CYCLOISOMERIZATION REACTIONS OF ENAMIDES AND RELATED COMPOUNDS USING PLATINUM(II), GOLD(I), AND SILVER(I) SALTS TO FORM COMPLEX RING SYSTEMS. THE TOTAL SYNTHESIS OF (+)-FAWCETTIDINE.

by

Jennifer Aiden Kozak

B. Sc. (Hons.), The University of British Columbia, 2005

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES
(Chemistry)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

August 2010

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Abstract

This dissertation presents investigations of enamides as π-nucleophiles within the context of electrophilic platinum(II) and gold(I) salt catalyzed cycloisomerization reactions.

Chapter 1 provides a brief overview of electrophilic metal salt catalyzed cycloisomerization reactions with a primary focus on platinum, gold, and silver salts.

Chapter 2 describes the first total synthesis of *Lycopodium* alkaloid (+)-fawcettidine (**2.5**), completed in sixteen synthetic operations from (*R*)-(+)-pulegone (**2.56**). The feature reaction in the sequence was a platinum(II)-catalyzed annulation of highly functionalized bicyclic enamide **2.124** to give tricycle **2.125**. This annulation reaction installed the quaternary stereocenter, placed the double bond of the enamine in the correct position, and formed an exocyclic alkene which was amenable to further manipulation. A thiolate anion addition to an enone and a Ramberg-Bäcklund reaction were other noteworthy steps for the completion of the synthesis of (+)-fawcettidine.

Chapter 3 describes the platinum(II)- and gold(I)-catalyzed cyclorearrangement of 1,2,3,4-tetrahydropyridine derivatives containing an aromatic substituted alkyne moiety tethered at the 3-position of the ring. The reactions proceeded by a tandem cycloisomerization/Friedel-Crafts addition process resulting from an initial 6-*endo-dig* cyclization, forming nitrogen-containing tetracyclic scaffolds featuring a quaternary carbon center. The 5-*exo-dig* mode of cyclization was observed to be a minor pathway. Platinum(II)-catalyzed cycloisomerization reactions formed the products in 51-98% yield. Gold(I)-catalyzed cycloisomerization reactions were lower yielding. An unexpected azocine derivative was observed when an enamide substrate was treated with 20 mol% of silverhexafluoroantimonate(V).

Chapter 4 describes the platinum(II)- and gold(I)-catalyzed cycloisomerization/Friedel-Crafts tandem process of acyclic enamine derivatives featuring 1-arylalkynes. Four tricyclic products were observed: two products were formed by initial 6-*endo-dig* (major pathway) or 5-*exo-dig* (minor pathway) cyclization. The alkene of the 6-*endo* product frequently isomerized under the reaction conditions to form a 1-aza-substituted indene derivative, and the 5-*exo* product often eliminated to form substituted naphthalene derivatives. Catalysis with a platinum(II) salt, a gold(I) species derived from the mixture of triphenylphosphine gold(I) chloride and silver hexafluoroantimonate(V), or [(2-biphenyl-bis-*t*butylphosphine)Au(I)·$NCCH_3]^+SbF_6^-$ (**1.70**) gave mixtures of products in 21-100% yield. Gold(I) catalyst **1.70** was the most effective of the catalysts tested.

Preface

A portion of the research reported in Chapter 2 was published in 2008: Jennifer A. Kozak and Gregory R. Dake. "Total Synthesis of (+)-Fawcettidine." *Angew. Chem., Int. Ed.* **2008**, *47*, 4221-4223. This chapter is written entirely by me. I performed all of the synthesis and characterization of the compounds. Starting material **2.119** was donated by fellow Dake group member Tyler Harrison. X-Ray crystallographic analyses were performed by UBC Professional Officer Brian O. Patrick.

A portion of the material reported in Chapter 3 was published in 2009: Jennifer A. Kozak, Jennifer M. Dodd, Tyler J. Harrison, Katherine J. Jardine, Brian O. Patrick, and Gregory R. Dake. "Enamides and Enesulfonamides as Nucleophiles: Formation of Complex Ring Systems through a Platinum(II)-Catalyzed Addition/Friedel-Crafts Pathway." *J. Org. Chem.* **2009**, *74*, 6929-6935. I wrote this chapter in its entirety and performed all synthesis and characterization. X-Ray crystallographic analyses were carried out by UBC Professional Officer Brian O. Patrick.

A portion of the material reported in Chapter 4 was submitted for publication on July 2, 2010: Jennifer A. Kozak, Brian O. Patrick, and Gregory R. Dake. "Platinum(II) and Gold(I)-Catalyzed Intramolecular Tandem Addition/Friedel-Crafts Reactions between Acyclic Enamides and 1-Arylalkynes." I wrote the chapter in its entirety and performed all syntheses and characterizations. Catalyst **1.70** was generously donated by fellow Dake group member Jennifer Dodd. X-Ray crystallographic analyses were carried out by UBC Professional Officer Brian O. Patrick.

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List of Abbreviations and Symbols

δ	chemical shift
δ^+	partial positive charge
1D	1 dimensional
2D	2 dimensional
Ac	acetyl
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
Anal.	analysis
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc-ON	2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile
bp	boiling point
br	broad
BRSM	based on recovered starting material
Bu	butyl
^{o} C	degrees Celsius
calcd	calculated
cap	caprolactamate
cat.	catalytic amount or catalyst
cm^{-1}	reciprocal centimeters
CoA	coenzyme A
COSY	correlational spectroscopy
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide

dd	doublet of doublets
DEAD	diethyl azodicarboxylate
dec	decomposed
DIAD	diisopropyl azodicarboxylate
dig	digonal
DMAP	*N*,*N*-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
dt	doublet of triplets
E	entgegen
E1	elimination unimolecular
E2	elimination bimolecular
ee	enantiomeric excess
EI	electron ionization
endo	endocyclic
eq(s)	equation(s)
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
exo	exocyclic
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMQC	^{1}H-detected heteronuclear multiple quantum coherence
HOAc	acetic acid

HRMS	high resolution mass spectrum
i	*iso*
IR	infrared
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	coupling constant
KAPA	potassium 3-aminopropylamide
L or L_n or L^*	undefined ligand(s)
lit.	literature
LG	leaving group
M	metal (generic), molarity, or parent mass
m	multiplet, milli
m	meta
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Met	metal (generic)
mg	milligram(s)
MHz	Mega Hertz
min	minute(s)
mmHg	millimeters of mercury
mmol	millimole(s)
μ	micro (SI) or bridging ligands
mL	milliliter(s)
mp	melting point
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
N,*N*-DMG	*N*,*N*-dimethylglycine hydrochloride
NpH	naphthalene
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NR	no reaction
Ns	4-nitrobenzenesulfonyl or nosyl
Nuc	nucleophile
[O]	oxidation

o	ortho
ORTEP	Oak Ridge thermal Ellipsoid plot
OTf	triflate, trifluoromethanesulfonate
p	para
%	percent
PG	protecting group
Ph	phenyl
pH	$-\log[H_3O^+]$
PhH	benzene
$PhCH_3$	toluene
ppm	parts per million
PPTs	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr	pyridine
Q	quaternary
q	quartet
qt	quintet
R	undefined portion of a molecule
R	rectus
RSM	recovered starting material
rt	room temperature
s	singlet
S	sinister
Sia	siamyl
SM	starting material
S_N2	substitution nucleophilic bimolecular
t	triplet
t	tertiary
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethyl silyl
td	triplet of doublets
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	toluenesulfonyl or tosyl
TsOH	*para*-toluenesulfonic acid
Ts_2O	*para*-toluenesulfonic anhydride
UBC	University of British Columbia
wt %	weight percent
Z	zusammen

Acknowledgements

First and foremost, I would like to thank my research supervisor, Professor Gregory Dake, for his guidance, support, encouragement, and patience over the last five years. In particular I am thankful for the time he took to help prepare this manuscript. Editing can be a very mundane exercise and I am nothing but grateful for his thorough proofreading.

I would like to acknowledge Jennifer Love for additional assistance in proofreading this document. Any errors that remain, either scientific in nature or grammatical, are my own.

I give a special thank you to those who shared this experience with me: Jenny, Julien, Emmanuel, Krystle, Tyler, Paul, Leah, and Erik, and the many visiting and undergraduate students we have had. Much of what I learned about chemistry (knowledge and technique) can only be attributed to helpful discussion with fellow group members. These people made my time in the lab enjoyable and I would have never survived without their companionship on late nights or early mornings.

There is nothing more therapeutic than being able to vent about work, study, or life in general over a box of wine and some terrible TV. For this privilege I must thank my Wednesday night friends (team models): Jackie, Brownyn, Shiva, Courtney, Louisa, Ali, Jaime, and Roxan. I want to thank to Ali and Louisa for taking me under their wing, Jackie for never-ending amusement involving slot machines, venn diagrams, and eating, Bronwyn for memorable quotations and her photogenicity, Shiva for always doing the mental math, and CT for her cardigans and mismatched socks. The majority of us has parted or will be parting ways, and I sincerely hope to continue the friendship no matter where we are.

I would like to thank my parents, Brian and Elizabeth Kozak, for their continued support and interested in my education. They have always taken an interest in everything that I do and have never hesitated to help me if I've needed it. Thanks to my brother Michael for not making *too* much fun of me for still being in school and for making visits home always entertaining.

The last two years have been some of the happiest I can remember. For this I have to thank Jay Turcot, whose love and support during the culmination of my career as a graduate student was unwavering.

Last but not least, I would like to thank the staff of the NMR Laboratory, the Mass Spectrometry/Microanalysis Laboratory, and the Mechanical Shop. Their continued support made the work presented in this dissertation possible. A special thank you to Ken Love for scooping tar out of our group’s pumps on more than one occasion, while continuing to be kind and patient. Thanks to Brian Patrick for the successful X-ray structure determination of my tiny, organic crystals. I would like to thank the Natural Sciences and Engineering Research Council (NSERC) and the University of British Columbia for funding leading up to and throughout my graduate degree.

Foreword

Synthetic organic chemistry can be divided into two closely related subdivisions: methodology and target-oriented synthesis. Methodology describes the development of a reaction method used to perform a particular chemical transformation. Target-oriented synthesis involves the selection of a molecule, often either a product of nature or a compound of practical interest, to be synthesized in the laboratory. A successful target-oriented synthesis, or total synthesis, begins with a strategic synthetic plan. It is common for the plan to be altered in the course of the synthesis, as certain reactions can fail and specific pathways prove to be unsuccessful. It is also possible that a particular chemical transformation is required for which there is no known methodology. This can lead to the development of new methods, and highlights the relationship between the two subdivisions of synthetic organic chemistry.

The following dissertation describes target-oriented synthesis as well as the development of chemical methods. Both topics highlight the use of enamine derivatives as π-nucleophiles within the context of electrophilic metal salt cycloisomerization reactions. This thesis is divided into four chapters. Chapter 1 provides a brief overview of the field of electrophilic metal salt-catalyzed cycloisomerization, focusing on reactions involving platinum, gold, and silver salts. A section dedicated to the use of this methodology within the context of target-oriented synthesis is provided.

In chapter 2, methodology developed in the Dake laboratory is applied to the total synthesis of (+)-fawcettidine. Initially, a discussion of previous synthetic routes towards structurally related fawcettimine is given. Two synthetic plans for the synthesis of (+)-fawcettidine are then described, followed by the implementation of these plans in two following sections. Problems that arise are methodologically solved before the description of the synthetic route continues.

In chapter 3, methodology studies on the platinum(II)-catalyzed addition/Friedel-Crafts tandem process of cyclic enamides is described. The chapter begins with a detailed description of the synthesis of the substrates. The following section describes the reactions of the substrates. Inefficient or non-existent platinum(II)-catalyzed cycloisomerization of particular substrates is described for the sake of completion in the final section.

Chapter 4 describes initial methodology studies on the platinum(II)- or gold(I)-catalyzed cycloisomerization of acyclic enamine derivatives. The format follows that of chapter 3, with an added discussion section to describe general trends and justify observed products.

The concluding chapter reiterates the successes of the research presented in the body chapters of the thesis. The significance and applicability of the research in the field of synthetic organic chemistry are discussed.

Chapter 1: Cycloisomerization Reactions Catalyzed by Platinum, Gold, and Silver Salts: A Review

1.1 Introduction

The science of the synthesis of complex molecules is an integral part of the pharmaceutical industry and of academic synthetic organic laboratories. Chemists from both fields rise to the challenge of constructing target molecules from readily available starting materials. Industrial and academic groups approach the synthesis of these molecules differently. Interestingly, academic laboratories focus on original and elegant methods of bond construction that may be applied in total synthesis. An arguable goal of an academic synthesis is creativity within a scholarly exercise. In an industrial process setting, the goal is to drive the synthesis towards commercial production.

From both an academic or industrial perspective, the challenges of synthesis are often met by the implementation of methods that improve *synthetic efficiency*. A *synthetically efficient* process can be defined by having one or more of the following characteristics: a) high yields, b) theoretical stoichiometry, c) a minimum number of physical operations, d) an increase in molecular complexity, e) high selectivity, and f) a small amount of byproducts or waste formed. One method employed by chemists to improve efficiency is through the use of catalysts. Jones defines a catalyst as "a species that functions to increase the rate of a chemical reaction by providing a lower energy pathway between the starting material and the product, while remaining unchanged by the reaction".[1] Types of catalysis include, but are not limited to, biocatalysis (enzymatic catalysis),[2] organocatalysis,[3, 4] electrocatalysis,[5, 6] and transition metal catalysis.[7, 8] Transition metal-catalysts can often enable reactions that are impossible by traditional methods. Homogenous transition metal-catalyzed reactions have been successful in achieving a certain level of *synthetic efficiency*.

One set of transition metal catalyzed reactions are *cycloisomerization* reactions. *Cycloisomerization* reactions traditionally describe the cyclization (cyclorearrangement) of 1,*n*-enynes and dienes. Within this review, *cycloisomerization* will describe the reaction where a portion of a molecule containing a carbon or carbon-heteroatom chain with at least two units of unsaturation is isomerized with the simultaneous formation of at least one ring.[8] These reactions are synthetically efficient since all of the atoms of the reactant are found in the product, and the only other reactant is used catalytically.

Cycloisomerization reactions involving transition metal catalysis have been thoroughly studied and reviewed in the last 15 years. Thus, this review will not be comprehensive and readers are directed to one of the many reviews in the primary literature.[8-30] This introduction will provide a brief historical perspective and only cover the aspects of platinum, gold, and silver catalysis within cycloisomerization reactions that are directly related to the body of work described in the thesis.

1.2 Activation of Alkynes by Late Transition Metal Coordination

The alkyne is an electron rich moiety that often acts as a nucleophile. It reacts with functional groups such as Brønsted acids and Lewis acids, including electrophilic metal salts derived from Pt(II), Au(I), and Au(III). Electrophilic metal salts react with the π-system of the alkyne as traditional Lewis acids would, and are therefore also called "π-acids".[16, 20]

Classic Inorganic Definition

It should be noted that "π-acid" is a term within inorganic chemistry that is used to describe particular ligands of metal-ligand complexes. An example is the carbonyl ligand. There are two predominant types of orbital interactions between a transition metal and a carbonyl ligand (Figure 1.1). The first is a weak σ-donation by the carbonyl ligand to an empty metal *d* orbital. Taking only this interaction into account, the role of the metal is that of a Lewis acid and the role of the ligand is that of a Lewis base. The roles are reversed as a second, stronger orbital interaction takes place: the filled *d* orbital on the metal donates electron density to the π^* orbital of the ligand.[31] This back donation from metal to ligand is described by the Dewar-Chatt-Duncanson model.[32-34] Since the carbonyl ligand is a weak σ-donor and a strong π-acceptor, it is referred to as a "π-acid" (i.e., the π-system of the ligand accepts electrons). The measurement of the CO stretching frequency can be used as a measure of electron density on a metal center. CO and related ligands are used to pull electron density away from the metal center, making the metal more electropositive.

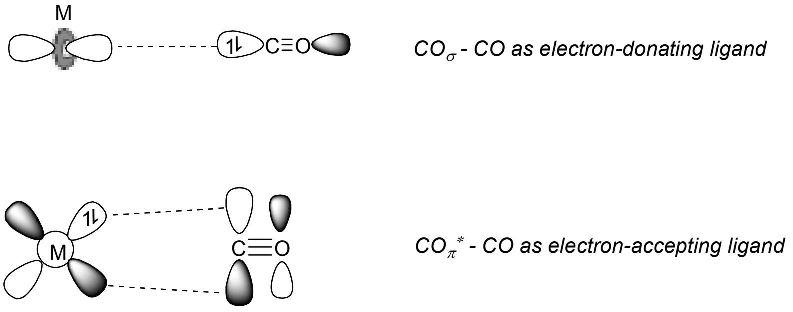

M
C≡O
CO_{σ} - CO as electron-donating ligand
M
C≡O
CO_{π}^{*} - CO as electron-accepting ligand

Figure 1.1: Metal-carbonyl ligand orbital interactions

Contemporary Organic Definition

Alkynes also act as ligands to form complexes with metal centers (Figure 1.2). The alkyne ligand donates electron density from the filled π-orbital to a metal *d* orbital, forming a σ-bond. In contrast to carbonyl ligands, there is little back donation from the filled metal *d* orbital to the empty π^*-orbital of the ligand. The σ-donation is therefore the dominant interaction and the metal remains the Lewis acid and the ligand a Lewis base. The Lewis acidic metal is interacting with a π-system; it is therefore a "π-acid" (i.e., the metal is accepting electrons from the π-system).[16, 20] Back-donation to the alkyne can be augmented by altering the ligands around the metal center. More electron-donating ligands will increase electron density at the metal center, thereby increasing its ability to back-donate. The measurement of the carbon-carbon bond length as well as the stretching frequency can be used as a measure of the electron density on the metal center.

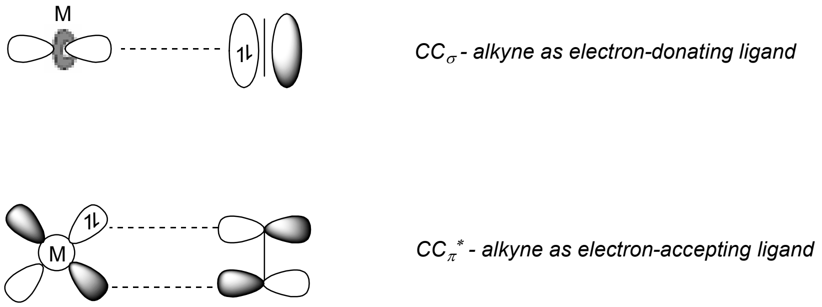
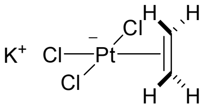

M
CC_{σ} - alkyne as electron-donating ligand
M
CC_{π}^{*} - alkyne as electron-accepting ligand

Figure 1.2: Metal-alkyne orbital interactions

Transition metal coordination renders the alkyne electrophilic. This alkyne activation is the basis for many Pt(II), Au(I), and Ag(I) cycloisomerization reactions.

1.3 Investigation of π-Coordination to Platinum, Gold, and Silver Centers

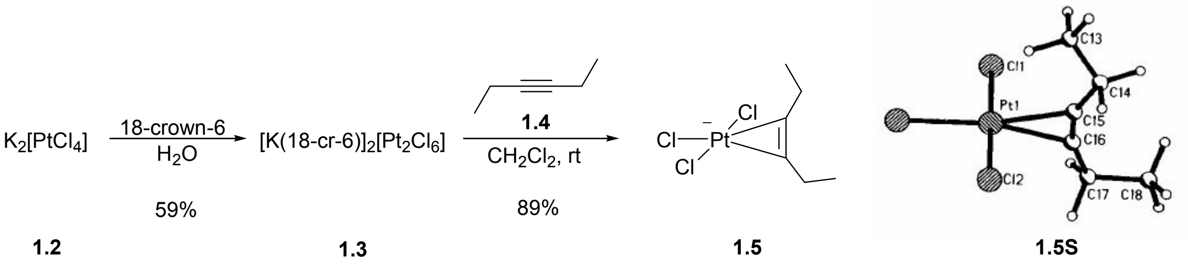
The isolation and characterization of organometallic complexes give insight into the orbital interactions and ultimate reactivity of the complex. The first example of a metal π complex – and of an organometallic complex in general – was potassium trichloro(ethane)platinate(II), or Zeise's salt **1.1** (Figure 1.3).[35] The complex was prepared in 1827, although its solid state molecular structure was not solved until 1954.[36] It was shown that the bound ethylene is oriented perpendicular to $PtCl_3^-$ plane and the carbon-carbon double bond length is only 2 pm longer than that of ethylene.[37, 38] Removal of electron density from the olefin renders it electrophilic and it can be attacked by nucleophiles, a reactivity that is mirrored in analogous palladium complexes. This is the basis for the Wacker-Hoechst oxidation.[39]



1.1

Figure 1.3: Schematic representation of the anion of Zeise's salt (**1.1**)[35]

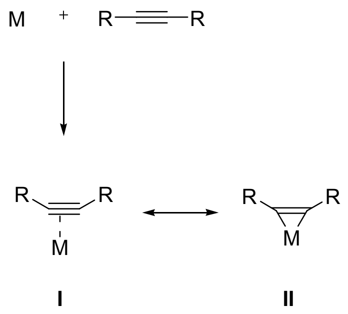
The synthesis of acetylenic platinum complexes was attempted following the successful complexation of olefins to platinum. Steinborn and coworkers reacted potassium tetrachloroplatinate **1.2** ($K_2[PtCl_4]$) and 18-crown-6 in water to give complex **1.3** as stable and isolable pink crystals (Scheme 1.1).[40] Compound **1.3** was then reacted with 3-hexyne (**1.4**) to give platinum-acetylene complex **1.5**, which was amenable to X-ray crystallographic analysis to give structure **1.5S**. The potassium crown-ether counterion is removed for clarity.

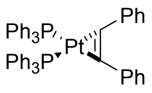


Scheme 1.1: Solid-state structure of the anion $[PtCl_3(EtC{\equiv}CEt)]^-$ and its schematic representation (**1.5**)[40]

Similarities between the coordination of an olefin and that of an alkyne are apparent when comparing structures **1.1** and **1.5**. The π-system of **1.5** is again oriented perpendicular to the $PtCl_3^-$ plane. Because there is only a small amount of back-donation by platinum, the carbon-

carbon triple bond is only slightly elongated relative to that of the uncoordinated alkyne. The back-donation is also responsible for the distortion of the alkyne away from linearity.





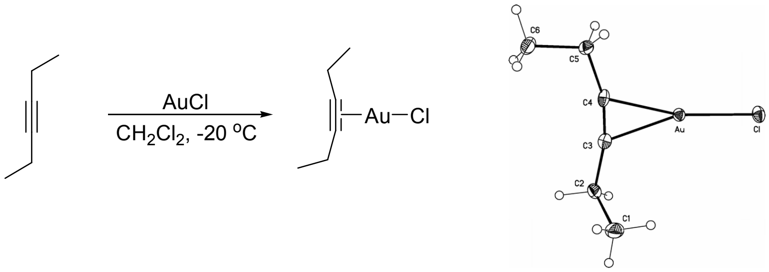
1.6

Glanville and coworkers

Scheme 1.2: Representations of metal-alkyne complexes

Depending on the environment around platinum, the π-ligand can be represented as a bound alkyne complex (**I**), or a metallocyclopropene (**II**) (Scheme 1.2). Metal-alkyne complexes with strong metal back-donation are best represented by structure **II**. Alteration of the ligands changes the ability of platinum to back-donate to a coordinated π-system. An example is the platinum(0)-acetylene complex **1.6** synthesized and structurally characterized by Glanville and coworkers.[41] The electron-donating triphenylphosphine ligands increase the electron density at the metal, augmenting its ability to back-donate. Complex **1.6** is best represented as a metallocyclopropene.

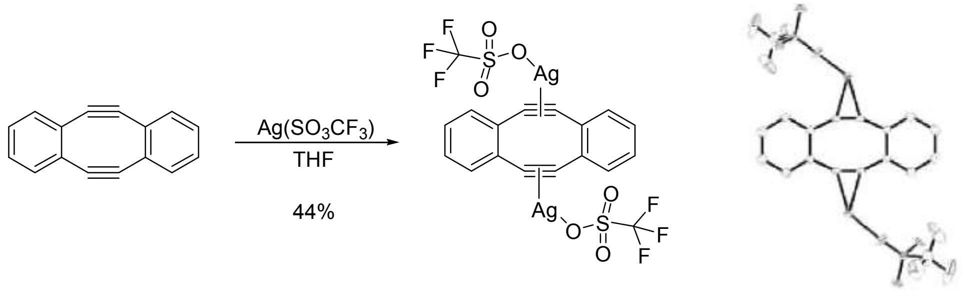
Although gold has been used extensively in cycloisomerization reactions for the last 15 years with simple terminal and internal alkynes, the only gold-alkyne complexes determined by X-ray crystallography are those containing strained alkynes and alkynes in a tethered framework.[42, 43] Recently, a simple gold complex of 3-hexyne was isolated and structurally characterized (Scheme 1.3).[44] Complex **1.7** was synthesized by reaction of 3-hexyne **1.4** with AuCl in dichloromethane at low temperature. The complex was air and temperature sensitive, but was stable for a few hours in solution at low temperature.



1.4 **1.7** **1.7S**

Scheme 1.3: Solid-state molecular structure of a linear gold(I)-alkyne complex (**1.7S**) and its schematic representation (**1.7**)[44]

Analyses of the structure show that the gold coordination environment is nearly linear, with a Cl-Au-centroid$_{C\equiv C}$ angle of 176.3°. The alkyne is oriented perpendicular to the gold-chloride bond and is distorted from complete linearity due to some back donation from the metal to the alkyne. Density functional theory[45-48] (DFT) calculations suggest that the alkyne of complex **1.7** is a strong σ-donor but a weak π-acceptor, which correlates with observations of other π-complexes with metals of moderate ability to back-donate.



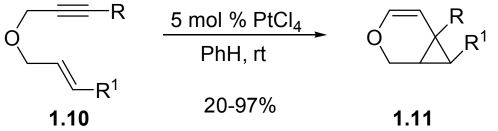
1.8 **1.9** **1.9S**

Scheme 1.4: Solid-state structure of a silver trifluoromethanesulfonate-alkyne complex **1.9S** and its schematic representation (**1.9**)[49]

The ability of silver(I) to coordinate to alkenes was discovered in the 1930's by Lucas and Winstein.[50, 51] Determination of the amount of alkene coordinated to the silver was performed using distribution measurements. Coordination of silver(I) to an alkyne was first reported in 1956 using similar measurements.[52] The coordination of alkenes and alkynes to silver(I) was studied by Lewandos and coworkers using IR spectroscopic and NMR techniques in 1976.[53] A common silver catalyst used in cycloisomerization reactions is silver(I) trifluoromethanesulfonate (triflate). Recently, Gleiter and coworkers isolated and structurally characterized a silver(I) triflate alkyne complex (**1.9**) (Scheme 1.4).[49] The complex was formed by treatment of 1 equivalent of silver(I) triflate with 1 equivalent of dialkyne **1.8** in THF at room temperature with the strict exclusion of light. The product precipitated out of solution and after removal of the solvent, compound **1.9** was isolated as a pale yellow solid. A crystal amenable to X-ray analysis was isolated by recrystallization from acetone. With the unambiguous structure in hand, the authors compared the bond lengths between the uncoordinated dialkyne **1.8** and that of the complex **1.9**. They found after complexation, the bond lengths of the alkyne increased from 1.202 Å to 1.204 Å. The coordination of the alkyne to silver weakens the C(sp)-C(sp) bond, thereby lowering the LUMO and allowing the alkyne to become electrophilic and able to undergo subsequent reactions.

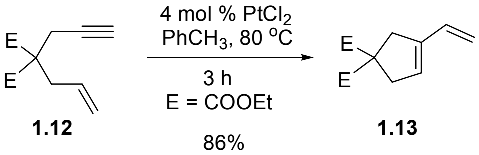
1.4 Early Metal Salt-Catalyzed Cycloisomerization Reactions

The first transition metal catalyzed cycloisomerization of 1,6-dienes was performed in 1971 by Malone and coworkers.[54] The first platinum-catalyzed cycloisomerization reaction was discovered by Blum and coworkers over 20 years later (Scheme 1.5).[55] Blum treated various allyl propargyl ethers (**1.10**) with a catalytic amount of platinum(IV) chloride at room temperature which gave 3-oxabicyclo[4.1.0]hept-4-ene derivatives **1.11**. The yields varied from 20-97% depending on the nature of substituents R and R^1.



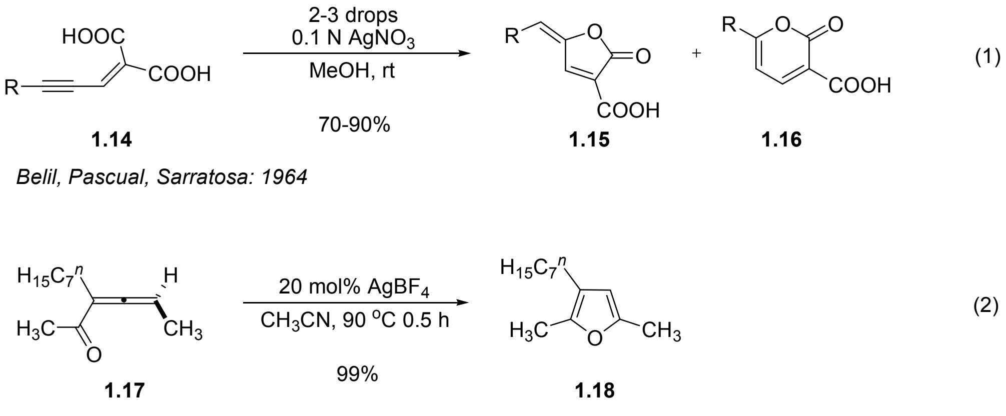
Scheme 1.5: Blum's platinum(IV) catalyzed cycloisomerization of allyl propargyl ethers[55]

The first platinum(II)-catalyzed reaction was carried out by Shinji Murai and coworkers in 1996.[56] In this elegant study, Murai found that 1,6-enynes (**1.12**) underwent cyclorearrangement when treated with a catalytic amount of platinum(II) chloride to yield 1-vinylcycloalkenes (**1.13**) (Scheme 1.6). The authors successfully cycloisomerized 13 different substrates using catalytic platinum(II) chloride in high yields (66-98 %). Treating 1,7-enynes under the same reaction conditions also gave cycloisomerized product, although the reaction time was long and the yield was poor. In the same study, the authors performed a deuterium labeling study and found that two distinct mechanistic pathways were operating for the single reaction. The nature of the substituents on the alkene or the alkyne functionality determined the course of the reaction. Mechanistic phenomena will be discussed in more detail in section 1.5.



Scheme 1.6: Murai's cyclorearrangement of enynes using platinum(II)-catalysis[56]

Silver catalyzed cycloisomerization has origins dating before the first cycloisomerization of enynes. Castañer and Pascual demonstrated in 1958 that propargylidene malonic acid underwent cycloisomerization in the presence of silver nitrate to form a carboxybutenolide.[57] Later, it was found that treatment of propargylidene malonic acids such as **1.14** with a catalytic amount of silver nitrate formed either carboxybutenolides depicted by **1.15** or α-pyrones such as **1.16** (Scheme 1.7, eq 1).[58] If R was aromatic, only carboxybutenolides were formed. If R was aliphatic, mixtures of butenolides and α-pyrones were formed.



Belil, Pascual, Sarratosa: 1964

Marshall and Robinson: 1990

Scheme 1.7: Silver-catalyzed cycloisomerization to form substituted furans[58, 59]

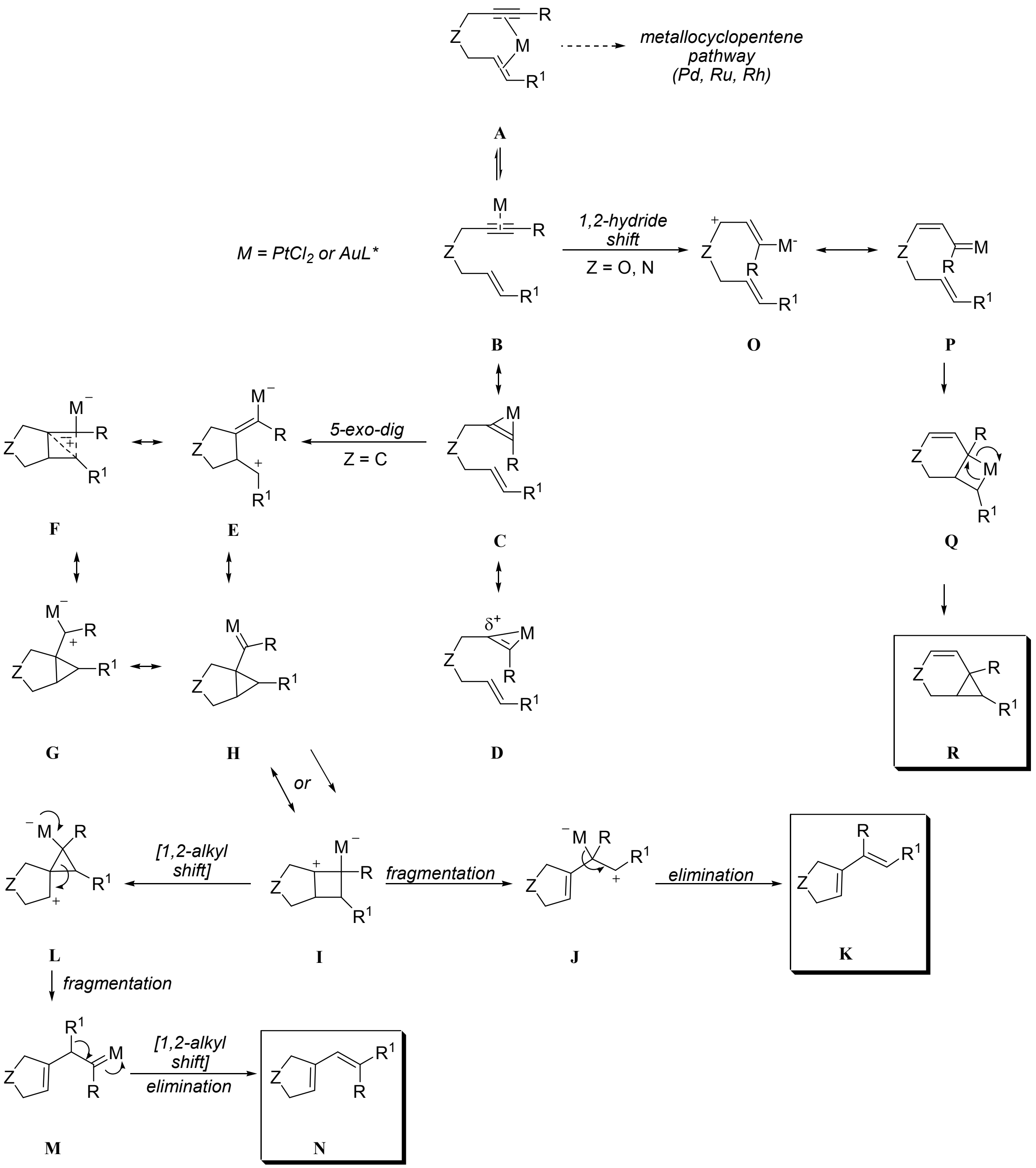
Although Belil and coworkers performed a cycloisomerization reaction that was presumably catalytic in silver salt, the amount of salt added was an inexact measure. It wasn't until much later that a rigorously measured catalytic silver(I) cycloisomerization was performed (Scheme 1.7, eq 2).[59] Marshall and Robinson found that allenone **1.17** reacted with a 20 mol% of silver(I) tetrafluoroborate to form furan **1.18** in high yield. The authors found that a variety of allenals and allenones react with a catalytic amount of either silver nitrate or silver(I) tetrafluoroborate to give furans in good yields ranging from 72-99 %.

1.5 Mechanistic Implications

In the last decade the mechanism of electrophilic metal salt catalyzed cycloisomerization reactions has been extensively probed. One unifying mechanistic framework has arisen from experimental data and DFT calculations (Scheme 1.8).[16, 18, 20, 24] The proposed mechanism is complicated. Depending on catalyst and substrate structure, the reactive intermediates on one hand can be described as non-classical carbocations. On the other hand, they can display carbene-like character. The proposed structures can be thought of as a series of resonance forms, the predominant form differing from reaction to reaction. It is likely that the reactive intermediate invokes more than one of these canonical-forms. It should be noted that there is no direct evidence of any of the proposed intermediates, and the mechanistic framework depicted in Scheme 1.8 is largely the result of interpretation of experimental results and theoretical calculations.[16, 20]

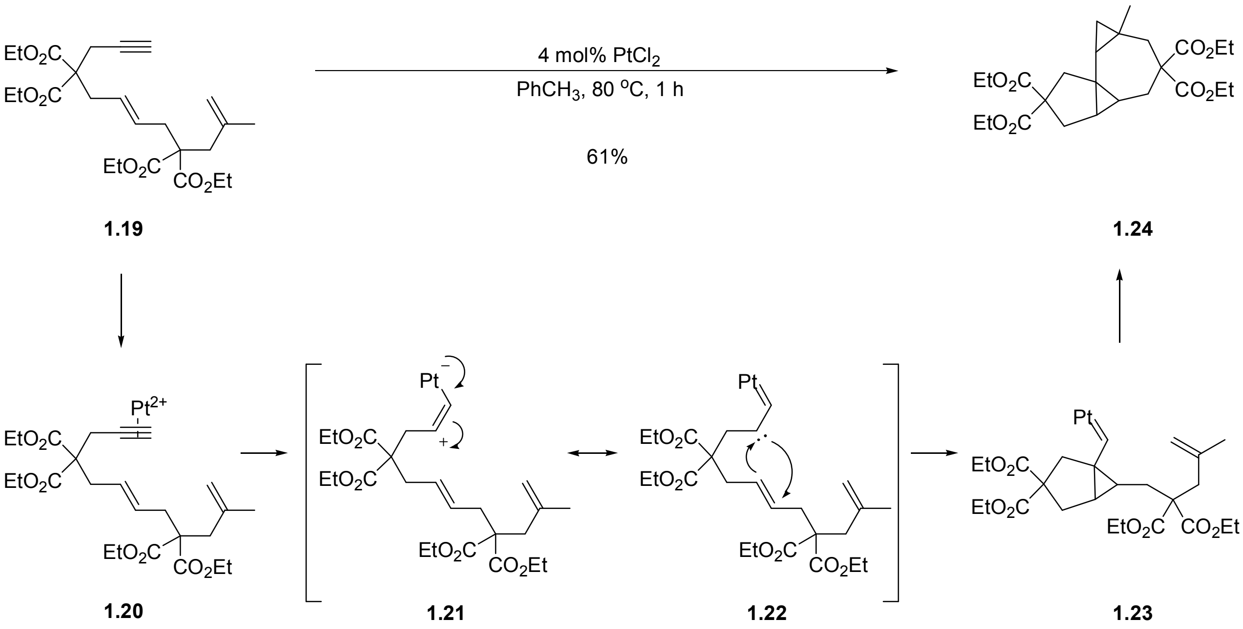
At the outset of a metal catalyzed reaction of a 1,6-enyne, the metal can coordinate to both the alkene and the alkyne (**A**), or to only the alkyne (**B**). It is likely that **A** and **B** are in equilibrium with each other. If the metal coordinates to both π-systems it is likely that it will go through a metallocyclopentene pathway (not shown) as described by Trost and coworkers in the context of palladium and ruthenium catalysis.[9, 13] When the metal is coordinated to only the alkyne, the mechanistic rationale described in Scheme 1.8 can be invoked.

Depending on the nature of the metal and of substituents on the alkyne, the metal bound alkyne complex can be drawn as a metallocyclopropene (**C**). The metal can also "slip" along the alkyne (going from η^2 towards η^1) and polarize it. In the case of complex **D**, the partial positive charge is formed on the carbon situated closest to the center of the molecule (proximal carbon). If Z = carbon, a nucleophilic alkene will attack to undergo a 5-*exo*-dig cyclization. Less common but observed pathways are 6-*endo*-dig cyclizations. These are omitted from this mechanistic scheme.


metallocyclopentene pathway (Pd, Ru, Rh)
A
M = PtCl2 or AuL*
1,2-hydride shift
Z = O, N
B
O
P
5-exo-dig
Z = C
C
Q
F
E
D
G
H
R
or
[1,2-alkyl shift]
fragmentation
elimination
L
I
J
K
fragmentation
[1,2-alkyl shift]
elimination
M
N

Scheme 1.8: A mechanistic rationale for the cycloisomerization of 1,6-enynes

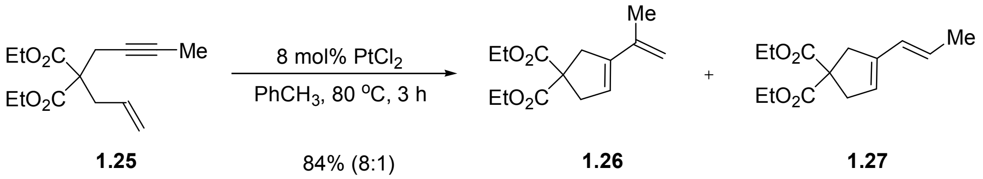
After the initial cyclization takes place, carbocationic intermediate **E** can be invoked. This intermediate is in resonance with structures **F-I**. Structures **E**, **F**, **G**, and **I** represent resonance structures of a non-classical carbocation. Structure **H** represents the carbene rendition, and is said to be invoked if there is enough back donation from the metal to the alkyne.[20] In an alternate explanation by Kozmin, the carbocationic pathway is a concerted process whereas the carbene pathway is a step-wise process.[18] The carbene type intermediate can be indirectly observed through trapping experiments. A functional group appropriately placed to trap the carbene will generate cyclopropane rings or C-H insertion products. Products resulting from the carbocationic resonance structures will be absent.



Scheme 1.9: Murai and coworkers: Trapping of a carbene intermediate using an olefin[60]

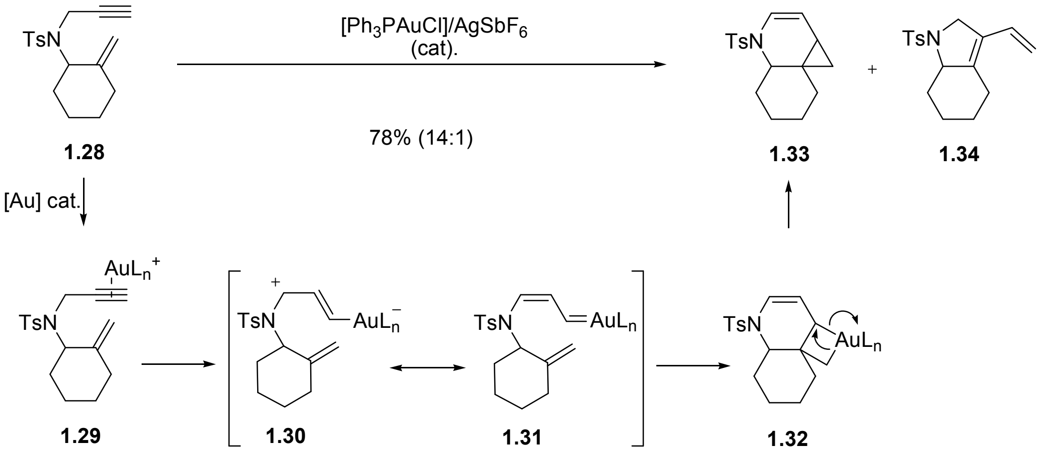
Another insightful study by Murai provides experimental support for the intermediary metal carbene (Scheme 1.9).[60] If an alkene was strategically placed within the substrate, it trapped the transient metal carbene to form a cyclopropane ring. Murai and coworkers treated dienyne **1.19** with a 4 mol% of platinum(II) chloride to give the complex tetracyclic product **1.24**. He speculated that after initial complexation of platinum to the alkyne in an η^2-fashion (**1.20**), the platinum slips to form η^1-complex **1.21**. This complex is in resonance with carbenoid **1.22**. Carbenoid **1.22** then attacks the pendant alkene, forming cycopropyl derivative **1.23**. Further trapping of the metal carbene by another alkene led to the formation of a tetracyclo[6.4.0.0^{1,9}0^{2,4}]dodecane derivative **1.24**.

As mentioned in section 1.4, Murai and coworkers discovered two operating mechanistic pathways in their cycloisomerizations of 1,*n*-enynes.[56] From resonance structure **I**, two options are possible: first, fragmentation can occur to open the cyclobutane ring, and subsequent elimination gives product **K**. Alternatively, from intermediate **I**, a 1,2-alkyne shift can occur to give a cyclopropyl intermediate (**L**). Fragmentation of this ring gives structure **M** that undergoes a second alkyl shift and elimination to give final product **N**. The experiment performed by Murai and coworkers is shown in Scheme 1.10. Treatment of enyne **1.25** with 8 mol% of platinum(II) chloride led to dienes **1.26** and **1.27** formed in 84 % yield as an 8:1 mixture. The mechanism described above accounts for the mixture of products observed.



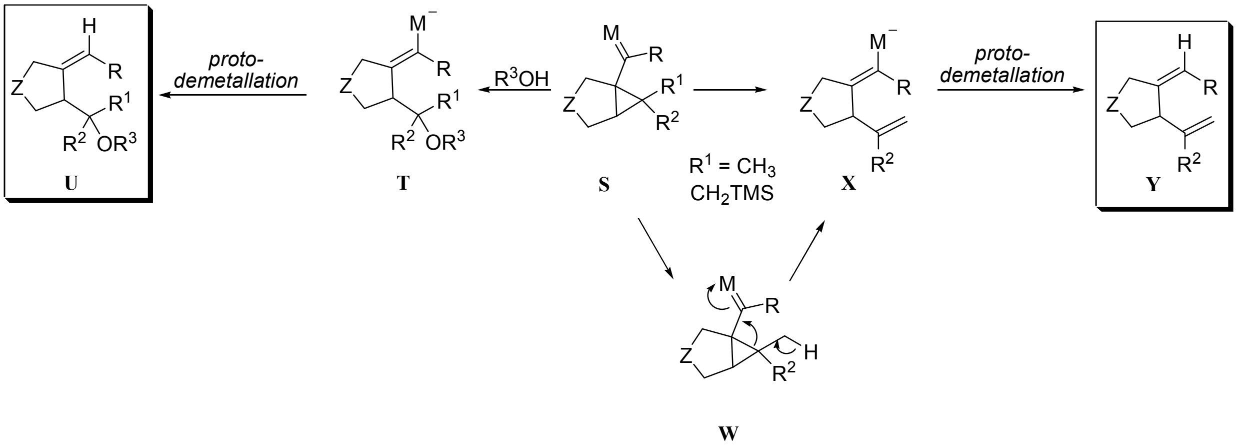
Scheme 1.10: Murai's discovery of two operating mechanistic pathways[56]

In Scheme 1.8, if Z = nitrogen or oxygen, then a 1,2-hydride migration occurs to form an alkenyl carbene **O** that is stabilized by the adjacent heteroatom Z. From resonance structure **P** one can envisage a [2+2] cycloaddition to form metallocyclobutane **Q**. Reductive elimination gives the bicycle[4.1.0]heptene products typically observed for 1,6-enynes containing a heteroatom in the tether. A specific example using gold catalysis comes from the work of Echavarren (Scheme 1.11).[61] He found that 1,6-enyne **1.28** reacted with the cationic gold catalytic system to afford products **1.33** and **1.34** in 78 % yield in a 14:1 ratio, with **1.33** being the major observed product. The major product arose from initial coordination of the gold to the alkyne, as in **1.29**, followed by a 1,2-hydride shift to give stabilized allenyl carbene **1.30** and its resonance structure **1.31**. Cycloaddition followed by reductive elimination of gold (**1.32**) yielded the major product **1.33**. The minor **1.34** product arose from initial 5-*exo*-dig attack of the alkene on the electrophilic alkyne.



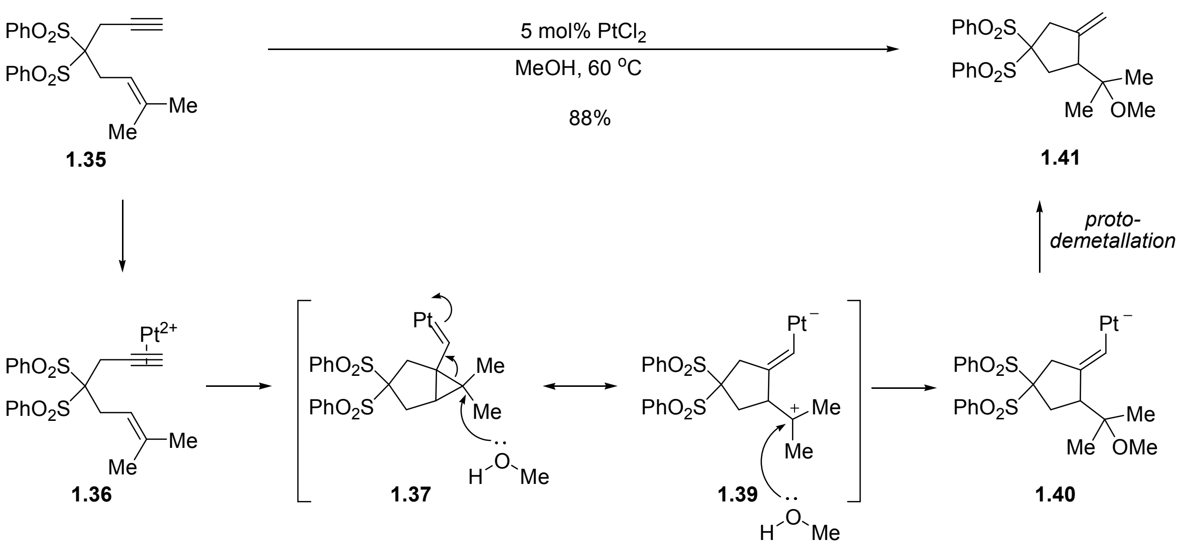
Scheme 1.11: Gold-catalyzed cycloisomerization of nitrogen-tethered enyne **1.28**[61]

The reaction outcome is strongly dependent on reaction conditions and substrate structure (Scheme 1.12). After initial 5-*exo*-dig cyclization, putative carbene intermediate **S** is presumably formed. If an external nucleophile such as R^3OH is present in the reaction media, it can react with carbene **S** to form intermediate **T**. Protodemetallation will give alkene **U**. If the substituent is $R^1 = CH_3$ or CH_2TMS, loss of either a proton (as shown in **W**) or of the TMS group will open the cyclopropane ring to give intermediate **X**. Protodemetallation gives diene **Y**.



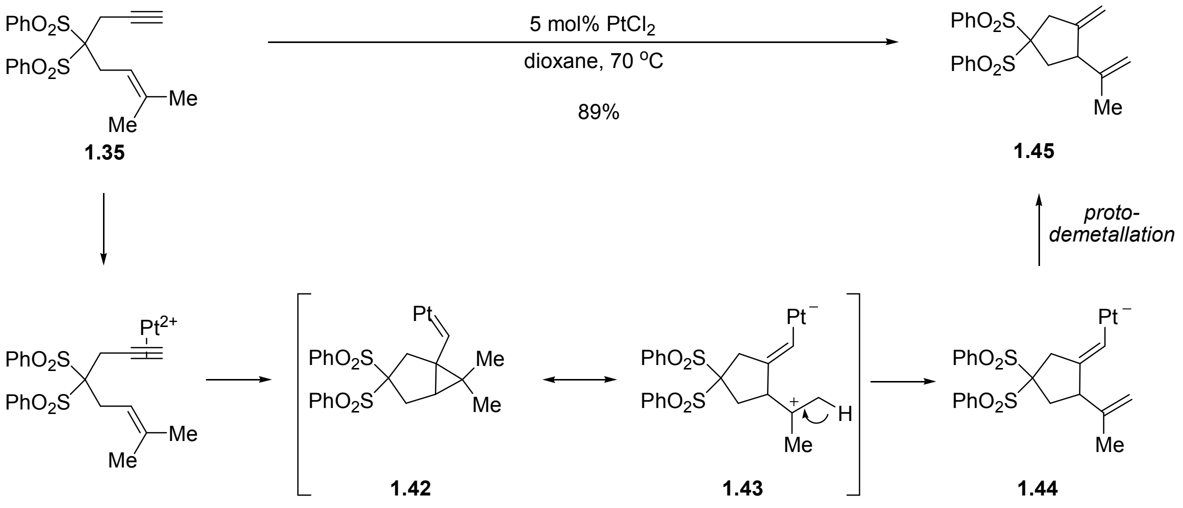
Scheme 1.12: Mechanistic rationale for observed product outcomes using an external nucleophile or a trisubstituted olefin

Echavarren and coworkers reported the platinum(II)-catalyzed alkoxy- and hydroxycyclizations on a series of 1,6-enynes.[62-64] In a specific example, the authors reacted trisubstituted olefin **1.35** with a 5 mol% of platinum(II) chloride in methanol (Scheme 1.13). The platinum coordinates to the alkyne to give η^2-complex **1.36**. Attack by the trisubstituted alkene gives metal carbene intermediate **1.37** or its cationic representation **1.39**. In either case, methanol acts as a nucleophile and either fragments the cyclopropane ring or attacks the tertiary carbocation to give complex **1.40**. Protodemetallation gives the product **1.41**.


5 mol% $PtCl_2$
MeOH, 60 °C
88%
1.35
1.41
proto-demetallation
1.36
1.37
1.39
1.40

Scheme 1.13: Platinum-catalyzed alkoxycyclization of enyne **1.35**[62]

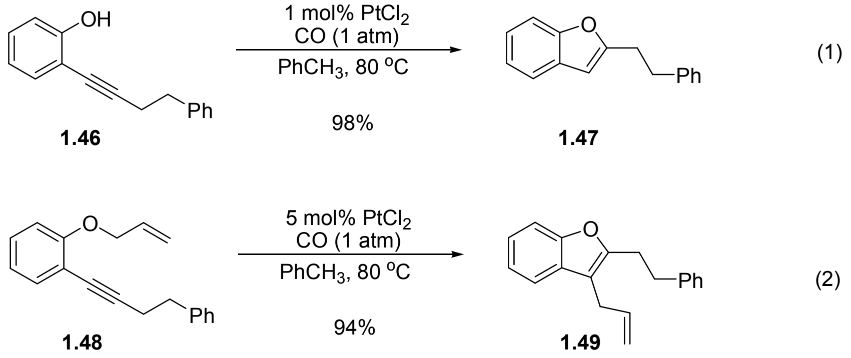
In a related reaction, Echavarren and coworkers ran the same reaction as in Scheme 1.13, but without methanol (Scheme 1.14).[64] After the formation of the two resonance related intermediates **1.42** and **1.43**, the C-H bond of the methyl substituent was eliminated to form a disubstituted double bond (**1.44**). Protodemetallation gave the final product **1.45**.


5 mol% $PtCl_2$
dioxane, 70 °C
89%
1.35
1.45
proto-demetallation
1.42
1.43
1.44

Scheme 1.14: Platinum-catalyzed cycloisomerization of an 1,6-enyne containing a trisubstituted olefin **1.35**[64]

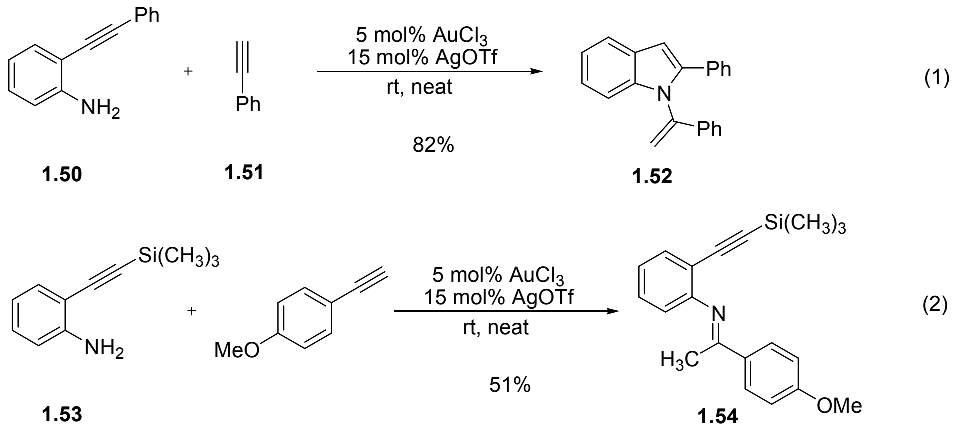
1.6 Other Nucleophiles Used in Cycloisomerization Reactions

A common nucleophile in the cycloisomerization of 1,*n*-enynes is the alkene functional group. Once the π-system has been activated, nucleophiles other than alkenes can attack. Heteroatoms are an obvious choice as they have lone pairs of electrons which can react with electrophilic species. As an example, Fürstner and coworkers exploited the oxygen atom of phenols as a nucleophile to form benzofurans. Phenol derivative **1.46** containing a pendent alkyne at the 2-position was reacted with 1 mol% of platinum(II) chloride to give benzofuran **1.47** in 98% yield (Scheme 1.15, eq 1).[65] No external base was necessary to promote the reaction in contrast to similar reactions reported in the past.[66] The authors also found that substitution on oxygen did not prevent cycloisomerization (Scheme 1.15, eq 2). Allyl ether **1.48** was treated with 5 mol% of platinum(II) chloride to give benzofuran **1.49** in 98% yield. The oxygen substituent was transferred to the 3-position of the benzofuran during the course of the reaction. The reactions proceeded under platinum(II)-catalysis but were accelerated under an atmosphere of carbon monoxide.[67, 68]



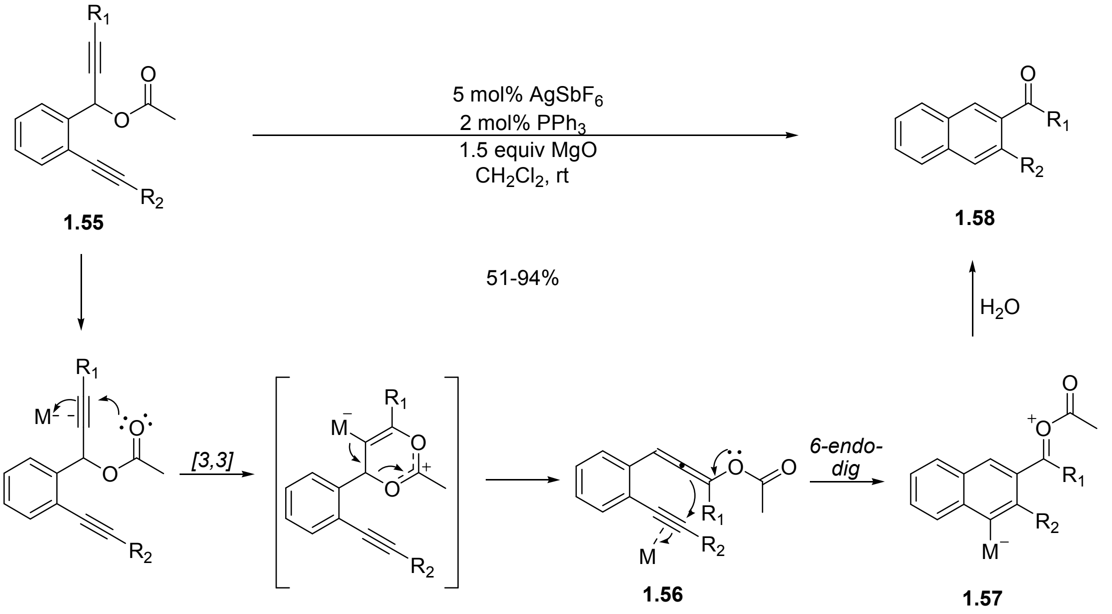
Scheme 1.15: Fürstner's hydroxylation of alkynes[65]

Nitrogen is a nucleophile used extensively in coinage metal catalyzed cycloisomerizations. Gold-catalyzed hydroamination reactions have received a lot of attention in the last year.[30, 69-79] Silver and platinum-catalyzed hydroamination reactions are less common.[80-85] An example of a gold-catalyzed double hydroamination reaction is shown in Scheme 1.16, eq 1.[86] *o*-Alkynylaniline **1.50** reacted with phenyl acetylene **1.51** under gold(III) catalysis to afford *N*-alkenylindole **1.52** in 82% yield. The authors found the reaction to work well with both electron rich and electron deficient arylacetylenes, but were less reactive towards aliphatic and alkenyl acetylenes. A bulky substituent on *o*-alkynylaniline **1.53** prevented the second hydroamination reaction, thereby giving imine **1.54** as the sole product (Scheme 1.16, eq 2).



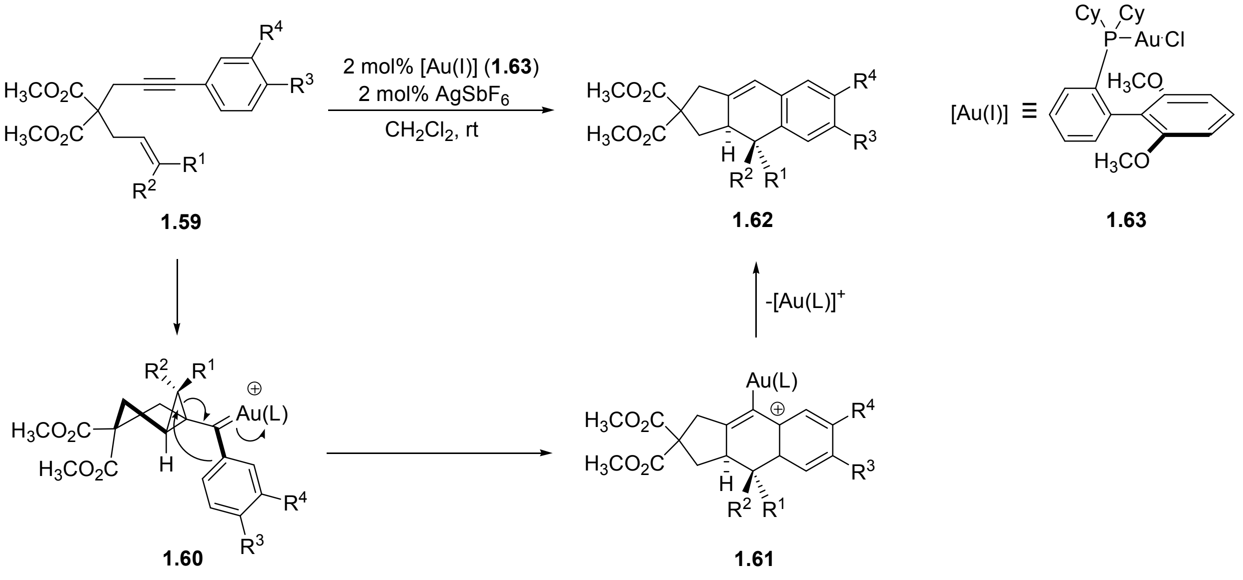
Scheme 1.16: Gold-catalyzed hydroamination: nitrogen as a nucleophile[86]

A silver-catalyzed cycloisomerization employing a nucleophilic ester comes from the Toste laboratory.[87] Toste and coworkers aimed to develop a transition-metal catalyzed Myers-Saito cyclization[88-91] of enyne allenes to form naphthyl ketones. They envisaged that an efficient synthesis of the required enyne allene could come from the transition metal-catalyzed rearrangement of propargyl acetates such as **1.55** (Scheme 1.17). Toste and coworkers reacted propargyl esters such as **1.55** with 5 mol% of silver(I) hexafluoroantimonate, 2 mol% of triphenylphosphine, and 1.5 equivalents of magnesium oxide at room temperature to form naphthylketones **1.58** in 51 to 94% yield. The proposed mechanism begins with the coordination of the metal to the alkyne followed by a *3*,*3*-sigmatropic rearrangement to give enyne allene **1.56**, the required substrate for the Myers-Saito cyclization. 6-*endo-dig* Cyclization of the activated alkyne furnishes naphthylene **1.57**. Upon workup, naphthyl ketone **1.58** is formed. The reaction also forms complex ring systems such as binaphthyl and anthracene derivatives. The specific catalytic system used by the authors was found serendipitously when running control reactions. The purpose of the magnesium oxide was to avoid the destruction of the silver catalyst by acetic acid produced during the course of the reaction.



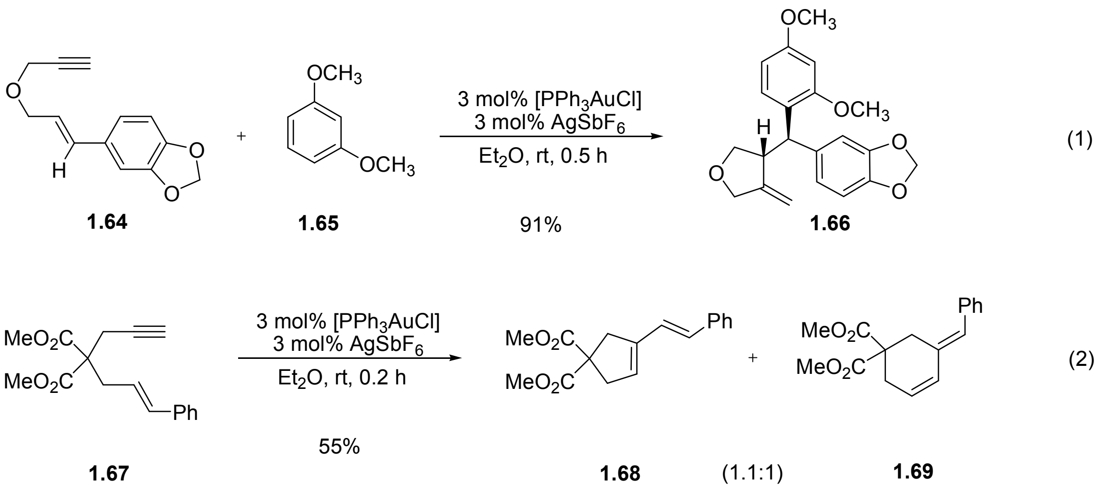
Scheme 1.17: Silver-catalyzed cycloisomerization with acetate as the nucleophile[87]

Cycloisomerizations have been performed in tandem with Friedel-Crafts reactions.[92-99] One example of a Friedel-Crafts reaction coupled with a gold-catalyzed cycloisomerization reaction comes from the laboratory of Echavarren (Scheme 1.18).[93, 94] Aryl enynes such as **1.59** were treated with 2 mol% of cationic gold catalyst **1.63** and 2 mol% of silver(I) hexafluoroantimonate to form naphthyl derivatives **1.62** via formal [4+2] cycloadditions. The reaction presumably occurs by initial 5-*exo-dig* cyclization to form gold carbene **1.60**. The authors speculate that a Nazarov type cyclization could then occur to form intermediate **1.61**, although it can also be viewed as opening of the cyclopropyl ring by the electron-rich aromatic ring. For a number of the substrates only one stereoisomer was formed during the course of the reaction, implying that the initial alkene configuration was retained.


2 mol% [Au(I)] (1.63)
2 mol% AgSbF6
CH2Cl2, rt
-[Au(L)]+
[Au(I)] ≡
1.59
1.60
1.61
1.62
1.63

Scheme 1.18: A cycloisomerization reaction coupled with a Friedel-Crafts reaction[93]

Gold-catalyzed cycloisomerizations coupled to Friedel-Crafts reactions also extend to intermolecular reactions. Michelet and coworkers reacted enyne **1.64** with a gold(I)-catalytic system and veratrole (**1.65**) as an external nucleophile to form compound **1.66** in high yield (Scheme 1.19, eq 1).[96] The authors speculate that the reaction mechanism is analogous to that described by Echavarren (Scheme 1.18). In the absence of veratrole (**1.65**), the reaction of enyne **1.67** forms the well-documented diene products **1.68** and **1.69** were observed (Scheme 1.19, eq 2). Diene **1.68** was the result of the metathesis-type pathway whereas **1.69** arose from 6-*endo-dig* cyclization. With veratrole present, alkene **1.66** was the only observable product. The reaction also took place with other electron-rich aromatics such as indole and pyrrole. The authors did not comment on the use of electron deficient aromatics.

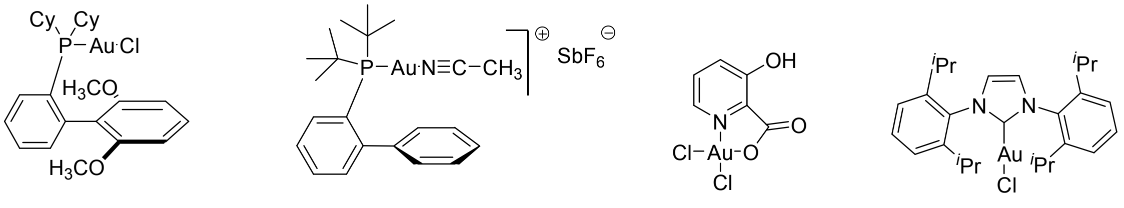

3 mol% [PPh3AuCl]
3 mol% AgSbF6
Et2O, rt, 0.5 h
91%
(1)
1.64
1.65
1.66
3 mol% [PPh3AuCl]
3 mol% AgSbF6
Et2O, rt, 0.2 h
55%
(2)
1.67
1.68
(1.1:1)
1.69

Scheme 1.19: Cycloisomerization coupling with an intermolecular Friedel-Crafts reaction[96]

1.7 Ligand Effects in Gold Catalysis

Catalysts are continually being modified in an attempt to make them more effective. Academic and industry groups have synthetic programs designed with the sole purpose of creating libraries of catalysts. The hope is that by changing the properties of the catalyst, one will emerge that is more efficient than the rest. Metal catalysts are altered in a number of ways. The ligands around the metal center are important for reactivity and selectivity, and can be modified by changing their steric and electronic properties. Placing electron-donating or electron-withdrawing groups on a ligand can change its electronic properties. Increasing the bulk of the ligand set, or by modifying the coordination number around the metal center can change the steric environment around the catalyst. The counter ion employed in cationic catalyst systems can also be altered.

Following the initial successes of gold(I)-catalyzed cycloisomerization, effort is underway to increase reactivity and impart selectivity by changing the environment around the gold center. Depicted in Figure 1.4 are a series of gold catalysts recently synthesized. Gold has been coordinated to Buchwald-type ligands such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) to give neutral gold complex **1.63**. Cationic gold(I) complexes such as **1.70** have also been prepared and are reported to be active catalysts towards a number of skeletal rearrangement reactions. Their use eliminates the need to run the reaction with a silver(I) salt, which in some cases leads to unwanted side products. Another desirable feature is that they are isolable white solids, making them easy to handle.[100-102]



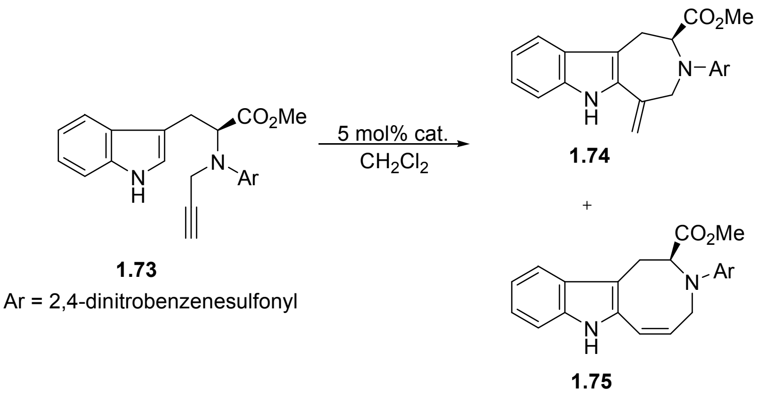
1.63 **1.70** **1.71** **1.72**

Figure 1.4: Examples of gold complexes used for cycloisomerization catalysis

Gold(III)-catalysis is also utilized in cycloisomerization reactions, although it is not as popular as gold(I). Hashmi and coworkers found gold(III) catalysts to be effective for the cycloisomerization of alkynyl furans to phenols, but catalyst stability was a concern.[103] They therefore created a set of gold(III) complexes with stabilizing ligands derived from pyridine

(Figure 1.4, **1.71**).[104] The ligand supported catalysts had turnover numbers of 1180 compared to 20-50 for gold(III) chloride. In an attempt to further increase the activity of gold(I) catalysts bearing biphenyl ligands, Widenhoefer turned to *N*-heterocyclic carbene based ligands (Figure 1.4, **1.72**).[105] Complex **1.72** allowed him to cyclize urea based substrates at room temperature rather than at 80 °C with phosphine supported gold catalysts.

As previously mentioned, the change of the ligand support system of a metal catalyst can alter its selectivity and reactivity in a reaction. Echavarren found that indole **1.73** could be catalytically transformed to either azepino[4,5-*b*]indole derivative **1.74** via a 7-*exo-dig* cyclization, or to indoloazocines **1.75** via a 8-*endo-dig* cyclization, depending on which catalyst is used (Scheme 1.20).[106, 107] Gold(I) chloride and gold(III) chloride gave the indoloazocine product **1.75** whereas cationic gold catalyst **1.70** formed only the azepino[4,5-*b*]indole product **1.74**.



1.73
Ar = 2,4-dinitrobenzenesulfonyl

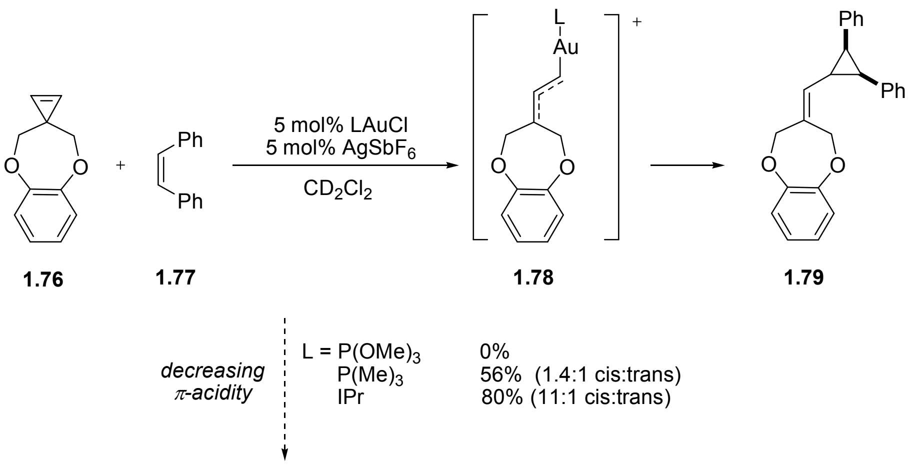
1.74

1.75

catayst	yield (%)	**1.74**:**1.75**
AuCl	75	0:100
AuCl$_3$	70	0:100
1.70	82	100:0

Scheme 1.20: Echavarren: 7-*exo-dig* vs. 8-*endo-dig* gold catalyzed hydroarylation[106, 107]

Extensive studies have been performed in an effort to understand ligand effects on the mechanism of cationic gold(I)-catalysis.[23] As mentioned in section 1.5, a possible intermediate along the mechanistic pathway is carbene-like in character. An isolable gold complex with carbenoid character has so far not been discovered despite experimental and theoretical accounts that they are indeed plausible.[28, 108] Studies done by Toste and Goddard determined that the amount of carbene character of a gold species is dictated by the ligands as well as the carbene substituents.[109] Based on their model, they speculate that there is a correlation between bonding and reactivity. Ancillary ligands that are largely σ-donating increase the amount of carbene character of the intermediate. Examples of strongly σ-donating ligands are *N*-heterocyclic carbene type ligands. In contrast, ligands that are highly π-acidic will decrease the overall amount of σ-donation, resulting in an intermediate that is carbocationic in nature.



L	Yield
L = P(OMe)$_3$	0%
P(Me)$_3$	56% (1.4:1 cis:trans)
IPr	80% (11:1 cis:trans)

Scheme 1.21: Ligand effects on the reactivity of gold(I) carbenes[109]

As an example, Toste and coworkers looked at the correlation between bonding and reactivity in gold-catalyzed cyclopropanation reactions (Scheme 1.21).[109] The reaction of compound **1.76** and *cis*-stilbene **1.77** was expected to proceed through a gold-carbene intermediate **1.78**. The authors found that when a highly π-acidic ligand such as trimethyl phosphite was used, no product was formed. However when a strongly σ-donating *N*-heterocyclic carbene ligand was used, the product **1.79** was formed in excellent yield and selectivity.

The use of chiral ligands to render a reaction asymmetric has also had a prominent role in electrophilic metal salt catalyzed cycloisomerization reactions. Although it will not be discussed here, readers are directed to examples of asymmetric gold-catalyzed[110-118] and platinum-catalyzed[97, 119, 120] cycloisomerization reactions in the primary literature.

1.8 Previous work from the Dake group

A long term goal of the Dake laboratory is to create complex nitrogen-containing ring systems which can be used towards the total synthesis of alkaloid natural products. The group has had success using the mild and functional group tolerant metal-catalyzed cycloisomerization reactions. Uniquely, Dake and coworkers form new carbon-carbon bonds through the use of enamides, enesulfonamides, and enecarbamates as nucleophiles (Figure 1.5). Enamide derivatives are useful because they are bifunctional: they can first be used as a mild nucleophile, and then harnessed as an electrophile to neutralize the positive charge of the azacarbenium ion. Enamines are unstable and are usually prepared *in situ*. Derivitization of the nitrogen atom with an electron withdrawing group renders the functionalized enamine stable and isolable, while still taking advantage of its reactivity. Enamides, enecarbamates, and enesulfonamides have generally been used as precursors to electrophilic species.[121-131] The mild nucleophilicity of derivatized enamines has also been exploited.[132-138] Transition metal catalyzed processes where the enamide reacts as a π-nucleophile have been studied to a lesser extent.[139-151] Readers interested in the use of enamides in organic synthesis are directed to a recent review by Carbury.[152]

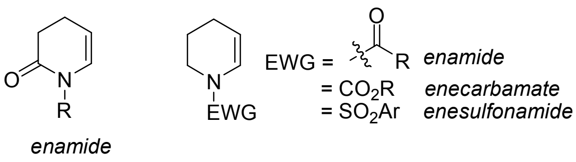
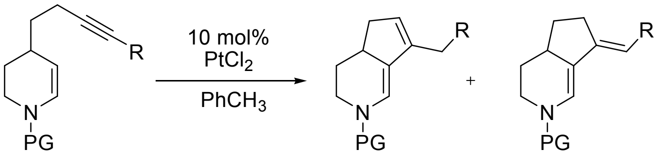


Figure 1.5: Enamine derivatives

The pioneering work of the Dake group was the metal catalyzed cycloisomerization of tetrahydropyridines (**1.80**) substituted with a tethered alkyne at the 4-position (Scheme 1.22).[153] Treatment of these substrates with a catalytic amount of platinum(II) or silver(I) salts caused them to cyclorearrange to 1,3-dienes. If R = CH_3, the double bond migrated into the ring to give **1.81** as the only product. If R = phenyl, a 1:1 mixture of products **1.81** and **1.82** were formed. If R = CO_2CH_3 the double bond stayed exocyclic to the newly formed 5-memebered ring and only **1.82** was isolated. The initial testing of these substrates was done with platinum(II) chloride, $[(dppb)Pt(\mu\text{-}OH)]_2(BF_4)_2$, and silver trifluoromethanesulfonate.

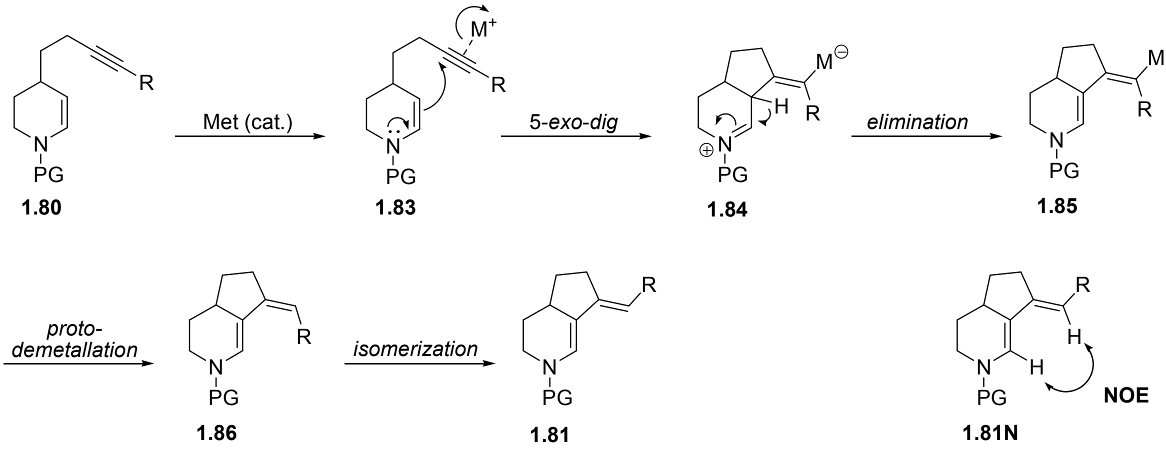


1.80 **1.81** **1.82**

R	yield (%)	**1.81**:**1.82**
CH_3	58	1:0
Ph	52	1:1
CO_2CH_3	69	0:1

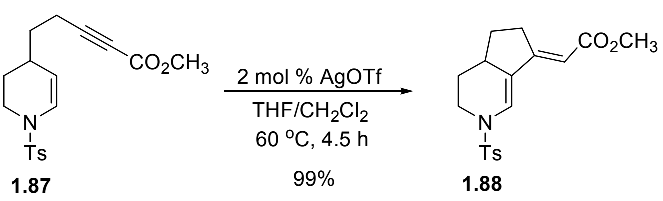
Scheme 1.22: Cycloisomerization of enesulfonamides and enecarbamates to form 1,3-dienes[153]

The proposed mechanism for the cycloisomerization of enamine derivatives is analogous to other cycloisomerization reactions in the literature.[154] Initial complexation of the metal salt to the alkyne of substrate **1.80** gives the activated complex **1.83** (Scheme 1.23). The alkyne is now sufficiently electron deficient for the nucleophilic enamide to attack in a 5-*exo-dig* fashion, forming a new carbon-carbon bond and 5-membered ring (**1.84**). A proton is lost to reform the enamide (**1.85**) since there is no other nucleophile to react with the putative azacarbenium ion. Protodemetallation gives compound **1.86**. Based on nuclear Overhauser effect (NOE) experiments (**1.81N**), it is likely that isomerization occurs at this stage to give 1,3-diene **1.81.**


R
N
PG
1.80
Met (cat.)
M+
R
N
PG
1.83
5-exo-dig
M⊖
H
R
⊕N
PG
1.84
elimination
M⊖
R
N
PG
1.85
proto-
demetallation
R
N
PG
1.86
isomerization
R
N
PG
1.81
R
H
N
H
PG
NOE
1.81N

Scheme 1.23: Proposed mechanism for the cycloisomerization of enamides, enecarbamates, and enesulfonamides[154]

The most effective combination of substrate and catalyst is shown in Scheme 1.24. Functionalizing the alkyne with an electron withdrawing group (**1.87**) was found to give the exocyclic alkene **1.88** as the sole product. Silver triflate was the best catalyst for the system, forming the product in a 99% yield compared to 69% with platinum(II) chloride and 86% with $[(dppb)Pt(\mu\text{-}OH)]_2(BF_4)_2$.


CO2CH3
N
Ts
1.87
2 mol % AgOTf
THF/CH2Cl2
60 °C, 4.5 h
99%
CO2CH3
N
Ts
1.88

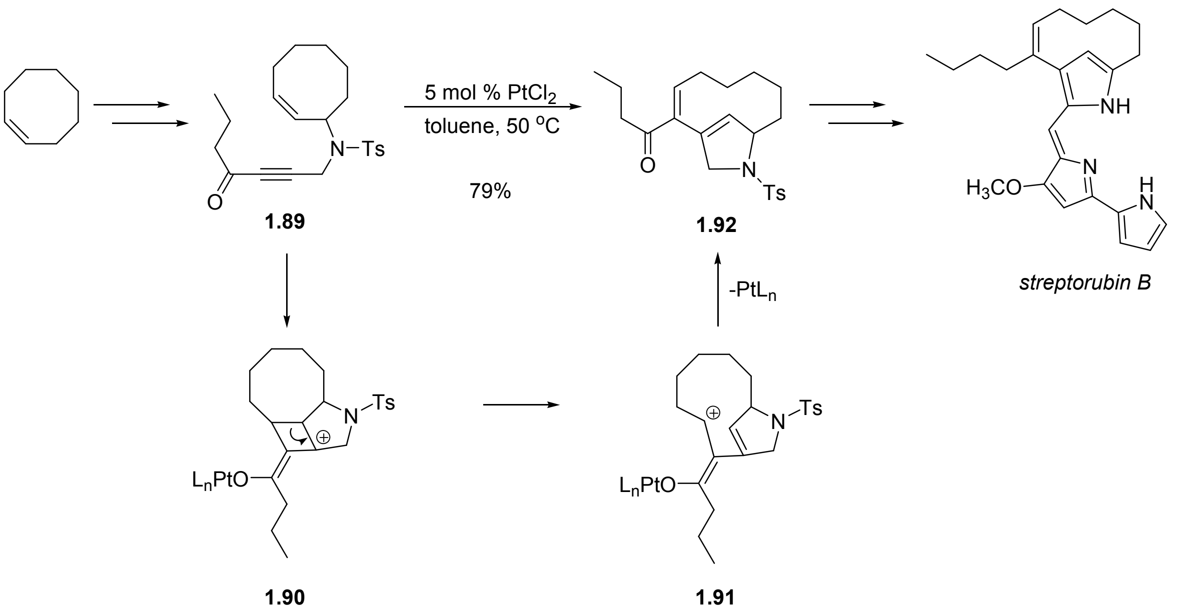
Scheme 1.24: Cycloisomerization of enesulfonamide **1.87** to form 1,3-diene **1.88**[153]

The 1,3-diene formed could be a handle to build further complexity. As an example, diene **1.88** was used in a Diels-Alder reaction to give a highly functionalized, nitrogen containing tricycle. The cycloisomerization and Diels-Alder reactions were optimized to a one-pot reaction with yields as high as 75% for the 2 steps.

1.9 The Use of Platinum, Gold, and Silver Catalyzed Cycloisomerization Reactions in Total Syntheses of Natural Products

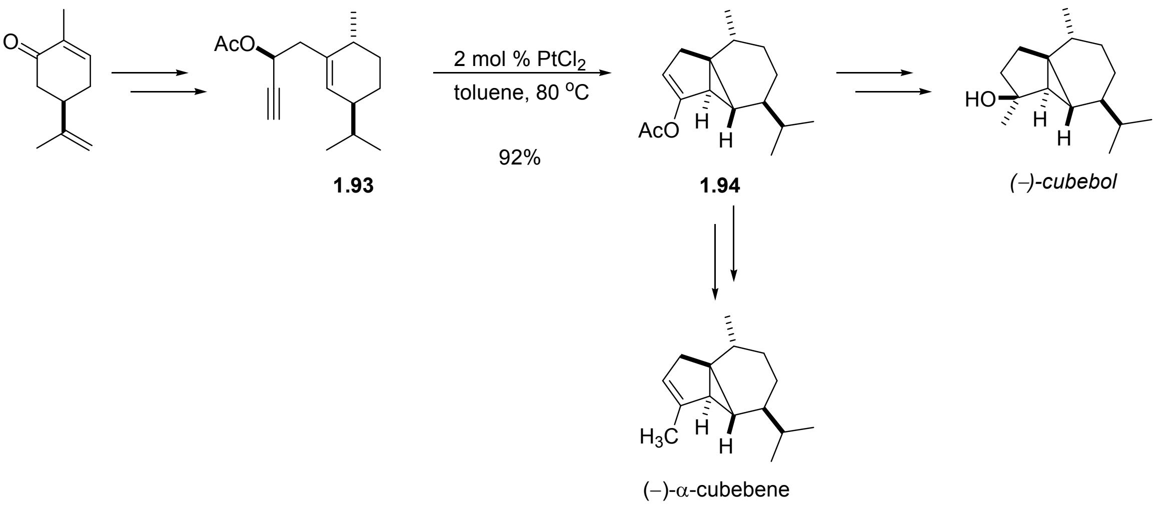
Other academic groups besides the Dake group are interested in using cycloisomerization towards the total synthesis of natural products. Applications of these reactions in total syntheses are not as common as the number of methodology publications put forward, but there have been some great successes.

The first use of platinum(II)-catalysis in the context of a total synthesis was performed by Fürstner when synthesizing the molecules streptorubin B and metacycloprodigiosin (Scheme 1.25).[155, 156] Fürstner treated enyne **1.89** with 5 mol% of platinum(II) chloride to give product **1.92** in 79% yield. The authors speculate that the reaction occurs through a pathway where one of the mesomeric intermediary carbocations is cyclobutane **1.90**. This intermediate can fragment to give carbocation **1.91**, which upon loss of the metal gives the ring expanded product **1.92**. Diene **1.92** was further elaborated to pyrrole containing natural product streptorubin B.



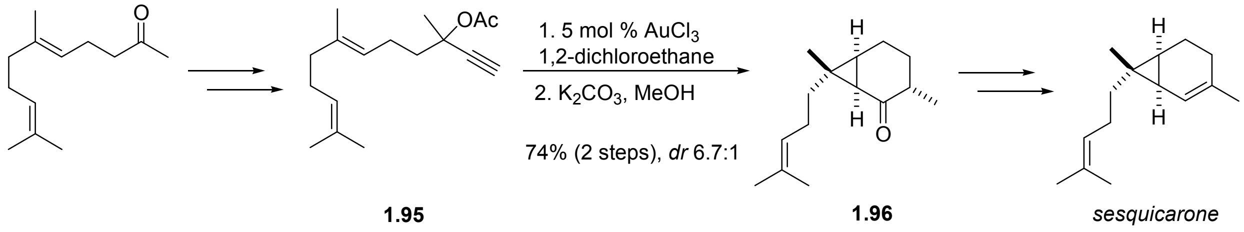
Scheme 1.25: Fürstner and co-workers formal synthesis of streptorubin B[155]

Fürstner and coworkers applied their methodology to a number of other total syntheses. In an elegant study, they completed the total synthesis of both (−)-cubebol and (−)-α-cubebene from one intermediary compound **1.94** (Scheme 1.26).[157] The syntheses of these natural products began with the functionalization of (*R*)-(−)-carvone to propargyl acetate **1.93**. Acetate **1.93** was then treated with 2 mol% of platinum(II) chloride in toluene at 80 °C to form cyclopropyl acetate **1.94** in 92% yield. At this stage, the acetate was converted to the corresponding ketone and treated with methyllithium to afford (−)-cubebol. Alternatively, acetate **1.94** was converted to the enol triflate and then cross coupled to form (−)-α-cubebene. The synthesis of (−)-cubebol using platinum, gold, and copper catalysis is also described in a separate publication by Fehr.[158]



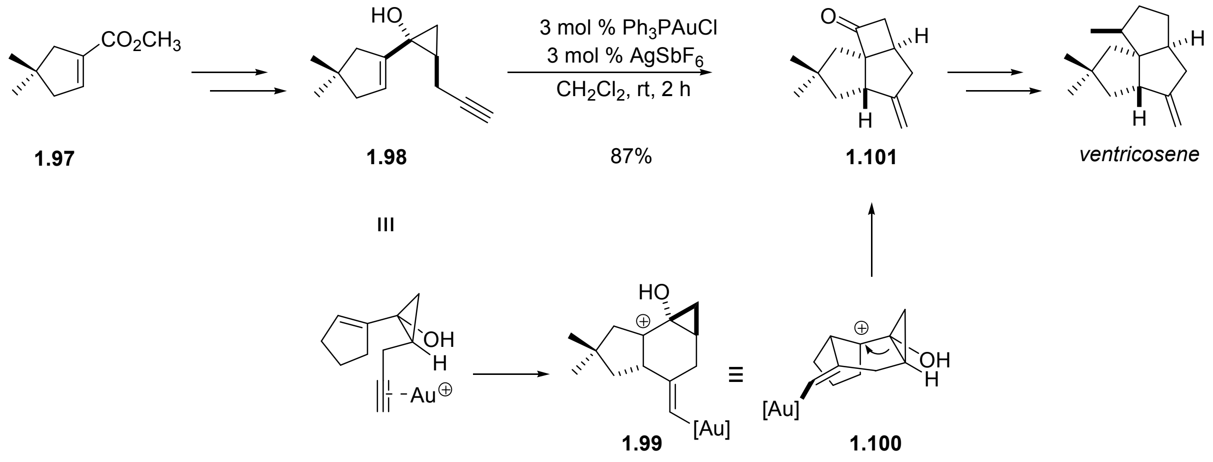
Scheme 1.26: Fürstner and co-workers synthesis of (−)-cubebol and (−)-α-cubebene[157]

In an effort to investigate the regiochemistry of the cycloisomerization reaction, Fürstner and coworkers investigated the total synthesis of sesquicarone (Scheme 1.27).[157] Acetate **1.95** was prepared as the key cyclization substrate from geranylacetone by two routine operations. Acetate **1.95** was tested first with platinum(II) chloride, and although the product was obtained, an allenylester byproduct was also formed. Silver catalysis gave solely the undesired allenylester. Treatment of acetate **1.95** with 1.5 mol% of gold(III) chloride gave the desired cycloisomerization product, with only minimal amounts of the byproduct. The acetate was removed to give product **1.96** in 74% yield over 2 steps. Ketone **1.96** was further elaborated to the natural product sesquicarone.


O
OAc
1. 5 mol % AuCl3
1,2-dichloroethane
2. K2CO3, MeOH
74% (2 steps), dr 6.7:1
H
H
O
H
H
1.95
1.96
sesquicarone

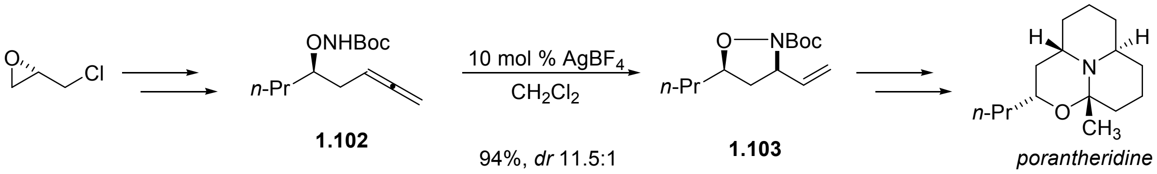
Scheme 1.27: Fürstner and co-workers synthesis of sesquicarone[157]

An interesting application of gold catalysis is demonstrated by Toste in his total synthesis of angular triquinane ventricosene (Scheme 1.28).[159] Commercially available ester **1.97** was first elaborated to cyclopropane **1.98**. Cyclopropane **1.98** was treated with 3 mol% [Ph_3PAuCl] and 3 mol% silver hexafluoroantimonate to afford cyclobutanone **1.101** in 87% yield. The authors speculate that the stereochemical outcome of the reaction can be rationalized by reaction through a boat transition state (**1.100**). Cycloisomerization of the enyne would give cyclohexyl cation **1.99**. A Wagner-Meerwein shift would then furnish the cyclobutanone product **1.100**. This key step can be viewed as a gold-catalyzed ring-expanding cycloisomerization reaction. Compound **1.101** was further elaborated to give the natural product ventricoscene.


CO2CH3
HO
3 mol % Ph3PAuCl
3 mol % AgSbF6
CH2Cl2, rt, 2 h
87%
O
H
H
H
H
1.97
1.98
1.101
ventricosene
≡
OH
H
-Au⊕
HO
⊕
[Au]
≡
⊕
OH
H
[Au]
1.99
1.100

Scheme 1.28: Toste's total synthesis of ventricosene[159]

A recent example using silver catalysis in a total synthesis comes from the group of Bates (Scheme 1.29).[160] Their program towards the synthesis of natural product porantheridine began with the elaboration of epichlorohydrin to allene **1.102**. Allene **1.102** was treated with 10 mol% of silver tetrafluoroborate to yield isoxazolidine **1.103** in 94% yield with 11.5:1 diastereoselectivity. Isoxazolidine **1.103** was used as an intermediate in the total synthesis of porantheridine.



Scheme 1.29: Bates' and co-workers formal synthesis of porantheridine[160]

1.10 Brønsted Acid Catalysis

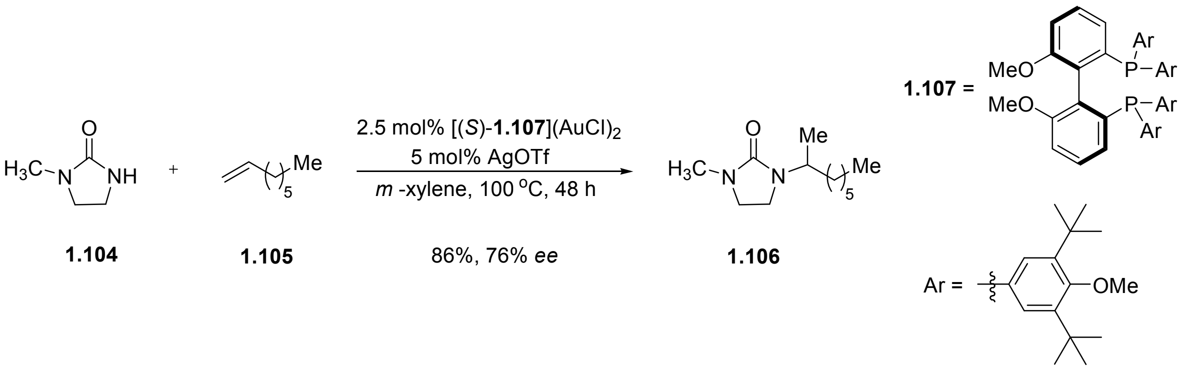
Water often plays a significant role in reactions. Side reactions involving water are avoided by rigorously drying glassware and solvents, and performing the reactions under an inert atmosphere. There is still the possibility that water may be formed during the reaction, or that adventitious water remains on the glassware. Transition metal catalysts with weakly coordinating anions are well known to undergo hydrolysis reactions with water to form metal hydroxide salts and protic species "H^+".[161] An ongoing controversy in metal catalyzed reactions is whether the metal itself is catalyzing the reaction, or whether "H^+" is responsible for catalysis.

$$M^{z+} + H_2O \rightleftharpoons M(OH)^{(z-1)+} + H^+$$

Fürstner and coworkers found that certain enynes cyclorearranged just as effectively with $BF_3{\cdot}OEt_2$ and HBF_4 as they did with $PtCl_2$.[162] Krische obtained similar results; his silver(I) catalyzed coupling of alkynes and carbonyl compounds in some cases was more effective using the Lewis acid BF_3 or Brønsted acid HBF_4.[163] The work by Krische was extended to an intramolecular coupling of alkynes with ketones using triflic acid catalysis by Yamamoto and coworkers.[164] Fürstner argued that the ability of Lewis and Brønsted acids to catalyze the same reactions as metal salts lends support to the proposed cationic nature of the reaction pathway, discussed in section 1.5.

The debate over metal versus proton-catalysis is more evident in the areas of metal catalyzed hydroamination and hydroalkoxylation.[165] Hii found copper(II) triflate to be a good catalyst for the hydroalkoxylation and hydroamination of alkenes. Experimental evidence led her to believe that triflic acid was being generated and was responsible for the catalytic activity observed.[166, 167] Shortly after, Hartwig[168] and He[169] found that triflic acid alone catalyzed hydroamination and hydroalkoxylation reactions. On the other hand, theoretical calculations performed on hydroamination reactions using catalytic PPh_3AuOTf suggest that the active pathway is the binding of the metal to the alkene.[170]

Persuasive evidence of the participation of the metal in hydroamination reactions comes from the laboratory of Widenhoefer.[171] He found that urea **1.104** underwent hydroamination with 1-octene (**1.105**) in the presence of 2.5 mol% of a chiral gold catalyst and 5 mol% of silver triflate to form urea **1.106** in 86% and 76% *ee* (Scheme 1.30). This lends support to gold playing a role and not only a proton, otherwise no *ee*'s would have been observed.



Scheme 1.30: Widenhoefer's enantioselective hydroamination[171]

A number of accounts of Brønsted acid catalysis are available for reactions other than hydroamination. Spencer found that the hetero-Michael addition of nitrogen, oxygen, and sulfur to α,β-unsaturated ketones was readily catalyzed by Brønsted acids,[172] and provides evidence that protons could be the active catalysts in Lewis-acid catalyzed reactions.[173] On the other hand, Kobayashi found in his metal-catalyzed aldol reaction that metal salts, even scandium(III) triflate were stable in water.[174, 175]

No matter how rigorously "dry" transition metal salt catalyzed reactions are performed, control experiments must be done to avoid misinterpretation of results. The most common control experiments are to run the reaction without the metal catalyst, to run the reaction with an acid in the place of a metal catalyst, or to run the reaction with an added base to test for metal-catalysis. Mechanistic pathways for both metal-catalysis and H^+-catalysis exist based on experimental evidence: it is difficult *a priori* to discern which catalytic system would be most beneficial for a given reaction.

1.11 Conclusion

Transition metal catalyzed cycloisomerization reactions, in particular coinage metal-catalyzed reactions, have increased in popularity in the last decade. Despite the many advances, metal catalyzed cycloisomerizations are far from reaching their full potential. There are still many discoveries to be made and likely alternate mechanistic pathways to be uncovered. Cycloisomerization reactions are garnering such attention because they are able to create complex molecules, including the formation of ring systems, from relatively simple starting materials. The major disadvantage of this chemistry is that there is, as of yet, no predictive ability. It is difficult to foresee which of the mechanistic pathways a particular reaction will follow, making it difficult to predict the product. Research is beginning to focus on DFT calculations of hypothetical reactive intermediates to discern which pathway a reaction will take, thereby predicting a product. The ability to envisage the product will render this chemistry more useful towards total synthesis of natural products and in the pharmaceutical industry. As ever, the “holy grail” of transition metal catalyzed cycloisomerization reactions is to have predictive ability coupled with high regio-, chemo-, diastereo-, and enantioselectivity.

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Chapter 2: The Total Synthesis of (+)-Fawcettidine[1]

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[1] Some material in this chapter has been published. See: Kozak, J. A.; Dake, G. R. "Total Synthesis of (+)-Fawcettidine" *Angew. Chem. Int. Ed.* **2008**, *47*, 4221-4223.

2.1 Introduction

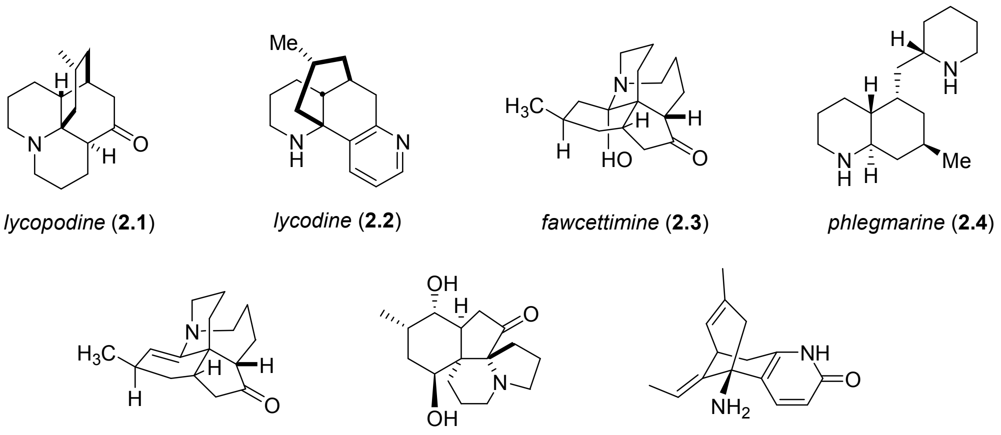
2.1.1 Alkaloid Natural Products

Alkaloid is a term used to describe a large family of structurally diverse natural products, many of which are pharmacologically significant. The term *alkaloid* was derived from the fact that the natural products are *alkali-like*, or basic in nature, and contain a minimum of one basic nitrogen atom.[1] After studies of the biogenetic origin of alkaloids, the definition of an *alkaloid* was extended to include its being derived from an amino acid, and that the nitrogen atom is confined to a heterocyclic ring. The discovery of alkaloids that were neutral or even acidic (i.e. colchicines, quaternary alkaloids), or contained the nitrogen atom in a chain (i.e. polyamines) illustrates difficulties in attempting to classify all alkaloids under one encompassing definition.

Alkaloids are a class of natural products that humans have contact with on what is likely a daily basis. Some specific examples are nicotine in tobacco, caffeine in coffee and tea, theobromine in chocolate, and capsaicin (spicy flavor) in various peppers, to name only a few. Other alkaloids are poisons, hallucinogenic agents, or are active as medicines. The pharmaceutical industry has had a longstanding interest in the use of alkaloids for medicinal applications and drug discovery because of their rich biological activity.[1-3] The complex structures and diversity of the nitrogen-containing ring systems within alkaloids make them inspiring targets for the synthetic organic community.[4-7]

2.1.2 The *Lycopodium* Alkaloid Family

One large family of alkaloids is the *Lycopodium* alkaloid family, members of which are depicted in Figure 2.1. *Lycopodium* alkaloids feature interesting and unusual skeletons that continue to pique the interest of researchers from both biological and total synthesis standpoints.[4, 8, 9] The first account of an isolation of a *Lycopodium* alkaloid is from Bödeker in 1881.[10] The natural product was isolated from the clubmoss *Lycopodium complanatum* (ground cedar) and is believed to be the substance now known as lycopodine (**2.1**) (Figure 2.1).[11] Between the years 1881 and 1994, there have been 201 *Lycopodium* alkaloids from 54 species of *Lycopodium* reported, with more being discovered every year.[4] The *Lycopodium* alkaloids are divided into four classes: the lycopodine class, the lycodine class, the fawcettimine class, and a miscellaneous class. The representative compounds from these classes are lycopodine (**2.1**), lycodine (**2.2**), fawcettimine (**2.3**), and phlegmarine (**2.4**), respectively (Figure 2.1)



lycopodine (**2.1**) *lycodine* (**2.2**) *fawcettimine* (**2.3**) *phlegmarine* (**2.4**)

(+)-fawcettidine (**2.5**) *serratinine* (**2.6**) *huperzine A* (**2.7**)

Figure 2.1: *Lycopodium* alkaloids

The structures of *Lycopodium* alkaloids have inspired many total syntheses. Prominent examples of these include the syntheses of lycopodine by Stork,[12] Ayer,[13] Heathcock,[14] Wenkert,[15] Kraus,[16, 17] Padwa,[18] and Grieco,[19] as well as the studies of lycopodine and annotinine by Weisner.[20-22] The total syntheses of fawcettimine will be discussed later in the chapter.

Some *Lycopodium* alkaloids display biological activity, typically in the form of acetocholinesterase inhibition.[4] Acetylcholine is a neurotransmitter active in the nervous systems of the human body. Degradation of acetylcholine or inhibition of acetylcholine receptors can lead to illnesses such as Alzheimer's disease. A number of alkaloids have been found to prevent the cholinesterase enzyme from degrading acetylcholine, leading to an increased level and duration of acetylcholine in the body. The most potent and biologically active member of the *Lycopodium* genus is huperzine A (**2.7**, Figure 2.1) a member of the lycopodine class. Huperzine A (**2.7**) has been investigated as a drug (an acetylcholinesterase inhibitor) that increases the efficiency for learning and memory in mammals and also shows promise in the treatment of Alzheimer's disease.[4, 23]

There have been many proposed biosynthetic pathways for the construction of *Lycopodium* alkaloids. There has been evidence to support aspects of these hypotheses, although the biosynthesis of these molecules has not been entirely elucidated. Based on the structure of annotinine (**2.8**), Conroy suggested that the biogenetic formation of many of the structurally related *Lycopodium* alkaloids starts with the condensation of two 8-carbon units (Figure 2.2).[24] He proposed that the 8-carbon units are similar to the polyacetate straight chains involved in fatty acid biosynthesis. The numbering system used for lycopodine is based on its biosynthesis from these 8-carbon units.

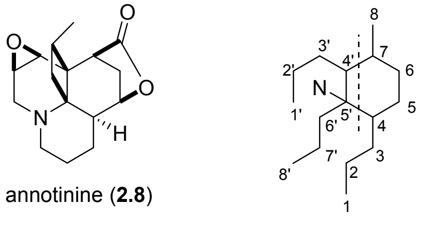
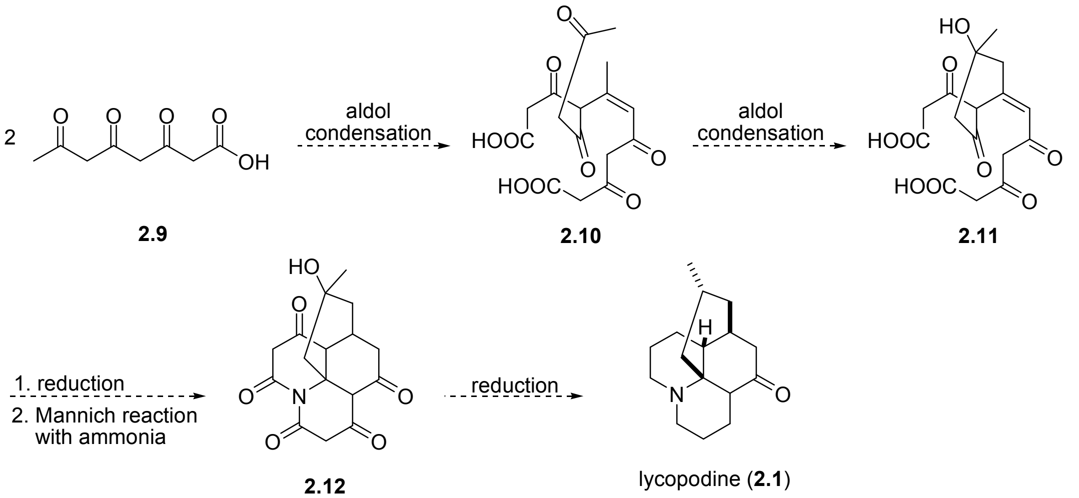

annotinine (**2.8**)
O
O
N
H
8
7
6
5
4
3
2
1
3'
4'
2'
N
5'
1'
6'
7'
8'

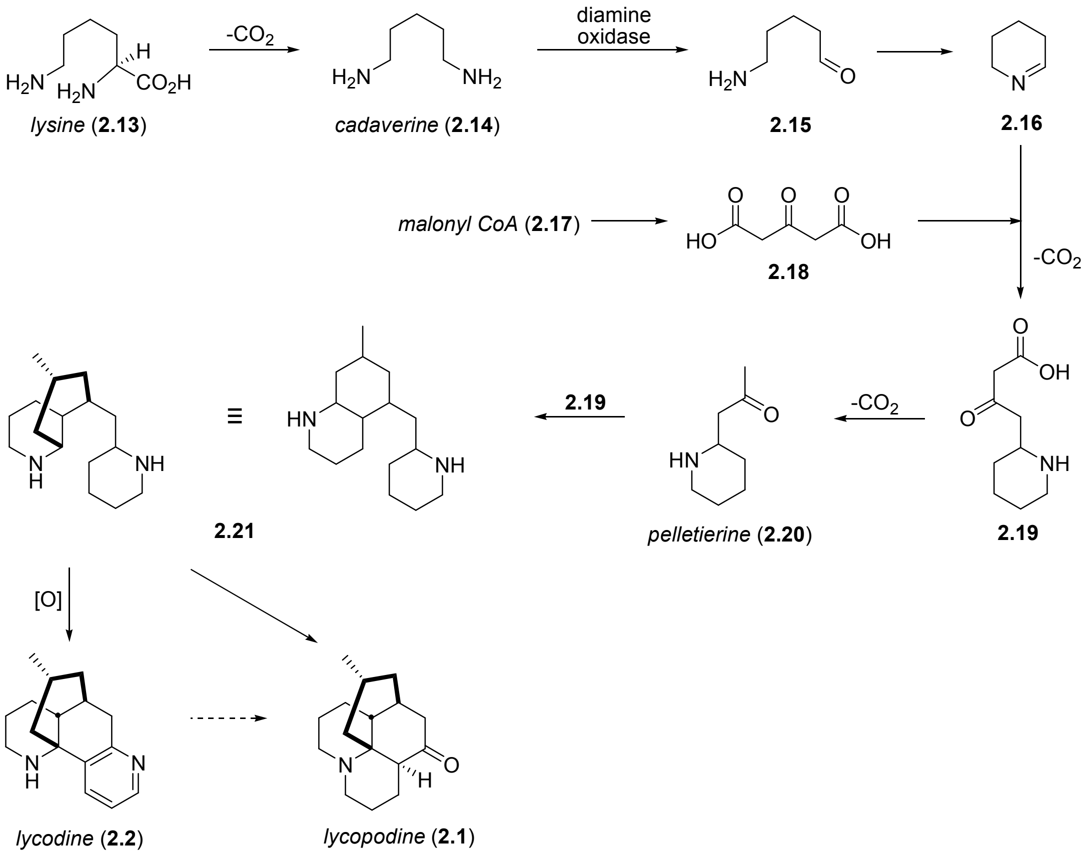
Figure 2.2: Mapping of two 8 carbon chains onto the core of annotinine (**2.8**)

Conroy's speculated biosynthesis of lycopodine (**2.1**) from two molecules of 3,5,7-triketo-octanoic acid (**2.9**) is shown in Scheme 2.1. The author notes that the order of the proposed steps is not certain, but are used rather for illustration. The two straight chain acids (**2.9**) first undergo an aldol condensation and dehydration to give diacid **2.10**. A second aldol condensation forms a 6-membered ring (**2.11**). After reduction of the double bond, a Mannich reaction occurs with a molecule of ammonia to give highly oxidized compound **2.12**. Reduction at carbons 1, 1', 3, 3', and 7' gives lycopodine (**2.1**).


2
OH
aldol condensation
HOOC
HOOC
aldol condensation
HOOC
HOOC
HO
1. reduction
2. Mannich reaction with ammonia
HO
N
reduction
H
N
2.9
2.10
2.11
2.12
lycopodine (**2.1**)

Scheme 2.1: Proposed biogenesis of Lycopodium alkaloid lycopodine **2.1**[24]

The investigation of the biosynthesis of lycopodine (**2.1**) and lycodine (**2.2**) by Spenser and coworkers suggests a very different pathway (Scheme 2.2).[25-28] The *Lycopodium* species of clubmoss from which lycopodine (**2.1**) was isolated could not be cultivated in a laboratory, making investigation of the biosynthetic pathway difficult. Spenser and coworkers fed ^{14}C- and ^{13}C-labeled precursors to the shoots of the plants as they were growing in their natural environment. After a few days, the shoots of the plants were harvested and the tissues were analyzed for incorporation of the label into the final alkaloid products or into potential pathway precursors. Evidence from these experiments led Spenser and coworkers to believe that the decarboxylation of lysine (**2.13**) produces cadaverine (**2.14**). Exposure to diamine oxidase converts one of the amine groups into an aldehyde (**2.15**) and intramolecular condensation gives piperideine (**2.16**). Two molecules of malonyl CoA (**2.17**) are condensed using a ketosynthase enzyme to give acetone dicarboxylic acid (**2.18**). Decarboxylation of one of the acids and reaction with piperideine (**2.16**) gives compound **2.19**. Decarboxylation of **2.19** leads to pelletierine (**2.20**). Further condensation of pelletierine (**2.20**) with compound **2.19** yields diamine **2.21**. It should be noted that this is the skeleton of *Lycopodium* alkaloid phlegmarine (**2.4**), meaning *Lycopodium* alkaloids from the miscellaneous class could also be accessed via this biosynthetic pathway through oxidations and other skeletal rearrangements. As shown in Scheme 2.2, oxidation of **2.21** could possibly lead to the formation of lycodine (**2.2**). Lycopodine (**2.1**) is hypothesized to also be derived from **2.21**.


-CO2
diamine oxidase
lysine (2.13)
cadaverine (2.14)
2.15
2.16
malonyl CoA (2.17)
2.18
-CO2
2.19
pelletierine (2.20)
-CO2
2.19
2.21
[O]
lycodine (2.2)
lycopodine (2.1)

Scheme 2.2: Biosynthetic pathway as proposed by Spenser

Both researchers believe that two 8-carbon chains are involved, but Conroy suggests that a molecule of ammonia is incorporated whereas Spenser claims the nitrogen atom originates from an amino acid. The fact that most alkaloids are derived from amino acids, and not ammonia, is also noted in other reviews.[1] Spenser also supports his pathway with experimental evidence, leading me to believe that his proposed pathway is more plausible than that proposed by Conroy.

2.1.3 (+)-Fawcettidine

(+)-Fawcettidine (**2.5**) is a member of the *Lycopodium* alkaloid family in the fawcettimine class. It was isolated by Burnell and coworkers in the late 1950's from a Jamaican Lycopodium plant *Lycopodium fawcetti*.[29, 30] There have been no reports about the biological activity of fawcettidine itself. Fawcettidine has a molecular mass of 245 and features a tetracyclic core and a quaternary stereocenter. It also contains an enamine functional group that is reported to be sensitive to aqueous acid.[4] The structural representation of (+)-fawcettidine can be drawn a number of ways, four of which are represented in Figure 2.3.

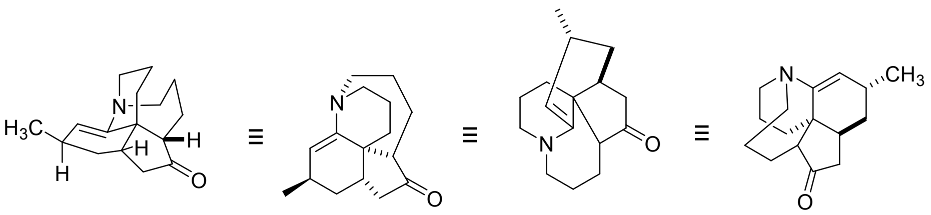


Figure 2.3: Different structural representations of (+)-fawcettidine (**2.5**)

Two different structural representations of (+)-fawcettidine are shown with its numbering pattern in Figure 2.4. The numbering system shown is consistent for all fawcettimine based *Lycopodium* alkaloids.

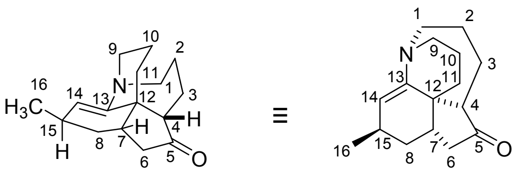
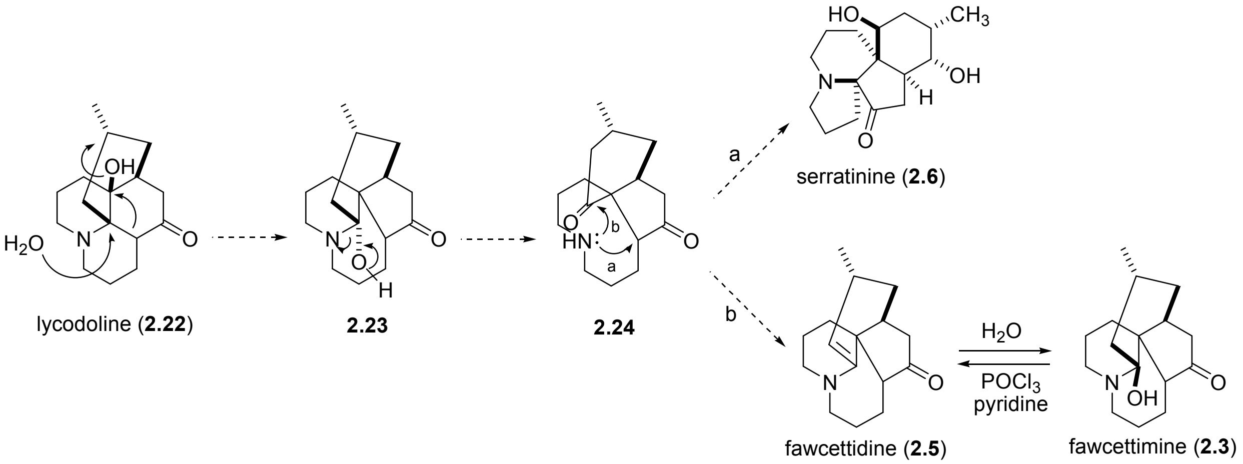


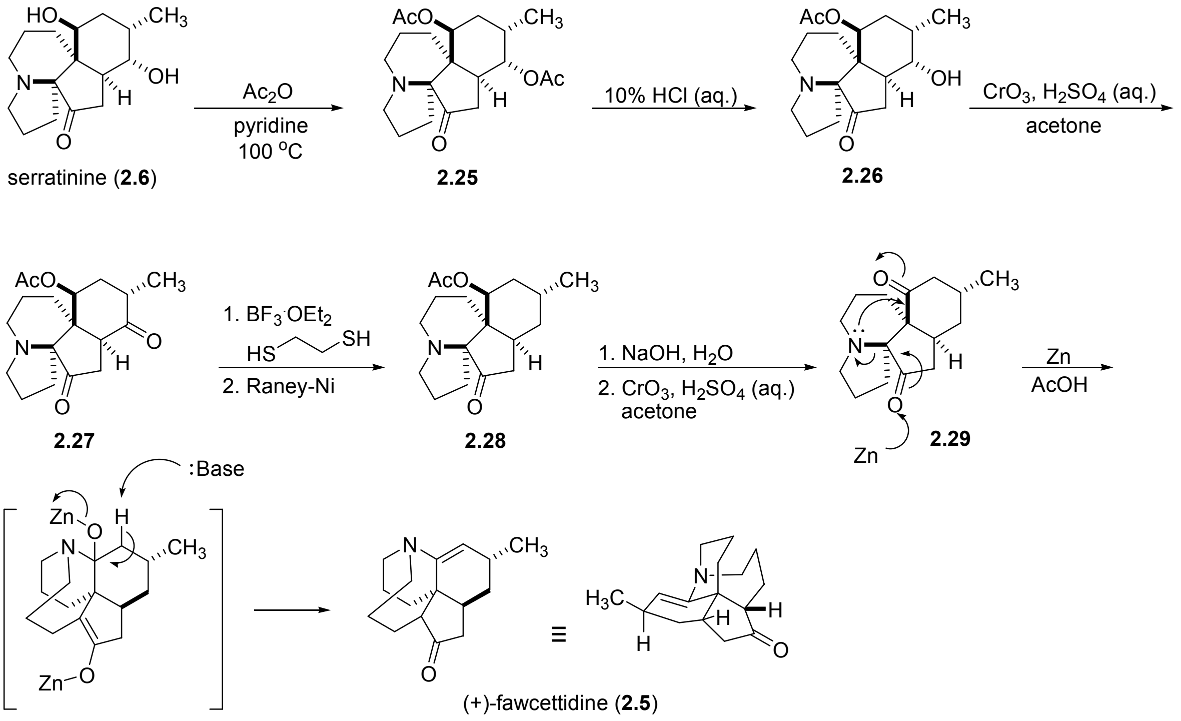
Figure 2.4: Numbering scheme for (+)-fawcettidine (**2.5**)

As mentioned in section 2.1.1, the proposed biogenesis of the *Lycopodium* class of alkaloids comes from two 8-carbon units which can be hypothetically reacted to form lycopodine **2.1**. Lycodoline (**2.22**) differs from lycopodine (**2.1**) by one hydroxyl group, suggesting they are biogenetically related. Inubushi postulates that serratinine (**2.6**), fawcettidine (**2.5**), and fawcettimine (**2.3**) are formed from lycodoline (**2.22**) (Scheme 2.3).[31] It is hypothesized that attack of a water molecule could occur at the tetrasubstituted carbon adjacent to the nitrogen atom in lycodoline, causing a carbon shift to occur to eliminate a hydroxyl group as water, affording compound **2.23**. The hydroxyl moiety of **2.23** could then form a carbonyl, breaking the carbon-nitrogen bond, forming a nitrogen-containing 9-membered ring (**2.24**). At this point compound **2.24** could form two new compounds, serratinine (**2.6**) and fawcettidine (**2.5**) as indicated by the arrows a and b. These arrows do not indicate electron movement, rather the bond that will be formed biosynthetically. If a C-N bond is formed between the nitrogen and the carbon α to the carbonyl indicated, serratinine (**2.6**) is formed (path a). If a C-N bond is formed between the nitrogen and the carbon of the carbonyl indicated, followed by dehydration of the alcohol, fawcettidine (**2.5**) is formed (path b). If dehydration does not occur, or water reacts with fawcettidine (**2.5**), fawcettimine is formed (**2.3**). One reported method to turn fawcettimine (**2.3**) into fawcettidine (**2.5**) is to treat it with phosphoryl chloride.[32] It should be noted that the hypothesis described in Scheme 2.3 has not been tested experimentally.



Scheme 2.3: Proposed biogenesis of serratinine (**2.6**) and fawcettidine (**2.5**)

Scheme 2.3 indicates one proposed biosynthetic pathway from lycodoline (**2.22**) a member of the lycopodine class of *Lycopodium* alkaloids, to serratinine (**2.6**), fawcettidine (**2.5**) and fawcettimine (**2.3**), members of the fawcettimine class. The structure of fawcettidine was elucidated by Inubushi and coworkers based on its formation from and correlation with serratinine (Scheme 2.4).[32, 33] Serratinine (**2.6**) was first acetylated to give diacetate **2.25**. Treatment with a dilute solution of aqueous hydrochloric acid selectively deacetylated one of the hydroxyl groups (**2.26**). Jones' oxidation then converted the alcohol to a ketone (**2.27**). The ketone on the 6-membered ring was then removed by conversion to the dithiane and reduction with Raney-nickel to give compound **2.28**. The second ester was then hydrolyzed and oxidized to give ketone **2.29**. At this stage, treatment of compound **2.29** with zinc under acidic conditions gave a structural rearrangement. The proposed mechanism is as follows: the zinc interacts with the carbonyl of the 5-membered ring forming the zinc enolate and breaking the C-N bond to form the nitrogen-containing 9-membered ring. The nitrogen then attacks the carbonyl of the 6-membered ring. Elimination of the zinc oxide species gives fawcettidine (**2.5**).


serratinine (2.6)
Ac2O
pyridine
100 °C
2.25
10% HCl (aq.)
2.26
CrO3, H2SO4 (aq.)
acetone
2.27
1. BF3·OEt2
HS SH
2. Raney-Ni
2.28
1. NaOH, H2O
2. CrO3, H2SO4 (aq.)
acetone
2.29
Zn
Zn
AcOH
:Base
(+)-fawcettidine (2.5)

Scheme 2.4: Structure elucidation of (+)-fawcettidine (**2.5**) based on its formation from serratinine (**2.6**)

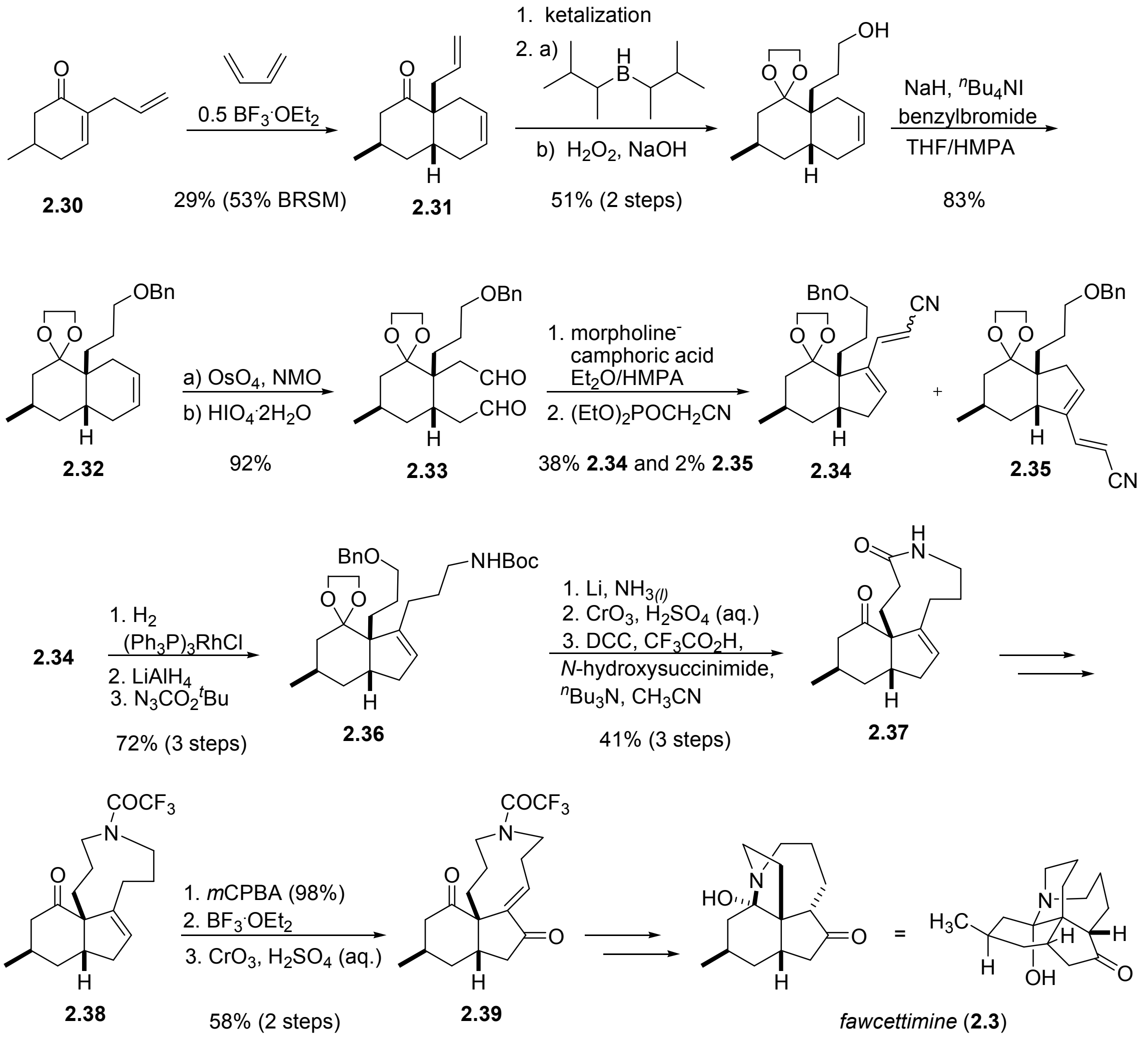
Fawcettidine has only ever been formed by semisynthesis from other *Lycopodium* alkaloid natural products. There has yet to be a reported total synthesis of the tetracyclic molecule.

2.2 Synthetic Approaches to the Total Synthesis of Fawcettimine

To date there have been four total syntheses and two formal syntheses of the *Lycopodium* alkaloid fawcettimine (**2.3**). Two of the total syntheses are racemic and two are enantioselective. The two formal syntheses are both enantioselective. Despite its near structural identity to (+)-fawcettimine, there have been no total syntheses reported for (+)-fawcettidine. The synthetic approaches used in creating (±)- and (+)-fawcettimine will be described in the following section. An abbreviated discussion of the total syntheses of fawcettimine will be presented, focusing on interesting or important transformations. These include formation of stereocenters, key steps as indicated by the authors, ring formation, or major structural changes. Synthetic studies towards the core of fawcettimine will not be described but interested readers are directed to a report in the primary literature.[34]

2.2.1 Inubushi and Coworkers' Total Synthesis of (±)-Fawcettimine

The first synthetic effort towards (±)-fawcettimine is described by Harayama, Takatani, and Inubushi (Scheme 2.5).[35] Their synthesis began with a Diels-Alder reaction between racemic enone **2.30** and 1,4-butadiene to give compound **2.31**. Ketalization, hydroboration, and primary alcohol protection gave ketal **2.32**. Inubushi and coworkers used the formation of a six-membered ring to set the relative stereochemistry, and subsequently oxidative cleaved the ring to give dialdehyde **2.33**. Intramolecular aldol condensation followed by Wadsworth-Emmons' homologation gave a mixture of nitriles **2.34** and **2.35**, favoring the desired product **2.34**.


2.30
0.5 $BF_3{\cdot}OEt_2$
29% (53% BRSM)
2.31
1. ketalization
2. a) H B
b) H_2O_2, NaOH
51% (2 steps)
OH
NaH, $^nBu_4NI$
benzylbromide
THF/HMPA
83%
OBn
2.32
a) OsO_4, NMO
b) $HIO_4{\cdot}2H_2O$
92%
CHO
CHO
2.33
1. morpholine⁻ camphoric acid Et_2O/HMPA
2. $(EtO)_2POCH_2CN$
38% 2.34 and 2% 2.35
BnO
CN
2.34
+
2.35
2.34
1. H_2 $(Ph_3P)_3RhCl$
2. $LiAlH_4$
3. $N_3CO_2{}^tBu$
72% (3 steps)
NHBoc
2.36
1. Li, $NH_{3(l)}$
2. CrO_3, H_2SO_4 (aq.)
3. DCC, CF_3CO_2H, N-hydroxysuccinimide, $^nBu_3N$, CH_3CN
41% (3 steps)
H N
O
2.37
$COCF_3$
N
2.38
1. mCPBA (98%)
2. $BF_3{\cdot}OEt_2$
3. CrO_3, H_2SO_4 (aq.)
58% (2 steps)
2.39
HO
=
H_3C
OH
H
fawcettimine (2.3)

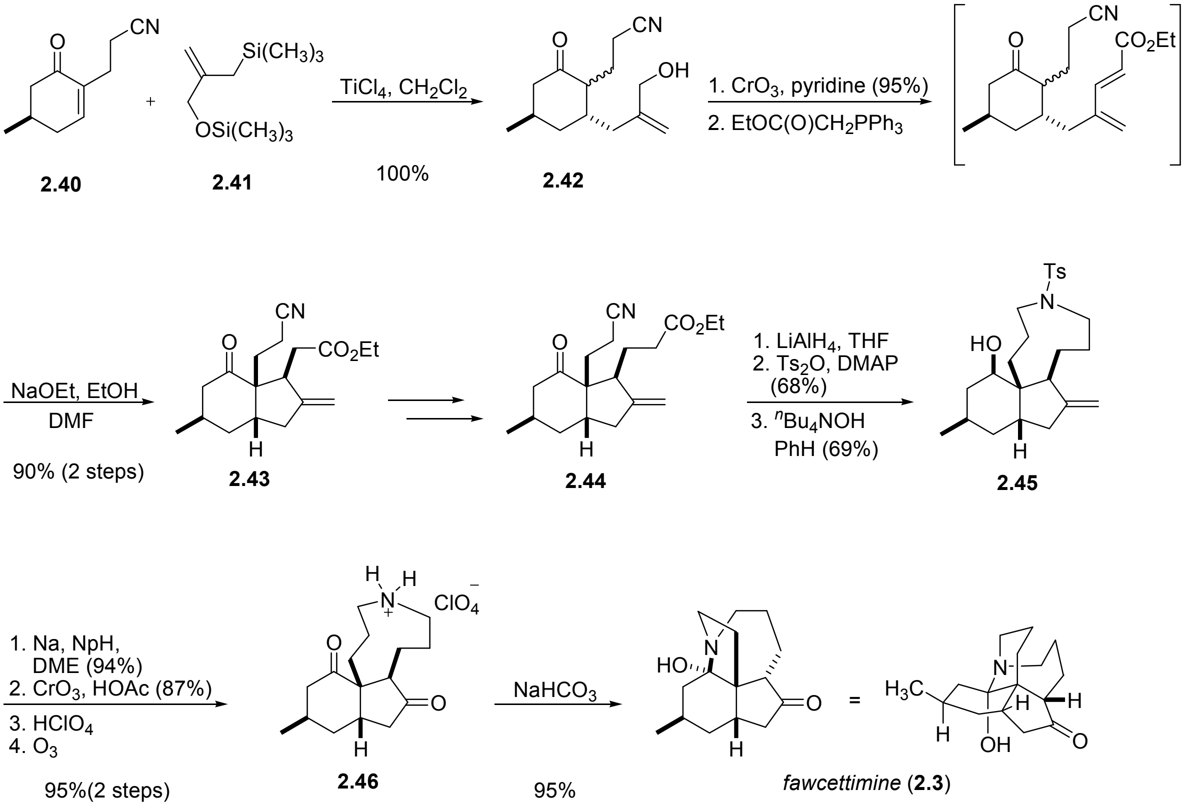
Scheme 2.5: Harayama, Takatani, and Inubushi's total synthesis of (±)-fawcettimine (**2.3**)[35]

Selective hydrogenation of the least substituted olefin with Wilkinson's catalyst, reduction of the nitrile to the primary amine, and protection as the *tert*-butyl carbonate gave compound **2.36** in 72% yield over three operations. The nine-membered ring lactam **2.37** was then formed following a three step procedure. Standard reactions furnished ketone **2.38** from **2.37**. Oxidation of **2.38** with *meta*-chloroperbenzoic acid (*m*CPBA) followed by treatment with a Lewis acid and oxidation gave enone **2.39**. Enone **2.39** was structurally similar to the keto-form of fawcettimine. After reduction of the olefin and hydrolysis of the nitrogen protecting group, the nitrogen atom of the nine-membered ring amine spontaneously condensed with the adjacent ketone functional group to give fawcettimine (**2.3**) in its natural carbinolamine form.

2.2.2 Heathcock and Coworkers' Total Synthesis of (±)-Fawcettimine

The second total synthesis of (±)-fawcettimine (**2.3**) was completed a decade later by Heathcock, Blumenkopf, and Smith (Scheme 2.6).[36] Their synthesis began with racemic cyano enone **2.40**.[37] Hosomi-Sakurai addition[38] of bis-silane **2.41** to cyano enone **2.40** gave compound **2.42** in excellent yield. Although the diastereomeric mixture formed α to the carbonyl was inconsequential, the reaction displayed high facial selectivity, resulting in product **2.42** with a solely *trans* relationship between the remaining two substituents. These reaction conditions were selected due to the high selectivity of this reaction compared to other known conditions.

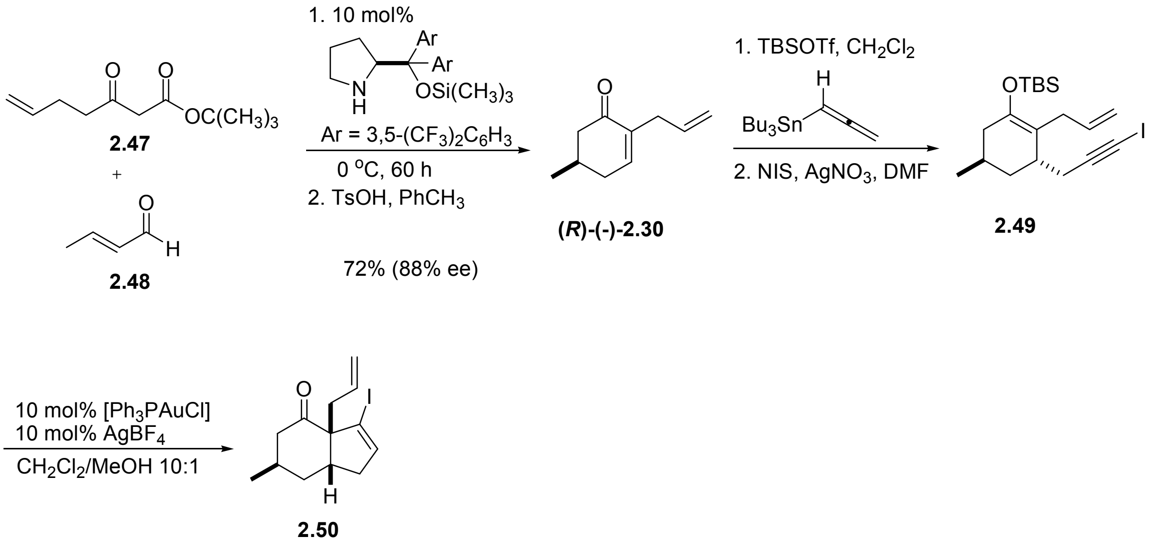
Oxidation and Wittig homologation of **2.42** followed by treatment with base gave the 6,5-ring system **2.43**. The transformation from **2.42** to **2.43** was carried out in one-pot due to the low solubility of the diene intermediate on large-scale. Ester **2.43** was homologated by one carbon atom to give ester **2.44** using a three operation Arndt-Eistert sequence.[39, 40] Standard synthetic operations gave compound **2.45** containing a nine-membered nitrogen containing ring. At this stage Heathcock and coworkers removed the *para*-toluenesulfonyl protecting group, oxidized the alcohol to the ketone, transformed the free amine to its perchlorate salt, and cleaved the exocyclic olefin to a ketone using ozone to give compound **2.46**. They found that perchlorate salt **2.46** only existed as the amino ketone tautomer. When the perchlorate salt was neutralized with base, the nitrogen collapsed onto the ketone (as seen in Inubushi's synthesis, Scheme 2.5) to give the carbinolamine form of fawcettimine (**2.3**).


2.40
2.41
TiCl$_4$, CH$_2$Cl$_2$
100%
2.42
1. CrO$_3$, pyridine (95%)
2. EtOC(O)CH$_2$PPh$_3$
NaOEt, EtOH
DMF
90% (2 steps)
2.43
2.44
1. LiAlH$_4$, THF
2. Ts$_2$O, DMAP (68%)
3. ^{n}Bu$_4$NOH PhH (69%)
2.45
1. Na, NpH, DME (94%)
2. CrO$_3$, HOAc (87%)
3. HClO$_4$
4. O$_3$
95%(2 steps)
2.46
NaHCO$_3$
95%
fawcettimine (2.3)

Scheme 2.6: Heathcock, Blumenkopf, and Smith's total synthesis of (±)-fawcettimine (**2.3**)[36]

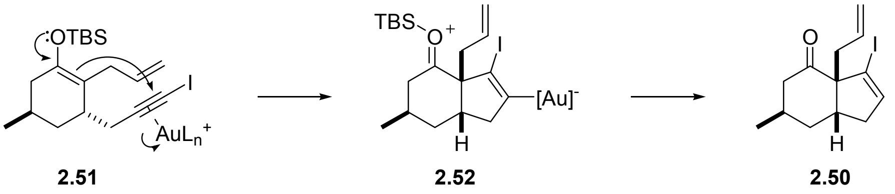
2.2.3 Toste and Coworkers' Total Synthesis of (+)-Fawcettimine

The first asymmetric synthesis of (+)-fawcettimine was achieved by Toste and coworkers in 2007 (Scheme 2.7).[41] The stereocenter at C15 was set by an organocatalytic Robinson annulation between keto ester **2.47** and crotonaldehyde (**2.48**) to give enone (*R*)-(−)-**2.30** in 72% yield and an enantiomeric excess of 88%. This reaction was successful on multigram scale. Enone (*R*)-(−)-**2.30** was then subjected to conjugate propargylation and iodination to give enyne **2.49**. Toste and coworkers then used chemistry developed by their group involving cationic gold(I)-catalysis to form the 6,5-ring system with a *cis*-ring junction (**2.50**).



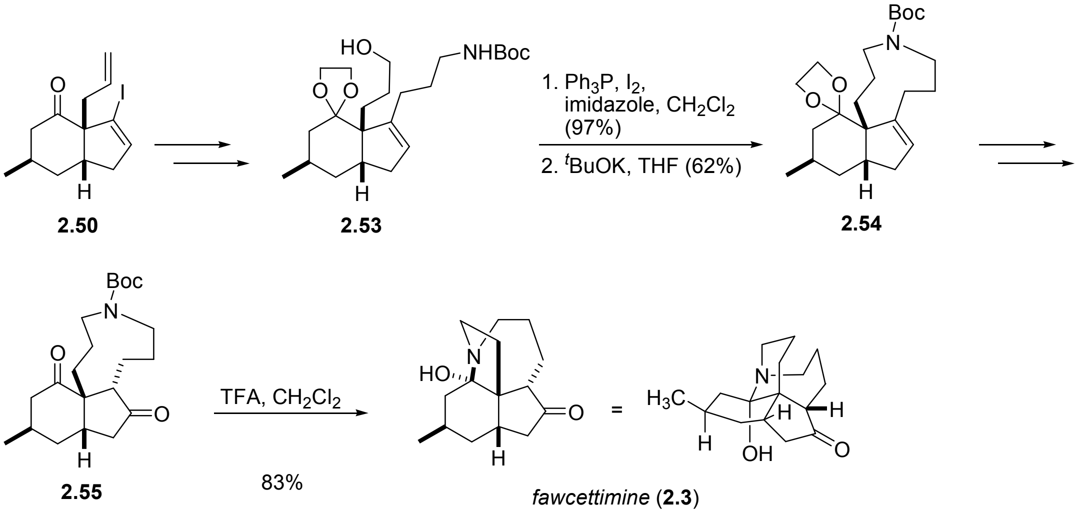
Scheme 2.7: Linghu, Kennedy-Smith, and Toste's total synthesis of (+)-fawcettimine[41]

The gold(I)-catalyzed annulation used is of particular interest as similar chemistry is employed in the Dake group. In this case, the silyl enol ether was used as a nucleophile as opposed to an enamine derivative (Scheme 2.8). First the gold presumably coordinates to the alkyne to give the activated complex **2.51**. The silyl enol ether can then attack the activated alkyne in a 5-*endo-dig* fashion to form the 5-membered ring intermediate **2.52**. Loss of the silyl group and protodemetallation gives the product **2.50**.



Scheme 2.8: Au(I)-catalyzed cycloisomerization as a key step in Toste's synthesis

A series of simple operations transformed vinyl iodide **2.50** into primary alcohol **2.53** (Scheme 2.9). The primary alcohol of **2.53** was then converted to an iodide using an Appel reaction.[42] Deprotonation of the nitrogen with base followed by S_N2 displacement of the iodide formed the 9-membered nitrogen-containing ring (**2.54**). Three functional group manipulations provided compound **2.55**, an intermediate that closely resembled the intermediates used by Inubushi (**2.39**) and Heathcock (**2.46**). Conversion of carbamate **2.55** into the natural product was performed in a similar manner. The nitrogen atom was deprotected using trifluoroacetic acid, causing the nitrogen to collapse onto the ketone to form the carbinolamine form of (+)-fawcettimine (**2.3**).

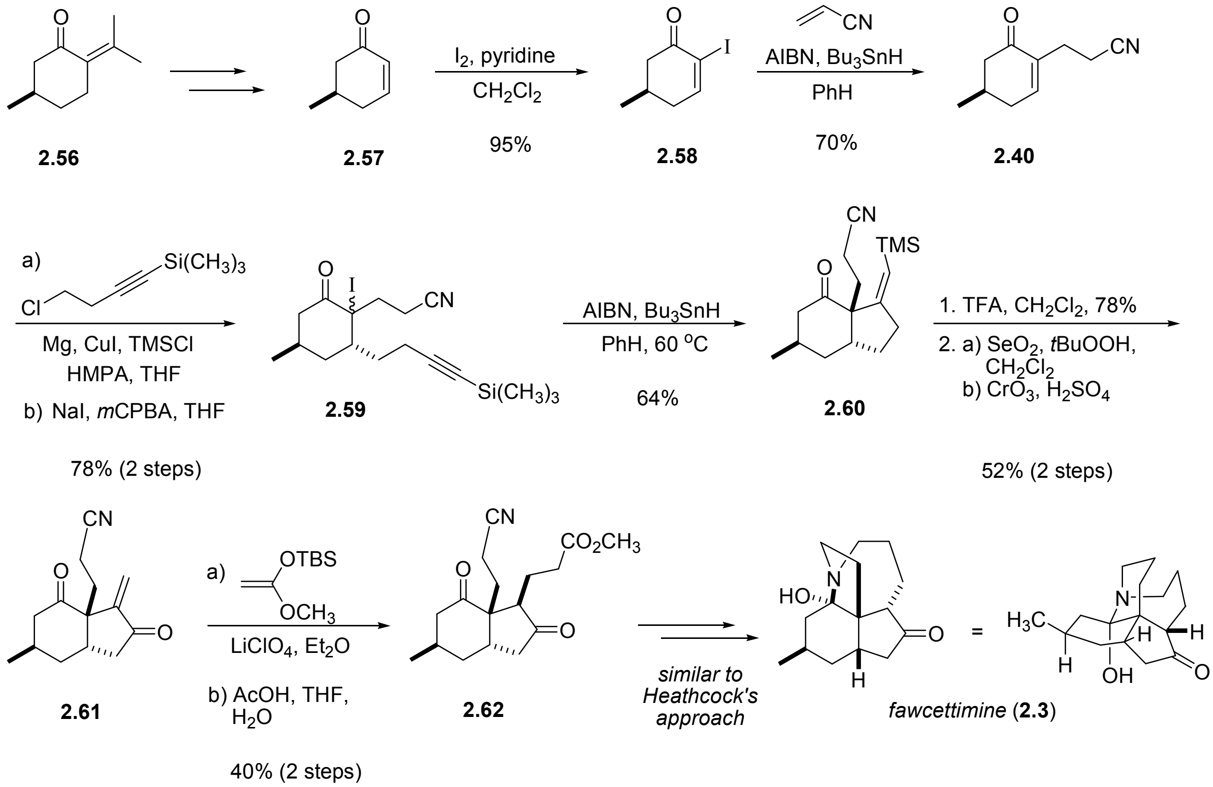


Scheme 2.9: The conclusion of Toste and co-worker's synthesis of (+)-fawcettimine

2.2.4 Sha and Coworkers' Formal Synthesis of (+)-Fawcettimine

Methodology developed in the Sha laboratory relates to intramolecular cyclization of α-carbonyl radicals. They have been successful in applying this methodology to a series of total syntheses.[43-48] Recently, they discovered the intermolecular radical addition of α-iodo cycloalkenones to electron deficient alkenes. To display the utility of their methodology within the context of total synthesis the authors applied it to the formal synthesis of (+)-fawcettimine.[49] This work was published just prior to our work on the total synthesis of (+)-fawcettidine (**2.5**).

Sha and coworkers started their formal synthesis from chiral pool starting material (*R*)-(+)-pulegone **2.56** (Scheme 2.10). (*R*)-(+)-Pulegone **2.56** was elaborated to enone **2.57** following established literature procedures.[50] The requisite vinyl iodide was installed by treatment of enone **2.57** with iodine and pyridine to give iodide **2.58** in 95% yield. The key step was then carried out on iodide **2.58**. α-Iodo alkenone **2.58** was treated under radical initiation conditions in the presence of acrylonitrile to form cyanoenone **2.40** in 70% yield. Conjugate addition of a trimethylsilyl protected alkyne functional group followed by insertion of an unstable α-iodide gave compound **2.59** in 78% yield over two steps. α-Iodo compound **2.59** was converted to compound **2.60** using other methodology developed by the Sha laboratory. α-Iodo compound **2.59** was treated under radical initiation conditions to form a radical α to the carbonyl. A 5-*exo-dig* cyclization then occured followed by hydrogen abstraction from the tributyl tin hydride to give the 6,5-membered ring system **2.60** with the correct stereochemistry. Removal of the trimethylsilyl group, allylic oxidation, and Jones' oxidation gave cyano enone **2.61** in moderate yield. Lithium perchlorate mediated conjugate addition of a ketene silyl acetal to enone **2.61** gave compound **2.62**.

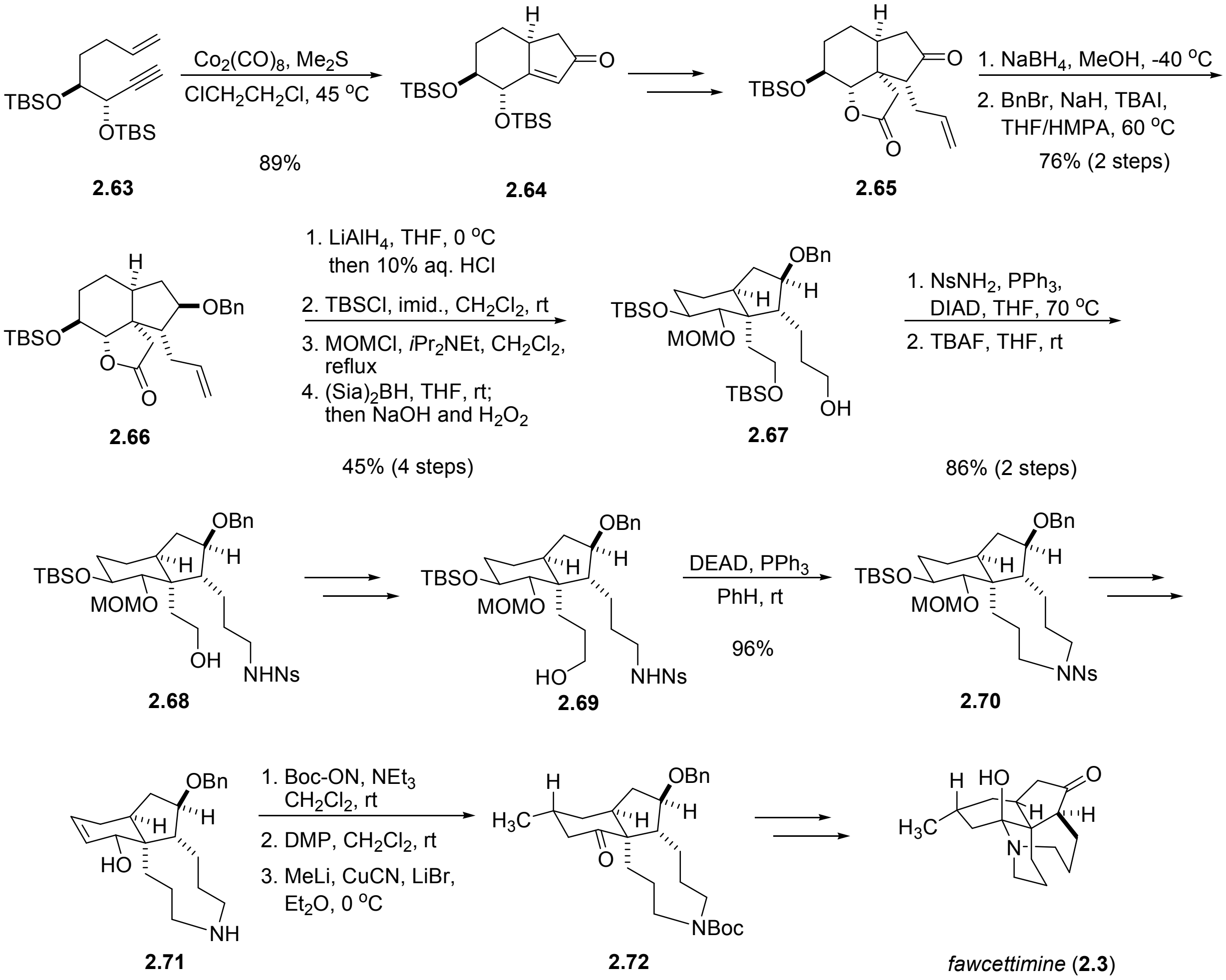

2.56
2.57
I2, pyridine
CH2Cl2
95%
2.58
CN
AIBN, Bu3SnH
PhH
70%
2.40
a) Cl, Si(CH3)3
Mg, CuI, TMSCl
HMPA, THF
b) NaI, mCPBA, THF
78% (2 steps)
2.59
AIBN, Bu3SnH
PhH, 60 °C
64%
TMS
2.60
1. TFA, CH2Cl2, 78%
2. a) SeO2, tBuOOH, CH2Cl2
b) CrO3, H2SO4
52% (2 steps)
2.61
a) OTBS, OCH3
LiClO4, Et2O
b) AcOH, THF, H2O
40% (2 steps)
CO2CH3
2.62
similar to Heathcock's approach
HO
N
H
H3C
OH
fawcettimine (2.3)

Scheme 2.10: Liu, Chau, and Sha's formal synthesis of (+)-fawcettimine[49]

Compound **2.62** is nearly structurally identical to an intermediate isolated by Heathcock in his total synthesis of (±)-fawcettimine. Sha and coworkers used intermediate **2.62** and followed steps similar to Heathcock's to complete the formal synthesis of (+)-fawcettimine (**2.3**).

2.2.5 Mukai and Coworkers' Total Synthesis of (+)-Fawcettimine

Mukai and coworkers have a program devoted to the total synthesis of naturally occurring alkaloids. Many of their syntheses use the same precursor, oxatricyclo[7.3.0.0^{1,5}]dodecanedione **2.65** (Scheme 2.11).[52, 53] This intermediate was synthesized commencing from chiral pool compound diethyl *L*-tartarate followed by elaboration to chiral enyne **2.63**. Enyne **2.63** was reacted under Pauson-Khand[54, 55] conditions to form cyclopentenone **2.64**. After a series of operations, intermediate **2.65** was formed.


2.63
Co$_2$(CO)$_8$, Me$_2$S
ClCH$_2$CH$_2$Cl, 45 °C
89%
2.64
2.65
1. NaBH$_4$, MeOH, -40 °C
2. BnBr, NaH, TBAI, THF/HMPA, 60 °C
76% (2 steps)
2.66
1. LiAlH$_4$, THF, 0 °C then 10% aq. HCl
2. TBSCl, imid., CH$_2$Cl$_2$, rt
3. MOMCl, *i*Pr$_2$NEt, CH$_2$Cl$_2$, reflux
4. (Sia)$_2$BH, THF, rt; then NaOH and H$_2$O$_2$
45% (4 steps)
2.67
1. NsNH$_2$, PPh$_3$, DIAD, THF, 70 °C
2. TBAF, THF, rt
86% (2 steps)
2.68
2.69
DEAD, PPh$_3$
PhH, rt
96%
2.70
2.71
1. Boc-ON, NEt$_3$ CH$_2$Cl$_2$, rt
2. DMP, CH$_2$Cl$_2$, rt
3. MeLi, CuCN, LiBr, Et$_2$O, 0 °C
2.72
fawcettimine (2.3)

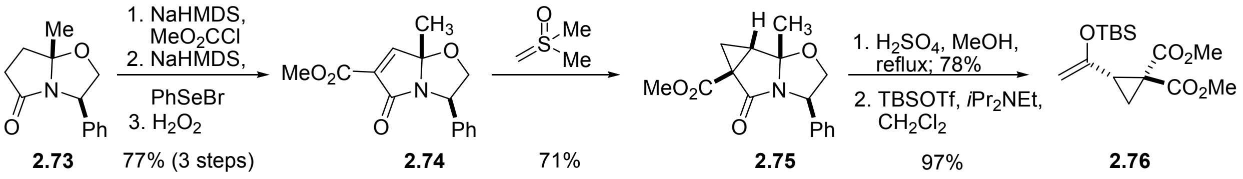
Scheme 2.11: Otsuka, Inagaki, and Mukai's total synthesis of (+)-fawcettimine[53]

This year, Mukai and coworkers elaborated intermediate **2.65** to the natural product (+)-fawcettimine.[53] After selective carbonyl reduction and benzylation, compound **2.66** was formed. The lactone of compound **2.66** was then reduced and two hydroxyl groups were selectively protected as the *tert*-butyldimethyl silyl ethers. The remaining secondary hydroxyl group was protected as a methoxymethyl (MOM) ether. Hydroboration of the alkene resulted in compound **2.67**. A key step as described by the authors is their use of the Mitsunobu reaction.[56-58] They first employed the reaction to convert the primary hydroxyl into a nosyl-protected nitrogen in an intermolecular Mitsunobu reaction. The TBS-protected primary alcohol was selectively deprotected to give alcohol **2.68**. A one-carbon homologation was then performed under standard procedures to give alcohol **2.69**. At this stage the second intramolecular Mitsunobu reaction took place to form the nitrogen-containing 9-membered ring (**2.70**) in excellent yield. A series of operations gave amine **2.71**. The nitrogen of **2.71** was protected as the *tert*-

butylcarbamate and the alcohol was oxidized to give an enone. A methyl substituent was then introduced using a copper-mediated conjugate addition reaction of methyllithium to give compound **2.71** in a highly stereoselective manner. Three more synthetic operations afforded the natural product (+)-fawcettimine (**2.3**).

2.2.6 Jung and Chang's Formal Synthesis of (+)-Fawcettimine

The most recent synthesis of (+)-fawcettimine comes from the laboratory of Jung and coworkers.[59] Jung's inspiration for the formal synthesis of (+)-fawcettimine was conceived from previous work done by the group on the acid-promoted Mukaiyama-Michael addition of hindered silyoxy dienes to hindered enones.[60] The formation of the hydrindanone core of (+)-fawcettimine was envisaged to come from this reaction.

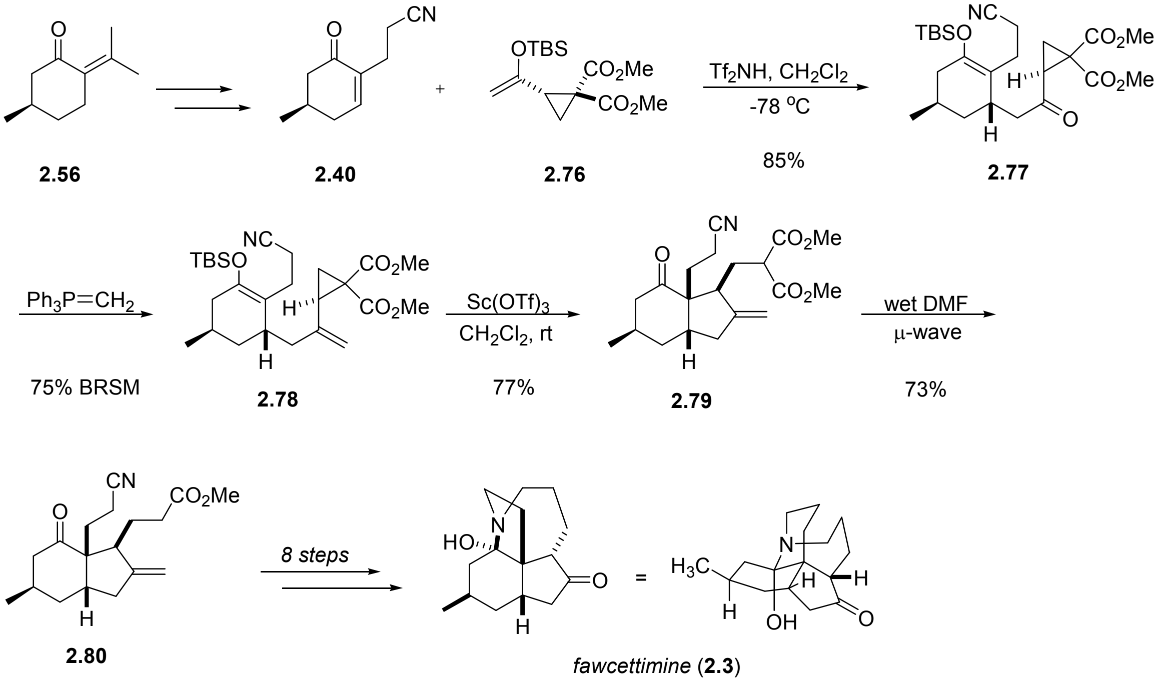


Scheme 2.12: Synthesis of the requisite (*S*)-silyl enol ether **2.76**

First the silyl enol ether (**2.76**) was built (Scheme 2.12). Jung and coworkers started from the known bicyclic lactam[61] **2.73** and elaborated it to methyl ester **2.74** using a modification of a Meyers' procedure.[62] The enone **2.74** was then cyclopropanated using the Corey-Chaykovsky reagent[63, 64] to give compound **2.75** in 71% yield as a single diastereomer. Hydrolysis of **2.75** gave a methyl ketone that was then deprotonated using Hünig's base and trapped using TBS triflate to give the desired cyclopropane **2.76**.

The coupling partner to cyclopropane **2.76** was derived from (*R*)-(+)-pulegone **2.56** (Scheme 2.13). Modification of known literature procedures gave cyano enone **2.40**.[50, 65, 66] Cyano enone **2.40** and cyclopropane **2.76** were then coupled in the presence of triflimide to yield the desired compound **2.77** in 85% yield as a single diastereomer. Wittig olefination afforded alkene **2.78** in 75% based on recovered starting material. Treatment of alkene **2.78** with scandium(III) triflate gave the desired ring opened product **2.79** in 77% yield. Krapcho decarboxylation[67-69] of compound **2.79** gave intermediate **2.80** which was nearly identical to that used by Heathcock in his total synthesis of (±)-fawcettimine (Section 2.2, Scheme 2.6).

Intermediate **2.80** was then elaborated following Heathcock's procedure in 8 steps to the final product (+)-fawcettimine (**2.3**).

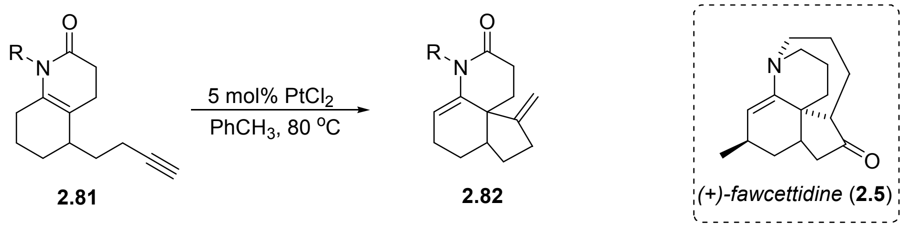

2.56
2.40
2.76
2.77
2.78
2.79
2.80
OTBS
CN
CO2Me
Tf2NH, CH2Cl2
-78 °C
85%
NC
TBSO
H
Ph3P=CH2
75% BRSM
Sc(OTf)3
CH2Cl2, rt
77%
wet DMF
μ-wave
73%
8 steps
HO
N
H3C
OH
fawcettimine (2.3)

Scheme 2.13: Completion of (+)-fawcettimine[59]

It should be noted that every synthesis of either (±)- or (+)-fawcettimine uses the same bond formation as the final step. All groups synthesize the azonane ring, and have it react with the carbonyl to form the final C13-N bond and to give fawcettimine in its natural carbinolamine form.

2.3 Model Studies: Progress Towards the Core of Fawcettidine

An ongoing project in the Dake laboratory is the platinum(II)-catalyzed cycloisomerization of enesulfonamides, enecarbamates, and enamides. This methodology has been successful in forming tricyclic nitrogen-containing compounds from less complex bicyclic enamides.[70] For example, enamides of structure **2.81** were treated with 5 mol% of platinum(II) chloride in toluene at 80 °C to give tricycles (**2.82**) containing a quaternary carbon center (Scheme 2.14). Application of this methodology could provide an effective route towards alkaloid ring systems structurally related to fawcettidine (**2.5**).



Scheme 2.14: Model studies for the application of the methodology towards the total synthesis of (+)-fawcettidine[70]

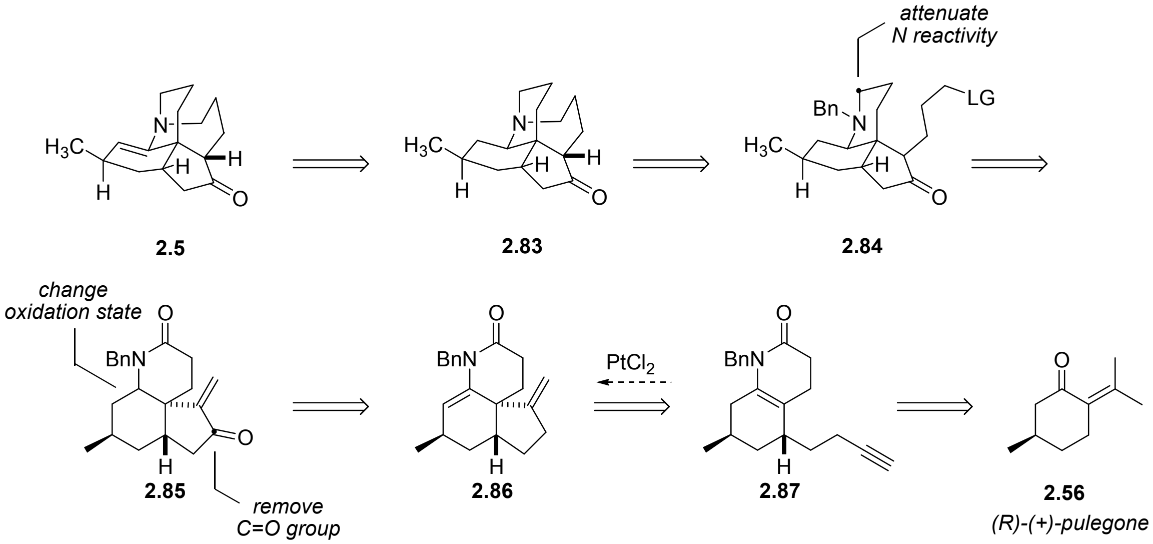
One goal of my PhD research was to extend the initial model studies to a completed total synthesis of (+)-fawcettidine (**2.5**). The remainder of the chapter will describe these efforts in detail. In the next section, two retrosynthetic analyses (Route A and Route B) of (+)-fawcettidine will be outlined. The subsequent section will describe the synthetic studies of Route A, followed by the synthetic studies of Route B. The experimental details of the project will be described in the final section of the chapter.

2.4 Retrosynthetic Analysis

A direct approach to (+)-fawcettidine was envisioned based on the model studies presented in Section 2.3.[70] The routes differ markedly from previous syntheses of (+)-fawcettimine (**2.3**), despite their structural similarity. Every reported synthesis of (+)-fawcettimine leaves the formation of the C13-N bond until the final step. The retrosynthetic routes described herein form this bond early, and leave the formation of the 7-membered ring to a later stage in the sequence.

Route A:

In Route A, the double bond of the enamine functional group would be installed in a final step to form (+)-fawcettidine (**2.5**) (Scheme 2.15). The disconnection of the 7-membered ring in compound **2.83** leaves a protected nitrogen atom and a carbon chain terminated with an appropriate leaving group (**2.84**). A potential solution for ring closure would be a direct S_N2 displacement of the leaving group by the nitrogen atom (*N*-alkylation). The reactivity of the amine in intermediate **2.84** would then be attenuated to give tricycle **2.85**. Functional group conversions and a change in oxidation state of the C13-C14 bond of intermediate **2.85** gave tricycle **2.86** that could undergo the key retro-annulation disconnection. Alkyne **2.87** could be converted directly to tricycle **2.86** using platinum(II)-catalysis. If successful, this transformation would form the necessary quaternary carbon center and provide an exocyclic alkene as a handle to add further functionalization that would facilitate the formation of the final 7-memebered ring of **2.5**. Chiral pool reagent (*R*)-(+)-pulegone **2.56** was identified as an appropriate starting material.

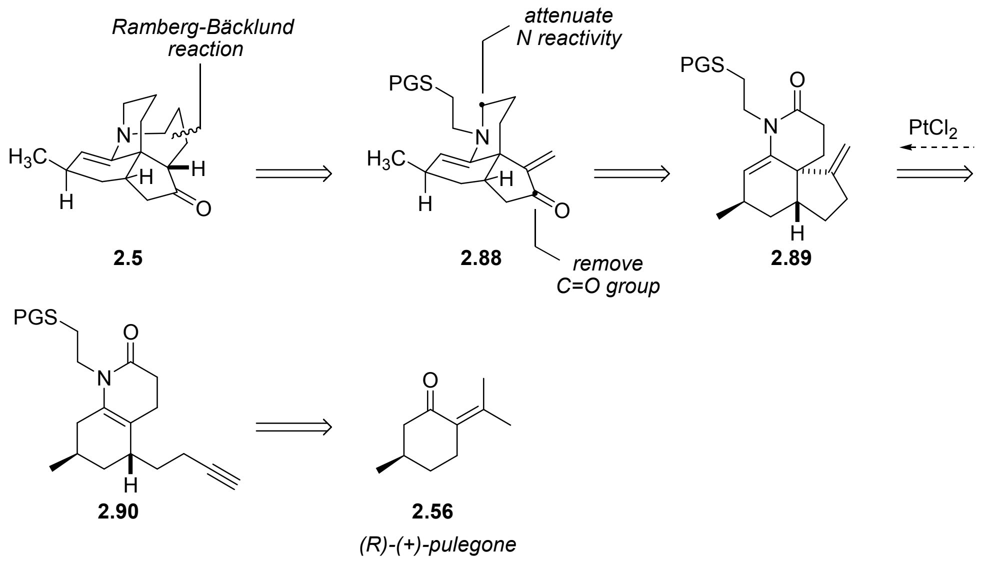


Scheme 2.15: Retrosynthetic analysis: Route A

Route B:

Retrosynthetic analysis of Route B uncovered the formation of the 7-membered ring at a late stage of the synthesis, as in Route A (Scheme 2.16). Disconnection of the 7-membered ring of **2.5** would give intermediate **2.88**. A Ramberg-Bäcklund reaction emerged as a potential solution for ring closure.[71-74] Functional group conversions of intermediate **2.88** would give tricycle **2.89** that could undergo the key retro-annulation disconnection. Alkyne **2.90** differs from alkyne **2.87** (Scheme 2.15) only in the protecting group on the nitrogen atom. Alkyne **2.90** could be converted directly to tricycle **2.89** using platinum(II)-catalysis. If successful, this transformation would install the C13-C14 double bond and establish the quaternary carbon center. The formation of the exocyclic alkene also provides a handle for further functionalization that would enable closure of the 7-membered ring. (*R*)-(+)-Pulegone (**2.56**) was again determined to be a suitable non-racemic starting material.

Of the two synthetic pathways envisaged, Route B is the more efficient. The platinum(II)-catalyzed annulation strategy installs three important features, one being the C13-C14 double bond. In Route A, the double bond is immediately removed to avoid functional group compatibility issues throughout the remainder of the synthesis. The extra steps involved in removing and replacing the key double bond are disadvantageous. In Route B, the C13-C14 double bond would remain throughout the synthesis, reducing the number of overall operations.

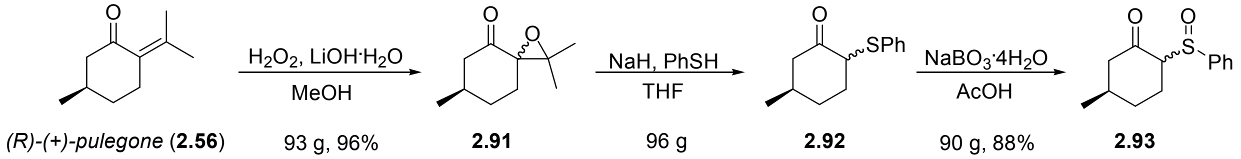


Scheme 2.16: Retrosynthetic analysis: Route B

At the outset of the project, the retrosynthetic analyses of both Routes A and B were established. It was unclear which route would be superior, therefore work began on both Route A and Route B simultaneously.

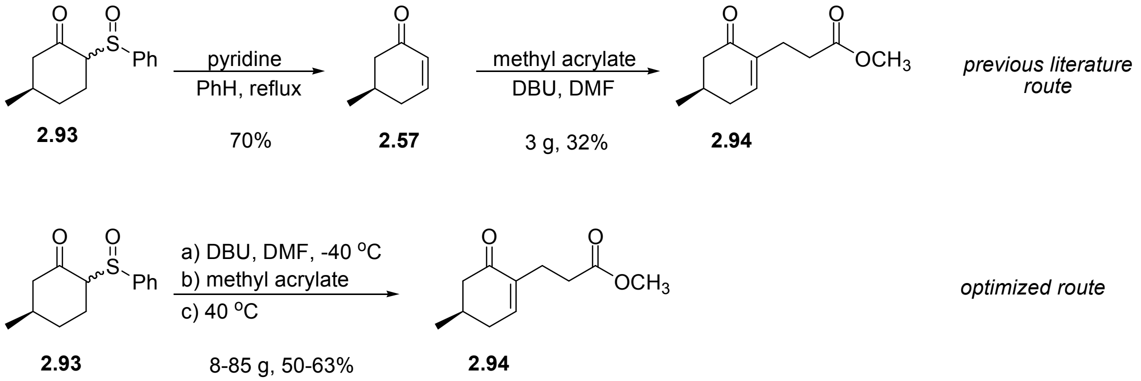
2.5 Synthesis of a Common Starting Material from (*R*)-(+)-Pulegone

Both Routes A and B began with elaboration of chiral pool starting material (*R*)-(+)-pulegone (**2.56**). (*R*)-(+)-Pulegone (**2.56**) was transformed to sulfoxide **2.93** by adaptation of established literature procedures (Scheme 2.17).[50, 65] Nucleophilic epoxidation afforded a 1:1 mixture of diastereomeric epoxides (**2.91**) in 96% yield on a 93 gram scale. A retro-aldol reaction of epoxide mixture **2.91** using sodium hydride and thiophenol gave a 1:1 diastereomeric mixture of sulfides (**2.92**). The crude mixture of sulfides (**2.92**) was moved onto the next reaction immediately as purification by column chromatography was inefficient and awkward. Treatment of sulfide mixture **2.92** with sodium perborate tetrahydrate in acetic acid gave sulfoxide **2.93** in 88% yield as an inconsequential mixture of diastereomers. Each step of this sequence was performed on an approximate 90 gram scale, resulting in the formation of a large amount of sulfoxide **2.93** necessary for elaboration to the natural product (**2.5**).


(R)-(+)-pulegone (2.56)
H_2O_2, $LiOH{\cdot}H_2O$
MeOH
93 g, 96%
2.91
NaH, PhSH
THF
96 g
SPh
2.92
$NaBO_3{\cdot}4H_2O$
AcOH
90 g, 88%
Ph
2.93

Scheme 2.17: Synthesis of sulfoxide **2.93**

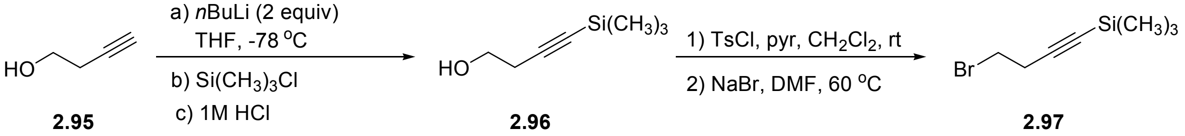
Next, sulfoxide **2.93** was treated with pyridine in toluene as a solvent under reflux conditions, resulting in thermal elimination of the sulfoxide and introduction of the enone functional group (**2.57**) (Scheme 2.18). Formation of the methyl ester **2.94** from enone **2.57** was attempted following a literature procedure.[75] Enone **2.57** was mixed with methyl acrylate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*,*N*-dimethylformamide in a thick-walled sealable tube. The sealed tube was heated in an oil bath at 180 °C for 24 hours. After work-up and purification, 32% of methyl ester **2.94** was isolated. This low yield was reproducible over several attempts as well as in the hands of fellow Dake group member Tyler Harrison. Changing the solvent from *N*,*N*-dimethylformamide to 1,3-dimethyl-2-imidazolidinone (as described in the literature procedure) also did not increase the reaction yield. Under these conditions, the reaction could be carried out on no more than a 3 gram scale due to practical considerations involving the volume allowed in the sealable tube. An alternate route was sought to increase the efficiency of formation of the methyl ester **2.94**.


Ph
2.93
pyridine
PhH, reflux
70%
2.57
methyl acrylate
DBU, DMF
3 g, 32%
OCH_3
2.94
previous literature route
Ph
2.93
a) DBU, DMF, -40 °C
b) methyl acrylate
c) 40 °C
8-85 g, 50-63%
OCH_3
2.94
optimized route

Scheme 2.18: Synthesis of ketoester **2.94**

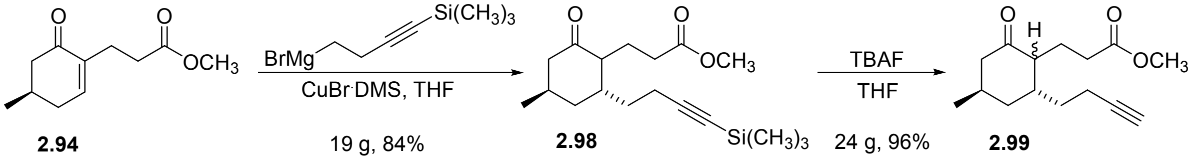
It was recognized that the acidity of the α-proton between the ketone and the sulfoxide in compound **2.93** could be exploited to add functionality at that position (Scheme 2.18). Sulfoxide

2.93 was treated with DBU at low temperature to deprotonate the α-proton, and then alkylated with methyl acrylate. Warming of the reaction mixture to 40 °C succeeded in the thermal elimination of the sulfoxide, affording methyl ester **2.94** in 50-63% yields depending on the scale of the process. Formation of the product was verified by the introduction of a 1-proton multiplet at a chemical shift of 6.72 ppm in the ^{1}H NMR spectrum, attributable to the vinyl proton of the enone moiety. A 3-proton singlet at a chemical shift of 3.63 ppm was also observed and is consistent with the introduction of a methyl ester. Important features of this optimized route are the following: a) it can be performed on a scale anywhere between 8 and 85 grams, b) it is a one-pot procedure, c) the yield is consistently higher than the 2-step procedure, and d) it is safer since it can be carried out in standard glassware rather than a high pressure sealable glass tube.



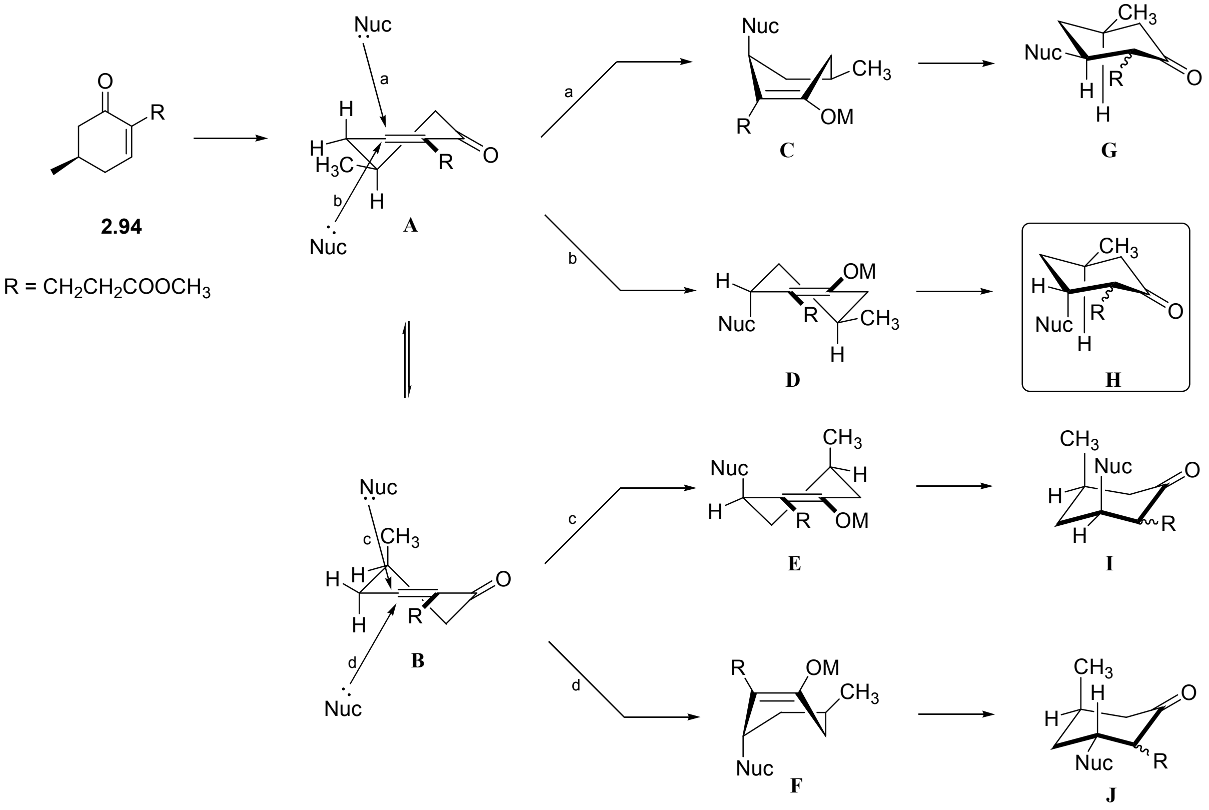
Scheme 2.19: Synthesis of the required bromide **2.97**

Methyl ester **2.94** was next elaborated to ketoester **2.99**, the final intermediate common to both Routes A and B. The alkyne portion of the substrate was introduced to methyl ester **2.94** via a cuprate addition of an appropriate Grignard reagent. The requisite bromide **2.97** was prepared following a literature procedure described by Holmes and coworkers (Scheme 2.19).[76] The dianion of 4-pentyn-1-ol (**2.95**) was generated by deprotonation with 2 equivalents of *n*-butyllithium and subsequently quenched with excess trimethylsilyl chloride to give a bis-silyl protected compound. Treatment with aqueous acid removed the silyl group from the alcohol, giving mono-silyl species **2.96**. Tosylation of alcohol **2.96** followed by displacement of the tosylate with a bromide ion gave bromide **2.97**. This series of reactions was carried out on a 20 gram scale.



Scheme 2.20: Synthesis of ketoester **2.99**

Bromide **2.97** was converted to a Grignard reagent and treated with copper(I) bromide dimethyl sulfide to form the cuprate reagent (Scheme 2.20). Addition of methyl ester **2.94** to a solution containing the cuprate reagent resulted in the formation of silylalkyne **2.98** in 84% yield as a 1:1 mixture of diastereomers at the carbon α to the carbonyl. The substituents at the 3- and 5-position of the cyclohexane ring were found to have a *trans* relationship. The rationale for the stereochemical outcome of the cuprate addition is described in Scheme 2.21.[77, 78] It is plausible that enone **2.94** can assume two different half chair conformations, **A** and **B**. The cuprate reagent must coordinate with the π-system of the enone functional group. For each conformation **A** and **B** then, attack can occur from two possible faces. This will lead to four possible intermediates (**C**, **D**, **E**, and **F**) and two products. Each of the two products can assume a different conformation (**G** and **I** = conformers; **H** and **J** = conformers). For each conformer, two of the possible transition states must assume boat conformations (**C** and **F**). Since the chair conformation is more stable than the boat conformation, paths a and d are ruled out. While both paths b and c lead to chair transition states, there is serious steric interference between the incoming nucleophile and the axial methyl substituent of **B** (pathway c). This leaves path b as the only operating pathway, resulting in a *trans*-relationship between the nucleophile and the methyl substituent (**H**).

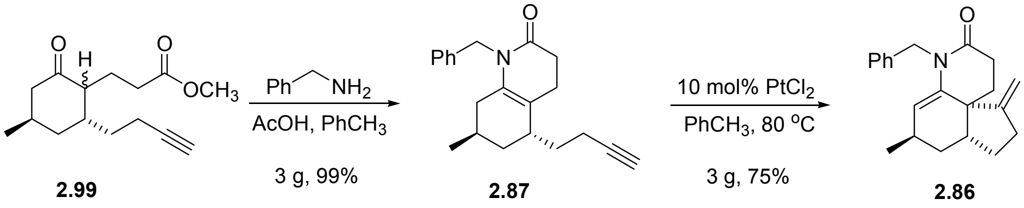


Scheme 2.21: Rationale for *trans* stereochemical outcome of compound **2.98**[77, 78]

Removal of the trimethylsilyl group of compound **2.98** by treatment with tetrabutylammonium fluoride gave alkyne **2.99** in 96% yield as a 1:1 mixture of diastereomers.

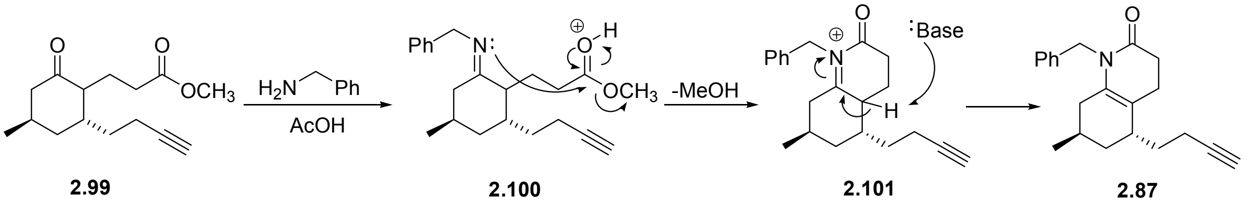
2.6 Synthetic Studies: Route A

With the synthesis of alkyne **2.99** completed, the route diverged to follow either Route A or Route B. This section will outline the efforts towards the total synthesis of (+)-fawcettidine (**2.5**) by Route A (Scheme 2.15). Following the procedure of Duval and Gomès, ketoester **2.99** was condensed with benzyl amine to afford enamide **2.87** in 99% yield (Scheme 2.22).[79] The mechanism of the condensation is outlined in Scheme 2.23. The amine reacts with the ketone in **2.99** to form an imine (**2.100**). Under acidic conditions, the carbonyl of the ester is protonated, making it susceptible to nucleophilic attack by the nitrogen atom of the imine. Methanol is eliminated and removed from the reaction, resulting in the formation of iminium ion intermediate **2.101**. Removal of a proton forms the enamide **2.87**. Enamide **2.87** was isolated as a 15:1 mixture of double bond isomers, with only the major isomer shown. The mixture of isomers was ultimately inconsequential to the following reaction.



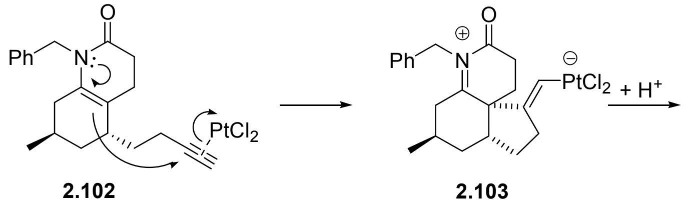
Scheme 2.22: Synthesis of **2.86** using a platinum(II)-catalyzed cycloisomerization

The key platinum(II)-catalyzed annulation reaction was tested on substrate **2.87**. Enamide **2.87** underwent smooth conversion to tricycle **2.86** by treatment with 10 mol% of platinum(II) chloride in toluene at 80 °C. Formation of the product (**2.86**) was verified by the appearance of a 1-proton doublet at a chemical shift of 5.02 ppm in the ^{1}H NMR spectrum which is attributed to the vinyl proton of the enamide. Diagnostic signals corresponding to the exocyclic olefin were also observed as two 1-proton singlets at chemical shifts of 4.92 ppm and 4.72 ppm.



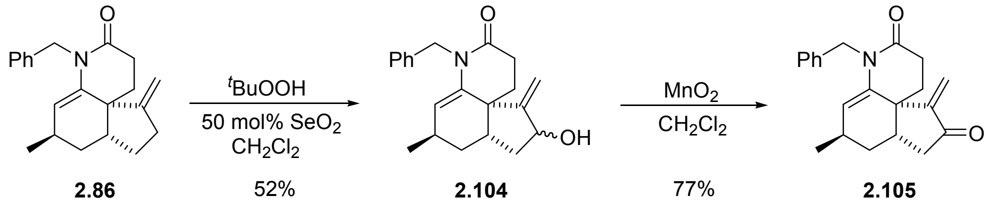
Scheme 2.23: Proposed mechanism for the condensation reaction leading to enamide **2.87**

The mechanism of the platinum(II)-catalyzed annulation reaction is shown in Scheme 2.24. The electrophilic metal first coordinates to form the activated platinum-alkyne π-complex (**2.102**). The nucleophilic enamide functional group then attacks the alkyne in a 5-*exo-dig* mode of cyclization to form tricycle **2.103**. Protodemetallation and reformation of the enamide give compound **2.86**. The platinum(II)-catalyzed annulation was successful in installing the quaternary stereocenter, the C13-C14 double bond (fawcettidine numbering), as well as the exocyclic alkene.



Scheme 2.24: Postulated mechanism of the key platinum(II)-catalyzed cycloisomerization step

The disubstituted alkene was utilized immediately in an attempt to oxidize the adjacent carbon atom (Scheme 2.25). If successful, the allylic oxidation would place the ketone at the correct position on the 5-membered ring for elaboration to (+)-fawcettidine (**2.5**). The double bond of the enamide functional group was left intact to observe any potential interference in the allylic oxidation reaction. Tricycle **2.86** was treated with an aqueous solution of *tert*-butyl hydroperoxide and 50 mol% of selenium dioxide to give alcohol **2.104** in 52% yield as a 1:1 mixture of diastereomers. The alcohol **2.104** was then further oxidized using manganese(IV) oxide to provide enone **2.105** in 77% yield.



Scheme 2.25: Allylic oxidation adjacent to the exocyclic olefin

Enone **2.105** was isolated as a white solid. Recrystallization of the solid from dichloromethane and hexanes gave X-ray quality crystals. The solid state molecular structure of **2.105** is shown in Figure 2.5. The X-ray structure confirms that the enone was formed in the desired position, that the C7 and C15 substituents are *trans* to one another, and that the quaternary carbon center was formed with the desired configuration. A C13-C14 bond length of 1.334(3) Å indicates that the double bond of the enamide remains.

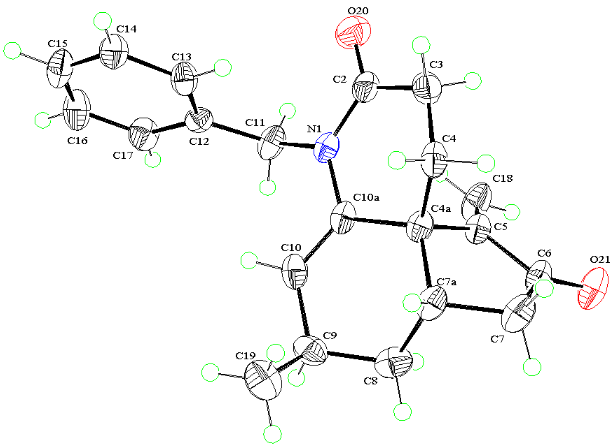
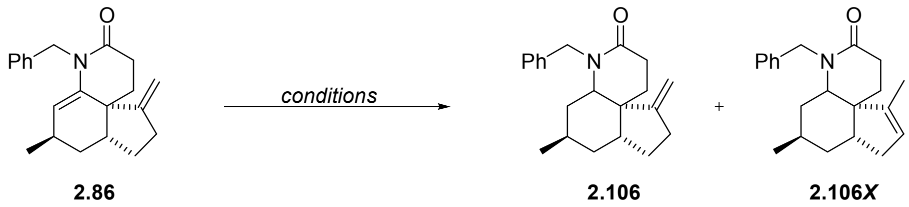


Figure 2.5: ORTEP representation of the solid state structure of enone **2.105**

The yield of the allylic oxidation was moderate at best. The low yield was potentially due to interference by the trisubstituted olefin, although there was no experimental evidence to support this claim. Nonetheless, it was decided that the double bond of the enamide would be removed to facilitate both the allylic oxidation and further operations following Route A.

The removal of the enamide double bond was not as straightforward as initially anticipated. A variety of reduction conditions were tested, the results of which are summarized in Table 2.1. Treatment of enamide **2.86** with triethylsilane and trifluoroacetic acid did not have any affect, and all of the starting material was recovered (entry 1). Sodium cyanoborohydride with acid (entry 2) or without acid but at reflux (entry 3) did not provide any product. Reaction of enamide **2.86** with 5 mol% of silver triflate and triethylsilane gave 15% (60% based on recovered starting material) isolated yield of the desired product **2.106** (entry 4). In an attempt to increase the yield, the amount of silver triflate was increased to 20 mol% and the reaction temperature was increased from 45 ^{o}C to 80 ^{o}C (entry 5). Increasing the catalyst load and the reaction temperature had no benefit and 92% of the starting material **2.86** was recovered. Next, a stronger reducing agent was tested (entries 6-9). Enamide **2.86** was treated with sodium borohydride and acetic acid in methanol as a solvent. Even after refluxing for 12 hours, no reaction was observed (entry 6). The same reaction conditions were tested again, but the methanol was removed and acetic acid was used as a solvent. After 12 hours at 85 ^{o}C, 14% (46% based on recovered starting material) of the desired product **2.106** was isolated (entry 7). When the reaction was repeated using trifluoroacetic acid – a much stronger acid – as a solvent, all of the starting material reacted to give one product in 84% yield (entry 8). The product formed unfortunately was solely tricycle **2.106*X***, where the exocyclic alkene had isomerized into the ring. Finally, enamide **2.86** was tested under the same conditions as entry 7, but at room temperature. The desired product **2.106** was isolated in 87% yield after a reaction time of 4 hours (entry 9). The configuration at C13 was not determined.

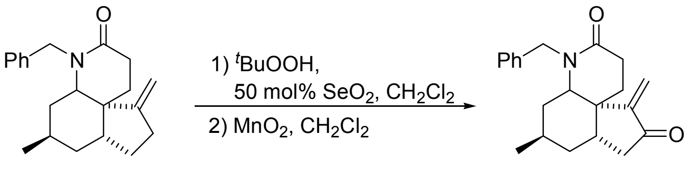
Table 2.1: Attempted reduction of enamide **2.86** to amide **2.106**



entry	conditions	result^{a,b,c}	ratio (2.106:2.106*X*)
1	Et_3SiH, TFA, CH_2Cl_2, 0 °C→rt, 12 h	NR (100% RSM)	-
2	$NaHBCN_3$, 2 M HCl-EtOH, MeOH, rt, 12 h	NR (88% RSM)	-
3	$NaHBCN_3$, MeOH, reflux, 20 h	NR (100% RSM)	-
4	5 mol% AgOTf, Et_3SiH, CH_2Cl_2, 45 °C, 12 h	15% (60% BRSM)	1:0
5	20 mol% AgOTf, Et_3SiH, $PhCH_3$, 80 °C, 20 h	trace (92% RSM)	-
6	$NaBH_4$, AcOH, MeOH, reflux, 12 h	NR (94% RSM)	-
7	$NaBH_4$, AcOH, 85 °C, 12 h	14% (46% BRSM)	1:0
8	$NaBH_4$, TFA, 85 °C, 3 h	84%	0:1
9	$NaBH_4$, TFA, rt, 4 h	87%	1:0

[a] Reported yields are isolated yields. [b] NR = no reaction; RSM = recovered starting material; BRSM = based on recovered starting material. [c] Reported yields are the maximum of single experiments.

With reduced compound **2.106** in hand, the allylic oxidation was repeated (Scheme 2.26). Amide **2.106** was first reacted with *tert*-butyl hydroperoxide and 50 mol% of selenium dioxide, followed by reaction with manganese(IV) oxide. Enone **2.85** was isolated in 54% after the two steps. The overall yield of the allylic oxidation increased, but not significantly. Other methods of allylic oxidation were therefore explored.

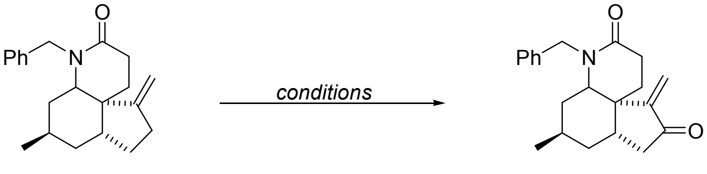


2.106 **2.85**

Scheme 2.26: First test allylic oxidation reaction of substrate **2.106**

First, variations using selenium dioxide were examined (Table 2.6.2). The conditions described in Scheme 2.26 were repeated, but 2 equivalents of water were added and the reaction mixture was stirred for 68 hours at reflux. Manganese(IV) oxide was again used to form the enone (entry 2). Longer reaction time and higher temperature did not increase the yield, and the product was isolated in 37% yield (41% based on recovered starting material). Changing the solvent from dichloromethane to 1,2-dichloroethane produced enone **2.85** in 47% yield (entry 3). Following a literature procedure, amide **2.106** was reacted with one equivalent of selenium dioxide in 1,4-dioxane at 85 °C (entry 4).[80] After complete oxidation using manganese(IV) oxide, 70% of enone **2.85** was isolated.

Table 2.2: Optimization of the allylic oxidation of compound **2.106**

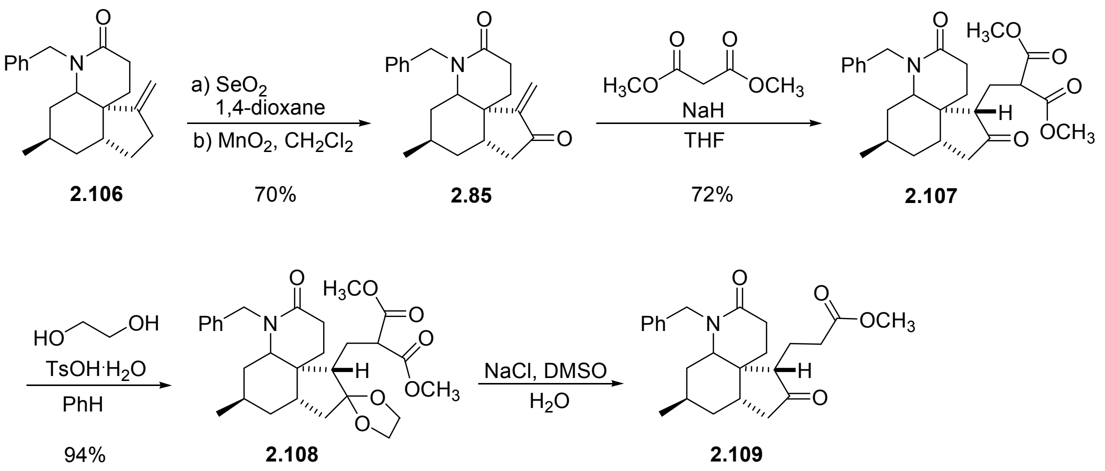


2.106 **2.85**

entry	conditions	yield 2.85 (%)[a,b,c]
1	1) 50 mol% SeO_2, *t*BuOOH, CH_2Cl_2, reflux, 12 h 2) MnO_2, CH_2Cl_2, rt, 12 h	54% (2 steps)
2	1) 50 mol% SeO_2, *t*BuOOH, H_2O, CH_2Cl_2, reflux, 68 h 2) MnO_2, CH_2Cl_2, rt, 24 h	37% (41% BRSM)
3	1) 50 mol% SeO_2, *t*BuOOH, H_2O, $ClCH_2CH_2Cl$, reflux, 1 h	47%
4	1) SeO_2, 1,4-dioxane, 85 °C, 1.5 h 2) MnO_2, CH_2Cl_2, rt, 24 h	70%
5	CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, reflux, 5.5 h	trace
6	CrO_3, pyridine, CH_2Cl_2, rt, 2 days	trace (71% RSM)
7	1 mol% $Rh_2(cap)_4$, *t*BuOOH, K_2CO_3, CH_2Cl_2, rt, 4 h	37% (41% BRSM)

[a]Reported yields are isolated yields. [b]RSM = recovered starting material; BRSM = based on recovered starting material. [c]Reported yields are the maximum of single experiments.

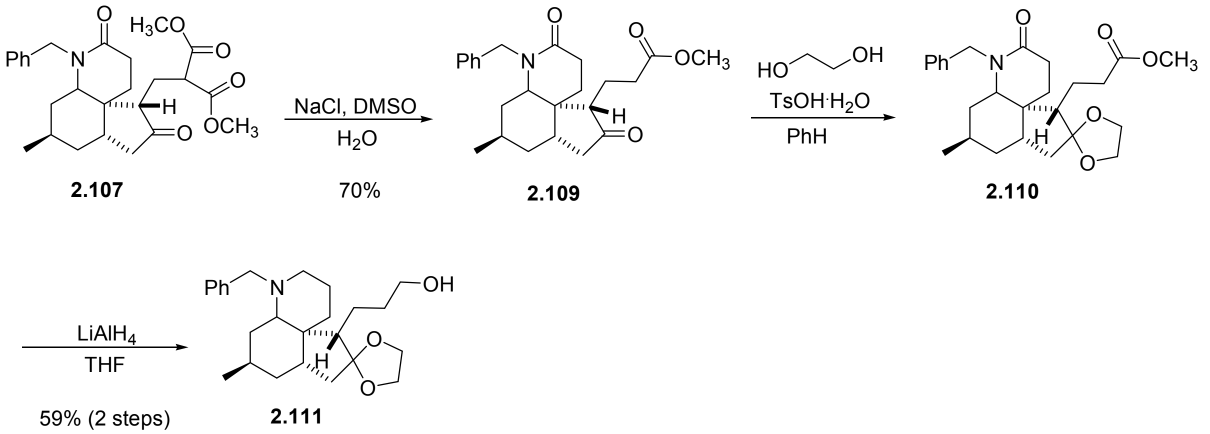
Chromium based allylic oxidations were also tested. Amide **2.106** was reacted with Corey's chromium trichloride-3,5-dimethylpyrazole reagent to give only a trace amount of product (entry 5).[81] The chromium trichloride-pyridine complex of Sarett also gave little product (entry 6).[82, 83] Treatment of amide **2.106** with 1 mol% of dirhodium(II) caprolactamate in the presence of *tert*-butyl hydroperoxide and base gave 37% (41% based on recovered starting material) of product **2.85** (entry 7).[84] The chromium and rhodium based oxidation systems have been exceptionally effective for allylic oxidation reactions in the literature. In this case it is possible that significant steric interference exists between compound **2.106** and the metal oxidants, impeding efficient allylic oxidation. Despite the overall disappointing results, the conditions described in entry 4 improved the yield of the allylic oxidation by close to 20% compared to the original oxidation conditions tested.



Scheme 2.27: Synthesis of diester **2.108** and an attempted Krapcho reaction

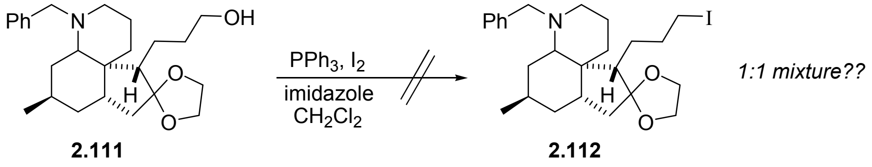
As mentioned, the purpose of the exocyclic alkene is to facilitate formation of the final 7-membered ring within (+)-fawcettidine (**2.5**). Functionalization was anticipated to be easily installed by taking advantage of the conjugate addition acceptor properties of enone functional group in **2.85** (Scheme 2.27). Enone **2.85** was reacted with dimethyl malonate and sodium hydride to form diester **2.107** in 72% as one diastereomer. To avoid future functional group compatibility issues involving the ketone, it was protected as a ketal (**2.108**). Subsequent Krapcho decarboxylation of ketal **2.108** resulted in its deprotection (**2.109**), rendering the previous protection strategy unnecessary.[67-69]

Alternatively, the Krapcho decarboxylation was performed first, affording methyl ester **2.109** in 70% yield from diester **2.107** (Scheme 2.28). The ketone was then protected as the ketal (**2.110**) followed by global reduction using lithium aluminum hydride to produce alcohol **2.111** in 59% yield over two steps.


Ph
N
O
H3CO
O
O
H
O
OCH3
2.107
NaCl, DMSO
H2O
70%
Ph
N
O
O
OCH3
H
O
2.109
HO
OH
TsOH·H2O
PhH
Ph
N
O
O
OCH3
O
H
O
2.110
LiAlH4
THF
59% (2 steps)
Ph
N
OH
O
H
O
2.111

Scheme 2.28: Synthesis of amine **2.111**

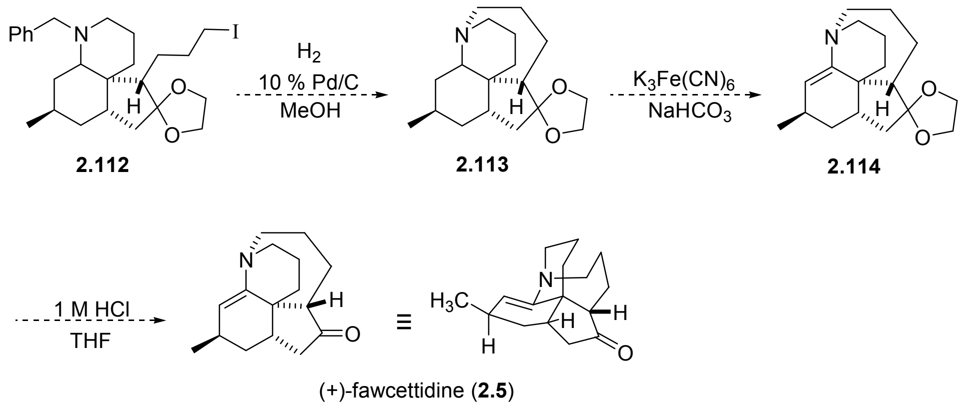
At this stage the attempted closure of the 7-membered ring took place. Ring closure was envisaged to occur by S_N2 displacement of an appropriate leaving group by the nitrogen atom. An iodine atom was recognized as an appropriate leaving group (**2.112**). Following the procedure for an Appel reaction, alcohol **2.111** was treated with triphenylphosphine and iodine (Scheme 2.29).[41, 42] The resulting product appeared to be a 1:1 mixture of compounds by ^{1}H NMR spectroscopy, but its identity could not be confirmed.


Ph
N
OH
O
H
O
2.111
PPh3, I2
imidazole
CH2Cl2
Ph
N
I
O
H
O
2.112
1:1 mixture??

Scheme 2.29: Attempted Appel reaction of alcohol **2.111**

The Appel reaction was the final experiment performed for Route A. Routes A and B were carried out simultaneously, and focus shifted to Route B as the better candidate for successful completion of (+)-fawcettidine (**2.5**). Route A was ultimately successful in achieving a late stage intermediate (**2.111**). Four steps would complete the synthesis of (+)-fawcettidine (**2.5**) following Route A, discounting any unforeseeable issues (Scheme 2.30). Conversion of the primary alcohol (**2.111**) to an iodine atom (or other appropriate leaving group) would give iodide

2.112. Removal of the benzyl protecting group would close the 7-membered ring by nucleophilic displacement of the iodine atom (**2.113**). Reintroduction of the enamine was expected to occur using the oxidant potassium ferricyanide,[85] affording compound **2.114**. Conversion of the ketal to the ketone under standard acidic conditions would yield (+)-fawcettidine (**2.5**).

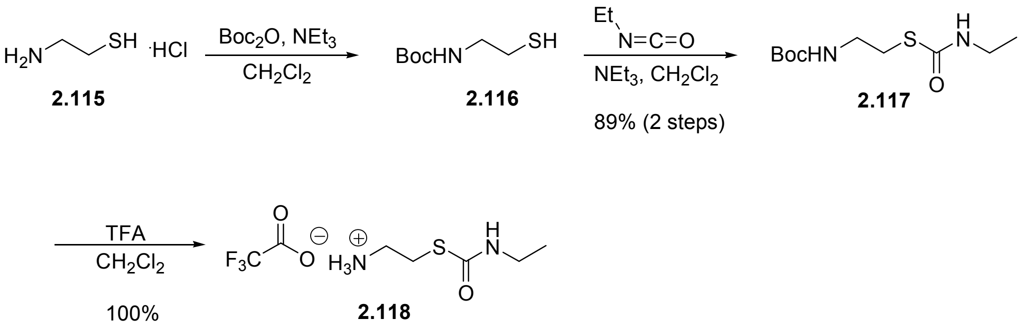


Scheme 2.30: Planned steps for the completion of (+)-fawcettidine via Route A

2.7 Synthetic Studies: Route B

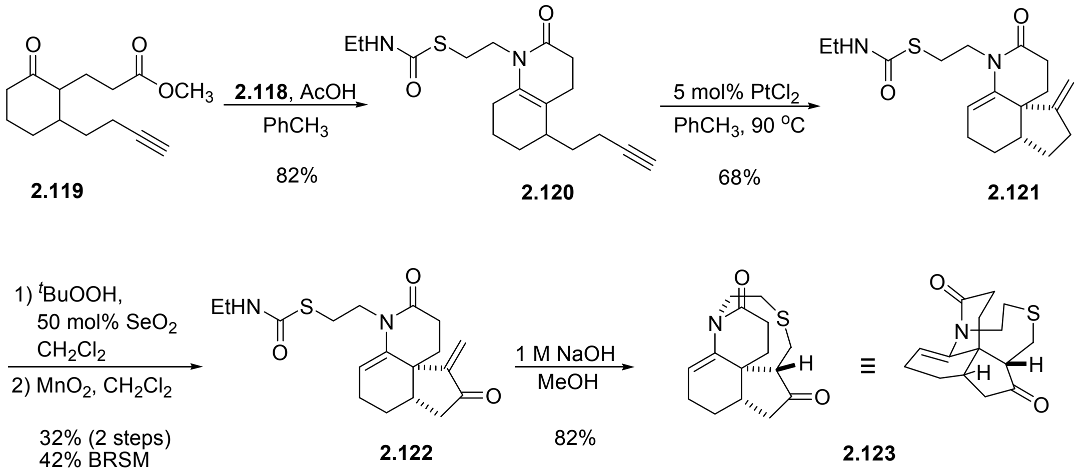
At the outset of Route B, a major question was the identity of a thiol protecting group that would be compatible with the platinum(II)-catalyzed annulation. A thiocarbamate protecting group was selected for the following reasons: a) it could be synthesized from a readily available mercaptoamine (**2.115**) and incorporated into the molecule during the condensation procedure, b) the electron-withdrawing nature of the thiocarbamate could reduce interference of the sulfur atom with the platinum(II) catalyst, and c) it could be easily hydrolyzed in base to free a thiolate anion.

The protecting group was synthesized following literature procedures (Scheme 2.31).[86] Mercaptoethylamine hydrochloride was selectively protected with di-*tert*-butyl-dicarbonate to give thiol **2.116**, followed by treatment with ethyl isocyanate to form thiocarbamate **2.117** in 89% over two steps. The *tert*-butyl carbamate protecting group was removed using trifluoroacetic acid to afford amine salt **2.118**. The amine salt was utilized directly in the condensation reaction.


2.115
Boc2O, NEt3
CH2Cl2
2.116
Et
N=C=O
NEt3, CH2Cl2
89% (2 steps)
2.117
TFA
CH2Cl2
100%
2.118

Scheme 2.31: Synthesis of amine salt **2.118**

The application of the thiocarbamate protecting group to the total synthesis of (+)-fawcettidine (**2.5**) was first investigated using model studies in an effort to conserve chiral starting material. Racemic ketoester **2.119** was contributed by fellow Dake group member Tyler Harrison for this purpose. Ketoester **2.119** condensed with amine salt **2.118** to form enamide **2.120** in 82% yield (Scheme 2.32). Next, the compatibility of the thiocarbamate protecting group under platinum(II)-catalysis was investigated. I was delighted to find that enamide **2.120** underwent smooth cyclization to form tricycle **2.121** in 68% yield. Allylic oxidation of tricycle **2.121** using a two-step procedure gave enone **2.122** in 32% yield (42% based on recovered starting material). Optimization of the allylic oxidation was not performed on the model compound **2.121** due to a minimal amount of material available, although enough remained to test the thiocarbamate deprotection procedure. Enone **2.122** was treated with 1M sodium hydroxide. The base successfully released the thiolate anion which added directly into the enone accepter, establishing the desired configuration at C4 and closing the final ring of the model compound (**2.123**).


2.119
2.118, AcOH
PhCH3
82%
2.120
5 mol% PtCl2
PhCH3, 90 °C
68%
2.121
1) tBuOOH, 50 mol% SeO2 CH2Cl2
2) MnO2, CH2Cl2
32% (2 steps)
42% BRSM
2.122
1 M NaOH
MeOH
82%
2.123

Scheme 2.32: Model study of base induced cyclization to form sulfide **2.123**

The solid state molecular structure of sulfide **2.123** is shown in Figure 2.6. The structure confirms the identity of the compound and the relative stereochemistry between the quaternary carbon center, C4, and C7. The model study was concluded with successful isolation of sulfide **2.123** since all the material had been consumed. The results using the thiocarbamate functional group were exciting overall, and it was decided that the synthesis following Route B should be tested using the chiral starting material (**2.99**).

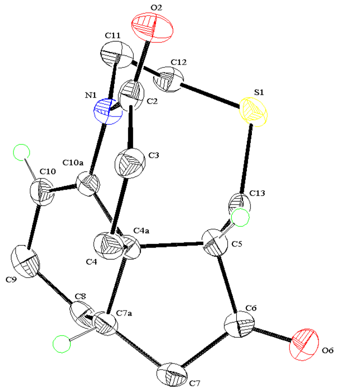
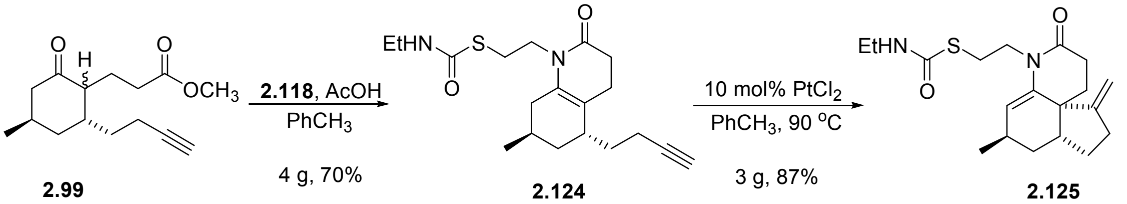


Figure 2.6: ORTEP representation of the solid state molecular structure of model compound **2.123**

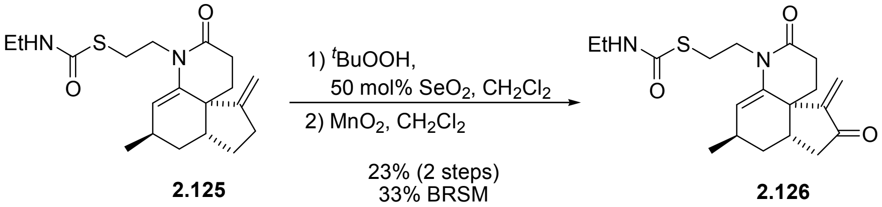
Identical procedures used in the model study were performed commencing with ketoester **2.99**. Chiral ketoester **2.99** was condensed with amine salt **2.118** to form enamide **2.124** in 70% yield on a 4 gram scale (Scheme 2.33). The subsequent platinum(II)-catalyzed cycloisomerization of enamide **2.124** afforded tricycle **2.125** in excellent yield. Product formation was verified by the appearance of two 1-proton singlets at chemical shifts of 4.87 ppm and 4.63 ppm in the ^{1}H NMR spectrum, attributable to the protons of the exocyclic alkene.



Scheme 2.33: Synthesis of **2.125** using a platinum(II)-catalyzed cycloisomerization

Allylic oxidation of chiral enamide **2.125** using the two-step procedure (50 mol% of selenium dioxide and *tert*-butyl hydroperoxide, followed by manganese(IV) oxide) gave enone

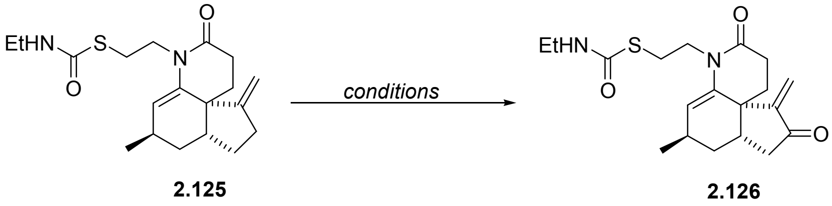
2.126 in 23% yield (33% yield based on recovered starting material) (Scheme 2.34). Optimization of the oxidation was deemed necessary for completion of the synthesis.



Scheme 2.34: First allylic oxidation of substrate **2.125**

The results of the optimization studies on the oxidation of enamide **2.125** are summarized in Table 2.7.1. The original conditions are displayed in entry 1. The addition of 2 equivalents of water to the reaction mixture seemed to increase the yield of product (**2.126**) slightly (entry 2). The same reagent combination in 1,2-dichloroethane as a solvent did not increase the yield of product isolated (entry 3). Treatment of enamide **2.125** with 1 equivalent of selenium dioxide in 1,4-dioxane at 85 °C gave enone **2.126** in 54% after 1.5 hours (entry 4).[80] Oxidation using 1 mol% of dirhodium caprolactamate, *tert*-butyl hydroperoxide, and base gave a complex mixture of unidentifiable products (entry 5).

Table 2.3: Optimization of the allylic oxidation of compound **2.125**

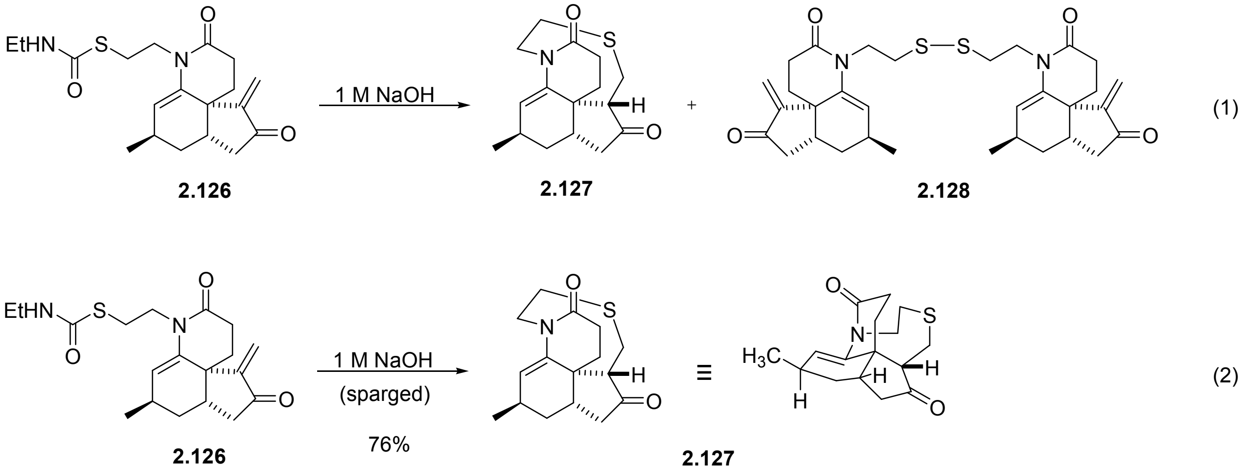


entry	conditions	yield 2.126 (%)[a,b,c]
1	1) 50 mol% SeO_2, *t*BuOOH, CH_2Cl_2, reflux, 2 days 2) MnO_2, CH_2Cl_2, rt, 18 h	23% (2steps; 33% BRSM)
2	1) 50 mol% SeO_2, *t*BuOOH, H_2O, CH_2Cl_2, reflux, 36 h 2) MnO_2, CH_2Cl_2, rt, 32 h	35% (42% BRSM)
3	1) 50 mol% SeO_2, *t*BuOOH, H_2O, $ClCH_2CH_2Cl$, reflux, 1 h	19%
4	1) SeO_2, 1,4-dioxane, 85 °C, 1.5 h	54%
5	1 mol% $Rh_2(cap)_4$, *t*BuOOH, K_2CO_3, CH_2Cl_2, rt, 4 h	complex mixture

[a]Reported yields are isolated yields. [b]BRSM = based on recovered starting material. [c]Reported yields are the maximum of single experiments.

The choice of allylic oxidation conditions tested was largely based on the results of the oxidation of compound **2.106**, summarized in Table 2.6.2, Section 2.6. Comparing the results for each, the optimal conditions for the allyic oxidation in both cases is 1 equivalent of selenium dioxide in 1,4-dioxane at 85 °C. With the optimized conditions for the formation of enone **2.126** in hand, synthesis towards (+)-fawcettidine continued.

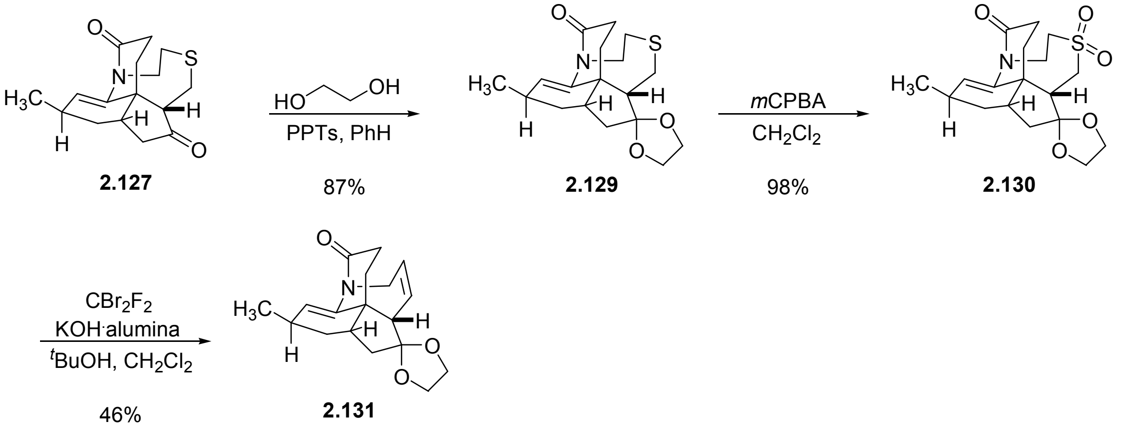
The thiocarbamate protecting group was next removed using 1M sodium hydroxide (Scheme 2.35). An interesting problem arose at this time: it was discovered that treatment of chiral enone **2.126** with aqueous base led to a small amount of product (**2.127**), and a large amount of a dimer (**2.128**) (Scheme 2.35, eq 1). The dimer was formed via disulfide linkage between the molecules. The dimerization was likely not observed during the model studies due to the deprotection being performed on such small scale: 0.018 grams (model study) versus 0.1 grams or more (this study). Disulfide formation is an oxidation reaction that can be caused by atmospheric oxygen, so removal of oxygen from the reaction mixture should eliminate this problem. To that end, the aqueous solution of 1M sodium hydroxide was sparged with argon prior to use to remove all oxygen, and the reaction was carried out under an atmosphere of nitrogen. Treatment of enone **2.126** with oxygen-free 1M sodium hydroxide formed tetracycle **2.127** in 76% yield, as evidenced by the disappearance of two 1-proton singlets at chemical shifts of 6.11 ppm and 5.20 ppm in the ^{1}H NMR spectrum which corresponded to the protons on the exocyclic alkene (Scheme 2.35, eq 2).



Scheme 2.35: Undesired dimer formation and a solution to the problem

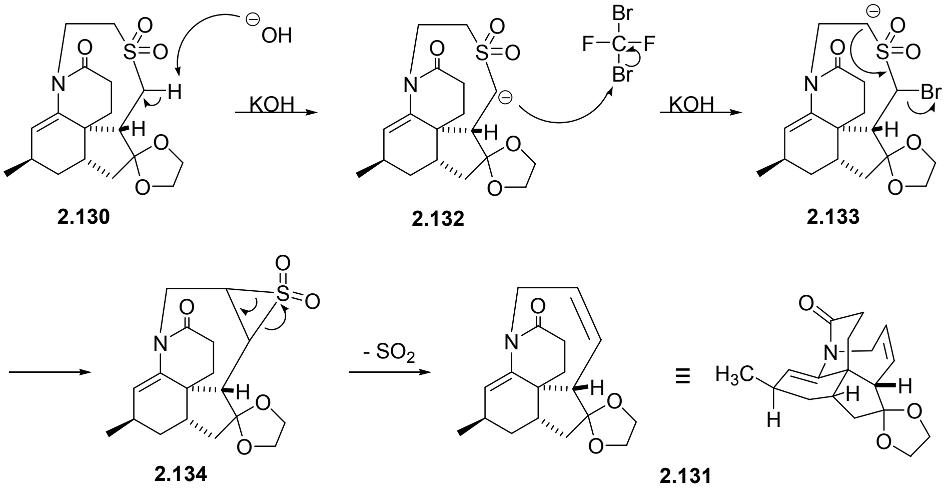
Although compound **2.127** is tetracyclic, the last ring must be contracted with the simultaneous expulsion of a sulfur atom, to form the all-carbon 7-membered ring present in (+)-fawcettidine (**2.5**). The focus therefore shifted towards the proposed Ramberg-Bäcklund reaction.[71-74] The requisite sulfone (**2.130**) was prepared in two steps (Scheme 2.36). First, the ketone (**2.127**) was protected as the ketal (**2.129**) by treatment with ethylene glycol and pyridinium *para*-toluenesulfonate. Oxidation of the sulfide (**2.129**) with *meta*-chloroperbenzoic acid afforded sulfone **2.130** in excellent yield.

Sulfone **2.130** was next tested for reactivity using conditions reported by Ramberg and Bäcklund. All attempts to carry out the Ramberg-Bäcklund reaction by the Meyers' procedure failed. However, the one-step procedure reported by Chan turned out to be successful (Scheme 2.36).[87] Treatment of sulfone **2.130** with dibromodifluoromethane in a *tert*-butyl alcohol/dichloromethane solvent mixture and in the presence of potassium hydroxide adsorbed onto alumina enabled the isolation of alkene **2.131** in 46% yield.



Scheme 2.36: Synthesis of compound **2.131** using a Ramberg-Bäcklund reaction

The mechanism of the Ramberg-Bäcklund reaction is outlined in Scheme 2.37. The acidic proton adjacent to the sulfone functional group in **2.130** is first deprotonated by the hydroxide base, followed by quenching with an electrophilic bromine atom from dibromodifluoromethane to give bromide **2.133**. Protons to the other side of the sulfone are also acidic, and one is deprotonated with excess base. The anion can then attack the carbon three atoms away and extrude the bromide ion, forming episulfone **2.134**. Cheletropic extrusion of sulfur dioxide gives alkene **2.131**. There are two points about the mechanism as illustrated in Scheme 2.37: a) both sets of protons adjacent to the sulfone in **2.130** are acidic, so the depicted site of deprotonation was chosen arbitrarily, and b) the formation of the episulfone and extrusion of sulfur dioxide is drawn as a stepwise procedure, but is likely a concerted mechanism. A mechanism involving a diradical anion species has also been suggested.[72, 74, 88]



Scheme 2.37: Mechanism of the Ramberg-Bäcklund reaction

Interestingly, crystals of alkene **2.131** were amenable to X-ray diffraction and a solid state structure was obtained (Figure 2.7). The bond lengths of 1.325(3) Å and 1.328(4) Å between C13-C14 and C2-C3 (fawcettidine numbering), respectively, indicate C-C double bond character. The correct configuration at C4 is also confirmed by the solid state molecular structure.

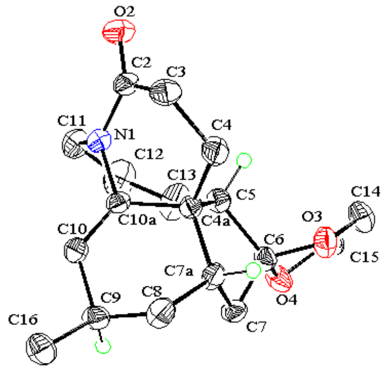
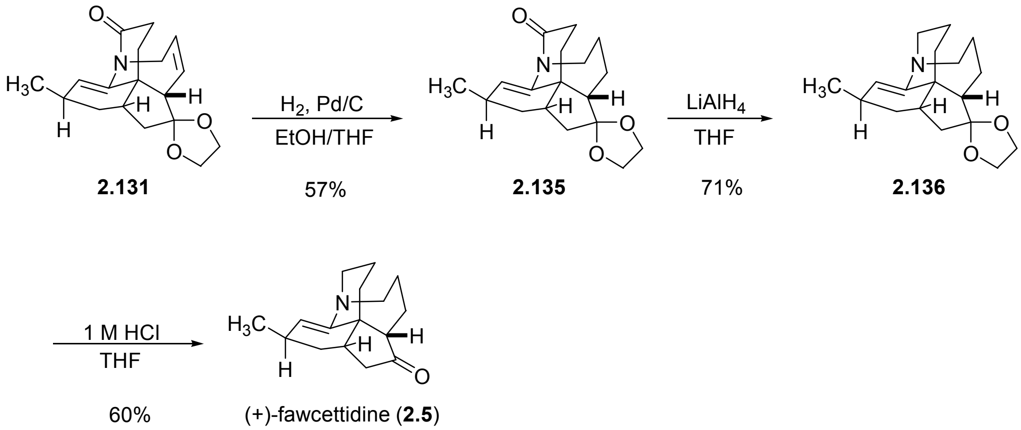


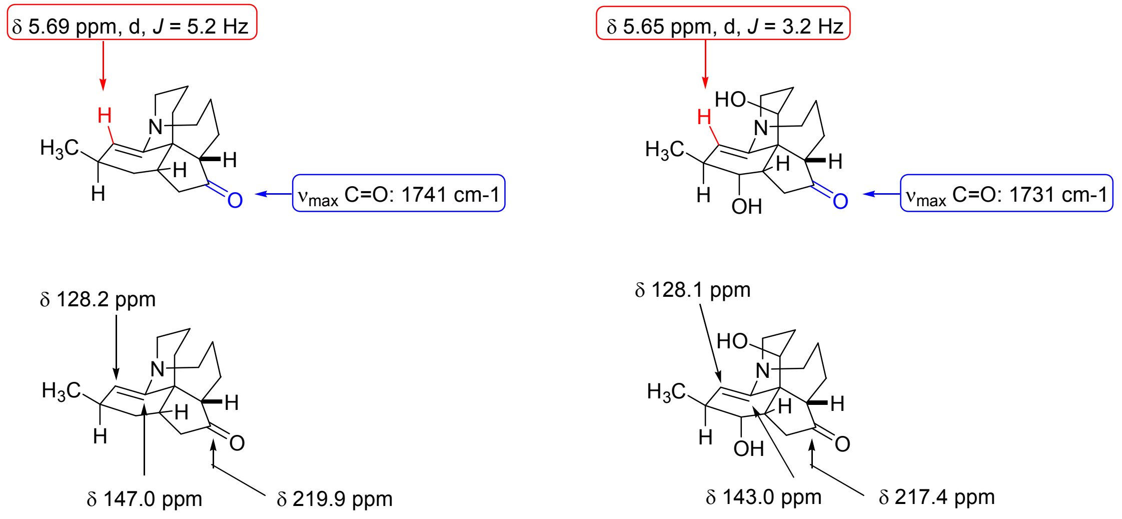
Figure 2.7: ORTEP representation of the solid state molecular structure of olefin **2.131**

The success of the Ramberg-Bäcklund reaction provided compound **2.131**, a molecule containing all the skeletal carbon atoms with the correct configuration of (+)-fawcettidine (**2.5**). Only a series of functional group manipulations was required to complete the synthesis. First, the C2-C3 double bond had to be removed (Scheme 2.38). This was accomplished by heterogeneous hydrogenation using a palladium on carbon catalyst in an ethanol/THF solvent mixture, giving compound **2.135** in 57% yield. Enamide **2.135** was reduced to enamine **2.136** using lithium aluminum hydride, and the ketal was removed using a solution of aqueous 1M hydrochloric acid in THF to afford (+)-fawcettidine (**2.5**).



Scheme 2.38: Completion of the total synthesis of (+)-fawcettidine

As the structure elucidation of (+)-fawcettidine was defined by its synthesis from other members of the *Lycopodium* alkaloid family, high-field NMR spectroscopic data are not available for comparison. It was therefore compared to recently isolated, hydroxylated derivatives of (+)-fawcettidine (Figure 2.8).[89] Key spectroscopic data include the ^{1}H NMR signal attributed to the enamine (5.69 ppm in **2.5**) which is consistent with that in 8α,11α-dihydrofawcettidine (5.65 ppm). The IR stretching frequency of the cyclopentane carbonyl is also consistent (1741 cm^{-1} versus 1740 cm^{-1}). The signals in the ^{13}C NMR spectra attributed to C13, C14, and C5 correspond well with the (+)-fawcettidine relative (**2.137**).


δ 5.69 ppm, d, J = 5.2 Hz
H
N
H3C
H
H
H
O
νmax C=O: 1741 cm-1
δ 5.65 ppm, d, J = 3.2 Hz
HO
H
N
H3C
H
H
H
OH
O
νmax C=O: 1731 cm-1
δ 128.2 ppm
N
H3C
H
H
H
O
δ 147.0 ppm
δ 219.9 ppm
δ 128.1 ppm
HO
N
H3C
H
H
H
OH
O
δ 143.0 ppm
δ 217.4 ppm

(+)-fawcettidine (**2.5**)

8α, 11α-dihydroxyfawcettidine (**2.137**)

Figure 2.8: Comparison of NMR and IR data of (+)-fawcettidine (**2.5**) and structurally related 8α,11α-dihydrofawcettidine (**2.137**)

Unfortunately, the optical rotation data obtained (in ethanol) for synthetic **2.5** is at odds with that reported in the original isolation literature.[30] The measured optical rotation of synthetic **2.5** was found to be +61° (c = 0.25, EtOH), whereas the measured literature value was +161° (c = 0.6, EtOH). However, the optical rotation of synthetic **2.5** in chloroform (+92° (c = 0.41, $CHCl_3$)) compares well with that reported for synthetic (+)-fawcettimine (**2.3**) (+89° (c = 0.55, MeOH)).[41]

2.8 Conclusion

The first reported total synthesis of (+)-fawcettidine (**2.5**) was carried out in 16 steps from chiral pool starting material (*R*)-(+)-pulegone (**2.56**). An important key feature of the successful synthesis (Route B) was a platinum(II)-catalyzed annulation of a highly functionalized enamide (**2.124**). In one step, the annulation reaction placed the double bond of the enamine in the correct position, set the quaternary carbon stereocenter, and provided an exocyclic alkene to facilitate further functionalization. Another important design feature was the selection of the thiocarbamate protecting group and its placement relative to an enone functional group. Deprotection of the thiocarbamate closed the final ring to form tetracycle **2.127** and ultimately set up the third key step, the Ramberg-Bäcklund reaction. Chan's one-pot Ramberg-Bäcklund conditions successfully contracted the 8-membered ring to the requisite 7-membered ring, extruding sulfur dioxide.

The study of (+)-fawcettidine (**2.5**) presented in this chapter was also successful in achieving a late stage intermediate (**2.111**) via Route A. The key step of the synthesis was also the platinum(II)-catalyzed annulation of enamide **2.87**. If the synthesis following Route A is completed in the future, another feature would be the oxidative reintroduction of the enamine at the culmination of the synthesis.

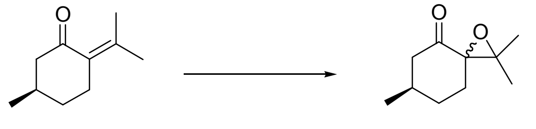
2.9 Experimental

2.9.1 General Experimental

All reactions sensitive to air or moisture were carried out in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Dichloromethane and triethylamine were distilled from calcium hydride and degassed by sparging with argon prior to use. Toluene was distilled from sodium and degassed by sparging with argon prior to use. All commercial reagents or materials were used without purification unless otherwise noted. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Triethylamine washed silica gel was stirred with triethylamine before packing and then sequentially flushing the silica gel with ethyl acetate followed by hexanes. To dry load crude compounds onto silica gel prior to column chromatography, the compound was dissolved in an appropriate solvent and dry silica gel was added. The solvent was then removed *in vacuo* until the silica gel was freely flowing. Buffered (pH 8) saturated aqueous ammonium chloride was prepared by adding 50 mL of ammonium hydroxide to 950 mL of saturated aqueous ammonium chloride solution. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform unless otherwise noted. Chemical shifts are recorded in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.27 ppm ^{1}H NMR; δ 77.0 ppm ^{13}C NMR). Data was recorded as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = tripet, q = quartet, qt = quintet, m = multiplet, br =

broad). Coupling constants (*J* values) are given in Hertz (Hz). The complexity of the ^{1}H NMR spectrum for mixtures of isomers does not allow for unequivocal assignment of each isomer. For mixtures of isomers, all of the signals in the ^{1}H NMR associated with the major isomer are assigned. The isolated signals associated with the minor isomer are assigned. In the ^{13}C NMR, all of the peaks for the mixture of two isomers are listed if they cannot be distinguished based on intensity of the signal. For mixtures >8:1, only the signals for the major isomer are listed. Low resolution ESI mass spectra were recorded on a Bruker Esquire-LC ion trap mass spectrometer equipped with an electrospray ion source. High resolution EI mass spectra were recorded on a Kratos MS-50 double focusing mass spectrometer. High resolution ESI mass spectra were recorded on a Waters/Micromass LCT time of flight (TOF) mass spectrometer equipped with an electrospray ion source. Microanalyses were recorded on a Fisons Instruments Carlo Erbal EA 1108 elemental analyzer. All mass analyses and microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia.

2.9.2 Synthesis of a Common Ketoester Starting Material

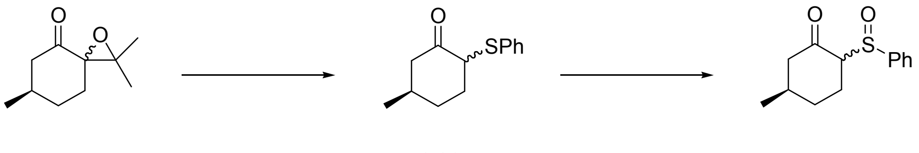


2.56 **2.91**

Epoxide (2.91)

A 2 L 3-neck round-bottomed flask was charged with 99.0 mL of *R*-(+)-pulegone (**2.56**) (609 mmol) and 400 mL of methanol. To the clear solution was added 104 mL of hydrogen peroxide (30 wt. % in H_2O, 913 mmol) in 20 mL portions. The reaction mixture was cooled to 18 ^{o}C using a cold water bath. A solution of 3.83 g of lithium hydroxide monohydrate (91.3 mmol) in 50 mL of water was added dropwise to the reaction mixture. The reaction mixture was stirred for 5.5 h while the temperature was maintained at 20-25 ^{o}C. The resulting white cloudy suspension was poured into 900 mL of a solution of brine and then extracted four times with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a clear liquid. The crude liquid was purified by distillation under reduced pressure to afford 98.4 g (96 %) of a 2:1 mixture of diastereomers of the title compound **2.91** as a clear liquid, bp = 80-85 ^{o}C, 0.5 mmHg (*lit.* 94-97 ^{o}C, 5 mm Hg).

IR (neat): 2958, 2873, 1721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39-2.29 (m, 3H), 2.00-1.87 (m, 4H), 1.36 (s, 3H), 1.15 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). Additional signals associated with the minor isomer: δ 2.53 (dt, J = 13.1, 3.0 Hz, 1H), 2.13 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.10 (dd, *J* = 13.3, 4.1 Hz, 1H), 1.85-1.74 (m, 2H), 1.73-1.66 (m, 2H), 1.36 (s, 3H), 1.14 (s, 3H), 1.01 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 207.6, 206.5, 70.3, 70.2, 63.5, 63.3, 51.5, 49.6, 34.1, 33.1, 30.8, 30.3, 30.1, 26.4, 22.1, 20.0, 19.8, 19.7, 19.5, 19.0. MS (APCI): 169 (M + H)$^+$. **2.91** has been previously prepared, see: Katsuhara, J. *J. Org. Chem.* **1967**, *32*, 797-799.



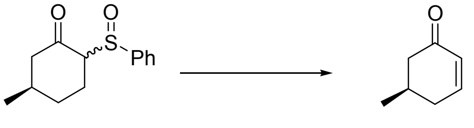
2.91 **2.92** **2.93**

(*R*)-5-methyl-2-(phenylsulfinyl)cyclohexanone (2.93)

To a solution of 20.5 g of sodium hydride (855 mmol) in 600 mL of THF was added a solution of 87.4 mL of thiphenol (855 mmol) in 60 mL of THF dropwise. To the resulting thick, white suspension was added dropwise a solution of 95.9 g of epoxide **2.91** (570 mmol) in 100 mL of THF. The resulting yellow suspension was heated to reflux and stirred for 19 h. The reaction mixture was cooled to rt and quenched with a saturated solution of sodium bicarbonate. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oily solid. The product was moved onto the next reaction with no further purification.

To a solution containing 90.1 g of crude compound **2.92** (409 mmol) in 700 mL of glacial acetic acid was added 62.9 g of sodium perborate tetrahydrate (409 mmol) in 10 g portions. In order to avoid over-oxidation to the sulfone, the reaction was monitored by thin layer chromatography after each addition of sodium perborate tetrahydrate. After the reaction was complete, the mixture was poured into a solution of 1 M HCl and extracted three times with diethyl ether. To the combined organic fractions was added ice cold water. To the biphasic solution was carefully added solid sodium bicarbonate until the aqueous layer tested neutral to litmus paper. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a thick orange oil. The crude oil was purified by column chromatography on silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 85.1 g (88% over 2 steps) of a 1:1 mixture of diastereomers of the title compound **2.93** as an orange oil.

IR (neat): 2956, 2872, 2238, 1712, 1044 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.68-7.62 (m, 4H), 7.58-7.56 (m, 2H), 7.51-7.47 (m, 4H), 3.68 (dd, *J* = 10.6, 5.8 Hz, 1H), 3.37-3.31 (m, 1H), 2.53-2.47 (m, 2H), 2.28-2.23 (m, 1H), 2.16-1.91 (m, 8H), 1.84-1.79 (m, 1H), 1.43-1.31 (m, 2H), 1.00 (d, *J* = 6.1 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 205.5, 205.3, 131.6, 131.1, 129.4, 129.2, 129.1, 126.0, 124.9, 124.7, 73.4, 73.2, 50.5, 50.4, 34.2, 34.1, 32.3, 32.2, 25.2, 23.0, 22.0, 21.6. MS (APCI): 237 (M + H)$^+$.



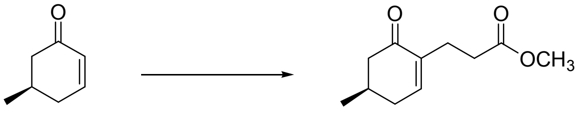
2.93 **2.57**

(*R*)-5-Methylcyclohex-2-enone (2.57)

To a solution of 1.2 g of sulfoxide **2.93** (5.1 mmol) in 50 mL of benzene was added 2.1 mL of pyridine (26 mmol). A condenser was attached to the round-bottomed flask and the reaction mixture was heated to reflux for 2 h. The solution was cooled to rt and the solvents were removed by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography on silica gel (10:1 hexanes:ethyl acetate) to afford 0.39 g (70 %) of the title compound **2.57** as a light yellow oil.

IR (neat): 2958, 1680, 880, 735 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.95 (ddd, *J* = 10.1, 5.3, 2.4 Hz, 1H), 6.00 (dd, *J* = 10.0, 2.6 Hz, 1H), 2.47 (dd, *J* = 15.7, 3.5 Hz, 1H), 2.45-2.38 (m, 1H), 2.25-2.16 (m, 1H), 2.14-2.10 (m, 1H), 2.01 (tt, *J* = 9.2, 2.6 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 201.3, 151.1, 130.6, 47.2, 35.0, 31.1, 22.2. $[\alpha]^{20}_D = -82^o$ (c = 0.60, CHCl$_3$).

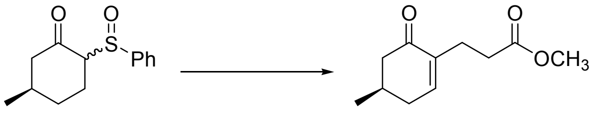
2.57 has been previously prepared, see: 1) Oppolzer, W.; Petrzilka, M. *Helv. Chem. Acta* **1978**, *61*, 2755-2762. 2) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P. *Tetrahedron Lett.* **1996**, *37*, 3125-3128.



2.57 **2.94**

(*R*)-Methyl 3-(4-methyl-6-oxocyclohex-1-enyl)propanoate (2.94)

A solution of 2.9 g of enone **2.57** (27 mmol), 3.6 mL of methyl acrylate (40 mmol), and 2.0 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (13 mmol) in 30 mL of *N*,*N*-dimethylformamide was prepared in a 100 mL thick-walled sealable vessel under an atmosphere of nitrogen. The vessel was sealed and the reaction mixture was heated to 180 °C for 24 h. The resulting dark red solution was cooled to rt and subsequently washed once with brine and once with water. The combined aqueous fractions were extracted four times with diethyl ether. The combined organic fractions were washed four times with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford an orange oil. The crude oil was purified by column chromatography on silica gel (10:1→5:1 hexanes:ethyl acetate) to afford 1.7 g (32 %) of the title compound **2.94** as a yellow oil.



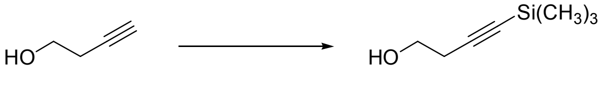
2.93 **2.94**

(*R*)-Methyl 3-(4-methyl-6-oxocyclohex-1-enyl)propanoate (2.94)

To a solution of 8.1 g of (*R*)-5-methyl-2-(phenylsulfinyl)cyclohexanone (**2.93**) (34 mmol) in 200 mL of DMF at −40 °C was added dropwise 6.2 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (41 mmol). The resulting orange solution was stirred at −40 °C for 0.25 h. Methyl acrylate (3.7 mL, 41 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −40 °C and then warmed to rt. The solution was heated to 40 °C for 2 h and then cooled to rt. The reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organics were washed five times with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a crude brown oil. The oil was purified by column chromatography on silica gel (5:1→4:1 hexanes:ethyl acetate) to give 4.2 g (63 %) of the title compound **2.94** as a light yellow oil.

IR (neat): 2995, 1739, 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.73-6.71 (m, 1H), 3.63 (s, 3H), 2.49-2.36 (m, 6H), 2.20-1.98 (m, 3H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 200.2, 174.5, 146.5, 138.7, 52.4, 47.5, 35.3, 34.0, 31.5, 26.3, 22.1. MS (ESI): 219 (M + Na)$^+$. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.56; H, 8.29. $[\alpha]^{20}_D = -39^o$ (c = 0.63, $CHCl_3$).



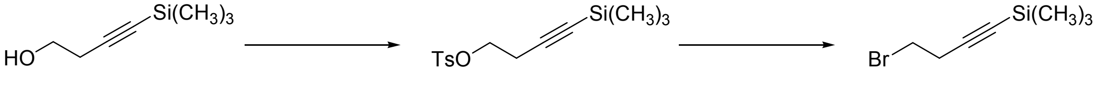
2.95 **2.96**

4-(Trimethylsilyl)but-3-yn-1-ol (2.96)

To a solution of 21.6 mL of 3-butyn-1-ol (**2.95**) (286 mmol) in 900 mL of THF at –78 °C was added 368 mL of a solution of *n*-butyllithium (1.55 M in hexanes, 571 mmol) dropwise over a period of 2 h. The yellow suspension was stirred at –78 °C for 0.5 h before 76.1 mL of chlorotrimethylsilane (599 mmol) was added dropwise over 0.5 h. The reaction mixture was stirred for an additional hour before being warmed to rt. To the reaction was added 300 mL of an aqueous 1M HCl solution and the resulting biphasic mixture was stirred at rt for 1 h. The layers were separated and the aqueous fraction was extracted twice with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude yellow oil. Purification of the crude material by distillation under reduced pressure afforded 39.4 g (97 %) of the title compound **2.96** as a colorless liquid, bp = 43-46 °C, 0.5 mmHg (*lit.* 72 °C, 12 mmHg).

IR (neat): 3340 (br), 2960, 2175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (t, J = 6.2 Hz, 2H), 2.48 (t, J = 6.3 Hz, 2H), 1.98 (s, 1H), 0.15 (s, 9H).

2.96 has been previously prepared, see: 1) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601-11624. 2) Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron* **1998**, *54*, 2149-2160.



2.96 **2.97**

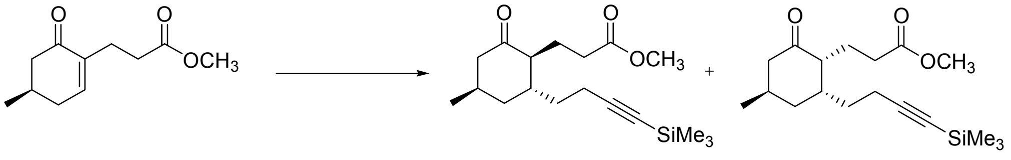
(4-Bromobut-1-ynyl)trimethylsilane (2.97)

To a solution of 39.4 g of **2.96** (277 mmol) and 68.7 g of *p*-toluenesulfonyl chloride (360 mmol) in 300 mL of dichloromethane at 0 °C was added 53.8 mL of pyridine (665 mmol). The reaction mixture was warmed to rt and stirred for 24 h. The resulting solution was washed four times with an aqueous 1M HCl solution. The combined aqueous fractions were extracted three times with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a pale yellow oil. The crude oil was purified by column chromatography on a plug of silica gel (10:1→6:1 hexanes:ethyl acetate) to afford a mixture of toluene-4-sulfonic acid 4-trimethylsilyl-but-3-ynyl ester and *p*-toluenesulfonyl chloride as a colorless oil. The material as used in the next reaction without further purification.

To a solution of the crude tosylate in 250 mL of DMF was added 34.2 g of sodium bromide (332 mmol) in one portion. The resulting suspension was stirred at 65 °C for 4 h. The reaction mixture was diluted with diethyl ether and washed with water. The aqueous fraction was extracted once with diethyl ether. The combined organic fractions were washed five times with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow liquid. The crude liquid was purified by distillation under reduced pressure to give 46.0 g (79 % over 2 steps) of the title compound **2.97** as a colorless liquid, bp = 38-40 °C, 0.5 mmHg (*lit.* 74-76 °C, 20 mmHg).

IR (neat): 2961, 2178 $\mathrm{cm^{-1}}$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 0.15 (s, 9H).

2.97 has been previously prepared, see: 1) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601-11624. 2) Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron* **1998**, *54*, 2149-2160.



2.94

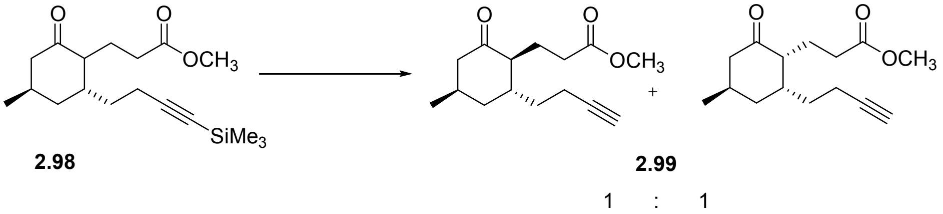
2.98

1 : 1

Methyl 3-((1S,4*R*,6*R*)-4-methyl-2-oxo-6-(4-(trimethylsilyl)but-3-ynyl)cyclohexyl)propanoate + Methyl 3-((1*R*,4*R*,6*R*)-4-methyl-2-oxo-6-(4-(trimethylsilyl)but-3-ynyl)cyclohexyl)propanoate (2.98)

To a suspension of 5.73 g of magnesium (236 mmol) in 200 mL of THF was added 34.9 g of 4-trimethylsilyl-1-bromo-3-butyne (170 mmol) in one portion. The reaction mixture was immediately cooled to 0 °C and stirred for 1 h. The cloudy grey solution was transferred dropwise to a suspension of 34.9 g of copper(I) bromide-dimethyl sulfide complex (170 mmol) in 400 mL of THF at −78 °C and stirred for 1 h. To the resulting dark red reaction mixture was added 12.7 mL of chlorotrimethylsilane (99.1 mmol) dropwise. A solution of 18.5 g of compound **2.94** (94.4 mmol) in 50 mL of THF was added to the red mixture. The resulting reaction mixture was stirred at −78 °C for 1 h then at −40 °C for 1 h before warming to rt. The mixture was quenched with basic ammonium chloride solution, diluted with diethyl ether, and the layers were separated. The organic layer was washed with basic ammonium chloride solution until the aqueous fraction was no longer blue. The organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil. The crude oil was dissolved in 300 mL of methanol and 3 mL of 3M HCl. The solution was stirred for 2 h at rt. The solvents were removed *in vacuo* to yield a crude yellow oil. The oil was purified by column chromatography on silica gel (10:1→5:1→3:1 hexanes:ethyl acetate) to give 25.6 g (84 %) of a 1:1 mixture of the title compound **2.98** as a pale yellow oil.

IR (neat): 2955, 2174, 1740, 1708 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 2.38-1.87 (m, 1H), 1.71-1.43 (m, 4H), 1.01-0.94 (dd, J = 14.0, 6.1 Hz, 3H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.2, 212.5, 174.8, 174.6, 107.2, 107.1, 86.3, 86.2, 55.0, 53.8, 52.5, 52.4, 51.2, 48.1, 40.5, 39.3, 37.3, 35.0, 33.0, 32.8, 32.7, 30.9, 30.5, 26.6, 25.8, 23.2, 22.7, 22.1, 18.6, 18.5, 1.1. MS (ESI): 345 (M + Na)$^+$. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.02; H, 9.33.

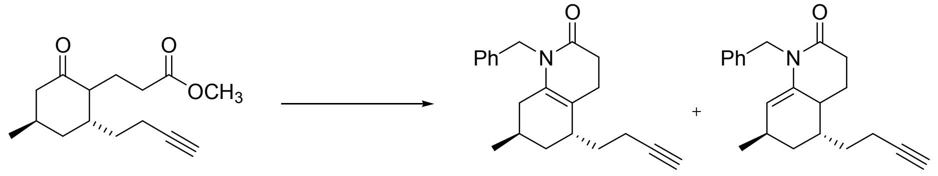


Methyl 3-((1*S*,2*R*,4*R*)-2-(but-3-ynyl)-4-methyl-6-oxocyclohexyl)propanoate + Methyl 3-((1*R*,2*R*,4*R*)-2-(but-3-ynyl)-4-methyl-6-oxocyclohexyl)propanoate (2.99)

To a solution of 23.7 g of compound **2.98** (73.6 mmol) in 400 mL of THF was added 73.6 mL of tetrabutylammonium fluoride (73.6 mmol, 1M in THF) in 10 mL portions. The resulting dark red reaction mixture was stirred for 0.10 h at rt before being diluted with diethyl ether. The solution was washed once with water and once with brine. The combined aqueous fractions were extracted three times with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give an orange-brown oil. The crude oil was purified by column chromatography on silica gel (4:1 hexanes:ethyl acetate) to afford 17.7 g (96 %) of a 1:1 mixture of the title compound **2.99** as a yellow oil.

IR (neat): 3288, 2953, 2360, 1738, 1708 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.66 (s, 3H), 2.42-1.88 (m, 12H), 1.74-1.46 (m, 4H), 1.00 (dd, J = 13.1, 6.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 214.3, 212.5, 174.8, 174.5, 84.4, 84.3, 69.9, 55.0, 53.9, 52.6, 52.5, 51.2, 48.1, 40.3, 39.4, 37.2, 34.9, 32.9, 32.8, 30.9, 30.5, 26.4, 26.1, 23.2, 22.8, 22.2, 17.1, 17.0. MS (ESI): 273 (M + Na)$^+$. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.63; H, 8.82.

2.9.3 Route A: Forward Synthesis



2.99

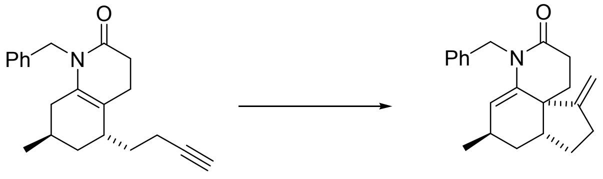
2.87

15 : 1

(5*R*,7*R*)-1-Benzyl-5-(but-3-ynyl)-7-methyl-3,4,5,6,7,8-hexahydroquinolin-2(1*H*)-one + (5*R*,7*R*)-1-Benzyl-5-(but-3-ynyl)-7-methyl-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (2.87)

To a solution of 3.1 g of compound **2.99** (12 mmol) in 40 mL of toluene were added 6.7 mL of benzylamine (61 mmol) and 12 mL of glacial acetic acid. A Dean-Stark apparatus was attached and the reaction mixture was heated to reflux and stirred for 2 h. The reaction mixture was cooled to rt and diluted with diethyl ether. The organic layer was washed twice with a saturated solution of sodium bicarbonate. The combined aqueous layers were extracted once with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a thick brown oil which solidified when cooled. The crude compound was purified by column chromatography on triethylamine washed silica gel (3:1 hexanes:ethyl acetate) to afford 3.7 g (99 %) of a 15:1 mixture of the title compound **2.87** as a thick orange oil.

IR (neat): 3294, 2927, 2115, 1664, 1496, 1392, 1187, 703, 643 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29-7.53 (m, 2H), 7.21-7.17 (m, 1H), 7.13-7.11 (m, 2H), 4.87 (s, 2H), 2.61-2.46 (m, 2H), 2.34-2.10 (m, 6H), 1.95 (t, J = 2.6 Hz, 1H), 1.77-1.69 (m, 2H), 1.66-1.60 (m, 1H), 1.51-1.38 (m, 2H), 1.25-1.15 (m, 1H), 1.89 (d, J = 6.5 Hz, 3H). Additional signals associated with the minor isomer: δ 5.12 (d, J = 15.7 Hz, 1H), 5.01 (d, J = 4.8 Hz, 1H), 4.74 (d, J = 16.1 Hz, 1H), 2.77-2.71 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.6, 139.5, 133.0, 129.5, 127.7, 127.1, 119.2, 85.1, 69.8, 44.7, 38.0, 34.9, 34.3, 33.1, 32.6, 25.4, 25.0, 22.5, 17.9. Additional signals associated with the minor isomer: δ 170.1, 138.7, 129.4, 127.6, 127.3, 112.9, 85.0, 69.7, 61.3, 47.8, 41.3, 34.0, 33.7, 32.7, 28.8, 26.2, 22.0, 16.9, 15.2. MS (ESI): 330 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.56; H, 7.96; N, 4.71.

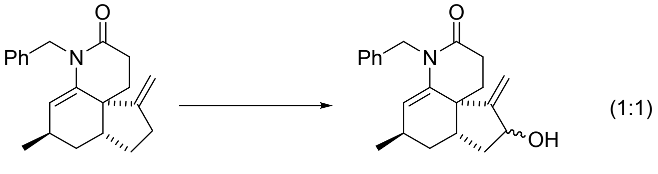


2.87 **2.86**

(4a*S*,7a*R*,9*R*)-1-Benzyl-9-methyl-5-methylene-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-2(1*H*)-one (2.86)

To a flask containing 2.65 g of compound **2.87** (8.61 mmol) and 0.229 g of platinum(II) chloride (0.861 mmol) was added 30 mL of toluene. The reaction mixture was heated to 80 °C and stirred for 2 h. The orange reaction mixture was cooled to rt and filtered through a plug of triethylamine washed silica gel, rinsing with diethyl ether. The solvents were removed *in vacuo* to give a bright yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (4:1 hexanes:ethyl acetate) to afford 2.69 g (75 %) of the title compound **2.86** as a yellow oil.

IR (neat): 2925, 2868, 1669, 1636, 1368, 12.01, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.16 (m, 5H), 5.39 (d, *J* = 15.7 Hz, 1H), 5.02 (d, *J* = 4.8 Hz, 1H), 4.92 (s, 1H), 4.73 (s, 1H), 4.52 (d, *J* = 15.7 Hz, 1H), 2.70-2.57 (m, 2H), 2.52-2.26 (m, 3H), 2.09-1.95 (m, 2H), 1.89-1.84 (m, 1H), 1.70-1.62 (m, 1H), 1.54-1.48 (m, 1H), 1.41-1.34 (m, 1H), 1.26-1.19 (m, 1H), 0.87 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 154.4, 140.1, 138.9, 129.5, 129.4, 127.7, 113.0, 109.6, 49.6, 48.9, 41.7, 33.6, 30.4, 29.7, 29.6, 29.3, 27.6, 22.4. MS (ESI): 330 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.85; H, 8.20; N, 4.74. $[\alpha]^{21}_{D} = +127^{\circ}$ (c = 1.91, $CHCl_3$).

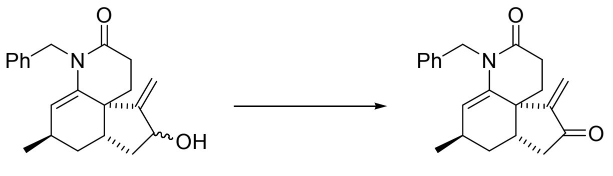


2.86 **2.104**

(4a*S*,7a*S*,9*R*)-1-Benzyl-6-hydroxy-9-methyl-5-methylene-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-2(1*H*)-one (2.104)

To a solution of 0.94 g of compound **2.86** (3.1 mmol) in 10 mL of dichloromethane was added 1.6 mL *t*-butylhydroperoxide (70 wt % solution in H_2O, 12 mmol) in one portion. To the biphasic reaction mixture was added 0.17 g of selenium dioxide (1.5 mmol) in one portion. The reaction mixture was stirred at rt for 48 h. The reaction was stopped by the addition of 6 mL of a saturated solution of sodium bicarbonate and 6 mL of a saturated solution of sodium bisulfite with vigorous stirring for 0.5 h. The orange suspension was diluted with dichloromethane, water, and the layers were separated. The aqueous fraction was extracted three times with dichloromethane. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography (4:1→1:1→1:3 hexanes:ethyl acetate) to give 0.52 g (52 %, 59 % BRSM) of the title compound **2.104** as a pale yellow oil.

IR (neat): 3398, 2868, 1626, 1496, 1402, 1202, 909, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H), 5.32 (d, *J* = 15.3 Hz, 1H), 5.22 (d, *J* = 6.5 Hz, 1H), 5.08-5.04 (m, 1H), 4.93-4.89 (m, 1H), 4.59-4.51 (m, 2H), 2.71-2.60 (m, 2H), 2.28-2.17 (m, 2H), 2.01-1.74 (m, 3H), 1.40-1.23 (m, 3H), 0.88 (d, *J* = 7.4, 3H). Additional signals associated with other isomer: δ 2.49-2.42 (m, 1H), 1.62-1.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.2, 157.8, 157.7, 140.3, 140.2, 138.7, 138.6, 129.5, 129.4, 127.8, 127.7, 114.3, 113.7, 113.5, 110.1, 75.2, 72.4, 61.4, 49.1, 48.9, 48.3, 47.9, 40.8, 40.0, 39.0, 38.3, 35.0, 33.9, 31.2, 30.9, 30.5, 28.8, 28.3, 22.3, 22.2, 22.0, 15.2. MS (EI): 323 $(M)^+$.

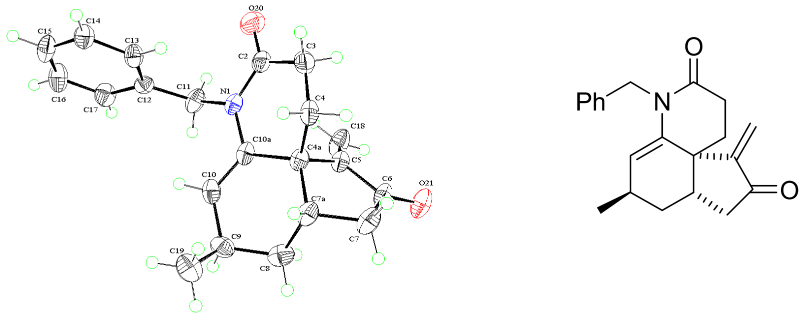


2.104 **2.105**

(4a*S*,7a*S*,9*R*)-1-Benzyl-9-methyl-5-methylene-3,4,7,7a,8,9-hexahydrocyclopenta[*e*]quinoline-2,6(1*H*,5*H*)-dione (2.105)

To a solution of 0.505 g of alcohol **2.104** (1.56 mmol) in 15 mL of dichloromethane was added 1.37 g of manganese dioxide (15.6 mmol) in one portion. The black suspension was stirred for 30 h at rt and subsequently filtered through Celite®, rinsing with ethyl acetate. The solvents were removed *in vacuo* to yield a pale yellow oil. The crude product was purified by column chromatography on triethylamine washed silica gel (2:3 hexanes:ethyl acetate) to afford 0.387 g (77 %) of the title compound **2.105** as a white solid.

IR (neat): 2928, 2869, 1728, 1669, 1636, 1496, 731 cm^{-1}. ^{1}H NMR (400 MHZ, CDCl$_3$): δ 7.31-7.18 (m, 5H), 6.09 (s, 1H), 5.36 (d, *J* = 15.7 Hz, 1H), 5.19 (s, 1H), 5.18 (s, 1H), 4.56 (d, *J* = 15.7 Hz, 1H), 2.78-2.65 (m, 2H), 2.58-2.48 (m, 1H), 2.37-2.28 (m, 2H), 2.07 (d, *J* = 18.7 Hz, 1H), 1.92-1.88 (m, 2H), 1.41-1.37 (m, 2H), 0.95 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 205.8, 169.5, 148.9, 139.3, 138.4, 129.6, 128.0, 127.7, 120.7, 113.7, 49.1, 46.8, 42.8, 36.0, 34.0, 30.5, 29.9, 29.0, 22.3. MS (EI): 321 (M)$^+$. $[\alpha]^{21}_D$ = +66.1° (c = 1.53, CHCl$_3$).



ORTEP representation of the solid state structure of **2.105**

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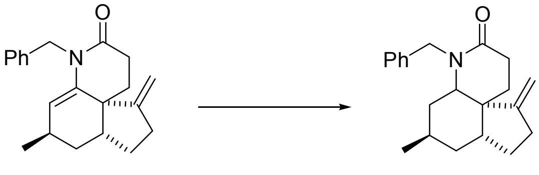
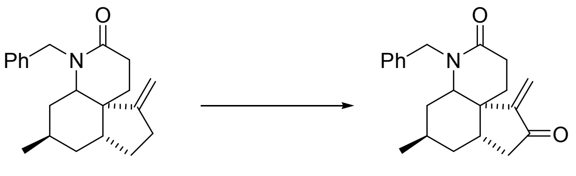


2.86 **2.106**

(4a*S*,7a*R*,9*R*)-1-Benzyl-9-methyl-5-methylene-decahydrocyclopenta[*e*]quinolin-2(1*H*)-one (2.106)

To a solution of 6.17 g of enamide **2.86** (20.1 mmol) in 60 mL of trifluoroacetic acid at 0 °C was added 1.52 g of sodium borohydride (40.1 mmol) slowly over 1 h. The reaction mixture was warmed to rt and stirred for 3 h. The solution was cooled to 0 °C and quenched slowly with a solution of 30 % NaOH until it tested neutral to pH paper. The aqueous solution was extracted three times with diethyl ether. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a brown oil. The crude oil was purified on silica gel (1:1 hexanes:ethyl acetate) to afford 5.42 g (87 %) of the title compound **2.106** as a single diastereomer.

IR (neat): 2955, 1738, 1642, 704 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32-7.20 (m, 5H), 5.39 (d, *J* = 15.7 Hz, 1H), 5.08 (s, 1H), 4.98 (s, 1H), 4.18 (d, *J* = 15.7, 1H), 3.70 (dd, *J* = 13.1, 3.9 Hz, 1H), 2.72-2.41 (m, 4H), 2.00-1.82 (m, 5H), 1.66 (dt, *J* = 12.2, 3.1 Hz, 1H), 1.59 (td, *J* = 13.1, 6.1 Hz, 1H), 1.30-1.19 (m, 3H), 0.71 (d, *J* = 7.0 Hz, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 172.9, 150.0, 138.9, 129.5, 128.3, 127.8, 110.8, 56.8, 50.5, 46.1, 43.1, 35.1, 31.3, 31.2, 30.7, 30.4, 28.6, 27.0, 19.1. MS (ESI): 310 (M + H)$^{+}$. $[\alpha]^{22}_{D} = -44°$ (c = 0.92, CHCl$_3$).

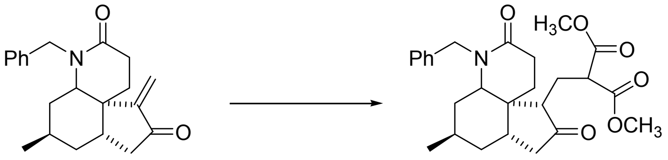


2.106 **2.85**

(4a*S*,7a*S*,9*R*)-1-Benzyl-9-methyl-5-methylene-3,4,7,7a,8,9-hexahydrocyclopenta[*e*]quinoline-2,6(1*H*,5*H*)-dione (2.85)

A solution of 0.17 g of amide **2.106** (0.55 mmol) and 0.061 g of selenium dioxide (0.55 mmol) in 7 mL of 1,4-dioxane was heated to 85 °C and stirred for 1.75 h. The brown solution was cooled to rt and the solvents were removed *in vacuo* to afford a red-brown residue. The residue was purified by column chromatography on silica gel (3:1→1:1→0:1 hexanes:ethyl acetate) to afford the crude product as a yellow oil. The silica gel was flushed with methanol to recover 0.080 g of the allylic alcohol (0.25 mmol). To a solution of the allylic alcohol in 4 mL of dichloromethane was added 0.22 g of activated manganese dioxide (2.6 mmol). The suspension was stirred for 24 h at rt and then filtered through Celite®, rinsing with ethyl acetate and methanol. The solution was concentrated *in vacuo* to afford a black film. The crude film was purified by column chromatography on silica gel (1:1→0:1 hexanes:ethyl acetate) to yield a second portion of the title compound **2.85** as a yellow oil. A total yield of 0.12 g (70 %) of the title compound **2.85** was obtained.

IR (neat): 2958, 2930, 1728, 1636, 1455, 1408, 731, 704 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35-7.22 (m, 5H), 6.29 (s, 1H), 5.43 (s, 1H), 5.43-5.40 (m, 1H), 4.20 (d, J = 15.3 Hz, 1H), 3.76 (dd, J = 12.6, 3.9 Hz, 1H), 2.71-2.63 (m, 2H), 2.58-2.53 (m, 1H), 2.21-2.15 (m, 1H), 2.04-1.77 (m, 5H), 1.64 (td, J = 12.8, 5.5 Hz, 1H), 1.43 (dt, J = 14.0, 4.9 Hz, 1H), 1.14-1.06 (m, 1H), 0.77 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 206.8, 172.2, 145.8, 138.5, 129.6, 128.3, 128.1, 121.9, 57.3, 48.4, 46.2, 43.1, 37.2, 36.5, 32.0, 31.3, 30.2, 27.6, 19.3. MS (ESI): 324 (M + H)$^{+}$. $[\alpha]^{22}_{D}$ = −109° (c = 2.03, CHCl$_3$).

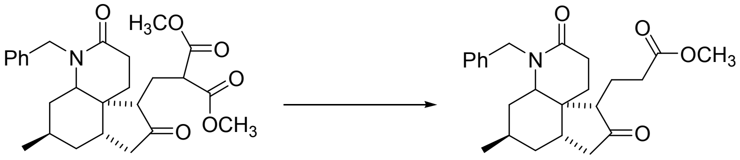


2.85 **2.107**

Dimethyl 2-(((4a*S*,7a*S*,9*R*)-1-benzyl-9-methyl-2,6-dioxo-dodecahydrocyclopenta[*e*]quinolin-5-yl)methyl)malonate (2.107)

To a suspension of 0.02 g of sodium hydride (0.7 mmol) in 2 mL of THF was added dropwise 0.1 mL of dimethyl malonate (0.7 mmol). The resulting solution was stirred for 0.1 h at rt. A solution of 0.1 g of enone **2.85** (0.3 mmol) in 4 mL of THF was added to the reaction mixture. The resulting yellow solution was heated to 50 °C and stirred for 2 h. The reaction mixture was cooled to rt, diluted with diethyl ether, washed once with a saturated solution of ammonium chloride and once with brine. The combined aqueous fractions were extracted once with diethyl ether. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield an orange oil. The crude oil was purified by column chromatography on silica gel (1:1→0:1 hexanes:ethyl acetate) to afford 0.1 g (72 %) of the title compound **2.107** as a white solid, mp:119-123 °C.

IR (film): 2954, 1734, 1646, 1437, 1412, 914, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.21-7.12 (m, 3H), 5.45 (d, *J* = 16.4 Hz, 1H), 4.22 (dd, *J* = 10.6, 3.9 Hz, 1H), 4.12 (d, *J* = 16.4 Hz, 1H), 3.95 (dd, *J* = 13.1, 3.5 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.76-2.67 (m, 2H), 2.63-2.55 (m, 1H), 2.42 (dd, *J* = 19.3, 7.6 Hz, 1H), 2.18-2.12 (m, 2H), 2.04-1.84 (m, 5H), 1.75-1.67 (m, 2H), 1.41-1.30 (m, 2H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.8, 172.3, 170.2, 169.8, 138.9, 128.7, 126.8, 126.3, 54.2, 52.8, 52.7, 49.4, 46.8, 45.9, 44.6, 42.5, 38.5, 34.5, 30.1, 29.8, 28.8, 27.2, 26.1, 18.0. MS (ESI): 456 (M + H)$^+$. Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.52; H, 7.36; N, 3.33. $[\alpha]^{22}_{D} = -131^{o}$ (c = 2.09, $CHCl_3$).

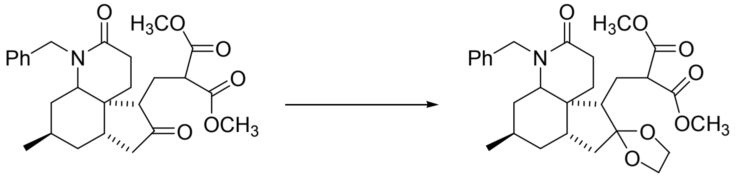


2.107 **2.109**

Methyl 3-((4a*S*,7a*S*,9*R*)-1-benzyl-9-methyl-2,6-dioxo-dodecahydrocyclopenta[*e*]quinolin-5-yl)propanoate (2.109)

To a solution of 0.5 g of diester **2.107** (1 mmol) in 15 mL of dimethyl sulfoxide were added 0.1 g of sodium chloride (2 mmol) and 0.06 mL of water (3 mmol). The reaction mixture was heated to 160 °C and stirred for 5 h. The solution was cooled to rt, poured into 40 mL of water, and extracted five times with diethyl ether. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford an orange oily solid. The crude solid was purified by column chromatography on silica gel (1:1→1:2→0:1 hexanes:ethyl acetate) to afford 0.3 g (70 %) of the title compound **2.109** as a yellow oil.

IR (neat): 2933, 1736, 1646, 1438, 1412, 730 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.16 (m, 5H), 5.40 (d, *J* = 16.1 Hz, 1H), 4.17 (d, *J* = 16.1 Hz, 1H), 3.97 (dd, *J* = 13.1, 3.5 Hz, 1H), 3.69 (s, 3H), 2.92-2.56 (m, 5H), 2.47-2.40 (m, 1H), 2.18-2.05 (m, 3H), 1.95-1.87 (m, 2H), 1.79-1.66 (m, 4H), 1.43-1.39 (m, 2H), 0.90 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 220.3, 175.1, 173.4, 139.8, 129.6, 127.7, 127.3, 55.4, 52.5, 48.8, 46.7, 45.5, 43.5, 39.4, 35.4, 32.4, 31.0, 30.9, 29.9, 28.2, 22.9, 18.8. MS (ESI): 420 (M + Na)$^+$. $[\alpha]^{22}_{D} = -116^{o}$ (c = 1.45, $CHCl_3$).

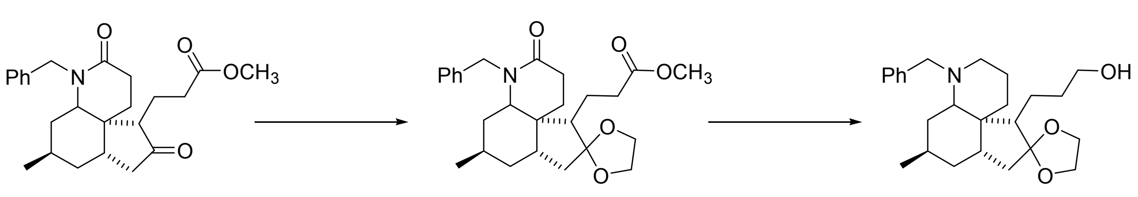


2.107 **2.108**

Ketal (2.108)

A solution of 0.07 g of compound **2.107** (0.2 mmol), 0.04 mL of ethylene glycol (0.6 mmol), and 6 mg of *p*-toluenesulfonic acid monohydrate (0.03 mmol) in 10 mL of benzene was heated to reflux using a Dean-Stark apparatus. The reaction mixture was stirred at reflux for 17.5 h. The solution was cooled to rt and carefully poured into a saturated solution of sodium bicarbonate. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a clear yellow oil. The crude oil was purified by column chromatography on silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 0.07 g (94 %) of the title compound **2.108** as a clear oil.

IR (film): 2956, 1749, 1733, 1647 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28-7.24 (m, 2H), 7.18-7.12 (m, 3H), 5.45 (d, *J* = 16.6 Hz, 1H), 4.15 (d, *J* = 16.6 Hz, 1H), 4.00-3.84 (m, 4H), 3.74 (s, 3H), 3.73 (d, *J* = 9.6 Hz, 1H), 3.68 (s, 3H), 3.56 (dd, *J* = 10.7, 4.1 Hz, 1H), 2.71-2.53 (m, 3H), 2.26-2.18 (m, 1H), 2.10-1.98 (m, 4H), 1.92-1.81 (m, 2H), 1.60-1.43 (m, 4H), 1.17 (dd, *J* = 14.2, 5.0 Hz, 1H), 0.81 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.7, 171.2, 170.9, 140.2, 129.5, 127.5, 127.2, 118.2, 65.2, 63.4, 55.2, 53.6, 53.3, 50.4, 47.7, 45.5, 43.8, 42.7, 42.4, 34.2, 31.3 30.0, 29.5, 28.1, 25.6, 19.0. MS (ESI): 500 (M + H)$^+$, 522 (M + Na)$^+$. $[\alpha]^{22}_D = -412^o$ (c = 0.11, CHCl$_3$).



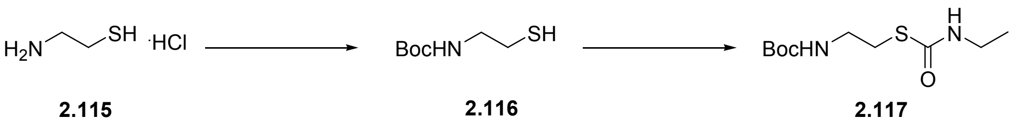
2.109 **2.110** **2.111**

Alcohol (2.111)

A solution of 0.90 g of compound **2.109** (2.3 mmol), 0.51 mL of ethylene glycol (9.1 mmol), and 0.086 g of *para*-toluenesulfonic acid monohydrate (0.45 mmol) in 40 mL of benzene was heated to reflux using a Dean-Stark apparatus. The reaction mixture was heated to reflux for 22 h. The solution was cooled to rt and carefully poured into a saturated solution of sodium bicarbonate and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford ketal **2.110** as a clear yellow oil. The crude material was used directly in the next reaction with no further purification.

To a suspension of 0.32 g of lithium aluminum hydride (8.5 mmol) in 5 mL of THF was added a solution of 0.75 g of ketal **2.110** (1.7 mmol) in 10 mL of THF. The suspension was heated to reflux and stirred for 5 h. The reaction mixture was cooled to rt and quenched by the slow, sequential addition of 0.32 mL of water, 0.32 mL of 15 % NaOH, and then 0.96 mL of water. The solution was stirred at rt for 0.5 h before filtering through a pad of Celite® covered with magnesium sulfate. The pad was rinsed exhaustively with diethyl ether. The filtrate was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a clear oil. The crude oil was purified by column chromatography on silica gel (30:1→20:1→10:1 dichloromethane:methanol) to afford 0.54 g (80 %; 59 % over 2 steps) of the title compound **2.111** as a clear oil.
IR (film): 3424 (br), 2953, 2791, 1713, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 4H), 7.22-7.16 (m, 1H), 4.03 (d, J = 12.8 Hz, 1H), 3.96-3.89 (m, 3H), 3.78-3.67 (m, 3H), 2.87-2.78 (m, 2H), 2.64-2.56 (m, 2H), 2.39 (dd, J = 12.3, 4.6 Hz, 1H), 2.21-2.16 (m, 1H), 2.09 (br s, 1H), 2.02-1.87 (m, 5H), 1.76-1.58 (m, 7H), 1.40 (d, J = 13.3 Hz, 1H), 1.34-1.32 (m, 1H), 1.26-1.19 (m, 1H), 1.04 (d, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 129.6, 129.1, 127.4, 119.4, 65.5, 65.4, 64.4, 63.7, 59.7, 56.4, 47.2, 47.6, 43.3, 42.1, 35.8, 34.9, 33.4, 30.9, 28.1, 24.6, 24.5, 21.0. MS (ESI): 400 $(M + H)^+$, 422 $(M + Na)^+$. $[\alpha]^{22}_D = +51.9^\circ$ (c = 3.16, $CHCl_3$).

2.9.4 Route B: Model Studies

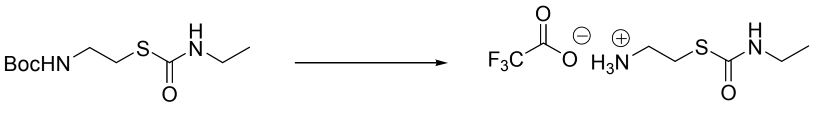


***tert*-Butyl 2-(ethylcarbamoylthio)ethylcarbamate (2.117)**

To a solution of 10.0 g of mercaptoethylamine hydrochloride (**2.115**) (88.0 mmol) in 200 mL of dichloromethane was added 12.2 mL of triethylamine (88.0 mmol) in one portion. The reaction mixture was stirred at rt for 0.2 h. To the solution was added 19.2 g of di-*t*-butyl dicarbonate (88.0 mmol) in one portion. The reaction mixture spontaneously heated to reflux and then cooled to rt. The resulting white suspension was then stirred at rt for 17 h. The mixture was washed twice with water. The combined aqueous fractions were extracted once with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford sulfide **2.116** a clear oil. The material was used in the next reaction with no further purification.

To a solution containing approximately 16 g of crude sufide **2.116** (89 mmol) in 200 mL of dichloromethane was added 3.7 mL of triethylamine (26 mmol) in one portion. To the resulting mixture was added 14 mL of ethyl isocyanate (1.8×10^2 mmol) very slowly. The reaction mixture was stirred at rt for 12 h. The solution was then washed five times with brine. The combined aqueous fractions were extracted once with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford and off-white solid. The solid was recrystallized in two crops from dichloromethane and hexanes to give 19 g (89 % over 2 steps) of the title compound **2.117** as white crystals.

IR (film): 3324, 2980, 2252, 1701, 1665 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.72 (br s, 1H), 5.04 (br s, 1H), 3.31 (t, *J* = 6.1 Hz, 4H), 3.00 (t, *J* = 6.4 Hz, 2H), 1.42 (s, 9H), 1.15 (t, *J* = 7.3 Hz, 3H).



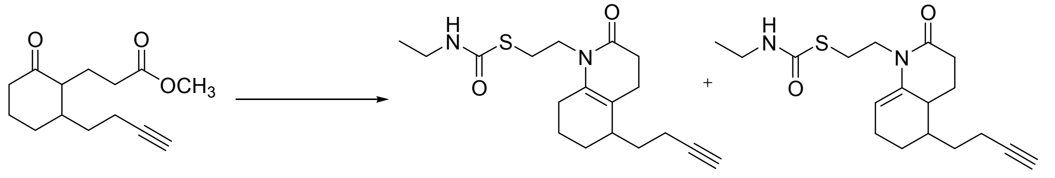
2.117 **2.118**

2-(Ethylcarbamoylthio)ethanaminium 2,2,2-trifluoroacetate (2.118)

To a solution of 19.4 g of thiocarbamate **2.117** (78.0 mmol) in 25 mL of dichloromethane was added 18.0 mL of trifluoroacetic acid (234 mmol) in two portions. The reaction mixture was stirred at rt for 20 h. The dichlormethane was removed by rotary evaporation *in vacuo*. The excess trifluoroacetic acid was removed by rotary evaporation under reduced pressure (0.5 mmHg) to afford a crude white solid. The crude solid was triterated with hexanes and then dried under vacuum to afford 20.4 g (100 %) of the title compound **2.118** as a white solid.

^{1}H NMR (400 MHz, DMSO): δ 8.20 (br s, 1H), 7.95 (br s, 3H), 3.16-3.09 (m, 2H), 3.02-2.96 (m, 4H), 1.00 (t, *J* = 7.3 Hz, 3H).

2.117 and **2.118** have been previously prepared, see: Anada, T.; Karinaga, R.; Mizu, M.; Kuomoto, K.; Matsumoto, T.; Numata, M.; Shinkai, S.; Sakurai, K. *e-J. Surf. Sci. Nanotechnol.* **2005**, *3*, 195-202.



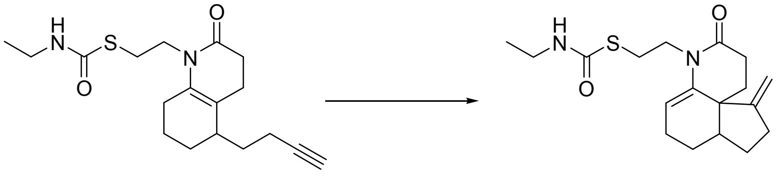
2.119 **2.120**

5 : 1

***S*-2-(5-(But-3-ynyl)-2-oxo-3,4,5,6,7,8-hexahydroquinolin-1(2*H*)-yl)ethyl ethylcarbamothioate + *S*-2-(5-(But-3-ynyl)-2-oxo-3,4,4a,5,6,7-hexahydroquinolin-1(2*H*)-yl)ethyl ethylcarbamothioate (2.120)**

A solution of 0.08 g of compound **2.119** (0.4 mmol), 0.3 g of ammonium salt **2.118** (1 mmol), and 0.4 mL of acetic acid in 5 mL of toluene was heated to reflux using a Dean-Stark apparatus. The reaction mixture was stirred for 2 h before cooling to rt. The solution was diluted with diethyl ether and carefully washed twice with a saturated solution of sodium bicarbonate. The aqueous fractions were then extracted twice with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate) to afford 0.09 g (82 %) of a 5:1 mixture of the title compound **2.120** as a pale yellow oil.

IR (neat): 3292, 2934, 2115, 1646, 1525 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (br s, 1H), 3.82-3.75 (m, 1H), 3.71-3.61 (m, 1H), 3.32-3.30 (m, 2H), 3.02-2.87 (m, 2H), 2.47-2.36 (m, 2H), 2.29-2.10 (m, 6H), 2.06-2.00 (m, 1H), 1.94 (t, *J* = 2.2 Hz, 1H), 1.88-1.62 (m, 4H), 1.47-1.32 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 3H). Additional signals associated with the minor isomer: δ 5.54 (br s, 1H), 4.02-3.95 (m, 1H), 2.63-2.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 169.8, 167.5, 139.0, 133.5, 119.5, 106.5, 85.2, 69.6, 69.5, 42.3, 41.0, 39.7, 38.0, 37.3, 33.7, 33.3, 32.8, 32.4, 29.0, 27.3, 27.2, 26.7, 25.9, 25.2, 24.7, 21.1, 17.3, 16.9, 15.9. MS (APCI): 349 $(M + H^+)$, 357 $(M + Na)^+$.

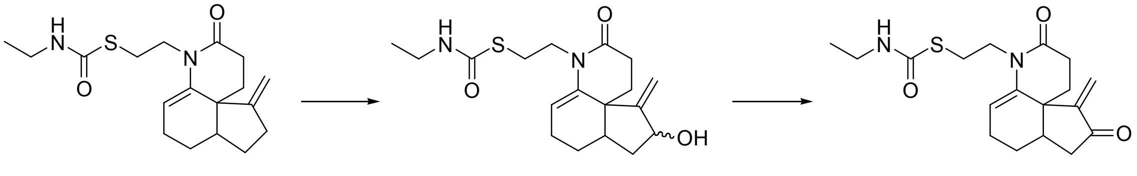


2.120 **2.121**

S-2-(5-Methylene-2-oxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2*H*)-yl)ethyl ethylcarbamothioate (2.121)

A solution containing 0.087 g of compound **2.120** (0.26 mmol) and 3.5 mg of platinum(II) chloride (0.013 mmol) in 5 mL of toluene was heated to 90 °C and stirred for 6 h. The reaction mixture was cooled to rt and filtered through a plug of triethylamine washed silica gel. The filtrate was concentrated by rotary evaporation *in vacuo* to afford an orange oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1 hexanes:ethyl acetate) to afford 0.059 g (68 %) of the title compound **2.121** as a clear oil.

IR (neat): 3297, 2924, 1630, 1527, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (br s, 1H), 5.55 (br s, 1H), 4.90 (s, 1H), 4.67 (s, 1H), 4.07-4.00 (m, 1H), 3.73-3.65 (m, 1H), 3.32 (qt, *J* = 6.5 Hz, 2H), 3.07-2.98 (m, 2H), 2.58-2.34 (m, 4H), 2.27-1.97 (m, 3H), 1.85-1.78 (m, 2H), 1.60-1.52 (m, 1H), 1.48-1.40 (m, 2H), 1.37-1.25 (m, 1H), 1.15 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 167.6, 154.4, 139.7, 109.4, 106.7, 49.5, 46.1, 45.8, 37.3, 30.3, 29.3, 29.1, 27.6, 27.5, 26.8, 25.4, 15.2. MS (ESI): 357 (M + Na)$^+$.

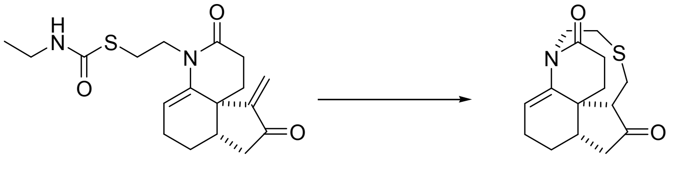


2.121 **2.122**

S-2-(5-Methylene-2,6-dioxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2*H*)-yl)ethyl ethylcarbamothioate (2.122)

To a solution of 0.06 g of compound **2.121** (0.2 mmol) in 4 mL of dichloromethane was added 0.07 mL of a solution of *tert*-butyl hydroperoxide (70 wt. % in H_2O, 0.5 mmol) in one portion. To the clear solution was added 9 mg of selenium dioxide (0.09 mmol) in one portion. The reaction mixture was stirred at rt for 24 h. The mixture was quenched with 2 mL of a saturated solution of sodium bicarbonate and 2 mL of a saturated solution of sodium bisulfite. The biphasic mixture was stirred vigorously at rt for 0.3 h. The reaction mixture was diluted with water and dichloromethane and the layers were separated. The aqueous layer was extracted three times with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford the crude alcohol as a clear oily film. The product was moved onto the next reaction with no further purification.

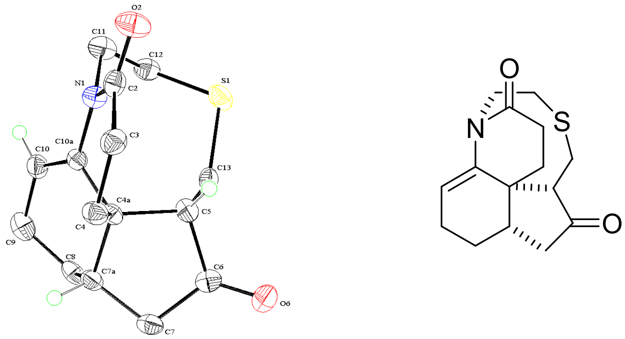
To an open atmosphere solution of 0.06 g of crude alcohol (0.2 mmol) in 7 mL of dichloromethane was added 0.2 g of manganese(IV) oxide (2 mmol) in one portion. The flask was capped and the resulting black suspension was stirred at rt for 22 h. The reaction mixture was filtered over Celite®, rinsing exhaustively with ethyl acetate. The filtrated was concentrated by rotary evaporation *in vacuo* to afford a clear oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (2:1→1:1 hexanes:ethyl acetate) to afford 0.02 g (32 % over 2 steps; 42 % BRSM) of the title compound **2.122** as a clear oil.
IR (neat): 3299, 2927, 1725, 1667, 1641, 1536, 757 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.13 (s, 1H), 5.74 (br s, 1H), 5.65 (br s, 1H), 5.21 (s, 1H), 4.14-4.06 (m, 1H), 3.71 (ddd, J = 13.5, 10.9, 5.7 Hz, 1H), 3.35 (qt, J = 6.1 Hz, 2H), 3.13-3.01 (m, 2H), 2.75 (dd, J = 18.7, 7.4 Hz, 1H), 2.61-2.55 (m, 1H), 2.47 (dd, J = 12.0, 7.2 Hz, 1H), 2.30-2.25 (m, 2H), 2.21-2.15 (m, 2H), 1.87-1.83 (m, 2H), 1.69-1.66 (m, 1H), 1.31-1.21 (m, 1H), 1.18 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 205.9, 169.2, 167.6, 149.1, 139.1, 120.5, 107.5, 46.7, 46.3, 43.0, 40.5, 37.4, 30.1, 29.8, 27.5, 27.4, 24.8, 15.2. MS (ESI): 371 (M + Na)$^+$.



Sulfide (2.123)

To a solution of 0.018 g of enone **2.122** (0.052 mmol) in 5 mL of methanol was added 7 mL of a solution of 1 M NaOH via pipette. The reaction mixture was stirred vigorously at rt for 0.3 h. The solution was extracted three times with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a white film. The film was purified by column chromatography on triethylamine washed silica gel (1:2→1:3 hexanes:ethyl acetate) to afford 0.012 g (82 %) of the title compound **2.123** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (q, *J* = 2.8 Hz, 1H), 4.74-4.67 (m, 1H), 3.34 (d, *J* = 10.0 Hz, 1H), 3.13 (d, *J* = 14.4 Hz, 1H), 3.00-2.88 (m, 2H), 2.75-2.69 (m, 3H), 2.61-2.56 (m, 1H), 2.52-2.49 (m, 1H), 2.39-2.15 (m, 4H), 2.05-1.89 (m, 2H), 1.78-1.73 (m, 1H), 1.33-1.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.2, 169.8, 139.0, 114.4, 78.2, 61.2, 44.1, 43.8, 42.4, 37.9, 34.8, 33.5, 29.4, 27.4, 23.9. MS (APCI): 294 $(M + H)^+$.



ORTEP representation of the solid state structure of **2.123**

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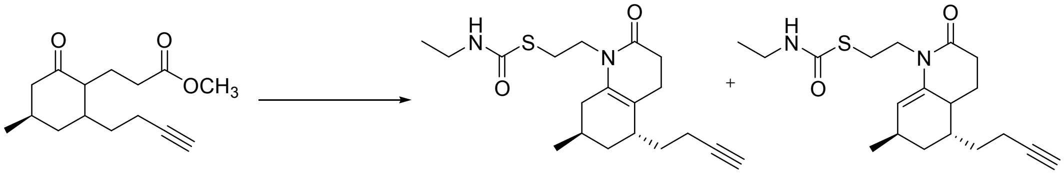
2.9.5 Route B: Forward Synthesis



2.99

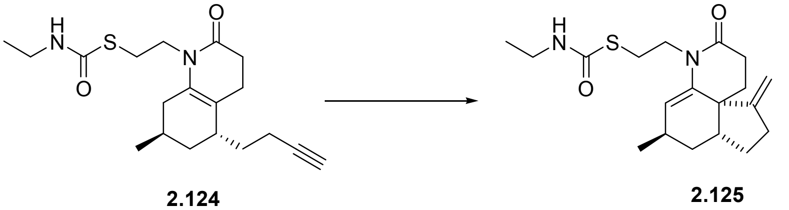
2.124

10 : 1

***S*-2-((5*R*,7*R*)-5-(But-3-ynyl)-7-methyl-2-oxo-3,4,5,6,7,8-hexahydroquinolin-1(2*H*)-yl)ethyl ethylcarbamothioate + *S*-2-((5*R*,7*R*)-5-(But-3-ynyl)-7-methyl-2-oxo-3,4,5,6,7,8-hexahydroquinolin-1(2*H*)-yl)ethyl ethylcarbamothioate (2.124)**

To a solution of 3.97 g of compound **2.99** (15.9 mmol) and 14.6 g of 2-(ethylcarbamoylthio)ethanaminium 2,2,2-trifluoroacetate (**2.118**) (55.5 mmol) in 40 mL of toluene was added 15.9 mL of acetic acid. A Deak-Stark apparatus was attached and the reaction mixture was heated to reflux and stirred for 4.5 h. The reaction mixture was cooled to rt, diluted with diethyl ether, and washed twice with a saturated solution of sodium bicarbonate. The combined aqueous fractions were extracted once with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1→0:1 hexanes:ethyl acetate) to afford 3.89 g (70 %) of the title compound **2.124** as a white solid, mp: 94-99 °C.

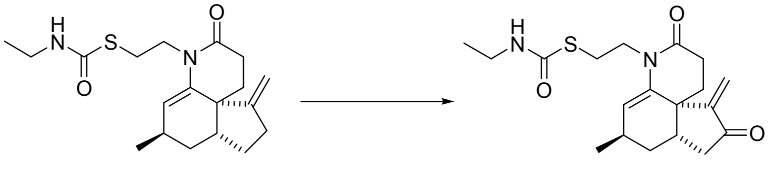
IR (neat): 3290, 2930 2360, 1651, 1525 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (br s, 1H), 3.73-3.66 (m, 2H), 3.29-3.26 (m, 2H), 2.93-2.89 (m, 2H), 2.44-1.99 (m, 8H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.83-1.65 (m, 3H), 1.53-1.20 (m, 3H), 1.11 (t, *J* = 7.3 Hz, 3H), 0.99 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 167.8, 133.0, 119.5, 85.6, 70.2, 42.6, 38.3, 37.7, 35.1, 34.8, 33.4, 33.1, 29.5, 26.0, 25.3, 22.9, 18.3, 16.3. Additional signals associated with the minor isomer: δ 170.7, 170.4, 138.8, 129.8, 128.0, 112.9, 85.4, 70.1, 41.7, 35.6, 34.5, 34.0, 29.2, 26.6, 17.5, 15.7. MS (APCI): 349 $(M + H)^+$. Anal. Calcd for $C_{19}H_{28}N_2O_2S$: C, 65.48; H, 8.10; N, 8.04. Found: C, 65.22; H, 8.10; N, 7.78. $[\alpha]^{20}_{D} = +24^{\circ}$ (c = 0.57, $CHCl_3$).



S-2-((9R)-9-Methyl-5-methylene-2-oxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[e]quinolin-1(2H)-yl)ethyl ethylcarbamothioate (2.125)

A solution containing 3.33 g of compound **2.124** (9.57 mmol) and 0.255 g of platinum(II) chloride (0.957 mmol) in 35 mL of toluene was heated to 90 °C and stirred for 5 h. The reaction mixture was then cooled to rt and filtered through a plug of triethylamine washed silica gel. The filtrate was concentrated by rotary evaporation *in vacuo* to give a thick brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1→0:1 hexanes:ethyl acetate) to afford 2.91 g (87 %) of the title compound **2.125** as a yellow foam.

IR (neat): 3288, 2955, 2244, 1657, 1631, 1527 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (br s, 1H), 5.45 (d, *J* = 3.5 Hz, 1H), 4.87 (s, 1H), 4.63 (s, 1H), 4.02-3.95 (m, 1H), 3.74-3.67 (m, 1H), 3.29 (t, *J* = 5.7 Hz, 2H), 3.00-2.98 (m, 2H), 2.51-2.30 (m, 5H), 2.03-1.95 (m, 2H), 1.79-1.75 (m, 1H), 1.57-1.45 (m, 2H), 1.38-1.33 (m, 1H), 1.22-1.17 (m, 1H), 1.12 (t, *J* = 7.0, 3H), 0.99 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 167.5, 154.3, 139.0, 112.7, 109.3, 49.3, 45.6, 41.8, 37.3, 33.5, 30.3, 29.7, 29.4, 29.3, 27.6, 27.4, 22.4, 15.9. MS (APCI): 349 $(M + H)^+$, 371 $(M + Na)^+$. $[\alpha]^{21}_{D} = +92^{\circ}$ (c = 0.99, $CHCl_3$).

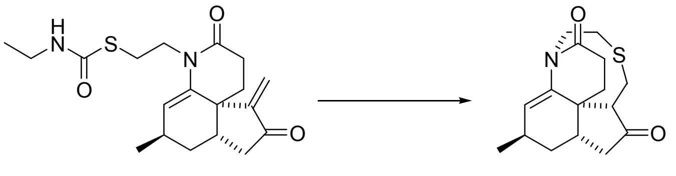


2.125 **2.126**

S-2-((9*R*)-9-Methyl-5-methylene-2,6-dioxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2H)-yl)ethyl ethylcarbamothioate (2.126)

A solution of 0.11 g of annulation product **2.125** (0.30 mmol) and 0.034 g of selenium dioxide (0.30 mmol) in 7 mL of 1,4-dioxane was heated to 85 °C and stirred for 1.75 h. The resulting brown solution was cooled to rt and the solvents were removed *in vacuo* to give a red-brown residue. The residue was purified by column chromatography on triethylamine washed silica gel (3:1→1:1→1:2→0:1 hexanes:ethyl acetate) to afford 0.060 g (54 %) of the title compound **2.126** as a pale yellow oil.

IR (neat): 3290, 2932, 2360, 1728, 1667, 1636, 1524 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H), 5.80 (br s, 1H), 5.66 (d, *J* = 4.8 Hz, 1H), 5.20 (s, 1H), 4.09-4.02 (m, 1H), 3.78-3.70 (m, 1H), 3.33 (qt, *J* = 6.1 Hz, 2H), 3.10-3.01 (m, 2H), 2.75 (dd, *J* = 18.7, 7.4 Hz, 1H), 2.60-2.30 (m, 4H), 2.15 (s, 1H), 1.91-1.79 (m, 2H), 1.44-1.41 (m, 2H), 1.16 (t, *J* = 7.4 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.9, 169.4, 167.4, 149.0, 138.5, 120.6, 113.3, 46.7, 46.0, 42.8, 37.4, 36.1, 34.0, 30.3, 29.8, 29.0, 27.5, 22.3, 15.9. MS (ESI): 385 $(M + Na)^+$. $[\alpha]^{20}_{D}$ = +40.6° (c = 1.58, $CHCl_3$).



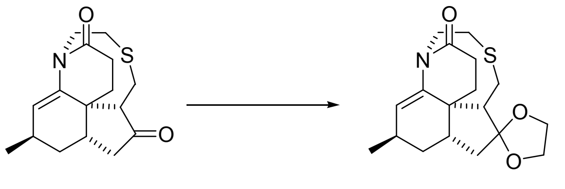
2.126 **2.127**

Sulfide (2.127)

A solution of 134 mg of enone **2.126** (0.37 mmol) in 20 mL of freshly sparged 1 M NaOH and 5 drops of dry dichloromethane was stirred vigorously for 12 h. The aqueous solution was extracted five times with dichloromethane. The combined organic fractions were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a clear oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1→1:2→0:1

hexanes:ethyl acetate) to yield 82.0 mg (76 %) of sulfide **2.127** as a white solid, mp: 155 °C (dec).

IR (film): 2928, 1734, 1636 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (d, *J* = 4.3 Hz, 1H), 4.71-4.64 (m, 1H), 3.36 (dt, *J* = 13.4, 4.6 Hz, 1H), 3.00-2.87 (m, 3H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.65-2.58 (m, 3H), 2.51 (d, *J* = 9.4 Hz, 1H), 2.36 (septet, *J* = 4.7 Hz, 1H), 2.17 (dd, *J* = 18.6, 4.3 Hz, 1H), 2.00-1.97 (m, 2H), 1.60-1.51 (m, 2H), 1.11 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.9, 169.9, 139.1, 120.6, 78.2, 61.5, 44.1, 43.5, 38.9, 37.1, 34.5, 33.6, 31.3, 29.6, 28.1, 22.1. MS (APCI): 292 $(M + H)^+$. $[\alpha]^{21}_{D}$ = +335° (c = 0.75, $CHCl_3$).

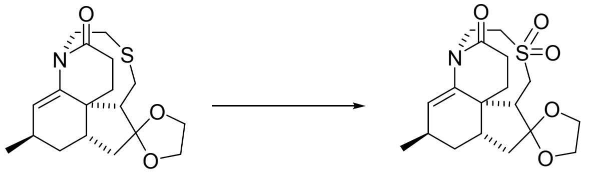


2.127 **2.129**

Ketal (2.129)

A solution of 0.35 g of sulfide **2.127** (1.2 mmol), 0.30 g of pyridinium *p*-toluenesulfonate (1.2 mmol), and 0.40 mL of ethylene glycol (7.1 mmol) in 15 mL of benzene was heated to reflux using a Dean-Stark apparatus. The reaction was refluxed with stirring for 30 h. It was then cooled to rt, diluted with diethyl ether, and poured into a solution of saturated sodium bicarbonate. The aqueous layer was separated and subsequently extracted three times with ethyl acetate. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated to yield a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→0:1 hexanes:ethyl acetate) to afford 0.35 g (87 %, 93 % BRSM) of ketal **2.129** as a pale yellow oil.

IR (neat): 2926, 1636 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.24 (d, *J* = 3.1 Hz, 1H), 4.66 (ddd, *J* = 13.7, 11.3, 5.9 Hz, 1H), 3.93-3.78 (m, 4H), 3.30 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.09 (d, *J* = 14.8 Hz, 1H), 3.05-2.97 (m, 1H), 2.82-2.57 (m, 3H), 2.38-2.32 (m, 1H), 2.23-2.06 (m, 4H), 1.92-1.85 (m, 1H), 1.80-1.57 (m, 3H), 1.41-1.33 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 140.4, 120.0, 116.6, 65.6, 64.8, 57.8, 44.5, 41.6, 41.2, 40.2, 35.3, 34.4, 34.2, 34.1, 30.3, 27.3, 22.4. MS (ESI): 358 $(M + Na)^+$. Anal. Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; H, 7.51; N, 4.18. Found: C, 64.36; H, 7.58; N, 3.99. $[\alpha]^{21}_{D}$ = + 206° (c = 0.26, $CHCl_3$).

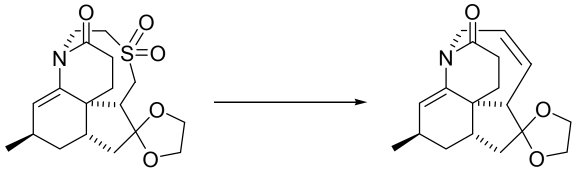


2.129 **2.130**

Sulfone 2.130

To a solution of 0.014 g of ketal **2.129** (0.042 mmol) in 1.5 mL of dichloromethane at −78 °C was added dropwise a solution of 0.021 g of *m*-chloroperbenzoic acid (0.12 mmol) in 2.5 mL of dichloromethane. The white suspension was stirred for 0.25 h at −78 °C, warmed to rt and stirred for a subsequent 2.5 h. The reaction mixture was diluted with dichloromethane, washed once with a saturated solution of sodium bicarbonate, once with a saturated solution of sodium bisulfite, and once with brine. The combined aqueous fractions were extracted once with dichloromethane. The combined organics were dried over sodium sulfate, filtered, and concentrated to afford a white film. The crude product was purified by column chromatography on triethylamine washed silica gel (1:1→0:1 hexanes:ethyl acetate) to afford 0.015 g (98 %) of sulfone **2.130** as a clear oil.

IR (neat): 2931, 1717, 1646 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.41 (d, *J* = 3.9 Hz, 1H), 5.22 (ddd, *J* = 14.6, 12.4, 6.1 Hz, 1H), 4.02-3.80 (m, 5H), 3.46 (d, *J* = 16.1, 1H), 3.34 (dd, *J* = 14.4, 5.8 Hz, 1H), 3.20-3.15 (m, 1H), 3.05-2.98 (m, 1H), 2.70-2.61 (m, 2H), 2.51-2.41 (m, 3H), 2.28-2.11 (m, 2H), 1.75-1.66 (m, 2H), 1.62-1.56 (m, 2H), 1.09 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 139.1, 119.9, 116.4, 65.7, 65.4, 58.3, 53.6, 48.0, 45.3, 41.4, 40.1, 37.0, 35.5, 33.9, 30.4, 28.2, 22.1. MS (APCI): 368 (M + H)$^+$. $[\alpha]^{20}_{D}$ = +149° (c = 1.23, CHCl$_3$).

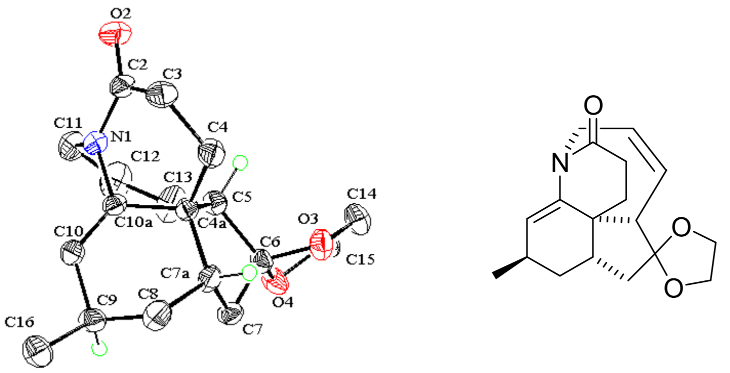


2.130 **2.131**

Olefin 2.131

A suspension of 0.031 g of sulfone **2.130** (0.084 mmol) and 0.30 g of alumina-supported potassium hydroxide in 1.75 mL of *tert*-butyl alcohol and 0.75 mL of dichloromethane was cooled to −15 °C. To the cold suspension was slowly added 0.1 mL of dibromodifluoromethane (1.1 mmol). The reaction mixture was stirred at −15 °C for 2.2 h and warmed to rt. The mixture was filtered over Celite®, rinsing exhaustively with dichloromethane, and concentrated to give a yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:0→3:1→1:1→0:1 hexanes:ethyl acetate) to afford 0.012 g (46 %) of olefin **2.131** as a clear film.

IR (neat): 2958, 1695, 1661 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65-5.62 (m, 1H), 5.54 (s, 1H), 5.39-5.35 (m, 1H), 5.04-5.00 (m, 1H), 3.95-3.89 (m, 4H), 3.62 (dd, *J* = 17.5, 2.0 Hz, 1H), 2.51-2.33 (m, 3H), 2.31-2.14 (m, 3H), 1.95-1.88 (m, 1H), 1.75-1.61 (m, 3H), 1.34 (ddd, *J* = 13.6, 10.8, 5.2 Hz, 1H), 1.04 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 141.6, 129.1, 127.1, 125.4, 116.5, 65.7, 64.4, 54.4, 51.0, 50.5, 41.1, 39.4, 37.2, 32.2, 31.3, 26.6, 22.3. MS (APCI): 302 $(M + H)^+$. $[\alpha]^{21}_{D}$ = +142° (c = 0.27, $CHCl_3$).



ORTEP representation of the solid state structure of **2.131**

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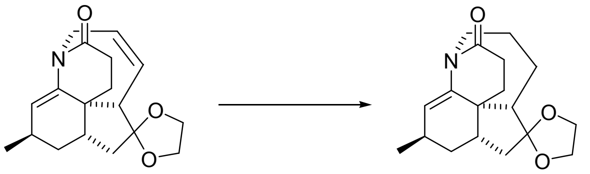
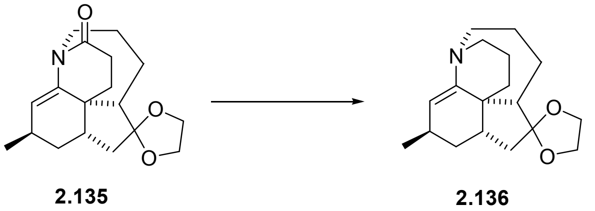


2.131 **2.135**

Enamide 2.135

The nitrogen atmosphere of a solution of 0.026 g of olefin **2.131** (0.086 mmol) and 9.0 mg of 5 % palladium on carbon (0.0043 mmol) in 3 mL of a 1:1 ethyl acetate:THF mixture was replaced by purging with hydrogen gas. A full hydrogen balloon was then attached and the reaction mixture was stirred at rt for 12 h. The black suspension was filtered through Celite®, rinsing exhaustively with methanol. The solution was then concentrated to give a yellow film. The crude film was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→1:5→0:1 hexanes:ethyl acetate) to afford 0.015 g (57 %) of enamide **2.135** as a white solid.

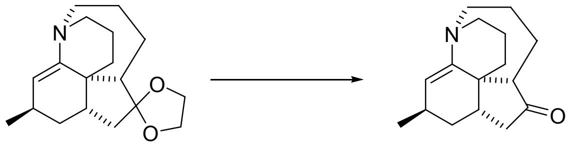
IR (film): 2927, 1738, 1688, 1657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (s, 1H), 4.38 (dt, *J* = 12.8, 3.0 Hz, 1H), 3.93-3.83 (m, 4H), 2.87 (ddd, *J* = 13.3, 9.3, 6.4 Hz, 1H), 2.40-2.20 (m, 4H), 2.16-2.09 (m, 1H), 1.95-1.85 (m, 2H), 1.78-1.57 (m, 6H), 1.34-1.25 (m, 2H), 1.05 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 143.0, 126.4, 115.8, 64.8, 63.5, 57.5, 49.9, 47.6, 41.5, 37.8, 37.6, 31.5, 31.3, 28.7, 28.3, 25.8, 21.5. MS (APCI): 304 $(M + H)^+$. $[\alpha]^{20}_{D}$ = +106° (c = 0.76, $CHCl_3$).



Enamide 2.136

To a suspension of 0.018 g of lithium aluminum hydride (0.48 mmol) in 2 mL of THF was added a solution of 0.015 g of enamide **2.135** (0.048 mmol) in 2 mL of THF. The reaction mixture was heated to reflux and stirred for 8 h. The grey suspension was cooled to rt, followed by the slow addition of 18 μL of water, 16 μL of 15 % NaOH, then another 54 μL of water. The biphasic mixture was stirred for 15 minutes at rt after which 0.2 g of magnesium sulfate was added. After stirring for another 30 minutes at rt, the mixture was filtered through a pad of Celite® and rinsed exhaustively with diethyl ether. The filtrate was concentrated *in vacuo* to afford a clear film. The crude product was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→1:5→0:1 hexanes:ethyl acetate) to afford 9.8 mg (71 %) of enamine **2.136** as a clear oil.

IR (neat): 2925, 2852, 1656, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (d, *J* = 1.7 Hz, 1H), 3.95-3.87 (m, 4H), 3.09-2.96 (m, 4H), 2.20-2.18 (m, 1H), 1.98-1.84 (m, 4H), 1.78-1.44 (m, 7H), 1.26-1.11 (m, 3H), 0.98 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 129.0, 117.3, 65.6, 64.4, 60.8, 56.3, 53.0, 46.8, 43.1, 40.5, 38.9, 33.3, 33.0, 30.0, 27.0, 25.2, 22.6. MS (APCI): 290 $(M + H)^+$. $[\alpha]^{20}_{D}$ = +91° (c = 0.95, $CHCl_3$).


2.136 **2.5**

(+)-Fawcettidine (2.5)

To a solution of 5.0 mg of enamine **2.136** (0.018 mmol) in 0.5 mL of THF at 0 °C was added 0.05 mL of 1 M HCl. The solution was stirred at rt for 17 h. The reaction mixture was neutralized with 0.05 mL of 1 M NaOH and then extracted twice with ethyl acetate. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (1:1→1:3→0:1 hexanes:ethyl acetate) to afford 3.0 mg (60 %) of (+)-fawcettidine (**2.5)** as a clear oil.

IR (neat): 2925, 2853, 1741, 1663 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.69 (d, *J* = 5.2 Hz, 1H), 3.14-2.98 (m, 4H), 2.74 (ddd, *J* = 16.6, 7.4, 1.3 Hz, 1H), 2.34-2.24 (m, 2H), 2.20-2.05 (m, 3H), 1.99-1.93 (m, 1H), 1.91-1.83 (m, 1H), 1.79-1.59 (m, 3H), 1.41-1.34 (m, 2H), 1.28-1.21 (m, 2H), 1.05 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 219.9, 147.0, 128.2, 61.4, 57.2, 53.0, 47.1, 45.1, 40.2, 38.3, 35.1, 32.4, 30.2, 28.7, 24.8, 21.8. MS (APCI): 246 (M + H)$^+$. $[\alpha]^{21}_D$ = +92° (c = 0.41, CHCl$_3$), $[\alpha]^{19}_D$ = +61° (c = 0.25, EtOH).

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Chapter 3: Enamides as Nucleophiles: Formation of Complex Ring Systems through a Platinum(II)-Catalyzed Addition/Friedel-Crafts Pathway[2]

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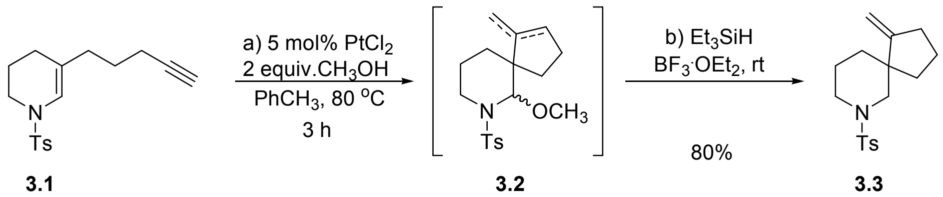
[2] Some material in this chapter has been published. See: Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. "Enamides and Enesulfonamides as Nucleophiles: Formation of Complex Ring Systems through a Platinum(II)-Catalyzed Addition/Friedel-Crafts Pathway" *J. Org. Chem.* **2009**, *74*, 6929-6935.

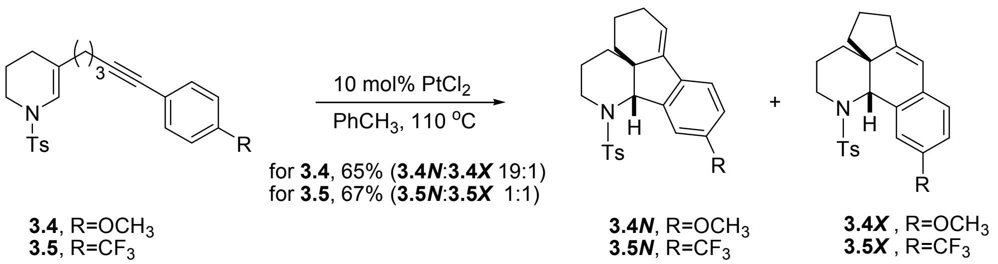
3.1 Introduction

The Dake group is interested in using enamides, enecarbamates, and enesulfonamides as nucleophiles in transition metal-catalyzed cycloisomerization reactions. Initial cycloisomerization reactivity was probed using tetrahydropyridine ring systems with an alkyne tethered at the 4-position, as described in the introductory chapter.[1] These investigations proved successful in forming structurally complex nitrogen-containing ring systems. The scope was therefore extended to substrates bearing the tethered alkyne at the 3-position of the tetrahydropyridine, or the β-position of the enesulfonamide.[2] Exchange of the proton at the β-position for an alkyl tether generates a quaternary carbon center upon cyclization. As an example, Dake and coworkers found that enesulfonamide **3.1** reacted with 5 mol% of platinum(II) chloride, resulting in a 5-*exo-dig* cyclization (Scheme 3.1). The putative azacarbenium ion was trapped using methanol to give compound **3.2**. Although compound **3.2** was isolable, the resulting 1:1 diastereomeric mixture made characterization difficult. A one-pot procedure was therefore developed to reduce the methoxy functionality to give spirocycle **3.3**.



Scheme 3.1: Platinum(II)-catalyzed synthesis of quaternary carbon centers[2]

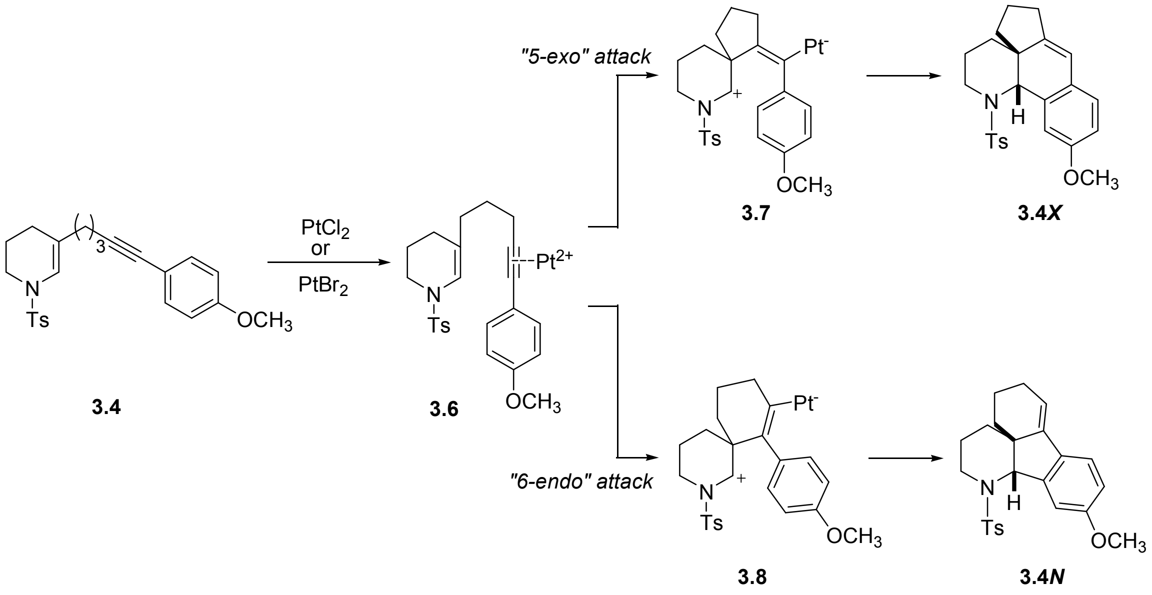
As discussed in section 1.6, pendent aromatic rings attack electrophilic sites by undergoing a Friedel-Crafts reaction. Dake and coworkers wanted to harness the electrophilicity of the intermediary azacarbenium ion in a similar manner. Friedel-Crafts/Pictet-Spengler-type cyclization of an aromatic ring onto the azacarbenium ion would greatly increase the structural complexity of the products formed (i.e., from bicycles to tetracycles). A series of enesulfonamides with arene-substituted alkynes were synthesized to test this reactivity (Scheme 3.2).[2] Enesulfonamide **3.4** with an electron-rich arene ring cycloisomerized to give tetracyclic products **3.4*N*** and **3.4*X*** in 65% yield and a regioisomeric ratio of 19:1. Enesulfonamide **3.5** bearing an electron-withdrawing arene ring cycloisomerized to give tetracyclic products **3.5*N*** and **3.5*X*** in 67% yield and a ratio of 1:1. The isomers were not separable by standard purification techniques. Since a substrate containing an electron-donating aromatic group cyclized with high selectivity, the process became synthetically useful.



10 mol% $PtCl_2$
$PhCH_3$, 110 °C
for **3.4**, 65% (**3.4*N*:3.4*X*** 19:1)
for **3.5**, 67% (**3.5*N*:3.5*X*** 1:1)
3.4, R=OCH_3
3.5, R=CF_3
3.4*N*, R=OCH_3
3.5*N*, R=CF_3
3.4*X*, R=OCH_3
3.5*X*, R=CF_3
N
Ts
H
R
3
+

Scheme 3.2: Platinum(II)-catalyzed cyclization to form tetracyclic products[2]

As shown in Scheme 3.2, two products result from the platinum(II)-catalyzed cyclization of enamides **3.4** and **3.5**. The regioisomeric products come from either an initial 5-*exo-dig* cyclization or a 6-*endo-dig* cyclization (Scheme 3.3). Enesulfonamide **3.4** first reacts with a platinum(II) salt to form an activated η^2 platinum-alkyne π-complex **3.6**. Attack of the nucleophilic enesulfonamide occurs at one of the two carbons of the alkyne. The nucleophile can attack in a 5-*exo-dig* mode of cyclization to form intermediate **3.7**. Alternatively, the nucleophile can attack in a 6-*endo-dig* fashion to form intermediate **3.8**. Both intermediates **3.7** and **3.8** then undergo Friedel-Crafts cyclization and protodemetallation to give either the "5-*exo*" tetracyclic product **3.4*X*** or the "6-*endo*" tetracyclic product **3.4*N***.

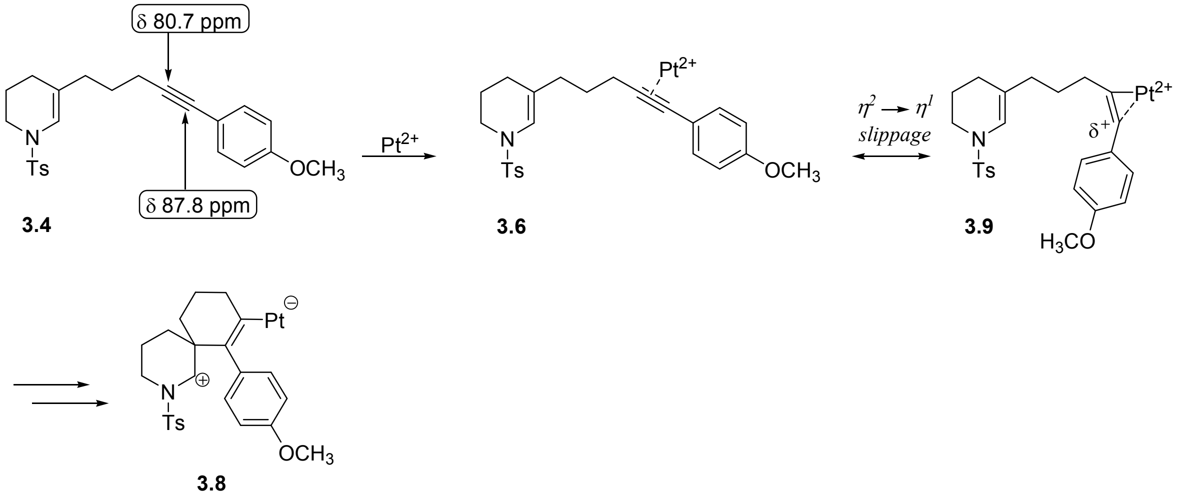


"5-exo" attack
"6-endo" attack
$PtCl_2$
or
$PtBr_2$
Pt^{2+}
Pt^-
OCH_3
N
Ts
H
3
+
3.4
3.6
3.7
3.8
3.4*X*
3.4*N*

Scheme 3.3: Formation of regioisomeric products

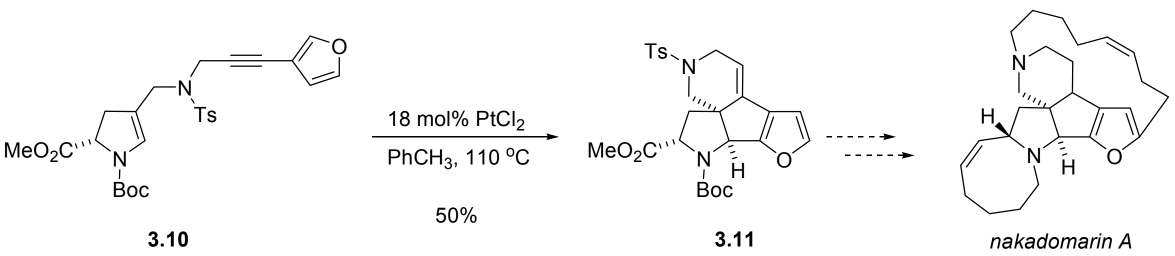
The suffixes "***N***" and "***X***" are used in the numbering system throughout this chapter and are derived as follows: products that results from an initial 6-*endo-dig* cyclization of the enamide to the alkyne are given the suffix "***N***", while products that derive from an intial 5-*exo-dig* cyclization are giving the suffix "***X***".

The majority of transition metal-catalyzed cycloisomerization reactions occur in a 5-*exo-dig* mode of cyclization, but can depend on the substituents on the alkyne.[3, 4] The tandem platinum(II)-catalyzed addition/Friedel-Crafts reaction developed by Dake depends specifically on the nature of the substituents located on the arene ring. Enesulfonamide **3.4** contains an electron-rich aromatic ring that pushes electron density onto the alkyne in a non-uniform manner (Scheme 3.4). The carbon closest to the aromatic ring (i.e., the proximal carbon) has a signal in the ^{13}C NMR spectrum with a chemical shift of 87.8 ppm. The ^{13}C NMR signal of the alkynyl carbon furthest from the aromatic ring (i.e., the distal carbon) has a chemical shift of 80.7 ppm. These chemical shifts reflect the electron density distribution in the alkyne. The majority of the electron density resides on the distal carbon due to a resonance contribution from the *para*-methoxy substituent on the arene ring. When a platinum(II) salt coordinates to the alkyne as in **3.6**, it slips along the alkyne to interact more strongly with the carbon that features more electron density (**3.9**). The partial positive character is associated with the proximal carbon atom. The nucleophile attacks at this position, resulting in a 6-*endo-dig* cyclization to give intermediate **3.8**.



Scheme 3.4: Rationale for observed isomer ratio of product

An application of the methodology developed by Dake is demonstrated in the core synthesis of the natural product nakadomarin A by Zhai and coworkers (Scheme 3.5).[5] Highly functionalized enecarbamate **3.10** with a pendant alkynyl furan moiety was treated with 18 mol% of platinum(II) chloride to give tetracyclic product **3.11** in a 50% yield. The authors speculate that the poor yield is due to substrate instability at the reaction temperature. To circumvent this, the substrate was added slowly via syringe pump. Despite the high catalyst loading and the moderate yield, the authors were successful in applying this methodology to complete the core of the complex natural product nakadomarin A.



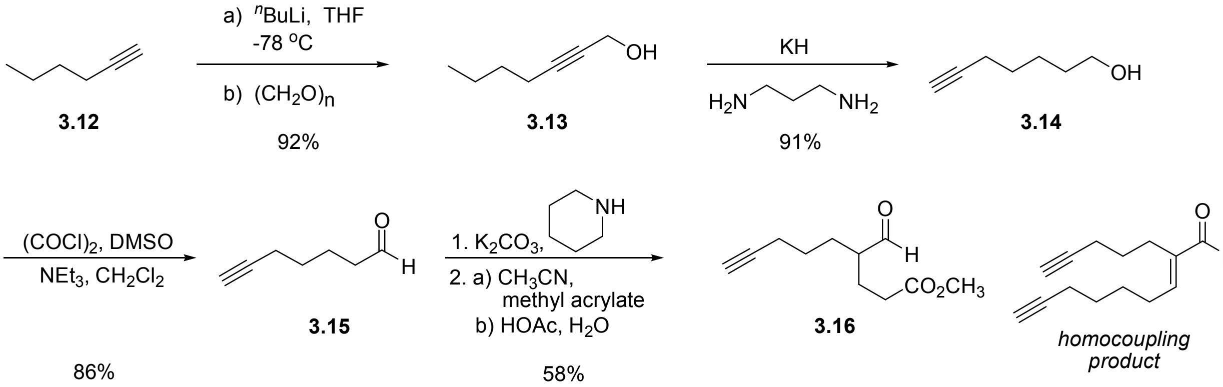
Scheme 3.5: Zhai and coworkers: Platinum(II)-catalyzed cycloisomerization towards the total synthesis of nakadomarin A[5]

A goal of my PhD research was to expand the scope of the tandem platinum(II)-catalyzed addition/Friedel-Crafts reaction described by Scheme 3.2. The remainder of this chapter will be divided into 3 sections. The next section will describe the synthesis of the substrates, with the following section describing the reactions of the substrates within the context of cycloisomerization reactions. The final section will disclose the experimental results for the reactions described in the previous sections.

3.2 Substrate Synthesis

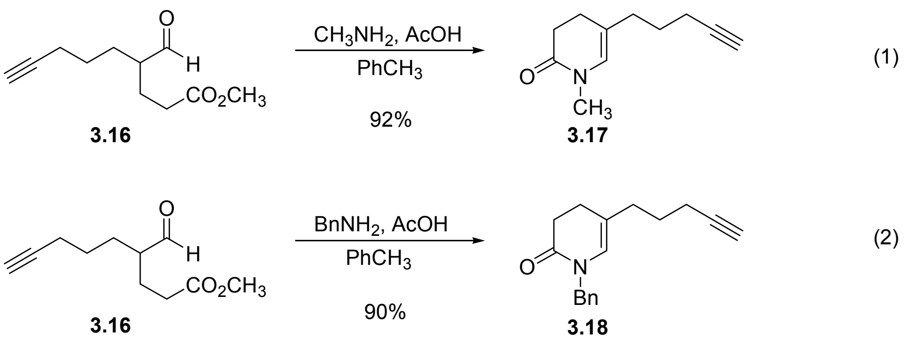
Aldehyde **3.16** was synthesized from commercially available 1-hexyne (**3.12**) in 4 steps (Scheme 3.6). 1-Hexyne (**3.12**) was homologated by deprotonation of the acetylenic proton and treated with paraformaldehyde to yield propargyl alcohol **3.13**. An acetylenic zipper reaction of alcohol **3.13** with potassium 3-aminopropylamide[6-9] (*KAPA* reagent: potassium hydride + 1,3-diaminopropane) gave 6-heptyn-1-ol (**3.14**) in 91% yield, as indicated by the appearance of a triplet at 1.94 ppm in the ^{1}H NMR spectrum attributed to the acetylenic proton. 6-Heptyn-1-ol

(**3.14**) was oxidized to aldehyde **3.15** in 86% yield using the Moffatt-Swern method. Following the procedure of Norman and Heathcock,[10] aldehyde **3.15** was converted into methyl ester **3.16** in 58% yield. The enamine of aldehyde **3.15**, created by treatment with piperidine under basic conditions, was added to methyl acrylate, a Michael acceptor. Acidic workup provided methyl ester **3.16**. All reagents and glassware were rigorously dried to ensure the success of the reaction, as water present in the reaction mixture led to a large amount of homocoupling product.


a) ^{n}BuLi, THF
-78 °C
b) $(CH_2O)_n$
92%
3.12
3.13
KH
H_2N NH_2
91%
3.14
$(COCl)_2$, DMSO
NEt_3, CH_2Cl_2
86%
3.15
1. K_2CO_3,
NH
2. a) CH_3CN,
methyl acrylate
b) HOAc, H_2O
58%
3.16
CO_2CH_3
OH
O
H
homocoupling product

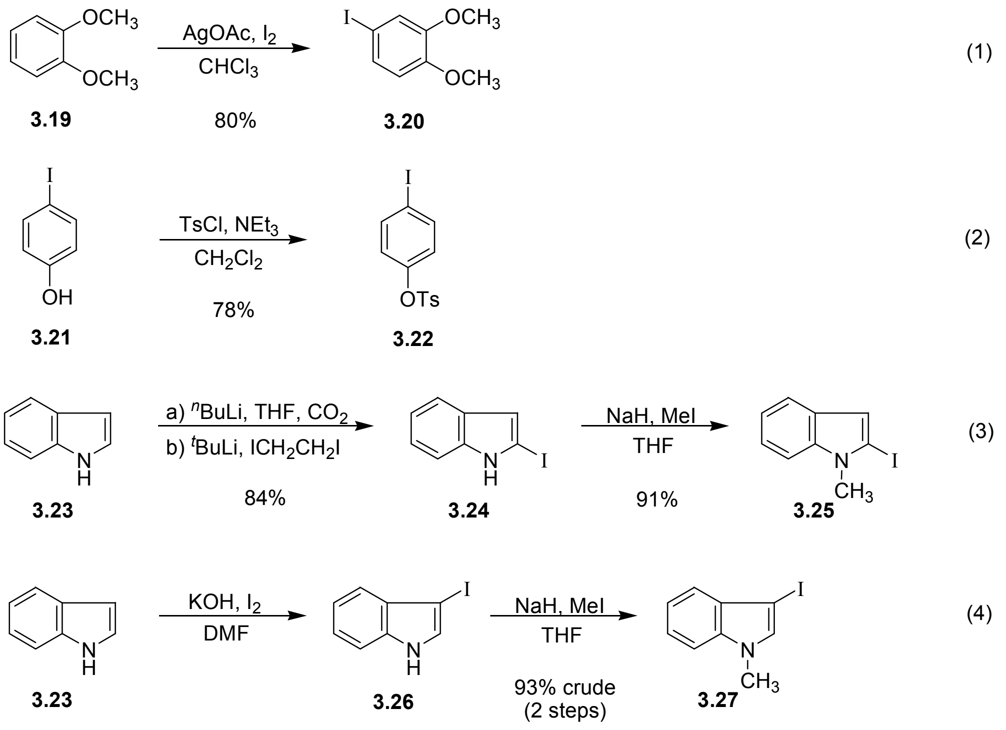
Scheme 3.6: Synthetic route for the construction of alkyne **3.16**

The synthetic route towards the cyclization substrates diverged at this point. Methyl ester **3.16** was used to synthesize both enamides **3.17** and **3.18** (Scheme 3.7). Condensation of ester **3.16** with either methylamine (eq 1) or benzylamine (eq 2) and acetic acid in toluene under dehydrating conditions gave enamides **3.17** and **3.18** in excellent yield. The formation of the product was verified by the disappearance of the signal attributed to the aldehyde proton in the ^1H NMR spectrum and the appearance of the enamide signal at 5.76 ppm and 5.81 ppm for **3.17** and **3.18**, respectively.


O
H
CO_2CH_3
3.16
CH_3NH_2, AcOH
$PhCH_3$
92%
O
N
CH_3
3.17
(1)
O
H
CO_2CH_3
3.16
$BnNH_2$, AcOH
$PhCH_3$
90%
O
N
Bn
3.18
(2)

Scheme 3.7: Condensation with primary amines to form enamides **3.17** and **3.18**

With enamides **3.17** and **3.18** in hand, the route again diverged to form the cycloisomerization substrates. The alkyne functionality of the enamides was coupled with various commercially available and non-commercially available aryl iodides. The non-commercially available iodides were synthesized according to Scheme 3.8. 4-Iodo-1,2-dimethoxybenzene (4-iodoveratrole, **3.20**) was synthesized in 80% yield from 1,2-dimethoxybenzene (veratrole, **3.19**) by treatment with silver acetate and iodine (Scheme 3.8, eq 1). This reaction was successfully performed on a 40 gram scale. 4-Iodophenyl 4-methylbenzenesulfonate (**3.22**) was synthesized in 78% yield by the treatment of 4-iodophenol (**3.21**) with *para*-toluenesulfonyl chloride and triethylamine (Scheme 3.8, eq 2). 2-Iodo-1-methyl-1*H*-indole **3.25** was synthesized in two steps from indole (**3.23**) (Scheme 3.8, eq 3). The nitrogen was first protected as the lithium carboxylate, and the 2-position was deprotonated with *tert*-butyllithium. The anion was finally quenched with 1,2-diiodoethane to give 2-iodoindole (**3.24**). Product formation was indicated by a 1-proton doublet at 6.74 ppm in the ^{1}H NMR spectrum attributed to the proton at the 3-position of compound **3.24**. Protection of the nitrogen using sodium hydride and methyl iodide gave the product **3.25** in 91% yield. 3-Iodo-1-methyl-1*H*-indole (**3.27**) was also synthesized in 2 steps from indole (**3.23**) (Scheme 3.8, eq 4). Indole (**3.23**) was treated with potassium hydroxide and iodine in *N*,*N*-dimethylformamide to give 3-iodoindole **3.26**. This product was unstable and decomposed rapidly; it was therefore treated directly with sodium hydride and methyl iodide to protect the nitrogen, yielding **3.27** in 93% crude yield over 2 steps. Even with the nitrogen protected, iodoindole **3.27** was generally less stable than the 2-substituted version (**3.25**).

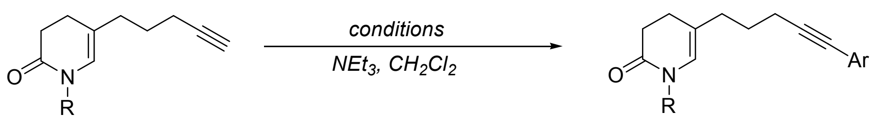

OCH3
OCH3
AgOAc, I2
CHCl3
80%
I
OCH3
OCH3
3.19
3.20
(1)
I
OH
TsCl, NEt3
CH2Cl2
78%
I
OTs
3.21
3.22
(2)
N
H
a) nBuLi, THF, CO2
b) tBuLi, ICH2CH2I
84%
N
H
I
NaH, MeI
THF
91%
N
CH3
I
3.23
3.24
3.25
(3)
N
H
KOH, I2
DMF
I
N
H
NaH, MeI
THF
93% crude
(2 steps)
I
N
CH3
3.23
3.26
3.27
(4)

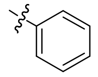
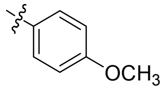
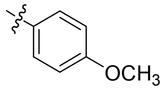
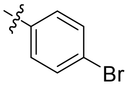
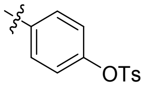
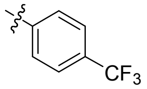
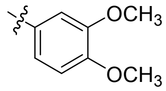
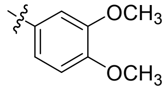
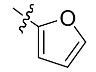
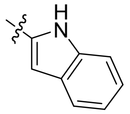
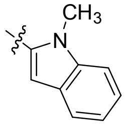
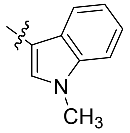
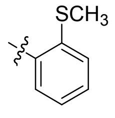
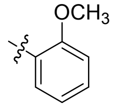
Scheme 3.8: Synthesis of non-commercially available aryl iodides

Enamides **3.17** and **3.18** were coupled with aryl iodides and aryl bromides using a Sonogashira coupling reaction (Table 3.1).[11] The reactions were run using 5 mol% of bis(triphenylphosphine)palladium(II) chloride and 10 mol% of copper(I) iodide in a dichloromethane-triethylamine solvent mixture, and were typically complete within 1-5 hours. Bromo-substituted coupling partners were not as reactive as iodide-substituted aromatics (entry 9). The reaction using 2-bromofuran had to be stirred for 24 hours before the reaction was complete. The reactions generally proceeded with good to excellent yields. The instability of the 3-iodo-1-methyl-1*H*-indole (**3.27**) (entry 12) is likely the reason for the low yield of the reaction.

Product formation was verified by the disappearance of the acetylenic proton at 1.94 ppm in the ^{1}H NMR spectrum for enamides **3.17** and **3.18** and the appearance of signals corresponding to the aromatic substituent employed. The enamide proton of the Sonogashira coupling products persisted in the ^{1}H NMR spectrum between 5.76 and 5.87 ppm for *N*-methyl substituted enamides and 5.81 and 5.85 ppm for the *N*-benzyl substituted enamides. With the successful installation of the aromatic functionality, the substrates were tested with platinum(II) chloride and platinum(II) bromide for cycloisomerization reactivity.

Table 3.1: Sonogashira coupling reactions of enamides

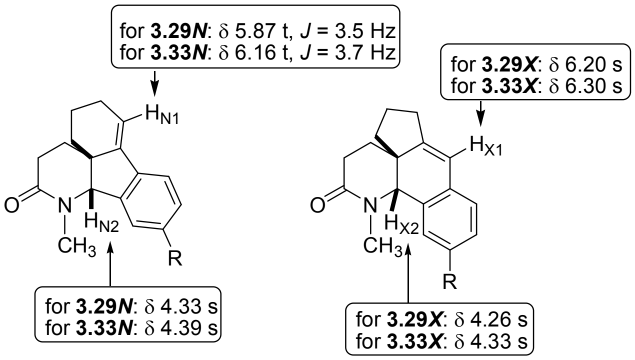


entry	substrate	R	conditions	product	Ar	yield (%)[a,b]
1	**3.18**	Bn	C_6H_5-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.28**		89
2	**3.17**	CH_3	(*p*-CH_3O)C_6H_4-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.29**		86
3	**3.18**	Bn	(*p*-CH_3O)C_6H_4-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.30**		59
4	**3.17**	CH_3	(*p*-Br)C_6H_4-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.31**		87
5	**3.17**	CH_3	**3.22**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.32**		56
6	**3.17**	CH_3	(*p*-CF_3)C_6H_4-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.33**		91
7	**3.17**	CH_3	**3.20**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.34**		69
8	**3.18**	Bn	**3.20**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.35**		92
9[c]	**3.17**	CH_3	Br-C_4H_3O, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.36**		95
10	**3.17**	CH_3	**3.24**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.37**		67
11	**3.17**	CH_3	**3.25**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.38**		94
12	**3.17**	CH_3	**3.27**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.39**		32
13	**3.17**	CH_3	(*o*-SCH_3)C_6H_4-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.40**		92
14	**3.17**	CH_3	(*o*-OCH_3)C_6H_4-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**3.41**		81

[a]Reported yields are isolated yields. [b]Reported yields are the maximum of single experiments. [c]1-bromofuran was synthesized by Dake group member Jennifer Dodd.

3.3 Reactions of Substrates

Platinum(II)-catalysis was tested on all enamide derivatives. The reactions were run with 10 mol% of platinum catalyst in toluene (0.2 M) in a thick-walled sealable tube at 110 °C (temperature of the oil bath). The reactions could not be tested for completion by thin layer chromatography, therefore a standard time of 16 hours was imposed for each reaction based on literature precedent.[2] The isomeric products of the reaction are not separable by column chromatography, therefore the amount of each isomer is measured based on the integration of key signals in the ^{1}H NMR spectrum. The signals were compared to previously reported values to confirm the formation of the products.[2] Distinguishing signals for the protons of each isomer are presented in Figure 3.1. The diagnostic signals are those attributed to the vinyl protons H_{N1} and H_{X1} and those for the benzylic protons H_{N2} and H_{X2}. The vinylic proton H_{N1} is a 1-proton triplet with a chemical shift varying between 5.87 ppm and 6.16 ppm and a characteristic coupling constant of approximately 3.6 Hz. The benzylic proton H_{N2} is a 1-proton singlet of between 4.30 and 4.40 ppm. The vinylic proton H_{X1} is shifted downfield relative to vinylic proton H_{N1}. The vinylic proton H_{X2} is a singlet between 6.20 and 6.30 ppm. The structures for products **3.33*N*** and **3.33*X*** were unambiguously characterized by X-ray crystallography.



3.29*N*, R=OCH_3
3.33*N*, R=CF_3

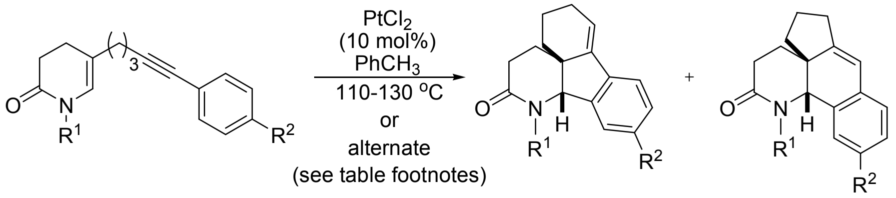
3.29*X*, R=OCH_3
3.33*X*, R=CF_3

Figure 3.1: Diagnostic signals in sample ^{1}H NMR analysis of **3.29*N*/3.33*X*** and **3.29*N* /3.33*X***

The first substrates tested were those with either *para*-substituted or unsubstituted aromatic rings on the alkyne functional group. The results are summarized in Table 3.2. All reactions were treated under the standard platinum(II)-catalysis conditions unless otherwise noted. The products of reactions carried out under platinum(II) chloride catalysis were generally isolated in good yield (entries 1, 3, 9-12). Less reactive substrates had to be heated to 130 °C instead of 110

°C to complete the reaction in 16 hours (entries 10 and 12). Reactions involving substrates with an unsubstituted arene ring resulted in ratios modestly favoring the 6-*endo* product (entries 1 and 2). When R^2 = OCH_3, the amount of 6-*endo* product formed increases (entries 3, 4 and 9). Electron-withdrawing groups on the aromatic ring decrease the reactivity of the substrate and the selectivity of the reaction (entries 10 and 11). Interestingly, aryl bromide **3.31** underwent cyclization under the reaction conditions, portraying the distinct behavior between platinum(II)- and palladium(0)-catalysis. Substrates with strongly electron-withdrawing groups also show decreased reactivity and favor the 5-*exo* isomer in a 1:2 6-*endo*:5-*exo* ratio (entry 12). The product mixture of substrate **3.33** was amenable to X-ray crystallographic analysis and the solid state structure of both isomers **3.33*N*** and **3.33*X*** were obtained.

Table 3.2: Evaluation of substrates having *para*- or unsubstituted arene rings



entry	substrate	R^1	R^2	products	yield (%)[a,b]	ratio[c]
1	**3.28**	Bn	H	**3.28*N*:3.28*X***	77	4:1
2[d]	**3.28**	Bn	H	**3.28*N*:3.28*X***	61	1.5:1
3	**3.29**	CH_3	OCH_3	**3.29*N*:3.29*X***	79	7:1
4[d]	**3.29**	CH_3	OCH_3	**3.29*N*:3.29*X***	88	9:1
5[e]	**3.29**	CH_3	OCH_3	**3.29*N*:3.29*X***	NR	nd
6[f]	**3.29**	CH_3	OCH_3	**3.29*N*:3.29*X***	41	3:1
7[g]	**3.29**	CH_3	OCH_3	**3.29*N*:3.29*X***	dec	nd
8[h]	**3.29**	CH_3	OCH_3	**3.29*N*:3.29*X***	11	nd
9	**3.30**	Bn	OCH_3	**3.30*N*:3.30*X***	79	18:1
10	**3.31**	CH_3	Br	**3.31*N*:3.31*X***	66	2:1
11	**3.32**	CH_3	OTs	**3.32*N*:3.32*X***	68	2:1
12	**3.33**	CH_3	CF_3	**3.33*N*:3.33*X***	52	1:2

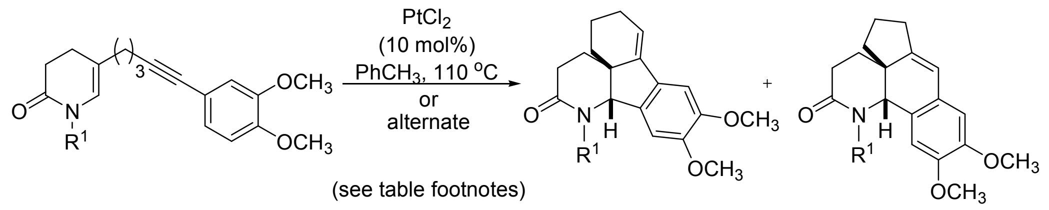
[a] Reported yields are isolated yields. NR=no reaction; dec=decomposition. [b] Reported yields are the maximum of single experiments. [c] Ratio was determined by inspection of ^{1}H NMR spectrum of product mixture. nd=not determined. [d] Reaction was carried out using $PtBr_2$ (10 mol%). [e] Reaction was carried out using AuCl, PPh_3, and $AgSbF_6$ (5 mol% each) at 60 °C. [f] Reaction was carried out using PPh_3AuCl and $AgSbF_6$ (5 mol% each) at 80 °C. [g] Reaction was carried out using S-PhosAuCl (**3.42**) and $AgSbF_6$ (5 mol% each) at 60 °C. [h] Reaction was carried out using $PtCl_2$ (10 mol%) and S-Phos (15 mol%).

Alternative catalytic systems were tested. Platinum(II) bromide was tested to determine if it would increase the yield or the regioselectivity of the cycloisomerization reaction (entries 2 and 4). While there seemed to be a decrease in yield and regioselectivity when reacted with enamide **3.28** (entry 2), treatment of enamide **3.29** with 10 mol% of platinum(II) bromide resulted in an increase in yield and regioselectivity (entry 4). These results do not provide meaningful information and are likely due to differences in technique when performing or purifying the reaction. Treatment of enamide **3.29** with a mixture of AuCl, PPh_3, and $AgSbF_6$ (5 mol% each) did not result in any observable cycloisomerization reaction (entry 5). A cationic gold(I) system (PPh_3AuCl and $AgSbF_6$: 5 mol% each) successfully cycloisomerized enamide **3.29** but the yield was poor and the regioselectivity was decreased relative to the platinum(II) catalytic system (entry 6). Reactions involving 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) as a ligand and part of a complex were examined based on successes in coinage metal catalysis from the primary literature.[12-16] Enamide **3.29** decomposed when treated with S-PhosAuCl (**3.42**) and $AgSbF_6$ (5 mol% each; entry 7). Adding S-Phos to a platinum(II) chloride catalyzed reaction gave only 11% of isolated product.

In general, enamide substrates with a *para*-methoxy substituent on the aromatic ring were more reactive and more selective for the 6-*endo* isomer than their phenyl and electron-withdrawing aromatic enamide counterparts. Consequently, a series of veratrole (1,2-dimethoxybenzene) derived substrates were tested. The results are summarized in Table 3.3.

Enamide **3.34** cycloisomerized smoothly with 10 mol% of platinum(II) chloride to give a 98% yield of products **3.34*N*** and **3.34*X*** in a 10:1 ratio (entry 1). Reaction of benzyl-protected enamide **3.35** proceeded with a lower yield (78%) but a more synthetically useful product ratio of 20:1 (entry 2). The major isomer **3.35*N*** was unambiguously characterized by X-ray crystallographic analysis. Treating enamide **3.35** with 10 mol% of platinum(II) bromide did not offer any advantage (entry 3).

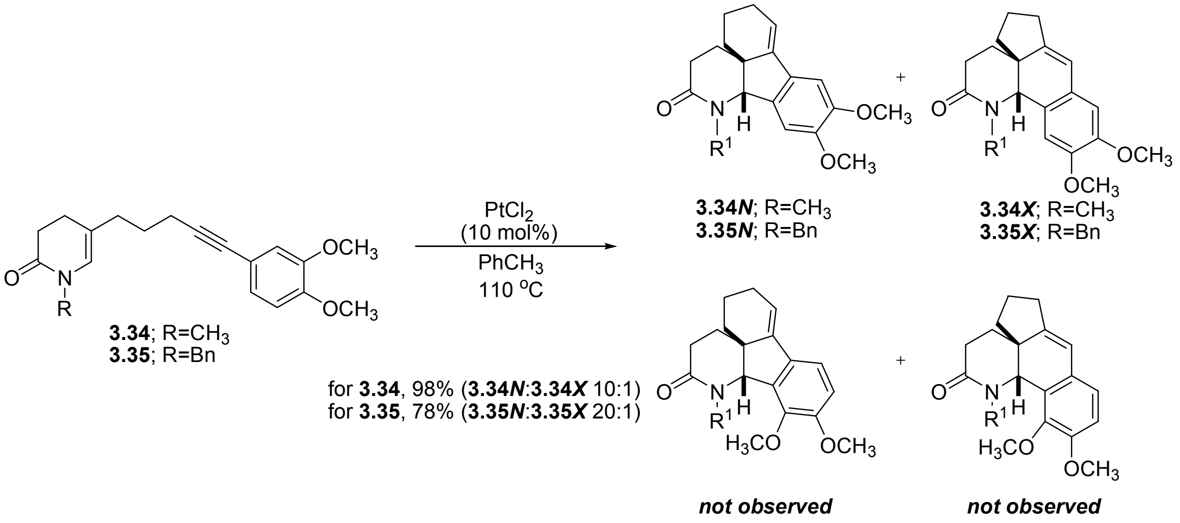
Table 3.3: Cyclization of veratrole derivatives


PtCl2
(10 mol%)
PhCH3, 110 °C
or
alternate
(see table footnotes)
OCH3
OCH3
R1
3
OCH3
OCH3
+
OCH3
OCH3
H
H

entry	substrate	R^1	products	yield (%)[a,b]	ratio[c]
1	**3.34**	CH_3	**3.34*N*:3.34*X***	98	10:1
2	**3.35**	Bn	**3.35*N*:3.35*X***	78	20:1
3[d]	**3.35**	Bn	**3.35*N*:3.35*X***	79	14:1

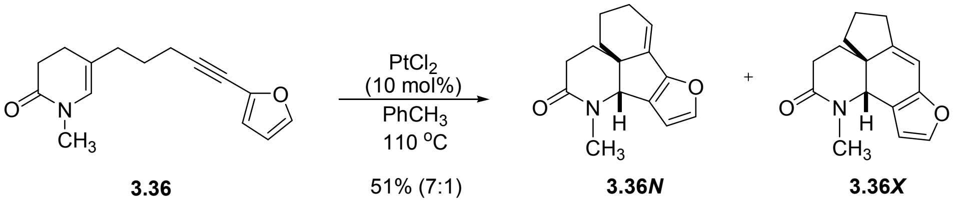
[a] Reported yields are isolated yields. [b] Reported yields are the maximum of single experiments. [c] Ratio was determined by inspection of ^{1}H NMR spectrum of product mixture. [d] Reaction was carried out using $PtBr_2$ (10 mol%).

In principle there are four possible products for the cyclization of the veratrole derivatives (Scheme 3.9). The Freidel-Crafts portion of the reaction has the opportunity to react at either the 2- or 6-position of the aromatic ring. The 2-position is directly adjacent to one of the methoxy substituents, and therefore is more sterically hindered than the 6-position. This steric hindrance is likely the reason for two of the four possible isomers not being observed.


3.34; R=CH3
3.35; R=Bn
PtCl2
(10 mol%)
PhCH3
110 °C
for 3.34, 98% (3.34N:3.34X 10:1)
for 3.35, 78% (3.35N:3.35X 20:1)
3.34N; R=CH3
3.35N; R=Bn
3.34X; R=CH3
3.35X; R=Bn
not observed
not observed
OCH3
H3CO
R1
H
+

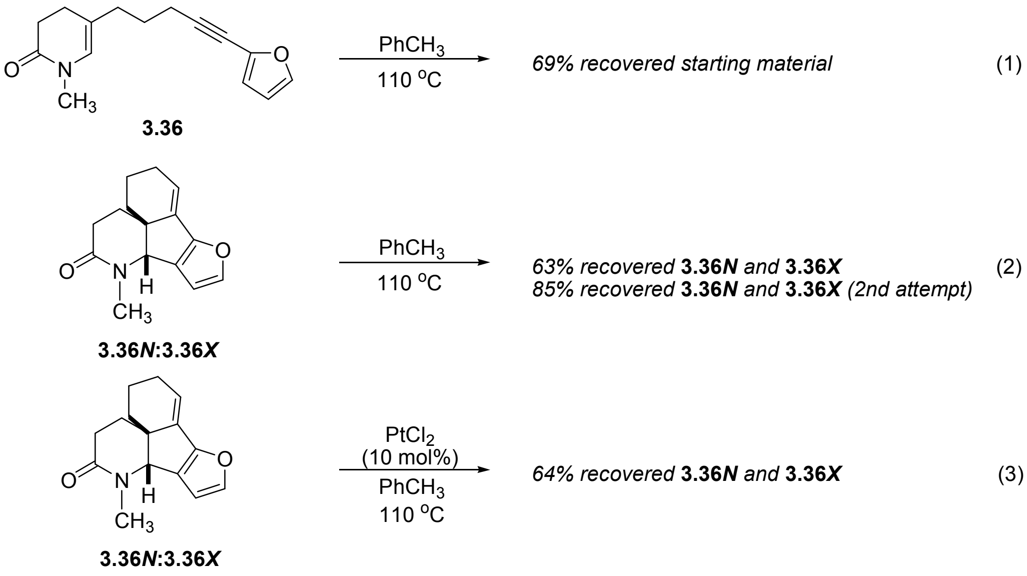
Scheme 3.9: Regioisomeric products were not observed

Electron-rich heteroaromatic systems were next tested for reactivity. The introduction of a heteroatom was desirable in order to increase the complexity of the products derived from the cycloisomerization reactions. Alkynyl furan substrate **3.36** was synthesized and tested for reactivity under platinum(II) chloride catalysis (Scheme 3.10). Treatment under standard conditions gave 51% yield of products **3.36*N*** and **3.36*X*** in a 7:1 ratio, again favoring the 6-*endo* isomer. The moderate yield of the reaction is possibly due to instability of the starting material, or the decomposition of one of the two products formed under the reaction conditions.



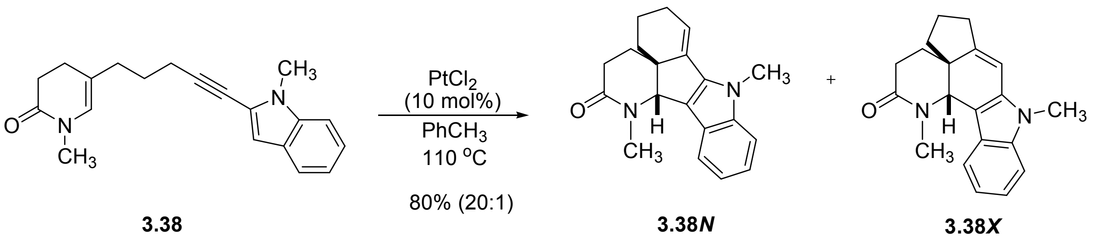
Scheme 3.10: Cyclization of furan derivative **3.36**

To test the stability of the starting material, enamide **3.36** was heated to 110 °C in toluene in the absence of the catalyst (Scheme 3.11, eq 1). The starting material **3.36** was recovered in 69% yield. Loss of starting material could be due to decomposition under the conditions or due to loss during workup and purification. The control experiment in this case is inconclusive. To test the stability of the products, two control experiments were performed. Heating of the products at 110 °C in toluene without catalyst resulted in the recovery of 63% of the products (Scheme 3.11, eq 2). In a second attempt, 85% of the products were recovered. Treatment of the products **3.36*N*** and **3.36*X*** under the standard cyclization conditions resulted in recovery of the products in 64% yield (Scheme 3.11, eq 3). It is therefore possible that the decrease in yield is due to the instability of the products under the reaction conditions, but is not conclusive.


3.36
PhCH3
110 °C
69% recovered starting material
(1)
3.36N:3.36X
PhCH3
110 °C
63% recovered 3.36N and 3.36X
85% recovered 3.36N and 3.36X (2nd attempt)
(2)
3.36N:3.36X
PtCl2
(10 mol%)
PhCH3
110 °C
64% recovered 3.36N and 3.36X
(3)

Scheme 3.11: Control experiments

The introduction of an indole moiety in the cyclization reaction could create products that could be structural mimics of indole alkaloids. Cyclization of the electron-rich *N*-methyl indole derivative **3.38** under the standard reaction conditions proceeded smoothly to afford 80% of the product **3.38*N*** and **3.38*X*** in a synthetically useful 20:1 ratio (Scheme 3.12).


PtCl2
(10 mol%)
PhCH3
110 °C
80% (20:1)
3.38
3.38N
3.38X

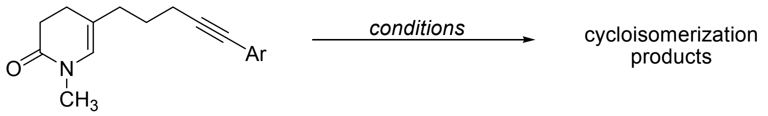
Scheme 3.12: Cyclization of 2-substituted indole derivative **3.38**

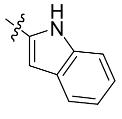
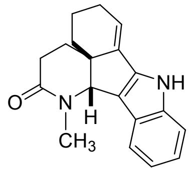
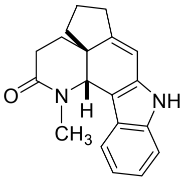
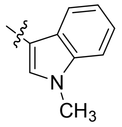
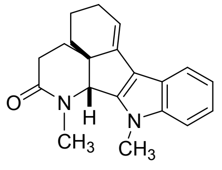
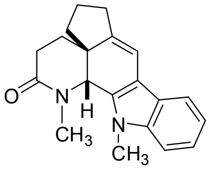
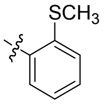
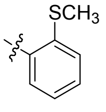
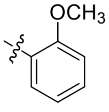
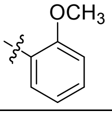
3.4 Unsuccessful Cyclization Reactions

The cyclization of a number of substrates proceeded smoothly in good yields and often with useful product ratios. Other substrates tested in this study did not succeed. These results are summarized in Table 3.4. While the *N*-methyl substituted indole derivative **3.38** reacted under the standard reaction conditions in good yield and regioselectivity, the *N*-H indole showed poor reactivity. Indole containing enamide **3.37** gave a 1.5:1 mixture of products **3.37*N*** and

3.37*X* in 27% yield (entry 1). Treatment of 3-alkynyl indole **3.39** under the standard reaction conditions resulted in cyclization to the product **3.39*N*** in 59% yield (entry 2). No minor isomer **3.39*X*** was observable by ^{1}H NMR. Isomer **3.39*N*** could not be fully characterized due to decomposition of the product. This is not surprising considering the instability of the 2-iodoindole compared to that of the 3-iodoindole. This substrate was generally less stable than its 2-substituted counterpart.

Table 3.4: Unsuccessful platinum(II)-catalyzed cycloisomerization/Friedel-Crafts reactions

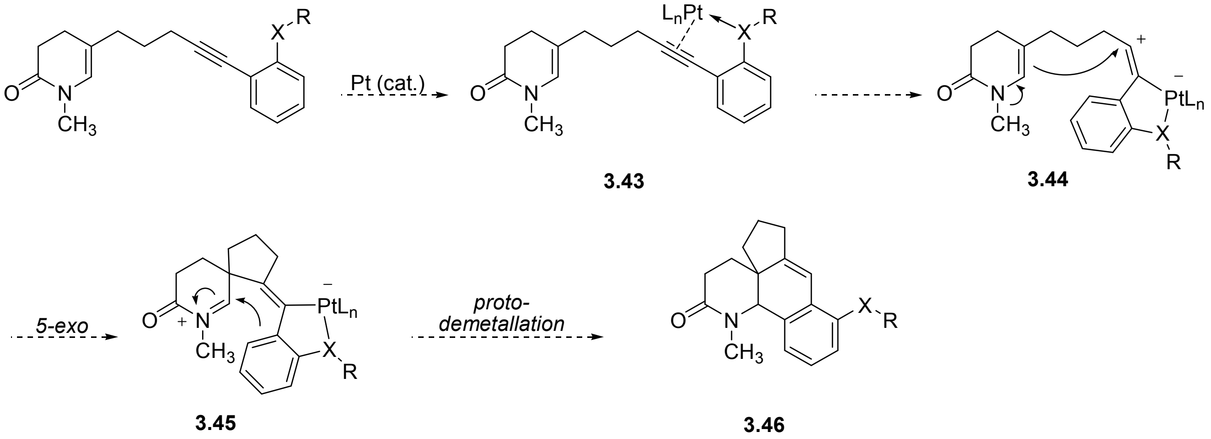


entry	substrate	Ar	conditions	products	yield (%)[a] (ratio)[b]
1	**3.37**		10 mol% PtCl$_2$, PhCH$_3$, 110 °C, 16 h	 +  **3.37*N*** **3.37*X***	27 (1.5:1)
2	**3.39**		10 mol% PtCl$_2$, PhCH$_3$, 110 °C, 16 h	 +  **3.39*N*** **3.39*X***	59 (95:5)
3	**3.40**		10 mol% PtCl$_2$, PhCH$_3$, 110 °C, 16 h	-	NR (55% RSM)
4	**3.40**		20 mol% PtCl$_2$, PhCH$_3$, 130 °C, 16 h	-	dec
5	**3.41**		10 mol% PtCl$_2$, PhCH$_3$, 110 °C, 16 h	-	NR
6	**3.41**		10 mol% PtCl$_2$, PhCH$_3$, 130 °C, 16 h	-	dec

[a]Reported yields are isolated yields. NR=no reaction; RSM=recovered starting material; dec=decomposition. [b]Ratio was determined by inspection of ^{1}H NMR spectrum of product mixture.

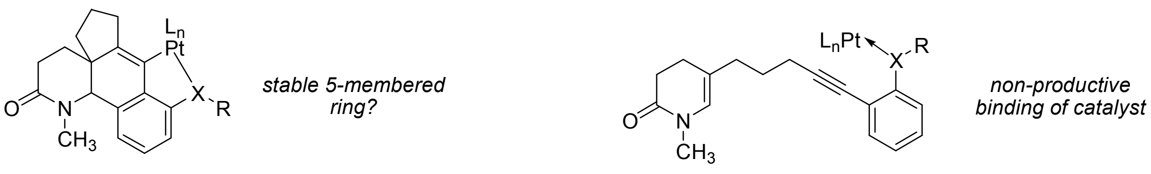
One goal of the project was to attempt to control the regioisomeric ratio in favor of the 5-*exo* isomer. The cycloisomerizations of substrates with strongly electron-withdrawing substituents on the aromatic ring were shown to favor the 5-*exo* isomer in a maximum of a 1:2 ratio (Table 3.3.1, entry 12, parent enamide **3.33**). Placing more strongly electron-withdrawing groups around the aromatic functionality will likely improve the isomeric ratio, but it will also potentially decrease the reactivity substantially, and therefore not be synthetically useful.

An alternative pathway to selectively form the 5-*exo* isomer is shown in Scheme 3.13. By substituting the *ortho*-position of the aromatic ring with a heteroatom containing functional group (X = heteroatom), the platinum will presumably coordinate to both the alkyne and the heteroatom (**3.43**). The platinum will slip to the carbon of the alkyne directly adjacent to the aromatic ring in order to form a stable 5-memebered ring (**3.44**). This slippage of the metal will make the carbon further from the arene ring more electropositive, as in **3.44**. The enamide will attack this position resulting in an initial 5-*exo* cyclization to form intermediate **3.45**. At this stage the Friedel-Crafts reaction will occur, followed by rearomatization and protodemetallation to give the 5-*exo* isomer product **3.46**.



Scheme 3.13: Selective formation of the 5-*exo* product using ortho-substituted aromatic rings

The heteroatoms chosen to test this hypothesis were sulfur (*ortho*-thioether) and an oxygen (*ortho*-methoxy). When enamide **3.40** was treated under the standard reaction conditions, no reaction was observed by thin layer chromatography and 55% of the starting material was recovered (entry 3). Increasing the catalyst loading to 20 mol% of platinum(II) chloride in addition to increasing the temperature to 130 °C resulted in decomposition of the starting material to products that were unidentifiable by ^{1}H NMR (entry 4). Replacing the *ortho*-thioether with an *ortho*-methoxy substituent was tested as an alternative. The results mirrored those of sulfur. Under standard conditions there was no observable reaction of enamide **3.41** (entry 5). Increasing the catalyst load and the temperature resulted in decomposition of the starting material into unidentifiable products (entry 6).



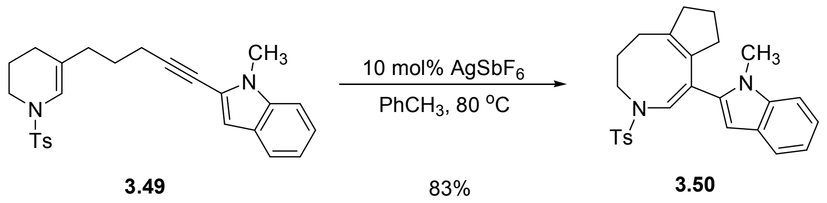
3.47 **3.48**

Scheme 3.14: Possible explanations for failure of cycloisomerization reactions when X = S, O

The reason for the inability of platinum to undergo cyclorearrangement reactions with substrates **3.40** and **3.41** is not clear. One possibility is the 5-membered ring is stable (**3.47**), and the catalyst is sequestered and unable to turnover to further catalyze the reaction (Scheme 3.14). Another possibility is the heteroatom binds to the metal as in **3.48**, sequestering it against further catalytic activity. Fürstner believes that inhibition of platinum by kinetically stable complexation to heteroatoms is unlikely since the platinum is carbophilic.[17] Also, the reaction proceeds smoothly with *para*-methoxy and veratrole derivatives therefore it is unlikely that the oxygen atom is binding to the platinum. The difference in reactivity is clearly influenced by the *position* of the substituents around the aromatic ring.

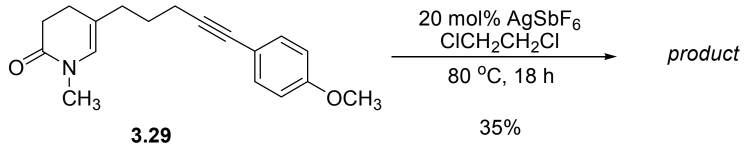
3.5 Unexpected Formation of an Azocine Derivative

Different catalysts were tested for reactivity in the cycloisomerization of enamides and enesulfonamides during the study. One catalyst system tested was silver hexafluoroantimonate without the presence of a gold catalyst. Fellow Dake group member Jennifer Dodd found that treatment of enesulfonamide **3.49** with 10 mol% of silver hexafluoroantimonate resulted in an 83% yield of azocine **3.50** (Scheme 3.15).[18] This compound was fully characterized by 2D NMR and X-ray crystallography.



Scheme 3.15: Formation of azocine derivative **3.50** by silver catalysis[18]

Treatment of enamide **3.29** using the same catalyst under slightly different reaction conditions was attempted (Scheme 3.16). Enamide **3.29** was treated with 20 mol% of silver hexafluoroantimonate in dichloroethane. The use of 20 mol% of catalyst was necessary to complete the reaction. Completion was necessary since the product of the reaction and the starting enamide **3.29** were not separable by column chromatography. The observed product did not share the same characteristic ^{1}H NMR signals as that of azocine derivative **3.50**, or of the tetracyclic products observed under platinum(II)-catalysis. The only identifiable signals were those of the aromatic ring, the *N*-methyl substituent, the *para*-methoxy substituent, and the enamide proton. All other signals were broad.



Scheme 3.16: Cycloisomerization of enamide **3.29** with silver hexafluoroantimonate as a catalyst

If an 8-membered ring were in fact formed, it would likely be conformationally flexible, and coalescence behavior might be observed. The product was therefore analyzed by variable temperature (low temperature) NMR. The variable temperature ^{1}H NMR data are shown in Figure 3.2. The spectrum taken at room temperature (25 °C) is the topmost trace. As the temperature is decreased, the broad signals separate into a series of signals with fine structure. The spectrum taken at either −40 °C or −50 °C contains all the signals and correct integration for azocine **3.51**. The purpose of this experiment was only to determine the identity of the product formed.

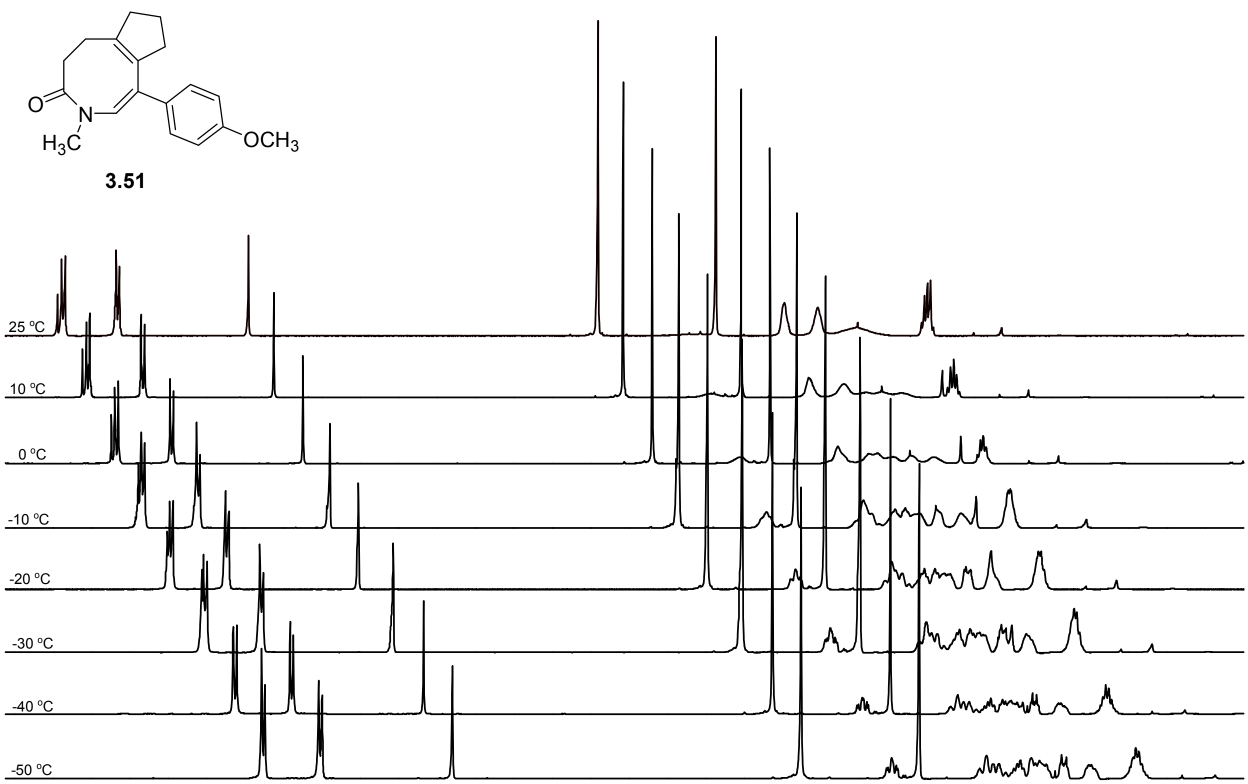


Figure 3.2: Variable-temperature NMR analysis of azocine **3.51**

The azocine product **3.51** was not unambiguously characterized using 1D ^{1}H NMR spectroscopy and was therefore subjected to ^{13}C NMR and 2D NMR spectroscopy (at −40 °C, high resolution mass spectrometry, and IR spectrometry (Figure 3.3).

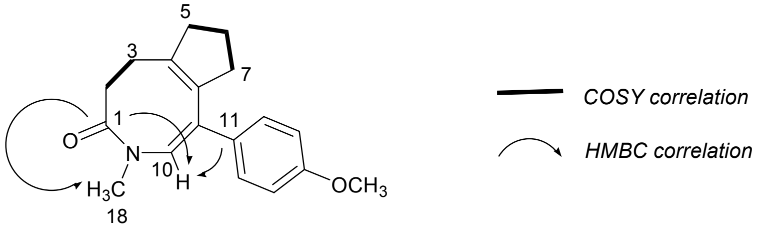
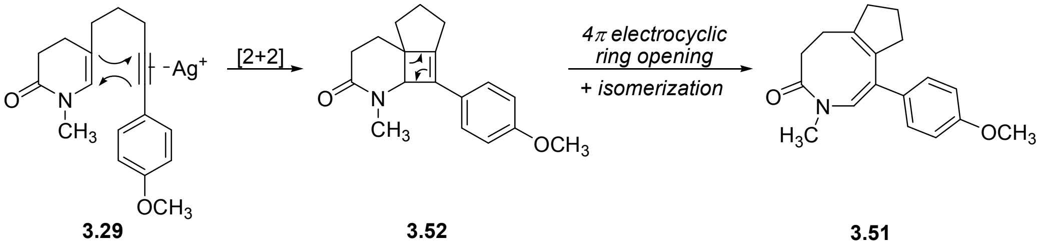


Figure 3.3: NMR correlations for azocine product **3.51**

Carbon 1 has a signal in the ^{13}C NMR spectrum with a chemical shift of 174.9 ppm; a typical chemical shift of an amide carbonyl. HMBC analysis of this signal shows correlations to the methyl group attached to the nitrogen, as well as the enamide proton 3-bonds away. Ipso carbon 11 of the *para*-anisole substituent also displays a 3-bond correlation to the enamide proton 10. Due to the symmetry of the 5-membered ring (carbons 4-8), it was difficult to assign those signals unambiguously.

One possible mechanism for the formation of azocine **3.51** is shown in Scheme 3.17. After coordination by silver a [2+2] cycloaddition could take place to form cyclobutene intermediate **3.52**. Conrotatory 4π electrocyclic ring opening and isomerization of the double bond gives azocine **3.51**. It is possible that the mechanism occurs in a stepwise manner versus a concerted reaction.



Scheme 3.17: Proposed mechanism for the formation of azocine **3.51**

Optimization and scope studies of the cycloisomerization of enamides and enesulfonamides under silver catalysis will not be discussed here. Readers interested in further studies and alternate proposed mechanisms of this reaction are directed to the Masters thesis of fellow Dake group member Jennifer Dodd.[18]

3.6 Conclusion

The platinum(II)-catalyzed cycloisomerization/Friedel-Crafts alkylation of enamides containing an aromatic functional group on the alkyne was effective in generating nitrogen-containing products of high structural complexity. Substrates with electron-rich aromatic substituents readily reacted with platinum(II) chloride to produce products in good yields and synthetically useful regioisomeric ratios resulting from an initial 6-*endo-dig* mode of cyclization. Substrates containing electron-withdrawing aromatic systems showed generally reduced reactivity and poor ratios. Heteroaromatic enamide **3.36** (furan substituted) reacted under the catalytic conditions to give product, albeit in poor yield and moderate selectivity. Alternatively, heteroaromatic enamide **3.38** (protected 2-substituted indole) reacted in good yield and excellent selectivity.

Some heteroaromatic substrates (unprotected indole and 3-substituted indole) were not compatible with the reaction conditions. This is likely due to instability of the reactants or the products. Substrates with a heteroatom-containing functional group at the *ortho*-position of the aromatic ring either did not react or decomposed under forcing reaction conditions.

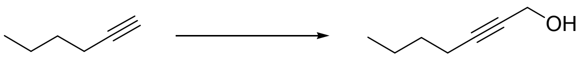
Silver(I)-catalysis of enamide **3.29** showed a new product unlike the tetracycles observed under platinum(II) catalytic conditions. Variable temperature NMR was used to determine that the structure formed was an azocine derivative (**3.51**).

3.7 Experimental

3.7.1 General Experimental

Please refer to the general experimental section in Chapter 2 for details.

3.7.2 Synthesis of Substrates



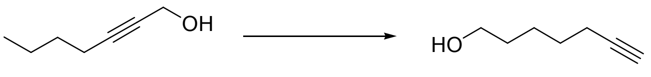
3.12 **3.13**

Hept-2-yn-1-ol (3.13)

To a solution of 20.0 mL of 1-hexyne (**3.12**) (174 mmol) in 300 mL of THF at -78 ^{o}C was added dropwise 114 mL of a solution of *n*-butyllithium (1.60 M in hexanes, 183 mmol). The resulting solution was stirred at −78 ^{o}C for 1 h. To the reaction mixture was added 5.48 g of paraformaldehyde (183 mmol) in small portions over 0.3 h. The resulting suspension was stirred at −78 ^{o}C for 1 h then warmed to rt and stirred for 20 h. The clear yellow solution was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by distillation under reduced pressure to afford 17.9 g (92 %) of hept-2-yn-1-ol (**3.13**) as a clear oil, bp = 46-49 ^{o}C, 0.5 mmHg (*lit*. 84-86 ^{o}C, 0.5 mmHg).

IR (neat): 3326 (br), 2935, 2226 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.19-4.18 (m, 2H), 2.76 (br s, 1H), 2.16 (tt, J = 7.0, 2.2 Hz, 2H), 1.52-1.28 (m, 4H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 87.1, 79.3, 52.0, 31.6, 22.9, 19.3, 14.5.

3.13 has been previously reported, see: 1) Kumar, G. D. K.; Baskaran, S. *J. Org.Chem.* **2005**, *70*, 4520-4523. 2) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090.



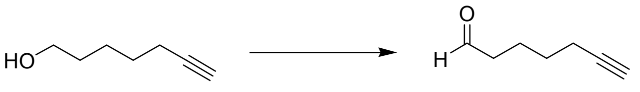
3.13 **3.14**

Hept-6-yn-1-ol (3.14)

To a flask containing 25.5 g of potassium hydride (637 mmol) was added 350 mL of 1,3-diaminopropane. The suspension was stirred for 1 h at rt. To the resulting green suspension was slowly added 17.9 g of hept-2-yn-1-ol (**3.13**) (159 mmol). The first ~2 g of the alcohol were added very carefully to avoid excessive frothing. After the addition of the alcohol, the reaction mixture was heated to 80 °C and stirred for 1.5 h. The mixture was then cooled to rt and carefully poured over 600 mL of crushed ice. The slurry was transferred to a separatory funnel and extracted four times with diethyl ether. The combined organics were washed twice with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by distillation under reduced pressure to afford 16.2 g of hept-6-yn-1-ol (**3.14**) (91 %) as a clear, colorless oil, bp = 60-65 °C, 0.5 mmHg (*lit.* 65-66 °C, 1 mmHg).

IR (neat): 3300 (br), 2938, 2117 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.64 (t, J = 6.5 Hz, 2H), 2.20 (td, J = 7.0, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.62-1.53 (m, 5H), 1.52-1.45 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 85.4, 69.3, 63.7, 33.2, 29.2, 25.9, 19.4.

3.14 has been previously reported, see: 1) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090. 2) Gung, B. W.; Gibeau, C.; Jones, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3107-3114.

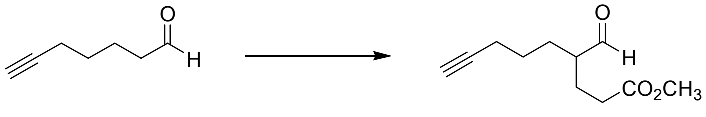


3.14 **3.15**

Hept-6-ynal (3.15)

To a solution of 4.0 mL of oxalyl chloride (46 mmol) in 100 mL of dichloromethane at −78 °C was added 5.0 mL of dimethyl sulfoxide (70 mmol) dropwise. The reaction mixture was stirred at −78 °C for 0.25 h. A solution of 3.9 g of hept-6-yn-1-ol (**3.14**) (35 mmol) in 14 mL of dichloromethane was slowly added to the cold solution. After stirring at −78 °C for 0.5 h, 24 mL of triethylamine (175 mmol) was added dropwise to the white suspension. The resulting reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were then washed once with 1 M HCl and once with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude yellow oil. The crude oil was purified by distillation under reduced pressure to afford 3.3 g (86 %) of the title compound **3.15** as a clear, colorless liquid, bp = 35-39 °C, 0.5 mmHg (*lit.* 78-80 °C, 20 mmHg).

3.15 has been previously prepared, see: Hopf, H.; Krüger, A. *Chem.− Eur. J.* **2001**, *7*, 4378-4385.

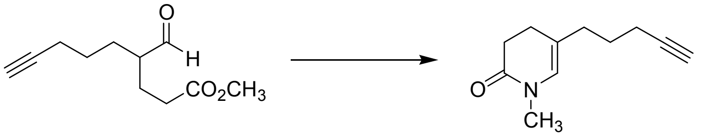


3.15 **3.16**

Methyl 4-formylnon-8-ynoate (3.16)

A 100 mL round-bottomed flask was charged with a stir bar, 2.95 g potassium carbonate (21.3 mmol), and then flame-dried. The flask was put under an atmosphere of nitrogen and 11.6 mL of freshly distilled piperidine (117 mmol) was added. The suspension was cooled to 0 °C and 5.87 g of hept-6-ynal (**3.15**) (53.3 mmol) was added via syringe pump (0.01 mL/min). The resulting yellow suspension was stirred at 0 °C for 3 h. The reaction mixture was filtered through oven-dried Celite®, rinsing with anhydrous diethyl ether. The solution was concentrated to afford a yellow oil. The crude oil was immediately put under an atmosphere of nitrogen. 55 mL of dry acetonitrile were added via syringe followed by 9.6 mL of freshly distilled methyl acrylate (107 mmol). The reaction mixture was heated to reflux for 22 h. The reaction mixture was cooled to rt and 25 mL of water and 5 mL of glacial acetic acid were added. The flask was opened to the atmosphere and heated to reflux for 16 h. The solution was then cooled to rt and extracted three times with diethyl ether. The combined organic fractions were washed once with 1 M HCl, once with a saturated solution of sodium bicarbonate, and once with brine. The organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford an orange oil. The crude oil was purified by column chromatography on silica gel (5:1→1:1 hexanes:ethyl acetate) to afford 6.10 g (58 %) of the title compound **3.16** as a yellow oil.

IR (neat): 3289, 2950, 2117, 1734, 1438 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.57 (d, *J* = 2.2 Hz, 1H), 3.64 (s, 3H), 2.35-2.30 (m, 3H), 2.19 (td, *J* = 7.0, 2.6 Hz, 2H), 1.98-1.93 (m, 2H), 1.82-1.74 (m, 2H), 1.60-1.48 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 204.8, 174.3, 84.5, 70.0, 52.6, 51.5, 32.2, 28.5, 26.5, 24.5, 19.3. HRMS (ESI) calcd for $C_{11}H_{16}O_3Na$ (M + Na)$^+$: 219.0997. Found: 219.1001.



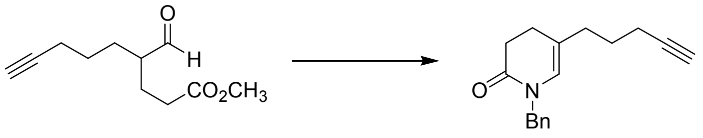
3.16 **3.17**

1-Methyl-5-(pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.17)

To a solution of 1.60 g of alkyne **3.16** (8.17 mmol) and 20.4 mL of methylamine (40.8 mmol, 2.0 M in THF) in 25 mL of toluene was added 8.2 mL of glacial acetic acid. A Dean-Stark apparatus was attached and the reaction mixture was heated to reflux and stirred for 4 h. The reaction mixture was cooled to rt, diluted with diethyl ether, and washed twice with a saturated solution of sodium bicarbonate. The combined aqueous fractions were extracted twice with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (6:1→3:1→1:1 hexanes:ethyl acetate) to give 1.33 g (92 %) of the title compound **3.17** as a yellow solid. The solid was recrystallized from ethanol and hexanes to give an off-yellow solid, mp = 64-66 °C.

IR (neat): 3305, 2939, 2117, 1660 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.76 (s, 1H), 2.99 (s, 3H), 2.47-2.43 (m, 2H), 2.21-2.10 (m, 6H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.64-1.57 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 127.0, 119.3, 84.9, 69.8, 34.6, 33.5, 32.0, 27.3, 25.1, 18.8. MS (ESI): 200 (M + Na)$^+$. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.45; H, 8.62; N, 7.71.

3.17 has been previously reported, see: Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367-370.

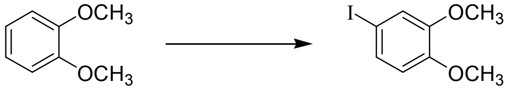


3.16 **3.18**

1-Benzyl-5-(pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.18)

To a solution of 1.04 g of alkyne **3.16** (5.32 mmol) and 2.9 mL of benzyl amine (26.6 mmol) in 25 mL of toluene was added 5.3 mL of glacial acetic acid. A Dean-Stark apparatus was attached and the reaction mixture was heated to reflux with stirring for 1.25 h. The reaction mixture was cooled to rt, diluted with diethyl ether, and washed twice with a saturated solution of sodium bicarbonate. The combined aqueous fractions were extracted three times with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to yield a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate) to afford 1.20 g (90 %) of the title compound **3.18** as a yellow oil.

IR (neat): 3294, 2937, 2116, 1667, 705 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.22 (m, 5H), 5.81 (t, *J* = 1.3 Hz, 1H), 4.66 (s, 2H), 2.57 (t, *J* = 8.1 Hz, 2H), 2.26 (t, *J* = 8.1 Hz, 2H), 2.18-2.09 (m, 4H), 1.94 (t, *J* = 2.6, 1H), 1.59 (qt, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 138.3, 129.6, 128.6, 128.4, 125.6, 120.0, 84.9, 69.8, 49.9, 33.6, 32.3, 27.3, 25.1, 18.8. MS (APCI): 254 (M + H)$^+$. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.63; H, 7.89; N, 5.55.



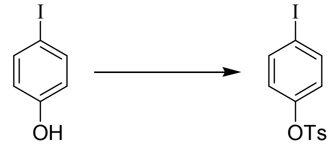
3.19 **3.20**

4-Iodo-1,2-dimethoxybenzene (4-Iodoveratrole) (3.20)

A 1 L, 3-necked round-bottomed flask was charged with 65.5 g of silver acetate (393 mmol) and then flame dried under reduced pressure. The flask was then cooled to rt and put under an atmosphere of nitrogen. The flask was charged with 50.0 mL of 1,2-dimethoxybenzene (**3.19**) (393 mmol). A solution of 99.7 g of iodine (393 mmol) in chloroform was added to the reaction mixture dropwise over a period of 2 h. The resulting red suspension was stirred at rt for 1.5 h. The reaction mixture was filtered and washed with chloroform. The filtrate was concentrated by rotary evaporation *in vacuo* to afford a dark red oil. To the red oil was added some dichloromethane and the solution was washed three times with a saturated solution of sodium thiosulfate. The combined aqueous fractions were extracted once with dichloromethane. The combined organic fractions were dried over sodium sulfate, concentrated by rotary evaporation *in vacuo* to afford a crude brown oil. The brown oil was purified by distillation under reduced pressure to give 83.4 g (80 %) of the title compound **3.20** as a clear brown oil (bp = 104 °C, 0.5 mmHg) that solidifies in the fridge. The solid was recrystallized from ethanol to afford white needles, mp = 35-36 °C (*lit.* 34-35 °C).

IR: 2999, 2955, 2837, 1583, 1500, 839, 798 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 150.2, 130.8, 121.4, 114.2, 83.4, 57.1, 56.9.

3.20 has been previously prepared, see: Janssen, D. E.; Wilson, C. V. *Org. Synth.* **1956**, *36*, 46-48.



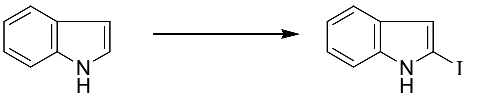
3.21 **3.22**

4-Iodophenyl 4-methylbenzenesulfonate (3.22)

To a solution of 3.03 g of 4-iodophenol (**3.21**) (13.8 mmol) and 3.41 g of *p*-toluenesulfonyl chloride (17.9 mmol) in 35 mL of dichloromethane was added 5.8 mL of triethylamine (41.3 mmol) dropwise. The resulting white suspension was stirred at rt for 5.5 h. The reaction mixture was diluted with dichloromethane and then washed four times with 1M HCl. The combined aqueous fractions were extracted once with dichloromethane. The combined organic fractions were washed once with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford an oil that solidifies under vacuum. The solid was purified by recrystallization from a mixture of dichloromethane and hexanes and then rinsed with diethyl ether to afford 4.02 g (78 %) of the title compound **3.22** as pink crystals, mp = 94-96 °C (*lit.* 99 °C).

IR (film): 2930, 1478, 876, 656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 146.7, 139.7, 133.1, 130.9, 129.5, 125.5, 92.7, 22.7.

3.22 has been previously prepared, see: 1) Matheson, D.; McCombie, H. *J. Chem. Soc.* **1931**, 1103-1110. 2) Lee, T.-S.; Kim, J.; Bae, J.-Y. *Polymer* **2004**, *45*, 5065-5076.

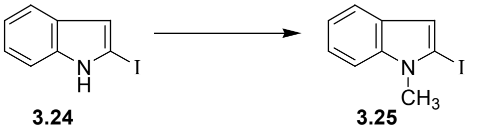


3.23 **3.24**

2-Iodo-1*H*-indole (3.24)

To a solution of 3.17 g of indole (**3.23**) (27.1 mmol) in 70 mL of THF at −78 °C was added dropwise 17.7 mL of a solution of *n*-butyllithium (1.61 M in hexanes, 28.4 mmol). The resulting milky white reaction mixture was stirred at −78 °C for 0.5 h. The nitrogen atmosphere was replaced with an atmosphere of carbon dioxide using a balloon. The carbon dioxide gas was bubbled through the reaction mixture for 0.25 h. The milky solution turned clear. The solvents were removed under reduced pressure to afford a white solid. The white solid was dissolved in 60 mL of THF and cooled to −78 °C before the dropwise addition of 20.0 mL of a solution of *t*-butyllithium (1.42 M in hexanes, 28.4 mmol). The resulting bright yellow solution was stirred at to −78 °C for 0.7 h. To the cold reaction mixture was added a solution of 7.64 g of 1,2-diiodoethane (27.1 mmol) in 10 mL of THF. The mixture was stirred for 0.75 h before being quenched with 2.7 mL of H_2O. The suspension was warmed to rt and poured into 150 mL of a saturated solution of ammonium chloride. The reaction mixture was diluted with diethyl ether and the layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography on silica gel (6:1 hexanes:ethyl acetate) to afford 5.53 g (84 %) of the title compound **3.24** as a white solid. The solid was recrystallized from hexanes and dichloromethane to afford the product **3.24** as shiny white crystals, mp = 78 °C (*lit*. 98-99 °C). IR (film): 3465, 2978, 2253, 1438, 654 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (br s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 7.09 (td, *J* = 7.6, 1.3 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H).

3.24 has been previously prepared, see: Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495-2497.



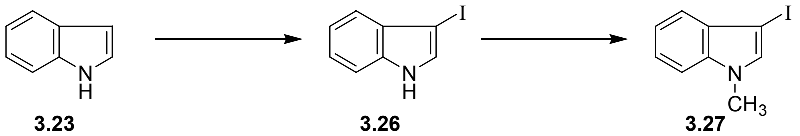
3.24 **3.25**

2-Iodo-1-methyl-1*H*-indole (3.25)

To a solution of 0.34 g of sodium hydride (14 mmol) in 25 mL of THF was slowly added a solution of 2.3 g of 2-iodo-1*H*-indole (**3.24**) (9.4 mmol) in 20 mL of THF. The reaction mixture was stirred at rt for 0.5 h. To the resulting yellow suspension was added 0.70 mL of methyl iodide (11 mmol) dropwise. The reaction mixture was stirred at rt for 2 h. The mixture was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated and the organic fraction was washed once with brine. The combined aqueous fractions were extracted once with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography on silica gel (10:1 hexanes:ethyl acetate) to afford 2.2 g (91 %) of the title compound **3.25** as an off-white solid. The solid was recrystallized from hexanes and dichloromethane to afford opaque beige crystals, mp = 72-73 °C (*lit*. 76 °C).

IR (film): 3052, 2938, 1456, 744 cm-1. ^{1}H NMR (400 MHz, CDCl3): δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.21-7.17 (m, 1H), 7.13-7.09 (m, 1H), 6.83 (d, *J* = 0.6 Hz, 1H), 3.78 (s, 3H).

3.25 has been previously prepared, see: Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495-2497.



3-Iodo-1-methyl-1*H*-indole (3.27)

To a solution of 4.00 g of indole (**3.23**) (34.1 mmol) and 4.79 g of potassium hydroxide (85.4 mmol) in 60 mL of *N*,*N*-dimethylformamide was added dropwise a solution of 8.84 g of iodine (34.8 mmol) in 60 mL of *N*,*N*-dimethylformamide. The resulting brown solution was stirred at rt for 3 h. The reaction mixture was poured into 800 mL of H_2O and ice containing 4 mL of ammonium hydroxide and 1 mL of sodium bisulfite. The resulting pink precipitate was filtered and washed with cold water. The crude product **3.26** was moved onto the next reaction with no further purification.

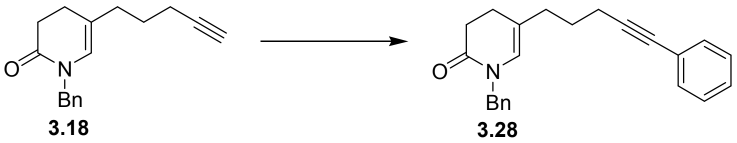
To a suspension of 1.64 g of sodium hydride (68.3 mmol) in 60 mL of THF was added a solution of 8.29 g of compound **3.26** (34.1 mmol) in 50 mL of THF dropwise. The resulting dark green solution was stirred at rt for 0.75 h. To the reaction mixture was added 2.6 mL of methyl iodide

(41.0 mmol) in one portion. The resulting red suspension was stirred at rt for 1 h. The reaction mixture was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated and the organic fraction was washed once with brine. The combined aqueous fractions were extracted once with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford 8.13 g (93 %) of the title compound **3.27** as a light red oil. The oil was not purified further due to instability on to heat and silica gel chromatography.

IR (neat): 2945, 2252, 1508, 727 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.33-7.31 (m, 2H), 7.28-7.24 (m, 1H), 7.14 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 137.8, 133.8, 131.5, 123.7, 122.2, 121.3, 110.5, 55.8, 34.1.

3.27 has been previously prepared, see: Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096-1097.

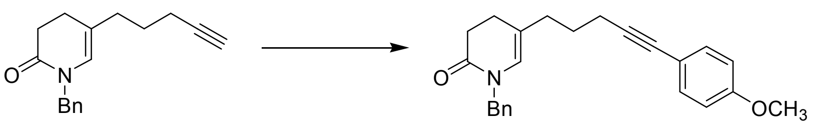
Representative Procedure for Sonogashira Coupling Reactions



1-Benzyl-5-(5-phenylpent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.28)

To a flask charged with 27 mg of bis(triphenylphosphine)palladium(II) chloride (0.038 mmol) and 15 mg of copper(I) iodide (0.076 mmol) was added 2 mL of triethylamine. To the resulting bright yellow mixture was added a solution of 0.19 g of enesulfonamide **3.18** (0.76 mmol) and 0.1 mL of iodobenzene (0.92 mmol) in 2 mL of dichloromethane in one portion. The flask was rinsed with 1 mL of triethylamine and added to the reaction mixture. The reaction vessel was wrapped in aluminum foil and stirred at rt for 2 h. The reaction mixture was filtered through a pipette of triethylamine washed silica gel using ethyl acetate eluent and then concentrated by rotary evaporation *in vacuo* to afford the a crude orange syrup. The crude material was purified by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate) to afford 0.22 g (89 %) of the title compound **3.28** as a clear, yellow oil.

IR (neat): 3031, 2933, 1668, 1599, 758 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.24 (m, 10H), 5.85 (t, *J* = 1.2 Hz, 1H), 4.68 (s, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.37 (t, *J* = 7.0, 2H), 2.30 (t, *J* = 7.8 Hz, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.69 (qt, *J* = 7.0, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 138.4, 132.5, 129.6, 129.2, 128.7, 128.6, 128.4, 125.5, 124.8, 120.1, 90.5, 82.2, 49.9, 33.8, 32.3, 27.6, 25.2, 19.8. HRMS (ESI) calcd for $C_{23}H_{23}NONa$ $(M + Na)^+$: 352.1677. Found: 352.1673.

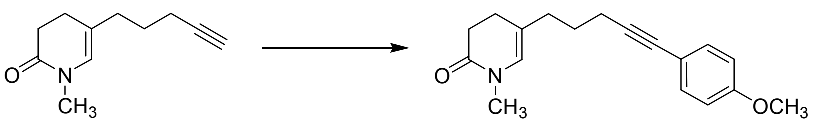


3.18 **3.30**

1-Benzyl-5-(5-(4-methoxyphenyl)pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.30)

Enamide **3.18** (0.20 g, 0.80 mmol), bis(triphenylphosphine)palladium(II) chloride (28 mg, 0.040 mmol), copper iodide (15 mg, 0.080 mmol), and 4-iodoanisole (0.22 g, 0.96 mmol) were combined according to the representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 5 h. After purification by column chromatography on triethylamine washed silica gel (4:1→1:1→1:3 hexanes:ethyl acetate), 0.17 g (59 %) of the title compound **3.30** was isolated as a clear, yellow oil.

IR (neat): 2934, 2836, 1668, 1606, 1510, 834, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 7H), 6.82 (d, *J* = 9.3 Hz, 2H), 5.83 (s, 1H), 4.66 (s, 2H), 3.79 (s, 3H), 2.61-2.55 (m, 2H), 2.36-2.25 (m, 4H), 2.15 (t, *J* = 7.1 Hz, 2H), 1.66 (qt, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 160.1, 138.4, 133.8, 129.6, 128.6, 128.4, 125.5, 120.2, 117.0, 114.9, 88.8, 81.9, 56.3, 49.9, 33.8, 32.3, 27.7, 25.2, 19.8. HRMS (ESI) calcd for $C_{24}H_{25}NO_2Na$ $(M + Na)^+$: 382.1783. Found: 382.1775.



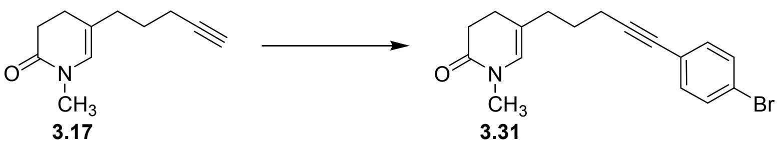
3.17 **3.29**

5-(5-(4-Methoxyphenyl)pent-4-ynyl)-1-methyl-3,4-dihydropyridin-2(1*H*)-one (3.29)

Enamide **3.17** (0.10 g, 0.56 mmol), bis(triphenylphosphine)palladium(II) chloride (20 mg, 0.028 mmol), copper iodide (11 mg, 0.056 mmol), and 4-iodoanisole (0.15 g, 0.62 mmol) were combined according to the representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 5 h. After purification by column chromatography on triethylamine washed silica gel (4:1→1:1→1:3 hexanes:ethyl acetate), 0.14 g (86 %) of the title compound **3.29** was isolated as a clear, yellow oil.

IR (neat): 2936, 1666, 1606, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-730 (m, 2H), 6.83-6.80 (m, 2H), 5.81 (t, *J* = 1.2 Hz, 1H), 3.79 (s, 3H), 3.02 (s, 3H), 2.51-2.47 (m, 2H), 2.40 (t, *J* =

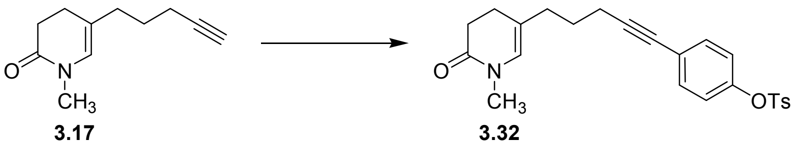
7.0 Hz, 2H), 2.27-2.23 (m, 2H), 2.19 (t, *J* = 7.4 Hz, 2H), 1.74-1.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 160.1, 133.8, 126.9, 119.6, 117.0, 114.9, 88.9, 81.9, 56.3, 34.6, 33.8, 32.1, 27.8, 25.2, 19.9. HRMS (ESI) calcd for $C_{18}H_{21}NO_2Na$ $(M + Na)^+$: 306.1470. Found: 306.1464.



5-(5-(4-Bromophenyl)pent-4-ynyl)-1-methyl-3,4-dihydropyridin-2(1*H*)-one (3.31)

Enamide **3.17** (0.21 g, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (42 mg, 0.060 mmol), copper iodide (23 mg, 0.12 mmol), and 1-bromo-4-iodobenzene (0.41 g, 1.4 mmol) were combined according to the representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 4 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.35 g (87 %) of the title compound **3.31** was isolated as a yellow oil.

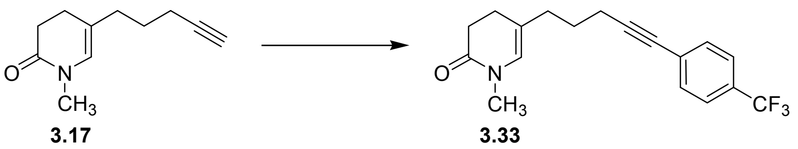
IR (neat): 3478, 2936, 1670, 825 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 5.79 (s, 1H), 3.01 (s, 3H), 2.50-2.46 (m, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.26-2.22 (m, 2H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.73-1.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 134.0, 132.4, 127.0, 123.8, 122.7, 119.4, 91.8, 81.2, 34.6, 33.8, 32.0, 27.6, 25.2, 19.9. HRMS (ESI) calcd for $C_{17}H_{18}NONa^{79}Br$ $(M + Na)^+$: 354.0469. Found: 354.0466.



4-(5-(1-Methyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)pent-1-ynyl)phenyl 4-methylbenzenesulfonate (3.32)

Enamide **3.17** (0.26 g, 1.5 mmol), bis(triphenylphosphine)palladium(II) chloride (52 mg, 0.075 mmol), copper iodide (28 mg, 0.15 mmol), and 4-iodophenyl 4-methylbenzenesulfonate (**3.22**) (0.55 g, 1.9 mmol) were combined according to the representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 3 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.36 g (56 %) of the title compound **3.32** was isolated as an orange oil.

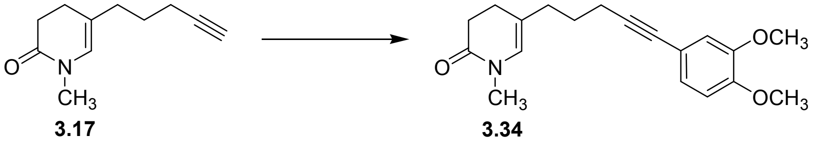
IR (neat): 2935, 1667, 862 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.68 (d, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.80 (s, 1H), 3.01 (s, 3H), 2.51-2.47 (m, 2H), 2.44 (s, 3H), 2.39 (t, *J* = 6.9 Hz, 2H), 2.26-2.22 (m, 2H), 2.17 (t, *J* = 7.2 Hz, 2H), 1.73-1.67 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 149.8, 146.5, 133.8, 133.2, 130.8, 129.5, 127.0, 123.9, 123.4, 119.4, 91.8, 80.9, 34.6, 33.8, 32.0, 27.6, 25.2, 22.7, 19.8. HRMS (ESI) calcd for $C_{24}H_{25}NO_4Na^{32}S$ (M + Na)$^+$: 446.1402. Found: 446.1413.



1-Methyl-5-(5-(4-(trifluoromethyl)phenyl)pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.33)

Enamide **3.17** (0.35 g, 2.0 mmol), bis(triphenylphosphine)palladium(II) chloride (69 mg, 0.10 mmol), copper iodide (38 mg, 0.20 mmol), and 4-iodobenzotrifluoride (0.4 mL, 2.4 mmol) were combined according to representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 4 h. After purification by column chromatography on triethylamine washed silica gel (4:1→2:1→1:1 hexanes:ethyl acetate), 0.58 g (91 %) of the title compound **3.33** was isolated as a yellow oil.

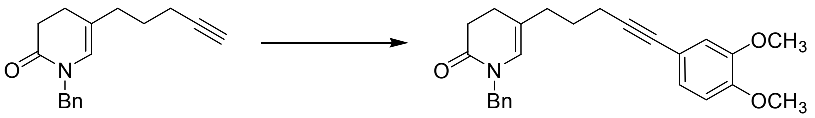
IR (neat): 3323, 2937, 1681, 843 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52-7.44 (m, 4H), 5.79 (s, 1H), 3.00 (s, 3H), 2.49-2.45 (m, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.25-2.21 (m, 2H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.74-1.67 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 132.7, 130.3 (q, *J* = 32 Hz), 128.7, 127.1, 126.1 (q, *J* = 4 Hz), 125.0 (q, *J* = 271 Hz), 119.3, 93.4, 81.0, 34.6, 33.7, 32.0, 27.5, 25.1, 19.8. HRMS (ESI) calcd for $C_{18}H_{18}NOF_3Na$ (M + Na)$^+$: 344.1238. Found: 344.1249.



5-(5-(3,4-dimethoxyphenyl)pent-4-ynyl)-1-methyl-3,4-dihydropyridin-2(1*H*)-one (3.34)

Enamide **3.17** (0.10 g, 0.56 mmol), bis(triphenylphosphine)palladium(II) chloride (20 mg, 0.028 mmol), copper iodide (11 mg, 0.056 mmol), and 4-iodoveratrole (0.16 g, 0.62 mmol) were combined according to the representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 5 h. After purification by column chromatography on triethylamine washed silica gel (4:1→1:1→1:3 hexanes:ethyl acetate), 0.12 g (69 %) of the title compound **3.34** was isolated a clear, yellow oil.

IR (neat): 2936, 1667, 854, 810, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.97 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.89 (d, *J* = 1.7, 1H), 6.76 (d, *J* = 8.3, 1H), 5.80 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.01 (s, 3H), 2.50-2.46 (m, 2H), 2.40 (t, *J* = 7.0, 2H), 2.27-2.23 (m, 2H), 2.18 (t, *J* = 7.4, 2H), 1.74-1.67 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.0, 150.0, 149.6, 127.0, 125.6, 119.6, 117.0, 115.3, 112.0, 88.8, 82.0, 56.9, 34.6, 33.8, 32.0, 27.8, 25.2, 19.9. HRMS (ESI) calcd for $C_{19}H_{23}NO_3Na$ (M + Na)$^+$: 336.1576. Found: 336.1568.

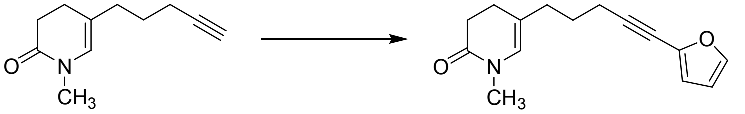


3.18 **3.35**

1-Benzyl-5-(5-(3,4-dimethoxyphenyl)pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.35)

Enamide **3.18** (0.14 g, 0.57 mmol), bis(triphenylphosphine)palladium(II) chloride (20 mg, 0.029 mmol), copper iodide (11 mg, 0.057 mmol), and 4-iodoveratrole (0.21 g, 0.8 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 2.5 h. After purification by column chromatography on triethylamine washed silica gel (4:1→1:1→1:3 hexanes:ethyl acetate), 0.20 g (92 %) of the title compound **3.35** was isolated as a clear, orange oil.

IR (neat): 2936, 1666, 1513, 732 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.23 (m, 5H), 6.96 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.84 (t, *J* = 1.2 Hz, 1H), 4.67 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.31-2.27 (m, 2H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.68 (qt, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.8, 150.0, 149.6, 138.3, 129.6, 128.5, 128.4, 125.6, 125.5, 120.2, 117.1, 115.3, 112.0, 88.8, 82.0, 56.9, 56.8, 49.9, 33.9, 32.3, 27.7, 25.2, 19.8. HMRS (ESI) calcd for $C_{25}H_{27}NO_3Na$ (M + Na)$^+$: 412.1889. Found: 412.1891.

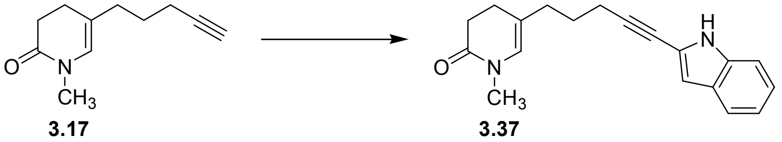


3.17 **3.36**

5-(5-(Furan-2-yl)pent-4-ynyl)-1-methyl-3,4-dihydropyridin-2(1*H*)-one (3.36)

Enamide **3.17** (0.30 g, 1.7 mmol), bis(triphenylphosphine)palladium(II) chloride (59 mg, 0.10 mmol), copper iodide (32 mg, 0.17 mmol), and 2-bromofuran (0.56 g, 88.6 wt %, 3.4 mmol) were combined according to the representative procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 24 h. After purification by column chromatography on triethylamine washed silica gel (4:1→2:1→1:1 hexanes:ethyl acetate), 0.39 g (95 %) of the title compound **3.36** was isolated as an orange oil.

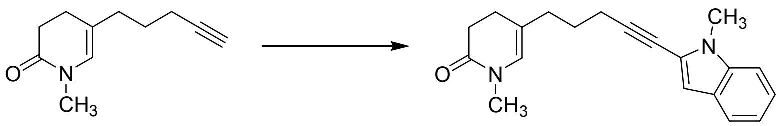
IR (neat): 3115, 2933, 2236, 1663, 744 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33 (d, *J* = 1.3 Hz, 1H), 6.47 (d, *J* = 3.1 Hz, 1H), 6.36-6.35 (m, 1H), 5.82 (s, 1H), 3.03 (s, 3H), 2.52-2.48 (m, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.72-2.23 (m, 2H), 2.19 (t, *J* = 7.4, 2H), 1.75-1.68 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.0, 143.8, 138.4, 127.1, 119.3, 114.8, 111.7, 94.9, 72.6, 34.6, 33.7, 32.0, 27.3, 25.2, 19.9. HRMS (ESI) calcd for $C_{15}H_{17}NO_2Na$ (M + Na)$^+$: 266.1157. Found: 266.1152.



5-(5-(1*H*-Indol-2-yl)pent-4-ynyl)-1-methyl-3,4-dihydropyridin-2(1*H*)-one (3.37)

Enamide **3.17** (83 mg, 0.047 mmol), bis(triphenylphosphine)palladium(II) chloride (16 mg, 0.023 mmol), copper iodide (9.0 mg, 0.047 mmol), and 2-iodo-1*H*-indole (**3.24**) (0.12 g, 0.51 mmol) were combined according to the representative procedure for Sonogashira coupling reactions. After purification by column chromatography on triethylamine washed silica gel (4:1→2:1→1:1 hexanes:ethyl acetate), 92 mg (67 %) of the title compound **3.37** was isolated as a brown oil.

IR (film): 3263, 2936, 2249, 1639, 806 cm-1. 1H NMR (400 MHz, CDCl3): δ 8.75 (br s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.0 Hz, 1H), 6.69 (d, *J* = 1.3 Hz, 1H), 5.82 (s, 1H), 3.06 (s, 3H), 2.56-2.52 (m, 2H), 2.47 (t, *J* = 7.0 Hz, 2H), 2.26 (t, *J* = 8.1 Hz, 2H), 2.21 (t, *J* = 7.6 Hz, 2H), 1.73 (qt, *J* = 7.3 Hz, 2H). 13C NMR (100 MHz, CDCl3): δ 170.2, 136.9, 128.7, 127.0, 124.0, 121.5, 121.2, 120.4, 119.6, 111.8, 108.5, 93.8, 74.9, 34.7, 33.8, 32.1, 27.5, 25.2, 20.0. MS (APCI): 293 (M + H)$^+$.

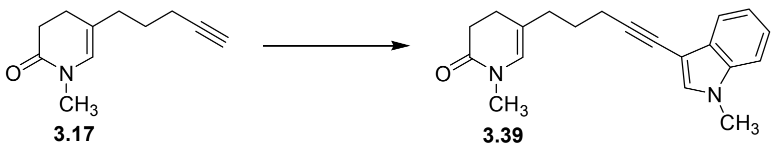


3.17 **3.38**

1-Methyl-5-(5-(1-methyl-1*H*-indol-2-yl)pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.38)

Enamide **3.17** (94 mg, 0.53 mmol), bis(triphenylphosphine)palladium(II) chloride (19 mg, 0.026 mmol), copper iodide (10 mg, 0.053 mmol), and 2-iodo-1-methyl-1*H*-indole (**3.25**) (0.18 g, 0.69 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 1 h. After purification by column chromatography on triethylamine washed silica gel (4:1→1:1→1:3 hexanes:ethyl acetate), 0.15 g (94 %) of the title compound **3.38** was isolated as a yellow oil.

IR (neat): 2936, 1667, 750 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.26-7.23 (m, 2H), 7.13-7.10 (m, 1H), 6.69 (s, 1H), 5.83 (s, 1H), 3.79 (s, 3H), 3.04 (s, 3H), 2.55-2.50 (m, 4H), 2.25 (dt, *J* = 15.5, 7.7 Hz, 4H), 1.78 (qt, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 137.9, 128.2, 127.1, 123.6, 121.7, 120.9, 119.3, 110.3, 107.3, 96.7, 74.0, 34.7, 33.8, 32.1, 31.5, 27.7, 25.2, 20.2. HRMS (ESI) calcd for $C_{20}H_{22}N_2ONa$ (M + Na)$^+$: 329.1630. Found: 329.1638.

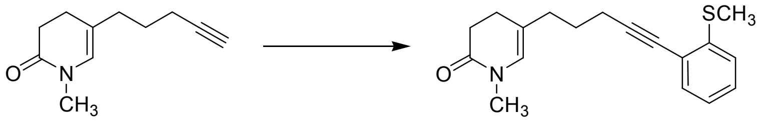


3.17 **3.39**

1-Methyl-5-(5-(1-methyl-1*H*-indol-3-yl)pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.41)

Enamide **3.17** (0.21 g, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (41 mg, 0.60 mmol), copper(I) iodide (22 mg, 0.12 mmol), and 3-iodo-1-methyl-1*H*-indole (**3.27**) (0.5 mL, 2 mmol) were combined according to the representative procedure, except that the reaction mixture was stirred for 22 h. After purification by column chromatography on triethylamine washed silica gel (4:1→2:1→1:1 hexanes:ethyl acetate), 0.12 g (32 %) of the title compound **3.39** was isolated as an orange oil.

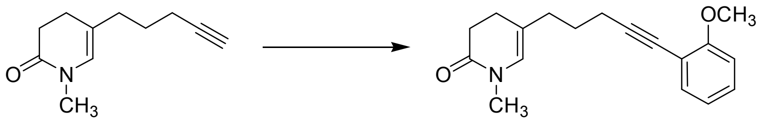
IR (film): 2935, 1659, 1541 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.31-7.24 (m, 2H), 7.20-7.17 (m, 2H), 5.83 (s, 1H), 3.75 (s, 3H), 3.03 (s, 3H), 2.52-2.49 (m, 4H), 2.26 (q, *J* = 8.0 Hz, 4H), 1.79-1.72 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.0, 137.1, 132.5, 130.3, 126.9, 123.5, 121.0, 120.9, 119.8, 110.5, 98.5, 91.5, 75.1, 34.6, 33.9, 33.8, 32.1, 28.1, 25.2, 20.2. HRMS (ESI) calcd for $C_{20}H_{22}N_2ONa$ (M + Na)$^+$: 329.1630. Found: 329.1624.


3.17 **3.40**

1-Methyl-5-(5-(2-(methylthio)phenyl)pent-4-ynyl)-3,4-dihydropyridin-2(1*H*)-one (3.40)

Enamide **3.17** (0.21 g, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (42 mg, 0.060 mmol), copper(I) iodide (23 mg, 0.12 mmol), and 2-iodo thioanisole (0.39 g, 1.6 mmol) were combined according to the representative procedure, except that the reaction mixture was stirred for 1 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.33 g (92 %) of the title compound **3.40** was isolated as a clear, yellow oil.

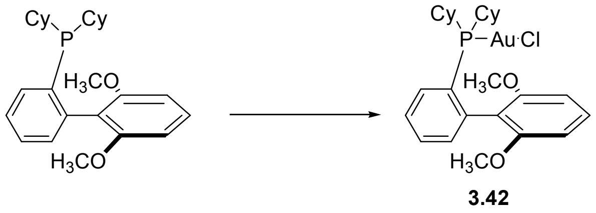
IR (neat): 2924, 1667, 753 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.28-7.24 (m, 1H), 7.13-7.11 (m, 1H), 7.06 (td, *J* = 7.4, 1.2 Hz, 1H), 5.87 (s, 3H), 3.02 (s, 3H), 2.52-2.49 (m, 4H), 2.47 (s, 3H), 2.29-2.25 (m, 4H), 1.78-1.71 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.0, 142.2, 133.2, 129.2, 127.1, 125.1, 124.7, 122.8, 119.5, 97.4, 79.8 34.6, 33.6, 32.1, 27.6, 25.2, 20.0, 16.0. HRMS (ESI) calcd for $C_{18}H_{21}NONaS$ (M + Na)$^+$: 322.1242. Found: 322.1246.


3.17 **3.41**

5-(5-(2-Methoxyphenyl)pent-4-ynyl)-1-methyl-3,4-dihydropyridin-2(1*H*)-one (3.41)

Enamide **3.17** (0.27 g, 1.5 mmol), bis(triphenylphosphine)palladium(II) chloride (54 mg, 0.076 mmol), copper(I) iodide (29 mg, 0.15 mmol), and 2-iodoanisole (0.3 mL, 2 mmol) were combined according to the representative procedure, except that the reaction mixture was stirred for 1 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.35 g (81 %) of the title compound **3.41** was isolated as a clear, yellow oil.

IR (neat): 2938, 1668, 755 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.27-7.22 (m, 1H), 6.89-6.84 (m, 2H), 5.83 (s, 1H), 3.86 (s, 3H), 3.01 (s, 3H), 2.48 (q, *J* = 7.1 Hz, 4H), 2.27-2.20 (m, 4H), 1.73 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.1, 160.0, 133.7, 129.2, 126.1, 120.6, 118.8, 113.1, 110.7, 93.8, 55.9, 33.7, 32.8, 31.2, 26.8, 24.3, 19.3. HRMS (ESI) calcd for $C_{18}H_{21}NO_2Na$ (M + Na)$^+$: 306.1470. Found: 306.1466.



Gold Complex (3.42)

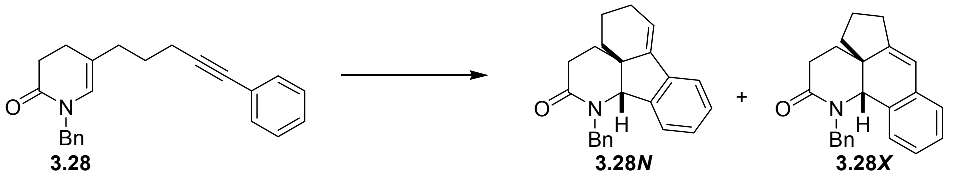
A filtering flask was charged with a solution of 0.18 g of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (*S*-Phos) (0.43 mmol) in 20 mL of ethanol. A solution of 72 mg of hydrogen tetrachloro(III)aurate hydrate (0.21 mmol) in 5 mL of ethanol was filtering into the flask, mixing with the solution contained inside. The solution was concentrated to half volume by rotary evaporation *in vacuo* to afford a solution containing a white precipitate. The precipitate was filtered and washed with ethanol. The white solid was recrystallized from dichloromethane and hexanes to afford 79 mg (58 %) of the title compound **3.42** as clear, colorless crystals, mp 251 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.42 (m, 4H), 7.22-7.18 (m, 2H), 6.66 (d, J = 8.5 Hz, 2H), 3.70 (s, 6H), 2.19-2.09 (m, 2H), 1.97-1.93 (m, 2H), 1.81-1.64 (m, 8H), 1.46-1.40 (m, 2H), 1.36-1.15 (m, 8H). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 39.2.

3.42 has been previously prepared, see: Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.

3.7.3 Reactions of Substrates

Representative Procedure for $PtCl_2$ and $PtBr_2$ Catalyzed Cycloisomerization Reactions



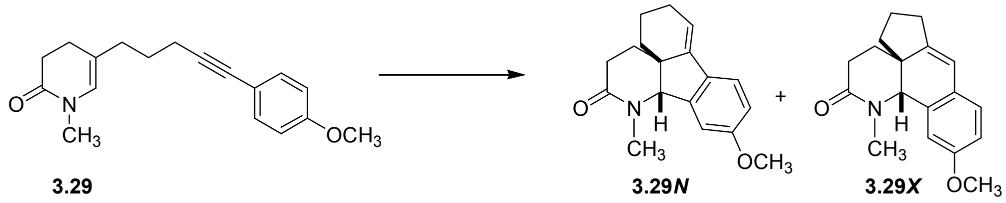
	3.28N		3.28X
$PtCl_2$:	4	:	1
$PtBr_2$:	1.5	:	1

Tetracycles 3.28*N* and 3.28*X*

Method A ($PtCl_2$ as a catalyst): A solution of 41 mg of enesulfonamide **3.28** (0.13 mmol) and 3.3 mg of platinum(II) chloride (0.013 mmol) in 0.5 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (3:1 hexanes:ethyl acetate) to afford 32 mg (77 %) of a 4:1 mixture of **3.28*N*** and **3.28*X*** as a white solid, mp: 117-119 °C.

Method B (PtBr$_2$ as a catalyst): A solution of 58 mg of enesulfonamide **3.28** (0.18 mmol) and 6.2 mg of platinum(II) bromide (0.018 mmol) in 1.2 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (3:1 hexanes:ethyl acetate) to afford 35 mg (61 %) of a 1.5:1 mixture of **3.28*N*** and **3.28*X*** as a white solid.

IR (film): 2933, 1649, 756 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.13 (m, 9H), 5.95 (t, *J* = 3.7 Hz, 1H), 5.67 (d, *J* = 14.6 Hz, 1H), 4.39 (s, 1H), 4.37 (d, *J* = 14.6 Hz, 1H), 2.41-2.33 (m, 1H), 2.30-2.22 (m, 1H), 2.19-2.08 (m, 1H), 2.02-1.93 (m, 2H), 1.77-1.66 (m, 4H), 1.25-1.23 (m, 1H). Additional signals associated with the minor isomer **3.28*X***: δ 7.05-7.03 (m, 1H), 6.21 (br s, 1H), 5.98 (d, *J* = 14.6 Hz, 1H), 4.30 (s, 1H), 3.73 (d, *J* = 13.9 Hz, 1H), 1.44-1.38 (m, 2H), 0.98-0.89 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.9, 171.2, 153.1, 145.0, 144.1, 141.0, 138.6, 138.4, 135.7, 135.4, 130.0, 129.7, 129.5, 129.1, 128.7, 128.6, 127.9, 127.8, 126.9, 125.4, 124.1, 121.2, 119.3, 70.0, 66.0, 51.6, 51.5, 46.7, 45.9, 35.6, 33.8, 33.0, 31.8, 30.0, 29.7, 25.3, 23.8, 23.5, 19.0. HRMS (ESI) calcd for C$_{23}$H$_{23}$NONa (M + Na)$^+$: 352.1677. Found: 352.1681.



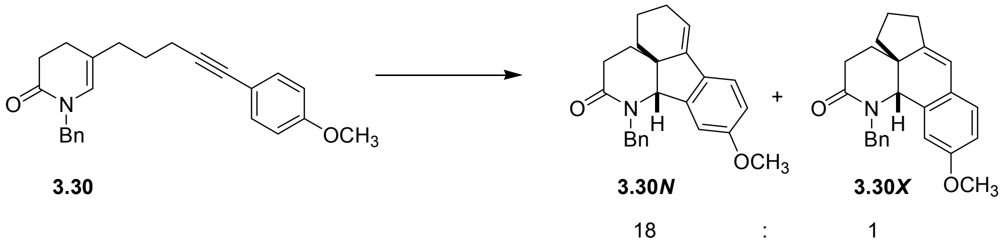
PtCl$_2$: 7 : 1
PtBr$_2$: 9 : 1

Tetracycles 3.29*N* and 3.29*X*

Method A: Enamide **3.29** (95 mg, 0.33 mmol), platinum(II) chloride (8.7 mg, 0.033 mmol), and 1.3 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 73 mg (79 %) of a 7:1 mixture of **3.29*N*** and **3.29*X*** was isolated as a yellow foam.

Method B: Enamide **3.29** (43 mg, 0.15 mmol), platinum(II) bromide (5.3 mg, 0.015 mmol), and 1.0 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 37 mg (88 %) of a 9:1 mixture of **3.29*N*** and **3.29*X*** was isolated as a yellow oil.

IR (film): 2936, 1642, 731 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30 (d, *J* = 8.3 Hz, 1H), 6.84-6.83 (m, 1H), 6.82-6.79 (m, 1H), 5.87 (t, *J* = 3.5 Hz, 1H), 4.33 (s, 1H), 3.80 (s, 3H), 3.36 (s, 3H), 2.40-2.32 (m, 1H), 2.28-2.21 (m, 1H), 2.18-2.07 (m, 2H), 1.88-1.69 (m, 5H), 1.57 (td, *J* = 13.1, 3.5 Hz, 1H). Addition signals associated with the minor isomer **3.29*X***: δ 7.18 (d, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 8.3 Hz,1H), 6.90 (d, *J* = 9.2 Hz, 1H), 6.20 (s, 1H), 4.26 (s, 1H), 3.83 (s, 2H), 3.80 (s, 3H), 3.24 (s, 3H), 2.78 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.1, 171.3, 161.0, 160.5, 150.1, 145.8, 144.0, 133.2, 131.0, 127.8, 122.4, 118.9, 117.4, 115.1, 115.0, 113.0, 112.3, 110.0, 74.0, 70.6, 56.5, 56.3, 46.9, 46.2, 38.0, 32.3, 30.4, 30.3, 25.3, 18.9. HRMS (ESI) calcd for $C_{18}H_{21}NO_2Na$ (M + Na)$^+$: 306.1470. Found: 306.1479.

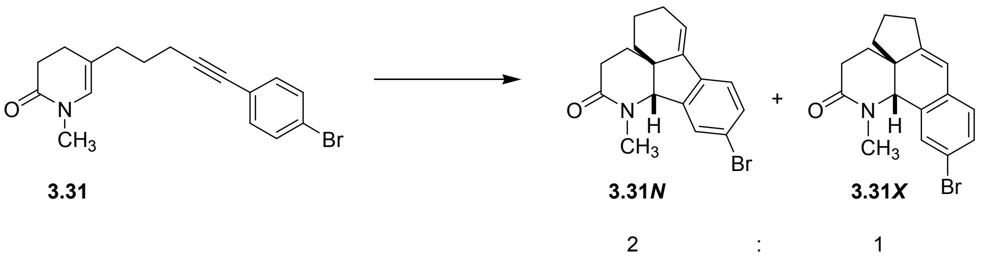


3.30 **3.30*N*** **3.30*X***

Tetracycles 3.30*N* and 3.30*X*

Method A: Enamide **3.30** (68 mg, 0.19 mmol), platinum(II) chloride (5.0 mg, 0.019 mmol), and 0.5 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (5:1→1:1 hexanes:ethyl acetate), 54 mg (79 %) of an 18:1 mixture of **3.30*N*** and **3.30*X*** was isolated as a white foam.

IR (film): 2938, 1642, 732, 648 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32-7.25 (m, 6H), 6.77 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.78 (t, *J* = 3.7 Hz, 1H), 5.34 (d, *J* = 14.5 Hz, 1H), 4.50 (d, *J* = 14.5 Hz, 1H), 4.39 (s, 1H), 3.68 (s, 3H), 2.39-2.32 (m, 1H), 2.27-2.20 (m, 1H), 2.18-2.11 (m, 1H), 2.05-1.93 (m, 2H), 1.78-1.63 (m, 4H), 1.32-1.25 (m, 1H). Additional signals associated with the minor isomer **3.30*X***: δ 6.97 (d, *J* = 8.2 Hz, 1H), 6.16 (s, 1H), 5.95 (d, *J* = 14.1 Hz, 1H), 4.26 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (100MHz, CDCl$_3$): δ 173.2, 161.1, 145.7, 144.5, 138.8, 133.7, 129.8, 129.7, 128.7, 122.0, 116.7, 115.8, 108.8, 70.5, 56.5, 52.0, 47.3, 34.4, 33.6, 32.1, 25.2, 19.0. HRMS (ESI) calcd for $C_{24}H_{25}NO_2Na$ (M + Na)$^+$: 382.1783. Found: 382.1771.



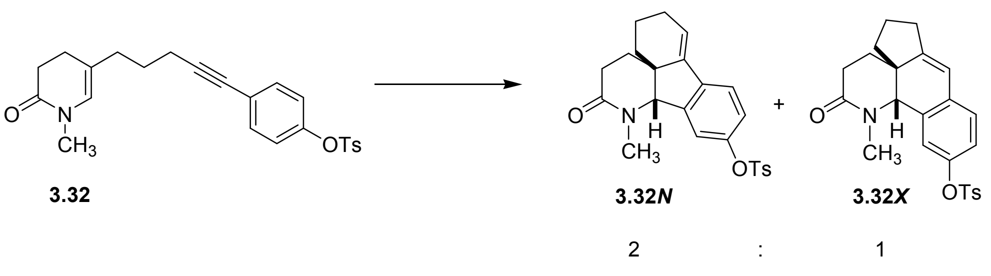
3.31 **3.31*N*** **3.31*X***

2 : 1

Tetracycles 3.31*N* and 3.31*X*

Method A: Enamide **3.31** (69 mg, 0.21 mmol), platinum(II) chloride (5.5 mg, 0.021 mmol), and 0.75 mL of toluene were combined according to the representative procedure, except that the reaction mixture was stirred at 130 °C for 16 h. After purification by column chromatography on triethylamine washed silica gel (5:1→1:1 hexanes:ethyl acetate), 46 mg (66 %) of an 2:1 mixture of **3.31*N*** and **3.31*X*** was isolated as a clear, yellow oil

IR (film): 3289, 2942, 1667, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.42-7.40 (m, 1H), 7.27-7.23 (m, 1H), 6.02 (t, J = 3.5 Hz, 1H), 4.33 (s, 1H), 3.32 (s, 3H), 2.61-2.30 (m, 2H), 2.28-2.21 (m, 1H), 2.19-2.03 (m, 2H), 1.96-1.65 (m, 4H), 1.63-1.53 (m, 1H). Additional signals associated with the minor isomer **3.31*X***: δ 7.34-7.31 (m, 1H), 7.16 (s, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.20 (s, 1H), 4.28 (s, 1H), 3.23 (s, 3H), 1.49-1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 171.1, 153.7, 146.2, 143.6, 139.4, 138.1, 134.0, 132.3, 131.7, 128.8, 128.2, 127.9, 122.4, 121.5, 120.7, 118.5, 73.7, 70.1, 46.8, 46.3, 38.4, 38.0, 35.9, 32.0, 31.1, 30.2, 30.1, 29.4, 25.5, 24.0, 23.8, 18.8. HRMS (ESI) calcd for $C_{17}H_{18}NONa^{79}Br$ $(M + Na)^+$: 354.0469. Found: 354.0476.



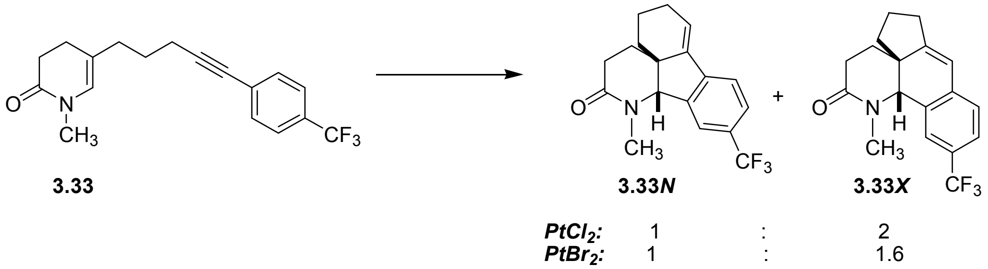
3.32 **3.32*N*** **3.32*X***

2 : 1

Tetracycles 3.32*N* and 3.32b

Enamide **3.32** (53 mg, 0.13 mmol), platinum(II) chloride (3.3 mg, 0.013 mmol), and 0.6 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→0:1 hexanes:ethyl acetate), 36 mg (68 %) of an 2:1 mixture of **3.32*N*** and **3.32*X*** was isolated as a clear, colorless oil.

IR (film): 2937, 1641, 812, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.31 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.68 (s, 1H), 5.99 (t, *J* = 3.5 Hz, 1H), 4.24 (s, 1H), 3.11 (s, 3H), 2.47 (s, 3H), 2.34-2.11 (m, 4H), 2.05-1.96 (m, 1H), 1.91-1.81 (m, 1H), 1.74-1.71 (m, 2H), 1.57-1.49 (m, 2H). Additional signals associated with the minor isomer **3.32*X***: δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.04-7.01 (m, 1H), 6.96-6.94 (m, 1H), 6.37 (s, 1H), 6.19 (s, 1H), 4.15 (s, 1H), 2.93 (s, 3H), 2.45 (s, 3H), 1.42-1.37 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 170.7, 153.8, 150.2, 149.9, 146.8, 146.6, 145.5, 143.4, 139.3, 137.6, 134.0, 133.3, 133.2, 130.8, 129.6, 129.5, 127.8, 123.7, 123.0, 122.5, 120.9, 119.9, 118.8, 118.2, 73.6, 70.0, 46.9, 46.1, 38.0, 37.7, 35.8, 32.0, 31.0, 30.1, 29.3, 25.5, 23.9, 23.8, 22.7, 18.7. HRMS (ESI) calcd for $C_{24}H_{26}NO4^{32}S$ $(M + H)^+$: 424.1583. Found: 424.1587.



Tetracycles 3.33*N* and 3.33*X*

Method A: Enamide **3.35** (43 mg, 0.13 mmol), platinum(II) chloride (3.5 mg, 0.013 mmol), and 0.6 mL of toluene were combined according to the representative procedure, except that the reaction mixture was stirred at 130 °C for 16 h. After purification by column chromatography on triethylamine washed silica gel (1:1 dichloromethane:hexanes→2:3 dichloromethane:diethyl ether→9:1 dichloromethane:methanol), 22 mg (52 %) of a 1:2 mixture of **3.33*N*** and **3.33*X*** was isolated as a white solid. X-ray quality crystals were obtained from methanol, mp: 145-147 °C.

Method B: Enamide **3.33** (55 mg, 0.17 mmol), platinum(II) bromide (6.1 mg, 0.017 mmol), and 1.0 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→0:1 hexanes:ethyl acetate), 25 mg (46 %) of a 1:1.6 mixture of **3.33*N*** and **3.33*X*** was isolated as a yellow crystalline solid. IR (film): 2943, 1631, 733 cm^{-1}. ^{1}H (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.49 (s, 1H), 7.14 (s, 1H), 6.30 (s, 1H), 4.33 (s, 1H), 3.26 (s, 3H), 2.66-2.07 (m, 5H), 2.00-1.46 (m, 5H). Additional signals associated with the minor isomer **3.33*N***: δ 7.51 (s, 1H), 7.46 (s, 1H), 7.12 (s, 1H), 6.16 (t,

J = 3.7 Hz, 1H), 4.39 (s, 1H), 3.37 (s, 3H). ^{13}C (100 MHz, CDCl$_3$): δ 170.8, 170.2, 155.3, 143.9, 143.0, 142.7, 137.7, 135.8, 130.2 (q, J = 32 Hz), 129.0 (q, J = 32 Hz), 126.1, 125.6 (q, J = 4 Hz), 125.0 (q, J= 4 Hz), 124.3 (q, J = 271 Hz), 124.2 (q, J = 271 Hz), 121.9, 121.4 (q, J = 4 Hz), 121.0, 120.7 (q, J = 4 Hz), 117.7, 72.9, 69.2, 46.0, 45.6, 37.6, 37.3, 35.0, 31.0, 30.3, 29.2, 29.0, 28.5, 24.7, 23.1, 22.8, 17.9. HRMS (ESI) calcd for $C_{18}H_{18}NOF_3Na$ $(M + Na)^+$: 344.1238. Found: 344.1236. Anal. Calcd for $C_{18}H_{18}F_3NO$: C, 67.28; H, 5.65; N, 4.36. Found: C, 67.09; H, 5.65; N, 4.43.

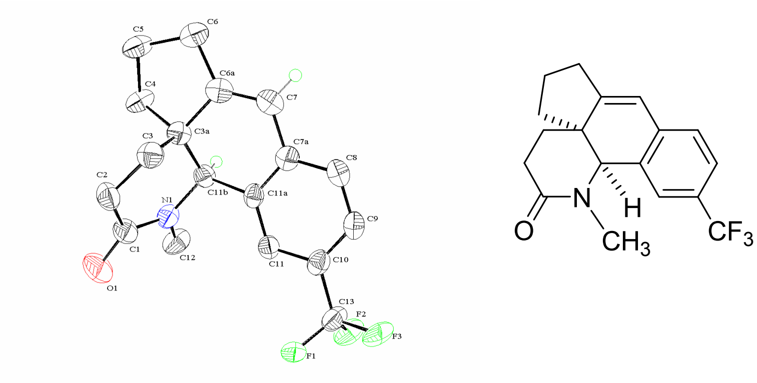

C5
C6
C6a
C7
C4
C3a
C3
C7a
C8
C2
C11b
C11a
N1
C9
C1
C12
C11
C10
O1
C13
F2
F3
F1
O
N
H
CH3
CF3

Figure 3.4: ORTEP representation of the solid state structure of **3.33*X***

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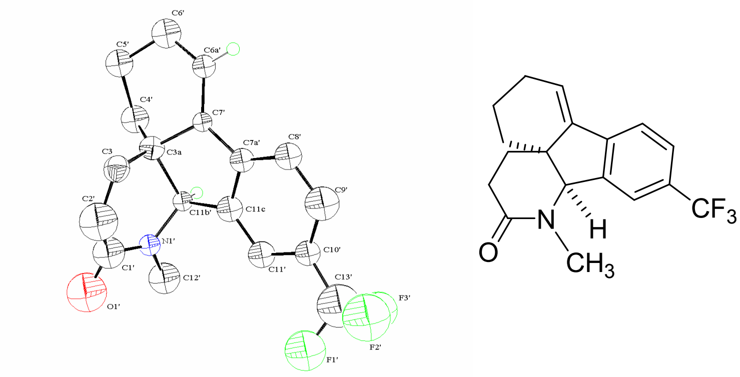
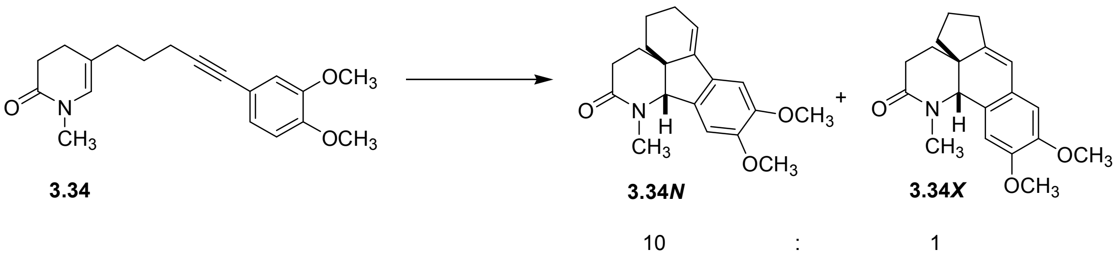

C6'
C5'
C6a'
C4'
C7'
C3
C3a
C7a'
C8'
C2'
C11b'
C11c
C9'
N1'
C1'
C12'
C11'
C10'
C13'
F3'
O1'
F2'
F1'
O
N
H
CH3
CF3

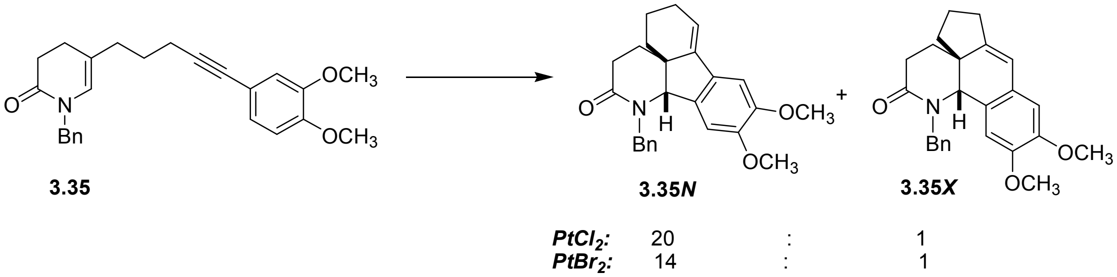
Figure 3.5: ORTEP representation of the solid state structure of **3.33*N***

……



Tetracycles 3.34*N* and 3.34*X*

Method A: Enamide **3.34** (34 mg, 0.11 mmol), platinum(II) chloride (2.8 mg, 0.011 mmol), and 0.5 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1 hexanes:ethyl acetate), 33 mg (98 %) of a 10:1 mixture of **3.34*N*** and **3.34*X*** was isolated as an off-white solid, mp: 132-134 ^{o}C. IR (neat): 2964, 1642, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.76 (s, 1H), 5.82 (br s, 1H), 4.33 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.33 (s, 3H), 2.37-2.22 (m, 3H), 2.14-2.03 (m, 2H), 1.90-1.83 (m, 2H), 1.77-1.71 (m, 2H), 1.62-1.52 (m, 1H). Additional signals associated with the minor isomer **3.34*X***: δ 6.60 (s, 2H), 6.15 (br s, 1H), 3.25 (s, 3H), 2.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 150.7, 150.6, 144.8, 136.4, 133.2, 116.9, 107.2, 104.0, 73.8, 57.1, 57.0, 47.0, 37.9, 32.8, 31.3, 30.6, 25.2, 18.9. HRMS (ESI) calcd for $C_{19}H_{23}NO_3Na$ (M + Na)$^+$: 336.1576. Found: 336.1570.



Tetracycles 3.35*N* and 3.35*X*

Method A: Enamide **3.35** (63 mg, 0.16 mmol), platinum(II) chloride (4.3 mg, 0.016 mmol), and 0.75 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 49 mg (78 %) of a 20:1 mixture of **3.35*N*** and **3.35*X*** was isolated as a white solid. X-ray quality crystals were obtained by recrystallization from dichloromethane and hexanes, mp: 147-149 ^{o}C.

Method B: Enamide **3.35** (48 mg, 0.12 mmol), platinum(II) bromide (4.4 mg, 0.012 mmol), and 0.75 mL of toluene were combined according to the representative procedure: After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 38 mg (79 %) of a 14:1 mixture of **3.35*N*** and **3.35*X*** was isolated as a white solid.

IR (film): 2939, 1644, 1497, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.36 (m, 2H), 7.34-7.28 (m, 3H), 6.82 (s, 1H), 6.19 (s, 1H), 5.74 (t, *J* = 3.7 Hz, 1H), 4.99 (d, *J* = 14.1 Hz, 1H), 4.74 (d, *J* = 14.5 Hz, 1H), 4.42 (s, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 2.35-2.27 (m, 1H), 2.24-2.23 (m, 1H), 2.22-2.12 (m, 1H), 2.02-1.86 (m, 2H), 1.77-.174 (m, 2H), 1.73-1.64 (m, 2H), 1.39-1.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 150.8, 150.6, 145.3, 139.2, 136.1, 133.6, 130.0, 129.8, 128.8, 116.1, 106.7, 103.4, 70.9, 57.1, 57.0, 52.4, 47.6, 35.2, 34.7, 32.5, 25.1, 19.1. HRMS (ESI) calcd for $C_{25}H_{27}NO_3Na$ $(M + Na)^+$: 412.1889. Found: 412.1877. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.03; H, 6.85; N, 3.55.

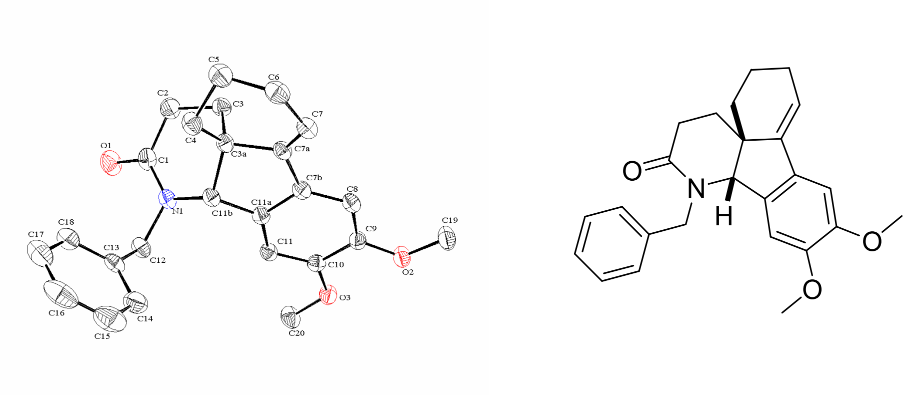
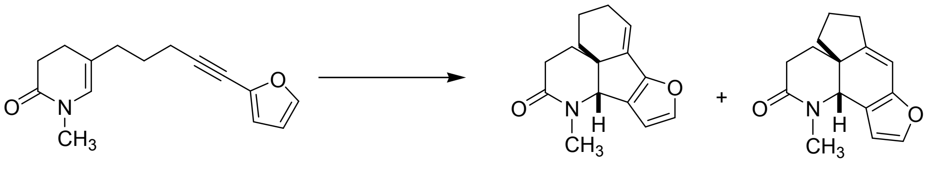


Figure 3.6: ORTEP representation of the solid state structure of **3.35*N***

……



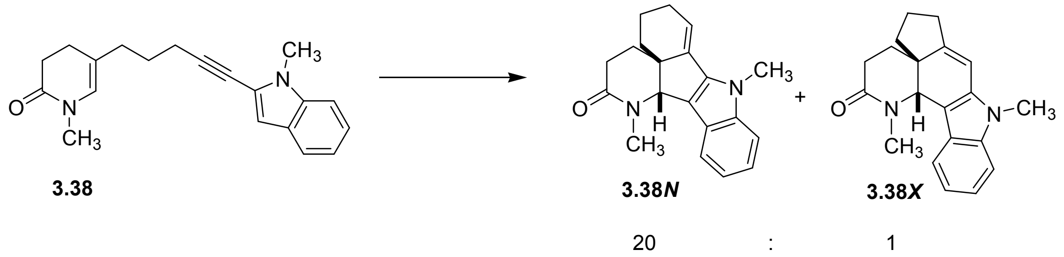
3.36 **3.36*N*** **3.36*X***

7 : 1

Tetracycles 3.36*N* and 3.36*X*

Method A: Enamide **3.36** (40 mg, 0.16 mmol), platinum(II) chloride (4.4 mg, 0.016 mmol), and 0.6 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1 hexanes:ethyl acetate), 21 mg (51 %) of a 7:1 mixture of **3.36*N*** and **3.36*X*** was isolated as a yellow oil.

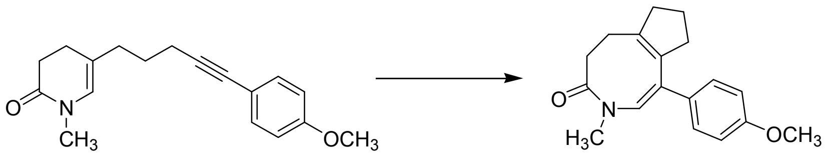
IR (film): 2941, 1638, 729 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35 (s, 1H), 6.36 (d, *J* = 1.8 Hz, 1H), 5.62 (t, *J* = 3.7 Hz, 1H), 4.22 (s, 1H), 3.15 (s, 3H), 2.44-2.32 (m, 2H), 2.30-2.20 (m, 2H), 2.15 (dt, *J* = 12.2, 3.0 Hz, 1H), 2.05-1.90 (m, 2H), 1.82-1.75 (m, 2H), 1.68-1.58 (m, 1H). Additional signals associated with the minor isomer **3.36*X***: δ 7.24 (s, 1H), 6.34 (s, 1H), 6.13 (s, 1H), 4.47 (s, 1H), 3.19 (s, 3H), 2.84 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.8, 158.8, 147.5, 135.7, 128.7, 114.4, 109.3, 67.6, 50.6, 35.3, 31.4, 30.4, 29.6, 24.3, 18.3. HRMS (ESI) calcd for $C_{15}H_{17}NO_2Na$ (M + Na)$^+$: 266.1157. Found: 266.1155.



Tetracycles 3.38*N* and 3.38*X*

Method A: Enamide **3.38** (43 mg, 0.14 mmol), platinum(II) chloride (3.7 mg, 0.014 mmol), and 1.2 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1 hexanes:ethyl acetate), 34 mg (80 %) of a 20:1 mixture of **3.38*N*** and **3.38*X*** was isolated as a yellow film.

IR (film): 2936, 1640, 731 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 7.23-7.20 (m, 1H), 7.13-7.09 (m, 1H), 5.81 (t, *J* = 3.9 Hz, 1H), 4.51 (s, 1H), 3.81 (s, 3H), 3.41 (s, 3H), 2.43-2.26 (m, 3H), 2.21-2.12 (m, 3H), 1.90-1.84 (m, 3H), 1.77-1.69 (m, 1H). Additional signals associated with the minor isomer **3.38*X***: δ 6.25 (s, 1H), 4.27 (s, 1H), 3.86 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.1, 144.3, 143.6, 138.8, 123.7, 123.1, 121.4, 121.0, 120.7, 116.4, 110.7, 69.6, 51.5, 37.3, 33.8, 32.9, 31.9, 30.7, 25.0, 18.5. HRMS (ESI) calcd for $C_{20}H_{22}N_2ONa$ (M + Na)$^+$: 329.1630. Found: 329.1619.



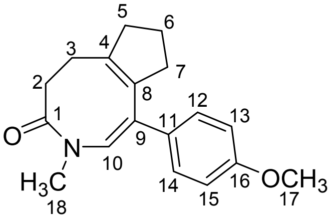
3.29 **3.51**

(*Z*)-1-(4-Methoxyphenyl)-3-methyl-5,6,8,9-tetrahydro-3*H*-cyclopenta[*d*]azocin-4(7*H*)-one (3.51)

A solution of 0.067 g of enamide **3.29** (0.24 mmol) and 0.016 g of silver hexafluoroantimonate(V) (0.047 mmol) in 2 mL of 1,2-dichloroethane was heated to 80 °C and stirred for 18 h. The reaction mixture was cooled to rt and filtered through a pipette of triethylamine washed silica gel. The filtrate was concentrated by rotary evaporation *in vacuo* to afford a brown oil. The crude oil was dry loaded onto triethylamine washed silica gel and purified by column chromatography (1:1→1:3 hexanes:ethyl acetate) to afford 0.023 g (35 %) of the title compound **3.51** as a clear, colorless oil.

IR (neat): 2949, 1652, 1510, 831, 731 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C):δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.05 (s, 1H), 3.83 (s, 3H), 3.08 (s, 3H), 2.64 (br s, 2H), 2.43 (br s, 2H), 2.18 (br s, 4H), 1.73 (qt, *J* = 7.5 Hz, 2H). ^{1}H NMR (400 MHz, CDCl$_3$, −40 °C): δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.06 (s, 1H), 3.83 (s, 3H), 3.30-3.22 (m, 1H), 3.08 (s, 3H), 2.70-2.54 (m, 2H), 2.50-2.43 (m, 1H), 2.39-2.24 (m, 2H), 2.17 (dt, *J* = 11.7, 3.8 Hz, 1H), 2.01-1.98 (m, 1H), 1.77-1.64 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.9, 160.2, 142.7, 136.2, 132.6, 131.2, 129.5, 126.6, 114.9, 56.3, 40.8, 39.6, 35.0, 32.3, 29.8, 23.0. HRMS (ESI) calcd for $C_{18}H_{22}NO_2$ $(M + H)^+$: 284.1651. Found: 284. 1656.

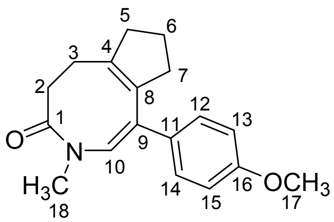
Table 3.5: NMR data for **3.51**



Carbon No.	^{13}C δ (ppm)[a]	Mult.	^{1}H δ (ppm) (mult., *J* (Hz)[b,c,d,e]	HMBC Correlations[e]
1	174.9	Q		H-10, H-18
2	32.3	CH_2	H-2a: 3.30-3.22 (m) H-2b: 2.17 (dt, 11.7, 3.8)	
3	29.8	CH_2	H-3a: 2.70-2.54 (m) H-3b: 2.70-2.54 (m)	H-2a, H-2b
4	142.7	Q		H-2a, H-2b, H-3a, H-3b, H-5a, H-5b, H-6a, H-6b, H-7a, H-7b
5	40.8	CH_2	H-5a: 2.50-2.42 (m) H-5b: 2.37-2.28 (m)	H-6a, H-6b
6	23.0	CH_2	H-6a: 1.77-1.64 (m) H-6b: 1.77-1.64 (m)	H-5a, H-5b, H-7a
7	39.6	CH_2	H-7a: 2.37-2.28 (m) H-7b: 2.00-1.97 (m)	H-6a, H-6b
8	131.2	Q		H-3a, H-3b, H-5a, H-5b, H-6a, H-6b, H-7a, H-7b
9	136.2	Q		H-10, H-12, H-14
10	126.6	CH	6.06 (s)	H-18
11	132.6	Q		H-10, H-13, H-15
12, 14	129.5	CH	H-12,14: 7.26 (d, 8.8)	H-13, H-15
13, 15	114.9	CH	H-13,15: 6.89 (d, 8.8)	H-12, H-14
16	160.2	Q		H-12, H-14, H-13, H-15, H-17
17	6.3	CH_3	H-17: 3.84 (s)	
18	35.0	CH_3	H-18: 3.08 (s)	H-10

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and COSY data. [d] Methylene protons are arbitrarily designated H-Xa and H-Xb. [e] Only those correlations which could be unambiguously assigned are recorded.

Table 3.6: NMR data for **3.51**



Proton No.	**^{1}H δ (ppm) (mult J (Hz))**[a,b]	**COSY Correlation**[c]
H-2a	3.30-3.22 (m)	H-2b, H-3a, H-3b
H-2b	2.17 (dt, 11.7, 3.8)	H-2a, H-3a, H-3b
H-3a	2.70-2.54 (m)	H-2a, H-2b, H-3b
H-3b	2.70-2.54 (m)	H-2a, H-2b, H-3a
H-5a	2.50-2.42 (m)	H-5b, H-6a, H-6b
H-5b	2.37-2.28 (m)	H-5a, H-6a, H-6b
H-6a	1.77-1.64 (m)	H-5a, H-5b, H-7a, H-7b
H-6b	1.77-1.64 (m)	H-5a, H-5b, H-7a, H-7b
H-7a	2.37-2.28 (m)	H-7b, H-6a, H-6b
H-7b	2.00-1.97 (m)	H-7a, H-6a, H-6b
H-10	6.06 (s)	
H-12, H-14	7.26 (d, 8.8)	H-13, H-15
H-13, H-15	6.89 (d, 8.8)	H-12, H-14
H-17	3.84 (s)	
H-18	3.08 (s)	

[a] Recorded at 400 MHz. [b] Assignements based on HMQC, HMBC, and COSY data.
[c] Only those correlations which could be unambiguously assigned are recorded.

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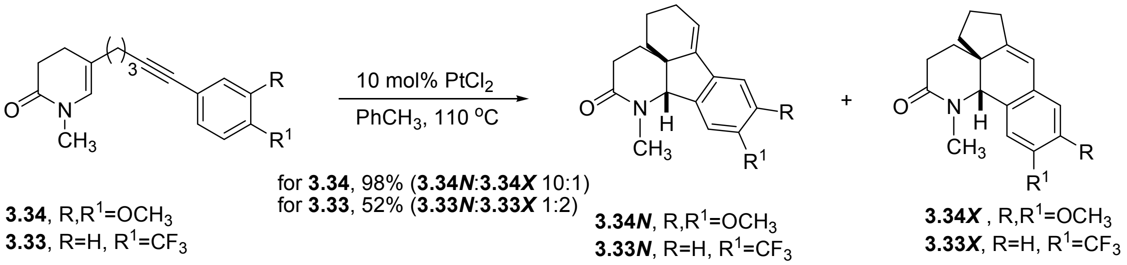
Chapter 4: Platinum(II) and Gold(I)-Catalyzed Intramolecular Tandem Addition/Friedel-Crafts Reactions between Acyclic Enamides and 1-Arylalkynes

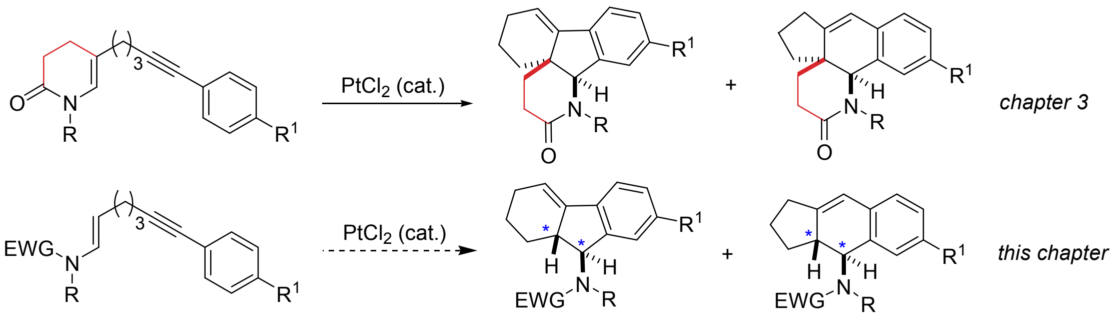
4.1 Introduction

The use of enamide derivatives as π-nucleophiles in platinum(II)-catalyzed cycloisomerization reactions was discussed in chapter 3 and proved to be an effective way to generate structurally complex nitrogen-containing tetracycles.[1] As an example, enamide **3.34**, a substrate that features an electron-rich aromatic ring, cyclized to products **3.34*N*** and **3.34*X*** in high yield and a 6-*endo* to 5-*exo* ratio of 10:1 (Scheme 4.1). Substrates employing electron deficient aromatic ring systems were generally less reactive. Enamide **3.33** was treated with 10 mol% platinum(II) chloride to give **3.33*N*** and **3.33*X*** in moderate yield and a regioisomeric ratio favoring the 5-*exo* isomer.


3
R
R1
O
N
CH3
10 mol% PtCl2
PhCH3, 110 °C
for 3.34, 98% (3.34N:3.34X 10:1)
for 3.33, 52% (3.33N:3.33X 1:2)
3.34, R,R1=OCH3
3.33, R=H, R1=CF3
H
3.34N, R,R1=OCH3
3.33N, R=H, R1=CF3
+
3.34X , R,R1=OCH3
3.33X, R=H, R1=CF3

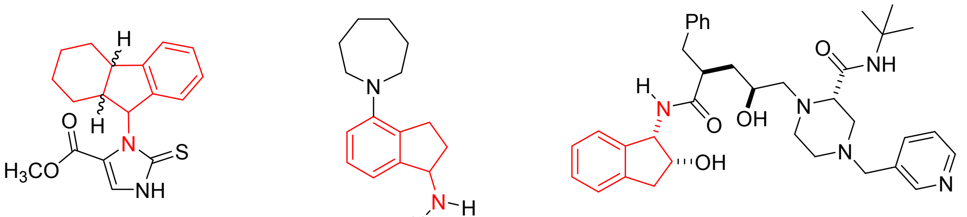
Scheme 4.1: Cycloisomerization/Friedel-Crafts addition reactions discussed in Chapter 3[1]

The enamide functional group within the substrates employed in chapter 3 was confined to a 6-membered ring, as illustrated by the red bonds in Scheme 4.2. It was proposed that a similar platinum(II)-catalyzed transformation could take place using *acyclic* enamine derivatives. Will the reactions proceed as predictably as with *cyclic* enamide substrates? Will the regiochemistry of the reaction change? What will be the stereochemical relationship between the two chiral centers (indicated by blue asterisks in Scheme 4.2)? This study presents initial work in addressing these questions.


PtCl2 (cat.)
R1
O
N
R
H
+
chapter 3
EWG
PtCl2 (cat.)
*
this chapter

Scheme 4.2: Acyclic version of the cycloisomerization of enamides

Cycloisomerization of acyclic enamides will give tricyclic structures featuring pendent amido functionalities. The nitrogen atom will not be confined to the ring system and could potentially be exploited to further functionalize the products. Biologically active compounds that are structurally related to the acyclic cycloisomerization products are shown in Figure 4.1 (common features are shown in red). Compound **4.1** has application in the agricultural industry as a herbicide.[2] Amine **4.2** is capable of controlling pain in mammals.[3] Structurally complex indinivir **4.3**, or Crixivan®, is currently used as a protease inhibitor as a part of a highly active antiretroviral therapy to treat HIV and AIDS. The platinum(II)-catalyzed cycloisomerization of acyclic enamides could be utilized to create structural analogs of these or other biologically active compounds of similar structure.



4.1 **4.2** *indinavir* (**4.3**)

Figure 4.1: Compounds structurally related to products of *acyclic* enamide cycloisomerization

The modular design of the acyclic enamide substrates should access a variety of product analogs (Figure 4.2). There are three areas of the substrates that could be altered to examine the substrate scope. First, the aromatic functional group can be easily altered to a variety of electron-donating, electron-withdrawing, or heteroaromatic moieties. Second, the enamine derivative can be changed to an enamide, an enesulfonamide, or an enecarbamate. Third, the tether can be changed by increasing or decreasing the length, as well as incorporating heteroatoms or branches if desired.

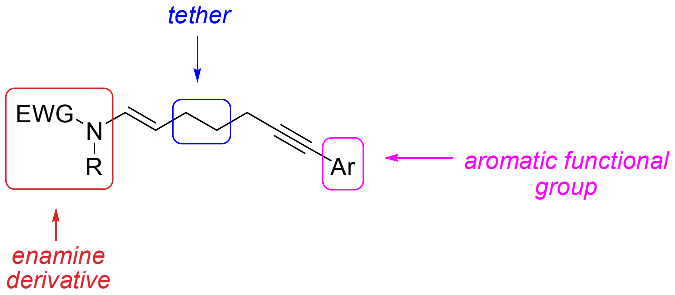
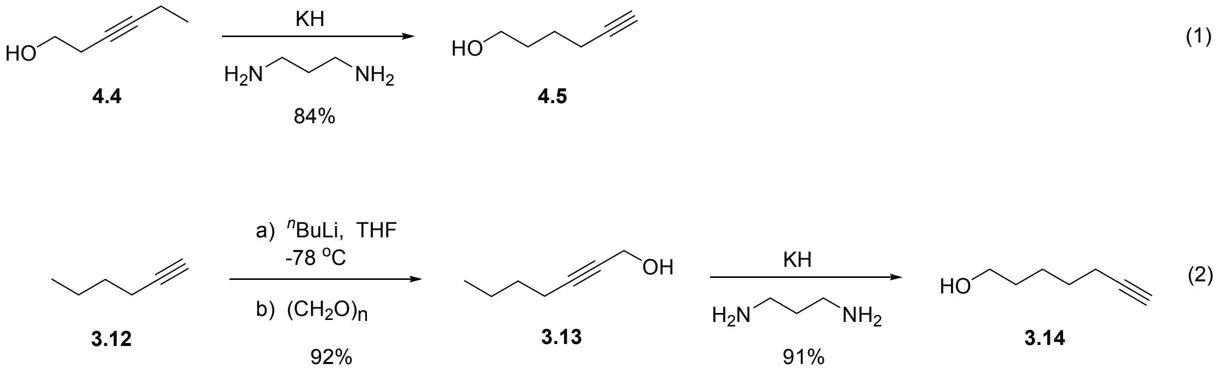


Figure 4.2: Opportunities for variation of the substrate set

The remainder of this chapter is divided into three sections. The first section describes the synthesis of the substrates that are used in the study. The following section discusses the reactions of these substrates within the context of cycloisomerization and will be followed by a brief discussion of the results. The final section describes the experimental procedures for the reactions described herein.

4.2 Synthesis of Substrates

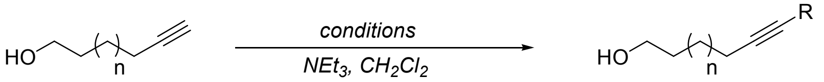
Substrate synthesis for this study commenced with the formation of hex-5-yn-1-ol (**4.5**) and hept-6-yn-1-ol (**3.14**) (Scheme 4.3). An acetylenic zipper reaction of commercially available hex-3-yn-1-ol **4.4** with potassium 3-aminopropylamide[4-7] (*KAPA* reagent: potassium hydride + 1,3-diaminopropane) gave hex-5-yn-1-ol (**4.5**) in 84% yield, as indicated by the appearance of a 1-proton triplet of doublets at 1.93 ppm in the ^{1}H NMR spectrum (Scheme 4.3, eq 1). Hept-6-yn-1-ol (**3.14**) was synthesized as described in chapter 3 (Scheme 4.3, eq 2). Deprotonation of 1-hexyne (**3.12**) and treatment with paraformaldehyde gave propargyl alcohol **3.13** in 92% yield. The acetylenic zipper reaction was applied to the propargyl alcohol **3.13** to yield hept-6-yn-1-ol (**3.14**) in 91% yield.

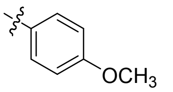
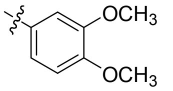
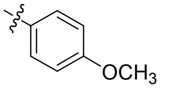
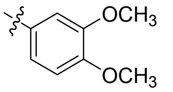
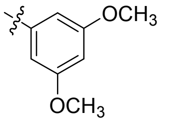
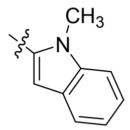
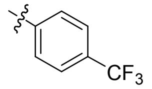
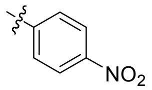


Scheme 4.3: Synthesis of alcohols **4.5** and **3.14**

With alkynes **4.5** and **3.14** in hand, the next step was to couple them using Sonogashira technology[8] to various aromatic iodides. All iodides were commercially available except for 4-iodo-1,2-dimethoxybenzene (4-iodoveratrole) (**3.20**) and 2-iodo-1-methyl-1*H*-indole (**3.25**). The synthesis of these compounds was described in detail in chapter 3 (Scheme 3.2.3, eqs 1 and 3). The Sonogashira coupling reactions were performed using 5 mol% of bis(triphenylphosphine)palladium(II) chloride and 10 mol% of copper(I) iodide in a dichloromethane-triethylamine solvent mixture. The results are summarized in Table 4.2.1. The reactions were generally finished within 1-3 hours and the products were isolated in good to excellent yields. The coupling of alcohol **3.14** with 1-bromo-3,5-dimethoxybenzene did not proceed as readily as with aryl iodides due to the decreased reactivity of the bromo-substituted coupling partner (entry 5). The reaction mixture was stirred at room temperature for 15 hours before being heated to 65 °C for a further two hours to complete the reaction. Product formation was verified by the disappearance of the acetylenic proton signals for alcohols **4.5** and **3.14** in the ^{1}H NMR spectrum and the appearance of signals corresponding to the aromatic functional group installed.

Table 4.1: Sonogashira coupling reactions of alkynols

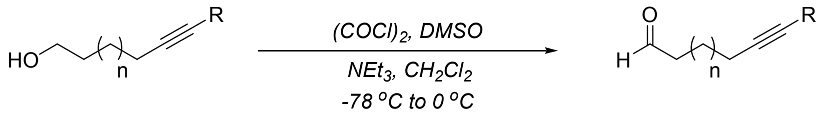


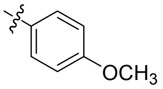
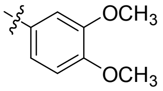
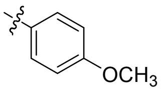
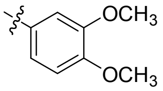
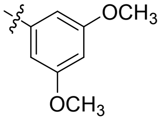
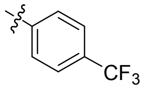
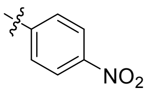
entry	substrate	n	R	conditions	product	yield (%)^{a,b}
1	**4.5**	1		(p-$CH_3O)C_6H_4$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.6**	74
2	**4.5**	1		(m,p-$CH_3O)_2C_6H_3$-I (**3.20**), 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.7**	83
3	**3.14**	2		(p-$CH_3O)C_6H_4$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.8**	83
4	**3.14**	2		(m,p-$CH_3O)_2C_6H_3$-I (**3.20**), 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.9**	83
5	**3.14**	2		(m,m-$CH_3O)_2C_6H_3$-Br, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.10**	70^c
6	**3.14**	2		2-iodo-1-methyl-1*H*-indole (**3.25**), 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.11**	83
7	**3.14**	2		(p-$CF_3)C_6H_4$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.12**	94
8	**3.14**	2		(p-$NO_2)C_6H_4$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.13**	88

^{a}Reported yields are isolated yields. ^{b}Reported yields are the maximum of single experiments ^{c}Requires heating to 65 °C for 2 h.

Once the aromatic functional groups were successfully installed on the alkyne, the alcohol portion of the substrates was oxidized to the aldehyde using the Moffatt-Swern method (Table 4.2.2). Moffatt-Swern oxidations were run using 1 equivalent of the alcohol, 1.3 equivalents of oxalyl chloride, 2 equivalents of dimethyl sulfoxide, and 5 equivalents of triethylamine in a solution of dichloromethane, and were stirred between 1 and 2.5 hours. The products were consistently isolated in high yield. Product formation was verified by the disappearance of the signal associated with the alcohol functionality and the appearance of a signal consistent with an aldehyde proton in the ^{1}H NMR spectrum. The aldehyde proton of the products had a diagnostic chemical shift of between 9.77 ppm and 9.83 ppm. The multiplicity of the signal was not consistent and varied between a singlet and a triplet with a small coupling constant of 1.4-1.7 Hz.

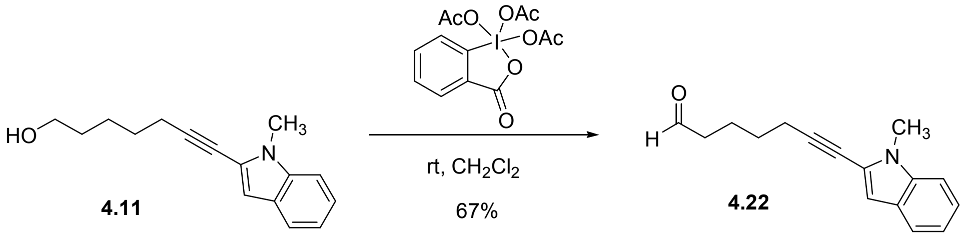
Table 4.2: Moffatt-Swern oxidation reactions



entry	substrate	n	R	product	yield (%)^{a,b}
1	**4.5**	1	H	**4.14**	69
2	**4.6**	1		**4.15**	80
3	**4.7**	1		**4.16**	88
4	**3.14**	2	H	**3.15**	86
5	**4.8**	2		**4.17**	86
6	**4.9**	2		**4.18**	87
7	**4.10**	2		**4.19**	84
8	**4.12**	2		**4.20**	84
9	**4.13**	2		**4.21**	84

[a]Reported yields are isolated yields. [b]Reported yields are the maximum of single experiments

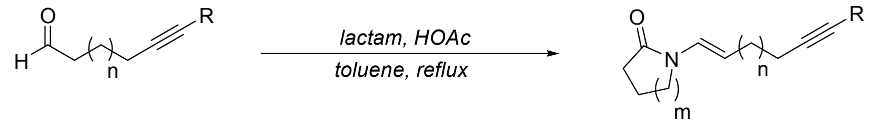
Moffatt-Swern oxidation of alcohol **4.11** formed the expected aldehyde **4.22** in a dismal yield of 5%, exemplifying the need for an alternative oxidation method. Oxidation using Dess-Martin periodinane was tested due to its ease of operation and tolerability of air and moisture (Scheme 4.4). Alcohol **4.11** was reacted with 1.2 equivalents of Dess-Martin periodinane in dichloromethane at room temperature to afford the desired aldehyde **4.22** in 67% yield. Although the reaction was not as high yielding as the Moffatt-Swern oxidations, the yield was synthetically useful and the product was carried on to the next step.

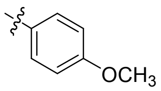
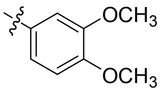
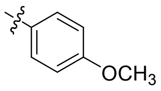
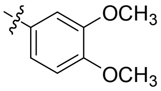
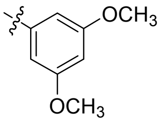
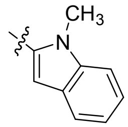
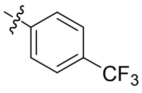
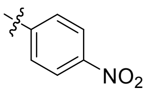


Scheme 4.4: Oxidation of alcohol **4.22**

With a series of aldehydes in hand, the next step was to form the enamide functional group that is crucial to the platinum(II)-catalyzed cycloisomerization reactions. The aldehydes were condensed with either 2-pyrrolidinone or δ-valerolactam to form the desired enamides (Table 4.2.3). The condensations were performed with 1 equivalent of aldehyde, between 2-5 equivalents of lactam, and acetic acid in toluene as a solvent. The reaction mixtures were heated to reflux and water was removed throughout the reaction by a Dean-Stark trap. The reactions were continued until starting material was not observed by thin layer chromatography. In some instances the starting material appeared to be consumed yet a small portion was recovered in the final purification step (entries 3 and 6). The yields of the process varied but were generally high. The formation of the enamides was verified by the appearance of two diagnostic signals in the ^{1}H NMR spectra. The signal corresponding to the vinylic proton adjacent to the nitrogen atom (α-enamide proton) appeared as a 1-proton doublet with a chemical shift between 7.31 ppm and 6.90 ppm. The coupling constant of the doublet was consistently between 14.3 Hz and 14.7 Hz, a characteristic of a proton in an *E*-olefin. The β-enamide proton signal appeared in the ^{1}H NMR spectrum as a 1-proton doublet of triplets with a chemical shift between 4.86 ppm and 5.04 ppm. The values of the coupling constants of these signals were between 14.3 and 14.6 Hz and between 7.0 and 7.2 Hz, also characteristic of an *E*-double bond.

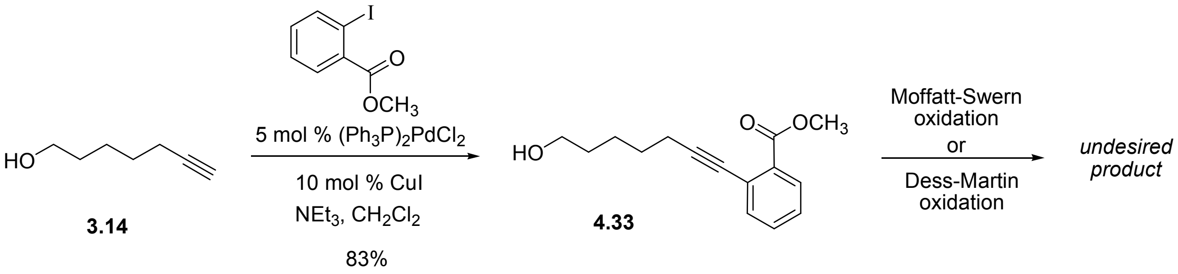
Table 4.3: Condensation of amides and aldehydes to form enamides



entry	substrate	R	lactam	n	m	product	yield (%)[a,b]
1	**3.15**	H	2-pyrrolidinone	2	1	**4.23**	100
2	**3.15**	H	δ-valerolactam	2	2	**4.24**	78
3	**4.15**		2-pyrrolidinone	1	1	**4.25**	67 (75)[c]
4	**4.16**		2-pyrrolidinone	1	1	**4.26**	74
5	**4.17**		2-pyrrolidinone	2	1	**4.27**	81
6	**4.18**		2-pyrrolidinone	2	1	**4.28**	65 (73)[c]
7	**4.19**		2-pyrrolidinone	2	1	**4.29**	91
8	**4.22**		2-pyrrolidinone	2	1	**4.30**	96
9	**4.20**		2-pyrrolidinone	2	1	**4.31**	92
10	**4.21**		2-pyrrolidinone	2	1	**4.32**	100

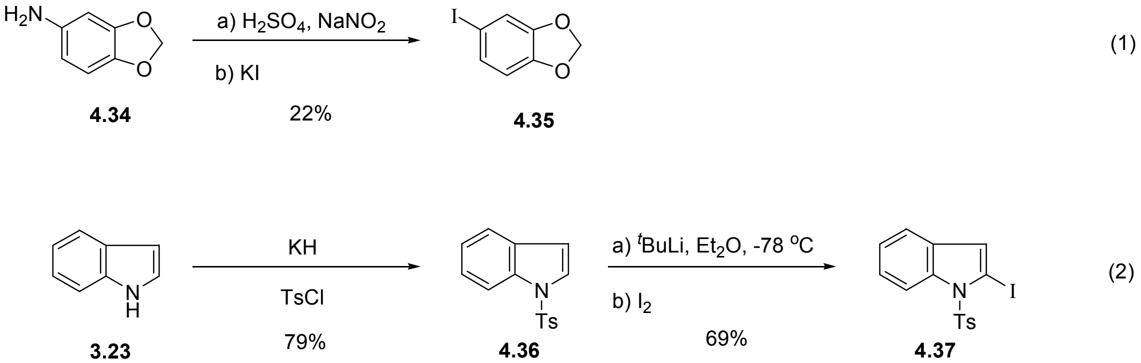
[a] Reported yields are isolated yields. [b] Reported yields are the maximum of single experiments [c] Yield (in parentheses) based on recovered starting material.

Although there was success using the synthetic route described above, not all substrates were amenable to the Moffatt-Swern oxidation or condensation conditions. For example, one desired substrate was an enamide that contained an aromatic ring functionalized with an *o*-carboxylate ester. Alcohol **3.14** underwent smooth Sonogashira coupling with methyl 2-iodobenzoate to form alcohol **4.33** in good yield (Scheme 4.5). When alcohol **4.33** was reacted under Moffatt-Swern oxidation conditions, an undesired oxidation product was formed that could not be characterized by ^{1}H NMR spectroscopy. The same result was found using Dess-Martin perodinane. To circumvent this problem, the enamide was installed prior to incorporation of the aromatic functional group. Modification of the route in this manner would make it more divergent, greatly reducing the number of synthetic operations to form the substrates. Originally, I had misgivings about the compatibility between the enamides and the Sonogashira coupling conditions. Tests with the substrate containing the *ortho*-ester functional group revealed that these concerns were unfounded, and a new set of substrates was formed using this approach.


I
O
OCH3
5 mol % (Ph3P)2PdCl2
10 mol % CuI
NEt3, CH2Cl2
83%
HO
3.14
HO
O
OCH3
4.33
Moffatt-Swern
oxidation
or
Dess-Martin
oxidation
undesired
product

Scheme 4.5: Attempted oxidation of alcohol **4.33**

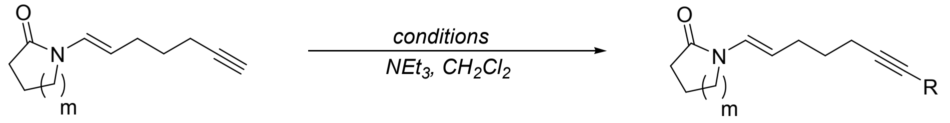
Two non-commercially available iodides were synthesized (Scheme 4.6). 5-Iodobenzo-1,3-dioxole (**4.35**) was formed from commercially available 3,4-methylenedioxyaniline (**4.34**) following a variation of the Sandmeyer protocol[9] (Scheme 4.6, eq 1). *para*-Toluenesulfonyl protected 2-iodoindole **4.37** was furnished in 2 steps (Scheme 4.6, eq 2). Indole (**3.23**) was first treated with base and *para*-toluenesulfonyl chloride to protect the nitrogen atom. Treatment of protected indole **4.36** with *tert*-butyllithium in ether, followed by quenching with iodine gave the desired 2-iodoindole (**4.37**) in acceptable yield.

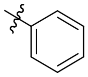
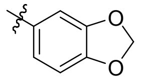
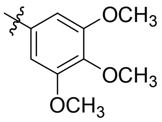
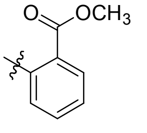
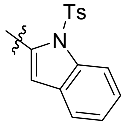
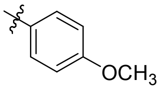
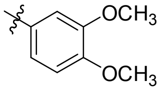

H2N
O
O
a) H2SO4, NaNO2
b) KI
22%
I
O
O
4.34
4.35
(1)
N
H
3.23
KH
TsCl
79%
N
Ts
4.36
a) tBuLi, Et2O, -78 °C
b) I2
69%
N
Ts
I
4.37
(2)

Scheme 4.6: Synthesis of non-commercially available iodides **4.35** and **4.37**

The synthesized iodides **4.35** and **4.37** and other commercially available iodides and bromides were reacted with either enamide **4.23** or enamide **4.24** to furnish a series of substrates suitable for cycloisomerization testing (Table 4.2.4). As seen previously, the bromo-substituted aromatic ring was less reactive and had to be heated to 60 °C for 22 hours before the reaction was complete (entry 3). Exposing enamides **4.23** and **4.24** to Sonogashira coupling conditions did not display any compatibility issues and the resulting substrates were isolated in overall good yields.

Table 4.4: Sonogashira coupling reactions of enamides

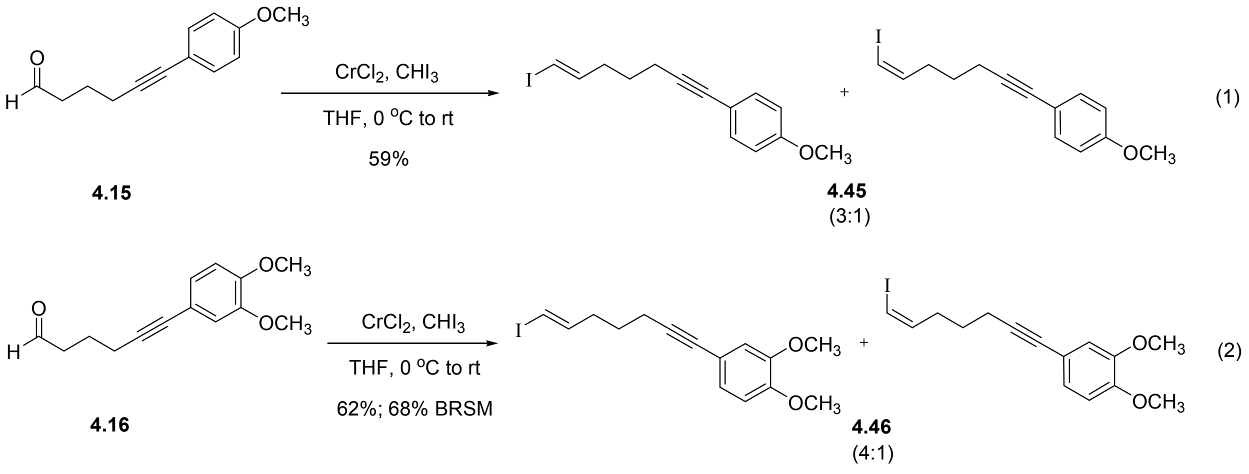


entry	substrate	m	R	conditions	product	yield (%)^{a,b}
1	**4.23**	1		C_6H_5-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.38**	85
2	**4.23**	1		**4.35**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.39**	91
3	**4.23**	1		$(o,m,p\text{-}CH_3O)_3C_6H_2$-Br, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.40**	68^{c}
4	**4.23**	1		$(o\text{-}C(O)OCH_3)C_6H_4$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.41**	55
5	**4.23**	1		**4.37**, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.42**	65
6	**4.24**	2		$(p\text{-}CH_3O)C_6H_4$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.43**	85
7	**4.24**	2		$(m,p\text{-}CH_3O)_2C_6H_3$-I, 5 mol% $(Ph_3P)_2PdCl_2$, 10 mol% CuI	**4.44**	90

[a] Reported yields are isolated yields. [b] Reported yields are the maximum of single experiments [c] Requires heating to 60 °C for 22 h.

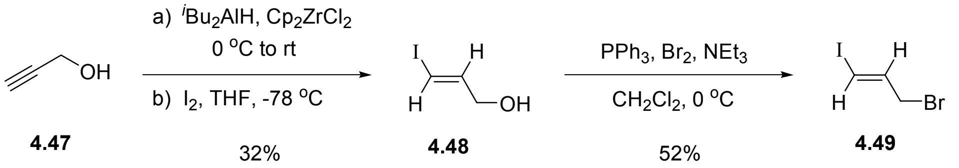
The set of substrates presented in Tables 4.2.3 and 4.2.4 were ready to be tested for cycloisomerization reactivity with platinum(II) chloride. Despite successful condensation of different lactams with aldehydes, it could not be extended to other nitrogen containing functionality. For example, attempted condensation of aldehyde **4.16** with *N*-methyl-*p*-toluenesulfonamide resulted in the recovery of the starting material, or unidentifiable decomposition products under more forcing reaction conditions. As a result, an alternative method to install the enamine functional group derivative was necessary in order to increase the substrate scope from simple enamides to enecarbamates and enesulfonamides.

The chosen method to synthesize the enamine derivatives was a copper(I)-catalyzed cross coupling reaction between an amide, sulfonamide, or carbamate, and a vinyl iodide.[10] A number of vinyl iodides were prepared, starting with **4.45** and **4.46** (Scheme 4.7). With aldehydes **4.15** and **4.16** already prepared, the best method to install the vinyl iodide with *E*-geometry around the double bond was the Takai reaction[11]. Aldehyde **4.15** was therefore treated with chromium(II) chloride and iodoform to give a mixture of *E*- and *Z*-vinyl iodides (represented as **4.45**) in 59% yield and a 3:1 mixture favoring the *E*-isomer (Scheme 4.7, eq 1). Veratrole derivative **4.16** was treated under the same conditions to give a mixture of iodides (represented as **4.46**) in a 68% yield (based on recovered starting material) and a 4:1 mixture favoring the *E*-isomer (Scheme 4.7, eq 2). Diagnostic signals in the ^{1}H NMR spectrum indicative of the *E*-isomer are a 1-proton doublet at approximately 6.07 ppm with a coupling constant of 14.3 Hz, attributable to the proton adjacent to the iodine atom. A 1-proton doublet of triplets with a chemical shift of approximately 6.54 ppm and coupling constants of 14.3 Hz and 7.2 Hz is attributable to the internal proton of the olefin.


OCH3
O
H
CrCl2, CHI3
THF, 0 °C to rt
59%
I
+
OCH3
OCH3
(1)
4.15
4.45
(3:1)
OCH3
OCH3
O
H
CrCl2, CHI3
THF, 0 °C to rt
62%; 68% BRSM
I
OCH3
OCH3
+
I
OCH3
OCH3
(2)
4.16
4.46
(4:1)

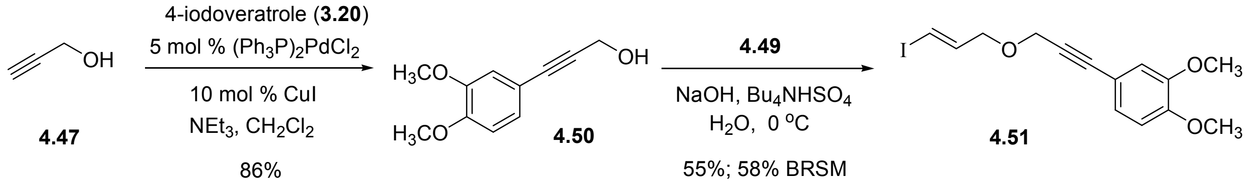
Scheme 4.7: Takai olefination of aldehydes **4.15** and **4.16**

As mentioned in section 4.1, the atoms in the tether can also be varied. All previous substrates featured all carbon tethers. The incorporation of heteroatoms into the tether was explored next. To begin, a vinyl iodide that also contained a portion of the molecule that could be displaced in an S_N2 fashion was synthesized (Scheme 4.8). Following the procedure of Negishi[12], vinyl iodide **4.48** was synthesized from propargyl alcohol (**4.47**) in 32% yield by treatment with diisobutylaluminum hydride and zirconocene dichloride, followed by quenching with iodine. The alcohol was then displaced using triphenylphosphine, bromine, and triethylamine[13] to give the desired vinyl iodide **4.49**. Although each of these two steps is low yielding, the reactions were successful in providing sufficient amounts of material to be used in subsequent reactions.


OH
a) iBu2AlH, Cp2ZrCl2
0 °C to rt
b) I2, THF, -78 °C
32%
I
H
H
OH
PPh3, Br2, NEt3
CH2Cl2, 0 °C
52%
I
H
H
Br
4.47
4.48
4.49

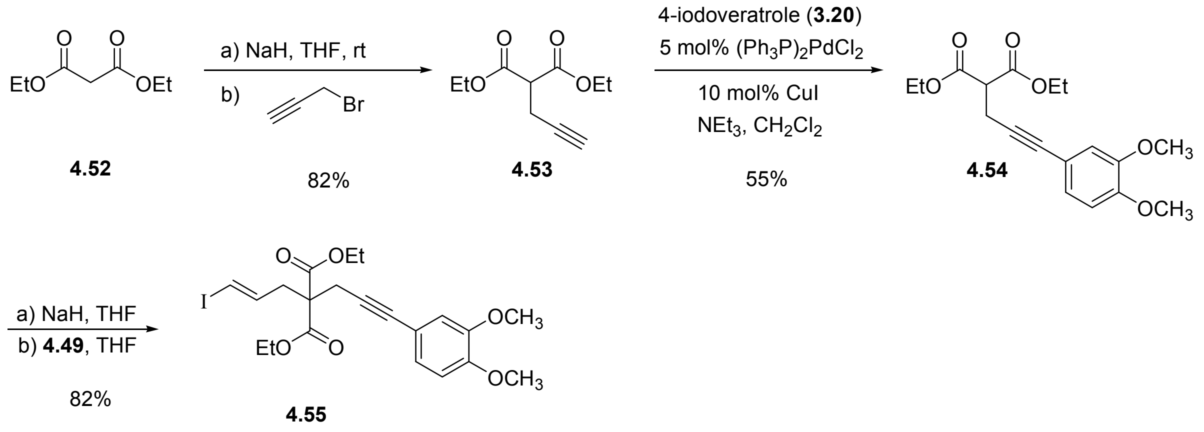
Scheme 4.8: Synthesis of vinyl iodide **4.49**

The first heteratom-containing tether that was synthesized incorporated an oxygen atom (Scheme 4.9). Propargyl alcohol (**4.47**) was subjected to a Sonogashira coupling reaction with 4-iodoveratrole (**3.20**). The Sonogashira conditions employed were identical to those reported for the synthesis of other substrates (Tables 4.2.1 and 4.2.4). Propargyl alcohol **4.50** was formed in excellent yield. At this stage, vinyl iodide **4.49** was reacted with propargyl alcohol **4.50** under basic conditions to form vinyl iodide **4.51** in 58% yield (based on recovered starting material).


4.47
4-iodoveratrole (3.20)
5 mol % $(Ph_3P)_2PdCl_2$
10 mol % CuI
NEt_3, CH_2Cl_2
86%
4.50
4.49
NaOH, Bu_4NHSO_4
H_2O, 0 °C
55%; 58% BRSM
4.51

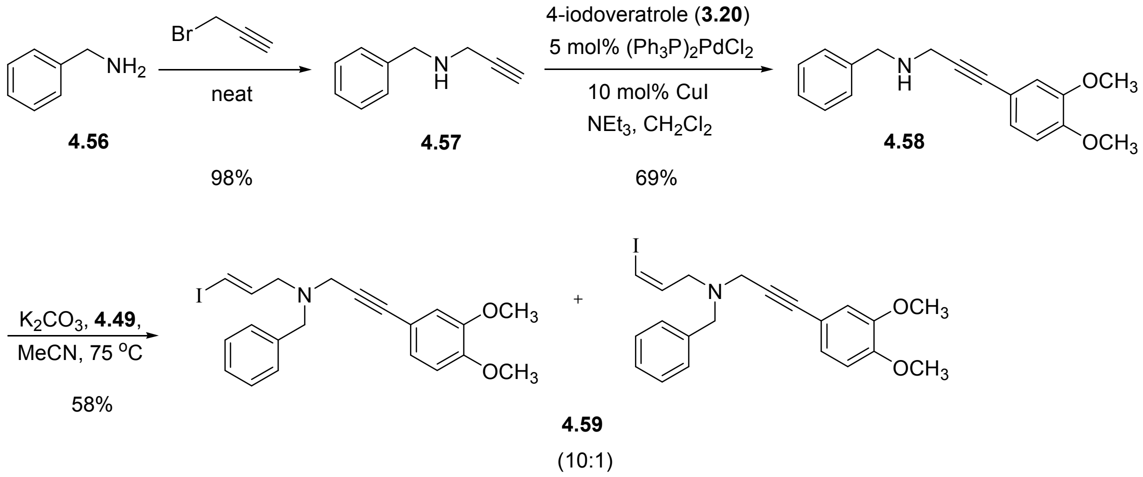
Scheme 4.9: Synthesis of iodide **4.51**

In addition to heteroatoms, other substitution on the tether could also make a difference in the reactivity of the substrate under cycloisomerization conditions. To this end, a substrate containing a geminal diester on the all carbon tether was synthesized according to Scheme 4.10. Diethyl malonate (**4.52**) was first alkylated with propargyl bromide to give diester **4.53** in 82% yield. Diester **4.53** was treated with 4-iodoveratrole (**3.20**) under Sonogashira coupling conditions to give diester **4.54** in 55% yield. Compound **4.54** was deprotonated with sodium hydride and alkylated with vinyl iodide **4.49** to form iodide **4.55** in 82% yield.


4.52
a) NaH, THF, rt
b)
82%
4.53
4-iodoveratrole (3.20)
5 mol% $(Ph_3P)_2PdCl_2$
10 mol% CuI
NEt_3, CH_2Cl_2
55%
4.54
a) NaH, THF
b) 4.49, THF
82%
4.55

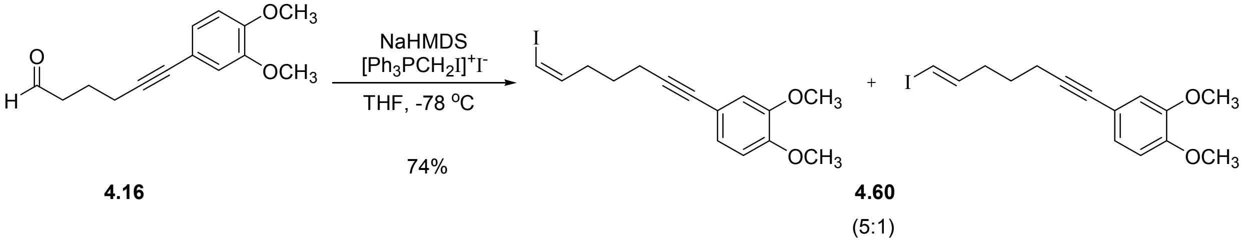
Scheme 4.10: Synthesis of iodide **4.55**

The substitution of a carbon atom with a nitrogen atom in the tether was also investigated. The requisite nitrogen-containing iodide precursor (**4.59**) was synthesized in three steps (Scheme 4.11). Alkylation of benzylamine (**4.56**) with propargyl bromide proceeded in near quantitative yield to form amine **4.57**. Sonogashira coupling of amine **4.57** with 4-iodoveratrole (**3.20**) gave amine **4.58** in 69% yield. Amine **4.58** was then treated with vinyl iodide **4.49** and base to install the iodide functionality, giving compound **4.59** in 58% yield and an isomeric mixture of 10:1 in favor of the *E*-isomer.


Br
NH2
neat
98%
4.56
N
H
4.57
4-iodoveratrole (3.20)
5 mol% (Ph3P)2PdCl2
10 mol% CuI
NEt3, CH2Cl2
69%
N
H
OCH3
OCH3
4.58
K2CO3, 4.49,
MeCN, 75 °C
58%
I
N
OCH3
OCH3
+
I
N
OCH3
OCH3
4.59
(10:1)

Scheme 4.11: Synthesis of iodide **4.59**

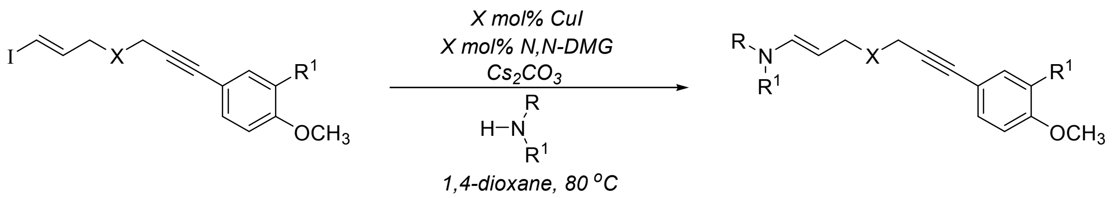
With a large amount of substrates disposed to form *E*-enamides, a *Z*-vinyl iodide was synthesized for the sake of comparison. Stork-Wittig homologation[14] of aldehyde **4.16** resulted in a 5:1 mixture of products (represented as **4.60**) favoring the *Z*-vinyl iodide (Scheme 4.12).

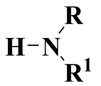
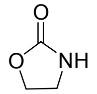
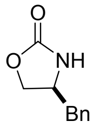
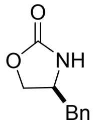
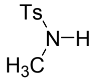
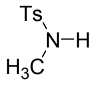
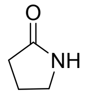
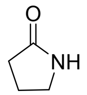
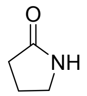
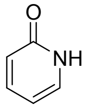
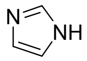

O
H
OCH3
OCH3
4.16
NaHMDS
[Ph3PCH2I]+I-
THF, -78 °C
74%
I
OCH3
OCH3
+
I
OCH3
OCH3
4.60
(5:1)

Scheme 4.12: Synthesis of *Z*-iodide **4.60**

With the series of vinyl iodides in hand, they were tested for reactivity under the copper(I)-catalyzed coupling conditions.[10] The results are summarized in Table 4.2.5. The reactions were run using 1 equivalent of iodide, 1.2 equivalents of the desired nitrogen-containing fragment, 10-20 mol% of copper(I) iodide, 15-30 mol% of *N*,*N*-dimethylglycine hydrochloride, and 2 equivalents of cesium carbonate in 1,4-dioxane as a solvent. The reactions were shielded from light and stirred at 80 °C until complete or until no further change was observable by thin layer chromatography.

Table 4.5: Copper-catalyzed formation of enamides and enesulfonamides

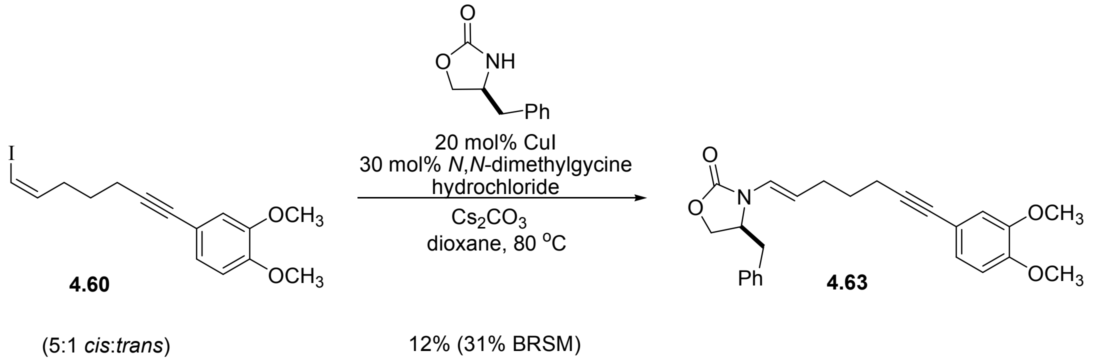


entry	substrate	x	R^1	 $\mathrm{H{-}N(R)R^1}$	mol % *N*,*N*-DMG[a]	mol % CuI	product	yield (%)[b,c]
1	**4.46**	CH_2	OCH_3		15	30	**4.61**	88[d]
2	**4.45**	CH_2	H		10	20	**4.62**	70
3	**4.46**	CH_2	OCH_3		20	30	**4.63**	76
4	**4.45**	CH_2	H		10	20	**4.64**	58
5	**4.46**	CH_2	OCH_3		20	30	**4.65**	96
6	**4.51**	O	OCH_3		15	30	**4.66**	82
7	**4.55**	$C(C(O)CH_2CH_3)_2$	OCH_3		20	30	**4.67**	79
8	**4.59**	NBn	OCH_3		15	30	**4.68**	65
9	**4.46**	CH_2	OCH_3		15	30	**4.69**	71
10	**4.46**	CH_2	OCH_3		15	30	**4.70**	46 (91)[e]

[a] *N*,*N*-DMG = *N*,*N*-Dimethylglycine hydrochloride. [b] Reported yields are isolated yields. [c] Reported yields are the maximum of single experiments [d] Product was isolated as an 8:1 mixture of *E*:*Z* isomers. [e] Yield (in parentheses) based on recovered starting material.

Carbamates reacted smoothly under the reaction conditions to furnish substrates **4.61**, **4.62**, and **4.63** in good yield (entries 1-3). Sulfonamides were also reactive: iodide **4.45** reacted with *N*-methyl-*p*-toluenesulfonamide to form enyne **4.64** in moderate yield (entry 4). When the amount of copper catalyst and amino acid promoter were increased, the yield increased dramatically (entry 5). 2-Pyrrolidinone was coupled with substrates containing an altered tether in moderate to good yields (entries 6-8). Substrates containing an aromatic heterocycle for the enamide portion of the molecule were also synthesized. Copper(I)-catalyzed coupling of iodide **4.46** with 2-hydroxypyridine gave product **4.69** in 71% yield (entry 9). Reaction of **4.46** with imidazole was not as reactive although the substrate was formed in moderate yield with the recovery of a large amount of starting material (entry 10).

Synthesis of the *Z*-enamide was attempted using the same copper(I)-catalyzed conditions employed for the formation of the *E*-enamides (Scheme 4.13).



Scheme 4.13: Attempted synthesis of a *Z*-enamide derivative

Vinyl iodide **4.60** was treated under the standard conditions for the copper(I)-catalyzed cross coupling with a carbamate[10], giving the *E*-isomer **4.63** in low yield. A mixture of *Z*/*E* vinyl iodides **4.60** were recovered, although the mixture was enriched in the Z-isomer as most of the *E*-vinyl iodide was converted to product (**4.63**). The steric strain present in the *Z*-substrate was too demanding for product formation to occur under the reaction conditions (Figure 4.3).

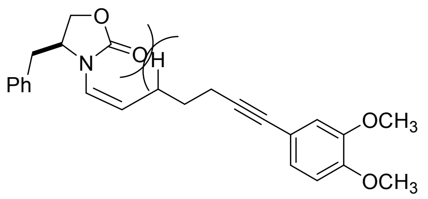
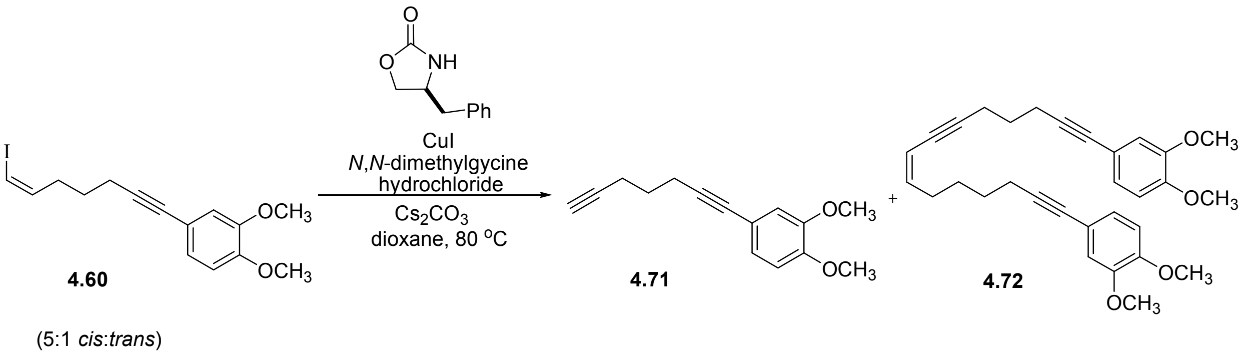


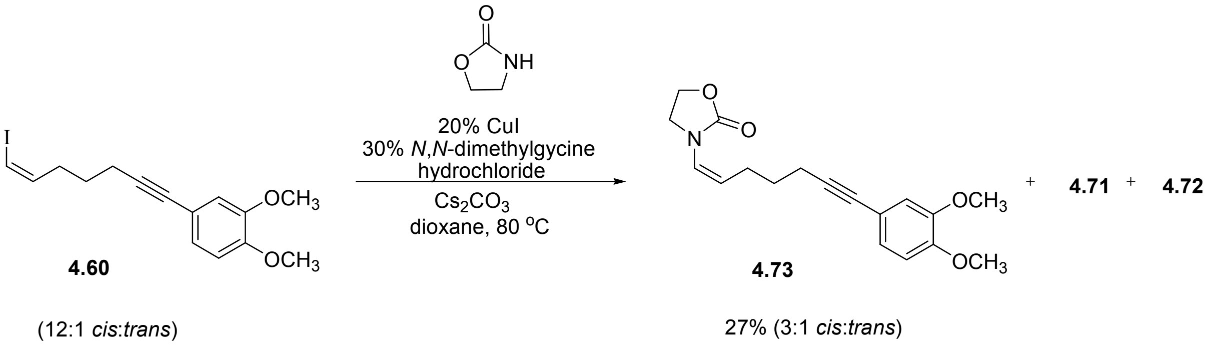
Figure 4.3: Steric interaction impedes formation of *Z*-enecarbamate

An attempt to force the *Z*-isomer to react was made by performing the reaction with 1 equivalent of copper(I) iodide as well as 1 equivalent of *N*,*N*-dimethylglycine hydrochloride, reagents that were previously used sub-stoichiometrically. The mixture of *Z*- and *E*-iodides **4.60** was reacted under the conditions shown to give an unexpected result (Scheme 4.14). After treatment with stoichiometric amounts of reagents, products **4.71** and **4.72** were isolated. Presumably the iodine atom was eliminated in an E2 manner to form dialkyne **4.71**. Then, under the cross-coupling conditions, this dialkyne was coupled with remaining iodide (**4.60**) to give cross-coupled product **4.72**.



Scheme 4.14: Unexpected results when attempting to for a *Z*-enamide derivative

The Evans' auxiliary derived enecarbamate was obviously too sterically encumbering to form the *Z*-enecarbamate. Synthesis of a *Z*-enecarbamate was attempted again using the smaller 2-oxazolidinone and a vinyl-iodide enriched in the *Z*-isomer (**4.60**) (Scheme 4.15). The reaction again failed to produce any useful amount of *Z*-enecarbamate. Treatment under the reaction conditions show resulted in the formation of **4.71**, **4.72**, and 27% of enecarbamate **4.73** as a 3:1 *Z*:*E* mixture.


I
OCH3
OCH3
4.60
(12:1 cis:trans)
O
O
NH
20% CuI
30% N,N-dimethylgycine hydrochloride
Cs2CO3
dioxane, 80 °C
O
O
N
OCH3
OCH3
4.73
27% (3:1 cis:trans)
+ 4.71 + 4.72

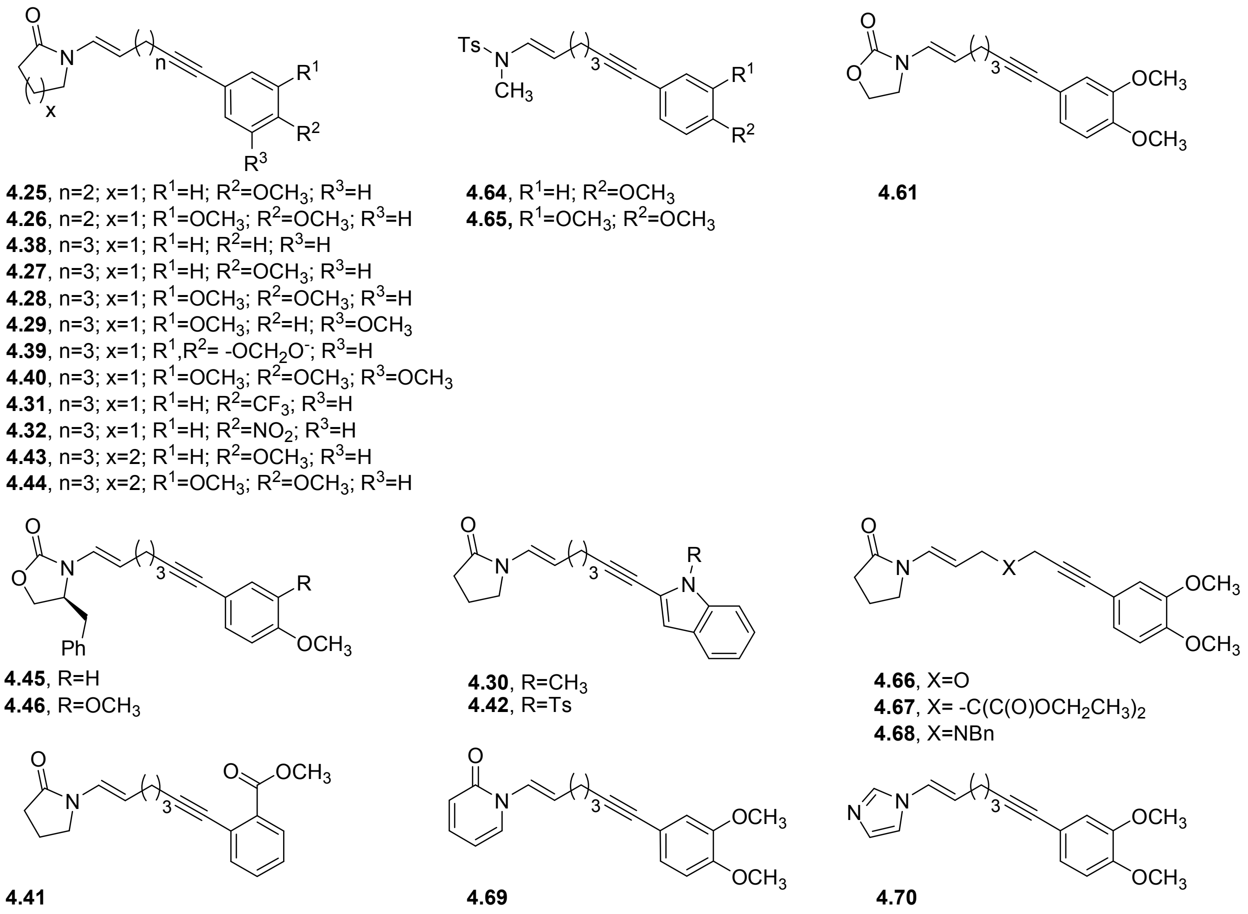
Scheme 4.15: Attempted formation of *Z*-enecarbamate **4.73**

The amount of *Z*-enecarbamate formed was not synthetically useful for investigation in cycloisomerization reactions.

Overall, 25 substrates were synthesized to be tested for reactivity in the platinum(II)-catalyzed cycloisomerization reactions.

4.3 Reactions of Substrates

Unlike the cycloisomerization of *cyclic* enamides described in chapter 3, cycloisomerization of *acyclic* enamides was proposed to form tricycles featuring a pendant amido-functional group and that lack a quaternary center. The initial investigation into the cyclorearrangement of acyclic enamides was to determine the level of reactivity of the substrates and the regio- and stereochemical outcome of the products.


O
N
n
x
R^1
R^2
R^3
Ts
N
CH_3
3
R^1
R^2
O
O
N
3
OCH_3
OCH_3
O
O
N
3
Ph
R
OCH_3
O
N
3
R
N
O
N
X
OCH_3
OCH_3
O
N
3
O
OCH_3
O
N
3
OCH_3
OCH_3
N
N
3
OCH_3
OCH_3

4.25, n=2; x=1; R^1=H; R^2=OCH_3; R^3=H
4.26, n=2; x=1; R^1=OCH_3; R^2=OCH_3; R^3=H
4.38, n=3; x=1; R^1=H; R^2=H; R^3=H
4.27, n=3; x=1; R^1=H; R^2=OCH_3; R^3=H
4.28, n=3; x=1; R^1=OCH_3; R^2=OCH_3; R^3=H
4.29, n=3; x=1; R^1=OCH_3; R^2=H; R^3=OCH_3
4.39, n=3; x=1; R^1,R^2= $-OCH_2O^-$; R^3=H
4.40, n=3; x=1; R^1=OCH_3; R^2=OCH_3; R^3=OCH_3
4.31, n=3; x=1; R^1=H; R^2=CF_3; R^3=H
4.32, n=3; x=1; R^1=H; R^2=NO_2; R^3=H
4.43, n=3; x=2; R^1=H; R^2=OCH_3; R^3=H
4.44, n=3; x=2; R^1=OCH_3; R^2=OCH_3; R^3=H

4.64, R^1=H; R^2=OCH_3
4.65, R^1=OCH_3; R^2=OCH_3

4.61

4.45, R=H
4.46, R=OCH_3

4.30, R=CH_3
4.42, R=Ts

4.66, X=O
4.67, X= $-C(C(O)OCH_2CH_3)_2$
4.68, X=NBn

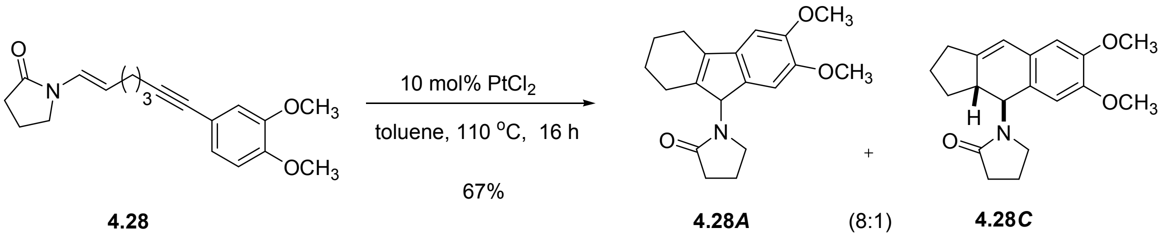
4.41

4.69

4.70

Figure 4.4: Substrates used in this study

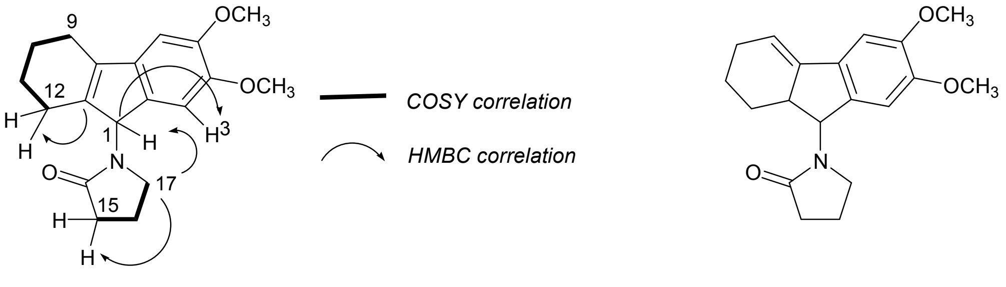
The substrates tested in this study are shown in Figure 4.4. The standard reaction conditions for investigating the cycloisomerization of acyclic substrates do not differ from the cyclic derivatives. Each reaction was run with 10 mol% of platinum(II) chloride in toluene at 110 °C for 16 hours in a thick-walled, sealable reaction tube. These conditions were first employed in the investigation of the cycloisomerization of enamide **4.28** (Scheme 4.16). The reaction resulted in the formation of two products, **4.28*A*** and **4.28*C*** in 67% yield and an 8:1 regioisomeric ratio.


O
N
3
OCH_3
OCH_3
10 mol% $PtCl_2$
toluene, 110 °C, 16 h
67%
OCH_3
OCH_3
O
N
+
OCH_3
OCH_3
H
O
N
(8:1)

4.28 **4.28*A*** **4.28*C***

Scheme 4.16: Initial test cycloisomerization of enamide **4.28**

The major product (**4.28*A***) was characterized by 1D ^{1}H and ^{13}C NMR and 2D spectroscopy (Scheme 4.17). The ^{1}H NMR spectrum of **4.28*A*** did not show a signal attributable to a vinyl proton as would be expected of the 6-*endo* product, but rather it displayed a sharp singlet with a chemical shift of 5.58 ppm. The multiplicity of the signal and the COSY data indicated that there were no adjacent protons. In addition, the ^{13}C NMR chemical shift of carbon 1 is significantly upfield (59.3 ppm) from a typical sp^2 carbon atom (105-145 ppm), suggesting that it is sp^3 hybridized. The 1D NMR data along with the COSY and HMBC correlations are indicative of the proposed product (see Experimental Section 4.7.3, Tables 4.7.3.1 and 4.7.3.2). Finally, the mass spectrum of the product was 314 *m/z*, indicating that a cycloisomerization occurred and no new atoms were incorporated into the product.

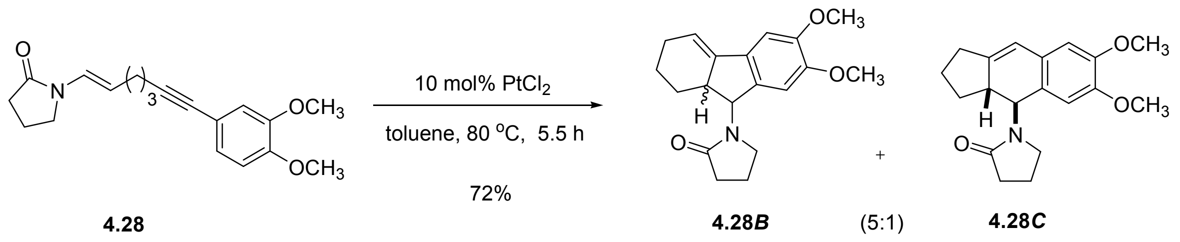


product formed

expected product

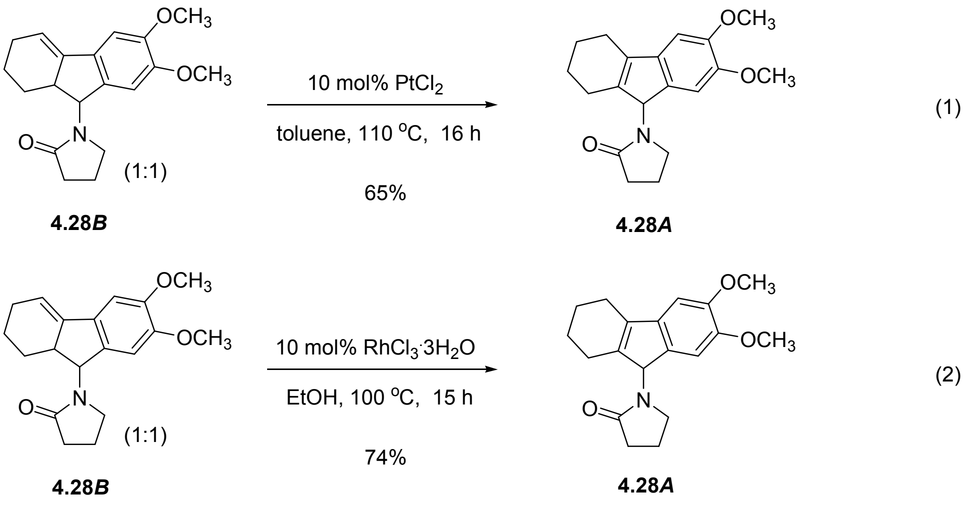
Figure 4.5: 2D NMR COSY and HMBC correlations for tricycle **4.28*A***

The major product **4.28*A*** is the result of a 6-*endo* mode of cyclization followed by alkene migration to the more substituted position under the reaction conditions. The minor product **4.28*C*** is the result of the less favored 5-*exo* cyclization pathway (isolated as a single diastereomer). Support for *in situ* alkene migration comes from the following experiments. Enamide **4.28** was subjected to the platinum(II) catalyst at a lower reaction temperature (80 °C) in a test-tube reaction flask. The reaction was monitored by thin layer chromatography until it appeared complete. Products **4.28*B*** and **4.28*C*** were isolated in 72% yield as a 5:1 mixture of isomers (Scheme 4.17). Interestingly, the resulting products did not match those of the reaction run under standard conditions. Under the lower temperature and decreased reaction time, the double bond did not isomerize into the more substituted position. Instead, a 1:1 diastereomeric mixture (represented as **4.28*B***) was isolated along with **4.28*C***.



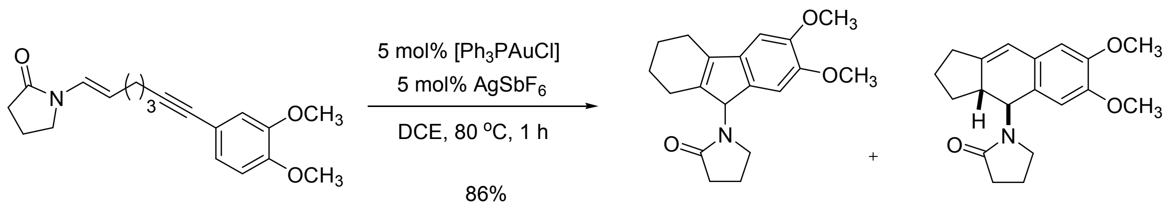
Scheme 4.17: Cycloisomerization of enamide **4.28** at lower temperature and decreased reaction time

Resubjecting **4.28*B*** to the standard reaction conditions (10 mol% platinum(II) chloride at 110 °C) converted the diastereomeric mixture to the previously observed cyclization product (**4.28*A***) in 65% yield (Scheme 4.18, eq 1). The isolated yield of **4.28*A*** suggests that both diastereomers (**4.28*B***) isomerize. Alternate methods to isomerize the double bond were also tested. Heating the mixture with DBU in solvent gave no reaction. Treating the mixture of diastereomers **4.28*B*** with 10 mol % of rhodium(III) chloride trihydrate at 100 °C in ethanol in a sealed tube resulted in alkene isomerization to give product **4.28*A*** in 74% yield (Scheme 4.18, eq 2). The rhodium(III)-catalyzed reaction provides a pathway to convert 1:1 diastereomeric mixtures into one compound, thereby facilitating the characterization of the products.



Scheme 4.18: Investigation of alkene isomerization

Further optimization studies led to the investigation of a gold(I) system as a potential catalyst. Enamide **4.28** was treated with 5 mol% of triphenylphosphine gold(I) chloride ([PPh_3AuCl]) and 5 mol% of silver hexafluoroantimonate in dichloroethane at 80 °C to give products **4.28*A*** and **4.28*C*** in 86% yield and a 13:1 regioisomeric ratio after only 1 hour (Scheme 4.19). These initial results suggested that gold(I)-catalysis was superior to platinum(II)-catalysis for the cyclorearrangement of acyclic enamide substrates. It was decided that all substrates would be tested using platinum(II)- and gold(I)-catalysis.



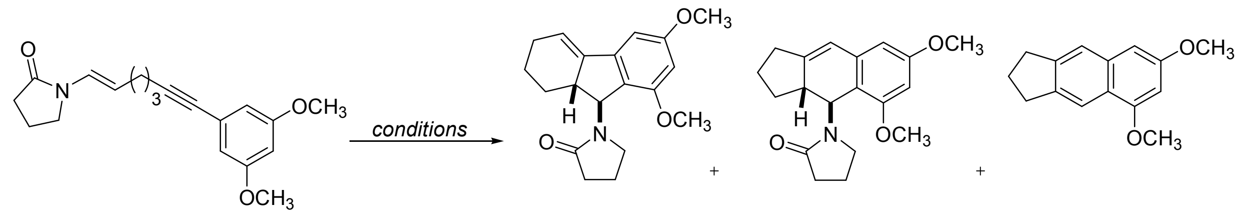
4.28 **4.28*A*** (13:1) **4.28*C***

Scheme 4.19: Initial cycloisomerization study using gold catalysis

A series of control experiments were performed on substrate **4.28**. Heating enamide **4.28** in toluene to 110 °C in the absence of a catalyst resulted in no reaction. The starting material was reisolated in 93% yield. Adding calcium hydride to a standard platinum(II)-catalyzed reaction did not have any effect. Treatment of enamide **4.28** with 20% HCl in toluene at 110 °C led to decomposition of the starting material. Treatment with Lewis acid borontrifluoride etherate in toluene at 110 °C also led to decomposition of the starting material.

Enamide **4.29** containing a symmetrically substituted arene ring was tested next. An unexpected product distribution was observed upon initial investigation (Table 4.3.1). Enamide **4.29** was first tested under the standard platinum(II) chloride reaction conditions. Examination of the reaction by thin layer chromatography after 16 hours showed two new products and complete consumption of the starting material. One product was isolated in 47% yield and the second product was isolated in 35% yield. Analysis by ^{1}H NMR spectroscopy revealed that the product formed in 47% yield was a 16:1 mixture of 6-*endo* and 5-*exo* regioisomers (**4.29*B*** and **4.29*C***). The product formed in 35% yield corresponds to **4.29*D***, a substituted naphthalene derivative.

Table 4.6: Investigation of product ratio of enamide **4.29**

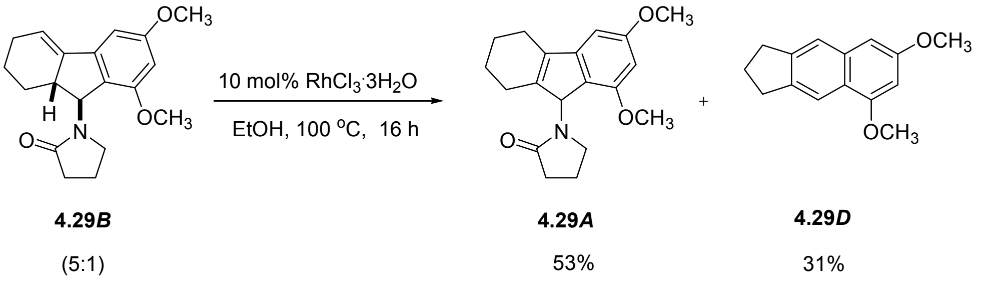


4.29 **4.29*B*** **4.29*C*** **4.29*D***

entry	conditions	yield (%)^{a,b} of 4.29*B* and 4.29*C*	ratio (4.29*B*:4.29*C*)^{c}	yield (%)^{a} of 4.29*D*
1	10 mol% $PtCl_2$, $PhCH_3$, 110 °C, 16 h	47	16:1	35
2	10 mol% $PtCl_2$, $PhCH_3$, 110 °C, 0.25 h	74	2:1	14
3	10 mol% $PtCl_2$, $PhCH_3$, 80 °C, 2 h	88	1:1	2
4	5 mol% [Ph_3PAuCl], 5 mol% $AgSbF_6$, $ClCH_2CH_2Cl$, rt, 8.5 h	87	2:1	4

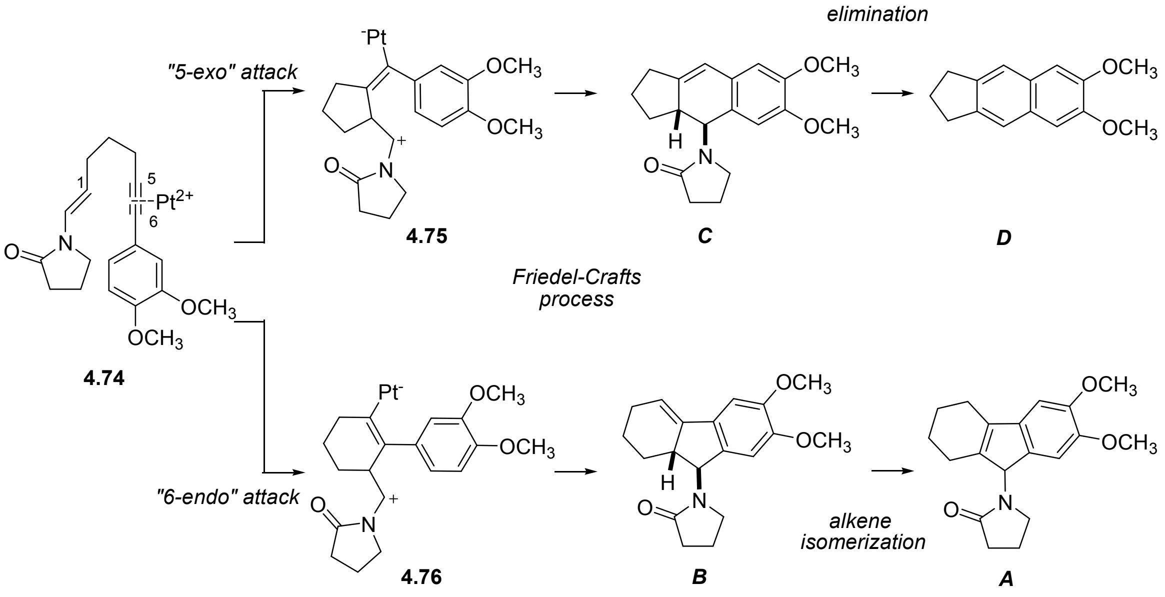
[a] Reported yields are isolated yields. [b] Reported yields are the maximum of single experiments [c] Ratio is based on integration of the ^{1}H NMR signals.

Unexpectedly, the olefin in the 6-*endo* product (**4.29*B***) did not isomerize. In an attempt to understand the product distribution, the reaction was tested at different temperatures, with different reaction times, and using gold(I)-catalysis. First, the reaction was run under the standard reaction conditions in a test-tube reaction flask in order to monitor the reaction (entry 2). After a reaction time of only 15 minutes, products **4.29*B*** and **4.29*C*** were formed in 74% yield, in a 2:1 ratio, each as a single diastereomer. The byproduct **4.29*D*** was formed in a 14% yield. It was hypothesized that under prolonged reaction conditions, the 5-*exo* product was decomposing to form the byproduct **4.29*D***. To further test this, enamide **4.29** was treated with 10 mol% platinum(II) chloride at 80 °C (entry 3). The reaction appeared to be complete after 2 hours. The products **4.29*B*** and **4.29*C*** were this time formed in an excellent yield of 88% and a ratio of 1:1. The byproduct was formed in only 2% yield, suggesting that under a lower temperature, the 5-*exo* product does not decompose to the substituted naphthalene product **4.29*D*** as fast as at higher temperature. For completeness, enamide **4.29** was treated with 5 mol% of triphenylphosphine gold(I) chloride and 5 mol% of silver hexafluoroantimonate (entry 4). The reaction occurred at room temperature, albeit for a longer time. Products **4.29*B*** and **4.29*C*** were isolated in 87% and a ratio of 2:1. Byproduct **4.29*D*** was isolated in 4% yield.


OCH3
H
N
O
OCH3
10 mol% RhCl3·3H2O
EtOH, 100 °C, 16 h
+
4.29*B*
(5:1)
4.29*A*
53%
4.29*D*
31%

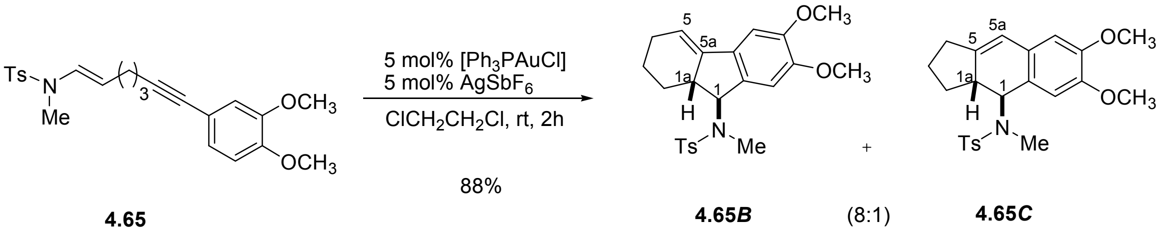
Scheme 4.20: Treatment of cyclization products **4.29*B*** and **4.29*C*** with $RhCl_3{\cdot}3H_2O$

The double bond of the isomeric mixture of compounds **4.29*B*** and **4.29*C*** was isomerized into the more substituted position to facilitate characterization. A 5:1 mixture of compounds **4.29*B*** and **4.29*C*** was treated with 10 mol% of rhodium(III) chloride trihydrate to give 53% of double bond migration product **4.29*A*** and 31% of naphthalene derivative **4.29*D*** (Scheme 4.20).


elimination
"5-exo" attack
⁻Pt
OCH3
+
N
O
1
5
6
Pt2+
4.74
4.75
C
D
H
Friedel-Crafts process
"6-endo" attack
Pt⁻
4.76
B
A
alkene isomerization

Scheme 4.21: Formation of regioisomeric products

The products mixtures resulting from the cycloisomerization of acyclic enamides are more complicated than those from cycloisomerization of cyclic enamides (Scheme 4.21). Coordination by the electrophilic platinum salt catalyst forms the activated η^2 platinum-alkyne π-complex **4.74**. Attack of the enamide nucleophile now takes place at one of the two activated carbons of the alkyne. Attack in a 5-*exo-dig* fashion will form a new five-membered ring, giving intermediary azacarbenium ion **4.75**. Attack in a 6-*endo-dig* fashion will form a new 6-membered ring, giving intermediate **4.76**. Both intermediates **4.75** and **4.76** then undergo Friedel-Crafts reaction and protodemetallation to give either the "5-*exo*" tricyclic product ***C*** or the "6-*endo*" tricyclic product ***B***. After the cycloisomerization event, the 5-*exo* product (***C***) can eliminate to give a substituted naphthalene derivative (***D***). The initial product resulting from 6-*endo* closure can undergo an alkene isomerization to form a 1-aza-substituted indene derivative (***A***).


Ts
N
Me
3
OCH3
OCH3
4.65
5 mol% [Ph3PAuCl]
5 mol% AgSbF6
ClCH2CH2Cl, rt, 2h
88%
5
5a
1a
1
H
OCH3
OCH3
Ts
N
Me
4.65B
+
(8:1)
5
5a
1a
1
H
OCH3
OCH3
Ts
N
Me
4.65C

Scheme 4.22: Gold(I)-catalysis of enesulfonamide **4.65**

Support for the product structures comes from the cycloisomerization of enesulfonamide **4.65**. Treatment of **4.65** with platinum(II) chloride unfortunately resulted in the decomposition of the starting material. Gold(I)-catalysis of enesulfonamide **4.65** gave products **4.65*B*** and **4.65*C*** in 88% yield and a regioisomeric mixture of 8:1 (Scheme 4.22). The product mixture was isolated as a white solid and was recrystallized from a mixture of dichloromethane and hexanes. The crystals were amenable to X-ray crystallographic analysis and solid state molecular structures of **4.65*B*** and **4.65*C*** were found.

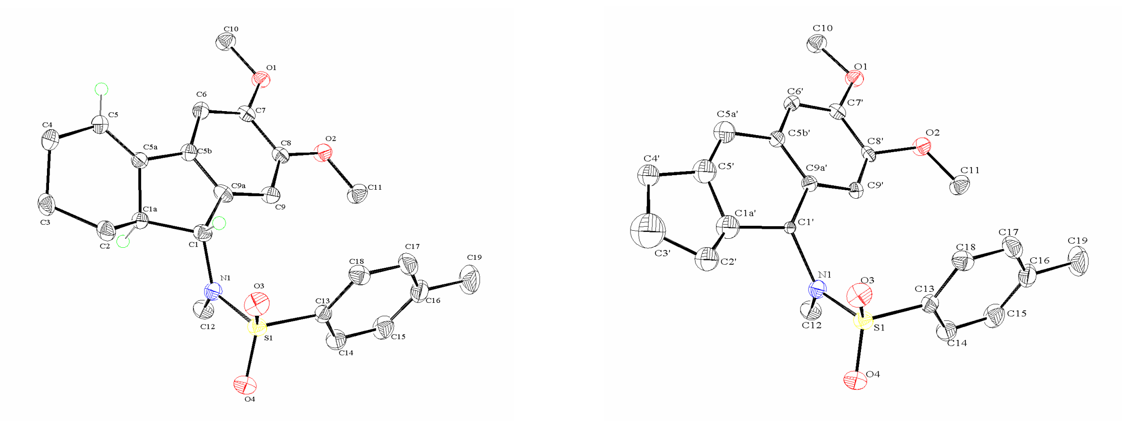
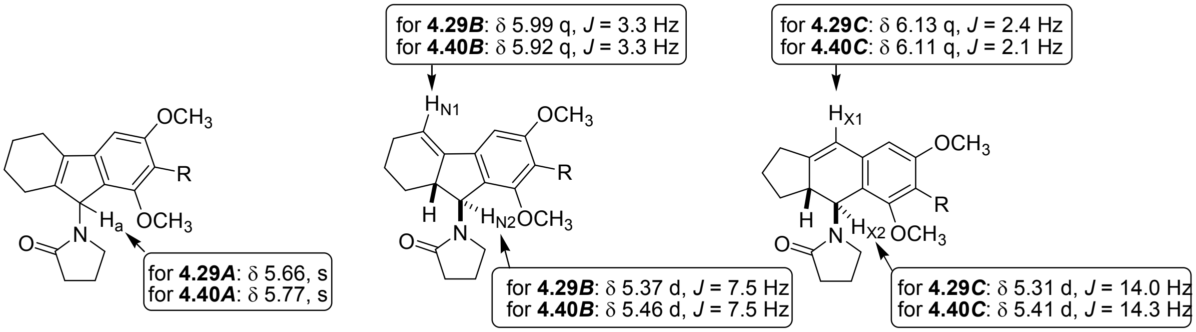

C10
O1
C6
C7
C5
C4
C5a
C5b
C8
O2
C11
C9a
C9
C3
C1a
C2
C1
C17
C19
C18
N1
O3
C13
C16
C12
S1
C15
C14
O4
C10
O1
C6'
C7'
C5a'
C5b'
O2
C8'
C4'
C5'
C9a'
C11
C9'
C1a'
C1'
C17
C19
C18
C16
C3'
C2'
N1
O3
C13
C15
C12
S1
C14
O4

Figure 4.6: ORTEP representation of the solid state molecular structures of 6-*endo* product **4.65*B*** and 5-*exo* product **4.65*C***

The isolated structures confirmed the identity of the 6-*endo* and 5-*exo* products. The alkene migration of the 6-*endo* product failed to occur, as indicated by the short C5-C5a bond length of 1.333(3) Å. The *anti*-relationship between the protons on C1 and C1a is also apparent. The solid state structure of 5-*exo* product **4.65*C*** indicates a short bond length of 1.22(3) Å between C5 and C5a.


OCH$_3$
R
H$_a$
OCH$_3$
N
O
for **4.29*A***: δ 5.66, s
for **4.40*A***: δ 5.77, s
for **4.29*B***: δ 5.99 q, *J* = 3.3 Hz
for **4.40*B***: δ 5.92 q, *J* = 3.3 Hz
H$_{N1}$
OCH$_3$
R
H
H$_{N2}$OCH$_3$
N
O
for **4.29*B***: δ 5.37 d, *J* = 7.5 Hz
for **4.40*B***: δ 5.46 d, *J* = 7.5 Hz
for **4.29*C***: δ 6.13 q, *J* = 2.4 Hz
for **4.40*C***: δ 6.11 q, *J* = 2.1 Hz
H$_{X1}$
OCH$_3$
R
H
H$_{X2}$ OCH$_3$
N
O
for **4.29*C***: δ 5.31 d, *J* = 14.0 Hz
for **4.40*C***: δ 5.41 d, *J* = 14.3 Hz

4.29*A* (R = H)
4.40*A* (R = OCH$_3$)

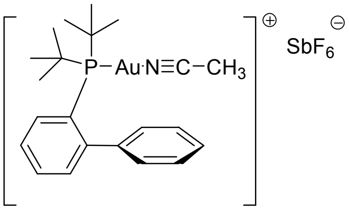
4.29*B* (R = H)
4.40*B* (R = OCH$_3$)

4.29*C* (R = H)
4.40*C* (R = OCH$_3$)

Figure 4.7: Diagnostic signals in sample ^{1}H NMR analysis of **4.29*A*/4.29*B*/4.29*C*** and **4.40*A*/4.40*B*/4.40*C***

The mixtures of products can be confusing to analyze by ^{1}H NMR. The diagnostic signals for each of the products formed in the cycloisomerization of enamides **4.29** and **4.40** are shown in Figure 4.7 for reference. The main diagnostic signal for the double bond migration products is a singlet approximately between the chemical shifts of 5.60 ppm and 5.80 ppm. The vinyl proton (H$_{N1}$) of the 6-*endo* product is a quartet with a characteristically small coupling constant of 3.3 Hz. Benzylic proton H$_{N2}$ is a 1-proton doublet with a chemical shift of approximately 5.50 ppm and a coupling constant of 7.5 Hz. The vinyl proton (H$_{X1}$) of the 5-*exo* product is shifted downfield relative of that in the 6-*endo* product. The coupling constant is also smaller (~2.4 Hz versus ~3.3 Hz). The benzylic proton (H$_{X2}$) of the 5-*exo* product is a 1-proton doublet with a coupling constant of around 14 Hz.

The substrates were tested with 10 mol% of platinum(II) chloride or the combination of 5 mol% of triphenylphosphine gold(I) chloride and 5 mol% of silver hexafluoroantimonate. Substrates that were not particularly reactive with either of those catalyst conditions were reacted with [(2-biphenyl-bis-*t*butylphosphine)Au(I)·NCCH$_3$]$^+$SbF$_6^-$ (**1.70**, Figure 4.8). Cationic gold catalyst **1.70** was synthesized by fellow Dake group member Jennifer Dodd. It is described to be a highly active catalyst for cycloisomerization reactions in the primary literature.[15-17]

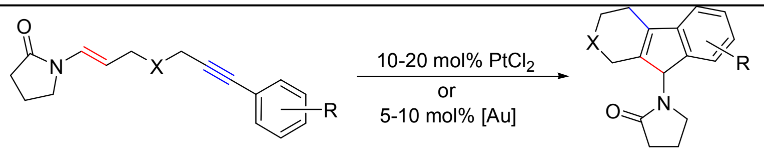


1.70

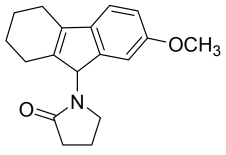
Figure 4.8: Gold complex **1.70** tested in select cycloisomerization reactions

The cycloisomerization results for 2-pyrrolidinone enamide derivatives are presented in Chart 4.1. The general reaction scheme is shown in the top of the chart. Enamide **4.27** featuring a mono-substituted aromatic ring cyclized with both catalyst systems to give compound ***4.27A*** (entry 1). The 5-*exo* isomer ***4.27C*** was not observed in the ^{1}H NMR spectrum. Enamides containing more electron-rich arene rings (**4.28**) cycloisomerized to form products in higher yield, but with reduced regioselectivity (entry 2). When the tether was shortened by one carbon, the reactivity of cycloisomerization decreased dramatically (entry 3). Treatment of enamide **4.26** with 10 mol% of platinum(II) chloride gave tricycle ***4.26A*** as the only observable product by ^{1}H NMR spectroscopy in 39% yield. The 4-*exo* product ***4.26C*** was not formed due to the strain associated with the formation of a 4-membered ring. Cycloisomerization of enamide **4.26** with either of the gold(I) catalytic systems did not increase the yield of the product isolated, it only decreased the reaction time.

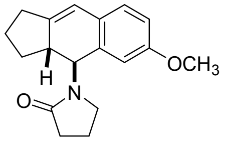
Chart 4.1: Cycloisomerization results for 2-pyrrolidinone derivatives


O
N
X
R
10-20 mol% $PtCl_2$
or
5-10 mol% [Au]
X
R
N
O

1



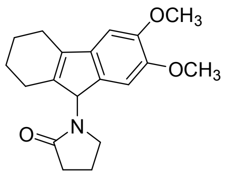
4.27*A*



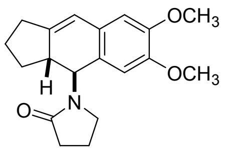
4.27*C*

a) $PtCl_2$[a] (10 mol%), 110 °C, 16 h	59% (>95:5)
b) [Au][b,c] (5 mol%), 80 °C, 1 h	64% (>95:5)

2


OCH3
OCH3
N
O

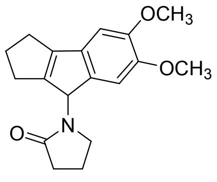
4.28*A*


OCH3
OCH3
H
N
O

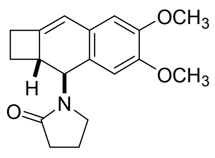
4.28*C*

a) $PtCl_2$ (10 mol%), 110 °C, 16 h	67% (8:1)
b) [Au] (5 mol%), 80 °C, 1 h	86% (13:1)

3


OCH3
OCH3
N
O

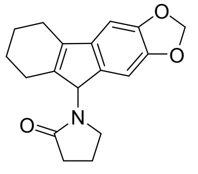
4.26*A*


OCH3
OCH3
H
N
O

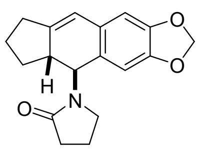
4.26*C*

a) $PtCl_2$ (10 mol%), 110 °C, 16 h	39% (>95:5)
b) [Au] (10 mol%), 80 °C, 3.5 h	21% (>95:5)
c) **1.70** (5 mol%), 80 °C, 2 h	34% (>95:5)

4



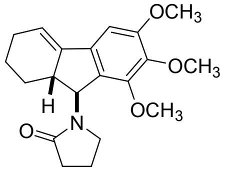
4.39*A*



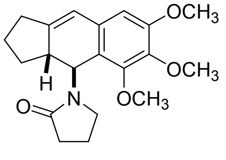
4.39*C*

a) $PtCl_2$ (10 mol%), 110 °C, 16 h	69% (13:1)
b) [Au] (5 mol%), 80 °C, 5 h	*not complete*
c) **1.70** (5 mol%), 80 °C, 5 h	*NR* (90% RSM)

5


OCH3
OCH3
OCH3
H
N
O

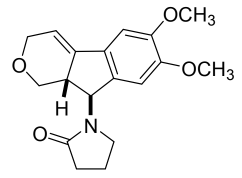
4.40*B*


OCH3
OCH3
OCH3
H
N
O

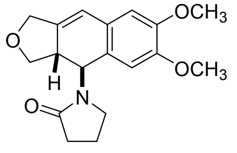
4.40*C*

a) $PtCl_2$ (10 mol%), 110 °C, 16 h	50% (21%)[d] (12:1)
b) [Au] (5 mol%), 80 °C, 0.5 h	81% (5:1)

6


OCH3
OCH3
O
H
N
O

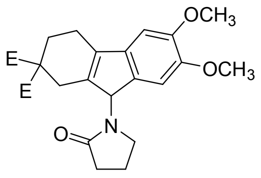
4.66*B*


OCH3
OCH3
O
H
N
O

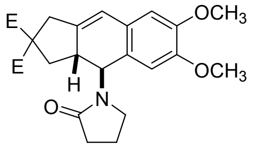
4.66*C*

a) $PtCl_2$ (10 mol%), 110 °C, 16 h	*decomposition*
b) [Au] (5 mol%), 80 °C, 0.25 h	69% (>95:5)
c) **1.70** (5 mol%), 80 °C, 1 h	98% (>95:5)

7


OCH3
OCH3
E
E
N
O

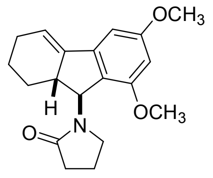
4.67*A*


OCH3
OCH3
E
E
H
N
O

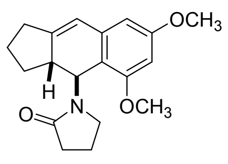
4.67*C*

a) $PtCl_2$ (10 mol%), 110 °C, 16 h	62% (2:1)
b) [Au] (5 mol%), 80 °C, 2 h	88% (2:1)
c) **1.70** (10 mol%), 80 °C, 1 h	79% (2:1)

8


OCH3
OCH3
H
N
O

4.29*B*


OCH3
OCH3
H
N
O

4.29*C*

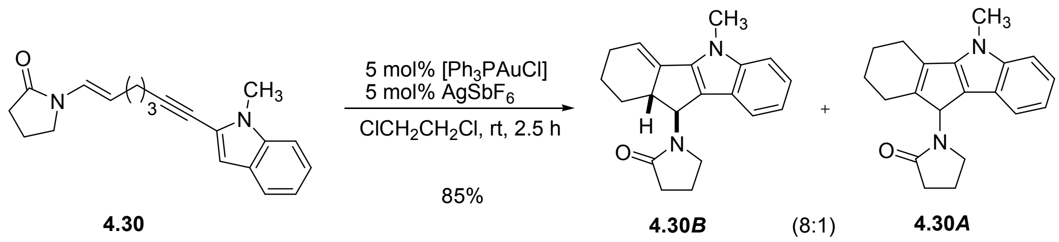
a) $PtCl_2$ (10 mol%), 110 °C, 16 h	47% (35%)[d] (16:1)
b) $PtCl_2$ (10 mol%), 110 °C, 0.25 h	74% (14%)[d] (2:1)
c) $PtCl_2$ (10 mol%), 80 °C, 2 h	88% (2%)[d] (1:1)
d) [Au] (5 mol%), rt, 8.5 h	87% (4%)[d] (2:1)

---

[a] Reactions using $PtCl_2$ were run in toluene. [b] [Au]= $[Ph_3PAuCl]/AgSbF_6$. [c] Reactions using [Au] were run in 1,2-dichloroethane.
[d] % yield of product resulting from elimination of the 5-*exo* isomer. NR = no reaction. RSM = recovered starting material.

The success of veratrole containing enamide **4.28** to the cycloisomerization conditions prompted the synthesis of related substrates. To this end, veratrole derivative **4.39** was synthesized and tested (entry 4). Enamide **4.39** was treated with 10 mol% platinum(II) chloride under the standard reaction conditions to form products **4.39*A*** and **4.39*C*** in 69% yield and a regioisomeric ratio of 13:1. Surprisingly, both of the gold(I) catalytic systems did not induce efficient cyclization of enamide **4.39**. Treatment of enamide **4.39** with 5 mol% of triphenylphosphine gold(I) chloride and 5 mol% of silver hexafluoroantimonate resulted in an incomplete reaction which was difficult to separate by standard purification methods. Treatment with 5 mol% of gold(I) catalyst **1.70** resulted in no reaction at all, and 90% of the starting material was recovered by column chromatography. To further increase the electron-density in the aromatic ring, enamide **4.40** containing three methoxy substituents on the arene ring was synthesized (entry 5). Treatment with platinum(II) chloride under the standard reaction conditions resulted in formation of products **4.40*B*** and **4.40*C*** in 50% yield and a ratio of 12:1 with 21% of the naphthalene derivative byproduct being formed. Gold(I)-catalysis was far superior and products **4.40*B*** and **4.40*C*** were formed in 81% yield and a 5:1 ratio after only thirty minutes. Under the reaction conditions, the double bond of tricycle **4.40*B*** did not isomerize and was formed as a single diastereomer.

The next substrate tested was enamide **4.66** that contained an oxygen atom in the tether (entry 6). Under the standard reaction conditions, only decomposition of the starting material into unidentifiable byproducts was observed. It is likely that enamide **4.66** is less stable than its all carbon tether counterparts, or the tricyclic product **4.66*B*** is less stable and is destroyed after its formation. Gold(I)-catalysis of enamide **4.66** was more successful. Treatment with the standard gold(I) catalytic system gave 69% of product **4.66*B***, the only observable product by ^{1}H NMR spectroscopy. Treatment with gold(I) catalyst **1.70** was even more successful and product **4.66*B*** was isolated in quantitative yield as a single diastereomer. Enamide **4.67** containing geminal diesters on the tether showed reactivity with all catalyst systems tested (entry 7). Gold(I)-catalysis was superior to platinum(II)-catalysis, but the regioisomeric ratio was not synthetically useful in any case. Symmetrically substituted enamide **4.29** was also tested and is included in the table for completeness (entry 8), although the results were discussed above (Table 4.3.1) and will not be repeated here.

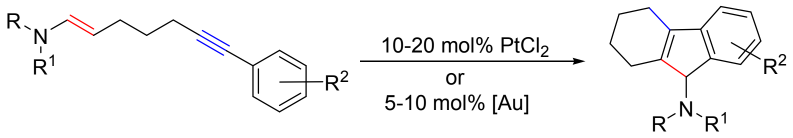


Scheme 4.23: Cycloisomerization of indole substituted enamide **4.30**

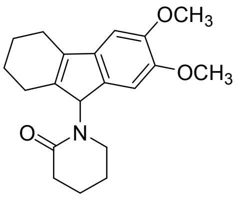
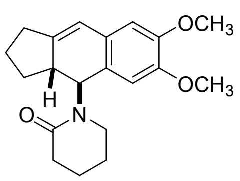
The cycloisomerization of enamide **4.30** is interesting as it does not feature an oxygen-substituted aromatic ring, but rather a relatively electron-rich indole moiety (Scheme 4.23). Indole substituted enamide **4.30** was sensitive, and under the standard reaction conditions decomposed to unidentifiable products. Gold(I)-catalysis under milder conditions (room temperature) resulted in the successful cycloisomerization of enamide **4.30** to give products **4.30*B*** and **4.30*A*** in 85% yield and a ratio of 8:1.

The next series of substrates tested were those with other electron-withdrawing substituents on the nitrogen atom of the enamine derivative (Chart 4.2). Enamide **4.44** was tested for reactivity under the standard reaction conditions as well as gold(I)-catalysis (entry 1). Surprisingly, **4.44** did not react as efficiently as enamide **4.28**, though they differ by only one carbon atom. Platinum(II)-catalyzed cycloisomerization of enamide **4.44** gave products **4.44*A*** and **4.44*C*** in 61% yield and a ratio of 12:1. Gold(I)-catalysis gave similar results. Next, enesulfonamides as nucleophiles were tested (entries 2 and 3). The use of enesulfonamides has had success in cycloisomerization reactions under platinum(II), silver(I) and gold(I) catalysis in the past.[1, 18, 19] Enesulfonamide **4.64** with an arene ring substituted with a *para*-methoxy substituent cyclized under the standard reaction conditions to give products **4.64*A*** and **4.64*C*** in 58% yield and an 8:1 ratio (entry 2). Enesulfonamide **4.64** was not stable to gold(I)-catalytic conditions and the reaction led to decomposition of the starting material. Enesulfonamide **4.65** was even less stable (or perhaps more reactive) than enesulfonamide **4.64** (entry 3). Treatment under standard reaction conditions resulted in decomposition to unidentifiable products. When treated with a gold(I)-catalytic system at room temperature, the products **4.65*B*** and **4.65*C*** were isolated in 88% and 85% yield and a regioisomeric ratio of 8:1. Interestingly, enesulfonamide **4.64** cycloisomerized and then had the alkene migrate into the more substituted position under the reaction conditions, whereas tricycle **4.65*B*** showed no alkene migration.

Chart 4.2: Cycloisomerization results for substrates with varying groups on nitrogen

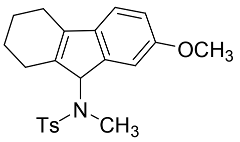
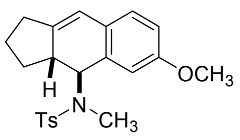


1

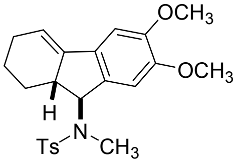
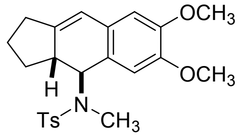
4.44*A*	**4.44*C***
a) $PtCl_2$[a] (10 mol%), 110 °C, 16 h	61% (12:1)
b) [Au][b,c] (5 mol%), 80 °C, 1 h	69% (12:1)

2

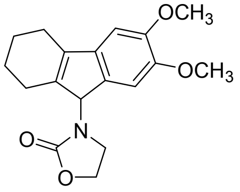
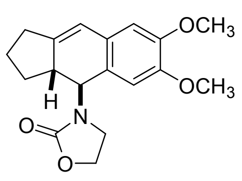
4.64*A*	**4.64*B***
a) $PtCl_2$ (10 mol%), 130 °C, 16 h	58% (8:1)
b) [Au] (5 mol%), 80 °C, 1 h	*decomposition*

3

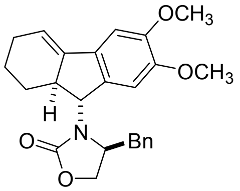
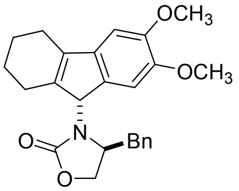
4.65*B*	**4.65*C***
a) $PtCl_2$ (10 mol%), 110 °C, 16 h	*decomposition*
b) [Au] (5 mol%), 80 °C, 1 h	*decomposition*
c) [Au] (5 mol%), rt, 2 h	88% (8:1)
d) **1.70** (5 mol%), rt, 1.5 h	85% (8:1)

4

4.61*A*	**4.61*C***
a) $PtCl_2$ (10 mol%), 110 °C, 16 h	57% (9%)[d] (>95:5)
b) [Au] (5 mol%), 80 °C, 21.5 h	*not complete*
c) **1.70** (5 mol%), 80 °C, 4 h	64% (9%)[d] (>95:5)

5

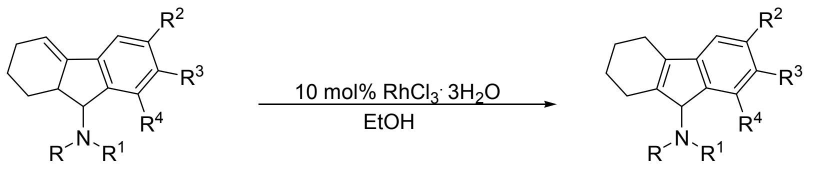
4.46*B*	**4.46*A***
a) $PtCl_2$ (10 mol%), rt, 54 h	52% (8:1)

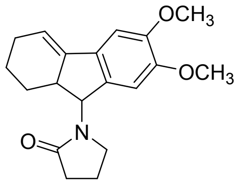
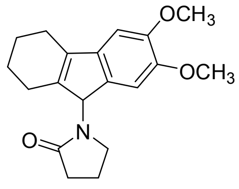
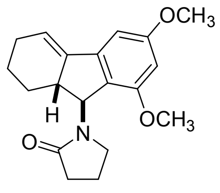
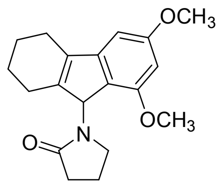
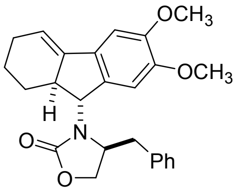
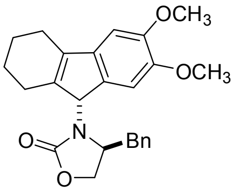
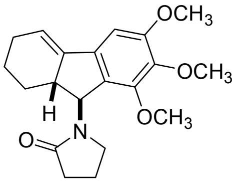
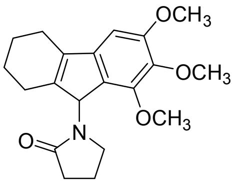
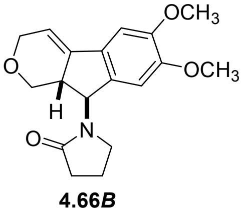
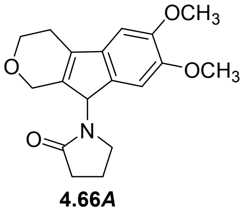
[a] Reactions using $PtCl_2$ were run in toluene. [b] [Au]= [Ph_3PAuCl]/$AgSbF_6$. [c] Reactions using [Au] were run in 1,2-dichloroethane. [d] % yield of product resulting from elimination of the 5-*exo* isomer.

The cycloisomerization of enecarbamates has been successful in the Dake laboratory and seemed to be the next logical progression into investigation of the acyclic substrate scope (entries 4 and 5).[1, 18, 19] Enecarbamate **4.61** was treated under standard platinum(II)-catalytic conditions to form double bond migration product **4.61*A*** in 57% yield (entry 4). The 5-*exo* product was not observed by ^{1}H NMR although 9% of the naphthalene byproduct was isolated. Treatment of enecarbamate **4.61** with 5 mol% [PPh_3AuCl] and 5 mol% of silver hexafluoroantimonate did not result in a complete reaction. Treatment of the enecarbamate with 5 mol% of catalyst **1.70** did not show any significant improvement relative to platinum(II)-catalysis. Enecarbamate **4.46** featuring an Evans' chiral auxiliary[20] was synthesized to be tested for cycloisomerization reactivity with the hopes of isolating a single diastereomer (entry 5). Under the standard reaction conditions it was found that the only product was tricycle **4.46*A***. In order to use the chiral auxiliary for any type of selectivity, the reaction had to be run at room temperature to avoid the migration of the double bond. After reaction at room temperature, products **4.46*B*** and **4.46*A*** were isolated in 52% yield and an 8:1 ratio.

To facilitate characterization and comparison of the cycloisomerization products, compounds that gave mixtures were reacted with rhodium(III) chloride trihydrate in ethanol to force alkene migration. These conditions were not compatible with all substrates as some were sensitive to heat. Substrates that decomposed when heated were characterized as a mixture of 5-*exo* and 6-*endo* products. The results of the isomerization to the tetrasubstituted double bond are shown in Table 4.7. Entries 1 and 2 were previously discussed. Enecarbamate **4.46*B*** featuring Evans' chiral auxiliary was isomerized to product **4.46*A*** in good yield (entry 3). Tricycle **4.40*B*** was isomerized to give the corresponding migration product **4.40*A*** in good yield, although some of the naphthalene byproduct was observed (entry 4). Tricycle **4.66*B*** with an oxygen in the tether was isomerized to give product **4.66*A*** in excellent yield (entry 5).

Table 4.7: Isomerization of products to tetrasubstituted double bond

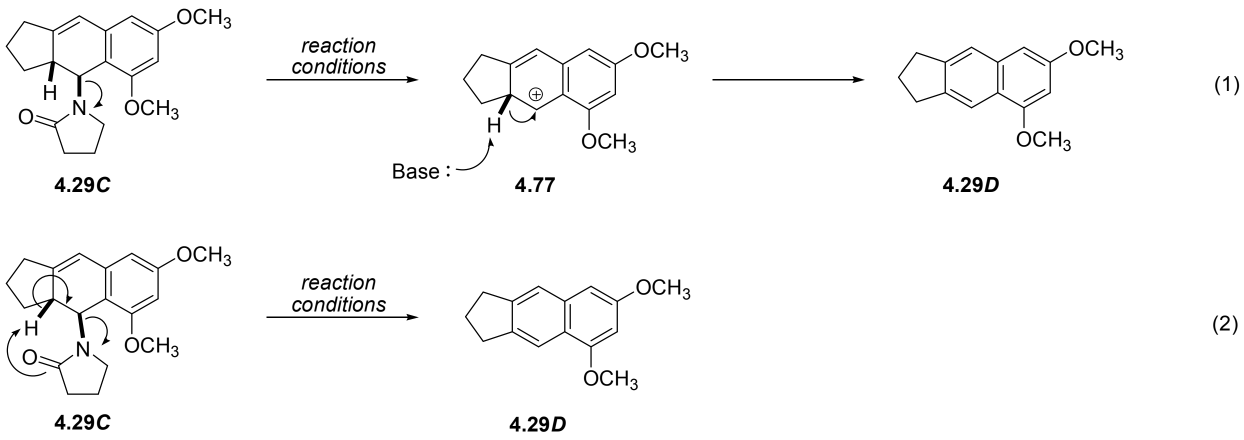


entry	substrate	temp (°C)	time (h)	product	yield (%)[a,b]
1	 **4.28*B***	100	16	 **4.28*A***	74
2	 **4.29*B***	100	16	 **4.29*A***	53 (31)[c]
3	 **4.46*B***	100	4	 **4.46*A***	78
4	 **4.40*B***	80	6	 **4.40*A***	77 (6)[d]
5	 **4.66*B***	80	2.5	 **4.66*A***	83

[a] Reported yields are isolated yields. [b] Reported yields are the maximum of single experiments [c] Amount of elimination product **4.29*D*** that was isolated. [d] Amount of elimination product **4.40*D*** that was isolated.

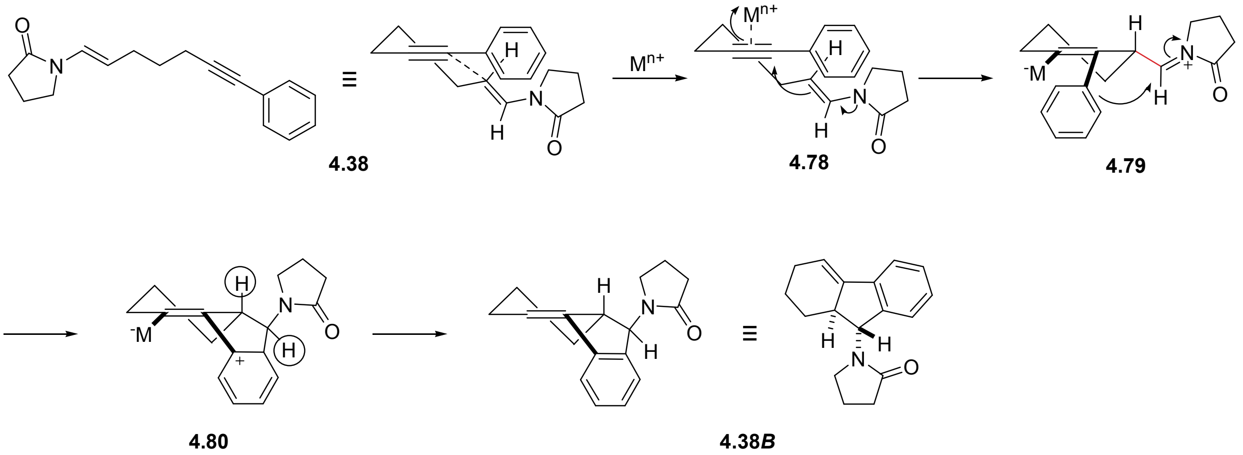
4.4 Discussion

The results discussed in Charts 4.1 and 4.2 lead to some general conclusions about the cycloisomerization of acyclic enamides. It appears that the more electron-rich the aromatic substituent is, the more efficient the cycloisomerization reaction will be. This observation can be rationalized by increased electron density of the arene ring being donated to the alkyne: more electron density on the alkyne causes an increased interaction with the Lewis acidic catalysts and an overall faster reaction. Generally, gold(I)-catalysis of the enamine derivatives resulted in higher overall yield of the products, lower reaction temperatures and shorter reaction times. One exception was enamide **4.39** (Chart 4.1, entry 4). Platinum(II) chloride effectively cycloisomerized the substrate (**4.39**) whereas the gold(I)-catalytic systems failed. Substrates having particularly electron-rich aromatic systems were prone to form substituted naphthalene derivatives. Gold(I)-catalysis was observed to minimize the elimination side reaction.



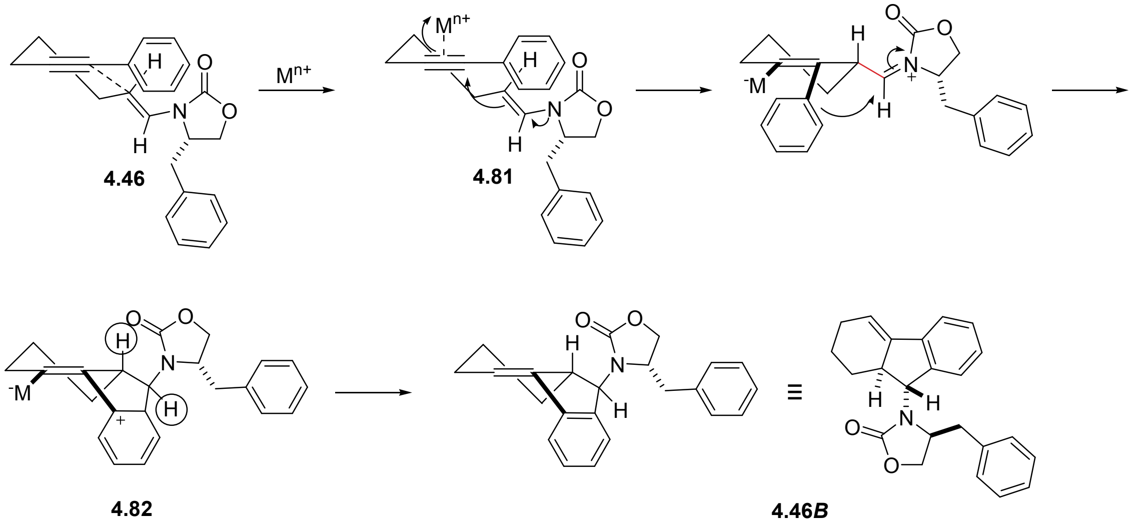
Scheme 4.24: Proposed mechanisms for the formation of naphthalene derivative **4.29*D***

From cycloisomerization experiments performed on the enamide featuring a symmetrically substituted aromatic ring (**4.29**) it was observed that lower temperatures and decreased reaction times minimized the amount of naphthalene byproduct formed and increased the amount of 5-*exo* product (**4.29*C***) observed. This suggests that the 5-*exo* product is decomposing to the naphthalene derivative **4.29*D***. Two proposed mechanisms for this process are shown in Scheme 4.24. The 5-*exo* product (**4.29*C***) under the reaction conditions can ionize to form cation **4.77** (Scheme 4.24, eq 1). The proton is then lost to form the stable, aromatic naphthalene derivative **4.29*D***. The mechanism likely proceeds via an E1-type elimination versus an E2-type elimination for the following reasons: a) the proton removed and the leaving group have a *syn* relationship, b) the position of the leaving group is benzylic and is therefore stabilized, and c) the amide leaving group is generally not a good leaving group under classic conditions. It is also possible that a syn-elimination can take place in one step to yield the final compound **4.29*D*** (Scheme 4.24, eq 2).



Scheme 4.25: Rationale for configuration of protons in the product **4.38*B***

The formation of a 1:1 diastereomeric mixture of products (represented as **4.28*B***, Scheme 4.17) occurred in the reaction of enamide **4.28** at 80 °C. Interestingly, only single diastereomers of 6-*endo* cyclization products were observed in those instances where alkene migration to indene derivatives did not occur spontaneously under the reaction conditions (Chart 4.3.1, entries 5, 6, and 8; Chart 4.3.2, entries 3 and 5). In these cases, the only diastereomers that are formed are with the protons *anti* to each other. This observation was not surprising as the *E*-configuration of the enamide substrates is being relayed to the relative configuration of the products. The stereochemical rationale is illustrated in Scheme 4.25 using enamide **4.38** as a hypothetical example. The new bond that is going to be formed is indicated by the dashed line. The alkyne is activated by treatment with a catalytic amount of a metal salt (**4.78**). The nucleophilic enamide then attacks to form compound **4.79**. At this point free-bond rotation can occur around the bond highlighted in red. Free rotation would give a mixture of diastereomers in the product. In the case of the cycloisomerization of enamide **4.38**, the Friedel-Crafts reaction happens faster than bond rotation, which leads to only one observable diastereomer. A possible alternate explanation is that the *anti* arrangement of protons is the most populated rotamer (**4.79**). The Friedel-Crafts reaction takes place to form compound **4.80**, with the two protons of the original olefin (the protons shown in circles) *anti* to each other. Finally, re-aromatization and protodemetallation occur to give the final product **4.38*B*** featuring the two protons with an *anti*-relationship.



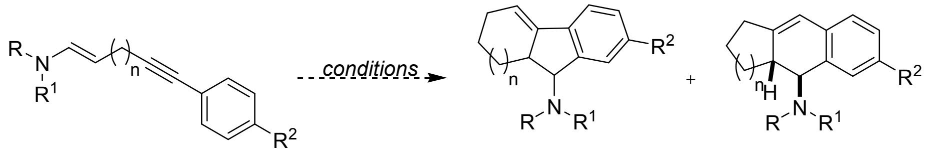
Scheme 4.26: Proposed stereochemical outcome of cyclization of enamide **4.46**

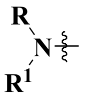
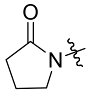
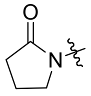
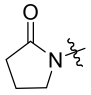
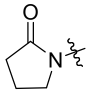
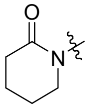
A similar rationale can be envisaged for the formation of tricycle **4.46*B***, the product of enamide **4.46** that features the Evans' auxiliary (Scheme 4.26). For clarity, the substituents on the aromatic ring have been removed. Assuming that the preferred rotamer of the enecarbamate is pictured, it is proposed that the alkyne is positioned close to the enamide on the *opposite* face from the benzyl functional group. Activation of the π-system with a platinum(II) or gold(I) salt then occurs followed by attack of the enamide to on the alkyne in a 6-*endo* mode of cyclization (**4.81**). The protons that resided on the olefin (bond shown in red) are now *anti* to each other (**4.82**). After Friedel-Crafts cyclization and protodemetallation the tricycle **4.46*B*** is formed. The absolute stereochemistry the products **4.46*A*** and **4.46*B*** could not be confirmed experimentally.

4.5 Unsuccessful Cycloisomerization Reactions of Acyclic Substrates

The cycloisomerization of acyclic enamides, enesulfonamides, and enecarbamates was shown to work well using either platinum(II)- or gold(I)-catalysis, with gold(I)-catalysis being slightly superior. In order to test the scope of the reaction, many substrates were tested for reactivity. Not all substrates resulted in clean cycloisomerization reactions. The results for substrates containing unsubstituted or *para*-substituted arene rings are summarized in Table 4.8.

Table 4.8: Unsuccessful cycloisomerization reactions containing unsubstituted and *para*-substituted arene rings

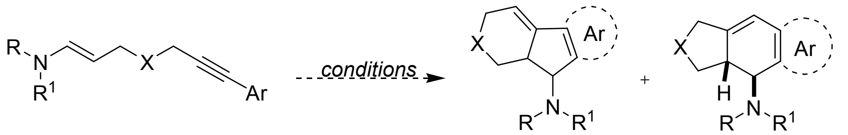


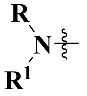
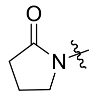
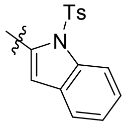
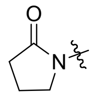
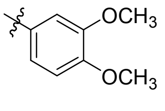
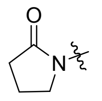
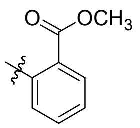
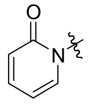
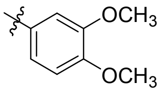
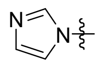
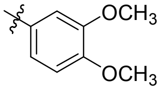
entry	substrate		R^2	conditions	result[a]
1	**4.25**		OCH_3	10 mol% $PtCl_2$, toluene, 130 °C, 16 h	NR
2	**4.38**		H	a) 10 mol% $PtCl_2$, toluene, 110 °C, 16 h	mixture
				b) 10 mol% [Ph_3PAuCl], 10 mol% $AgSbF_6$, 1,2-dichloroethane, 80 °C, 1.5 h	mixture
3	**4.31**		CF_3	a) 20 mol% $PtCl_2$, toluene, 130 °C, 16 h	mixture
				b) 5 mol% [Ph_3PAuCl], 5 mol% $AgSbF_6$, 1,2-dichloroethane, 80 °C, 5 h	mixture
4	**4.32**		NO_2	a) 10 mol% $PtCl_2$, toluene, 130 °C, 16 h	mixture
				b) 5 mol% [Ph_3PAuCl], 5 mol% $AgSbF_6$, 1,2-dichloroethane, 80 °C, 4 h	mixture
5	**4.43**		OCH_3	10 mol% $PtCl_2$, toluene, 110 °C, 16 h	mixture

[a] NR = no reaction.

Enamide **4.25** was treated under the standard reaction conditions but did not cyclize (entry 1). The temperature of the reaction was therefore increased to 130 °C. This did not have any effect as no reaction was observed under these conditions. Enamide **4.38** containing an unsubstituted arene ring was reacted with platinum(II) chloride as well as the combination of triphenylphosphine gold(I) chloride and silver hexafluoroantimonate (entry 2). Both conditions resulted in a mixture of unidentifiable products. Substrates containing an electron-withdrawing group on the aromatic substituent were also tested (entries 3 and 4). As shown in Chapter 3, the cycloisomerization of cyclic substrates containing a strongly electron withdrawing functionality on the aromatic ring resulted in a ratio favoring the 5-*exo* isomer.[1] Acyclic substrates with an electron-withdrawing substituted arene ring were tested to see if a similar pattern would be observed. First, enamide **4.31** containing a strongly electron withdrawing *para*-trifluoromethyl substituent on the arene ring was treated with 20 mol% of platinum(II) chloride at 130 °C to give a mixture of unidentifiable products (entry 3). The large catalyst loading and high reaction temperature was due to the low reactivity of the substrate. Treatment of enamide **4.31** with the cationic gold(I) system did not show better results. Unfortunately, treatment of enamide **4.32** containing a *para*-nitro substituent on the arene ring showed similar behavior (entry 4). Treatment of enamide **4.43** with platinum(II) chloride gave a mixture of unidentifiable compounds (entry 5). While these reactions were not promising using these catalytic systems, unreactive substrates could be coerced to cycloisomerize using other catalytic systems.

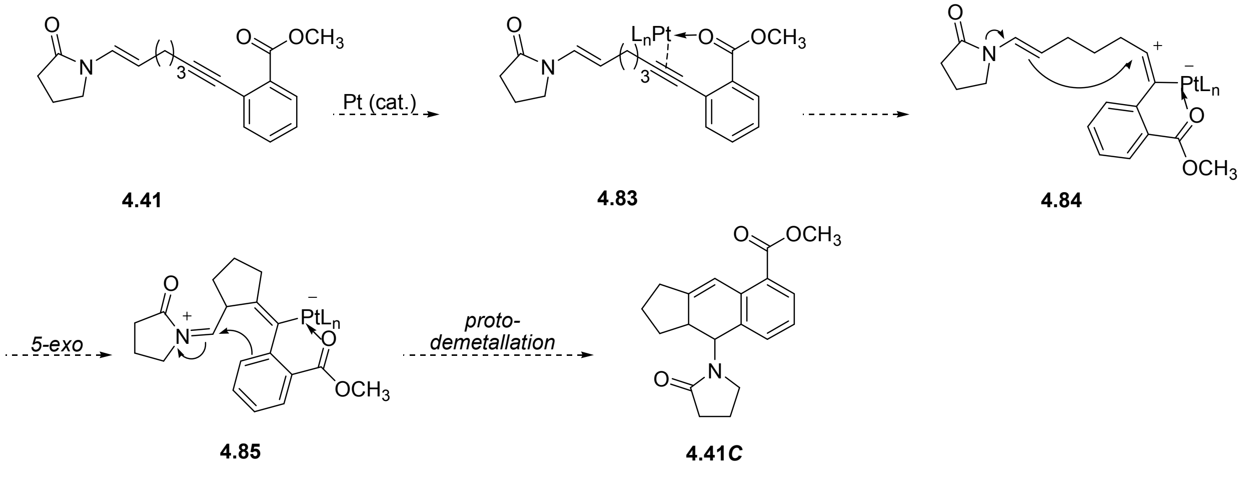
Table 4.9: Unsuccessful cycloisomerization reactions of enamides containing other electron-withdrawing substituents on the nitrogen atom of the enamine derivative



entry	substrate		Ar	X	conditions	result[a]
1	**4.42**			CH2	a) 10 % $PtCl_2$, toluene, 110 °C, 16 h	decomp.
					b) 5 mol % $[Ph_3PAuCl]$, 5 mol % $AgSbF_6$, 1,2-dichloroethane, 80 °C, 24 h	NR
					c) 10 mol % **1.70**, 1,2-dichloroethane, 80 °C, 24 h	NR
2	**4.68**			NBn	a) 10 % $PtCl_2$, toluene, 110 °C, 16 h	NR
					b) 10 mol % **1.70**, 1,2-dichloroethane, 80 °C, 4 h	NR
3	**4.41**			CH2	a) 10 % $PtCl_2$, toluene, 110 °C, 16 h	NR
					b) 20 % $PtCl_2$, toluene, 130 °C, 16 h	mixture
4	**4.69**			CH2	a) 10 % $PtCl_2$, toluene, 110 °C, 16 h	NR
					b) 5 mol % $[Ph_3PAuCl]$, 5 mol % $AgSbF_6$, 1,2-dichloroethane, 80 °C, 6 h	trace
5	**4.70**			CH2	a) 10 % $PtCl_2$, toluene, 110 °C, 16 h	NR
					b) 10 mol % **1.70**, 1,2-dichloroethane, 80 °C, 4 h	NR

[a]NR = no reaction.

A variety of other substrates, including substrates with heteroaromatic groups, *ortho*-substituents, or substituents in a 2,3-disubstituted pattern around the aromatic ring were tested in an effort to increase the substrate scope of the cycloisomerization reaction. The results are summarized in Table 4.9. Due to the instability of the indole containing enamide **4.30** under platinum(II)-catalysis, enamide **4.42** was synthesized in an attempt to decrease the reactivity and perhaps sensitivity of the indole moiety (entry 1). Protecting the nitrogen atom of the indole with a *para*-toluenesulfonyl group was too electron-withdrawing and decreased the reactivity of the enamide to a larger extent than anticipated. When treated with 10 mol% of platinum(II) chloride, only decomposition of the starting material was observed. When reacted with either of the gold(I) catalytic systems used in this study, no reaction was observed even at 80 °C. Enamide **4.68** was treated with 10 mol% of platinum(II) chloride but showed no reactivity (entry 2). Even treatment of enamide **4.68** with catalyst **1.70** did not induce cyclization. The low reactivity of the compound is proposed to be due to the nitrogen atom interfering with the catalyst. Protecting the nitrogen atom in the tether with a more electron withdrawing substituent such as *para*-toluenesulfonyl or *tert*-butylcarbamate could perhaps increase the reactivity of the substrate for cyclorearrangement.



Scheme 4.27: Selective formation of the 5-*exo* product using aromatic rings substituted with an *ortho*-ester

Two substrates containing an aromatic heterocyclic enamide were tested (entries 4 and 5). Enamide **4.69** containing a pyridone functionality was subjected to the standard reaction conditions but showed no reactivity (entry 4). Treatment with the more active catalyst **1.70** only gave a trace amount of what was presumably product but it could not be fully identified by standard characterization techniques. Imidazole enamine derivative **4.70** was tested under similar reaction conditions (entry 5). In both cases, no reaction was observed.

Enamide **4.41** featuring an *ortho*-methyl ester substituent on the aromatic ring was synthesized in an attempt to influence the selectivity of the reaction (Scheme 4.27). The electrophilic metal could presumably coordinate to both the alkyne and the oxygen atom of the ester carbonyl (**4.83**). The metal could associate with the carbon of the alkyne directly adjacent to the aromatic ring, forming a stable 6-membered ring (**4.84**). Interaction of the metal with the other carbon atom of the alkyne would lead to a less stable 7-membered ring. The enamide will attack the most electrophilic position (distal carbon of the alkyne) resulting in an initial 5-*exo* cyclization to form intermediate **4.85**. At this stage the Friedel-Crafts reaction will occur, followed by rearomatization and protodemetallation to give the 5-*exo* isomer product **4.41*C***. When treated under the standard reaction conditions, enamide **4.41** did not react to give product. The catalyst load was increased to 20 mol% and the temperature to 130 ^{o}C but then a mixture of unidentifiable products was observed, including a large amount of unreacted starting material.

4.6 Conclusion

Platinum(II)- and gold(I)-catalyzed cycloisomerization/Friedel-Crafts alkylation of acyclic enamides containing an aromatic functional group on the alkyne was effective in generating structurally complex 1-aza-substituted indene derivatives. Substrates with electron-rich aromatic substituents reacted with the electrophilic metal salt catalysts to form tricycles in good yields and satisfactory regioisomeric ratios, favoring products arising from an initial 6-*endo*-*dig* mode of cyclization. The reaction was extended to enesulfonamides, enecarbamates, and 6-membered ring enamides.

The product distribution of the reactions varied between reactions run at high temperature and reactions run at a lower temperature. At high temperature it was common to observe the isomerization of the double bond into the ring junction. This alkene migration was not observed for all products. Also, at high temperature the product from an initial 5-*exo* cyclization underwent elimination of the amide functional group to form a substituted naphthalene derivative as a major byproduct.

The question of stereoselectivity of the cycloisomerization reactions was a point of investigation in this study. It was found that substrates featuring an *E*-enamide derivative gave only the product where the two protons originating from the olefin are *anti* to each other in the product. This was observed for all substrates except for enamide **4.28**, where a 1:1 mixture of diastereomers was observed (represented as **4.28*B***). In most cases the double bond of the product was isomerized into the more substituted position for ease of characterization.

Not all substrates were reactive under platinum(II)- or gold(I)-catalysis. Substrates containing an electron withdrawing substituent on the aromatic ring reacted to give a mixture of unidentifiable products. Enamide **4.68** containing a basic nitrogen atom in the tether did not react. Substrates containing an aromatic enamine derivative also did not react.

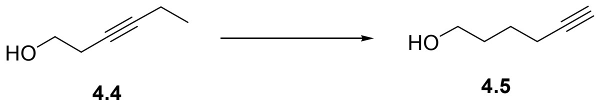
Despite the low reactivity of many of the substrates, it does not mean that they are inert to cycloisomerization. Other catalysts could be tested to find one that is active enough to carry out the transformation. Future work could also include using a chiral catalyst to carry out the reaction in an enantioselective manner.

4.7 Experimental

4.7.1 General Experimental

Please refer to the general experimental section in Chapter 2 for details.

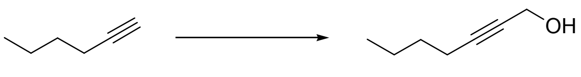
4.7.2 Synthesis of Substrates



Hex-5-yn-1-ol (4.5)

To a flask containing 29.4 g of potassium hydride (732 mmol) was added 350 mL of 1,3-diaminopropane. The suspension was stirred for 1 h at rt. To the resulting green suspension was slowly added 20.0 mL of hex-3-yn-1-ol (**4.4**) (183 mmol). The first ~2 g of the alcohol were added very carefully to avoid excessive frothing. After the addition of the alcohol, the reaction mixture was heated to 60 °C and stirred for 1.25 h. The mixture was then cooled to rt and carefully poured over 600 mL of crushed ice. The slurry was transferred to a separatory funnel and extracted four times with diethyl ether. The combined organics were washed twice with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by distillation under reduced pressure to afford 15.1 g of hex-5-yn-1-ol (**4.5**) (84 %) as a clear, colorless liquid, bp = 42-44 °C, 0.5 mmHg (*lit.* 73-75 °C, 15 mmHg).

IR (neat): 3418 (br), 2939, 2867, 2116 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.60 (td, *J* = 6.3, 1.7 Hz, 2H), 2.54 (br s, 1H), 2.21-2.17 (m, 2H), 1.93 (td, *J* = 2.7, 1.0 Hz, 1H), 1.66-1.54 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 84.4, 68.7, 62.1, 31.7, 24.9, 18.3.



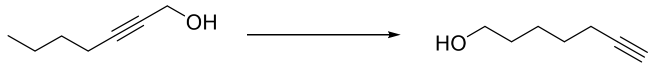
3.12 **3.13**

Hept-2-yn-1-ol (3.13)

To a solution of 20.0 mL of 1-hexyne (**3.12**) (174 mmol) in 300 mL of THF at -78 °C was added dropwsie 114 mL of a solution of *n*-butyllithium (1.60 M in hexanes, 183 mmol). The resulting solution was stirred at −78 °C for 1 h. To the reaction mixture was added 5.48 g of paraformaldehyde (183 mmol) in small portions over 0.3 h. The resulting suspension was stirred at −78 °C for 1 h then warmed to rt and stirred for 20 h. The clear yellow solution was quenched with a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by distillation under reduced pressure to afford 17.9 g (92 %) of hept-2-yn-1-ol (**3.13**) as a clear oil, bp = 46-49 °C, 0.5 mmHg (*lit*. 84-86 °C, 0.5 mmHg).

IR (neat): 3326 (br), 2935, 2226 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.19-4.18 (m, 2H), 2.76 (br s, 1H), 2.16 (tt, *J* = 7.0, 2.2 Hz, 2H), 1.52-1.28 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 87.1, 79.3, 52.0, 31.6, 22.9, 19.3, 14.5.

3.13 has been previously reported, see: 1) Kumar, G. D. K.; Baskaran, S. *J. Org.Chem.* **2005**, *70*, 4520-4523. 2) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090.



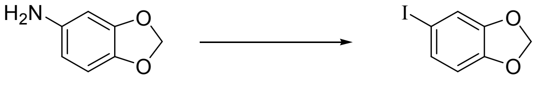
3.13 **3.14**

Hept-6-yn-1-ol (3.14)

To a flask containing 25.52 g of potassium hydride (636.5 mmol) was added 350 mL of 1,3-diaminopropane. The suspension was stirred for 1 h at rt. To the resulting green suspension was slowly added 17.85 g of hept-2-yn-1-ol (**3.13**) (159.1 mmol). The first ~2 g of the alcohol were added very carefully to avoid excessive frothing. After the addition of the alcohol, the reaction mixture was heated to 80 °C and stirred for 1.5 h. The mixture was then cooled to rt and carefully poured over 600 mL of crushed ice. The slurry was transferred to a separatory funnel and extracted four times with diethyl ether. The combined organics were washed twice with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by distillation under reduced pressure to afford 16.24 g of hept-6-yn-1-ol (**3.14**) (91 %) as a clear, colorless oil, bp = 60-65 °C, 0.5 mmHg (*lit.* 65-66 °C, 1 mmHg).

IR (neat): 3300 (br), 2938, 2117 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.64 (t, *J* = 6.5 Hz, 2H), 2.20 (td, *J* = 7.0, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.62-1.53 (m, 5H), 1.52-1.45 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 85.4, 69.3, 63.7, 33.2, 29.2, 25.9, 19.4.

3.14 has been previously reported, see: 1) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087-6090. 2) Gung, B. W.; Gibeau, C.; Jones, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3107-3114.



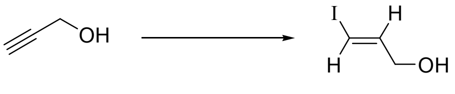
4.34 **4.35**

5-Iodobenzo-1,3-dioxole (4.35)

To a solution of 1.06 g of 3,4-methylenedioxyaniline (**4.34**) (7.73 mmol) in 40 mL of a 50 % solution of sulfuric acid at 0 °C was added an aqueous solution of 0.560 g of sodium nitrite (8.12 mmol) dropwise. The resulting dark green solution was stirred at 0 °C for 1 h. To the cold reaction mixture was added an aqueous solution of 1.35 g of potassium iodide (8.12 mmol). The solution was warmed to rt and stirred for 21 h. A solution of 1 M NaOH was added until the reaction mixture was basic by litmus paper. The solution was extracted three times with dichloromethane. The combined organic fractions were washed twice with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a black, oily solid. The crude solid was purified by column chromatography on silica gel (1:0→2:1 hexanes:ethyl acetate) to afford 0.424 g (22 %) of the title compound **4.35** as an off-white oily solid.

IR (neat): 2892, 799, 569 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.15-7.12 (m, 2H), 6.60 (d, *J* = 7.9 Hz, 1H), 5.95 (s, 2H).

4.35 has been previously reported, see: He, H.; Zatorska, D.; Kim, J.; Aguirre, J.; Llauger, L.; She, Y.; Wu, N.; Immormino, R. M.; Gewirth, D. T.; Chiosis, G. *J. Med. Chem.* **2006**, *49*, 381-390.



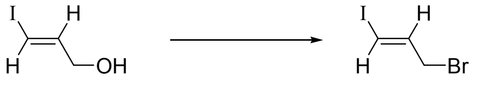
4.47 **4.48**

(*E*)-3-Iodoprop-2-en-1-ol (4.48)

To a solution of 5.6 g of zirconocene dichloride (19 mmol) in 20 mL of THF at 0 °C was slowly added 19 mL of a solution of diisobutylaluminum hydride (1.0 M in hexanes, 19 mmol). The resulting white suspension was stirred at 0 °C for 0.5 h. To the cold reaction mixture was carefully added a solution of 1.0 mL of propargyl alcohol (**4.47**) (17 mmol) in 10 mL of THF. The reaction mixture was warmed to rt and stirred for 1 h. The solution was then cooled to −78 °C and a solution of 5.7 g of iodine (23 mmol) in 25 mL of THF was added dropwise. The reaction mixture was stirred at −78 °C for 0.75 h. The dark red solution was quenched with 1 M HCl and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with a saturated solution of sodium thiosulfate and once with brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude yellow oil. The crude oil was purified by column chromatography on silica gel (3:1→1:1 hexanes:ethyl acetate), to afford 1.0 g (32 %) of (*E*)-3-iodoprop-2-en-1-ol (**4.48**) as a dark green oil.

IR (neat): 3390 (br), 2918, 1709, 1608 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.70 (dt, *J* = 14.6, 5.4 Hz, 1H), 6.40 (dt, *J* = 14.4, 1.4 Hz, 1H), 4.09 (dd, *J* = 5.4, 1.5 Hz, 2H), 1.97 (br s, 1H).

4.48 has been previously prepared, see: Huang, Z.; Negishi, E.-I. *Org. Lett.* **2006**, *8*, 3675-3678.



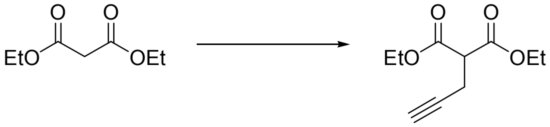
4.48 **4.49**

(*E*)-3-Bromo-1-iodoprop-1-ene (4.49)

To a solution of 1.6 g of triphenylphosphine (6.1 mmol) in 6.5 mL of dichloromethane at 0 °C was added dropwise 0.31 mL of bromine (6.1 mmol). The mixture was stirred at 0 °C for 0.2 h. To the bright yellow suspension was added a solution of 0.94 g of alkene **4.48** (5.1 mmol) and 0.85 mL of triethylamine (6.1 mmol) in 5.5 mL of dichloromethane dropwise. The reaction mixture was stirred at 0 °C for 0.2 h. The suspension was concentrated *in vacuo* to afford a crude brown solid. The solid was stirred vigorously with pentane for 4 h and then filtered through a pad of Celite®. The filtrate was concentrated by rotary evaporation *in vacuo* to afford 0.65 g (52 %) of the title compound **4.49** as a dark yellow oil.

IR (neat): 3049, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (t, *J* = 14.8, 7.5 Hz, 1H), 6.53 (d, *J* = 14.8 Hz, 1H), 3.86 (d, *J* = 7.5 Hz, 2H).

4.49 has been previously prepared, see: Brasseur, D.; Marek, I.; Normant, J.-F. *Tetrahedron* **1996**, *52*, 7235-7250.



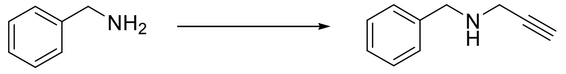
4.52 **4.53**

Diethyl 2-(prop-2-ynyl)malonate (4.53)

To a solution of 0.58 g of sodium hydride (24 mmol) in 20 mL of THF was added 3.1 mL of diethyl malonate (**4.52**) (20 mmol) dropwise. The reaction mixture was stirred at rt for 1 h. To the solution was slowly added 1.0 mL of a solution of propargyl bromide (80 wt. % in toluene, 6.7 mmol). The resulting yellow suspension was stirred at rt for 1 h. The reaction mixture was then quenched with a saturated solution of ammonium chloride. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic fractions were washed once with brine, dried over sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The product was separated by distillation under reduced pressure (0.5 mmHg) to afford 1.1 g (82 %) of the title compound **4.53** as a clear oil. The product was used with no further purification.

IR: 3287, 2984, 2940, 1736, 657 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.23 (q, *J* = 7.3 Hz, 4H), 3.57 (t, *J* = 7.7 Hz, 1H), 2.78 (dd, *J* = 7.5, 2.4 Hz, 2H), 2.03-2.02 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 6H).

4.53 has been previously prepared, see: Czekelius, C.; Hafer, J.; Tonzetich, Z, J.; Schrock, R. R.; Christensen, R. L.; Müller, P. *J. Am. Chem. Soc.* **2006**, *128*, 16664-16675.



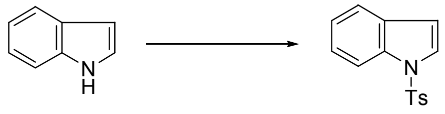
4.56 **4.57**

N-Benzylprop-2-yn-1-amine (4.57)

To a solution of 15 mL of benzylamine (**4.56**) (1.4 × 10^2 mmol) was added 3.4 mL of a solution of propargyl bromide (80 wt. % in toluene, 23 mmol) dropwise over a period of 0.75 h. The resulting peach colored solution was stirred at rt for 19 h. The reaction mixture was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with a saturated solution of sodium bicarbonate. The organic layer was then dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a clear yellow oil. The crude oil was purified by column chromatography on silica gel (1:0→5:1→1:1 hexanes:ethyl acetate) to give 3.2 g (98 %) of the title compound **4.57** as a clear, colorless oil.

IR (neat): 3292, 2840, 1454, 738, 699, 647 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.28 (m, 5H), 3.90 (s, 2H), 3.44 (d, *J* = 2.4 Hz, 2H), 2.29 (t, *J* = 2.4 Hz, 1H), 1.53 (br s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.6, 128.60, 128.58, 127.3, 82.3, 71.8, 52.4, 37.5.

4.57 has been previous prepared, see: Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076-8077.



3.23 **4.36**

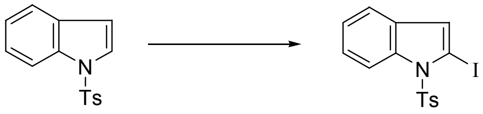
1-Tosyl-1*H*-indole (4.36)

To a solution of 2.49 g of indole (**3.23**) (21.2 mmol) in 50 mL of THF was added 5.96 g of powdered potassium hydroxide (106 mmol) in one portion. The reaction mixture was stirred at rt for 0.5 h. To the resulting bright blue suspension was added 4.45 g of *p*-toluenesulfonyl chloride (23.3 mmol) in one portion. The resulting peach colored reaction mixture was stirred at rt for 20

h. The solid was removed by filtration through Celite®, rinsing exhaustively with dichloromethane. The filtrate was concentrated by rotary evaporation *in vacuo* to afford a pink oil. Recrystallization from the oil using methanol gave 4.52 g (79 %) of the 1-tosyl-1*H*-indole (**4.36**) as white crystals, mp = 84-85 °C (*lit.* 83-85 °C).

IR (film): 3066, 2255, 1446, 1132, 732, 680 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 3.8 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.34-7.30 (m, 1H), 7.25-7.21 (m, 3H), 6.67 (d, *J* = 3.8 Hz, 1H), 2.34 (s, 3H).

4.36 has been previously synthesized, see: Wagger, J.; Svete, J.; Stanovnik, B. *Synthesis* **2008**, *9*, 1436-1442.



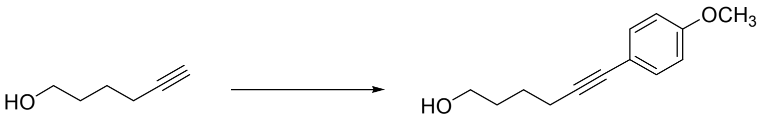
4.36 **4.37**

2-Iodo-1-tosyl-1*H*-indole (4.37)

To a solution of 1.0 g of 1-tosyl-1*H*-indole (**4.36**) (3.8 mmol) in 20 mL of diethyl ether at −78 °C was added dropwise 2.7 mL of a solution of *t*-butyllithium (1.6 M in hexanes, 4.2 mmol). The resulting white suspension was stirred at −78 °C for 0.5 h. To the cold suspension was added dropwise a solution of 1.1 g of iodine (4.2 mmol) in 10 mL of diethyl ether. The suspension becomes dark red. The reaction mixture was stirred at −78 °C for 0.5 h before quenching with a saturated solution of ammonium chloride. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed twice with a saturated solution of sodium thiosulfate, and once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a thick, pink oil. Recrystallization from the oil using methanol afforded 1.1 g (69 %) of the title compound **4.37** as pink crystals, mp = 77-79 °C.

IR (film) 3065, 1597, 1176, 746, 674 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.28 (td, *J* = 7.5, 1.4 Hz, 1H), 7.24-7.21 (m, 3H), 7.00 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 145.3, 138.6, 135.4, 131.9, 129.9, 126.9, 125.0, 124.3, 123.8, 119.8, 115.6, 75.5, 21.7. HRMS (ESI) calcd for $C_{15}H_{13}NO_2SI$ $(M + H)^+$: 397.9712. Found: 397.9720.

Representative Procedure for Sonogashira Coupling Reactions



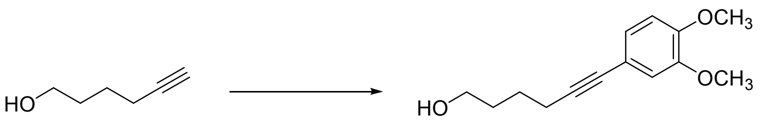
4.5 4.6

6-(4-Methoxyphenyl)hex-5-yn-1-ol (4.6)

To a flask charged with 0.187 g of bis(triphenylphosphine)palladium(II) chloride (0.266 mmol) and 0.101 g of copper(I) iodide (0.532 mmol) was added 3 mL of triethylamine. To the resulting bright yellow suspension was added a solution of 0.522 g of hex-5-yn-1-ol (**4.5**) (5.32 mmol) and 1.50 g of 4-iodoanisole (6.38 mmol) in 3 mL of dichloromethane in one portion. The flask was rinsed with 1 mL of triethylamine and added to the reaction mixture. The reaction vessel was wrapped in aluminum foil and stirred at rt for 1 h. The mixture was filtered through a pipette of silica gel using ethyl acetate eluent and then concentrated by rotary evaporation *in vacuo* to afford a brown, oily solid. The crude product was dry loaded onto silica gel and purified by column chromatography (5:1→3:1→1:1 hexanes:ethyl acetate) to afford 0.803 g (74 %) of the title compound **4.6** as an orange oil.

IR (neat): 3364 (br), 2937, 1607, 832 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.72 (q, J = 5.8 Hz, 2H), 2.45 (t, J = 6.7 Hz, 2H), 1.79-1.66 (m, 4H), 1.35 (t, J = 5.4 Hz, 1H).

4.6 has been previously prepared, see: Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270-4279.

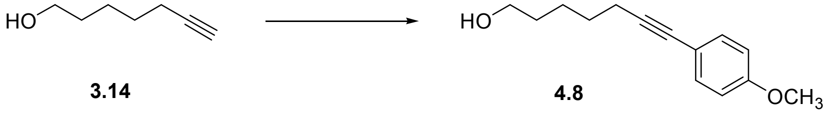


4.5 4.7

6-(3,4-Dimethoxyphenyl)hex-5-yn-1-ol (4.7)

Hex-5-yn-1-ol (**4.5**) (0.531 g, 5.41 mmol), bis(triphenylphosphine)palladium(II) chloride (0.190 g, 0.271 mmol), copper(I) iodide (0.103 g, 0.541 mmol), and 4-iodoveratrole (**3.20**) (1.72 g, 6.50 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography (3:1→1:1→1:3 hexanes:ethyl acetate), 1.05 g (83 %) of the title compound **4.7** was isolated as an orange oil.

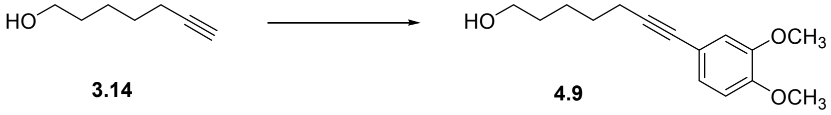
IR (neat): 3508 (br), 3404, 2937, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.99 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.91 (d, *J* = 1.7 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.72 (q, *J* = 6.0 Hz, 2H), 2.45 (t, *J* = 6.8 Hz, 2H), 1.80-1.68 (m, 4H), 1.38 (t, *J* = 5.3 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.1, 148.7, 124.7, 116.3, 114.5, 111.1, 88.3, 80.9, 62.6, 56.0, 32.1, 25.3, 19.3. HMRS (ESI) calcd for $C_{14}H_{18}O_3Na$ (M + Na)$^+$: 257.1154. Found: 257.1158.



7-(4-Methoxyphenyl)hept-6-yn-1-ol (4.8)

Hept-6-yn-1-ol (**3.14**) (0.637 g, 5.68 mmol), bis(triphenylphosphine)palladium(II) chloride 0.199 g, 0.284 mmol), copper(I) iodide (0.108 g, 0.568 mmol), and 4-iodoanisole (1.59 g, 6.81 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 1.02 g (83 %) of the title compound **4.8** was isolated as an orange oil.

IR (neat): 3346 (br), 2936, 1607, 833 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 3.67-3.63 (m, 2H), 2.40 (t, *J* = 6.8 Hz, 2H), 1.72-1.69 (m, 1H), 1.66-1.58 (m, 4H), 1.56-1.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 133.0, 116.3, 114.0, 88.6, 80.6, 63.0, 55.4, 32.5, 28.8, 25.3, 19.6. HRMS (ESI) calcd for $C_{14}H_{19}O_2$ (M + H)$^+$: 219.1385. Found: 219.1381.

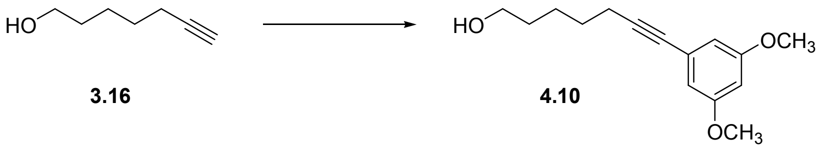


7-(3,4-Dimethoxyphenyl)hept-6-yn-1-ol (4.9)

Hept-6-yn-1-ol (**3.14**) (0.52 g, 4.6 mmol), bis(triphenylphosphine)palladium(II) chloride (0.16 g, 0.23 mmol), copper(I) iodide (0.088 g, 0.46 mmol), and 4-iodoveratrole (**3.22**) (1.5 g, 5.5 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography (3:1→1:1→0:1 hexanes:ethyl acetate), 0.94 g (83 %) of the title compound **4.9** was isolated as an orange oil.

IR (neat): 3512 (br), 2936, 1601, 809, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.96 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 3.83 (s, 6H), 3.64-3.59 (m, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.67 (t, *J* = 5.3 Hz, 1H), 1.63-1.56 (m, 4H), 1.54-1.49 (m, 2H). ^{13}C

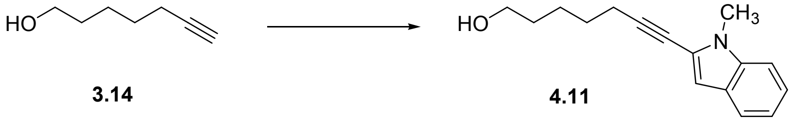
NMR (100 MHz, $CDCl_3$): δ 149.0, 148.7, 124.7, 116.4, 114.5, 111.1, 88.6, 80.7, 62.9, 56.0, 32.4, 28.8, 25.3, 19.5. HMRS (ESI) calcd for $C_{15}H_{20}O_3Na$ $(M + Na)^+$: 271.1310. Found: 271.1313.



7-(3,5-Dimethoxyphenyl)hept-6-yn-1-ol (4.10)

Hept-6-yn-1-ol (**3.16**) (0.718 g, 6.40 mmol), bis(triphenylphosphine)palladium(II) chloride (0.225 g, 0.320 mmol), copper(I) iodide (0.122 g, 0.640 mmol), and 1-bromo-3,5-dimethoxybenzene (1.67 g, 7.68 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred at rt for 15 h. The reaction mixture was then heated to 65 °C and stirred for 2 h before cooling to rt. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 1.12 g (70 %) of the title compound **4.10** was isolated as a peach colored oil.

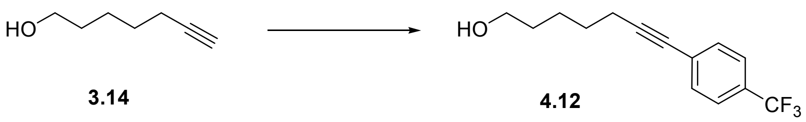
IR (neat): 3365 (br), 2937, 1598, 833, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.56 (d, $J = 2.2$ Hz, 2H), 6.41 (t, $J = 2.4$ Hz, 1H), 3.78 (s, 6H), 3.68 (t, $J = 6.2$ Hz, 2H), 2.43 (t, $J = 6.8$ Hz, 2H), 1.69-1.60 (m, 4H), 1.58-1.54 (m, 2H), 1.31 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 125.4, 109.5, 101.2, 89.9, 80.9, 63.0, 55.5, 32.4, 28.6, 25.2, 19.5. HRMS (ESI) calcd for $C_{15}H_{20}O_3Na$ $(M + Na)^+$: 271.1310. Found: 271.1313.



7-(1-Methyl-1*H*-indol-2-yl)hept-6-yn-1-ol (4.11)

Hept-6-yn-1-ol (**3.14**) (0.621 g, 5.53 mmol), bis(triphenylphosphine)palladium(II) chloride (0.194 g, 0.277 mmol), copper(I) iodide (0.105 g, 0.553 mmol), and iodoindole **3.25** (1.71 g, 6.64 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 3 h. After purification by column chromatography (5:1→3:1→1:1 hexanes:ethyl acetate), 1.11 g (83 %) of the title compound **4.11** was isolated as an orange oil.

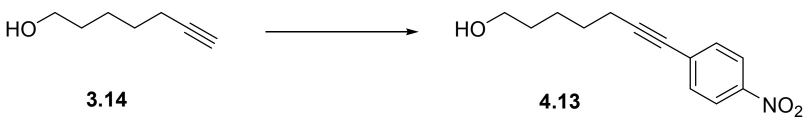
IR (neat): 3356 (br), 2936, 1462, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, $J = 8.2$ Hz, 1H), 7.29-7.26 (m, 2H), 7.17-7.13 (m, 1H), 6.73 (s, 1H), 3.81 (s, 3H), 3.70-3.66 (m, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.83 (t, *J* = 5.0 Hz, 1H), 1.73 (qt, *J* = 7.2 Hz, 2H), 1.67-1.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 127.4, 123.0, 122.7, 120.9, 120.1, 109.5, 106.3, 96.5, 72.7, 62.9, 32.4, 30.6, 28.6, 25.3, 19.9. HRMS (ESI) calcd for $C_{16}H_{19}NONa$ $(M + Na)^+$: 264.1364. Found: 264.1367.



7-(4-(Trifluoromethyl)phenyl)hept-6-yn-1-ol (4.12)

Hept-6-yn-1-ol (**3.14**) (0.61 g, 5.4 mmol), bis(triphenylphosphine)palladium(II) chloride (0.19 g, 0.27 mmol), copper(I) iodide (0.10 g, 0.54 mmol), and 4-iodobenzotrifluoride (1.0 mL, 6.5 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 2 h. After purification by column chromatography (5:1→3:1 hexanes:ethyl acetate), 1.3 g (94 %) of the title compound **4.12** was isolated as an orange oil.

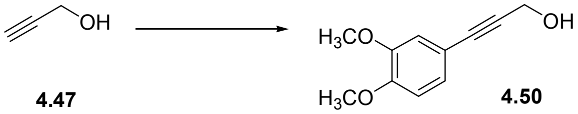
IR (neat): 3338 (br), 2939, 2235, 1616, 843 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 1.68-1.60 (m, 4H), 1.58-1.50 (m, 2H), 1.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.9, 129.4 (q, *J* = 32 Hz), 128.0, 125.2 (q, *J* = 4 Hz), 124.2 (q, *J* = 271 Hz), 93.1, 79.8, 62.9, 32.4, 28.5, 25.2, 19.5. HMRS (ESI) calcd for $C_{14}H_{15}OF_3Na$ $(M + Na)^+$: 279.0973. Found: 279.0970.



7-(4-Nitrophenyl)hept-6-yn-1-ol (4.13)

Hept-6-yn-1-ol (**3.14**) (0.646 g, 5.76 mmol), bis(triphenylphosphine)palladium(II) chloride (0.202 g, 0.288 mmol), copper(I) iodide (0.110 g, 0.576 mmol), and 1-iodo-4-nitrobenzene (1.72 g, 6.92 mmol) were combined accor6ding to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 2 h. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 1.18 g (88 %) of the title compound **4.13** was isolated as an orange oil.

IR (neat): 3365 (br), 2939, 2233, 1594, 1517, 1343, 854 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 3.67-3.63 (m, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.85 (t, *J* = 5.1 Hz, 1H), 1.68-1.57 (m, 4H), 1.56-1.47 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 146.7, 132.4, 131.3, 123.6, 96.6, 79.6, 62.8, 32.3, 28.4, 25.3, 19.7. HMRS (ESI) calcd for $C_{13}H_{15}NO_3Na$ (M + Na)$^+$: 256.0950. Found: 256.0957.

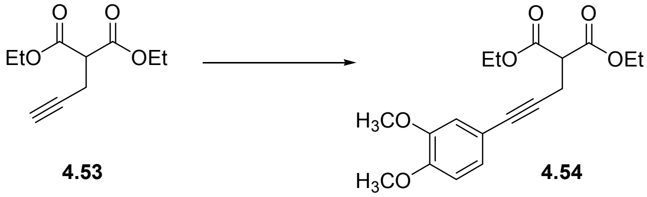


3-(3,4-Dimethoxyphenyl)prop-2-yn-1-ol (4.50)

Propargyl alcohol (**4.47**) (0.3 mL, 5 mmol), bis(triphenylphosphine)palladium(II) chloride (0.2 g, 0.3 mmol), copper(I) iodide (0.1 g, 0.5 mmol), and 4-iodoveratrole (**3.22**) (2 g, 7 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.9 g (86 %) of the title compound **4.50** was isolated as an orange oil.

IR (neat): 3475 (br), 2936, 2225, 1600, 732 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.00 (d, *J* = 7.2 Hz, 1H), 6.92 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.46 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 2.54 (br s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.7, 148.7, 125.1, 114.9, 114.6, 111.2, 86.1, 85.7, 56.0, 51.6.

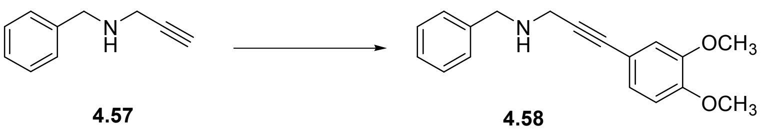
4.50 has been previously prepared, see: Stevenson, R.; Weber, J. V. *J. Nat. Prod.* **1989**, *52*, 367-375.



Diethyl 2-(3-(3,4-dimethoxyphenyl)prop-2-ynyl)malonate (4.54)

Diethyl 2-(prop-2-ynyl)malonate (**4.53**) (1.1 g, 5.2 mmol), bis(triphenylphosphine)palladium(II) chloride (0.18 g, 0.26mmol), copper(I) iodide (0.099 g, 0.52 mmol), and 4-iodoveratrole (1.6 g, 6.2 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 3.5 h. After purification by column chromatography on silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.96 g (55 %) of the title compound **4.54** was isolated as an orange oil.

IR (neat): 2981, 1732, 1514, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.89 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.16 (q, *J* = 6.8 Hz, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 3.57 (t, *J* = 7.7 Hz, 1H), 2.92 (d, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.1, 149.3, 148.6, 124.8, 115.5, 114.4, 111.0, 83.9, 82.4, 61.9, 61.7, 55.9, 51.6, 19.5, 14.1. HRMS (ESI) calcd for $C_{18}H_{22}O_6Na$ (M + Na)$^+$: 357.1314. Found: 357.1307.

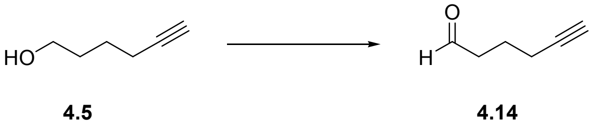


N-Benzyl-3-(3,4-dimethoxyphenyl)prop-2-yn-1-amine (4.58)

Amine **4.57** (0.53 g, 3.6 mmol), bis(triphenylphosphine)palladium(II) chloride (0.13 g, 0.18 mmol), copper(I) iodide (0.069 g, 0.36 mmol), and 4-iodoveratrole (1.1 g, 4.4 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography on silica gel (5:1→1:1 hexanes:ethyl acetate), 1.0 g (100 %) of the title compound **4.58** was isolated as an orange oil.

IR (neat): 2934, 1600, 1513, 734 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 (dt, *J* = 14.7, 7.3 Hz, 4H), 7.29-7.23 (m, 1H), 7.05 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 3.96 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.65 (s, 2H), 1.66 (br s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.5, 148.8, 139.7, 128.7, 128.6, 128.5, 127.3, 125.0, 115.6, 114.6, 111.2, 86.1, 83.8, 56.0, 52.8, 38.5. HRSM (ESI) calcd for $C_{18}H_{20}NO_2$ (M + H)$^+$: 282.1494. Found: 282.1487.

Representative Procedure for the Moffatt-Swern Oxidation

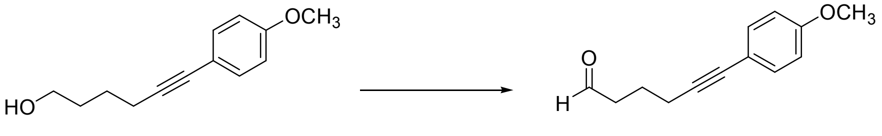


Hex-5-ynal (4.14)

To a solution of 4.7 mL of oxalyl chloride (54 mmol) in 100 mL of dichloromethane at −78 °C was added 5.9 mL of dimethyl sulfoxide (83 mmol) dropwise. The reaction mixture was stirred at −78 °C for 0.25 h. A solution of 4.1 g of hex-5-yn-1-ol (**4.5**) (42 mmol) in 14 mL of dichloromethane was slowly added to the cold solution. After stirring at −78 °C for 0.5 h, 29 mL of triethylamine (2.1 × 10^2 mmol) was added dropwise to the white suspension. The resulting reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were then washed once with 1 M HCl and once with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude yellow oil. The crude oil was purified by distillation under reduced pressure to afford 2.7 g (69 %) of the title compound **4.14** as a clear, colorless liquid, bp = 37-40 °C, 0.5 mmHg (*lit.* 61-62 °C, 30 mmHg).

IR (neat): 3288, 2959, 2116, 1713, 634 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 2.60 (td, *J* = 7.2, 1.4 Hz, 2H), 2.27 (td, *J* = 6.8, 2.7 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.85 (qt, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 83.3, 69.5, 42.7, 21.0, 17.9.

4.14 has been previously prepared, see: 1) Felix, D.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 52-56. 2) Böttcher, T.; Sieber, S. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4600-4603.

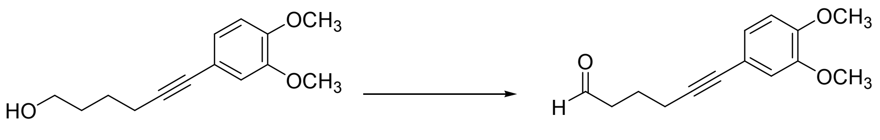


4.6 **4.15**

6-(4-Methoxyphenyl)hex-5-ynal (4.15)

Alcohol **4.6** (0.8 g, 4 mmol), oxalyl chloride (0.4 mL, 5 mmol), dimethyl sulfoxide (0.6 mL, 8 mmol), and triethylamine (3 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffat-Swern oxidation, except that the reaction mixture was stirred at 0 °C for 2.25 h. After purification by column chromatography (5:1→1:1 hexanes:ethyl acetate), 0.6 g (80 %) of the title compound **4.15** was isolated as an orange oil.

IR (neat): 2937, 1723, 1606, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (t, *J* = 1.4 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.64 (td, *J* = 7.2, 1.4 Hz, 2H), 2.47 (t, *J* = 6.8 Hz, 2H), 1.93 (qt, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 159.4, 133.0, 115.9, 114.0, 87.2, 81.6, 55.4, 43.0, 21.5, 19.0. HRMS (ESI) calcd for $C_{13}H_{14}O_2Na$ (M + Na)$^+$: 225.0891. Found: 225.0888.

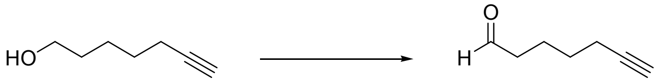


4.7 **4.16**

6-(3,4-Dimethoxyphenyl)hex-5-ynal (4.16)

Alcohol **4.7** (1 g, 4 mmol), oxalyl chloride (0.5 mL, 5 mmol), dimethyl sulfoxide (0.6, 8 mmol), and triethylamine (3 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffatt-Swern oxidation, except that the reaction mixture was stirred at 0 °C for 2.25 h. After purification by column chromatography (5:1→1:1 hexanes:ethyl acetate), 0.8 g (88 %) of the title compound **4.16** was isolated as an orange oil.

IR (neat): 2937, 1722, 811, 763 $\mathrm{cm^{-1}}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (t, *J* = 1.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.85 (s, 6H), 2.63 (td, *J* = 7.2, 1.4 Hz, 2H), 2.46 (t, *J* = 6.8 Hz, 2H), 1.92 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 149.2, 148.7, 124.8, 116.0, 114.5, 111.2, 87.2, 81.7, 56.0, 43.0, 21.4, 19.0. HRMS (ESI) calcd for $C_{14}H_{16}O_3Na$ $(M + Na)^+$: 255.0997. Found: 255.0994.



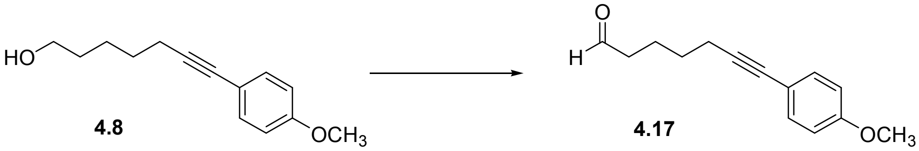
3.14 **3.15**

Hept-6-ynal (3.15)

Hept-6-yn-1-ol (**3.14**) (3.9 g, 35 mmol), oxalyl chloride (4.0 mL, 46 mmol), dimethyl sulfoxide (5.0 mL, 70 mmol), and triethylamine (24 mL, 1.8 × 10^2 mmol) were combined according to the general procedure for the Moffat-Swern oxidation. After purification under reduced pressure, 3.3 g (86 %) of hept-6-ynal (**3.15**) was isolated as a clear, colorless liquid, bp = 35-39 °C, 0.5 mmHg (*lit.* 78-80 °C, 20 mmHg).

IR (neat): 3293, 2944, 2116, 1724, 641 $\mathrm{cm^{-1}}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 2.47 (td, *J* = 6.8, 1.4 Hz, 2H), 2.22 (td, *J* = 6.9, 2.6 Hz, 2H), 1.96 (t, *J* = 2.4 Hz, 1H), 1.80-1.73 (m, 2H), 1.62-1.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 83.9, 68.9, 43.5, 28.0, 21.3, 18.4.

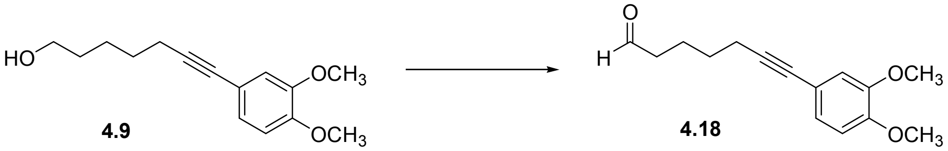
3.15 has been previously prepared, see: Hopf, H.; Krüger, A. *Chem.− Eur. J.* **2001**, *7*, 4378-4385.



7-(4-Methoxyphenyl)hept-6-ynal (4.17)

Alcohol **4.8** (1 g, 5 mmol), oxalyl chloride (0.5 mL, 6 mmol), dimethyl sulfoxide (0.6 mL, 9 mmol), and triethylamine (3 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffatt-Swern oxidation. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 0.8 g (86 %) of the title compound **4.17** was isolated as a pale yellow oil.

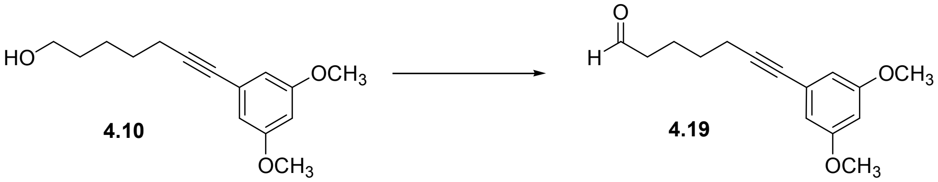
IR (neat): 2937, 1723, 1606, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.32 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.49 (t, *J* = 7.3 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 1.81 (qt, *J* = 7.5 Hz, 2H), 1.63 (qt, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 159.3, 133.0, 116.1, 114.0, 88.0, 81.0, 55.4, 43.5, 28.3, 21.5, 19.3. HRMS (ESI) calcd for $C_{14}H_{17}O_2$ $(M + H)^+$: 217.1229. Found : 217.1232.



7-(3,4-Dimethoxyphenyl)hept-6-ynal (4.18)

Alcohol **4.9** (0.9 g, 4 mmol), oxalyl chloride (0.4 mL, 5 mmol), dimethyl sulfoxide (0.5 mL, 7 mmol), and triethylamine (3 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffatt-Swern oxidation. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 0.8 g (87 %) of the title compound **4.18** was isolated as a yellow oil.

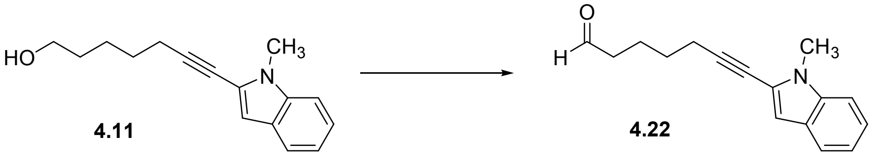
IR (neat): 2937, 1721, 811, 762 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 6.99 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.91 (d, *J* = 1.4 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.87 (s, 6H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.44 (d, *J* = 6.8 Hz, 2H), 1.86-1.79 (m, 2H), 1.65 (qt, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 149.1, 148.7, 124.8, 116.2, 114.5, 111.1, 87.9, 81.1, 56.0, 43.6, 28.3, 21.5, 19.4. HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $(M + H)^+$: 247.1334. Found: 247.1338.



7-(3,5-Dimethoxyphenyl)hept-6-ynal (4.19)

Alcohol **4.10** (1 g, 4 mmol), oxalyl chloride (0.5 mL, 6 mmol), dimethyl sulfoxide (0.6 mL, 9 mmol), and triethylamine (3.0 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffatt-Swern oxidation, except that the reaction mixture was stirred at 0 °C for 2.3 h. After purification by column chromatography (5:1 hexanes:ethyl acetate), 0.8 g (84 %) of the title compound **4.19** was isolated as a yellow oil.

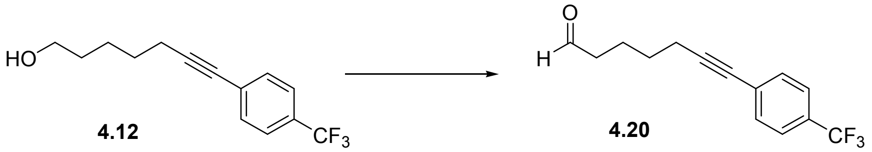
IR (neat): 2940, 1723, 1589, 841, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (t, *J* = 1.7 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 2H), 6.40 (t, *J* = 2.2 Hz, 1H), 3.76 (s, 6H), 2.45 (td, *J* = 7.3, 1.5 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 1.84-1.74 (m, 2H), 1.67-1.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 160.6, 125.3, 109.5, 101.3, 89.2, 81.2, 55.5, 43.5, 28.2, 21.4, 19.3. HRMS (ESI) calcd for $C_{15}H_{18}O_3Na$ $(M + Na)^+$: 269.1154. Found: 269.1156.



7-(1-Methyl-1*H*-indol-2-yl)hept-6-ynal (4.22)

To an open atmosphere solution of 0.501 g of alcohol **4.11** (2.08 mmol) in 10 mL of dichloromethane was added 1.06 g of Dess-Martin periodinane (2.49 mmol) in one portion. The reaction mixture turns from an orange solution to a forest green suspension. The suspension was stirred at rt for 0.1 h. The mixture was quenched with a saturated solution of sodium bicarbonate and stirred vigorously for 0.5 h. The layers were separated and the aqueous layer extracted twice with ethyl acetate. The combined organic fractions were washed twice with brine. The organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a brown oil. The crude oil was dry loaded onto silica gel and purified by column chromatography (3:1→1:1 hexanes:ethyl acetate) to afford 0.335 g (67 %) of the title compound **4.22** as a yellow oil.

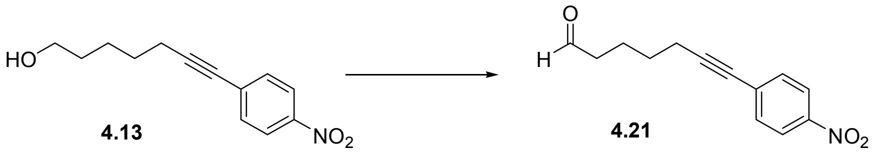
IR (neat): 2940, 1721, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (t, *J* = 1.7 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.28-7.24 (m, 2H), 7.13 (ddd, *J* = 7.9, 5.4, 2.4 Hz, 1H), 6.70 (s, 1H), 3.79 (s, 3H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.51 (td, *J* = 7.2, 1.4 Hz, 2H), 1.88-1.81 (m, 2H), 1.74-1.67 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 202.2, 137.1, 127.4, 122.8, 122.8, 120.9, 120.1, 109.5, 106.4, 95.8, 73.0, 43.5, 30.6, 28.2, 21.5, 19.7. HRMS (ESI) calcd for $C_{16}H_{18}NO$ $(M + H)^+$: 240.1388. Found: 240.1384.



7-(4-(Trifluoromethyl)phenyl)hept-6-ynal (4.20)

Alcohol **4.12** (1 g, 4 mmol), oxalyl chloride (0.5 mL, 6 mmol), dimethyl sulfoxide (0.7 mL, 9 mmol), and triethylamine (3 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffatt-Swern oxidation, except that the reaction mixture was stirred at 0 ^{o}C for 1.5 h. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 1 g (84 %) of the title compound **4.20** was isolated as a clear, yellow oil.

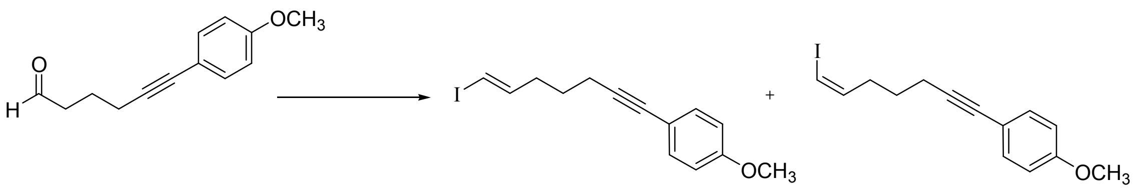
IR (neat): 2942, 2236, 1725, 1616, 844 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.79 (t, *J* = 1.7 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 2.50 (td, *J* = 7.2, 1.7 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.85-1.77 (m, 2H), 1.69-1.62 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 202.1, 131.9, 129.5 (q, *J* = 32 Hz), 127.9, 125.2 (q, *J* = 4 Hz), 124.1 (q, *J* = 272 Hz), 92.4, 80.1, 43.4, 28.0, 21.4, 19.3. HRMS (ESI) calcd for $C_{14}H_{14}OF_3$ $(M + H)^+$: 255.0997. Found: 255.0991.



7-(4-Nitrophenyl)hept-6-ynal (4.21)

Alcohol **4.13** (1 g, 5 mmol), oxalyl chloride (0.5 mL, 6 mmol), dimethyl sulfoxide (0.7 mL, 9 mmol), and triethylamine (3 mL, 2 × 10^1 mmol) were combined according to the general procedure for the Moffatt-Swern oxidation, except that the reaction mixture was stirred at 0 ^{o}C for 2 h. After purification by column chromatography (3:1→1:1 hexanes:ethyl acetate), 0.9 g (84 %) of the title compound **4.21** was isolated as an orange oil.

IR (neat): 2940, 2232, 1723, 1517, 1343, 854 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.78 (t, *J* = 1.7 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 2.52-2.45 (m, 4H), 1.83-1.76 (m, 2H), 1.69-1.61 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 202.1, 146.8, 132.4, 131.0, 123.6, 95.8, 79.9, 43.4, 27.9, 21.4, 19.5. HRMS (ESI) calcd for $C_{13}H_{14}NO_3$ $(M + H)^+$: 232.0974. Found: 232.0969.



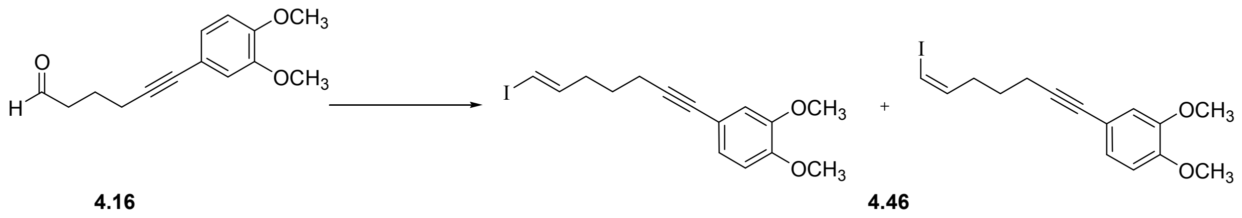
4.15 **4.45**

3 : 1

(*E*)-1-(7-Iodohept-6-en-1-ynyl)-4-methoxybenzene + (*Z*)-1-(7-iodohept-6-en-1-ynyl)-4-methoxybenzene (4.45)

To a solution of 1.32 g of chromium(II) chloride (10.8 mmol) in 10 mL of THF at 0 °C was added dropwise a mixture of 0.363 g of aldehyde **4.15** (1.80 mmol) and 1.41 g of iodoform (3.59 mmol) in 10 mL of THF. The resulting dark red suspension was stirred at 0 °C for 0.25 h and then warmed to rt and stirred for 1 h. The reaction mixture was then quenched with water and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed twice with brine. The organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude brown oil. The crude oil was dry loaded onto silica gel and purified by column chromatography (1:0→10:1→5:1 hexanes:ethyl acetate) to afford 0.349 g (59 %) of a 3:1 mixture of the title compound **4.45** as a clear, colorless oil.

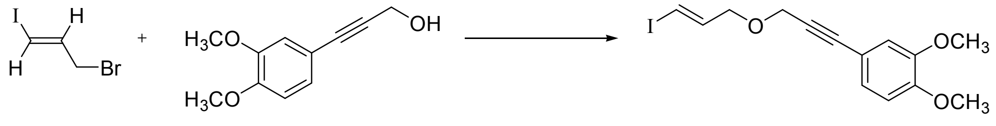
IR (neat): 2933, 2835, 1606, 831 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.55 (dt, J = 14.3, 7.2 Hz, 1H), 6.08 (d, J = 14.3 Hz, 1H), 3.80 (s, 3H), 2.42 (t, J = 7.0 Hz, 2H), 2.24 (q, J = 7.4 Hz, 2H), 1.72-1.66 (m, 2H). Additional signals associated with the minor isomer: δ 6.28-6.22 (m, 2H), 3.83 (s, 3H), 2.46 (t, J = 7.5 Hz, 2H), 2.34 (q, J = 7.1 Hz, 2H), 1.79-1.73 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.3, 145.7, 140.5, 133.0, 130.1, 116.2, 116.1, 114.0, 113.9, 88.0, 87.8, 83.3, 81.2, 81.1, 75.6, 55.4, 35.2, 34.1, 27.5, 27.4, 19.2, 18.8. HRMS (ESI) calcd for $C_{14}H_{16}OI$ $(M + H)^+$: 327.0246. Found: 327.0241.



(*E*)-4-(7-Iodohept-6-en-1-ynyl)-1,2-dimethoxybenzene + (*Z*)-4-(7-iodohept-6-en-1-ynyl)-1,2-dimethoxybenzene (4.46)

To a solution of 5.36 g of chromium(II) chloride (43.6 mmol) in 15 mL of THF at 0 °C was added dropwise a mixture of 1.01 g of aldehyde **4.16** (4.36 mmol) and 3.43 g of iodoform (8.72 mmol) in 20 mL of THF. The resulting dark red suspension was stirred at 0 °C for 0.5 h and then warmed to rt and stirred for 1 h. The reaction mixture was then quenched with water and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed twice with brine. The organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude yellow oil. The crude oil was purified by column chromatography on silica gel (1:0→5:1 hexanes:ethyl acetate) to afford 0.965 g (62 %; 68% BRSM) of a 4:1 mixture of the title compound **4.46** as a clear, colorless oil.

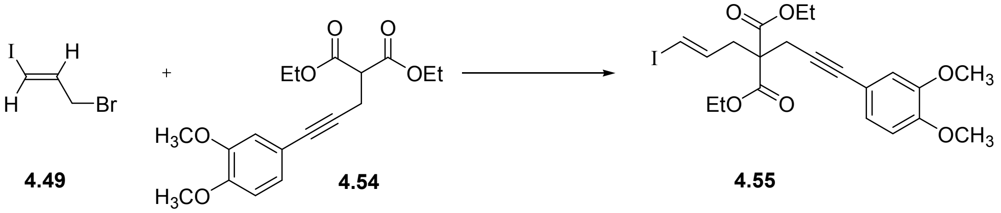
IR (neat): 2934, 1601, 808, 762, 656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 7.9 Hz, 1H), 6.89 (s, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.53 (dt, *J* = 14.3, 7.2 Hz, 1H), 6.06 (d, *J* = 14.3 Hz, 1H), 3.85 (s, 6H), 2.39 (t, *J* = 7.2 Hz, 2H), 2.22 (q, *J* = 7.4 Hz, 2H), 1.71-1.62 (m, 2H). Additional signals associated with the minor isomer: δ 7.00 (s, 1H), 6.91 (s, 1H), 6.26-6.19 (m, 2H), 3.85 (s, 3H), 2.45-2.41 (m, 2H), 2.31 (q, *J* = 6.9 Hz, 2H), 1.77-1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 149.1, 145.7, 140.5, 124.8, 124.7, 116.3, 116.2, 114.6, 114.5, 111.2, 88.0, 87.7, 83.4, 81.3, 81.2, 75.6, 56.0, 35.2, 34.1, 27.5, 27.3, 19.1, 18.9. HRMS (ESI) calcd for $C_{15}H_{17}O_2NaI$ $(M + Na)^+$: 379.0171. Found: 379.0166.



(*E*)-4-(3-(3-Iodoallyloxy)prop-1-ynyl)-1,2-dimethoxybenzene (4.51)

To a solution of 0.47 g of bromide **4.49** (1.9 mmol), 0.054 g of tetrabutylammonium hydrogen sulfate (0.16 mmol), and 3 mL of a 50 % (w/w) solution of sodium hydroxide in H_2O at 0 °C was added 0.3 mL of alcohol **4.50** (2 mmol). Dichloromethane was added to homogenize the mixture. The ice bath was removed and the reaction mixture was stirred vigorously for 1 h. The mixture was extracted three times with diethyl ether. The combined organic fractions were washed once with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a crude orange oil. The orange oil was purified by column chromatography on silica gel (7:1→5:1→1:1 hexanes:ethyl acetate) to afford 0.37 g (55 %, 58 % BRSM) of the title compound **4.51** as a clear, colorless oil.

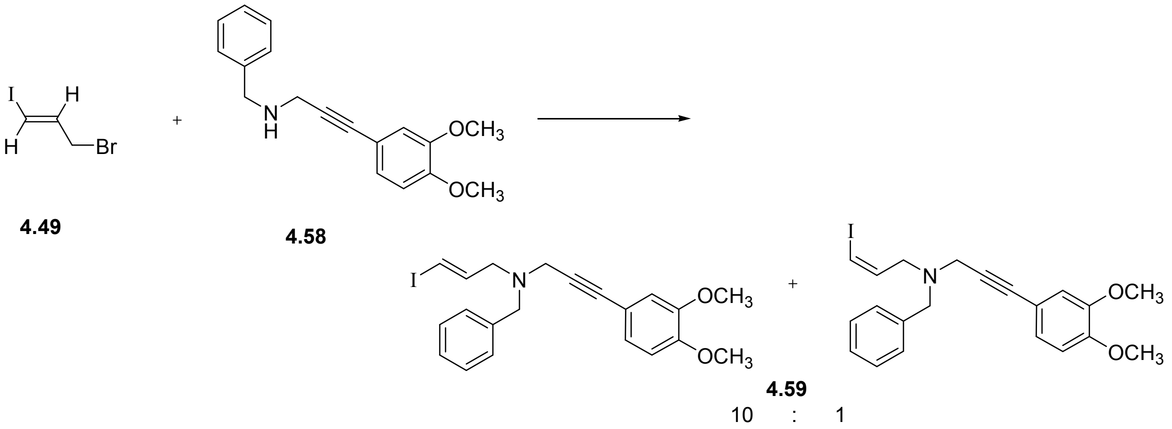
IR (neat): 2934, 2836, 2225, 1600, 1514, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.01 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.92 (s, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.63 (dt, *J* = 14.3, 5.8 Hz, 1H), 6.42 (d, *J* = 14.7 Hz, 1H), 4.32 (s, 2H), 4.02 (d, *J* = 5.8 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.8, 148.7, 142.0, 125.3, 114.7, 114.6, 111.1, 86.9, 83.3, 79.7, 71.4, 58.3, 56.1, 56.0. HRMS (ESI) calcd for $C_{14}H_{15}O_3NaI$ (M + Na)$^+$: 380.9964. Found: 380.9955.



(*E*)-Diethyl 2-(3-(3,4-dimethoxyphenyl)prop-2-ynyl)-2-(3-iodoallyl)malonate (4.55)

To a solution of 0.031 g of sodium hydride (1.3 mmol) in 3 mL of THF was added dropwise to a mixture of 0.42 g of malonate **4.54** (1.3 mmol) in 3 mL of THF. The mixture was stirred at rt for 0.3 h. A solution of 0.33 g of alkene **4.49** (1.3 mmol) in 2 mL of THF was added dropwise to the reaction mixture. The resulting brown suspension was stirred at rt for 24 h. The reaction mixture was quenched with water and diluted with diethyl ether. The layers were separated and the organic fraction was washed once with water. The combined aqueous fractions were extracted once with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a red orange oil. The crude oil was purified by column chromatography on silica gel (3:1→1:1 hexanes:ethyl acetate) to afford 0.52 g (82 %) of the title compound **4.55** as a clear, colorless oil.

IR (neat): 2980, 1732, 1514, 733 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.95 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.85 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.45 (dt, *J* = 14.3, 7.2 Hz, 1H), 6.24 (d, *J* = 14.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 2.99 (s, 2H), 2.83 (d, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.5, 149.5, 148.7, 140.2, 125.0, 115.4, 114.5, 111.1, 84.0, 82.4, 79.5, 62.0, 56.7, 56.03, 56.02, 39.1, 24.1, 14.3. HRMS (ESI) calcd for $C_{21}H_{25}O_6NaI$ (M + Na)$^+$: 523.0594. Found: 523.0583.

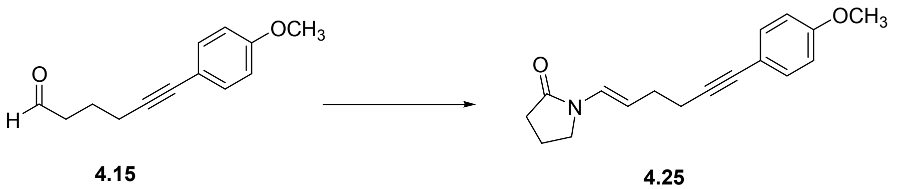


(*E*)-*N*-Benzyl-*N*-(3-(3,4-dimethoxyphenyl)prop-2-ynyl)-3-iodoprop-2-en-1-amine + (*Z*)-*N*-benzyl-*N*-(3-(3,4-dimethoxyphenyl)prop-2-ynyl)-3-iodoprop-2-en-1-amine (4.59)

A suspension of 0.63 g of potassium carbonate (4.5 mmol), 0.22 g of alkene **4.49** (0.91 mmol), and 0.26 g of amine **4.58** (0.91 mmol) in 5 mL of acetonitrile was heated at 75 °C for 16 h. The reaction mixture was cooled to rt and subsequently filtered through Celite®, rising exhaustively with diethyl ether and ethyl acetate. The filtrate was concentrated by rotary evaporation *in vacuo* to give a crude brown oil. The crude oil was dry loaded onto silica gel and purified by column chromatography (10:1→5:1→3:1 hexanes:ethyl acetate) to afford 0.24 g (58 %) of a 10:1 mixture of the title compound **4.59** as a clear, yellow oil.

IR (neat): 2915, 1513, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 4H), 7.30-7.26 (m, 1H), 7.08 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.97 (d, *J* = 2.1 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.70-6.63 (m, 1H), 6.37 (d, *J* = 14.7 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.72 (s, 2H), 3.53 (s, 2H), 3.23 (dd, *J* = 6.8, 1.4 Hz, 2H). Additional signals associated with the minor isomer: δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.05 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.94 (d, *J* = 1.7 Hz, 1H), 6.63-6.57 (m, 2H), 3.90 (s, 6H), 3.77 (s, 2H), 3.57 (s, 2H), 3.49 (s, 1H), 3.17 (dd, *J* = 6.8, 1.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 148.8, 143.5, 138.5, 129.2, 128.5, 127.4, 125.2, 115.5, 114.6, 111.2, 86.0, 82.6, 78.8, 57.9, 57.7, 56.1, 56.0, 42.5. Additional signals associated with the minor isomer **x**: δ 149.6, 143.0, 139.2, 128.4, 127.4, 115.3, 82.2, 79.2, 77.4, 57.8, 42.7. HRMS (ESI) calcd for $C_{21}H_{23}NO_2I$ (M + H)$^+$: 448.0774. Found: 448.768.

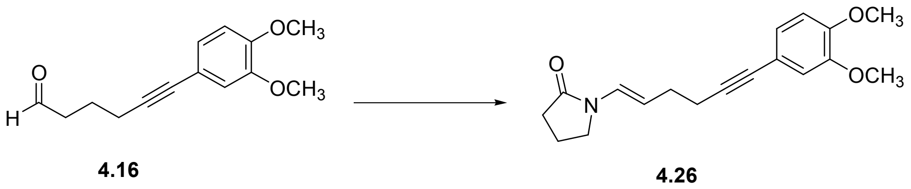
Representative Procedure for the Formation of Enamides



(*E*)-1-(6-(4-Methoxyphenyl)hex-1-en-5-ynyl)pyrrolidin-2-one (4.25)

A solution of 0.3 g of aldehyde **4.15** (1.5 mmol), 0.1 mL of 2-pyrrolidinone (1 mmol), and 1 mL of acetic acid in 5 mL of toluene was heated to reflux using a Dean-Stark apparatus. The reaction mixture was stirred at reflux for 4 h before cooling to rt. The solution was diluted with diethyl ether and carefully washed twice with a saturated solution of sodium bicarbonate. The aqueous fractions were then extracted twice with diethyl ether. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated by rotary evaporation *in vacuo* to afford a brown oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate) to afford 0.3 g (67 %; 75 % BRSM) of the title compound **4.25** as a pale yellow solid, mp: 85-86 °C.

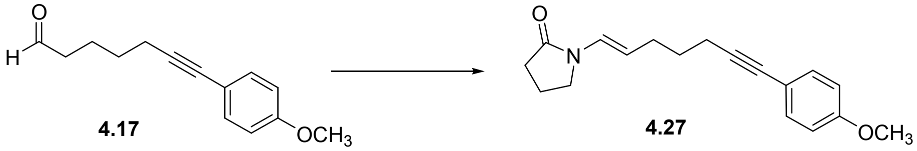
IR (neat): 2937, 1696, 1662, 843, 732 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.31 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 14.3 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 5.03 (dt, *J* = 14.3, 7.0 Hz, 1H), 3.78 (s, 3H), 3.50 (t, *J* = 7.2 Hz, 2H), 2.48-2.44 (m, 4H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.07 (qt, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.1, 159.3, 133.1, 124.9, 116.1, 114.0, 110.4, 87.8, 81.2, 55.4, 45.4, 31.4, 29.8, 20.8, 17.6. HRMS (ESI) calcd for $C_{17}H_{19}NO_2Na$ (M + Na)$^+$: 292.1313. Found: 292.1311. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.63; H, 7.06; N, 5.27.



(*E*)-1-(6-(3,4-Dimethoxyphenyl)hex-1-en-5-ynyl)pyrrolidin-2-one (4.26)

Aldehyde **4.16** (0.4 g, 2 mmol), 2-pyrrolidinone (0.7 mL, 9 mmol), and acetic acid (2 mL) in 7 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 2 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.4 g (74 %) of the title compound **4.26** was isolated as a pale orange solid, mp: 66-68 °C.

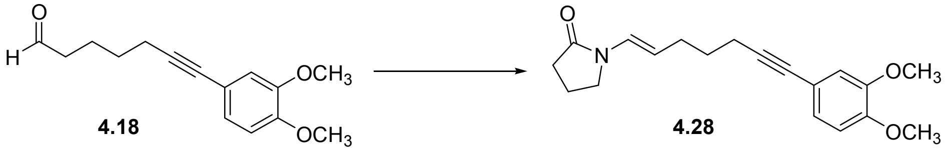
IR (neat): 2934, 1699, 1663, 731 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.05-7.03 (m, 1H), 7.01-7.00 (m, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.04 (dt, *J* = 14.2, 7.0 Hz, 1H), 3.87 (s, 6H), 3.53 (t, *J* = 7.3 Hz, 2H), 2.52-2.48 (m, 4H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.10 (qt, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.0, 149.1, 148.7, 125.0, 124.8, 116.2, 114.6, 111.1, 110.3, 87.8, 81.3, 56.0, 45.3, 31.4, 29.8, 20.7, 17.6. HRMS (ESI) calcd for $C_{18}H_{21}NO_3Na$ (M + Na)$^+$: 322.1419. Found: 322.1413.



(*E*)-1-(7-(4-Methoxyphenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.27)

Aldehyde **4.17** (0.3 g, 2 mmol), 2-pyrrolidinone (0.3 mL, 3.5 mmol), acetic acid (1 mL), and 5 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 6 h. After purification by column chromatography on triethylamine washed silica gel (1:1 hexanes:ethyl acetate), 0.3 g (81 %) of the title compound **4.27** was isolated as a thick yellow oil.

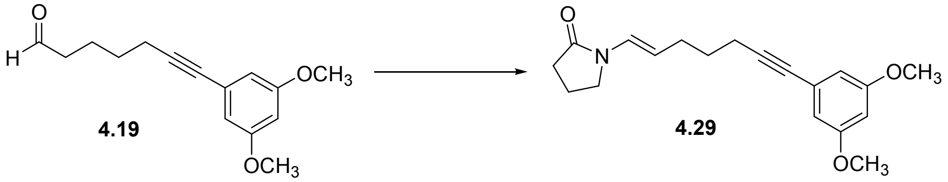
IR (neat): 2935, 1694, 834 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 14.3 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 4.91 (dt, *J* = 14.5, 7.1 Hz, 1H), 3.76 (s, 3H), 3.45 (t, *J* = 7.2 Hz, 2H), 2.45-2.41 (m, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.21 (q, *J* = 6.9 Hz, 2H), 2.04 (dt, *J* = 15.3, 7.6 Hz, 2H), 1.66 (qt, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 159.2, 133.0, 124.4, 116.2, 113.9, 111.3, 88.3, 80.9, 55.4, 45.4, 31.4, 29.4, 29.3, 18.9, 17.6. HRMS (ESI) calcd for $C_{18}H_{21}NO_2Na$ (M + Na)$^+$: 306.1470. Found: 306.1478.



(*E*)-1-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.28)

Aldehyde **4.18** (0.2 g, 0.9 mmol), 2-pyrrolidinone (0.2 mL, 3 mmol), acetic acid (0.9 mL), and 5 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was heated at reflux for 6 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.19 g (65 %; 73 % BRSM) of the title compound **4.28** was isolated as a pale yellow oil.

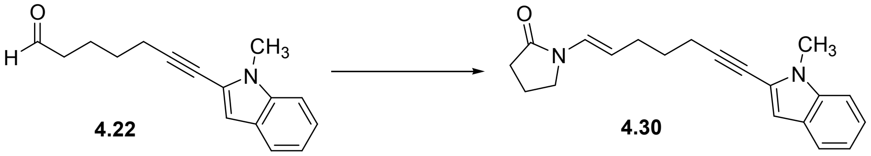
IR (neat): 2935, 1699, 763 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.97 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.91 (d, *J* = 14.3 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 4.92 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.46 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.22 (q, *J* = 7.2 Hz, 2H), 2.05 (dt, *J* = 15.4, 7.9 Hz, 2H), 1.67 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 149.0, 148.7, 124.7, 124.5, 116.3, 114.5, 111.2, 111.1, 88.2, 81.0, 56.0, 45.4, 31.4, 29.4, 29.3, 18.9, 17.6. HRMS (ESI) calcd for $C_{19}H_{23}NO_3Na$ $(M + Na)^+$: 336.1576. Found: 336.1574.



(*E*)-1-(7-(3,5-Dimethoxyphenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.29)

Aldehyde **4.19** (0.3 g, 2 mmol), 2-pyrrolidinone (0.4 mL, 5 mmol), acetic acid (1 mL) and 5 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 3.25 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.3 g (91 %) of the title compound **4.29** was isolated as a pale yellow oil.

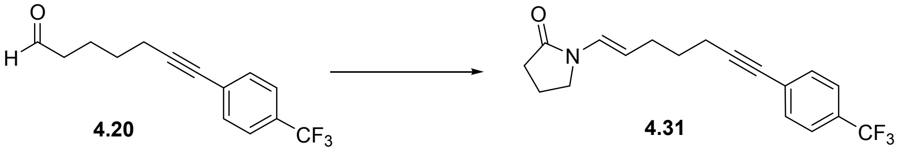
IR (neat): 2938, 2245, 1694, 1597, 835, 732 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.92 (d, *J* = 14.7 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 2H), 6.38 (t, *J* = 2.4 Hz, 1H), 4.93 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.75 (s, 6H), 3.47 (t, *J* = 7.2 Hz, 2H), 2.47-2.43 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.23 (q, *J* = 6.8 Hz, 2H), 2.06 (qt, *J* = 7.6 Hz, 2H), 1.68 (qt, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 160.6, 125.4, 124.5, 111.2, 109.5, 101.3, 89.6, 81.1, 55.5, 45.4, 31.4, 29.4, 29.2, 18.9, 17.6. HRMS (ESI) calcd for $C_{19}H_{23}NO_3Na$ $(M + Na)^+$: 336.1576. Found: 336.1584.



(*E*)-1-(7-(1-Methyl-1*H*-indol-2-yl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.30)

Aldehyde **4.22** (0.3 g, 2 mmol), 2-pyrrolidinone (0.4 mL, 5 mmol), acetic acid (1 mL), and 5 mL of toluene were combined according the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 2.5 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.4 g (96 %) of the title compound **4.30** was isolated as a clear yellow oil.

IR (neat): 3245, 2937, 1693, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.9 Hz, 1H), 7.29-7.21 (m, 2H), 7.10 (ddd, *J* = 7.9, 6.1, 2.1 Hz, 1H), 6.96 (d, *J* = 14.3 Hz, 1H), 6.68 (s, 1H), 4.95 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.79 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.47 (t, *J* = 8.2 Hz, 2H), 2.29 (q, *J* = 7.2 Hz, 2H), 2.05 (qt, *J* = 7.7 Hz, 2H), 1.77 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 137.0, 127.4, 124.7, 122.9, 122.6, 120.8, 120.0, 111.0, 109.4, 106.3, 96.2, 72.9, 45.4, 31.4, 30.7, 29.5, 29.1, 19.2, 17.6. HRMS (ESI) calcd for $C_{20}H_{22}N_2ONa$ $(M + Na)^+$: 329.1630. Found: 329.1639.

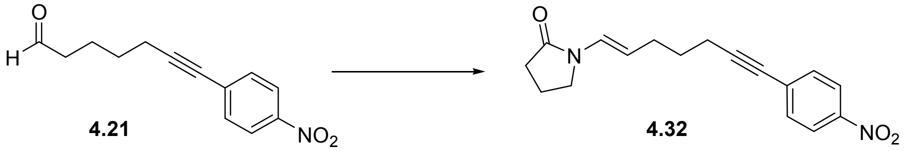


(*E*)-1-(7-(4-(Trifluoromethyl)phenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.31)

Aldehyde **4.20** (0.3 g, 2 mmol), 2-pyrrolidinone (0.4 mL, 5 mmol), acetic acid (2 mL) and 5 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 2 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.4 g (92 %) of the title compound **4.31** was isolated as a yellow oil.

IR (neat): 2935, 2229, 1698, 1615, 844 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 14.7 Hz, 1H), 4.92 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.47 (t, *J* = 7.2 Hz, 2H), 2.47-2.40 (m, 4H), 2.23 (q, *J* = 7.1 Hz, 2H), 2.06 (qt, *J* = 7.7 Hz, 2H), 1.69 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 131.0, 129.4 (q, *J* = 32 Hz), 128.0, 125.2

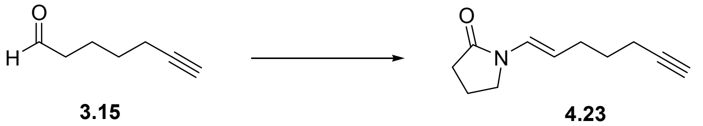
(q, J = 4 Hz), 124.6, 124.1 (q, J = 271 Hz), 110.9, 92.8, 80.1, 45.3, 31.4, 29.4, 29.0, 18.9, 17.5. HRMS (ESI) calcd for $C_{18}H_{18}NOF_3Na$ (M + Na)$^+$: 344.1238. Found: 344.1236.



(*E*)-1-(7-(4-Nitrophenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.32)

Aldehyde **4.21** (0.3 g, 1 mmol), 2-pyrrolidinone (0.4 mL, 5 mmol), acetic acid (1 mL), and 5 mL toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 2.5 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.4 g (100 %) of the title compound **4.32** was isolated as a yellow oil.

IR (neat): 3273, 2937, 2225, 1714, 1515, 1338, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 14.3 Hz, 1H), 4.91 (dt, J = 14.3, 7.2 Hz, 1H), 3.48 (t, J = 7.2 Hz, 2H), 2.47-2.42 (m, 4H), 2.22 (q, J = 7.1 Hz, 2H), 2.07 (qt, J = 7.6 Hz, 2H), 1.69 (qt, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 146.7, 132.4, 131.2, 124.7, 123.6, 110.7, 96.3, 79.8, 45.4, 31.4, 29.3, 28.8, 19.0, 17.6. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3$ (M + H)$^+$: 299.1396. Found: 299.1398.

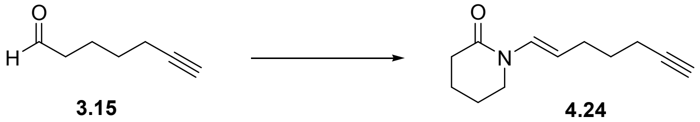


(*E*)-1-(Hept-1-en-6-ynyl)pyrrolidin-2-one (4.23)

Hept-6-ynal (**3.15**) (0.31 g, 2.8 mmol), 2-pyrrolidinone (1.1 mL, 14 mmol), acetic acid (2.8 mL), and 5 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 1 h. After purification by column chromatography on triethylamine washed silica gel (3:1 hexanes:ethyl acetate), 0.50 g (100 %) of the title compound **4.23** was isolated as a clear, colorless oil.

IR (neat): 3293, 3245, 2938, 2115, 1697, 642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (d, J = 14.3 Hz, 1H), 4.86 (dt, J = 14.3, 7.2 Hz, 1H), 3.44 (t, J = 2.7 Hz, 2H), 2.42 (t, J = 8.0 Hz, 2H), 2.16-2.11 (m, 4H), 2.04 (qt, J = 7.7 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.56 (qt, J = 7.3 Hz, 2H).

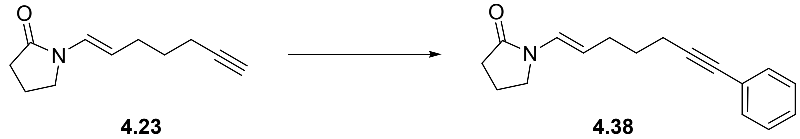
^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 124.5, 111.0, 84.2, 68.7, 45.3, 31.3, 29.1, 28.9, 17.8, 17.5. HRMS (ESI) calcd for $C_{11}H_{15}NONa$ (M + Na)$^+$: 200.1051. Found: 200.1047.



(*E*)-1-(Hept-1-en-6-ynyl)piperidin-2-one (4.24)

Hept-6-ynal (**3.15**) (1.11 g, 10.1 mmol), δ-valerolactam (4.01 g, 40.4 mmol), acetic acid (10 mL), and 15 mL of toluene were combined according to the general procedure for the formation of enamides, except that the reaction mixture was stirred at reflux for 1.5 h. After purification by column chromatography on triethylamine washed silica gel (3:1 hexanes:ethyl acetate), 1.51 g (78 %) of the title compound **4.24** was isolated as a pale yellow oil.

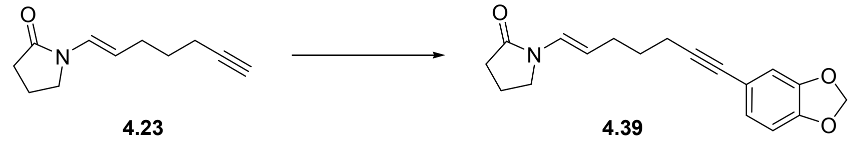
IR (neat): 3293, 3243, 2941, 2115, 1647 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.31 (d, J = 14.7 Hz, 1H), 4.89 (dt, J = 14.6, 7.2 Hz, 1H), 3.28 (t, J = 6.1 Hz, 2H), 2.36 (t, J = 6.7 Hz, 2H), 2.13-2.07 (m, 4H), 1.87 (t, J = 2.6 Hz, 1H), 1.82-1.76 (m, 2H), 1.73-1.67 (m, 2H), 1.52 (qt, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.2, 127.6, 109.9, 84.2, 68.7, 45.2, 32.9, 29.4, 29.1, 22.7, 20.7, 17.8. HRMS (ESI) calcd for $C_{12}H_{17}NONa$ (M + Na)$^+$: 214.1208. Found: 214.1202.



(*E*)-1-(7-Phenylhept-1-en-6-ynyl)pyrrolidin-2-one (4.38)

Compound **4.23** (0.1 g, 0.6 mmol), bis(triphenylphosphine)palladium(II) chloride (0.02 g, 0.03 mmol), copper(I) iodide 0.01 g, 0.06 mmol), and iodobenzene (0.1 mL, 0.8 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred at rt for 0.5 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.1 g (85 %) of the title compound **4.38** was isolated as an orange oil.

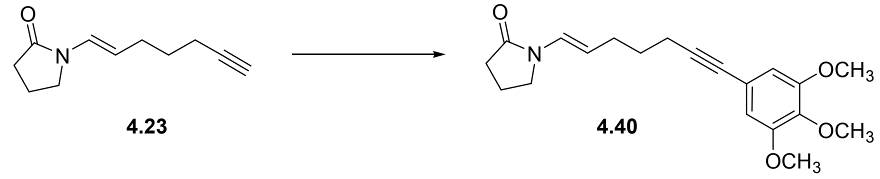
IR (neat): 2933, 1701, 1663, 758, 693 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37 (dd, J = 6.8, 2.4 Hz, 2H), 7.25-7.22 (m, 3H), 6.91 (d, J = 14.3 Hz, 1H), 4.92 (dt, J = 14.3, 7.2 Hz, 1H), 3.44 (t, J = 7.2 Hz, 2H), 2.47-2.38 (m, 4H), 2.23 (q, J = 6.8 Hz, 2H), 2.03 (qt, J = 7.7 Hz, 2H), 1.68 (qt, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 131.7, 128.3, 127.7, 124.5, 124.1, 111.2, 90.0, 81.2, 45.4, 31.4, 29.4, 29.2, 18.9, 17.6. HRMS (ESI) calcd for $C_{17}H_{19}NONa$ (M + Na)$^+$: 276.1364. Found: 276.1369.



(*E*)-1-(7-(Benzo-1,3-dioxol-5-yl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.39)

Compound **4.23** (0.13 g, 0.73 mmol), bis(triphenylphosphine)palladium(II) chloride (0.025 g, 0.036 mmol), copper(I) iodide 0.014 g, 0.073 mmol), and 5-iodobenzo-1,3-dioxole (**4.35**) (0.22 g, 0.87 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.20 g (91 %) of the title compound **4.39** was isolated as a pale yellow oil.

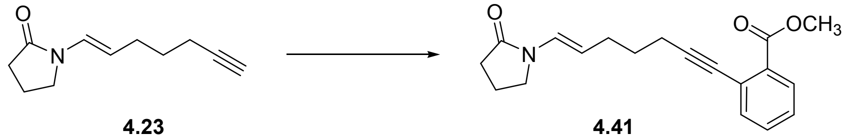
IR (neat): 2931, 1694, 1662, 812 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92-6.87 (m, 2H), 6.82 (d, *J* = 1.4 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 5.91 (s, 2H), 4.91 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.46 (d, *J* = 7.2 Hz, 2H), 2.44 (d, *J* = 8.0 Hz, 2H), 2.36 (d, *J* = 7.2 Hz, 2H), 2.21 (q, *J* = 7.2 Hz, 2H), 2.05 (qt, *J* = 7.7 Hz, 2H), 1.65 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 147.42, 147.39, 126.0, 124.5, 117.3, 111.7, 111.2, 108.4, 101.3, 88.1, 80.9, 45.4, 31.4, 29.4, 29.3, 18.8, 17.6. HRMS (ESI) calcd for $C_{18}H_{19}NO_3Na$ (M + Na)$^+$: 320.1263. Found: 320.1259.



(*E*)-1-(7-(3,4,5-Trimethoxyphenyl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.40)

Compound **4.23** (0.21 g, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (0.041 g, 0.059 mmol), copper(I) iodide 0.022 g, 0.11 mmol), and 5-bromo-1,2,3-trimethoxybenene (0.35 g, 1.4 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After stirring at rt for 1 h, the reaction mixture was heated to 60 ^{o}C and stirred for 22 h before cooling to rt. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.27 g (68 %) of the title compound **4.40** was isolated as a pale yellow oil.

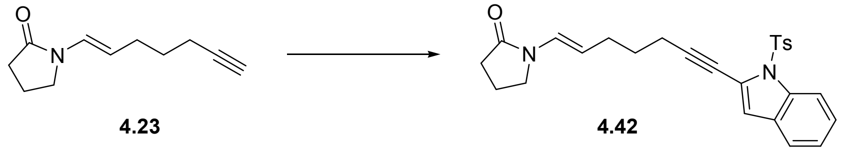
IR (neat) 2938, 2247, 1697, 1663, 731 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.91 (d, *J* = 14.7 Hz, 1H), 6.61 (s, 2H), 4.91 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.81 (s, 9H), 3.46 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 8.2 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.21 (q, *J* = 6.9 Hz, 2H), 2.05 (qt, *J* = 7.6 Hz, 2H), 1.66 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 153.1, 138.4, 124.5, 119.1, 111.1, 108.8, 89.0, 81.1, 61.0, 56.2, 45.4, 31.4, 29.4, 29.1, 18.8, 17.5. HRMS (ESI) calcd for $C_{20}H_{25}NO_4Na$ (M + Na)$^+$: 366.1681. Found: 366.1678.



(*E*)-Methyl 2-(7-(2-oxopyrrolidin-1-yl)hept-6-en-1-ynyl)benzoate (4.41)

Compound **4.23** (0.4 g, 3 mmol), bis(triphenylphosphine)palladium(II) chloride (0.1 g, 0.2 mmol), copper(I) iodide 0.05 g, 0.2 mmol), and methyl 2-iodobenzoate (0.6 mL, 4 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 3 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.4 g (55 %) of the title compound **4.41** was isolated as a yellow oil.

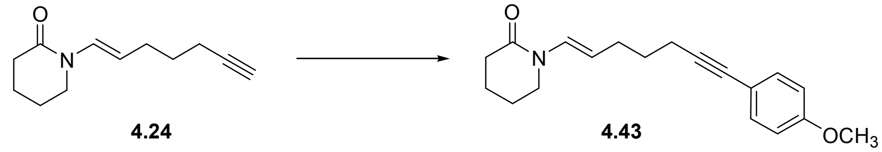
IR (neat): 2946, 1731, 1661, 761, 702 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.49-7.47 (m, 1H), 7.39 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28 (td, *J* = 7.5, 1.4 Hz, 1H), 6.92 (d, *J* = 14.3 Hz, 1H), 4.93 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.88 (s, 3H), 3.45 (t, *J* = 7.3 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.45-2.41 (m, 2H), 2.25 (q, *J* = 7.2 Hz, 2H), 2.04 (dt, *J* = 15.4, 7.7 Hz, 2H), 1.70 (qt, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.9, 167.0, 134.3, 132.0, 131.6, 130.2, 127.3, 124.5, 111.2, 95.5, 79.8, 52.2, 45.4, 31.4, 29.4, 29.2, 19.3, 17.6. HRMS (ESI) calcd for $C_{19}H_{22}NO_3$ (M + H)$^+$: 312.1600. Found: 312.1602.



(*E*)-1-(7-(1-Tosyl-1*H*-indol-2-yl)hept-1-en-6-ynyl)pyrrolidin-2-one (4.42)

Compound **4.23** (0.21 g, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (0.041 g, 0.059 mmol), copper(I) iodide 0.022 g, 0.12 mmol), and 2-iodo-1-tosyl-1*H*-indole (**4.37**) (0.56 g, 1.4 mmol) were combined according to the general procedure for Sonogashira coupling reactions, except that the reaction mixture was stirred for 3.5 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.34 g (65 %) of the title compound **4.42** was isolated as a pale yellow oil.

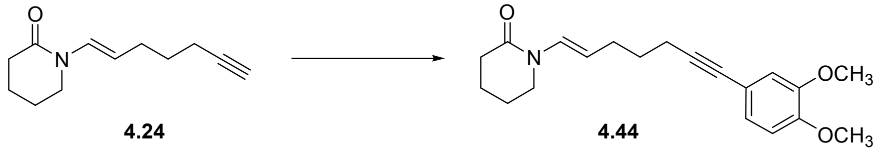
IR (neat): 2931, 2239, 1693, 1176, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24-7.20 (m, 3H), 6.95 (d, *J* = 14.7 Hz, 1H), 6.78 (s, 1H), 4.98 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.49 (d, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.47 (t, *J* = 8.0 Hz, 2H), 2.34 (s, 3H), 2.30 (q, *J* = 6.8 Hz, 2H), 2.07 (qt, *J* = 7.5 Hz, 2H), 1.79 (qt, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 145.1, 136.4, 136.0, 129.8, 129.2, 127.1, 125.6, 124.6, 123.9, 121.6, 120.9, 116.4, 114.8, 111.1, 98.3, 72.2, 45.4, 31.4, 29.5, 28.8, 21.7, 19.4, 17.6. HRMS (ESI) calcd for $C_{26}H_{26}N_2O_3NaS$ (M + Na)$^+$: 469.1562. Found: 469.1571.



(*E*)-1-(7-(4-Methoxyphenyl)hept-1-en-6-ynyl)piperidin-2-one (4.43)

Compound **4.24** (0.24 g, 1.3 mmol), bis(triphenylphosphine)palladium(II) chloride (0.045 g, 0.064 mmol), copper(I) iodide (0.024 g, 0.13 mmol), and 4-iodoanisole (0.36 g, 1.5 mmol) were combined according to the general procedure for Sonogashira coupling reactions After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.32 g (85 %) of the title compound **4.43** was isolated as a clear, yellow oil.

IR (neat): 2937, 1651, 833 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 14.7 Hz, 1H), 7.31 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 2H), 5.01 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.77 (s, 3H), 3.36 (t, *J* = 6.1 Hz, 2H), 2.45 (t, *J* = 6.5 Hz, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.24 (q, *J* = 7.2 Hz, 2H), 1.88-1.82 (m, 2H), 1.79-1.73 (m, 2H), 1.67 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 159.2, 133.0, 127.6, 116.3, 113.9, 110.4, 88.4, 80.8, 55.4, 45.3, 33.0, 29.7, 29.5, 22.8, 20.7, 18.9. HRMS (ESI) calcd for $C_{19}H_{24}NO_2$ (M + H)$^+$: 298.1807. Found: 298.1814.

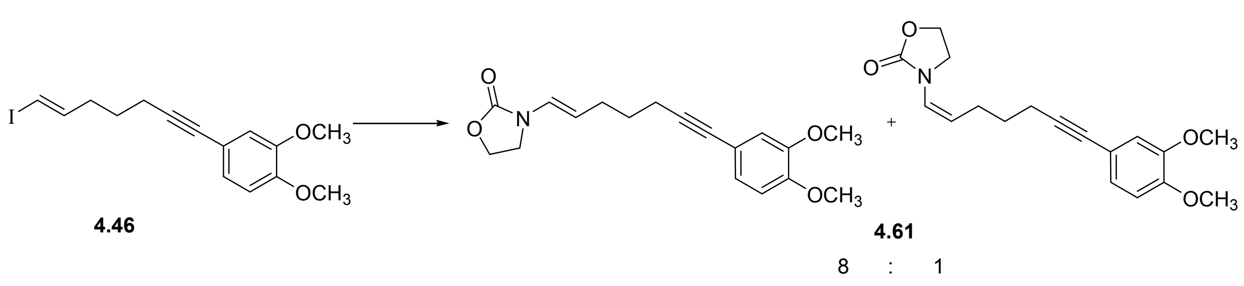


(*E*)-1-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)piperidin-2-one (4.44)

Compound **4.24** (0.29 g, 1.5 mmol), bis(triphenylphosphine)palladium(II) chloride (0.053 g, 0.076 mmol), copper(I) iodide (0.029 g, 0.15 mmol), and 4-iodoveratrole (**3.22**) (0.48 g, 1.8 mmol) were combined according to the general procedure for Sonogashira coupling reactions. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.45 g (90 %) of the title compound **4.44** was isolated as a clear, yellow oil.

IR (neat): 2936, 1651, 810, 762 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (d, *J* = 14.3 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.00 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.84 (s, 6H), 3.35 (t, *J* = 6.1 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.23 (q, *J* = 6.9 Hz, 2H), 1.87-1.81 (m, 2H), 1.79-1.73 (m, 2H), 1.67 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 149.0, 148.7, 127.6, 124.7, 116.4, 114.5, 111.1, 110.3, 88.3, 81.0, 56.0, 45.3, 33.0, 29.7, 29.5, 22.8, 20.7, 18.9. HRMS (ESI) calcd for $C_{20}H_{25}NO_3Na$ (M + Na)$^+$: 350.1732. Found: 350.1735.

Representative Procedure for the Copper-Catalyzed Formation of Enamides and Enesulfonamides

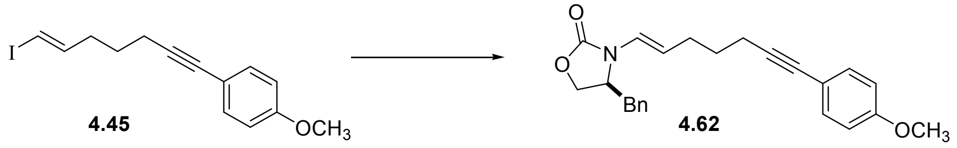


(*E*)-3-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)oxazolidin-2-one + (*Z*)-3-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)oxazolidin-2-one (4.61)

A solution of 0.25 g of iodide **4.46** (0.63 mmol), 0.066 g of 2-oxazolidinone (0.76 mmol), 0.018 g of copper(I) iodide (0.095 mmol), 0.026 g of *N*,*N*-dimethylglycine hydrochloride (0.19 mmol), and 0.41 g of cesium carbonate (1.3 mmol) in 1.5 mL of dioxane was prepared in a large test tube reaction flask in the absence of light. The reaction mixture was heated to 80 °C for 72 h.

The resulting blue suspension was cooled to rt and filtered through a pipette of triethylamine washed silica gel. The solution was concentrated by rotary evaporation *in vacuo* to afford a yellow oil. The crude oil was purified by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate) to afford 0.18 g (88 %) of an 8:1 mixture of the title compound **4.61** as a clear, colorless oil.

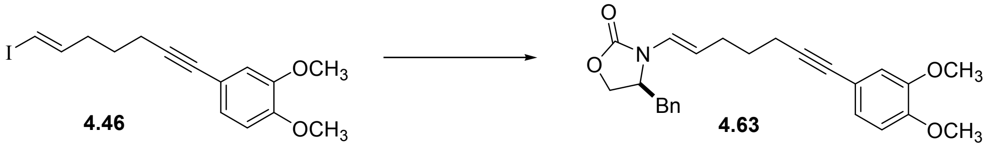
IR (neat): 3503, 2935, 2253, 1755, 1671, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.89 (d, *J* = 1.4 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 14.3 Hz, 1H), 4.80 (dt, *J* = 14.3, 7.2 Hz, 1H), 4.40-4.36 (m, 2H), 3.84 (s, 6H), 3.66-3.62 (m, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.22 (q, *J* = 7.2 Hz, 2H), 1.67 (qt, *J* = 7.1 Hz, 2H). Additional signals associated with the minor isomer **x**: δ 6.93 (d, *J* = 1.4 Hz, 1H), 6.87 (s, 1H), 6.27 (d, *J* = 9.6 Hz, 1H), 4.28-4.24 (m, 2H), 3.99-3.95 (m, 2H), 2.43-2.41 (m, 2H), 2.37-2.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 149.1, 148.7, 124.72, 124.69, 116.3, 114.5, 111.2, 110.1, 88.1, 81.1, 62.3, 56.0, 42.7, 29.2, 29.1, 18.8. Additional signals associated with the minor isomer **x**: δ 149.3, 148.8, 124.6, 123.4, 116.1, 114.5, 88.1, 81.2, 45.8, 25.6. HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ (M + Na)$^+$: 338.1368. Found: 338.1365.



(*S*,*E*)-4-Benzyl-3-(7-(4-methoxyphenyl)hept-1-en-6-ynyl)oxazolidin-2-one (4.62)

Iodide **4.45** (0.16 g, 0.51 mmol), (*S*)-(−)-4-benzyl-2-oxazolidinone (0.11 g, 0.61 mmol), copper(I) iodide (9.6 mg, 0.051 mmol), *N*,*N*-dimethylglycine hydrochloride (0.014 g, 0.10 mmol), cesium carbonate (0.33 g, 1.0 mmol), and 1.0 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 94 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.13 g (70 %) of the title compound **4.62** was isolated as a clear, yellow oil.

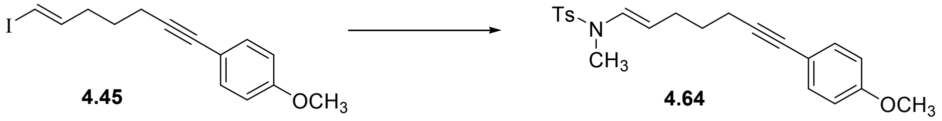
IR (neat): 2933, 1770, 1668, 835, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.9 Hz, 2H), 7.34-7.27 (m, 3H), 7.17 (d, *J* = 6.8 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 14.7 Hz, 1H), 5.11 (dt, *J* = 14.6, 7.2 Hz, 1H), 4.29-4.15 (m, 3H), 3.80 (s, 3H), 3.22 (dd, *J* = 14.0, 2.7 Hz, 1H), 2.78 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.45(t, *J* = 7.0 Hz, 2H), 2.34-2.28 (m, 2H), 1.74 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 155.3, 135.5, 133.0, 129.4, 129.1, 127.5, 123.6, 116.2, 114.0, 111.1, 88.1, 81.1, 66.6, 55.4, 55.1, 36.4, 29.5, 29.3, 19.0. HRMS (ESI) calcd for $C_{24}H_{25}NO_3Na$ $(M + Na)^+$: 398.1732. Found: 398.1739. $[\alpha]^{24}_D$ = +22 °C (c = 0.74, $CHCl_3$).



(*S*,*E*)-4-Benzyl-3-(7-(3,4-dimethoxyphenyl)hept-1-en-6-ynyl)oxazolidin-2-one (4.63)

Iodide **4.46** (0.22 g, 0.63 mmol), (*S*)-(−)-4-benzyl-2-oxazolidinone (0.13 g, 0.75 mmol), copper(I) iodide (0.024 g, 0.13 mmol), *N*,*N*-dimethylglycine hydrochloride (0.026 g, 0.19 mmol), cesium carbonate (0.41 g, 1.3 mmol), and 1.5 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides. After purification by column chromatography on triethylamine washed silica gel (1:0→3:1→1:1 hexanes:ethyl acetate), 0.19 g (76 %) of the title compound **4.63** was isolated as a clear, yellow oil.

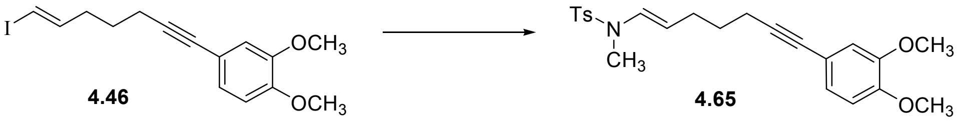
IR (neat): 2935, 1747, 1669, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.16 (d, *J* = 6.8 Hz, 2H), 7.00 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.92 (d, *J* = 1.7 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 14.7 Hz, 1H), 5.1 (dt, *J* = 14.6, 7.2 Hz, 1H), 4.27-4.13 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.20 (dd, *J* = 14.0, 2.7 Hz, 1H), 2.77 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.30 (q, *J* = 7.2 Hz, 2H), 1.74 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 149.1, 148.7, 135.5, 129.4, 129.1, 127.5, 124.8, 123.6, 116.3, 114.5, 111.2, 111.0, 88.1, 81.2, 66.6, 56.0, 55.1, 36.4, 29.5, 29.2, 18.9. HRMS (ESI) calcd for $C_{27}H_{27}NO_4Na$ $(M + Na)^+$: 428.1838. Found: 428.1834. $[\alpha]^{21}_D$ = +12.9 °C (c = 3.44, $CHCl_3$).



(*E*)-*N*-(7-(4-Methoxyphenyl)hept-1-en-6-ynyl)-*N*,4-dimethylbenzenesulfonamide (4.64)

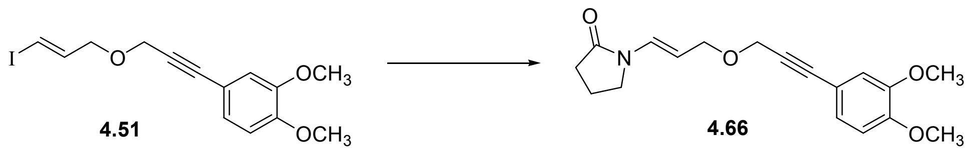
Iodide **4.45** (0.12 g, 0.34 mmol), *N*-methyl-*p*-toluenesulfonamide (0.082 g, 0.44 mmol), copper(I) iodide (7.0 mg, 0.034 mmol), *N*,*N*-dimethylglycine hydrochloride (0.010 g, 0.074 mmol), cesium carbonate (0.24 g, 0.74 mmol), and 1.0 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 76 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1 hexanes:ethyl acetate), 0.082 g (58 %) of the title compound **4.64** was isolated as a clear, colorless oil.

IR (neat): 2933, 1655, 1606, 1509, 959, 833, 662 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 14.0 Hz, 1H), 4.69 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.81 (s, 3H), 2.83 (s, 3H), 2.42 (s, 3H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.21 (q, *J* = 7.1 Hz, 2H), 1.67-1.60 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 143.8, 134.6, 133.0, 129.8, 128.7, 127.2, 116.2, 114.0, 110.7, 88.1, 81.0, 55.4, 32.4, 29.2, 29.1, 21.7, 18.6. HRMS (ESI) calcd for $C_{22}H_{25}NO_3NaS$ (M + Na)$^+$: 406.1453. Found: 406.1447.



(*E*)-*N*-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)-*N*,4-dimethylbenzenesulfonamide (4.65) Iodide **4.46** (0.23 g, 0.66 mmol), *N*-methyl-*p*-toluenesulfonamide (0.15 g, 0.79 mmol), copper(I) iodide (0.025 g, 0.13 mmol), *N*,*N*-dimethylglycine hydrochloride (0.028 g, 0.20 mmol), cesium carbonate (0.43 g, 1.3 mmol), and 1.5 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 48 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.26 g (96 %) of the title compound **4.64** was isolated as a clear, yellow oil.

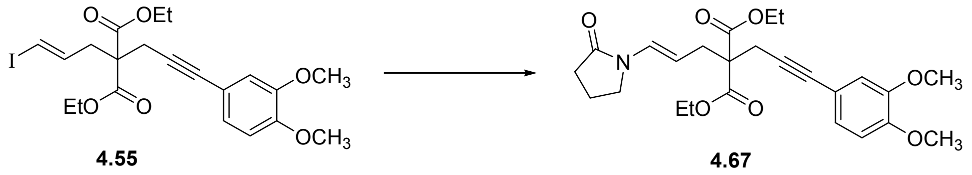
IR (neat): 2934, 1599, 1165, 813, 763, 662 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.64 d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.93 (s, 1H), 6.81-6.76 (m, 2H), 4.68 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.85 (s, 6H), 2.81 (s, 3H), 2.39 (s, 3H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.20 (q, *J* = 6.9 Hz, 2H), 1.62 (qt, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.1, 148.7, 143.8, 134.6, 129.8, 128.7, 127.2, 124.7, 116.3, 114.5, 111.2, 110.5, 88.0, 81.2, 56.02, 56.01, 32.4, 29.2, 29.0, 21.6, 18.6. HRMS (ESI) calcd for $C_{23}H_{27}NO_4NaS$ (M + Na)$^+$: 436.1559. Found: 436.1547.



(*E*)-1-(3-(3-(3,4-Dimethoxyphenyl)prop-2-ynyloxy)prop-1-enyl)pyrrolidin-2-one (4.66)

Iodide **4.51** (0.2 g, 0.6 mmol), 2-pyrrolidinone (0.1 mL, 1 mmol), copper(I) iodide (0.02 g, 0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.03 g, 0.2 mmol), cesium carbonate (0.4 g, 1 mmol), and 1.5 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 45 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→0:1 hexanes:ethyl acetate), 0.2 g (82 %) of the title compound **4.66** was isolated as a clear, pale yellow oil.

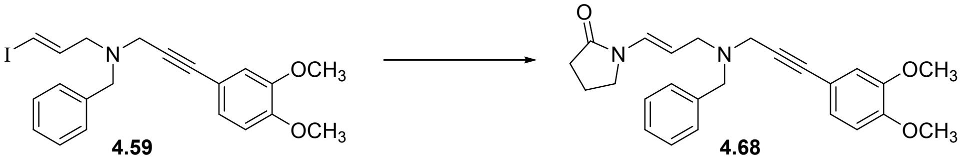
IR (neat): 2937, 2247, 1702, 1662, 1514, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 14.3 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.94 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 5.04 (dt, *J* = 14.3, 7.0 Hz, 1H), 4.31 (s, 2H), 4.13 (d, *J* = 7.2 Hz, 2H), 3.84 (s, 6H), 3.50 (t, *J* = 7.0 Hz, 2H), 2.45 (t, *J* = 8.2 Hz, 2H), 2.07 (qt, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 149.7, 148.7, 128.1, 125.2, 114.9, 114.7, 111.1, 106.7, 86.5, 83.7, 68.7, 57.6, 56.0, 55.9, 45.2, 31.3, 17.6. HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ $(M + Na)^+$: 338.1368. Found: 338.1364.



(*E*)-Diethyl 2-(3-(3,4-dimethoxyphenyl)prop-2-ynyl)-2-(3-(2-oxopyrrolidin-1-yl)allyl)malonate (4.67)

Iodide **4.55** (0.2 g, 0.5 mmol), 2-pyrrolidinone (0.1 mL, 1 mmol), copper(I) iodide (0.02 g, 0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.02 g, 0.1 mmol), cesium carbonate (0.3 g, 1 mmol), and 1.5 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 67 h. After purification by column chromatography on triethylamine washed silica gel (5:1→3:1→1:1 hexanes:ethyl acetate), 0.2 g (79 %) of the title compound **4.67** was isolated as a clear, pale yellow oil.

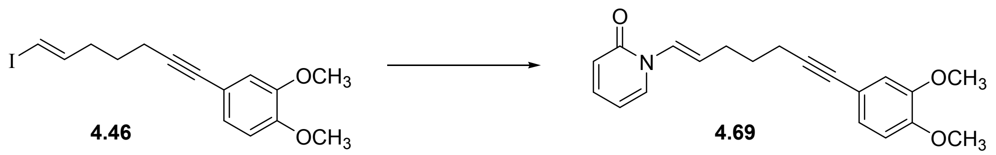
IR (film): 2980, 2254, 1732, 1661, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (d, *J* = 14.3 Hz, 1H), 6.94 (d, *J* = 9.6 Hz, 1H), 6.85 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.77-4.69 (m, 1H), 4.18 (q, *J* = 6.5 Hz, 4H), 3.82 (s, 3H), 3.81 (s, 3H), 3.42 (t, *J* = 7.0 Hz, 2H), 2.94 (s, 2H), 2.83 (d, *J* = 7.5 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 2.02 (qt, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 169.9, 149.4, 148.7, 127.3, 125.0, 115.5, 114.5, 111.1, 104.5, 83.8, 82.7, 61.7, 57.7, 56.0, 55.9, 45.2, 33.3, 31.2, 23.7, 17.5, 14.2. HRMS (ESI) calcd for $C_{25}H_{31}NO_7Na$ $(M + Na)^+$: 480.1998. Found: 480.2003.



(*E*)-1-(3-(Benzyl(3-(3,4-dimethoxyphenyl)prop-2-ynyl)amino)prop-1-enyl)pyrrolidin-2-one (4.68)

Iodide **4.59** (0.2 g, 0.4 mmol), 2-pyrrolidinone (0.1 mL, 1 mmol), copper(I) iodide (0.01 g, 0.05 mmol), *N*,*N*-dimethylglycine hydrochloride (0.02 g, 0.1 mmol), cesium carbonate (0.2 g, 0.7 mmol), and 1 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 65 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1 hexanes:ethyl acetate), 0.09 g (65 %) of the title compound **4.68** was isolated as a clear, pale yellow oil.

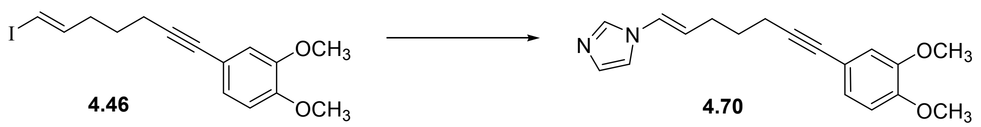
IR (neat): 2934, 1737, 1704, 1661, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H), 7.13 (d, *J* = 14.3 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.98 (s, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.01 (dt, *J* = 14.3, 7.1 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.72 (s, 2H), 3.52-3.50 (m, 4H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 8.0 Hz, 2H), 2.09 (qt, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 149.5, 148.8, 138.9, 129.3, 128.5, 127.3, 126.7, 125.2, 115.6, 114.7, 111.2, 108.7, 85.9, 82.8, 57.7, 56.1, 56.0, 54.0, 45.4, 42.3, 31.4, 17.6. HRMS (ESI) calcd for $C_{25}H_{29}N_2O_3$ $(M + H)^+$: 405.2178. Found: 405.2170.



(*E*)-1-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)pyridin-2(1*H*)-one (4.69)

Iodide **4.46** (0.2 g, 0.6 mmol), 2-hydroxypyridine (0.1 g, 1 mmol), copper(I) iodide (0.02 g, 0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.03 g, 0.2 mmol), cesium carbonate (0.5 g, 2 mmol), and 1.5 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 69 h. After purification by column chromatography on triethylamine washed silica gel (5:1→1:1→0:1 hexanes:ethyl acetate) 0.2 g (71 %) of the title compound **4.69** was isolated as a clear, pale yellow oil.

IR (neat): 2935, 1666, 1592, 762 cm-1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 5.8 Hz, 1H), 7.30-7.26 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 6.13 (t, *J* = 6.7 Hz, 1H), 5.80 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.84 (s, 6H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.37 (q, *J* = 7.3 Hz, 2H), 1.76 (qt, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 149.1, 148.7, 139.6, 133.8, 127.5, 124.5, 122.3, 121.4, 116.2, 114.5, 111.1, 106.5, 87.9, 81.3, 56.0, 29.4, 28.4, 19.0. HRMS (ESI) calcd for $C_{20}H_{21}NO_3Na$ $(M + Na)^+$: 346.1419. Found: 146.1413.



(*E*)-1-(7-(3,4-Dimethoxyphenyl)hept-1-en-6-ynyl)-1*H*-imidazole (4.70)

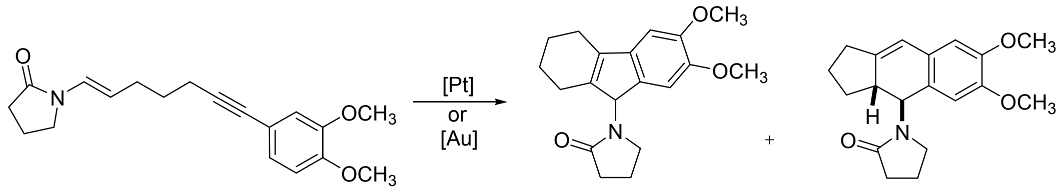
Iodide **4.46** (0.2 g, 0.7 mmol), imidazole (0.1 g, 0.1 mmol), copper(I) iodide (0.02 g, 0.1 mmol), *N*,*N*-dimethylglycine hydrochloride (0.03 g, 0.2 mmol), cesium carbonate (0.4 g, 1 mmol), and 1.5 mL of dioxane were combined according to the general procedure for the copper-catalyzed formation of enamides, except that the reaction mixture was stirred for 69 h. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→0:1 hexanes:ethyl acetate) 0.09 g (46 %; 91 % BRSM) of the title compound **4.70** was isolated as a clear, pale yellow oil.

IR (neat): 2936, 2254, 1513, 1497, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (br s, 1H), 7.05 (br d, *J* = 15.4 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.68

(d, J = 14.3 Hz, 1H), 5.79 (dt, J = 14.2, 7.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.41 (t, J = 7.0 Hz, 2H), 2.28 (q, J = 7.2 Hz, 2H), 1.71 (qt, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.1, 148.7, 136.0 (br), 130.1 (br), 124.7, 124.1, 119.0, 116.4 (br), 116.1, 114.4, 111.1, 87.7, 81.3, 56.0, 28.9, 28.4, 18.9. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ (M + H)$^+$: 297.1603. Found: 297.1594.

4.7.3 Reactions of Substrates

Representative Procedures:



4.28 **4.28*A*** **4.28*C***

13 : 1

1-(6,7-Dimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)pyrrolidin-2-one (4.28*A*) + 1-(6,7-Dimethoxy-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-4-yl)pyrrolidin-2-one (4.28*C*)

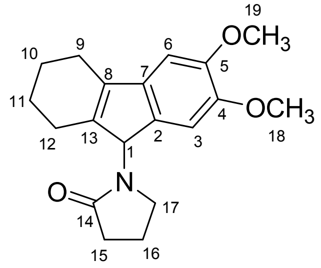
Method A (PtCl$_2$ as the catalyst): A solution of 0.045 g of enamide **4.28** (0.14 mmol) and 3.8 mg of platinum(II) chloride (0.014 mmol) in 0.7 mL of toluene was stirred in a sealed tube at 110 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 0.031 g (67 %) of an 8:1 mixture of the title compounds **4.28*A*** and **4.28*C*** as a clear, yellow oil.

Method B ([Ph$_3$PAuCl] and AgSbF$_6$ as the catalyst system): A solution of 0.028 g of enamide **4.28** (0.090 mmol), 2.2 mg of [Ph$_3$PAuCl] complex (0.0045 mmol), and 1.6 mg of silver hexafluoroantimonate(V) (0.0045 mmol) in 0.5 mL of 1,2-dichloroethane was stirred in a large test tube reaction flask at 80 °C for 1 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 0.024 g (86 %) of a 13:1 mixture of the title compounds **4.28*A*** and **4.28*C*** as a clear, yellow oil.

Method C (gold complex 1.70 as the catalyst): Please see the experimental details for the cyclization of compound **4.26** for details.

IR (film): 2936, 2250, 1677, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.73 (s, 1H), 5.58 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.90-2.76 (m, 2H), 2.52 (t, *J* = 8.1 Hz, 2H), 2.43-2.38 (m, 2H), 2.29-2.23 (m, 1H), 2.09-2.06 (m, 1H), 2.03-1.91 (m, 2H), 1.86-1.68 (m, 4H). Additional signals associated with the minor isomer **4.28*C***: δ 6.63 (s, 1H), 6.44 (s, 1H), 6.19 (d, *J* = 2.1 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.51-3.38 (m, 1H), 3.35-3.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 149.4, 147.6, 138.8, 138.4, 138.1, 133.8, 110.3, 102.4, 59.3, 56.3, 56.4, 42.7, 31.4, 23.6, 22.9, 22.6, 22.4, 18.1. HRMS (ESI) calcd for $C_{19}H_{24}NO_2$ (M + H)$^+$: 314.1756. Found: 314.1751.

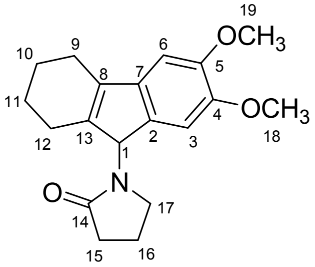
Table 4.10: NMR data for **4.28*A***



Carbon No.	^{13}C δ (ppm)[a]	Mult.	^{1}H δ (ppm) (mult., *J* (Hz)[b,c,d,e]	HMBC Correlations[e]
1	59.3	CH	H-1: 5.58 (s)	H-3
2	138.1	Q		H-3, H-12a, H-12b
3	107.9	CH	H-3: 6.88 (s)	H-6
4	149.4	Q		H-3, H-6, H-18
5	147.6	Q		H-3, H-6, H-19
6	102.4	CH	H-6: 6.73 (s)	H-3
7	133.8	Q		H-1, H-6
8	138.4	Q		H-6, H-12a, H-12b
9	22.4	CH_2	H-9a: 2.43-2.38 (m) H-9b: 2.43-2.38 (m)	
10	22.6	CH_2	H-10a: 1.83-1.79 (m) H-10b: 1.83-1.79 (m)	H-9a, H-9b
11	22.9	CH_2	H-11a: 1.83-1.79 (m) H-11b: 1.75-1.67 (m)	
12	23.6	CH_2	H-12a: 2.29-2.23 (m) H-12b: 2.09-2.06 (m)	
13	138.8	Q		H-1, H-11a, H-11b, H-12a, H-12b
14	176.1	Q		H-15a, H-15b, H-17a, H-17b
15	31.4	CH_2	H-15a: 2.52 (t, 8.1) H-15b: 2.52 (t, 8.1)	H-17a, H-17b
16	18.1	CH_2	H-16a: 2.03-1.91 (m) H-16b: 2.03-1.91 (m)	H-15a, H-15b, H-17a, H-17b
17	42.7	CH_2	H-17a: 2.90-2.76 (m) H-17b: 2.90-2.76 (m)	H-1, H-15a, H-15b
18	56.4	CH_3	H-18: 3.91 (s)	

[a] Recorded at 100 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC and COSY data. [d] Methylene protons are arbitrarily designated H-Xa and H-Xb. [e] Only those correlations which could be unambiguously assigned are recorded.

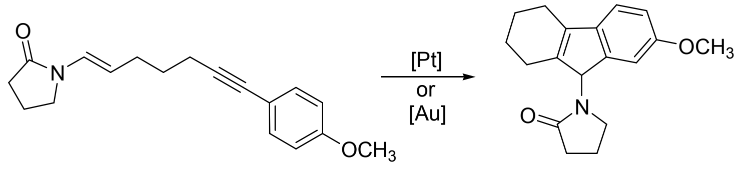
Table 4.11: NMR data for **4.28*A***



Proton No.[a]	^{1}H δ (ppm) (mult J (Hz))[a,b]	COSY Correlation[c]
H-1	5.58 (s)	
H-3	6.88 (s)	
H-6	6.73 (s)	
H-9a	2.43-2.38 (m)	H-10a, H-10b
H-9b	2.43-2.38 (m)	H-10a, H-10b
H-10a	1.83-1.79 (m)	H-9a, H-9b, H-11a, H-11b
H-10b	1.83-1.79 (m)	H-9a, H-9b, H-11a, H-11b
H-11a	1.83-1.79 (m)	H-10a, H-10b, H-12a, H-12b
H-11b	1.75-1.67 (m)	H-10a, H-10b, H-12a, H-12b
H-12a	2.29-2.23 (m)	H-11a, H-11b, H-12b
H-12b	2.09-2.06 (m)	H-11a, H-11b, H-12a
H-15a	2.52 (t, 8.1)	H-16a, H-16b
H-15b	2.52 (t, 8.1)	H-16a, H-16b
H-16a	2.03-1.91 (m)	H-15a, H-15b, H-17a, H-17b
H-16b	2.03-1.91 (m)	H-15a, H-15b, H-17a, H-17b
H-17a	2.90-2.76 (m)	H-16a, H-16b
H-17b	2.90-2.76 (m)	H-16a, H-16b
H-18	3.91 (s)	
H-19	3.86 (s)	

[a] Recorded at 400 MHz. [b] Assignements based on HMQC, HMBC, and COSY data.

[c] Only those correlations which could be unambiguously assigned are recorded.



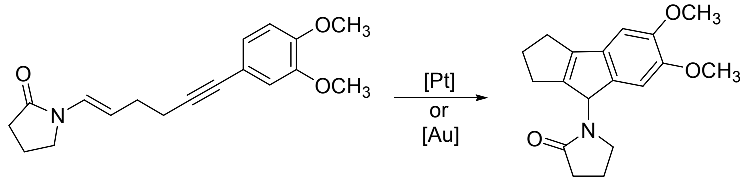
4.27 4.27*A*

1-(7-Methoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)pyrrolidin-2-one (4.27*A*)

Method A: Enamide **4.27** (0.054 g, 0.19 mmol), platinum(II) chloride (5.0 mg, 0.019 mmol), and 0.7 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.032 g (59 %) of the title compound **4.27*A*** was isolated as a yellow foam.

Method B: Enamide **4.27** (0.038 g, 0.13 mmol), [Ph_3PAuCl] complex (3.3 mg, 0.0066 mmol), silver hexafluoroantimonate(V) (2.3 mg, 0.0066 mmol), and 0.65 mL of 1,2-dichloroethane were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.024 g (64 %) of the title compound **4.27*A*** was isolated as a yellow foam.

IR (film): 2934, 1713, 1685, 816 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, $J = 8.2$ Hz, 1H), 6.88 (d, $J = 2.0$ Hz, 1H), 6.80 (dd, $J = 8.2, 2.4$ Hz, 1H), 5.62 (s, 1H), 3.79 (s, 3H), 2.88-2.76 (m, 2H), 2.51 (t, $J = 8.2$ Hz, 2H), 2.38 (br s, 2H), 2.29-2.22 (m, 1H), 2.06-2.01 (m, 1H), 1.99-1.90 (m, 2H), 1.84-1.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 158.3, 143.6, 138.5, 138.1, 137.9, 118.4, 112.8, 110.4, 59.4, 55.8, 42.7, 31.3, 23.6, 22.9, 22.6, 22.4, 18.1. HRMS (ESI) calcd for $C_{18}H_{22}NO_2$ $(M + H)^+$: 284.1651. Found: 284.1647.



4.26 4.26*A*

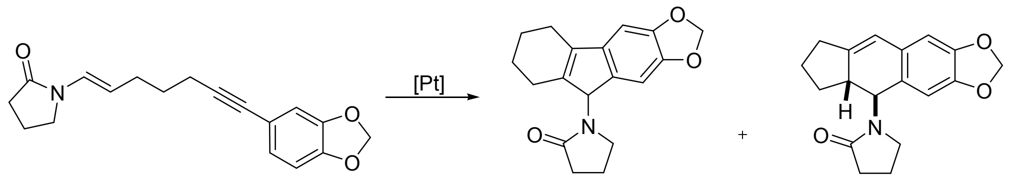
1-(5,6-Dimethoxy-1,2,3,8-tetrahydrocyclopenta[*a*]inden-8-yl)pyrrolidin-2-one (4.26*A*)

Method A: Enamide **4.26** (0.041 g, 0.14 mmol), platinum(II) chloride (3.6 mg, 0.014 mmol), and 0.6 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.016 g (39 %) of the title compound **4.26*A*** was isolated as a yellow foam.

Method B: Enamide **4.26** (0.060 g, 0.20 mmol), [Ph_3PAuCl] complex (0.010 g, 0.021 mmol), silver hexafluoroantimonate(V) (6.9 mg, 0.021 mmol), and 0.75 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred for 4 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.013 g (21 %) of the title compound **4.26*A*** was isolated as a yellow foam.

Representative Procedure for Method C (gold complex 1.70 as the catalyst): A solution of 0.029 g of enamide **4.26** (0.095 mmol) and 3.7 mg of catalyst **1.70** (0.0048 mmol) in 0.5 mL of 1,2-dichloroethane was stirred in a large test tube reaction flask at 80 °C for 3 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 9.6 mg (34 %) of compound **4.26*A*** as a clear, yellow oil.

IR (film): 2954, 2251, 1674, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.73 (s, 1H), 5.61 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.97 -2.91 (m, 1H), 2.87-2.81 (m, 1H), 2.63-2.55 (m, 2H), 2.53-2.49 (m, 3H), 2.48-2.35 (m, 3H), 2.02-1.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 150.1, 149.1, 148.4, 147.1, 139.4, 134.1, 108.7, 103.7, 56.6, 56.3, 54.8, 43.1, 31.3, 28.5, 28.1, 26.8, 18.1. HRMS (ESI) calcd for $C_{18}H_{22}NO_3$ $(M + H)^+$: 300.1600. Found: 300.1608.



4.39 **4.39*A*** **4.39*C***

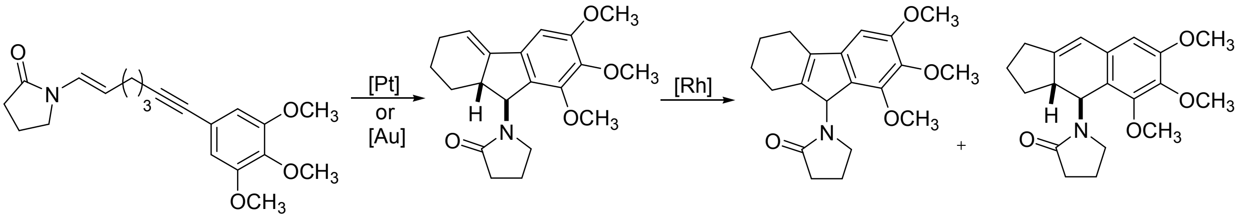
13 : 1

1-(6,7,8,9-Tetrahydro-5*H*-fluoreno[3,2-*d*][1,3]dioxol-9-yl)pyrrolidin-2-one (4.39*A*) + 5-*Exo* isomer (4.39*C*)

Method A: Enamide **4.39** (0.042 g, 0.14 mmol), platinum(II) chloride (3.8 mg, 0.014 mmol), and 0.7 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3

hexanes:ethyl acetate), 0.029 g (69 %) of a 13:1 mixture of the title compounds **4.39*A*** and **4.39*C*** was isolated as a clear oil.

IR (film): 2933, 2241, 1678, 937, 645 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.80 (s, 1H), 6.66 (s, 1H), 5.95 (d, *J* = 3.8 Hz, 2H), 5.55 (s, 1H), 2.87-2.77 (m, 2H), 2.50 (t, *J* = 8.0 Hz, 2H), 2.35 (br s, 2H), 2.26-2.18 (m, 1H), 2.05-1.92 (m, 3H), 1.79-1.68 (m, 4H). Additional signals associated with the minor isomer **4.39*C***: δ 6.58 (s, 1H), 6.40 (s, 1H), 6.17 (s, 1H), 5.16 (d, *J* = 14.7 Hz, 1H), 3.46-3.36 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 176.1, 147.7, 145.7, 139.3, 139.2, 138.3, 135.2, 105.2, 101.2, 99.9, 59.1, 42.6, 31.3, 23.6, 22.8, 22.5, 22.3, 18.1. HRMS (ESI) calcd for $C_{18}H_{20}NO_3$ (M + H)$^+$: 298.1443. Found: 298.1449.



4.40 **4.40*B*** **4.40*A*** **4.40*C***

10 : 1

1-(6,7,8-Trimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)pyrrolidin-2-one (4.40*A*) + 1-(6,7-Dimethoxy-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-4-yl)pyrrolidin-2-one (4.40*C*)

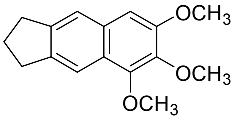
Method A: Enamide **4.40** (0.041 g, 0.12 mmol), platinum(II) chloride (3.1 mg, 0.012 mmol), and 0.6 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.021 g (50 %) of compound **4.40*B*** was isolated as a clear oil, along with 6.4 mg (21 %) of elimination product 5,6,7-trimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.40*D***) as a yellow solid.

Method B: Enamide **4.40** (0.038 g, 0.11 mmol), [Ph$_3$PAuCl] complex (2.8 mg, 0.0056 mmol), silver hexafluoroantimonate(V) (1.9 mg, 0.0056 mmol), and 0.55 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred at 80 °C for 0.5 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.031 g (81 %) of compound **4.40*B*** was isolated as a clear oil.

Isomerization of the Double Bond Using Rhodium(III)

A solution of 0.073 g of compound **4.40*B*** (0.21 mmol), 5.6 mg of rhodium(III) chloride trihydrate (0.021 mmol) and 1 mL of ethanol was stirred in a large test tube reaction flask at 80 °C for 6 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 0.056 g (77 %) of a 10:1 mixture of the title compounds **4.40*A*** and **4.40*C*** as a clear oil, along with 3.0 mg (6 %) of the elimination product 5,6,7-trimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.40*D***) as a off-white solid.

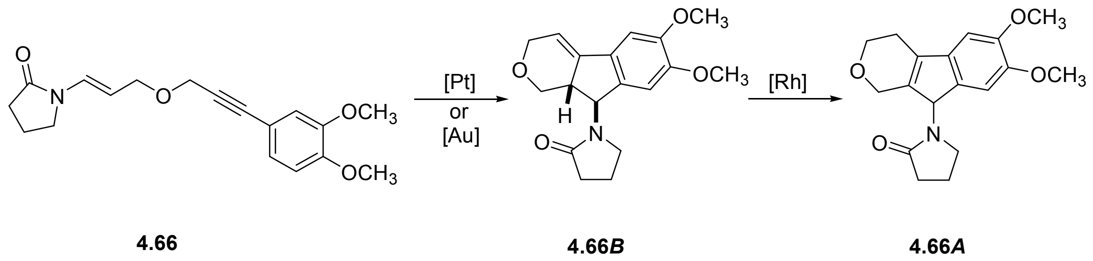
IR (neat): 2935, 1677, 645 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.53 (s, 1H), 5.77 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 2.87-2.78 (m, 2H), 2.52-2.48 (m, 2H), 2.37-2.36 (m, 2H), 2.28-2.23 (m, 1H), 2.08-2.03 (m, 1H), 1.98-1.91 (m, 2H), 1.82-1.67 (m, 4H). Additional signals associated with the minor isomer **4.40*C***: δ 6.41 (s, 1H), 6.12 (d, *J* = 2.4 Hz, 1H), 5.43 (d, *J* = 14.3 Hz, 1H), 3.85 (s, 6H), 3.69 (s, 3H), 3.39-3.35 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 175.6, 154.5, 150.3, 141.4, 140.9, 139.7, 137.8, 123.7, 98.5, 61.3, 60.6, 58.2, 56.4, 42.9, 31.3, 23.4, 22.8, 22.6, 22.3, 18.1. HRMS (ESI) calcd for $C_{20}H_{25}NO_4Na$ (M + Na)$^+$: 366.1681. Found: 366.1674.



4.40*D*

5,6,7-trimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (4.40*D*)

^{1}H NMR (400 MHz, CDCl$_3$): 7.87 (s, 1H), 7.52 (s, 1H), 6.89 (s, 1H), 4.04 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 3.04 (q, *J* = 7.2 Hz, 4H), 2.13 (qt, *J* = 7.3 Hz, 2H).



4.66 **4.66*B*** **4.66*A***

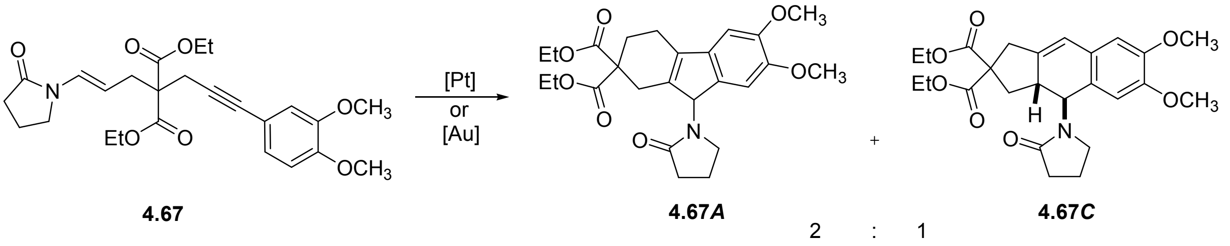
1-(6,7-Dimethoxy-1,3,4,9-tetrahydroindeno[2,1-*c*]pyran-9-yl)pyrrolidin-2-one (4.66*A*)

Method B: Enamide **4.66** (0.041 g, 0.13 mmol), [Ph_3PAuCl] complex (3.2 mg, 0.0064 mmol), silver hexafluoroantimonate(V) (2.2 mg, 0.0064 mmol), and 0.6 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred at 80 °C for 0.25 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.028 g (69 %) of compound **4.66*B*** was isolated as a clear oil.

Method C: Enamide **4.66** (0.044 g, 0.14 mmol), gold complex **1.70** (0.011 g, 0.014 mmol), and 0.6 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred for 1 h. After purification by column chromatography on triethylamine washed silica gel (1:1→0:1 hexanes:ethyl acetate), 0.043 g (98 %) of compound **4.66*B*** was isolated as a clear, yellow oil.

A solution of 0.049 g of compound **4.66*B*** (0.15 mmol), 4.0 mg of rhodium(III) chloride trihydrate (0.015 mmol) and 1 mL of ethanol was stirred in a large test tube reaction flask at 80 °C for 2.5 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1→0:1 hexanes:ethyl acetate) to afford 0.040 g (83 %) of the title compound **4.66*A*** as a clear oil.

IR (film): 2925, 2250, 1674, 647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.91 (s, 1H), 6.78 (s, 1H), 5.72 (s, 1H), 4.44 (d, J = 16.7 Hz, 1H), 4.22 (d, J = 16.7 Hz, 1H), 4.05 (dt, J = 11.2, 4.8 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.90-3.82 (m, 1H), 2.96-2.90 (m, 1H), 2.87-2.81 (m, 1H), 2.66-2.57 (m, 1H), 2.53-2.49 (m, 3H), 2.01-1.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 149.6, 147.8, 136.8, 136.7, 136.6, 133.8, 108.0, 102.7, 65.0, 64.3, 57.5, 56.6, 56.4, 42.7, 31.2, 23.3, 18.1. HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ $(M + Na)^+$: 338.1368. Found: 338.1362.



Diethyl 6,7-dimethoxy-9-(2-oxopyrrolidin-1-yl)-3,4-dihydro-1*H*-fluorene-2,2(9*H*)-dicarboxylate (4.67*A*) + Diethyl 6,7-dimethoxy-4-(2-oxopyrrolidin-1-yl)-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalene-2,2(3*H*)-dicarboxylate (4.67*C*)

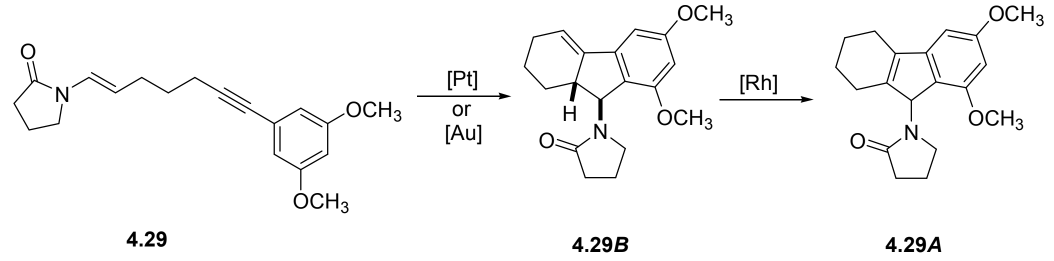
Method A: Enamide **4.67** (0.046 g, 0.10 mmol), platinum(II) chloride (2.7 mg, 0.010 mmol), and 0.5 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.028 g (62 %) of a 2:1 mixture of the title compounds **4.67*A*** and **4.67*C*** was isolated as a clear oil.

Method B: Enamide **4.67** (0.041 g, 0.089 mmol), [Ph_3PAuCl] complex (2.2 mg, 0.0045 mmol), silver hexafluoroantimonate(V) (1.5 mg, 0.0045 mmol), and 0.5 mL of 1,2-dichloroethane were combined according to the general procedure above, except that the reaction mixture was stirred at 80 ^{o}C for 2 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.036 g (88 %) of a 2:1 mixture of the title compounds **4.67*A*** and **4.67*C*** was isolated as a clear oil.

Method C: Enamide **4.67** (0.041 g, 0.090 mmol), gold complex **x** (6.9 mg, 0.0090 mmol), and 0.5 mL of 1,2-dichloroethane were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.032 g (79 %) of a 2:1 mixture of the title compounds **4.67*A*** and **4.67*C*** was isolated as a clear oil.

IR (film): 2980, 1730, 1681, 876 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.71 (s, 1H), 5.63 (s, 1H), 4.25-4.12 (m, 4H), 3.90 (s, 3H), 3.86 (s, 3H), 3.47-3.41 (m, 1H), 3.30-3.15 (m, 1H), 2.80-2.72 (m, 2H), 2.61-2.46 (m, 4H), 2.26-2.11 (m, 2H), 2.07-1.91 (m, 2H), 1.28-1.22 (m, 6H). Additional signals associated with the minor isomer **4.67*C***: δ 6.63 (s, 1H), 6.43 (s, 1H), 6.23 (d, *J* = 2.4 Hz, 1H), 5.28 (d, *J* = 15.0 Hz, 1H), 4.27-4.11 (m, 4H), 3.85 (s, 3H), 3.82 (s, 3H), 3.10-3.01 (m, 3H), 2.67 (s, 1H), 2.63-2.36 (m, 6H), 2.06-1.91 (m, 2H), 1.28-1.22 (m, 6H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 176.3, 176.2, 171.8, 171.5, 171.1, 171.0, 149.5, 148.4, 148.0, 147.6, 141.2, 137.3, 136.8, 136.0, 133.9, 129.0, 125.1, 119.4, 110.6, 108.1, 107.9, 102.7, 61.9, 61.8, 61.7, 61.6, 59.3, 58.9, 56.6, 56.4, 56.3, 56.2, 56.1, 53.9, 43.0, 42.6, 41.3, 38.6, 38.4, 31.6, 31.4, 29.4, 27.9, 19.8, 19.1, 18.2, 18.1, 14.2, 14.1. HRMS (ESI) calcd for $C_{25}H_{31}NO_7Na$ $(M + Na)^+$: 480.1998. Found: 480.1990.



1-(6,8-Dimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)pyrrolidin-2-one (4.29*A*)

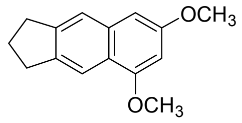
Method A: Enamide **4.29** (0.044 g, 0.14 mmol), platinum(II) chloride (3.7 mg, 0.014 mmol), and 0.6 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.021 g (47 %) of compound **4.29*B*** was isolated as a clear oil, along with 0.011 g (35 %) of elimination product 5,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.29*D***) as a yellow solid.

Method B: Enamide **4.29** (0.050 g, 0.16 mmol), [Ph_3PAuCl] complex (3.9 mg, 0.0079 mmol), silver hexafluoroantimonate(V) (2.7 mg, 0.0079 mmol), and 0.75 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred at rt for 8.5 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.043 g (87 %) of compound **4.29*B*** was isolated as a clear oil, along with 1.5 mg (4 %) of elimination product 5,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.29*D***) as a off-white solid.

Isomerization of the Double Bond Using Rhodium(III)

A solution of 0.088 g of compound **4.29*B*** (0.28 mmol), 7.4 mg of rhodium(III) chloride trihydrate (0.028 mmol) and 1 mL of ethanol was stirred in a sealed tube at 100 °C for 16 h. The reaction mixture was cooled to rt and directly purified by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate) to afford 0.047 g (53 %) of the title compound **4.29*A*** as a clear oil, along with 0.020 g (31 %) of the elimination product 5,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.29*D***) as a off-white solid.

IR (film): 2932, 1682, 821 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.38 (d, *J* = 1.7 Hz, 1H), 6.26 (d, *J* = 2.1 Hz, 1H), 5.66 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.78 (t, *J* = 7.0 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 2H), 2.36 (br s, 2H), 2.28-2.23 (m, 1H), 2.09-2.04 (m, 1H), 1.96-1.87 (m, 2H), 1.81-1..66 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 175.6, 162.2, 156.2, 147.9, 142.1, 137.8, 119.1, 96.8, 95.4, 57.8, 55.7, 55.6, 42.9, 31.3, 23.4, 22.9, 22.6, 22.3, 18.2. HRMS (ESI) calcd for $C_{19}H_{24}NO_3$ (M + H)$^+$: 314.1756. Found: 314.1749.



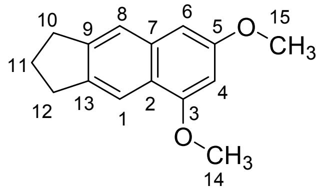
4.29*D*

5,7-Dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (4.29*D*)

mp = 85-88 °C.

IR (film): 2956, 2843, 2252, 1615, 825 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.98 (s, 1H), 7.52 (s, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.03 (t, *J* = 7.3 Hz, 4H), 2.13 (qt, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.6, 156.5, 144.7, 140.6, 134.6, 121.1, 121.0, 116.5, 98.1, 96.9, 55.6, 55.4, 32.8, 32.7, 26.3. HRMS (ESI) calcd for $C_{15}H_{17}O_2$ (M + H)$^+$: 229.1229. Found: 229.1231.

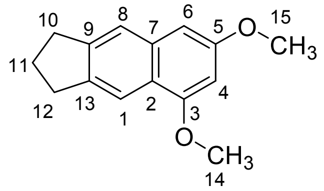
Table 4.12: NMR data for **4.29*D***



Carbon No.	^{13}C δ (ppm)[a]	^{1}H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations
1	116.5	H-1: 7.98 (s)	H-12a, H-12b
2	121.0		
3	156.5		H-1, H-4, H-14
4	96.9	H-4: 6.45 (d, 2.4)	H-6
5	157.6		H-4, H-6, H-15
6	98.1	H-6: 6.69 (d, 2.1)	H-4, H-8
7	134.6		H-1, H-8
8	121.1	H-8: 7.52 (s)	H-6, H-10a, H-10b
9	140.6		H-8, H-10a, H-10b, H-11a, H-11b, H-12a, H-12b
10	32.8	H-10a: 3.03 (t, 7.3) H-10b: 3.03 (t, 7.3)	H-8, H-11a, H-11b, H-12a, H-12b
11	26.3	H-11a: 2.13 (qt, 7.3) H-11b: 2.13 (qt, 7.3)	H-10a, H-10b, H-12a, H-12b
12	32.7	H-12a: 3.03 (t, 7.3) H-12b: 3.03 (t, 7.3)	H-1, H-10a, H-10b, H-11a, H-11b
13	144.7		H-1, H-10a, H-10b, H-11a, H-11b, H-12a, H-12b
14	55.6	H-14: 4.00 (s)	
15	55.4	H-15: 3.94 (s)	

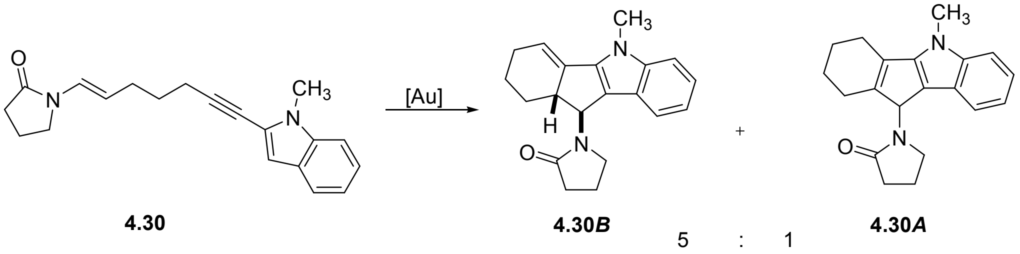
[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Assignments based on HMQC and COSY data. [d]Methylene protons are arbitrarily designated H-Xa and H-Xb. [e]Only those correlations which could be unambiguously assigned are recorded.

Table 4.13: NMR data for **4.29*D***



Proton No.	^{1}H δ (ppm) (mult J (Hz))[a,b]	COSY Correlation[c]
H-1	7.98 (s)	
H-4	6.45 (d, 2.4)	H-6
H-6	6.69 (d, 2.1)	H-4
H-8	7.52 (s)	
H-10a	3.03 (t, 7.3)	H-11a, H-11b
H-10b	3.03 (t, 7.3)	H-11a, H-11b
H-11a	2.13 (qt, 7.3)	H-10a, H-10b, H-12a, H-12b
H-11b	2.13 (qt, 7.3)	H-10a, H-10b, H-12a, H-12b
H-12a	3.03 (t, 7.3)	H-11a, H-11b
H-12b	3.03 (t, 7.3)	H-11a, H-11b

[a] Recorded at 400 MHz. [b] Assignements based on HMQC, HMBC, and COSY data.
[c] Only those correlations which could be unambiguously assigned are recorded.

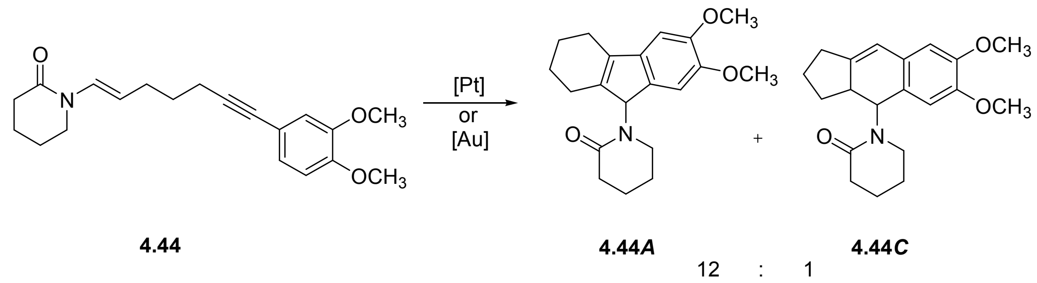


1-(5-Methyl-1,2,3,5,10,10a-hexahydroindeno[1,2-*b*]indol-10-yl)pyrrolidin-2-one (4.30*B*) + 1-(5-Methyl-1,2,3,4,5,10-hexahydroindeno[1,2-*b*]indol-10-yl)pyrrolidin-2-one (4.30*A*)

Method B: Enamide **4.30** (0.022 g, 0.071 mmol), [Ph$_3$PAuCl] complex (3.5 mg, 0.0071 mmol), silver hexafluoroantimonate(V) (2.4 mg, 0.0071 mmol), and 0.35 mL of 1,2-dichloroethane were combined according to the general procedure above, except that the reaction mixture was stirred at rt for 2.5 h. After purification by column chromatography on triethylamine washed silica gel

(1:1→1:3 hexanes:ethyl acetate), 0.018 g (85 %) of a 8:1 mixture of the title compounds **4.30*B*** and **4.30*A*** was isolated as a clear oil.

IR (film): 2930, 2241, 1670 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 7.35 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 3.8 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.10-7.06 (m, 1H), 5.87 (q, *J* = 3.1 Hz, 1H), 5.54 (d, *J* = 5.8 Hz, 1H), 3.83 (s, 3H), 3.37-3.30 (m, 2H), 3.01-2.96 (m, 1H), 2.61-2.51 (m, 2H), 2.34-2.32 (m, 1H), 2.27-2.18 (m, 2H), 2.07-2.00 (m, 3H), 1.68-1.62 (m, 2H). Additional signals associated with the minor isomer **4.30*A***: δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.40-7.38 (m, 1H), 7.16 (ddd, *J* = 8.0, 5.5, 2.6 Hz, 1H), 5.60 (s, 1H), 4.24-4.20 (m, 1H), 3.84 (s, 3H), 3.21-3.15 (m, 1H), 2.93-2.83 (m, 1H), 1.84-1.80 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 175.5, 143.9, 142.6, 133.7, 124.0, 122.1, 120.1, 119.2, 118.9, 116.1, 109.7, 55.5, 51.0, 44.0, 32.2, 31.0, 27.5, 25.1, 22.5, 18.4. HRMS (ESI) calcd for $C_{20}H_{22}N_2ONa$ $(M + Na)^+$: 329.1630. Found: 329.1638.

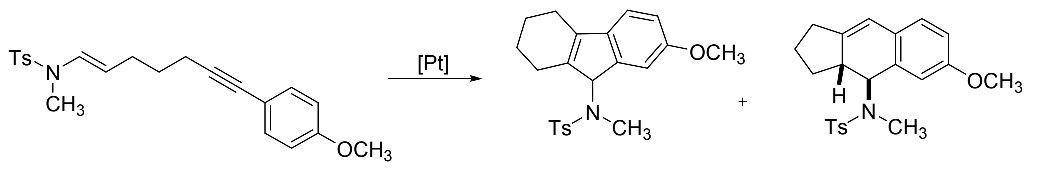


1-(6,7-Dimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)piperidin-2-one (4.44*A*) + 1-(6,7-dimethoxy-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-4-yl)piperidin-2-one (4.44*C*)

Method A: Enamide **4.44** (0.066 g, 0.20 mmol), platinum(II) chloride (5.3 mg, 0.020 mmol), and 1 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.040 g (61 %) of a 12:1 mixture of title compounds **4.44*A*** and **4.44*C*** was isolated as a yellow oil.

Method B: Enamide **4.44** (0.060 g, 0.18 mmol), [Ph$_3$PAuCl] complex (9.1 mg, 0.018 mmol), silver hexafluoroantimonate(V) (6.3 mg, 0.018 mmol), and 0.6 mL of 1,2-dichloroethane were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.042 g (69 %) of a 12:1 mixture of title compounds **4.44*A*** and **4.44*C*** was isolated as a yellow oil.

IR (film): 2934, 2250, 1633, 730 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.89 (s, 1H), 6.73 (s, 1H), 6.21 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.68-2.59 (m, 2H), 2.56 (t, *J* = 6.7 Hz, 2H), 2.40-2.39 (m, 2H), 2.29-2.23 (m, 1H), 2.09-2.04 (m, 1H), 1.85-1.75 (m, 6H), 1.71-1.60 (m, 2H). Additional signals associated with the minor isomer **4.44*C***: δ 6.90 (s, 1H), 6.62 (s, 1H), 6.50 (s, 1H), 5.87 (d, *J* = 15.3 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.9, 149.3, 147.2, 139.3, 138.6, 138.5, 134.3, 107.9, 102.3, 61.0, 56.7, 56.3, 41.9, 32.7, 23.6, 23.3, 22.9, 22.7, 22.5, 21.7. HRMS (ESI) calcd for $C_{20}H_{25}NO_3Na$ (M + Na)$^+$: 350.1732. Found: 350.1727.



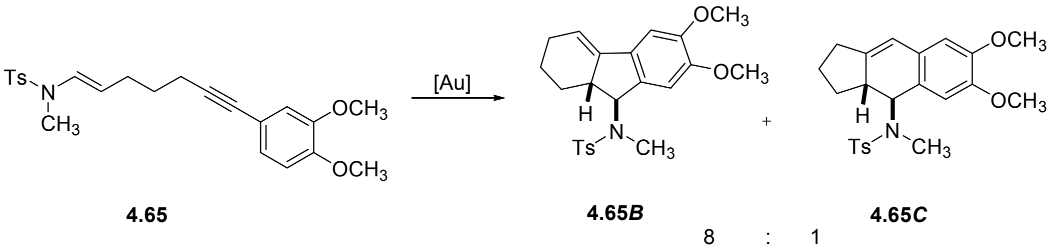
4.64 **4.64*A*** **4.64*C***

8 : 1

N-(7-Methoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)-*N*,4-dimethylbenzenesulfonamide (4.64*A*) + *N*-(6-Methoxy-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-4-yl)-*N*,4-dimethylbenzenesulfonamide (4.64*C*)

Method A: Enamide **4.64** (0.034 g, 0.090 mmol), platinum(II) chloride (2.4 mg, 0.0090 mmol), and 0.5 mL of toluene were combined according to the representative procedure, except that the reaction mixture was heated to 130 °C. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.020 g (58 %) of an 8:1 mixture of the title compounds **4.64*A*** and **4.64*C*** was isolated as a clear yellow oil.

IR (film): 2935, 2255, 1608, 1167, 733 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.75 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 5.25 (s, 1H), 3.64 (s, 3H), 2.47 (s, 3H), 2.35 (s, 3H), 2.35-2.31 (m, 2H), 2.06 (br s, 2H), 1.76-1.66 (m, 4H). Additional signals associated with the minor isomer **4.64*C***: δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.68 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.44 (br s, 1H), 6.19 (s, 1H), 5.13 (d, *J* = 14.7 Hz, 1H), 3.62 (s, 3H), 2.88 (s, 3H), 2.44 (s, 3H), 2.18-2.11 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.1, 143.4, 142.9, 138.5, 138.2, 137.8, 137.6, 129.9, 127.4, 118.4, 113.7, 110.1, 65.2, 55.6, 29.0, 23.3, 22.9, 22.5, 22.3, 21.6. HRMS (ESI) calcd for $C_{22}H_{25}NO_3NaS$ (M + Na)$^+$: 406.1453. Found: 406.1447.

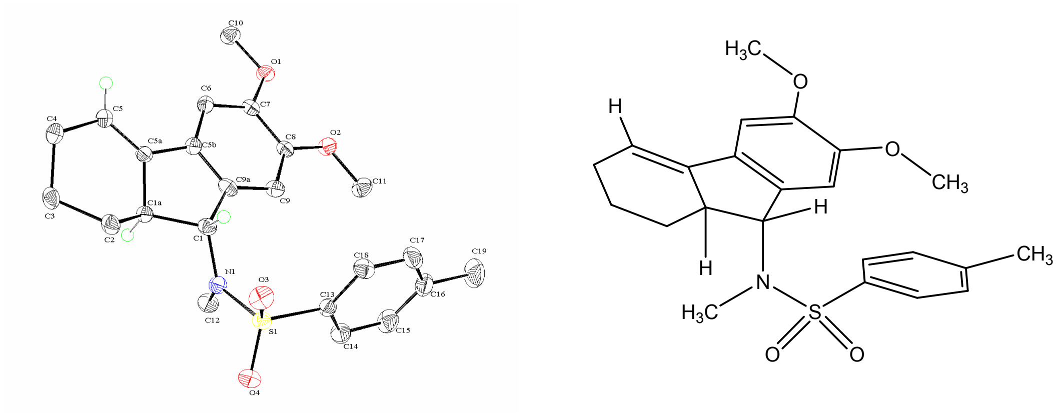


N-(6,7-Dimethoxy-1,2,3,9,9a-pentahydro-3*H*-fluoren-9-yl)-*N*,4-dimethylbenzenesulfonamide (4.65*B*) + *N*-(6,7-Dimethoxy-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-4-yl)-*N*,4-dimethylbenzenesulfonamide (4.65*C*)

Method B: Enamide **4.65** (0.030 g, 0.073 mmol), [Ph$_3$PAuCl] complex (1.8 mg, 0.0037 mmol), silver hexafluoroantimonate(V) (1.3 mg, 0.0037 mmol), and 0.4 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred at rt for 2 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.027 g (88 %) of an 8:1 mixture of the title compounds **4.65*B*** and **4.65*C*** was isolated as an off-white solid. X-ray quality crystals were formed by recrystallization of the solid with a mixture of dichloromethane and hexanes.

Method C: Enamide **4.65** (0.033 g, 0.079 mmol), gold complex **1.70** (6.1 mg, 0.0079 mmol), and 0.5 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred at rt for 1.5 h. After purification by column chromatography on triethylamine washed silica gel (6:1→3:1→1:1 hexanes:ethyl acetate), 0.028 g (85 %) of an 8:1 mixture of the title compounds **4.65*B*** and **4.65*C*** was isolated as an off white solid.

IR (film): 2935, 1604, 1498, 1164, 731, 664 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.84 (s, 1H), 5.86 (s, 1H), 5.86-5.84 (m, 1H), 5.06 (d, J = 7.9 Hz, 1H), 3.86 (s, 3H), 3.54 (s, 3H), 2.74 (s, 3H), 2.71-2.65 (m, 1H), 2.44 (s, 3H), 2.28-2.15 (m, 2H), 2.07-2.02 (m, 1H), 1.94-1.91 (m, 1H), 1.53-1.48 (m, 1H), 1.40-1.31 (m, 1H). Additional signals associated with the minor isomer **4.65*C***: δ 7.78 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.57 (s, 1H), 6.33 (s, 1H), 6.15 (br s, 1H), 5.13 (d, J = 14.7 Hz, 1H), 3.84 (s, 3H), 3.49 (s, 1H), 2.89 (s, 3H), 2.84 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.9, 149.6, 143.4, 139.3, 138.0, 133.5, 132.4, 130.1, 127.4, 116.6, 106.7, 102.7, 66.3, 56.1, 55.8, 45.5, 29.6, 26.8, 25.0, 22.4, 21.6. HRMS (ESI) calcd for $C_{23}H_{27}NO_4NaS$ $(M + Na)^+$: 436.1559. Found: 436.1572.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O1
C6
C7
C5
C4
C5a
C5b
C8
O2
C11
C9a
C9
C3
C1a
C2
C1
N1
O3
C12
S1
C13
C18
C17
C16
C19
C15
C14
O4
H3C
O
H
O
CH3
H
H
N
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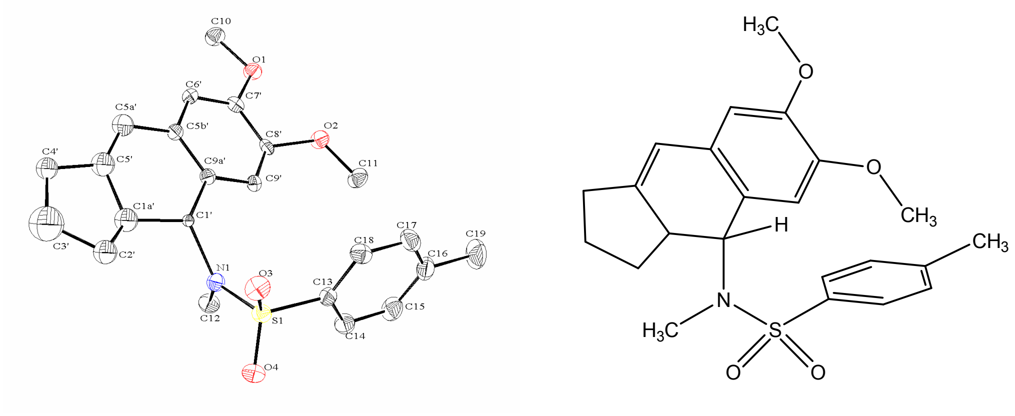
S
O
O
CH3

ORTEP representation of the solid state structure of **4.65*B***

……


C10
O1
C6'
C7'
C5a'
C5b'
C8'
O2
C4'
C5'
C9a'
C9'
C11
C1a'
C1'
C3'
C2'
N1
O3
C13
C18
C17
C16
C19
C12
S1
C14
C15
O4
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CH3
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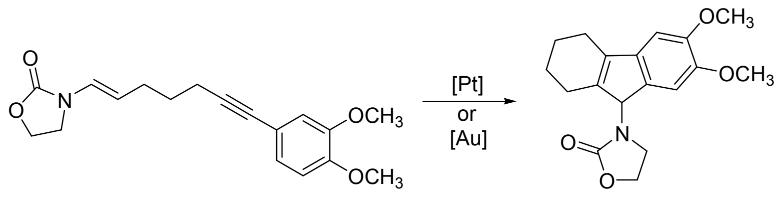
S
O
O

ORTEP representation of the solid state structure of **4.65*C***

……



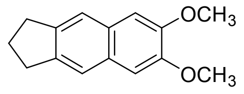
4.61 **4.61*A***

3-(6,7-Dimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)oxazolidin-2-one (4.61*A*)

Method A: Enamide **4.61** (0.046 g, 0.15 mmol), platinum(II) chloride (3.9 mg, 0.015 mmol), and 0.7 mL of toluene were combined according to the representative procedure. After purification by column chromatography on triethylamine washed silica gel (3:1→1:1→1:3 hexanes:ethyl acetate), 0.027 g (57 %) of the title compound **4.61*A*** was isolated as a clear oil, along with 3.1 mg (9 %) of elimination product 6,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.61*D***) as a yellow solid.

Method C: Enamide **4.61** (0.025 g, 0.079 mmol), gold complex **1.70** (3.1 mg, 0.0040 mmol), and 0.5 mL of 1,2-dichloroethane were combined according to the representative procedure, except that the reaction mixture was stirred for 4 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.016 g (64 %) of the title compound **4.61*A*** was isolated as a clear oil, along with 1.7 mg (9 %) of elimination product 6,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (**4.61*D***) as a yellow solid.

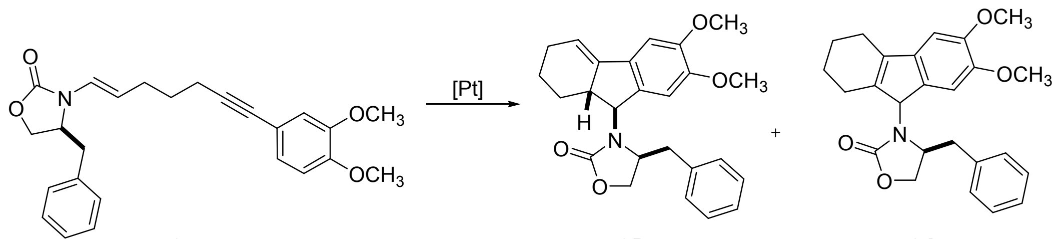
IR (film): 2935, 2252, 1747, 760 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.97 (s, 1H), 6.72 (s, 1H), 5.27 (s, 1H), 4.35-4.25 (m, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.06-2.94 (m, 2H), 2.39-2.38 (m, 2H), 2.33-2.27 (m, 1H), 2.16-2.11 (m, 1H), 1.83-1.69 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.5, 149.7, 147.5, 138.9, 137.9, 137.8, 132.9, 108.0, 102.6, 62.7, 61.1, 56.6, 56.3, 40.4, 23.6, 22.8, 22.5, 22.4. HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ (M + Na)$^+$: 338.1368. Found: 338.1366.



4.61*D*

6,7-Dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene (4.61*D*)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52 (s, 2H), 7.07 (s, 2H), 3.99 (s, 6H), 3.03 (t, *J* = 7.2 Hz, 4H), 2.13 (qt, *J* = 7.3 Hz, 2H).



4.46 **4.46*B*** **4.46*A***

8 : 1

(*S*)-4-Benzyl-3-((9*S*,9a*R*)-6,7-dimethoxy-1,2,3,9,9a-pentahydro-3*H*-fluoren-9-yl)oxazolidin-2-one (4.46*B*) + (4,*S*)-4-Benzyl-3-(6,7-dimethoxy-1,2,3,4,9-pentahydro-4*H*-fluoren-9-yl)oxazolidin-2-one (4.46*A*)

Method A: Enamide **4.46** (0.040 g, 0.098 mmol), platinum(II) chloride (5.2 mg, 0.020 mmol), and 0.5 mL of toluene were combined according to the representative procedure, except that the reaction mixture was stirred at rt for 54 h. After purification by column chromatography on triethylamine washed silica gel (1:1→1:3 hexanes:ethyl acetate), 0.021 g (52 %) of a mixture of the title compounds **4.46*B*** and **4.46*A*** was isolated as a clear oil.

IR (film): 2937, 2253, 1742, 650 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.22 (m, 3H), 6.97 (s, 1H), 6.94 (d, *J* = 6.4 Hz, 2H), 6.71 (s, 1H), 5.90 (q, *J* = 3.3 Hz, 1H), 5.08 (d, *J* = 7.6 Hz, 1H), 4.21-4.06 (m, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.02 (dd, *J* = 13.0, 2.9 Hz, 1H), 2.99-2.94 (m, 1H), 2.71-2.63 (m, 1H), 2.43-2.31 (m, 1H), 2.28-2.19 (m, 2H), 2.01-1.97 (m, 1H), 1.61-1.49 (m, 2H). Additional signals associated with the minor isomer **4.46*A***: δ 5.41 (s, 1H), 3.76-3.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 150.2, 149.8, 139.5, 135.8, 133.9, 131.8, 129.2, 129.1, 127.4, 116.4, 106.9, 103.1, 67.4, 63.0, 56.6, 56.2, 48.9, 40.7, 27.8, 25.0, 22.5. HRMS (ESI) calcd for $C_{25}H_{27}NO_4Na$ $(M + Na)^+$: 428.1838. Found: 428.1847.

4.8 References

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Conclusions

The introduction to this thesis described the symbiotic relationship between the two subfields of synthetic organic chemistry: methodology and target-oriented synthesis. The research presented in this dissertation describes examples of both, and exemplifies the relationship between them.

The initial project proposed at the outset of my graduate research was whether the platinum(II) chloride catalyzed cycloisomerization of a bicyclic enamide could be applied to the total synthesis of the alkaloid natural product (+)-fawcettidine. The first total synthesis reported of this natural product was described in Chapter 2. Two versions of a retrosynthetic plan were outlined, and both undertaken simultaneously. Problems that were encountered *en route* to the natural product were solved using methodological studies. One synthetic plan led to the construction of a late stage intermediate, while the other synthetic plan concluded with the successful formation of the natural product. I am grateful to have worked on this project, as it has exposed me to a variety of chemical reactions that would be unnecessary in methodology studies.

Chapter 3 describes the platinum(II) chloride catalyzed addition/Friedel-Crafts tandem reaction of 1,2,3,4-tetrahydropyridine derivatives containing an aromatic substituted alkyne moiety tethered at the 3-position of the ring. The products of this cyclization of simple monocylic substrates are tetracyclic, nitrogen containing ring systems featuring a quaternary carbon center. The substrates were non-commercially available and synthesized in 6 steps. Of the 14 substrates synthesized, 10 were successfully cycloisomerized using platinum(II) chloride. Treatment of a substrate with a catalytic amount of silver hexafluoroantimonate resulted in the unexpected formation of an azocine derivative.

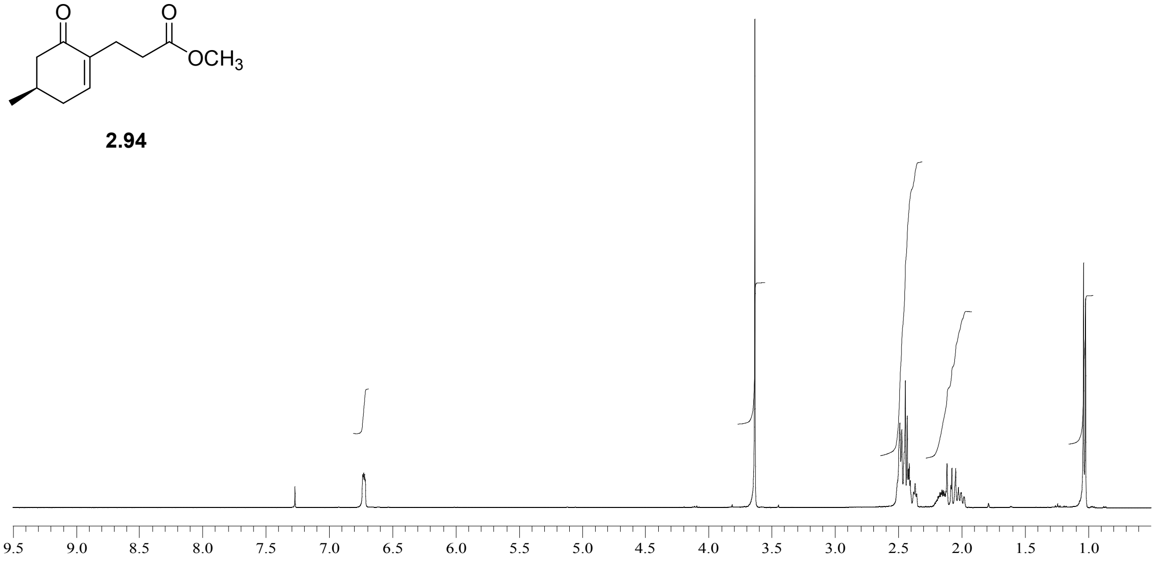
Chapter 4 describes the platinum(II) or gold(I) salt catalyzed addition/Friedel-Crafts tandem process of acyclic enamine derivatives featuring 1-arylalkynes. The product distribution was more complicated than that described in Chapter 3. Initial products resulting from initial 6-*endo* and 5-*exo* cyclization pathways were observed. The 6-*endo* product could then undergo an alkene isomerization, and the 5-*exo* product could eliminate to form substituted naphthalene derivatives. If alkene migration did not occur, it was forced using rhodium(III)-catalysis. The major products of the process were 1-aza-substituted indene derivatives. The substrates used in this study were not commercially available and were synthesized in 5-9 steps. Of the 25 substrates synthesized, 14 were successfully isomerized using either platinum(II) or gold(I) salts.

This thesis discloses the successful synthesis of 205 compounds, 168 of which were previously unknown, resulting from 1309 experiments over the course of my graduate degree. Overall, investigations of enamine derivatives as π-nucleophiles within the context of electrophilic metal salt cycloisomerization reactions were extended to the substrates described in Chapters 3 and 4, and applied to the total synthesis of a natural product in Chapter 2. This dissertation exemplifies the ability of this methodology to be applied to the synthesis of complex products from comparatively simple starting materials.

A strength of the method described in this thesis is its ability to incorporate enamine derivatives in catalysis, thereby introducing a nitrogen-based functionality to a number of novel compounds. Sequencing metal-catalyzed rearrangement with latent enamide nucleophiles greatly increases the complexity of the products relative to the starting materials in a single operation. The incorporation of a nitrogen atom into ring systems exemplifies the application of this research towards the synthesis of alkaloid natural products or alkaloid analogs. Limitations to the research disclosed include harsh reaction conditions and a relatively narrow substrate scope.

In the future, fine tuning either the catalyst or the substrates could achieve higher 6-*endo*:5-*exo* selectivities and even select which regioisomer is formed preferentially. Alteration of the catalyst could improve catalytic performance using milder reaction conditions. Achievements in these areas coupled with substrate scope expansion would dramatically increase the structural variation that could be accessed by this chemistry. A logical extension of this work is enantioselective platinum(II) or gold(I) salt catalyzed cycloisomerization reactions. A deeper understanding of the mechanism is necessary to efficiently improve a specific reaction. Mechanistic studies of the platinum(II)- and gold(I)-catalyzed cycloisomerization reactions have yet to be carried out for the particular system presented in this thesis. Aspects of the mechanism could be discovered by monitoring an NMR-tube reaction by ^{195}Pt NMR over certain time intervals, and extracting information about the rate of the reaction. Deuterium labeling experiements may also shed light on the mechanism of the alkene isomerizations or the amide eliminations described in Chapter 4.

Appendix A: Selected Spectra for Chapter 2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4.5
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3.0
2.5
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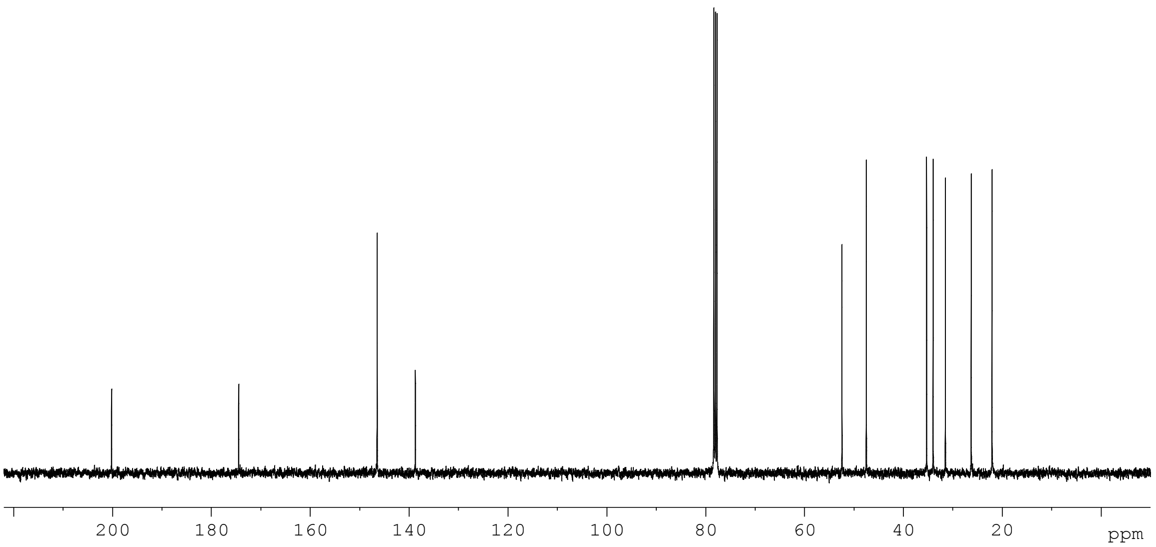
1.5
1.0

2.94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180
160
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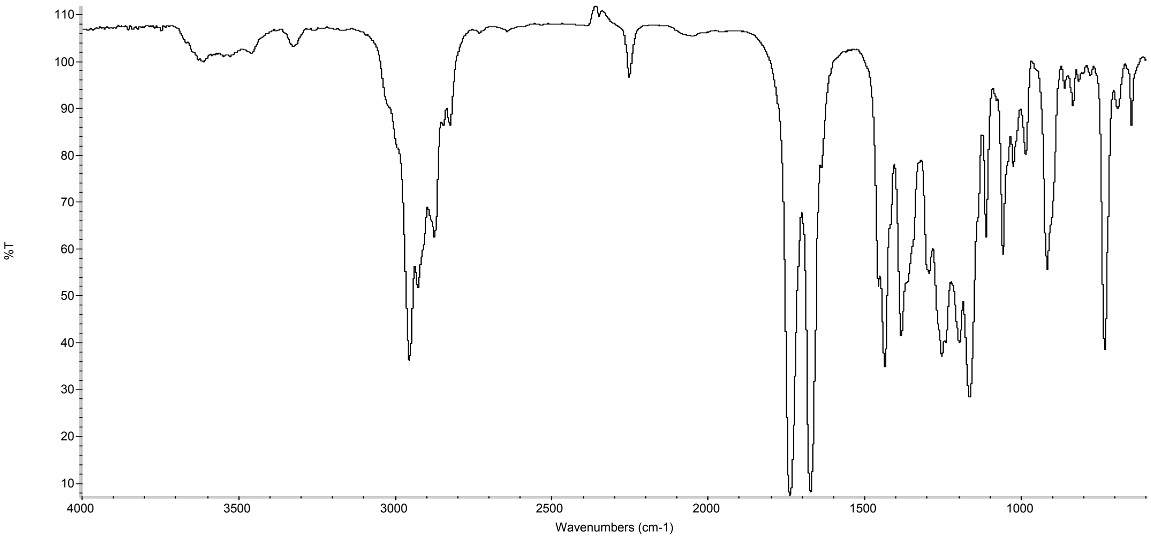
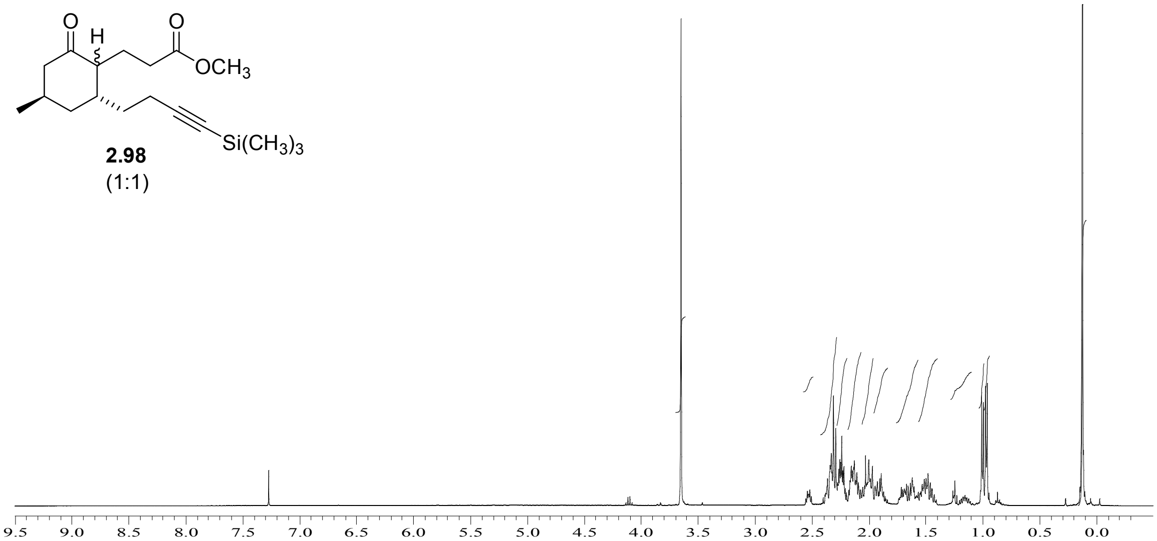
120
100
80
60
40
20
ppm


110
100
90
80
70
60
50
40
30
20
10
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)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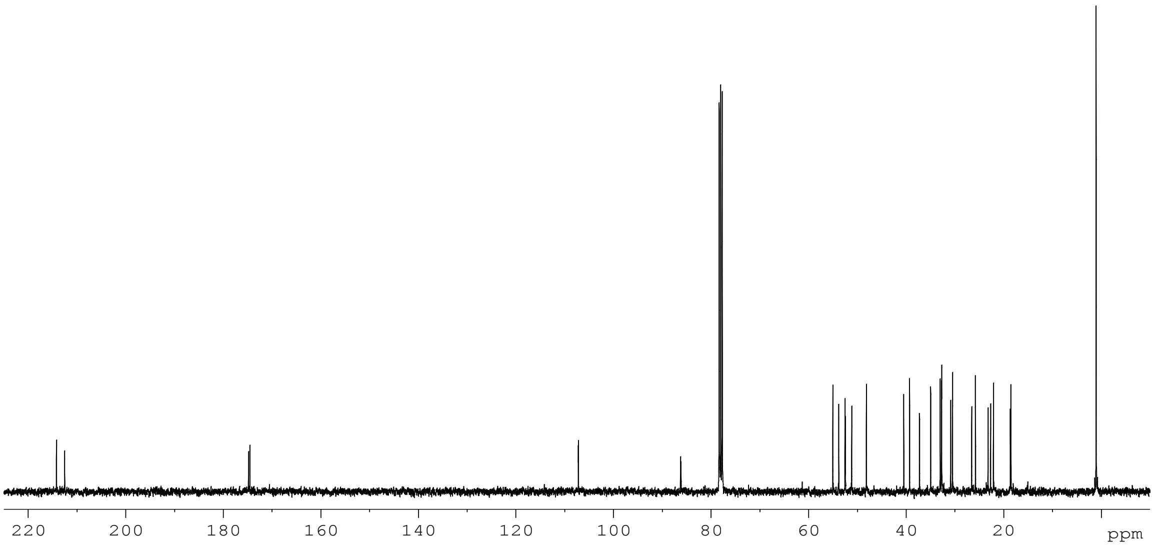
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20
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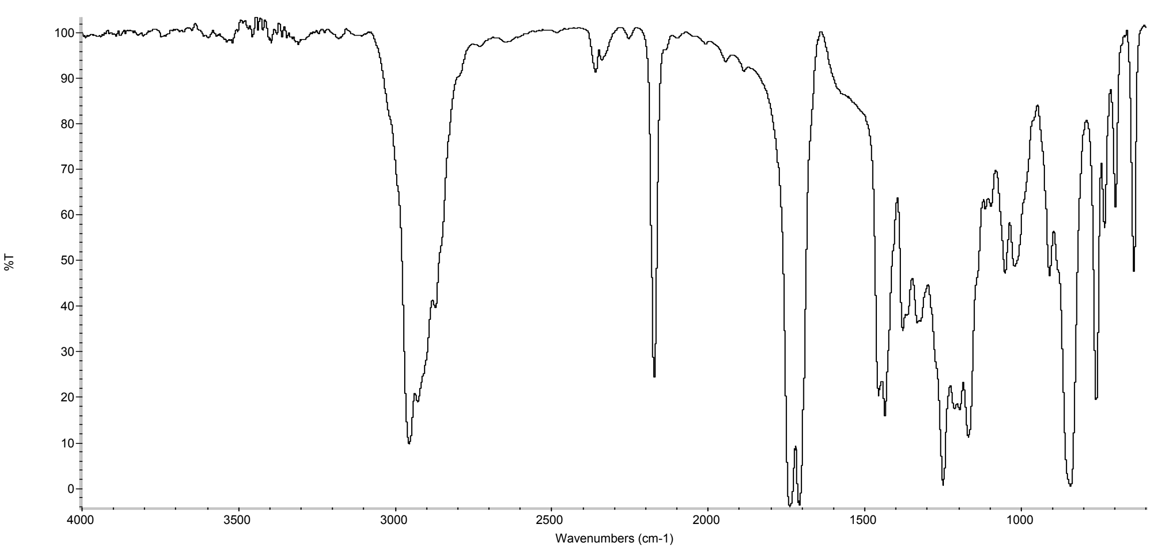
%T
100
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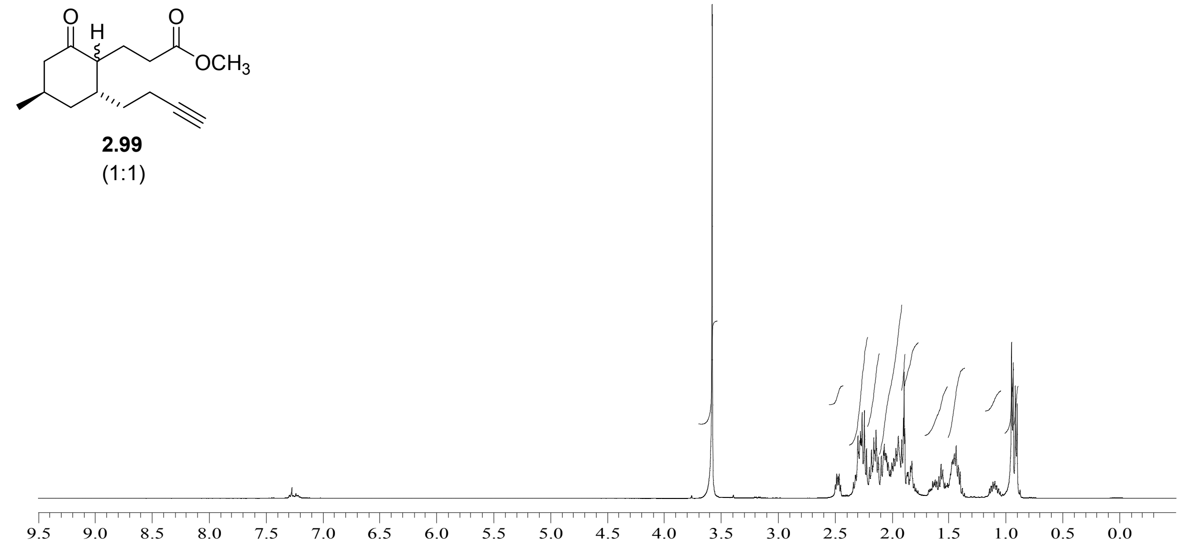
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)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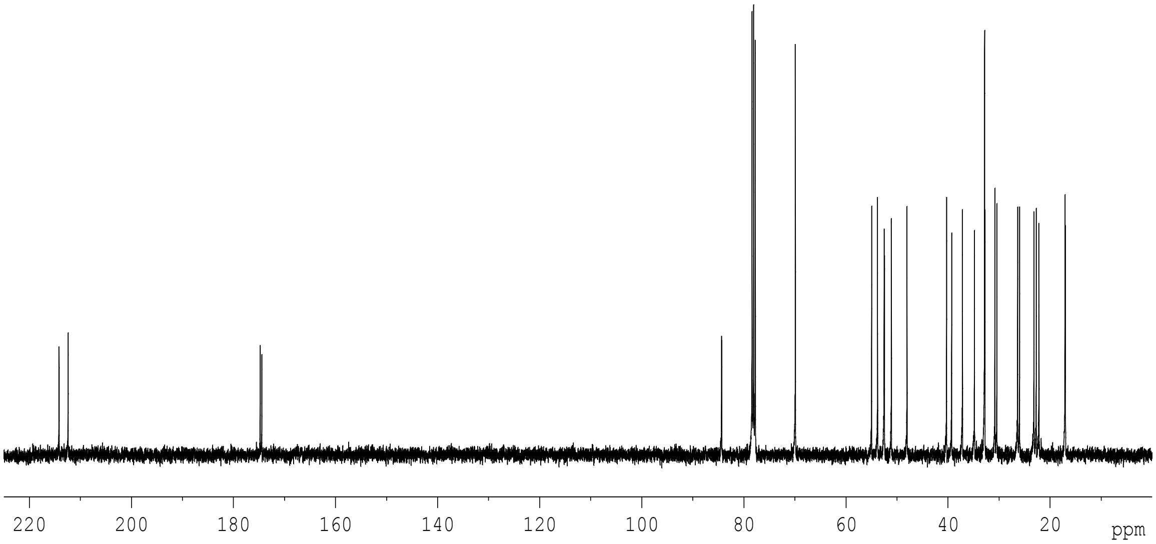
0.0

2.99
(1:1)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120
100
80
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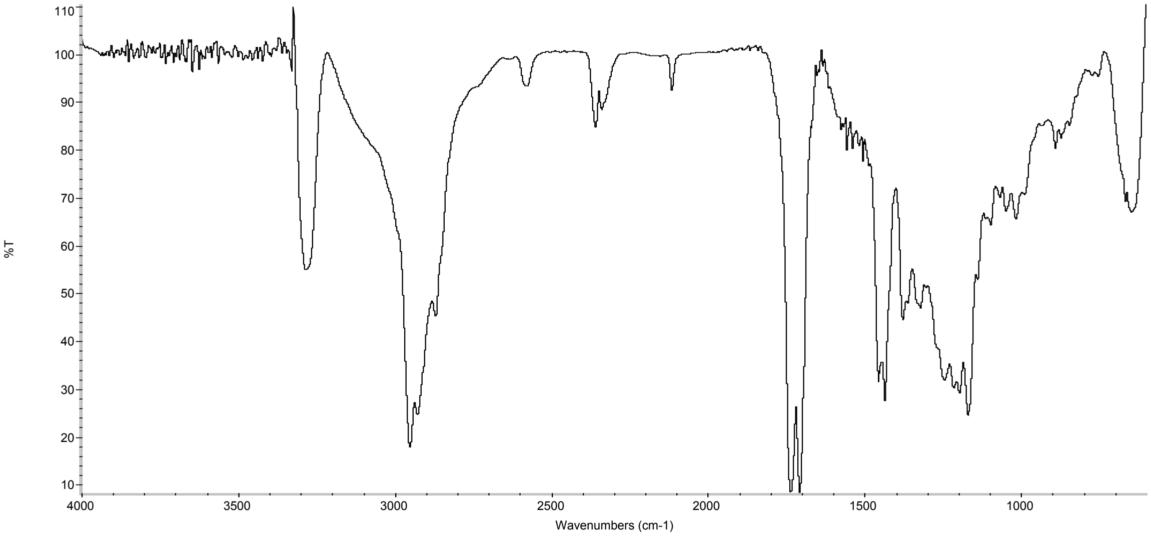
20
ppm


110
100
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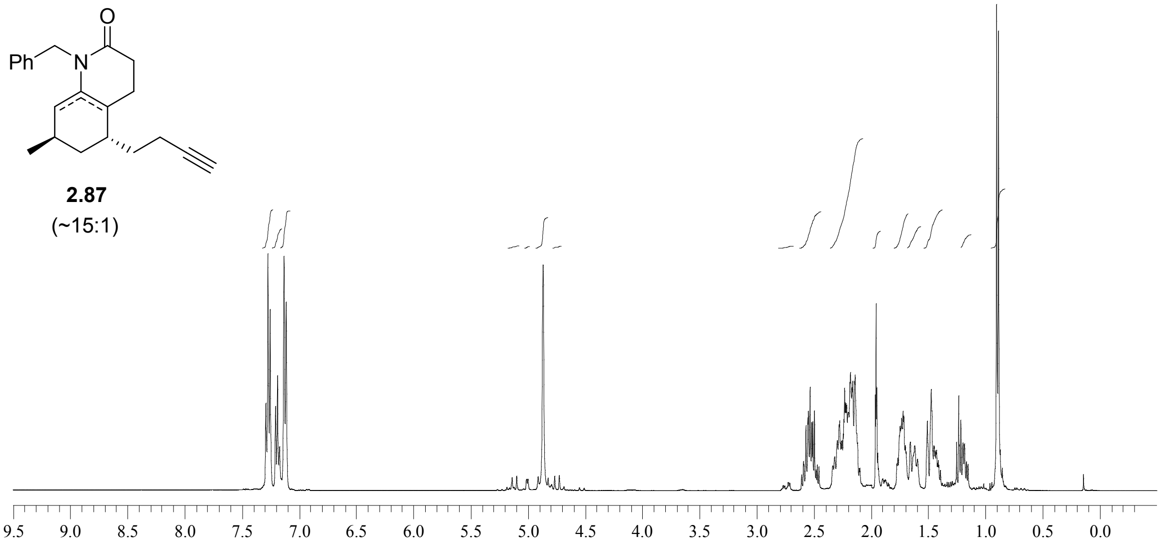
1000
Wavenumbers (cm-1)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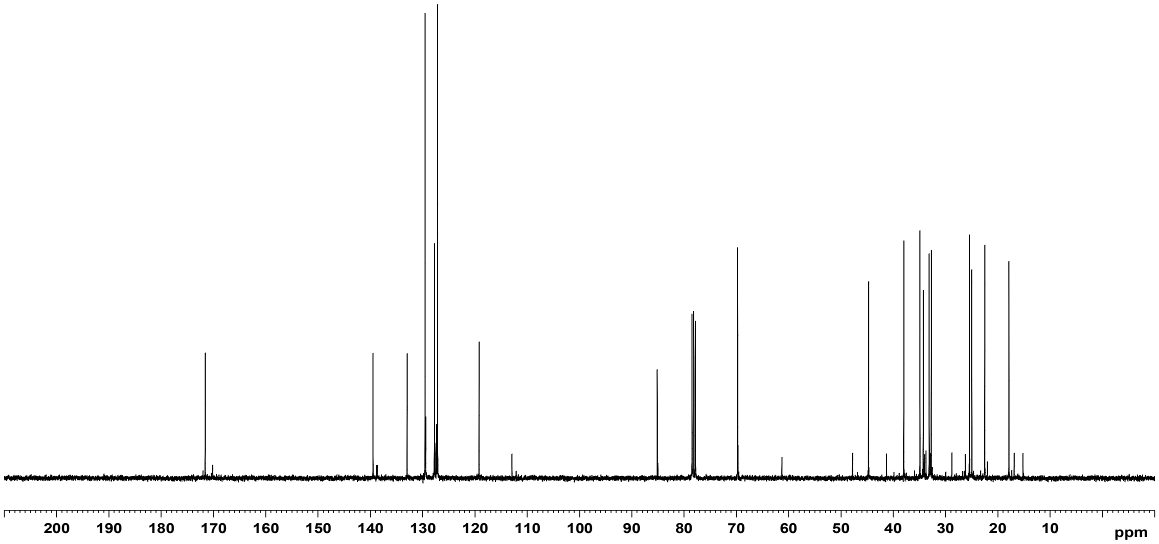
2.87
(~15:1)


200
190
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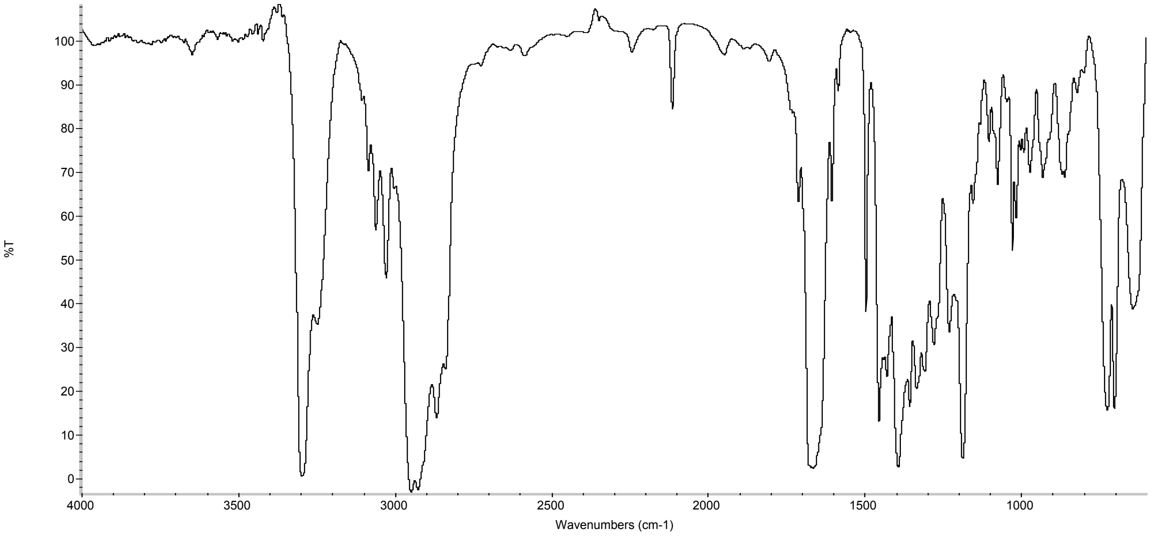
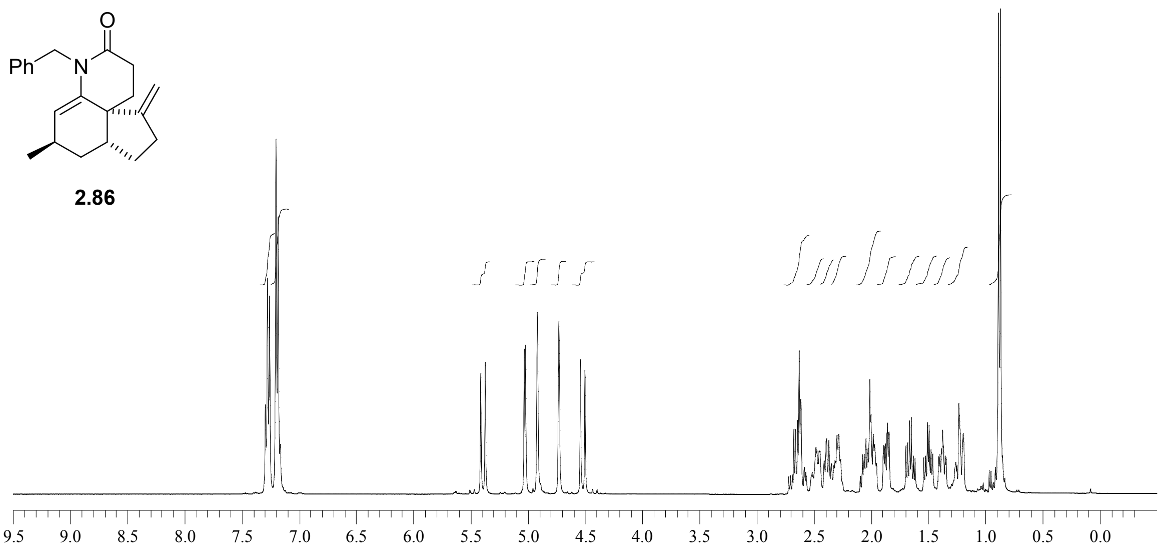
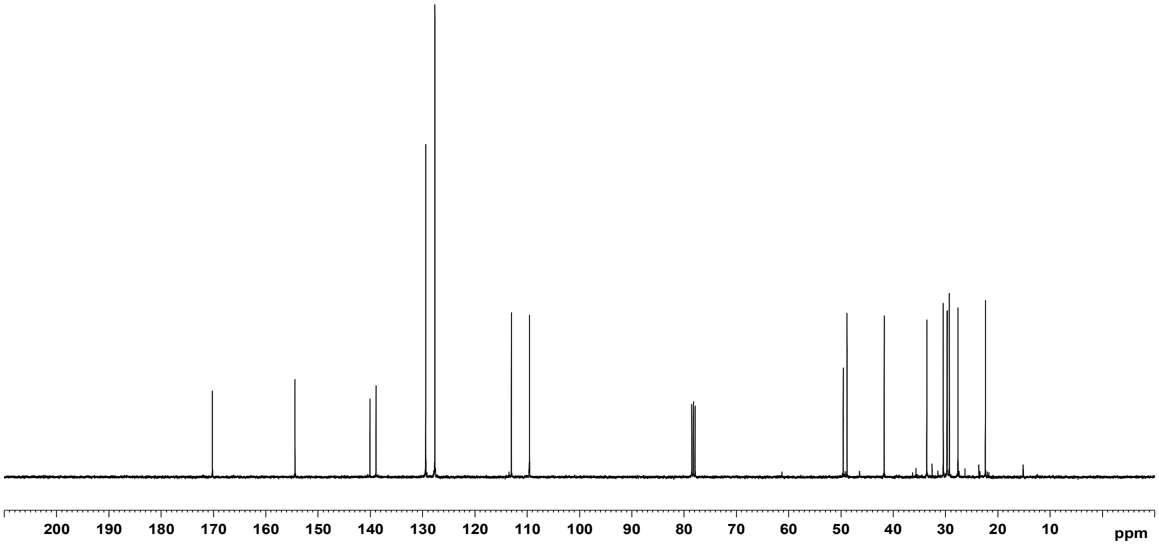
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


2.86
O
N
Ph
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


200
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180
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150
140
130
120
110
100
90
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70
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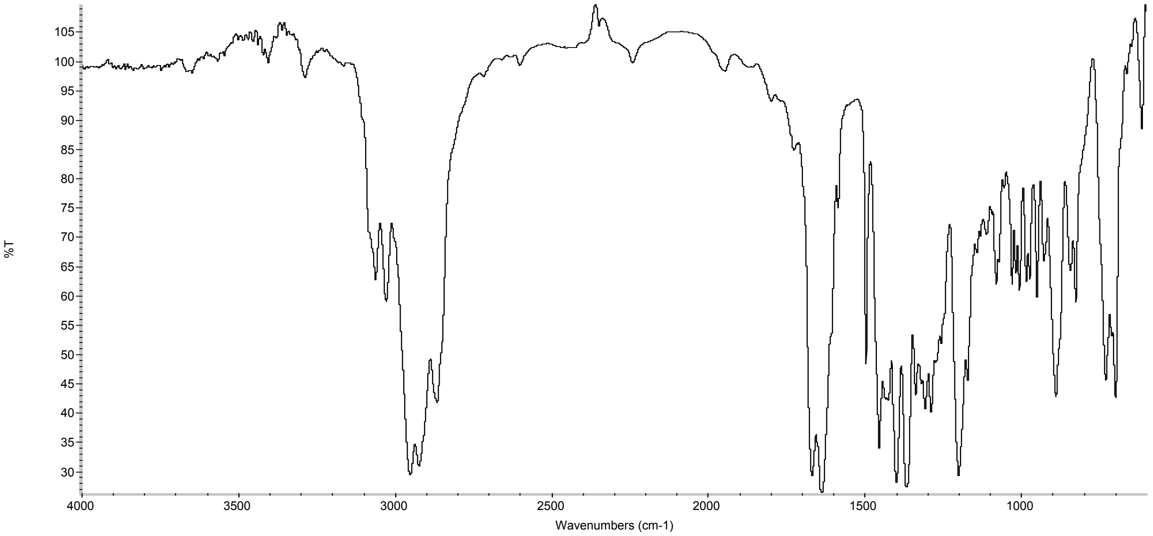
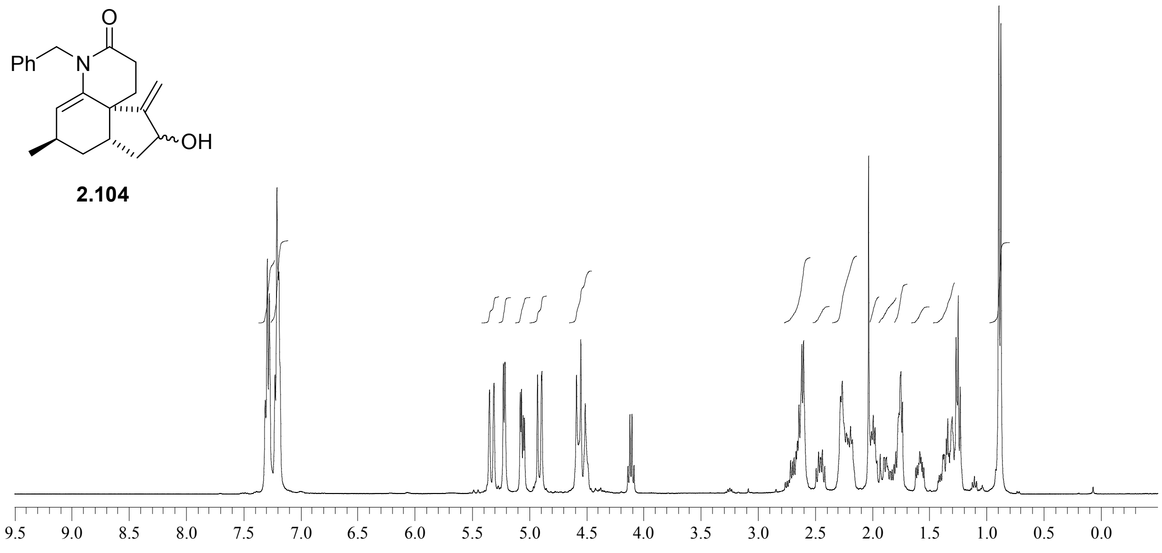
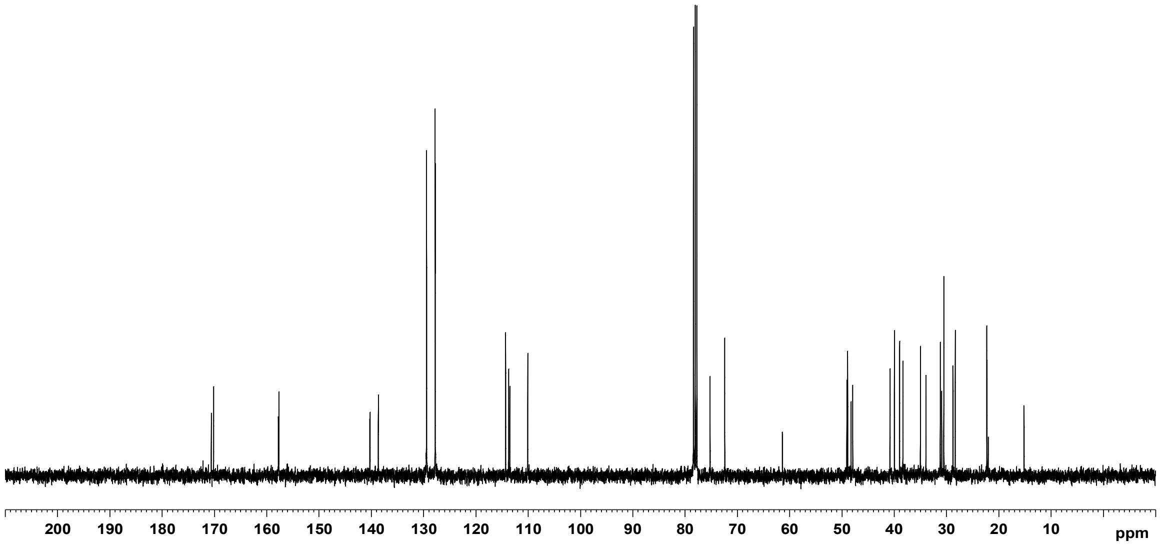
30
20
10
ppm


%T
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
Ph
N
OH
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.104


200
190
180
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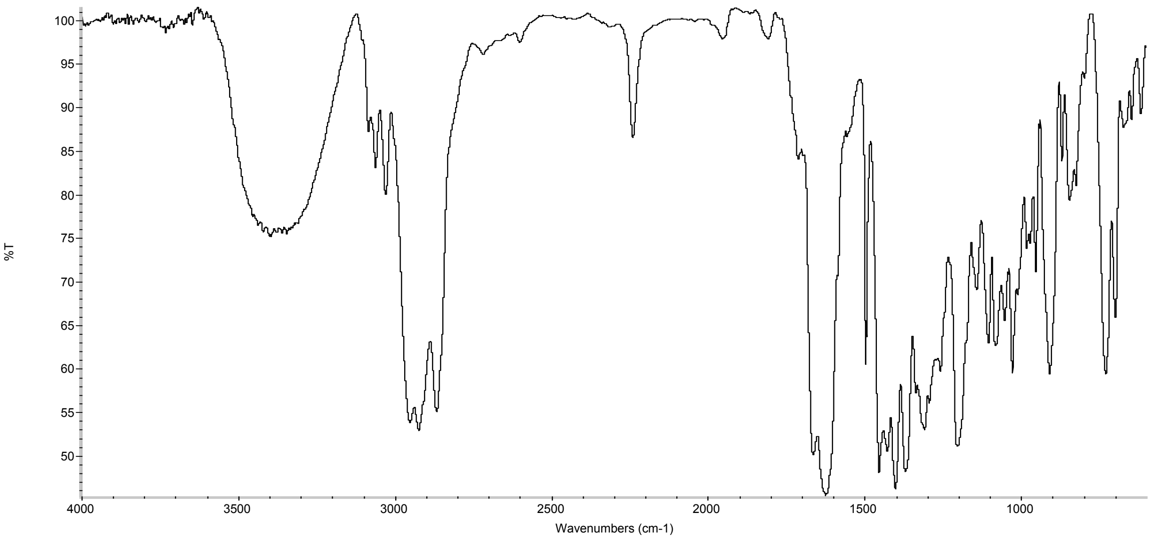
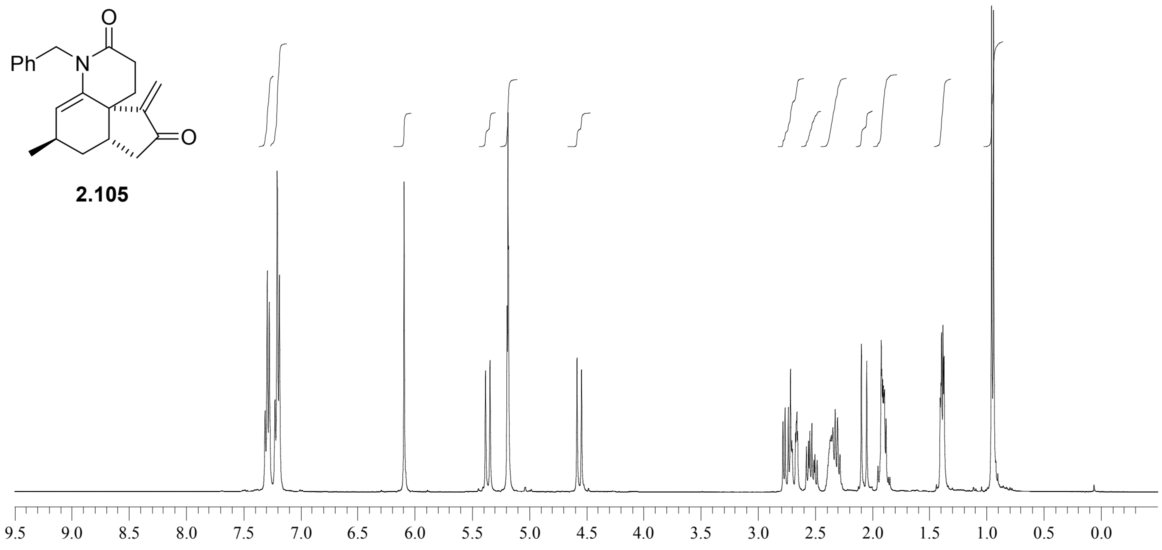
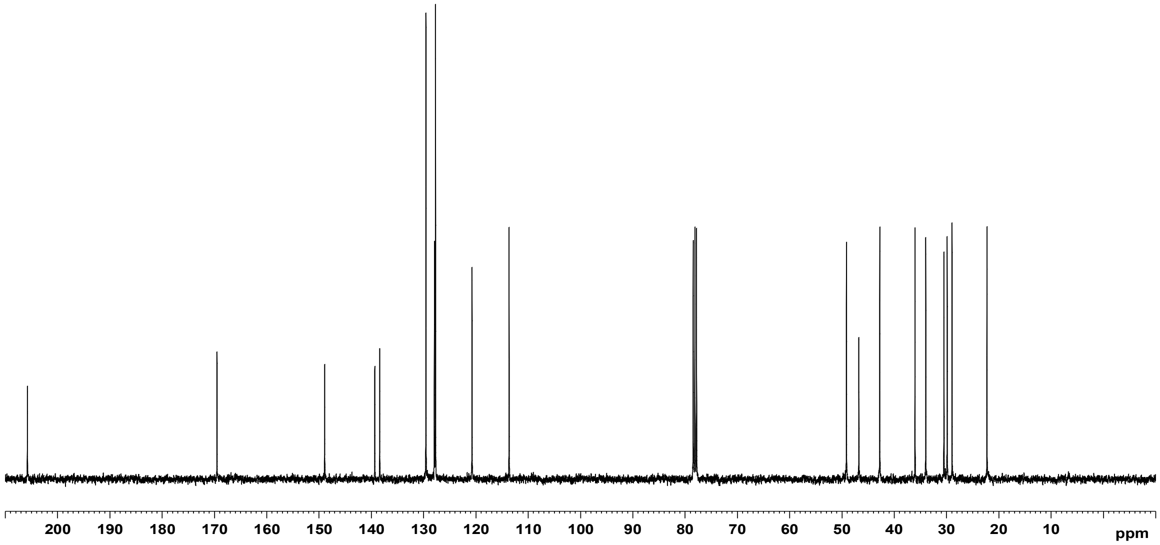
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


100
95
90
85
80
75
70
65
60
55
50
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
Ph
N
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.105


200
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180
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120
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100
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70
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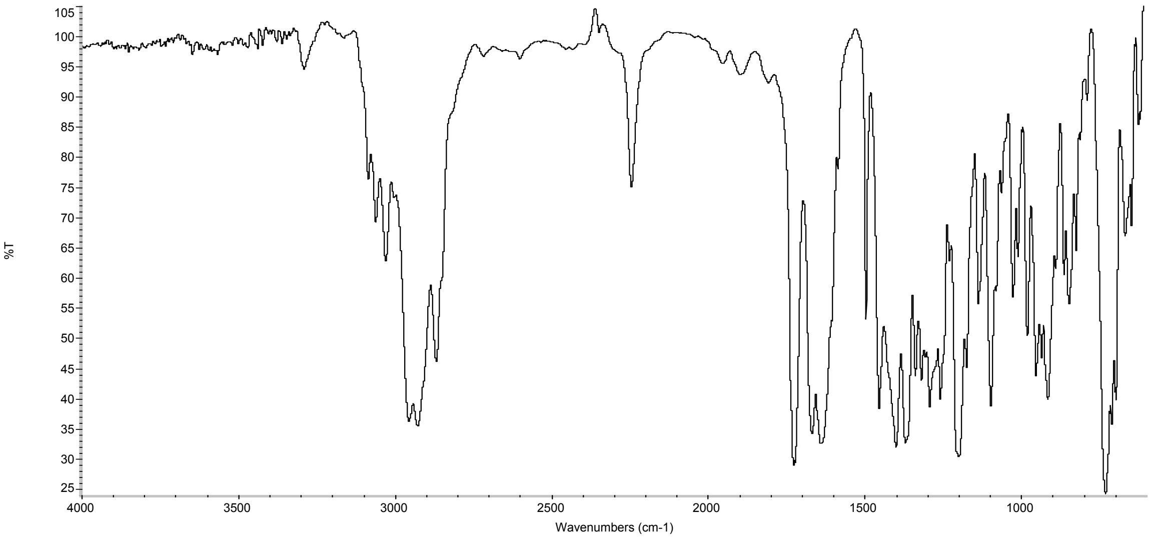
10
ppm


%T
105
100
95
90
85
80
75
70
65
60
55
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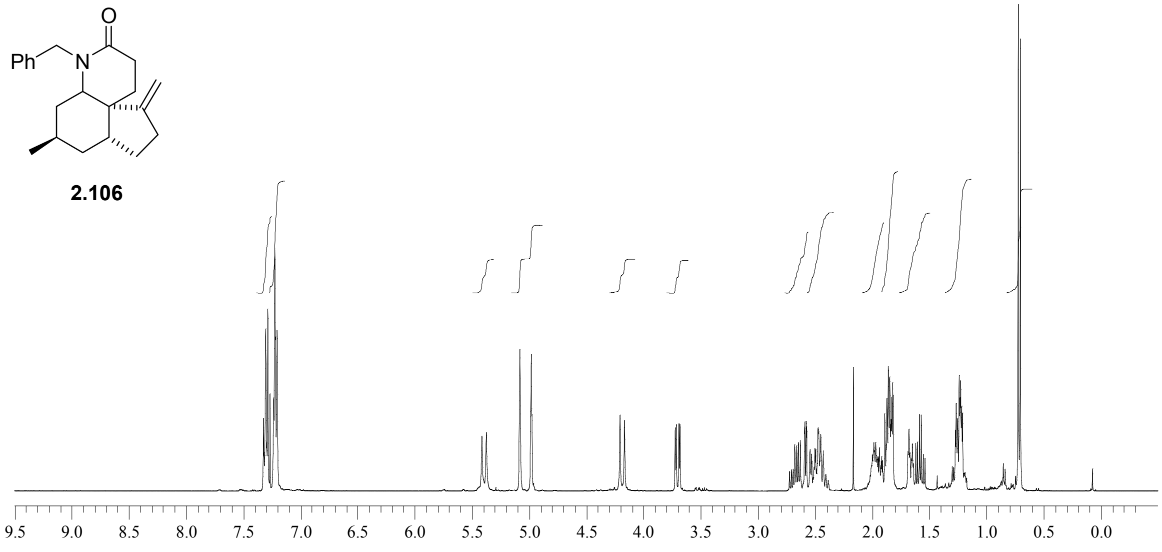
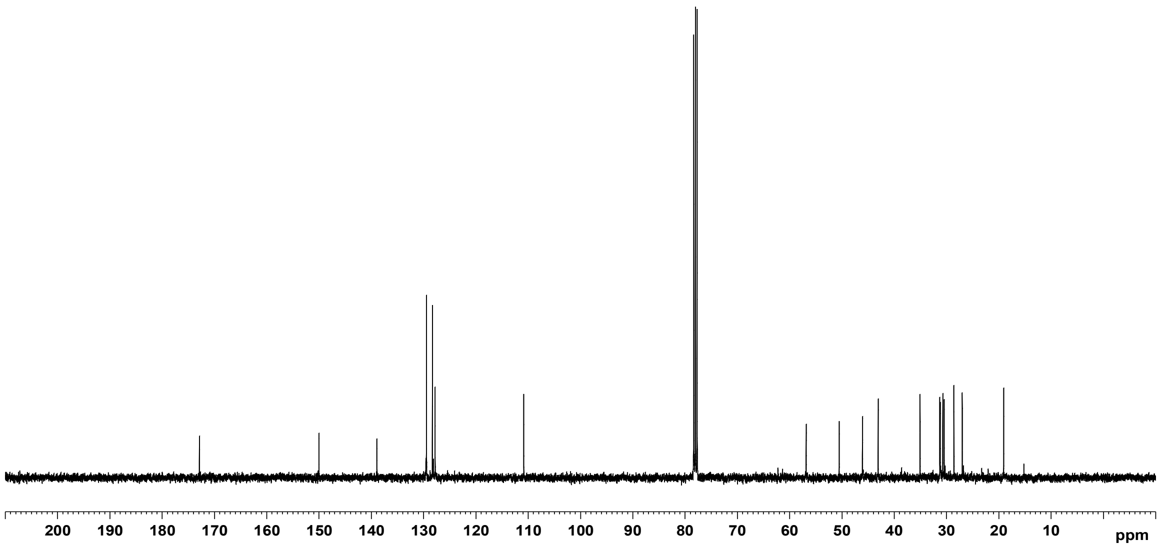
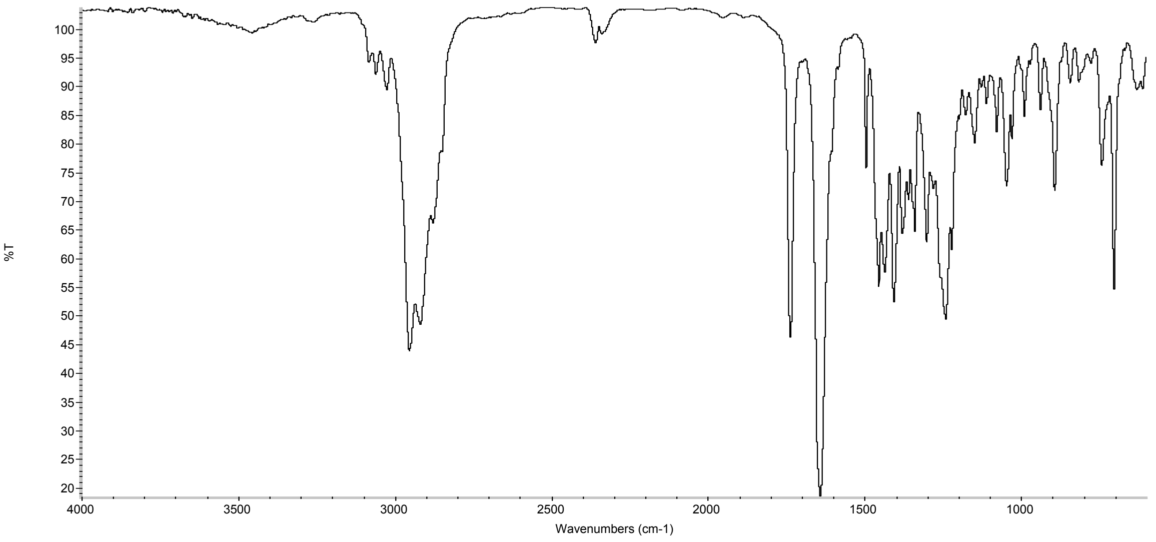
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
Ph
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.106


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
95
90
85
80
75
70
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55
50
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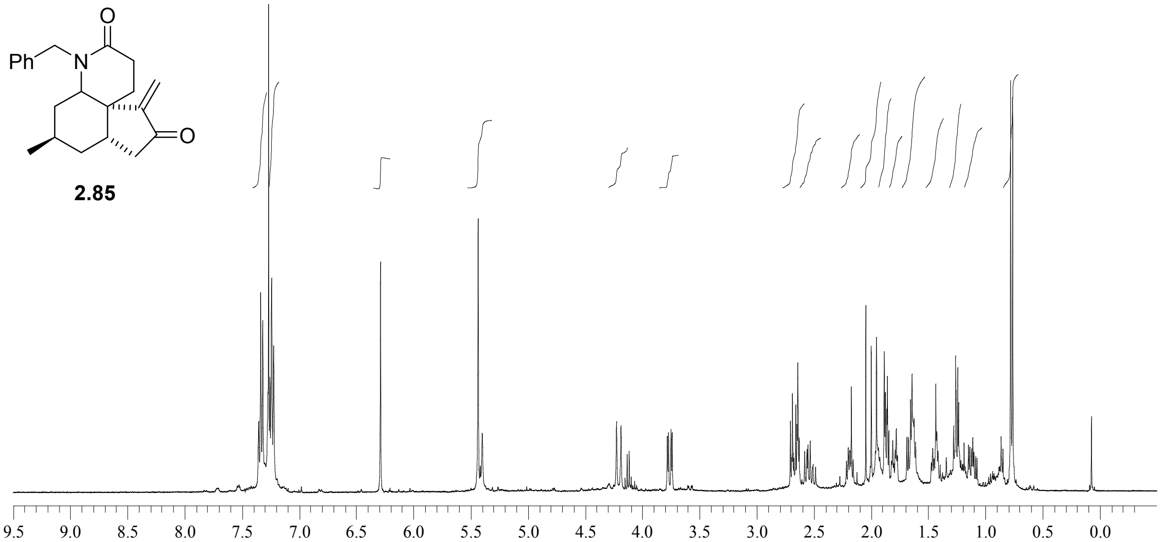
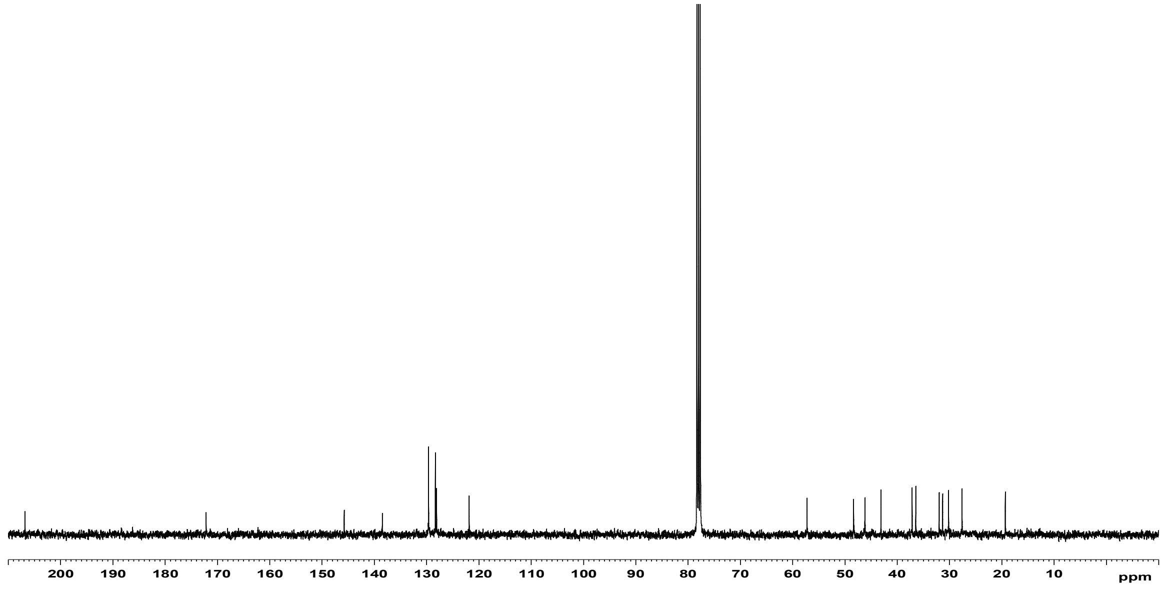
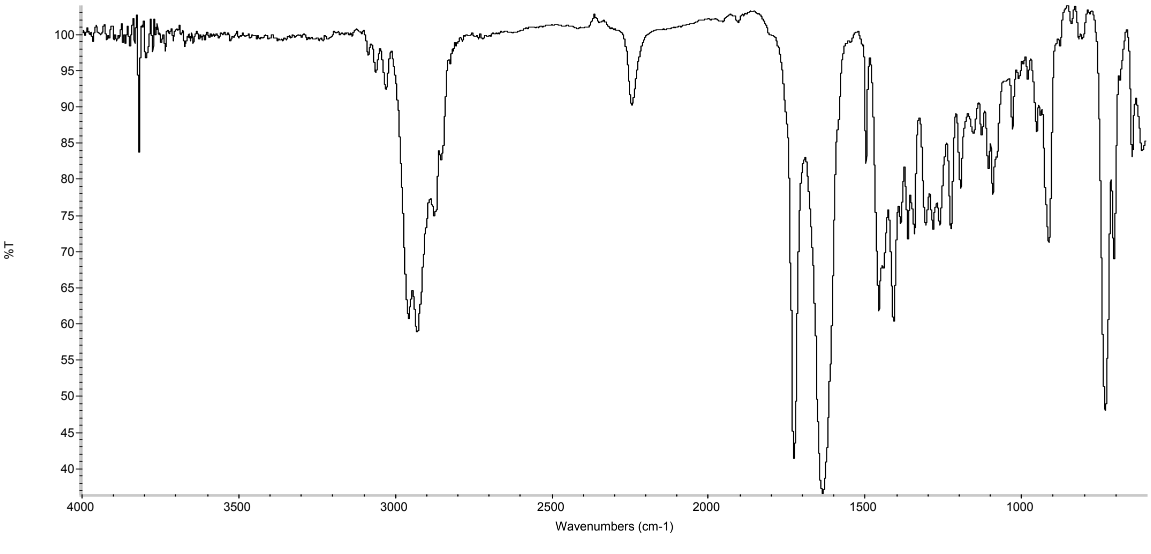
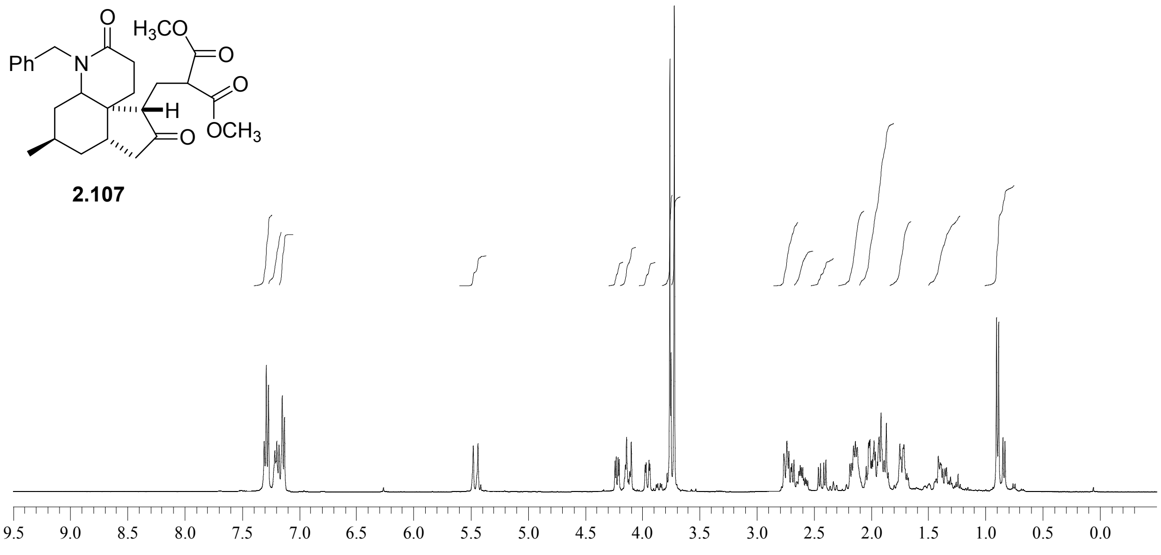
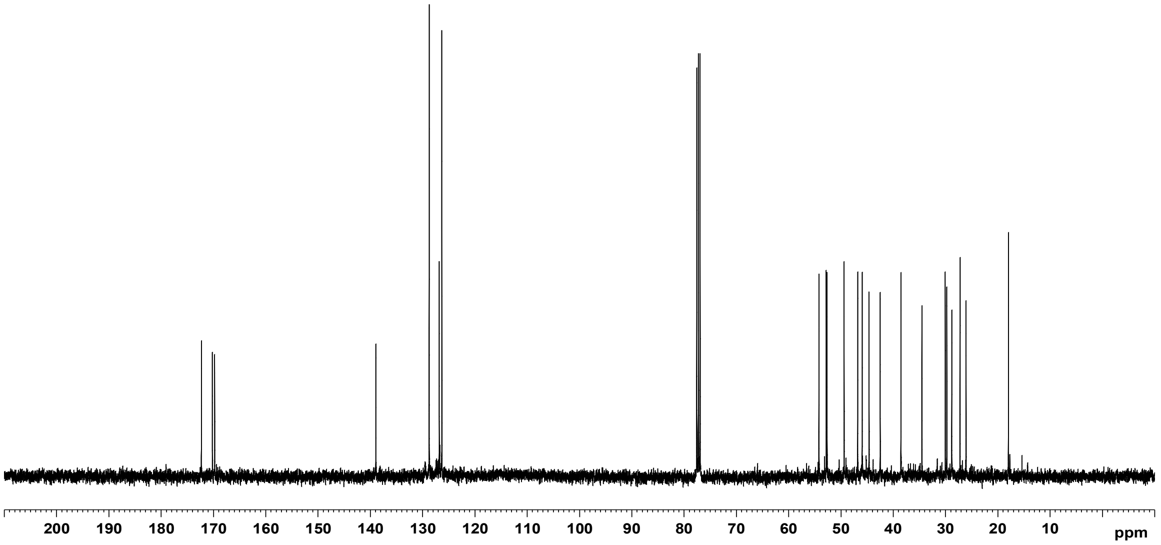
40
35
30
25
20
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

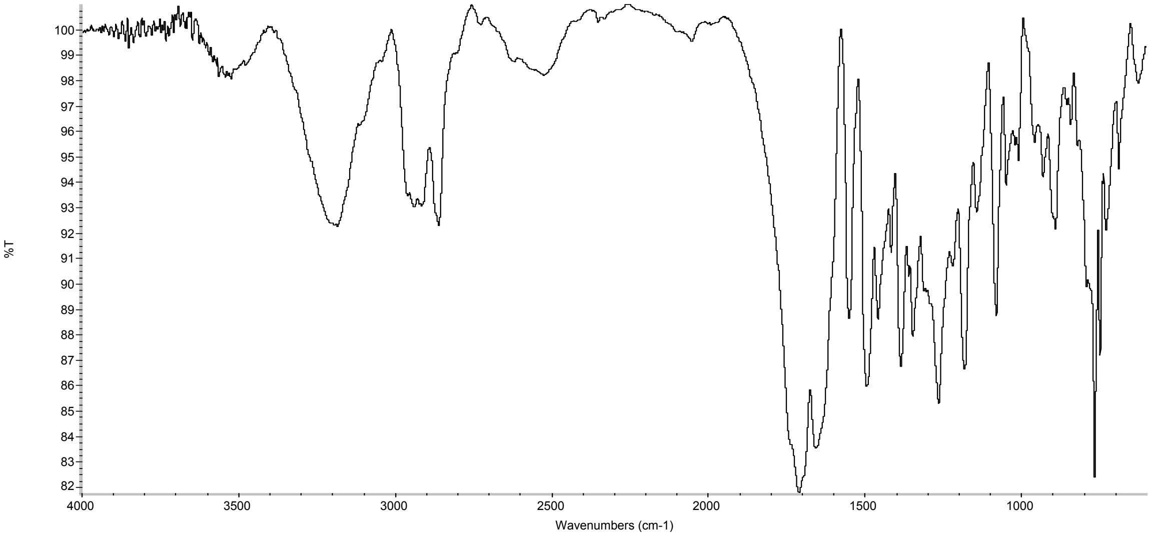

Ph
N
O
O
2.85
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

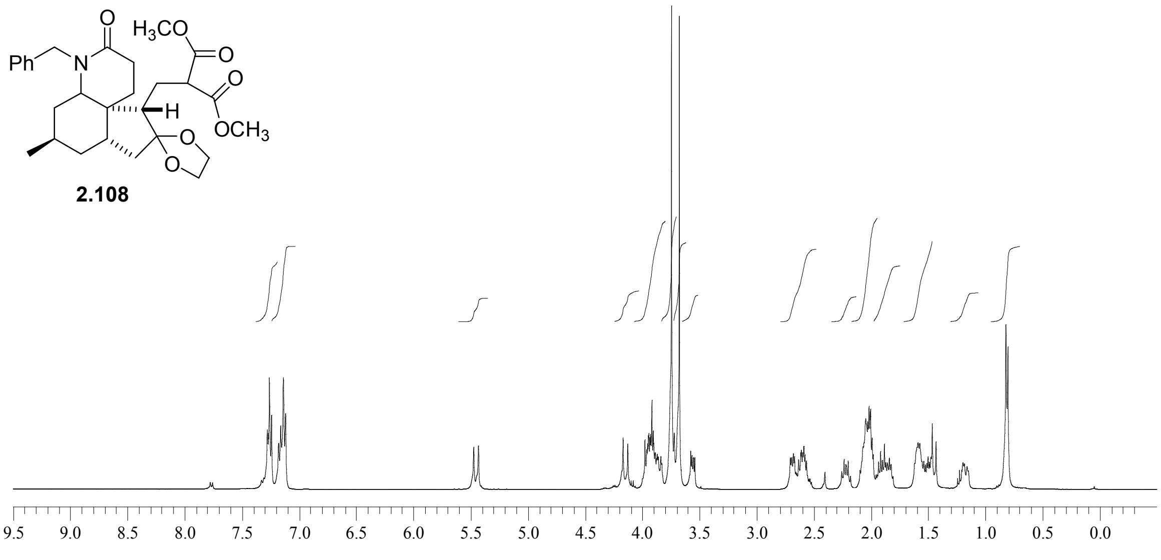

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

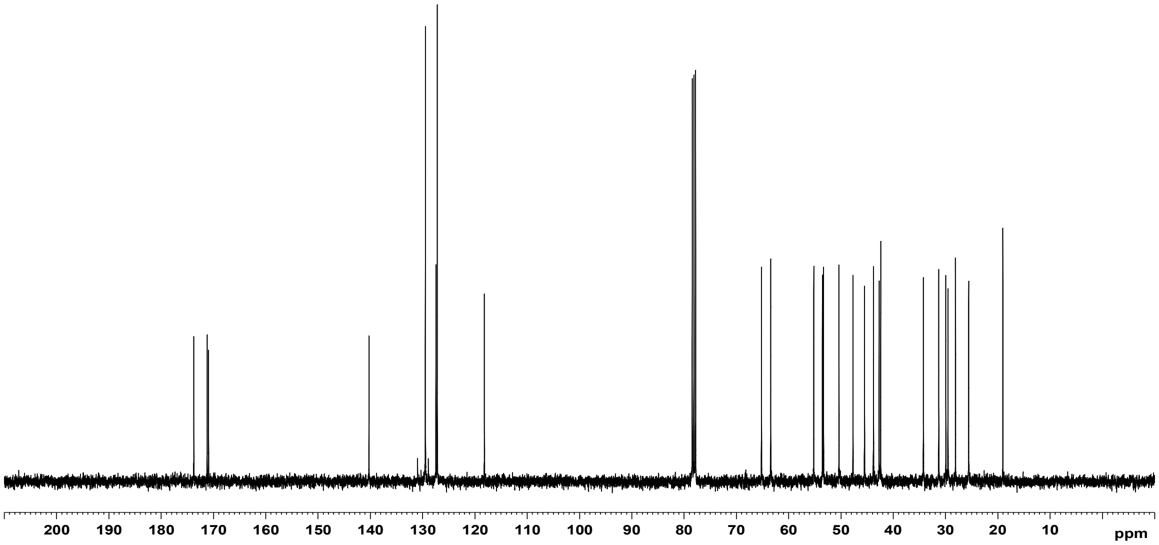

O
H3CO
O
Ph
N
H
O
O
OCH3
2.107
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

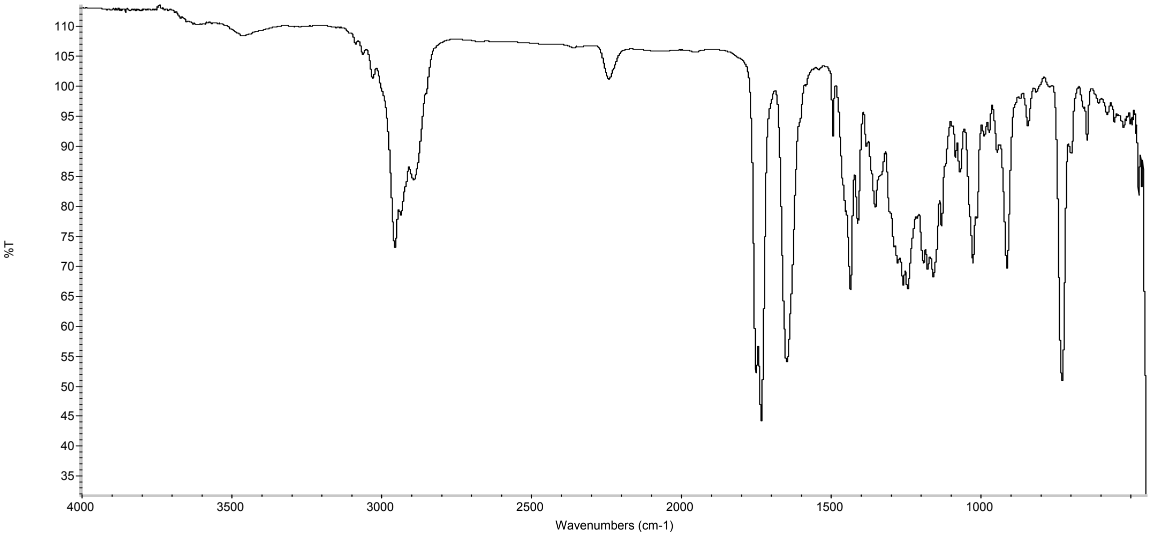

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

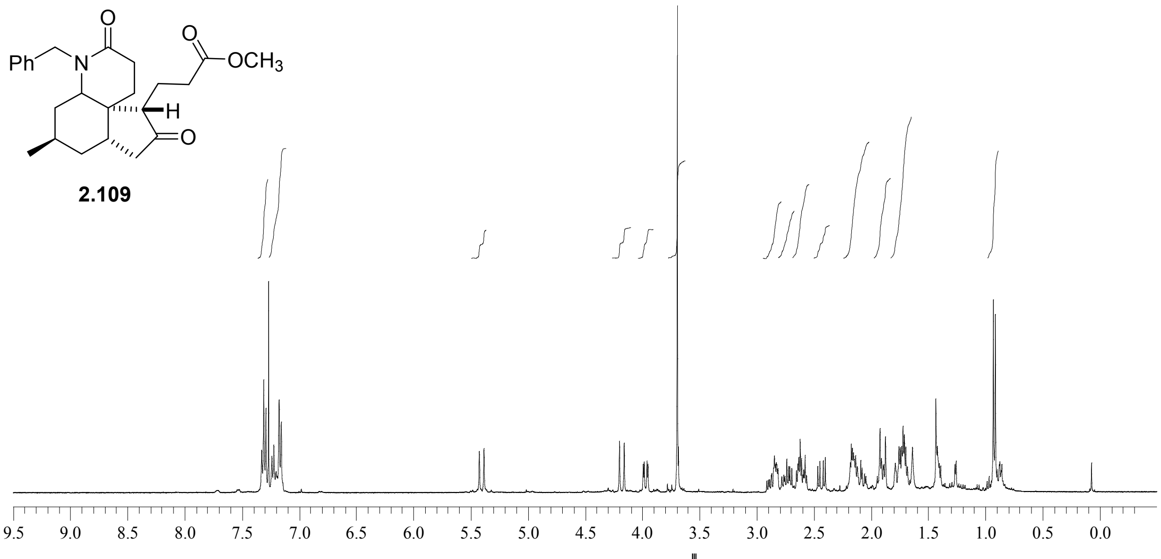

%T
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


Ph
N
O
H3CO
O
O
OCH3
H
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.108

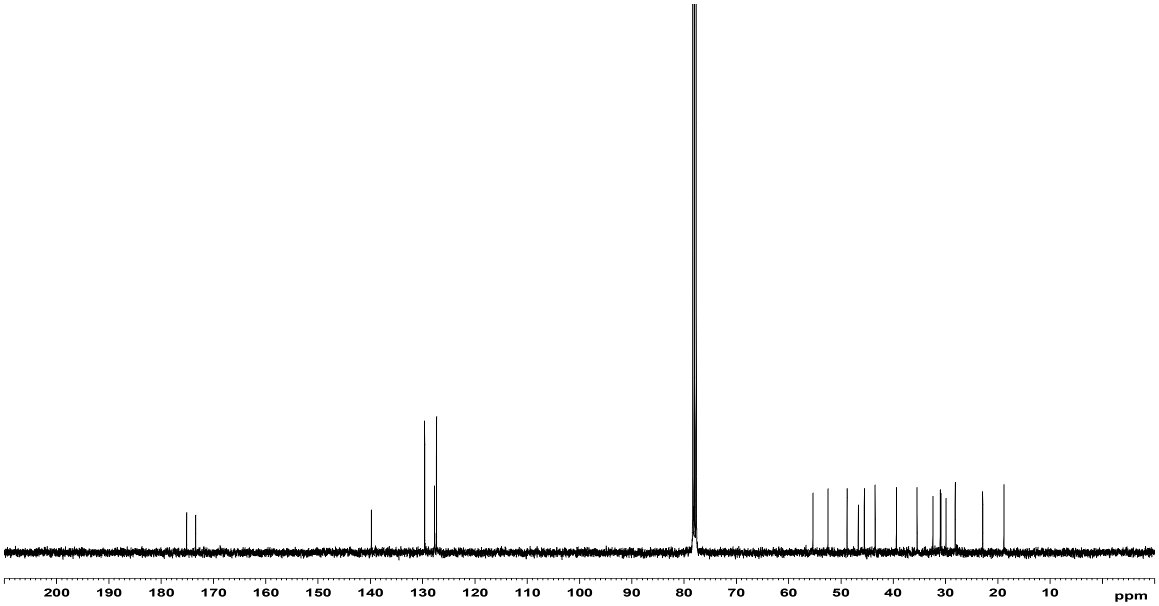

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

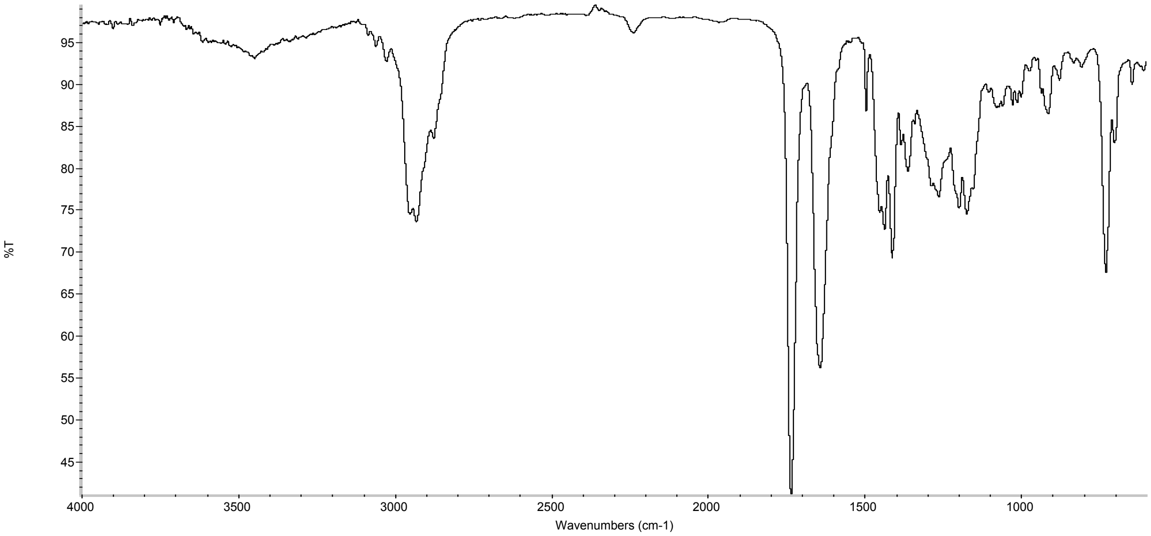


Ph
N
O
O
OCH3
H
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

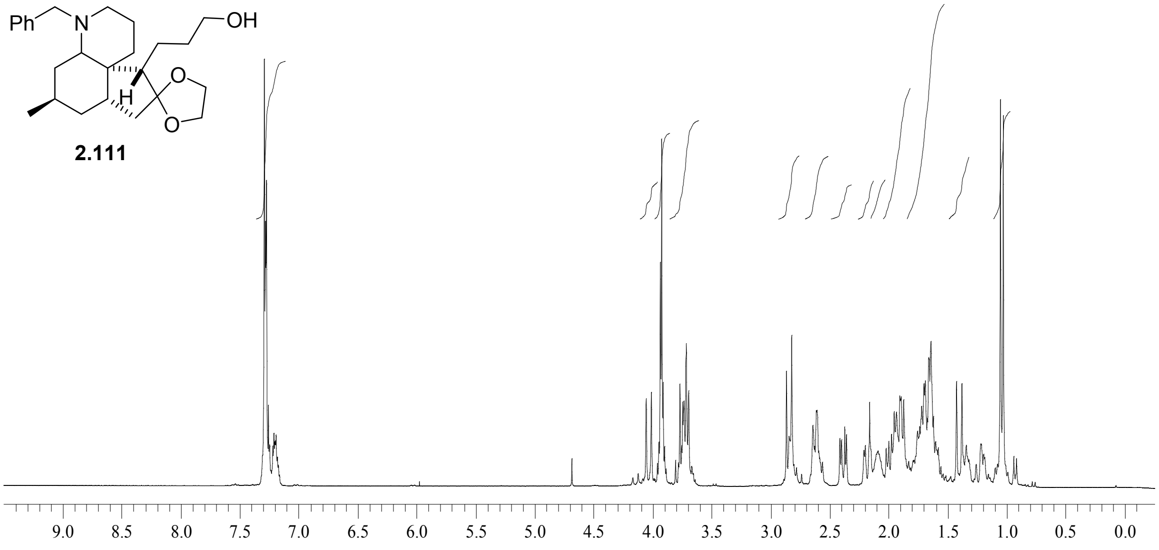
2.109



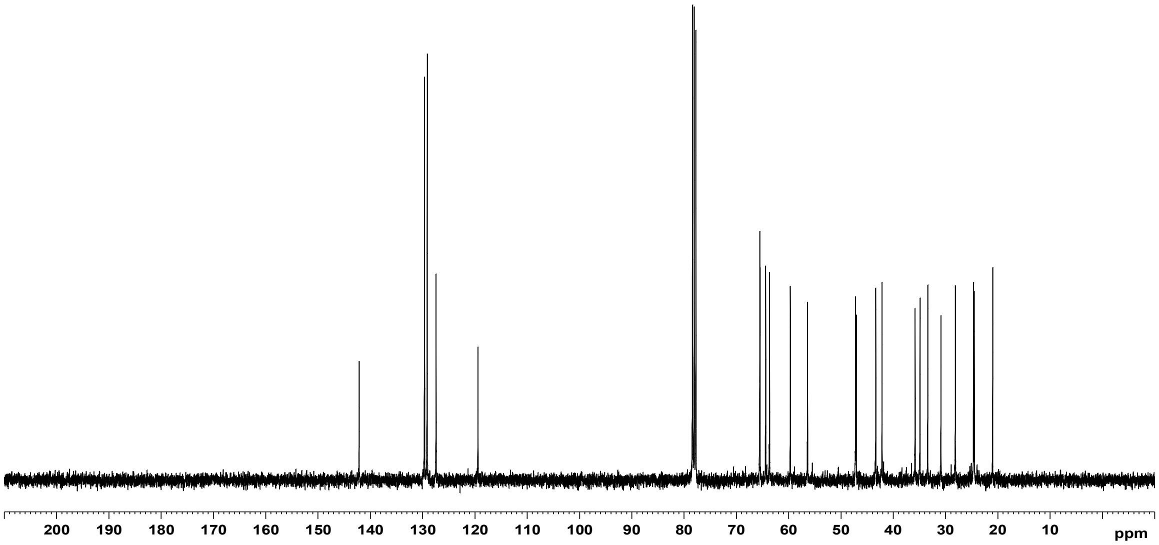
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

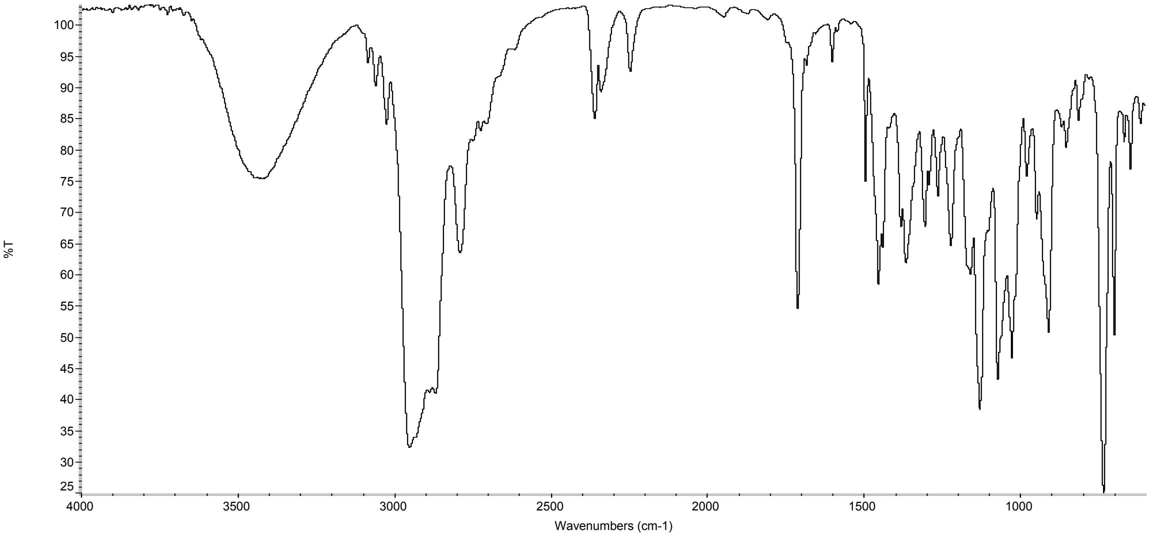


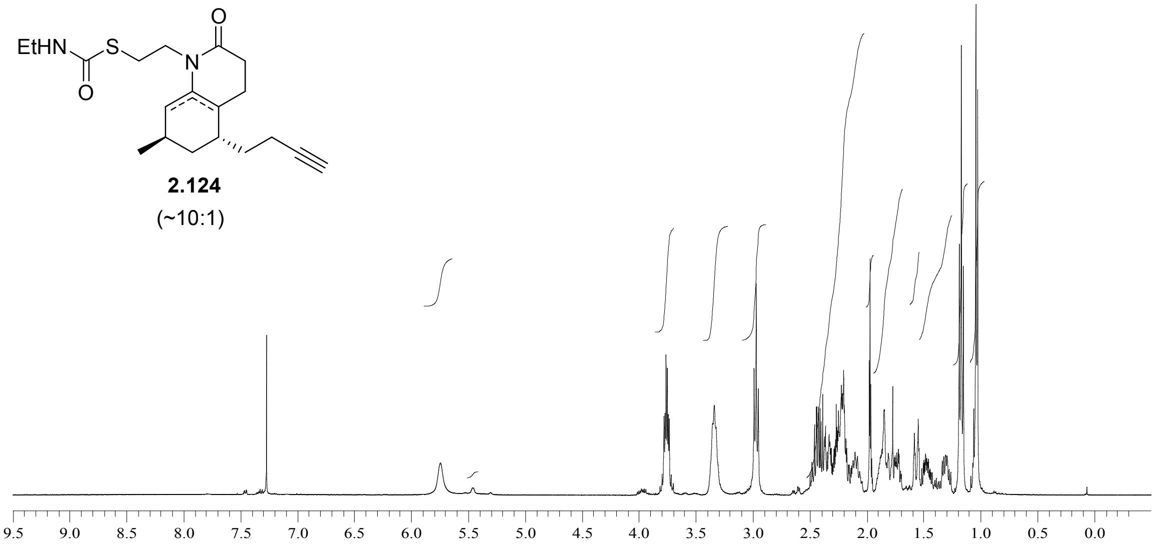
%T
95
90
85
80
75
70
65
60
55
50
45
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


Ph
N
OH
O
O
H
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.111

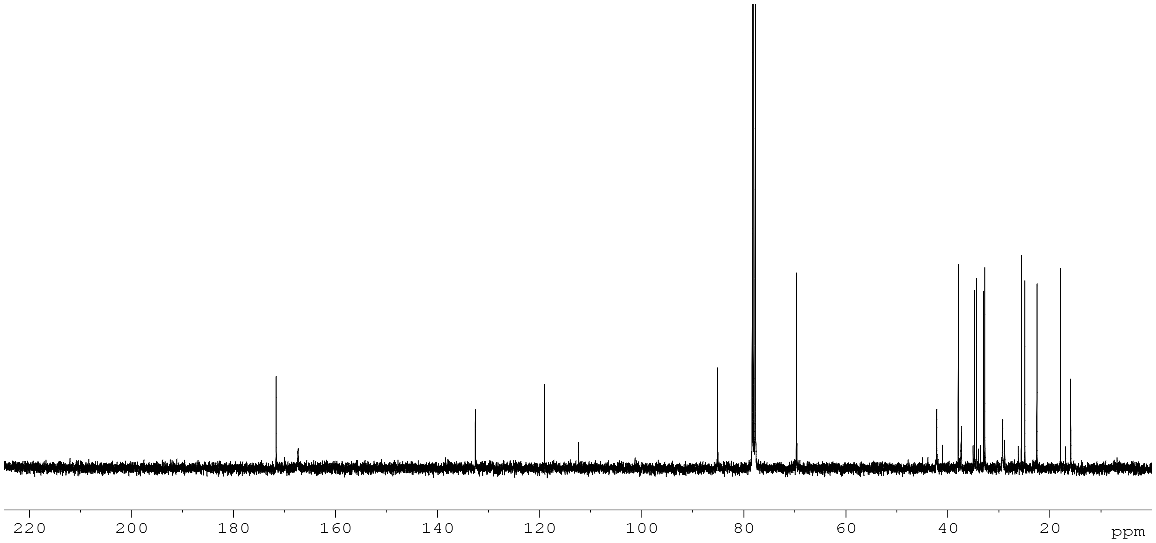

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

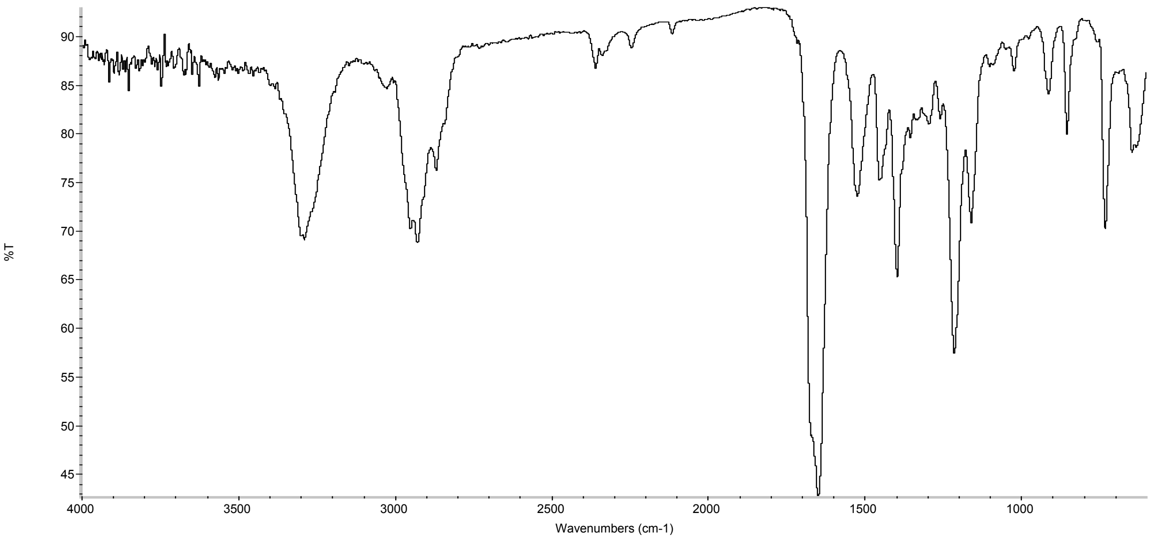

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

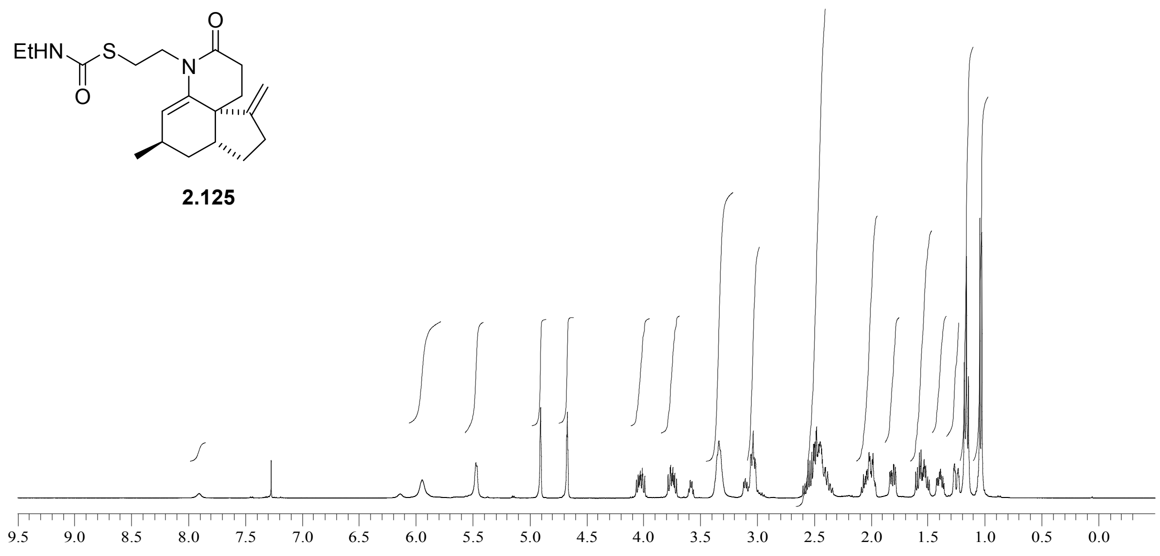

EtHN
S
N
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.124

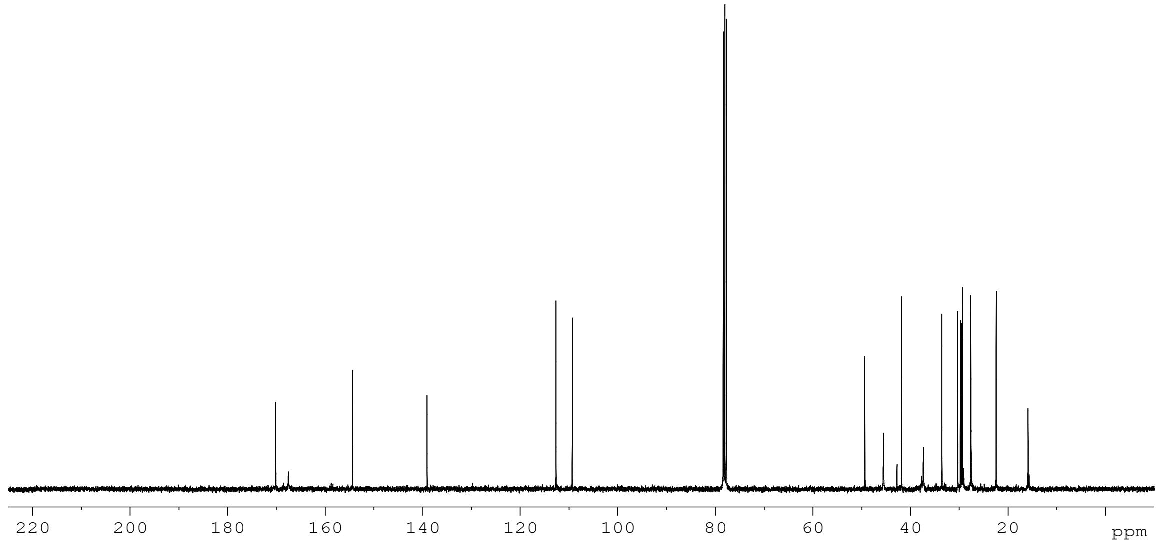
(~10:1)


220
200
180
160
140
120
100
80
60
40
20
ppm


%T
90
85
80
75
70
65
60
55
50
45
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


EtHN
S
N
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.125


220
200
180
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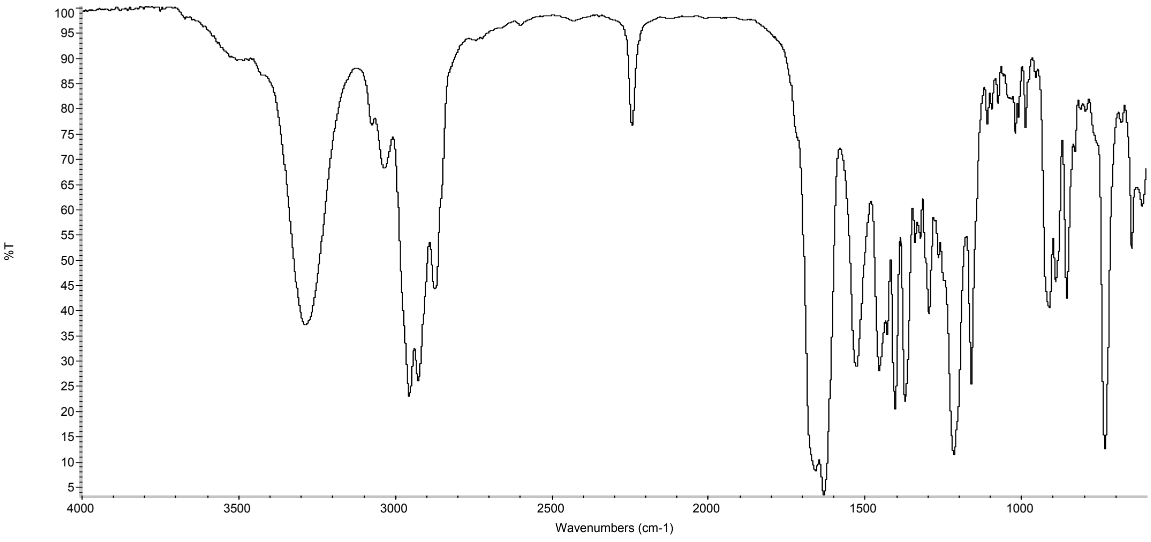
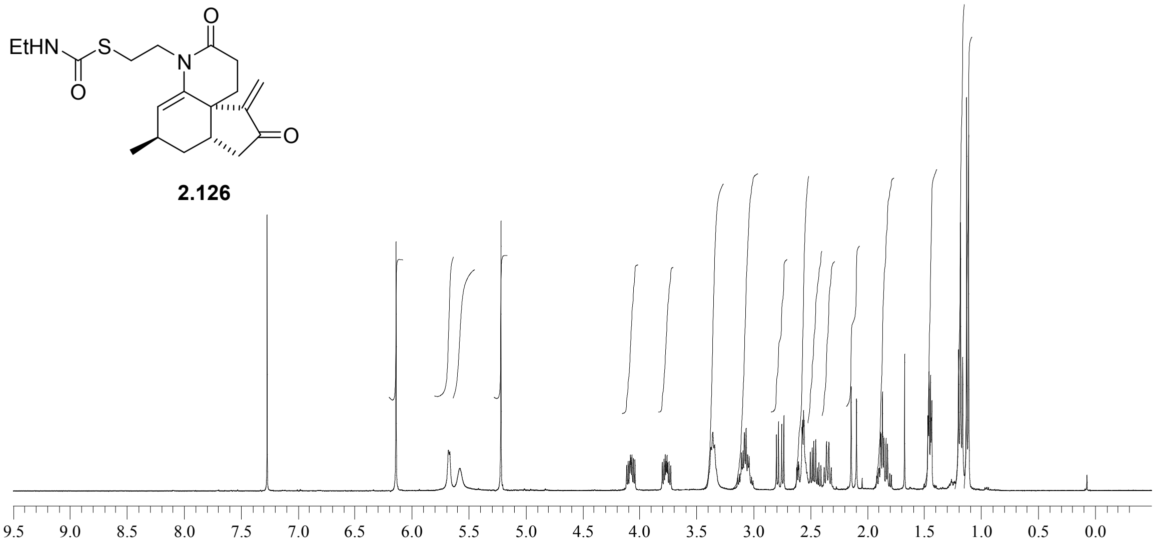
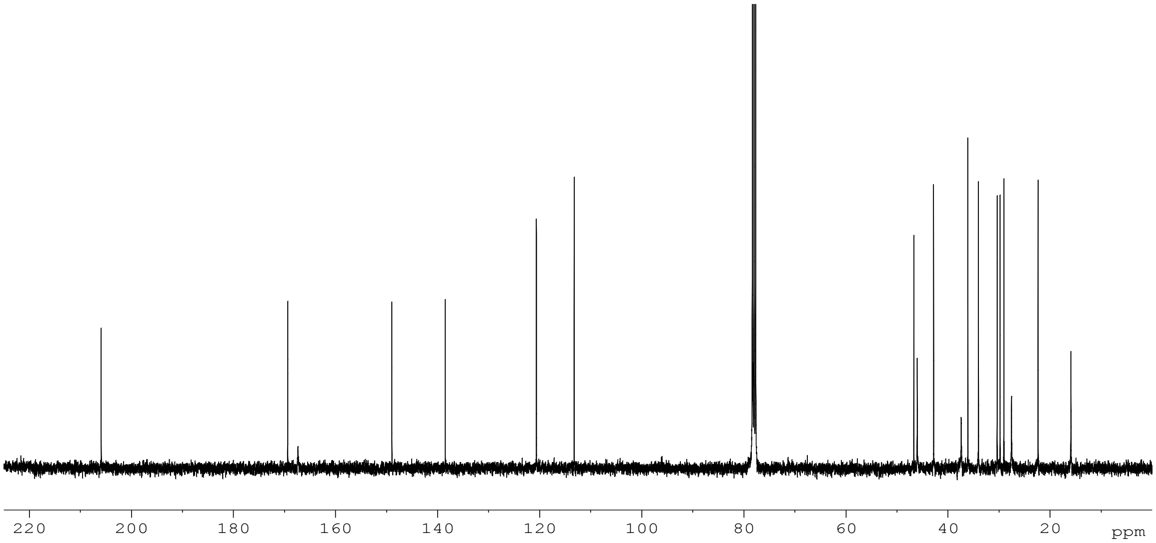
140
120
100
80
60
40
20
ppm


%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

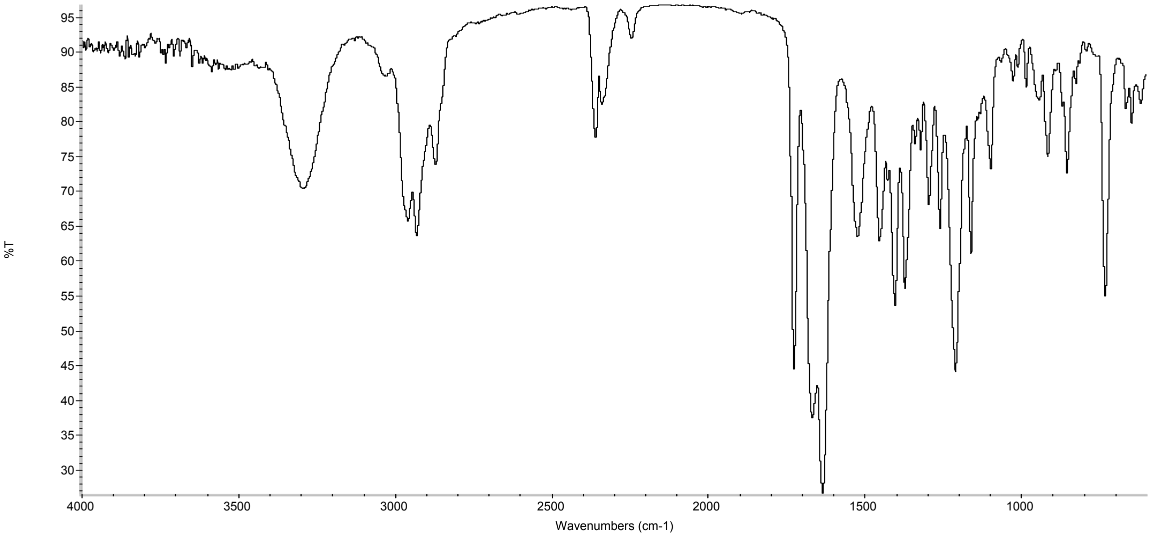


2.126

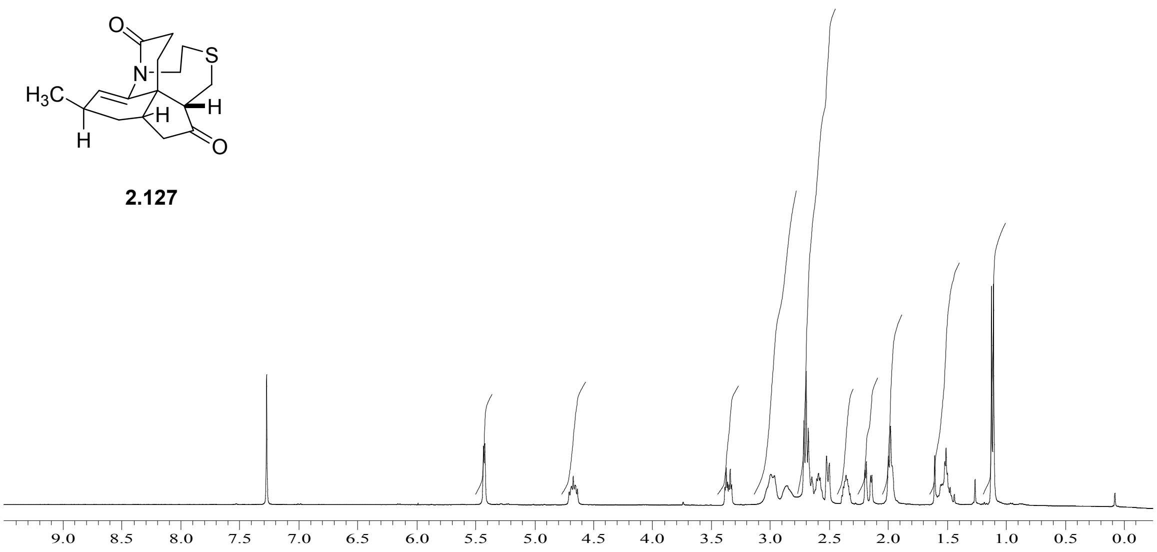
EtHN
S
N
O
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



220
200
180
160
140
120
100
80
60
40
20
ppm

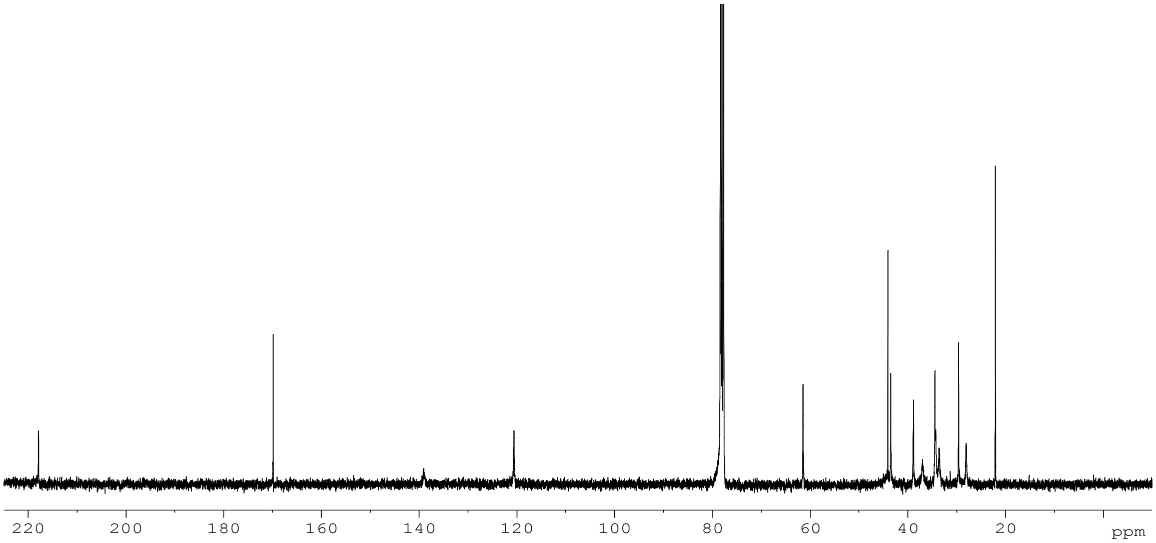


%T
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

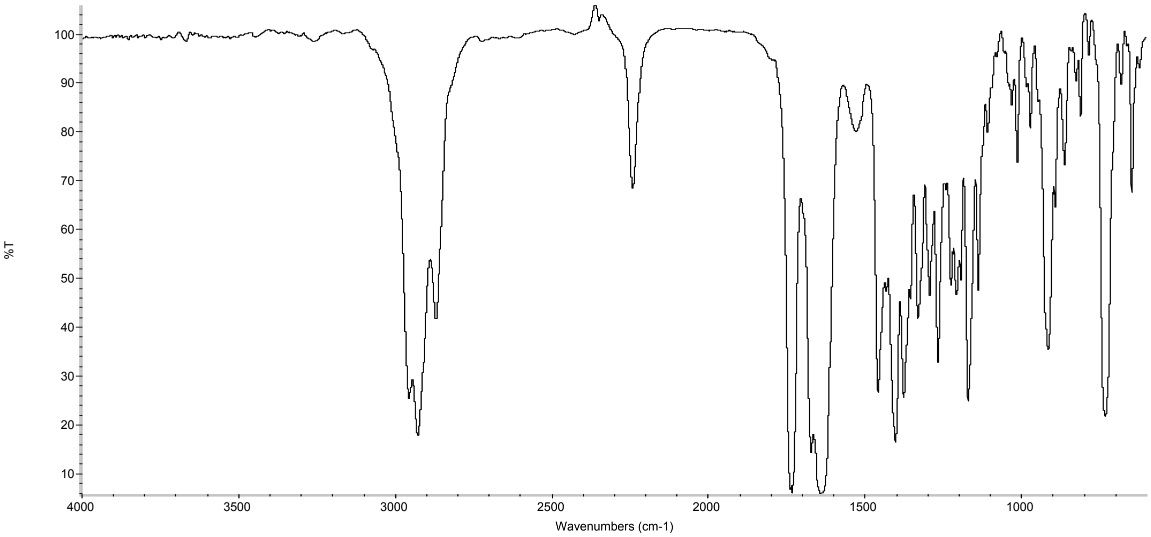


2.127

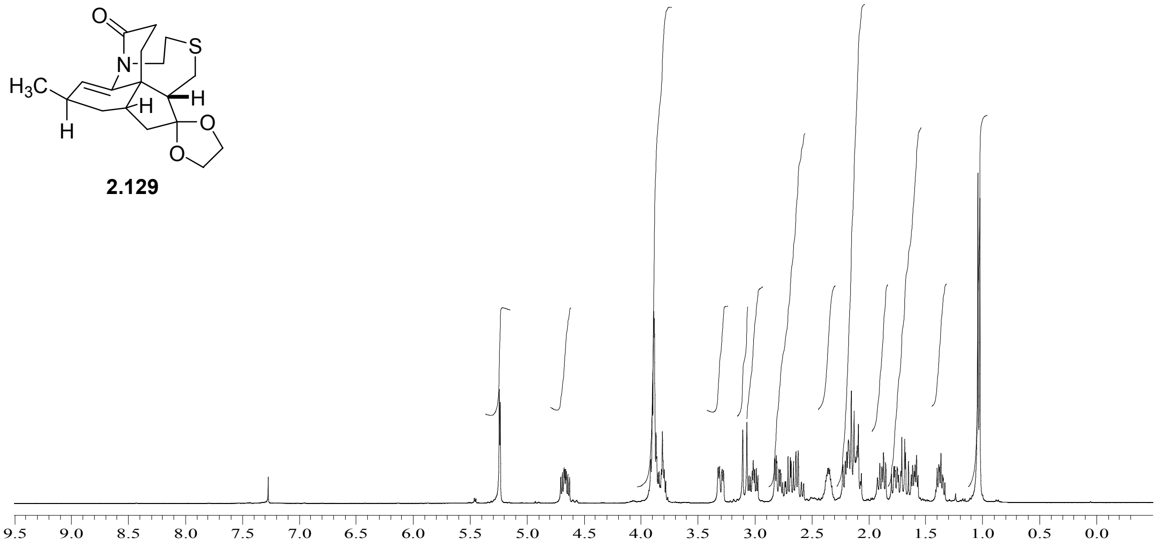
H$_3$C
N
S
H
H
H
O
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



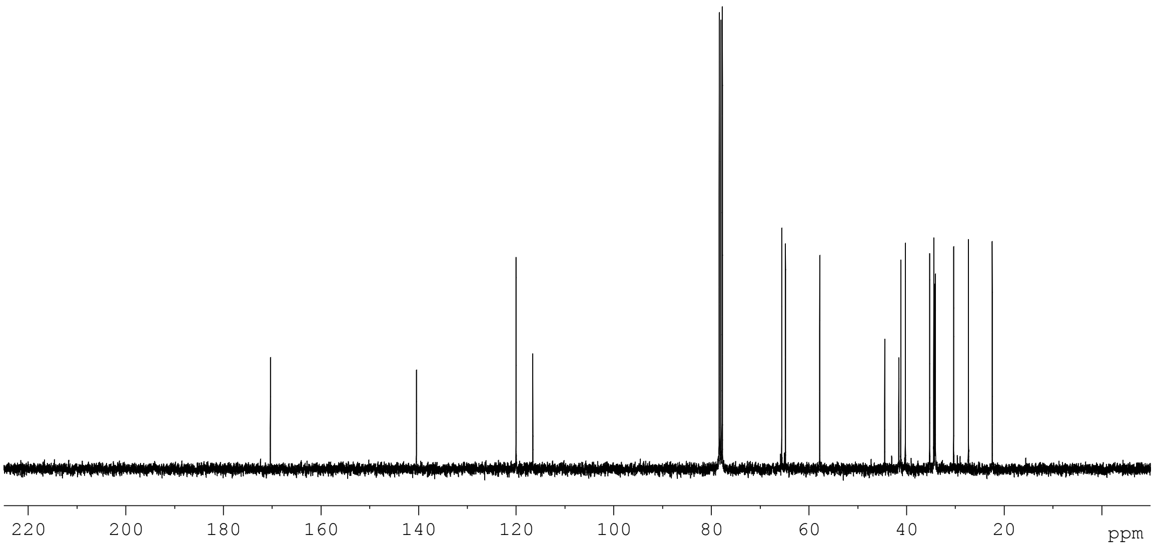
220
200
180
160
140
120
100
80
60
40
20
ppm

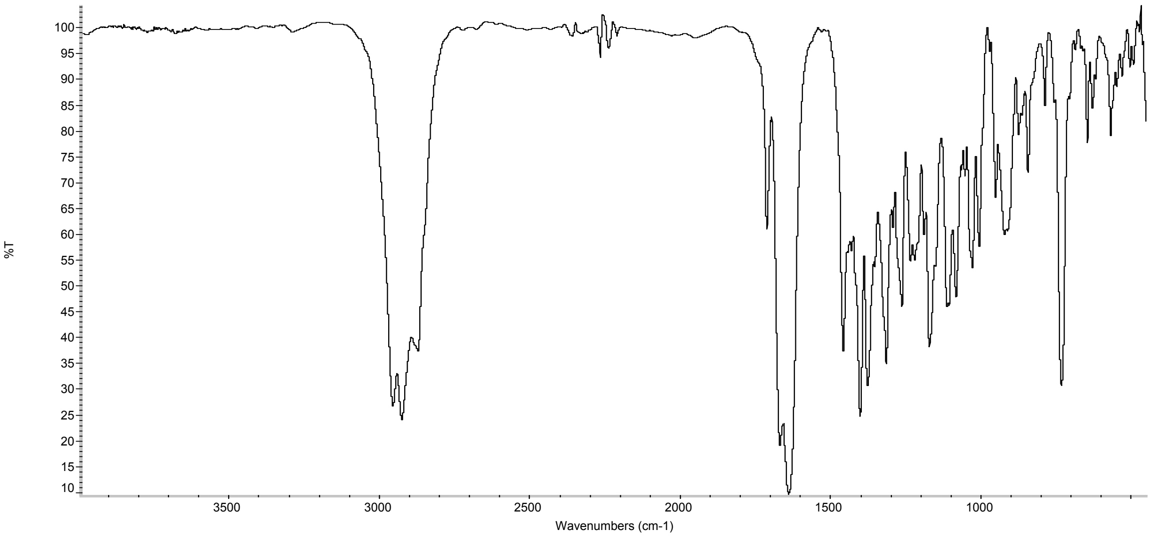


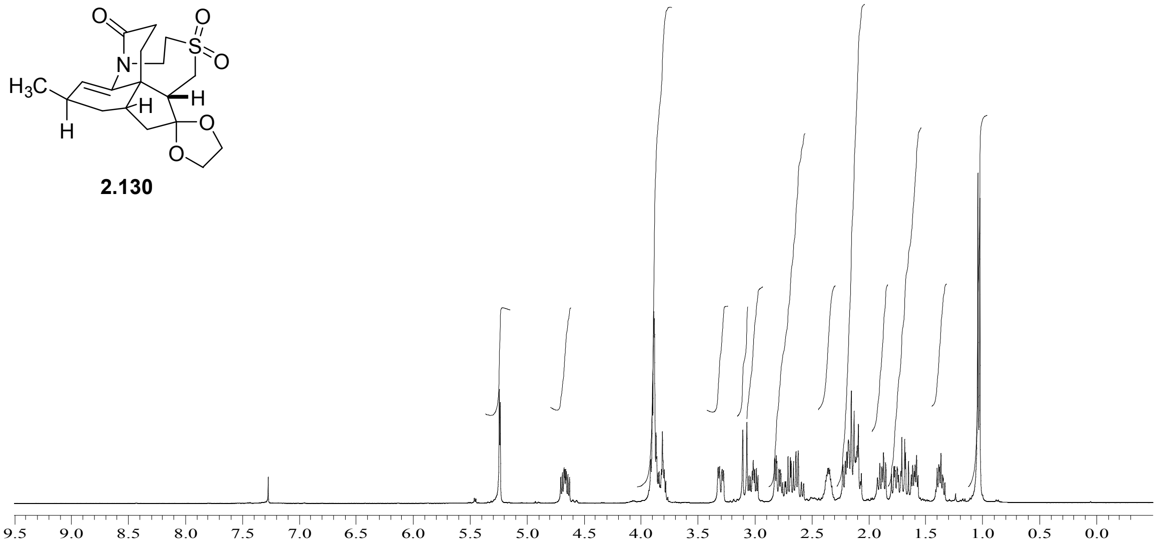
%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
S
H3C
H
H
H
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

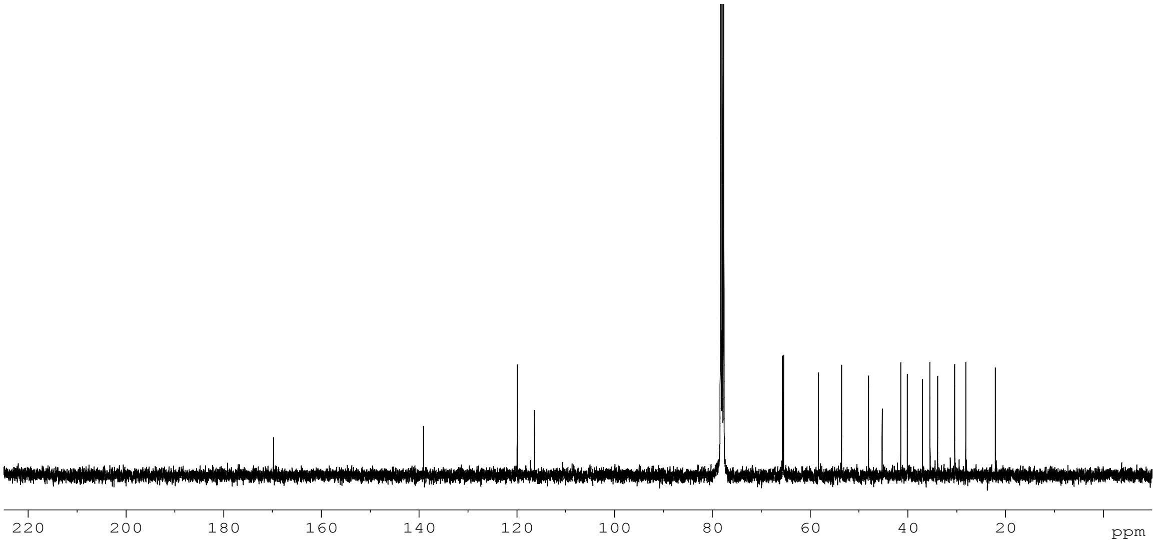
2.129


220
200
180
160
140
120
100
80
60
40
20
ppm


%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


2.130

H$_3$C
H
N
O
S
O
O
H
H
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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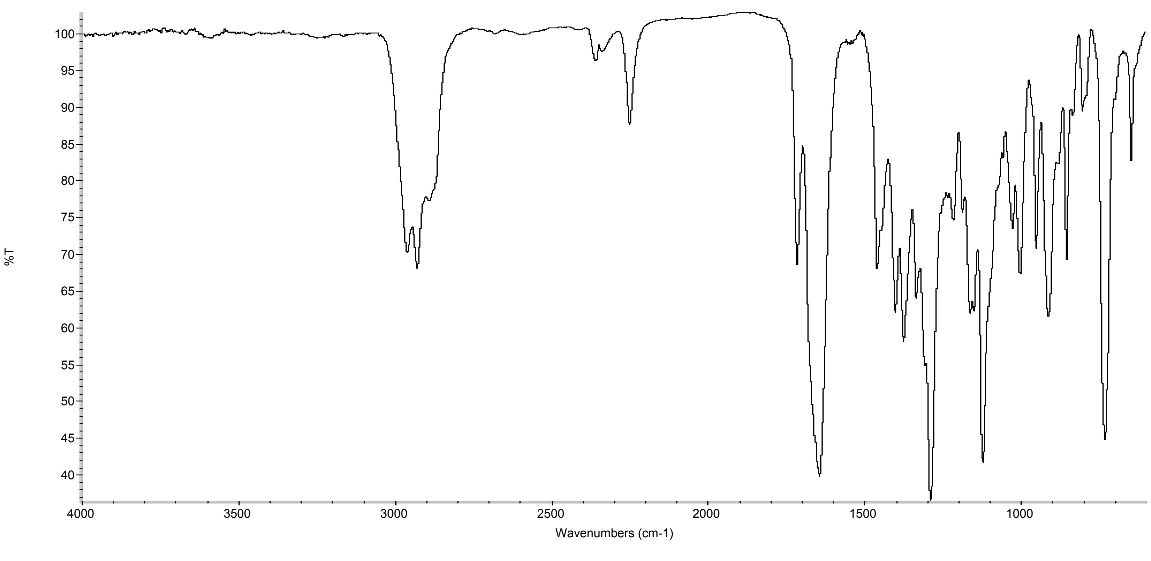
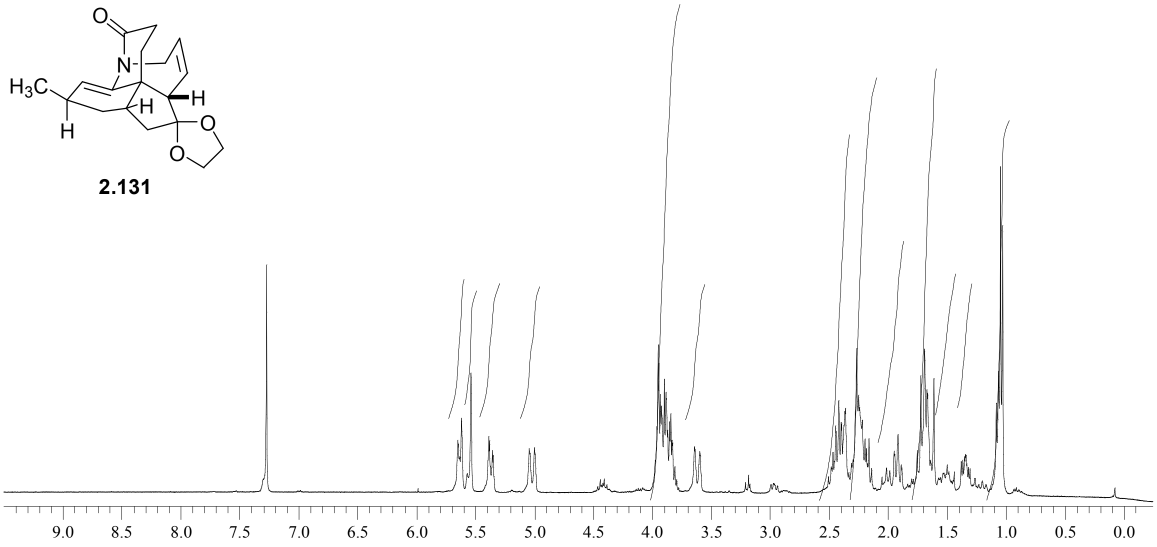
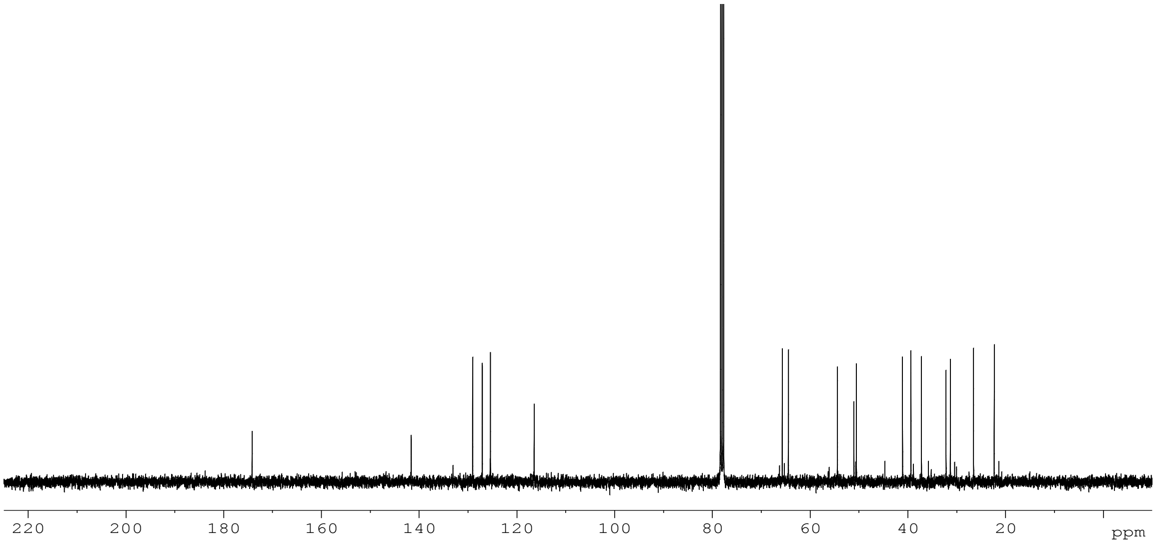
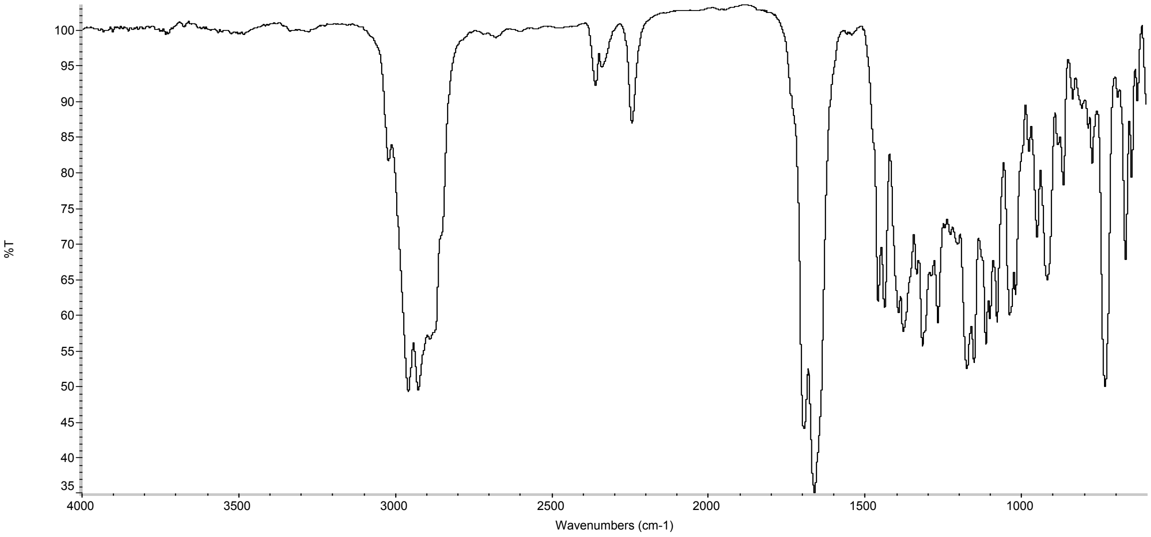
200
180
160
140
120
100
80
60
40
20
ppm

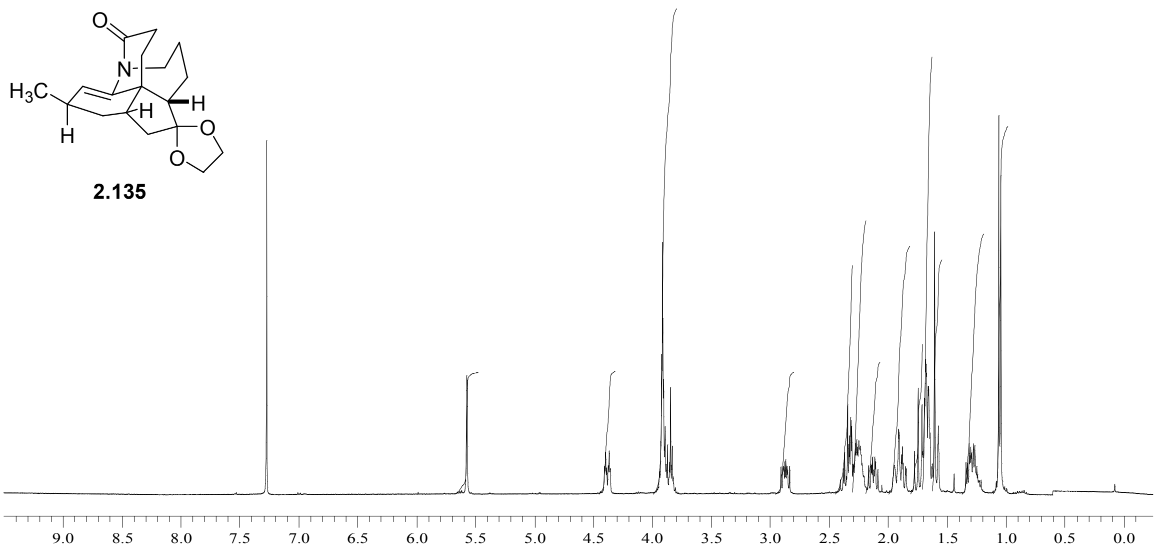

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


H3C
H
N
O
H
H
O
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

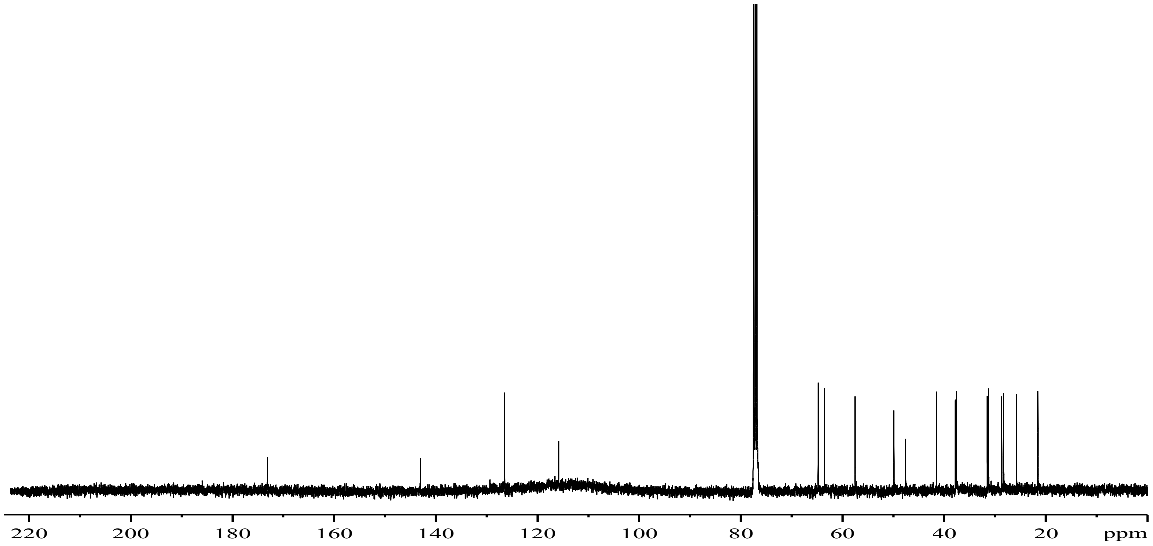
2.131

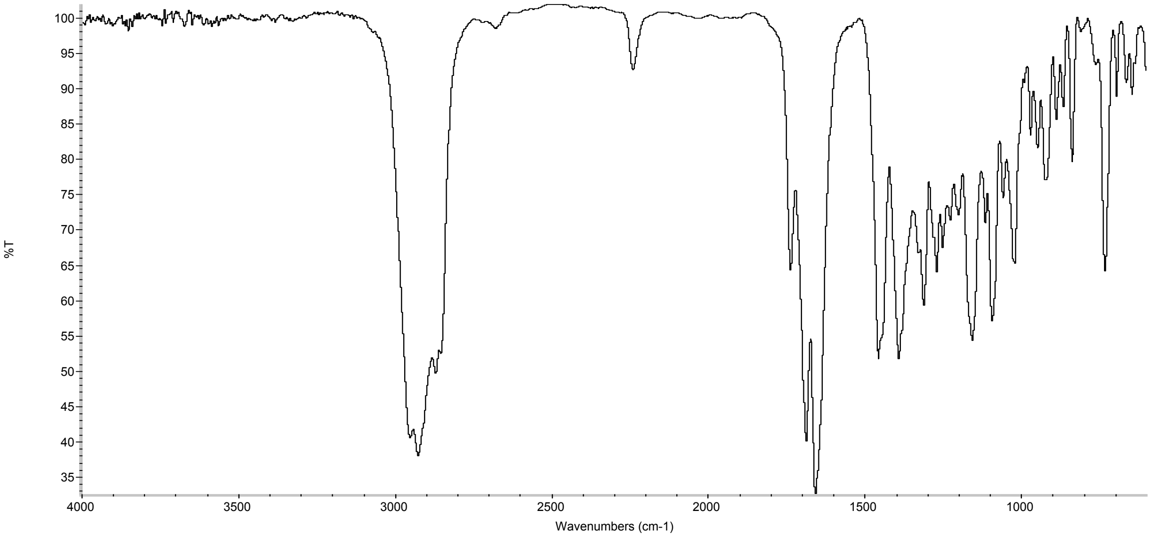

220
200
180
160
140
120
100
80
60
40
20
ppm

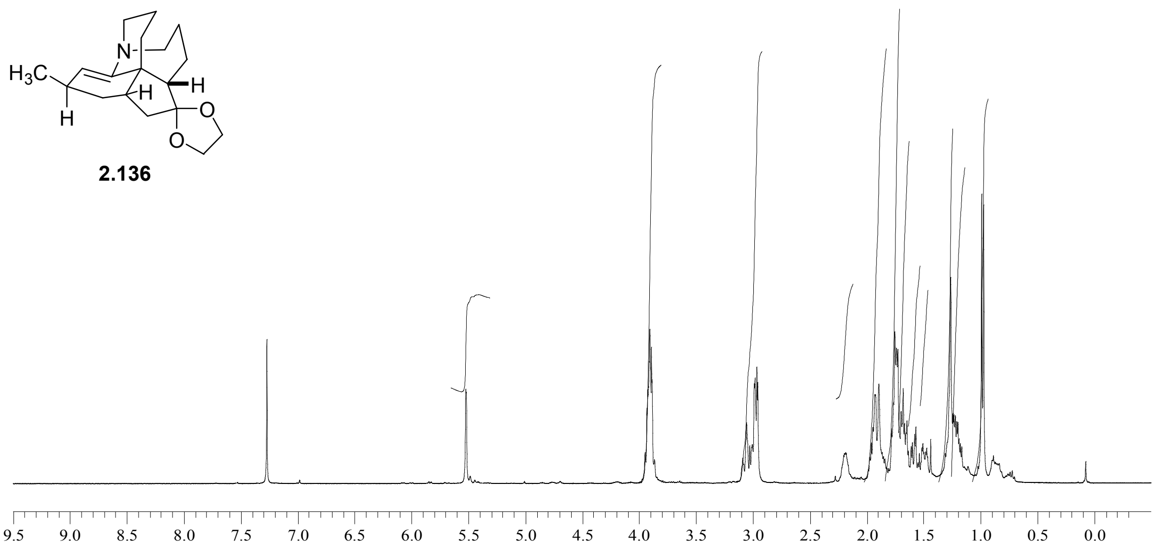

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
H3C
H
H
H
O
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

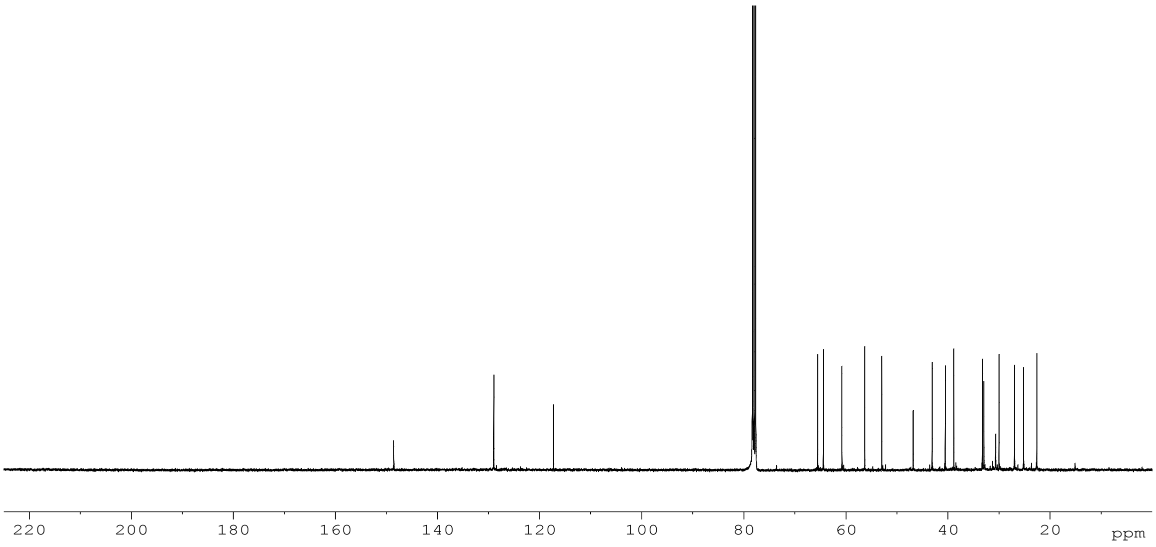
2.135

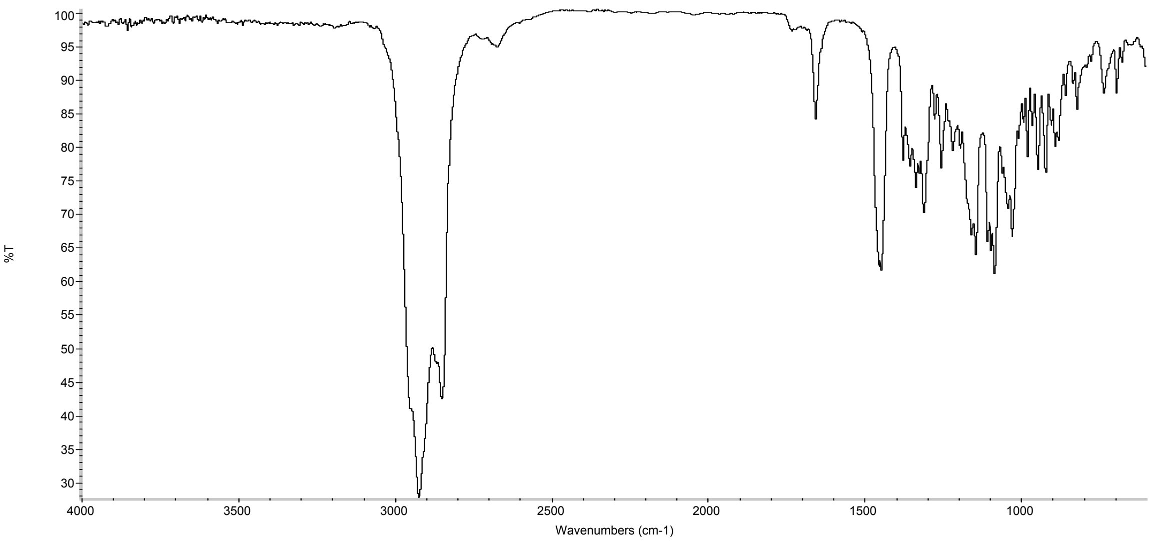

220
200
180
160
140
120
100
80
60
40
20
ppm

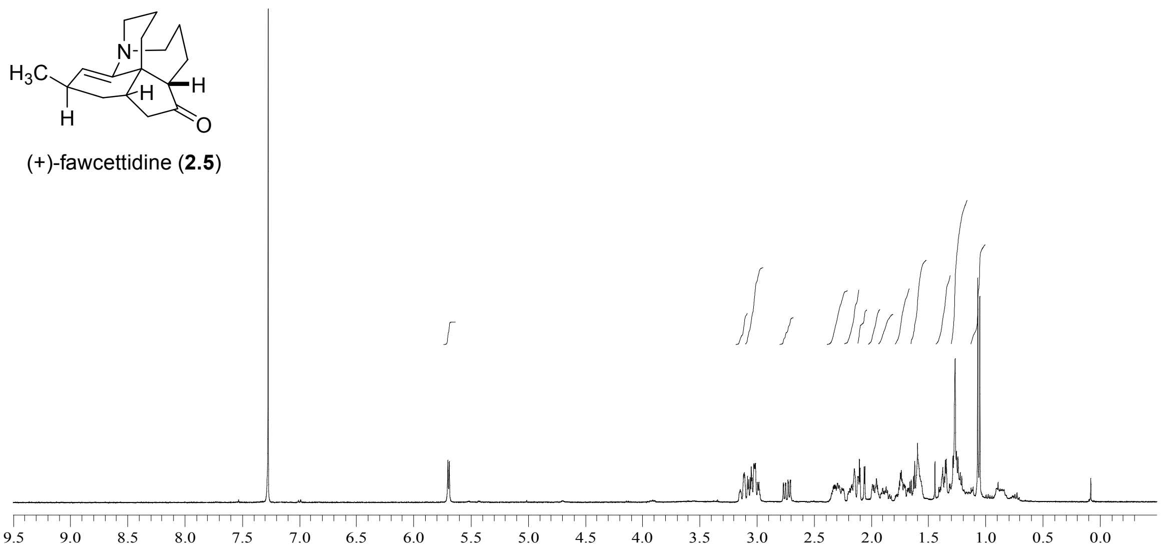

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


H3C
N
H
H
H
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

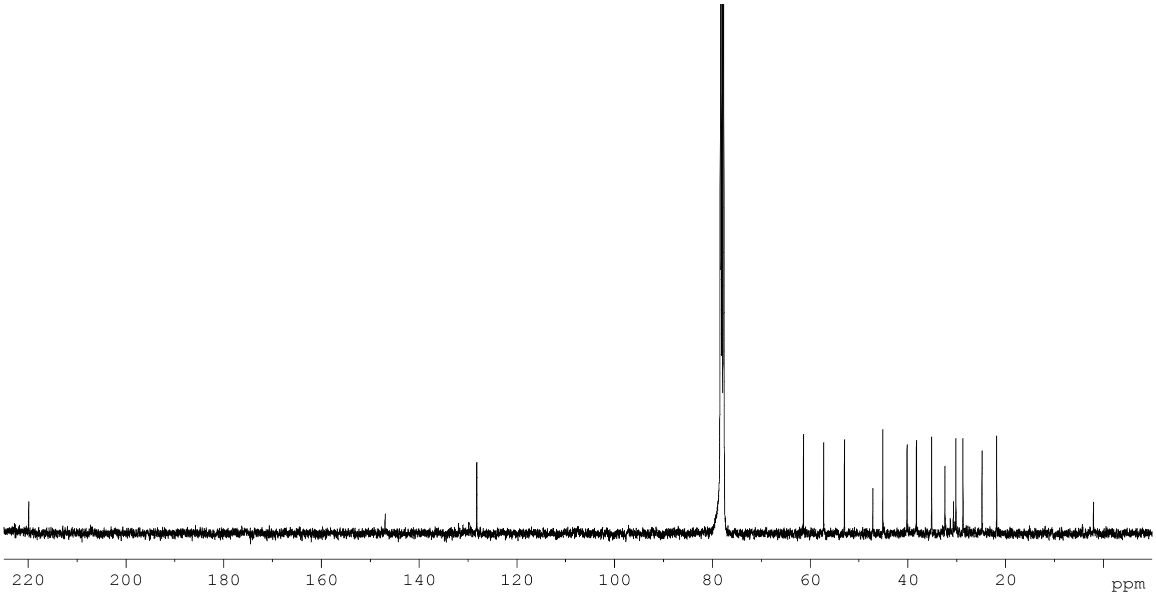
2.136

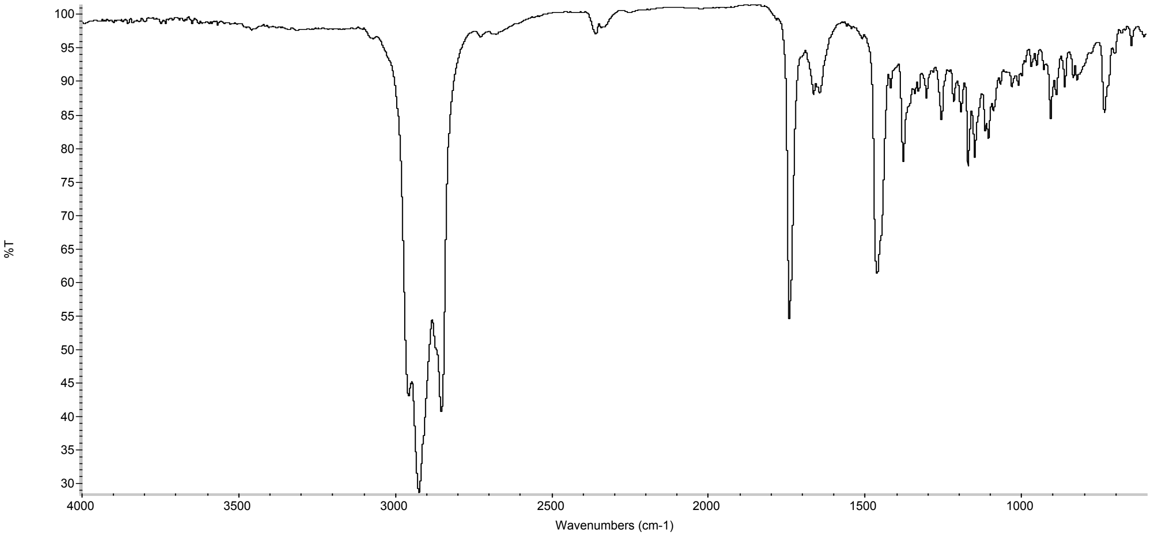

220
200
180
160
140
120
100
80
60
40
20
ppm


%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

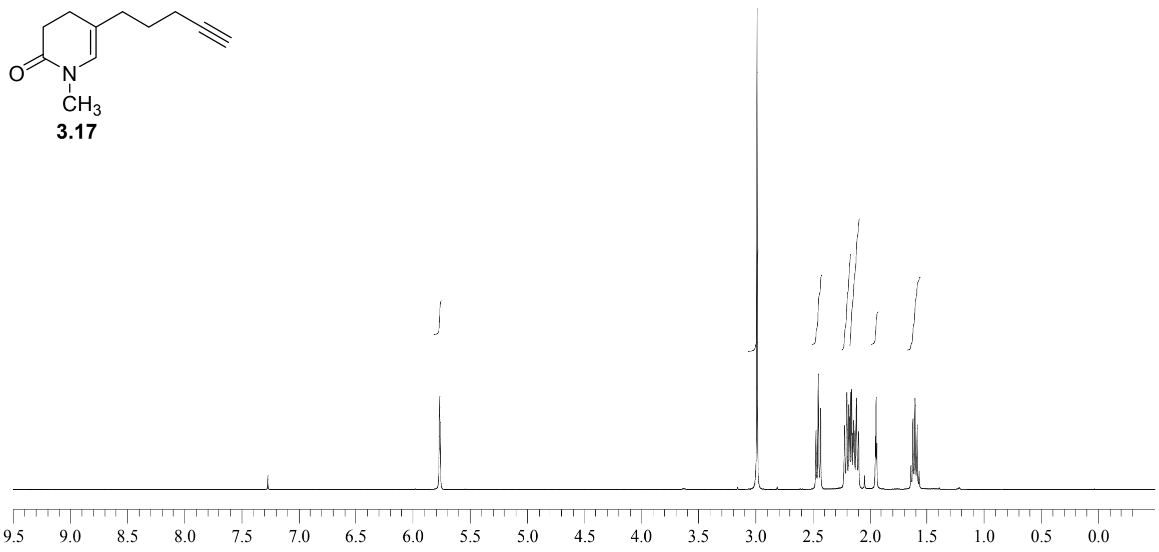


(+)-fawcettidine (**2.5**)

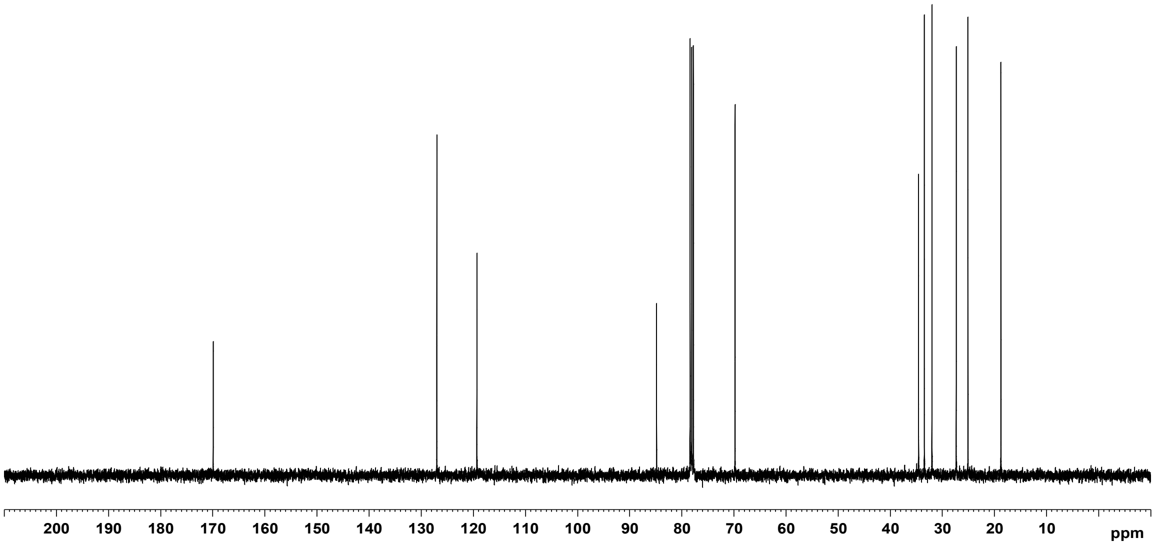


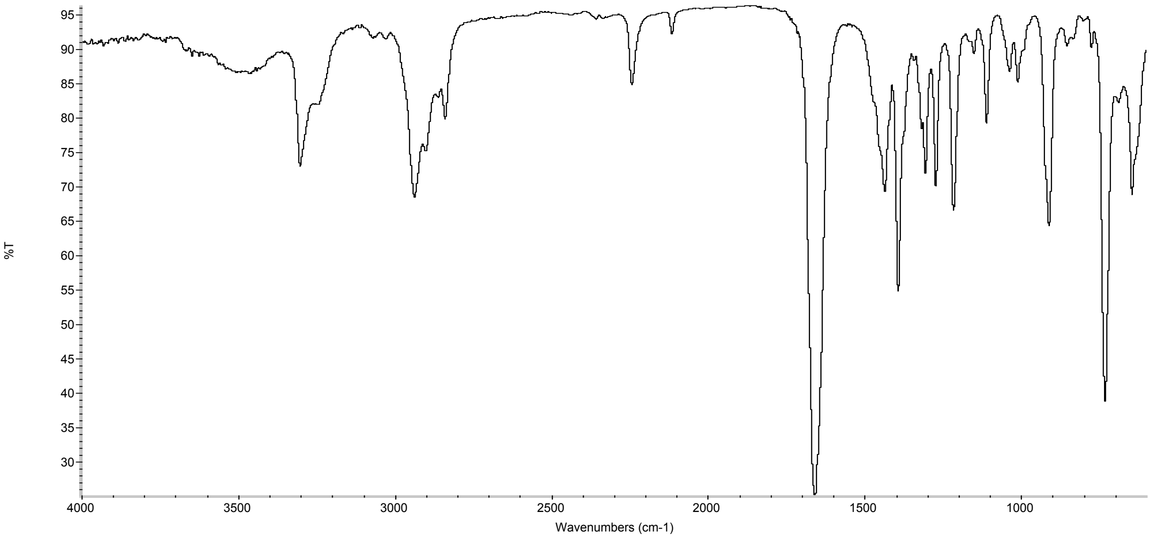


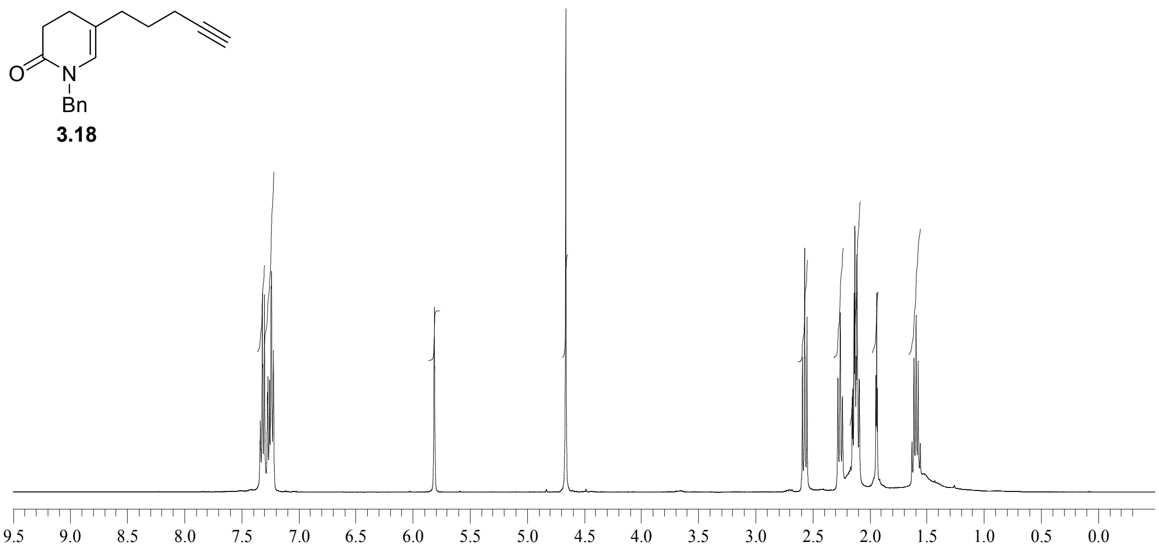
Appendix B: Selected Spectra for Chapter 3


O
N
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

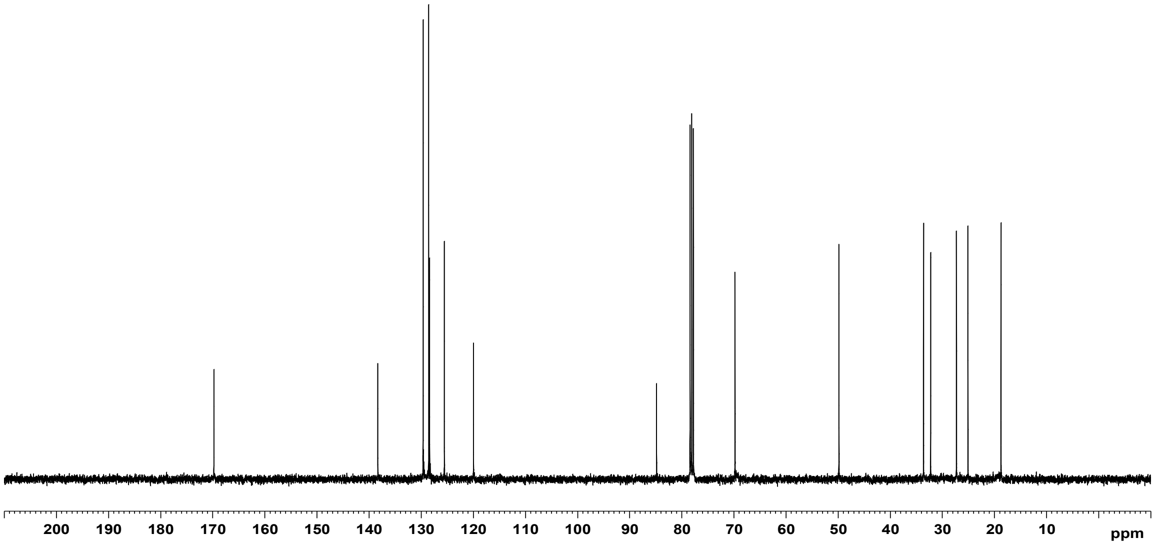
3.17

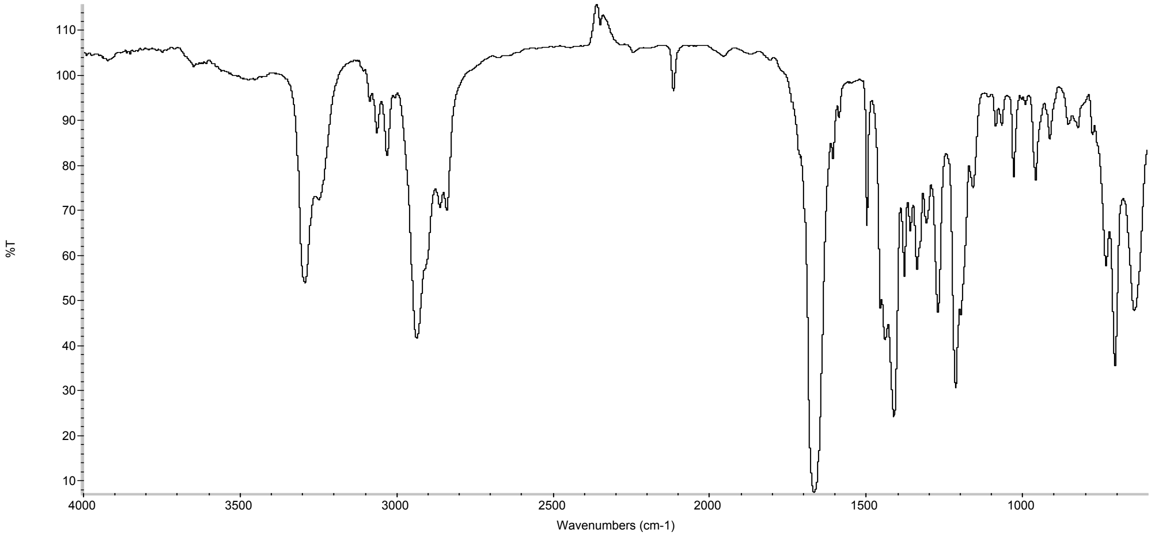

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

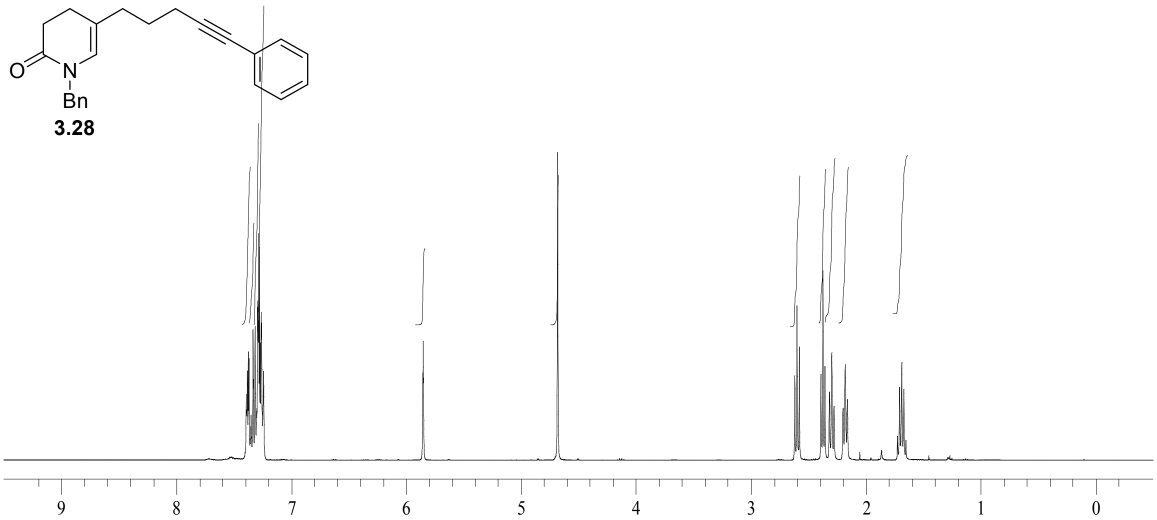

95
90
85
80
75
70
65
60
55
50
45
40
35
30
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
Bn
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

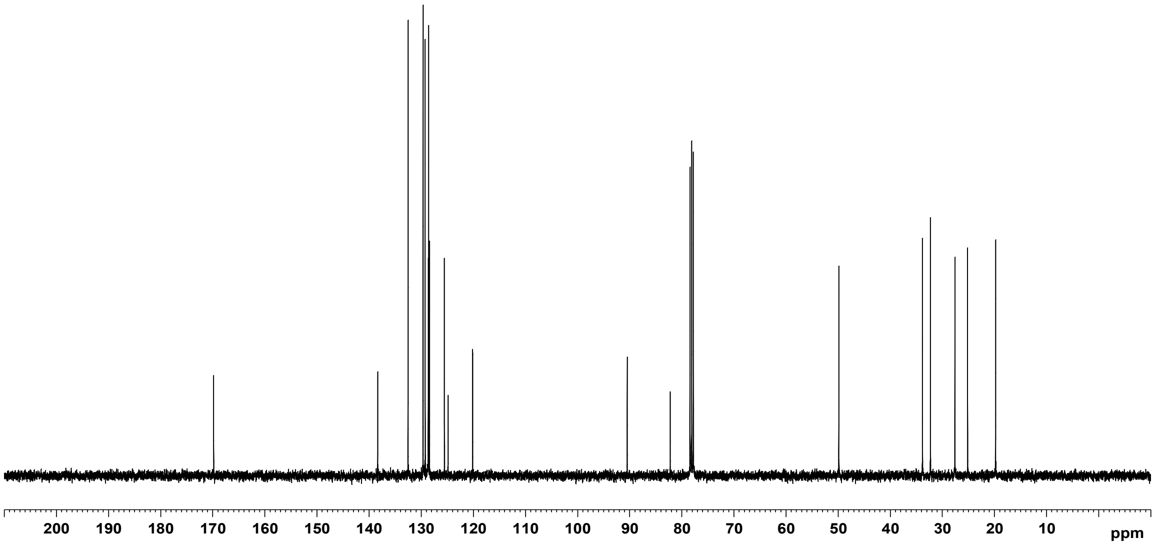
3.18

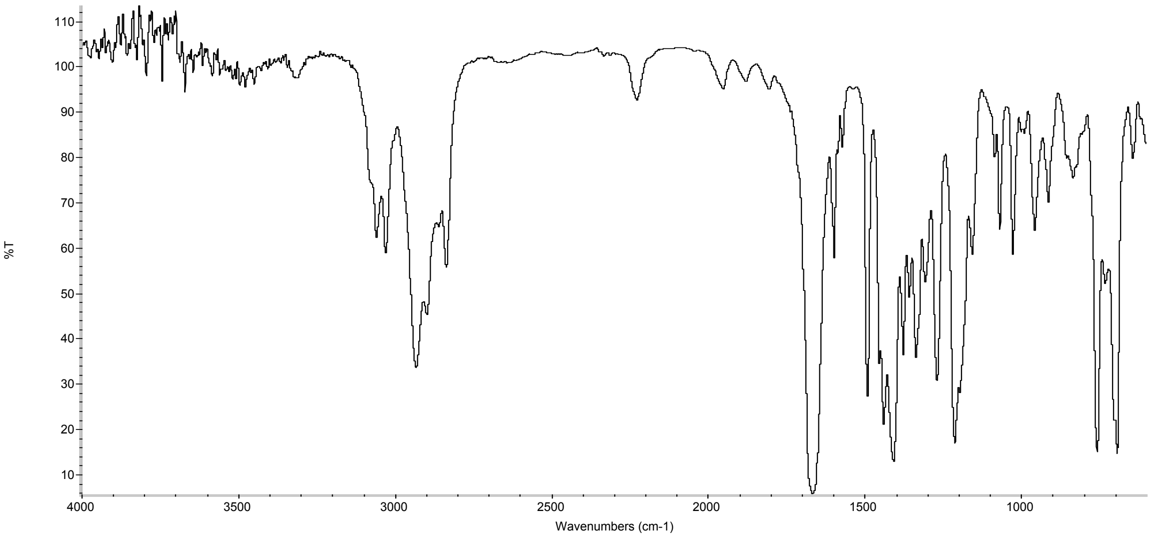

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

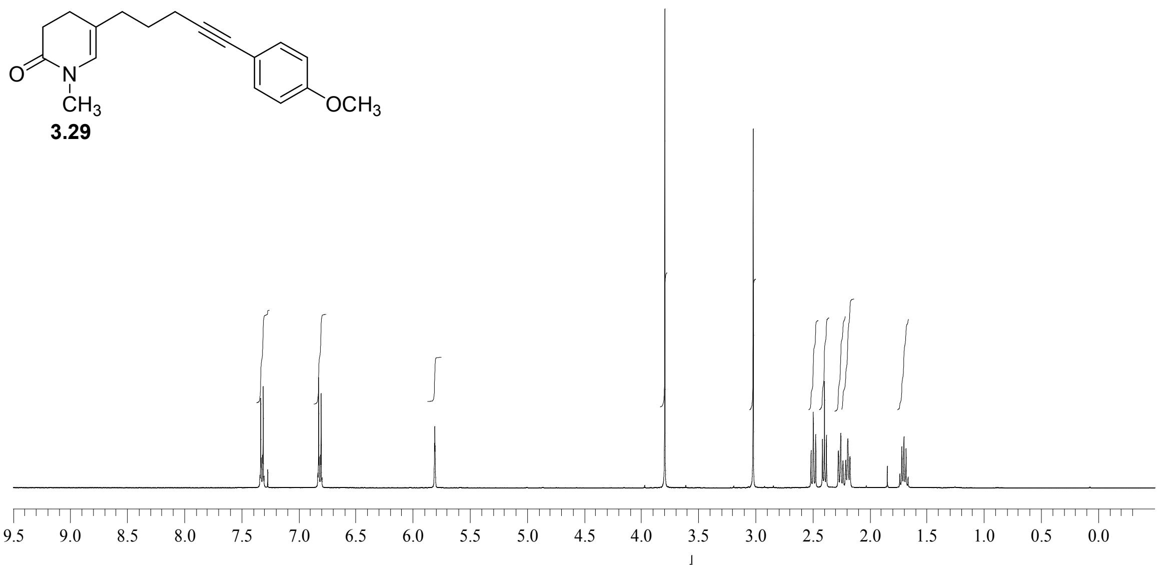

%T
110
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

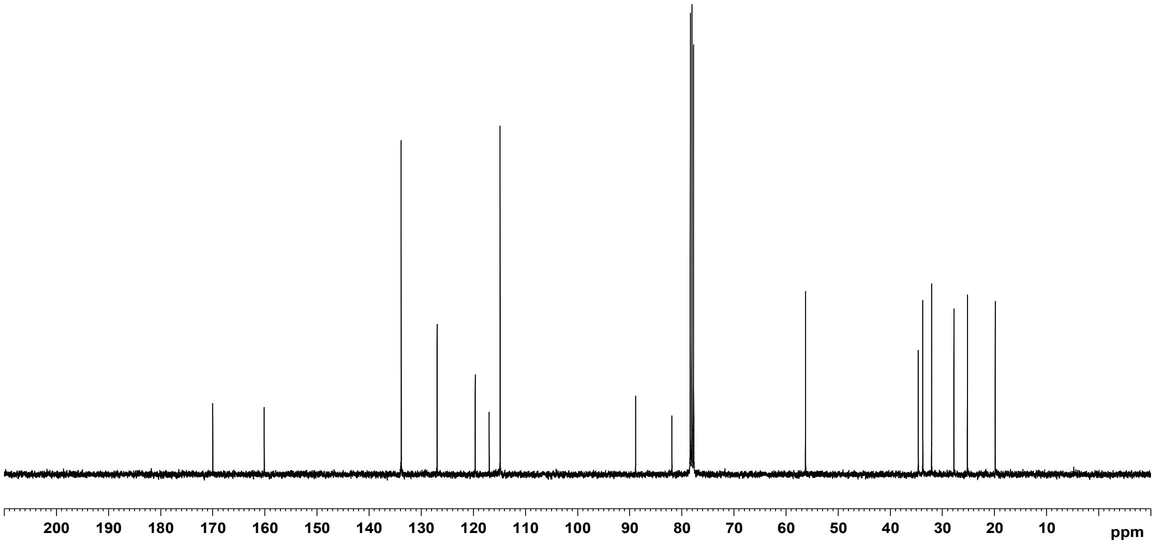

O
N
Bn
9
8
7
6
5
4
3
2
1
0

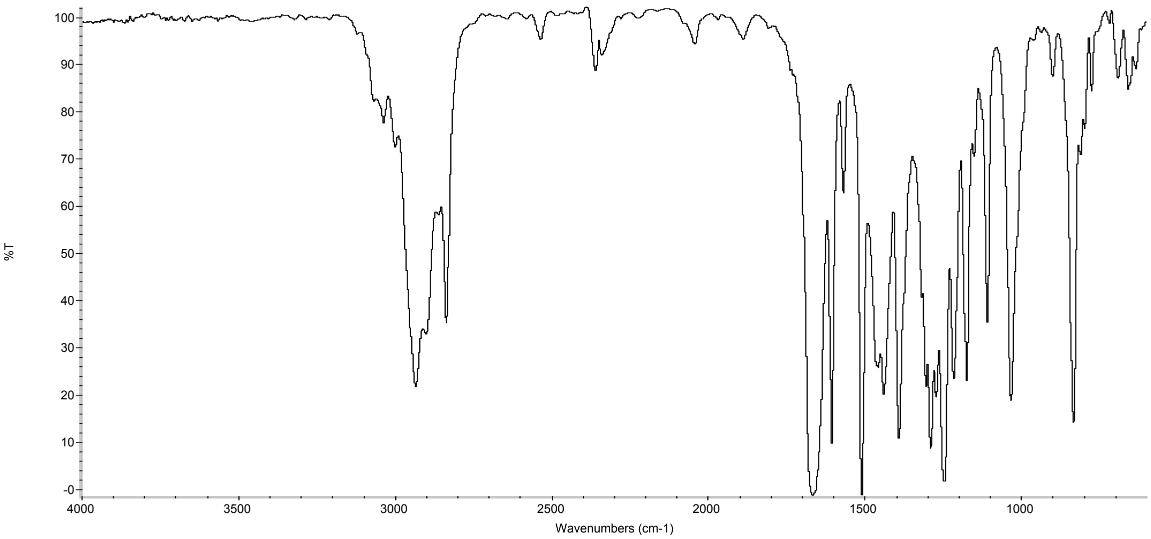
3.28

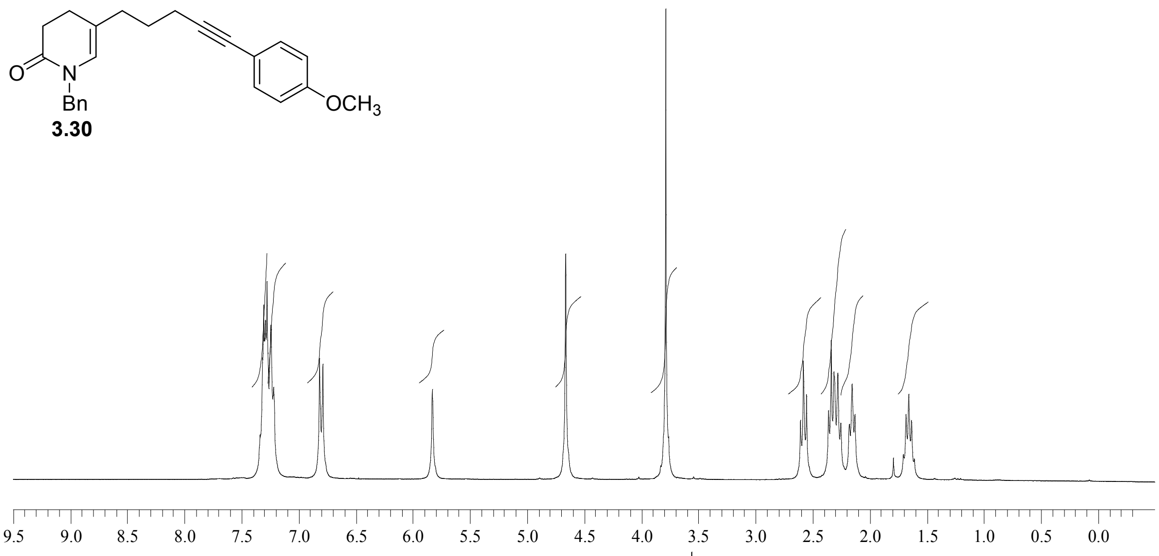

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


110
100
90
80
70
60
50
40
30
20
10
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

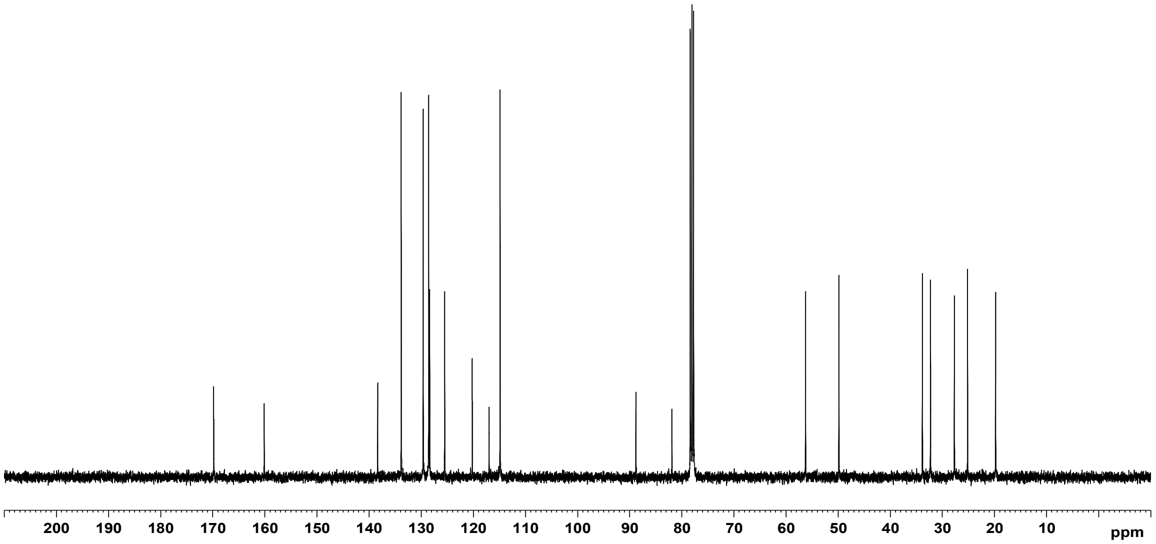

3.29
O
N
CH3
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

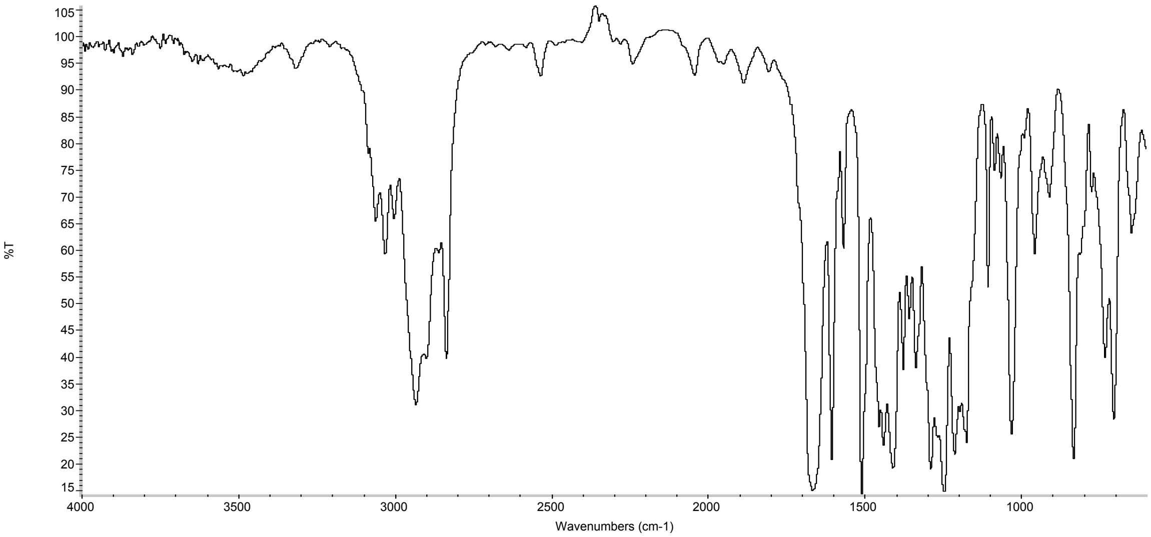

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

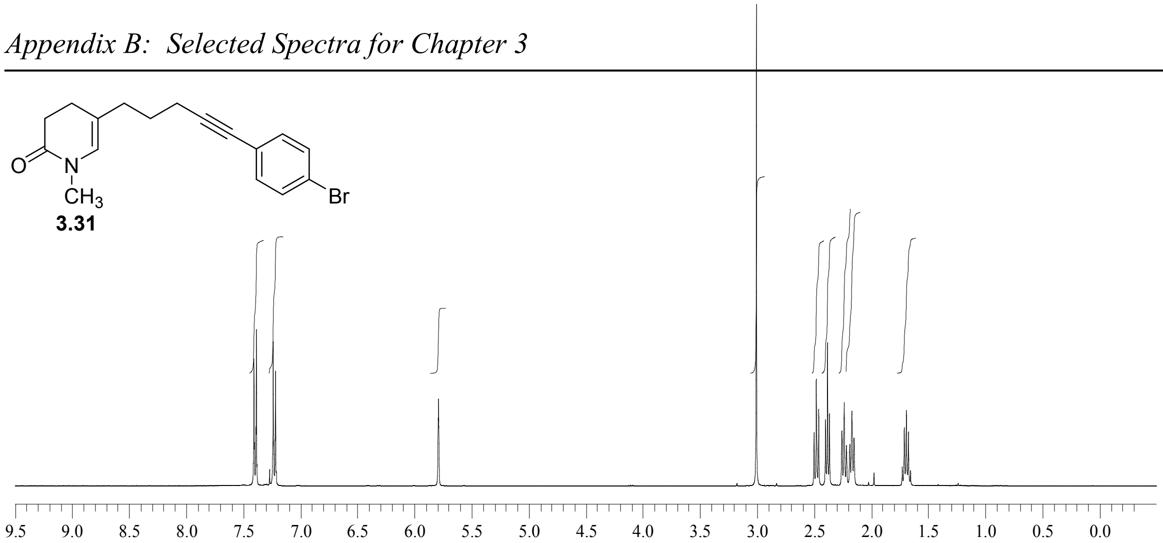

%T
100
90
80
70
60
50
40
30
20
10
-0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
Bn
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

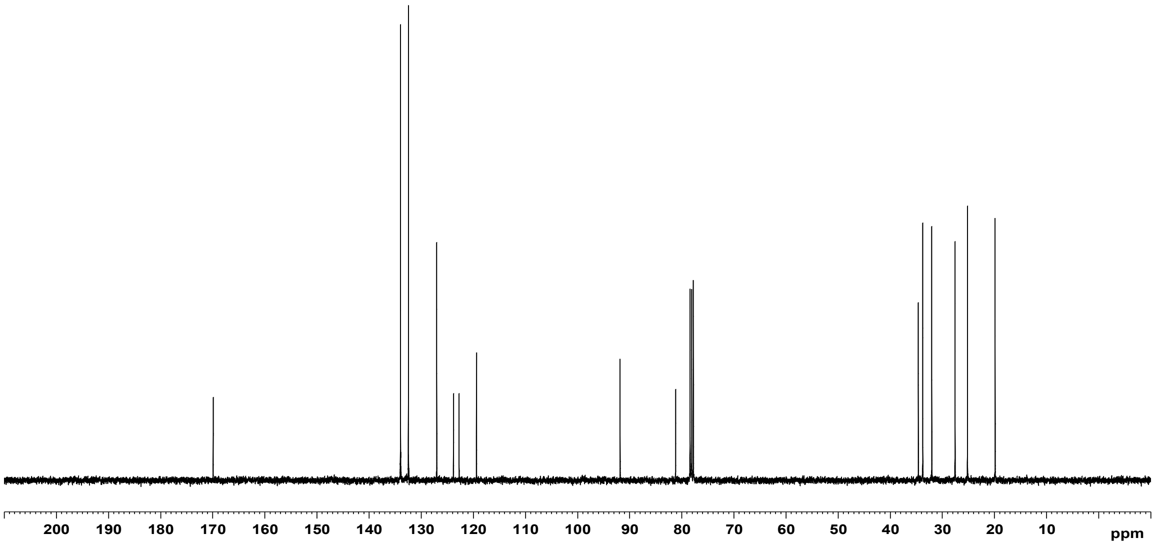
3.30

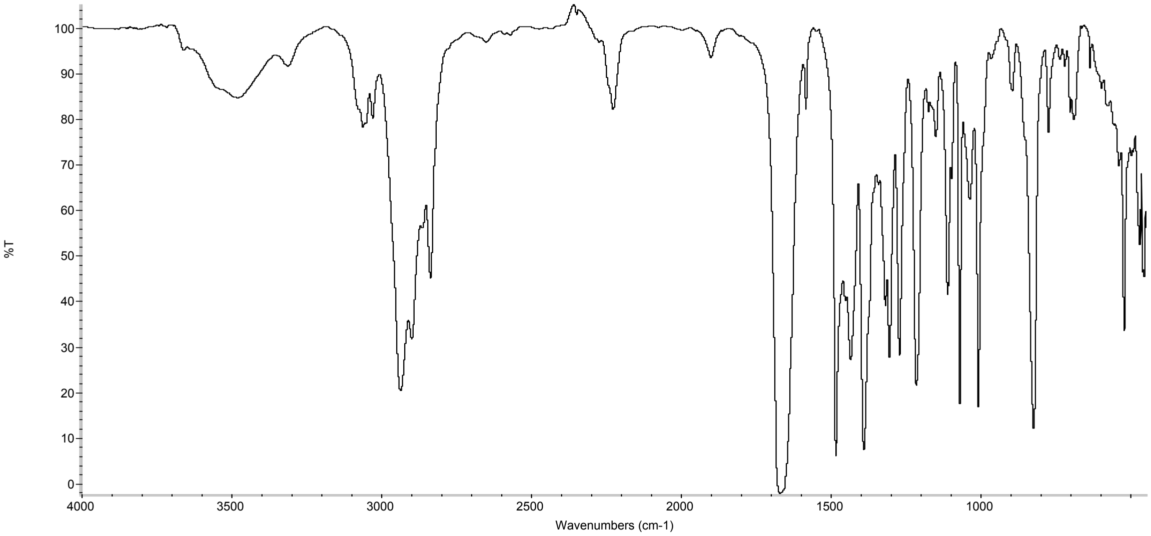

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

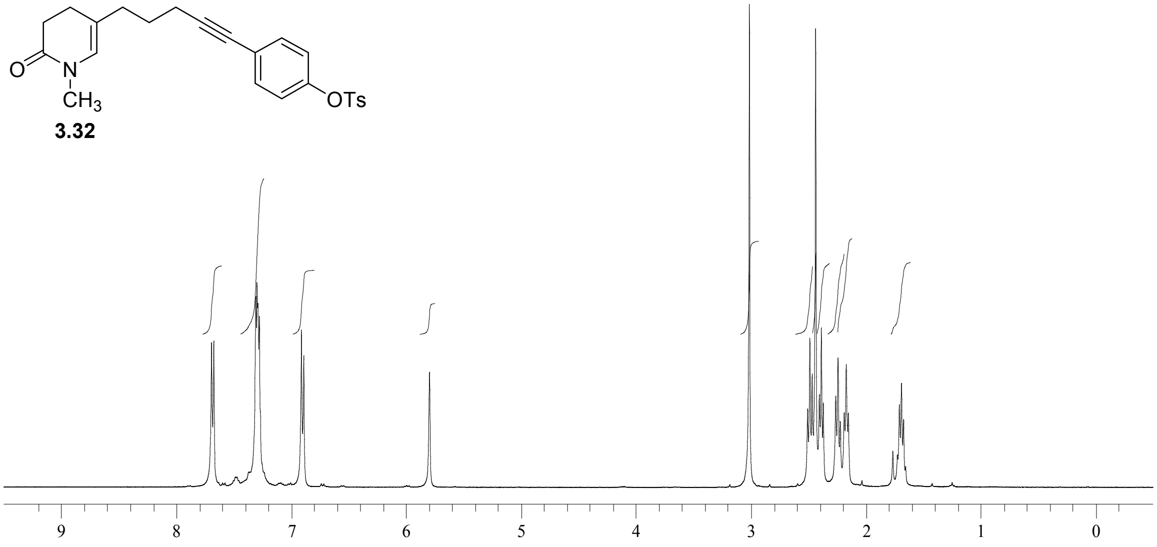

%T
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
CH3
Br
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

3.31

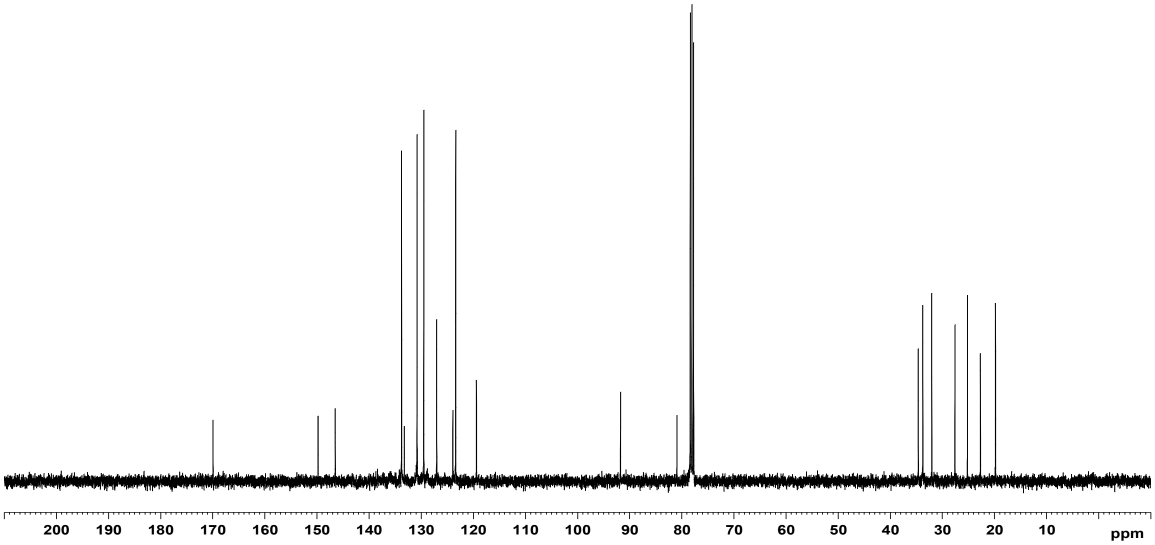

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

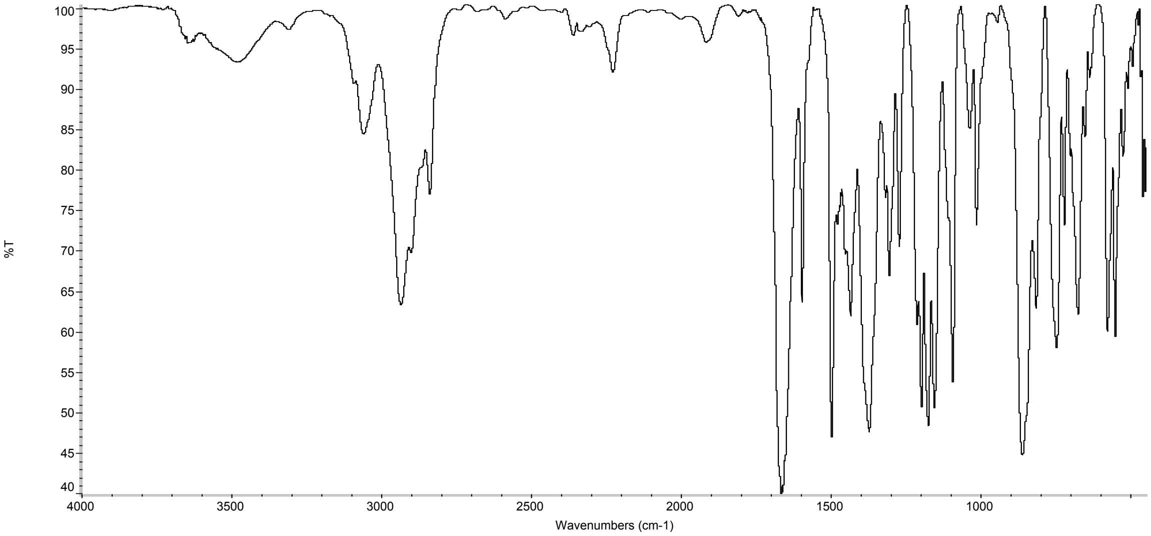


3.32

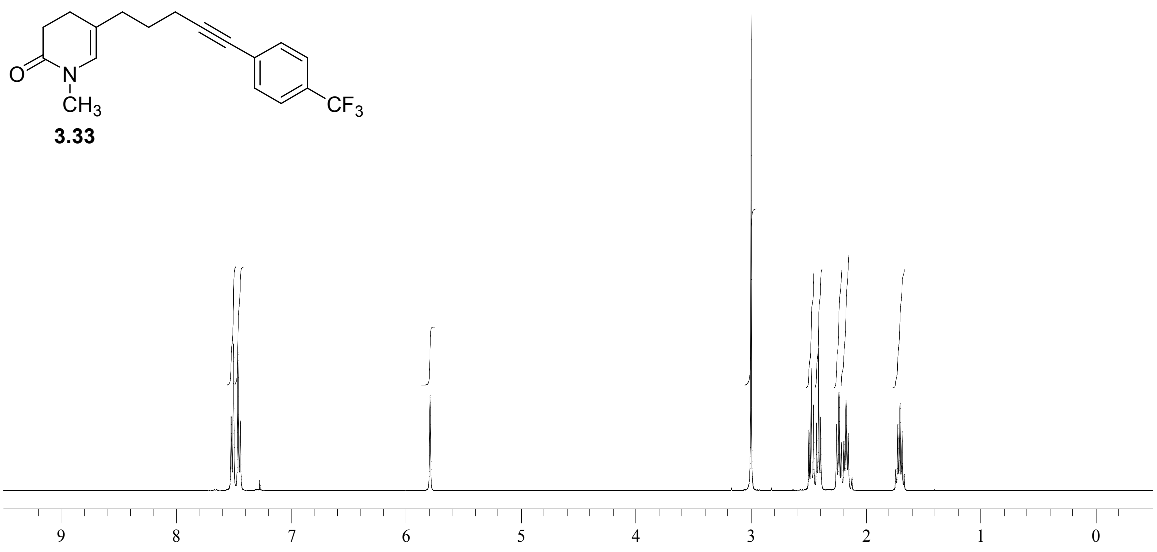
O
N
CH3
OTs
9
8
7
6
5
4
3
2
1
0



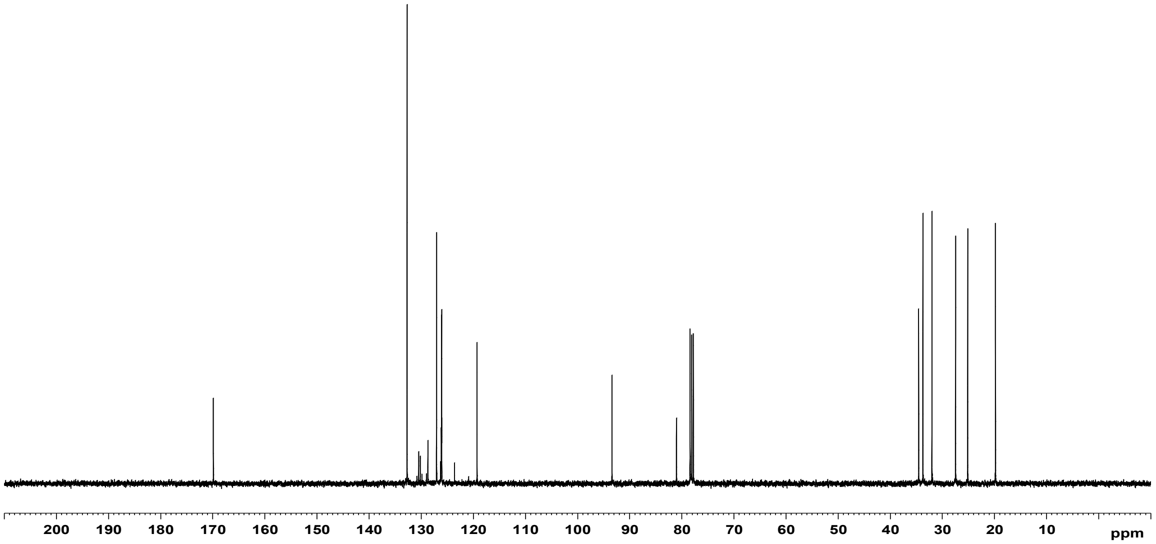
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

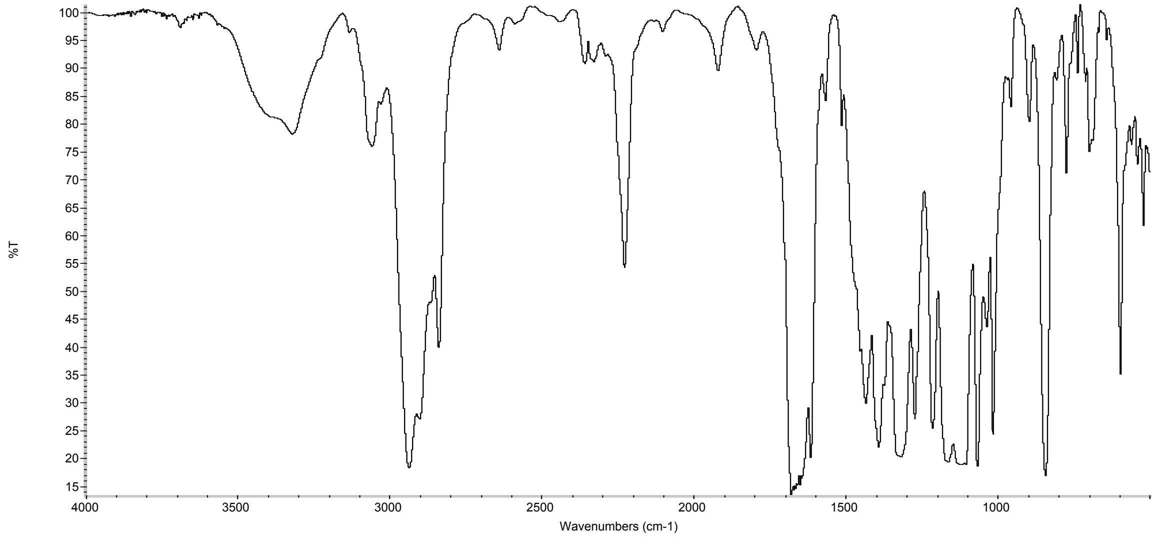


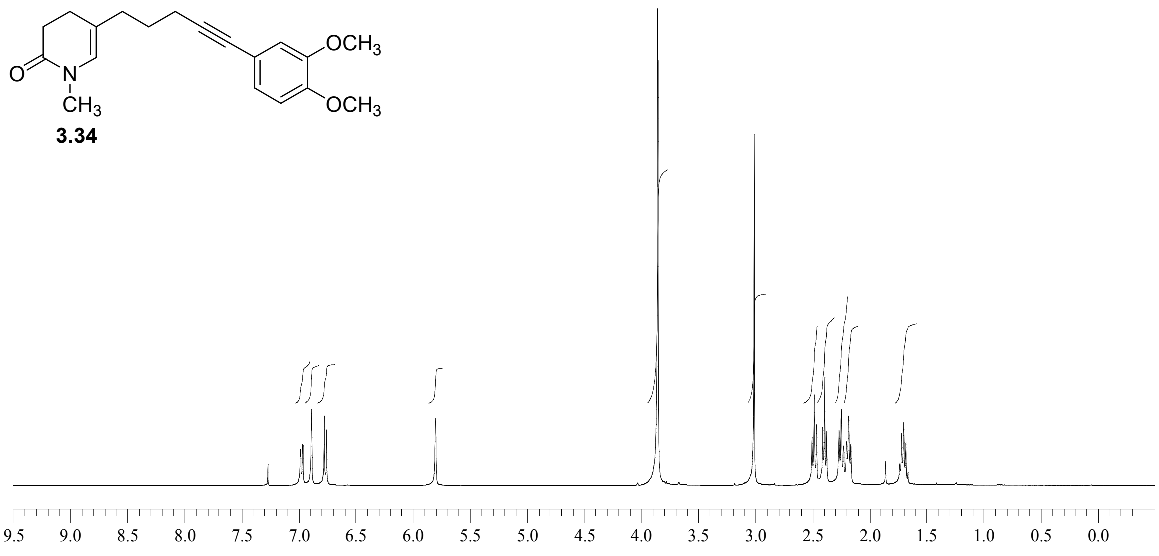
%T
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
CH3
CF3
9
8
7
6
5
4
3
2
1
0

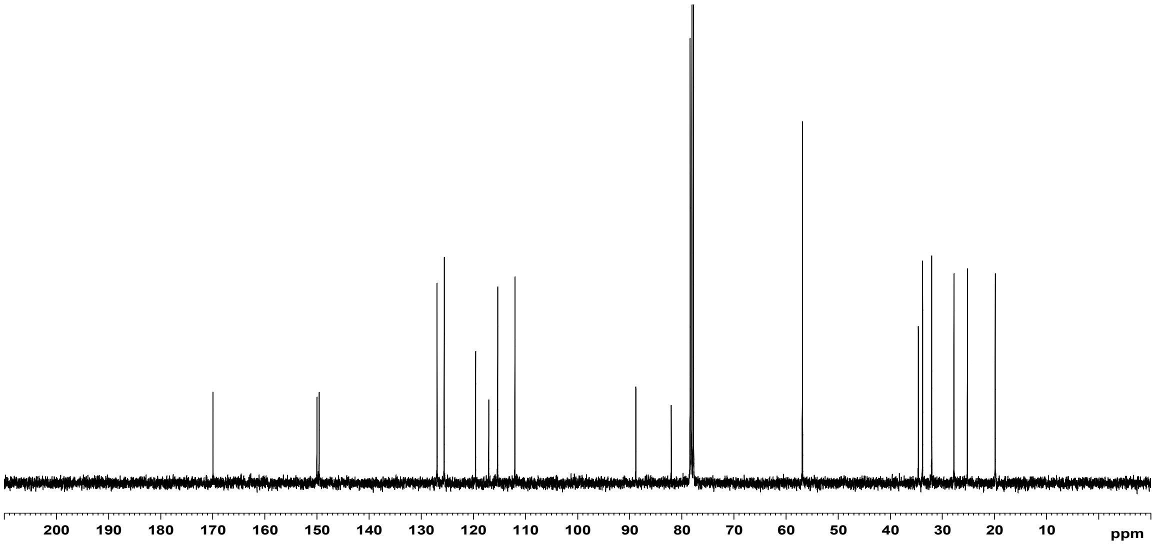
3.33

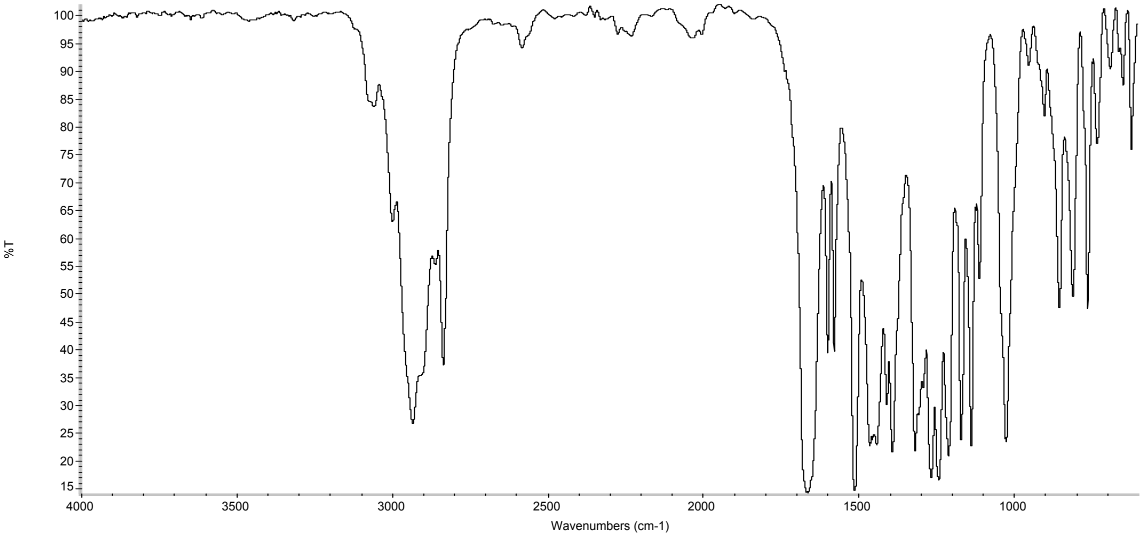

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

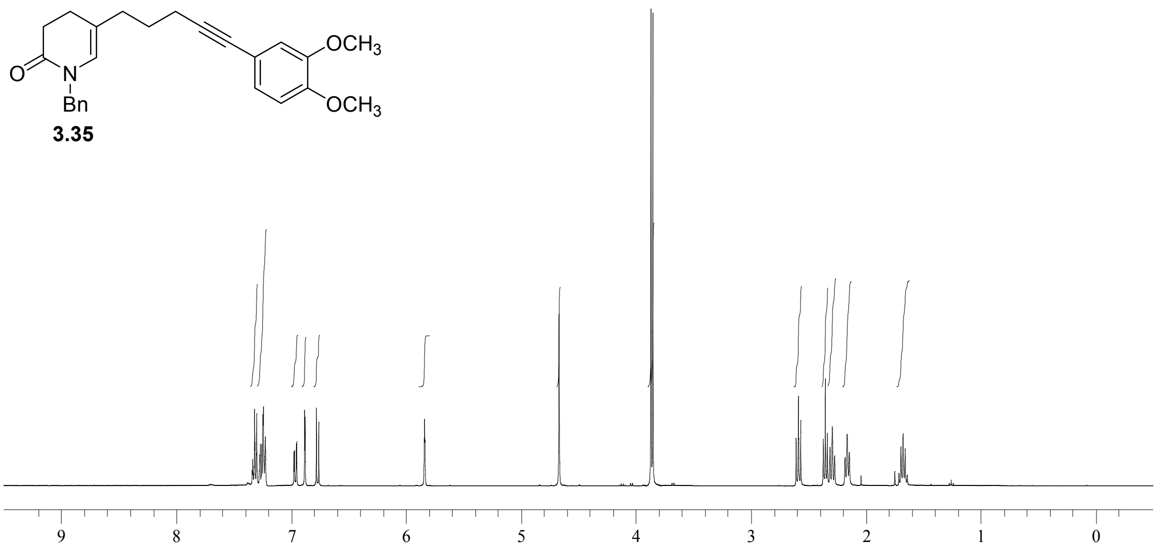

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


OCH3
OCH3
O
N
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

3.34

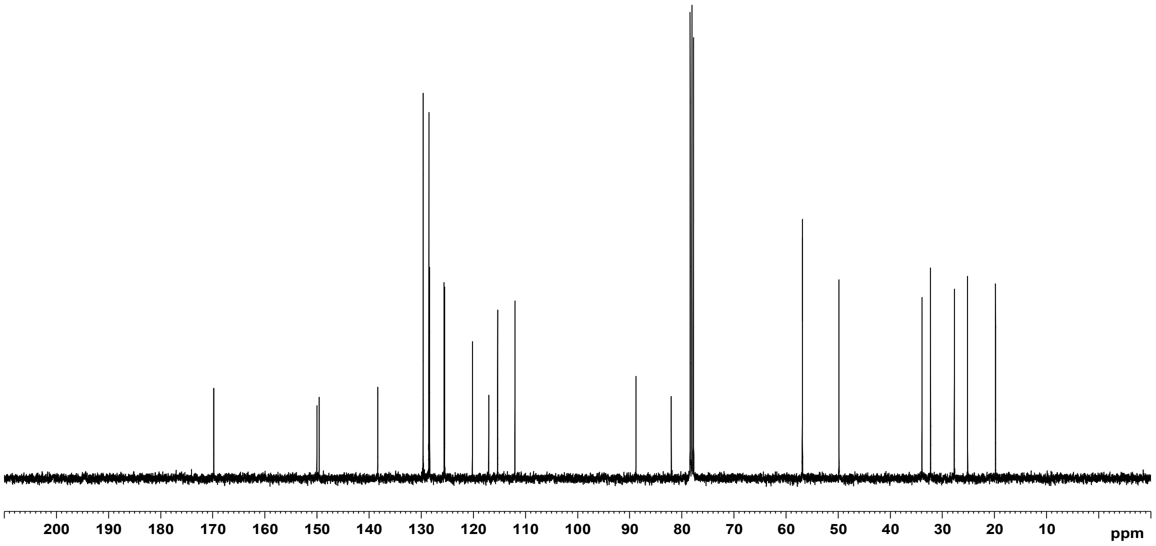

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

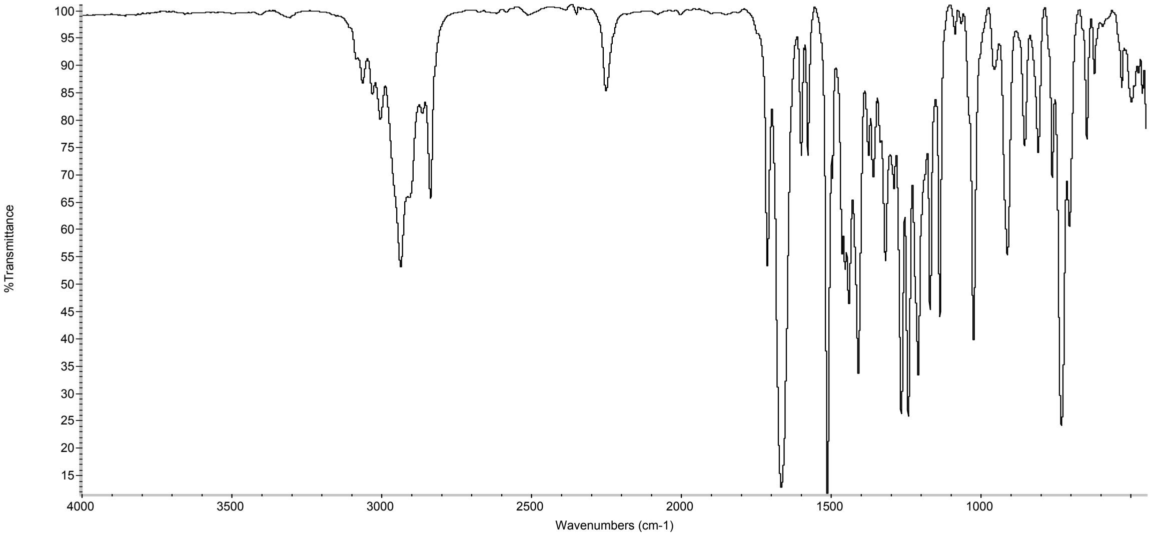

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

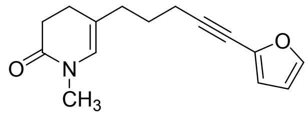


3.35

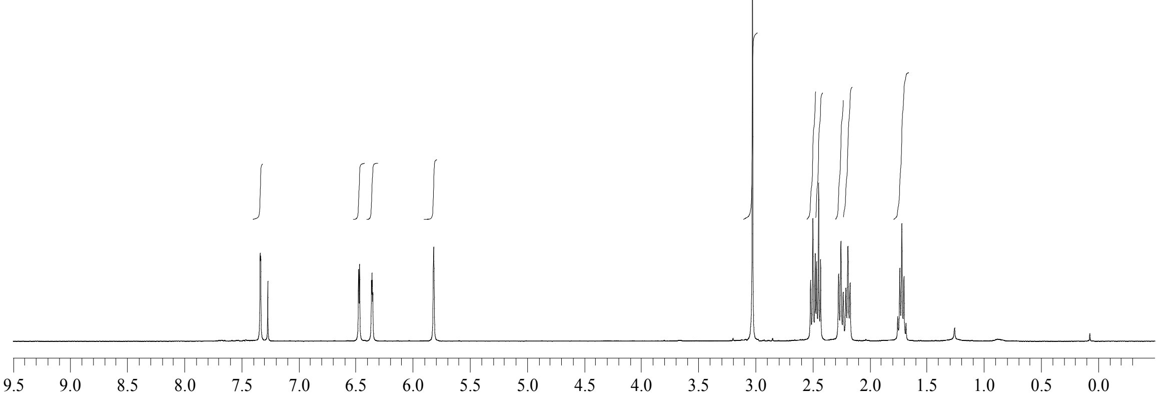
OCH3
OCH3
O
N
Bn
9
8
7
6
5
4
3
2
1
0

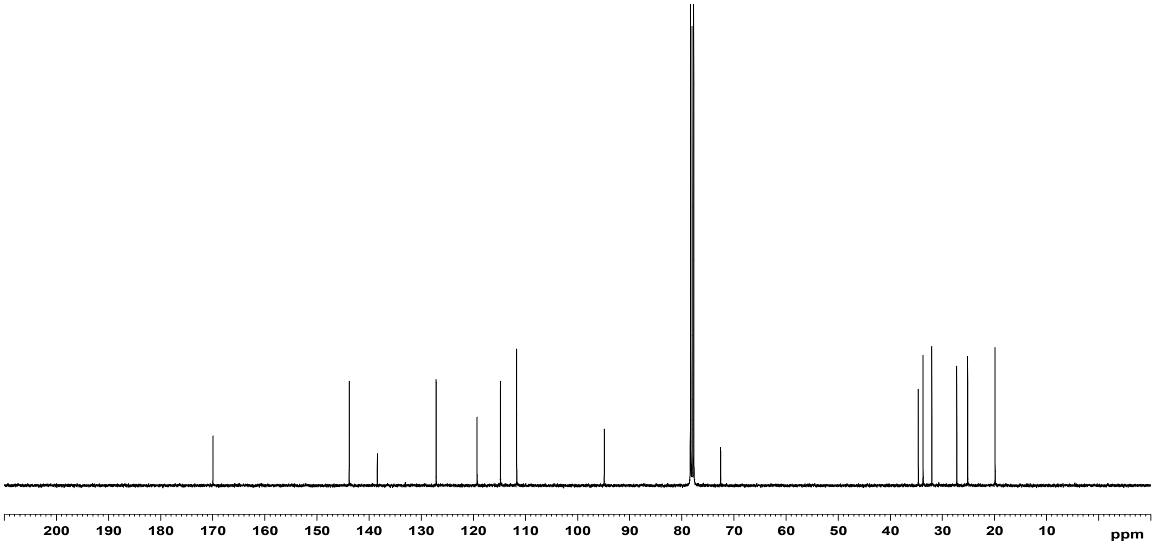

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

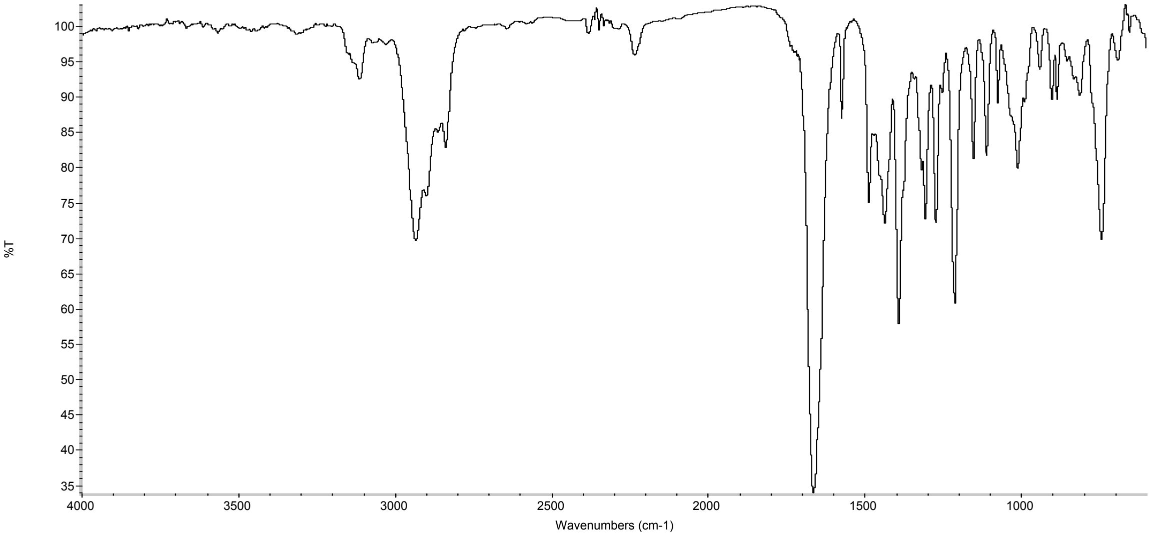

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

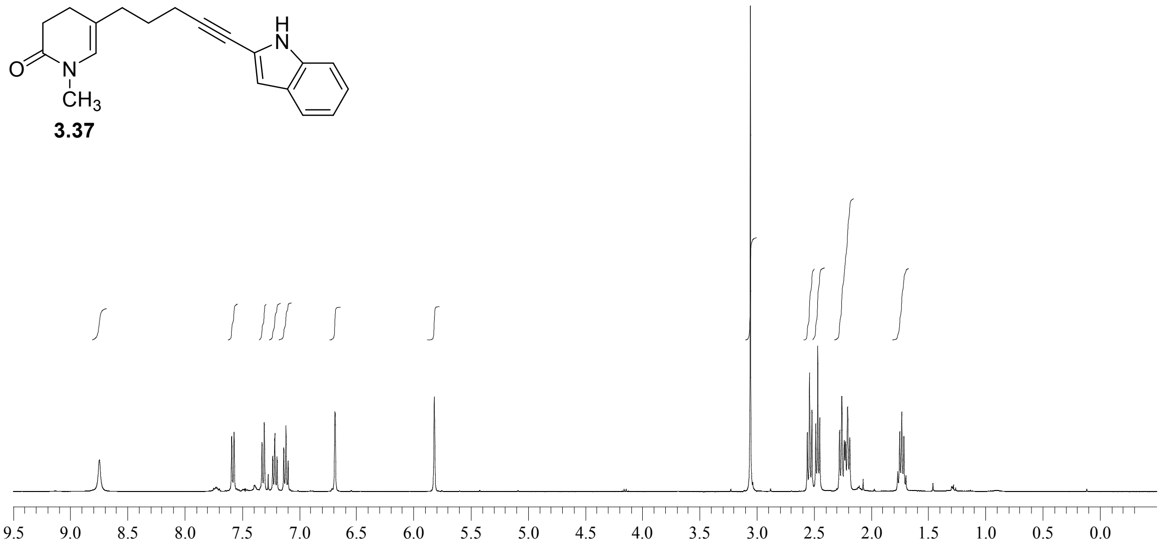

O
N
CH3
O

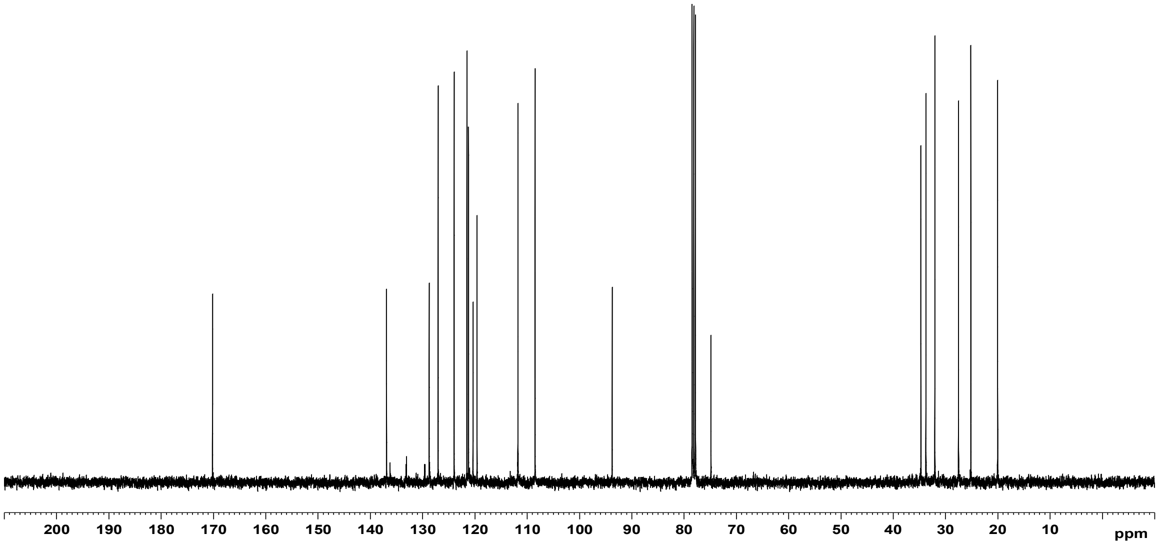
3.36

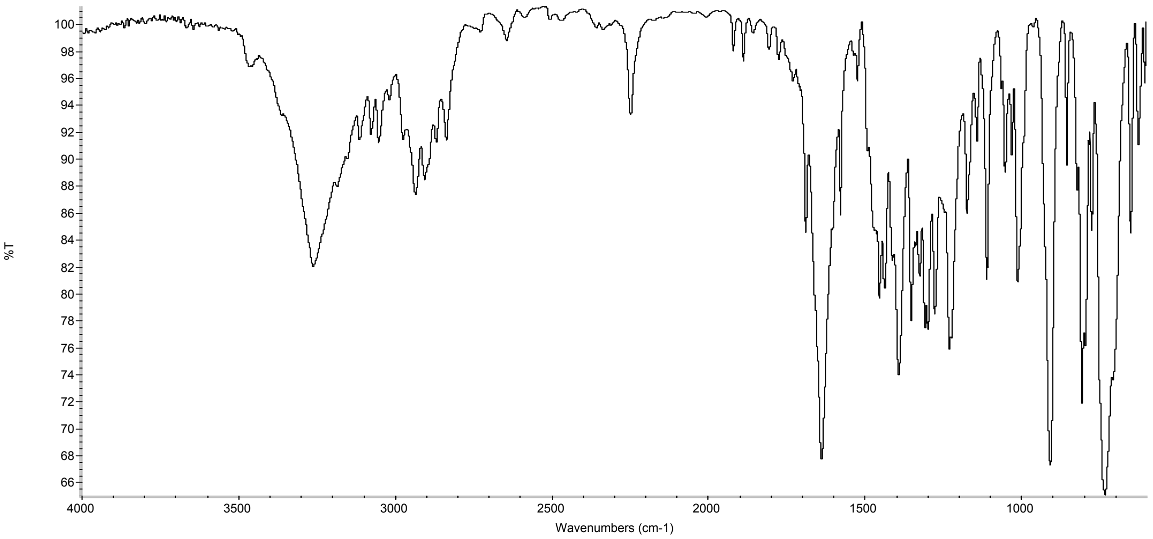

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

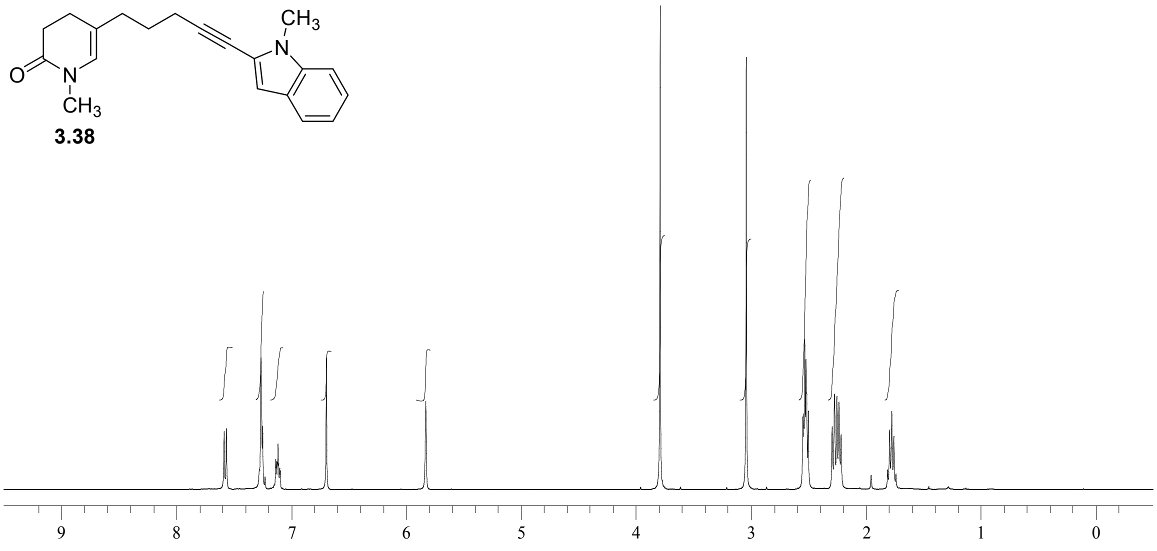

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


H
N
O
N
CH3
3.37
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

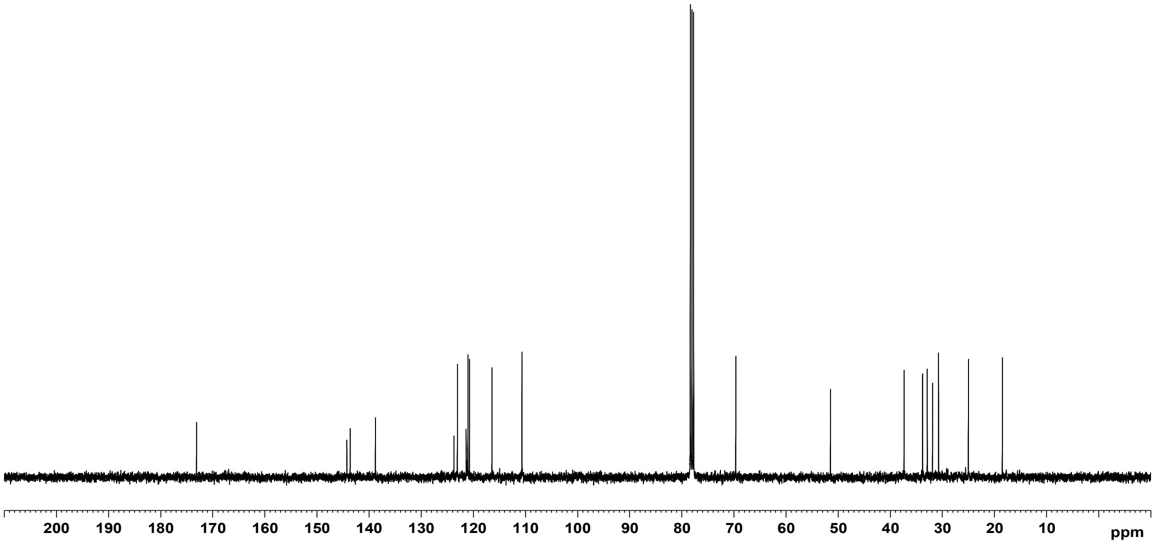

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

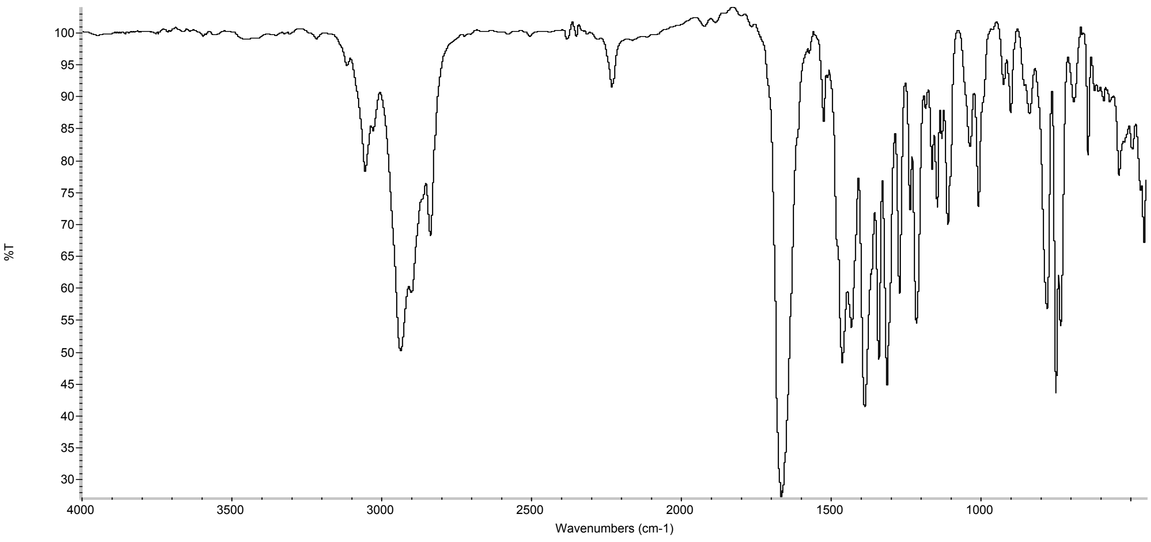


O
N
CH3
N
CH3
9
8
7
6
5
4
3
2
1
0

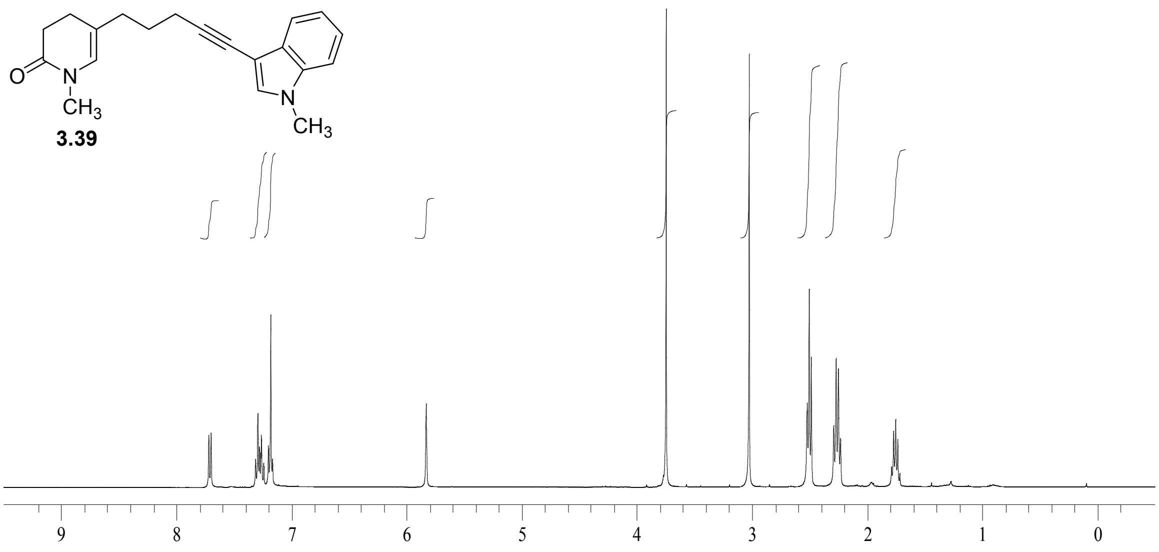
3.38



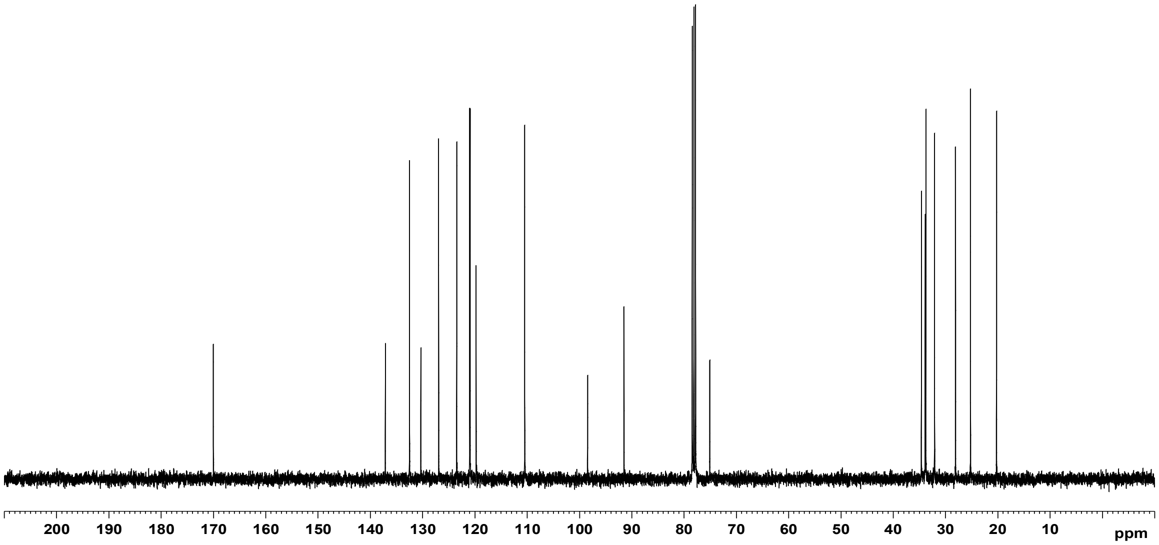
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

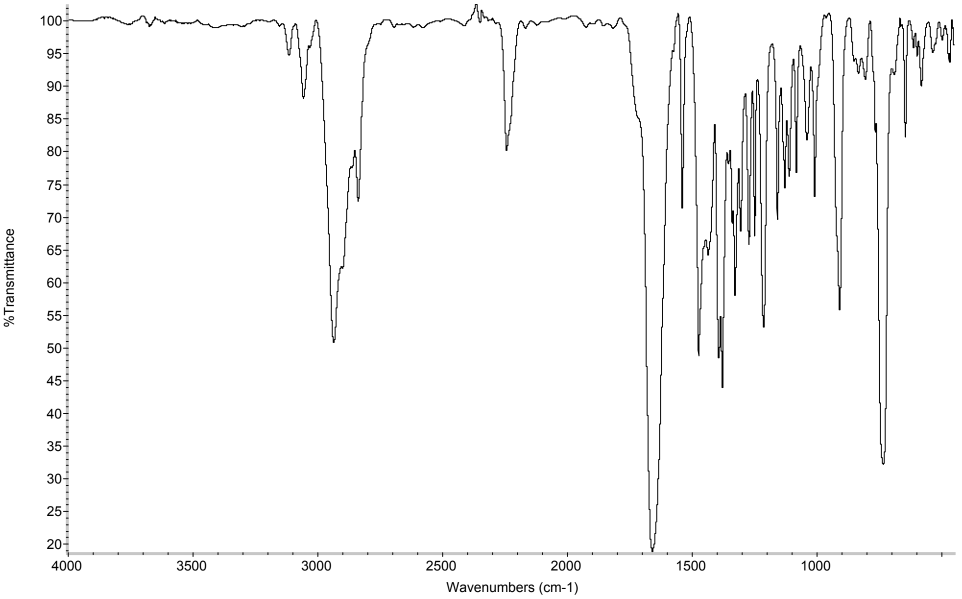


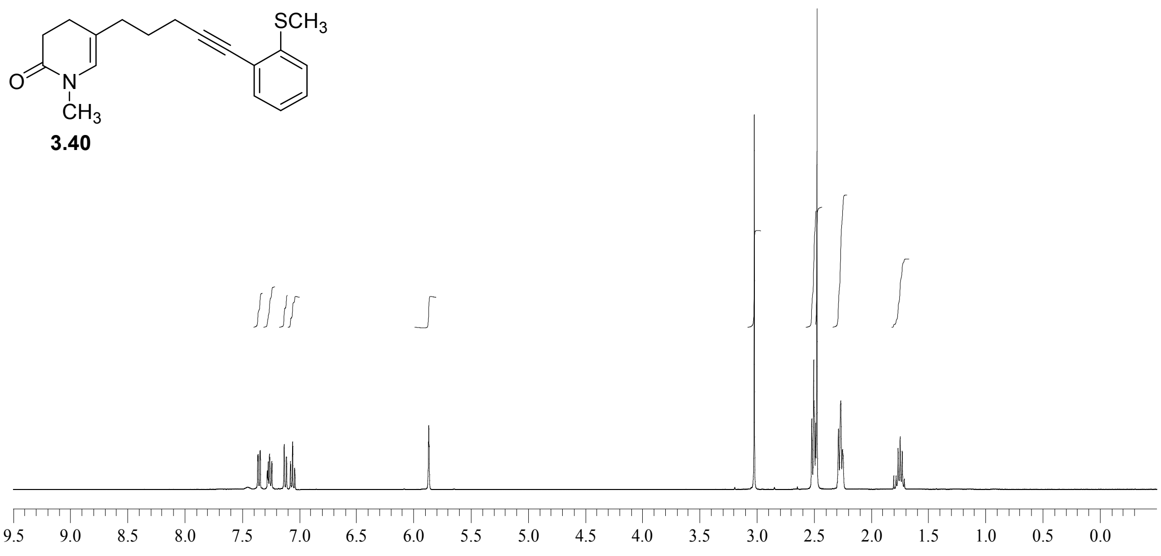
%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

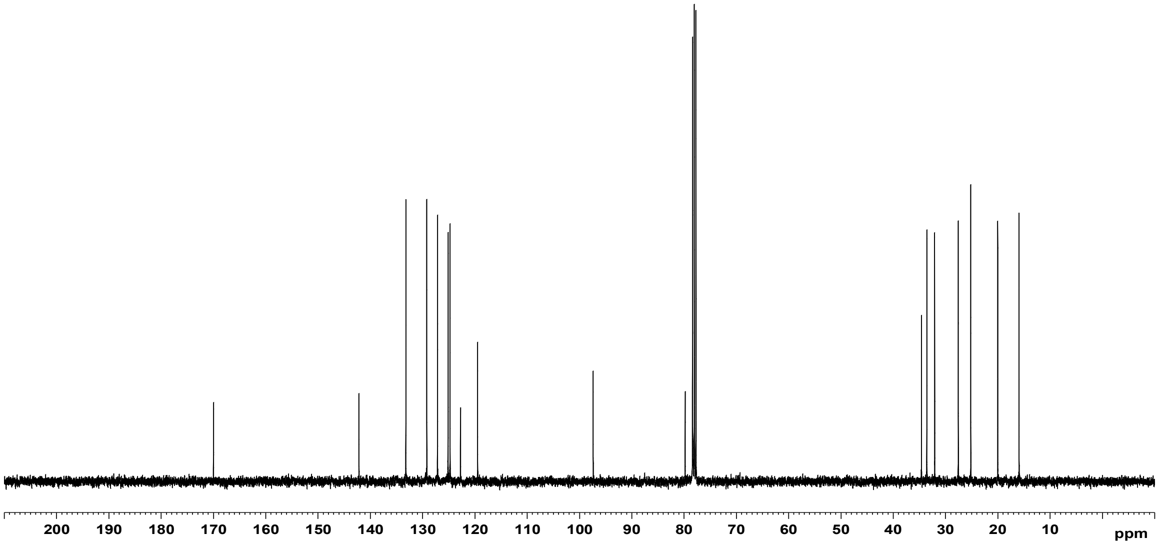

O
N
CH$_3$
N
CH$_3$
9
8
7
6
5
4
3
2
1
0

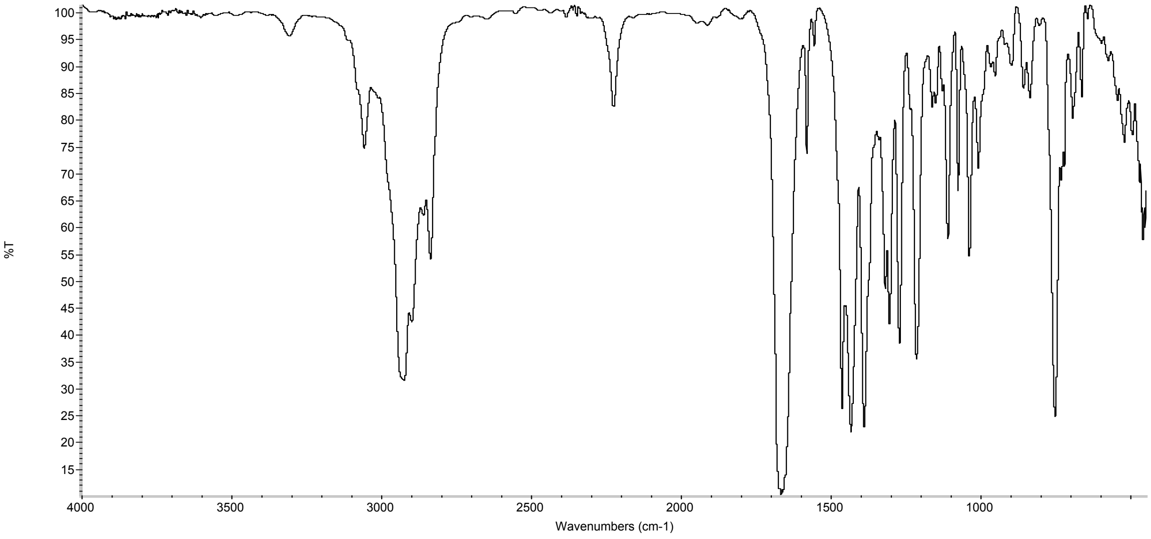
3.39

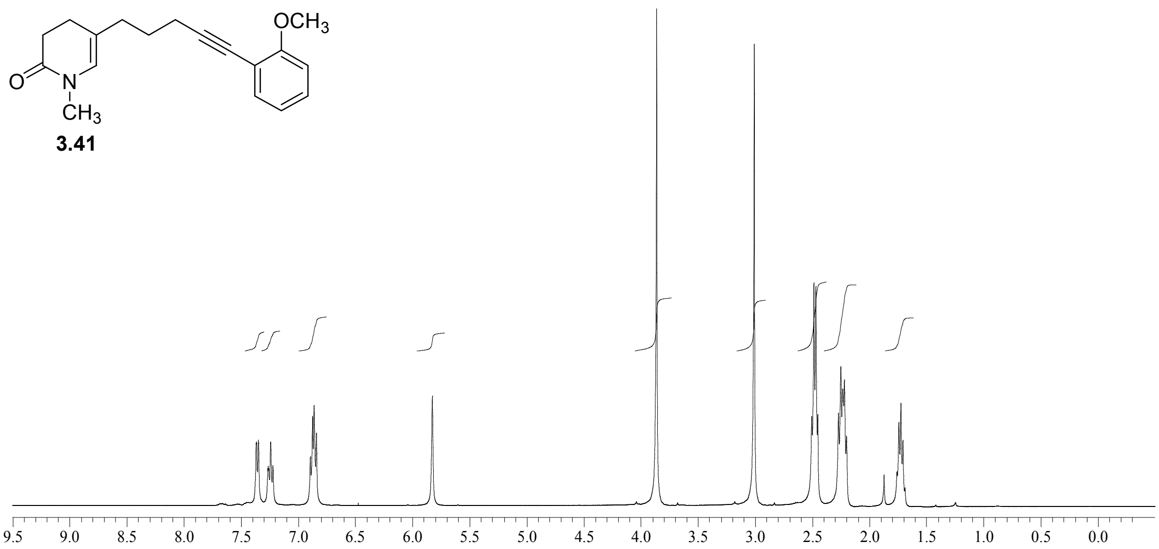

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

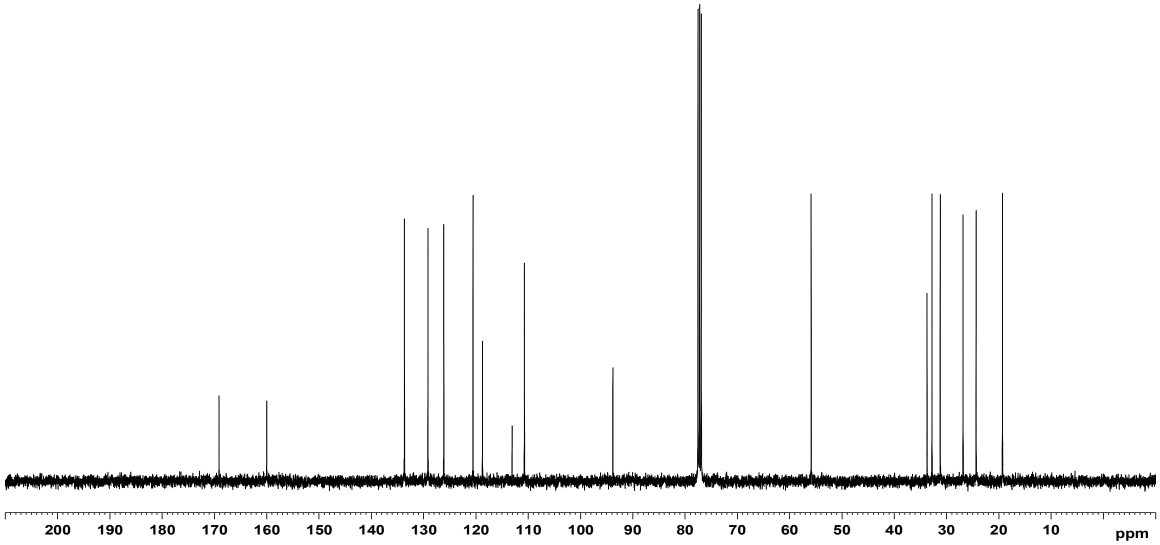

3.40
SCH3
O
N
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

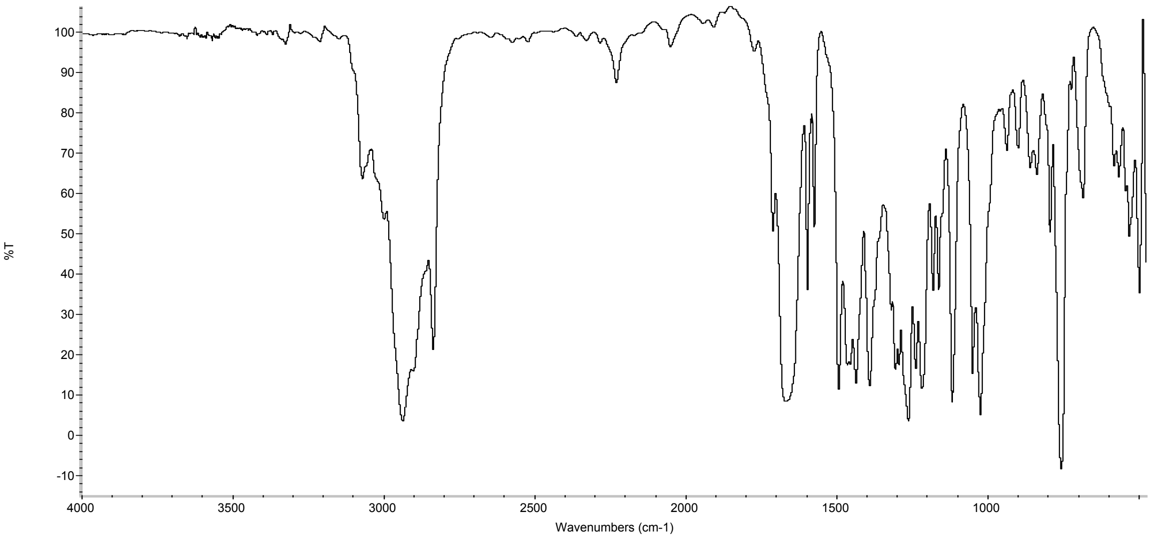

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

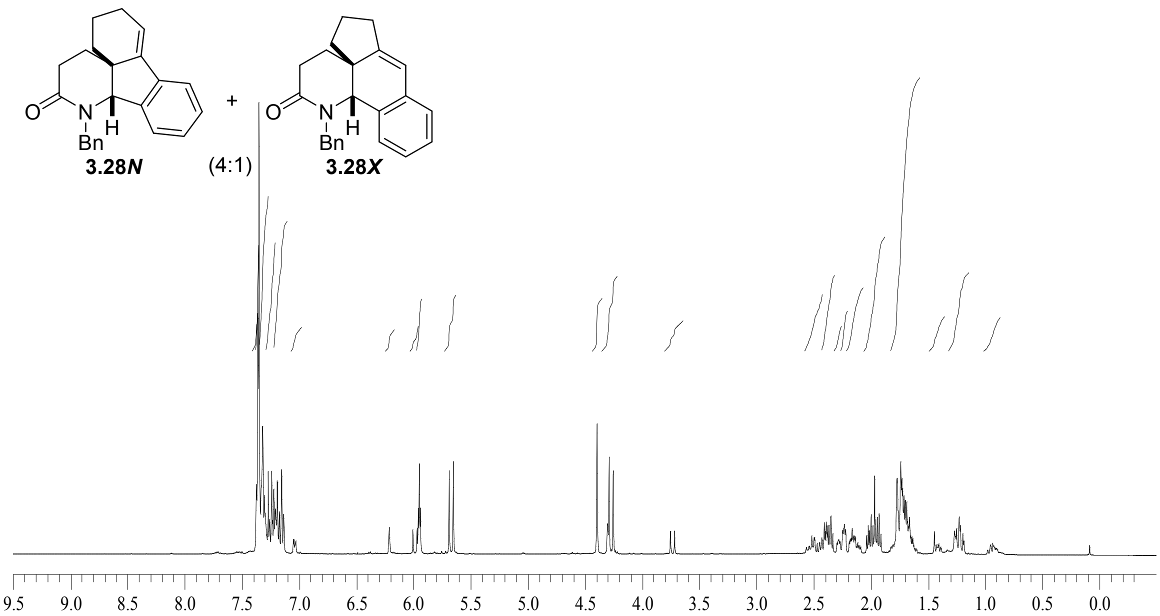

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

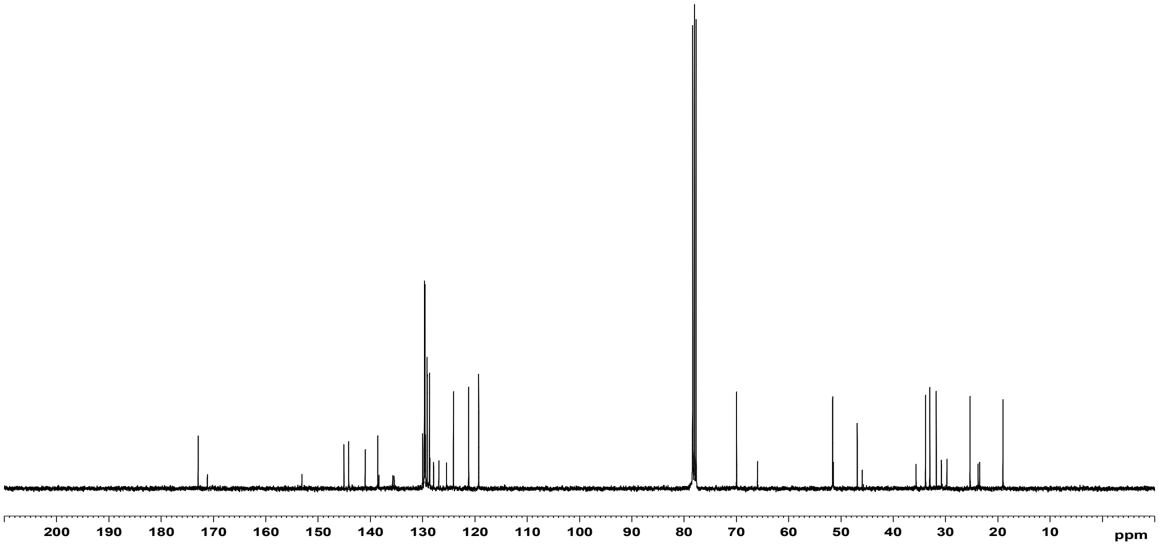

OCH3
O
N
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

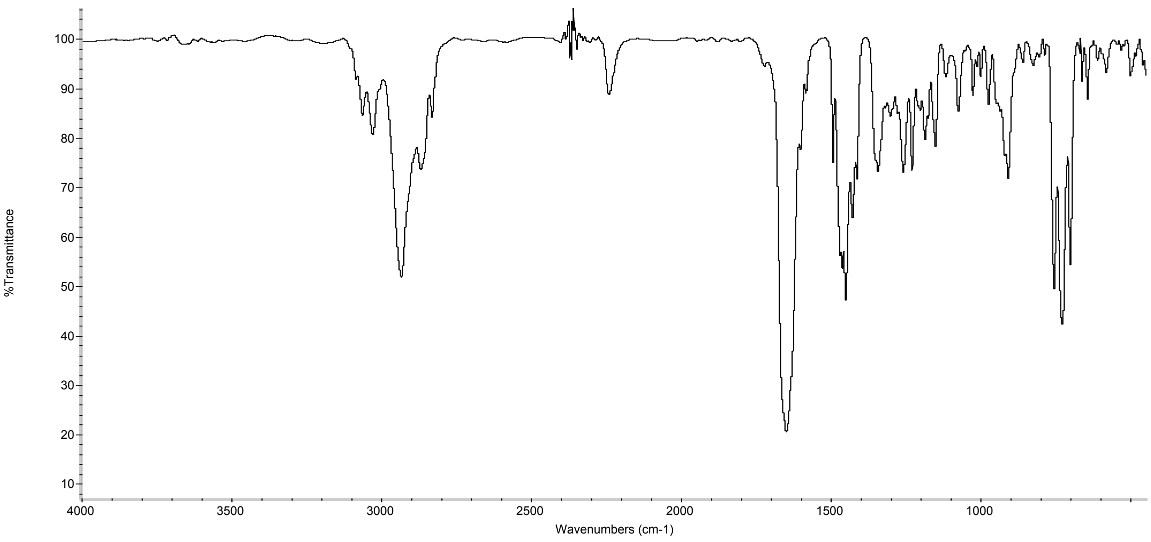
3.41


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
0
-10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

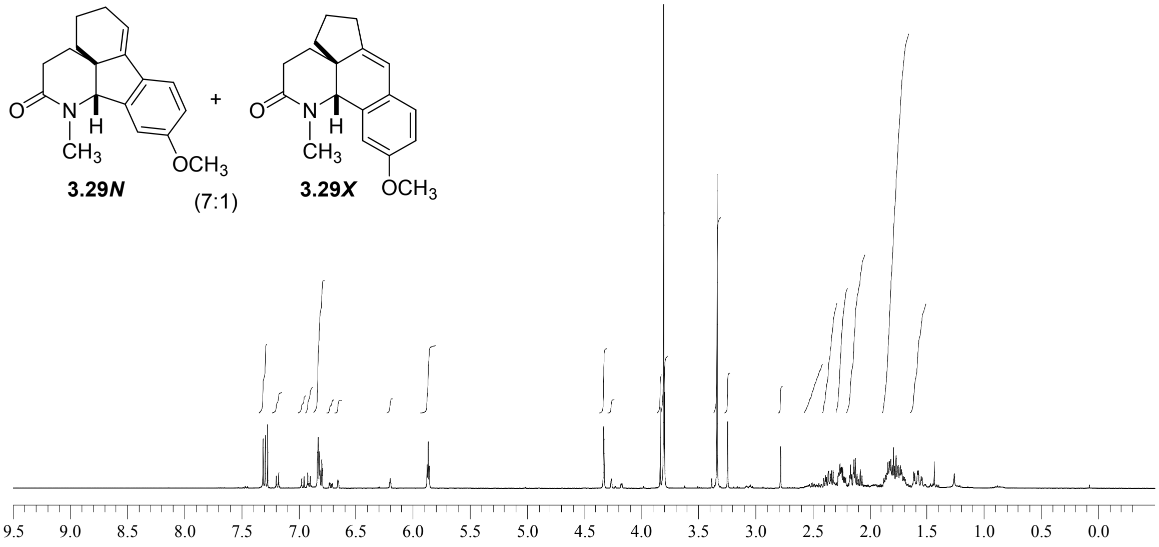

O
N
H
Bn
3.28N
+
(4:1)
O
N
H
Bn
3.28X
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

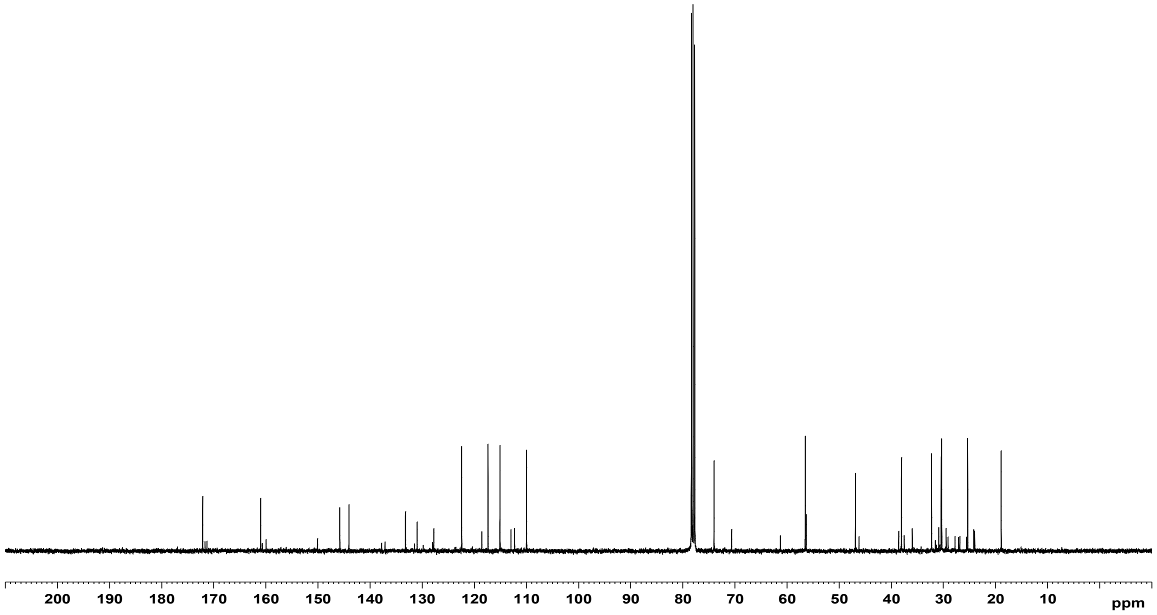

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

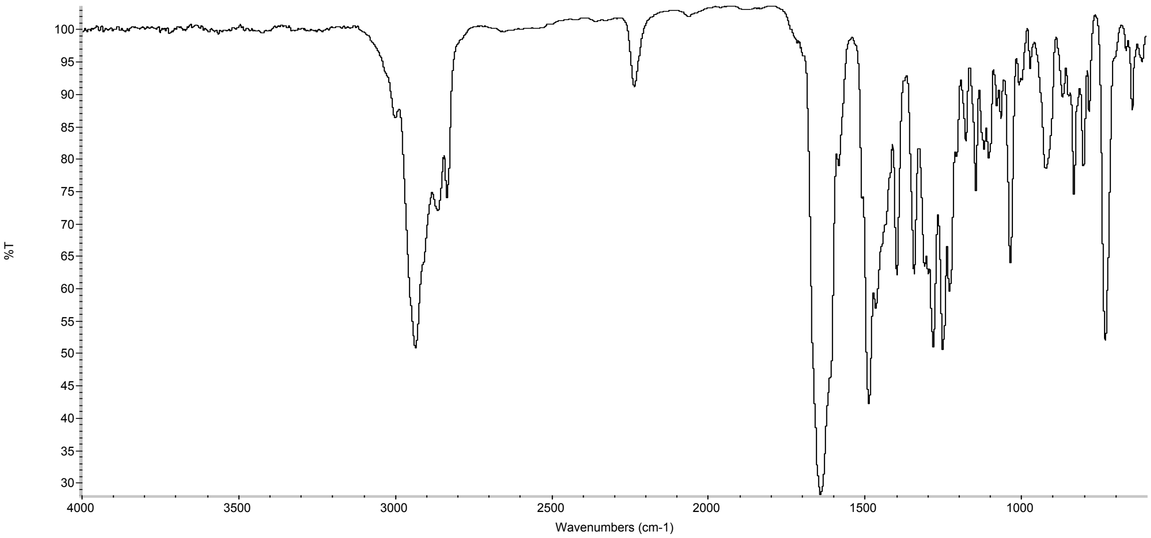

%Transmittance
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

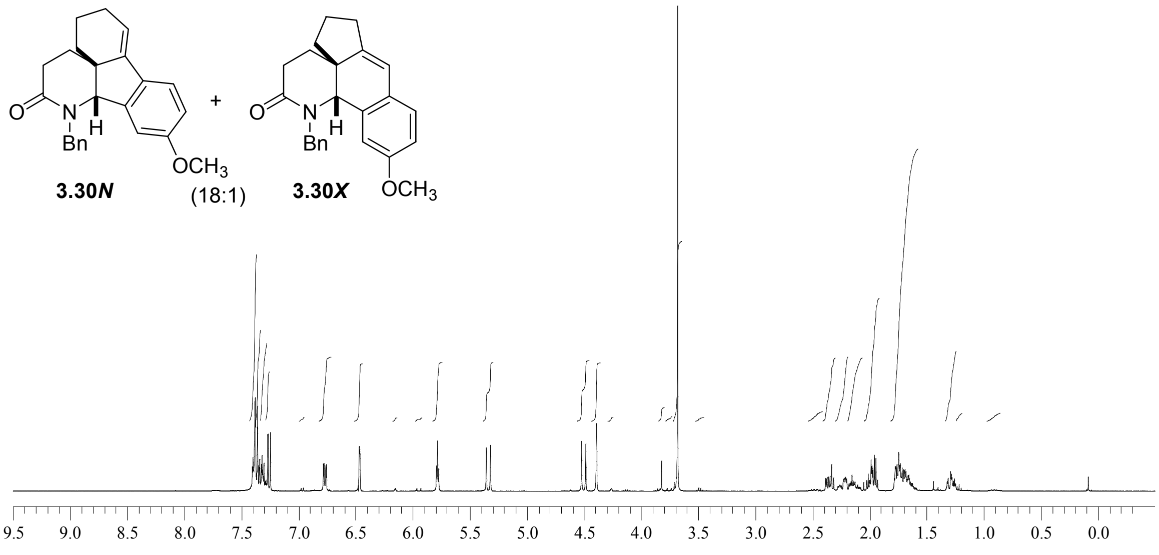
O
N
H
CH3
OCH3
+
O
N
H
CH3
OCH3

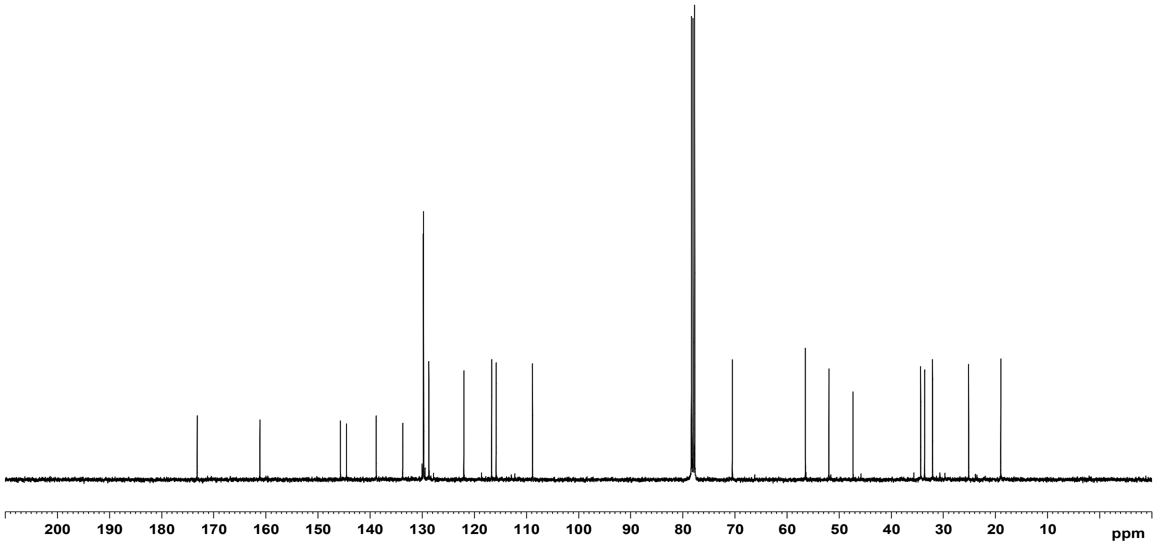
3.29*N* (7:1) **3.29*X***

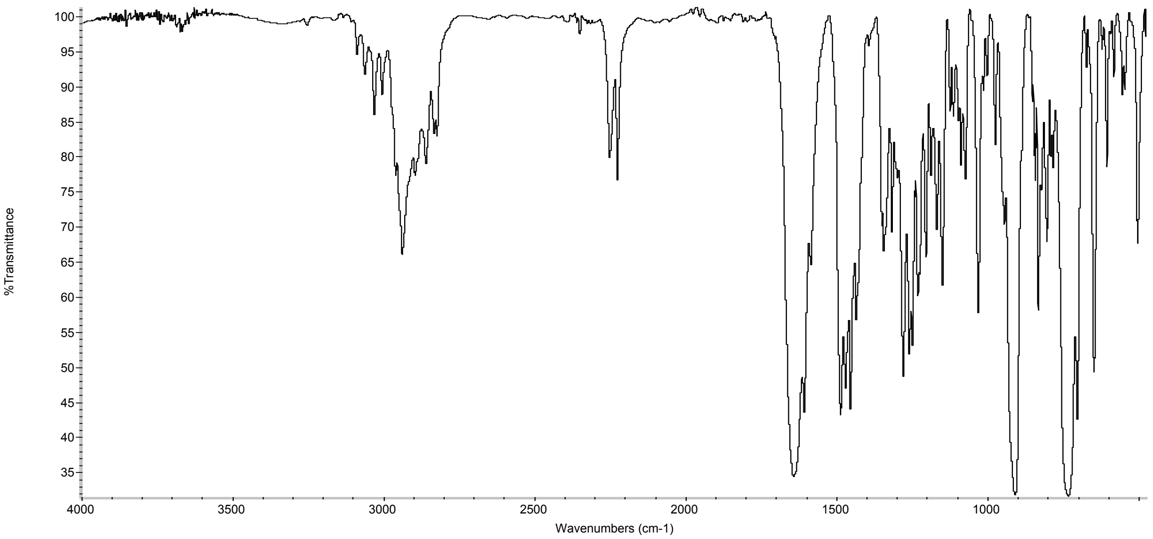

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

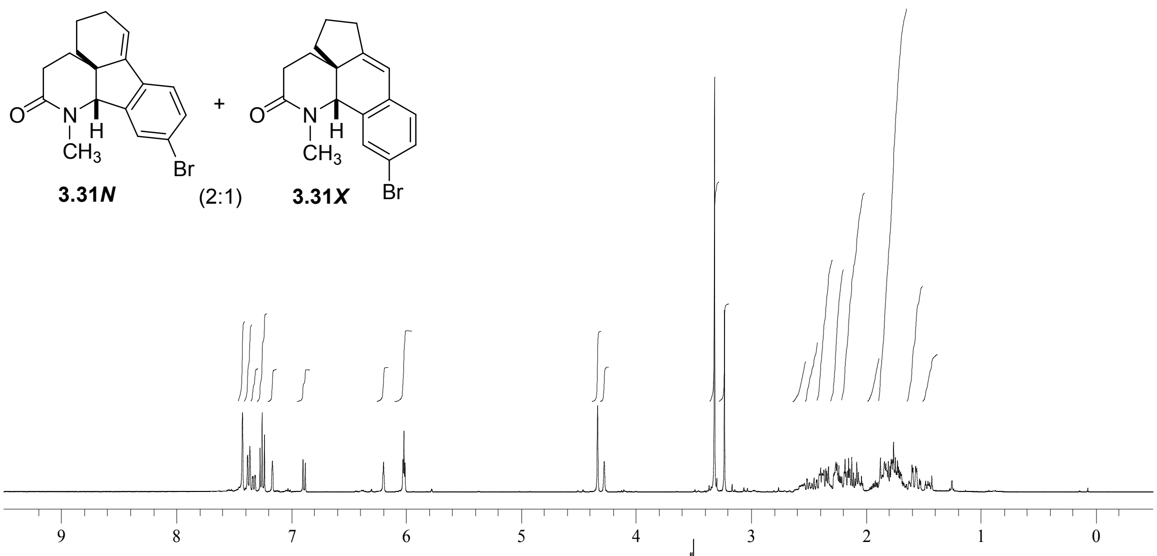

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

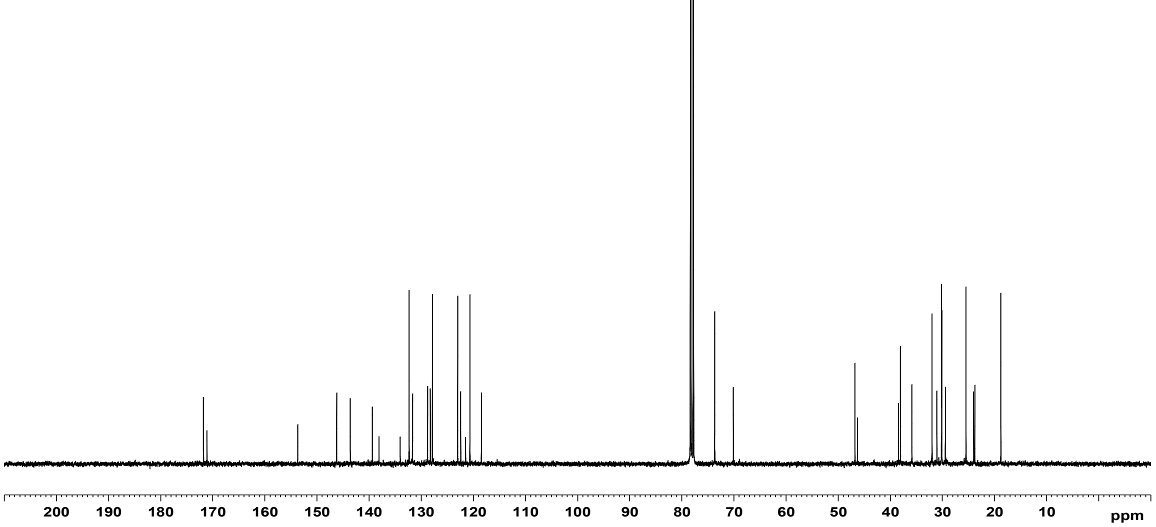

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

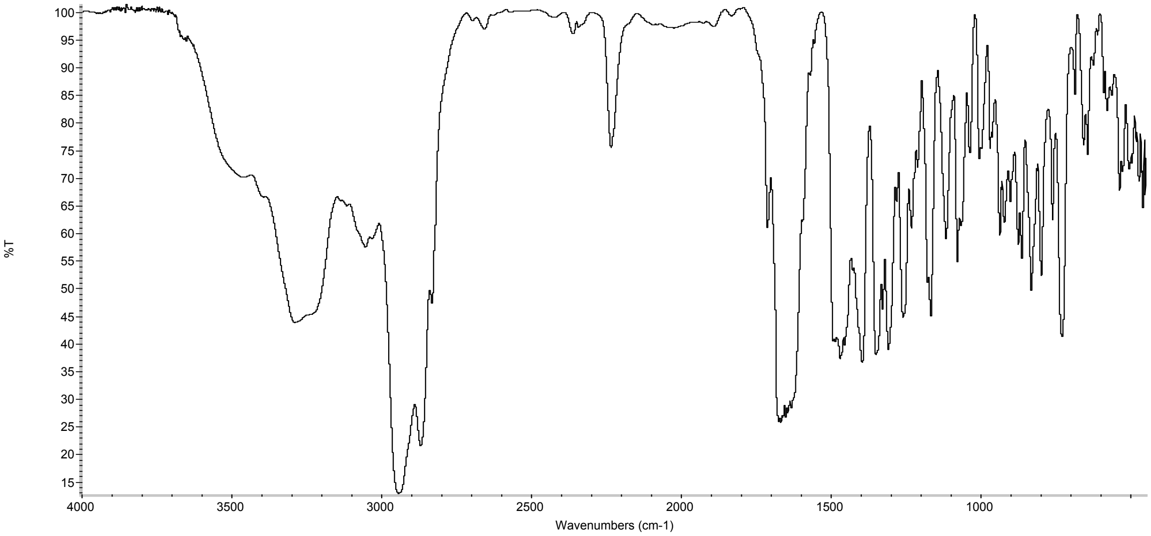

O
N
H
Bn
OCH3
3.30N
+
(18:1)
O
N
H
Bn
3.30X
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

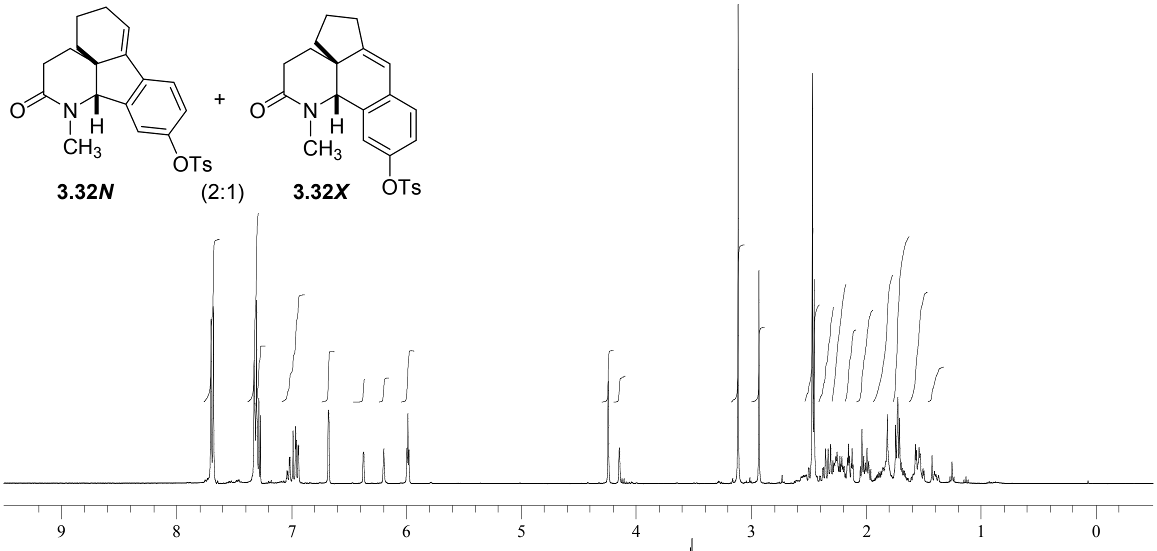

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

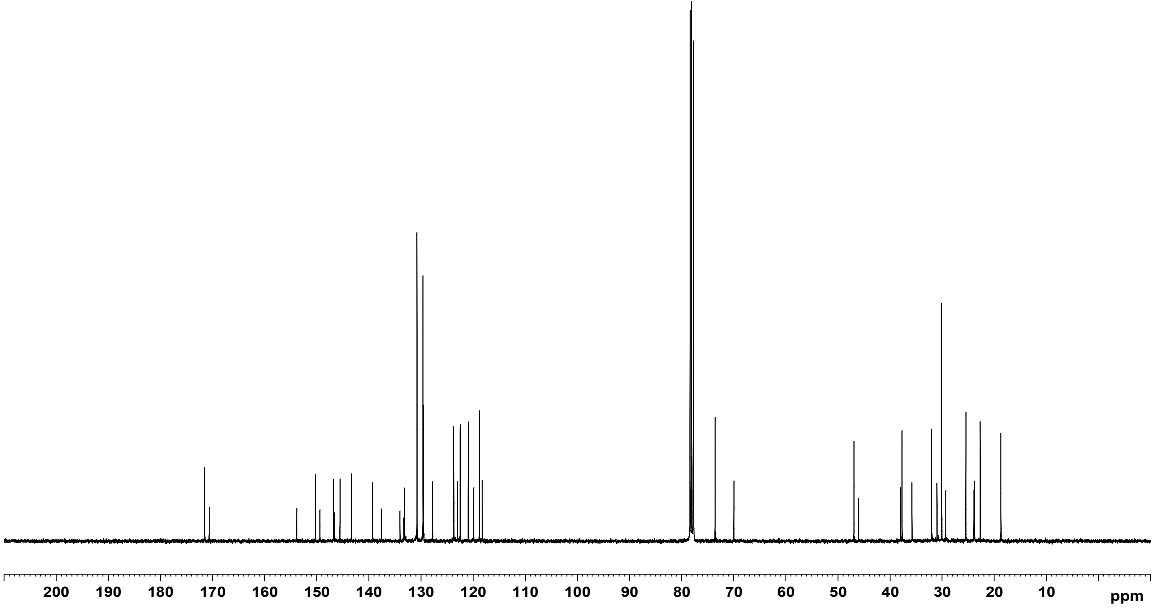

O
N
H
CH3
Br
3.31N
+
(2:1)
O
N
H
CH3
3.31X
Br
9
8
7
6
5
4
3
2
1
0

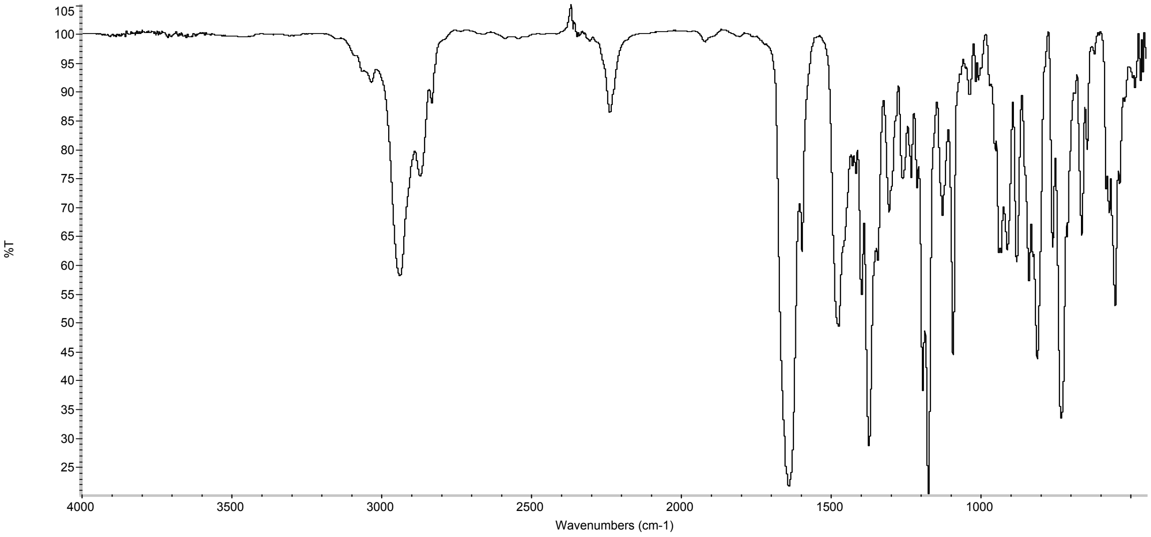

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

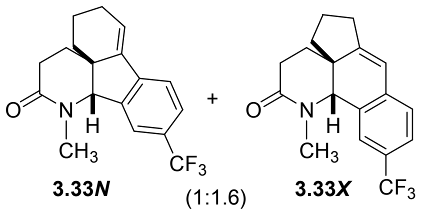

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
H
CH3
OTs
+
O
N
H
CH3
OTs
9
8
7
6
5
4
3
2
1
0

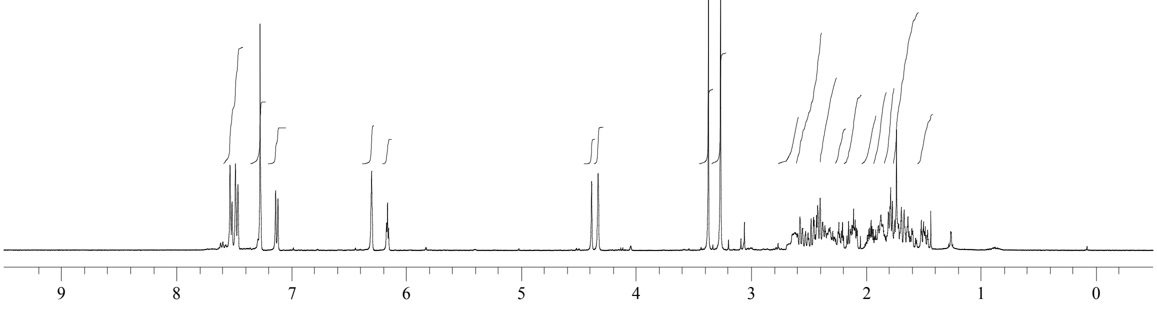
3.32*N* (2:1) **3.32*X***

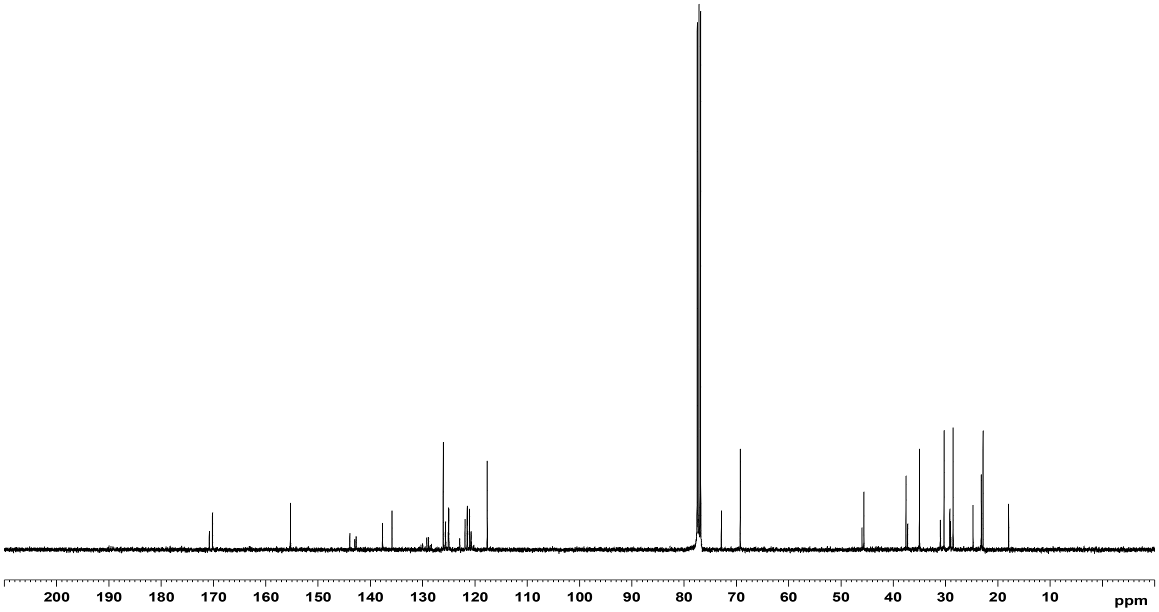

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

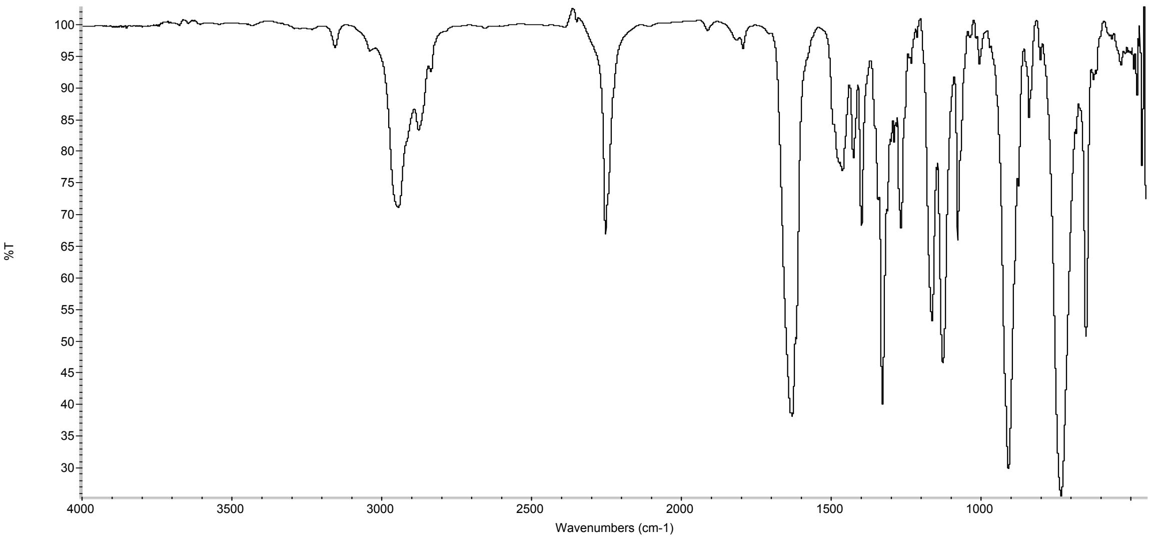

105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

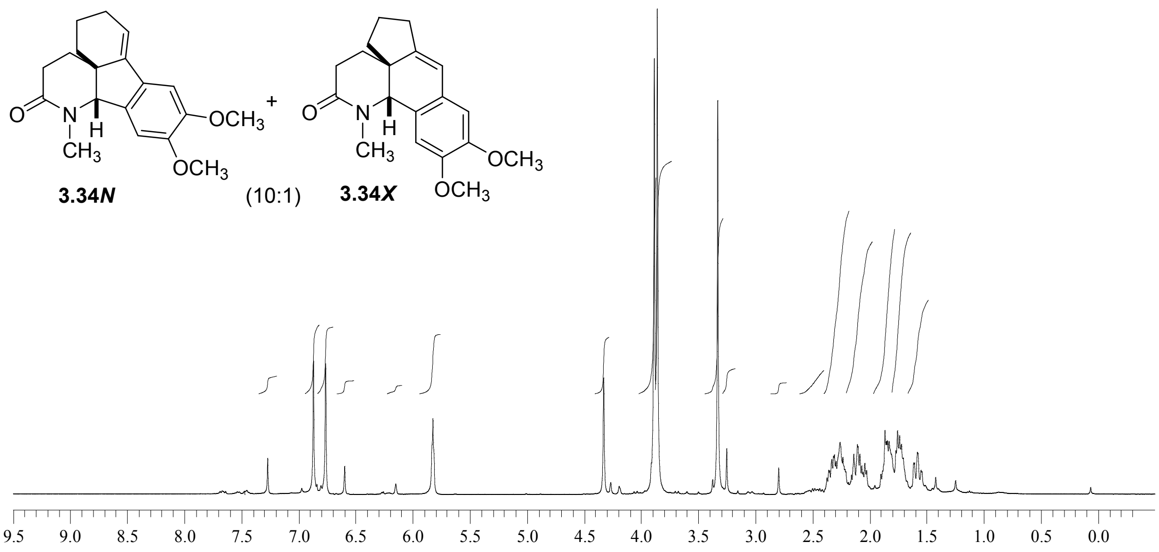


3.33*N* (1:1.6) **3.33*X***

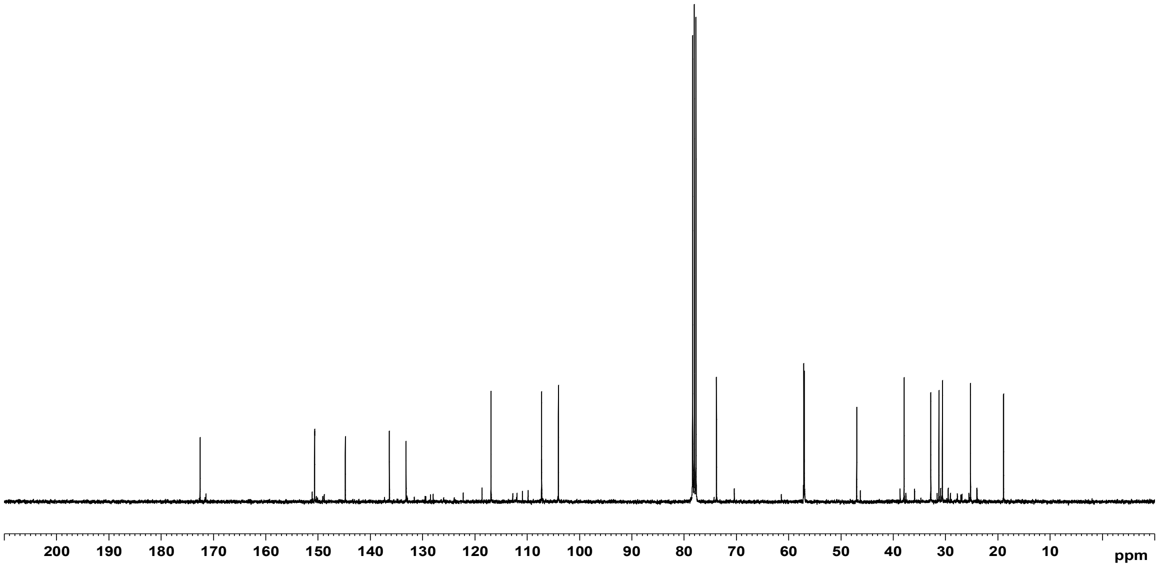




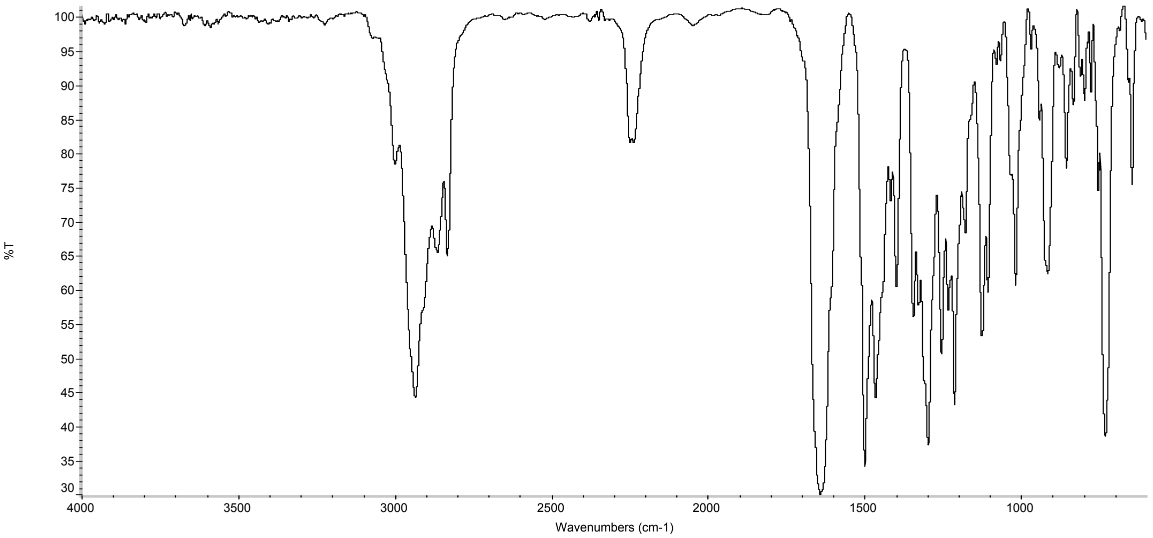




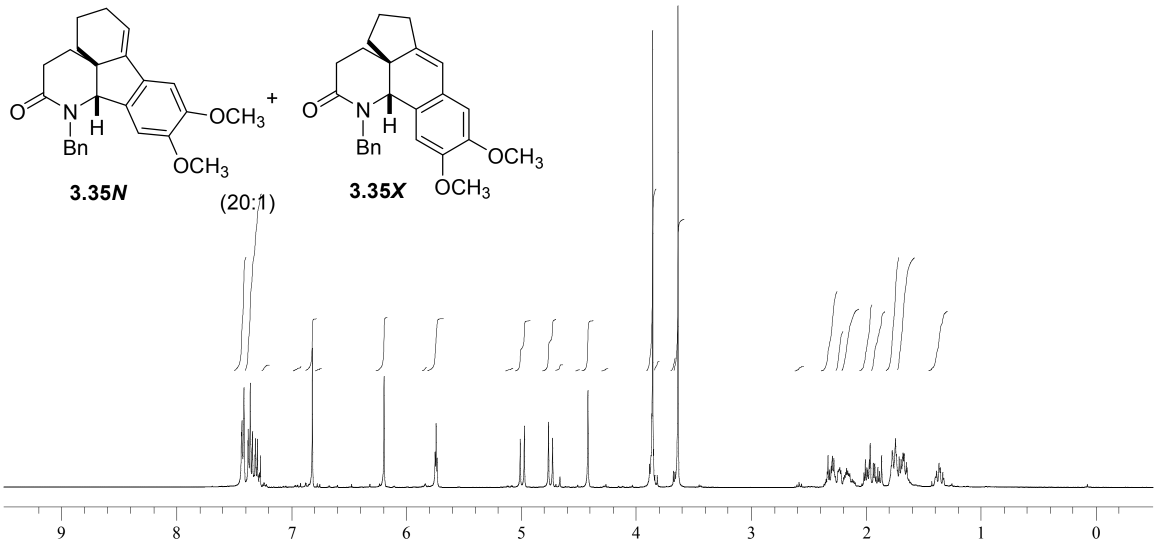
O
N
H
CH3
OCH3
OCH3
+
3.34N
(10:1)
3.34X
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



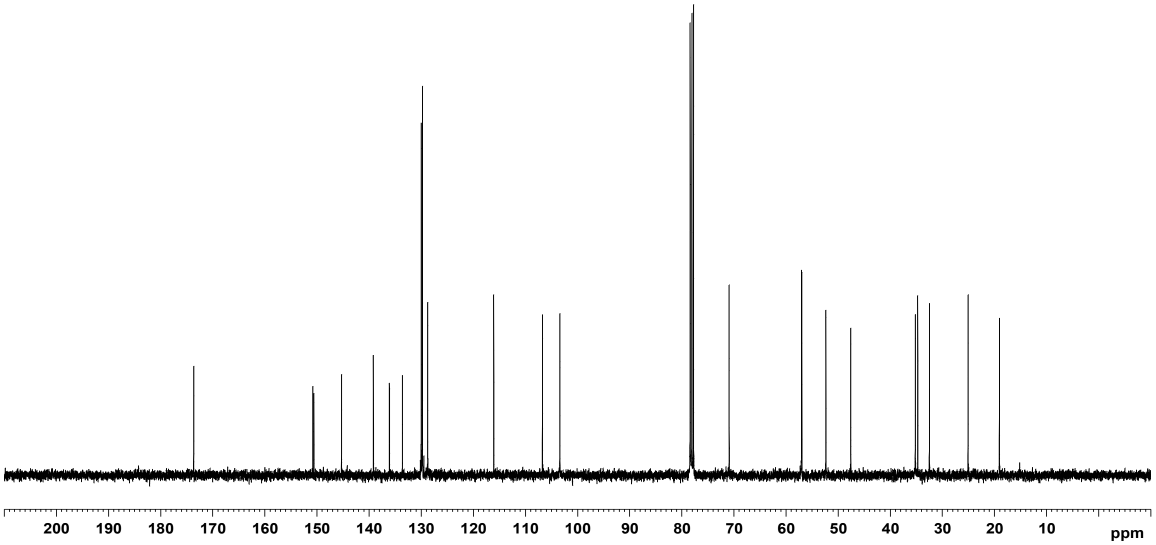
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

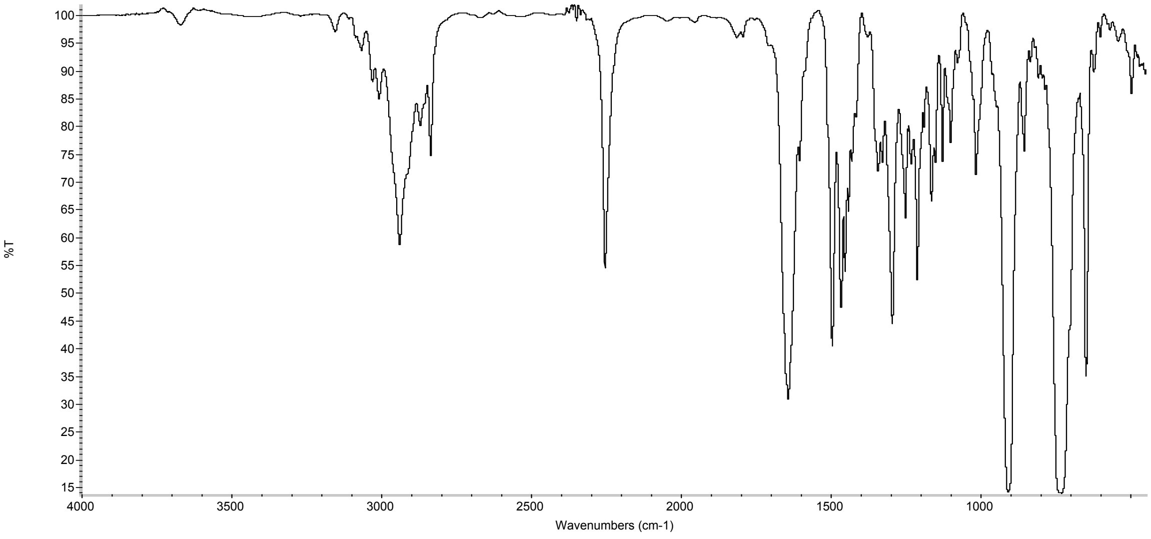


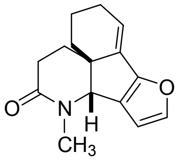
%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



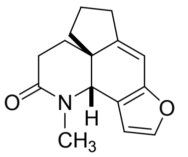
3.35*N* (20:1) **3.35*X***



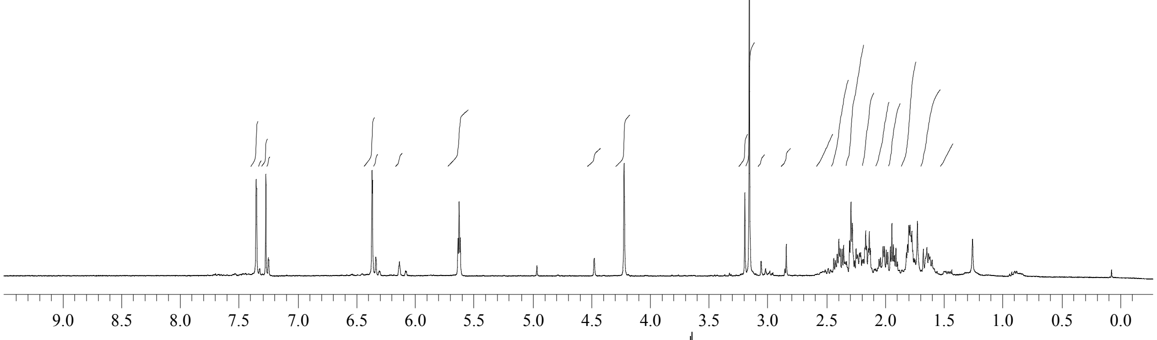


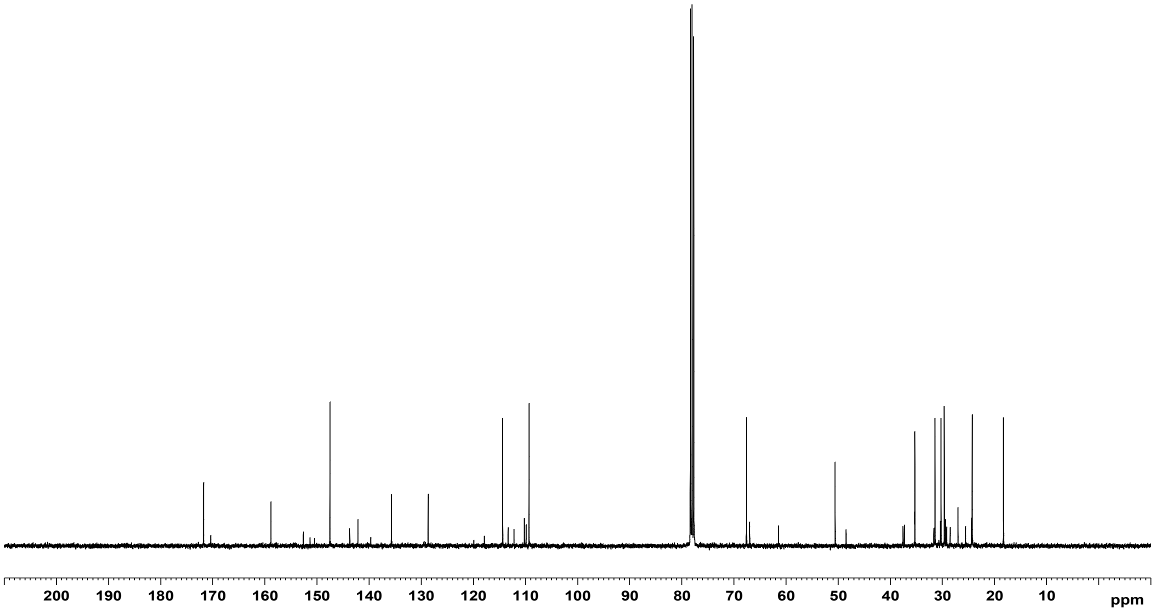

O
O
N
H
CH3

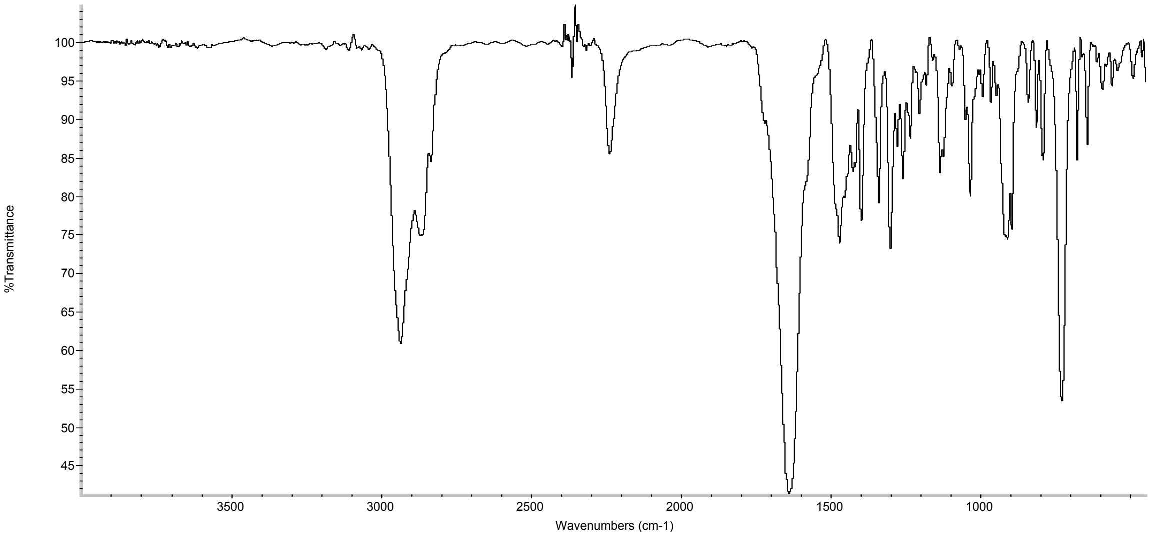
+

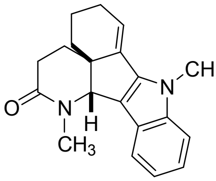

O
O
N
H
CH3

3.36*N* (7:1) **3.36*X***


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

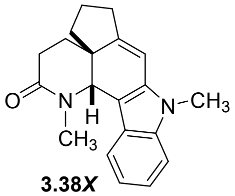

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

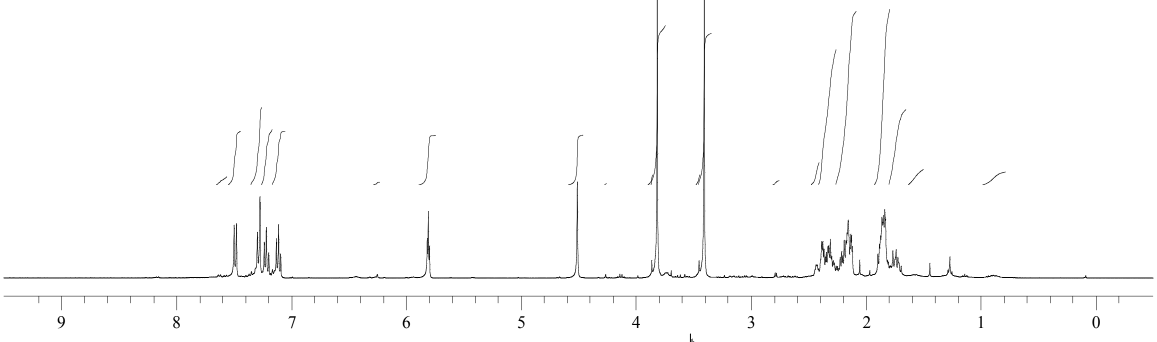

O
N
H
CH3
N
CH3

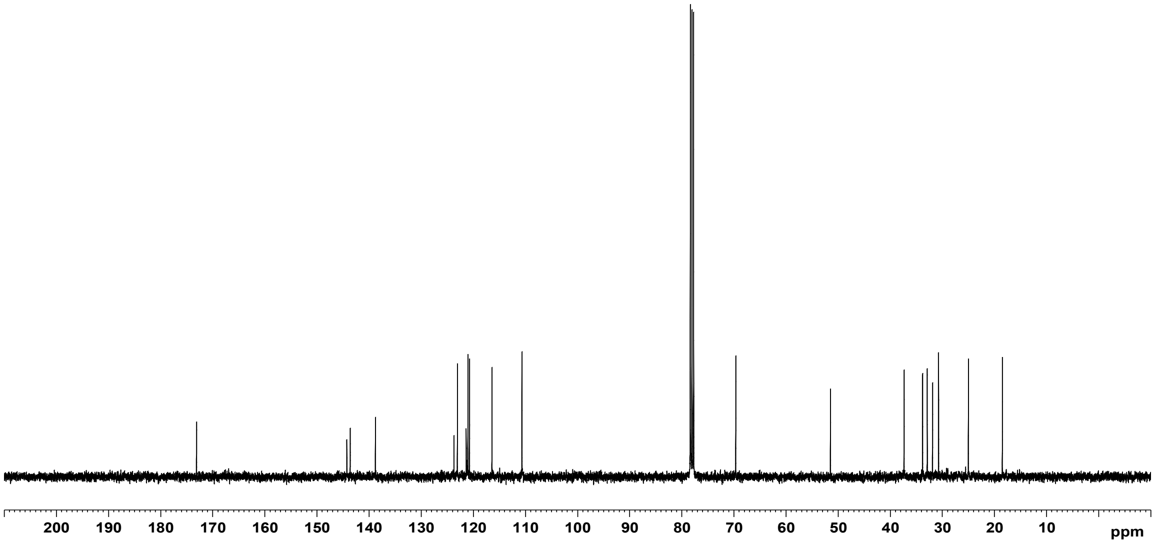
3.38*N*

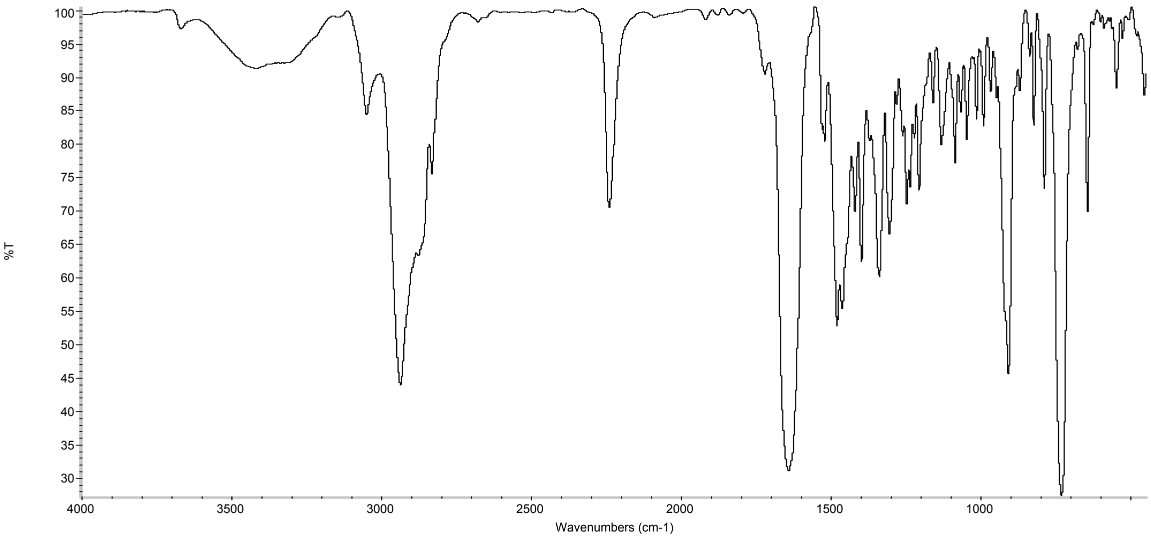
+


O
N
H
CH3
N
CH3

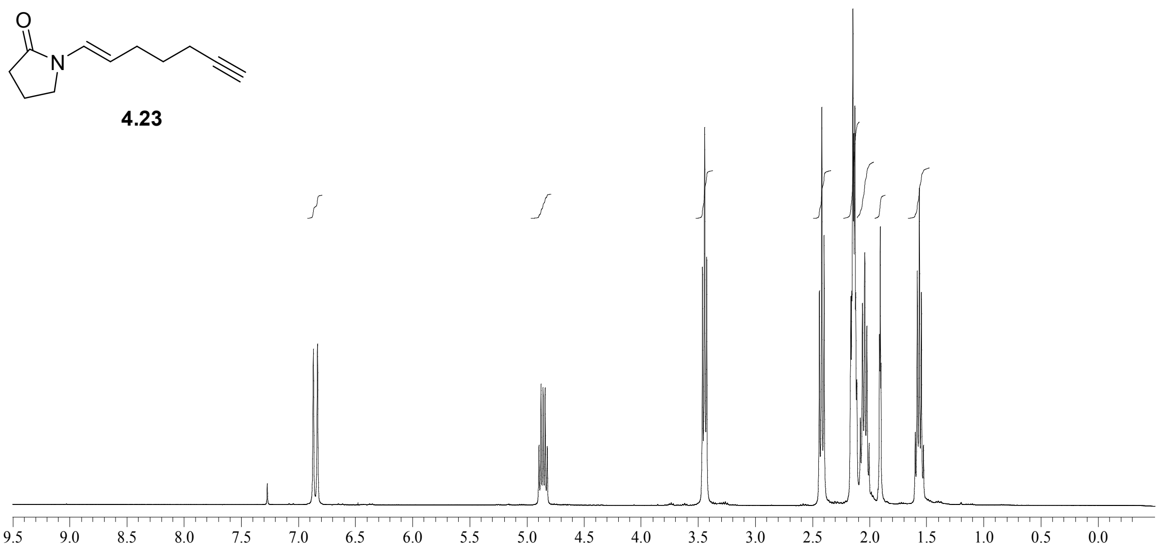
3.38*X*


9
8
7
6
5
4
3
2
1
0

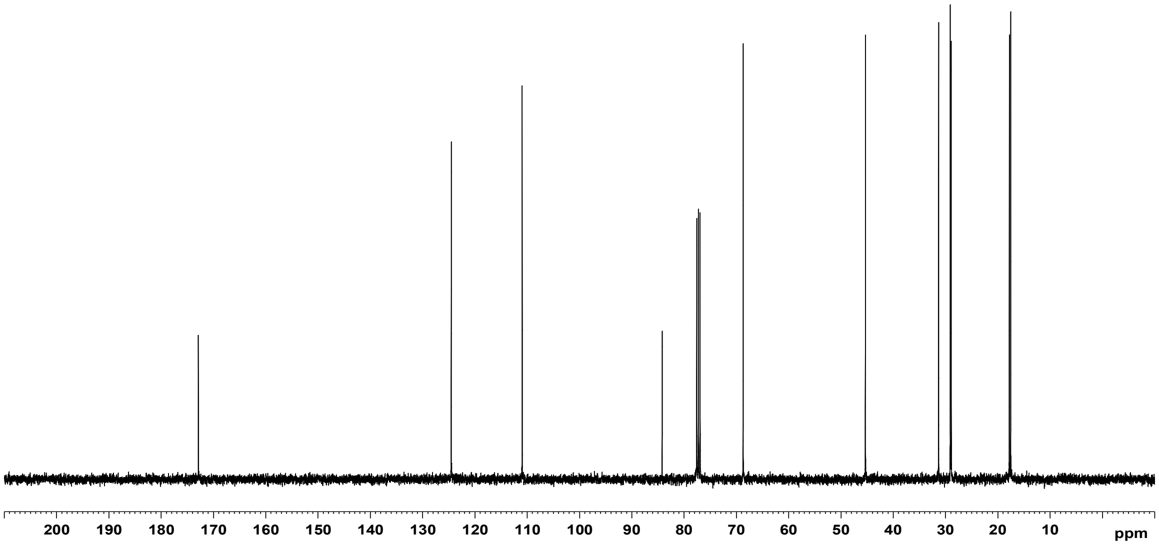

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

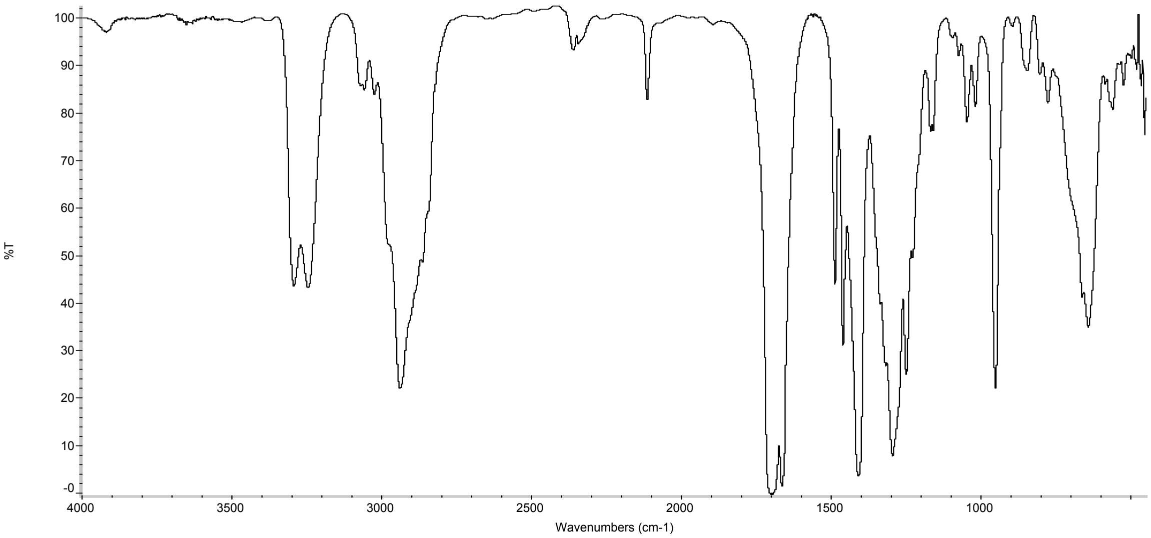

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

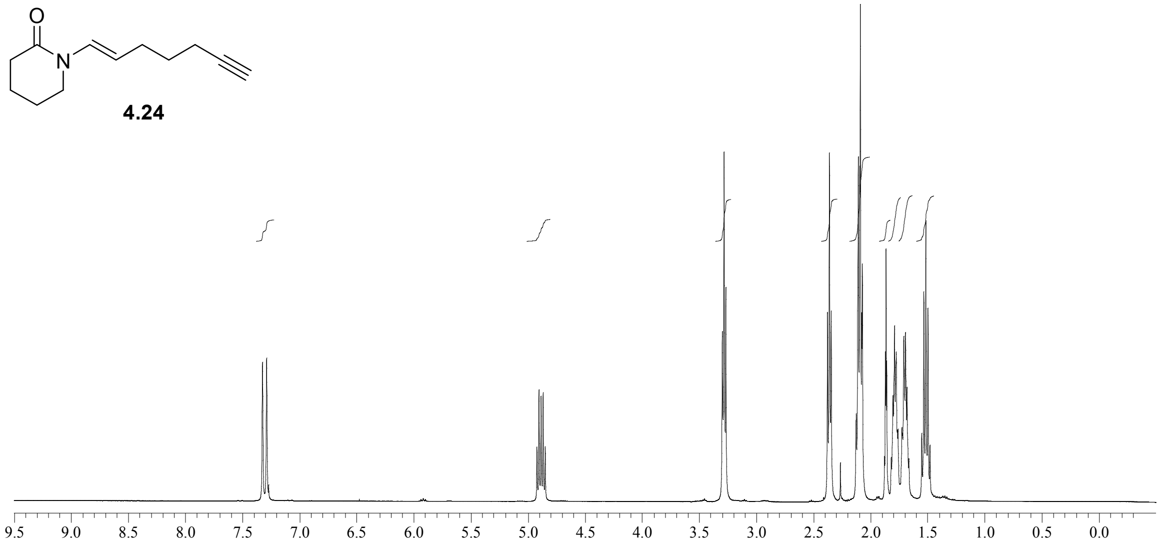
Appendix C: Selected Spectra for Chapter 4


O
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

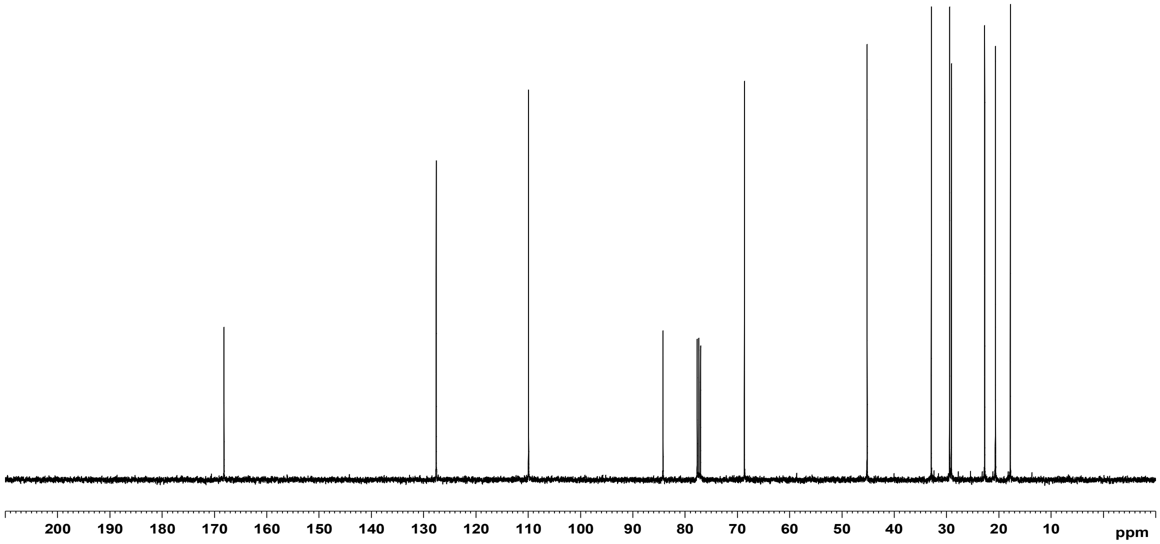
4.23

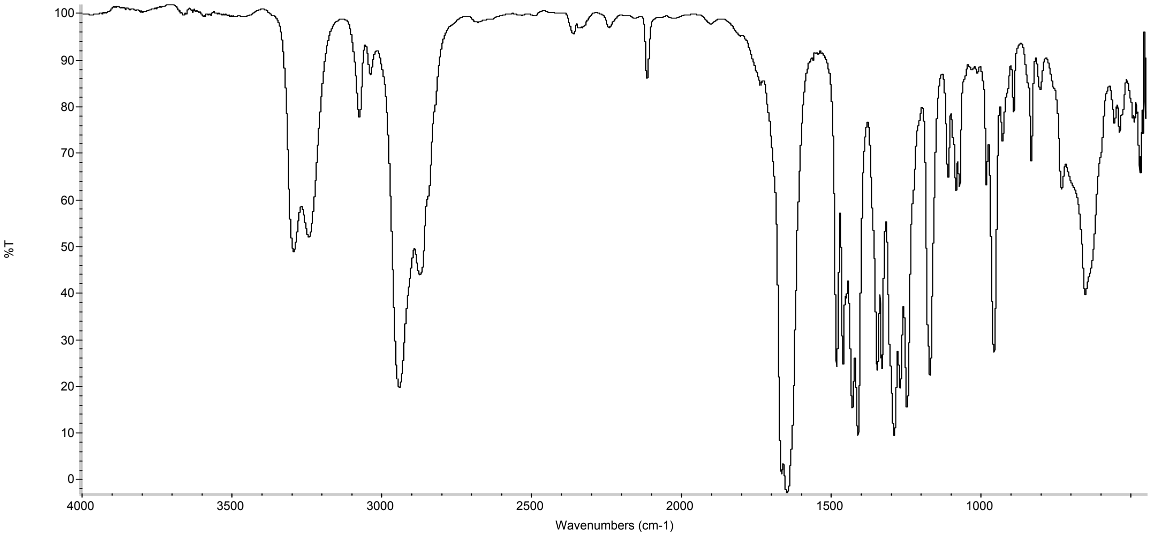

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

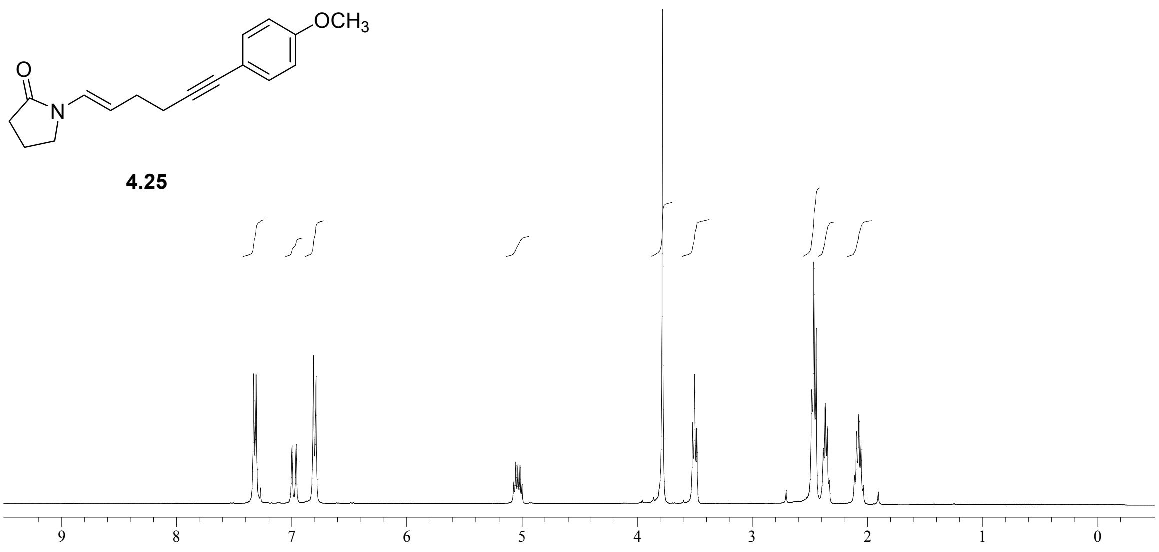

%T
100
90
80
70
60
50
40
30
20
10
-0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

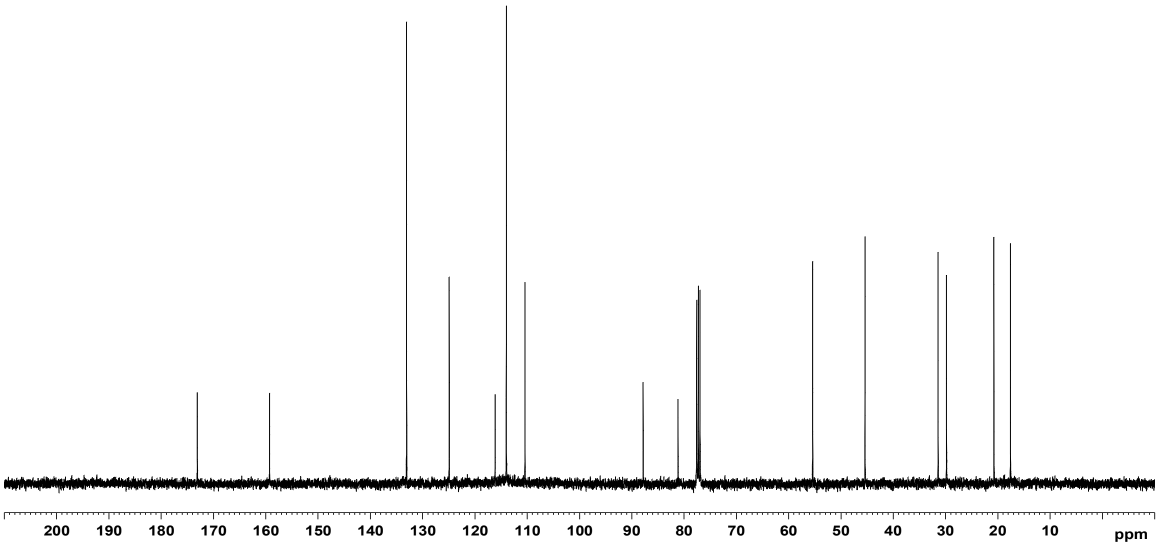
4.24

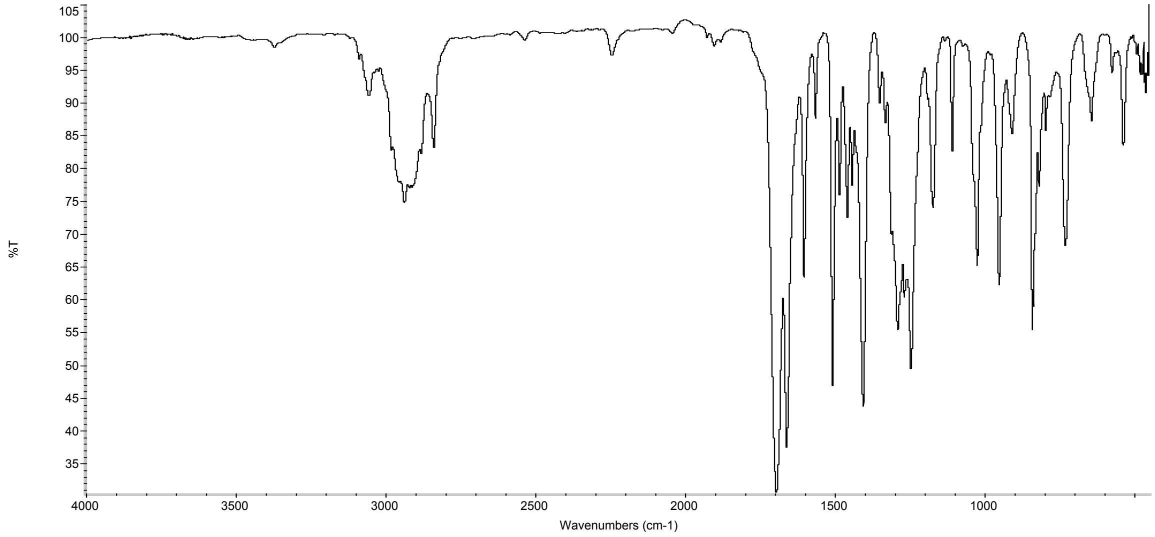

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

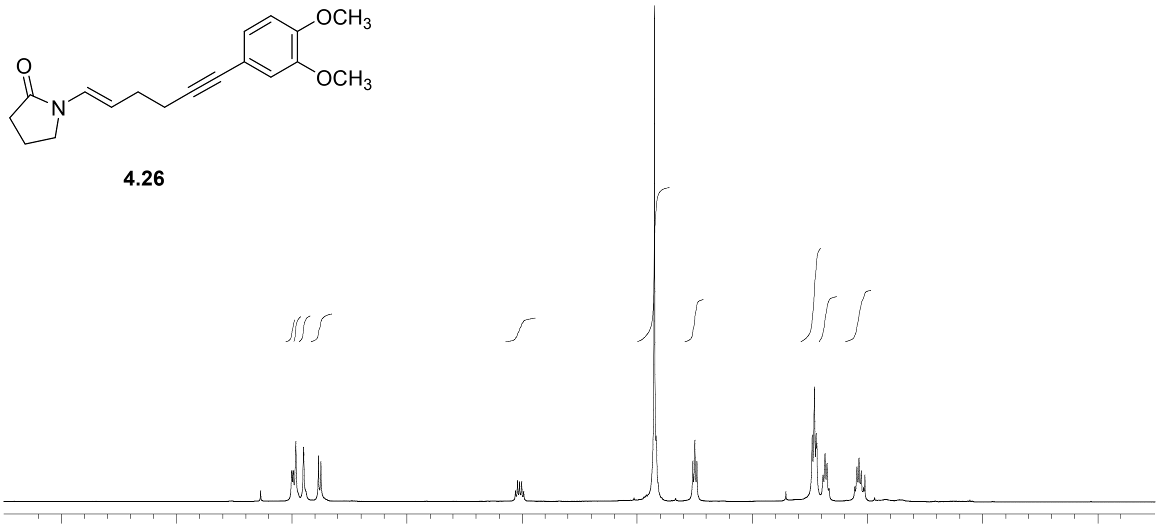

100
90
80
70
60
50
40
30
20
10
0
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

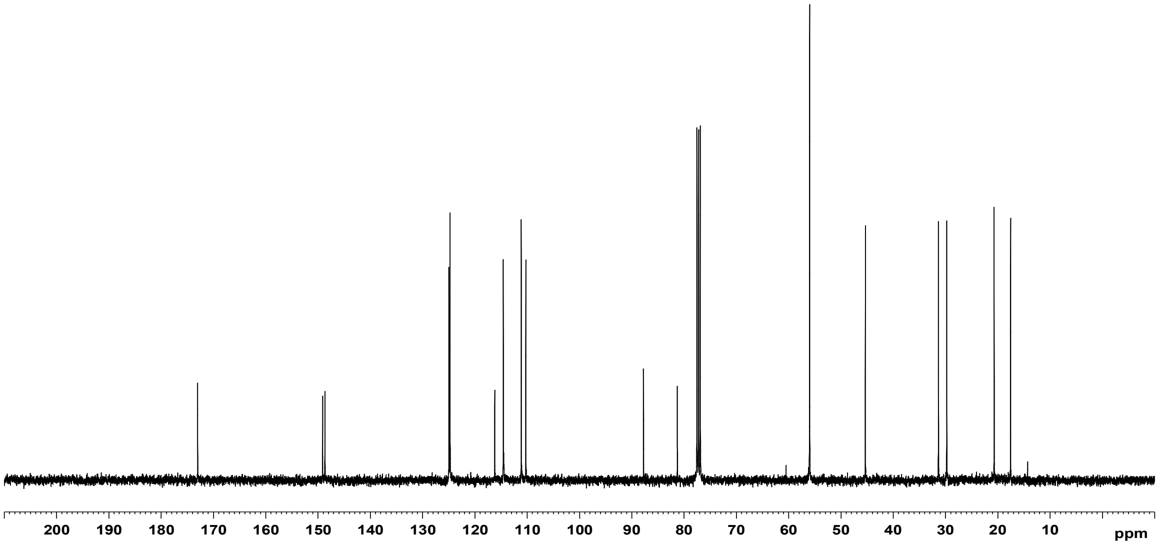

OCH3
O
N
9
8
7
6
5
4
3
2
1
0

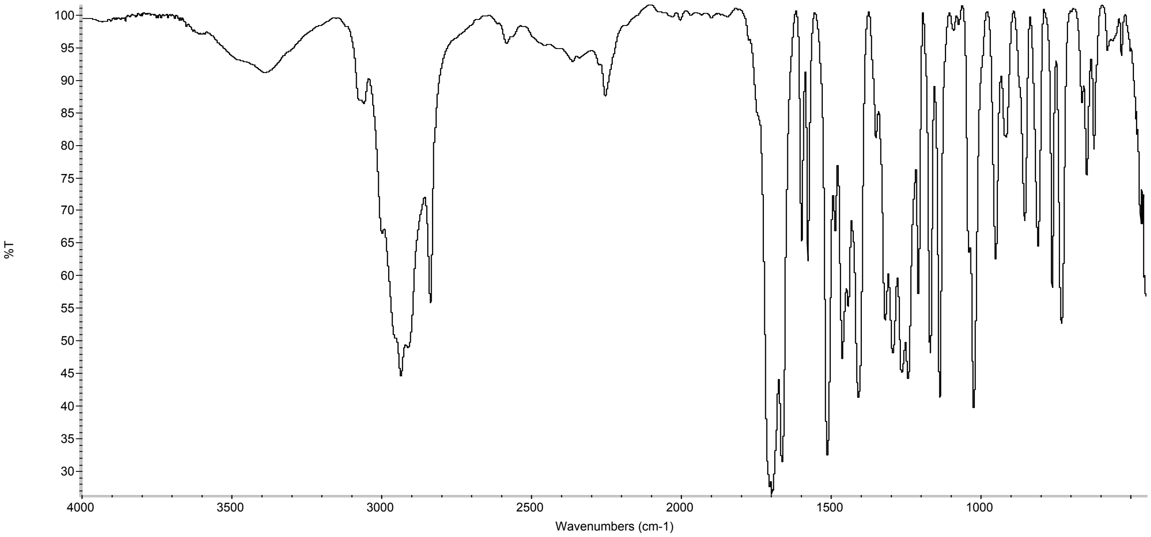
4.25

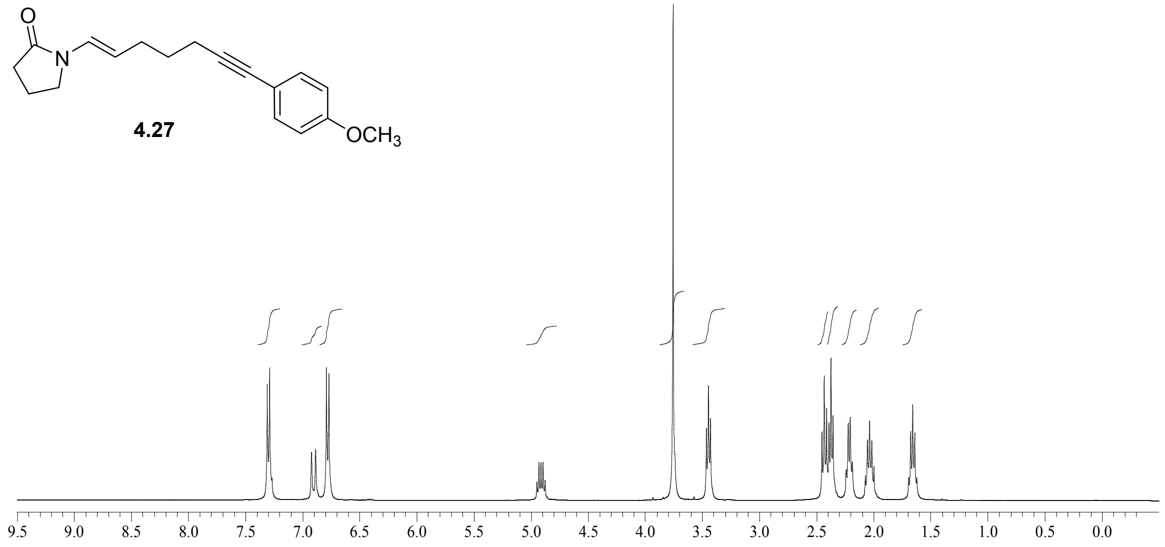

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

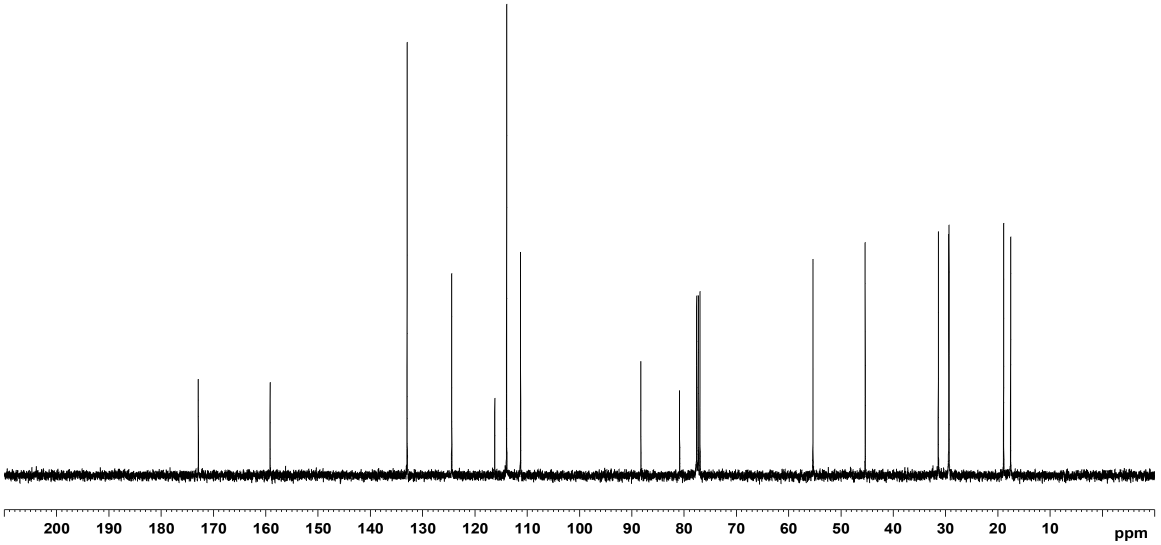

OCH3
OCH3
O
N
4.26
9
8
7
6
5
4
3
2
1
0

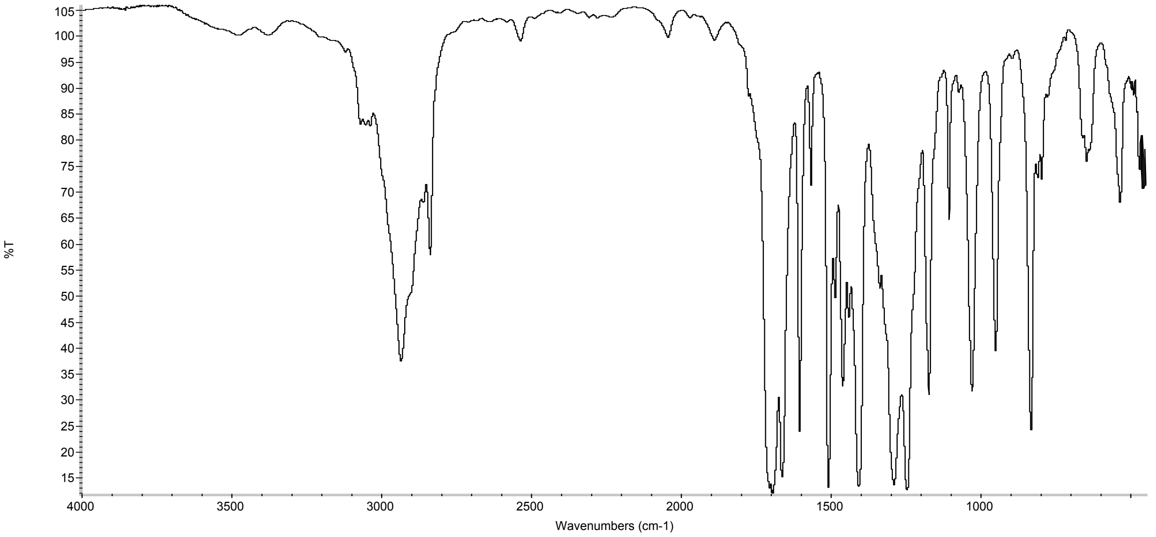

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

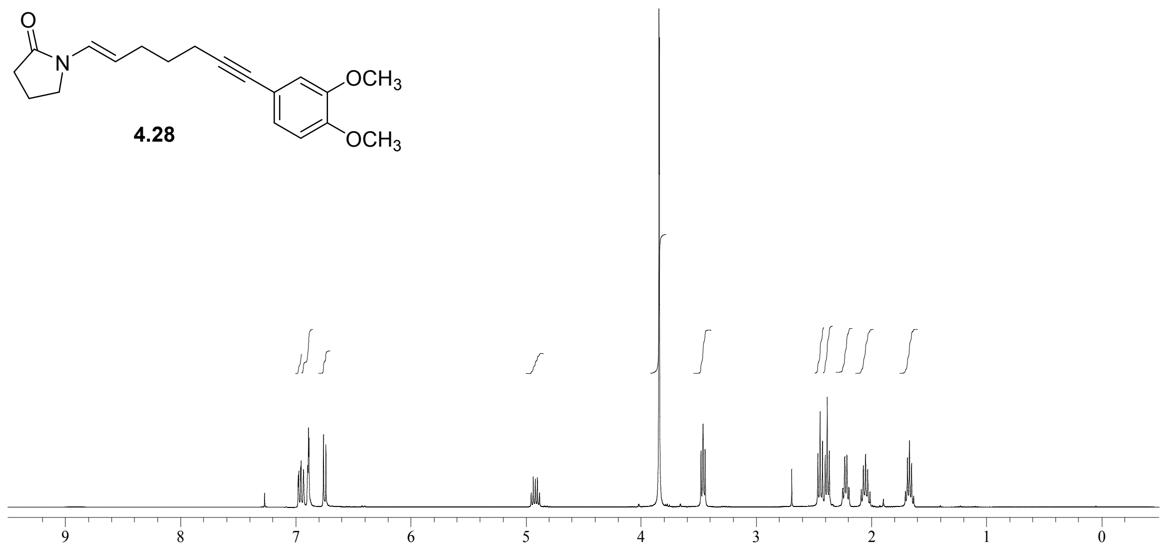

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

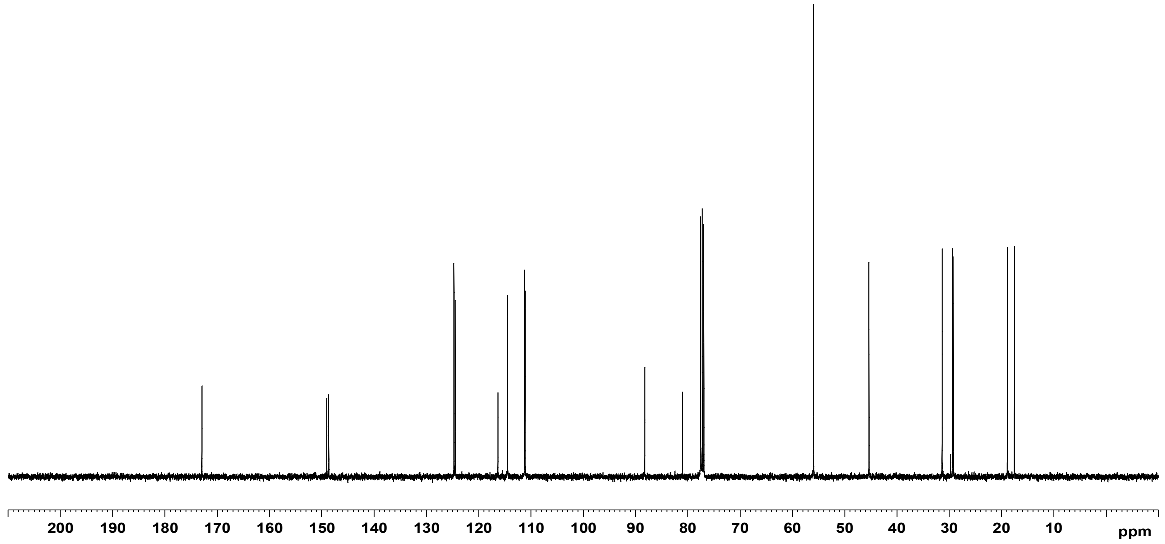

O
N
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

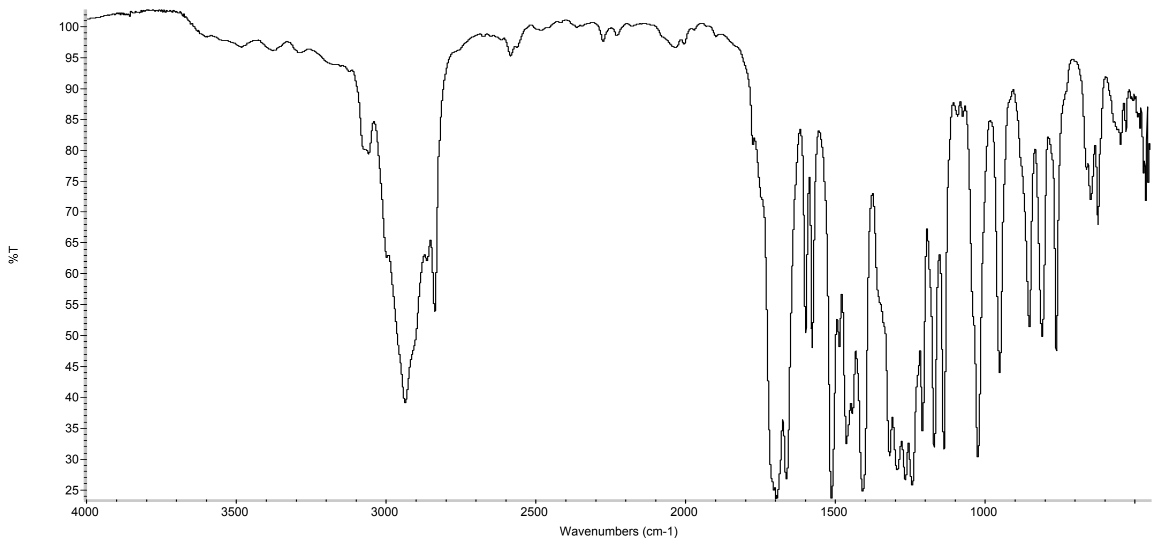
4.27

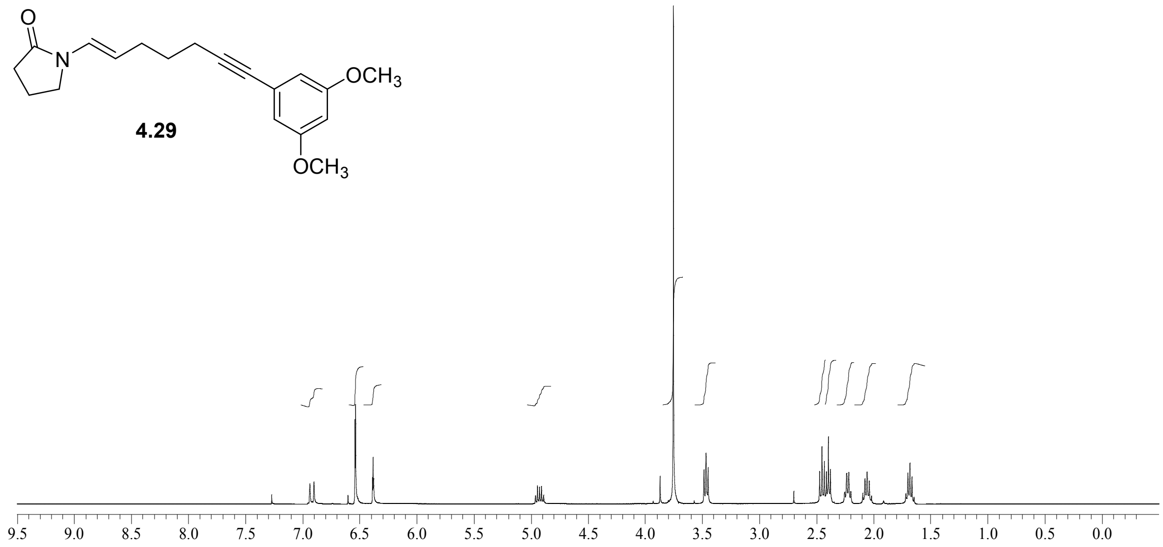

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

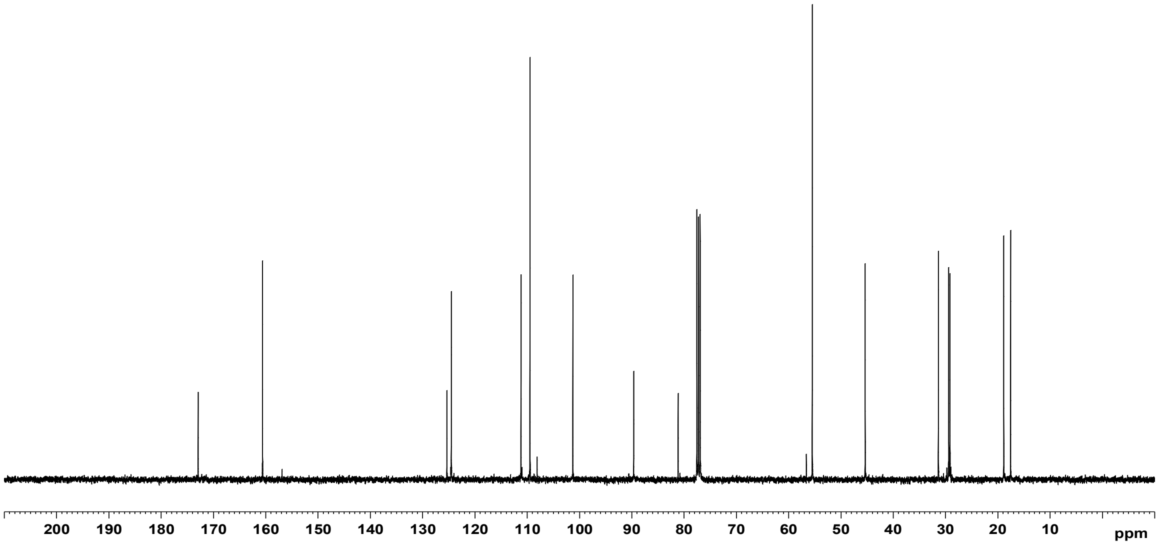

4.28
O
N
OCH$_3$
OCH$_3$
9
8
7
6
5
4
3
2
1
0

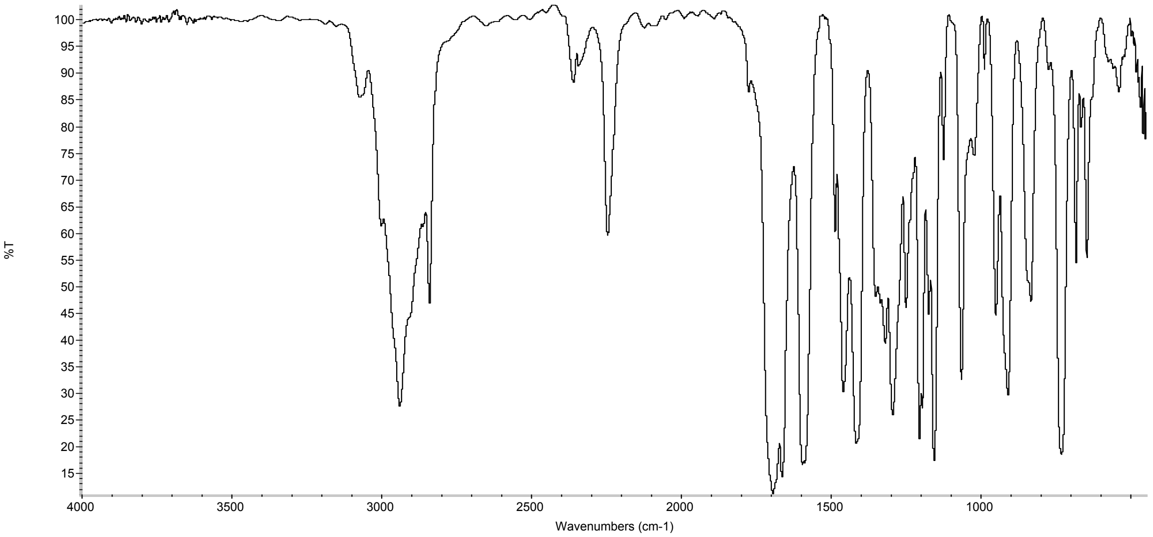

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

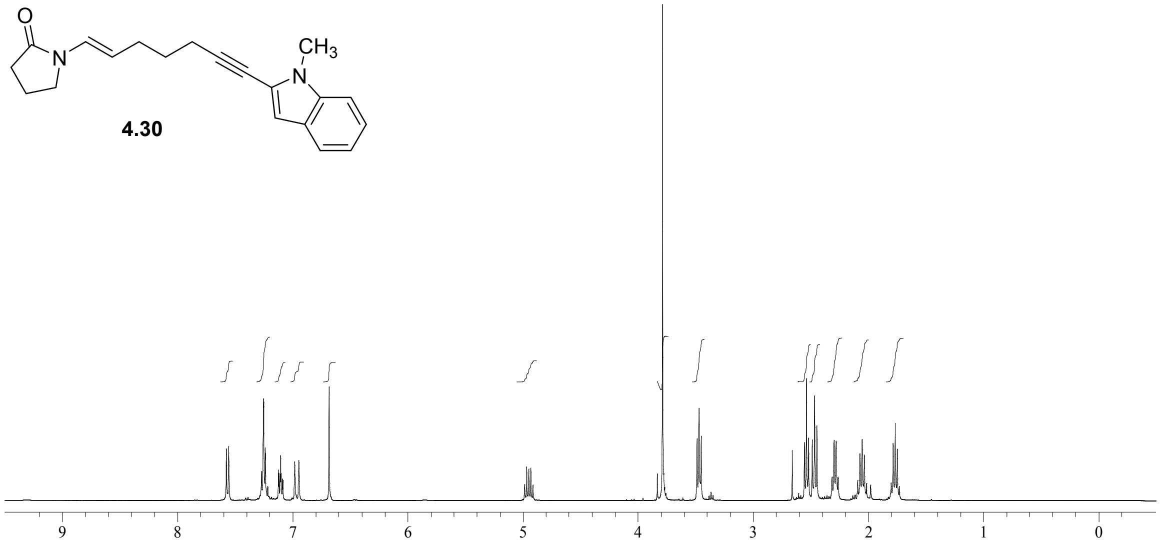

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
OCH$_3$
OCH$_3$
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

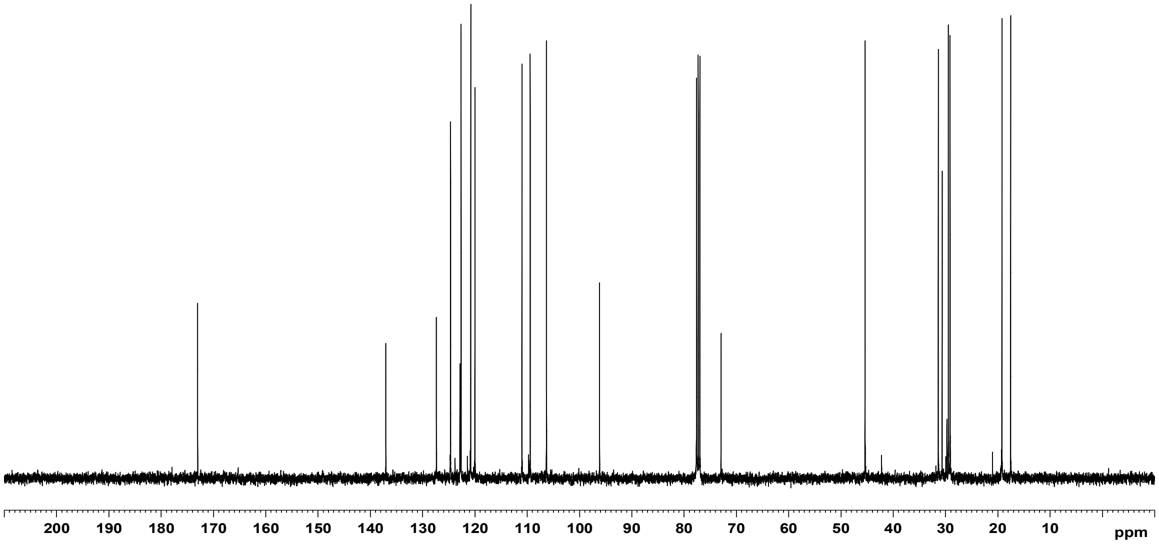
4.29

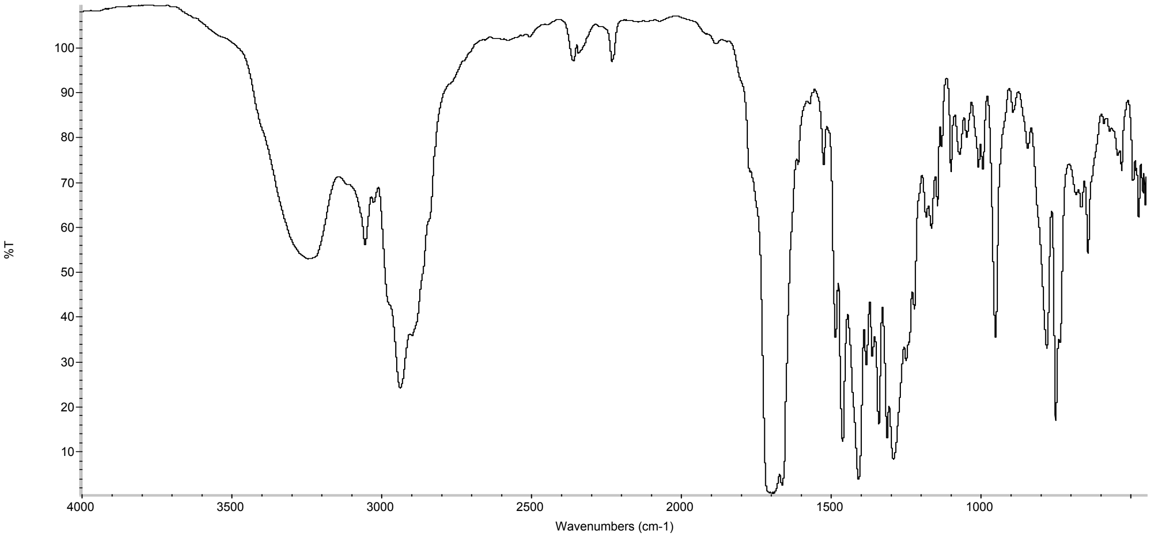

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

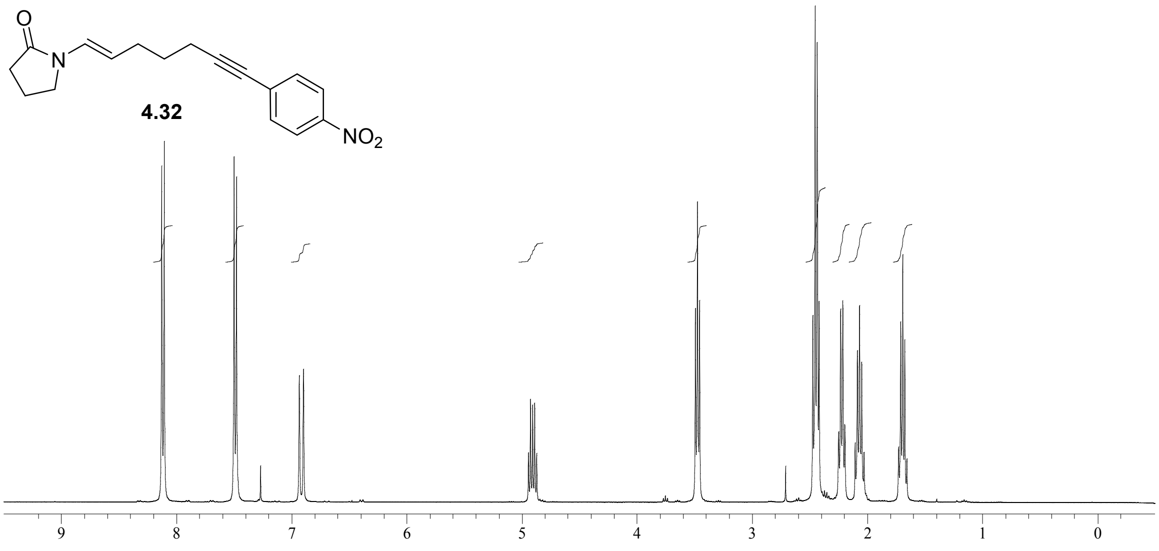

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
CH3
N
9
8
7
6
5
4
3
2
1
0

4.30

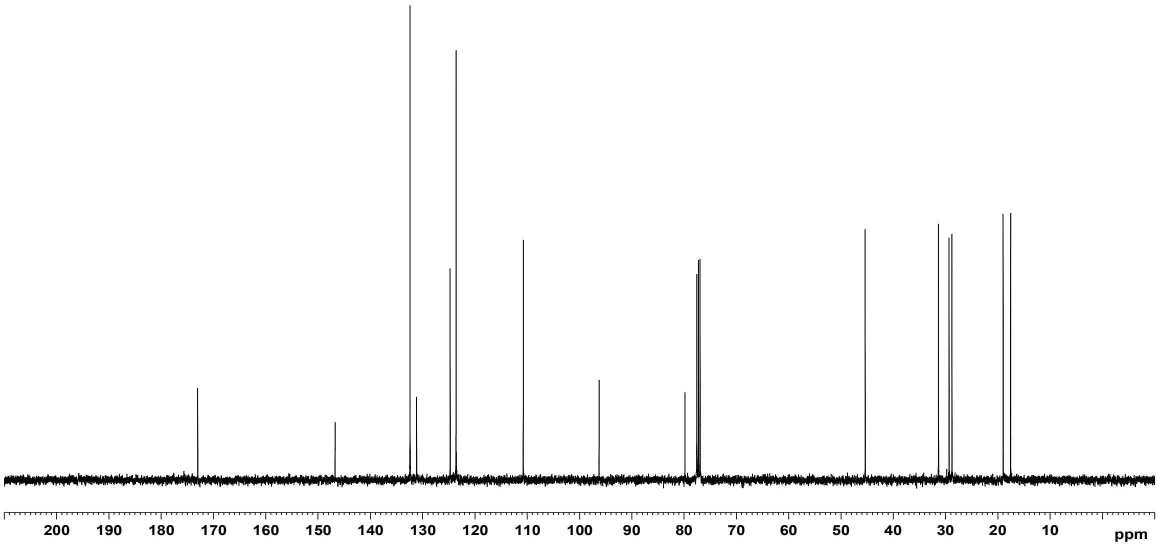

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

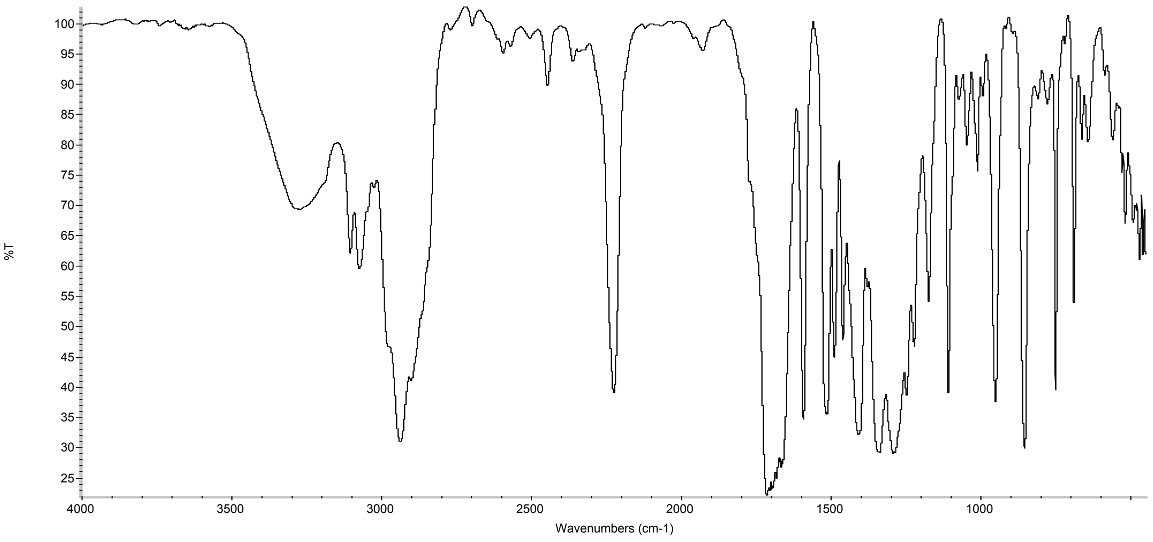


4.32

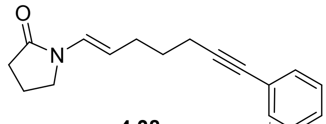
O
N
NO$_2$
9
8
7
6
5
4
3
2
1
0



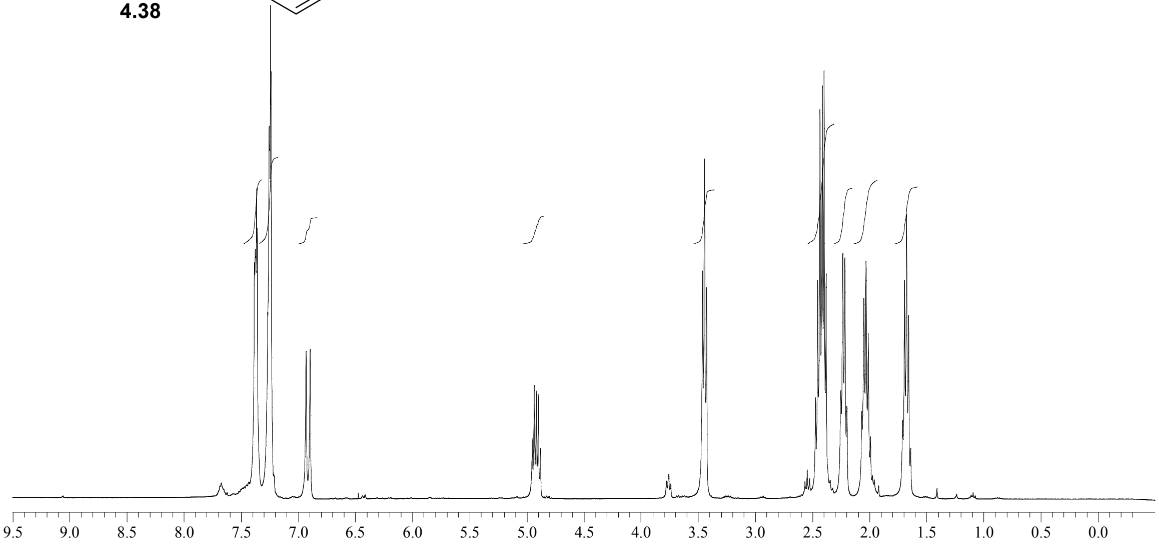
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

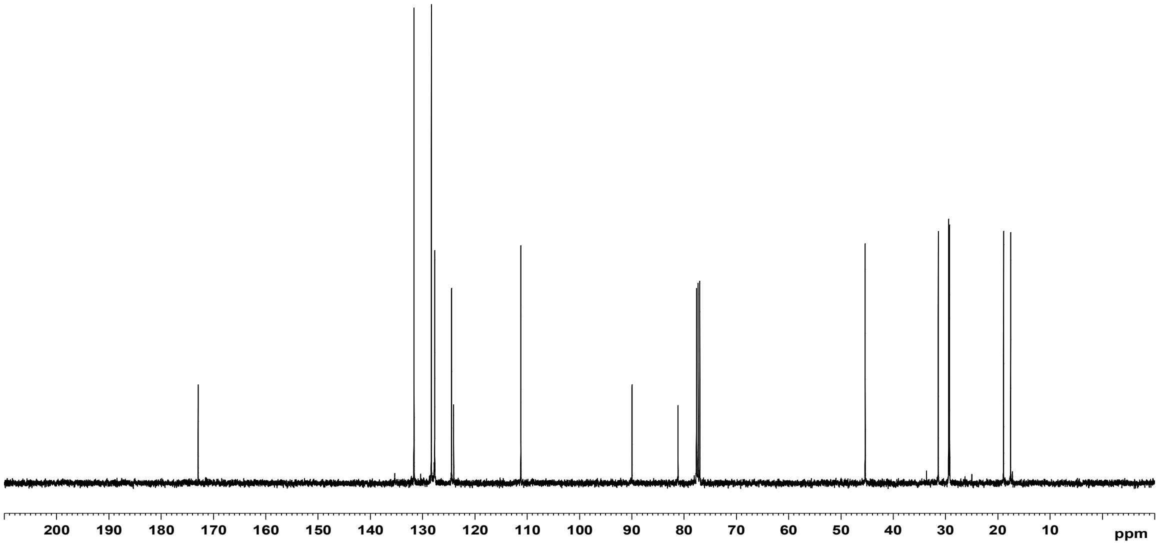


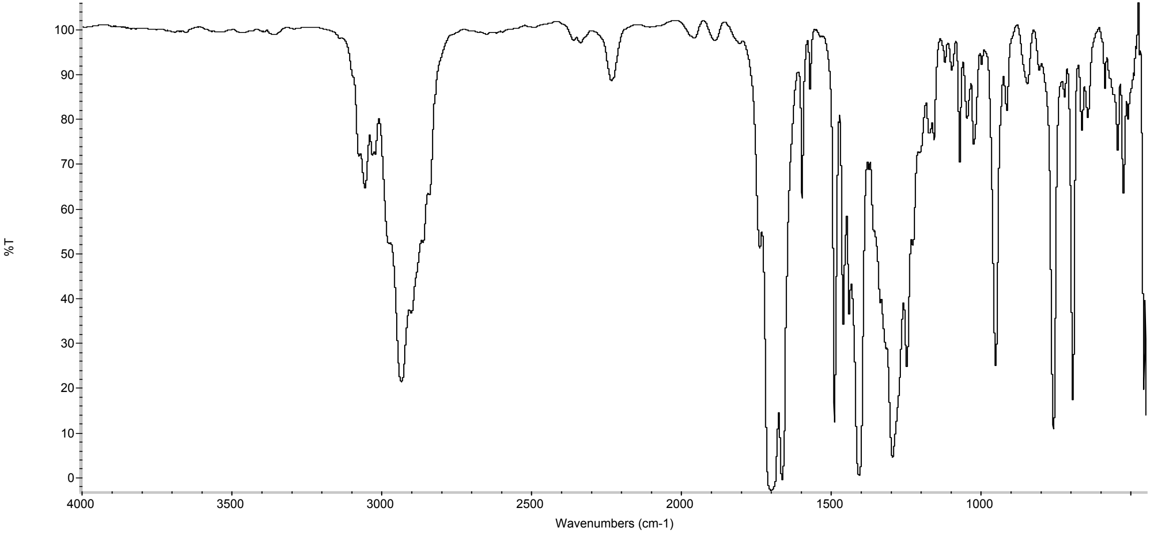
%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

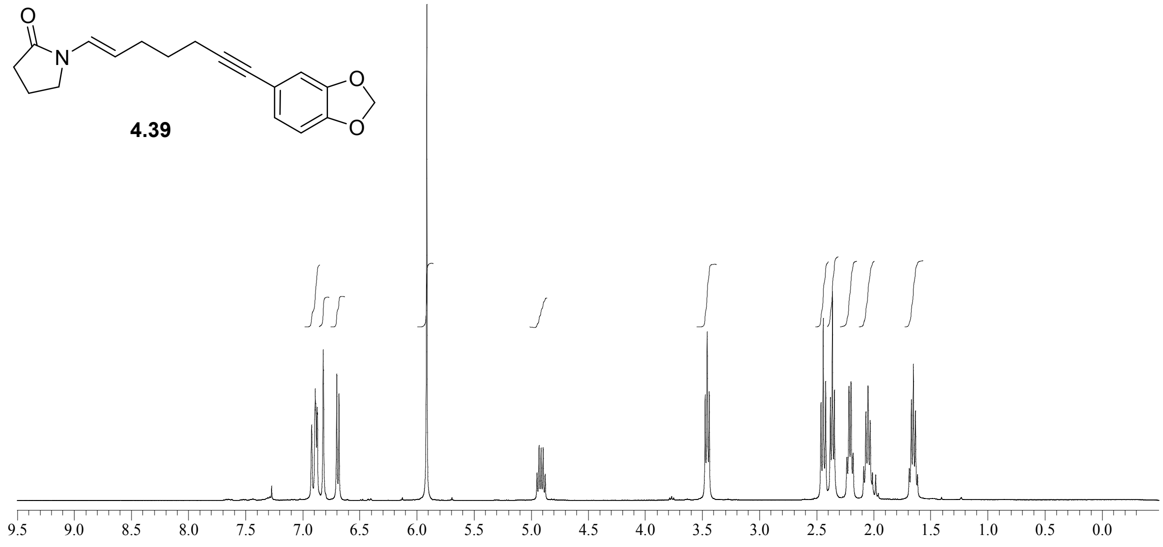

O
N

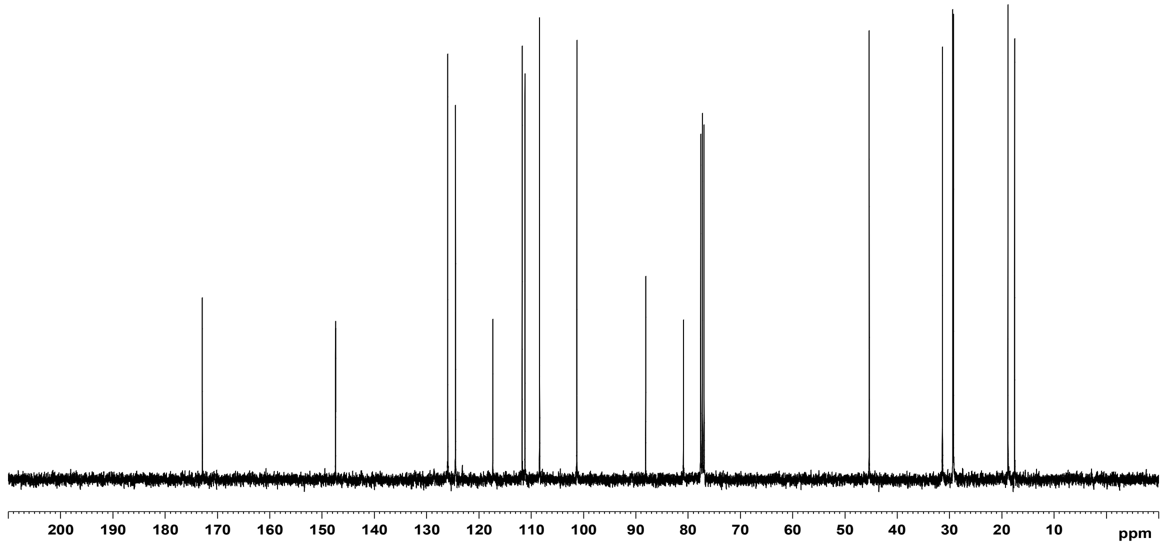
4.38

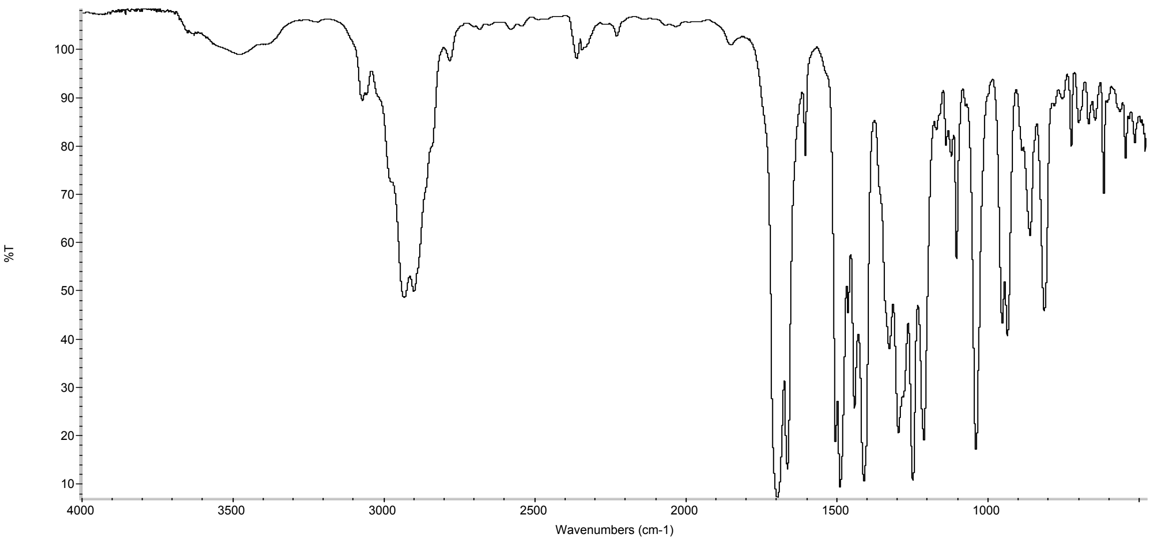

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

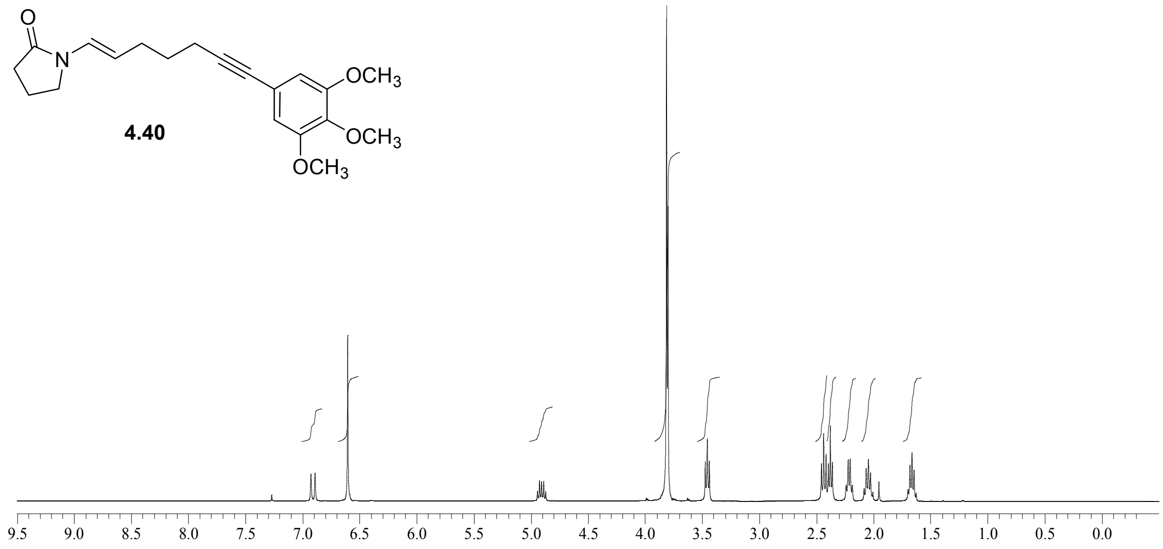

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

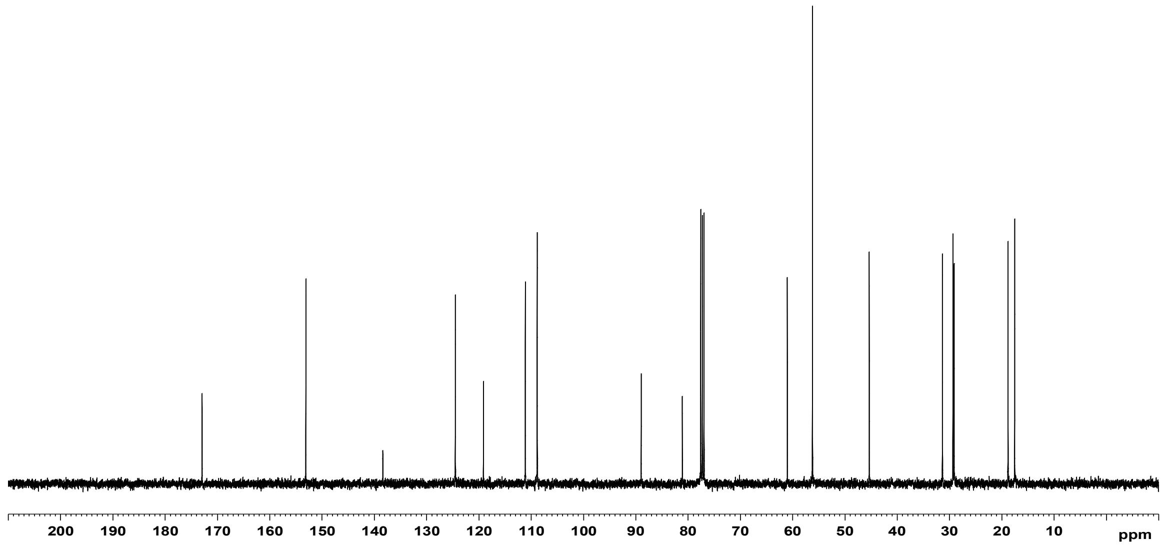

%T
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

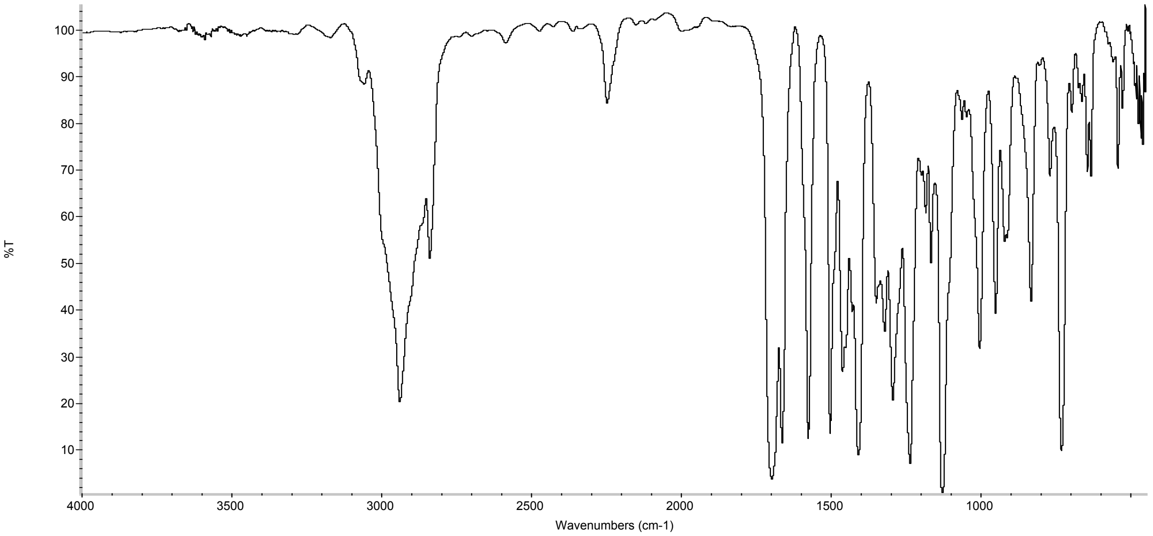

4.39
O
N
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

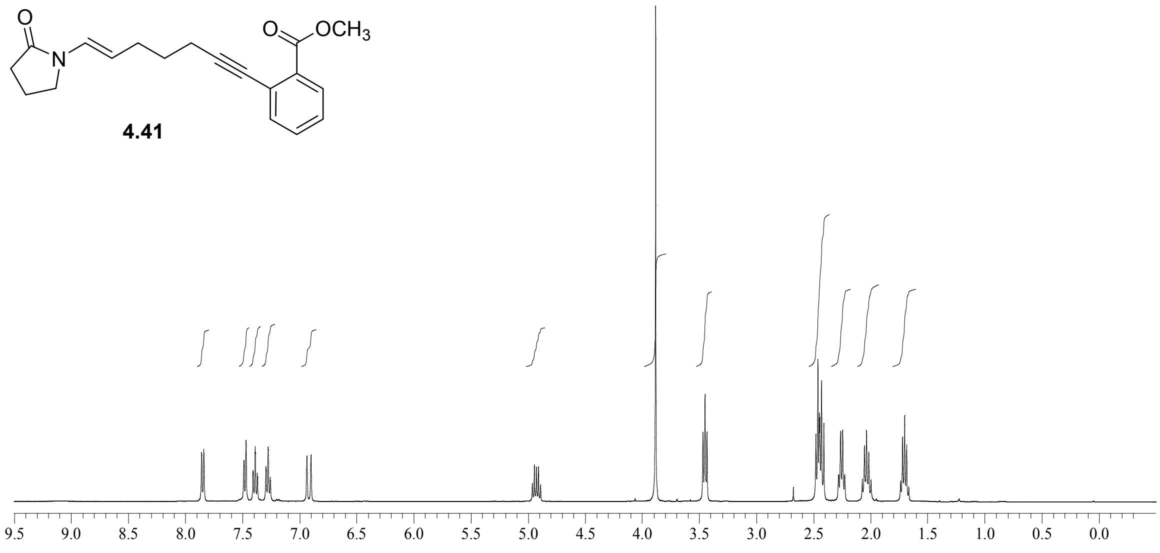

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
OCH3
4.40
OCH3
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

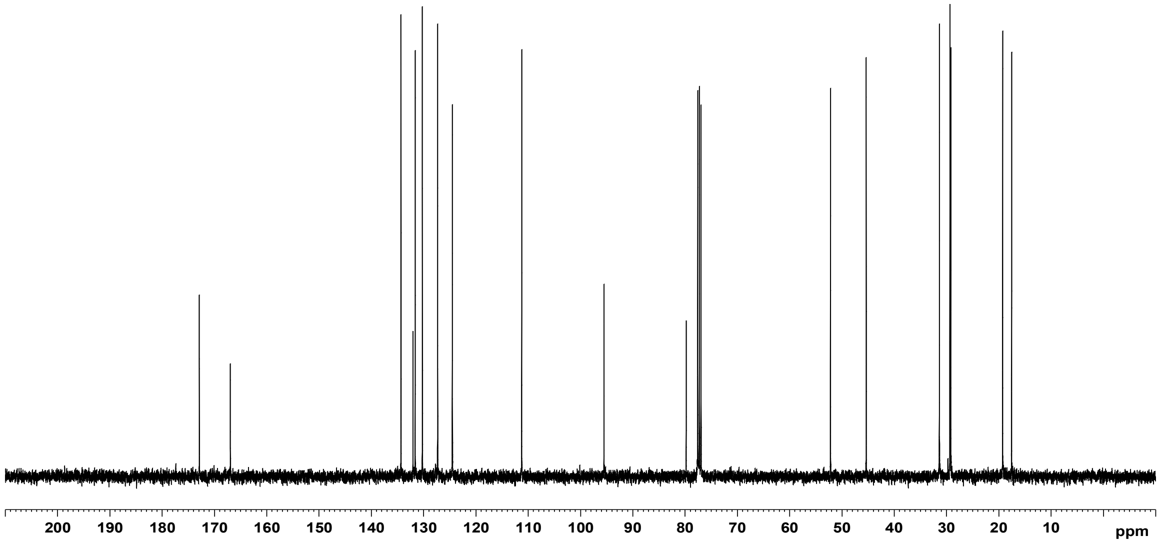

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

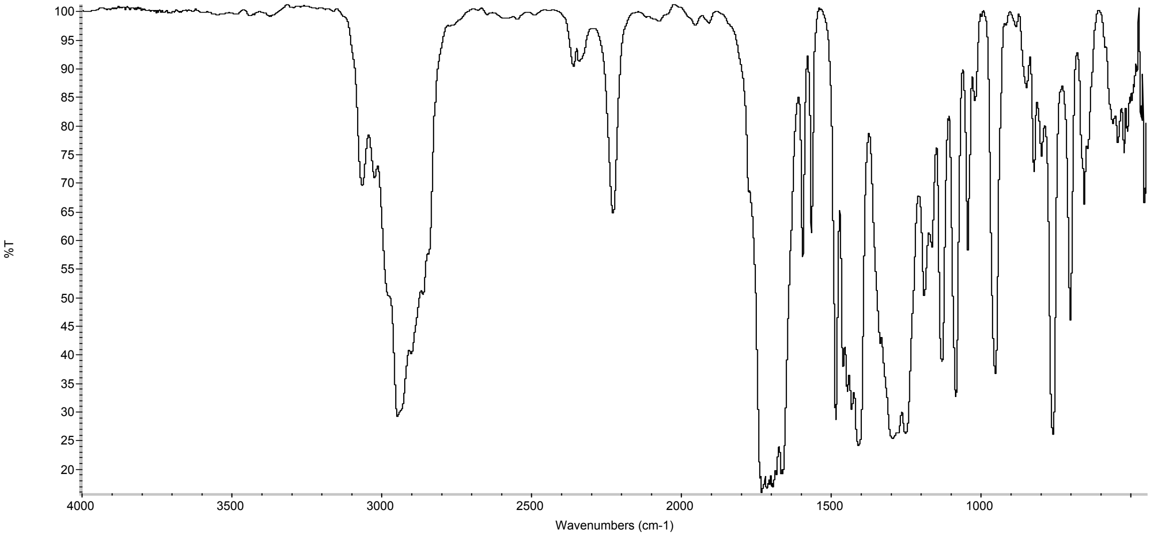


4.41

O
N
O
OCH$_3$
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



%T
100
95
90
85
80
75
70
65
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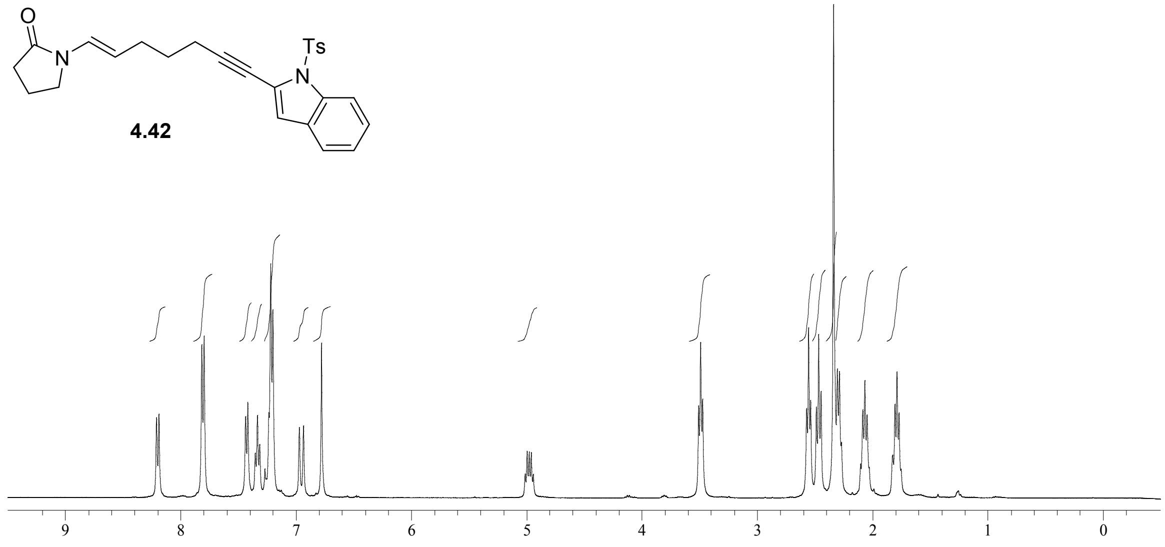
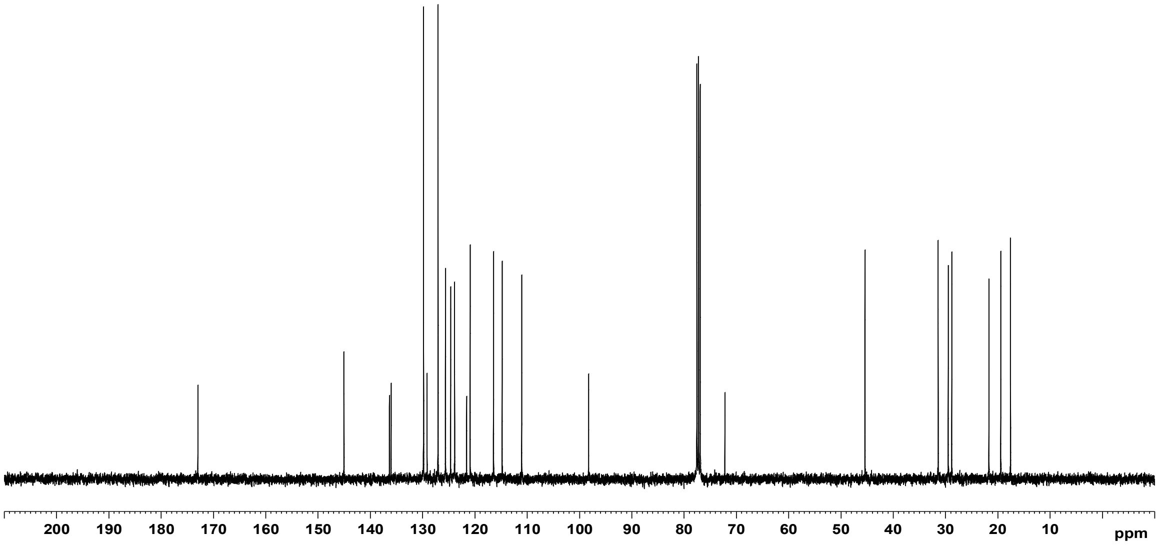
40
35
30
25
20
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
Ts
N
9
8
7
6
5
4
3
2
1
0

4.42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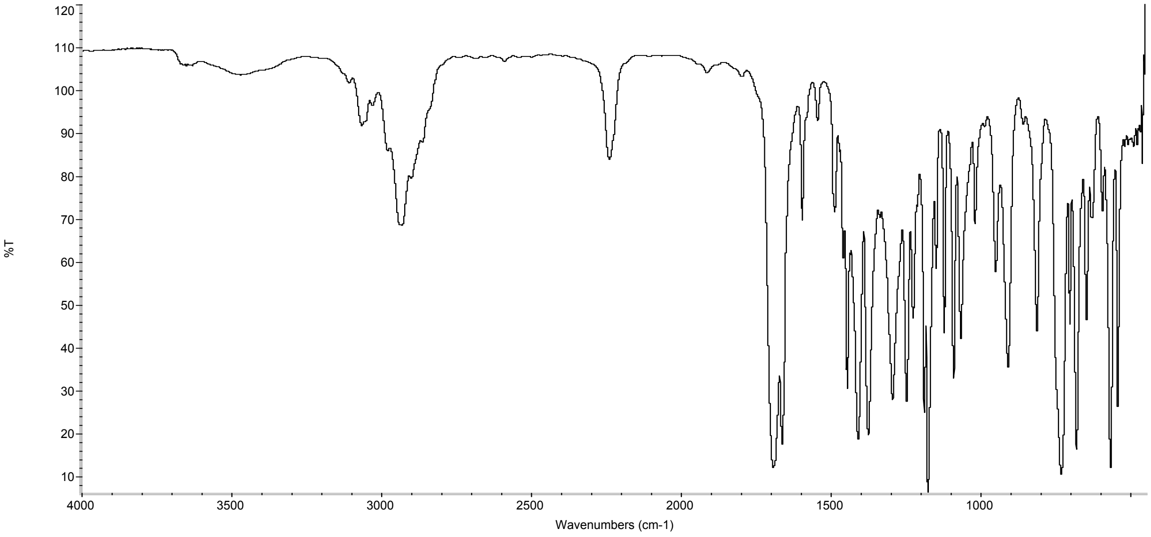
20
10
ppm


%T
120
110
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40
30
20
10
4000
3500
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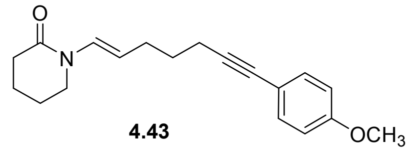
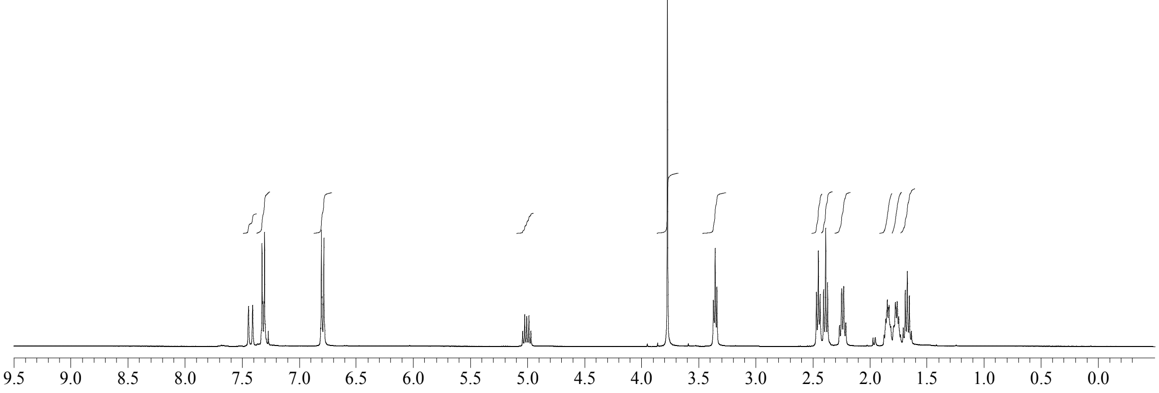
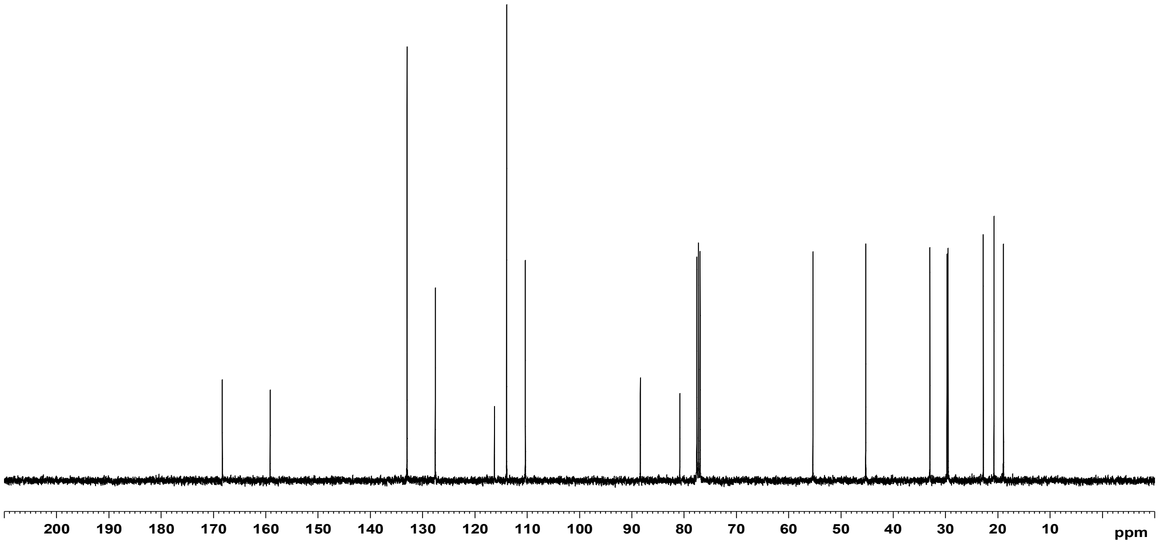
2500
2000
1500
1000
Wavenumbers (cm-1)


O
N
OCH3

4.43


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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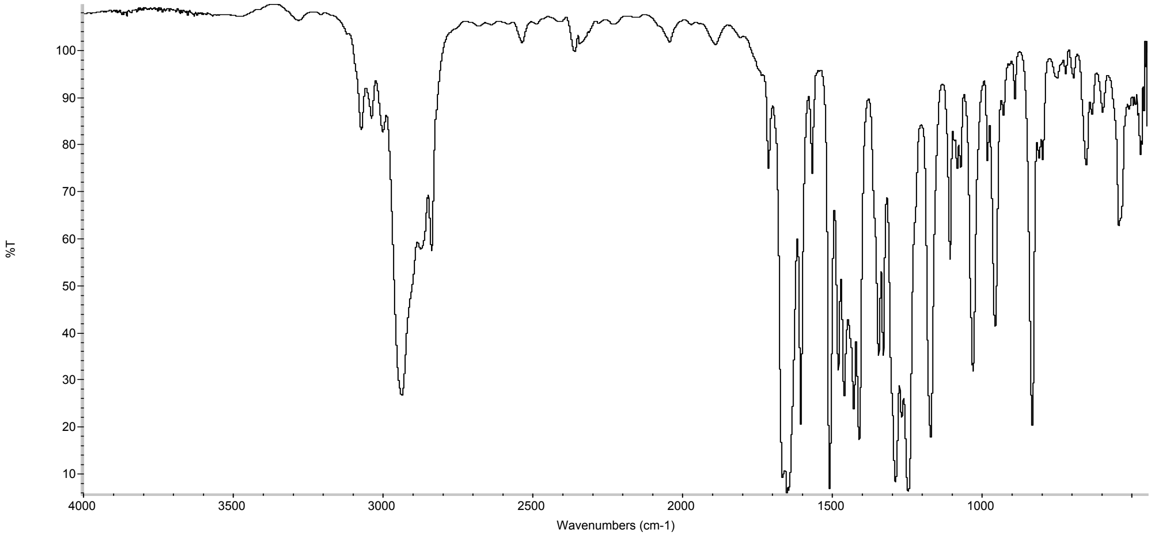
ppm


%T
100
90
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40
30
20
10
4000
3500
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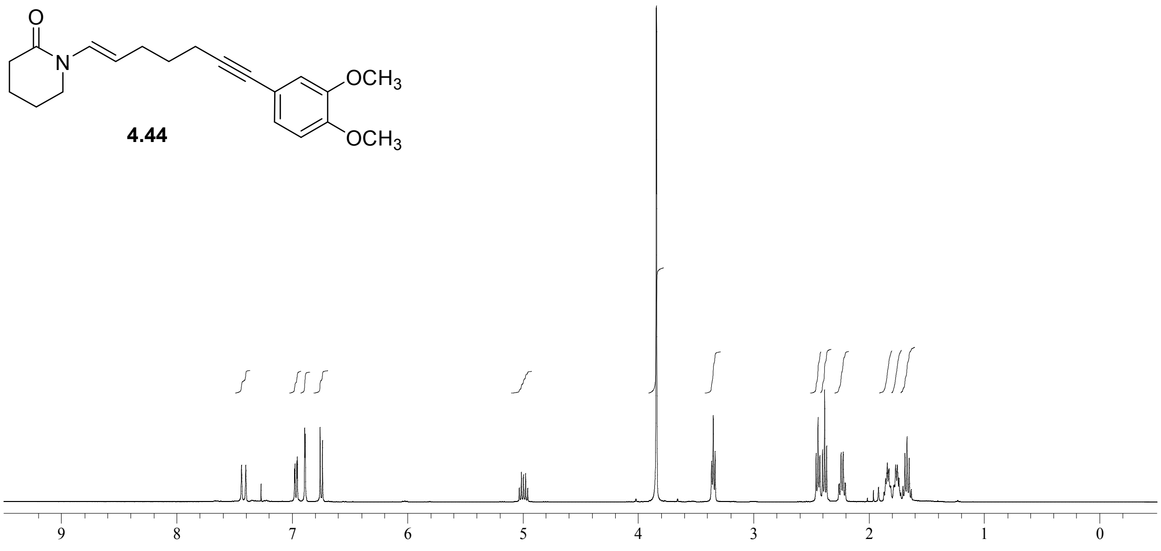
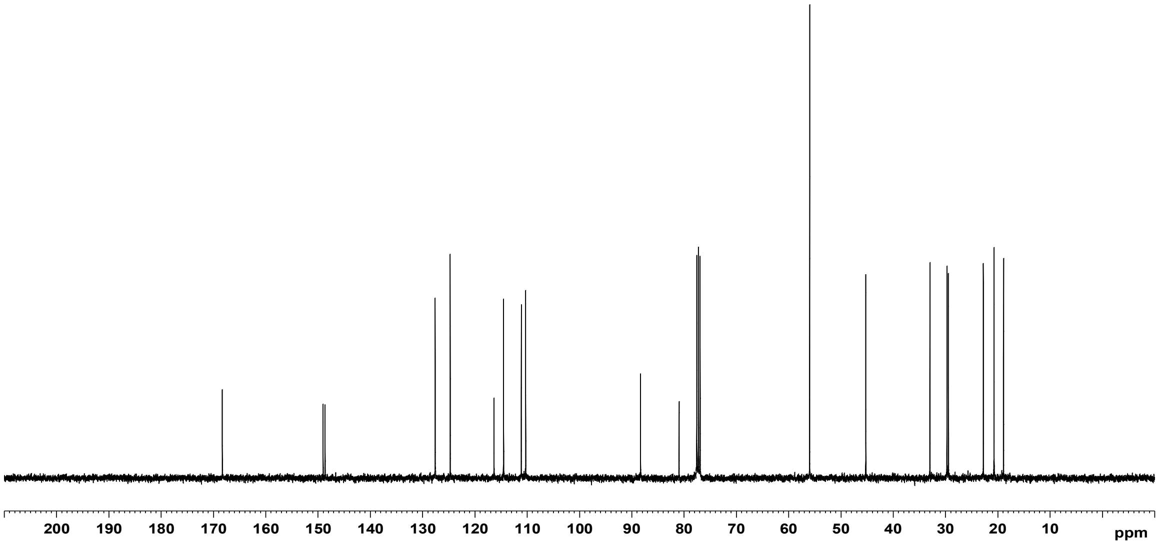
2500
2000
1500
1000
Wavenumbers (cm-1)



4.44

O
N
OCH3
OCH3
9
8
7
6
5
4
3
2
1
0



200
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180
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160
150
140
130
120
110
100
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70
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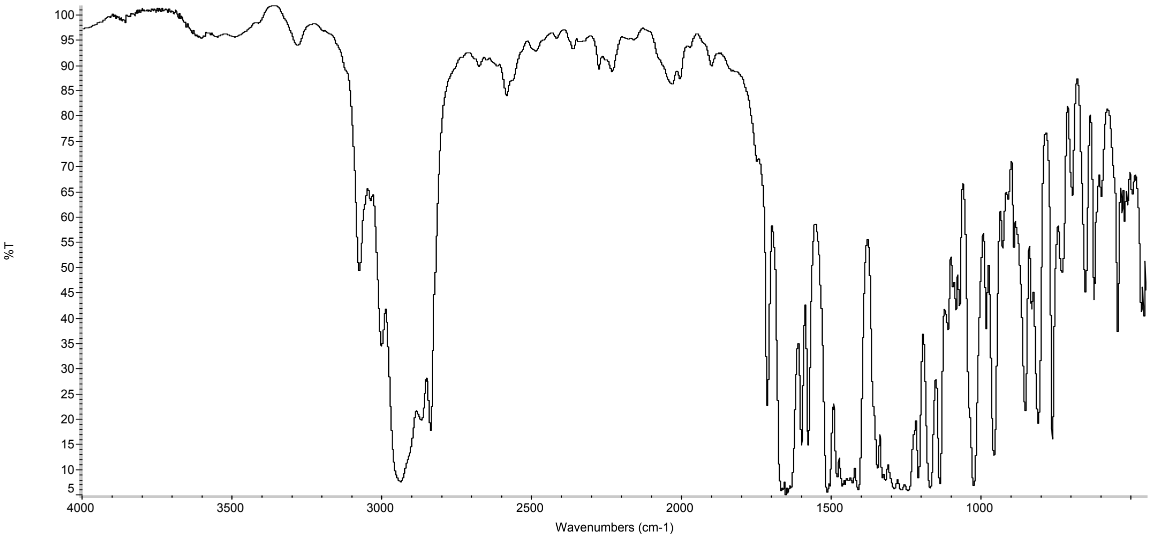
10
ppm



%T
100
95
90
85
80
75
70
65
60
55
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40
35
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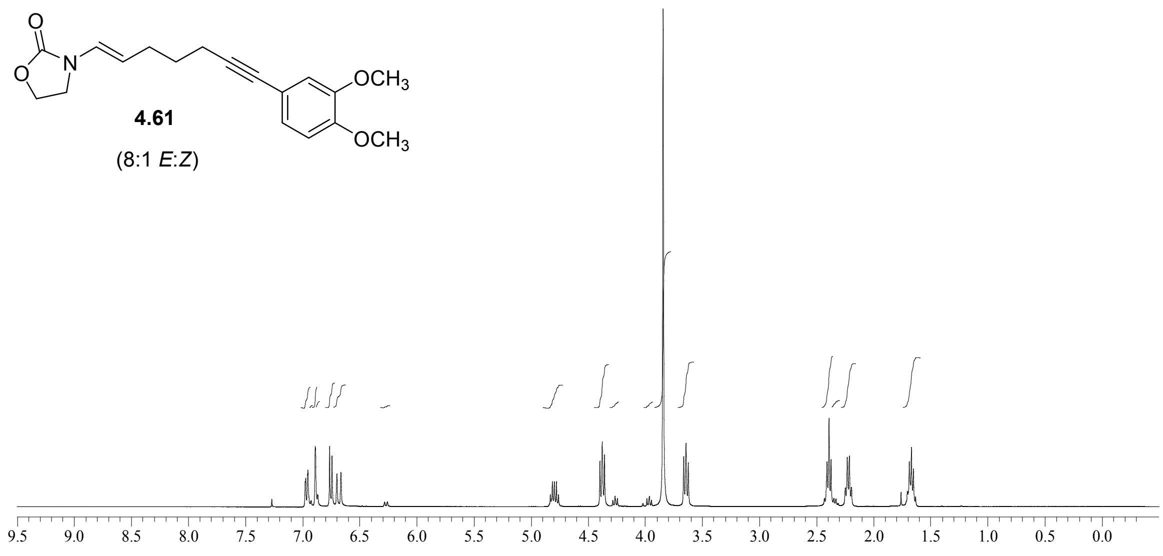
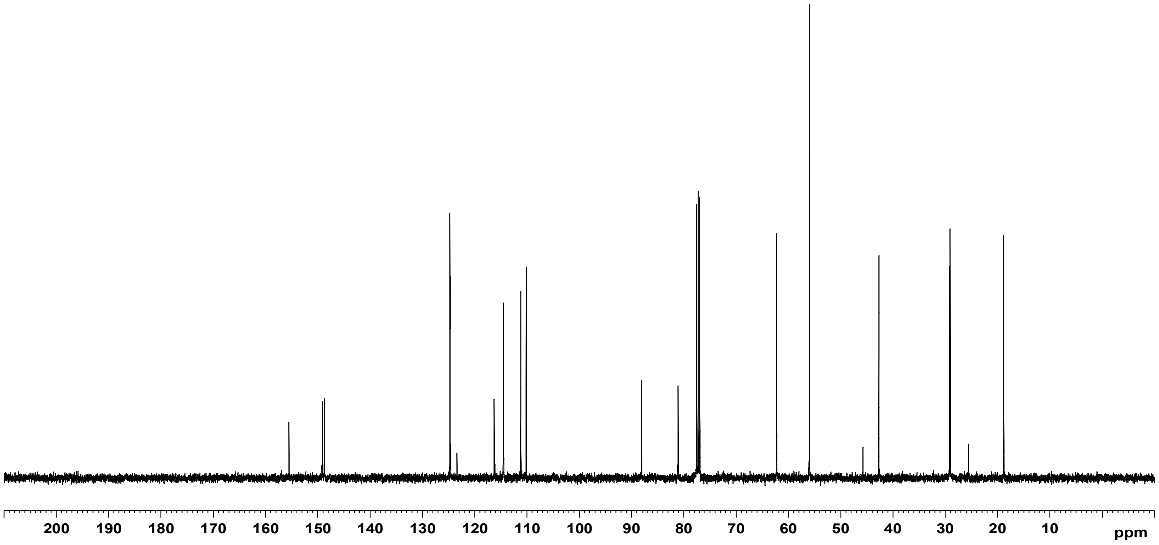
25
20
15
10
5
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


OCH3
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

4.61

(8:1 *E*:*Z*)


200
190
180
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160
150
140
130
120
110
100
90
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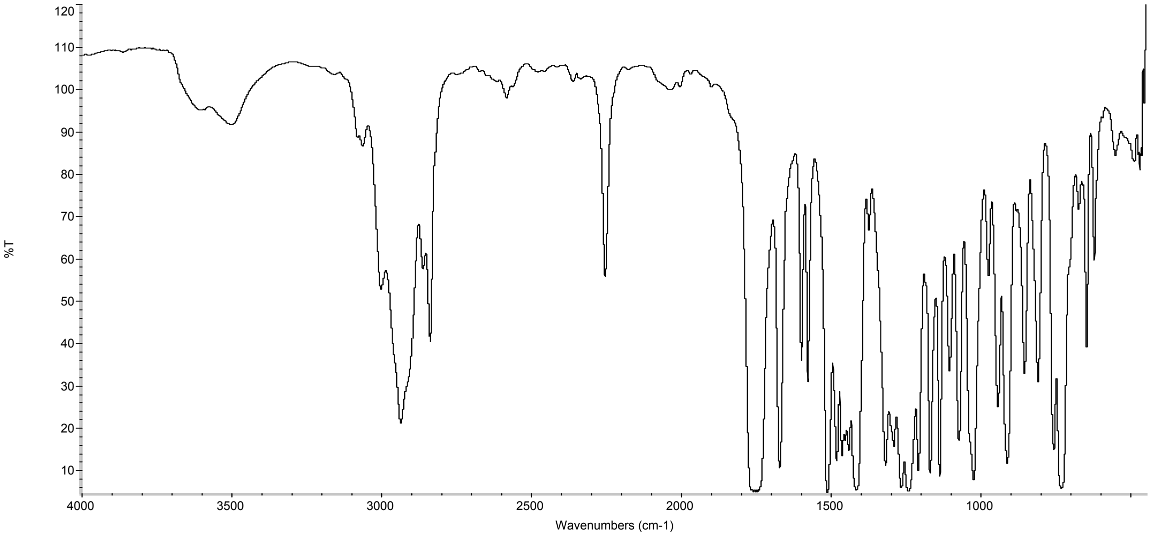
70
60
50
40
30
20
10
ppm


%T
120
110
100
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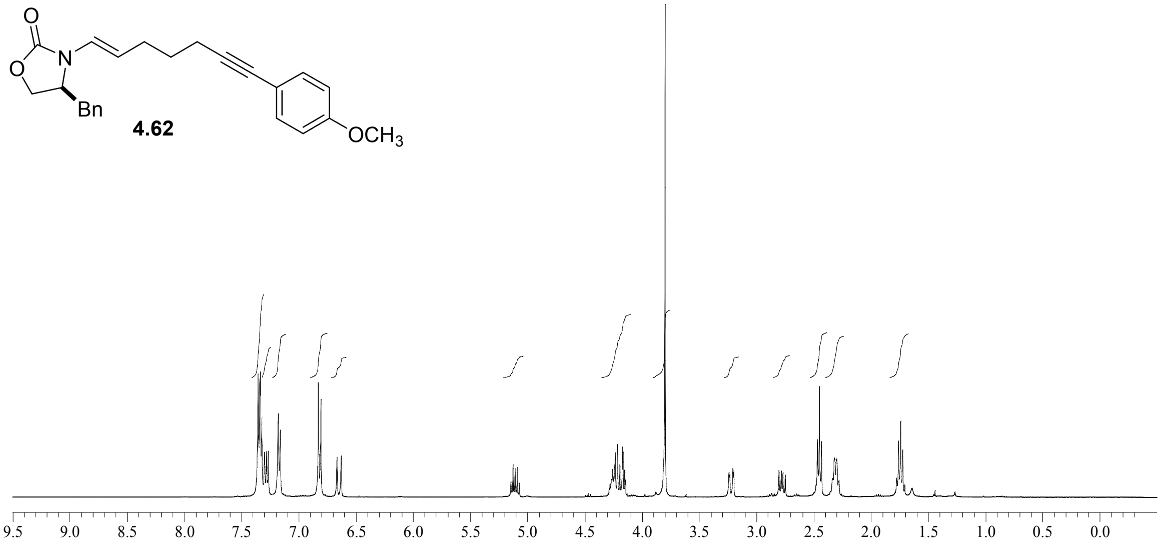
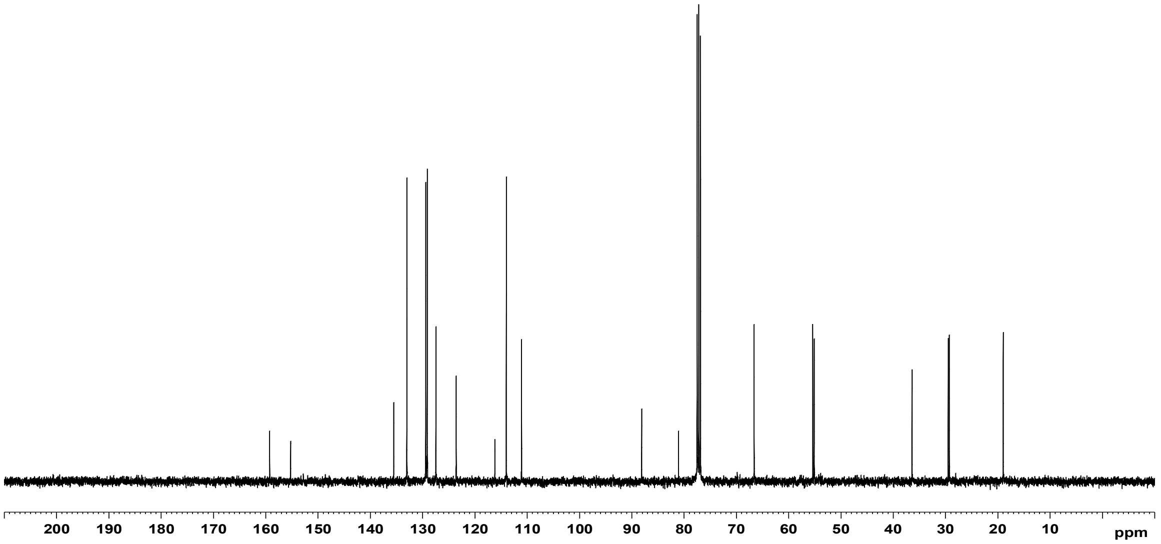
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


O
O
N
Bn
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

4.62


200
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180
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150
140
130
120
110
100
90
80
70
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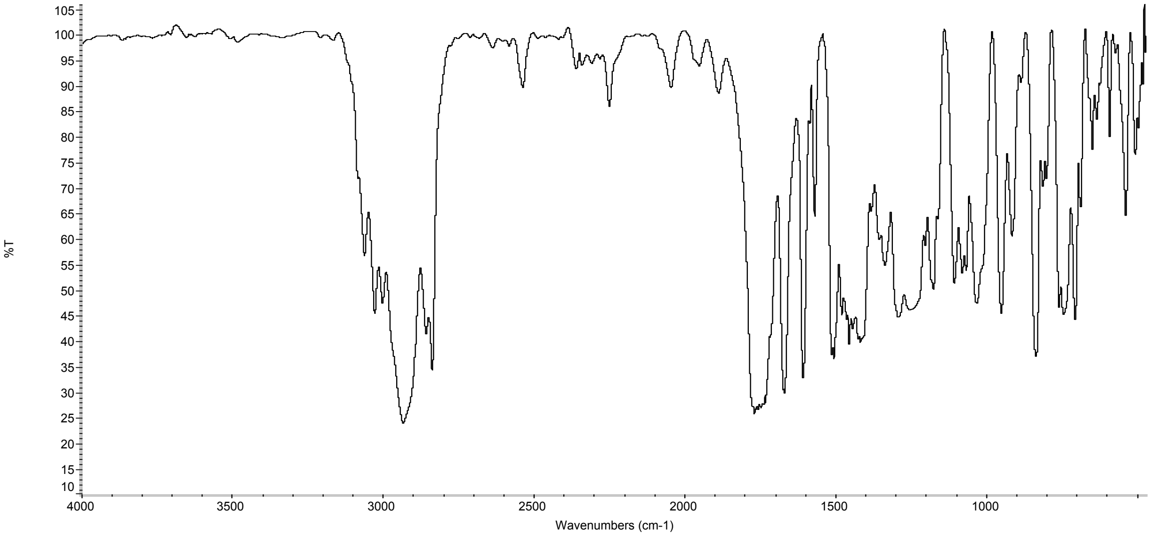
50
40
30
20
10
ppm


%T
105
100
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90
85
80
75
70
65
60
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45
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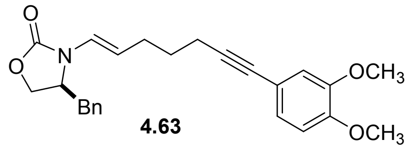
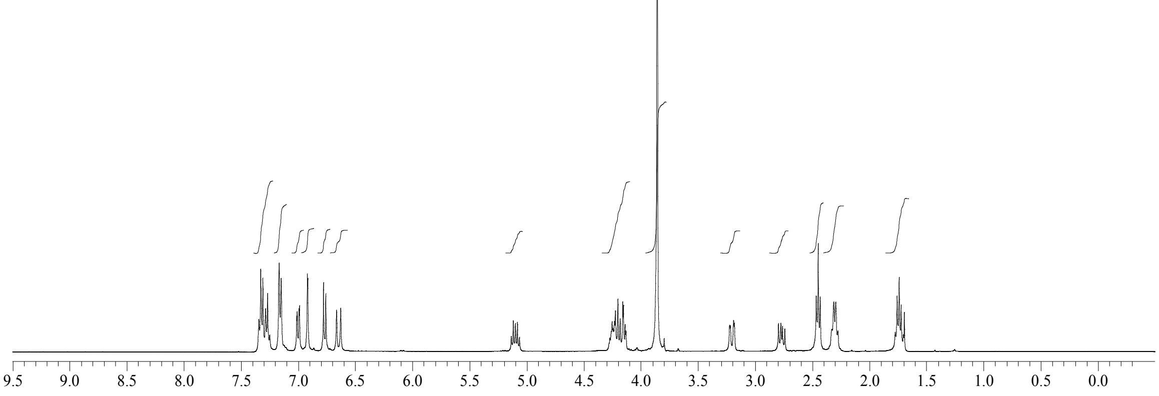
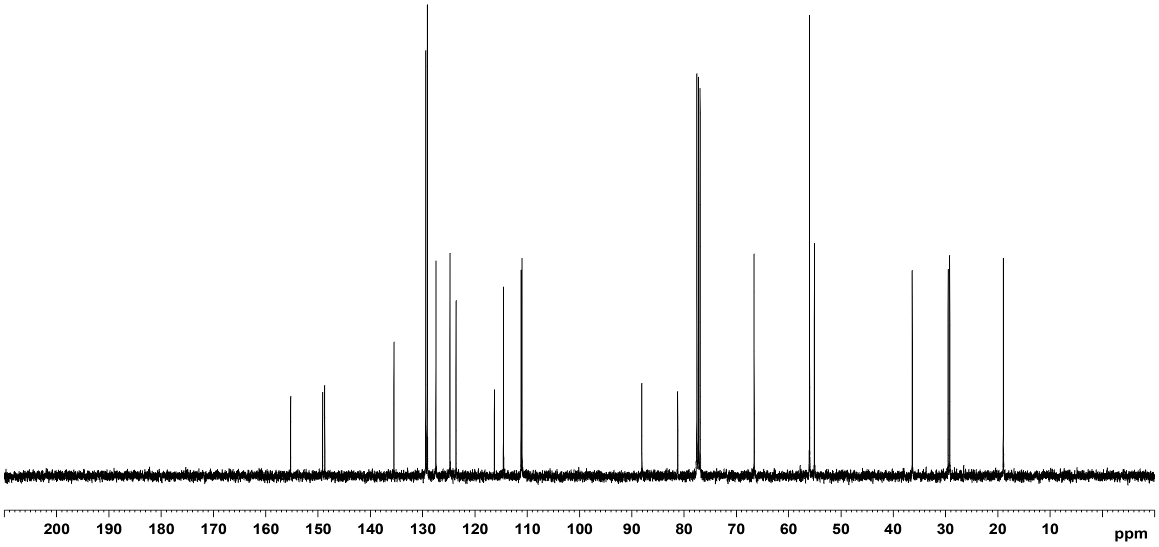
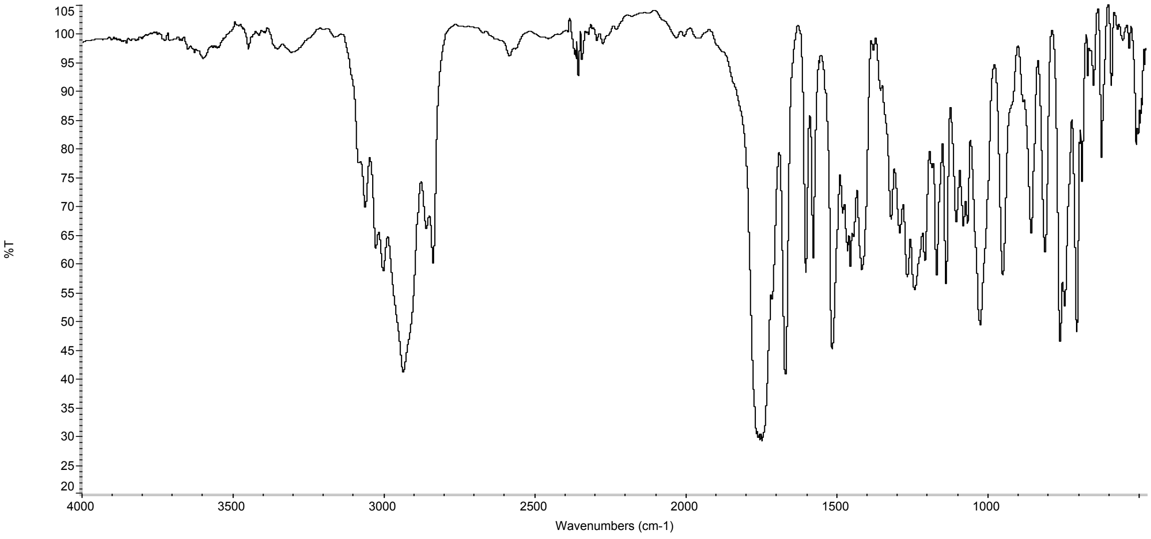
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

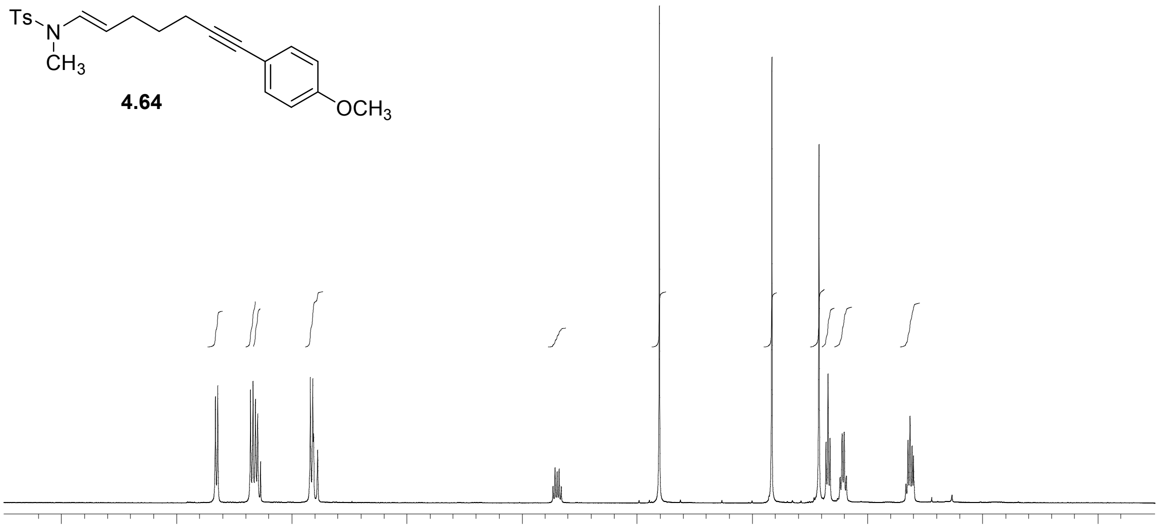

O
O
N
Bn
OCH3
OCH3

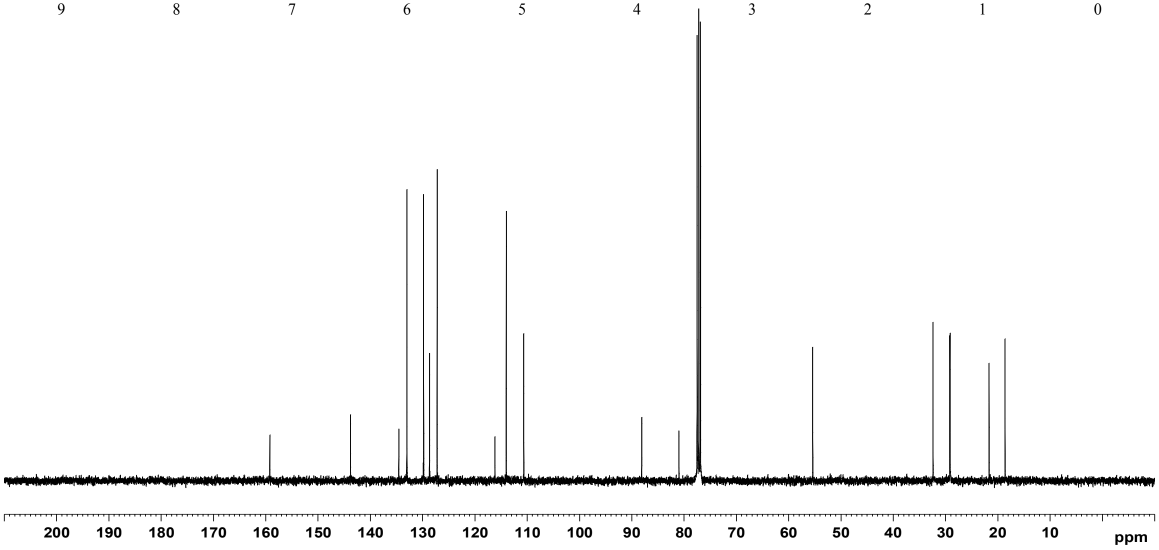
4.63


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


4.64
Ts
N
CH3
OCH3
9
8
7
6
5
4
3
2
1
0


200
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180
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150
140
130
120
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100
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70
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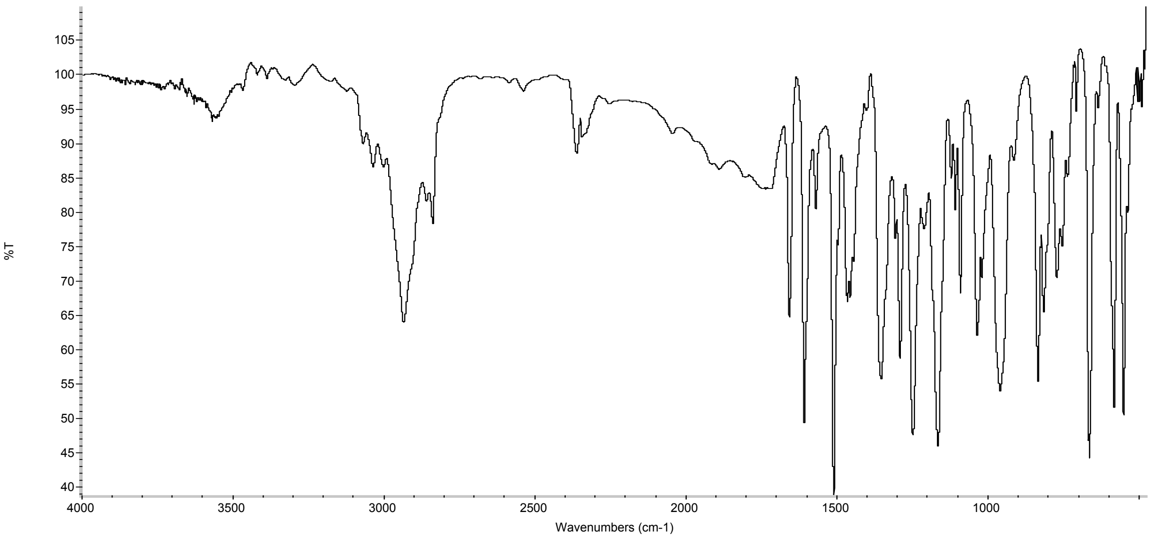
30
20
10
ppm


%T
105
100
95
90
85
80
75
70
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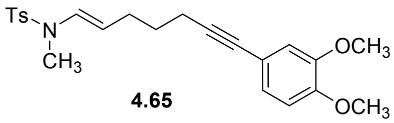
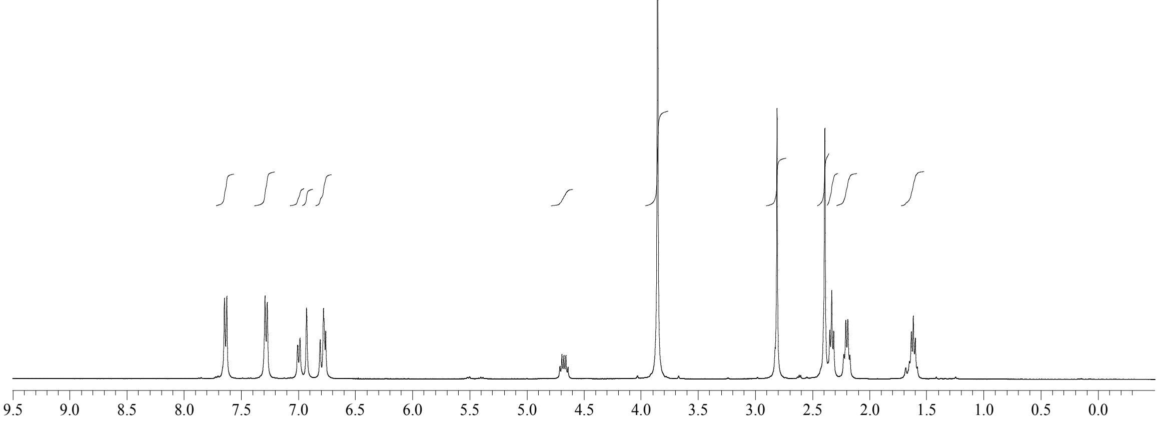
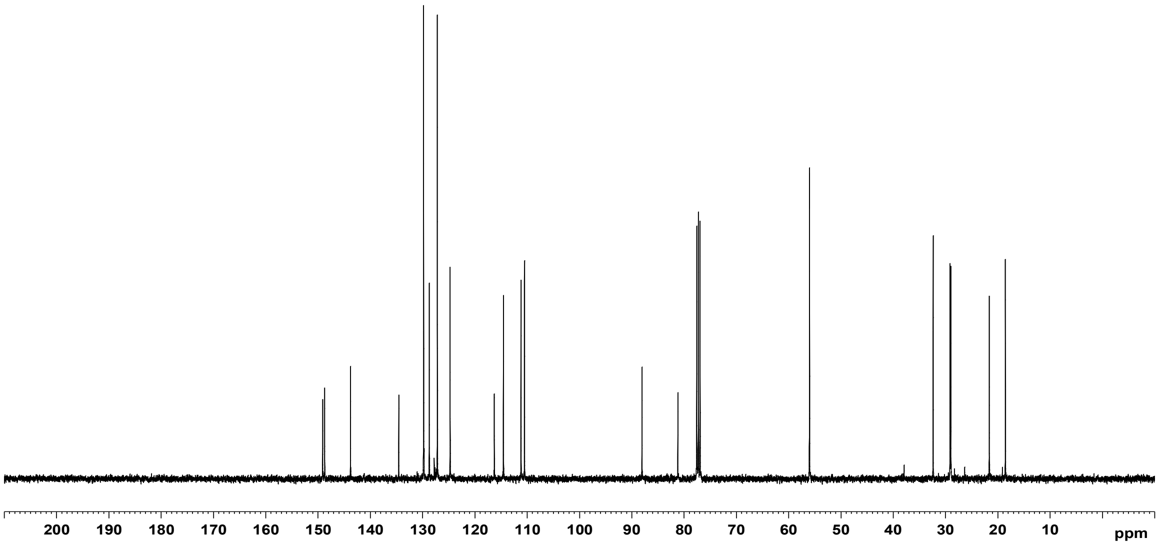
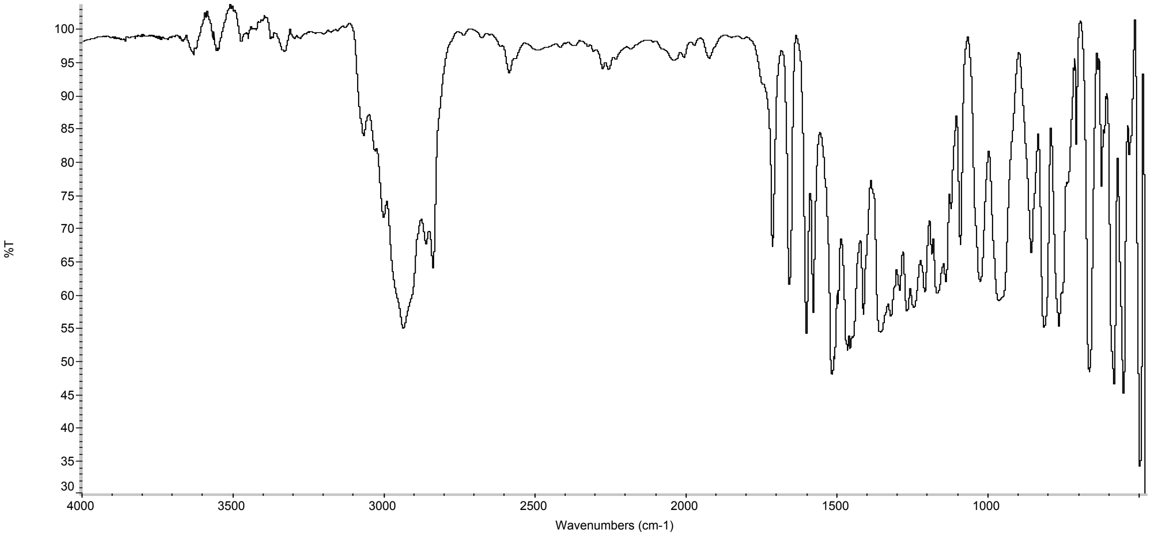
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

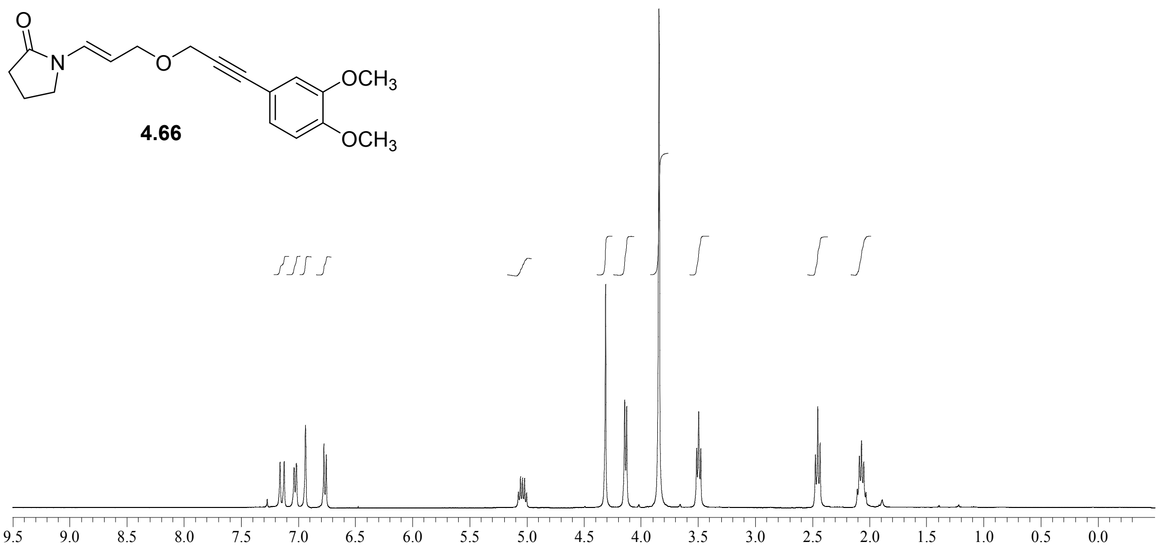

Ts
N
CH3
OCH3
OCH3

4.65

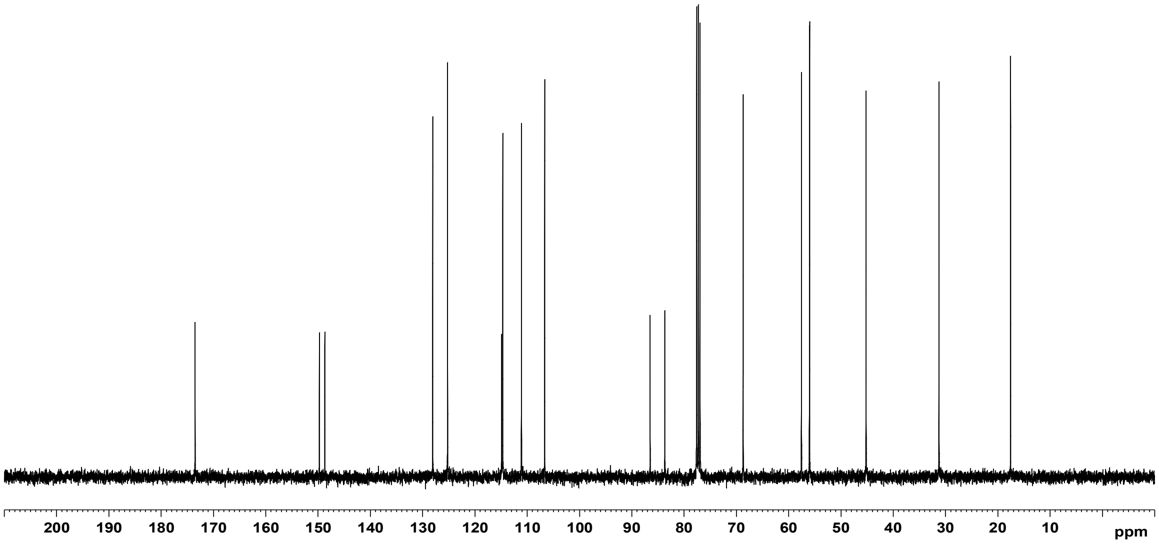

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

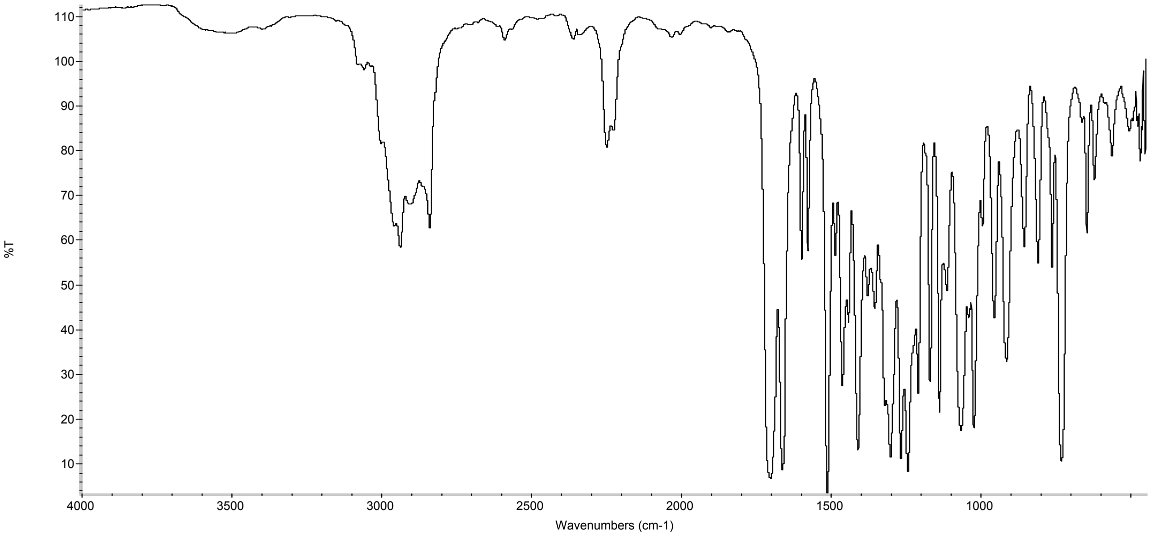

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

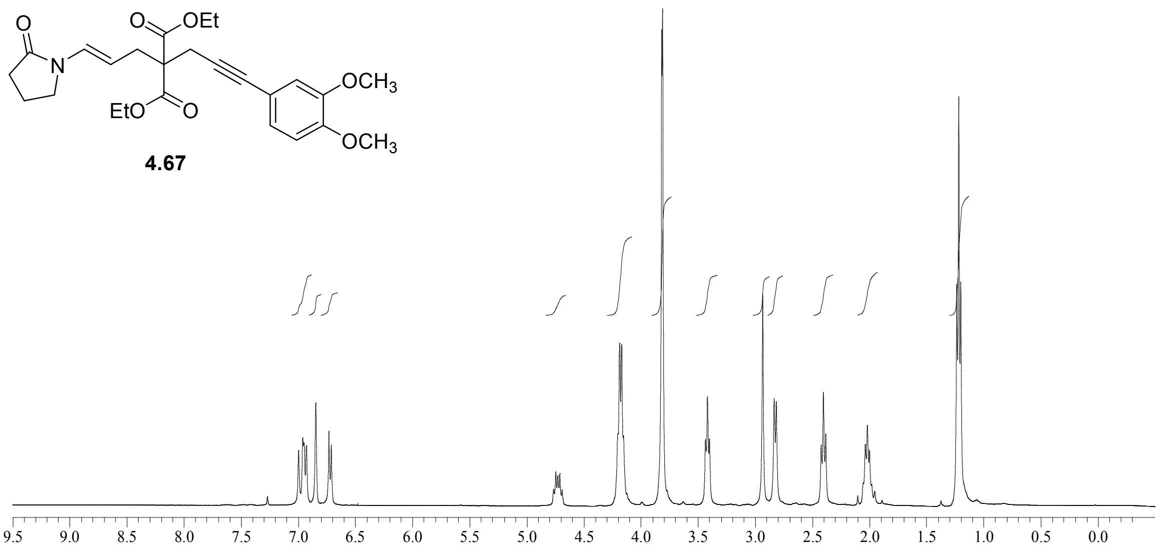

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

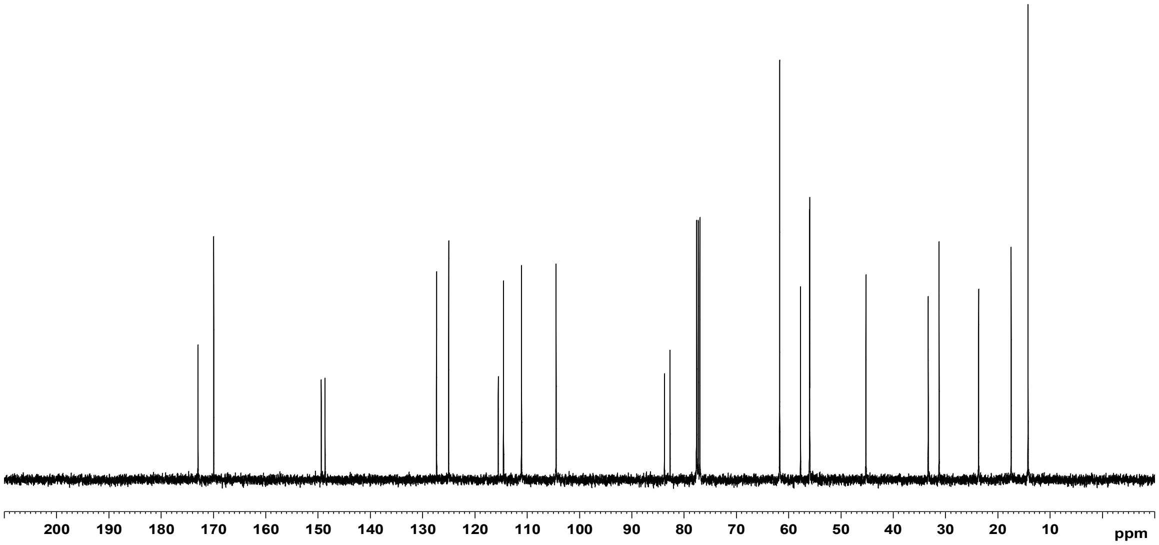

4.66

OCH3
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
110
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


4.67
O
N
O
OEt
EtO
O
OCH3
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


200
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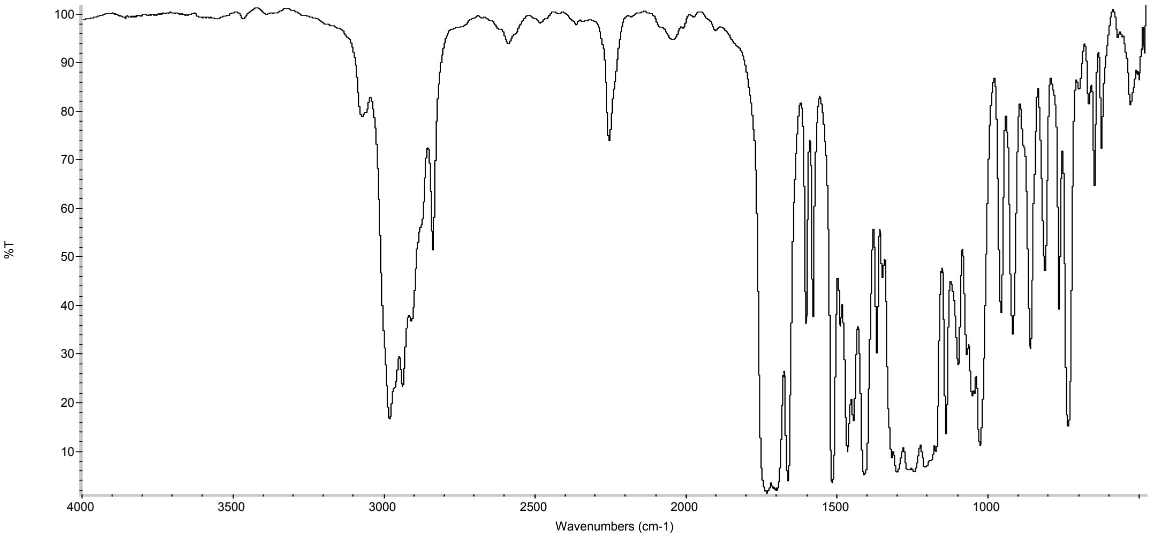
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
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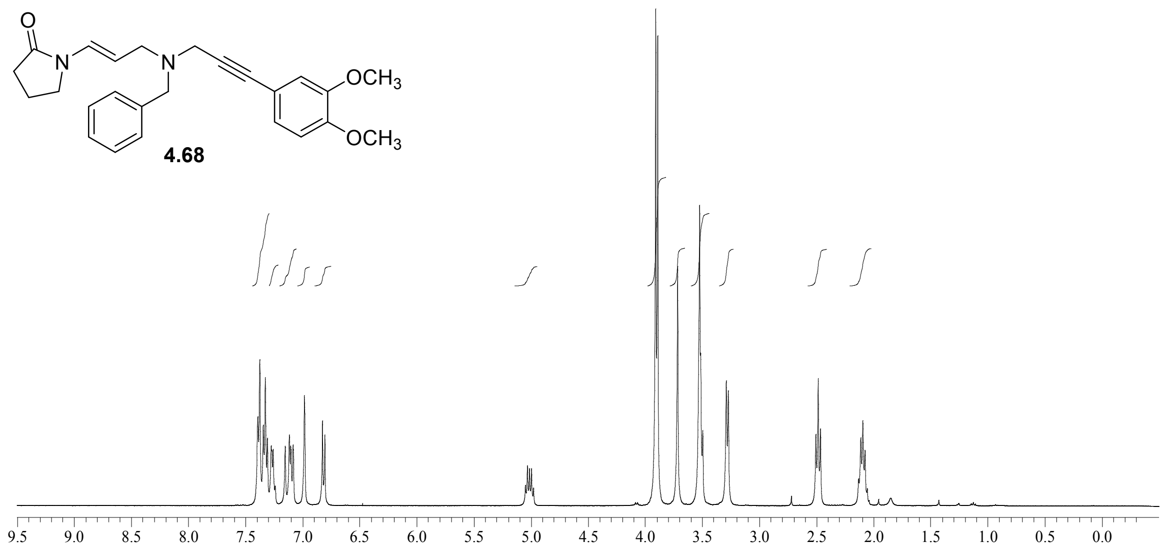
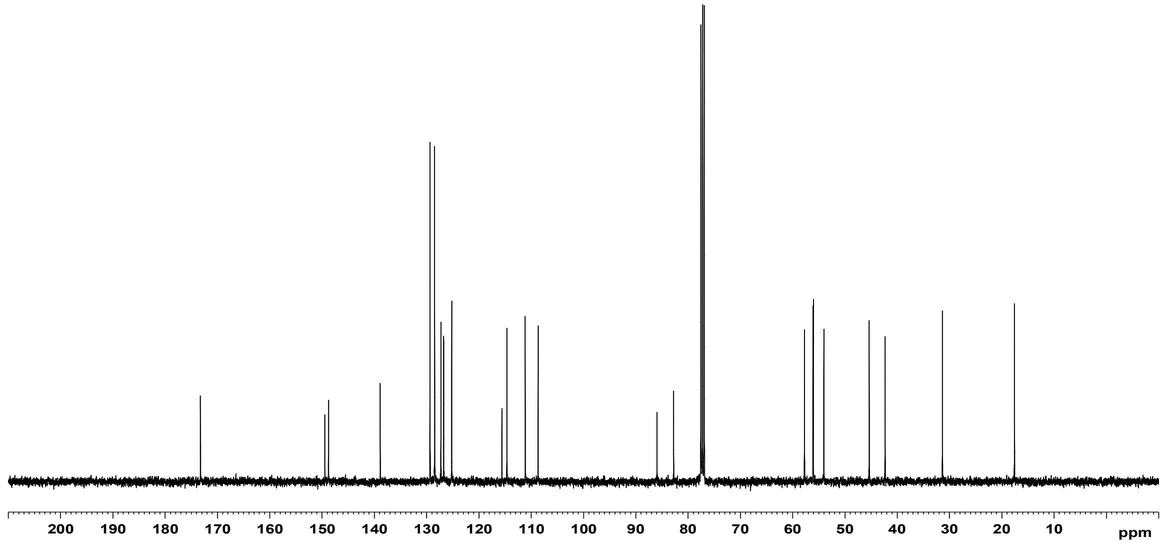
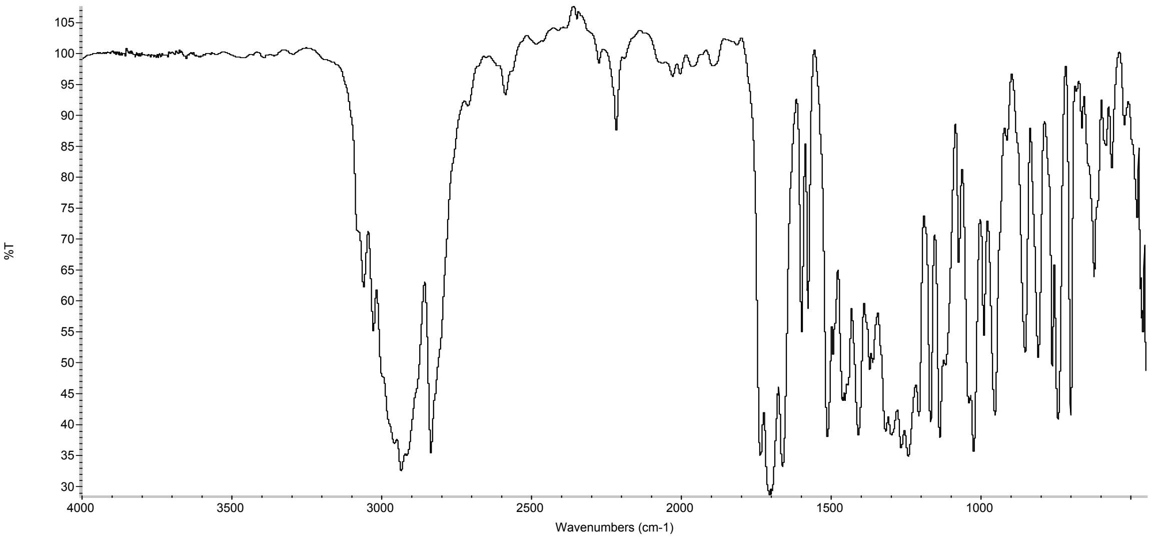
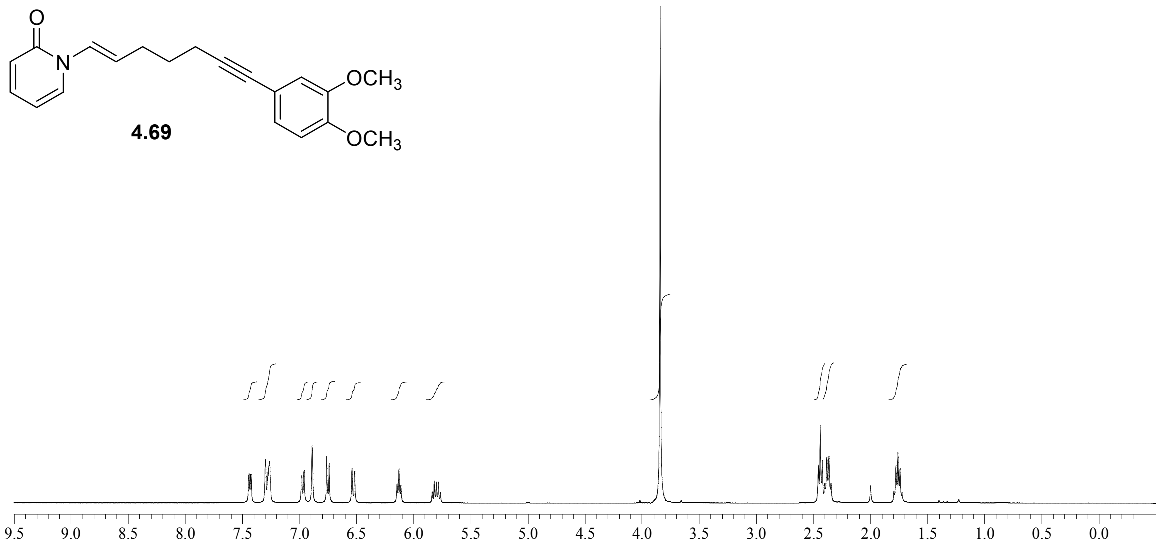
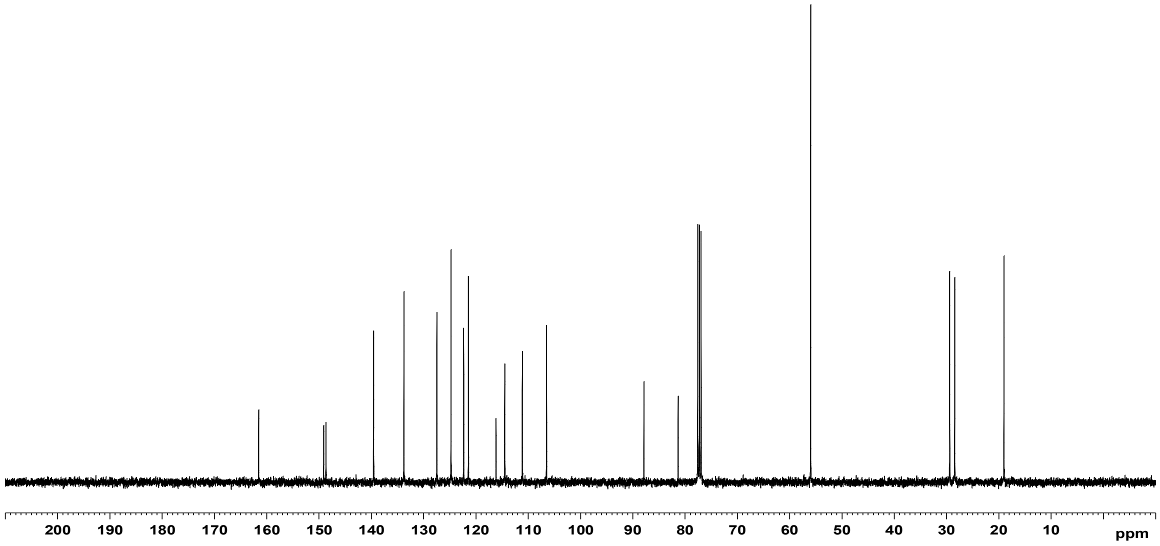
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

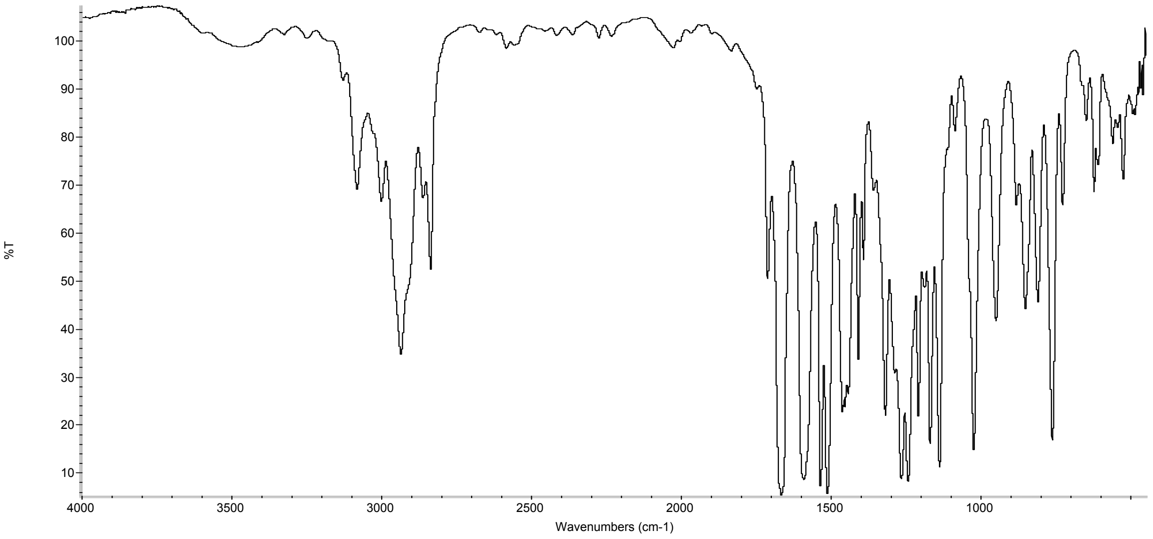

4.68
O
N
N
OCH$_3$
OCH$_3$
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

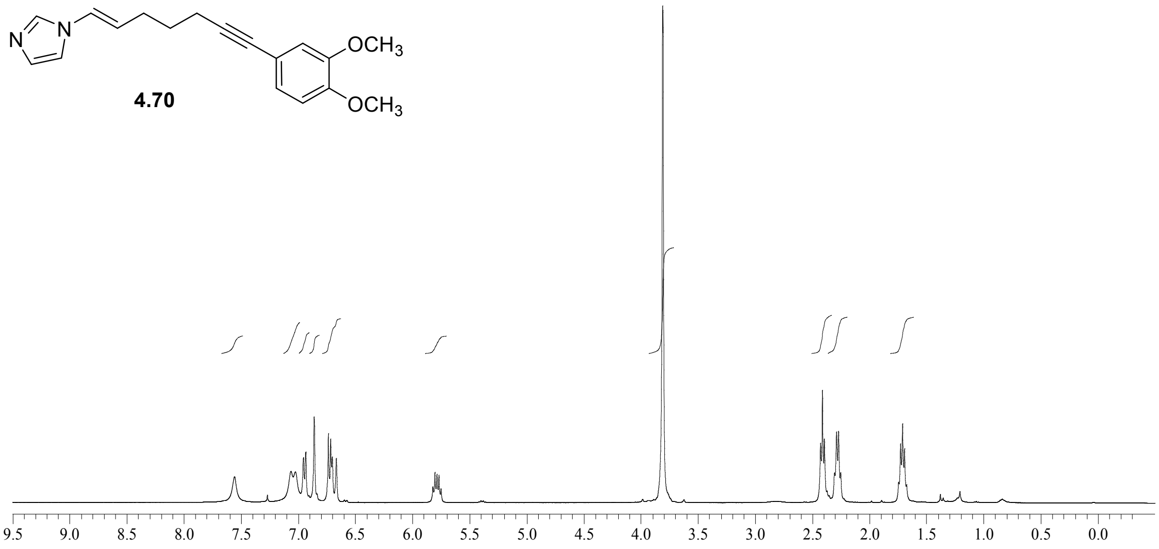

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

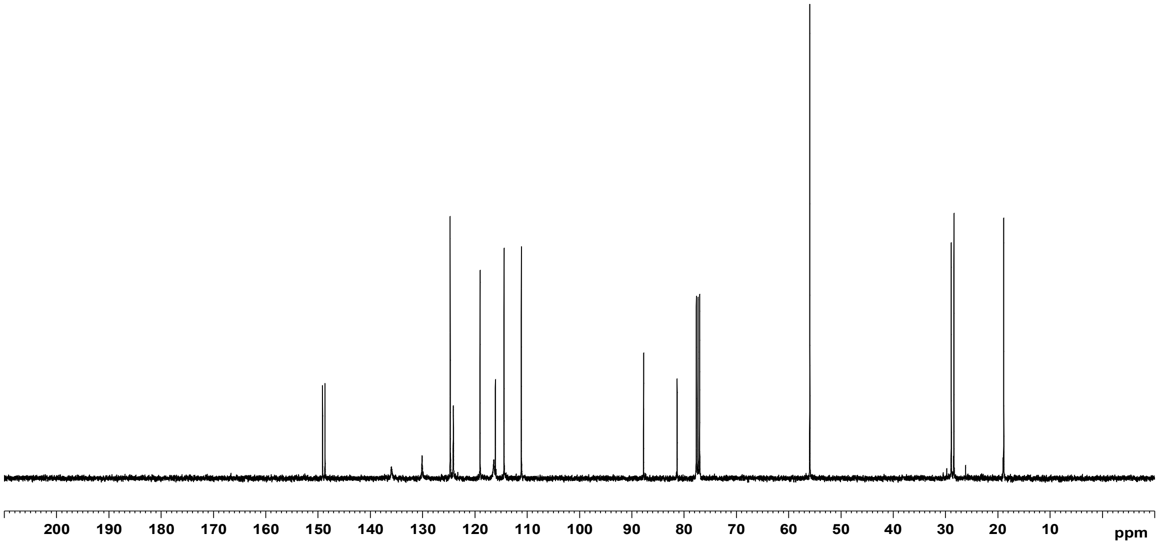

%T
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

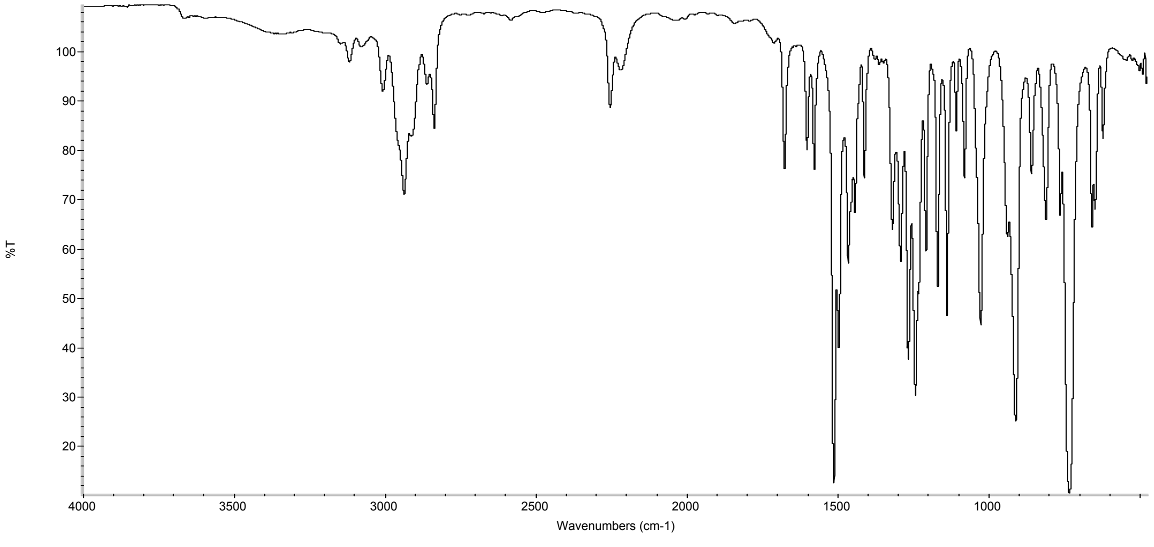

O
N
OCH3
OCH3
4.69
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

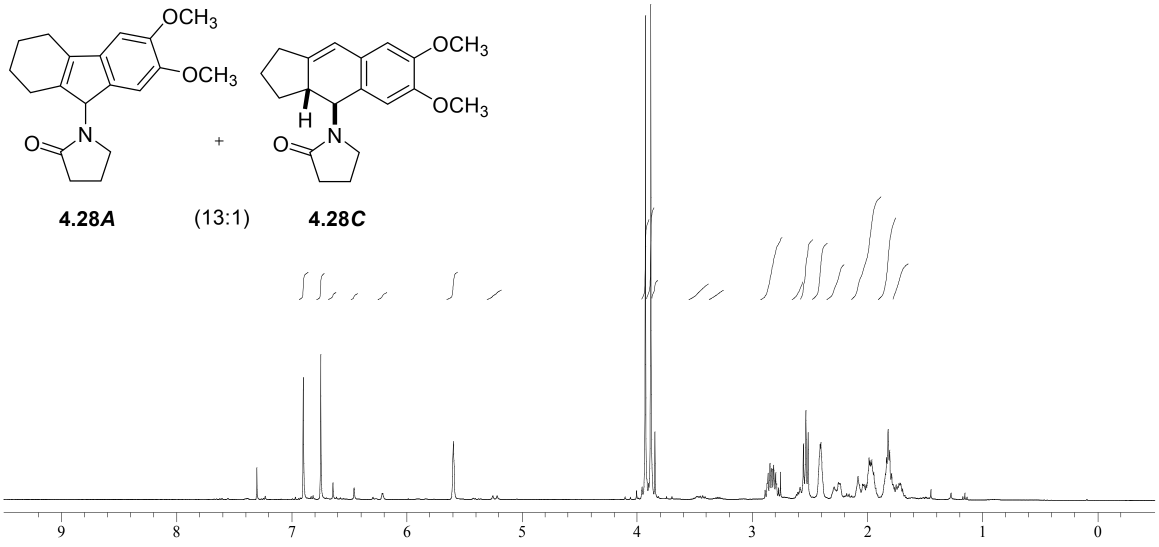

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

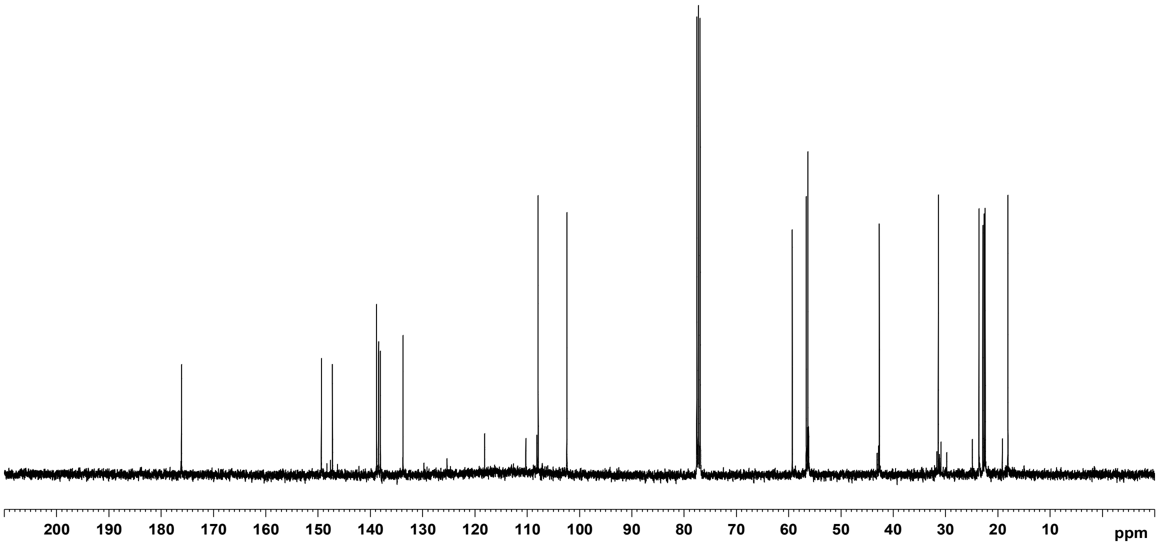

%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

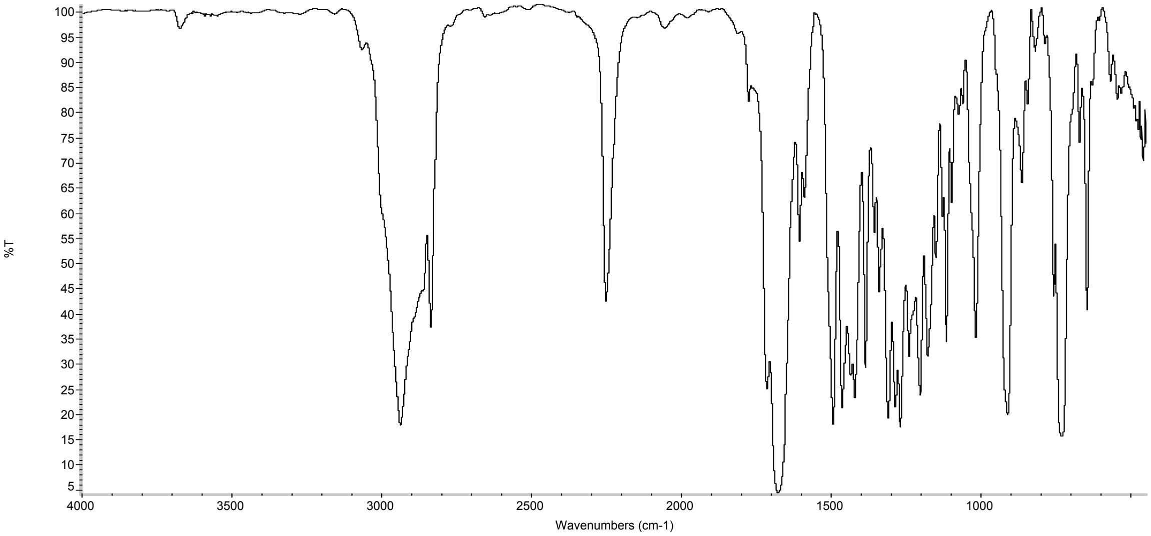

N
N
OCH3
OCH3
4.70
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

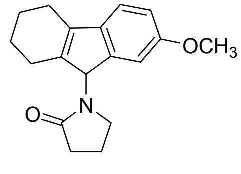

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

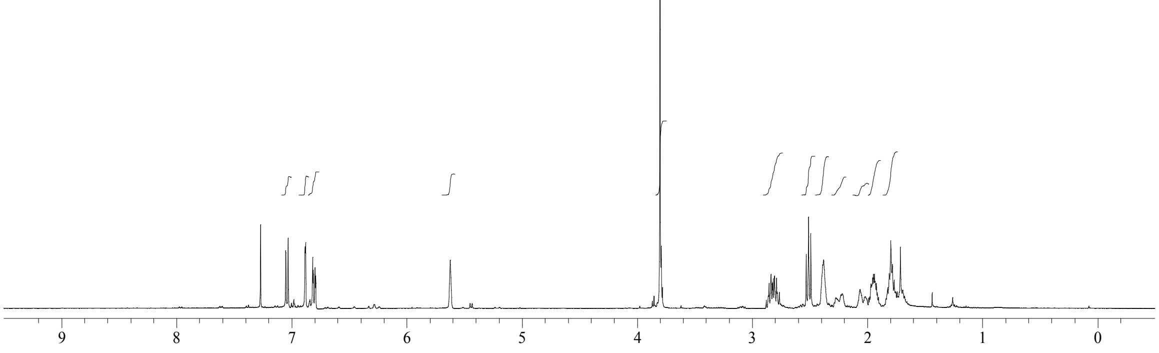

OCH3
OCH3
N
O
+
H
N
O
OCH3
OCH3
4.28*A*
(13:1)
4.28*C*
9
8
7
6
5
4
3
2
1
0

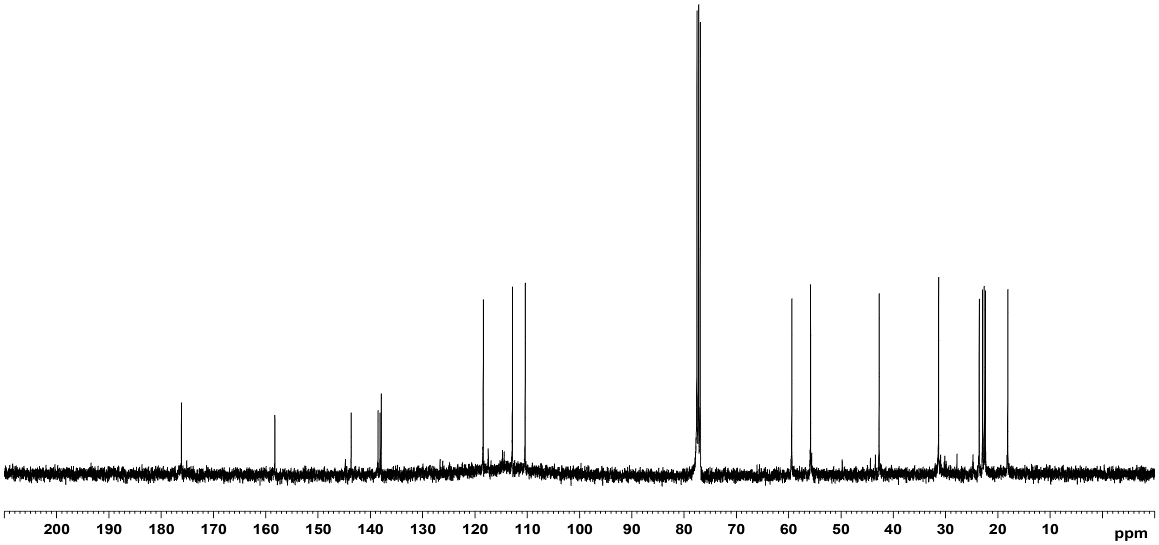

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

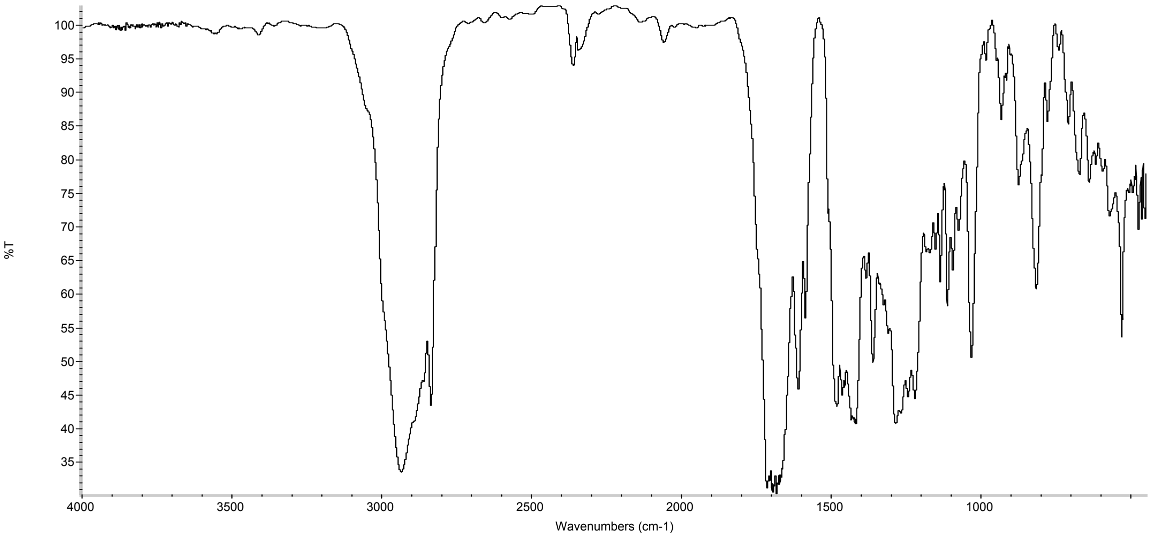

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

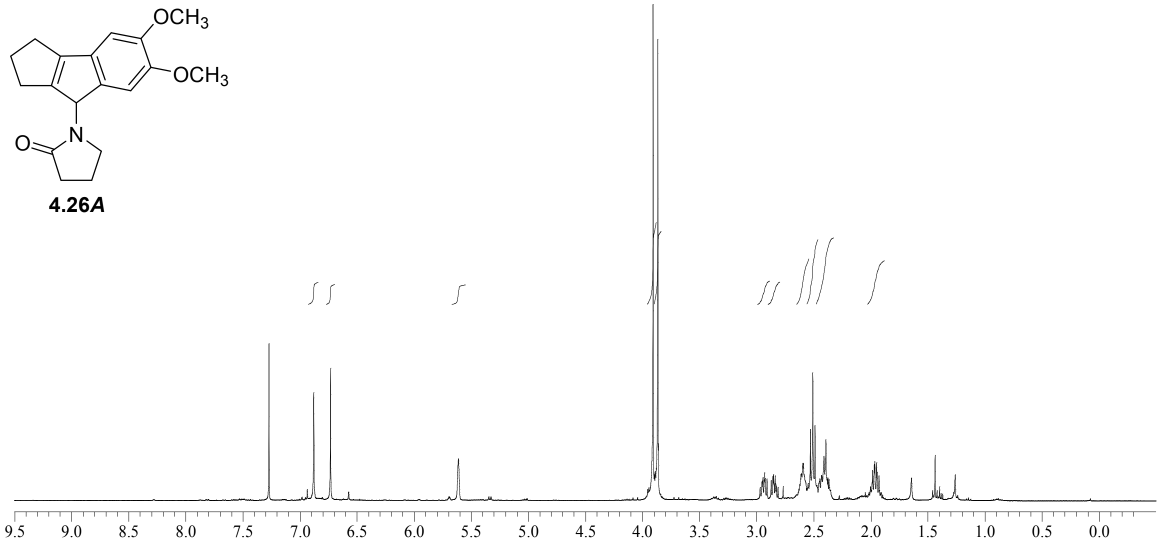

OCH3
N
O

4.27*A*

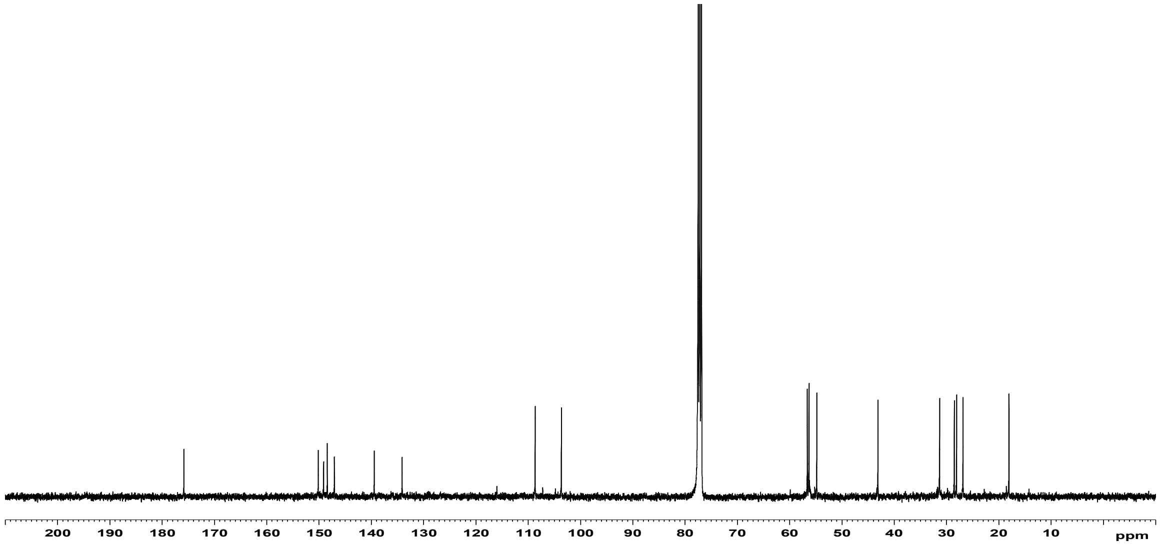

9
8
7
6
5
4
3
2
1
0

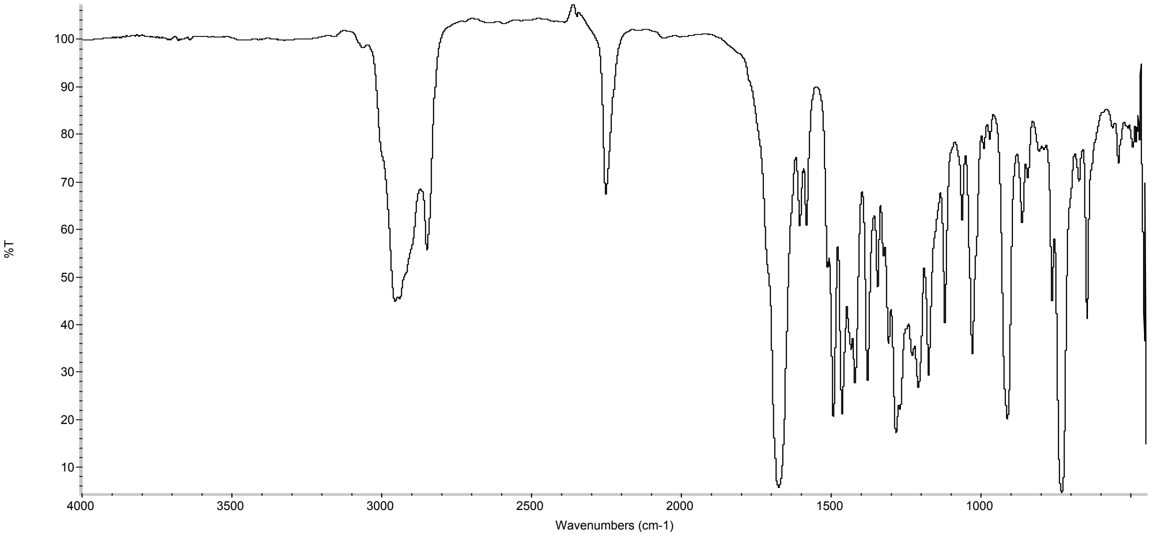

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

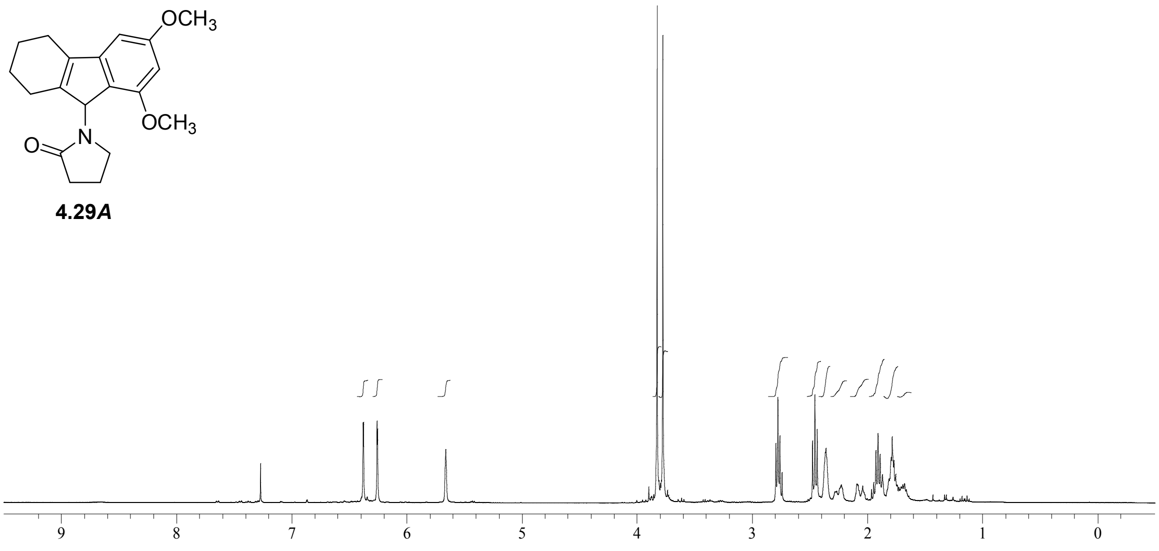

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


OCH3
OCH3
O
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

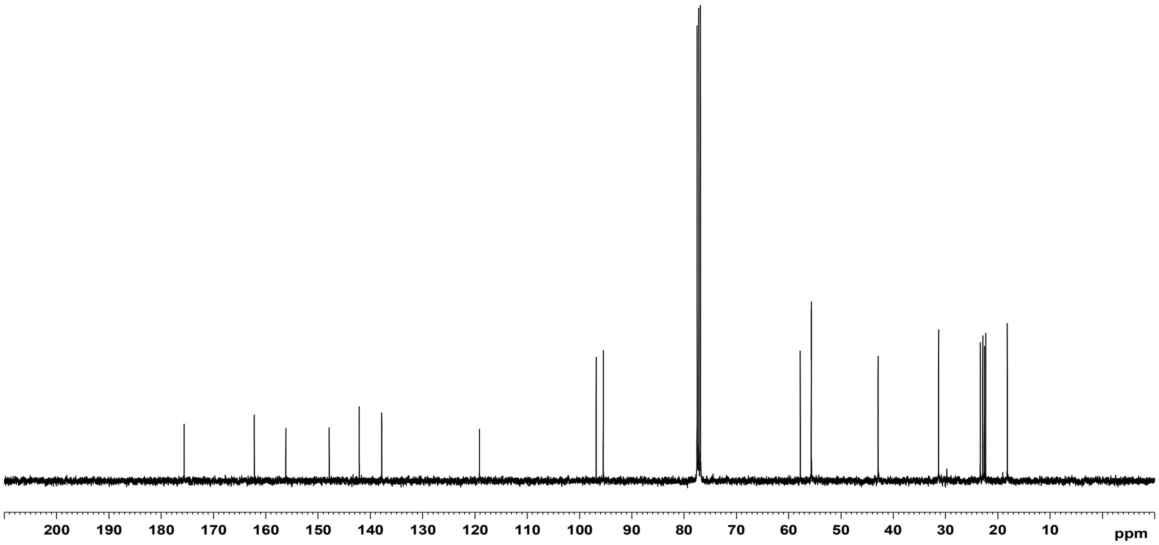
4.26*A*

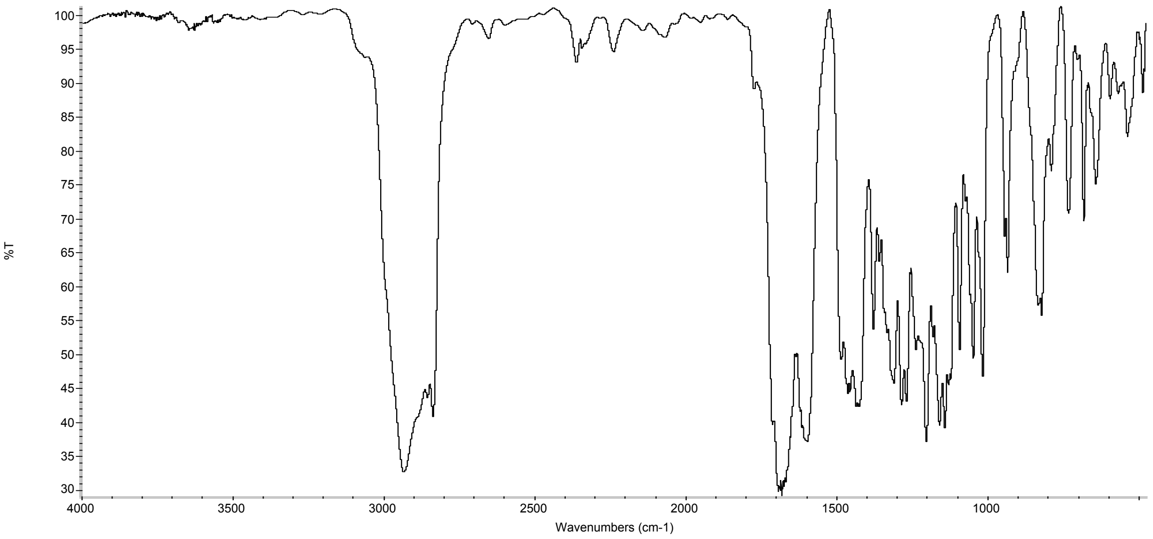

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

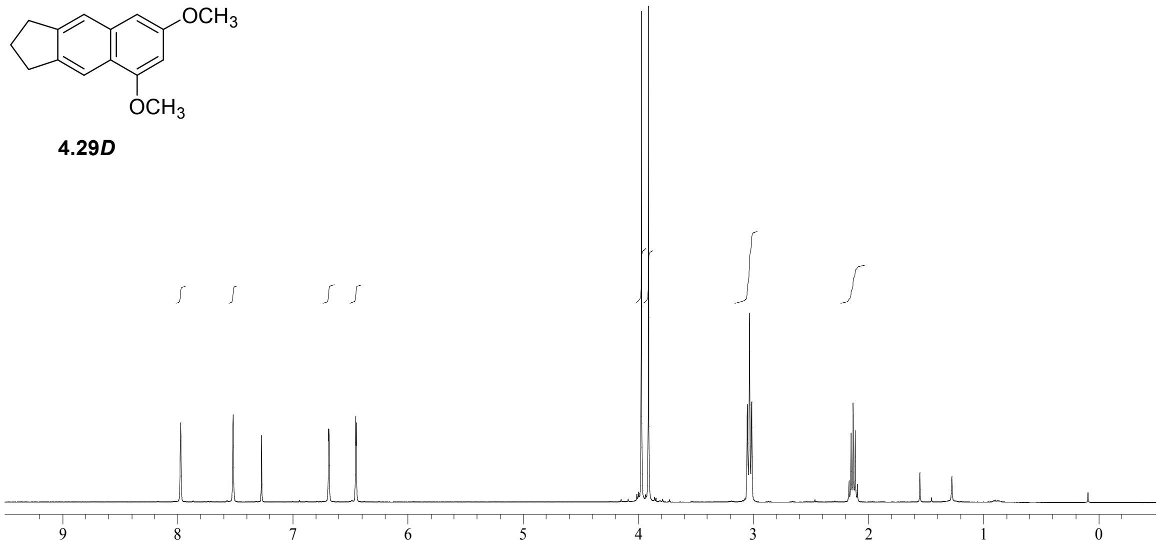

100
90
80
70
60
50
40
30
20
10
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


OCH3
OCH3
O
N
9
8
7
6
5
4
3
2
1
0

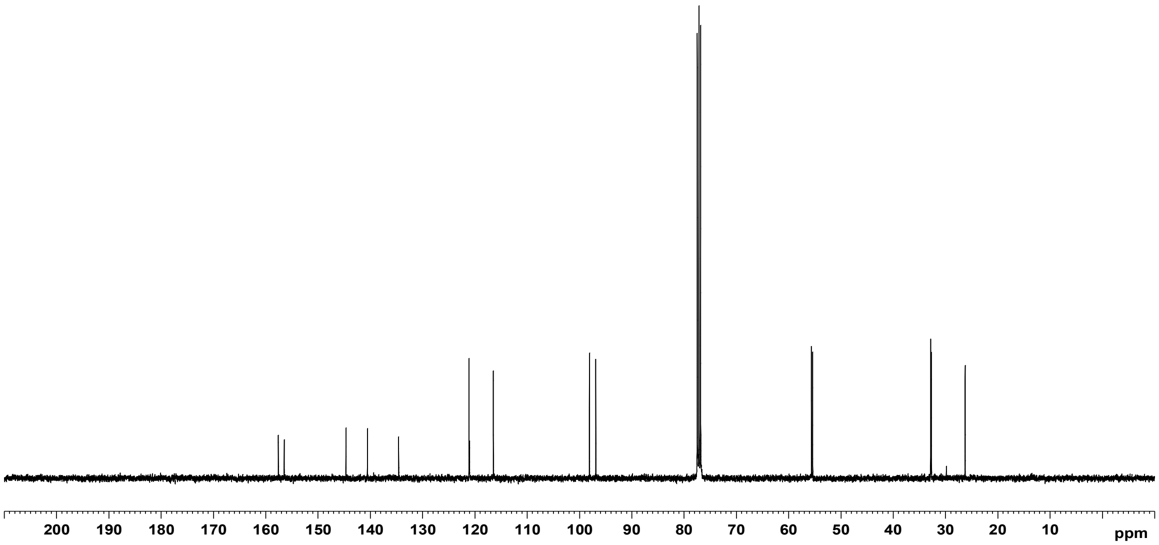
4.29*A*

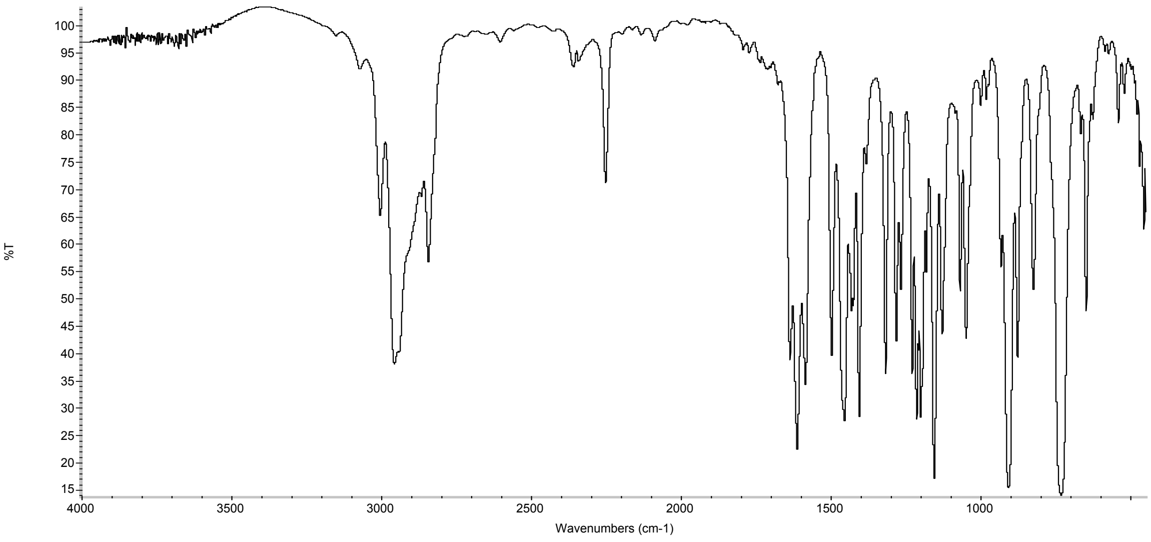

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

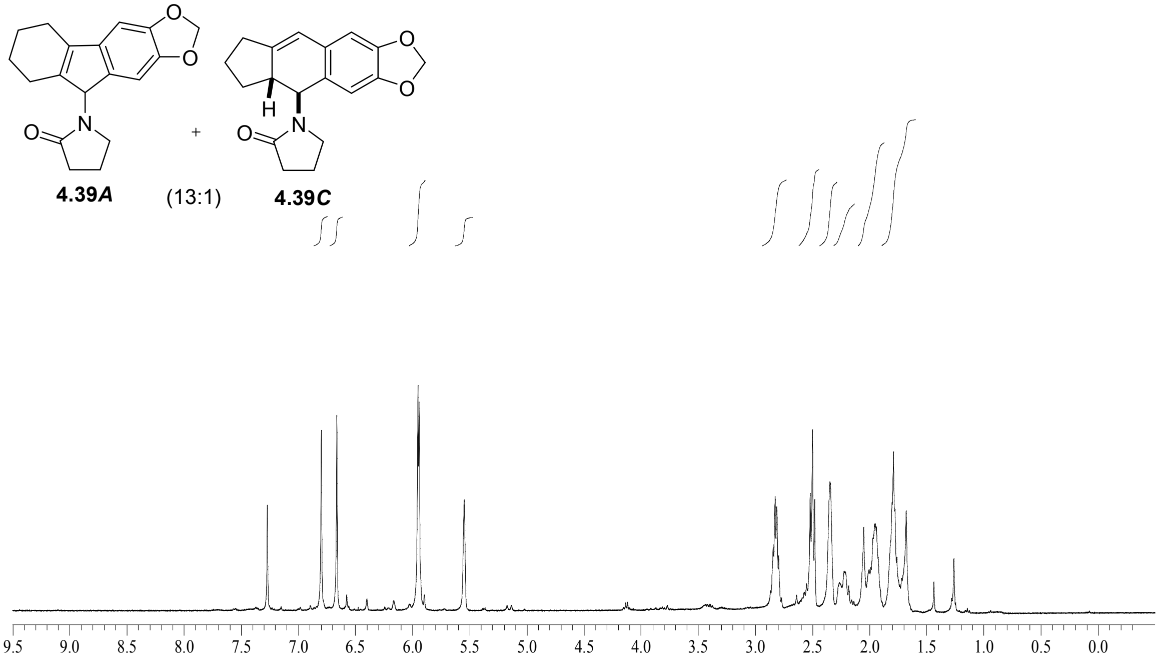

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

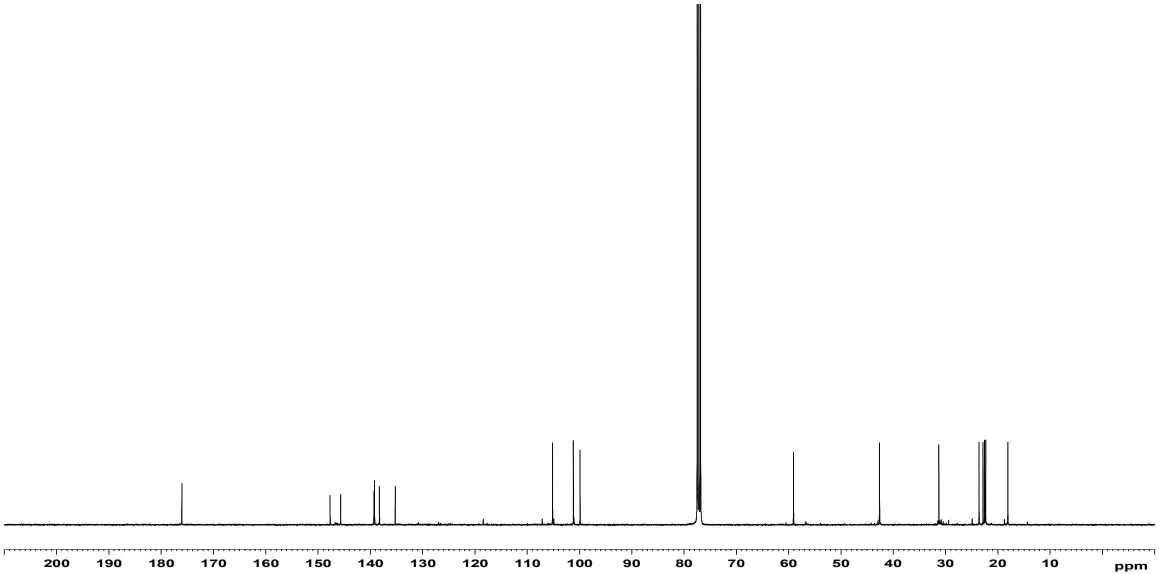

OCH3
OCH3
9
8
7
6
5
4
3
2
1
0

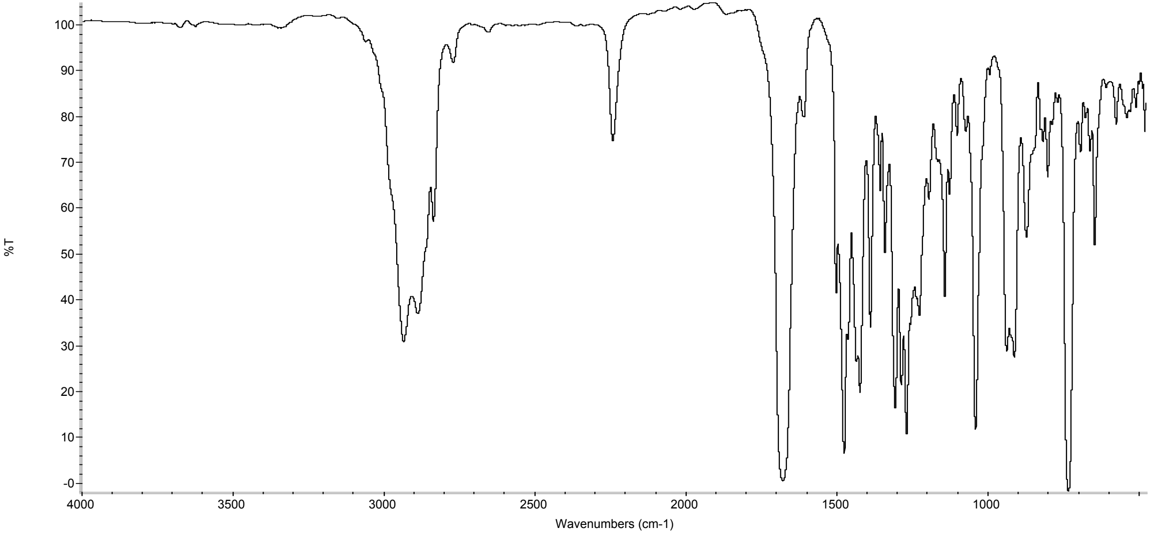
4.29*D*

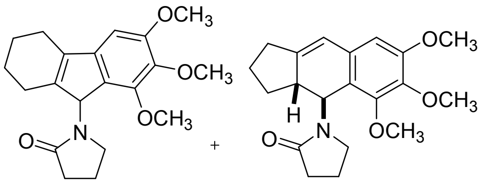

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

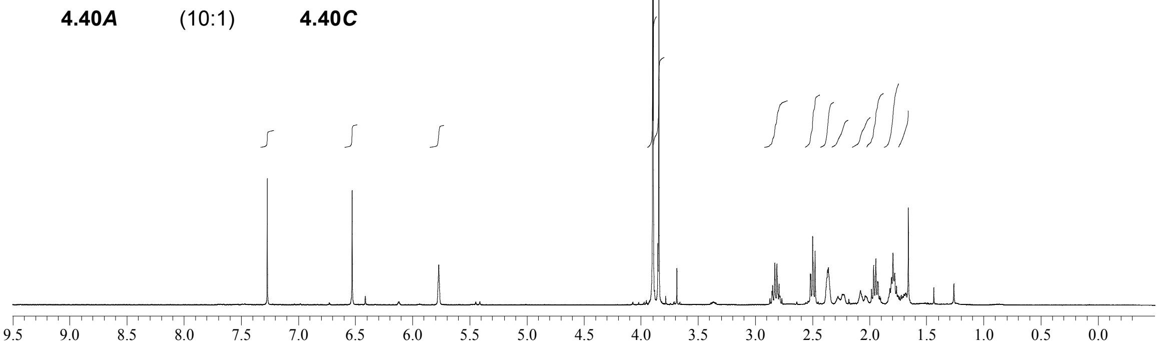

4.39*A*
+
(13:1)
4.39*C*
H
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

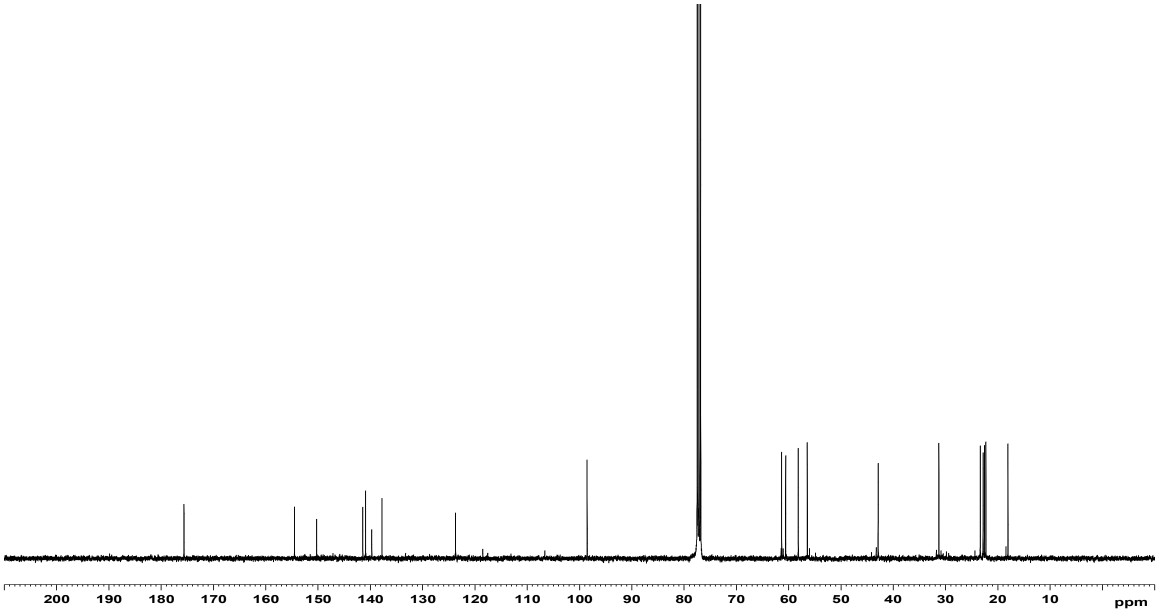

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

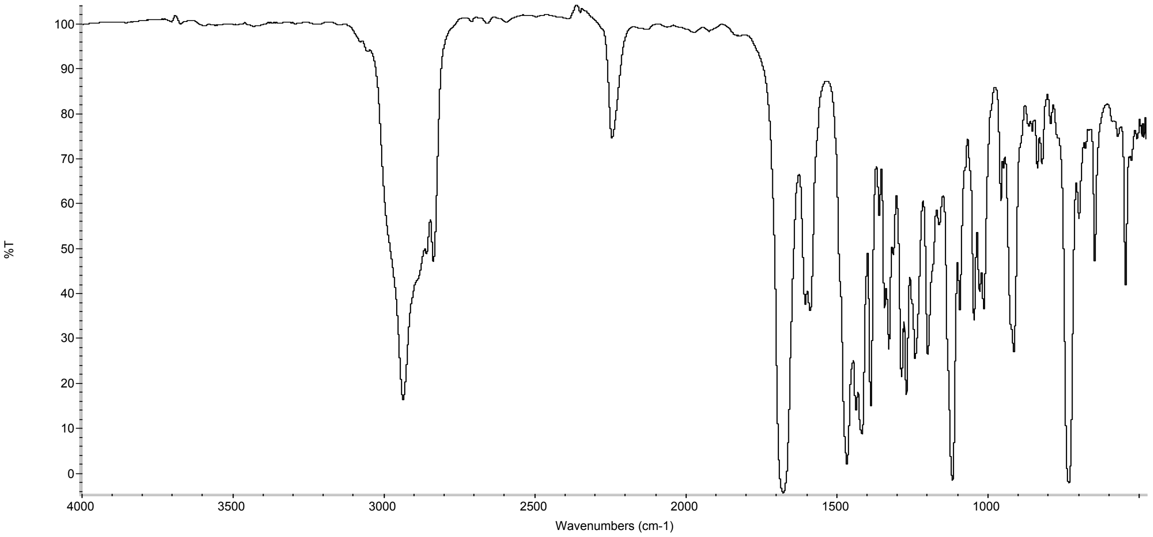

%T
100
90
80
70
60
50
40
30
20
10
-0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

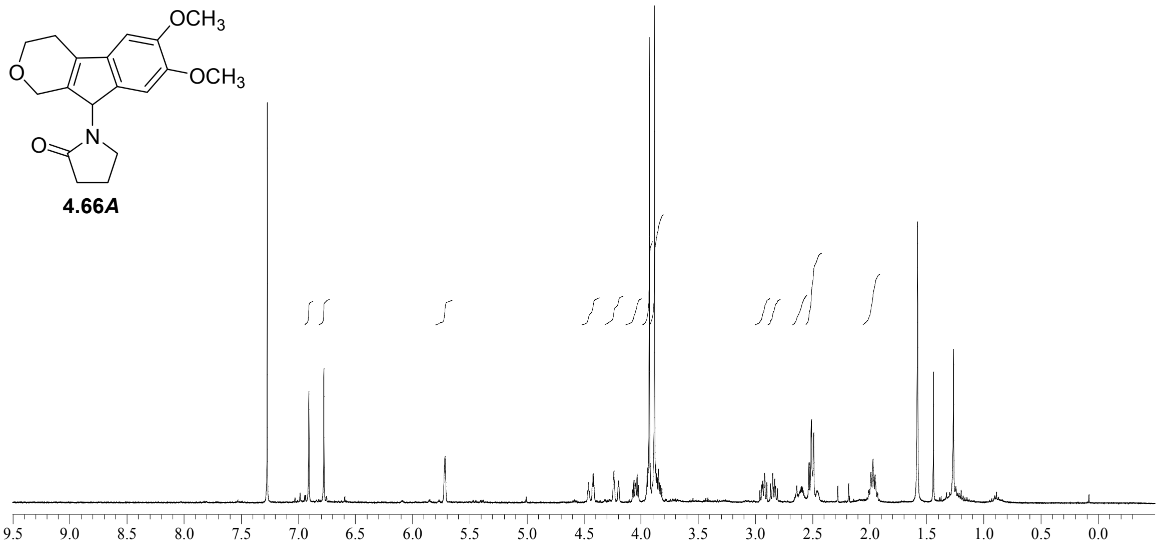

OCH3
OCH3
OCH3
N
O
+
H
N
O
OCH3
OCH3
OCH3

4.40*A* (10:1) **4.40*C***

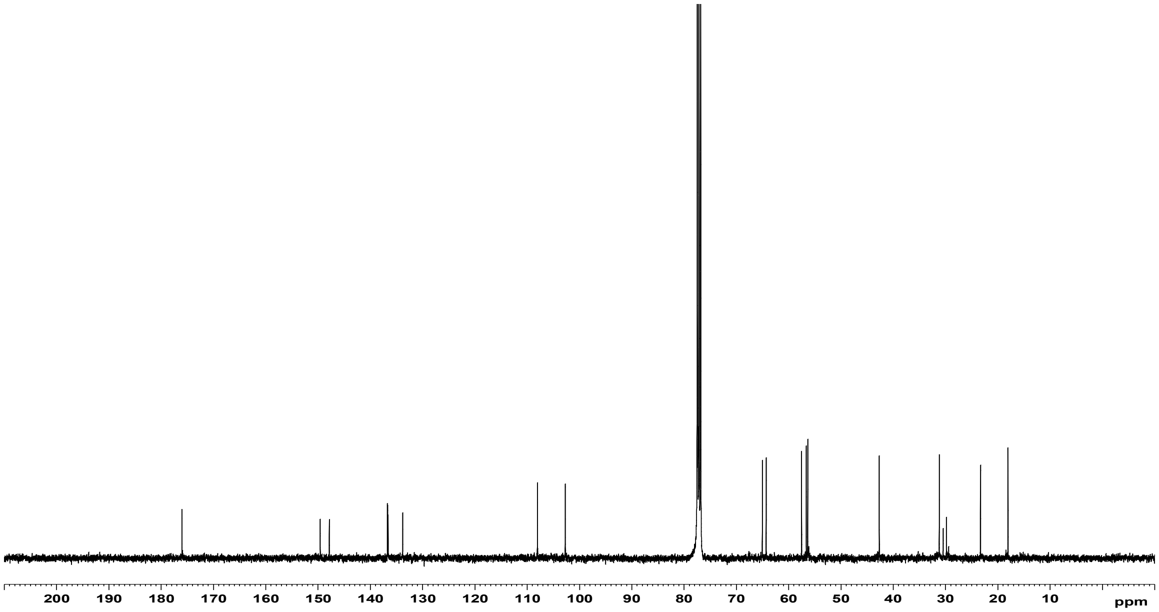


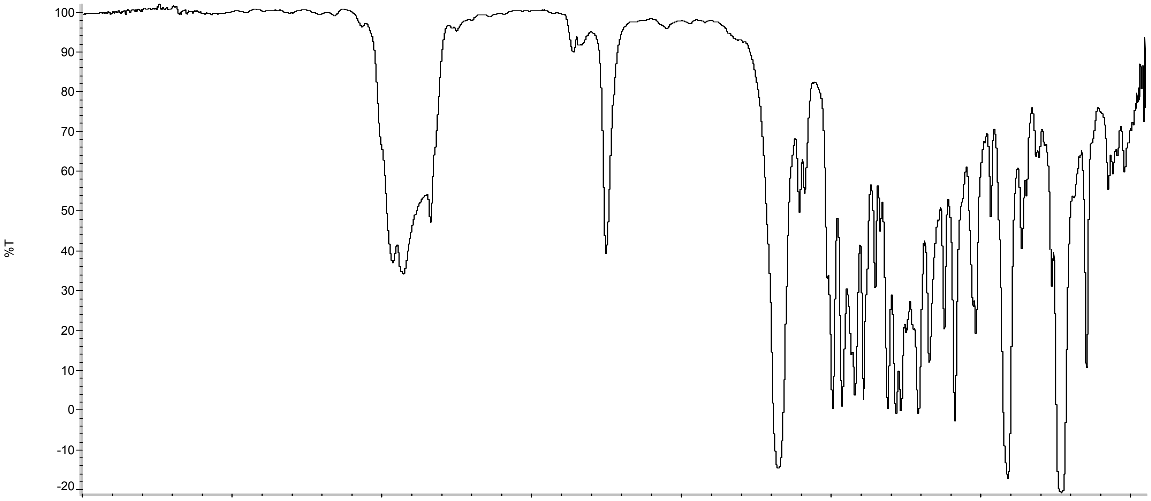


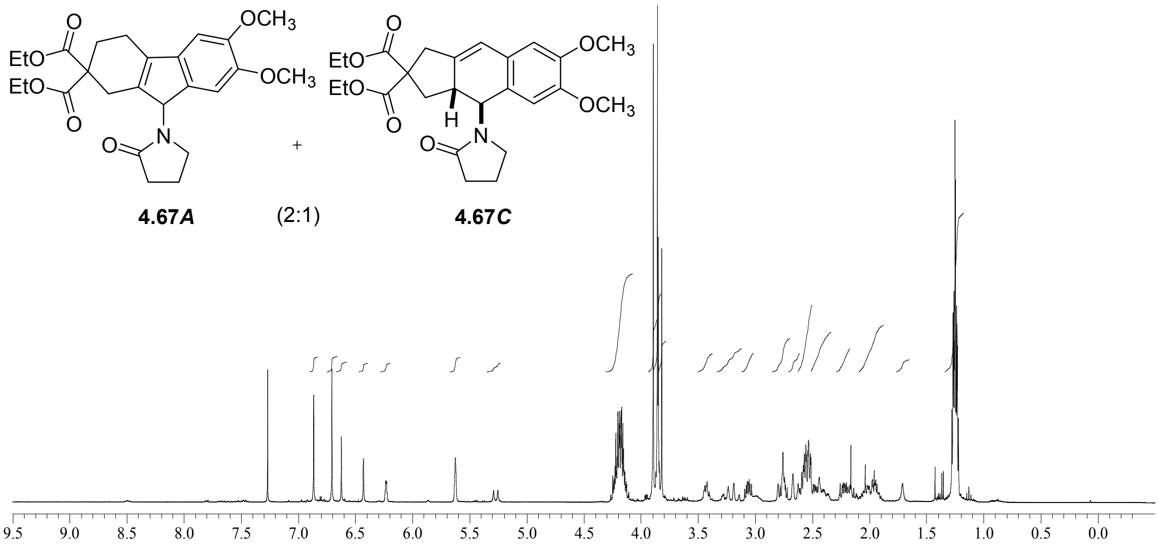



OCH3
OCH3
O
N
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

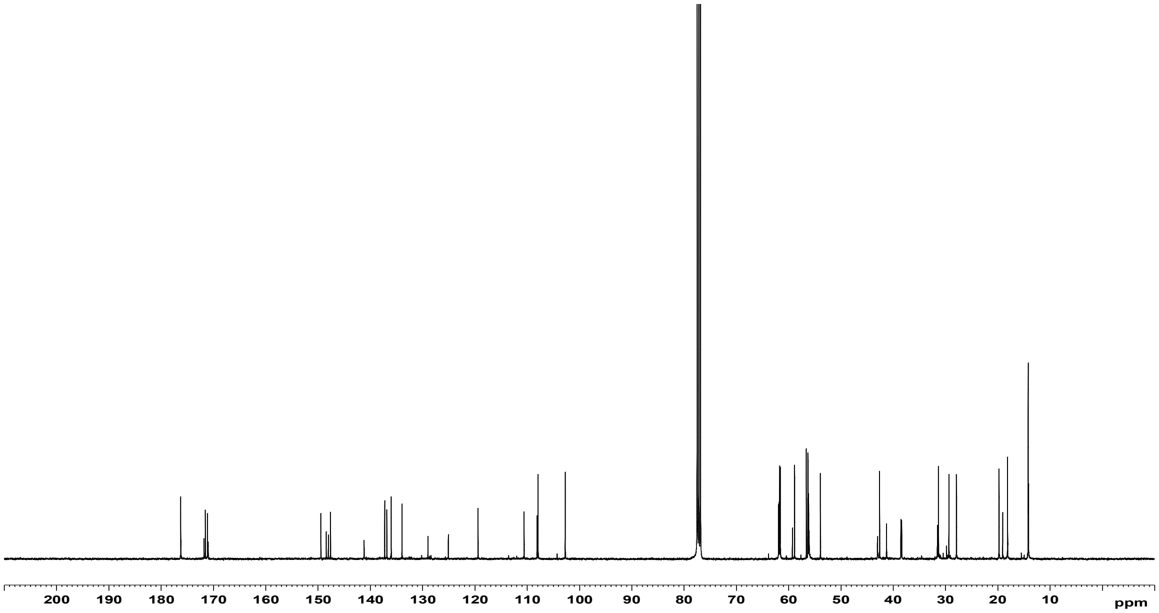
4.66*A*

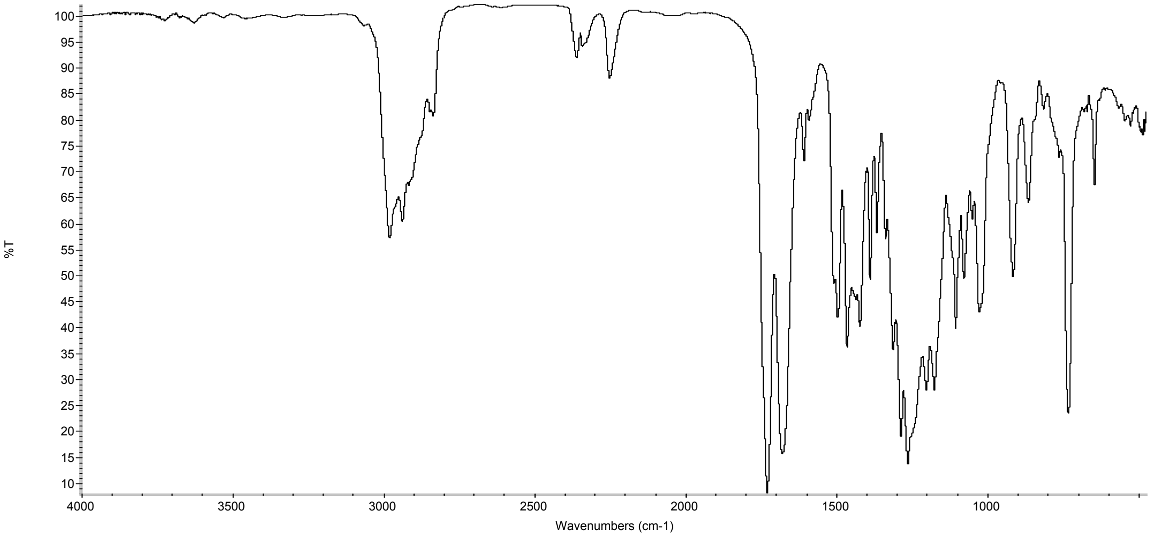

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

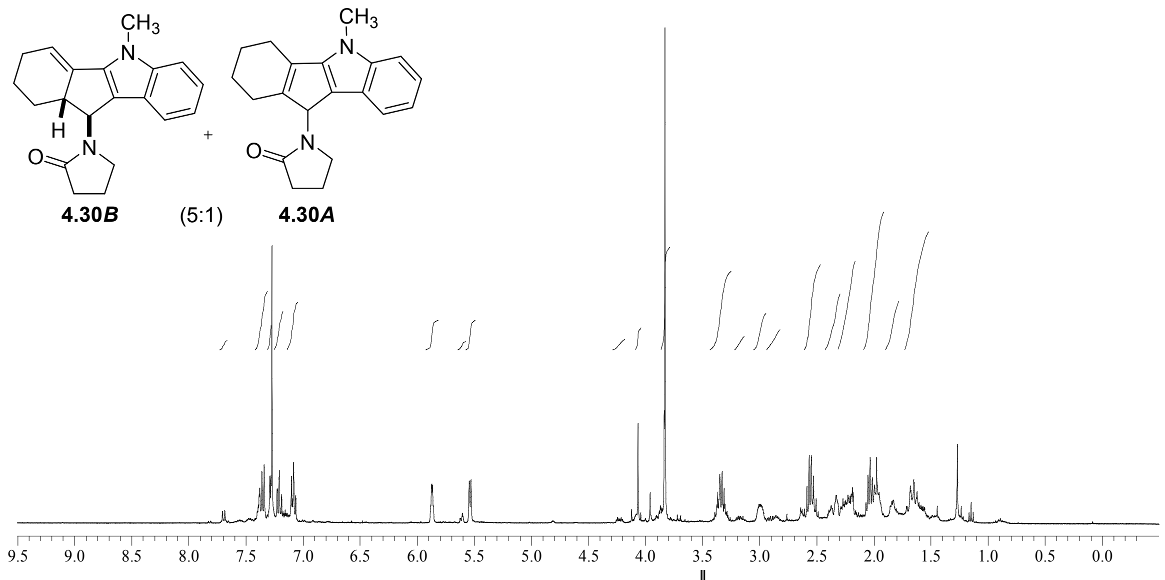

%T
100
90
80
70
60
50
40
30
20
10
0
-10
-20
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


EtO
EtO
O
O
OCH3
OCH3
N
O
+
H
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

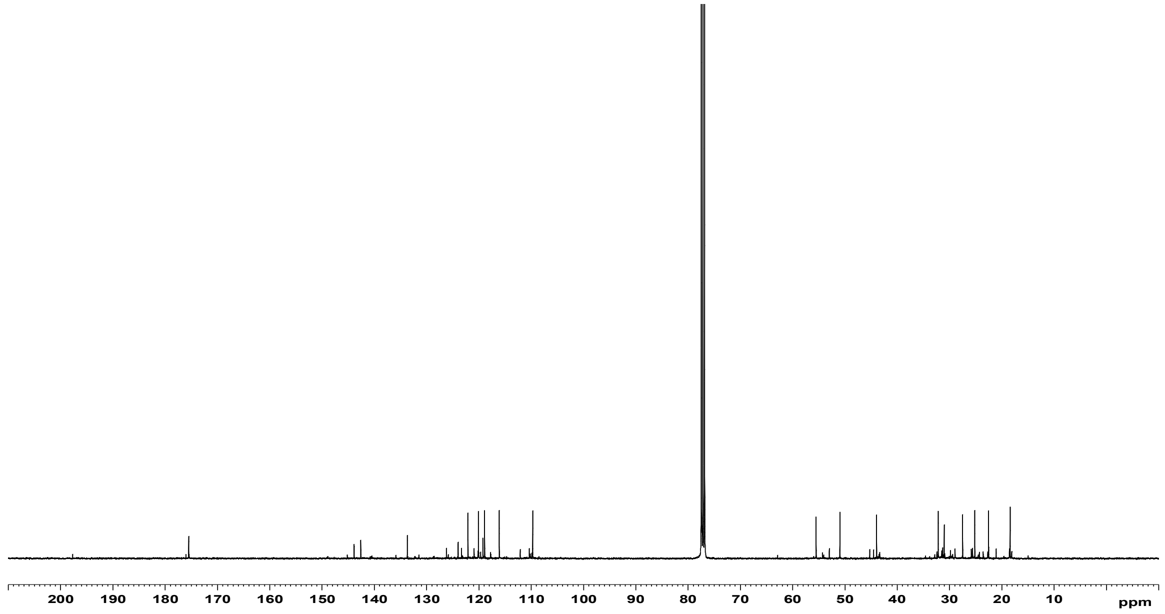
4.67*A* (2:1) **4.67*C***

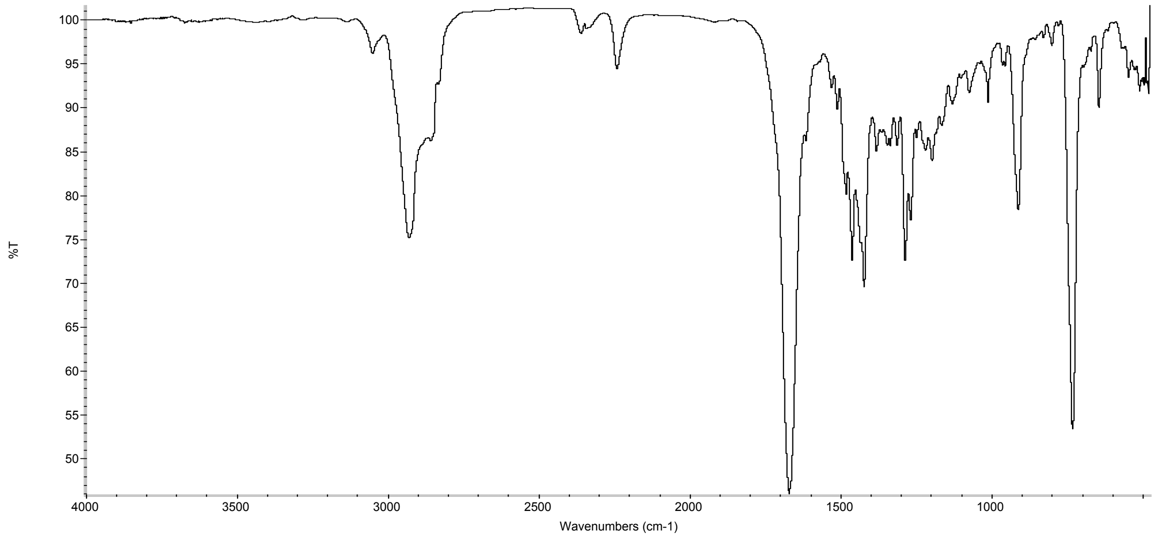

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

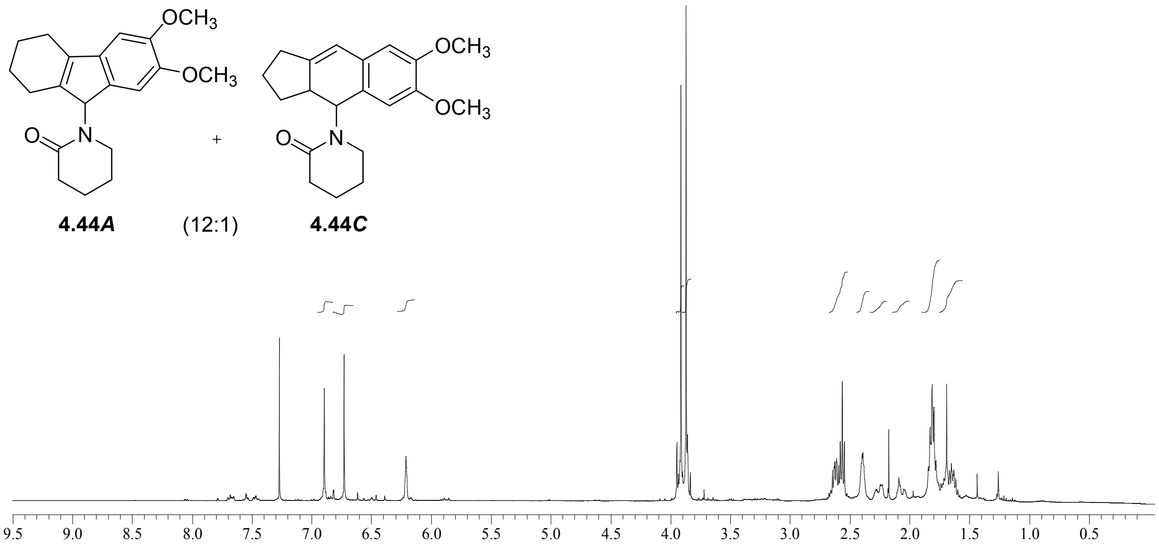

%T
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


4.30*B* (5:1) **4.30*A***

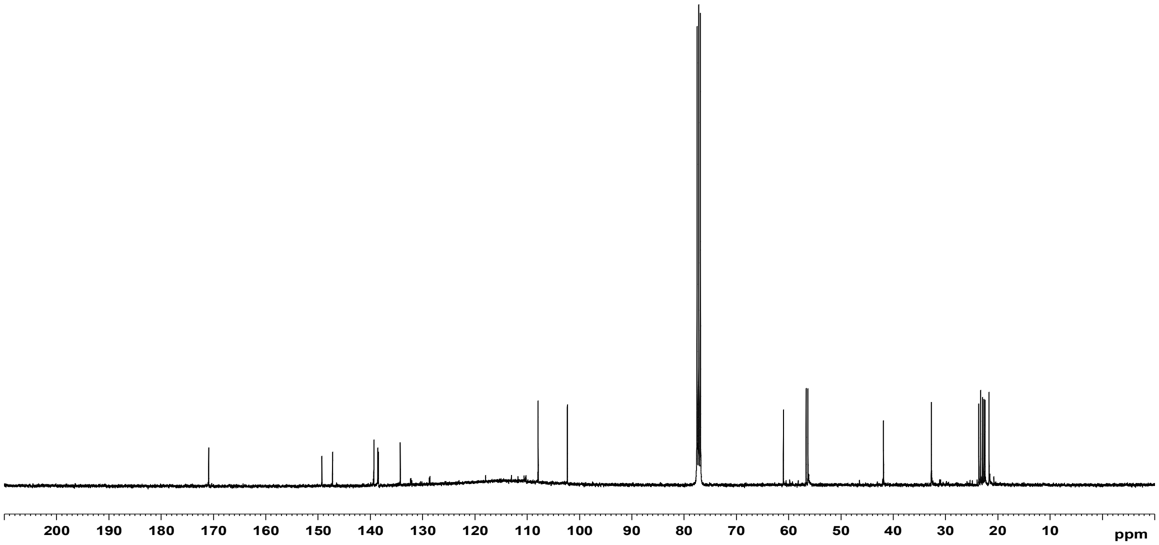
CH3
N
H
O
N
+
CH3
N
O
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

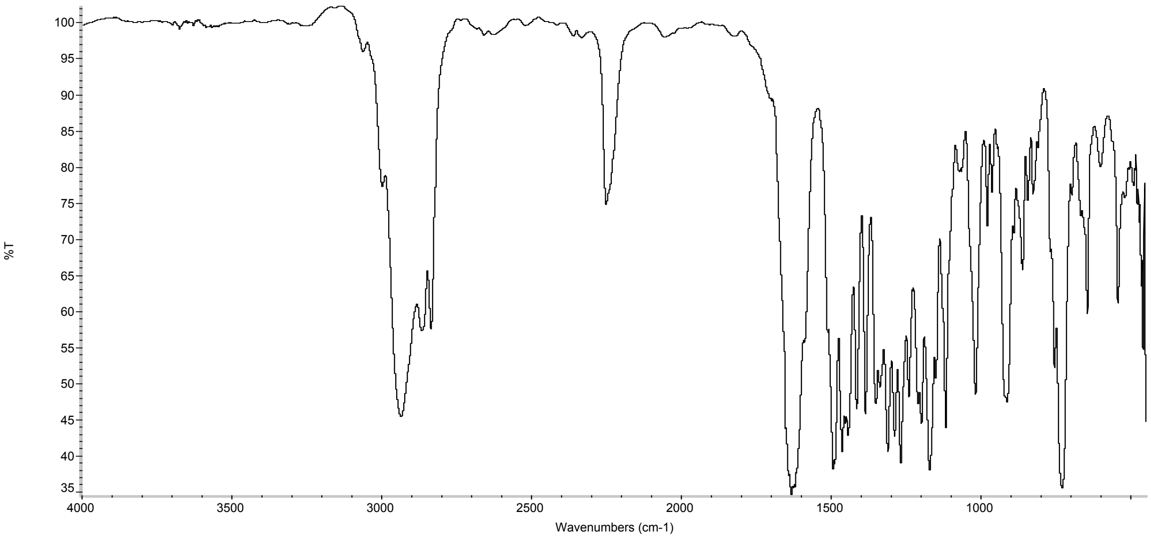

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

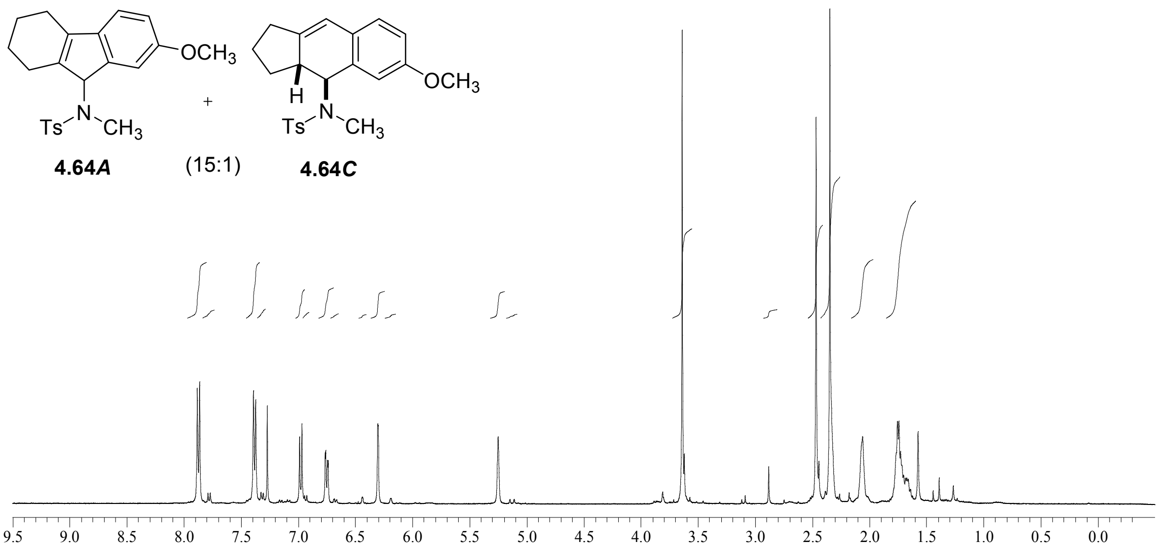

100
95
90
85
80
75
70
65
60
55
50
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



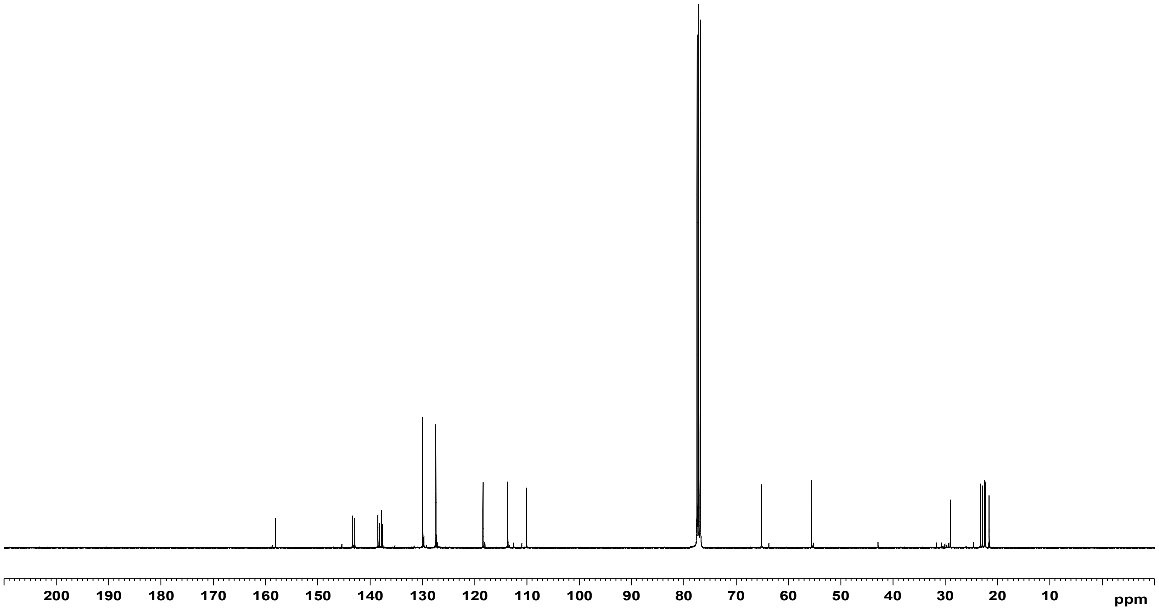
4.44*A* (12:1) **4.44*C***

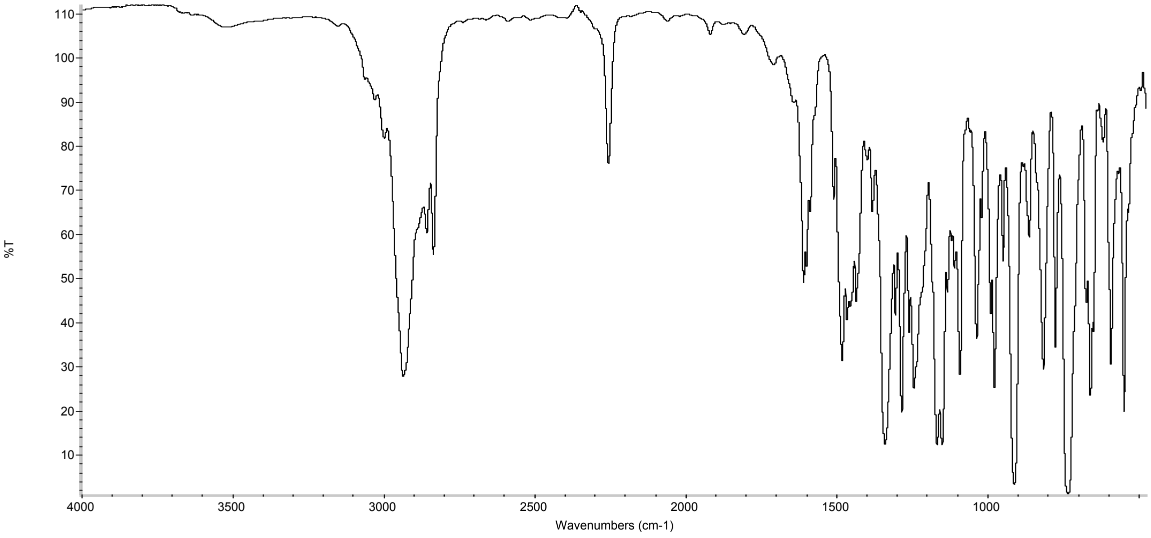


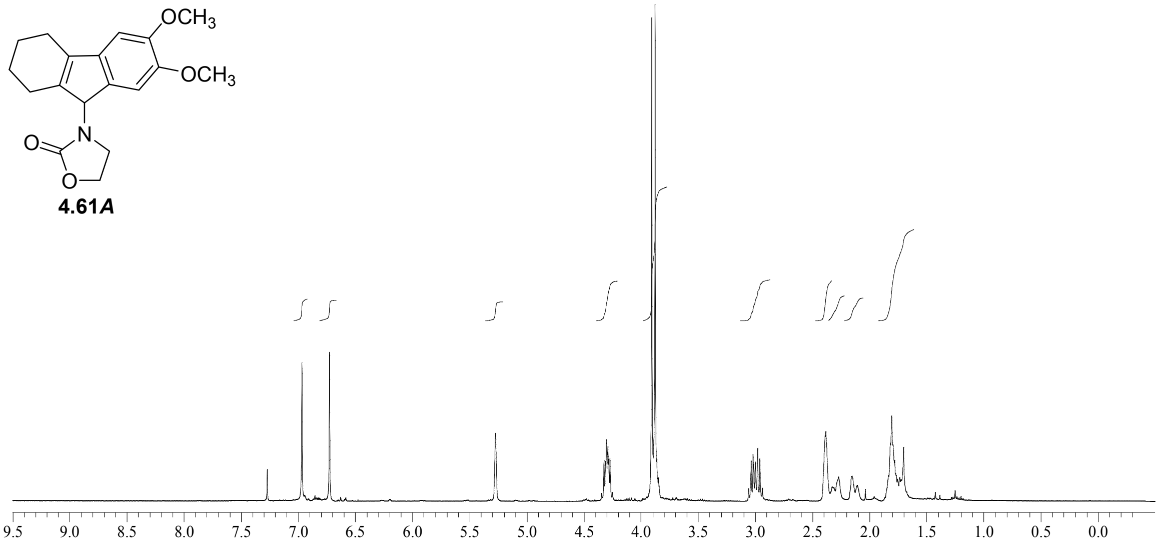




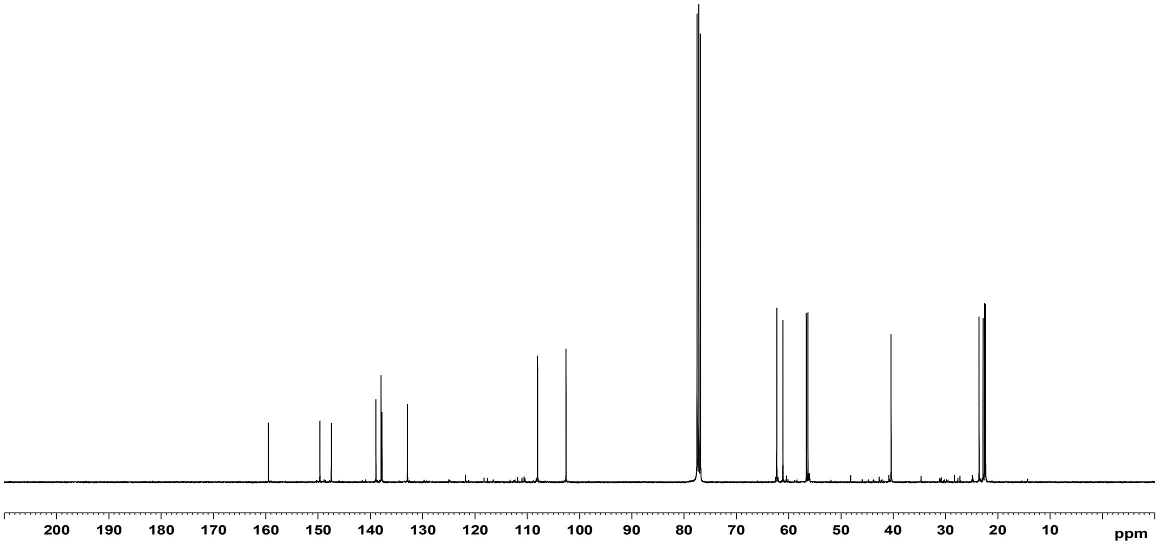
4.64*A* (15:1) **4.64*C***

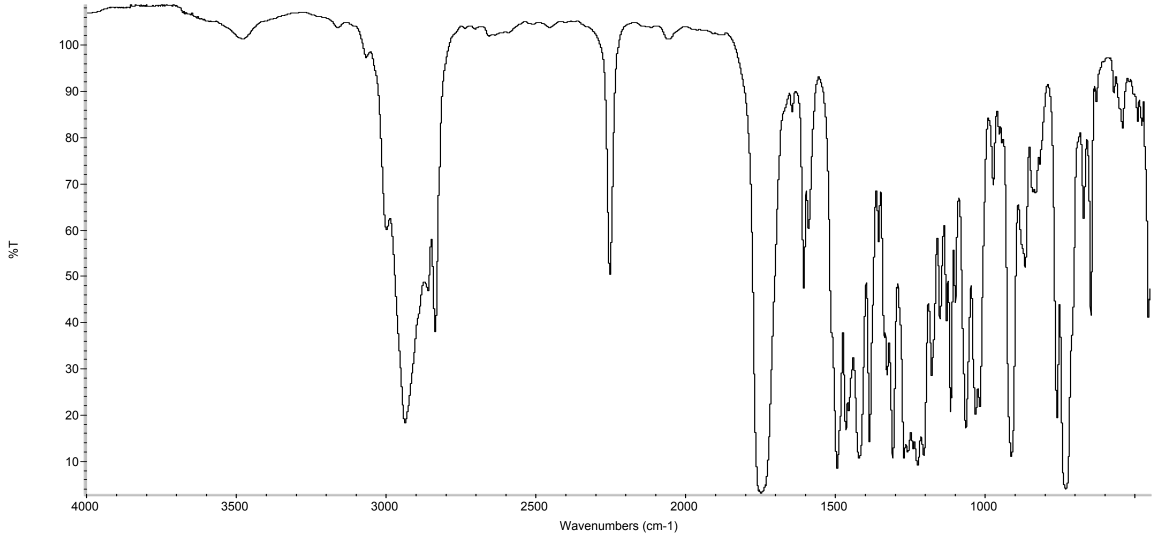


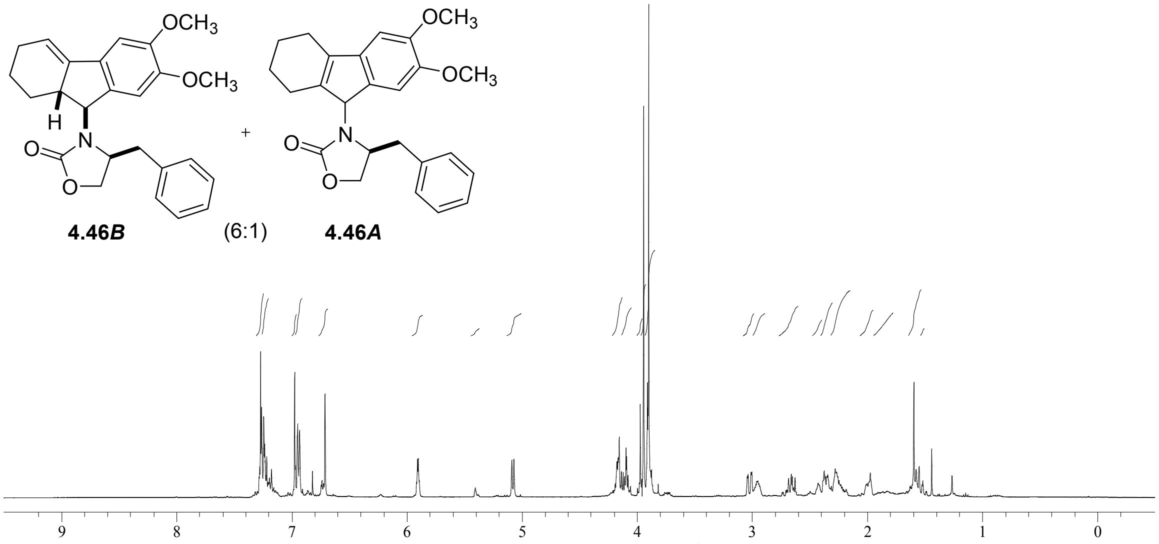


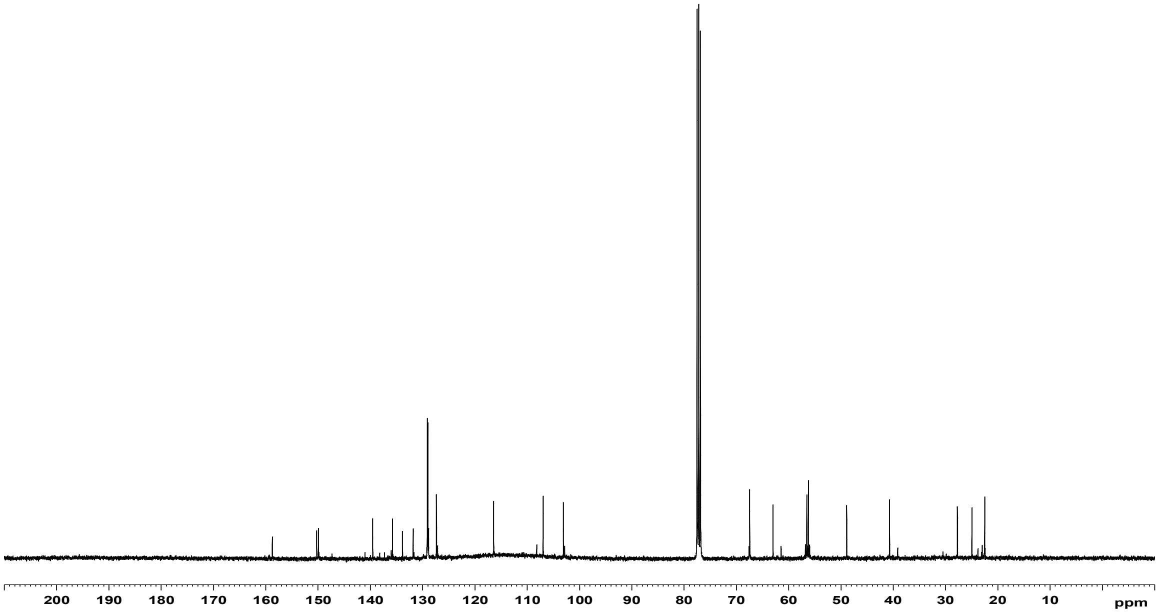

OCH3
OCH3
N
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

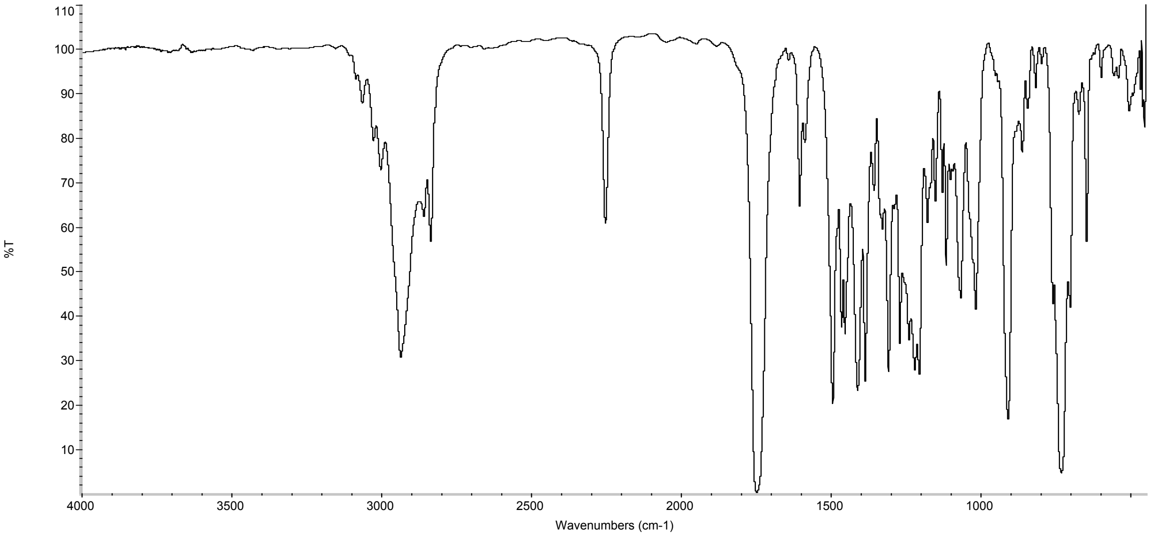
4.61*A*


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)


OCH3
OCH3
H
O
N
O
+
OCH3
OCH3
O
N
O
4.46B
(6:1)
4.46A
9
8
7
6
5
4
3
2
1
0


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


110
100
90
80
70
60
50
40
30
20
10
%T
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

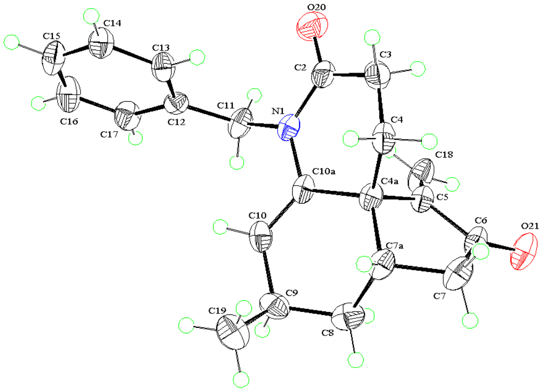
Appendix D: X-ray Crystallographic Data

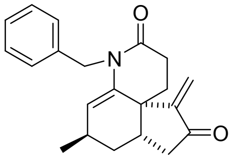
Table D.1: X-ray crystallography data for compounds **2.105**, **2.123**, and **2.131**

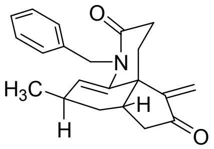
Compound	**2.105**[a]	**2.123**[a]	**2.131**[a]
formula	$C_{22}H_{25}NO_2$	$C_{15}H_{19}NO_2S$	$C_{18}H_{23}NO_3$
formula weight	335.77	277.37	301.37
color, habit	colorless, irregular	colorless, irregular	colorless, plate
crystal size (mm)	0.15 × 0.20 × 0.50	0.10 × 0.10 × 0.10	0.10 × 0.25 × 0.50
crystal system	primitive	primitive	primitive
lattice type	monoclinic	orthorhombic	monoclinic
space group	$P\,6_5$ (#170)	$P\,2_12_12_1$ (#19)	$P\,2_1$ (#4)
a (Å)	21.065(3)	8.462(1)	7.7440(8)
b (Å)	21.065	8.531(1)	8.2110(9)
c (Å)	6.9665(8)	18.001(2)	24.427(3)
α (deg)	90.0	90.0	90.0
β (deg)	90.0	90.0	91.840(6)
γ (deg)	120.0	90.0	90.0
V (Å^3)	2674.8(5)	1299.5(3)	1552.4(3)
Z	6	4	4
D_{calc} (g/cm^3)	1.251	1.418	1.289
F_{000}	1082.00	592.00	648.00
μ (MoKα) (cm^{-1})	0.79	2.47	0.87
$2\theta_{max}$ (deg)	44.8	50.3	56.0
total no. reflections	18722	15779	26893
no. unique reflections	2310	2308	7243
Residuals (F^2, all data) R_1; wR_2	0.043; 0.078	0.037; 0.067	0.054; 0.109
Residuals (F) R_1; wR_2	0.033; 0.074	0.029; 0.064	0.044; 0.103
Goodness of fit indicator	1.06	1.03	1.05

[a] Sample run on Bruker X8 Apex diffractometer.

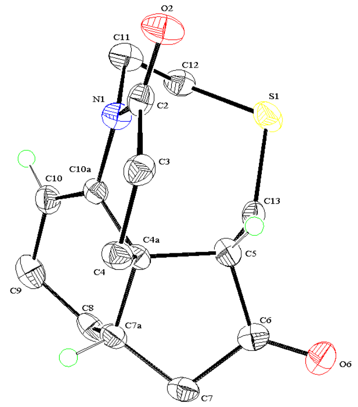
Compound **2.105**

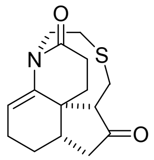

C15
C14
C13
C16
C17
C12
C11
N1
O20
C2
C3
C4
C18
C10a
C4a
C5
C6
O21
C10
C7a
C7
C9
C19
C8

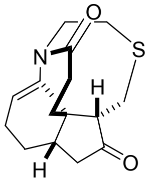




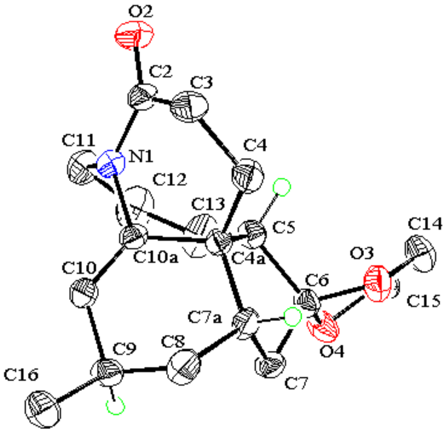
Compound **1.123**

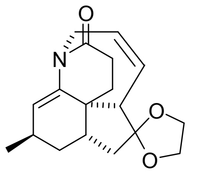

O2
C11
C12
N1
C2
S1
C3
C10a
C10
C13
C4a
C4
C5
C9
C8
C7a
C6
O6
C7

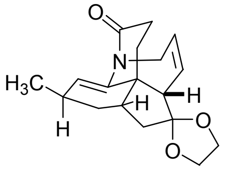




Compound **2.131**


O2
C2
C3
C11
N1
C4
C12
C13
C5
C14
O3
C10
C10a
C4a
C6
C15
C7a
C8
O4
C9
C7
C16




O
N
H_3C
H
H
H
O
O

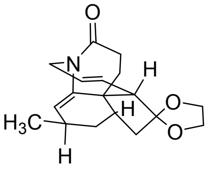
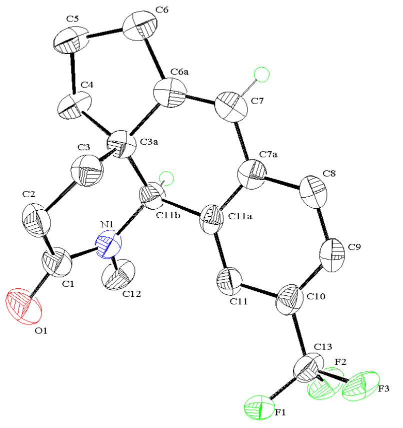

O
N
H
H
H_3C
H
O
O

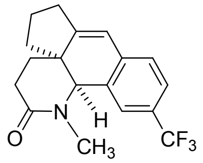
Table D.2: X-ray crystallography data for compounds **3.33*X*/3.33*N***, **3.35*N***, and **4.65*B*/4.65*C***

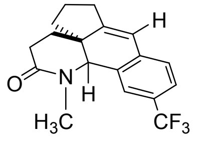
Compound	**3.33*X*/3.33*N*** [a]	**3.35*N*** [a]	**4.65*B*/4.65*C*** [a]
formula	$C_{18}H_{18}NOF_3$	$C_{25}H_{27}NO_3$	$C_{23}H_{27}NO_4S$
formula weight	321.33	389.48	413.52
color, habit	colorless, irregular	colorless, prism	colorless, irregular
crystal size (mm)	0.35 × 0.42 × 0.45	0.34 × 0.50 × 0.55	0.30 × 0.37 × 0.40
crystal system	primitive	primitive	primitive
lattice type	triclinic	monoclinic	monoclinic
space group	*P* -1 (#2)	$P\ 2_1/c$ (#14)	$P\ 2_1/c$ (#14)
a (Å)	9.2986(10)	9.6061(3)	8.6256(4)
b (Å)	9.4653(10)	26.6832(9)	21.8854(11)
c (Å)	9.7386(10)	8.2419(3)	11.1823(5)
α (deg)	109.869(5)	90.0	90.0
β (deg)	106.046(5)	107.540(2)	103.520(2)
γ (deg)	97.731(5)	90.0	90.0
V (Å^3)	749.55(14)	2014.4(1)	2052.4(2)
Z	2	4	4
D_{calc} (g/cm^3)	1.424	1.284	1.338
F_{000}	336.00	832.00	880.00
μ (MoKα) (cm^{-1})	1.13	0.84	1.88
$2\theta_{max}$ (deg)	56.0	56.3	55.8
total no. reflections	16480	28130	37034
no. unique reflections	3595	4910	4919
Residuals (F^2, all data) R_1; wR_2	0.063; 0.148	0.051; 0.111	0.060; 0.112
Residuals (F) R_1; wR_2	0.052; 0.139	0.041; 0.103	0.041; 0.101
Goodness of fit indicator	1.03	1.02	1.01

[a] Sample run on Bruker X8 Apex diffractometer.

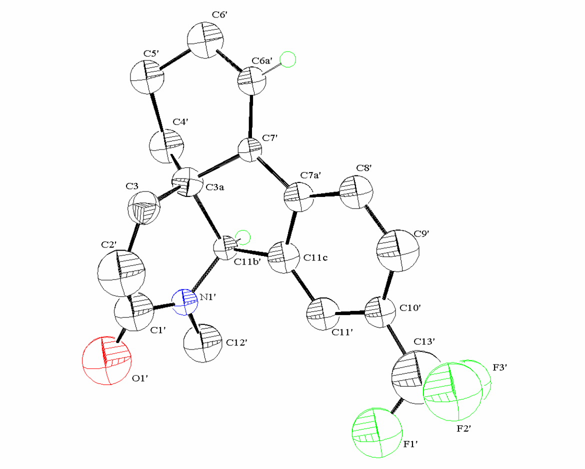
Compound **3.33*X***:

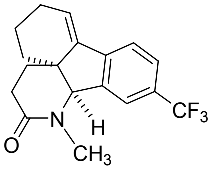

C5
C6
C6a
C4
C7
C3a
C3
C7a
C8
C2
N1
C11b
C11a
C9
C1
C12
C11
C10
O1
C13
F2
F3
F1

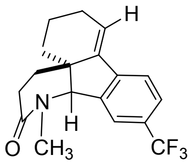



H
O
N
H
H_3C
CF_3

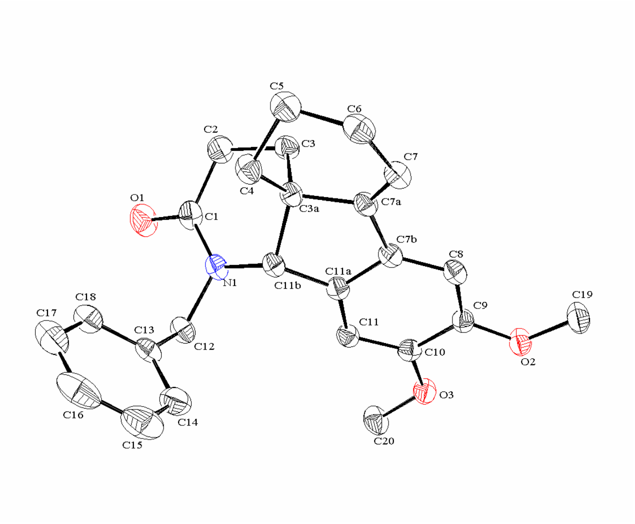
Compound **3.33*N***:

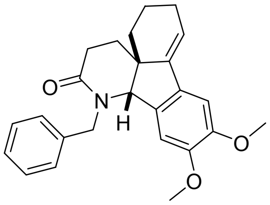

C6'
C5'
C6a'
C4'
C7'
C3
C7a'
C8'
C3a
C2'
C9'
C11b'
C11c
N1'
C1'
C12'
C11'
C10'
C13'
O1'
F3'
F2'
F1'

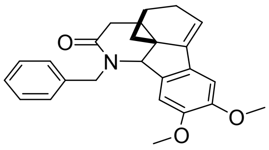



H
O
N
H
CH_3
CF_3

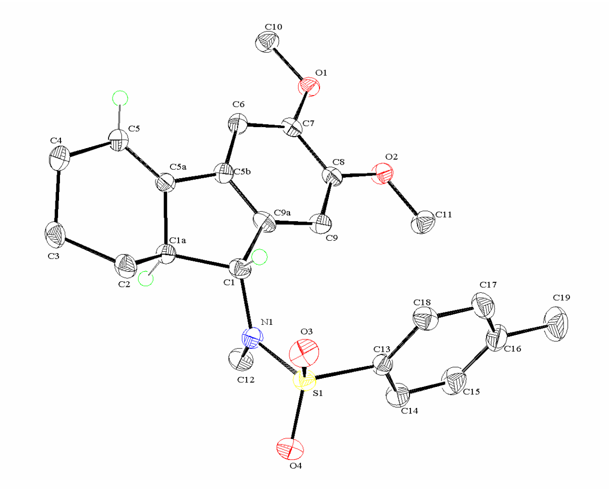
Compound **3.35*N***:

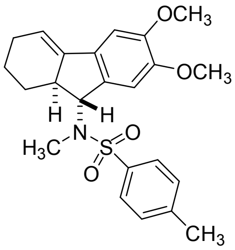

C5
C6
C2
C3
C7
C4
C3a
C7a
O1
C1
C7b
C8
N1
C11b
C11a
C18
C17
C13
C9
C19
C12
C11
C10
O2
C16
C14
O3
C15
C20

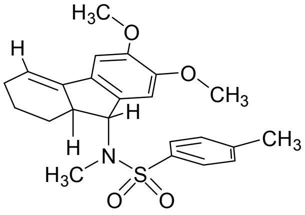




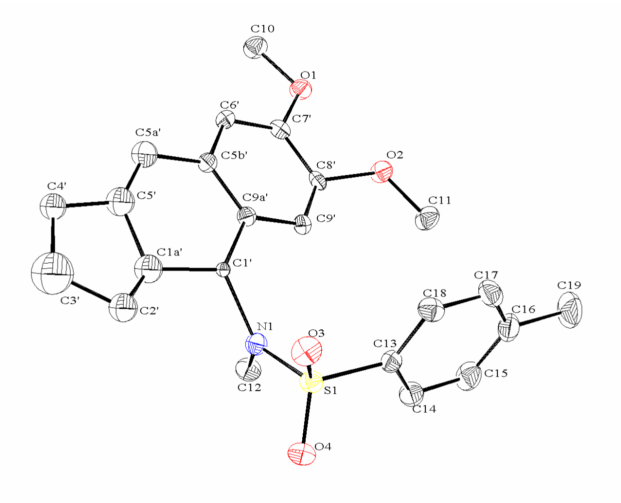
Compound **4.65*B***:

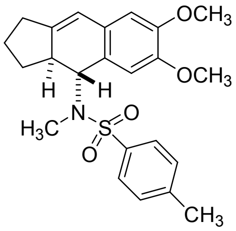

C10
O1
C6
C7
C5
C4
C5a
C5b
C8
O2
C9a
C11
C1a
C9
C3
C2
C1
C18
C17
C19
N1
O3
C13
C16
C12
S1
C14
C15
O4

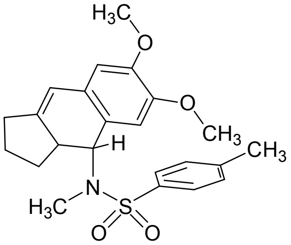

OCH3
OCH3
H
H
N
S
O
O
H3C
CH3


H3C
O
H
O
CH3
H
H
N
S
CH3
H3C
O
O

Compound **4.65*C***:


C10
O1
C6'
C7'
C5a'
C5b'
C8'
O2
C4'
C5'
C9a'
C11
C9'
C1a'
C1'
C3'
C2'
C17
C19
C18
C16
N1
O3
C13
C15
C12
S1
C14
O4


OCH3
OCH3
H
H
H3C
N
S
O
O
CH3


H3C
O
O
CH3
H
CH3
N
H3C
S
O
O