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Gold(I)-catalyzed cycloisomerization reactions of allenes:
An exploration of ligand effects and the total synthesis of *flinderole* B and C

by

Rachel Motove Zeldin

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor F. Dean Toste, Chair
Professor Richmond Sarpong
Professor Len Bjeldanes

Spring 2011

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Abstract

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The modern era of synthetic chemistry can be characterized by increased understanding, development and application of transition metal complexes to traditionally organic transformations. While the field has focused largely on the chemistry of group 4-8 metals (and in particular, rhodium and palladium), there has been growing interest in the past decade in using so-called “coinage metals”—gold, silver and copper—as catalysts for organic reactions.

Gold(I) metal complexes have been shown to effect a range of organic transformations that proceed through π -activation mechanisms, often with greater selectivity than other transition metal complexes. Additionally, in contrast to more established transition metal reactions, gold(I) processes can be conducted at low temperature and in the presence of water and air. Because of their mild conditions and high degree of control, gold(I) reactions are ideal for application to total synthesis. In the first chapter of this text, we discuss the current state of the art of gold(I)-catalysis in the context of complex molecule synthesis.

The reactivity exhibited by gold(I) complexes is highly controlled by choice of catalyst ligand. In the second chapter, we discuss the development of ligand-controlled intramolecular reaction of dienes and allenes to afford selectively either [4+2]- or [4+3] cycloadducts. The purpose of this discussion is two-fold: first, to demonstrate the effect that stabilization of reactive intermediates has on the course of gold(I) reactions, and second, to develop methodologies aimed at constructing novel, complex ring structures.

In the third chapter of this text, we take one of the reactions discovered in the course of our work in diene-allene cycloadditions and apply it to the total synthesis of antimalarial bisindole alkaloids flinderols B and C. The key step, a gold(I)-catalyzed hydroarylation of an allene using a C2-indole nucleophile, simultaneously installs three of four unique structural motifs of this natural product.

Dedicated to my parents, whose support made all of this possible.

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Preface: A case for total synthesis

Why total synthesis?

Few dispute that organic chemists have arrived at the point where, with enough time, effort, and capital, any molecule can be made. If we view total synthesis as solely **end-oriented**—the principle objective is to arrive at a natural product, without regard for the compound's novelty or the chemistry used to get there—the sustained interest in complex molecule synthesis puzzles. The preponderance of research groups with active total synthesis programs suggests other motivations exist for this work.

One frequently cited rationale for total synthesis emphasizes organic chemists' ability to make compounds in greater quantity and purity than is possible using natural sources. In this paradigm, total synthesis is **function-oriented**: chemists produce complex molecules with the aim of developing a better understanding of their capacity for use. Total synthesis has been instrumental in providing access to new medicines, agricultural chemicals, and materials. Beyond the targets themselves, chemical synthesis opens up opportunities for making structural perturbations to existing natural products so that we can better understand their mode of action and optimize the structures to better suit our needs.

Natural products often feature more complex architectures and functional group density than a chemist encounters when working with petroleum-based chemicals. Operating in this type of complicated framework requires broad knowledge of different types of organic reactions, and it presents a unique set of problems regarding chemoselectivity and synthetic efficiency. Thus, an additional reason for pursuing total synthesis is **education-oriented**. When seen as a training exercise, designing and completing a total synthesis provides unrivaled experience for a scientist interested in pursuing medicinal or materials chemistry.

While the above philosophies regarding total synthesis are important drivers of the field, the most advances to organic chemistry generally come from **designed-oriented** syntheses. The design-oriented chemist is concerned with employing novel disconnections—and often, as a consequence, new organic reactions—for constructing complex molecules, and focuses on the inherent elegance of total synthesis.

As with any theoretical framework, the reason an organic chemist pursues a total synthesis lies somewhere between these extremes. From accounts of novel types of natural products now accessible through methodology development; observations of fundamental catalyst reactivity gleaned from an interest in making complex ring structures; strategies toward an economical and flexible synthesis of biologically active antimalarial compounds; or just the overwhelming sense of accomplishment found in completing a monumental task; all four of the motivating factors described above played a role in driving this research. I hope that the work that appears in the following pages inspires you, the reader, to consider the important role total synthesis plays in organic chemistry, and to further develop your own opinion regarding the utility of this difficult, yet rewarding, pursuit.

Acknowledgments

The freedom to lead and plan your own life is frightening if you have never faced it before. It is frightening when a woman finally realizes that there is no answer to the question 'who am I' except the voice inside herself. – Betty Friedan, “The Feminine Mystique”

I began the process of my graduate education with a clear vision and intention for how the experience would unfold: I would gain mastery in the science of organic chemistry, and then I would find a job in the field. Within even a few months of starting this journey, I discovered that beyond lists of named reactions and physical organic principles, I needed to learn to become creative, adaptive, and accepting of the myriad unexpected changes thrown my way, be them in the laboratory or in life. This process of abandoning “Rachel’s Rigid Rules” has been a lifelong challenge, and I would like to acknowledge the people in my life who have enabled my seeing beyond these self-imposed restrictions.

Organic chemistry is a vast field, and not all topics are equally compelling to every chemist. I thank Dean for allowing me the freedom to discover and explore the parts of organic chemistry which I am passionate about and for granting me permission to pursue the untraditional and unexpected. I will be forever grateful for your understanding and your willingness to accommodate my personal needs and goals.

Being flexible as a scientist is dependent on possessing the tools with which to operate. Many of the skills now at my disposal I learned with the continued guidance and mentorship of Blaine Hackman, Lisa Jones, Kate Longcore, Liz Mieuli, Adam Schrier, and Lauren Sirois. This former undergraduate (and little cousin) could not have asked for better teachers.

The experience of graduate school is as much about the experiments you run as it is the people with whom you work and learn. The support provided by my fellow students and coworkers at Berkeley has been invaluable; I would like to extend a special thanks to my labmates in 619—Skip Brenzovich and Hunter Shunatona—and to my classmates—Steve Heller, Kyle Kimmel, Jane Wang, and Rhia Martin—for providing an audience for my daily frustrations, putting up with my loud and eclectic music taste, and engaging in general silliness between the hours of five and seven.

I never would have learned to let go and live a little without the insight, intelligence, tolerance and compassion of those I am fortunate to count as my friends: Jasmine Aarons, Adelina Acuña, Liane Al-Ghusain, Baiju Bhatt, Lena Buell, Tarik Bushnak, Marcus Carr, Jennifer Cook, Danny Cullenward, Melissa Fry, Priyanka Jacob, Erik Nygren, David Pfau, Santiago Ripley, Adrienne Sussman, and Katherine Tinch.

To my parents: your unflagging support through the years has provided me room to fully explore my potential; know that I am grateful for the sacrifices you made to give me this freedom. Mom, you have shown me how to face problems with a positive attitude and determination. Your unceasing optimism, humor, and grace has made the past few years bearable, even as we have faced some seemingly insurmountable obstacles. Dad, you taught me to be inquisitive and to never be satisfied with the answer provided by “the establishment”. Even if I groan, your healthy skepticism and your puns always make me laugh. And underneath the joking, your unwavering dedication to our family is truly inspirational. I love you both so much.

Chapter 1: Gold chemistry in total synthesis

Below contains a discussion of reported uses of gold(I)- and gold(III)-catalyzed reactions toward the total synthesis of natural products. The syntheses contained are discussed by the type of gold transformation employed, with a particular emphasis placed on unique mechanistic facets of gold chemistry that make these reactions well-suited for complex molecule synthesis.

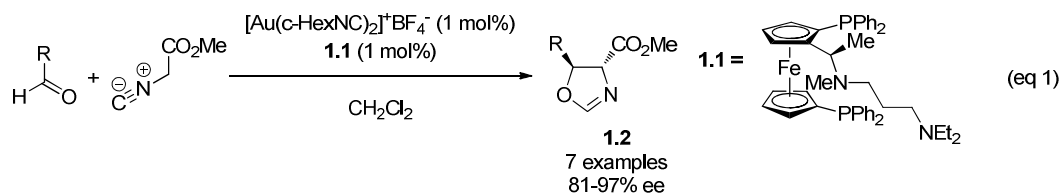
1.1) Introduction

Homogeneous gold catalysis has emerged as vibrant area of inquiry in organometallic chemistry.¹ While the explosion of new gold-catalyzed reactions is in part due to sheer novelty—gold's economic and social value hinges on its relative inertness toward acids and oxidants, and as such gold was long presumed nonreactive in organic reactions—gold catalysis has also provided access to previously underdeveloped mechanistic manifolds. Gold(I) and gold(III) catalysts typically act by π -activation of an alkyne, allene, or carbonyl toward nucleophilic attack. While cationic palladium, platinum, and rhodium catalysts can also act as π -acids, their propensity toward redox processes often leads to unwanted side-reactions. Gold complexes, with their high oxidation potentials, are far less prone toward redox chemistry.² Thus, the development of gold catalysis methodologies has allowed unprecedented access to highly chemoselective π -acid reactivity.

Gold catalysis has also opened the door to new disconnections for the total synthesis of complex molecules.³ Gold catalysis methodologies are attractive for organic chemists planning a synthesis for three reasons: (a) gold(I) chemistry allows for a rapid increase in molecular complexity from simple substrates, (b) gold(I) reactions are highly chemoselective, and (c) gold(I) catalysis conditions are mild, an important consideration when working with advanced synthetic intermediates.⁴ A number of total syntheses implementing homogeneous gold chemistry have been described; below, we highlight syntheses which use gold catalysis to achieve novel reactivity, with emphasis placed on the mechanistic aspects of gold chemistry that makes these disconnections unique.⁵

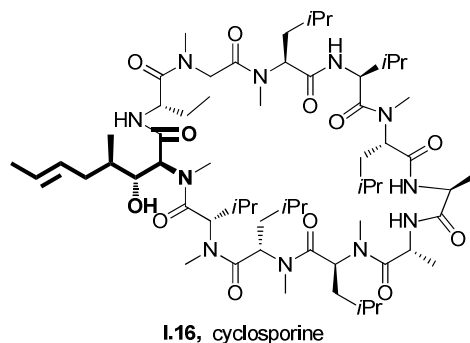
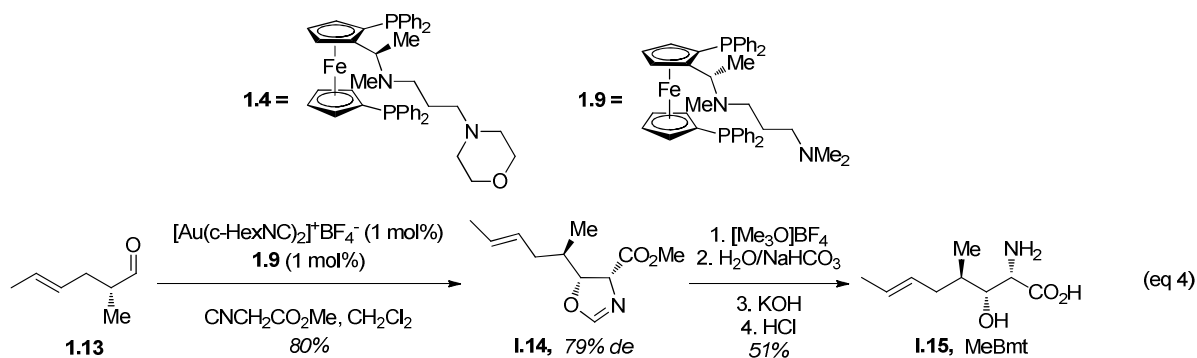
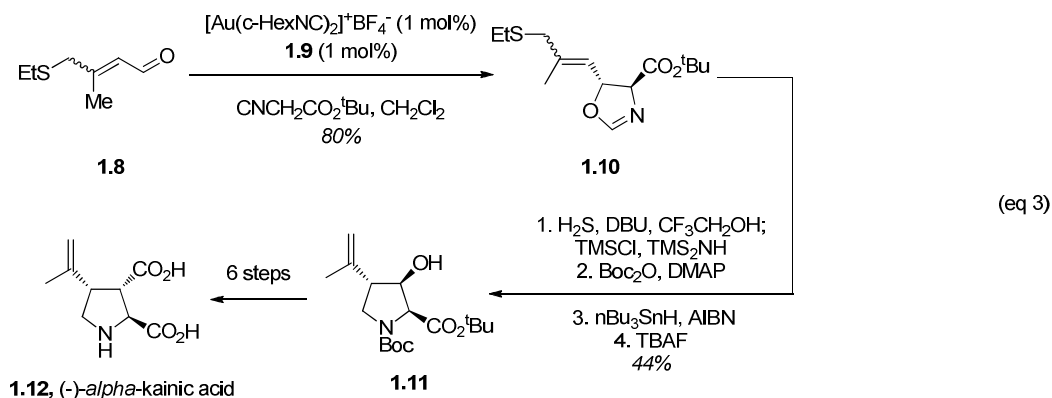
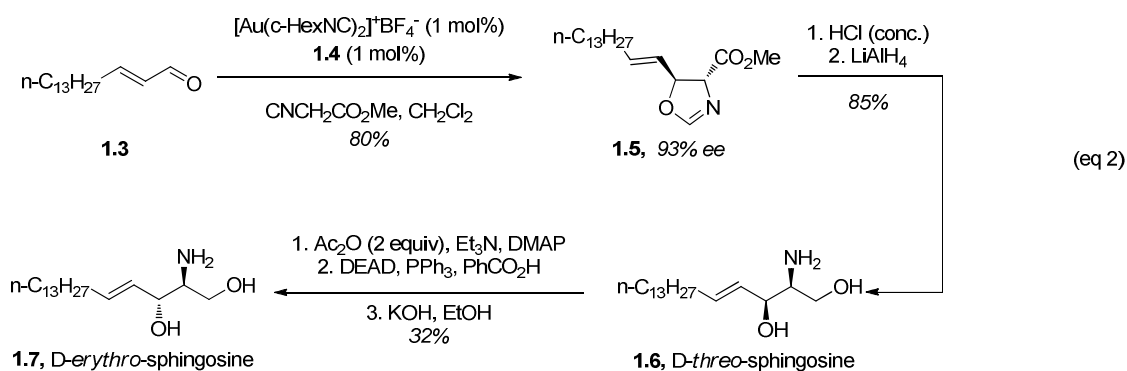
1.2) Gold-catalyzed aldol reactions

In 1986, Ito and Hayashi reported an asymmetric aldol reaction of isocyanates and aldehydes promoted by a chiral ferrocenylphosphinegold(I) catalyst, notable as the first known enantioselective gold(I) method developed (eq 1).⁶

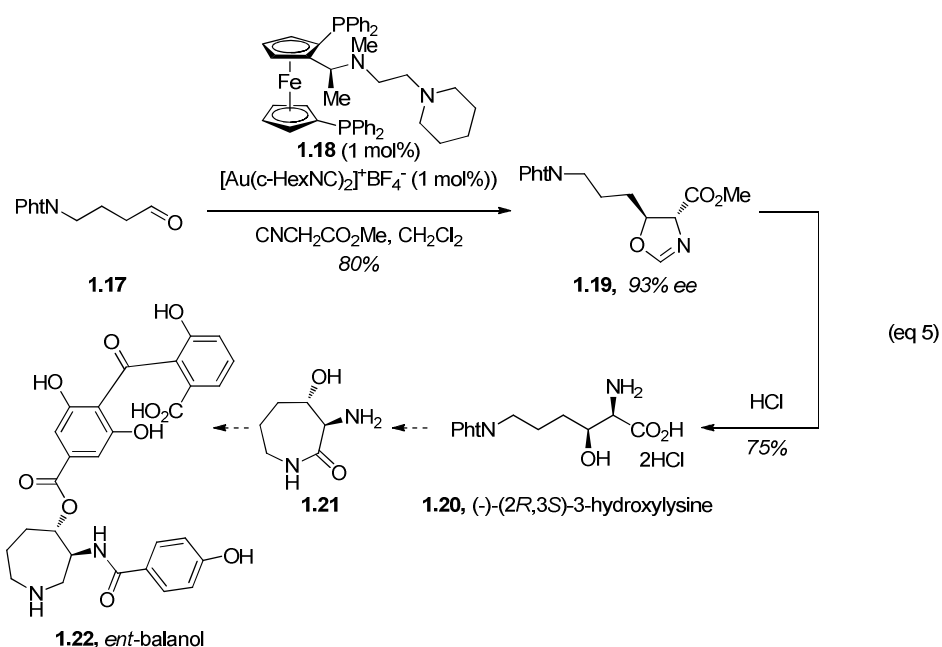


The 5-alkyl-2-oxazoline-4-carboxylates (**1.2**) formed in this reaction can readily be transformed to reveal β -hydroxyamines, a common motif in complex molecule natural products. Ito and Hayashi applied their methodology to the synthesis of *D-threo*-sphingosine (**1.6**) and *D-erythro*-sphingosine (**1.7**) (eq 2). The same catalyst system was used in the asymmetric synthesis of neurotransmitter (–)-kainic acid (eq 3).⁷

Low catalyst loading, recyclability of the ligand, and the crystalline nature of the heterocyclic cycloadducts make Ito and Hayashi's aldol reaction well-suited to the large scale synthesis of β -hydroxyamino acids. Reaction of readily available (2*R*,4*E*)-2-methylhex-4-enal (**1.13**) with methyl 2-isocyanoacetate under these conditions, followed by ring opening and hydrolysis, was used to furnish rare amino acid MeBmt (**1.15**), a component of cyclic peptide natural product cyclosporine (**1.16**) (eq 4).⁸



In studies toward the total synthesis of (-)-balanol (1.22), Hughes and coworkers used this methodology to make *threo*-3-hydroxylysine (1.16), which they envisioned using as the precursor to the azepine core of the natural product (1.21) (eq 5).⁹



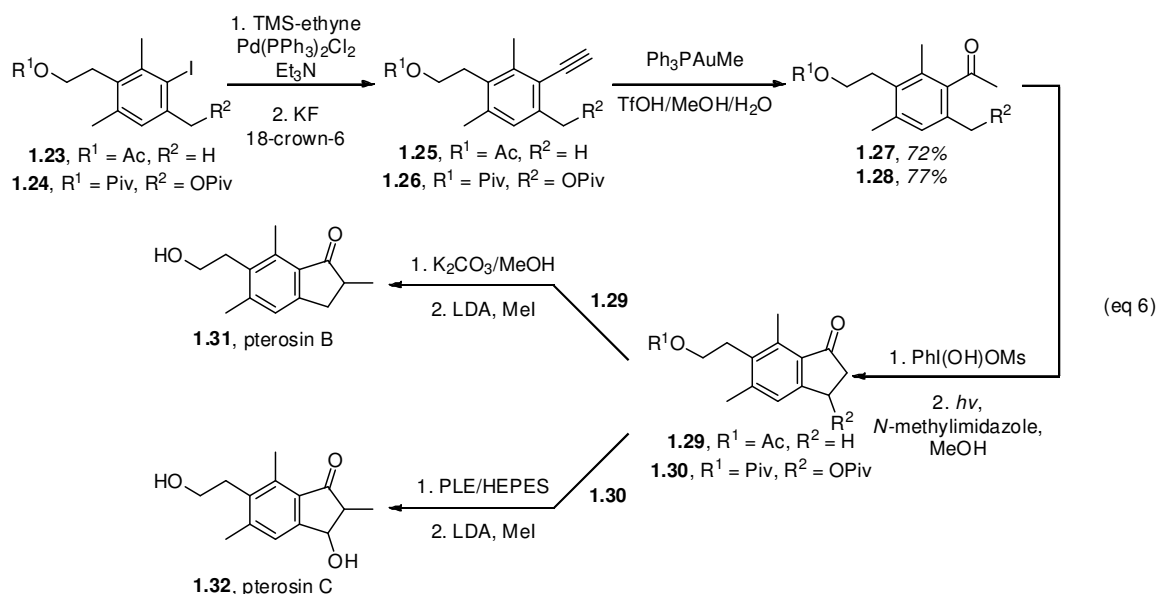
While this approach yielded pure (–)-*threo*-3-hydroxylysine in 55% yield over 2 steps, balanol was found to have the opposite absolute configuration; another synthetic sequence was developed to generate (+)-*threo*-3-hydroxylysine for completion of the total synthesis.¹⁰

1.3) Introduction of heteroatoms

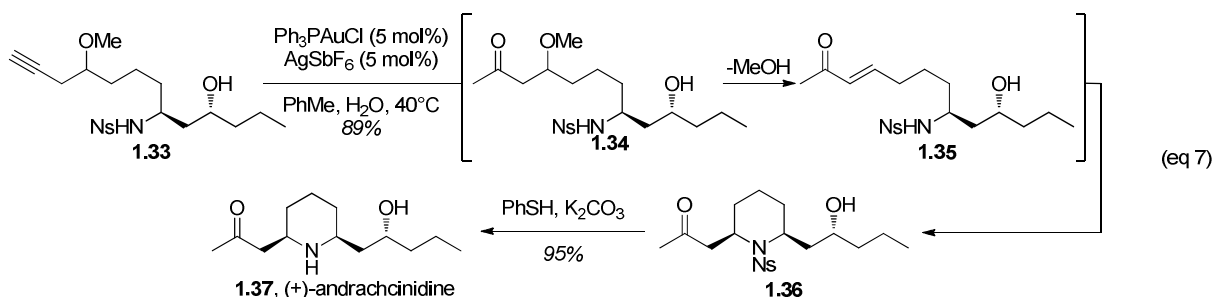
The current investigation on the reactivity of gold complexes in organic transformations began with Teles' 1998 report of gold(I)-catalyzed intermolecular addition of alcohols to alkynes.¹¹ Since then, gold(I) and gold(III) complexes have been shown to catalyze a number of transformations, both inter- and intramolecular, which introduce a heteroatom by activating a π -system toward nucleophilic attack. Reactions of this class include the hydroalkoxylation of alkynes;¹² hydroamination of alkynes;¹³ hydrofluorination of alkynes;¹⁴ hydroalkoxylation of allenes;¹⁵ and hydroamination of allenes.¹⁶ In addition to the reactions described above, a number of cascade processes featuring gold-promoted nucleophilic attack have been developed for making complex molecular architectures.¹⁷ These transformations are generally regioselective for the Markovnikov-type addition products, making them a useful way to introduce oxygen and nitrogen functionalities during a natural product synthesis.

1.3.1) Intermolecular disconnections

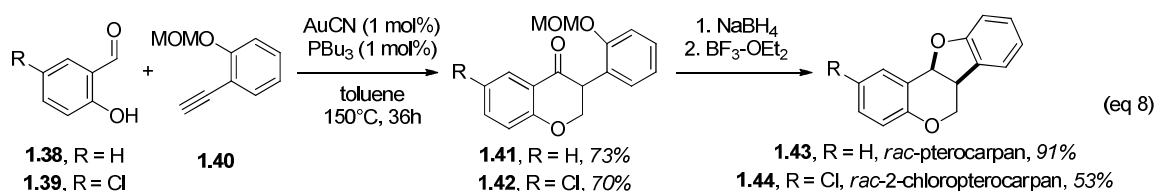
The robust nature of gold(I)-catalyzed additions of oxygen nucleophiles to alkynes enables these groups to serve as ketone synthons. This is a valuable strategy when trying to install multiple oxygen functionalities in a complex molecule. During the synthesis of pterosins B (**1.31**) and C (**1.32**), use of gold(I)-catalyzed hydration reaction of an aryl alkyne allowed for introduction of an acyl group using milder conditions than generally found with more traditional oxidative or coupling chemistry (eq 6).¹⁸



The alkyne can also serve as a masked α,β -unsaturated ketone: in the synthesis of (+)-andrachcinidine (**1.37**), triphenylphospinegold(I) chloride was used in conjunction with silver(I) hexafluoroantimonate to promote hydration of alkyne **1.33** to form β -methoxy ketone **1.34**. After acid-catalyzed loss of methanol yielded enone intermediate **1.35**, cyclization formed desired piperidine **1.36** (eq 7).¹⁹

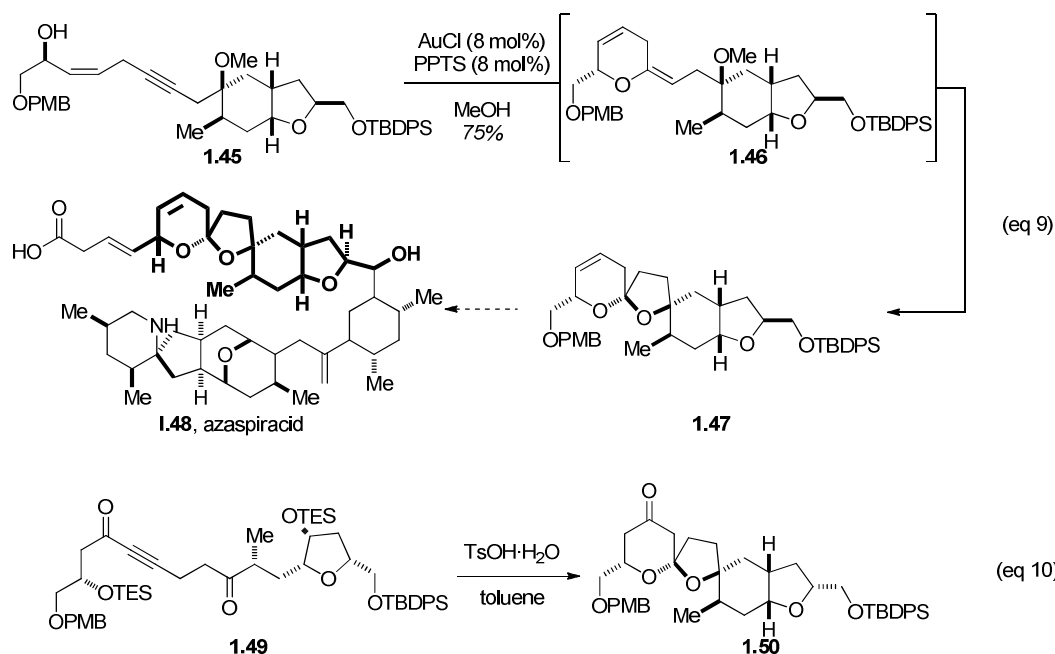


A gold(I)-catalyzed cascade was also used in the racemic synthesis of isoflavone natural products pterocarpan (**1.43**) and 2-chloropterocarpan (**1.44**) (eq 8).²⁰ The key step of this reaction most likely proceeds by gold(I) activation of the alkyne, followed by an unusual anti-Markovnikov attack by the phenolic oxygen and trapping by the pendant aldehyde.^{21, 22}

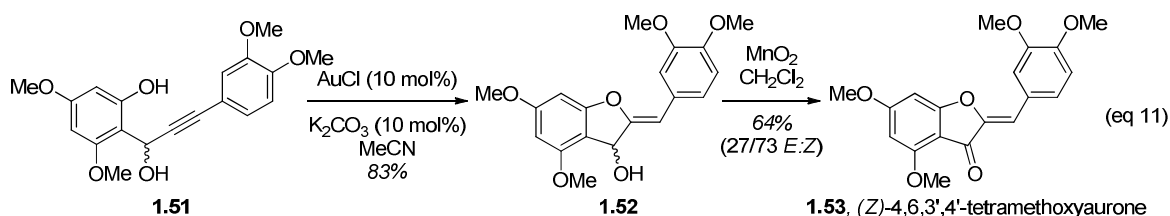


1.3.2) Intramolecular disconnections

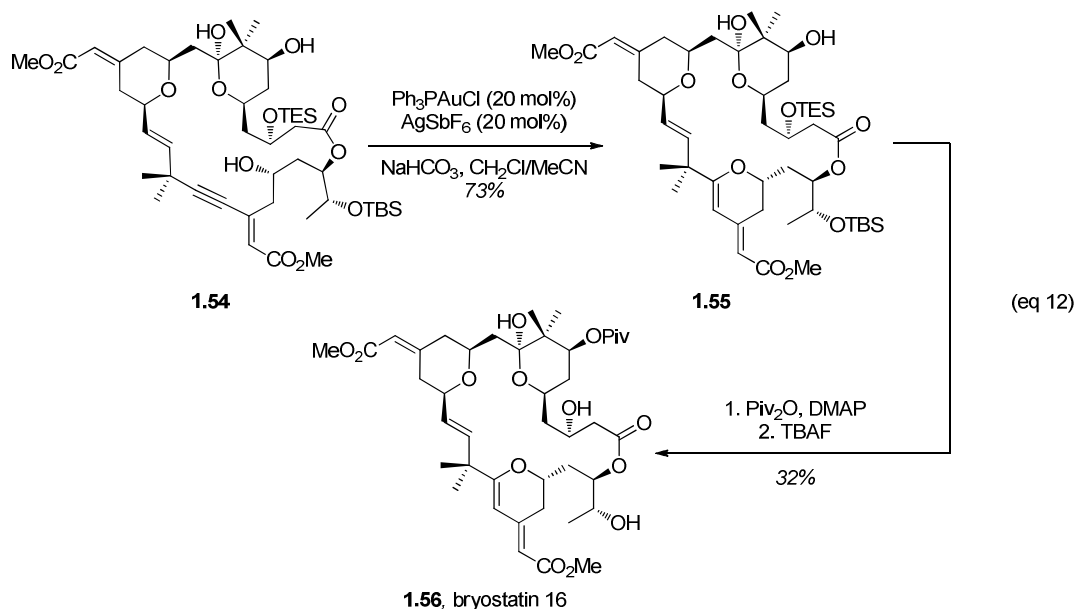
Gold-catalyzed additions of heteroatom nucleophiles to carbon-carbon multiple bonds is a potent strategy for generating heterocycles.²³ Transformations which form heterocycles serve an important role in total synthesis, as these motifs are frequently found in natural products and are particularly prevalent in compounds shown to have biological activity.²⁴



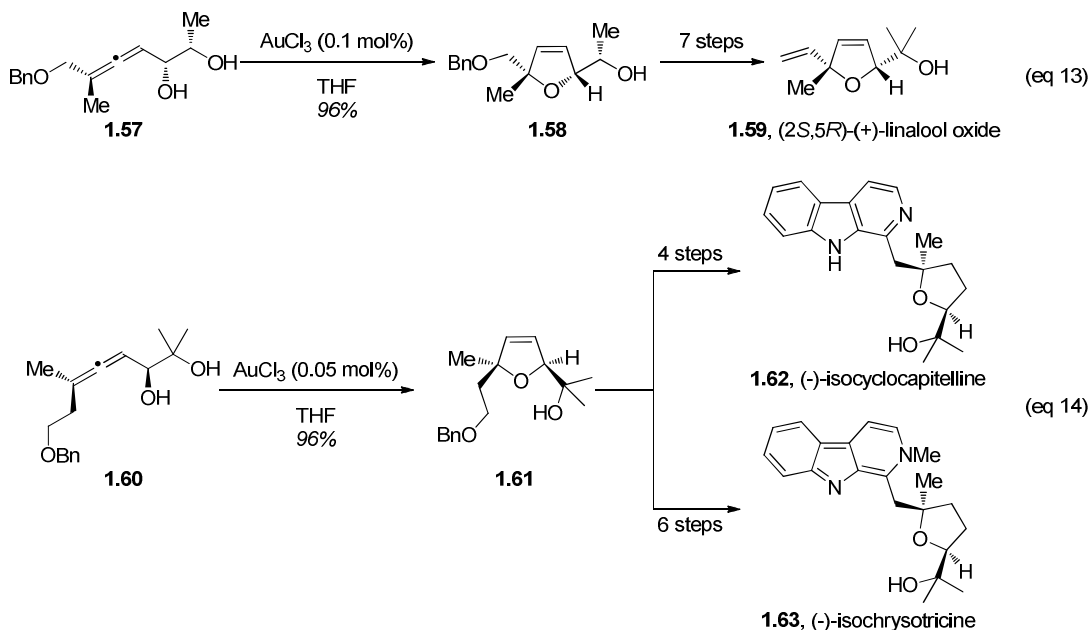
Gold-catalyzed intramolecular additions of alcohols to alkynes can proceed in either the *exo* sense to generate oxolanes or tetrahydropyrans with an exocyclic olefin, or in the *endo* sense, forming the *2H*-dihydropyran. 6-*Exo*-dig cyclization of **1.45** was affected using catalytic gold(I) chloride and protic acid, yielding tetrahydropyran **1.46**; acid-promoted ketalization of this intermediate followed by loss of dimethyl ether afforded the tetracyclic core (**1.47**) of the azaspiracid class of natural products (**1.48**) (eq 9).²⁵ Unlike the previously developed double intramolecular hetero-Michael addition approach to this scaffold (eq 10), using gold(I)-catalyzed conditions obviated the need for β -oxygenation of the alkyne and reduced the number of subsequent steps necessary to yield the natural product.²⁶ Catalytic gold(I) chloride in the presence of potassium carbonate selectively promoted 5-*exo*-dig cyclization of 2-(1-hydroxyprop-2-ynyl)phenols (**1.51**) to generate aurones (**1.52**) over isomeric flavones. Previous methodologies were either unable to generate the aurone scaffold selectively or employ harsh conditions that result in low yields of desired product.²⁷ These conditions were used in the synthesis of (*Z*)-4,6,3',4'-tetramethoxyaurone (**1.48**) (eq 11).



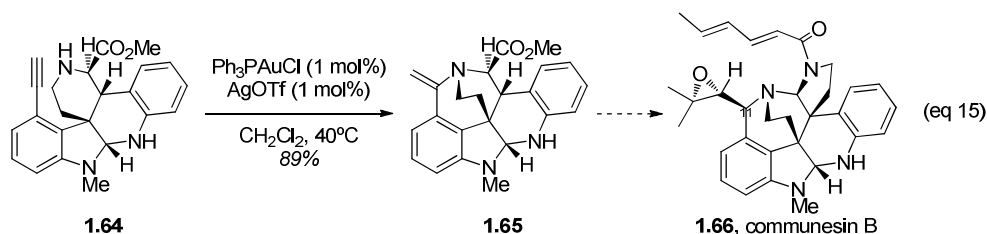
The previous examples both featured gold-catalyzed *exo* cyclizations; *endo* cyclizations featuring intramolecular addition of oxygen to unsaturated carbon bonds have also been used in the course of complex molecules synthesis. In the Trost synthesis of bryostatin 16 (**1.56**), gold(I)-catalyzed 6-*endo*-dig cyclization of **1.54** was used to form the C ring dihydropyran after palladium conditions gave poor *endo*/*exo* selectivity (eq 12).²⁸



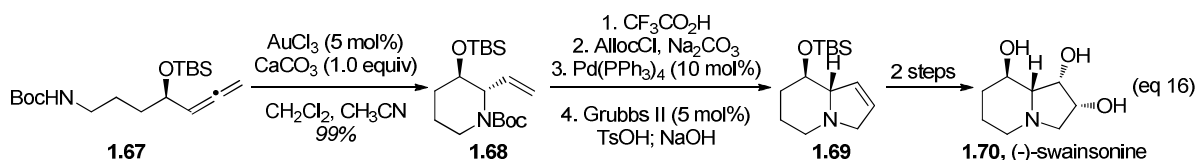
Gold(III) chloride was found to promote the diastereoselective *endo*-cyclization of dihydroxyallene **1.57** to 2,5-dihydrofuran **1.58** in the synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1.59**) (eq 13); a similar reaction generated common intermediate **1.60** in the synthesis of related compounds (–)-isocyclocapitelline (**1.62**), and (–)-isochrysotricine (**1.63**) (eq 14).²⁹



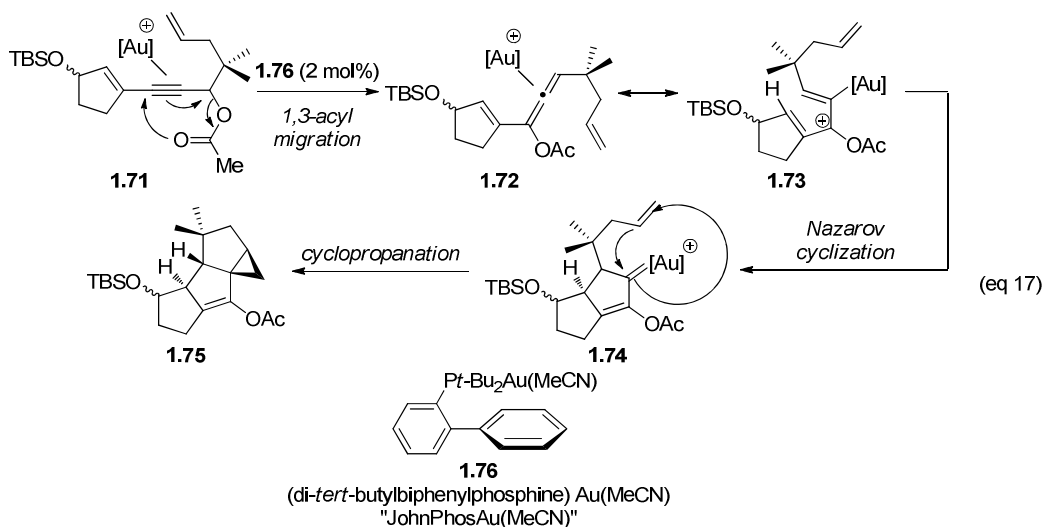
Intramolecular additions of amine nucleophiles to alkynes and allenes allow for the synthesis of nitrogen-containing heterocycles. In work toward communesin B (**1.64**), Funk and coworkers used a gold(I)-catalyzed intramolecular hydroamination reaction of *ortho*-acetylene and piperidine in order to make the hexacyclic core found in the natural product (**1.65**) (eq 13). This approach proved advantageous for three reasons: (a) the alkyne was easily installed and tolerant of preceding chemical transformations, (b) the ethynyl moiety was small enough to allow formation of pentacycle **1.66**, and (c) the resulting exocyclic olefin provided a handle for later installation of the epoxide at C11.



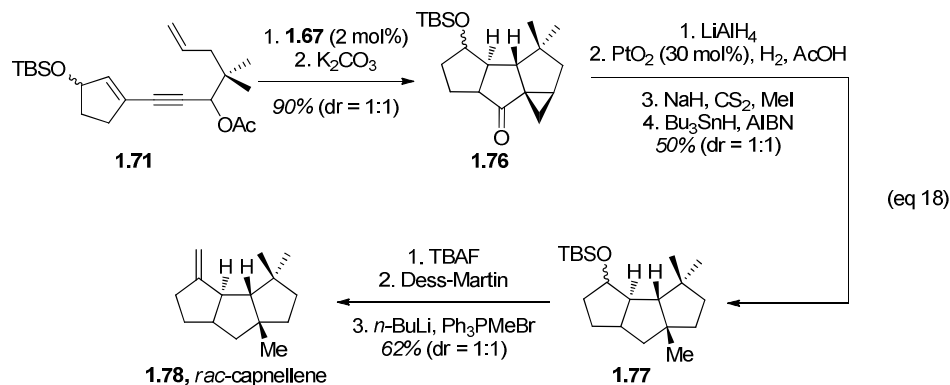
In a formal synthesis of (–)-swainsonine (**1.58**), the authors envisioned setting the stereochemistry about the ring fusion by gold(III)-catalyzed intramolecular hydroamination of allene **1.55** (eq 14).³⁰ Amine deprotection, allylation and cross metathesis yielded a known intermediate along a previous route to the natural product.³¹



Two of the more widely studied gold(I)-catalyzed reactions are the 1,2- and 1,3-acyl migrations of propargyl acetates.³² In processes phenomenologically similar to Wittig and Claisen rearrangements, these reactions feature attack of an alkyne by a neighboring acetate group, followed by sigmatropic rearrangement to furnish either a gold-carbene or a gold-activated allene, which then can go on to do further chemistry.³³



In an example of this type of transformation, a 1,3-acyl rearrangement/metal-Nazarov/cyclopropanation cascade was used to construct the tricyclic core (**1.75**) of triquinane $\Delta^{(9,12)}$ – capnellene (**1.78**) (eq 17).³⁴ The key gold(I)-catalyzed rearrangement occurred stereoselectively and was unaffected by the remote stereocenter. Conversion of the cyclopropane to the angular methyl group, deoxygenation and olefination provided the natural product in 15 steps in one of the more efficient syntheses to date (eq 18).



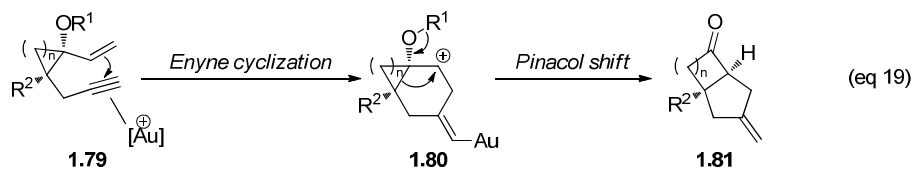
1.4) Enyne cyclizations

In what can be considered a variation of the ene reaction, the intramolecular enyne cycloisomerization features reaction between an alkyne and an alkene to form cyclic 1,3-dienes.³⁵ Though this process was first developed using metal-carbene catalysts, the enyne scaffold is reactive toward a wide range of transition metals—notably rhodium, ruthenium, platinum, palladium and gold—through metathesis, redox, or π -activation mechanisms.³⁶ The scope of the transformation can be extended by trapping reactive intermediates with other nucleophiles, thereby introducing further molecular complexity.³⁷

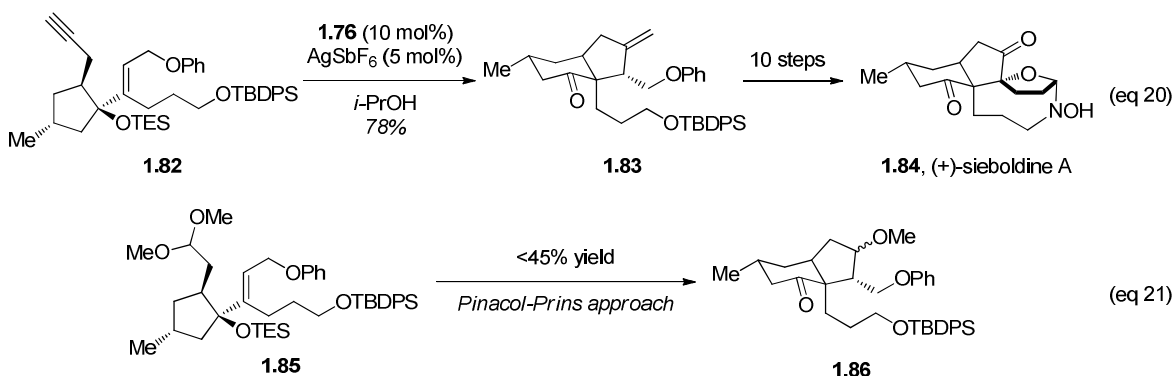
A principle challenge of developing enyne methodologies which proceed by π -activation has been achieving chemoselectivity, as the final protodemetalation step can occur via multiple pathways.³⁸ Gold(I) complexes are among the more selective catalysts used in these transformations and thus are particularly appropriate choices to promote enyne cascades in total syntheses.

1.4.1) Enyne-Pinacol cascades

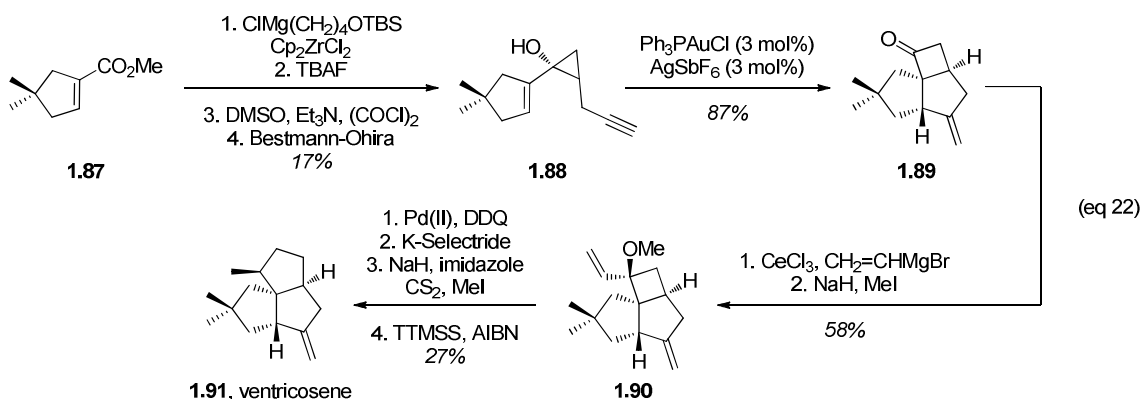
Enyne-Pinacol cascades resulted when cationic intermediates generated from nucleophilic attack by an alkene on an alkyne (**1.80**) were intercepted by a pinacol 1,2-shift to generate a ring-expanded ketone (**1.81**) (eq 19).³⁹ The reaction proceeded stereospecifically to form a *cis*-fused bicycle.



This methodology was applied to the total synthesis of (+)-sieboldine A (**1.84**) after the investigators saw limited reactivity with a more traditional Pinacol-Prins type disconnection (eq 20-21).⁴⁰

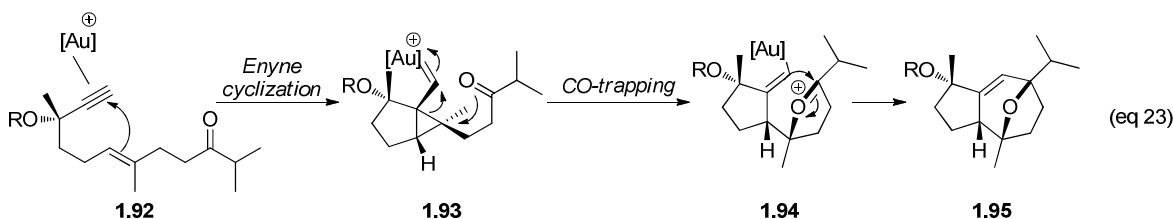


A similar sequence was used to set the angular tricyclic ring system of ventricosene (**1.91**), a novel sesquiterpene triquinane natural product (eq 22).⁴¹



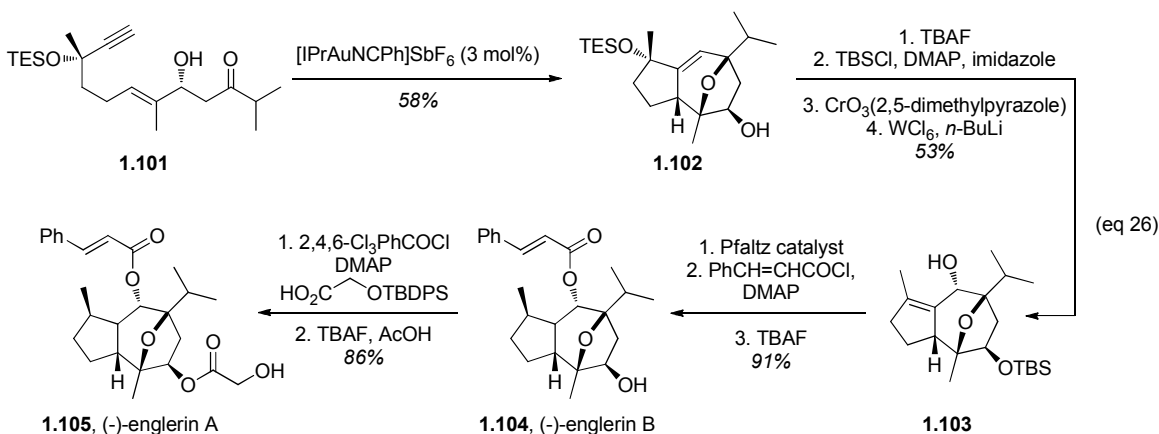
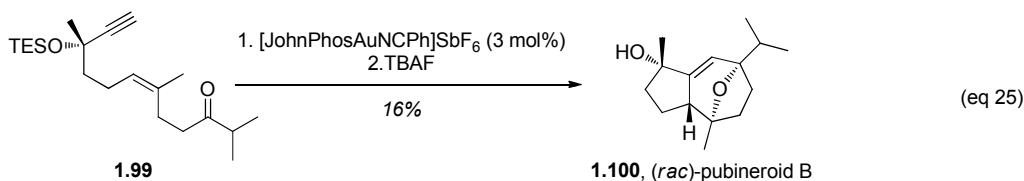
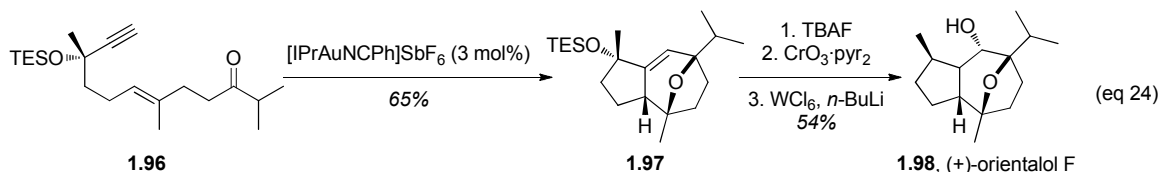
1.4.2) [2+2+2] enyne/carbonyl cycloadditions

A pendant carbonyl to a 1,6-enyne can trap the cationic intermediate of the gold(I)-promoted step through attack of the oxygen, giving an oxatricyclic product such as **1.95** (eq 23).



Given the functional group density of this type of substrate, it was important to find conditions that suppressed undesired reaction pathways (such as Meyer-Schuster rearrangements or protodemetalation); it was found that using the highly electron-donating *N*-heterocyclic carbene complex IPrAuCl selectively gave the desired product as a single diastereomer.⁴² This method

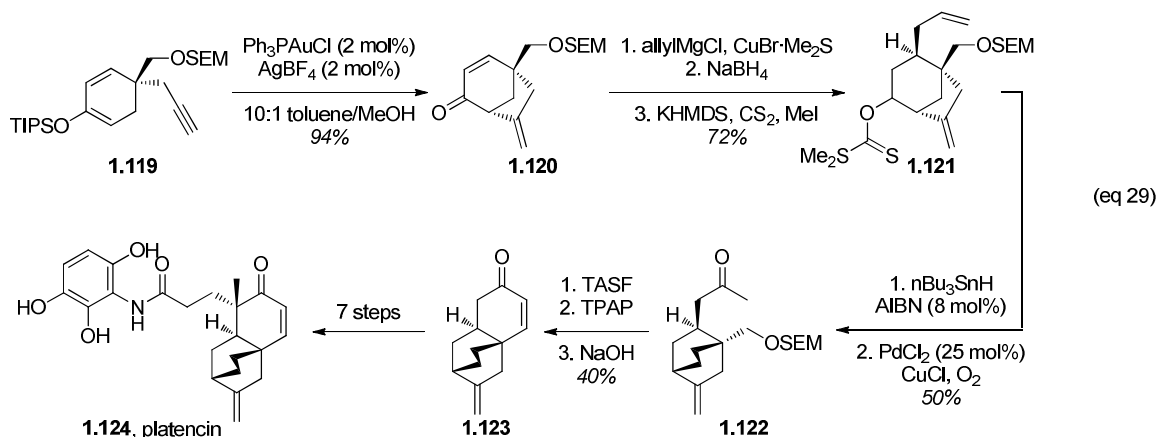
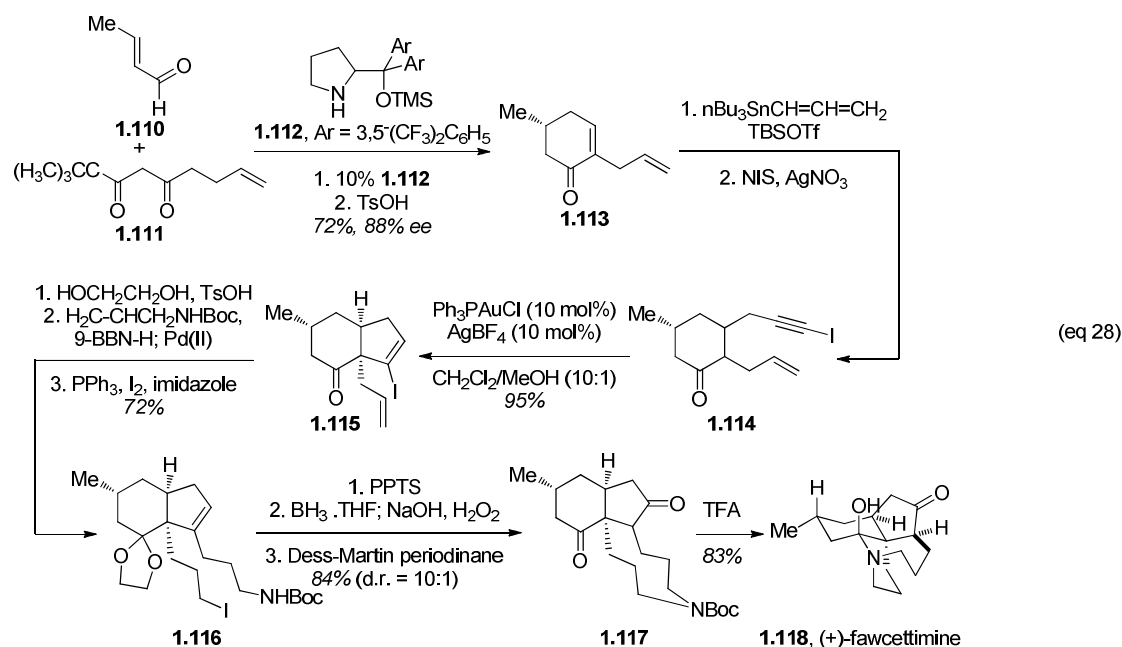
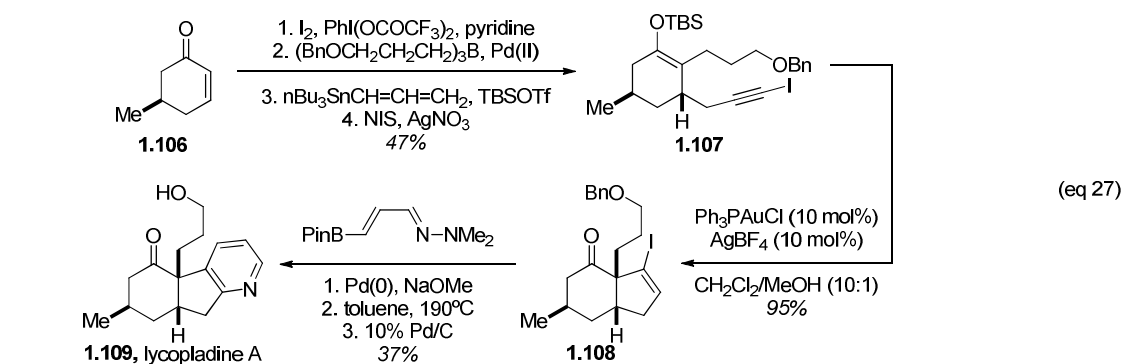
was used to construct the tricyclic framework of guaiane sesquiterpenes (+)-orientalol F (**1.98**), (+)- and (-)-pubinernoid B (**1.100**), and (-)-englerins A (**1.105**) and B (**1.104**) (eq 24-26).^{43,44}



1.4.3) The Conia-Ene reaction

Discovered in 1967 by Conia and coworkers, the Conia-Ene reaction describes the thermal reaction of a 1,3-diketone and an alkyne to form a five-membered ring with a quaternary center.⁴⁵ Until recently, these types of transformations required high temperatures, strong acids, preformation of the enolate, or photochemical activation to proceed. Thus, the development of a mild, gold(I)-catalyzed variant of this reaction by our group represented a significant advancement of this methodology.⁴⁶ One drawback of the classic Conia-Ene reaction scaffold is the requirement for a β -ketoester substrate, which can be difficult to manipulate in subsequent steps. However, we showed that the reaction scope can be extended to silyl enol ether nucleophiles, making this type of transformation more feasible for application to complex molecule synthesis.⁴⁷

We demonstrated the utility of the gold(I)-catalyzed Conia-Ene reaction in the asymmetric syntheses of *Lycopodium* alkaloids (+)-lycopoladine A (**1.109**) and (+)-fawcettimine (**1.118**) (eq 27).^{33,48} Nicolaou and coworkers also used a gold(I)-catalyzed Conia-Ene cyclization of a silyl enol ether to construct [3.2.1]-bicyclic enone **1.120** in their route toward platencin (**1.124**) (eq 29).⁴⁹ The xanthate ester formed from **1.120** was then poised to undergo the key homoallylic radical rearrangement, leading to the platencin core (**1.123**).

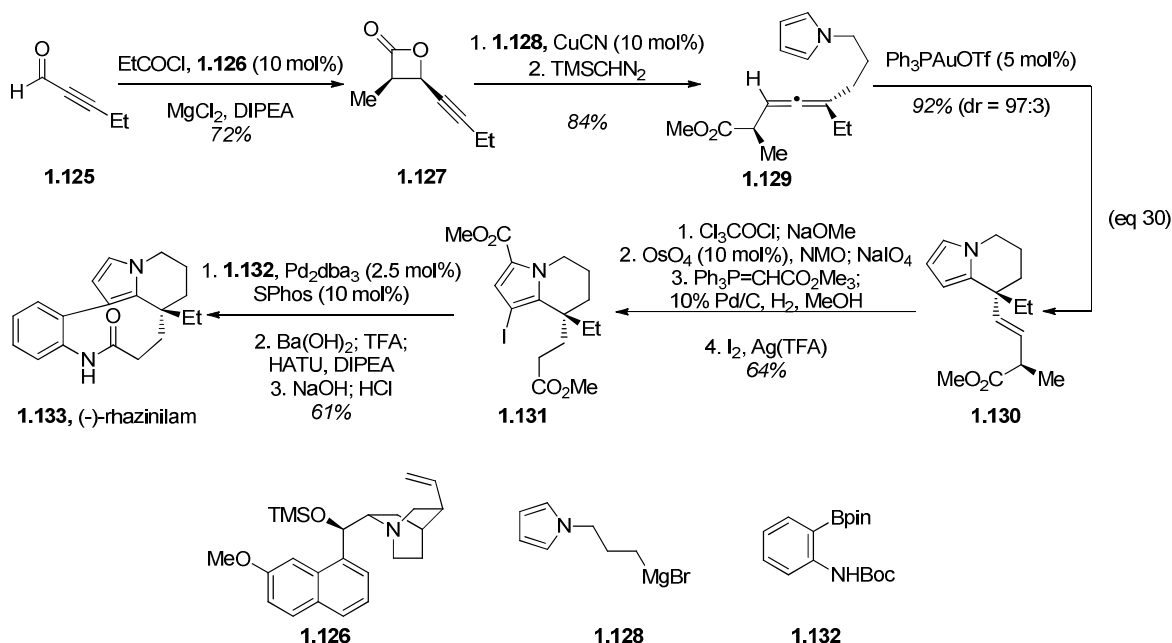


1.5) Hydroarylation reactions

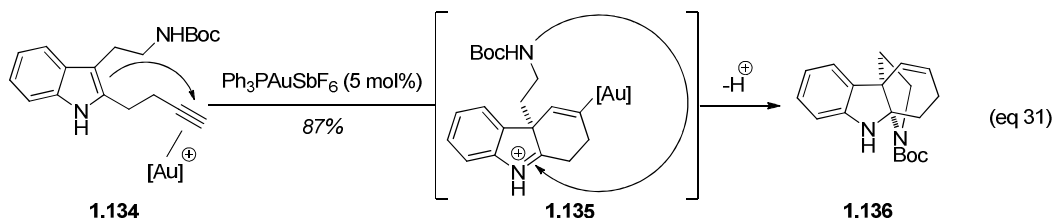
The ability to selectively functionalize heterocycles is important for constructing natural products. A common method by which heterocycles are elaborated is electrophilic aromatic

substitution, and gold complexes are capable of promoting these types of transformations. Aromatic nucleophiles which have been used in gold-catalyzed hydroarylation reactions include furan,⁵⁰ benzofuran,⁵¹ indole,⁵² pyrrole,⁵³ and electron-rich benzene derivatives.⁵⁴ Like in hydroalkoxylation and hydroamination reactions, gold catalysis conditions are often both milder and more selective than older methods and thus we begin to see these transformation used in complex molecule synthesis.

The key structural component of cyclic aspidospermine alkaloid (–)-rhazinilam (**1.133**) is a tetrahydroindolizine core featuring an all carbon quarternary center.⁵⁵ An intramolecular gold(I)-catalyzed addition of pyrrole to chiral allene (**1.129**) allowed for diastereoselective formation of desired heterocycle **1.130**; cross-coupling of aniline **1.132** and subsequent amide coupling afforded the natural product (eq 30). The authors turned to gold catalysis after silver(I) and palladium(II) catalysts led to racemization of the allene stereocenter and poor yields.

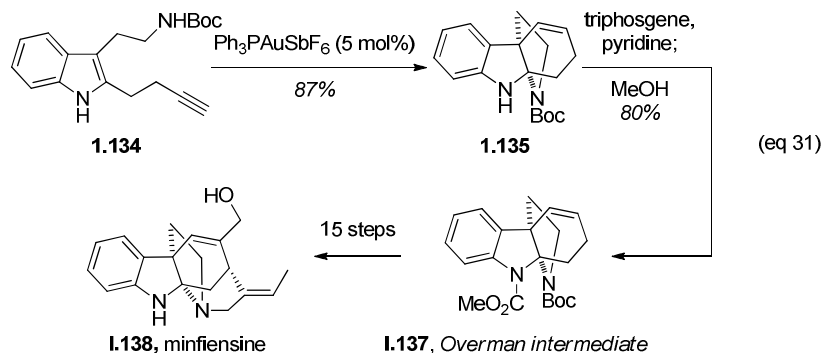


In the formal synthesis of minfiensine (**1.138**), a 6-*endo*-dig cyclization of tryptamine-alkyne **1.134** was used to establish the carbazole ring system; cationic gold(I) intermediate **1.135** was then trapped by the protected tryptamine side-chain, forming tetracycle **1.136** (eq 31).⁵⁶



Formation of the methyl carbamate at the N9 position allows the authors to intercept intermediate **1.137** from Overman's minfiensine synthesis (eq 31).⁵⁷ Not only does the gold(I) approach allow the authors to reach this compound in four fewer synthetic steps than the original synthesis, but it also enabled the authors to generate the tetracyclic core of minfiensine in one pot.

This type of disconnection again demonstrates the utility of gold(I)-catalysis for promoting complex reaction cascades.



1.6) Conclusions

Organic reactions promoted by gold are uniquely mild and chemoselective among the multitude of transition metal-catalyzed transformations. Additionally, the diverse array of reaction pathways catalyzed by gold allows for development of tandem reactions which can be used to make complex molecular frameworks in one synthetic step. As such, gold(I) reactions are well-suited for making complex molecules. The examples shown above represent the first forays into applying gold chemistry to complex systems; no doubt we shall see many more syntheses featuring gold catalysis in the years to come.

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Chapter 2. Demonstration of ligand effects in gold(I)-catalyzed diene-allene cycloadditions

Herein we describe the development of two ligand-controlled gold(I)-catalysis manifolds for selectively obtaining different products from the intramolecular cycloaddition of diene-allenes. Using highly electron-rich gold(I) catalysts favors formation of heptadiene products arising from a formal [4+3] cycloaddition, whereas using less donating catalysts favors formation of the [4+2] adduct. Mechanistic considerations and substrate effects are also discussed.

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2.1) Introduction

In the rapidly developing field of homogeneous gold catalysis, gold(I)-promoted cycloisomerization reactions of unsaturated systems have attracted considerable attention.¹ The reason for this focus is two-fold. First, gold(I)-catalyzed cycloisomerizations are often more selective and higher yielding than previously developed transition metal- or acid-catalyzed methodologies, allowing for greater functional group tolerance and gentler reaction conditions.² Second, carbocyclization reactions have provided an excellent platform for probing the different types of mechanistic alternatives accessible through gold(I) catalysis.

One of the greatest challenges in developing cycloisomerization reactions is achieving chemoselectivity. An attractive feature of transition metal catalysis is the capacity to control the course of the reaction by changing the complex's ancillary ligands.³ While initial forays into gold(I) chemistry showed that the choice of ligand has a significant impact on the yield of a transformation, using ligand effects as a way to obtain divergent reactivity from the same substrate remains elusive.⁴ Achieving such ligand-controlled reactivity represents a fundamental leap in understanding homogeneous gold(I) catalysis.

Cationic gold(I) catalysts are proposed to initiate cycloisomerization reactions by activating an electrophilic π -system toward attack by a pendant carbon nucleophile.⁵ The resulting positively-charged intermediate can be depicted by two major resonance forms (Figure 1).

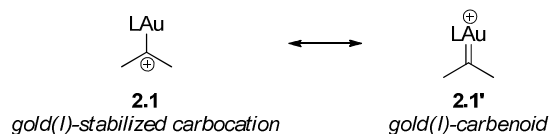


Figure 1. Two different resonance forms exist for gold(I)-stabilized intermediates, the carbocationic structure **2.1** and the metallocarbenoid structure **2.1'**.

In the first structure, positive charge is centered on the α -carbon of the reactive intermediate species to give a gold(I)-stabilized carbocation (**2.1**). The positive charge can also reside on the metal atom; this type of structure is described as a gold(I)-carbenoid (**2.1'**). Most gold(I) intermediates exist somewhere on the spectrum between these two canonical representations; chemoselectivity is observed in gold(I) reactions by shifting toward either carbocationic or carbenoid extremes.^{6,7} Selecting a catalyst with an electron-rich σ -donor ligand allows for greater stabilization of positive charge on the metal center; thus, this type of catalyst could preferentially react through gold(I)-carbenoid pathways.

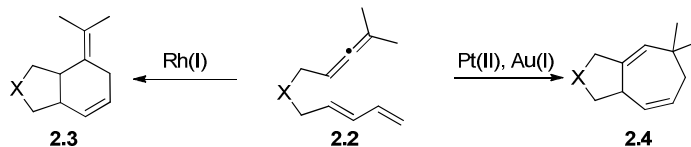


Figure 2. Ambident reactivity has been demonstrated for intramolecular cycloadditions of diene-allenes (**2.2**); changing the metal catalyst used can give either the [4+2] product **2.3** or the [4+3] product **2.4**.

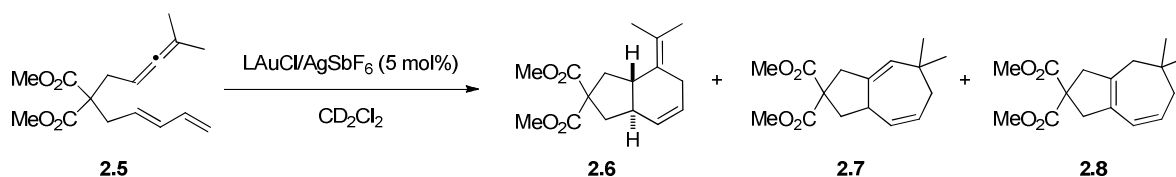
To further probe the effect that ligand choice has on the reactivity of gold(I)-cationic intermediates, we wanted to investigate the reactivity of a substrate class with demonstrated

divergent reactivity. For this reason we opted to study the gold(I)-catalyzed cycloadditions of tethered diene-allenes, as both [4+2]⁸ and [4+3]⁹ type reactivities are known for these substrates (Figure 2).

2.2) Preliminary demonstration of ligand effects

Initial exposure of tethered diene-allene substrate **2.6** to triphenylphosphinegold(I) led to a 2:1 mixture of [4+2] and [4+3] products **2.7** and **2.8** (Table 1, entry 1). As we anticipated, changing the ligand of the gold(I) catalyst to the highly σ -donating IPr *N*-heterocycliccarbene (**2.13**) favors the [4+3] pathway (entry 6). Similarly, using electron-rich phosphine ligands such as the Takasago BRIDP (**2.9-2.11**) ligands and di-*tert*-butyldiphenylphosphine (**2.14**) led to almost exclusive formation of the seven-membered ring product (entries 2-5).

Table 1. Gold(I)-catalyst screen for diene-allene cycloisomerization reactions.^a



entry	catalyst	yield	2.6:2.7:2.8 ^b
1	Ph ₃ PAuCl	80	2:1:0
2	cy-cBRIDPAuCl (2.11)	66	1:3:1:0
3	cy-vBRIDPAuCl (2.9)	73	1:6:1:0
4	cBRIDPAuCl (2.12)	74	1:7:7:1
5	vBRIDPAuCl (2.10)	80	7:87:6
6	IPrAuCl (2.13)	75	7:89:4
7	(di- <i>tert</i> -butylbiphenylphosphine) AuCl (2.14)	89	1:24:0
8	(tris (2,4-di- <i>tert</i> -butyl phenyl) phosphite) AuCl (2.15)	91	1:0:0
9	(PhO) ₃ PAuCl	89	1:0:0
10	AuCl ^c	39 ^d	0:1:0

^a Reaction conditions: 0.1 M diene-allene **2.5** in CD₂Cl₂, 5% mol of gold catalyst, 5% AgSbF₆, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard. ^c Reaction performed in the absence of AgSbF₆. ^d 51% of starting material was recovered.

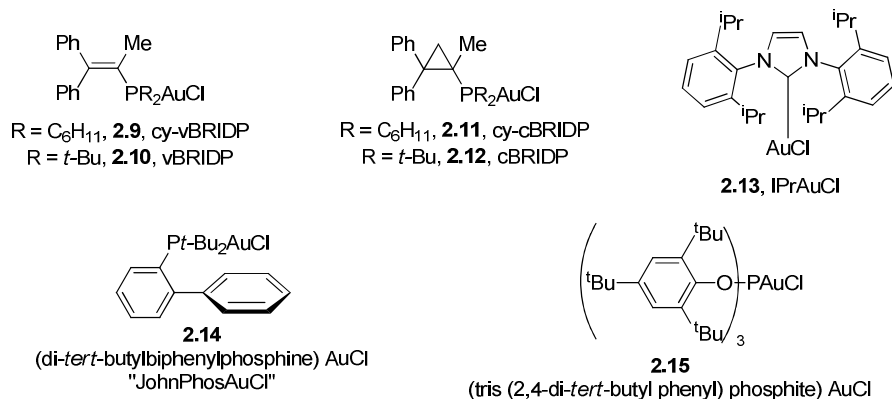


Table 2. Temperature dependence on product distribution in triphenylphosphinegold(I)-catalyzed diene-allene cycloisomerization reactions.^a

2.5		2.6	2.7
entry	temperature (°C)	conversion ^b	2.6:2.7 ^c
1	-20	50	5:1
2	0	60	3.5:1
3	25	80	2:1
4	50	80	2:1

^a Reaction conditions: 0.1 M diene-allene **2.5** in CD₂Cl₂, 5% mol of Ph₃PAuCl, 5% AgSbF₆.

^b Conversions were determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard; the rest of the starting material was not consumed. ^c Product distributions determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard.

In the process of optimizing the reaction conditions with the triphenylphosphinegold(I) catalyst, a significant temperature dependence on product selectivity was observed (Table 2). As the reaction temperature decreased, selectivity for the [4+2] product increased, reaching a ratio as high as 5:1 at a reaction temperature of -20°C. These observations led us to conclude that, at least with this catalyst, formation of the [4+2] product is kinetically more accessible. These results also prompted us to guess that the [4+2] pathway is favored when using catalysts with less electron-donating ligands.¹⁰ Accordingly, we hypothesized that using the more weakly electron donating triarylphosphite ligands would favor formation of the cyclohexene product **2.6**. We were pleased to observe that this is in fact the case: using phosphite complexes **2.15** and triphenylphosphitegold(I) chloride provided solely the [4+2] product in good yield (Table 1, entries 8-9).

The product distributions obtained proved largely insensitive to changes in reaction solvent (Table 3). However, using more coordinating counterions such as triflate, *para*-nitrobenzoate, or TRIP (**2.16**) led to a complete loss of reactivity (Table 3, entries 7-9). The need for a noncoordinating counteranion indicates that a strongly electropositive gold(I) species is required for reactivity in this system. Accordingly, using the weak trimeric gold(I)-oxo catalyst led to no reactivity (Table 4, entry 1). Gold(III) complexes also catalyzed the cycloisomerization of diene-allenes, albeit in decreased yield and extended reaction times (Table 4, entries 2-3).

Table 3. Solvent and counterion screen for triphenylphosphinegold(I)-catalyzed diene-allene cycloisomerization reactions.^a

entry	solvent	X	yield	2.6:2.7 ^b
1	CH ₂ Cl ₂	BF ₄	80	2:1
2	dichloroethane	BF ₄	80	2:1
3	MeNO ₂	BF ₄	80	2:1
4	toluene	BF ₄	0	—
5	CH ₂ Cl ₂	SbF ₆	75	2:1
6	CH ₂ Cl ₂	PF ₆	72	2:1
7	CH ₂ Cl ₂	OTf	0	—
8	CH ₂ Cl ₂	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂	0	—
9	CH ₂ Cl ₂	2.16	0	—

^a Reaction conditions: 0.1 M diene-allene **2.5** in solvent, 5% mol Ph₃PAuCl, 5% AgX, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard.

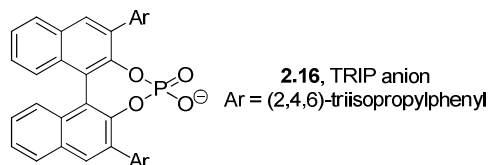
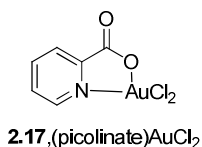


Table 4. Gold-oxo and gold(III) catalysts for diene-allene cycloisomerization reactions.^a

entry	catalyst	yield	2.6:2.7 ^b
1	[(Ph ₃ PAu) ₃ O]BF ₄	0	—
2	AuCl ₃	57 ^c	0:1
3	(picolinate)AuCl ₂ (2.17)	75 ^d	0:1

^a Reaction conditions: 0.1 M diene-allene **2.15** in CD₂Cl₂, 5% mol of gold catalyst, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard. ^c Starting material (25%) was recovered. ^d Starting material (9%) was recovered.



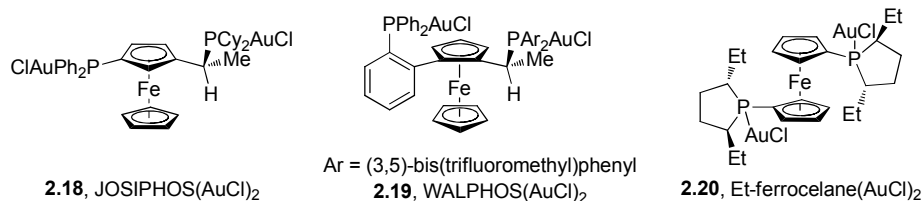
2.3) Dinuclear gold(I) catalysts

Having developed conditions for the racemic [4+2] and [4+3] reactions, we were interested in rendering these transformations enantioselective. Regrettably, preliminary experiments using dinuclear gold(I) catalysts were unsuccessful (Table 5). Racemic BINAP(AuCl)₂ was able to catalyze the cycloaddition of diene-allene **2.5** but was insufficiently selective, yielding a 2:1 mixture of the desired cycloheptadiene **2.7** and the [4+2] product **2.6**. Catalysts which bore more bulky, electron-rich bidentate phosphines such as JOSIPHOS(AuCl)₂ (**2.18**), WALPHOS(AuCl)₂ (**2.19**), and Et-ferrocene(AuCl)₂ (**2.20**) were similarly unsuccessful (Table 5, entries 2-4). When a 1:1 ratio of gold(I) and silver(I) was employed in making the active catalyst, a complex mixture of products was observed (entries 4-5); using one equivalent of AgSbF₆ with respect to the dinuclear catalyst Et-ferrocene(AuCl)₂ did lead to formation of desired product; unfortunately, the selectivity of this transformation was a modest 5:2 in favor of the [4+3] product. In light of the poor chemoselectivity observed in these preliminary experiments, we decided not to pursue this avenue of inquiry.¹¹

Table 8. Cycloisomerization of diene-allenes—dinuclear gold(I) catalysts.^a

2.5		2.6	2.7
entry	catalyst	% AgSbF ₆	2.6:2.7^b
1	BINAP(AuCl) ₂ ^c	5	1:2
2	JOSIPHOS(AuCl) ₂ (2.18)	10	complex mixture
3	WALPHOS(AuCl) ₂ (2.19)	10	complex mixture
4	Et-ferrocene(AuCl) ₂ (2.20)	10	complex mixture
5	Et-ferrocene(AuCl) ₂ (2.20)	5	5:2

^a Reaction conditions: 0.1 M diene-allene 10 in CD₂Cl₂, 5% mol of gold catalyst, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[tert-butyl]benzene as an internal standard. ^c Reaction run with 2.5% catalyst.



2.4) Mechanistic considerations

Based on previous work investigating mechanisms of gold(I)-catalyzed cycloisomerizations of allenes, we proposed two different types of mechanisms leading to formation of the cyclohexene and cyclopentadiene products observed. First, we considered a stepwise pathway (Figure 3).¹² Nucleophilic attack by the diene onto gold(I)-activated allene proceeds in 5-*exo*-dig

fashion, leading to carbocationic intermediate **2.21**. Subsequent intramolecular trapping of this intermediate with the distal allene olefin then gives rise to metallocarbenoid intermediate **2.22**, which undergoes a 1,2-hydride shift to give cycloheptadiene **2.23**. Alternatively, the carbocation can be intercepted by the gold(I)-carbon bond to give cyclohexene product **2.25**.

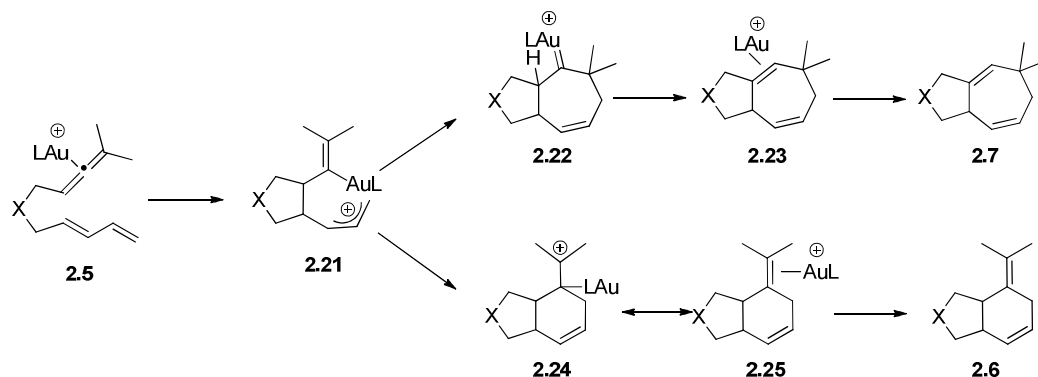
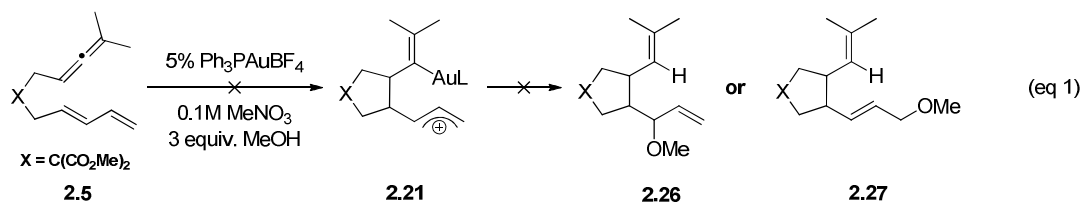
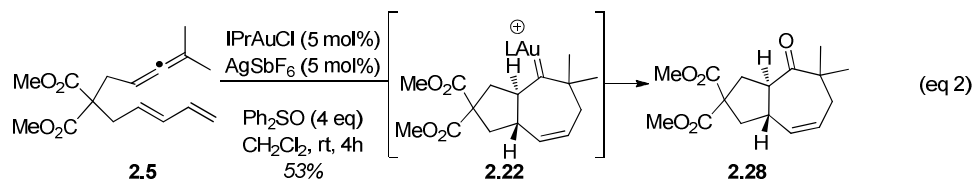


Figure 3. A stepwise mechanism for formation of cycloheptadiene (**2.7**) and cyclohexene (**2.6**) products from diene-allene **2.5** features nucleophilic attack by the diene followed by electrophilic trapping of a vinyl-gold species **2.21**.

To test the plausibility the mechanism described above, we attempted to trap the proposed cationic intermediate with methanol (eq 1). Surprisingly, none of the expected methyl ether products **2.26** or **2.27** were observed. These results, while not conclusive, prompted us to think of mechanistic alternatives which do not require a discrete carbocationic intermediate.



In light of the failed trapping experiment described above, we investigated the possibility of a concerted cycloaddition mechanism, where both the six- and seven-membered ring products arise from common gold(I)-carbenoid intermediate **2.22** (Figure 4). This compound forms as the result of a concerted cycloaddition between the diene and allene fragments: protodemetalation via a 1,2-hydride shift then yields cycloheptadiene product **2.23** or a 1,2-alkyl shift occurs to give the cyclohexene product **2.25**.¹³



In order to test for the presence of gold-carbenoid intermediate **2.22**, we exposed substrate **2.5** to excess diphenylsulfoxide with the *N*-heterocyclic carbene-gold(I) catalyst; this method had

was previously developed to oxidatively trap *N*-heterocycliccarbenegold(I)-carbenoid species.¹⁴ Gratifyingly, ketone **2.28** was isolated in 53% yield under these conditions, indicating that a gold(I)-carbenoid species akin to **2.22** is present when the *N*-heterocycliccarbeneligated catalyst IPrAuCl is used (eq 2).¹⁵

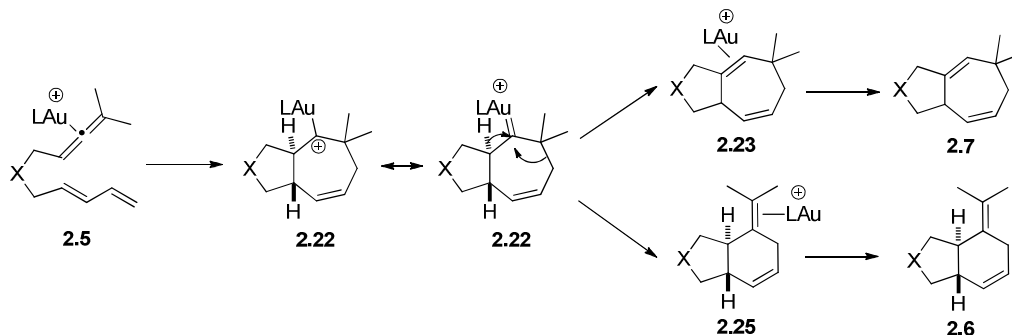


Figure 4. A concerted mechanism of diene-allene **2.5** featuring a common gold-carbenoid intermediate (**2.22**) for both cycloheptadiene (**2.7**) and cyclohexene (**2.6**) products.

The oxidative trapping experiment also allowed us to probe the relative stereochemistry about the newly-formed cyclopentane ring. Should both the cycloheptadiene and cyclohexene products arise from the same intermediate, we expect the stereochemistry about the five-membered ring to be shared by both product classes. Correlation experiments performed on **2.28** in tandem with a crystal structure of **2.34** showed both products as having *trans* relative stereochemistry about the cyclopentane ring. In addition to suggesting that both products arise from a common intermediate, these findings also indicate that the initial cycloaddition occurs with *endo* orientation in the transition state.¹⁶

2.5) Substrate scope

With a greater understanding of the interplay between the mechanism and chemoselectivity observed for gold(I)-catalyzed cycloisomerizations of diene-allenes, we sought to explore whether altering the substrate scaffold has any impact on the degree of ligand-controlled reactivity observed. When examining potential modifications to substrate **2.5**, we decided to focus on changes to the tether type (section 2.5.1), tether length (section 2.5.2), substitution about the diene (section 2.5.3) and allene fragments (section 2.5.4), and substitution on the tether (section 2.5.5).

2.5.1 – Tether type

Altering the tether type did not effect how the diene-allene substrates behaved toward either the triarylphosphitegold(I) or the JohnPhosgold(I) catalysts (Table 5). A notable exception to this trend is the reaction of bissulfonyl-tethered substrate **2.29** with the JohnPhos-ligated catalyst; we were unable to obtain exclusivity with this substrate for the [4+3] product.

Table 5. Effects of tether substitution of product distribution.^a

entry	X	yield	product ^b	entry	X	yield	product ^b
1	C(CO ₂ Me) ₂ (2.5)	89%	C(CO ₂ Me) ₂ (2.6)	5	C(CO ₂ Me) ₂ (2.5)	85%	C(CO ₂ Me) ₂ (2.6)
2	C(SO ₂ Ph) ₂ (2.29)	80%	C(SO ₂ Ph) ₂ (2.34)	6	NTs (2.29)	83%	NTs (2.39)
3	NTs (2.30)	83%	NTs (2.35)	7	O (2.30)	n.r.	--
4	O (2.31)	n.r.	--				
entry	X	yield	a:b	entry	X	yield	a:b
8	C(CO ₂ Me) ₂ (2.5)	80%	2 2.6 : 1 2.7				
9	C(CO ₂ Et) ₂ (2.32)	76%	2 2.36 : 1 2.40				
10	C(CO ₂ Bn) ₂ (2.33)	45%	2 2.37 : 1 2.41				
11	C(SO ₂ Ph) ₂ (2.29)	80%	1 2.34 : 0 2.38				
12	NTs (2.30)	90%	10 2.35 : 1 2.39				
13	O (2.31)	n.r.	--				
entry	X	yield	a:b:c	entry	X	yield	a:b:c
14	C(CO ₂ Me) ₂ (2.5)	75%	7 2.6 : 89 2.7 : 4 2.8				
15	C(CO ₂ Et) ₂ (2.32)	48%	0 2.36 : 1 2.40				
16	C(CO ₂ Bn) ₂ (2.33)	64%	0 2.37 : 1 2.41				
17	C(SO ₂ Ph) ₂ (2.29)	80%	1 2.34 : 2 2.38				
18	NTs (2.30)	90%	4 2.35 : 5 2.39 : 1 2.42				
19	O (2.31)	n.r.	--				

^a Reaction conditions: 0.1 M diene-allene in CD₂Cl₂, 5% mol of LAuCl, 5% AgSbF₆, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[tert-butyl]benzene as an internal standard.

More subtle effects of tether choice can be seen in results obtained using triphenylphosphinegold(I) and the *N*-heterocycliccarbene-ligated gold(I) complexes. Changing the type of malonate from methyl to ethyl (**2.32**) (entries 9, 15) or benzyl (**2.33**) (entries 10, 16) had no observable effect on the product distribution; however, the dibenzyl malonate-linked substrate showed decreased reactivity toward both catalysts, even with prolonged reaction times.

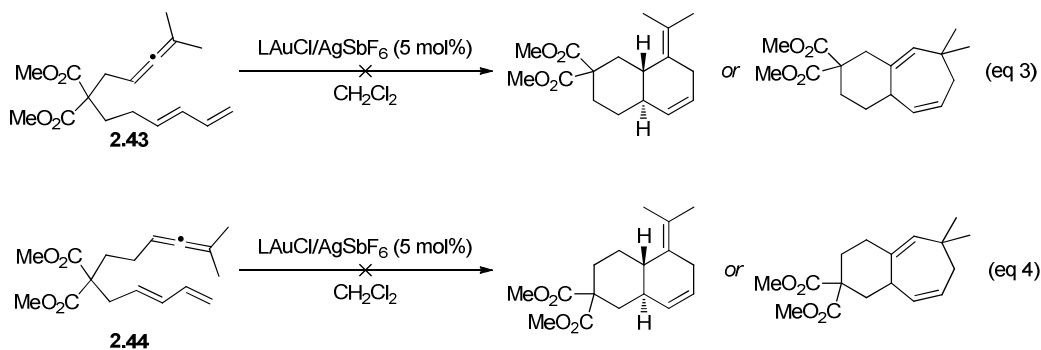
Compared to the malonate compounds, bissulfonyl-tethered substrate **2.29** and *N*-toluenesulfonamide substrate **2.30** demonstrated greater preference toward [4+2]-type reactivity. Unlike the malonate substrates, which gave a 2:1 ratio of [4+2] to [4+3] products with triphenylphosphinegold(I), **2.29** gave exclusively the [4+2] adduct **2.34** when this catalyst was used (entry 11); the *N*-toluenesulfonamide-tethered substrate **2.30** gave the [4+2] product **2.35** in ten-fold excess to the [4+3] product **2.39** (entry 12).

Given the increased selectivity for the [4+2] pathway shown by substrates **2.29** and **2.30** with triphenylphosphinegold(I), it is not surprising that utilizing the NHC catalyst IPrAuCl with these compounds resulted in more modest selectivity than with the malonate substrates (entries 17-18). Reaction with bissulfonyl substrate **2.29** gave a 2:1 selectivity in favor of the [4+3] product **2.38**, and *N*-toluenesulfonamide substrate **2.30** gave a 5:1:4 mixture of [4+3] adduct **2.39**, isomerized [4+3] adduct **2.40**, and [4+2] adduct **2.35**. This erosion in selectivity indicates that increasing the tether's bulk leads to a preference for the [4+2] pathway. These results also suggested to us that in addition to the electronic ligand effects already noted, sterics also contribute significantly to controlling the product distribution.

Effecting reactivity with ether-tethered substrate **2.31** proved unsuccessful, regardless of the catalyst used or reaction temperature¹⁷ (entries 4, 7, 13, 19). Remarkably, allene isomerization—a common side-reaction in gold(I)-catalyzed processes involving allenes—was not observed, suggesting that the gold(I) catalyst does not productively bind the allene. The lack of reactivity is most likely due to the electron-withdrawing effect of the β -oxygen on the allenyl π -system, leaving the allene insufficiently electron-rich to productively bind gold(I) catalyst.¹⁸

2.5.2 – Tether length

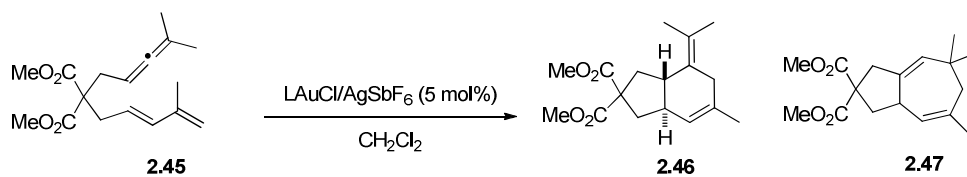
We were unsuccessful in our attempts to generate 6/6 and 6/7 fused bicycles using this chemistry; elongating the tether from five to six carbons shut down reactivity. Both homodienyl substrate **2.43** and homoallenyl substrate **2.44** were inactive to gold(I) catalysis, even at elevated reaction temperatures and extended reaction times (eq 3-4).



2.5.3 – Diene substitution

The diene alkylating agent necessary to get methyl substitution at the 4-position of canonical substrate **2.5** is readily prepared through formylation of 2-methyl-1-buten-3-yne followed by lithium aluminum hydride reduction to form the diene-ol.¹⁹ This compound was used to prepare 4-methyl substituted diene-allene **2.45**.

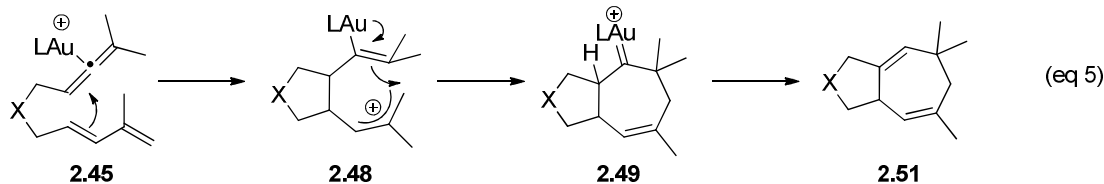
Table 6. Effects of 4-methyl substitution of product distribution.^a



entry	ligand	yield	2.46:2.47 ^b
1	tri- <i>tert</i> -butylphosphite (2.15)	92%	4:1
2	PPh ₃	>95%	2:1
3	IPr (2.13)	73%	0:1
4	JohnPhos (2.14)	81%	0:1

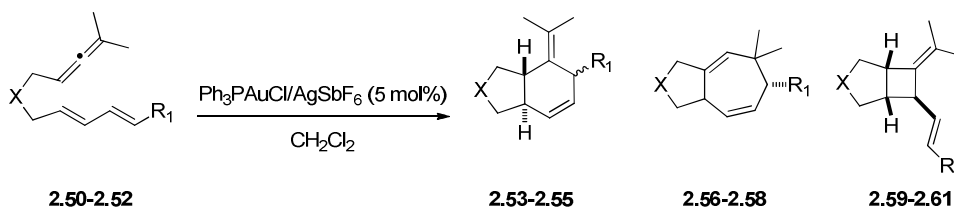
^a Reaction conditions: 0.1 M diene-allene in CD₂Cl₂, 5% mol of **2.45**, 5% AgSbF₆, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard.

Similar ligand effects were observed with 4-substituted substrate **2.45** as for unsubstituted substrate **2.5**, particularly with *N*-heterocyclic carbene and JohnPhos-ligated catalysts (entries 3-4). Notably, erosion in selectivity was observed when using phosphite-ligated **2.15** (entry 1). A possible explanation for these results are that structural perturbations resulting from the additional substitution at the diene lead to decreased preference for an [1,3]-alkyl shift over a [1,2]-hydride shift. Alternatively, the observed decrease in selectivity could be due to a change in the reaction mechanism toward a step-wise pathway: the presence of the methyl group on the diene backbone would provide additional stabilization for an allylic-cation such as **2.48** (eq 5). This mechanism favors formation of the seven-membered ring intermediate **2.49**, with the vinyl-gold(I) species trapping the allylic cation. Proto-deauration through a [1,2]-hydride shift afford the [4+3] product **2.47** in a process analogous to the concerted mechanism shown in Figure 4.

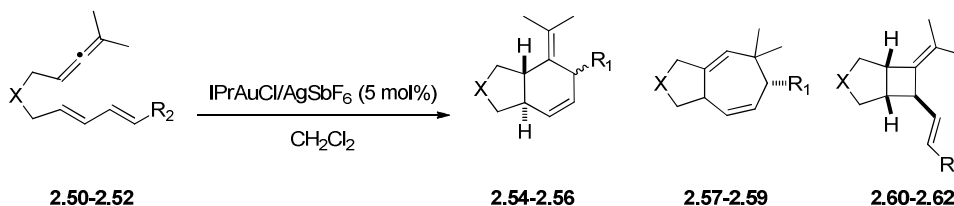


Terminal substitution of the diene resulted in significant loss in selectivity when using triphenylphosphinegold(I) (Table 7). With this catalyst, dimethylmalonate-linked terminal methyl-substituted compound **2.50** and terminal phenyl-substituted compound **2.51** gave, in addition to cyclohexene and cycloheptadiene products, the unexpected [2+2] cyclized products **2.59** and **2.61**; in the case of **2.51**, the cyclobutane product was the major product formed. As a concerted [2+2] mechanism is thermally disallowed, these results indicate that a stepwise mechanism in the formation of these products (eq 5). This proposal is also supported by the (1 β , 5 β , 6 α) configuration about the newly formed cyclobutane ring, as similar stereochemical relationships were observed in the stepwise gold(I)-catalyzed [2+2] cycloaddition of eneallenes.¹³

Table 7. Effects of terminal diene substitution of product distribution.^a



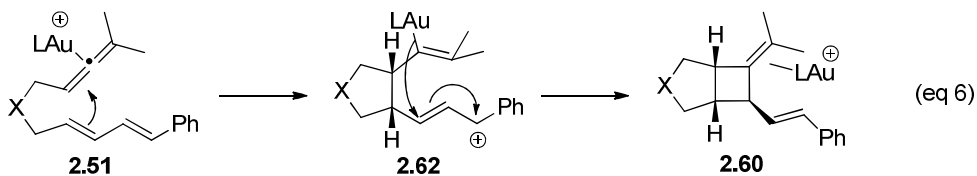
entry	substrate	yield	a:b:c ^b
1	X = C(CO ₂ Me) ₂ , R ₁ = Me (2.50)	67%	10 2.53 : 7 2.56 : 6 2.59
2	X = C(CO ₂ Me) ₂ , R ₁ = Ph (2.51)	71%	1 2.54 : 0 2.57 : 3 2.60
3	X = NTs, R ₁ = Me (2.52)	70%	20 2.55 : 4 2.58 : 1 2.61



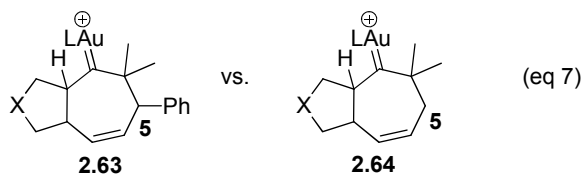
entry	substrate	yield	a:b:c ^b
4	X = C(CO ₂ Me) ₂ , R ₁ = Me (2.50)	84%	0 2.53 : 1 2.56 : 0 2.59
5	X = C(CO ₂ Me) ₂ , R ₁ = Ph (2.51)	71%	4 2.54 : 6 2.57 : 1 2.60
6	X = NTs, R ₁ = Me (2.52)	80%	2 2.55 : 8 2.58 : 1 2.61

^a Reaction conditions: 0.1 M diene-allene in CD₂Cl₂, 5% mol of LAuCl, 5% AgSbF₆, room temperature. ^b Product distributions determined by NMR using 1,3,5-tri[*tert*-butyl]benzene as an internal standard.

The observed change in mechanism can be rationalized by considering the frontier molecular orbitals of the diene portion of **2.51**. The electron-donating phenyl group inductively enhances the nucleophilicity of the proximal diene carbon, making initial nucleophilic attack on the gold(I)-activated allene more feasible. Additionally—and perhaps more significantly—the carbocationic character of C6 is enhanced with respect to the benzylic position due to resonance stabilization. As such, the vinyl-gold(I) intermediate preferentially traps at C6 to give the cyclobutane product.

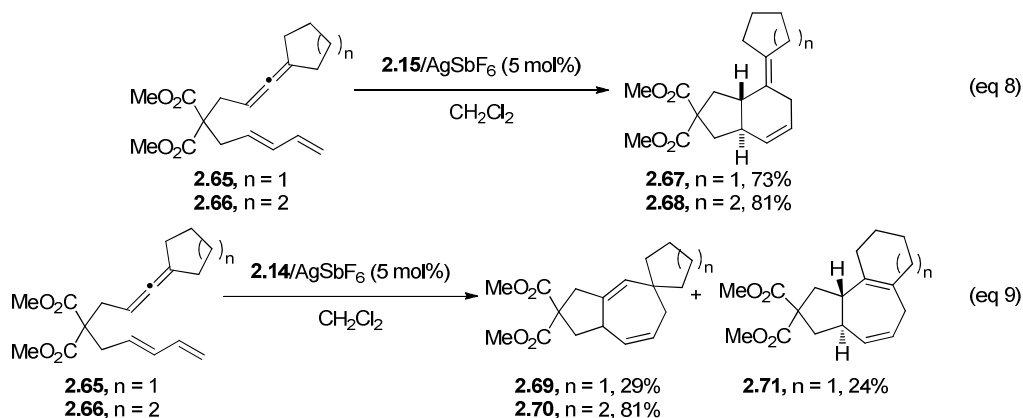


With the *N*-heterocycliccarbene-ligated catalyst, terminal methyl substitution had little effect on the products observed (entries 4, 6). For phenyl-substituted compound **2.51**, selectivity for the favored [4+3] adduct was reduced to 6:4:1 over the [4+2] and [2+2] products (entry 5). The increased preponderance of the [4+2] product can be rationalized by invoking the greater migratory aptitude of benzylic carbon C5 in intermediate **2.63** as compared to secondary alkyl carbon in the unsubstituted system **2.64** (eq 6), which favors a [1,3]-alkyl shift.

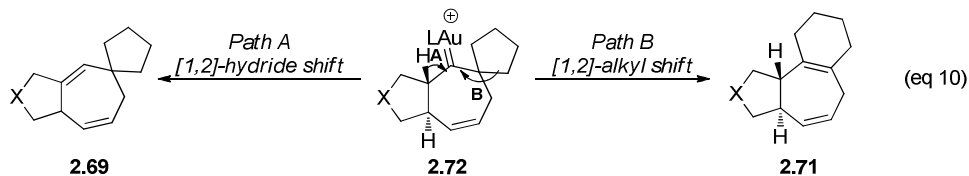


2.5.4 - Allene substitution

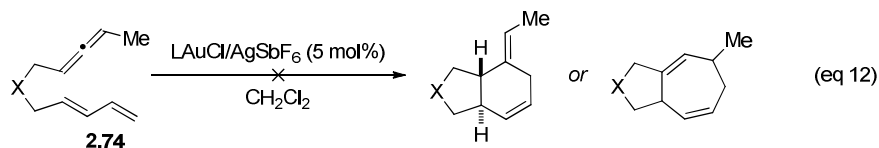
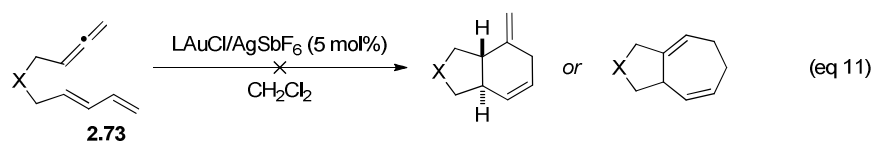
The tri-*tert*-butylphenylphosphinegold(I)-catalyzed [4+2] cycloaddition reaction exhibited good tolerance for varied types of terminal substitution at the allene. Both cyclopentyl (**2.65**) and cyclohexyl (**2.66**) allene substrates reacted under these conditions to give the desired [4+2] adducts **2.67** and **2.68** (eq 8).



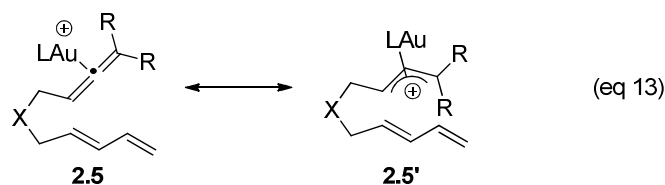
Cyclohexyl substrate **2.66** also performed well under the Johnphosgold(I) reaction conditions to give selectively the tricyclic cycloheptadiene compound **2.68**, which contains a spirocyclic cyclohexyl moiety difficult to access synthetically by other means (eq 9). Unfortunately, reaction of cyclopentyl substrate **2.64** with this catalyst resulted in a 5:4 mixture of the desired spirocyclic compound **2.69** and the ring-expanded cyclohexene product **2.71**, resulting from a [1,2]-alkyl shift (eq 10, path B).



Mono- and disubstituted allene substrates **2.73** and **2.74** showed no reactivity toward either tri-*tert*-butylphenylphosphitegold(I) or Johnphosgold(I) catalysts (eq 11-12).

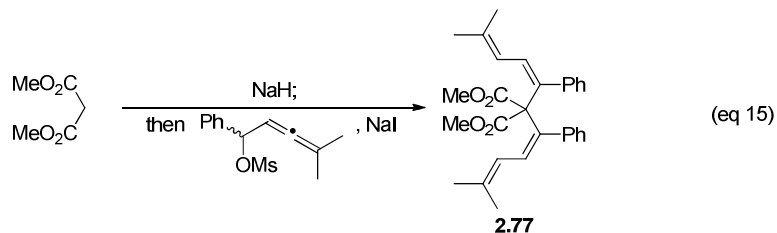
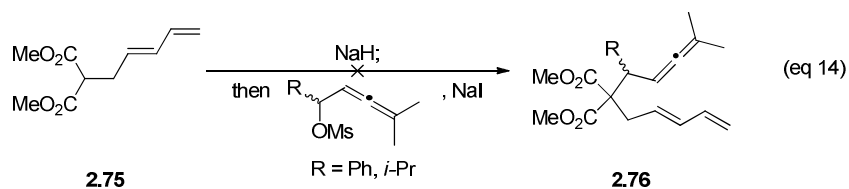


These observations suggest that significant carbocationic character builds up at the terminal carbon of the allene fragment, supporting our hypothesis that the cycloaddition proceeds through concerted reaction of the diene fragment with a gold(I)-stabilized allyl cation (eq 13).



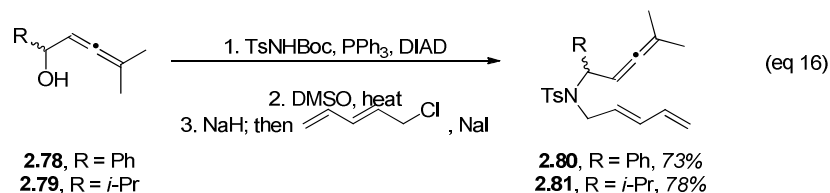
2.5.5 - Tether Substitution

We sought to examine the diastereoselectivity of gold(I)-catalyzed cycloaddition reactions of diene-allenes possessing substitution at the α -position of the allene fragment. Initially, dimethyl malonate-tethered substrate **2.76** was targeted; unfortunately, attempts to install the allene fragment on monoalkylated diene compound **2.75** led to a complex mixture of products (eq 14). Attempts at reversing the order of alkylation, forming monoalkylated dimethylmalonate with a substituted allene moiety, led to exclusive formation of bisalkylated, isomerized compound **2.77** (eq 15).

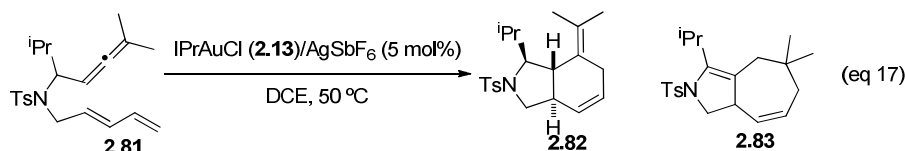


Thus, efforts were redirected toward making *N*-toluenesulfonamide tethered substrates **2.80** and **2.81**. Mitsunobu reaction of *tert*-butyl tosylcarbamate with allenyl alcohols **2.78** and **2.79**

followed by thermal Boc deprotection and alkylation with *trans*-5-chloropenta-1,3-diene afforded the desired compounds in 73% and 78% overall yield, respectively (eq 16).



Initially, exposing isopropyl-substituted substrate **2.81** to tri-*tert*-butylphenylphosphitegold(I) and Johnphosgold(I) catalysts at room temperature led to no reaction; however, trace product was observed using IPrgold(I) at room temperature. Increasing the temperature to 45°C and changing the solvent to dichloroethane resulted in full conversion of starting material to a mixture of [4+2] product **2.82** and isomerized [4+3] product **2.83**. Product **2.82** was formed as a single diastereomer, indicating that gold(I)-coordination of the allene occurs stereospecifically.

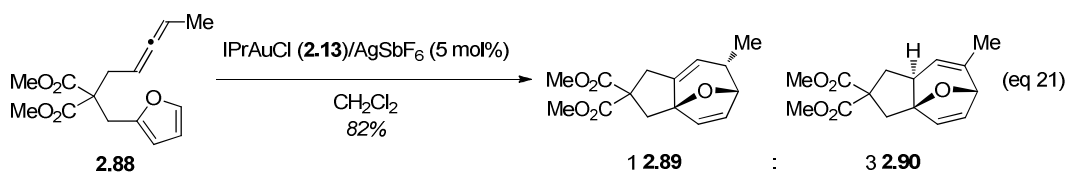
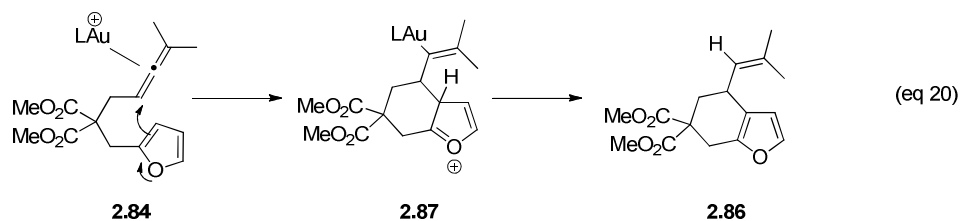
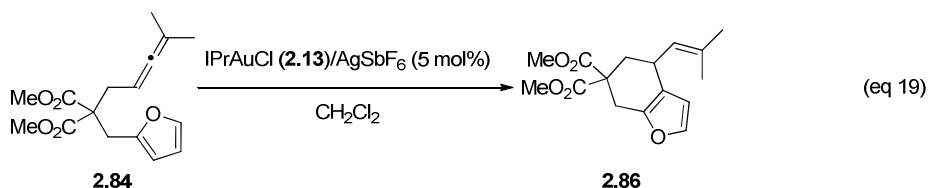
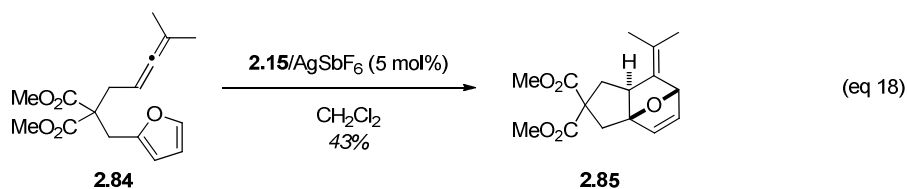


2.6) Intramolecular reactions of heterocycles with allenes

Given the privileged status of heterocycles in natural products, medicinal and materials chemistry, we were interested in how nucleophilic heterocycles with a pendant allene would behave toward gold(I) catalysts. As such, we examined the reactivity of furan-, benzofuran- and indole-allene compounds under the gold(I) catalysis conditions we developed for intramolecular diene-allene cycloadditions.

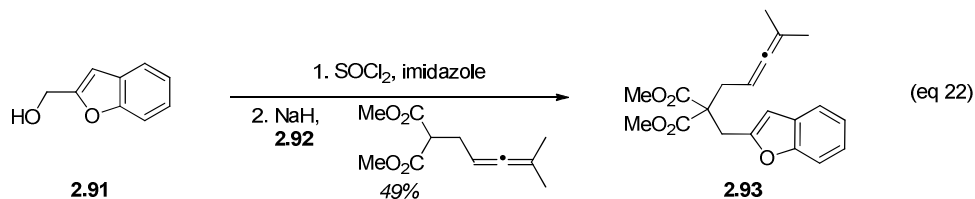
The use of furans in intramolecular Diels-Alder (IMDA) reactions with allenes is well precedented, featuring prominently in the total synthesis of phorbol esters, (+)-giberrelin A5, and 11-ketotestosterone.²⁰ Work published by Mascareñas during the course of our investigation on gold(I)- and platinum(II)-catalyzed [4+3] cycloadditions of diene-allenes suggested that furan would participate in a gold(I)-catalyzed intramolecular cycloaddition with an allene.²¹ Indeed, furan substrate **2.84** reacted in the presence of tri-*tert*-butylphenylphosphitegold(I) catalyst to give the expected [4+2] product **2.85** (eq 18). Unexpectedly, when exposed to the NHC-gold(I) catalyst IPrAuCl, the hydroarylation product **2.86** was observed (eq 19). Formation of **2.86** most likely occurs through furan attacking gold(I)-activated allene; protodeauration of intermediate **2.87** then gives the cyclized product.

It is interesting to note that the Mascareñas group report formation of [4+3] products **2.89** and **2.90** when using trisubstituted allene substrate **2.88** and IPrAuCl; this result suggests that the increase bulk of the tetrasubstituted allene inhibits the cycloaddition pathway.

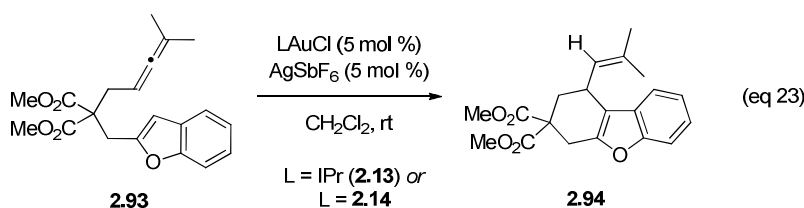


After observing this different mode of reactivity, we became more interested in exploring gold(I)-catalyzed hydroarylation reactions of allenes with heterocycle nucleophiles. Several known reactions involving gold catalyzed hydroarylation of carbon π -systems with heterocycles were known at the time of this investigation; notably, gold(III)-catalyzed intermolecular additions to electron deficient alkenes and alkynes,²² gold(I)- and gold(III)-intramolecular additions of indole to tethered alkynes,²³ and gold(I)-catalyzed inter- and intramolecular addition of indole to allenes at C2.^{24,25,26} We believed that we could use our knowledge of ligand effects to expand the scope of these types of transformations.

First, we synthesized benzofuran substrate **2.93** with C2- allene functionality installed by alkylation of monoalkylated compound **2.92** with crude 2-(chloromethyl)benzofuran (**2.91**) (eq 22).²⁷



Exposure of **2.93** to JohnPhosgold(I) and IPrgold(I) led to exclusive formation of *exo*-cyclized hydroarylation product **2.94** (eq 22). Analogous to the reaction with furan, this transformation most likely proceeds by gold(I)-activation of the allene, followed by Friedel-Crafts arylation and protodemetalation to give observed the observed six-membered ring product.



Lastly, we were interested in further developing gold(I)-catalyzed allene hydroarylations with indole. Previous gold(I)-catalyzed indole hydroarylation reactions have employed C3 as the nucleophilic position; we wanted to see if C2 could act as the nucleophilic carbon if (a) the allene subunit were appended at the N^{in} position and, (b) if the C3 were blocked (Figure 5A). With this substrate, reaction would proceed through indole-C2 attack on the gold(I)-activated allene to afford pyrrolidines of type **2.97**.²⁸

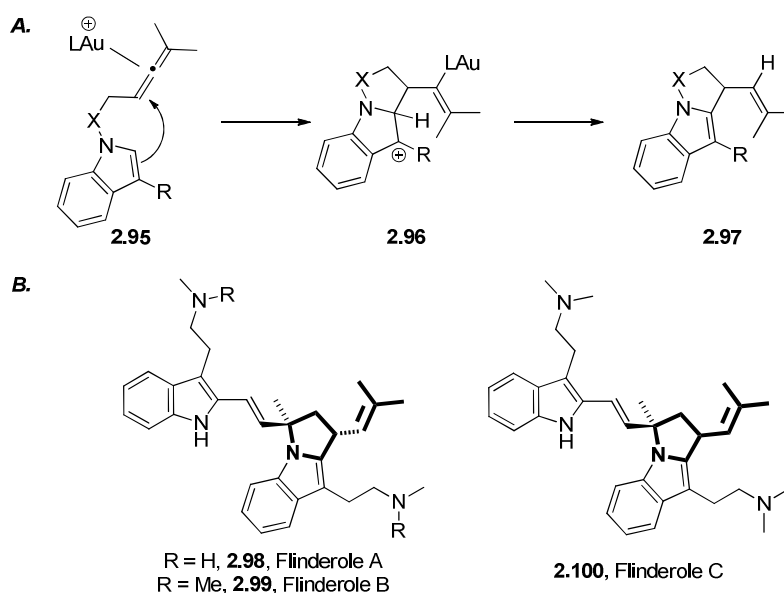
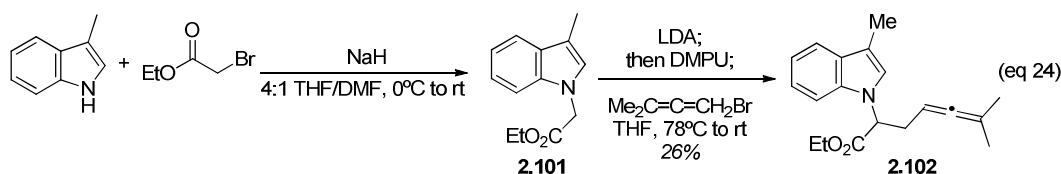
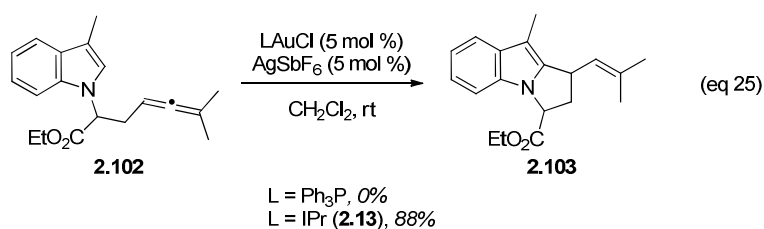


Figure 5. Hydroarylation of allenes with C2 of indole provide pyrrolidine products such as **2.97**; this structural motif is seen in the flinderole natural products **2.98-2.100**.

Additional motivation for developing this transformation came from the reported isolation of flinderoles A-C (**2.98-2.100**), novel antimalarial bisindole alkaloids featuring this type of heterocyclic framework (Figure 3B).^{29,30}

N-alkylation of 3-methylindole with ethyl bromoacetate afforded ethyl 2-(3-methyl-1*H*-indol-1-yl)acetate (**2.101**);³¹ alkylation of the lithium enolate of this compound gave desired substrate **2.102** in 27% yield over two steps (eq 23).³²





Exposure of **2.102** to triphenylphosphinegold(I) failed to promote cyclization, even after prolonged reaction times. However, switching to the more active *N*-heterocycliccarbenegold(I) catalyst IPrAuSbF₆ led to formation of the desired cyclized product in 88% isolated yield (eq 25).

2.7) Conclusions

Transition metal catalysis is defined by the interplay between the stereoelectronic properties of the metal complex employed and the organic substrate with which it reacts. The chemoselective methods described above for transforming diene-allenes into both [4+3]- and [4+2]- type cycloadducts demonstrates how intelligent choice of catalyst ligand can drastically impact the outcome of gold(I)-catalyzed reactions by changing the degree of stabilization of gold(I)-carbenoid intermediates. This reaction system is the first that exploits the ambident nature of gold(I) species to choose between forming two different products from the same substrate. It is our hope that by continuing to develop a comprehensive understanding of ligand effects in gold(I) transformations, we will be able to harness the full potential of gold(I) catalysis.

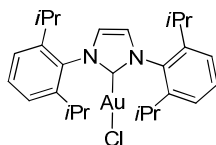
Additional Supporting Information

General Information

Unless otherwise noted, all reagents were obtained commercially and used without further purification. All reaction mixtures excluding the gold(I)-catalysis mixtures were stirred with a magnetic stir bar in flame-dried glassware under a nitrogen atmosphere. The ligands vBRIDP, cBRIDP, cy-vBRIDP and cy-cBRIDP were donated by Takasago and used without further purification. Tetrahydrofuran (THF), diethyl ether (Et₂O) and dichloromethane (CH₂Cl₂) were dried by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Triethylamine (Et₃N) was distilled from CaH₂.³³ Dry DMSO and DMF were obtained from Acros. Extracts were dried over MgSO₄ or Na₂SO₄ and solvents were removed in a rotary evaporator. TLC analysis of reaction mixtures was performed on Merck silica gel 60 F254 TLC plates. Unless otherwise indicated, chromatography was carried out on ICN SiliTech 32-63 D 60 Å silica gel. ¹H, ¹³C NMR and ³¹P NMR spectra were recorded with Bruker AMX-300, AVQ-400, AVB-400, DRX-500 and AV-500 spectrometers and referenced to CDCl₃ or CD₂Cl₂. The order of citation in parentheses is a) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, a = apparent), b) number of protons, and c) coupling constants. Structures were confirmed using NOESY, COSY and HSQC experiments. Mass spectra data were obtained at the Micro-Mass/Analytical Facility in the College of Chemistry, University of California, Berkeley.

1. Preparation of Au(I) catalysts

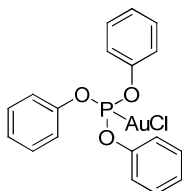
Ph_3PAuCl ³⁴ was prepared according to literature procedures. The spectral data obtained for this compound matched those reported in the literature.



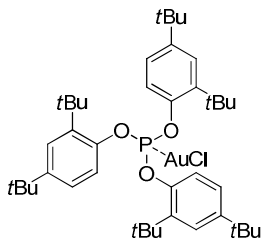
IPrAuCl (2.13). Synthesized via modification of a procedure reported by Nolan.³⁵ Silver oxide (82 mg, 0.355 mmol, 0.5 equiv) was added in one portion to a solution of the imidazolium salt (300 mg, 0.710 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL). After 3 hours at room temperature, a solution of $(\text{Me}_2\text{S})\text{AuCl}$ (209 mg, 0.710, 1.0 equiv) in CH_2Cl_2 (7 mL) was added dropwise, and the resulting solution was stirred at room temperature and stirred for two hours. The reaction solution was filtered through celite and concentrated via a rotary evaporator to yield the desired Au(I) complex. ^1H NMR (400 MHz, CD_2Cl_2): δ 7.57 (t, 2H, $J = 7.8$ Hz), 7.35 (d, 4H, $J = 7.8$ Hz), 7.24 (s, 2H), 2.57 (septet, 4H, $J = 6.8$ Hz), 1.34 (d, 12H, $J = 6.8$ Hz), 1.23 (d, 12H, $J = 6.8$ Hz). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 175.0, 145.7, 134.0, 130.6, 124.2, 123.3, 28.7, 24.1, 23.7.

Phosphine- and phosphite-Au(I) complexes

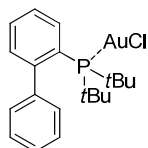
$\text{Tris}(2,4\text{-di-}t\text{-butylphenyl})\text{phosphiteAuCl}$,⁵ triphenylphosphite-AuCl,³⁶ di-*t*-butylbiphenylphosphine-AuCl³⁷, vBRIDPAuCl³⁸, cBRIDPAuCl,⁶ cy-vBRIDPAuCl,⁶ and cy-cBRIDPAuCl⁶ were synthesized via modification of a procedure reported by Puddephat.³⁹ In a 20 mL screw-top vial was dissolved $(\text{Me}_2\text{S})\text{AuCl}$ (1 equiv) in CH_2Cl_2 , and the resulting solution was cooled in an ice bath. A solution of the desired ligand (0.5 equiv) in CH_2Cl_2 was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred for two hours. After TLC indicated complete consumption of the starting material, the reaction solution was concentrated in a rotary evaporator to yield the desired Au(I) complexes.



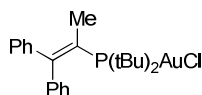
Triphenylphosphite-AuCl. ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.19 (m, 15H). ^{31}P NMR (166 MHz, CDCl_3): δ 109.9.



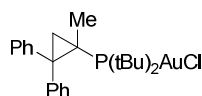
Tris(2,4-di-*t*-butylphenyl)phosphiteAuCl (2.15). ^1H NMR (400 MHz, CDCl_3): δ 7.42 (s, 1H), 7.41 (m, 1H), 7.13 (dd, 1H, $J = 8.4, 2.4$ Hz), 1.45 (s, 9H), 1.29 (s, 9H). ^{31}P NMR (166 MHz, CDCl_3): δ 100.5.



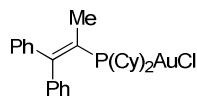
Di-*t*-butylbiphenylphosphine-AuCl (2.14). ^1H NMR (400 MHz, CDCl_3): δ 7.87 (td, 1H, J = 7.7 Hz, 1.7 Hz), 7.51 (m, 5H), 7.31 (m, 1H), 7.13 (dd, 2H, J = 8.0 Hz, 1.0 Hz), 1.41 (s, 9H), 1.38 (s, 9H). ^{31}P NMR (166 MHz, CDCl_3): δ 59.84.



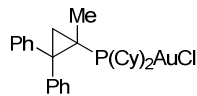
vBRIDP-AuCl (2.10). Purified by layered recrystallization from dichloromethane/hexanes. ^1H NMR (400 MHz, CDCl_3): δ 7.41 (t, 1H, J = 7.6 Hz), 7.30-7.34 (m, 4H), 7.19 (t, 1H, J = 7.2 Hz), 2.07 (d, 1H, J = 7.2 Hz), 1.52 (s, 9H), 1.48 (s, 9H). ^{31}P NMR (166 MHz, CDCl_3): δ 77.2. HRMS (ESI^+): calculated for $\text{C}_{23}\text{H}_{31}\text{AuP}$ 535.1824, found 535.1816.



cBRIDP-AuCl (2.12). Purified by layered recrystallization from dichloromethane/hexanes. ^1H NMR (400 MHz, CDCl_3): δ 7.46 (broad s, 2H), 7.36-7.39 (m, 2H), 7.22-7.26 (m, 5H), 7.14 (t, 1H, J = 7.2 Hz), 2.40 (dd, 1H, J = 16.0 Hz, 5.2 Hz), 1.43-1.60 (m, 18H), 1.42 (d, 3H, J = 7.6 Hz). ^{31}P NMR (166 MHz, CDCl_3): δ 66.4. HRMS (ESI^+): calculated for $\text{C}_{24}\text{H}_{33}\text{AuP}$ 549.1980, found 549.1968.

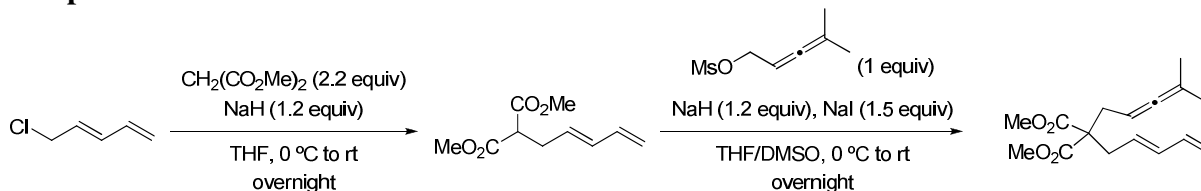


cy-vBRIDPAuCl (2.9). Purified by layered recrystallization from dichloromethane/hexanes. ^1H NMR (400 MHz, CDCl_3): δ 7.46 (m, 2H), 7.36-7.39 (m, 2H), 7.22-7.26 (m, 4H), 7.10 (at, 2H, J = 7.2 Hz), 1.38-2.13 (m, 22H), 1.91 (d, 3H, J = 8.8 Hz). ^{31}P NMR (166 MHz, CDCl_3): δ 43.7. HRMS (ESI^+): calculated for $\text{C}_{27}\text{H}_{35}\text{AuP}$ 587.2137, found 587.2125.



cy-cBRIDPAuCl (2.11). Purified by layered recrystallization from dichloromethane/hexanes. ^1H NMR (400 MHz, CDCl_3): δ 7.46 (m, 2H), 7.31-7.39 (m, 2H), 7.22-7.26 (m, 5H), 7.14 (t, 1H, J = 7.2 Hz), 2.40 (dd, 1H, J = 16.0 Hz, 5.2 Hz), 1.43-1.60 (m, 18H), 1.42 (d, 3H, J = 7.6 Hz). ^{31}P NMR (166 MHz, CDCl_3): δ 59.1. HRMS (ESI^+): calculated for $\text{C}_{27}\text{H}_{35}\text{AuP}$ 601.2283, found 601.2283.

2. Preparation of diene-allenes

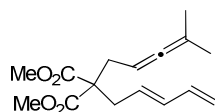


Prepared by a modification of a procedure reported by Yoshinao.⁴⁰ To a solution of 1,4-pentadien-3-ol (4.00 g, 47.6 mmol, 1 equiv) in CH_2Cl_2 (95 mL) at 0 °C was added dropwise thionyl chloride (6.79 g, 57.1 mmol, 1.2 equiv). The reaction mixture was warmed to room temperature and stirred 2 hours. The reaction was quenched with water, the layers were separated and the aqueous phase was washed with CH_2Cl_2 . The combined organic layers were then dried over Na_2SO_4 and concentrated via a rotary evaporator to afford a yellow oil. The crude mixture was purified by Kugelrohr distillation (80 °C, 1 atm) to give a clear oil (3.07 g, 63%). Spectral data was consistent with that reported in the literature.

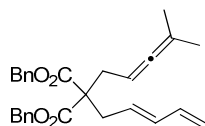
To a suspension of NaH (177 mg, 12.3 mmol, 1.2 equiv) in anhydrous DMSO (5 mL) and THF (50 mL) at 0 °C was added dropwise a solution of dimethyl malonate (2.98 g, 22.56 mmol, 2.2 equiv) in THF (5 mL). After 30 minutes at 0 °C, a solution of the dienyl chloride (1.00 g, 10.25 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water (50 mL), diluted with EtOAc (25 mL), the layers were separated and the water layer was washed with EtOAc (3x25 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude oil was purified by flash chromatography (EtOAc:hexanes 1:10) to afford the desired product.

To a solution of 4-methyl-2,3-pentadienol⁴¹ (371 mg, 3.78 mmol, 1.0 equiv), Et_3N (0.78 mL, 5.67 mmol, 1.5 equiv) and DMAP (45 mg, 0.37 mmol, 0.1 equiv) in 20 mL of CH_2Cl_2 at -40 °C was added dropwise methanesulfonyl chloride (0.45 mL, 5.67 mmol, 1.5 equiv). The reaction was stirred at -40 °C for one hour. The mixture was quenched with water (20 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in a rotary evaporator. The resulting oil was used without further purification.

To a stirred suspension of NaH (152 mg, 3.78 mmol, 1.5 equiv) in THF (10 mL) at 0 °C was added a solution of the previously prepared diene-malonate (500 mg, 2.52 mmol, 1.0 equiv) in THF (2 mL). After 30 minutes at 0 °C, the crude mesylate (1.5 equiv) dissolved in DMSO (1.5 mL) and NaI (566 mg, 3.78 mmol, 1.5 equiv) were sequentially added. The mixture was brought to room temperature and stirred for two hours. The reaction was quenched with saturated NaHCO_3 (15 mL), washed with EtOAc (3x10 mL), dried over MgSO_4 , and concentrated in a rotary evaporator. The resulting oil was purified by flash chromatography (EtOAc: hexanes, 1:15) to afford the desired allene-diene (52%).

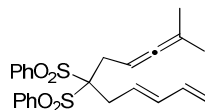


Dimethyl (4-methylpenta-2,3-dien-1-yl)[(2E)-penta-2,4-dien-1-yl]propanedioate (2.5). ¹H NMR (400 MHz, CDCl₃): δ 6.25 (dt, 1H, *J* = 17.2 Hz, 10.4 Hz), 6.05 (dd, 1H, *J* = 15.2, 10.4 Hz), 5.46 (dt, 1H, *J* = 17.2 Hz, 10.0 Hz), 5.08 (d, 1H, *J* = 17.2 Hz), 4.97 (d, 1H, *J* = 10.4 Hz), 4.77-4.67 (m, 1H), 3.66 (s, 6H), 2.68 (d, 2H, *J* = 7.6 Hz), 2.49 (d, 2H, *J* = 7.6 Hz), 1.61 (s, 3H), 1.60 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 203.7, 171.0, 136.6, 135.0, 127.9, 116.3, 95.1, 82.6, 58.0, 52.3, 35.4, 32.7, 32.6, 30.2, 20.4. HRMS (EI) calculated for C₁₆H₂₂O₄Na 301.1410, found 301.1416.



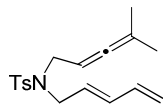
Dibenzyl (4-methylpenta-2,3-dien-1-yl)[(2E)-penta-2,4-dien-1-yl]propanedioate (2.33).

Prepared using dibenzyl malonate to yield the product as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.37 (m, 6H), 7.29-7.33 (m, 4H), 6.26 (dt, 1H, *J* = 16.8 Hz, 10.4 Hz), 6.06 (dd, 1H, *J* = 14.8 Hz, 10.4 Hz), 5.51 (dt, 1H, *J* = 14.8 Hz, 7.6 Hz), 5.03-5.23 (m, 6H), 4.80 (m, 1H), 2.81 (d, 2H, *J* = 8.0 Hz), 2.66 (d, 2H, *J* = 7.6 Hz), 1.74 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 203.9, 170.4, 141.8, 136.7, 135.5, 135.2, 128.6, 128.4, 128.3, 128.2, 116.5, 95.3, 82.6, 67.0, 58.2, 52.5, 35.4, 32.97, 20.6.



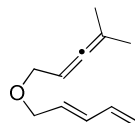
1,1'-(4-methylpenta-2,3-dien-1-yl)[(2E)-penta-2,4-dien-1-yl](bisphenyl)sulfonylmethane (2.29).

Prepared from bis(phenylsulfonyl) methane to yield the product (65%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, 4H, *J* = 7.6 Hz), 7.71 (t, 2H, *J* = 7.2 Hz), 7.59 (t, 4H, *J* = 7.8 Hz), 6.28 (dt, 1H, *J* = 17.2 Hz, 10 Hz), 6.10 (dd, 1H, *J* = 15.2 Hz, 10.4 Hz), 5.80 (dt, 1H, *J* = 15.2 Hz, 6.8 Hz), 5.25-5.10 (m, 1H), 5.20 (d, 1H, *J* = 17.2 Hz), 5.11 (d, 1H, *J* = 10.4 Hz), 3.12 (d, 2H, *J* = 6.4 Hz), 2.99 (d, 2H, *J* = 7.2 Hz), 1.69 (s, 3H), 1.68 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 204.4, 136.8, 136.3, 135.8, 134.5, 131.5, 128.4, 125.4, 117.2, 96.3, 90.7, 32.1, 29.8, 20.2. HRMS (FAB+H⁺): calculated for C₂₄H₂₆O₄S₂ 443.1351, found 443.1325.

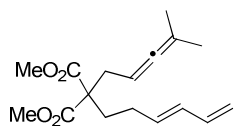


N,N'-(4-methylpenta-2,3-dien-1-yl)[(2E)-penta-2,4-dien-1-yl]-N-toluenesulfonamide (2.30).

Prepared by the method described by Wender to give the product (78%) as a clear oil.^{9a} ¹H NMR (400 MHz, CDCl₃): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.25 (dt, *J* = 17.2 Hz, 10 Hz, 1H), 6.10 (dd, 1H, *J* = 15.2 Hz, 10.4 Hz), 5.47 (dt, 1H, *J* = 15.2 Hz, 6.8 Hz), 5.26 (d, 1H, *J* = 15.8 Hz), 5.08 (d, 1H, *J* = 10.4 Hz), 4.71 (m, 1H), 3.89 (d, 2H, *J* = 6.7 Hz), 3.78 (d, 2H, *J* = 7.0 Hz), 2.41 (s, 3H), 1.64 (s, 3H), 1.63 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 203.3, 143.6, 137.6, 135.9, 134.6, 129.7, 127.9, 127.2, 117.9, 96.7, 84.2, 47.9, 46.6, 21.5, 20.3 (2C). HRMS (FAB+H⁺): calculated for C₁₈H₂₄NO₂S 318.1539, found 318.1535.

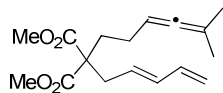


(3E)-5-[(4-methylpenta-2,3-dien-1-yl)oxy]penta-1,3-diene (2.31).⁴² To a stirred suspension of NaH (60% in mineral oil) (122 mg, 3.06 mmol, 1.1 equiv) in THF (9 mL) at 0 °C under N₂ atmosphere was added dropwise 4-methyl-2,3-pentadienol (273 mg, 2.78 mmol, 1 equiv) and 5-chloro-*E,E*-1,3-pentadiene (314 mg, 3.06 mmol, 1.1 equiv). The reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with ice and the organic and aqueous layers were separated. The water layer was washed with Et₂O (3 x 5 mL) and the combined organic layers were washed with brine (1 x 10 mL), dried over Mg₂SO₄ and concentrated by in vacuo. The crude mixture was purified by flash chromatography (1% EtOAc in hexanes) to yield a yellow oil (58%). Spectroscopic data were identical to previously reported values. ¹H NMR (400 MHz, CDCl₃): δ 6.41 (dt, 1H, *J* = 10.4 Hz, 10.0 Hz), 6.29 (dd, 1H, *J* = 15.2 Hz, 10.4 Hz), 5.81 (dt, 1H, *J* = 15.2 Hz, 6.0 Hz), 5.28 (d, 1H, *J* = 16.4 Hz), 5.15 (d, 1H, *J* = 9.2 Hz), 5.07-5.13 (m, 1H), 4.04 (d, 2H, *J* = 6.0 Hz), 4.01 (d, 2H, *J* = 6.4 Hz), 1.75 (s, 3H), 1.74 (s, 3H).



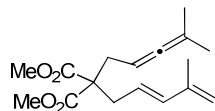
(E)-dimethyl 2-(hexa-3,5-dien-1-yl)-2-(4-methylpenta-2,3-dien-1-yl)malonate (2.43).

Prepared using dimethyl 2-(4-methylpenta-2,3-dien-1-yl)malonate and (*E*)-hexa-3,5-dien-1-ol to yield the product as a colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 6.28 (dt, 1H, *J* = 16.8 Hz, 10.4 Hz), 6.08 (dd, 1H, *J* = 15.2 Hz, 10.8 Hz), 5.51 (dt, 1H, *J* = 15.2 Hz, 7.6 Hz), 5.12 (d, 1H, *J* = 16.4 Hz), 5.01 (d, 1H, *J* = 10.0 Hz), 4.87-4.92 (m, 1H), 3.702 (s, 3H), 2.67 (d, 2H, *J* = 7.6 Hz), 1.90-1.96 (m, 2H), 1.82-1.88 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H).



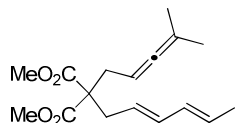
(E)-dimethyl 2-(5-methylhexa-4,3-dien-1-yl)-2-(penta-2,4-dien-1-yl)malonate (2.44).

Prepared using (*E*)-dimethyl 2-(penta-2,4-dien-1-yl)malonate and 5-methylhexa-3,4-dien-1-ol to yield the product as a colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 6.28 (dt, 1H, *J* = 17.2 Hz, 10.0 Hz), 6.05 (dd, 1H, *J* = 15.2 Hz, 10.0 Hz), 5.64 (dt, 1H, *J* = 15.6 Hz, 6.4 Hz), 5.09 (d, 1H, *J* = 16.8 Hz), 4.97 (d, 1H, *J* = 10.4 Hz), 4.70-4.77 (m, 1H), 3.71 (s, 3H), 2.56 (d, 2H, *J* = 5.2 Hz), 1.88-2.07 (m, 4H), 1.66 (s, 3H), 1.65 (s, 3H).

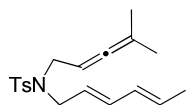


Dimethyl [(2E)-4-methylpenta-2,4-dien-1-yl](4-methylpenta-2,3-dien-1-yl)propanedioate (2.45).

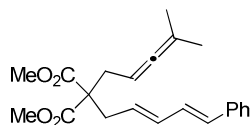
Prepared using dimethyl 2-(4-methylpenta-2,3-dienyl)malonate and (*E*)-5-bromo-2-methylpenta-1,3-diene to yield the product (84%) as a colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 6.10 (d, 1H, *J* = 15.5 Hz), 5.38 (dt, 1H, *J* = 15.5 Hz, 7.6 Hz), 4.82 (d, 1H, *J* = 6.5 Hz), 4.68-4.47 (m, 1H), 2.67 (d, 2H, *J* = 7.6 Hz), 2.48 (d, 2H, *J* = 7.6 Hz), 1.72 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 203.6, 171.1, 171.0, 141.4, 136.8, 123.5, 115.6, 94.9, 82.5, 58.0, 52.1, 35.5, 32.3, 20.3, 18.3.



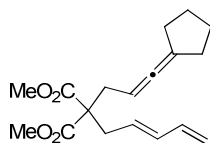
Dimethyl 2-((2E,4E)-hexa-2,4-dienyl)-2-(4-methylpenta-2,3-dienyl)malonate (2.50). Prepared using dimethyl 2-((2E,4E)-hexa-2,4-dienyl)malonate and (*E*)-5-bromo-2-methylpenta-1,3-diene to yield the product as a colorless oil. ^1H NMR (400 MHz, CDCl_3): 5.97 (apparent quintet, 2H, $J = 11.6$ Hz), 5.58 (dq, 1H, $J = 14.0$ Hz, 6.8 Hz), 5.32 (dt, 1H, $J = 14.4$ Hz, 7.6 Hz), 4.72-4.78 (m, 1H), 3.69 (s, 3H), 2.67 (d, 2H, $J = 7.6$ Hz), 2.52 (d, 2H, $J = 7.6$ Hz), 1.68 (d, 3H, $J = 8.0$ Hz), 1.64 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 203.8, 171.2, 134.6, 131.2, 128.6, 124.4, 95.1, 82.7, 58.1, 52.4, 35.5, 32.7, 20.5, 18.0.



***N,N'*-(4-methylpenta-2,3-dien-1-yl)[(2E,4E)-5-penta-2,4-dien-1-yl]-*N*-toluenesulfonamide (2.51).** Prepared by the method described by Wender to give the product (52%) as a white solid.^{9a} ^1H NMR (400 MHz, CDCl_3): δ 7.70 (d, 2H, $J = 8.0$ Hz), 7.29 (d, 2H, $J = 8.4$ Hz), 6.08-5.93 (m, 2H), 5.64 (dq, 1H, $J = 15.2$ Hz, 6.4 Hz), 5.31 (dt, 1H, $J = 15.2$ Hz, 6.8 Hz), 4.73-4.65 (m, 1H), 3.86 (d, 2H, $J = 6.8$ Hz), 3.76 (d, 2H, $J = 6.8$ Hz), 2.41 (s, 3H), 1.74 (d, 3H, $J = 6.8$ Hz), 1.64 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 203.2, 143.0, 137.7, 134.5, 134.1, 130.5, 126.8, 124.8, 124.3, 96.6, 84.2, 48.1, 46.3, 21.5, 20.3 (2C), 18.1. HRMS (FAB): calculated for $\text{C}_{19}\text{H}_{25}\text{NO}_2\text{S}$ 331.1606, found 331.1606.

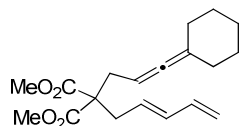


Dimethyl (4-methylpenta-2,3-dien-1-yl)[(2E, 4E)-5-phenylpenta-2,4-dien-1-yl]propanedioate (2.52). Prepared using dimethyl 2-((2E,4E)-5-phenylpenta-2,4-dienyl)malonate⁴³ and (*E*)-5-bromo-2-methylpenta-1,3-diene⁴⁴ to yield the product (28%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.38 (d, 2H, $J = 7.4$ Hz), 7.30 (t, 2H, $J = 7.6$ Hz), 7.21 (t, 1H, $J = 7.2$ Hz), 6.74 (dd, 1H, $J = 16$ Hz, 10 Hz), 6.47 (d, 1H, $J = 16$ Hz), 6.26 (dd, 1H, $J = 15$ Hz, 11 Hz), 5.64 (dt, 1H, $J = 15$ Hz, 7.6 Hz), 4.74-4.84 (m, 1H), 3.73 (6H, s), 2.80 (d, 2H, $J = 7.7$ Hz), 2.60 (d, 2H, $J = 7.6$ Hz), 1.68 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 203.8, 171.2, 137.3, 134.6, 131.4, 129.1, 128.7, 128.2, 127.5, 126.4, 95.2, 82.7, 58.2, 52.5, 35.9, 32.9, 20.5. HRMS (EI) calc for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{Na}$ 377.1723, found 377.1731.

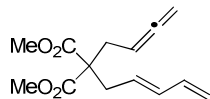


Dimethyl (3-cyclopentylideneprop-2-en-1-yl)[(2E)-penta-2,4-dien-1-yl]propanedioate (2.65). Prepared using using dimethyl 2-(4-methylpenta-2,3-dienyl)malonate and 3-cyclopentylideneprop-2-en-1-ol to yield the product as a clear oil. ^1H NMR (400 MHz, CDCl_3): δ 6.22 (dt, 1H, $J = 16.8$ Hz, 10.4 Hz), 6.04 (dd, 1H, $J = 15.2$ Hz, 10.4 Hz), 5.46 (dt, 1H, $J = 15.2$ Hz, 7.6 Hz), 5.05 (d, 1H, $J = 16.8$ Hz), 4.95 (d, 1H, $J = 10.4$ Hz), 4.79-4.96 (m, 1H), 3.65 (s,

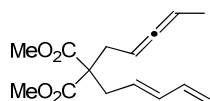
6H), 2.67 (d, 1H, $J = 7.6$ Hz), 2.51 (d, 1H, $J = 7.6$ Hz), 2.24-2.29 (m, 2H), 1.58-1.62 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 199.1, 171.0, 136.6, 134.9, 128.0, 116.6, 84.2, 74.8, 58.1, 52.5, 35.8, 32.1.



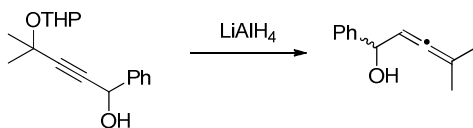
Dimethyl (3-cyclohexylideneprop-2-en-1-yl)[(2E)-penta-2,4-dien-1-yl]propanedioate (2.66). Prepared using using dimethyl 2-(4-methylpenta-2,3-dienyl)malonate and 3-cyclohexylideneprop-2-en-1-ol to yield the product (59%) as a clear oil.⁴⁵ ^1H NMR (400 MHz, CDCl_3): δ 6.26 (dt, 1H, $J = 17.2$ Hz, 10.4 Hz), 6.08 (dd, 1H, $J = 15.2$ Hz, 10.4 Hz), 5.50 (dt, 1H, $J = 15.2$ Hz, 7.6 Hz), 5.21 (d, 1H, $J = 17.2$ Hz), 5.00 (d, 1H, $J = 10$ Hz), 4.76 (m, 1H), 3.70 (s, 6H), 2.71 (d, 2H, $J = 7.6$ Hz), 2.55 (d, 2H, $J = 8.0$ Hz), 2.08-2.03 (m, 4H), 1.59-1.51 (m, 4H), 1.50-1.45 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 200.4, 171.1, 136.6, 134.9, 128.0, 116.3, 102.3, 82.3, 58.0, 52.3 (2C), 35.3, 33.0, 31.4 (2C), 27.1 (2C), 25.9. HRMS (FAB+ H^+): calculated for $\text{C}_{19}\text{H}_{27}\text{O}_4$ 319.1909, found 319.1904.



(E)-dimethyl 2-(buta-2,3-dien-1-yl)-2-(penta-2,4-dien-1-yl)malonate (2.73). Prepared from (E)-dimethyl 2-(penta-2,4-dien-1-yl)malonate and buta-2,3-dien-1-ol to yield the product as a clear oil (50%). ^1H NMR (400 MHz, CDCl_3): δ 6.28 (dt, 1H, $J = 17.2$ Hz, 10.0 Hz), 6.09 (dd, 1H, $J = 14.8$ Hz, 10.4 Hz), 5.50 (dt, 1H, $J = 14.8$ Hz, 7.6 Hz), 5.12 (d, 1H, $J = 16.8$ Hz), 5.02 (tt, 1H, $J = 8.0$ Hz, 6.8 Hz), 4.67 (tt, 1H, $J = 6.8$ Hz, 2.4 Hz), 3.72 (s, 6H), 2.71 (d, 2H, $J = 7.6$ Hz), 2.59 (dt, 2H, $J = 8.0$ Hz, 2.4 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 210.1, 171.1, 136.7, 135.3, 127.7, 116.5, 85.6, 84.1, 58.0, 52.4, 35.6, 32.5, 14.3.

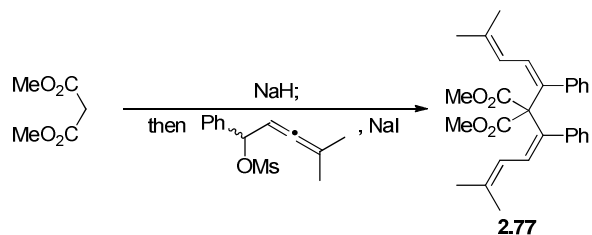


(E)-dimethyl 2-(penta-2,3-dienyl)-2-(penta-2,4-dienyl)malonate (2.74). Prepared from (E)-dimethyl 2-(penta-2,4-dien-1-yl)malonate and penta-2,3-dien-1-ol to a clear oil. ^1H NMR (400 MHz, CDCl_3): δ 6.26 (dt, 1H, $J = 16.8$ Hz, 10.4 Hz), 6.08 (dd, 1H, $J = 15.2$ Hz, 11.2 Hz), 5.49 (dt, 1H, $J = 15.2$ Hz, 7.6 Hz), 5.10 (d, 1H, $J = 16.8$ Hz), 5.04 (tt, 1H, $J = 6.8$ Hz, 2.4 Hz), 5.00 (d, 1H, $J = 9.2$ Hz), 4.81-4.89 (m, 1H), 3.70 (s, 6H), 2.70 (d, 2H, $J = 7.6$ Hz), 2.13 (dd, 2H, $J = 14.2$ Hz, 2.0 Hz), 1.61 (dd, 3H, $J = 6.8$ Hz, 2.8 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 206.6, 171.0, 136.6, 135.1, 127.8, 116.5, 85.6, 84.1, 58.0, 52.4, 35.6, 32.5, 14.3.

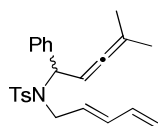


4-methyl-1-phenylpenta-2,3-dien-1-ol (2.78). To a stirred suspension of LiAlH_4 (208.7 mg, 5.5 mmol, 1.1 equiv) in Et_2O (25 mL) at 0°C was added dropwise by syringe a solution of the alkyne in Et_2O (5 mL) by canula over five minutes. The reaction stirred at this temperature for three

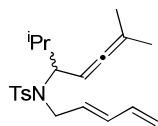
hours. The reaction was quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ and was allowed to stir for two hours at room temperature. The salts were removed by gravity filtration; the salts were washed with Et_2O (2 x 5 mL) and the resulting filtrate was concentrated by rotary evaporator. The crude isolate indicated both the presence of the desired product and undesired THP protected alkene. The product was isolated as a 1:1 mixture of diastereomers from the crude mixture as a clear oil (368 mg, 42%) by silica gel chromatography (20% EtOAc in hexanes, followed by 30% EtOAc in hexanes). ^1H NMR (400 MHz, CDCl_3): δ 7.36-7.43 (m, 4H), 7.27-7.32 (m, 1H), 5.26-5.32 (m, 1H), 5.20 (d, 1H, $J = 6.0$ Hz), 2.53 (d, 1H, $J = 12.0$ Hz), 1.77 (d, 3H, $J = 2.8$ Hz), 1.75 (d, 3H, $J = 3.2$ Hz).



Dimethyl 2,2-bis((Z)-4-methyl-1-phenylpenta-1,3-dien-1-yl)malonate (2.77). Prepared from dimethyl malonate and 4-methyl-1-phenylpenta-2,3-dien-1-ol to give the bisalkylated product as a clear oil. ^1H NMR (400 MHz, CDCl_3): δ 7.437 (d, 4H, $J = 7.6$ Hz), 7.343 (t, 4H, $J = 7.6$ Hz), 7.264 (t, 2H, $J = 7.6$ Hz), 6.956 (d, 2H, $J = 15.6$ Hz), 6.797 (d, 2H, $J = 16.0$ Hz), 3.202 (s, 6H), 1.980 (s, 6H), 1.965 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 140.7, 136.5, 129.3, 128.9, 128.7, 128.0, 126.6, 119.4, 39.4, 20.3, 19.6.

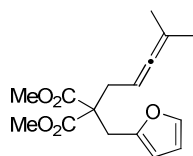


***N,N'*-(4-methyl-1-phenylpenta-2,3-dienyl)(penta-2,4-dienyl)-*N*-toluenesulfonamide (2.80).** Prepared by the method described by Wender to give the product as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, 2H, $J = 8.4$ Hz), 7.25-7.37 (m, 7H), 6.06 (dt, 1H, $J = 17.2$ Hz, 10.0 Hz), 5.87 (dd, 1H, $J = 15.2$ Hz, 10.4 Hz), 5.73 (d, 1H, $J = 6.8$ Hz), 5.27 (dt, 1H, $J = 15.2$ Hz, 6.8 Hz), 5.18-5.21 (m, 1H), 5.06 (d, 1H, $J = 16.8$ Hz), 4.99 (d, 1H, $J = 10.4$ Hz), 3.87 (dd, 1H, $J = 16.4$ Hz, 6.8 Hz), 3.76 (dd, 1H, $J = 16.4$ Hz, 6.4 Hz), 2.42 (s, 3H), 1.62 (t, 6H, $J = 3.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 202.8, 142.8, 139.1, 138.6, 136.0, 133.2, 130.2, 129.4, 128.2 (two peaks), 127.6, 127.5, 117.2, 98.0, 87.7, 60.8, 46.7, 21.5, 20.1.

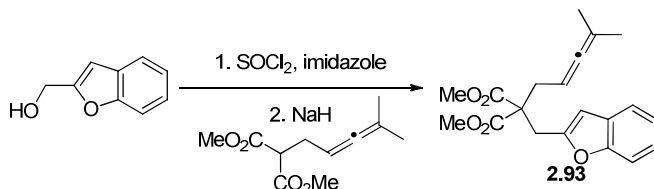


***N,N'*-(1,6-dimethylhepta-4,5-dienyl)(penta-2,4-dienyl)-*N*-toluenesulfonamide (2.81).** Prepared by the method described by Wender to give the product (78%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.67 (d, 2H, $J = 8.0$ Hz), 7.22 (d, 2H, $J = 8.0$ Hz), 6.22 (dt, 1H, $J = 17.2$ Hz, 10.0 Hz), 6.08 (dd, 1H, $J = 15.2$ Hz, 10.8 Hz), 5.65 (dt, 1H, $J = 15.2$ Hz, 6.8 Hz), 5.13 (d, 1H, $J = 16.8$ Hz), 5.04 (d, 1H, $J = 10.0$ Hz), 4.68-4.79 (m, 1H), 3.95 (dd, 1H, $J = 10.4$ Hz, 7.2 Hz), 3.81 (dd, 1H, $J = 16.0$ Hz, 5.6 Hz), 3.75 (dd, 1H, $J = 16.0$ Hz, 8.0 Hz), 2.39 (s, 3H), 1.73-1.84 (m, 1H), 1.62 (d, 3H, $J = 2.8$ Hz), 1.56 (d, 3H, $J = 2.8$ Hz), 0.98 (d, 3H, $J = 6.8$ Hz),

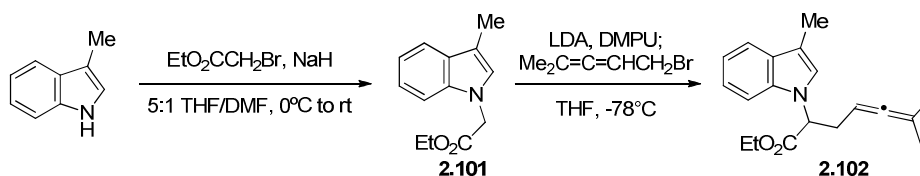
0.92 (d, 3H, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 202.9, 142.8, 138.6, 136.1, 133.2, 131.0, 129.4, 127.4, 117.4, 96.8, 87.2, 64.8, 46.1, 30.6, 21.5, 20.7, 20.3, 20.2, 19.9.



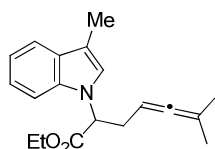
Dimethyl (furan-2-ylmethyl)(4-methylpenta-2,3-dien-1-yl)propanedioate (2.84). Prepared using dimethyl (furan-2-ylmethyl)propanedioate to yield the product (31%) as a clear oil.⁴⁶ ^1H NMR (400 MHz, CDCl_3): δ 7.28 (m, 1H), 6.27 (dd, 1H, $J = 2.8$ Hz, 1.6 Hz), 6.05 (d, 1H, $J = 3.2$ Hz), 4.85 (m, 1H), 3.74 (s, 6H), 3.34 (s, 2H), 2.49 (d, 2H, $J = 7.6$ Hz), 1.68 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 203.8, 170.7, 150.5, 141.8, 110.1, 108.2, 95.1, 82.5, 57.7, 52.4, 32.2, 30.6, 20.4. HRMS (EI^+): calculated for $\text{C}_{16}\text{H}_{20}\text{O}_5$ 292.1311, found 292.1304.



Dimethyl (1-benzofuran-2-ylmethyl)(4-methylpenta-2,3-dien-1-yl)propanedioate (2.93). To a stirred suspension of imidazole (149 mg, 2.19 mmol, 1.25 equiv) and thionyl chloride (414 mg, 2.19 mmol, 1.25 equiv) at 0°C in CH_2Cl_2 (20 mL) was added by canula a solution of 2-hydroxymethylbenzofuran (260 mg, 1.75 mmol, 1.0 equiv).⁴⁷ The reaction mixture stirred 30 min. The reaction mixture was then quenched with water (1 x 2 mL); the layers were separated, and the aqueous layer was extracted once with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and concentrated to yield the crude 2-chloromethylbenzofuran. To a stirred suspension of NaH (60% in mineral oil) (88 mg, 2.19 mmol, 1.5 equiv) in DMF (0.7 mL) at 0°C was added a solution of dimethyl 2-(4-methylpenta-2,3-dienyl)malonate (310 mg, 1.46 mmol, 1.0 equiv) in DMF (0.5 mL). After 15 min, a solution of 2-chloromethylbenzofuran in DMF (1 mL) was added dropwise by syringe followed by NaI (262 mg, 1.75 mmol, 1.2 equiv) in one portion. The reaction stirred overnight, warming to room temperature. The reaction mixture was quenched with water (2 mL) and the resulting slurry was extracted with Et_2O (3 x 2 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (3 x 3 mL), brine (1 x 3 mL), dried over MgSO_4 and concentrated. The product was isolated as a clear oil (244 mg, 0.713 mmol, 49%) by silica gel chromatography (5% EtOAc in hexanes). ^1H NMR (400 MHz, CDCl_3): δ 7.49 (d, 1H, $J = 8.0$ Hz), 7.38 (d, 1H, $J = 8.4$ Hz), 7.16-7.23 (m, 2H), 6.47 (s, 1H), 4.89-4.95 (m, 1H), 3.78 (s, 6H), 3.53 (s, 2H), 2.60 (d, 2H, $J = 7.6$ Hz), 1.72 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 204.0, 170.7, 154.8, 153.8, 128.4, 123.7, 122.6, 120.5, 110.8, 105.3, 95.4, 82.6, 57.7, 52.7, 32.4, 31.2, 20.5.



Ethyl (3-methyl-1H-indol-1-yl)acetate (2.101).⁴⁸ To a solution of NaH (60% in mineral oil) (0.976 g, 24.4 mmol, 3.2 equiv) in 4:1 THF/DMF (75 mL) at 0°C was added a solution of 3-methylindole (1.0 g, 7.62 mmol, 1.0 equiv) in THF (10 mL). After stirring for 45 min, ethyl bromoacetate (4.08 g, 24.4 mmol, 3.2 equiv) was added dropwise by syringe. The reaction mixture turned bright yellow as it was warmed to room temperature. The reaction was allowed to stir overnight, at which time the reaction mixture was quenched by pouring over a separatory funnel with an ice/H₂O mixture. The products were extracted with Et₂O (1 x 100 mL). The organic layer was then washed with H₂O (1 x 50 mL), dried over Na₂SO₄, and concentrated. The product was isolated as a yellow oil (1.36 g, 6.27 mmol, 82%) by silica gel chromatography (25% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, 1H, *J* = 6.4 Hz), 7.26-7.32 (m, 2H), 7.22 (ddd, 1H, *J* = 6.4 Hz, 4.8 Hz, 1.2 Hz), 6.91 (d, 1H, *J* = 0.8 Hz), 4.81 (s, 2H), 4.27 (q, 2H, *J* = 5.7 Hz), 2.42 (s, 3H), 1.33 (t, 3H, *J* = 5.8 Hz).



Ethyl 6-methyl-2-(3-methyl-1H-indol-1-yl)hepta-4,5-dienoate (2.102). To a stirred solution of DIPA (75 mg, 0.745 mmol, 1.2 equiv) and n-BuLi (2.5 M in hexanes) (0.27 mL, 0.683 mmol, 1.1 equiv) in THF (3 mL) at -78°C was added a solution of **2.101** (130 mg, 0.621 mmol, 1.0 equiv) in THF (3.5 mL). This mixture stirred 1 h at -78°C; DMPU (87.5 mg, 0.683 mmol, 1.1 equiv) was then added. After five minutes, a solution of the bromide (100 mg, 0.621 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise by syringe. The reaction mixture stirred 2 h at -78°C; the reaction mixture was then warmed to -10°C and stirred an additional 90 min. The reaction mixture was then quenched with saturated aqueous NaHCO₃ (5 mL) and the resulting biphasic solution was extracted with Et₂O (1 x 10 mL). The organic layer was then washed with brine (1 x 5 mL), dried over MgSO₄ and concentrated. The product was isolated as a yellow oil (61 mg, 0.204 mmol, 33%) by silica gel chromatography (5% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.57 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 7.5 Hz), 7.13 (t, 1H, *J* = 7.3 Hz), 7.08 (s, 1H), 5.04 (dd, 1H, *J* = 9.0 Hz, 6.5 Hz), 4.86-4.92 (m, 1H), 4.14-4.21 (m, 2H), 2.90 (dt, 1H, *J* = 15.0 Hz, 6.3 Hz), 2.77 (ddd, 1H, *J* = 15.3 Hz, 9.0 Hz, 6.5 Hz), 2.35 (s, 3H), 4.81 (s, 2H), 4.27 (q, 2H, *J* = 5.7 Hz), 2.42 (s, 3H), 1.52 (d, 3H, *J* = 2.5 Hz), 1.43 (d, 3H, *J* = 2.5 Hz), 1.24 (t, 3H, *J* = 7.0 Hz). ¹³C NMR (100 MHz, CDCl₃): 202.6, 170.6, 136.8, 128.9, 122.9, 121.5, 119.0, 111.4, 109.0, 96.9, 83.8, 61.5, 57.6, 31.7, 20.2, 20.1, 14.1, 9.7.

3. Au(I)-catalyzed rearrangements of diene-allenes

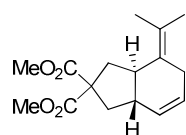
Method A: To a small vial was added AgSbF₆ (0.005 mmol, 0.05 equiv) and tris(2,4-di-*t*-butylphenyl)phosphitegold(I) chloride (**2.15**) (0.005 mmol, 0.05 equiv) in CH₂Cl₂ (0.2 mL). The mixture was stirred for five minutes at room temperature, and then the suspension was filtered

through glass fiber and added to a solution of the corresponding allene-diene (0.1 mmol, 1.0 equiv) in CH₂Cl₂ (0.8 mL). The reaction mixture was stirred for 30 minutes at room temperature, then filtered through a short pad of silica and washed with CH₂Cl₂. Solvent was removed in a rotary evaporator and the corresponding cycloadduct was isolated by flash chromatography.

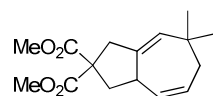
Method B: To a small vial was added AgSbF₆ (0.005 mmol, 0.05 equiv) and di-*t*-butylbiphenylphosphinegold(I) chloride (**2.14**) (0.005 mmol, 0.05 equiv) in CH₂Cl₂ (0.2 mL). The mixture was stirred for five minutes at room temperature, and then the suspension was filtered through glass fiber and added to a solution of the corresponding allene-diene (0.1 mmol, 1.0 equiv) in CH₂Cl₂ (0.8 mL). The reaction mixture was stirred for 30 minutes at room temperature, then filtered through a short pad of silica and washed with CH₂Cl₂. Solvent was removed in a rotary evaporator and the corresponding cycloadduct was isolated by flash chromatography.

Method C: To a small vial was added AgSbF₆ (0.005 mmol, 0.05 equiv) and triphenylphosphinegold(I) chloride (0.005 mmol, 0.05 equiv) in CH₂Cl₂ (0.2 mL). The mixture was stirred for five minutes at room temperature, and then the suspension was filtered through glass fiber and added to a solution of the corresponding allene-diene (0.1 mmol, 1.0 equiv) in CH₂Cl₂ (0.8 mL). The reaction mixture was stirred for 30 minutes at room temperature, then filtered through a short pad of silica and washed with CH₂Cl₂. Solvent was removed in a rotary evaporator and the corresponding cycloadduct was isolated by flash chromatography.

Method D: To a small vial was added AgSbF₆ (0.005 mmol, 0.05 equiv) and IPrgold(I) chloride (**2.13**) (0.005 mmol, 0.05 equiv) in CH₂Cl₂ (0.2 mL). The mixture was stirred for five minutes at room temperature, and then the suspension was filtered through glass fiber and added to a solution of the corresponding allene-diene (0.1 mmol, 1.0 equiv) in CH₂Cl₂ (0.8 mL). The reaction mixture was stirred for 30 minutes at room temperature, then filtered through a short pad of silica and washed with CH₂Cl₂. Solvent was removed in a rotary evaporator and the corresponding cycloadduct was isolated by flash chromatography.

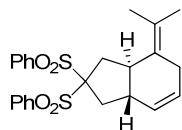


2.6. Prepared from **2.5** using method A to give the product (89%) as a clear oil. ¹H NMR (400 MHz, CDCl₃): δ 5.85 (broad d, 1H, *J* = 9.6 Hz), 5.75-5.71 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.00 (dd, 1H, *J* = 19.2 Hz, 11.6 Hz), 2.86 (d, 1H, *J* = 20.0 Hz), 2.73 (broad d, 1H, *J* = 20.0 Hz), 2.66 (dd, 1H, *J* = 13.2 Hz, 6.8 Hz), 2.20-2.15 (m, 2H), 1.81 (s, 3H), 1.64 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 173.2, 173.0, 129.1, 127.9, 123.9, 121.7, 58.4, 52.8 (2C), 48.1, 44.2, 39.7, 37.4, 31.8, 21.9, 21.8. HRMS (EI⁺): calculated for C₁₆H₂₂O₄ 278.1518, found 278.1514.

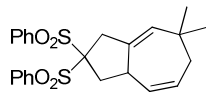


2.7. Prepared from **2.5** using method B to yield the product (85%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.69 (broad s, 2H), 5.16 (broad s, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.54 (m,

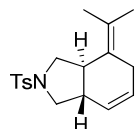
1H), 2.98 (d, 1H, $J = 16.4$ Hz, 1H), 2.89 (dt, 1H, $J = 16.4$ Hz, 2.4 Hz), 2.60 (dd, 1H, $J = 12.4$ Hz, 8.4 Hz), 2.50 (dd, 1H, $J = 12.4$ Hz, 4.8 Hz), 2.07 (t, 1H, $J = 11.6$ Hz), 1.86 (m, 1H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.3, 172.1, 136.6, 135.0, 132.5, 129.1, 58.3, 52.8, 52.7, 41.9, 41.0, 39.1, 39.0, 34.3, 31.6, 28.7. HRMS (EI+) calc. for $\text{C}_{16}\text{H}_{22}\text{O}_4$ 278.1518, found 278.1514.



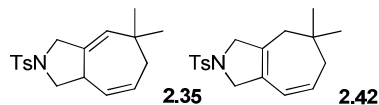
2.34. Prepared from **2.29** by method A to give the product (86%) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 8.09 (dd, $J = 7.2$ Hz, 5.2 Hz, 4H), 7.72 (m, 2H), 7.62-7.59 (m, 4H), 5.83 (broad d, 1H, $J = 9.6$ Hz), 5.76-5.71 (m, 1H), 3.02 (dd, 1H, $J = 14.4$ Hz, 5.6 Hz), 2.82 (d, 1H, $J = 20.4$ Hz), 2.75-2.61 (m, 3H), 2.37-2.27 (m, 2H), 2.14 (dd, 1H, $J = 14.0$ Hz, 12.0 Hz), 1.69 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 136.5, 136.4, 134.6, 134.5, 131.5, 128.7, 128.6, 128.5, 128.0, 127.3, 124.3, 47.4, 43.7, 37.0, 35.2, 31.4, 22.0, 21.8. HRMS (FAB + H^+): calculated for $\text{C}_{24}\text{H}_{26}\text{O}_4\text{S}_2$ 443.1351, found 443.1345.



2.38. Prepared from **2.29** by method D to give the product (80%) as a 2:1 mixture with **xx**. The peak assignments below correspond to the product drawn above. ^1H NMR (400 MHz, CDCl_3): δ 5.64-5.58 (m, 1H), 5.68 (d, 1H, $J = 10$ Hz), 5.04 (broad s, 1H), 3.62-3.70 (m, 1H), 3.30 (d, 1H, $J = 18$ Hz), 3.21 (d, 1H, $J = 18$ Hz), 2.84 (dd, 1H, $J = 15$ Hz, 9.2 Hz), 2.60 (dd, 1H, $J = 15$ Hz, 11 Hz), 2.30-2.40 (m, 1H), 1.81 (dd, 1H, $J = 14$ Hz, 6.6 Hz), 0.95 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 136.9, 136.5, 134.6, 134.5, 133.5, 131.5, 131.2, 131.0, 128.7, 124.3, 92.0, 90.1, 47.3, 43.6, 39.8, 39.7, 38.9, 38.5, 35.2, 31.4, 28.4, 21.9, 21.8. HRMS (FAB): calc for $\text{C}_{24}\text{H}_{27}\text{O}_4\text{S}_2$ 443.1314, found 443.1351. R_f : 0.40 (20% EtOAc in hexanes).

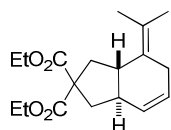


2.35. Prepared by from **2.30** using method A to give the product (83%) as a colorless oil. ^1H NMR (400 MHz, C_6D_6): δ 7.86 (d, 2H, $J = 8.4$ Hz), 6.85 (d, 2H, $J = 8.4$ Hz), 5.51 (broad s, 2H), 4.12 (dd, 1H, $J = 9.2$ Hz, 6.0 Hz), 3.66 (dd, 1H, $J = 9.2$ Hz, 7.6 Hz), 3.43 (dd, 1H, $J = 11.2$ Hz, 9.2 Hz), 2.89 (dd, 1H, $J = 11.2$ Hz, 9.2 Hz), 2.54 (d, 1H, $J = 20.4$ Hz), 2.38 (d, 1H, $J = 20.4$ Hz), 2.01 (m, 2H), 1.93 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 142.4, 135.9, 129.4, 129.3, 128.4, 125.7, 125.2, 124.2, 52.1, 50.4, 46.7, 42.7, 30.9, 21.2, 21.0, 20.7. HRMS (FAB): calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_2\text{S}$ 318.1528, found 318.1525.

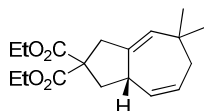


2.35+2.42. Prepared from **2.30** using method B to yield the product (83%) as a colorless oil. In this case, partial isomerization to a conjugated diene (86:14 ratio in favor of the non-conjugated product) was detected in the crude reaction mixture regardless of the catalyst employed. Major

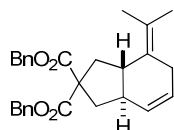
isomer **2.35**: ^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, 2H, $J = 8.0$ Hz), 7.34 (d, 2H, $J = 8.0$ Hz), 5.74 (m, 1H), 5.57 (dt, 1H, $J = 10.4$ Hz, 2.4 Hz), 5.16 (broad s, 1H), 3.94 (d, 1H, $J = 13.2$ Hz), 3.77 (t, 1H, $J = 8.8$ Hz), 3.64 (m, 1H), 3.52 (dt, 1H, $J = 13.2$ Hz, 2.0 Hz), 2.76 (t, 1H, $J = 9.6$ Hz), 2.44 (s, 3H), 2.51-2.40 (m, 1H), 1.89 (dd, 1H, $J = 13.6$ Hz, 7.2), 0.99 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.5, 133.6, 132.5, 131.3, 130.2, 129.7, 128.0, 127.4, 54.0, 53.6, 39.5, 39.1, 34.2, 31.4, 28.3, 21.6. HRMS (FAB): calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_2\text{S}$ 318.1528, found 318.1526. Minor isomer **2.42**, diagnostic peaks: ^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, 2H, $J = 7.6$ Hz), 7.34 (d, 2H, $J = 7.6$ Hz), 5.74 (dd, 1H, $J = 9.4$ Hz, 3.2 Hz), 5.42 (ddd, 1H, $J = 9.4$ Hz, 7.6 Hz, 1.6 Hz), 3.59 (d, 1H, $J = 8.8$ Hz), 3.52 (d, 1H, $J = 9.2$ Hz), 3.08 (dd, 1H, $J = 9.6$ Hz, 4.4 Hz), 3.05 (d, 1H, $J = 9.2$ Hz), 1.69 (ddd, 1H, $J = 17.2$ Hz, 6.4 Hz, 1.6 Hz), 1.44 (s, 3H), 1.02 (s, 3H), 0.97 (m, 1H), 0.85 (s, 3H).



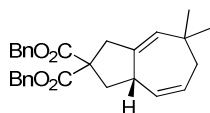
2.36. Prepared from (*E*)-diethyl 2-(4-methylpenta-2,3-dien-1-yl)-2-(penta-2,4-dien-1-yl)malonate (**2.32**)⁴⁹ using method C to give the product (76%) as a clear oil. ^1H NMR (400 MHz, CDCl_3): δ 5.850 (m, 1H, $J = 9.2$ Hz), 5.67-5.76 (m, 1H), 4.12-4.25 (m, 4H), 2.898 (dd, 1H, $J = 19.2$, 12.0 Hz), 2.82-2.99 (m, 1H), 2.792 (broad d, 1H, $J = 25.2$ Hz), 2.55-2.73 (m, 1H), 2.16-2.23 (m, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.20-1.27 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.8, 135.2, 129.2, 128.0, 127.9, 123.8, 61.4, 58.5, 48.1, 44.2, 39.6, 38.9, 37.3, 31.5, 21.9, 21.8, 14.0.



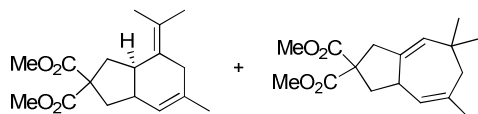
2.40. Prepared from (*E*)-diethyl 2-(4-methylpenta-2,3-dien-1-yl)-2-(penta-2,4-dien-1-yl)malonate using method D to give the product (48%) as a colorless oil.⁸ ^1H NMR (400 MHz, CDCl_3): δ 5.70-5.73 (m, 2H), 5.16-5.19 (m, 1H), 4.14-4.23 (m, 4H), 3.554 (t, 1H, $J = 9.2$ Hz), 2.95 (d, 1H, $J = 16.4$ Hz), 2.87 (d, 1H, $J = 16.4$ Hz), 2.58 (dd, 1H, $J = 12.8$ Hz, 8.4 Hz), 2.50 (m, 1H), 2.07 (dd, 1H, $J = 12.4$ Hz, 11.6 Hz), 1.84-1.89 (m, 1H), 1.20-1.27 (m, 6H), 1.00 (s, 3H), 0.95 (s, 3H).



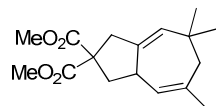
2.37. Prepared from **2.33** using method C to give the product (64%) as a 2:1 mixture with **2.41**. ^1H NMR (400 MHz, CDCl_3): δ 7.27-7.35 (m, 6H), 7.21-7.26 (m, 4H), 5.83 (m, 2H, $J = 10$ Hz), 5.70-5.75 (m, 1H), 5.05-5.12 (m, 4H), 3.01 (d, 1H, $J = 8.0$ Hz), 2.85 (broad d, 2H, $J = 22$ Hz), 2.73 (broad d, 2H, $J = 22$ Hz), 2.60-2.79 (m, 2H), 2.53 (d, 1H, $J = 14$ Hz), 2.16-2.23 (m, 2H), 1.77 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.4, 135.5, 132.5, 129.1, 128.5, 128.2, 127.9, 123.9, 67.1, 58.5, 48.1, 44.2, 39.6, 37.3, 31.5, 29.7, 21.8. R_f : 0.70 (20% EtOAc in hexanes).



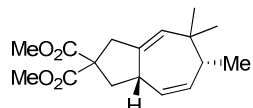
2.41. Prepared from **2.33** using method D above to yield the product (64%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.35 (m, 6H), 7.21-7.27 (m, 4H), 5.71 (m, 2H), 5.16-5.19 (m, 1H), 5.15 (d, 2H, $J = 3.6$ Hz), 5.12 (d, 2H, $J = 3.2$ Hz), 3.57 (t, 1H, $J = 9.2$ Hz), 3.02 (d, 2H, $J = 16.4$ Hz), 2.92 (d, 2H, $J = 16.4$ Hz), 2.45-2.55 (m, 1H), 2.13 (at, 1H, $J = 11.8$ Hz), 1.84-1.89 (m, 1H), 1.01 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 171.4, 171.2, 136.6, 135.5, 135.4, 135.1, 132.5, 128.9, 128.5, 128.2, 127.9, 127.8, 67.1, 58.5, 41.9, 40.9, 39.0, 38.9, 34.2, 31.5, 29.7, 28.6.



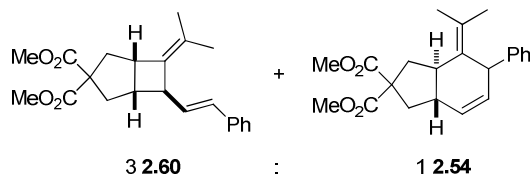
2.46. Prepared from **2.45** using method B to give the above mixture of products (92% combined yield) as a colorless oil. This example was isolated as a 81:19 inseparable mixture of the [4 + 2] adduct **2.46** and [4 + 3] adduct **2.47**, respectively. The following assignments correspond to the major isomer. ^1H NMR (CDCl_3 , 400 MHz): δ 5.51 (s, 1H), 3.71 (s, 6H), 2.98-2.88 (m, 1H), 2.65 (s, 1H), 2.62-2.55 (m, 3H), 2.08 (m, 3H), 1.76 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 173.2 (2C), 135.5, 128.0, 123.4, 123.2, 58.5, 52.7, 52.6, 48.2, 44.6, 39.6, 37.7, 36.7, 22.7, 21.8, 21.7. HRMS (EI): calculated for $\text{C}_{17}\text{H}_{24}\text{O}_4$ 292.1675, found 292.1673.



2.47. Prepared from **2.45** using method B to yield the product (81%) as a colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 5.41 (s, 1H), 5.01 (s, 1H), 3.71 (d, 6H, $J = 11.5$ Hz), 3.71-3.68 (m, 1H), 3.42 (t, 1H, $J = 9.6$ Hz), 2.94 (d, 1H, $J = 17.0$ Hz), 2.86 (d, 1H, $J = 16.0$ Hz), 2.65 (d, 1H, $J = 12.5$ Hz), 2.57 (dd, 1H, $J = 13.5$ Hz, 8.7 Hz), 2.02 (t, 1H, $J = 12.5$ Hz), 1.71 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 172.1, 172.0, 137.1, 136.7, 58.2, 52.6, 44.1, 41.6, 41.1, 38.6, 34.0, 32.0, 28.2, 26.0. HRMS (EI) calculated for $\text{C}_{17}\text{H}_{24}\text{O}_4$ 292.1675, found 292.1669.

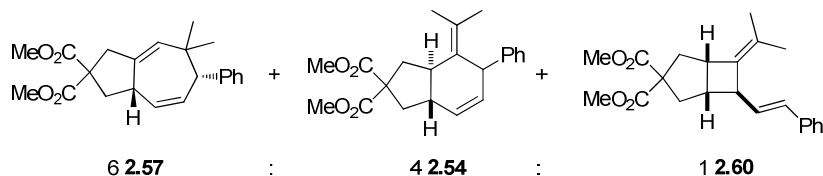


2.56. Prepared from **2.50** using method D to yield the product (84%) as a colorless oil. ^1H NMR (CDCl_3 , 400 MHz): δ 5.62 (d, 1H, $J = 10.0$ Hz), 5.36 (ddq, 1H, $J = 10.0$ Hz, 6.8 Hz, 2.8 Hz), 5.14 (d, 1H, $J = 2.0$ Hz), 3.74 (s, 3H), 3.71 (s, 3H), 3.50 (m, 1H), 2.98 (d, 1H, $J = 16.8$ Hz), 2.89 (d, 1H, $J = 16.4$ Hz), 2.59 (dd, 1H, $J = 13.4$ Hz, 7.8 Hz), 2.07 (apparent t, 1H, $J = 11.8$ Hz), 0.99 (s, 3H), 0.98 (d, 3H, $J = 8.0$ Hz), 0.86 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 172.3, 172.1, 136.8, 134.7, 133.7, 132.5, 58.2, 52.8, 42.1, 41.1, 40.2, 36.8, 29.0, 23.5, 16.3. HRMS (EI) calculated for $\text{C}_{17}\text{H}_{24}\text{O}_4$ 292.1675, found 292.1669.

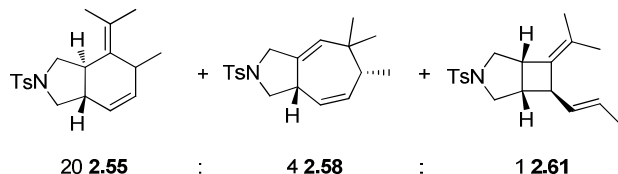


2.60, 2.54. Prepared from **2.50** using method C to give the product (71%) as a 3:1 mixture. The assignments for the major isomer are listed below. ^1H NMR (400 MHz, CDCl_3): δ 7.35 (d, 1H, J

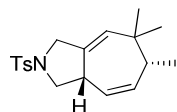
= 7.6 Hz), 7.22-7.31 (d, 2H, m), 7.18 (t, 1H, $J = 7.3$ Hz), 6.33 (d, 1H, $J = 15.6$ Hz), 6.25 (dd, 1H, $J = 15.8$ Hz, 7.4 Hz), 3.73 (s, 3H), 3.69 (s, 3H), 3.50 (m, 1H), 3.29 (m, 1H), 2.68 (t, 2H, $J = 13.2$), 2.32 (dd, 1H, $J = 13.2$ Hz, 7.6 Hz), 2.21 (dd, 1H, $J = 13.4$ Hz, 8.8 Hz), 1.57 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.9, 171.9, 144.6, 137.7, 133.2, 132.3, 131.1, 129.8, 129.9, 128.0, 127.5, 62.5, 52.8, 52.7, 49.5, 45.0, 43.7, 41.4, 39.7, 39.0, 19.0, 18.6. HRMS (EI+) calc. for $\text{C}_{22}\text{H}_{26}\text{O}_4$ 354.1831, found 354.1834.



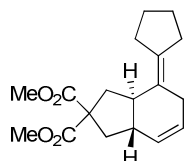
2.57, 2.54, 2.60. Prepared from **2.51** using method D to give the product (71%) as a 4:6:1 mixture of the compounds shown above. The assignments for the major isomer as listed below. ^1H NMR (400 MHz, CDCl_3): δ 7.2-7.3 (m, 5H), 5.82 (dd, 1H, $J = 11$ Hz, 7.6 Hz), 5.73 (d, 1H, $J = 11$ Hz), 5.20 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.60-3.66 (m, 2H), 3.08 (d, 1H, $J = 17$ Hz), 3.01 (d, 1H, $J = 17$ Hz), 2.17 (t, 1H, $J = 12$ Hz), 0.94 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.2, 172.0, 142.3, 133.3, 132.7, 131.7, 131.4, 129.9, 128.3, 127.7, 126.2, 58.4, 58.0, 54.2, 52.8, 41.9, 41.2, 39.6, 37.6, 31.0, 21.9. HRMS (EI+) calc. for $\text{C}_{22}\text{H}_{26}\text{O}_4$ 354.1831, found 354.1834.



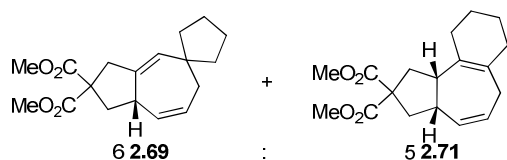
2.55, 2.58, 2.61. Prepared from **2.52** using method C to give the above mixture of products (92% combined yield) as a colorless oil (71%). The peaks assigned below correspond to the major isomer. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 5.61 (broad d, 1H, $J = 11$ Hz), δ 5.50-5.56 (m, 1H), 3.89 (dd, 1H, $J = 8.8$ Hz, 5.2 Hz), 3.45-3.51 (m, 2H), 3.10-3.17 (m, 1H), 2.83 (dd, 1H, $J = 9.2$ Hz, 7.2 Hz), 2.43 (s, 3H), 2.15-2.22 (m, 2H), 1.68 (s, 3H), 1.65 (s, 3H), 0.95 (d, 3H, $J = 7.6$ Hz). HRMS (EI+) calc. for $\text{C}_{19}\text{H}_{25}\text{NO}_2\text{S}$ 331.1606, found 331.1606.



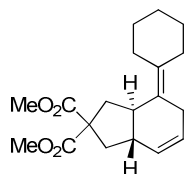
2.59. Prepared by method B to yield the product (75%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.70 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz), 5.74 (broad d, 1H, $J = 10.0$ Hz), 5.40-5.36 (m, 1H), 5.12 (broad s, 1H), 3.94 (d, 1H, $J = 13.0$ Hz), 3.75 (t, 1H, $J = 8.8$ Hz), 3.60 (m, 1H), 3.52 (dt, 1H, $J = 13.0$ Hz, 2.0 Hz), 2.74 (t, 1H, $J = 9.6$ Hz), 2.55 (m, 1H), 2.43 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.3, 133.4, 132.1, 131.1, 130.0, 129.4, 128.1, 127.4, 54.3, 53.7, 39.6, 39.0, 34.1, 31.2, 28.2, 21.5, 20.1. HRMS (FAB): calculated for $\text{C}_{19}\text{H}_{26}\text{NO}_2\text{S}$ 332.1684, found 332.1680.



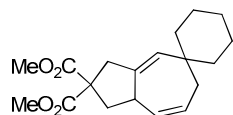
2.67. Prepared from **2.65** by method A to give the product (73%) as a colorless oil. ^1H NMR (400 MHz, C_6D_6): δ 5.78 (d, 1H, J = 9.6 Hz), 5.55-5.64 (m, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.19 (d, 1H, J = 7.2 Hz), 2.86 (dd, 1H, J = 12.8 Hz, 6.4 Hz), 2.67 (d, 1H, J = 20.8 Hz), 2.54 (d, 1H, J = 20.8 Hz), 2.39-2.44 (m, 2H), 2.22-2.27 (m, 2H), 2.03-2.12 (m, 2H), 1.87-1.98 (m, 2H), 1.32-1.54 (m, 4H).



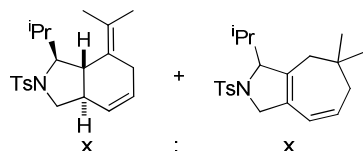
2.69, 2.71. Prepared from **2.65** by method B to give the products (53%) as a 6:5 mixture of products. Diagnostic peaks for each product are listed below. **2.69:** ^1H NMR (500 MHz, CDCl_3): δ 5.69 (s, 1H), 5.56 (s, 1H), 5.30 (s, 1H), 3.72-3.80 (m, 1H), 3.33 (s, 3H), 3.28 (s, 3H), 3.23 (d, 1H, J = 15.0 Hz), 3.12 (d, 1H, J = 16.5 Hz). **2.71:** ^1H NMR (500 MHz, CDCl_3): δ 5.69 (s, 1H), 5.56 (s, 1H), 3.32 (s, 3H), 3.28 (s, 3H), 2.90-2.97 (m, 1H), 2.40-2.51 (m, 1H).



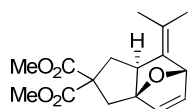
2.68. Prepared from **2.66** by method A to give the product (81%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.86 (d, 1H, J = 9.2 Hz), 5.79-5.71 (m, 1H), 3.73 (s, 6H), 2.98 (d, 1H, J = 8.4 Hz), 2.84 (d, 2H, J = 9.6 Hz), 2.65 (dd, 1H, J = 12.8 Hz, 6.0 Hz), 2.30-2.05 (m, 6H), 1.74 (t, 2H, J = 12.6 Hz), 1.65-1.45 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 173.2, 133.5, 129.3, 128.2, 128.0, 116.4, 102.3, 82.3, 58.0, 52.4, 35.3, 33.0, 31.4, 27.2, 26.0. HRMS (EI): calculated for $\text{C}_{19}\text{H}_{26}\text{O}_4$ 318.1831, found 318.1829.



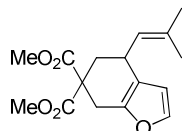
2.70. Prepared from **2.66** by method B to yield the product (81%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.71-5.69 (m, 2H), 5.38 (broad s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.56 (m, 1H), 3.06 (d, 1H, J = 16.4 Hz), 2.96 (d, 1H, J = 16.4 Hz), 2.65 (dd, 1H, J = 12.4 Hz, 8.4 Hz), 2.29-2.20 (m, 2H), 2.11 (t, 1H, J = 12.4 Hz), 1.45-1.65 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.3, 172.1, 137.6, 133.5, 131.7, 128.3, 58.1, 52.8, 52.7, 42.1, 41.2, 39.9, 38.0, 37.0, 36.9, 29.7, 26.3, 21.9, 21.8. HRMS (FAB): calculated for $\text{C}_{19}\text{H}_{26}\text{O}_4$ 318.1831, found 318.1829.



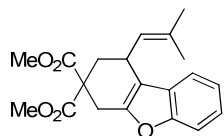
2.82, 2.83. Prepared by method D from **2.81** with additional heating to 50°C in dichloroethane to yield the product. ¹H NMR (500 MHz, CDCl₃): δ 7.75 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, 7.5 Hz), 5.60-5.64 (m, 1H), 5.54 (d, 1H, *J* = 9.0 Hz), 4.46 (dd, 1H, *J* = 10.5 Hz, 3.5 Hz), 3.75 (dd, 1H, *J* = 11.8 Hz, 6.8 Hz), 2.94 (d, 1H, *J* = 19.0 Hz), 2.76 (t, 1H, *J* = 12.0 Hz), 2.62 (d, 1H, *J* = 20.0 Hz), 2.42 (s, 3H), 2.39-2.42 (m, 1H), 2.32 (t, 1H, *J* = 11.0 Hz), 2.00-2.27 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.05 (d, 3H, *J* = 7.0 Hz), 0.98 (d, 3H, *J* = 7.0 Hz). **2.83:** ¹H NMR (500 MHz, CDCl₃): δ 7.75 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, 7.5 Hz), 5.77 (dd, 1H, *J* = 10.0 Hz, 3.0 Hz), 5.39 (ddd, 1H, *J* = 9.0 Hz, 7.0 Hz, 2.0 Hz), 3.67 (d, 1H, *J* = 4.0 Hz), 3.53 (d, 1H, *J* = 11.0 Hz), 3.48 (d, 1H, *J* = 11.0 Hz), 3.48 (q, 1H, *J* = 7.0 Hz), 2.45 (s, 3H), 2.41 (m, 1H), 2.05-2.09 (m, 1H), 1.56-1.64 (m, 1H), 1.44-1.49 (m, 1H), 0.93 (d, 3H, *J* = 7.0 Hz), 0.88 (d, 3H, *J* = 6.5 Hz), 0.82 (s, 3H), 0.55 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 143.2, 136.7, 129.6, 127.1, 125.2, 123.5, 68.8, 54.2, 36.2, 34.3, 33.8, 29.7, 29.4, 29.2, 28.0, 26.9, 21.4, 19.1, 17.2.



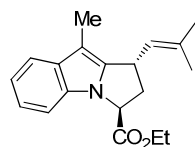
2.85. Prepared from **2.84** using method A and isolated flash chromatography using basic aluminum oxide (Brockman I, 50-200 μm) in EtOAc:hexanes (1:9) to give the product (82%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 6.40 (dd, 1H, *J* = 5.5 Hz, 1.0 Hz), 6.31 (d, 1H, *J* = 6.0 Hz), 5.20 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 2.84 (d, 1H, *J* = 16 Hz), 2.77 (d, 1H, *J* = 16 Hz), 2.68 (dd, 1H, *J* = 13 Hz, 8.0 Hz), 2.40 (t, 1H, *J* = 9.0 Hz), 2.23 (dd, 1H, *J* = 14 Hz, 11 Hz) 1.70 (s, 3H), 1.64 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 173.1, 171.7, 135.8, 135.1, 134.6, 124.2, 98.1, 80.9, 62.5, 53.0, 52.8, 47.7, 38.1, 36.2, 29.7, 21.4.



2.86. Prepared from **2.84** according to method D to give the product as a clear oil.



2.94. Prepared from **2.93** according to method A to give the product as a clear oil. ¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 7.2 Hz), 7.21 (d, 1H, *J* = 7.6 Hz), 7.15 (d, 1H, *J* = 7.6 Hz), 5.12 (d, 1H, *J* = 9.6 Hz), 3.79-3.86 (m, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.55 (d, 1H, *J* = 17.2 Hz), 3.20 (dd, 1H, *J* = 17.2 Hz, 3.2 Hz), 2.62 (dd, 1H, *J* = 13.6 Hz, 5.6 Hz), 1.88-1.92 (m, 1H), 1.89 (s, 3H), 1.87 (s, 3H).

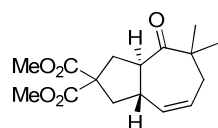


2.103. Prepared from **2.102** according to method D to give the product (88%) as a clear oil. ¹H NMR (400 MHz, CDCl₃): δ 7.46 (dd, 1H, *J* = 6.4 Hz, 1.6 Hz), 7.04-7.13 (m, 3 H), 5.26 (dt, 1H, *J* = 9.6 Hz, 1.3 Hz), 4.85 (dd, 1H, *J* = 8.4 Hz, 6.0 Hz), 4.26 (q, 2H, *J* = 7.1 Hz), 4.11-4.19 (m,

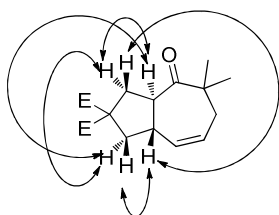
1H), 3.17 (dt, 1H, $J = 13.2$ Hz, 8.8 Hz), 2.39 (dt, 1H, $J = 13.2$ Hz, 5.8 Hz), 2.17 (s, 3H), 1.83 (s, 3H), 1.64 (s, 3H), 1.52 (d, 3H, $J = 2.5$ Hz), 1.43 (d, 3H, $J = 2.5$ Hz), 1.25 (t, 3H, $J = 7.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3): 202.6, 170.6, 136.8, 128.9, 122.9, 121.5, 119.0, 111.4, 109.0, 96.9, 83.8, 61.5, 57.6, 31.7, 20.2, 20.1, 14.1, 9.7.

4. Au(I)-catalyzed [4+3]-rearrangements of allene-diene 1: oxidative trapping.

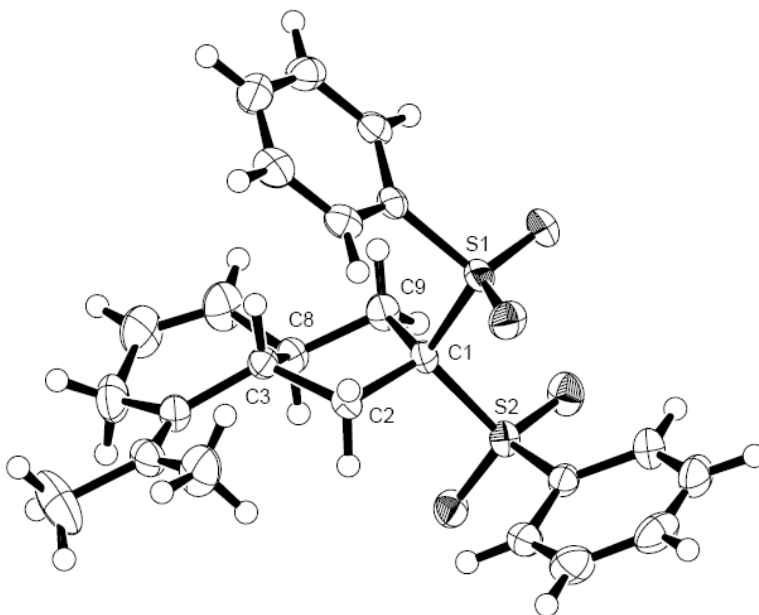
A mixture of AgSbF_6 (1.4 mg, 0.004 mmol, 0.05 equiv) and IPrAuCl (2.6 mg, 0.004 mmol, 0.05 equiv) in CD_2Cl_2 (0.2 mL) was premixed for five minutes at room temperature. The solution was filtered through glass fiber and added to a solution of **2.5** (23 mg, 0.09 mmol, 1.0 equiv) and diphenylsulfoxide (67 mg, 0.36 mmol, 4.0 eq) in CD_2Cl_2 (0.8 mL), and the resulting mixture was stirred for 4 hours at room temperature. The reaction was then concentrated in a rotary evaporator and the crude oil was purified by flash chromatography (4% EtOAc in hexanes) to afford the desired ketone (13 mg, 53%).



2.28. ^1H NMR (400 MHz, CDCl_3): δ 5.76 (2H, s), 3.78 (3H, s), 3.77 (3H, s), 3.35 (ddd, 1H, $J = 11.0$ Hz, 8.0 Hz, 7.2 Hz), 2.90 (1H, dd, $J = 12.8$ Hz, 7.2 Hz), 2.62-2.58 (2H, m), 2.57-2.47 (2H, m), 2.05-1.92 (2H, m), 1.04 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, CD_3Cl): 212.1, 172.9, 172.5, 131.5, 127.2, 56.7, 52.9, 52.7, 47.7, 44.4, 41.6, 37.7, 34.7, 27.1, 25.2. Important observed ^1H nOe correlations indicated below:



5. X-ray crystal data of compound 2.34



Discussion

The compound crystallizes in the centrosymmetric space group P-1, with one molecule in the asymmetric unit. The juncture of the five- and six-membered rings is disordered with a refined occupancy ratio of 75:25. The carbon atoms of the minority component of the disorder were refined with isotropic thermal parameters and the majority component with anisotropic thermal parameters. The anisotropic thermal parameters of the rest of the molecule include the effects of the disorder, as can be seen by inspection of the figures. Hydrogen atoms were included in calculated positions. The disorder was expressed in the positions of the hydrogen atoms attached to the disordered atoms, but the other hydrogens affected by the disorder were modeled by increasing their thermal parameters rather than attempting to include fractional electrons separated by distances far less than the resolution of the data set. Bond distances in the fused ring system are undoubtedly affected by the disorder in systematic ways and should not be analyzed for small differences. That being said, the location of the double bonds is unequivocal and all bond distances are in normal ranges.

Experimental

A fragment of a colorless plate-like crystal of $S_2O_4C_{24}H_{26}$ having approximate dimensions of 0.05 x 0.25 x 0.26 mm was mounted on a Kapton loop using Paratone N hydrocarbon oil. All measurements were made on a Bruker APEX⁵⁰ CCD area detector with graphite monochromated Mo-K α radiation.

Cell constants and an orientation matrix, obtained from a least-squares refinement using the measured positions of 2709 centered reflections with $I > 10\sigma$ in the range $5.00 < 2\theta < 50.00^\circ$ corresponded to a primitive triclinic cell with dimensions:

$$\begin{aligned} a &= 8.804(1) \text{ \AA} & \alpha &= 108.289(2)^\circ \\ b &= 12.052(2) \text{ \AA} & \beta &= 108.256(2)^\circ \\ c &= 12.271(2) \text{ \AA} & \gamma &= 105.125(2)^\circ \\ V &= 1076.8(2) \text{ \AA}^3 \end{aligned}$$

For $Z = 2$ and F.W. = 442.59, the calculated density is 1.37 g/cm³. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be P -1 (#2).

The data were collected at a temperature of $-129 \pm 1^\circ\text{C}$. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3° counted for a total of 10.0 seconds per frame.

Data Reduction

Data were integrated by the program SAINT⁵¹ to a maximum 2θ value of 50.7° . The data were corrected for Lorentz and polarization effects. Data were analyzed for agreement and possible absorption using XPREP.⁵² An empirical absorption correction based on comparison of redundant and equivalent reflections was applied using SADABS.⁵³ ($T_{\text{max}} = 1.00$, $T_{\text{min}} = 0.86$).

Structure Solution and Refinement

The structure was solved by direct methods⁵⁴ and expanded using Fourier techniques.⁵⁵ Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement⁵⁶ was based on 2952 observed reflections ($I > 3.00\sigma(I)$) and 280 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.039$$

$$R_w = [(\sum w (|F_o| - |F_c|)^2 / \sum w F_o^2)]^{1/2} = 0.051$$

The standard deviation of an observation of unit weight⁵⁷ was 1.75. The weighting scheme was based on counting statistics and included a factor ($p = 0.040$) to downweight the intense reflections. Plots of $\sum w (|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.38 and $-0.21 \text{ e}^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.⁵⁸ Anomalous dispersion effects were included in F_{calc} ;⁵⁹ the values for D_f' and D_f'' were those of Creagh and McAuley.⁶⁰ The values for the mass attenuation coefficients are those of Creagh and Hubbel.⁶¹ All calculations were performed using the teXsan⁶² crystallographic software package of Molecular Structure Corporation.

A. Crystal Data

Empirical Formula	$\text{S}_2\text{O}_4\text{C}_{24}\text{H}_{26}$
Formula Weight	442.59
Crystal Color, Habit	colorless, plate-like
Crystal Dimensions	0.05 X 0.25 X 0.26 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	$a = 8.804(1) \text{ \AA}$ $b = 12.052(2) \text{ \AA}$ $c = 12.271(2) \text{ \AA}$ $\alpha = 108.289(2)^\circ$ $\beta = 108.256(2)^\circ$ $\gamma = 105.125(2)^\circ$ $V = 1076.8(2) \text{ \AA}^3$
Space Group	P -1 (#2)
Z value	2
D_{calc}	1.365 g/cm^3
F_{000}	468.00
$\mu(\text{MoK}\alpha)$	2.76 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker APEX CCD
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Radiation	MoK α ($\lambda = 0.71069$ Å)
Detector Position	graphite monochromated
Exposure Time	60.00 mm
Scan Type	10.0 seconds per frame.
$2\theta_{\max}$	ω (0.3 degrees per frame)
No. of Reflections Measured	50.7°
Corrections	Total: 9159 Unique: 2866 ($R_{\text{int}} = 0.019$)
	Lorentz-polarization
	Absorption (Tmax = 1.00 Tmin = 0.86)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (F_o - F_c)^2$
Least Squares Weights	$1/\sigma^2(F_o) = 4F_o^2/s^2(F_o^2)$
p-factor	0.0400
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	2952
No. Variables	280
Reflection/Parameter Ratio	10.54
Residuals: R; Rw; Rall	0.039 ; 0.051; 0.054
Goodness of Fit Indicator	1.75
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	$0.38 \text{ e}^-/\text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.21 \text{ e}^-/\text{\AA}^3$

Table 1. Atomic coordinates and $B_{\text{iso}}/B_{\text{eq}}$ and occupancy

atom	x	y	z	B_{eq}	occ
S1	0.45046(8)	0.22320(5)	0.12062(5)	2.11(1)	
S2	0.84440(8)	0.34972(5)	0.23841(5)	2.07(1)	
O1	0.4328(2)	0.3423(1)	0.1442(2)	2.79(4)	
O2	0.4467(2)	0.1516(2)	0.0007(1)	3.02(4)	
O3	0.8501(2)	0.2772(2)	0.1235(2)	2.89(4)	
O4	0.9890(2)	0.3889(1)	0.3579(1)	2.52(4)	
C1	0.6538(3)	0.2519(2)	0.2481(2)	1.76(5)	
C2	0.6562(3)	0.3147(2)	0.3810(2)	1.82(5)	
C3	0.6304(7)	0.2069(3)	0.4238(3)	1.91(8)	0.746(10)
C4	0.6883(3)	0.2407(2)	0.5662(2)	2.60(5)	
C5	0.7478(4)	0.1462(3)	0.6073(3)	3.53(7)	
C6	0.7253(4)	0.0289(3)	0.5038(3)	4.15(8)	
C7	0.7106(4)	0.0199(2)	0.3920(3)	3.46(7)	
C8	0.7375(6)	0.1397(3)	0.3741(3)	2.15(9)	0.746
C9	0.6740(3)	0.1251(2)	0.2372(2)	2.30(5)	
C10	0.6709(3)	0.3344(2)	0.6470(2)	2.92(6)	
C11	0.6007(4)	0.4274(3)	0.6155(3)	4.03(7)	
C12	0.7244(5)	0.3588(4)	0.7847(3)	5.80(10)	
C13	0.2869(3)	0.1264(2)	0.1447(2)	1.98(5)	

C14	0.2270(3)	-0.0052(2)	0.0846(2)	2.28(5)	
C15	0.1010(3)	-0.0782(2)	0.1068(2)	2.81(5)	
C16	0.0384(3)	-0.0208(3)	0.1887(3)	2.98(6)	
C17	0.0981(3)	0.1108(2)	0.2475(2)	2.78(6)	
C18	0.2204(3)	0.1850(2)	0.2244(2)	2.32(5)	
C19	0.8107(3)	0.4845(2)	0.2283(2)	2.02(5)	
C20	0.7584(3)	0.4866(2)	0.1100(2)	2.88(6)	
C21	0.7223(3)	0.5874(3)	0.0972(3)	3.28(6)	
C22	0.7355(3)	0.6833(2)	0.2009(3)	3.35(6)	
C23	0.7904(4)	0.6824(2)	0.3189(3)	3.39(6)	
C24	0.8302(3)	0.5828(2)	0.3343(2)	2.58(5)	
C25	0.720(2)	0.238(1)	0.450(1)	1.9(2)	0.254
C26	0.623(2)	0.1015(10)	0.3434(10)	2.3(3)	0.254
H1	0.7646	0.3844	0.4386	2.1829	
H2	0.5642	0.3432	0.3744	2.1829	
H3	0.5109	0.1501	0.3790	2.2891	3/4
H4	0.8682	0.1894	0.6641	4.2326	
H5	0.6835	0.1204	0.6507	4.2326	
H6	0.7215	-0.0435	0.5202	4.9760	
H7	0.6842	-0.0588	0.3252	4.1468	
H8	0.8576	0.1949	0.4202	2.5790	3/4
H9	0.5656	0.0543	0.1835	2.7587	
H10	0.7572	0.1150	0.2052	2.7587	
H11	0.4972	0.3825	0.5382	4.8340	
H12	0.5755	0.4715	0.6821	4.8340	
H13	0.6853	0.4867	0.6065	4.8340	
H14	0.8005	0.3181	0.8068	6.9614	
H15	0.6237	0.3256	0.7968	6.9614	
H16	0.7827	0.4479	0.8372	6.9614	
H17	0.2717	-0.0444	0.0293	2.7338	
H18	0.0571	-0.1685	0.0653	3.3662	
H19	-0.0462	-0.0717	0.2049	3.5731	
H20	0.0544	0.1497	0.3038	3.3337	
H21	0.2590	0.2751	0.2623	2.7851	
H22	0.7477	0.4189	0.0385	3.4554	
H23	0.6884	0.5906	0.0172	3.9301	
H24	0.7065	0.7514	0.1914	4.0247	
H25	0.8011	0.7505	0.3900	4.0688	
H26	0.8697	0.5820	0.4154	3.0924	
H27	0.8415	0.2622	0.4735	2.2506	1/4
H28	0.5017	0.0694	0.3185	2.7493	1/4

$$B_{eq} = 8/3 p^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos g + 2U_{13}(aa^*cc^*)\cos b + 2U_{23}(bb^*cc^*)\cos a)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S1	0.0294(3)	0.0274(3)	0.0201(3)	0.0099(2)	0.0064(3)	0.0117(2)
S2	0.0297(3)	0.0295(3)	0.0250(3)	0.0143(3)	0.0142(3)	0.0139(2)
O1	0.035(1)	0.0322(9)	0.041(1)	0.0143(8)	0.0097(8)	0.0232(8)
O2	0.043(1)	0.0420(10)	0.0197(9)	0.0089(8)	0.0117(8)	0.0106(7)

O3	0.046(1)	0.0392(10)	0.0351(10)	0.0224(8)	0.0268(9)	0.0157(8)
O4	0.0266(9)	0.0393(9)	0.0331(9)	0.0138(7)	0.0106(8)	0.0211(8)
C1	0.026(1)	0.024(1)	0.019(1)	0.0118(9)	0.0097(10)	0.0110(9)
C2	0.023(1)	0.026(1)	0.019(1)	0.0116(9)	0.0083(10)	0.0090(9)
C3	0.022(2)	0.026(2)	0.024(2)	0.009(2)	0.009(2)	0.013(1)
C4	0.032(1)	0.038(1)	0.028(1)	0.010(1)	0.013(1)	0.017(1)
C5	0.046(2)	0.061(2)	0.041(2)	0.024(1)	0.019(1)	0.035(1)
C6	0.069(2)	0.047(2)	0.057(2)	0.034(2)	0.024(2)	0.037(2)
C7	0.063(2)	0.038(1)	0.048(2)	0.033(1)	0.027(2)	0.026(1)
C8	0.029(3)	0.029(2)	0.027(2)	0.015(2)	0.012(2)	0.014(1)
C9	0.038(1)	0.026(1)	0.028(1)	0.017(1)	0.016(1)	0.013(1)
C10	0.031(1)	0.049(2)	0.026(1)	0.009(1)	0.016(1)	0.012(1)
C11	0.076(2)	0.044(2)	0.051(2)	0.029(2)	0.047(2)	0.018(1)
C12	0.084(3)	0.115(3)	0.033(2)	0.055(2)	0.029(2)	0.029(2)
C13	0.024(1)	0.028(1)	0.021(1)	0.0106(10)	0.0043(10)	0.0128(9)
C14	0.028(1)	0.030(1)	0.022(1)	0.011(1)	0.005(1)	0.0096(10)
C15	0.031(1)	0.030(1)	0.036(1)	0.009(1)	0.006(1)	0.015(1)
C16	0.023(1)	0.051(2)	0.042(2)	0.013(1)	0.010(1)	0.030(1)
C17	0.024(1)	0.047(2)	0.036(1)	0.020(1)	0.012(1)	0.017(1)
C18	0.027(1)	0.030(1)	0.027(1)	0.016(1)	0.005(1)	0.011(1)
C19	0.025(1)	0.027(1)	0.027(1)	0.0093(10)	0.011(1)	0.0141(10)
C20	0.042(2)	0.041(1)	0.030(1)	0.015(1)	0.016(1)	0.020(1)
C21	0.039(2)	0.047(2)	0.043(2)	0.014(1)	0.014(1)	0.032(1)
C22	0.036(2)	0.034(1)	0.063(2)	0.014(1)	0.017(1)	0.030(1)
C23	0.050(2)	0.026(1)	0.047(2)	0.013(1)	0.018(1)	0.013(1)
C24	0.033(1)	0.029(1)	0.028(1)	0.008(1)	0.009(1)	0.012(1)

The general temperature factor expression:

$$\exp(-2p^2(a^*U_{11}h^2 + b^*U_{22}k^2 + c^*U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
S1	O1	1.433(2)	S1	O2	1.438(2)
S1	C1	1.832(2)	S1	C13	1.768(2)
S2	O3	1.431(2)	S2	O4	1.441(2)
S2	C1	1.844(2)	S2	C19	1.760(2)
C1	C2	1.558(3)	C1	C9	1.553(3)
C2	C3	1.538(4)	C2	C25	1.53(1)
C3	C4	1.538(4)	C3	C8	1.538(6)
C3	C25	0.69(1)	C4	C5	1.527(4)
C4	C10	1.329(3)	C4	C25	1.53(1)
C5	C6	1.490(4)	C6	C7	1.303(4)
C7	C8	1.498(4)	C7	C26	1.55(1)
C8	C9	1.529(4)	C8	C26	0.88(1)
C9	C26	1.58(1)	C10	C11	1.506(4)
C10	C12	1.511(4)	C13	C14	1.388(3)
C13	C18	1.393(3)	C14	C15	1.381(3)
C15	C16	1.379(4)	C16	C17	1.386(4)
C17	C18	1.373(3)	C19	C20	1.389(3)
C19	C24	1.383(3)	C20	C21	1.376(4)
C21	C22	1.372(4)	C22	C23	1.380(4)

C23	C24	1.385(4)	C25	C26	1.54(2)
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Table 4. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
C2	H1	0.95	C2	H2	0.95
C3	H3	0.95	C5	H4	0.95
C5	H5	0.95	C6	H6	0.95
C7	H7	0.95	C8	H8	0.95
C9	H9	0.95	C9	H10	0.95
C11	H11	0.95	C11	H12	0.95
C11	H13	0.95	C12	H14	0.95
C12	H15	0.95	C12	H16	0.95
C14	H17	0.95	C15	H18	0.95
C16	H19	0.95	C17	H20	0.95
C18	H21	0.95	C20	H22	0.95
C21	H23	0.95	C22	H24	0.95
C23	H25	0.95	C24	H26	0.95
C25	H27	0.95	C26	H28	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
O1	S1	O2	119.4(1)	O1	S1	C1	107.93(9)
O1	S1	C13	107.3(1)	O2	S1	C1	108.3(1)
O2	S1	C13	109.15(10)	C1	S1	C13	103.6(1)
O3	S2	O4	118.4(1)	O3	S2	C1	108.11(10)
O3	S2	C19	108.4(1)	O4	S2	C1	104.64(10)
O4	S2	C19	109.3(1)	C1	S2	C19	107.5(1)
S1	C1	S2	110.8(1)	S1	C1	C2	111.0(2)
S1	C1	C9	111.3(1)	S2	C1	C2	111.1(1)
S2	C1	C9	106.3(1)	C2	C1	C9	106.2(2)
C1	C2	C3	103.9(2)	C1	C2	C25	103.8(4)
C2	C3	C4	119.3(2)	C2	C3	C8	101.5(3)
C4	C3	C8	109.9(3)	C3	C4	C5	114.5(2)
C3	C4	C10	124.5(2)	C5	C4	C10	120.5(2)
C5	C4	C25	109.1(4)	C10	C4	C25	126.8(4)
C4	C5	C6	116.3(2)	C5	C6	C7	123.8(2)
C6	C7	C8	116.7(2)	C6	C7	C26	115.6(4)
C3	C8	C7	109.9(3)	C3	C8	C9	102.1(3)
C7	C8	C9	117.0(2)	C1	C9	C8	103.7(2)
C1	C9	C26	102.6(4)	C4	C10	C11	125.7(2)
C4	C10	C12	121.6(3)	C11	C10	C12	112.7(2)
S1	C13	C14	120.1(2)	S1	C13	C18	118.7(2)
C14	C13	C18	121.2(2)	C13	C14	C15	118.7(2)
C14	C15	C16	120.4(2)	C15	C16	C17	120.4(2)
C16	C17	C18	120.1(2)	C13	C18	C17	119.1(2)
S2	C19	C20	117.8(2)	S2	C19	C24	120.7(2)
C20	C19	C24	121.5(2)	C19	C20	C21	119.4(2)
C20	C21	C22	119.6(2)	C21	C22	C23	120.9(2)
C22	C23	C24	120.4(2)	C19	C24	C23	118.1(2)
C2	C25	C4	120.3(7)	C2	C25	C26	101.9(9)
C4	C25	C26	109.7(9)	C7	C26	C9	111.2(7)

C7 C26 C25 106.5(9)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C1	C2	H1	110.9	C1	C2	H2	110.9
C3	C2	H1	110.9	C3	C2	H2	110.9
C25	C2	H1	87.4	C25	C2	H2	131.7
H1	C2	H2	109.5	C2	C3	H3	108.5
C4	C3	H3	108.5	C8	C3	H3	108.5
C4	C5	H4	107.7	C4	C5	H5	107.7
C6	C5	H4	107.7	C6	C5	H5	107.7
H4	C5	H5	109.5	C5	C6	H6	118.1
C7	C6	H6	118.1	C6	C7	H7	121.7
C8	C7	H7	121.7	C26	C7	H7	112.4
C3	C8	H8	109.1	C7	C8	H8	109.1
C9	C8	H8	109.1	C1	C9	H9	110.9
C1	C9	H10	110.9	C8	C9	H9	110.9
C8	C9	H10	110.9	C26	C9	H9	81.3
C26	C9	H10	137.1	H9	C9	H10	109.5
C10	C11	H11	109.5	C10	C11	H12	109.5
C10	C11	H13	109.5	H11	C11	H12	109.5
H11	C11	H13	109.5	H12	C11	H13	109.5
C10	C12	H14	109.5	C10	C12	H15	109.5
C10	C12	H16	109.5	H14	C12	H15	109.5
H14	C12	H16	109.5	H15	C12	H16	109.5
C13	C14	H17	120.6	C15	C14	H17	120.6
C14	C15	H18	119.8	C16	C15	H18	119.8
C15	C16	H19	119.8	C17	C16	H19	119.8
C16	C17	H20	120.0	C18	C17	H20	120.0
C13	C18	H21	120.4	C17	C18	H21	120.4
C19	C20	H22	120.3	C21	C20	H22	120.3
C20	C21	H23	120.2	C22	C21	H23	120.2
C21	C22	H24	119.5	C23	C22	H24	119.5
C22	C23	H25	119.8	C24	C23	H25	119.8
C19	C24	H26	120.9	C23	C24	H26	120.9
C2	C25	H27	108.1	C4	C25	H27	108.1
C26	C25	H27	108.2	C7	C26	H28	112.9
C9	C26	H28	113.2	C25	C26	H28	112.7

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
S1	C1	S2	O3	-65.8(1)	S1	C1	S2	O4	167.1(1)
S1	C1	S2	C19	51.0(1)	S1	C1	C2	C3	107.1(2)
S1	C1	C2	C25	133.7(6)	S1	C1	C9	C8	-136.2(2)
S1	C1	C9	C26	-102.5(5)	S1	C13	C14	C15	179.1(2)
S1	C13	C18	C17	-177.6(2)	S2	C1	S1	O1	-67.6(1)
S2	C1	S1	O2	62.9(1)	S2	C1	S1	C13	178.8(1)
S2	C1	C2	C3	-129.1(2)	S2	C1	C2	C25	-102.5(6)
S2	C1	C9	C8	103.0(2)	S2	C1	C9	C26	136.7(5)
S2	C19	C20	C21	176.7(2)	S2	C19	C24	C23	-175.7(2)
O1	S1	C1	C2	56.4(2)	O1	S1	C1	C9	174.3(1)

O1	S1	C13	C14	155.2(2)	O1	S1	C13	C18	-24.6(2)
O2	S1	C1	C2	-173.1(1)	O2	S1	C1	C9	-55.1(2)
O2	S1	C13	C14	24.5(2)	O2	S1	C13	C18	-155.4(2)
O3	S2	C1	C2	170.3(2)	O3	S2	C1	C9	55.3(2)
O3	S2	C19	C20	13.6(2)	O3	S2	C19	C24	-168.5(2)
O4	S2	C1	C2	43.2(2)	O4	S2	C1	C9	-71.8(2)
O4	S2	C19	C20	144.0(2)	O4	S2	C19	C24	-38.2(2)
C1	S1	C13	C14	-90.7(2)	C1	S1	C13	C18	89.4(2)
C1	S2	C19	C20	-103.0(2)	C1	S2	C19	C24	74.9(2)
C1	C2	C3	C4	158.6(3)	C1	C2	C3	C8	37.7(4)
C1	C2	C25	C4	-161.2(8)	C1	C2	C25	C26	-39(1)
C1	C9	C8	C3	38.9(3)	C1	C9	C8	C7	159.0(3)
C1	C9	C26	C7	-154.2(6)	C1	C9	C26	C25	-42.3(10)
C2	C1	S1	C13	-57.3(2)	C2	C1	S2	C19	-72.9(2)
C2	C1	C9	C8	-15.4(3)	C2	C1	C9	C26	18.3(5)
C2	C3	C4	C5	-149.3(3)	C2	C3	C4	C10	38.4(5)
C2	C3	C8	C7	-172.8(2)	C2	C3	C8	C9	-47.9(4)
C2	C25	C4	C5	174.4(7)	C2	C25	C4	C10	-27(1)
C2	C25	C8	C3	-77(1)	C2	C25	C26	C7	166.4(6)
C2	C25	C26	C9	50(1)	C3	C2	C1	C9	-14.0(3)
C3	C4	C5	C6	-5.9(4)	C3	C4	C10	C11	-3.3(4)
C3	C4	C10	C12	177.5(3)	C3	C8	C7	C6	-48.3(5)
C4	C3	C8	C7	60.0(4)	C4	C3	C8	C9	-175.1(2)
C4	C5	C6	C7	21.6(4)	C4	C25	C26	C7	-65(1)
C4	C25	C26	C8	-120(1)	C4	C25	C26	C9	179.3(6)
C5	C4	C3	C8	-32.8(4)	C5	C4	C10	C11	-175.1(2)
C5	C4	C10	C12	5.7(4)	C5	C4	C25	C26	56(1)
C5	C6	C7	C8	6.8(5)	C5	C6	C7	C26	-30.8(7)
C6	C5	C4	C10	166.7(2)	C6	C5	C4	C25	-33.2(6)
C6	C7	C8	C9	-164.1(3)	C6	C7	C26	C9	158.6(5)
C6	C7	C26	C25	51(1)	C7	C8	C26	C9	-122.5(3)
C8	C3	C4	C10	155.0(3)	C9	C1	S1	C13	60.7(2)
C9	C1	S2	C19	172.0(1)	C9	C1	C2	C25	12.7(6)
C9	C8	C3	C25	-115(1)	C9	C8	C3	C26	66.2(8)
C9	C8	C7	C26	-67.3(7)	C10	C4	C25	C26	-144.6(7)
C11	C10	C4	C25	28.6(8)	C12	C10	C4	C25	-150.5(7)
C13	C14	C15	C16	-1.0(4)	C13	C18	C17	C16	-2.0(4)
C14	C13	C18	C17	2.6(4)	C14	C15	C16	C17	1.5(4)
C15	C14	C13	C18	-1.0(4)	C15	C16	C17	C18	-0.0(4)
C19	C20	C21	C22	-1.1(4)	C19	C24	C23	C22	-0.9(4)
C20	C19	C24	C23	2.1(4)	C20	C21	C22	C23	2.3(4)
C21	C20	C19	C24	-1.1(4)	C21	C22	C23	C24	-1.3(4)

Table 8. Non-bonded Contacts out to 3.75 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O1	C21	3.317(3)	66502	O1	C11	3.510(3)	66602
O2	C9	3.297(3)	65502	O3	C14	3.198(3)	65502
O3	C15	3.312(3)	65502	O3	C17	3.636(3)	65501
O3	C18	3.690(3)	65501	O4	C24	3.472(3)	76602
O4	C11	3.563(3)	76602	O4	O4	3.579(3)	76602
O4	C2	3.675(3)	76602	O4	C17	3.693(3)	65501

C5	C16	3.606(4)	65602	C5	C6	3.703(4)	65602
C5	C23	3.708(4)	76602	C6	C16	3.742(4)	65602
C9	C17	3.747(4)	65501	C12	C20	3.680(4)	55601
C13	C15	3.572(3)	2	C13	C16	3.748(3)	2
C14	C16	3.597(4)	2	C14	C15	3.690(4)	2
C14	C17	3.736(3)	2	C15	C18	3.713(3)	2
C21	C21	3.485(5)	66502	C24	C25	3.57(1)	76602

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

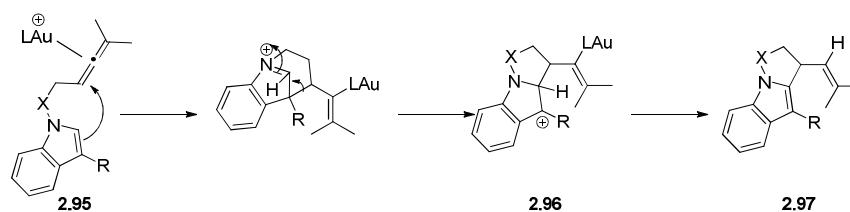
(1) X, Y, Z (2) -X, -Y, -Z

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Chapter 3. Total synthesis of flinderoles B and C

Herein is described the total synthesis of flinderoles B-C, members of a new class of antimalarial bisindole alkaloids isolated from plants of the Flindersia genus. The synthesis features a diastereoselective gold(I)-catalyzed C2-hydroarylation of indole with a pendant allene to form the distinctive pyrrolidine and the isobutenyl functionalities found in these compounds. Other key steps of the synthesis include a convergent Horner-Wadsworth-Emmons olefination to construct the bridging alkene and a new strategy for α -indole enolate alkylations.

3.1) Introduction

Malaria presents a significant disease burden in the developing world, causing one in five childhood deaths as well as decreasing economic growth in countries with high rates of transmission.¹ As such, malaria prevention and treatment are an integral part of alleviating poverty worldwide. Malaria is currently treatable—a wide variety of compounds have been developed as antimalarial agents (Figure 1). However, the *Plasmodium* parasites which cause this disease have begun exhibiting multi-drug resistance; thus, the majority of these drugs are now dosed as combination therapies, leading to greater treatment costs and lower patient compliance.² Because of this emerging resistance, there is great demand for antimalarial therapeutics that act orthogonally to existing drugs.

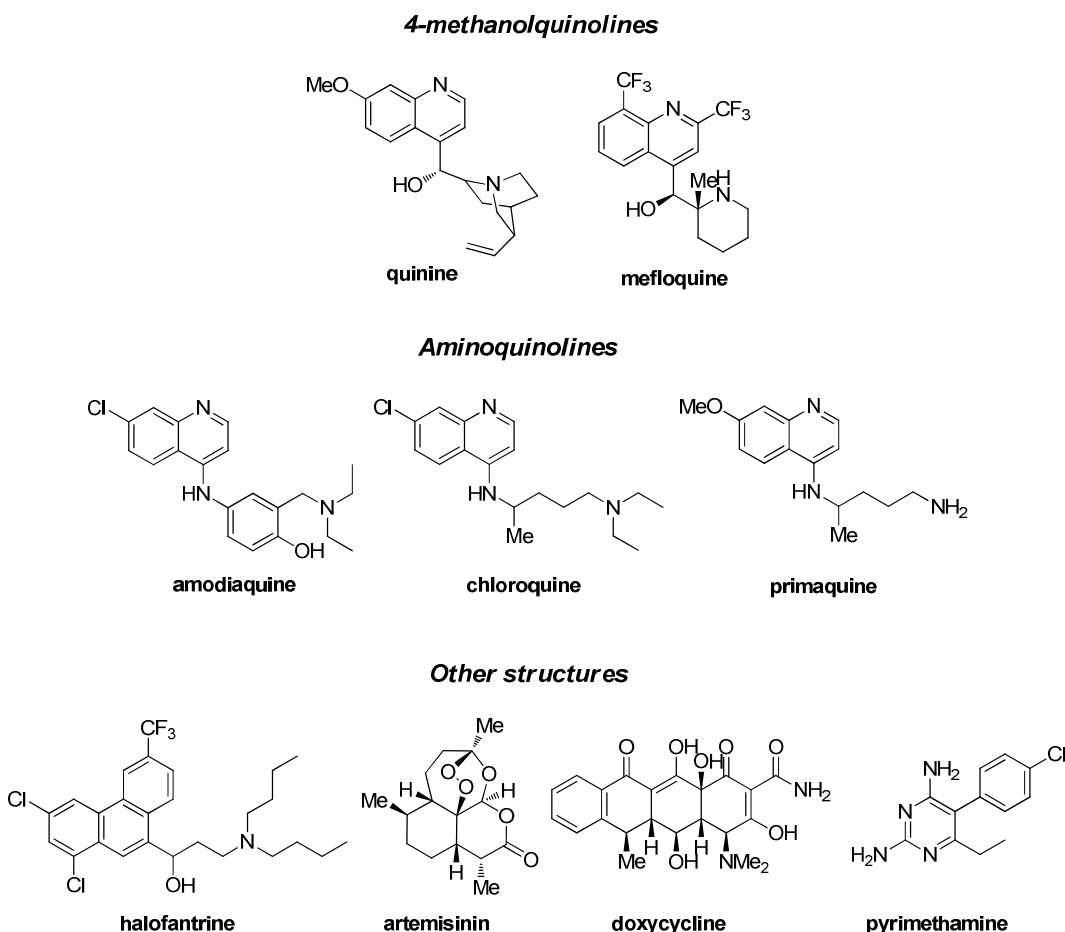


Figure 1. Current drugs indicated for the treatment of malaria include 4-methanolquinolines; aminoquinolines; and other structures such as sesquiterpene lactones and tetracyclic polyketides.

Given the historical precedent of using natural products as antimalarial drugs, the scientific community has again turned to nature in search for new therapies. In the process of such a screening campaign, novel bisindole alkaloid flinderole A (**3.1**), isolated from the Papua New Guinean plant *Flindersia acuminata*, and the related molecules flinderoles B (**3.2**) and C (**3.3**) from *F. ambionensis*, were identified as having antimalarial activity (Figure 2). These

compounds demonstrated selective growth inhibition against Dd2 (chloroquine-resistant) *P. falciparum* malaria strain with IC₅₀ values between 0.15–1.42 μ M.³

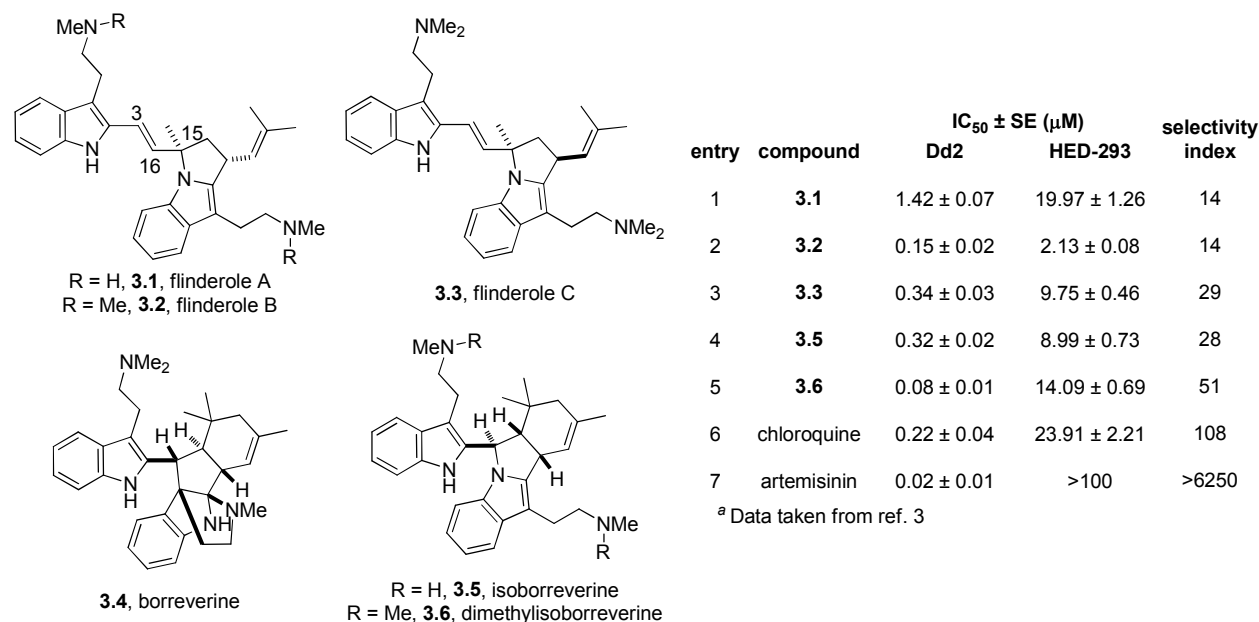


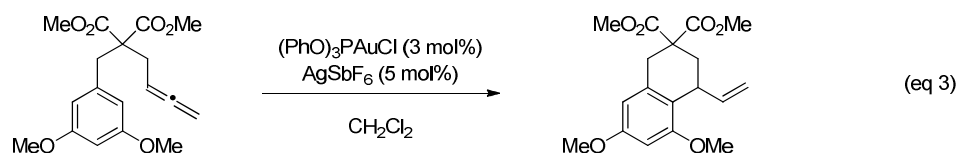
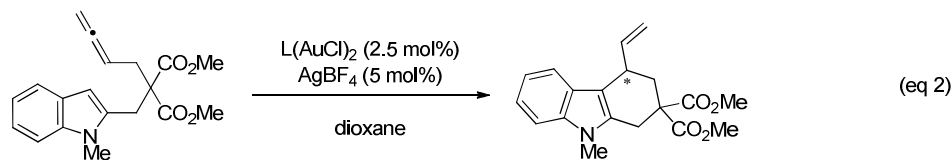
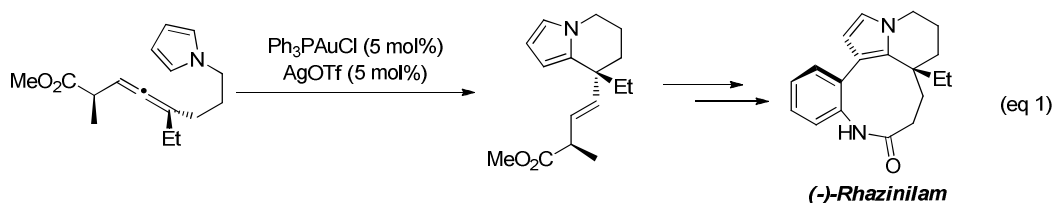
Figure 2. Flinderoles A-C (**3.1-3.3**) and the structurally related borreverine class of bisindole alkaloids (**3.4-3.6**) display potent, selective antimalarial activity.

The flinderoles are distinguished from the isomerically related borreverines (**3.4-3.6**)⁴ by three unique structural features: the C3-C16 *trans*-disubstituted olefin linking the two tryptamine subunits, the pyrrolidine ring featuring an isobutenyl side-chain on the eastern portion of the molecule, and the methyl quaternary center at C15.⁵ We believe that the flinderoles are an attractive target for total synthesis not only for their impressive biological activity but also because of their structural novelty. Additionally, a successful total synthesis of these compounds and analogous structures will allow for further investigation in to the mechanism by which these compounds inhibit malarial parasite growth.⁶

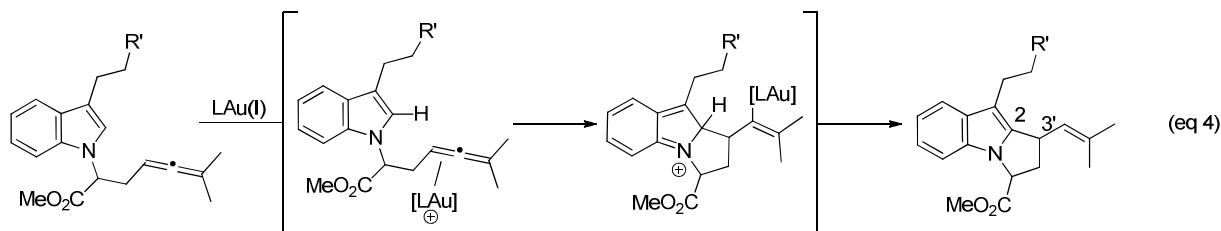
3.2) Retrosynthetic strategy

Aside from the flinderoles' impressive biological activity, we viewed the flinderole scaffold as a platform to showcase our understanding allene reactivity toward gold(I) catalysis. Given the synthetic community's current interest in gold(I) chemistry, it is not surprising that several gold(I)-catalyzed reactions of allenes with aromatic nucleophiles have been recently developed. In the context of complex molecule synthesis, Nelson, et. al. used triphenylphosphinegold(I) to promote the intramolecular hydroarylation of pyrrole with an enantioenriched allene, allowing for diastereoselective construction of the bicyclic core of (–)-rhazinalam. They turned to gold(I) catalysis after employing palladium(II) gave poor selectivity and silver(I) led to no reaction (eq 1).⁷ Most relevant to this work is the gold(I)-catalyzed asymmetric hydroarylation of 2-allenyl indoles as described by Wiedenhoefer; in this method, a chiral dinuclear gold(I) catalyst is employed to promote enantioselective nucleophilic addition of the C3 position of indole to an

allene to form six- and seven-membered rings (eq 2).⁸ Gagné extended this chemistry to the hydroarylation of allenes with electron-rich, all-carbon aromatic nucleophiles by moving to the weakly basic triphenylphosphitegold(I) catalyst (eq 3).



With these examples at hand, we proposed making the key disconnection along the C2-C3' bond; we envisioned simultaneously forming the pyrrolidine and the isobutenyl functionality at C3' by using a gold(I)-catalyzed hydroarylation of an allene electrophile with the C2 position of indole (eq 4).



We designed a convergent retrosynthetic strategy, shown in Figure 4, to best take advantage of this disconnection. We planned to arrive at the natural products **3.2** and **3.3** through Horner-Wadsworth-Emmons olefination of phosphonate **3.7** and aldehyde **3.8**, followed by deprotection and functional group manipulation to afford the *N*-dimethyltryptamine side chain. Desired phosphonate **3.7** could arise from radical bromination and Arbuzov reaction of protected 2-methyltryptamine **3.9**. The pyrrolidine **3.8** is formed through gold(I)-catalyzed cyclization of indole-allene **3.10** followed by enolate alkylation to install the necessary all-carbon quaternary center at C15. Indole-allene substrate **3.10** is constructed through two sequential alkylation steps: *N*^α-alkylation to install the ester, forming **3.11**, followed by *α*-*N*ⁱⁿ-indole enolate alkylation to introduce the allene. We believe that the convergent nature of this synthesis allows for rapid assembly of this complex molecule as well lending easy access to a broad array of flinderole analogs.

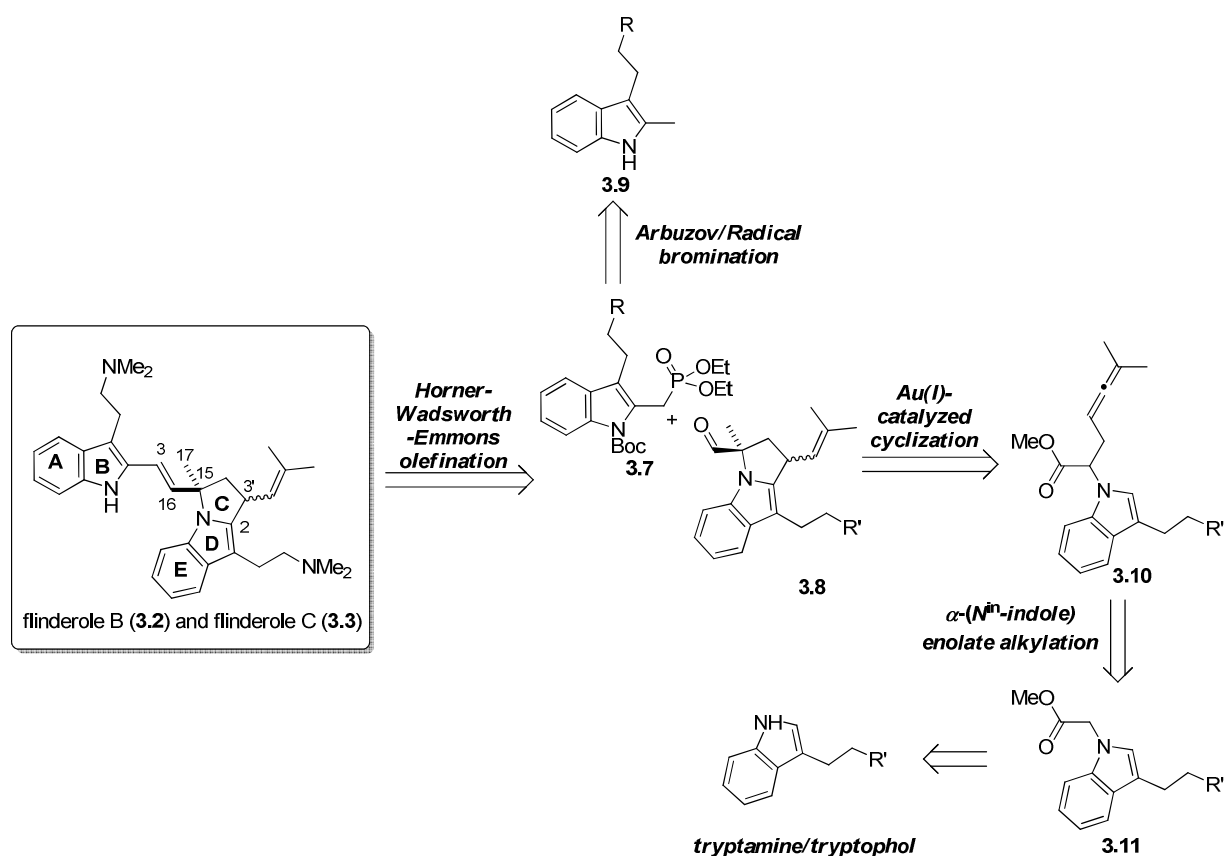
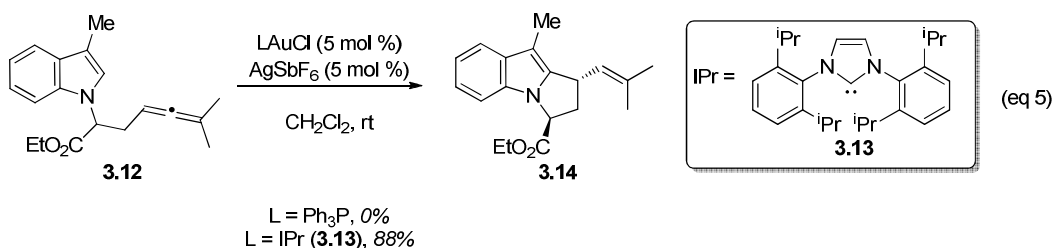


Figure 3. Retrosynthesis strategy for flinderoles B (**3.2**) and C (**3.3**).

3.3) Model system⁹

During our investigation of the reactivity of allenes toward diene nucleophiles, we prepared *N*-allenyl-3-methylindole substrate **3.12**. Though this compound proved unreactive to triphenylphosphinegold(I), we were pleasantly surprised to discover that, upon exposure to *N*-heterocyclic carbene-ligated catalyst IPrAuCl (**3.13**), pyrrolidine **3.14** was formed as a single diastereomer in 88% yield (eq 5). These positive results encouraged us to begin synthesis of the eastern fragment of the flinderole skeleton.



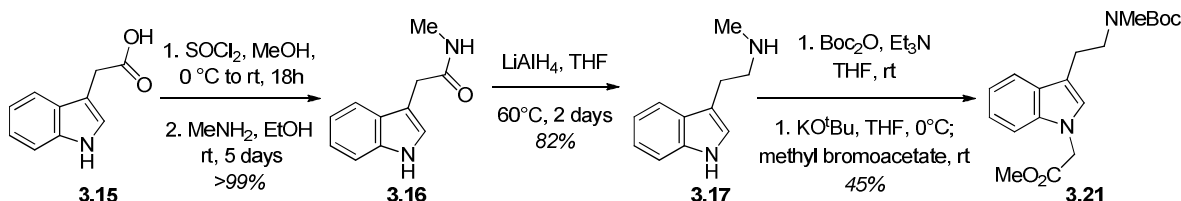
3.4) Synthesis of aldehyde **3.8**

By far the more complicated portion of flinderole at first glance, the eastern fragment posed two key problems: installation of the allene moiety and diastereoselective formation of the quaternary center at C15. The discussion of the synthesis of eastern fragment **3.8** will be framed by describing how we met these two challenges.

3.4.1) Installation of the allene moiety

We based our strategy for synthesizing the substrate for the key gold(I) step around enolate alkylation of an N^{in} -indole acetate. From a retrosynthetic standpoint, we took this approach for three reasons: a) it provided a handle for later installation of the C17 methyl group at C15, b) the ester masked the aldehyde necessary for the Horner-Wadsworth-Emmons olefination, and c) enolate alkylations provided entry to a chiral auxiliary-based enantioselective synthetic strategy. Additionally, we had ample experience using allenyl bromides in alkylation reactions.

We began our synthesis of flinderole's eastern fragment by making *N*-methyltryptamine (**3.17**) (Scheme 1). Starting from commercially available 3-indole acetic acid (**3.15**), methyl esterification followed by transamidation with methylamine gave 3-indole acetamide (**3.16**). Reduction of **3.16** in THF with 4.4 equivalents LiAlH_4 over 48 h produced desired *N*-methyltryptamine in 97% yield over three steps.

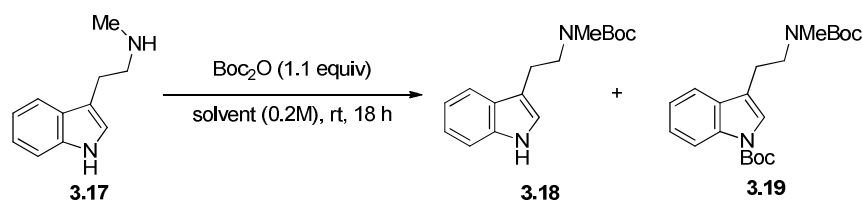


Scheme 1. Synthesis of methyl (*N*-indole) acetate **3.21**. (a) SOCl_2 (1.2 equiv), MeOH, 0°C to rt, 18h; >99%. (b) MeNH_2 (excess), EtOH, rt, 5 days; >99%. (c) LiAlH_4 (6 equiv), THF, 0°C to 60°C , 48 h; 82%. (d) Boc_2O (1.1 equiv), Et_3N (2.0 equiv), DMF, rt, 18 h; 72%. (e) KO^tBu (2.2 equiv), 0°C , 1 h; methyl bromoacetate (3.2 equiv), rt, 6 h; 62% (94% BORSM).

Next, we sought to protect the amine side-chain such that we could selectively build the flinderole C ring off the N^{in} -nitrogen. We selected the Boc protecting group in order to gain access to all three flinderoles: the methylamine side-chain of flinderole A could be accessed by cleavage of protecting group,¹⁰ whereas the dimethylamine side-chain of flinderoles B and C could be generated through complete reduction of the carbamate to a methyl group.¹¹ We hypothesized that we could selectively protect the N^α -nitrogen over the indole N^{in} position by leveraging the secondary amine's greater nucleophilicity. We first tried this transformation using a slight excess (1.1 equivalents) of Boc_2O and catalytic DMAP in a variety of solvents; unfortunately, the major product observed under these conditions was doubly Boc-protected **3.19** (Table 1, entries 1-3). We theorized that our lack of selectivity was due to the increased acidity of the indole N^{in} proton ($\text{pK}_a = 21$) versus the alkyl amine ($\text{pK}_a \approx 40\text{-}44$).¹² Further investigation on the mechanism of DMAP catalyzed Boc protections supports this hypothesis, implicating a

Boc-DMAP complex as the active acyl-transfer reagent.¹³ In order to counteract this deleterious acidity effect, we tried using stoichiometric triethylamine to effect the Boc protection (Table 1, entry 4); gratifyingly, these conditions gave solely the *N*^α-Boc product **3.18**, albeit in moderate yield. Attempts to increase the yield by adding DMAP back in to the reaction mixture resulted in erosion of chemoselectivity (Table 1, entry 5); however, increasing the equivalents of triethylamine to two allowed for 72% conversion to desired product **3.18** (Table 1, entry 6).

Table 1. Development of selective Boc protection conditions for *N*^α-tryptamines.^a



entry	base	solvent	3.18	3.19
1	DMAP (10 mol%)	MeCN	—	47%
2	DMAP (10 mol%)	CH ₂ Cl ₂	—	53%
3	DMAP (10 mol%)	THF	—	56%
4	Et ₃ N (1.0 equiv)	DMF	53%	—
5	Et ₃ N (1.0 equiv), DMAP (10 mol%)	DMF	55%	11%
6	Et ₃ N (2.0 equiv)	DMF	72%	—

^a Reaction conditions: 0.2 M **3.18** in solvent, base and Boc₂O stirred 18 h at room temperature.

With the *N*^α-amine protected, we were poised to alkylate the *N*ⁱⁿ position (Table 2). We began with alkyl bromoacetates as our alkylating agents because the resulting ester provides a general handle with which install a broad array of chiral auxiliaries. We began exploring this transformation by using an excess of sodium hydride as the base and ethyl bromoacetate as the alkylating agent (Table 2, entries 1-3): we were surprised to find that even at elevated temperatures and prolonged reaction times, we isolated a 3:1 mixture of desired product **3.20** and recovered starting material **3.18**. We propose that the observed product distribution is due to formation of a C3-alkylated intermediate that decomposes upon aqueous work-up.¹⁴ Switching to potassium *tert*-butoxide allowed for reduced reaction time—most likely due to the increased solubility of the potassium-indole ion pair—but the percent conversion of the reaction remained unchanged (Table 2, entry 4).

Another challenge we faced with this step was poor separation between starting material and the ethyl *N*-indoleacetate; however, we discovered that the more polar methyl *N*-indoleacetate (**3.21**) was easily isolated with silica gel chromatography to yield 62% of the pure desired product (Table 2, entry 5). While the yield of methyl ester **3.21** was slightly lower than that of the ethyl derivative **3.20**, we found that the increased ease of purification made these conditions optimal for our purposes.

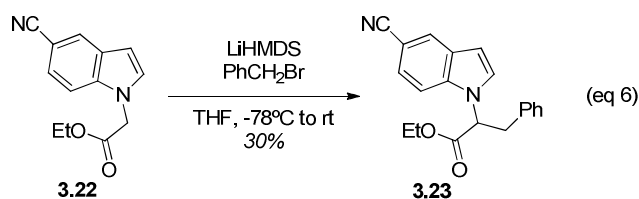
Table 2. Optimization of N^{in} -alkylation of *N*-Boc-*N*-methyltryptamine (3.19**).^{a,b,c}**

3.19 **3.20/3.21**
R = Et, **3.20**
R = Me, **3.21**

entry	R	conditions	3.20/3.21	3.19^b
1	Et	NaH (3.2 equiv), rt, 18 h	69%	31%
2	Et	NaH (3.2 equiv), 50 °C, 24 h	40%	60%
3	Et	NaH (2.2 equiv), rt, 5 days	59%	20%
4	Et	KO ^t Bu (2.2 equiv), rt, 6 h	70%	30%
5	Me	KO ^t Bu (2.2 equiv), rt, 6 h	62%	34%

^a Reaction conditions: 0.2 M **3.19** in THF at 0 °C with base for 1 h, followed by addition of bromoacetate and warming to specified temperature. ^b Yield based on recovered **3.19** after saponification. ^c Yield based on isolation following flash chromatography.

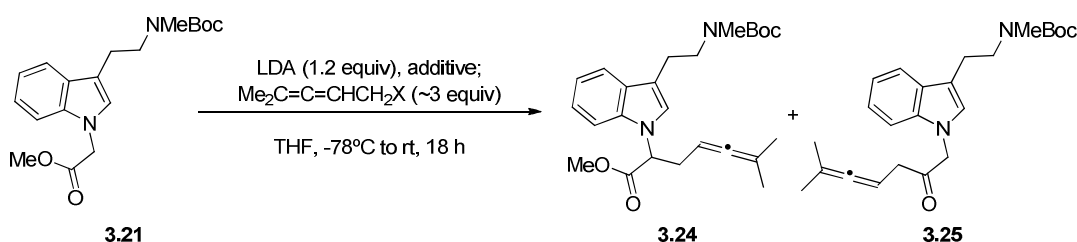
Though aldol reactions of α - N^{in} -indole enolates are known,¹⁵ alkylations of these anions are not well precedented. As of this writing, the only reported reaction of this type is benzylation of ethyl (α - N^{in} -indole)-ester enolate **3.22**, reported by Batt and coworkers as part of their investigation of 5-amidinoindoles as coagulation factor IXA and XA inhibitors (eq 6).¹⁶ While they achieve the desired transformation, they observe only 30% of benzylated product. Despite this poor yield, we believed that these results, combined with our successful synthesis of model system **3.12**, suggested that we could achieve allenylation of compound **3.21**.



We first attempted to use the conditions employed in our synthesis of **3.12**; with one equivalent each of LDA and DMPU and stirring overnight, we observed 26% of the desired allene **3.24** and 11% of recovered ester **3.21** (Table 3, entry 1). Increasing the equivalents of DMPU led to complete decomposition of starting material (Table 3, entry 2). While we observed that DMPU was required for alkylation to occur in our synthesis of **3.12**, we wondered if a more reactive alkylating agent would obviate the need for a cation scavenger; unfortunately, no desired product was observed when an allenyl mesylate was used (Table 3, entry 3).

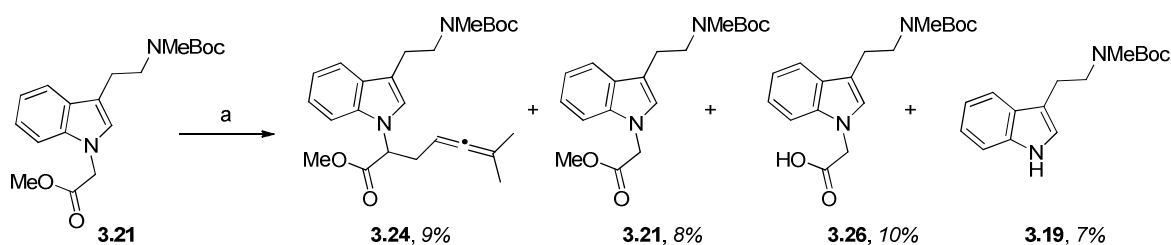
Upon trying HMPA as the cation scavenger, we primarily observed decomposition of the starting material; however, we isolated ketone **3.25** as a major component of the product mixture. Intrigued by this unexpected result, we returned to our original conditions and further examined the product distribution (Scheme 2).

Table 3. Attempts at methyl α - N^{in} -indole enolate alkylation.^a



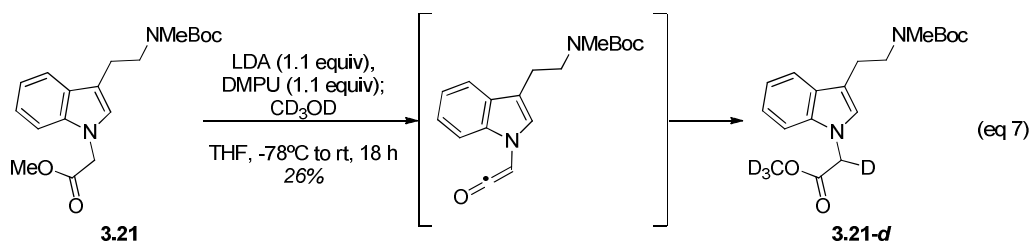
entry	additive	X	yield	3.24 : 3.21 : 3.25
1	DMPU (1.3 equiv)	Br	37%	1: 2.4:0
2	DMPU (2.2. equiv)	Br	decomposition	—
3	—	OMs	—	—
4	HMPA	Br	xx%	0:0:1

^a Reaction conditions: To a stirred solution of LDA in THF at -78°C was added a solution of **3.21** in THF for a final concentration of 0.1 M **3.21** in THF. After 1 h, the allene was added and the reaction proceeded until **3.21** was consumed or 18 h had elapsed.

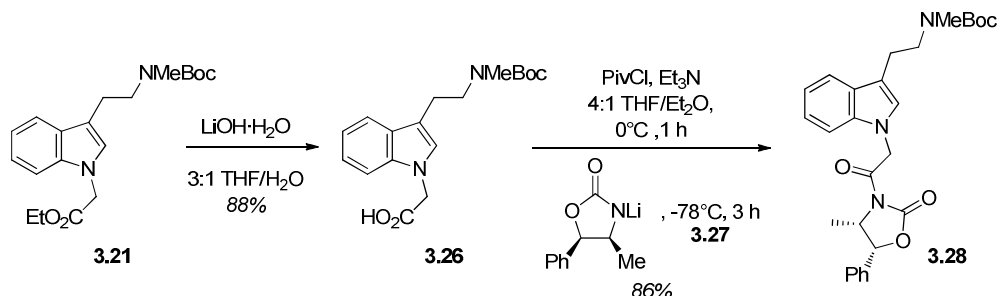


Scheme 2. Decomposition pathways of methyl α - N^{in} -indoleacetate **3.21** under enolate alkylation conditions. (a) LDA (1.1 equiv), **3.21** (1.0 equiv), -78°C , 1 h; DMPU (1.1 equiv), -78°C ; $\text{Me}_2\text{C}=\text{C}=\text{CHCH}_2\text{Br}$ (2.0 equiv), rt, 18 h.

In addition to desired product and starting material, we also observed acid **3.26** and N^{in} -H indole **3.19**. After examining these products, we proposed that, in the presence of a cation scavenger, the enolate of **3.21** reacts with an electrophile through two competing pathways: (a) predicted nucleophilic enolate addition to afford indole-allene **3.24**, or (b) decomposition to the ketene. This intermediate yields carboxylic acid **3.26** upon aqueous work-up; in the presence of a strong cation scavenger such as HMPA, it can also be intercepted by the alkylating agent to form ketone **3.25**. In order to probe the validity of this hypothesis, we quenched the anionic species formed using LDA and DMPU with deuterated methanol (CD_3OD). The resulting methyl ester exhibited full deuterium incorporation (**3.21-d**), suggesting that trapping of the enolate occurred through a ketene intermediate (eq 7).

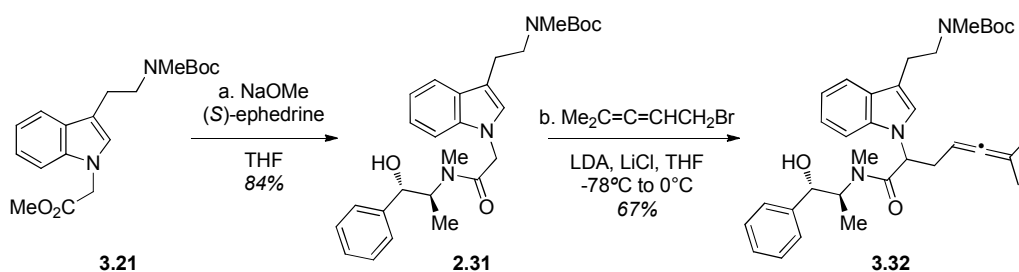


Concurrently with the racemic work described above, using chiral auxiliaries for an enantioselective approach to flinderole was also tried. We began with the Evans oxazolidinone auxiliaries, using (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone to make optically active *N*ⁱⁿ-indoleamidate compound **3.28** (Scheme 3).



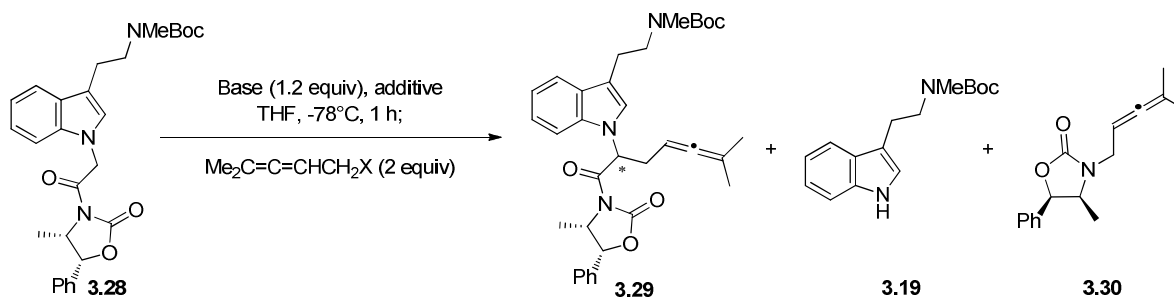
Scheme 3. Loading of the Evans oxazolidinone on the *N*ⁱⁿ-indoleacetate scaffold. (a) LiOH · H₂O (3.0 equiv), 3:1 THF/water, rt, 1 h; 88%. (b) Et₃N (1.1 equiv), PivCl (1.0 equiv) < 4:1 THF/Et₂O, -78°C, 1 h; **3.28**, -78°C, 3 h; 86%.

Unfortunately, exposure of this compound to a wide range of Evans alkylation conditions resulted in limited reactivity, providing only trace amounts of **3.29** (Table 4). Notably, with extended reaction time (Table 4, entry 4) and stronger base/ion scavenger combinations (Table 4, entries 5-6), decomposition of the oxazolidinone complex to **3.19** and **3.30** was observed. Faced with the poor reactivity and stability of these oxazolidinone anions, we moved toward other chiral auxiliary methodologies. Encouraged by the syntheses of unnatural amino acids using Myers' pseudoephedrine auxiliaries, we opted to try this alkylation under Myers' conditions.¹⁷ Gratifyingly, (*S*)-pseudoephedrine-derived compound **3.31** underwent alkylation cleanly to afford allene **3.32** in 67% yield; however, no diastereoselectivity was obtained (Scheme 4).



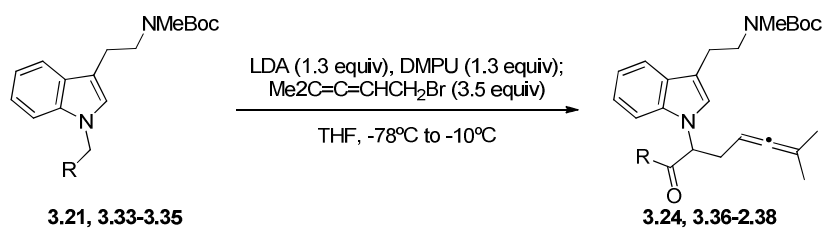
Scheme 4. Synthesis and alkylation of (–)-pseudoephedrine amide **3.32**.

Combining our observations from ester, oxazolidinone, and pseudoephedrine amide alkylations, we hypothesized that the poor reactivity and decomposition pathways we observed arose from the destabilizing influence of the α -indole nitrogen. We felt that if we could both enhance the enolate's reactivity and minimize the propensity for elimination to the ketene, we could favor the alkylation pathway and generate a majority of the desired allene product. To this end, we set about making the *tert*-butyl ester (**3.33**), dimethylamide (**3.34**) and nitrile (**3.35**) derivatives of methyl ester **3.21**; unfortunately, none of these compounds improved upon the parent structure (Table 5).

Table 4. Attempts at Evans alkylation of indole-acetamide 3.28^a

entry	base	additive	alkylation temperature	time	% 3.29	% 3.19	% 3.30
1	LDA	DMPU	-78°C	5 h	0	0	0
2	LDA	DMPU	-5°C	1 h	0	0	0
3	LDA	DMPU	-5°C	5 h	5	0	0
4	LDA	DMPU	-5°C	8 h	trace	trace	0
5	KHMDS	18-crown-6	25°C	18 h	0	0	trace
6	LiHMDS	--	25°C	18 h	0	0	0

^a Reaction conditions: To a stirred solution of base in THF at -78°C was added a solution of **3.28** in THF for a final concentration of 0.1 M **3.28** in THF. After 1 h, the allene was added and the reaction slowly warmed to the specified temperature over the time allotted.

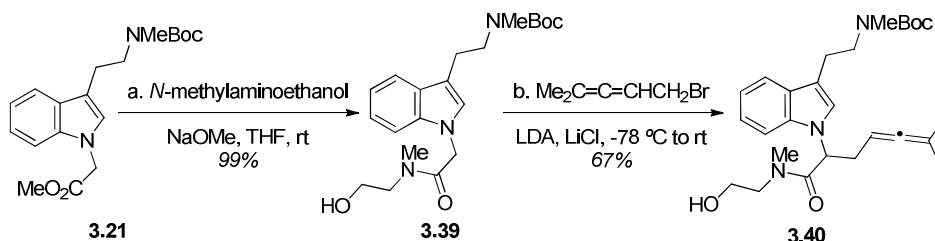
Table 5. Attempts at racemic enolate alkylation.^a

entry	R	yield
1	CO_2Me (3.21)	26 (3.24)
2	$\text{CO}_2t\text{-Bu}$ (3.33)	12 (3.36)
3	NMe_2 (3.34)	trace (3.37)
4	CN (3.35)	20 (3.38)

^a Reaction conditions: To a stirred solution of base in THF at -78°C was added a solution of the ester in THF for a final concentration of 0.1 M ester in THF. After 1 h, the allene was added and the reaction slowly warmed to the specified temperature over the time allotted.

Given our success with the Myers' auxiliary, we wondered if pseudoephedrine's amidoethanol motif presents a privileged structure for alkylating α -nitrogen enolates. Formation of a double anion and aggregate effects caused by adding exogenous lithium chloride are

proposed to increase pseudoephedrine amide enolates' reactivity and stability when compared to corresponding ester enolates.¹⁸ Thus, we believed that a similar increase in reactivity could be obtained by using racemic *N*-methylaminoethanol derived amide **3.39** with the Myers' alkylation conditions; we were pleased to observe that we were able to obtain allene **3.40** in 67% yield using this methodology, a greater than two-fold increase from the ester reaction (Scheme 5).

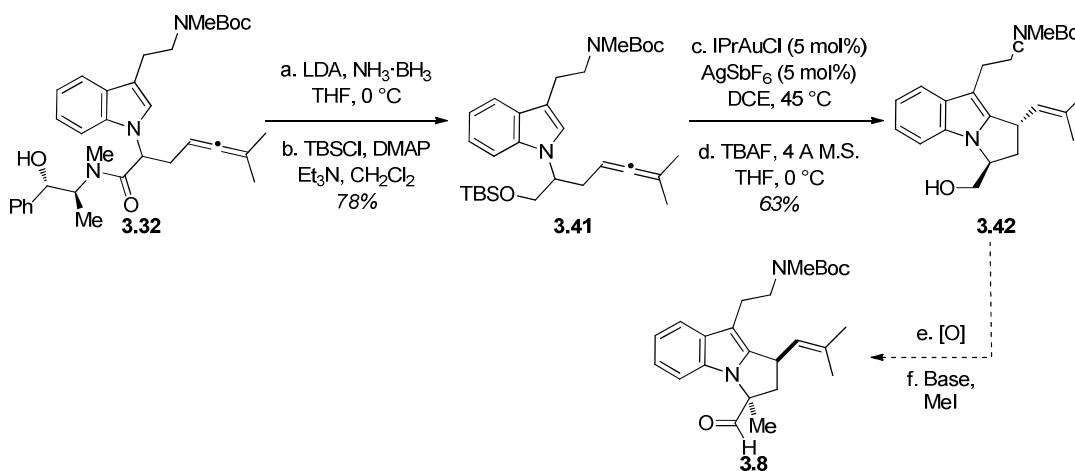


Scheme 5. Synthesis and alkylation of *N*-methyl-*N*-(2-hydroxyethyl)amide **3.39**. (a) *N*-methylaminoethanol (2.0 equiv), NaOMe (50 mol%), THF, rt, 2 h; 99%. (b) DIPA (2.25 equiv), *n*-BuLi (2.08 equiv), LiCl (6 equiv), THF, -78 °C, 1 h; 0 °C, 15 min; rt, 5 min; allene (3.0 equiv), 0 °C, 2 h; 67%.

3.4.2) Construction and elaboration of the pyrrolidine C ring

As we examined our approach to the flinderole C ring, we identified four necessary tasks: 1) cleavage of the amidoethanol auxiliary, 2) gold(I)-catalyzed hydroarylation to construct the pyrrolidine C ring, 3) installation of the C17 quaternary methyl group, and 4) functional group manipulation of the oxidized C15 position to generate an aldehyde. Designing our synthesis of the C ring involved not only optimizing the individual steps in the route but also the order in which they were performed.

The first approach took toward constructing the flinderole C ring began with reductive cleavage of the amidoethanol auxiliary to the alcohol. We envisioned performing the gold(I)-catalyzed cyclization after protecting the alcohol at C15; deprotecting and forming the aldehyde at this position would allow for alkylation to install the C17 methyl group (Scheme 6).¹⁹



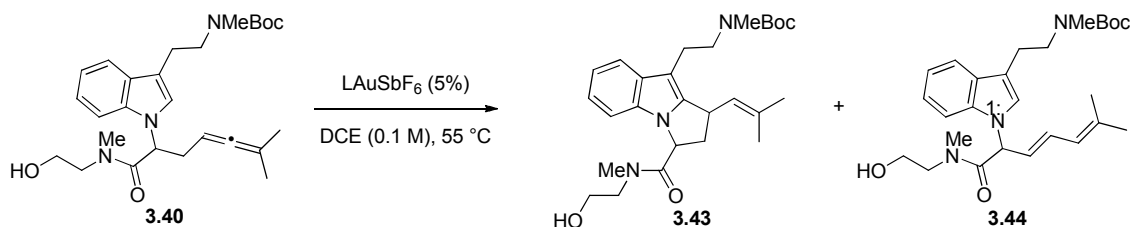
Scheme 6. First generation approach to the flinderole C ring. (a) *n*-BuLi (3.9 equiv), DIPA (4.2 equiv), BH₃·NH₃ (4.0 equiv), 0 °C to rt, 2 h; 92%. (b) TBSCl (1.2 equiv), Et₃N

(1.25 equiv), DMAP (10 mol%), CH₂Cl₂, rt, 5 h; 85%. (c) IPrAuCl (5 mol%), AgSbF₆ (5 mol%), DCE, 45°C, 4 h; 98%. (d) TBAF (1.1 equiv), 4 Å mol. sieves, THF, 0°C, 4 h; 65%.

Reduction of the pseudoephedrine auxiliary using lithium amidoborane, followed by TBS protection, gave the substrate for the gold(I)-catalyzed cyclization (**3.41**) in 78% yield over two steps. Treating **3.41** with 5 mol % IPrAuSbF₆ at 45°C over 4 h yielded the desired pyrrolidine as a single diastereomer in 98% yield; subsequent silyl deprotection with TBAF generated 64% of the alcohol **3.42**. Unfortunately, exposure of **3.42** to gentle oxidation conditions such as the Parikh-Doering (SO₃·pyridine/Et₃N/DMSO) or Dess-Martin periodinane led to complete decomposition of the starting material.

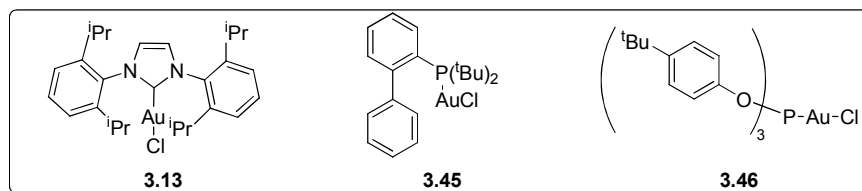
We hypothesized that the α-proton at C15 was impeding our attempts at oxidizing **3.42**. With this in mind, we redesigned our synthesis route to accommodate installation of the methyl group before performing oxidative chemistry. In our second strategy toward the pyrrolidine C ring, we would leave the amidoethanol auxiliary intact during the gold(I)-catalyzed cyclization and then use the Myers' alkylation conditions to methylate C15. Reductive cleavage of the amidoethanol auxiliary followed by oxidation of the resulting alcohol would then yield **3.8**.

Table 6. Gold(I)-catalyzed cyclization of amidate **3.40.^{a,b}**



entry	L	3.43 ^b : 3.44 : 3.40 ^c
1	IPr (3.13)	1.9:1:0
2	<i>t</i> -Bu ₃ P	2:1:0
3	JohnPhos (3.45)	3:1:10
4	(<i>p</i> - <i>t</i> -BuPhO) ₃ P (3.46)	--

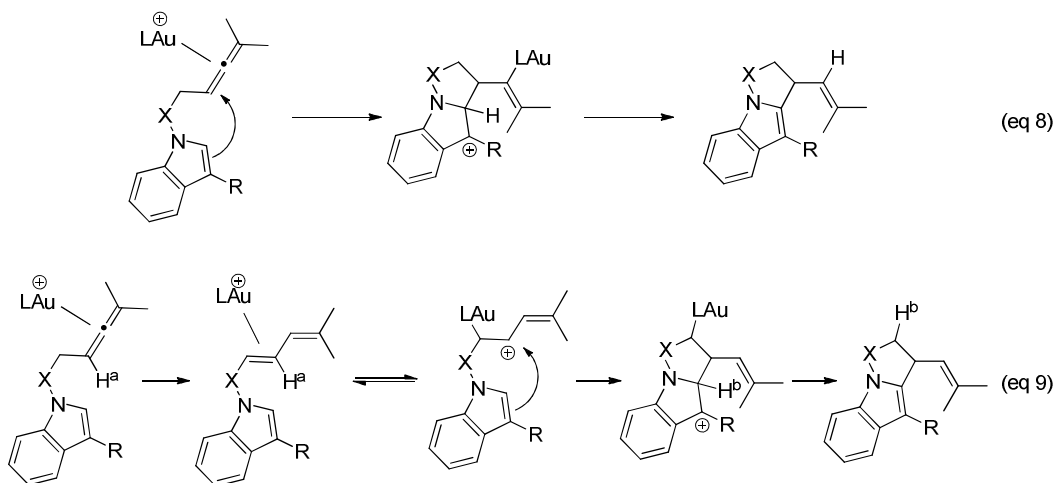
^aLAuCl (5 mol%), AgSbF₆ (5 mol%), DCE, 5 min; then **3.40** (0.1 M in DCE), 50 °C, 18 h. ^bIsolated as a 1:1 mixture of diastereomers. ^cProduct distributions were determined by ¹NMR after reduction with lithium amidoborane (LAB)



When we submitted **3.40** to gold(I) catalysis conditions, we noticed that protracted reaction times (18 h) and elevated temperatures (55°C) were required to see complete conversion of starting material. We also observed erosion in chemoselectivity: not only did we obtain a 1:1 ratio of *anti* and *syn* diastereomers of pyrrolidine product **3.43**, we also generated appreciable amounts of diene **3.44**. Attempts to increase selectivity by changing the gold(I) catalyst was

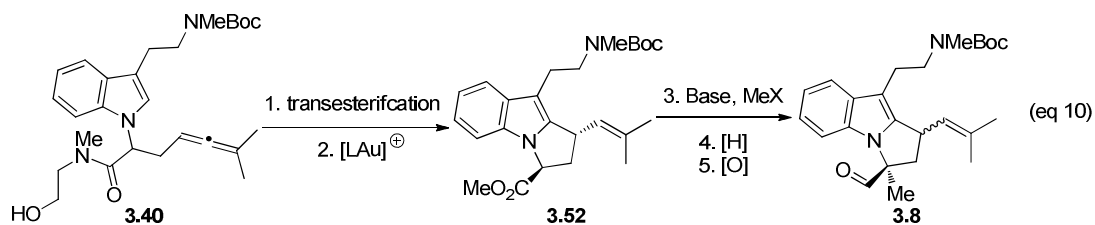
unsuccessful (Table 6). Tri-*tert*-butylphosphinegold(I) proved no different from the NHC-ligated catalyst (Table 6, entries 1-2); and while bulky biphenylphosphine-ligated catalyst JohnPhosgold(I) was more selective for the pyrrolidine, conversion was drastically lowered (Table 6, entry 3). The poor behavior of substrate **3.40** toward gold(I) catalysis probably results from the amide and alcohol functionalities' ability to act as gold(I) ligands.²⁰ We viewed this obstacle as insurmountable and thus concluded that it was necessary to cleave the amidoethanol auxiliary prior to the gold(I) step.

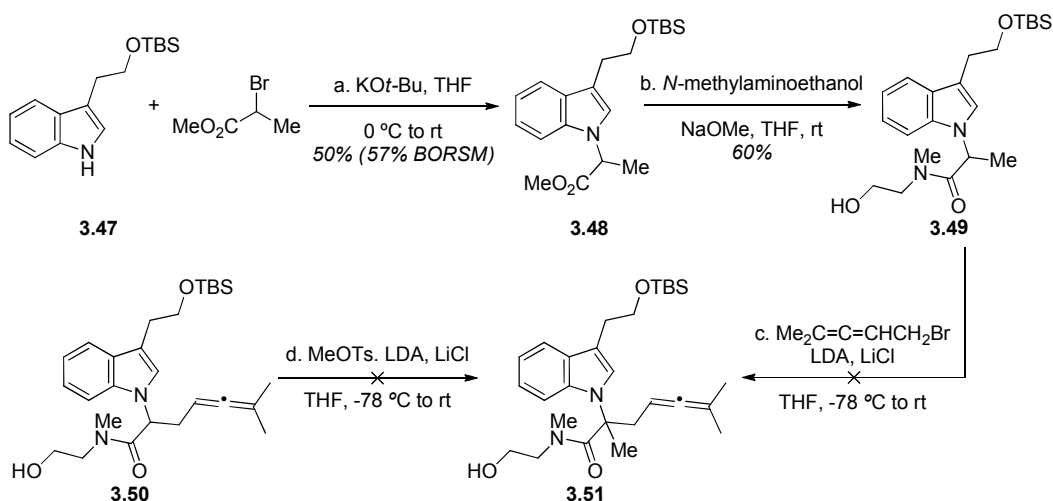
While the above route proved unsuccessful from a synthetic perspective, it provides some insight as to the mechanism of gold(I)-catalyzed hydroarylation reaction (eq 8). Our isolating significant quantities of diene **3.44** suggests that allene isomerization to the diene does not precede nucleophilic attack (eq 9).



Next, we reengineered our approach to the C ring to allow for cleavage of the amidoethanol auxiliary prior to the gold(I) step and methylation of C15 before generation of the aldehyde. Introducing both the methyl group and the allene prior to the gold(I)-cyclization meets both of these requirements; additionally, it was anticipated that this give better control over the relative stereochemistry at C15 and C2. To this end, methyl (*N*ⁱⁿ-indole)propionate **3.48** was prepared. After transamidation to the *N*-methylethanolamide **3.49**, installation of the allene was attempted; unfortunately, none of the desired product **3.51** was obtained. Reversing the order of steps such that the allene was installed first also failed to generate the quarternary center at C15 (Scheme 7).

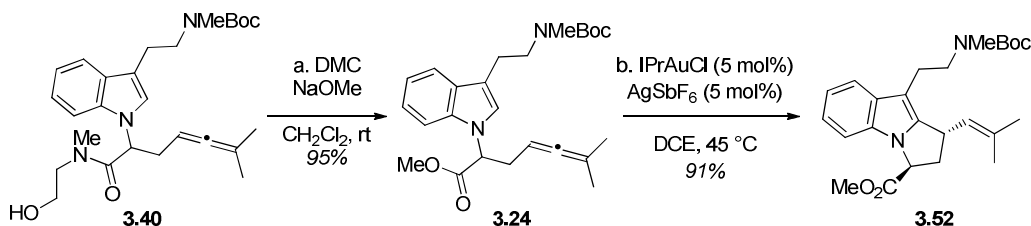
Applying our observations from our previous routes, we developed our final strategy: transesterification of the amide auxiliary regenerates the methyl ester; after the gold(I)-cyclization, the enolate of this ester is used to install the methyl group at C15. Lastly, oxidative manipulation of the ester provides aldehyde **3.8** (eq 10).





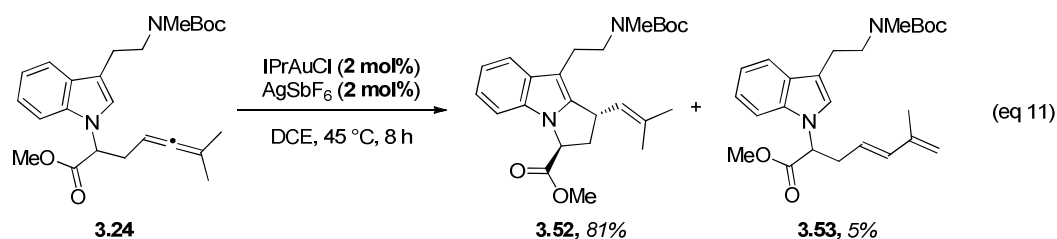
Scheme 6. Attempts to install the C15 quarternary center prior to gold(I)-cyclization. (a) KOt-Bu (2.2 equiv), methyl bromopropionate (3.2 equiv), THF, 0 °C to rt, 18 h; 50% (57% BORSM). (b) *N*-methylaminoethanol (2.0 equiv), NaOMe (50 mol%), THF, rt, 18 h; 60%. (c) *n*-BuLi (2.08 equiv), DIPA (2.25 equiv), LiCl (6.0 equiv), -78 °C, 1 h; 0 °C, 15 min; rt, 5 min; Me₂C=C=CHCH₂Br (3.0 equiv), 0 °C. (d) *n*-BuLi (2.08 equiv), DIPA (2.25 equiv), LiCl (6.0 equiv), -78 °C, 1 h; 0 °C, 15 min; rt, 5 min; MeOTs (10 equiv), 0 °C.

Transesterification using excess dimethyl carbonate and sodium methoxide cleanly furnished desired methyl ester **3.24** in 95% yield.²¹ Gold(I)-catalyzed hydroarylation of allene **3.24** with IPrAuSbF₆ gave the desired pyrrolidine **3.52** as a single diastereomer in 91% yield (Scheme 7).



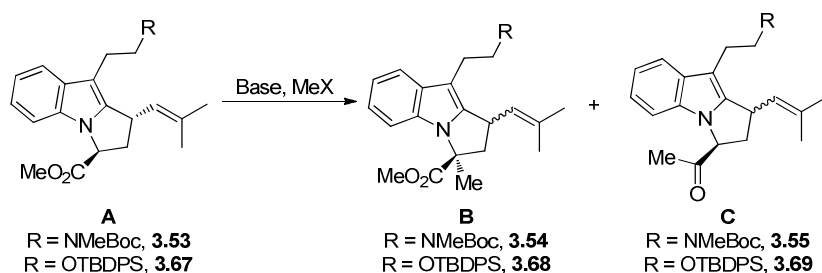
Scheme 7. Synthesis of methylation precursor **3.52**. (a) dimethyl carbonate (6.2 equiv), NaOMe (10.0 equiv), CH₂Cl₂, rt, 18 h; 95%. (b) IPrAuCl (5 mol%), AgSbF₆ (5 mol%), DCE, 45 °C; 91%.

We found that the catalyst loading for the gold(I) cyclization of **3.40** could be reduced to 2%, providing 81% yield of the desired product as well as 5% yield of terminal diene **3.53** (eq 11). Due to the decreased yield with lower catalyst loading, we opted to continue to use 5% loading in future cyclization reactions.



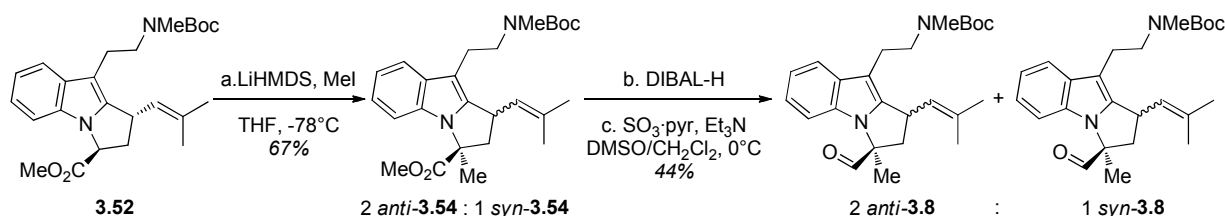
With the C ring established, we were poised to introduce the C17 methyl group. Using optimized conditions for alkylating methyl ester **3.21** with allenyl bromide gave a 2:3 mixture of starting material and ketone **3.55**, both isolated as a 1:1 mixture of diastereomers (Table 7, entry 1); when the cation scavenger was omitted, no reaction occurred (Table 7, entry 3). Based on these results and observations from the allene alkylation, we hypothesized that we were again accessing a ketene-like reactive intermediate. Thus, we felt that a softer electrophile such as methyl toluenesulfonate (MeOTs) would prove more compatible with the soft enolate anion and generate primarily desired methylated product **3.54**. While this theory proved correct, the yield with these conditions, 30%, was too low to be useful in the synthesis route (Table 7, entry 2). At this juncture, other bases were examined. While NaHMDS failed to promote reactivity of TBDPS-ether **3.67** (Table 7, entry 3), and potassium *tert*-butoxide yielded exclusively ketone **3.70** (Table 7, entry 4), LiHMDS was shown to generate solely the desired methylated compound **3.68** and **3.50** (Table 7, entries 6-7) in 94% yield as a 2:1 mixture of *anti* and *syn* diastereomers.²² Reduction of the methyl ester with DIBAL-H and subsequent Parikh-Doering oxidation yielded aldehyde **3.8** in 44% yield over two steps (Scheme 8).

Table 7. Methylation of pyrrolidine 3.53/3.67.^a



entry	R	Base	Additive	MeX	A ^b :B ^c :C ^{d,e}
1	NMeBoc (3.53)	LDA	DMPU	MeI	2 3.53 : 0 : 3 3.55
2	NMeBoc	LDA	DMPU	MeOTs	0 : 1 3.54 : 0
3	OTBDPS (3.67)	LDA	—	MeI	1 3.67 : 0 : 0
4	OTBDPS	KOt-Bu	—	MeI	0 : 0 : 1 3.69
5	OTBDPS	NaHMDS	—	MeI	1 3.67 : 0 : 0
6	OTBDPS	LiHMDS	—	MeI	0 : 1 3.68 : 0
7	NMeBoc	LiHMDS	—	MeI	0 : 1 3.54 : 0

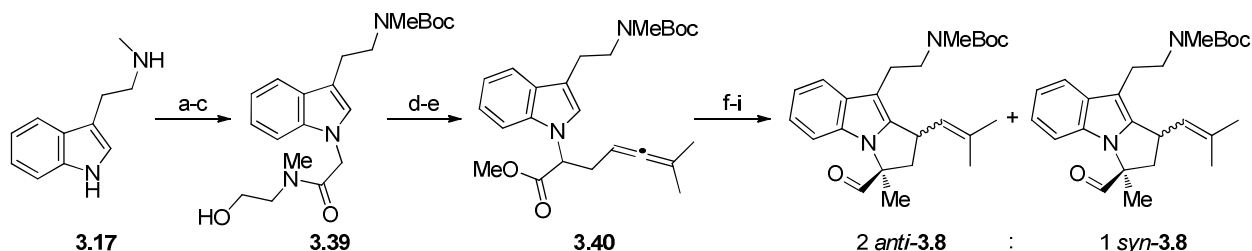
^a Reaction conditions: 0.1 M **A** in THF with base at -78°C for 1 h, followed by addition of additive and MeX and stirring at -78°C for 1 h. ^b Product isolated as a 1:1 mixture of diastereomers. ^c Product isolated as a 2:1 mixture of *anti* and *syn* diastereomers. Yield based on isolation following flash chromatography. ^d Product isolated as a 1:1 mixture of diastereomers. ^e Product distributions determined by NMR.



Scheme 8. Methylation and oxidative manipulation to yield aldehydes *anti*-**3.8** and *syn*-**3.8**. (a) LiHMDS (1.2 equiv), THF, -78°C, 1 h; MeI (10 equiv), 1 h; 94%. (b) DIBAL-H (1.2 equiv), toluene, -78°C, 6 h; 56%. (c) SO₃·pyr (8.3 equiv), Et₃N (10.0 equiv), 1:1 DMSO/CH₂Cl₂, 0°C, 1 h; 75%.

While poor facial selectivity is observed in the methylation reaction, both isomers are *en route* to natural products—the *anti* diastereomer gives flinderoles **A** and **B**, whereas the *syn* diastereomer gives flinderole **C**. The diastereomeric mixtures of the methyl esters and the reduced alcohol products proved inseparable; however, the aldehydes are readily purified by silica gel chromatography, providing diastereomerically pure *anti*-**3.8** and *syn*-**3.8**.

The aldehydes *anti*-**3.8** and *syn*-**3.8** were generated in 11% yield over nine steps from known compound *N*-methyltryptamine (Scheme 9). Key steps include a chemoselective Boc protection of an alkylamine, the use of an activated *N*-methylamidoethanol auxiliary to allow for alkylation of an α -*N*ⁱⁿ-indole enolate with high yields, gold(I)-catalyzed hydroarylation of an allene with indole at the C2 position, and chemoselective methylation of an ambident enolate to install a methyl quarternary center at C15.

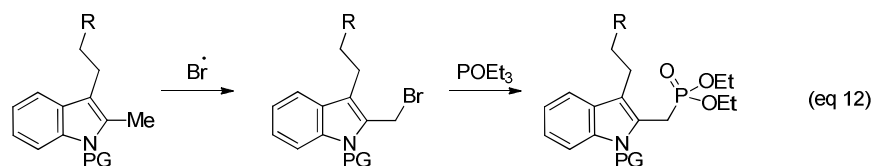


Scheme 9. Synthesis of eastern fragment **3.8**. (a) Boc₂O (1.1 equiv), Et₃N (2.0 equiv), DMF, rt, 18 h; 72%. (b) KO^{*t*}-Bu (2.2 equiv), 0°C, 1 h; methyl bromoacetate (3.2 equiv), rt, 6 h; 62% (94% BORSM). (c) *N*-methylaminoethanol (2.0 equiv), NaOMe (50 mol%), THF, rt, 2 h; 99%. (d) DIPA (2.25 equiv), *n*-BuLi (2.08 equiv), LiCl (6 equiv), THF, -78°C, 1 h; 0°C, 15 min; rt, 5 min; allene (3.0 equiv), 0°C, 2 h; 67%. (e) dimethyl carbonate (6.2 equiv), NaOMe (10.0 equiv), CH₂Cl₂, rt, 18 h; 95%. (f) IPrAuCl (5 mol%), AgSbF₆ (5 mol%), DCE, 45°C, 4 h; 91%. (g) LiHMDS (1.2 equiv), THF, -78°C, 1 h; MeI (10 equiv), 1 h; 67%. (h) DIBAL-H (1.2 equiv), toluene, -78°C, 6 h; 56%. (i) SO₃·pyr (8.3 equiv), Et₃N (10.0 equiv), 1:1 DMSO/CH₂Cl₂, 0°C, 1 h; 75%.

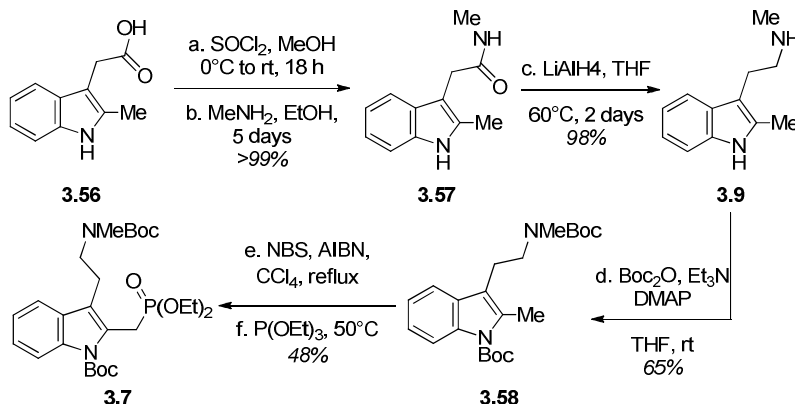
3.5) Synthesis of phosphonate **3.7**

Our strategy toward flinderole hinges on uniting the two flinderole fragments by a Horner-Wadsworth-Emmons olefination, requiring synthesis of a tryptamine derivative possessing a

benzylic phosphonate at the C2 position (eq 12). In our retrosynthetic analysis of this compound, we propose a selective bromination at C2 of a 2-methylindole derivative followed by an Arbuzov reaction to introduce the phosphonate functionality.



Starting with commercially available 2-methyl-3-indole acetic acid (**3.56**), we prepared doubly – Boc protected 2-methyl tryptamine **3.58** (Scheme 10).²³ Methyl esterification, transamidation with methylamine, and reduction with lithium aluminum hydride provided 2, *N*-dimethyltryptamine (**3.9**) in 97% yield over three steps. Then, *N*-Boc protected compound **3.58** was obtained in 65% yield using our previously developed methodology for one-pot double – Boc protections of both *N*^α- and *N*ⁱⁿ-nitrogens of tryptamine.



Scheme 10. Synthesis of tryptamine phosphonate **3.7**. (a) SOCl₂ (1.2 equiv), MeOH, 0°C to rt, 18h; >99%. (b) MeNH₂ (excess), EtOH, rt, 5 days; >99%. (c) LiAlH₄ (6 equiv), THF, 0°C to 60°C, 48h; 98%. (d) Boc₂O (2.2 equiv), Et₃N (4.0 equiv), DMAP (10 mol%), THF, rt, 18h; 65%. (e) NBS (1.0 equiv), AIBN (10 mol%), CCl₄, 75°C, 18h. (f) P(OEt)₃ (7.0 equiv), 55°C, 48h; 48%.

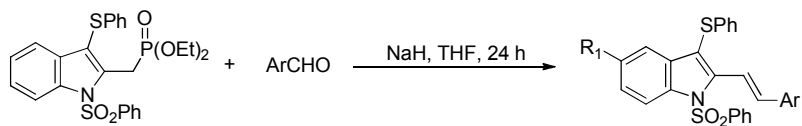
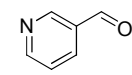
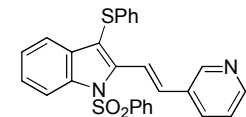
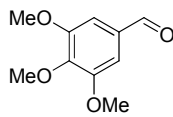
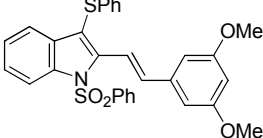
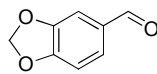
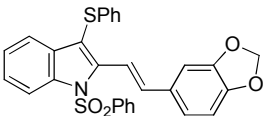
Our primary concern in developing this synthesis route was achieving selectivity for benzylic bromination at C2 over C3. Work performed by Dmitrienko and coworkers suggested that, through appropriate selection of bromination conditions, we could achieve selective modification of the C2 position.²⁴ Indeed, we were pleased to find that radical bromination proceeds cleanly to afford only the 2-(bromomethyl)indole product. Subsequent Arbuzov reaction gave phosphonate **3.7** in 45% yield over two steps.

3.6) Construction of the flinderole skeleton

With aldehydes *anti*-**3.8** and *syn*-**3.8** and phosphonate **3.7** in hand, we were poised to perform the Horner-Wadsworth-Emmons olefination that would unite the two halves of the flinderole scaffold. Olefination reactions of 2-indolephosphonates and aromatic aldehydes have been reported by Srinivasan and coworkers; the authors use sodium hydride as the base, and require

elevated temperature and long reaction times to obtain full conversion to the alkene product (Table 8).²⁵

Table 8. Precedents for Horner-Wadsworth-Emmons olefinations of 2-indolephosphonates^{a,b}

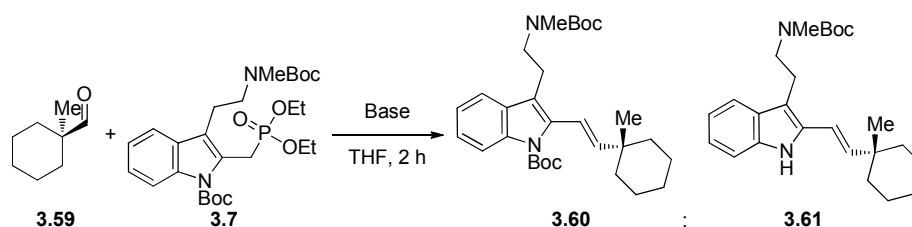
			
entry	aldehyde	indole	yield ^c
1			82%
2			72%
3			70%

^aResults from ref. xb. ^bReaction conditions: phosphonate (1.0 equiv), aldehyde (1.25 equiv), NaH (2.0 equiv), THF (0.1 M), 24h, 5 °C to rt. ^cYields of isolated product.

3.6.1) Horner-Wadsworth-Emmons olefination: a significant counteraction effect

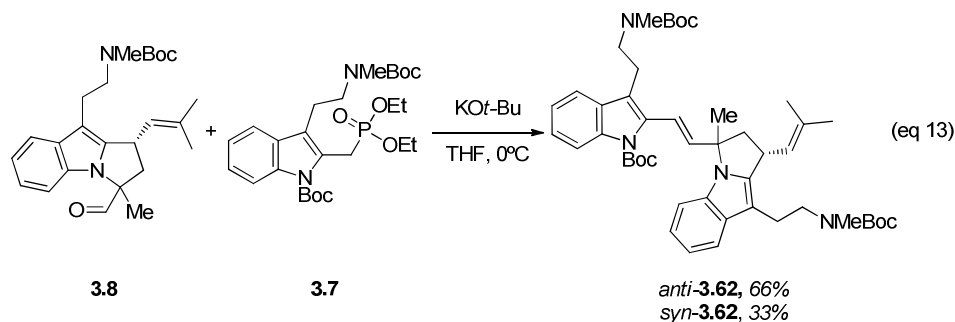
We began by considering the reaction of *anti*-**3.8** and **3.7**. Where Srinivasan and coworkers found success using sodium hydride as a base, we observed no reaction with these conditions. Given these preliminary negative results, a variety of bases were examined using phosphonate **3.7** and cyclic quarternary aldehyde **3.59** as a model system (Table 9). During this investigation, it was found that potassium bases were required to generate the desired olefin; sodium, lithium and cesium bases failed to promote the reaction (Table 9, entries 1-4). While both potassium *tert*-butoxide and KHMDS effected the coupling reaction, using KHMDS was significantly less selective for olefinated products (Table 9, entries 4-5). With potassium *tert*-butoxide, significant cleavage of the *N*ⁱⁿ-Boc carbamate was observed at 0 °C; this side reactivity was quelled by dropping the temperature to -40 °C (Table 9, entry 6). Using these conditions, the (*E*)-alkenes *anti*-**3.62** and *syn*-**3.62** were obtained from aldehydes *anti*-**3.8** and *syn*-**3.8** with phosphonate **3.7** in 66% and 33% yield²⁶ respectively (eq 13).

Table 9. Base screen for Horner-Wadsworth-Emmons olefination of phosphonate **3.7^a**



entry	base	temperature	3.60 : 3.61 ^b
1	NaH	0°C	--
2	<i>n</i> -BuLi	0°C	--
3	Cs ₂ CO ₃	0°C	--
4	KOt-Bu	0°C	2:1
5	KHMDS	0°C	1:0
6	KOt-Bu	-40°C	1:0

^aReaction conditions: phosphonate **3.7** (1.0 equiv), aldehyde **3.59** (1.1 equiv), base (1.2 equiv), THF (0.1 M), 2 h, temperature. ^bDetermined by ¹H NMR.



3.6.2) Horner-Wadsworth-Emmons olefination: a significant counteraction effect

With olefin **3.62** in hand, the last remaining hurdles were reduction of the –Boc groups to form the dimethylamine side-chains and cleavage of the –Boc group from the *N*ⁱⁿ position. Ideally, we hoped to achieve both of these synthetic manipulations in one step; previously reported examples suggested that *N*ⁱⁿ-Boc carbamates would be cleaved under reducing conditions.²⁷ Reduction of *anti*-**3.62** with excess of lithium aluminum hydride proceeded to give the natural product flinderole B (**3.2**); however, we were unable to isolate the natural product in pure form using this route.²⁸

3.7) Alcohols as an alkyl amine synthon

At this juncture, we considered using hydroxyl groups as masked amines in an alternative approach to installing the *N,N*-dimethylamine groups found in flinderoles B and C. We saw three potential routes to transforming a hydroxyl group to an amine: reductive amination, S_N2 substitution, and Mitsunobu reaction (Figure 4). With this synthesis strategy, we hoped to apply

the chemistry developed for the *N*-methyltryptamine compounds toward making tryptophol-based analogs.

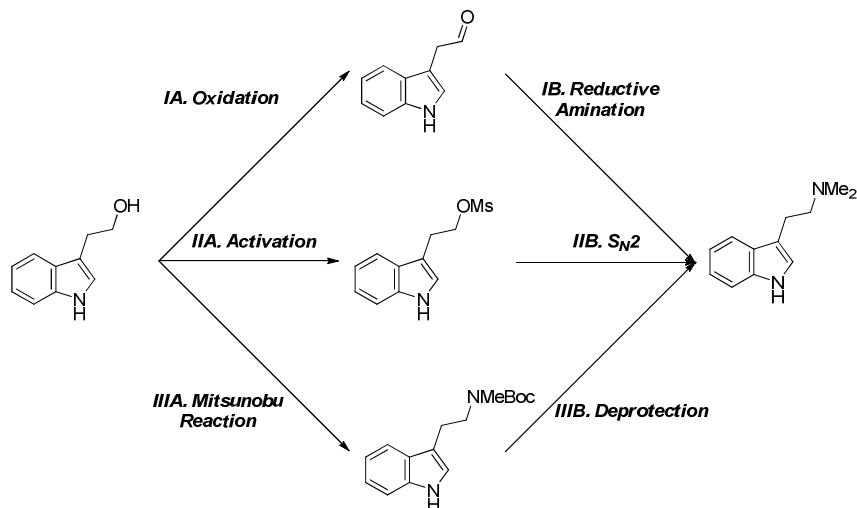
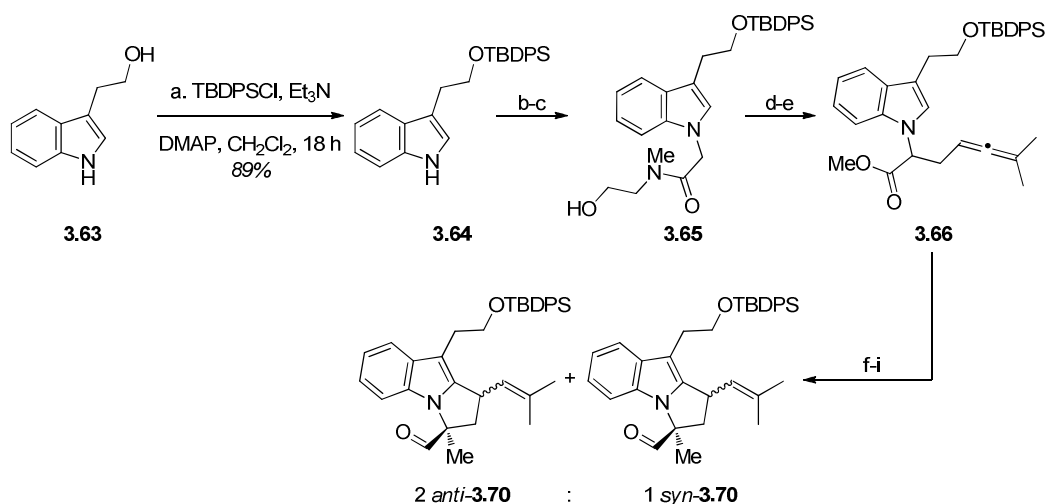


Figure 4. Potential ways to transform an alcohol in to a dimethyl amine include (I) oxidation/reductive amination, (II) activation/substitution, and (III) Mitsunobu reaction/deprotection.

3.7.1) Synthesis of tryptophol derived aldehyde **3.70**.

We elected to start by protecting tryptophol²⁹ (**3.63**) as the *tert*-butyldiphenylsilyl (TBDPS) ether: though more difficult to install and deprotect, the TBDPS group is less prone to hydrolysis by alkoxide bases than other commonly used silyl ethers. TBDPS-protected tryptophol proved amenable to the reaction sequence developed for tryptamine-based analogs—many reactions were in fact higher yielding with this type of substrate—allowing access to aldehydes *anti*-**3.70** and *syn*-**3.70** in 21% yield over nine steps (Scheme 11).



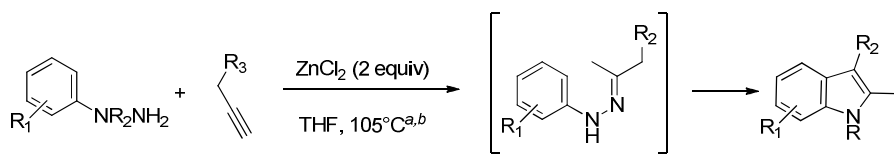
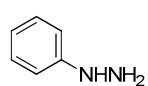
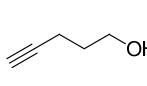
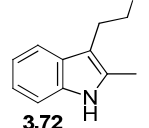
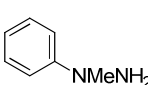
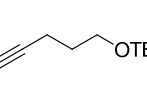
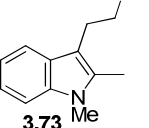
Scheme 11. Synthesis of tryptophol-derived aldehyde **3.70**. (a) TBDPSCl (1.0 equiv), Et₃N (1.2 equiv), DMAP (5 mol%), CH₂Cl₂, 18 h, rt; 89%. (b) KO^t-Bu (2.2 equiv), 0°C, 1 h; methyl

bromoacetate (3.2 equiv), rt, 18 h; 50% (72% BORSM). (c) *N*-methylaminoethanol (2.0 equiv), NaOMe (50 mol%), THF, rt, 2 h; 73%. (d) DIPA (2.25 equiv), *n*-BuLi (2.08 equiv), LiCl (6 equiv), THF, -78°C, 1 h; 0°C, 15 min; rt, 5 min; allene (3.0 equiv), 0°C, 2 h; 93%. (e) dimethyl carbonate (6.2 equiv), NaOMe (10.0 equiv), CH₂Cl₂, rt, 18 h; 96%. (f) IPrAuCl (5 mol%), AgSbF₆ (5 mol%), DCE, 45°C; 88%. (g) LiHMDS (1.2 equiv), THF, -78°C, 1 h; MeI (10 equiv), 1 h; 93%. (h) DIBAL-H (1.2 equiv), toluene, -78°C, 6 h; 90%. (i) SO₃·pyr (8.3 equiv), Et₃N (10.0 equiv), 1:1 DMSO/CH₂Cl₂, 0°C, 1 h; 75%.

3.7.2) Synthesis of tryptophol derived phosphonates **3.76** and **3.77**: Zinc(II)-promoted hydrohydrazination/Fischer indole cascade to generate 2,3-substituted indoles

We envisioned arriving at the necessary tryptophol-derived 2-indolephosphonate from 2-methyltryptophol (**3.72**). While this compound can be made by LiAlH₄ reduction of 2-methyl-3-indoleacetate, we felt we could access greater quantities of the desired product by constructing the indole core from simpler starting materials. A particularly attractive option was the zinc(II)-promoted hydrohydrazination reaction developed by Beller (Table 10).³⁰ The authors propose that the reaction proceeds by zinc(II)-catalyzed Markovnikov addition of a hydrazine to an alkyne, forming an imine; the Lewis acidic zinc salts also promote a subsequent Fischer indole-type sequence of (1) isomerization to the more stable enamine, (2) [3,3]-sigmatropic rearrangement, (3) cyclic amination formation and (4) elimination of ammonia to produce the 2-methylindole product. They report a number of hydrazine/alkyne reaction partners; of greatest relevance to this work are the syntheses of 2-methyltryptophol derivatives **3.72** and **3.73**.

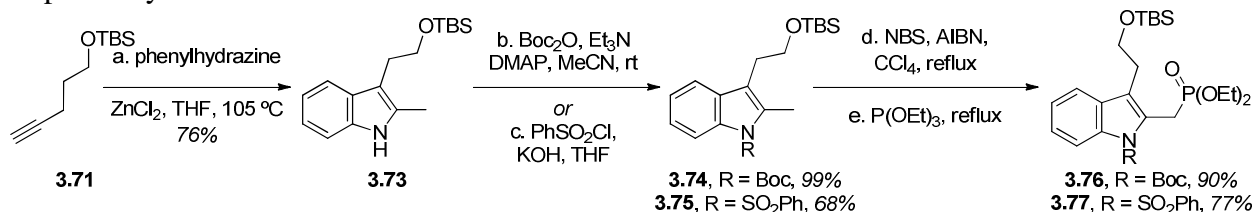
Table 9. Zinc(II)-promoted indole synthesis from phenylhydrazine and alkynes^{a,b}

				
entry	phenylhydrazine	alkyne	indole	yield ^c
1			 3.72	97%
2		 3.71	 3.73	82%

^aResults from ref. x. ^bReaction conditions: alkyne (1.0 equiv), N-methyl-N-phenylhydrazine or N-phenylhydrazine (1.3 equiv), ZnCl₂ (3.0 equiv), THF (0.38 M), 105°C, 24 h. ^cYield of isolated product.

In our hands, stirring phenylhydrazine and TBS-protected pentyn-4-ol (**3.71**) with an excess of zinc(II) chloride in THF at 105°C gave desired TBS-protected 2-methyltryptophol (**3.73**) in

76% yield. Protection of the N^{in} -position occurred cleanly using Boc_2O , triethylamine, and catalytic DMAP to give Boc-protected compound **3.74**; at this time, phenylsulfonyl-protected compound **3.75** was also prepared. Performing a radical bromination/Arbuzov sequence on 2-methyltryptophols **3.74** and **3.75** afforded phosphonates **3.76** and **3.77** in 90% and 77% yield, respectively.



Scheme 12. Synthesis of phosphonates **3.76** and **3.77**. (a) phenylhydrazine (1.5 equiv), **3.71** (1.0 equiv), ZnCl_2 (3.0 equiv), THF, 105°C , 18 h; 76%. (b) Boc_2O (1.1 equiv), Et_3N (2.0 equiv), DMAP (10 mol%), MeCN, rt, 18 h; 99%. (c) PhSO_2Cl (3.0 equiv), KOH (5.0 equiv), THF, 0°C to rt, 18 h; 68%. (d) NBS (1.0 equiv), AIBN (10 mol%), CCl_4 , 75°C , 18 h. (e) $\text{P}(\text{OEt})_3$ (7.0 equiv), 55°C , 48 h; **3.76**, 90%; **3.77**, 77%.

In summary, we were able to make desired coupling partners **3.76** and **3.77** in 53% and 40% yields, respectively, over four steps from known compounds phenylhydrazine and TBS-protected pentynol **3.71**.

3.8) Total synthesis of flinderols B and C

Having successfully completed the synthesis of tryptophol-based aldehydes *anti*-**3.70** and *syn*-**3.70** and phosphonates **3.76** and **3.77**, the remaining steps toward completion of flinderols B and C were (a) olefination to effect coupling of the two indole fragments, (b) selective deprotection of the side-chain silyl ethers, (c) elaboration of the ethoxy side-chains to dimethylamines, and (d) deprotection of the N -indole protecting group.

At this point in our investigation, Dethe and coworkers reported the biomimetic total synthesis of flinderols B and C using a Lewis-acid catalyzed [3+2] reaction to assemble the pyrrolidine C ring (Figure 5).³¹ The route they describe nicely matched our plan to introduce the amine side-chains by reductive amination; we decided to adopt their strategy in order to complete the total synthesis of these two compounds.

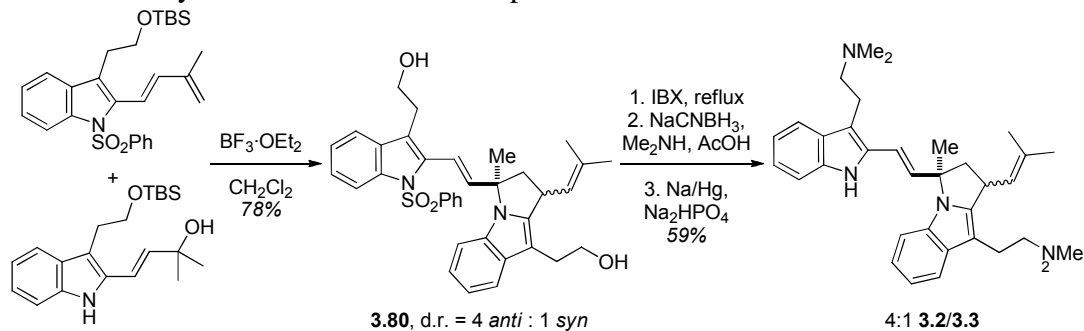
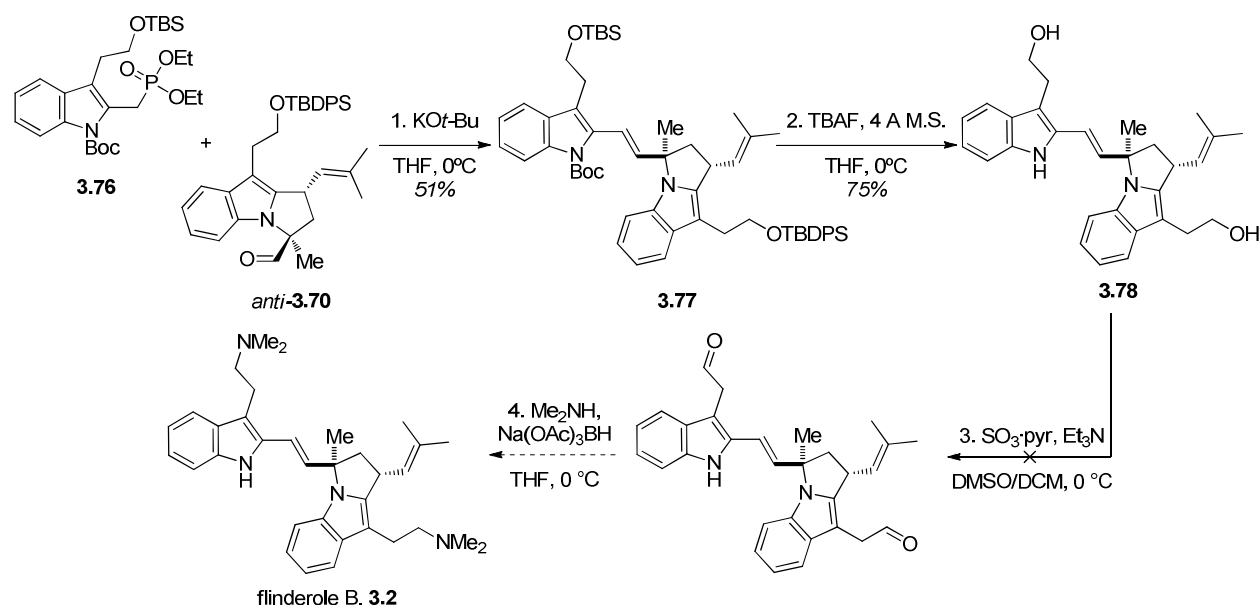


Figure 5. Total synthesis of flinderols B (**3.2**) and C (**3.3**) by a Lewis-Acid catalyzed [3+2] cycloaddition.

3.8.1) Formation and global deprotection of N^{in} -Boc protected bisindole olefin **3.78**

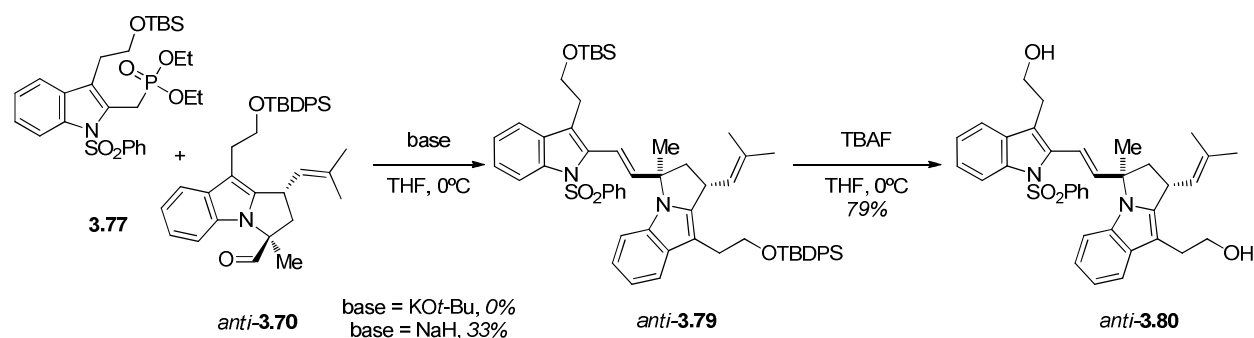
When beginning experiments toward the flinderole end-game, we opted to start with N^{in} -Boc protected phosphonate **3.76**. Exposure of phosphonate **3.76** and aldehyde *anti*-**3.70** gave coupled product *anti*-**2.78** in 51% yield. Subsequent removal of the silyl ethers with TBAF in THF resulted in cleavage of both alcohol protecting groups as well as partial removal of the N^{in} -indole Boc carbamate; more TBAF was added to give globally deprotected diol **3.79** in 75% yield. Oxidation of this compound using Parikh-Doering conditions was unsuccessful, leading to decomposition of the bisindole starting material.



Scheme 13. N -Boc protecting group approach to flinderole B (**3.2**). (a) **3.76** (1.0 equiv), **3.70** (1.0 equiv), $\text{KO}^t\text{-Bu}$ (2.0 equiv), THF, 0°C , 1 h; 51%. (b) TBAF (5.0 equiv), 4 Å mol. sieves, THF, 0°C , 18 h; 75%.

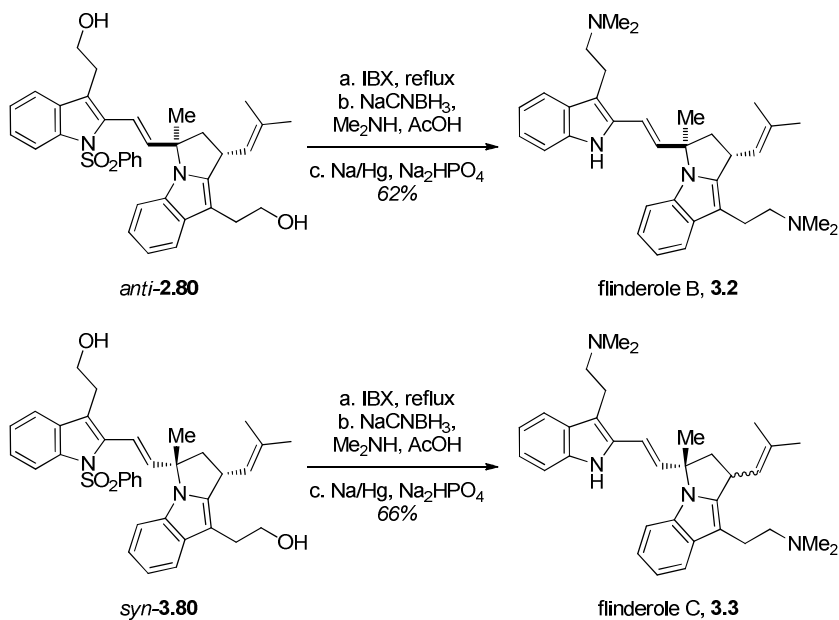
3.8.2) Formation and global deprotection of N -Boc protected bisindole olefin **3**: total synthesis of flinderole B (**3.2**) and C (**3.3**)

Given the demonstrated success of performing an oxidation/reductive amination cascade on diol **3.80**, we decided to shift our efforts toward optimizing this system. Surprisingly, when potassium *tert*-butoxide was used as the base with the phenylsulfonamide-protected phosphonate **3.77** in the presence of aldehydes *anti*-**3.70** and *syn*-**3.70**, no formation of the desired olefin product was observed. Upon reexamining the work reported by Srinivasan concerning the reactivity of 2-methylindole phosphonate esters (Table 8), we wondered if the conformational perturbation as one changed from a bulky carbamate to a planar sulfonamide protecting group was effecting the activity of the phosphonate-stabilized carbanion species. Switching to sodium hydride as the base in the olefination reaction allowed for formation of desired coupled products *anti*-**3.79** and *syn*-**3.79** (Scheme 14). Cleavage of the silyl ethers using TBAF then led to synthesis of Dethe's intermediate *anti*-**3.80**.



Scheme 13. Synthesis of Dethe intermediate *anti*-**2.79**. (n) **2.70** (1.0 equiv), **2.77** (1.5 equiv), NaH (1.8 equiv), THF, 0°C, 1 h; *anti*-**2.79**: 33%, *syn*-**2.79**: 32%. (o) TBAF (12.0 equiv), THF, rt, 7 h; *anti*: 79%, *syn*: 74%.

With the diol in hand, we set to complete the synthesis of flinderoles B and C following the route developed by Dethe. Oxidation of diols *anti*-**3.80** and *syn*-**3.80** with IBX cleanly afforded the dial in both cases; after filtration to remove the insoluble oxidant, the reductive amination was achieved using dimethylamine and sodium(triacetoxy)borohydride. Lastly, removal of the phenylsulfonamide using Na/Hg amalgam afforded the natural products flinderole B (**3.2**) and flinderole C (**3.3**) in 62% and 66% yields, respectively (Scheme 14).



Scheme 14. Synthesis of flinderoles B (**3.2**) and C (**3.3**). (a) IBX (6.0 equiv), EtOAc, 80°C, 1 h. (b) Me₂NH (8.0 equiv), NaCNBH₃ (4.0 equiv), 1:39 AcOH/MeOH, rt, 18 h; *anti*: 68%, *syn*: 73%. (c) Na/Hg (20 equiv), Na₂HPO₄ (20 equiv), MeOH, rt, 3 h; **3.2**, 95%; **3.3**, 91%.

3.9) Studies toward a catalytic asymmetric route

Given the utility of catalytic, enantioselective transformations in synthetic chemistry, we were interested in developing a route which employed an asymmetric gold(I)-catalyzed reaction as our key step.³²

3.9.1) Enantioselective gold(I)-catalyzed cycloisomerization strategy

The first approach we took toward an asymmetric synthesis of flinderole features the same fundamental disconnections as the racemic work: we still envisioned building the pyrrolidine C ring through a gold(I)-catalyzed hydroarylation of indole and aimed to install the allene through alkylation of an N^{in} -indole acetate. In order to render the starting material for the gold(I) step achiral, we envisioned using a dialkyl malonate linker to connect the allene and the indole groups (Figure 6).

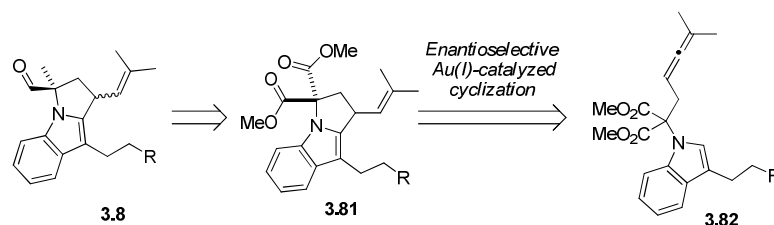
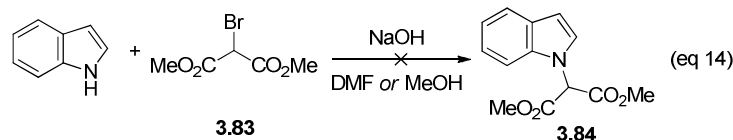
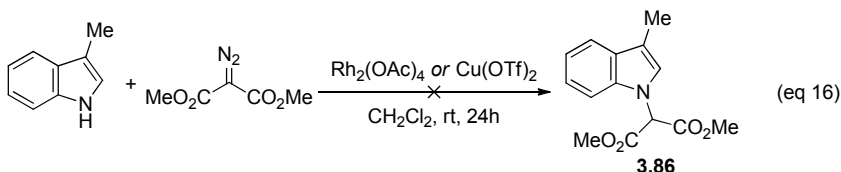
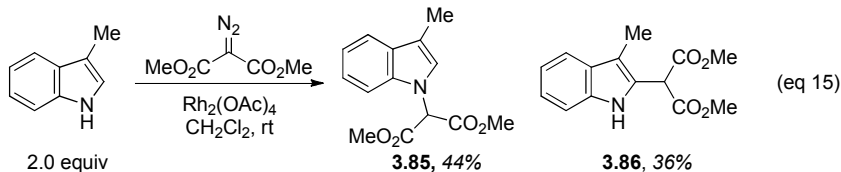


Figure 6. Asymmetric retrosynthetic analysis of the flinderole eastern fragment.

Our first thought for making substrate **3.82** was to perform N^{in} -alkylation of indole using dimethyl 2-bromomalonate (**3.83**). Attempts at achieving this transformation on indole with sodium hydroxide as the base yielded none of the desired product **3.84** (eq 14).



After this reaction failed, we searched for precedented transformations that generate 2- N^{in} -(indole)malonate structures. The synthesis of dimethyl malonate compounds **3.85** and **3.86** by treatment dimethyl diazomalonate with two equivalents of 3-methylindole in the presence of catalytic rhodium(II)acetate (10 mol%) has been reported (eq 15).³³ However, the use of excess indole (two equivalents) and the lack of chemoselectivity make this reaction difficult in the context of this total synthesis: given that the indole portion of the molecule is more synthetically intensive, an early-stage transformation with only 22% yield is impractical. When we attempted to use this methodology with a slight excess of the 3-methylindole with respect to dimethyl diazomalonate, we observed no reaction; we saw the same result when we used copper(II) triflate as the catalyst (eq 16).



The difficulty of making 2-indolemalonates led us to reshape our strategy to have assembly of the indole nucleus follow *N*-alkylation of an aniline. In this approach, we planned to start with 2-iodoaniline (**3.88**): *N*-alkylation with dimethyl 2-bromomalonate (**3.82**), Sonogashira coupling with trimethylsilylacetylene, and alkylation with allenyl bromide **3.89** would lead to the necessary substrate for a one-pot gold(I)-catalyzed indole synthesis/hydroarylation reaction (Figure 7).

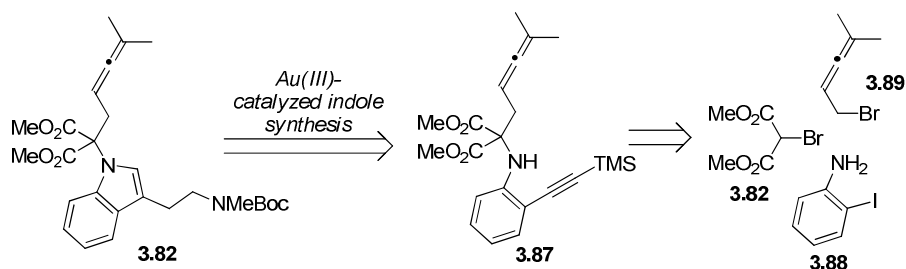
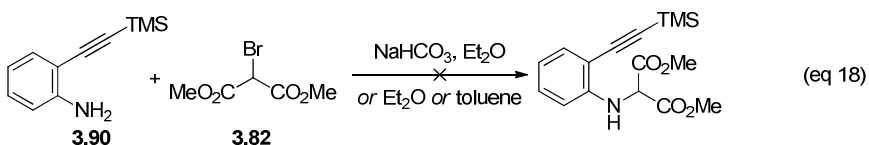
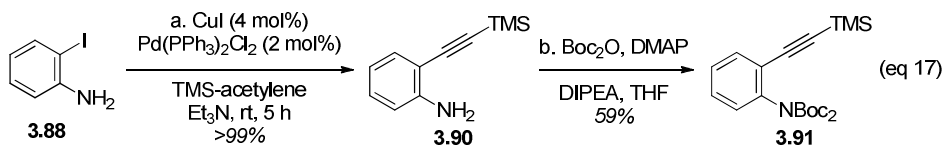
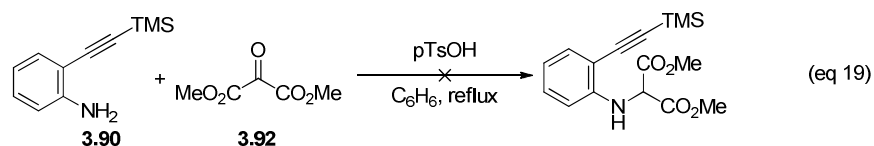


Figure 7. Gold(III)/gold(I)-catalyzed indole synthesis/hydroarylation cascade to assemble the flinderole eastern fragment.

Sonogashira coupling of 2-iodoaniline (**3.88**) with trimethylacetylene using 2 mol % bis(triphenylphosphine)palladium(II) chloride and 4 mol % copper(I) iodide yielded the desired alkynylaniline **3.90** in >99% yield. Next, we attempted to form the aniline –Boc carbamate, both to protect this acidic functionality and to increase the aniline's nucleophilicity; however, attempts at –Boc protection resulted in sole isolation of doubly protected compound **3.91** (eq 17). Alkylating the free aniline **3.90** with dimethyl 2-bromomalonate (**3.82**) was also unsuccessful (eq 18), as was condensation with dimethyl 2-oxomalonate (**3.92**) (eq 19).





3.9.2) An asymmetric induction approach: chirality transfer from an enantioenriched allene

When attempts to make substrates for a catalytic, enantioselective rendition of the gold(I)-catalyzed hydroarylation reaction proved unsuccessful, we analyzed our synthesis route for other opportunities to catalytically introduce chiral information. We decided to try introducing asymmetry prior to the gold(I)-catalyzed formation of pyrrolidine **3.67**. The high diastereoselectivity of the cyclization reaction should allow for chirality transfer to the C3' position; this C3' chiral center in turn sets the chirality of the C17 methyl group.

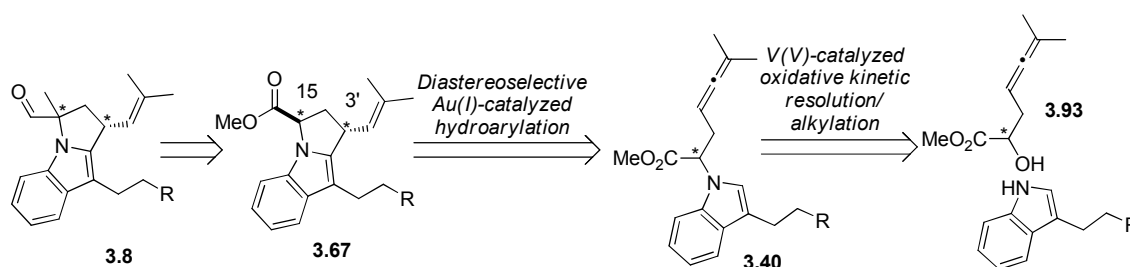


Figure 8. Vanadium(V)-catalyzed oxidative kinetic resolution/chirality transfer approach to an asymmetric synthesis of the flinderole eastern fragment **3.8**.

To accommodate this type of disconnection, we developed a retrosynthetic strategy, depicted in Figure 8, which intercepts indole-allene intermediate **3.40** from the racemic synthesis of flinderoles B and C. We intend to render this substrate optically active through N^{in} -indole alkylation with enantioenriched glycolic ester **3.93**. We hoped to employ the vanadium(V)-catalyzed oxidative kinetic resolution of glyoxylates developed in our group to generate **3.93**.³⁴ This methodology takes advantage of the differing rates of reaction of matched and mismatched transition states for the oxidation of glycolic esters in the presence of a chiral vanadium catalyst. We were encouraged that this reaction could provide us with chiral **3.93** by the moderate to high selectivities obtained using glycolic esters with alkene, alkyne, and alkane substitution (eq 20); Table 10 features some of the more relevant examples. This methodology has been applied by our group to the convergent synthesis of (—)-octalactin A.³⁵

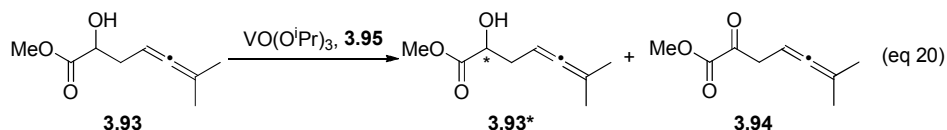


Table 10. Vanadium(V)-catalyzed oxidative kinetic resolution of glycolic esters.^a

Reaction scheme showing the kinetic resolution of a chiral glycolic ester derivative using $\text{VO}(\text{O}-i\text{-Pr})_2$ (5 mol%) and **2.95** (5.5 mol%) in acetone, O_2 , rt. The reaction yields a chiral glycolic ester derivative and a ketone byproduct.

Reaction conditions: 5 mol% $\text{VO}(\text{O}-i\text{-Pr})_2$, 5.5 mol% **2.95**, acetone, O_2 , rt.

Reaction scheme:

$$\text{R}_1\text{CH}(\text{OH})\text{C}(=\text{O})\text{OR}_2 \xrightarrow[\text{acetone, O}_2, \text{rt}]{5 \text{ mol\% VO}(\text{O}-i\text{-Pr})_2, 5.5 \text{ mol\% } \mathbf{2.95}} \text{R}_1\text{CH}(\text{OH})\text{C}(=\text{O})\text{OR}_2 + \text{R}_1\text{C}(=\text{O})\text{OR}_2$$

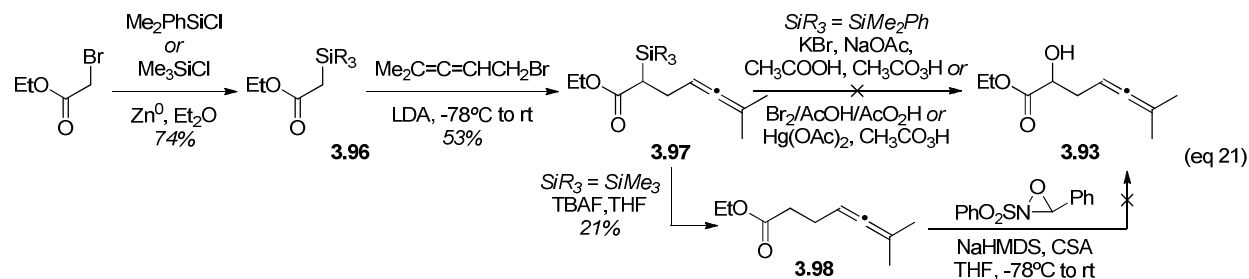
Structure of **2.95** (shown in the original image):

2.95

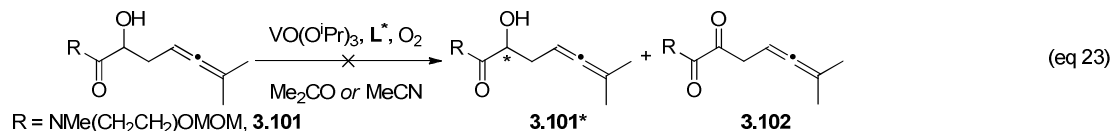
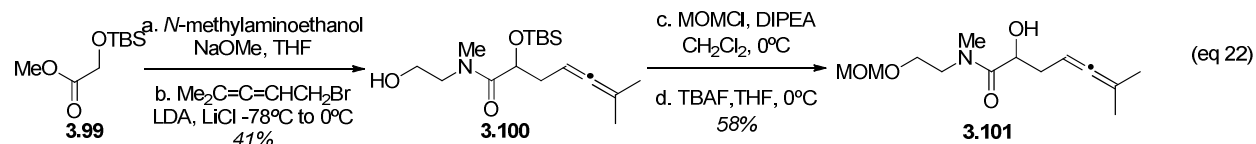
entry	R ₁	R ₂	conversion	isolated yield	ee	s
1	Ph	OEt	51%	49% (95%)	99%	>50
2		OBn	57%	45% (90%)	92%	18
3		OEt	47%	53% (85%)	50%	6
4		OMe	51%	48% (95%)	90%	42

^a See ref. xx.

Our strategy for arriving at racemic alcohol **3.93** hinges on enolate alkylation of a methyl ethanoate derivative featuring a heteroatom mask for the necessary secondary alcohol. We first attempted to use a Tamao-Fleming oxidation of dimethylphenylsilyl derivative **3.97**. Substitution of ethyl bromoacetate with chlorodimethylphenylsilyl provides ethyl 2-(dimethylphenylsilyl)acetate (**3.96**); alkylation of the corresponding enolate gives allene **3.97**. Unfortunately, exposure of this compound to a wide variety of Tamao-Fleming oxidation conditions failed to produce the desired alcohol **3.93**; attempts to perform an α -oxidation on reduced allene ester **3.98** using Davis oxaziridine conditions were also unsuccessful.

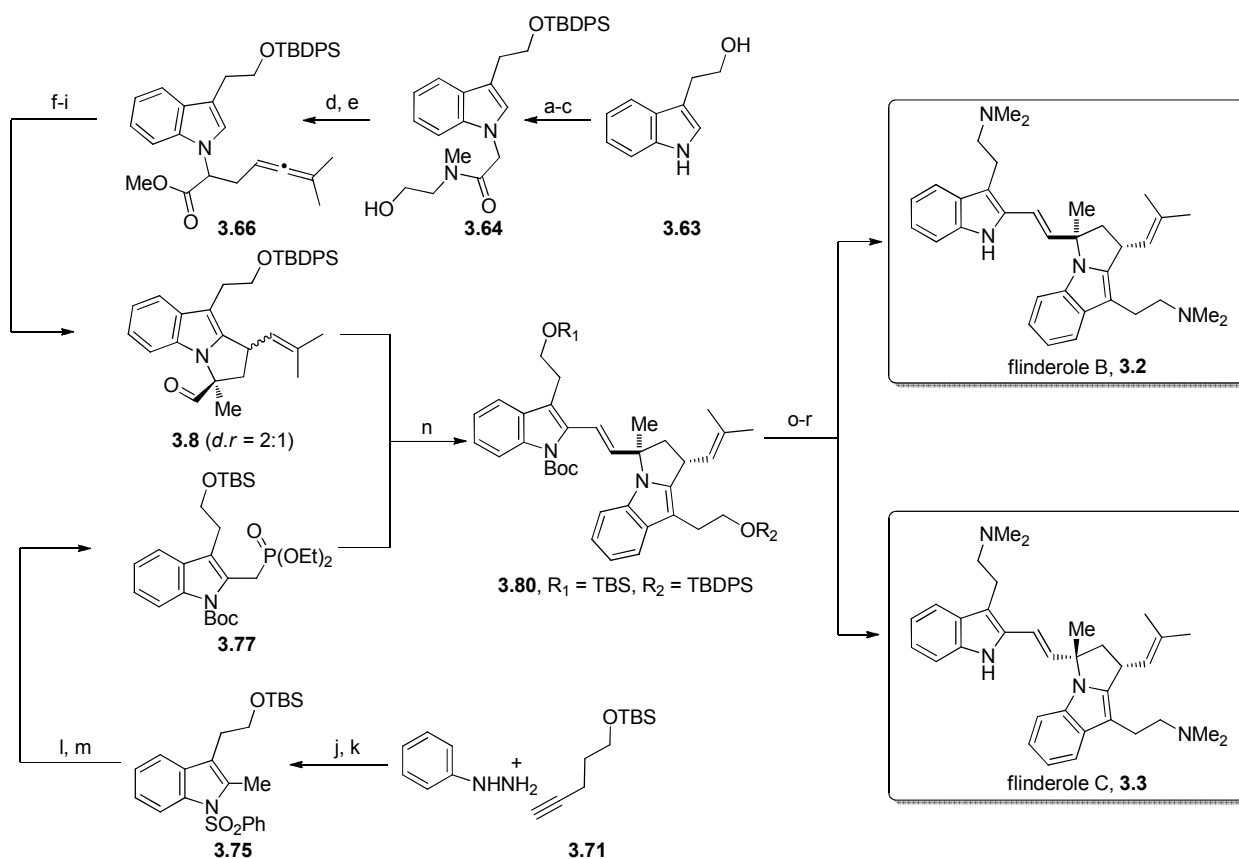


With α -oxidation in the presence of an allene proving difficult, we turned to alkylation of silyl-protected methyl glycolic ester **3.99**. Alkylation of this compound led to rapid decomposition of starting material; fortunately, using the *N*-methyamidoethanol auxiliary developed for alkylating α -*N*ⁱⁿ-indole enolates allowed us access to the alkylated compound **3.100**, demonstrating that this is a general strategy for achieving difficult ester alkylation reactions. Protection of the terminal alcohol as the MOM ether followed by TBAF deprotection yielded α -hydroxy amide **3.101** (eq 22). Regrettably, exposure of this substrate to the vanadium(V) kinetic oxidative resolution conditions gave none of the desired ketone product (eq 23). Given the poor yields and high step count required to generate structures such as **3.93** and **3.101**, we decided at this point to abandon this synthesis strategy and focus our efforts on the racemic route.



2.10) Conclusions

The total synthesis of antimalarial bisindole alkaloids flinderole B (**3.2**) and C (**3.3**) was successfully completed with 18 steps (14 longest linear sequence) in 4% overall yield from the commercially available tryptophol **3.63** (Scheme 15). The three unique structural features of the flinderole molecular scaffold—the pyrrolidine C ring, the C3' isobutenyl functionality, and the unsaturation at C16—are formed through a gold(I)-catalyzed intramolecular hydroarylation of a pendant allene. The synthesis also highlights a novel approach to α -heteroatom enolate alkylations as well as Horner-Wadsworth-Emmons olefination of an electron-rich phosphonate and a hindered alkyl aldehyde.



Scheme 12. Synthesis of flinderoles B (**3.2**) and C (**3.3**). (a) TBDPSCl (1.0 equiv), Et₃N (1.2 equiv), DMAP (5 mol%), CH₂Cl₂, 18 h, rt; 89%. (b) KO^t-Bu (2.2 equiv), 0°C, 1 h; methyl

bromoacetate (3.2 equiv), rt, 18 h; 50% (72% BORSM). (c) *N*-methylaminoethanol (2.0 equiv), NaOMe (50 mol%), THF, rt, 2 h; 73%. (d) DIPA (2.25 equiv), *n*-BuLi (2.08 equiv), LiCl (6 equiv), THF, -78°C, 1 h; 0°C, 15 min; rt, 5 min; allene (3.0 equiv), 0°C, 2 h; 93%. (e) dimethyl carbonate (6.2 equiv), NaOMe (10.0 equiv), CH₂Cl₂, rt, 18 h; 96%. (f) IPrAuCl (5 mol%), AgSbF₆ (5 mol%), DCE, 45°C; 88%. (g) LiHMDS (1.2 equiv), THF, -78°C, 1 h; MeI (10 equiv), 1 h; 93%. (h) DIBAL-H (1.2 equiv), toluene, -78°C, 6 h; 90%. (i) SO₃·pyr (8.3 equiv), Et₃N (10.0 equiv), 1:1 DMSO/CH₂Cl₂, 0°C, 1 h; 75%. (j) phenylhydrazine (1.5 equiv), **2.71** (1.0 equiv), ZnCl₂ (3.0 equiv), THF, 105°C, 18 h; 76%. (k) PhSO₂Cl (3.0 equiv), KOH (5.0 equiv), THF, 0°C to rt, 18 h; 68%. (l) NBS (1.0 equiv), AIBN (10 mol%), CCl₄, 75°C, 18 h. (m) P(OEt)₃ (7.0 equiv), 55°C, 48 h; 77%. (n) **3.70** (1.0 equiv), **3.77** (1.5 equiv), NaH (1.8 equiv), THF, 0°C, 1 h; *anti*-**3.80**: 33%, *syn*-**3.80**: 32%. (o) TBAF (12.0 equiv), THF, rt, 7h; *anti*: 79%, *syn*: 74%. (a) IBX (6.0 equiv), EtOAc, 80°C, 1 h. (b) Me₂NH (8.0 equiv), NaCNBH₃ (4.0 equiv), 1:39 AcOH/MeOH, rt, 18 h; *anti*: 68%, *syn*: 73%. (c) Na/Hg (20 equiv), Na₂HPO₄ (20 equiv), MeOH, rt, 3 h; **3.2**, 95%; **3.3**, 91%.

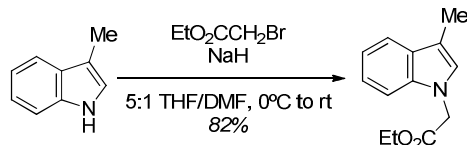
Aside from the new types of disconnections explored in the course of this investigation, our work also highlights the value of learning to think within a complex structural framework. Issues of chemoselectivity and neighboring group effects—daily concerns for any organic chemist—reach a new level of importance when working with molecules that possess several diverse reactive functionalities. Most of the reactions developed in the course of completing flinderole showcase the necessity of taking a holistic approach to total synthesis. Through intelligent selection and proper optimization of reaction conditions, we are able to develop selective, efficient, and often elegant, solutions to the construction of complex molecules.

Additional Supporting Information

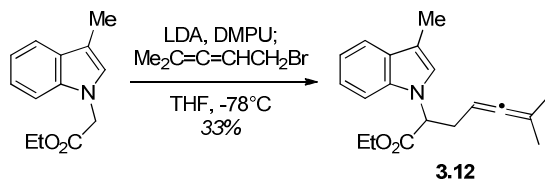
General Information

Unless otherwise noted, all reagents were obtained commercially and used without further purification. All reaction mixtures were stirred with a magnetic stir bar in flame-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and triethylamine (Et₃N) were dried were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns. Diisopropylamine (ⁱPr₂NH) and acetonitrile (MeCN) were distilled over CaH₂.³⁶ Dry DMSO and methanol were obtained from Acros. Lithium chloride was dried overnight while stirring at 150°C under vacuum. Extracts were dried over MgSO₄ or Na₂SO₄ and solvents were removed via a rotary evaporator. TLC analysis of reaction mixtures was performed on Merck silica gel 60 F254 TLC plates. Unless otherwise indicated, chromatography was carried out on ICN SiliTech 32-63 D 60 Å silica gel. ¹H, ¹³C NMR and ³¹P NMR spectra were recorded with Bruker AMX-300, AVQ-400, AVB-400, DRX-500 and AV-500 spectrometers and referenced to CDCl₃ or D₆-DMSO. The order of citation in parentheses is a) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, a = apparent), b) number of protons, and c) coupling constants calculated to two significant figures. Structures were confirmed using NOESY, COSY, ROESY and HSQC experiments. Mass spectra data were obtained at the Micro-Mass/Analytical Facility in the College of Chemistry, University of California, Berkeley.

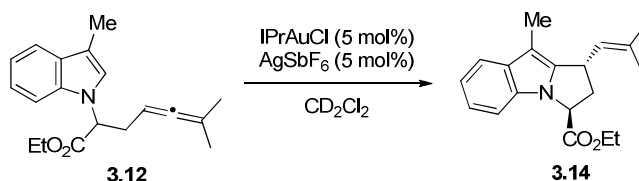
1. Model studies of the gold(I)-catalyzed hydroarylation reaction



Ethyl (3-methyl-1*H*-indol-1-yl)acetate. To a solution of NaH (60% in mineral oil) (0.976 g, 24.4 mmol, 3.2 equiv) in 4:1 THF/DMF (75 mL) at 0°C was added a solution of 3-methylindole (1.0 g, 7.62 mmol, 1.0 equiv) in THF (10 mL). After stirring for 45 min, ethyl bromoacetate (4.08 g, 24.4 mmol, 3.2 equiv) was added dropwise by syringe. The reaction mixture turned bright yellow as it was warmed to room temperature. The reaction was allowed to stir overnight, at which time the reaction mixture was quenched by pouring over a separatory funnel with an ice/WATER mixture. The products were extracted with Et₂O (1 x 100 mL). The organic layer was then washed with WATER (1 x 50 mL), dried over Na₂SO₄, and concentrated. The product was isolated as a yellow oil (1.36 g, 6.27 mmol, 82%) by silica gel chromatography (25% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, 1H, *J* = 6.4 Hz), 7.26-7.32 (m, 2H), 7.217 (ddd, 1H, *J* = 6.4 Hz, 4.8 Hz, 1.2 Hz), 6.91 (d, 1H, *J* = 0.8 Hz), 4.81 (s, 2H), 4.27 (q, 2H, *J* = 5.7 Hz), 2.42 (s, 3H), 1.33 (t, 3H, *J* = 5.8 Hz).

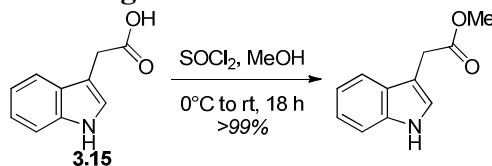


Ethyl 6-methyl-2-(3-methyl-1*H*-indol-1-yl)hepta-4,5-dienoate (3.12). To a stirred solution of DIPA (75 mg, 0.745 mmol, 1.2 equiv) and *n*-BuLi (2.5 M in hexanes) (0.27 mL, 0.683 mmol, 1.1 equiv) in THF (3 mL) at -78°C was added a solution of the ester (130 mg, 0.621 mmol, 1.0 equiv) in THF (3.5 mL). This mixture stirred 1 h at -78°C; DMPU (87.5 mg, 0.683 mmol, 1.1 equiv) was then added. After five minutes, a solution of the allene (100 mg, 0.621 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise by syringe. The reaction mixture stirred 2 h at -78°C; the reaction mixture was then warmed to -10°C and stirred an additional 90 min. The reaction mixture was then quenched with saturated aqueous NaHCO₃ (5 mL) and the resulting biphasic solution was extracted with Et₂O (1 x 10 mL). The organic layer was then washed with brine (1 x 5 mL), dried over MgSO₄ and concentrated. The product was isolated as a yellow oil (61 mg, 0.204 mmol, 33%) by silica gel chromatography (5% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.57 (d, 1H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 7.5 Hz), 7.13 (t, 1H, *J* = 7.3 Hz), 7.08 (s, 1H), 5.04 (dd, 1H, *J* = 9.0 Hz, 6.5 Hz), 4.86-4.92 (m, 1H), 4.14-4.21 (m, 2H), 2.90 (dt, 1H, *J* = 15.0 Hz, 6.3 Hz), 2.77 (ddd, 1H, *J* = 15.3 Hz, 9.0 Hz, 6.5 Hz), 2.35 (s, 3H), 4.81 (s, 2H), 4.27 (q, 2H, *J* = 5.7 Hz), 2.42 (s, 3H), 1.52 (d, 3H, *J* = 2.5 Hz), 1.43 (d, 3H, *J* = 2.5 Hz), 1.24 (t, 3H, *J* = 7.0 Hz). ¹³C NMR (100 MHz, CDCl₃): 202.6, 170.6, 136.8, 128.9, 122.9, 121.5, 119.0, 111.4, 109.0, 96.9, 83.8, 61.5, 57.6, 31.7, 20.2, 20.1, 14.1, 9.7.

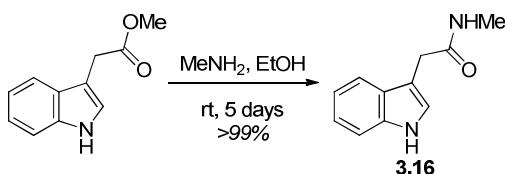


Ethyl 9-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate (3.14). IPrAuCl (3.1 mg, 0.005 mmol, 5 mol %) and AgSbF₆ (1.7 mg, 0.005 mmol, 5 mol %) in CD₂Cl₂ (0.5 mL) were mixed in the dark in a sealed vial. After five minutes, the catalyst mixture was passed through a glass wool filter in to a solution of **3.12** (30 mg, 0.100 mmol, 1.0 equiv) in CD₂Cl₂ (0.5 mL). The filter was washed with dichloroethane (2 x 0.1 mL) and then the reaction vessel was sealed and submerged in a 50°C oil bath for 1 h. The reaction mixture was then filtered over a silica gel plug to give the pure product as a yellow oil (26 mg, 0.875 mmol, 88%). ¹H NMR (400 MHz, CDCl₃): δ 7.46 (dd, 1H, *J* = 6.4 Hz, 1.6 Hz), 7.04-7.13 (m, 3 H), 5.26 (dt, 1H, *J* = 9.6 Hz, 1.3 Hz), 4.85 (dd, 1H, *J* = 8.4 Hz, 6.0 Hz), 4.26 (q, 2H, *J* = 7.1 Hz), 4.11-4.19 (m, 1H), 3.17 (dt, 1H, *J* = 13.2 Hz, 8.8 Hz), 2.39 (dt, 1H, *J* = 13.2 Hz, 5.8 Hz), 2.167 (s, 3H), 1.83 (s, 3H), 1.64 (s, 3H), 1.52 (d, 3H, *J* = 2.5 Hz), 1.43 (d, 3H, *J* = 2.5 Hz), 1.25 (t, 3H, *J* = 7.0 Hz). ¹³C NMR (100 MHz, CDCl₃): 202.6, 170.6, 136.8, 128.9, 122.9, 121.5, 119.0, 111.4, 109.0, 96.9, 83.8, 61.5, 57.6, 31.7, 20.2, 20.1, 14.1, 9.7.

3. *N*-Boc-*N*-methyltryptamine analogs

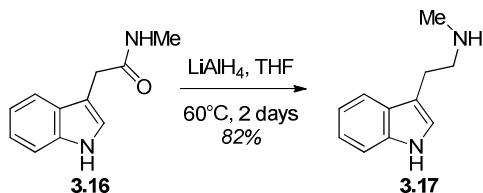


Methyl 3-indoleacetate. To a stirred solution of 3-indoleacetic acid (25 g, 143 mmol, 1 equiv) in methanol (1 L) cooled to 7°C in a 2L two-necked flask fitted with an addition funnel and a thermometer was added SOCl₂ (20.4 g, 171 mmol, 1.2 equiv) over 45 minutes, maintaining a constant internal temperature of 10°C. The reaction stirred overnight at room temperature. Solid NaHCO₃ (50 g) was added portionwise over twenty minutes, and the resulting mixture was decanted and concentrated to give a solid residue. The residue was dissolved in Et₂O (200 mL) and water (200 mL) and the layers were separated. The aqueous layer was then washed with Et₂O (2 x 200 mL) and the combined organic layers were washed with brine (1 x 200 mL), dried over MgSO₄ and concentrated by rotary evaporator. The resulting product (27 g) was isolated as a red oil and used without further purification. Spectroscopic data obtained for this product were consistent with those previously reported by Kessler, et. al.³⁷ ¹H NMR (400 MHz, CDCl₃): δ 8.09 (broad s, 1H), 7.63 (d, 1H, *J* = 8.0 Hz), 7.36 (d, 1H, *J* = 8.4 Hz), 7.21 (ddd, 1H, *J* = 8.0 Hz, 7.0 Hz, 1.0 Hz), 7.16 (s, 1H), 7.147 (ddd, 1H, *J* = 8.0 Hz, 7.0 Hz, 0.8 Hz), 3.89 (s, 2H), 3.711 (s, 3H).

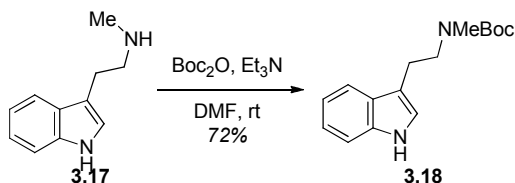


***N*-methyl 3-indoleacetamide (3.16).** Methyl 3-indoleacetate (27 g, 143 mmol, 1 equiv) was dissolved in MeNH₂ (33% wt in EtOH) (100 mL) and was stirred at room temperature for two

days. The product was isolated by removal of the volatile compounds by rotary evaporator followed by azeotrope with EtOAc (2 x 100 mL), toluene (1 x 100 mL), EtOAc (1 x 100 mL), and chloroform (1 x 100 mL)). The product was isolated as a tan solid after drying while stirring under reduced pressure (2 atm). ^1H NMR (400 MHz, CDCl_3): δ 8.78 (broad s, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.25 (ddd, 1H, J = 8.0 Hz, 8.0 Hz, 1.2 Hz), 7.15 (ddd, 1H, 8.0 Hz, 8.0 Hz, 1.0 Hz), 7.13 (s, 1H), 5.76 (broad s, 1H), 3.76 (s, 2H), 2.72 (d, 1H, J = 4.8 Hz).

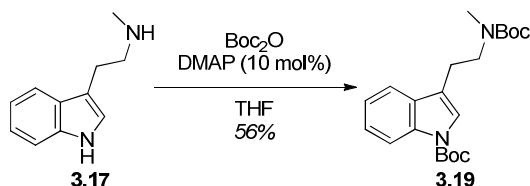


N-methyl tryptamine (3.17). To stirred suspension of LiAlH_4 (5.9 g, 156 mmol, 6 equiv) in THF (100 mL) at 0°C was added dropwise by canula over ten minutes a solution of **3.16** (4.9 g, 26.0 mmol, 1 equiv) in THF. The reaction stirred fifteen minutes at 0°C and was then transferred to an oil bath. The flask was fitted with a reflux condenser and the bath was then heated to 60°C and the mixture stirred for forty-eight hours. The flask was then cooled to 0°C by submerging in an ice bath, and the remaining aluminum reagent was quenched with solid $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ (20 g) over thirty minutes. Additional THF (100 mL) was then added to facilitate stirring. The salts digested overnight, forming a white powder. The salts were removed by sequential vacuum and gravity filtration, and the resulting red solution was concentrated by rotary evaporator and dried while stirring under reduced pressure (2 atm) to yield the product (3.71 g) in 82% yield as a red solid. ^1H NMR (400 MHz, CDCl_3): δ 8.37 (broad s, 1H), 7.64 (d, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.21 (t, 1H, J = 7.0 Hz), 7.15 (7.0 Hz), 7.02 (d, 1H, J = 1.2 Hz), 3.00 (dd, 2H, J = 6.4 Hz, 1.6 Hz), 2.92 (dd, 2H, J = 6.4 Hz, 2.0 Hz), 2.44 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3): δ 136.5, 127.4, 122.2, 122.0, 119.2, 118.8, 111.3, 68.0, 51.8, 36.1, 25.5. HRMS (ESI^+): calculated for $\text{C}_{11}\text{H}_{15}\text{N}_2$ 175.1230, found 175.1235.



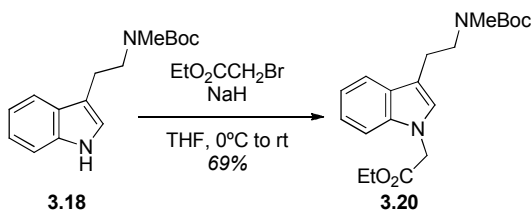
N-tert-butylcarbonylamino-N-methyl tryptamine (3.18). To a solution of **3.17** (3.71 g, 21.3 mmol, 1 equiv) and Boc_2O (5.11 g, 23.4 mmol, 1.1 equiv) in DMF (110 mL) was added slowly by syringe Et_3N (4.31 g, 42.6 mmol, 2.0 equiv). The mixture stirred overnight at room temperature. The reaction was quenched with water, and the mixture was then diluted with EtOAc (100 mL). The two layers were separated, and the water layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with a 1:1 water/brine mixture (2 x 100 mL), saturated aqueous NaHCO_3 (2 x 100 mL), and brine (1 x 100 mL). The resulting red solution was dried with MgSO_4 and concentrated by rotary evaporator. The crude mixture was purified by flash chromatography (25% EtOAc in hexanes) to give the product (4.2 g, 72%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3 ; reported as a mixture of rotamers): δ 8.42 (broad s, 1H), 7.66 (d, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.14 (t, 1H, J = 7.4 Hz), 6.98 (s, 1H), 3.54 (broad s, 2H), 3.15 (broad s, 2H), 2.90 (broad s, 3H), 1.30-1.60 (broad d, rotamers, 9H). ^{13}C NMR (400 MHz, CDCl_3): δ 155.9, 136.4, 127.5, 122.0, 121.9, 119.2, 118.7,

113.1, 111.3, 79.2, 49.7, 34.3, 28.4, 28.3, 24.0. HRMS (ESI⁺): calculated for C₁₁H₁₅N₂ 175.1230, found 175.1235.



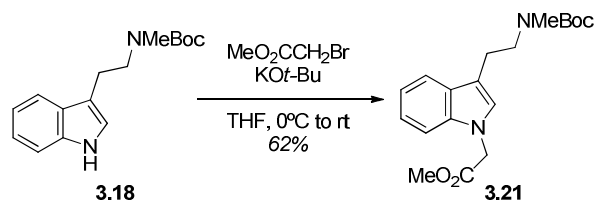
tert-butyl 3-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-indole-1-carboxylate (3.19).

To a solution of *N*-methyltryptamine (1.0 g, 5.74 mmol, 1.0 equiv) in THF (29 mL) at room temperature was added Boc₂O (1.38 g, 6.31 mmol, 1.1 equiv) and DMAP (70 mg, 0.57 mmol, 10 mol%). The reaction stirred overnight at room temperature. The reaction mixture was then quenched with water (15 mL); the resulting biphasic solution was extracted with Et₂O (3 x 15 mL). The combined organic layers were dried over MgSO₄ and concentrated. The product (658 mg, 1.76 mmol, 56%) was isolated by silica gel chromatography as a fluorescent yellow solid. ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 8.14 (broad s, 1H), 7.56 (broad s, 1H), 7.23-7.37 (m, 3H), 3.52 (broad s, 2H), 2.90 (m, 5H), 1.67 (s, 9H), 1.30-1.60 (broad d, rotamers, 9H). HRMS (ESI⁺ + Na⁺): calculated for C₂₁H₃₀N₂O₄Na 397.2098, found 397.2104.

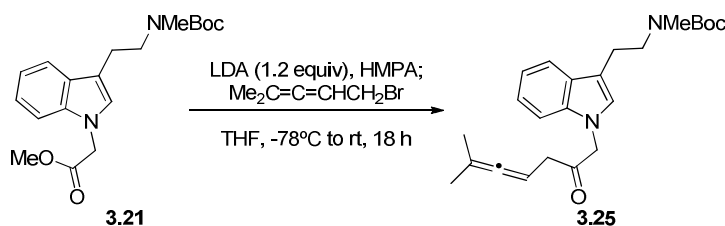


Ethyl 2-(3-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-indol-1-yl)acetate (3.20).

To a stirred suspension of NaH (60% in mineral oil) (117 mg, 2.915 mmol, 3.2 equiv) in THF (4 mL) at 0°C was added a solution of indole **3.18** (250 mg, 0.911 mmol, 1.0 equiv) in THF (0.5 mL). After the reaction mixture stirred at 0°C for 40 min, ethyl bromoacetate (487 mg, 2.915 mmol, 3.2 equiv) was added to the now heterogeneous mixture in one portion by syringe. The reaction mixture was allowed to warm to room temperature, turning a light yellow as it stirred overnight. The reaction was then submerged in an ice bath and quenched with water (5 mL). The resulting mixture was diluted with Et₂O (5 mL) and the layers were separated. The water layer was then extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with saturated aqueous NaHCO₃ (3 x 10 mL) and brine (1 x 10 mL). The organic layer was then dried over MgSO₄ and concentrated by rotary evaporator. Crude ¹H NMR analysis demonstrates a mixture of desired product and starting material. Flash chromatography (25% EtOAc in hexanes) was performed to separate the product from the starting material; the product was isolated as a 2:1 mixture of product to starting material. ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.626 (broad s, 1H), 7.17-7.22 (m, 2H), 7.10-7.14 (m, 1H), 6.91-6.97 (broad d, rotamers, 1H), 4.78 (s, 2H), 4.18-4.23 (m, 2H), 3.50 (broad s, 2H), 2.96 (broad s, 2H), 2.85-2.89 (m, rotamers, 3H), 1.30-1.60 (broad d, rotamers, 9H), 1.19-1.29 (m, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 168.7, 155.8, 136.4, 127.5, 126.3, 122.1, 119.5, 119.2, 111.3, 109.0, 79.3, 61.7, 49.7, 47.7, 28.5, 14.2.

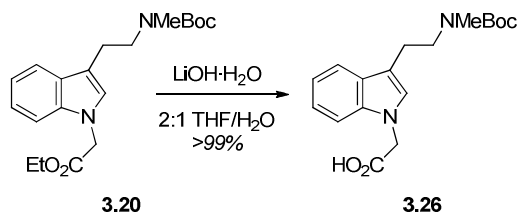


Methyl 2-(3-(2-(*tert*-butoxycarbonyl(methyl)amino)ethyl)-1*H*-indol-1-yl)acetate (3.21). To a stirring solution of **3.18** (3.37 g, 12.8 mmol, 1 equiv) in THF (38 mL) at 0°C was added dropwise by syringe potassium *tert*-butoxide (1.0 M in THF) (25.6 mL, 25.6 mmol, 2.2 equiv). As the base was added, the solution turned from yellow and clear to dark orange and cloudy. This mixture stirred at 0°C for one hour, at which time methyl bromoacetate (6.27 g, 41.0 mmol, 3.2 equiv) was added slowly by syringe. The reaction was allowed to warm to room temperature, and further salt formation was observed immediately. The reaction stirred overnight at room temperature. The reaction was then submerged in an ice bath and quenched with water (20 mL). The resulting mixture was diluted with EtOAc (20 mL) and the layers were separated. The water layer was then extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with saturated aqueous NaHCO₃ (3 x 20 mL) and brine (1 x 20 mL). The organic layer was then dried over MgSO₄ and concentrated by rotary evaporator. Crude ¹H NMR analysis demonstrates a mixture of desired product and starting material. Flash chromatography (25% EtOAc in hexanes) was performed to separate the product from the starting material; 2.75 g (62%; 94% BORSM) of product was isolated as a yellow oil, and 1.19 g (34%) of starting material was recovered as a yellow solid. ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.66 (broad s, 1H), 7.25 (m, 2H), 7.17 (t, 1H, *J* = 7.4 Hz), 6.91-6.97 (broad d, rotamers, 1H), 4.84 (s, 2H), 3.77 (s, 3H), 3.53 (broad s, 2H), 2.99 (broad s, 2H), 2.85-2.89 (m, rotamers, 3H), 1.30-1.60 (broad d, rotamers, 9H). ¹³C NMR (500 MHz, CDCl₃): δ 169.2, 155.8, 136.9, 128.2, 126.2, 122.2, 119.5, 119.1, 113.4, 109.0, 79.2, 52.5, 49.7, 47.5, 34.4, 28.4, 24.0. HRMS (ESI⁺ + Na⁺): calculated for C₁₉H₂₆N₂O₄Na 369.1785, found 369.1799.

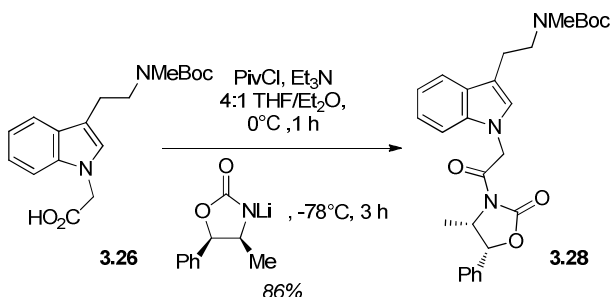


***tert*-butyl methyl(2-1-(6-methyl-2-oxohepta-4,5-dien-1-yl)-1*H*-indol-3-yl)ethylcarbamate (3.25).** To a stirred solution of methyl ester **3.21** (275 mg, 1.00 mmol, 1.0 equiv), in THF (4 mL) at -78°C was added a solution of LDA (1.10 mmol, 1.1 equiv) at -78°C by canula over five minutes. The resulting solution stirred 50 min at -78°C; HMPA (197 mg, 1.1 mmol, 1.1 equiv) was then added dropwise by syringe. After stirring 5 min at -78°C, a solution of the bromide (480 mg, 3.00 mmol, 3.0 equiv) in THF (1 mL) was added dropwise by syringe. The reaction mixture was warmed to 0°C, turning bright red in the process. The reaction mixture stirred overnight; the reaction mixture was then quenched with saturated aqueous NaHCO₃ (5 mL) and the resulting biphasic solution was extracted with EtOAc (5 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2 x 5 mL) and brine (1 x 5 mL), dried over MgSO₄, and concentrated. The product was isolated as a yellow oil (xxmg, xxmmol, xx%) by silica gel chromatography (10% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.56-7.74 (m, 1H), 7.25 (s, 2H), 7.16 (broad s, 1H), 6.90-7.00 (m, 1H), 5.08-5.15 (m,

1H), 4.83 (s, 2H), 4.61 (d, 2H, $J = 7.0$ Hz), 3.52-3.64 (broad s, 2H), 2.98-2.08 (m, 2H), 2.84-2.97 (m, 3H), 1.61 (s, 6H), 1.40-1.60 (m, 15H).

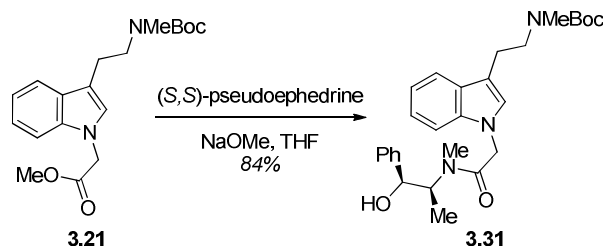


2-(3-(2-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)-1*H*-indol-1-yl)acetic acid (3.26).³⁸ To a solution of ethyl ester **3.21** (181 mg, 0.503 mmol, 1.0 equiv) in THF (15 mL) was added lithium hydroxide monohydrate (63 mg, 1.51 mmol, 3.0 equiv) as a solution in water (9 mL). The reaction mixture immediately turned bright yellow. The reaction stirred one hour at room temperature, at which time the reaction was cooled to 0°C. The reaction mixture was acidified to pH 1 using HCl (conc); the reaction mixture turned clear. The reaction mixture was extracted with CH₂Cl₂ (2 x 25 mL) and the combined organic layers were washed with brine (1 x 25 mL), dried over MgSO₄ and concentrated. The product was azeotroped with benzene (3 x 5 mL) and used without further purification. ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.59-7.61 (m, 1H), 7.20-7.22 (m, 2H), 7.10-7.16 (m, 1H), 6.80-7.00 (m, 1H), 4.951 (s, 2H), 3.50 (broad s, 2H), 3.09 (broad s, 2H), 2.94 (broad s, 3H), 1.40-1.60 (m, 15H). HRMS (ESI + Na⁺): calculated for C₁₉H₂₄N₂O₄Na 355.1628, found 355.1640.

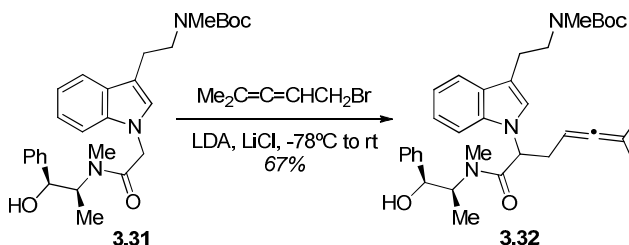


***tert*-butyl methyl (2-(1-(2-((4*S*,5*R*)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)-2-oxoethyl)-1*H*-indol-3-yl)ethyl)carbamate (3.28).** To a solution of **3.26** (2.58 g, 7.75 mmol, 1.0 equiv) in 3:1 THF/Et₂O (24 mL) at 0°C was added Et₃N (0.862 mg, 8.52 mmol, 1.1 equiv) and PivCl (0.943 g, 7.75 mmol, 1.0 equiv). The reaction stirred 1 h, turning yellow and cloudy as the salts crashed out of the reaction mixture and the mixed anhydride formed. While this reaction stirred, *n*-BuLi (2.5 M in hexanes) (3.72 mL, 9.30 mmol, 1.2 equiv) was added to a solution of (4*S*,5*R*)-(-)-4-methyl-5-phenyl-2-oxazolidinone (1.50 g, 8.52 mmol, 1.1 equiv) in THF (17 mL) at -78°C; the reaction mixture stirred 30 min. The mixed anhydride was then cooled to -78°C and the reaction mixture containing the deprotonated oxazolidinone was added by canula. Et₂O (7 mL) was added to ensure that the Et₃N·HCl salts remained as solids. The reaction mixture stirred at -78°C for 3 h. The reaction mixture was then quenched with saturated aqueous NH₄Cl (20 mL) and the resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over Na₂SO₄ and concentrated. The product, a yellow oil (3.26 g, 6.63 mmol, 86%), was isolated by silica gel chromatography (40% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.65 (broad s, 1H), 7.43 (d, 3H, $J = 6.8$ Hz), 7.31 (d, 2H, $J = 6.8$ Hz), 7.26 (s, 1H), 7.22 (s, 1H), 7.14 (broad s, 1H),

6.90-7.00 (m, 1H), 5.78 (d, 1H, $J = 7.2$ Hz), 5.47 (s, 2H), 4.76 (t, 1H, $J = 6.8$ Hz), 3.51-3.53 (m, 2H), 2.98-3.10 (m, 2H), 2.80-2.95 (m, 2H), 1.35-1.50 (m, 9H), 0.93 (d, 3H, $J = 6.8$ Hz).

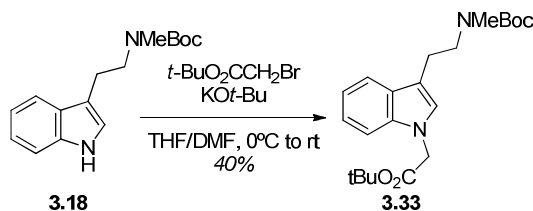


***tert*-butyl (2-(1-(2-(((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-2-oxoethyl)-1*H*-indol-3-yl)ethyl)(methyl)carbamate (3.31).** To a solution of **3.21** (2.25 g, 6.51 mmol, 1.0 equiv) and (*S,S*)-pseudoephedrine (1.08 g, 6.51 mmol, 1.0 equiv) in THF (33 mL) was added dropwise by syringe NaOMe (30 wt% in MeOH) (583 mg, 3.25 mmol, 50 mol%). The reaction mixture stirred 90 min, and then the mixture was quenched with water (15 mL) and the resulting slurry was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (3 x 15 mL), brine (1 x 30 mL), dried over MgSO₄ and concentrated. The product (2.62 g, 5.47 mmol, 84%), a white foam, was used without further purification. ¹H NMR (500 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.50-7.55 (m, 1H), 7.46 (d, 1H, $J = 7.5$ Hz), 7.38 (t, 1H, $J = 7.5$ Hz), 7.29-7.33 (m, 2H), 7.23-7.30 (m, 1H), 7.09-7.18 (m, 2H), 6.92 (broad s, 1H), 4.99 (s, 1H), 4.87 (s, 1H), 3.20-3.80 (m, 6H), 2.80-3.10 (m, 8H), 1.93 (s, 1H), 1.30-1.60 (broad d, rotamers, 9H).



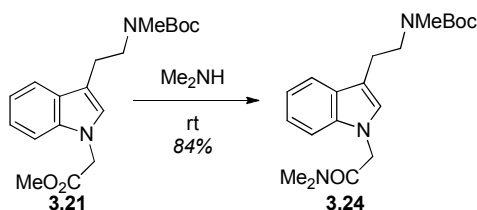
***tert*-butyl (2-(1-(1-(((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-6-methyl-1-oxohepta-4,5-dien-2-yl)-1*H*-indol-2-yl)ethyl)(methyl)carbamate (3.32).**^{18a} To a stirred solution of DIPA (732 mg, 7.22 mmol, 2.25 equiv) and LiCl (1.55 g, 19.3 mmol, 6.0 equiv) in THF (4 mL) at -78°C was added dropwise by syringe *n*-BuLi (2.5 M in hexanes) (2.67 mL, 6.68 mmol, 2.08 equiv). The temperature was raised to 0°C and the solution stirred thirty minutes. The temperature was then lowered to -78°C and a solution of **3.31** (1.50 g, 3.21 mmol, 1.0 equiv) in THF (4 mL) was added dropwise by syringe, gradually turning a deep red. This mixture stirred for one hour at -78°C, followed by fifteen minutes at 0°C and five minutes at room temperature. The reaction temperature was then lowered again to 0°C and the allene (1.55 g, 9.64 mmol, 3.0 equiv) was added dropwise. This mixture stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous NH₄Cl (5 mL) and the resulting slurry was diluted with water (5 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (1 x 15 mL), dried over MgSO₄ and concentrated by rotary evaporator. The resulting orange oil was purified by using flash chromatography (1% MeOH in CH₂Cl₂) to yield the product as a yellow foam (1.20 g, 2.15 mmol, 67%). Due to the complexity of the spectra—a mixture of diastereomers and

rotamers—a copy of the ^1H spectra is included in Appendix 2, but no tabulation of peaks is performed. Reductive cleavage of the auxiliary using lithium amidoborane was performed to ascertain the identity of the isolated product (see preparation of **3.41**).



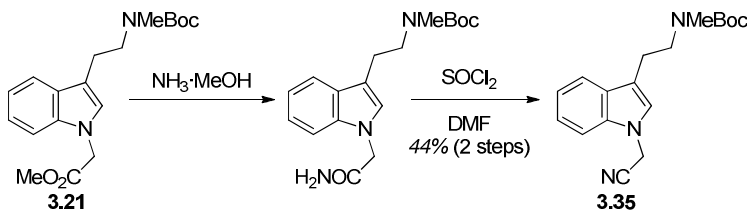
tert-butyl 2-(3-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-indol-1-yl)acetate (3.33).

Prepared analogously to **3.21** from **3.18** (743 mg, 2.71 mmol, 1.0 equiv) using *tert*-butylbromoacetate (1.16 g, 5.96 mmol, 2.2 equiv) to yield the product (423 mg, 1.09 mmol, 40%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3 ; reported as a mixture of rotamers): δ 7.63 (broad s, 1H), 7.22 (s, 1H), 7.12-7.22 (m, 1H), 6.89-6.95 (broad d, rotamers, 1H), 4.68 (s, 2H), 3.45-3.60 (m, 2H), 2.94-3.05 (m, 2H), 2.78-2.87 (m, rotamers, 3H), 1.30-1.60 (broad d, rotamers, 9H), 1.40 (s, 9H).



tert-butyl (2-(1-(2-(dimethylamino)-2-oxoethyl)-1H-oxoethyl)-1H-indol-3-yl)ethyl(methyl)carbamate (3.24).

The methyl ester **3.21** (153 mg, 0.441 mmol, 1.0 equiv) was dissolved in a solution of Me_2NH (2.0 M in THF) (1.5 mL, 3 mmol, 8 equiv) and stirred over 2 days. The reaction was quenched with 1M HCl (1 mL) and the resulting slurry was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over MgSO_4 and concentrated. The product was obtained as a red oil and used without further purification. ^1H NMR (400 MHz, CDCl_3 ; rotameric peaks indicated with an asterisk when applicable) δ 7.62-7.63 (m, 1H), 7.09-7.28 (m, 3H), 6.88-6.92 (m, 1H), 4.824* (s, 1H), 4.775* (s, 1H), 3.55-3.70 (m, 2H), 2.90-3.00 (m, 8H), 2.78-2.88 (m, 3H), 1.35-1.50 (m, 9H).

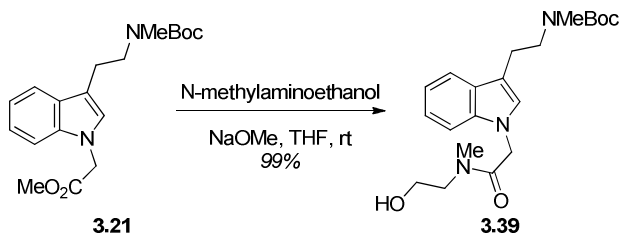


tert-butyl (2-(1-(2-amino-2-oxoethyl)-1H-indol-3-yl)ethyl(methyl)carbamate.

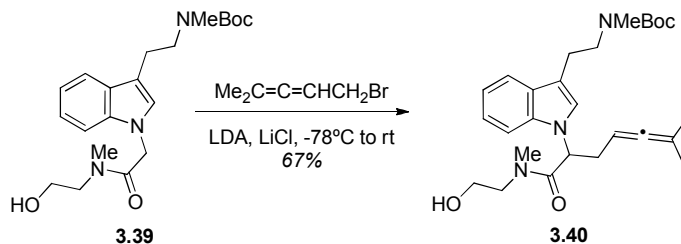
A solution of methyl ester **3.21** (250 mg, 0.722 mmol, 1.0 equiv) in excess $\text{NH}_3 \cdot \text{MeOH}$ (2.5 mL) stirred at room temperature for 24 h. The reaction was quenched with 1M HCl (3 mL) and the resulting aqueous solution was extracted with EtOAc (3 x 3 mL); the combined organic layers were washed with brine (1 x 5 mL), dried over MgSO_4 and concentrated. The product was used without further purification. ^1H NMR (400 MHz, CDCl_3 ; rotameric peaks indicated with an asterisk when applicable) δ 7.66 (d, 1H, $J = 8.0$ Hz), 7.28-7.32 (m, 2H), 7.15-7.22 (m, 1H), 6.92-

6.98 (m, 1H), 6.18*, 6.02*, 5.70* , 5.46* (m, 2H), 4.75 (s, 2H), 3.56 (t, 2H, $J = 6.8$ Hz), 3.00 (t, 2H, $J = 6.8$ Hz), 2.90 (s, 3H), 1.40* (s, 9H).

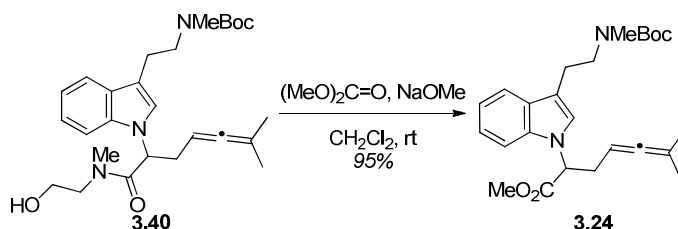
tert-butyl (2-(1-(cyanomethyl)-1H-indol-3-yl)ethyl)(methyl)carbamate (3.35). SOCl_2 (100 mg, 0.85 mmol, 0.06 mL) was added dropwise to DMF (1.5 mL) at -60°C . The reaction mixture was warmed to 0°C and stirred 5 min. A solution of the amide (0.772 mmol) in DMF (2 mL) was then added dropwise. The reaction mixture turned bright pink. After stirring 18 h, the reaction temperature was dropped to 0°C and the mixture was quenched by slow addition of saturated aqueous NaHCO_3 . After the solution reached pH 6, the mixture was diluted with EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with water (2 x 10 mL), dried over MgSO_4 and concentrated. The product was isolated as a clear oil (106 mg, 0.337 mmol, 44%) by silica gel chromatography (40% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, 1H, $J = 7.2$ Hz), 7.27-7.32 (m, 2H), 7.17-7.22 (m, 1H), 6.87-6.93 (m, 1H), 4.93 (s, 2H), 3.42-3.62 (m, 2H), 2.92-2.98 (m, 2H), 2.75-2.85 (m, 3H), 1.25-1.50 (m, 9H).



tert-Butyl 2-(1-(2-((2-hydroxyethyl)(methyl)amino)-2-oxoethyl)-1H-indol-3-yl)ethyl(methyl)carbamate (3.39). To a solution of **3.21** (750 mg, 2.17 mmol, 1 equiv) and *N*-methylaminoethanol (326 mg, 4.34 mmol, 2.0 equiv) in THF (12 mL) was added dropwise by syringe NaOMe (30 wt% in MeOH) (194 mg, 1.08 mmol, 0.50 equiv). The mixture stirred at room temperature for five hours. The reaction was then quenched with water (10 mL) and the resulting slurry was diluted with EtOAc (10 mL). The layers were separated, and the water layer was then washed with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (1 x 15 mL) and brine (1 x 15 mL), dried over MgSO_4 and concentrated by rotary evaporator. The remaining volatiles were removed by reduced pressure (2 atm) overnight. The product was isolated as a pale yellow foam (840 mg, 99%) and was used without further purification. ^1H NMR (500 MHz, CDCl_3 ; reported as a mixture of rotamers): δ 7.640 (broad s, 1H), 7.23-7.30 (m, 1H), 7.09-7.18 (m, 2H), 6.92 (broad s, 1H), 4.99 (s, 1H), 4.87 (s, 1H), 3.20-3.80 (m, 6H), 2.80-3.10 (m, 8H), 1.93 (s, 1H), 1.30-1.60 (broad d, rotamers, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 169.2, 155.8, 136.9, 128.2, 126.2, 122.2, 119.5, 119.1, 113.4, 109.0, 79.2, 52.5, 49.7, 47.5, 34.4, 28.4, 24.0. HRMS ($\text{ESI}^+ + \text{Na}^+$): calculated for $\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_4\text{Na}$ 412.2207, found 412.2212.



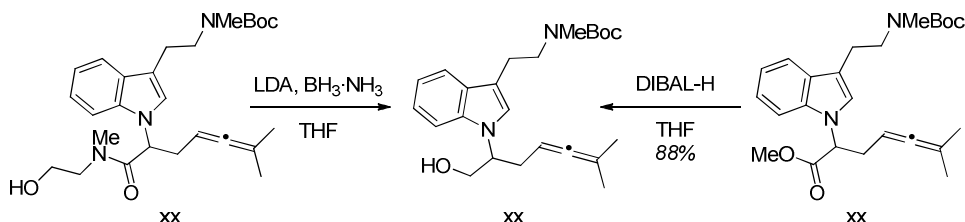
tert-Butyl 2-(1-(1-((2-hydroxyethyl)(methyl)amino)-6-methyl-1-oxohepta-4,5-dien-2-yl)-1H-indol-3-yl)ethyl(methyl)carbamate (3.40). To a stirred solution of DIPA (340 mg, 3.38 mmol, 2.25 equiv) and LiCl (380 mg, 9.00 mmol, 6.0 equiv) in THF (7 mL) at -78°C was added dropwise by syringe *n*-BuLi (2.05 M in hexanes) (1.50 mL, 3.12 mmol, 2.08 equiv). The temperature was raised to 0°C and the solution stirred thirty minutes. The temperature was then lowered to -78°C and a solution of **3.39** (608 mg, 1.56 mmol, 1.0 equiv) in THF (7 mL) was added dropwise by syringe, gradually turning a deep red. This mixture stirred for one hour at -78°C, followed by fifteen minutes at 0°C and five minutes at room temperature. The reaction temperature was then lowered again to 0°C and a solution of the allene in THF (1 mL) was added dropwise. This mixture stirred for one hour at room temperature. The reaction was quenched with saturated aqueous NH₄Cl (5 mL) and the resulting slurry was diluted with water (5 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (1 x 15 mL), dried over MgSO₄ and concentrated by rotary evaporator. The resulting orange oil was purified by using flash chromatography (2% MeOH in CH₂Cl₂; 75 mL of silica gel) to yield the product as a yellow foam (1.04 g, 67%). The identity of the product was verified by comparing the product of reductive cleavage of **3.40** to the product of reduction of methyl ester **3.24**. ¹H NMR (500 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.65 (d, 1H, *J* = 7.60 Hz), 7.40 (dd, 1H, *J* = 22.4 Hz (rotamers), 8.0 Hz), 7.18-7.24 (m, 1H), 7.14-7.16 (m, 1H), 7.07 (d, 1H, *J* = 12.8 Hz), 5.20-5.42 (dt, 1H, *J* = 53.2 Hz (rotamers), *J* = 7.2 Hz), 4.93 (d, 1H, *J* = 26.4 Hz (rotamers)), 3.20-4.10 (m, 6H), 2.70-3.10 (m, 9H), 2.50-2.70 (m, 1H), 1.93 (s, 1H), 1.50-1.80 (m, 6H), 1.30-1.60 (broad d, rotamers, 9H). ¹³C NMR (500 MHz, CDCl₃): δ 202.6, 169.7, 156.0, 136.4, 128.0, 123.7, 122.0, 119.4, 119.3, 119.2, 112.8, 108.8, 96.5, 95.1, 85.0, 84.6, 79.4, 61.2, 54.9, 51.6, 49.0, 36.9, 34.2, 32.9, 32.3, 28.3, 23.5, 20.4, 20.1. HRMS (ESI⁺ + Na⁺): calculated for C₂₇H₃₉N₃O₄Na 492.2833, found 492.2851.



Methyl 2-(3-(2-(tert-butoxycarbonyl(methyl)amio)ethyl)-1H-indol-1-yl)acetate (3.24).

To a stirred solution of **3.40** (304 mg, 0.628 mmol, 1.0 equiv) in CH₂Cl₂ (12 mL) was added dropwise by syringe dimethyl carbonate (356 mg, 3.95 mmol, 6.2 equiv), followed by NaOMe (30 wt% in methanol) (1.13 g, 6.28 mmol, 10.0 equiv). The reaction mixture stirred overnight at room temperature. The reaction mixture was then quenched with saturated NaHCO₃ (aq) (5 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over MgSO₄ and concentrated. The product was isolated by flash chromatography (5% EtOAc in hexanes) to give the product as a yellow oil (262 mg, 0.596 mmol, 95%). ¹H NMR (500 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.61 (m, 1H), 7.31 (d, 1H, *J* = 8.0 Hz), 7.21 (t, 1H, *J* = 7.4 Hz), 7.07-7.14 (m, 2H), 5.04 (t, 1H, *J* = 7.6 Hz), 4.80-4.90 (m, 1H), 3.69 (s, 3H), 3.40-3.55 (broad s, 2H), 2.88-2.97 (m, 2H), 2.78-2.86 (m, 4H), 2.69-2.77 (m, 1H), 1.40-1.60 (m, 15H). ¹³C NMR (125 MHz, CDCl₃): δ 202.6, 171.0, 155.7, 136.9, 128.1, 123.1, 121.9, 119.4, 119.0, 113.3, 109.3, 97.2,

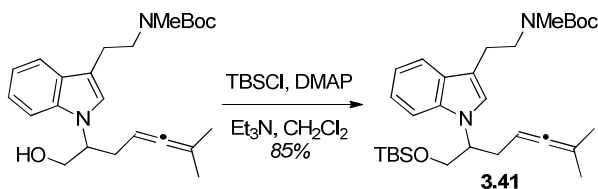
83.8, 79.2, 57.6, 52.5, 49.9, 34.5, 31.6, 28.5, 24.2, 20.2. HRMS (ESI⁺ + Na⁺): calculated for C₂₅H₃₅N₂O₄ 427.2591, found 427.2596.



tert-Butyl 2-(1-(1-hydroxy-6-methylhepta-4,5-dien-2-yl)-1H-indol-3-yl)ethyl(methyl)carbamate. This compound was prepared in two ways so as to verify the assignments of **xx** and **xx**; as such, representative procedures for both are shown below.

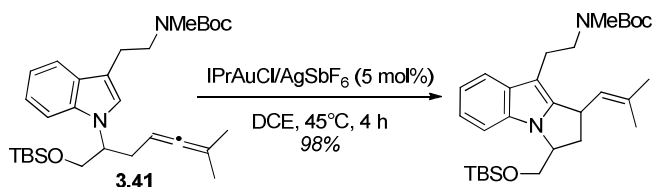
LAB reduction of hydroxyamides 3.32/3.40: A solution of *n*-BuLi (2.05 M in hexanes) (0.83 mmol, 0.40 mL, 39 equiv) was added to a stirred solution of DIPA (0.88 mmol, 0.12 mL, 42 equiv) in THF (9.5 mL) at -78°C. This mixture stirred at -78°C for ten minutes; the temperature was then raised to 0°C and stirred an additional ten minutes. BH₃·NH₃ (25 mg, 0.84 mmol, 40 equiv) was then added in one portion; this mixture stirred at 0°C for fifteen minutes, followed by fifteen minutes at room temperature. The temperature was again dropped to 0°C; 0.1 mL of this solution was then added dropwise to a solution of **3.40** (10 mg) in THF (0.1 mL) at 0°C. This mixture was allowed to warm to room temperature and stirred two hours. The reaction was quenched with a few drops of 1M HCl and was diluted with water (0.80 mL). The resulting slurry was extracted with EtOAc (2 x 1 mL) and the combined organic layers were dried over MgSO₄ and concentrated by rotary evaporator. The crude spectra of this compound was then compared with the spectra obtained through reduction of methyl ester **3.24**.

Reduction of methyl ester 3.24:³⁹ To a solution of **3.24** (145 mg, 0.340 mmol, 1 equiv) in THF (3.4 mL) at 0°C was added dropwise by syringe DIBAL-H (1.0 M in hexanes) (0.68 mL, 0.68 mmol, 2.0 equiv). The reaction was brought to room temperature and stirred two hours. The reaction was then cooled to 0°C and was quenched with Na₂SO₄·10H₂O; the quench was allowed to stir for ninety minutes. The solution was then suspended in EtOAc (5 mL) and the salts were removed by gravity filtration. The filtrate was concentrated by rotary evaporator to yield the product (119 mg, 0.298 mmol, 88%) as a clear oil; this was used without further purification. ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.60 (d, 1H, *J* = 7.60 Hz), 7.38 (d, 1H, *J* = 8.4 Hz), 7.18 (t, 1H, *J* = 7.4 Hz), 7.12 (t, 1H, *J* = 7.6 Hz), 7.03 (broad s, 1H), 4.82-4.84 (m, 1H), 4.42-4.48 (m, 1H), 4.05-4.13 (m, 2H), 3.78-3.81 (m, 1H), 3.43-3.70 (m, 1H), 2.95 (t, 2H, *J* = 7.2 Hz), 2.84 (s, 3H), 2.53-2.67 (m, 2H), 1.49 (d, 3H, *J* = 2.8 Hz), 1.30-1.60 (broad d, 12H). HRMS (ESI⁺): calculated for C₂₄H₃₅N₂O₃ 399.2642, found 399.2640.

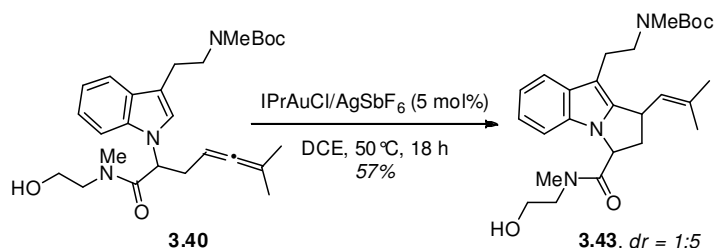


tert-butyl 2-(1-(1-((tert-butyldimethylsilyl)oxy)-6-methylhepta-4,5-dien-2-yl)-1H-indol-3-yl)ethyl(methyl)carbamate (3.41). To a solution of the alcohol (393 mg, 0.988 mmol, 1.0 equiv) was in CH₂Cl₂ (5 mL) was added Et₃N (125 mg, 1.235 mmol, 1.25 equiv), *tert*-butyldimethylsilyl chloride (179 mg, 1.185 mmol, 1.20 equiv) and DMAP (6 mg, 0.049 mmol, 5

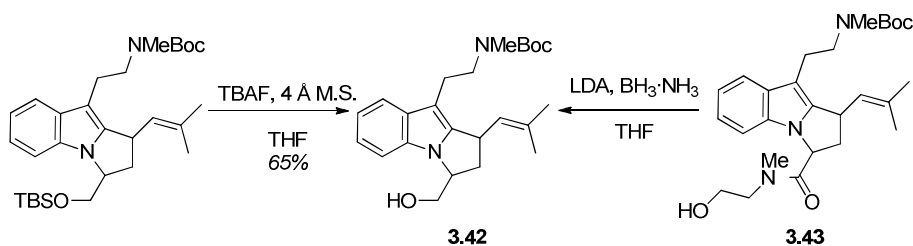
mol%). This mixture stirred at room temperature for five hours. The reaction mixture was quenched with saturated aqueous NaHCO₃ (2 mL) and the layers were separated. The aqueous layer extracted with CH₂Cl₂ (1 x 2 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (2 x 4 mL) and brine (1 x 4 mL), dried over MgSO₄ and concentrated by rotary evaporator. The product was isolated by silica gel chromatography (25% EtOAc in hexanes) to give the product as a yellow oil (435 mg, 85%). ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.591 (d, 1H, *J* = 7.2 Hz), 7.309 (d, 1H, *J* = 8.0 Hz), 7.260 (dd, 1H, *J* = 7.6 Hz, 7.2 Hz), 7.15-7.19 (m, 1H), 7.072 (dd, 1H, *J* = 7.6 Hz, 7.2 Hz), 7.030 (broad s, 1H), 4.84-4.85 (m, 1H), 4.40-4.46 (m, 1H), 3.79-3.84 (m, 2H), 3.43-3.53 (m, 2H), 2.80-3.00 (m, 5H), 2.63-2.70 (m, 1H), 2.50-2.61 (m, 1H), 1.492 (d, 3H, *J* = 2.8 Hz), 1.30-1.50 (m, 15H), 0.832 (s, 9H), -0.092 (s, 6H).



tert-butyl (2-(3-(((tert-butyldimethylsilyl)oxy)methyl)-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate. IPrAuCl (15.4 mg, 0.025 mmol, 5 mol %) and AgSbF₆ (8.5 mg, 0.025 mmol, 5 mol %) in dichloroethane (1 mL) were mixed in the dark in a sealed vial. After five minutes, the catalyst mixture was passed through a glass wool filter in to a solution of **3.41** (254 mg, 0.496 mmol, 1.0 equiv) in dichloroethane (1.5 mL). The filter was washed with dichloroethane (2 x 0.1 mL) and then the reaction vessel was sealed and submerged in a 45°C oil bath for four hours. The reaction mixture was then filtered over a silica gel plug to give the pure product as a yellow oil (249 mg, 98%). ¹H NMR (400 MHz, CDCl₃; reported as a mixture of rotamers): δ 7.49-7.72 (m, 1H), 7.42 (d, 1H, *J* = 7.6 Hz), 7.09 (t, 1H, *J* = 6.4 Hz), 7.05 (t, 1H, *J* = 6.4 Hz), 5.30 (d, 1H, *J* = 9.6 Hz), 4.51 (broad s, 1H), 4.46 (ddd, 1H, *J* = 9.6 Hz,), 4.10 (dd, 2H, *J* = 10.0 Hz, 5.2 Hz), 3.83 (ddd, 1H, *J* = 10.0 Hz, 6.0 Hz, 5.6 Hz), 3.47-3.57 (m, 1H), 3.29-3.41 (m, 1H), 3.86-3.97 (m, 1H), 3.48-3.58 (m, 1H), 3.09-3.21 (m, 1H), 2.93 (dt, 1H, *J* = 13.2 Hz, 8.4 Hz), 2.86 (broad s, 3H), 2.76-2.83 (m, 2H), 2.12 (dt, 1H, *J* = 13.2 Hz, 5.2 Hz), 1.83 (s, 3H), 1.77 (s, 3H), 1.33-1.50 (m, 9H), 0.89 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H).



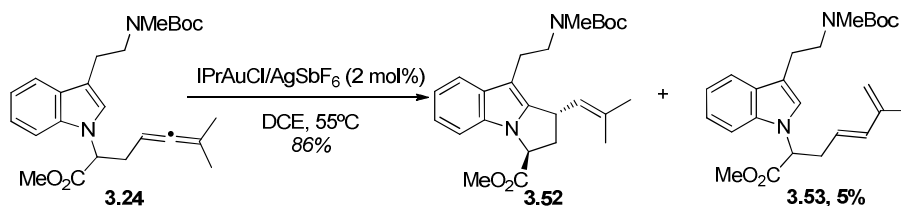
tert-butyl (2-(3-((2-hydroxyethyl)(methyl)(carbamoyl)-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate (3.43). Prepared analogously to cyclization of **3.41** from **3.40** (277 mg, 0.591 mmol, 1.0 equiv) to yield the product (157 mg, 0.300 mmol, 57%) as a white foam. To to the complexity of the spectra, peaks are not assigned; reduction of the amide by lithium amidoborane was used to verify this compound's identity (see preparation of **3.42**).



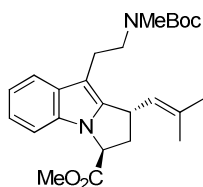
tert-butyl (2-(3-(hydroxymethyl)-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate (3.42). This compound was prepared in two ways so as to verify the assignments of **3.43**; as such, representative procedures for both are shown below.

TBS deprotection. A solution of TBAF (1.0 M in THF, ca. 5% water) (0.57 mL, 0.572 mmol, 1.1 equiv) and 4 Å molecular sieves in THF (3 mL) was stirred for ten minutes. Then, a solution of the TBS ether (266 mg, 0.520 mmol), 1.0 equiv) in THF (2.5 mL) was added dropwise by syringe. The reaction mixture stirred at room temperature for four hours. The mixture was then quenched with saturated aqueous NaHCO_3 (4 mL) and the resulting slurry was extracted with EtOAc (1 x 10 mL). The organic layer was washed with saturated aqueous NaHCO_3 (2 x 5 mL) and brine (1 x 5 mL), dried over MgSO_4 and concentrated by rotary evaporator. The product was isolated by silica gel chromatography (40% EtOAc in hexanes) to give the product as a yellow solid (207 mg, 65%).

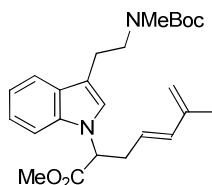
LAB reduction of hydroxyamide 3.43: Prepared according to the procedure given for the reduction of **3.32/3.40** to give the product as a yellow solid. The crude spectra of this compound was then compared with the spectra obtained through deprotection of the TBS ether. ^1H NMR (600 MHz, CDCl_3 ; reported as a mixture of rotamers): δ 7.49-7.72 (m, 1H), 7.33-7.55 (m, 1H), 7.09-7.14 (m, 1H), 7.07 (t, 1H, $J = 7.2$ Hz), 5.31 (d, 1H, $J = 8.4$ Hz), 4.51 (broad s, 1H), 4.17 (broad s, 1H), 4.15-4.22 (m, 1H), 4.09-4.14 (m, 1H), 3.86-3.97 (m, 1H), 3.48-3.58 (m, 1H), 3.09-3.21 (m, 1H), 2.92 (dt, $J = 12.6$ Hz, 8.4 Hz), 2.86 (broad s, 3H), 2.76-2.83 (m, 2H), 2.05-2.14 (m, 1H), 1.82 (s, 3H), 1.77 (s, 3H), 1.33-1.45 (m, 9H). HRMS (ESI^+): calculated for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_3$ 399.2642, found 399.2647.



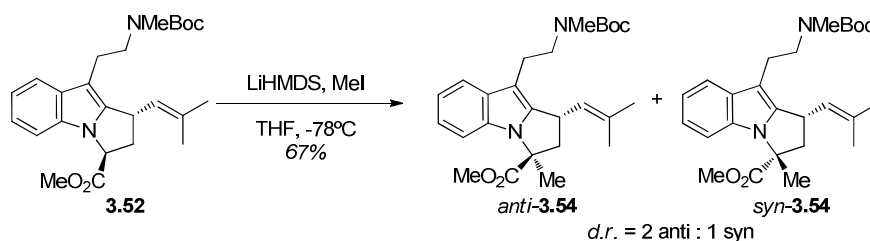
Methyl 9-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate (3.52). IPrAuCl (31.4 mg, 0.050 mmol, 2 mol%) and AgSbF_6 (17.2 mg, 0.050 mmol, 2 mol%) in dichloroethane (2 mL) were mixed in the dark in a sealed vial. After five minutes, the catalyst mixture was passed through a glass wool filter in to a solution of **3.24** (1.08 g, 2.53 mmol, 1.0 equiv) in dichloroethane (20 mL). The filter was washed with dichloroethane (3 x 1 mL) and then the reaction vessel was sealed and submerged in a 55°C oil bath for six hours. The reaction mixture was then filtered over a silica gel plug and the filtrate was concentrated *in vacuo*. The products were isolated as a single diastereomer by flash chromatography (5% EtOAc in hexanes) as white solids (**3.52**: 877 mg, 2.06 mmol, 81%; **3.53**: 50 mg, 0.125 mmol, 5%).



^1H NMR (500 MHz, CDCl_3) δ 7.53-7.65 (m, 1H), 7.06-7.13 (m, 3H), 5.30 (d, 1H, $J = 9.5$ Hz), 4.85 (at, 1H, $J = 7.5$ Hz), 4.10-4.20 (m, 1H), 3.74 (s, 3H), 3.20-3.60 (m, 2H), 3.15 (dt, 1H, $J = 13.0, 8.5$ Hz), 2.86 (broad s, 3H), 2.75-2.90 (m, 2H), 2.43 (dt, 1H, $J = 13.0, 6.5$ Hz), 1.82 (s, 3H), 1.77 (s, 3H), 1.36-1.46 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 155.7, 143.6, 133.1, 132.9, 125.1, 121.0, 119.4, 118.6, 109.9, 104.3, 79.1, 57.3, 52.6, 49.7, 40.9, 35.2, 34.0, 28.4, 25.8, 22.7, 18.2.

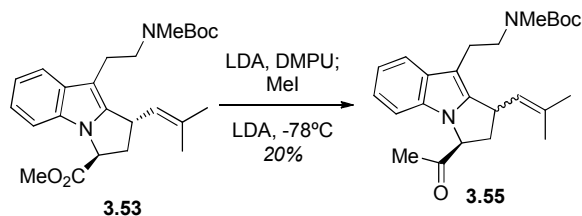


^1H NMR (500 MHz, CDCl_3) δ 7.53-7.65 (m, 1H), 7.30-7.34 (m, 1H), 7.20-7.26 (m, 1H), 7.11-7.18 (m, 2H), 6.24 (d, 1H, $J = 15.5$ Hz), 5.44-5.48 (m, 1H), 5.04 (t, 1H, $J = 12.5$ Hz), 4.92 (d, 1H, $J = 12.5$ Hz), 3.73 (s, 3H), 3.20-3.60 (m, 2H), 2.75-2.99 (m, 7H), 1.72 (s, 3H), 1.36-1.46 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 155.7, 141.4, 136.7, 128.2, 123.3, 122.0, 119.5, 116.3, 109.3, 97.2, 83.7, 79.2, 57.6, 52.5, 49.9, 35.4, 28.5, 25.8, 24.2, 20.2, 18.5.

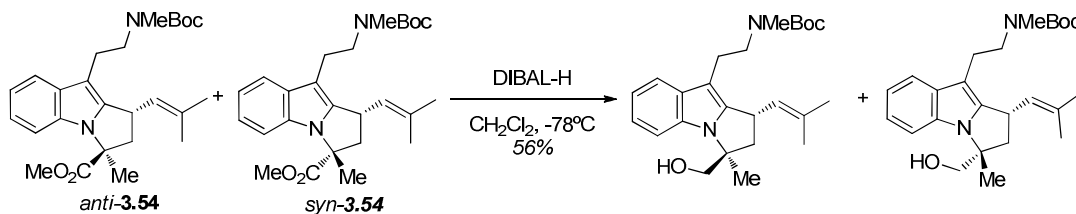


Methyl 9-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate (3.54). To a solution of **3.52** (165 mg, 0.387 mmol, 1.0 equiv) in THF (3 mL) at -78°C was added dropwise by syringe LiHMDS (1.0 M in THF) (0.45 mL, 0.450 mmol, 1.2 equiv). Upon addition of base, the reaction mixture turned bright yellow. The reaction mixture stirred at -78°C for one hour, at which time methyl iodide (532 mg, 3.75 mmol, 9.7 equiv) was added in one portion. The reaction mixture stirred for one hour at -78°C , and the reaction mixture was then quenched with 0.01 M NaHSO_4 (3 mL). The resulting slurry was extracted with EtOAc (3 x 3 mL), and the combined organic layers were washed with brine (1 x 6 mL), dried over MgSO_4 , and concentrated *in vacuo*. The product, a yellow oil, was isolated as an inseparable 2:1 mixture of *anti*-**3.54** and *syn*-**3.54** (115 mg, 0.261 mmol, 67%) by flash chromatography (10% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3 ; minor diastereomer peaks indicated with an asterisk when applicable) δ 7.55-7.75 (m, 1H), 7.33-7.42 (m, 1H), 7.06-7.23 (m, 2H), 5.20-5.45 (m, 1H), 4.15-4.30 (m, 1H), 3.717 (s, 3H), 3.50-3.65 (m, 1H), 3.25-3.40 (m, 1H), 3.19 (dt, 1H, $J = 12.5, 8.5$ Hz), 2.75-2.95 (m, 5H), 2.23 (m, 1H), 1.99 (s, 3H), 1.82 (s, 3H), 1.87 (s, 3H), 1.85 (s, 3H), 1.82* (s, 3H), 1.78* (s, 3H), 1.36-1.46 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3 ; minor diastereomer peaks indicated with an asterisk when applicable) δ 173.4, 155.8, 143.4, 133.8, 133.3, 131.8, 124.9, 120.7, 119.0, 110.2, 104.1, 79.2,

65.0, 64.6*, 57.3*, 52.7, 52.6*, 49.9, 49.8*, 49.5, 49.0*, 35.2, 34.7*, 28.5, 25.8, 22.7, 18.3, 18.2*. HRMS (ESI) calc'd for $[C_{26}H_{36}O_4N_2Na]^+$ 463.2567, found 463.2574.

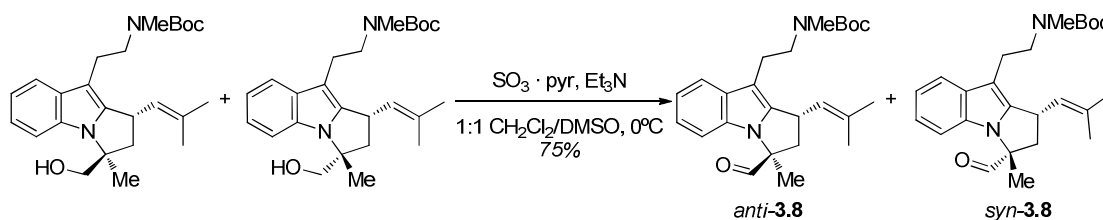


tert-butyl (2-(3-acetyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate (3.55). To a solution of ester **3.53** (43 mg, 0.100 mmol, 1.0 equiv) in THF (0.5 mL) at -78°C was added dropwise by syringe a solution of LDA (0.110 mmol, 1.1 equiv) in THF (0.5 mL). The reaction mixture stirred 1 h at -78°C ; then DMPU (14 mg, 0.110 mmol, 13 μL) and methyl iodide (142 mg, 1.00 mmol, 10 equiv) were added dropwise by syringe. The reaction mixture stirred overnight, slowly warming to room temperature. The reaction mixture was then quenched with saturated aqueous NaHCO_3 (1 mL) and the resulting biphasic mixture was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over MgSO_4 and concentrated. The product (8 mg, 0.020 mmol, 20%) was isolated by silica gel chromatography (10% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3) δ 7.56-7.75 (m, 1H), 7.10-7.16 (m, 3H), 5.78 (t, 1H, $J = 7.4$ Hz), 5.35 (d, 1H, $J = 8.4$ Hz), 4.24-4.30 (m, 1H), 3.44-3.58 (m, 1H), 3.41 (ddd, 1H, $J = 13.4$ Hz, 8.4 Hz, 7.4 Hz), 3.25-3.37 (m, 1H), 2.81-2.97 (m, 5H), 2.23-2.41 (m, 1H), 2.35 (s, 3H), 1.86 (s, 3H), 1.82 (s, 3H), 1.36-1.50 (m, 9H).

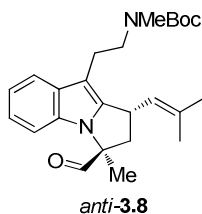


tert-butyl (2-(3-(hydroxymethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate. To a stirred solution of **3.54** (115 mg, 0.261 mmol, 1.0 equiv) in toluene (2.6 mL) at -78°C was added dropwise by syringe a solution of diisobutylaluminum hydride (1.0 M in cyclohexane) (0.31 mL, 0.31 mmol, 1.2 equiv). The reaction temperature was allowed to reach room temperature while stirring. The reaction mixture stirred 6 h at room temperature, at which time the reaction mixture was quenched by addition of $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$. The salts digested overnight and were removed by filtration. The filtrate was washed with EtOAc (2 x 5 mL) and concentrated *in vacuo*. The product was isolated as an inseparable mixture of diastereomers (2 : 1) (60.0 mg, 0.145 mmol, 56%) by flash chromatography (25% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk when applicable) δ 7.56 (broad d, 1H), 7.30-7.50 (broad m, 1H), 7.05-7.15 (broad d, 2H), 5.34* (broad d, 1H), 5.25 (broad s, 1H), 4.15-4.52 (m, 1H), 3.8-4.0 (m, 1H), 3.57-3.72 (m, 2H), 3.23-3.25 (broad s, 1H), 2.75-2.95 (m, 6H), 2.51 (d, 1H, $J = 8.5$ Hz), 2.08-2.12 (m, 1H), 1.86 (s, 3H), 1.82 (s, 3H), 1.75 (s, 3H), 1.23-1.46 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk when applicable): δ 159.7, 155.8, 155.5*, 144.7*, 144.3, 133.9*, 133.3, 132.9, 131.3, 131.0*, 128.4, 126.2, 126.1*, 120.3, 119.9*, 118.9*, 118.7, 114.3, 109.9, 109.7*, 103.4*, 103.2, 80.1, 79.3*, 68.8*, 68.7, 67.6, 64.8*,

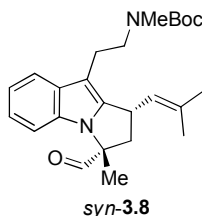
64.6, 64.5, 58.5, 57.1*, 55.3, 52.7, 49.9, 49.5*, 47.9*, 47.8, 46.0*, 35.9*, 35.4, 35.0*, 34.5, 34.0, 27.4*, 28.3, 28.2*, 25.8, 22.9, 22.1*, 18.3. HRMS (ESI) calc'd for $[C_{25}H_{37}O_3N_2]^+$ 413.2799, found 413.2807.



tert-butyl (2-(3-formyl-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate (3.8). To a solution of the alcohol (523 mg, 1.27 mmol, 1.0 equiv) in 1:1 $\text{CH}_2\text{Cl}_2/\text{DMSO}$ (13 mL) at 0°C was added Et_3N (1.28 g, 12.7 mmol, 10 equiv) followed by sulfur trioxide pyridine complex (1.69 g, 10.5 mmol, 8.3 equiv). The reaction mixture stirred for 1 h at 0°C . The reaction mixture was then quenched with 1:1 $\text{NaHCO}_3:\text{H}_2\text{O}$ (10 mL) and the layers were separated. The organic layer was washed with water (3 x 5 mL) and brine (1 x 5 mL), dried over Na_2SO_4 , and concentrated. The two diastereomers were separated by column chromatography (10 % EtOAc in hexanes; 25% EtOAc in hexanes) to yield the *anti* diastereomer *anti*-3.8 (295 mg, 0.718 mmol) as a yellow oil and *syn* diastereomer *syn*-3.8 (96 mg, 0.233 mmol) as a yellow foam in 75% total yield.

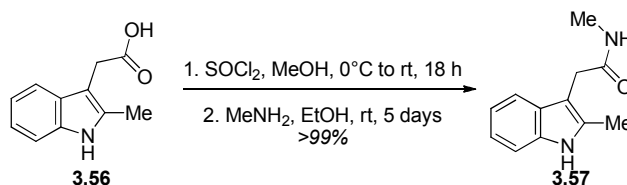


***anti*-tert-butyl (2-(3-formyl-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate (*anti*-3.8).** ^1H NMR (500 MHz, CDCl_3) δ 9.62 (s, 1H), 7.50-7.70 (broad d, 1H), 7.23 (broad s, 1H), 7.10-7.20 (m, 2H), 5.27 (d, 1H, $J = 9.0$ Hz), 4.15-4.25 (m, 1H), 3.49-3.59 (m, 1H), 3.23-3.33 (m, 1H), 3.07 (dd, 1H, $J = 13.0, 8.5$ Hz), 2.75-2.95 (m, 5H), 2.17 (dd, 1H, $J = 13.5$ Hz, 7.5 Hz), 1.82 (s, 3H), 1.80 (s, 6H), 1.23-1.46 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.6, 159.6, 155.6, 143.5, 133.7, 131.6, 128.3, 125.1, 123.1, 122.9, 122.7, 121.1, 119.5, 114.3, 109.3, 104.9, 79.2, 68.6, 55.3, 52.6, 49.7, 46.0, 35.0, 28.3, 25.7, 19.7, 18.2. HRMS (ESI) calc'd for $[C_{25}H_{34}O_3N_2\text{Na}]^+$ 433.2462, found 433.2470.

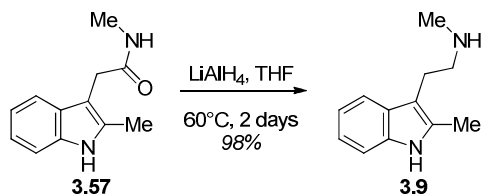


***syn*-tert-butyl (2-(3-formyl-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl)(methyl)carbamate (*syn*-3.8).** ^1H NMR (500 MHz, CDCl_3) δ 9.64 (s, 1H), 7.50-7.70 (broad d, 1H), 7.10-7.20 (m, 3H), 5.24-5.30 (m, 1H), 4.25-4.35 (m, 1H), 3.49-3.59 (m, 1H), 3.50-3.60 (m, 1H), 3.20-3.30 (m, 1H), 2.75-2.95 (m, 5H), 2.52 (dd, 1H, $J = 13.0, 8.0$ Hz), 2.43 (dd, 1H, $J = 13.0, 8.0$ Hz), 1.83 (s, 3H), 1.79 (s, 3H), 1.59 (s, 3H), 1.23-1.46

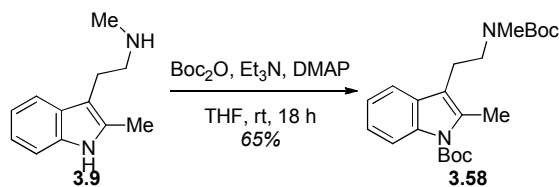
(m, 9H). ^{13}C NMR (125 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk when applicable): δ 144.8, 144.7*, 135.7*, 135.6, 134.2, 134.1*, 133.7*, 133.5, 132.9, 132.6*, 131.2, 129.6, 129.5*, 127.6, 126.0*, 127.6*, 120.3*, 120.2, 119.1, 118.8*, 118.7, 109.7, 109.4*, 103.1*, 102.8, 68.8, 67.7*, 64.7, 64.6*, 64.5, 47.7, 46.0*, 35.4, 34.5*, 27.4*, 27.0, 25.7, 22.9, 22.1*, 19.3, 18.3. HRMS (ESI) calc'd for $[\text{C}_{25}\text{H}_{34}\text{O}_3\text{N}_2\text{Na}]^+$ 433.2462, found 433.2469.



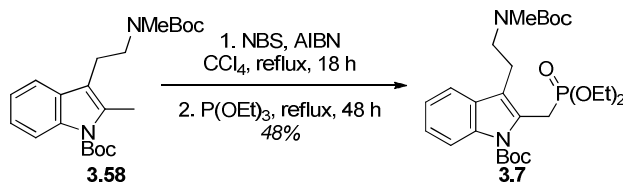
N-methyl-2-(2-methyl-1H-indol-3-yl)acetamide (3.57). To a solution of 2-methyl-3-indoleacetic acid (1.0 g, 5.29 mmol, 1.0 equiv) in anhydrous methanol (35 mL) submerged in a 0°C bath was added SOCl_2 (754 mg, 6.34 mmol, 1.2 equiv) dropwise by syringe. The reaction mixture stirred overnight while slowly warming to room temperature. The reaction temperature was then dropped to 0°C and the excess SOCl_2 was quenched with solid NaHCO_3 (2 g) and stirred 30 minutes. The salts were removed by filtration and the solvent was removed by rotary evaporator. The resulting yellow oil was portioned between Et_2O (10 mL) and water (10 mL). The aqueous layer was washed with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated by rotary evaporator. The resulting yellow oil was then dissolved in MeNH_2 (2.0 M in EtOH) (4 mL) and stirred at room temperature for five days. The volatiles were removed by rotary evaporator, and the resulting orange oil was azeotroped with EtOAc (2 x 20 mL), toluene (1 x 20 mL), EtOAc (1 x 20 mL), and CHCl_3 (1 x 20 mL) to yield the product as a yellow solid (1.06 g, 5.24 mmol, 99%). ^1H NMR (500 MHz, CDCl_3): δ 9.08 (s, 1H), 7.431 (d, 1H, $J = 7.5$ Hz), 7.32 (d, 1H, $J = 8.0$ Hz), 7.16 (t, 1H, $J = 7.5$ Hz), 7.11 (t, 1H, $J = 7.5$ Hz), 5.81 (broad s, 1H), 3.82 (s, 2H), 2.71 (d, 3H, $J = 5.0$ Hz), 2.38 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 176.7, 135.6, 133.8, 128.3, 121.5, 119.8, 117.6, 110.8, 104.2, 32.1, 26.4, 11.6.



2-methyl-N-methyltryptamine (3.9). To a stirred suspension of LiAlH_4 (0.979 g, 25.8 mmol, 4.9 equiv) in LiAlH_4 (20 mL) at 0°C was added slowly by cannula a solution of amide **3.57** (1.06 g, 5.24 mmol, 1.0 equiv) in THF (10 mL). The reaction temperature was brought to 60°C and stirred over 2 days. The reaction mixture was then cooled to 0°C ; the excess LiAlH_4 was then quenched with $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$. After stirring at room temperature for 6 h, the aluminum salts were removed by vacuum filtration and the eluent was concentrated by rotary evaporator to give the product as a red oil (0.970 g, 5.15 mmol, 98%). ^1H NMR (500 MHz, CDCl_3): δ 8.10 (broad s, 1H), 7.54 (d, 1H, $J = 8.0$ Hz), 7.25 (d, 1H, $J = 7.5$ Hz), 7.12 (t, 1H, $J = 7.5$ Hz), 7.08 (t, 1H, $J = 7.5$ Hz), 2.93 (t, 2H, $J = 6.5$ Hz), 2.87 (t, 2H, $J = 6.5$ Hz), 2.44 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 135.4, 131.8, 128.8, 121.0, 119.1, 118.0, 110.3, 109.4, 52.4, 36.5, 24.7, 11.7.

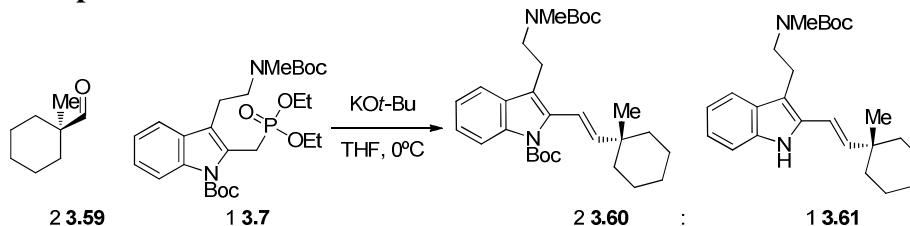


2-methyl-1,2,3,4-tetrahydro-1H-indole-3-carbonitrile derivative 3.58. To a stirred mixture of tryptamine **3.9** (970 mg, 5.15 mmol, 1.0 equiv), Et_3N (2.08 g, 20.6 mmol, 4.0 equiv), and Boc_2O (2.47 g, 11.3 mmol, 2.2 equiv) in THF (26 mL) was added a catalytic amount of DMAP (63 mg, 0.515 mmol, 10 mol%). The reaction mixture stirred 18 h at room temperature. The reaction mixture was quenched with saturated NaHCO_3 (aq) (15 mL). The resulting biphasic mixture was extracted with EtOAc (1 x 15 mL) and the organic layer was washed with saturated NaHCO_3 (aq) (2 x 15 mL) and brine (1 x 15 mL), dried over MgSO_4 and concentrated by rotary evaporator. The product (1.31 g, 3.37 mmol, 65%), a yellow oil, was isolated by column chromatography (10% EtOAc in hexanes; 25% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3 , isolated as a mixture of rotamers): δ 8.10 (broad s, 1H), 7.45 (m, 1H), 7.24 (t, 1H, $J = 7.5$ Hz), 7.21 (t, 1H, $J = 7.0$ Hz), 3.38 (t, 2H, $J = 7.0$ Hz), 2.64-2.90 (m, 5H), 2.54 (broad s, 3H), 1.65 (s, 9H), 1.20-1.40 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 155.6, 150.1, 135.8, 133.8, 129.9, 123.4, 122.5, 117.4, 115.5, 83.5, 79.3, 48.9, 34.5, 28.3, 22.9, 13.8.

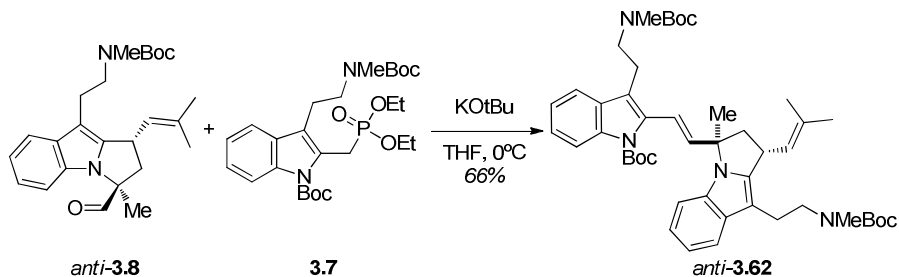


2-((diethoxyphosphoryl)methyl)-1,2,3,4-tetrahydro-1H-indole-3-carbonitrile derivative 3.7. A stirred solution of 2-methyl tryptamine **3.58** (1.31 g, 3.37 mmol, 1.0 equiv), recrystallized *N*-bromosuccinimide (0.600 g, 3.37 mmol, 1.0 equiv) and catalytic AIBN (55 mg, 0.337 mmol, 10 mol%) in CCl_4 (17 mL) was refluxed at 75°C for 18 h. The reaction temperature was then lowered to room temperature and the reaction mixture was quenched with water (10 mL); the product was then extracted in to CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (1 x 15 mL), dried over MgSO_4 and concentrated. The resulting brown oil was suspended in triethylphosphite (3.5 mL) and this solution was stirred at 55°C for 48 h. The excess triethylphosphite was removed by rotary evaporator, and the product was isolated by flash chromatography (1% methanol in CH_2Cl_2 ; 2% methanol in CH_2Cl_2) to give an orange oil (0.843 g, 1.61 mmol, 48% over 2 steps). ^1H NMR (500 MHz, CDCl_3 , isolated as a mixture of rotamers): δ 8.054 (broad s, 1H), 7.40-7.60 (m, 1H), 7.20-7.26 (m, 2H), 4.00 (q, 4H, $J = 7.0$ Hz), 3.80-3.90 (m, 2H), 3.43 (broad s, 2H), 2.941 (broad s, 2H), 2.75-2.90 (m, 3H), 1.68 (s, 9H), 1.30-1.40 (m, 9H), 1.21 (t, 6H, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ 155.6, 150.5, 136.9, 129.3, 127.2, 124.1, 122.5, 118.1, 115.6, 84.2, 79.5, 62.1, 48.8, 28.5, 28.2, 26.1, 24.9, 16.4.

A representative procedure for base screen for HWE reaction:

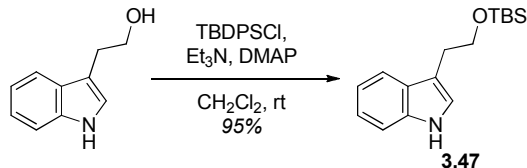


tert-butyl 3-(2-((tert-butoxycarbonyl)(methylamino)ethyl)-2-(2-(1-methylcyclohexylvinyl)-1H-indole-1-carboxylate (3.60) and tert-butyl methyl(2-(2-(2-(1-methylcyclohexylvinyl)-1H-indol-3-yl)ethyl)carbamate (3.61). A mixture of **3.7** (41 mg, 0.100 mmol, 1.0 equiv) and potassium *tert*-butoxide (1.0 M in THF) (0.12 mL, 0.12 mmol, 1.2 equiv) in THF (0.5 mL) was stirred at 0°C for fifteen minutes. To this was added a solution of aldehyde **3.59** (18 mg, 0.110 mmol, 1.1 equiv). The reaction mixture turned bright red and was allowed to stir at 0°C for 2 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ (1 mL) and the resulting mixture was washed with ethyl acetate (3 x 2 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over Na₂SO₄, and concentrated by rotary evaporator. The product distribution was analyzed by ¹H NMR; diagnostic peaks are listed below. ¹H NMR (500 MHz, CDCl₃; peaks assigned to **3.61** noted with an asterisk): δ 8.91* (broad s, 1H), 8.20 (broad s, 1H), 7.51-7.61 (m, 1H), 7.31 (d, 1H, *J* = 8.5 Hz), 7.35* (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 9.5 Hz), 7.13-7.18 (m, 1H), 7.07-7.12 (m, 1H), 6.45-6.60 (m, 1H), 6.02 (d, 1H, *J* = 17.0 Hz), 3.10-3.42 (m, 2H), 2.74-3.00 (m, 5H).

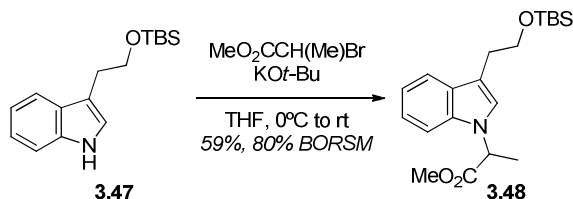


anti tert-butyl 3-(2-(((tert-butoxycarbonyl)(methylamino)ethyl)-2-((E)-2-(9-(2((tert-butoxycarbonyl)(methylamino)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-3-yl)vinyl)-1H-indole-1-carboxylate (3.62). To mixture of **3.8** (78 mg, 0.190 mmol, 1.0 equiv) and **3.7** (150 mg, 0.284 mmol, 1.5 equiv) in THF (2.0 mL) at 0°C was added potassium *tert*-butoxide (1.0 M in THF) (0.34 mL, 0.340 mmol, 1.8 equiv). The reaction mixture turned bright red and was allowed to stir at 0°C for 1 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ (1 mL) and the resulting mixture was washed with ethyl acetate (3 x 2 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over Na₂SO₄, and concentrated by rotary evaporator. The product was isolated by column chromatography (10% EtOAc in hexanes; 25% EtOAc in hexanes) to yield the product as a yellow foam (92 mg, 0.125 mmol, 66% yield). Due to rotamers, the peaks for this compound are not tabulated. Please see Appendix 2 for spectra.

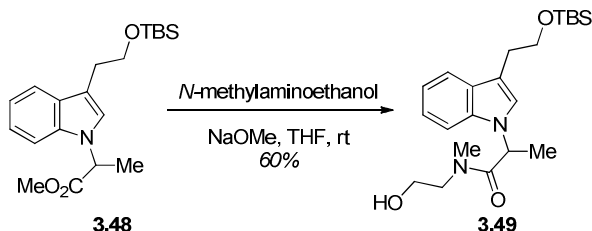
4. TBS-ether analogs



3-(2-(*tert*-butyldimethylsiloxy)ethyl)indole (3.47). To a solution of tryptophol (1.00 g, 6.21 mmol, 1 equiv) in CH₂Cl₂ (31 mL) was added Et₃N (0.785 g, 7.76 mmol, 1.25 equiv), *tert*-butyldimethylsilyl chloride (1.12 g, 7.45 mmol, 1.2 equiv) and DMAP (37.9 mg, 0.31 mmol, 5 mol%). The reaction mixture stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous NaHCO₃ (15 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL) and the combined organic layers were dried over MgSO₄ and concentrated by rotary evaporator. The product was isolated as a yellow oil (1.63 g, 5.91 mmol, 95%) by flash chromatography (5% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.96 (broad s, 1H), 7.62 (d, 1H, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 8.0 Hz), 7.20 (t, 1H, *J* = 7.5 Hz), 7.13 (t, 1H, *J* = 7.3 Hz), 7.05 (s, 1H), 3.89 (t, 2H, *J* = 6.8 Hz), 3.01 (t, 2H, *J* = 7.3 Hz), 0.91 (s, 9H), 0.04 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 136.1, 127.7, 122.0, 121.9, 119.3, 118.9, 113.2, 111.0, 63.9, 29.0, 26.0, 18.4, -5.3.

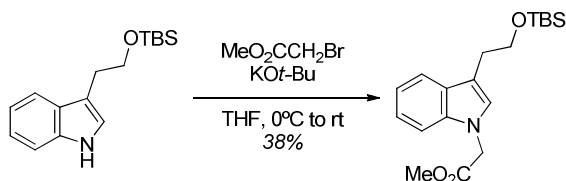


Methyl 2-(3-(2-(*tert*-butyldimethylsiloxy)ethyl)-1*H*-indol-1-yl)propionate (3.48). Prepared according to the procedure above using **3.47** (338 mg, 1.23 mmol) and methyl 2-bromopropionate (656 mg, 3.93 mmol). The product was isolated as a 3:1 mixture of desired product **3.48** and starting material **3.47** (80% total yield). ¹H NMR (500 MHz, CDCl₃): δ 7.65 (d, 1H, *J* = 7.5 Hz), 7.33 (d, 1H, *J* = 8.5 Hz), 7.24 (t, 1H, *J* = 7.5 Hz), 7.17 (t, 1H, *J* = 7.5 Hz), 7.15 (s, 1H), 5.15 (q, 1H, *J* = 7.0 Hz), 3.93 (t, 2H, *J* = 7.5 Hz), 3.73 (s, 3H), 3.04 (s, 2H, *J* = 7.5 Hz), 1.82 (d, 3H, *J* = 7.0 Hz), 0.83 (s, 9H), 0.08 (s, 6H).

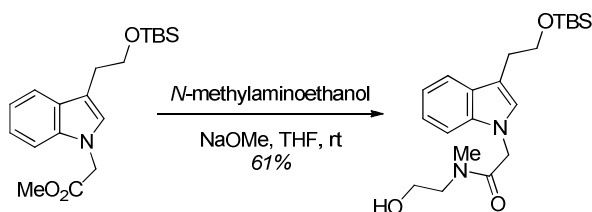


2-(3-(3-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indol-1-yl)-*N*-(2-hydroxyethyl)-*N*-methylpropanamide (3.49). Prepared analogously to **3.39** from **3.48** (268 mg, 0.780 mmol, 1.0 equiv) to yield the product as a iridescent foam (190 mg, 0.470 mmol, 60%) as a 2:1 mixture of rotamers. ¹H NMR (500 MHz, CDCl₃; minor rotamer peaks are indicated with an asterisk when applicable): δ 7.60 (apparent t, 1H, *J* = 7.8 Hz), 7.40* (d, 1H, *J* = 8.0 Hz), 7.31 (d, 8.0 Hz), 7.19-7.24 (m, 1H), 7.09-7.15 (m, 1H), 7.06* (s, 1H), 7.01 (s, 1H), 5.55-5.59* (m, 1H), 5.28 (q, 1H, *J* = 6.7 Hz), 3.85-3.89 (m, 2H), 3.74-3.75 (m, 2H), 3.60-3.63 (m, 1H), 3.48-3.51 (m, 1H), 3.48-

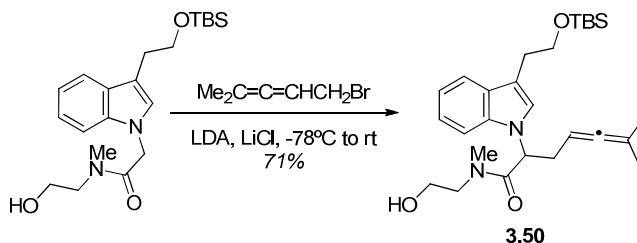
3.51* (m, 2H), 3.25-3.28* (m, 1H), 3.13-3.16* (m, 1H), 2.96-2.99 (m, 2H), 2.95* (s, 3H), 2.93 (s, 3H), 1.62 (d, 3H, $J = 6.5$ Hz), 1.60-1.61* (m, 3H), 1.01 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3): δ 171.7, 135.5, 128.5, 123.3, 122.0, 119.5, 119.4, 113.5, 108.6, 63.8, 61.1, 51.9, 51.2*, 36.4, 34.2*, 29.0, 26.0, 18.4, 18.0, -5.3.



Methyl 2-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indol-1-yl)acetate. Prepared analogously to **3.21** using **3.47** (564 mg, 2.05 mmol) and methyl bromoacetate (1.00 g, 6.55 mmol). The product was isolated as a 3:1 mixture of desired product and starting material for an overall yield of 50%. ^1H NMR (500 MHz, CDCl_3): δ 7.70 (d, 1H, $J = 7.5$ Hz), 7.27-7.32 (m, 2H), 7.19-7.24 (m, 1H), 6.99 (s, 1H), 4.85 (s, 2H), 3.98 (t, 2H, $J = 7.3$ Hz), 3.80 (s, 3H), 3.08 (t, 2H, $J = 7.3$ Hz), 1.00 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3): δ 169.3, 136.8, 128.5, 126.5, 122.1, 119.4, 119.3, 113.2, 108.9, 63.9, 52.5, 47.6, 29.0, 26.1, 18.5, -5.2.



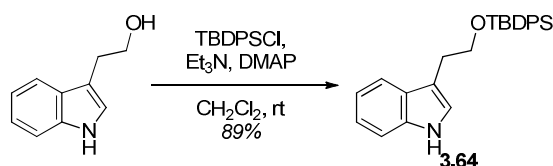
2-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indol-1-yl)-*N*-(2-hydroxyethyl)-*N*-methylacetamide. Prepared analogously to **3.39** from the ester depicted above (270 mg, 0.777 mmol, 1.0 equiv). The product was isolated as a 2:1 mixture of rotamers by flash chromatography (2% methanol in CH_2Cl_2) as a iridescent solid (184 mg, 0.471 mmol, 61%). ^1H NMR (500 MHz, CDCl_3 ; minor rotamer peaks are indicated with an asterisk where applicable) δ 7.622 (t, H, $J = 8.0$ Hz), 7.09-7.30 (m, 3H), 6.93 (s, 1H), 4.95* (s, 2H), 4.84* (s, 2H), 3.91 (t, 2H, $J = 7.5$ Hz), 3.71* (t, 1H, $J = 5.0$ Hz), 3.49* (t, 1H, $J = 5.0$ Hz), 3.45-3.47* (m, 1H), 3.15-3.25* (m, 1H), 3.01-3.03 (m, 2H), 3.01* (s, 2H), 2.84* (s, 1H), 0.95 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H).



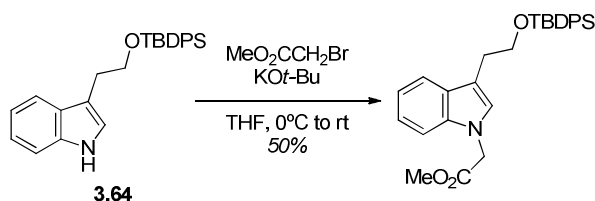
2-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indol-1-yl)-*N*-(2-hydroxyethyl)-*N*,6-dimethylhepta-4,5-dienamide (3.50**).** Prepared analogously to **3.40** from the ethanolamide depicted above (125 mg, 0.384 mmol, 1.0 equiv); isolated as a white foam (129 mg, 0.274 mmol, 71%) as a 2:1 mixture of rotamers. ^1H NMR (500 MHz, CDCl_3 ; minor rotamer peaks are indicated with an asterisk when applicable): δ 7.58 (apparent t, 1H, $J = 8.5$ Hz), 7.39* (d, 1H, $J = 8.5$ Hz), 7.33 (d, 8.5 Hz), 7.18-7.22 (m, 1H), 7.07-7.13 (m, 1H), 7.05* (s, 1H), 5.42* (t, 1H, $J = 7.3$ Hz), 5.21 (t, 1H, $J = 7.0$ Hz), 4.87-5.01 (m, 1H), 4.81-4.87* (m, 1H), 3.84-3.87 (m, 2H),

3.71-3.75 (m, 2H), 3.60-3.63 (m, 1H), 3.48-3.51 (m, 1H), 3.48-3.51* (m, 2H), 3.25-3.28* (m, 1H), 3.13-3.16* (m, 1H), 2.96-2.99 (m, 2H), 2.95* (s, 3H), 2.93 (s, 3H), 1.62 (d, 3H, $J = 6.5$ Hz), 1.60-1.61* (m, 3H), 1.01 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3): δ 171.7, 135.5, 128.5, 123.3, 122.0, 119.5, 119.4, 113.5, 108.6, 63.8, 61.1, 51.9, 51.2*, 36.4, 34.2*, 29.0, 26.0, 18.4, 18.0, -5.3.

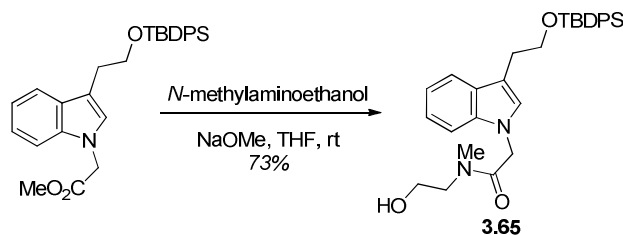
5. TBDPS-protected tryptophol analogs



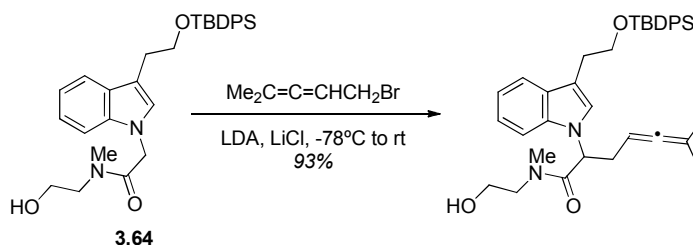
3-(2-(*tert*-butyldiphenylsiloxy)ethyl)indole (3.64). To a solution of tryptophol²⁹ (17.9 g, 111 mmol, 1.0 equiv) in CH_2Cl_2 (500 mL) was added first Et_3N (13.5 g, 133 mmol, 1.2 equiv), followed by dropwise addition of *tert*-butyldiphenylchlorosilane (TBDPSCl) (30.5 g, 111 mmol, 1.0 equiv). Catalytic 4-dimethylaminopyridine (DMAP) (0.680 g, 5.55 mmol, 5 mol%) was then added in one portion. The reaction mixture stirred at room temperature for 18 h. The reaction mixture was then quenched with saturated NaHCO_3 (400 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL) and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The product was isolated as a pink oil (39.60 g, 89%) by flash chromatography (2% EtOAc in hexanes; 10% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3) δ 7.90 (broad s, 1H), 7.66 (d, 4H, $J = 7.5$ Hz), 7.32-7.44 (m, 8H), 7.17 (t, 1H, $J = 7.5$ Hz), 7.05 (t, 1H, $J = 7.5$ Hz), 7.00 (d, 1H, $J = 2.0$ Hz), 3.94 (t, 2H, $J = 7.5$ Hz), 3.04 (t, 2H, $J = 7.5$ Hz), 1.09 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 136.1, 135.6, 134.0, 129.5, 127.7, 127.6, 122.2, 121.8, 119.2, 118.9, 113.1, 110.1, 64.5, 28.7, 26.9, 19.2. HRMS (ESI) calc'd for $[\text{C}_{26}\text{H}_{29}\text{ONNaSi}]^+$ 422.1911, found 422.1905.



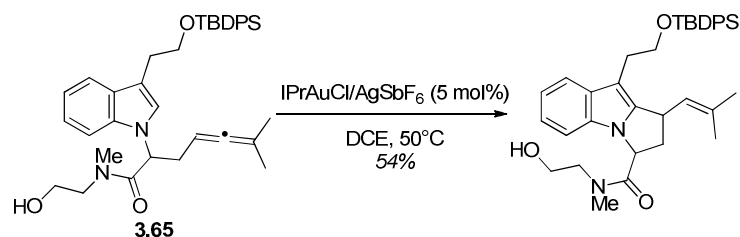
3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1H-indole. Prepared analogously to **3.21**; the product (23.4 g, 49.6 mmol, 50%, 72% BORSM) was separated from the unconsumed starting material (12.3 g, 30.7 mmol, 31%) by flash chromatography (2% EtOAc in hexanes; 3% EtOAc in hexanes; 10% EtOAc in hexanes) and was isolated as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, 4H, $J = 7.0$ Hz), 7.41 (t, 2H, $J = 7.0$ Hz), 7.32-7.37 (m, 5H), 7.18-7.19 (m, 2H), 7.04-7.07 (m, 1H), 6.87 (s, 1H), 4.77 (s, 2H), 3.93 (t, 2H, $J = 7.5$ Hz), 3.69 (s, 3H), 3.04 (t, 2H, $J = 7.5$ Hz), 1.08 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.2, 135.7, 134.0, 129.6, 128.4, 127.7, 126.5, 122.0, 119.3, 113.0, 108.8, 64.4, 52.5, 47.6, 28.6, 26.9, 19.2. HRMS (ESI) calc'd for $[\text{C}_{29}\text{H}_{34}\text{O}_3\text{NSi}]^+$ 472.2302, found 472.2292.



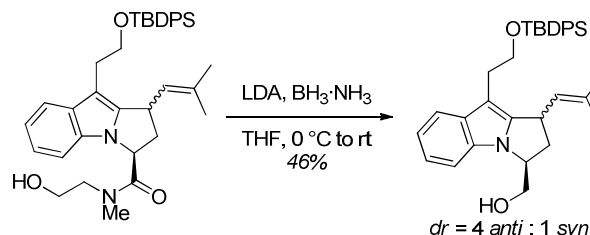
2-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1H-indol-1-yl)-N-(2-hydroxyethyl)-N-methylacetamide (3.65). Prepared analogously to **3.39** from the ester shown above (11.61 g, 24.8 mmol, 1.0 equiv). The product was isolated as a 2:1 mixture of rotamers by flash chromatography (2% methanol in CH₂Cl₂) as a iridescent solid (9.34 g, 18.1 mmol, 73%). ¹H NMR (500 MHz, CDCl₃; minor rotamer peaks are indicated with an asterisk where applicable) δ 7.68 (d, 4H, *J* = 6.5 Hz), 7.425 (t, 1H, *J* = 7.0 Hz), 7.33-7.38 (m, 6H), 7.12-7.22 (m, 2H), 7.01-7.05 (m, 1H), 6.85 (s, 1H), 4.88* (s, 2H), 4.76* (s, 2H), 3.94 (t, 2H, *J* = 7.5 Hz), 3.65 (t, 2H, *J* = 5.0 Hz), 3.43 (t, 2H, *J* = 5.0 Hz), 3.39-3.41* (m, 2H), 3.20-3.22* (m, 2H), 3.04 (t, 2H, *J* = 7.5 Hz), 2.92 (s, 3H), 2.76* (s, 3H), 1.08 (s, 9H). ¹³C NMR (125 MHz, CDCl₃; minor rotamer peaks are indicated with an asterisk where applicable) δ 169.1, 136.8, 135.6, 134.0, 129.6, 128.4, 127.7, 126.8*, 126.5, 121.9, 121.7*, 119.3, 119.2, 119.1*, 118.9*, 112.6, 109.3*, 109.0, 64.6*, 64.5, 60.7*, 58.9, 51.5*, 51.1, 48.0, 35.8, 33.5, 28.7, 27.0, 19.3. HRMS (ESI) calc'd for [C₃₁H₃₉O₃N₂Si]⁺ 515.2724, found 515.2716.



2-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1H-indol-1-yl)-N-(2-hydroxyethyl)-N,6-dimethylhepta-4,5-dienamide (3.65). Prepared analogously to **3.40** from **3.64** (5.15 g, 10.0 mmol, 1.0 equiv). The product was isolated as a yellow foam (5.39 g, 9.27 mmol, 93%) by flash chromatography (1% methanol in CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃; minor rotamer peaks are indicated with an asterisk where applicable) δ 7.65-7.67 (m, 4H), 7.42 (t, 2H, *J* = 7.0 Hz), 7.32-7.38 (m, 6H), 7.20 (t, 1H, *J* = 7.5 Hz), 7.04-7.10 (m, 2H), 5.41-5.43* (m, 1H), 5.19 (t, 1H, *J* = 7.0 Hz), 4.88-5.00 (m, 1H), 4.82-4.84* (m, 1H), 3.90-3.94 (m, 2H), 3.68-3.72 (m, 2H), 3.50-3.55* (m, 2H), 3.43-3.48 (m, 2H), 3.25-3.29* (m, 1H), 3.15-3.19* (m, 1H), 3.00-3.04 (m, 2H), 2.91* (s, 3H), 2.86 (s, 3H), 2.64-2.69* (m, 2H), 2.50-2.60 (m, 2H), 1.58 (d, 3H, *J* = 2.5 Hz), 1.54* (d, 3H, *J* = 2.5 Hz), 1.50 (d, 3H, *J* = 2.5 Hz), 1.41* (d, 3H, *J* = 2.5 Hz), 1.19 (s, 9H). ¹³C NMR (125 MHz, CDCl₃; minor rotamer peaks are indicated with an asterisk where applicable) δ 202.7*, 202.5, 170.8, 136.1, 135.6, 134.0, 129.6, 128.5, 127.7, 124.0, 121.8, 121.7*, 119.5, 119.4, 119.3*, 119.1*, 113.1, 108.8, 96.4, 96.0*, 84.9, 84.7*, 64.3, 61.2, 59.7*, 55.8, 55.2*, 52.0, 51.4*, 36.6, 34.3*, 33.0*, 32.3, 28.8, 26.9, 20.5, 20.4*, 20.2*, 20.1, 19.3. HRMS (ESI) calc'd for [C₃₇H₄₇O₃N₂Si]⁺ 595.3350, found 595.3352.

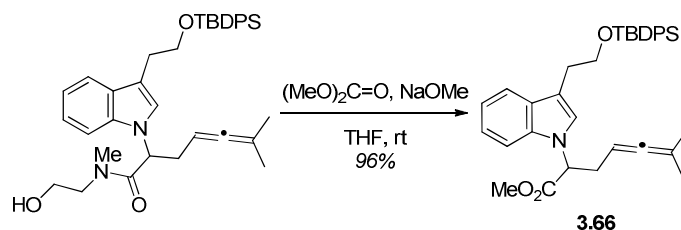


9-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-*N*-(2-hydroxyethyl)-*N*-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1.2-*a*]indole-3-carboxamide. The gold(I) catalyst was prepared by stirring IPrAuCl (55 mg, 0.089 mmol, 5 mol%), and AgSbF₆ (30 mg, 0.089 mmol, 5 mol%) in dichloromethane (2 mL) for five minutes in the dark. The resulting purple slurry was filtered through glass wool to remove the AgCl. This solution was then added to a stirring solution of **3.65** (1.06 g, 1.78 mmol, 1.0 equiv) in DCE (16 mL) at 0°C. The reaction flask was fitted with a reflux condenser and the reaction mixture was then heated to 45°C and stirred overnight. The reaction mixture was then cooled to room temperature and was poured over a silica gel plug (5% methanol in CH₂Cl₂) and the crude products were eluted (5% methanol in CH₂Cl₂). The filtrate was concentrated and the product was isolated as a yellow foam (626 mg, 1.05 mmol, 62%; *dr* = 4 *anti* : 1 *syn*) by flash chromatography (0.5% methanol in CH₂Cl₂; 5% methanol in CH₂Cl₂). Characterization of these compounds, as well as determination of the diastereomeric ratio, was confirmed by lithium amidoborane reduction to form the alcohol (see below).

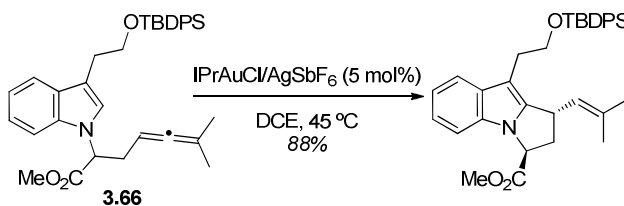


(9-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-3-yl)methanol. A solution of LDA was prepared by adding *n*-BuLi (2.12 M in hexanes) (0.23 mL, 0.485 mmol, 3.9 equiv) dropwise by syringe to a solution of DIPA (53 mg, 0.521 mmol, 4.0 equiv) in THF (0.6 mL) at -78°C. The solution stirred at -78°C for ten minutes and then the reaction temperature was increased to 0°C. After stirring for an additional ten minutes, borane–ammonia complex (15 mg, 0.496 mmol, 4.0 equiv) was added in one portion. The resulting suspension was stirred at 0°C for fifteen minutes and then at room temperature for fifteen minutes. The reaction mixture was then cooled to 0°C and a solution of the amide (74 mg, 0.124 mmol, 1.0 equiv) in THF (0.6 mL) was added dropwise. The reaction mixture stirred for two hours, gradually increasing in temperature to 10°C. The lithium amidoborane was then quenched with 1.0 M HCl (aq) (0.5 mL), and the resulting mixture was extracted with EtOAc (2 x 1 mL). The combined organic layers were dried over MgSO₄ and concentrated by rotary evaporator. The products were isolated as a yellow oil (30 mg, 0.0573 mmol, 46%; *dr* = 4 *anti* : 1 *syn*) by flash chromatography (40% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃; minor diastereomer peaks are indicated with an asterisk where applicable): δ 7.57-7.66 (m, 4H), 7.27-7.43 (m, 8H), 7.08 (t, 1H, *J* = 7.5 Hz), 6.99 (t, 1H, *J* = 7.5 Hz), 5.24 (d, 1H, *J* = 9.5 Hz), 5.12* (d, 1H, *J* = 9.5 Hz), 4.54-4.58* (m, 1H), 4.48 (m, 1H), 4.19-4.26* (m, 1H), 4.12 (dd, 1H, *J* = 12.0 Hz, 4.0 Hz), 4.06 (td, 1H, *J* = 9.5 Hz, 5.5 Hz), 3.92-3.98* (m, 2H), 3.85-3.90 (m, 1H), 3.82 (t, 2H, *J* = 7.5 Hz), 2.92-3.00 (m, 2H), 2.88 (dt, 1H, *J* = 13.0 Hz, 8.5 Hz), 2.60-2.63* (m, 1H), 2.35*

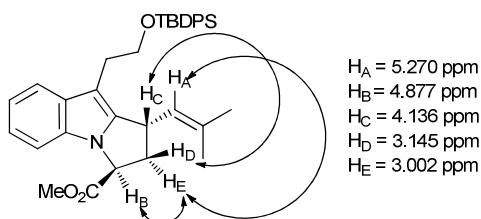
(dt, 1H, $J = 13.0$ Hz, 8.5 Hz), 2.14 (dt, 1H, $J = 13.0$ Hz, 5.5 Hz), 1.78* (s, 3H), 1.78 (s, 3H), 1.74* (s, 3H), 1.69 (s, 3H), 1.08* (s, 9H), 1.08 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk where applicable): δ 145.0, 144.1*, 135.6, 135.6*, 134.2, 134.1*, 133.3, 133.2*, 133.1*, 132.4, 132.1, 132.0*, 129.6*, 129.5, 127.7*, 127.6, 126.1, 125.3*, 120.5*, 120.4, 119.0*, 118.9, 118.9, 118.8*, 109.7, 109.5*, 103.2*, 103.0, 64.9*, 64.7*, 64.6, 64.5, 58.4, 57.5*, 39.6*, 38.7, 35.5*, 34.9, 27.6, 27.4*, 26.9, 25.7, 19.2, 18.2. HRMS ($\text{ESI}^+ + \text{H}^+$): calculated for $\text{C}_{34}\text{H}_{42}\text{O}_2\text{NSi}$ 524.2979, found 524.2969.



Methyl 2-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1H-indol-1-yl)-6-methylhepta-4,5-dienoate (3.66). Prepared analogously to **3.24** from the allene showed above (1.60 g, 2.69 mmol, 1.0 equiv). The product was isolated by flash chromatography (5% EtOAc in hexanes) to give the product as a yellow oil (1.42 g, 2.57 mmol, 96%). ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.71 (m, 4H), 7.42-7.45 (m, 2H), 7.35-7.39 (m, 5H), 7.33 (d, 1H, $J = 8.5$ Hz), 7.21 (t, 1H, $J = 7.5$ Hz), 7.12 (s, 1H), 7.07 (t, 1H, $J = 7.5$ Hz), 5.05 (dd, 1H, $J = 8.5, 6.5$ Hz), 4.88-4.90 (m, 1H), 3.96 (t, 2H, $J = 7.0$ Hz), 3.66 (s, 3H), 3.06 (t, 2H, $J = 7.0$ Hz), 2.91 (dt, 1H, $J = 15.0, 6.5$ Hz), 2.73 (ddd, 1H, $J = 15.0, 8.5, 6.0$ Hz), 1.52 (d, 3H, $J = 3.0$ Hz), 1.42 (d, 3H, $J = 2.5$ Hz), 1.10 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 202.6, 171.0, 136.7, 135.7, 134.0, 129.6, 128.4, 127.7, 123.4, 121.7, 119.2, 119.1, 112.9, 109.2, 83.9, 64.4, 57.7, 52.4, 31.5, 28.8, 27.0, 20.3, 20.2, 19.3. HRMS (ESI) calc'd for $[\text{C}_{35}\text{H}_{42}\text{O}_3\text{NSi}]^+$ 552.2928, found 552.2934.

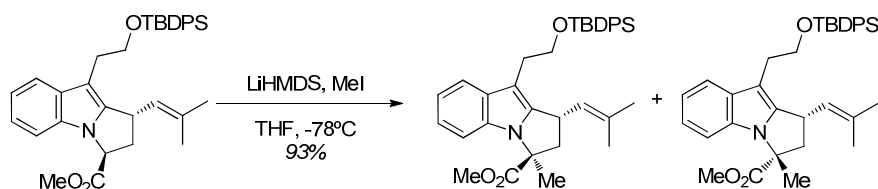


Methyl 9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate. Prepared analogously to **3.52** from **3.66** (489 mg, 0.886 mmol, 1.0 equiv). The product was isolated as a single diastereomer by flash chromatography (5% EtOAc in hexanes) as a white solid (432 mg, 0.783 mmol, 88%). Important nOe correlations are indicated below:



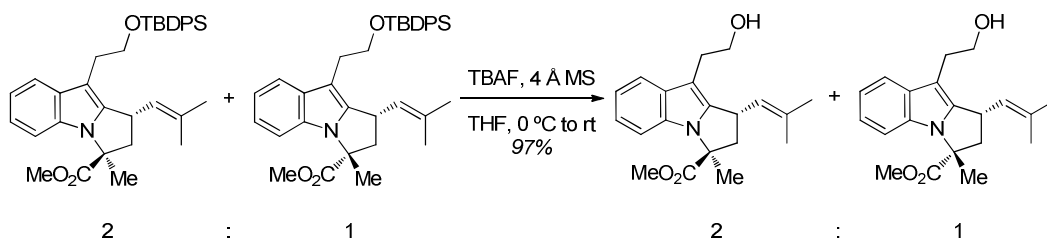
^1H NMR (500 MHz, CDCl_3) δ 7.69 (d, 2H, $J = 6.5$ Hz), 7.65 (d, 2H, $J = 7.0$ Hz), 7.45 (t, 2H, $J = 7.0$ Hz), 7.32-7.37 (m, 5H), 7.12-7.18 (m, 2H), 7.05 (t, 1H, $J = 7.0$ Hz), 5.27 (d, 1H, $J = 9.5$ Hz), 4.88 (dd, 1H, $J = 8.5, 5.5$ Hz), 4.14 (ddd, 1H, $J = 9.5, 9.0, 5.5$ Hz), 3.88 (t, 2H, $J = 7.5$ Hz), 3.73

(s, 3H), 3.15 (ddd, 1H, $J = 13.0$ Hz, 9.0 Hz, 8.5 Hz), 3.00 (t, 2H, $J = 7.5$ Hz), 2.45 (dt, 1H, $J = 13.0$ Hz, 5.5 Hz), 1.59 (s, 3H), 1.49 (s, 1H), 1.08 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): 171.8, 144.1, 135.6, 134.1, 134.0, 133.3, 132.8, 132.3, 129.5, 127.6, 125.0, 120.8, 119.2, 119.0, 109.7, 103.6, 64.5, 57.2, 52.6, 43.6, 40.9, 35.2, 27.7, 26.9, 25.7, 19.3, 18.1. HRMS (ESI) calc'd for $[\text{C}_{35}\text{H}_{42}\text{O}_3\text{NSi}]^+$ 552.2928, found 552.2937.



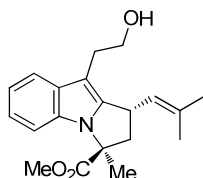
d.r. = 2 anti : 1 syn

Methyl 9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate. To a solution of the methyl ester (442 mg, 0.801 mmol, 1.0 equiv) in THF (8 mL) at -78°C was added dropwise by syringe LiHMDS (1.0 M in THF) (0.88 mL, 0.88 mmol, 1.1 equiv). Upon addition of base, the reaction mixture turned bright yellow. The reaction mixture stirred at -78°C for one hour, at which time methyl iodide (1.14 g, 8.01 mmol, 10 equiv) was added in one portion. The reaction mixture stirred for one hour at -78°C , and the reaction mixture was then quenched with 0.01 M NaHSO_4 (8 mL). The resulting slurry was extracted with EtOAc (3 x 8 mL), and the combined organic layers were washed with brine (1 x 16 mL), dried over MgSO_4 , and concentrated *in vacuo*. The product, a yellow oil, was isolated as an inseparable 2:1 mixture of *anti* and *syn* diastereomers (422 mg, 0.745 mmol, 93%) by flash chromatography (5% EtOAc in hexanes). The diastereochemistry of the two isomers was confirmed by silyl deprotection to afford the readily separable alcohols shown below. ^1H NMR (500 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk when applicable): δ 7.68 (d, 2H, $J = 6.5$ Hz), 7.60 (d, 2H, $J = 8.0$ Hz), 7.28-7.45 (m, 8H), 7.19* (d, 1H, $J = 8.0$ Hz), 7.11 (t, 1H, $J = 7.5$ Hz), 7.01 (t, 1H, $J = 7.5$ Hz), 5.22 (at, 1H, $J = 9.5$ Hz), 4.22 (m, 1H), 4.20* (m, 1H), 3.85 (t, 2H, $J = 7.5$ Hz), 3.76* (s, 3H), 3.62 (s, 3H), 3.18 (dd, 1H, $J = 13.0, 8.0$ Hz), 2.93-3.02 (m, 2H), 2.69-2.72* (m, 2H), 2.19 (dd, 1H, $J = 13.0, 8.5$ Hz), 1.96 (s, 3H), 1.81 (s, 3H), 1.78 (s, 3H), 1.75* (s, 3H), 1.75* (s, 3H), 1.07 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk when applicable): δ 173.9*, 173.6, 143.8, 143.6*, 135.6, 134.1, 134.0*, 133.9, 133.5, 133.0*, 131.6, 131.3*, 129.5, 129.4, 127.6, 124.8, 120.6*, 120.5, 119.0*, 118.9, 109.9, 103.5, 103.4*, 65.0, 64.5, 64.4*, 52.8*, 52.7, 49.6, 49.1*, 35.3, 34.7*, 27.5*, 27.3, 26.9, 25.7, 23.8, 22.9*, 19.2, 18.3, 18.2*. HRMS (ESI) calc'd for $[\text{C}_{36}\text{H}_{44}\text{O}_3\text{NSi}]^+$ 566.3085, found 566.3090.

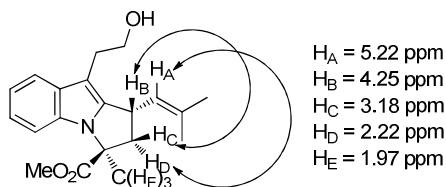


Methyl 9-(2-hydroxyethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate. A solution of TBAF (1.0 M in THF, ca. 5% water) (5.0 mL, 5.0 mmol, 3.0 equiv) in THF (10 mL) was stirred at room temperature with 4 Å molecular sieves

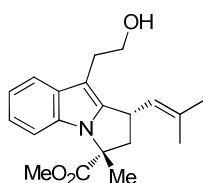
for twenty minutes. The temperature of this mixture was dropped to 0°C, at which time a solution of the silyl ether (959 mg, 1.69 mmol, 1.0 equiv; 2:1 *d.r.*) in THF (5 mL) was added by cannula. The reaction temperature was increased to room temperature and the reaction was allowed to stir for 5 h. The reaction mixture was then quenched with saturated NaHCO₃ (10 mL). The resulting slurry was extracted with EtOAc (20 mL) and the layers were separated. The organic layer was washed with saturated NaHCO₃ (2 x 10 mL) and brine (1 x 10 mL), dried over MgSO₄ and concentrated *in vacuo*. The products were separated by flash chromatography (15% EtOAc in hexanes; 20% EtOAc in hexanes) to yield the *anti* alcohol (359 mg, 1.09 mmol) and *syn* diastereomer (180 mg, 0.551 mmol) in 97% yield as yellow oils.



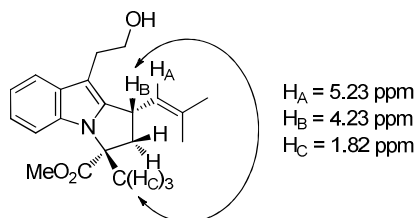
***anti* - Methyl 9-(2-hydroxyethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate.** ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, 1H, *J* = 7.0 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.14 (d, 1H, *J* = 7.0 Hz), 7.10 (d, 1H, *J* = 7.0 Hz), 5.22 (d, 1H, *J* = 9.5 Hz), 4.25 (dd, 1H, *J* = 9.0, 8.5 Hz), 3.80 (t, 2H, *J* = 6.5 Hz), 3.70 (s, 3H), 3.18 (dd, 1H, *J* = 13.5, 8.5 Hz), 2.87-2.97 (m, 2H), 2.22 (dd, 1H, *J* = 13.5, 9.0 Hz), 1.97 (s, 3H), 1.83 (s, 3H), 1.78 (s, 3H). Important nOe correlations are shown below:



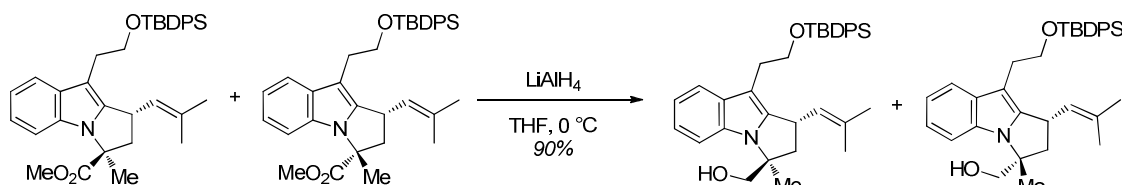
¹³C NMR (125 MHz, CDCl₃): δ 173.4, 144.3, 134.2, 133.4, 131.8, 124.7, 120.9, 119.2, 118.8, 110.2, 103.0, 65.1, 63.2, 52.8, 49.5, 35.3, 27.3, 25.8, 23.7, 18.3. HRMS (ESI) calc'd for [C₂₀H₂₆O₃N]⁺ 328.1907, found 328.1914.



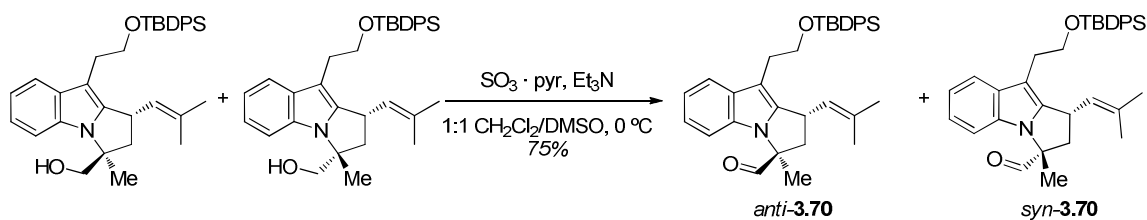
***syn* -Methyl 9-(2-hydroxyethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carboxylate.** ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, 1H, *J* = 7.5 Hz), 7.20 (d, 1H, *J* = 7.5 Hz), 7.06-7.13 (m, 2H), 5.23 (d, 1H, *J* = 10.0 Hz), 4.23 (dd, 1H, *J* = 16.5, 8.5 Hz), 3.80 (t, 2H, *J* = 6.5 Hz), 3.76 (s, 3H), 2.85-2.96 (m, 2H), 2.67-2.78 (m, 2H), 1.82 (s, 3H), 1.76 (s, 6H). Important nOe correlations are shown below:



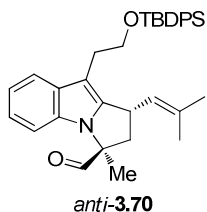
^{13}C NMR (125 MHz, CDCl_3): δ 173.4, 144.3, 134.2, 133.4, 131.8, 124.7, 120.9, 119.2, 118.8, 110.2, 103.0, 65.1, 63.2, 52.8, 49.5, 35.3, 27.3, 25.8, 23.7, 18.3. HRMS (ESI) calc'd for $[\text{C}_{20}\text{H}_{26}\text{O}_3\text{N}]^+$ 328.1907, found 328.1912.



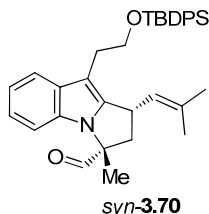
9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-3-yl)methanol. To a stirred suspension of LiAlH_4 (48 mg, 1.27 mmol, 1.2 equiv) in THF (5 mL) at 0°C was added dropwise by cannula a solution of the methyl ester (598 mg, 1.06 mmol, 1.0 equiv). The reaction stirred for 2h at 0°C . The reaction was then quenched with $\text{Na}_2\text{SO}_4 \cdot 10 \text{ H}_2\text{O}$, and the salts were allowed to digest overnight. The salts were then removed by gravity filtration, and the filtrate was concentrated. The product was isolated as an inseparable 2:1 mixture of diastereomers (515 mg, 0.958 mmol, 90%) by flash chromatography (10% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3): δ 7.66 (d, 2H, $J = 6.5$ Hz), 7.61 (d, 2H, $J = 7.0$ Hz), 7.28-7.45 (m, 8H), 7.08 (t, 1H, $J = 7.5$ Hz), 7.00 (t, 1H, $J = 7.5$ Hz), 5.27* (d, 1H, $J = 10.5$ Hz), 5.18 (d, 1H, $J = 9.5$ Hz), 4.19-4.24 (m, 1H), 3.95 (d, 1H, $J = 6.5$ Hz), 3.83 (t, 2H, $J = 7.5$ Hz), 3.73-3.80* (m, 2H), 3.69-3.73 (m, 1H), 2.93-3.02 (m, 2H), 2.86 (dd, 1H, $J = 13.0$ Hz, 8.5 Hz), 2.48* (d, 2H, $J = 8.0$ Hz), 2.07 (dd, 1H, $J = 13.0$ Hz, 8.5 Hz), 1.81* (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H), 1.72* (s, 3H), 1.58* (s, 3H), 1.06 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3 ; minor diastereomer peaks are indicated with an asterisk when applicable): δ 144.8, 144.7*, 135.7*, 135.6, 134.2, 134.1*, 133.7*, 133.5, 132.9, 132.6*, 131.2, 129.6, 129.5*, 127.6, 126.0*, 127.6*, 120.3*, 120.2, 119.1, 118.8*, 118.7, 109.7, 109.4*, 103.1*, 102.8, 68.8, 67.7*, 64.7, 64.6*, 64.5, 47.7, 46.0*, 35.4, 34.5*, 27.4*, 27.0, 25.7, 22.9, 22.1*, 19.3, 18.3. δ HRMS (ESI $^+$ + H^+): calculated for $\text{C}_{35}\text{H}_{44}\text{O}_2\text{NSi}$ 538.3136, found 538.3120



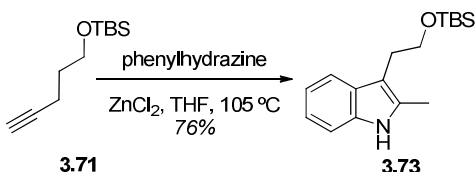
9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carbaldehyde (3.70). Prepared analogously to **3.8** from the alcohol (515 mg, 0.958 mmol, 1.0 equiv). The two diastereomers were separated by column chromatography (2 % EtOAc in hexanes; 10% EtOAc in hexanes) to yield the *anti* diastereomer *anti*-**3.70** (278.6 mg, 0.520 mmol) as a yellow oil and *syn* diastereomer *syn*-**3.70** (108.2 mg, 0.202 mmol) as a yellow oil in 75% total yield.



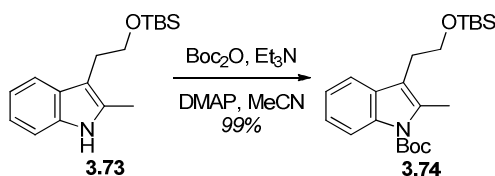
***anti*-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carbaldehyde (*anti*-3.70).** ¹H NMR (500 MHz, CDCl₃): δ 9.55 (s, 1H), 7.64 (d, 2H, *J* = 7.0 Hz), 7.57 (d, 2H, *J* = 7.0 Hz), 7.28-7.44 (m, 7H), 7.19 (d, 1H, *J* = 8.0 Hz), 7.09 (t, 1H, *J* = 7.5 Hz), 7.03 (t, 1H, *J* = 7.5 Hz), 5.20 (d, 1H, *J* = 9.5 Hz), 4.18 (ddd, 1H, *J* = 9.5 Hz, 8.5 Hz, 7.0 Hz), 3.83 (t, 2H, *J* = 7.5 Hz), 3.02 (dd, 1H, *J* = 13.5 Hz, 8.5 Hz), 2.92-3.00 (m, 2H), 2.13 (dd, 1H, *J* = 13.5 Hz, 7.0 Hz), 1.77 (s, 6H), 1.73 (s, 3H), 1.04 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 198.9, 144.1, 135.6, 134.1, 134.0, 133.9, 133.6, 131.5, 129.6, 129.5, 127.6, 125.2, 120.9, 119.3, 109.2, 104.4, 68.6, 64.3, 46.0, 35.1, 27.4, 26.9, 25.7, 19.8, 19.2, 18.2. HRMS (ESI⁺ + H⁺): calculated for C₃₅H₄₄O₂NSi 538.3136, found 538.3120



***syn*-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-3-carbaldehyde (*syn*-3.70).** ¹H NMR (500 MHz, CDCl₃): δ 9.629, 7.629 (d, 2H, *J* = 6.5 Hz), 7.494 (d, 2H, *J* = 7.0 Hz), 7.33-7.43 (m, 5H), 7.283 (t, 1H, *J* = 7.5 Hz), 7.05-7.09 (m, 2H), 6.99-7.02 (m, 1H), 5.158 (d, 1H, *J* = 9.5 Hz), 4.255 (ddd, 1H, *J* = 9.5 Hz, 8.0 Hz, 7.5 Hz), 3.820 (t, 2H, *J* = 7.5 Hz), 2.92-3.00 (m, 2H), 2.496 (dd, 1H, *J* = 13.0 Hz, 8.0 Hz), 2.404 (dd, 1H, *J* = 13.0 Hz, 7.5 Hz), 1.777 (s, 3H), 1.735 (s, 3H), 1.569 (s, 3H), 1.041 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 199.4, 143.7, 135.6, 134.1, 134.0, 133.9, 133.5, 131.3, 129.5, 127.6, 127.5, 124.4, 121.0, 119.4, 119.3, 108.9, 104.5, 67.9, 64.4, 45.4, 35.0, 35.0, 27.3, 26.9, 25.7, 19.2, 18.2. HRMS (ESI⁺ + H⁺): calculated for C₃₅H₄₂O₂NSi 536.2979, found 536.2972.

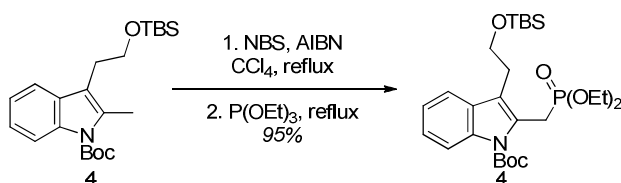


3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-methyl-1H-indole (3.73).³⁰ A sealed flask was loaded with phenylhydrazine (1.62 g, 15 mmol, 1.5 equiv), pentyn-3-ol **3.71** (1.98 g, 10 mmol, 1.0 equiv) and zinc(II) chloride (4.10 g, 30 mmol, 3.0 equiv) in THF (25 mL). The reaction mixture was heated to 110 °C over 18 h. The reaction mixture was then cooled and the zinc salts were removed by filtration. The product was isolated as an orange oil (2.20 g, 7.60 mmol, 76%) and used without further purification. ¹H NMR (500 MHz, CDCl₃): δ 7.80 (s, 1H), 7.62 (d, 1H, *J* = 7.0 Hz), 7.31 (d, 1H, *J* = 8.5 Hz), 7.18-7.26 (m, 2H), 3.91 (t, 2H, *J* = 7.5 Hz), 3.06 (t, 2H, *J* = 7.5 Hz), 2.43 (s, 3H), 1.04 (s, 9H), 0.16 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 135.3, 131.9, 129.0, 120.9, 119.2, 118.0, 110.4, 108.3, 63.8, 28.3, 26.2, 18.6, 12.7, -5.2.

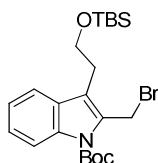


***tert*-butyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methyl-1*H*-indole-1-carboxylate (3.74).**

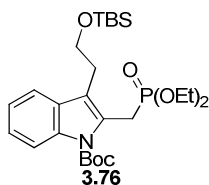
To a solution of indole **3.73** (1.62 g, 5.60 mmol, 1.0 equiv) and Et₃N (850 mg, 8.40 mmol, 1.5 equiv) in MeCN (28 mL) was added Boc₂O (1.34 mg, 8.40 mmol, 1.5 equiv) and DMAP (68 mg, 0.560 mmol, 10 mol%). The reaction mixture stirred 1 h at room temperature. The reaction was quenched with a 1:1 brine/water mixture (15 mL) and the resulting slurry was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (3 x 40 mL) and brine (1 x 40 mL), dried over MgSO₄ and concentrated. The product was isolated as a yellow oil (2.15 g, 5.52 mmol, 99%) by silica gel chromatography (5% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃): δ 8.16 (d, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 7.0 Hz), 7.24–7.30 (m, 2H), 3.81 (t, 2H, *J* = 7.5 Hz), 2.96 (t, 2H, *J* = 7.5 Hz), 2.41 (s, 3H), 1.86 (s, 9H), 0.99 (s, 9H), 0.07 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 150.8, 135.8, 134.1, 130.2, 123.3, 122.4, 117.8, 115.4, 115.0, 83.4, 62.9, 28.4, 28.0, 27.5, 26.0, 18.4, 14.1, -5.3.



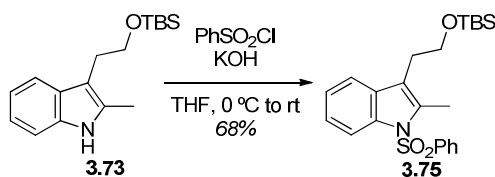
***tert*-butyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-((diethoxyphosphoryl)methyl)-1*H*-indole-1-carboxylate (3.76).** Prepared analogously to **3.7** from **3.74** (2.16 g, 5.52 mmol, 1.0 equiv). **3.76** was purified by column chromatography to give a red oil (2.60 g, 5.25 mmol) 90% yield over two steps.



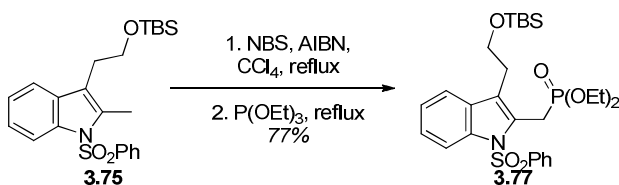
¹H NMR (500 MHz, CDCl₃): δ 8.18 (d, 1H, *J* = 8.5 Hz), 7.53 (d, 1H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 5.29 (s, 2H), 3.85 (t, 2H, *J* = 7.0 Hz), 3.00 (t, 2H, *J* = 7.0 Hz), 1.74 (s, 9H), 0.92 (s, 9H), -0.11 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 149.9, 136.7, 132.7, 129.1, 125.5, 122.9, 120.3, 119.2, 115.9, 84.5, 62.3, 28.1, 28.0, 25.9, 25.8, 25.4, 18.4, -5.3.



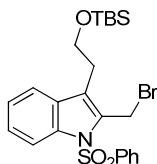
¹H NMR (500 MHz, CDCl₃): δ 8.24 (d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.39 (t, 1H, *J* = 7.8 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 5.12 (s, 2H), 3.90 (t, 2H, *J* = 7.0 Hz), 3.05 (t, 2H, *J* = 7.0 Hz), 1.73 (s, 9H), 0.80 (s, 9H), 0.09 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 149.9, 136.8, 132.6, 129.1, 125.5, 122.9, 120.3, 119.2, 116.0, 84.5, 62.3, 28.2, 28.1, 26.0, 25.4, 18.4, -5.3. HRMS (ESI⁺ + H⁺): calculated for C₂₆H₄₅O₆NPSi 526.2748, found 526.2737.



3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methyl-1-(phenylsulfonyl)-1H-indole (3.75). To a stirring solution of indole **3.73** (1.32 g, 4.56 mmol, 1.0 equiv) in THF (8 mL) at 0 °C was added powdered anhydrous potassium hydroxide (1.28 g, 22.8 mmol, 5.0 equiv). Benzenesulfonyl chloride (2.42 g, 13.7 mmol, 3.0 equiv) was then added dropwise. The reaction temperature was raised to room temperature and the reaction stirred overnight, turning heterogeneous. The reaction mixture was then quenched with water and the organic products were extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ (1 x 40 mL) and brine (1 x 40 mL), dried over MgSO₄ and concentrated by rotary evaporator. The product was purified from the resulting resin by serial silica gel chromatography (first 1% EtOAc in toluene; then 2.5% EtOAc in hexanes) to yield the product as an orange oil (1.32 g, 3.10 mmol, 68%). ¹H NMR (500 MHz, CDCl₃): δ 8.22 (d, 1H, *J* = 8.0 Hz), 7.77 (d, 2H, *J* = 8.0 Hz), 7.51 (dd, 1H, *J* = 7.5, 7.0 Hz), 7.42 (t, 3H, *J* = 8.0 Hz), 7.40 (d, 1H, *J* = 7.5 Hz), 7.28 (dd, 1H, *J* = 7.5 Hz, 7.0 Hz), 7.24 (dd, 1H, *J* = 7.5 Hz, 7.0 Hz), 3.72 (t, 2H, *J* = 7.0 Hz), 2.84 (t, 2H, *J* = 7.0 Hz), 2.56 (s, 3H), 0.82 (s, 9H), -0.23 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 139.4, 136.4, 133.7, 133.5, 130.7, 129.3, 126.3, 124.0, 123.3, 118.5, 117.5, 114.5, 62.6, 28.0, 25.9, 18.3, 12.9, -5.5. HRMS (ESI⁺ + H⁺ - TBS): calculated for C₁₇H₁₇O₃NS 315.0929, found 316.1003.

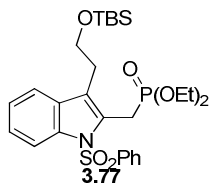


Diethyl ((3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1H-indol-2-yl)methyl)phosphonate (3.77). A stirred solution of 2-methylindole **3.75** (1.05 g, 2.43 mmol, 1.0 equiv), recrystallized *N*-bromosuccinimide (0.432 g, 2.43 mmol, 1.0 equiv) and catalytic AIBN (40 mg, 0.243 mmol, 10 mol%) in CCl₄ (12 mL) was refluxed at 75 °C for 6 h. The reaction temperature was then lowered to room temperature and the reaction mixture was quenched with water (10 mL); the product was then extracted in to CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine (1 x 15 mL), dried over MgSO₄ and concentrated.

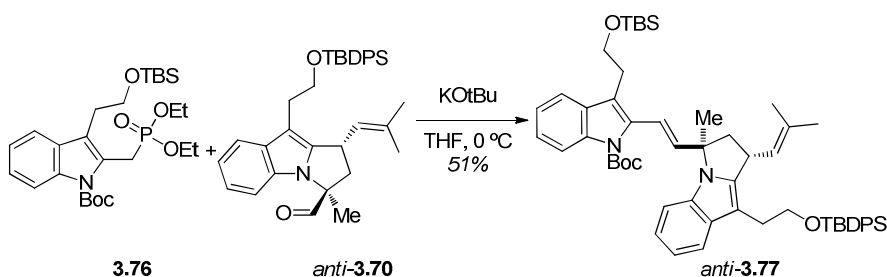


¹H NMR (500 MHz, CDCl₃): δ 8.13 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 2H, *J* = 7.5 Hz), 7.51 (d, 2H, *J* = 7.5 Hz), 7.40 (t, 2H, *J* = 7.5 Hz), 7.35 (dd, 1H, *J* = 8.0 Hz, 7.5 Hz), 7.26 (t, 1H, *J* = 7.5 Hz), 5.14 (s, 2H), 3.84 (t, 2H, *J* = 6.5 Hz), 2.97 (t, 2H, *J* = 6.5 Hz), 0.82 (s, 9H), -0.11 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 138.7, 136.7, 133.9, 133.2, 129.9, 129.2, 126.9, 126.0, 123.8, 123.3, 119.8, 115.0, 61.9, 28.1, 25.9, 23.2, 18.3, -5.4.

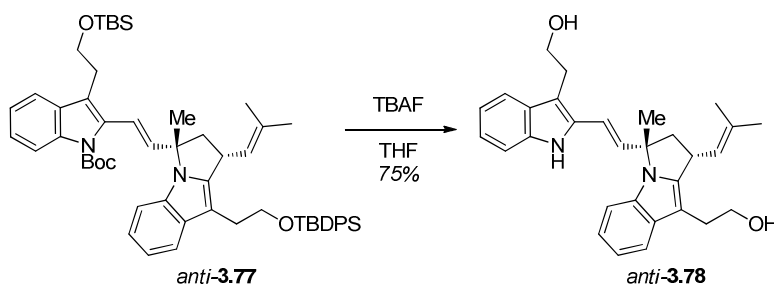
The resulting brown oil was suspended in triethylphosphite (3.5 mL) and this solution was stirred at 55°C for 48 h. The excess triethylphosphite was removed by rotary evaporator, and the product was isolated by flash chromatography (1% methanol in CH₂Cl₂) to give an orange oil (0.843 g, 1.61 mmol, 77% over 2 steps).



¹H NMR (500 MHz, CDCl₃): δ 8.05 (broad s, 1H), 7.40-7.60 (m, 1H), 7.20-7.26 (m, 2H), 4.00 (q, 4H, *J* = 7.0 Hz), 3.80-3.90 (m, 2H), 3.43 (broad s, 2H), 2.94 (broad s, 2H), 2.75-2.90 (m, 3H), 1.68 (s, 9H), 1.30-1.40 (m, 9H), 1.21 (t, 6H, *J* = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 155.6, 150.5, 136.9, 129.3, 127.2, 124.1, 122.5, 118.1, 115.6, 84.2, 79.5, 62.1, 48.8, 28.5, 28.2, 26.1, 24.9, 16.4. HRMS (ESI⁺ + H⁺): calculated for C₂₇H₄₁O₆NPSSi 566.2156, found 566.2164.

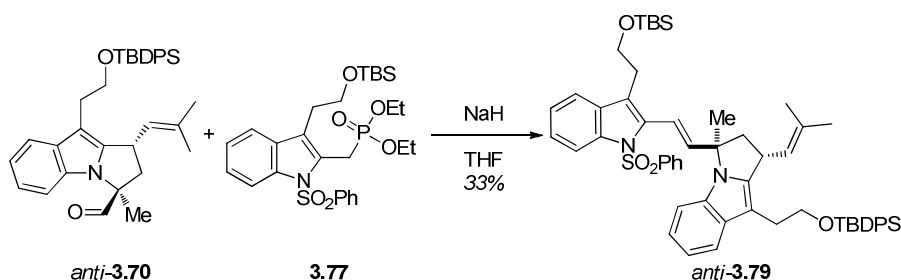


tert-butyl 3-(2-(((tert-butyldimethylsilyl)oxy)ethyl)-2-((*E*)-2-(*anti*-9-(2-(((tert-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-3-yl)vinyl)-1H-indole-1-carboxylate (*anti*-3.77). Prepared analogously to *anti*-xx using aldehyde *anti*-3.70 (65 mg, 0.122 mmol, 1.0 equiv) and phosphonate **3.76** (64 mg, 0.122 mmol, 1.0 equiv) to give the product as an iridescent foam (50 mg, .062 mmol, 51%) . ¹H NMR (500 MHz, CDCl₃): 7.98 (d, 1H, *J* = 8.0 Hz), 7.68 (dd, 4H, *J* = 9.5 Hz, 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.35-7.41 (m, 6H), 7.19-7.26 (m, 4H), 6.99-7.02 (m, 1H), 6.94-6.96 (m, 1H), 6.30 (d, 1H, *J* = 16.0 Hz), 6.11 (d, 1H, *J* = 16.0 Hz), 5.27 (d, 1H, *J* = 9.5 Hz), 4.30 (dd, 1H, *J* = 9.5, 8.5 Hz), 3.84 (t, 2H, *J* = 7.5 Hz), 3.78 (t, 2H, *J* = 7.5 Hz), 2.94-2.99 (m, 4H), 2.84 (dd, 1H, *J* = 12.5 Hz, 8.0 Hz), 2.24-2.30 (m, 1H), 1.93 (s, 3H), 1.83 (s, 3H), 1.77 (s, 3H), 1.07 (s, 9H), 0.85 (s, 9H), -0.05 (s, 6H).

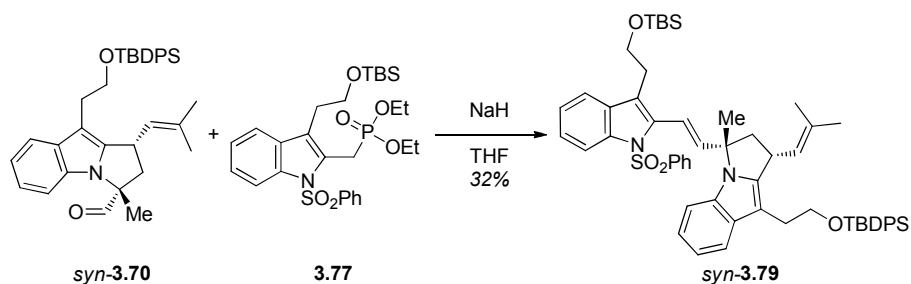


***anti*-2-(3-((*E*)-2-(3-(2-hydroxyethyl)-1H-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-9-yl)ethanol (*anti*-xx).** To a stirred mixture of TBAF (1.0 M in THF, ca. 5% water) (1.25 mL, 1.24 mmol, 5.0 equiv) and 4 Å molecular sieves at 0°C

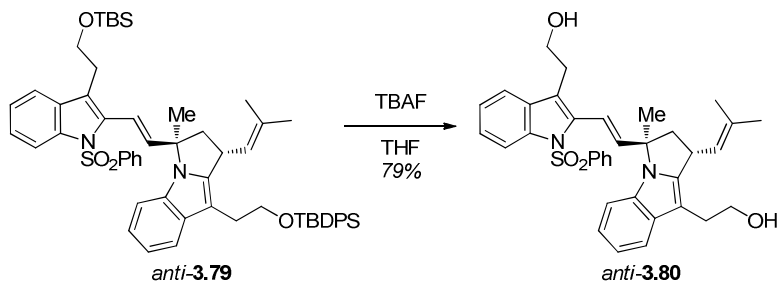
was added a solution of bisindole *anti*-**3.77** (200 mg, 0.248 mmol, 1.0 equiv) in THF (1.25 mL). The reaction mixture warmed slowly to room temperature overnight. The reaction mixture was then quenched with saturated aqueous NaHCO₃ (2 mL) and the resulting biphasic mixture was extracted with EtOAc (1 x 2 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2 x 2 mL) and brine (1 x 2 mL), dried over Na₂SO₄ and concentrated. The product was isolated as a white foam (85 mg, 0.187 mmol, 75%) by silica gel chromatography (10% EtOAc in hexanes; 40% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃): 8.13 (s, 1H), 7.58-7.60 (m, 1H), 7.47 (d, 1H, *J* = 8.0 Hz), 7.34-7.36 (m, 1H), 7.21 (d, 1H, *J* = 8.0 Hz), 7.15 (d, 1H, *J* = 7.5 Hz), 7.08-7.10 (m, 2H), 7.05 (t, 1H, *J* = 7.5 Hz), 6.11 (d, 1H, *J* = 16.0 Hz), 5.87 (d, 1H, *J* = 16.0 Hz), 5.29 (d, 1H, *J* = 9.5 Hz), 4.19 (dd, 1H, *J* = 9.5, 8.5 Hz), 3.80-3.87 (m, 2H), 3.58 (t, 2H, *J* = 6.5 Hz), 2.96 (t, 2H, *J* = 6.5 Hz), 2.76-2.79 (m, 2H), 2.68-2.75 (m, 1H), 2.31 (dd, 1H, *J* = 12.5 Hz, 8.5 Hz), 1.99 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 144.3, 136.4, 133.8, 133.3, 132.1, 131.8, 130.7, 128.7, 124.7, 123.1, 120.6, 119.7, 119.0, 118.8, 118.7, 117.2, 112.3, 110.6, 110.4, 102.8, 64.0, 63.3, 62.9, 51.6, 34.8, 27.7, 27.2, 25.8, 18.2.



***anti*-3-((*E*)-2-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)vinyl)-9-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole** (*anti*-**3.79**). To a stirred solution of aldehyde *anti*-**3.70** (332 mg, 0.620 mmol, 1.0 equiv) and phosphonate **3.77** (526 mg, 0.930 mmol, 1.5 equiv) in THF (6 mL) was added in one portion NaH (60% in mineral oil) (45 mg, 1.12 mmol, 1.8 equiv). The reaction mixture stirred 1 h at which point the aldehyde had been consumed. The reaction mixture was quenched with saturated aqueous NaHCO₃ (10 mL) and the resulting biphasic mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 15 mL), dried over MgSO₄ and concentrated. The product *anti*-**3.79** was isolated as an iridescent foam (209 mg, 0.221 mmol, 33%) by silica gel chromatography (5% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃): 8.18 (d, 1H, *J* = 8.0 Hz), 7.67 (d, 2H, *J* = 7.0 Hz), 7.64 (d, 2H, *J* = 7.0 Hz), 7.51 (d, 2H, *J* = 7.5 Hz), 7.36-7.41 (m, 4H), 7.33-7.35 (m, 5H), 7.28-7.30 (m, 3H), 7.21 (q, 2H, *J* = 7.5 Hz), 7.03 (t, 1H, *J* = 7.5 Hz), 6.99 (t, 1H, *J* = 7.5 Hz), 6.94 (d, 1H, *J* = 8.0 Hz), 6.93 (d, 1H, *J* = 7.5 Hz), 6.24 (d, 1H, *J* = 16.0 Hz), 6.17 (d, 1H, *J* = 16.0 Hz), 5.25 (d, 1H, *J* = 9.0 Hz), 4.35 (q, 1H, *J* = 8.0 Hz), 3.80-3.86 (m, 2H), 3.72-3.79 (m, 2H), 2.97-3.03 (m, 2H), 2.80-2.86 (m, 3H), 2.29 (dd, 1H, *J* = 13.5 Hz, 7.0 Hz), 1.99 (s, 3H), 1.80 (s, 3H), 1.76 (s, 3H), 1.04 (s, 9H), 0.75 (s, 9H), -0.24 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 143.8, 138.9, 138.6, 136.2, 135.7, 135.6, 134.5, 134.3, 134.2, 133.9, 133.5, 133.4, 131.6, 131.0, 129.6, 128.9, 127.0, 126.5, 125.0, 124.9, 123.6, 120.4, 119.5, 119.4, 119.0, 118.7, 118.5, 114.9, 110.2, 103.1, 65.0, 63.9, 62.9, 51.3, 35.0, 28.7, 27.6, 27.0, 26.0, 25.8, 25.7, 19.4, 18.4, -5.4, -5.5. HRMS (ESI⁺ + H⁺ - TBS): calculated for C₅₂H₅₇O₄N₂Ssi 833.3808, found 833.3800.

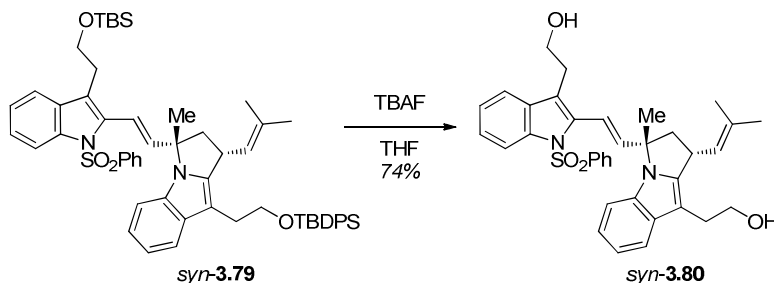


***syn*-3-((*E*)-2-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)vinyl)-9-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (*syn*-3.79).** Prepared analogously to *anti*-3.79 using aldehyde *syn*-3.70 (136 mg, 0.254 mmol, 1.0 equiv) and phosphonate 3.77 (216 mg, 0.381 mmol, 1.5 equiv) to give *syn*-3.79 as an iridescent foam (76 mg, 0.084 mmol, 32%). ¹H NMR (500 MHz, CDCl₃): 8.19 (d, 1H, *J* = 8.5 Hz), 7.67 (d, 2H, *J* = 8.5 Hz), 7.65 (d, 2H, *J* = 8.5 Hz), 7.60 (d, 2H, *J* = 7.0 Hz), 7.34-7.46 (m, 8H), 7.29-7.32 (m, 3H), 7.21-7.24 (m, 3H), 6.96-7.00 (m, 2H), 6.37 (d, 1H, *J* = 17.0 Hz), 5.29 (d, 1H, *J* = 9.0 Hz), 4.25 (q, 1H, *J* = 8.5 Hz), 3.84 (t, 2H, *J* = 7.5 Hz), 3.75-3.80 (m, 2H), 2.96-3.01 (m, 2H), 2.88-2.93 (m, 2H), 2.72 (dd, 1H, *J* = 12.5 Hz, 8.0 Hz), 2.39 (dd, 1H, *J* = 12.5 Hz, 8.0 Hz), 1.81 (s, 3H), 1.78 (s, 3H), 1.75 (s, 3H), 1.05 (s, 9H), 0.68 (s, 9H), -0.29 (s, 3H), -0.32 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 143.2, 140.2, 138.4, 136.3, 135.6, 134.8, 134.2, 134.1, 133.4, 133.3, 133.0, 131.3, 131.2, 129.5, 129.4, 128.9, 127.6, 127.5, 126.6, 125.4, 125.0, 123.6, 120.4, 120.2, 119.7, 118.8, 118.6, 115.0, 110.0, 103.0, 64.7, 62.9, 62.8, 51.8, 35.2, 28.6, 27.5, 26.9, 25.8, 25.7, 23.0, 19.2, 18.2, 18.1, -5.6, -5.7. HRMS (ESI⁺ + H⁺ - TBS): calculated for C₅₂H₅₇O₄N₂Si 833.3808, found 833.3804.

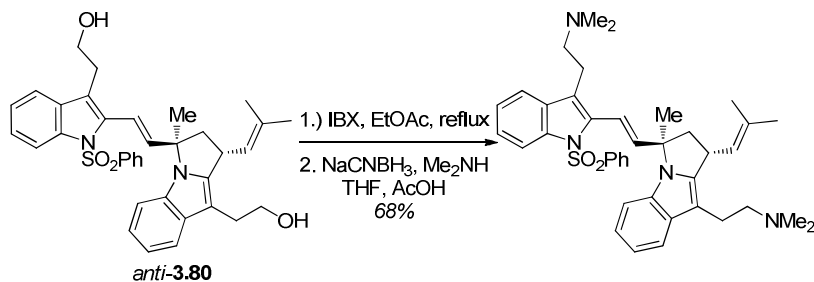


***anti*-2-(3-((*E*)-2-(3-(2-hydroxyethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)ethanol (*anti*-3.80).** To a solution of bisindole *anti*-3.79 (209 mg, 0.221 mmol, 1.0 equiv) in THF (1.1 mL) was added TBAF (1.0 M in THF, ca. 5% water) (2.7 mL, 2.65 mmol, 12.0 equiv) in three aliquots over six hours. The reaction mixture was then quenched with saturated aqueous NaHCO₃ and the resulting slurry was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over Na₂SO₄ and concentrated. The diol was isolated as a iridescent foam (104 mg, 0.175 mmol, 79%) by flash chromatography (40% EtOAc in hexanes). ¹H NMR (600 MHz, CDCl₃): 8.16 (d, 1H, *J* = 8.4 Hz), 7.61-7.65 (m, 1H), 7.44-7.48 (m, 1H), 7.39 (d, 2H, *J* = 7.8 Hz), 7.32-7.35 (m, 3H), 7.29 (t, 1H, *J* = 7.8 Hz), 7.20 (t, 1H, *J* = 7.8 Hz), 7.06 (t, 1H, *J* = 7.8 Hz), 6.22 (d, 1H, *J* = 15.6 Hz), 6.14 (d, 1H, *J* = 15.6 Hz), 5.31 (d, 1H, *J* = 9.6 Hz), 4.42 (q, 1H, *J* = 8.4 Hz), 3.81 (t, 2H, *J* = 6.0 Hz), 3.64-3.69 (m, 2H), 2.94-3.01 (m, 2H), 2.86 (dd, 1H, *J* = 12.6, 7.8 Hz), 2.82 (t, 2H, *J* = 6.0 Hz), 2.35 (dd, 1H, *J* = 12.0 Hz, 9.6 Hz), 2.06 (s, 3H), 1.83 (s, 3H), 1.82 (s, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 144.3, 138.9, 138.0, 136.3, 134.7, 134.1, 133.5,

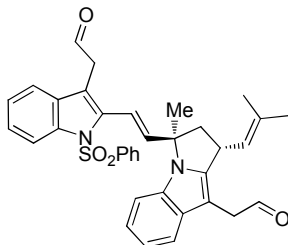
133.3, 133.0, 131.8, 130.8, 128.9, 126.3, 125.1, 124.5, 123.8, 120.6, 119.1, 119.0, 118.8, 118.1, 115.1, 110.3, 103.1, 64.0, 63.2, 62.0, 53.3, 51.0, 35.0, 28.3, 28.2, 27.3, 25.7, 25.5, 20.7, 18.2, 14.0. HRMS (ESI⁺ + H⁺): calculated for C₃₆H₃₉O₄N₂S 595.2625, found 595.2624.



***syn*-2-(3-((*E*)-2-(3-(2-hydroxyethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)ethanol** (*syn*-3.80). Prepared analogously to *anti*-3.80 using bisindole *syn*-3.79 (76 mg, 0.080 mmol, 1.0 equiv) give the diol *syn*-3.80 as an iridescent foam (35 mg, 0.059 mmol, 74%). ¹H NMR (600 MHz, CDCl₃): 8.20 (d, 1H, *J* = 8.4 Hz), 7.62 (d, 1H, *J* = 7.8 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.45 (d, 2H, *J* = 7.2 Hz), 7.43 (d, 1H, *J* = 7.2 Hz), 7.33 (t, 1H, *J* = 7.8 Hz), 7.21-7.27 (m, 4H), 7.07 (t, 1H, *J* = 7.8 Hz), 7.04 (t, 1H, *J* = 7.8 Hz), 6.95 (d, 1H, *J* = 16.2 Hz), 6.34 (d, 1H, *J* = 16.2 Hz), 5.35 (d, 1H, *J* = 9.6 Hz), 4.31 (q, 1H, *J* = 9.0 Hz), 3.79-3.86 (m, 2H), 3.72 (t, 2H, *J* = 7.2 Hz), 2.97-3.00 (m, 1H), 2.89-2.95 (m, 3H), 2.82 (dd, 1H, *J* = 12.6, 8.4 Hz), 2.44 (dd, 1H, *J* = 12.6, 7.2 Hz), 1.86 (s, 6H), 1.79 (s, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 143.8, 140.2, 138.1, 136.5, 135.0, 133.6, 133.4, 133.3, 131.5, 130.9, 128.9, 126.5, 125.3, 123.9, 120.5, 119.6, 119.4, 119.0, 118.8, 115.2, 110.1, 102.6, 63.2, 62.2, 51.6, 35.2, 28.3, 27.5, 25.7, 23.2, 20.6, 18.2, 13.9. HRMS (ESI⁺ + H⁺): calculated for C₃₆H₃₉O₄N₂S 595.2625, found 595.2624.

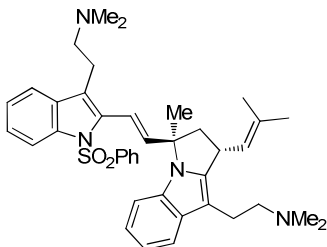


***anti*-2-(3-((*E*)-2-(3-(2-(dimethylamino)ethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-*N,N*-dimethylethanamine**.³¹ A mixture of *anti*-3.80 (41 mg, 0.068 mmol, 1.0 equiv) and 2-iodoxybenzoic acid (114 mg, 0.409 mmol, 6.0 equiv) in EtOAc (4.5 mL) was heated to reflux (80°C) for 1 h. The reaction mixture was then cooled to room temperature and poured over celite. The filtrate was washed with EtOAc (6 x 5 mL) and concentrated. The resulting dial was used without further purification.

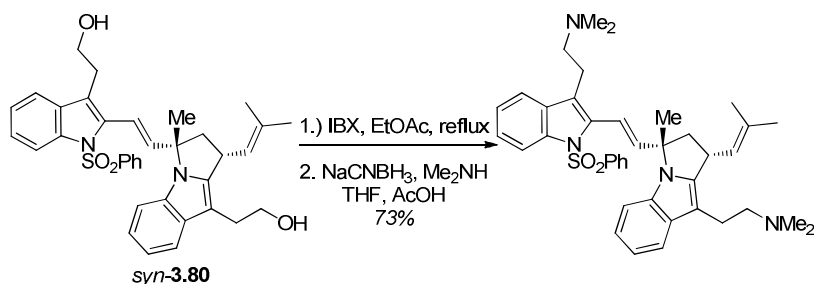


^1H NMR (600 MHz, CDCl_3): 9.64 (s, 1H), 9.57 (s, 1H), 8.19 (d, 1H, $J = 8.4$ Hz), 7.47-7.53 (m, 1H), 7.41-7.46 (m, 1H), 7.32-7.40 (m, 5H), 7.14-7.17, (m, 3H), 7.05 (t, 1H, $J = 7.8$ Hz) 6.17 (d, 1H, $J = 15.6$ Hz), 5.98 (d, 1H, $J = 16.2$ Hz), 5.25 (d, 1H, $J = 9.6$ Hz), 4.43 (dt, 1H, $J = 9.6$, 7.2 Hz), 3.66 (d, 2H, $J = 1.8$ Hz), 3.66 (d, 2H, $J = 7.2$ Hz), 2.85 (dd, 1H, $J = 12.6$ Hz, 7.2 Hz), 2.38 (dd, 1H, $J = 12.6$, 9.6 Hz), 2.05 (s, 3H), 1.82 (s, 6H), 1.80 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 200.0, 198.0, 145.1, 139.6, 138.1, 136.0, 135.6, 135.1, 133.7, 133.1, 131.7, 130.1, 129.6, 129.0, 127.7, 126.3, 125.6, 124.0, 123.7, 121.2, 119.5, 118.7, 118.4, 118.2, 114.9, 112.4, 96.7, 64.3, 51.0, 40.2, 38.9, 34.9, 29.7, 26.5, 25.7, 25.3, 18.3.

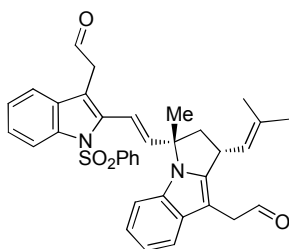
To a stirred solution of Me_2NH (2.0 M in THF) (0.27 mL, 0.545 mmol, 8.0 equiv) and NaCNBH_3 (17 mg, 0.272 mmol, 4.0 equiv) in 2.5% AcOH in anhydrous MeOH (2 mL) was added a solution of the dial (40 mg, 0.068 mmol, 1.0 equiv) in anhydrous MeOH (2 mL). The reaction stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous NaHCO_3 (4 mL). The resulting slurry was extracted with EtOAc (3 x 4 mL), and the combined organic layers were washed with brine (1 x 4 mL), dried over Na_2SO_4 and concentrated. The resulting diamine was isolated by silica gel chromatography (10% MeOH in CH_2Cl_2 ; 20% MeOH in CH_2Cl_2) as a white solid (30 mg, 0.0462 mmol, 68%).



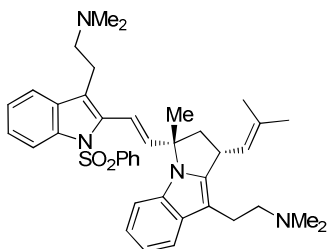
^1H NMR (600 MHz, CD_3OD): 8.06 (d, 1H, $J = 8.4$ Hz), 7.61-7.62 (m, 1H), 7.50-7.52 (m, 1H), 7.46 (d, 1H, $J = 7.8$ Hz), 7.43 (t, 1H, $J = 7.8$ Hz), 7.39 (d, 2H, $J = 7.8$ Hz), 7.27 (t, 1H, $J = 7.8$ Hz), 7.22 (t, 1H, $J = 7.8$ Hz), 7.17 (t, 2H, $J = 7.8$ Hz), 7.09-7.11 (m, 2H), 6.20 (d, 1H, $J = 16.2$ Hz), 5.98 (d, 1H, $J = 16.2$ Hz), 5.37 (d, 1H, $J = 9.6$ Hz), 4.55 (dt, 1H, $J = 9.6$, 7.8 Hz), 3.12-3.18 (m, 2H), 3.01-3.10 (m, 3H), 2.87-2.95 (m, 4H), 2.73 (s, 6H), 2.40 (s, 6H), 2.07 (s, 3H), 1.85 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): δ 144.0, 138.4, 137.5, 136.2, 134.3, 134.0, 133.6, 132.5, 131.8, 130.4, 128.8, 126.0, 125.0, 124.3, 123.8, 120.6, 119.1, 118.9, 118.8, 118.3, 118.0, 114.7, 110.2, 100.9, 64.9, 64.2, 58.7, 57.7, 50.4, 43.3, 42.7, 34.9, 24.5, 24.4, 21.4, 19.6, 19.5, 17.1, 12.7. HRMS ($\text{ESI}^+ + \text{H}^+$): calculated for $\text{C}_{40}\text{H}_{49}\text{O}_2\text{N}_4\text{S}$ 649.3571, found 649.3564.



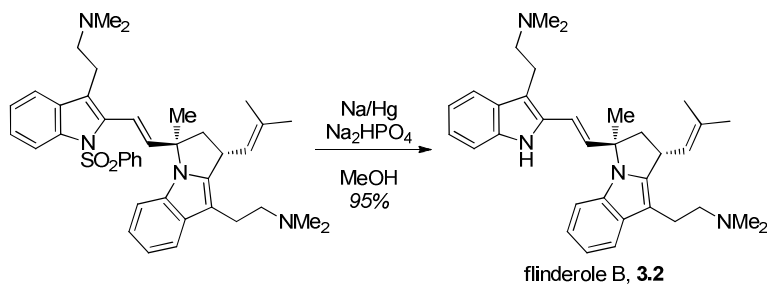
***syn*-2-(3-((*E*)-2-(3-(2-(dimethylamino)ethyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-en-1-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-*N,N*-dimethylethanamine.** Prepared analogously to the diamine shown above using alcohol *syn*-**3.80** (35 mg, 0.059 mmol, 1.0 equiv) to give the diamine as a white solid (28 mg, 0.043 mmol, 73%) over two steps.



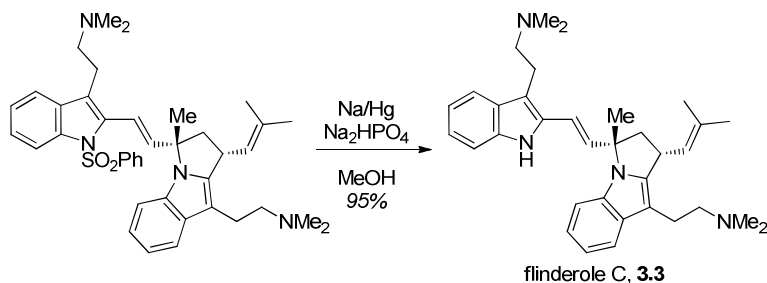
^1H NMR (600 MHz, CDCl_3): 9.661 (s, 1H), 9.603 (s, 1H), 8.190 (d, 1H, $J = 8.4$ Hz), 7.642 (d, 2H, $J = 7.8$ Hz), 7.43-7.48 (m, 2H), 7.33-7.39 (m, 3H), 7.26-7.29 (m, 3H), 7.02-7.16 (m, 4H), 6.134 (d, 1H, $J = 16.2$ Hz), 5.284 (d, 1H, $J = 9.0$ Hz), 4.313 (dt, 1H, $J = 9.0, 7.8$ Hz), 3.75-3.79 (m, 2H), 3.64-3.69 (m, 2H), 2.813 (dd, 1H, $J = 12.6$ Hz, 7.8 Hz), 2.435 (dd, 1H, $J = 12.6, 7.8$ Hz), 1.862 (s, 3H), 1.831 (s, 3H), 1.784 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 199.8, 197.8, 144.5, 140.7, 138.1, 136.2, 135.9, 134.3, 133.7, 133.1, 131.4, 130.3, 129.3, 128.1, 127.8, 126.5, 125.7, 124.4, 124.2, 121.0, 119.8, 119.5, 119.0, 118.4, 115.0, 113.3, 110.1, 96.7, 63.4, 51.5, 40.2, 39.0, 35.2, 29.7, 25.6, 25.1, 25.0, 18.2.



^1H NMR (500 MHz, CD_3OD): 8.15 (d, 1H, $J = 8.0$ Hz), 7.58-7.62 (m, 3H), 7.51-7.55 (m, 3H), 7.32-7.37 (m, 3H), 7.30 (t, 1H, $J = 8.0$ Hz), 7.03-7.10 (m, 2H), 6.95 (d, 1H, $J = 16.0$ Hz), 6.26 (d, 1H, $J = 16.0$ Hz), 5.52 (d, 1H, $J = 10.0$ Hz), 4.46 (dt, 1H, $J = 9.5, 8.0$ Hz), 2.90-3.10 (m, 7H), 2.92 (s, 6H), 2.58 (dd, 1H, $J = 13.0$ Hz, 7.5 Hz), 2.51 (s, 6H), 1.91 (s, 6H), 1.84 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 144.2, 140.2, 139.3, 137.3, 136.3, 135.0, 133.8, 132.4, 131.4, 129.9, 129.0, 127.4, 126.1, 125.4, 125.0, 124.1, 120.5, 119.4, 119.1, 118.9, 118.1, 114.8, 110.1, 99.3, 64.4, 63.2, 58.0, 56.3, 42.3, 41.9, 35.2, 34.0, 25.5, 24.5, 24.2, 21.8, 19.5, 19.3, 19.1, 17.0, 12.6, 12.5. HRMS ($\text{ESI}^+ + \text{H}^+$): calculated for $\text{C}_{40}\text{H}_{49}\text{O}_2\text{N}_4\text{S}$ 649.3571, found 649.3565.



Flinderole B (3.2). To a stirred solution of the diamine (12 mg, 0.018 mmol, 1.0 equiv) in anhydrous MeOH (2 mL) was added Na/Hg (6%) (90 mg, 0.406 mmol, 20 equiv) and $\text{Na}_2\text{HPO}_4 \cdot 7 \text{ H}_2\text{O}$ (108 mg, 0.406 mmol, 20 equiv). The reaction stirred 3 hr at room temperature. The reaction was then quenched with water and the resulting solution was extracted with Et_2O (3 x 2 mL). The combined organic layers were washed with brine (1 x 4 mL), dried over Na_2SO_4 and concentrated. The product was isolated by silica gel chromatography (1:9:90 $\text{Et}_3\text{N}/\text{MeOH}/\text{CH}_2\text{Cl}_2$) to yield a white solid (9 mg, 0.018 mmol, 95%). Spectroscopic data matches that from ref. 31. ^1H NMR (500 MHz, d_6 -DMSO): 10.93 (s, 1H), 7.43 (d, 1H, $J = 7.2$ Hz), 7.58-7.62 (m, 3H), 7.51-7.55 (m, 3H), 7.32-7.37 (m, 3H), 7.30 (t, 1H, $J = 8.0$ Hz), 7.03-7.10 (m, 2H), 6.95 (d, 1H, $J = 16.0$ Hz), 6.26 (d, 1H, $J = 16.0$ Hz), 5.52 (d, 1H, $J = 10.0$ Hz), 4.46 (dt, 1H, $J = 9.5, 8.0$ Hz), 2.90-3.10 (m, 7H), 2.92 (s, 6H), 2.58 (dd, 1H, $J = 13.0$ Hz, 7.5 Hz), 2.51 (s, 6H), 1.91 (s, 6H), 1.84 (s, 3H). ^{13}C NMR (150 MHz, d_6 -DMSO): δ 143.1, 136.8, 132.9, 132.8, 132.0, 131.6, 131.3, 128.4, 125.5, 122.4, 120.4, 118.9, 118.7, 118.6, 113.1, 111.1, 110.5, 104.0, 64.0, 61.0, 60.7, 51.3, 45.5, 45.3, 34.8, 25.9, 25.8, 22.0, 21.8, 18.4. HRMS ($\text{ESI}^+ + \text{H}^+$): calculated for $\text{C}_{34}\text{H}_{45}\text{N}_4$ 509.3639, found 509.3634.

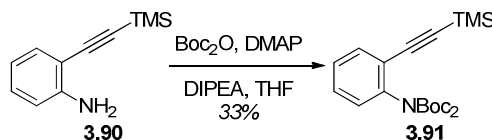


Flinderole C (3.3). Prepared analogously to flinderole B (**3.2**) using bisindole the *syn* diamine (28 mg, 0.059 mmol, 1.0 equiv) to give flinderole C as a white solid (xx mg, xx mmol, xx%). Spectroscopic data matches that from ref. 31. ^1H NMR (500 MHz, d_6 -DMSO): 11.08 (s, 1H), 7.42 (d, 1H, $J = 7.8$ Hz), 7.41 (d, 1H, $J = 8.4$ Hz), 7.24 (d, 1H, $J = 8.4$ Hz), 7.22 (d, 1H, $J = 7.2$ Hz), 7.03 (dd, 1H, $J = 7.8$ Hz, 7.2 Hz), 6.89-6.93 (m, 3H), 6.58 (d, 1H, $J = 16.0$ Hz), 6.55 (d, 1H, $J = 16.0$ Hz), 5.24 (d, 1H, $J = 9.6$ Hz), 4.26 (dt, 1H, $J = 9.6, 7.8$ Hz), 2.66-2.76 (m, 6H), 2.27-2.33 (m, 4H), 2.18 (s, 6H), 2.11 (s, 6H), 1.80 (s, 3H), 1.71 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (150 MHz, d_6 -DMSO): δ 143.0, 136.9, 133.1, 132.8, 132.3, 132.2, 131.3, 129.9, 128.5, 126.5, 126.0, 122.5, 120.2, 118.9, 118.8, 118.7, 118.2, 113.4, 111.2, 110.3, 104.1, 63.3, 61.0, 51.5, 45.5, 45.4, 35.1, 26.0, 25.8, 23.6, 22.1, 18.4. HRMS ($\text{ESI}^+ + \text{H}^+$): calculated for $\text{C}_{34}\text{H}_{45}\text{N}_4$ 509.3639, found 509.3631.

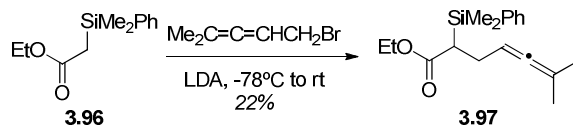
6. Substrates toward asymmetric synthesis



2-((trimethylsilyl)ethynyl)aniline (3.90). To a solution of 2-iodoaniline (1.5 g, 6.85 mmol, 1.0 equiv), copper(I) iodide (52 mg, 0.274 mmol, 4 mol%) and bis(triphenylphosphine)palladium(II) chloride (96 mg, 0.137 mmol, 2 mol%) in degassed Et_3N (35 mL) was added trimethylsilylacetylene (6.73 g, 68.5 mmol, 10 equiv) dropwise by syringe. This stirred for 5 hours with a continuous stream of nitrogen bubbled through the reaction mixture. The catalyst was removed by filtering the reaction mixture through celite, and the resulting filtrate was concentrated. The product was isolated as black needles (1.60 g, 6.85 mmol, >99%) by silica gel chromatography (10% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3): 7.28-7.31 (m, 1H), 7.11 (dt, 1H, $J = 6.0$ Hz, 1.2 Hz), 6.65-6.71 (m, 2H), 0.24 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 148.3, 132.2, 129.1, 117.8, 114.2, 107.8, 99.8, 0.2.

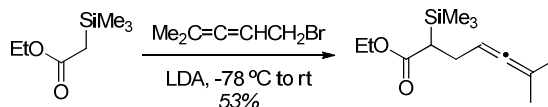


Di-Boc-2-((trimethylsilyl)ethynyl)aniline (3.91). To a solution of aniline **3.90** (500 mg, 2.64 mmol, 1.0 equiv) and Boc_2O (634 mg, 2.91 mmol, 1.1 equiv) in THF (13 mL) was added dropwise DIPEA (375 mg, 2.91 mmol, 1.1 equiv). The reaction stirred overnight at room temperature. Catalytic DMAP was added after no reaction had proceeded overnight. After stirring an additional day, the reaction was quenched with saturated aqueous NaHCO_3 . The reaction was extracted with EtOAc (1 x 10 mL) and the organic layer was washed with brine, dried over MgSO_4 and concentrated. The product was isolated by silica gel chromatography (10% EtOAc in hexanes) as a black solid (335 mg, 0.85 mmol, 33%). ^1H NMR (400 MHz, CDCl_3): δ 7.45 (dd, 1H, $J = 7.8$ Hz, 1.2 Hz), 7.29 (dt, 1H, $J = 6.0$ Hz, 1.2 Hz), 7.22 (t, 1H, $J = 6.8$ Hz), 7.12 (d, 1H, $J = 8.0$ Hz), 1.37 (s, 18H), 0.21 (s, 9H).

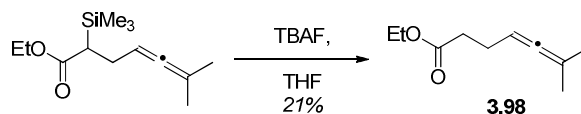


Ethyl 2-(dimethylphenylsilyl)-6-methylhepta-4,5-dienoate (3.97). To a stirred solution of LDA (1.20 mmol, 1.2 equiv) in THF (8 mL) at -78°C was added by syringe a solution of ethyl 2-(dimethylphenylsilyl)acetate⁴⁰ (222 mg, 1.00 mmol, 1.0 equiv) in THF (2 mL). The resulting solution stirred 1 h at -78°C ; the allenyl bromide (187 mg, 1.91 mmol, 1.9 equiv) was added dropwise by syringe. The reaction mixture was warmed to 0°C and stirred for 90 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl (5 mL) and the resulting biphasic solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over MgSO_4 and concentrated. The product (78 mg, 0.215 mmol, 22%) was isolated as a clear oil by silica gel chromatography (5% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3): δ 7.51-7.55 (m, 2H), 7.35-7.38 (m, 3H), 4.95-4.98 (m, 1H), 3.97-4.07

(m, 2H), 2.40-2.47 (m, 1H), 2.32 (dd, 1H, $J = 12.0$ Hz, 2.5 Hz), 2.01 (ddd, 1H, $J = 12.0$ Hz, 6.0 Hz, 2.5 Hz), 1.66 (s, 3H), 1.65 (s, 3H), 1.16-1.18 (s, 3H), 0.45 (s, 6H).



Ethyl 6-methyl-2-(trimethylsilyl)hepta-4,5-dienoate. Prepared analogously from ethyl 2-(trimethylsilyl)acetate (160 mg, 1.0 mmol, 1.0 equiv) to form the product (128 mg, 0.533 mmol, 53%) as a clear oil. ^1H NMR (500 MHz, CDCl_3): δ 4.95-4.99 (m, 1H), 4.06-4.09 (m, 2H), 2.39-2.46 (m, 1H), 2.08 (d, 1H, $J = 13.5$), 2.02 (d, 1H, $J = 13.5$ Hz), 1.65 (s, 3H), 1.61 (s, 3H), 1.21-1.24 (m, 3H), 0.62 (s, 9H).



Ethyl 6-methylhepta-4,5-dienoate (3.98).⁴¹ To a solution of the β -silyl allene (100 mg, 0.416 mmol, 1.0 equiv) in THF (7 mL) at -78°C was added TBAF (1.0 M in THF, ca. 5% water) (0.46 mL, 0.458 mmol, 1.1 equiv). After stirring for 20 min the reaction temperature was increased to 0°C ; the reaction mixture then stirred an additional 1 h. The reaction mixture was brought to room temperature and stirred 2 h. The reaction mixture was then diluted with Et_2O (5 mL) and the remaining TBAF was quenched with saturated aqueous NaHCO_3 (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (1 x 5 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over MgSO_4 and concentrated. The product (35 mg, 0.208 mmol, 21%) was isolated as a clear oil and used without further purification. ^1H NMR (400 MHz, CDCl_3): δ 4.96-5.00 (m, 1H), 4.10 (q, 2H, $J = 7.2$ Hz), 2.34-2.49 (m, 2H), 2.16-2.26 (m, 2H), 1.64 (s, 3H), 1.63 (s, 3H), 1.12-1.25 (m, 3H).

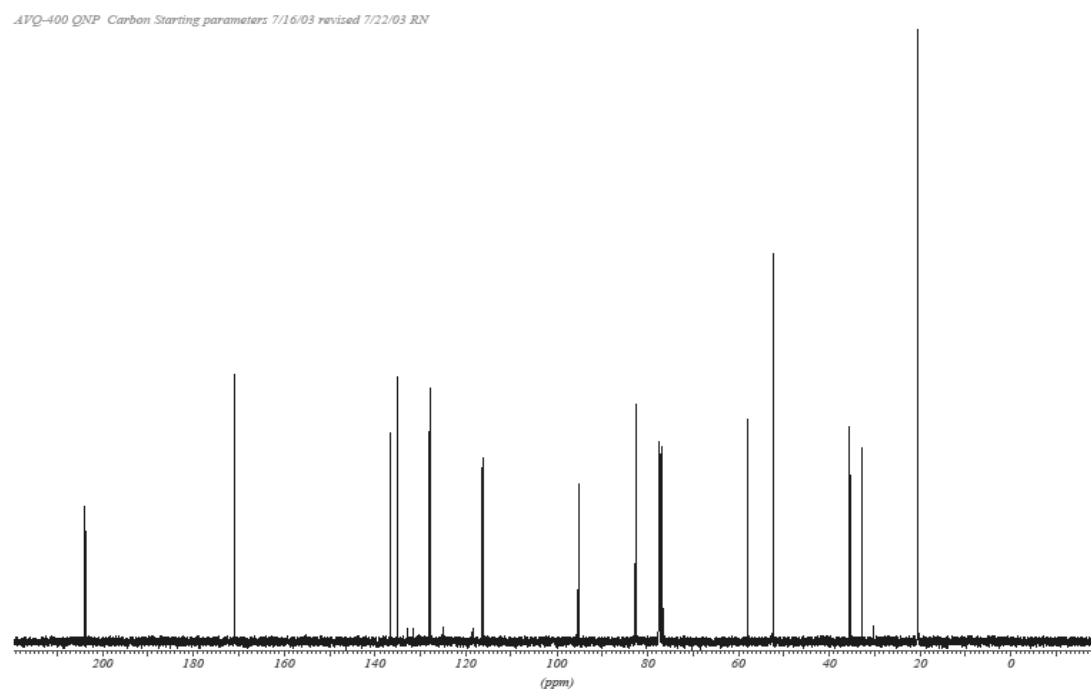
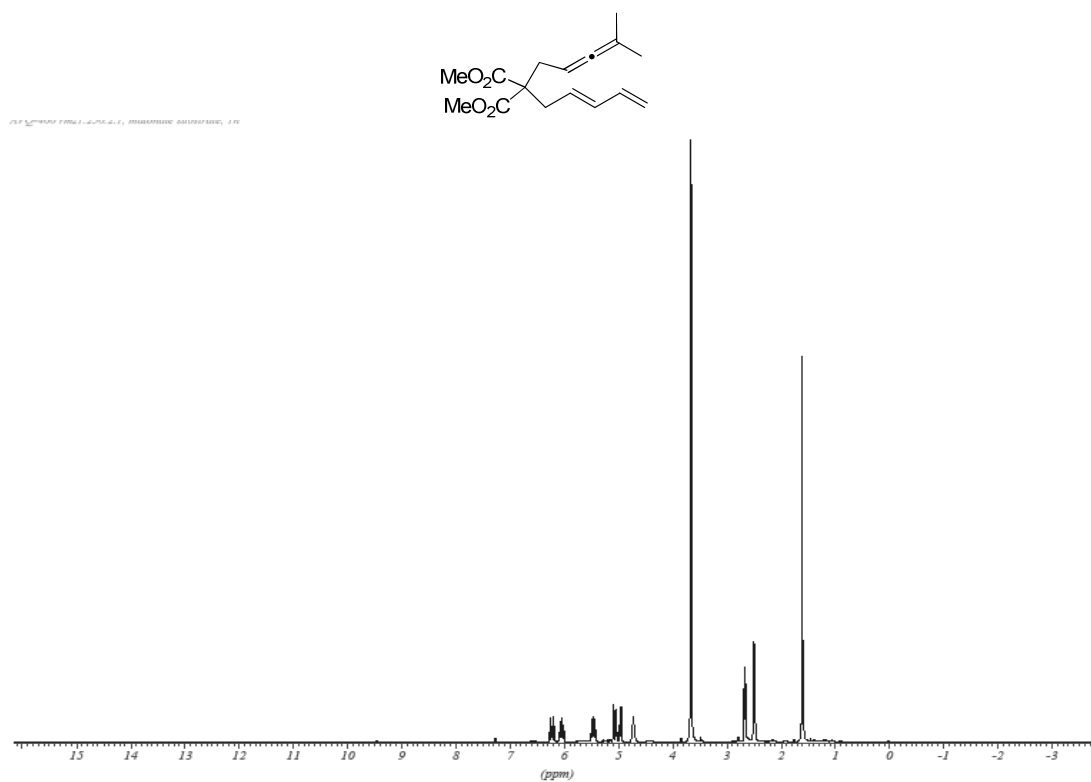
References

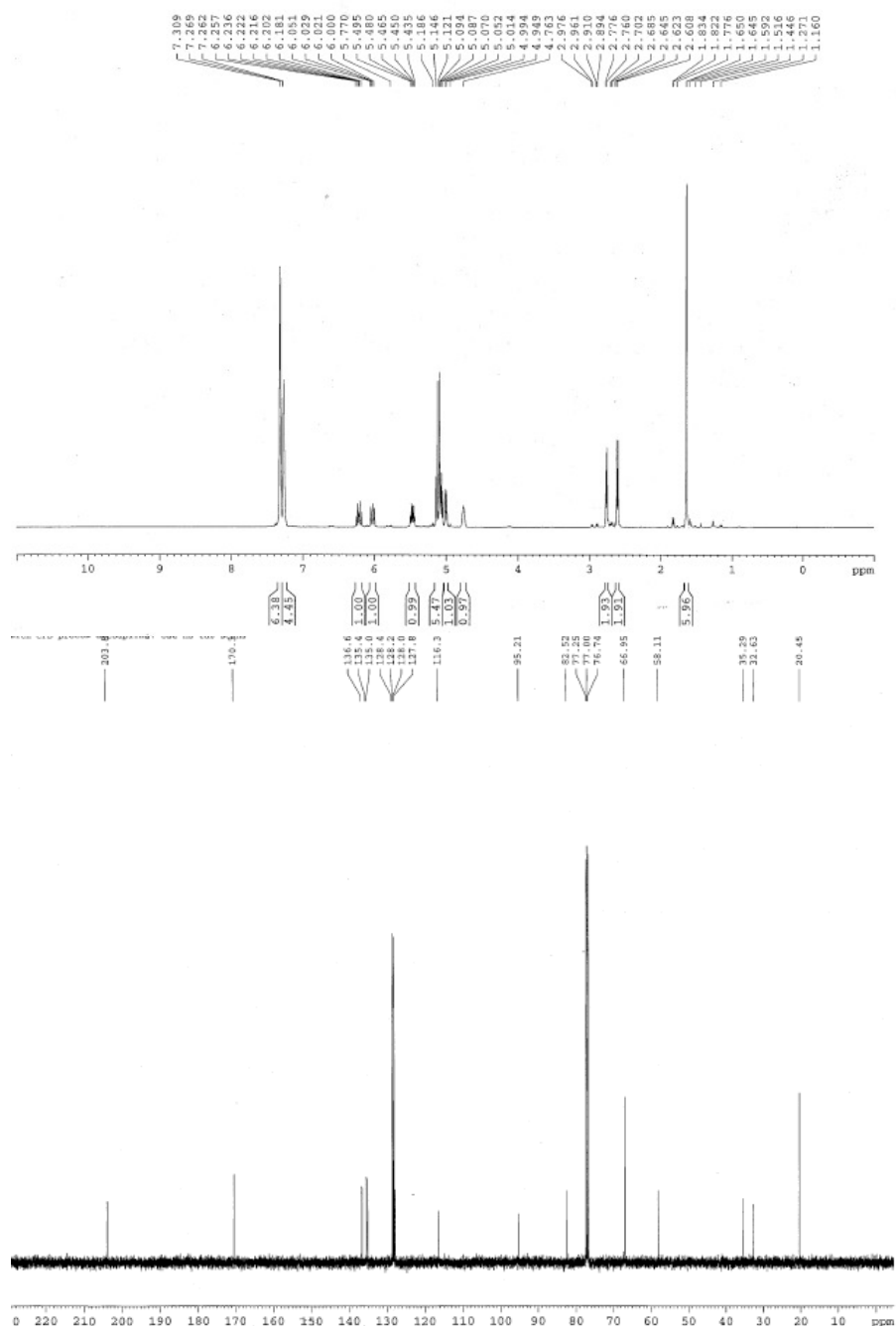
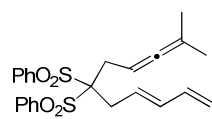
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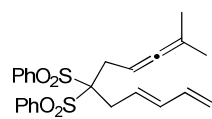
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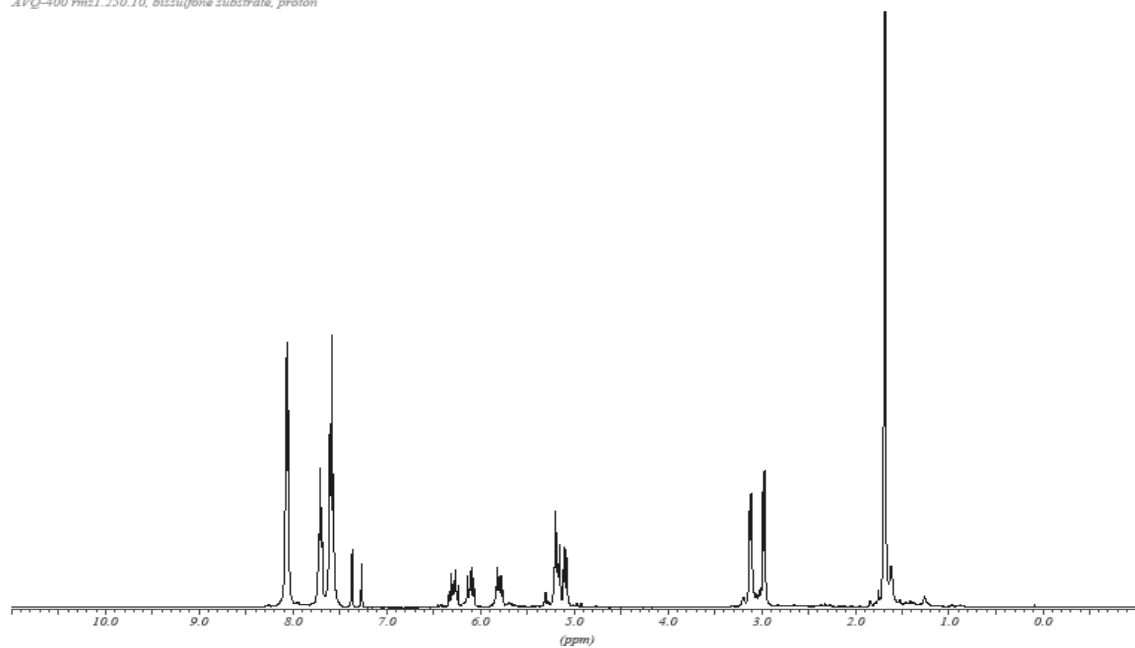
Appendix 1 – Additional Supporting Information for Chapter 2 (NMR Spectra)



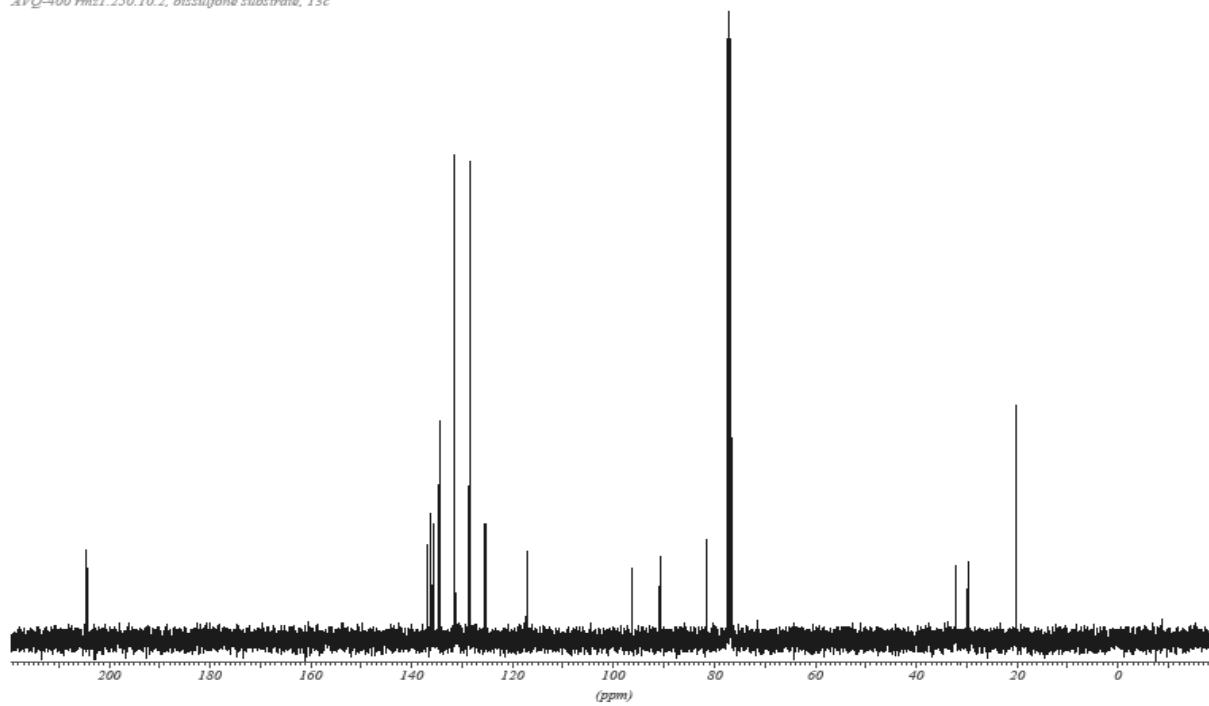


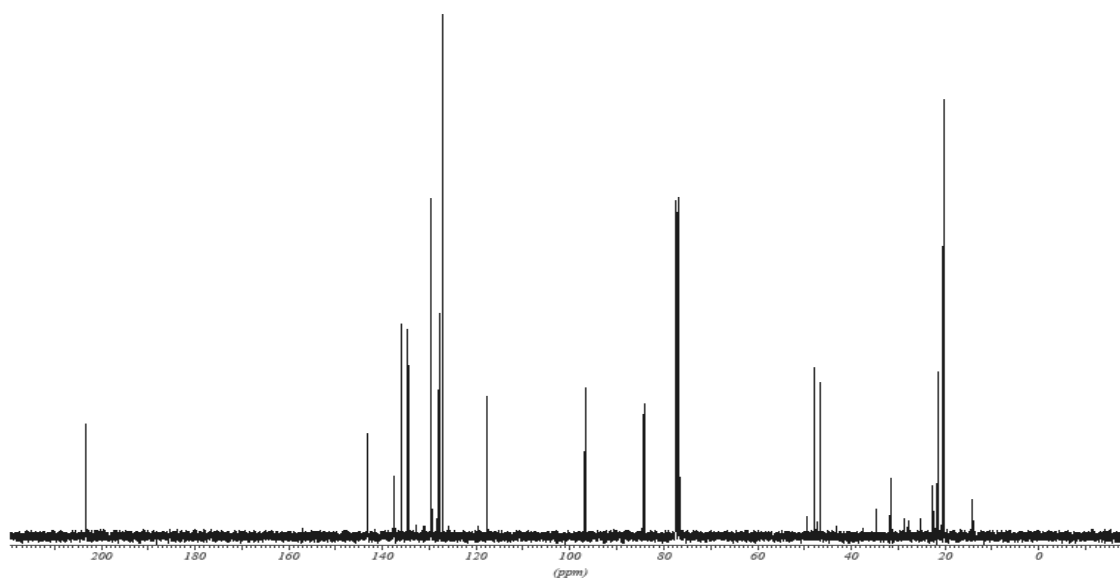
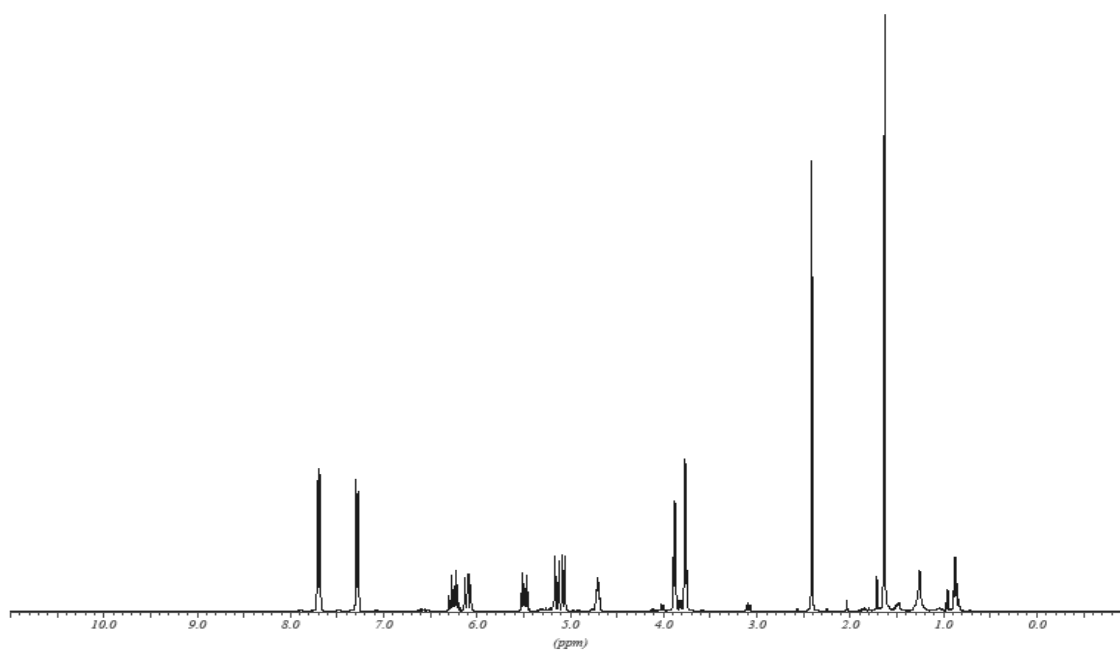
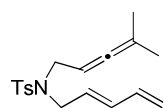


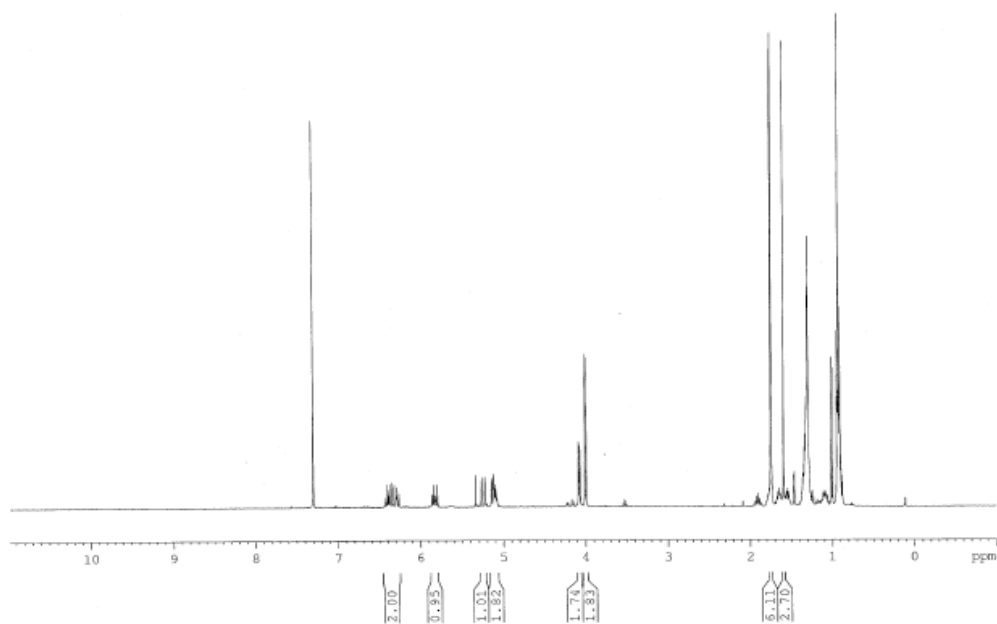
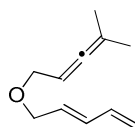
AVQ-400 rmz1.250.10, bissulfone substrate, proton

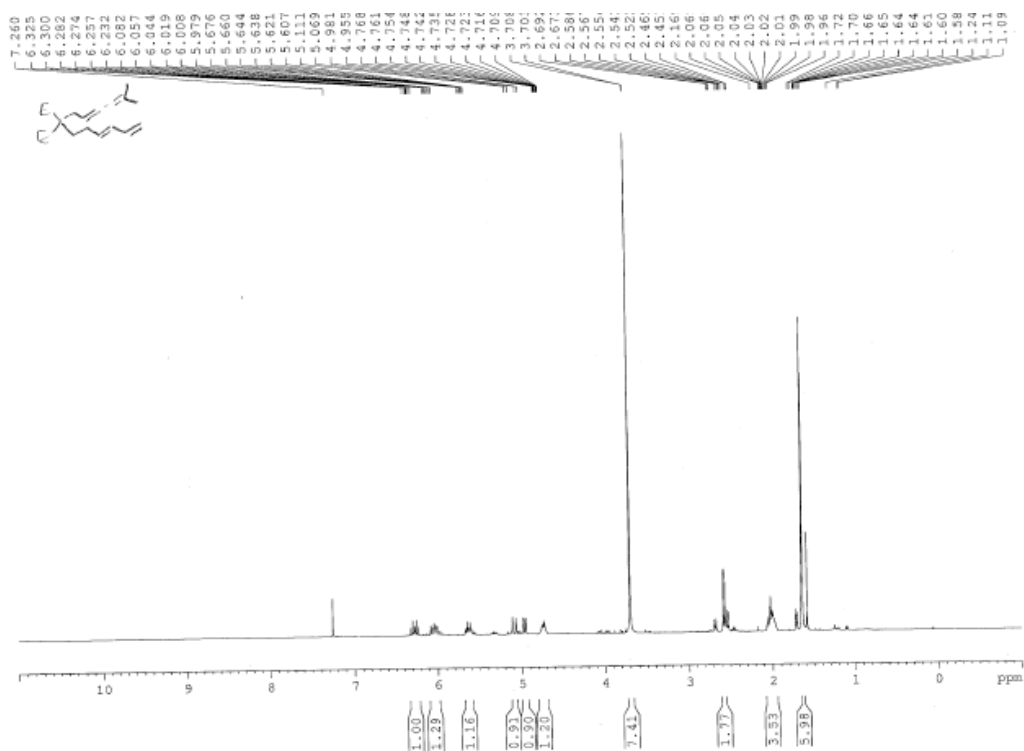
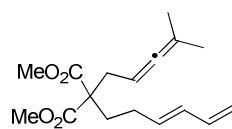


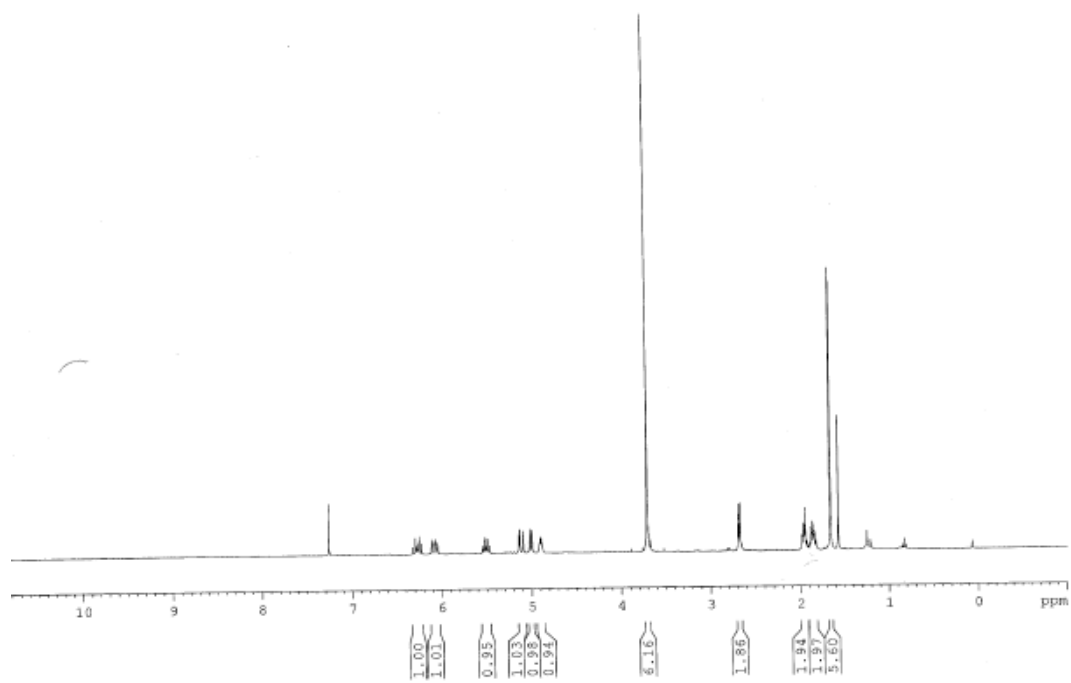
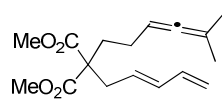
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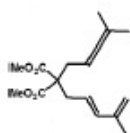






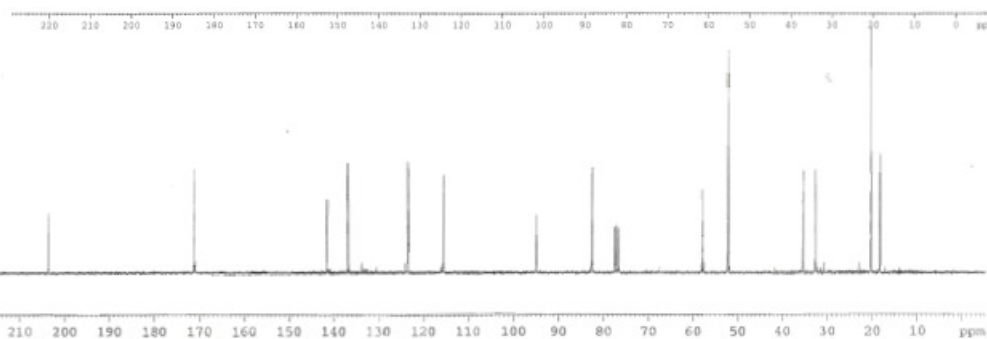
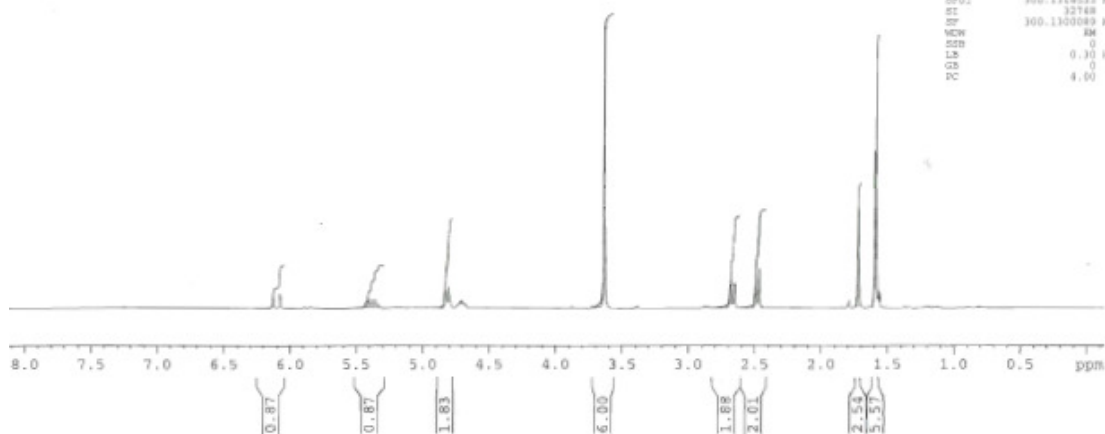


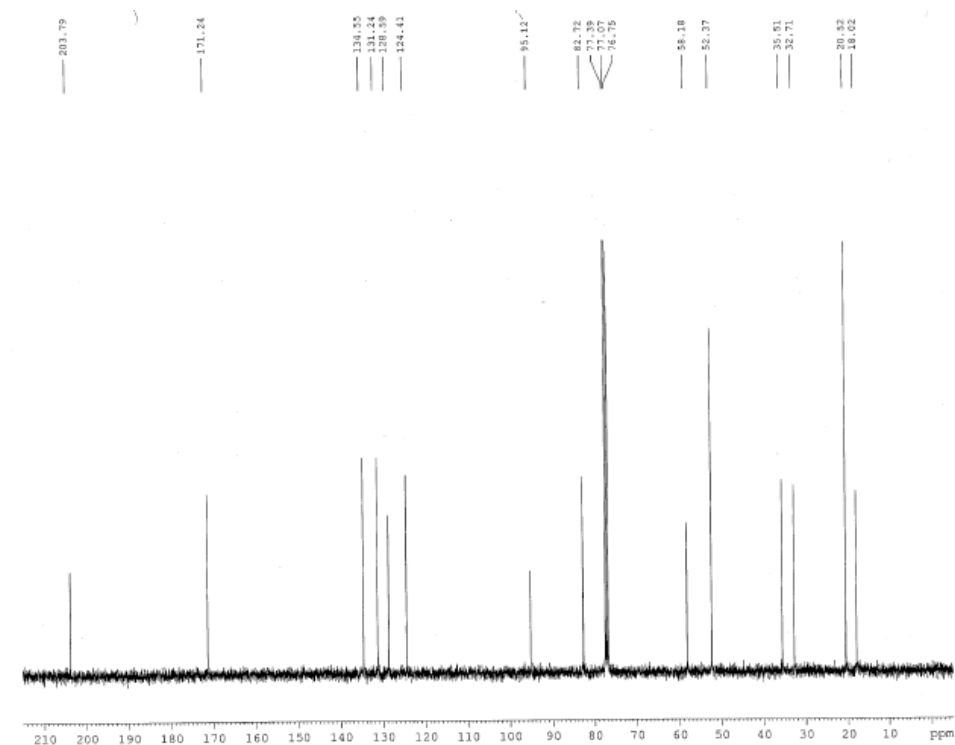
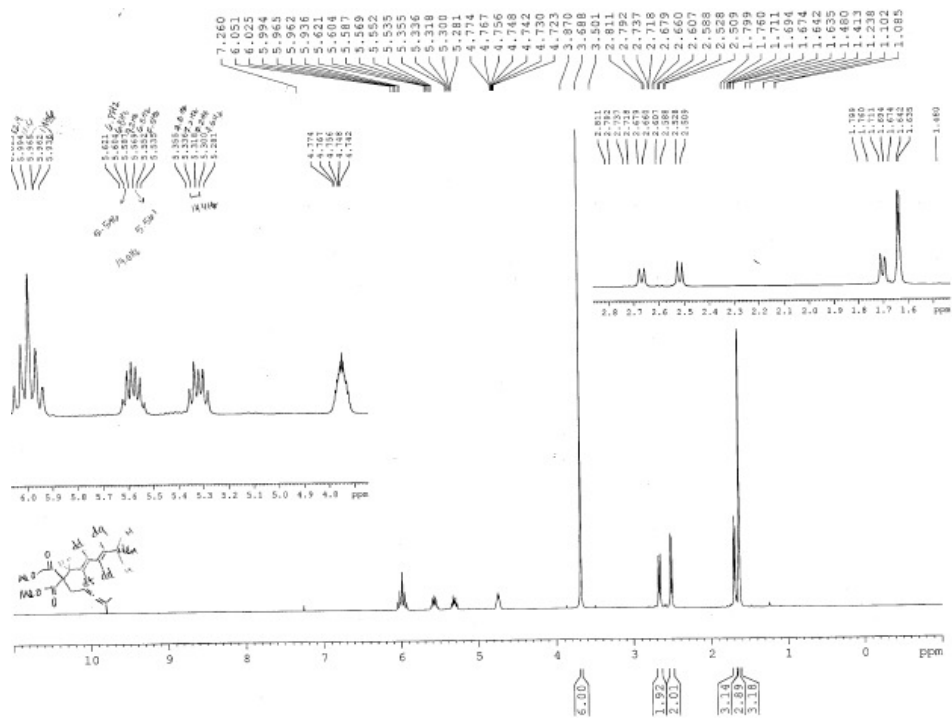
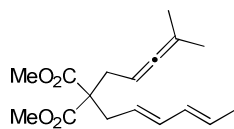


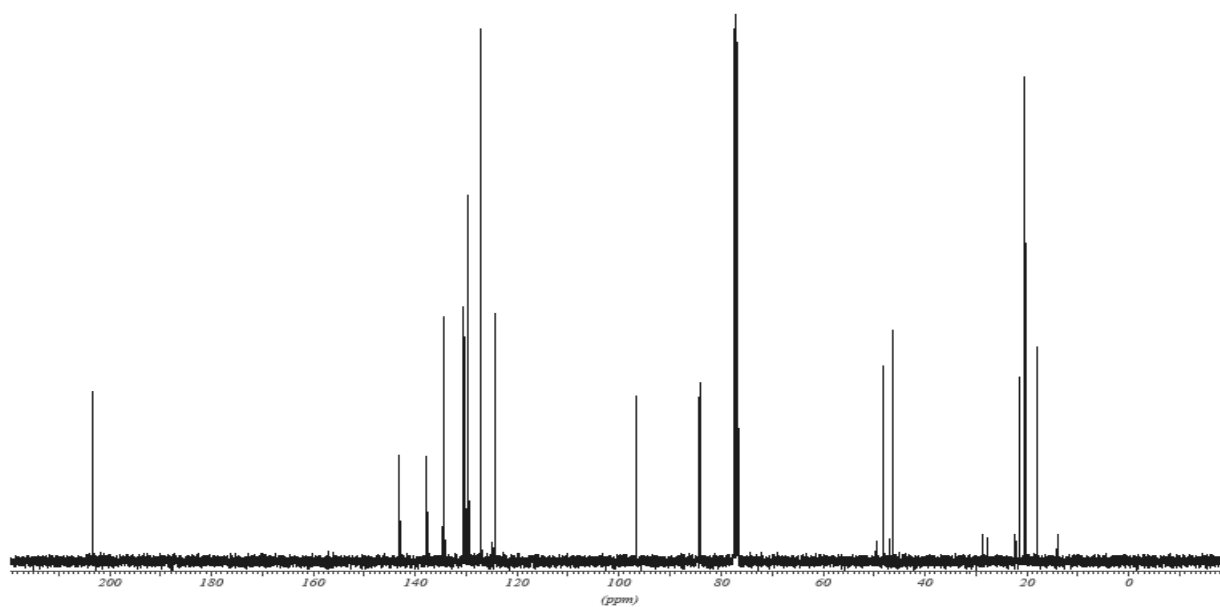
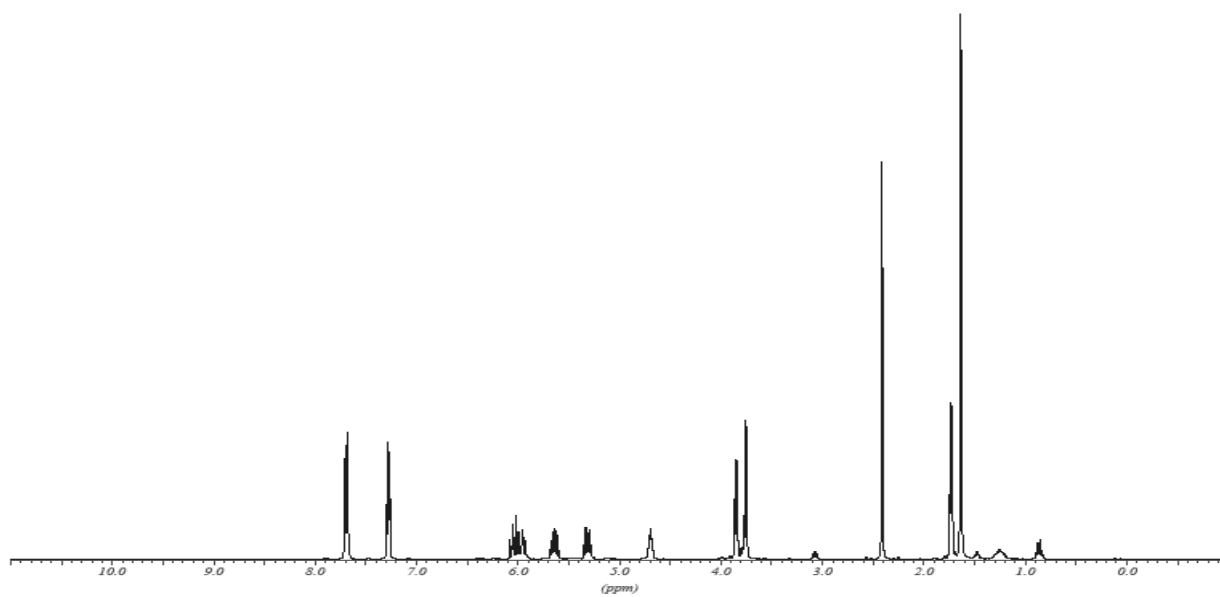
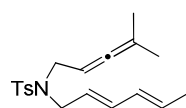


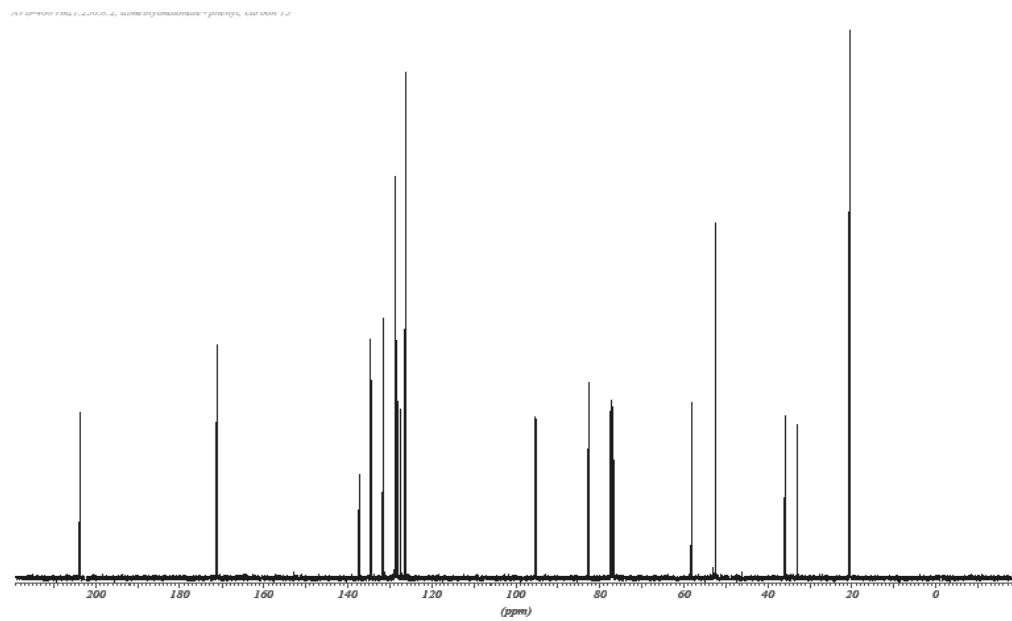
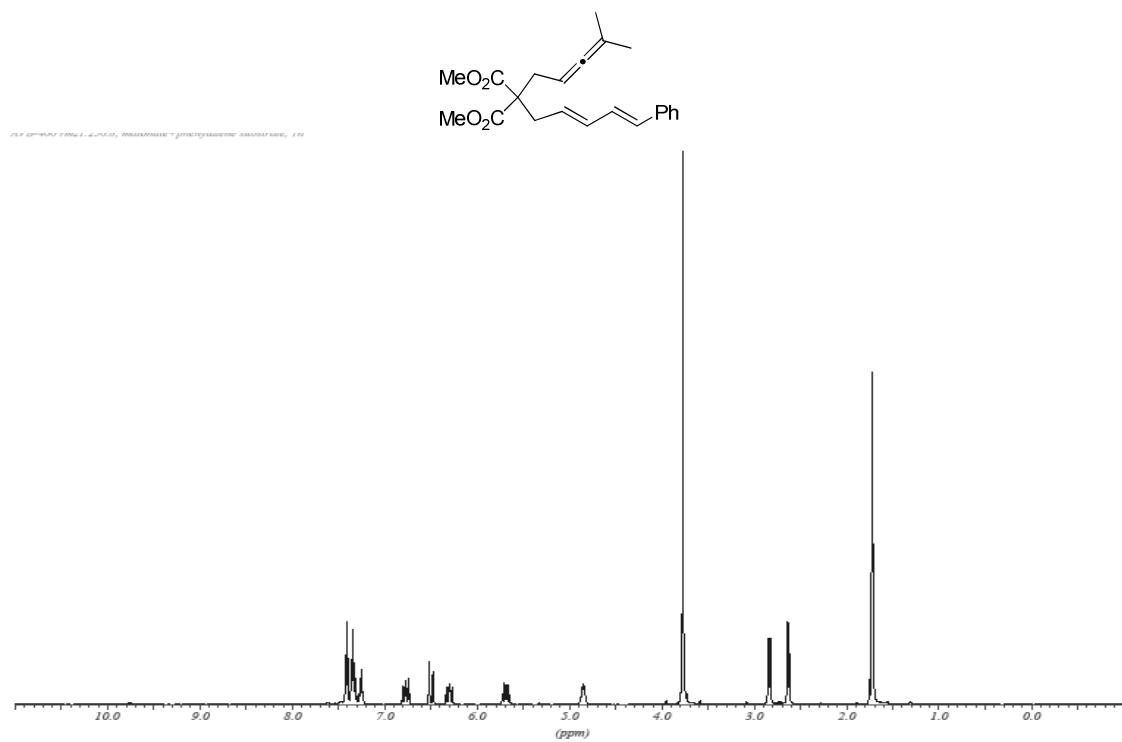
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 PROCNO 1
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 Time 13.11
 INSTRUM av-300
 PROBRD 5 mm Dual 13C/
 PULPROG zgpg30
 TO 65534
 SOLVENT CDCl3
 NS 4
 DS 0
 SWH 6170.833 Hz
 FIDRES 0.094190 Hz
 AQ 5.3084660 sec
 RG 28.5
 CW 41.000 use
 TC 4.00 use
 TE 294.0 K
 DC 0.2000000 sec
 MCKEY 0.0000000 sec
 MCHKE 0.0150000 sec

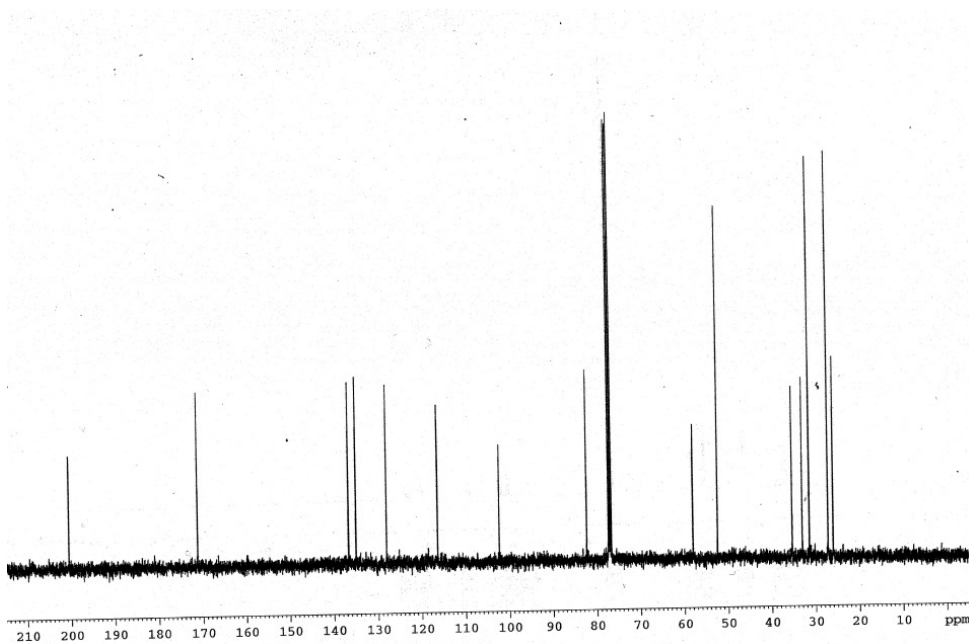
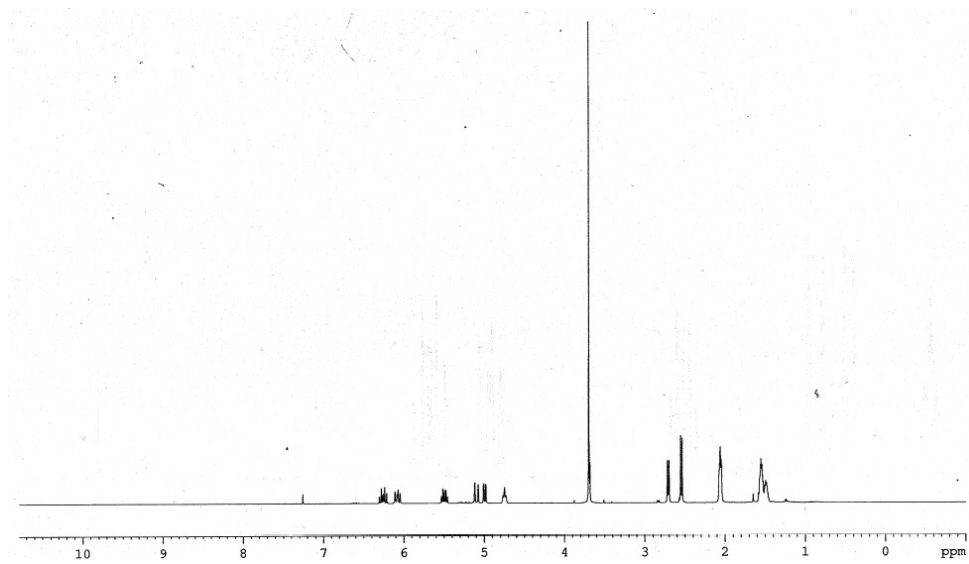
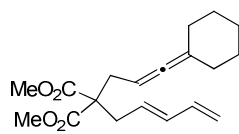
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 P1 11.00 use
 PL1 -1.00 dB
 SFO1 100.1314013 MHz
 ST 32748
 SW 100.1300049 MHz
 MW 0
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 4.00

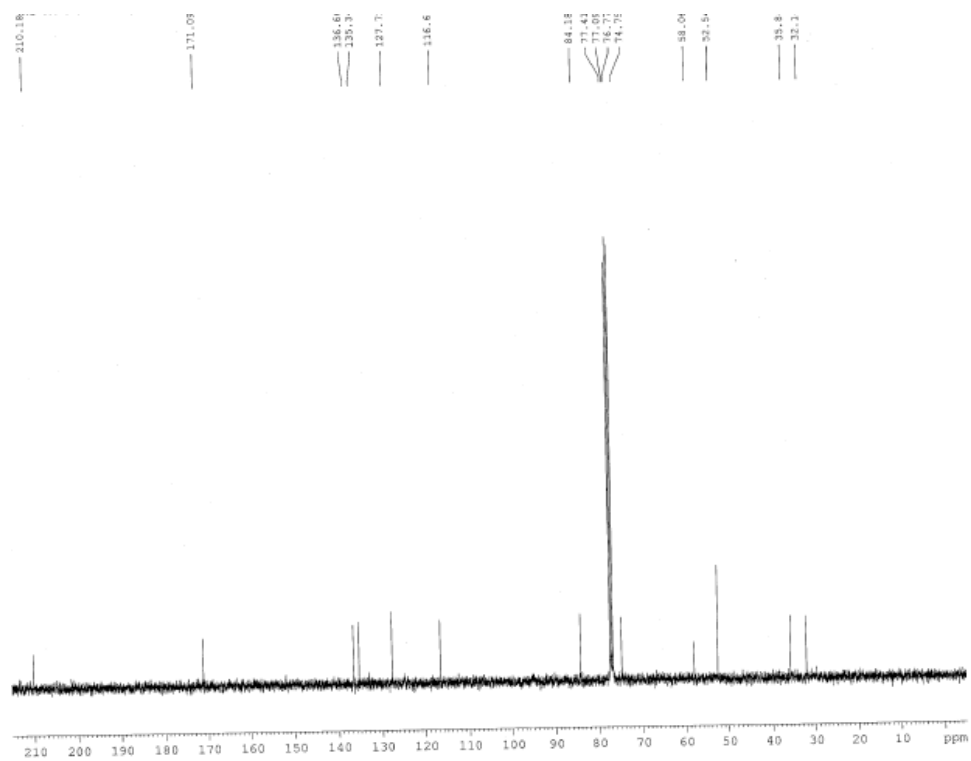
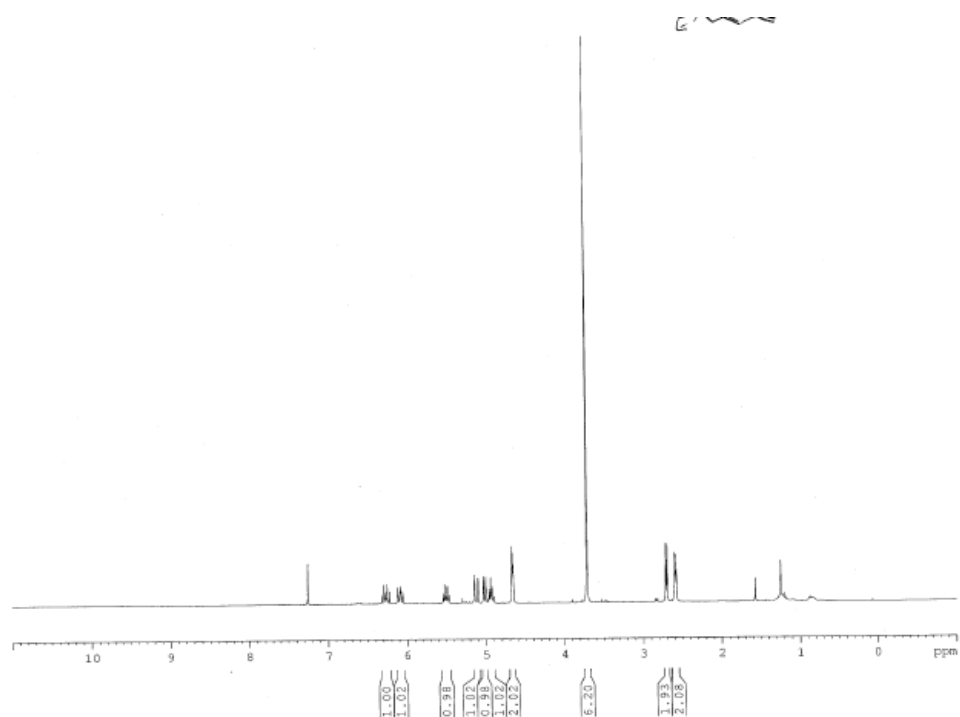
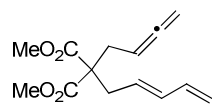


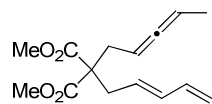




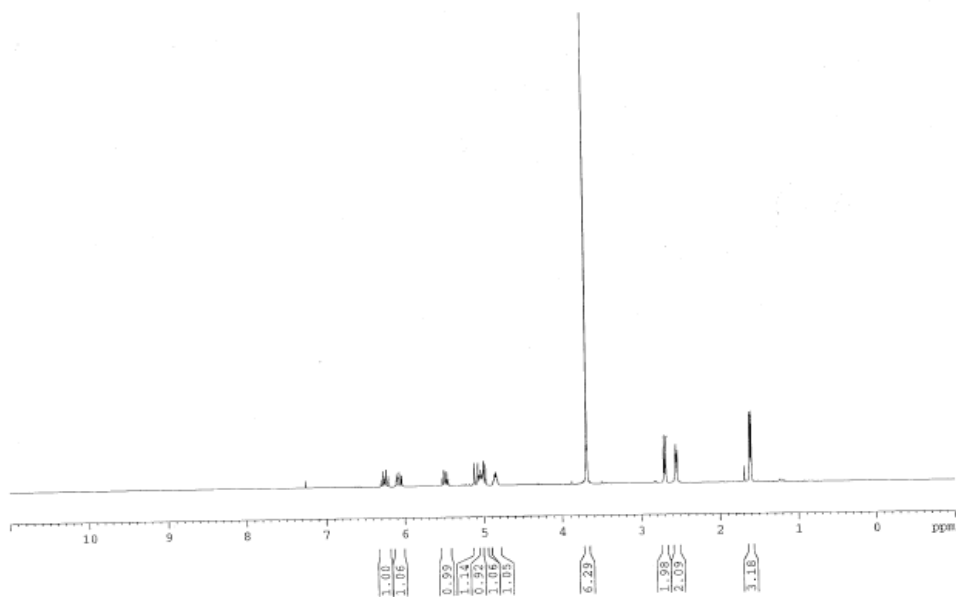




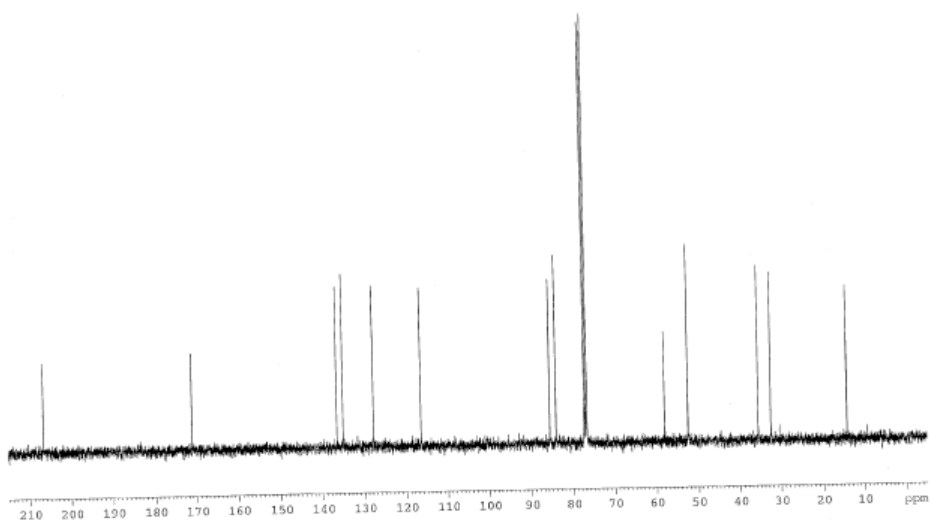


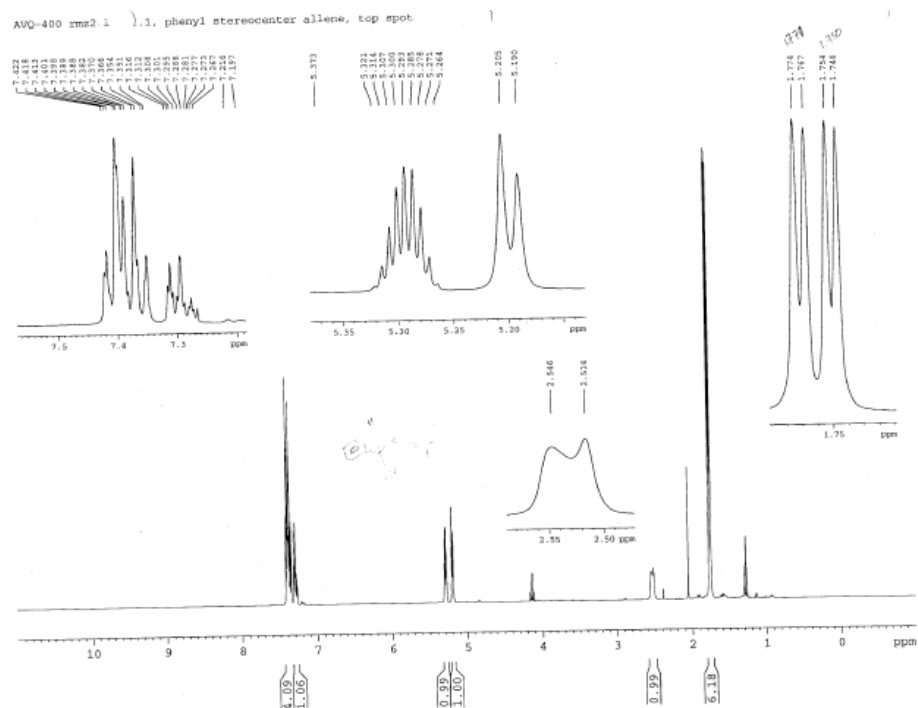


82.5
14.25



AVQ-400 QNP C4x4 Starting Parameters 7/16/03 revised 7/22/03

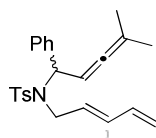




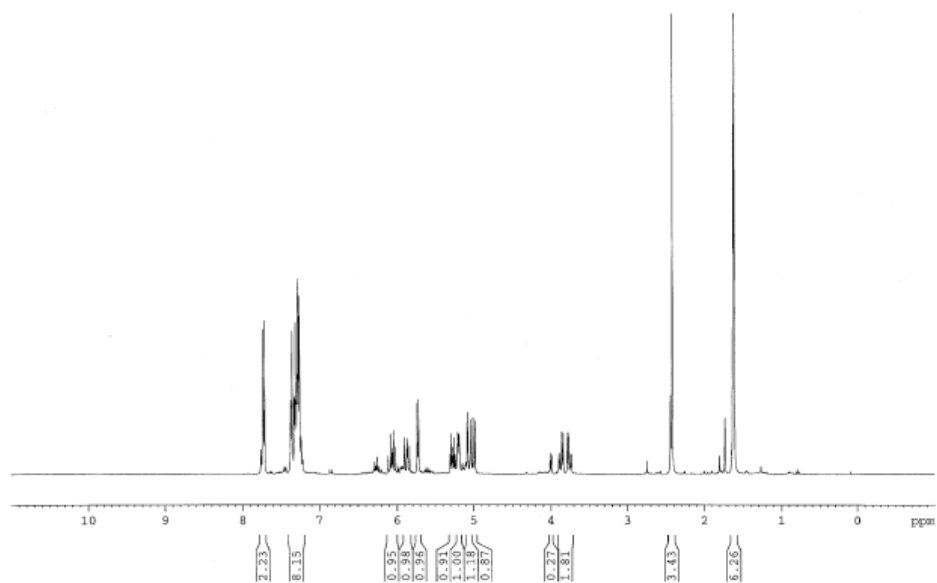


tasting parameters 7/16/03 revised

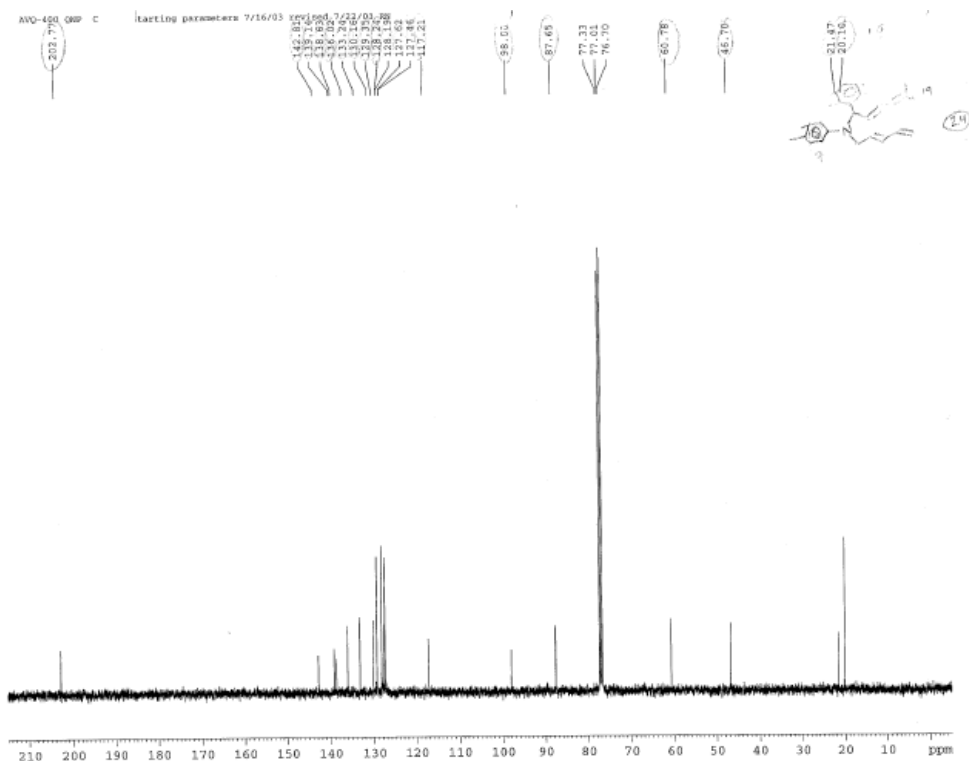


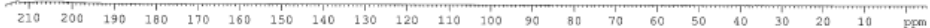
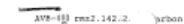


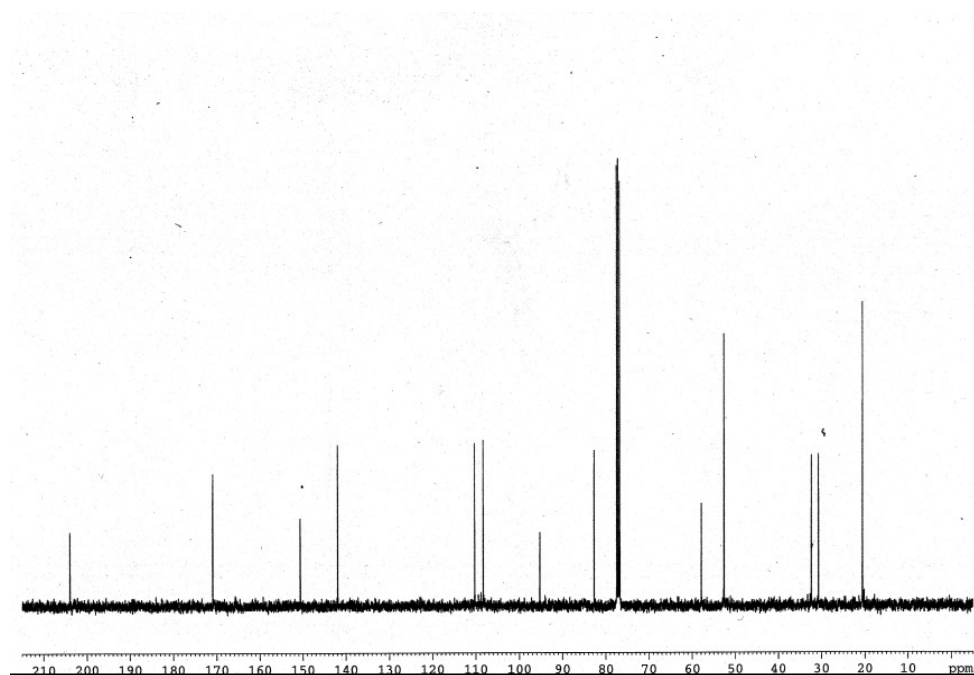
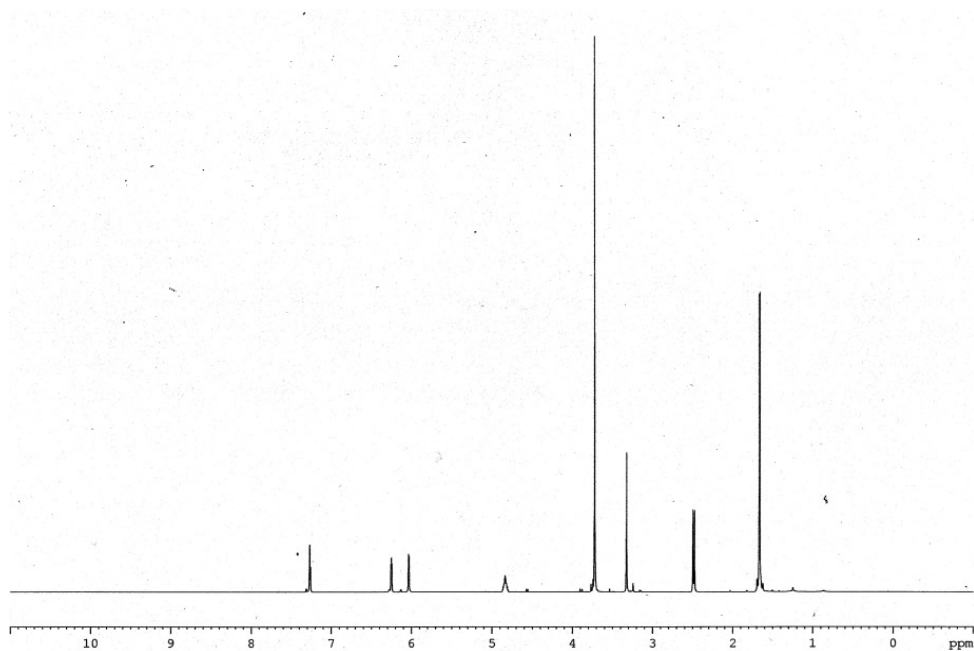
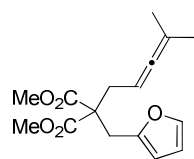
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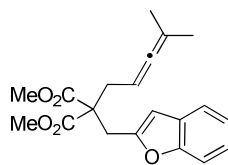


AVQ-400 QNP C 1, top spot

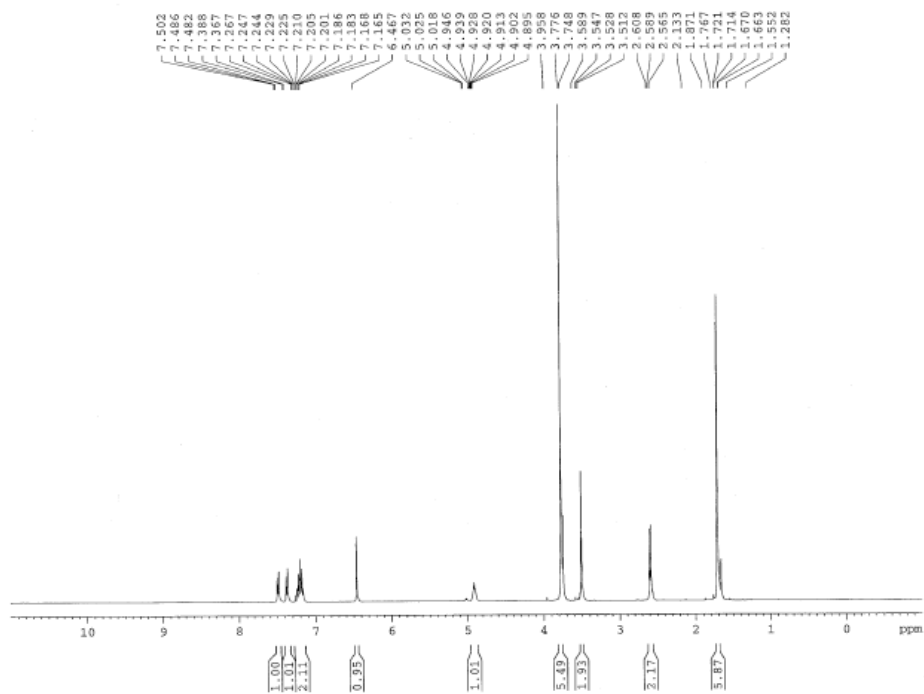




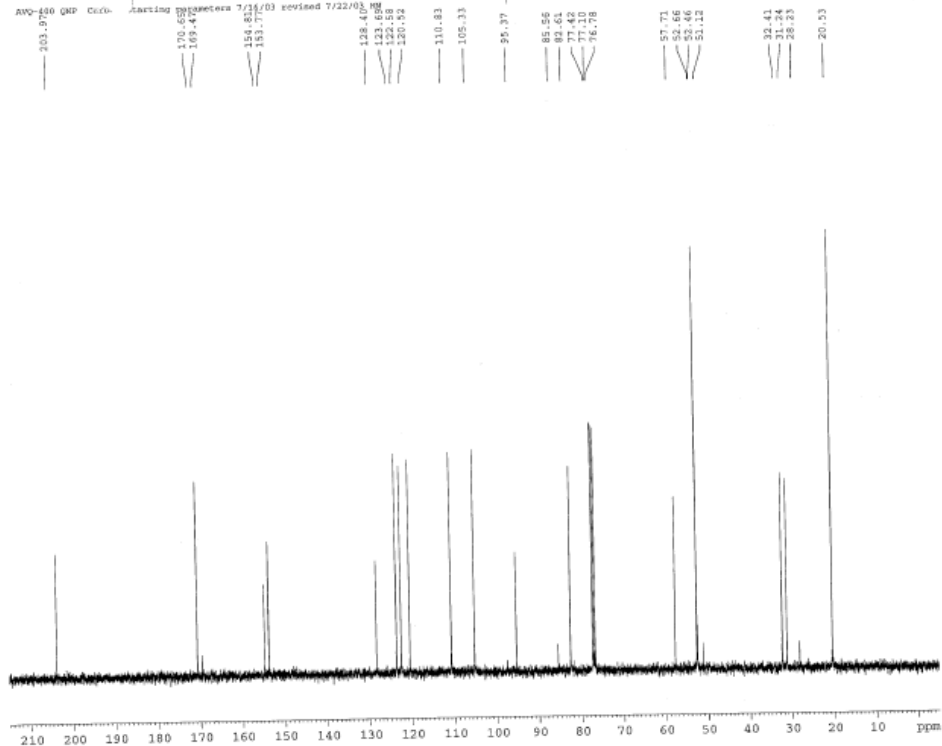


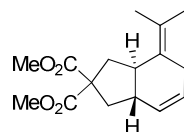


AVQ-400 MHz ¹H, benzofuran substrate, 1h

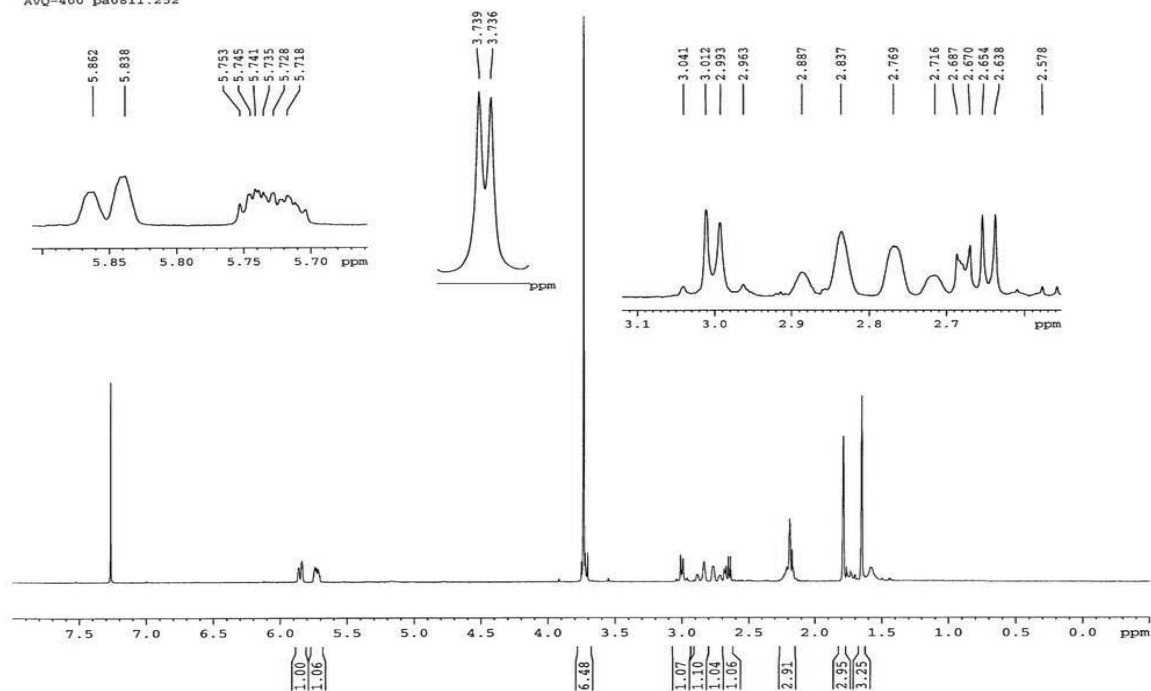


AVQ-400 QNP ¹³C, starting parameters 7/22/03 revised 7/22/03

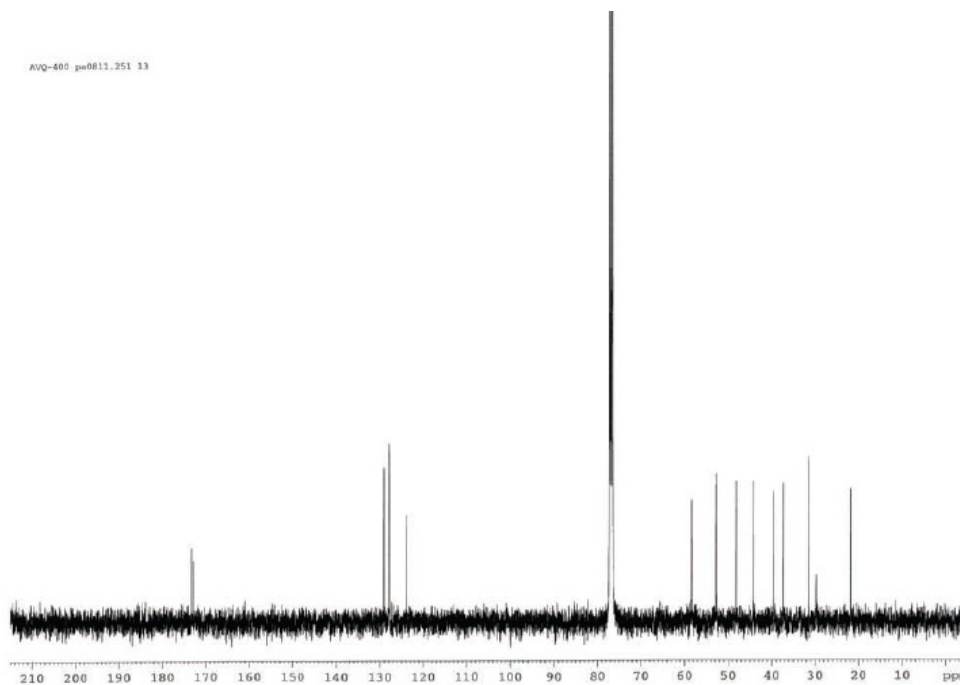


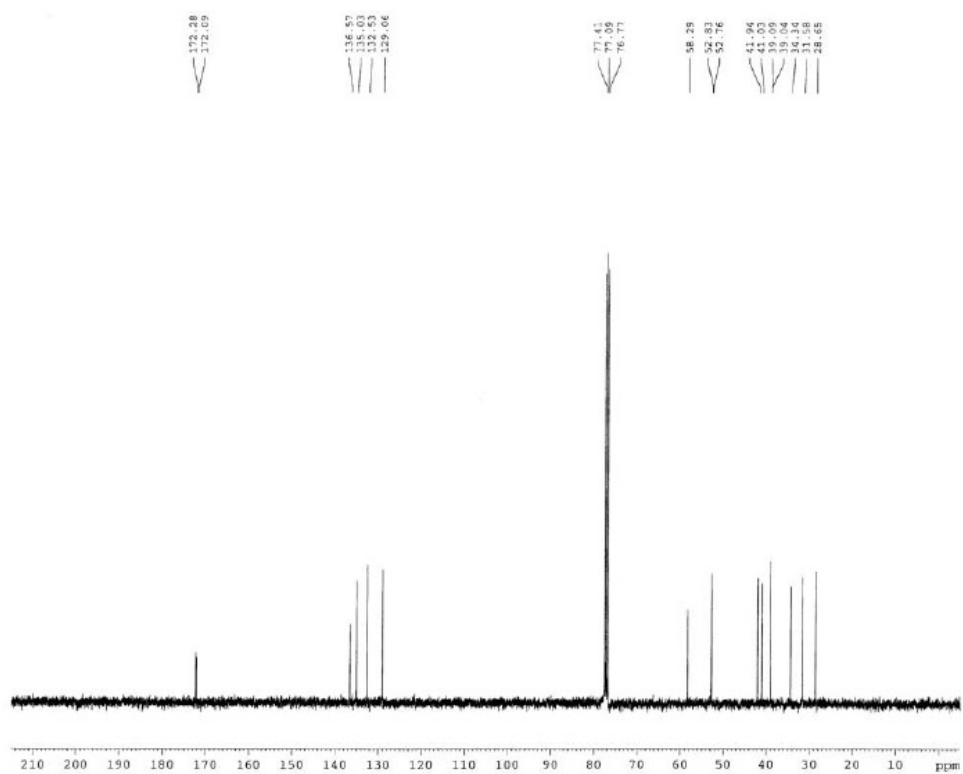
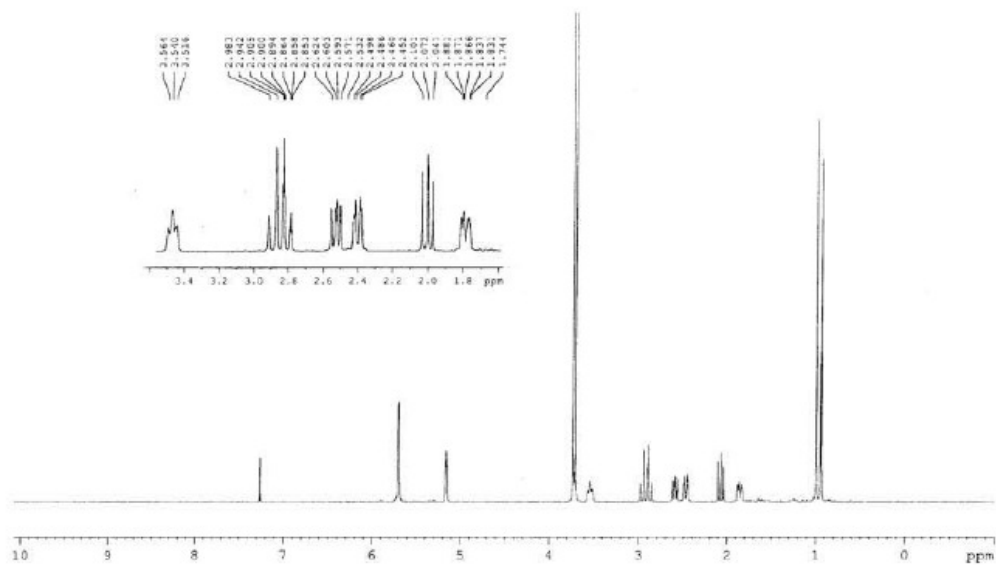
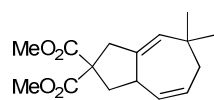


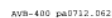
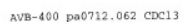
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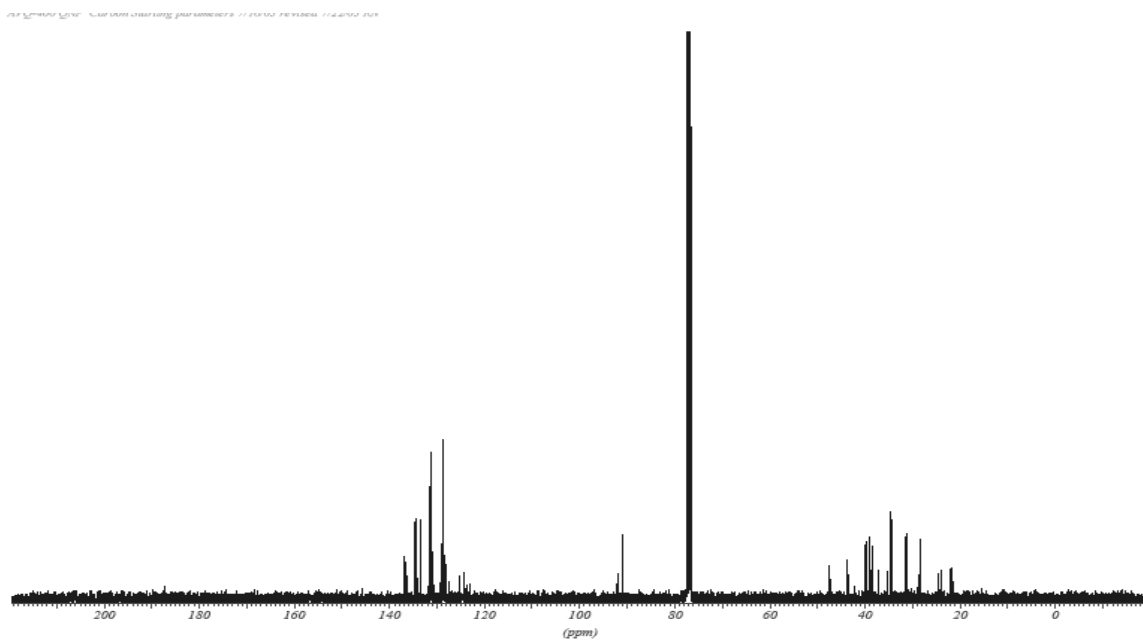
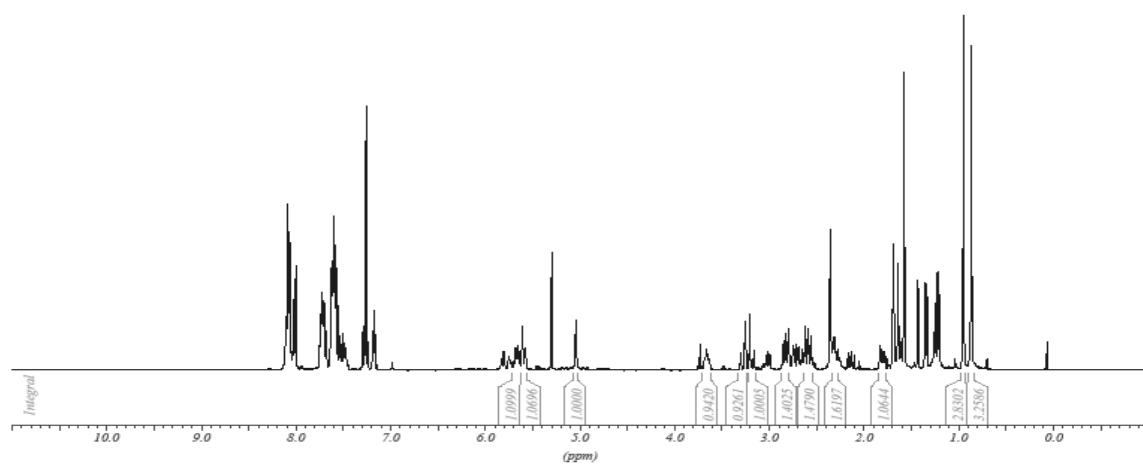
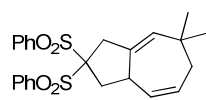


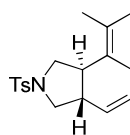
AVQ-400 pa0811.251 33



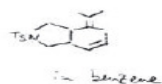
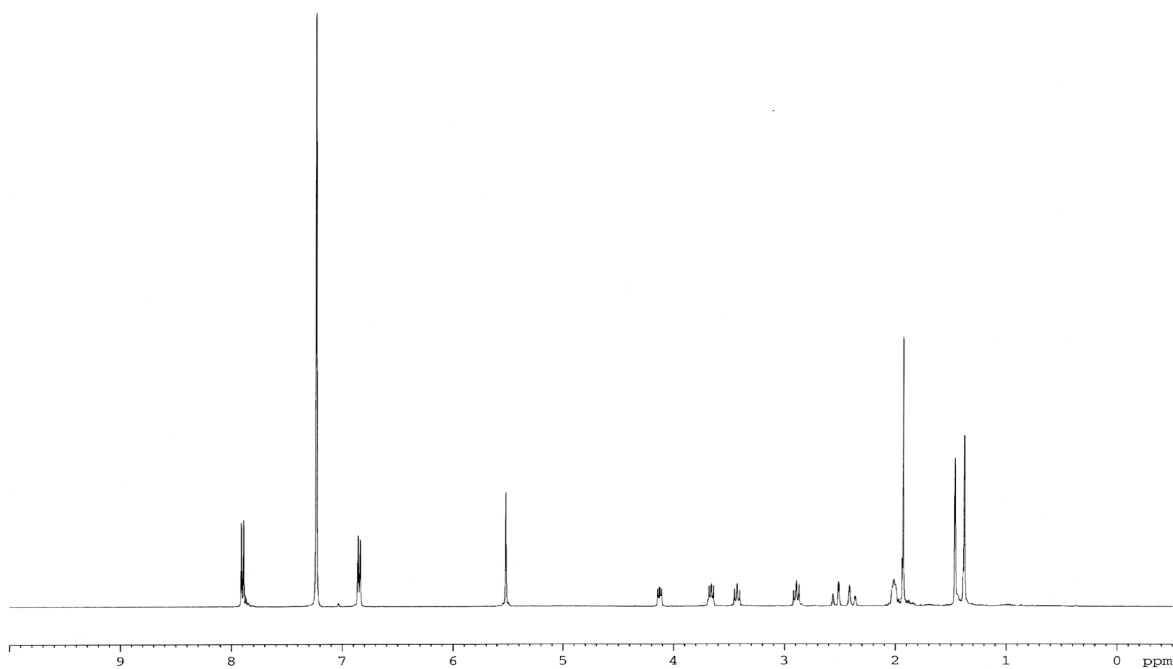




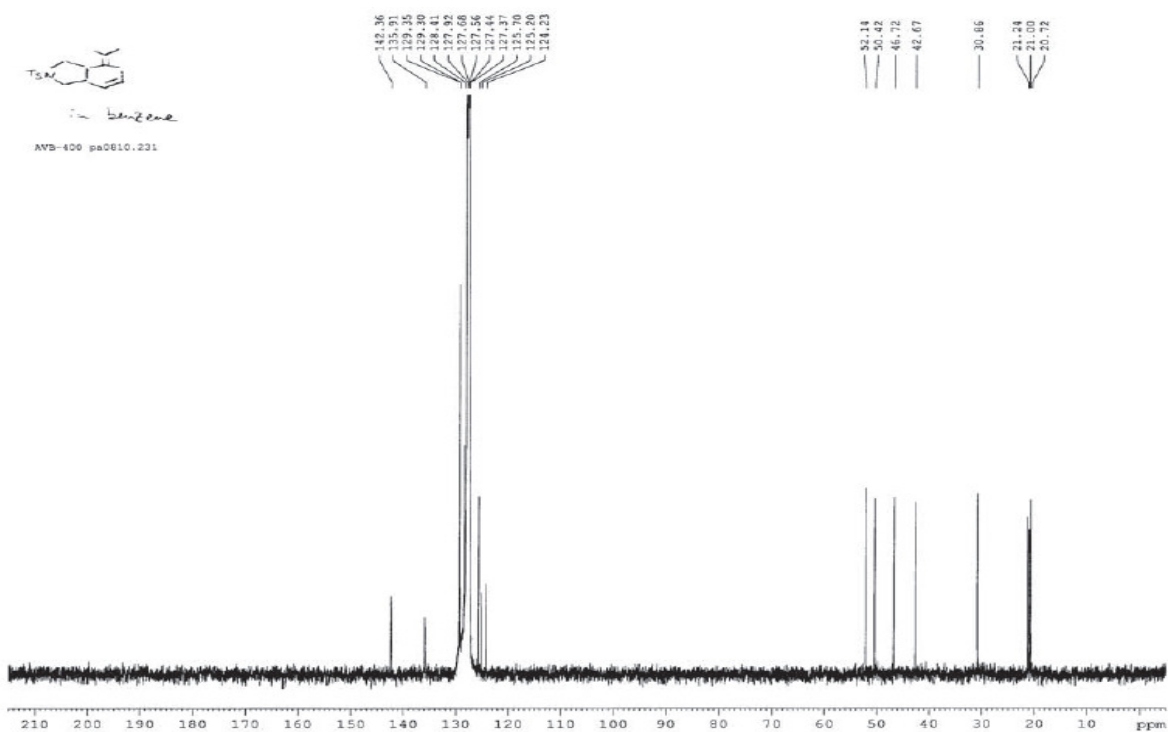


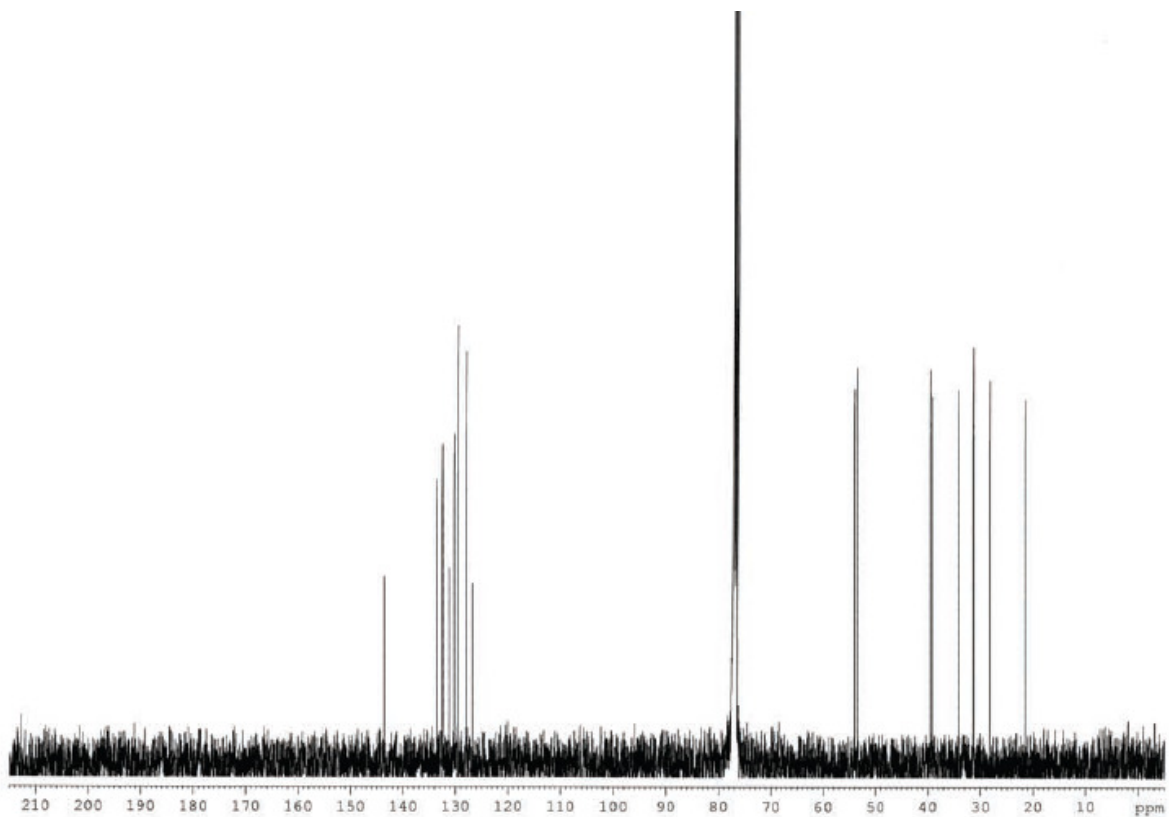
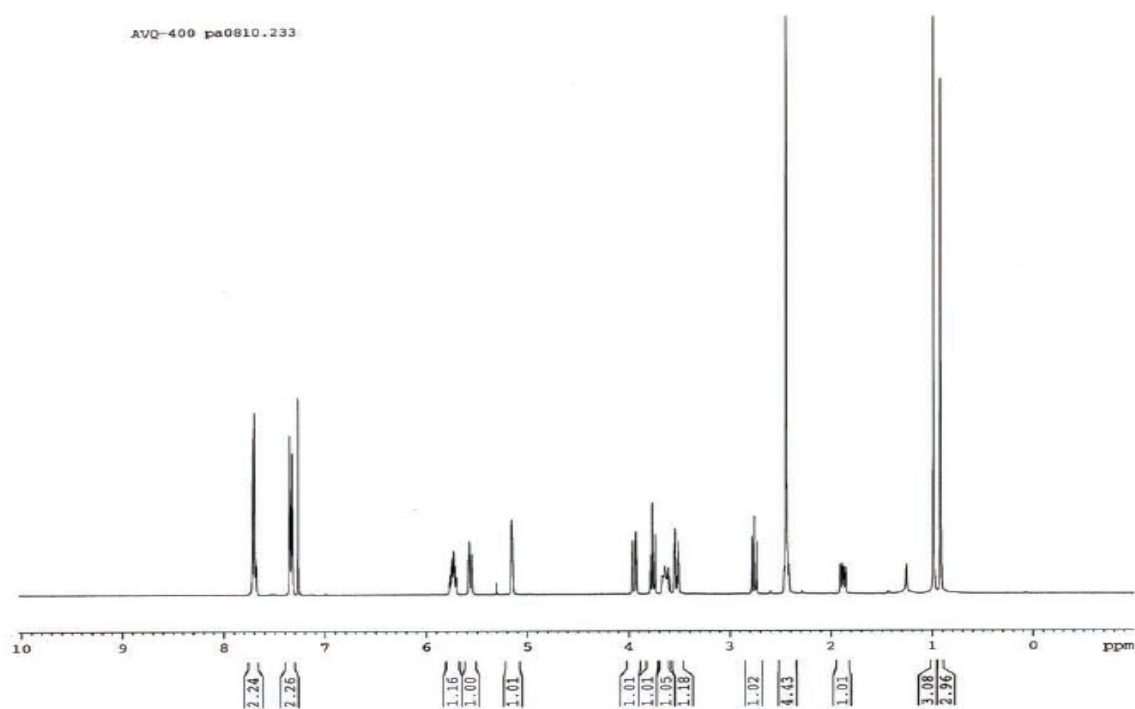
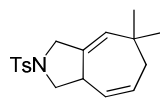


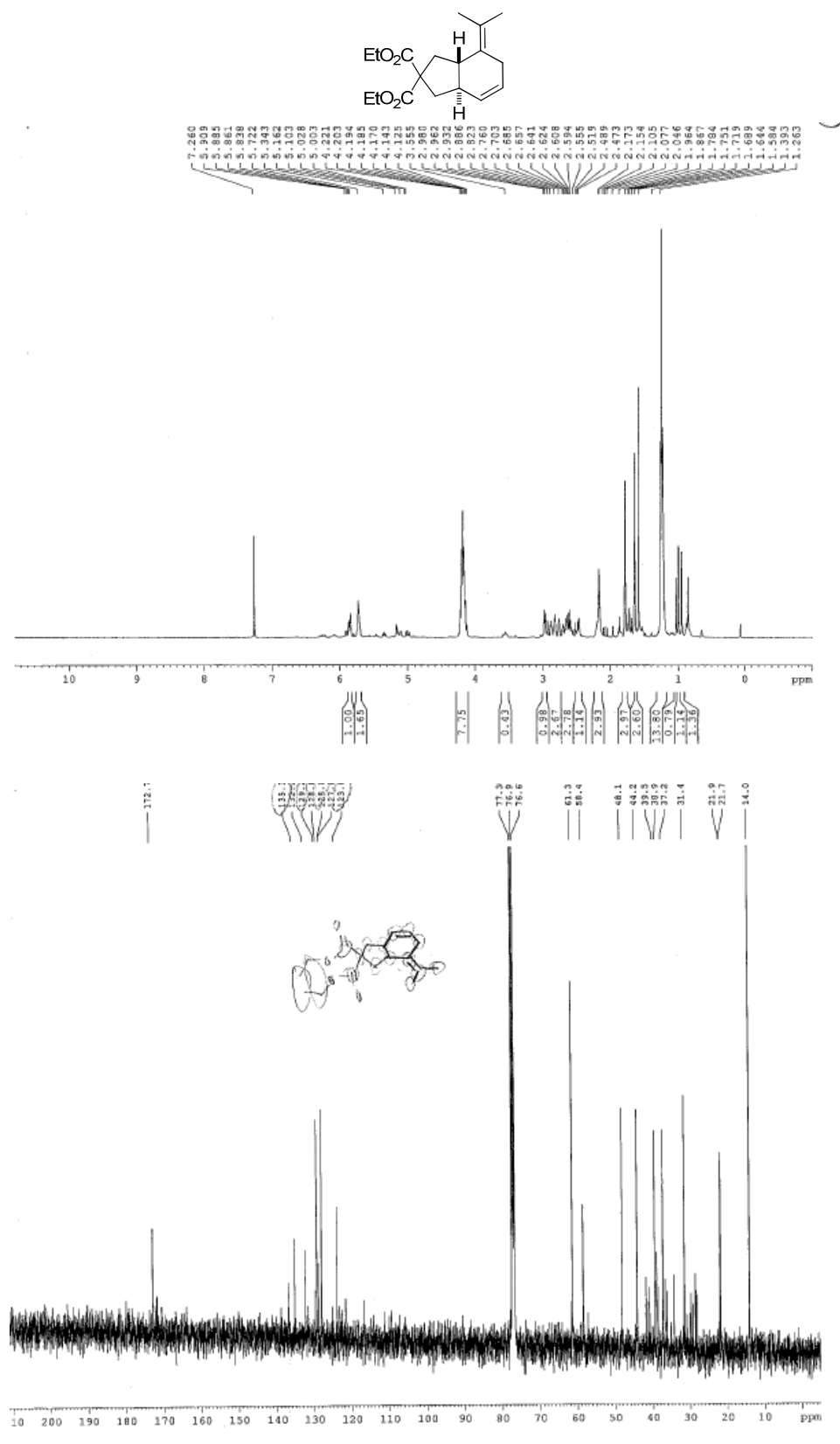
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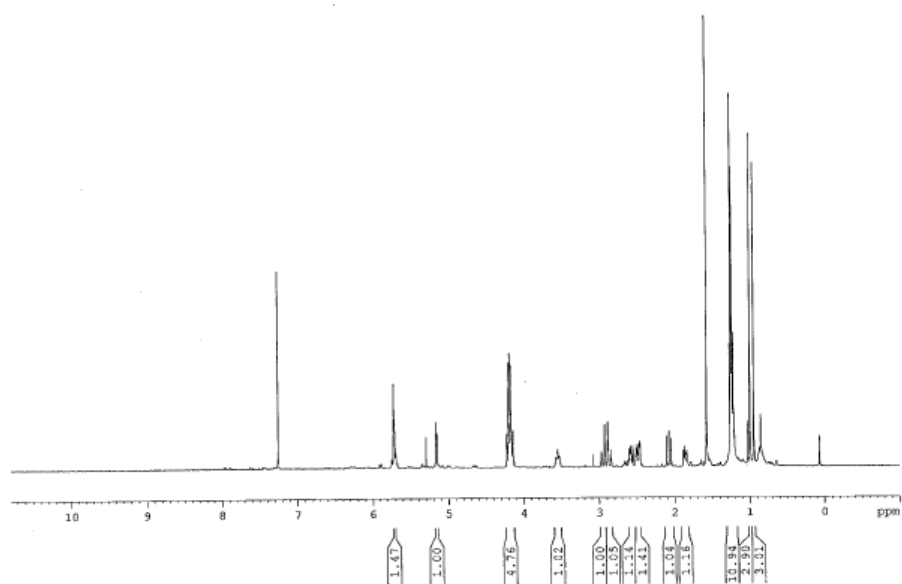
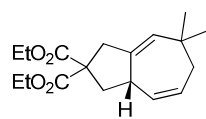


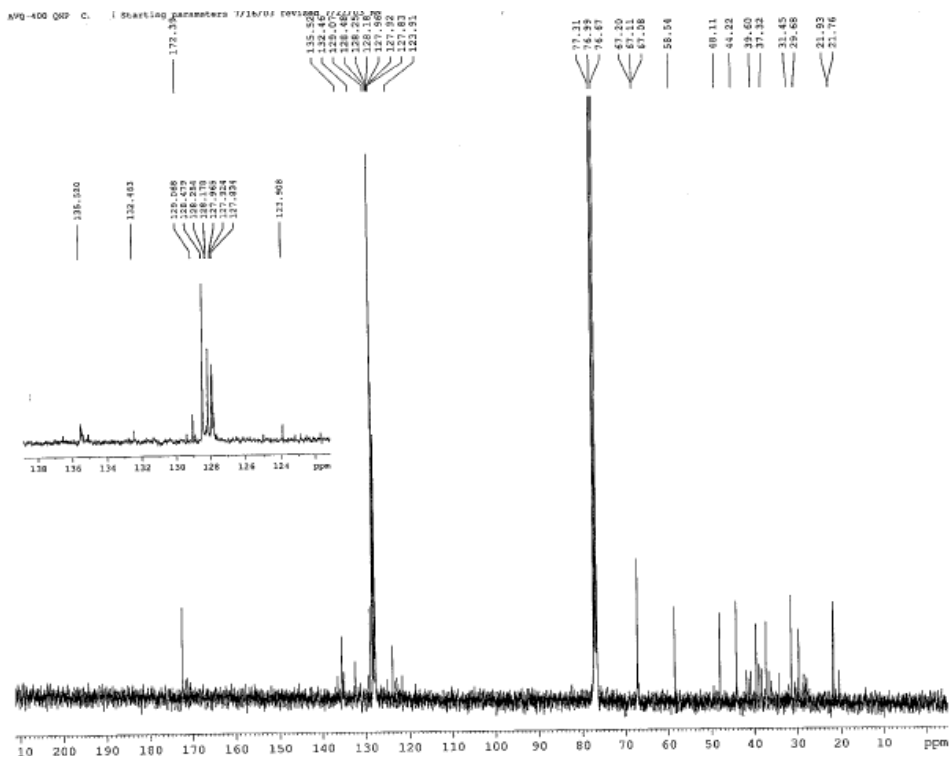
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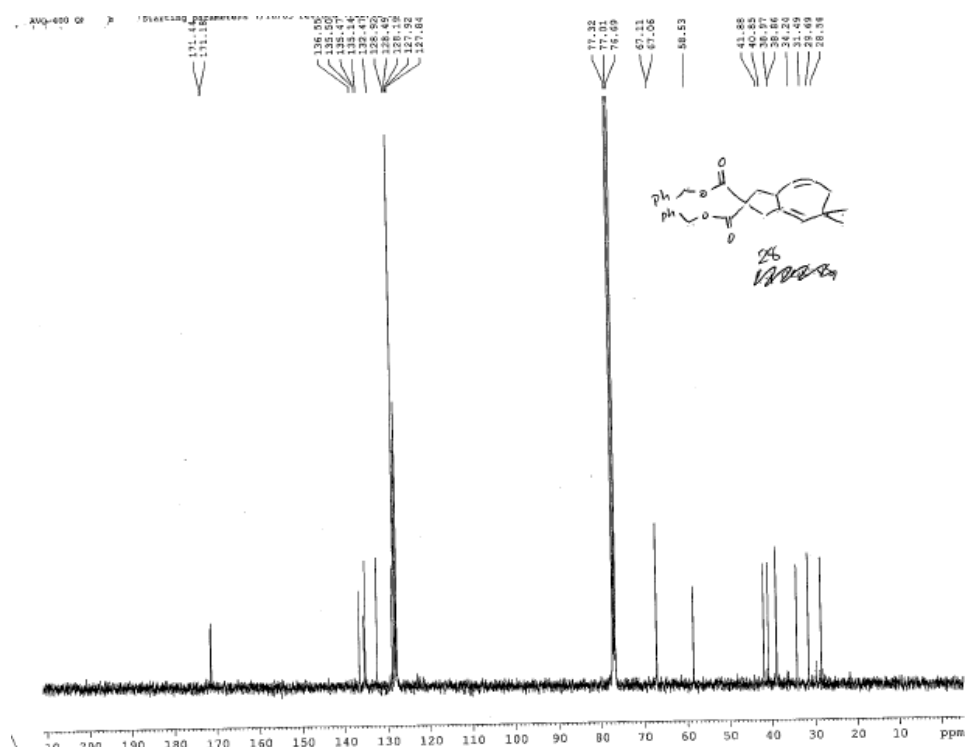
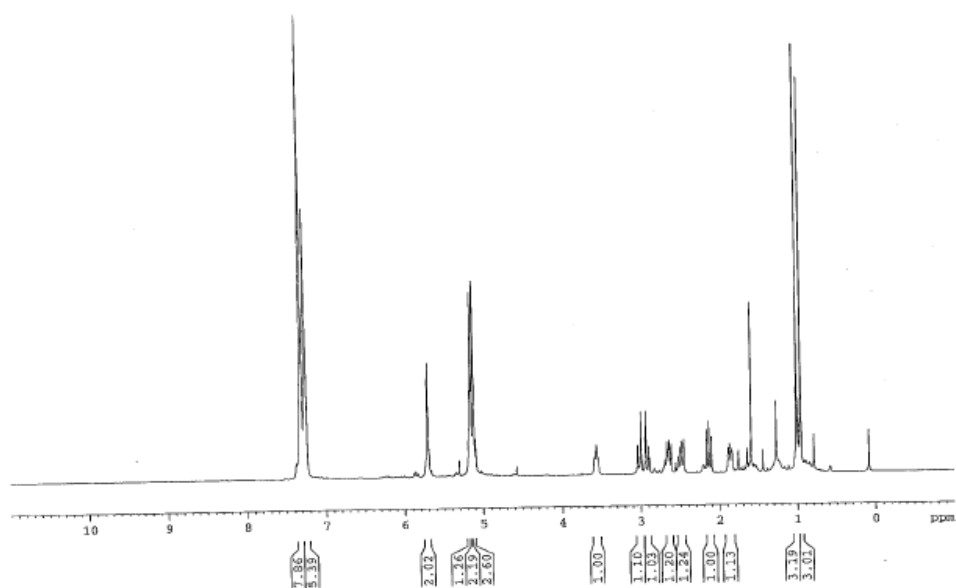
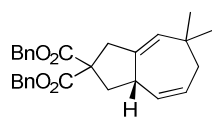


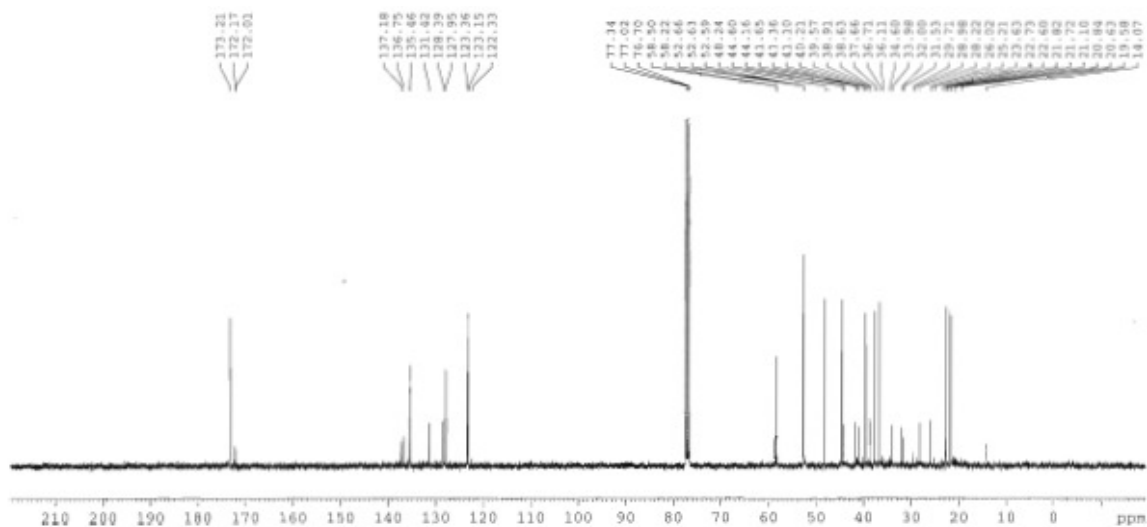
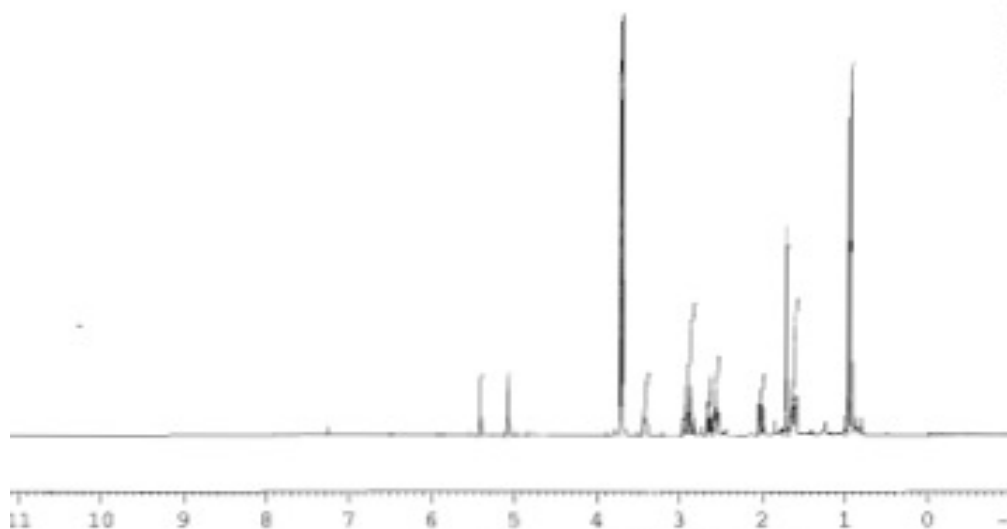
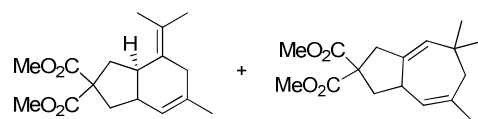


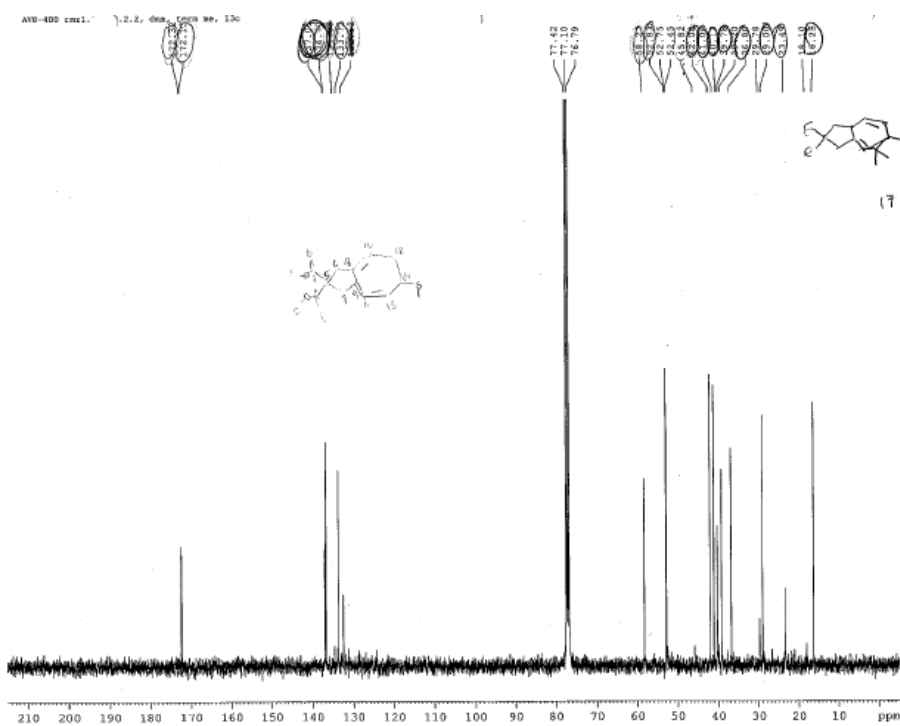
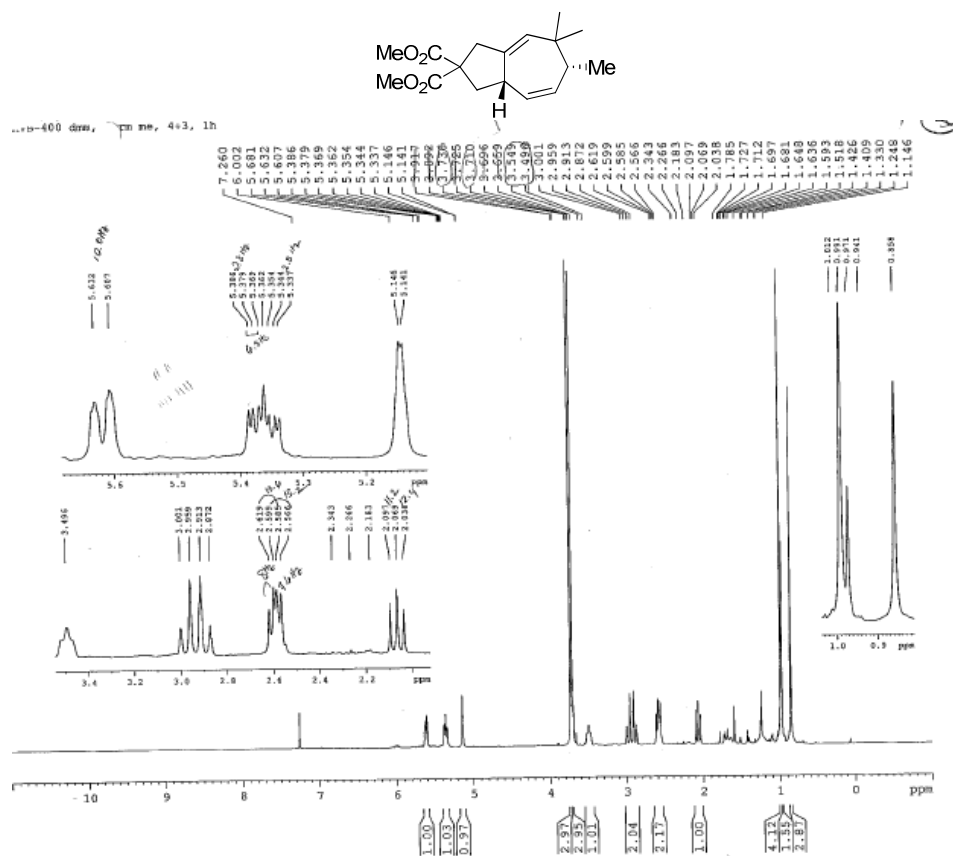


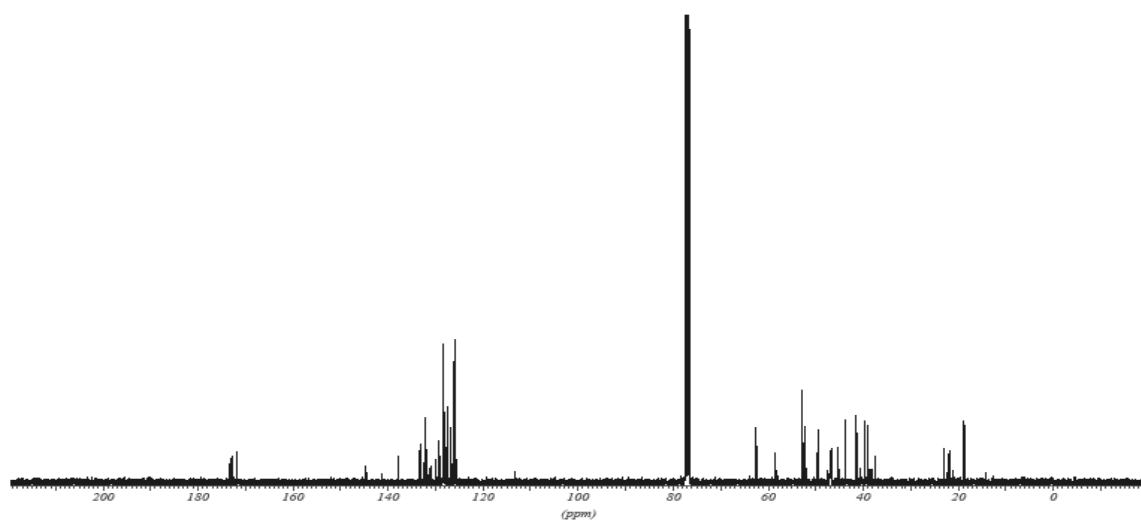
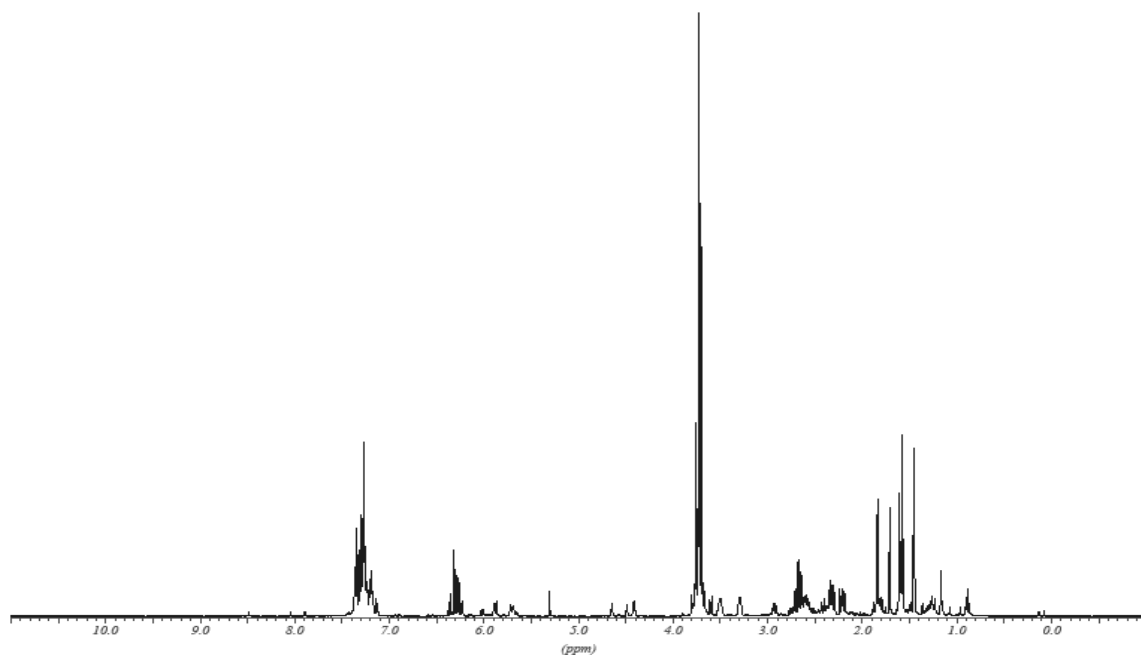
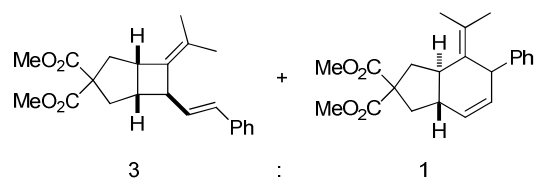


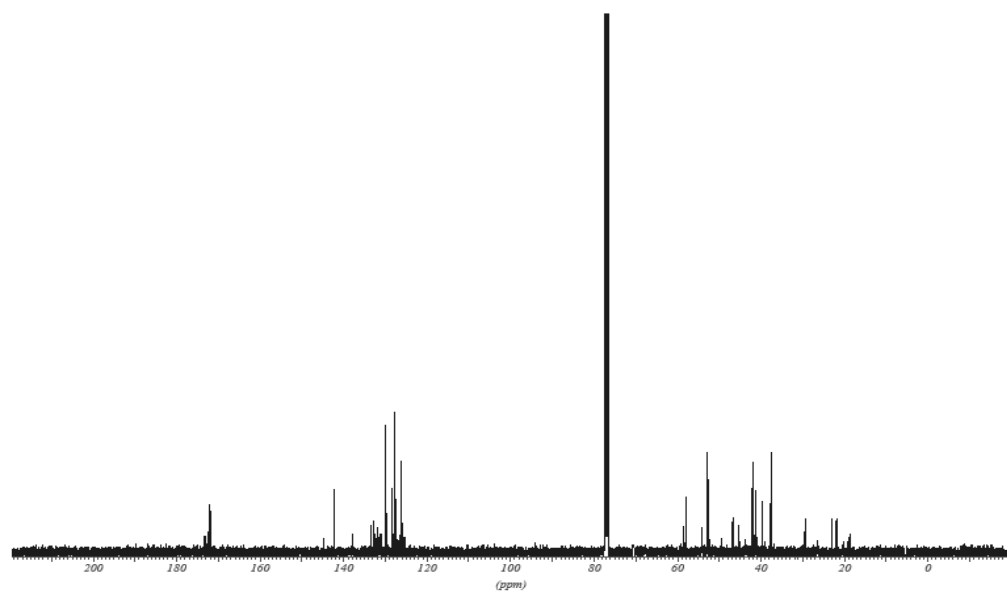
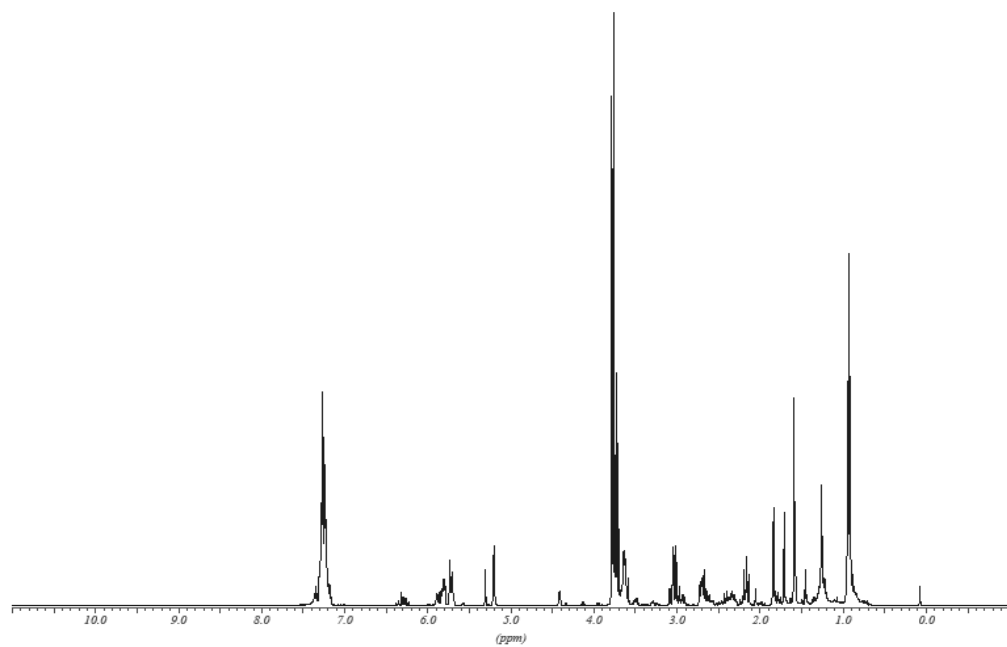
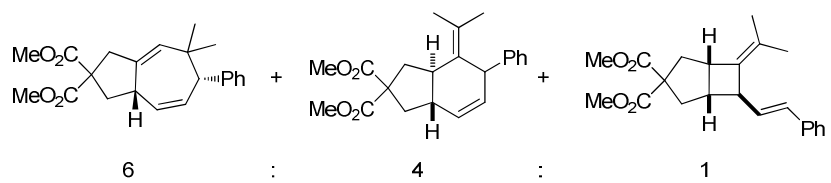


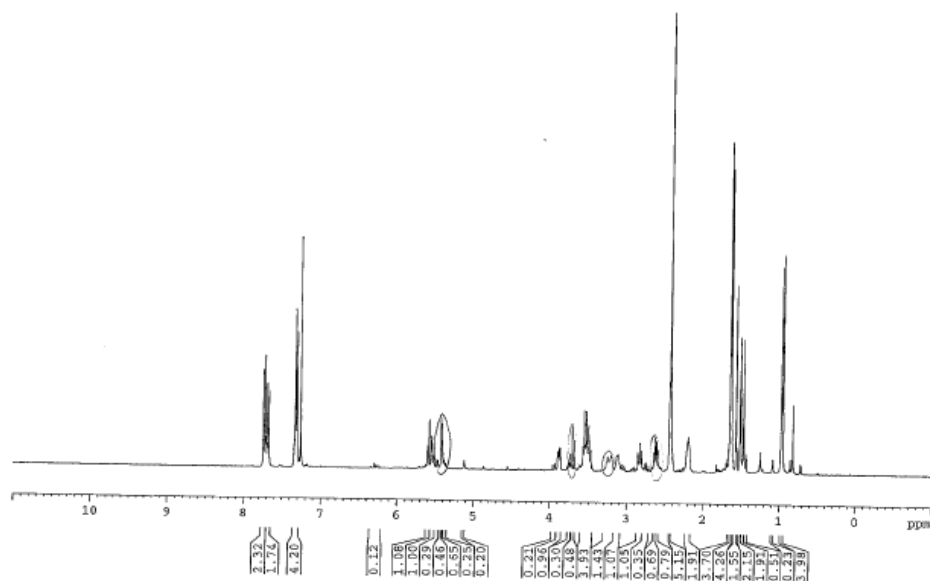
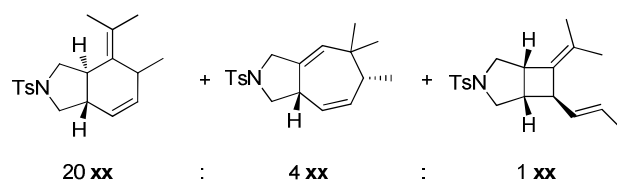


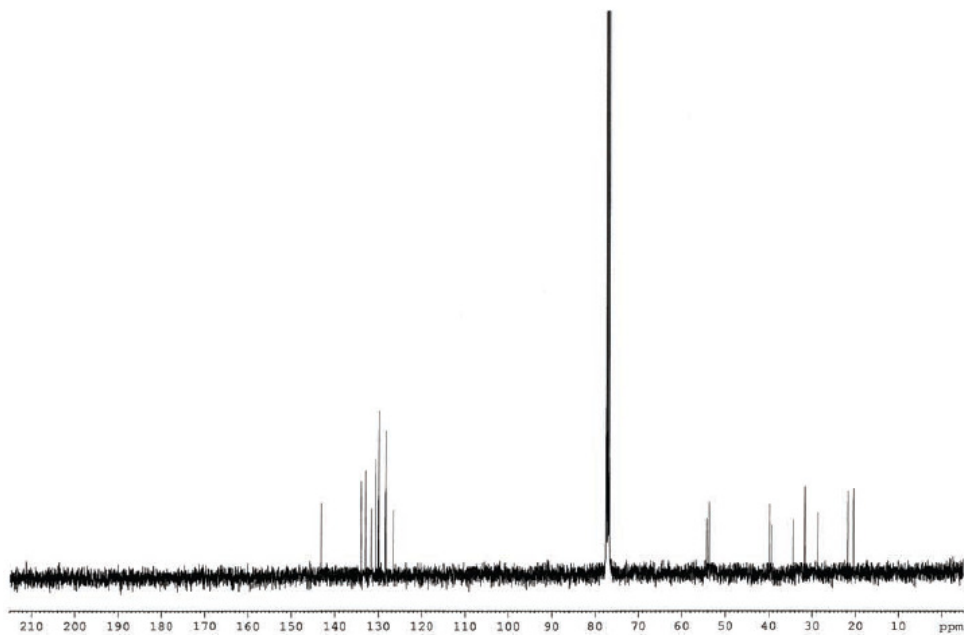
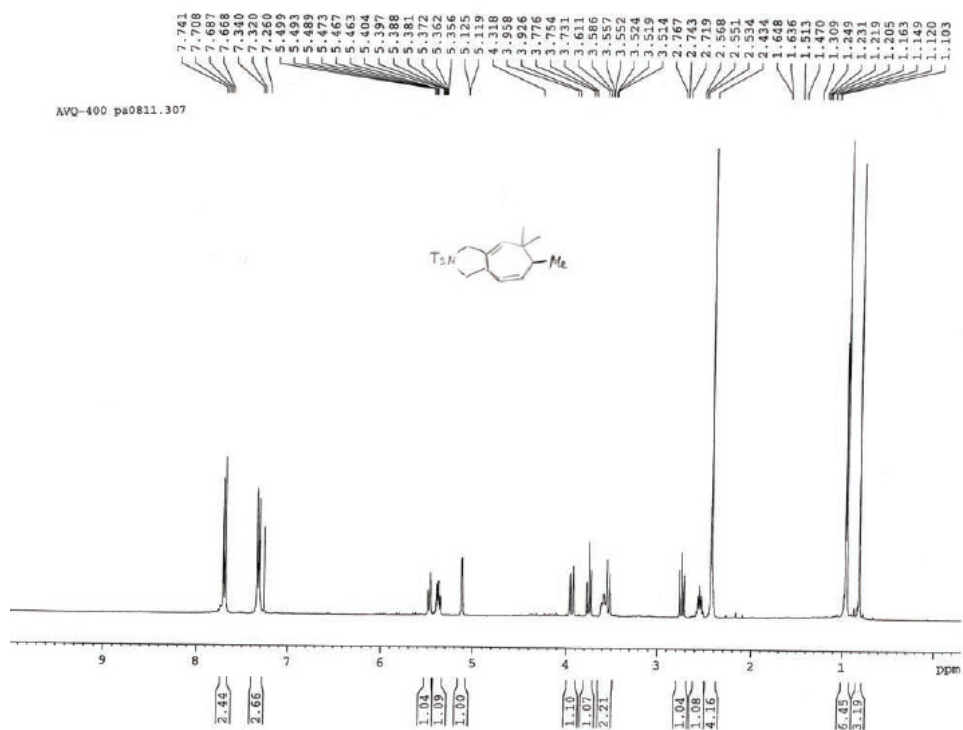
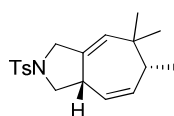


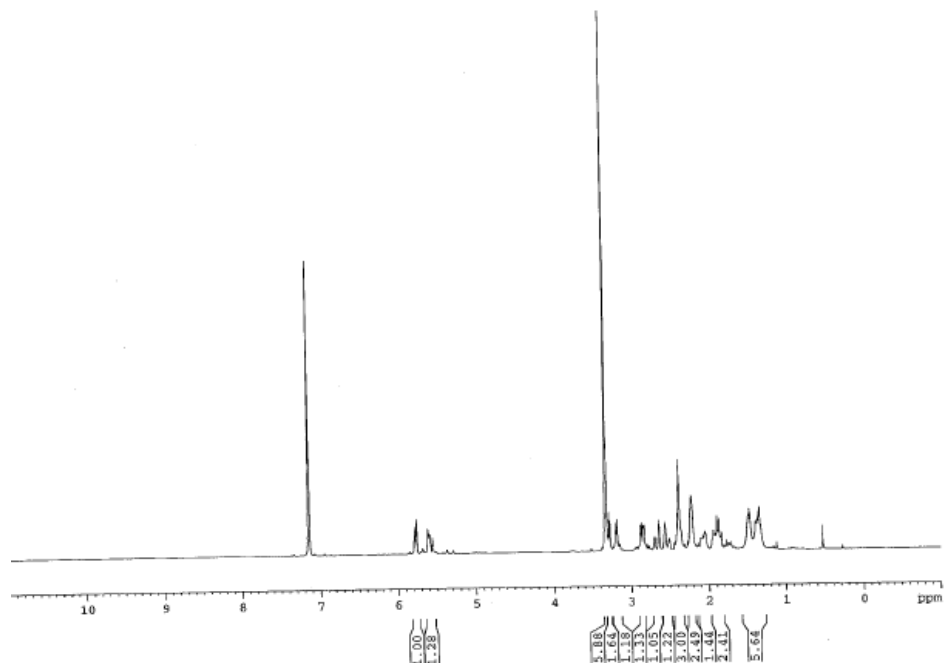
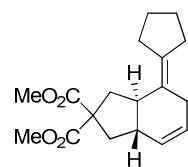


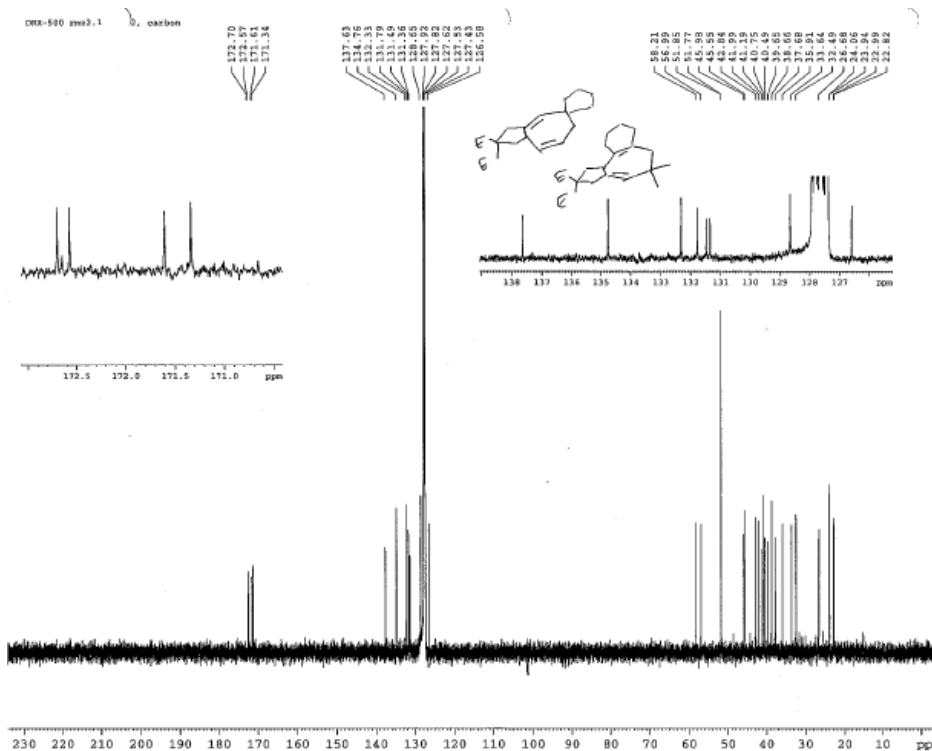
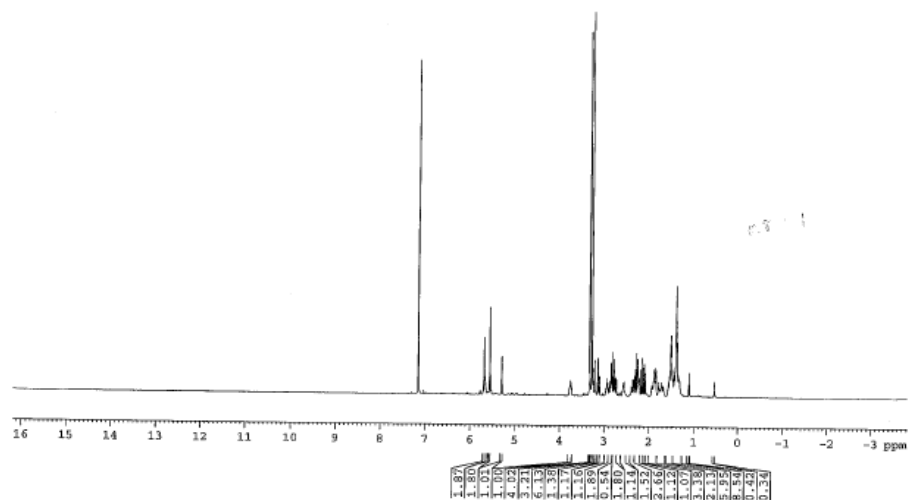
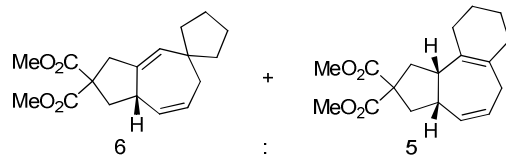


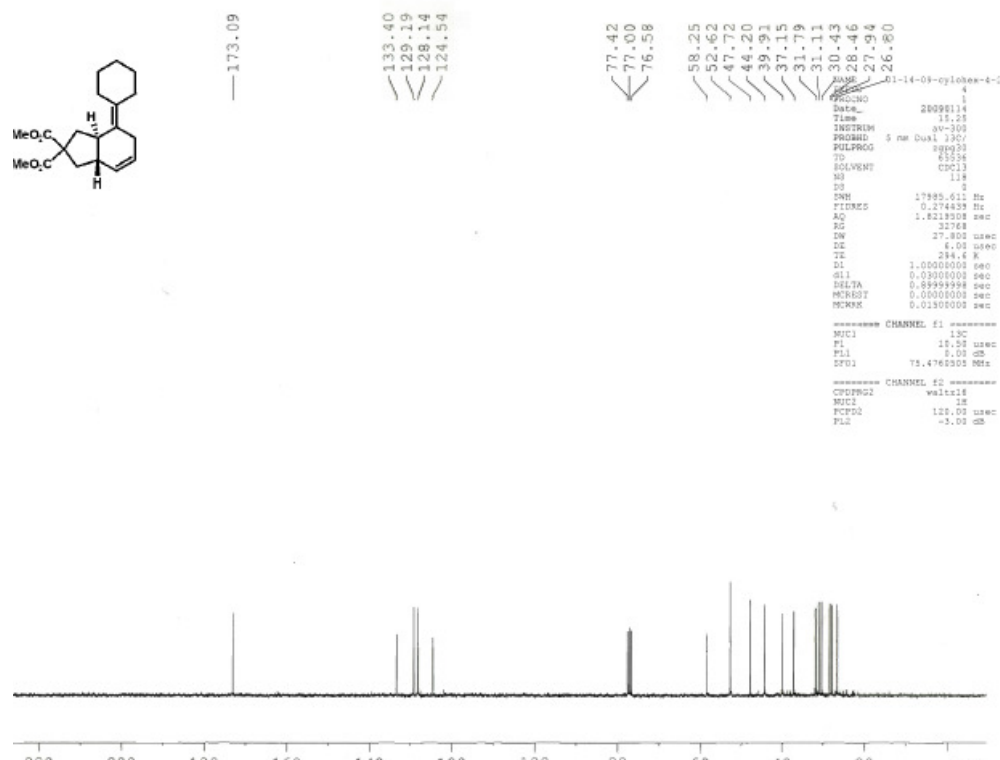
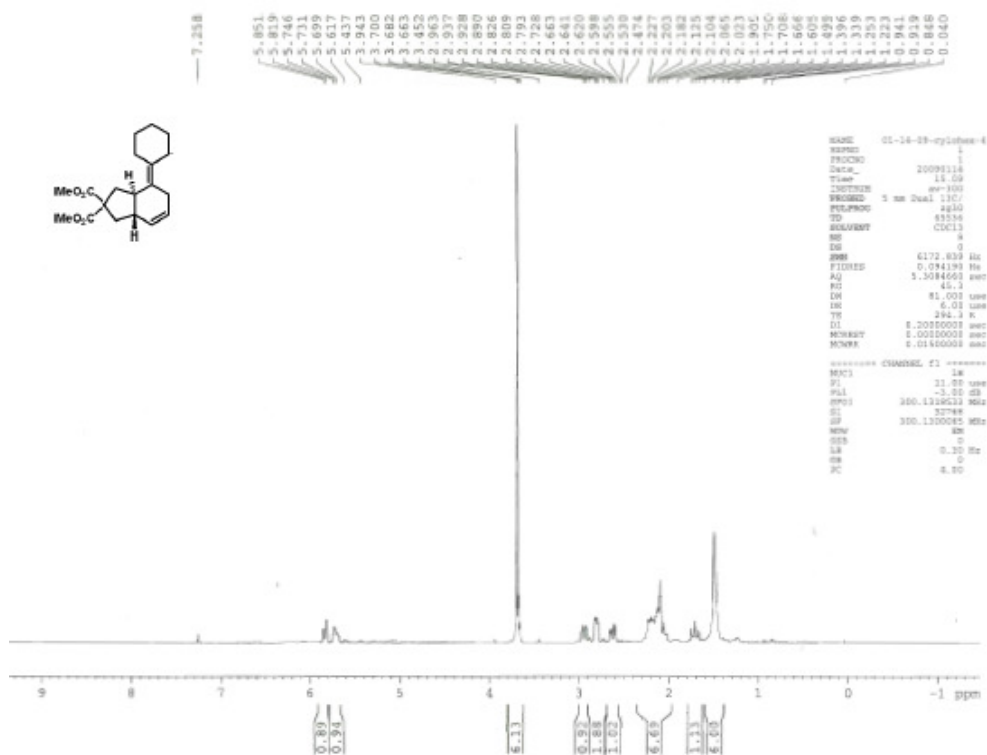


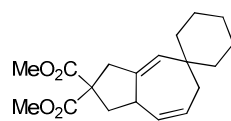




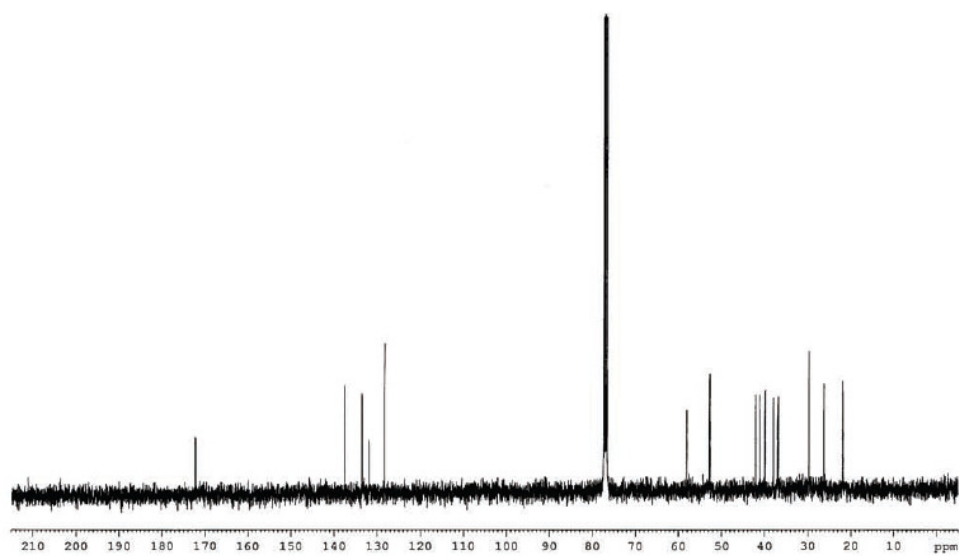
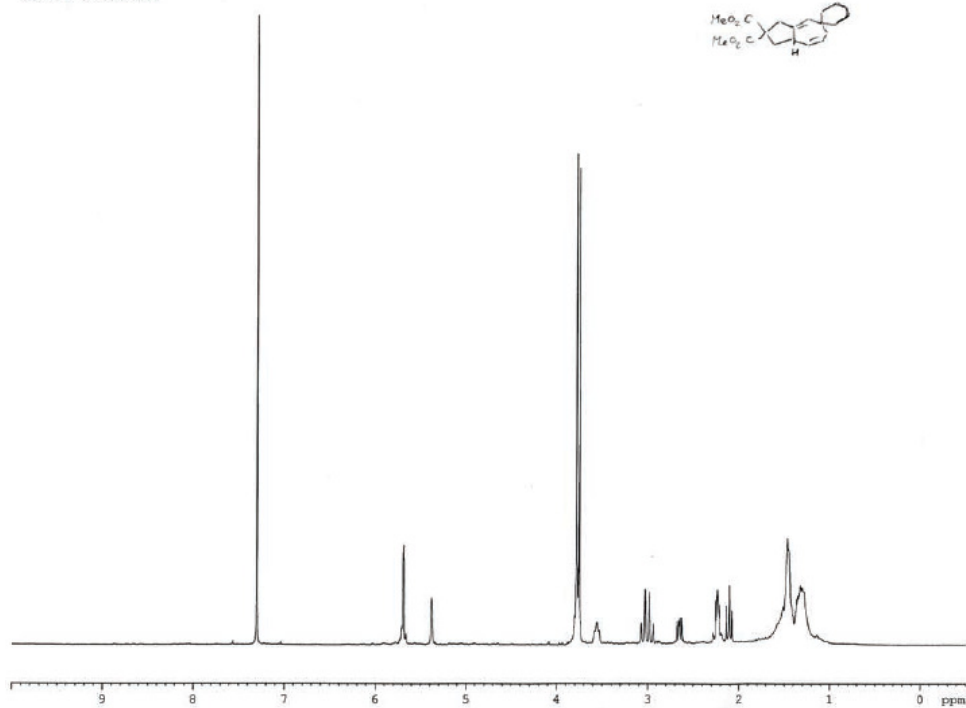
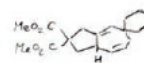


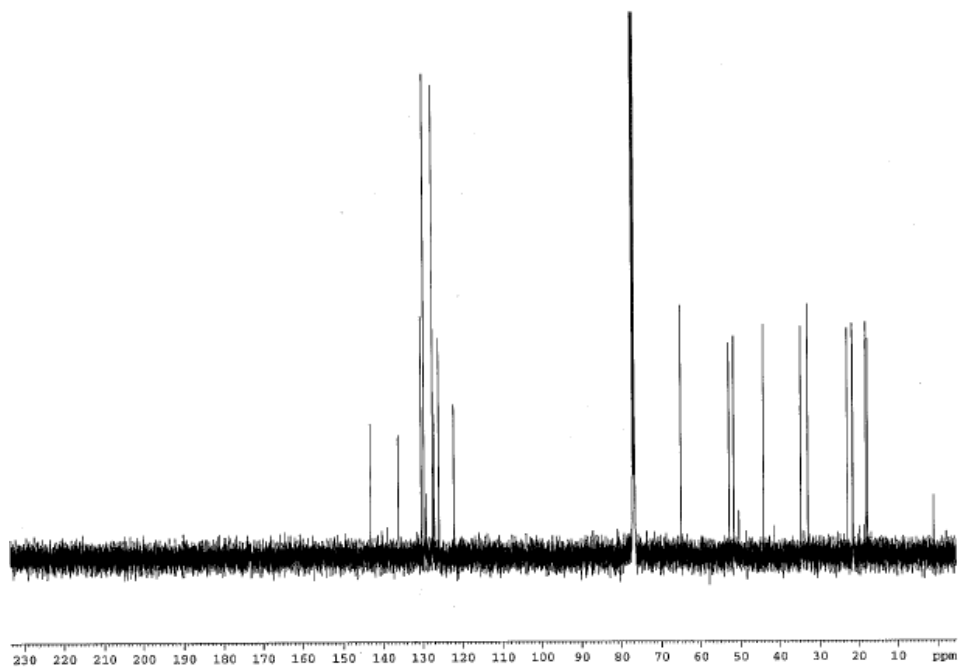
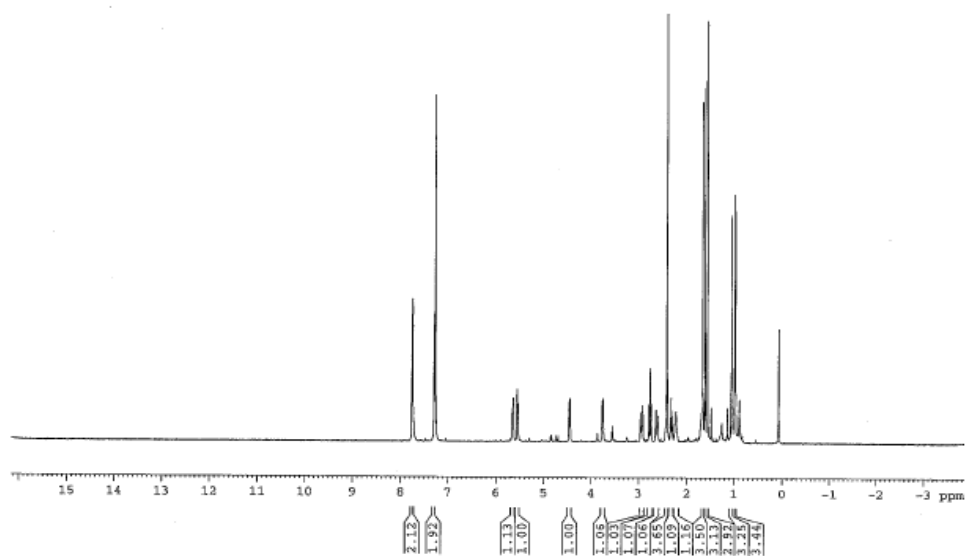
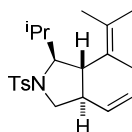


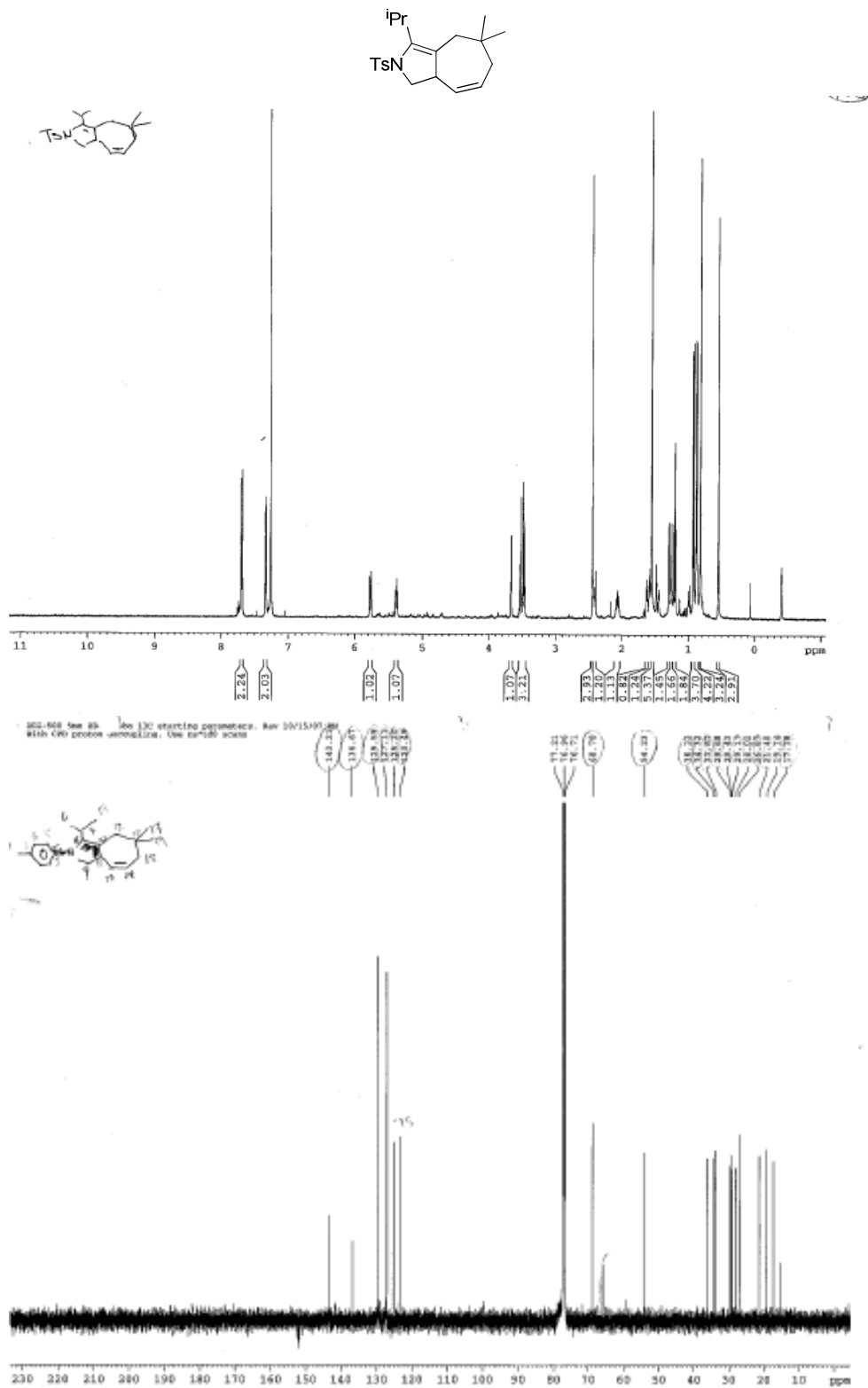


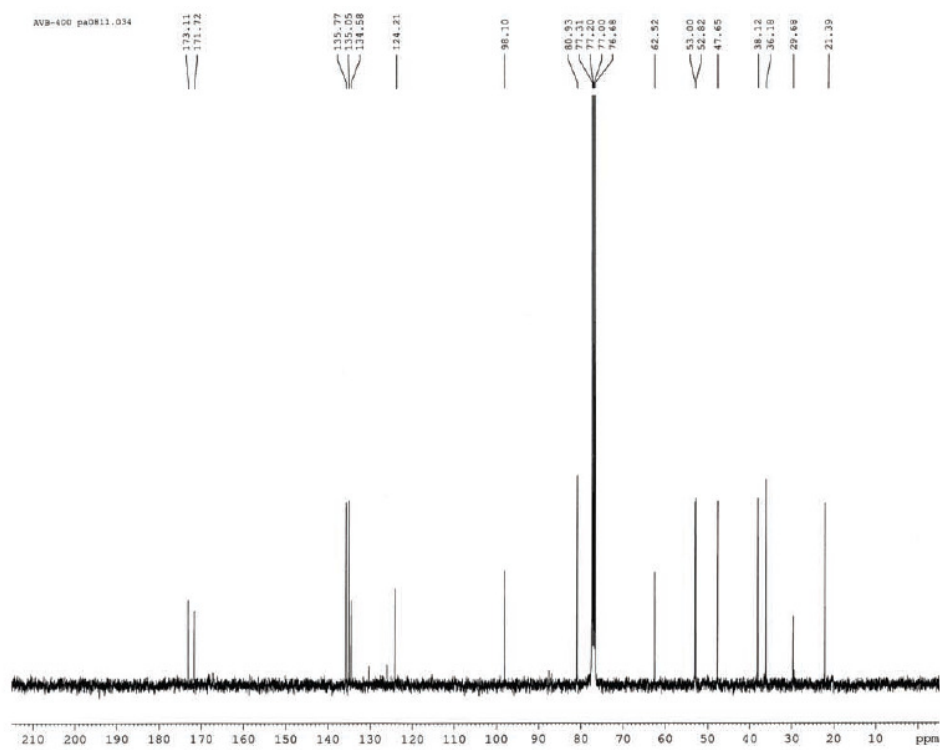
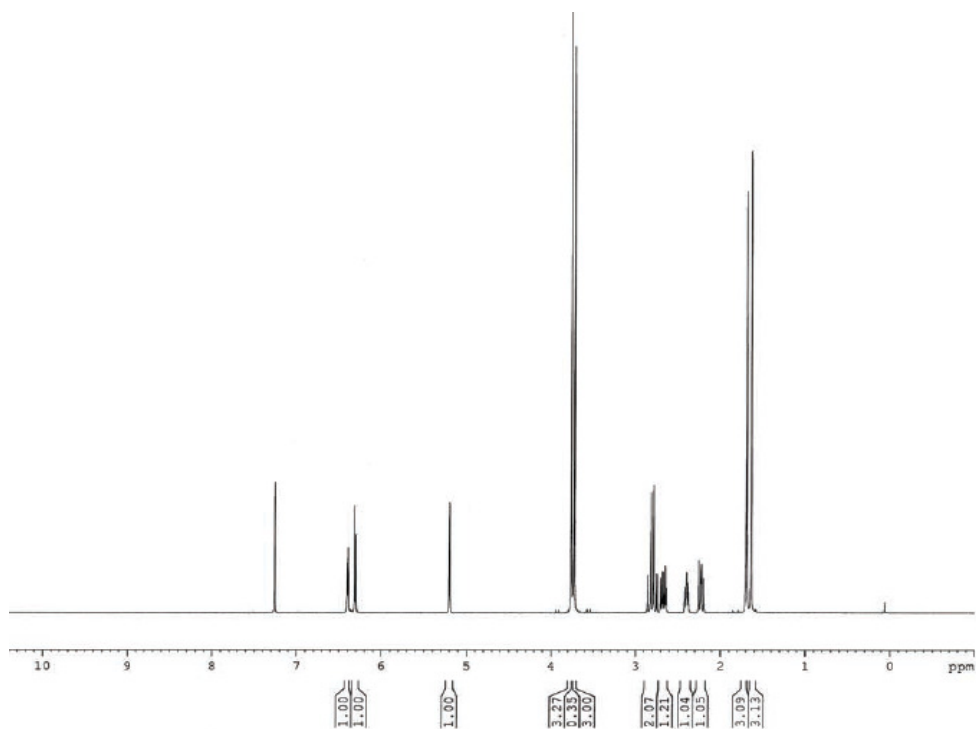
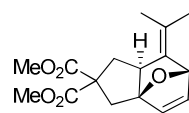


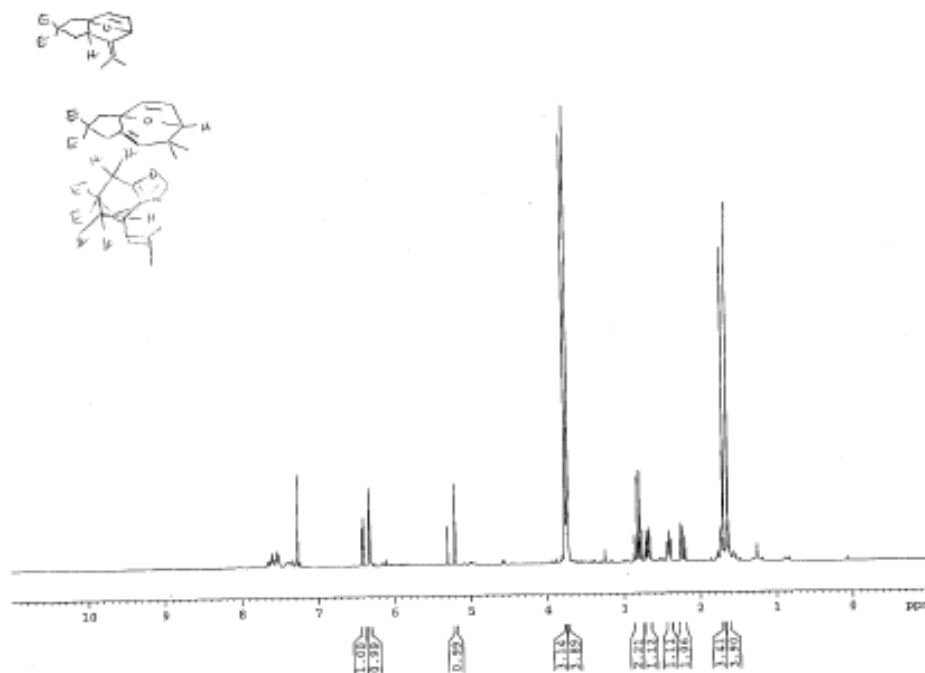
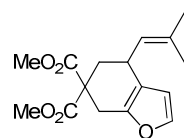
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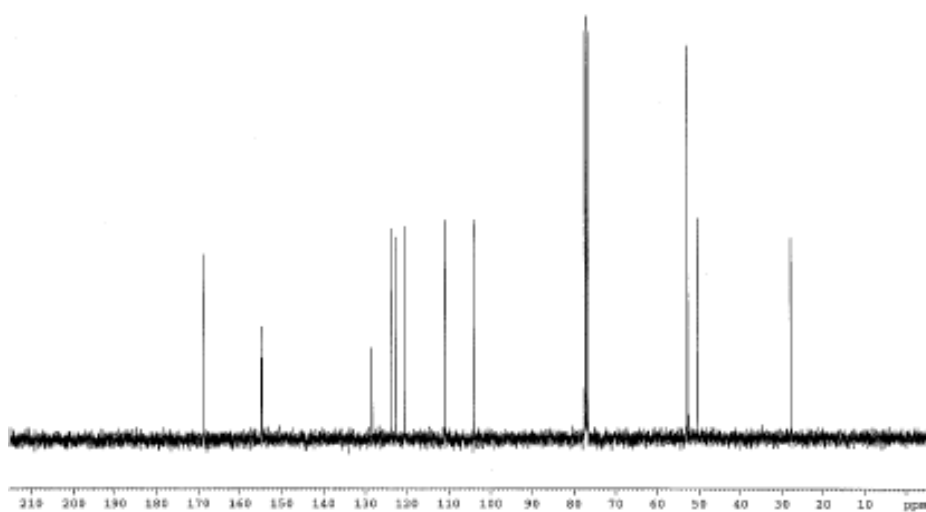
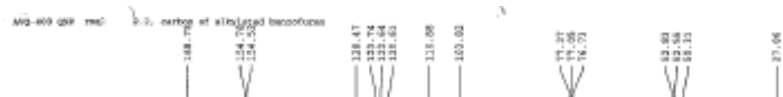
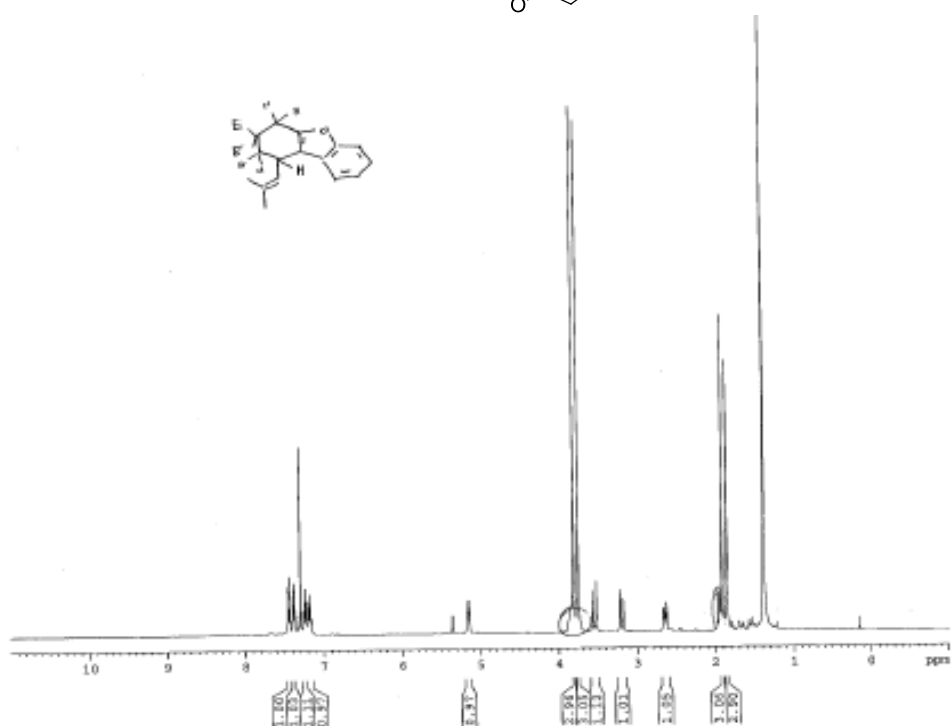
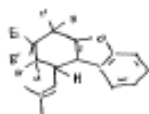
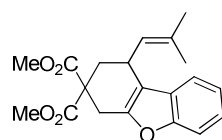




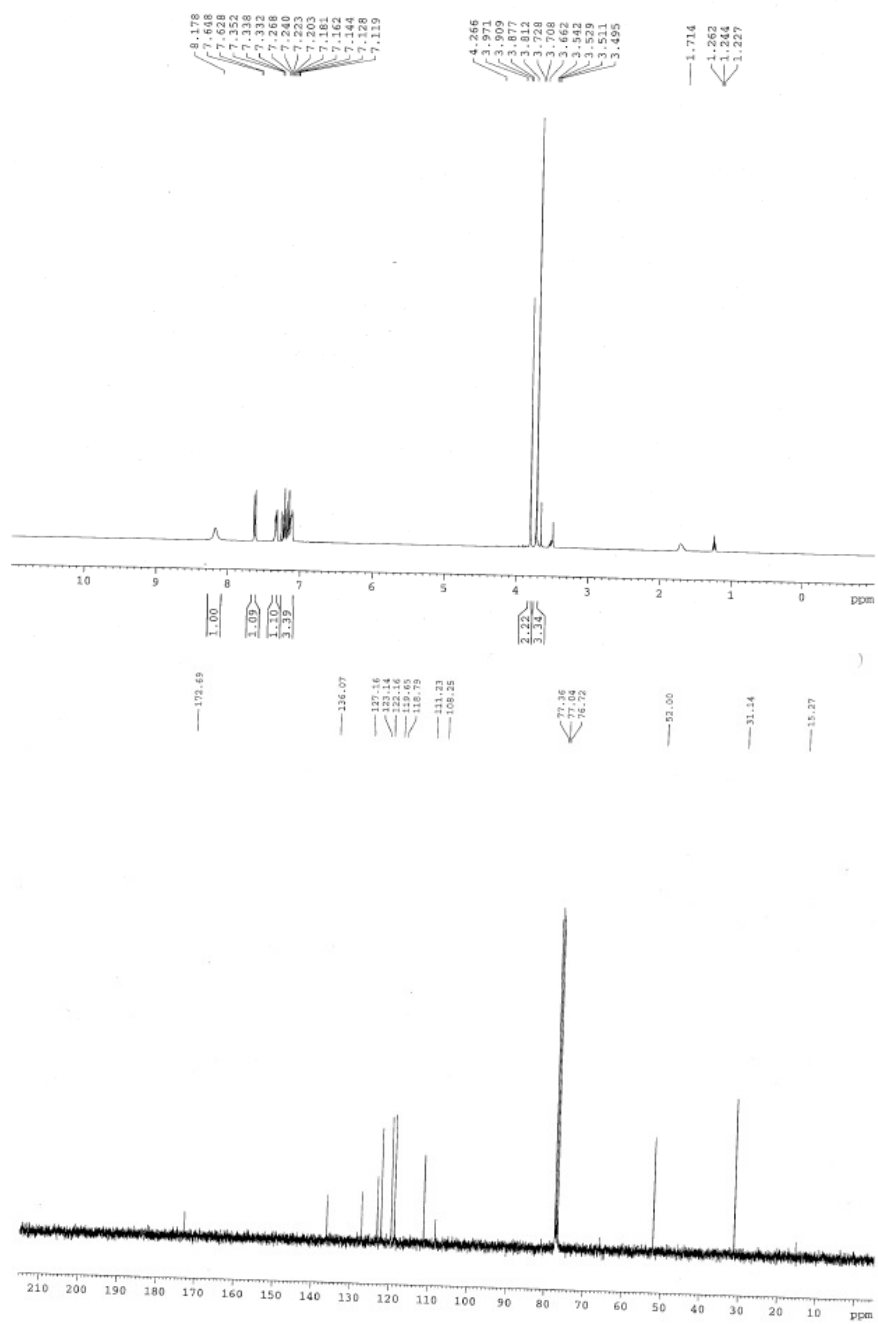
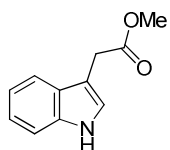


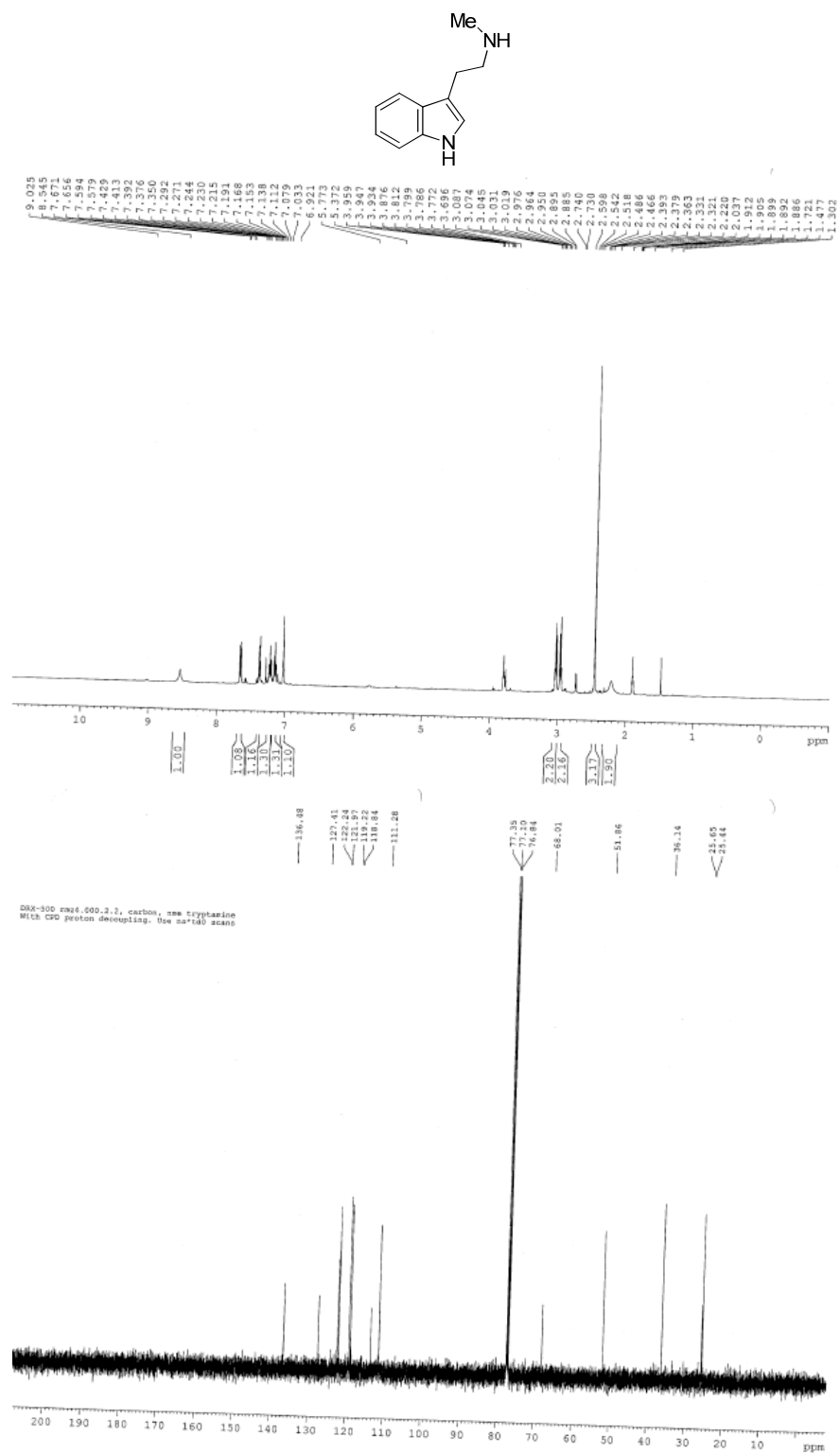


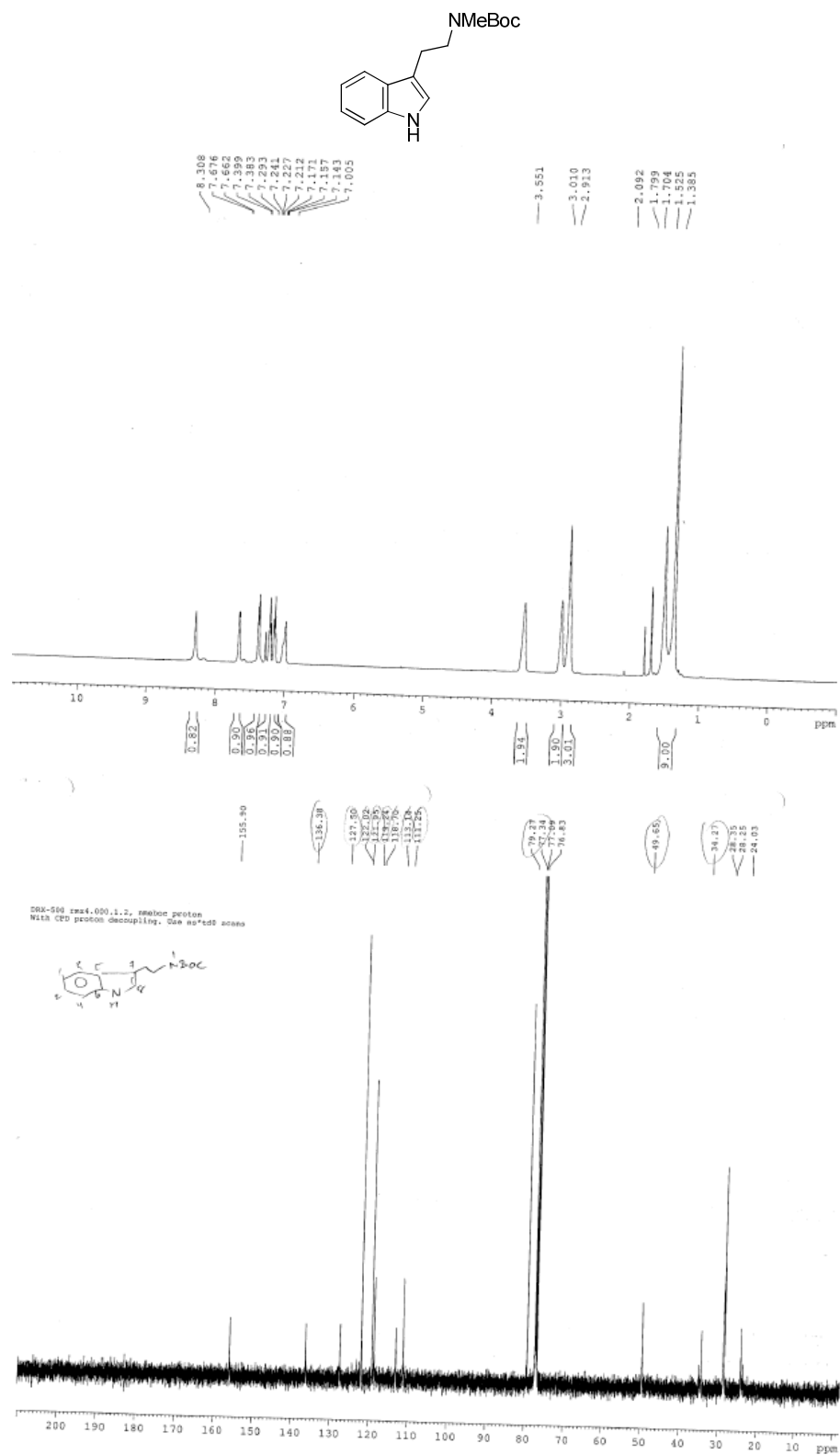


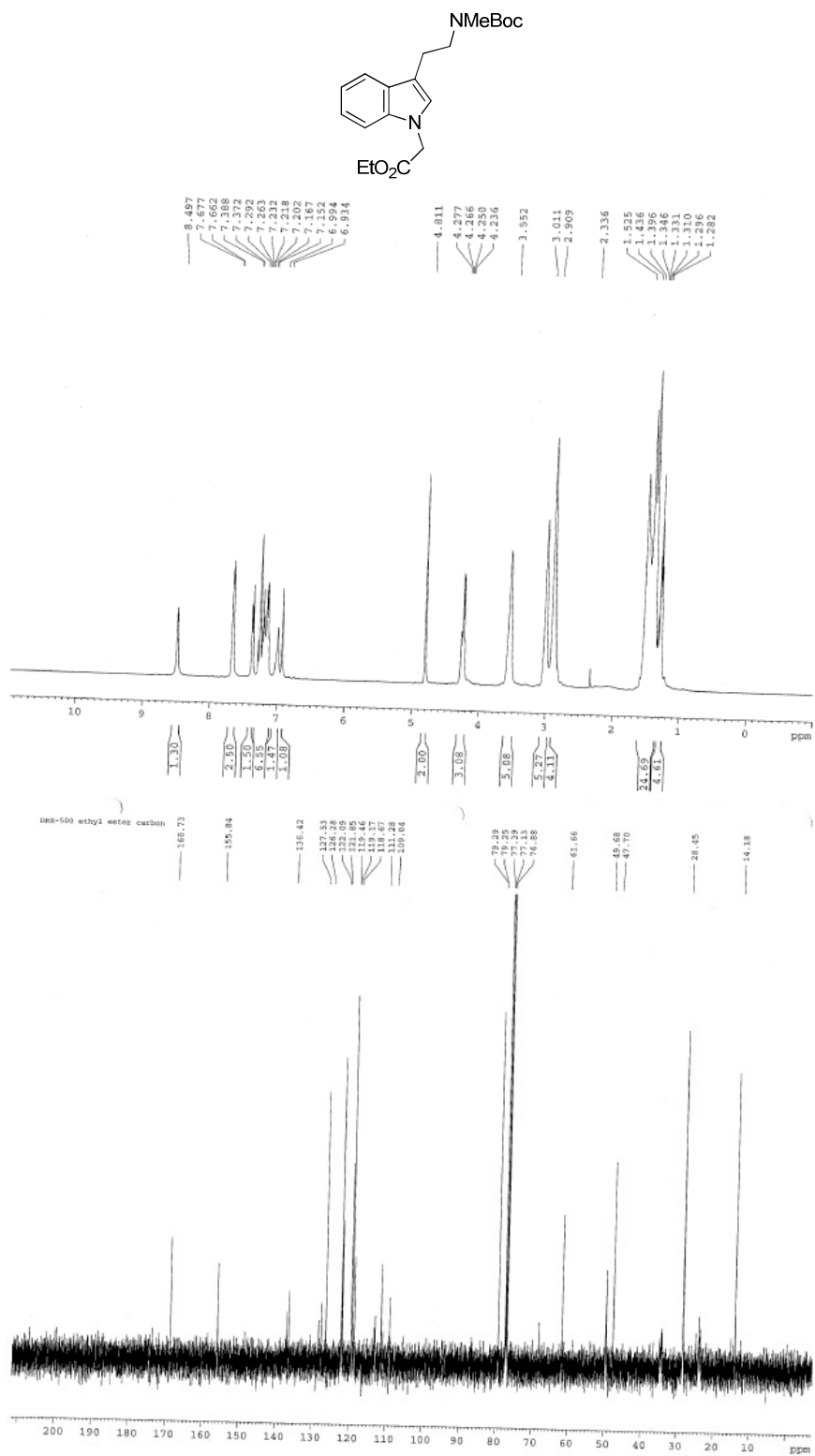


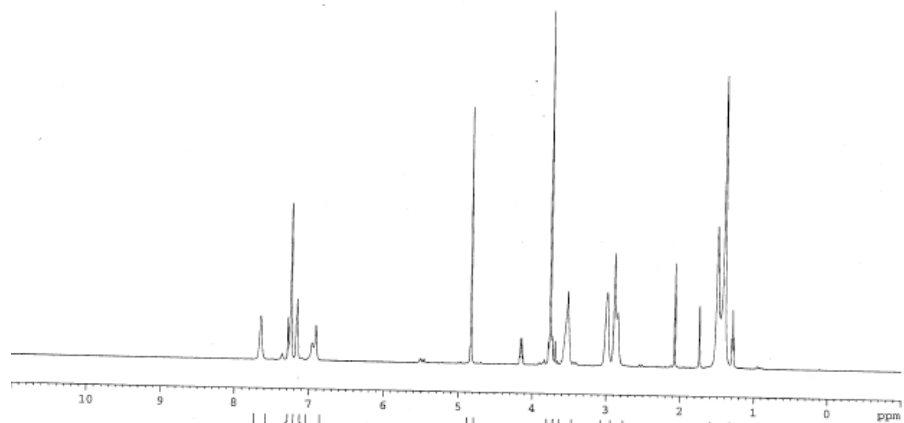
Appendix 2 – Additional Supporting Information for Chapter 3 (NMR Spectra)

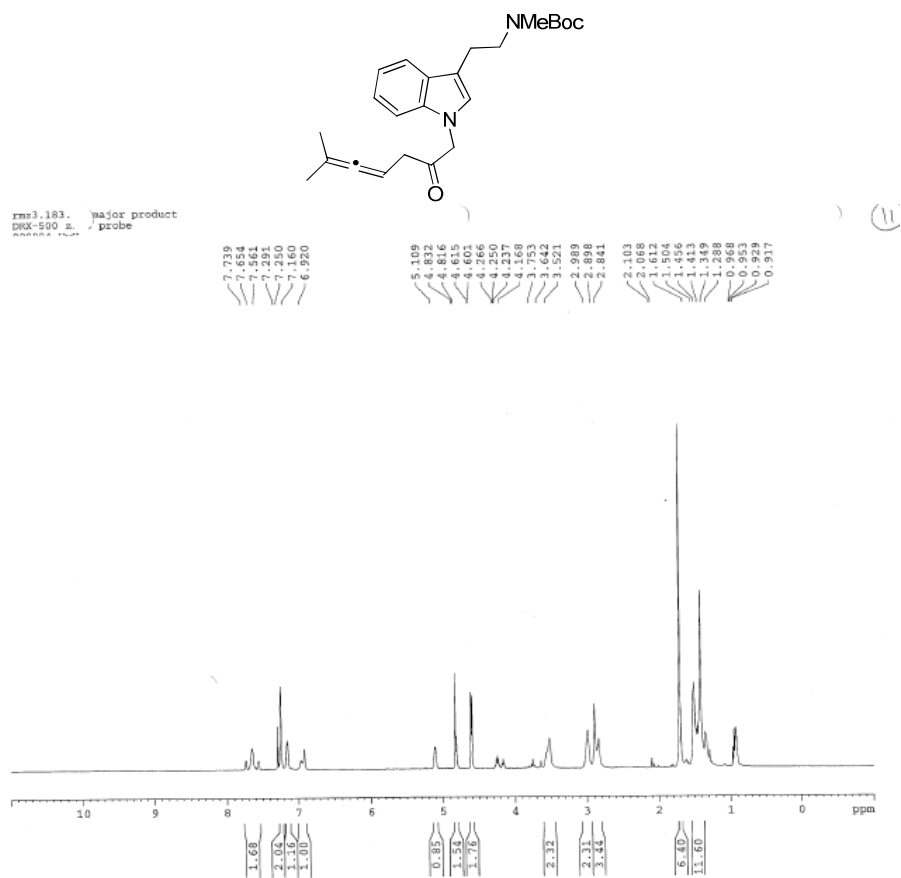


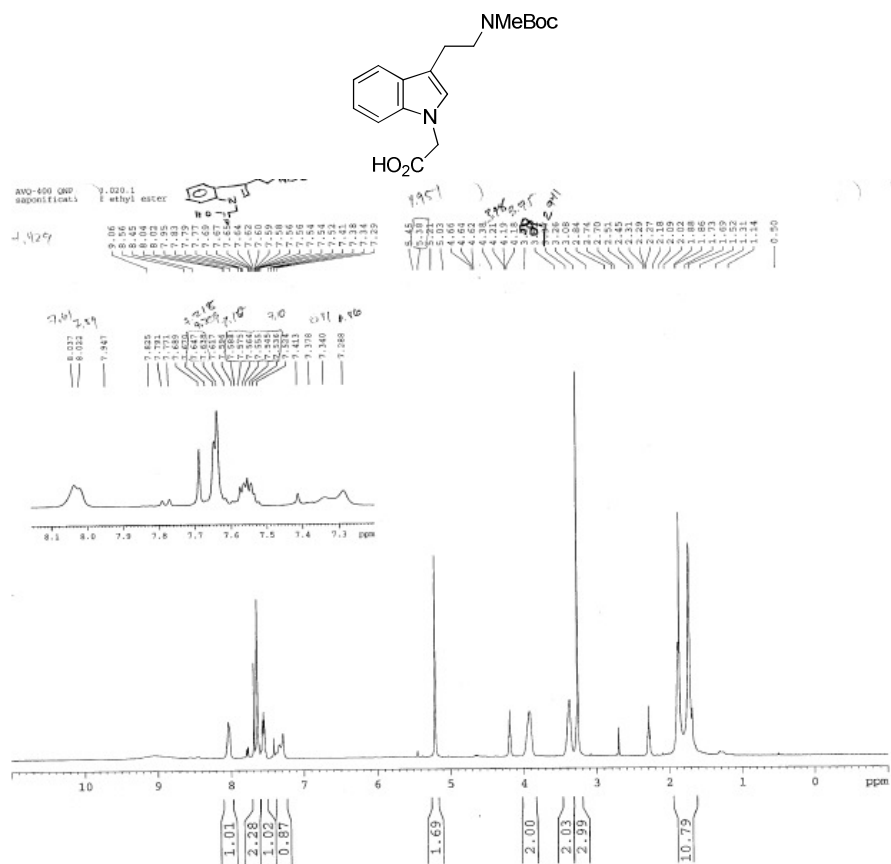


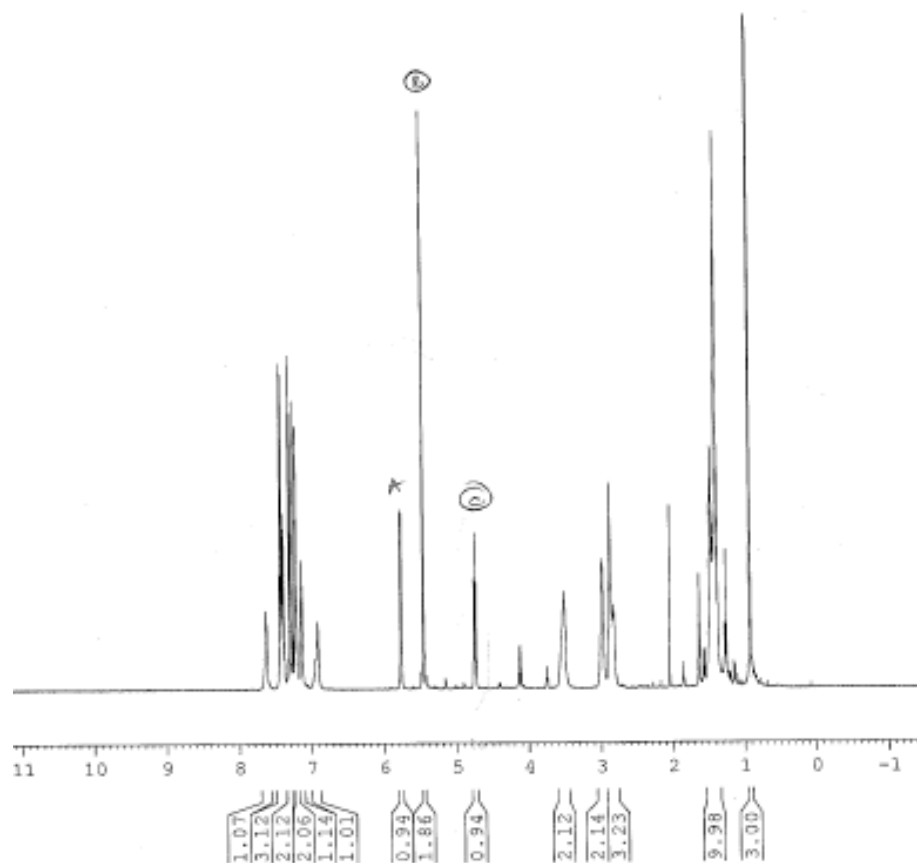
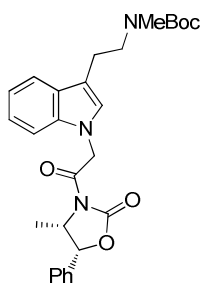


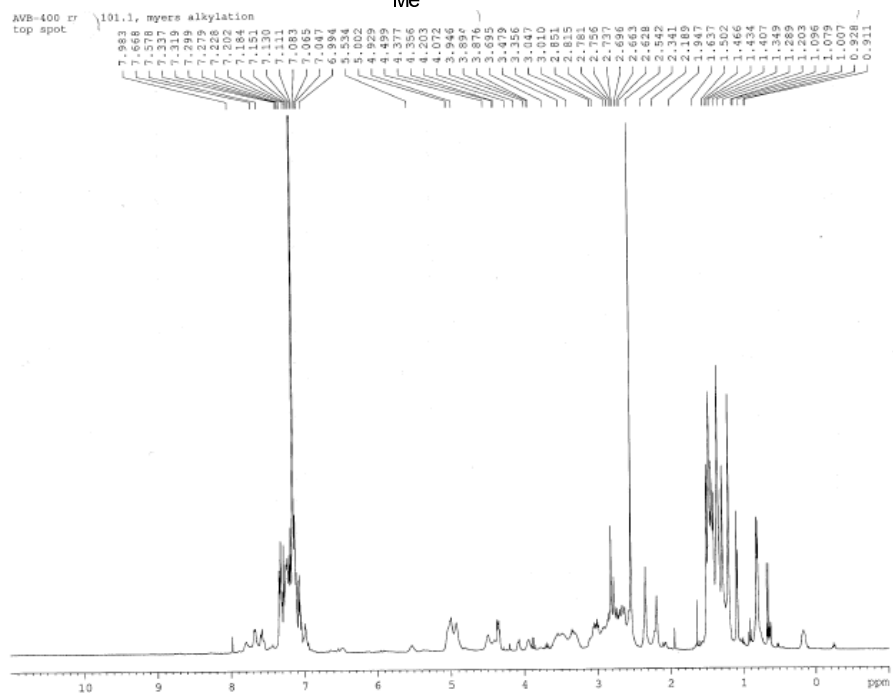


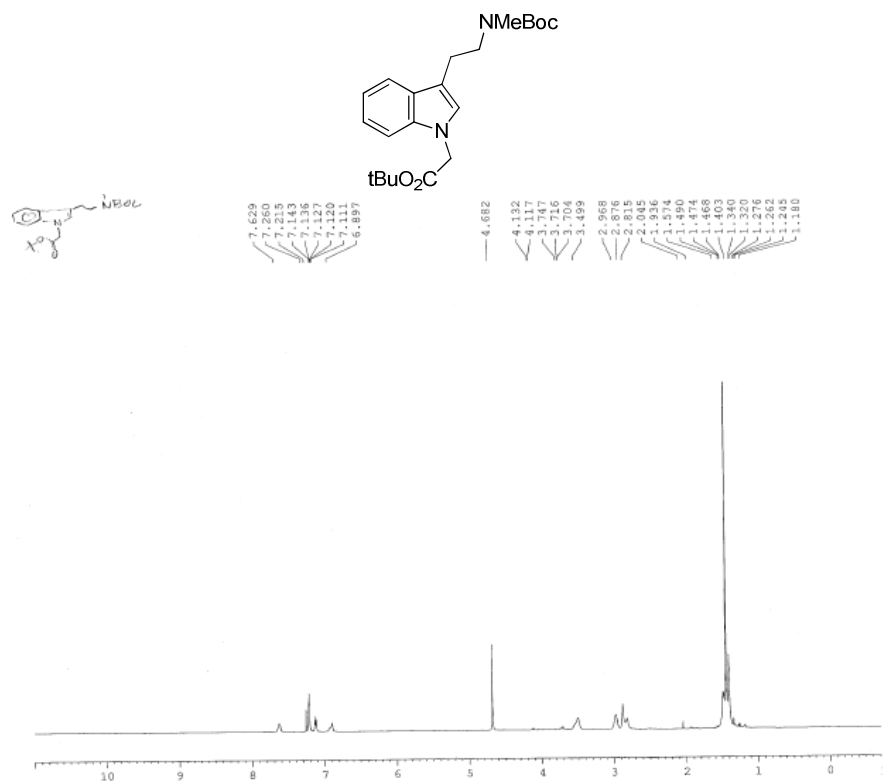


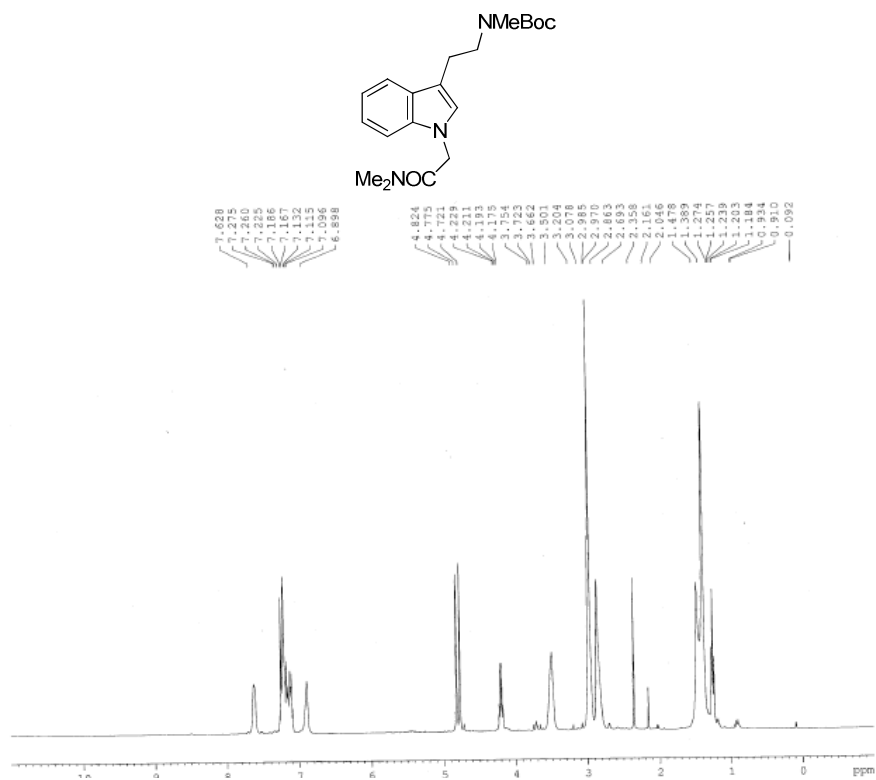


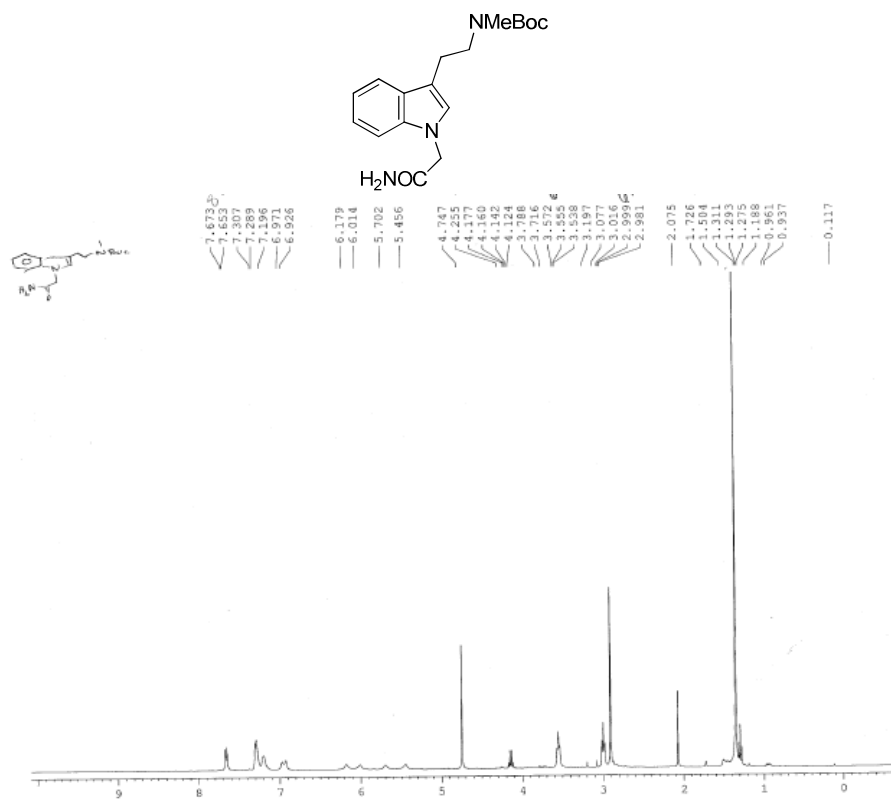


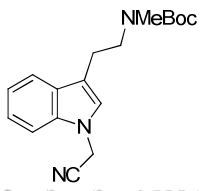


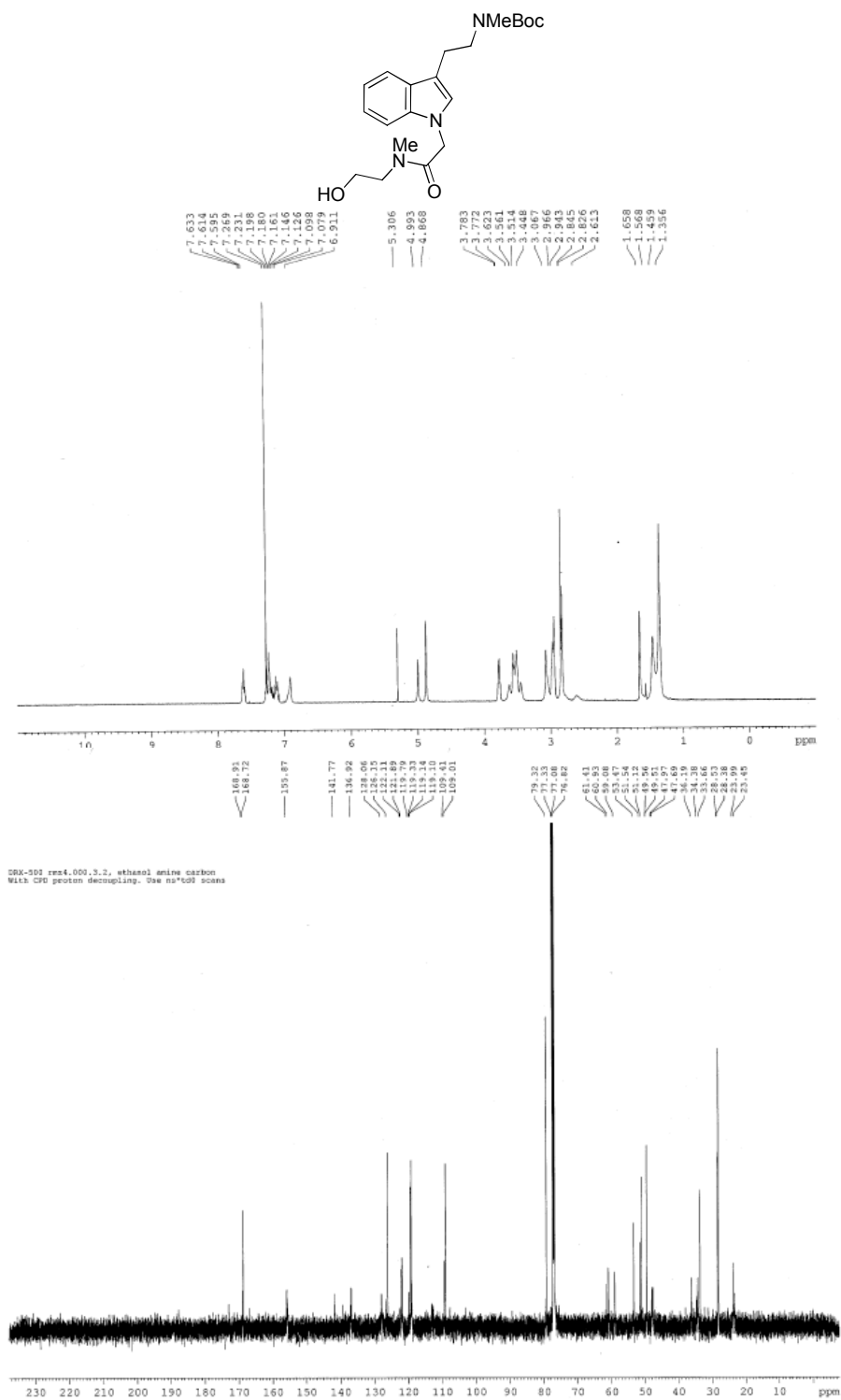


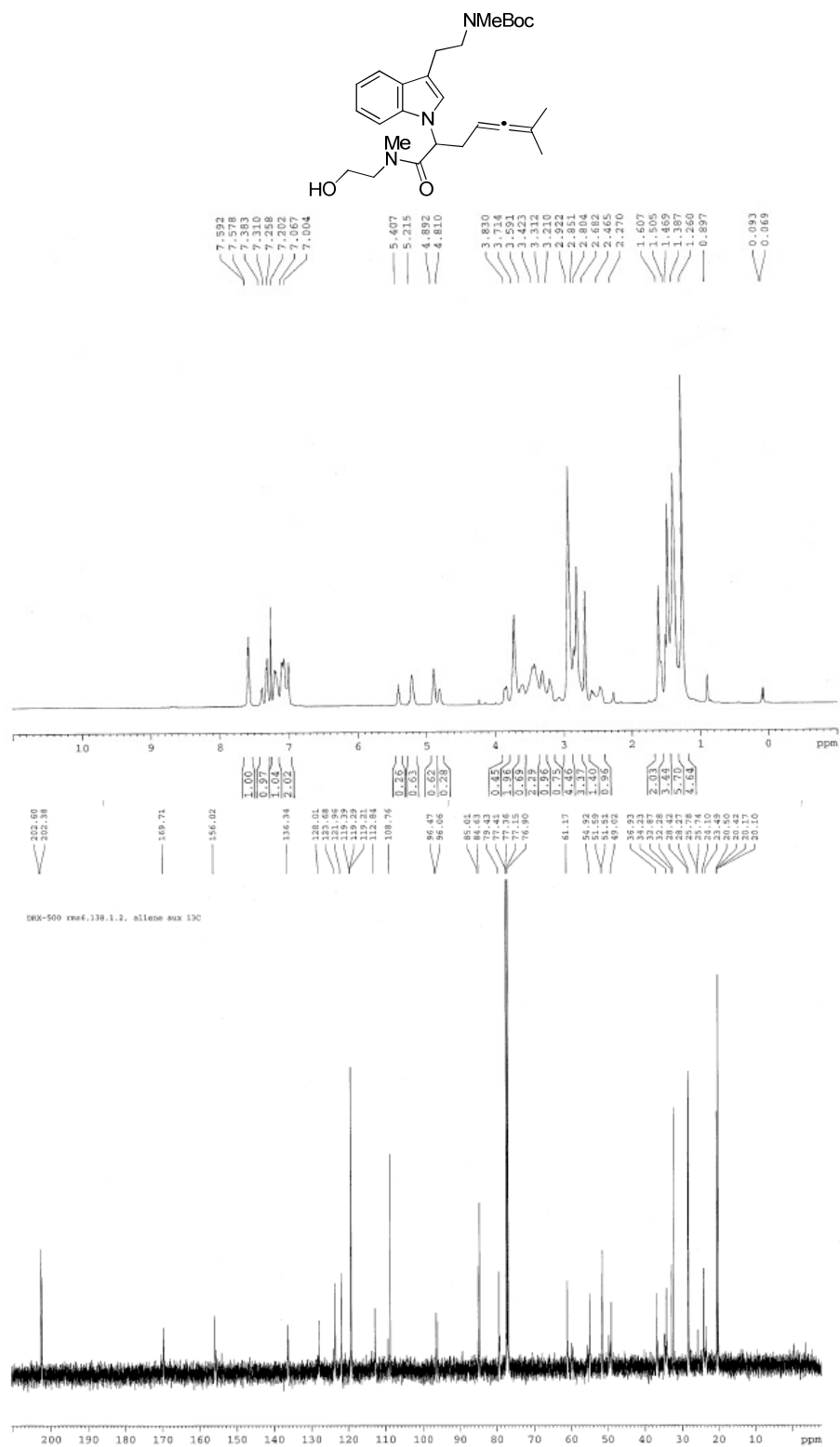


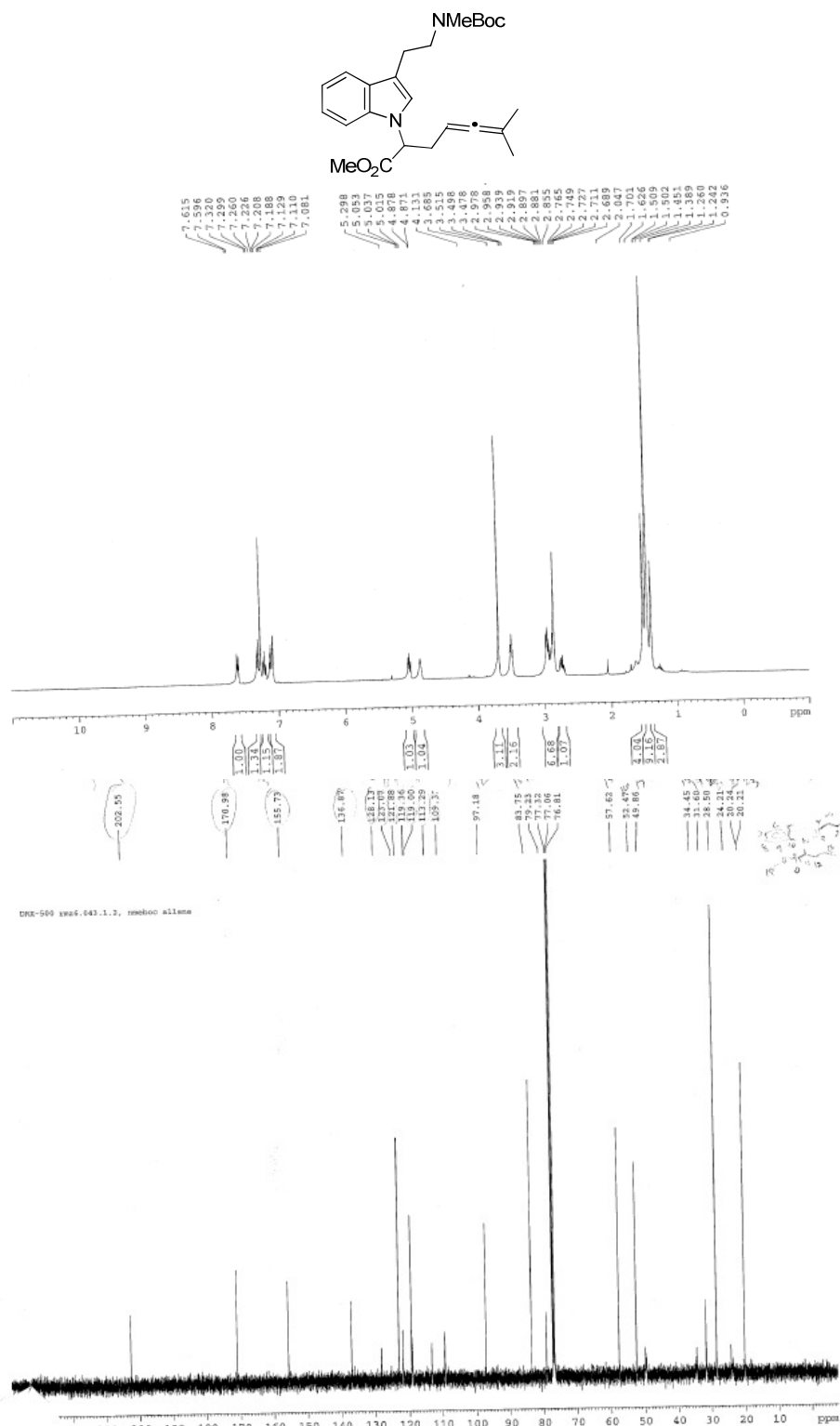


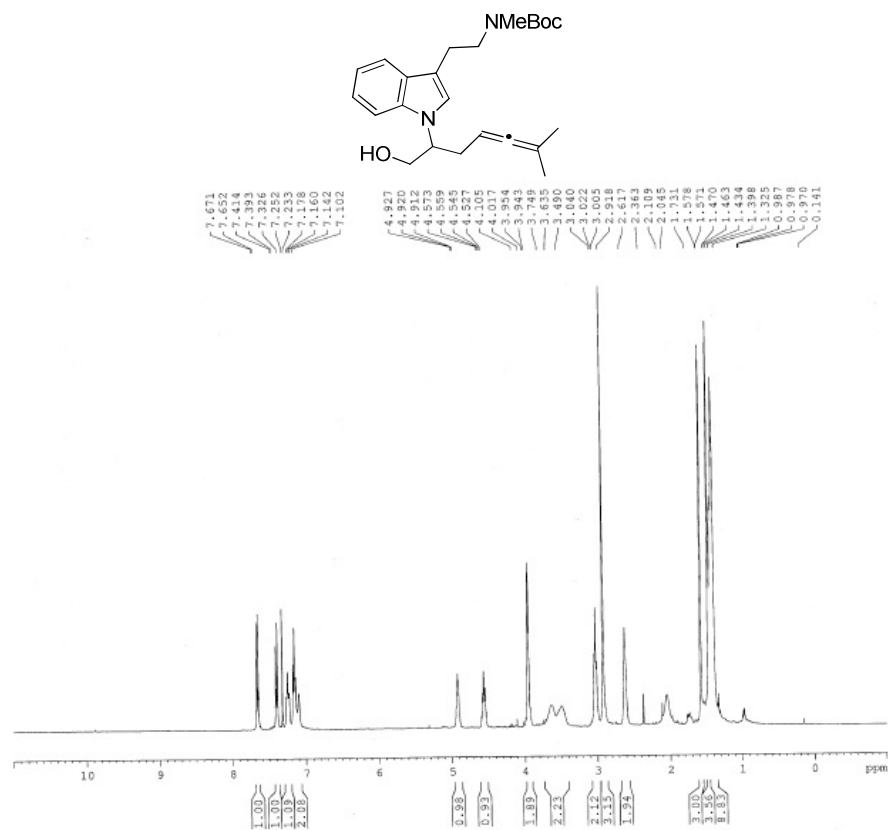


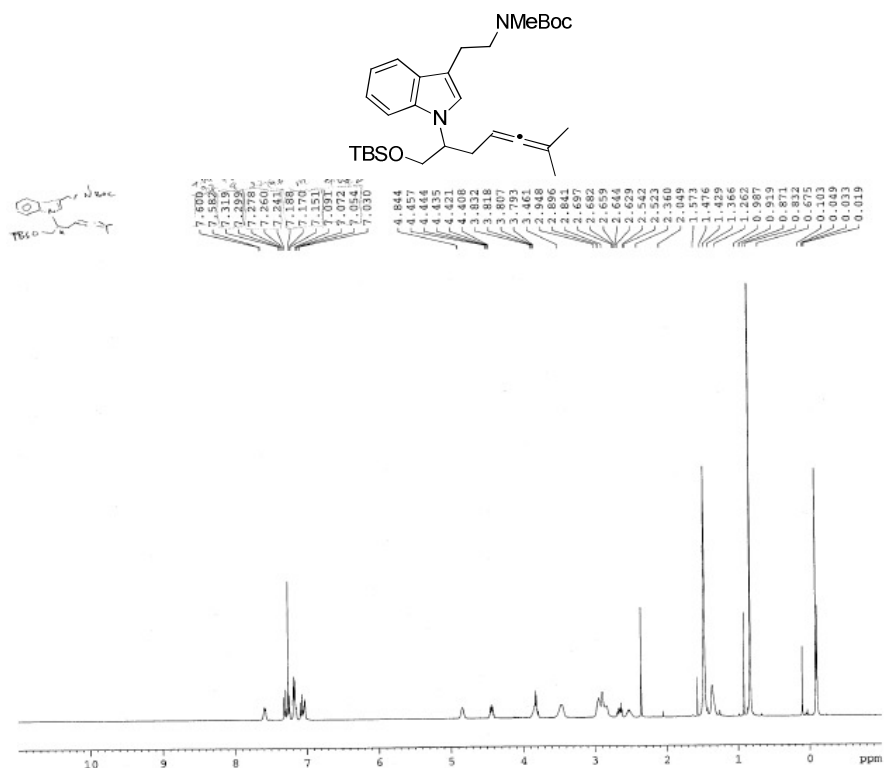






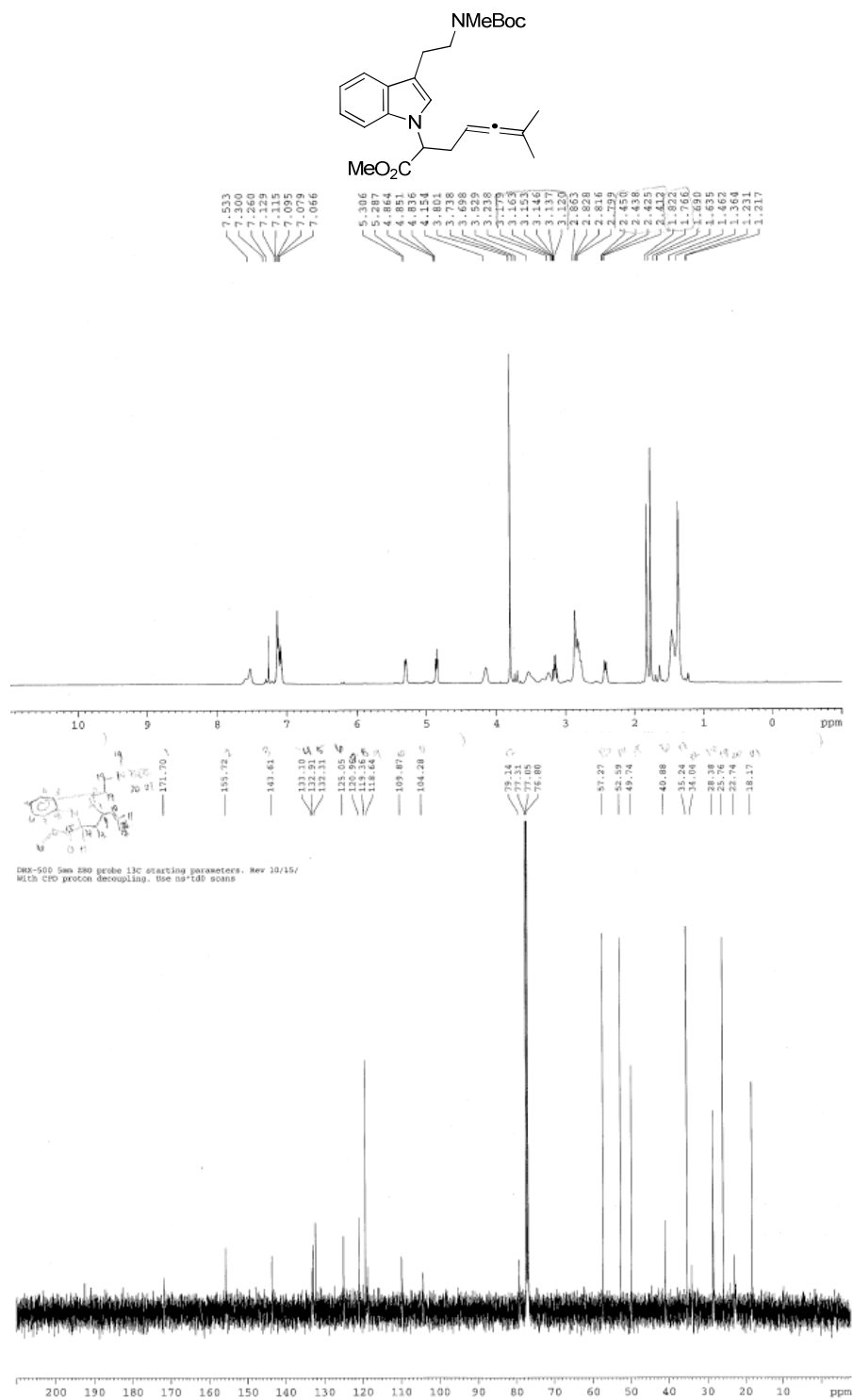


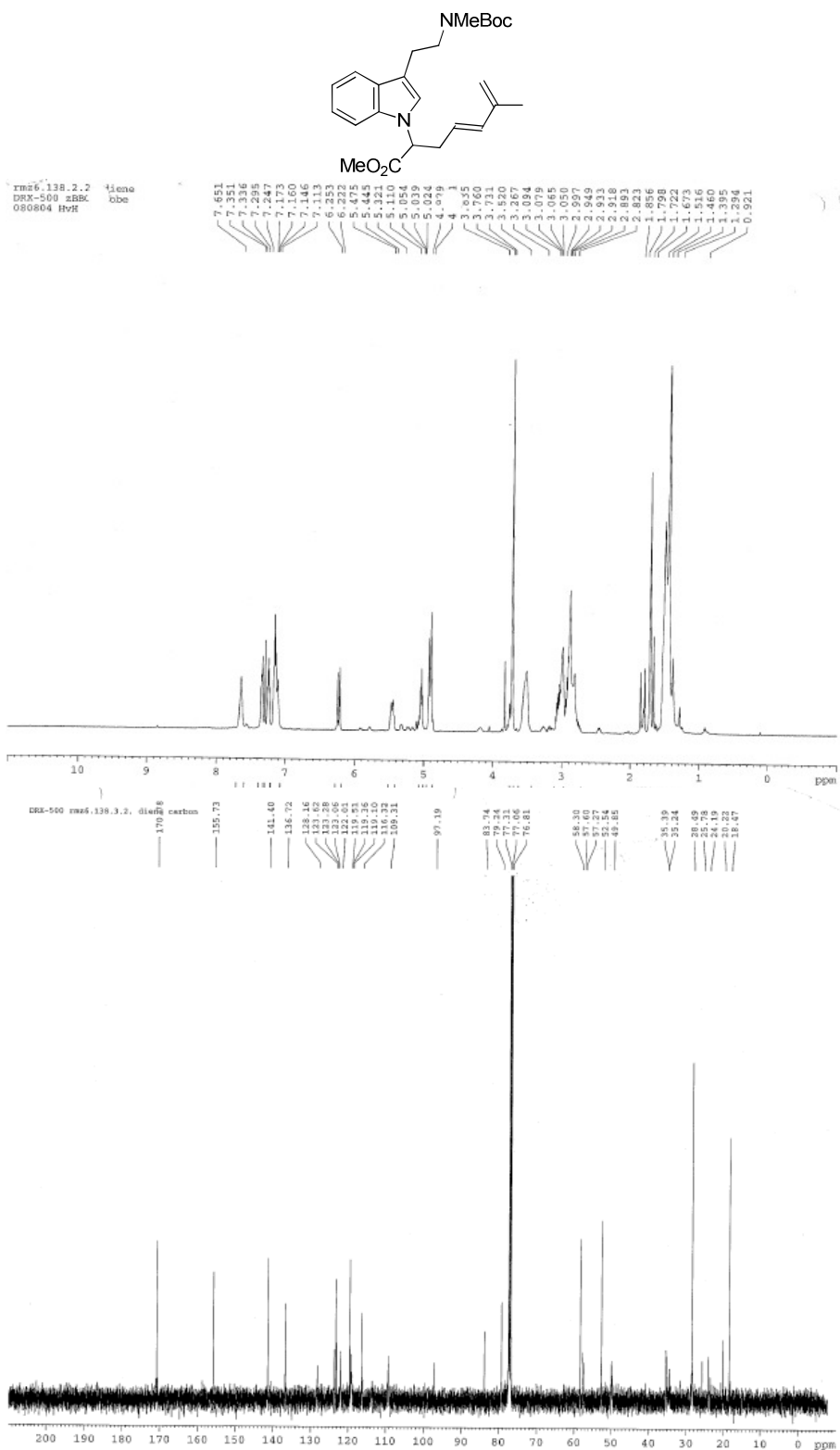


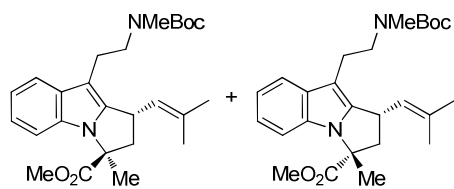




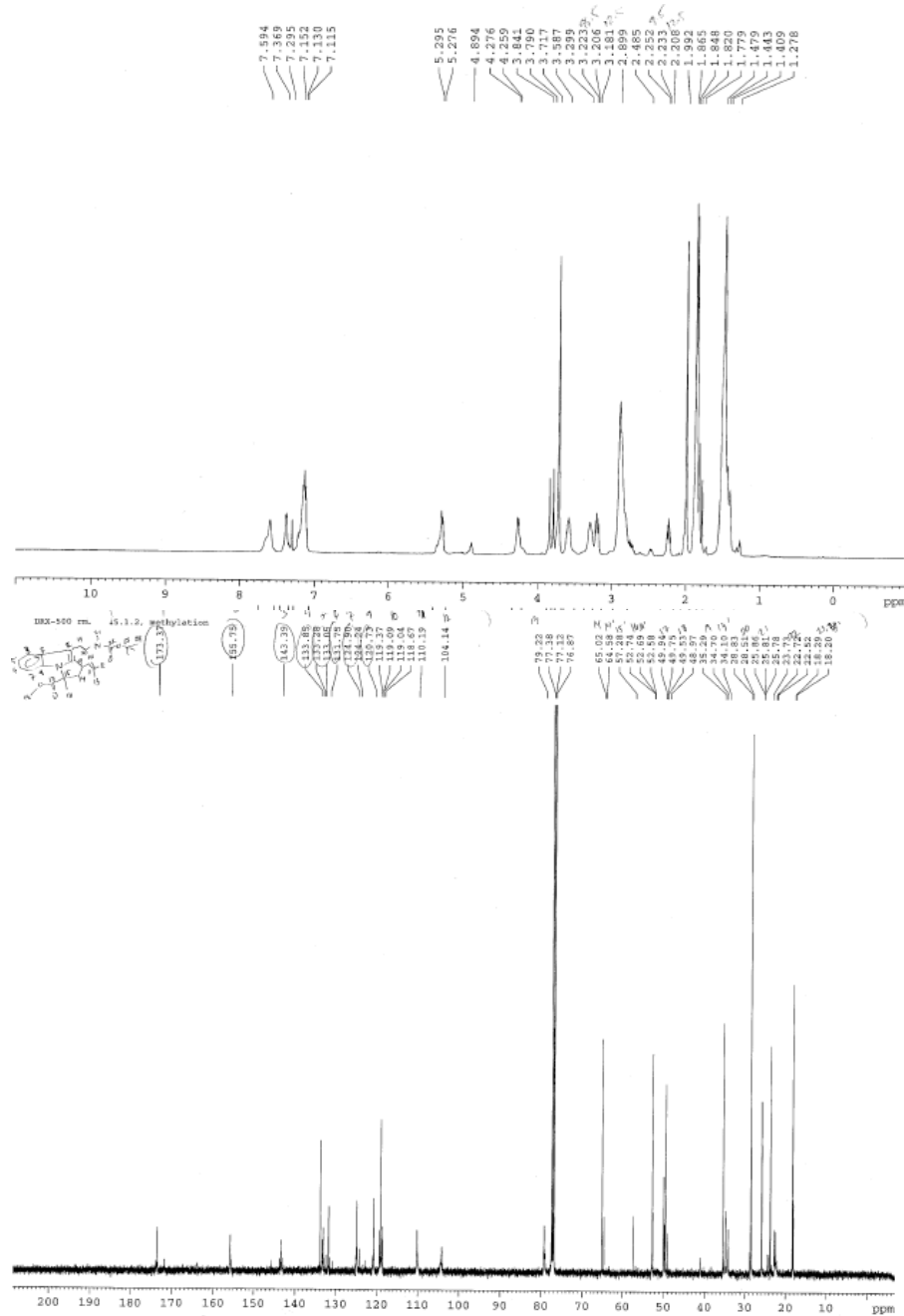


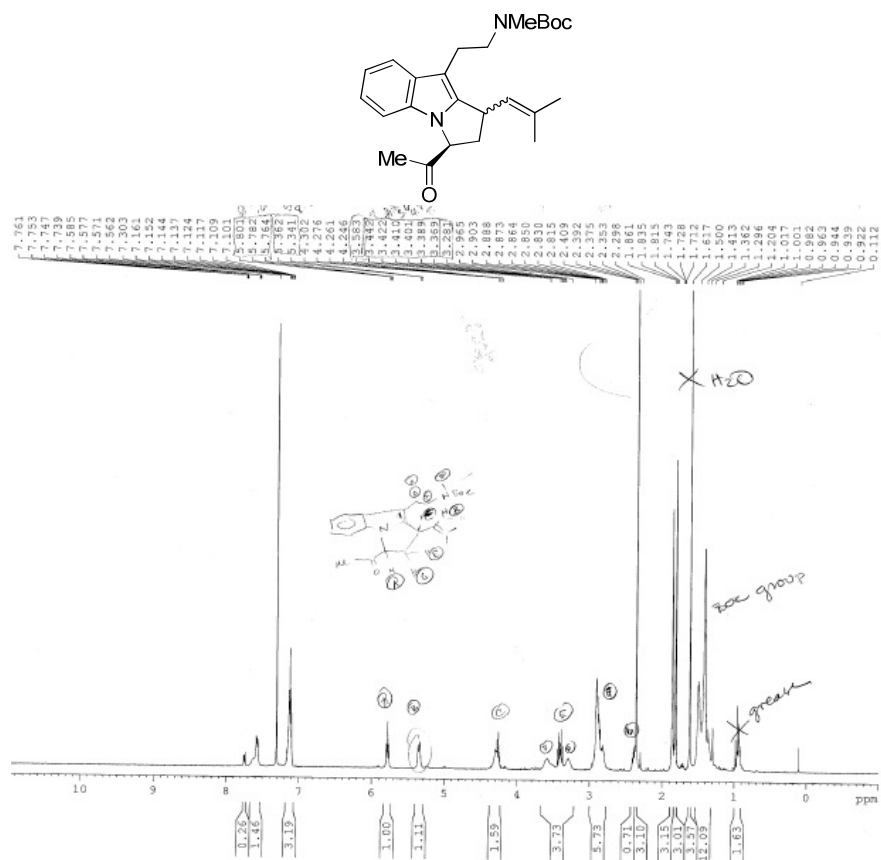




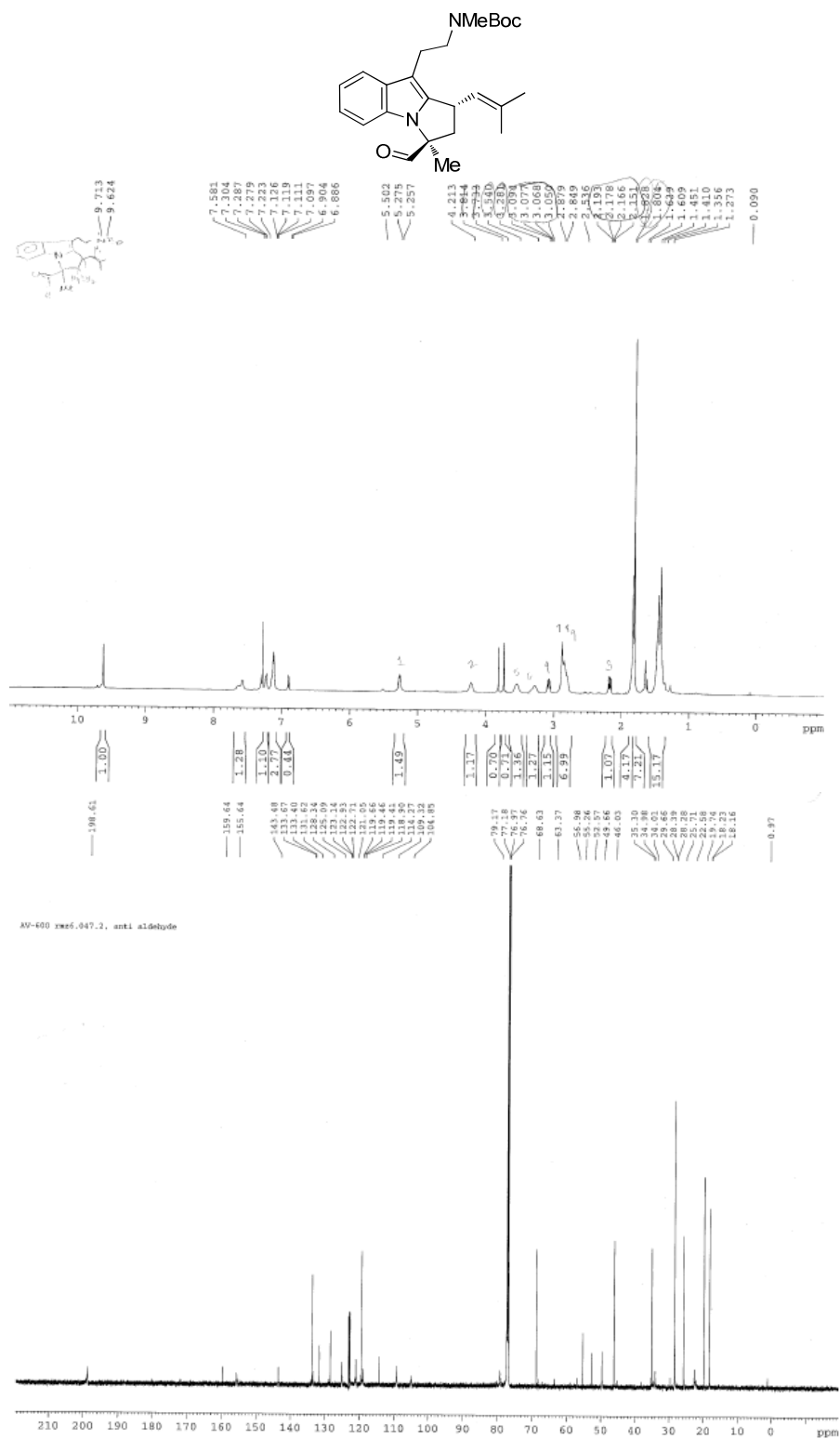


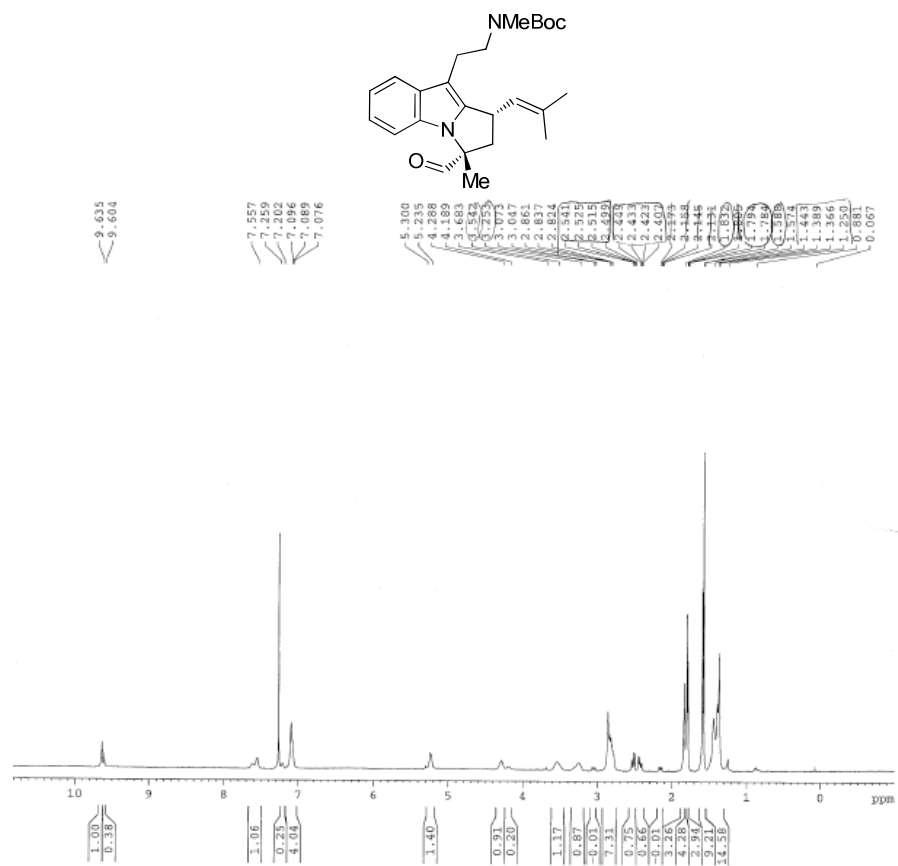
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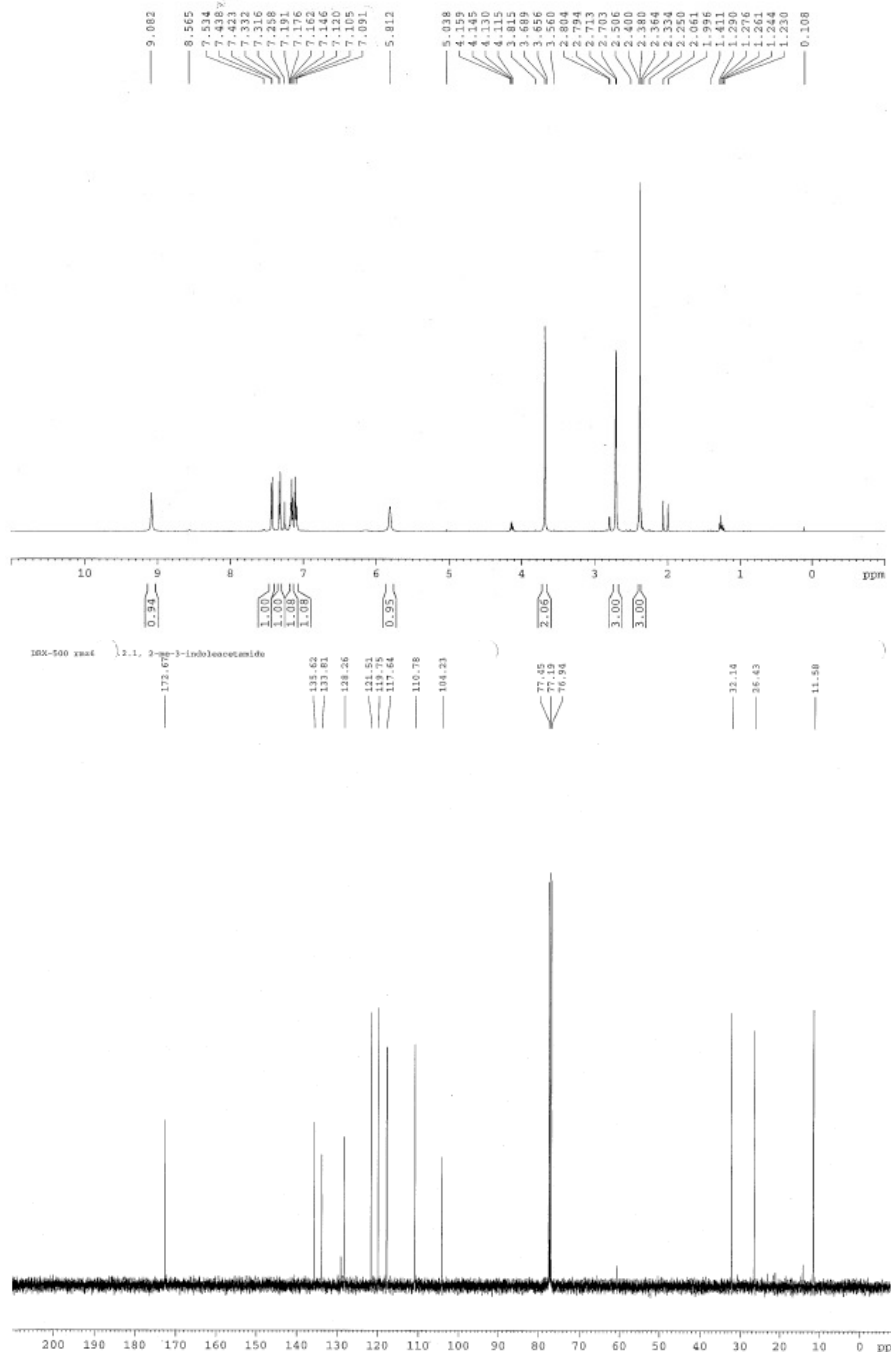
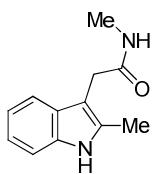


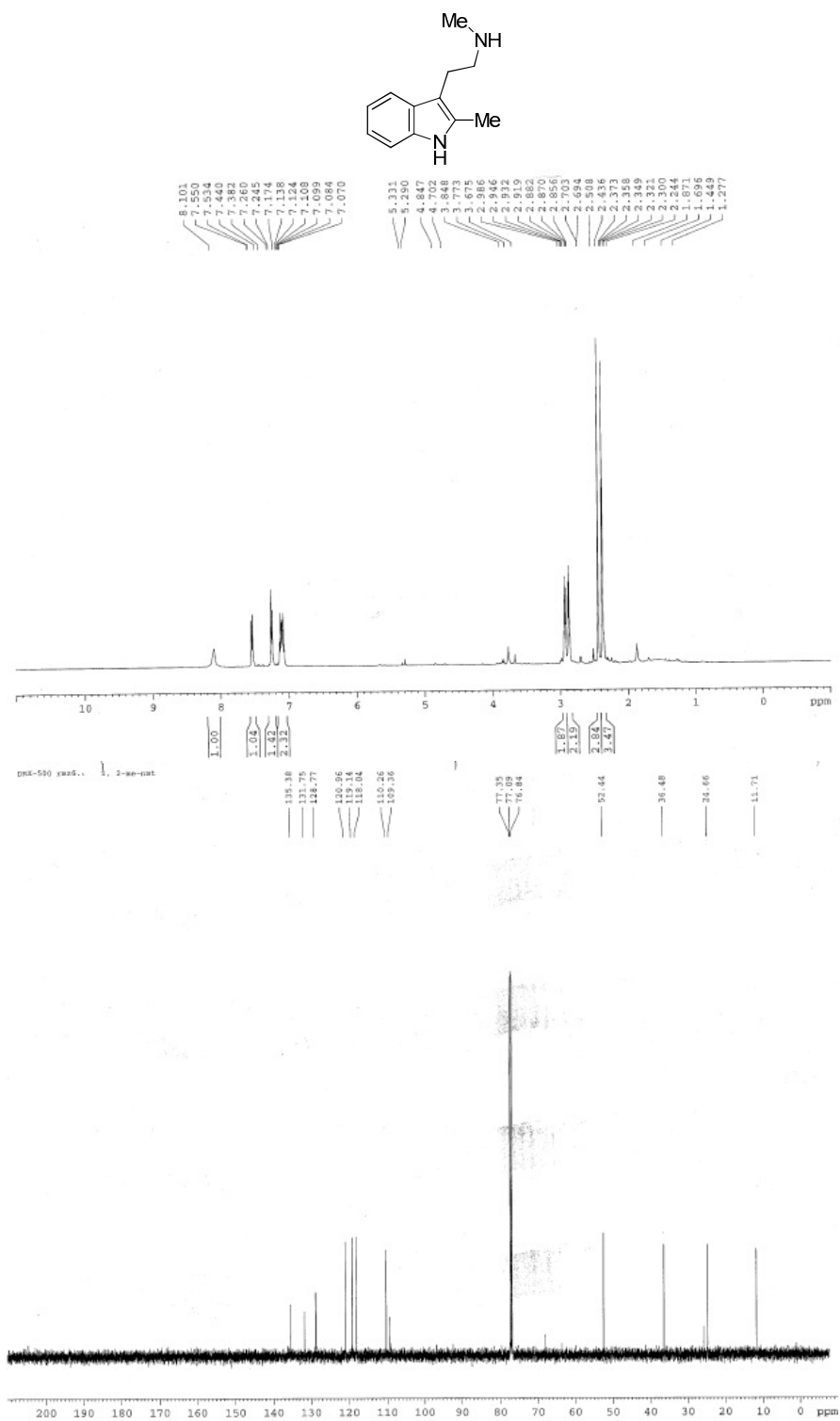


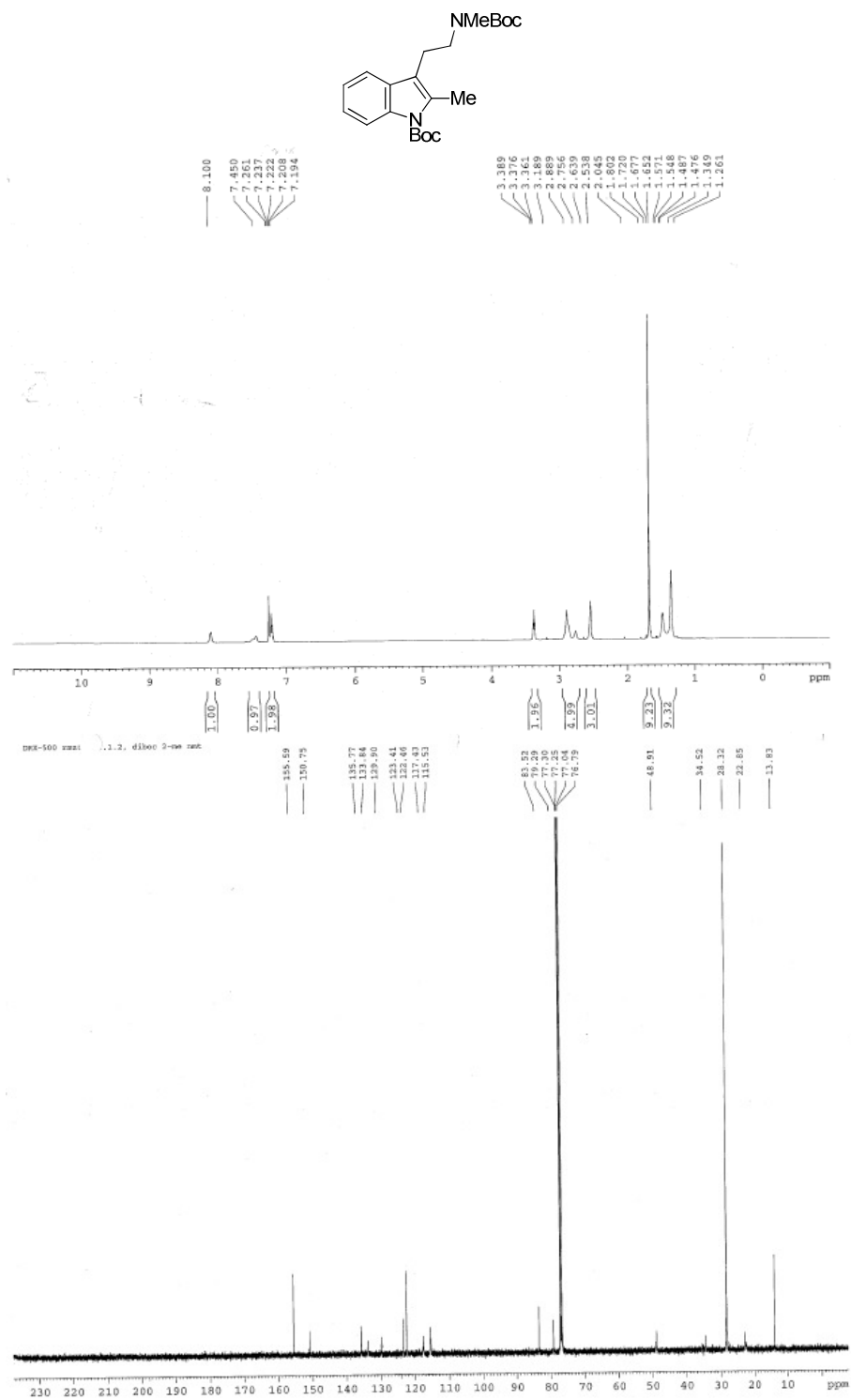


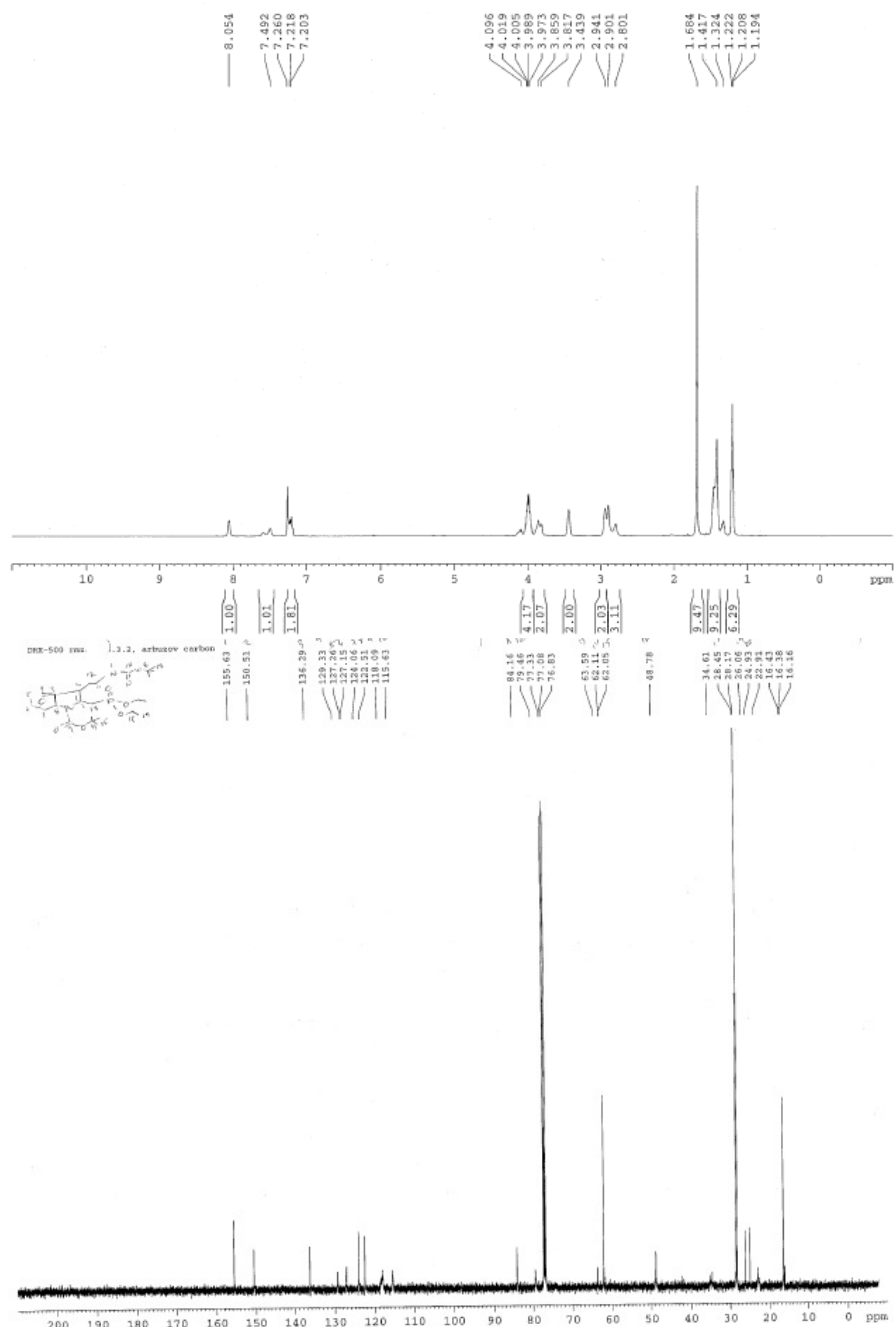


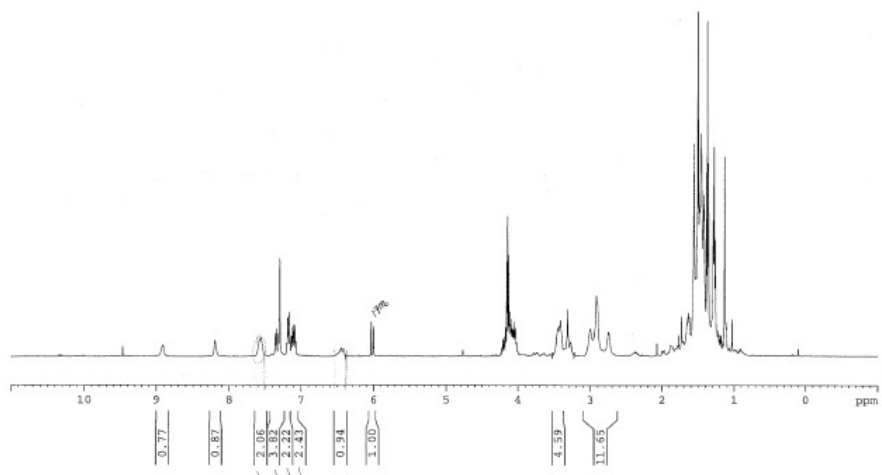
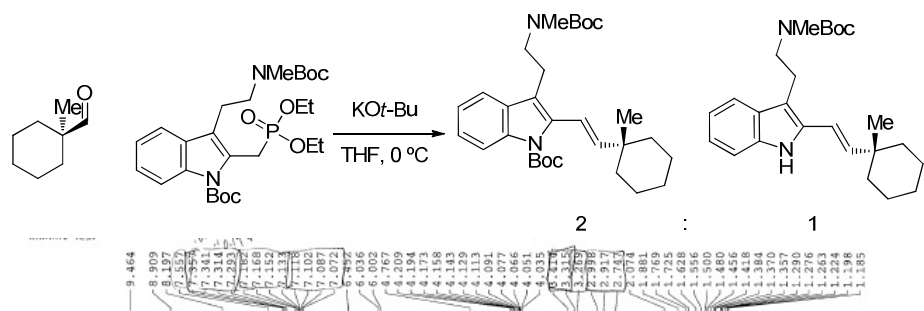


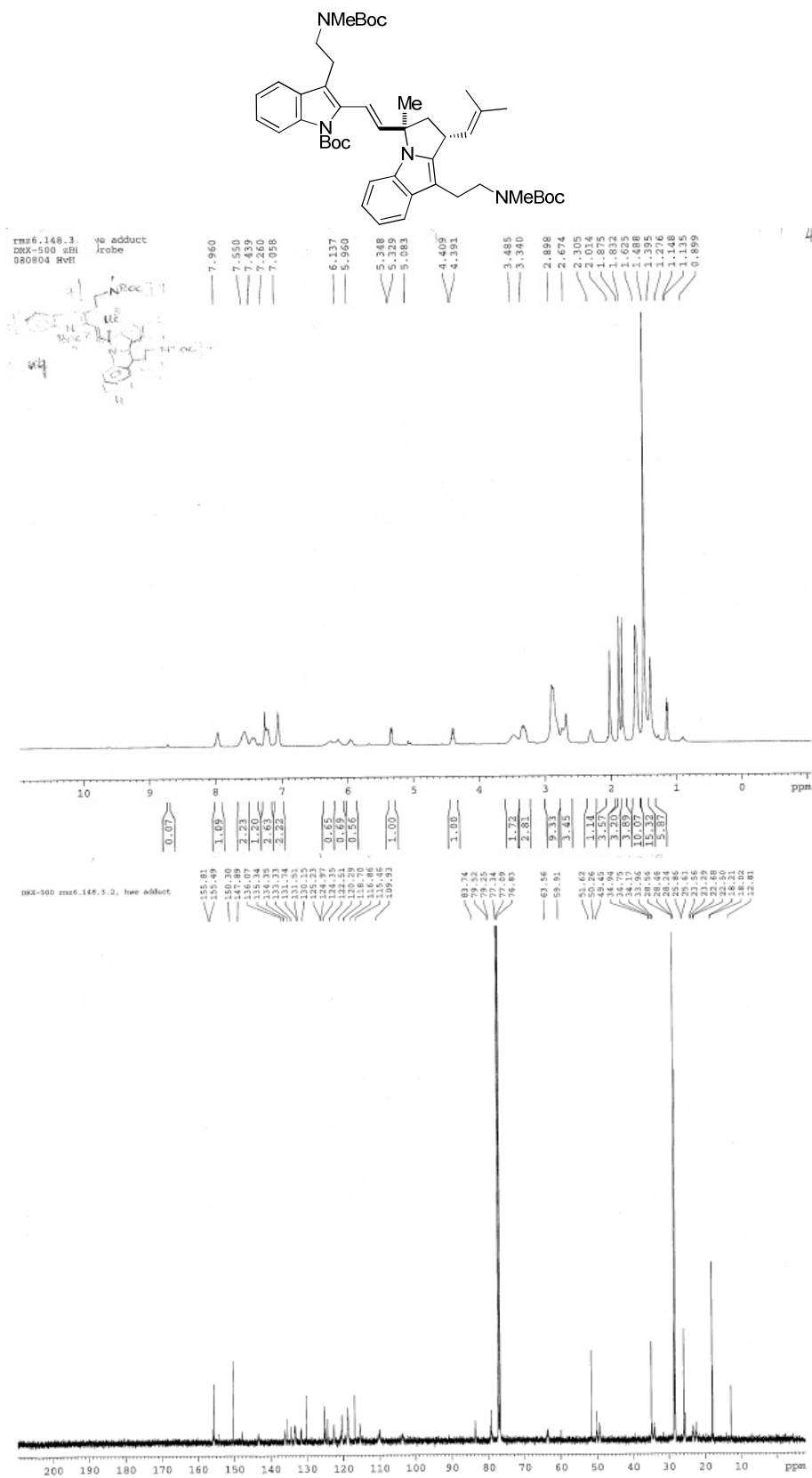


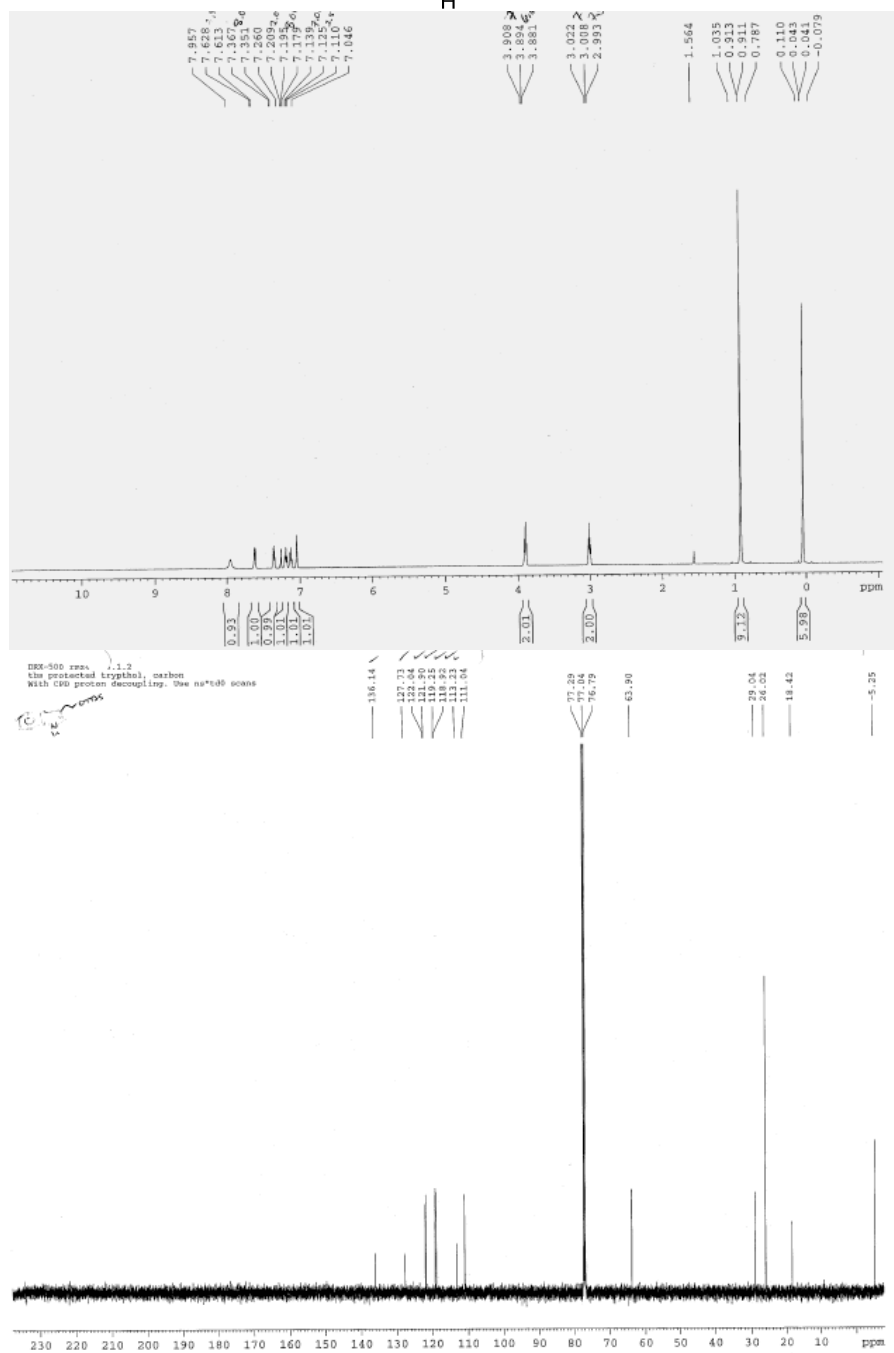
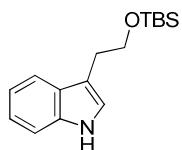






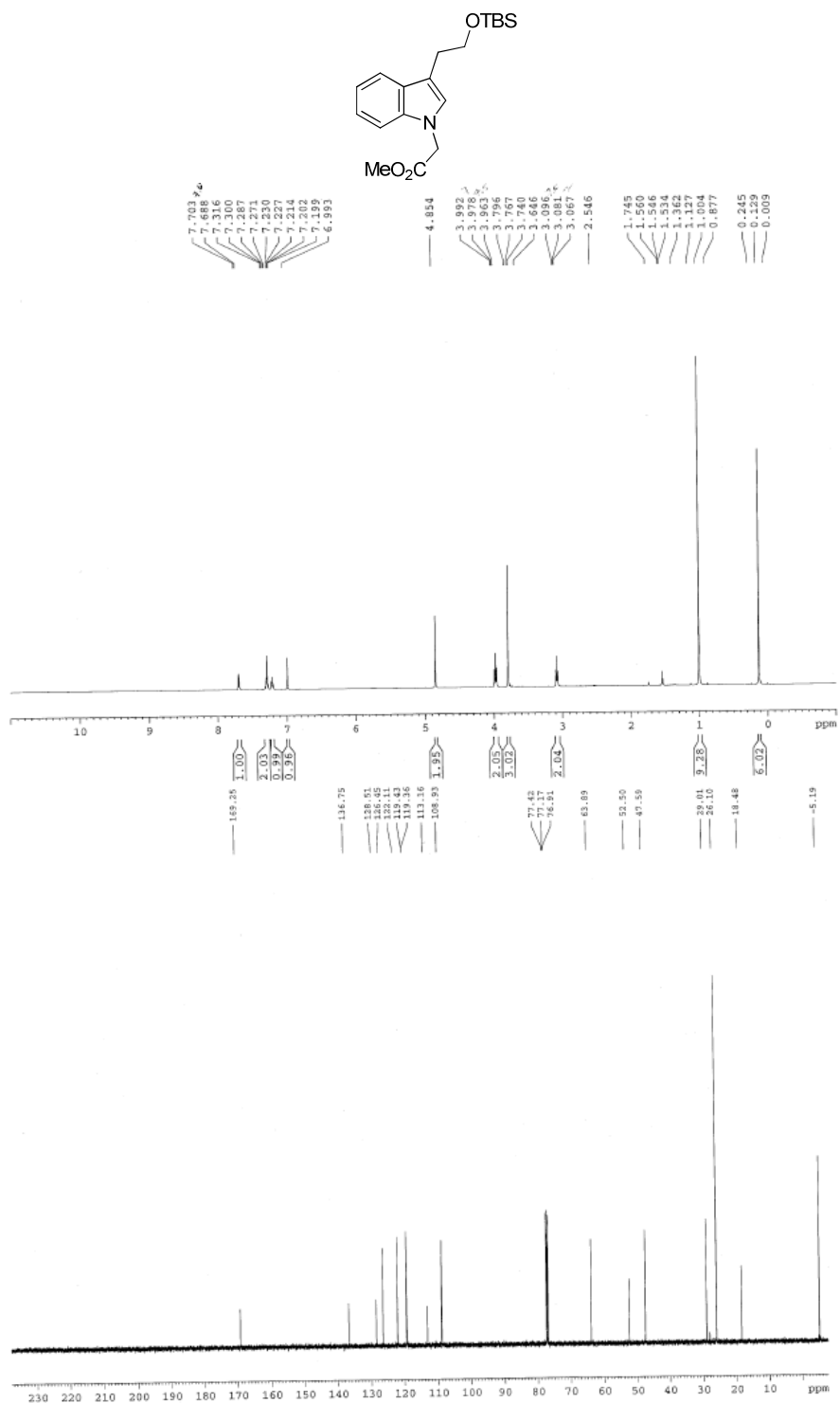




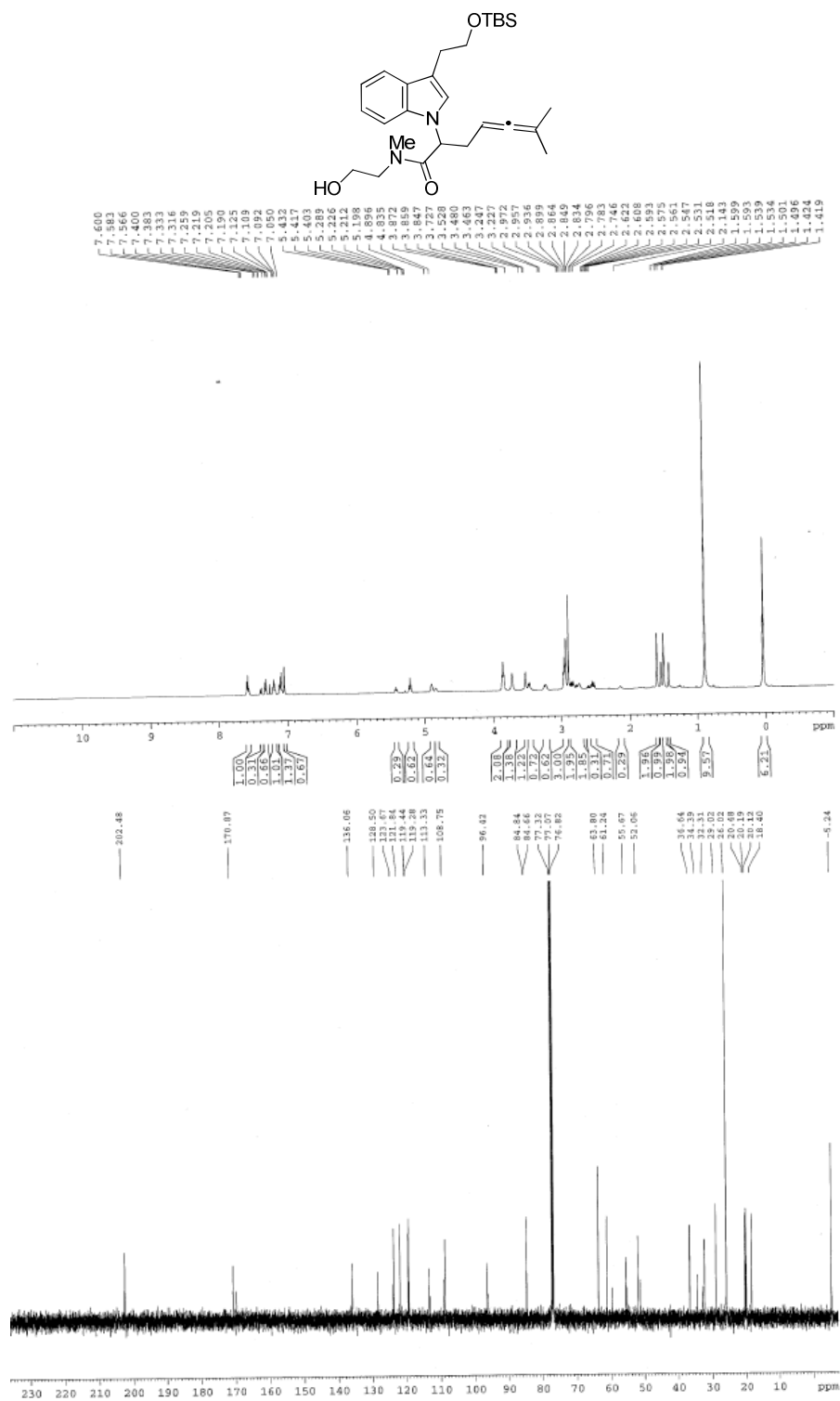


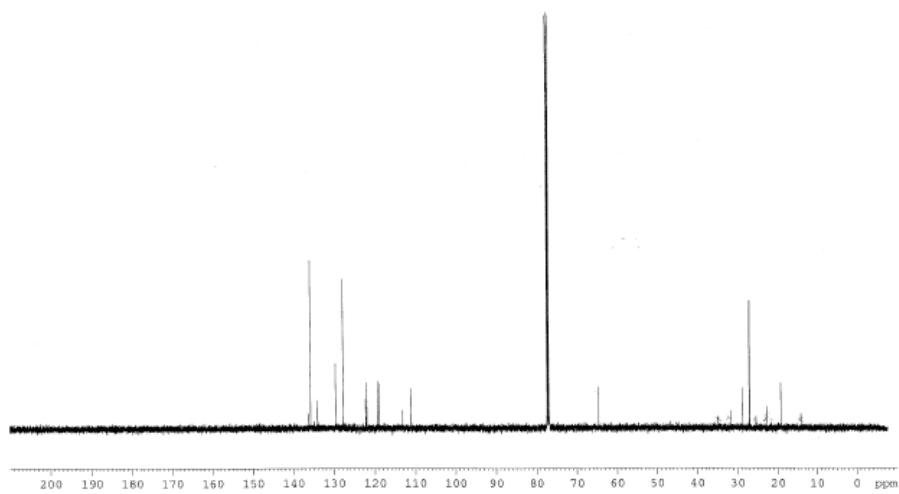
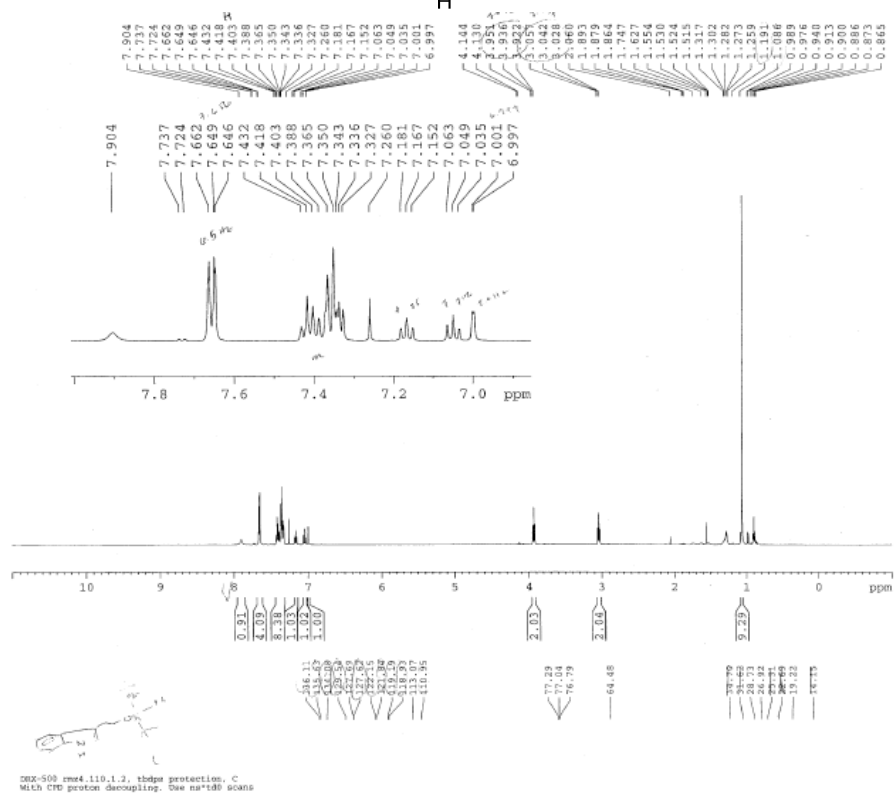


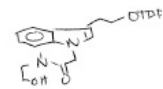


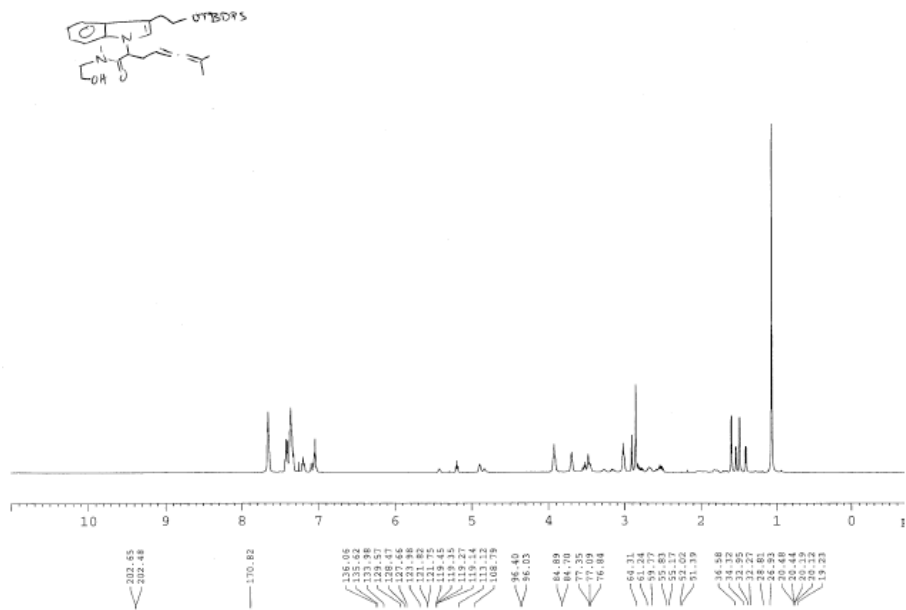
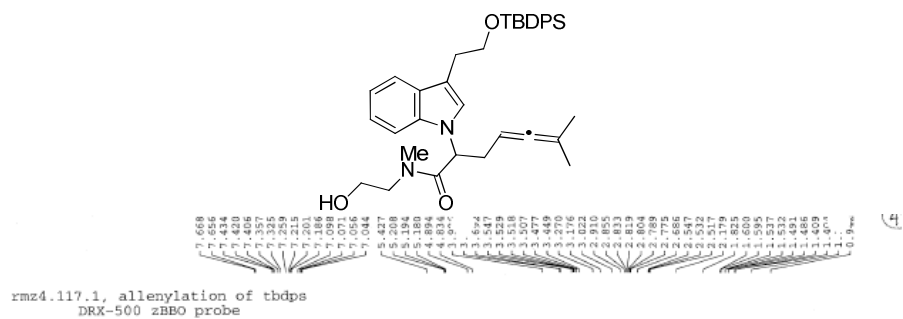


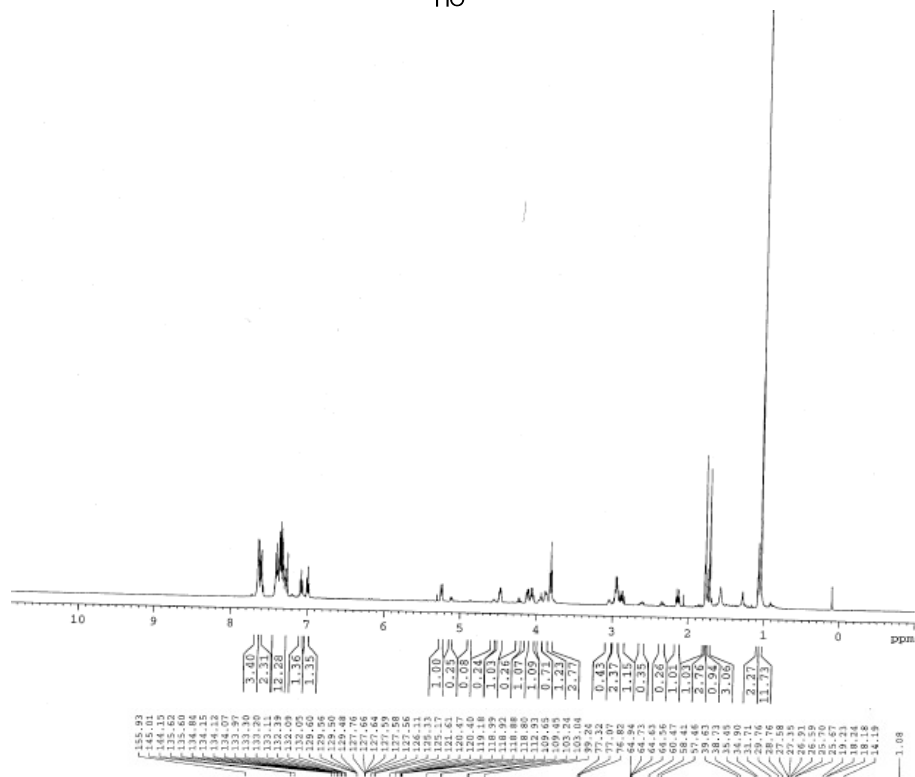


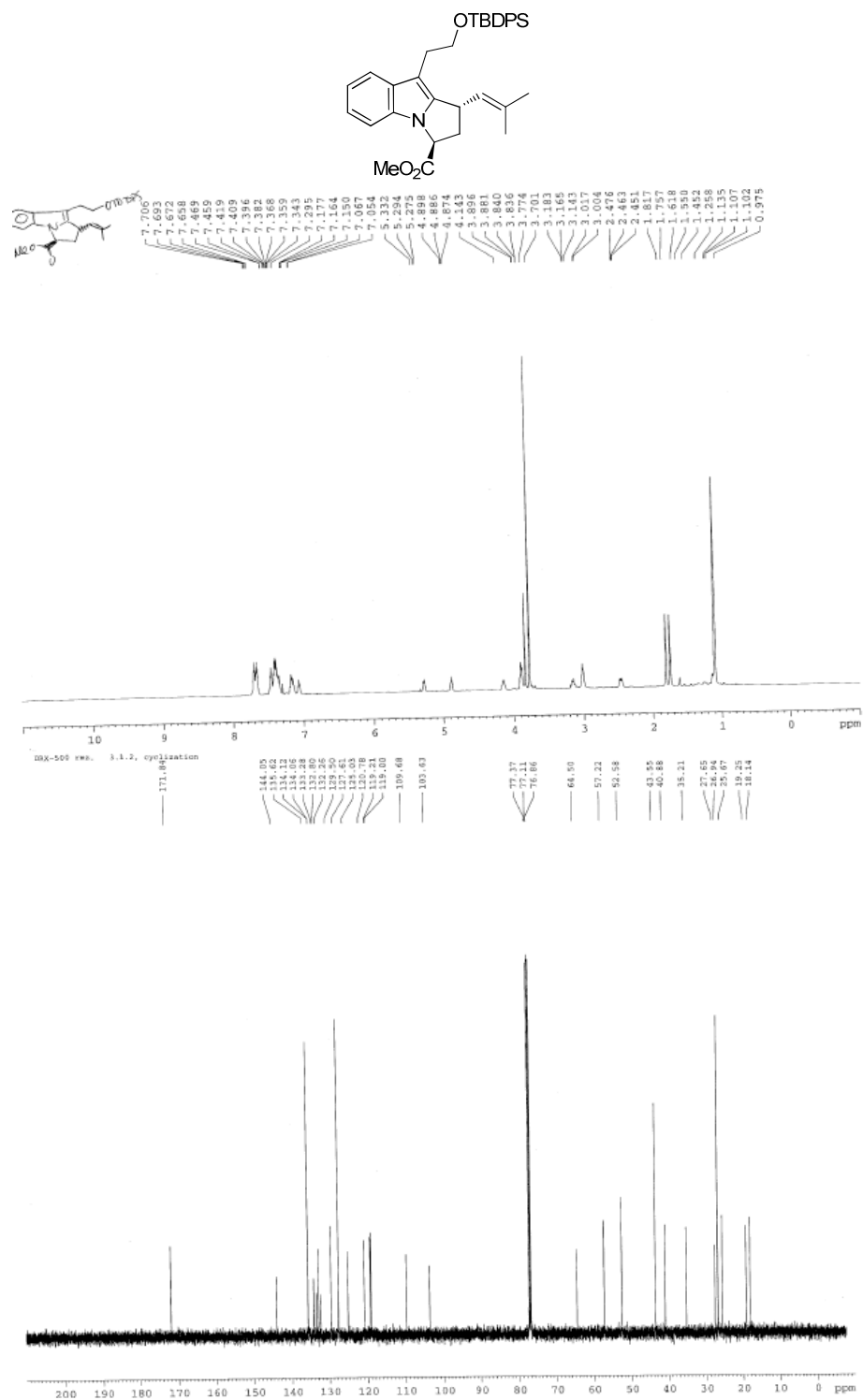


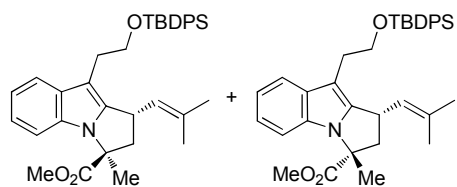




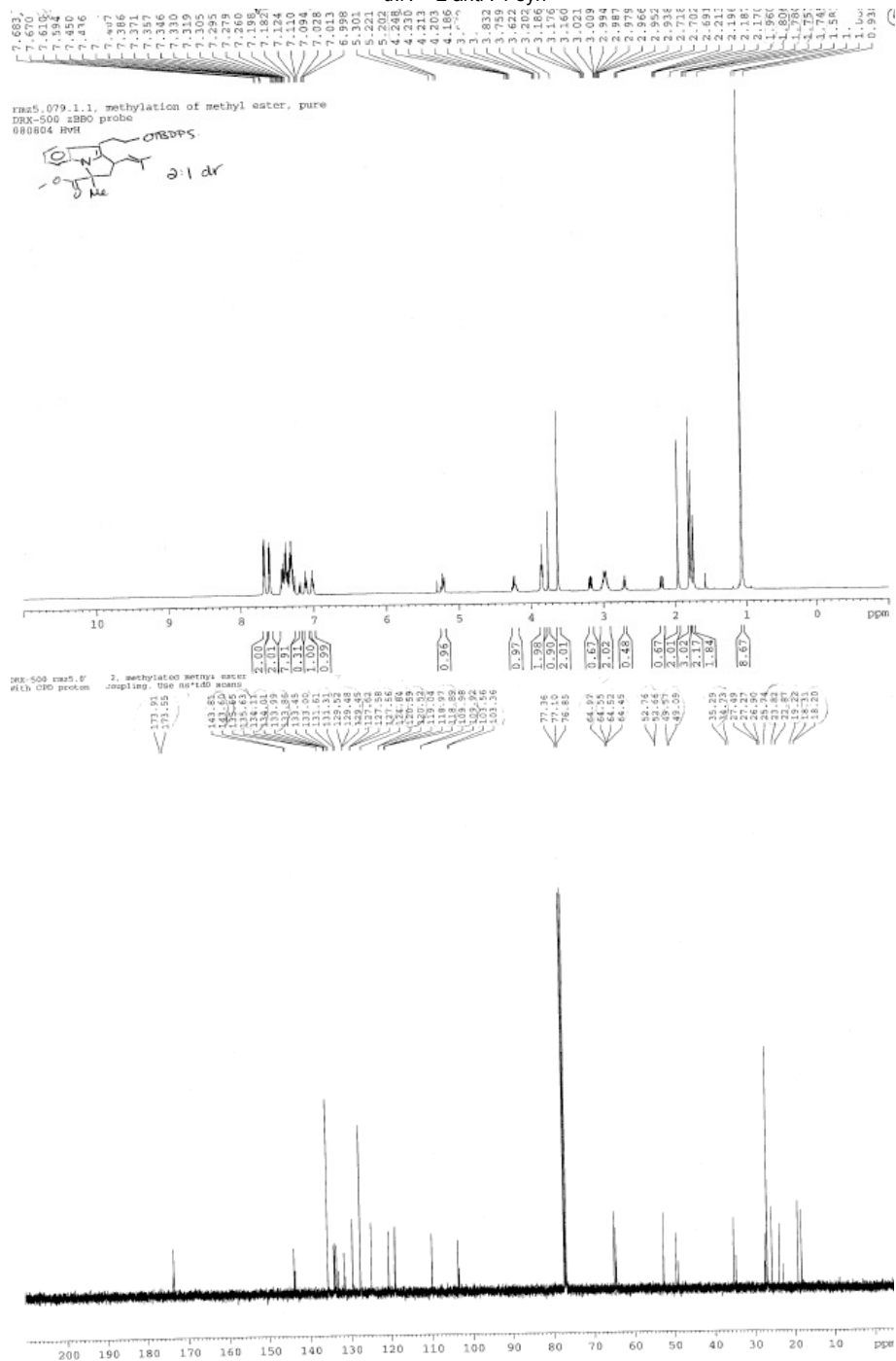


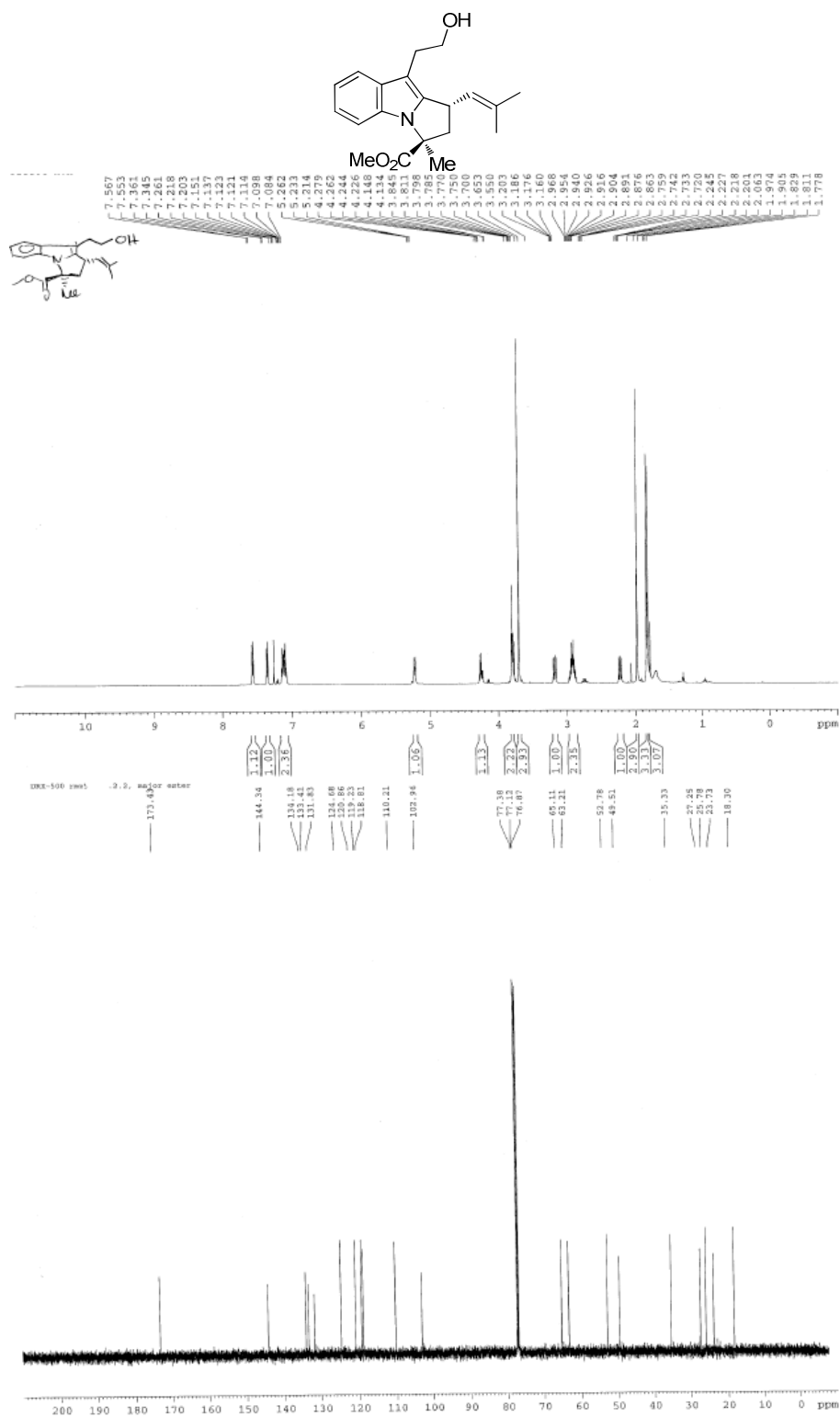


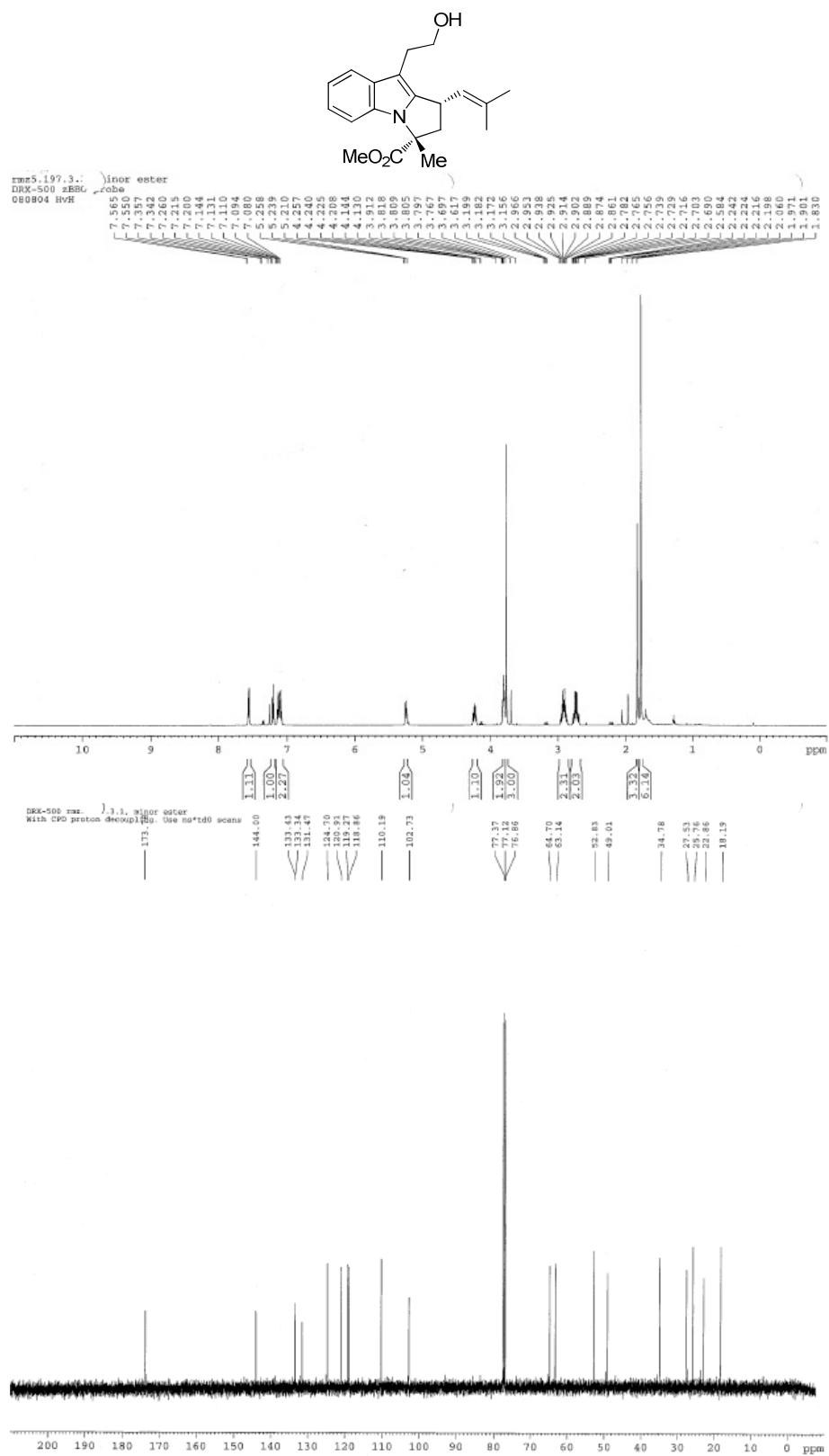




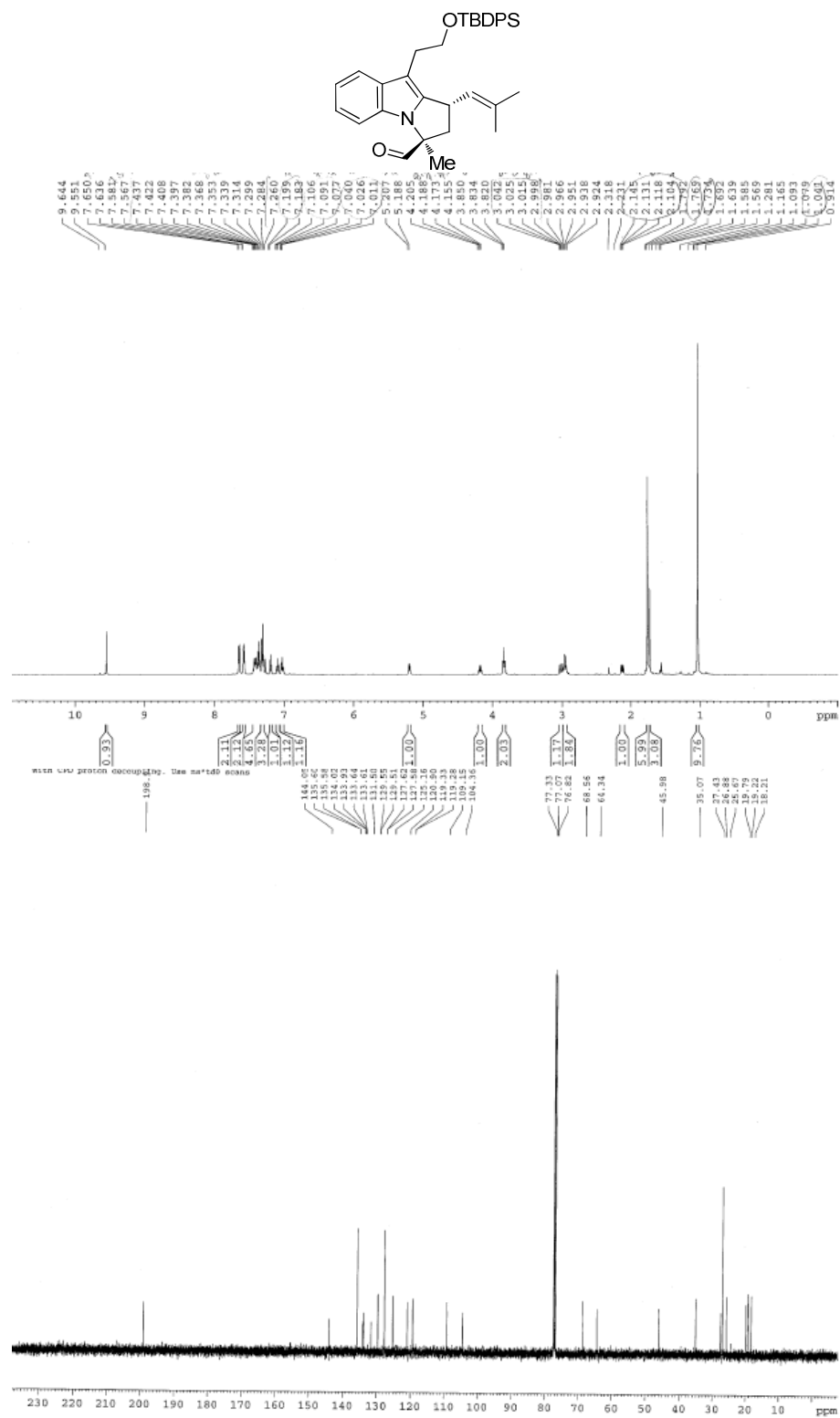
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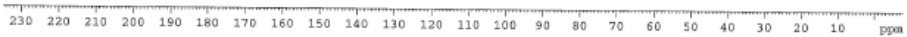


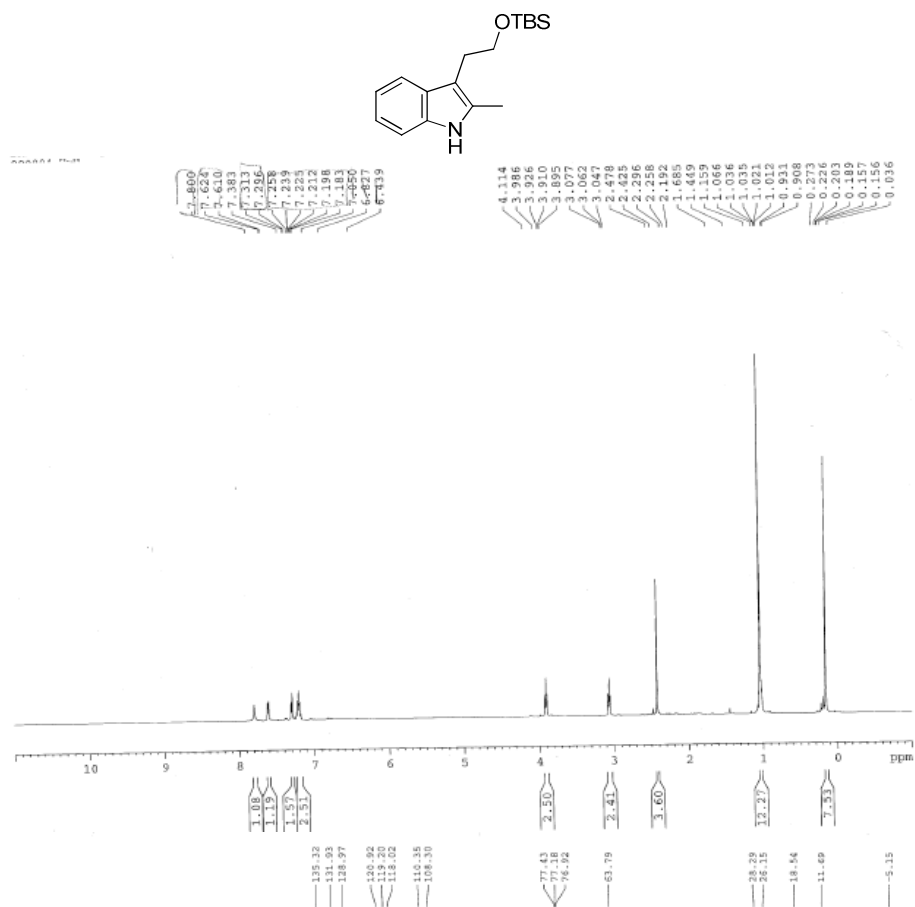




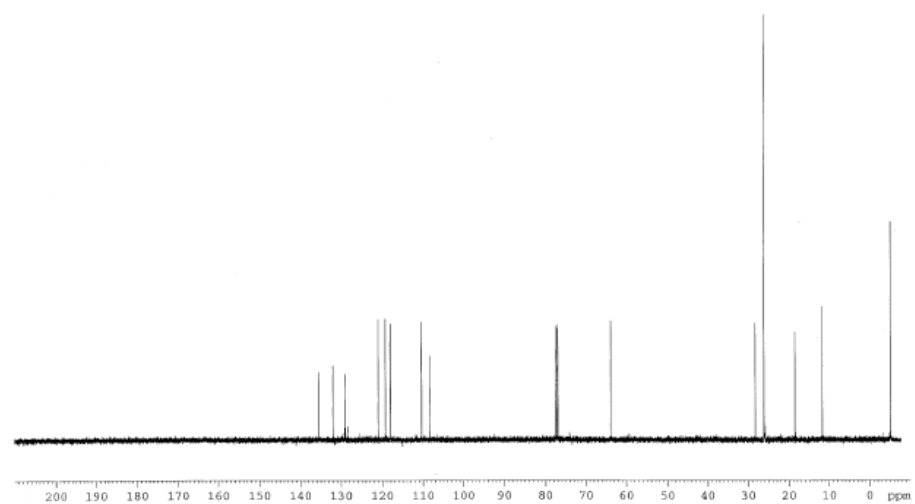


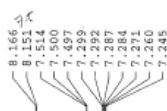


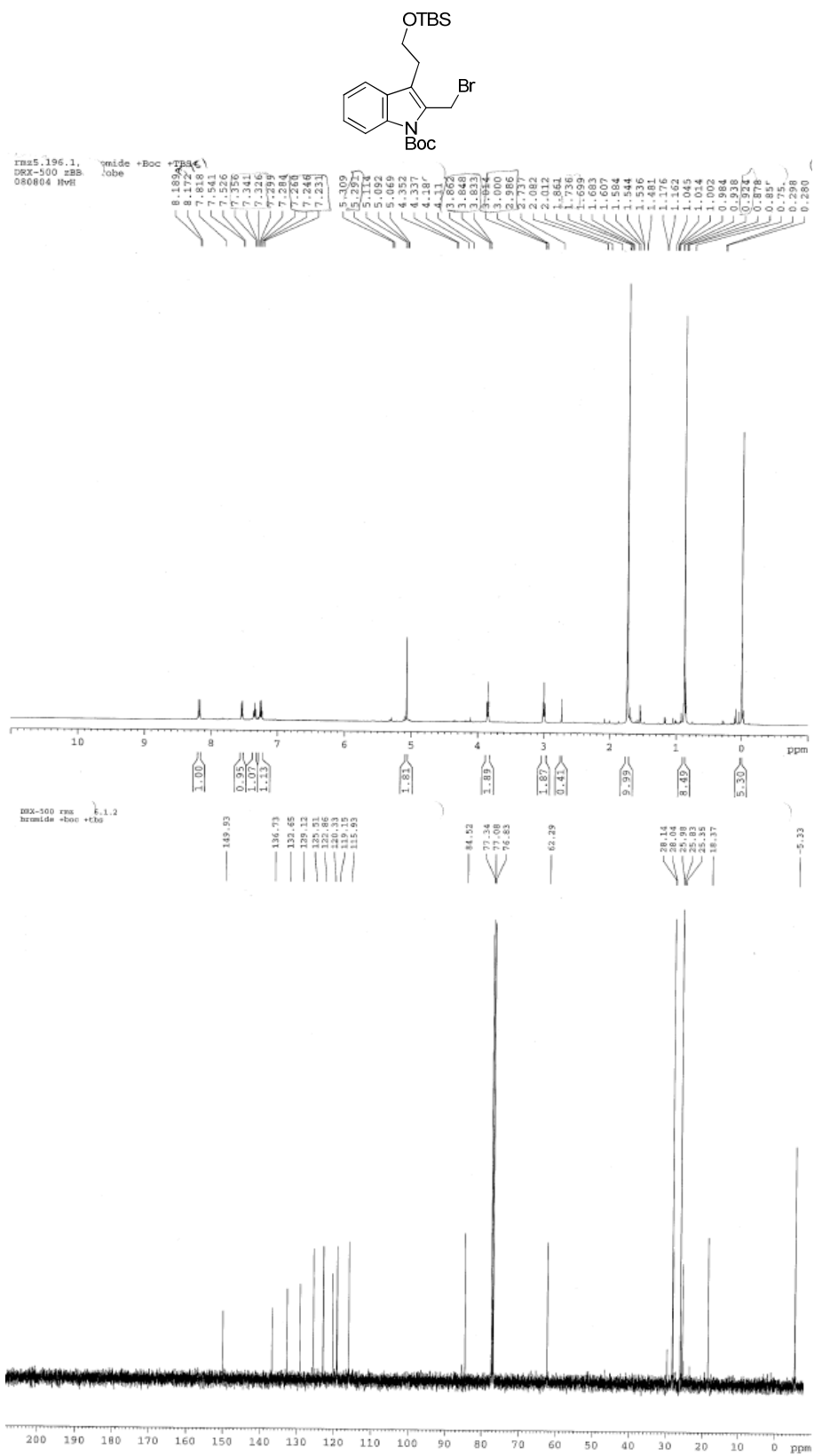


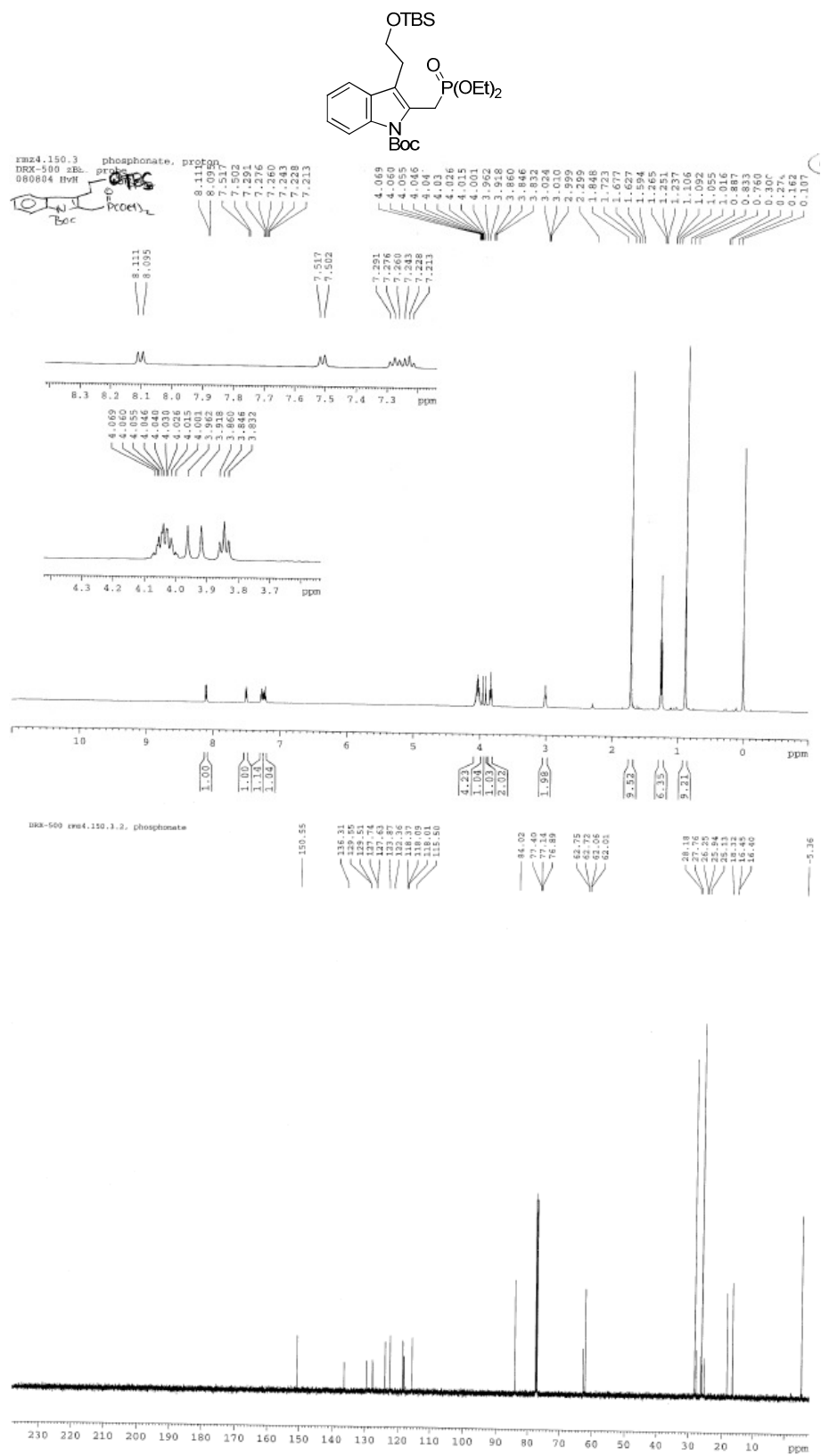


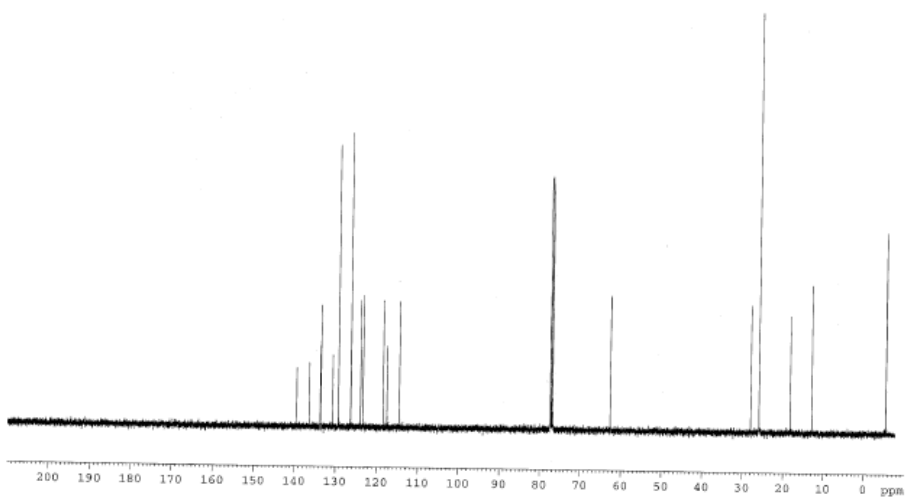
DEX-505 500 MHz probe 13C starting parameters. Rev 10/15/
With CPD proton decoupling. Use n2-t0H scans

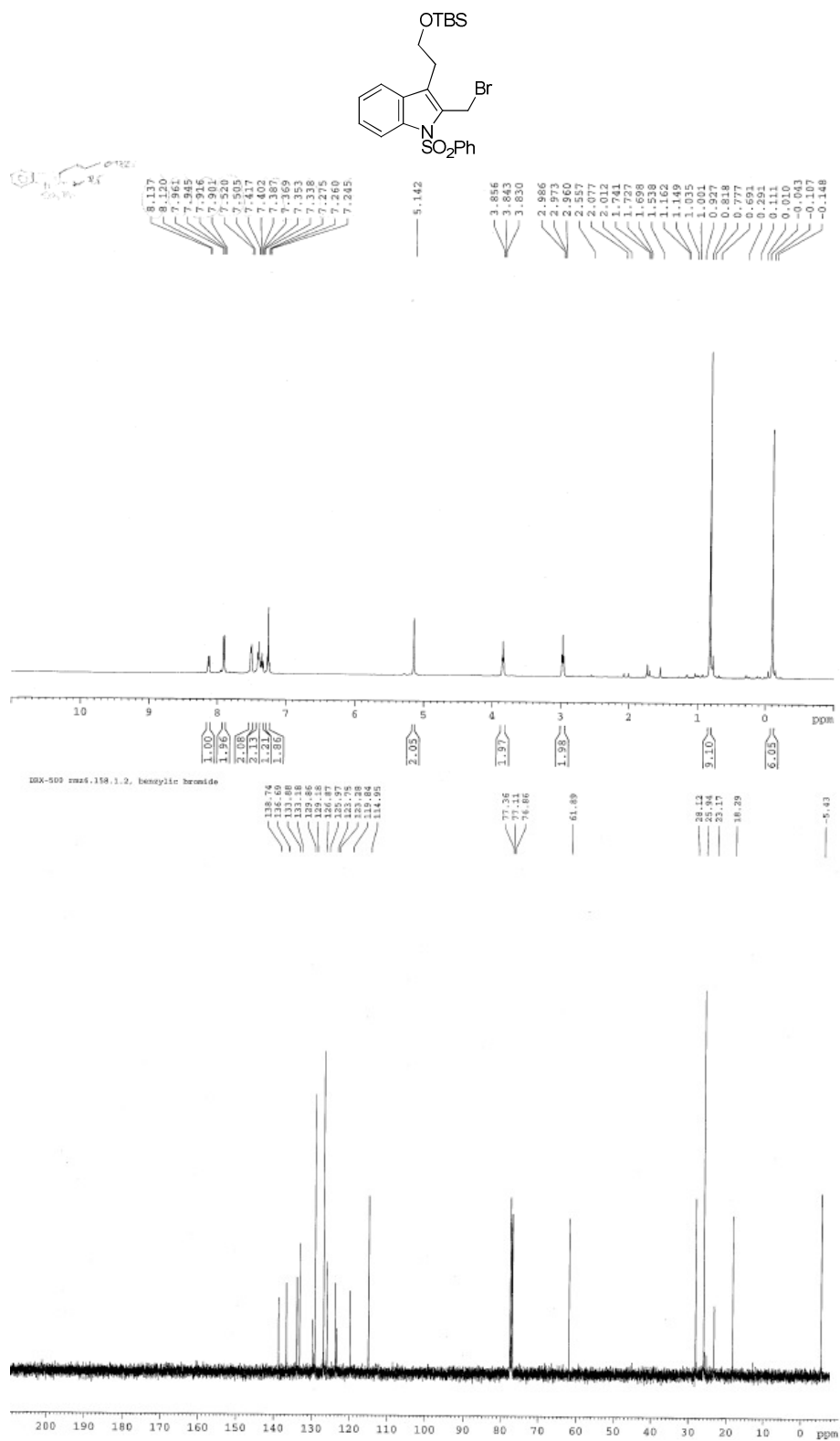




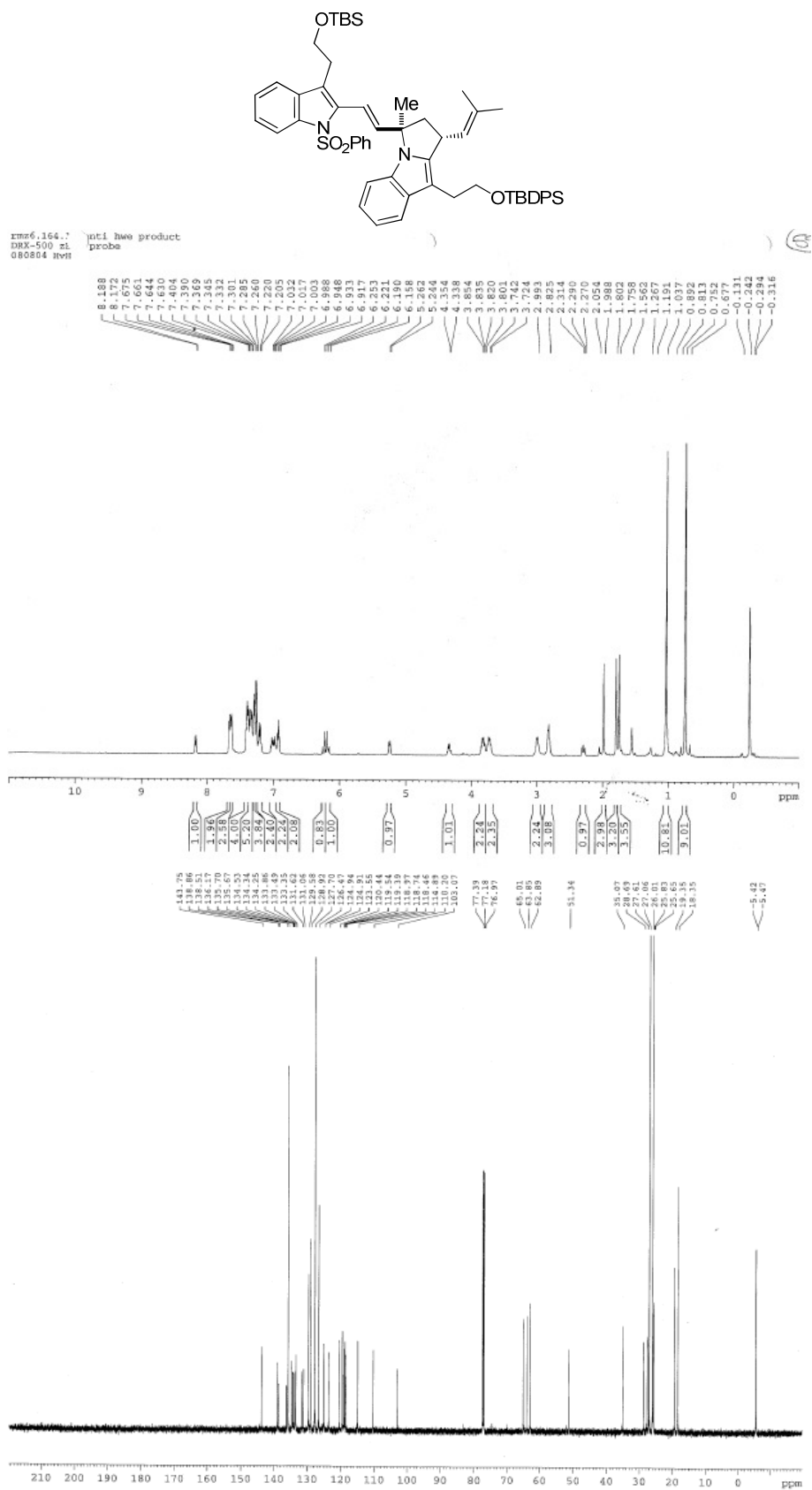


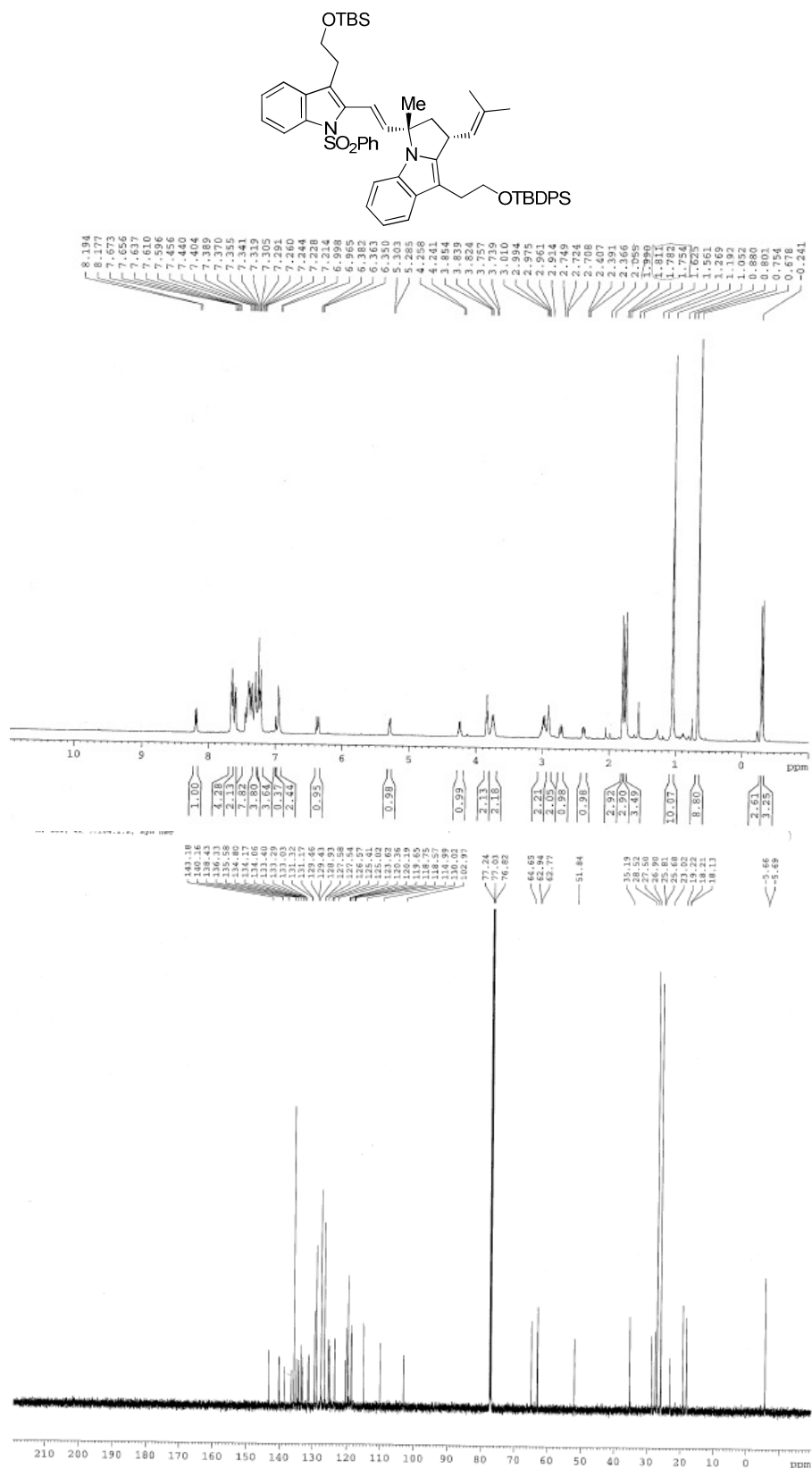


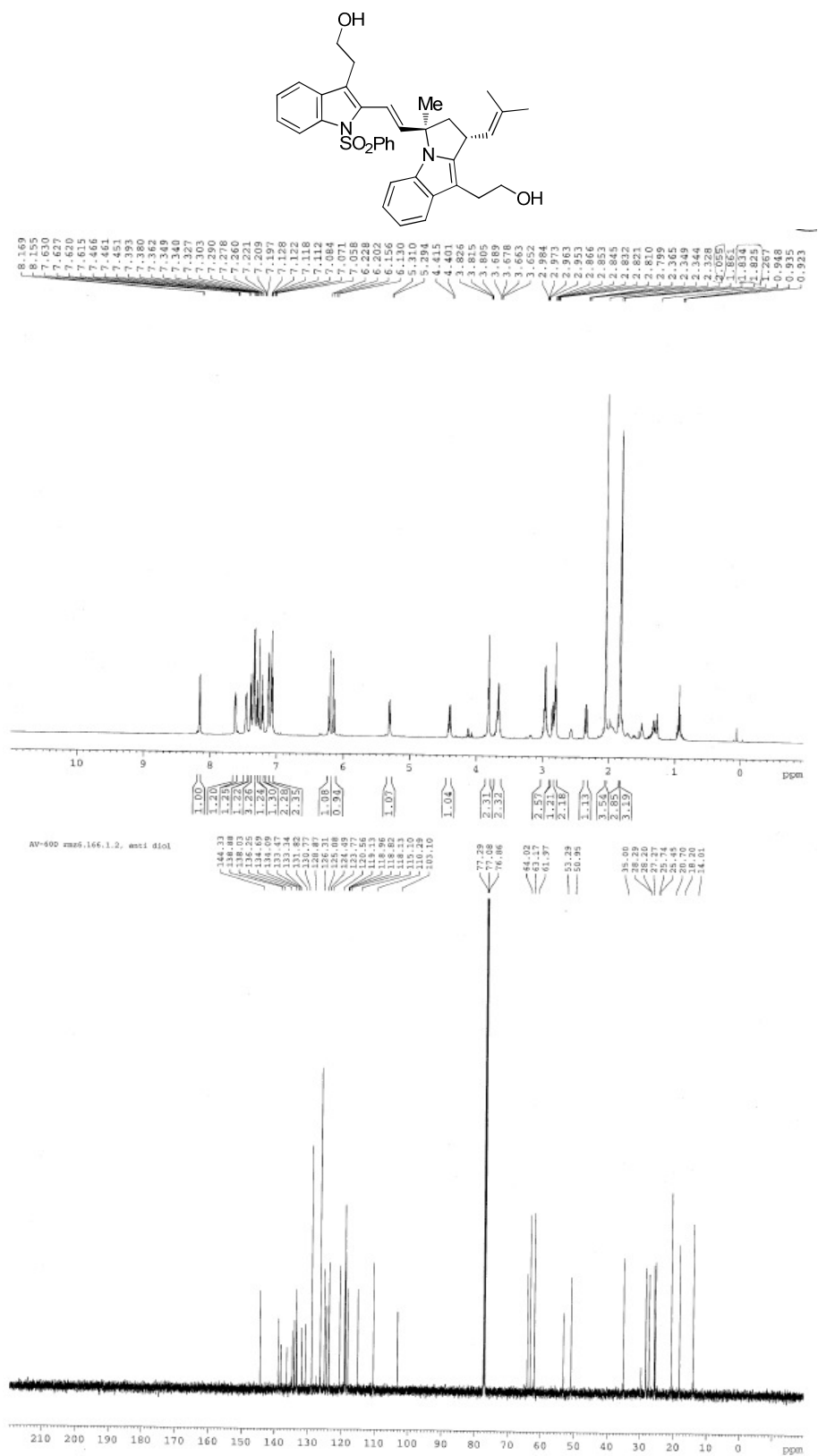


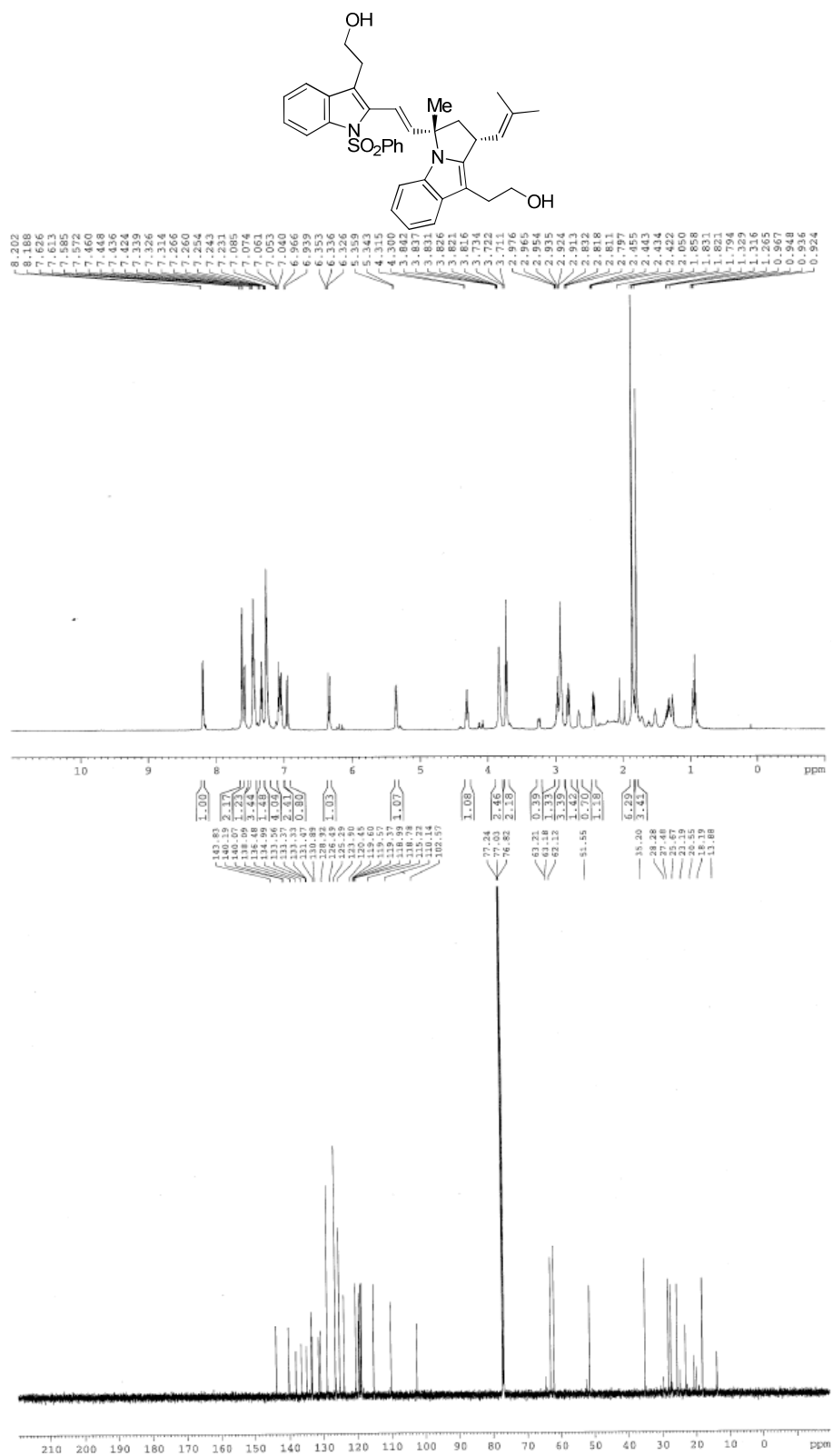


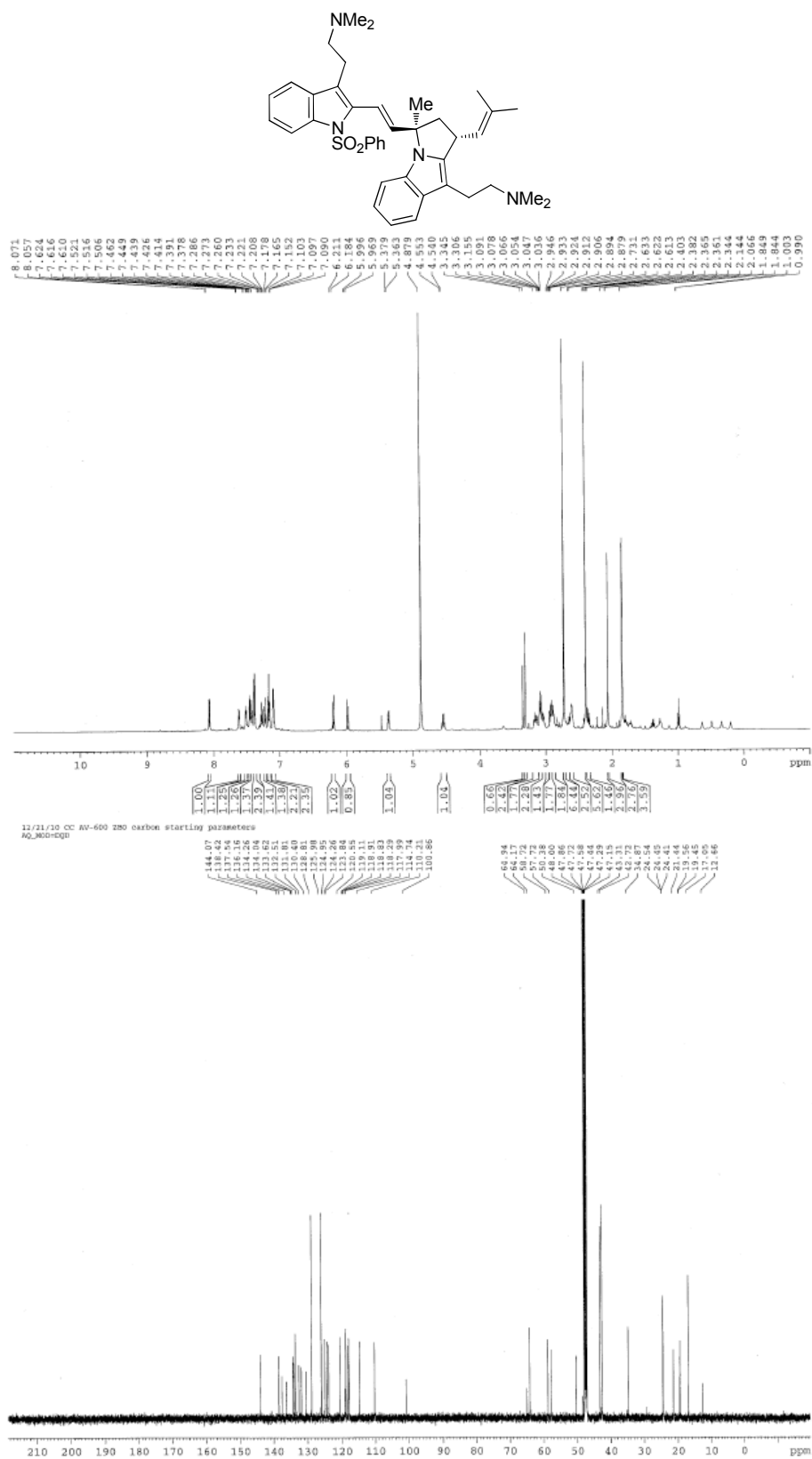




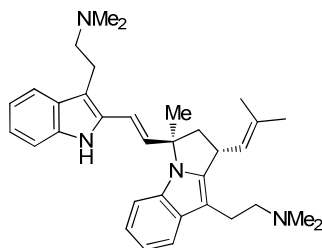












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