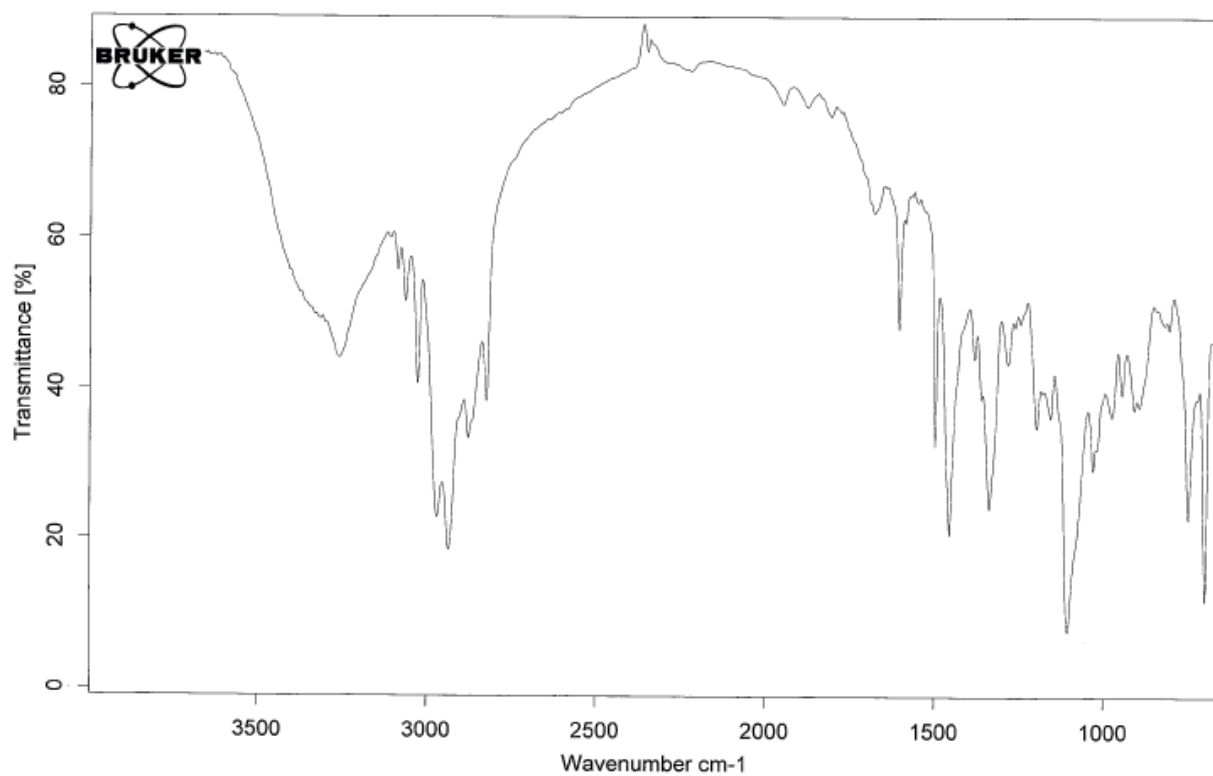
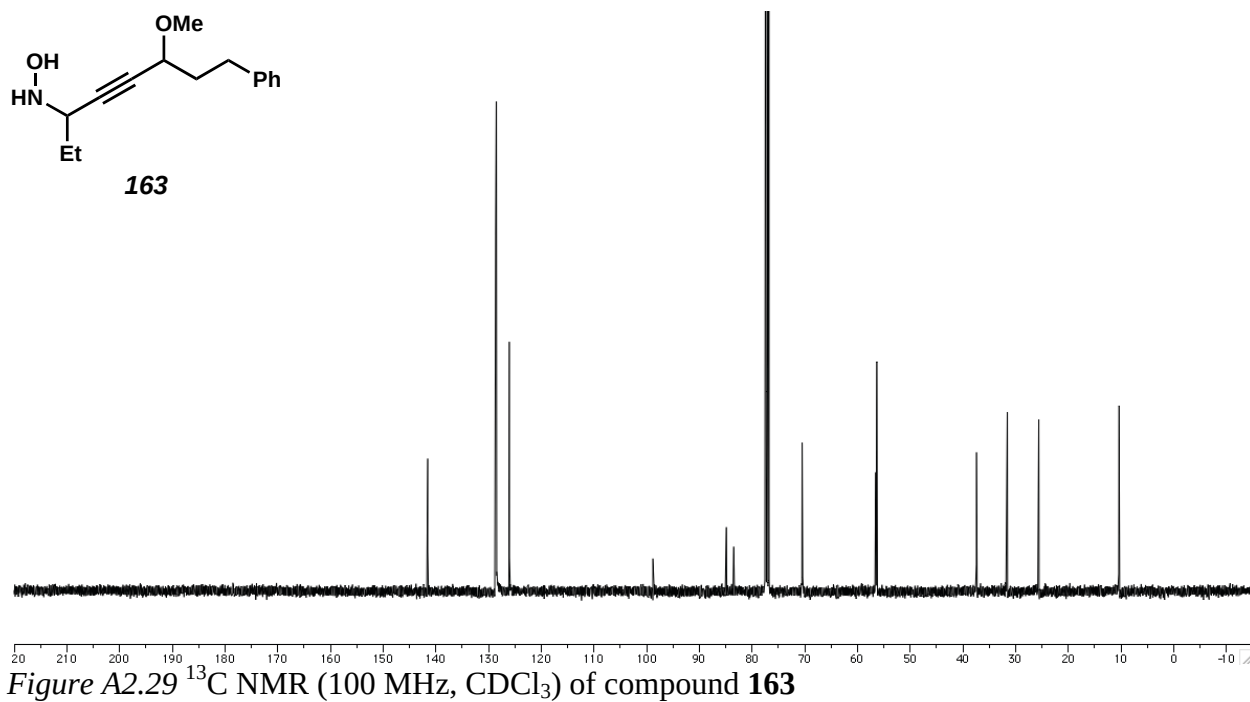


Figure A2.28 ¹H NMR (400 MHz, CDCl₃) of compound **163**



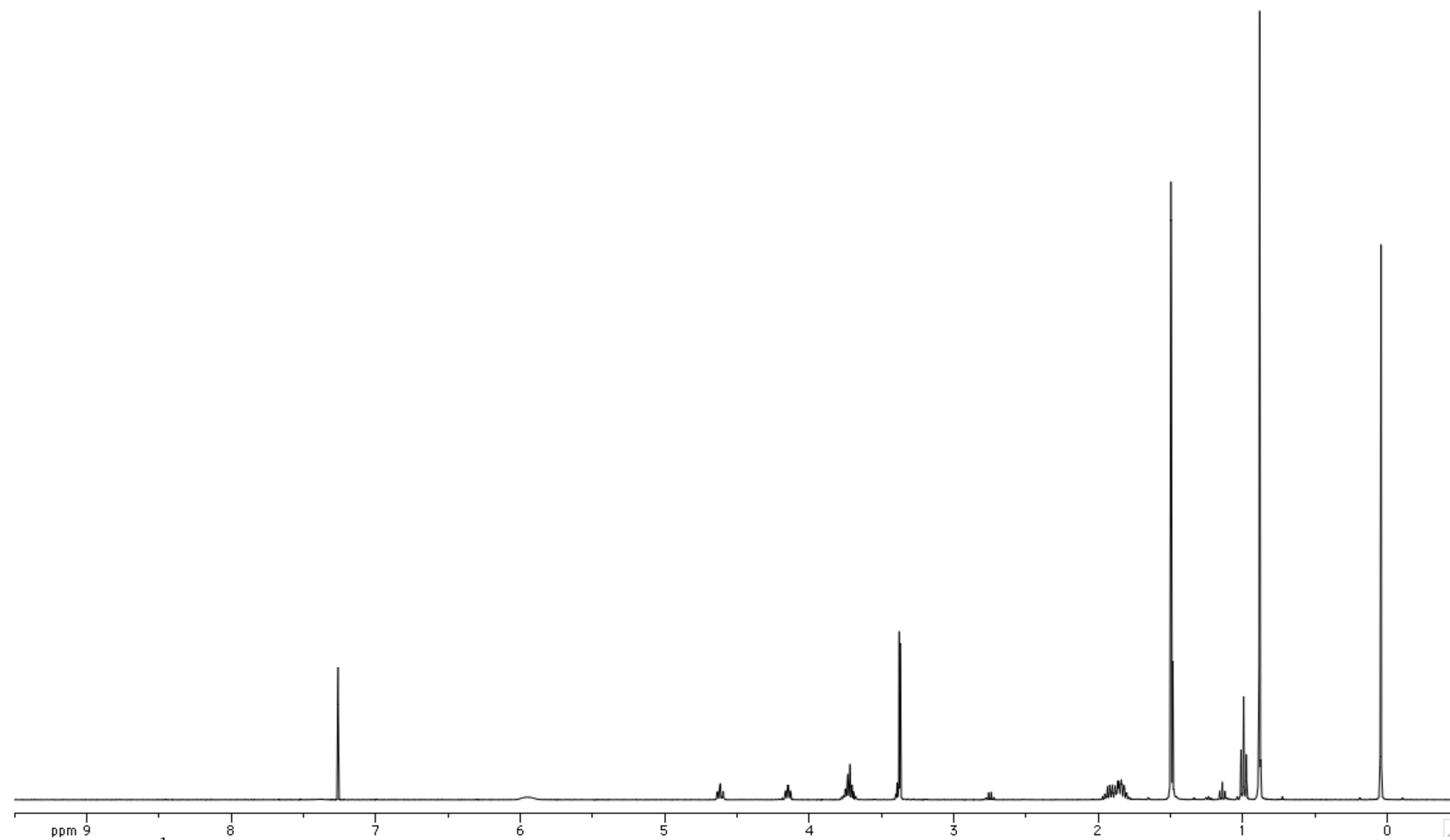
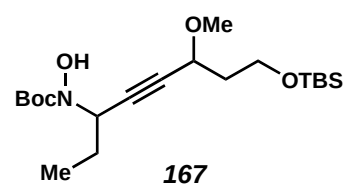
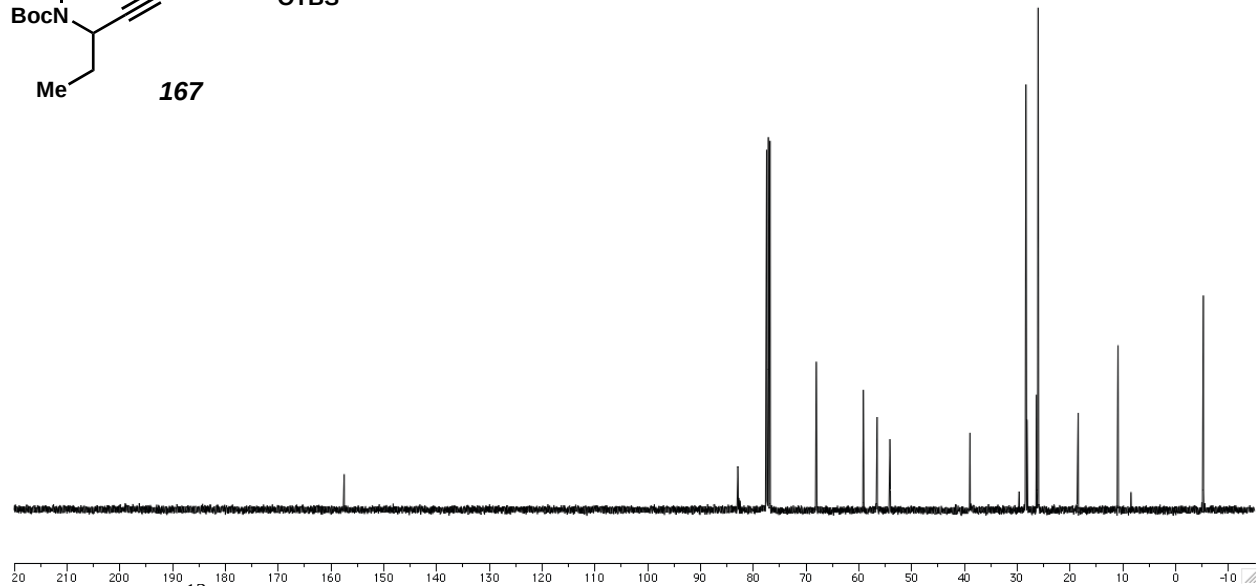


Figure A2.31 ^1H NMR (400 MHz, CDCl_3) of compound **167**



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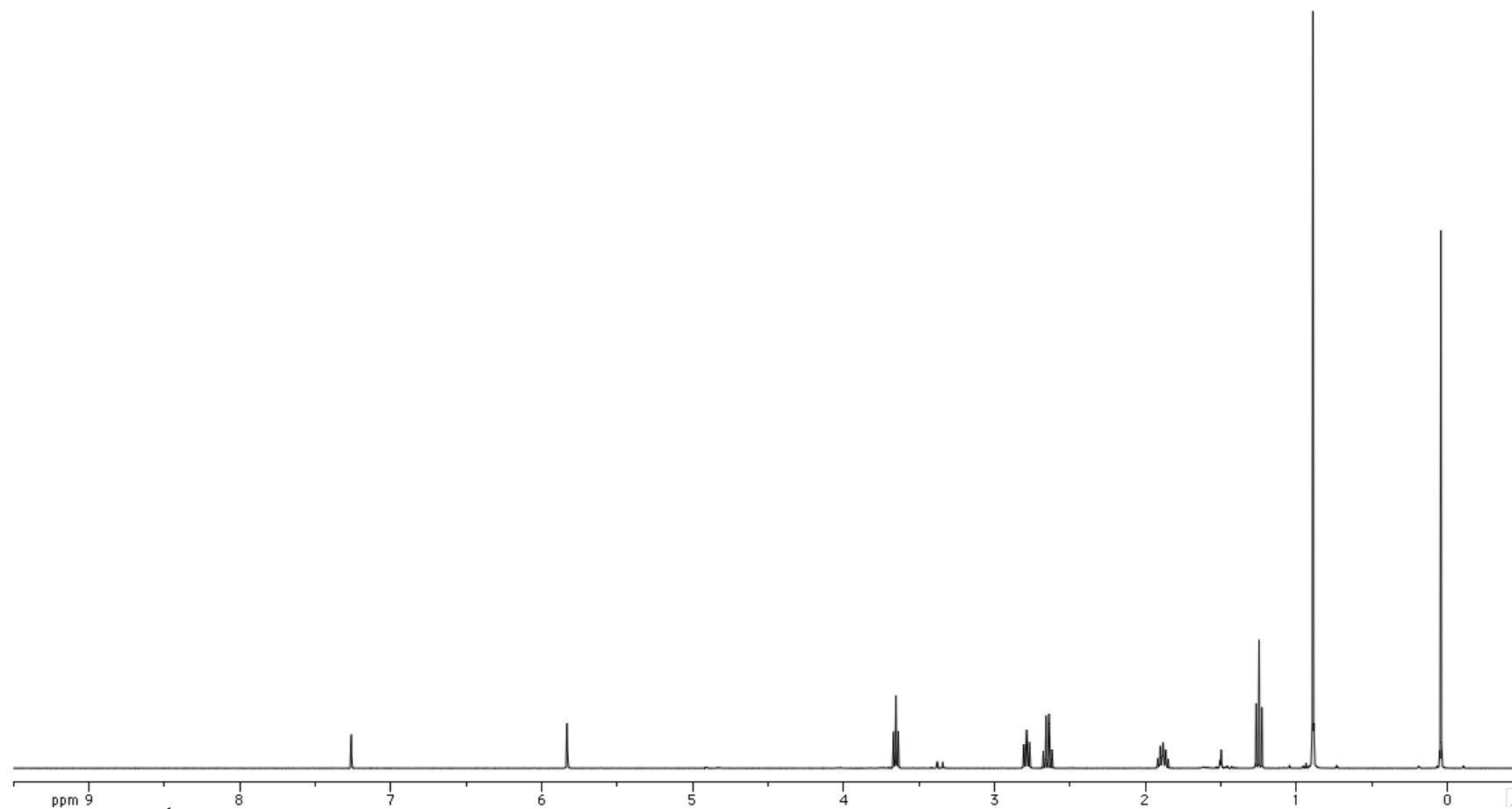
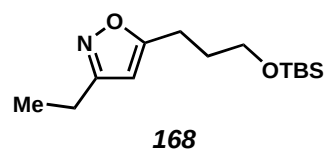
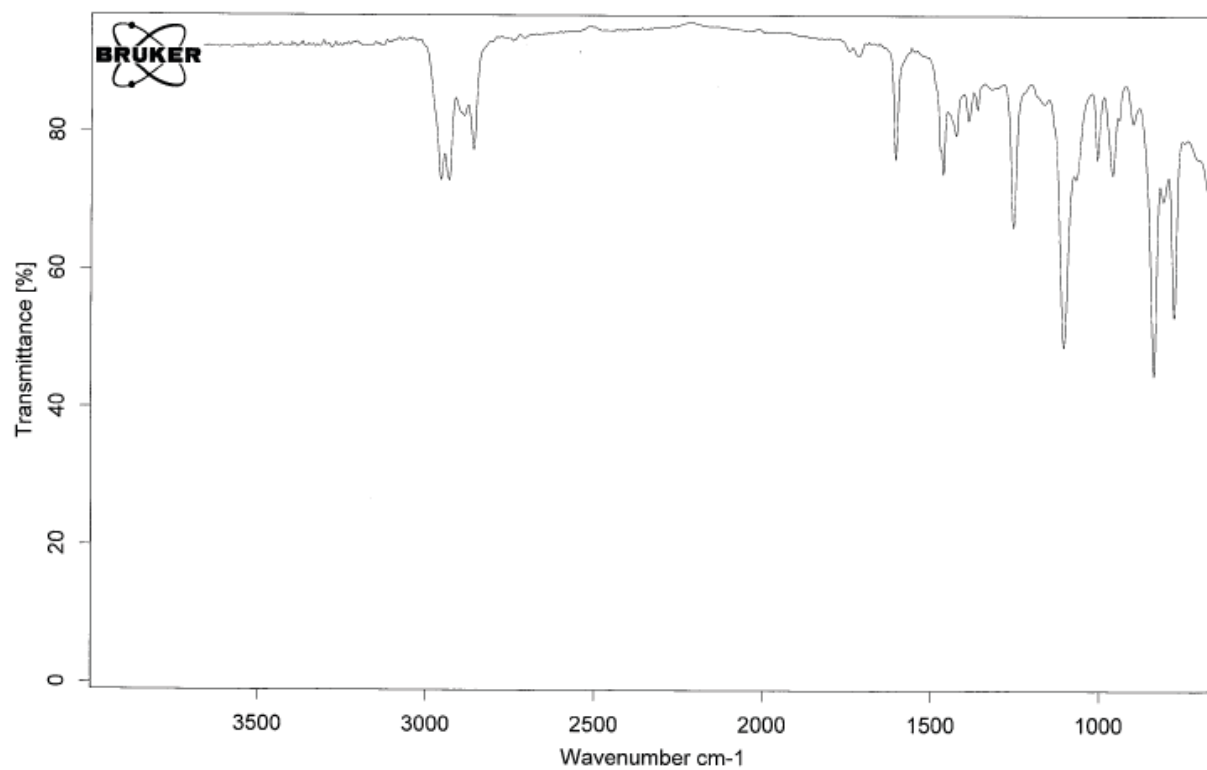
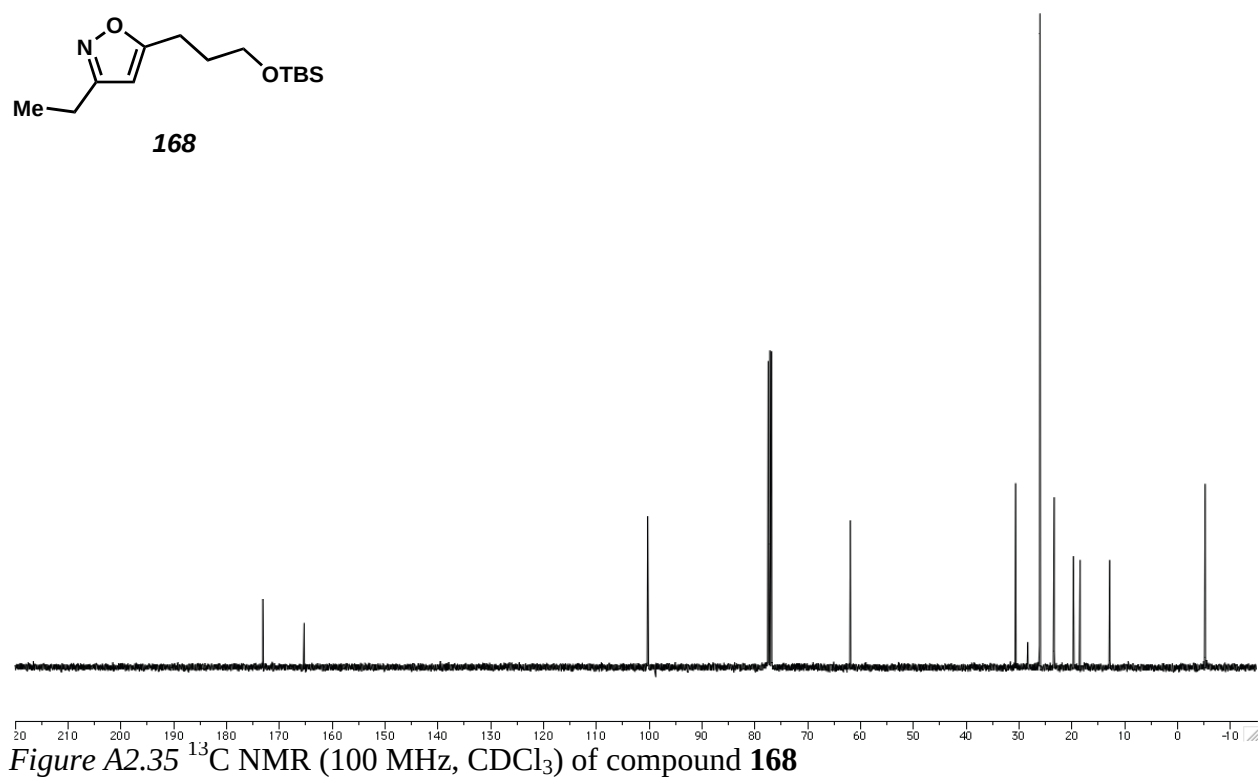
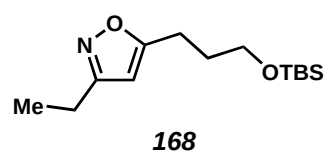


Figure A2.34 ^1H NMR (400 MHz, CDCl_3) of compound **168**



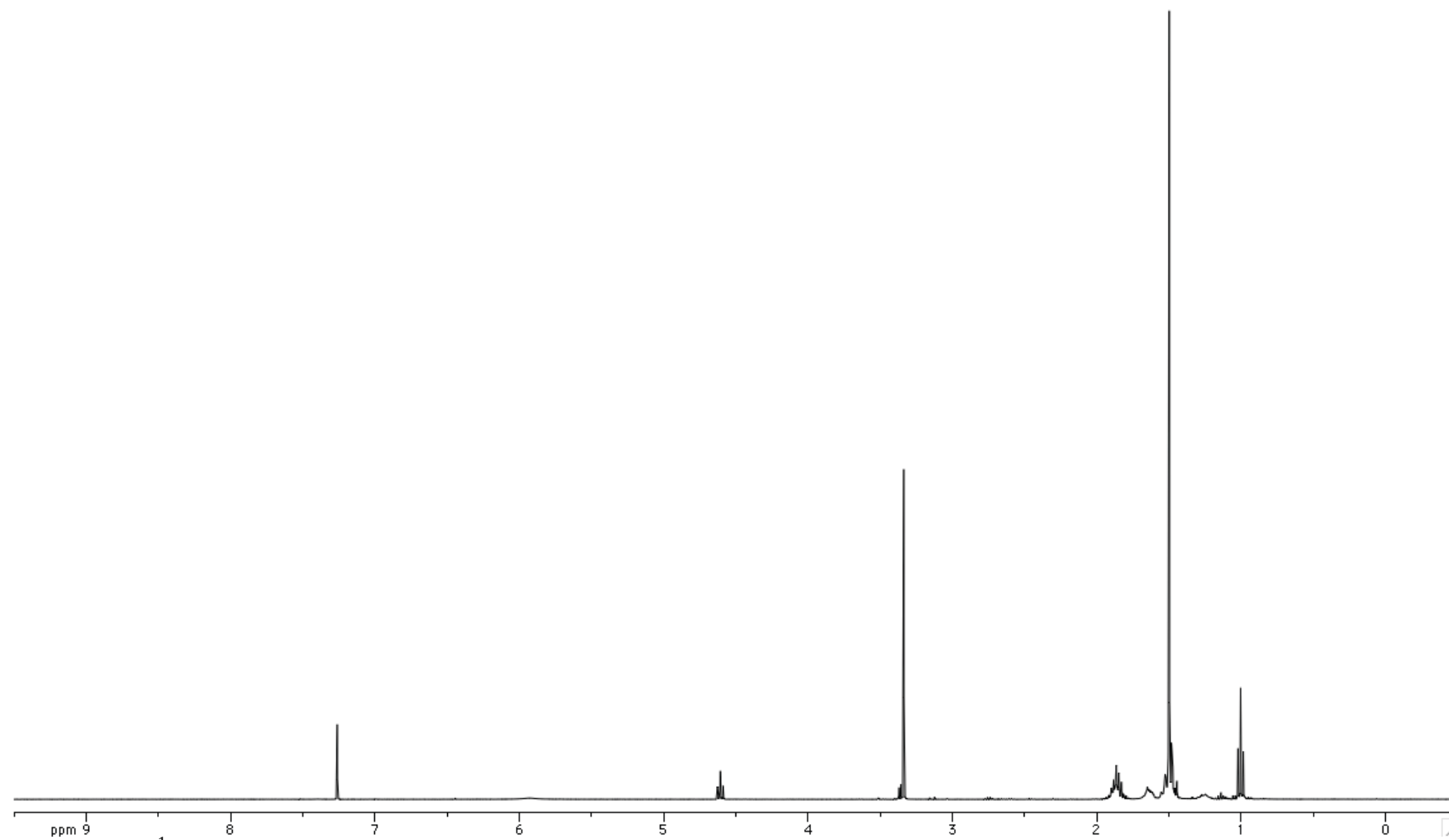
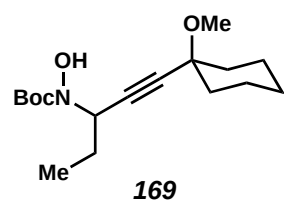


Figure A2.37 ^1H NMR (400 MHz, CDCl_3) of compound **169**

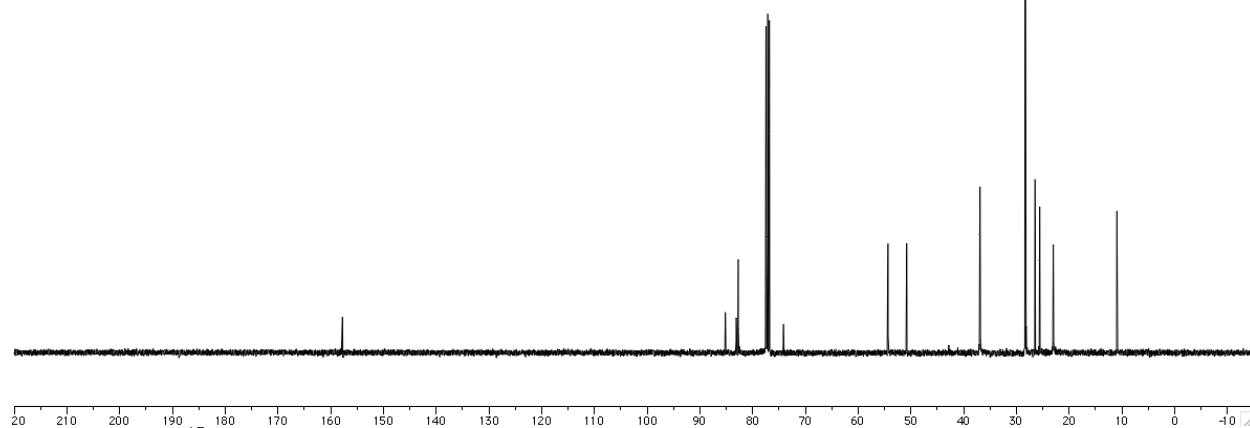
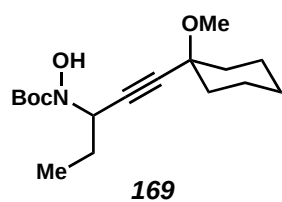


Figure A2.38 ^{13}C NMR (100 MHz, CDCl_3) of compound **169**

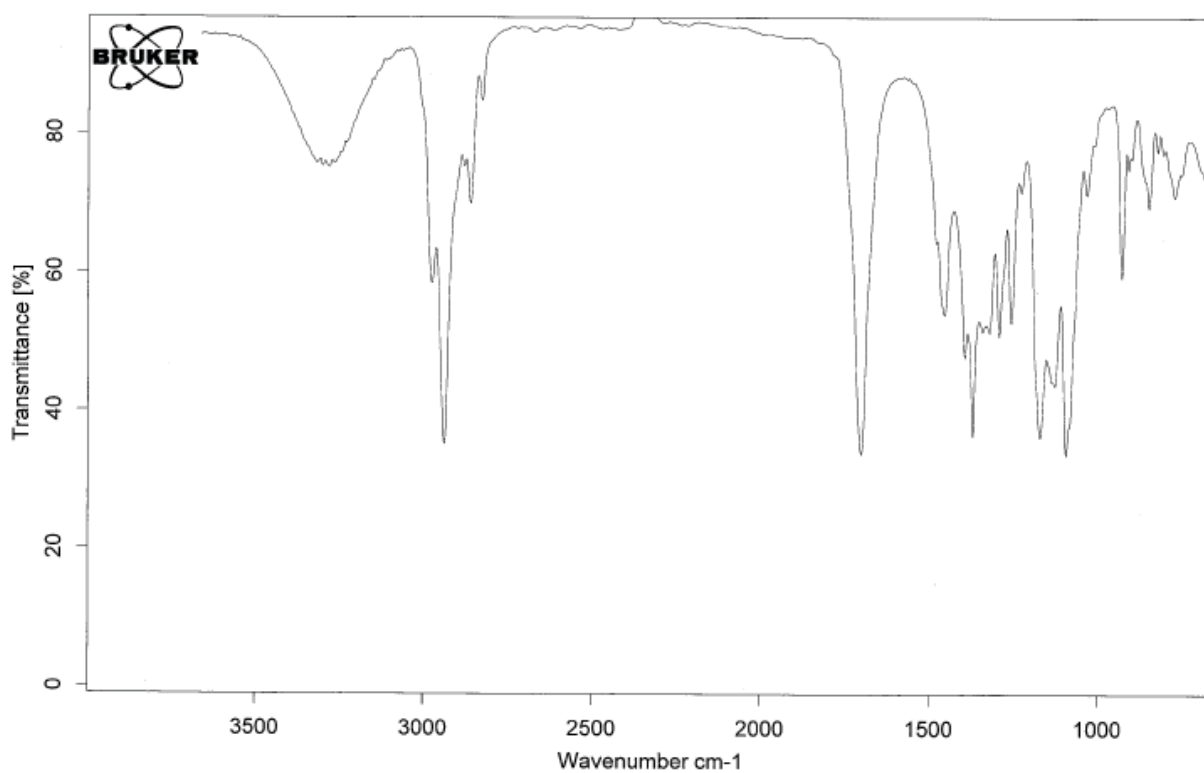


Figure A2.39 Infrared spectrum (thin film) of compound **169**

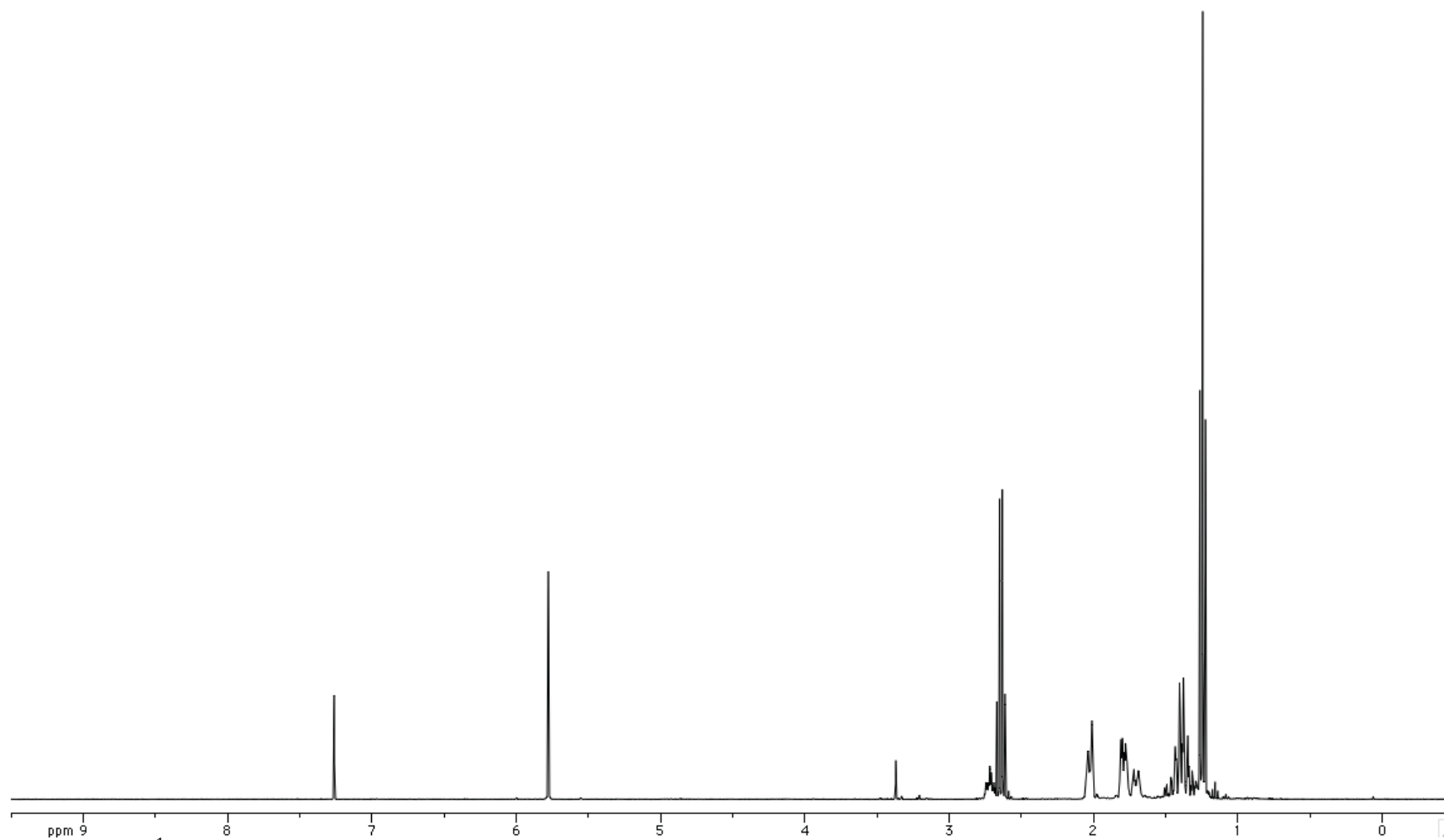
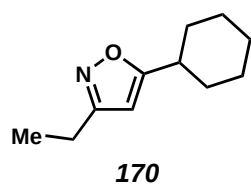


Figure A2.40 ^1H NMR (400 MHz, CDCl_3) of compound **170**

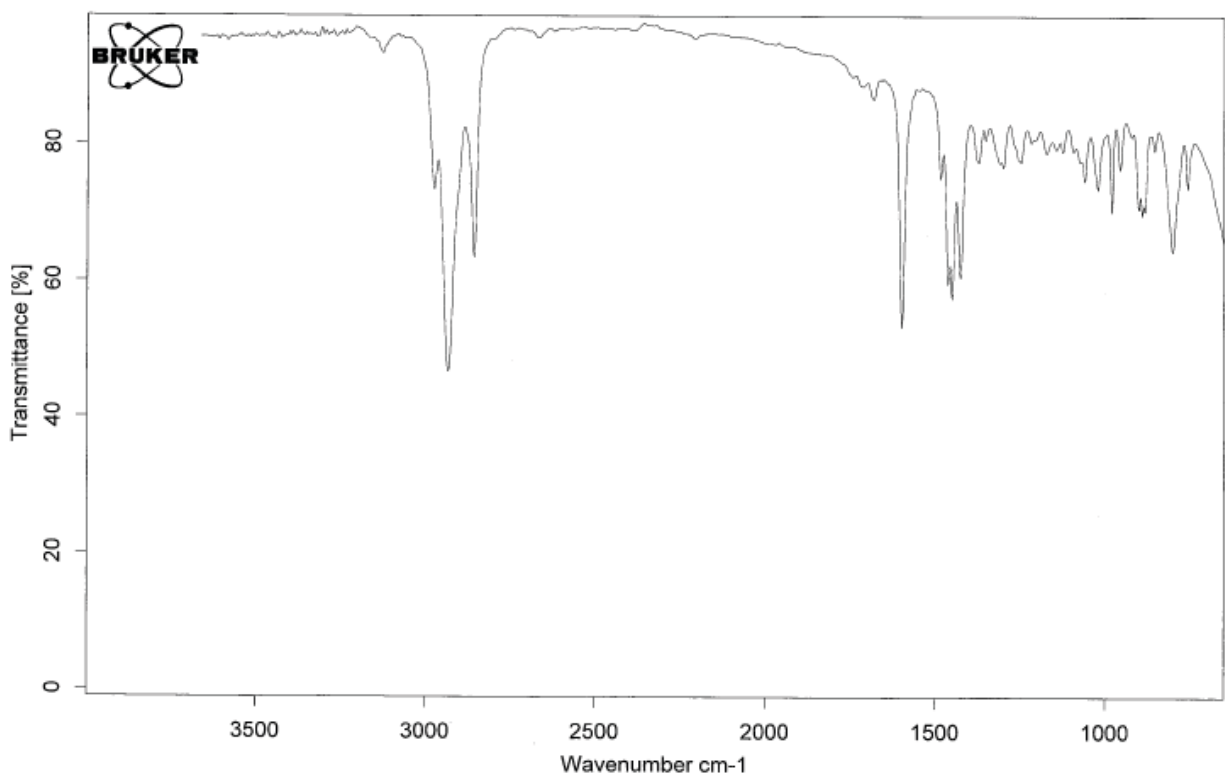
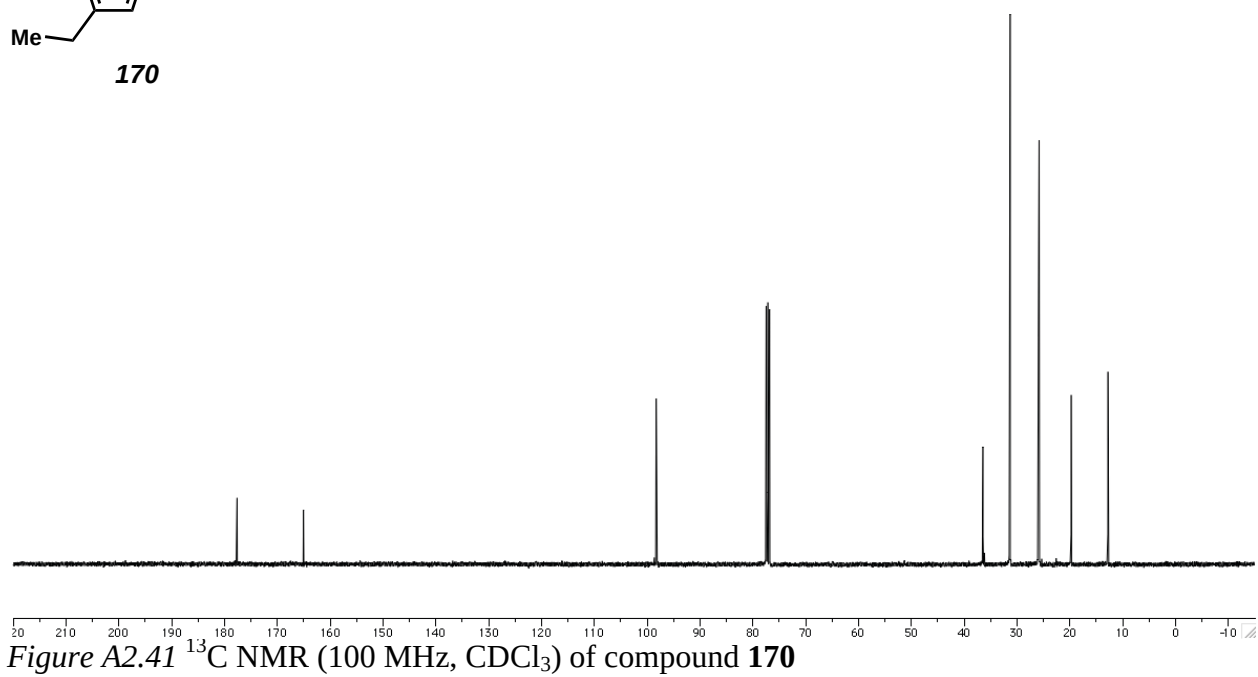
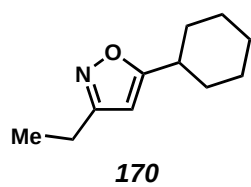


Figure A2.42 Infrared spectrum (thin film) of compound **170**

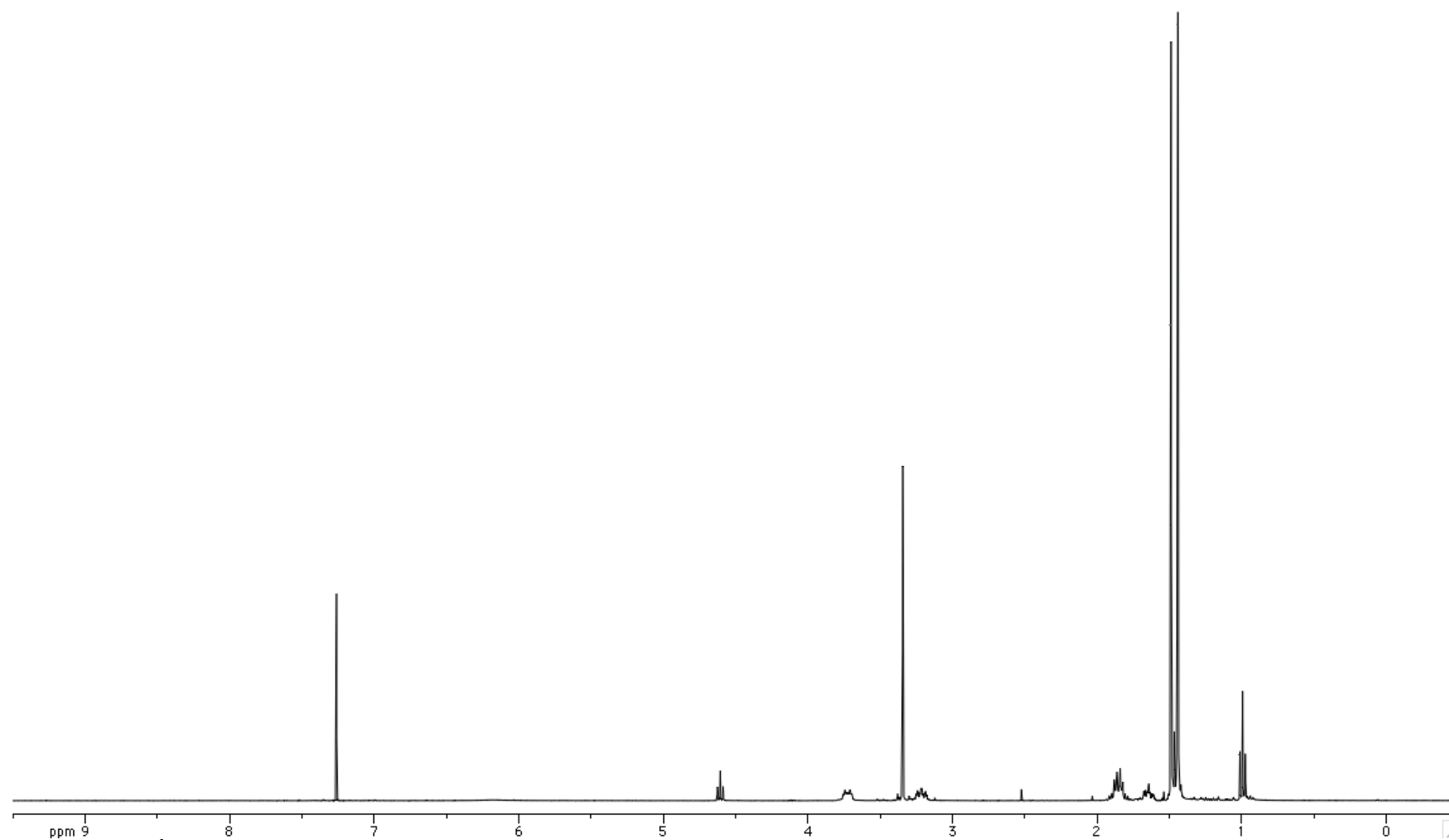
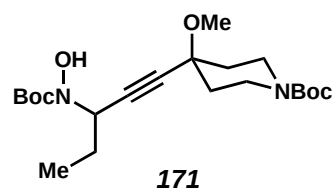


Figure A2.43 ^1H NMR (400 MHz, CDCl_3) of compound **171**

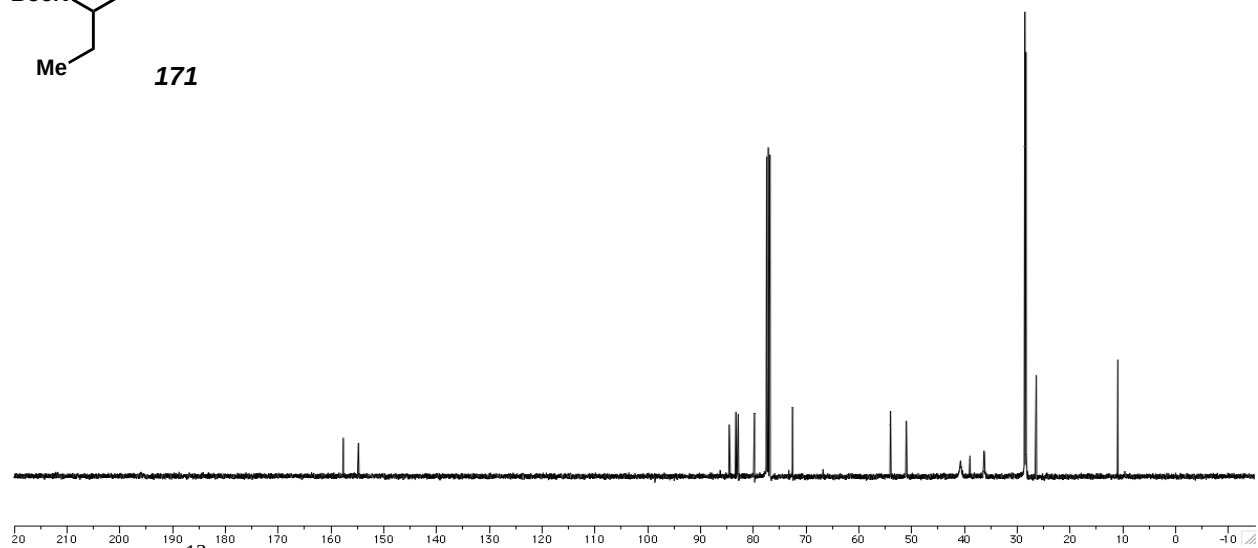
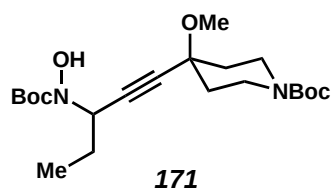


Figure A2.44 ^{13}C NMR (100 MHz, CDCl_3) of compound **171**

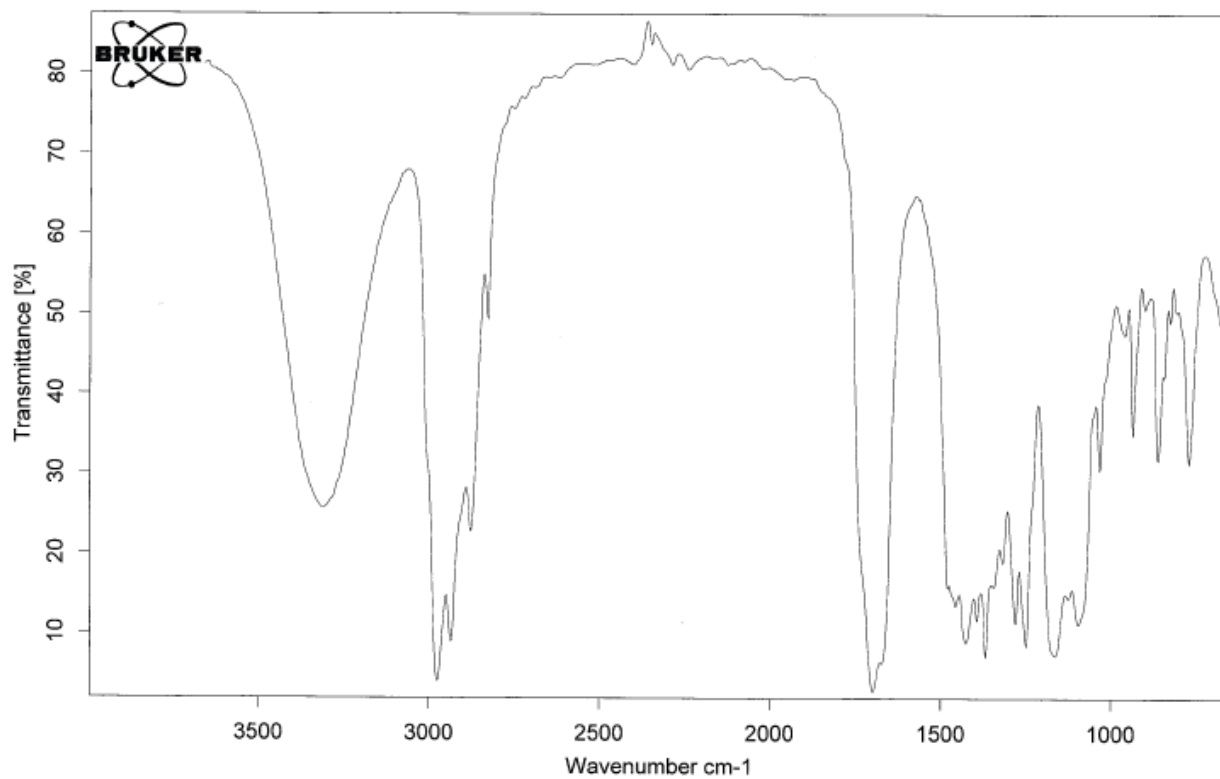


Figure A2.45 Infrared spectrum (thin film) of compound **171**

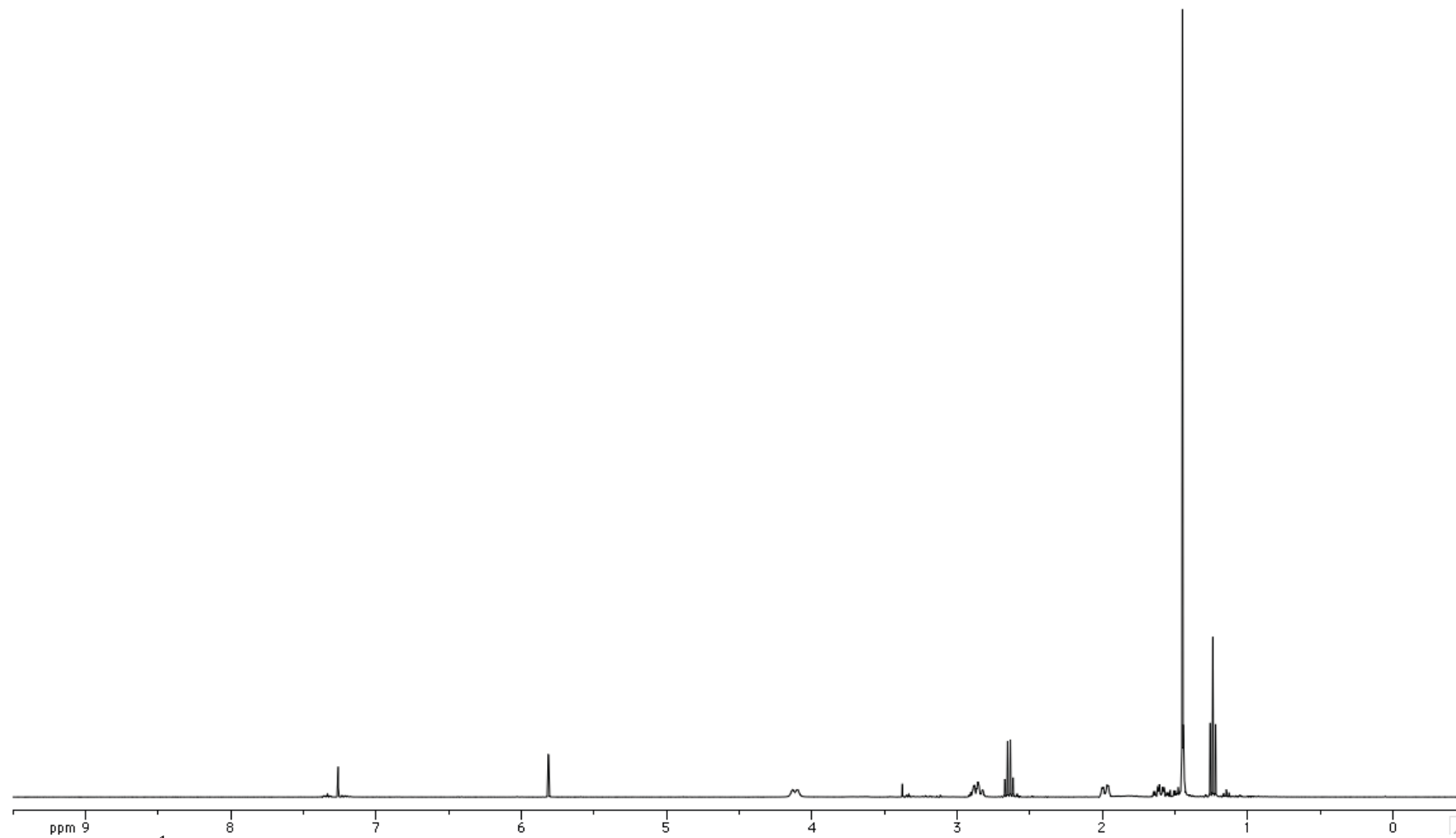
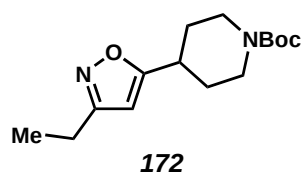
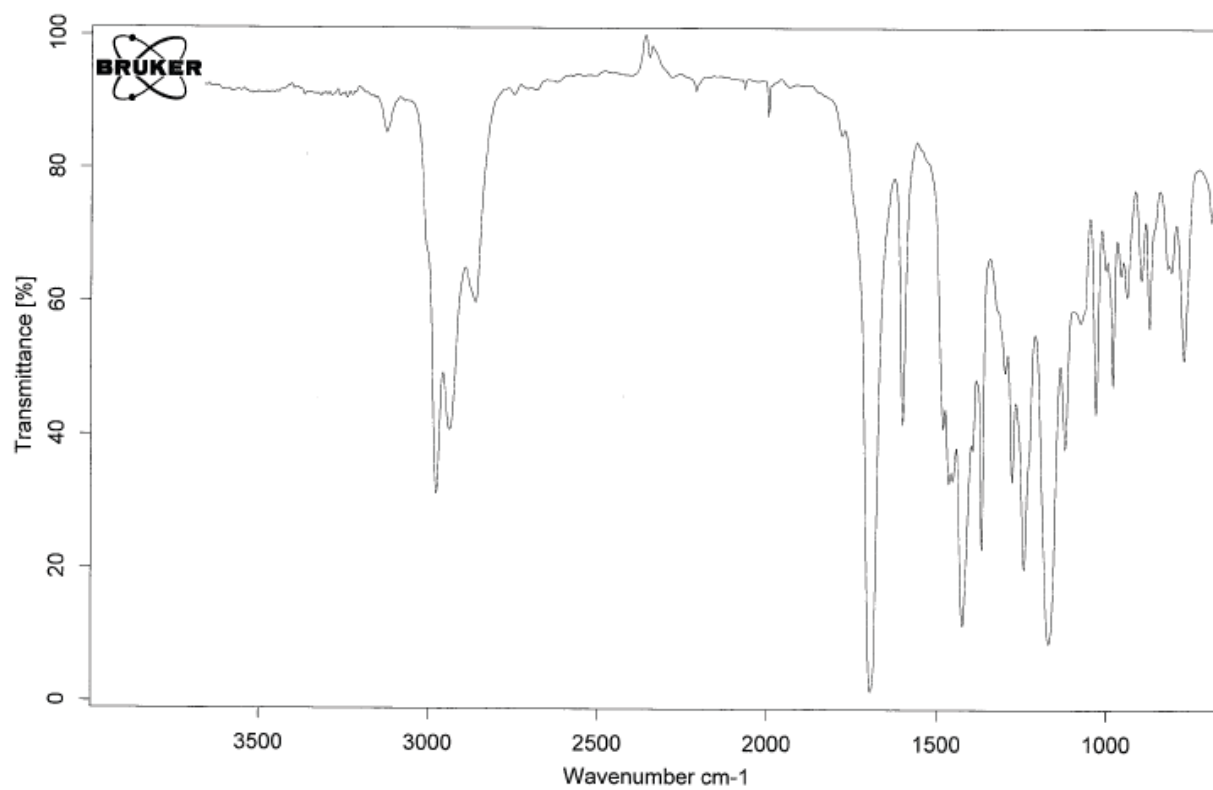
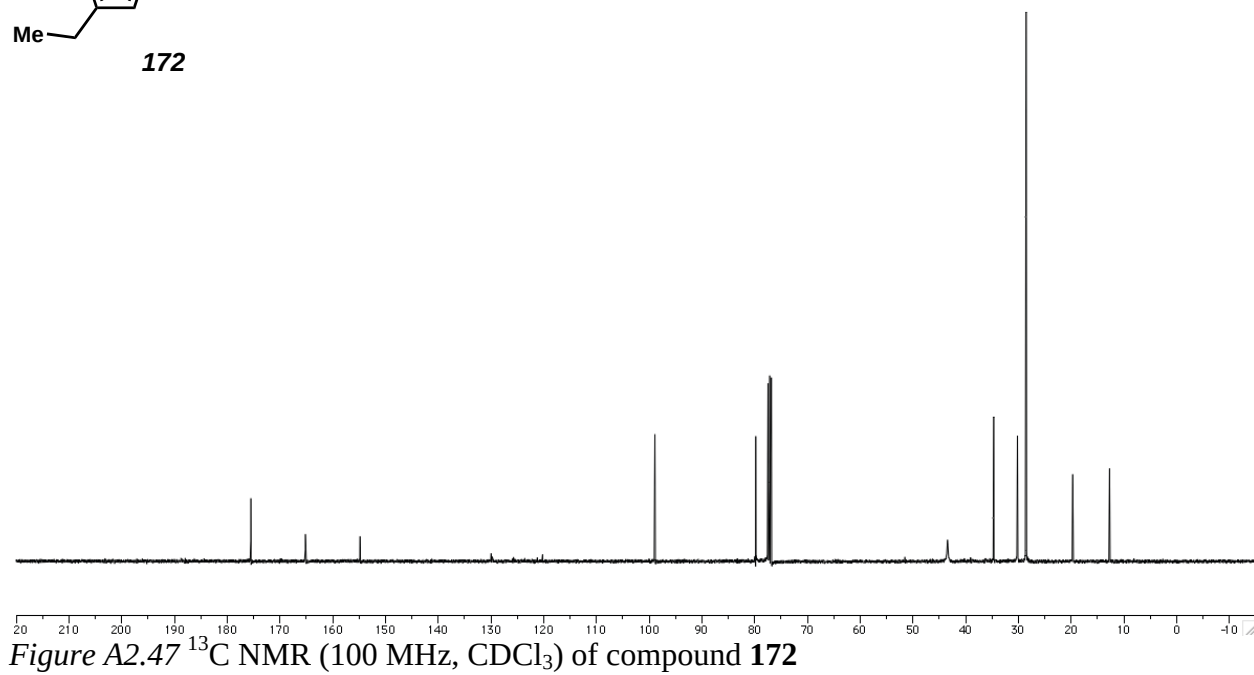
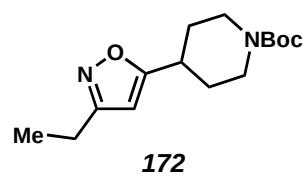


Figure A2.46 ^1H NMR (400 MHz, CDCl_3) of compound **172**



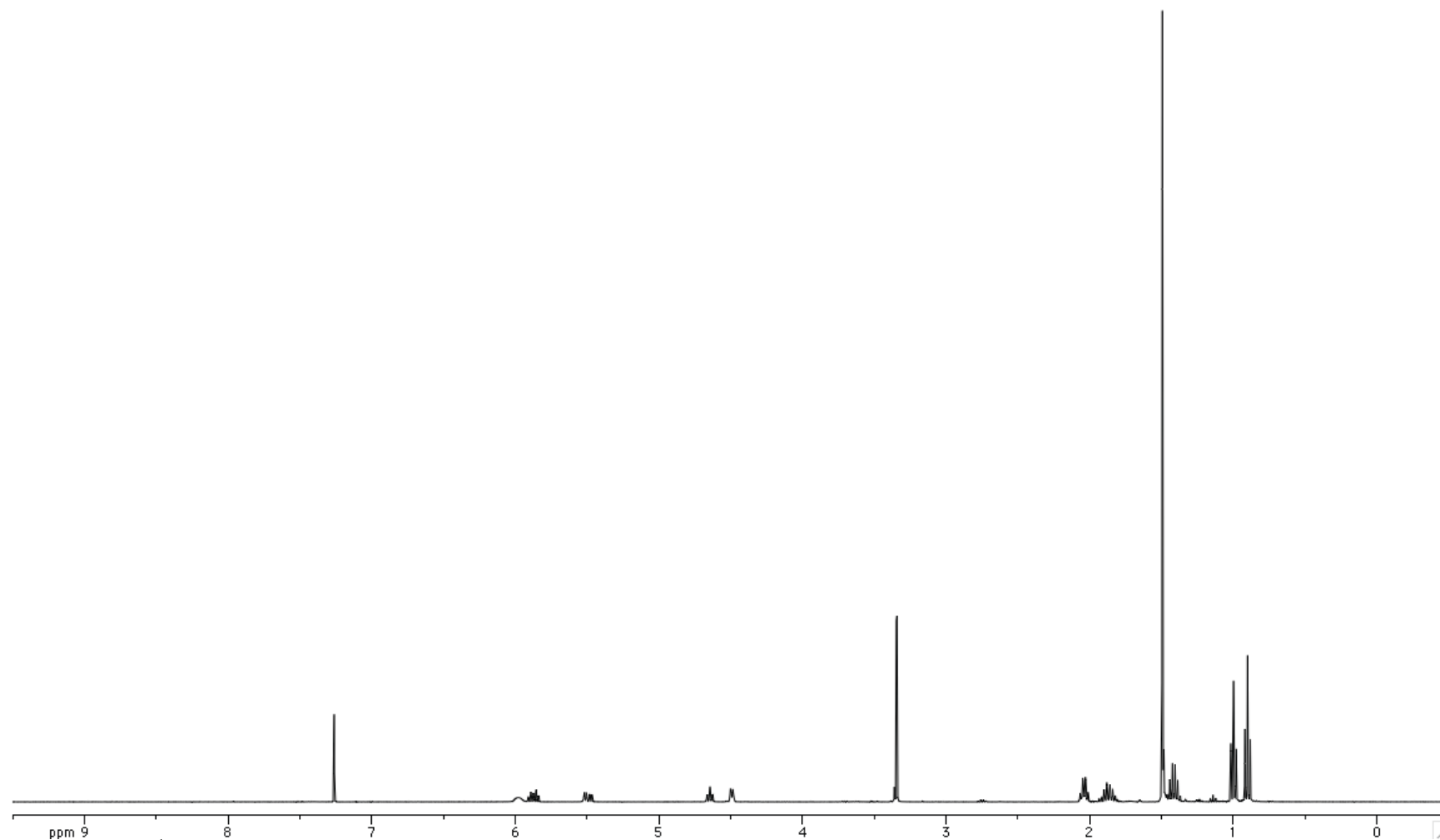
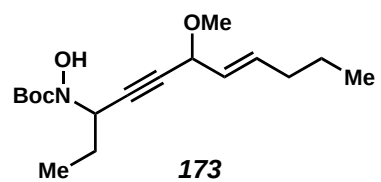


Figure A2.49 ^1H NMR (400 MHz, CDCl_3) of compound **173**

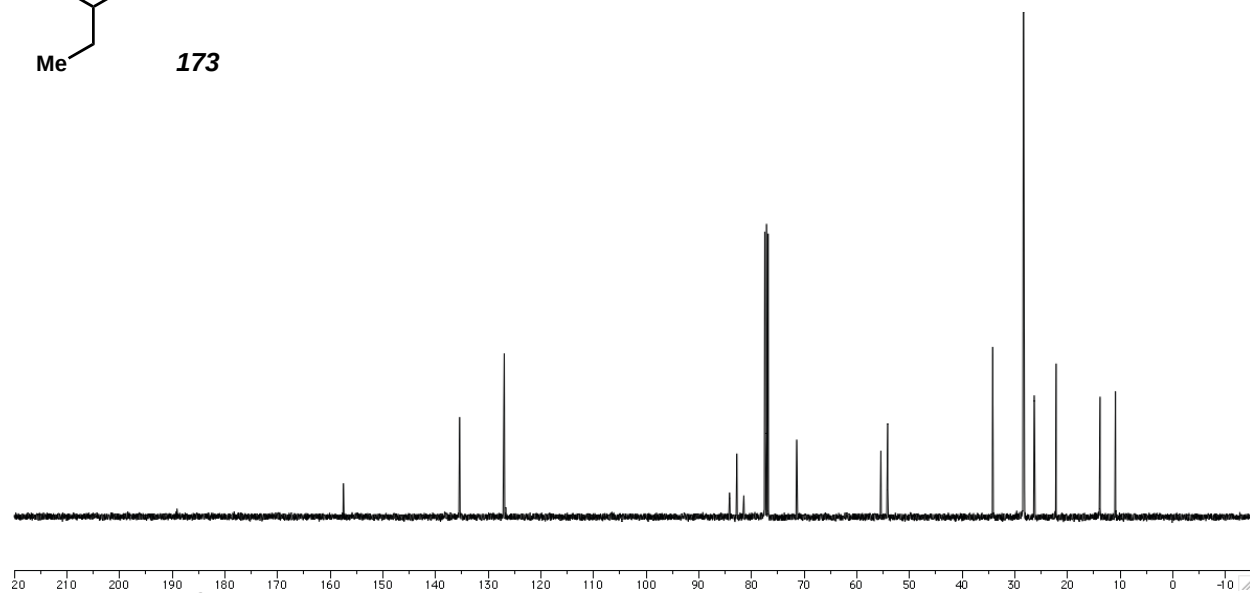
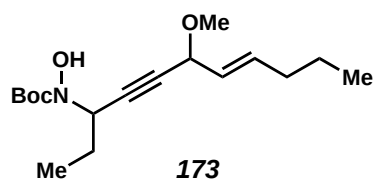


Figure A2.50 ^{13}C NMR (100 MHz, CDCl_3) of compound **173**

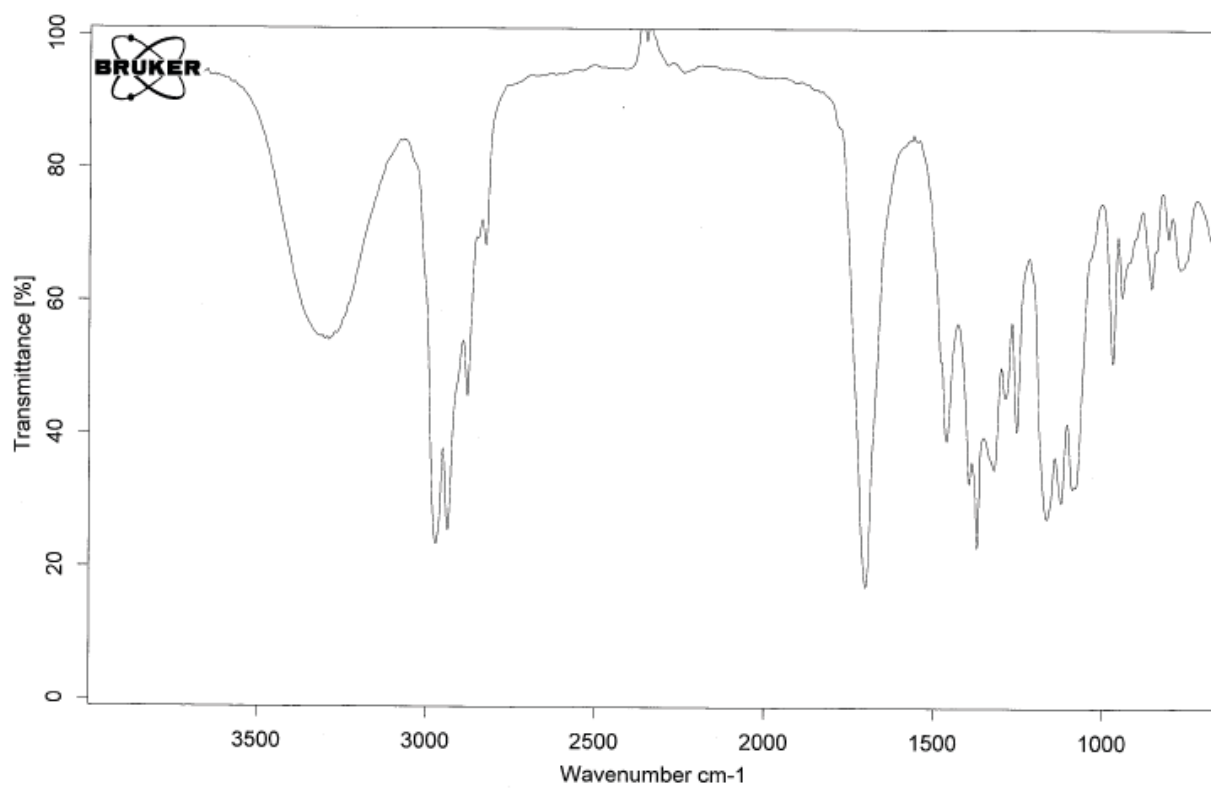


Figure A2.51 Infrared spectrum (thin film) of compound **173**

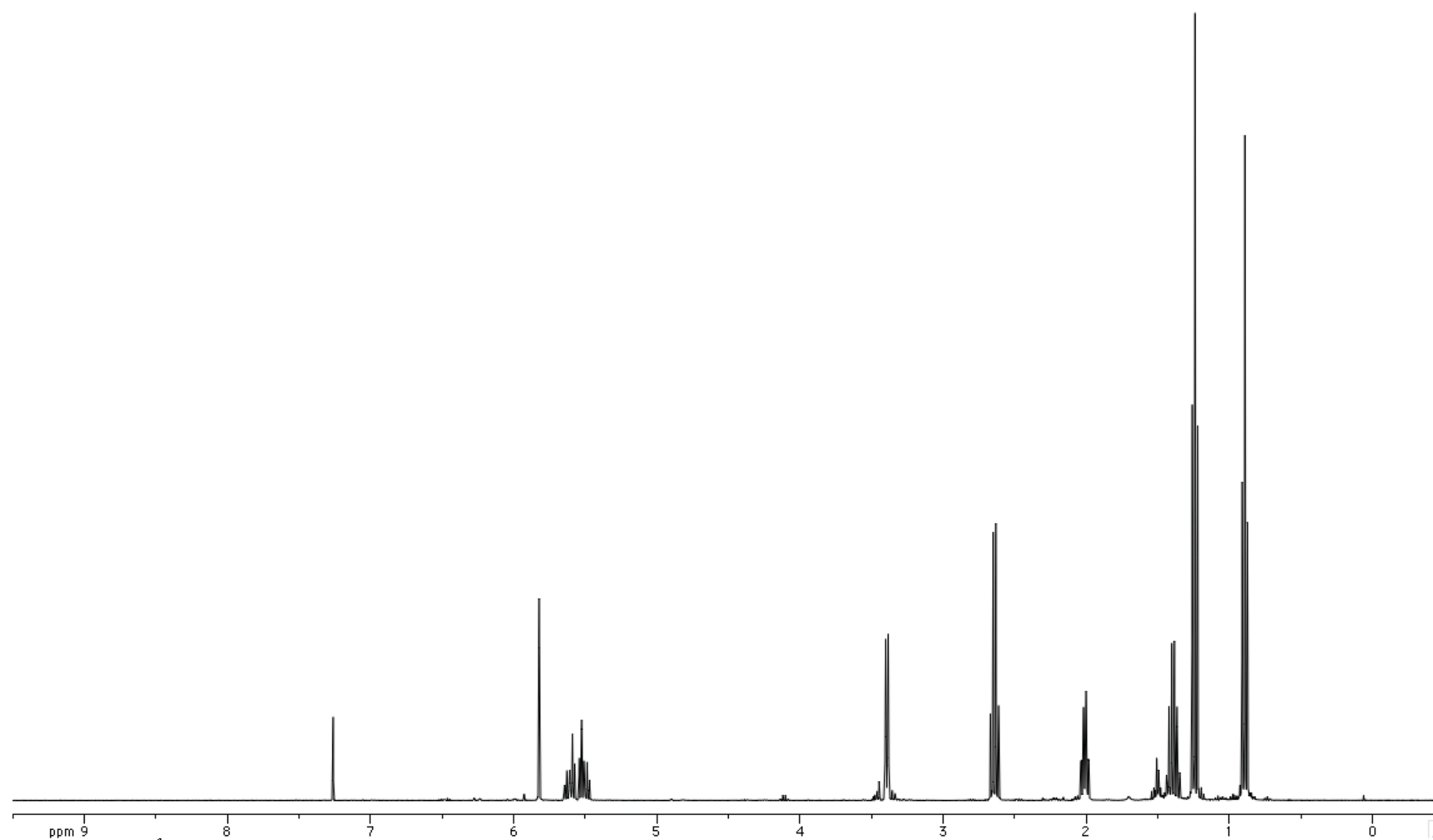
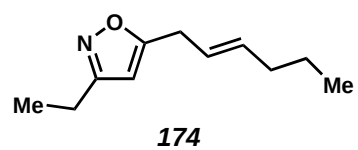
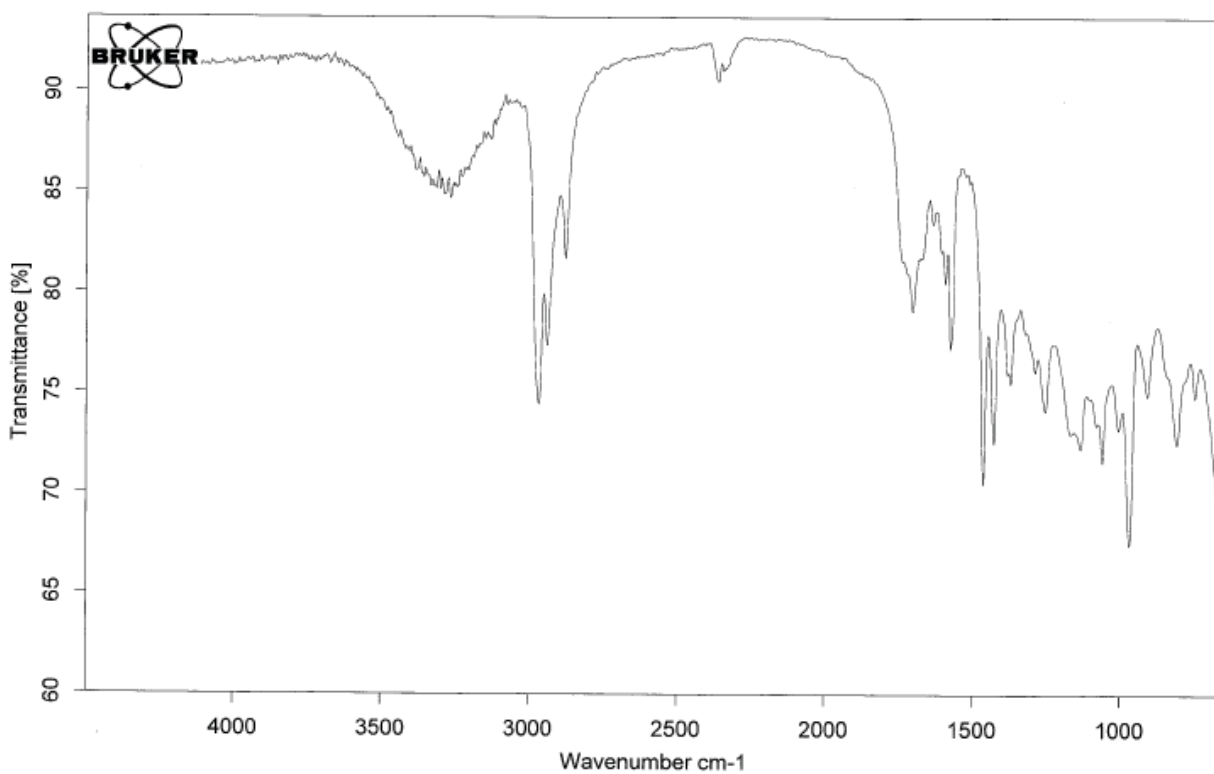
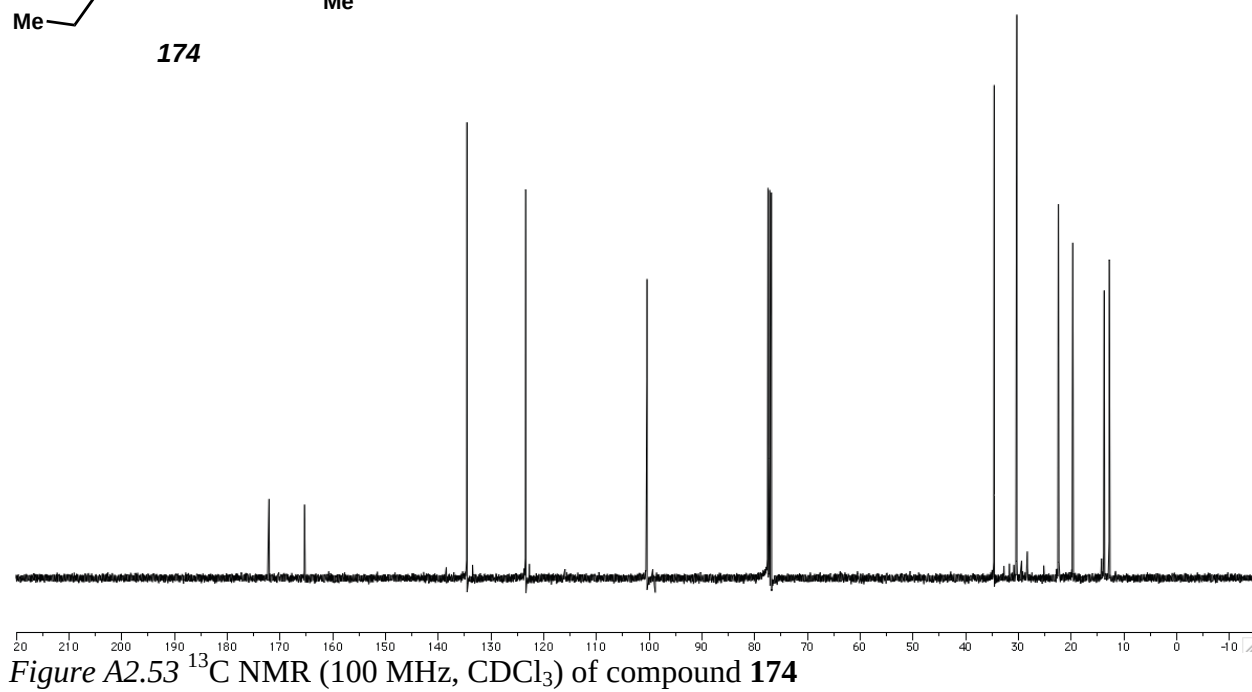
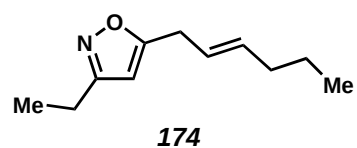


Figure A2.52 ^1H NMR (400 MHz, CDCl_3) of compound **174**



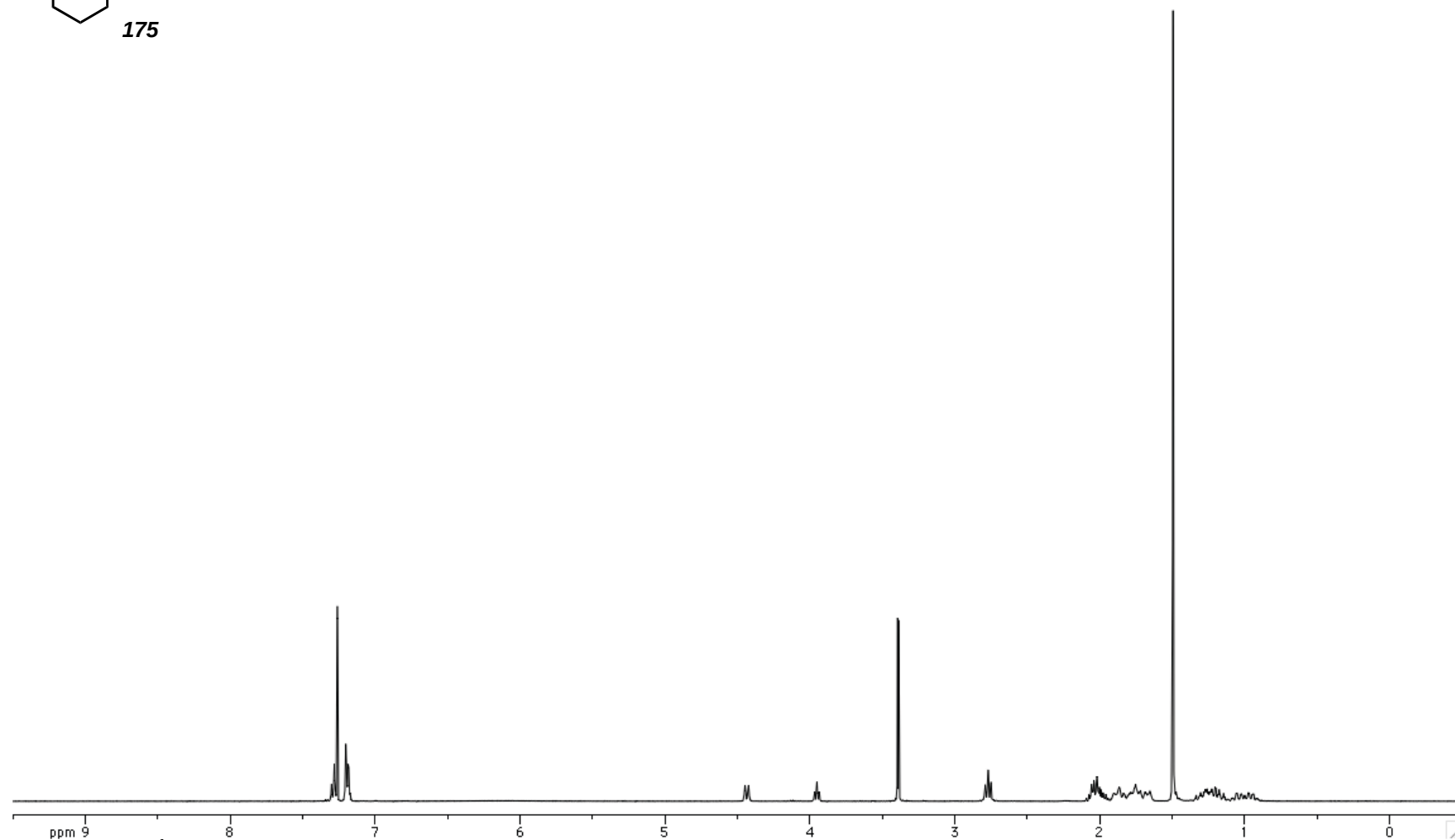
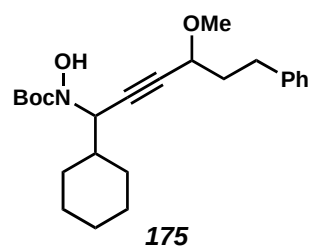
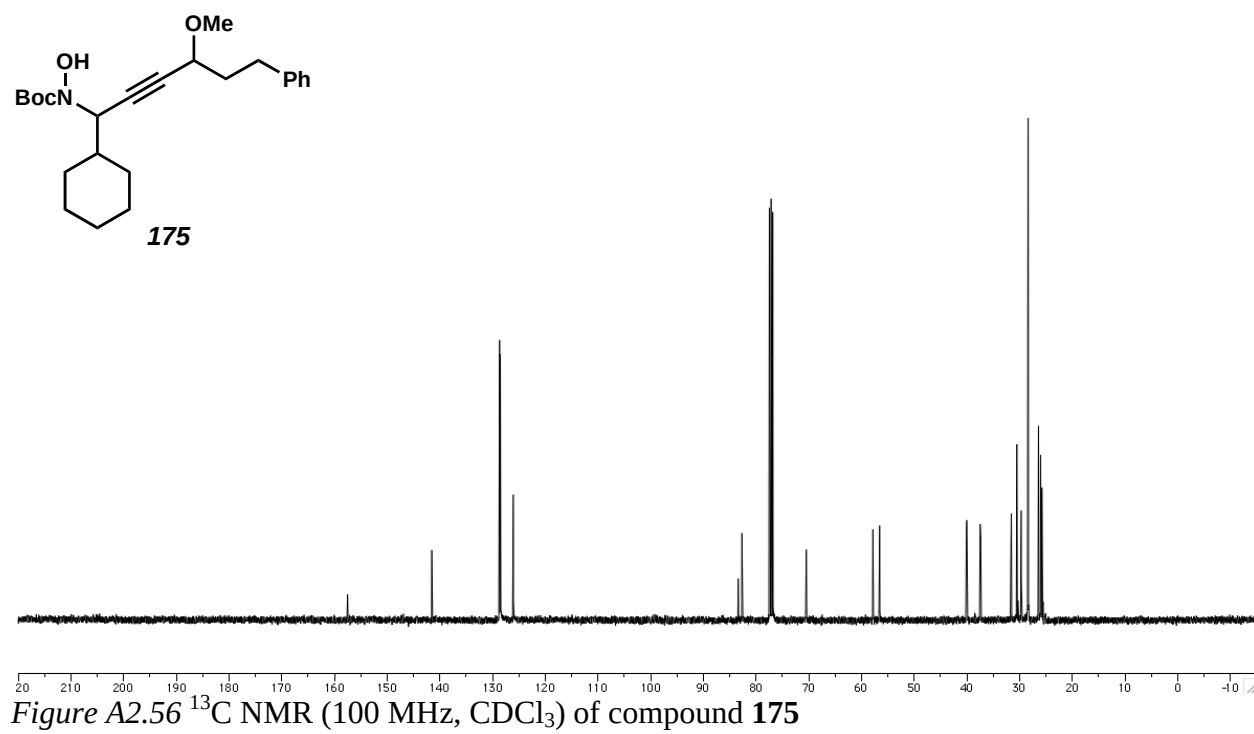


Figure A2.55 ^1H NMR (400 MHz, CDCl_3) of compound **175**



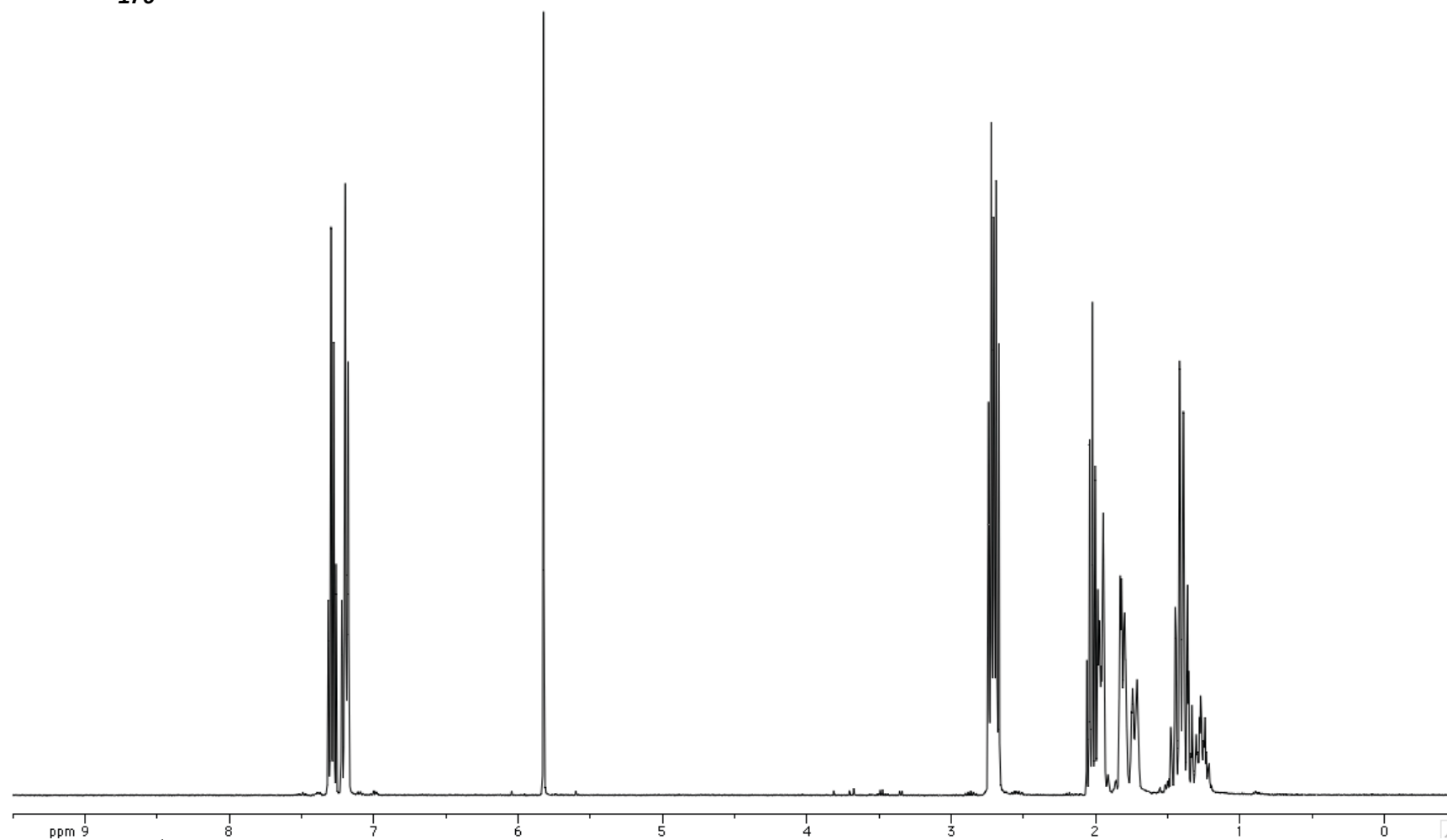
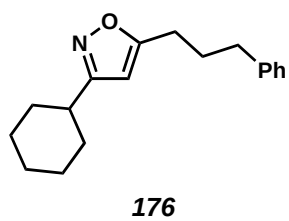
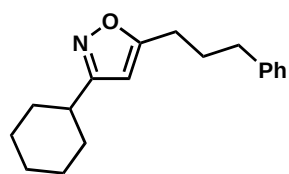


Figure A2.57 ^1H NMR (400 MHz, CDCl_3) of compound **176**



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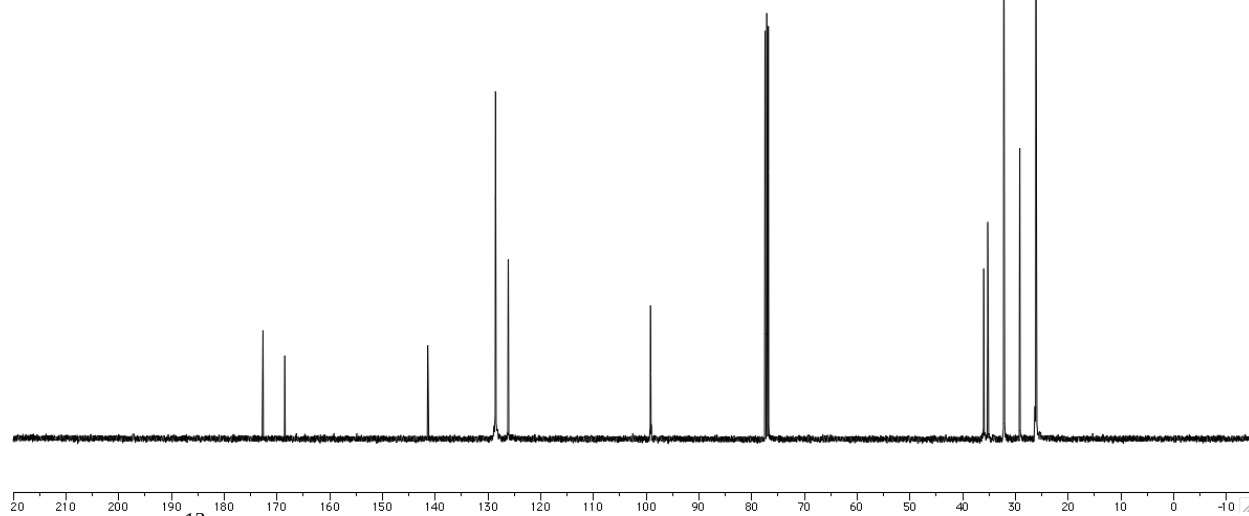


Figure A2.58 ^{13}C NMR (100 MHz, CDCl_3) of compound **176**

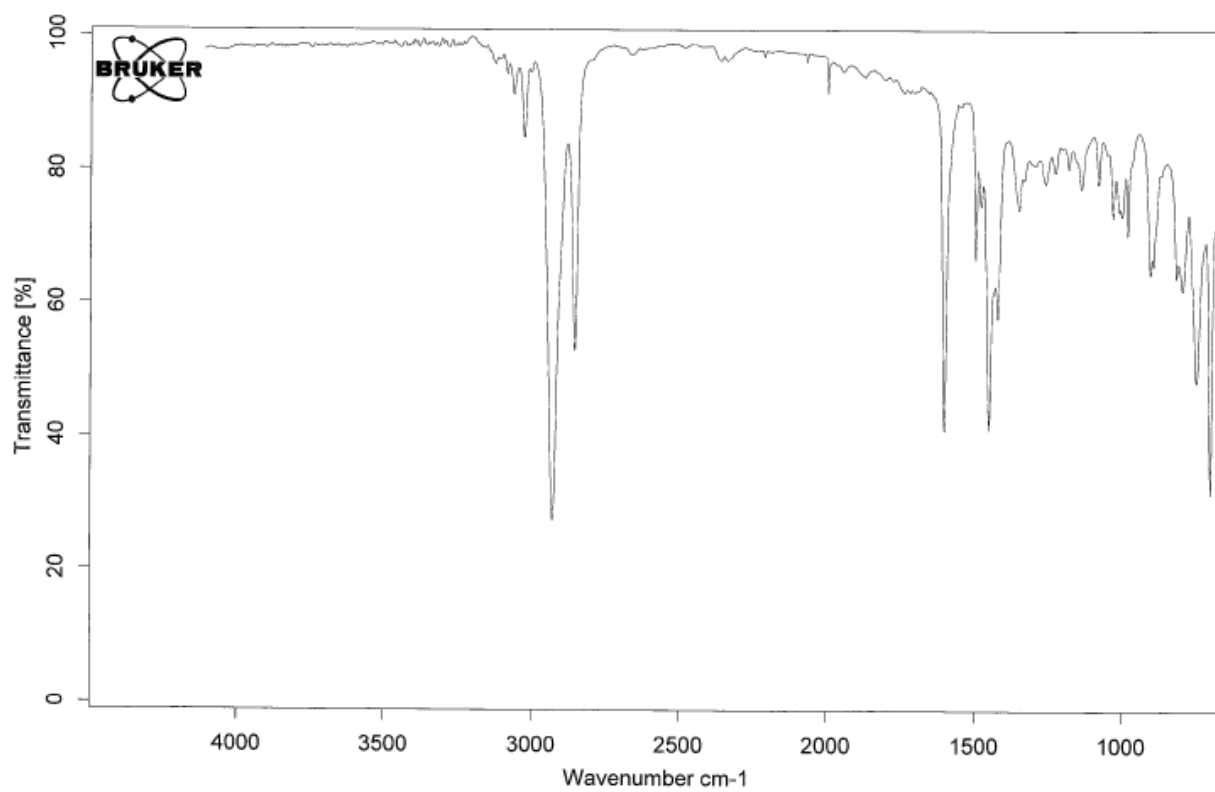


Figure A2.59 Infrared spectrum (thin film) of compound **176**

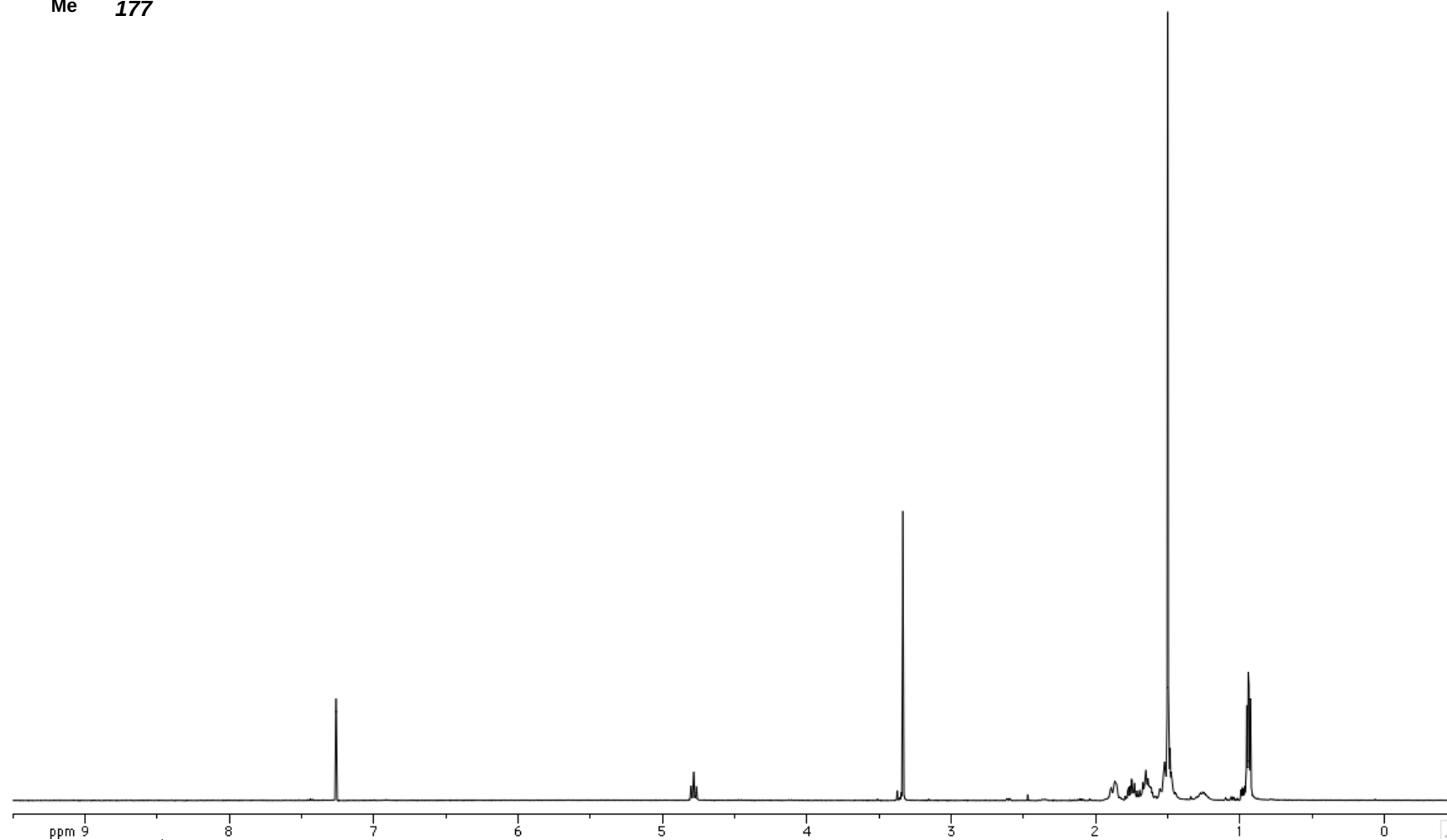
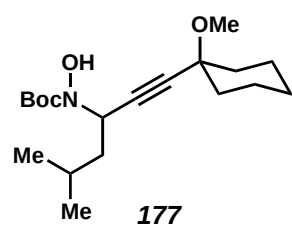


Figure A2.60 ^1H NMR (400 MHz, CDCl_3) of compound **177**

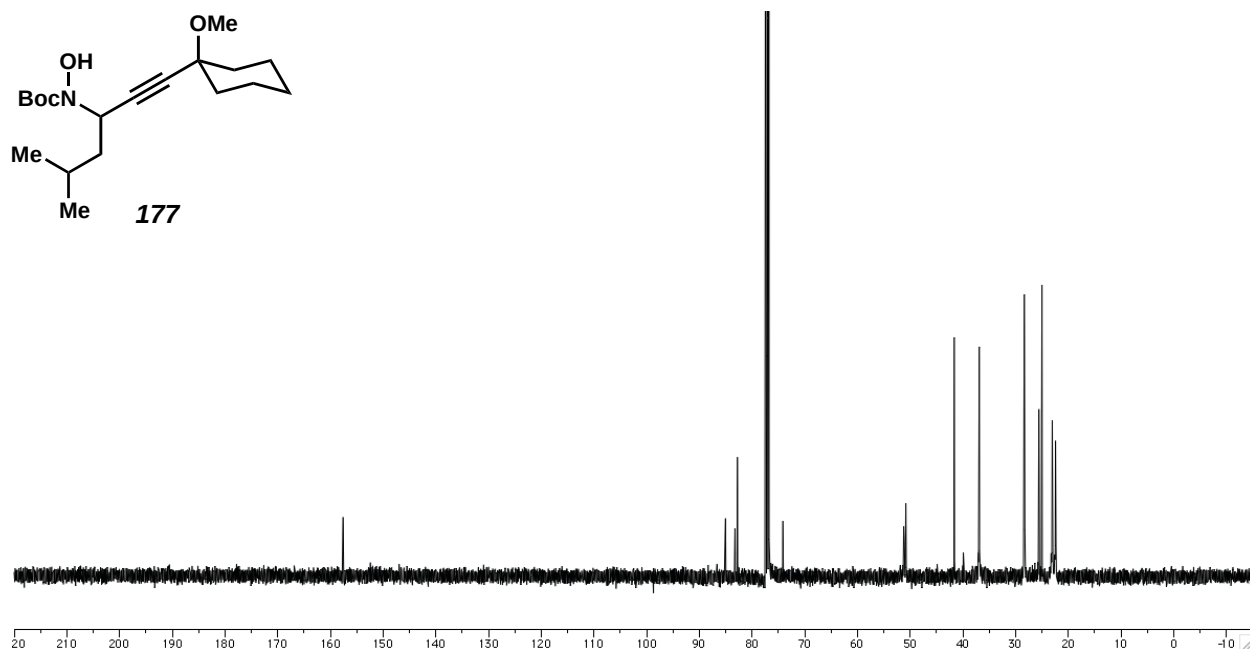


Figure A2.61 ^{13}C NMR (100 MHz, CDCl_3) of compound **177**

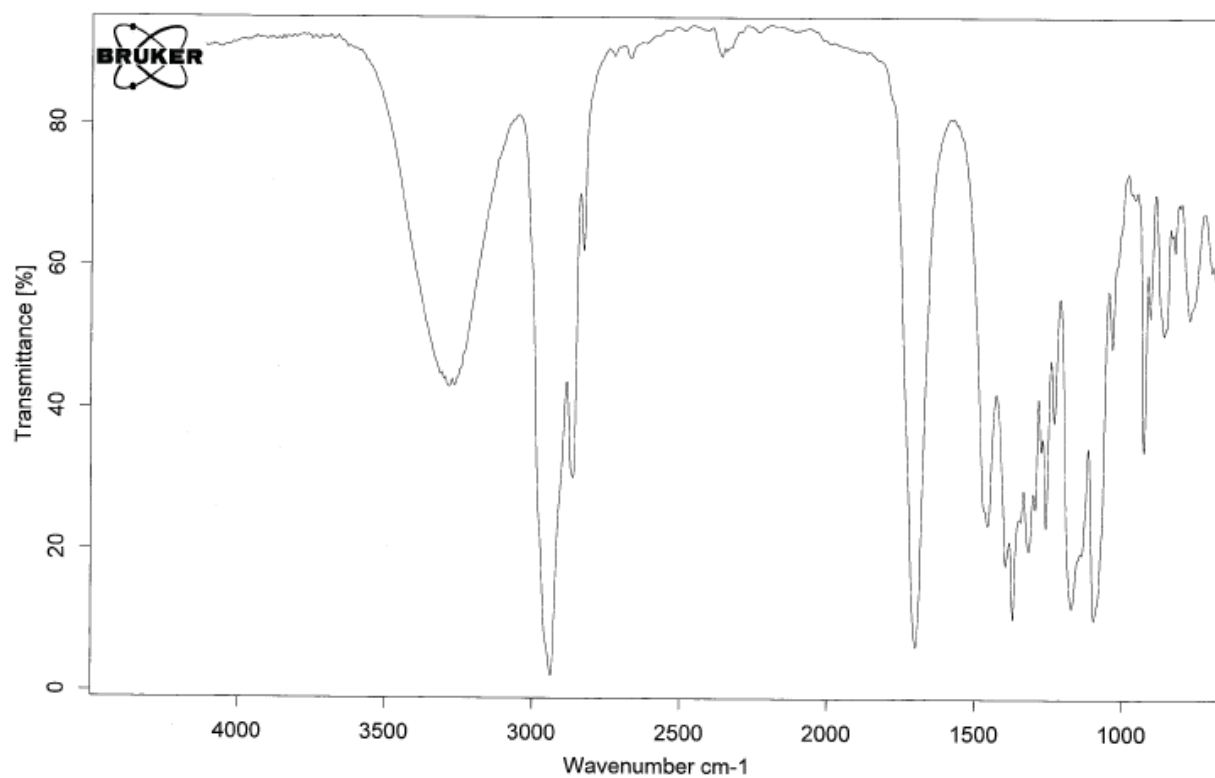


Figure A2.62 Infrared spectrum (thin film) of compound **177**

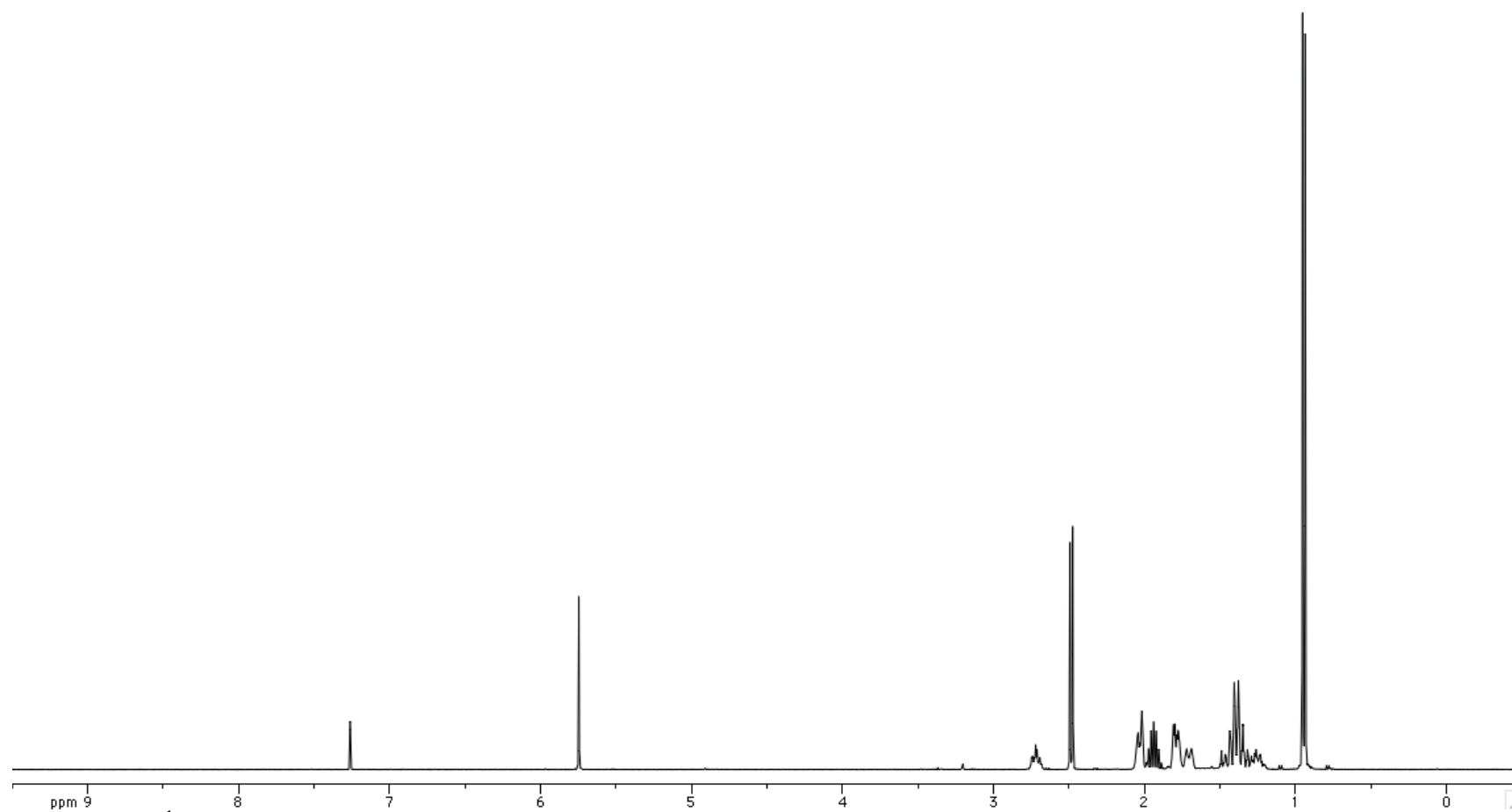
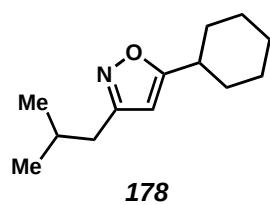


Figure A2.63 ^1H NMR (400 MHz, CDCl_3) of compound **178**

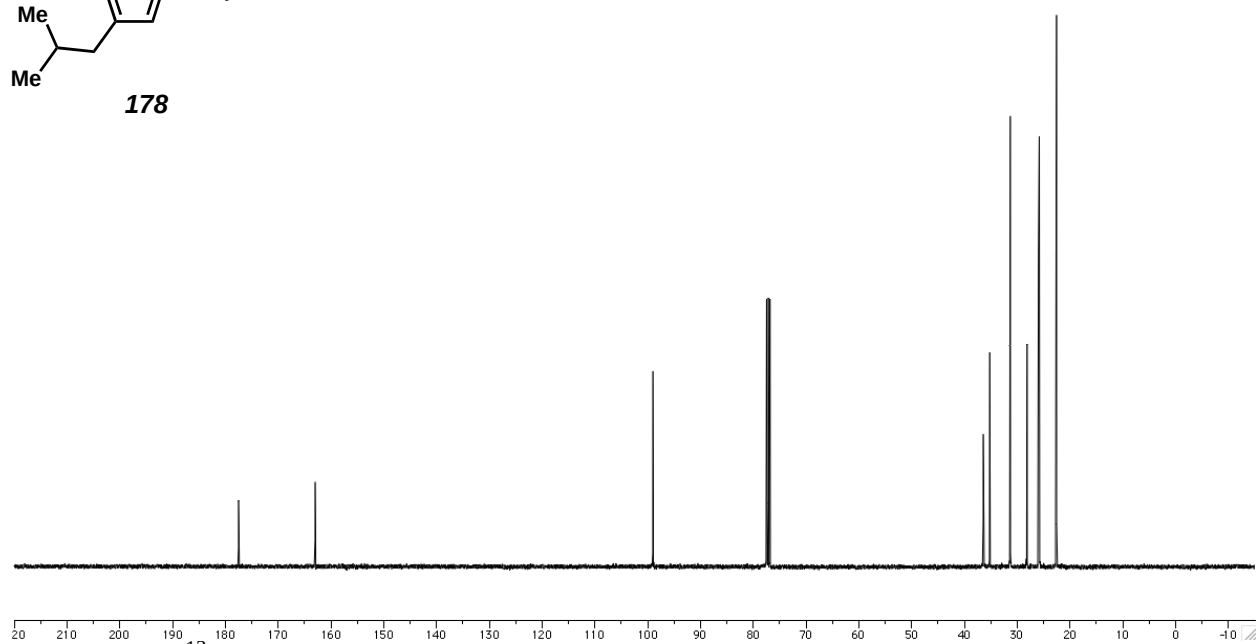
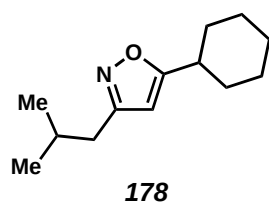


Figure A2.64 ^{13}C NMR (100 MHz, CDCl_3) of compound **178**

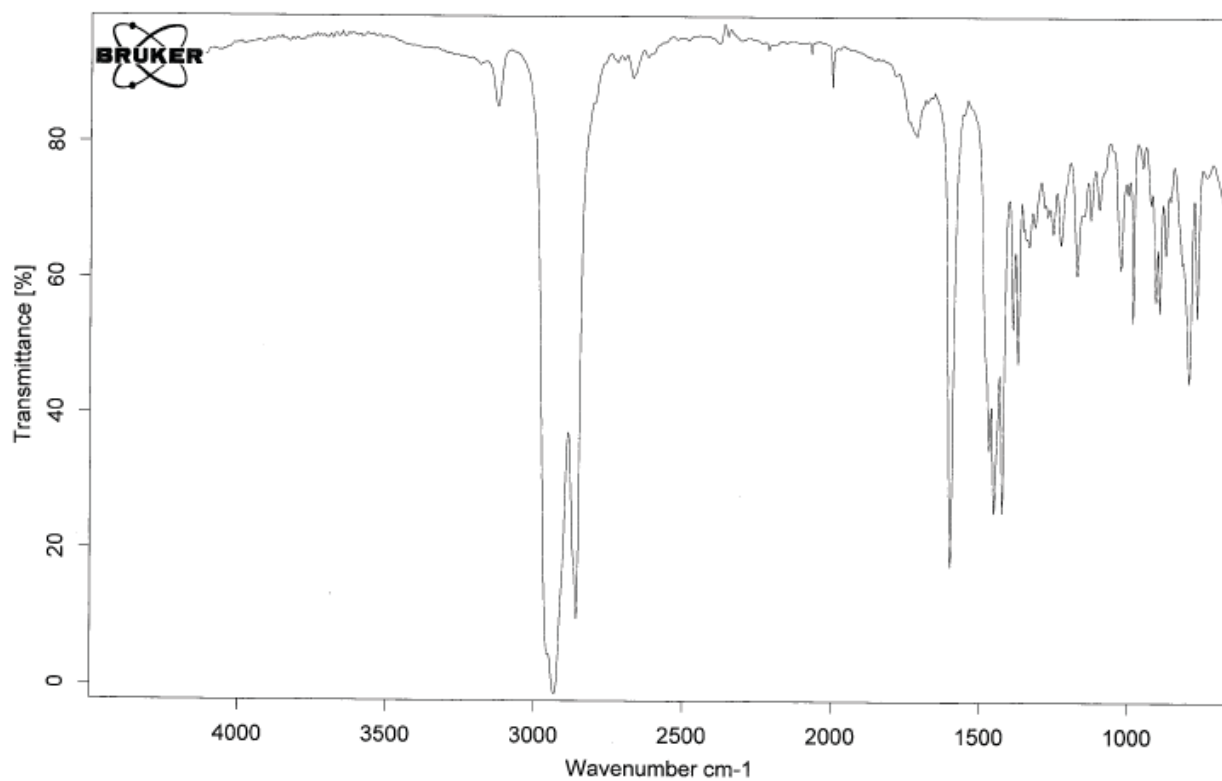
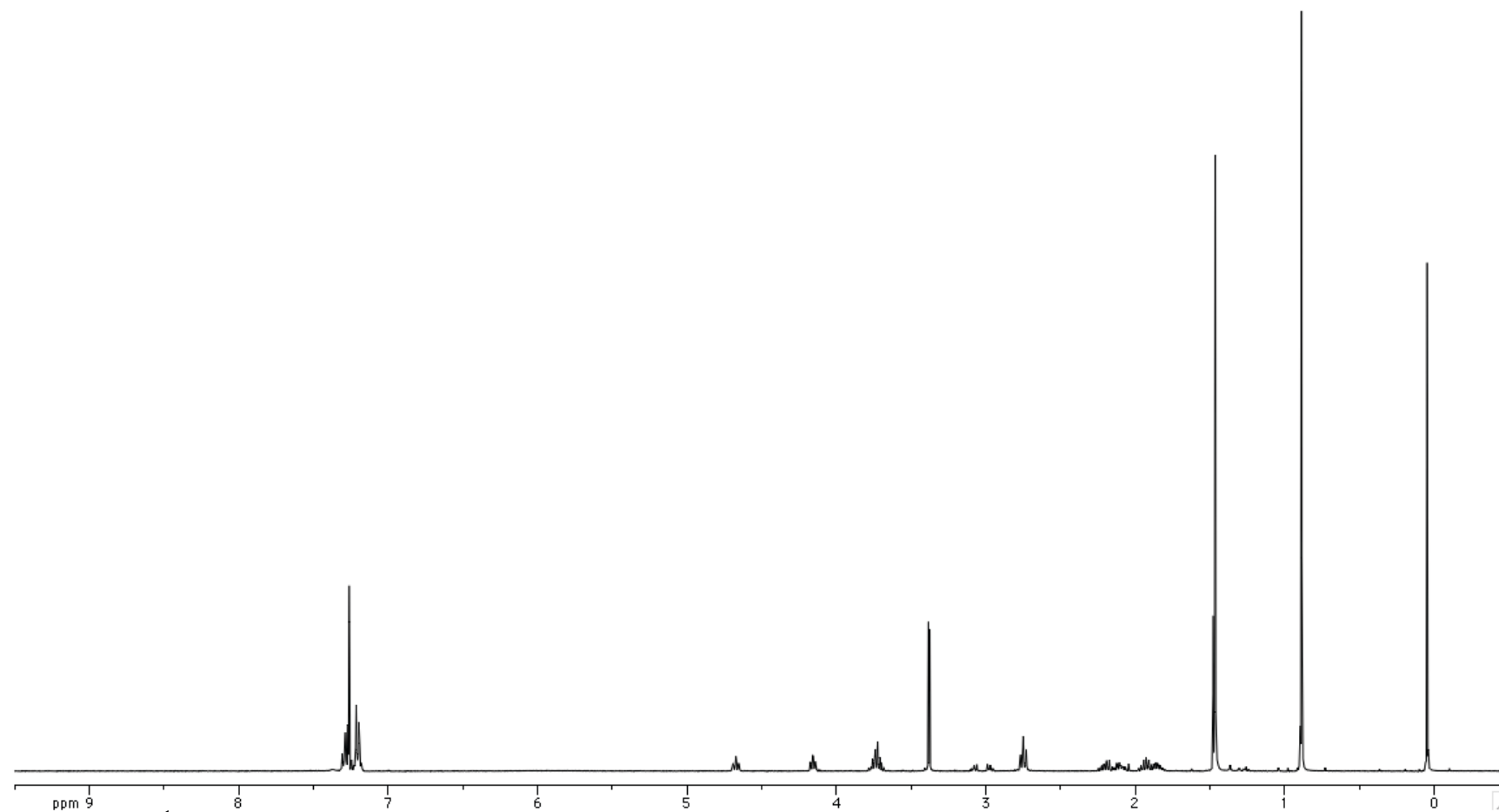


Figure A2.65 Infrared spectrum (thin film) of compound **178**



499

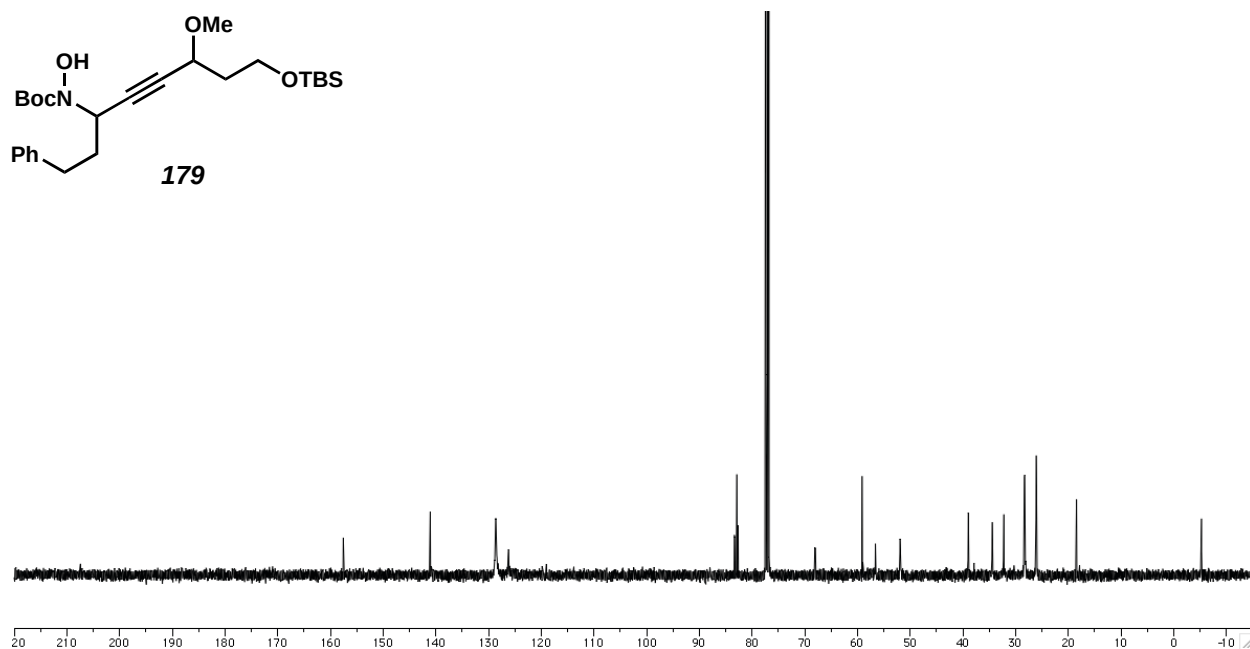


Figure A2.67 ¹³C NMR (100 MHz, CDCl₃) of compound **179**

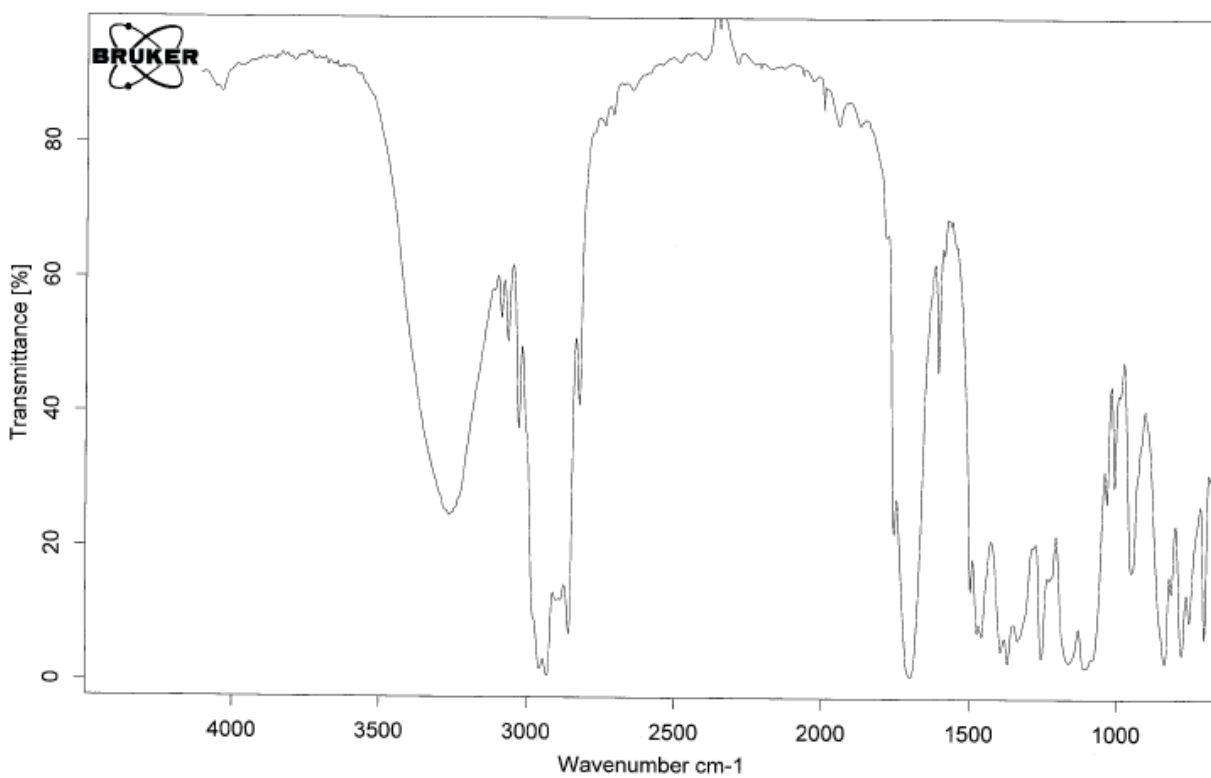


Figure A2.68 Infrared spectrum (thin film) of compound **179**

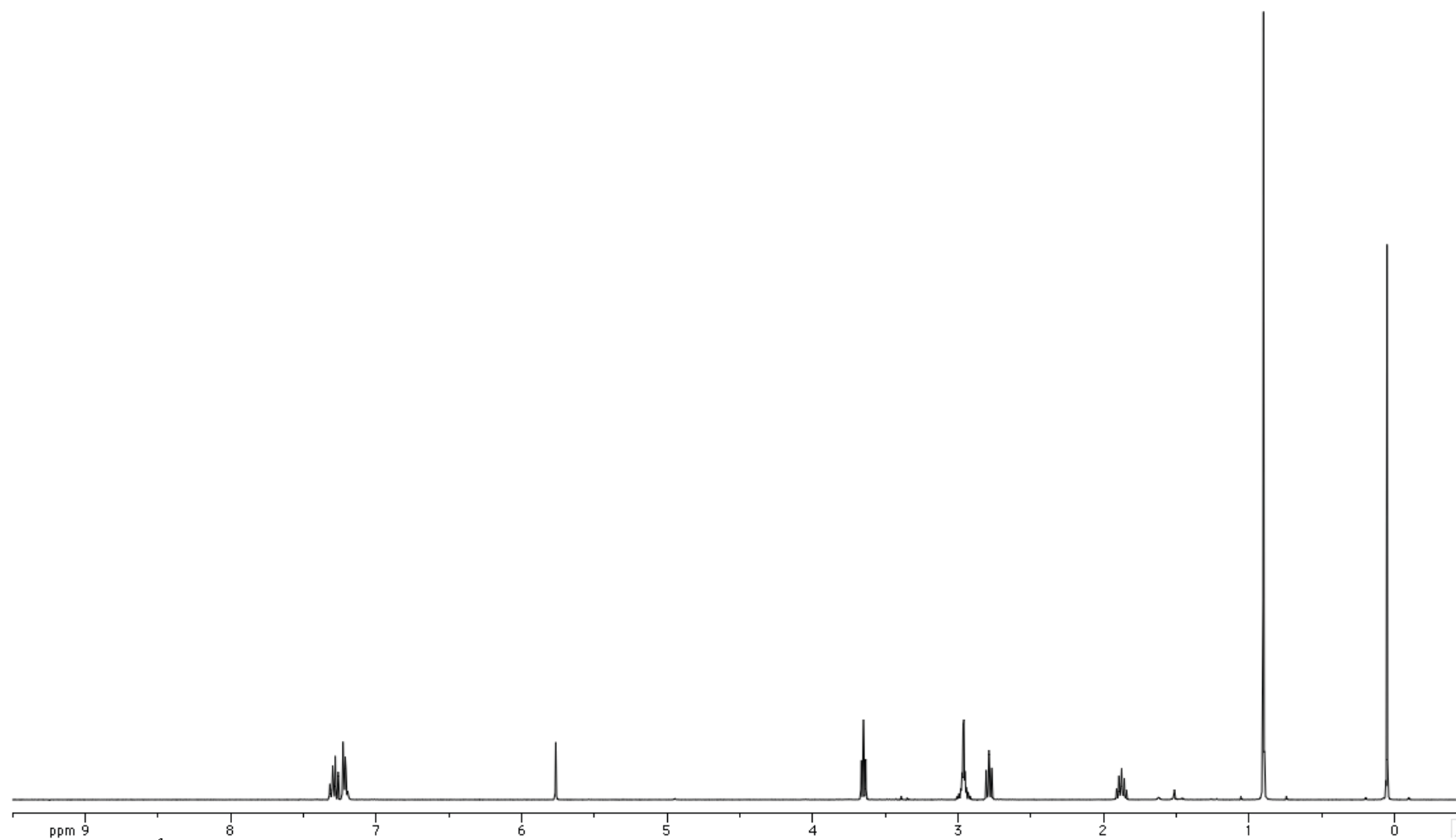
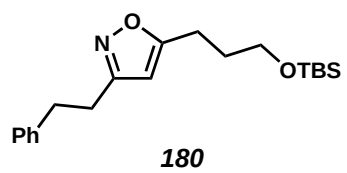
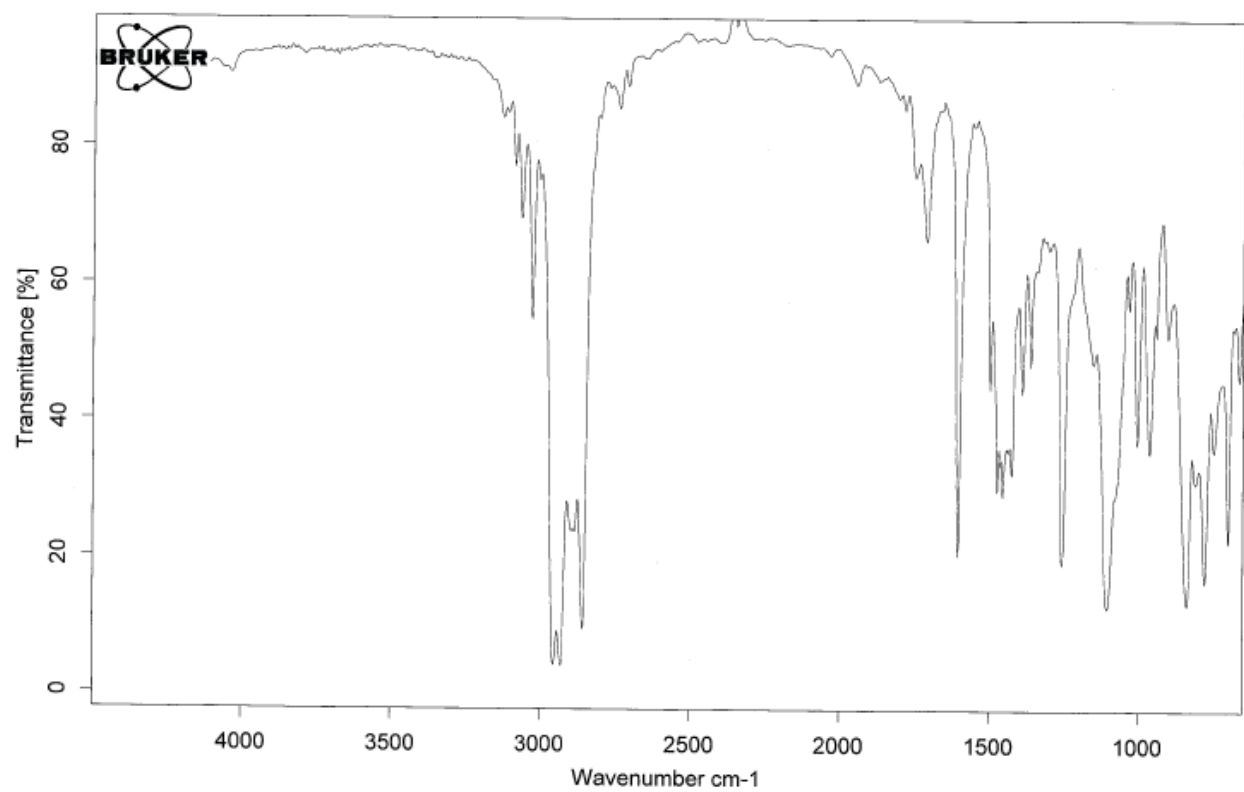
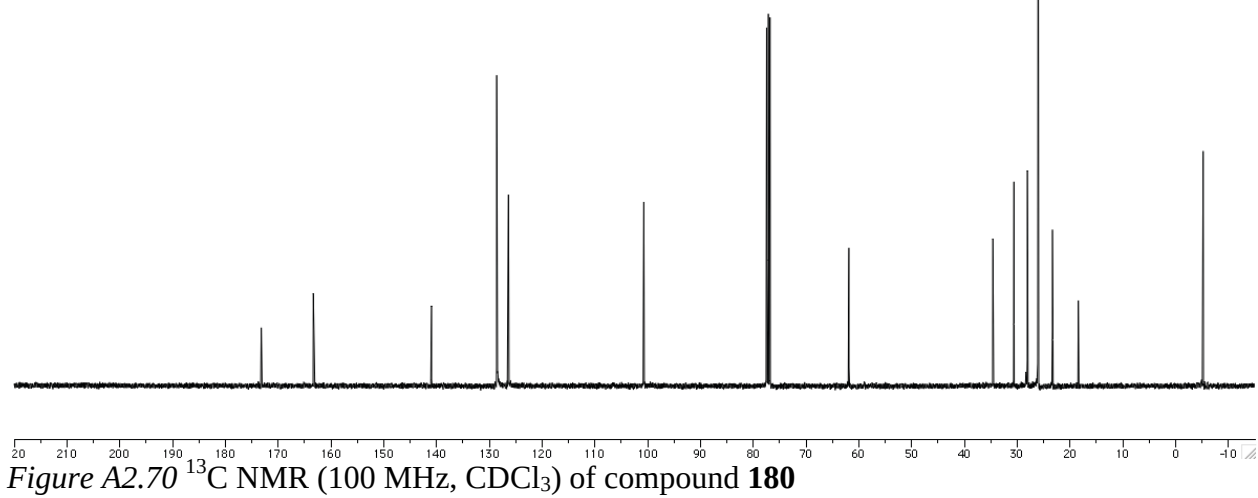
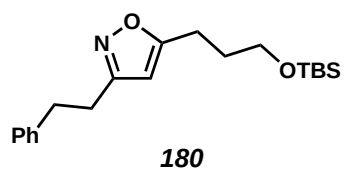


Figure A2.69 ^1H NMR (400 MHz, CDCl_3) of compound **180**



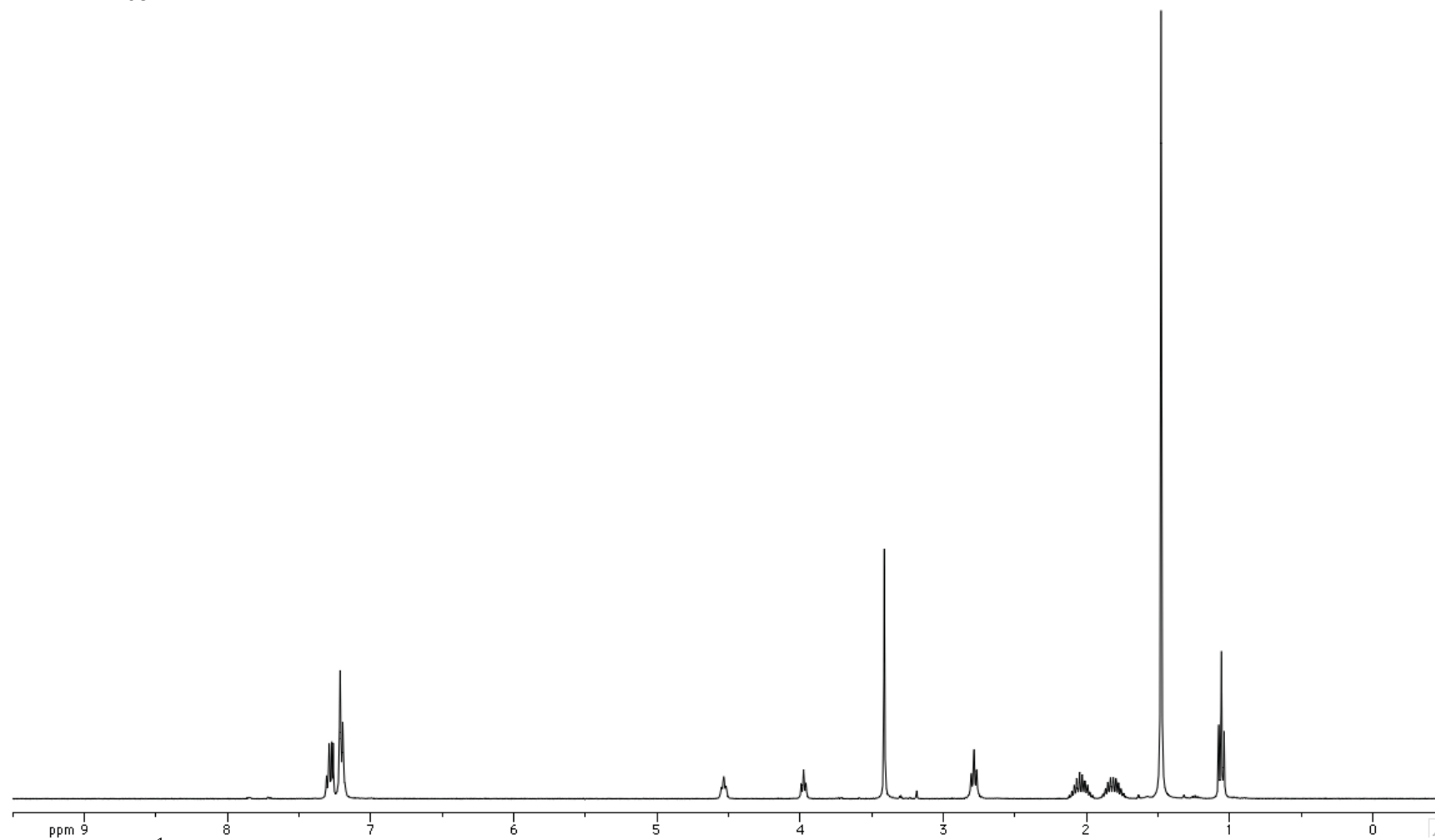
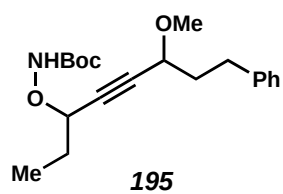
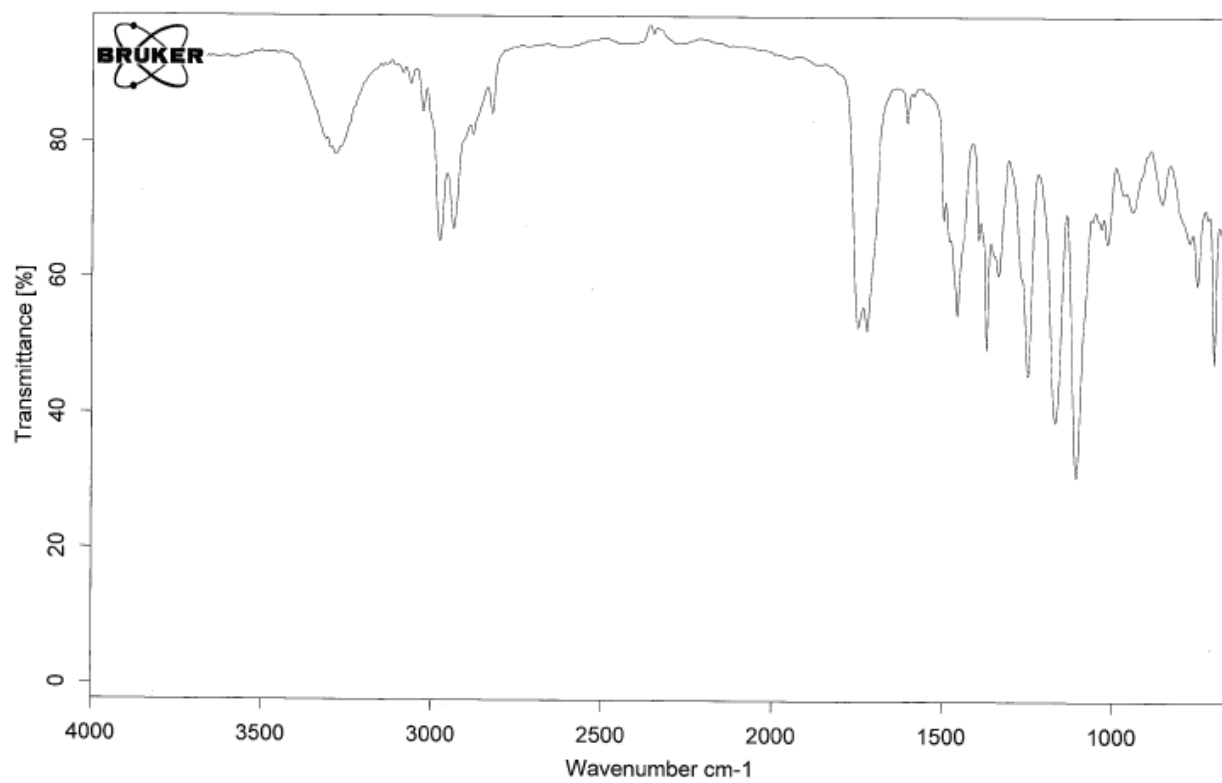
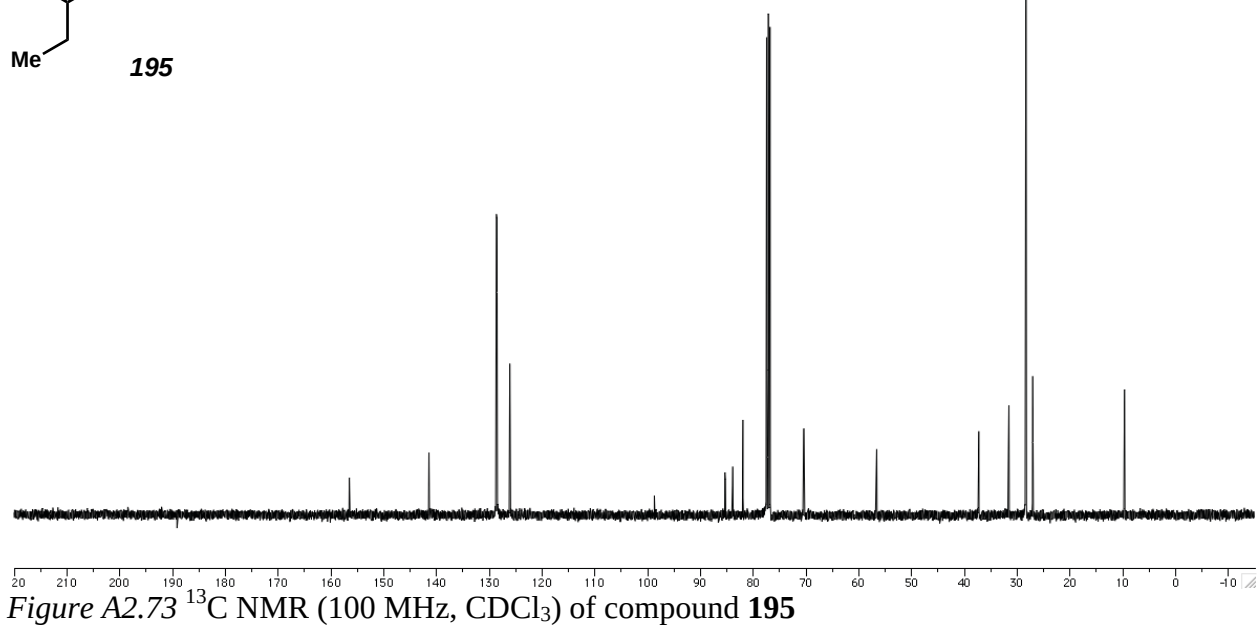
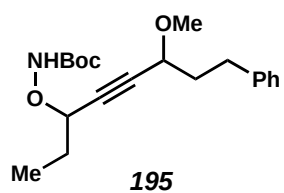


Figure A2.72 ^1H NMR (400 MHz, CDCl_3) of compound **195**



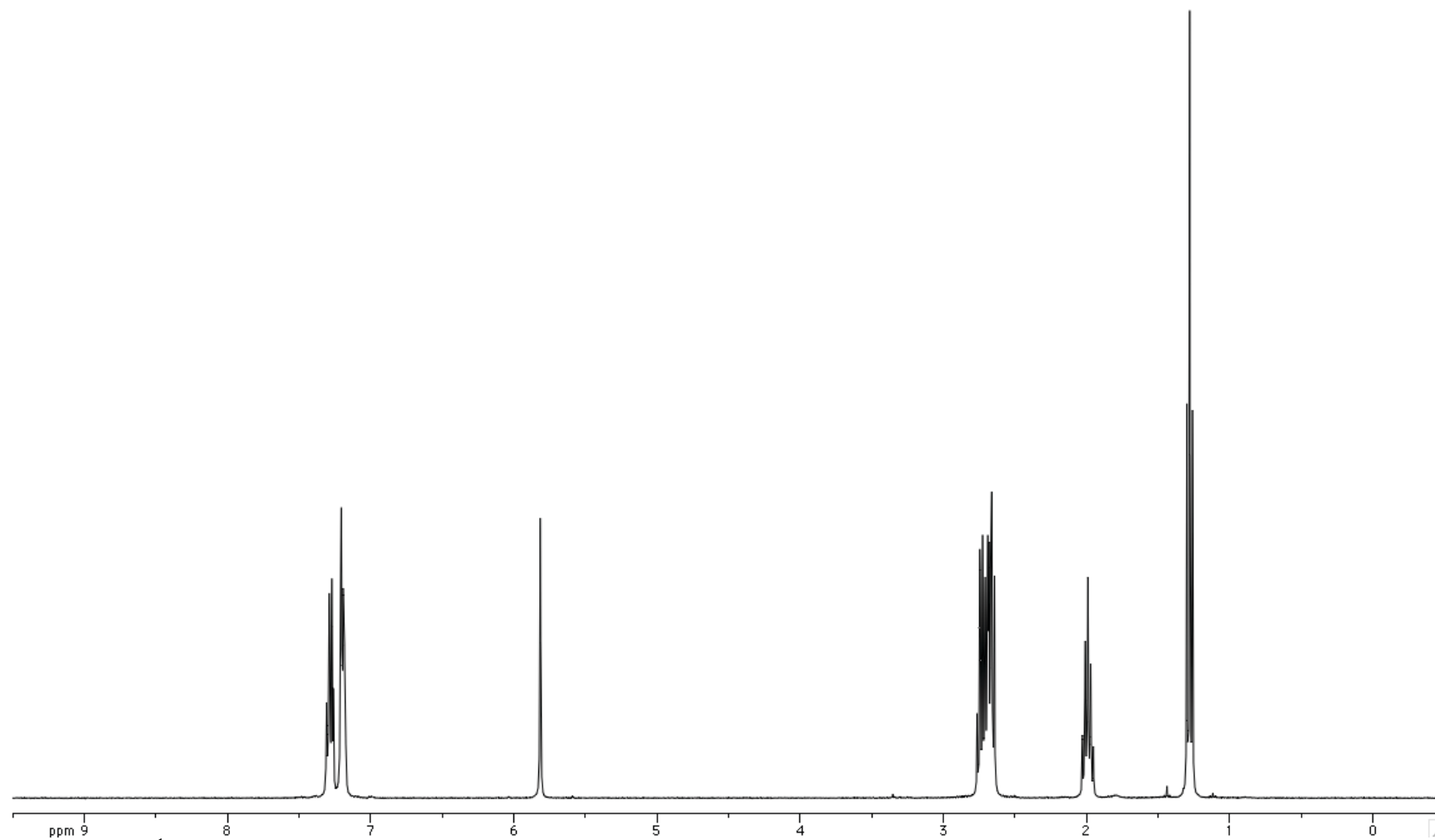
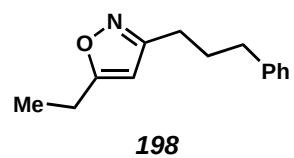
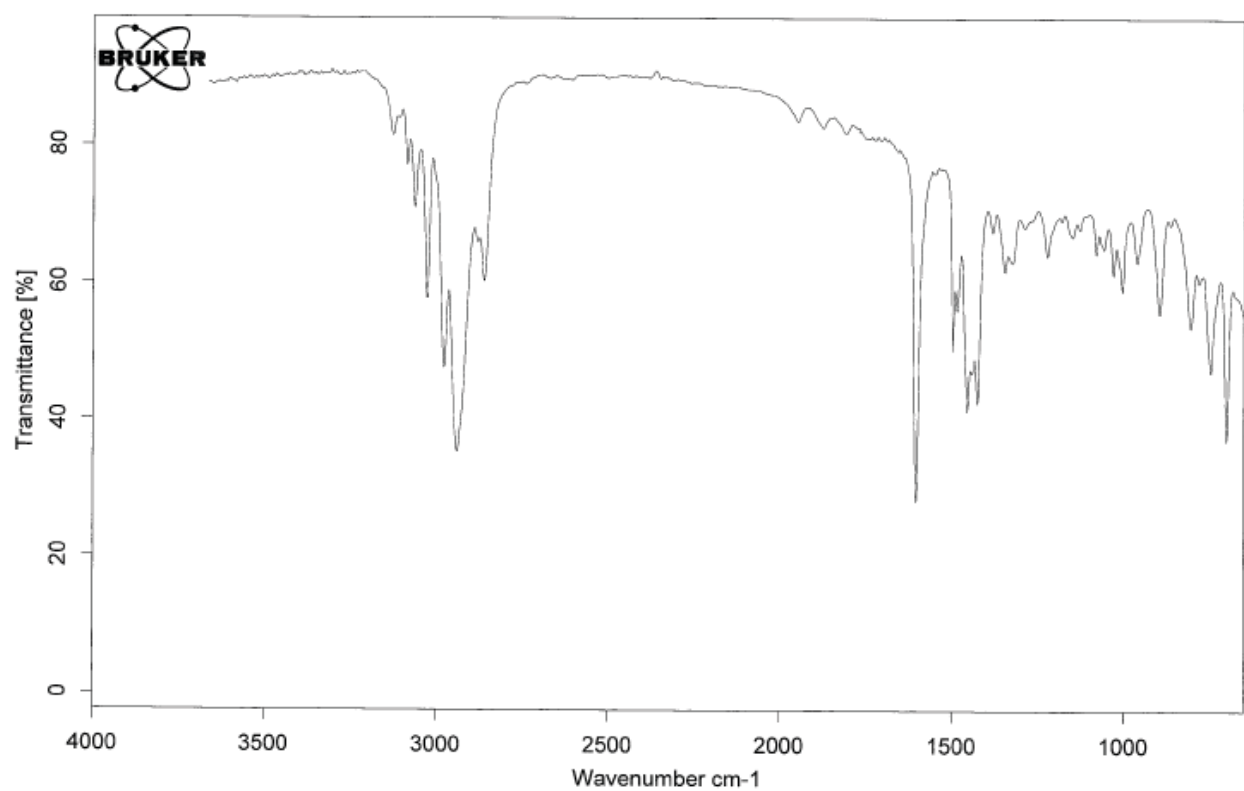
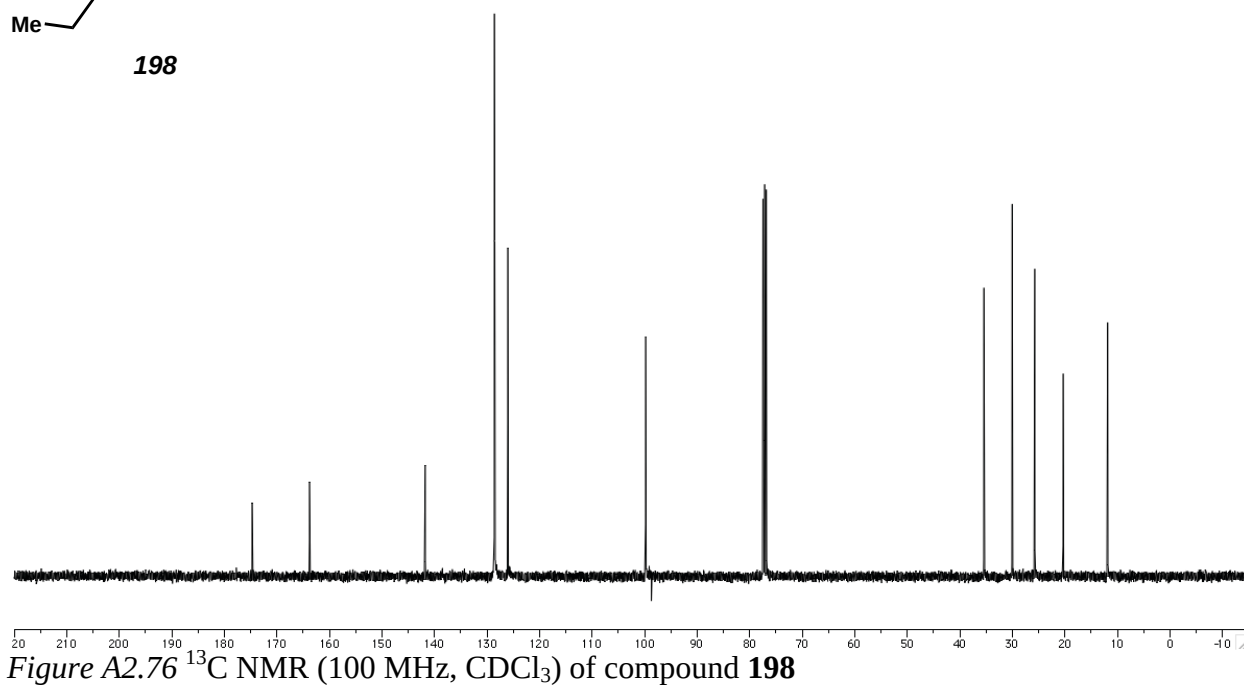
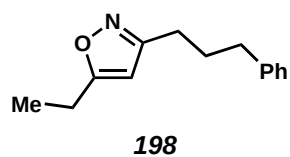


Figure A2.75 ^1H NMR (400 MHz, CDCl_3) of compound **198**



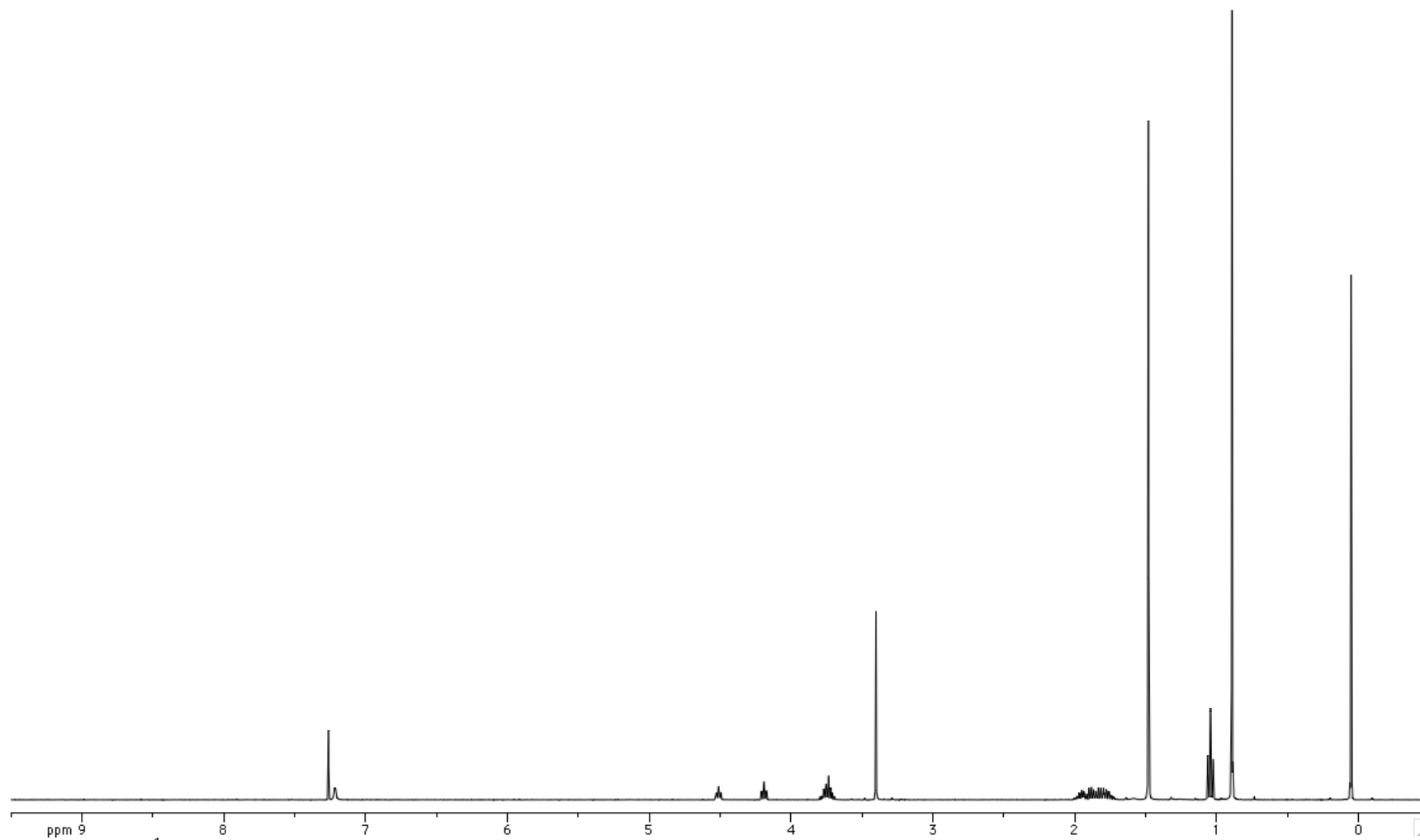
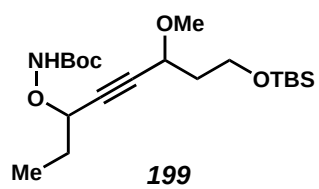


Figure A2.78 ^1H NMR (400 MHz, CDCl_3) of compound **199**

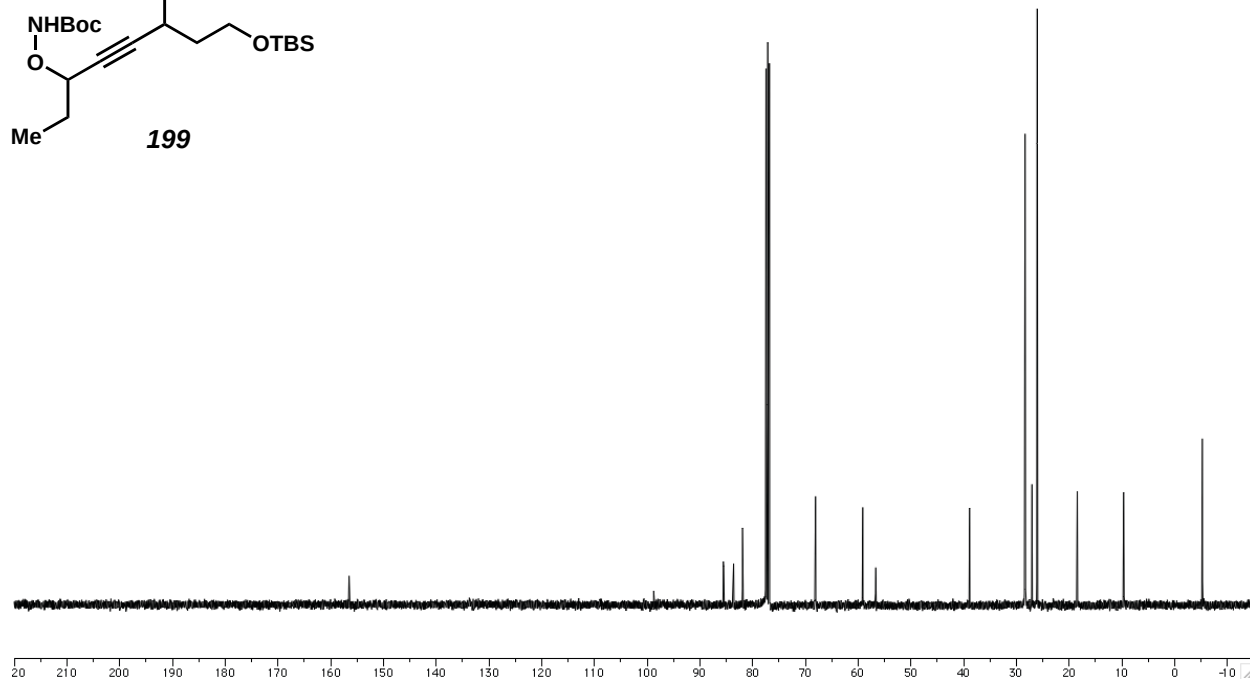


Figure A2.80 Infrared spectrum (thin film) of compound **199**

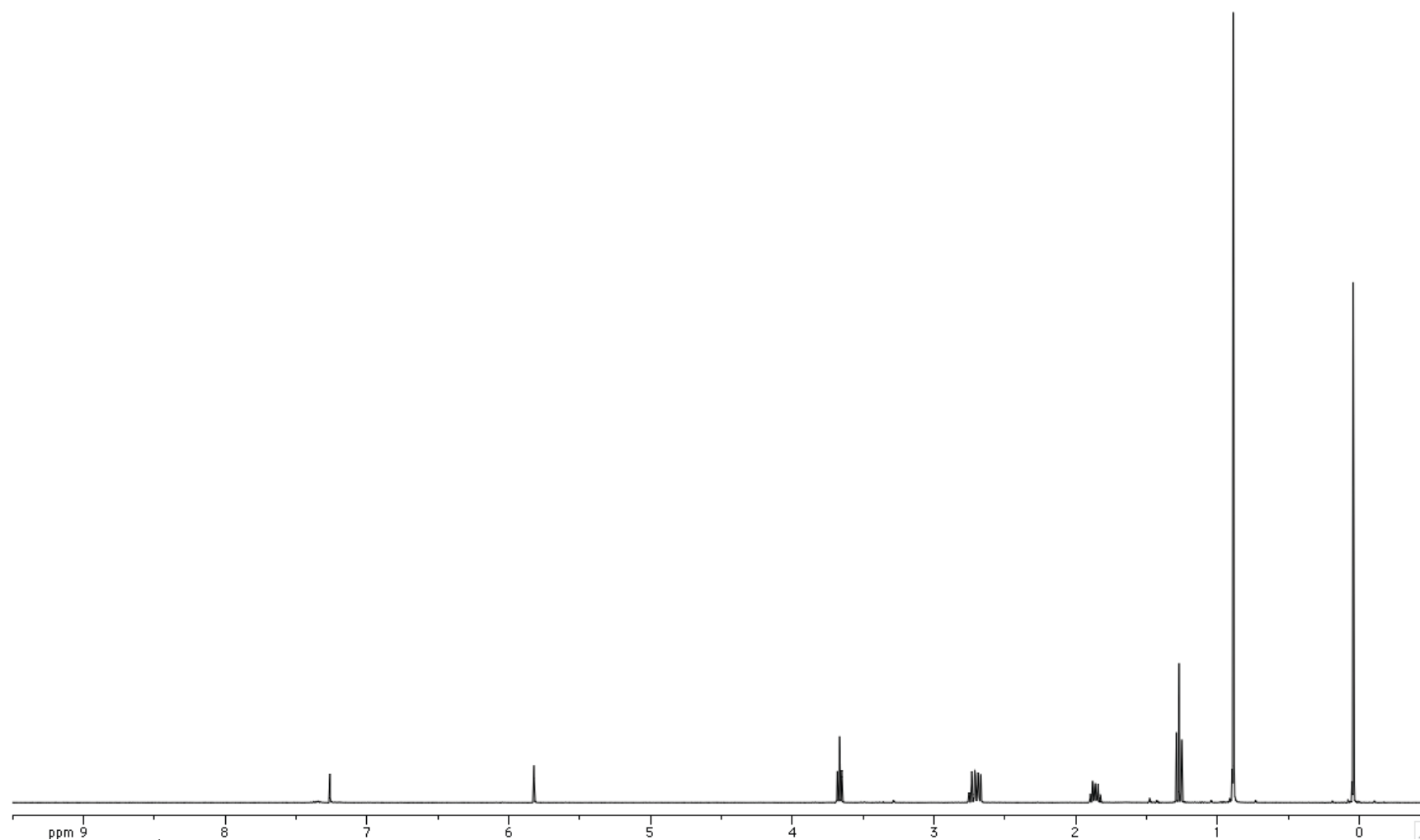
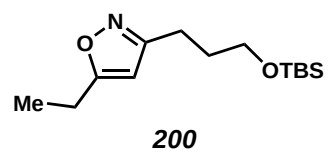


Figure A2.81 ^1H NMR (400 MHz, CDCl_3) of compound **200**

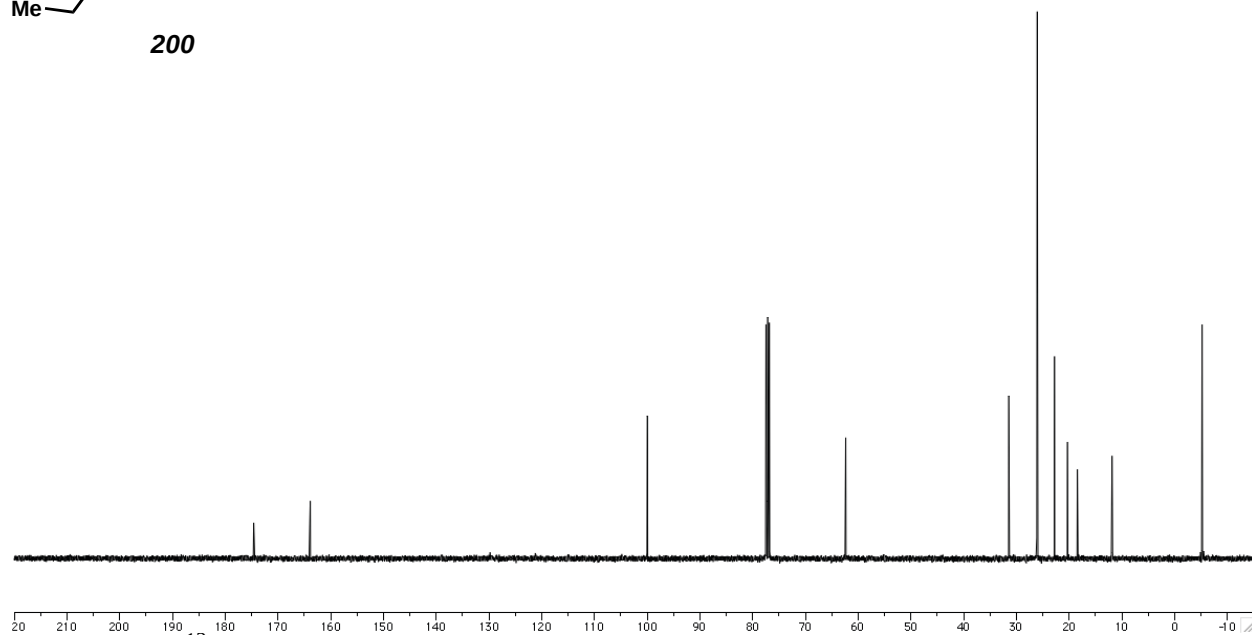
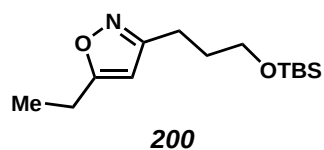


Figure A2.82 ^{13}C NMR (100 MHz, CDCl_3) of compound **200**

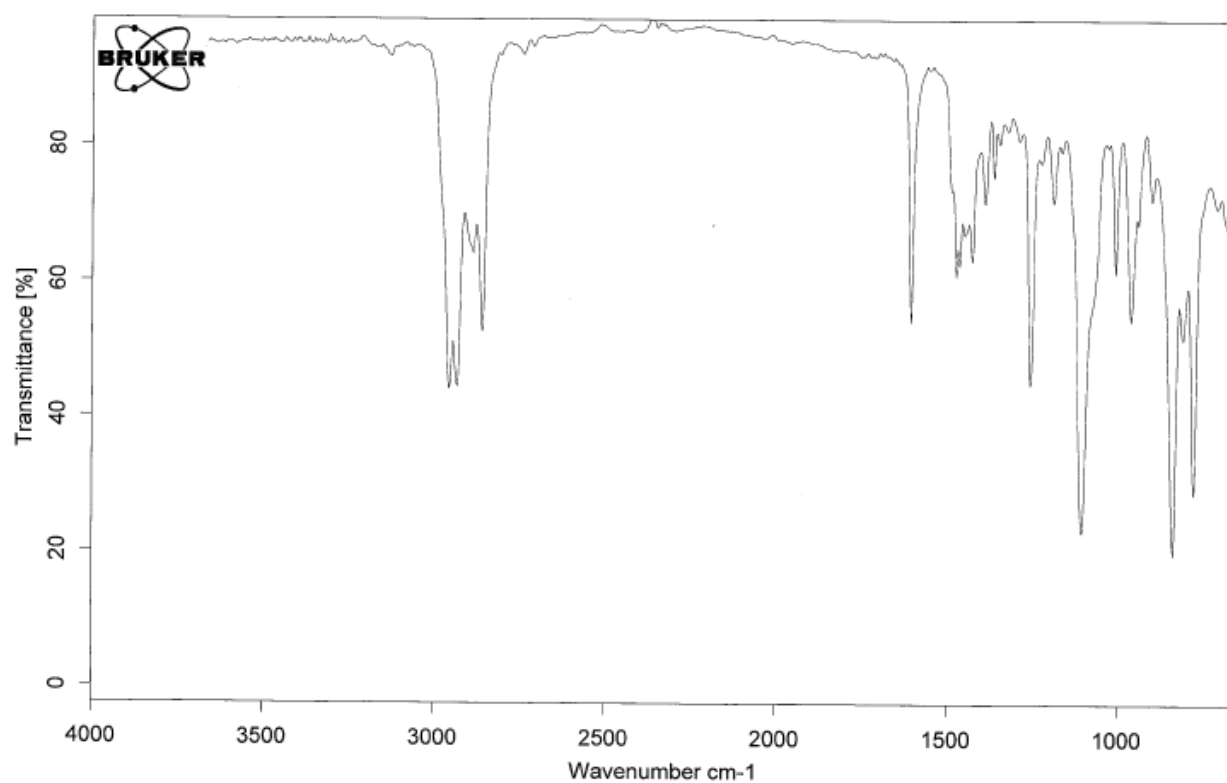


Figure A2.83 Infrared spectrum (thin film) of compound **200**

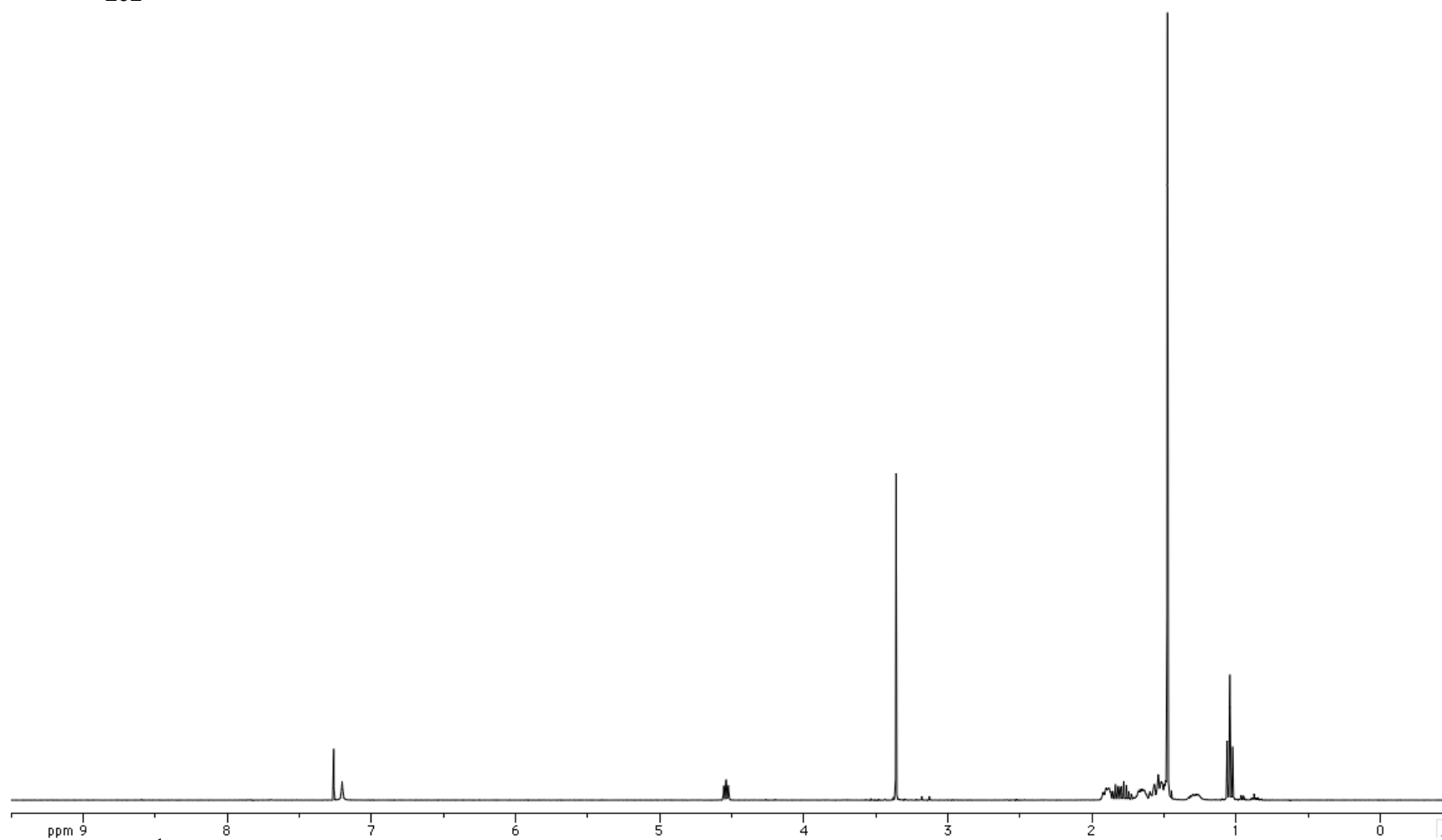
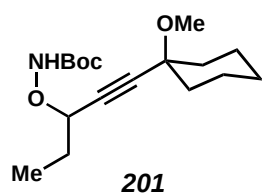


Figure A2.84 ^1H NMR (400 MHz, CDCl_3) of compound **201**

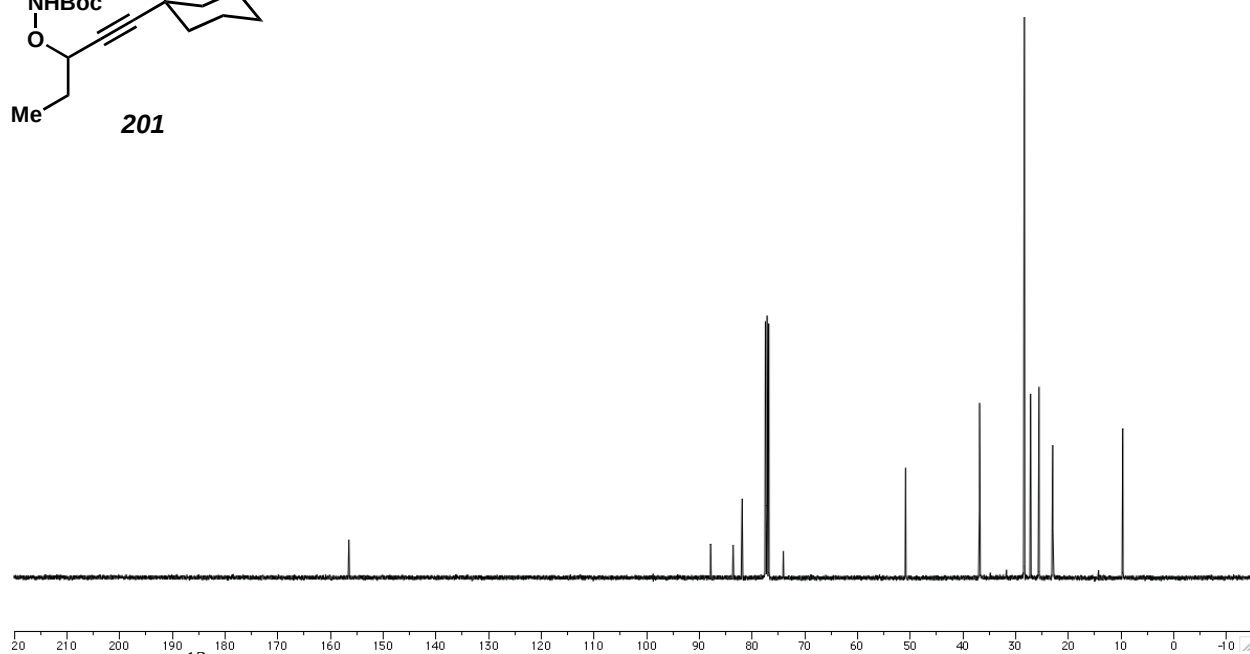
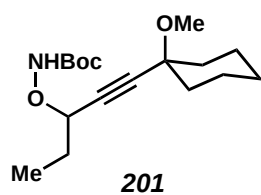


Figure A2.85 ^{13}C NMR (400 MHz, CDCl_3) of compound **201**

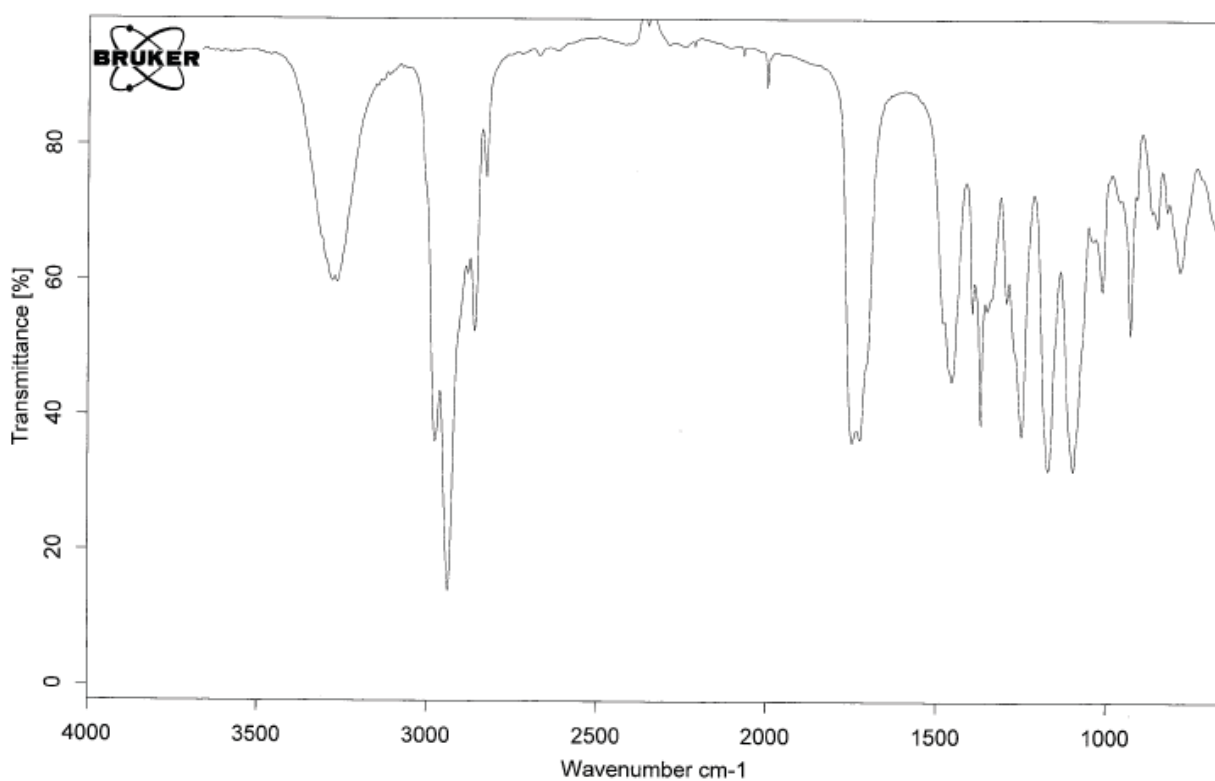


Figure A2.86 Infrared spectrum (thin film) of compound **201**

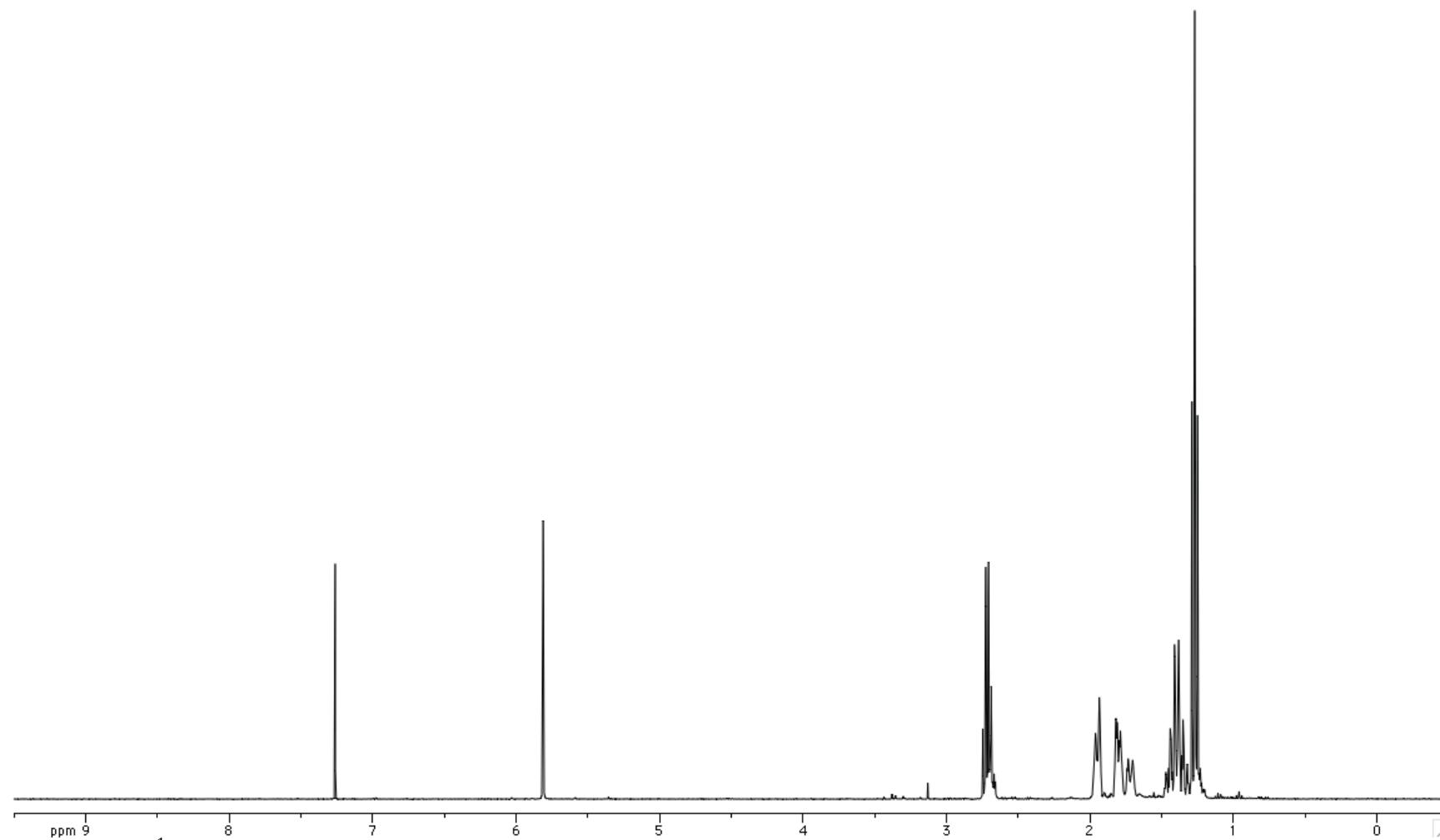
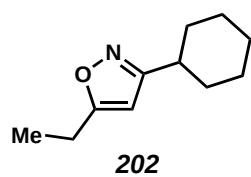
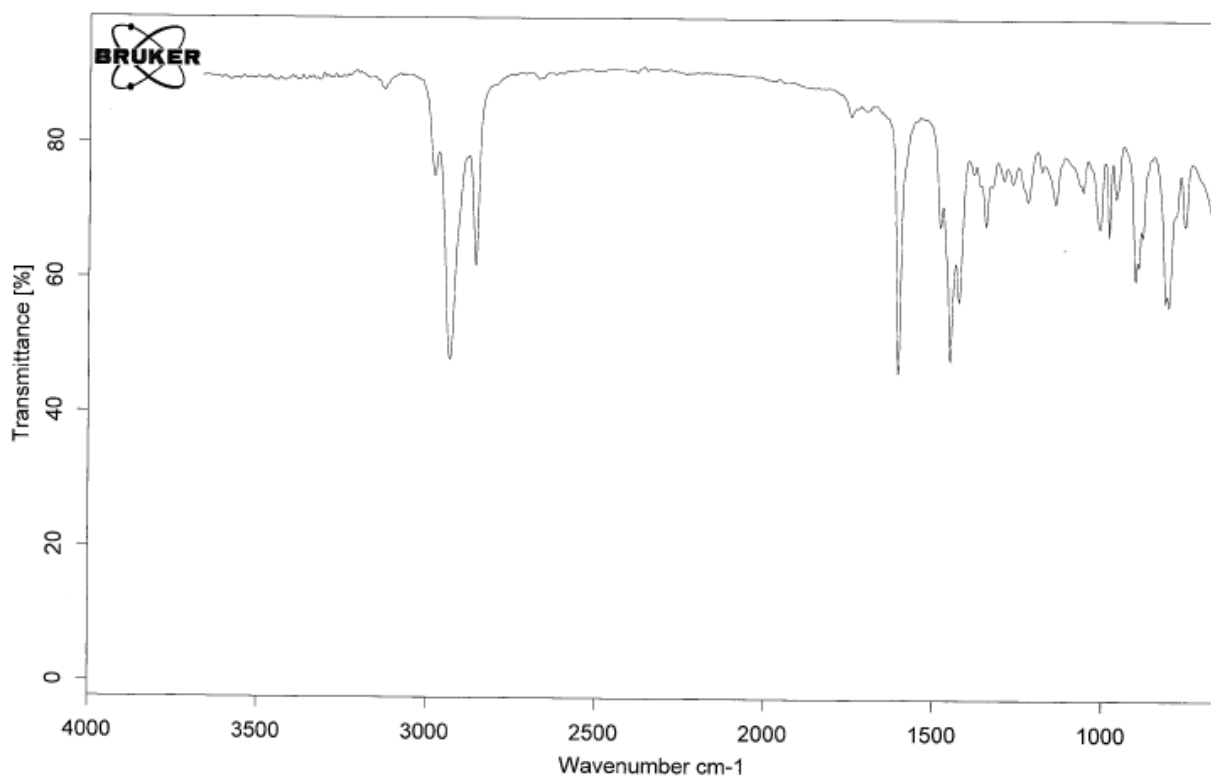
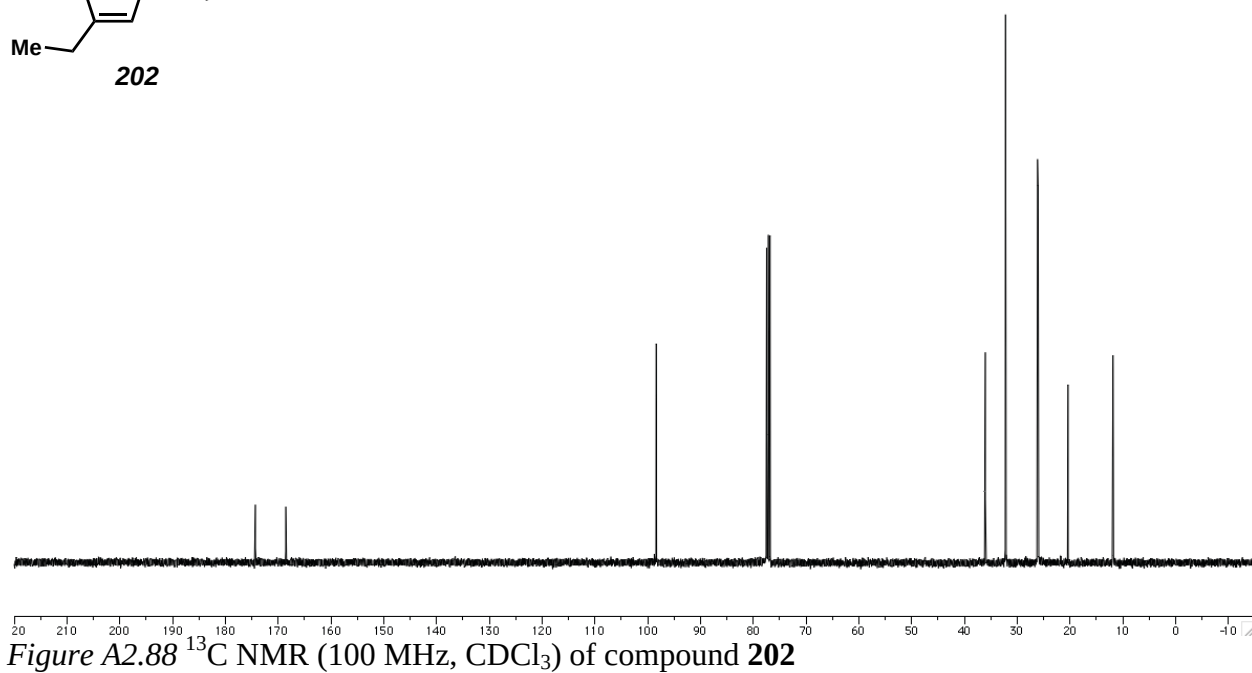
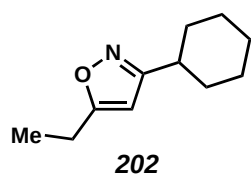
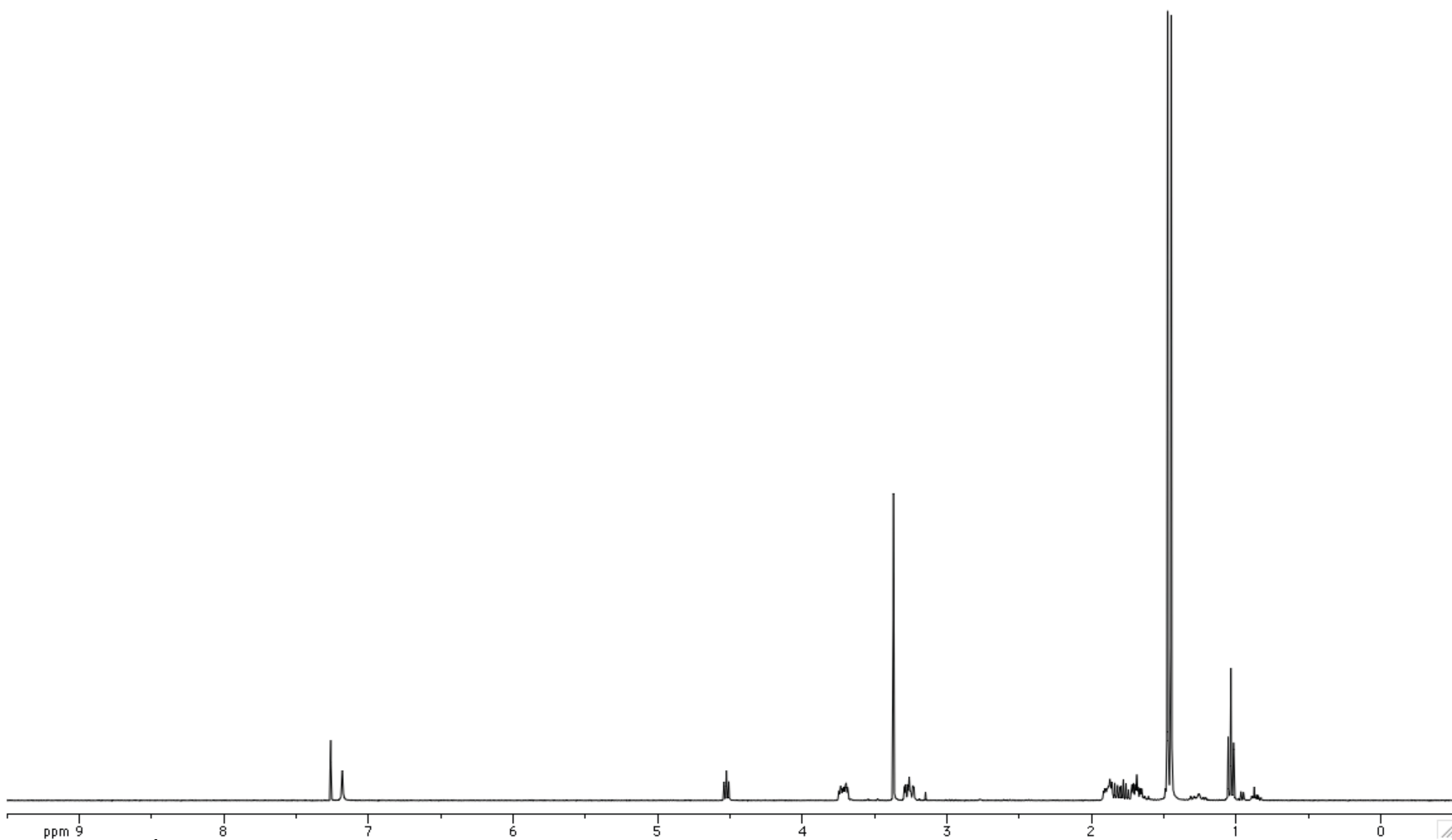
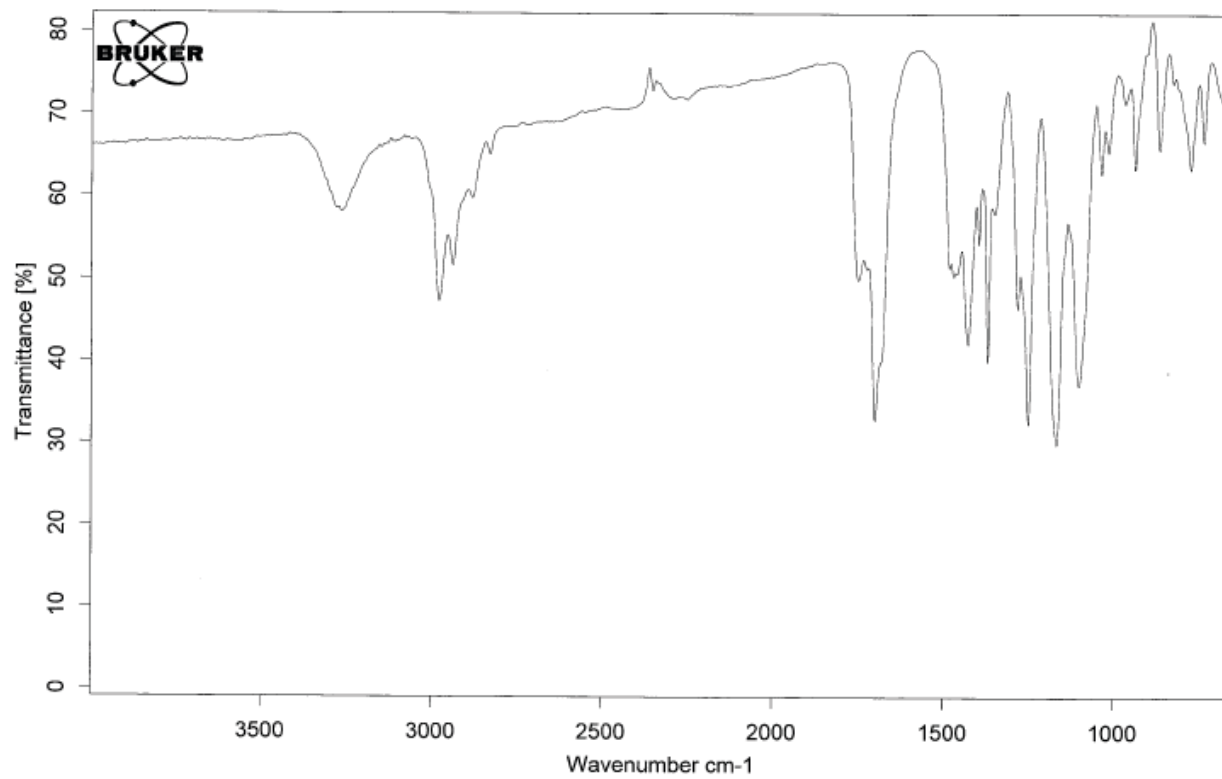
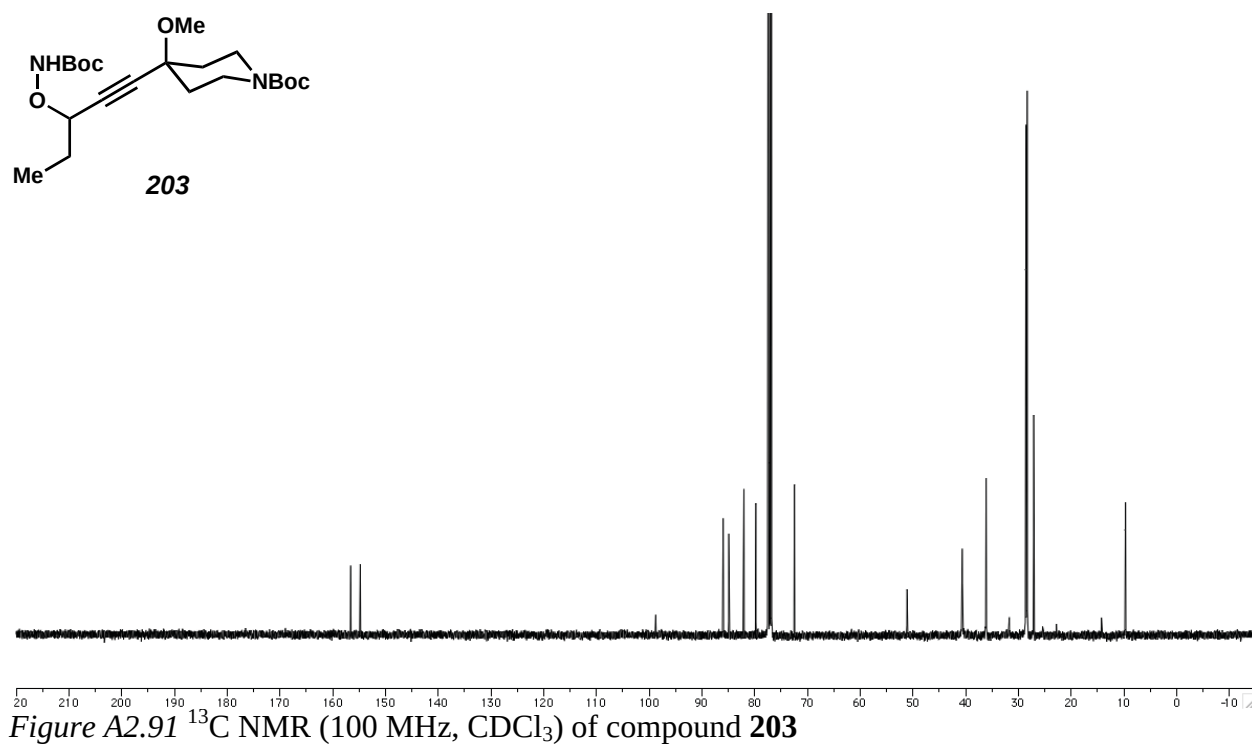


Figure A2.87 ^1H NMR (400 MHz, CDCl_3) of compound **202**





515



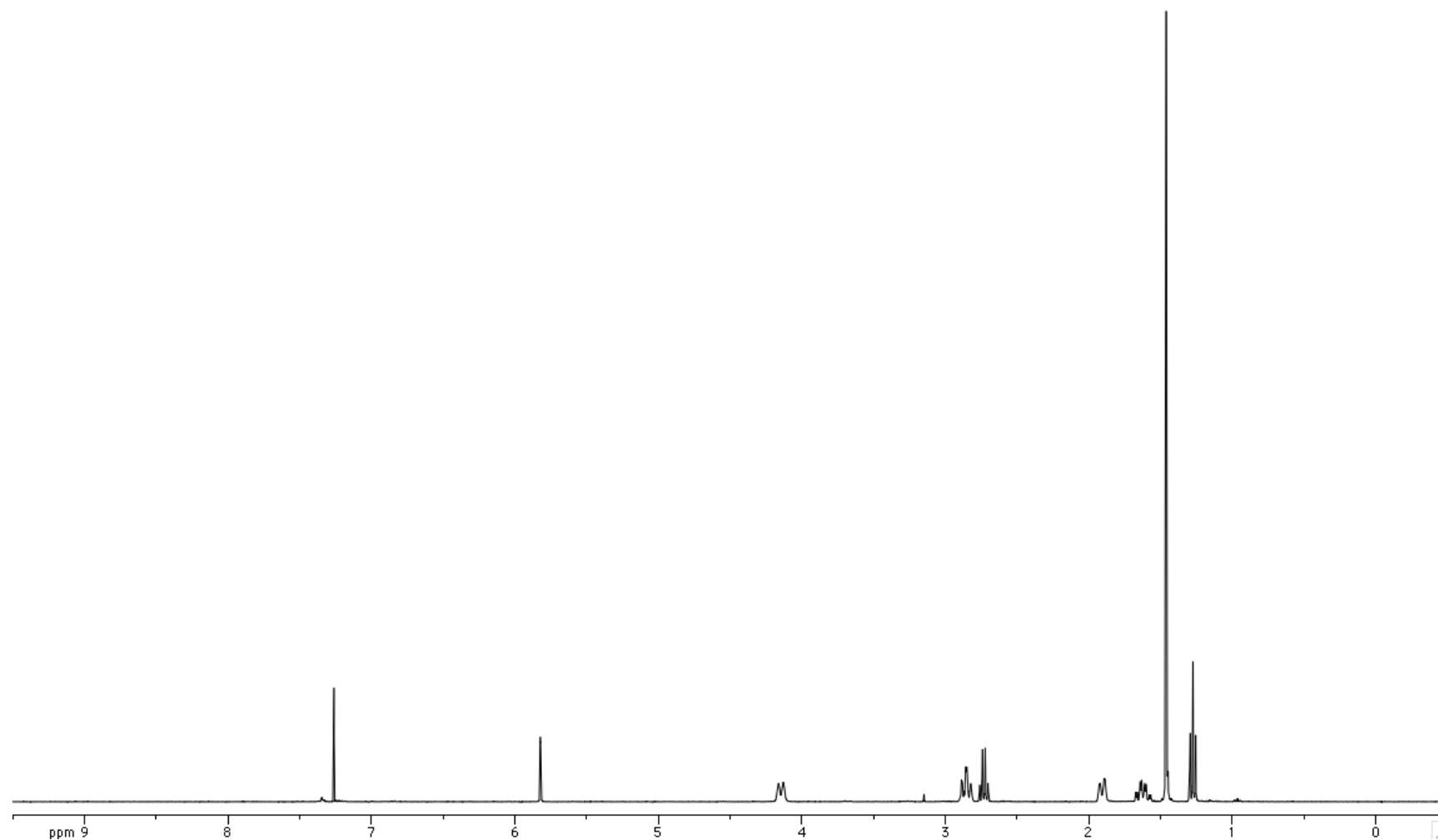
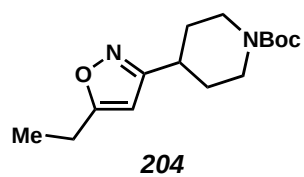


Figure A2.93 ^1H NMR (400 MHz, CDCl_3) of compound **204**

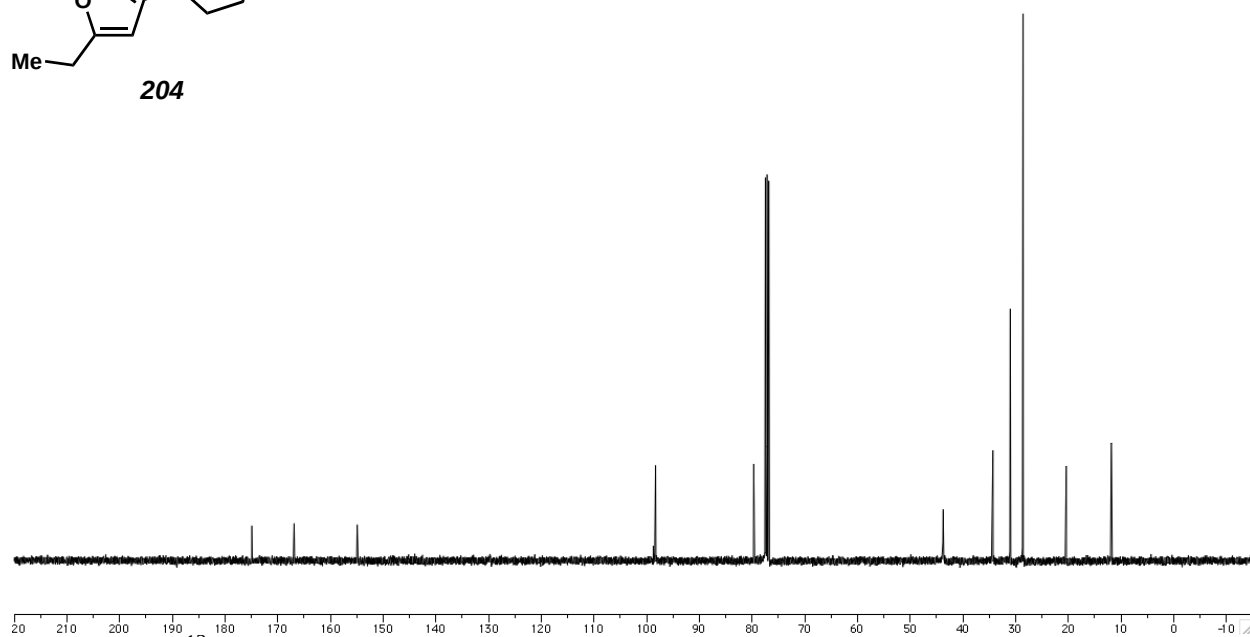
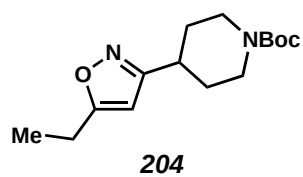


Figure A2.94 ^{13}C NMR (100 MHz, CDCl_3) of compound **204**

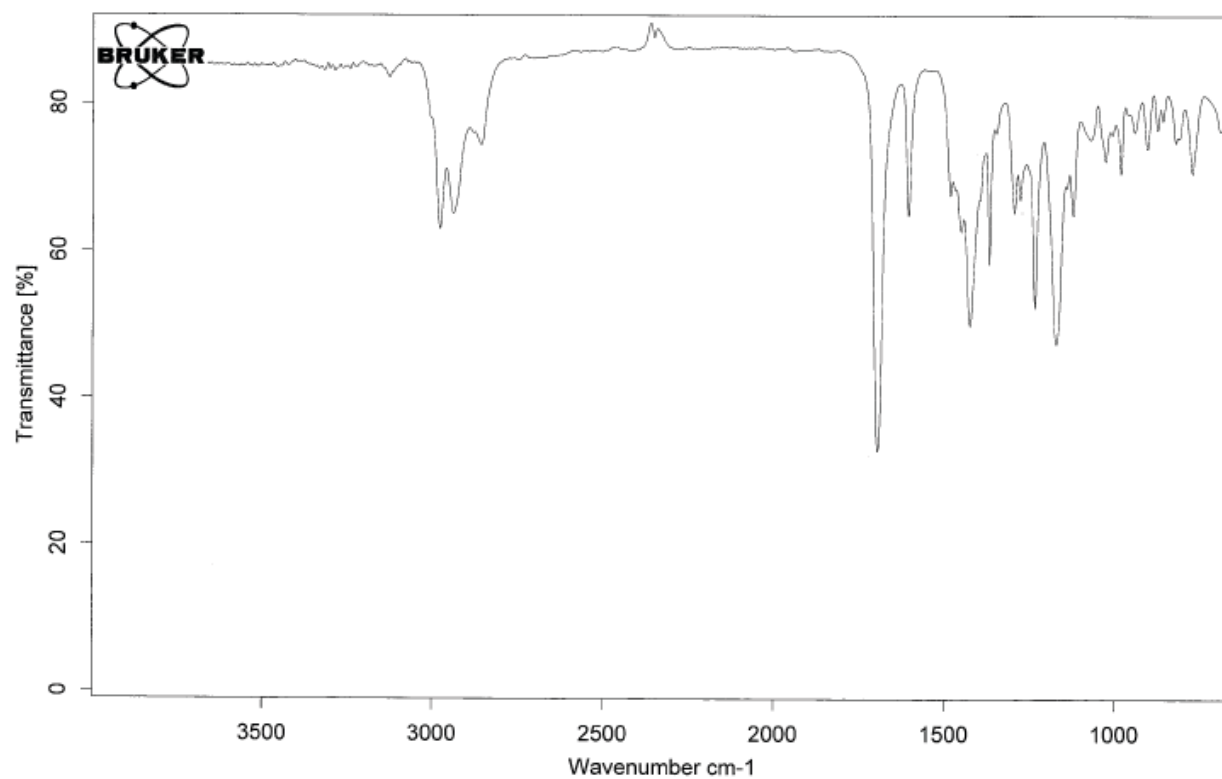


Figure A2.95 Infrared spectrum (thin film) of compound **204**

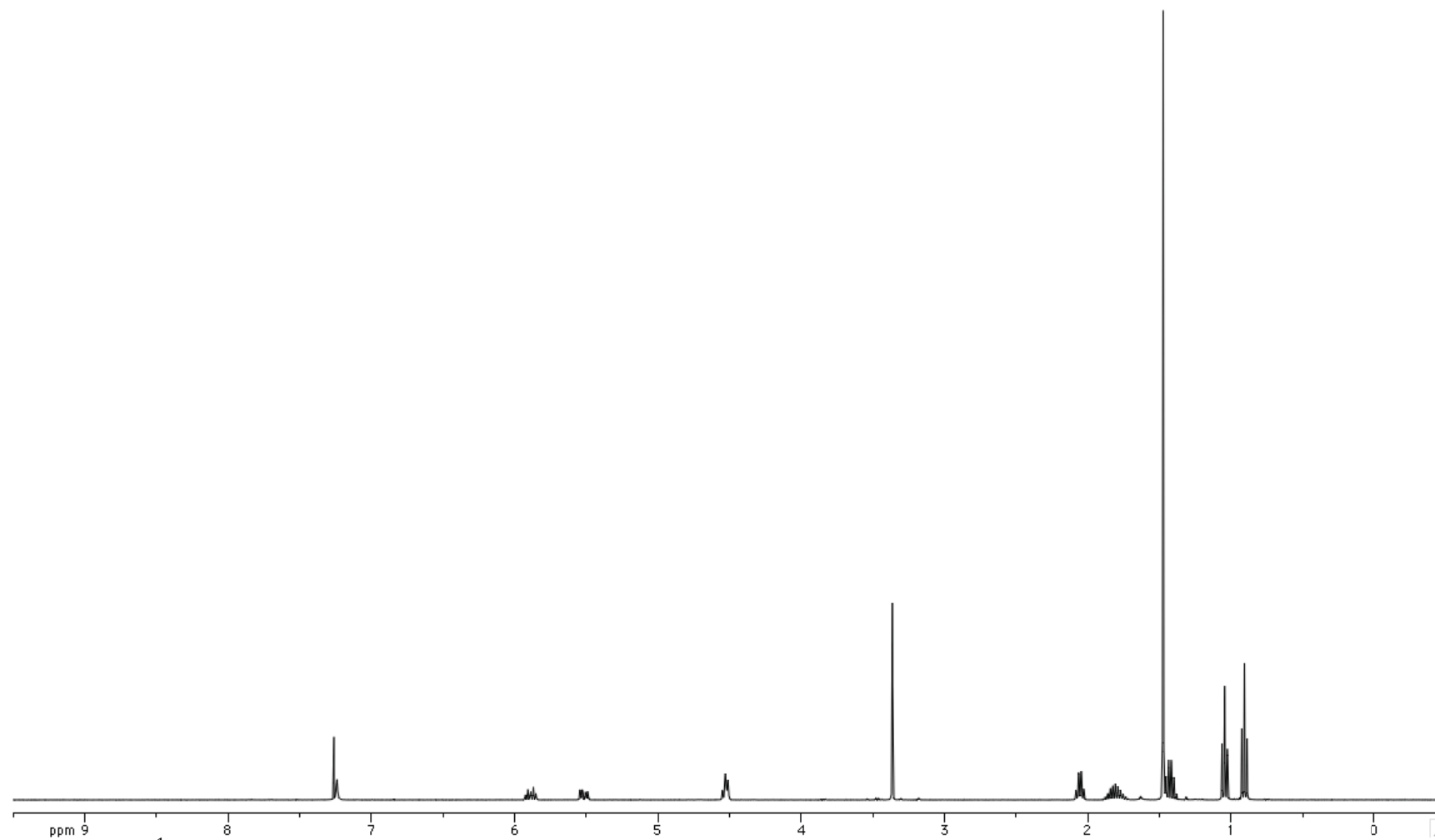
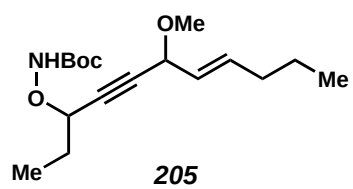


Figure A2.96 ^1H NMR (400 MHz, CDCl_3) of compound **205**

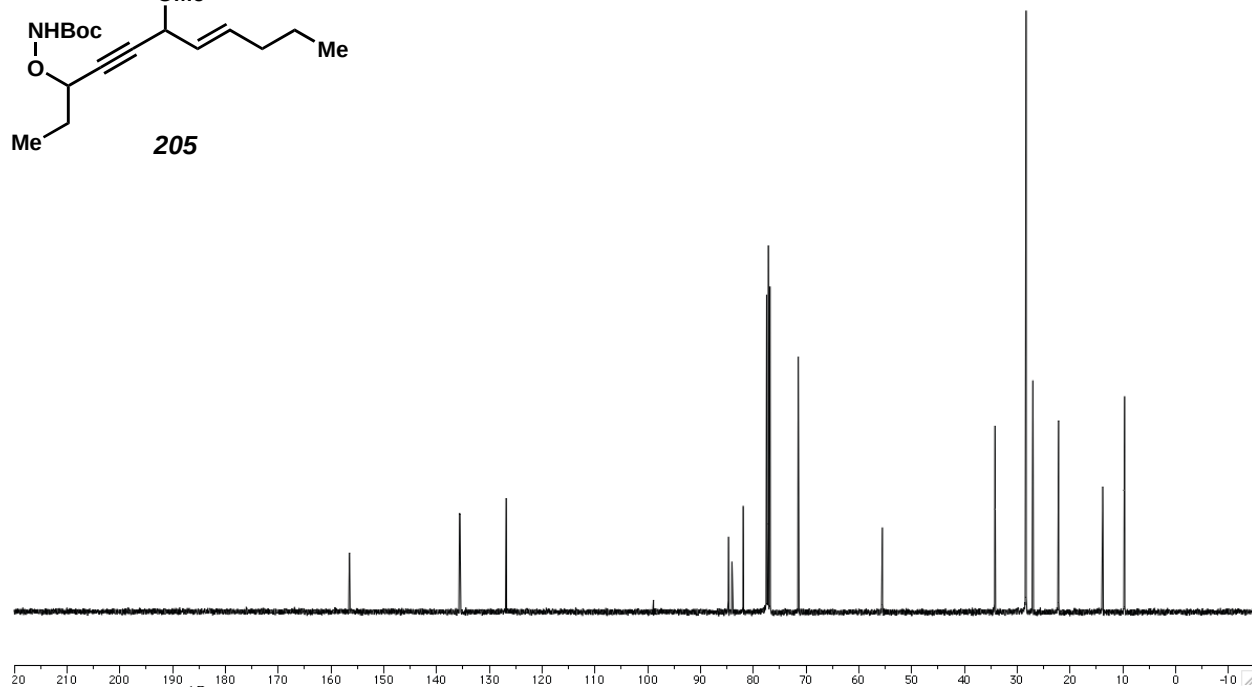
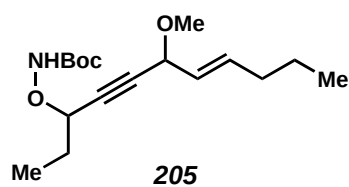


Figure A2.97 ¹³C NMR (100 MHz, CDCl₃) of compound **205**

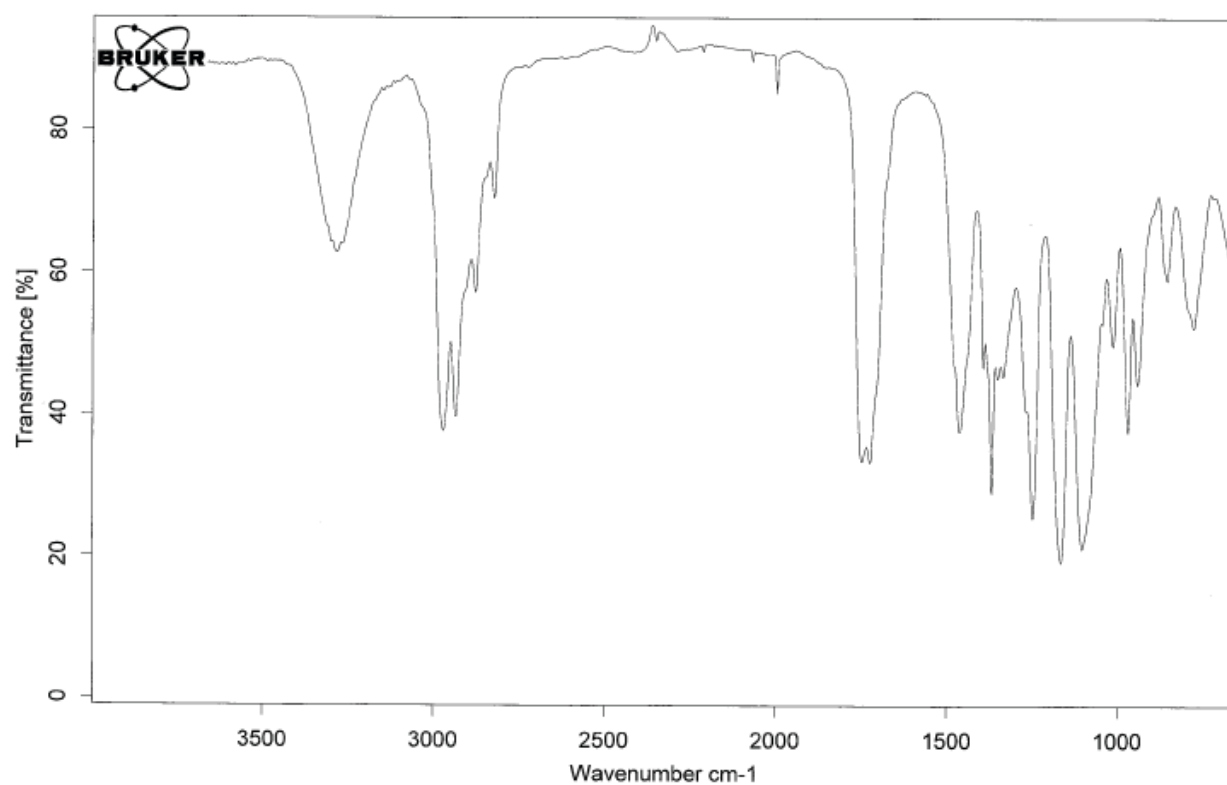


Figure A2.98 Infrared spectrum (thin film) of compound **205**

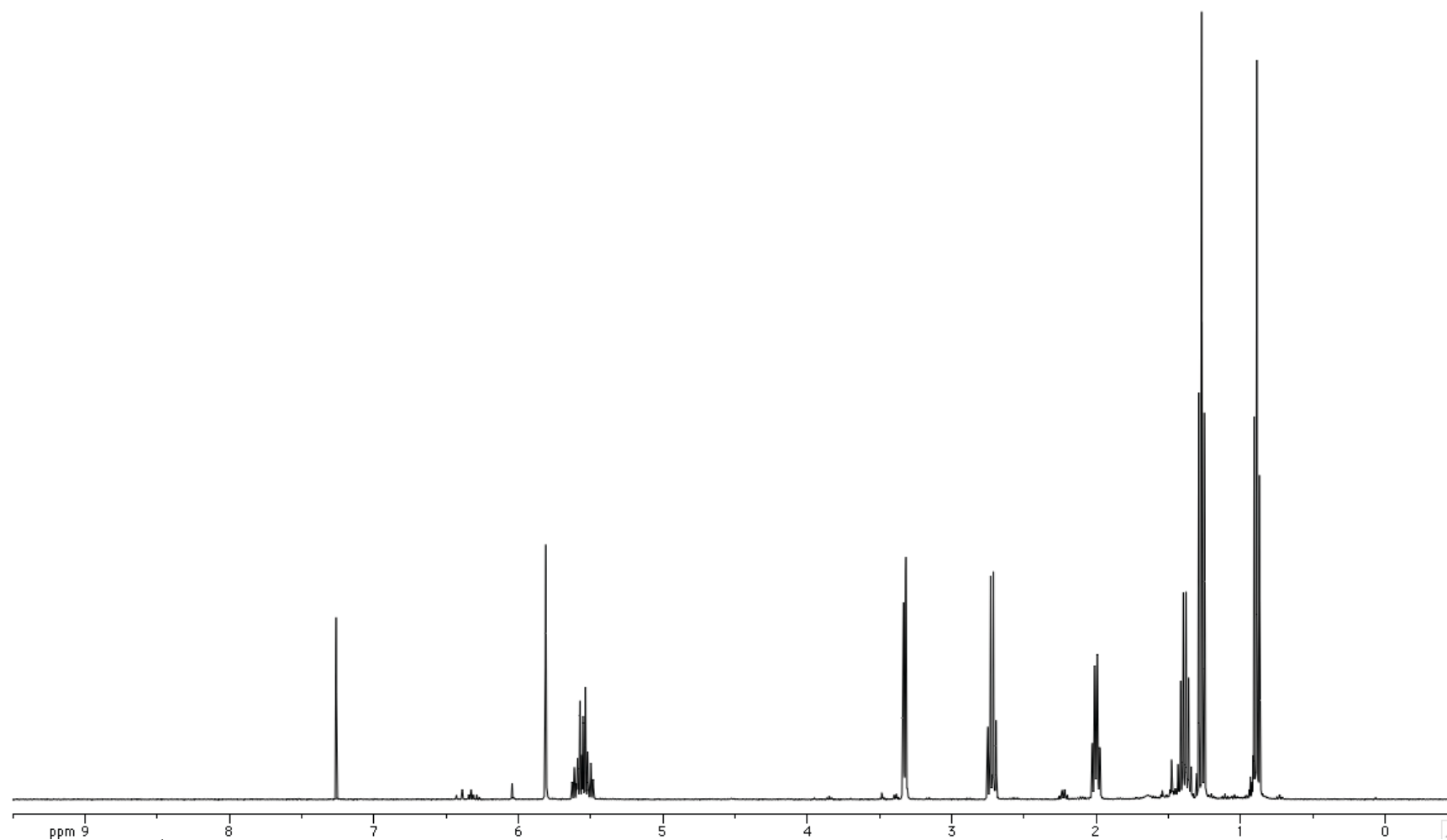
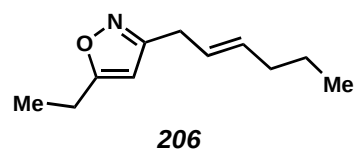


Figure A2.99 ^1H NMR (400 MHz, CDCl_3) of compound **206**

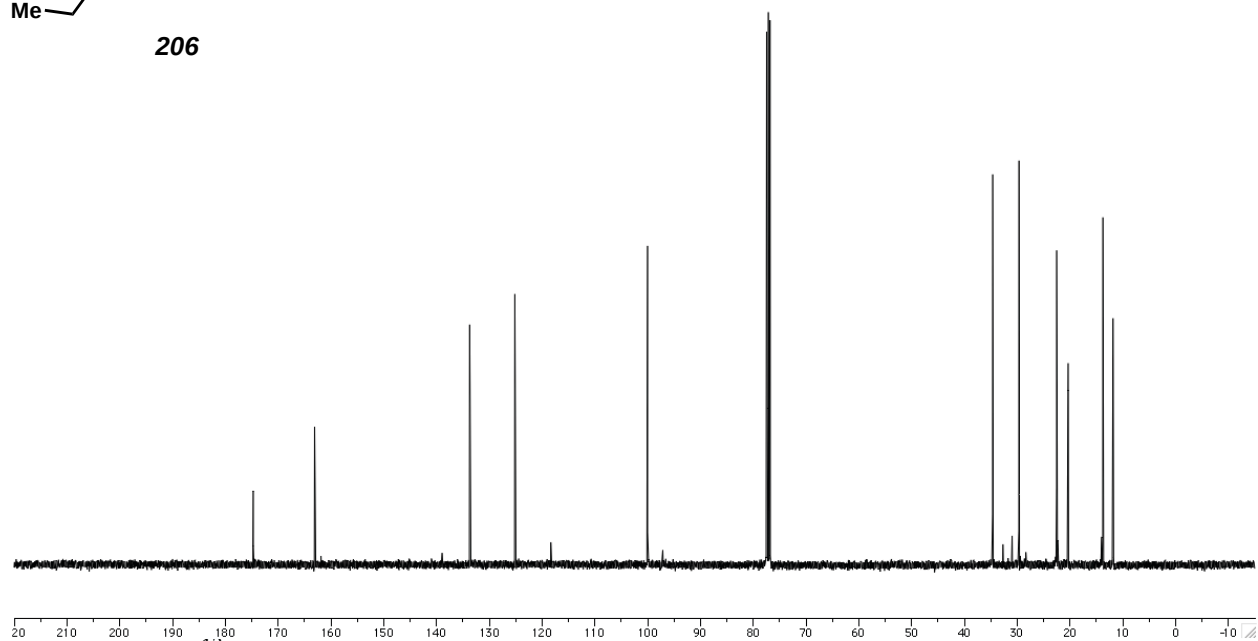
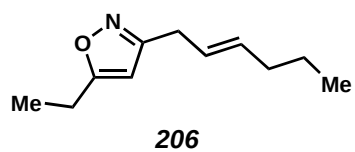


Figure A2.100 ^{13}C NMR (100 MHz, CDCl_3) of compound **206**

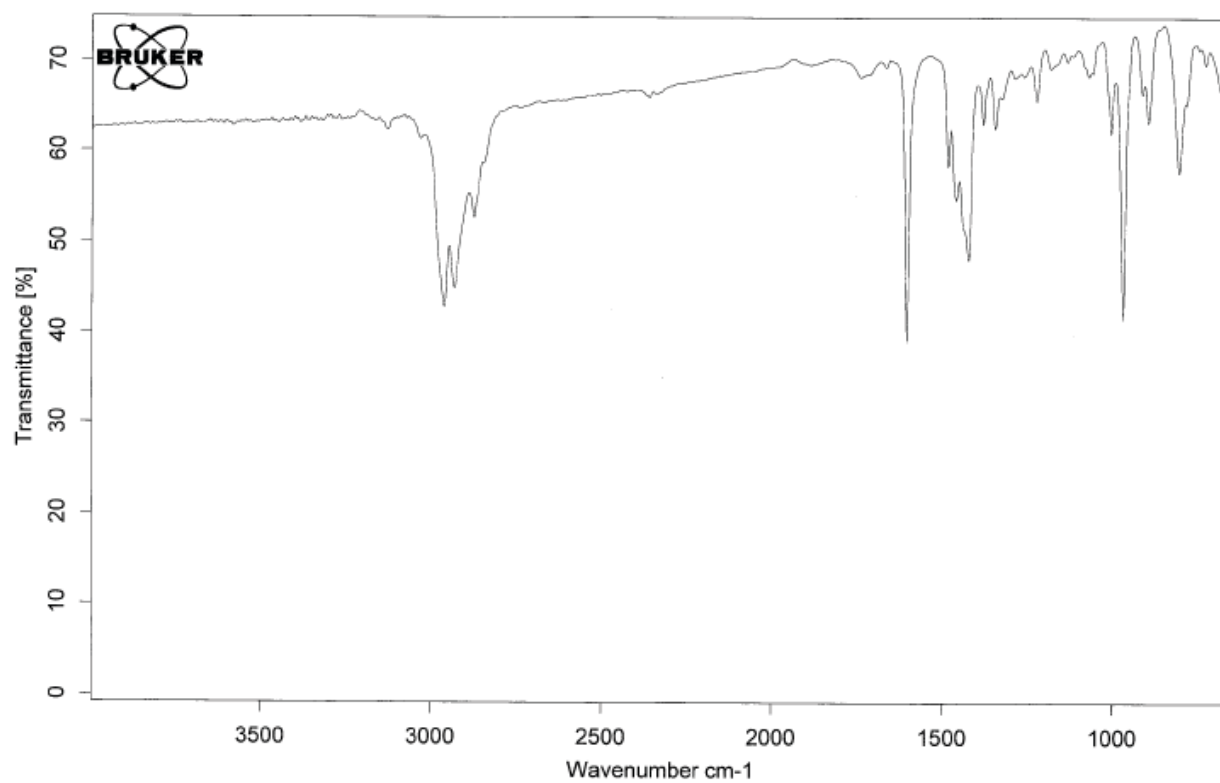


Figure A2.101 Infrared spectrum (thin film) of compound **206**

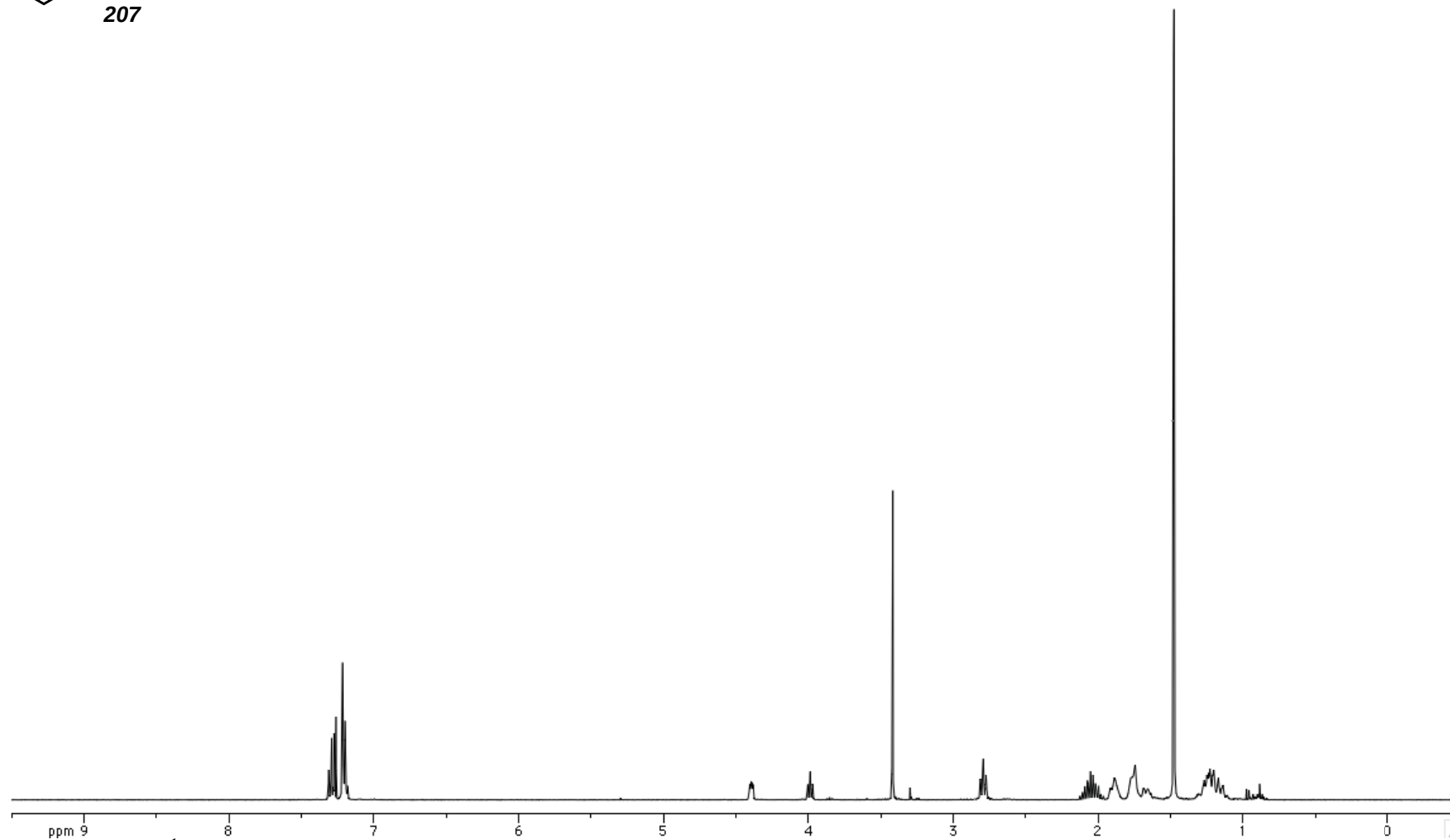
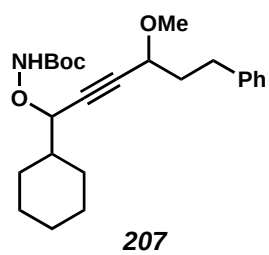
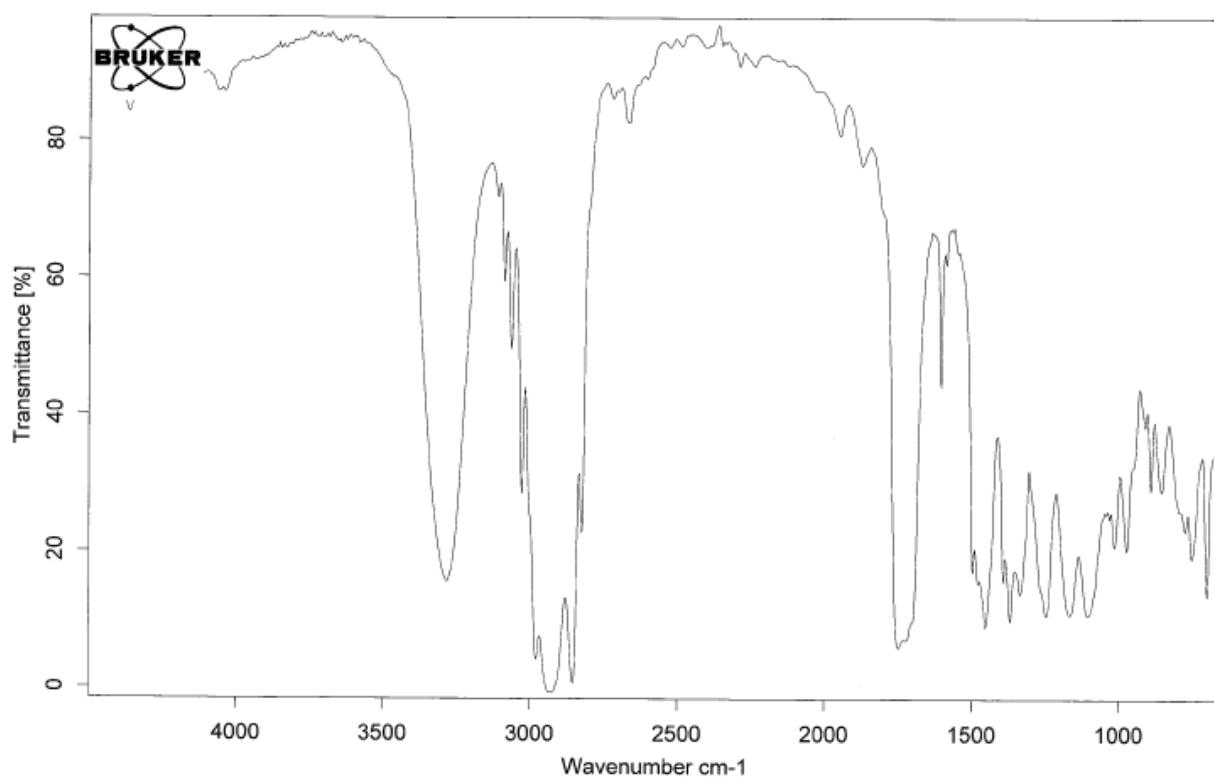
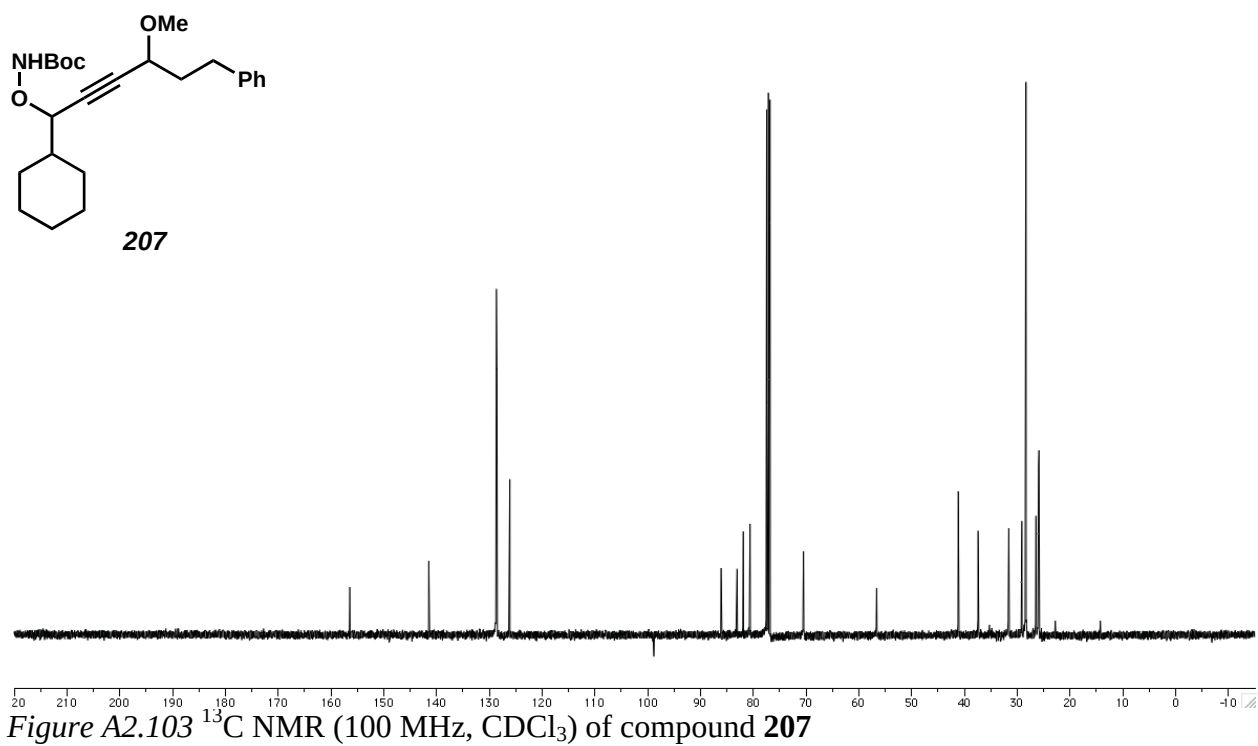
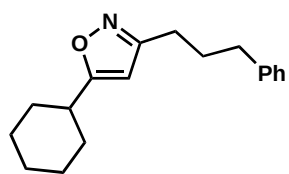


Figure A2.102 ^1H NMR (400 MHz, CDCl_3) of compound **207**





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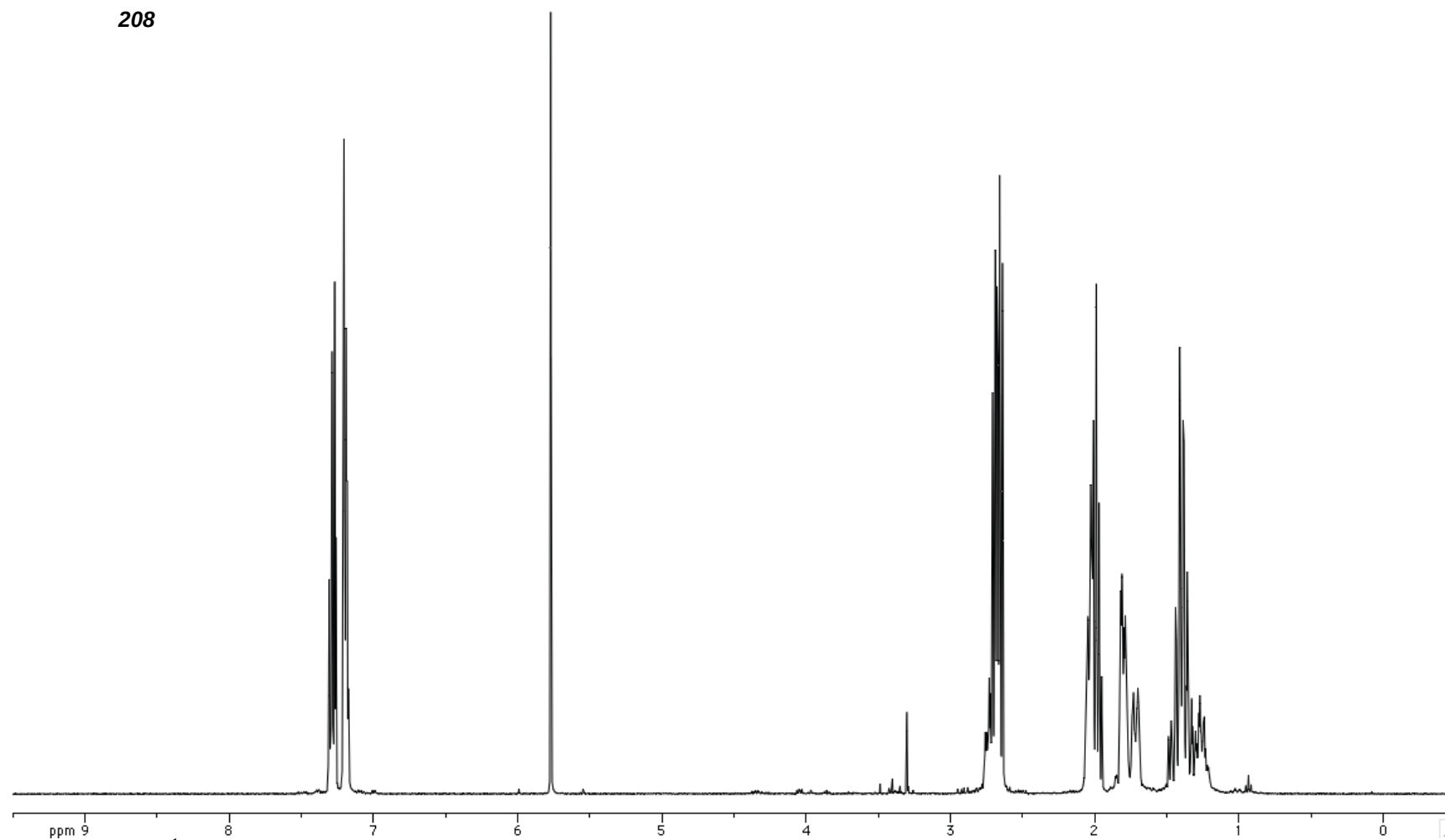
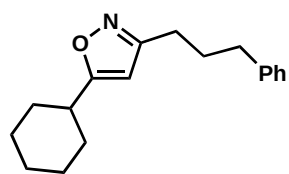


Figure A2.105 ¹H NMR (400 MHz, CDCl₃) of compound **208**



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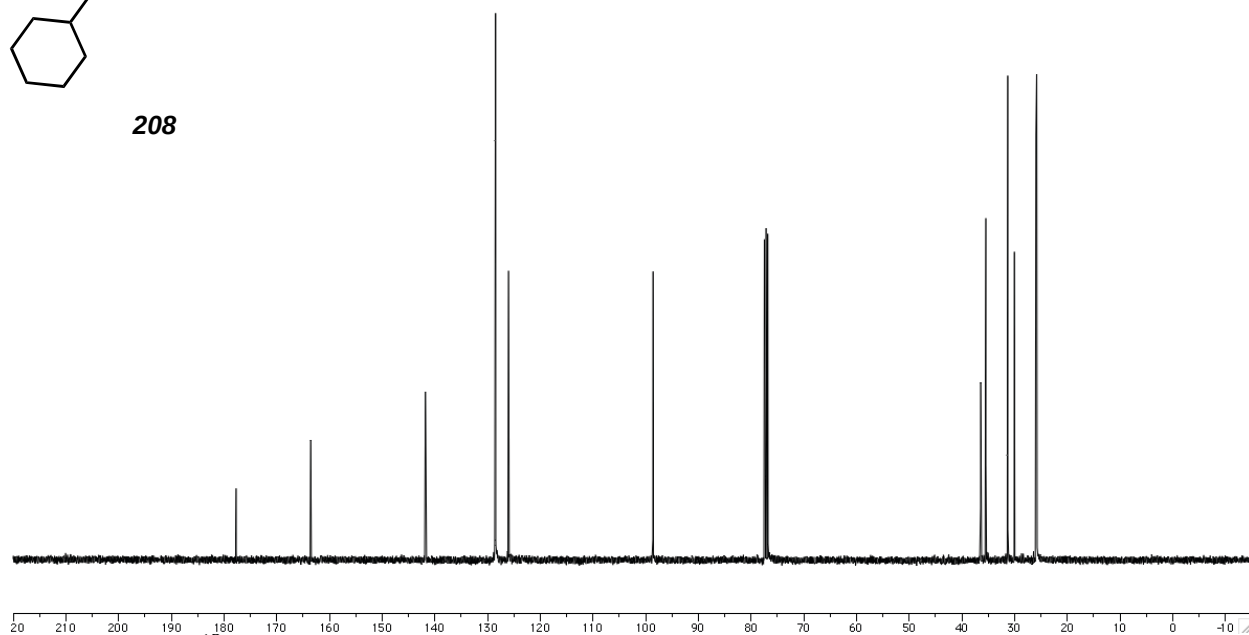


Figure A2.106 ^{13}C NMR (100 MHz, CDCl_3) of compound **208**

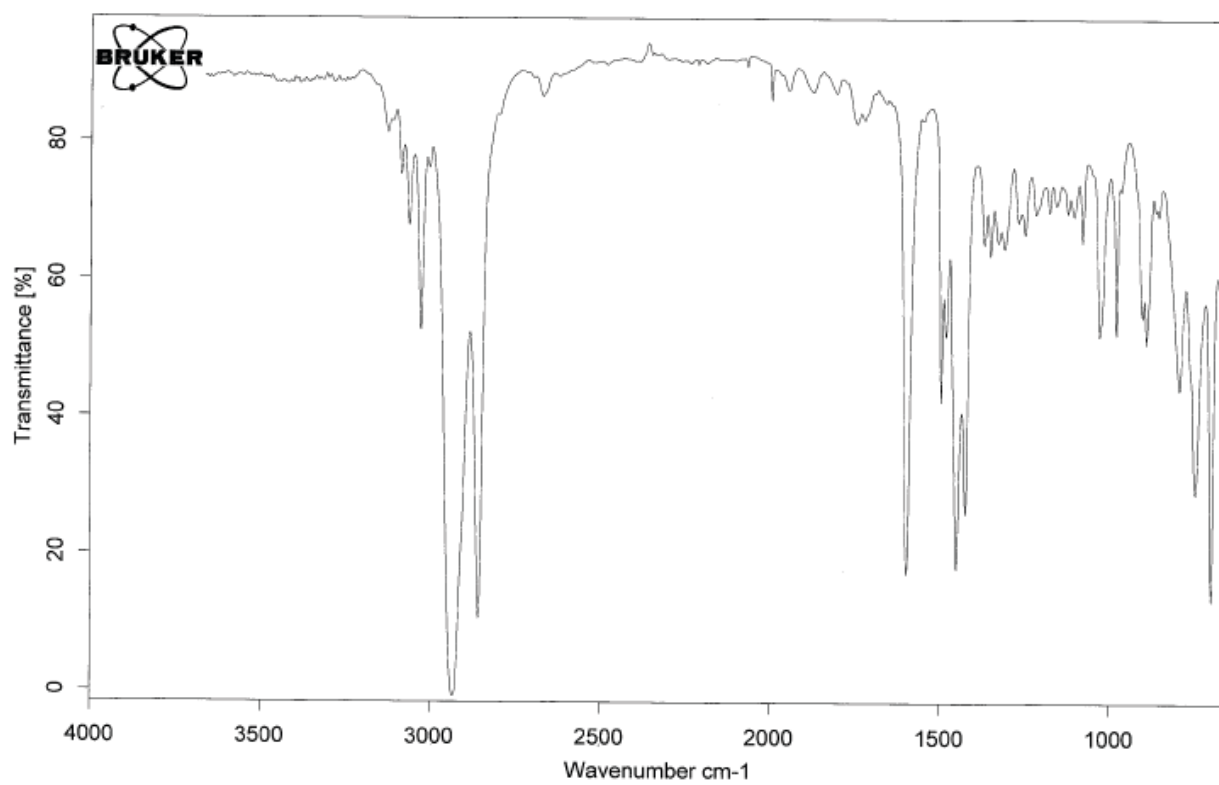


Figure A2.107 Infrared spectrum (thin film) of compound **208**

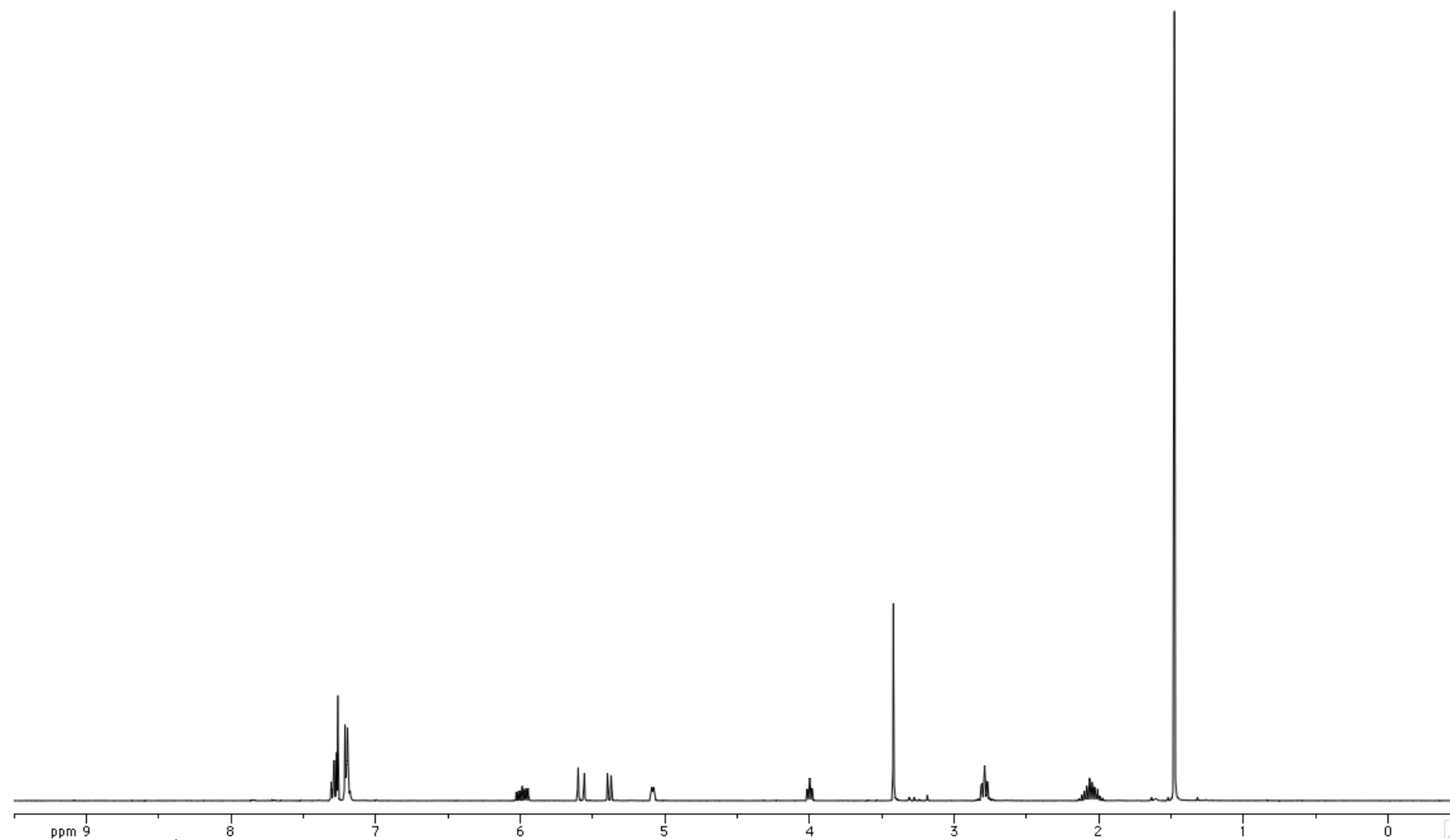
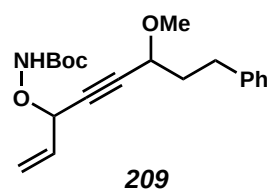
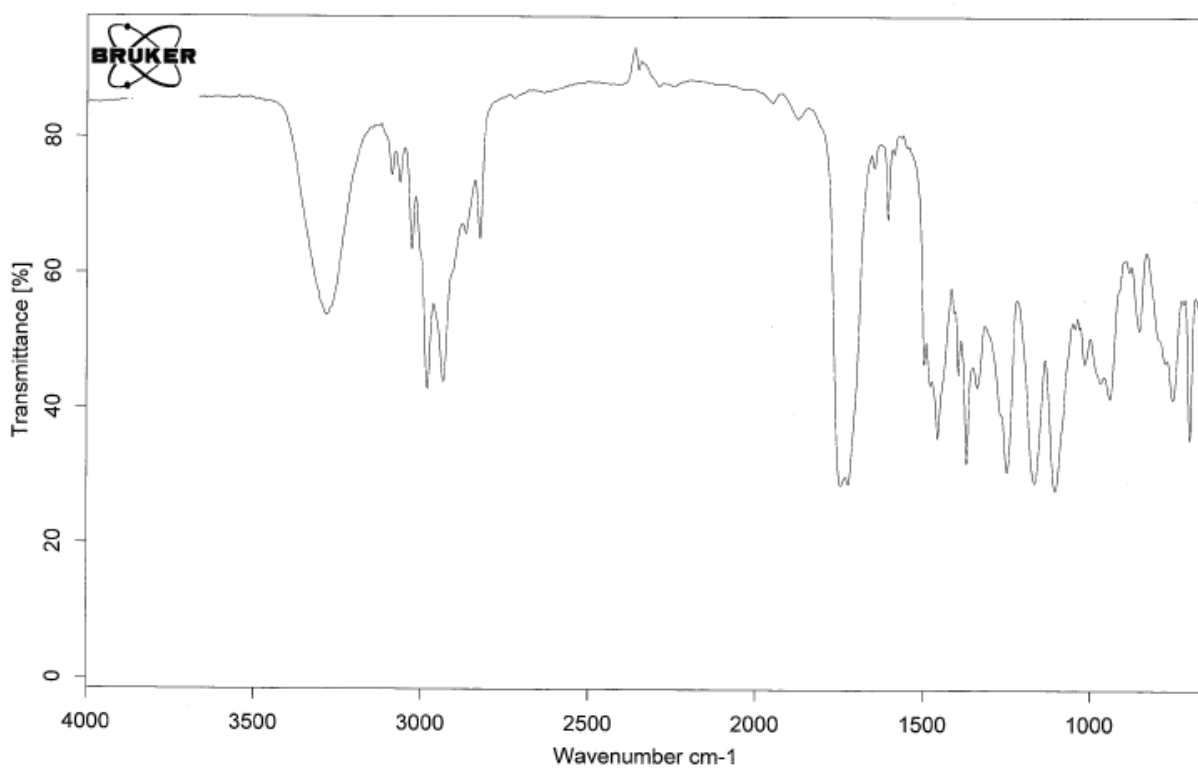
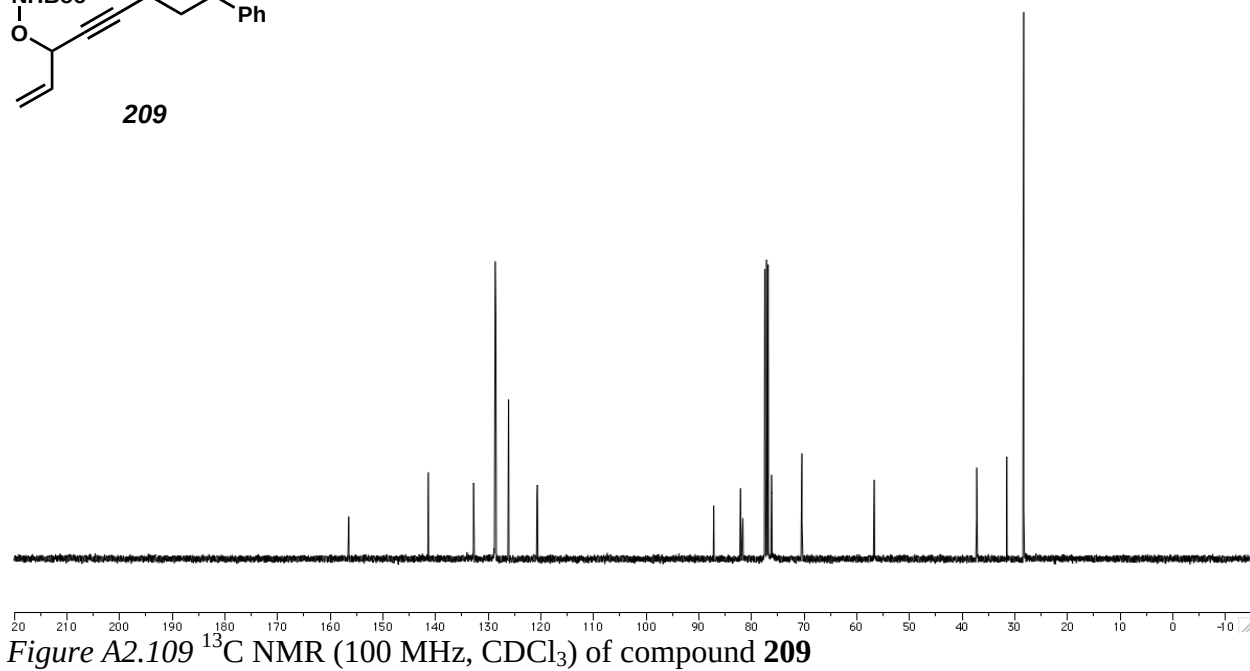
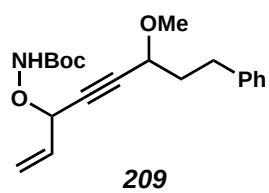
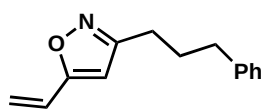


Figure A2.108 ^1H NMR (400 MHz, CDCl_3) of compound **209**





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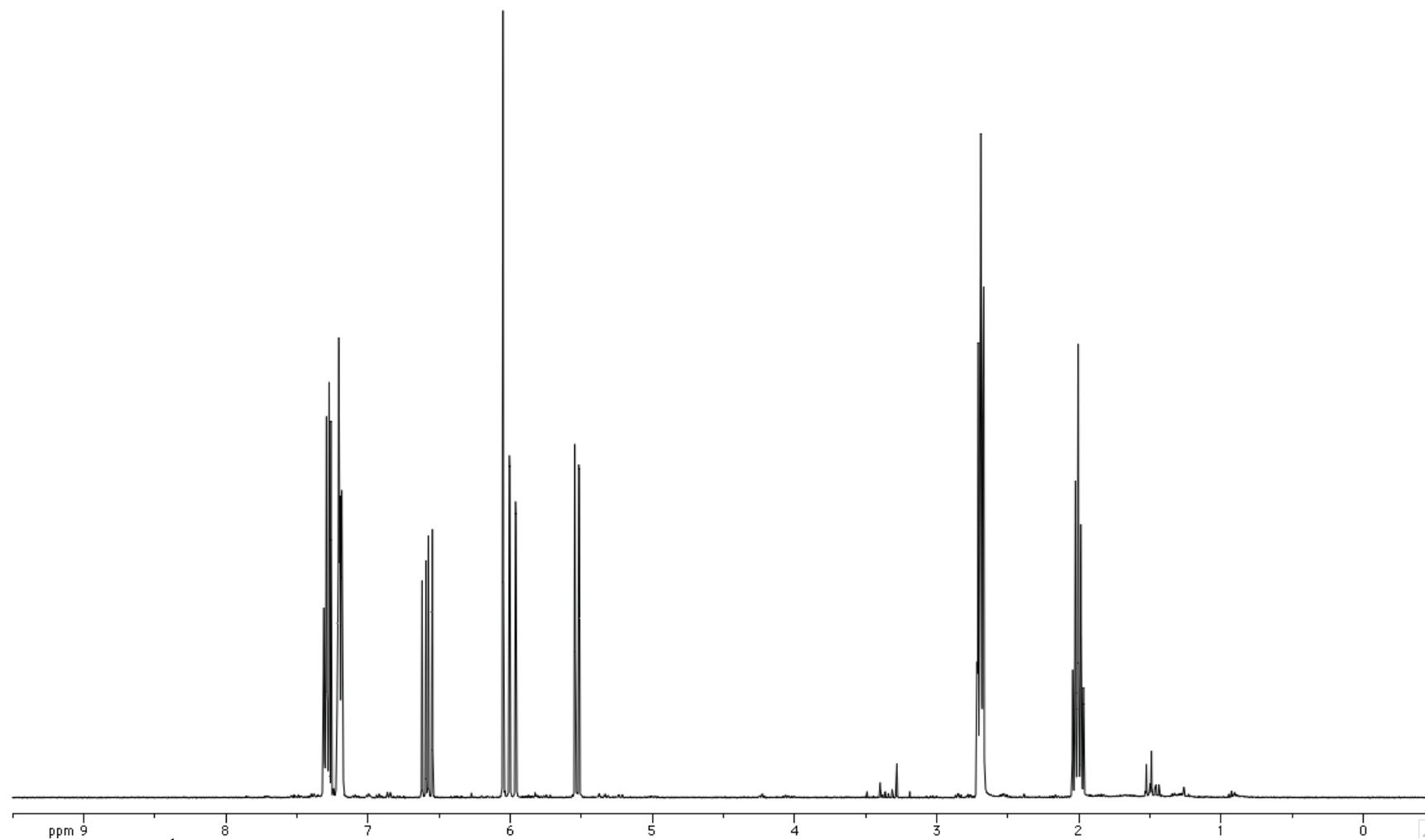
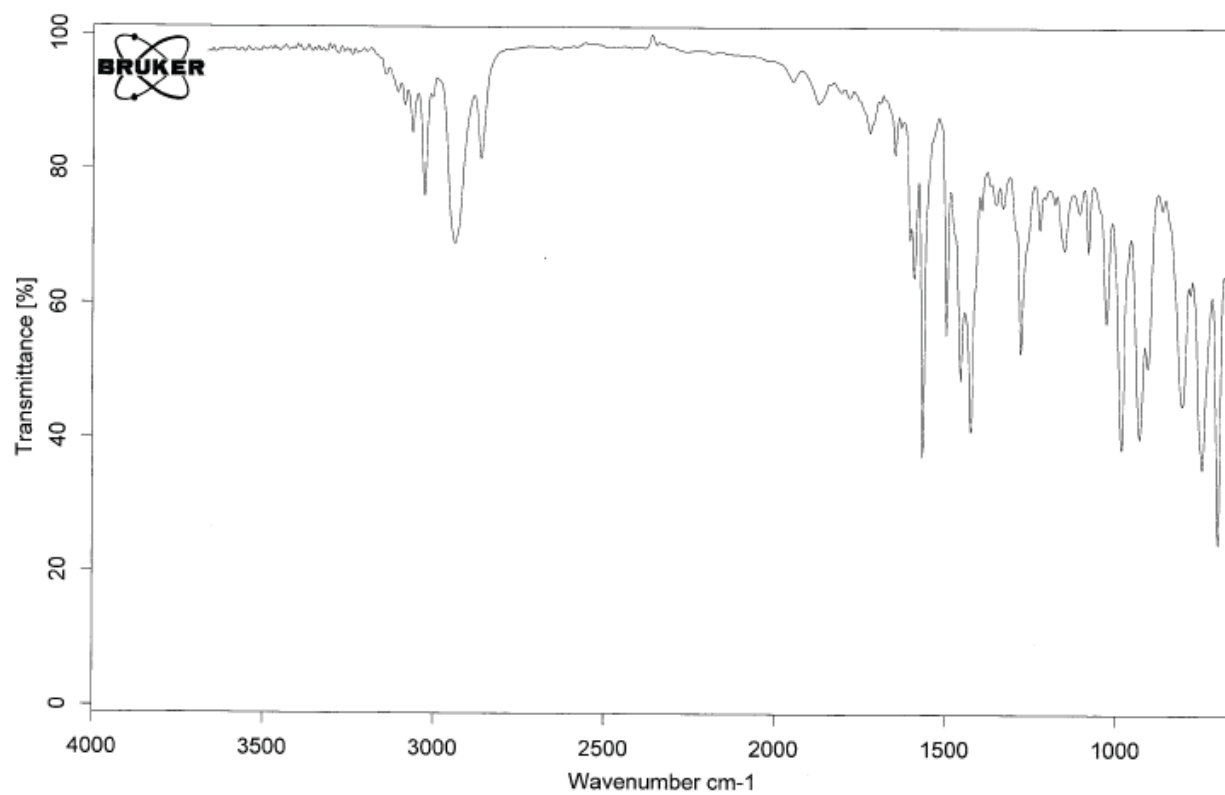
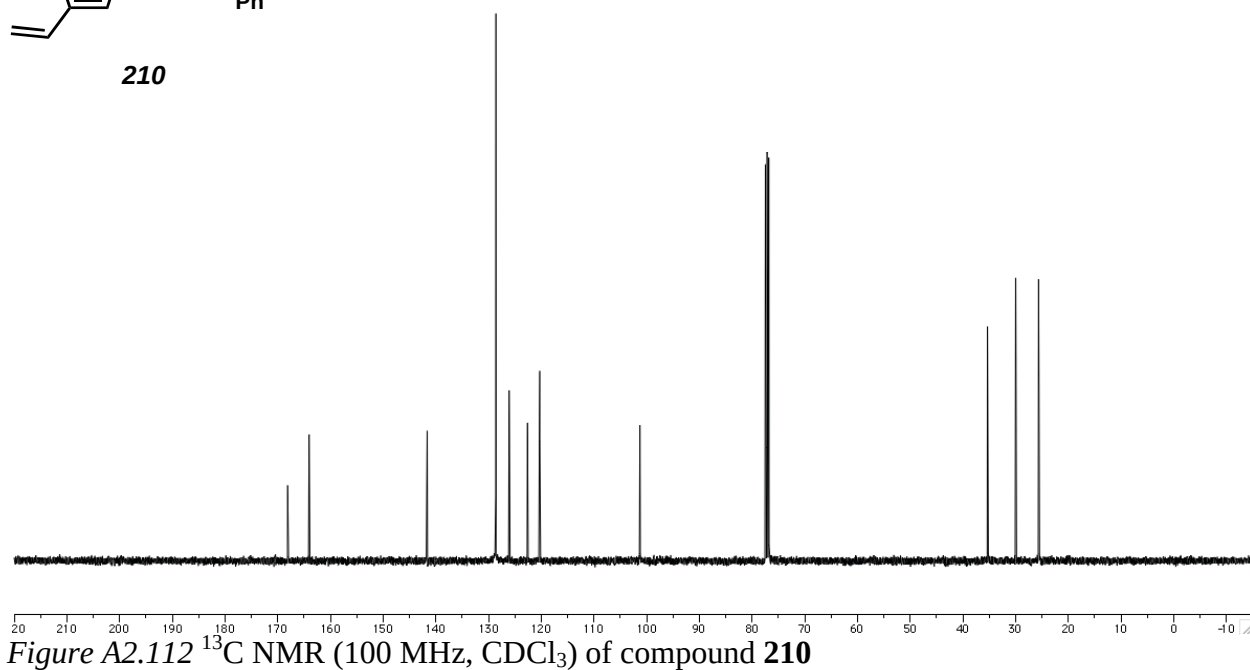
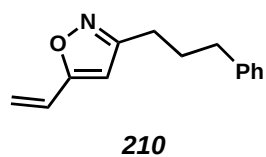


Figure A2.111 ^1H NMR (400 MHz, CDCl_3) of compound **210**



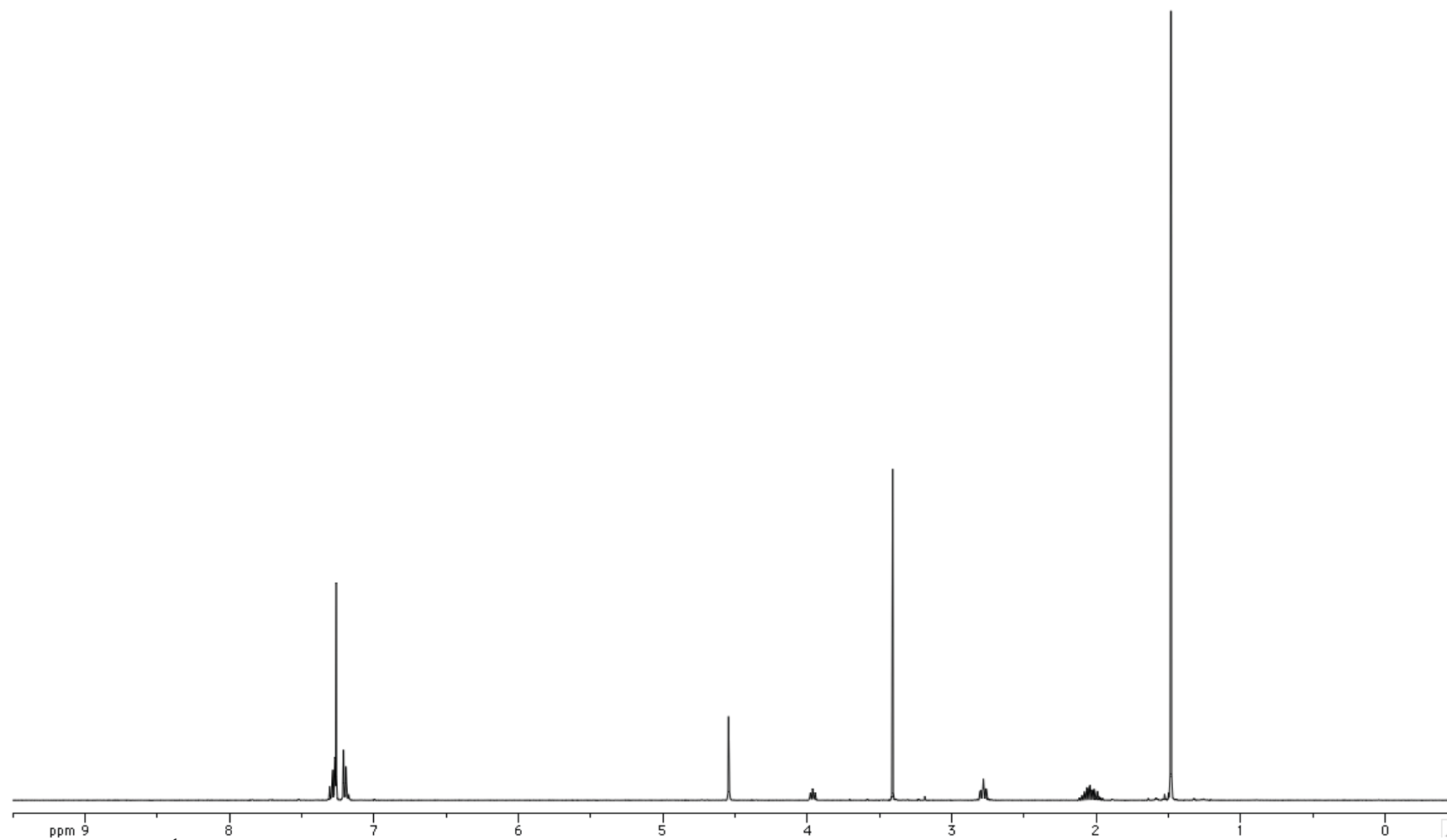
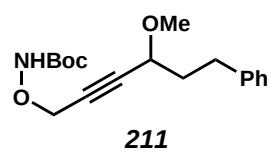
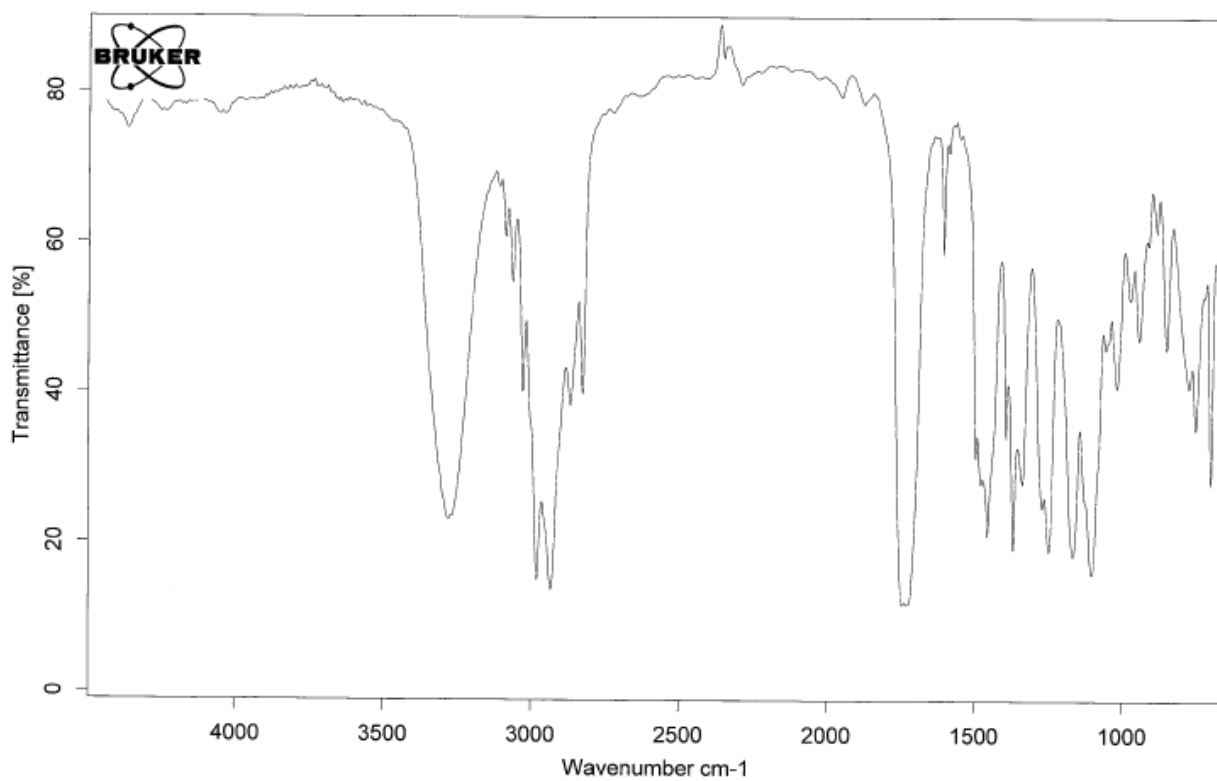
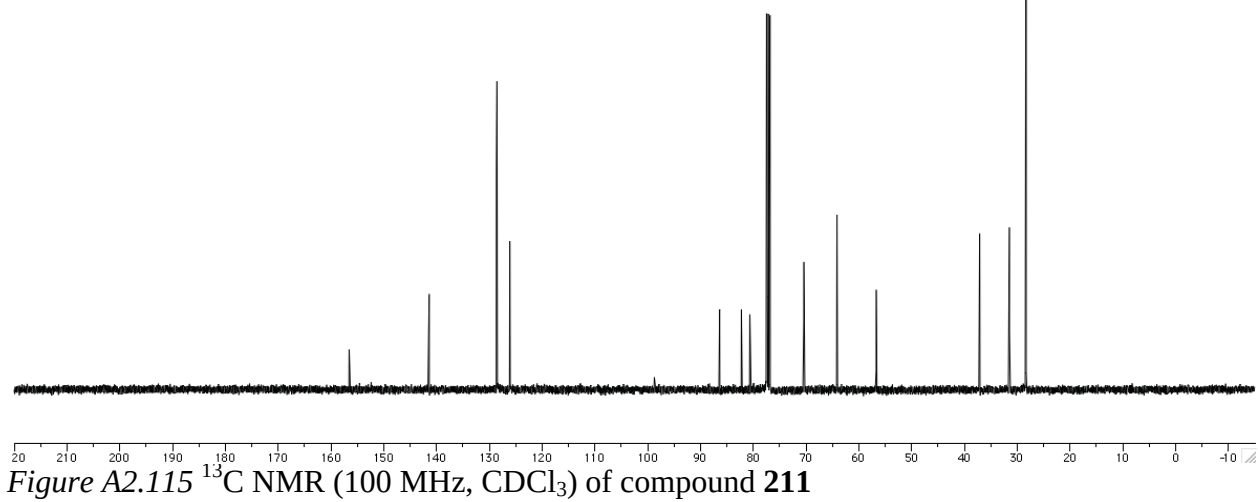
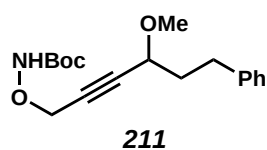


Figure A2.114 ^1H NMR (400 MHz, CDCl_3) of compound **211**



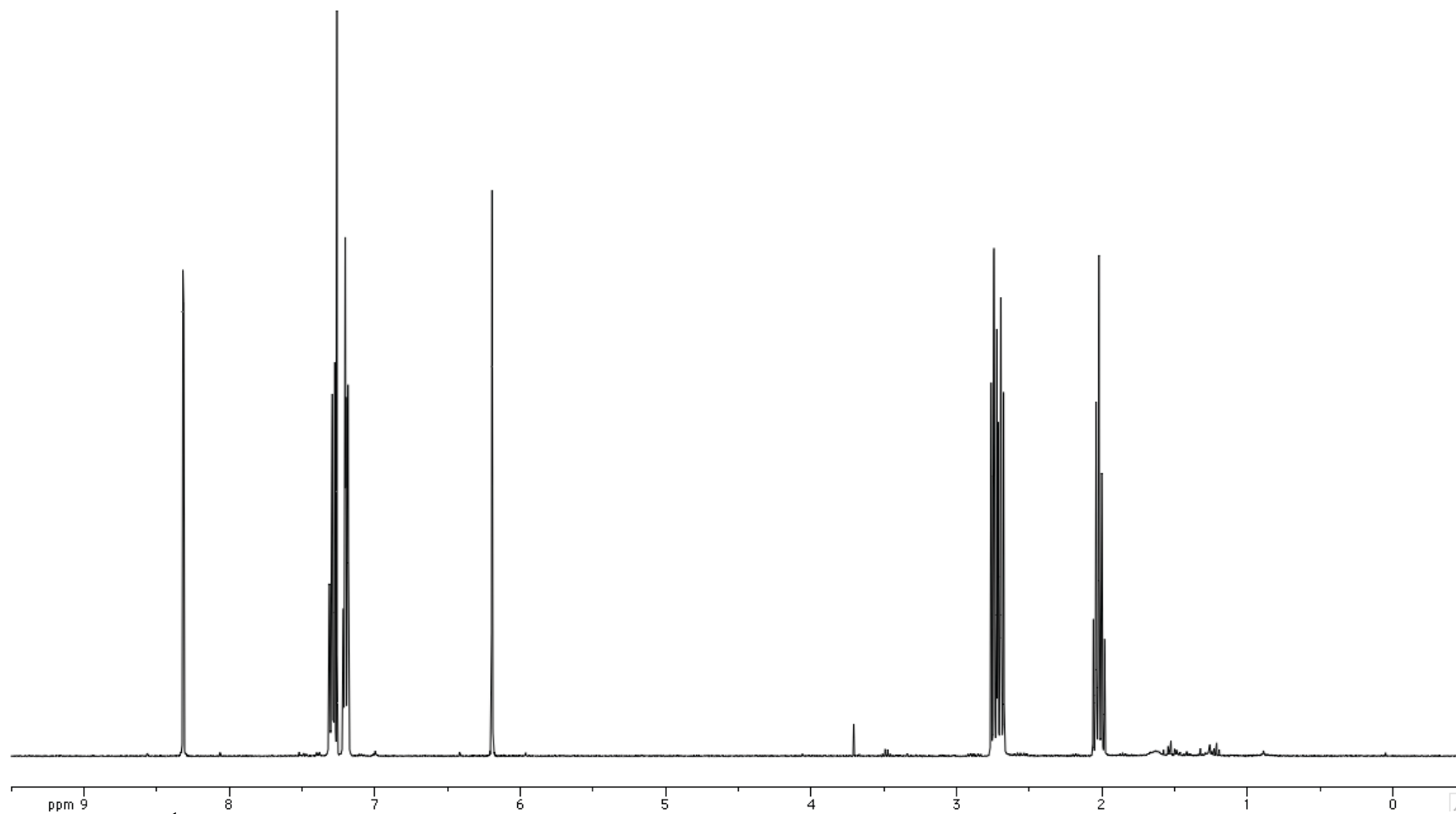
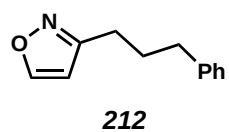
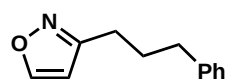


Figure A2.117 ^1H NMR (400 MHz, CDCl_3) of compound **212**



212

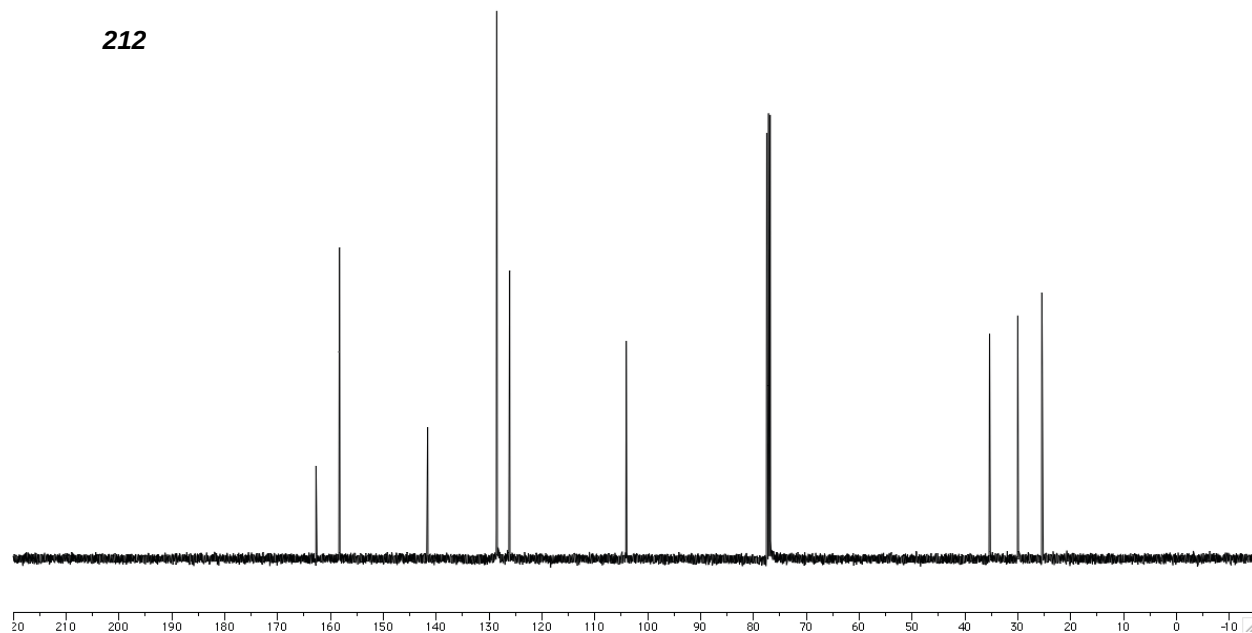


Figure A2.118 ^{13}C NMR (100 MHz, CDCl_3) of compound **212**

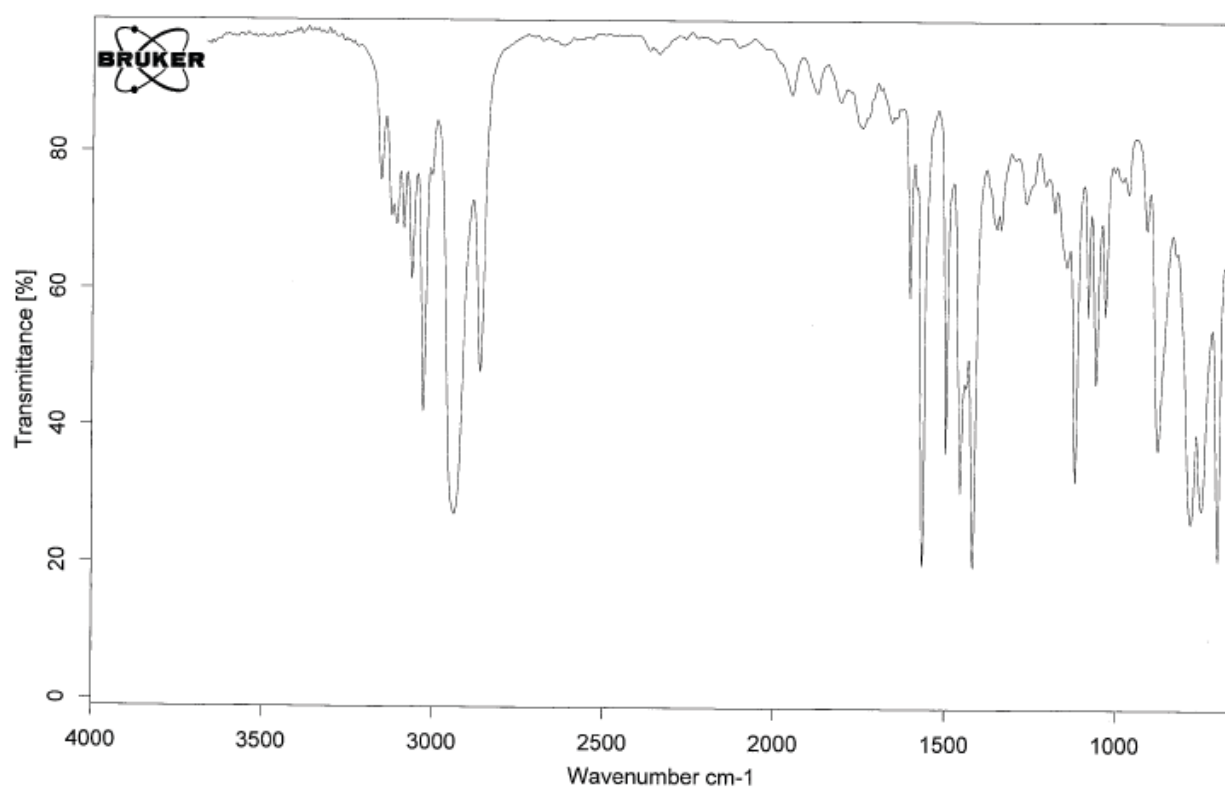


Figure A2.119 Infrared spectrum (thin film) of compound **212**

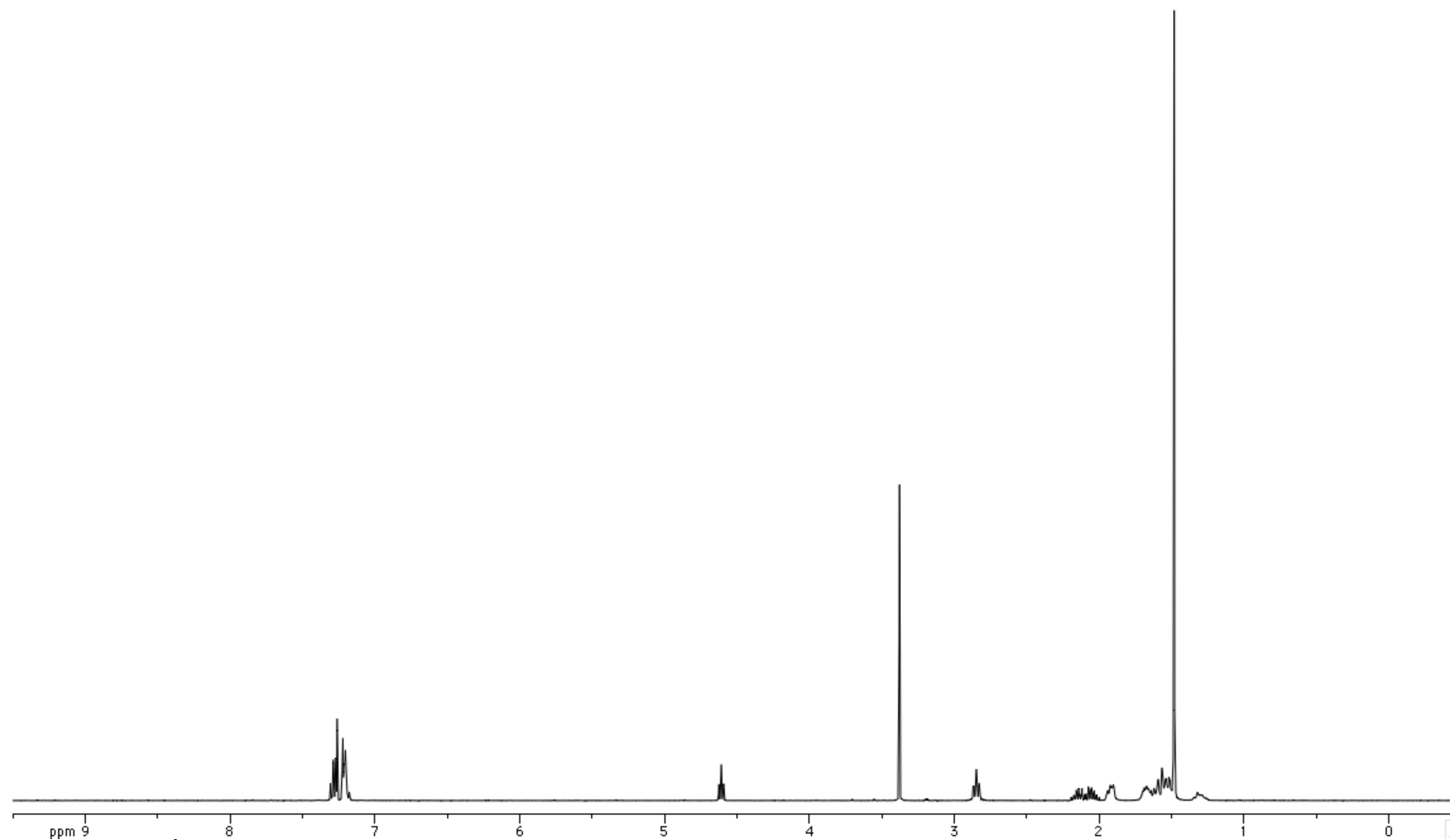
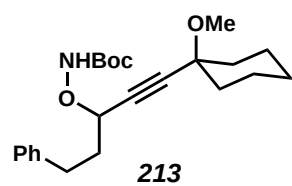
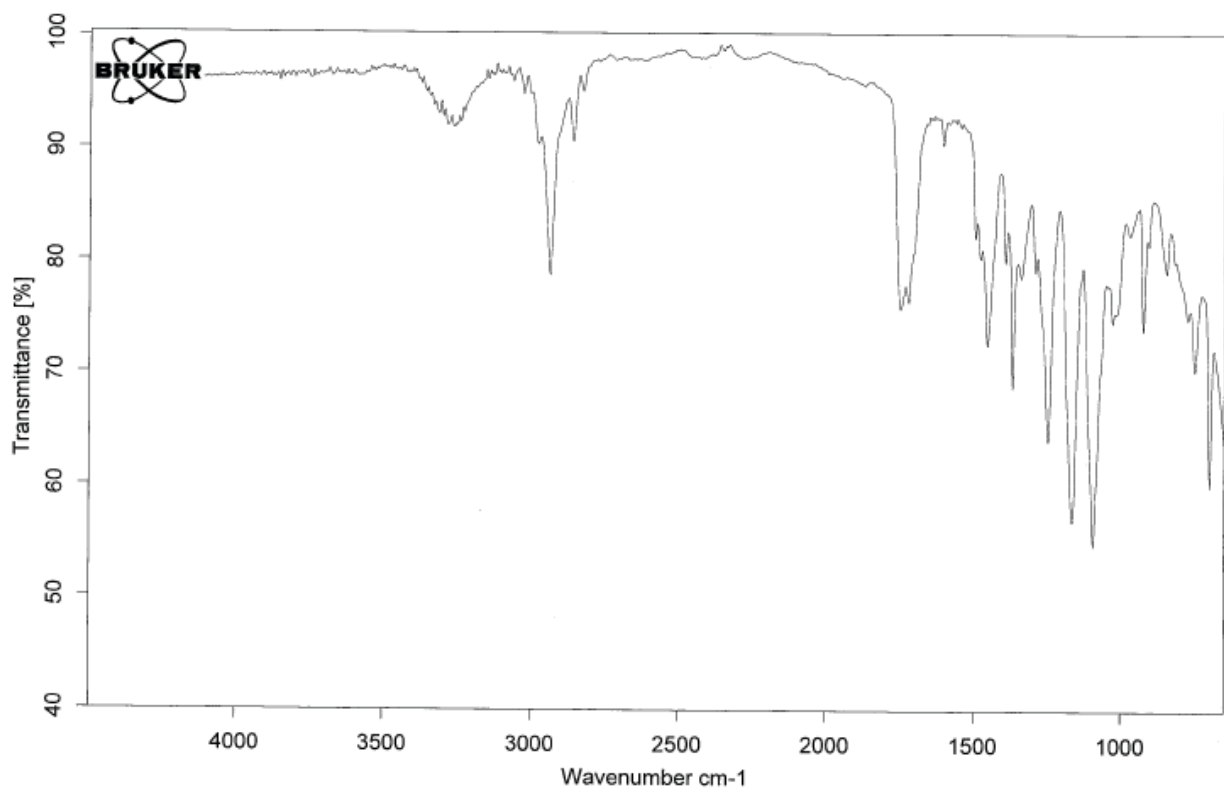
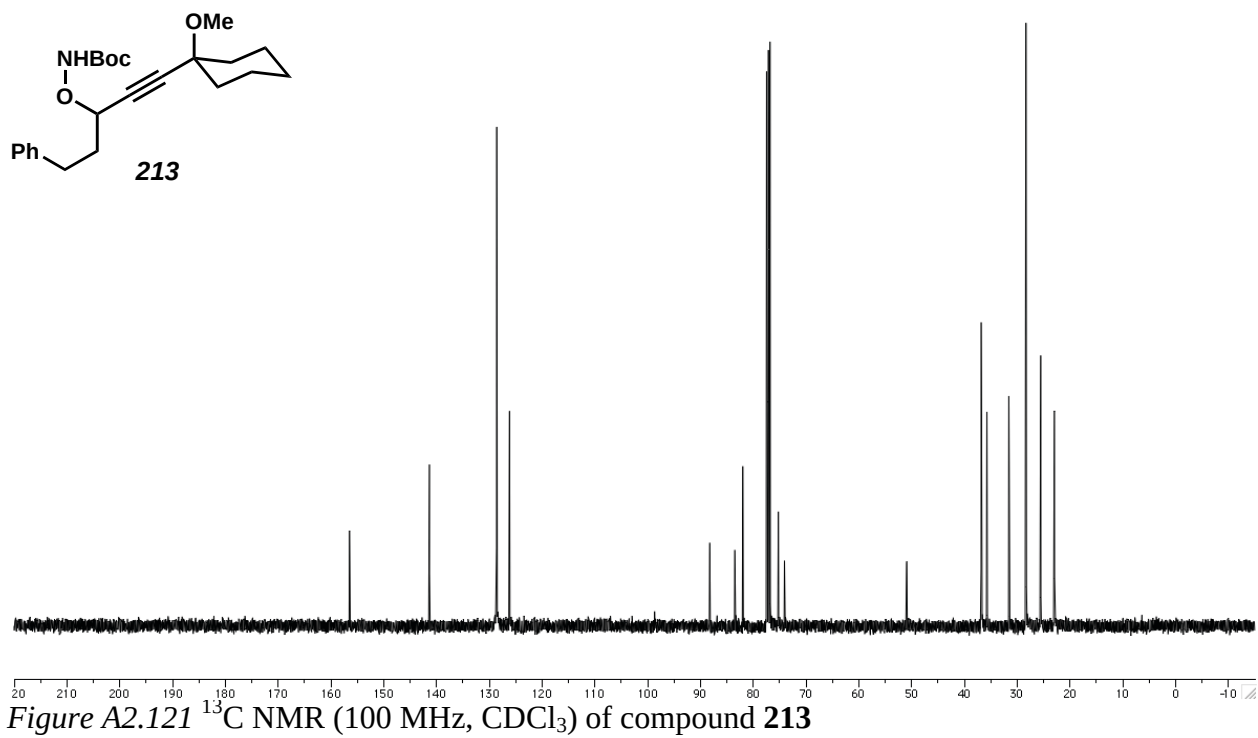


Figure A2.120 ^1H NMR (400 MHz, CDCl_3) of compound **213**



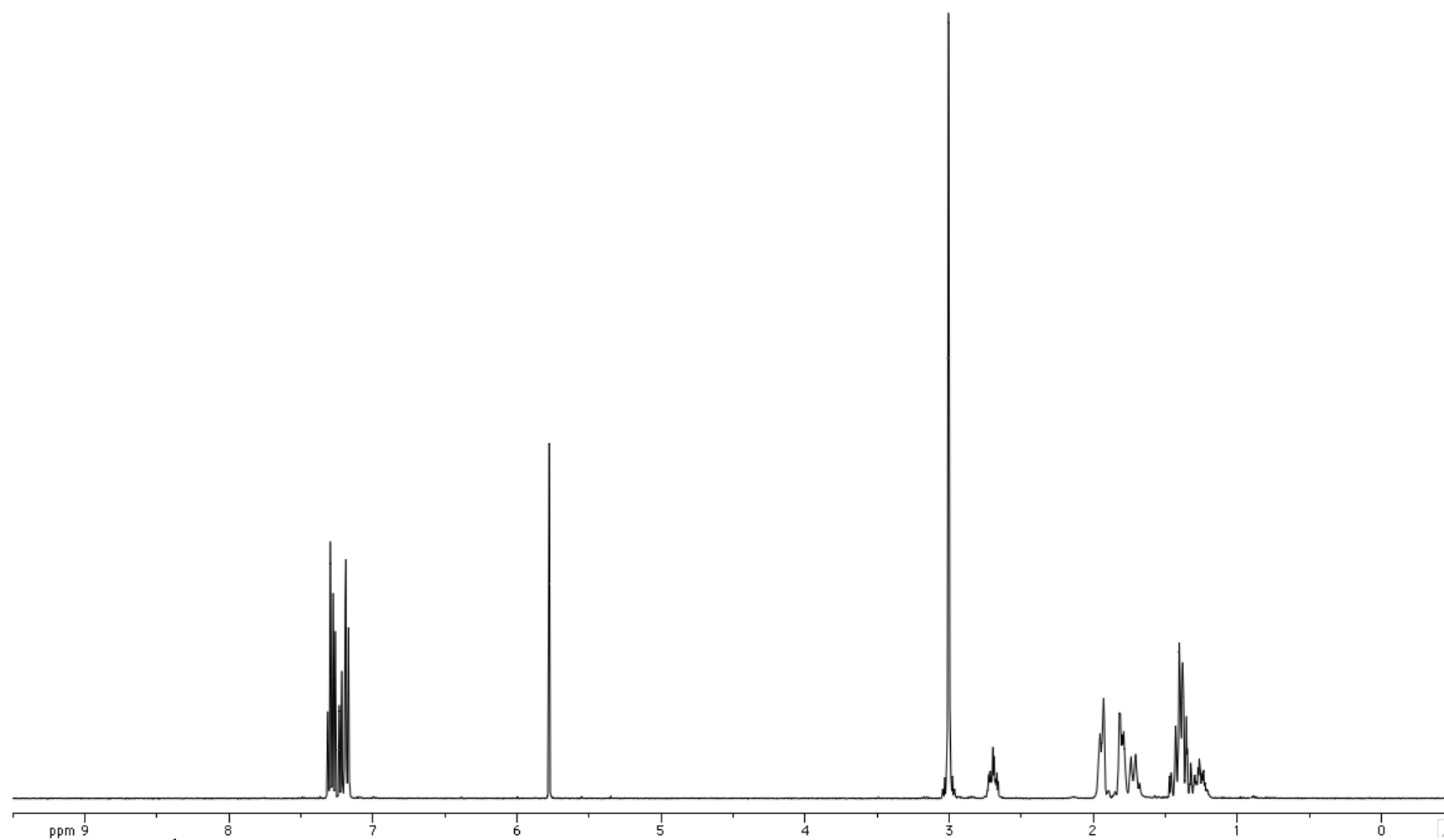
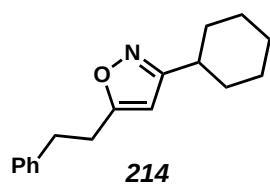


Figure A2.123 ^1H NMR (400 MHz, CDCl_3) of compound **214**

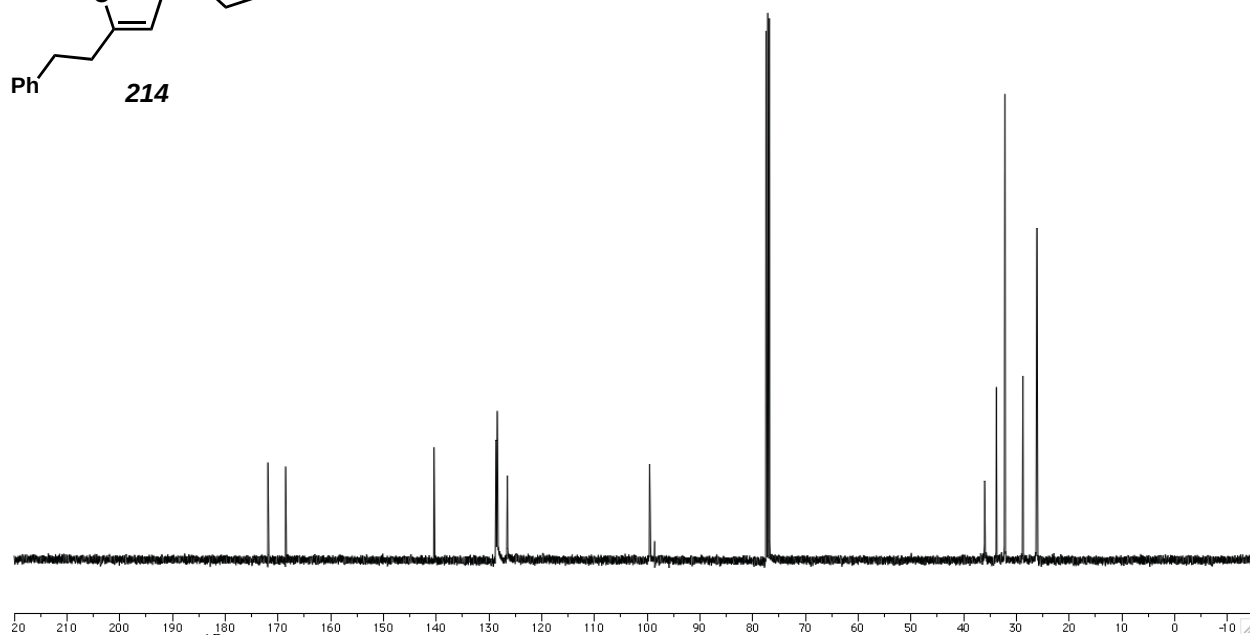
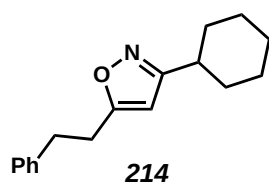


Figure A2.124 ^{13}C NMR (100 MHz, CDCl_3) of compound **214**

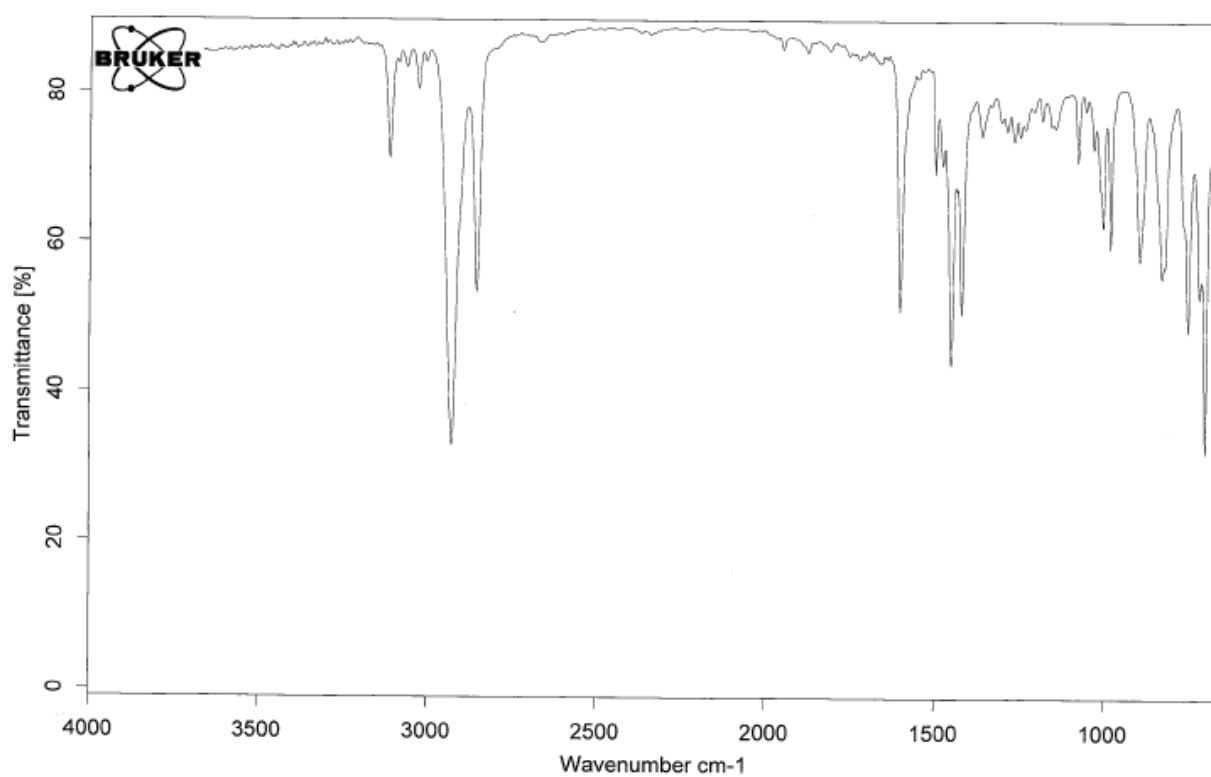


Figure A2.125 Infrared spectrum (thin film) of compound **214**

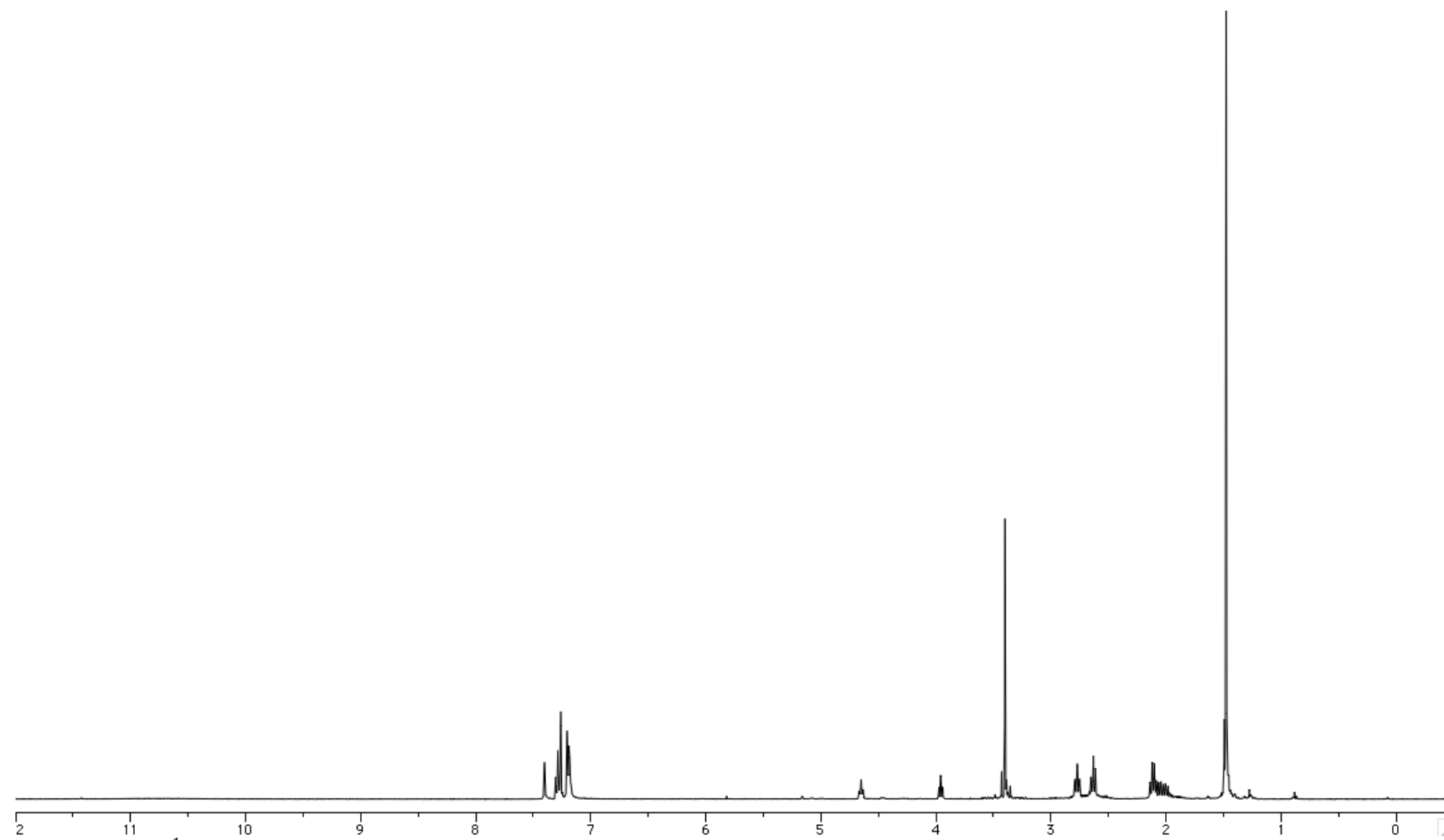
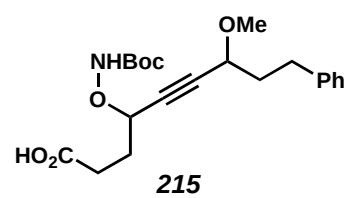
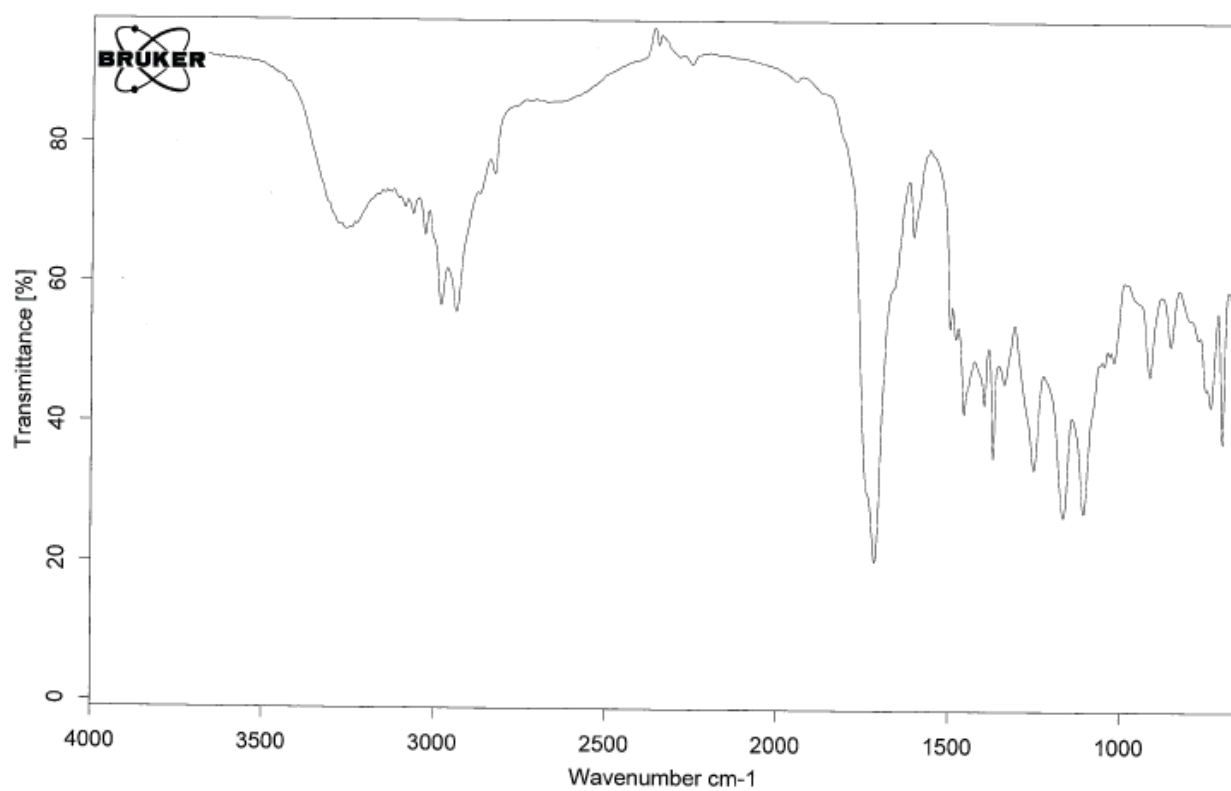
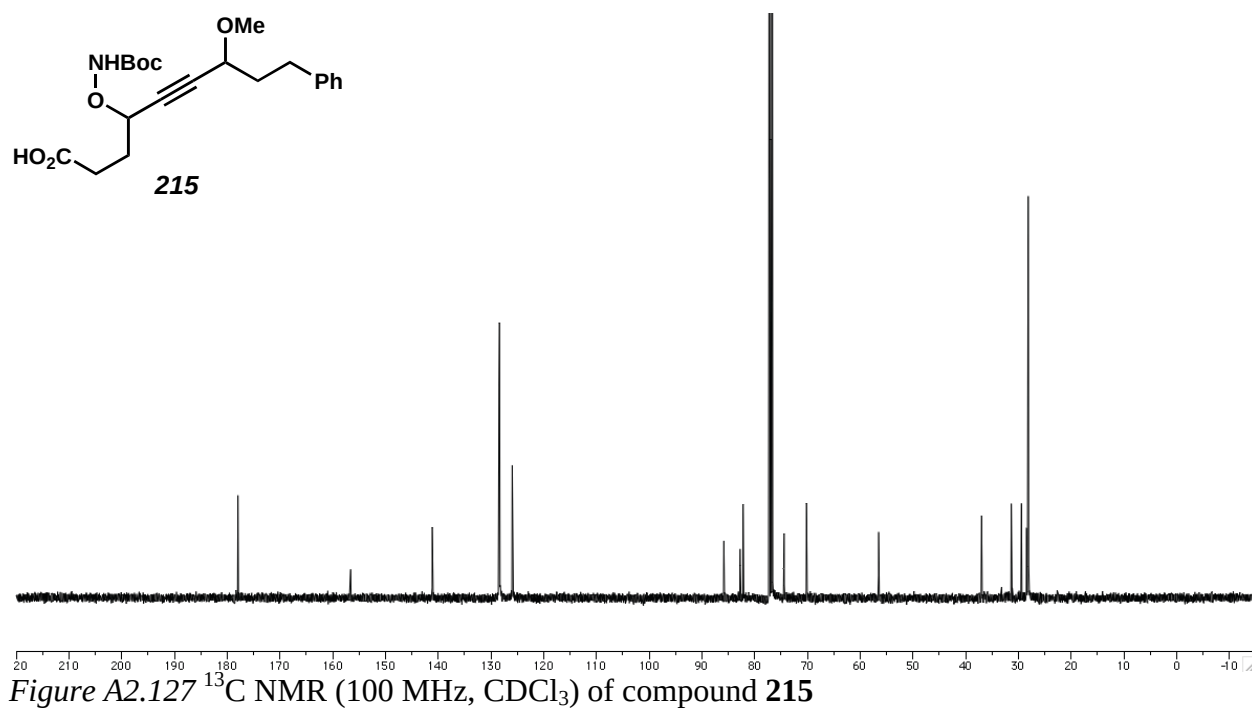


Figure A2.126 ^1H NMR (400 MHz, CDCl_3) of compound **215**



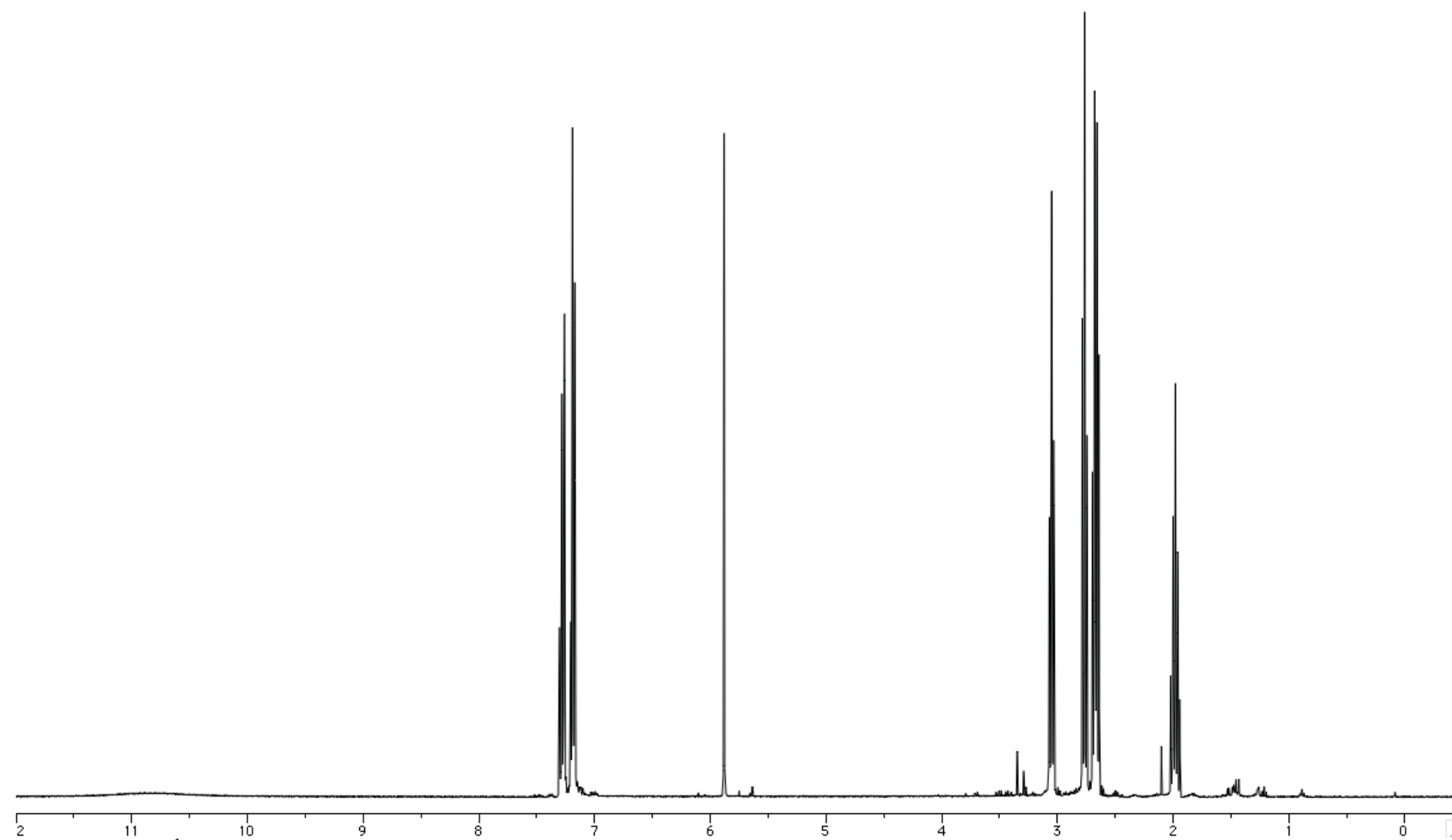
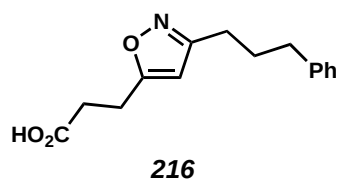


Figure A2.129 ^1H NMR (400 MHz, CDCl_3) of compound **216**

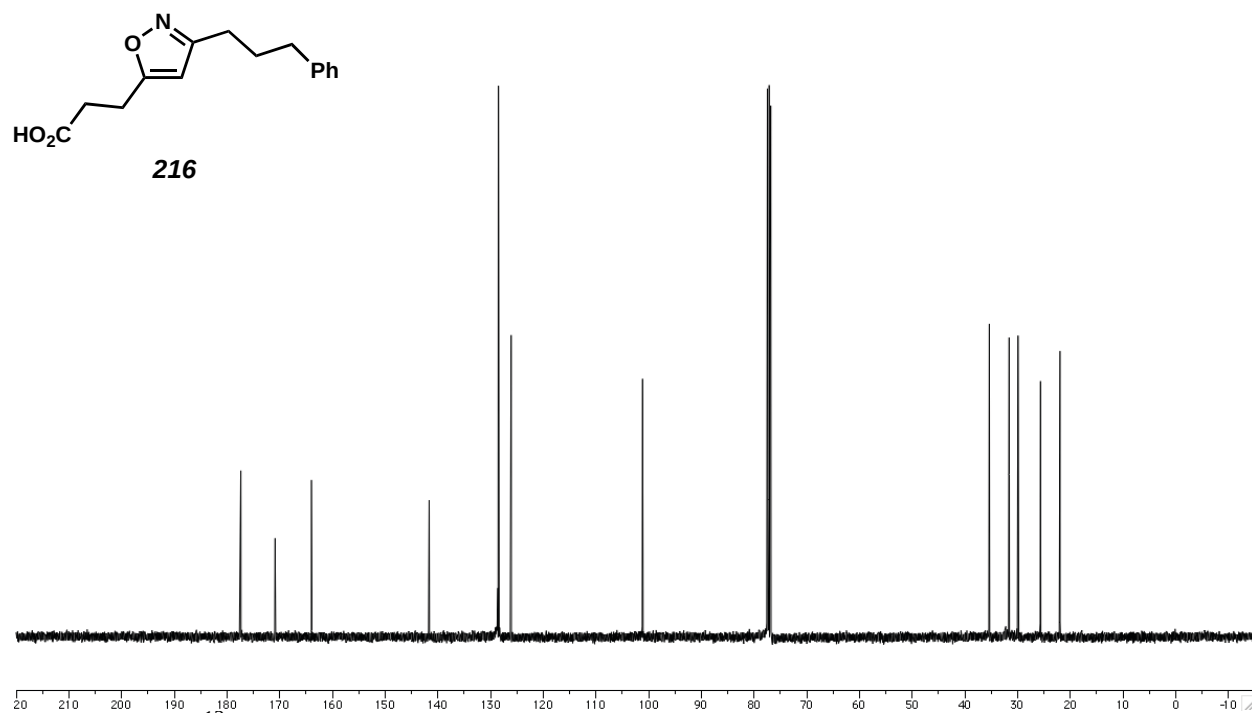


Figure A2.130 ^{13}C NMR (100 MHz, CDCl_3) of compound **216**

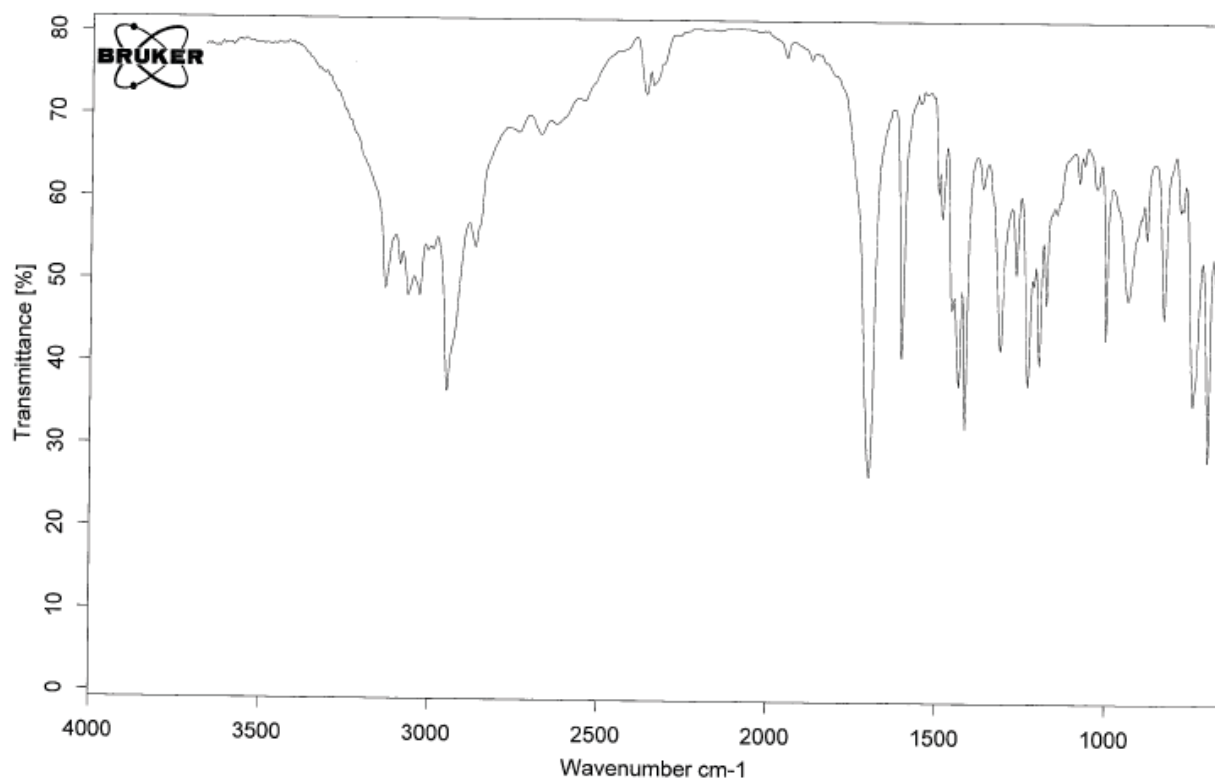


Figure A2.131 Infrared spectrum (thin film) of compound **216**

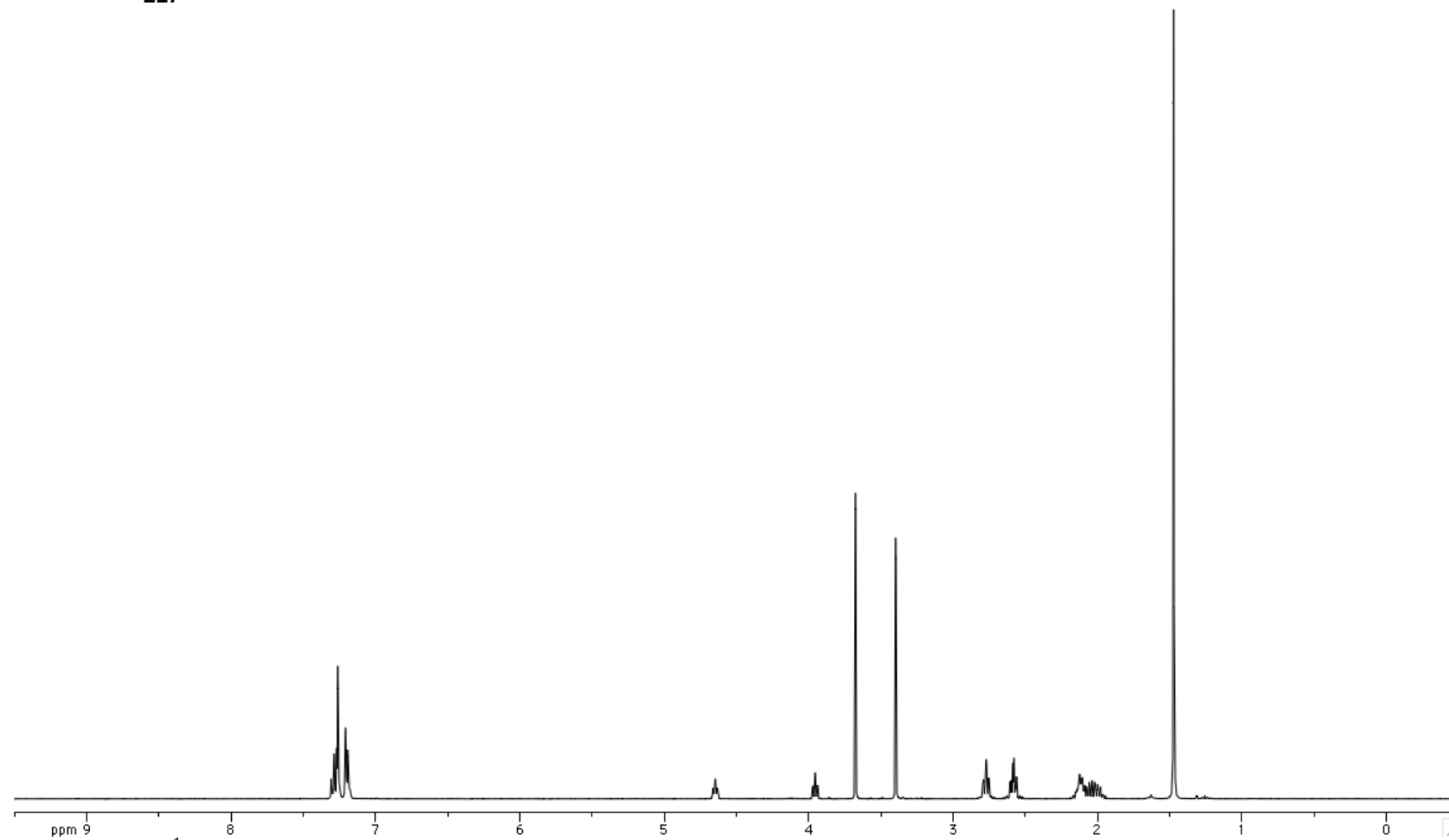
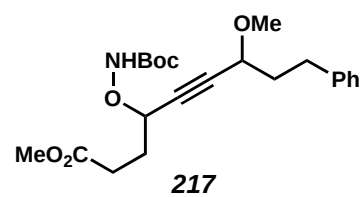
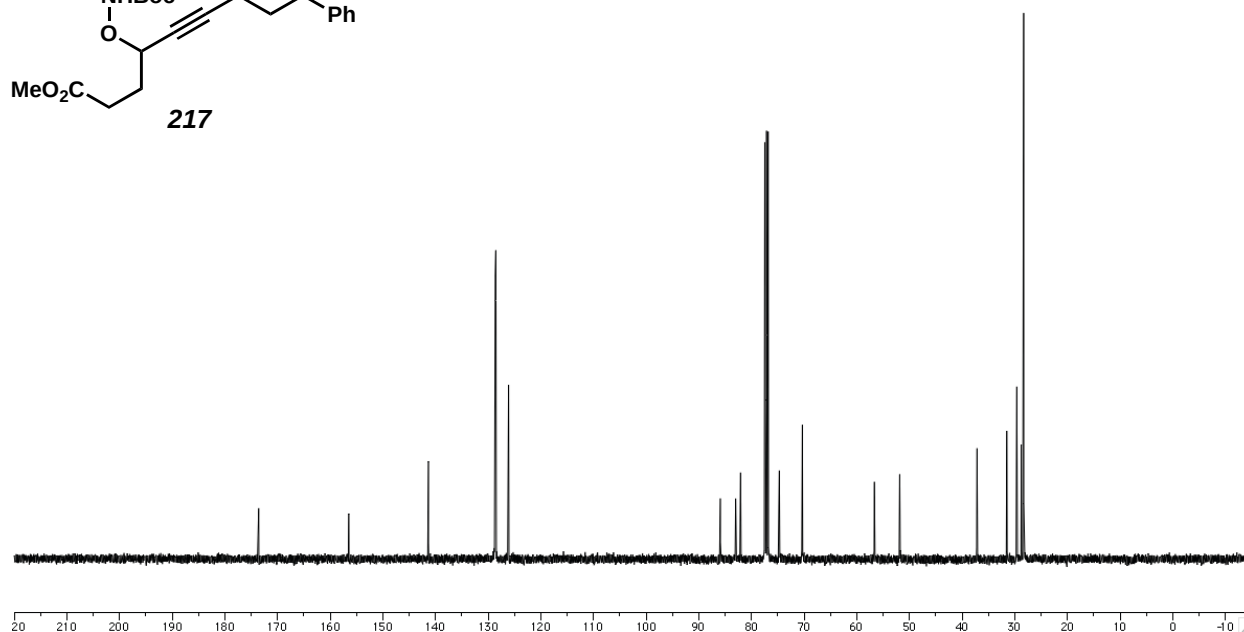


Figure A2.132 ¹H NMR (400 MHz, CDCl₃) of compound **217**



544

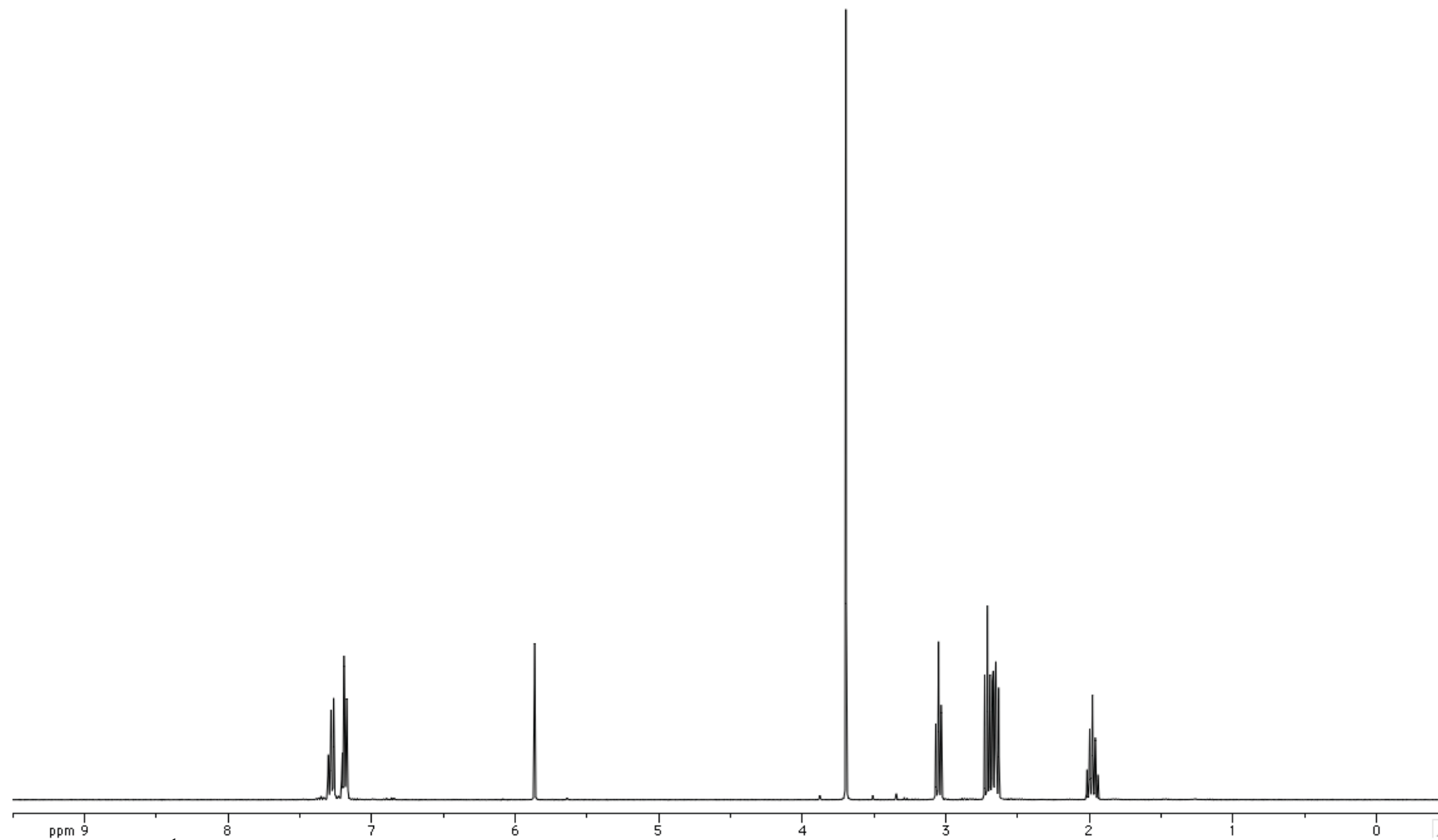
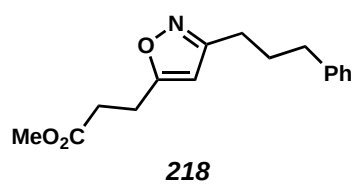
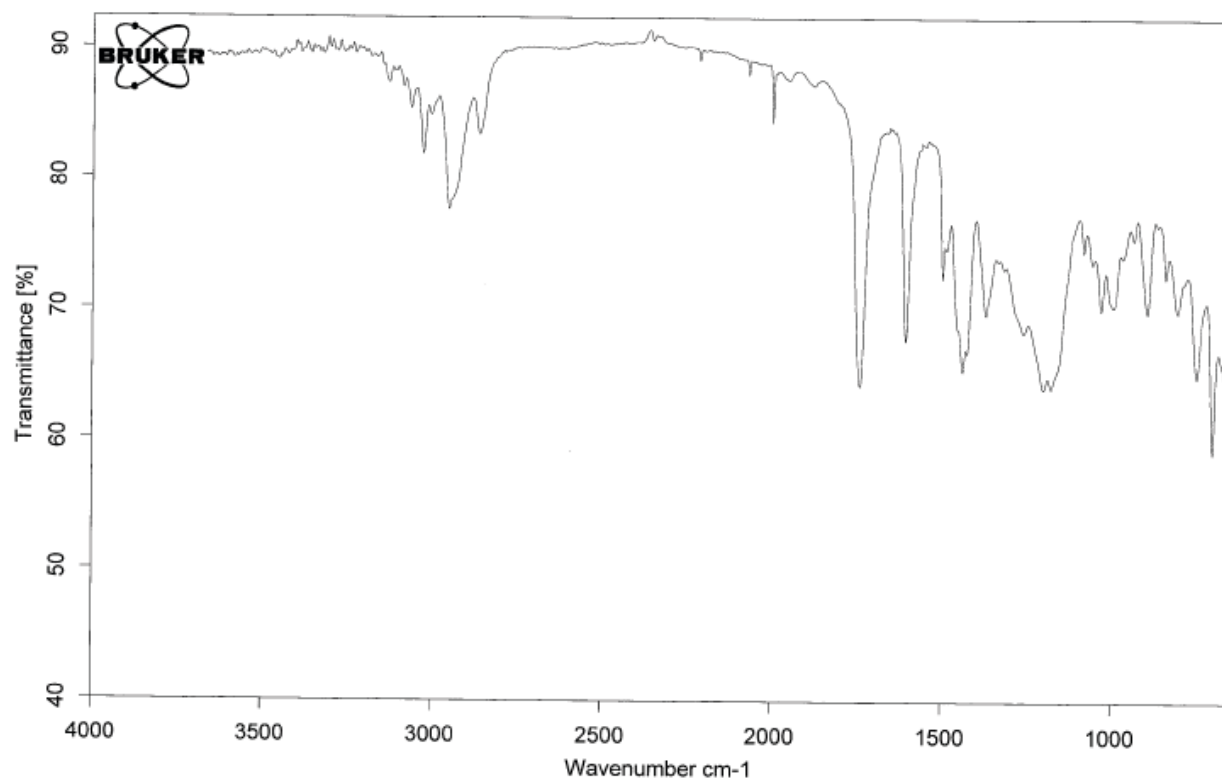
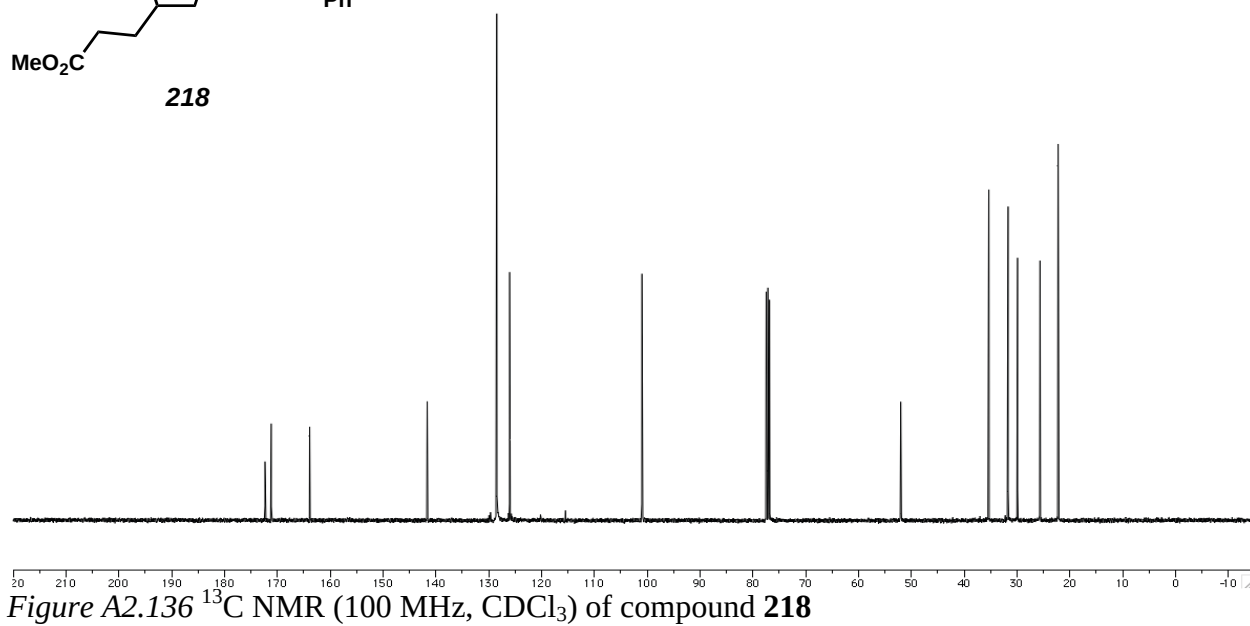
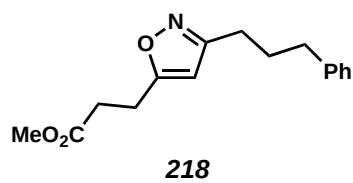


Figure A2.135 ^1H NMR (400 MHz, CDCl_3) of compound **218**



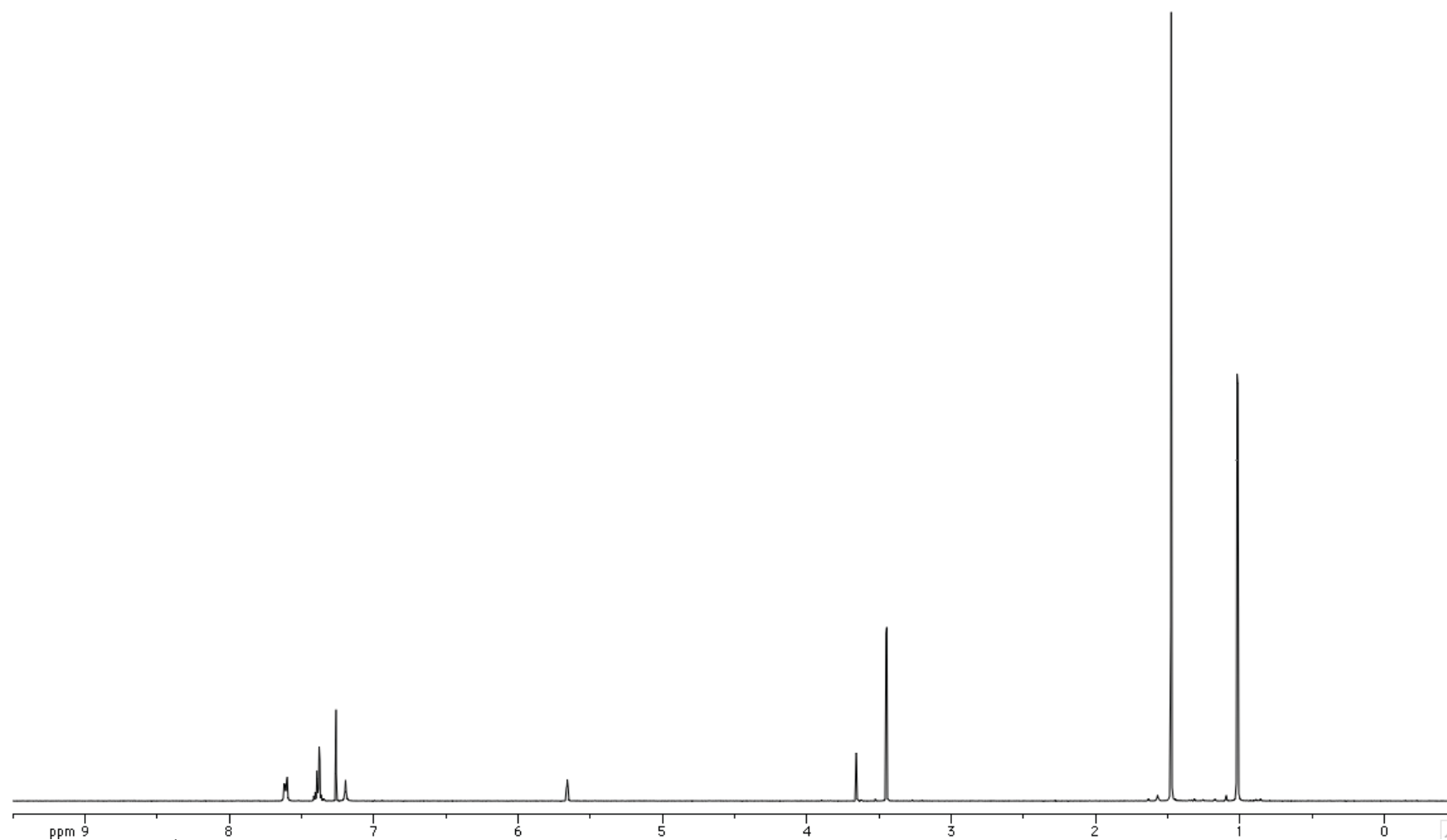
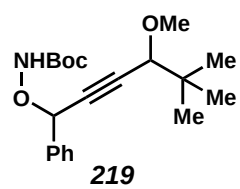


Figure A2.138 ^1H NMR (400 MHz, CDCl_3) of compound **219**

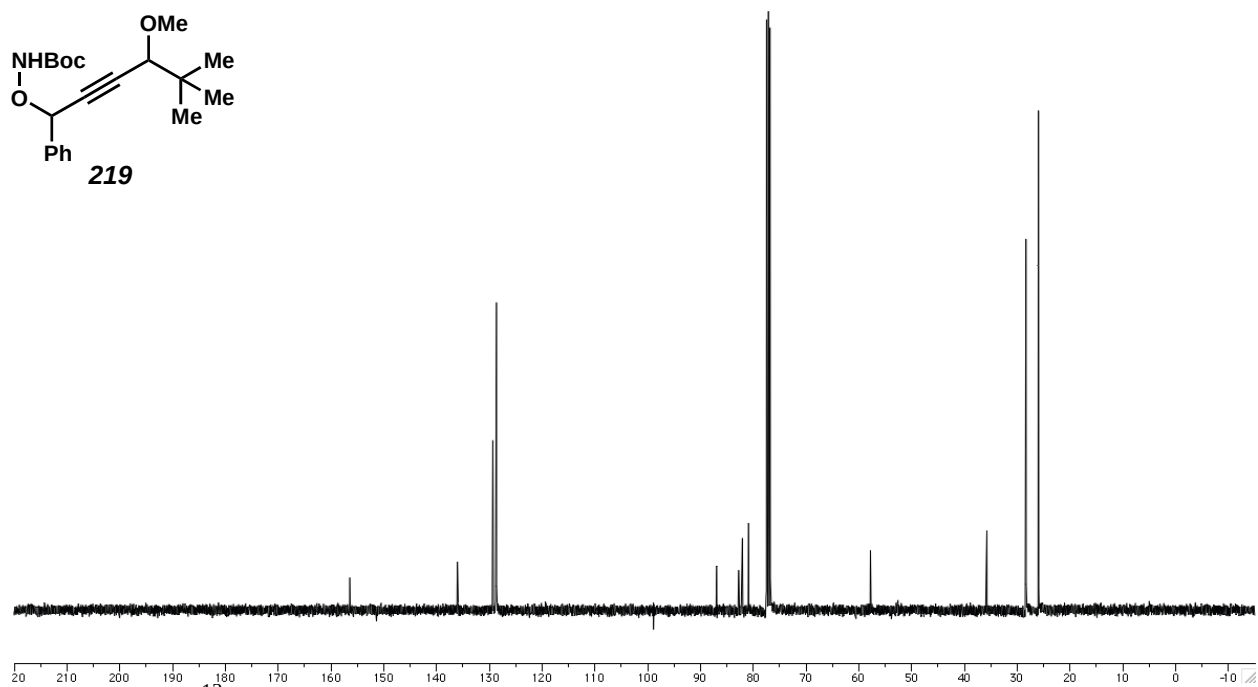


Figure A2.139 ^{13}C NMR (100 MHz, CDCl_3) of compound **219**

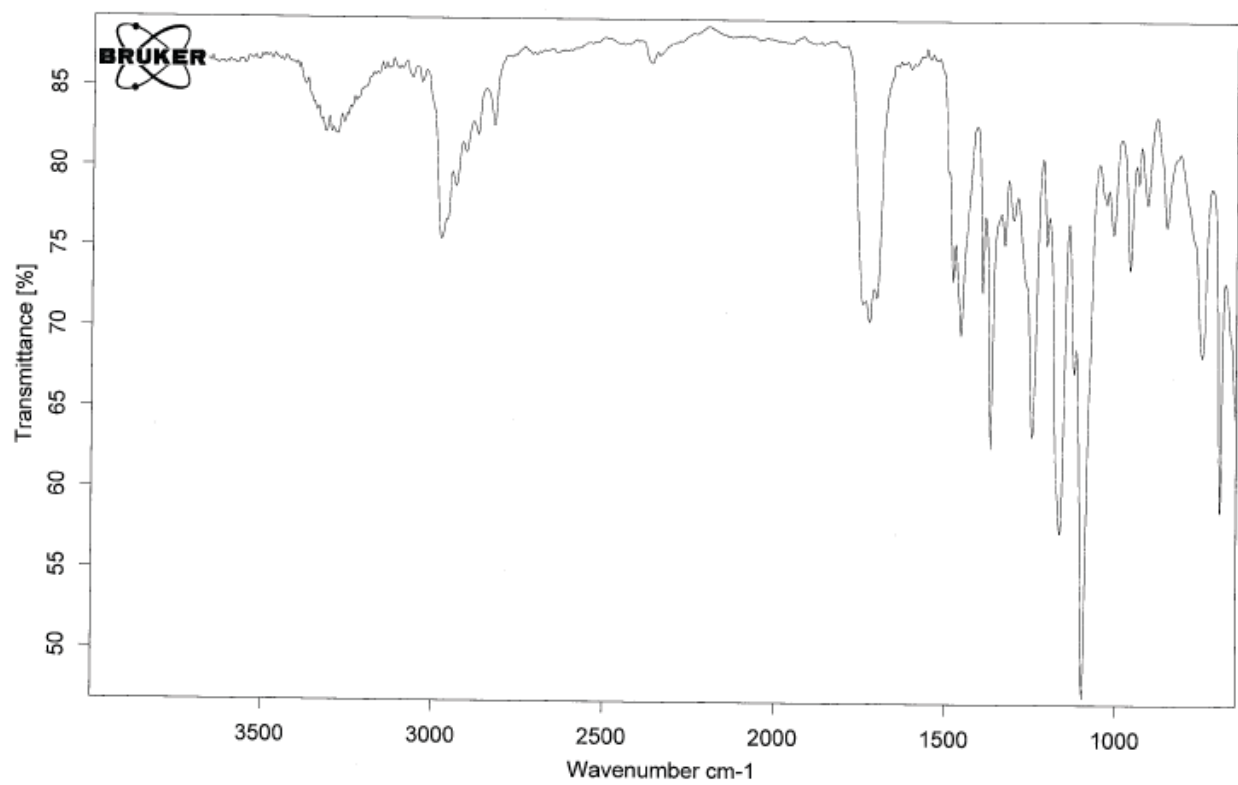


Figure A2.140 Infrared spectrum (thin film) of compound **219**

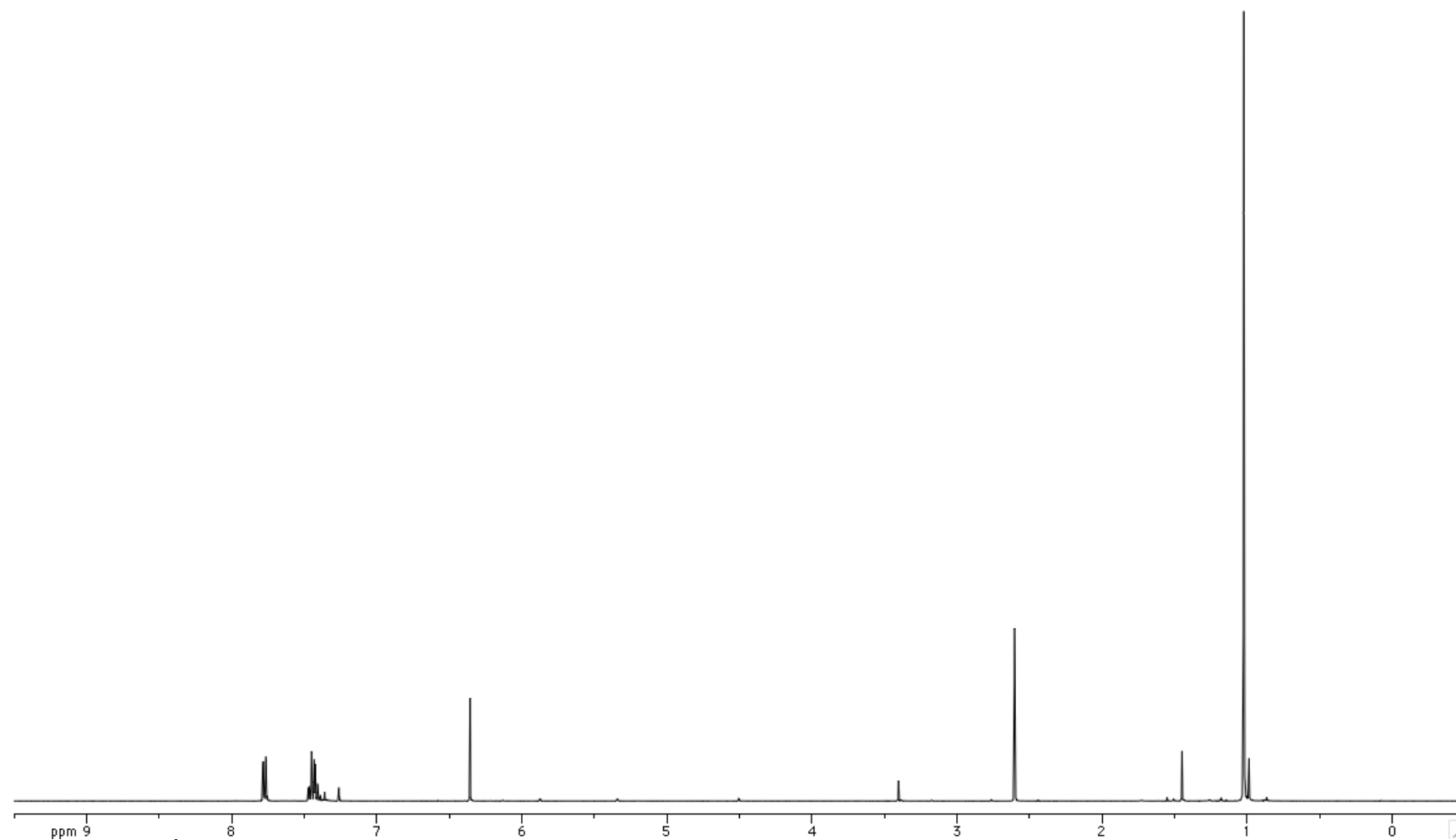
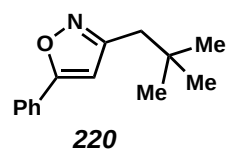
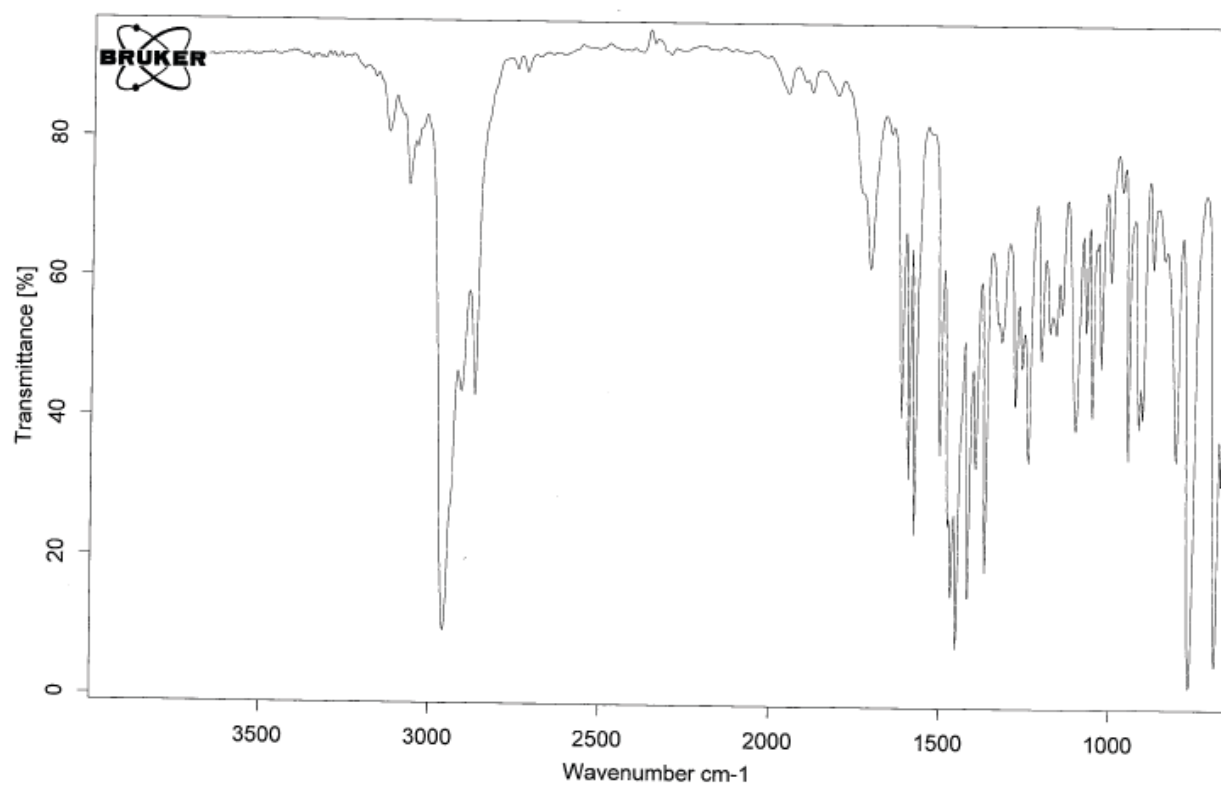
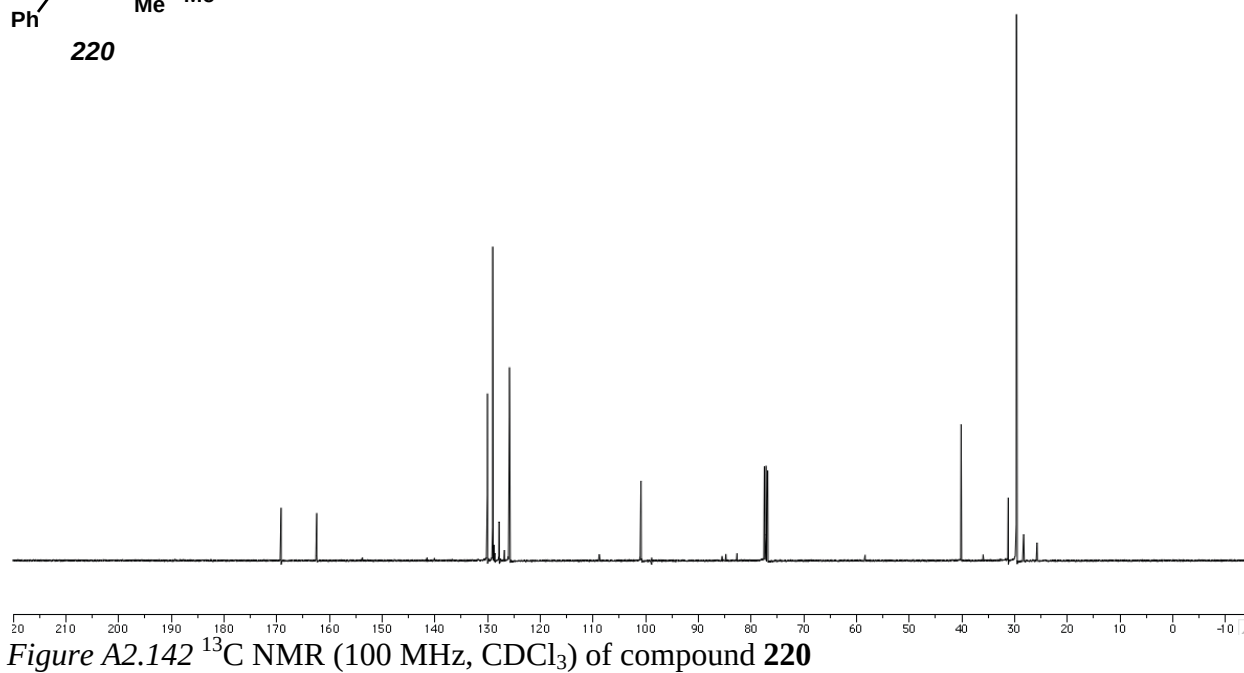
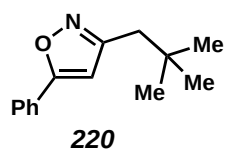


Figure A2.141 ^1H NMR (400 MHz, CDCl_3) of compound **220**



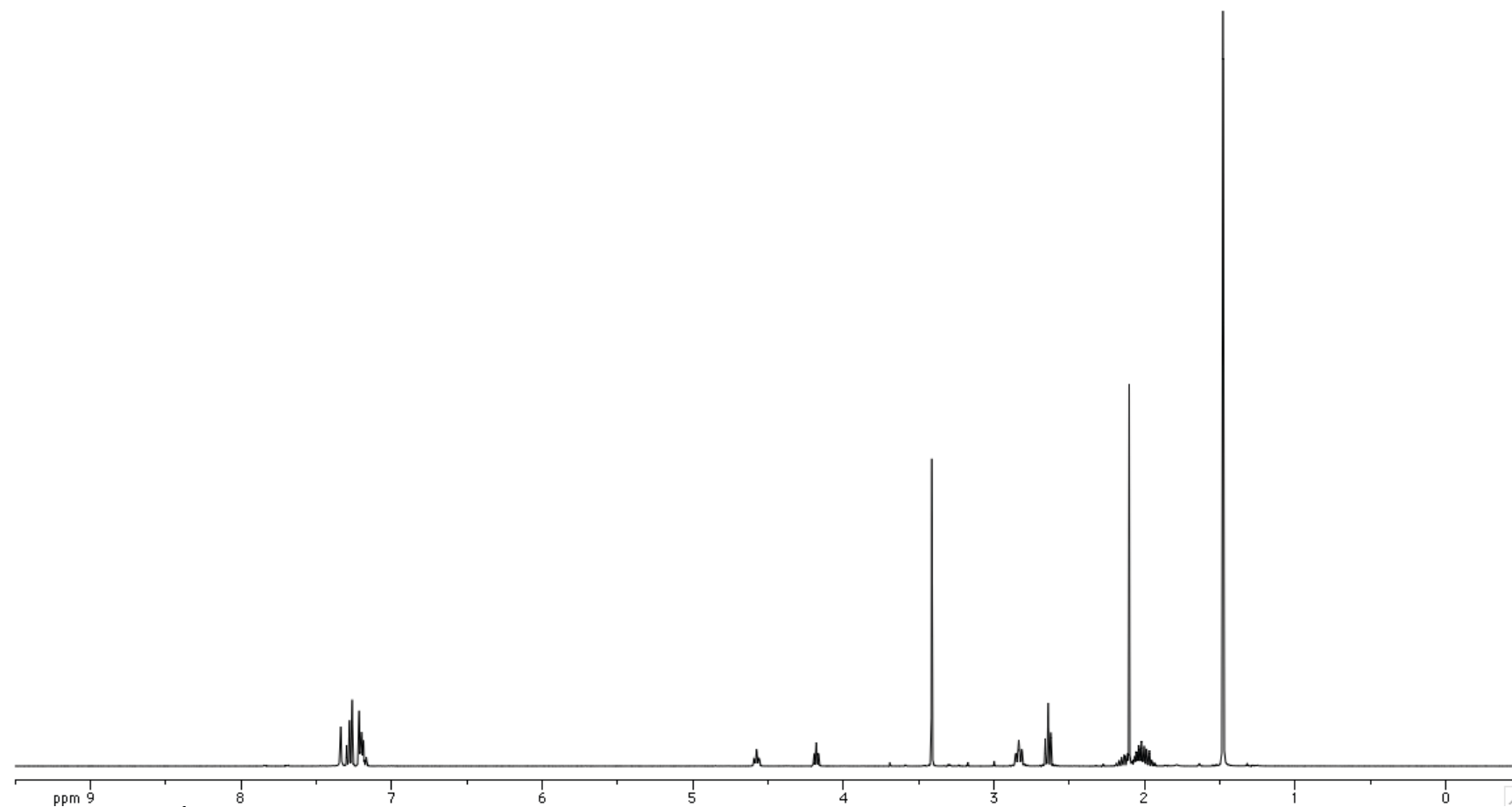
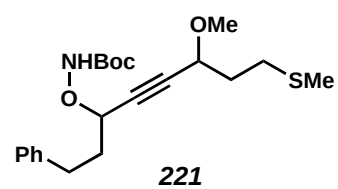
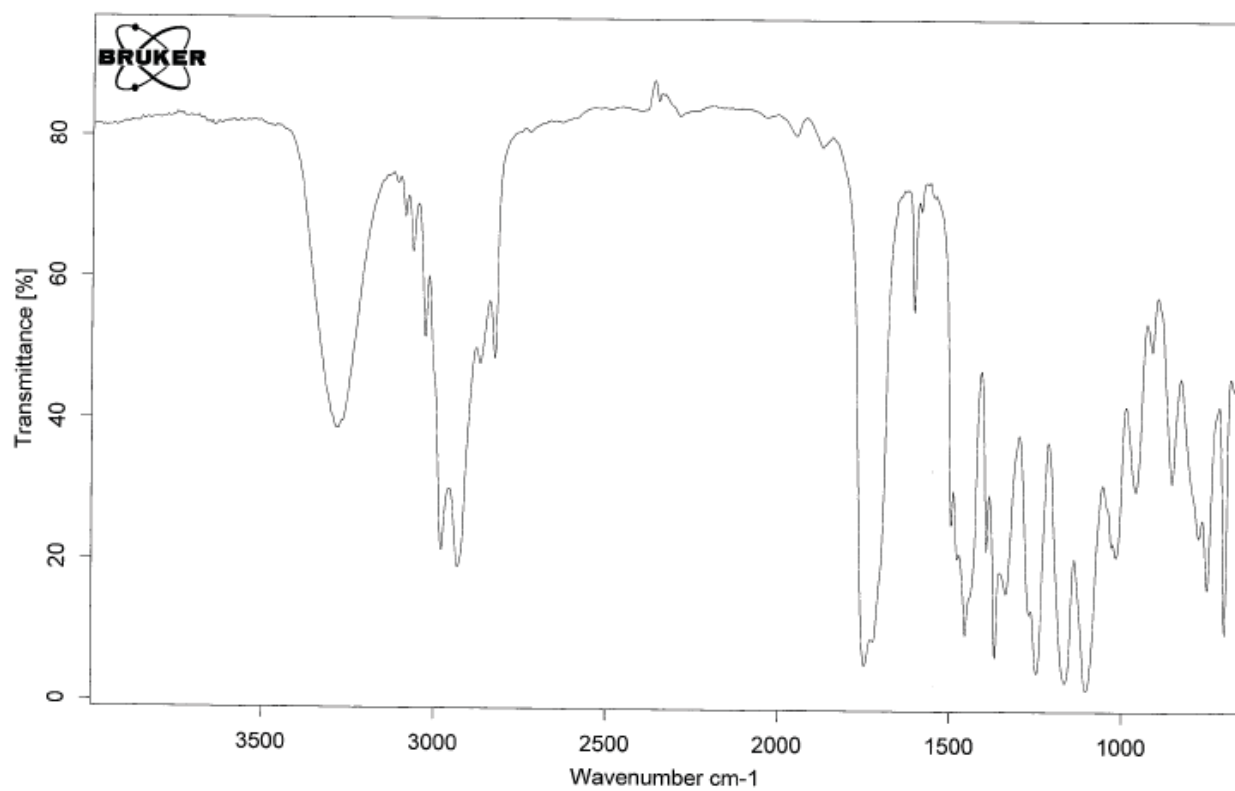
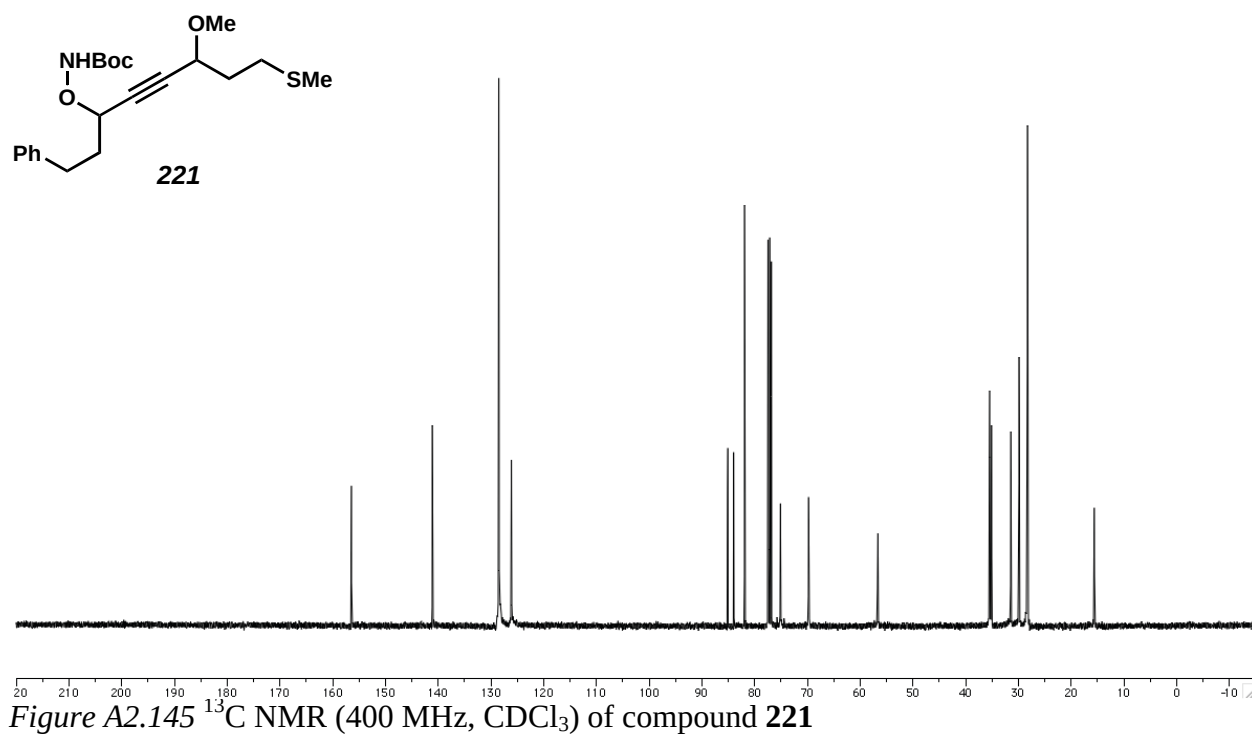


Figure A2.144 ^1H NMR (400 MHz, CDCl_3) of compound **221**



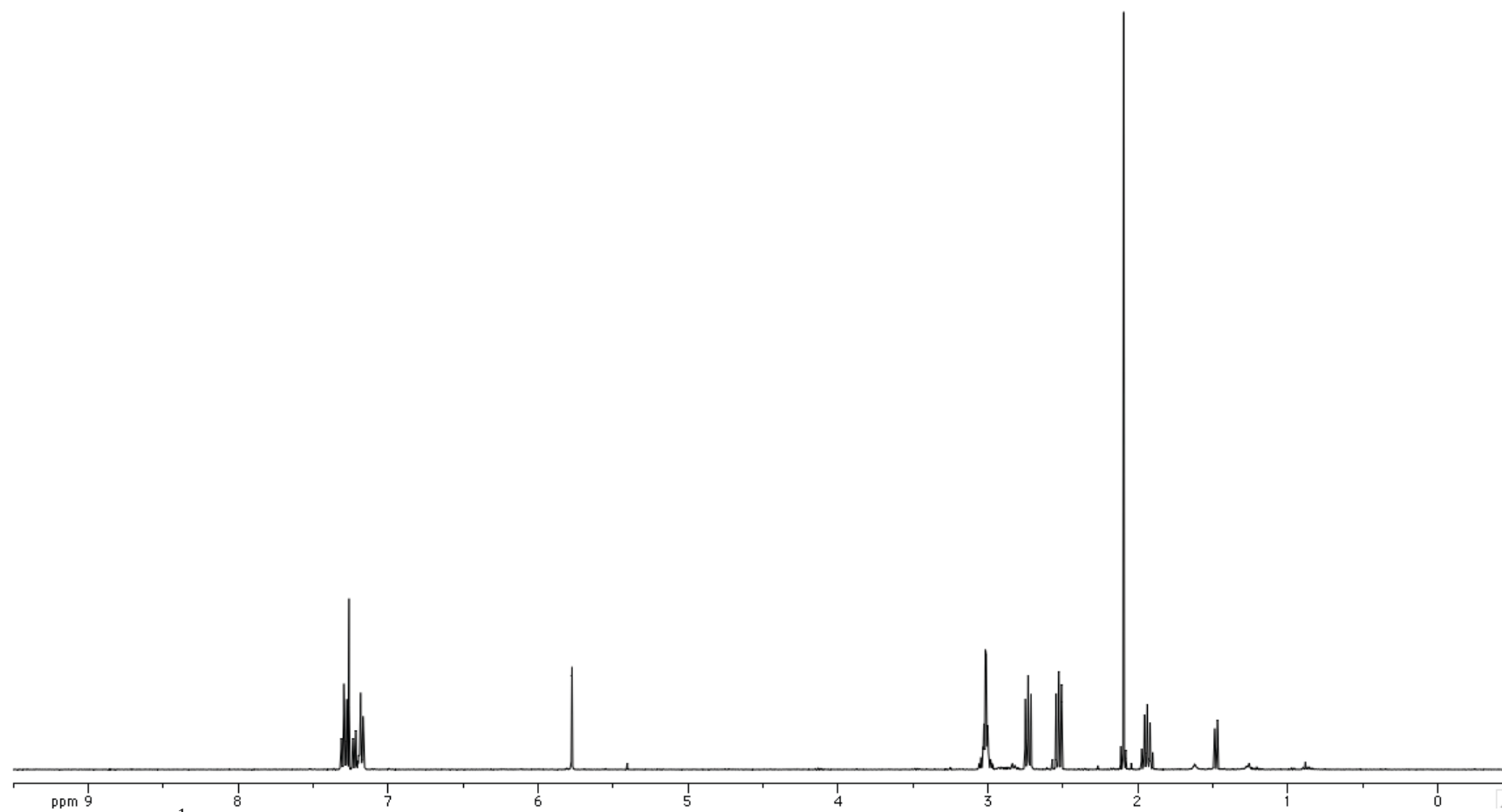
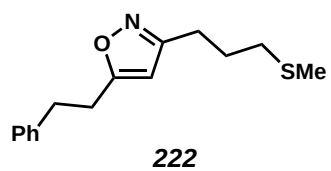
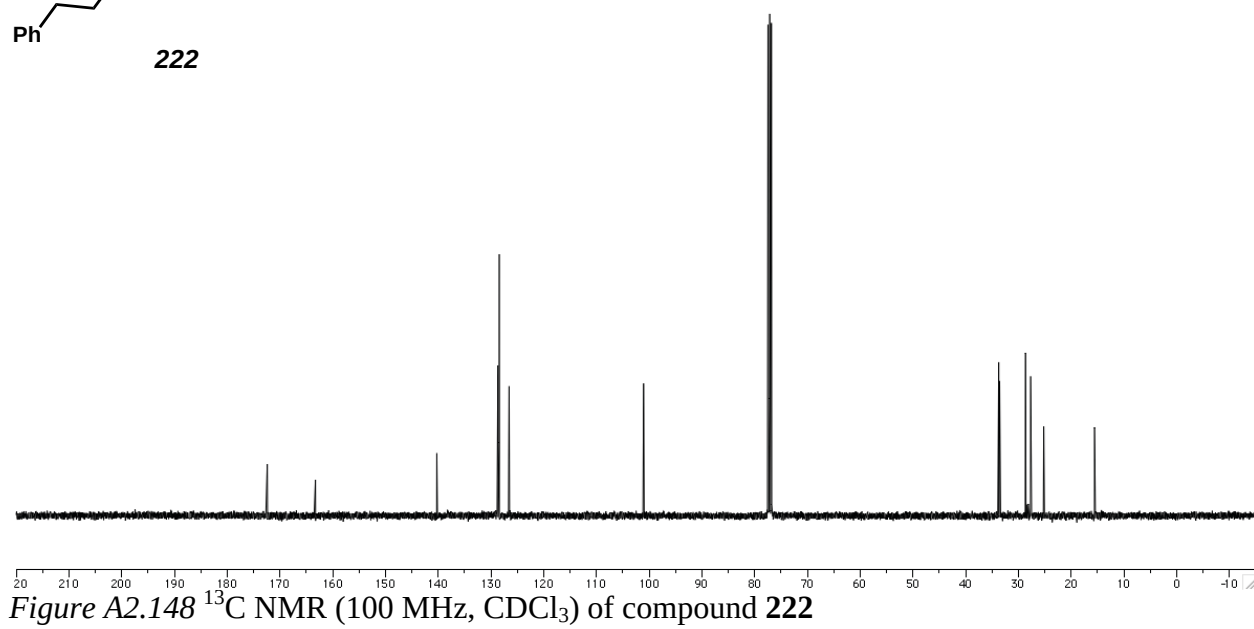
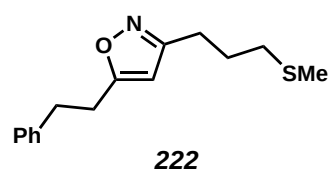


Figure A2.147 ^1H NMR (400 MHz, CDCl_3) of compound **222**



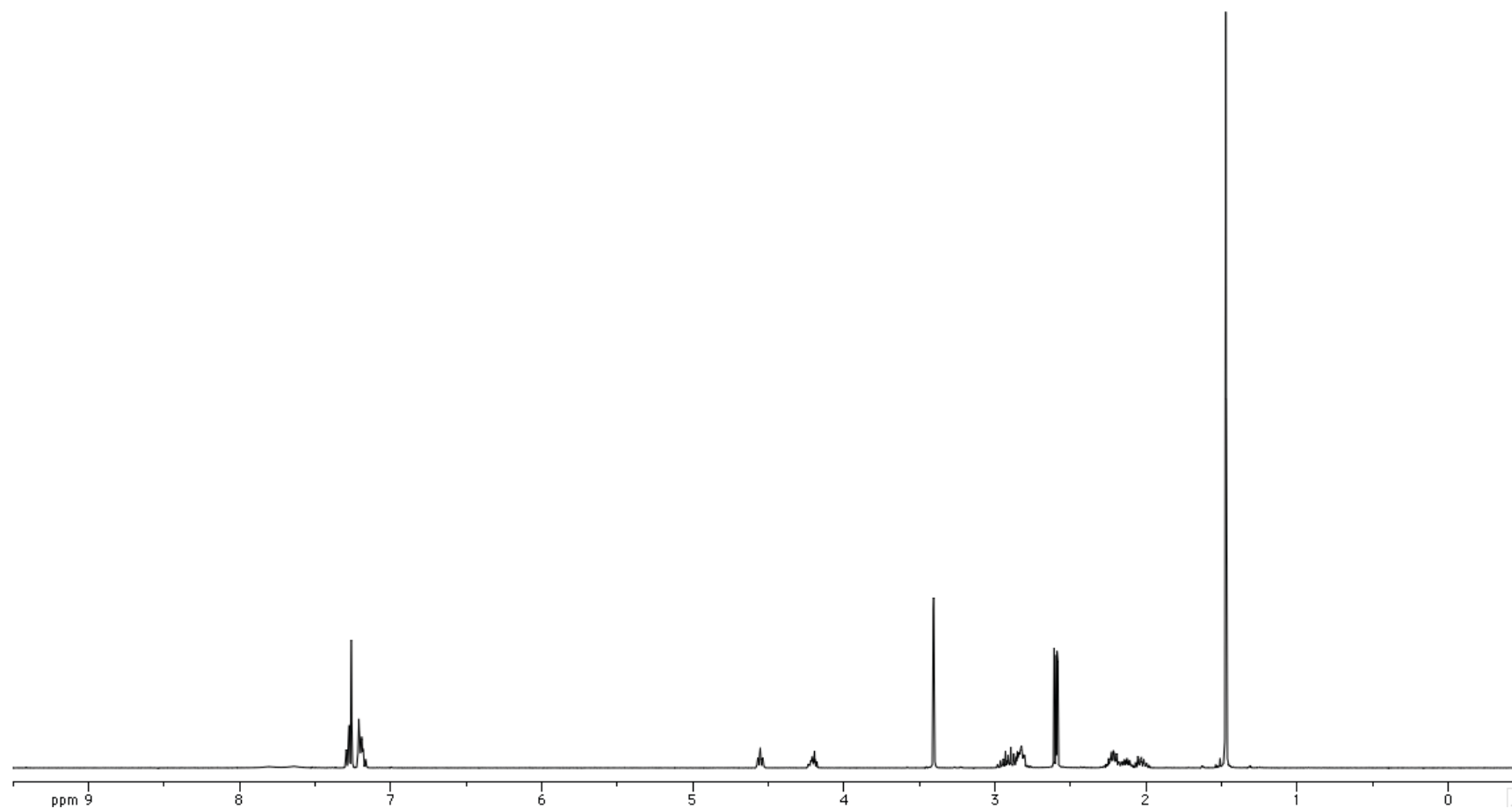
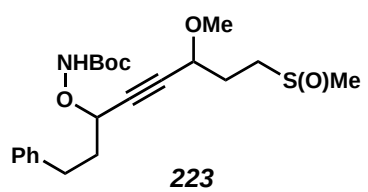
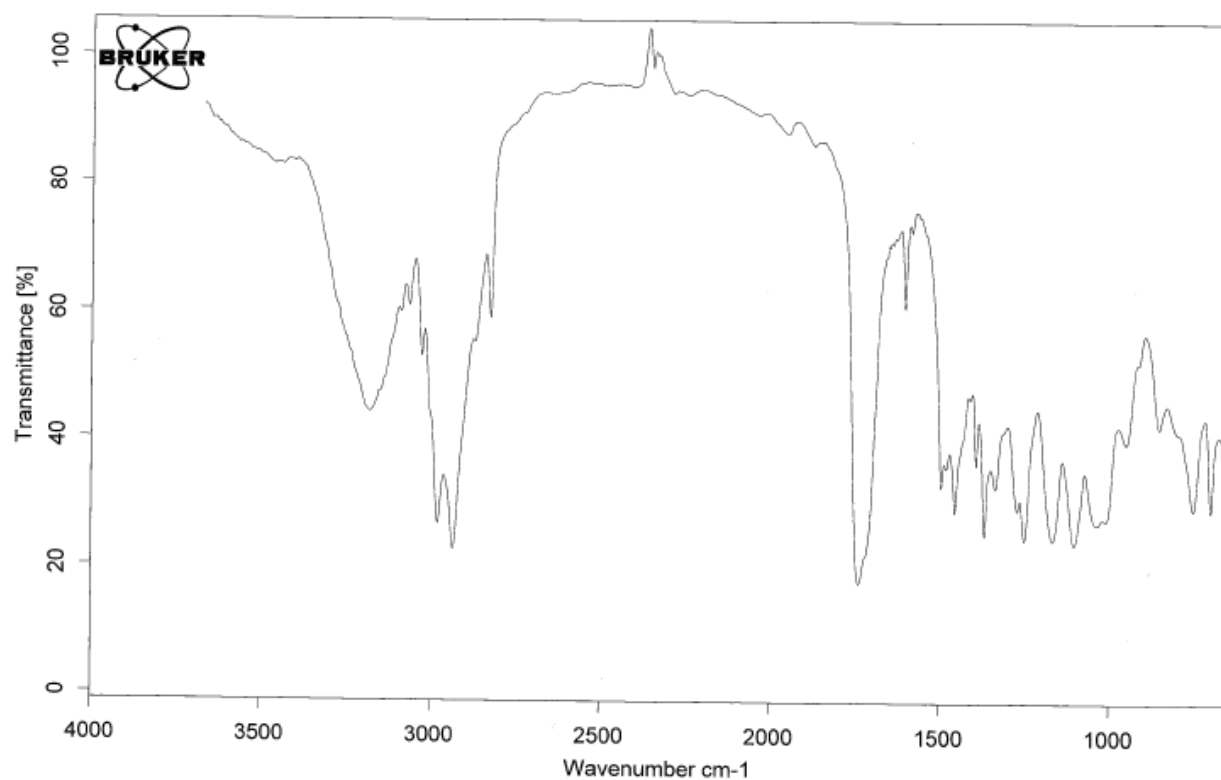
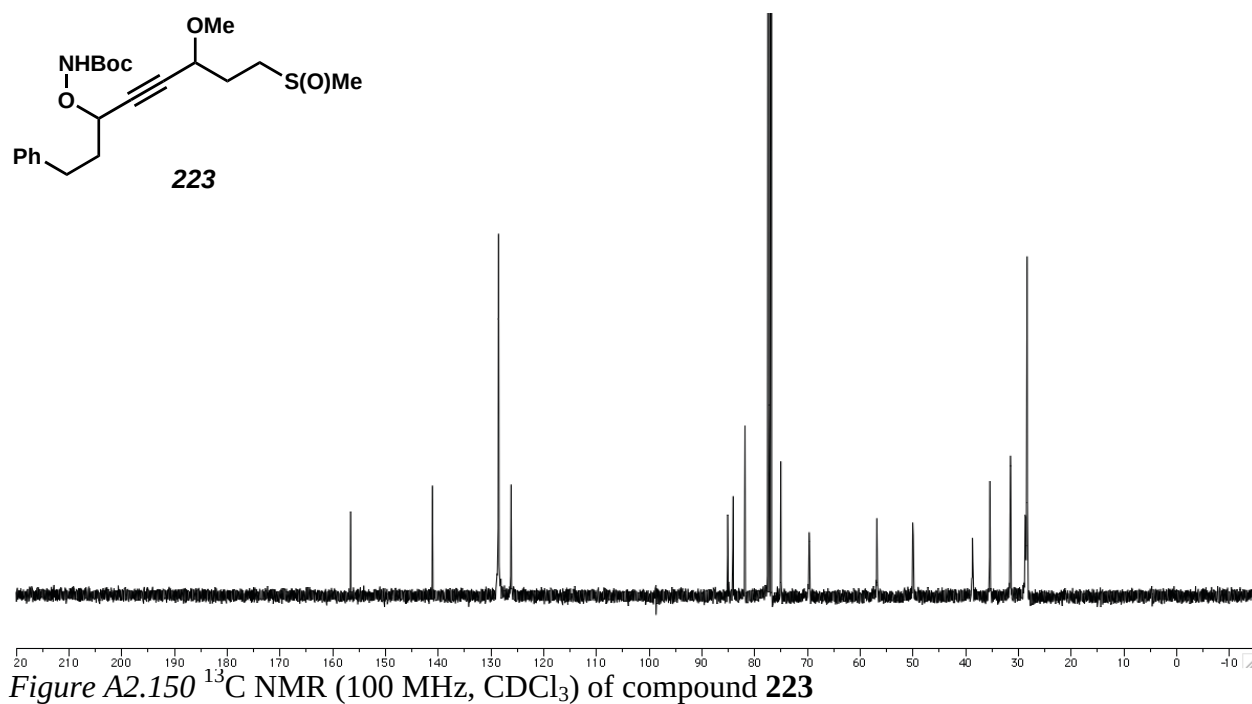


Figure A2.149 ^1H NMR (400 MHz, CDCl_3) of compound **223**



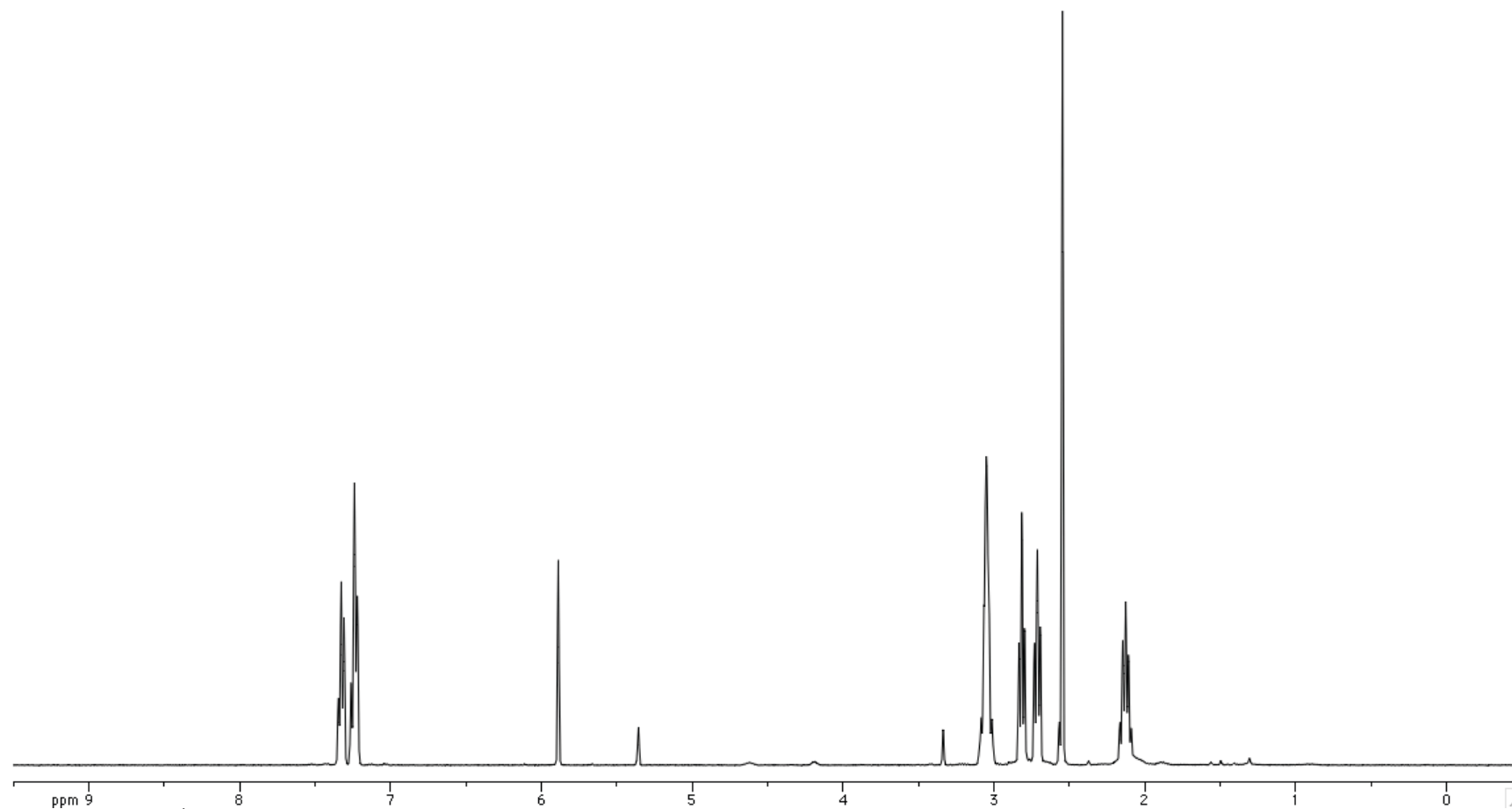
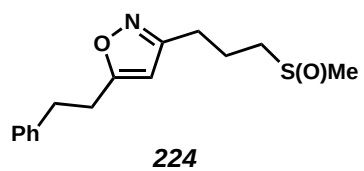
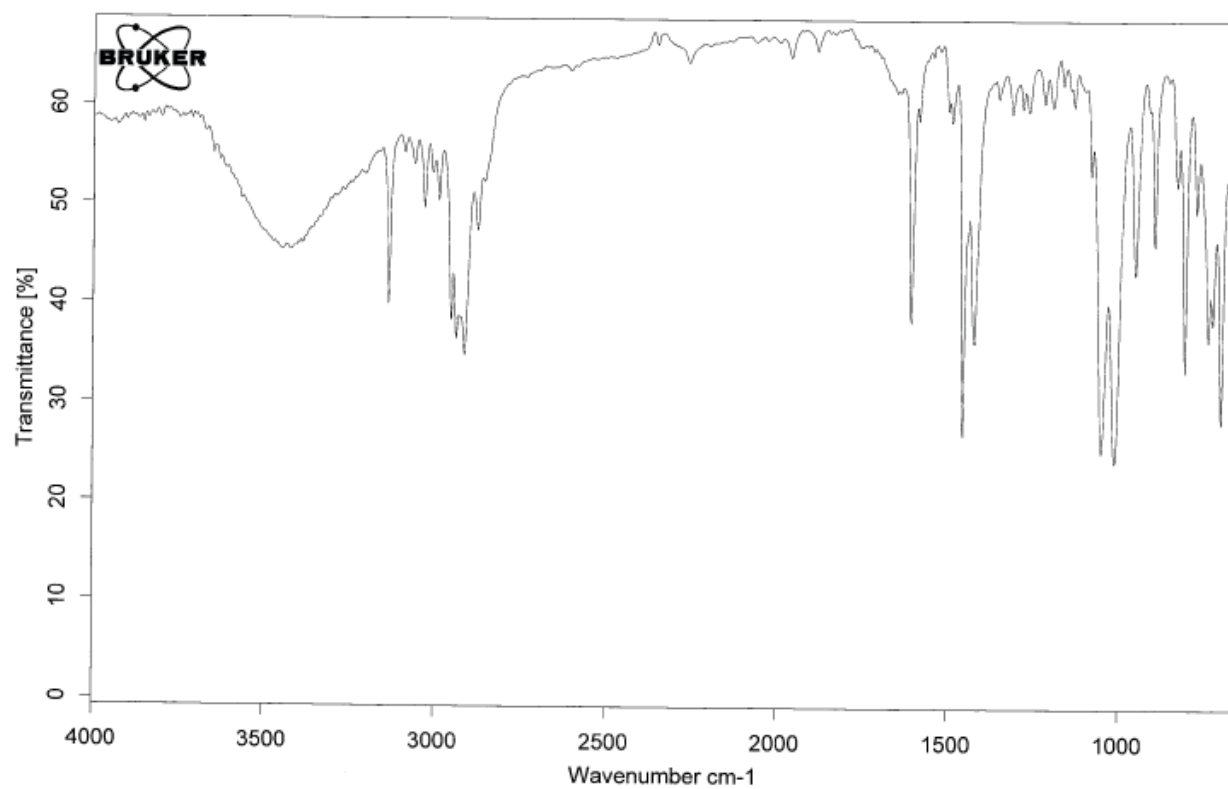
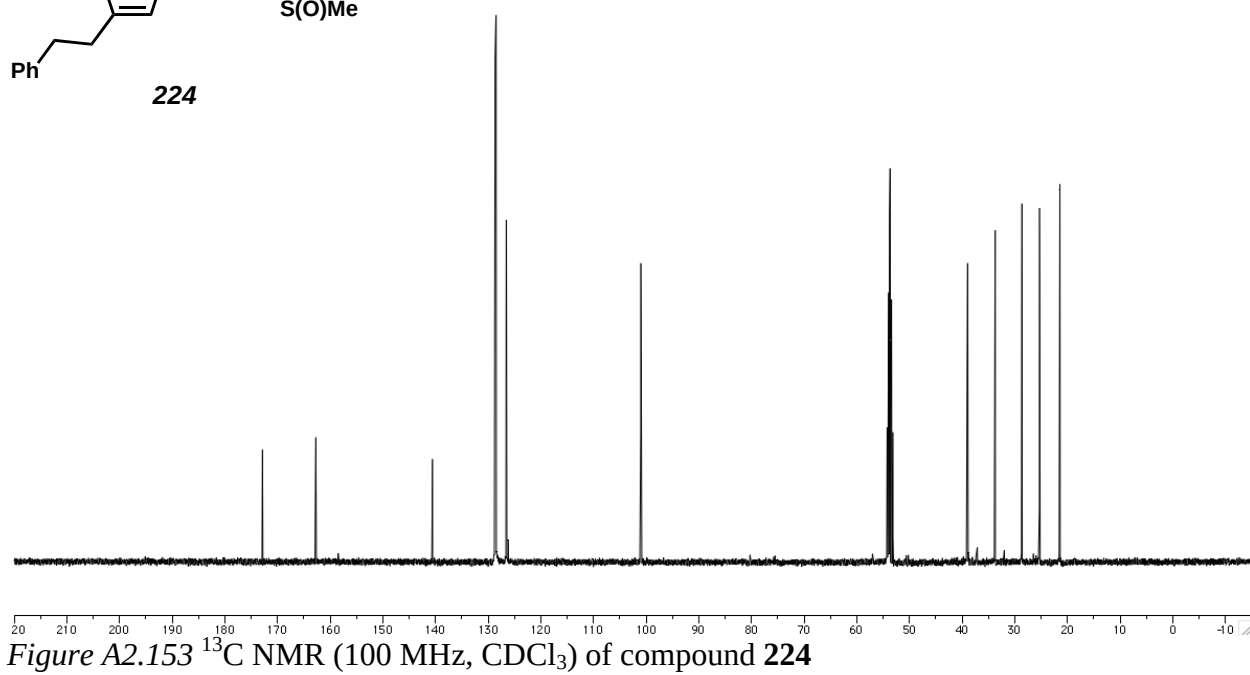
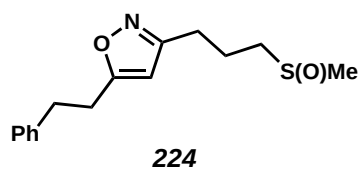


Figure A2.152 ^1H NMR (400 MHz, CDCl_3) of compound **224**



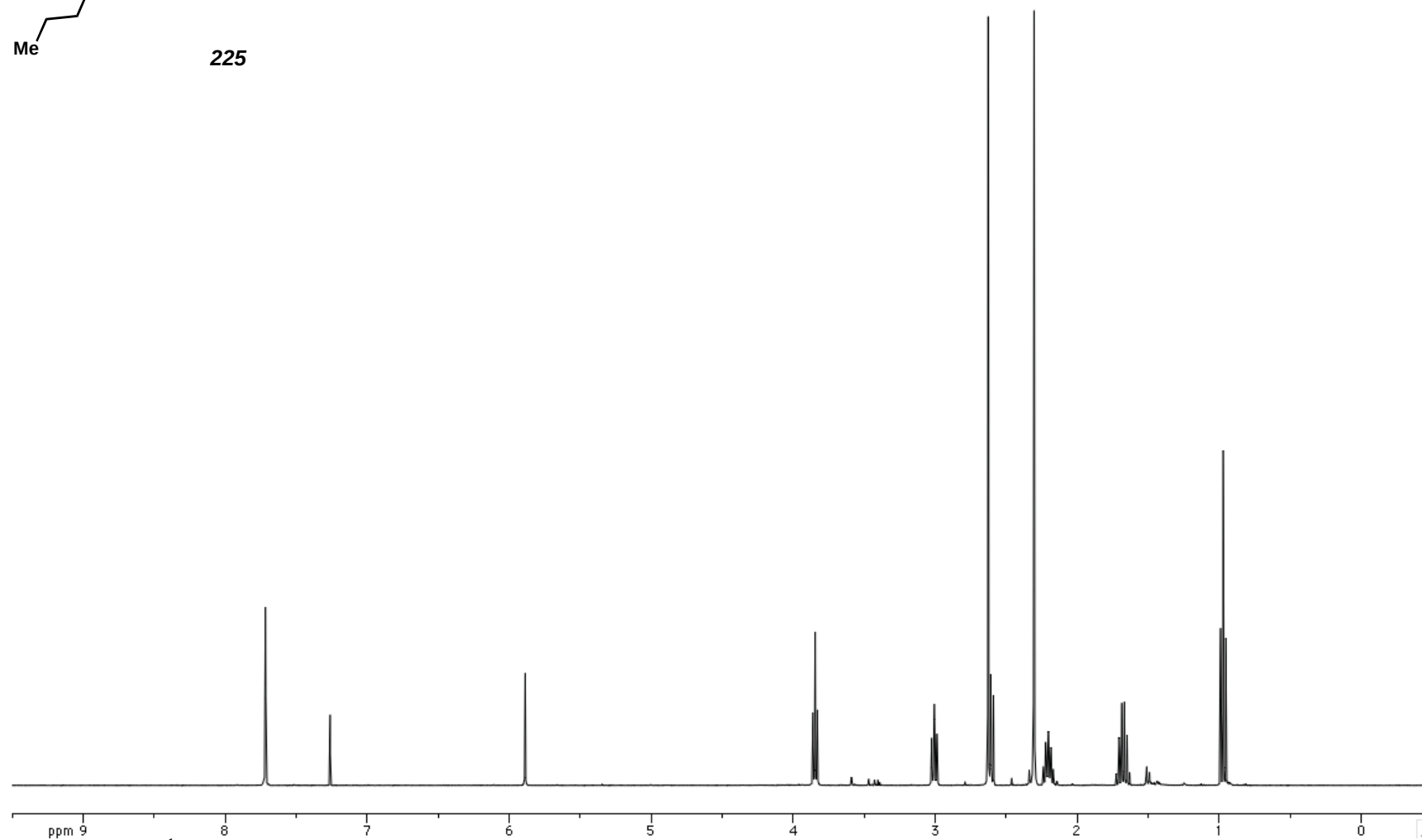
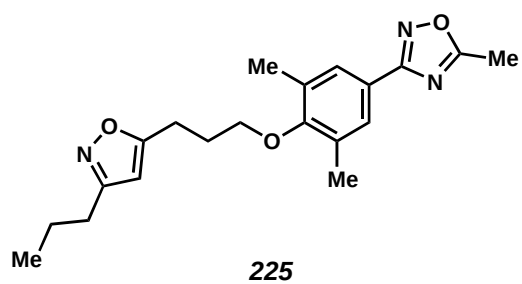
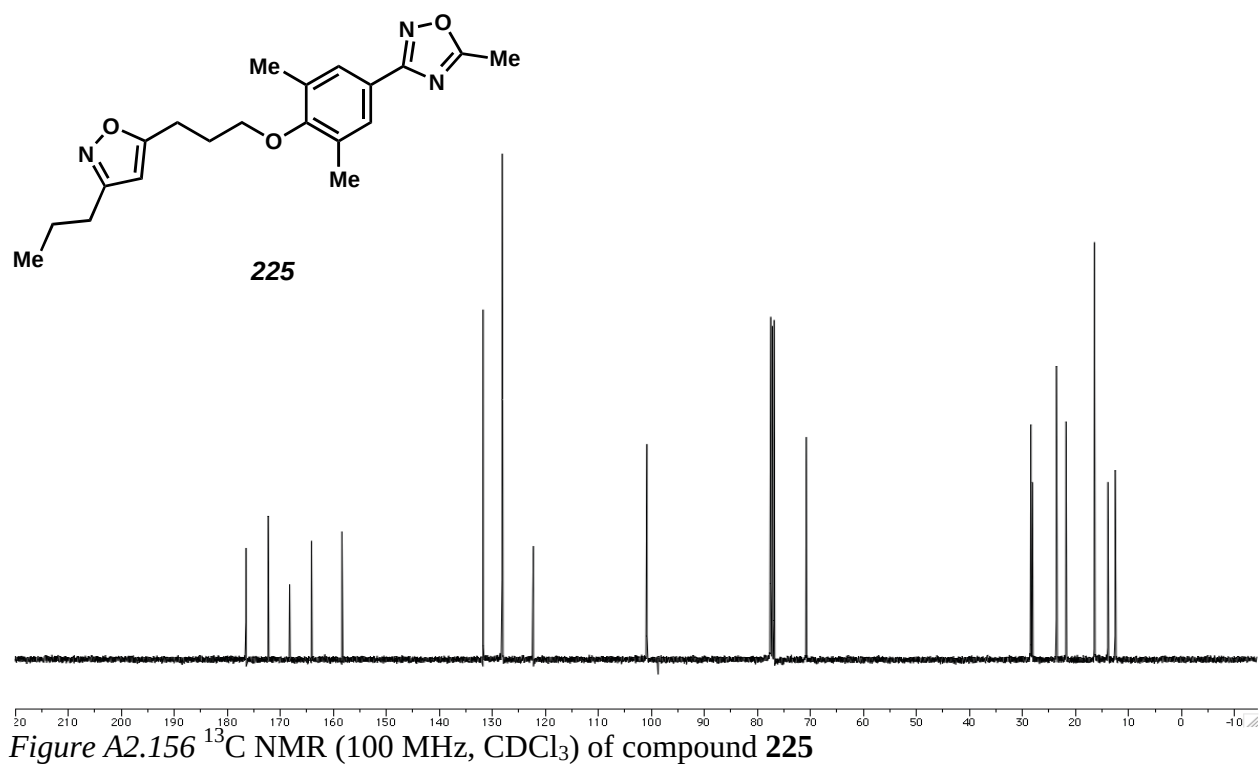


Figure A2.155 ¹H NMR (400 MHz, CDCl₃) of compound **225**



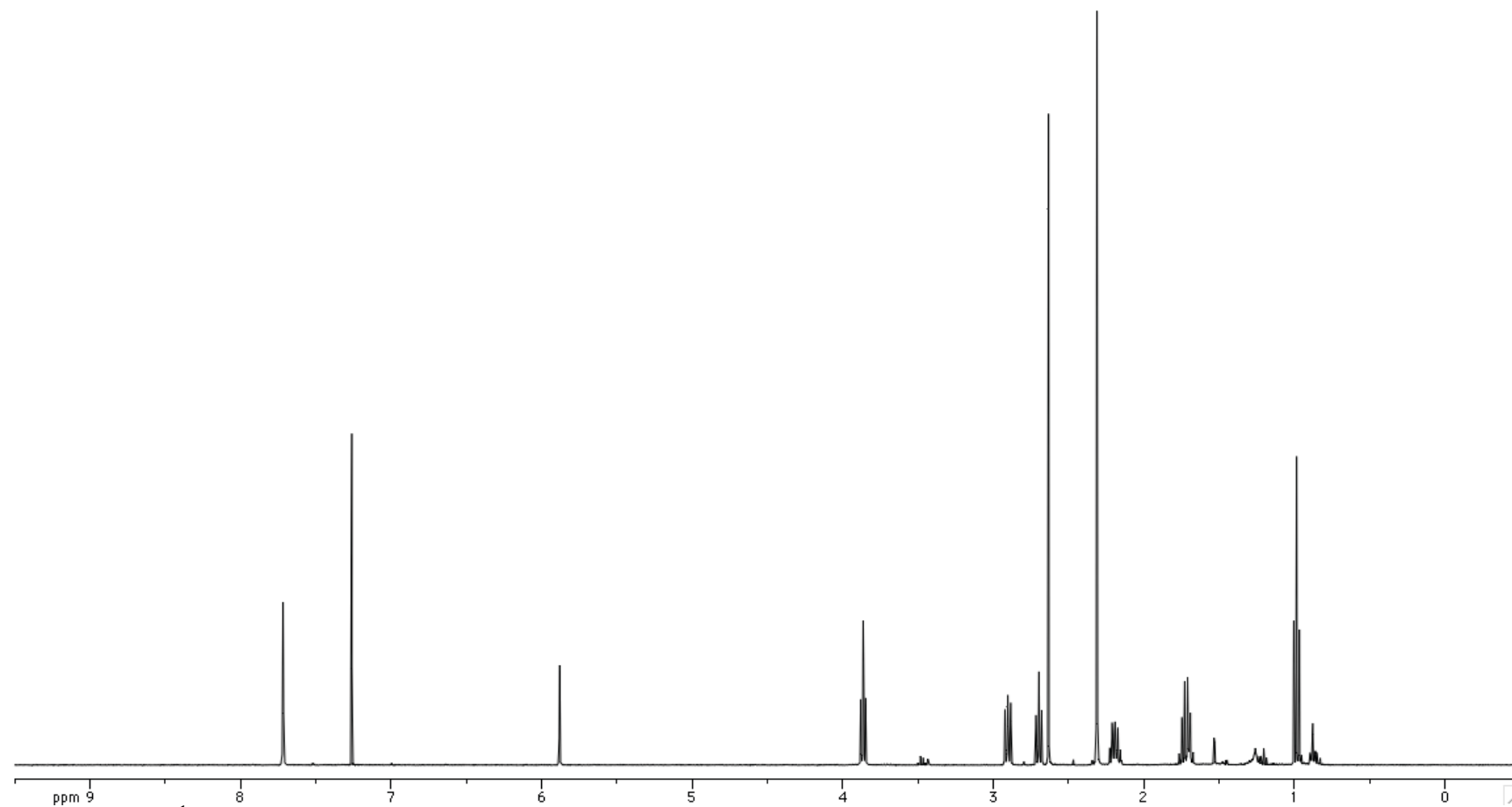


Figure A2.157 ^1H NMR (400 MHz, CDCl_3) of compound **226**

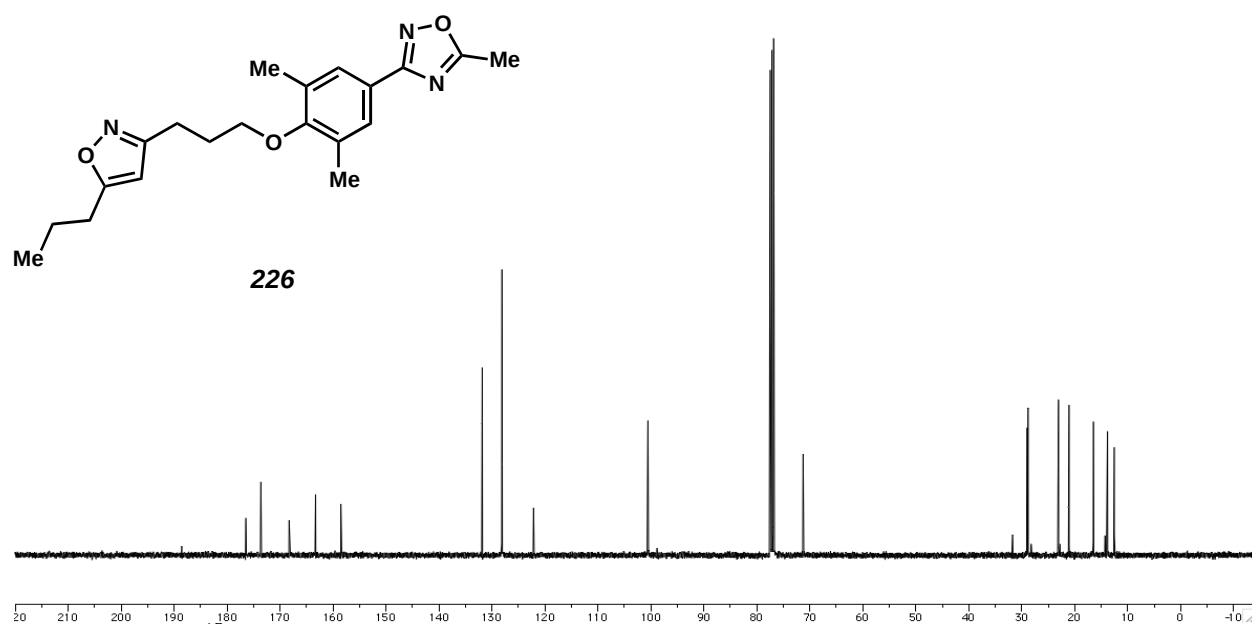


Figure A2.158 ^{13}C NMR (100 MHz, CDCl₃) of compound 226

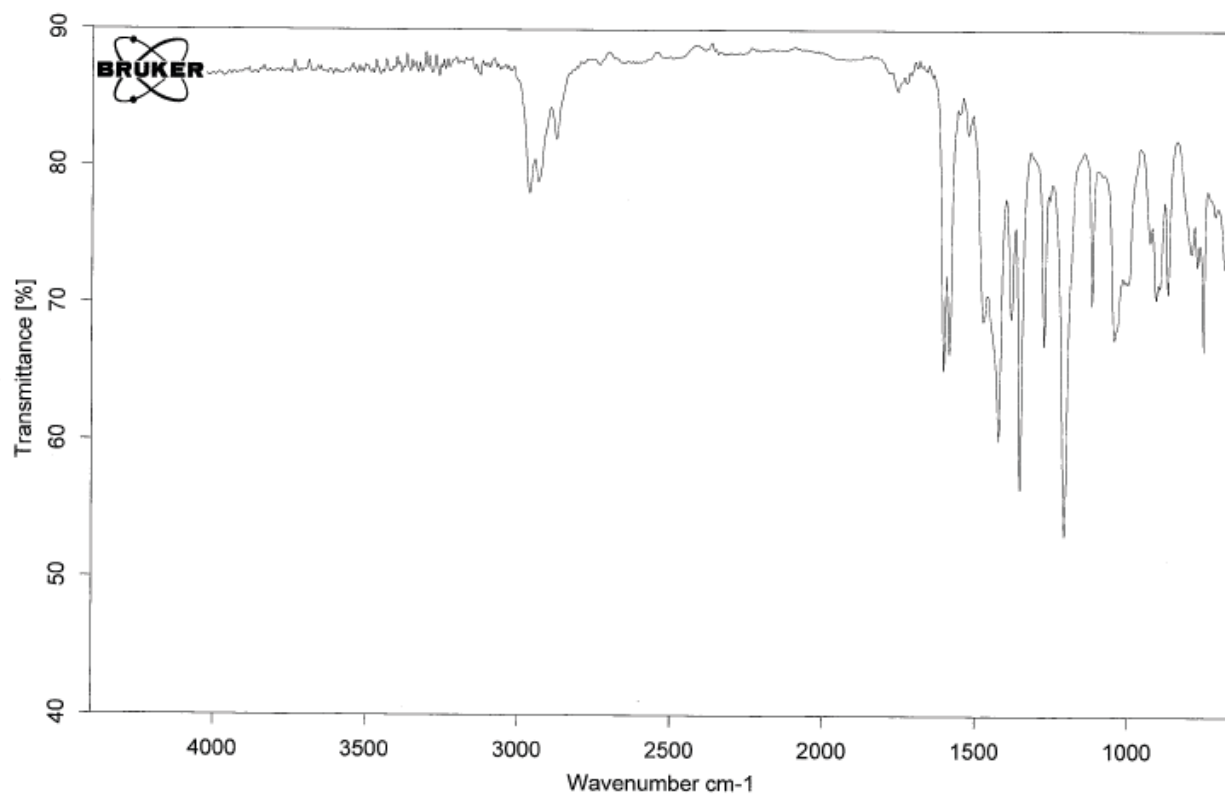


Figure A2.159 Infrared spectrum (thin film) of compound 226

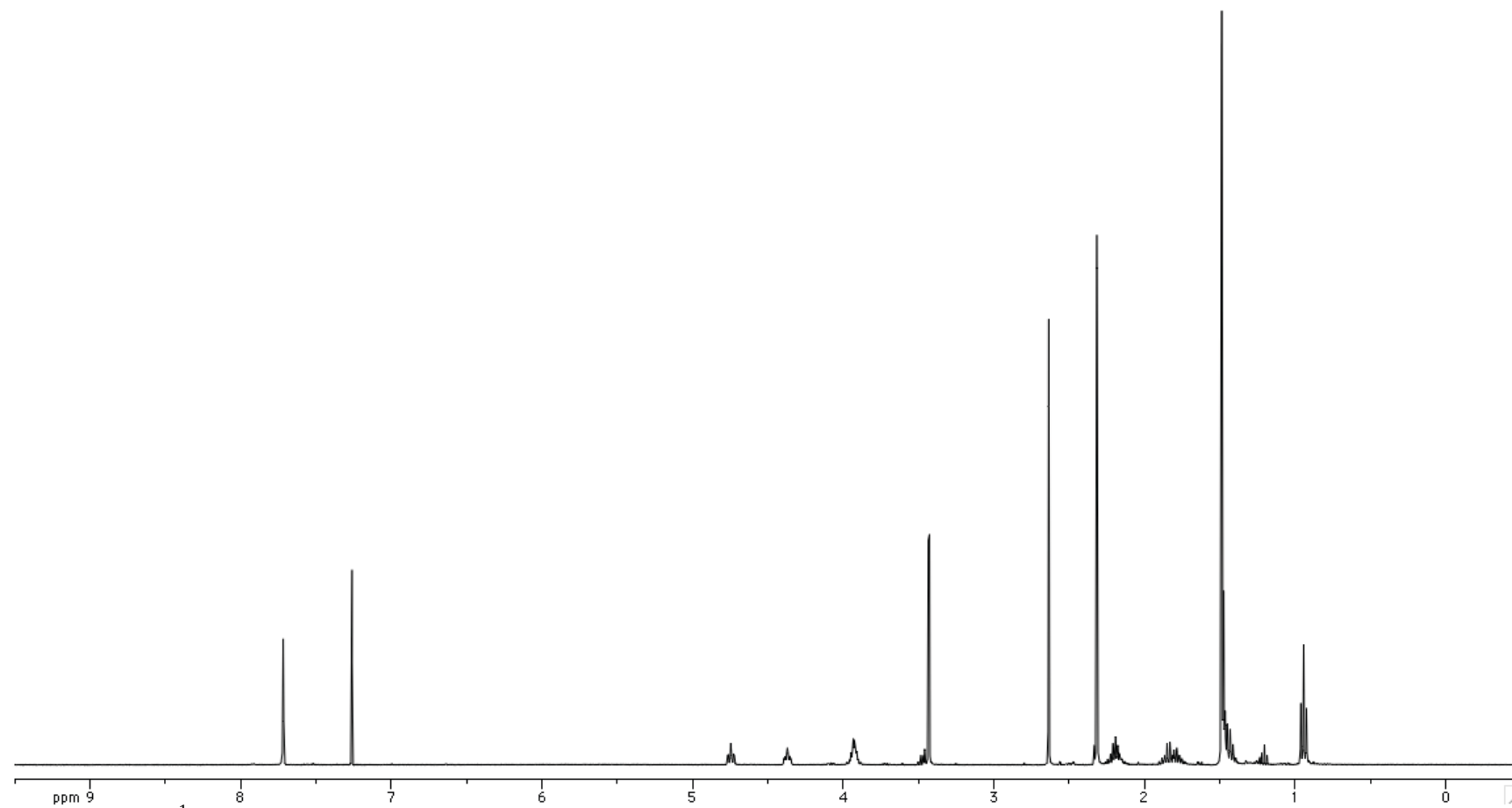
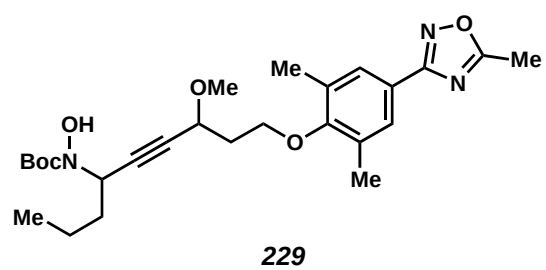


Figure A2.160 ^1H NMR (400 MHz, CDCl_3) of compound **229**

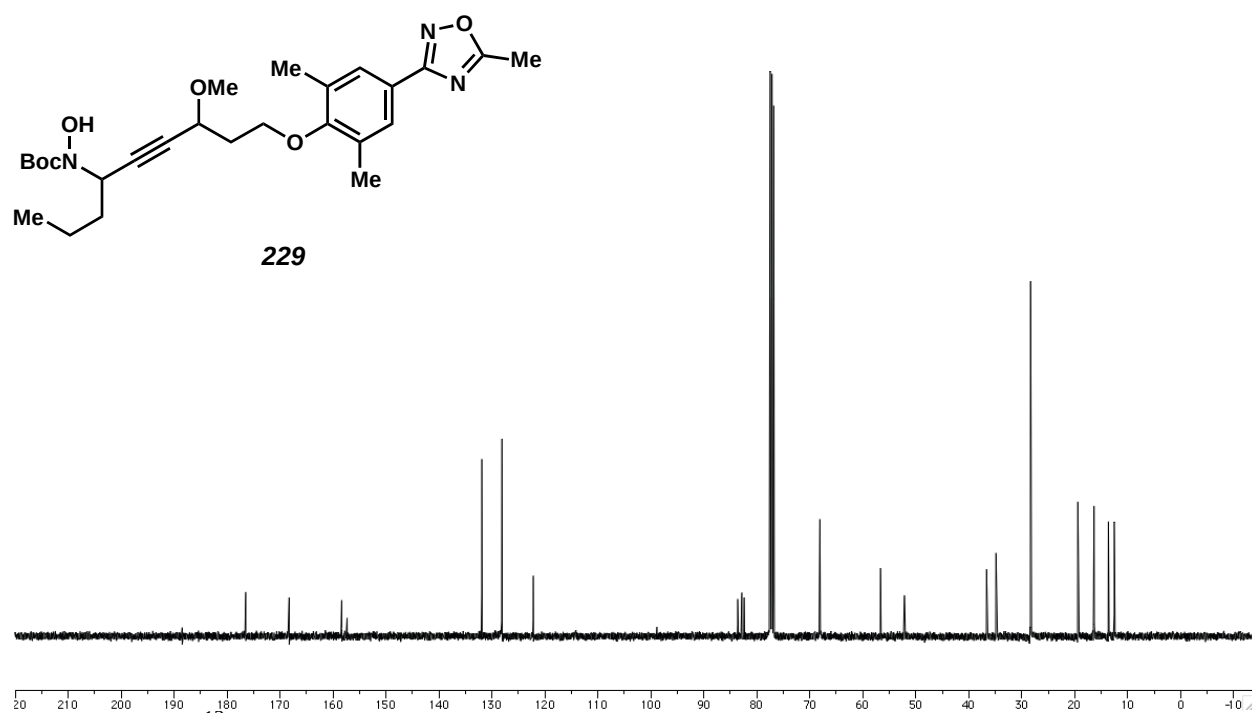


Figure A2.161 ^{13}C NMR (100 MHz, CDCl_3) of compound **229**

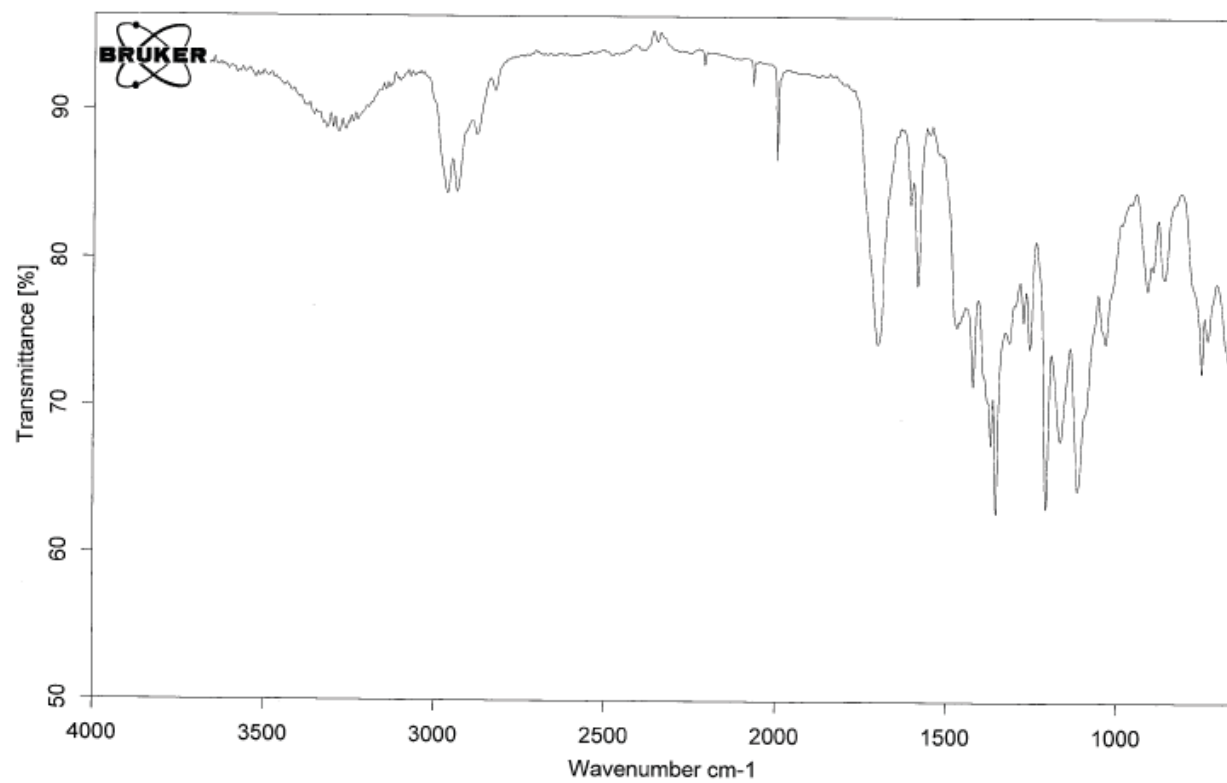
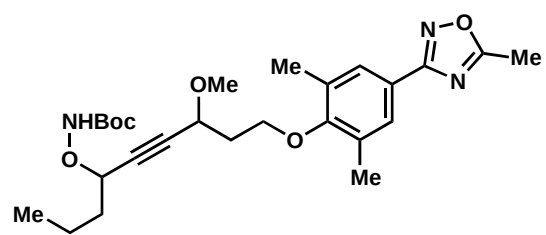


Figure A2.162 Infrared spectrum (thin film) of compound **229**



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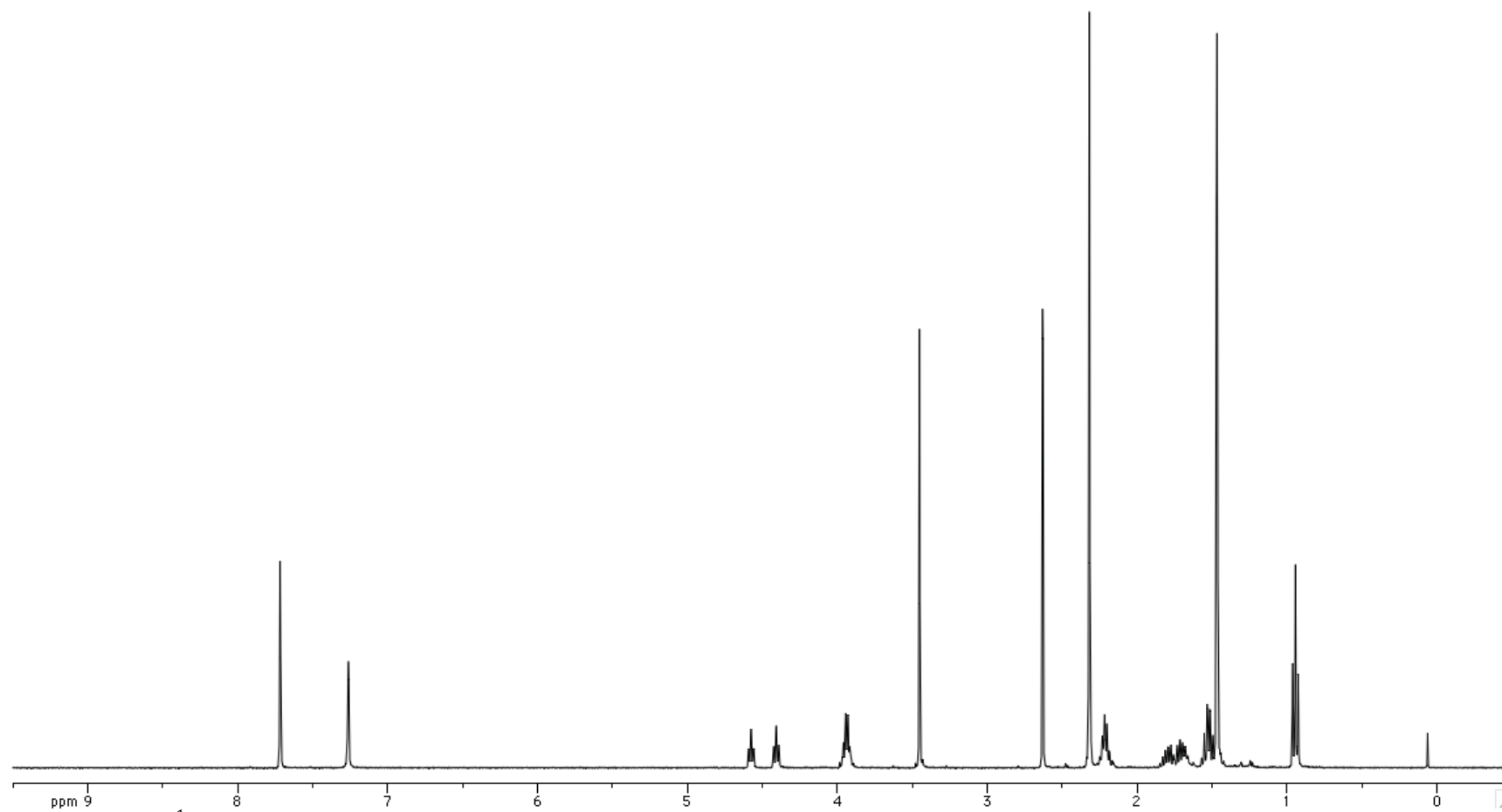


Figure A2.163 ^1H NMR (400 MHz, CDCl_3) of compound **230**

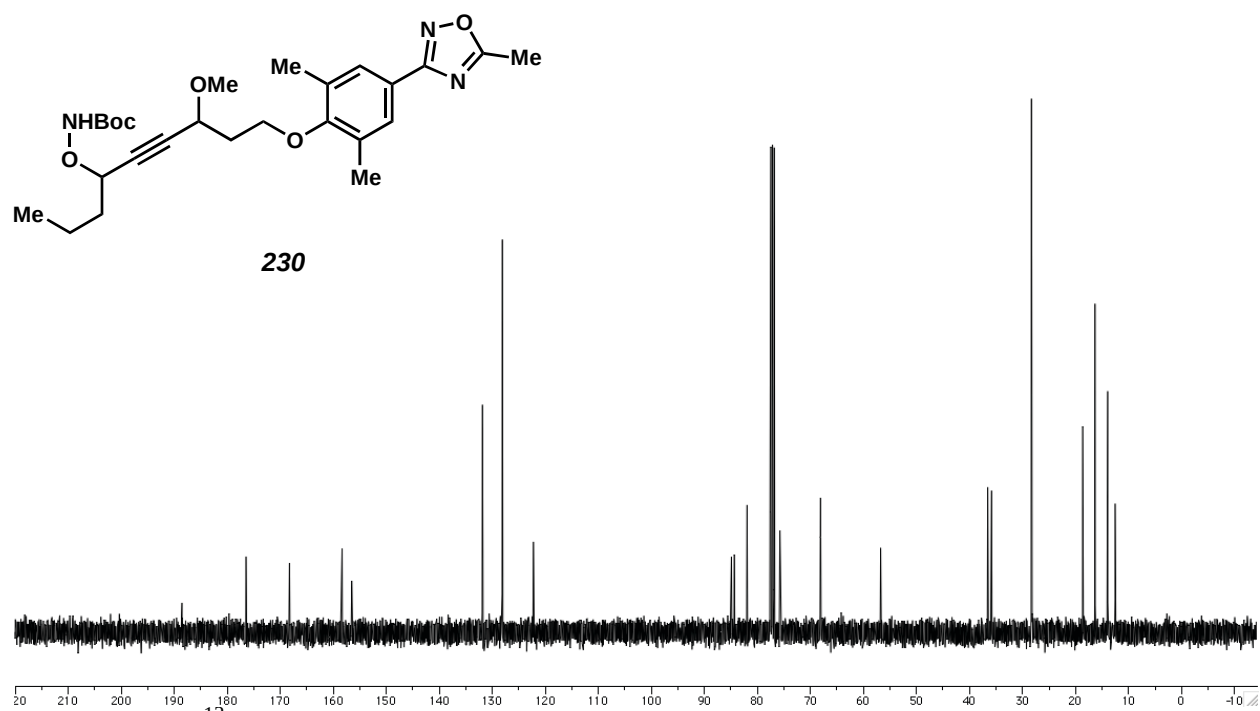


Figure A2.164 ^{13}C NMR (100 MHz, CDCl_3) of compound **230**

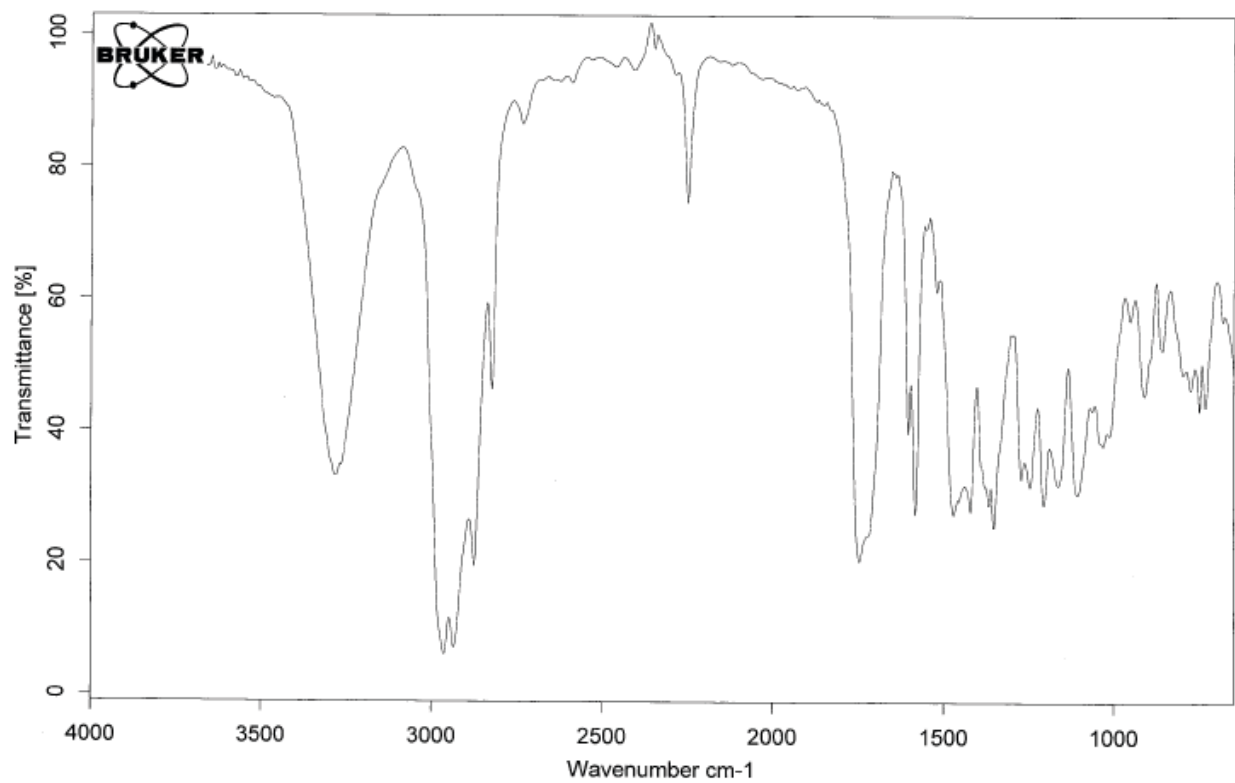


Figure A2.165 Infrared spectrum (thin film) of compound **230**

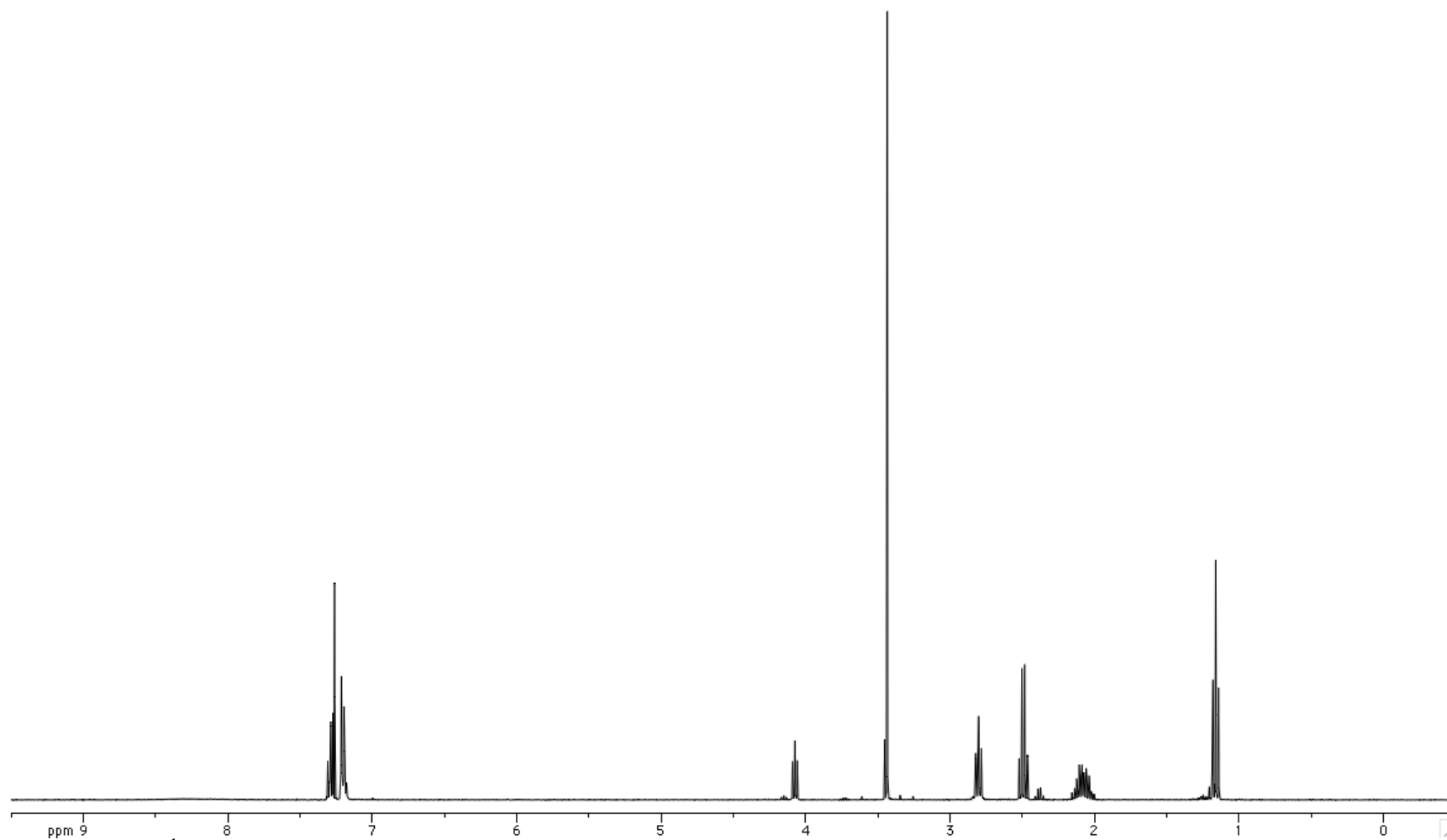
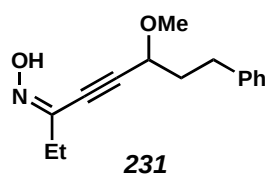
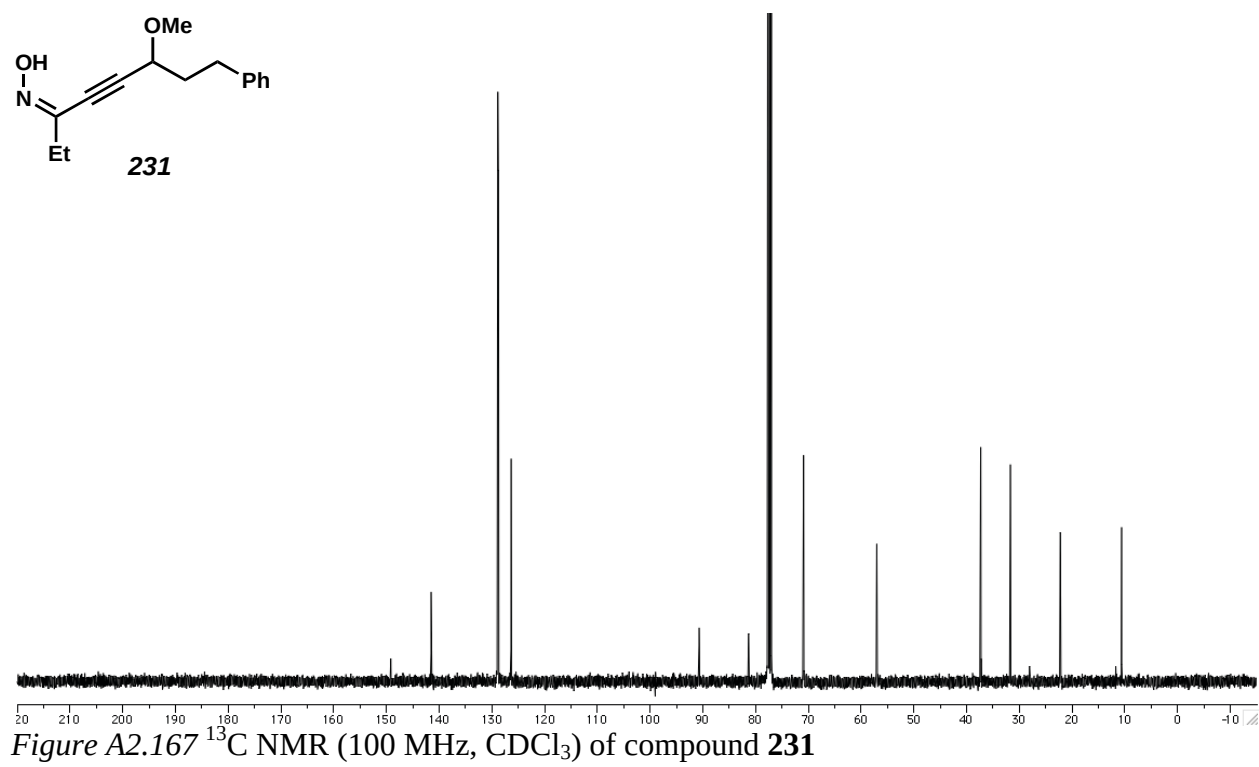
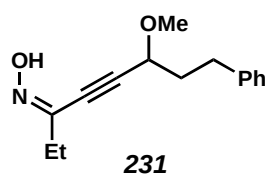


Figure A2.166 ^1H NMR (400 MHz, CDCl_3) of compound **231**



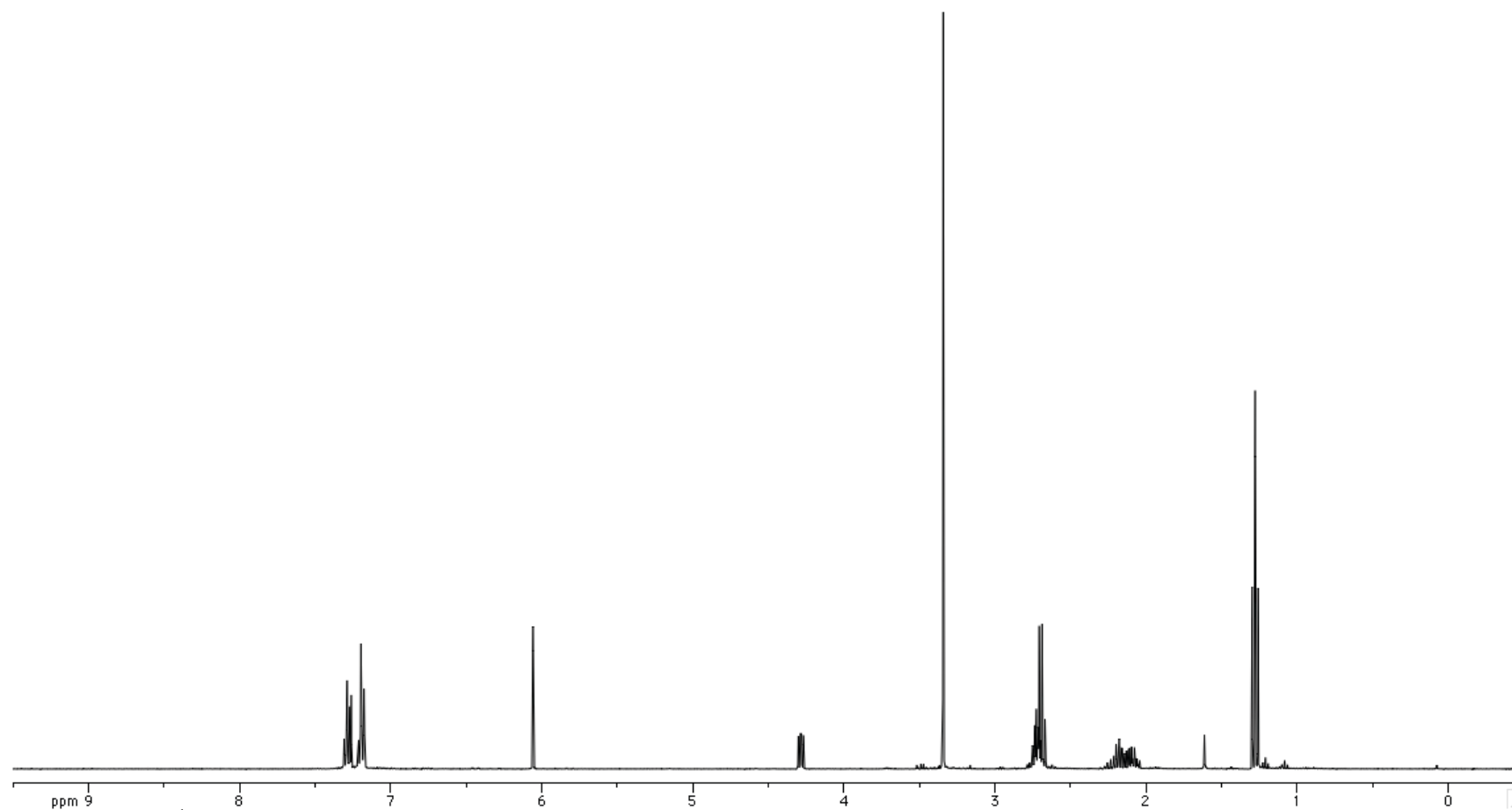
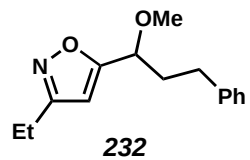
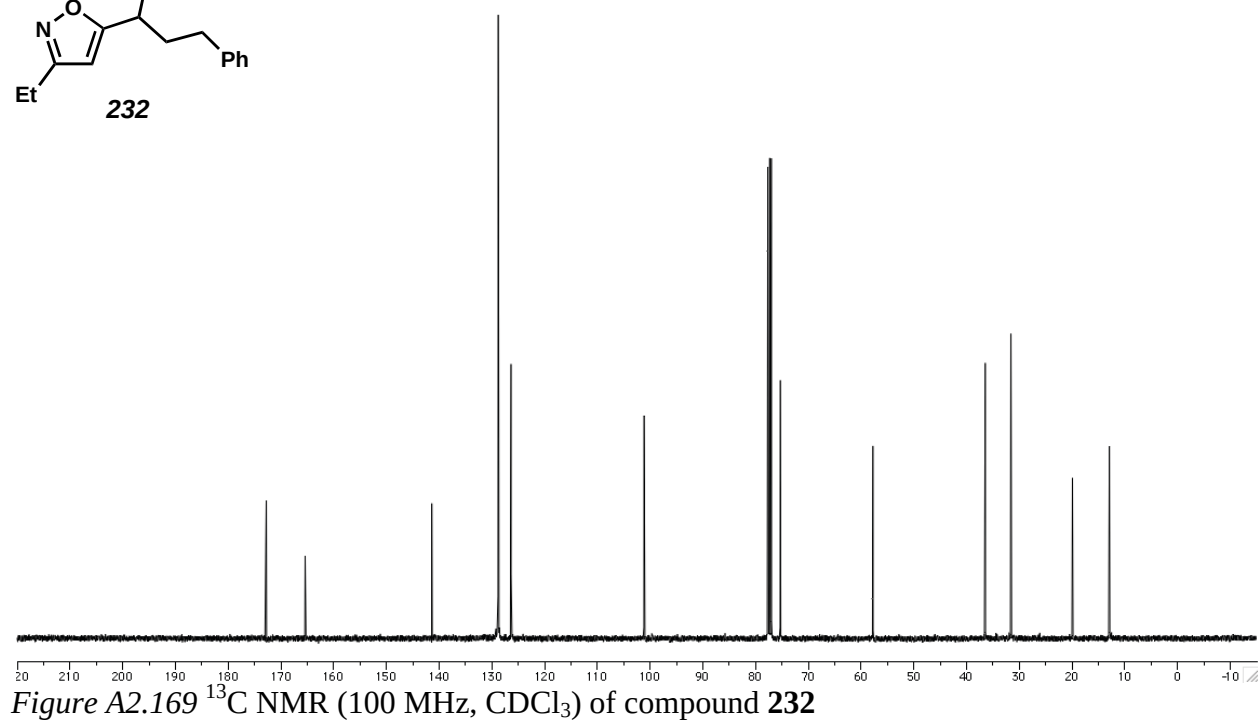
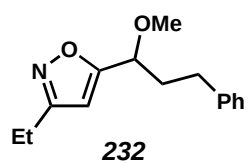


Figure A2.168 ^1H NMR (400 MHz, CDCl_3) of compound **232**



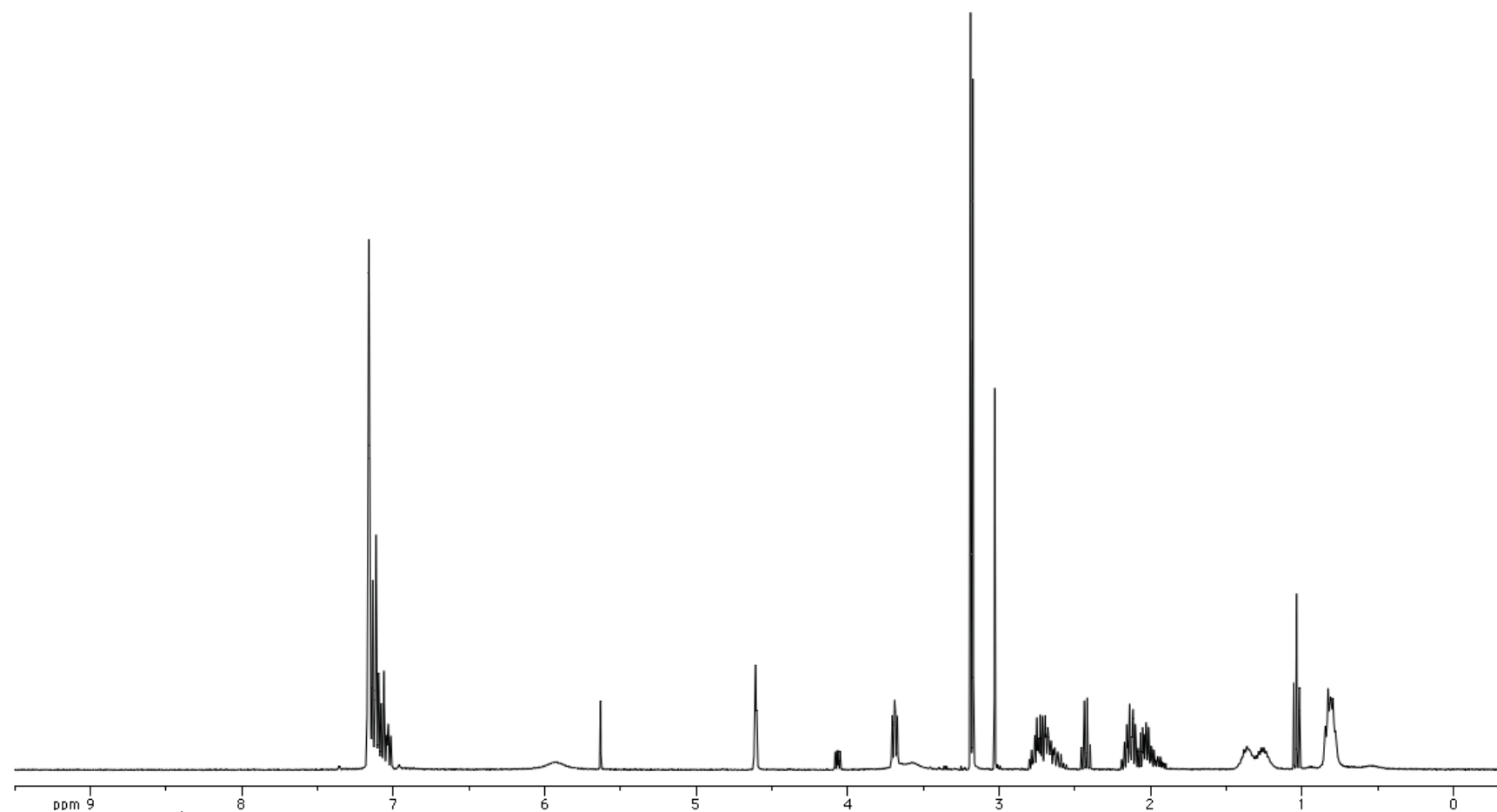
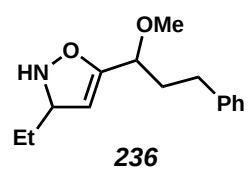


Figure A2.170 ^1H NMR (400 MHz, C_6D_6) of compound **236**

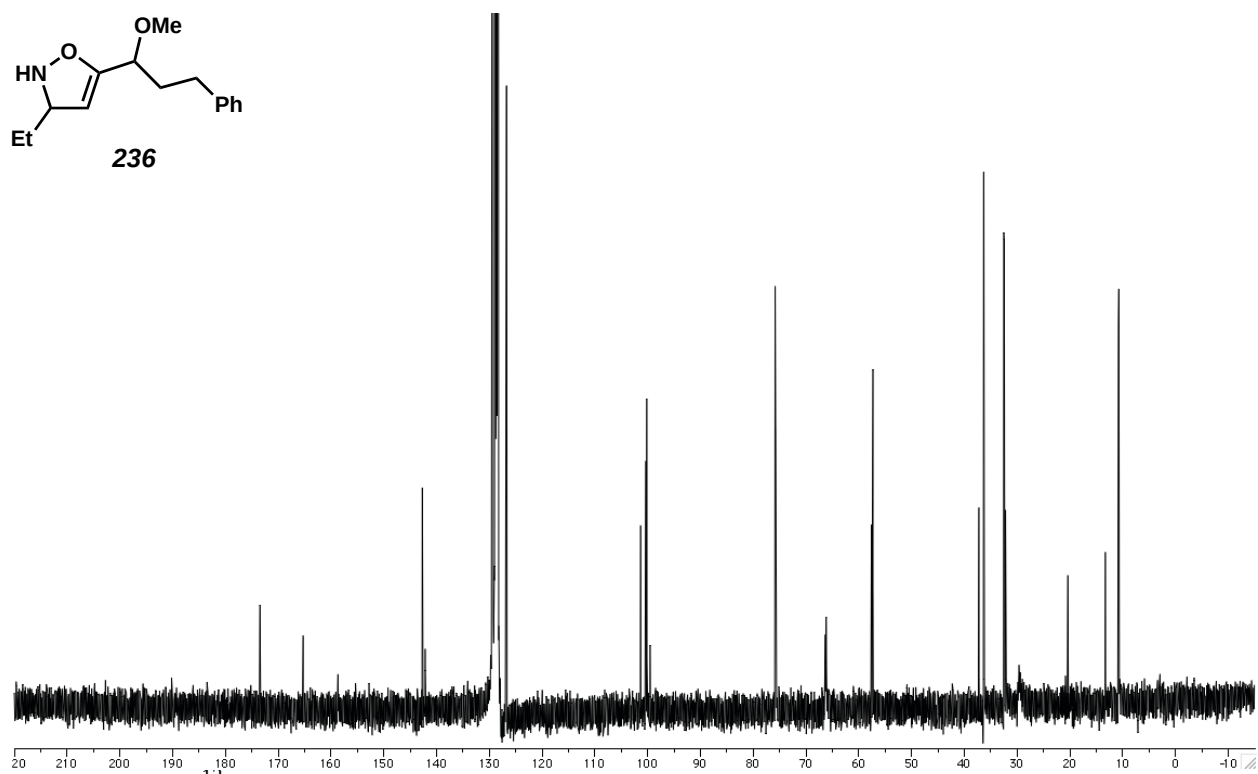
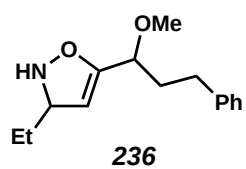
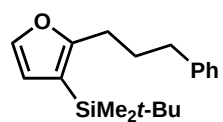


Figure A2.171 ^{13}C NMR (100 MHz, C_6D_6) of compound **236**

APPENDIX THREE

Spectra Relevant to Chapter Four

Support for the Formation of α,β -Unsaturated Platinum Carbenes



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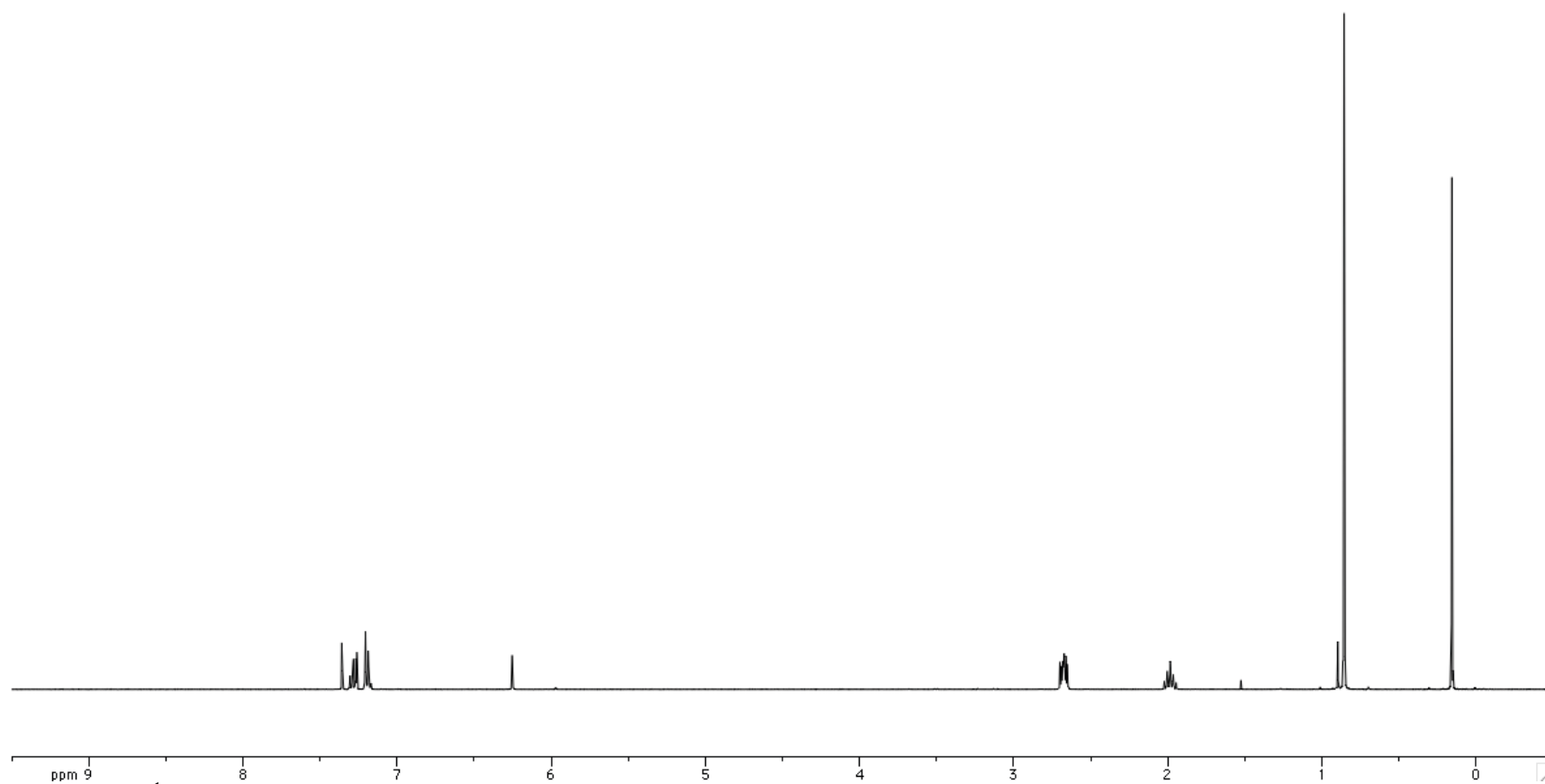
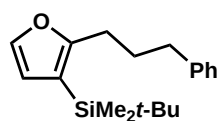


Figure A3.1 ¹H NMR (400 MHz, CDCl₃) of compound **295**



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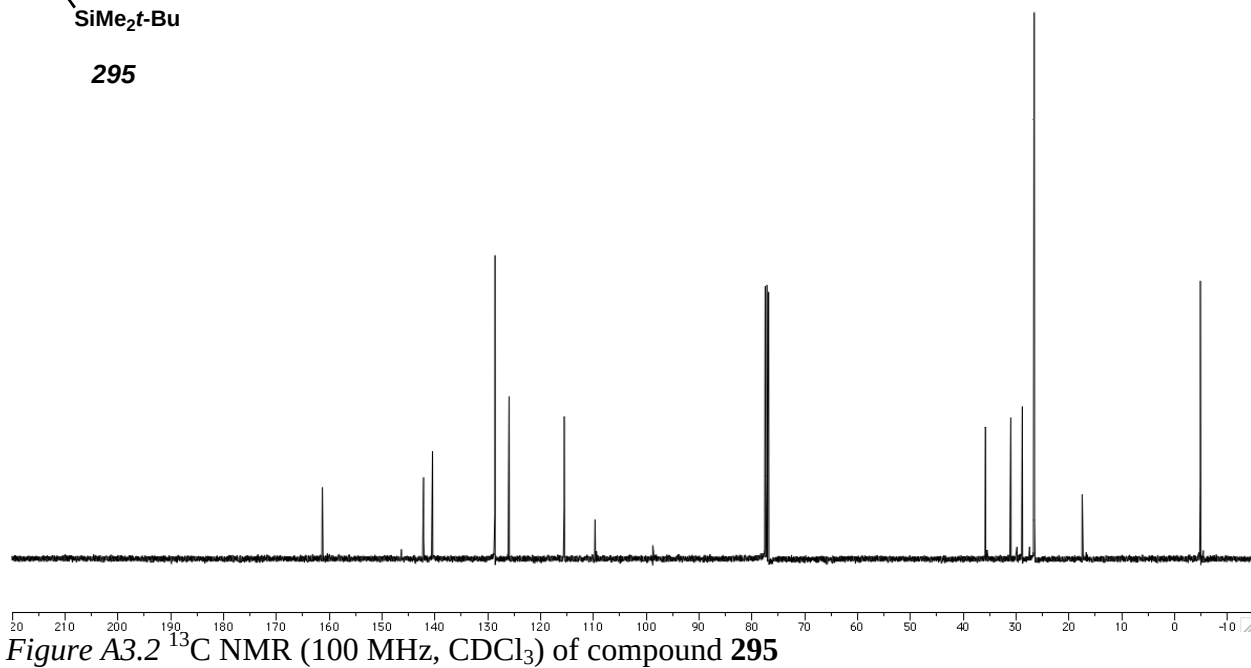


Figure A3.2 ^{13}C NMR (100 MHz, CDCl_3) of compound **295**

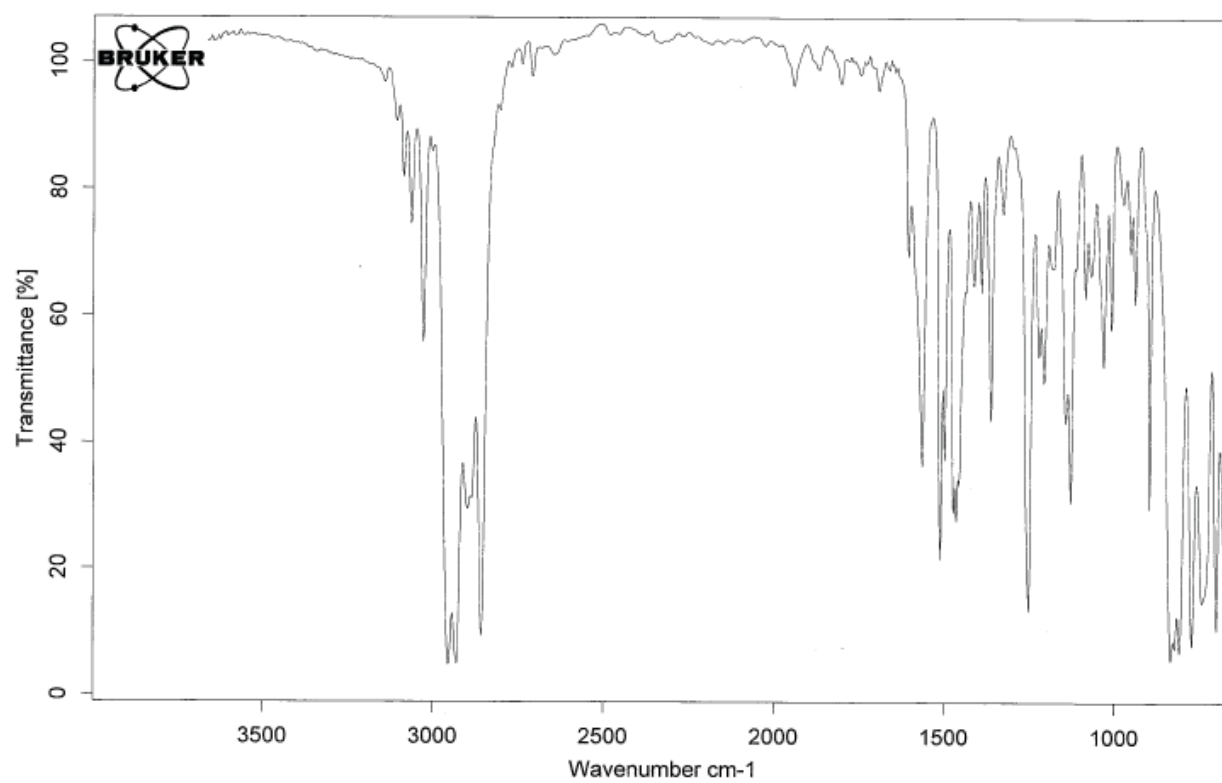


Figure A3.3 Infrared spectrum (thin film) of compound **295**

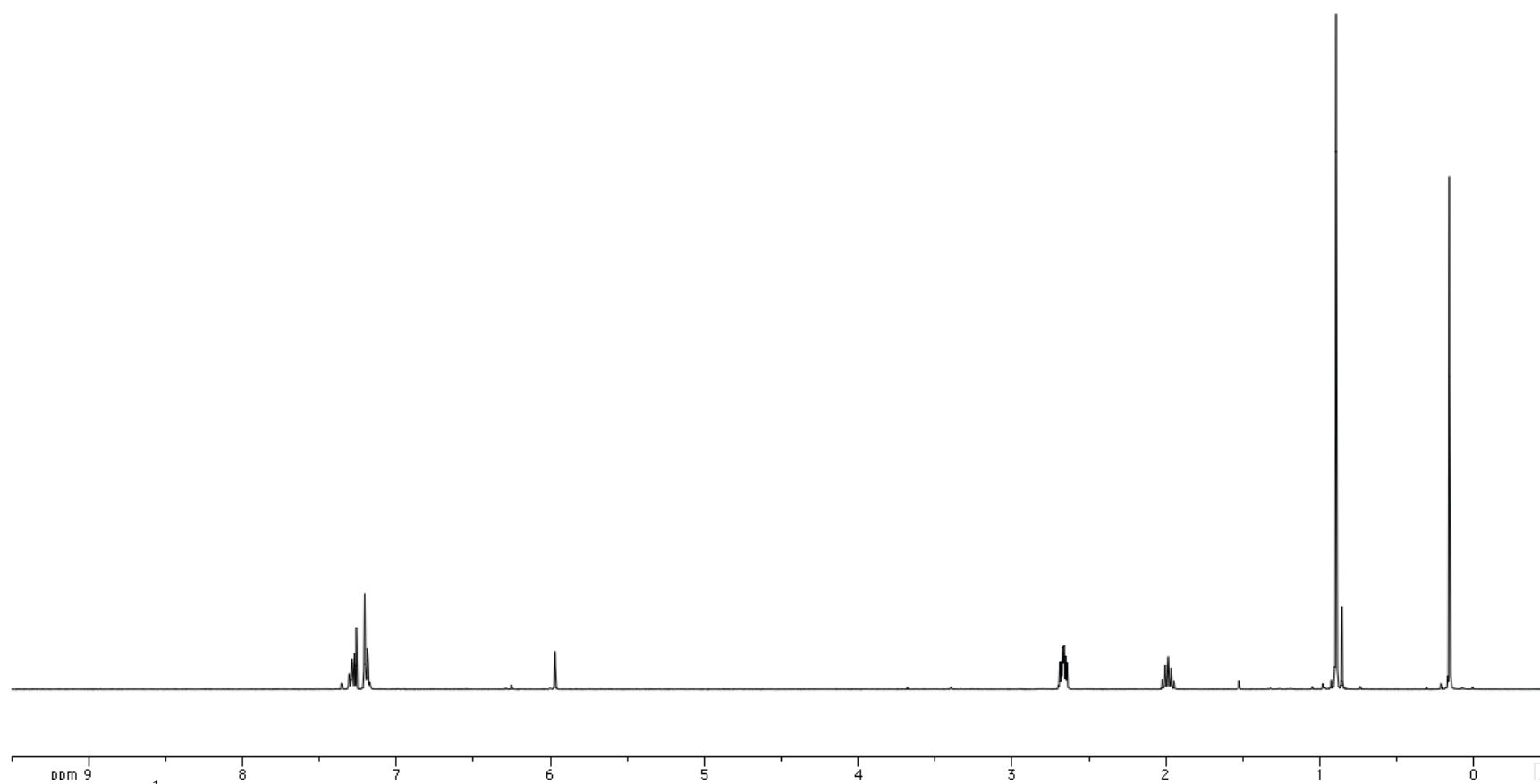
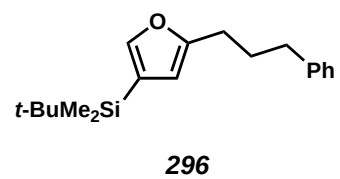
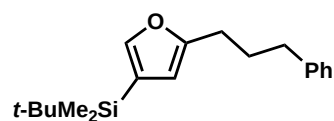


Figure A3.4 ^1H NMR (400 MHz, CDCl_3) of compound **296**



296

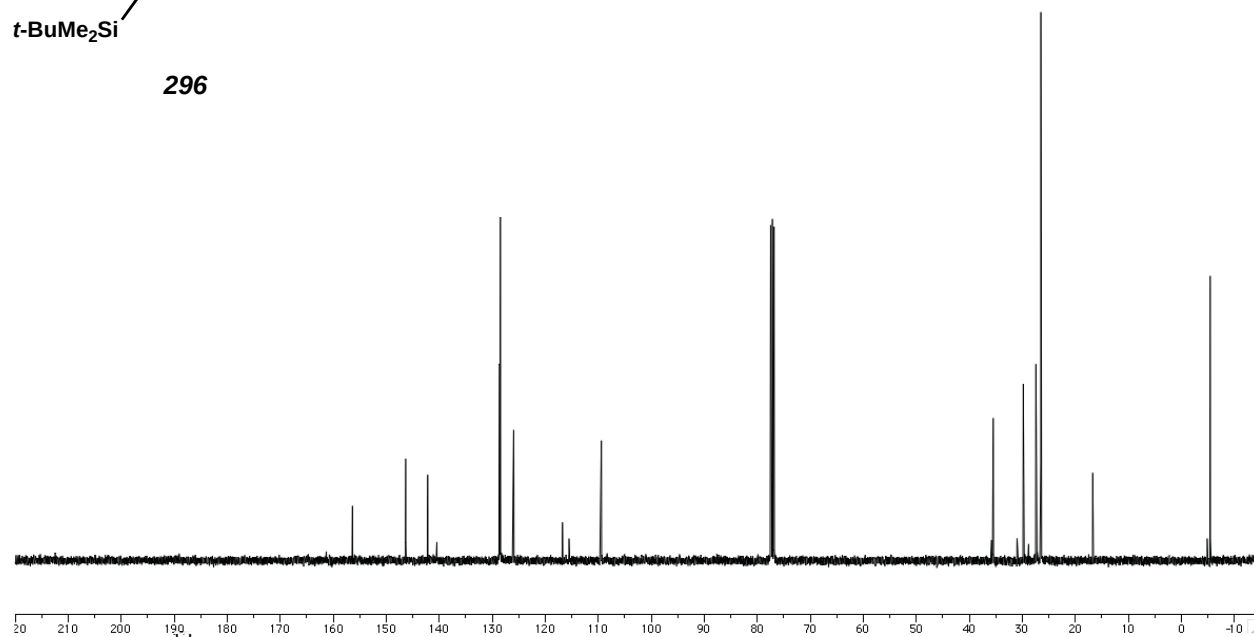


Figure A3.5 ^{13}C NMR (100 MHz, CDCl_3) of compound **296**

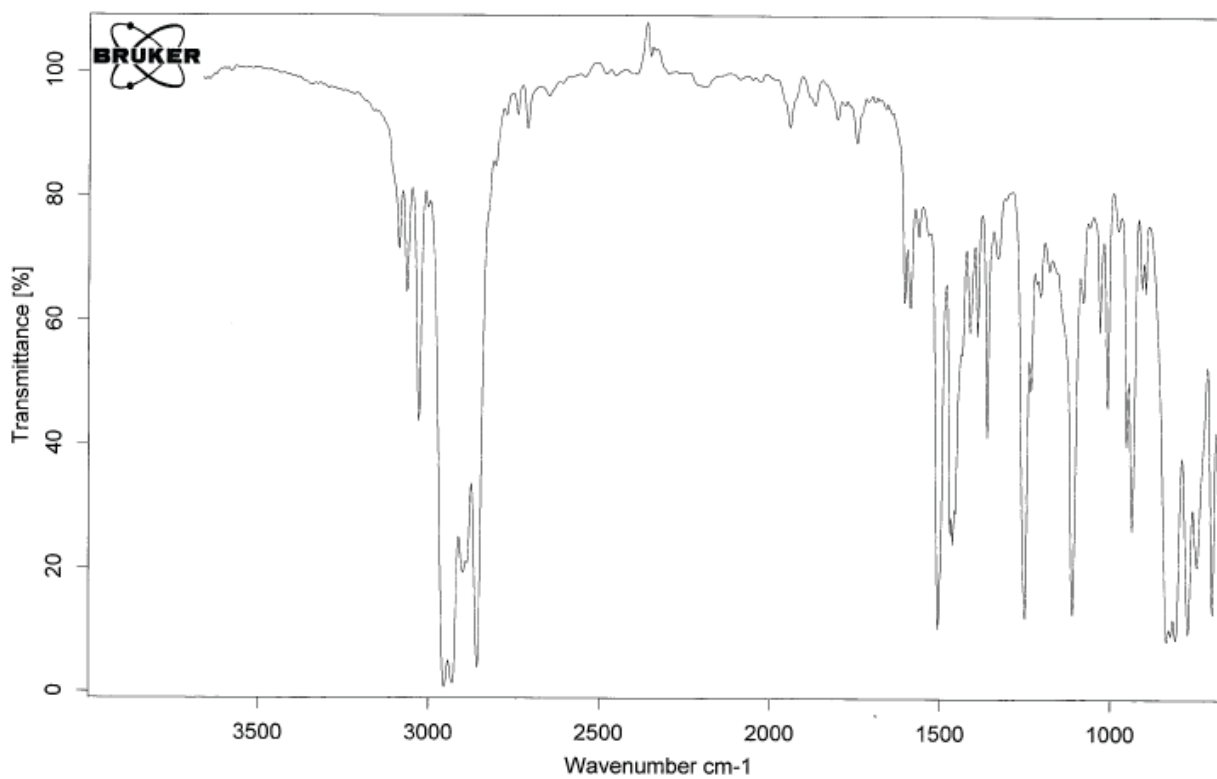


Figure A3.6 Infrared spectrum (thin film) of compound **296**

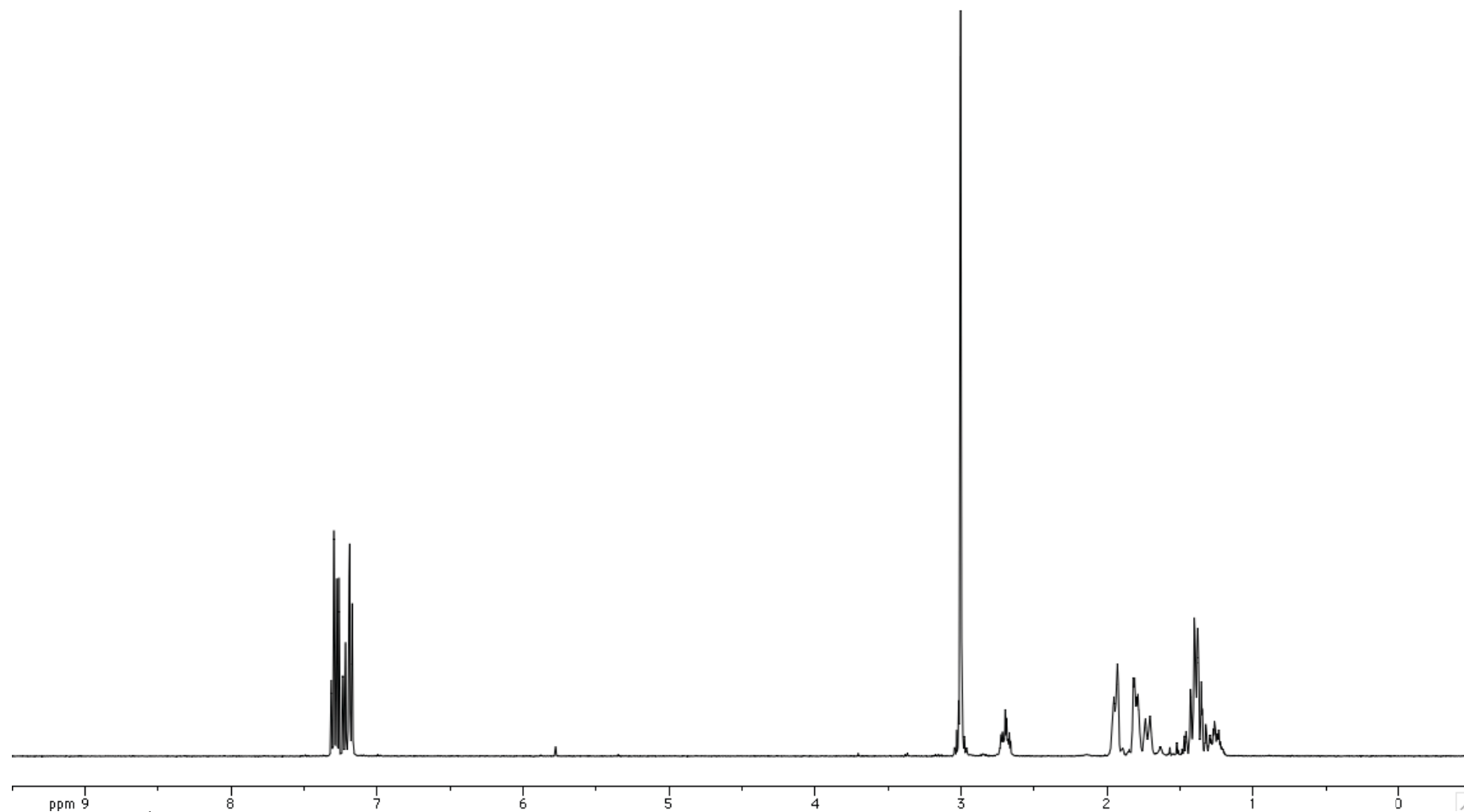
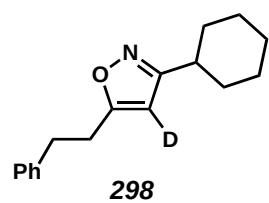
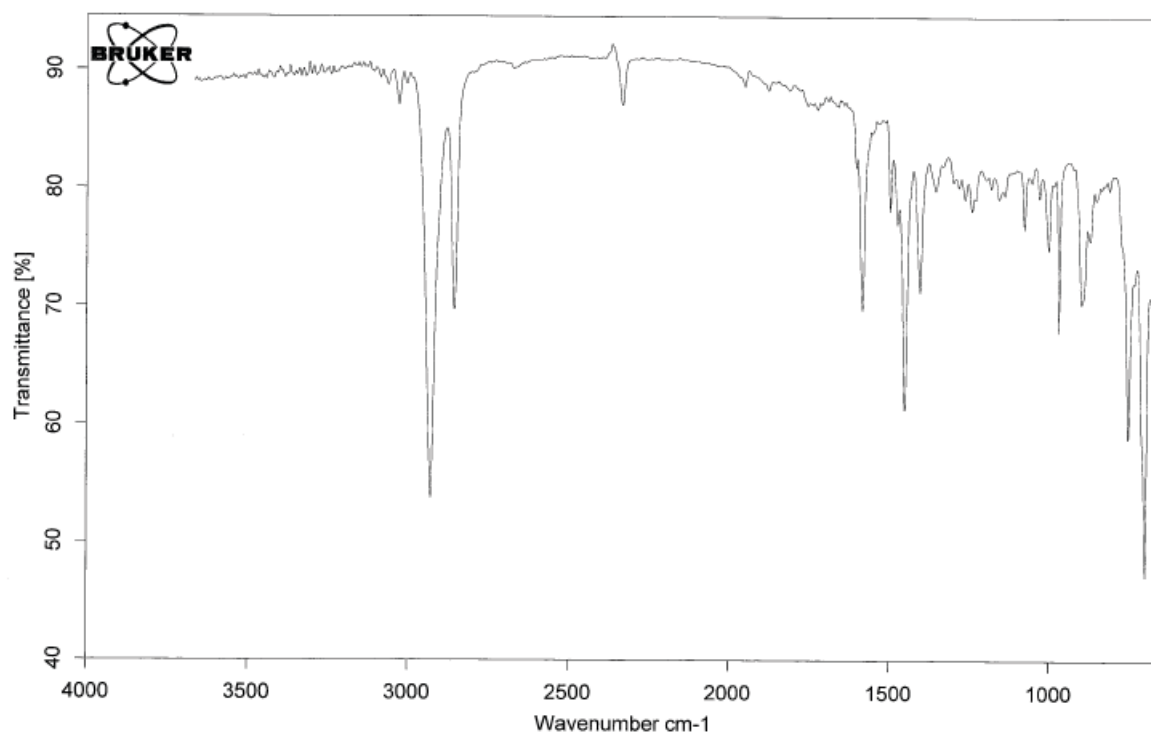
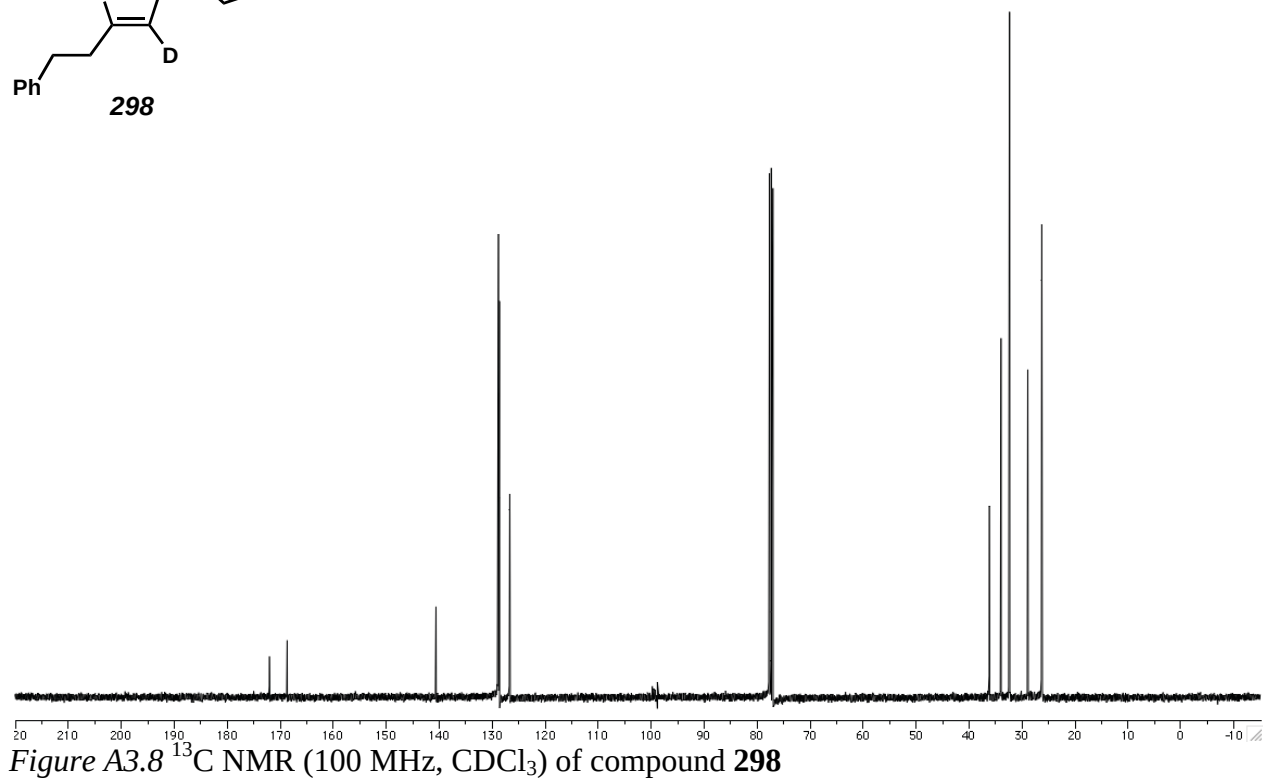
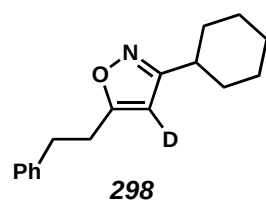


Figure A3.7 ^1H NMR (400 MHz, CDCl_3) of compound **298**



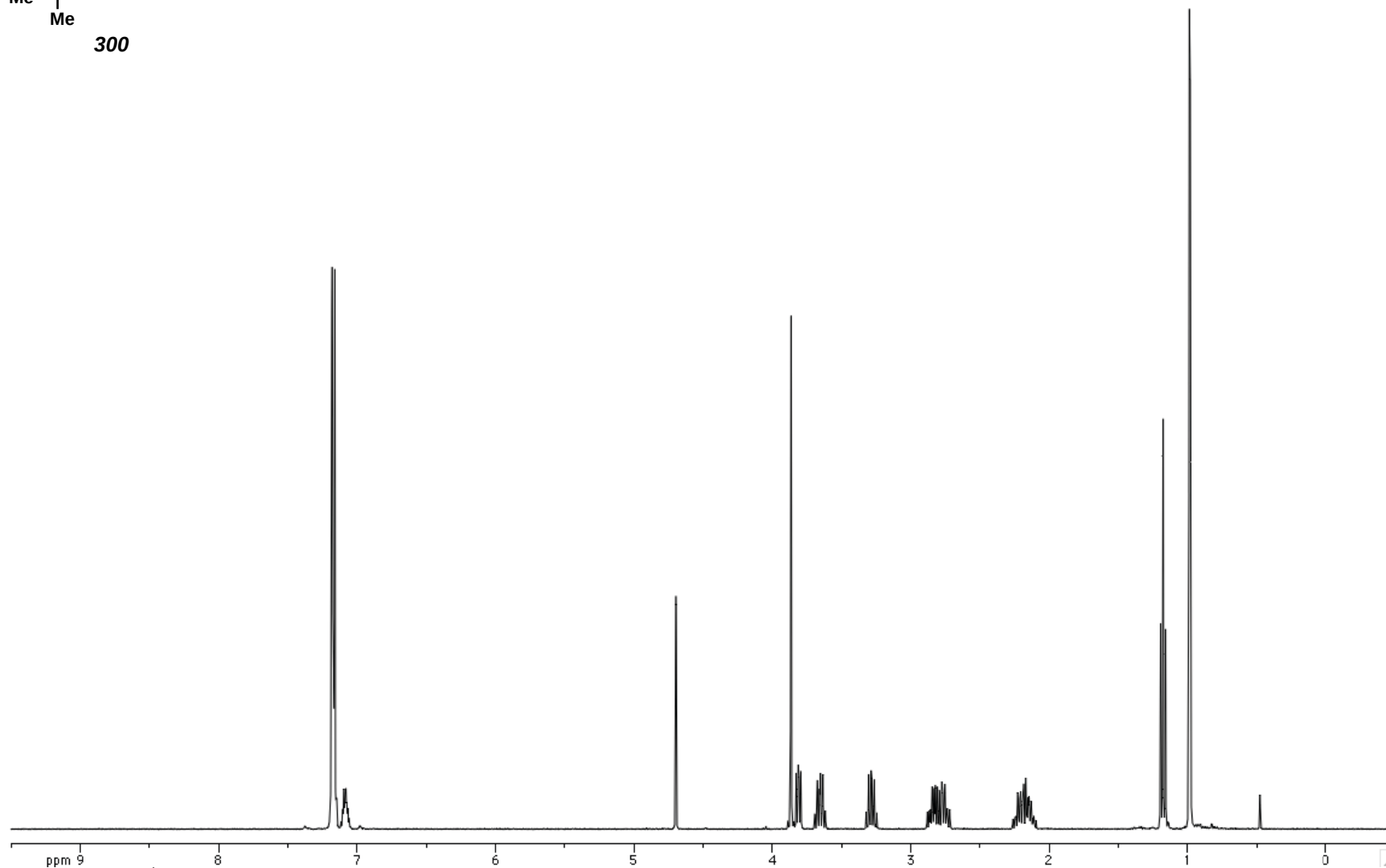
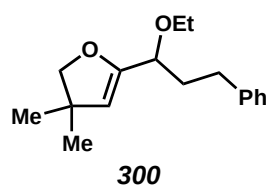


Figure A3.10 ^1H NMR (400 MHz, C_6D_6) of compound **300**

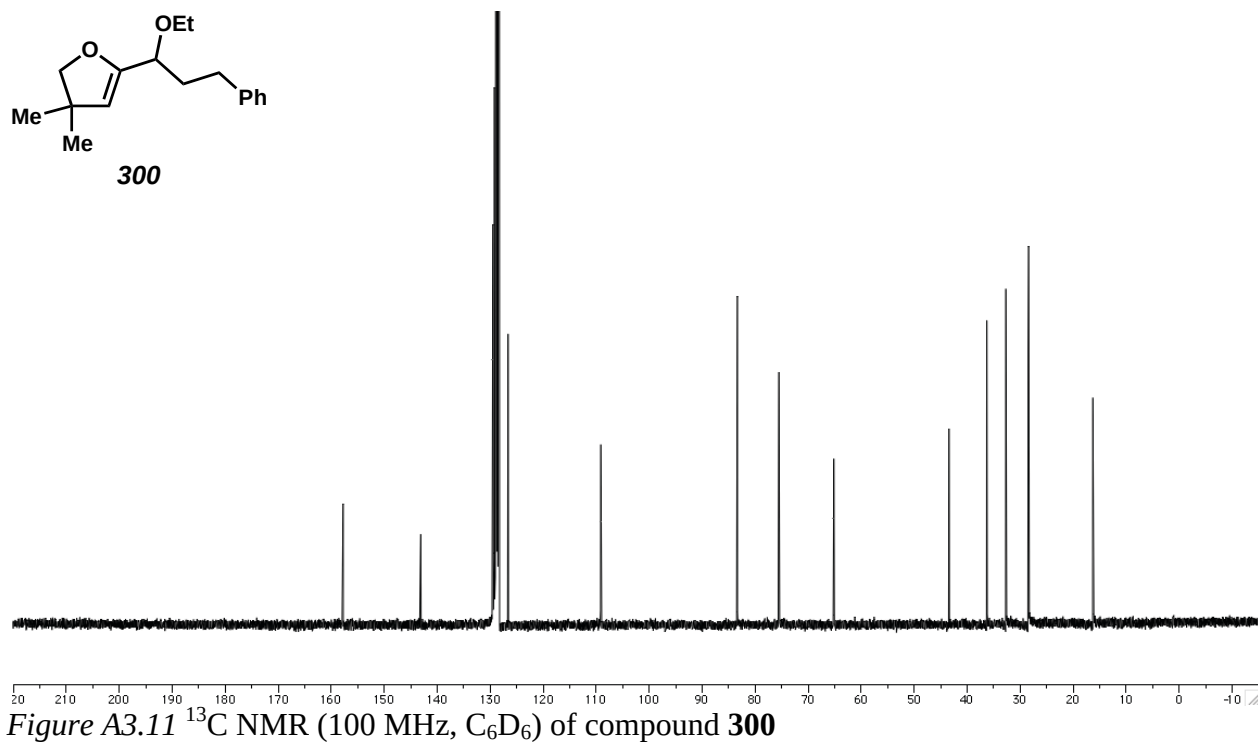


Figure A3.11 ^{13}C NMR (100 MHz, C_6D_6) of compound **300**

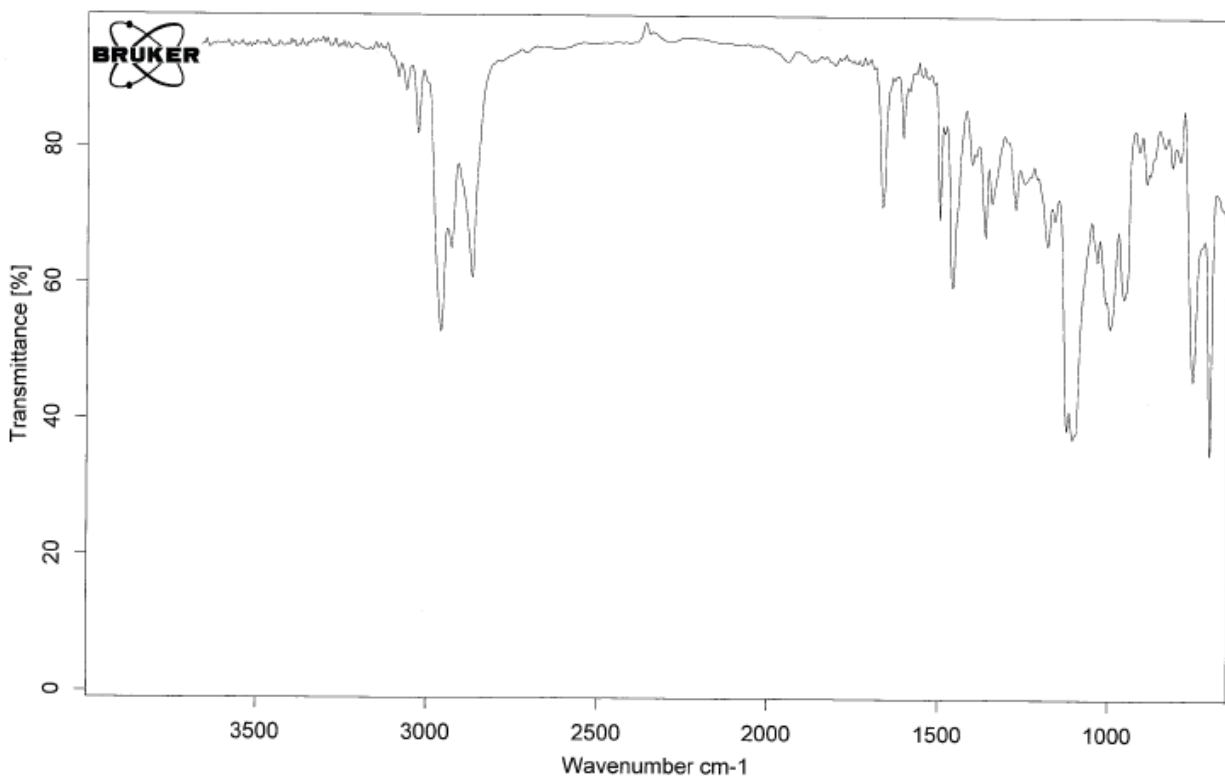


Figure A3.12 Infrared spectrum (thin film) of compound **300**

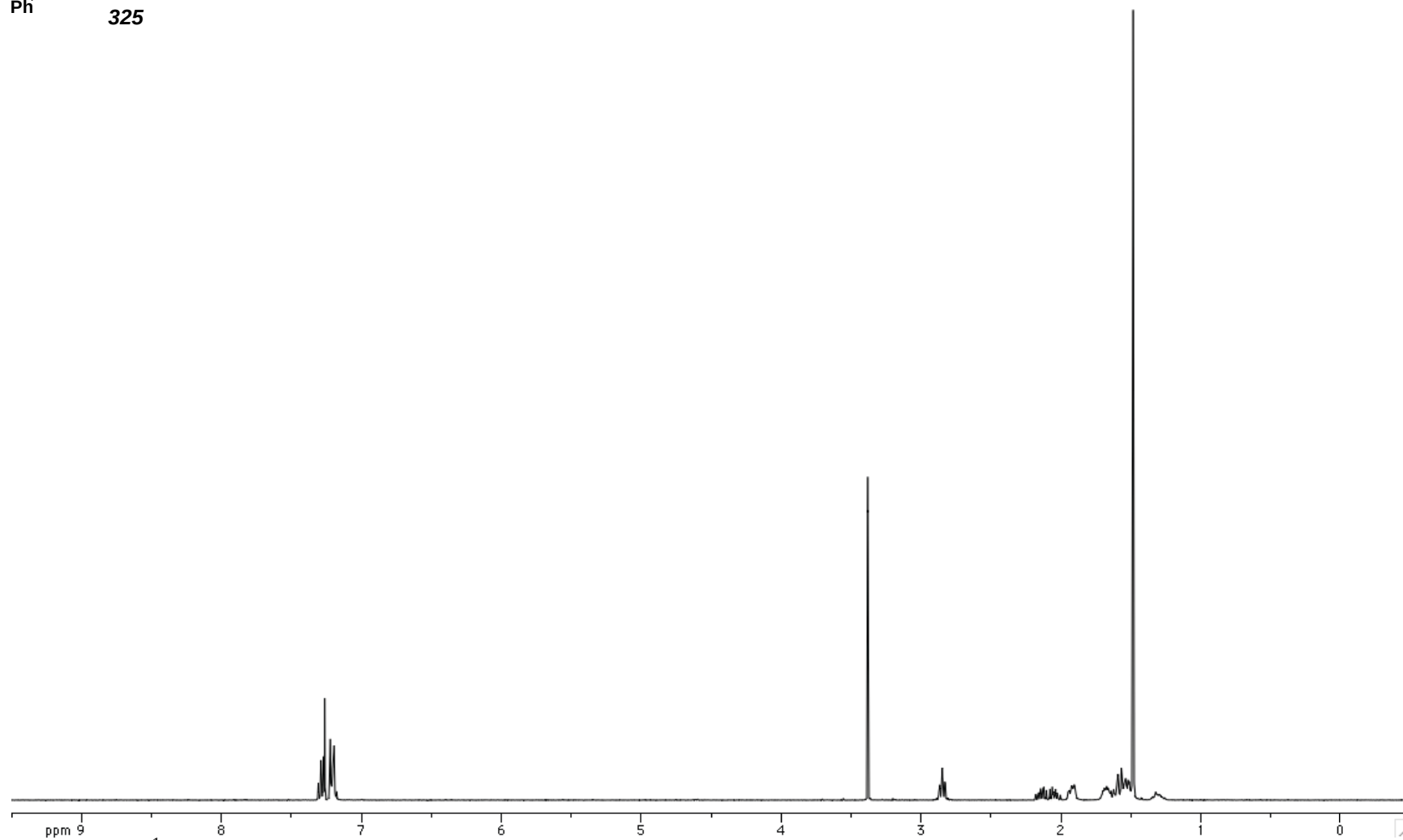
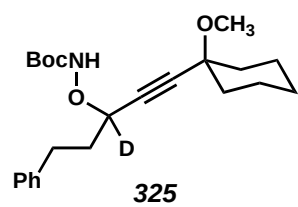


Figure A3.13 ¹H NMR (400 MHz, CDCl₃) of compound **325**

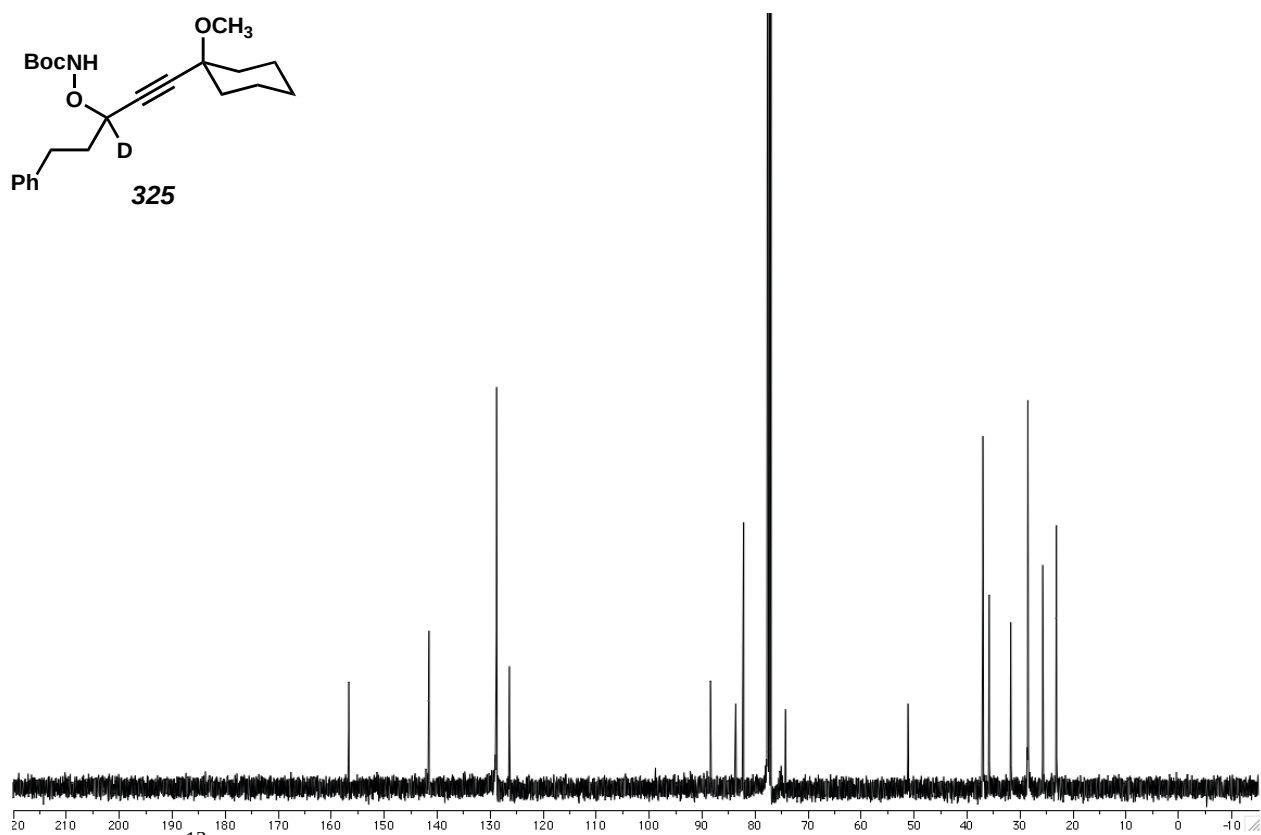
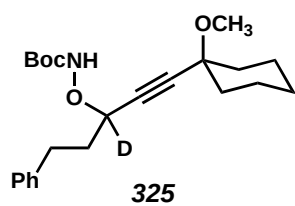


Figure A3.14 ^{13}C NMR (100 MHz, CDCl_3) of compound 325

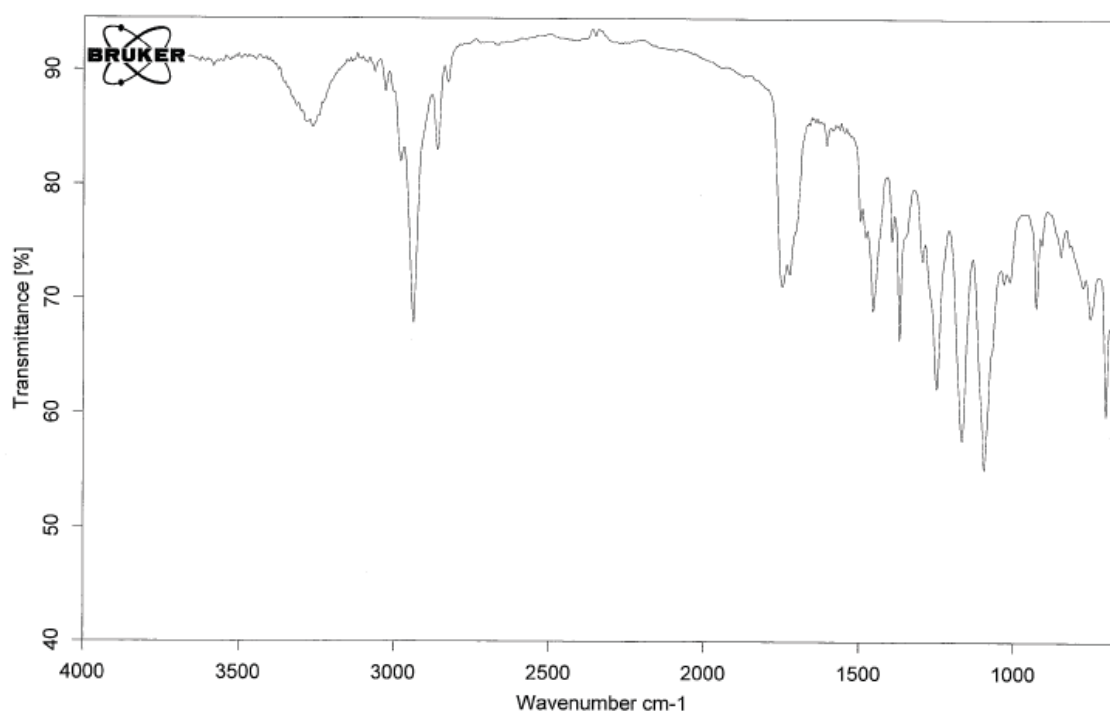


Figure A3.15 Infrared spectrum (thin film) of compound 325

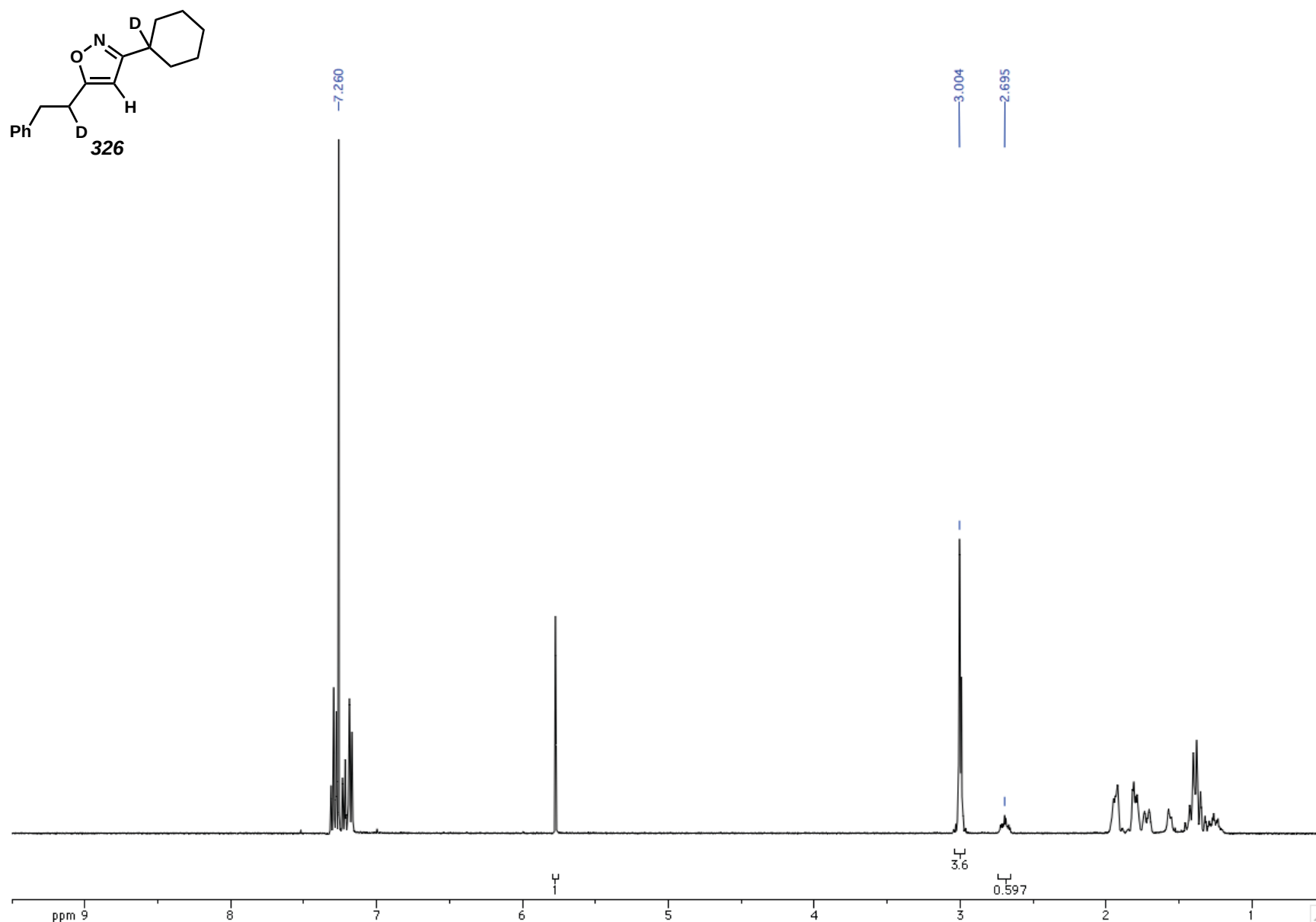


Figure A3.16 ^1H NMR (400 MHz, CDCl_3) of compound **326**

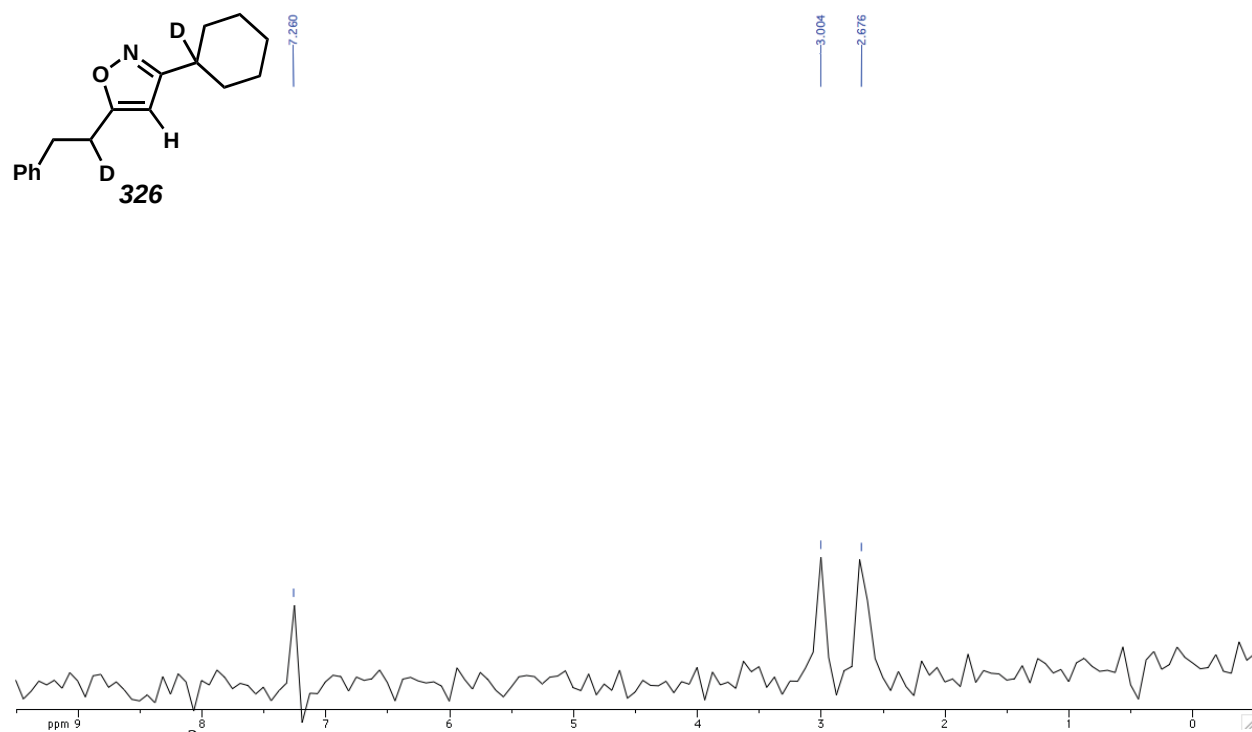


Figure A3.17 ^2H NMR (400 MHz, CDCl_3) of compound **326**

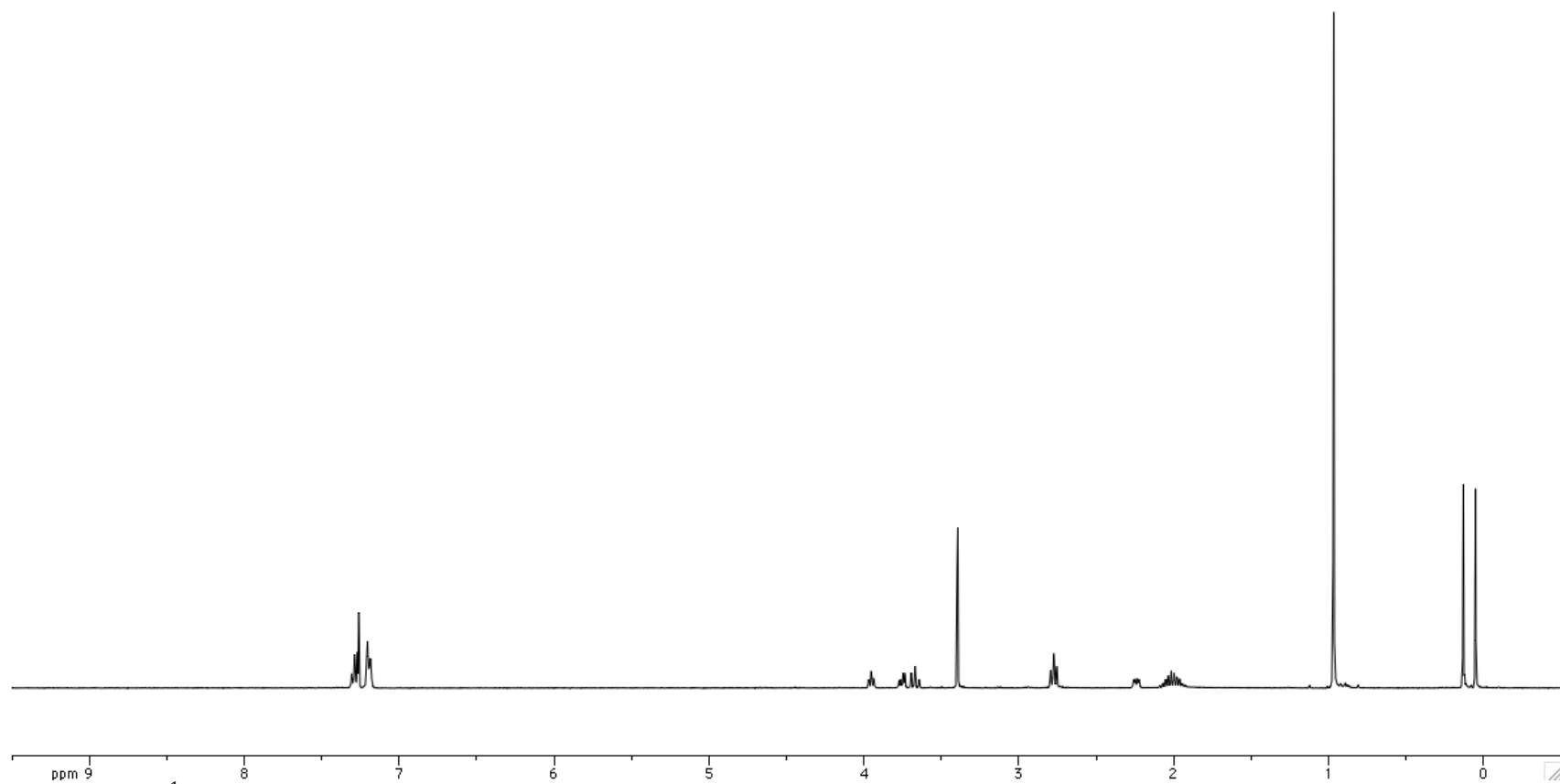
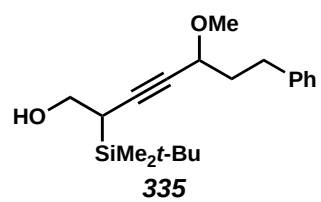
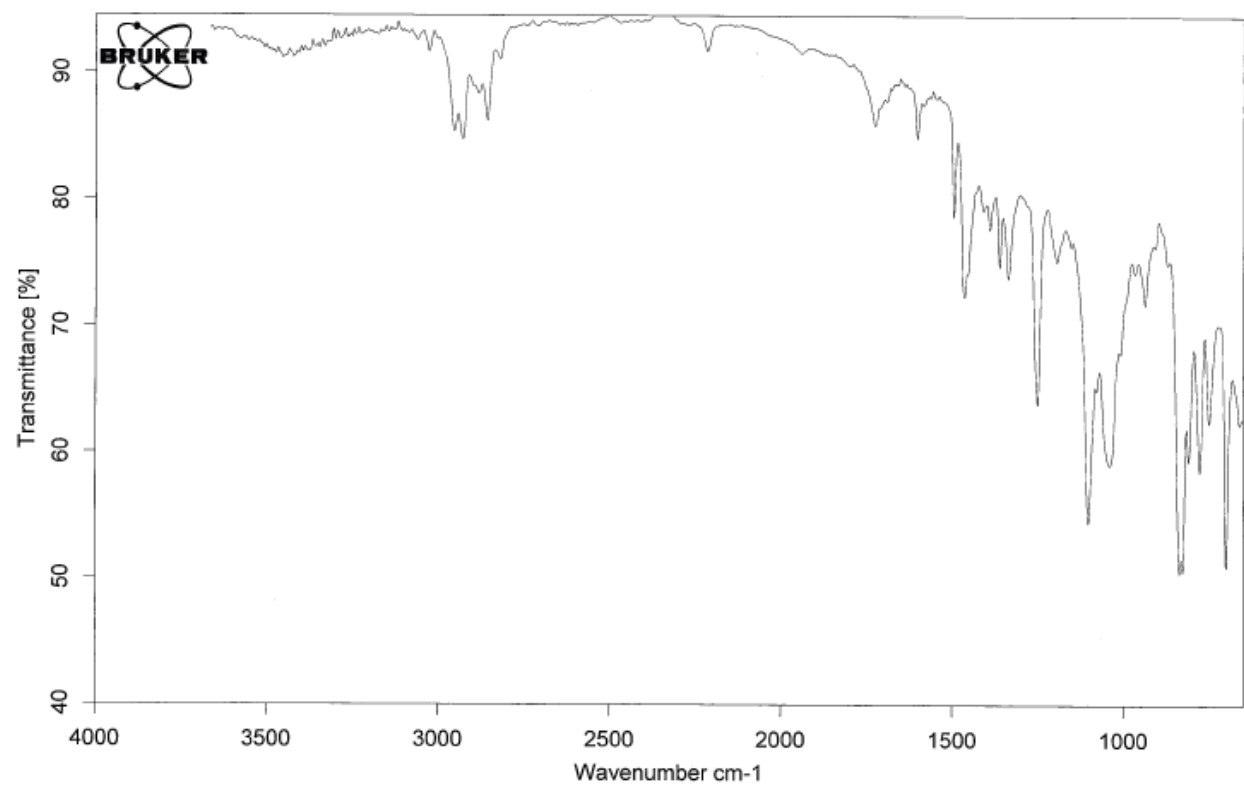
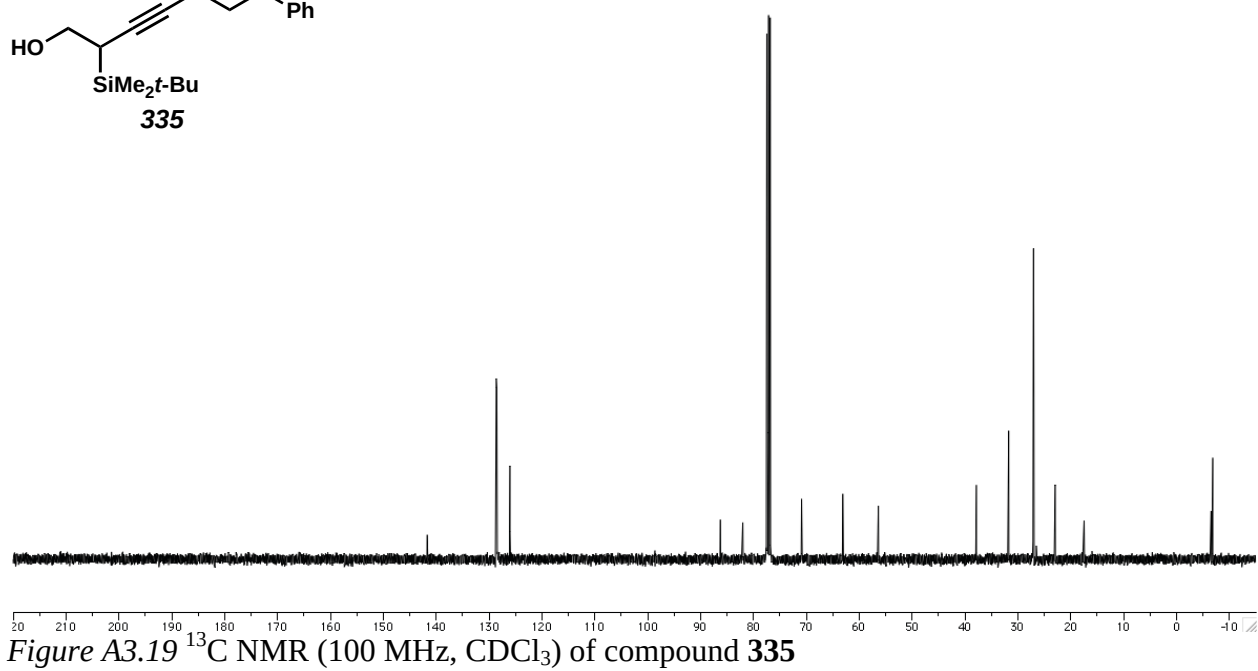
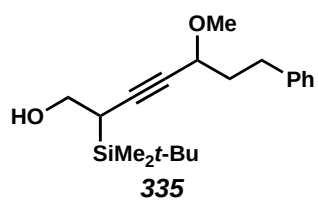


Figure A3.18 ^1H NMR (400 MHz, CDCl_3) of compound **335**



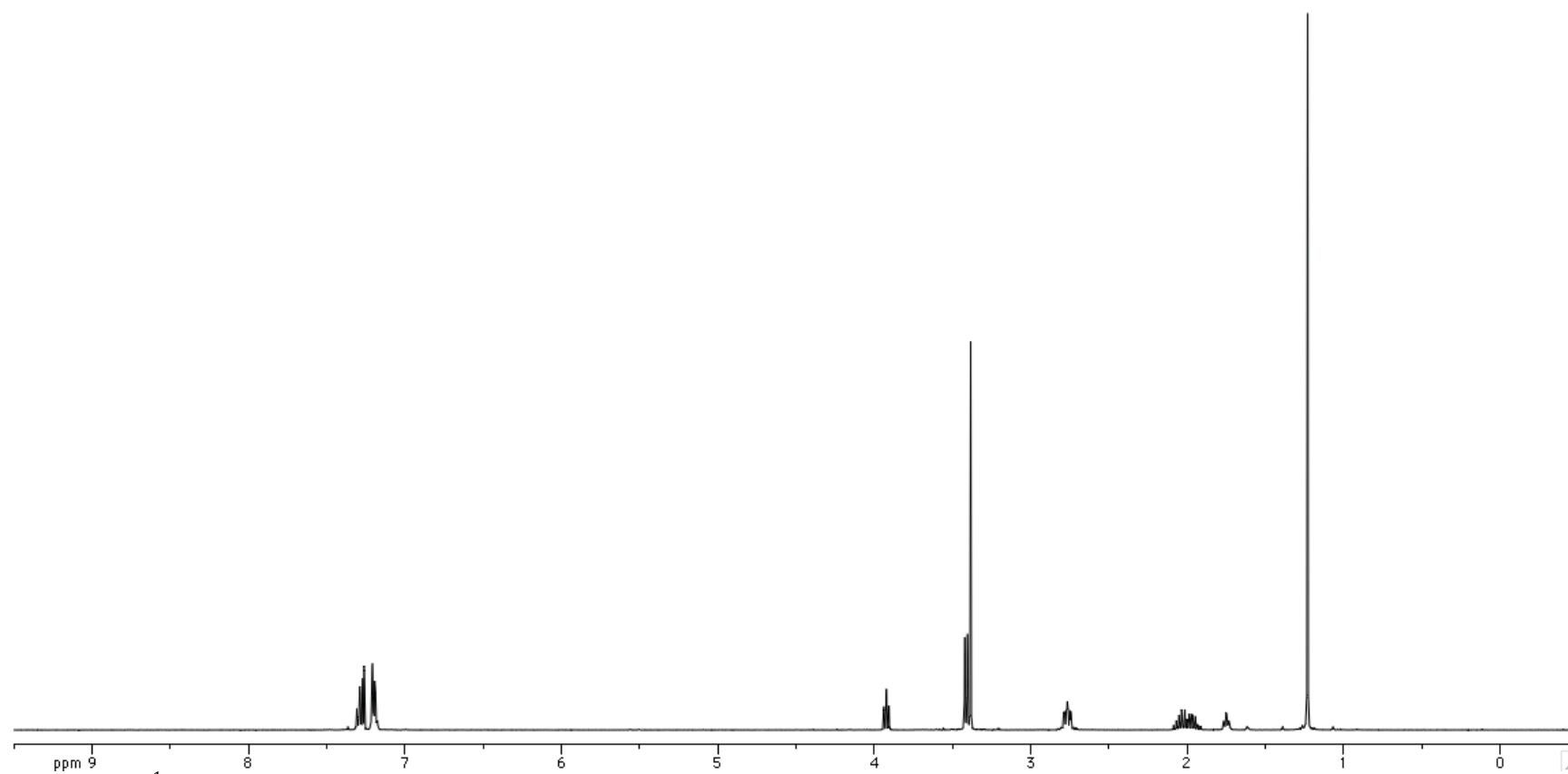
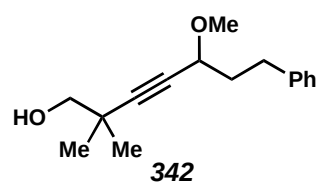


Figure 3.21 ^1H NMR (400 MHz, CDCl_3) of compound **342**

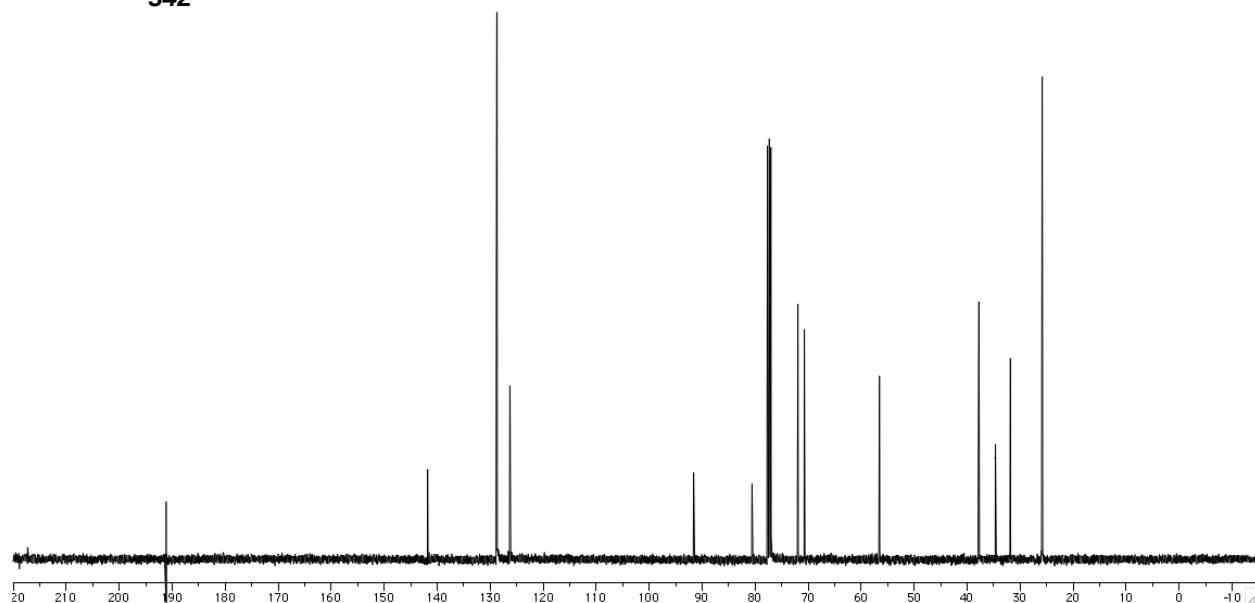
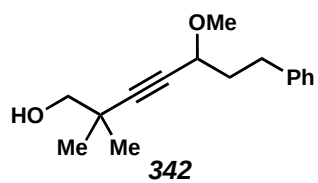


Figure A3.22 ^{13}C NMR (100 MHz, CDCl_3) of compound **342**

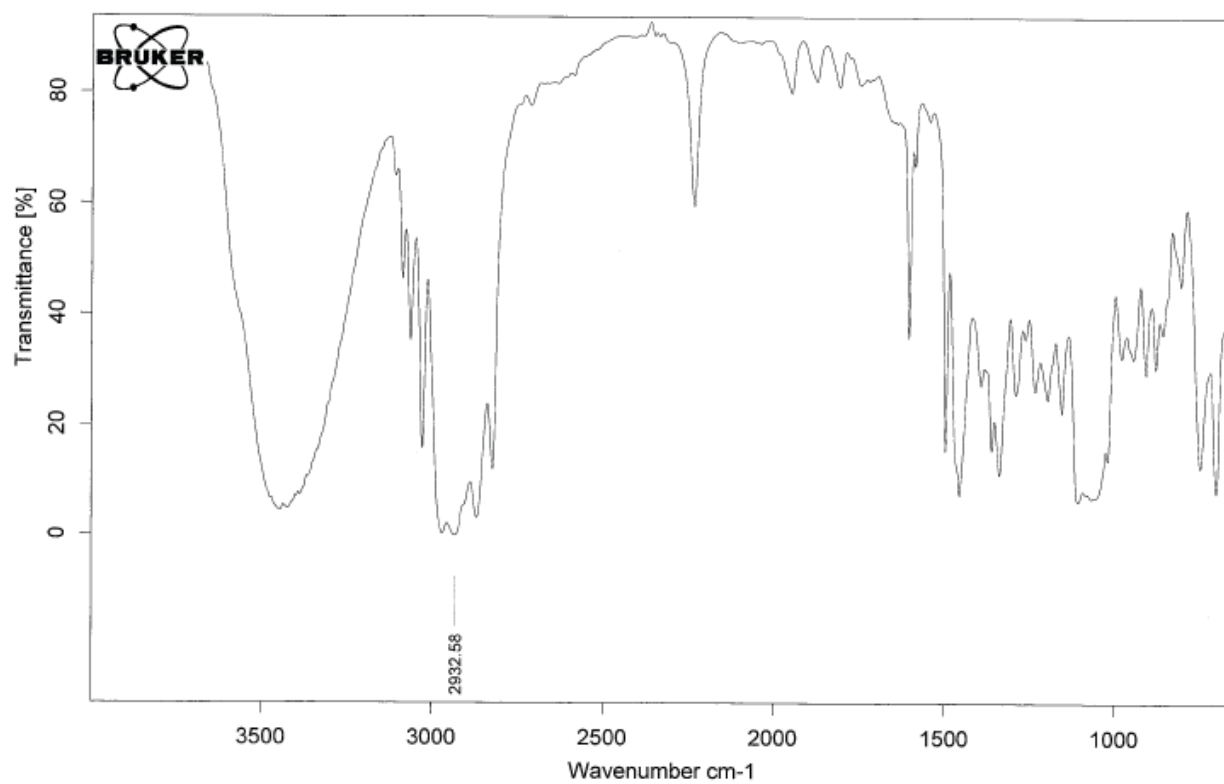


Figure A3.23 Infrared spectrum (thin film) of compound **342**

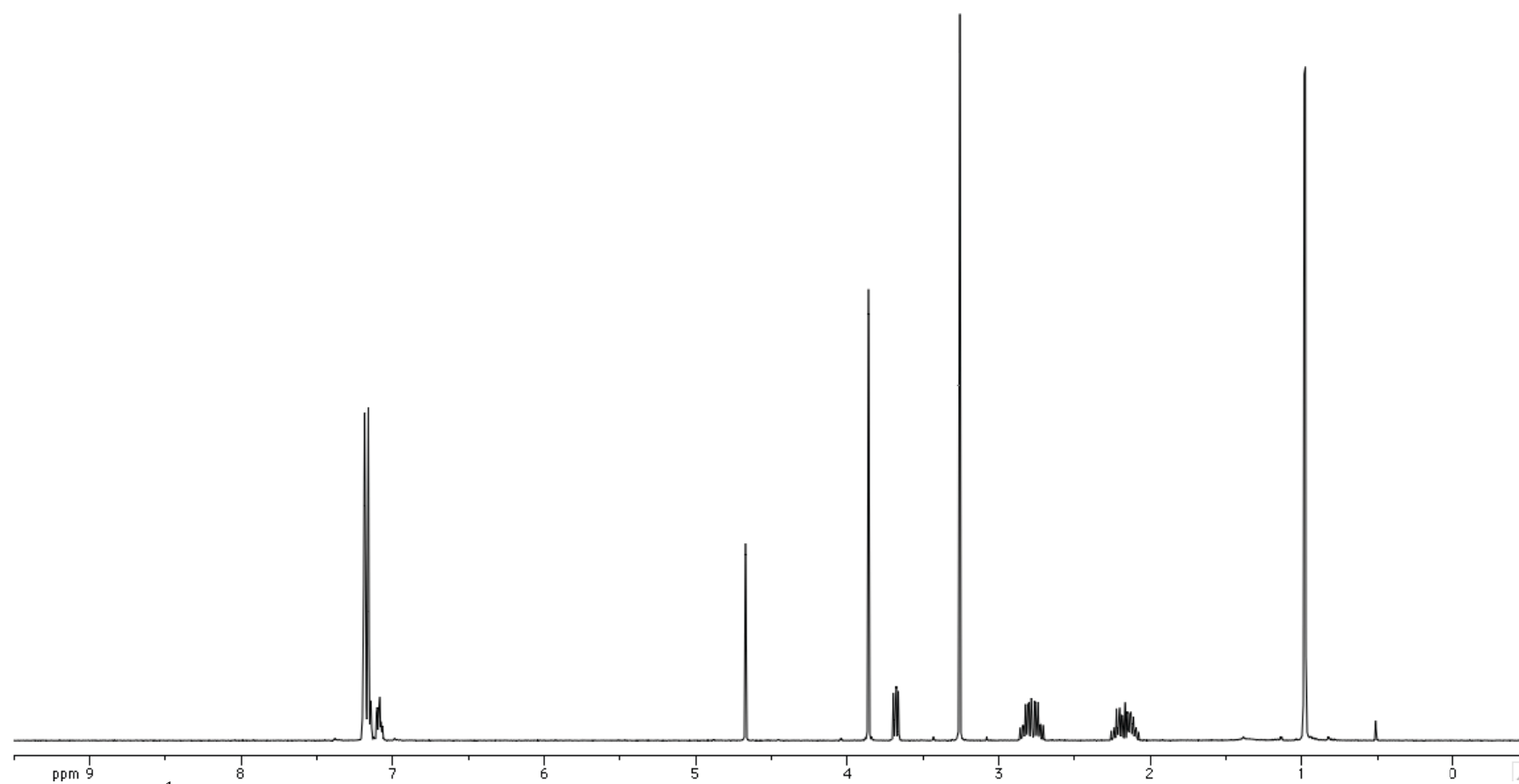
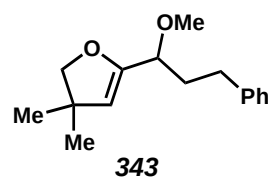
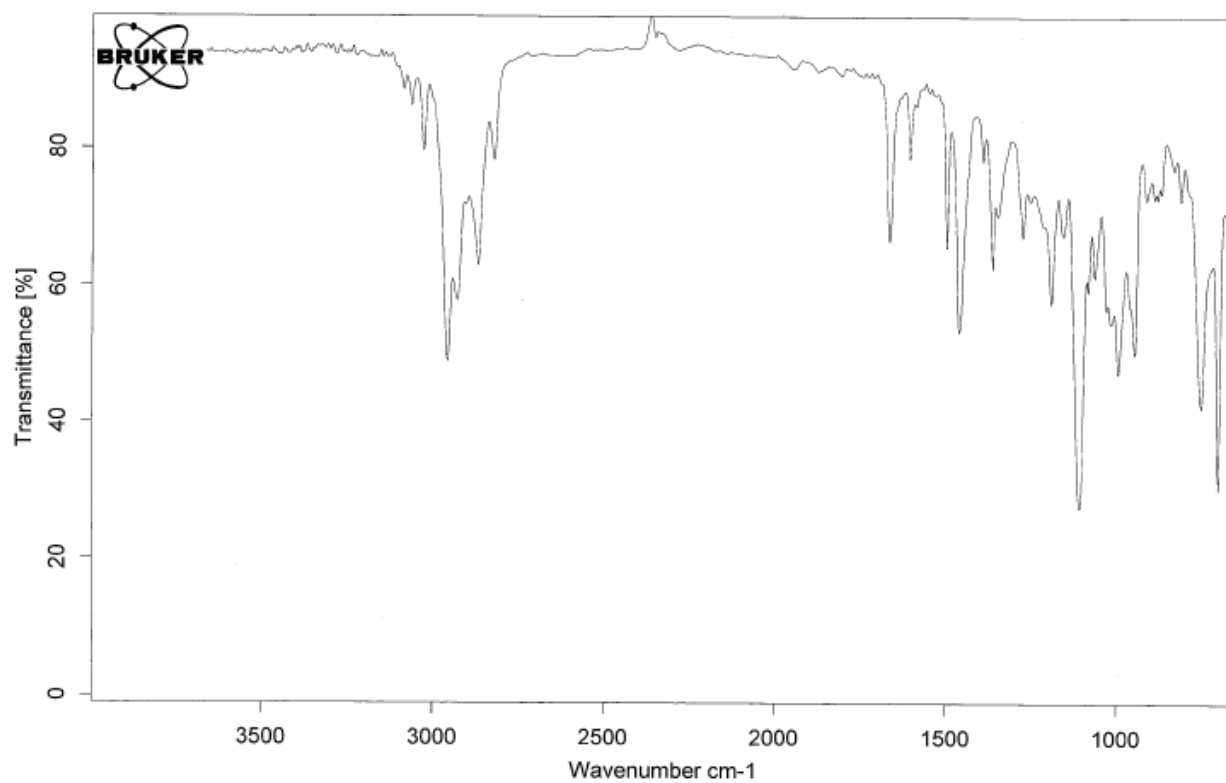
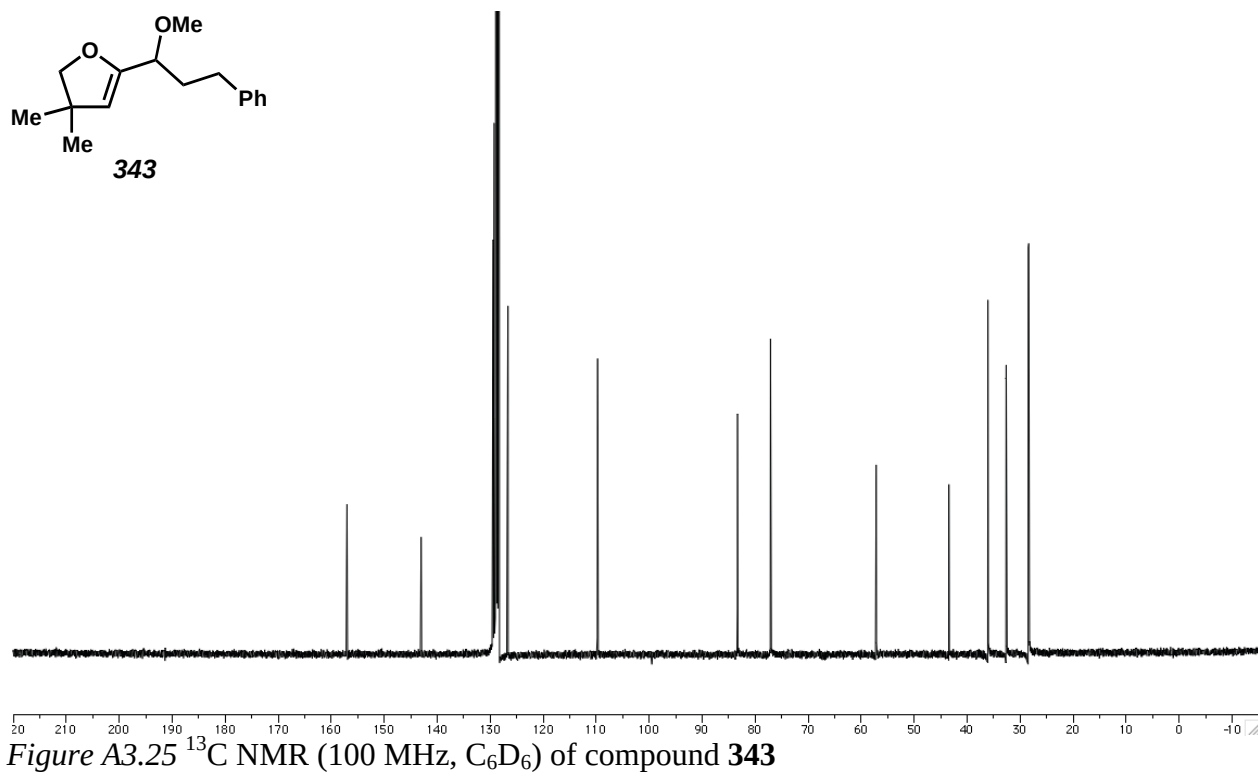


Figure A3.24 ^1H NMR (400 MHz, C_6D_6) of compound **343**



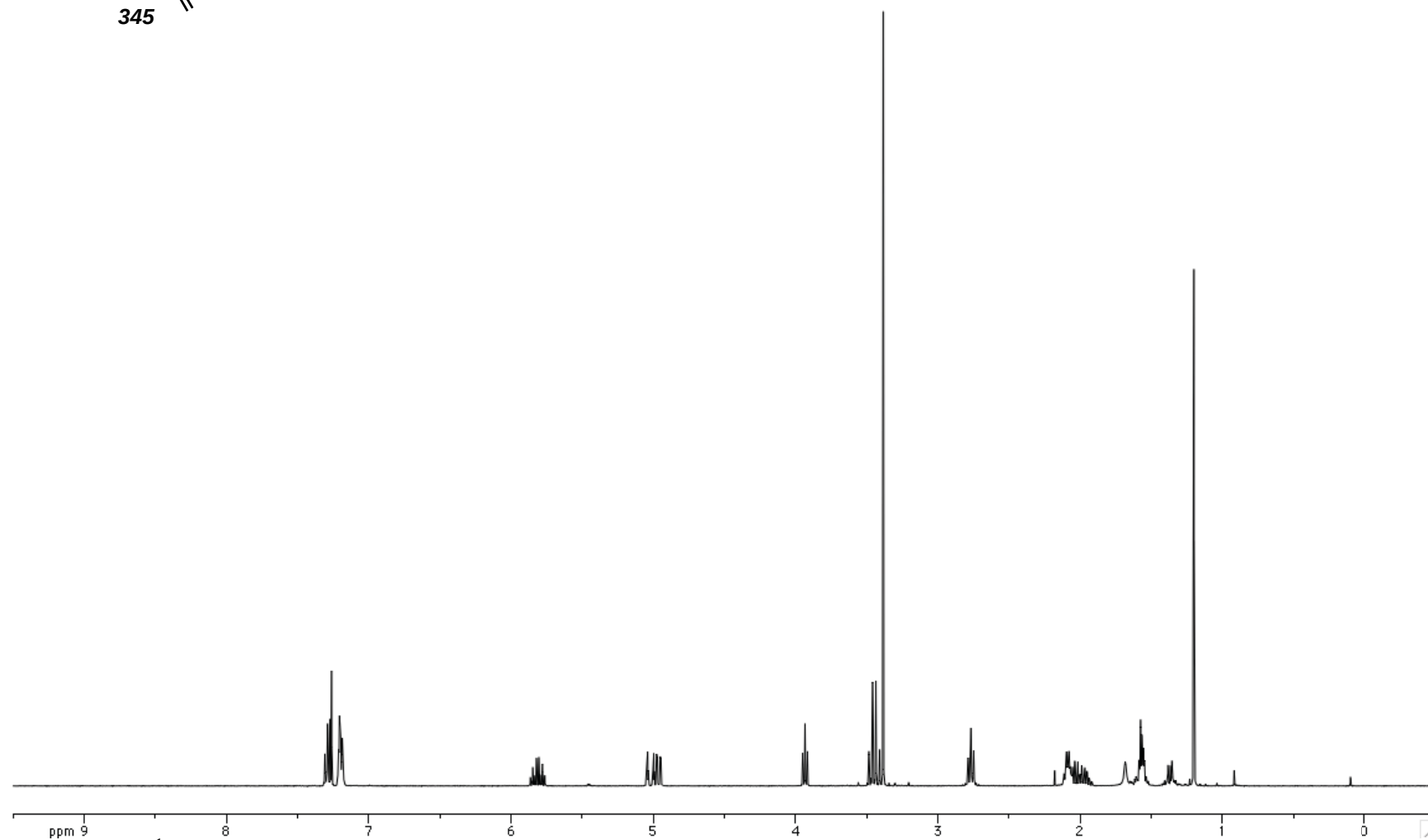
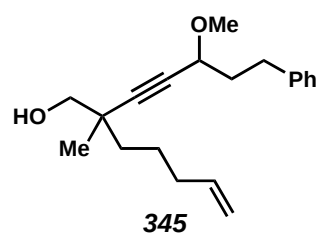


Figure A3.27 ^1H NMR (400 MHz, CDCl_3) of compound **345**

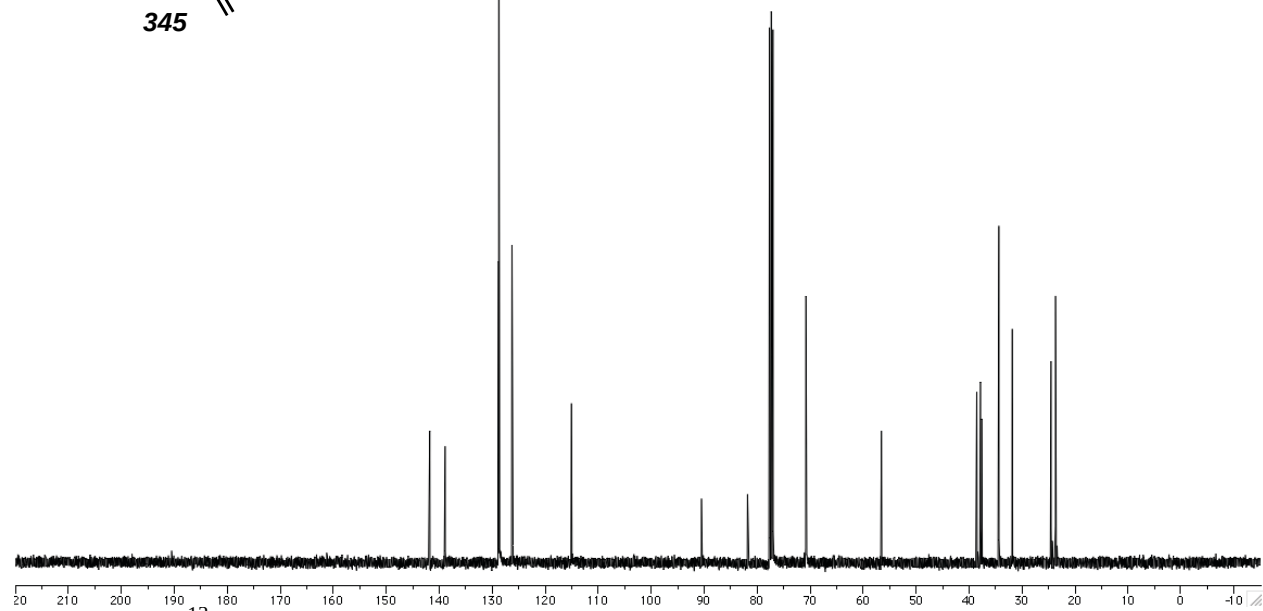
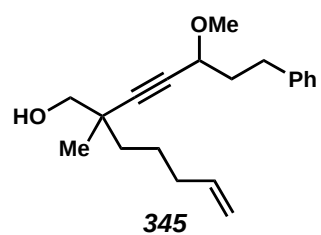


Figure A3.28 ¹³C NMR (100 MHz, CDCl₃) of compound 345

APPENDIX FOUR

Spectra Relevant to Chapter Five

Synthesis of Vicinal Bisheterocycles from Propargylic Methyl Ethers

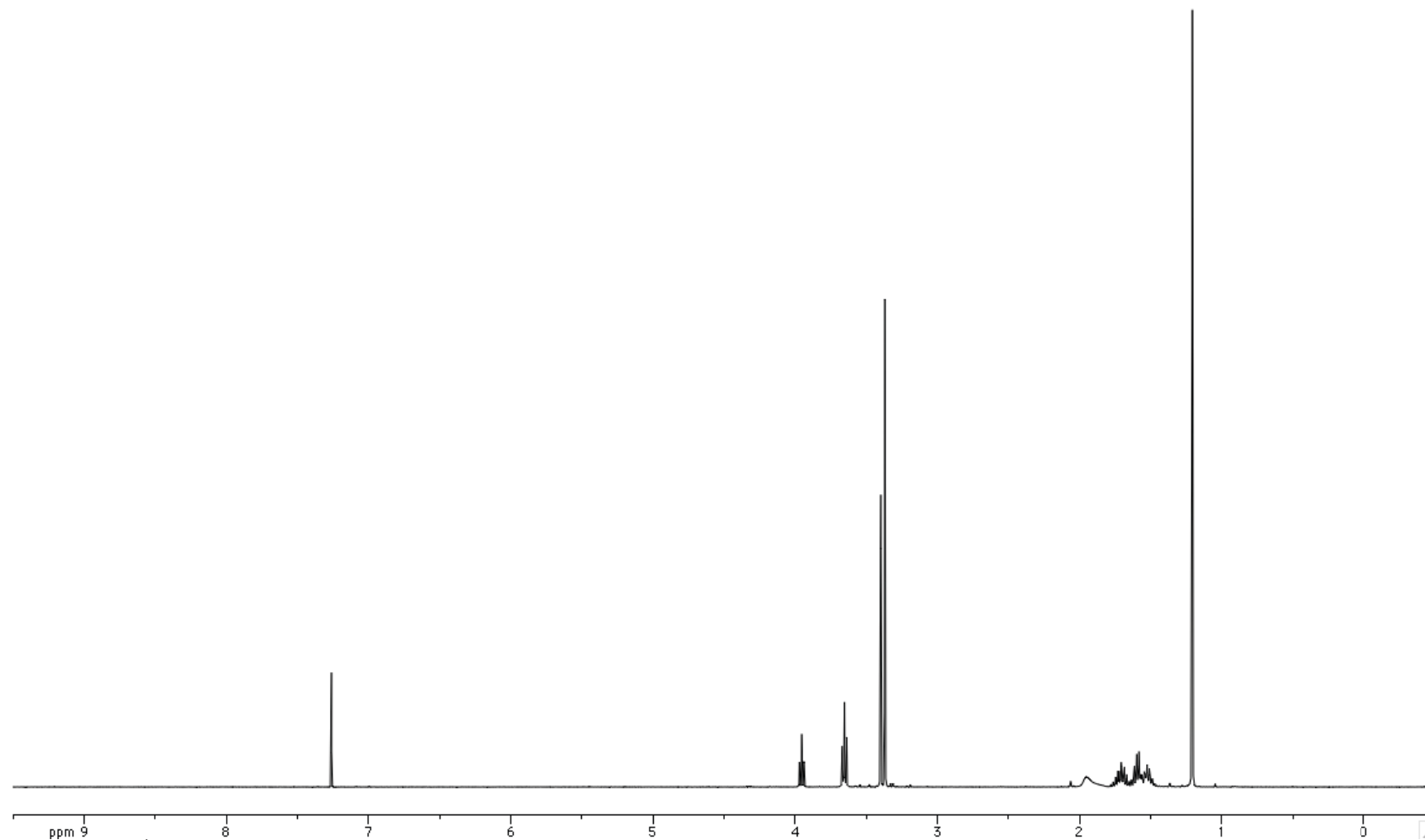
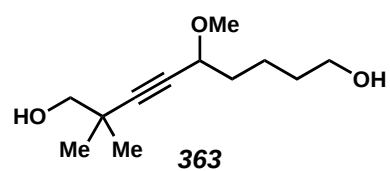


Figure A4.1 ¹H NMR (400 MHz, CDCl₃) of compound **363**

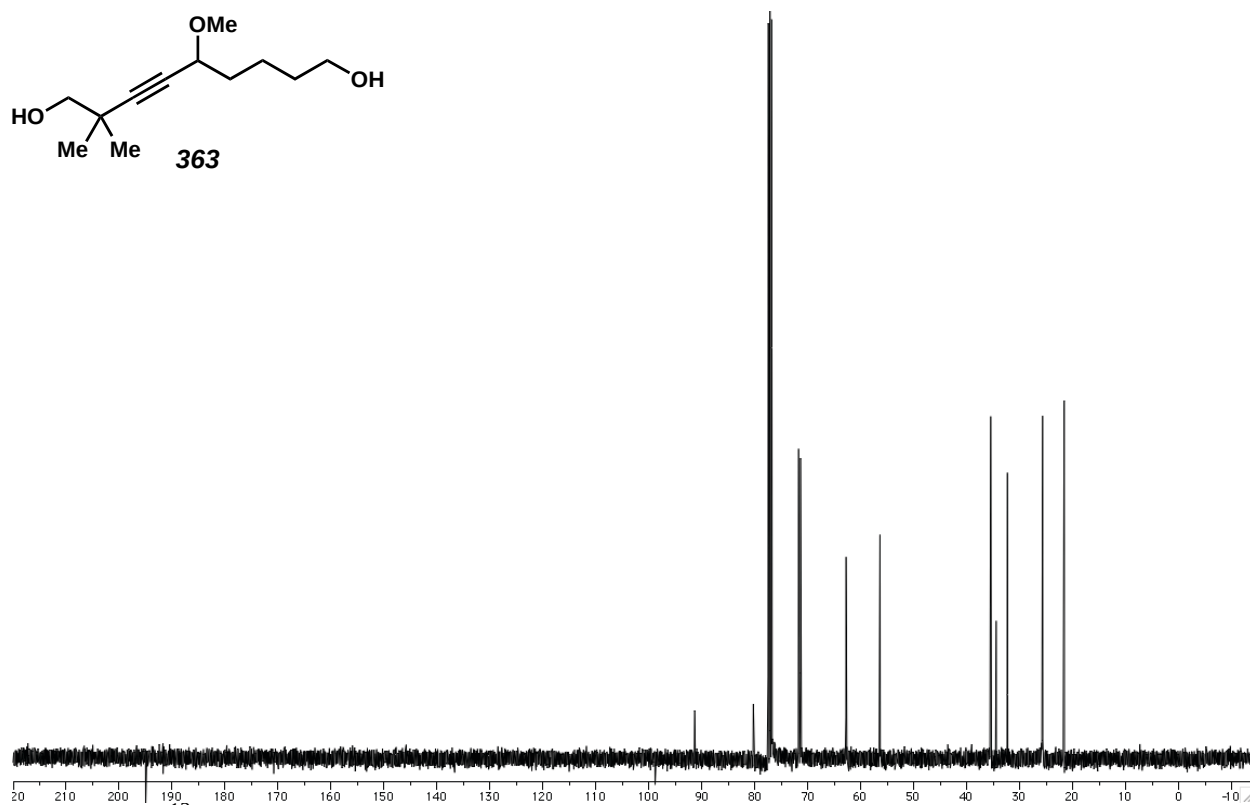


Figure A4.2 ^{13}C NMR (100 MHz, CDCl_3) of compound 363

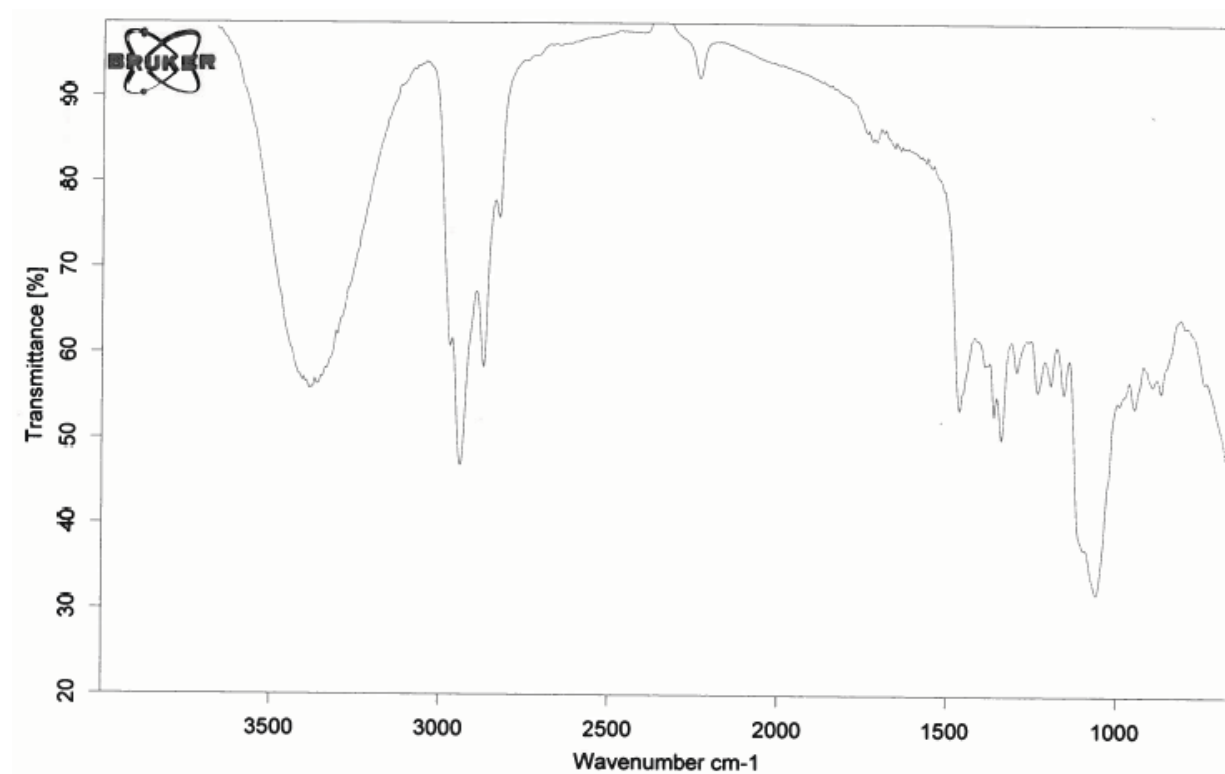


Figure A4.3 Infrared spectrum (thin film) of compound 363

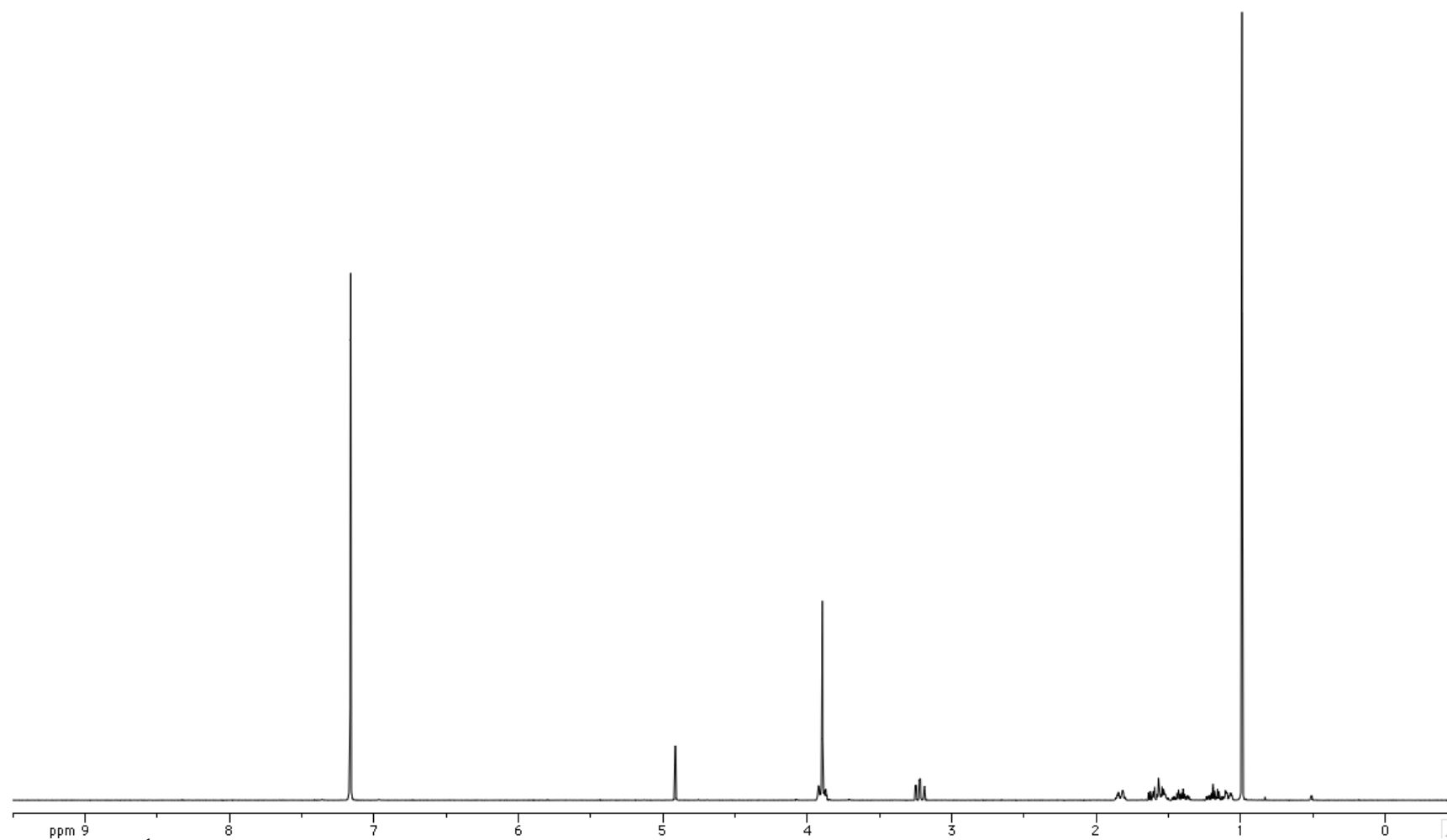
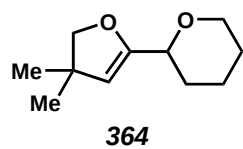


Figure A4.4 ^1H NMR (400 MHz, C_6D_6) of compound **364**

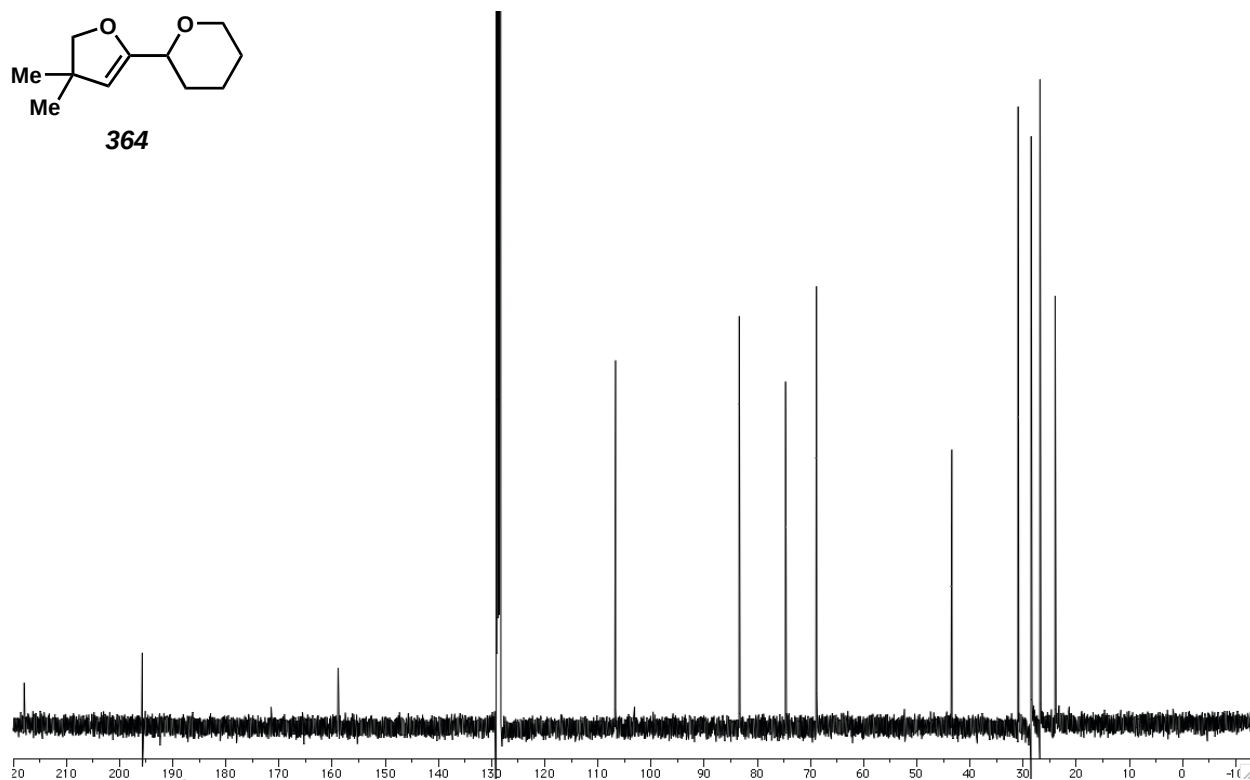


Figure A4.5 ^{13}C NMR (100 MHz, C_6D_6) of compound **364**

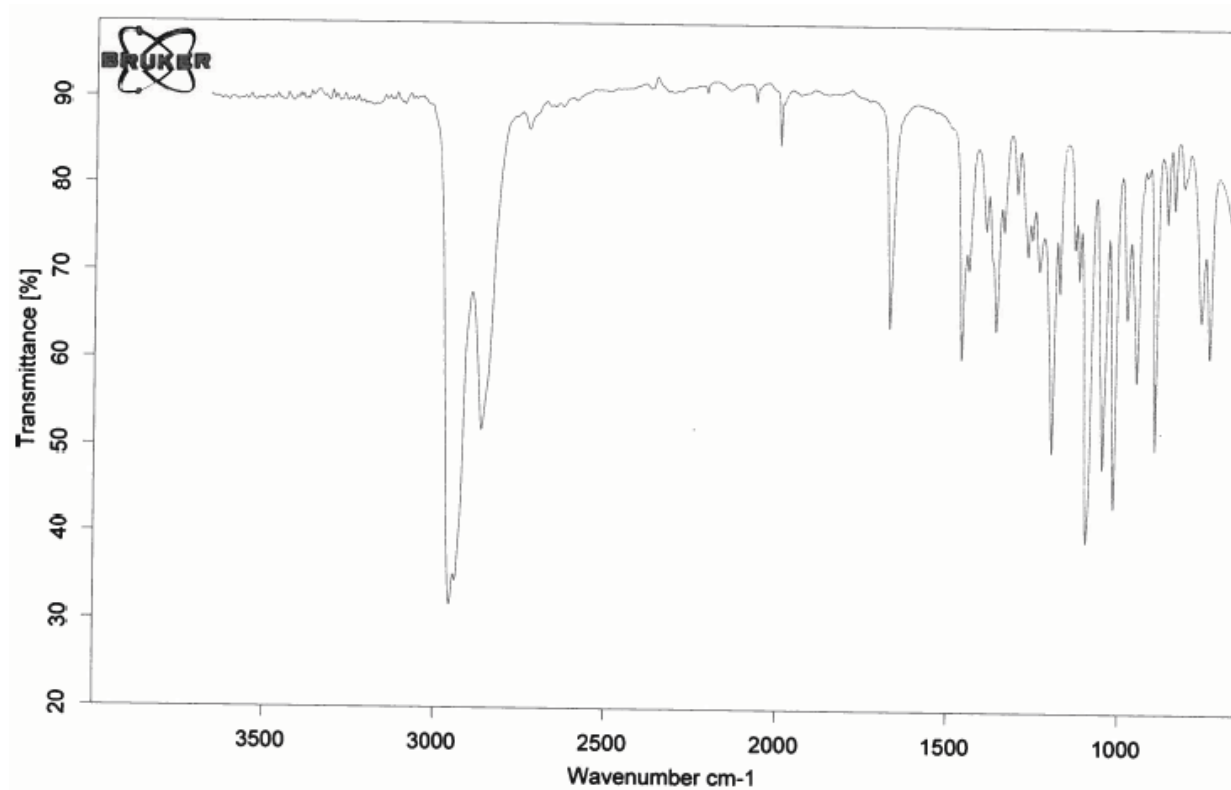


Figure A4.6 Infrared spectrum (thin film) of compound **364**

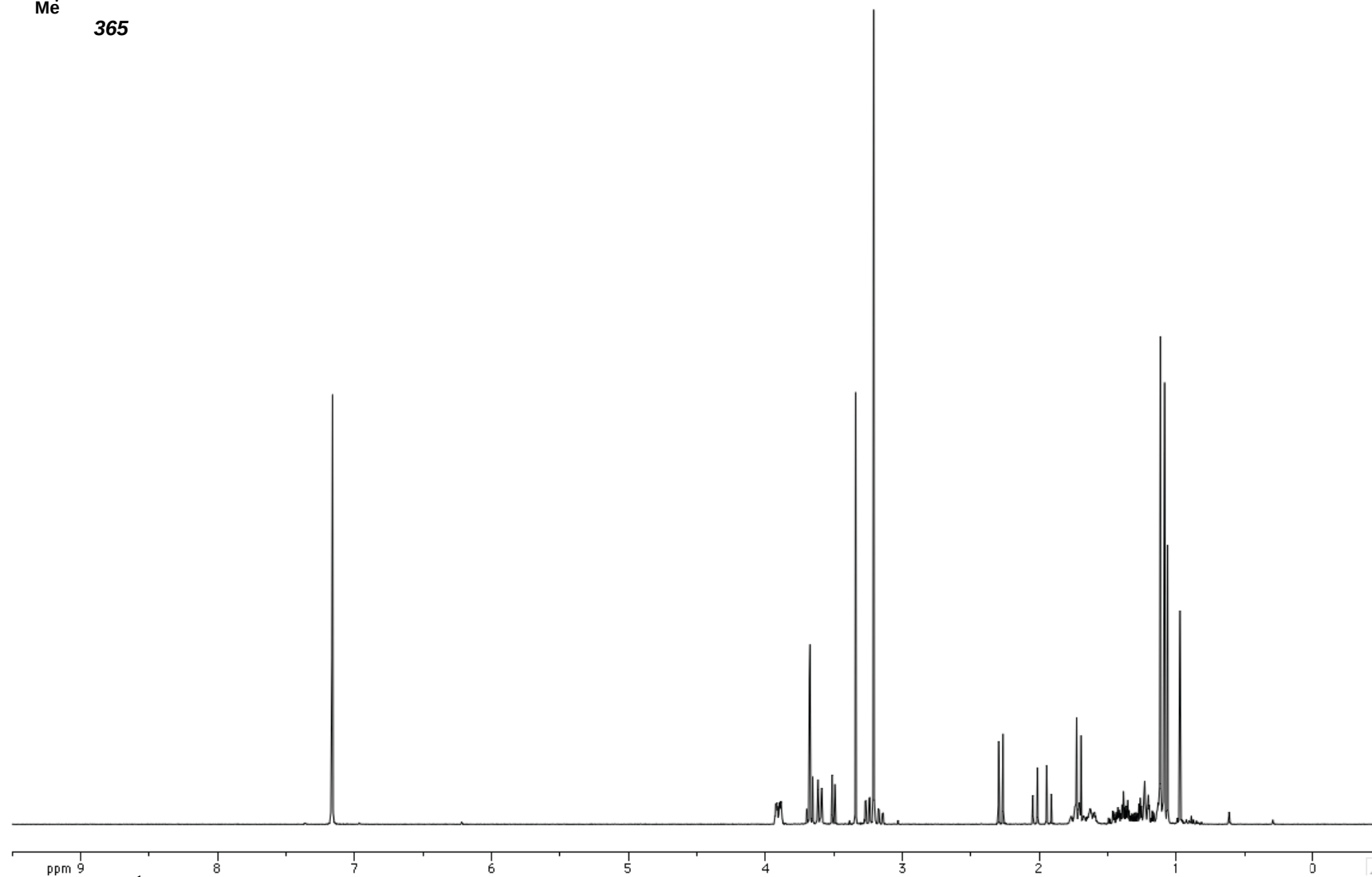
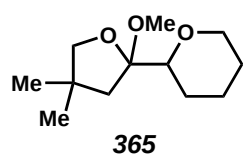


Figure A4.7 ^1H NMR (400 MHz, C_6D_6) of compound **365**

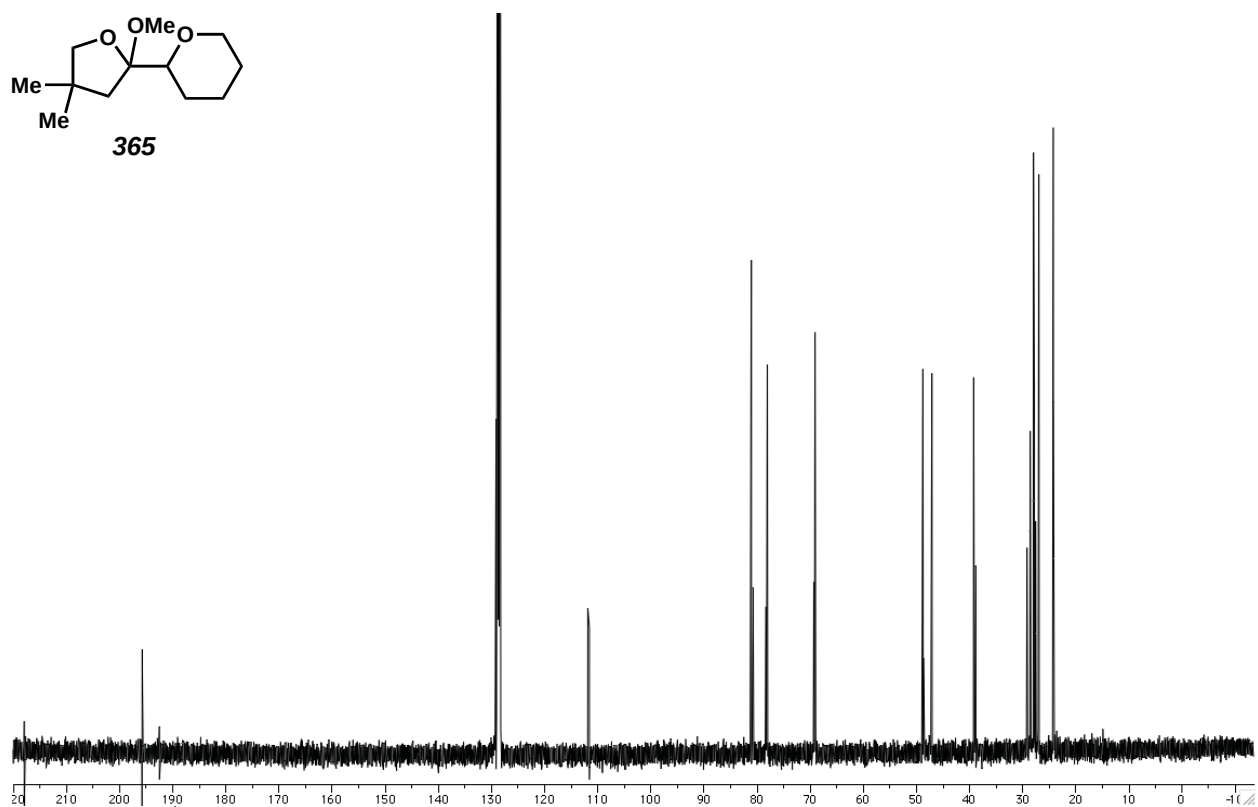
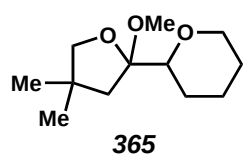


Figure A4.8 ^1H NMR (100 MHz, C_6D_6) of compound **365**

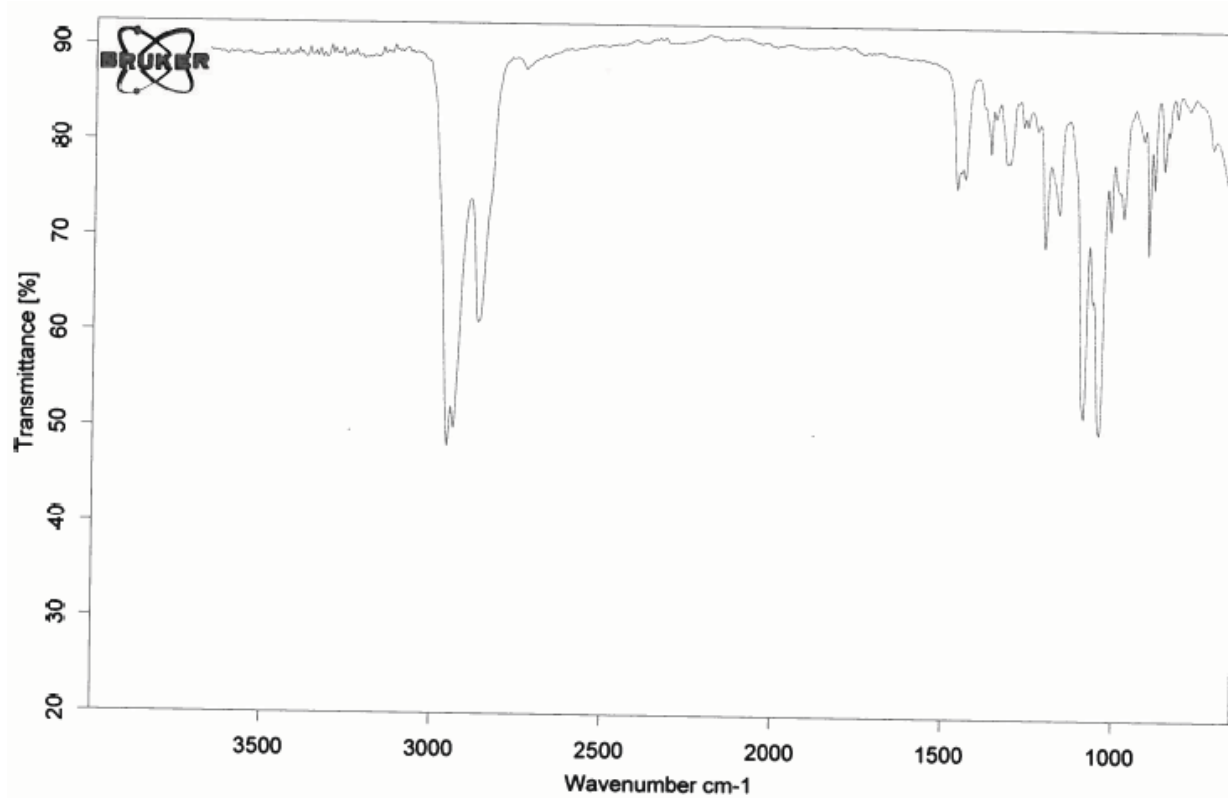


Figure A4.9 Infrared spectrum (thin film) of compound **365**

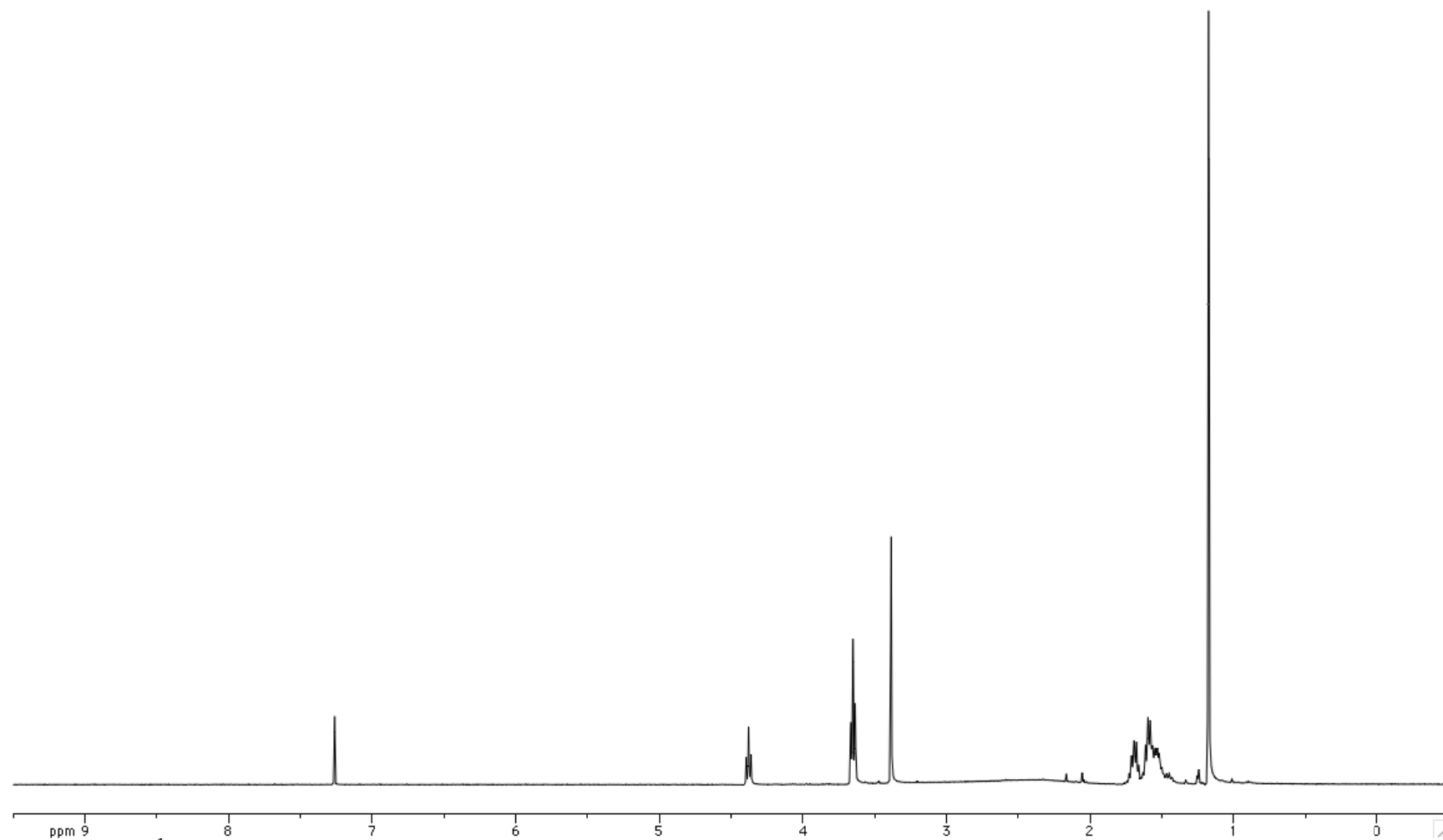
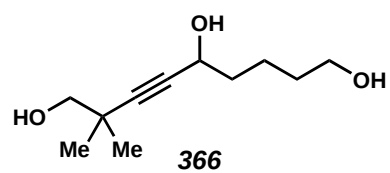
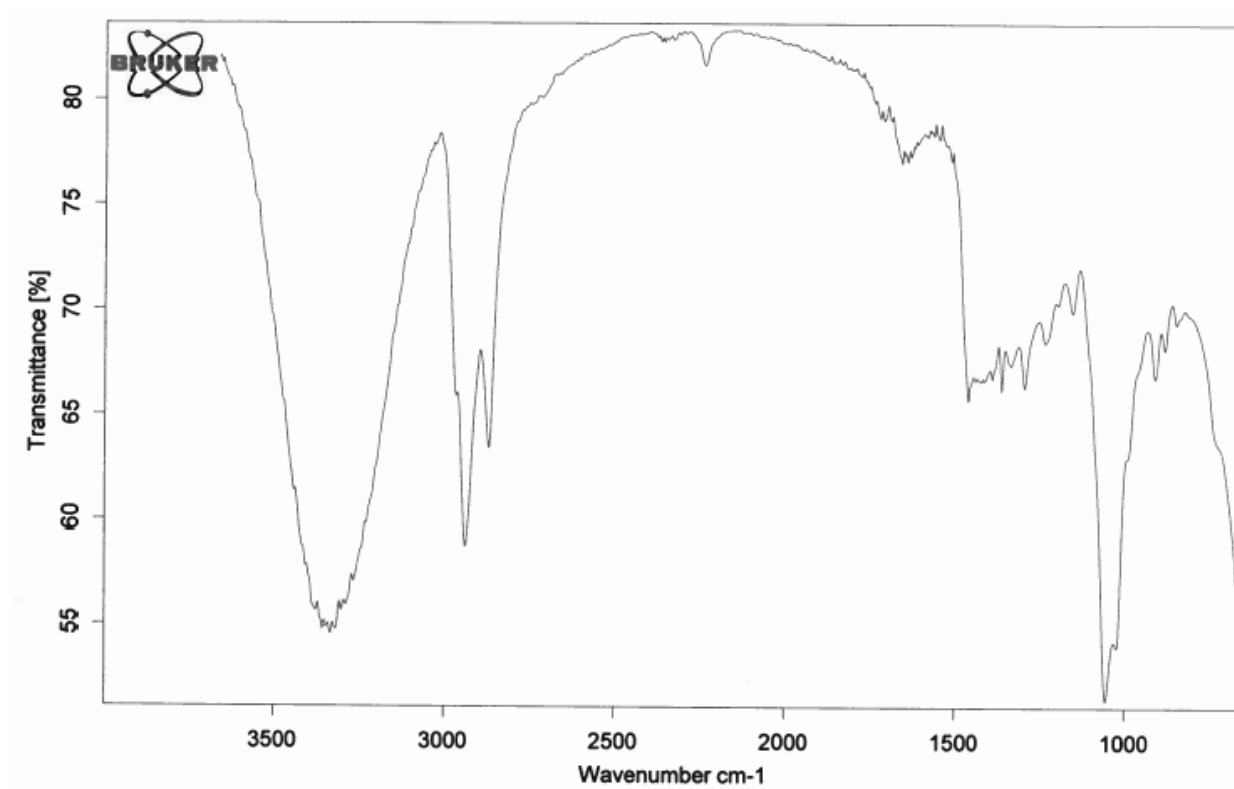
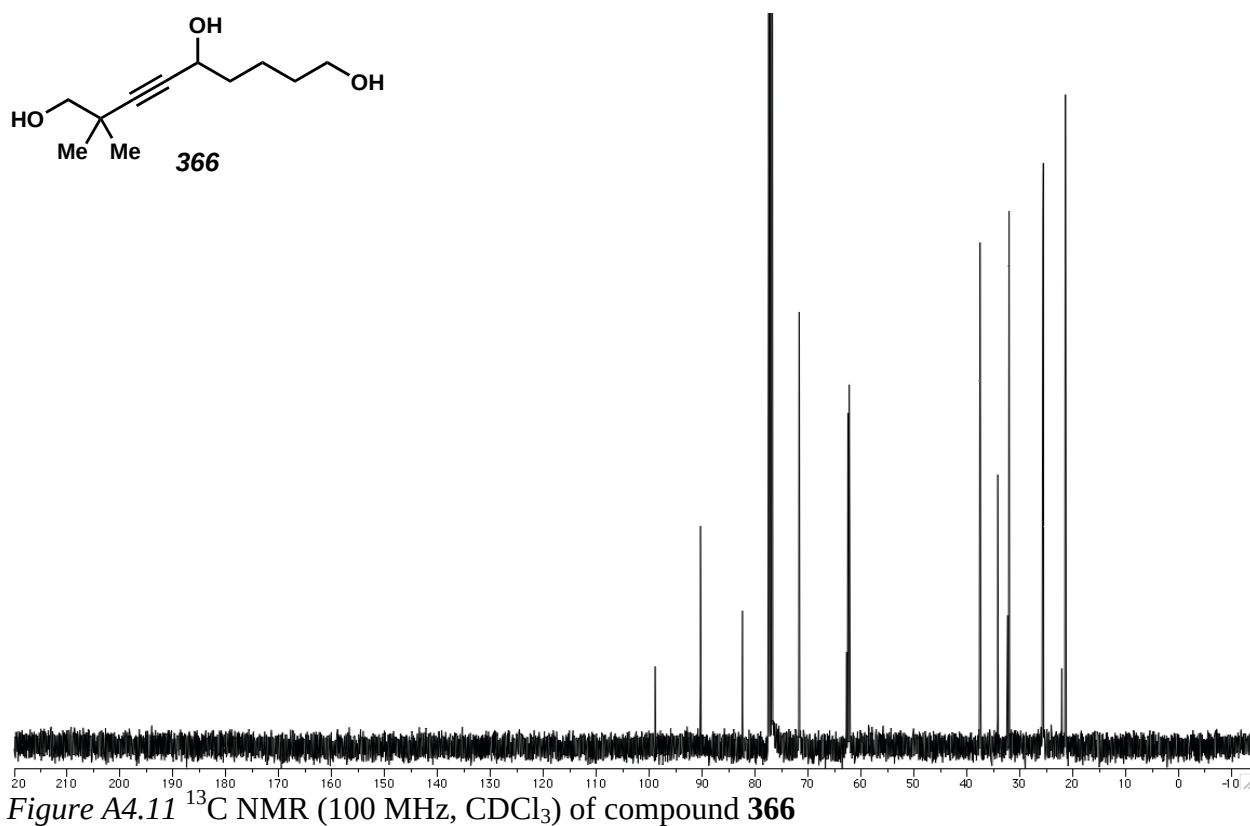


Figure A4.10 ¹H NMR (400 MHz, CDCl₃) of compound **366**



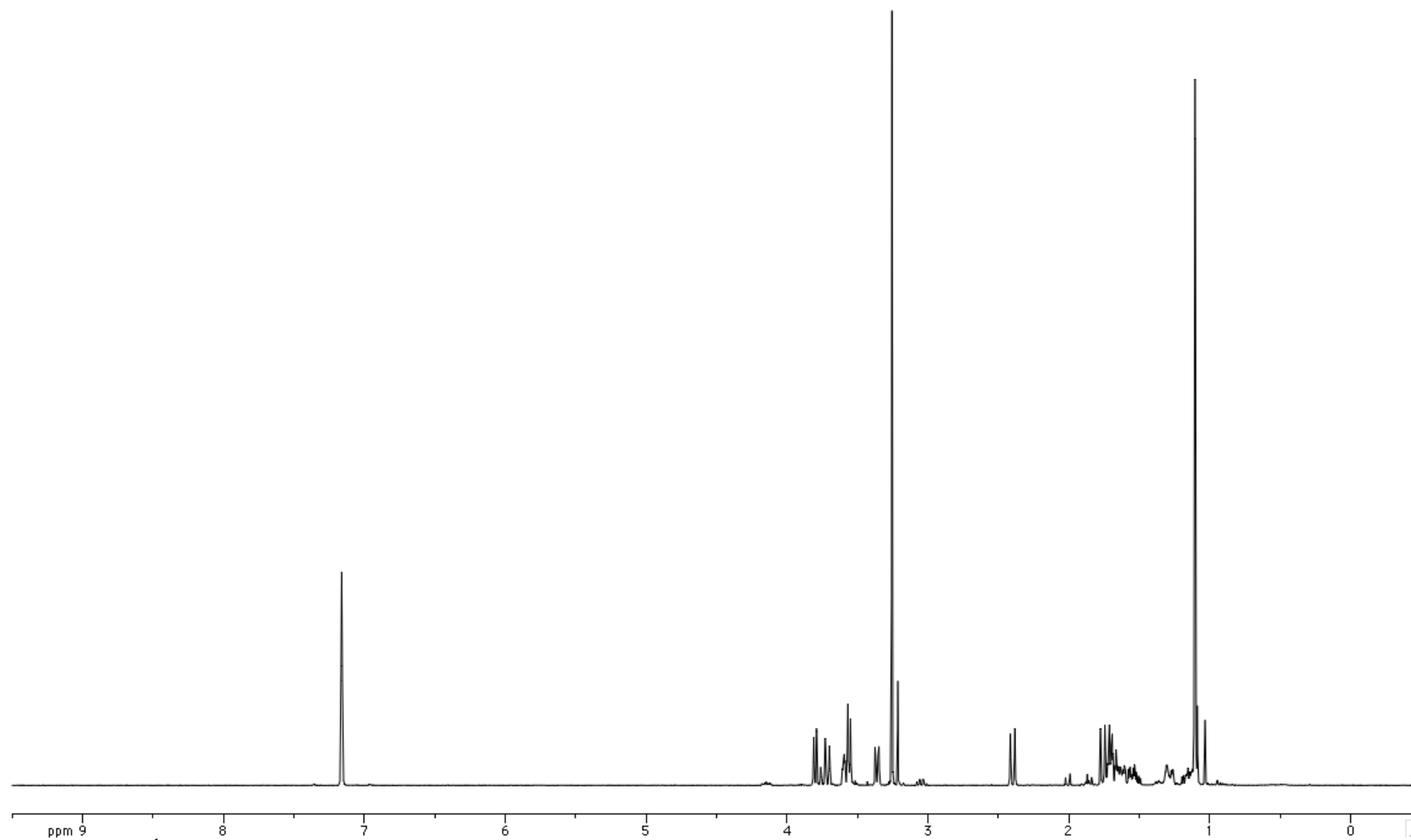
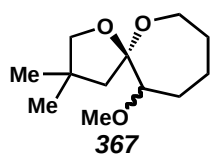


Figure A4.13 ^1H NMR (400 MHz, CDCl_3) of compound **367**

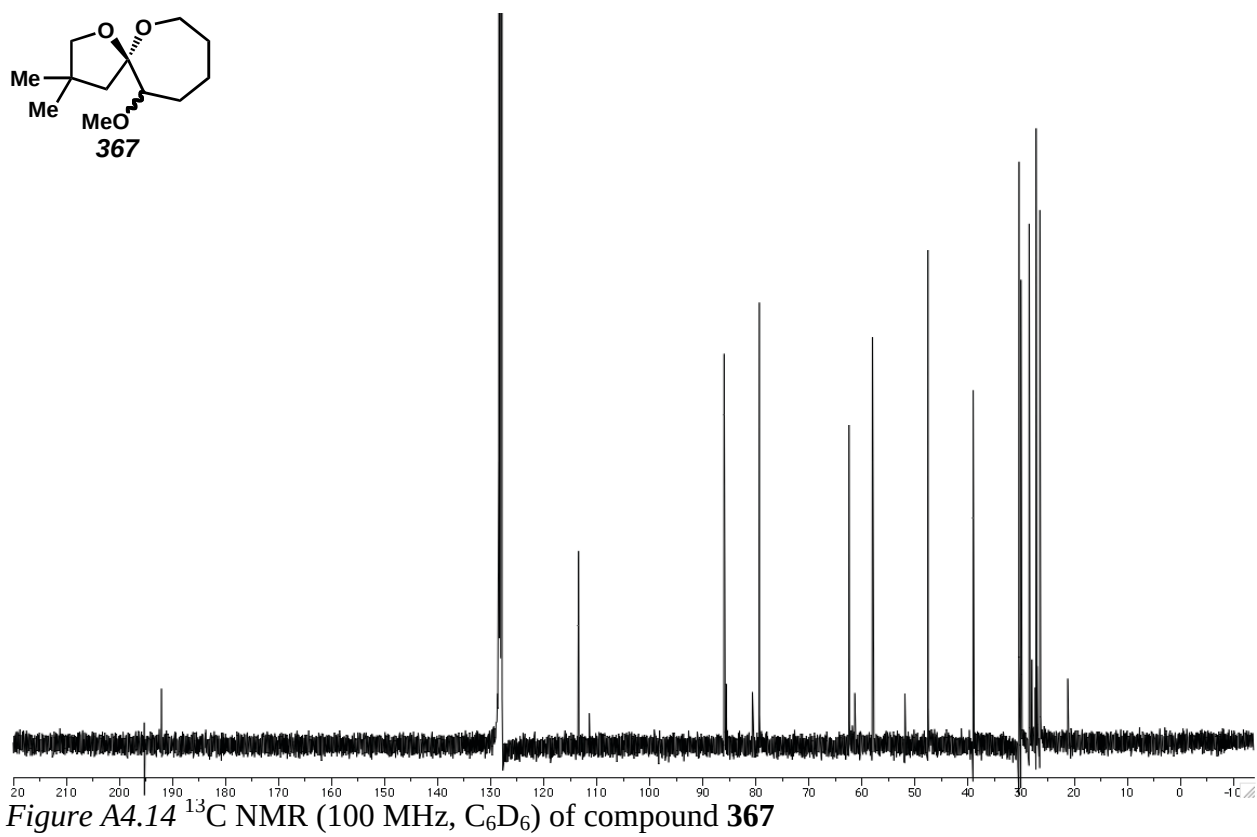
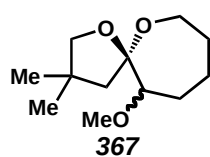


Figure A4.14 ^{13}C NMR (100 MHz, C_6D_6) of compound 367

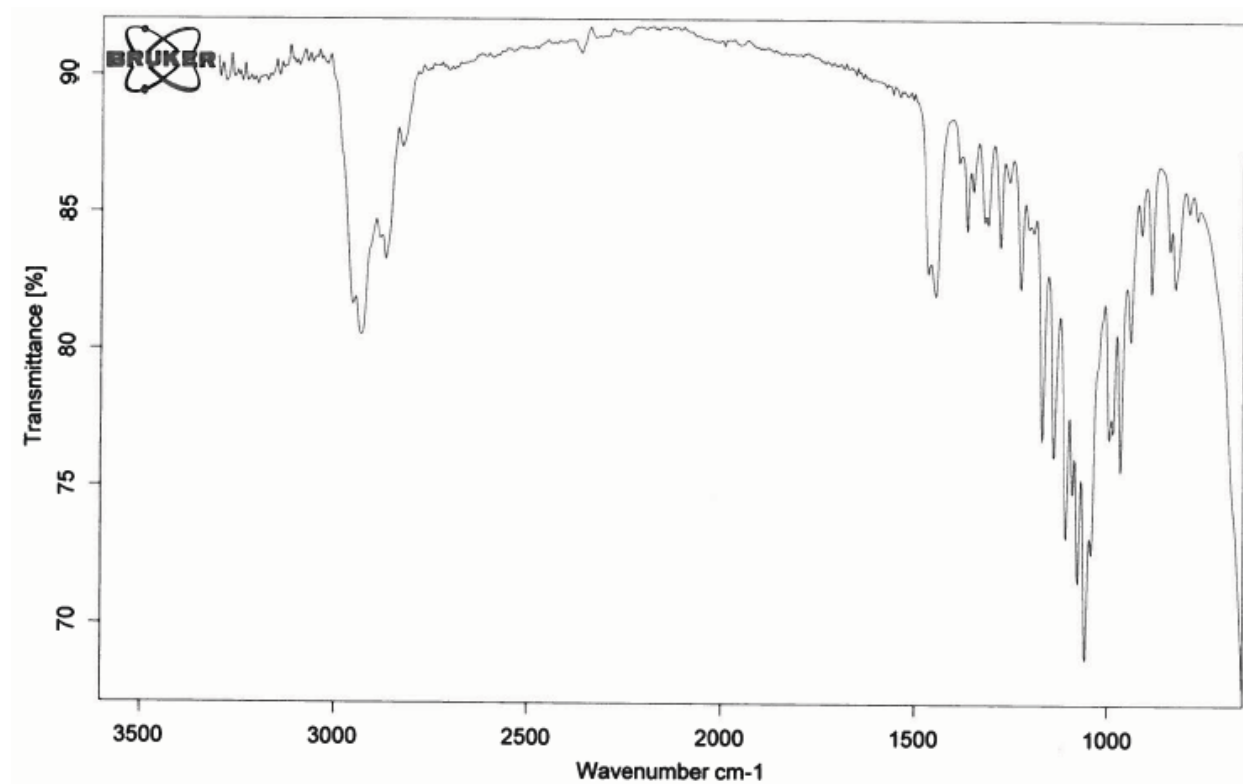
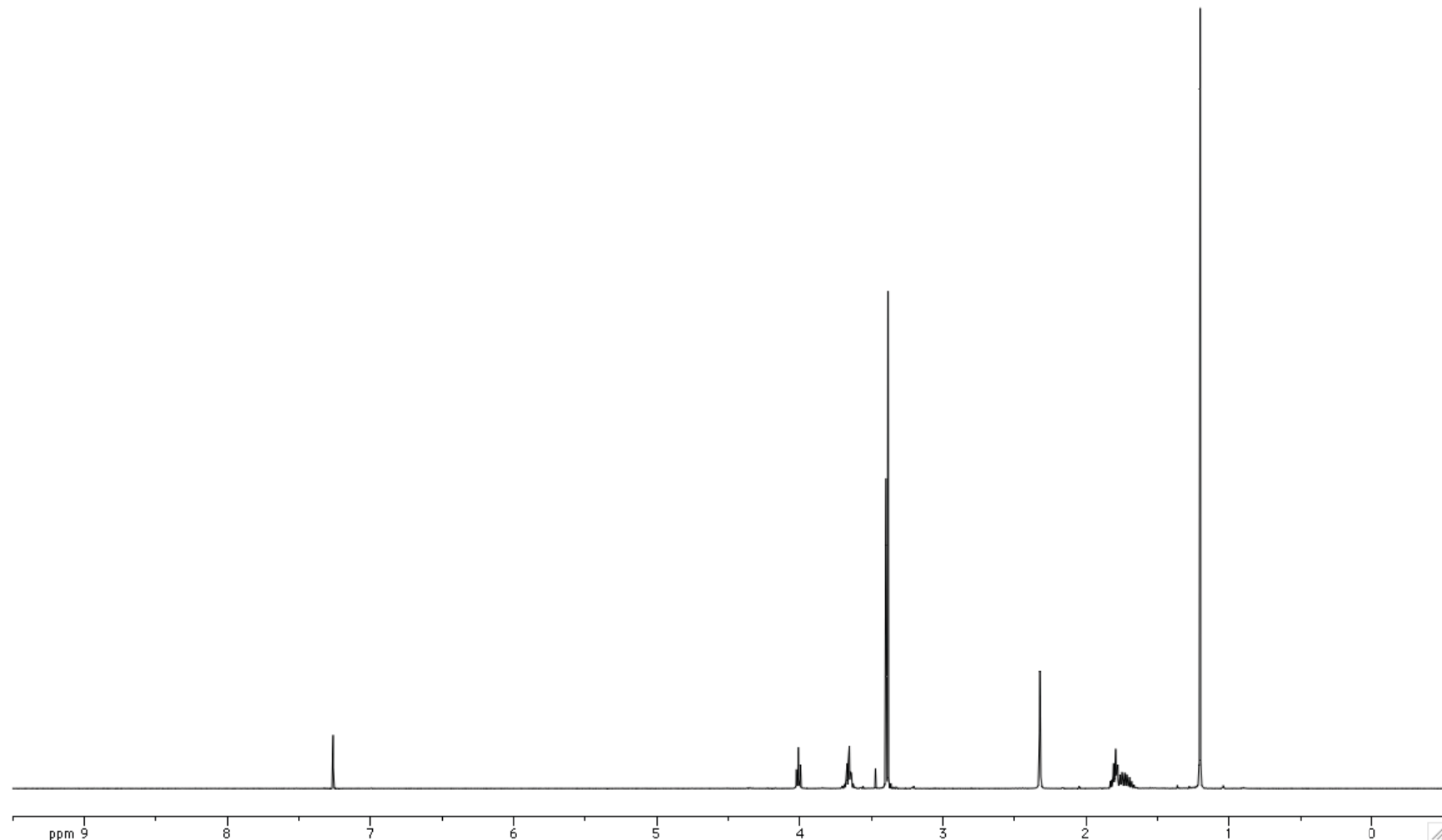
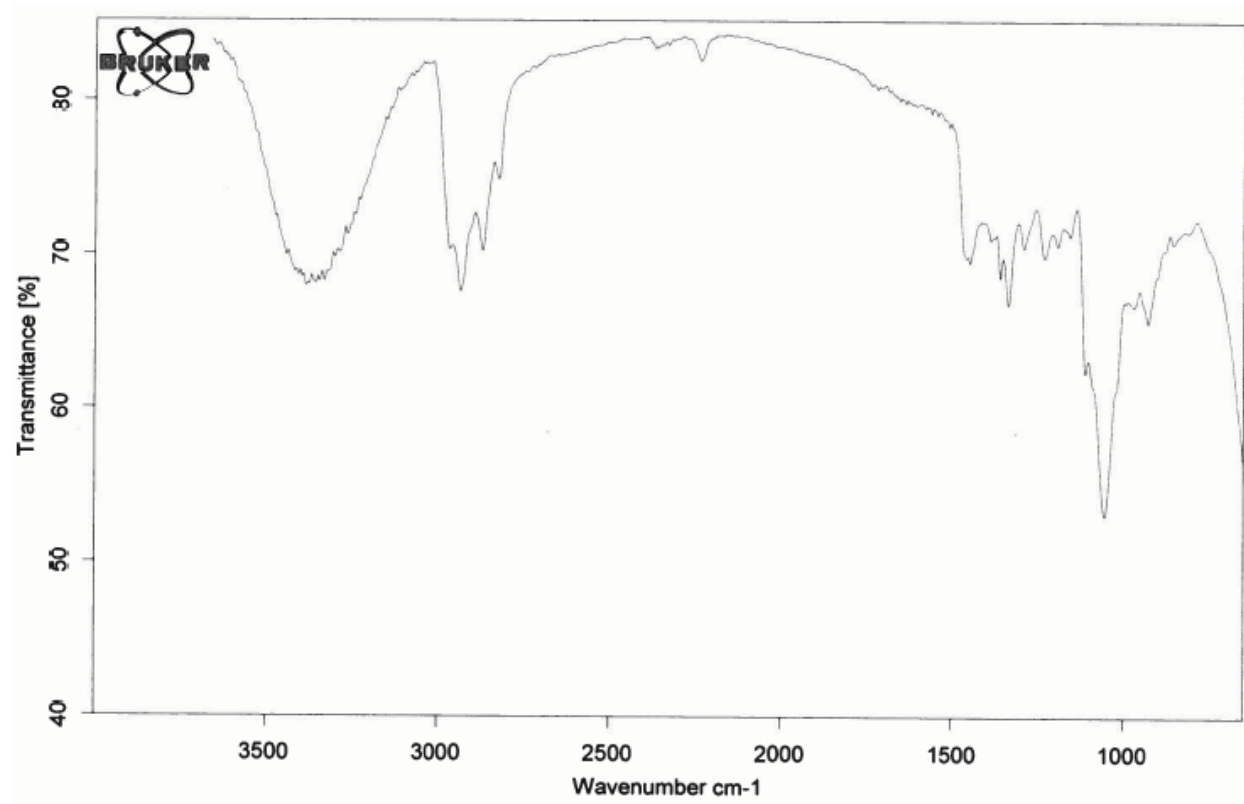
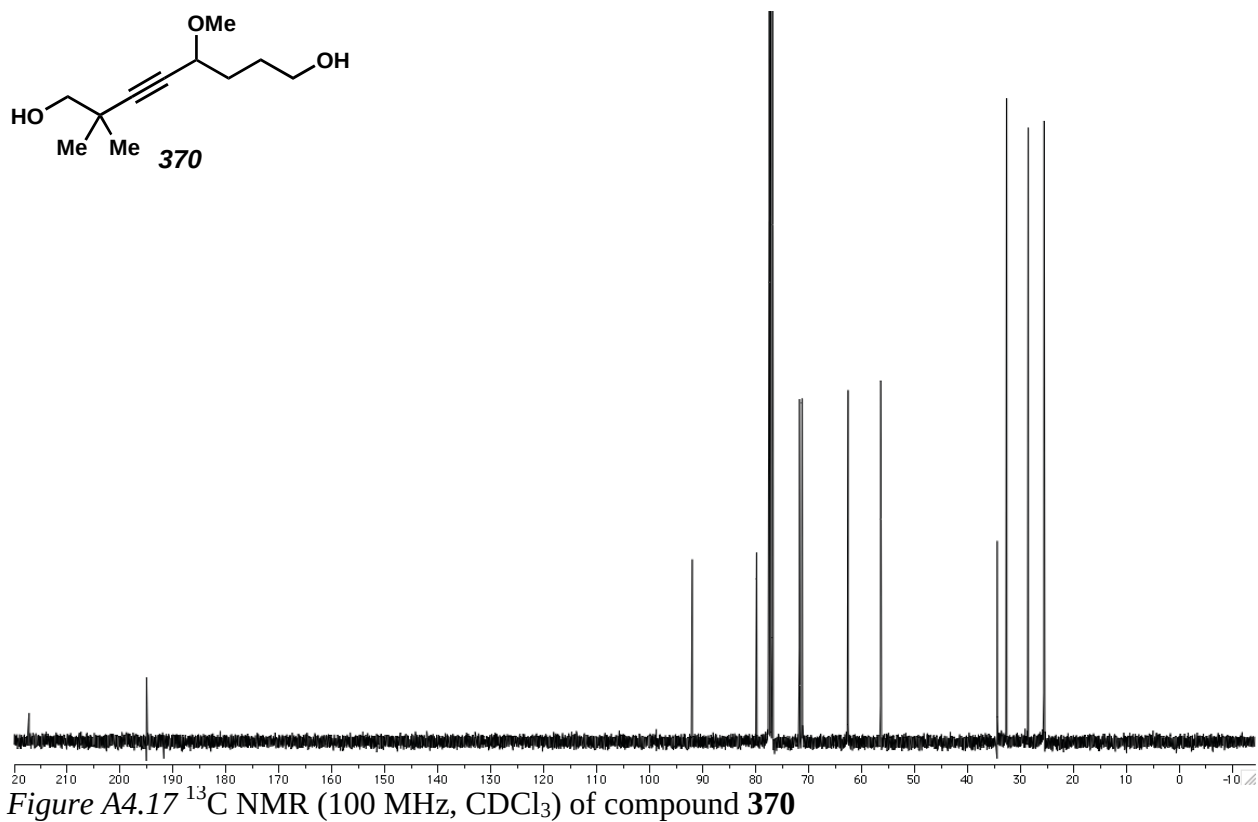


Figure A4.15 Infrared spectrum (thin film) of compound 367



605



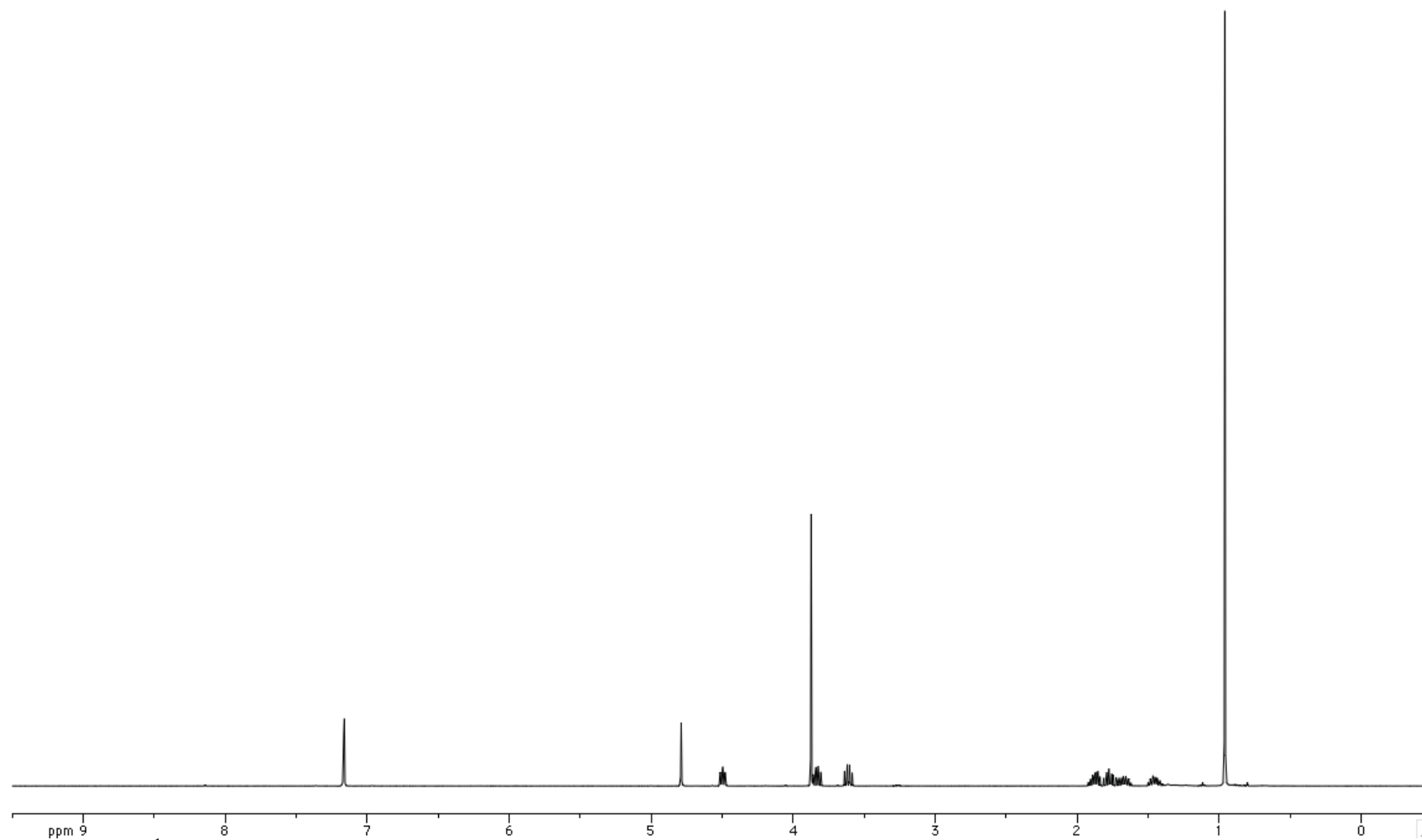
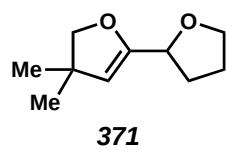


Figure A4.19 ^1H NMR (400 MHz, C_6D_6) of compound **371**

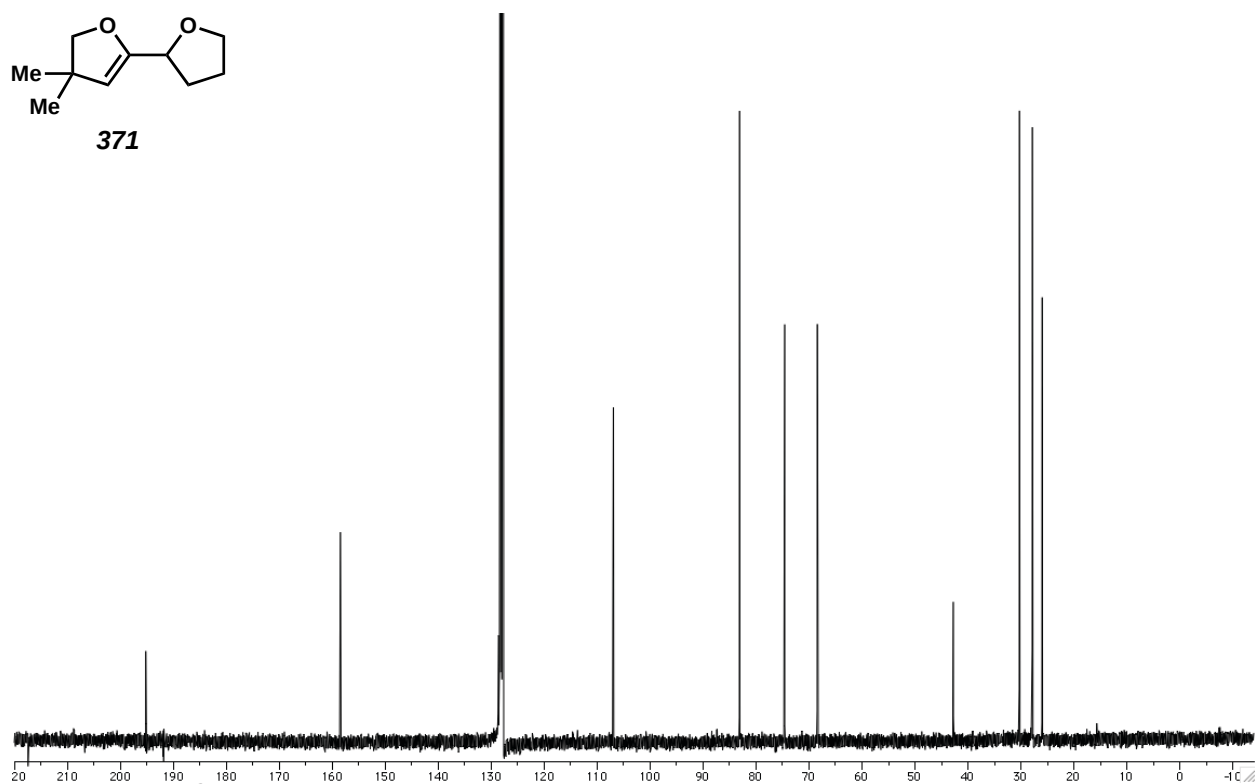
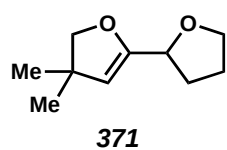


Figure A4.20 ^{13}C NMR (100 MHz, C_6D_6) of compound **371**

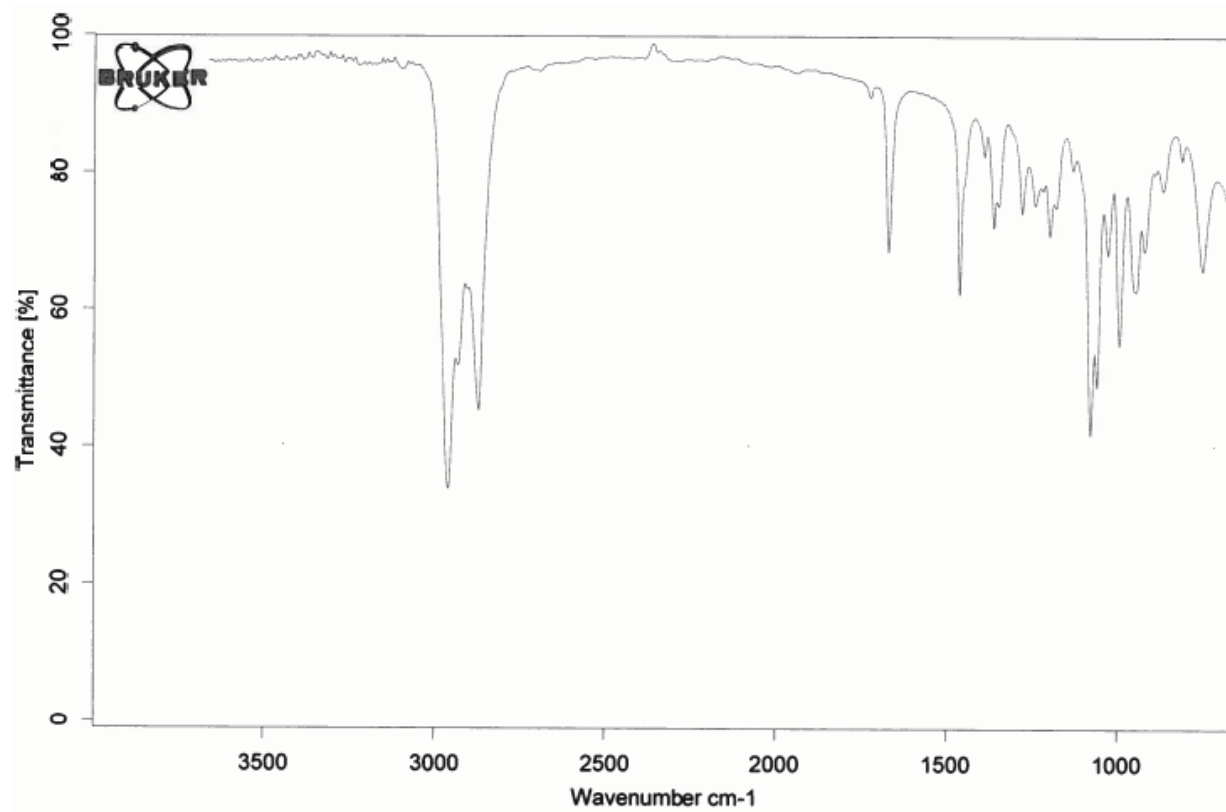


Figure A4.21 Infrared spectrum (thin film) of compound **371**

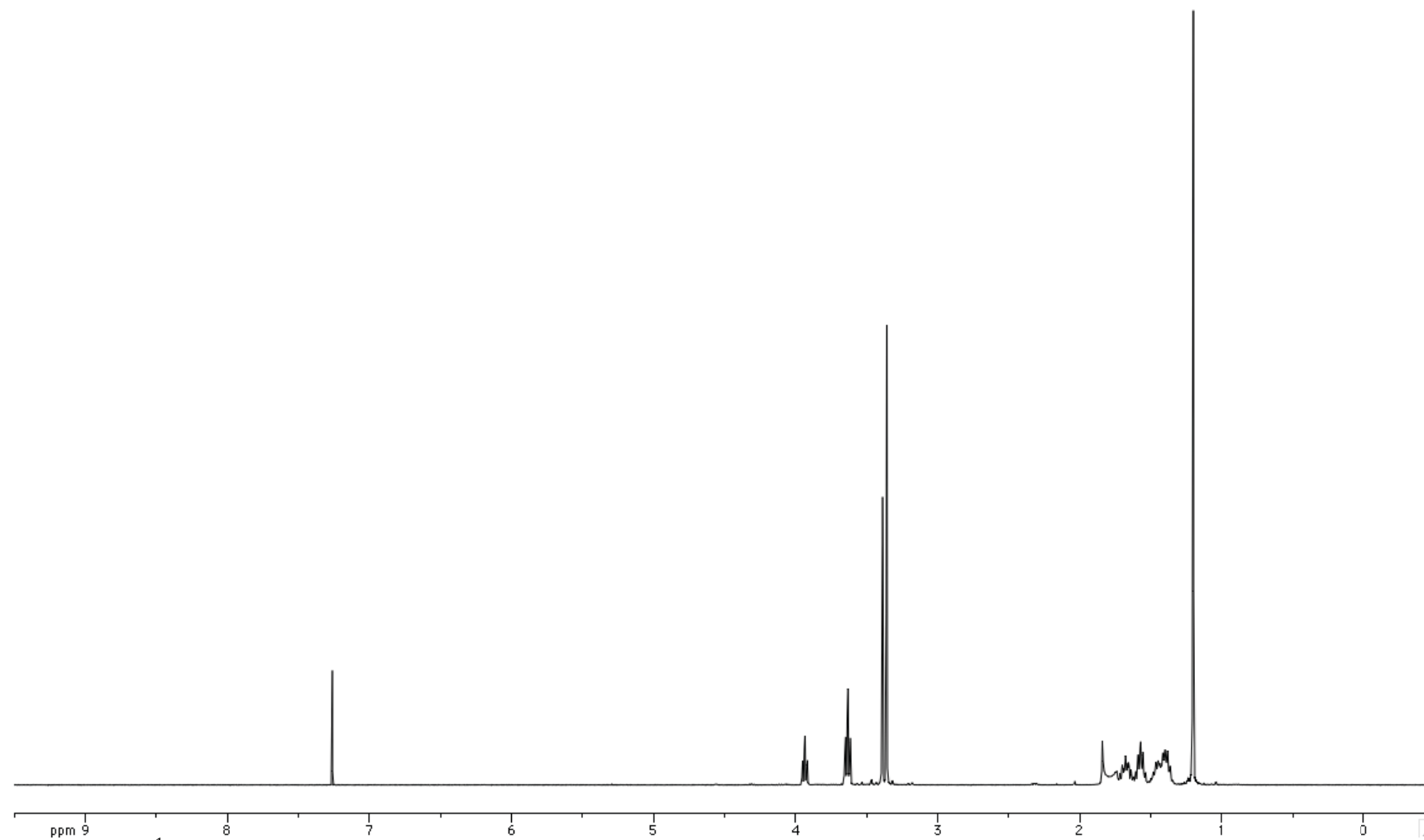
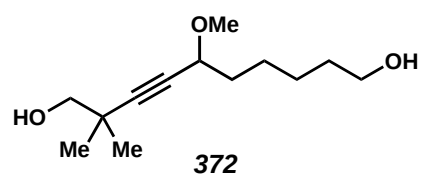
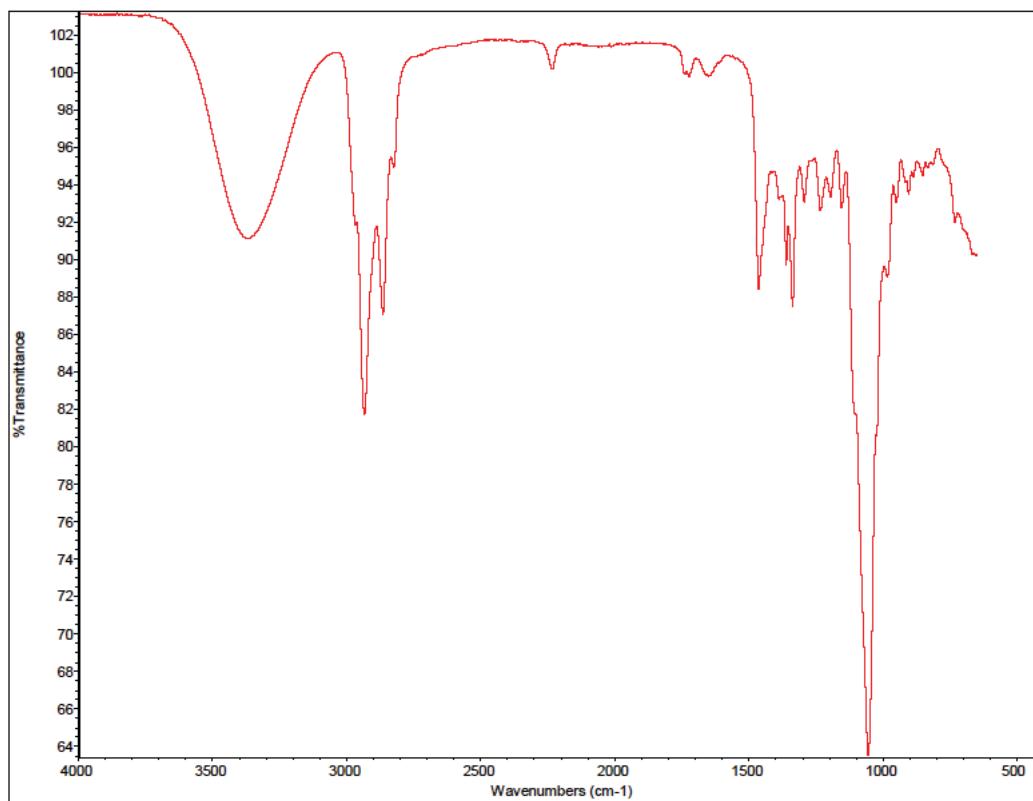
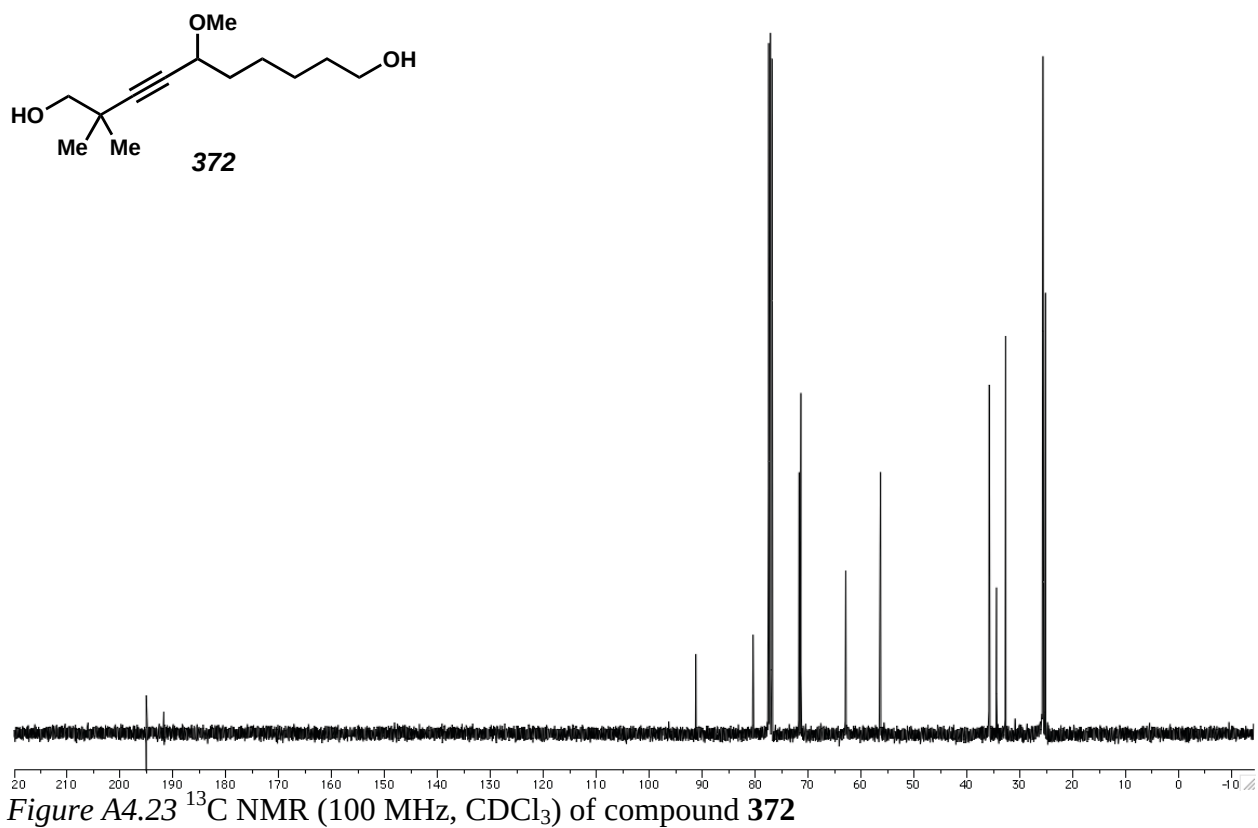


Figure A4.22 ^1H NMR (400 MHz, CDCl_3) of compound **372**



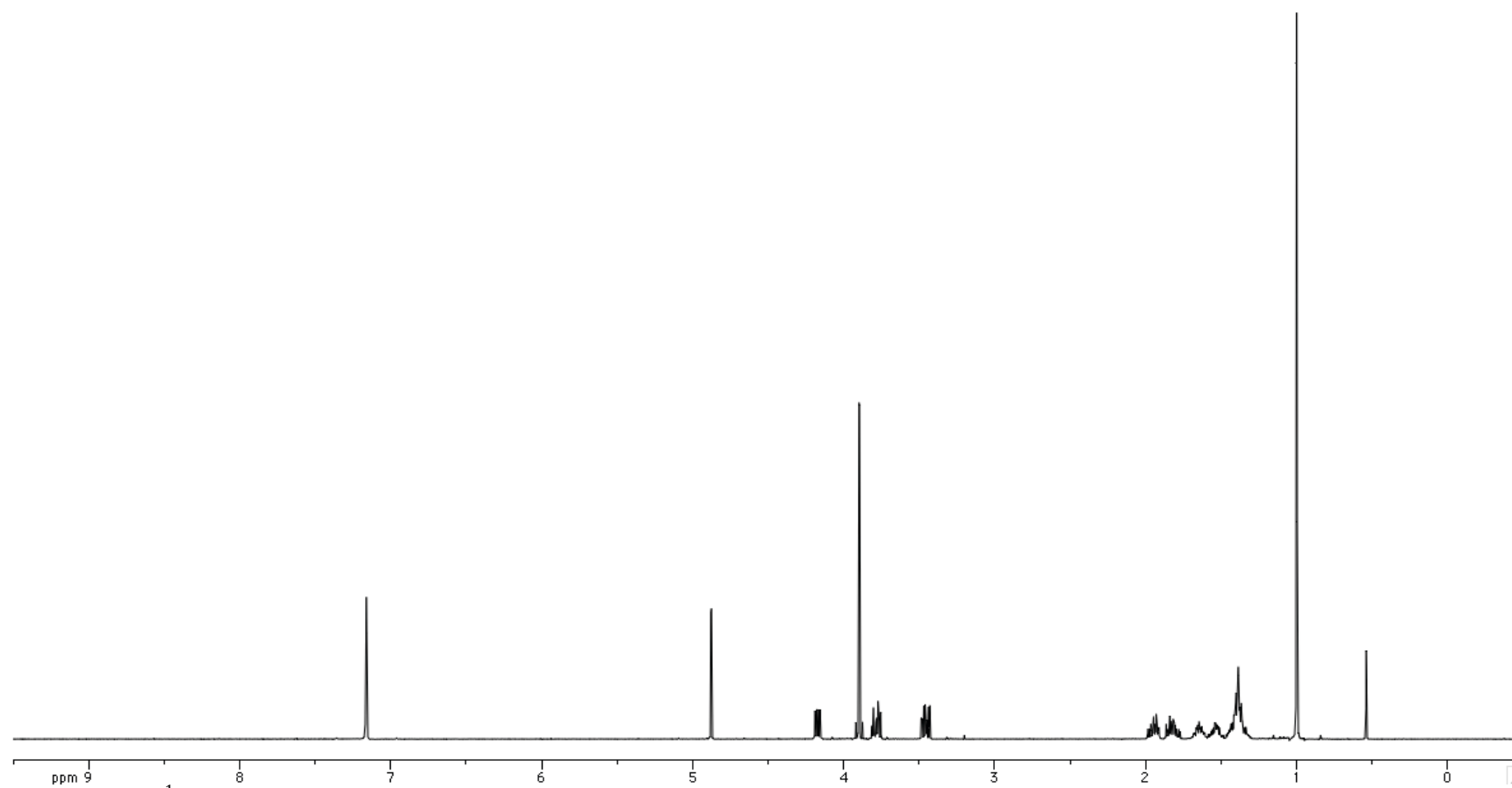
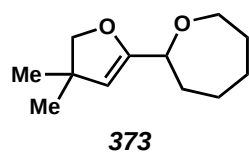
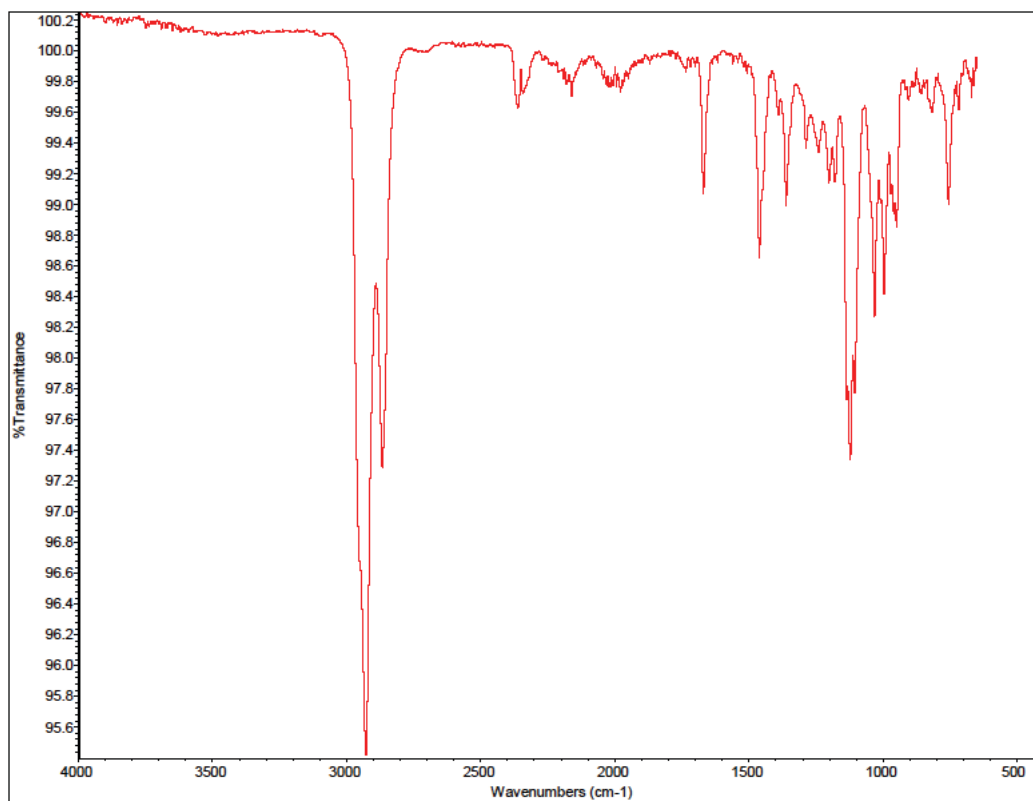
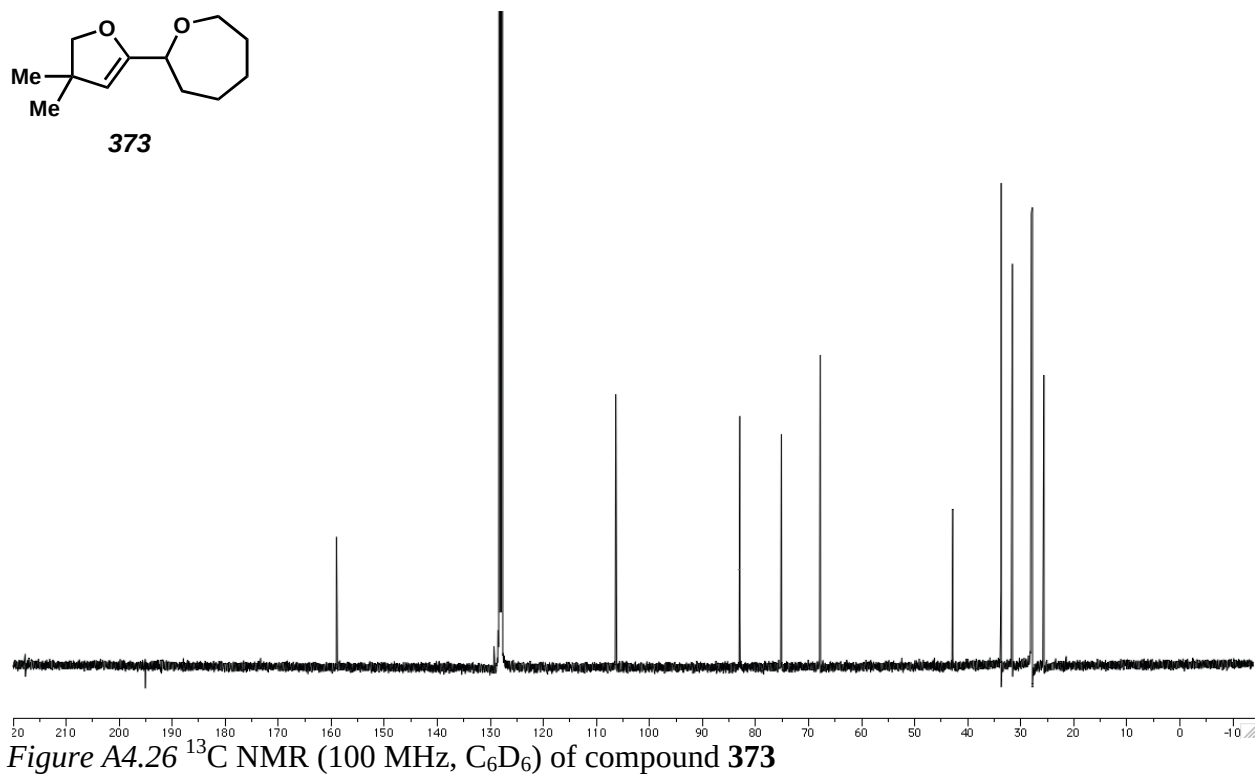


Figure A4.25 ^1H NMR (400 MHz, CDCl_3) of compound **373**



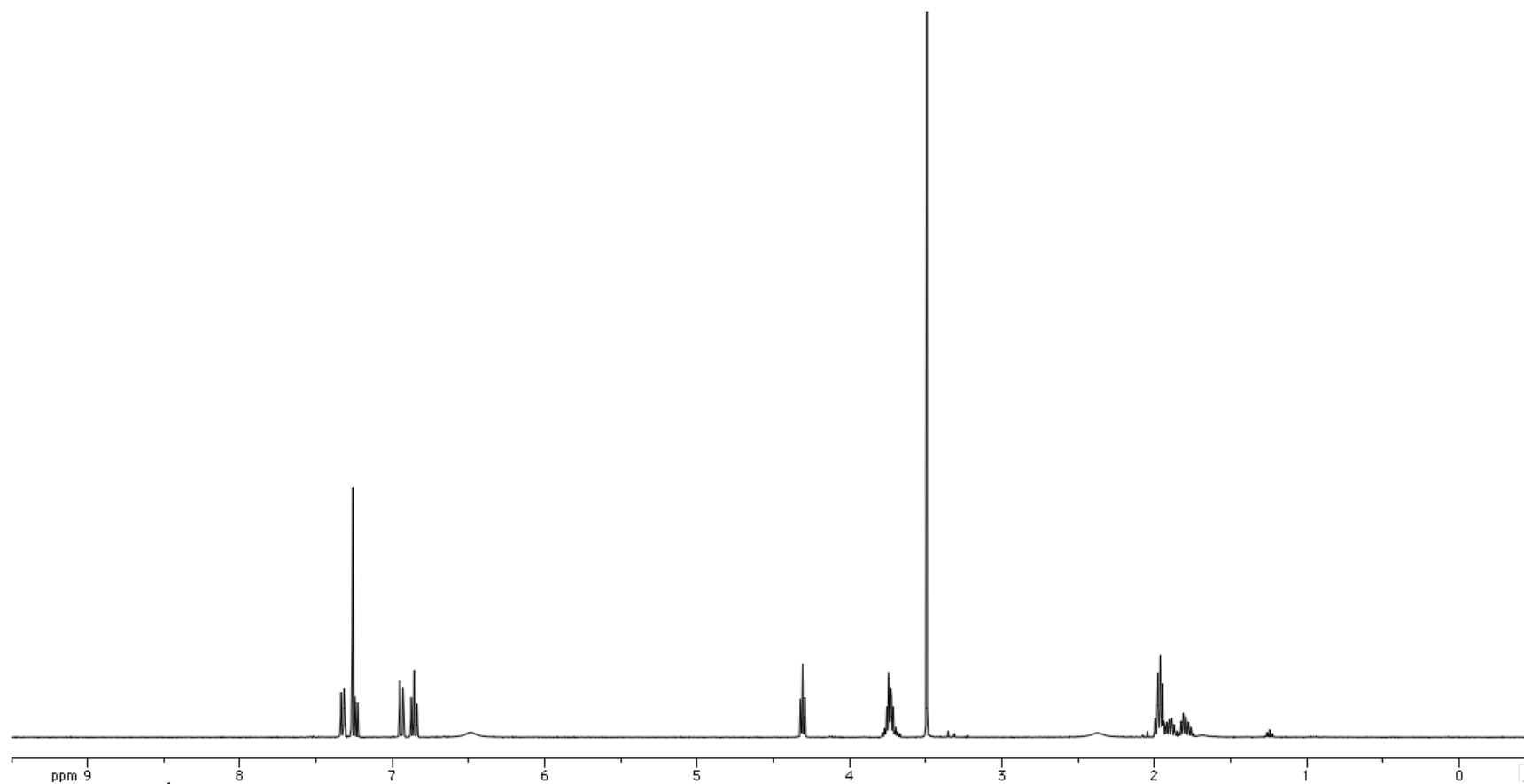
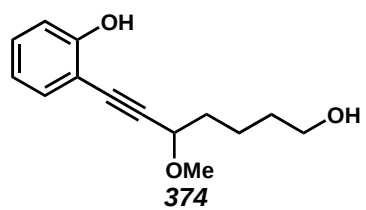
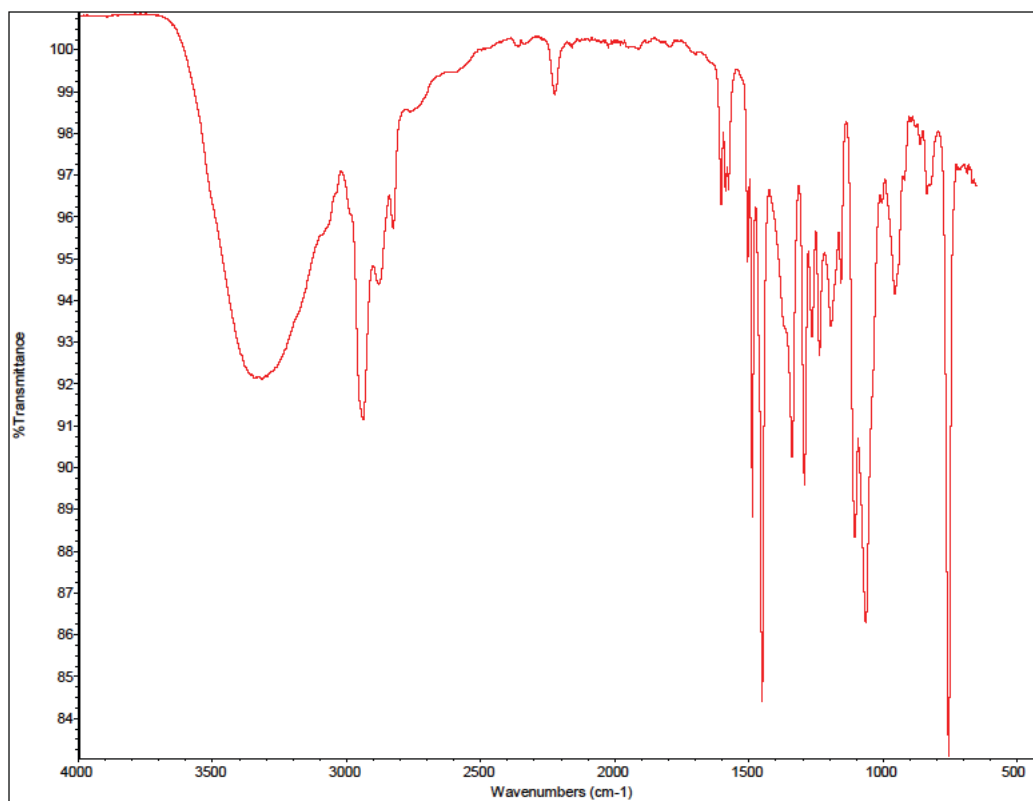
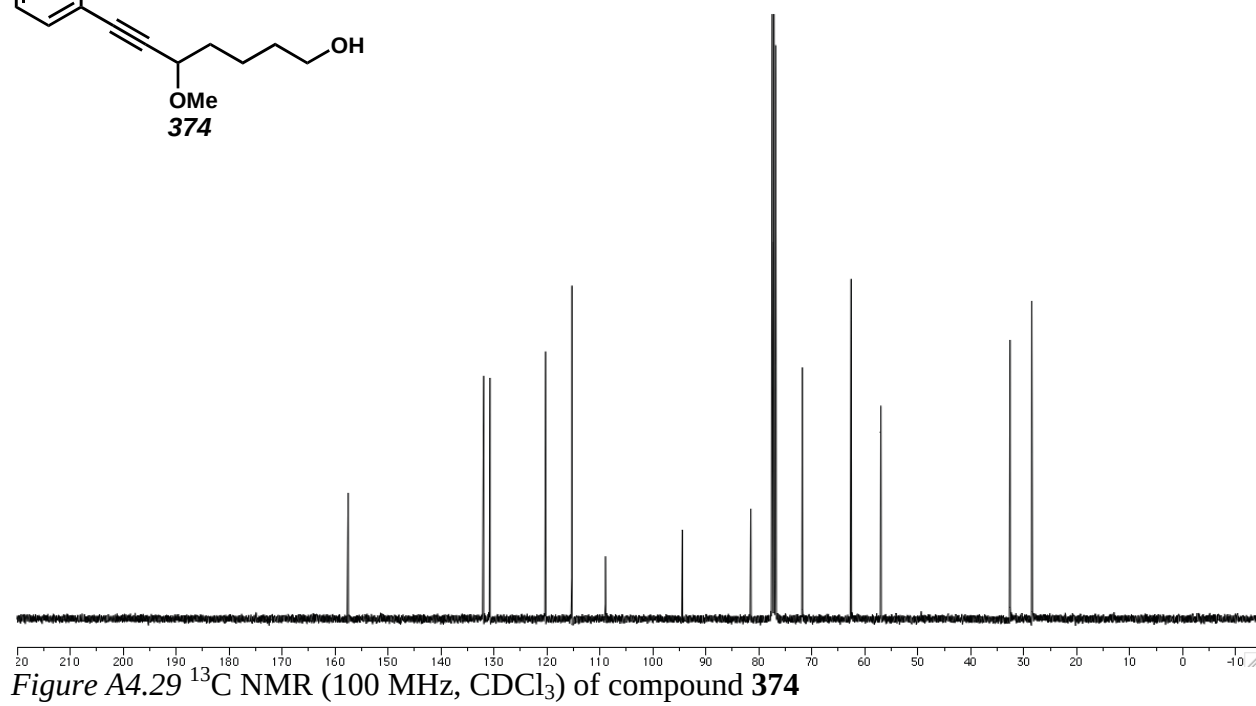
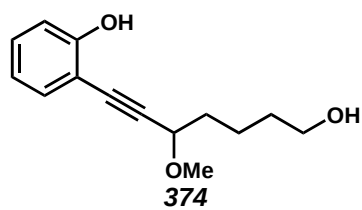
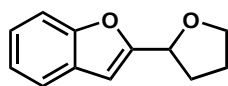


Figure A4.28 ^1H NMR (400 MHz, CDCl_3) of compound **374**





375

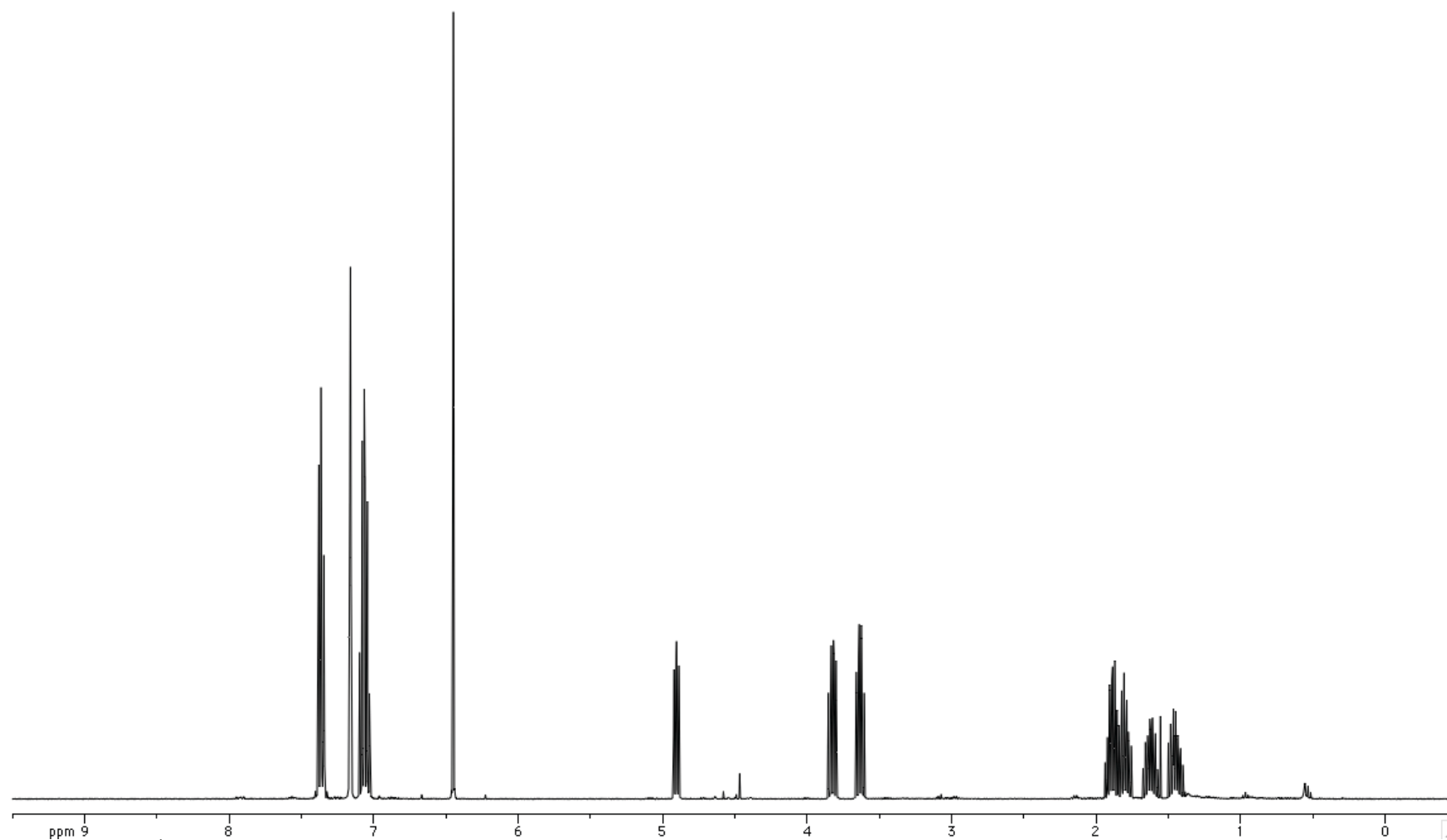
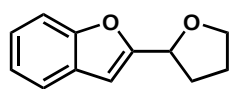
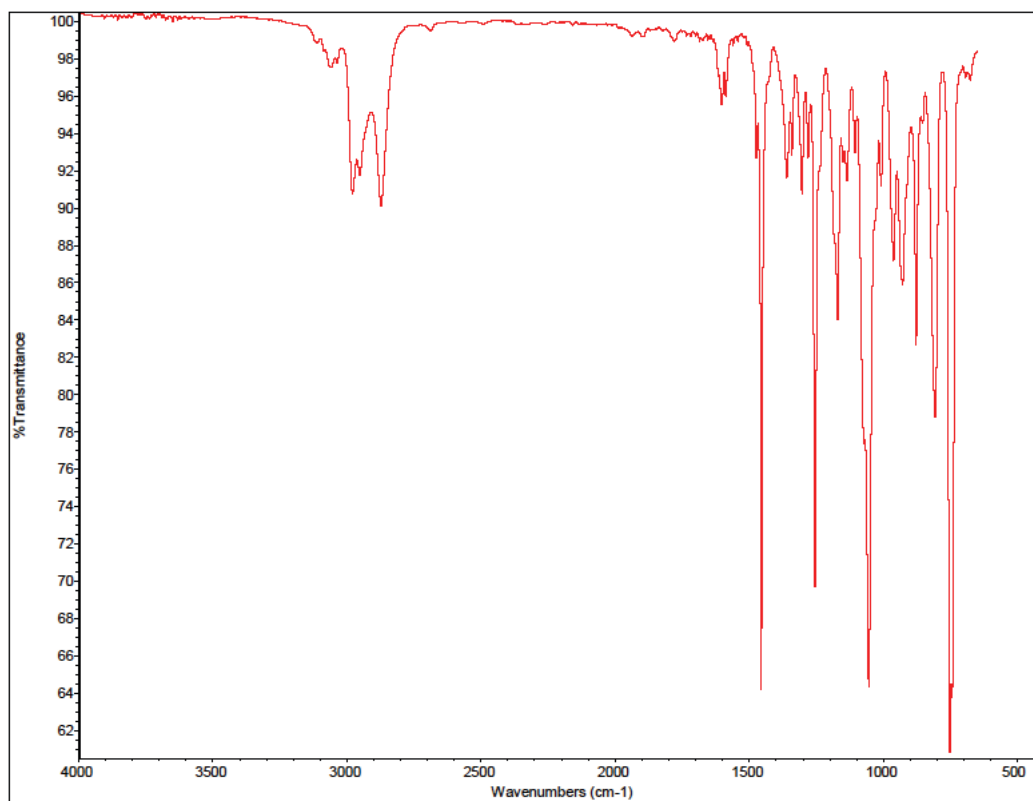
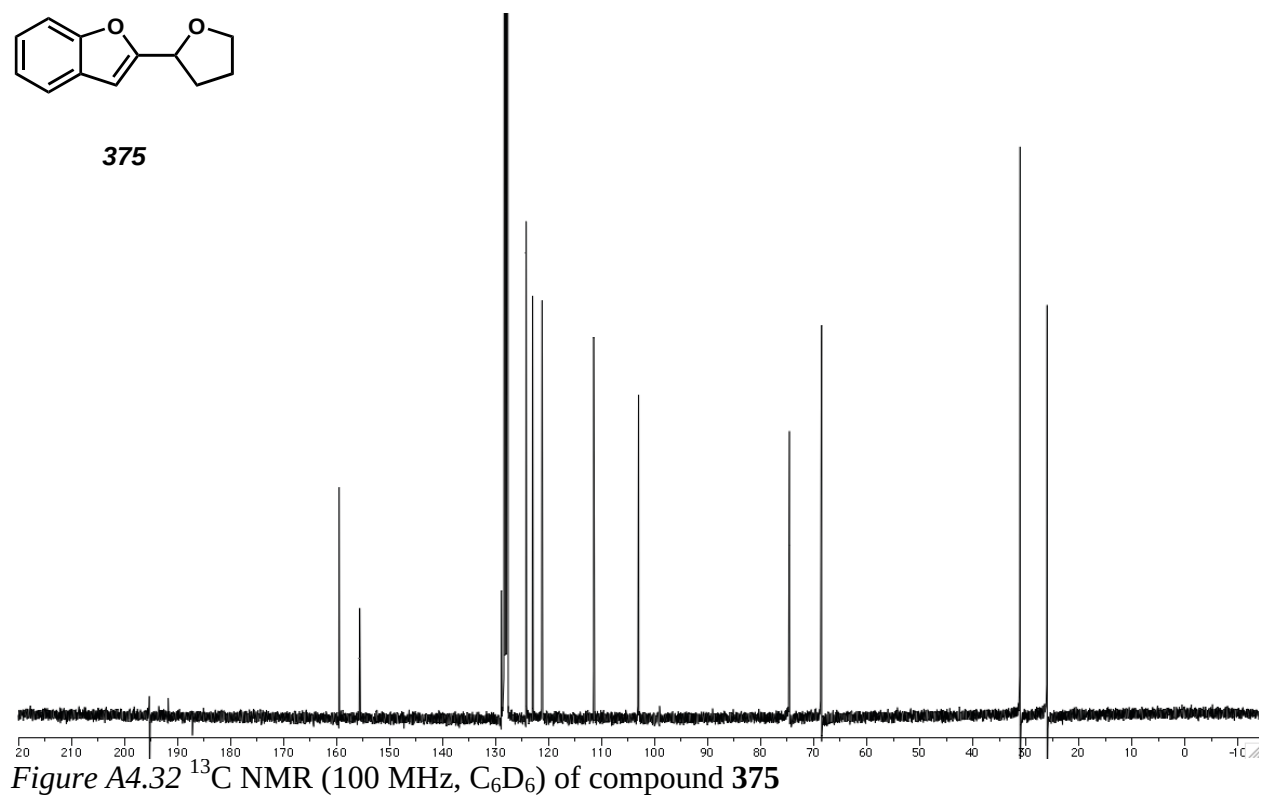


Figure A4.31 ^1H NMR (400 MHz, C_6D_6) of compound 371



375



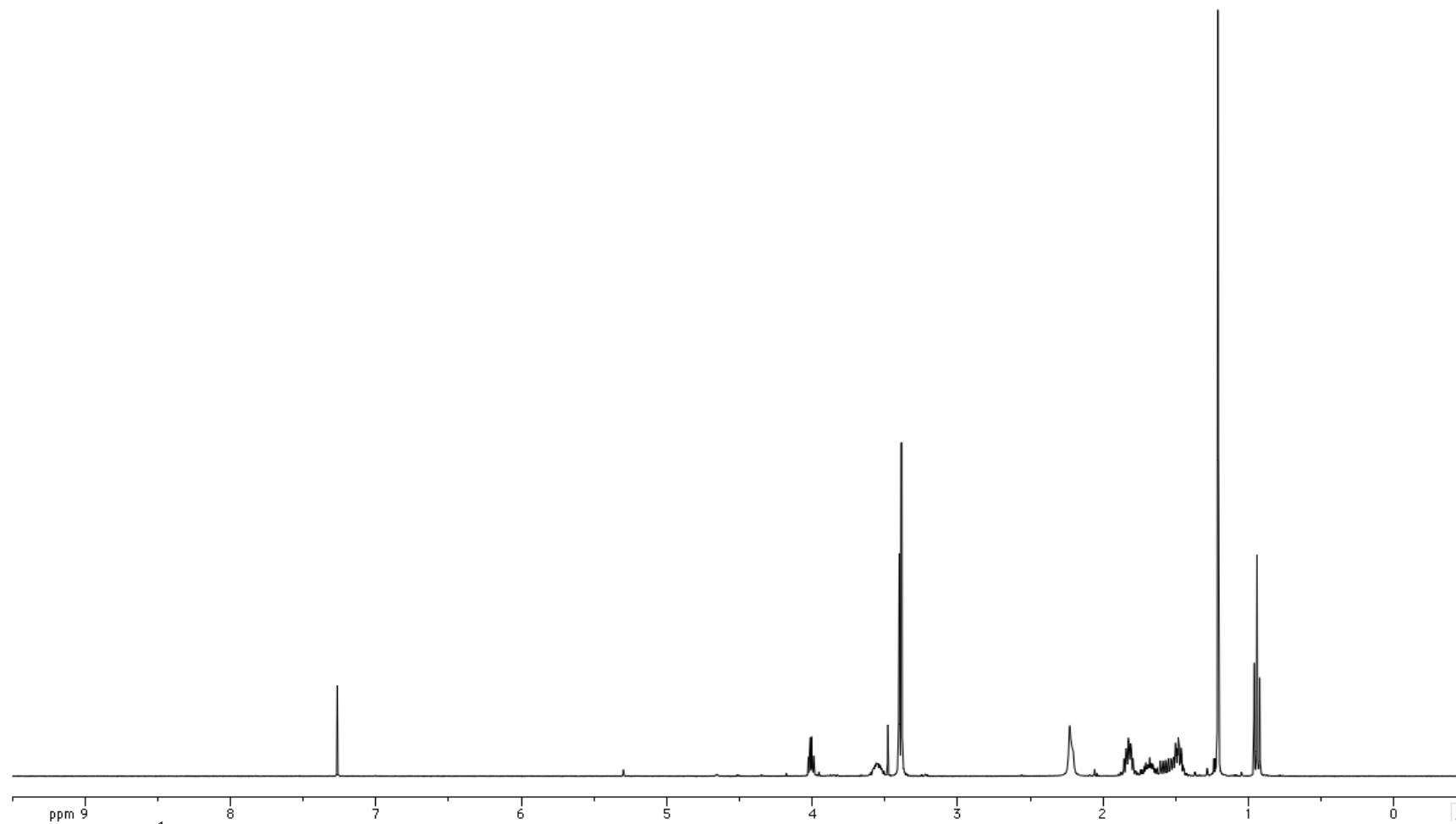
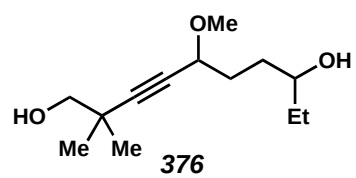
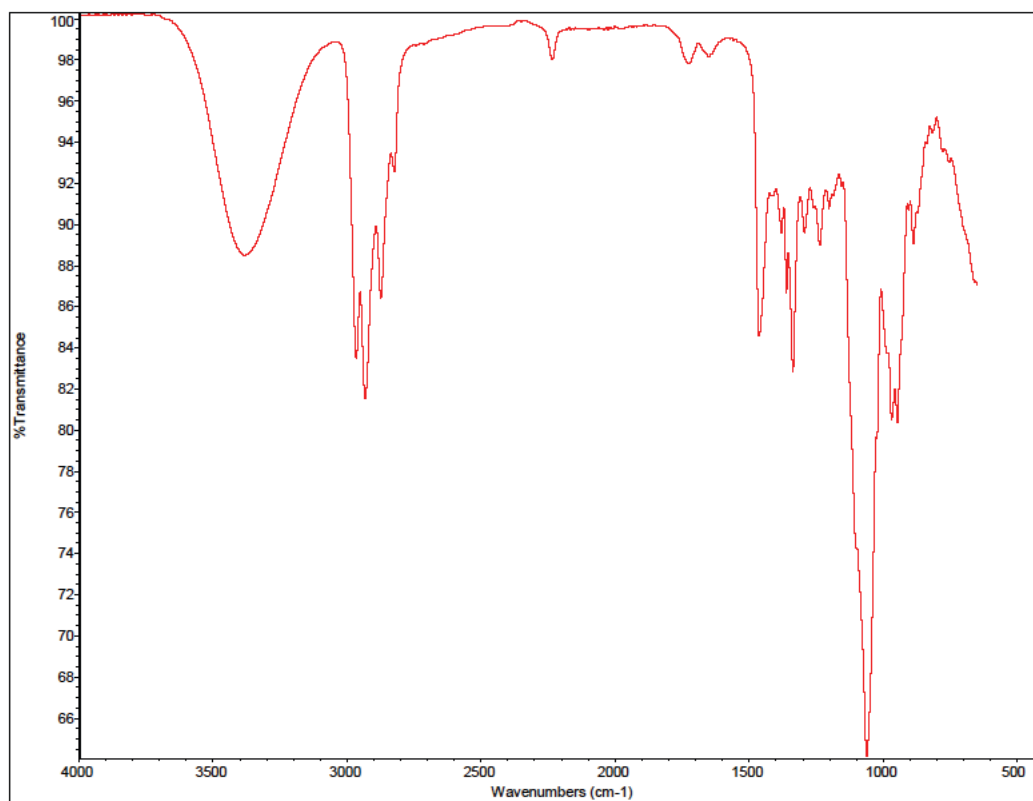
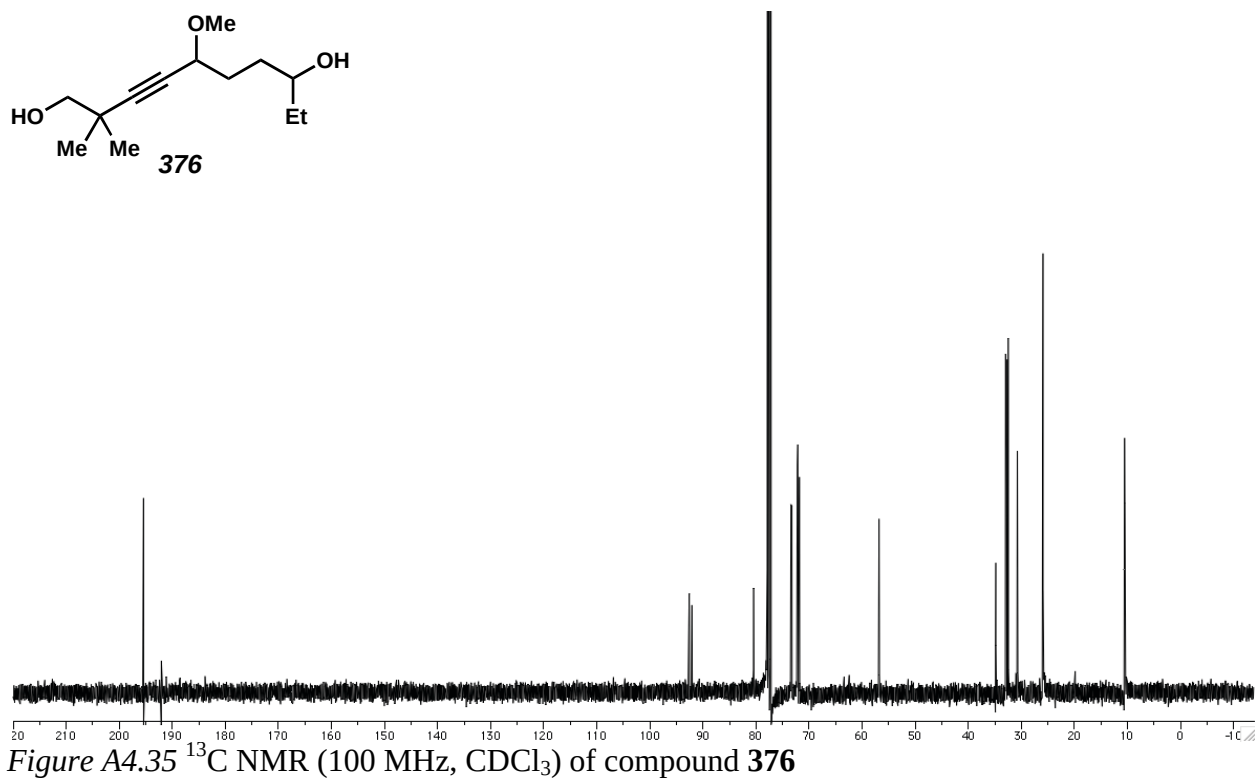


Figure A4.34 ^1H NMR (400 MHz, CDCl_3) of compound **376**



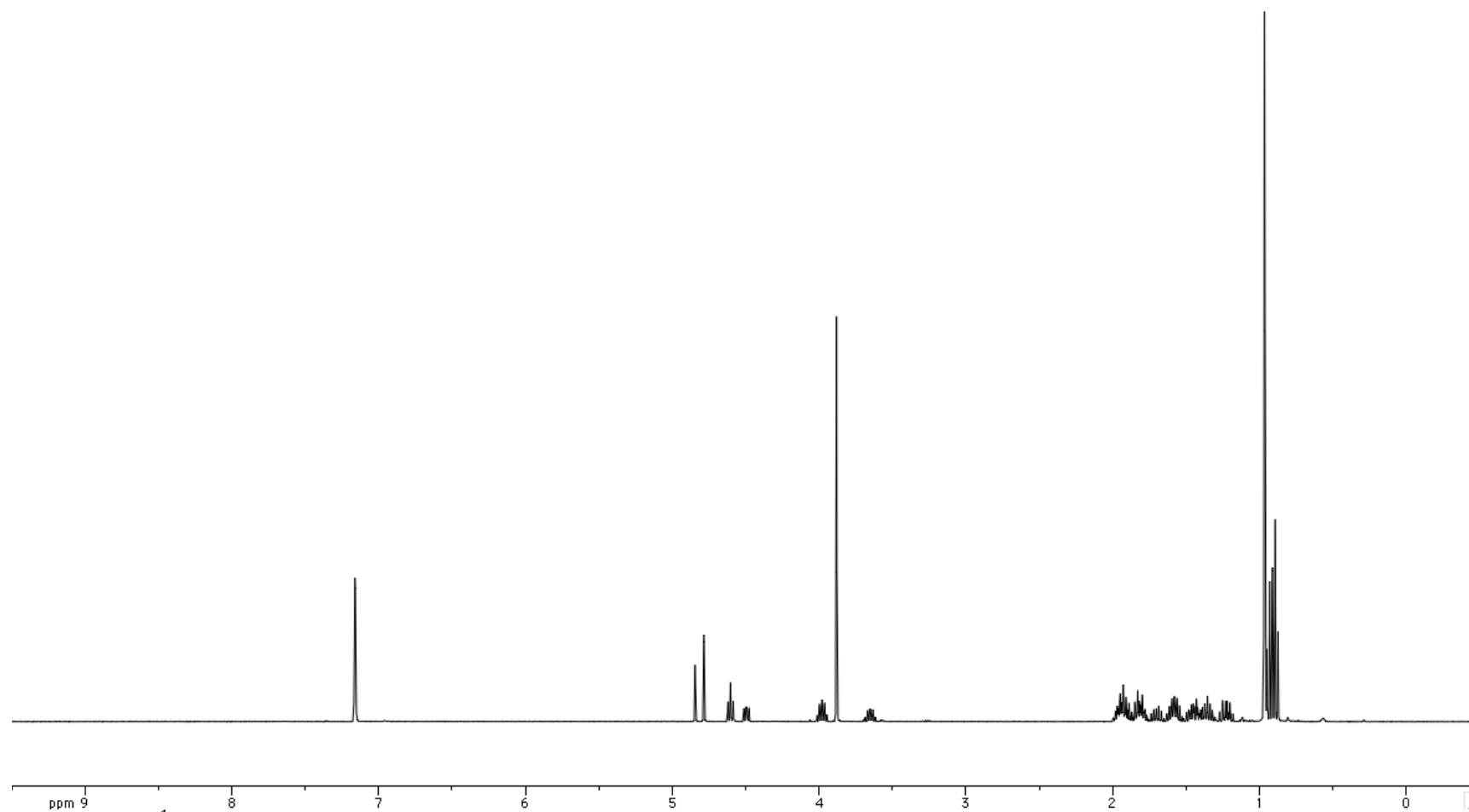
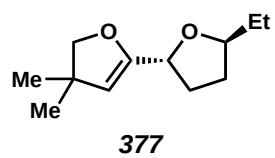


Figure A4.37 ^1H NMR (400 MHz, C_6D_6) of compound **377**

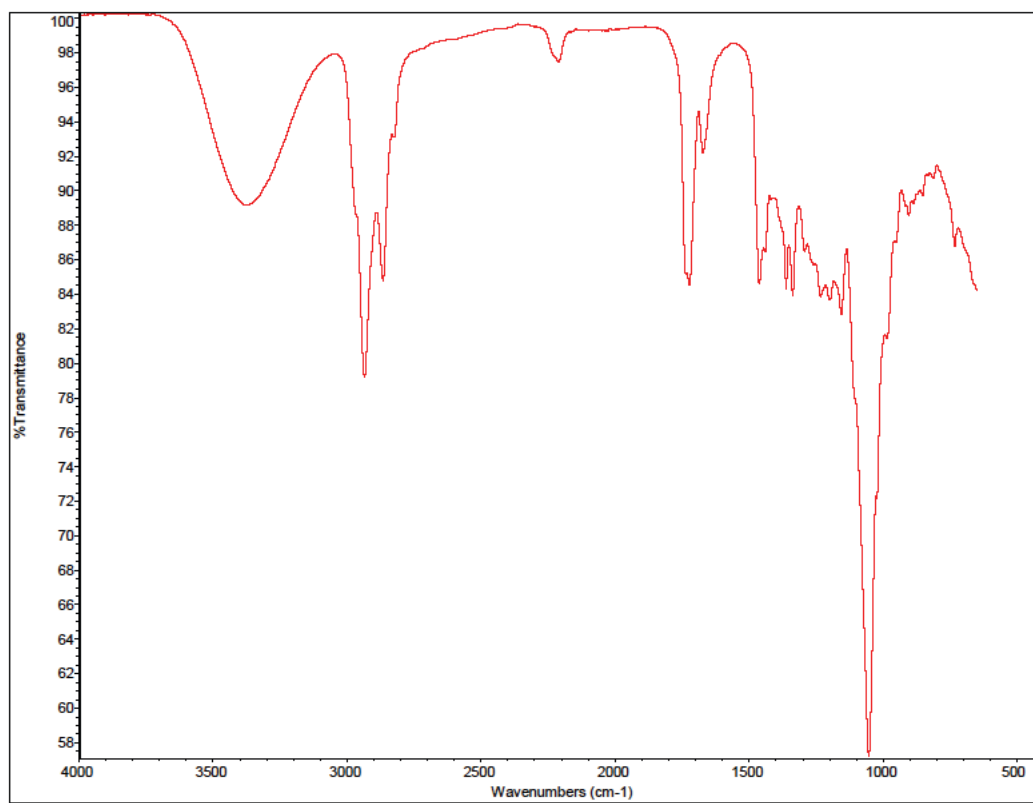
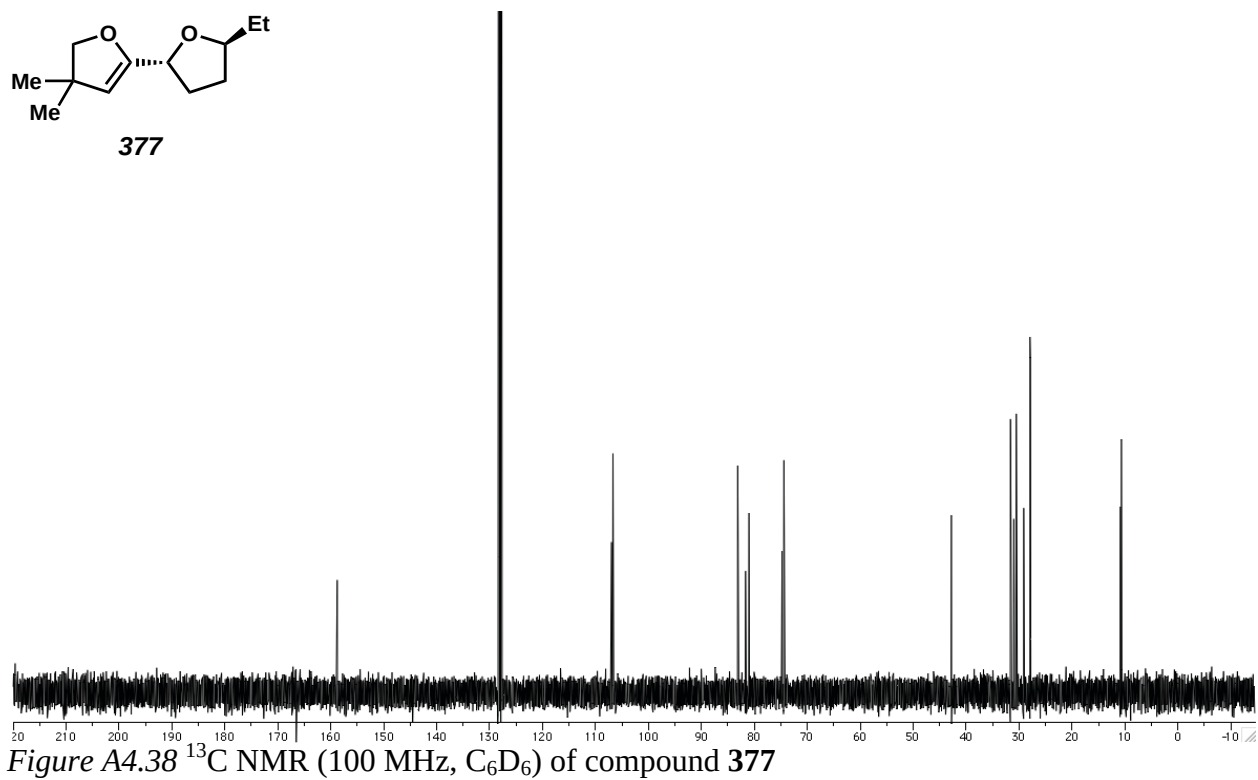


Figure A4.39 Infrared spectrum (thin film) of compound **377**

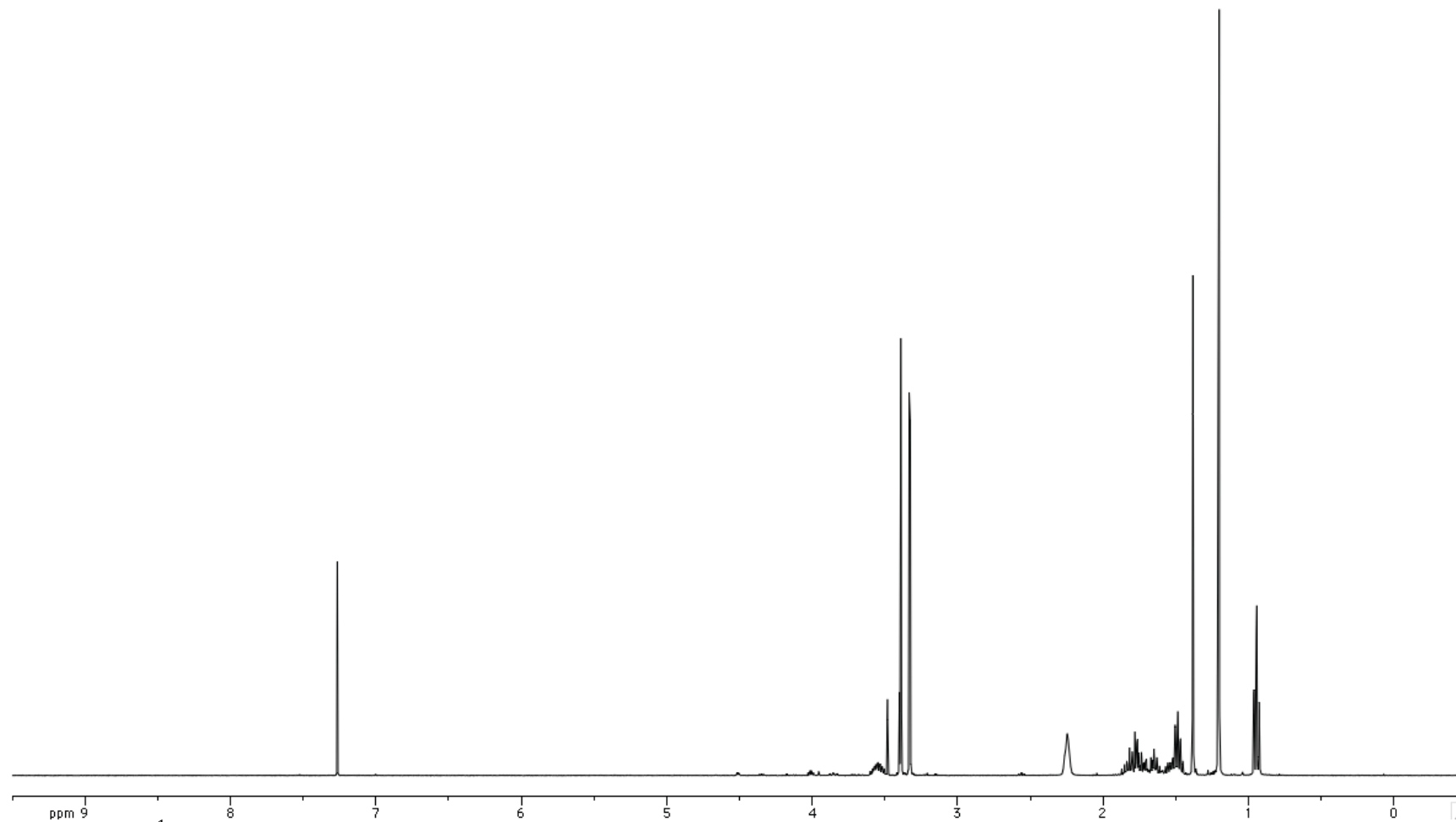
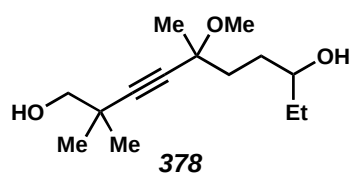
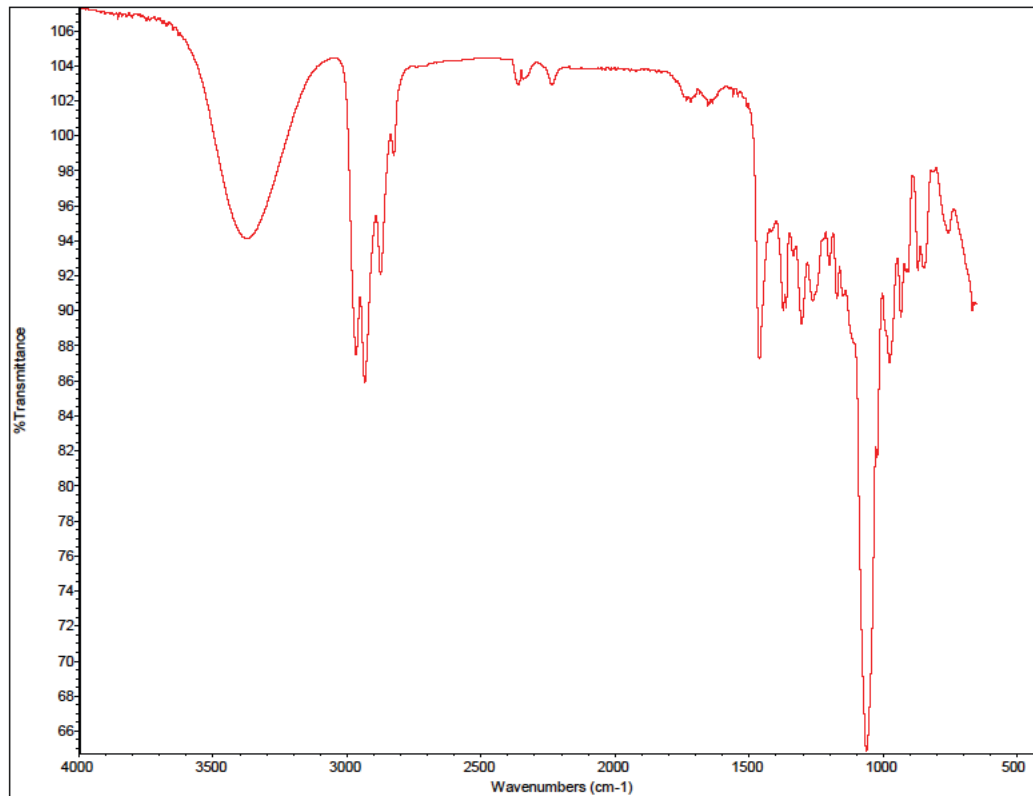
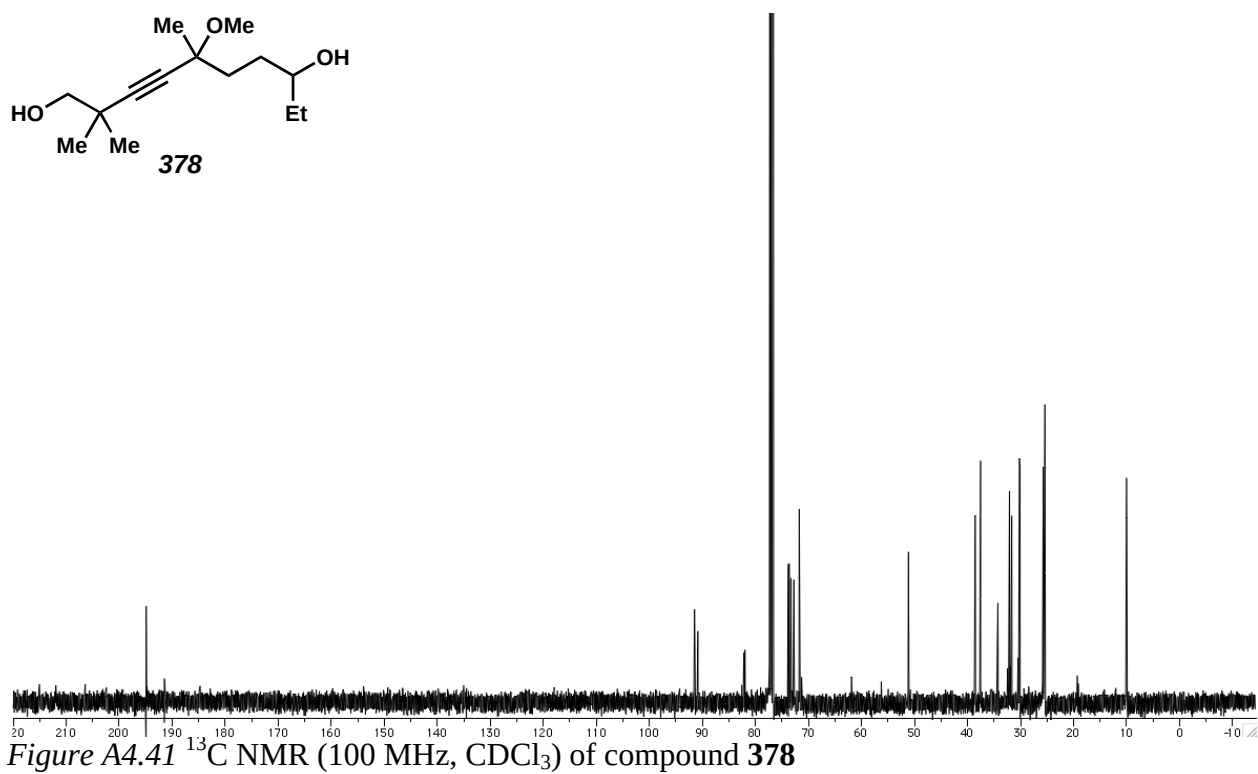


Figure A4.40 ¹H NMR (400 MHz, CDCl₃) of compound 378



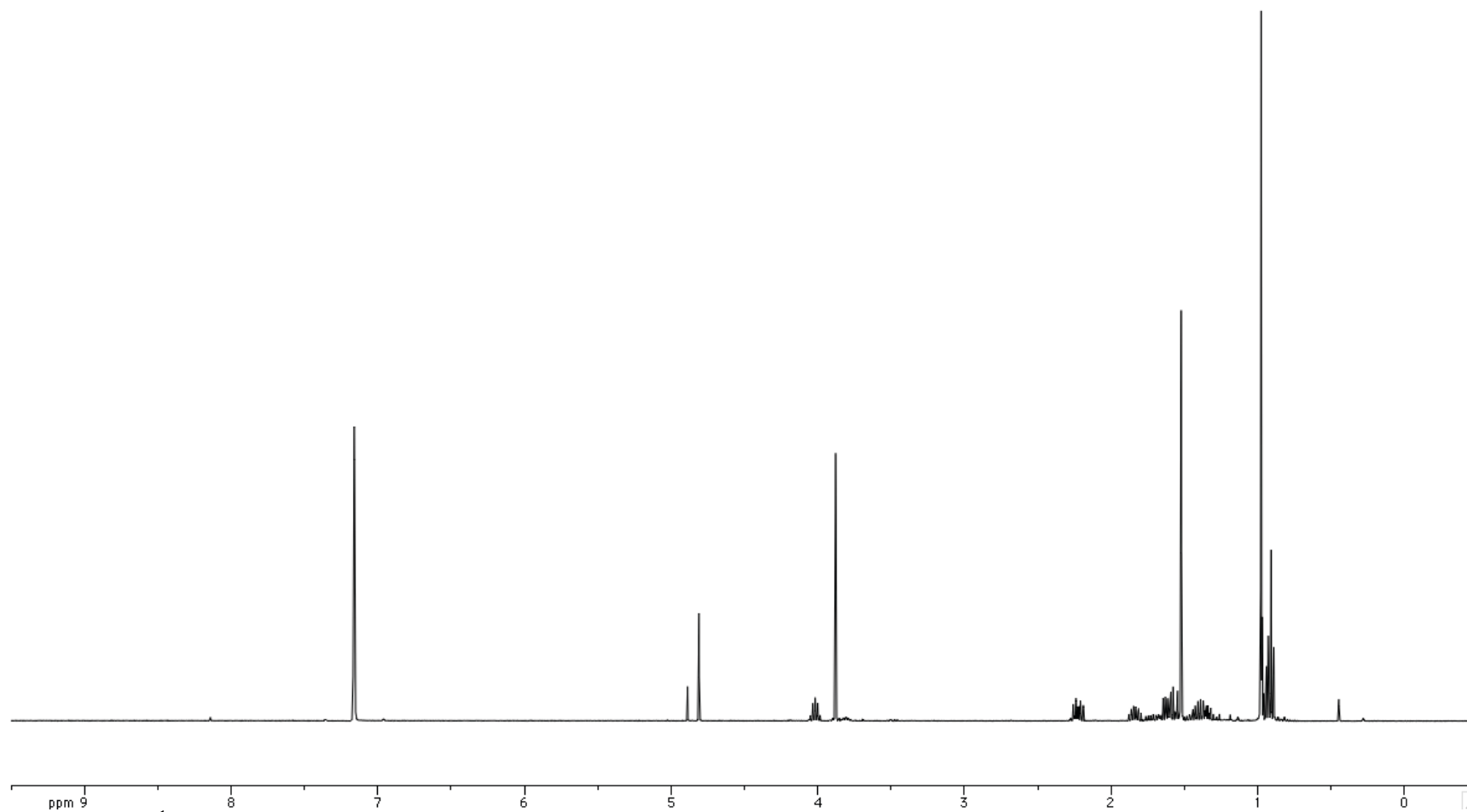
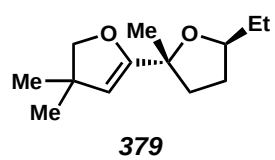


Figure A4.43 ^1H NMR (400 MHz, C_6D_6) of compound **379**

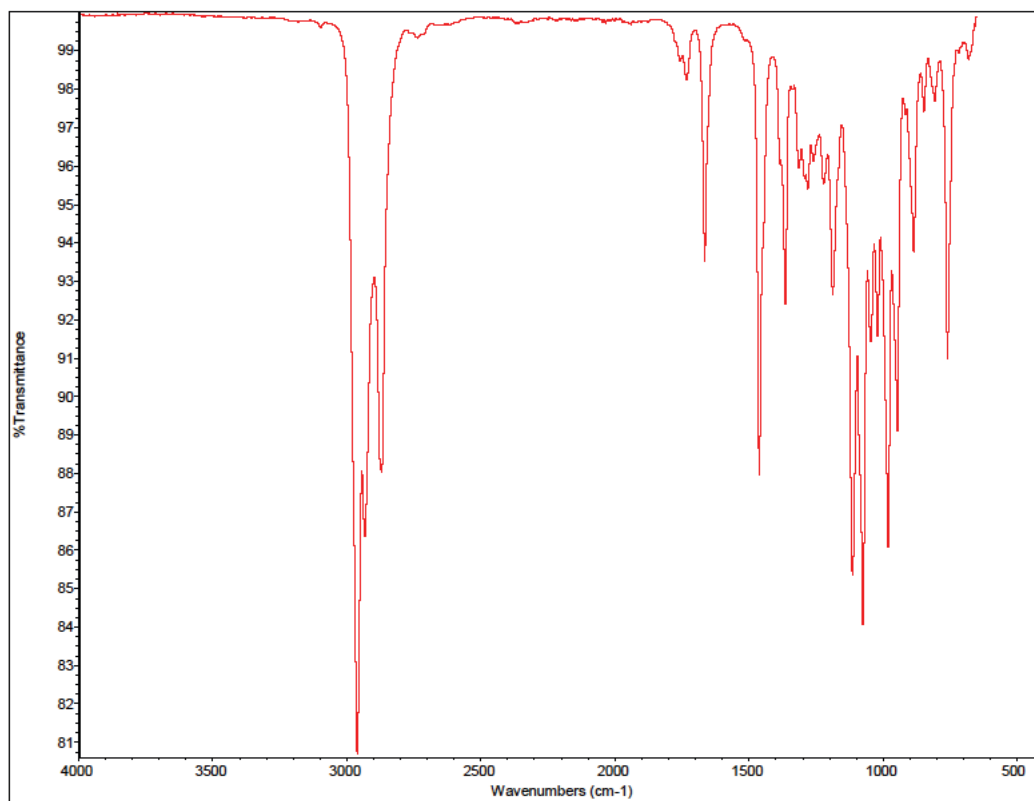
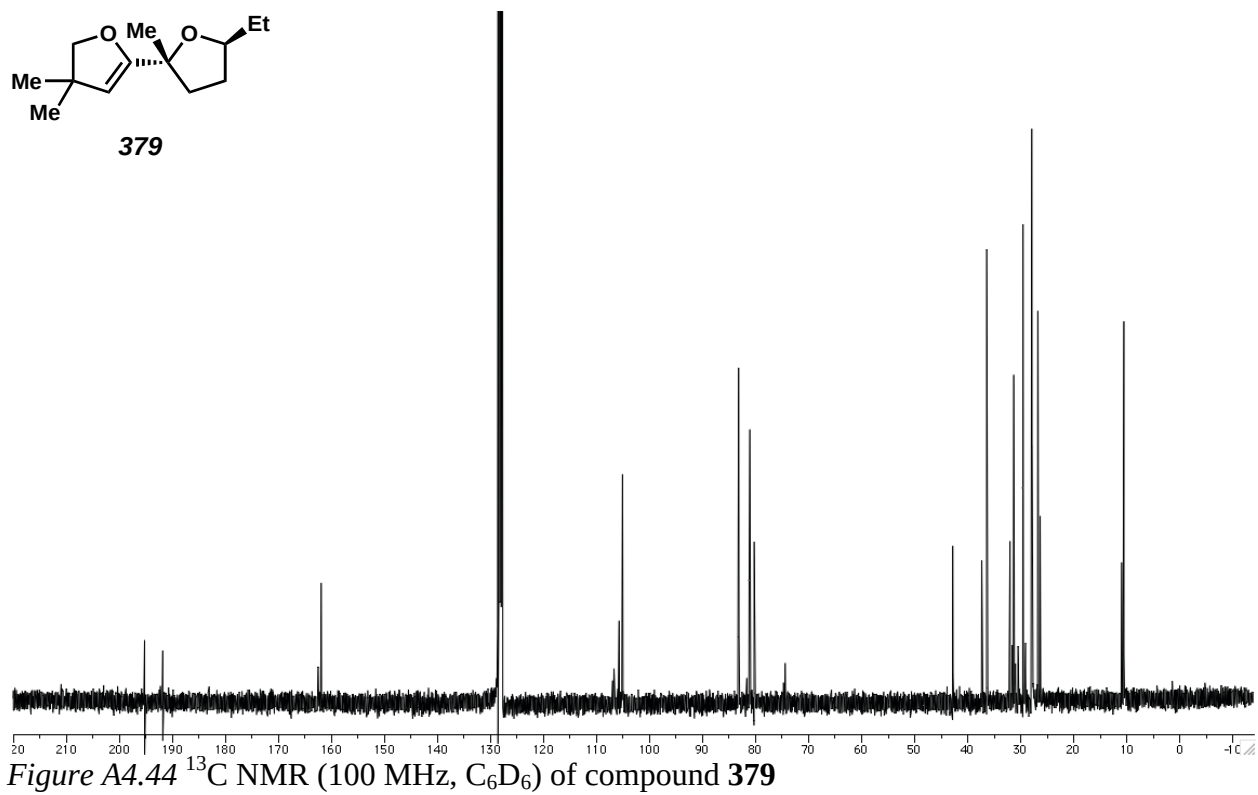


Figure A4.45 Infrared spectrum (thin film) of compound **379**

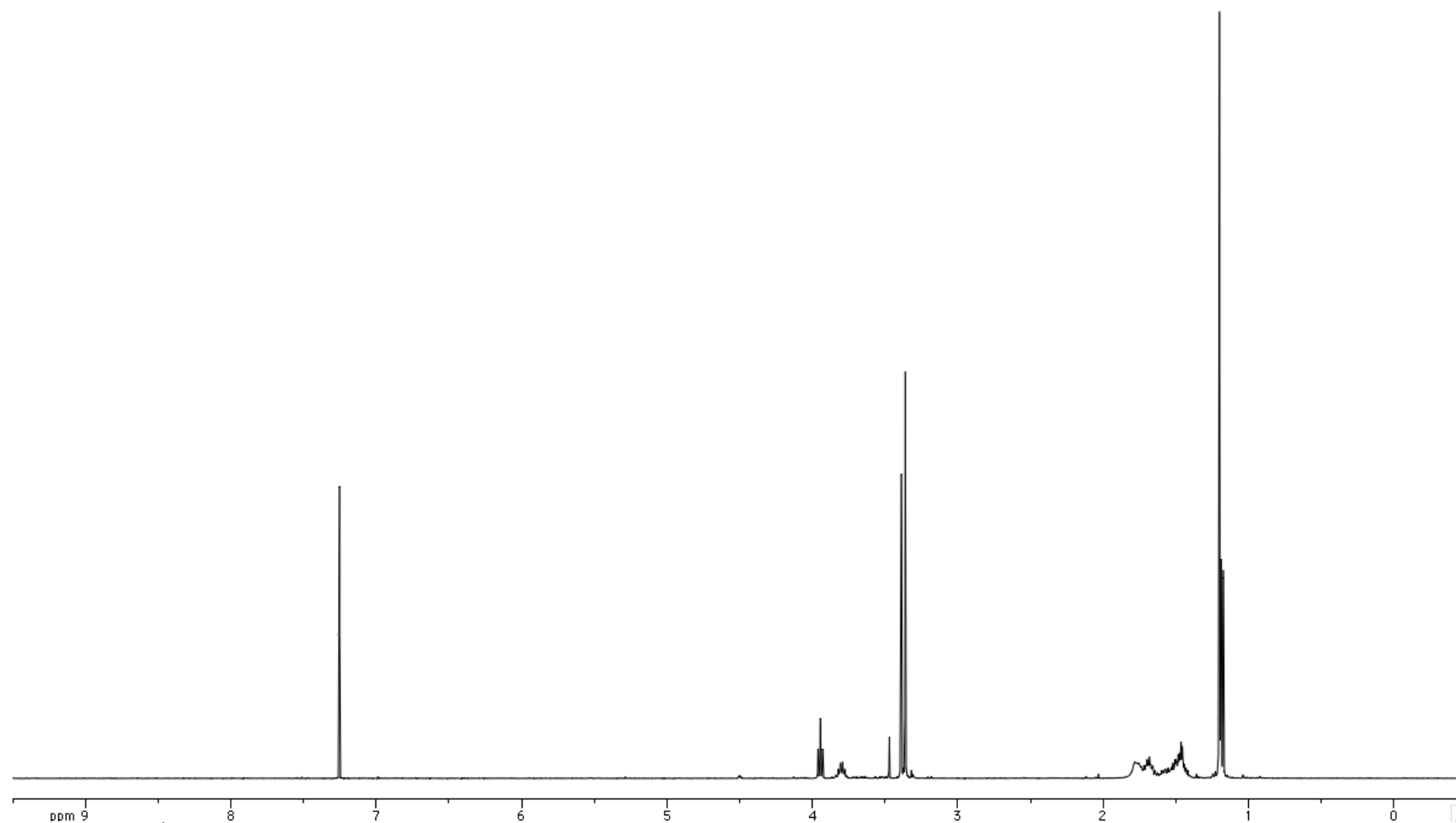
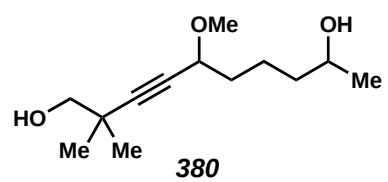
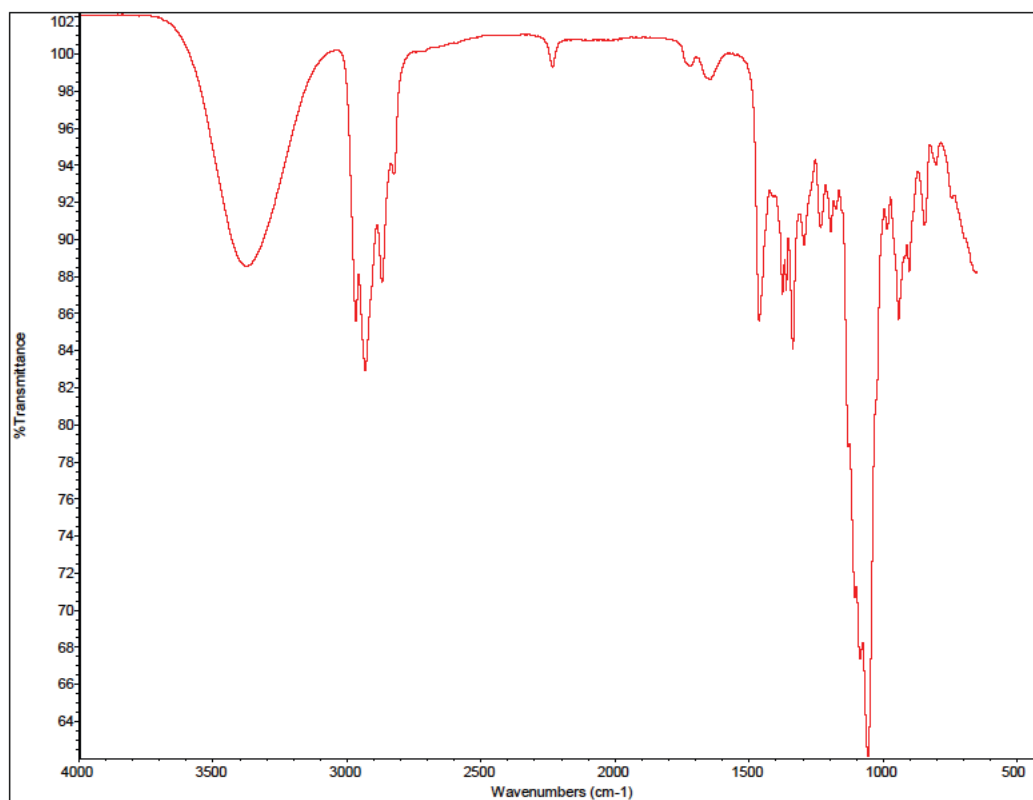
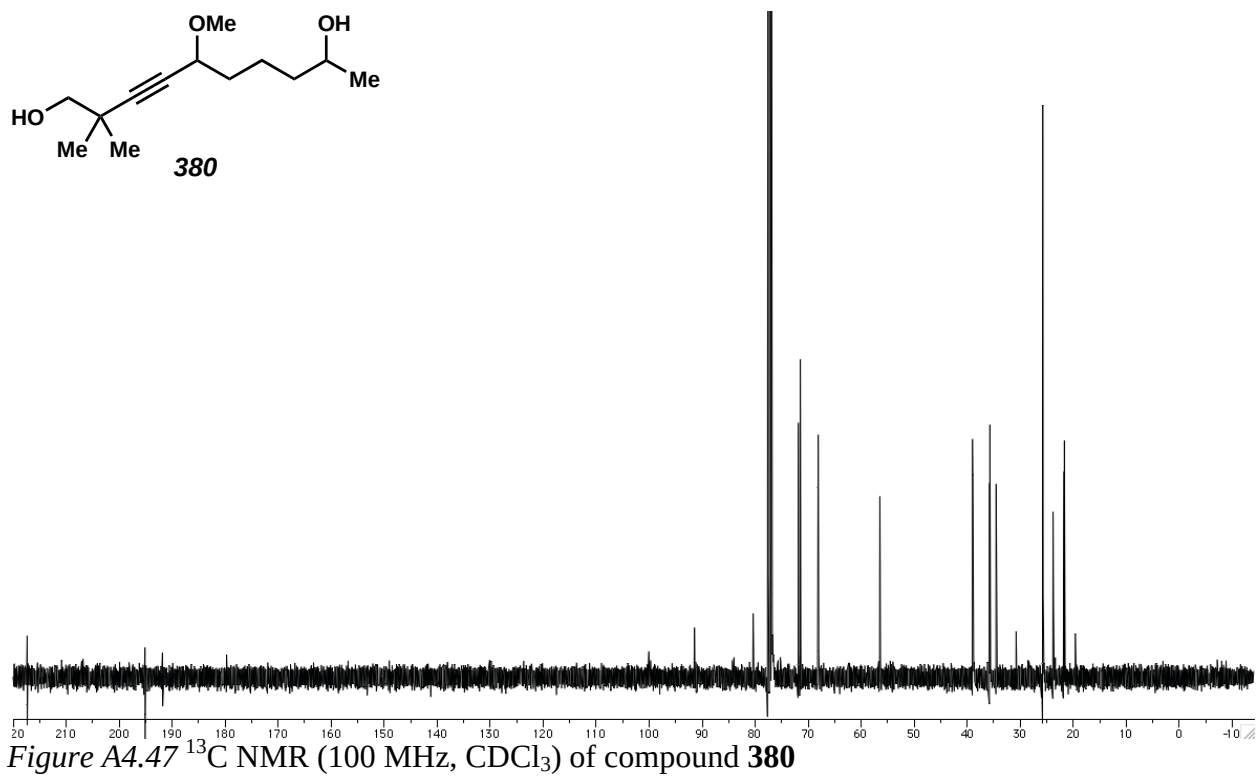


Figure A4.46 ^1H NMR (400 MHz, CDCl_3) of compound **380**



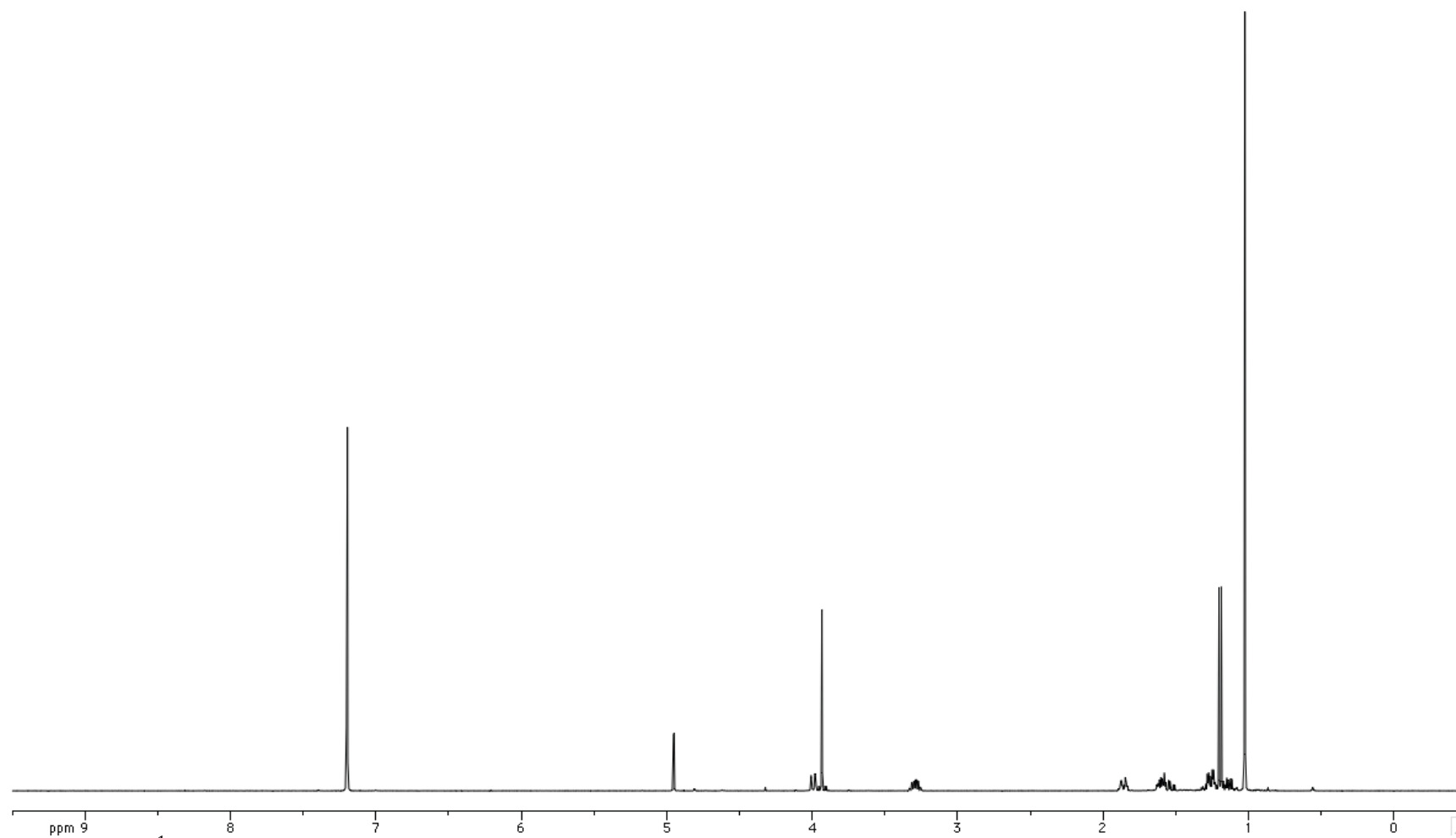
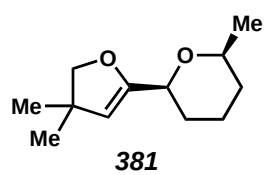
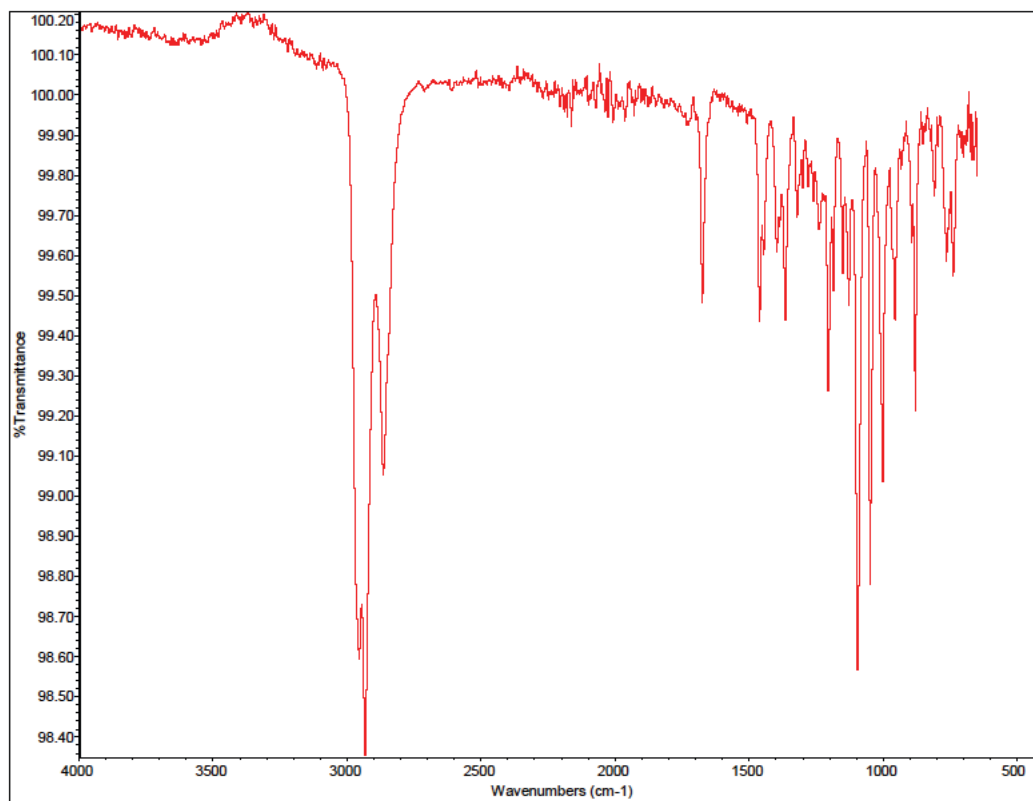
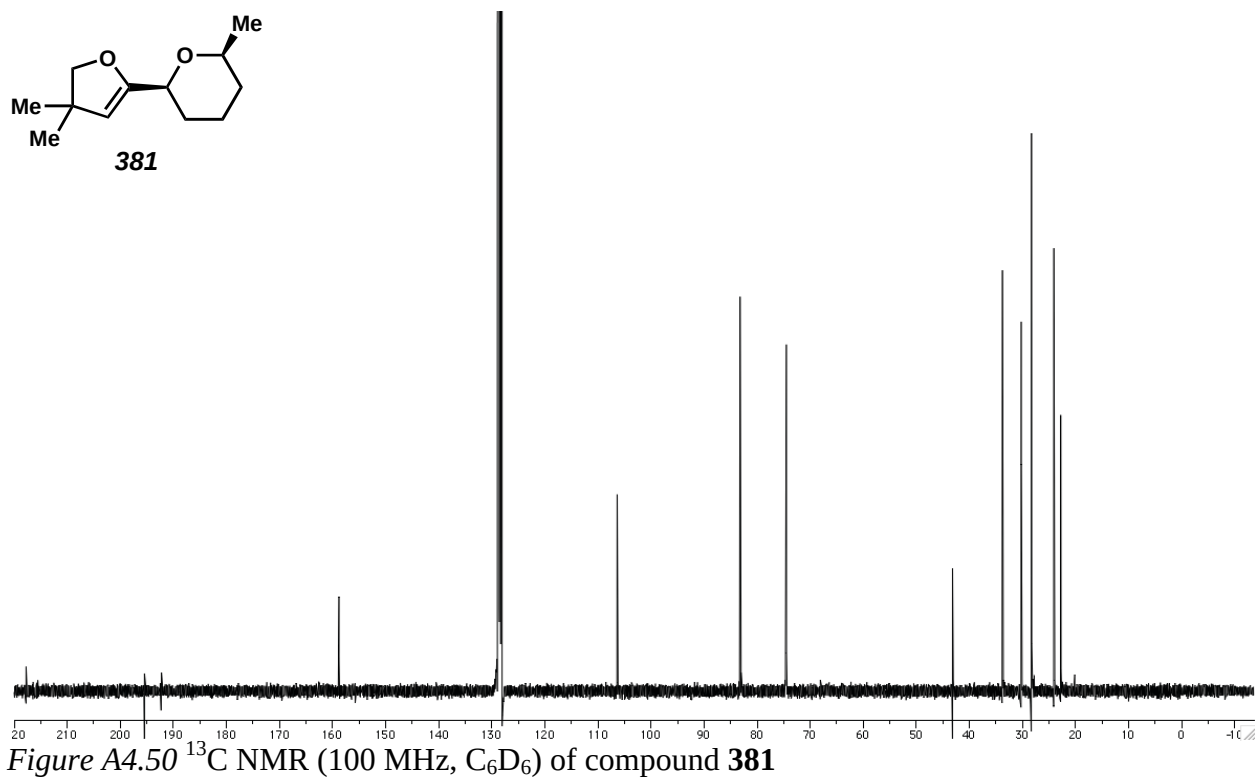


Figure A4.49 ^1H NMR (400 MHz, C_6D_6) of compound **381**



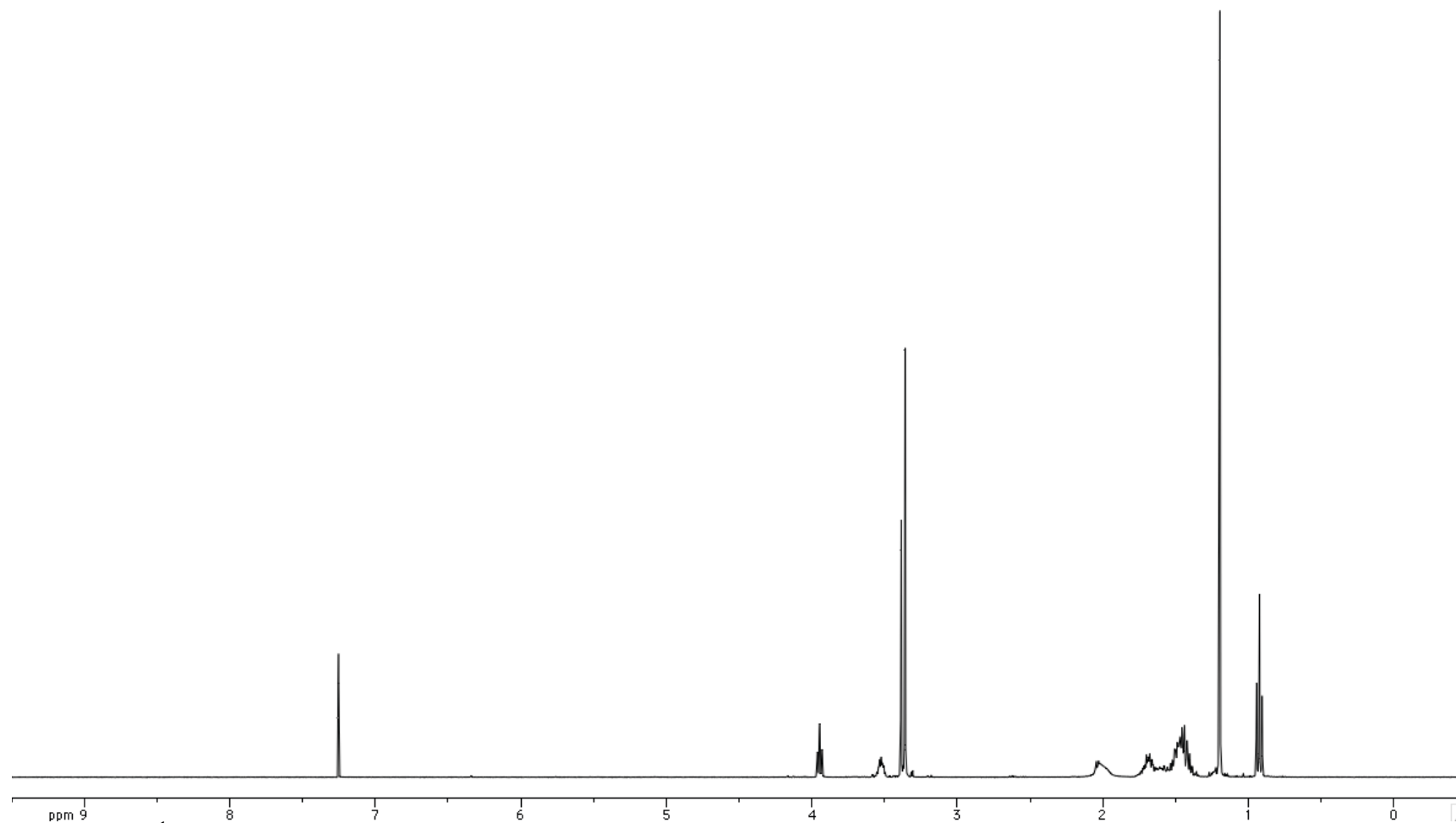
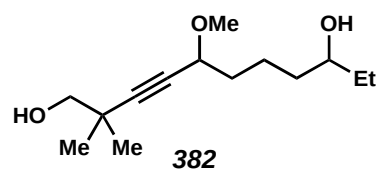


Figure A4.52 ¹H NMR (400 MHz, CDCl₃) of compound **382**

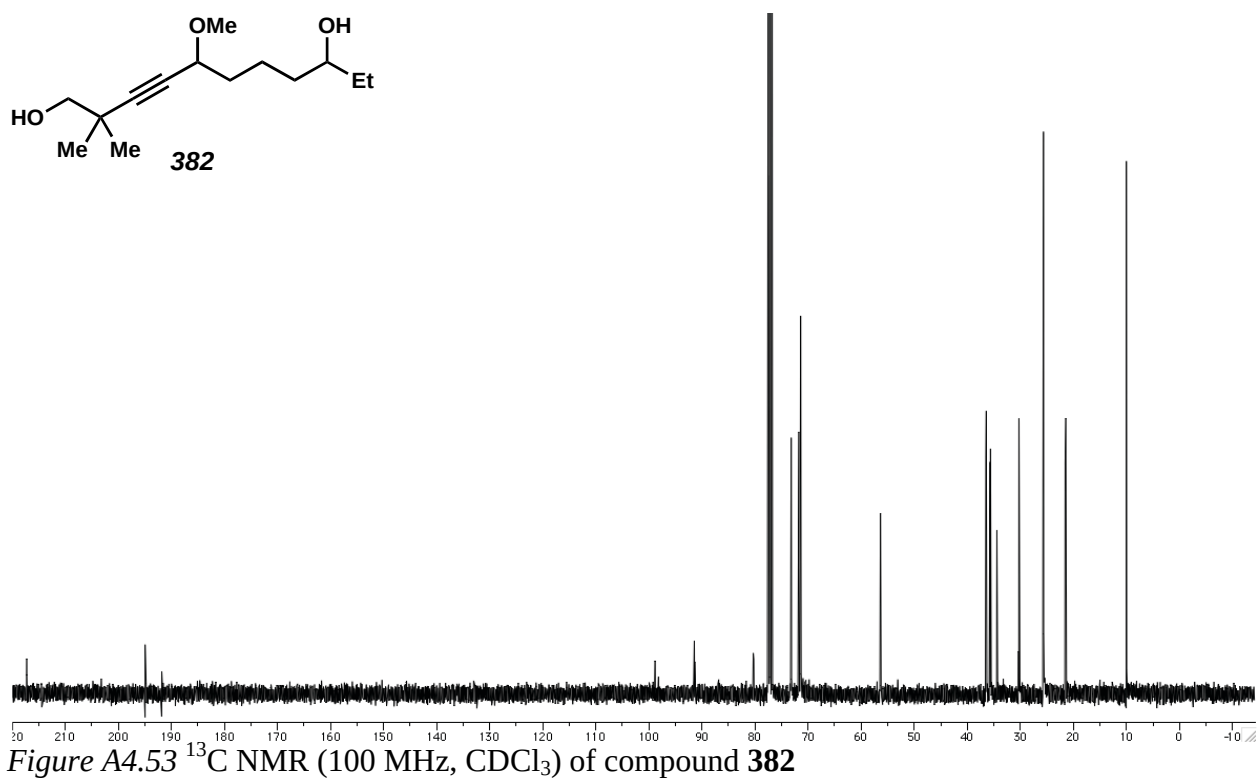


Figure A4.53 ¹³C NMR (100 MHz, CDCl₃) of compound **382**

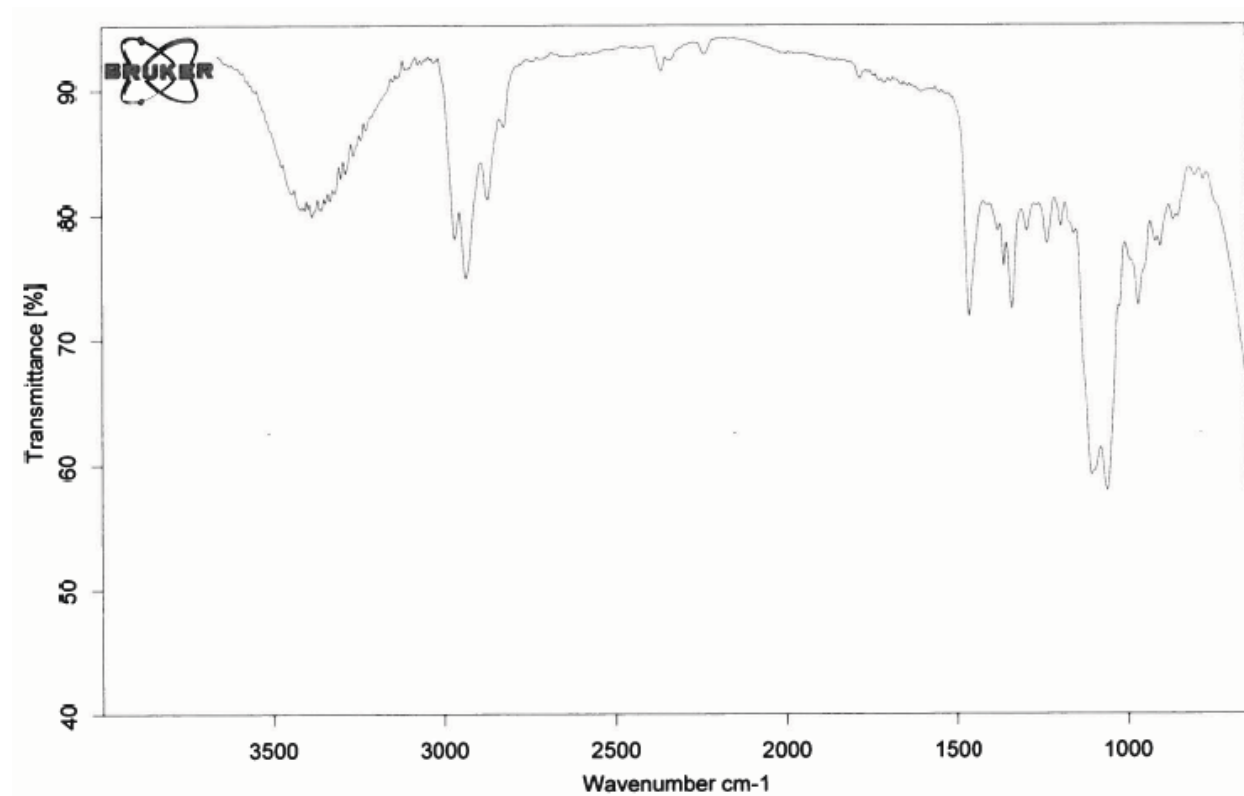


Figure A4.54 Infrared spectrum (thin film) of compound **382**

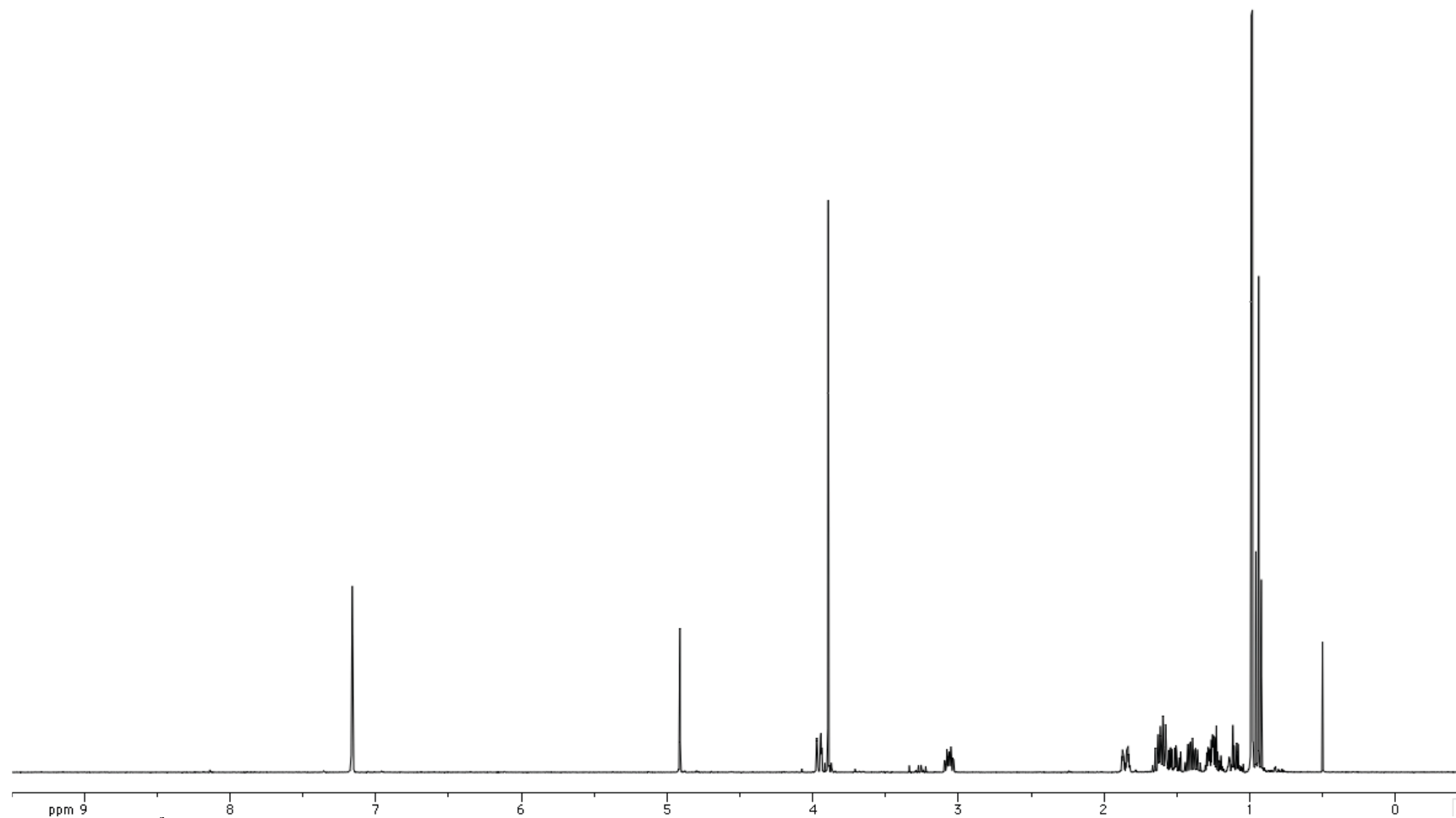
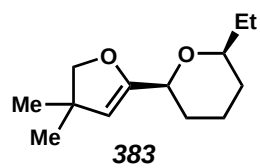
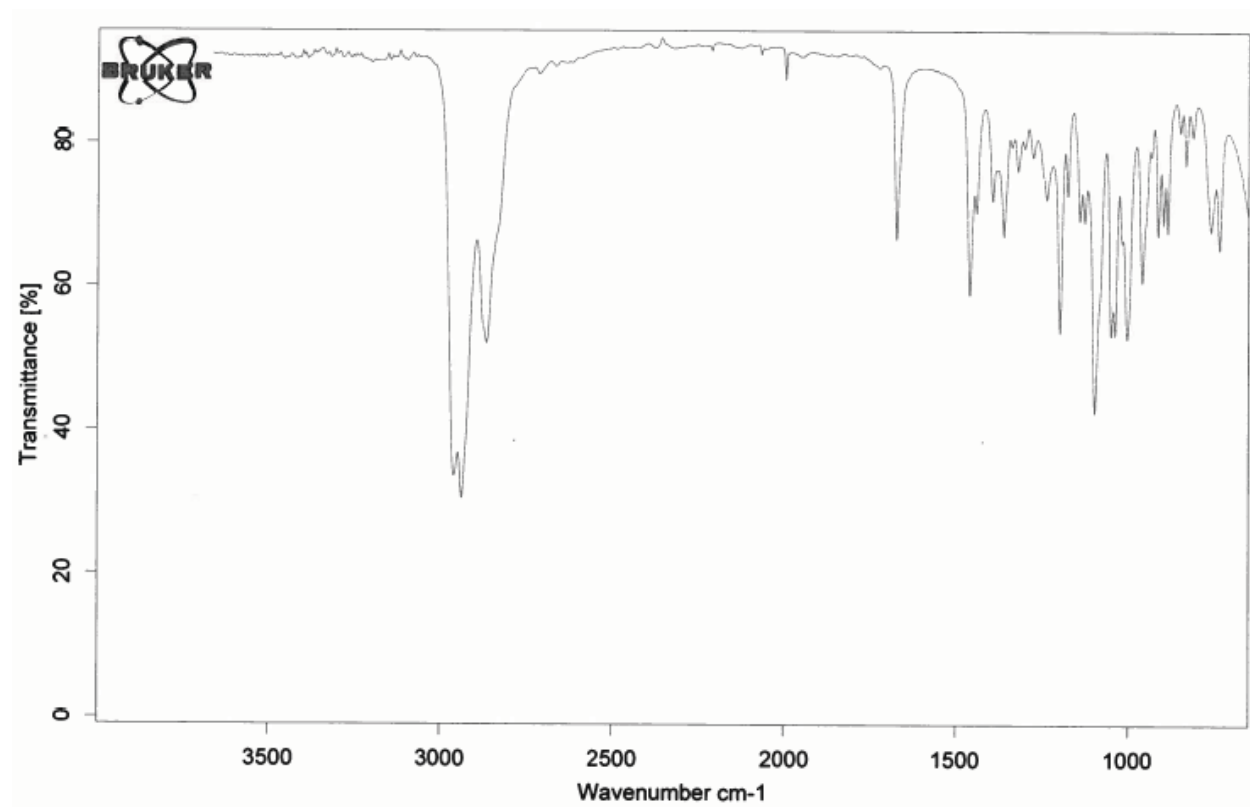
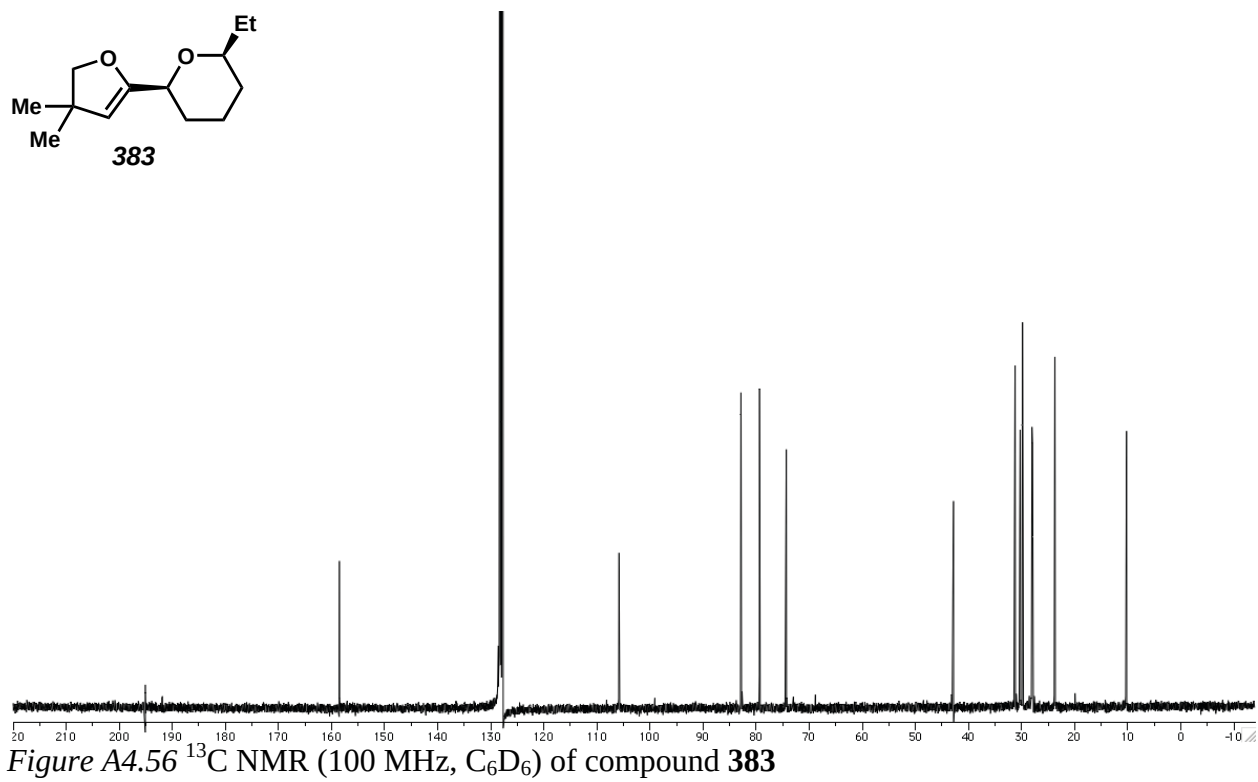


Figure A4.55 ^1H NMR (400 MHz, C_6D_6) of compound **383**



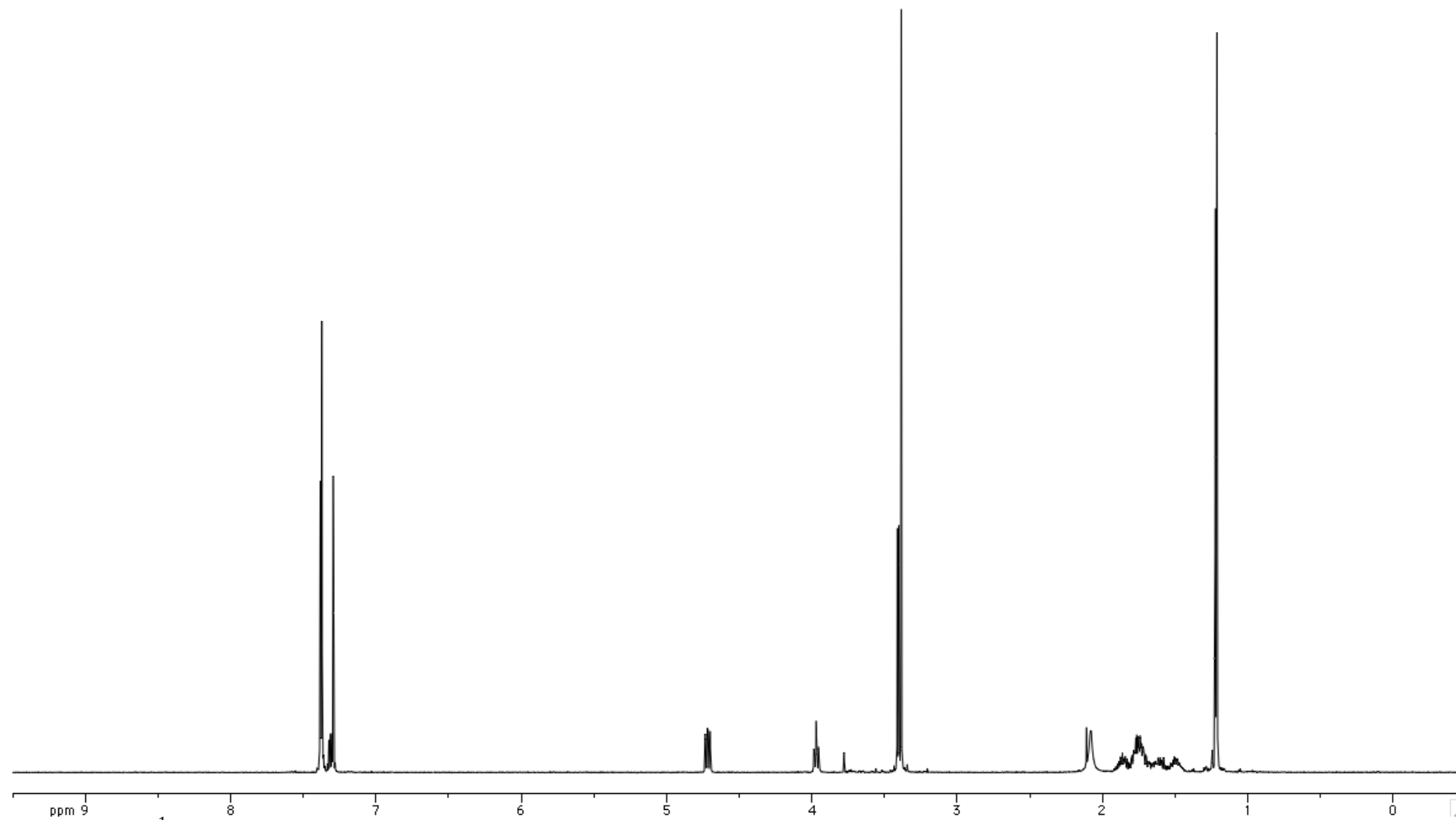
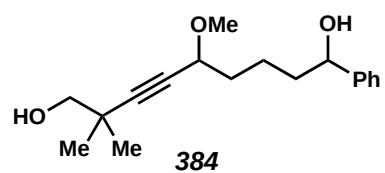


Figure A4.58 ^1H NMR (400 MHz, CDCl_3) of compound **384**

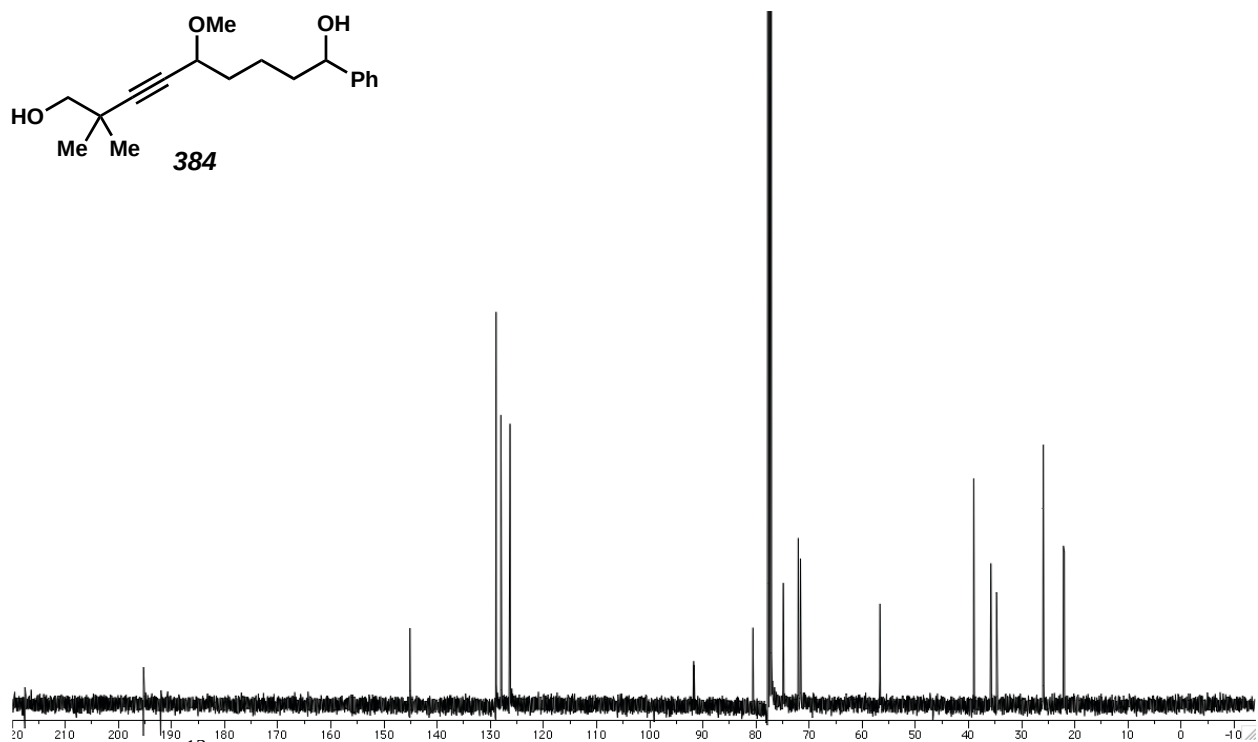


Figure A4.59 ^{13}C NMR (100 MHz, CDCl_3) of compound **384**

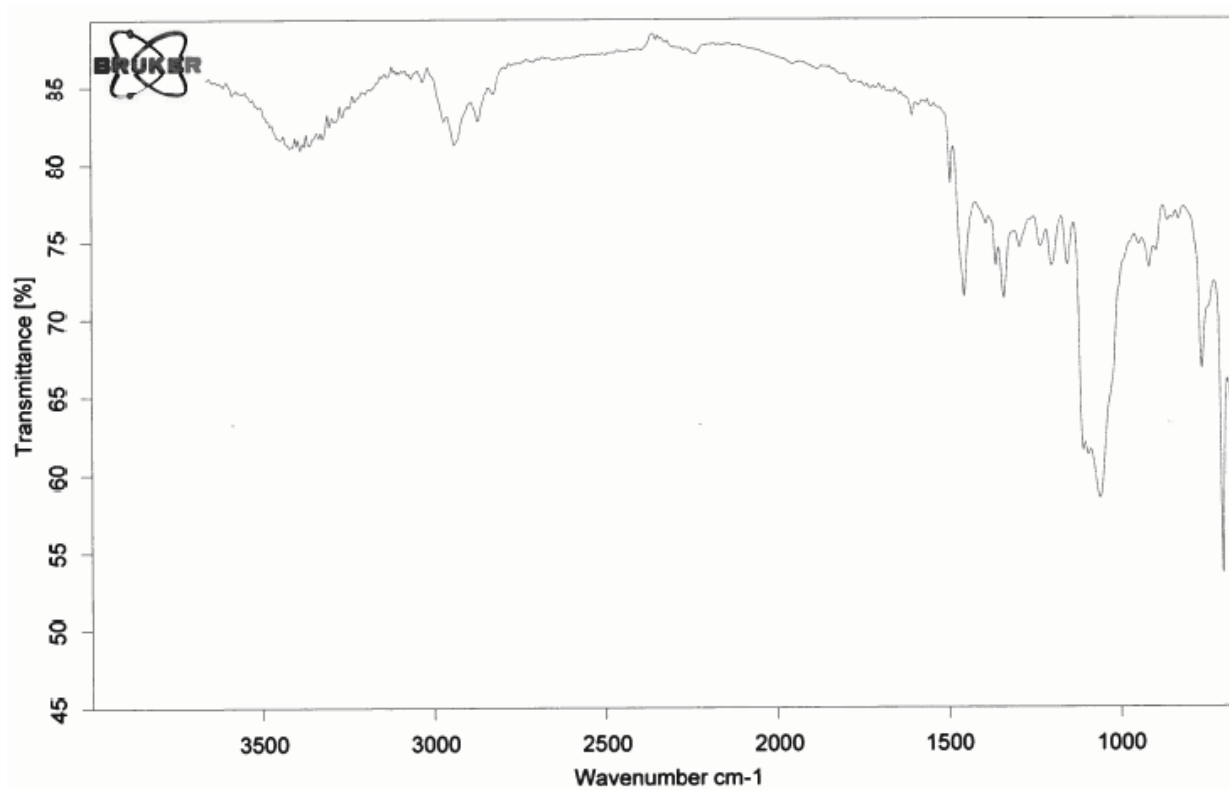


Figure A4.60 Infrared spectrum (thin film) of compound **384**

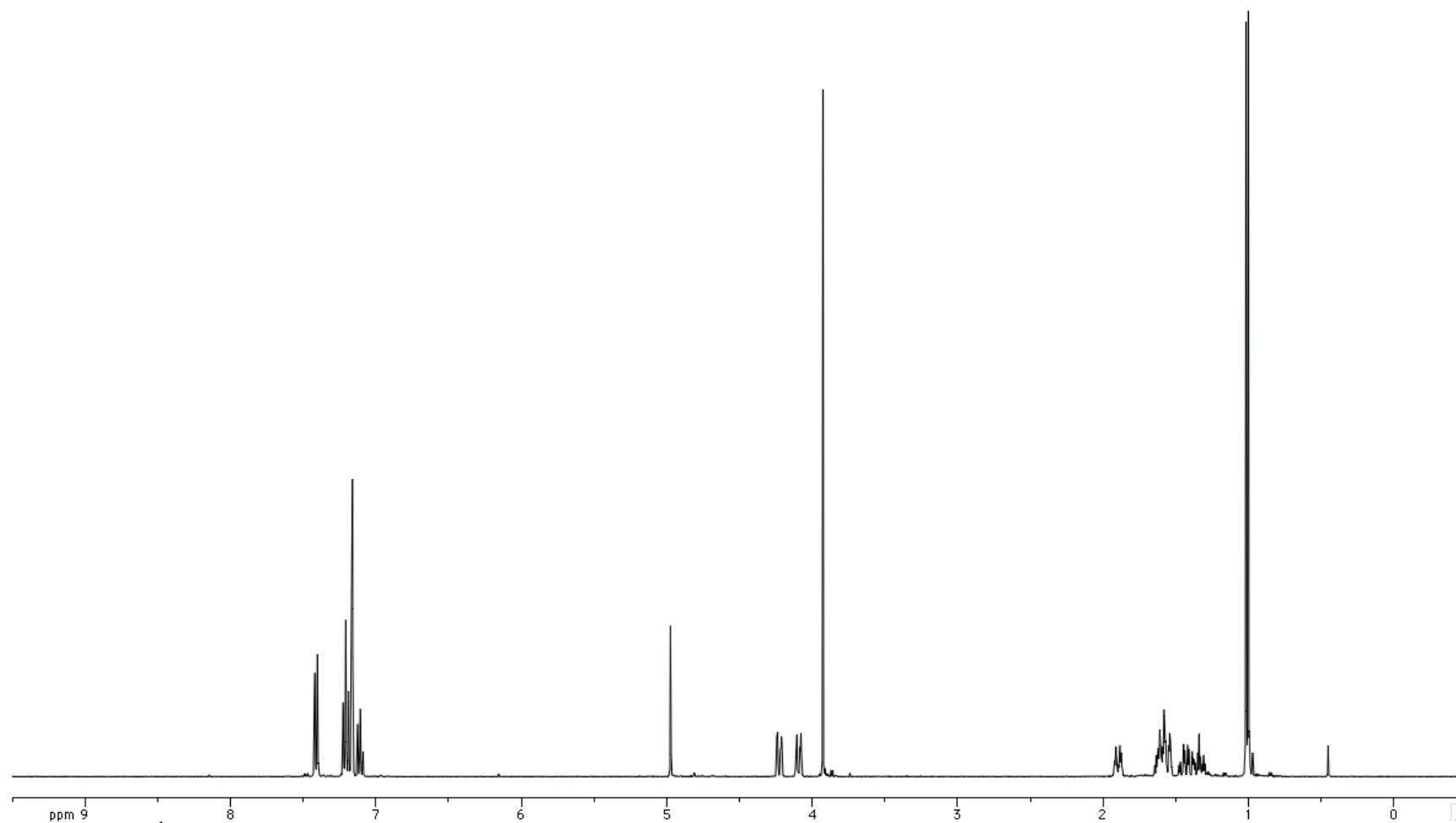
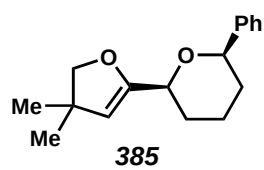
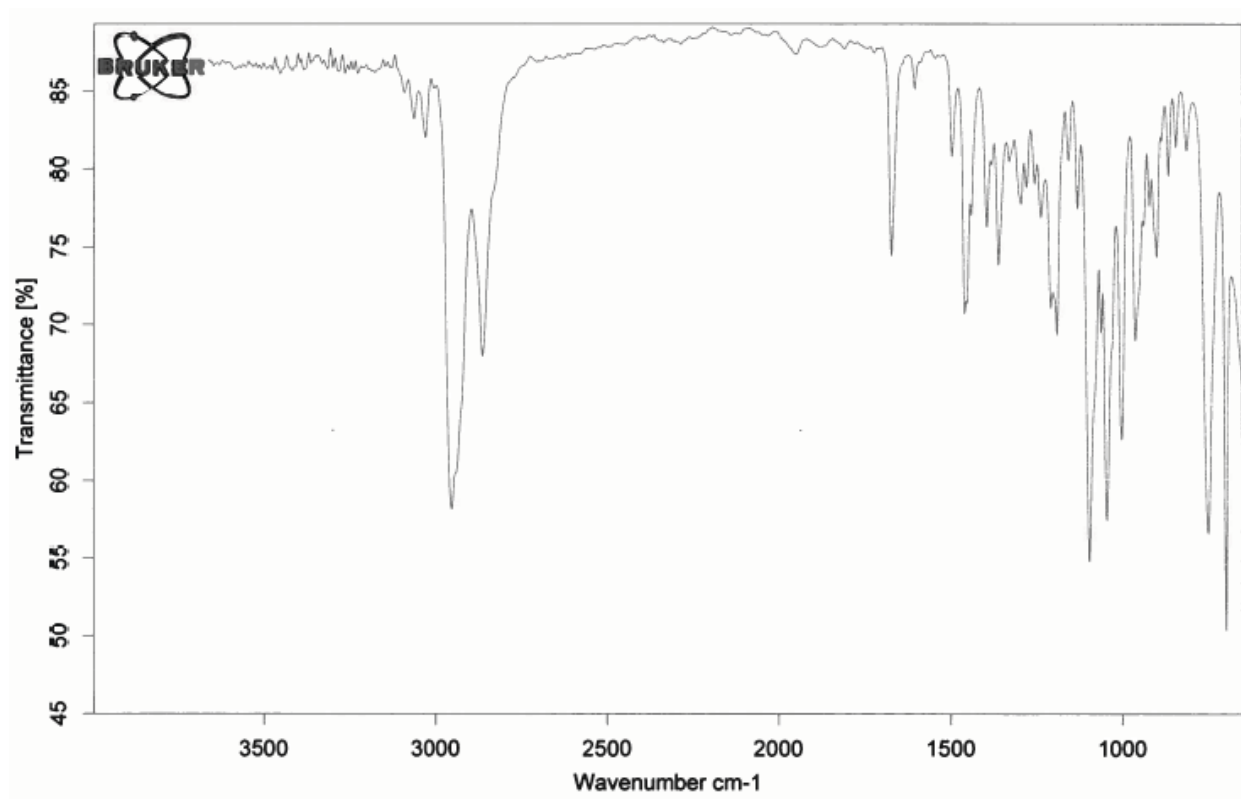
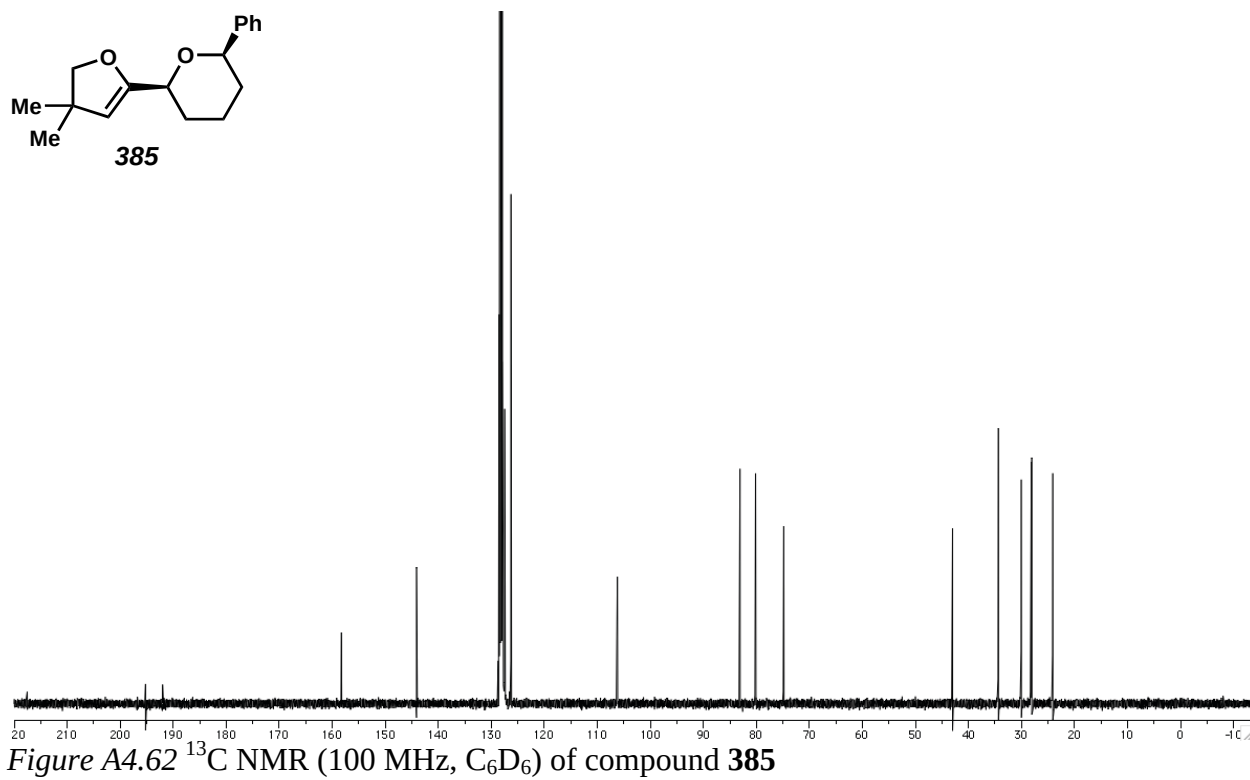


Figure A4.61 ^1H NMR (400 MHz, C_6D_6) of compound **385**



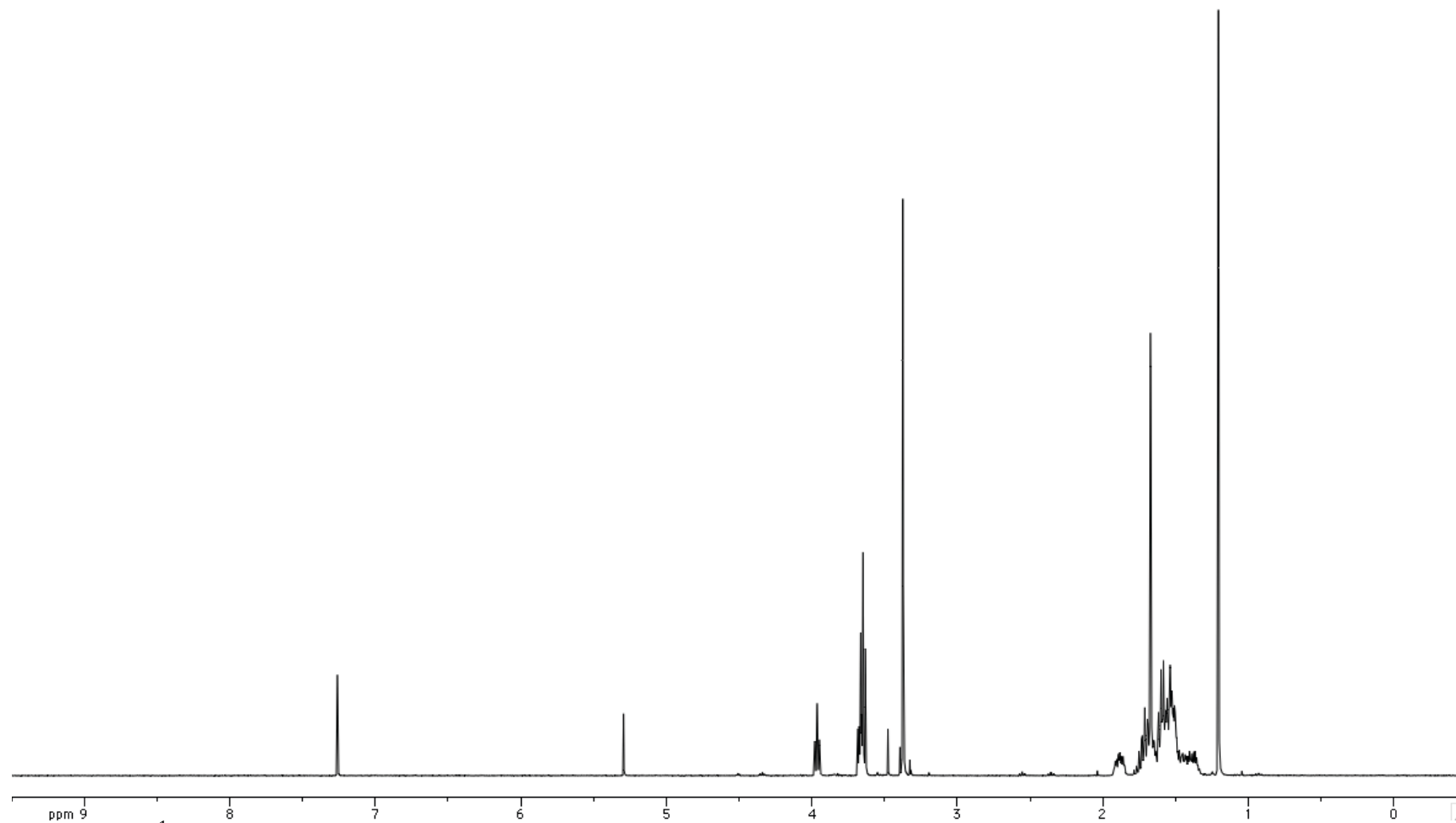
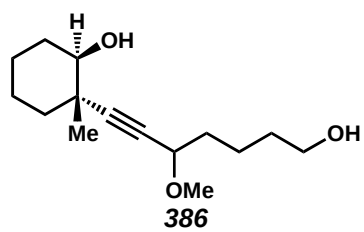


Figure A4.64 ^1H NMR (400 MHz, CDCl_3) of compound **386**

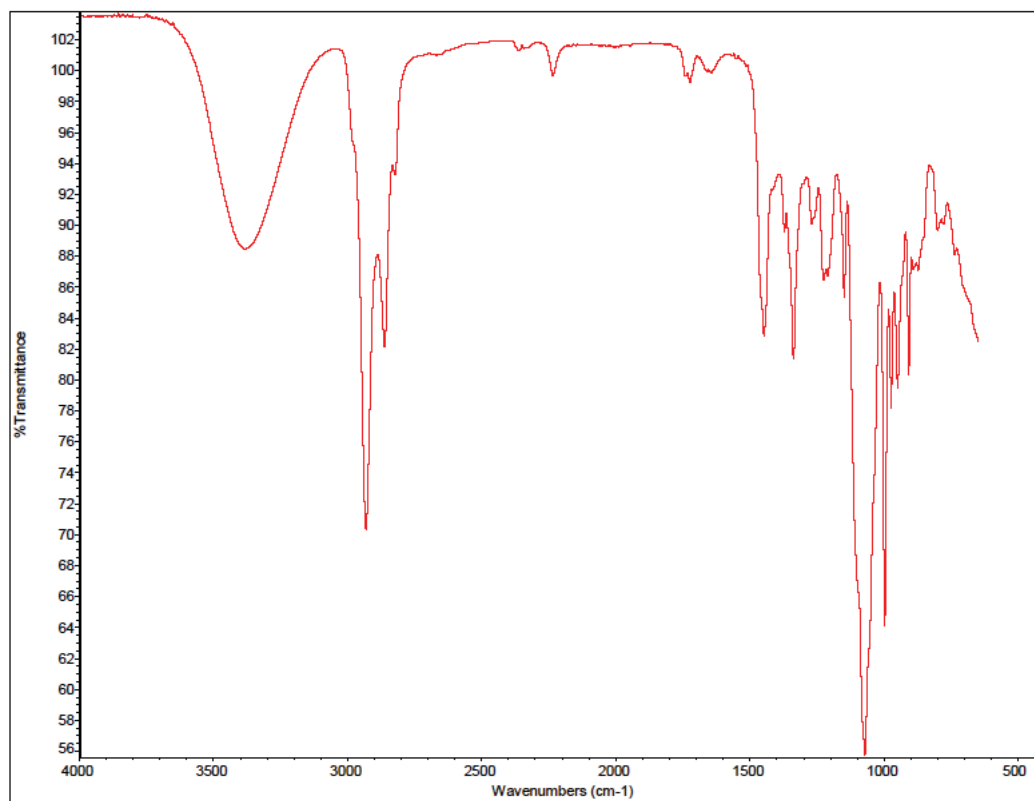
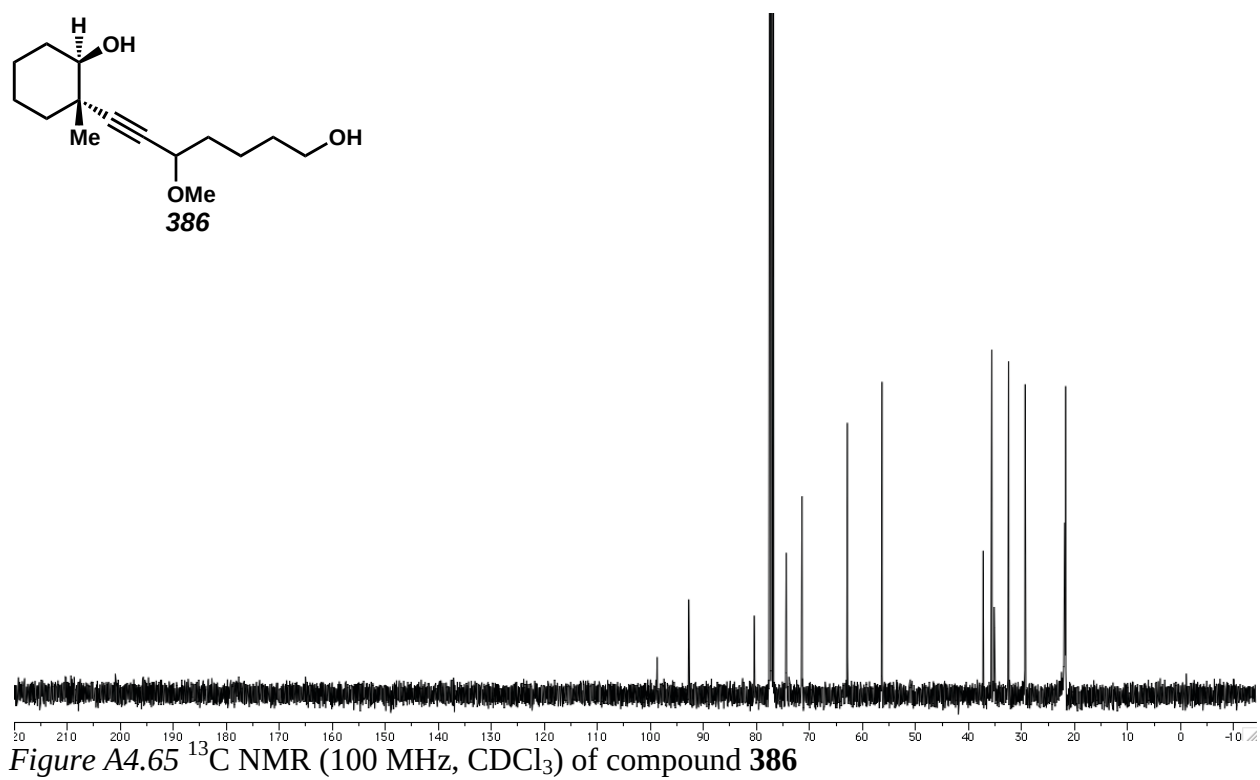
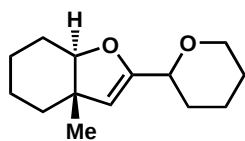


Figure A4.66 Infrared spectrum (thin film) of compound **386**



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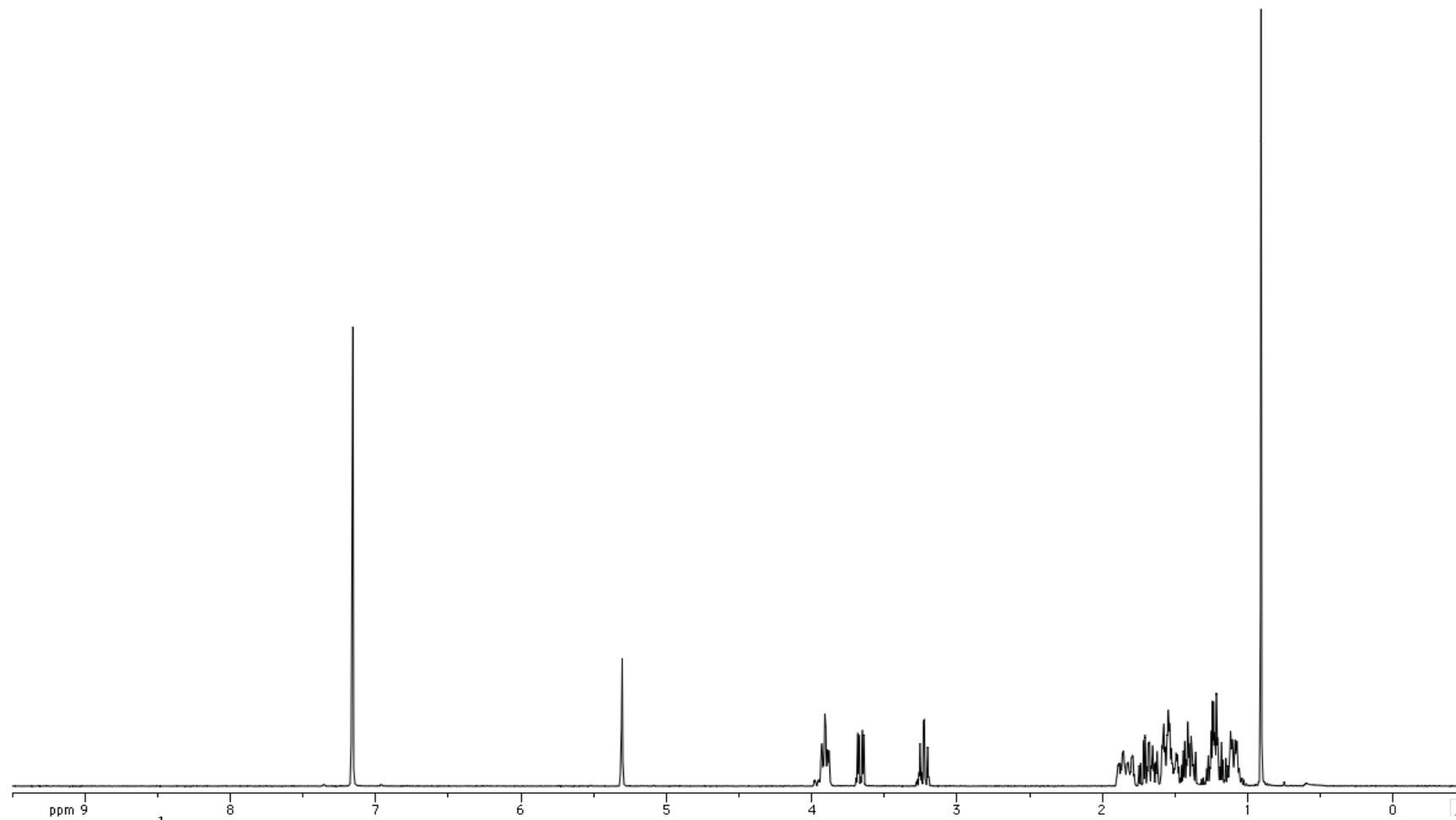
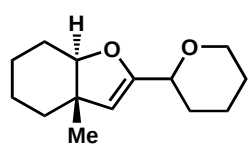


Figure A4.67 ^1H NMR (400 MHz, C_6D_6) of compound **387**



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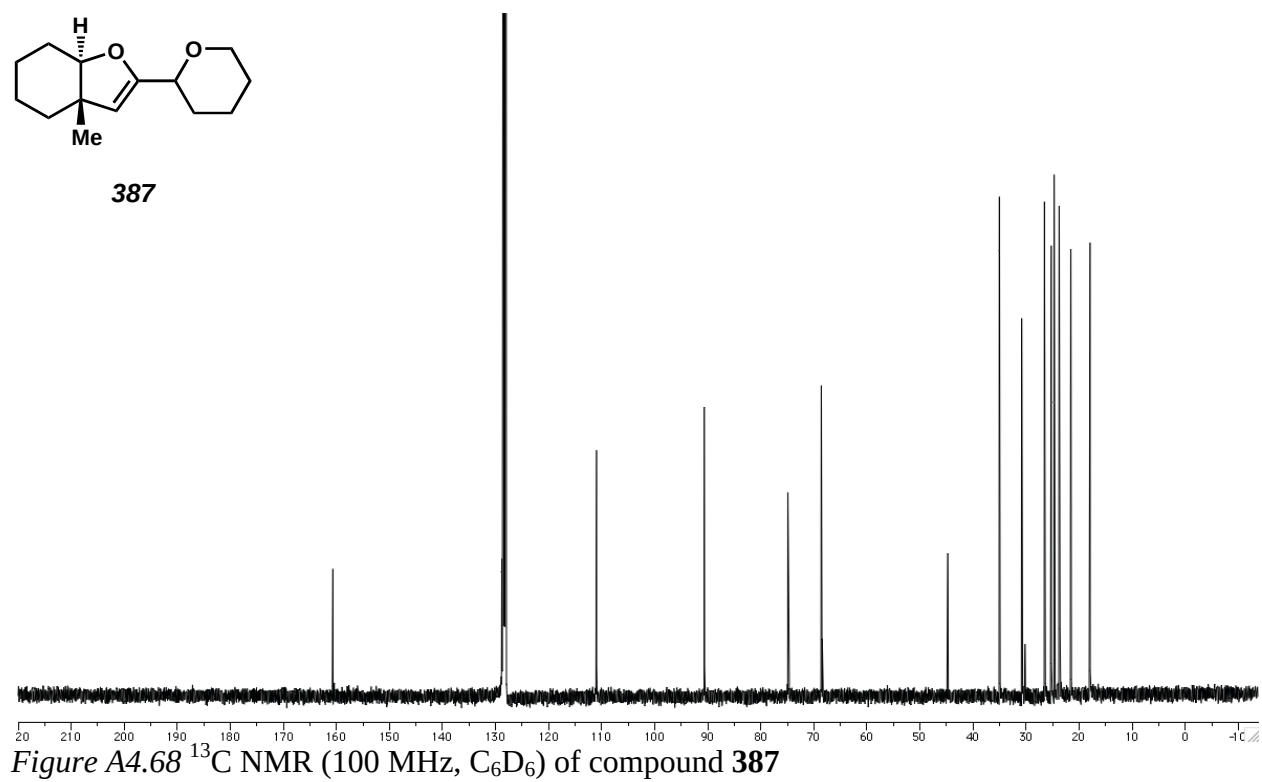


Figure A4.68 ^{13}C NMR (100 MHz, C_6D_6) of compound **387**

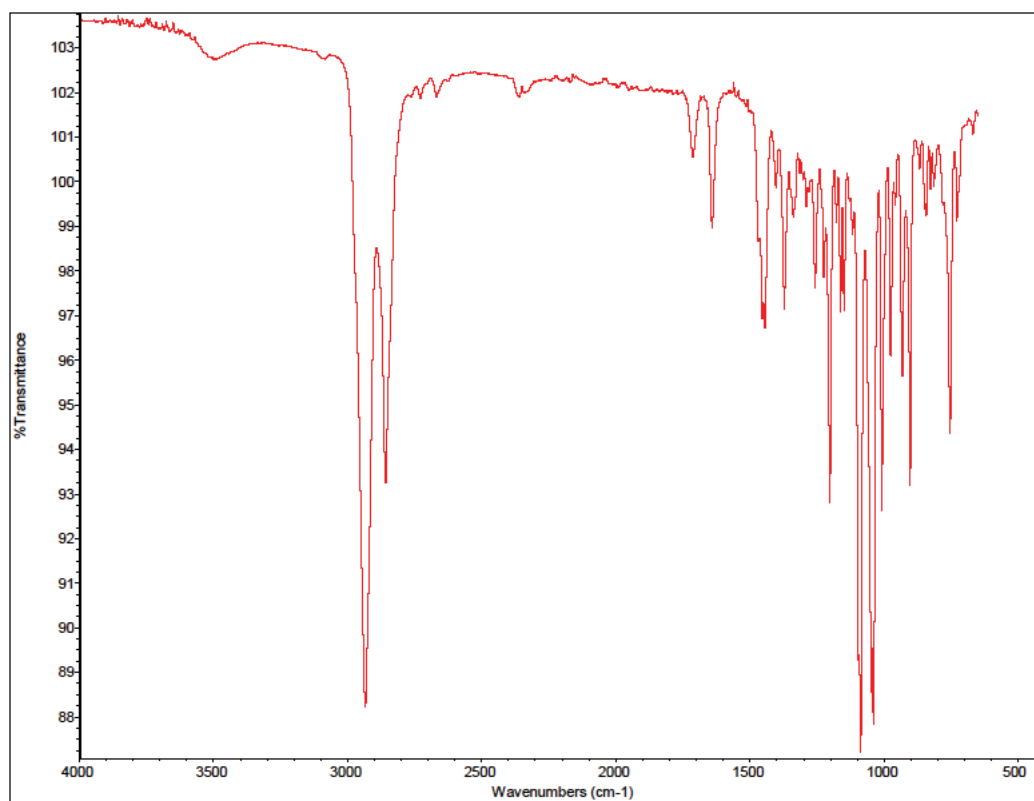


Figure A4.69 Infrared spectrum (thin film) of compound **387**

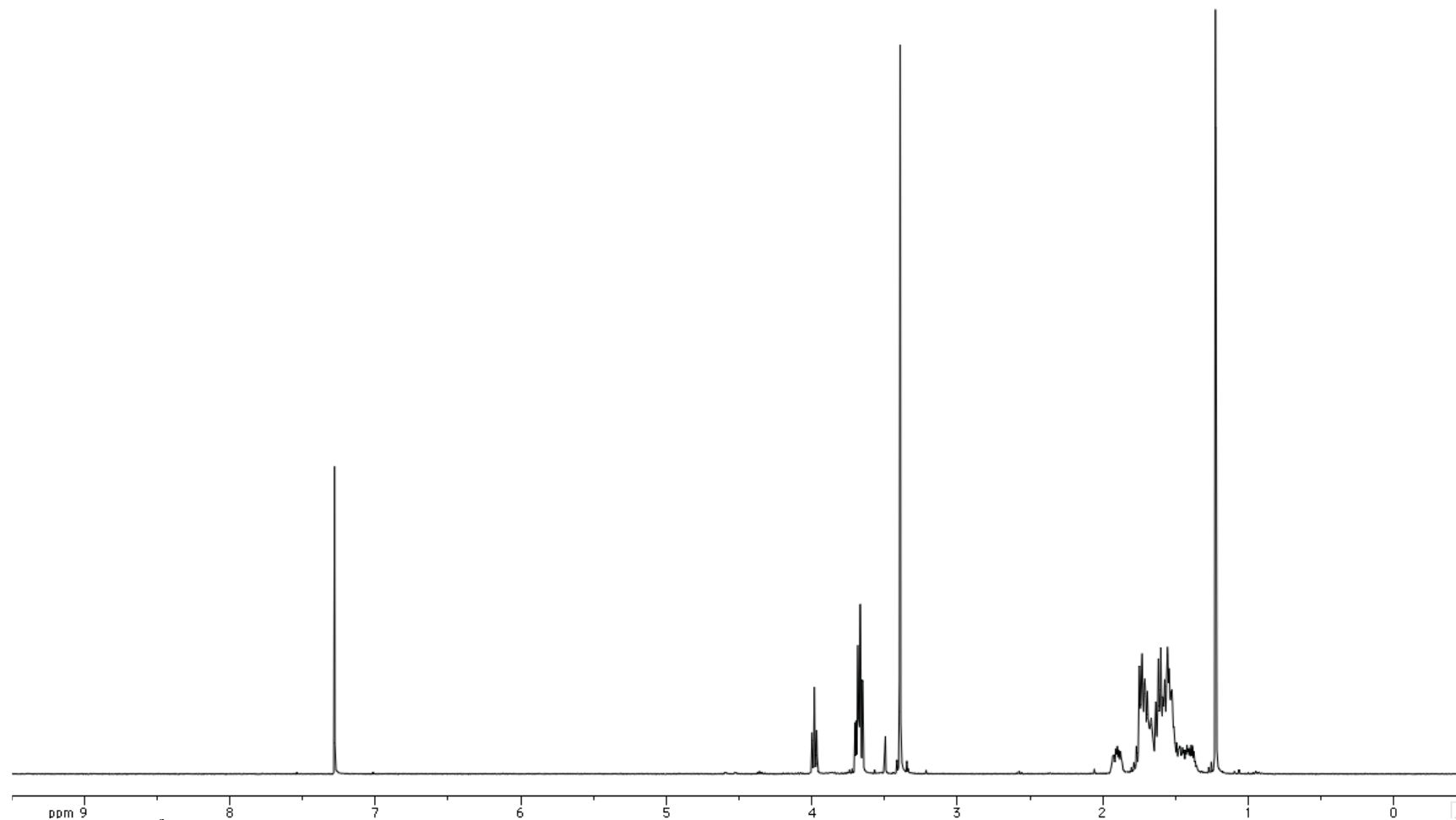
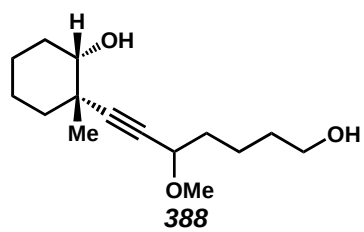
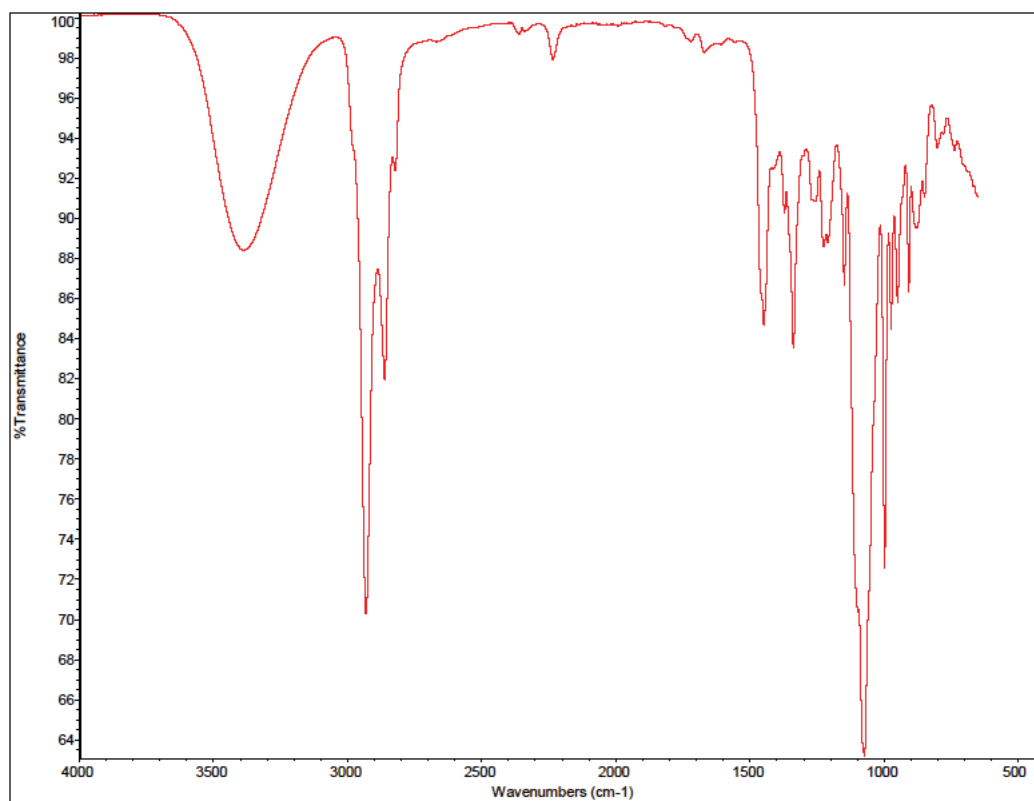
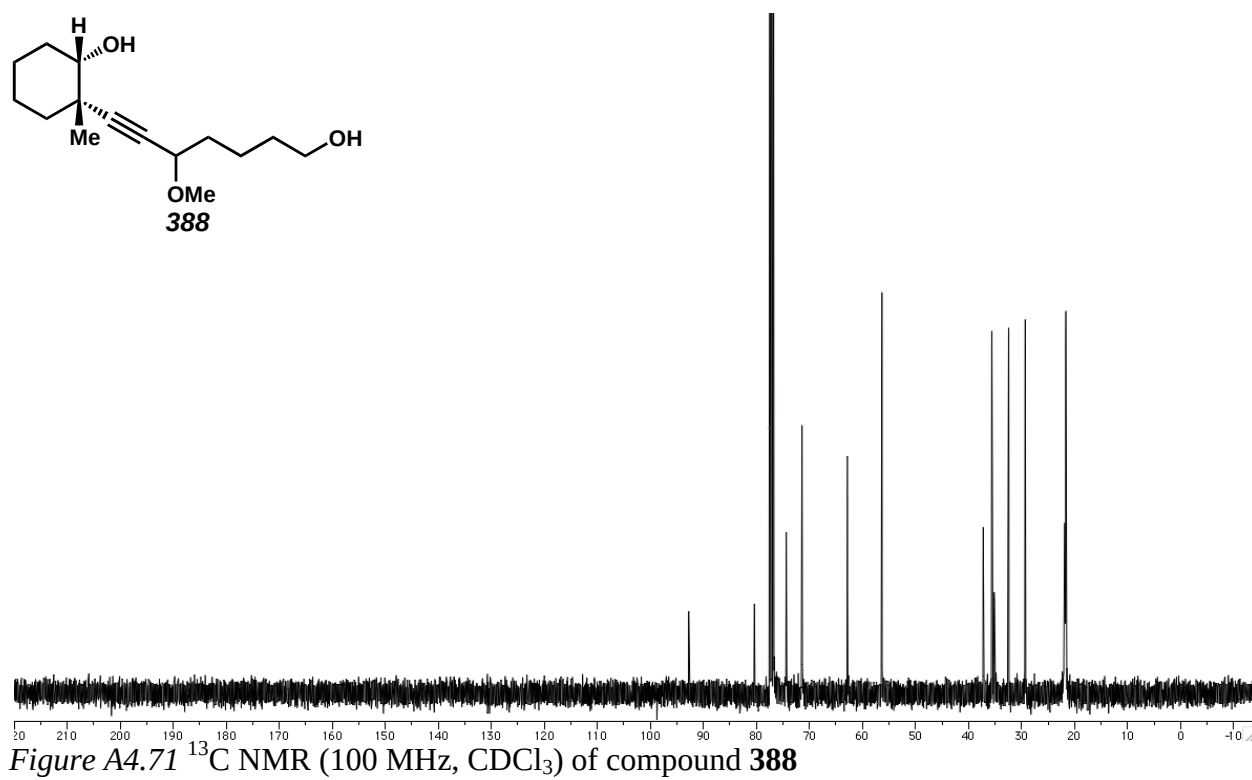
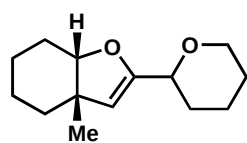


Figure A4.70 ¹H NMR (400 MHz, CDCl₃) of compound **388**





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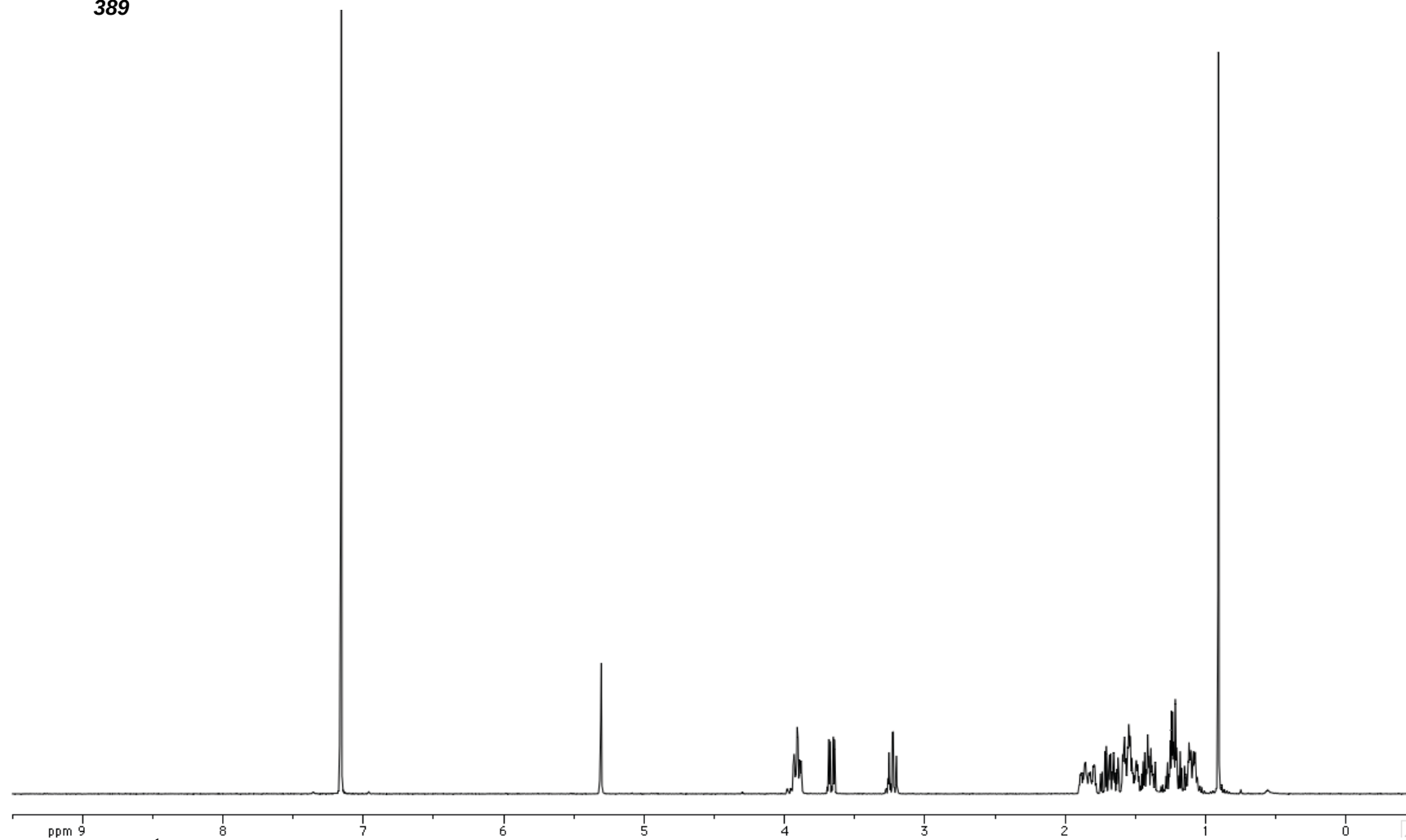


Figure A4.73 ^1H NMR (400 MHz, C_6D_6) of compound **389**

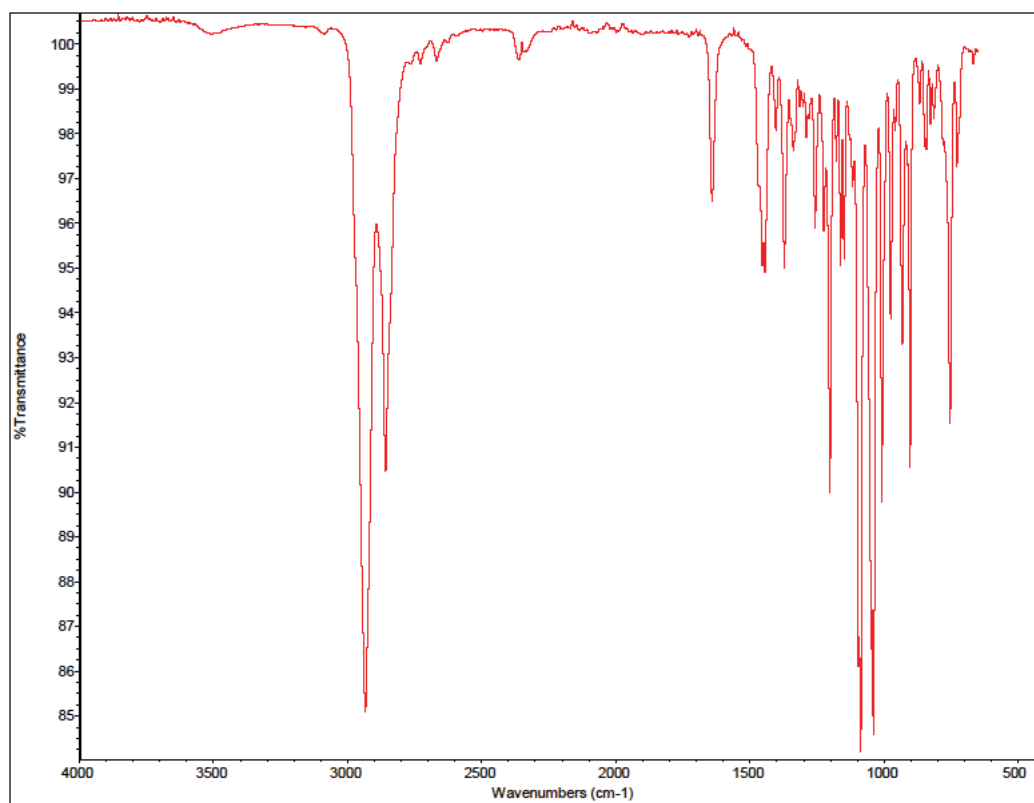
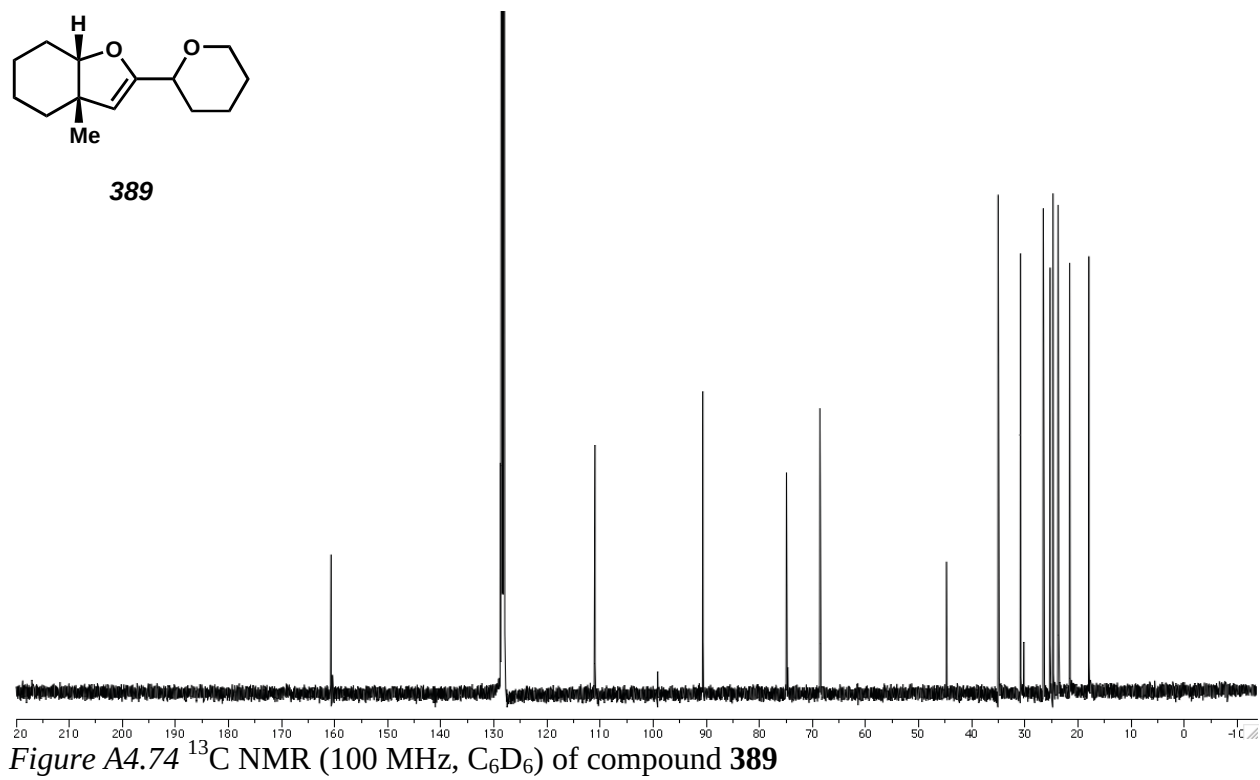


Figure A4.75 Infrared spectrum (thin film) of compound **389**

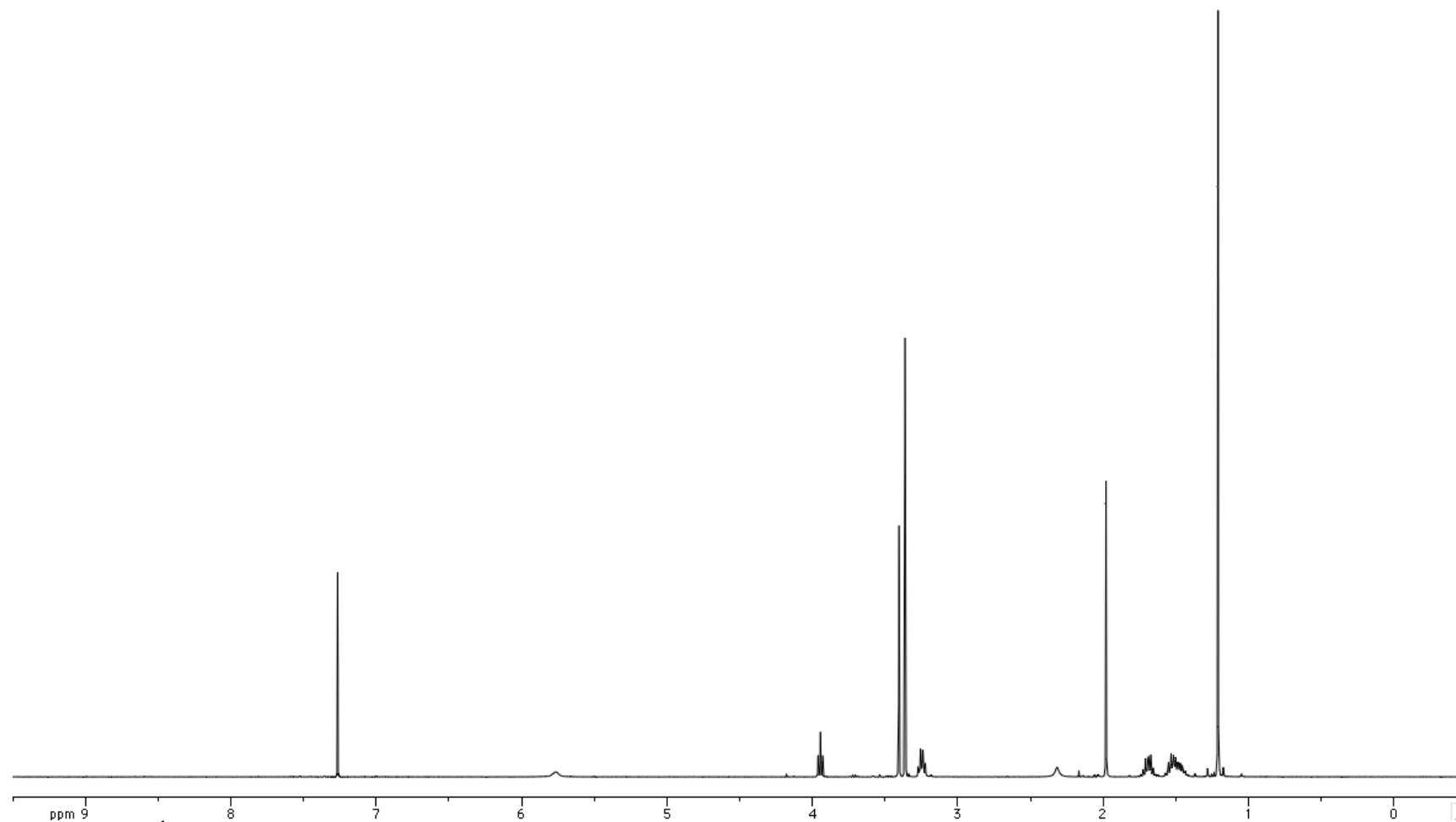
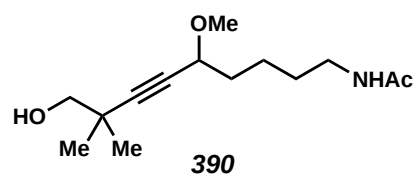


Figure A4.76 ¹H NMR (400 MHz, CDCl₃) of compound **390**

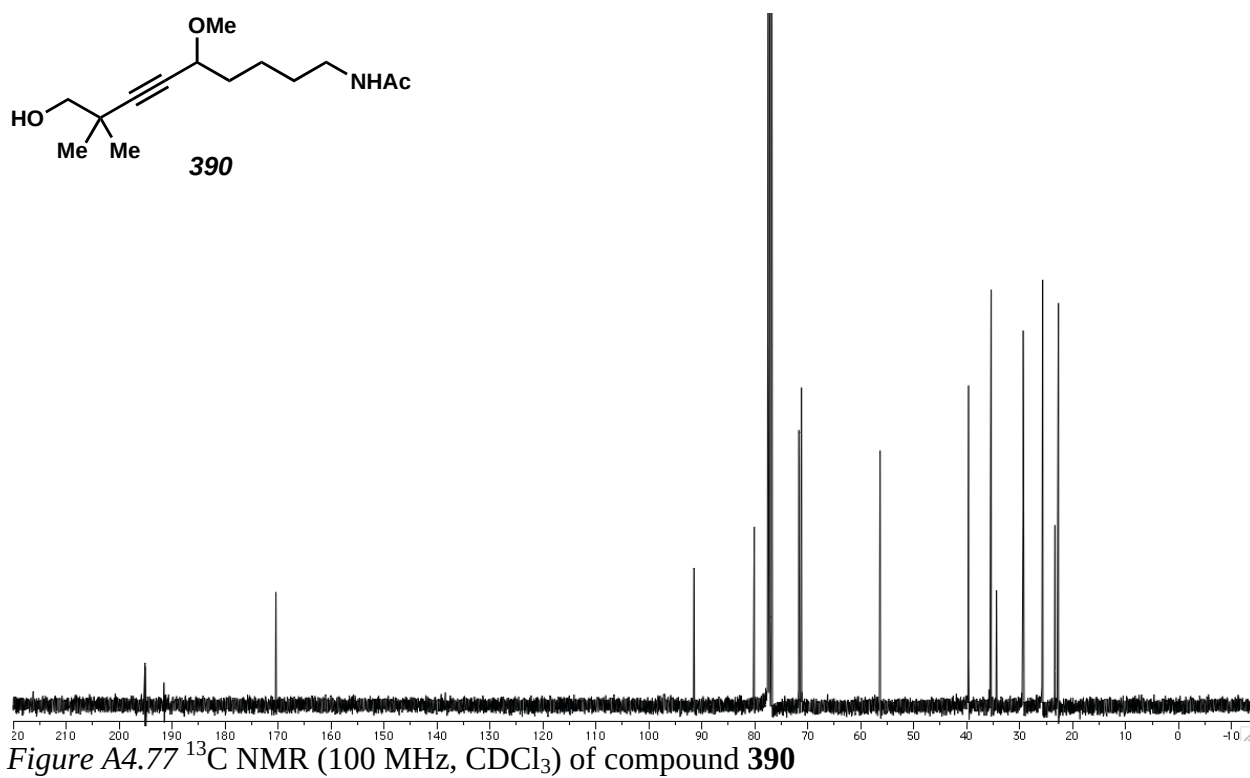


Figure A4.77 ¹³C NMR (100 MHz, CDCl₃) of compound **390**

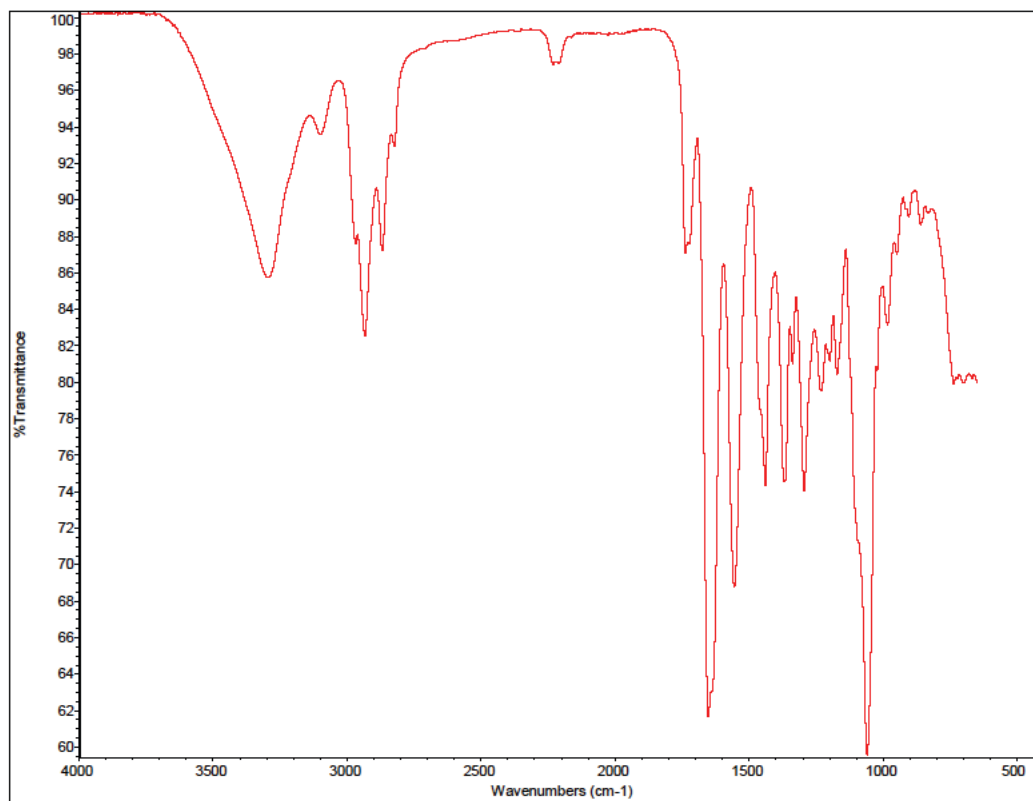


Figure A4.78 Infrared spectrum (thin film) of compound **390**

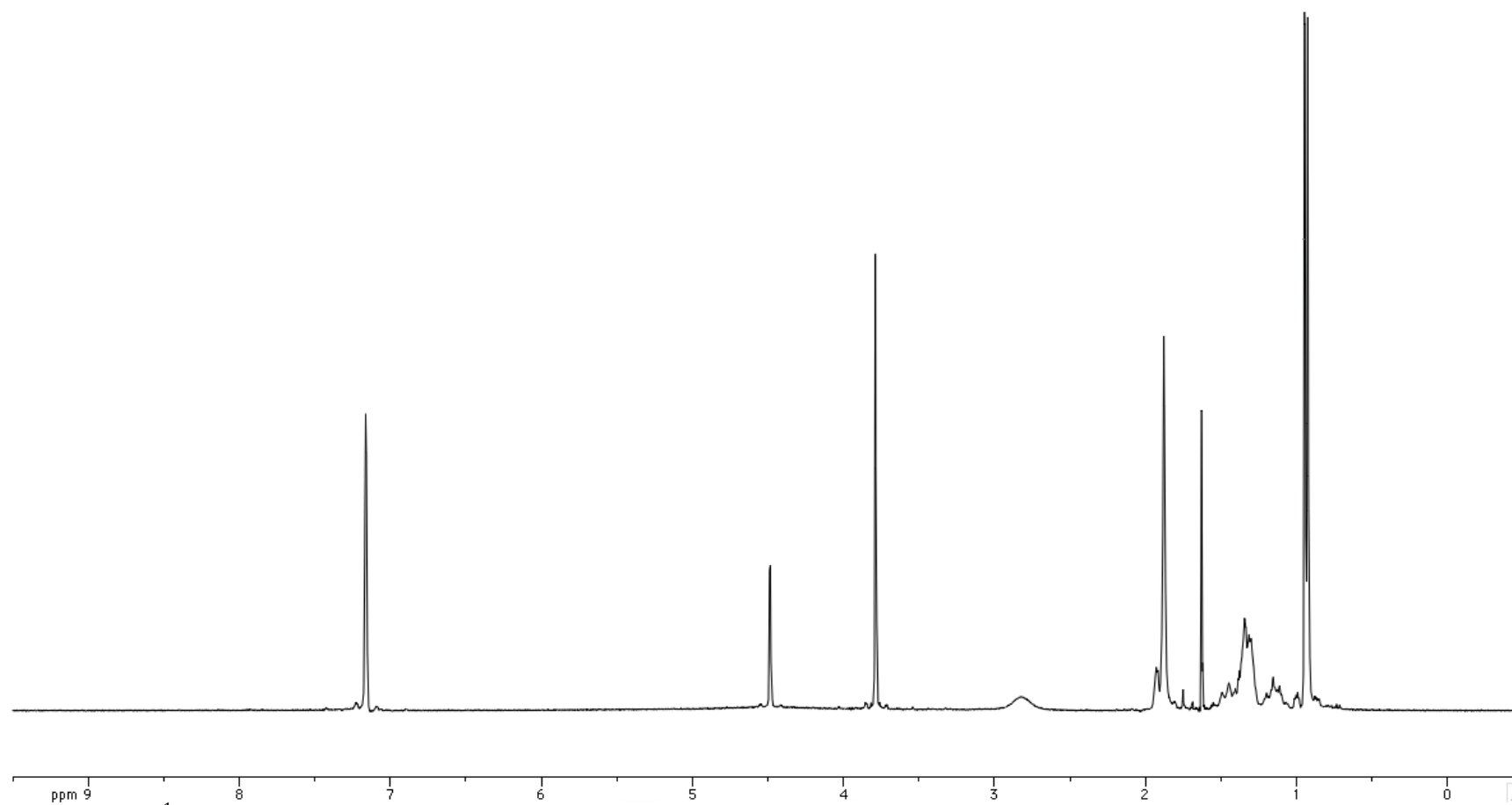
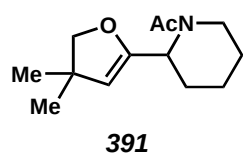
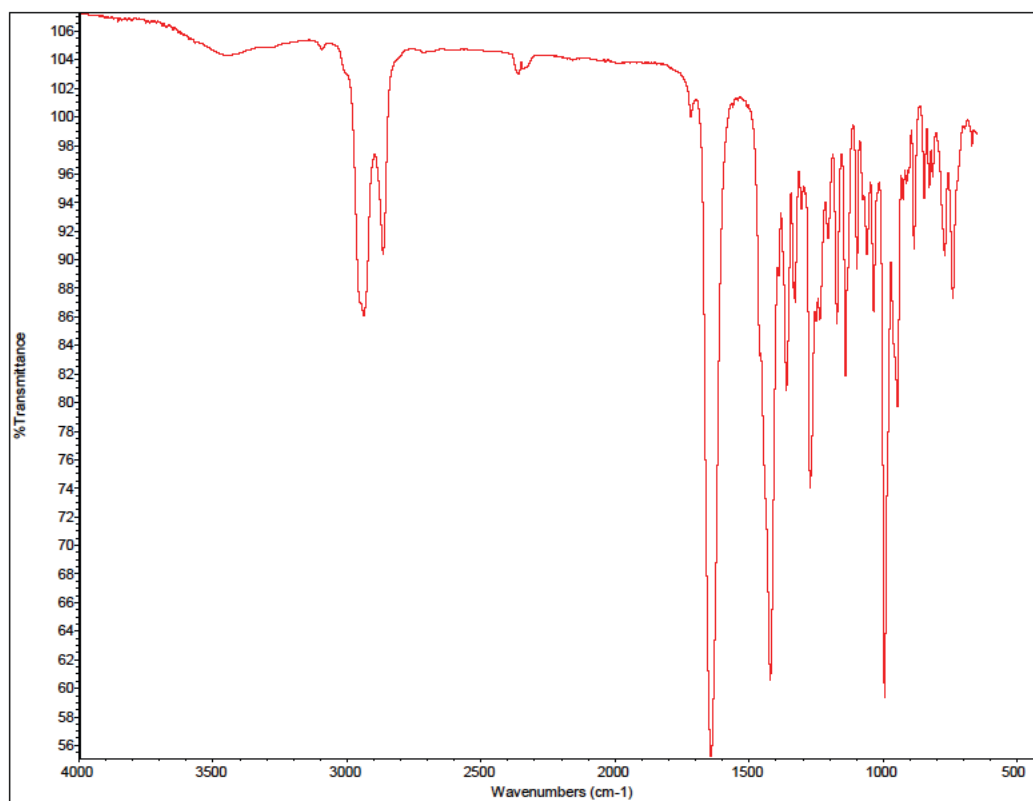
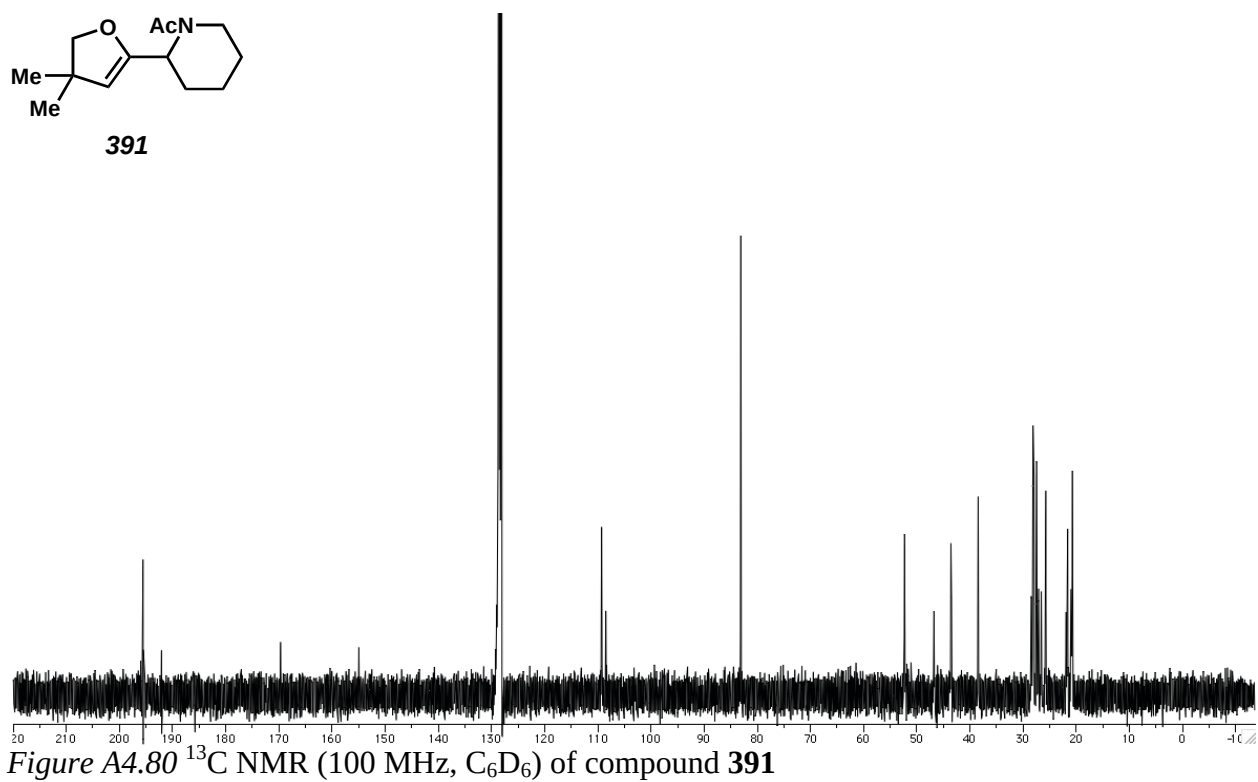


Figure A4.79 ^1H NMR (400 MHz, C_6D_6) of compound **391**



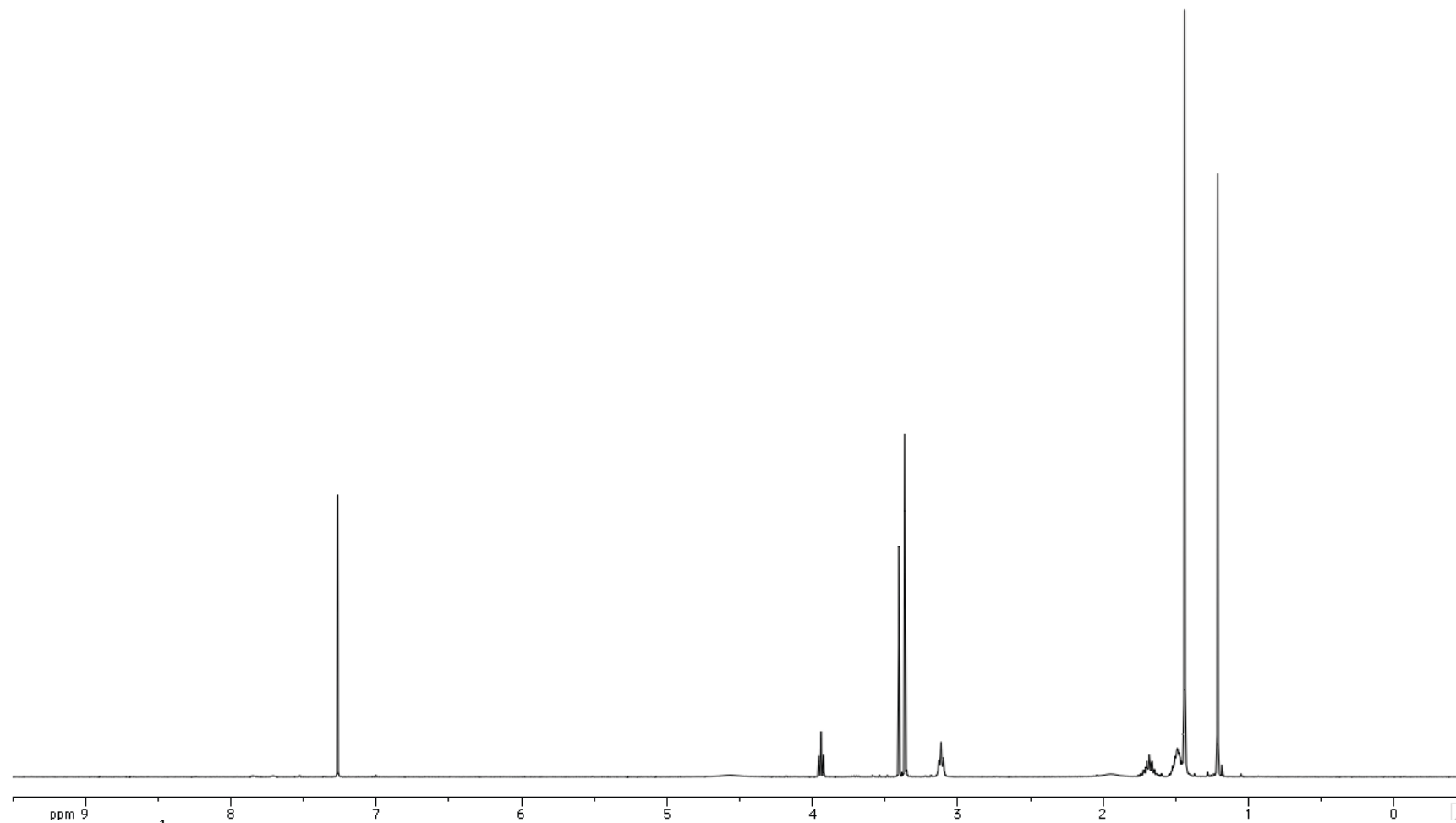
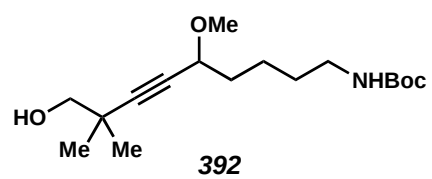


Figure A4.82 ^1H NMR (400 MHz, CDCl_3) of compound **392**

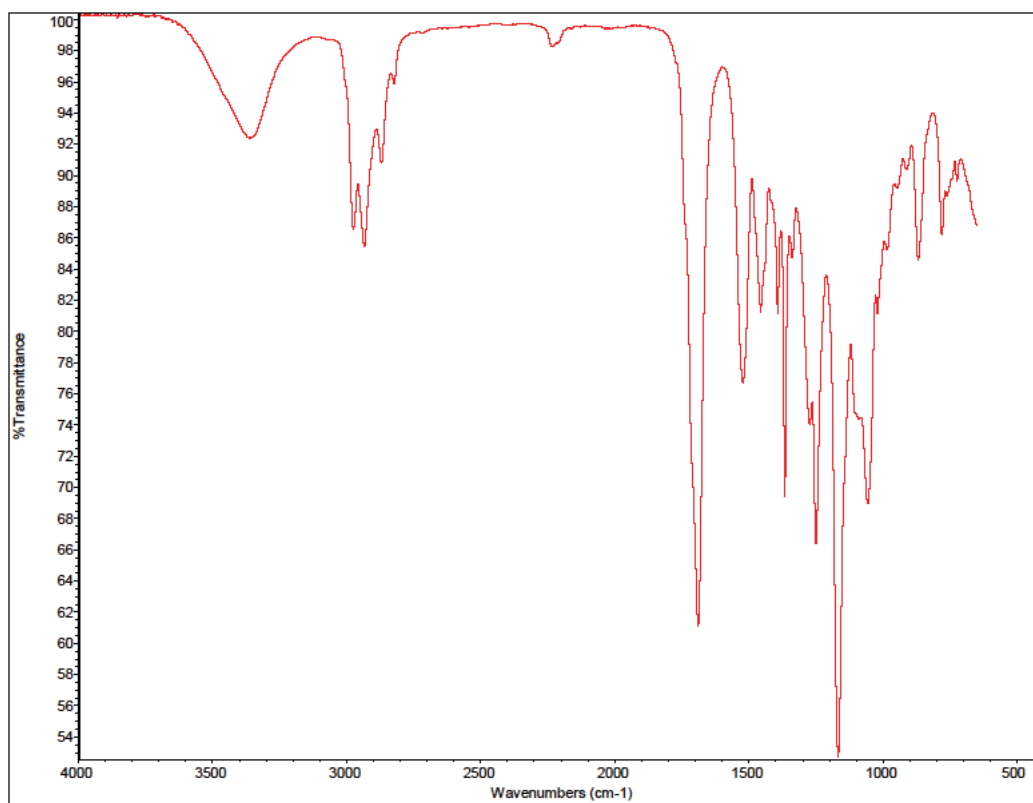
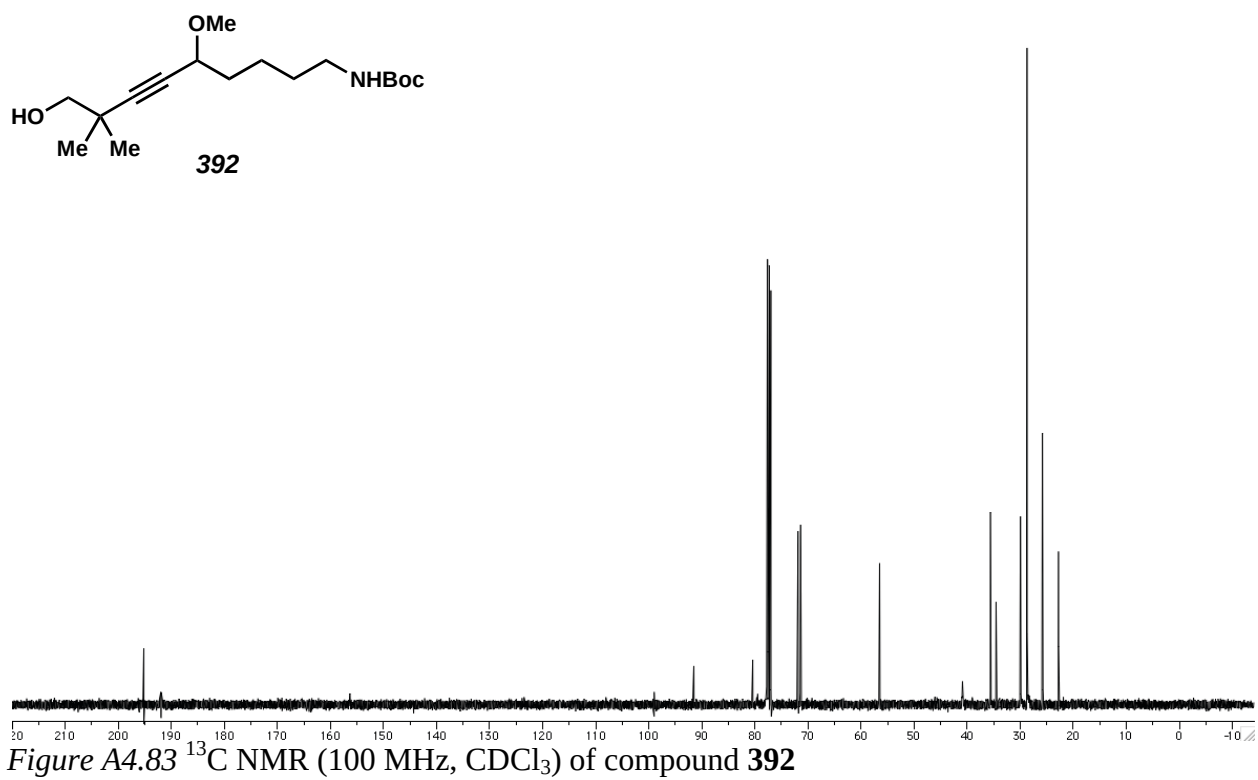


Figure A4.84 Infrared spectrum (thin film) of compound **392**

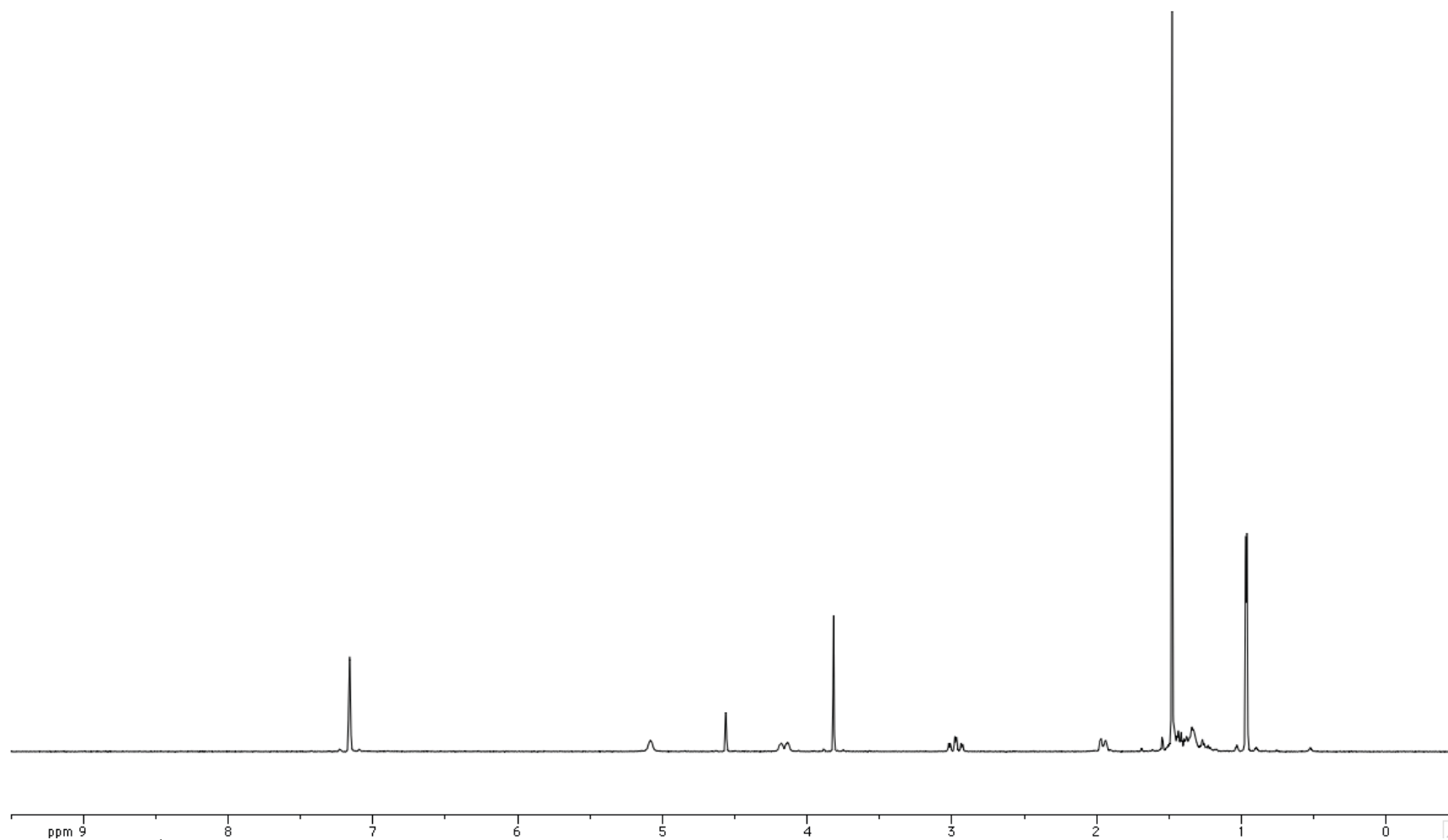
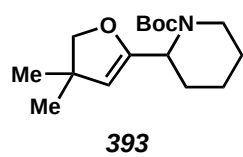


Figure A4.85 ^1H NMR (400 MHz, C_6D_6) of compound **393**

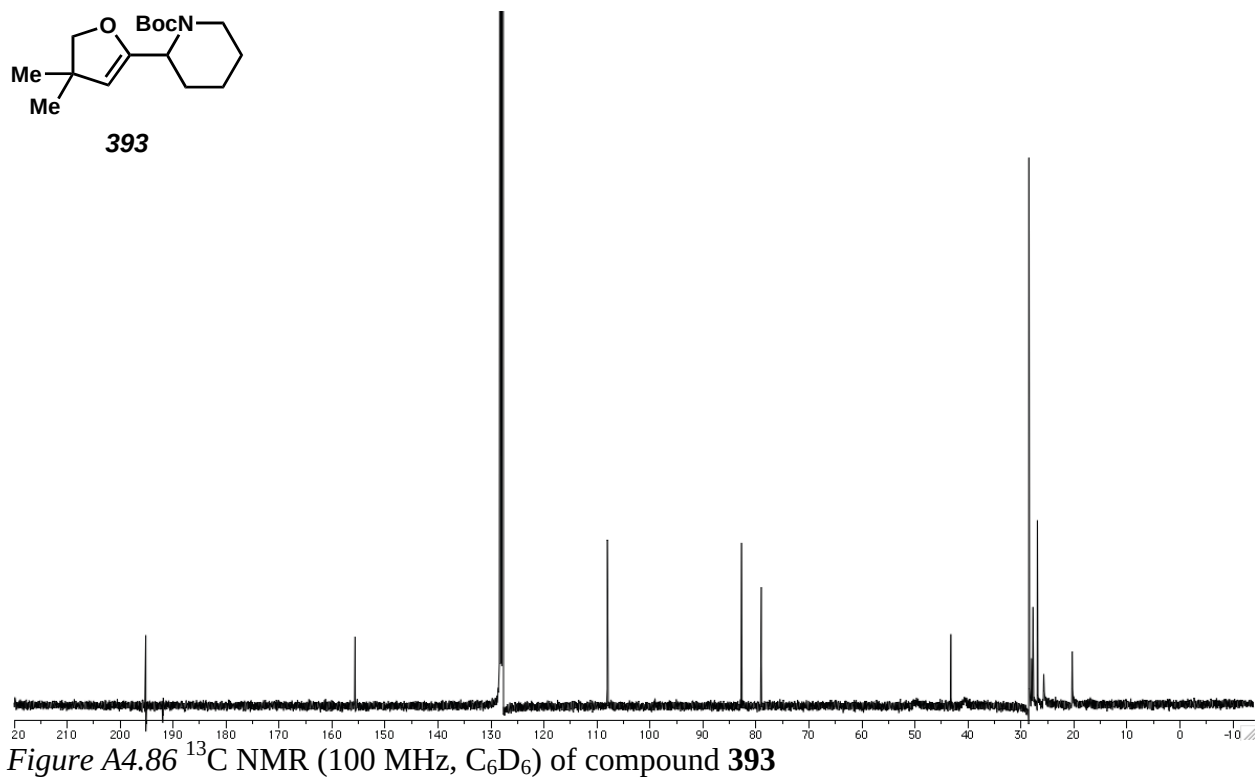


Figure A4.86 ^{13}C NMR (100 MHz, C_6D_6) of compound **393**

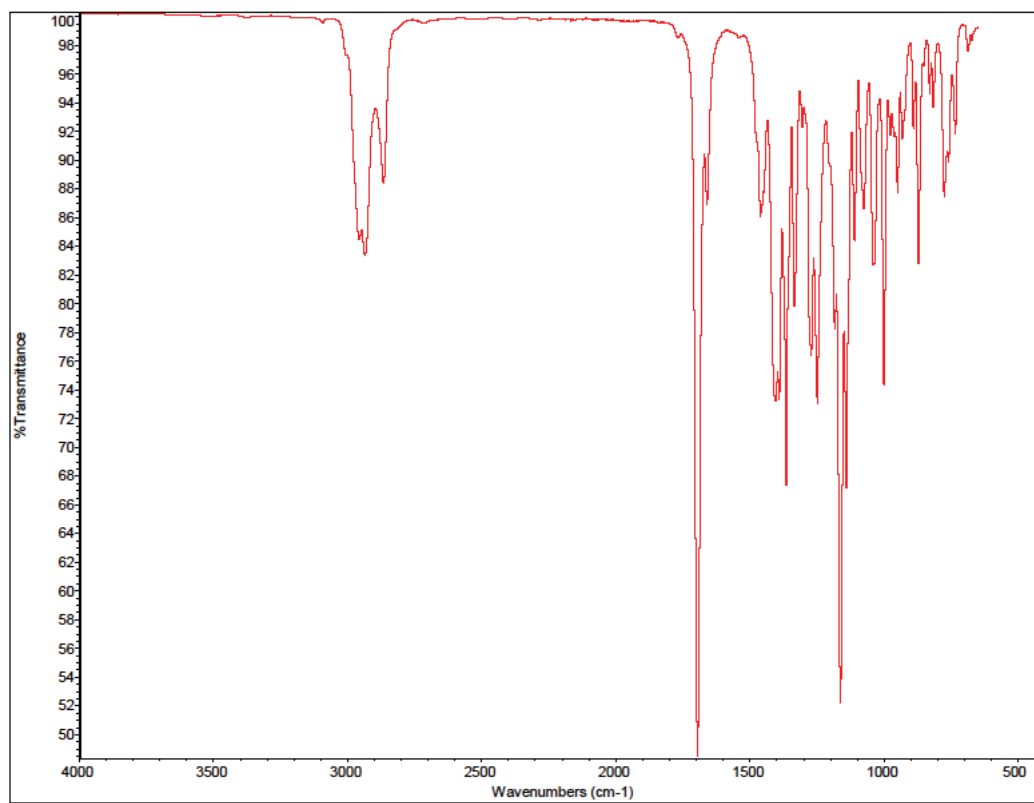


Figure A4.87 Infrared spectrum (thin film) of compound **393**

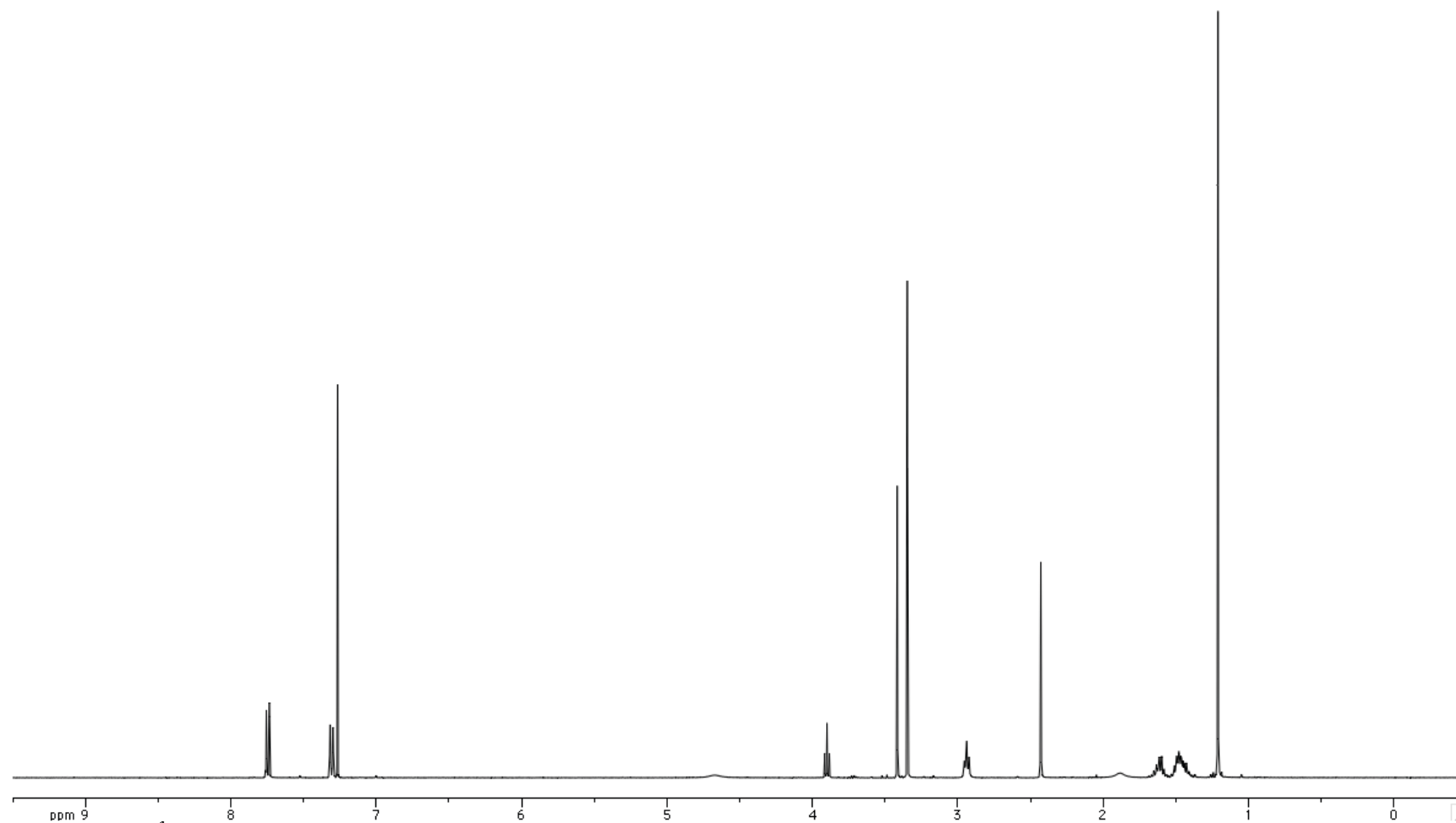
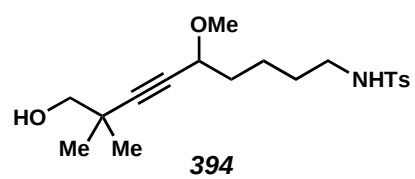


Figure A4.88 ¹H NMR (400 MHz, CDCl₃) of compound **394**

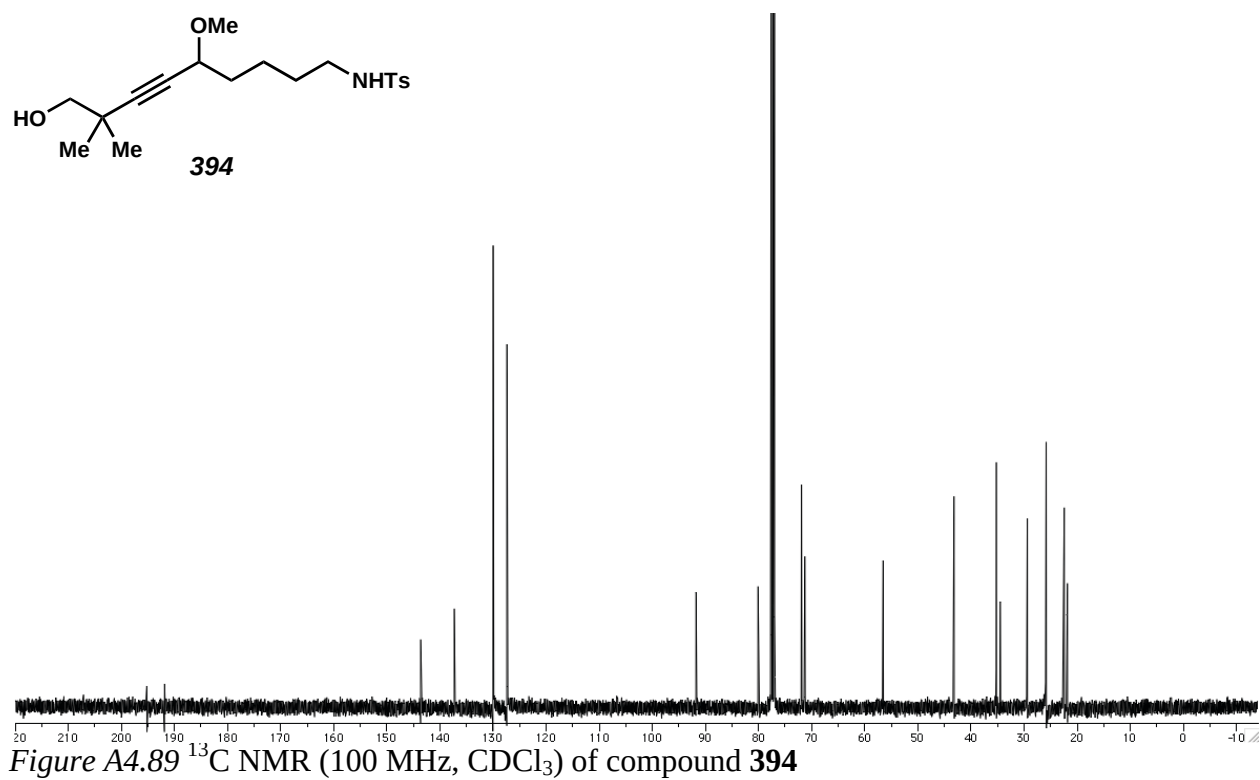


Figure A4.89 ^{13}C NMR (100 MHz, CDCl_3) of compound **394**

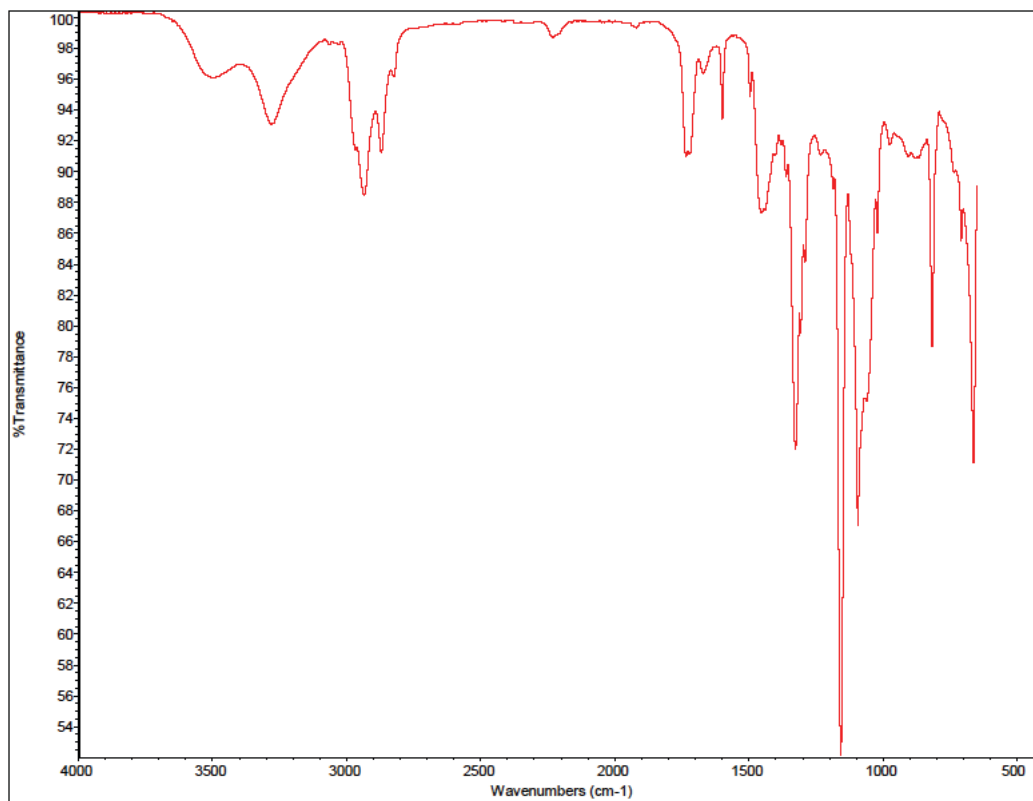
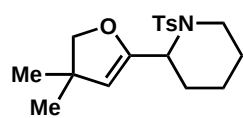


Figure A4.90 Infrared spectrum (thin film) of compound **394**



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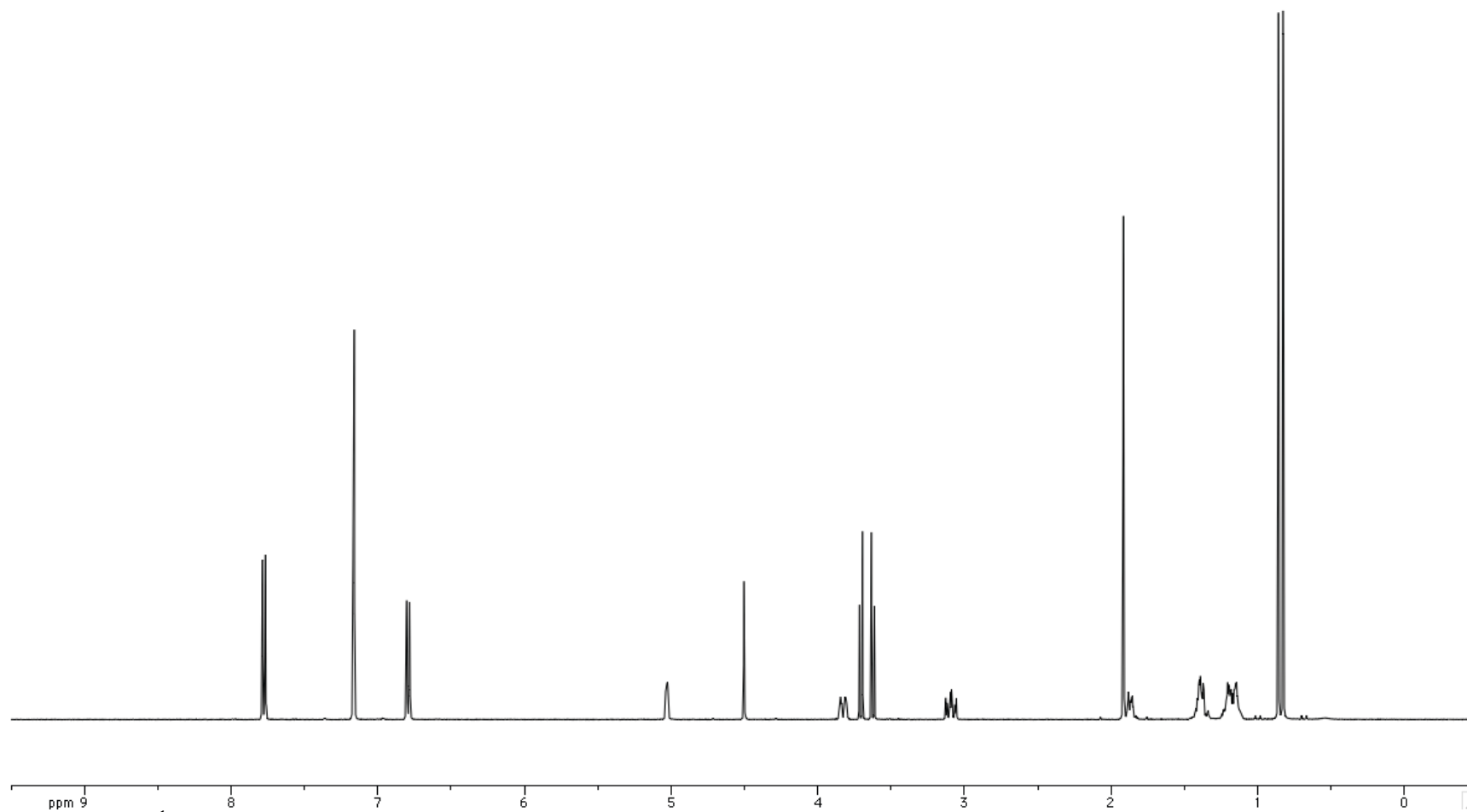
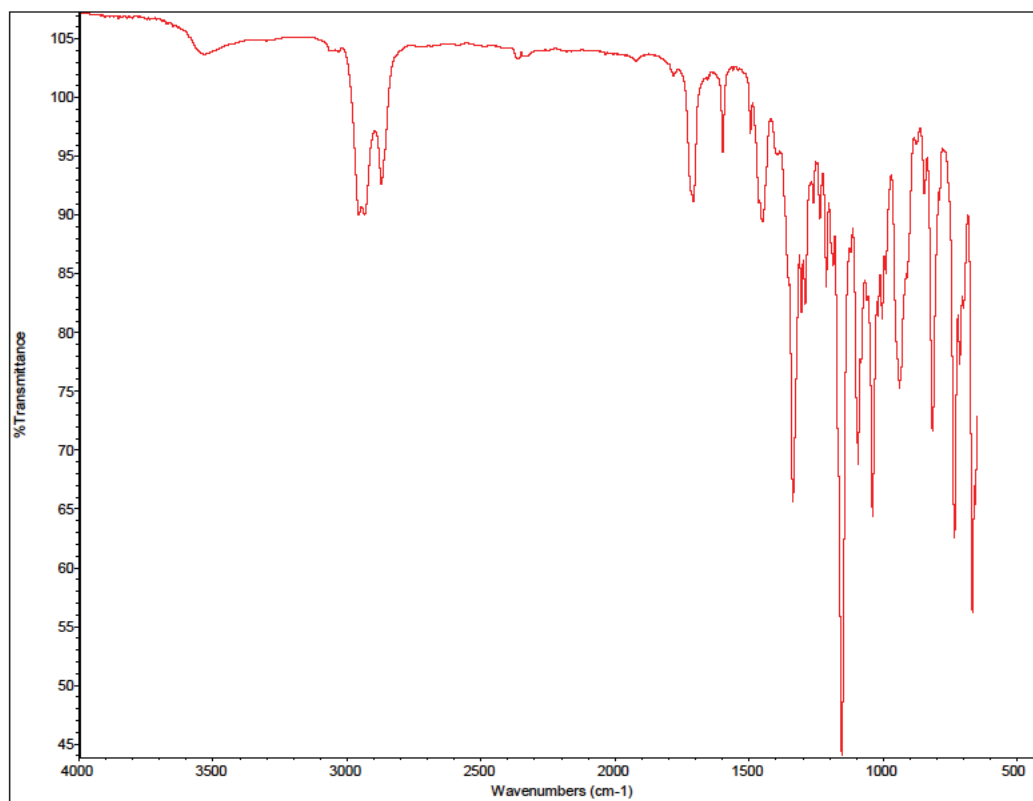
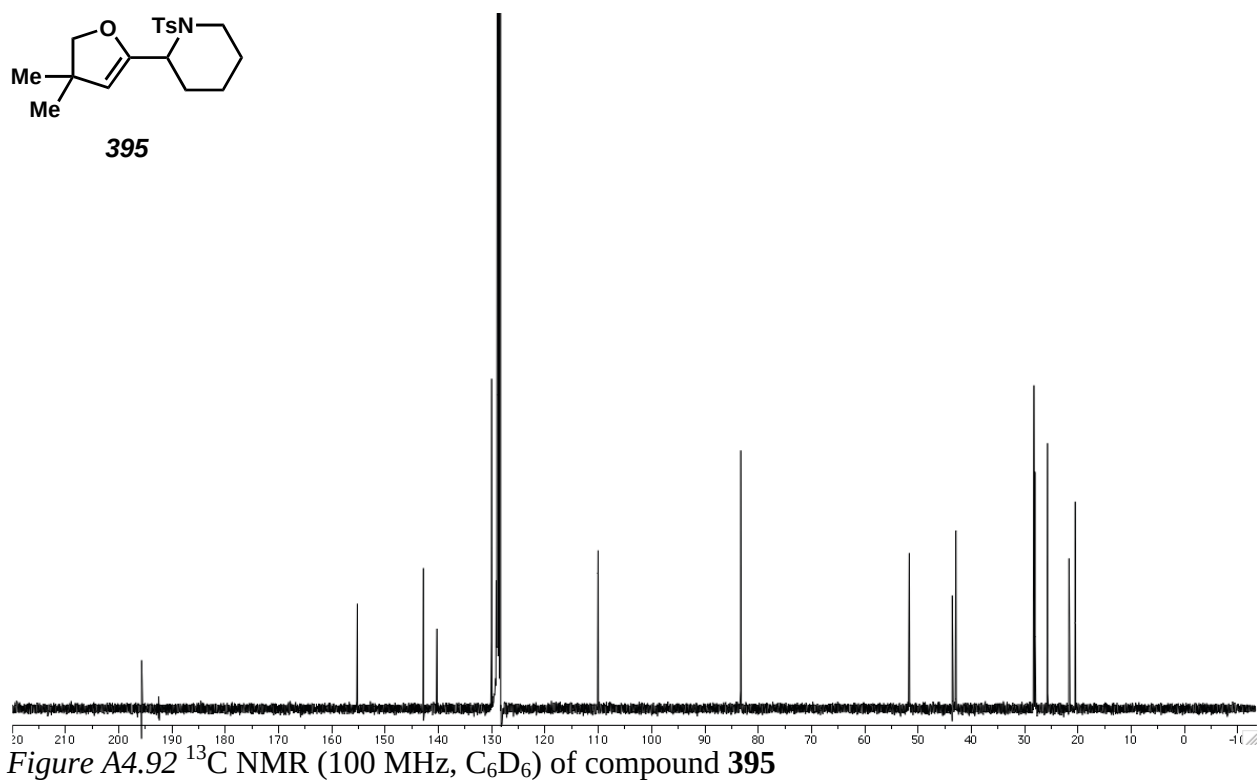


Figure A4.91 ^1H NMR (400 MHz, C_6D_6) of compound **395**



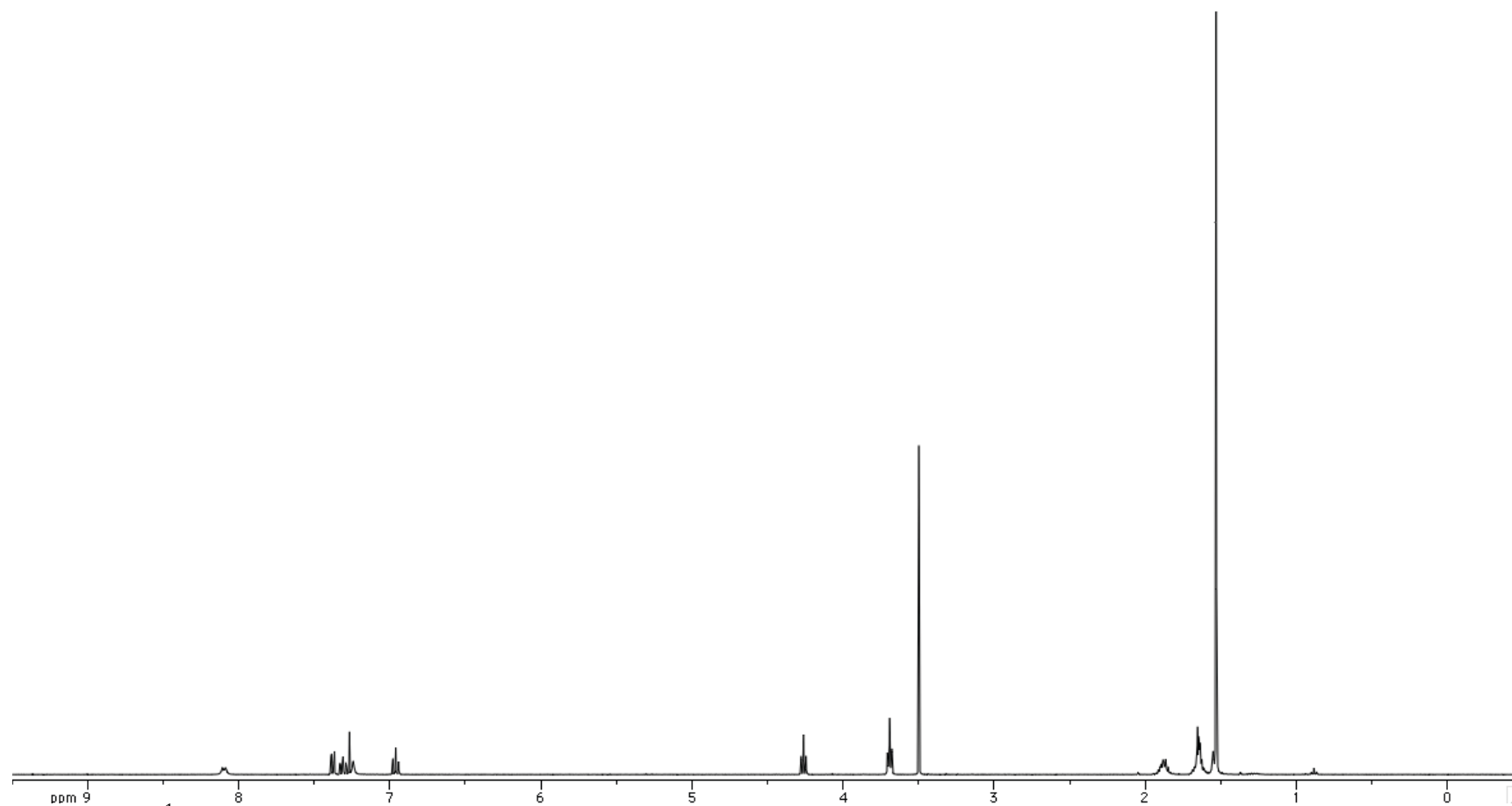
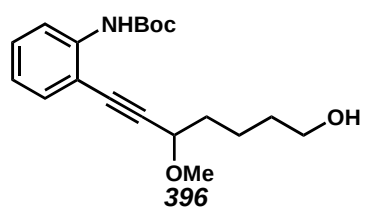


Figure A4.94 ^1H NMR (400 MHz, CDCl_3) of compound **396**

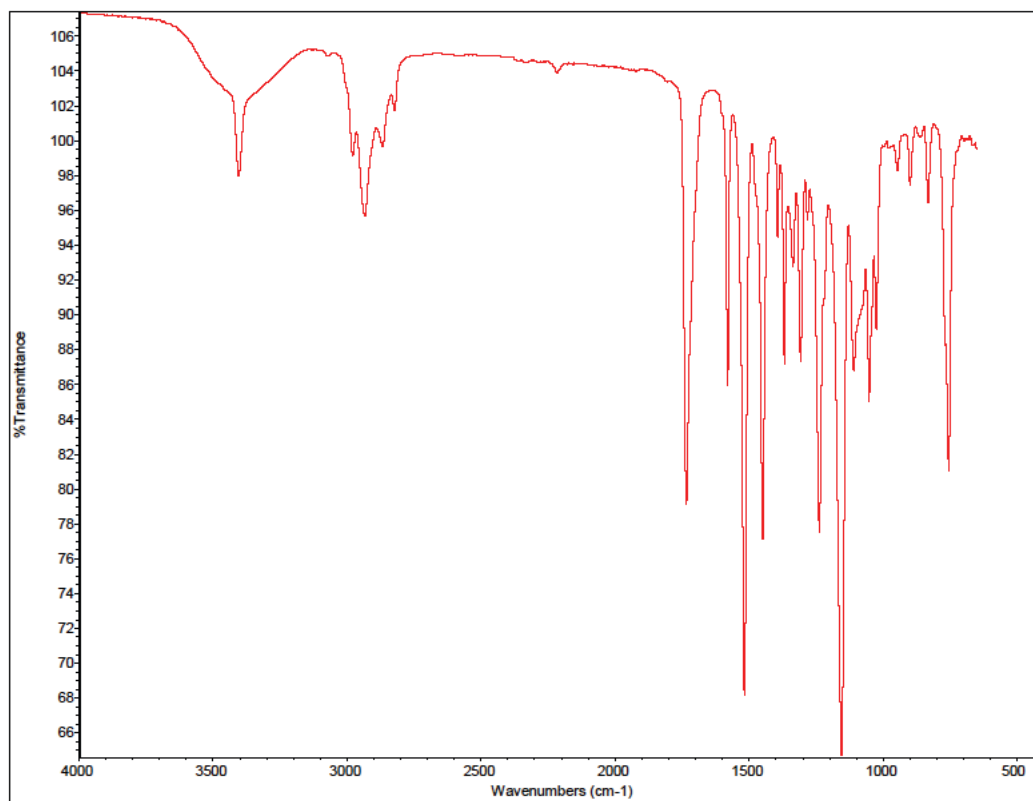
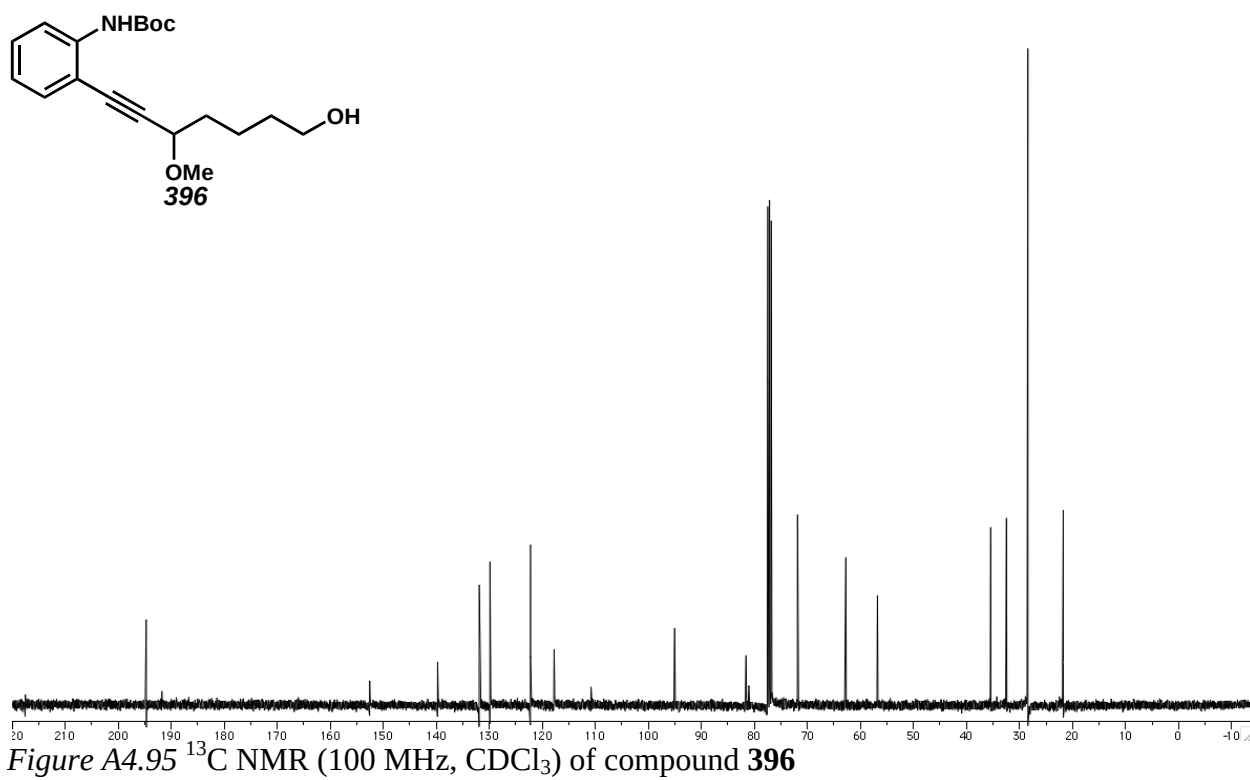
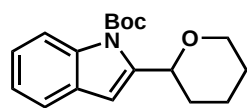


Figure A4.96 Infrared spectrum (thin film) of compound **396**



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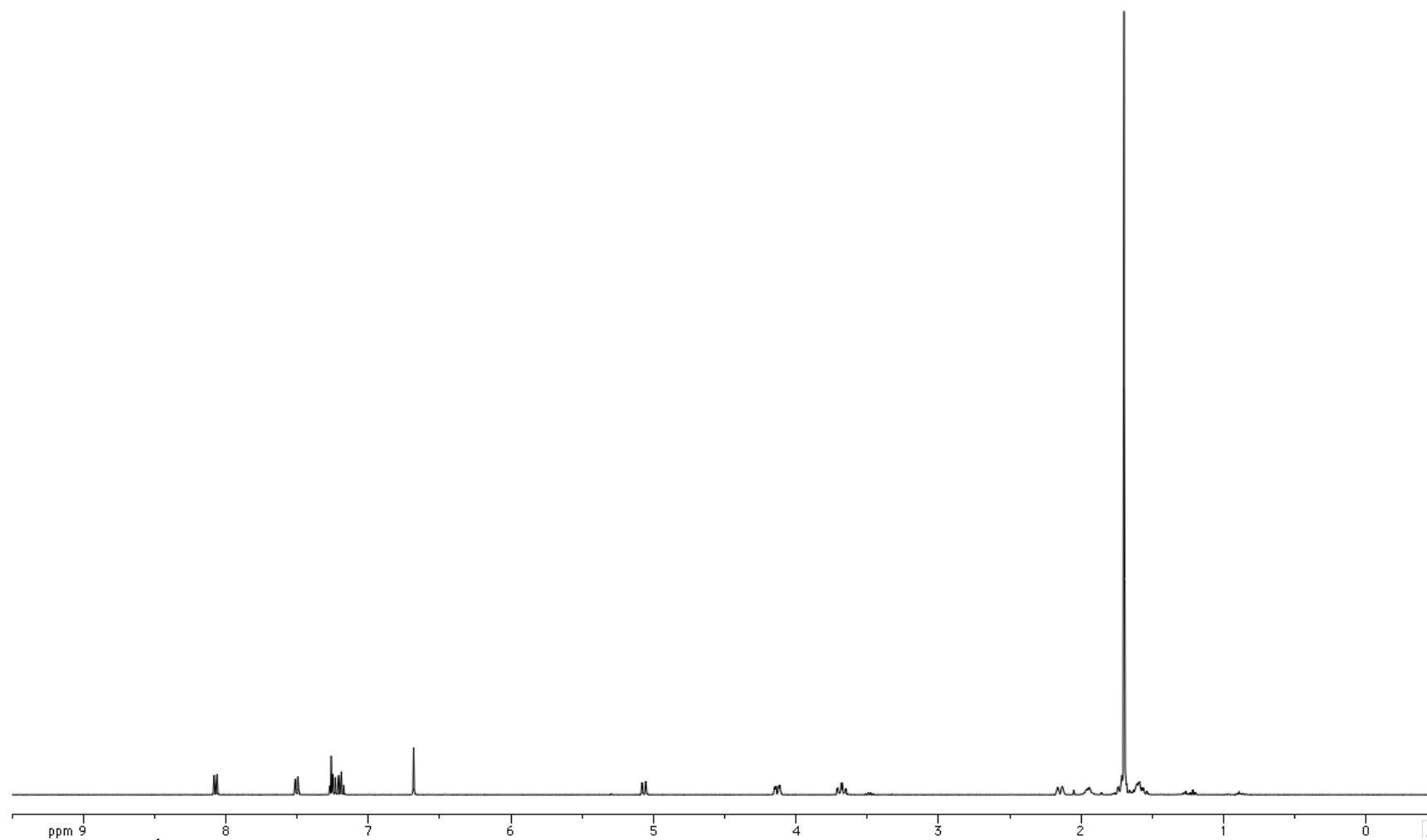
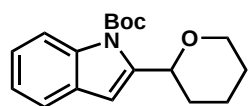


Figure A4.97 ^1H NMR (400 MHz, CDCl_3) of compound **397**



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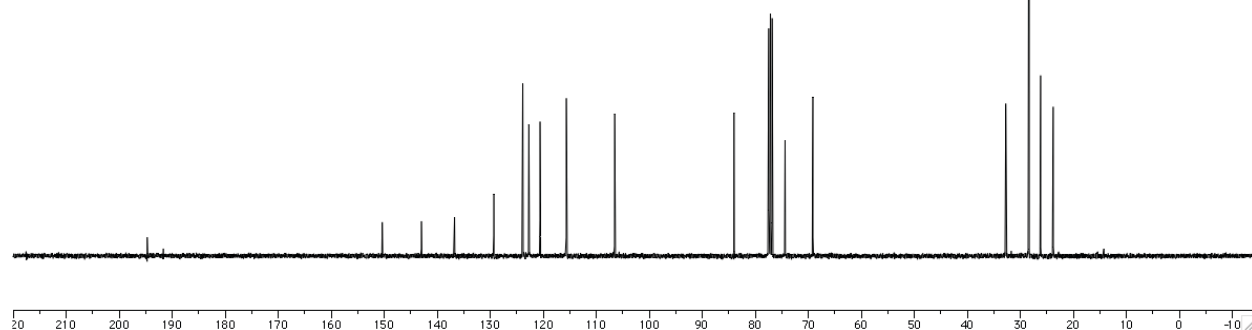


Figure A4.98 ^{13}C NMR (100 MHz, CDCl_3) of compound **397**

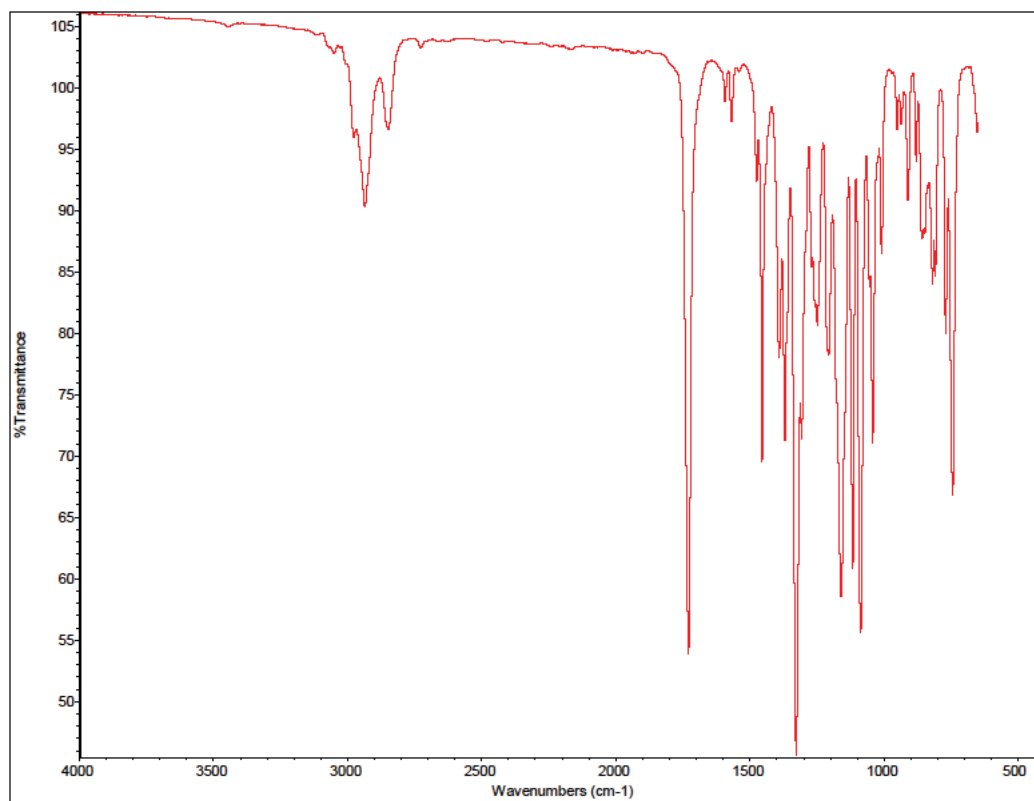


Figure A4.99 Infrared spectrum (thin film) of compound **397**

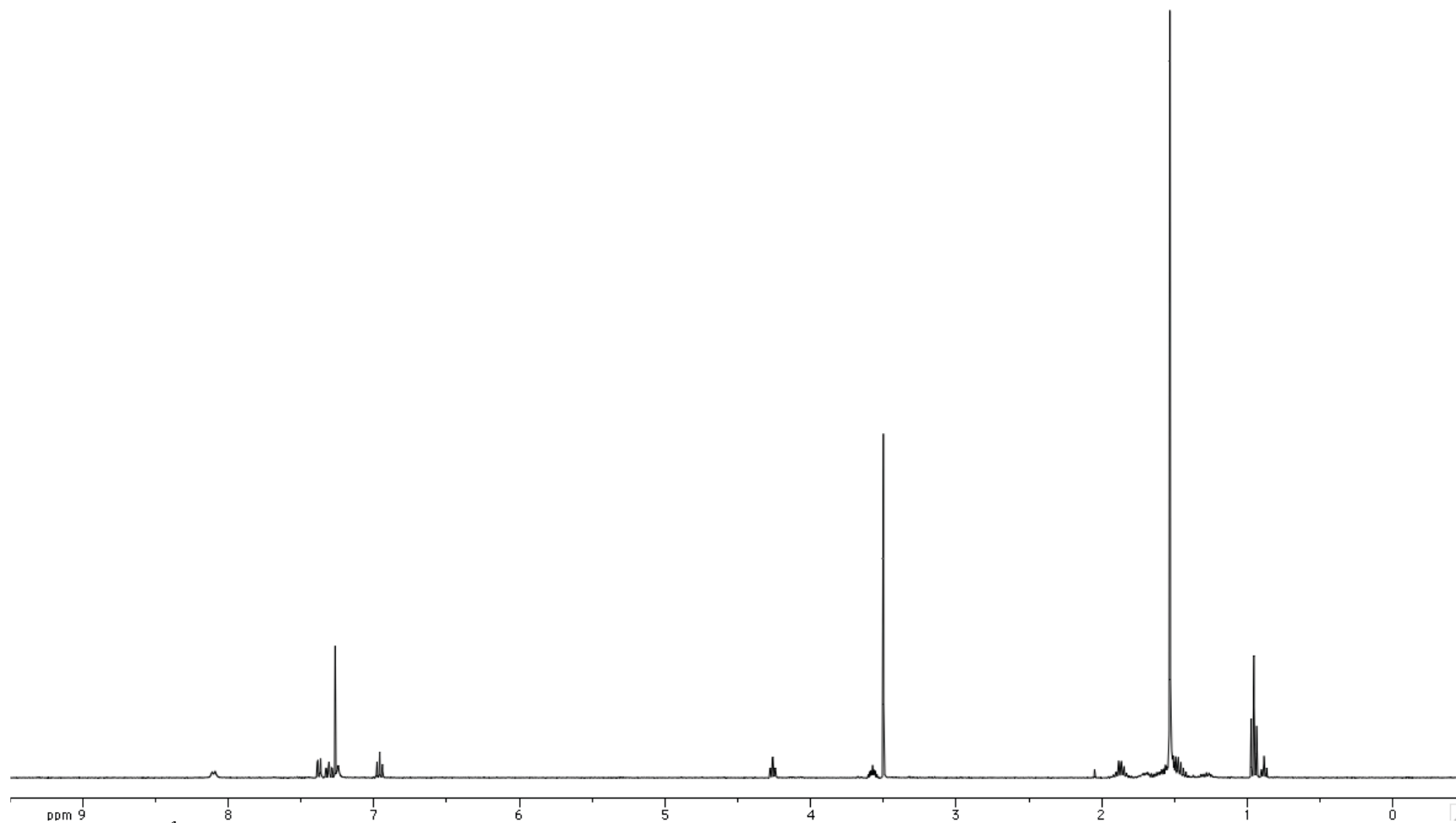
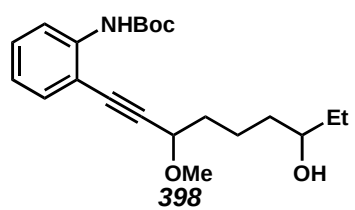
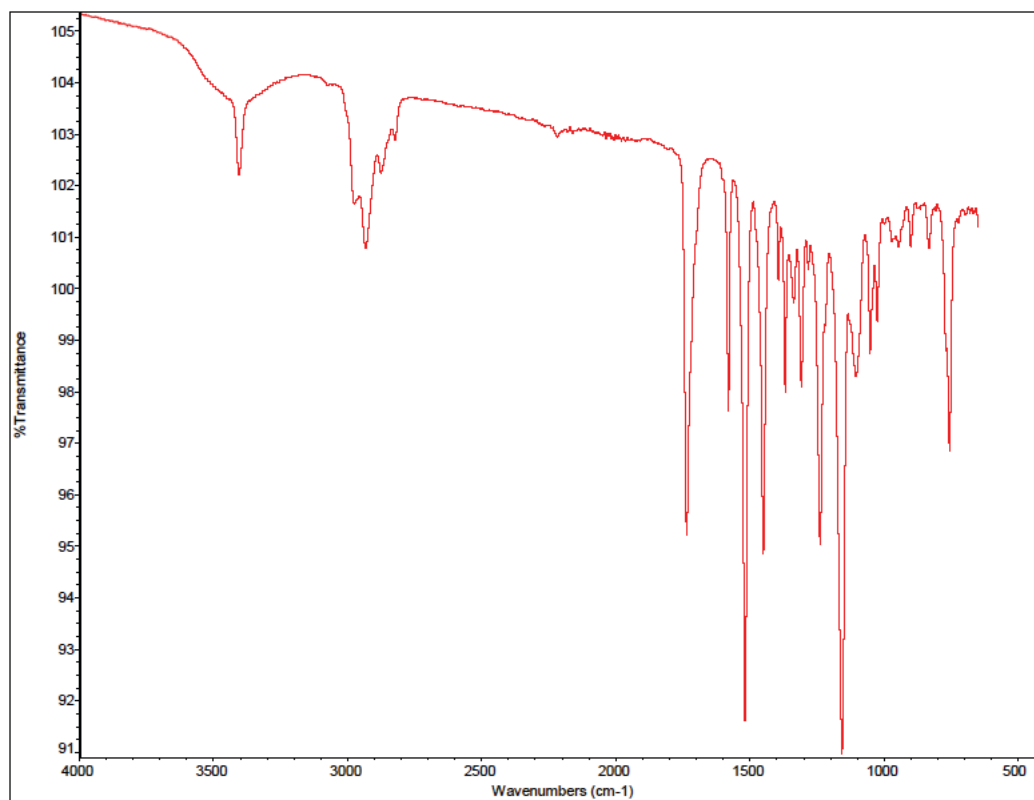
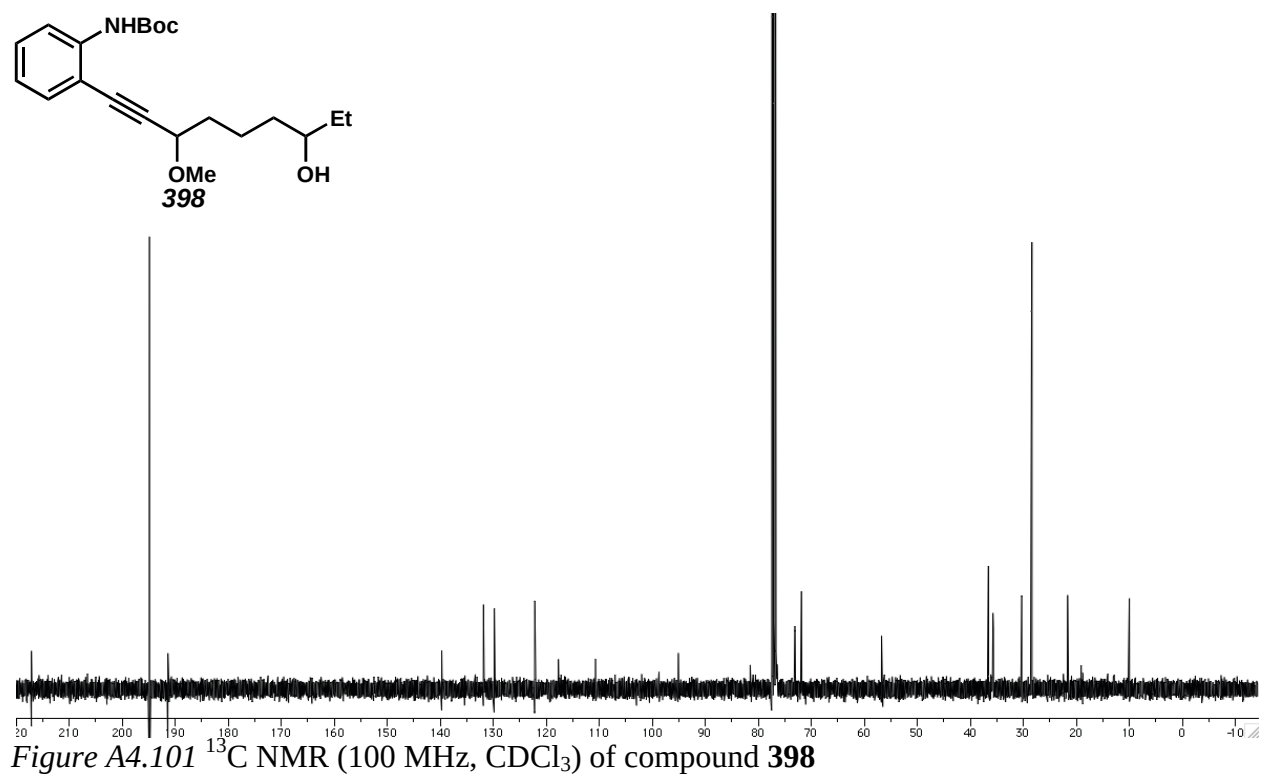


Figure A4.100 ^1H NMR (400 MHz, CDCl_3) of compound **398**



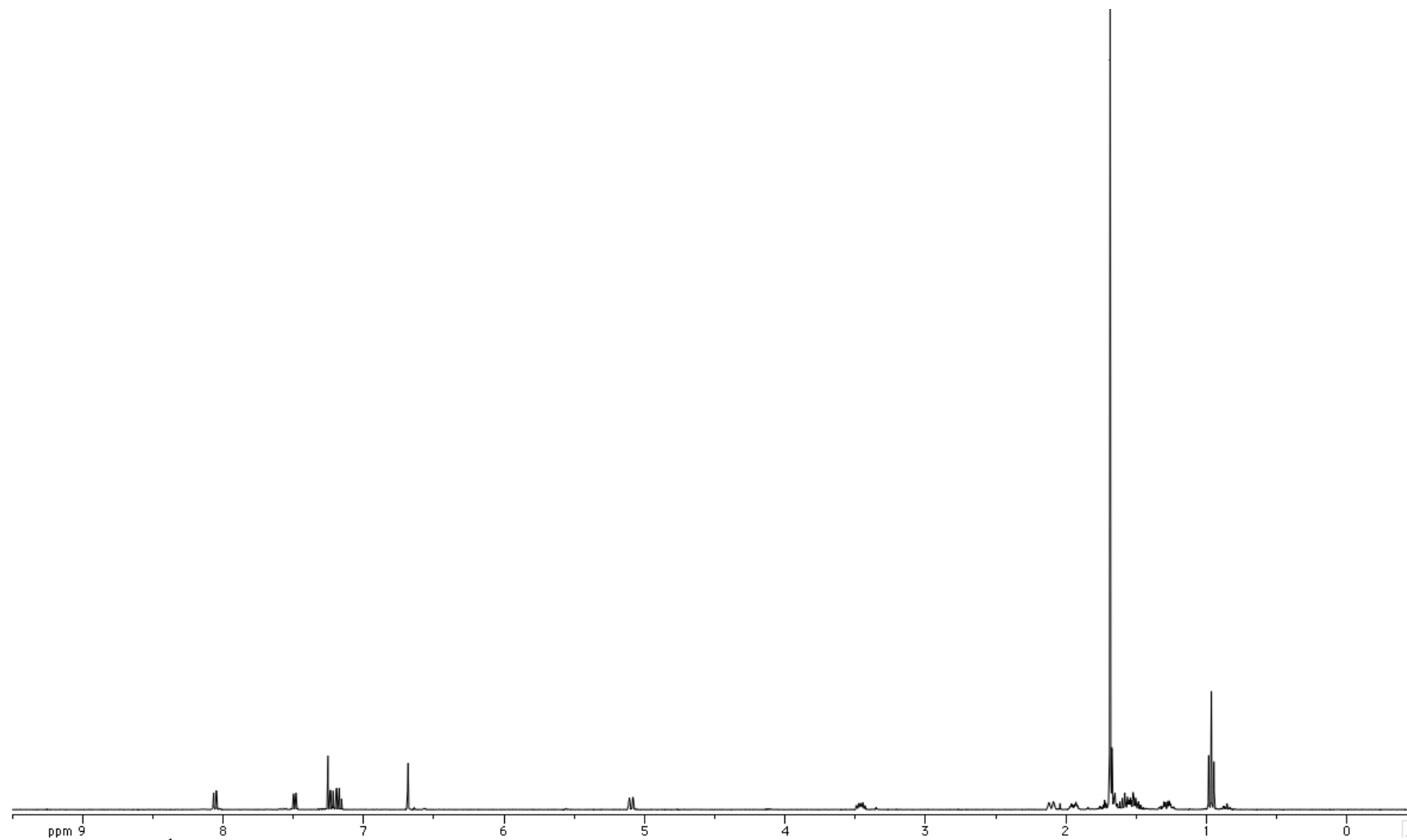
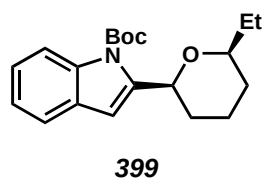


Figure A4.103 ^1H NMR (400 MHz, CDCl_3) of compound **399**

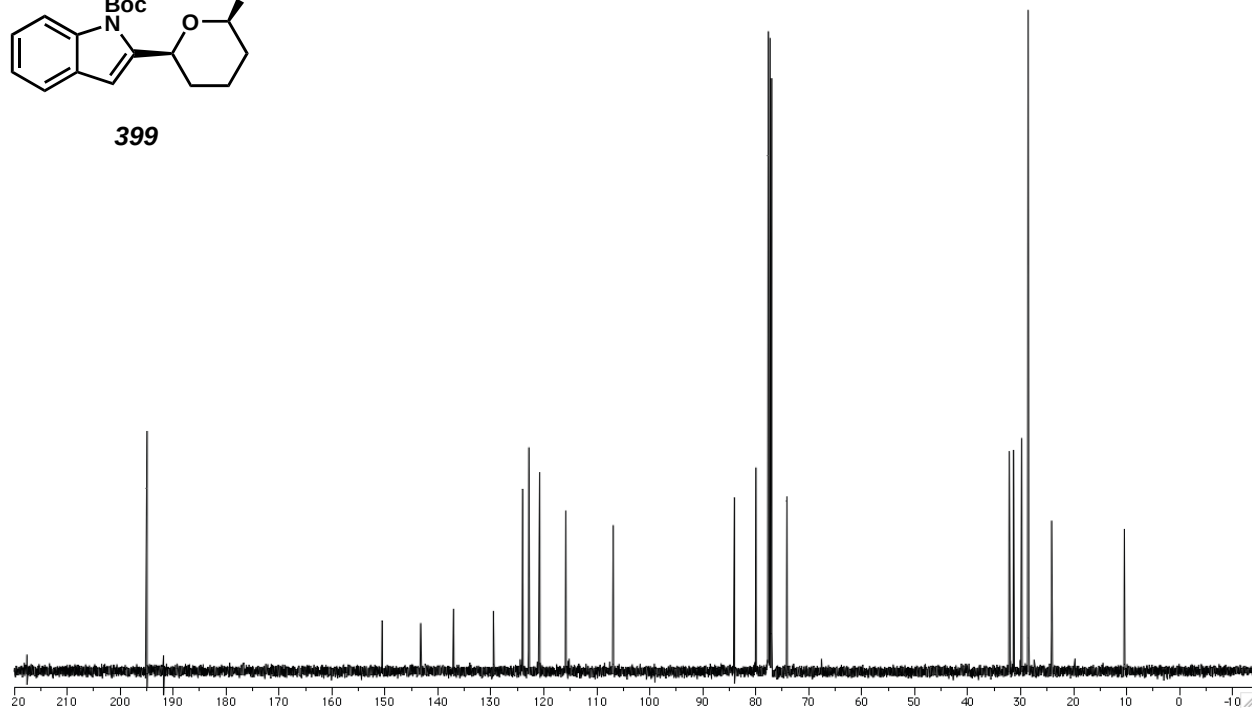
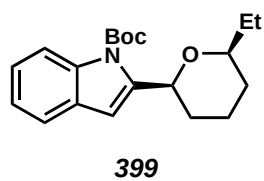


Figure A4.104 ^{13}C NMR (100 MHz, CDCl_3) of compound **399**

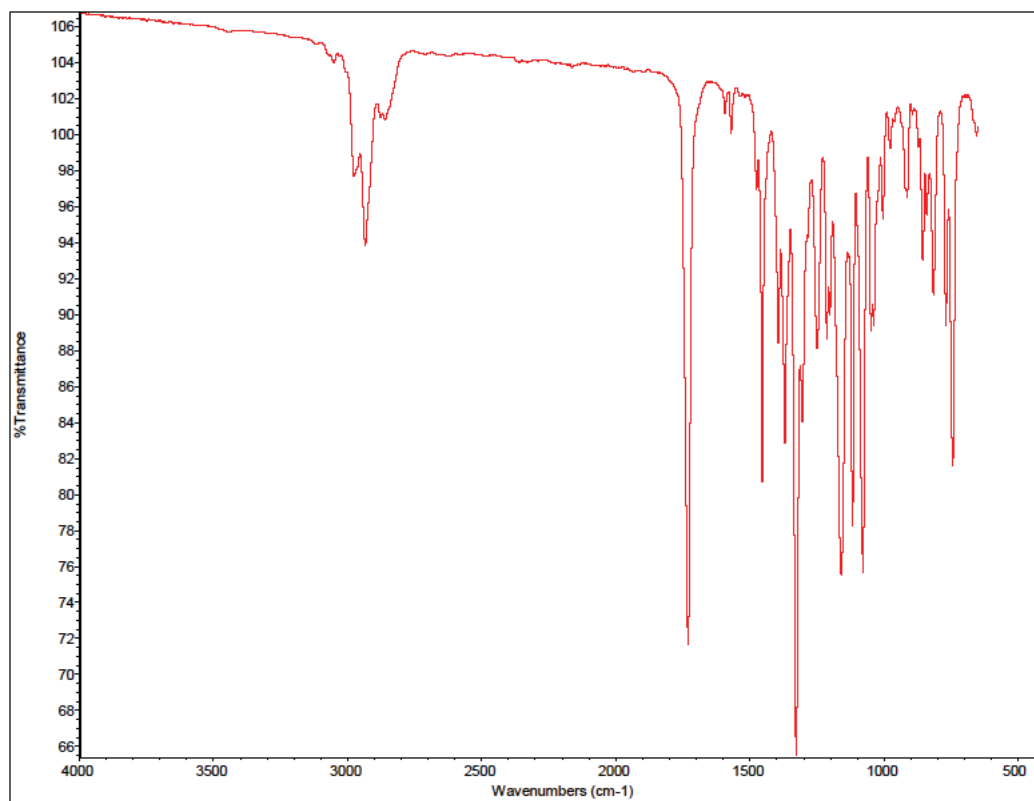


Figure A4.105 Infrared spectrum (thin film) of compound **399**

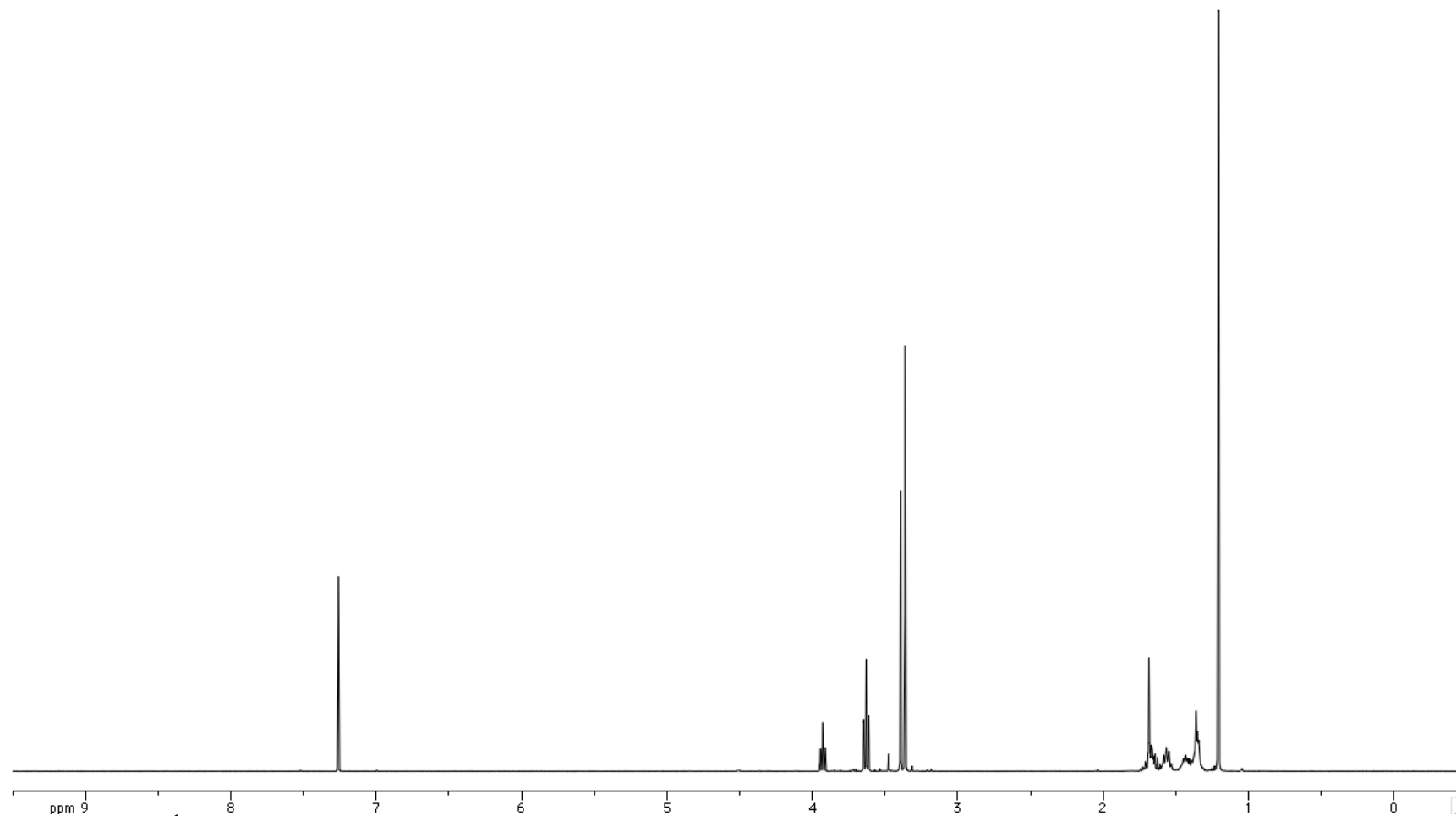
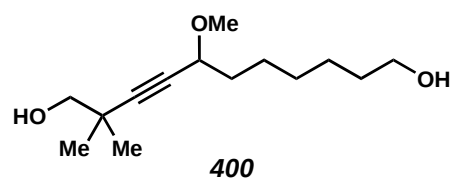
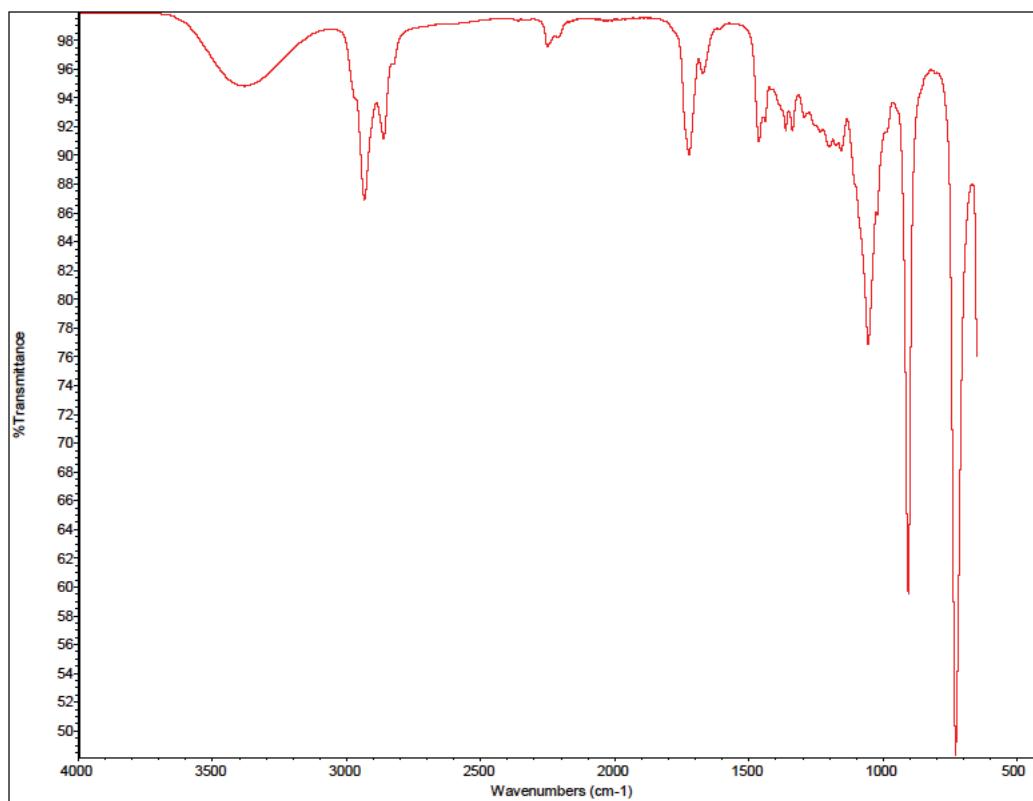
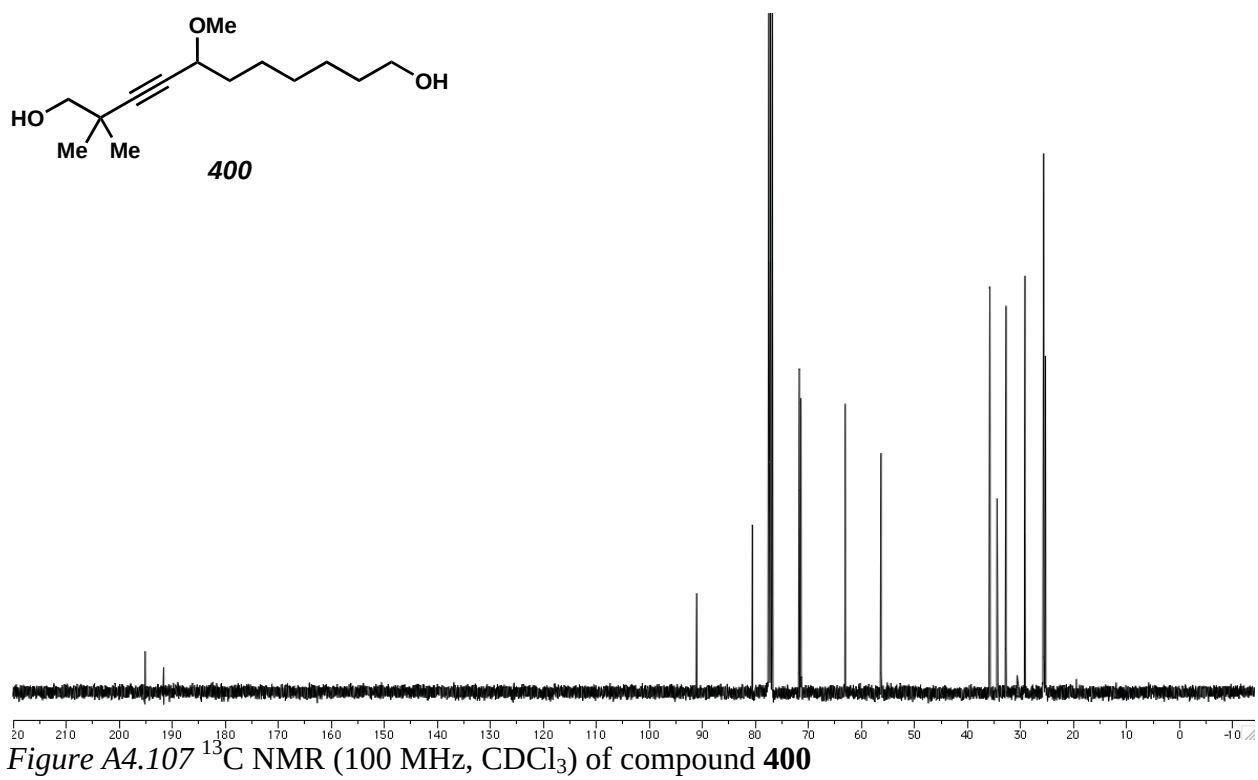


Figure A4.106 ^1H NMR (400 MHz, CDCl_3) of compound **400**



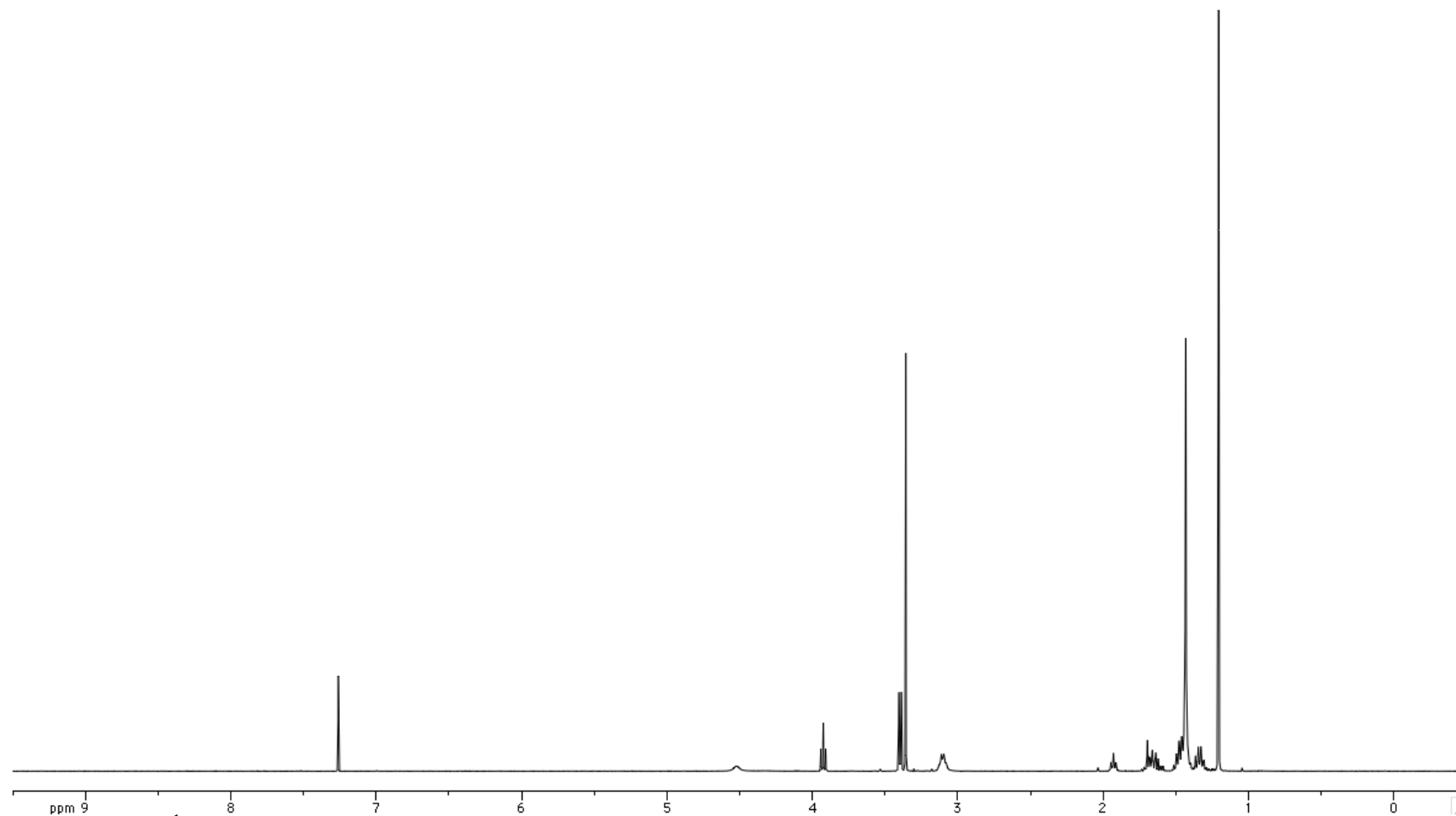
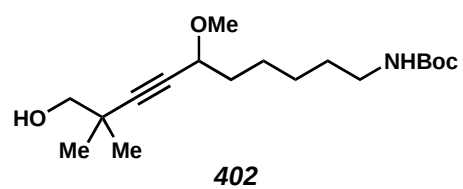
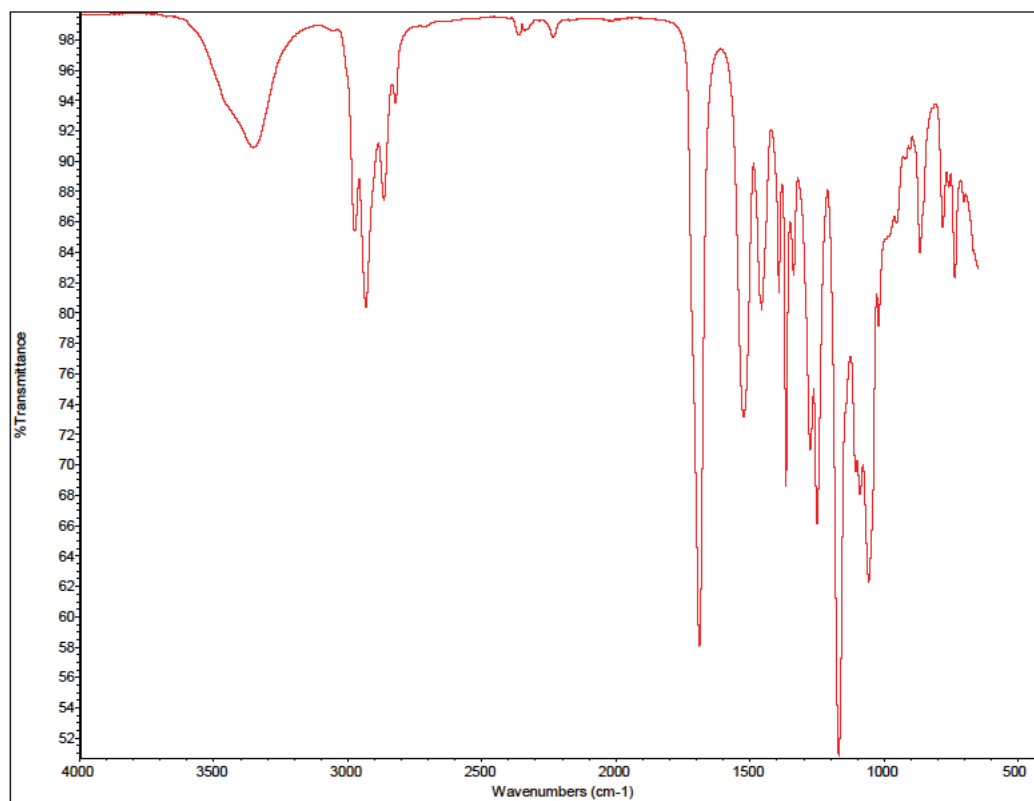
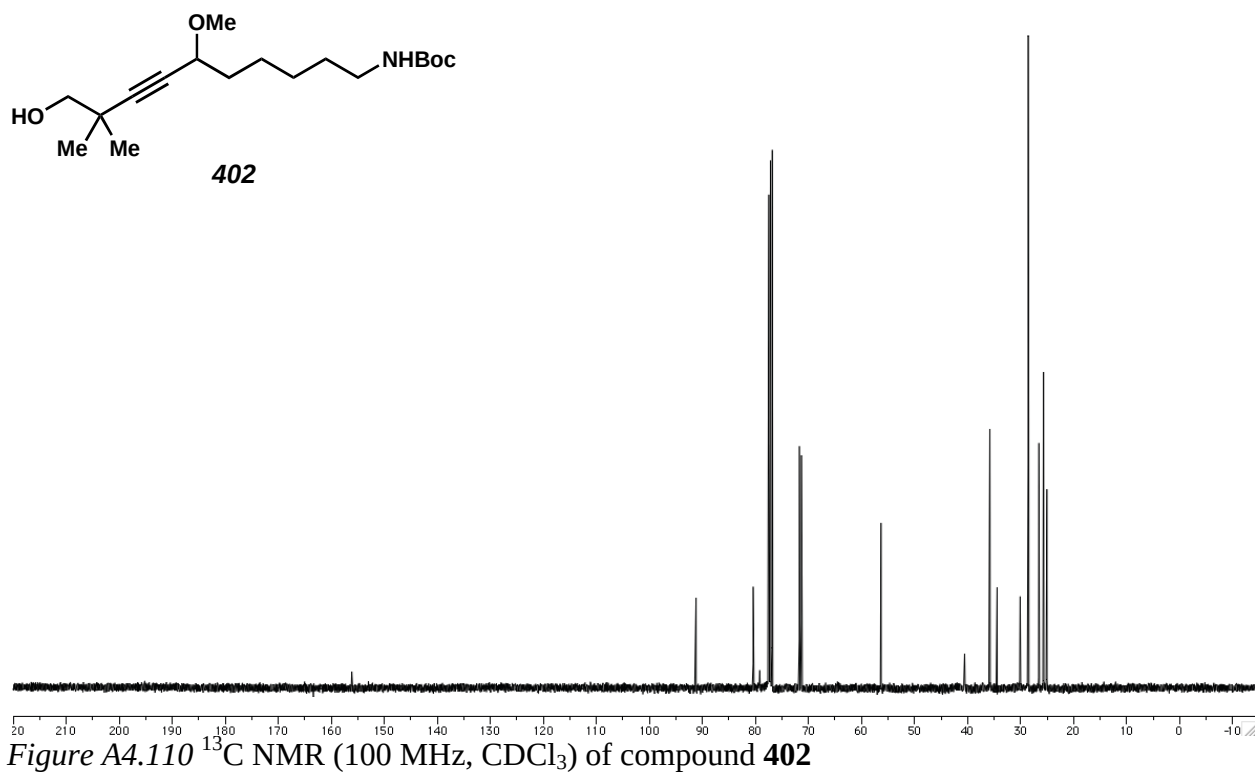


Figure A4.109 ¹H NMR (400 MHz, CDCl₃) of compound **402**



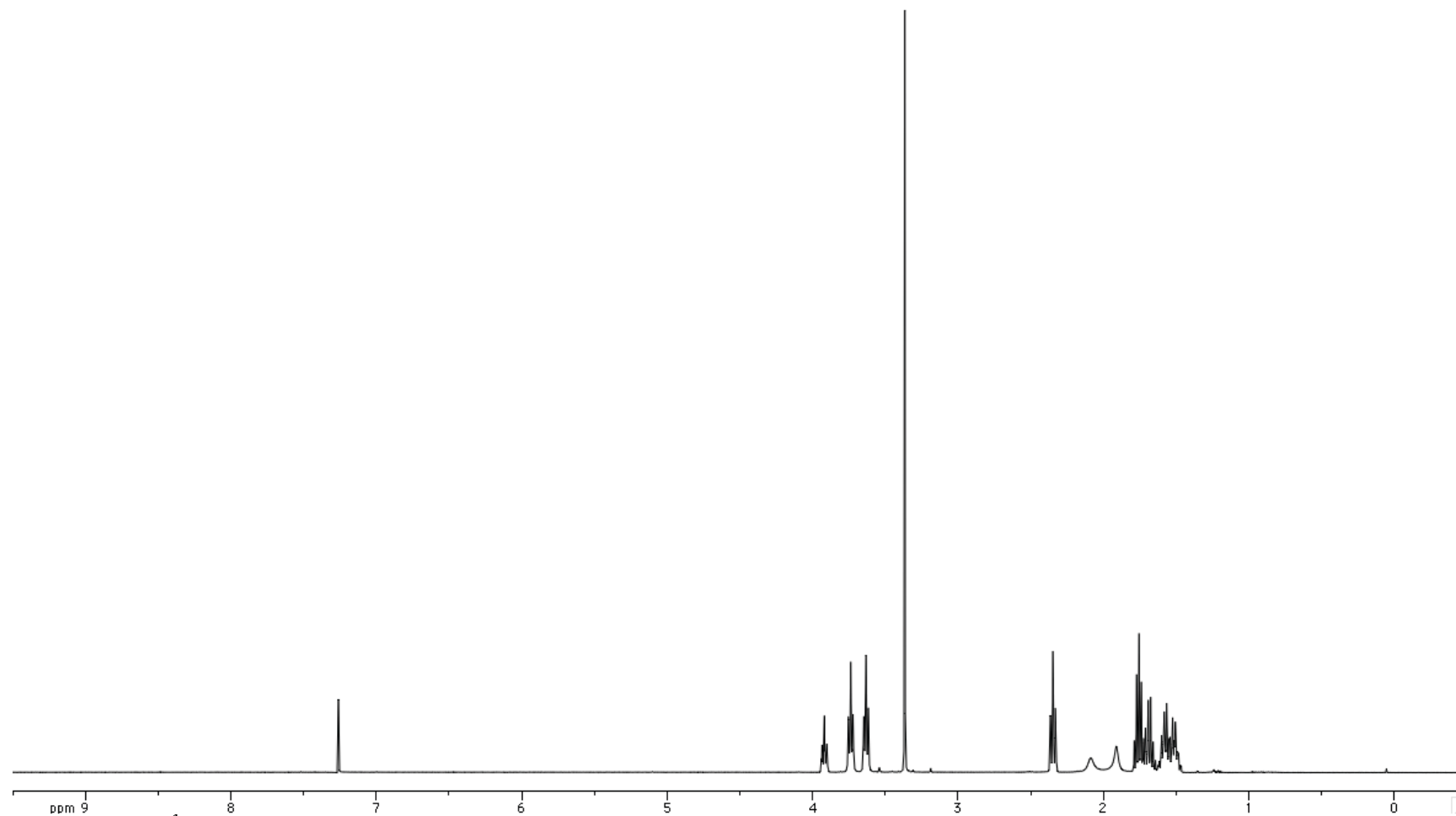
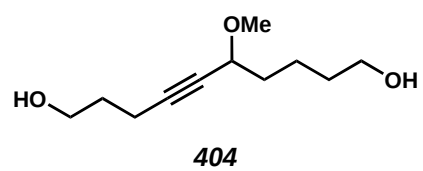
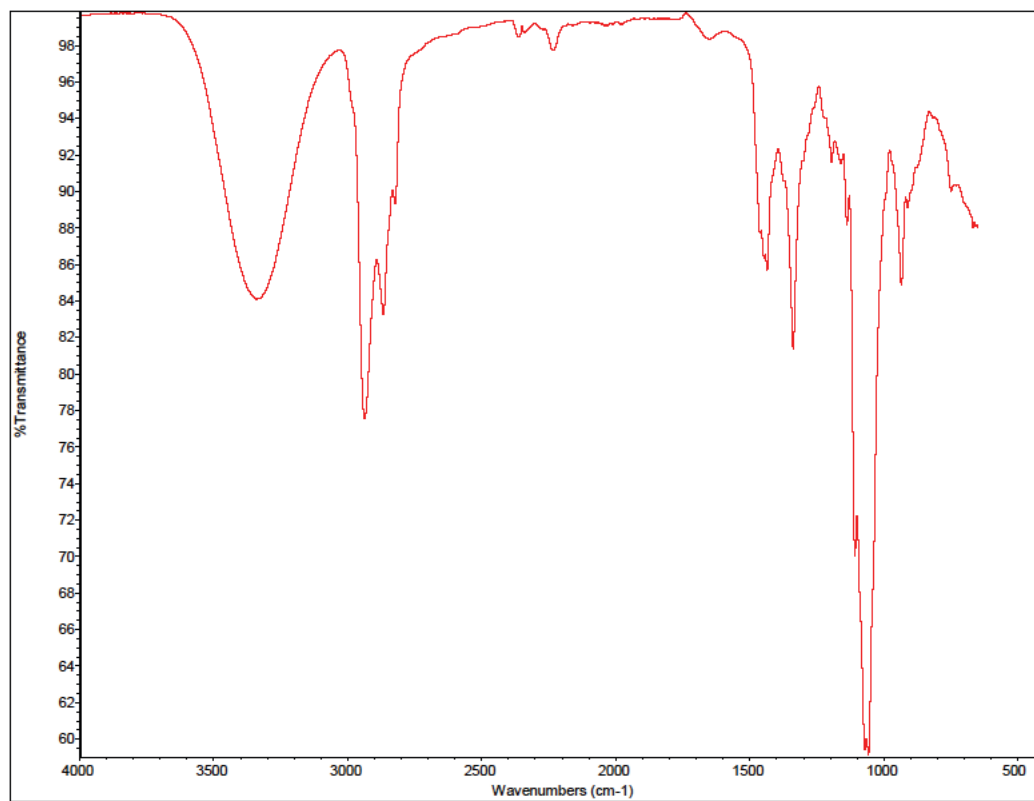
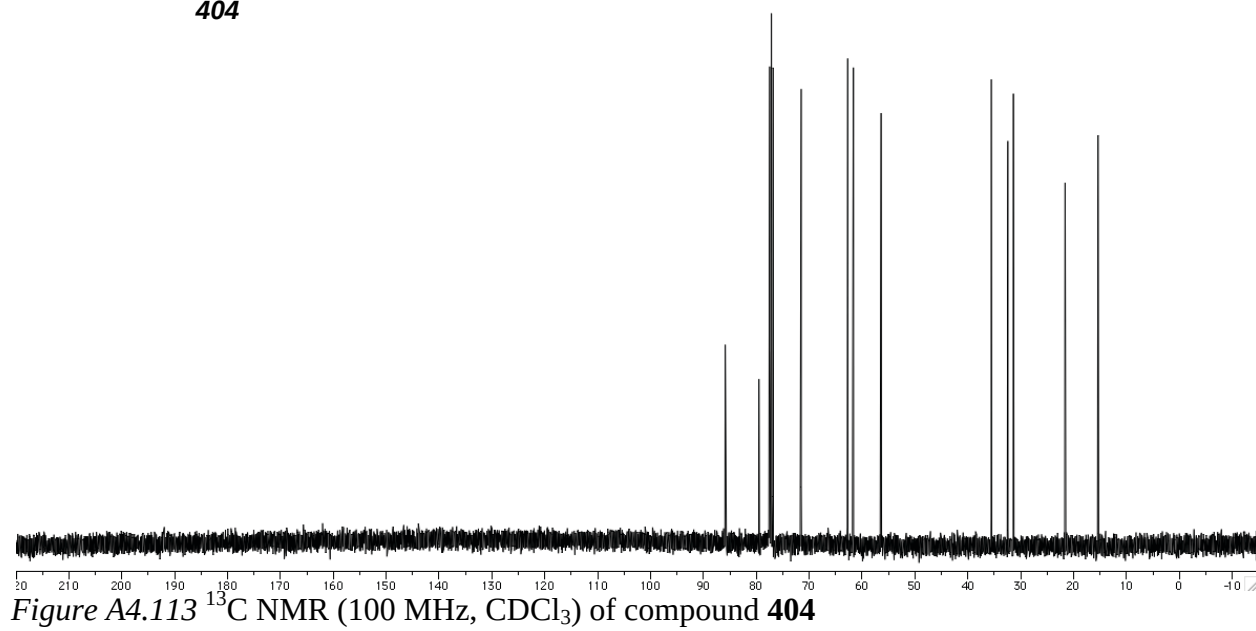
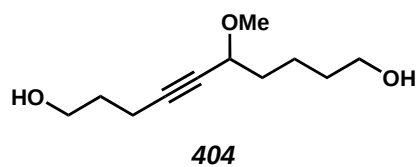


Figure A4.112 ^1H NMR (400 MHz, CDCl_3) of compound **404**



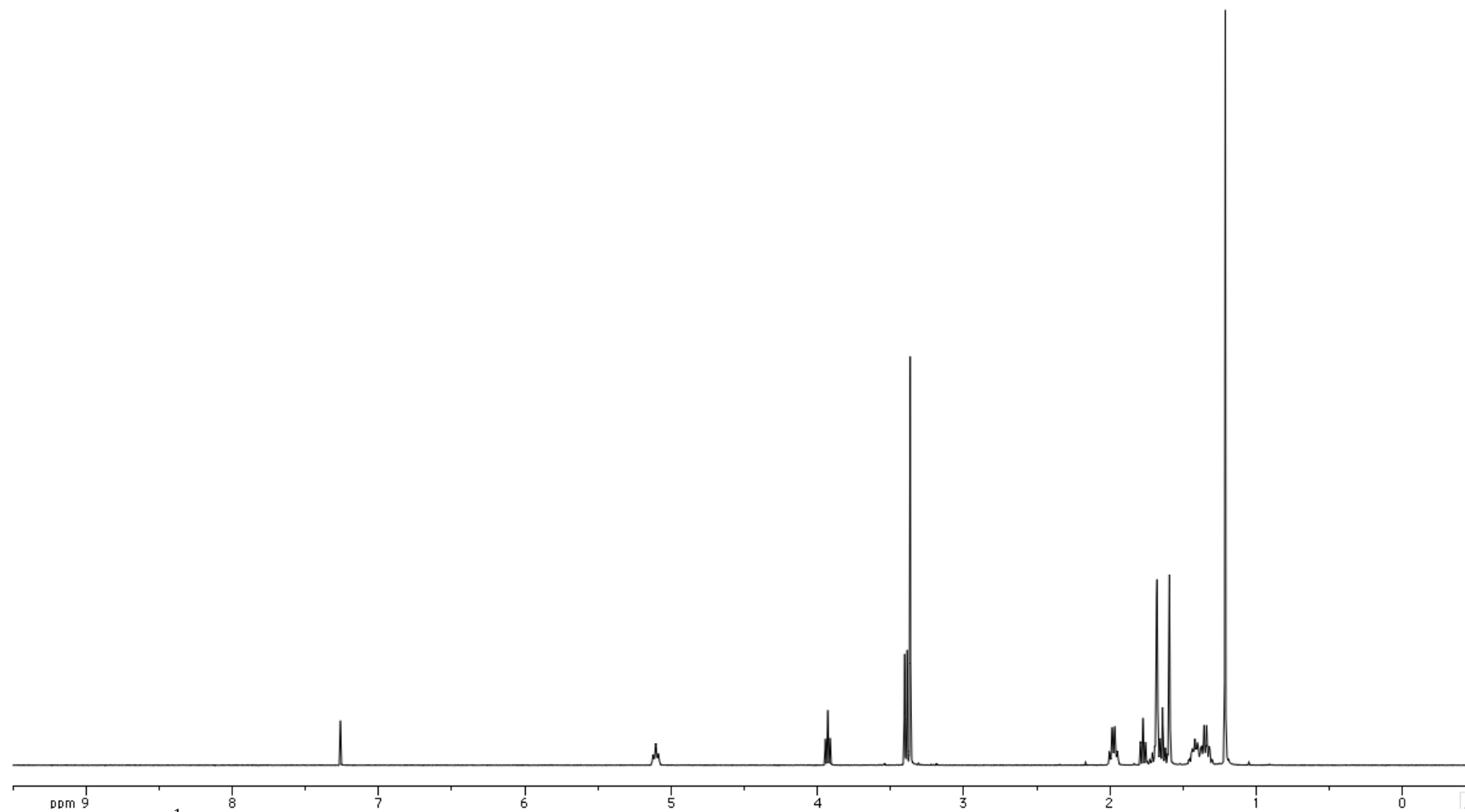
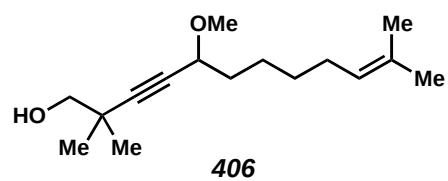


Figure A4.115 ^1H NMR (400 MHz, CDCl_3) of compound **406**

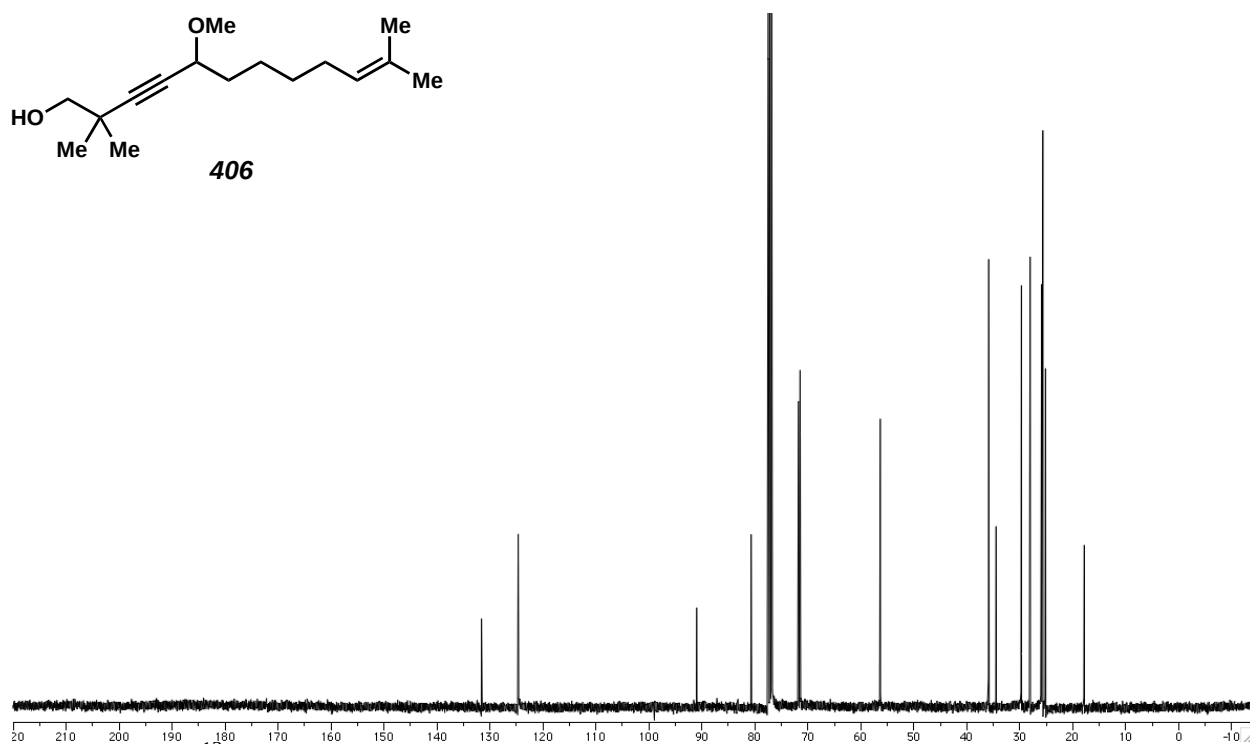


Figure A4.116 ¹³C NMR (100 MHz, CDCl₃) of compound **406**

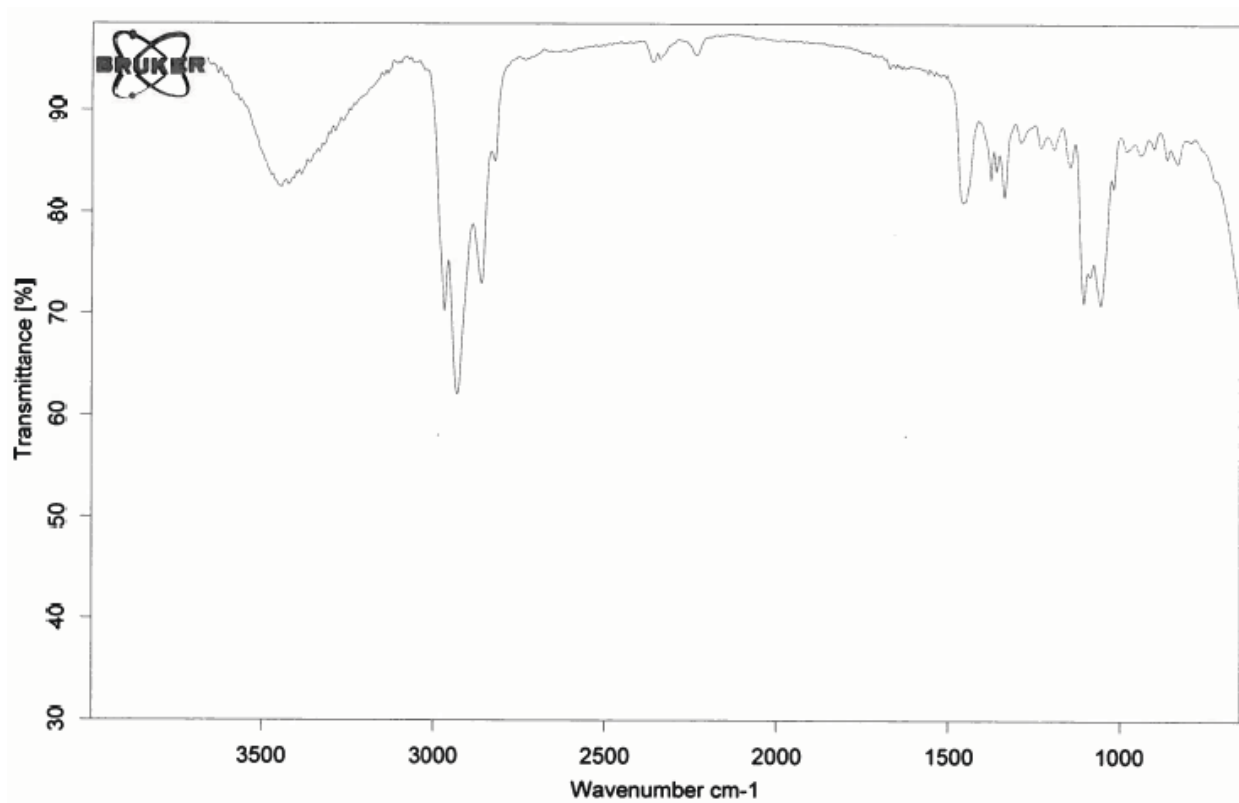


Figure A4.117 Infrared spectrum (thin film) of compound **406**

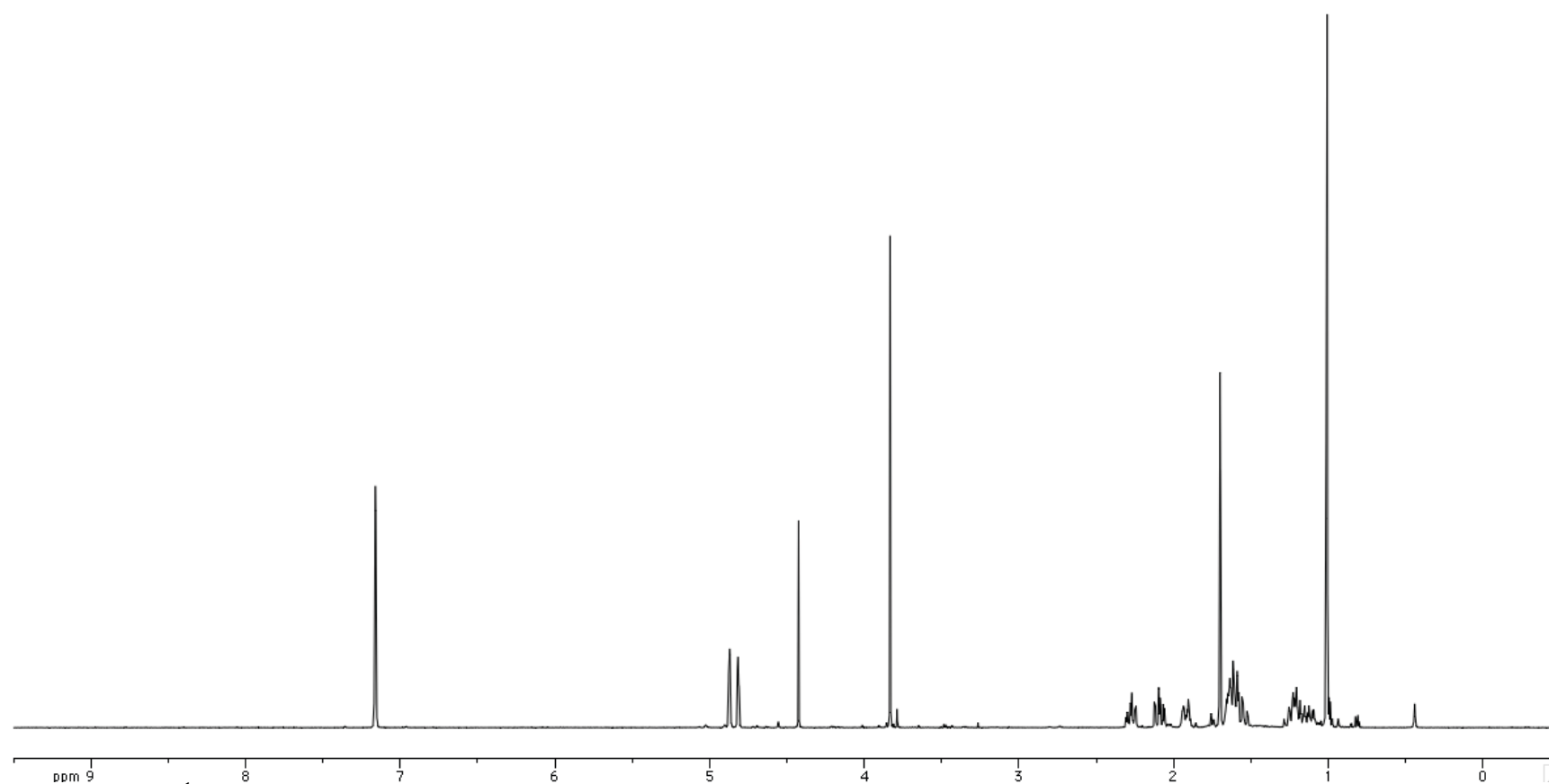
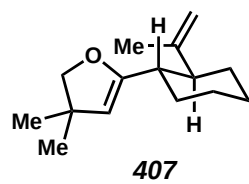


Figure A4.118 ¹H NMR (400 MHz, C₆D₆) of compound **407**

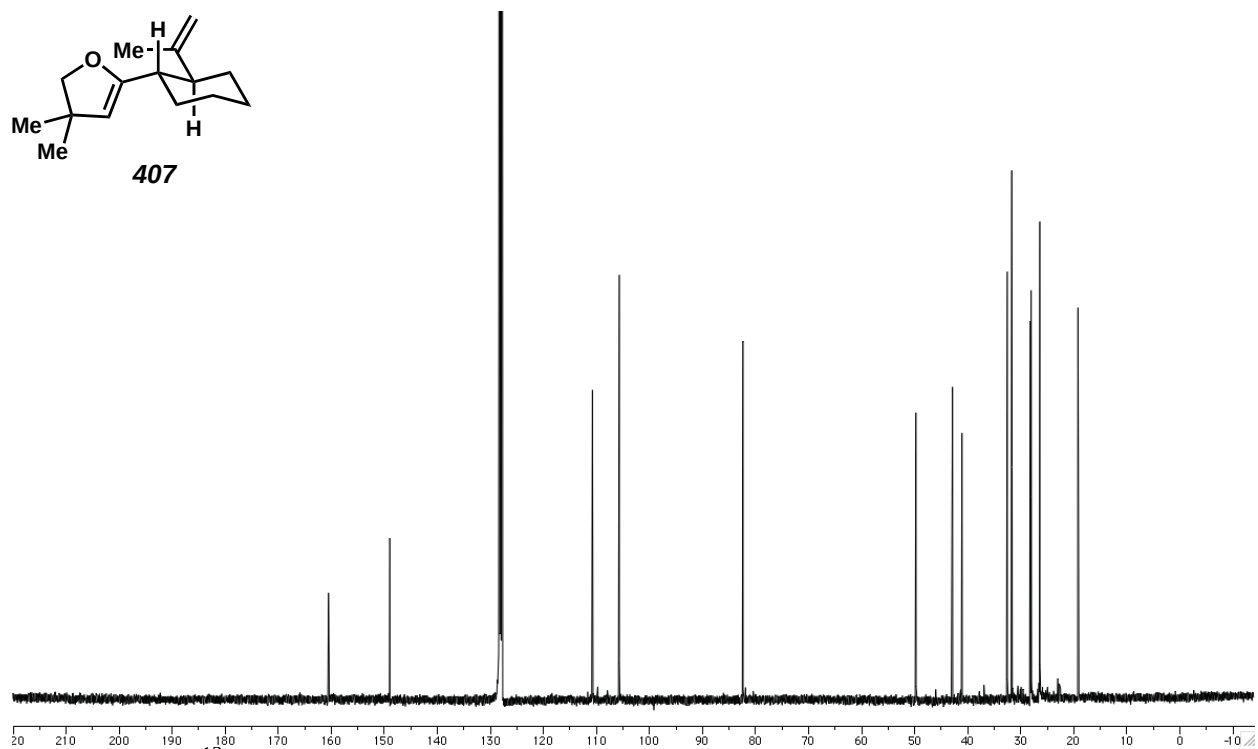


Figure A4.119 ^{13}C NMR (100 MHz, C_6D_6) of compound **407**

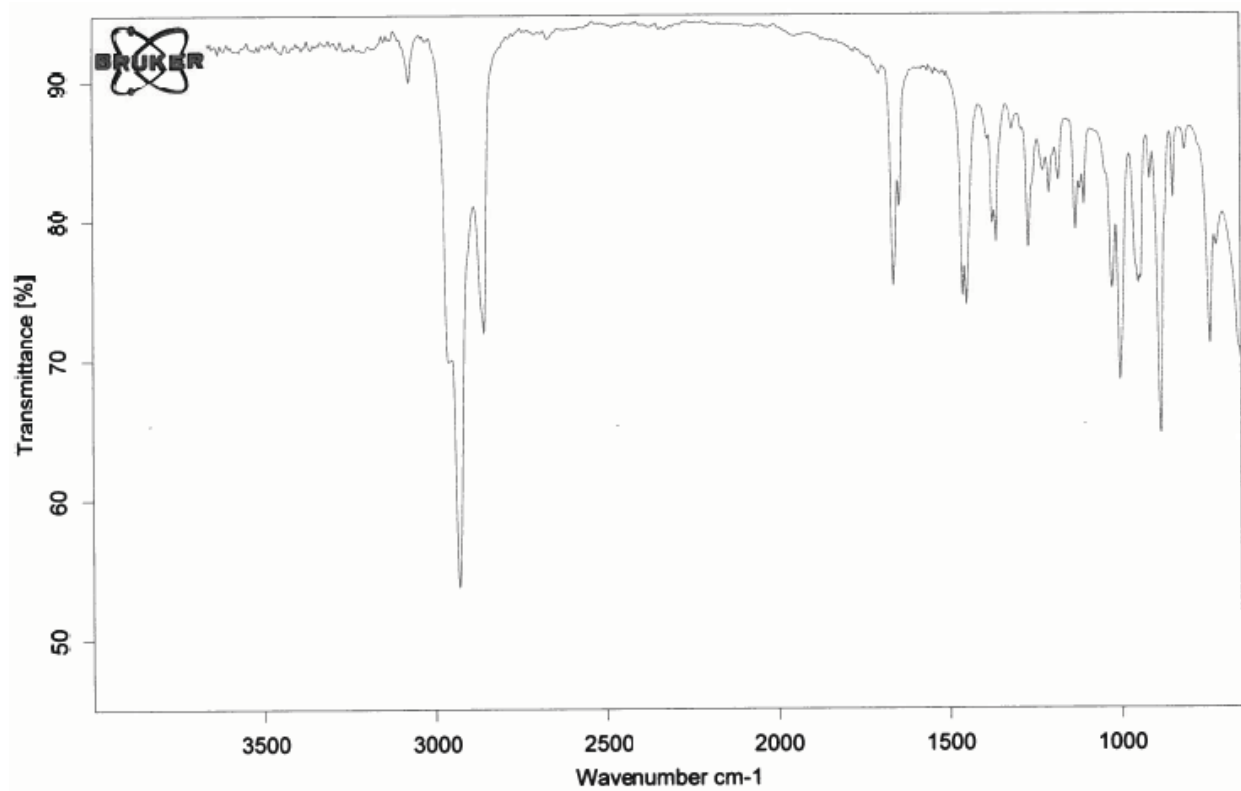


Figure A4.120 Infrared spectrum (thin film) of compound **407**

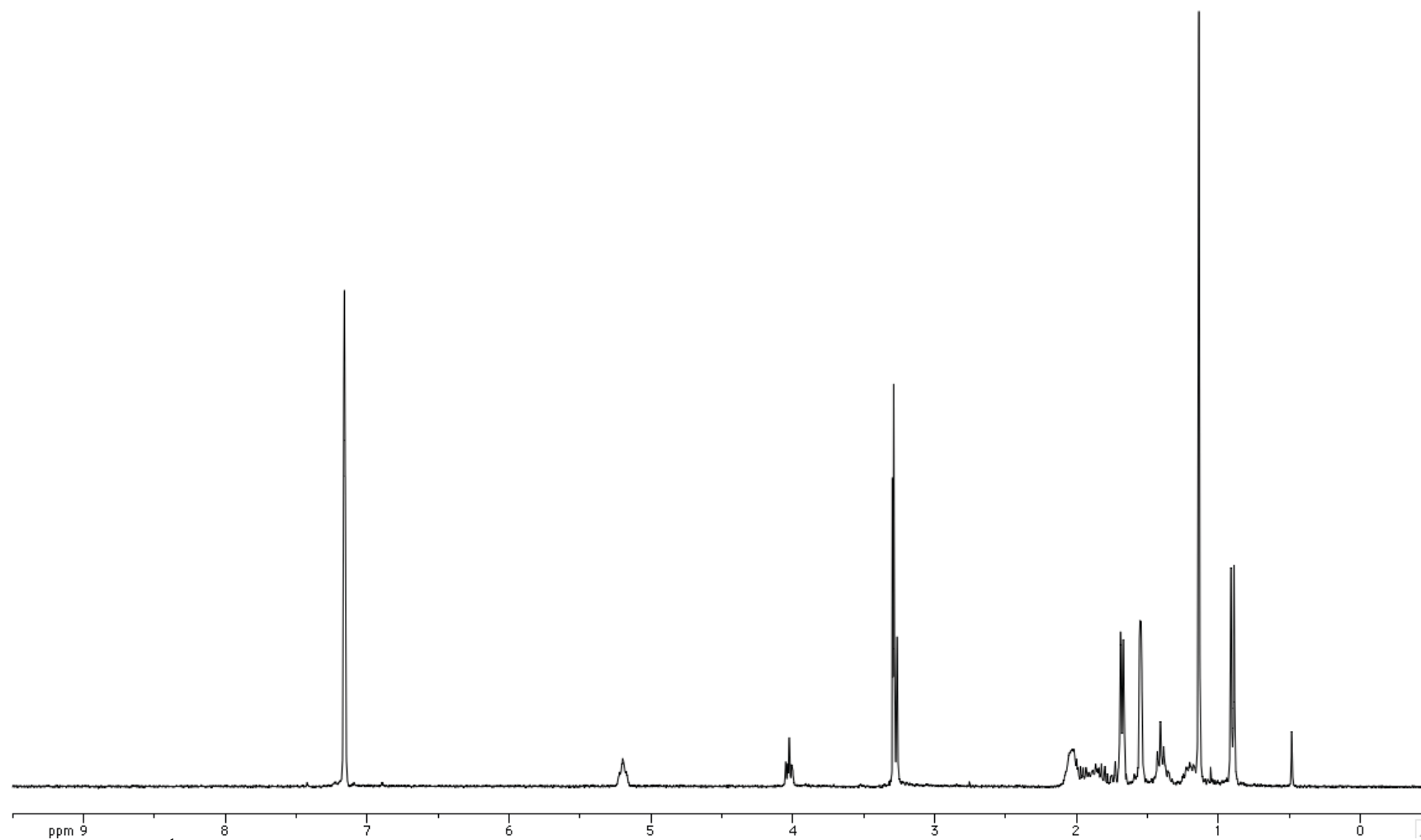
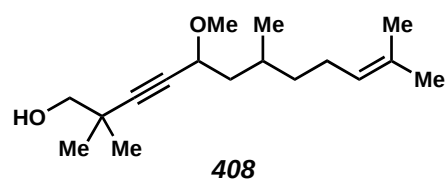


Figure A4.121 ^1H NMR (300 MHz, C_6D_6) of compound **408**

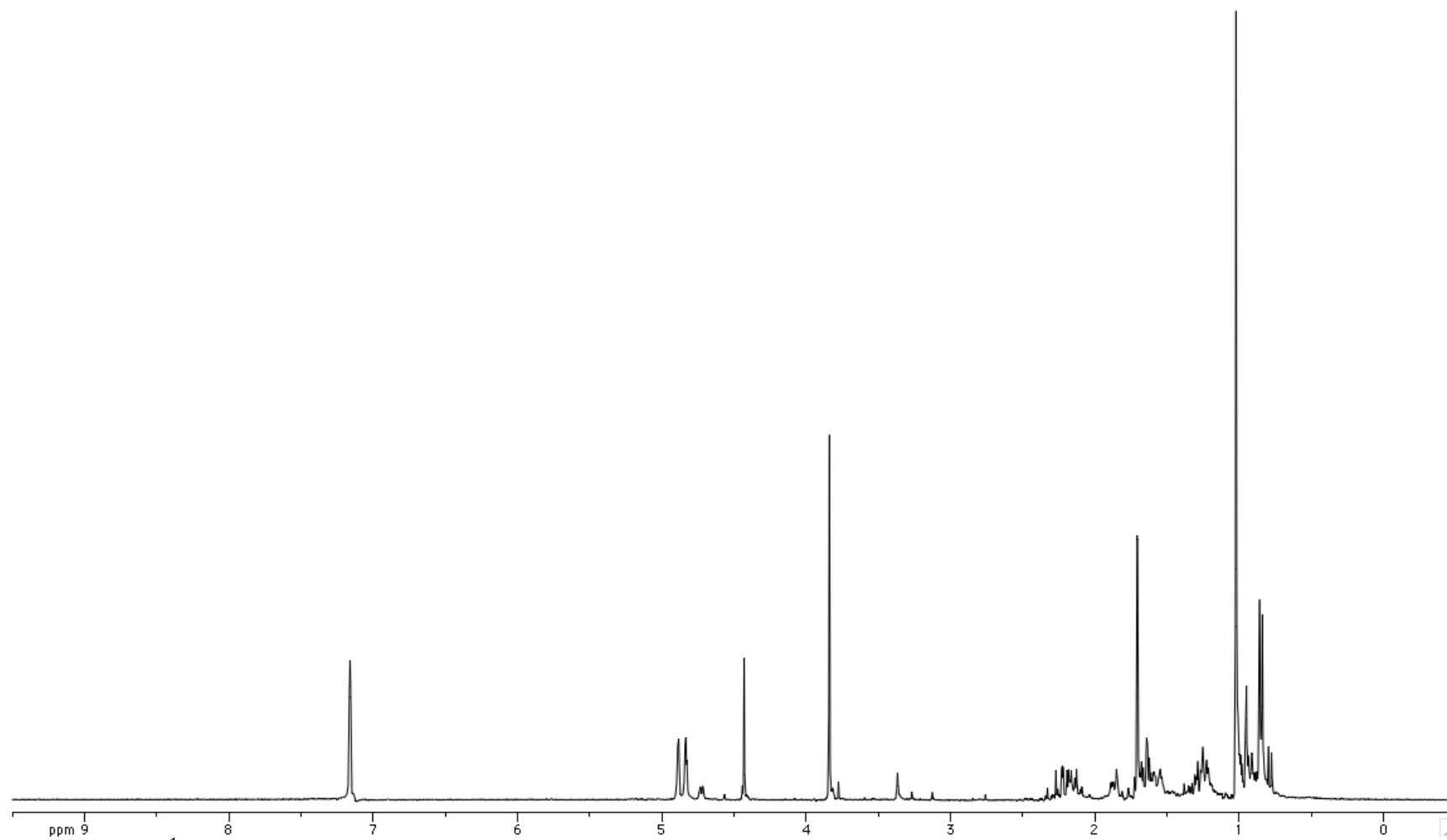
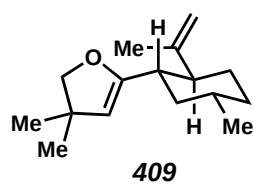


Figure A4.122 ^1H NMR (300 MHz, C_6D_6) of compound **409**

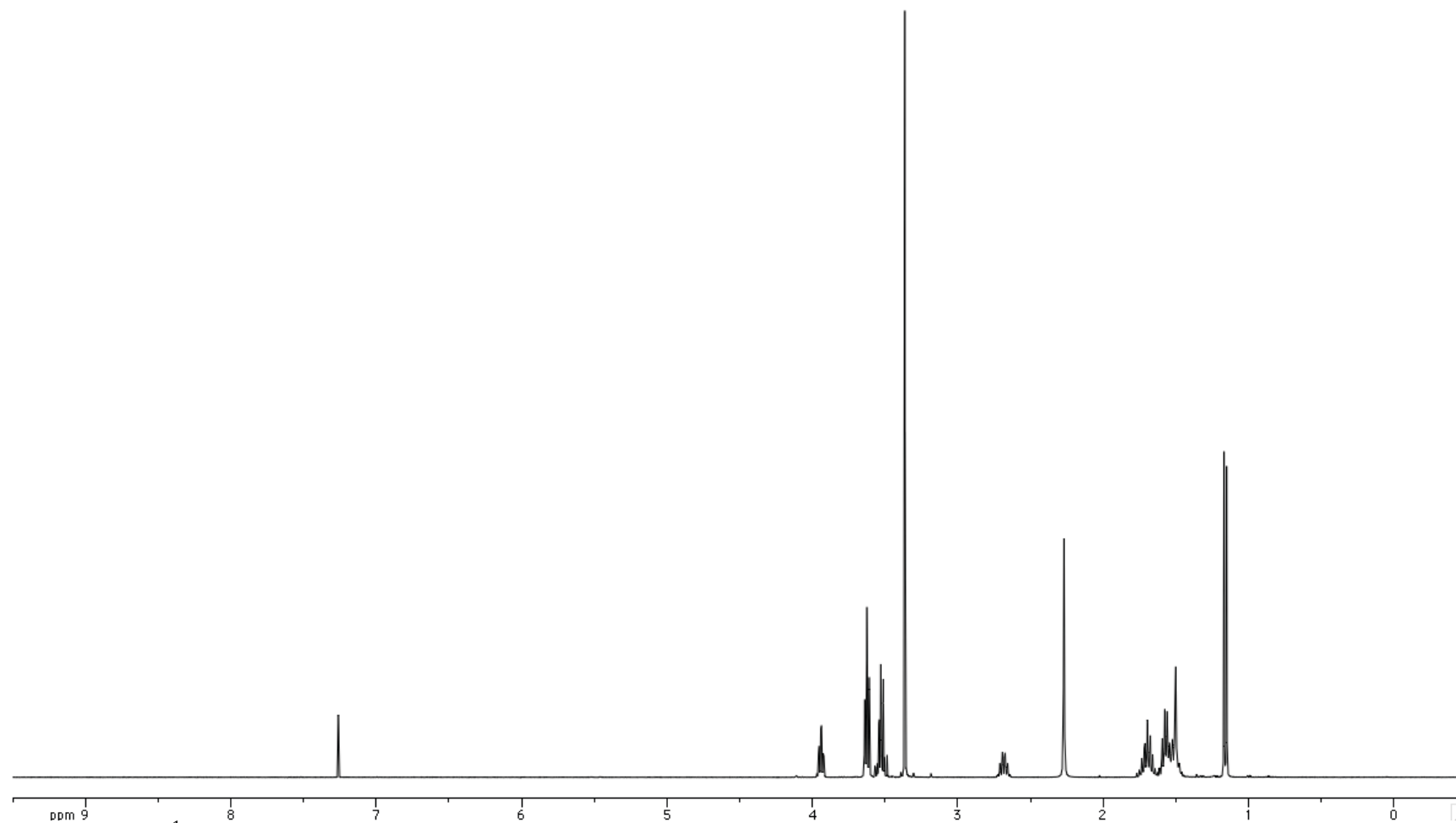
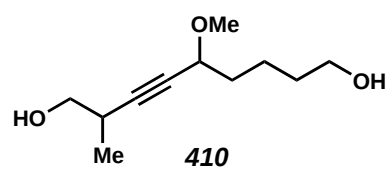
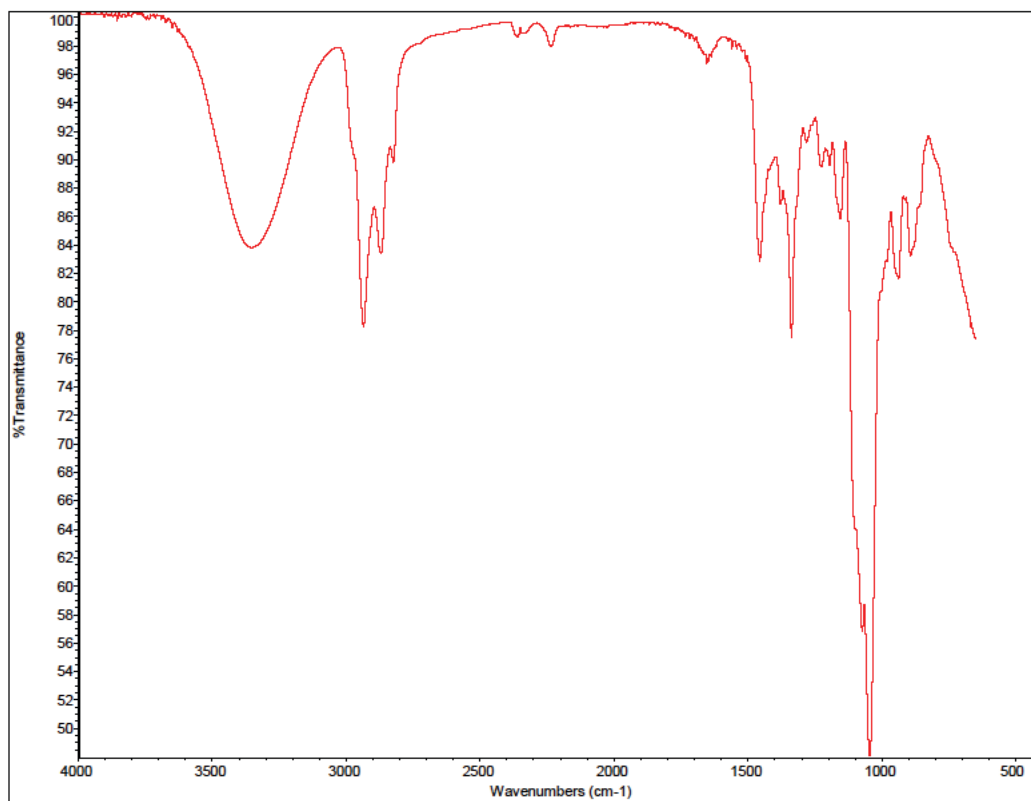
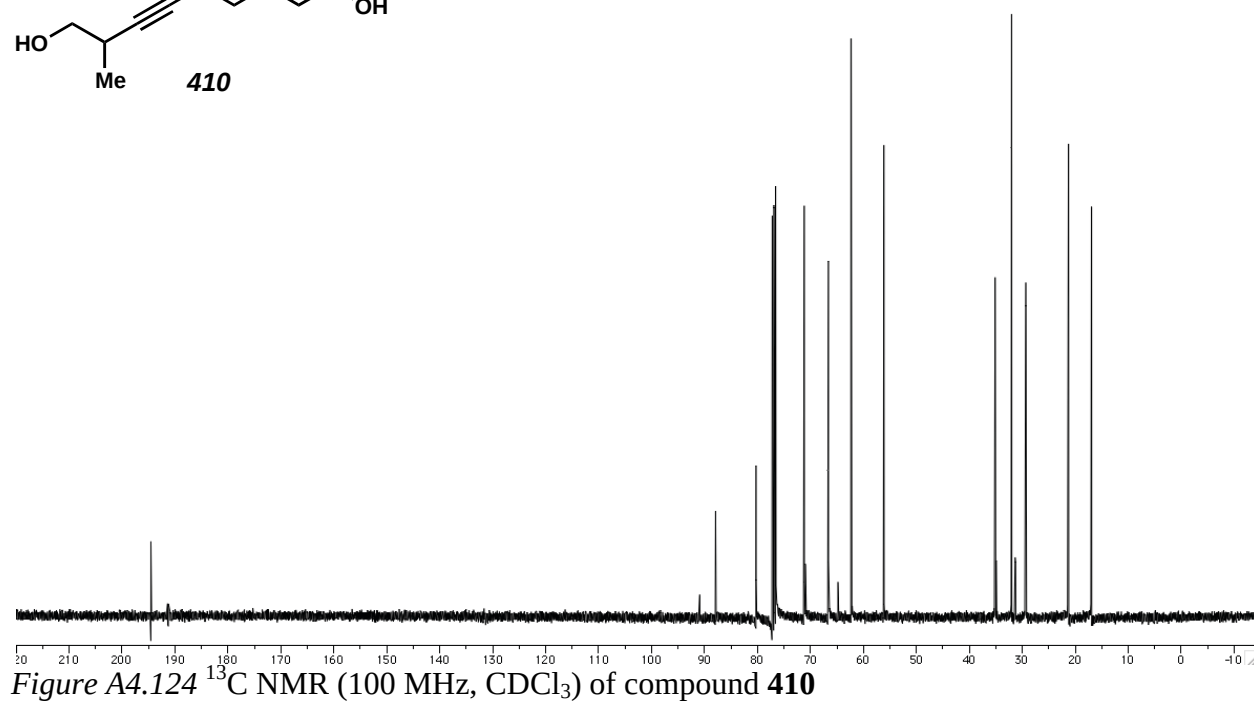
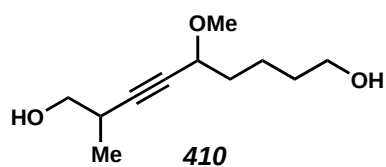
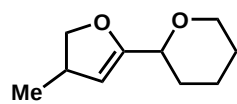


Figure A4.123 ^1H NMR (400 MHz, CDCl_3) of compound **410**





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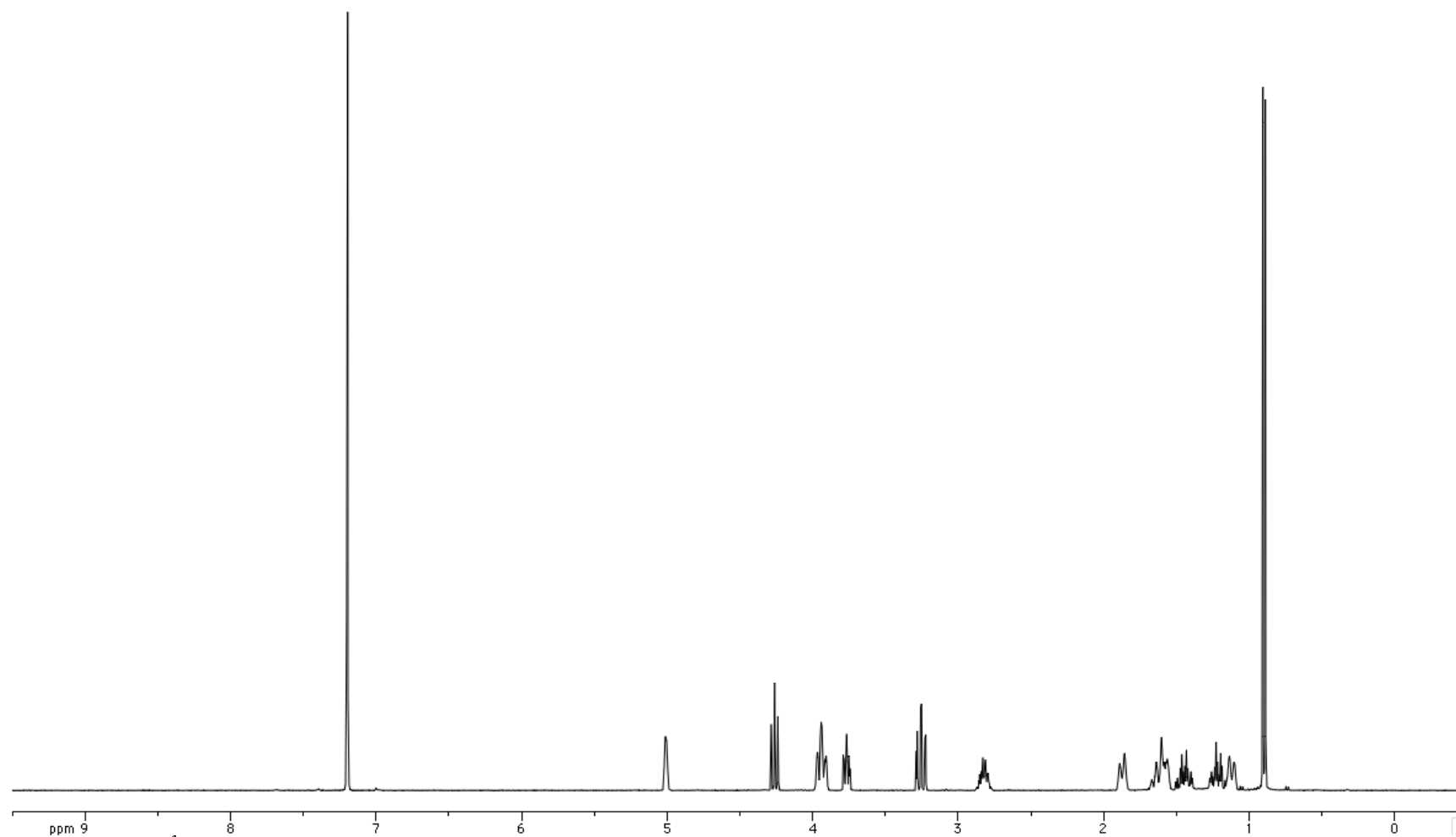
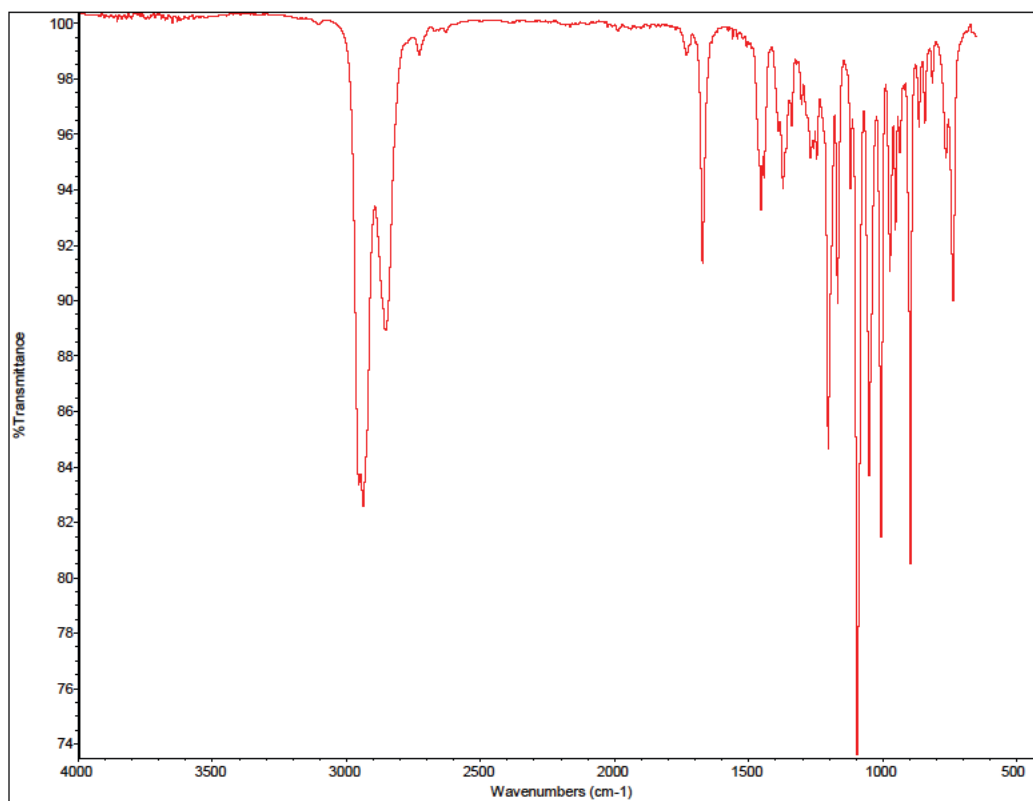
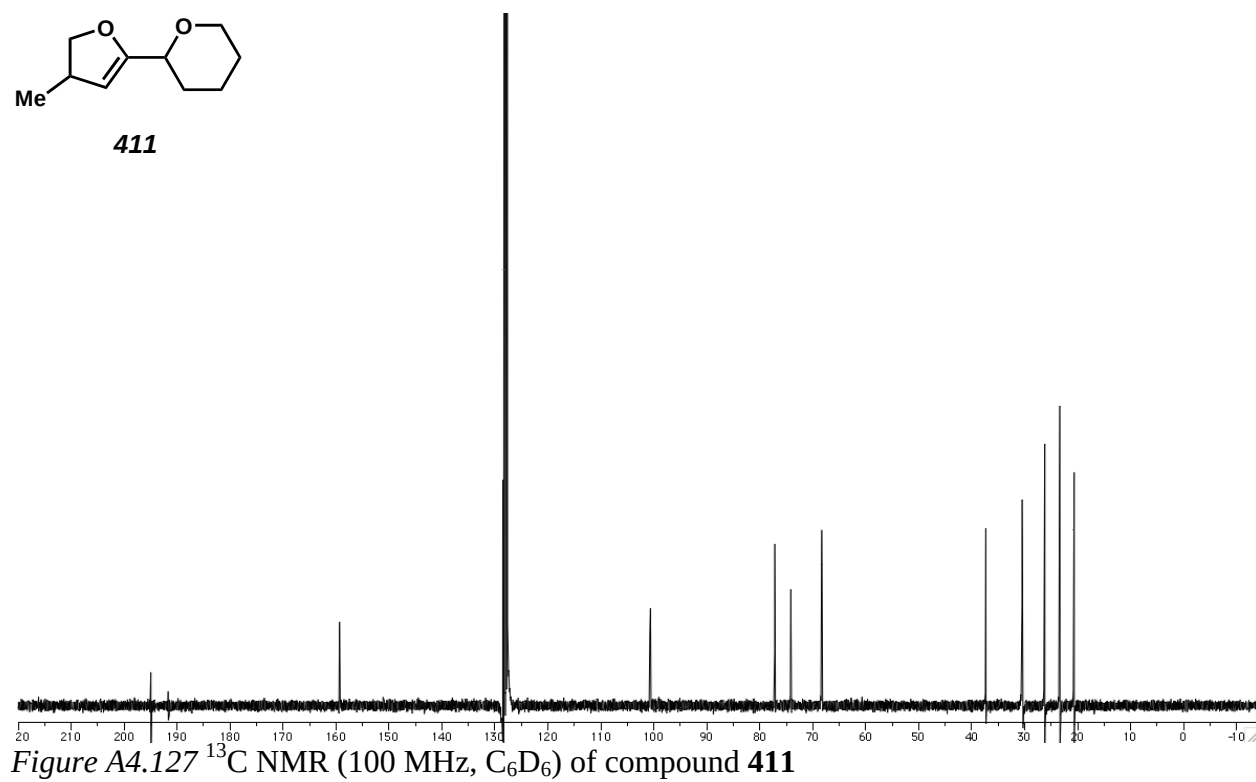
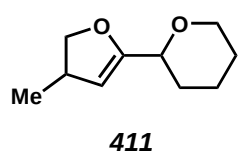
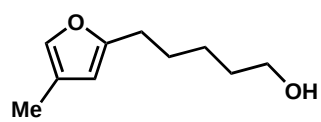


Figure A4.126 ¹H NMR (400 MHz, C₆D₆) of compound **411**





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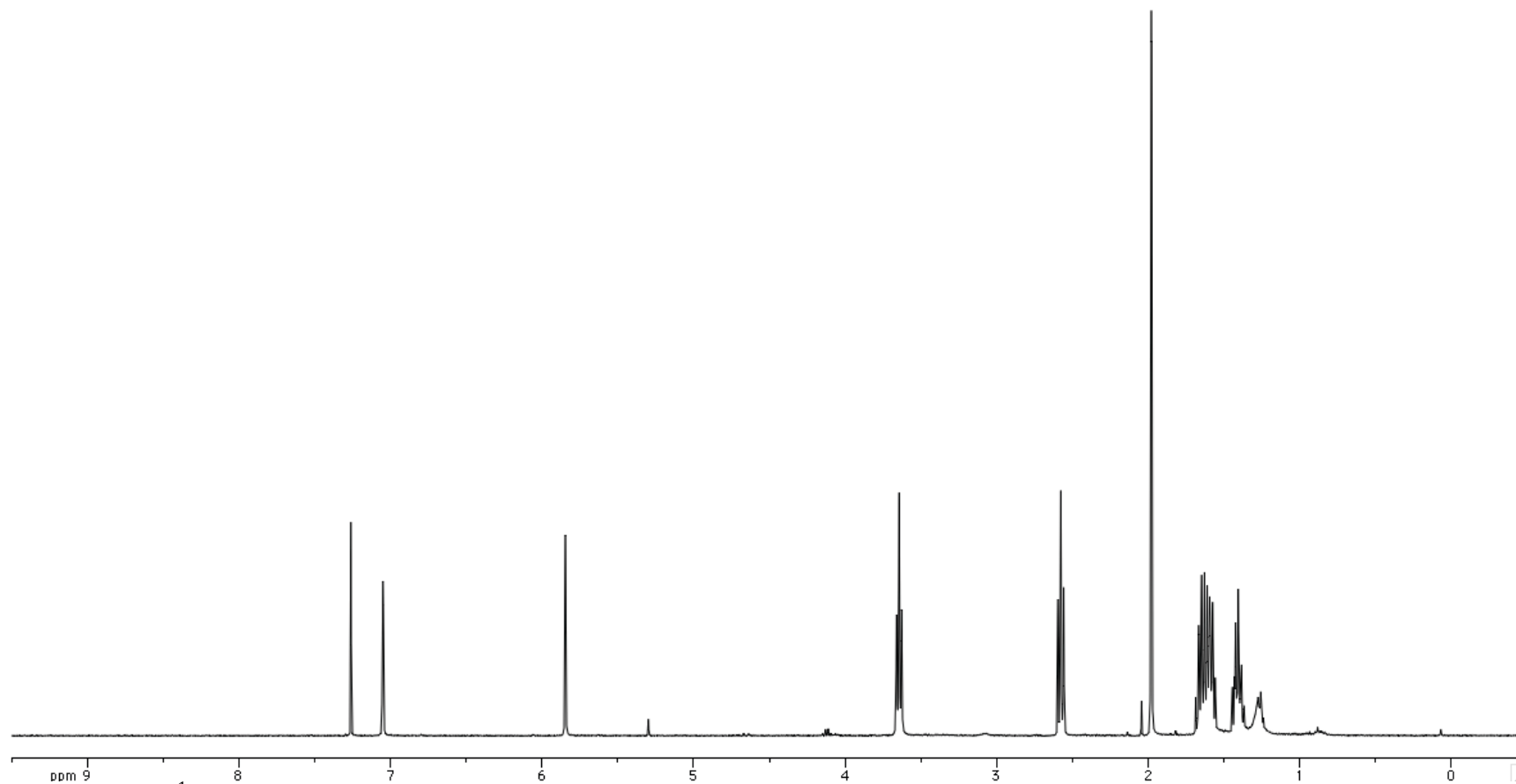
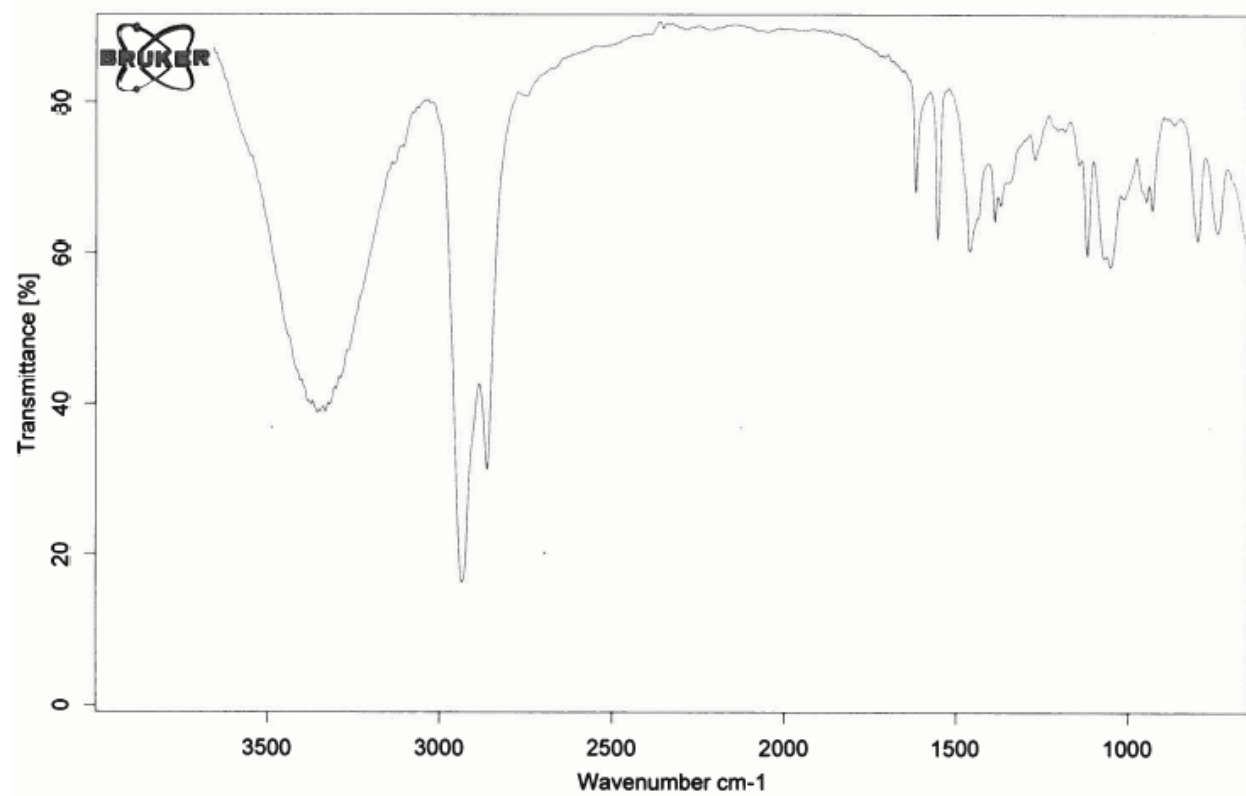
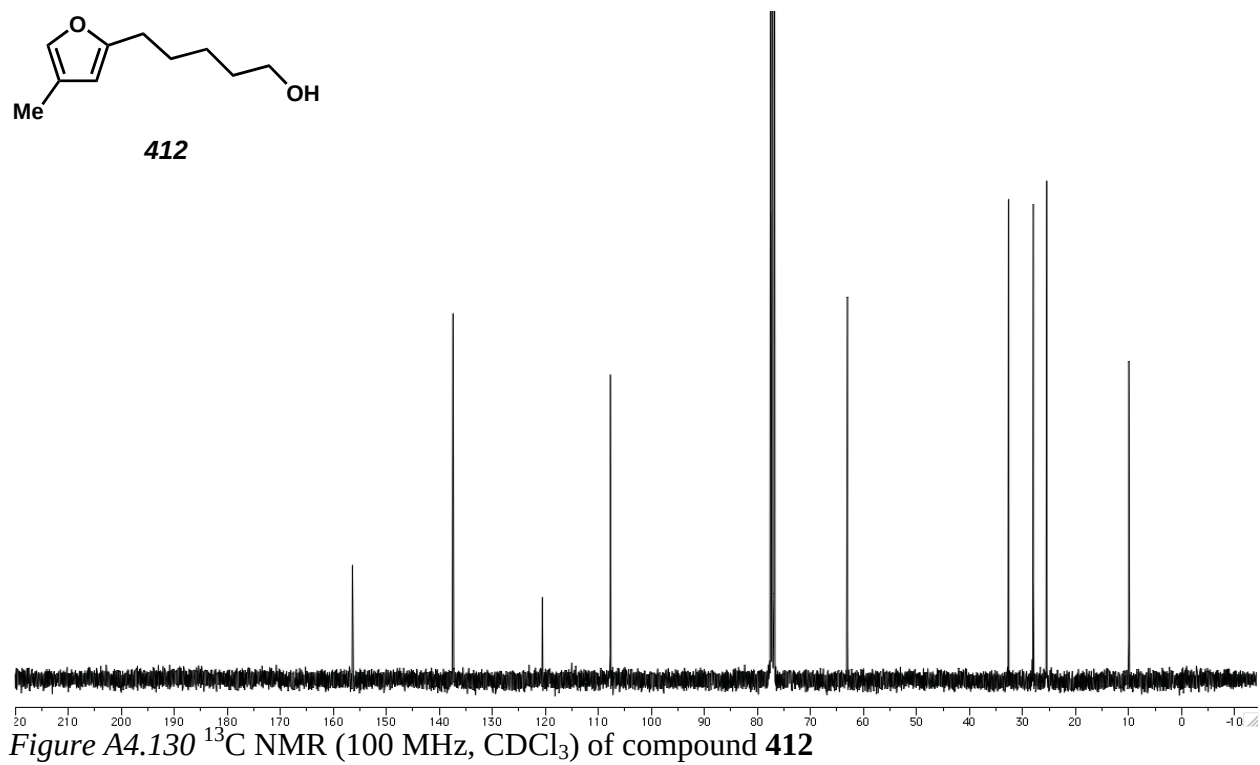
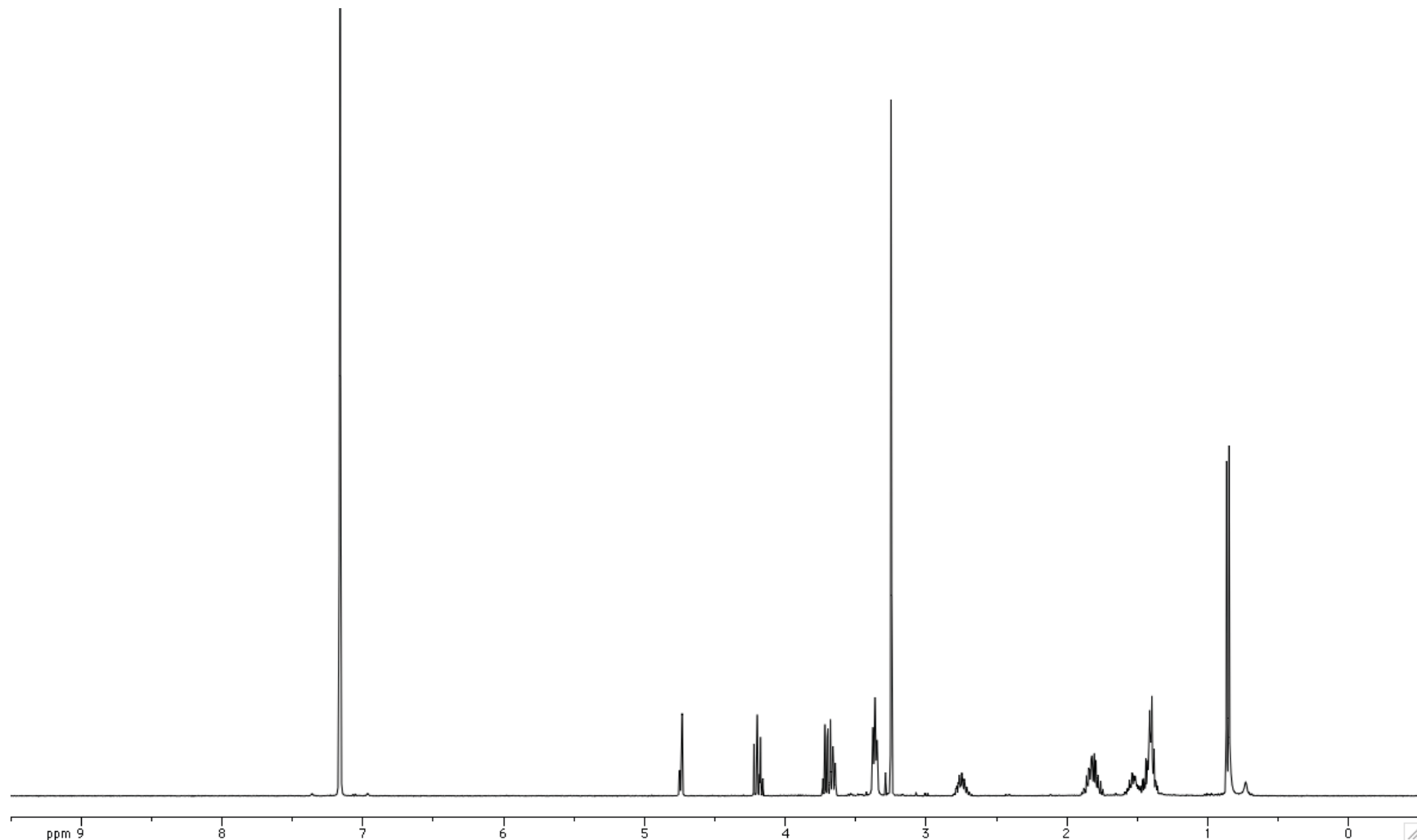


Figure A4.129 ^1H NMR (400 MHz, CDCl_3) of compound **412**





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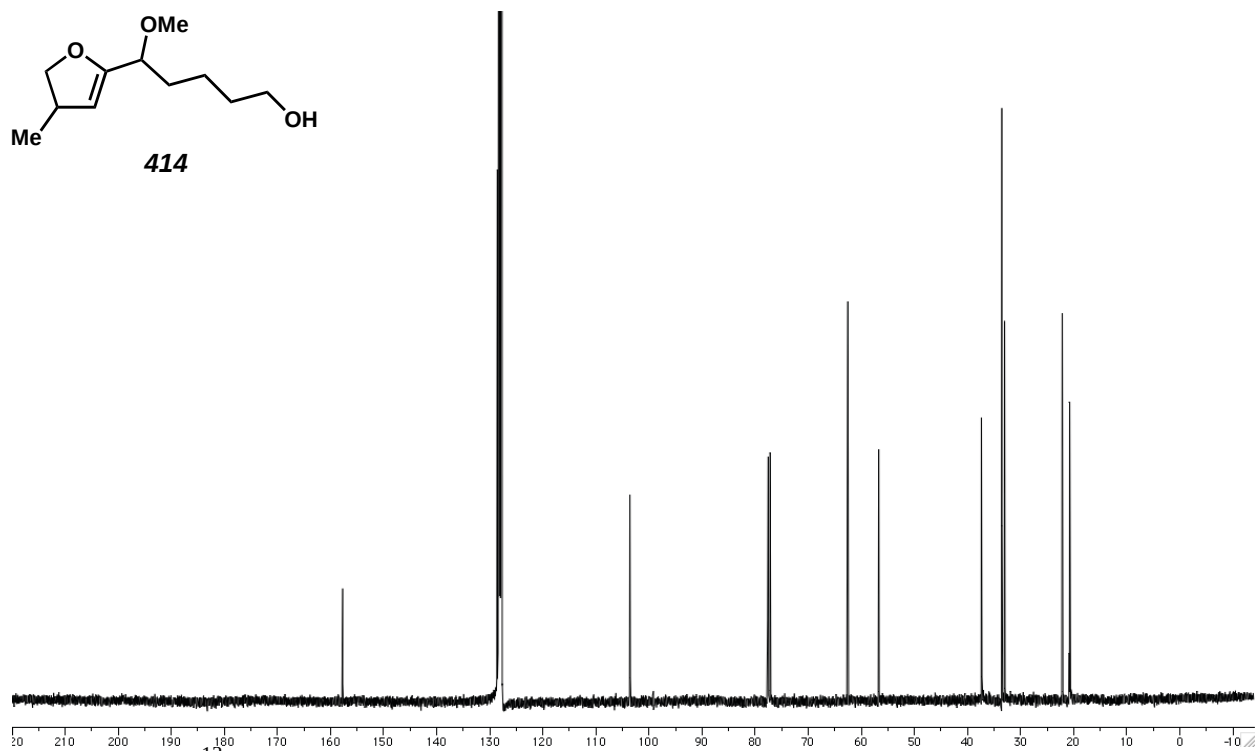


Figure A4.133 ^{13}C NMR (100 MHz, C_6D_6) of compound **414**

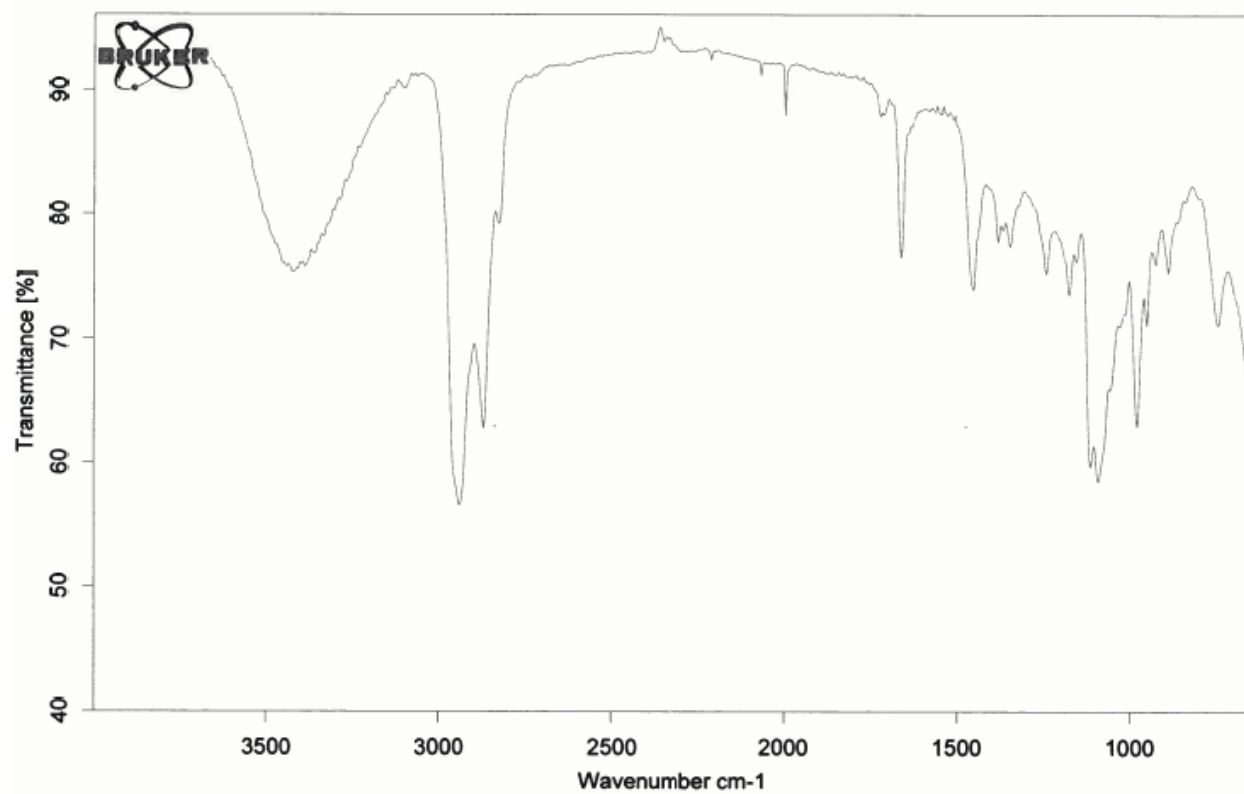


Figure A4.134 Infrared spectrum (thin film) of compound **414**

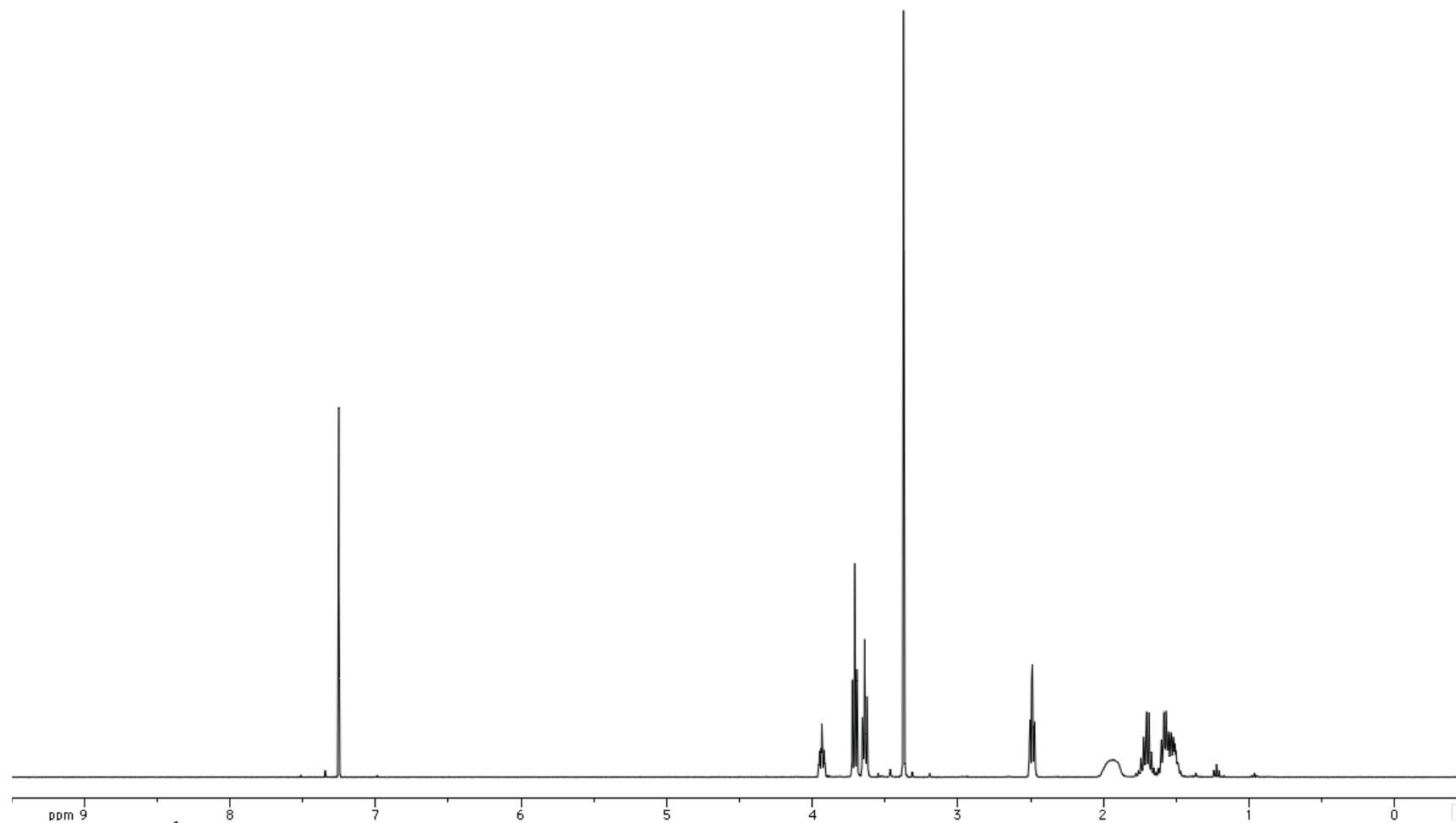
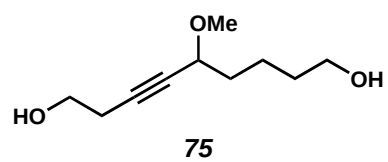
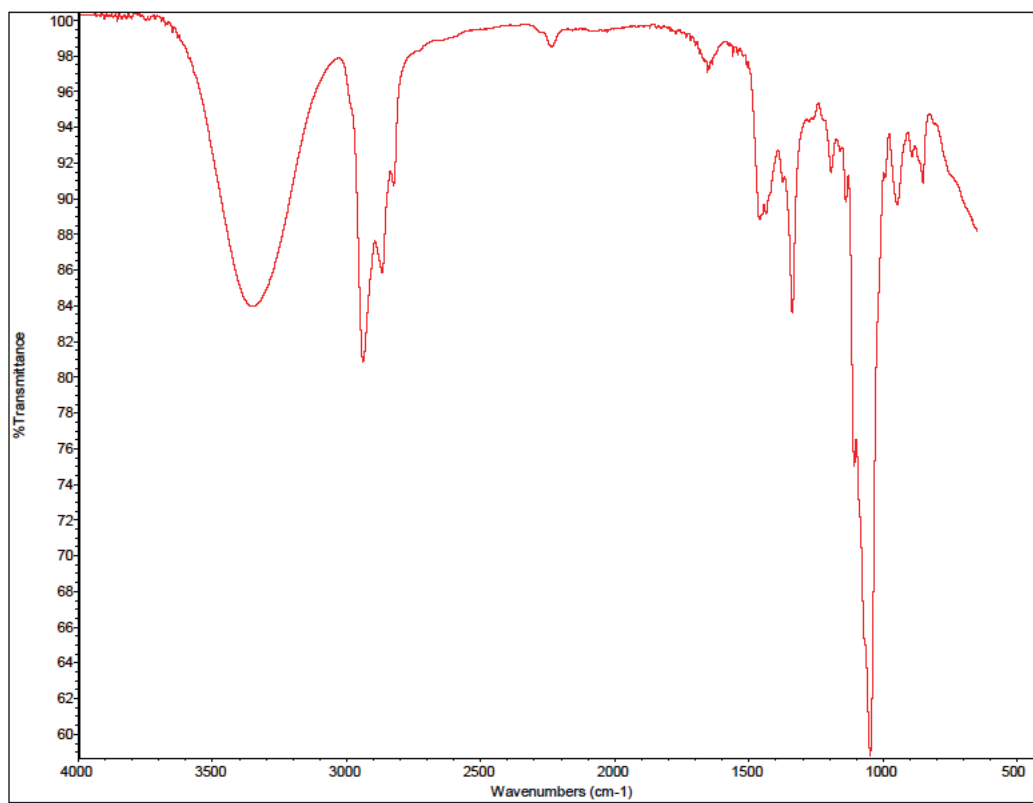
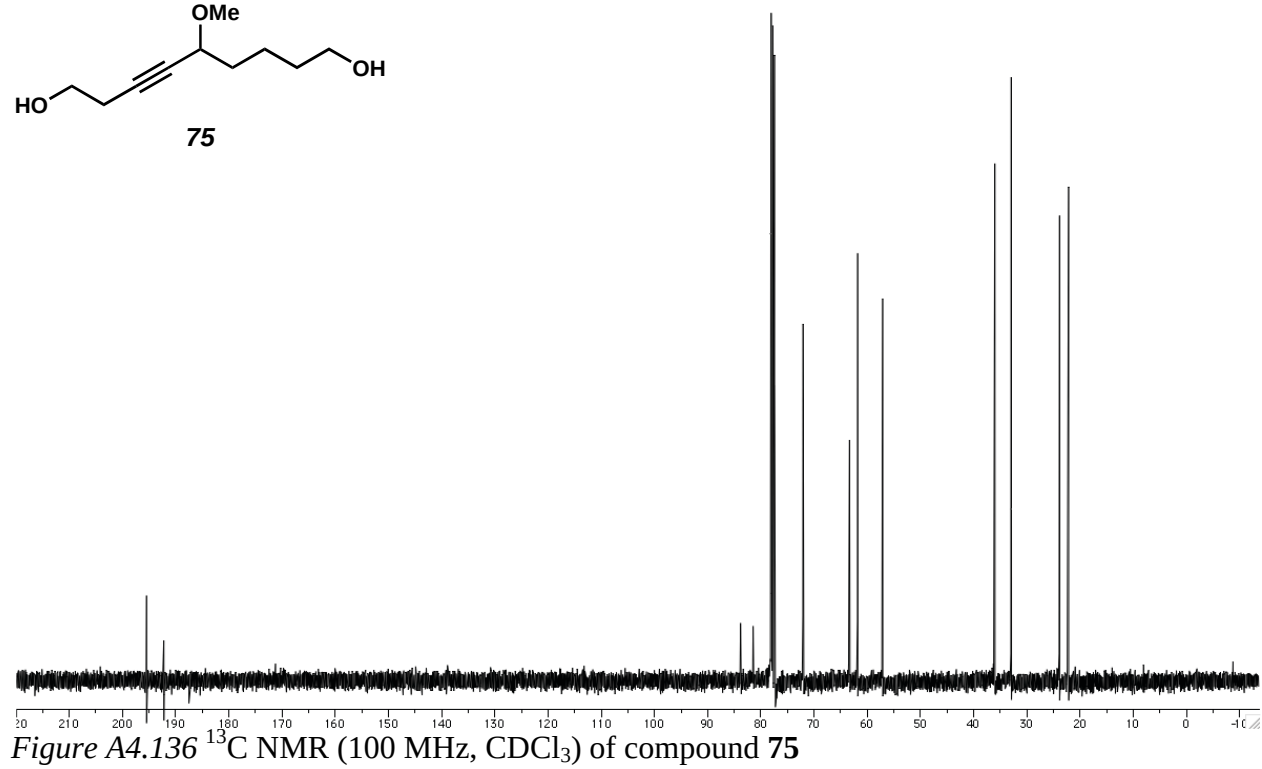
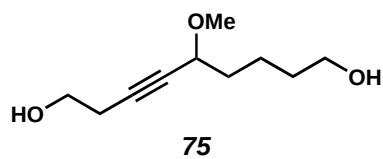


Figure A4.135 ^1H NMR (400 MHz, CDCl_3) of compound 75



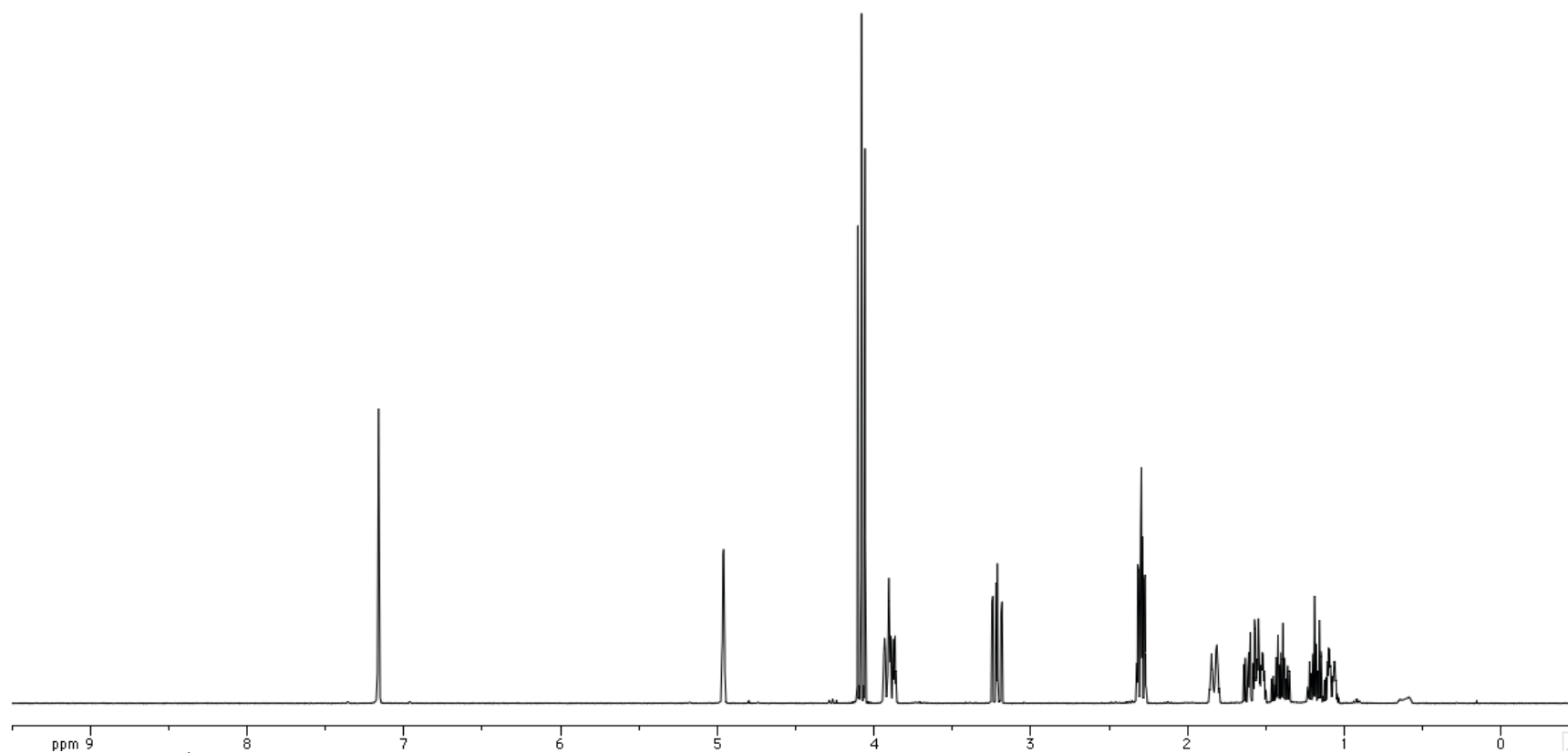
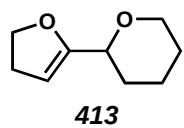
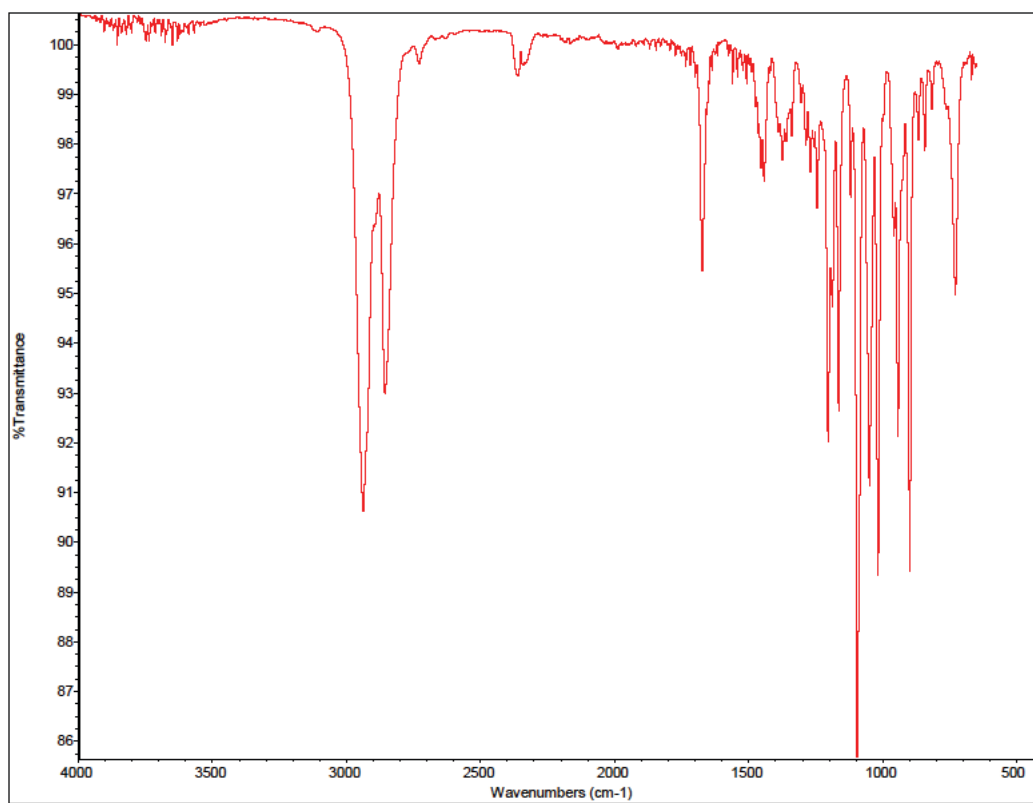
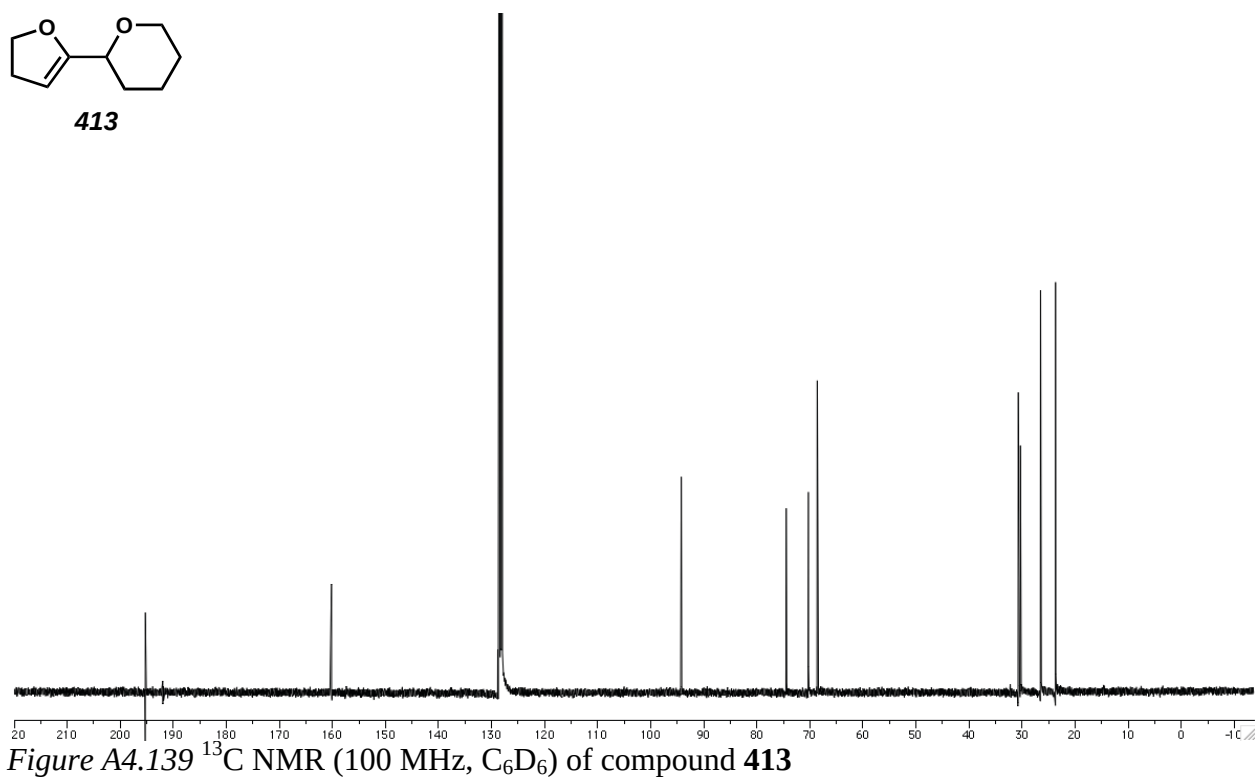
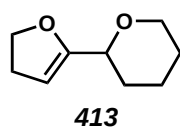


Figure A4.138 ¹H NMR (400 MHz, C₆D₆) of compound **413**



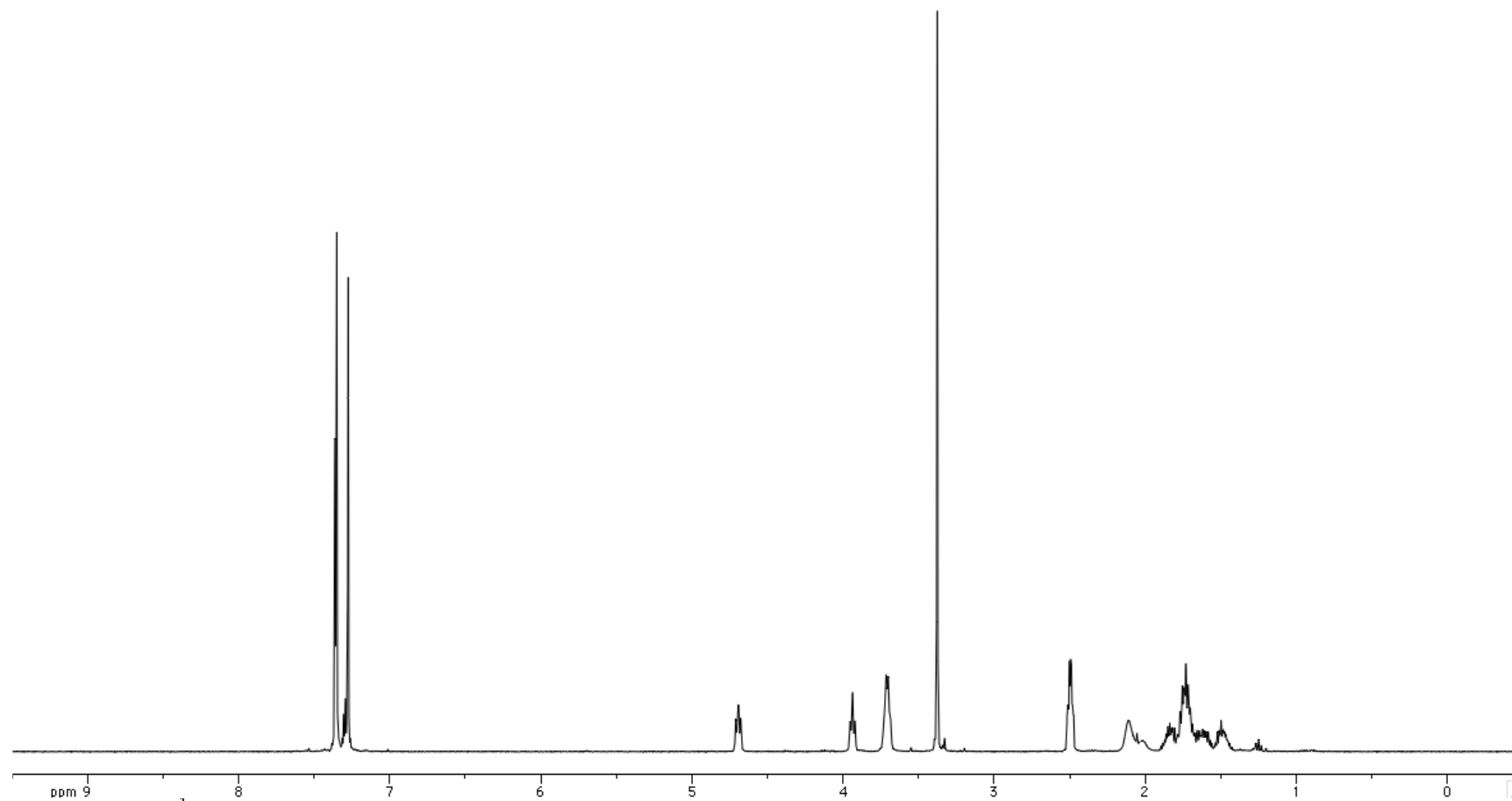
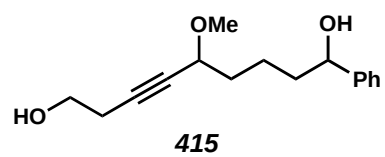


Figure A4.141 ^1H NMR (400 MHz, CDCl_3) of compound **415**

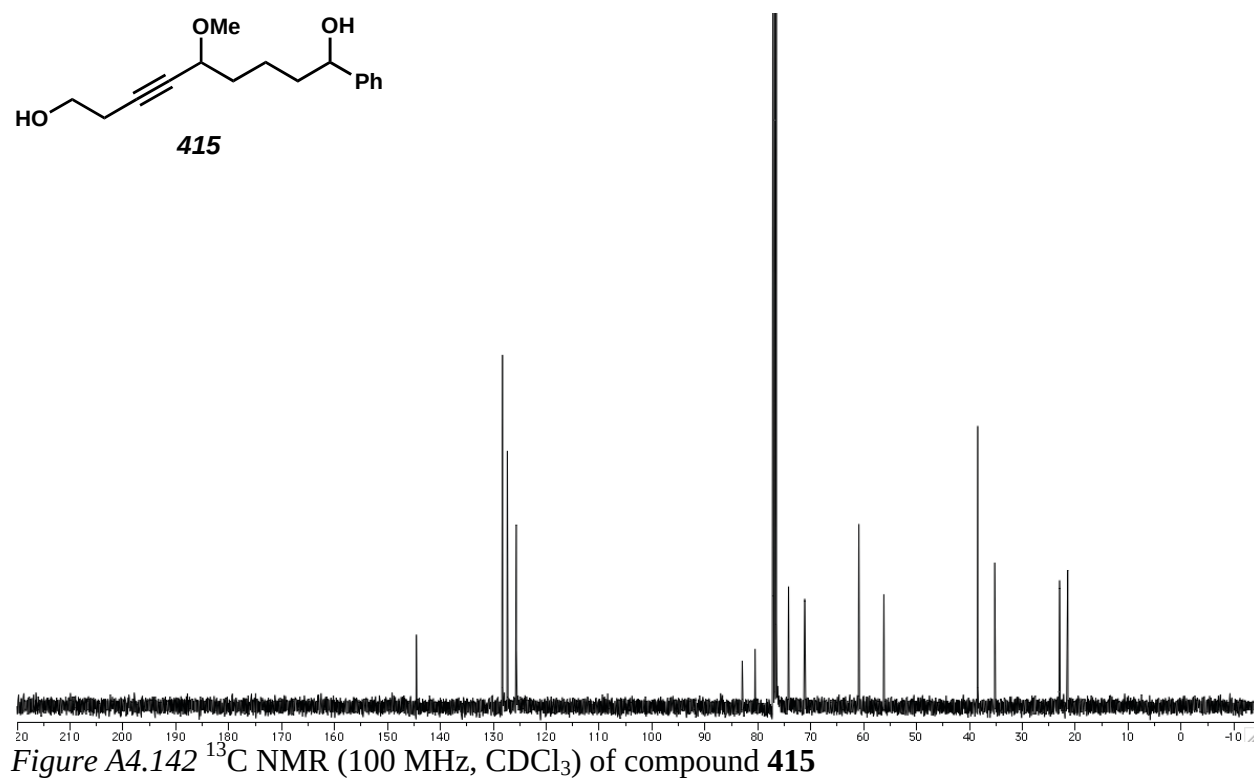
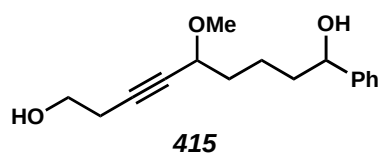


Figure A4.142 ¹³C NMR (100 MHz, CDCl₃) of compound **415**

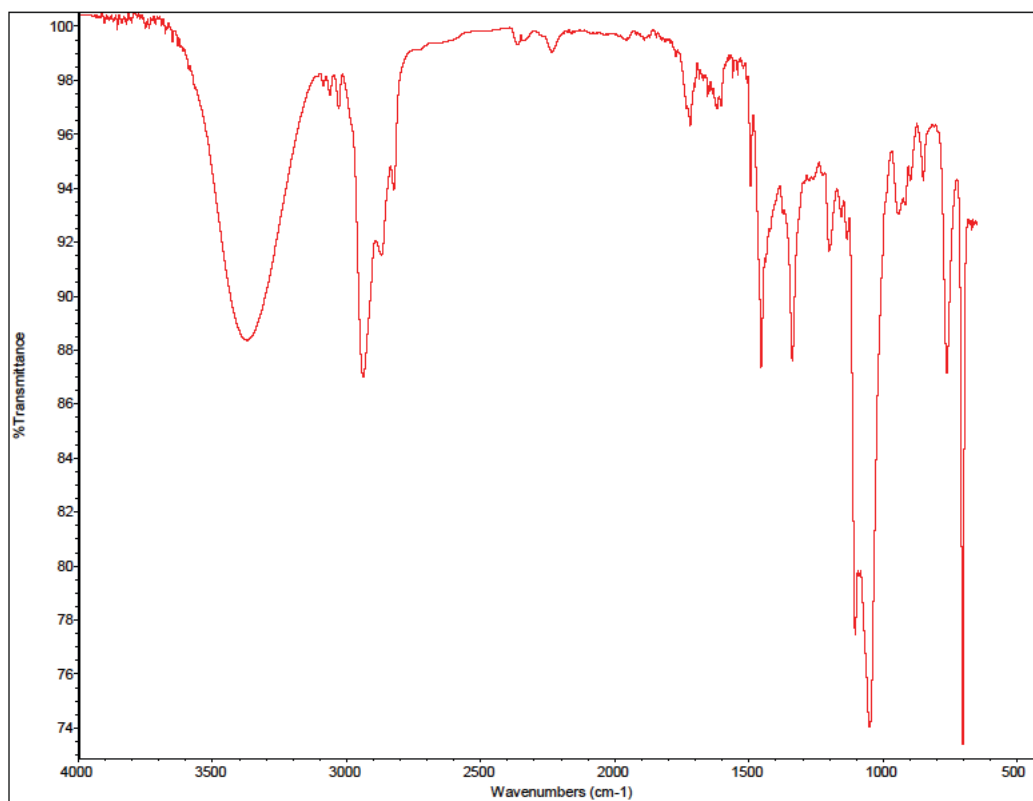


Figure A4.143 Infrared spectrum (thin film) of compound **415**

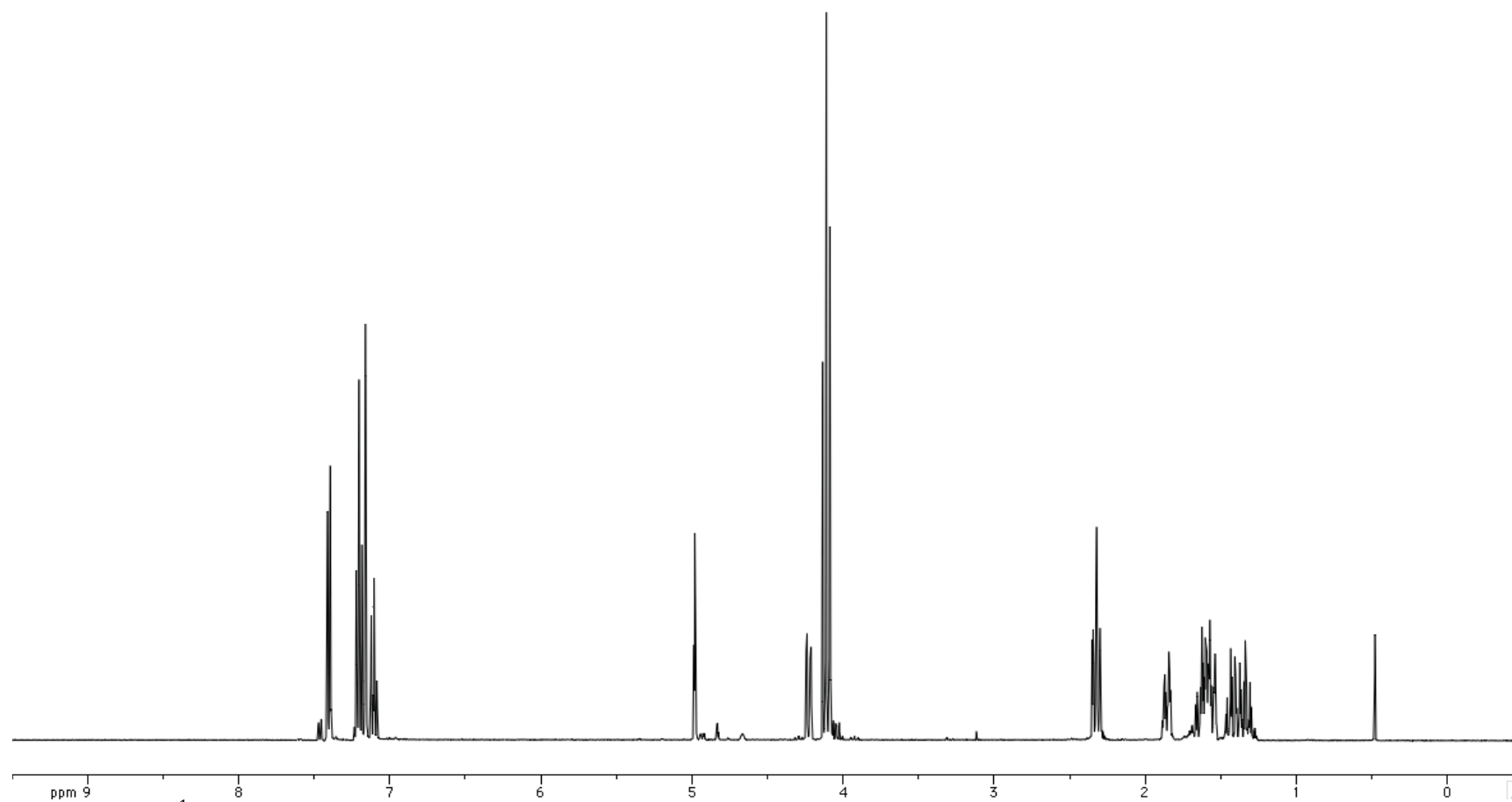
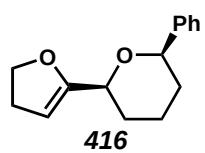


Figure A4.144 ^1H NMR (400 MHz, C_6D_6) of compound **416**

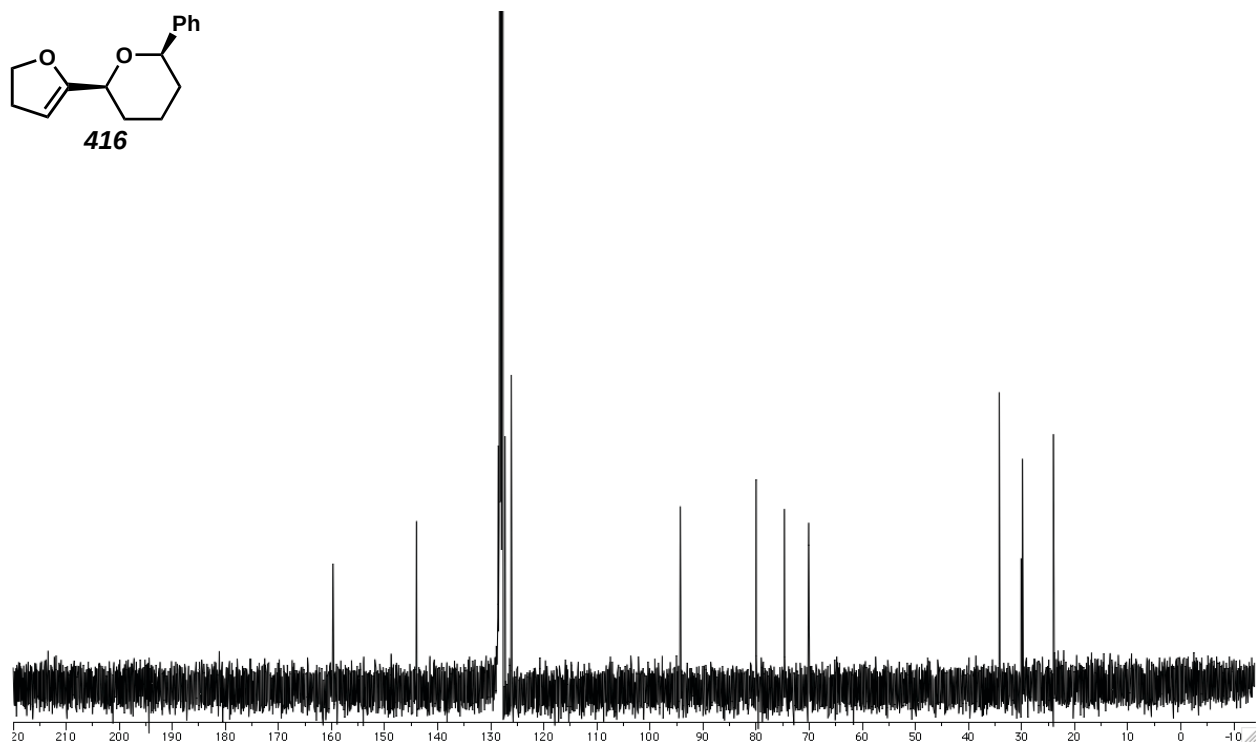


Figure A4.145 ¹³C NMR (100 MHz, C₆D₆) of compound **416**

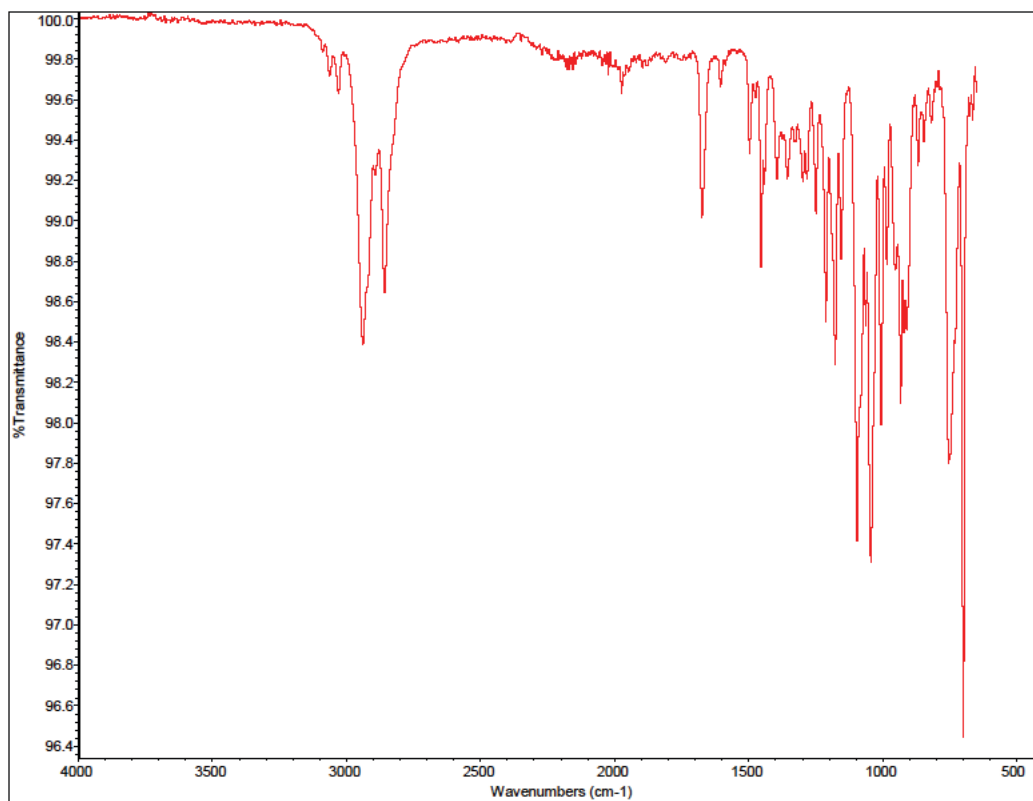


Figure A4.146 Infrared spectrum (thin film) of compound **416**

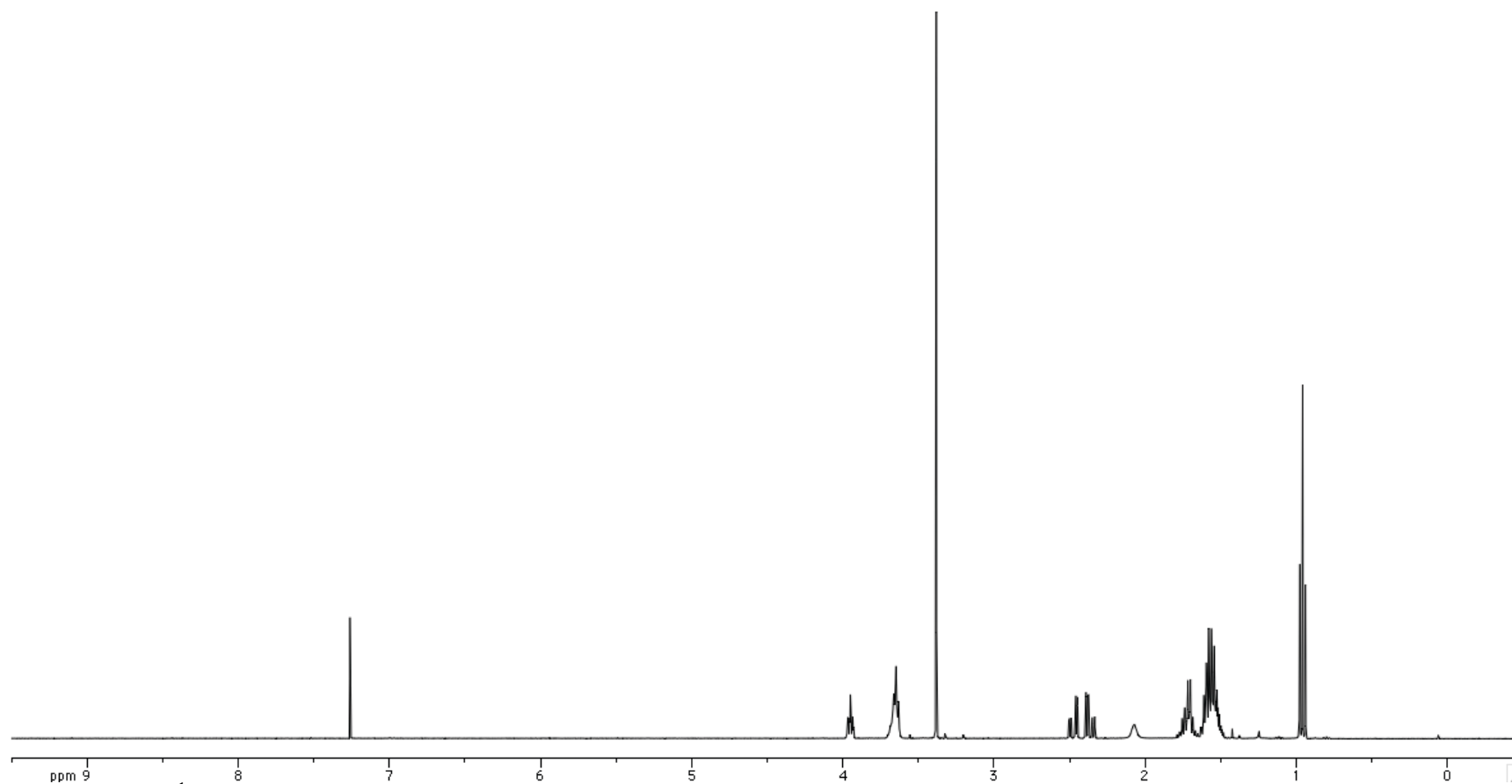
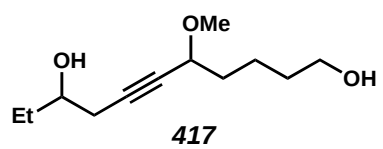
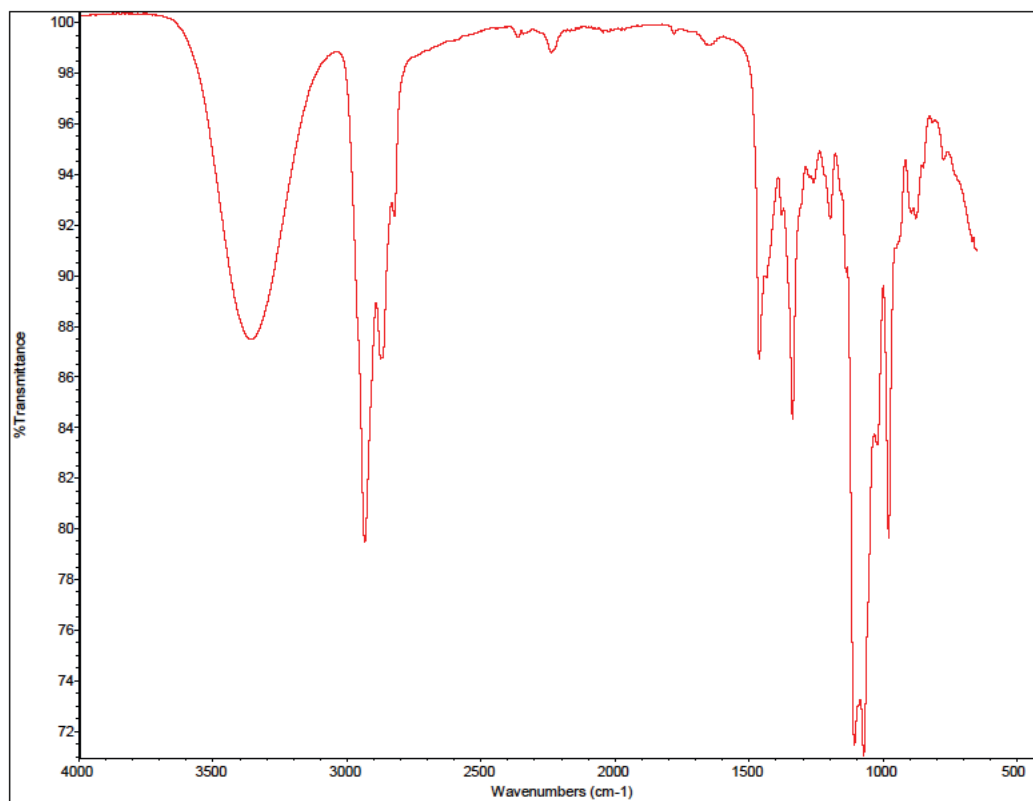
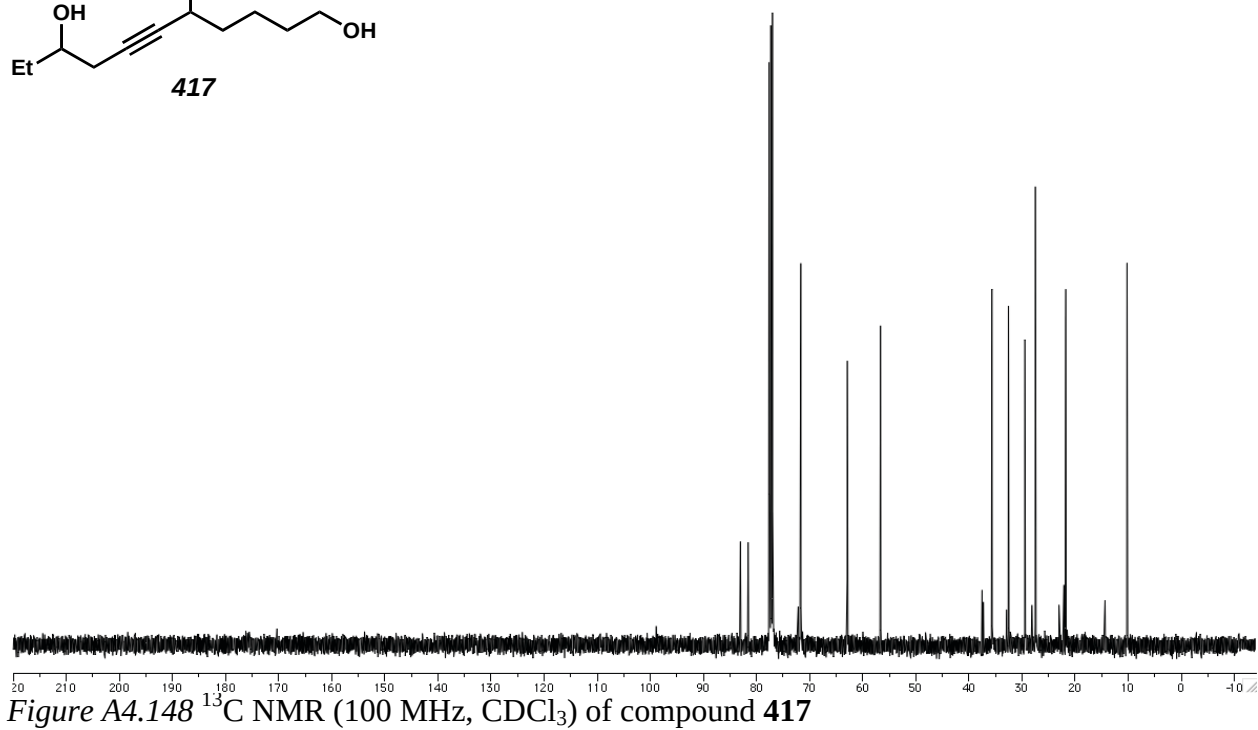
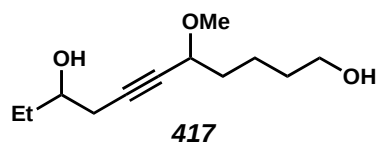


Figure A4.147 ^1H NMR (400 MHz, CDCl_3) of compound **417**



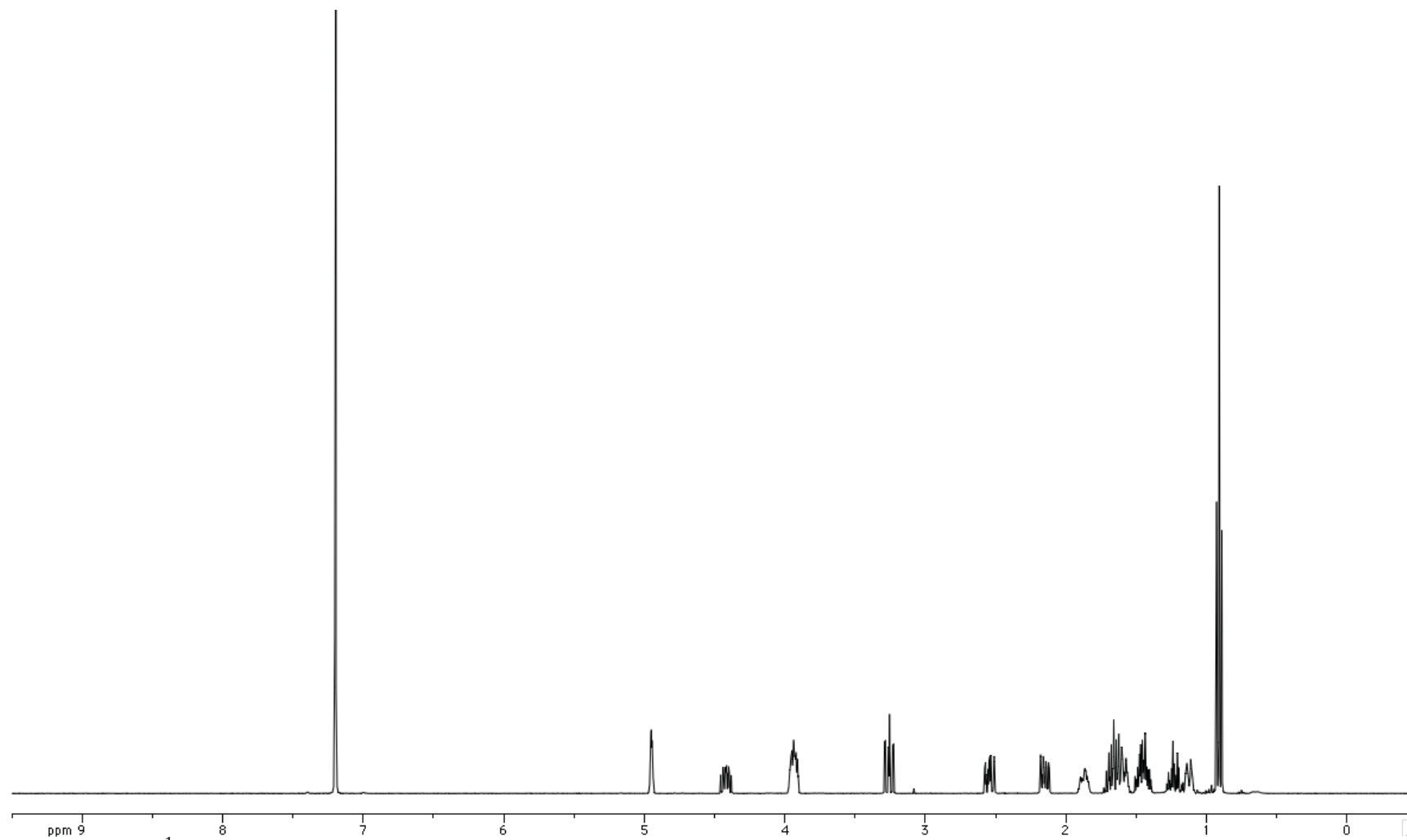
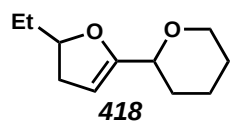


Figure A4.150 ^1H NMR (400 MHz, C_6D_6) of compound **418**

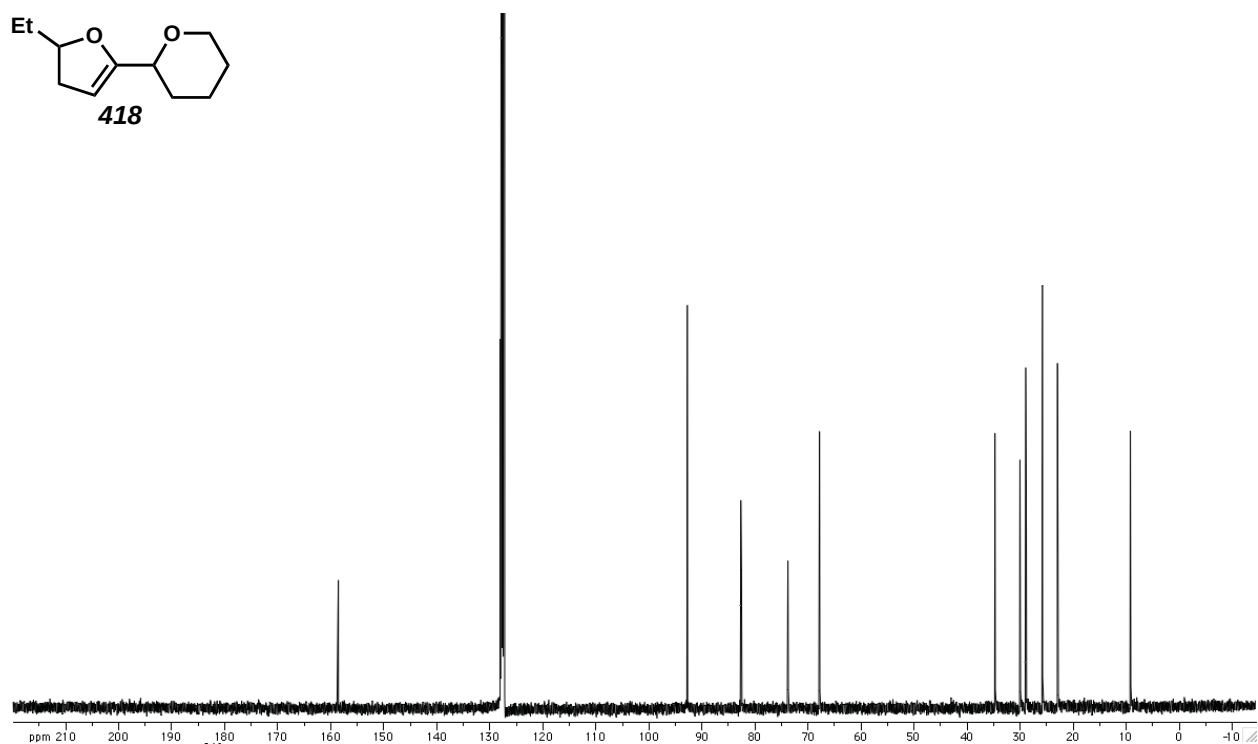
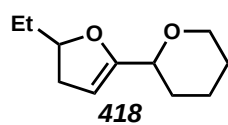


Figure A4.151 ^{13}C NMR (100 MHz, C_6D_6) of compound **418**

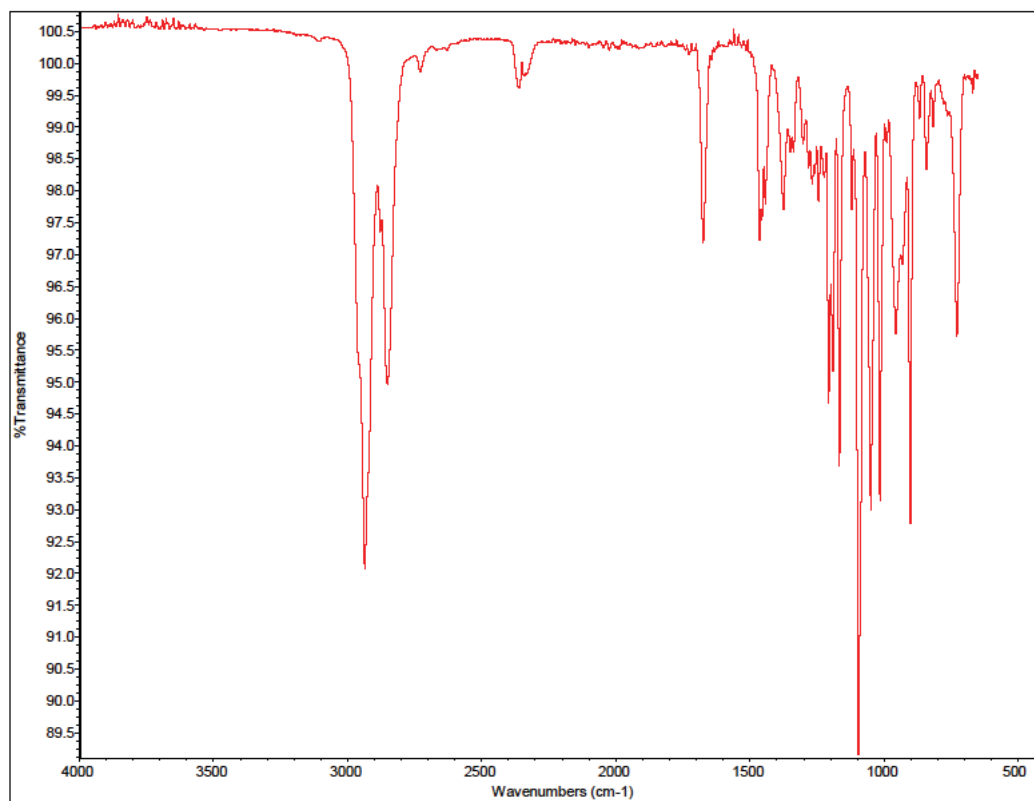
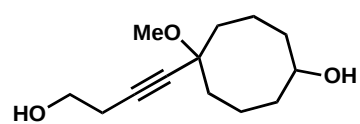


Figure A4.152 Infrared spectrum (thin film) of compound **418**



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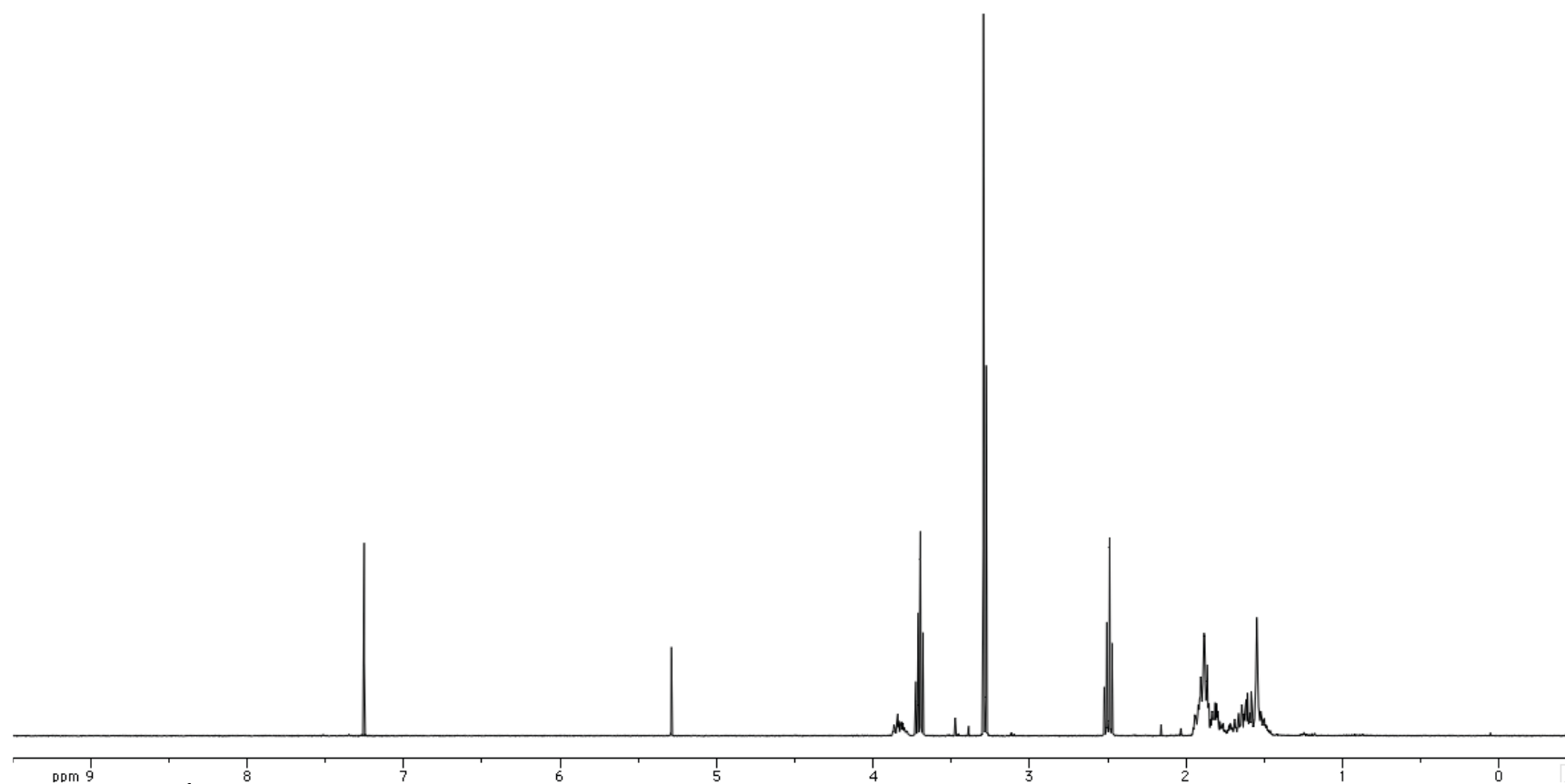
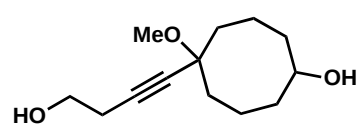


Figure A4.153 ¹H NMR (400 MHz, CDCl₃) of compound **419**



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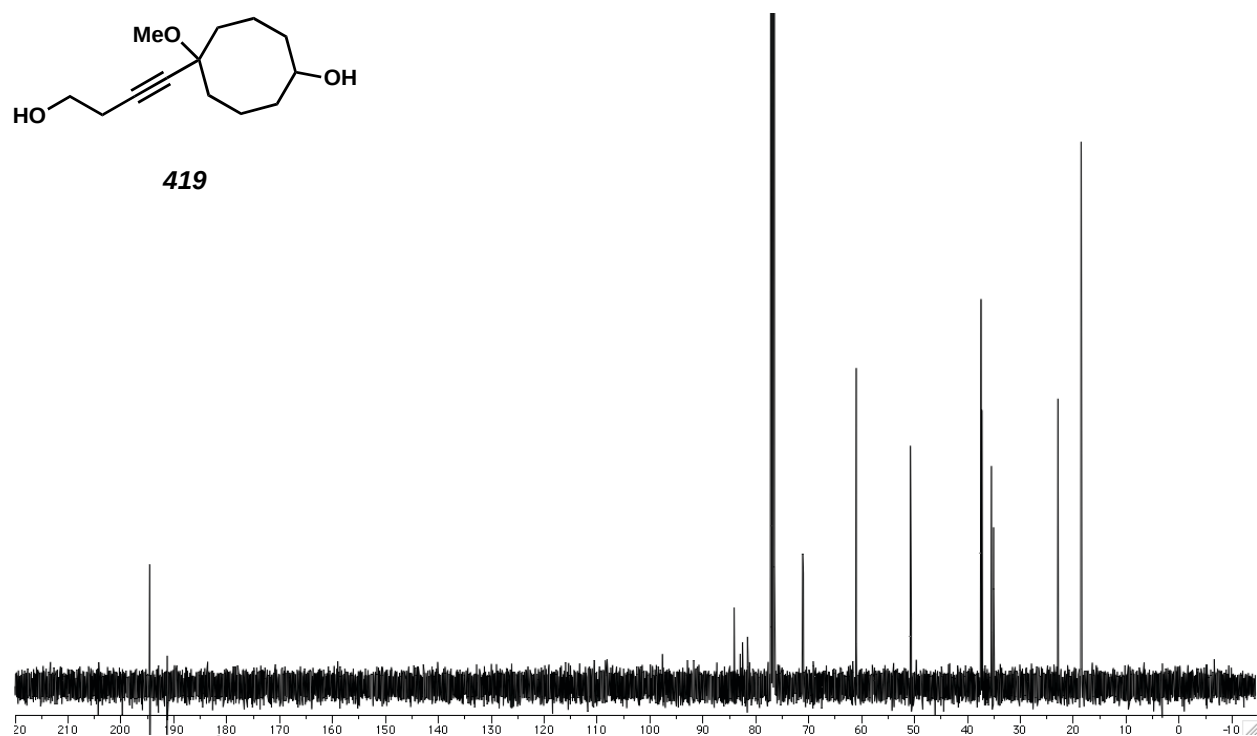


Figure A4.154 ^{13}C NMR (100 MHz, CDCl_3) of compound **419**

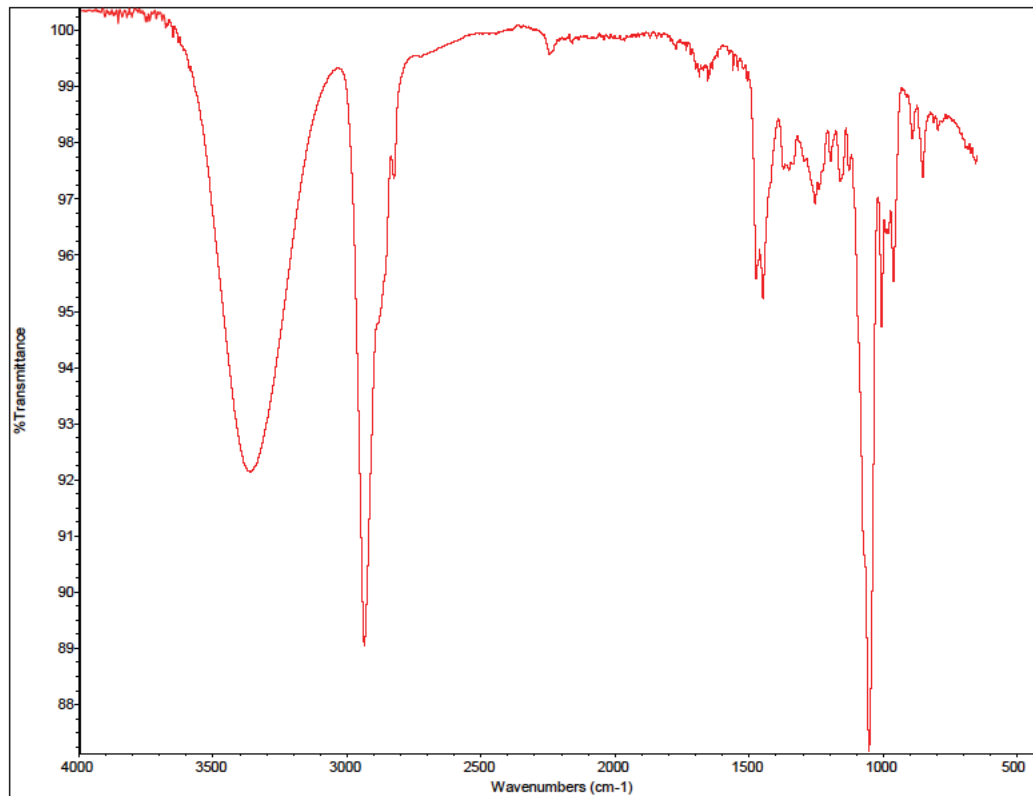


Figure A4.155 Infrared spectrum (thin film) of compound **419**

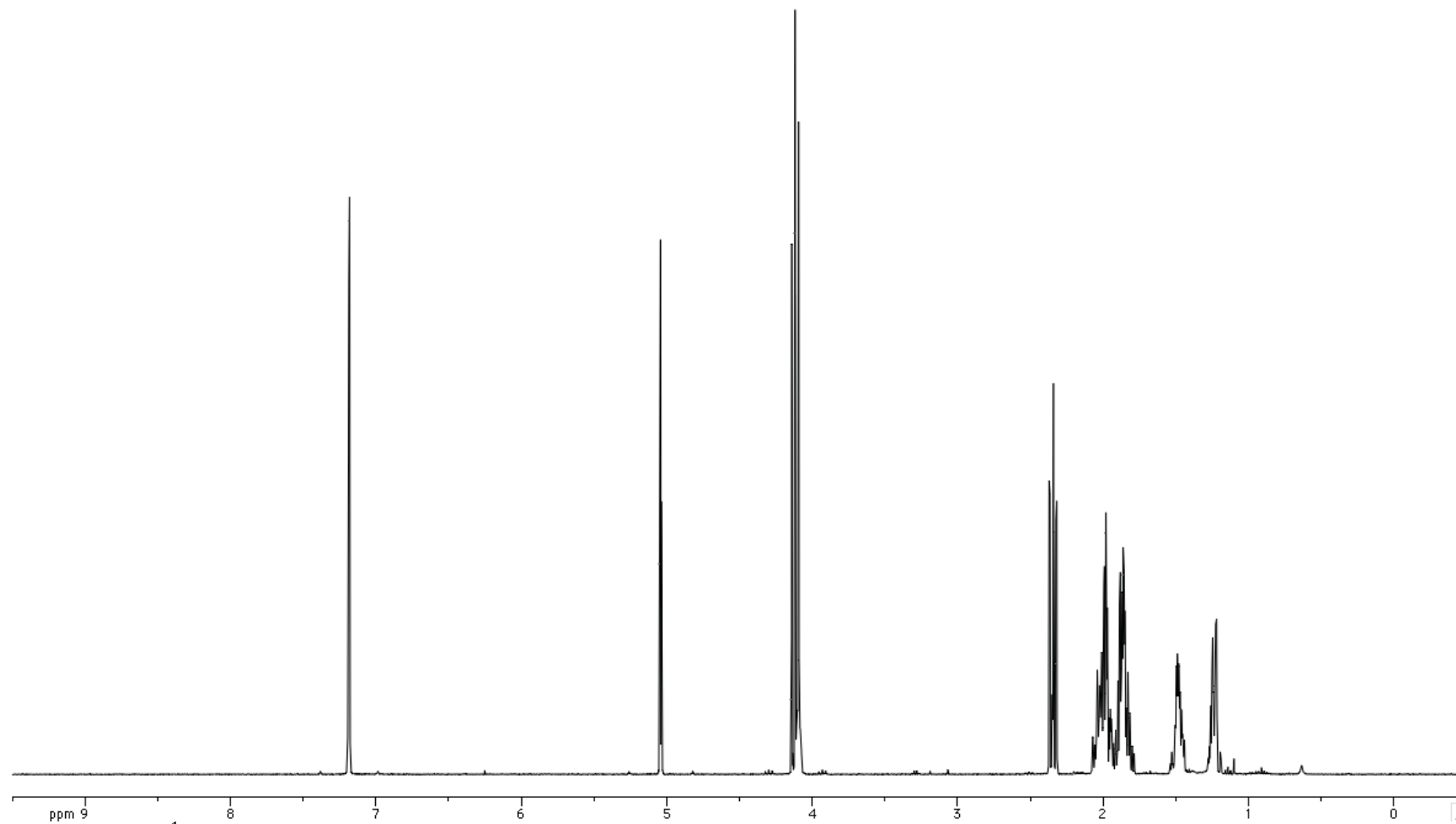
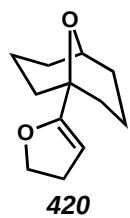
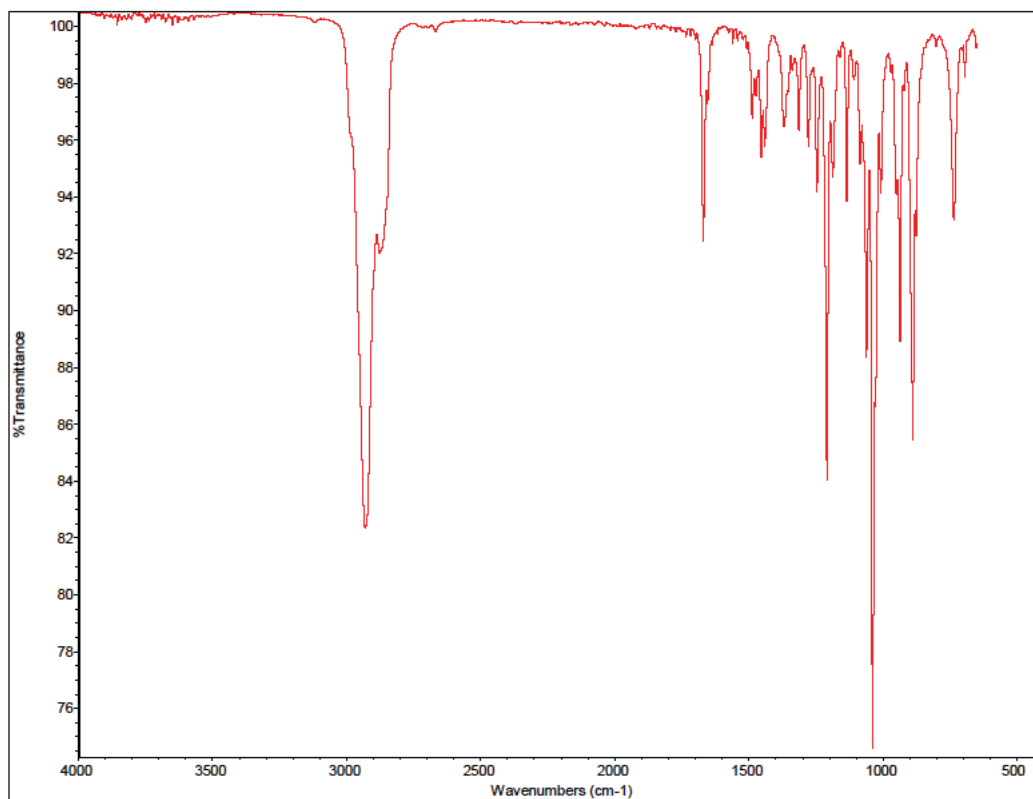
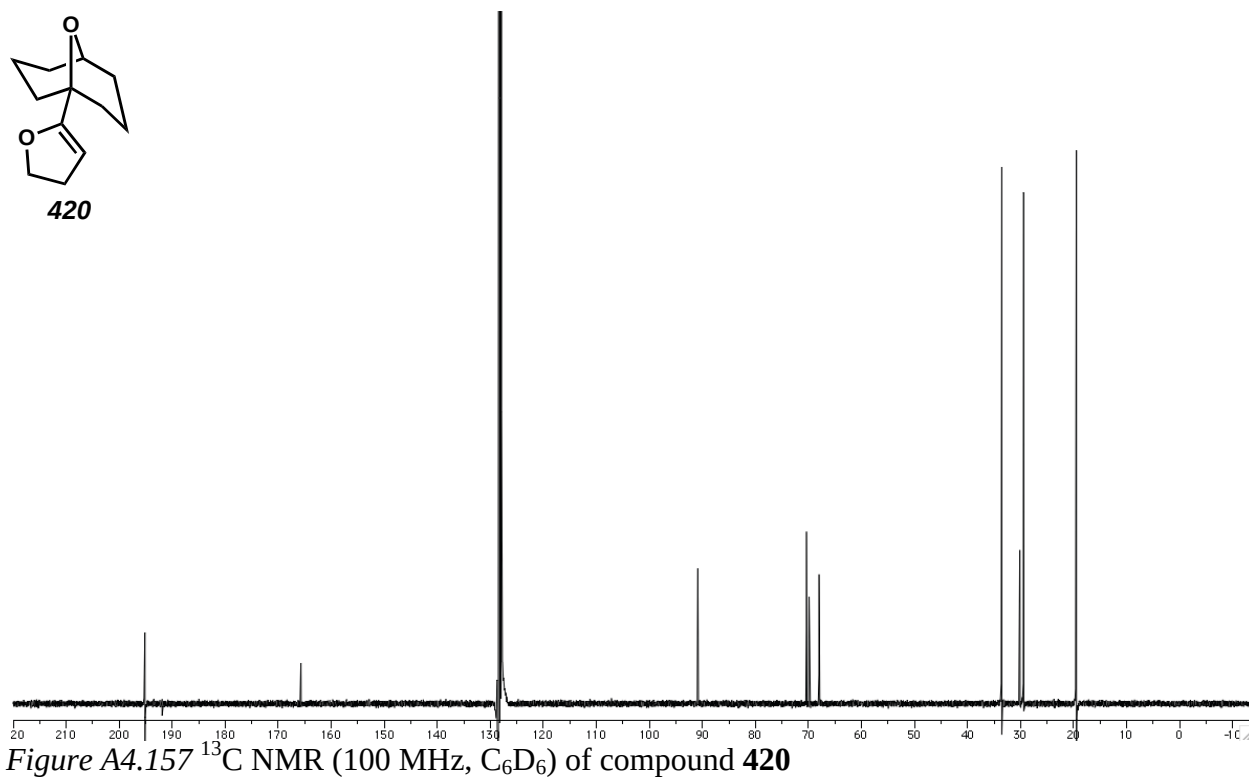


Figure A4.156 ^1H NMR (400 MHz, C_6D_6) of compound **420**



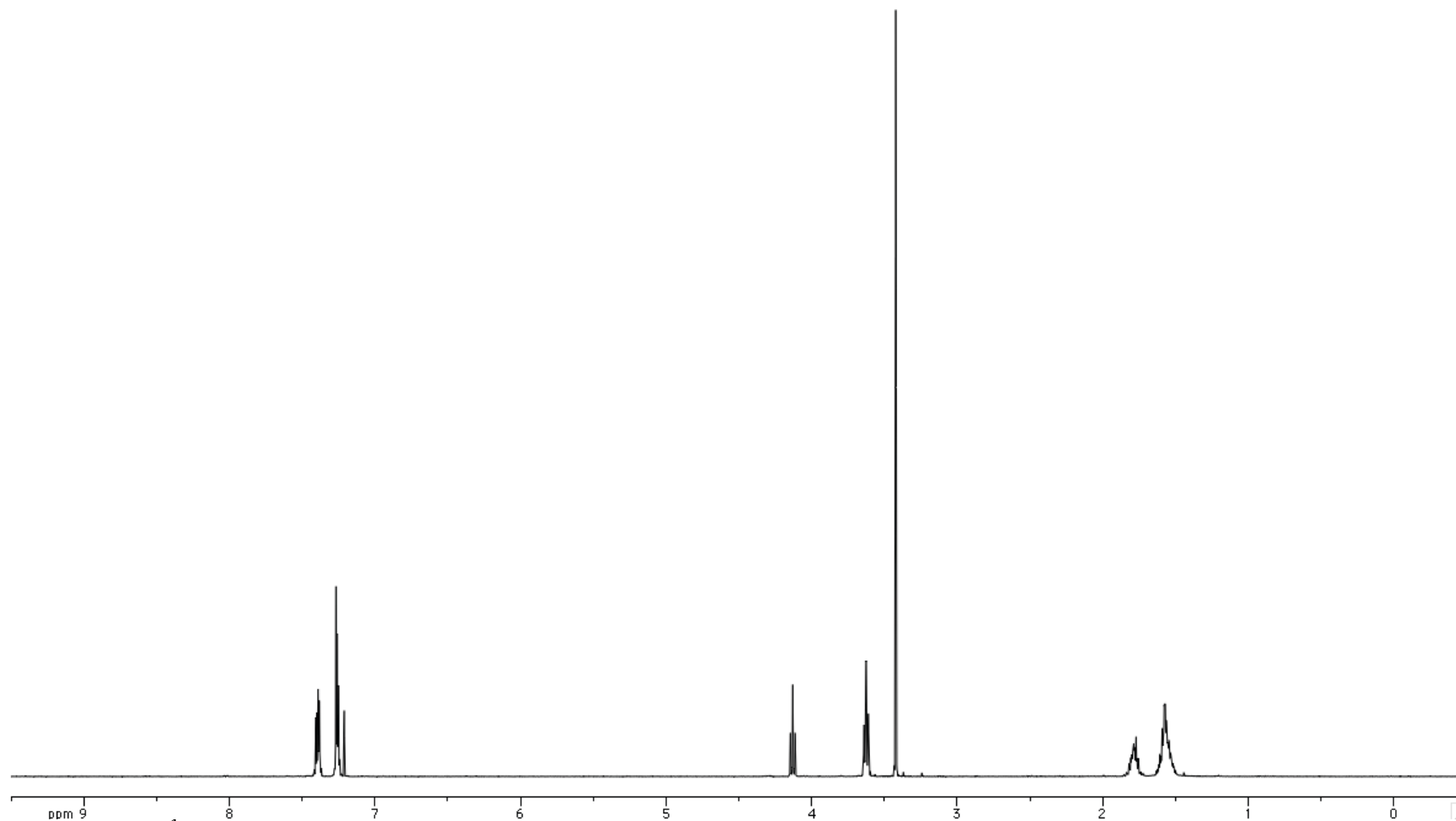
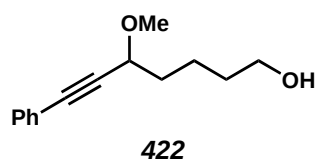


Figure A4.159 ^1H NMR (400 MHz, CDCl_3) of compound **422**

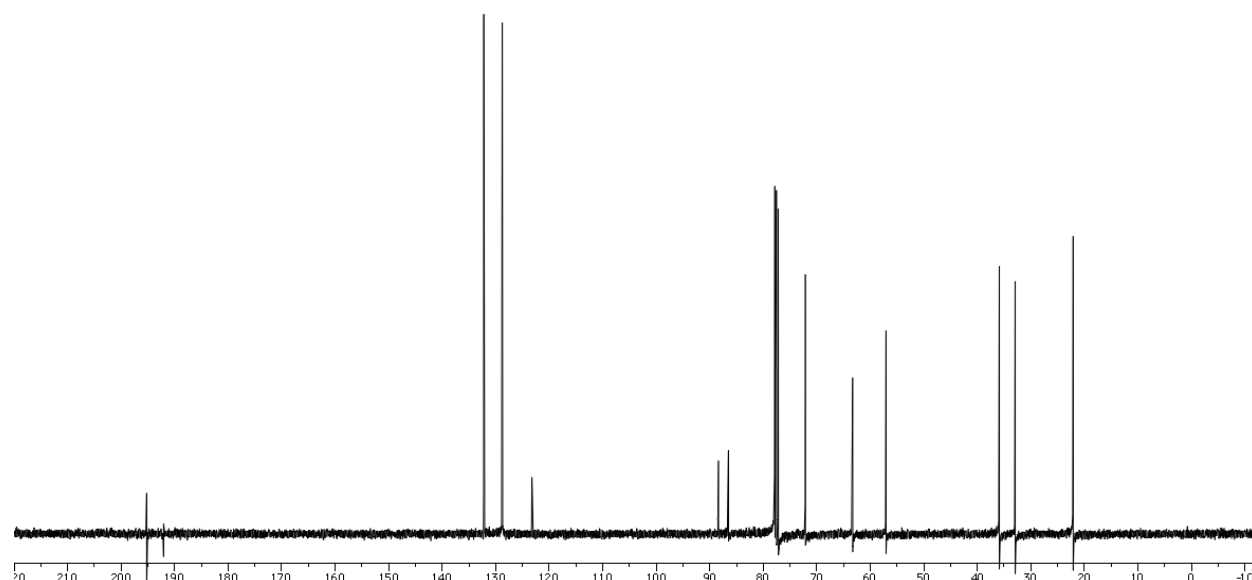
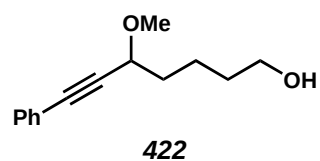


Figure A4.160 ^{13}C NMR (100 MHz, CDCl_3) of compound **422**

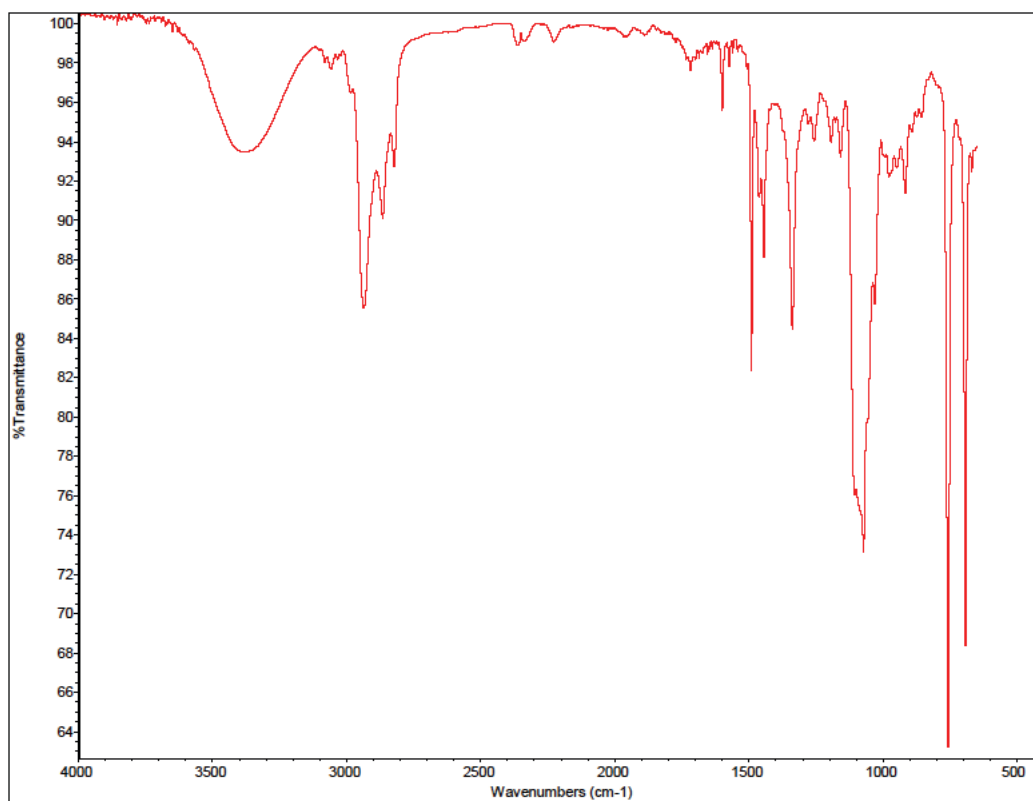


Figure A4.161 Infrared spectrum (thin film) of compound **422**

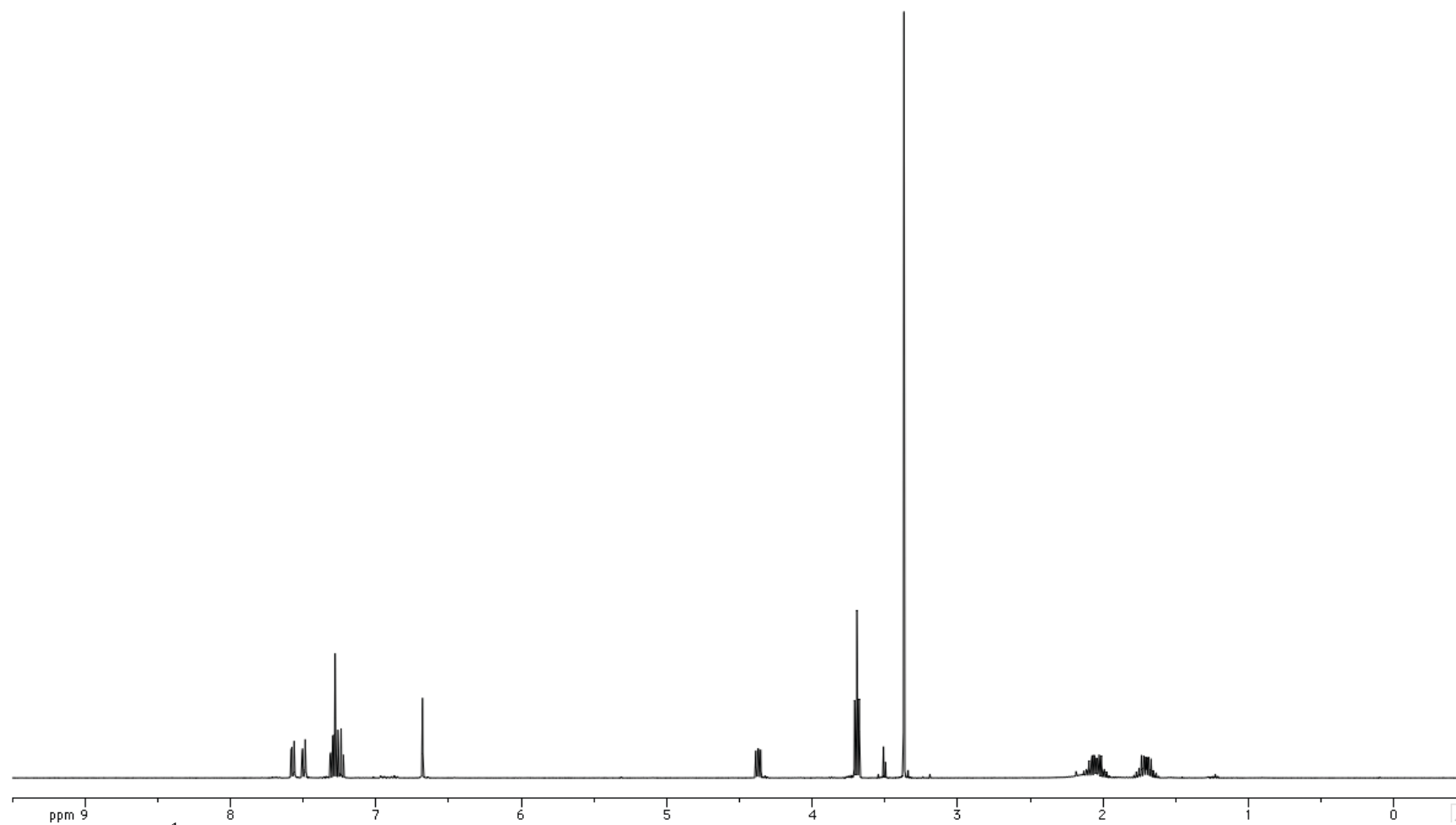
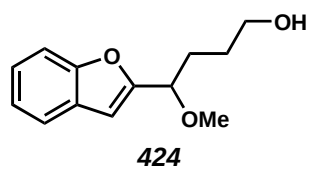
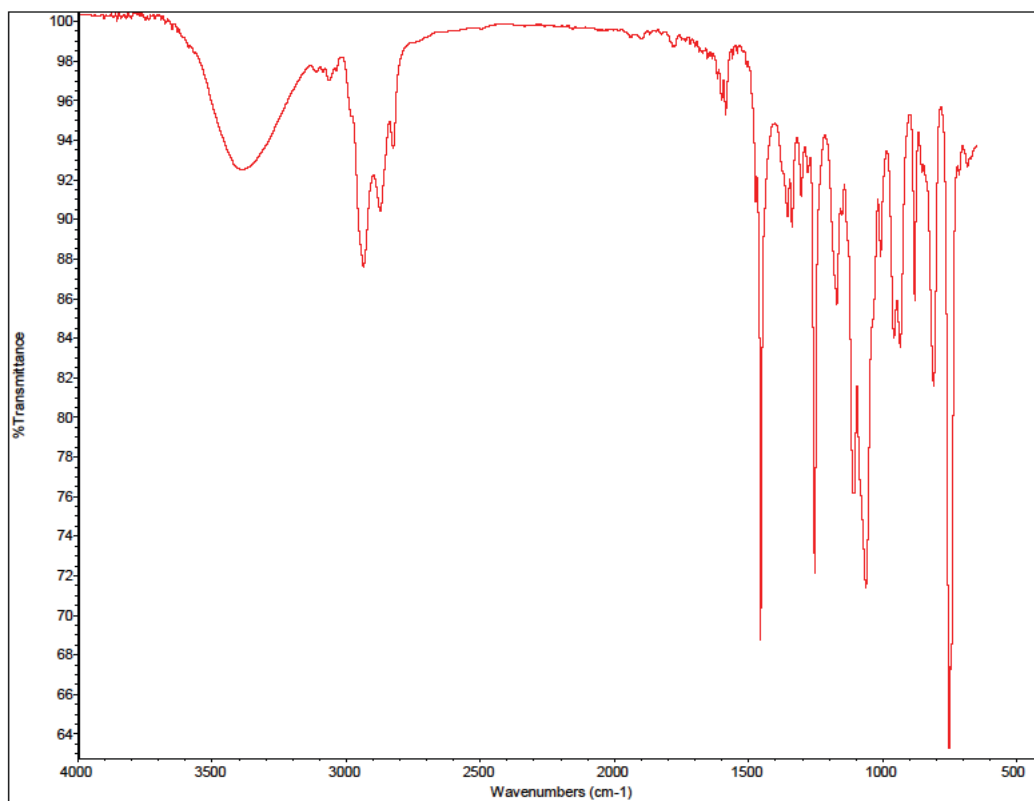
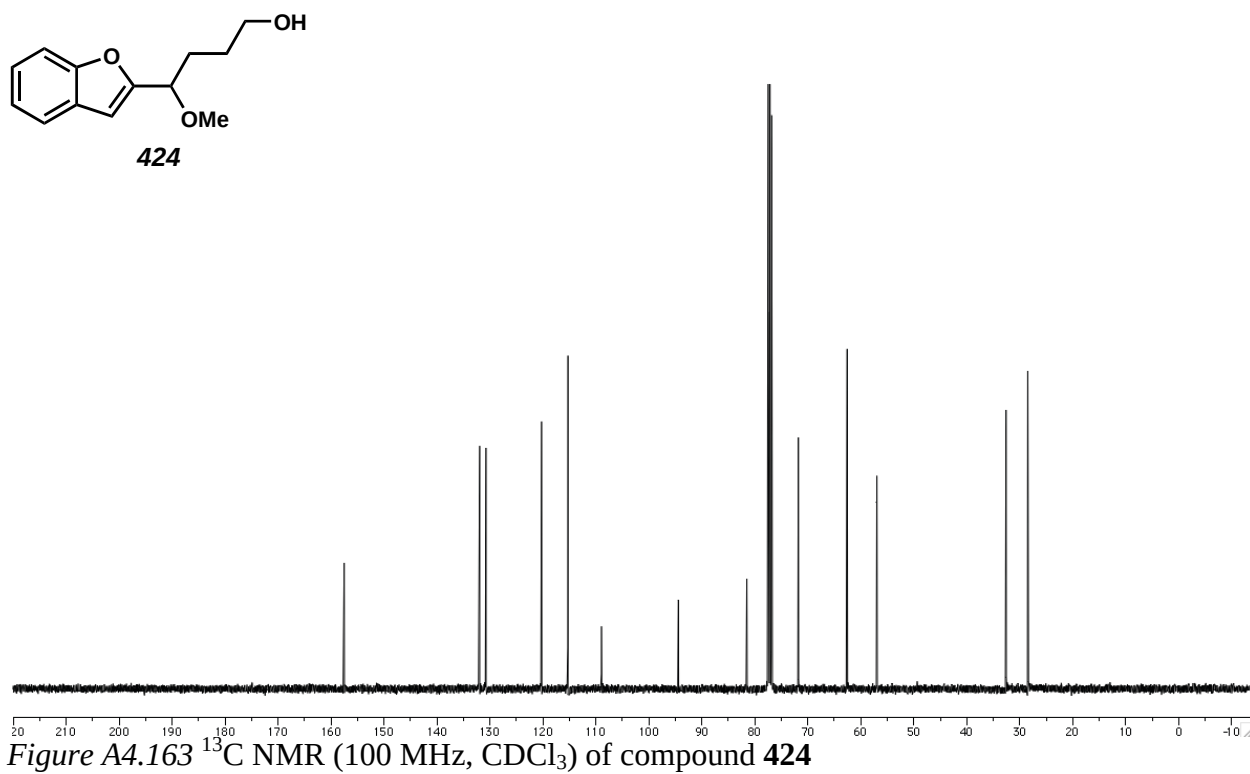


Figure A4.162 ^1H NMR (400 MHz, CDCl_3) of compound **424**



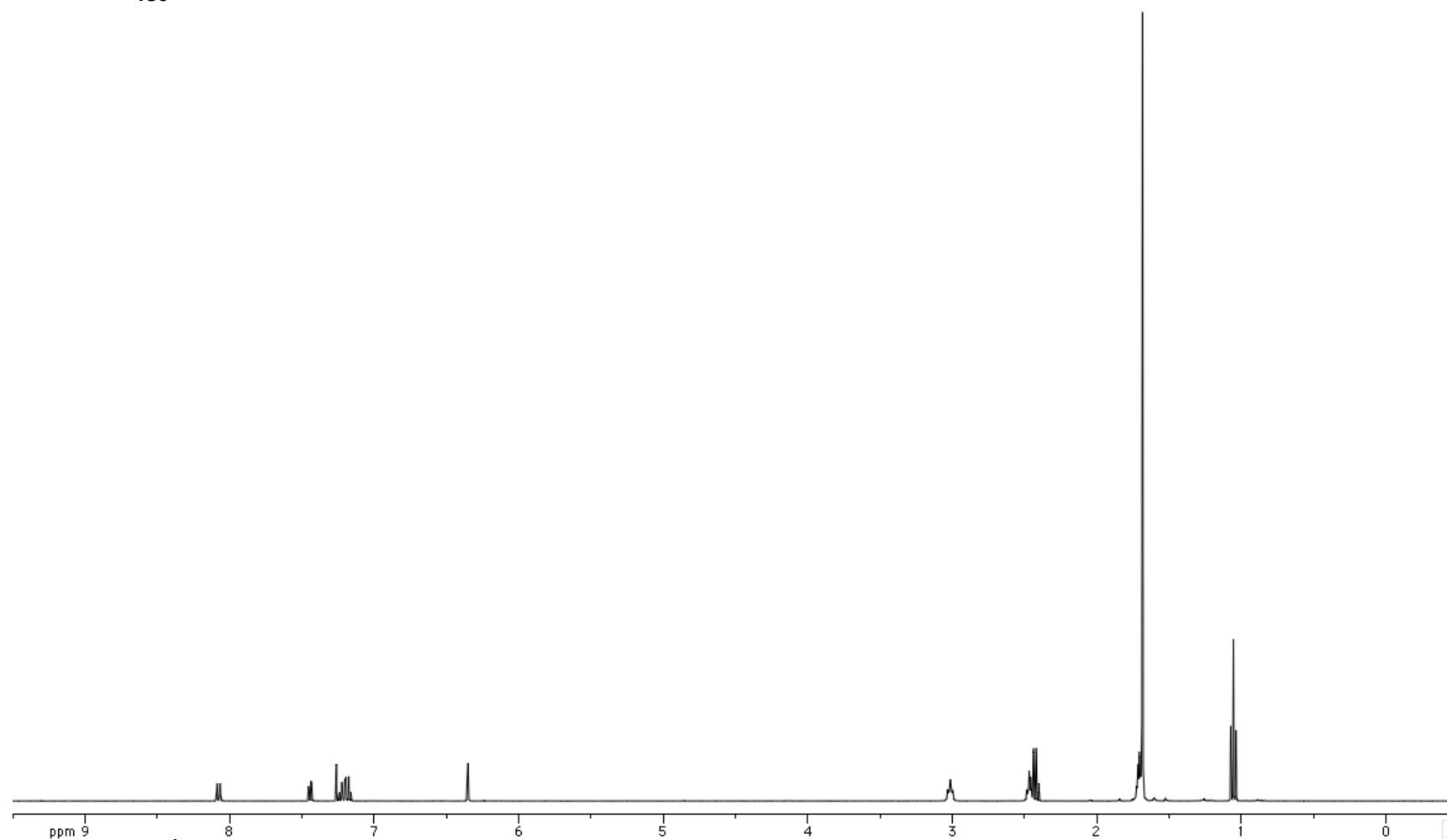
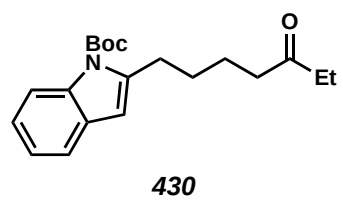


Figure A4.165 ^1H NMR (400 MHz, CDCl_3) of compound **430**

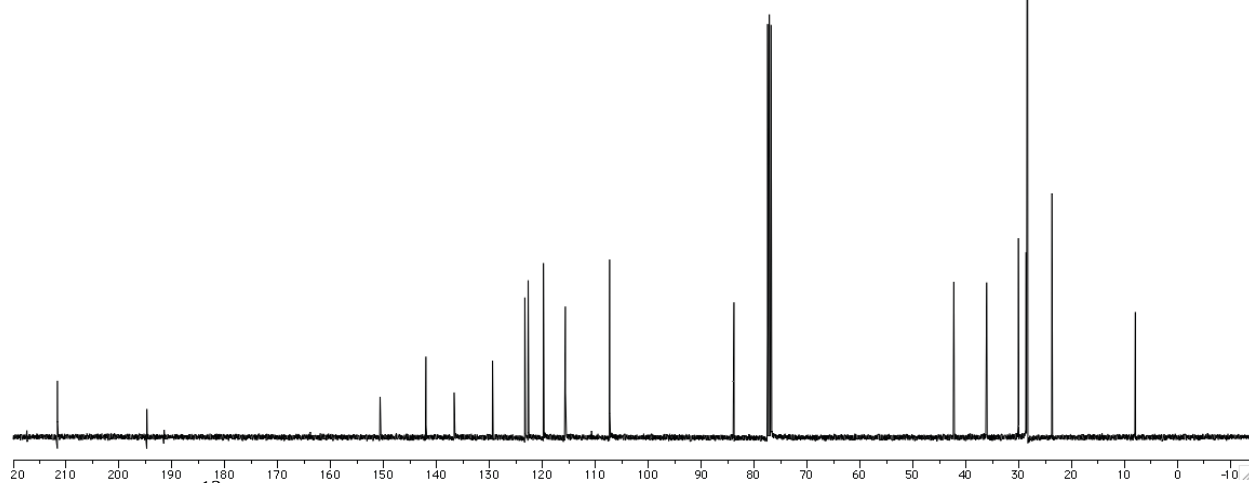
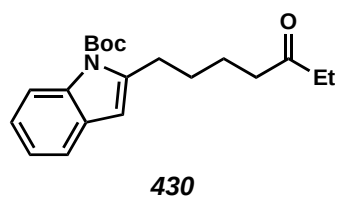


Figure A4.166 ^{13}C NMR (100 MHz, CDCl_3) of compound **430**

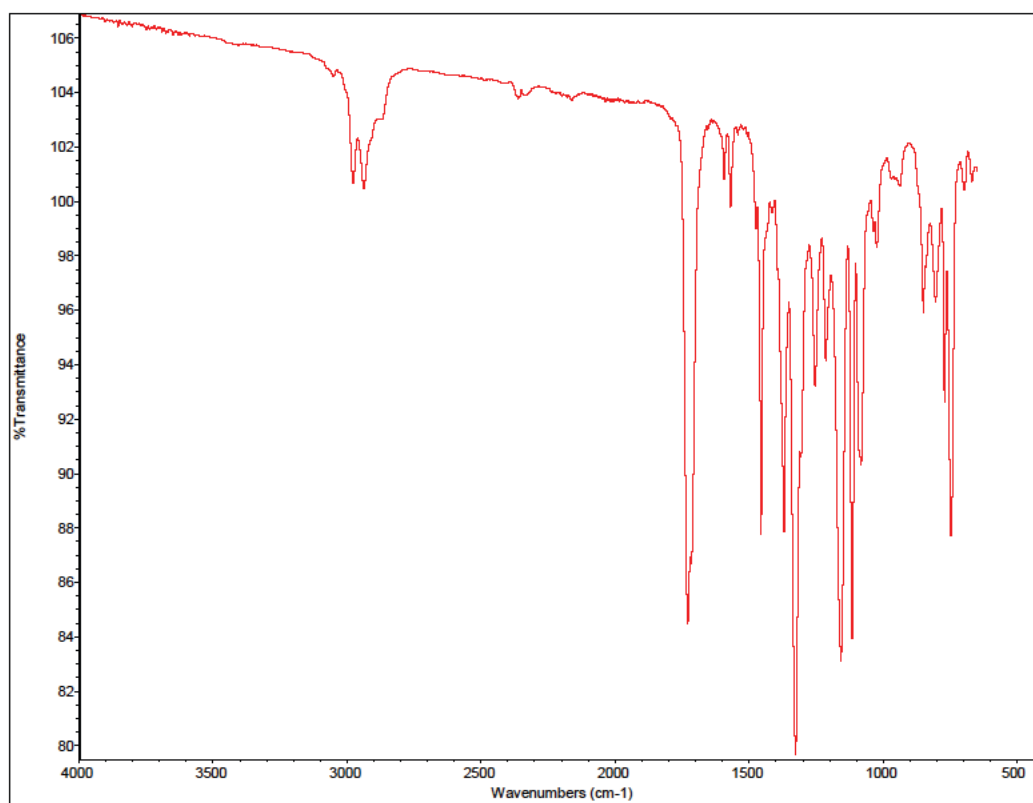


Figure A4.167 Infrared spectrum (thin film) of compound **430**

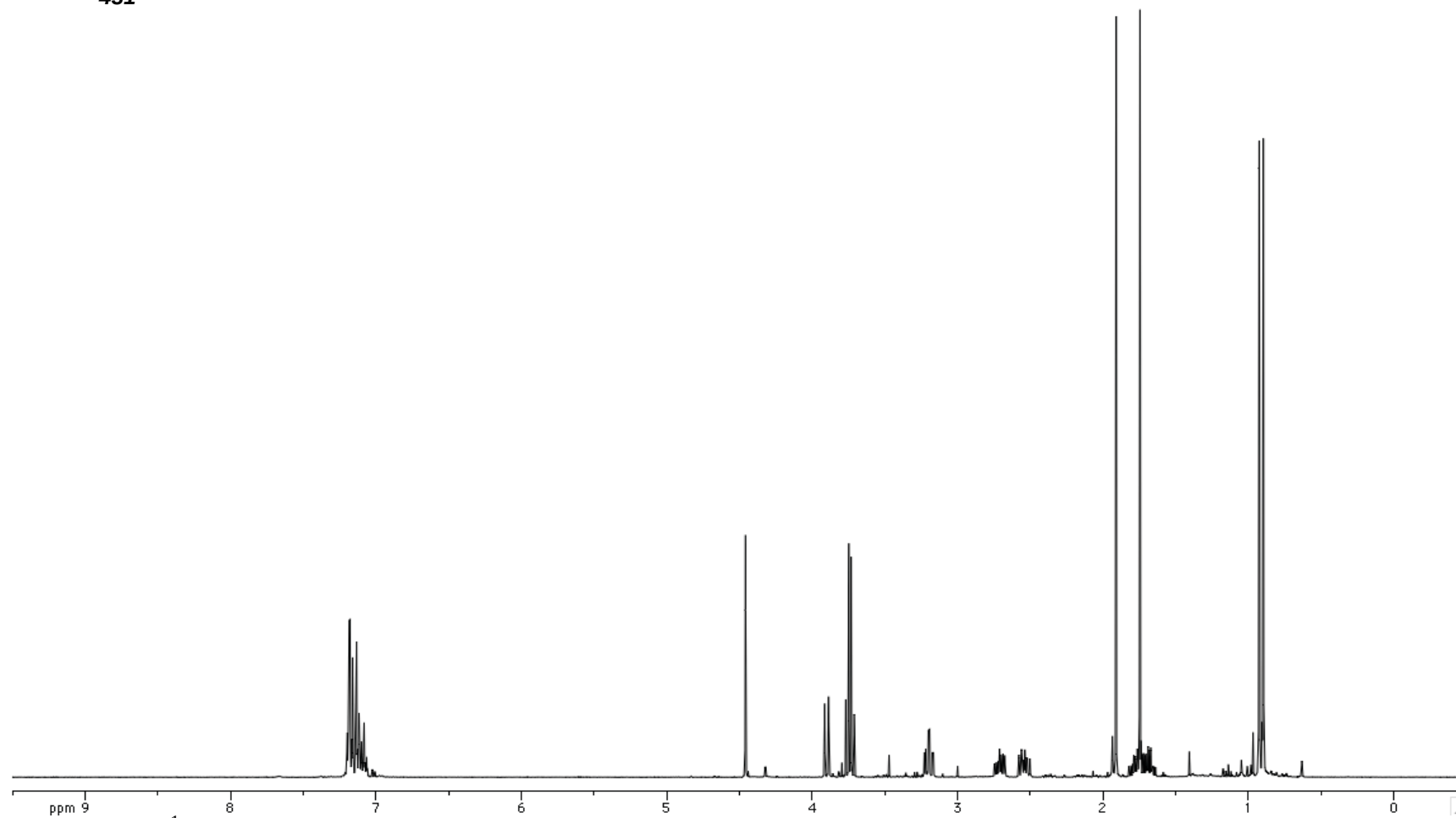
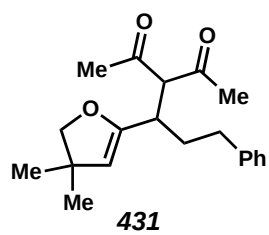
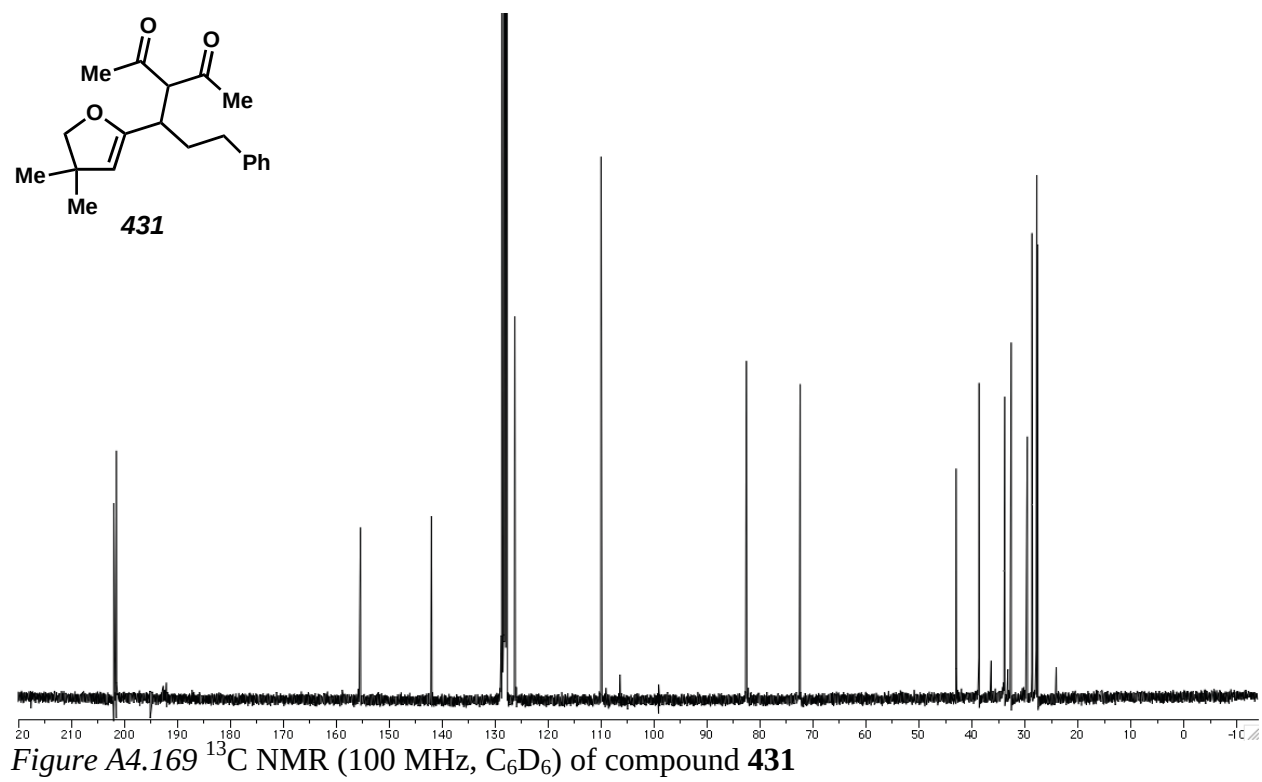
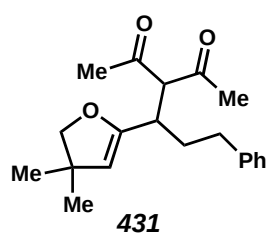


Figure A4.168 ^1H NMR (400 MHz, C_6D_6) of compound **431**



APPENDIX FIVE

Notebook Cross-Reference

The following notebook cross-reference information is included to facilitate access to the original spectroscopic data obtained for the compounds presented in this dissertation. Electronic copies of the original ^1H and ^{13}C NMR FID files and pdf copies of the original IR files are stored on the Ferreira Group computer and back-up hard drive. All files are organized by lab notebook and are identified by my initials followed by the notebook and page numbers (eg. PAA-07-17). Hard copies of the Mass spectra can be found in folders that have been arranged in the order that the compound appear in this dissertation.

Table A5.1. Compounds in Chapter Two Listed as They Appear

Synthesis of Polysubstituted Furans via 1,2-Hydride Migrations into Platinum Carbenes

Compound	^1H NMR	^{13}C NMR	IR
23	PAA-02-13clm	N/A	N/A
24	PAA-02-67clm_8-9	N/A	N/A
25	PAA-02-67benzene	N/A	N/A
31	PAA-07-17	PAA-07-17	PAA-12-13
39	PAA-12-02	PAA-12-02	PAA-12-02
40	PAA-09-22	PAA-09-22	PAA-09-22
41	PAA-09-20	PAA-09-20	PAA-09-20
42	PAA-09-23	PAA-09-23	PAA-09-23
43	PAA-11-35	PAA-11-35	PAA-11-35
45	PAA-09-24	PAA-09-24	PAA-09-24
46	PAA-08-30	PAA-08-30	PAA-08-30
47	PAA-08-34	PAA-08-34	PAA-08-34
48	PAA-08-31	PAA-08-31	PAA-08-31
49	PAA-08-35	PAA-08-35	PAA-08-35
50	PAA-07-51	PAA-07-51	PAA-11-74

51	PAA-11-76	PAA-11-76	PAA-11-76
52	PAA-10-49	PAA-10-49	PAA-10-49
53	PAA-10-60	PAA-10-60	PAA-10-60
54	PAA-11-38clm2	PAA-11-38clm2	PAA-11-38
55	PAA-10-85	PAA-10-85	N/A
56	PAA-12-22	PAA-12-22	PAA-12-22
57	PAA-12-25	PAA-12-25	PAA-12-25
58	PAA-08-81	PAA-08-81	PAA-08-81
59	PAA-08-82	PAA-08-82	PAA-08-82
60	PAA-09-53	PAA-09-53	PAA-09-53
61	PAA-09-56	PAA-09-56	PAA-09-56
62	PAA-08-59	PAA-08-59	PAA-08-59
63	PAA-08-66	PAA-08-66	PAA-08-66
64	PAA-08-58	PAA-08-58	PAA-08-58
65	PAA-08-67	PAA-08-67	PAA-08-67
66	PAA-07-62	PAA-07-62	PAA-08-69
67	PAA-11-79	PAA-11-79	PAA-11-79
68	PAA-11-73	PAA-11-73	PAA-11-73
69	PAA-11-91	PAA-11-91	PAA-11-91
70	PAA-11-95	PAA-11-95	PAA-11-95
80	PAA-14-49	PAA-14-49	PAA-14-49

Table A5.2. Compounds in Chapter Three Listed as They Appear
 Synthesis of Complementary Positional Isomers of Isoxazoles

Compound	¹ H NMR	¹³ C NMR	IR
153	PAA-14-70	PAA-14-70	PAA-14-70
154	PAA-19-68b	PAA-19-68b	PAA-14-74
155	PAA-19-68a	PAA-19-68a	PAA-19-68a
157	PAA-15-08	PAA-15-08	PAA-15-08
158	PAA-15-02	PAA-15-02	PAA-15-02
159	PAA-15-09	PAA-15-09	PAA-15-09
160	PAA-15-10	PAA-15-10	PAA-15-10
161	PAA-16-69	PAA-16-69	PAA-16-69
162	PAA-17-59	PAA-17-59	PAA-17-59
163	PAA-17-83	PAA-17-83	PAA-17-30
167	PAA-16-80	PAA-16-80	PAA-16-80

168	PAA-16-84	PAA-16-84	PAA-16-84
169	PAA-16-29	PAA-16-29	PAA-16-29
170	PAA-16-35	PAA-16-35	PAA-16-35
171	PAA-16-02	PAA-16-02	PAA-16-02
172	PAA-16-18	PAA-16-18	PAA-16-18
173	PAA-17-58	PAA-17-58	PAA-17-58
174	PAA-17-60	PAA-17-60	PAA-17-60
175	PAA-17-91	PAA-17-91	N/A
176	PAA-17-95	PAA-17-95	PAA-17-95
177	PAA-18-91	PAA-18-91	PAA-18-91
178	PAA-18-95	PAA-18-95	PAA-18-95
179	PAA-18-92	PAA-18-92	PAA-18-92
180	PAA-18-96	PAA-18-96	PAA-18-96
195	PAA-16-87	PAA-16-87	PAA-16-87
198	PAA-17-08	PAA-17-08	PAA-17-08
199	PAA-17-18	PAA-17-18	PAA-17-18
200	PAA-17-25	PAA-17-25	PAA-17-25
201	PAA-17-19	PAA-17-19	PAA-17-19
202	PAA-17-26	PAA-17-26	PAA-17-26
203	PAA-17-23	PAA-17-23	PAA-17-23
204	PAA-17-27	PAA-17-27	PAA-17-27
205	PAA-17-52	PAA-17-52	PAA-17-52
206	PAA-17-55	PAA-17-55	PAA-17-55
207	PAA-17-78	PAA-17-78	PAA-17-78
208	PAA-17-80	PAA-17-80	PAA-17-80
209	PAA-18-19	PAA-18-19	PAA-18-19
210	PAA-18-25	PAA-18-25	PAA-18-25
211	PAA-19-12	PAA-19-12	PAA-19-12
212	PAA-19-13	PAA-19-13	PAA-19-13
213	PAA-18-79	PAA-18-79	PAA-18-79
214	PAA-18-84	PAA-18-84	PAA-18-84
215	PAA-18-15	PAA-18-15	PAA-18-15
216	PAA-18-16	PAA-18-16	PAA-18-16
217	PAA-18-07	PAA-18-07	PAA-18-07
218	PAA-18-10	PAA-18-10	PAA-18-10
219	PAA-17-51	PAA-17-51	PAA-17-51
220	PAA-17-54	PAA-17-54	PAA-17-54
221	PAA-19-46	PAA-19-46	PAA-19-46
222	PAA-18-81	PAA-18-81	N/A
223	PAA-19-47	PAA-19-47	PAA-19-47
224	PAA-19-53	PAA-19-53	PAA-19-53

225	PAA-20-72	PAA-20-72	PAA-20-72
226	PAA-20-67	PAA-20-67	PAA-20-67
229	PAA-20-71	PAA-20-71	PAA-20-71
230	PAA-20-63	PAA-20-63	PAA-20-63
231	PAA-15-63	PAA-15-63	N/A
232	PAA-15-22	PAA-15-22	N/A
236	PAA-15-64clm	PAA-15-64clm	N/A

Table A5.3. Compounds in Chapter Four Listed as They Appear

Support for the Formation of α,β -Unsaturated Platinum Carbenes

Compound	^1H NMR	^{13}C NMR	IR
295	PAA-11-104	PAA-11-104	PAA-11-104
296	PAA-11-106	PAA-11-106	PAA-11-106
298	PAA-18-83	PAA-18-83	PAA-18-83
300	PAA-13-90A	PAA-13-90A	PAA-13-90A
325	PAA-18-80	PAA-18-80	PAA-18-80
326	PAA-18-85	N/A	N/A
335	PAA-11-34	PAA-11-34	PAA-11-34
342	PAA-13-32	PAA-13-32	PAA-13-32
343	PAA-13-90B	PAA-13-90B	PAA-13-90B
345	PAA-14-18	PAA-14-18	N/A

Table A5.4. Compounds in Chapter Five Listed as They Appear

Synthesis of Vicinal Bisheterocycles from Propargylic Methyl Ethers

Compound	^1H NMR	^{13}C NMR	IR
363	PAA-22-71	PAA-22-71	PAA-22-71
364	PAA-22-84	PAA-22-84	PAA-22-84
365	PAA-22-85	PAA-22-85	PAA-22-89
366	PAA-22-72	PAA-22-72	PAA-22-72
367	PAA-22-87	PAA-22-87	PAA-22-88
370	PAA-21-94	PAA-21-94	PAA-21-94
371	PAA-22-98	PAA-22-98	PAA-22-98

372	PAA-22-48	PAA-22-48	PAA-22-48
373	PAA-22-11	PAA-22-11	PAA-22-11
374	PAA-26-49	PAA-26-49	PAA-26-49
375	PAA-23-86	PAA-23-86	PAA-23-86
376	PAA-23-46	PAA-23-46	PAA-23-46
377	PAA-23-48	PAA-23-48	PAA-23-48
378	PAA-23-63	PAA-23-63	PAA-23-63
379	PAA-23-66	PAA-23-66	PAA-23-66
380	PAA-23-26	PAA-23-26	PAA-23-26
381	PAA-23-27	PAA-23-27	PAA-23-27
382	PAA-23-06	PAA-23-06	PAA-23-06
383	PAA-23-12	PAA-23-12	PAA-23-12
384	PAA-23-07	PAA-23-07	PAA-23-07
385	PAA-23-11	PAA-23-11	PAA-23-11
386	PAA-25-38	PAA-25-38	PAA-25-38
387	PAA-25-41	PAA-25-41	PAA-25-41
388	PAA-24-79	PAA-24-79	PAA-24-79
389	PAA-25-16	PAA-25-16	PAA-25-16
390	PAA-23-52	PAA-23-52	PAA-23-52
391	PAA-23-65	PAA-23-65	PAA-23-65
392	PAA-23-54	PAA-23-54	PAA-23-54
393	PAA-23-56	PAA-23-56	PAA-23-56
394	PAA-23-53	PAA-23-53	PAA-23-53
395	PAA-23-57	PAA-23-57	PAA-23-57
396	PAA-24-55	PAA-24-55	PAA-24-55
397	PAA-24-56	PAA-24-56	PAA-24-56
398	PAA-24-47	PAA-24-47	PAA-24-47
399	PAA-24-49_rf55	PAA-24-49_rf55	PAA-24-49_rf55
400	PAA-23-62	PAA-23-62	PAA-23-62
402	PAA-26-34	PAA-26-34	PAA-26-34
404	PAA-24-80	PAA-24-80	PAA-24-80
406	PAA-26-09	PAA-26-09	PAA-26-09
407	PAA-26-11	PAA-26-11	PAA-26-11
408	PAA-21-63	N/A	N/A
409	PAA-21-66	N/A	N/A
410	PAA-24-12	PAA-24-12	PAA-24-12
411	PAA-24-21	PAA-24-21	PAA-24-21
412	PAA-26-13	PAA-26-13	PAA-26-13
75	PAA-24-34	PAA-24-34	PAA-24-34
413	PAA-24-40	PAA-24-40	PAA-24-40
414	PAA-26-14	PAA-26-14	PAA-26-14

415	PAA-25-79	PAA-25-79	PAA-24-38
416	PAA-25-87	PAA-25-87	PAA-25-87
417	PAA-25-02	PAA-25-02	PAA-25-02
418	PAA-25-19	PAA-25-19	PAA-25-19
419	PAA-24-33	PAA-24-33	PAA-24-33
420	PAA-24-41	PAA-24-41	PAA-24-41
422	PAA-24-10	PAA-24-10	PAA-24-10
424	PAA-23-75	PAA-23-75	PAA-23-75
430	PAA-24-49_rf35	PAA-24-49_rf35	PAA-24-49_rf35
431	PAA-22-14	PAA-22-14	N/A