The Pennsylvania State University

The Graduate School

Department of Chemistry

INTRAMOLECULAR [3 + 2] CYCLOCONDENSATIONS OF

ALKENES WITH INDOLIDENE AND INDOLIDENIUM CATION

INTERMEDIATES: APPLICATION TOWARDS THE TOTAL

SYNTHESIS OF LECANINDOLE D

A Dissertation in

Chemistry

by

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ABSTRACT

An allenyl azide cyclization reaction was developed to access the skeleton of the indolosesquiterpene family of natural products, while addressing the challenges of synthesizing indole-fused *trans* hydrindanes. This cyclization cascade is triggered by the irradiation of an allenyl azide functionality and is presumed to go through a highly reactive indolidene intermediate. This electrophilic indolidene intermediate is then trapped by a pendant alkene nucleophile to afford a tetracyclic adduct, containing an indole-fused *trans* hydrindane unit. In addition, a Lewis acid-mediated bicyclization also was explored involving the solvolysis of indole 2-(methyl alcohol) derivatives to deliver indolidenium cation intermediates, which also are trapped by alkene nucleophiles. Regiochemical and stereochemical questions for both cyclization strategies, as well as efforts to favor C–C bond forming products, have been explored. The application of the photochemical [3 + 2] cyclization reaction was demonstrated in the synthesis of the indolosesquiterpene core of lecanindole D, a potent and selective agonist for the human progesterone receptor. Efforts towards the total synthesis of lecanindole D also are discussed, including the installation of the challenging vicinal all carbon stereogenic centers.

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Chapter 1

Introduction

1.1 Introduction

The development of novel and efficient methodologies for the synthesis of complex molecules targeted for pharmaceutical applications has been a major focus in organic chemistry for many decades. A class of compounds that has received a lot of attention are those containing heterocyclic rings, due to the biological activity exhibited by many of them.[1] In particular, the indole ring (**1**) is one example of a heterocycle that is widely found in nature and embedded in many complex biological molecules; for example, the indole core is built into proteins in the form of the amino acid tryptophan (**2**) (Figure 1).

indole **1**   tryptophan **2**
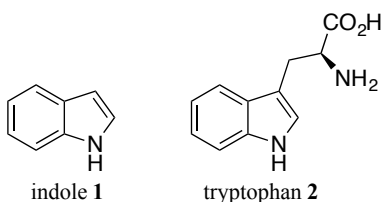
Figure 1. Structures of indole (**1**) and tryptophan (**2**).

Indole-containing molecules often display therapeutic properties, and as such many of them are currently used to treat diseases such as HIV, some types of cancer, depression, infections, etc.[2] Examples of important indole-containing drug molecules (**3–7**) are depicted in Figure 2. Due to this practical utility, the development of new efficient synthesis methods for the construction of complex indole-containing molecules is of great interest.
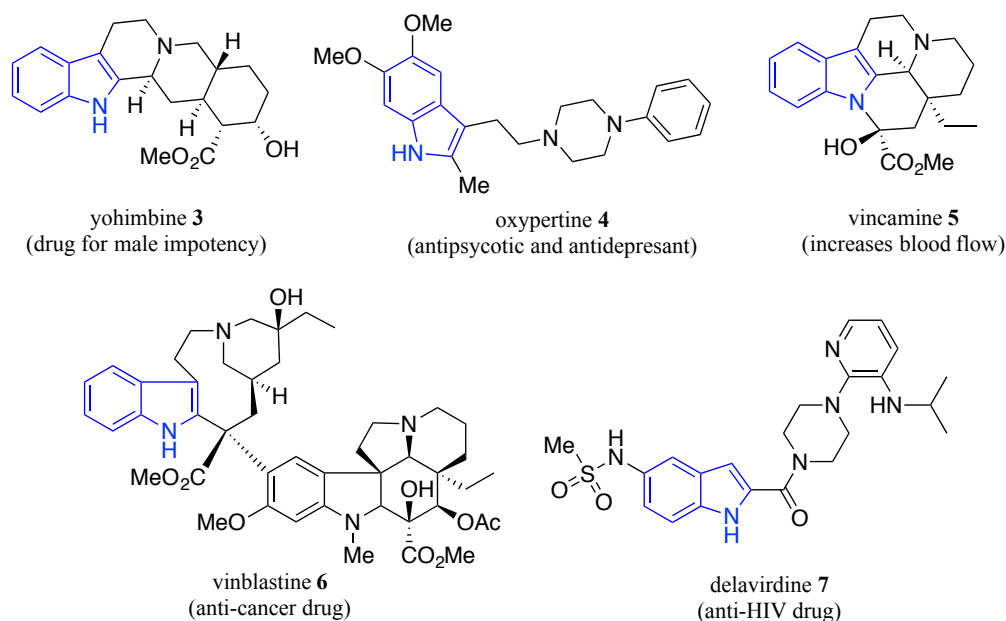
Figure 2. Indole-containing drug molecules.

1.2 Indolidene and Indolidenium Cation Intermediates

The synthesis and functionalization of the indole core has been widely explored and several reviews have been published outlining the different approaches.[3] One relatively underutilized method that has nevertheless been valuable in the construction of functionalized indoles features indolidene (**8**) and indolidenium cation (**9**) intermediates (Figure 3). Indolidenes and the related indolidenium cations are highly electrophilic and susceptible to nucleophilic addition at the C(3) and C(8) positions. These reactive species have been typically generated as transient intermediates derived by the removal of a leaving group at the C(8) carbon of an indole precursor through acid catalysis, eliminations and rearrangements.[4] Indolidenes and indolidenium cation intermediates occasionally have been utilized in C–C bond-forming processes, which have been pivotal in the construction of complex natural products.[4-15]

indolidene **8**   indolidenium cation **9**
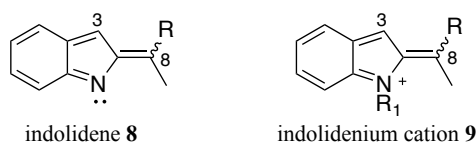
Figure 3. Structures of indolidene (**8**) and indolidenium cation (**9**) intermediates.

1.3 Application of Indolidene and Indolidenium Cation Intermediates in Natural Product Synthesis

1.3.1 Indolidene Intermediates

The first description of a transient indolidene intermediate was reported by Büchi and Manning (1964) in their synthesis of voacangine (**14**) (Figure 4), an important precursor in the synthesis of the antimalarial drug voacamine (vide infra).[5] The reaction of the naturally occurring ibogaine (**10**) with *tert*-butyl hypochlorite resulted in the chlorination of the C(3) carbon within **10** to afford chloroindolenine (**11**), which, upon the loss of hydrochloric acid, generated the presumed indolidene intermediate **12**. This reactive species was trapped with cyanide to afford the highly hindered nitrile adduct **13** as a single isomer. This nitrile was functionalized to afford voacangine (**14**) via known procedures.

Figure 4. Büchi and Manning's approach in the synthesis of voacangine (**14**) via indolidene intermediate **12**.
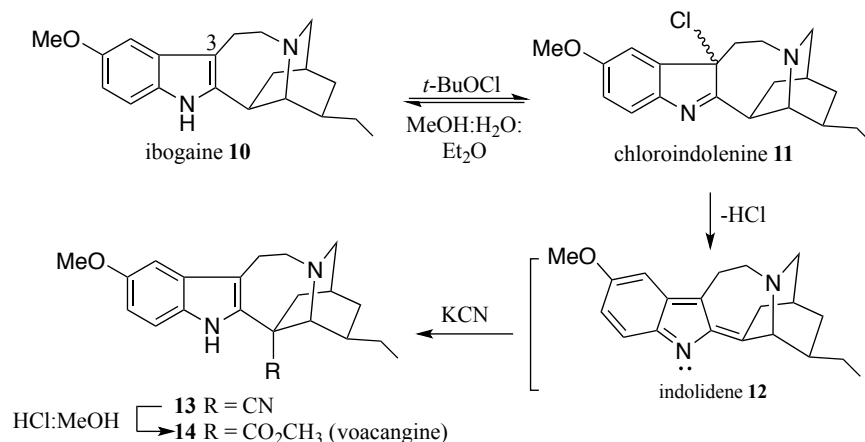
In 1966, Büchi and Manning also hinted at the possibility of utilizing indolidene chemistry as a viable way to access the cancer drug vinblastine (**6**) from the more abundant naturally occurring catharanthine (**15**) and vindoline (**17**).[6] Although efforts through the years have been centered towards the direct coupling of these natural products via indolidene intermediates,[7] it was not until 2009 that Boger and coworkers reported an FeCl₃-mediated single-step biomimetic coupling of catharanthine (**15**) and vindoline (**17**) to afford vinblastine (**6**) in moderate yield (Figure 5).[7] Upon addition of FeCl₃ to catharanthine (**15**), a rearrangement occurred resulting in the formation of presumed indolidene intermediate **16**, which was intercepted by the nucleophilic C(13) position of vindoline (**17**) to afford vinblastine (**6**) upon subsequent redox events. Interestingly, Boger and coworkers have recently published a novel approach for the total synthesis of a potent vinblastine derivative in which indolidene chemistry again was essential in the construction of the critical C(16) all-carbon quaternary stereogenic center.[8]
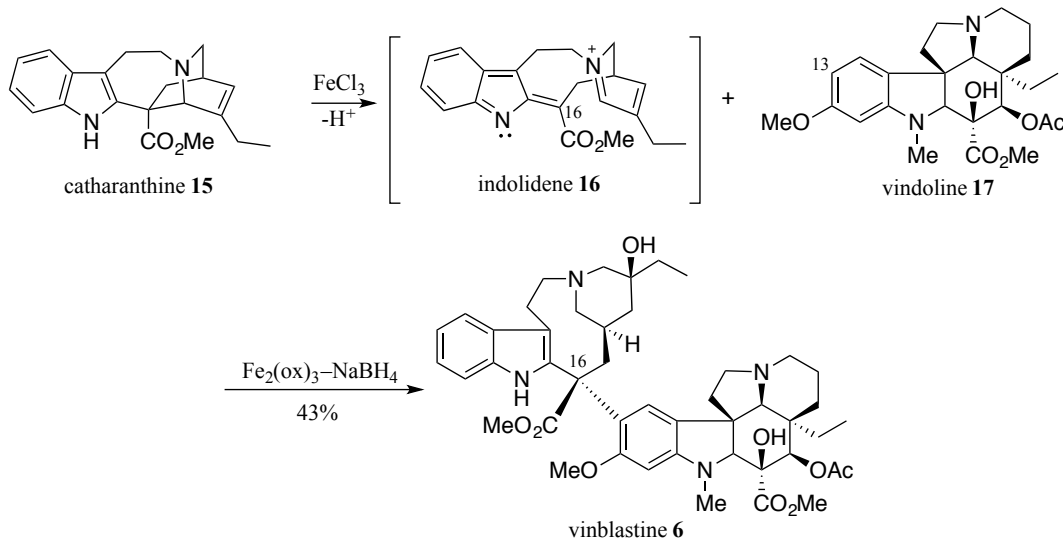
Figure 5. Boger's application of indolidene intermediates in the synthesis of vinblastine (**6**).

It is important to highlight that the indolidene intermediates which are derived from N–H indoles are depicted as neutral species upon the loss of the *N*-hydrogen (Figures 5 and 6).[8–9] In other

examples, the protonated intermediate is shown instead (labeled as an indolidenium cation), as it remains difficult to predict whether the nitrogen is protonated or not.

Indolidene intermediates also has been applied to the biomimetic synthesis of the dimeric borrevine and flinderole alkaloids.[9] For example, Vallakati and May documented the biomimetic synthesis of antimalarial flinderole A (**21**) via indolidene intermediates (Figure 6).[9c] The addition of trifluoroacetic acid to borrerine **18** resulted in the formation of indolidene **19** through ring opening; this species engaged in an intermolecular formal [3 + 2] cycloaddition with the terminal olefin of **20** (a tautomer of **19**) to afford flinderole A (**21**) as well as its diastereomer (not shown).
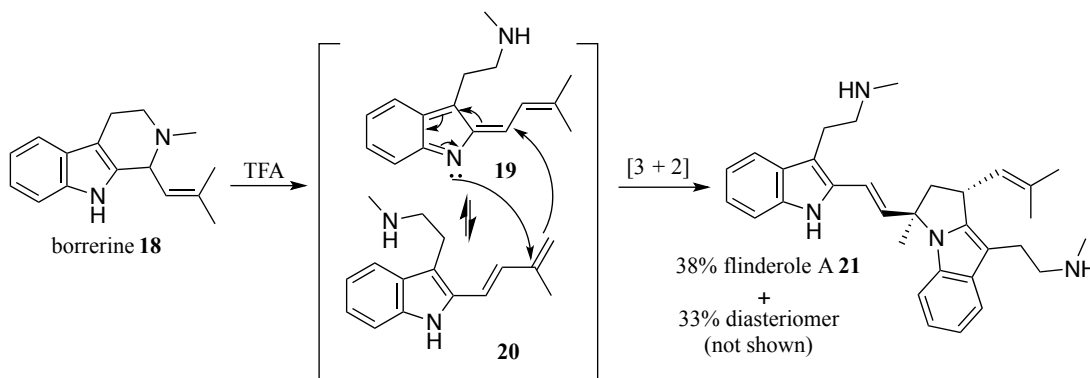
Figure 6. Application of indolidene intermediates in the biomimetic synthesis of flinderole A (**21**).

1.3.2 Indolidenium Cation Intermediates

Büchi and coworkers first postulated the intermediacy of an indolidenium cation in the synthesis of the antimalarial drug voacamine (**25**) via Brønsted acid-mediated solvolysis of the naturally occurring vobasinol (**22**) (Figure 7).[6] In the presence of methanolic hydrochloric acid, vobasinol (**22**) underwent loss of the alcohol moiety to afford indolidenium cation **24**, followed by nucleophilic addition by the C(13) carbon of voacangine (**14**) to afford voacamine (**25**) upon tautomerization. This reaction resulted in high levels of stereoselectivity, presumably as a result of the steric bulk present in the "top" face of the indolidenium cation intermediate **24**.
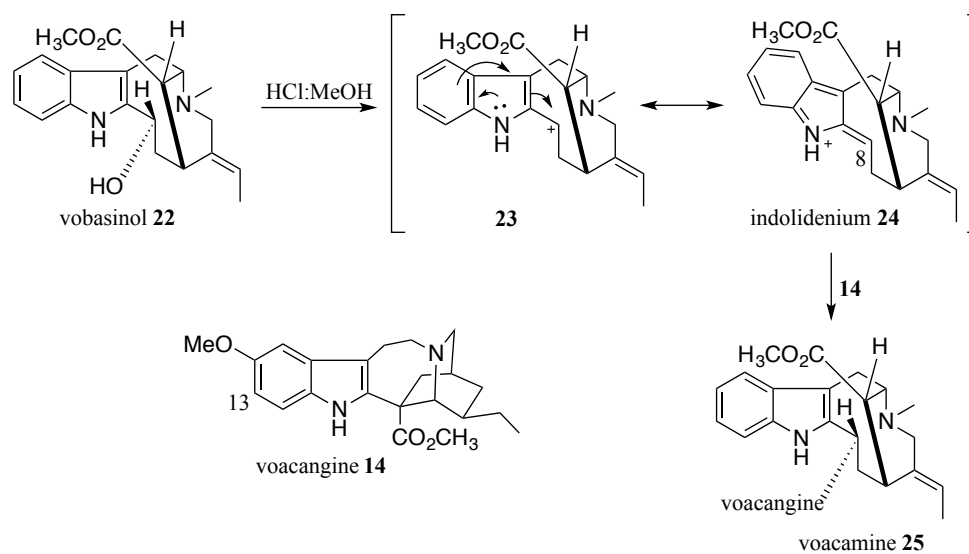
Figure 7. Büchi's approach in the synthesis of voacamine (**25**) from voacangine (**14**) and vobasinol (**22**) via indolidenium cation intermediate **24**.

Indolidenium cations also have been shown to be key intermediates in the synthesis of C(2)-C(3)-cycloheptannylated indoles. Martin and coworkers reported a Lewis acid-mediated formal [4 + 3] cycloaddition for the synthesis of actinophillic acid (**31**), a potential therapeutic for the treatment of thrombotic diseases (Figure 8).[4m] Addition of trimethylsilyl triflate to **26** resulted in the formation of indolidenium cation intermediate **27**, which reacted with aminodiene **28** to produce a conjugated iminium intermediate **29**. Ring closure via a nucleophile attack from the indole C(3) then occurred to afford indole-annelated cycloheptanyl adduct **30** upon tautomerization and TBS removal.
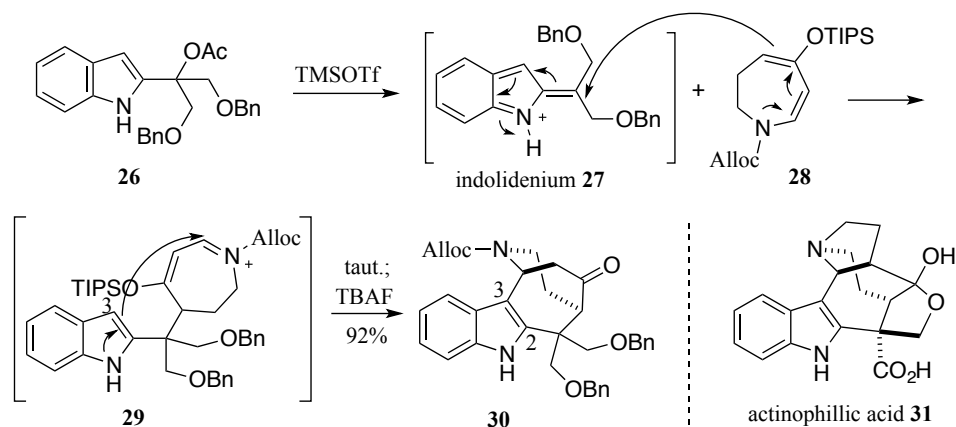
Figure 8. Application of indolidenium cations in the synthesis of actinophillic acid (**31**).

The utility of indolidene and indolidenium cation intermediates also has been demonstrated in the synthesis of aspevering,[10] gilbertene,[11] ibogaine,[5,12] mersicarpine,[4l] normacusine,[5] tronoharine,[4p,13] yuehchukene,[4e,14] and yuremamine[15] and some of their analogues.

1.4 The Feldman Group's Approach Towards the Synthesis of Indolidene and Indolidenium Cation Intermediates

The Feldman group has been interested in developing new ways to synthesize indolidene and indolidenium cation intermediates. In earlier work, our group developed a novel approach for the formation of indolidenes featuring the photolysis or thermolysis of allenyl azides like **32** (Figure 9).[17] Upon irradiation or heat the allene moiety reacts with the azide via a [3 + 2] cycloaddition to generate triazoline intermediate **33**, a species that undergoes spontaneous nitrogen extrusion to provide the indolidene intermediate **34**.
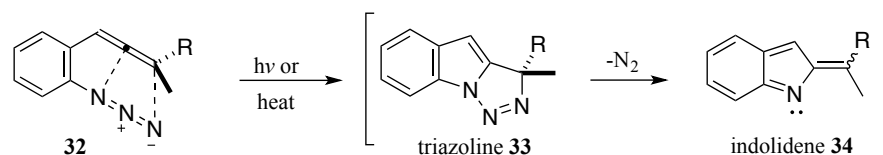
Figure 9. Feldman group's approach for the synthesis of indolidene intermediates via allenyl azides (**32**).

The mechanism of the generation of indolidene **34** from triazoline precursor **33** was studied via Density Functional Theory (DFT) calculations, which were performed by our collaborator, Dr. Carlos Silva Lopez from the University of Vigo, Spain.[18] Upon investigating the mechanism of thermal formation of indolidene intermediates, an interesting result was obtained: the loss of N_2 was predicted to occur via a concerted pathway.[18] This transformation is a formal $[10\pi + 2\pi]$ thermal, suprafacial retrocycloaddition, which is not formally allowed under the established Woodward-Hoffman rules.[19] Support for the proposed mechanism lies in the values obtained for the activation barriers calculated for formation of the diazo diradiacal **35** (25.0 kcal/mol), accessed by stepwise bond scission, and indolidene **37** formation, derived by concerted bond scission (17.4 kcal/mol) (Figure 10).
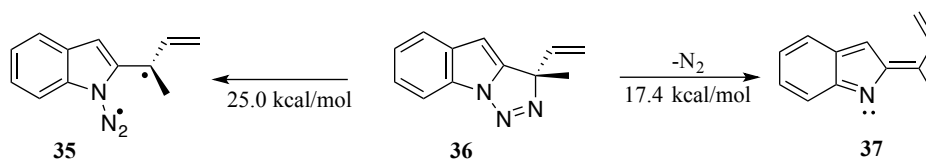
Figure 10. Activation barriers for stepwise vs. converted loss of N_2.

In addition, an electron density picture for the removal of N_2 from **36** was generated via an anisotropy of the current induced density (ACID) calculation, which helps visualize electron density in the bonding regions of molecules.[20] The ACID representation for the delocalization of electron density in the transition state **38** is depicted in Figure 11a.[18] There is virtually no electron density in the fragmenting C–N and N–N bond regions. Thus, the electronic communication between both π systems is practically nonexistent. This result is not true for the similar Diels–Alder cycloreversion between butadiene and N_2, where electron delocalization is evident at the cleavage points (Figure 11b). This electronic argument suggests that the Woodward-Hoffman rules do not apply for the concerted loss of N_2 from **36**, as the two π systems are effectively orthogonal.
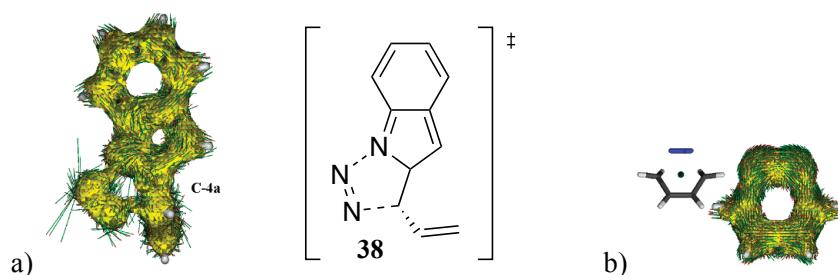
Figure 11. ACID isosurface for the transition state in the a) concerted loss of N_2 from **36** and b) Diels–Alder cycloreversion between butadiene and N_2.

The Feldman group also has explored the synthesis and reactivity of indolidenium cation intermediates. Previously, it was demonstrated that the reaction of indolenyl ether **39** with a catalytic amount of a Lewis acid, such as scandium triflate, resulted in a putative reactive indolidenium cation intermediate **40**, which was intercepted by furan to provide **41** in very good yield (unpublished results, Figure 12). Reactions with other nucleophiles are of current interest.
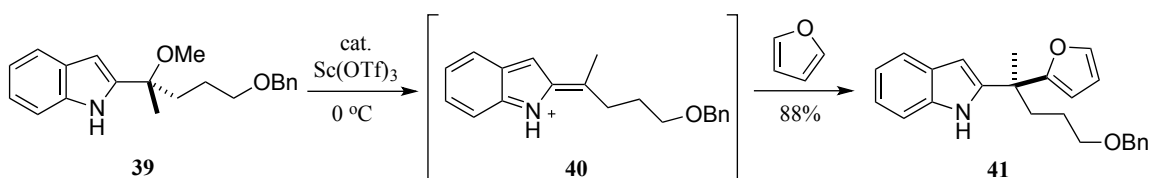
Figure 12. Reactive indolidenium cation intermediate **40** trapped by furan.

1.5 Application of Allenyl Azide-Derived Indolidene Intermediates in Natural Product Synthesis

Efforts towards investigating the reactivity profile of indolidene intermediates have resulted in novel modes of functionalization via the C(3) or C(8) electrophilic positions. In our laboratory, indolidene intermediates derived from allenyl azides were applied to efforts towards the total synthesis of the indole alkaloid gilbertine (**45**, Figure 13).[21] Irradiation of allenyl azide **42** generated the indolidene intermediate **43**, which was intercepted by a pendant alcohol nucleophile followed by proton transfer to generate the cyclized product **44**. The allenyl azide **42** also was subjected to thermolysis, delivering the desired cyclized adduct **44** in lower yield. Both reactions proceeded with complete stereochemical control derived from the preexisting stereogenic centers.
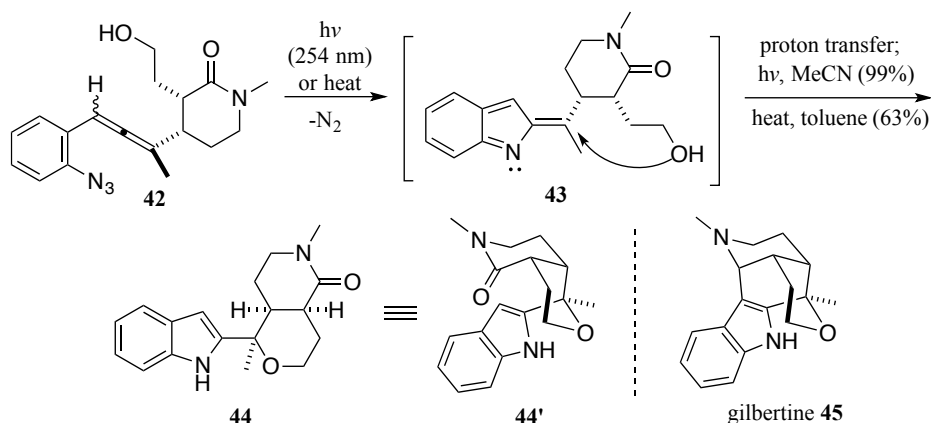
Figure 13. Feldman group's approach towards the total synthesis of gilbertine (**45**) via indolidenes.

Indolidene chemistry also has been utilized to access the core of the fisherindole family of natural products, such as fisherindole L (**49**) (Figure 14).[17b] This reaction featured the generation of an indolidene intermediate **47** from allenyl azide **46**. This indolidene intermediate was subsequently trapped by an internal alkene in an 12π electrocyclization reaction to afford the cyclopentannelated indole product **48**. Interestingly, higher levels of regiochemical control were observed when a copper source was added, hinting towards a possible N–Cu favorable interaction.
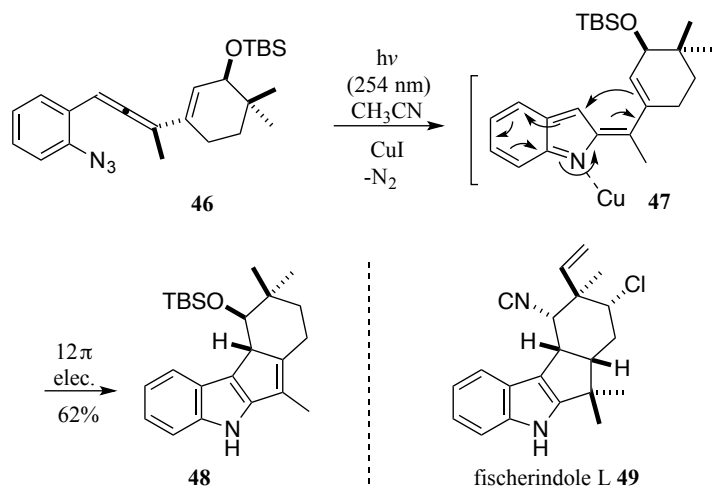
Figure 14. Feldman group's approach in the synthesis of the fischerindole core via indolidenes.

1.6 Proposal for the Synthesis of the Skeleton of the Indolosesquiterpene Family of Natural Products via Indolidene and Indolidenium Cation Chemistry

1.6.1 Challenges in the Synthesis of Indolosesquiterpenoids

Could this chemistry be expanded and applied in the synthesis of biologically active compounds containing an indolosesquiterpene core (the carbon skeleton in **52**, Figure 15) such as lecanindole D (**50**), nodulisporic acid D (**51**), paspaline (**52**), paspalinine (**53**), peritrem D (**54**), and other related natural products (Figure 15)? There are several challenges posed by these complex terpene-indole alkaloids; for example, the presence of vicinal all carbon quaternary stereocenters (C(3) and C(4) in **50**) and the *trans* stereochemistry at the 5,6 ring junction (C(3) and C(12) in **50**) are likely to be difficult to establish.[22] Indeed, one of the major challenges in the synthesis of indoloterpenoids lies in the stereoselective formation of the *trans* 5,6-fused rings because *trans* hydrindanes are typically less thermodynamically stable than *cis*-hydrindanes due to ring strain.[23] Thus, careful strategic planning is required to access this unit with high stereoselectivity.
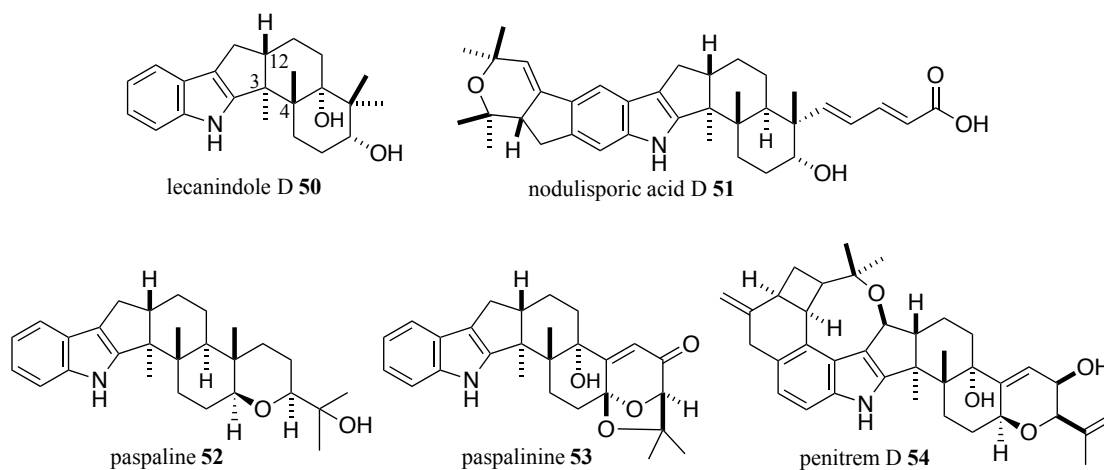
Figure 15. Representative terpene-indole alkaloids.

Several completed syntheses of highly complex indoloterpenoids have been achieved throughout the years.[24–26] These efforts are mainly attributable to Amos B. Smith III from the University of Pennsylvania, who has been a pioneer in this area. In the past 30 years, Smith and

coworkers have completed 8 total syntheses of terpene-indole alkaloids containing the indolosesquiterpene core.[24] In 1985, Smith et al. first disclosed the total synthesis of (–)-paspaline (**52**), which was accomplished in 23 steps while highlighting the challenges posed by the vicinal quaternary stereocenters and the *trans* 5,6-fused ring system (Figure 16).[24a] Reductive alkylation of enone **55** resulted in the formation of **56** with the quaternary center at C(12b) *trans* to the angular methyl at the C(12c) carbon, although in poor yield. However, the undesired diastereomer was observed in a greater quantity.
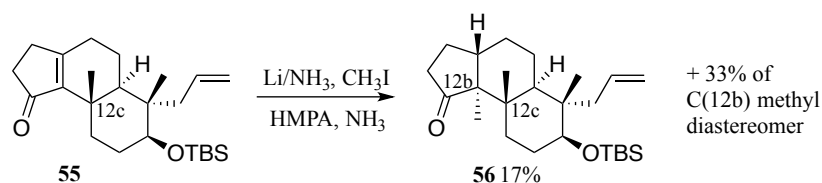
Figure 16. Installation of the vicinal quaternary stereocenters and *trans* 5,6-fused rings in the total synthesis of paspaline (**52**).

The later syntheses of terpene-indole alkaloids reported by the Smith group focused on addressing the challenges faced in the installation of the vicinal quaternary stereocenters and 5,6-fused rings, and as a result more efficient approaches have been developed.[25b–25l] Their most recent work features the total synthesis of (–)-nodulisporic acid D (**51**), in which the key stereogenic centers in the E ring are set with the correct stereochemistry prior to ring closure.[25m] (Figure 17). Conjugate addition of a vinyl appendage at the C(12) position within **57** proceeded with high stereocontrol driven by the steric congestion presented by the angular methyl at C(4). The resultant silyl enol ether adduct **58** was then successfully transformed into the quaternary center C(3) within **59** via cleavage of the silyl group followed by methyl addition opposite to the angular methyl at C(4). The *trans* hydrindane adduct **60** was synthesized in 3 steps from **59** involving an additional oxidation step.
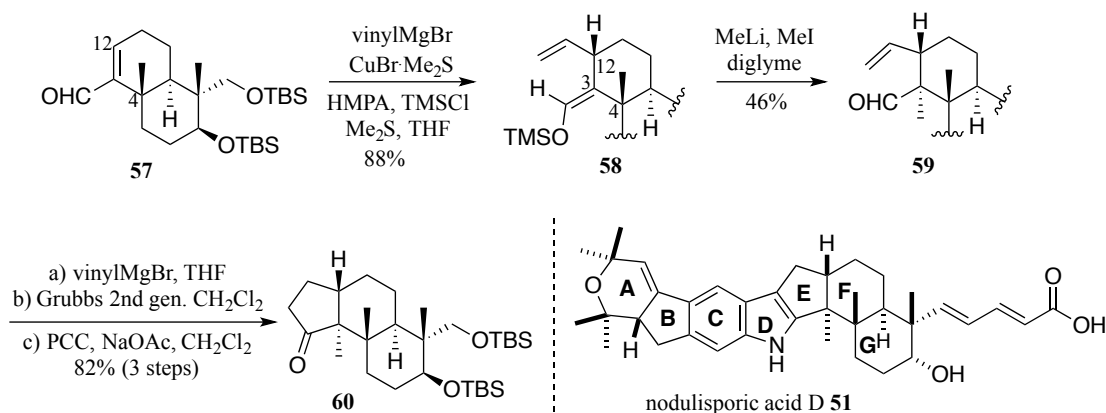
Figure 17. Smith's approach for the synthesis of (–)-nodulisporic acid D (**51**).

The Kuwahara, Johnson and Pronin groups also have contributed towards the total synthesis of terpene-indole alkaloids containing the indolosesquiterpene core. Kuwahara and coworkers reported a total synthesis of paspalinine (**53**) that featured a hydroxyl-directed cyclopropanation approach to install the key C(3) stereogenic center (Figure 18).[25] Selective reduction of the carbonyl within **61** was achieved to produce **62** as a single isomer. An alcohol-directed Simmons-Smith cyclopropanation was employed to install the C(3) stereocenter within (**63**). A re-oxidation event followed by a reductive cleavage generated **65** with the required vicinal quaternary stereocenters along with the 5,6-fused rings containing the desired *trans* stereochemistry. While successful in constructing a *trans* hydrindane, this approach is not redox economical, an important consideration in planning/executing total syntheses. This chemistry also was applied in the total synthesis of lecanindole D[26] (**50**, vide infra) as well as terpendole E[27] (not shown).
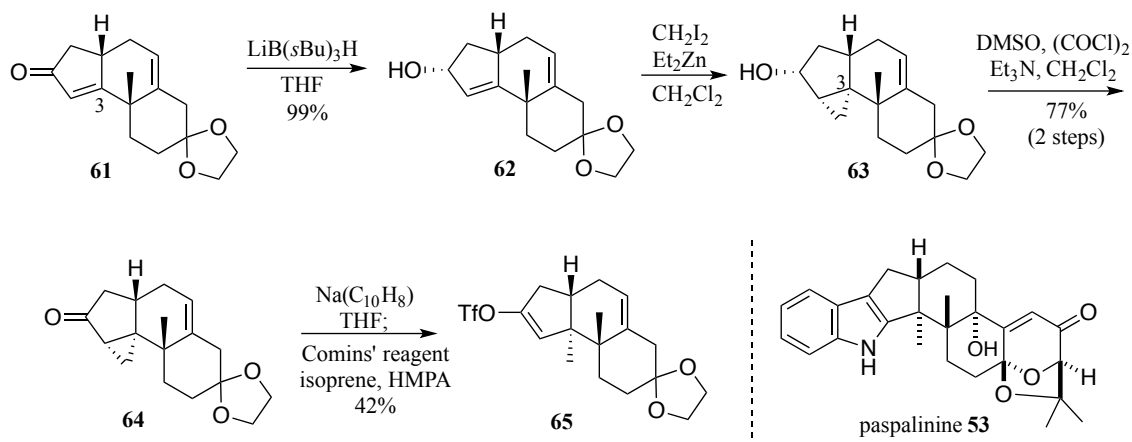
Figure 18. Kuwahara's approach for the synthesis of paspalinine (**53**).

Sharpe and Johnson described a different approach for the installation of the vicinal quaternary stereocenters and 5,6-fused rings, with the required relative stereochemistry, in the total synthesis of (–)-paspaline (**54**) (Figure 19).[28] A selective C–H activation method was utilized to produce the stereogenic center at C(12) within **67**. This strategy relied on the position of the oxime in **66'** being in plane with the equatorial methyl group, resulting in a stereo-controlled C–H activation event to attain the vicinal quaternary centers with the correct relative stereochemistry. Seven additional steps, including uneconomical redox manipulations, also were required to install the *trans* hydrindanes moiety within **69**.
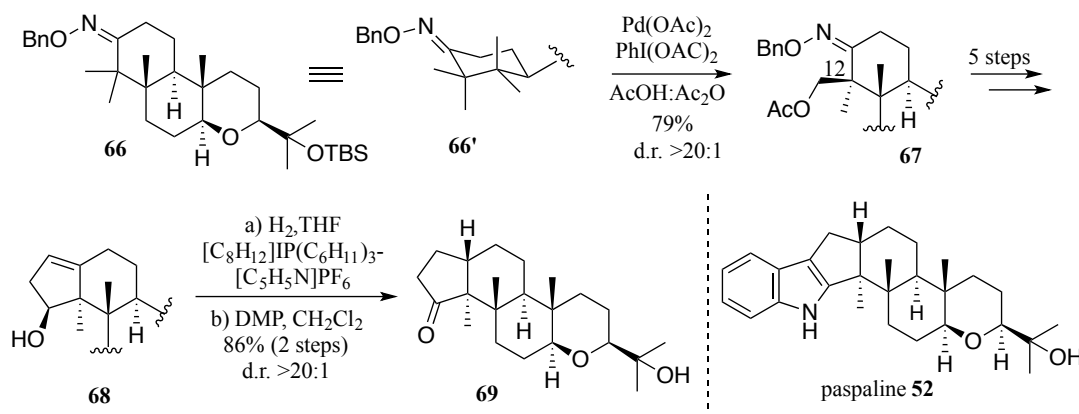
Figure 19. Sharpe and Johnson's approach for the synthesis of (–)-paspaline (**52**).

The most recent approach for the synthesis of the indoloterpenoid emindole SB (**74**), the simplest member of the paxilline family of natural products, was reported by Pronin and coworkers (Figure 20).[29] This new strategy relied on the alkenylation of cyclopentanone derivative **70** to install the quaternary center at the C(3) carbon of **71** with the correct stereochemistry required to install the *trans* 5,6-fused rings. After 5 subsequent steps, hemiaminal **72** was generated as a single diastereomer that underwent a tandem radical addition reaction to afford **73** containing the vicinal quaternary stereogenic centers with the correct relative stereochemistry. Although Pronin's approach is more efficient than those previously discussed in this section,[24–28] there still is room for improvement. We believe that indolidene and indolidenium cation intermediates could be key players in the concise construction of the aforementioned terpene-indole alkaloids.
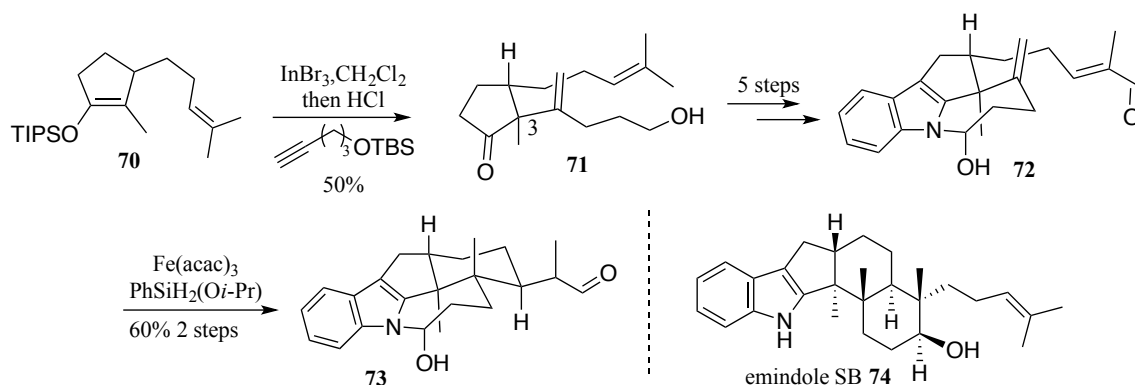
Figure 20. Pronin's approach for the synthesis of emindole SB (**74**).

1.6.2 Indolidene and Indolidenium Cation Intermediates in the Synthesis of the Indolosesquiterpene Family of Natural Products

We propose that the formation of these reactive intermediates (**75** and **76**) could be realized in the presence of a pendant nucleophile, which then could react via a formal [3 + 2] cycloaddition to afford the core of the indolosesquiterpenoids as depicted in Figure 21. This pentacyclic adduct **78** should contain the desired *trans* stereochemistry at the 5,6 ring junction as well as the vicinal all carbon

stereogenic centers with the correct relative stereochemistry. The stereochemical preference for *trans* ring fusion is anticipated by invoking a chairlike transition state (**75** and **76**) where the alkene substituents undergoing C–C bond formation are placed in a pseudoequatorial position to avoid unfavorable diaxial interactions. As a result, the correct relative stereochemistry of the vicinal quaternary centers also should be achieved.
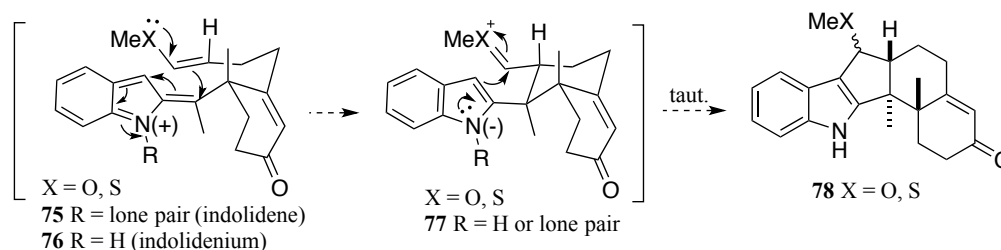
Figure 21. Indolidene and indolidenium cation intermediates in the synthesis of the skeleton of indolosesquiterpenoids.

1.7 Aim of this Dissertation

The goal of this dissertation is to showcase the efforts made towards the execution of intramolecular formal [3 + 2] cycloadditions involving indolidene and indolidenium cation intermediates, while addressing the challenges of synthesizing indole-fused *trans* hydrindanes. Chapter 2 describes a Lewis acid-mediated bicyclization involving the solvolysis of indole 2-(methyl alcohol) derivatives to deliver indolidenium cation intermediates, which are trapped by alkenes. Regiochemical problems arise and our efforts to favor C–C bond formation are described. Through this project, a synthesis methodology for the carbofunctionalization of 2-bromo-*N*-benzylated indole also was developed, an important reaction in the synthesis of the indolidenium/alkene cyclization precursor. In Chapter 3, a light-promoted tricyclization reaction involving indolidene intermediates and an alkenyl sulfide nucleophile, is presented. Issues with stereochemistry and regiochemistry, as well as mechanistic studies, also are discussed. Finally, the aim of Chapter 4 is to demonstrate the application of the indolidene chemistry shown in Chapter 3 to the synthesis of the indolosesquiterpene core of the

progesterone agonist lecanindole D. Efforts towards the total synthesis of lecanindole D also are discussed, including the installation of the vicinal all carbon stereogenic centers.

Chapter 2

[3 + 2] Cyclocondensations of Alkenes with Indolidenium Cation Intermediates

2.1 Background

The Feldman group has been investigating the reactivity of indolidenium cation intermediates in C–C bond-forming processes. In efforts directed towards the synthesis of the pentacyclic core of the indolosesquiterpenoids, a model reaction involving indolidenium cation intermediates and alkenes was designed to install the *trans* 5,6-fused rings of the target structure (Figure 22). This proposed intramolecular formal [3 + 2] cyclocondensation reaction features a Lewis acid-mediated solvolysis of 2-(methyl alcohol) derivatives **79** to produce indolidenium cation intermediates **80**. These reactive species **80** then could be intercepted by a pendant alkene nucleophile, such as methyl vinyl ether, to generate oxocarbenium ion intermediate **81**, containing the *trans* stereochemistry present at the 5,6 ring junction. This stereochemical outcome (*trans* substituents) is anticipated by reaction through a chairlike construct. The subsequent nucleophilic attack by the indole C(3) carbon on the oxocarbenium within **81** could produce the tetracycle indole **83** upon deprotonation.
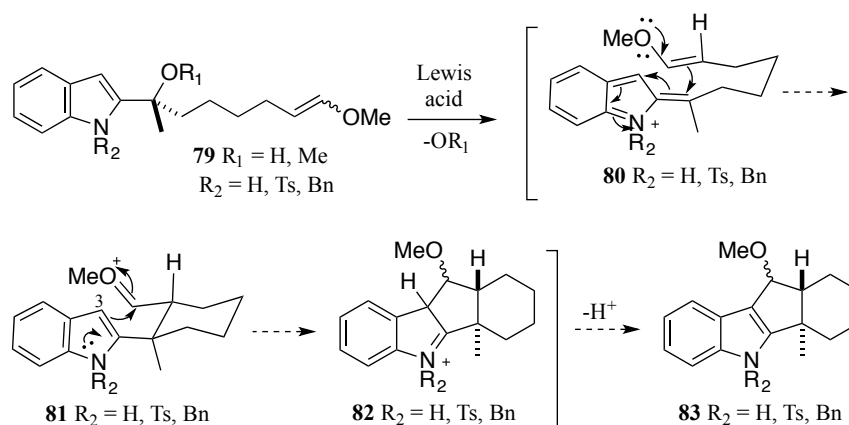
Figure 22. Proposed intramolecular [3 + 2] cyclocondensation reaction via indolidenium cations.

2.2 Intermolecular Addition of Alkenes to Indolidenium Cation Intermediates

Initial efforts to explore the proposed [3 + 2] cyclocondensation reaction via indolidenium cation intermediates were pursued via an intermolecular approach (Figure 23). We envisioned that 2-methyl alcohol substrate **84** should generate the indolidenium intermediate **86**, which could react with the external nucleophile methyl vinyl ether (**85**) to generate cyclopentannelated indole **88** upon deprotonation.
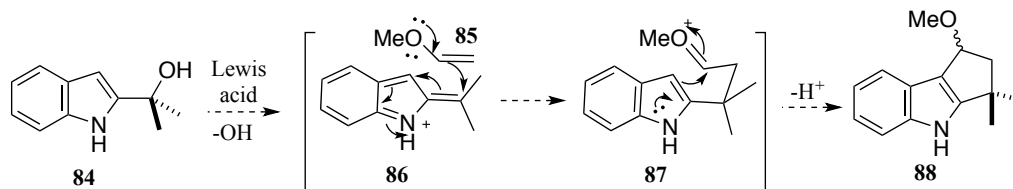
Figure 23. Intermolecular approach for the formation of cyclopentannelated indole **88** via indolidenium cation intermediate **86**.

The starting indolenyl alcohol **84** was synthesized from commercially available 2-indole-carboxylic acid (**89**) by 2 sequential methylations in excellent yield (Figure 24). Unfortunately, the initial cyclization attempts with **84** and methyl vinyl ether (**85**) produced a complex mixture of products; consequently, no characterizable products were isolated and identified. The ^{1}H NMR spectrum did not display an N–H peak, suggesting that the unprotected nitrogen could be a problem, which might be circumvented by incorporating a nitrogen-protecting group.
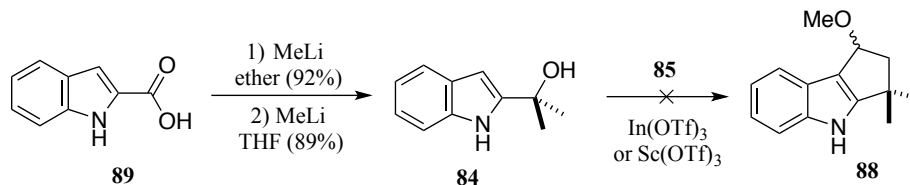
Figure 24. Synthesis of indolenyl alcohol **84** and cyclization attempt.

We blocked the reactive nitrogen with a tosyl protecting group (Figure 25). Attempts to tosylate 2-indolic alcohol **84** proved unsuccessful, as only unreacted starting material was observed. Ultimately,

we opted for installing the isopropyl unit on *N*-tosyl indole **90**, which resulted in the desired tosylated 2-indolic alcohol **92** in very good yield (Figure 25).
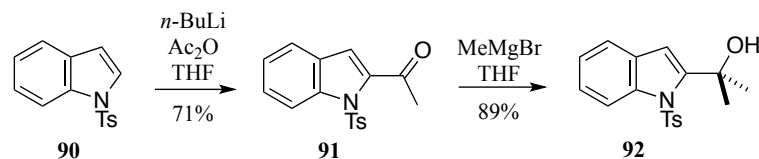
Figure 25. Synthesis of tosylated indole **92**.

The cyclization precursor **92** and the ethyl vinyl ether nucleophile were exposed to a combination of different Lewis acids, solvents, and temperatures, and the results are depicted in Table 1 and Figure 26. Unfortunately, the desired cyclized product **94** was never detected and elimination product **93** was observed in every cyclization attempt (entries 1–9). An aldehyde-containing product also was detected in some of the reactions (entries 3, 4 and 7). Efforts to elucidate its structure proved unsuccessful, as the compound could not be isolated in pure form. In order to favor the desired addition pathway over elimination, the number of equivalents of the ethyl vinyl ether nucleophile **85** was increased (1.2 to 5 to 20 eq., entries 1–3, respectively), which only resulted in polymerization of the ethyl vinyl ether nucleophile. We suspected that the Lewis acid could be the catalyst for this polymerization, and indeed control experiments demonstrated that the Lewis acids catalyze the polymerization of **85**. Interestingly, it also was discovered that the unknown aldehyde observed in entries 3, 4 and 7 derived from the reaction of ethyl vinyl ether (**85**) and the listed Lewis acid. These results suggest that ethyl vinyl ether (**85**) is not a suitable nucleophile for this annelation reaction.
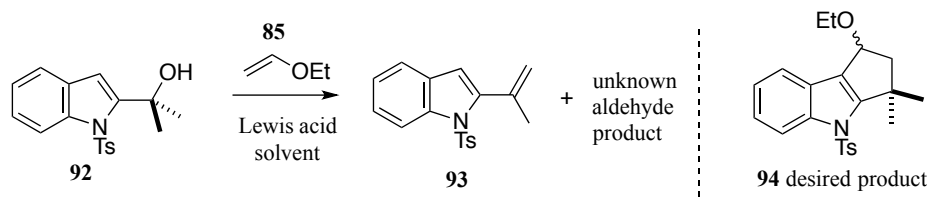
Figure 26. Cyclization attempt for tosylated indole **92**.

Table 1. Product of the reaction of ethyl vinyl ether **85** and tosylated indole **92**

entry	eq. **85**	Lewis acid	temp.	solvent	products
1	1.2	In(OTf)$_3$	-78 °C	toluene	**93**
2	5	In(OTf)$_3$	0 °C	toluene	**93** + aldehyde + polymers of **85**
3	20	In(OTf)$_3$	0 °C	toluene	**93** + aldehyde + polymers of **85**
4	5	SnCl$_4$	-40 °C	CH$_3$CN	**93** + polymers of **85**
5	5	SnCl$_4$	-78 °C	toluene	**93** + polymers of **85**
6	5	SnCl$_4$	-78 °C	CH$_2$Cl$_2$	**93** + polymers of **85** + unreacted **92**
7	5	BF$_3$·Et$_2$O	-78 °C	toluene	**93** + aldehyde + polymers of **85**
8	5	BF$_3$·Et$_2$O	-78 °C	CH$_2$Cl$_2$	**93** + polymers of **85** + unreacted **92**
9	1.5	TMSOTf	-40 °C	CH$_3$CN	**93**

Other nucleophiles screened with the tosylated substrate **92** included Danishefsky diene (**95**) and methoxy trimethylsilyl enol ether (not shown); however, only the undesired elimination product **93** was observed with these highly nucleophilic reactants. We reasoned that the electron deficient tosyl group was promoting the elimination pathway due to the enhanced electrophilicity of the indolidenium cation intermediate. To test this hypothesis, Danishefsky diene (**95**) was combined with the nonprotected 2-indolic alcohol **84** (Figure 27). Indeed, cycloheptannelated adduct **97** was formed in moderate yield, presumably from a novel formal [4 + 3] cycloaddition reaction between indolidenium intermediate **96** and Danishefsky diene (**95**). Alas, Martin and coworkers published a very similar transformation (Figure 8) around the same time of this discovery,[4m] so we turned our attention to the proposed intramolecular alternative involving indolidenium cations and alkene nucleophiles.
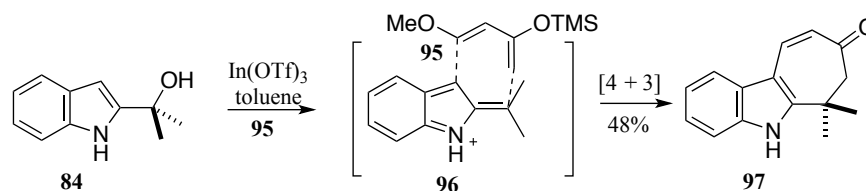
Figure 27. Formation of cycloheptenone-annelated indole **97** from the reaction of Danishefsky diene (**95**) and indolidenium cation intermediate **96**.

2.3 Intramolecular Cyclization Studies of the Reaction of Indolidenium Cation Intermediates with Alkene Nucleophiles

2.3.1 Methyl Vinyl Ether Nucleophile

We were interested in exploring whether indolidenium cation intermediates would engage in an intramolecular [3 + 2] cyclocondensation with pendant alkenes, as proposed in Figure 22. In parallel work to the intermolecular studies, Christopher Glinkerman, an undergraduate in our group, demonstrated that the reaction of indole **98** with a catalytic amount of the Lewis acid indium triflate afforded formal [3 + 2] cycloadducts (**100**–**103**) as a mixture of *cis* and *trans* *N*-cyclized stereoisomers (Figure 28).[30] However, these *N*-cyclized products do not match the skeleton of the indolosesquiterpenoids. To promote the desired C-cyclization, we sought to install an *N*-protecting group in order to avoid the formation of *N*-cyclized products.

	100 *19%*	**101** *17%*	**102** *13%*	**103** *2%*
predicted J_{ab} (Hz)	8.8	5.4	1.0	4.3
observed J_{ab} (Hz)	8.5	5.6	1.0	4.9
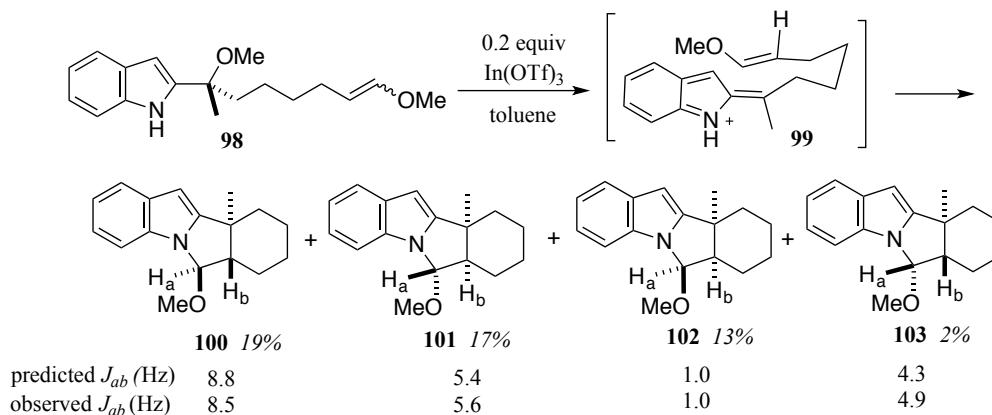
Figure 28. Synthesis of enol ether indole substrate **98** and Lewis acid-mediated [3 + 2] cyclocondensation.

A new cyclization precursor was synthetized using an *N*-benzyl protecting group. We opted for a benzyl instead of a tosyl protecting group because we hypothesized that the NBn would boost the nucleophilicity of the C(3) carbon to make the C–C bond-forming pathway more favorable. The benzylated methyl vinyl ether adduct **112** was synthetized via a 7-step route in collaboration with Christopher Glinkerman (Figure 29).[30] Commercially available 3-heptyn-1-ol (**104**) was first

isomerized to the terminal alkyne via a zipper reaction. Alkynol **105** was oxidized under Parik-Doering

conditions and the generated aldehyde **106** was converted into the methyl vinyl ether **107**, as a 1.7:1

mixture of *E* and *Z* isomers, through a Wittig reaction. The methyl vinyl ether substrate **107** was

coupled to 2-azidobenzaldehyde (**108**) and the resulting alkoxide was trapped with acetic anhydride to

afford **109** in good yield. Allenyl azide substrate **110** was obtained via an S$_N$2' reaction on the

propargylic acetate in **109** using a MeCu complex, which was formed by the combination of MeMgBr,

CuI, and LiBr. The desired benzylated cyclization precursor **111** was obtained by irradiating or heating

allenyl azide **110** in methanol, resulting in adduct **98** (vide infra) followed by benzyl protection using

standard conditions.
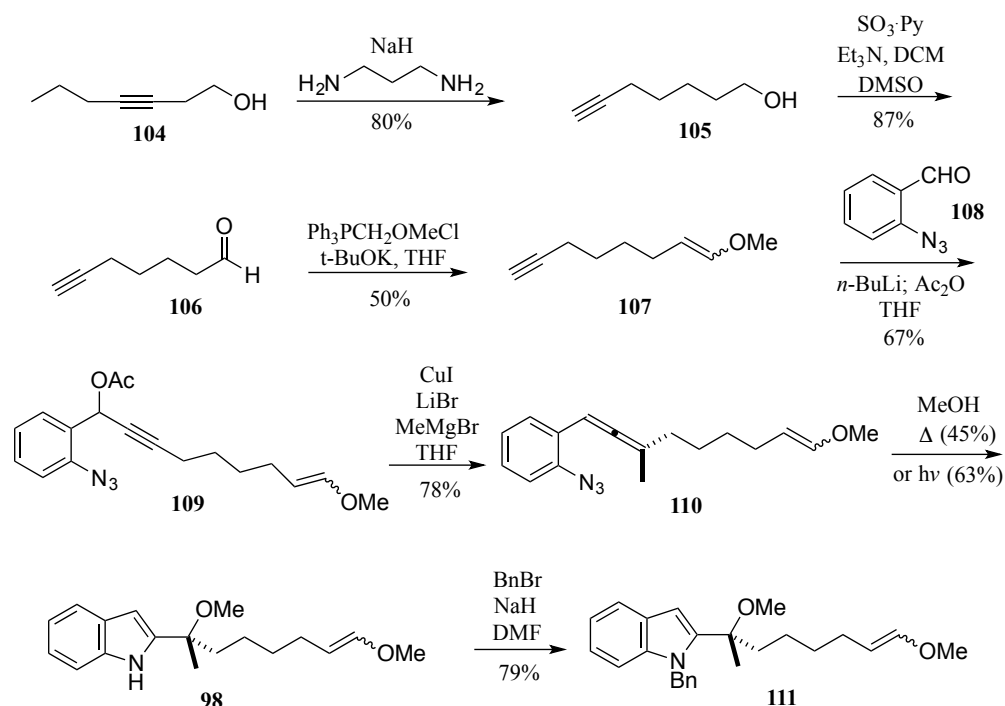
Figure 29. Synthesis of *N*-benzyl enol ether indole substrate **111**.

Upon treatment of **111** with indium triflate in toluene, no trace of the desired C-cyclized

product **113** was observed.[30b] Instead, a mixture of products was obtained, two of which were

successfully isolated via column chromatography. The major product, acetal **112**, was identified via a

combination of characterization techniques: NMR (^{1}H, ^{13}C, and DEPT) and Mass Spectrometry (MS) (Figure 30). The mechanism by which this product was formed remains a matter of speculation. The second product appears to be a dimer (^{1}H NMR, ^{13}C NMR and MS identification), although the exact structure could not be secured. In an attempt to suppress dimerization, the concentration of the reactants was drastically reduced (80 mM to 4 mM) and although no dimerization was observed, only the acetal product **112** was detected along with other uncharacterized species; the desired C-cyclized product **113** still was not detected.
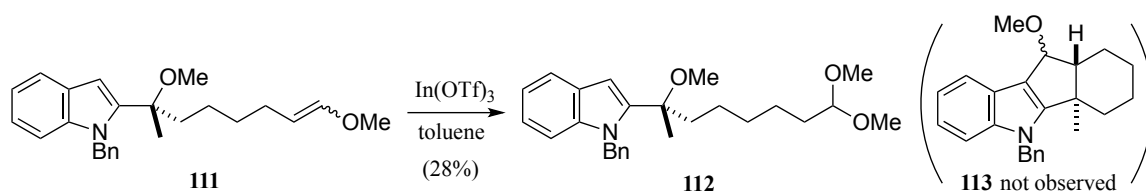
Figure 30. Reaction of *N*-benzyl enol ether indole substrate **111** with indium triflate.

2.3.2 Methyl Vinyl Sulfide Nucleophile

Since no evidence for the addition of the C(3) carbon to the oxocarbenium ion within **81** was obtained, we decided to explore the intramolecular cyclization with the related vinyl sulfide nucleophile (Figure 31). This choice was predicated upon the notion that the "softer" sulfur-stabilized carbocation intermediate **116** (analogous to **81**) may be a better reactivity match for the "soft" C(3) indole carbon nucleophile.
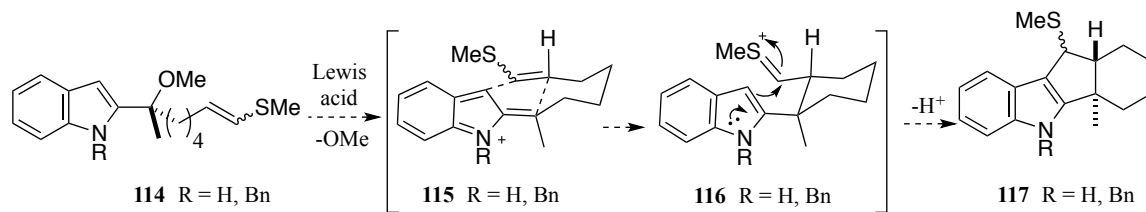
Figure 31. Proposed Lewis acid-mediated [3 + 2] cyclocondensations via indolidenium cation intermediate **115** and a methyl vinyl sulfide nucleophile.

The synthesis of the alkenyl sulfide cyclization precursor proved to be straightforward, as a similar synthesis approach previously applied to the synthesis of the methyl vinyl ether substrate **111** (Figure 29) was employed (Figure 32).
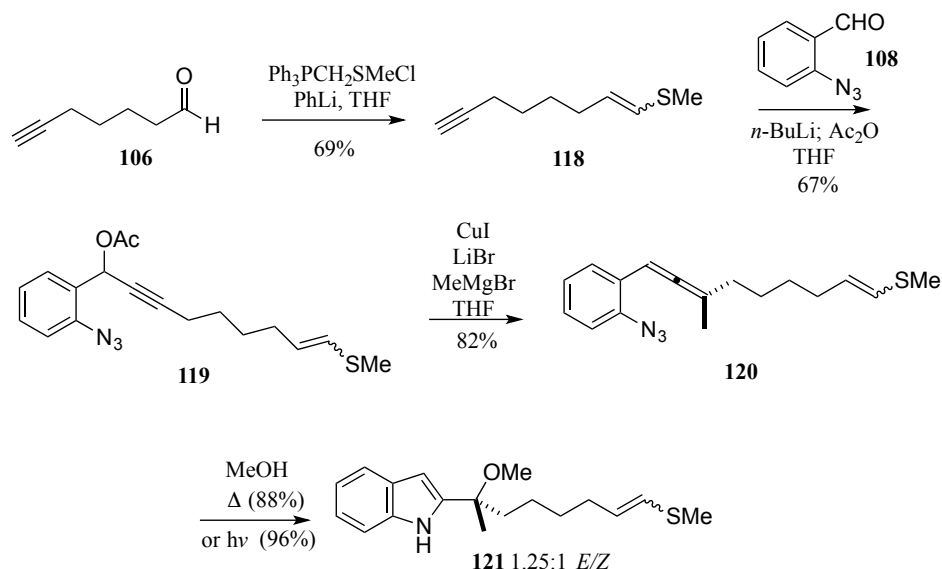
Figure 32. Synthesis of alkenyl sulfide cyclization substrate **121**.

The alkenyl sulfide substrate **121** then was exposed to indium triflate and the results are depicted in Table 2 and Figure 33.[30] Note that the benzyl protecting group is not (yet) attached to the indole nitrogen. Gratifyingly, the results in toluene solvent indicated that a mixture of the desired C-cyclized products **123/124** was formed in addition to *N*-cyclized product **126**. By replacing the oxygen atom with a sulfur, we seem to have found a better electronic match between the heteroatom stabilized-carbocation and the C(3) carbon nucleophile. Furthermore, the desired *trans* stereochemistry at the ring junction within C-cyclized products **123/124** also was favored, as predicted. The C- and *N*-cyclized products were isolated via column chromatography. However, the mixture of C-cyclized stereoisomers **123–125** was inseparable via chromatography; a suitable solvent was not found and all 3 products co-eluted. Fortunately, the major isomer **123** was isolated via preparatory HPLC and fully characterized

(^{1}H NMR, ^{13}C NMR, HMBC, HMQC, DEPT, MS, and IR [NOE spectrum was inconclusive]). The analysis of product stereochemistry is discussed below.

This Lewis acid-mediated cyclization reaction was explored further by increasing the polarity of the solvent in an effort to increase the yield/selectivity for the C-cyclized products **123/124** (Table 2, entries 2 and 3).[30] In acetonitrile and CH$_2$Cl$_2$, this cyclization reaction led strictly to the formation of C-cyclized products **123–125**, although the selectivity for the desired *trans* isomers **123/124** decreased. In a control experiment, submission of the *N*-cyclized product **126** to the same reaction conditions in entries 2 and 3 resulted in a mixture of unidentifiable products. Thus, any *N*-cyclized material that might have been formed under the reaction conditions in entries 2 and 3 likely was destroyed. The cyclization reaction also was performed in CH$_3$CN at a lower temperature (entry 4) and with catalytic amount of Sc(OTf)$_3$ (entry 5), but the yield of the major C-cyclized product **123** remained similar to the yield for the reaction in toluene (entry 1).
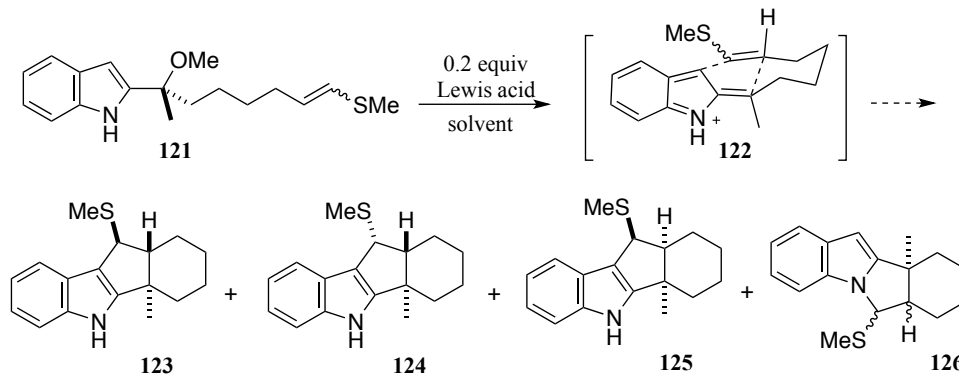
Figure 33. Synthesis of alkenyl sulfide indole substrate **121** and Lewis acid-mediated [3 + 2] cyclocondensation.

Table 2. Product yields as a function of Lewis acid, temperature and solvent for the [3 + 2] cyclocondensation of alkenyl sulfide indole substrate **121**

entry	Lewis acid	temp.	solvent	**123**[a]	**124**[a]	**125**[a]	**126**[b]
1	In(OTf)$_3$	0 °C	toluene	46	6	-	38
2	In(OTf)$_3$	0 °C	CH$_2$Cl$_2$	18	2	trace	-
3	In(OTf)$_3$	0 °C	CH$_3$CN	34	4	13	-
4	In(OTf)$_3$	-40 °C	CH$_3$CN	46	-	3	-
5	Sc(OTf)$_3$	0 °C	CH$_3$CN	37	5	13	-

[a]Isolated percent yield of pure **123**/**124**/**125** combined; ratio determined by integration of characteristic signals in the ^{1}H NMR spectrum. [b]Percent yield of isolated, pure product.

The relative stereochemistry within the C–C bonded products **123–125** was assigned by comparing the calculated coupling constant values between H$_a$–H$_b$, derived from energy-minimized structures (see Appendix A for calculational details), with the observed coupling constant values (Figure 34). In addition, the major isomer **123** was subjected to reduction conditions to remove the methyl sulfide moiety (vide infra), and the spectral data for the *trans* desulfurized product **127** matched the data reported for authentic **127**.[4h] The ^{1}H NMR signal for the angular methyl in the *trans*-fused species **127** was given as 0.98 ppm (CDCl$_3$)[4h] and the experimental value obtained for the desulfurized products **127** was 1.02 ppm (CDCl$_3$); the value reported for the angular methyl in the *cis* adduct was 1.29 ppm.[4h] Furthermore, a mixture of *trans*- and *cis*-ring-fused C-cyclized adducts (**123**/**125** = 3.7:1) also was submitted to the reduction conditions, and the same ratio of *cis*-to-*trans*-ring-fused products was obtained for the desulfurized products **127** and **128** (Figure 35).

	123	**124**	**125**
predicted J_{ab} (Hz)	11.1	6.6	6.5
observed J_{ab} (Hz)	10.1	6.1	8.4
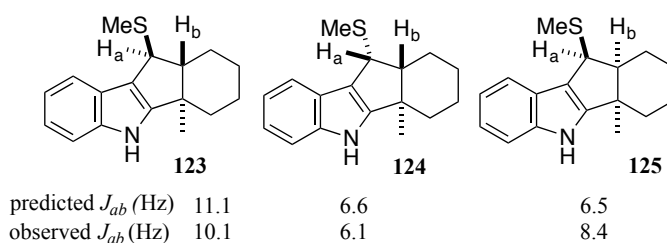
Figure 34. Predicted values for the coupling constant values between H$_a$-H$_b$.
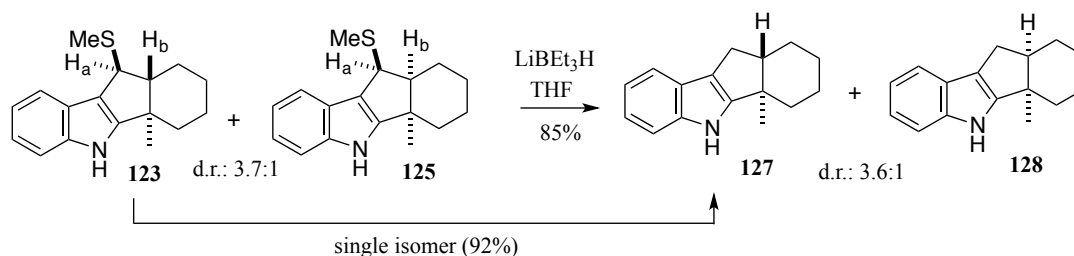
Figure 35. Removal of methyl sulfide moiety.

In an attempt to eliminate the formation of any *N*-cyclized product, the nitrogen was again protected with a benzyl group.[30] In this instance, a more direct route was devised to access the desired benzylated cyclization precursor **136** (Figure 36). Commercially available isatin (**129**) was benzylated and reduced to oxindole **131** under Wolff-Kishner conditions. Oxindole **131** was then brominated using phosphorous oxybromide and imidazole[31] to generate **132**, which was coupled via lithium-halogen exchange to methyl vinyl sulfide-bearing ketone **135** (made in two steps from 1-methylcyclohexene (**133**)). The benzylated cyclization precursor **136** was produced in high yield as a 1.6:1 mixture of *E/Z* alkenyl sulfide isomers (Figure 36). The lithium-halogen exchange strategy on a benzylated indole molecule had not been fully explored earlier. Thus, we also studied the scope and limitations of this process (see Section 2.6 for a chapter insert outlining these results).
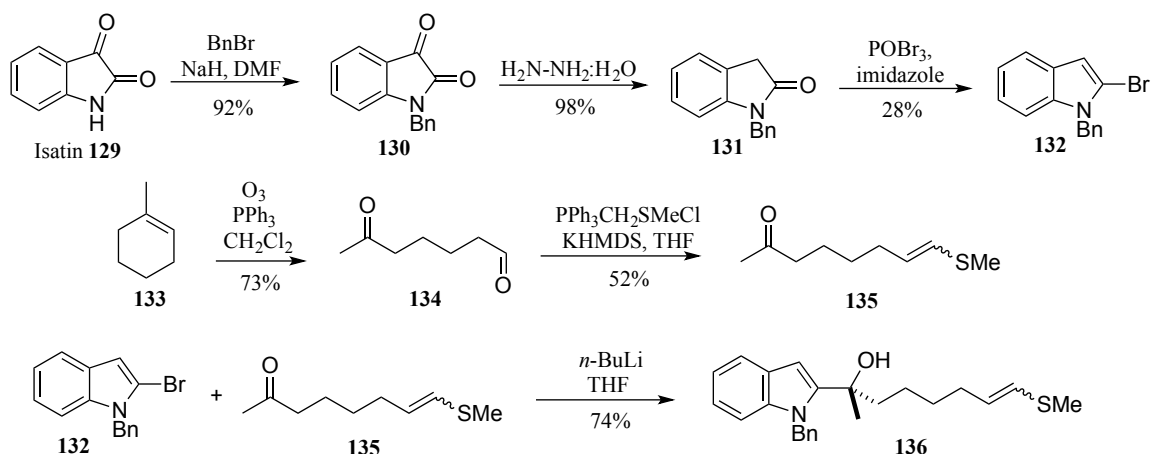
Figure 36. Synthesis of *N*-benzyl indole alkenyl sulfide substrate **136** using alternate route.

The free alcohol **136** then was exposed to indium triflate in different solvents and the results are depicted in Table 3 and Figure 37.[30] In both toluene and CH_2Cl_2, the C-cyclized products were obtained in poor yield and stereoselectivity, inferior to the results presented in Table 2 for the free indole substrate **121**. To our delight, when the cyclization reaction was run in CH_3CN, a mixture of the C-cyclized epimers **137** and **138** was isolated in excellent yield (Figure 37). The major product was isolated via column chromatography and fully characterized (^1H NMR, ^{13}C NMR, MS, and IR). The stereochemistry again was assigned by comparing experimental *J*-coupling constants to calculated values. The major isomer **137** also contained the desired *trans* 5,6 ring juncture present in the skeleton of the indolosesquiterpenoids.
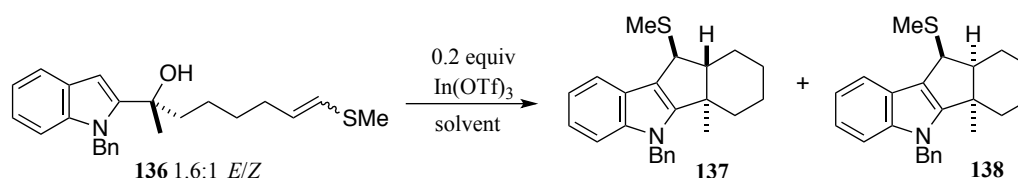
Figure 37. Indium triflate-mediated [3 + 2] cyclocondensation of *N*-benzyl indole alkenyl sulfide substrate **136**.

Table 3. Product yields as a function of solvent for the In(OTf)$_3$-mediated [3 + 2] cyclocondensation of *N*-benzyl indole alkenyl sulfide substrate **136**

entry	solvent	**137**[a]	**138**[a]
1	toluene	30	12
2	CH_2Cl_2	25	19
3	CH_3CN	61	24

[a]Isolated percent yields of pure **137**/**138** combined; ratio determined by integration of characteristic signals in the ^1H NMR spectrum.

2.4 Mechanistic Proposal for Intramolecular Cyclizations of Indolidenium Cation Intermediates and Alkene Nucleophiles

The results for the Lewis acid-mediated bicyclizations can be rationalized by the intermediacy of a highly reactive indolidenium cation species **139** or **140**, which react with a pendant alkenyl sulfide

nucleophile via a chairlike transition state (Figure 38). The alkene nucleophile can be aligned pseudoequatorially or pseudoaxially with the electrophilic indolidenium moiety to afford the sulfur-stabilized cationic intermediates **116/141**. These sulfur-stabilized carbocations within **116/141** can be trapped by either the C(3) carbon (for the R = H and R = Bn systems) to afford the C-cyclized products **123–125** and **137/138** or the nitrogen (for the R = H substrate) to generate *N*-cyclized product **126**.

The observed stereoselectivity for the *trans* isomer can be attributed to the position of the alkenyl sulfide moiety in a chairlike transition state (**139/140**, Figure 38). The alkenyl sulfide nucleophile preferentially resides in a pseudoequatorial position (e. g., **139**) as opposed to the energetically disfavored pseudoaxial equivalent (e. g., **140**). Moreover, the difference in product distribution for the oxygen substrate **98** and its sulfur analogue **121** can be rationalized by citing our design criteria; in the proposed intermediates **81** and **116**, the "soft" sulfur-stabilized carbocation exhibits a better reactivity match for the softer C(3) carbon nucleophile compared to the "hard" oxocarbenium ion, which might prefer the "harder" nitrogen nucleophile.
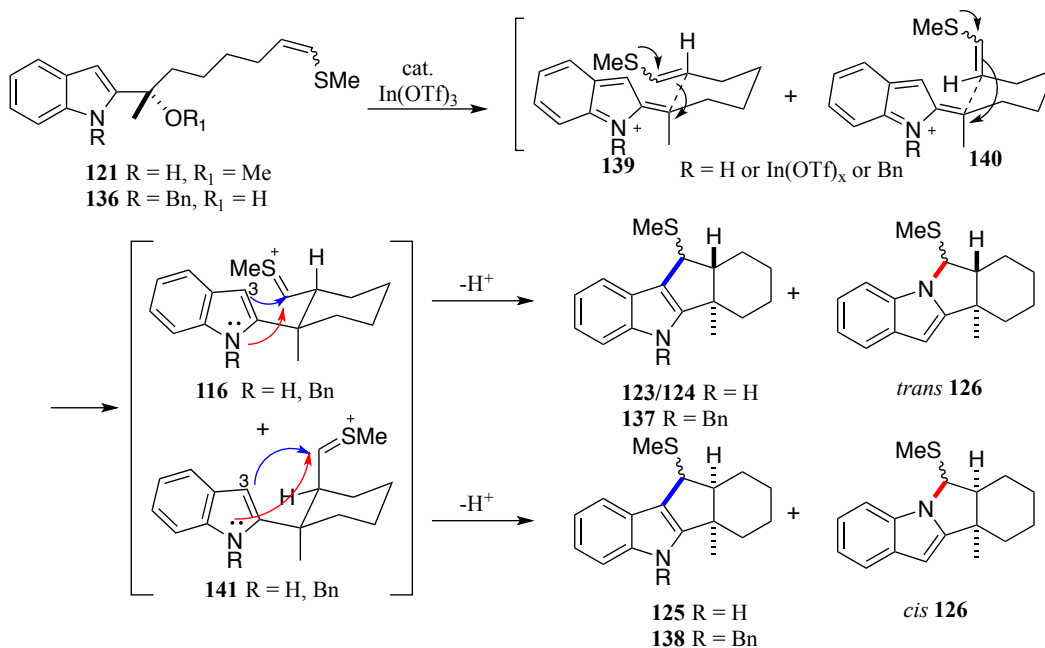
Figure 38. A mechanistic proposal for the indium triflate-mediated bicyclization for **123** and **138**.

2.5 Conclusion

A novel intramolecular Lewis acid-mediated [3 + 2] bicyclization was developed for alkenyl sulfide species **121** and **136** involving indolidenium cation intermediates and alkenyl sulfide nucleophiles. The resulting tetracyclic products **123/124** and **137** contain a *trans* 5,6-fused ring system and two new C–C bonds, both of which were created with control of regiochemistry and stereochemistry. This reaction showcases the utility of indolidenium cation intermediates in C–C bond-forming processes for the construction of the challenging *trans* hydrindanes unit within the indolosesquiterpenoids. Moreover, these results now serve as precedent for the synthesis of the core of the indolosesquiterpenoids.

2.6 Chapter Insert

2.6.1 Lithium-Bromide Exchange: Carbofunctionalization of 2-Bromo-*N*-Benzyl Indole

The introduction of a carbon substituent at the indolic 2-position is essential to the synthesis of C-2-functionalized indoles. This bond-forming process has been accomplished by a variety of different approaches utilizing transition metals, for example, Heck,[32] Sonogashira,[33] Stille,[34] and Suzuki[35] cross-coupling reactions using the corresponding 2-halogenated indoles. An attractive alternative is the direct C–H lithiation of the 2-indole position, which has been realized using *N*-methyl indoles as well as with indoles bearing a variety of nitrogen protecting groups.[36] However, this process is problematic for *N*-benzyl indoles due to competing benzylic deprotonation.[36b,37] It has been documented that at low temperatures, metalation of *N*-benzyl indole (**142**) using *n*-BuLi occurs at the benzylic position to afford alkylated product **144** following an acetophenone quench. On the other hand, C-2 alkylation is preferred at refluxing temperatures, although in poor yield[38] and uncharacterized debenzylated products are generated[39] (Figure 39). Therefore, the direct metalation of *N*-benzyl indoles is not the best approach for the construction of 2-substituted-*N*-benzyl indoles in high yields.[40]
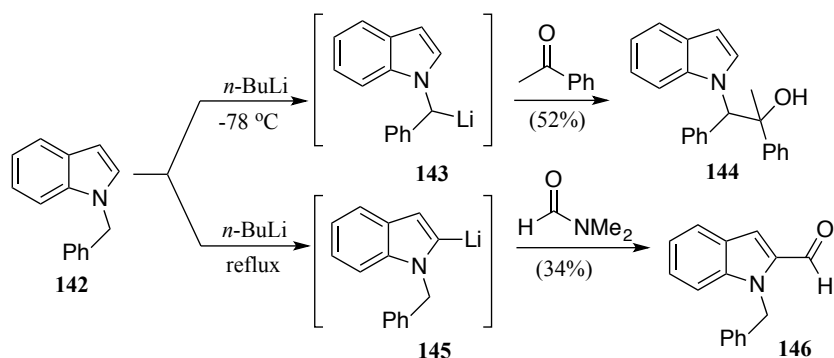
Figure 39. Regiospecific alkylations of *N*-benzyl indole (**142**) at the C-2 and benzylic positions as a function of temperature.

The carbofunctionalization of 2-halogenated *N*-benzyl indoles via a lithium-halogen exchange approach presents another alternative. Previous work by Merlic and coworkers on the synthesis of indole 2-boronic esters hinted that this transformation could be possible using *n*-BuLi instead of the highly reactive and dangerous *t*-BuLi.[38a] Motivated by their findings, we set out to execute a lithium-bromide exchange reaction within 2-bromo-*N*-benzyl indole (**132**) using *n*-BuLi, and react the derived 2-lithioindole with carbonyl compound **135** to generate a new C–C bond.[30a] The proposed lithium-halogen exchange reaction resulted in the formation of alcohol product **136** in very good yield, which served as the cyclization precursor for the Lewis acid-mediated bicyclization described in section 2.3.2 (Figure 36).[30a] This simple but previously unexplored method is therefore a better alternative for the carbofunctionalization of the indolic 2-position than the direct C-H lithiation approach. Thus, in collaboration with Jocelyn Brown, an undergraduate in the Feldman group, we proceeded to explore the reaction's scope and limitations.

Several carbonyl electrophiles were screened, starting with acetophenone (**147**), and the tertiary alcohol product **148** was produced in good yield when *n*-BuLi was employed in the metal exchange (Figure 40). The lithium base *n*-BuLi proved effective at metalation and the use of the more dangerous *s*- or *t*-BuLi was not necessary to achieve this transformation. The number of equivalents of *n*-BuLi was

important in the success of the reaction. Initially, we reasoned that the addition of 2 equivalents would facilitate HBr elimination from the presumed intermediate *n*-BuBr, an electrophile generated in situ that could potentially further react with the lithiated indole. Unfortunately, this procedure was complicated by a competition between the 2-lithioindole and unreacted *n*-BuLi for the carbonyl electrophile. Therefore, the use of 1 equivalent of *n*-BuLi relative to the brominated indole was employed for the subsequent lithium-halogen exchange reactions and the resultant *n*-BuBr did not present a problem for this chemistry.
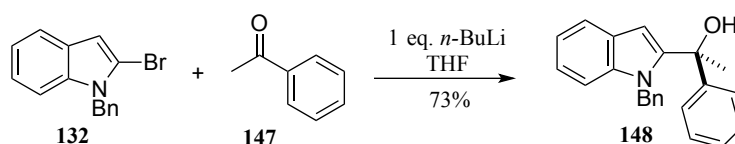
Figure 40. C-2 carbofunctionalization of 2-bromo-*N*-benzyl indole (**132**) via lithium halogen exchange using acetophenone (**147**) as the electrophile, performed by Jocelyn Brown.

We screened different ketones and aldehydes, and the resulting C-2 functionalized indoles are depicted in Figure 41. Electron donating or withdrawing groups were incorporated within the aryl ring of acetophenone (**147**), and similar yields were obtained for **149** and **150**, respectively, as in the electronically unperturbed case. Installing vicinal quaternary centers posed a challenge, as addition of the 2-lithioindole intermediate to hindered pinacolone only provided trace amounts of the alcohol product **151**, even after prolonged reaction time at room temperature or at reflux. However, the less hindered methyl isopropyl ketone electrophile did participate in the reaction and delivered coupled product **152** in good yield. An α,β-unsaturated ketone (methyl vinyl ketone) also participated in the reaction, although reduced yields were observed for **153** due to the formation of unidentified by-products.

149 78%   **150** 75%   **151** trace   **152** 67%[a]

153 53%   **154** 84%   **155** 70%   **156** 76%
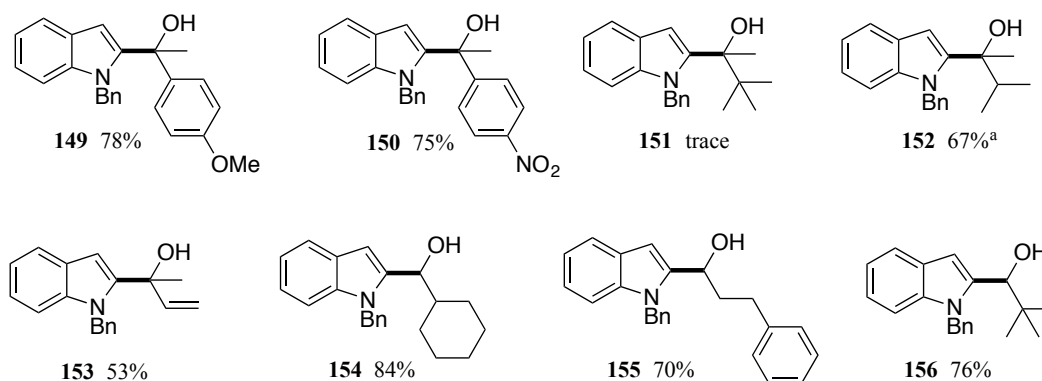
a) Product **152** was synthetized and characterized by Jocelyn Brown.

Figure 41. Lithium-bromide exchange and additions to selected ketones and aldehydes.

Aldehydes such as cyclohexane carboxaldehyde and hydrocinnaldehyde were suitable electrophiles in the addition reaction as well, delivering their respective alcohol products **154** and **155** in very good yields. Surprisingly, nucleophilic addition to hindered pivaldehyde afforded the desired product **156** in very good yield after only 3 hours of stirring, which clearly demonstrates that sterics are not an insurmountable impediment for aldehyde addition to the lithiate derived from **132**. In all the presented entries, alkylation at the benzylic position was not observed; it has been documented that lithium-halogen exchange can sometimes exceed the rate of proton transfer.[41]

We anticipated that the reaction of the 2-lithiated *N*-benzyl indole **157** with ketones and aldehydes possessing α-protons could be problematic; α-deprotonation of the carbonyl compound could occur to afford 2-H-*N*-benzyl indole instead of the desired C-2 functionalized adduct. Since this competitive reaction might contribute to limiting the yield of product formation, deuterium labeling studies were conducted to probe for this mechanistic option in collaboration with Jocelyn Brown (Figure 42). Deuterated acetophenone (**158**) was treated with lithiated *N*-benzyl indole **157** and the resulting alcohol product **159** was fully deuterated at the methyl group; no 2-deuterated *N*-benzylindole (**160**) was observed. This experiment confirms that the rate of addition of the lithiated indole **157** to the carbonyl of the added electrophile is faster than the proton transfer pathway.
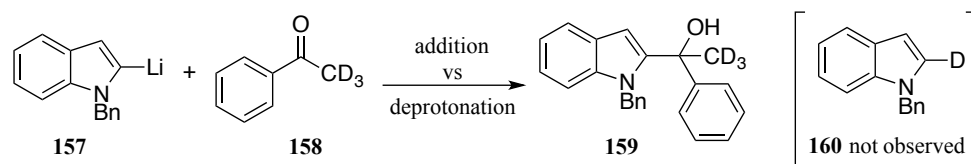
Figure 42. Deuterium labeling studies in the reaction of lithiated *N*-benzyl indole (**157**) with deuterated acetophenone (**158**).

Chapter 3

Intramolecular [3 + 2] Cyclocondensations of Alkenes with Indolidene Intermediates

3.1 Background

The use of indolidene intermediates, derived from allenyl azide cyclizations, followed by a nucleophilic trapping reaction is an effective method for the construction of functionalized indoles, as depicted in Figures 13 and 14 (Chapter 1). Extensions of these transformations also are of current interest in the Feldman group. As an outgrowth to the indolidenium cation-derived [3 + 2] cyclocondensation reaction presented in Chapter 2, we proceeded to explore an alternative using the related indolidene intermediates. We describe a formal [3 + 2] cycloaddition of indolidenes and alkenes in an effort to access the core of the indolosesquiterpene family of natural products (Figure 43). The new design strategy features an allenyl azide cyclization precursor **161** containing a cyclohexenone moiety bearing a pendant alkene nucleophile. Upon irradiation or thermolysis, the allenyl azide portion of **161** is converted to an indolidene intermediate **75**. This indolidene then may be intercepted by the pendant alkene at the C(8) position to produce a new 6-membered ring. This ring closure event is critical in the cyclization cascade as both the *trans* stereochemistry at the 5,6 ring junction and the vicinal quaternary stereogenic centers of the indolosesquiterpenes are set in the same step (**75**, Figure 43). During the C–C bond forming cyclization, the alkene nucleophile should be in a pseudoequatorial position, opposite from the indolidene moiety and the axial methyl, to prevent unfavorable sterics interactions. Likewise, the indolidene moiety also should be positioned in a pseudoequatorial position to avoid unfavorable steric interactions with the cyclohexenone part of the molecule, thus placing the adjacent methyl groups opposite to each other as required for the indolosesquiterpene core. The

resulting heteroatom-stabilized carbocation within **77** should react with the C(3) indole nucleophilic site to form in the final C–C bond of the pentacyclic core **78**, after tautomerization.
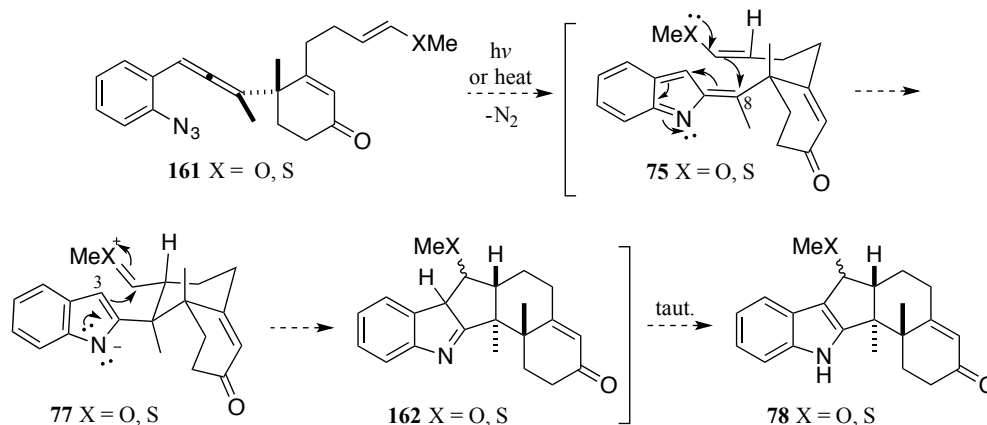
Figure 43. Indolidene intermediates in the synthesis of the indolosesquiterpene core via a formal [3 + 2] cycloaddition reaction.

3.2 Model System for the Intramolecular Formal [3 + 2] Cycloaddition

A model reaction was designed to probe the feasibly of constructing the *trans* 5,6-fused rings of the indolosesquiterpenes via indolidene intermediates (Figure 44). An alkyl chain containing a pendant methyl vinyl ether nucleophile, **110**, was chosen for the initial cyclization attempts. This intramolecular cyclization cascade would result in the formation of two C–C bonds, one C–N bond and three fused rings. Of course, regiochemical and stereochemical problems can arise resulting in a mixture of undesired products.
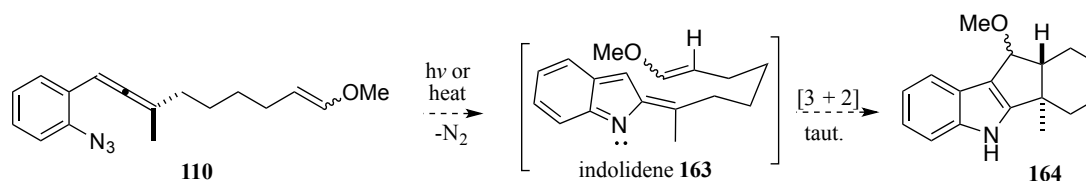
Figure 44. Proposed intramolecular formal [3 + 2] cycloaddition reaction of an indolidene with a pendant methyl vinyl ether nucleophile: model system.

3.3 Potential Problems for the Proposed Cycloaddition

The initial allenyl azide cyclization step, which results in the formation of the indolidene intermediate, is not problematic; however, the formation of undesired stereoisomers and regioisomers instead of, or in addition to, the projected cycloadducts could be a potential problem during the formation of the two C–C bonds. Although we predict that the *trans* stereochemistry at the 5,6 ring junction should be preferred, the generation of *cis* products is still a possibility. Moreover, regiochemical problems also could arise due to the competition between C–C vs C–N bond formation if the indolidene moiety is formed as a mixture of *E* and *Z* geometrical isomers (Figure 45).
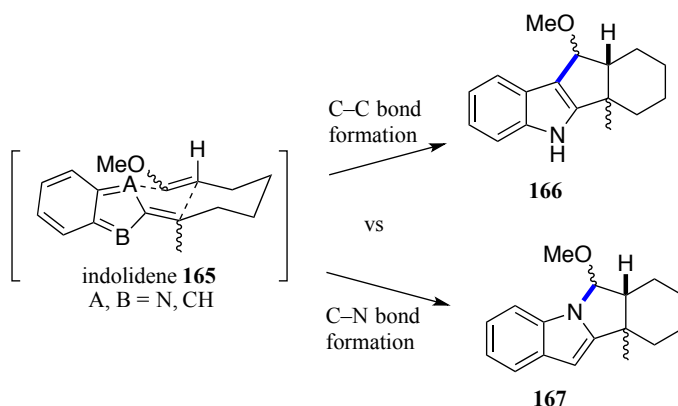
Figure 45. Regiochemical problems: C–C vs C–N bond formation.

One competitive reaction that could be encountered in the proposed cyclization is the elimination of one of the hydrogens adjacent to the indolidene (H_a or H_b) via a formal [1,7]-H-shift to promote indole formation (Figure 46). Hence, if the pendant alkene is not nucleophilic enough, a mixture of "ene" type products **168/169** could be formed. If H_a is eliminated, a terminal alkene will be generated. However, a mixture of geometrical isomers could be formed if H_b participates instead, thus complicating the isolation and characterization steps.
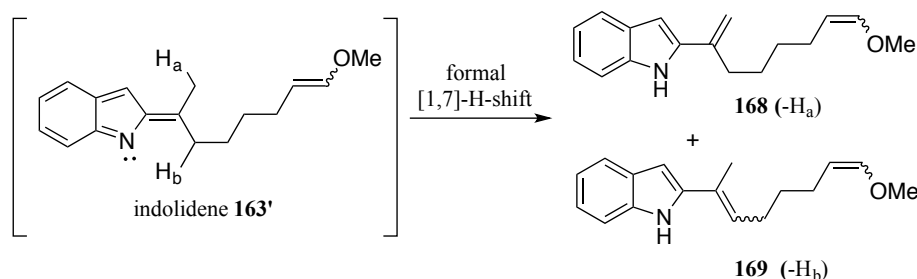
Figure 46. Formation of undesired elimination products via a formal [1,7]-H-shift.

3.4 Allenyl Azide Cyclization Results: Methyl Vinyl Ether Nucleophile

The viability of the proposed [3 + 2] cycloaddition initially was examined under photochemical conditions (Figure 47) in collaboration with Christopher Glinkerman. The cyclization precursor **110**, synthetized in five steps from **104** (Chapter 2, Figure 29), first was irradiated in acetonitrile, the solvent known to deliver the best cyclization results in similar systems.[30] This experiment resulted in a complex mixture of products (~11 spots on TLC) and no characterizable product was isolated. It is possible that the desired C-cyclized product was formed and immediately destroyed under the photochemical conditions; we noticed that a new product would form (shown by TLC) and then disappear before the starting material was completely consumed. Moreover, the reaction was run under both thermal (reflux) and photochemical (350, 300, and 254 nm wavelengths) conditions in other solvents, such as toluene and benzene, and similar results were obtained; no cyclized product **164** was observed. Instead, elimination product **168** appeared to be a major product in these reactions. Unfortunately, it was not possible to isolate pure **168** as other impurities co-eluted during the purification steps via column chromatography.
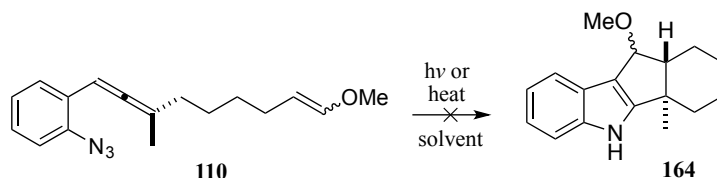
Figure 47. Cyclization attempt for the methyl vinyl ether substrate **110**.

3.5 Allenyl Azide Cyclization Results: Methyl Vinyl Sulfide Nucleophile

We reasoned that by replacing the methyl vinyl ether nucleophile with the analogous methyl vinyl sulfide, a better reactivity match could be achieved, a hypothesis guided by the results obtained for the indolidenium-derived [3 + 2] cyclocondensation with the vinyl sulfide nucleophile described in Chapter 2. Thus, the alkenyl sulfide allenyl azide substrate **120**, synthetized in 5 steps from **104** (Chapter 2, Figure 32), was examined under both photochemical and thermal conditions and the results are depicted in Figure 48 and Table 4.[30]
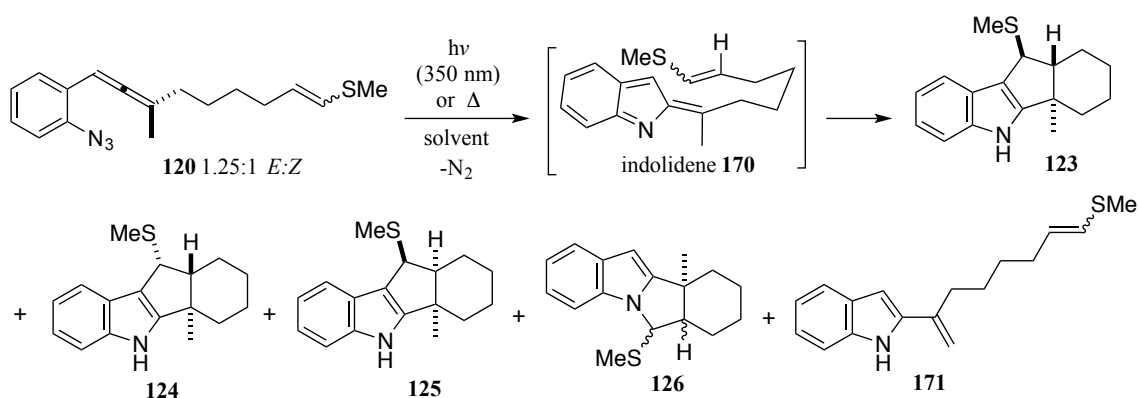
Figure 48. Photochemical [3 + 2] cyclocondensation of alkenyl sulfide substrate **120**.

Table 4. Product yields for the irradiation and thermolysis of allenyl azide **120**[a]

Entry	Conditions	Cat.	**123**	**124**	**125**	**126**	**171**
1	**hν, MeCN**	-	**44**[b]	**2**[b]	**9**[b]	**9**	**3**
2	hν, CH$_2$Cl$_2$	-	trace	-	-	22	-
3	hν, toluene	-	trace	-	-	-	20
4	hν, DMF	-	trace	-	-	-	73
5	hν, MeCN	CuI	trace	-	-	-	-
6	hν, MeCN	In(OTf)$_3$	-	-	-	-	-
7	reflux, MeCN	-	trace		trace	-	40

a) Isolated yields. b) Isolated yield of **123**/**124**/**125** combined; ratio by integration of characteristic signals in the ^{1}H NMR spectrum.

The cyclization precursor **120** was irradiated in CH$_3$CN and to our delight, the desired C-cyclized product **123** was obtained as the major isomer, in moderate yield (Table 4, entry 1); *cis*-

hydrindane **125**, *N*-cyclized species **126**, as well as elimination product **171** also were observed in small but detectable amounts. As a foundational experiment, this result demonstrated the feasibility of the proposed formal [3 + 2] indolidene-based cycloaddition for the formation of indole-fused *trans* hydrindanes. The stereochemical preference for *trans* ring fusion in the C-cyclized products **123/124** (*trans*:*cis*, 8:1) can be rationalized by invoking a chairlike transition state **170** where the methyl vinyl sulfide moiety is placed in the pseudoequatorial position, thus favoring the *trans* stereochemistry. In order to explore and optimize this reaction, CH$_3$CN was exchanged for less polar solvents (CH$_2$Cl$_2$ and toluene). Interestingly, only trace amounts of the desired C-cyclized product **123** was observed and undesired *N*-cyclized species **126** and elimination product **171** were isolated instead (entries 2 and 3). These results show that the cyclization cascade reaction appears to be solvent dependent, which could indicate that stabilization of charge in the proposed intermediates is crucial for obtaining cyclization products in good yield. However, when DMF, a more polar solvent, was screened, only the undesired elimination product **171** was isolated (entry 4). With CH$_3$CN as the chosen solvent, other parameters then were explored. We envisioned that by employing an additive that could coordinate to the nitrogen (see Chapter 1, Figure 14), we could bias the reaction toward the desired C-cyclized products **123/124** and possibly avoid the formation of *N*-cyclized product **126** as well as other side reactions. Unfortunately, when catalytic CuI was employed, only trace amounts of the C–C bonded product **123** was observed via ^{1}H NMR/TLC; the ^{1}H NMR spectrum did not provide evidence for a C(3) peak, suggesting that this nucleophilic site had reacted (entry 5). However, the ^{1}H NMR spectrum showed a messy aliphatic region suggesting product decomposition, which possibly could be attributed to the high affinity of copper for sulfur. Switching to a coordinating metal such as In(OTf)$_3$ led to virtually the same results as observed for the copper additive (entry 6). The next plan was to use heat as opposed to irradiation as the initiating event. To our surprise, when allenyl azide **120** was refluxed in CH$_3$CN, the elimination product **171** was the major isolate, and only trace amounts of the desired C-cyclized

product **123** was detected by ¹H NMR (entry 7), results that are notably inconsistent with those obtained for irradiation. Attempts to boost the yield of the desired C-cyclized products **123/124** included variations of the temperature (0 °C instead of 28 °C) and concentration (3 mM vs 10 mM), but all led to essentially the same results as shown in entry 1. Moreover, at lower wavelengths (300 and 254 nm) the desired C- and *N*-cyclized products were formed but the yield could not be calculated due to impurities co-eluting with the cyclized products; ¹H NMR spectroscopy showed a messy aliphatic region and the overall yield of the desired product appeared to be lessened compared to the 350 nm experiments.

In order to gain further mechanistic insight, we turned our attention to a baseline control experiment: reaction of an unadorned alkene. We synthesized the simple alkene **174** using the same strategy as was used for the preparation of the methyl vinyl ether substrate **110** (Chapter 2, Figure 29), but oct-1-en-7-yne (**172**)⁴² was instead utilized to install the alkene nucleophile (Figure 49). This simple alkene substrate **174** was submitted to photochemical reaction conditions. Upon irradiation of the allenyl azide cyclization precursor, only elimination products **175** were isolated and there was no trace of the desired cyclized product. These results indicate that the simple alkene is not nucleophilic enough to react with the indolidene intermediate, and therefore the default is proton shift.
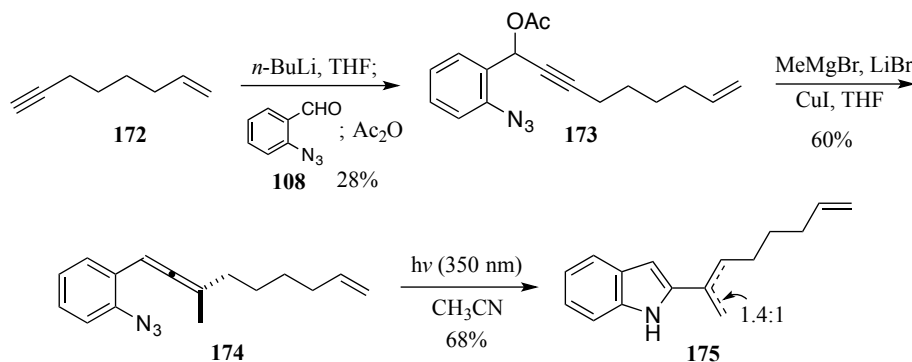
Figure 49. Synthesis of the alkene cyclization precursor **174** and cyclization attempt.

3.6 Cyclization Results for Pure *E*- and *Z*- Alkenyl Sulfide Substrates 120

Initially, the cyclization experiments with **120** were conducted using a 1.25:1 mixture of alkenyl sulfide geometrical isomers. We wondered about the role of alkene geometry during the course of the reaction; therefore we sought to test each isomer individually. The *E* and *Z* isomers were inseparable via column chromatography using SiO_2 as the stationary phase. Fortunately, when the silica gel was impregnated with silver nitrate by following the published protocol of Li and coworkers,[43] the geometrical isomers were successfully separated and each isomer was examined under the same photochemical conditions. A separate chromatography was necessary prior to the cyclization attempts in order to remove any trace of silver contaminants. To our surprise, when pure *E* isomer **120-*E*** was submitted to the cyclization conditions, the desired tetracyclized product **123** was obtained as the major product in very good yield, with excellent control of stereochemistry and regiochemistry compared to the results obtained for the original *E*/*Z* mixture of isomers (Figure 50).[30b] On the other hand, the pure *Z* isomer **120-*Z*** afforded the C-cyclized products as a ~1:1 mixture of *trans* **123/124** and *cis* **125** isomers in low yield along with significant decomposition (Figure 50). Thus, the moderate yield originally obtained for the formation of the C–C bonded products **123/134** from *E/Z* **120** was largely due to the unfavorable reactivity of the *Z*-alkenyl sulfide component of the mixture. Moreover, the formation of the minor *N*-cyclized product appears to be derived from the *E* isomer, as it was only detected in trace amounts when starting with the *Z* alkene isomer.
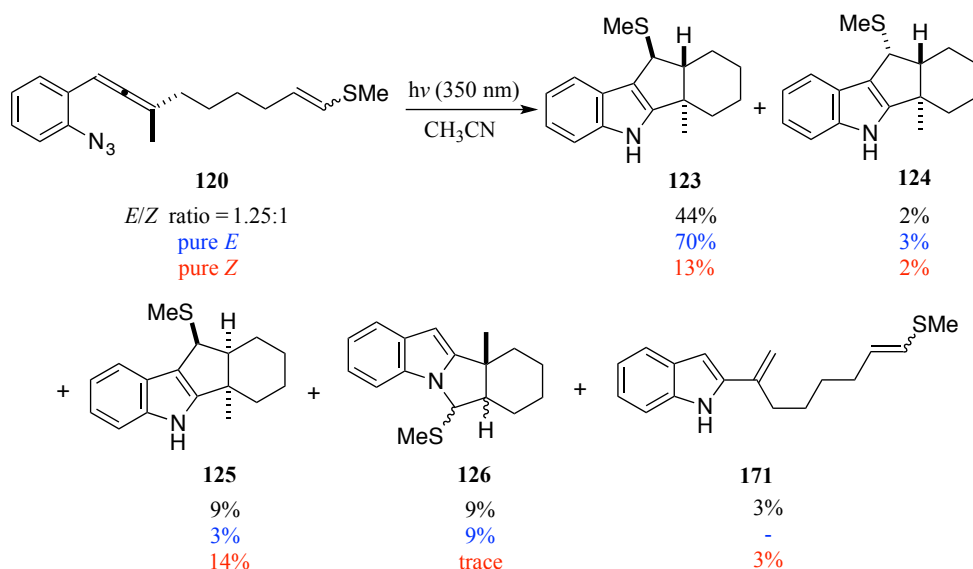
Figure 50. Product distribution as a function of alkene geometry.

Each isomer also was subjected to different UV wavelengths and the results are depicted in Table 5.[30b] The wavelength applied to the system appeared to be crucial for the success of the *E*-alkenyl sulfide isomer reaction but not the *Z* isomer. Irradiation of **120-E** at lower UV wavelengths (300 and 254 nm) afforded the desired C-cyclized products **123**/**124** although the yield had decreased; ^{1}H NMR spectroscopy showed the formation of an unknown indole-containing byproduct in addition to a messy aliphatic region (entries 2 and 3). In contrast, the *Z*-alkenyl sulfide isomer resulted in consistently poor yields of *trans* C–C bonded products **123**/**124** at all three wavelengths along with a plethora of decomposition products (entries 4–6).

Table 5. Products yields as a function of wavelength for the photochemical [3 + 2] reaction of pure *E*- and *Z*-alkenyl sulfide **120**.

entry	substrate	wavelength (nm)	123[a]	124[a]	125[a]	127[a]	171-*E* or 171-*Z*
1	**120-*E***	**350**	**70**	**3**	**3**	**9**	**-**
2	120-*E*	300	50	3	3	13	2
3	120-*E*	254	42	trace	9	5	-
4	120-*Z*	350	13	2	14	trace	3
5	120-*Z*	300	13	2	19	trace	2
6	120-*Z*	254	13	1	16	trace	4

[a]Percent yields determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures relative to the internal standard 1,4-dimethoxybenzene.

The lower yields obtained with lower wavelengths can be explained by examining the UV/vis absorption spectrum for the C-cyclized product **123** (Figure 51).[30b] At 350 nm, there is virtually no UV absorption, but absorption clearly occurs at both the 300 and 254 nm wavelengths, suggesting that product destruction at the lower wavelengths is a real possibility. Control experiments showed that irradiation of **123/124** mixtures at 350 nm for 1 hour resulted in partial decomposition (Figure 52). On the other hand, **123/124** completely reacts to deliver unidentifiable products when the same experiment was repeated with either 254 or 300 nm wavelength light.
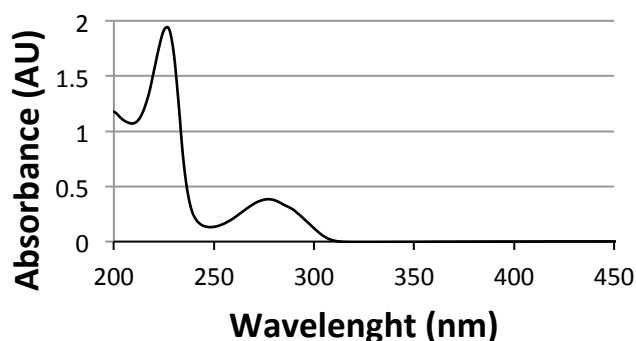
Figure 51. Absorption spectra for the C-cyclized product **123**.
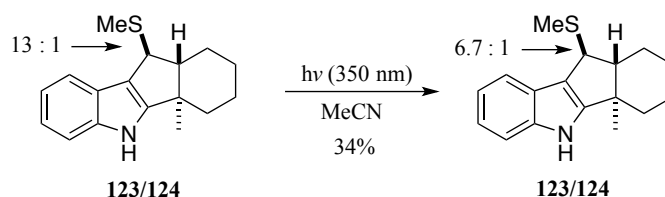
Figure 52. Irradiation of C-cyclized products **123/124** in acetonitrile to probe for stability.

The photochemical reaction for both *E*- and *Z*-alkenyl sulfide isomers **120** at 350 nm also was monitored over time and the results are presented in Figure 53 and Table 6. [30b] After 30 min of irradiating **120-E**, 59% of the major C–C bonded product **123** was present and only 18% of unreacted **120-E** (entry 1). The reaction was monitored at 45, 50, and 60 min, and alkene isomer **120-Z** was never detected via ^{1}H NMR spectroscopy, indicating that no isomerization occurs during the reaction (entries 2–4). After an hour, there was full consumption of the starting allenyl azide and no elimination product **171-E** was observed (entry 4).
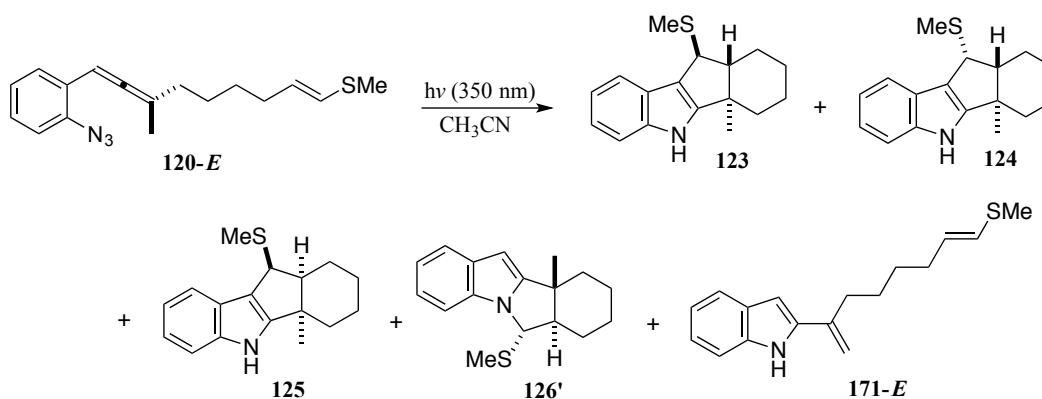
Figure 53. Photochemical [3 + 2] cyclocondensation of pure *E*-alkenyl sulfide substrate **120-E**.

Table 6. Products yield as a function of reaction time for the photochemical [3 + 2] cyclocondensation of pure *E*-alkenyl sulfide substrate **120-E** at 350 nm

entry	time (min)	**120-E**	**120-Z**	**123**[a]	**124**[a]	**125**[a]	**126'**[a]	**171-E**[a]
1	30	18	-	59	1	1	10	5
2	45	4	-	66	3	3	6	3
3	50	5	-	65[b]	5[b]	4[b]	3	4
4	60	-	-	70	3	3	9	-

a) Percent yields determined through integration of the ^{1}H NMR spectra of the crude reaction mixtures relative to the internal standard 1,4-dimethoxybenzene. b) Isolated yield of pure **123/124/125** combined; ratio by integration of characteristic signals in the ^{1}H NMR spectrum.

It is worth noting that while the formal "ene" type product **171-E** was detected while the reaction was being monitored over time (Table 6, entries 1–3), it was not observed upon full consumption of the starting material. We wondered whether the formation of this side product was due to some unreacted indolidene intermediate, which in the absence of light would undergo proton transfer to generate the aromatic indole moiety. To probe for the stability of the indolidene intermediate, we monitored the reaction by taking the UV absorption spectrum of the cyclization reaction every minute (see Appendix B).[30b] We were hoping to detect a least a new absorption peak distinct from the starting material and C-cyclized product. Unfortunately, there was no detectable absorption for the transient intermediate. Nevertheless, these results suggest that perhaps the putative indolidene moiety is short lived and reacts rapidly via either nucleophilic addition or proton shift and is never present at a detectable concentration. In order to build the case for an indolidene intermediate, the "trap" methanol was added to the reaction at an intermediate time point, since it has been shown to be a good nucleophile with the indolidene species (vide infra). Unfortunately, there was no methanol adduct detected. A control experiment was designed to test the stability of the elimination product **171-E**. By submitting pure **171-E** to the established conditions, the elimination product **171-E** was found to decompose over time. Thus, most of the **171-E** formed during the cyclization reaction is destroyed and thus not detected at the completion of the reaction.

The photochemical reaction of the *Z*-alkenyl sulfide isomer at 350 nm also was monitored over time and the results are depicted in Figure 54 and Table 7.[30b] After irradiating the *Z* isomer for 30 min, there was only 21% of the C–C bonded products (**123**/**125**) along with 8% of unreacted starting material **120-Z** present and with other unidentifiable products (entry 1); ^{1}H NMR spectroscopy again showed the formation of an unknown indole-containing byproduct along with a messy aliphatic region. Even after prolonged irradiation, there was no increase in product formation (entries 2 and 3). Furthermore, there was absolutely no isomerization of the *Z* alkene moiety in **120-Z** into an *E* alkene. It is important to note that there was almost no C–N bonded products **126** obtained from the *Z*-alkenyl sulfide isomer **120-Z** (Table 7, entries 2 and 3) compared to the small amount detected in the *E* isomer reactions (Table 6, entries 1–4). The unexpected difference in product distribution for the *E*- and *Z*-alkenyl sulfide isomers brings forth the question of whether these two alkene isomers are operating via the same or different mechanisms.
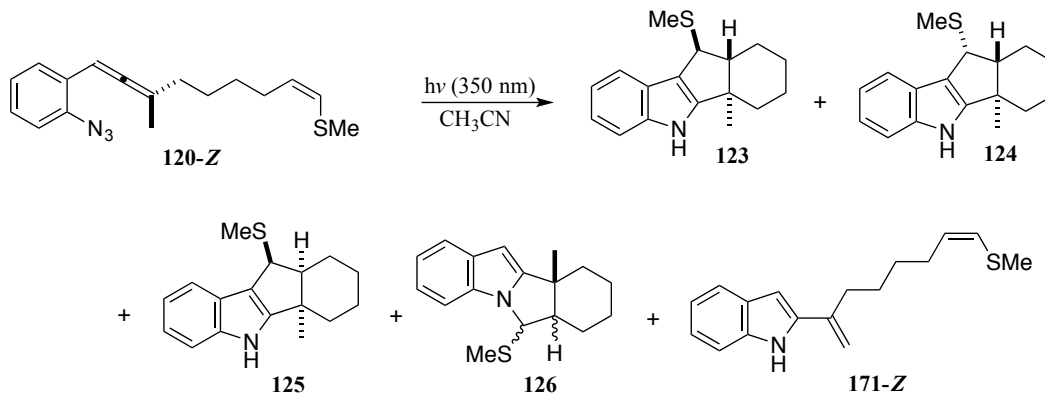
Figure 54. Photochemical [3 + 2] cyclocondensation of pure *Z*-alkenyl sulfide substrate **120-Z**.

Table 7. Product yields as a function of reaction time for the photochemical [3 + 2] cyclocondensation of pure *Z*-alkenyl sulfide substrate **120-Z** at 350 nm

entry	time (min)	**120-*E***	**120-*Z*[a]**	**123[a]**	**124[a]**	**125[a]**	**126[a]**	**171-*E*[a]**
1	30	-	8	10	-	11	-	6
2	60	-	trace	16	trace	20	-	12
3	120	-	-	13	2	14	trace	3

[a]Percent yields determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures relative to the internal standard 1,4-dimethoxybenzene.

3.7 Mechanistic Insights for the Photochemical [3 + 2] Cycloadditions

Multiple mechanistic possibilities governing the formation of the cyclization products can be formulated for each isomer. Both *E*- and *Z*-alkenyl sulfide isomers **120** could be operating via a stepwise mechanism, perhaps promoted by a photo-initiated single-electron transfer (SET) (Figure 55). In this scenario, indolidene intermediate **170** would be formed as a mixture of geometrical isomers that might easily interconvert under irradiation; it has been reported that alkene isomerization in a similar model system has a calculated barrier to rotation of about 33 kcal/mol.[17c] A SET event could occur between the methyl vinyl sulfide and the indolidene moieties in either or both indolidene intermediates **170-*E*** or **170-*Z***, resulting in a pair of singlet diradical indole-based zwitterionic species **172** and **174**. It is in these species that the stereochemistry of the 5,6 ring fusion is set, depending on the position of the generated sulfur-stabilized carbocation in the chairlike transition state. The diradical species **172/174** immediately can undergo diradical closure to form a 6-membered ring containing either an equatorial thionium appendage (e.g., **173**) or an axial thionium alternative (e.g., **175**). The resulting dipolar intermediates **173/175** resemble the proposed intermediates operating in a mechanistic proposal reported for the reaction of alkenes with fulvenes in a formal [6 + 2] cycloaddition.[44] The next step in this mechanistic proposal involves the nucleophilic addition of either the indole C(3) or nitrogen nucleophilic site to the sulfur-stabilized carbocation within **173/175** to close the final 5-membered ring and generate either C–C (**123–125**) or C–N (**126**) bonded products after tautomerization.
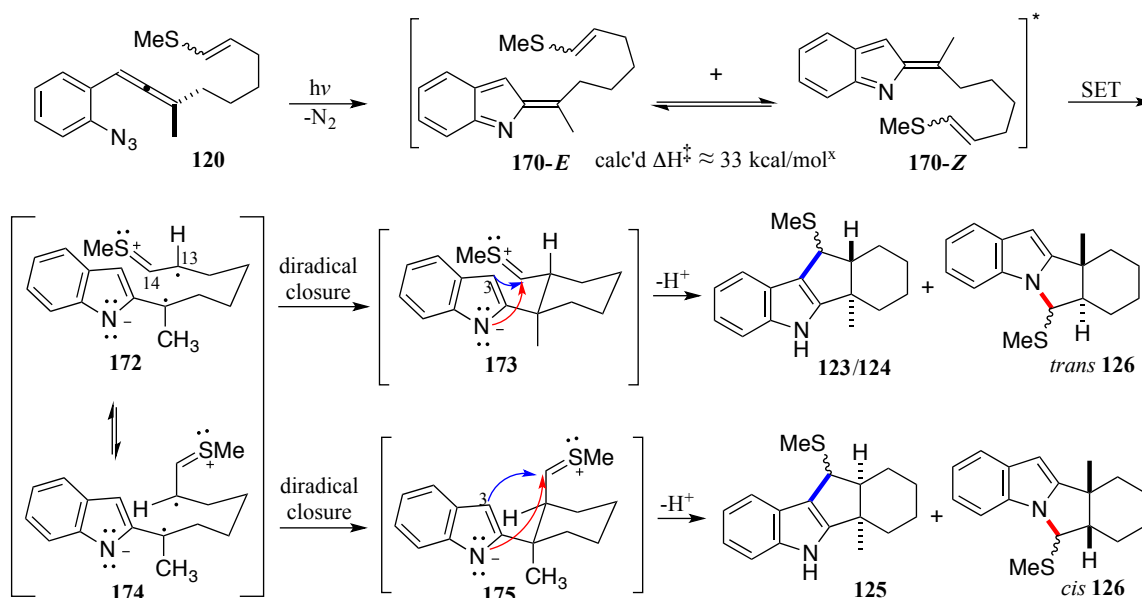
Figure 55. Stepwise single electron transfer-mediated mechanistic proposal for indolidene cyclization of **120** to give tetracyclic products.

The multiple reaction pathways resulting from the SET mechanism coincide with the multiple products seen with the *Z* isomer. In contrast, the high selectivity observed with the *E*-alkenyl sulfide starting material **120-E** in the formation of the *trans* C–C bonded product **123** suggests the possibly of a concerted mechanism for this geometrical isomer. This highly speculative pathway, a formal (and unprecedented) [10π + 2π] photochemical cycloaddition, merits discussion, as the geometrical information from the alkene nucleophile within **120-E** was retained in the major product **123**. The orbital picture for the LUMO of an indolidene moiety was modeled by DFT calculations at the B3LYP/6-31G** level with Jaguar V7.8 (see Appendix C), and the picture generated (**176**) displays an evident suprafacial symmetry mismatch with the alkenyl sulfide HOMO, suggesting that this mechanism may not be operational (Figure 56). However, computational studies published by Dreyer and Klessinger on the photochemistry conversion of benzene to fulvene revealed a possible workaround to this problem.[45] It was suggested that, upon excitation, fulvene undergoes an approximately 90° rotation about the exocyclic alkene to generate a singlet twisted "alkene". Using this model as a

foundation, we can propose that the related indolidene could access a twisted intermediate like **177**, which might allow sufficient orbital overlap with the lobes of the alkene HOMO to provide cycloaddition (Figure 56). As a result, a concerted mechanism could be operational, although not necessarily synchronous in bond formation at C(8) and C(3) (or at N), as depicted in Figure 57. The conceptual reverse of this cycloaddition process, the concerted (but asynchronous) discharge of N_2 from triazoline **36**, emerged as a viable pathway for indolidene formation through computational analysis (Chapter 1, Figure 10).
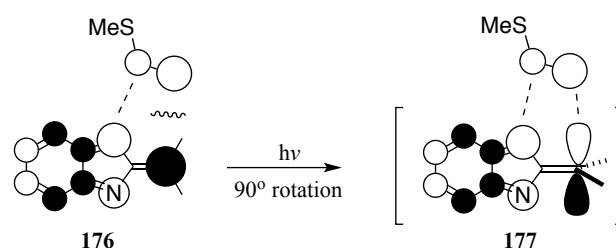
Figure 56. Molecular Orbital picture of indolidene upon irradiation, obtained from DFT calculations.
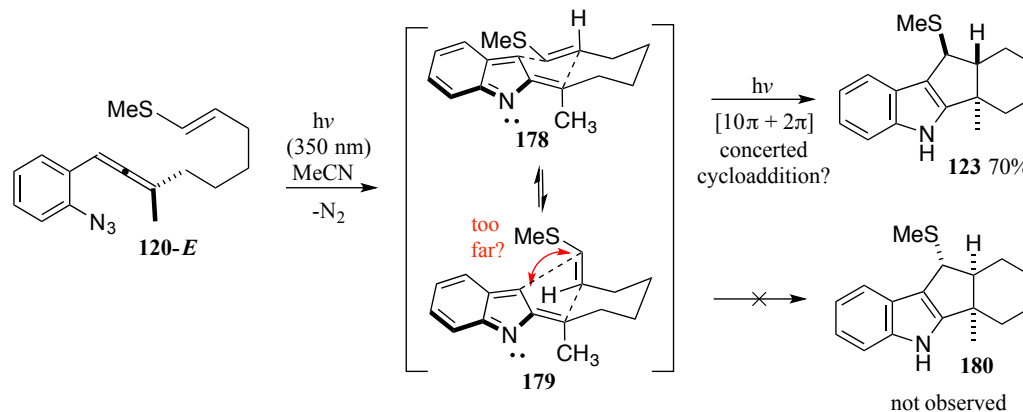
Figure 57. Alternative mechanistic proposal for the reaction with *E*-alkenyl sulfide substrate **120-*E***; possible intervention of a concerted photochemical $[10\pi + 2\pi]$ cycloaddition.

This orbital alignment argument could hold for the indolidene intermediate containing the *E*-alkenyl sulfide nucleophile in a pseudoequatorial position (**178**) but it should be much more problematic for its pseudoaxial counterpart (**179**). The placement of the alkenyl sulfide moiety (in **179**)

in the pseudoaxial position would result in poor alignment for the cycloaddition with the indolidene, which could explain why the cycloadduct **180** was not observed (Figure 57). The proposed concerted pathway might not be favorable for the *Z*-alkenyl sulfide adduct **120-Z** as steric interactions could arise between the pseudoequatorial thiomethyl appendage and the twisted indolidene, as depicted in the transition state **181** (Figure 58). Hence, the stereochemical scrambling observed for the *Z*-alkenyl sulfide isomer could have resulted from a nonconcerted pathway such as the SET process illustrated in Figure 55. Moreover, although we believe that the high selectivity observed in the *E*-alkenyl sulfide adduct could be attributed to an unprecedented concerted cycloaddition, the trace amounts of **124/125** detected also could imply a possible competition between concerted and SET pathways.
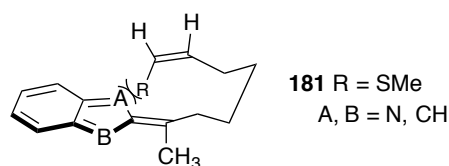
Figure 58. *Z*-Alkenyl substrate-derived indolidene intermediate in the transition state.

The difference in product distribution for the *E*- and *Z*-alkenyl sulfide isomers **120** suggests an interesting mechanistic intricacy. This divergence requires that either (a) these starting materials do not converge in their mechanism to a common intermediate like **172** and **174** in the proposed SET pathway, or (b) they do converge, but C–C single bond rotation in this common intermediate is slower than ring closure to create the new C–C/C–N bonds. At this moment, these possibilities cannot be distinguished. If it turns out that C–C bond rotation between C(13) and C(14) (see **172** in Figure 55) is faster than ring closure, then (i) the *E*- and *Z*-alkenyl sulfide isomers **120** must operate through different mechanisms, and (ii) the *Z* isomer must operate through a stepwise process like the proposed SET pathway to account for the observed stereochemical scrambling. This argument builds supports for the case that the *E*-alkene isomer **120-E** reacts via a concerted cycloaddition upon irradiation.

The "ene" type products **171** and **174** observed in the cyclization attempts could be attributed to a formal [1,7]-proton shift (Figure 59). Upon formation of the indolidene intermediate **182**, a proton shift of H_a (or H_b to form **174'**) is presumed to occur to either the C(3) carbon or the nitrogen to provide a mixture of geometrical isomers (**171/174"**). The rate of this formal "ene" type reaction seems to be slow compared to the addition of the alkene under photochemical conditions. Moreover, if the alkene is not nucleophilic enough, the formation of elimination products is favored, as revealed by the results obtained for the simple alkene nucleophile **173** (Section 3.5, Figure 49).
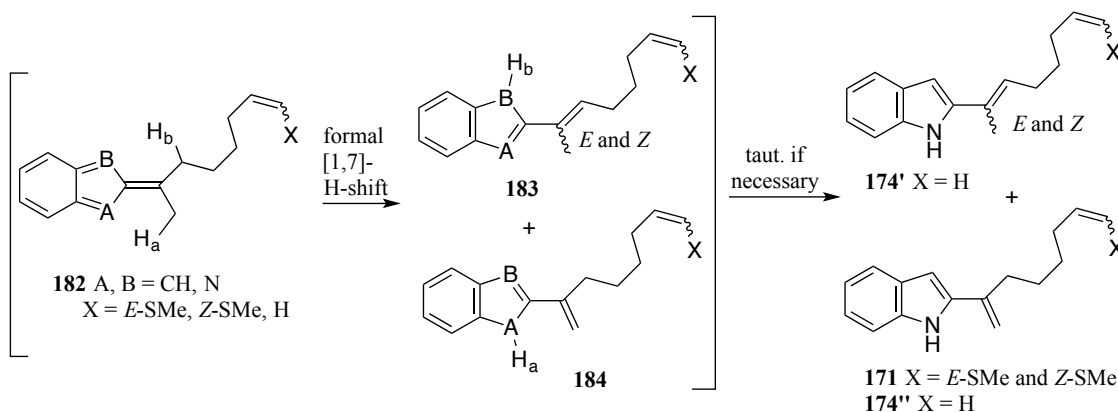
Figure 59. Proposal for the formation of the minor formal "ene" products **171** and **174**.

3.8 Conclusion

An intramolecular cyclization reaction between an indolidene intermediate and an alkene nucleophile was developed. This light-promoted [3 + 2] cyclocondensation addresses a major challenge faced in the synthesis of the indolosesquiterpenoids: the formation of the *trans* hydrindane (e.g. **123**) over the thermodynamically preferred *cis* hydrindane. The *E*-alkenyl sulfide allenyl azide cyclization in particular is a powerful transformation since it not only creates two C–C bonds, one C–N bond and three fused rings, but it does so with complete control of stereochemistry and regiochemistry. The cyclization product maps precisely onto the skeleton of the indolosesquiterpenes. Moreover, the remarkable selectivity observed suggests that we may have identified a new reaction, a [10π + 2π]

photochemical concerted cycloaddition. Application of this methodology to the indolosesquiterpenoid lecanindole D is presented in Chapter 4.

Chapter 4

Photochemical [3 + 2] Cyclocondensation in the Synthesis of the Indolosesquiterpenoid Core: Application to Lecanindole D

4.1 Introduction

The successful results obtained for the [3 + 2] cyclocondensation reactions discussed in Chapter 2 and 3 serve as a foundation for a more concise synthesis of the indolosesquiterpene skeleton via indolidene and indolidenium cation intermediates. Guided by the remarkable regioselectivity and stereoselectivity obtained for the *E*-alkenyl sulfide isomer described in Figure 50, we propose a modification to this allenyl azide-derived [3 + 2] tricyclization reaction for application in the synthesis of indolosesquiterpenoids (Figure 60). This variation features an allenyl azide substrate **185** containing a cyclohexenone moiety, which would become the E ring in **187**. The cyclohexenone ring bears an alkyl chain terminating in an *E*-alkenyl sulfide unit. An additional methyl group is incorporated at the C(9) carbon, which is required for the installation of the vicinal stereogenic centers in the indolosesquiterpenoids. We envisioned that selectivity for the *trans* 5,6-fused rings should be enhanced due to the preexisting pseudoaxial methyl at the C(9) carbon, which would promote the placement of the vinyl sulfide unit in a pseudoequatorial position to avoid unfavorable diaxial interactions in the transition state **186**. Moreover, the methyl groups at the C(8) and C(9) carbons should be positioned opposite to each other as required for the indolosesquiterpenoids, as a consequence of placing the indole unit in a pseudoequatorial position to avoid steric interactions with the cyclohexenone ring. A fallback route involving the Lewis acid-mediated bicyclization presented in Chapter 2 also could be developed if the proposed photochemical route proved unsuccessful. This chemistry may be applicable to the synthesis of many important indolosesquiterpenes such as lecanindole D (**50**), a natural product

of interest in the Feldman group. The potential interfering photochemical reactivity of the enone function is a point of concern, and this issue will have to be probed through experiment.
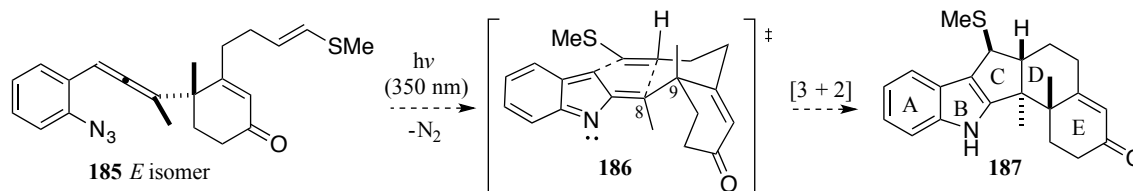
Figure 60. Proposed photochemical [3 + 2] cyclocondensation reaction for the synthesis of the indolosesquiterpene core.

4.2 Lecanindole D and Biological Importance

Lecanindole D (**50**) is an indole sesquiterpenoid that was isolated in 2009 from fermentations of the terrestrial fungus *Verticillium lecanii* 6144 along with lecanindoles A–C (**188**–**190**, respectively, Figure 61).[46] Lecanindole D (**50**) was the only alkaloid from this family to exhibit biological activity; it was found to be a potent and selective agonist for the human progesterone receptor (hPR) with an EC_{50} value of 1.1 ± 0.4 nM in a cell-based luciferase receptor assay. Importantly, lecanindole D (**50**) was inactive ($EC_{50} > 10000$) in transcriptional assays performed with other receptors such as the human mineralocorticoid, glucocorticoid, androgen, and estrogen receptors. All current commercial hPR agonists (= oral contraceptives) are steroid based and they can interact with other hormone receptors to cause undesirable side affects including increased blood pressure and weight gain. Therefore, the profound selectivity of lecanindole D (**50**) suggests great promise in the development of new progesterone agonist drug leads. As a result, the synthesis of lecanindole D (**50**) via the proposed photochemical [3 + 2] cyclocondensation reaction may help identify new leads for selective progesterone agonists.
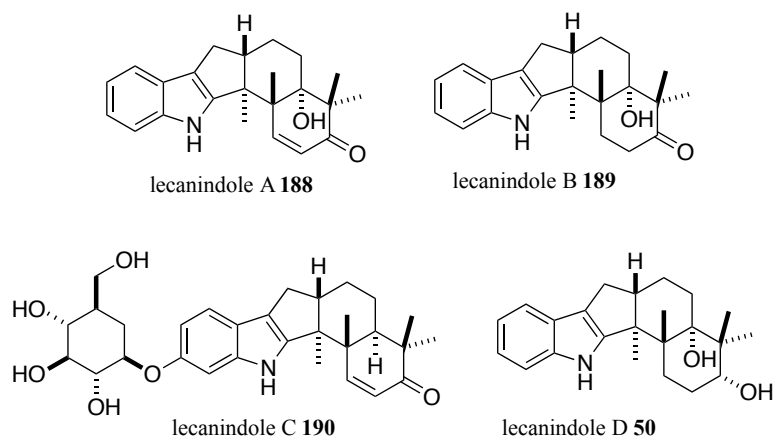
Figure 61. Structures for lecanindoles A–D.

4.3 Kuwahara's Approach to the Synthesis of Lecanindole D

To date, there has only been one reported total synthesis for racemic lecanindole D (**50**), which was accomplished by Kuwahara and coworkers in 2013 (Figure 62).[26] The synthesis route featured the same hydroxyl-directed Simmons-Smith cyclopropanation approach that was utilized in their synthesis of paspalinine (**53**, Figure 18) to install the key C(3) quaternary stereogenic center. However, prior to the reductive cleavage of the cyclopropane ring to produce the required vicinal quaternary stereocenters and 5,6-fused rings, the dihydroxyl/dimethyl units in the E ring were installed in a 4-step sequence starting from cyclohexanone **192** (Figure 62). Base-mediated α-dimethylation of **192** followed by selective ketone reduction within **193** yielded the major alcohol product **194** as a 2:1 mixture of inseparable diastereomers. These diastereomers were carried on to the next step and separated via their derived epoxides, to generate isomer **195**. Selective reductive epoxide opening **195** afforded the tertiary alcohol **196** to complete the required functionalization of the E ring. After some protecting group and redox manipulations, cyclopropane reductive cleavage generated a vinyl triflate adduct **198**, which contained the *trans* 5,6-fused rings and the vicinal quaternary stereogenic centers. The installation of the indole moiety was completed according to the published protocol for the synthesis of paspalinine

(53).[25] The total synthesis of lecanindole D (50) was accomplished in 20 steps as a racemic mixture. It

included a variety of uneconomical redox and protecting group steps.
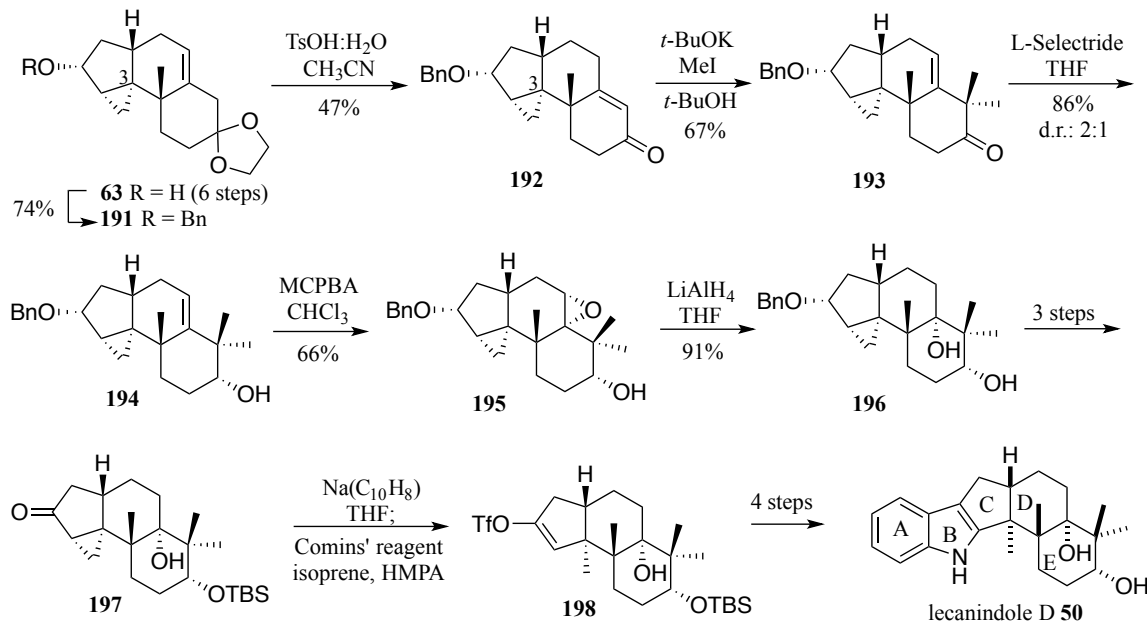
Figure 62. Kuwahara's approach for the total synthesis of lecanindole (50).

We envisioned that the proposed photochemical [3 + 2] cyclocondensation reaction could be

applied towards completing a more concise total synthesis of lecanindole D (50) (Figure 63). The

cyclocondensation adduct 187 is projected to be converted into the natural product 50 using the same

steps applied by Kuwahara, described in Figure 62, which also have been explored in our laboratory on

a model system derived from the Weiland–Meischer ketone.
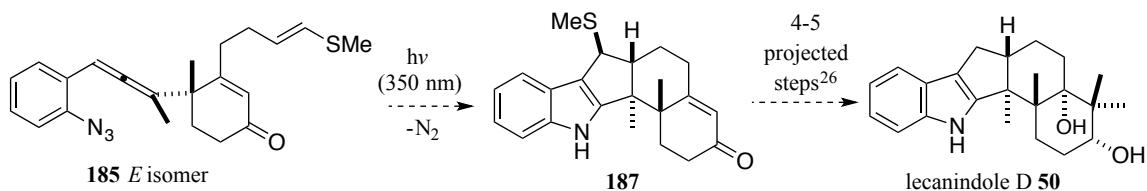
Figure 63. New approach towards the total synthesis of lecanindole (50).

4.4 Removal of the Methyl Sulfide Moiety from the Cycloadduct: Model System

In order for the proposed cyclization to be applicable in the total synthesis of lecanindole D and other indolosesquiterpenoids, the C(13) methyl sulfide attached to the cyclopentane ring must be cleaved. To achieve this conversion, a variety of reducing agents were screened with model substrate **123/124** and the results are illustrated in Table 8.[30] Raney nickel was the first reductant employed, which is the reagent used by default in desulfurization reactions.[47] Unfortunately, reaction of **123/124** with Raney nickel at room and at refluxing temperatures did not afford the desired product **127** (entries 1 and 2). Instead, a mixture of unidentifiable products resulted under refluxing conditions. We then switched to LiAlH$_4$, which at room temperature only delivered trace amounts of the desired product **127** as well as unreacted starting material **123/124**. However, when **123/124** was refluxed with LiAlH$_4$, the desired desulfurized product **127** was obtained in moderate yield (entry 4). Other reductants, such as sodium/naphthalene, DIBAH, Ni(COD)$_2$/HSiEtMe$_2$, and H$_2$-Pd/C (entries 5–8, respectively), did not react with the starting material **123/124**. In addition, when HSiEt$_3$ was used in conjunction with TFA or Hg(OAc)$_2$ (entries 9 and 10), a mixture of uncharacterizable products was obtained and the desired product was not formed. Fortunately, the reaction of **123/124** with HBEt$_3$ ("superhydride") afforded the desulfurized product **127** as a single isomer in excellent yield (92%) (entry 11). With these results in hand, we proceeded with studies directed towards the proposed photochemical [3 + 2] cyclocondensation reaction.
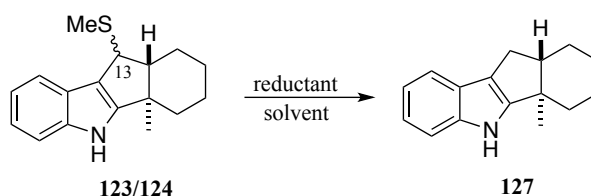
Figure 64. Removal of the methyl sulfide moiety from **123/124**.

Table 8. Reductive removal of the methyl sulfide moiety from **123/124** as a function of reductant, temperature and solvent

entry	reductant	temp.	solvent	results
1	Raney Nickel	rt	EtOH	unreacted **123/124**
2	Raney Nickel	reflux	EtOH	multiple products
3	LiAlH$_4$	rt	THF	trace amounts of **127** and unreacted **123/124**
4	LiAlH$_4$	reflux	THF	44% of **127**
5	Na, Naphthalene	-78 °C	THF	unreacted **123/124**
6	DIBAH	rt	THF	unreacted **123/124**
7	Ni(COD)$_2$, HSiEtMe$_2$	90 °C	PhMe	unreacted **123/124**
8	H$_2$, Pd/C	rt	EtOAc	unreacted **123/124**
9	HSiEt$_3$	rt	TFA	multiple products
10	HSiEt$_3$, Hg(OAc)$_2$	rt	CH$_2$Cl$_2$	multiple products
11	**HBEt$_3$**	**rt**	**THF**	**92%** of **127**

4.5 Efforts Towards the Total Synthesis of Lecanindole D: Enone Allenyl Azide Substrate

A retrosynthetic analysis for the synthesis of the allenyl azide precursor **185** is presented in Figure 65. Our plan was to derive **185** from **199** via an S$_N$2' reaction of the propargylic acetate/carbonate within **199**. The internal alkyne substrate **199**, in turn, was the intended product of a coupling reaction between 2-azidobenzaldehyde (**108**) and the alkyne substrate **200**. We anticipated that this transformation could be complicated by the enone unit. Disconnection of the alkyl chain bearing an *E*-alkenyl sulfide revealed enone **201**, which is a known compound.
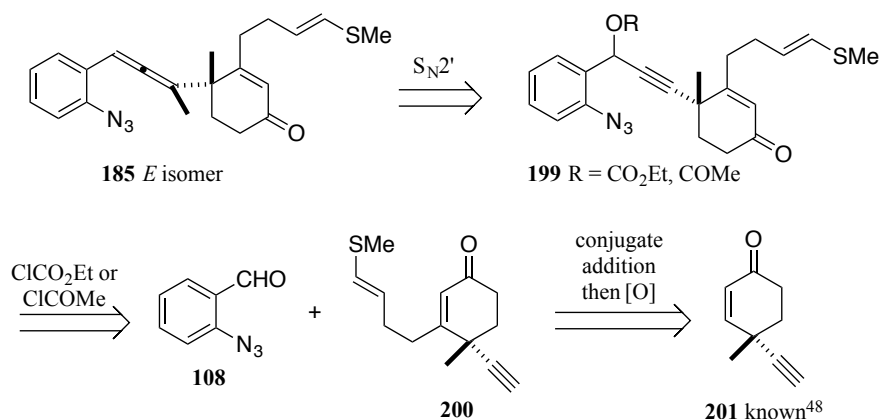
Figure 65. Proposed retrosynthesis for the allenyl azide cyclization precursor **185**.

4.5.1 New Approach for the Synthesis for Enone 201

The synthesis of known alkyne substrate **201** has been reported in 6 steps.[48] We anticipated that a shorter route could be achieved by applying a Diels-Alder approach followed by a one-carbon homologation event (Figure 66). A Diels-Alder cycloaddition between Danishefsky diene (**95**) and methacrolein (**202**) should afford the silyl enol ether adduct **203**[49], which, upon exposure to mild acidic conditions, should deliver enone **204**. The conversion of aldehydes to alkynes has been well documented; common named reactions are the Seyfert-Gilbert homologation, Colvin rearrangement and Corey-Fuchs reactions.[50] Although there was no precedence for the homologation procedure in the presence of an unprotected enone, we proceeded to test the reaction via known procedures.
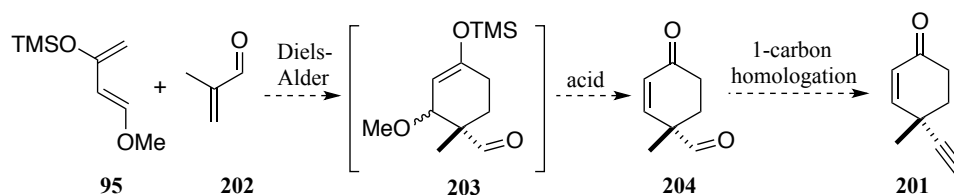
Figure 66. Proposed synthesis for alkyne substrate **201**.

The proposed Diels-Alder reaction followed by TMS cleavage generated the dicarbonyl adduct **204** in good yield (Figure 67). However, the formation of the terminal alkyne from the aldehyde within **204** proved unsuccessful. Submitting aldehydes **204** (or **203**) to the common conditions for either the

Colvin rearrangements or Seyfert-Gilbert homologation delivered a complex mixture of products, and no isolable species were obtained. It is possible that the free enone in **204** reacted under these conditions; in the literature, carbonyls are protected under similar circumstances.[51] Moreover, with **203** as the substrate, the highly basic conditions might not have been compatible with the TMS unit; the ^{1}H NMR spectrum of the crude product mixture showed a significant decrease in the TMS methyl peaks suggesting cleavage of the labile TMS group.
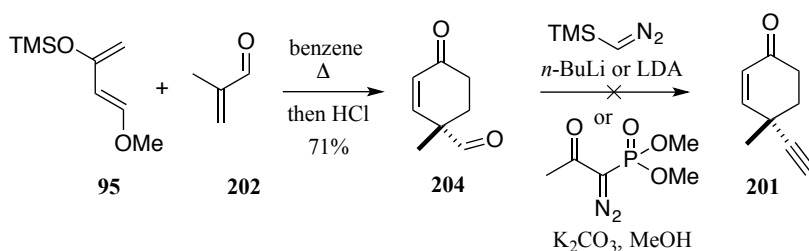
Figure 67. Initial approach for the synthesis of alkyne substrate **201**.

In light of the difficulties to access alkyne **201** in one step from **204**, installation of the alkynyl moiety via the well-described Corey-Fuchs 2-step sequence was explored. This transformation has been shown to be successful in the presence of an enone, which was protected in situ as a lithium enolate.[52] As expected, the first step of the Corey-Fuchs approach, a Wittig reaction, delivered the vinyl dibromide adduct **205** in good yield. In the second step, this vinyl dibromide **205** was converted to a terminal alkyne in moderate yield via a base-mediated rearrangement of the 1,1-dibromoolefin unit in **206**. Overall, the synthesis of this alkyne adduct **201** was achieved in 3 steps as opposed to the 6-step published protocol.
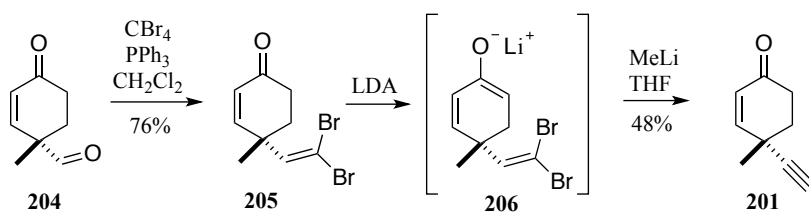
Figure 68. Corey-Fuchs reaction: successful approach for the synthesis of alkyne substrate **201**.

4.5.2 Conjugate Addition Approach to Install the β-Alkyl Chain via Vinyl Dibromide Substrate

205: Model System

At this point, the synthesis plan called for the installation of an alkyl chain bearing the *E*-alkenyl sulfide unit, a process that ideally would proceed by conjugate addition of an organocuprate reagent to enone **201** followed by oxidation. An intrinsic problem with this approach is the presence of a terminal alkyne, which could be problematic due to the competitive deprotonation and addition of the cuprate reagent to the alkyne. As a workaround, the conjugate addition to the enone containing the vinyl dibromide **205** was examined instead. A model dibutyl cuprate reagent participated in conjugate addition to enone **205**, followed by oxidation of the intermediate enolate, to deliver enone **209** in good yield (Figure 69).
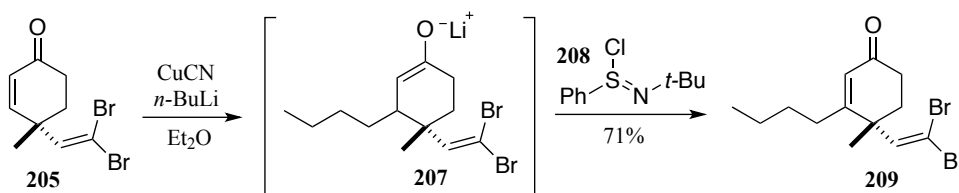
Figure 69. Conjugate addition to the enone **205** followed by oxidation: model substrate.

An advantage of this conjugate addition procedure is the utilization of oxidant **208**[53], which is typically added after the formation of the enolate within **207** to perform the oxidation in one-pot, and avoid the typical 2-step Saegusa-Ito oxidation procedure[54]. The sulfur containing oxidant **208** is commercially available; however, it was synthetized in the laboratory via known procedures[55] shown in Figure 70 to access larger quantities.
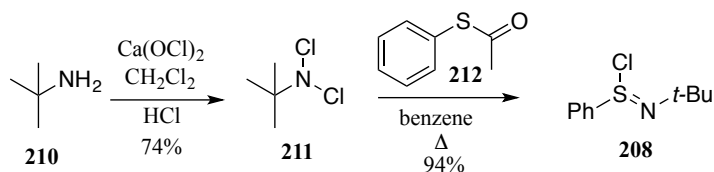
Figure 70. Synthesis of known oxidant **208**.

4.5.3 Conjugate Addition Approach to Install the *E*-Alkenyl Sulfide Alkyl Chain via the Vinyl Dibromide Substrate 205

Accessing the real cyclization substrate involved the synthesis of the cuprate reagent bearing the *E*-alkenyl sulfide moiety for the addition to enone **205** (Figure 71). The installation of a pure *E* alkene was crucial, as evidenced by the cyclization results obtained in the model system studies (Figure 50). An alkyne hydrozirconation reaction[16] was utilized in collaboration with Spencer Schrock, an undergraduate in our group, which afforded the *E*-alkenyl iodide as a single regioisomer, followed by metal-iodide exchange to install the required vinyl sulfide unit in **215** (Figure 71). This regiospecific transformation was efficient and afforded the desired *E*-alkenyl sulfide **215** in good yield overall. One of the major problems encountered with this compound, aside from its pungent smell, was its instability at room temperature. Storing compound **215** in solution at -60 °C slowed down this decomposition process, although typically **215** was carried on to the next step immediately after its synthesis.
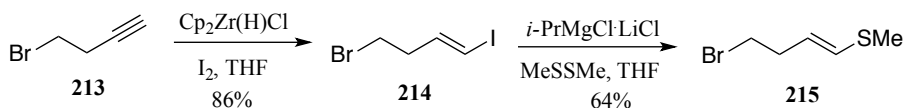
Figure 71. Synthesis of *E*-alkenyl sulfide substrate **215**.

Initial attempts at cuprate addition to **205** utilized an intermediate Grignard reagent. However, the addition of activated magnesium to bromide **215** only delivered trace amounts of the desired Grignard species (assayed by the addition to benzaldehyde (**217**)) as well as unreacted starting material **215**. In order to push this project further, we turned our attention to a lithium-halogen exchange approach. The lithiation of **215** was performed by *t*-BuLi, and the resultant lithiate **216** was combined with benzaldehyde (**216**) (test electrophile) to afford alcohol **218** in moderate yield (Figure 72).
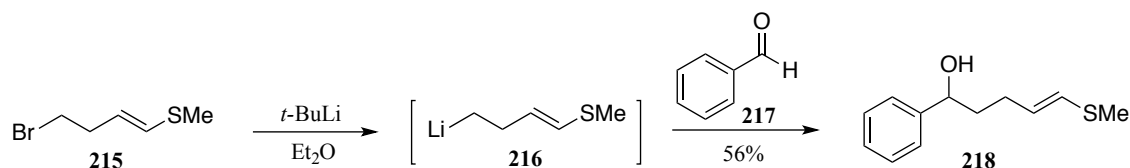
Figure 72. Lithiation of the methyl vinyl sulfide substrate **215** followed by addition to benzaldehyde (**217**).

Following these results, we proceeded to test the conjugate addition of the lithiate **216** on enone substrate **205** without adding oxidant in an attempt to isolate the saturated ketone. The results are depicted in Figure 73 and Table 9. The cuprate reaction was initially performed with 1 eq. of *t*-BuLi and CuCN, and only unreacted starting material **205** was recovered (entry 1). We questioned whether the byproduct generated from the lithium-halogen exchange step (*t*-BuBr) could be interacting with the copper reagent. Thus, 2 eq. of *t*-BuLi was employed to promote the elimination of HBr from *t*-BuBr, but only starting material **205** was observed (entry 2). We suspected that the known affinity of copper for sulfur could be a major problem in the formation of the cuprate reagent. Based on this argument, copper cyanide was replaced by a copper bromide dimethyl sulfide complex, in anticipation that the interaction between copper and the alkenyl sulfide moiety would be suppressed by the Me$_2$S present. Fortunately, the conjugate addition reaction with the new copper reagent delivered the desired β-alkylated product **219** in moderate-to-good yield (entry 3), suggesting that, indeed, the formation of the cuprate reagent was a problem in the reaction with copper cyanide. Surprisingly, the alkylated product **219** appeared to be a single diastereomer, as evidenced by ^{1}H NMR spectroscopy. Although the NOE spectrum of **219** proved to be inconclusive, we hypothesized that the alkyl chain would most likely add to the face of the alkene that is opposite to the adjacent vinyl dibromide unit as a consequence of the steric hindrance imposed by the bulky vinyl dibromide moiety.
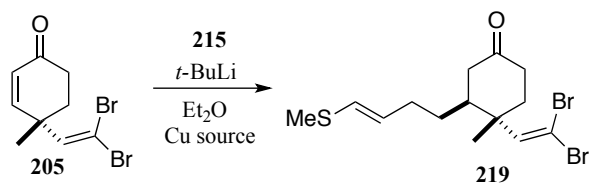
Figure 73. Conjugate addition to enone **205**: no oxidant.

Table 9. Reaction conditions for the cuprate addition to enone **205**

entry	eq. *t*-BuLi	Cu source	**219** (%)
1	1	CuCN	-
2	2	CuCN	-
3	2	CuBr·SMe$_2$	40-70

The final step of the planned cuprate addition sequence was to incorporate the oxidation reaction following cuprate addition. The results are depicted in Figure 74 and Table 10. In the first attempt, the enone product **220** was produced in poor yield (entry 1). By reducing the number of equivalents of the oxidant **208**, the yield only increased slightly (entry 2). We suspected that the oxidant might be interacting with the sulfur reagent, resulting in uncharacterizable byproducts. Nevertheless, this cuprate reaction, oxidation sequence was run on a large scale to obtain sufficient enone **220**, which was carried forward in efforts to access the cyclization precursor to test the proposed cyclocondensation reaction.

Figure 74. Installation of the *E*-alkenyl sulfide alkyl chain via conjugate addition to enone **205** followed by oxidation.

Table 10. Cuprate addition to enone **205** as a function of oxidant equivalents

entry	eq. **208**	**220** (%)
1	3	16
2	1.1	28

4.5.4 Efforts Towards the Synthesis of Functionalized Alkyne 224 with an Unprotected Enone: Model Substrate

With the functionalized enone in hand, the second part of the Corey-Fuchs reaction then was pursued to deliver the terminal alkyne from the dibromide within **220**. We carried out initial scouting experiments with model substrate **209** in order to avoid sacrificing the precious vinyl sulfide adduct **220** (Figure 75). LDA first was added to **209** to protect the enone in situ as its enolate, followed by MeLi addition, which resulted in the formation of acetylide intermediate **221**. Protonation of **221** delivered alkyne substrate **222** in moderate yield.
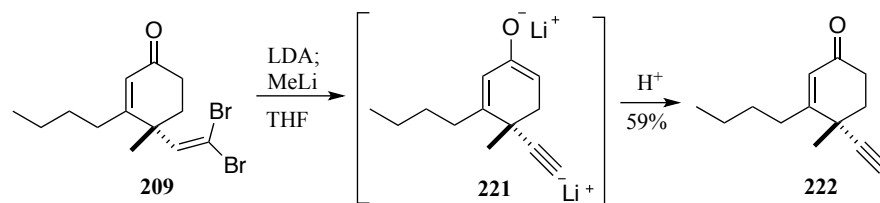
Figure 75. Second part of the Corey-Fuchs reaction via in situ protection of the enone within model substrate **209**.

This transformation was particularly promising since the reaction yielded an acetylide intermediate, which was necessary for the planned subsequent coupling with 2-azidobenzaldehyde (**108**). However, the presence of the lithium enolate in **221** could interfere with the desired reaction course. We envisioned that the addition of the acetylide within **221** to azidobenzaldehyde (**108**) should be the preferred reaction outcome as opposed to the competing aldol pathway, which is a reversible process (Figure 76). The resulting alkoxide then could be reacted with ethyl chloroformate to achieve the formation of functionalized alkyne **224**.
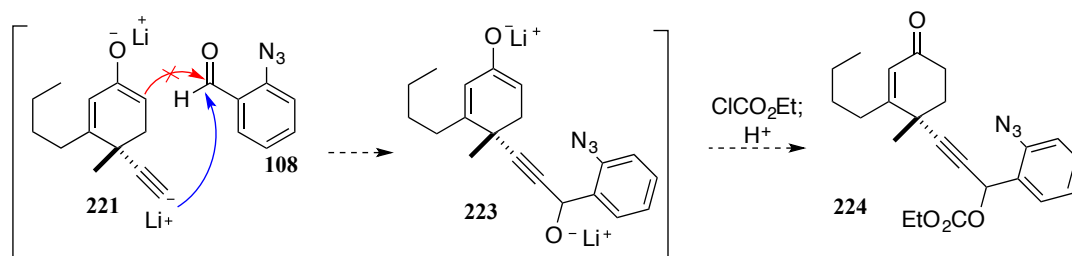
Figure 76. Proposed reaction of acetylide **221** with azidobenzaldehyde **108** to deliver functionalized alkyne substrate **224**.

To test this hypothesis, acetylide **221** was synthesized from the reaction of 2 eq. of LDA with **222**, and then azidobenzaldehyde (**108**) was added to this dianion (**221**) followed by acid quench to probe for alkyne addition (Figure 77). Unfortunately, attempts to isolate the desired functionalized alkyne product proved unsuccessful. Instead, the aldol product **225** was isolated after reaction at -78 °C, as well as unreacted alkyne starting material; multiple unidentified spots were visualized on TLC as the reaction temperature was changed from -78 °C at 0 °C. A TLC experiment was conducted to monitor this reaction as a function of temperature and the results are depicted in Table 11 and Figure 77. At -78 °C, there was only the aldol product **225** spot as well as unreacted starting material **222** (entry 1). The reaction mixture was warmed to -40 °C, but the results appeared to remain the same (entry 2); however, at -29 °C, other spots started to appear (entry 3). Interestingly, when the reaction solution was warmed to -13 °C, the starting material **222** spot appeared to be darker than at -29 °C compared to aldol product **225** (entry 4), suggesting that the equilibrium for the aldol reaction shifted to the enolate at this temperature. Nevertheless, at 0 °C, there was no longer a starting material spot and multiple spots appeared instead. Note that in Chapter 2, the acetylide derived from **118** also had to be warmed to 0 °C for the addition to azidobenzaldehyde (**108**) to occur (Figure 32). Attempts to trap the enolate with TMSCl also proved unsuccessful, as the acetylide reacted with TMSCl instead.
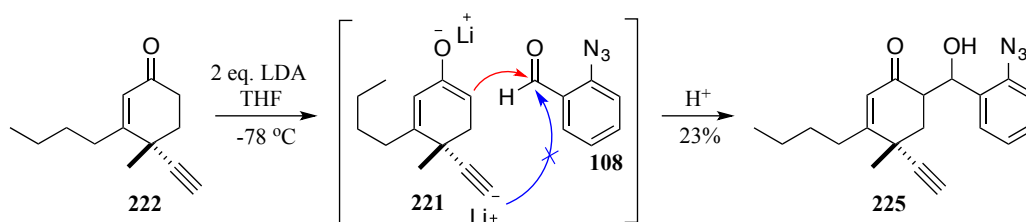
Figure 77. Deprotonation of alkyne substrate **222** with 2 eq. of LDA: formation of undesired aldol product **225**.

Table 11. Addition of azidobenzaldehyde (**108**) **to** acetylide **221** reaction as a function of temperature: monitored by TLC every hour

entry	temp.	observation: product spots on TLC
1	-78 ^{o}C	**225** and unreacted **222**
2	-40 ^{o}C	**225** and unreacted **222**
3	-29 ^{o}C	dark **225**, faint unreacted **222** as well as two new faint spots
4	-13 ^{o}C	faint **225**, dark unreacted **222**, and multiple faint spots
5	0 ^{o}C	multiple spots

In light of the unsuccessful results with the dianionic species **221**, we questioned the need for enone protection (by enolate formation) within **222**. Deuterium labeling studies to probe this point were conducted by addition of 1 equivalent of LDA at -78 °C to **222** followed by D$_2$O quench. Surprisingly, this reaction delivered the deuterated alkyne and left the α-protons unreacted (Figure 78). This result was encouraging because it showed that the alkyne anion could be formed without protection of the enone. We then tested this procedure with 2-azidobenzaldehyde (**108**) as the electrophile. However, no reaction occurred at -78 °C and warming the solution to 0 °C only resulted in a complex mixture of products from which no characterizable product could be isolated.
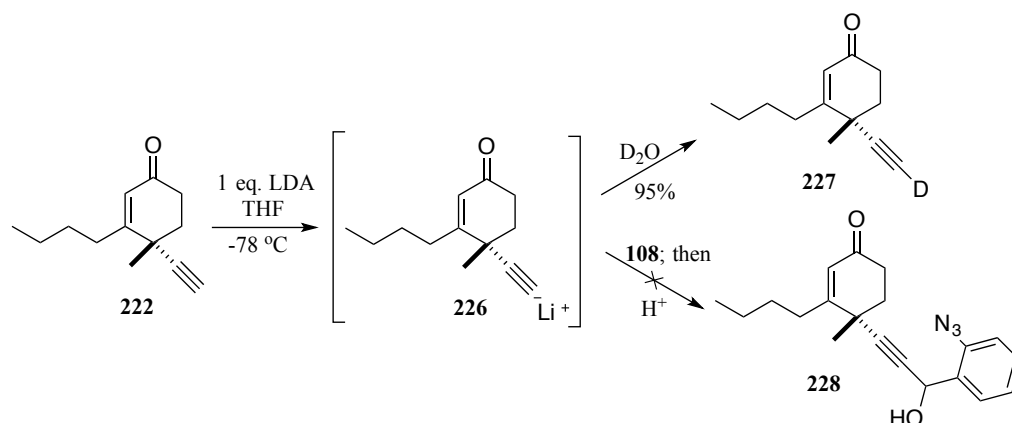
Figure 78. Deprotonation of alkyne **222** with 1 eq. of LDA followed by a) D₂O quench and b) addition of **108** followed by proton quench.

4.5.5 Synthesis of Functionalized Alkyne 232 Containing the *E*-alkenyl Sulfide Unit and a TBS-Protected Enone

Evidently, a problem with addition of the acetylide derived from **222** to azidobenzaldehyde (**108**) was the presence of either a free enone or an enolate as in **221**. Unable to achieve this transformation, we were forced to revise the initial strategy. Protecting the enone as a silyl enol ether prior to the addition to 2-azidobenzaldehyde (**108**) should avoid these problems. In addition, the TBS protecting group could be added to dibromide substrate **220** (before alkyne formation), which could be advantageous as a one-pot reaction could be developed for the conversion of TBS-protected dibromide **229** to functionalized alkyne **232** (Figure 79).
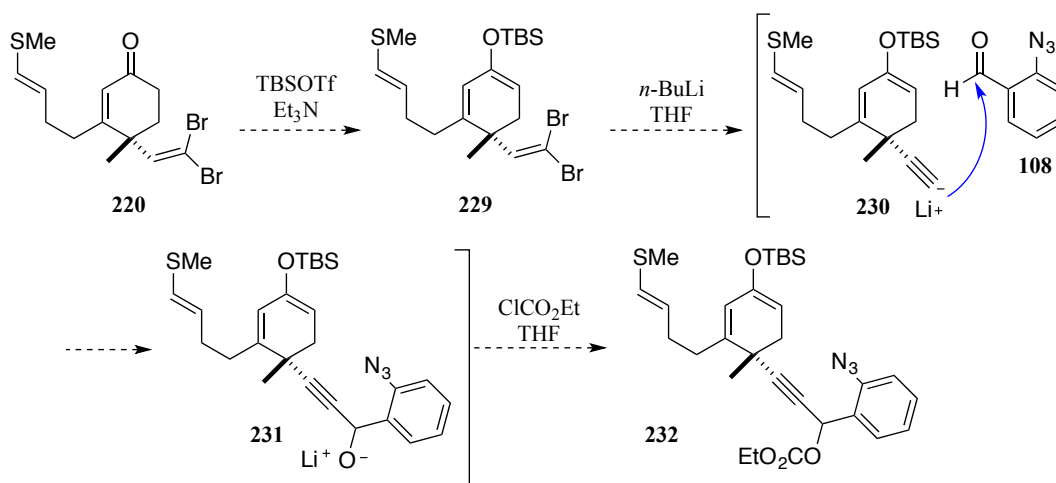
Figure 79. Proposed synthesis of TBS-protected propargylic carbonate **232** via the direct protection of *E*-alkenyl sulfide **220** followed by the coupling of the resultant TBS dibromide **229** with azidobenzaldehyde (**108**).

The direct protection of the enone within **220** with TBSOTf resulted in the silyl enol ether adduct **229** as a single isomer, suggesting that the vinyl dibromide moiety blocks the deprotonation of the adjacent γ-protons (Figure 80). Fortunately, the conversion of the vinyl dibromide unit within the TBS protected **229** to the propargylic carbonate **232**, was accomplished in high yield. This one-pot conversion proved to be efficient since three transformations were accomplished: a) conversion of the gem-dibromide to the acetylide, b) addition of the resulting acetylide to azidobenzaldehyde, and c) alkoxide trapping with ethyl chloroformate.
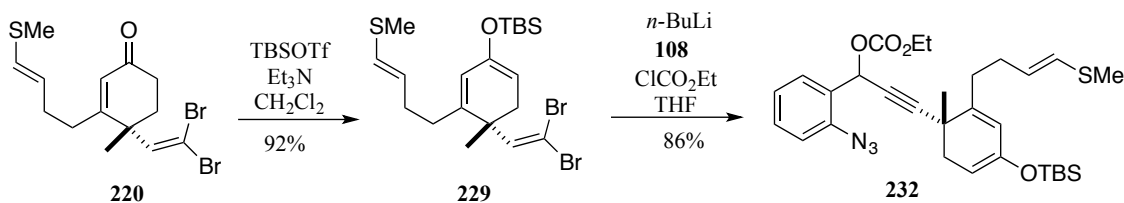
Figure 80. TBS protection of *E*-alkenyl sulfide **220** followed by the synthesis of propargylic carbonate **232** from dibromide **229**.

4.5.6 Synthesis of Enone Allenyl Azide Precursor 185 and Cyclization Attempt

The last operation in the synthesis of the allenyl azide cyclization precursor **185**, in addition to TBS removal, was conversion of the propargylic carbonate in **232** into an allene. Initial attempts to convert **232** into **233** proved unsuccessful; an unidentified product was formed (Figure 81). ^{1}H NMR spectral analysis showed the presence of the allenyl azide and alkenyl sulfide units but provided no evidence for alkenes and the TBS group from the diene ring. To circumvent this problem, TBS was first removed from **232**, and the S_N2' reaction was performed on the enone substrate **234** instead. To our delight, the desired allenyl azide adduct **185** was successfully produced as a 1:1 mixture of allene isomers containing the *E*-alkenyl sulfide moiety. The enone unit did not interfere with the cuprate chemistry.
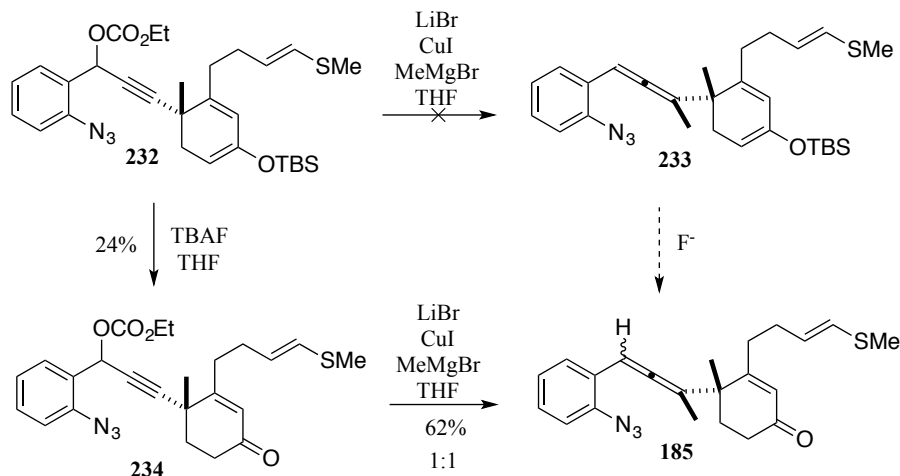
Figure 81. TBS removal and synthesis of allenyl azide substrate **185**.

The allenyl azide substrate **185** was subjected to the photochemical [3 + 2] cyclocondensation conditions (Figure 82). Unfortunately, irradiation of **185** at 350 nm in MeCN did not produce the desired pentacyclic core **187**. Instead, the elimination product **235** was the only product observed via ^{1}H NMR.
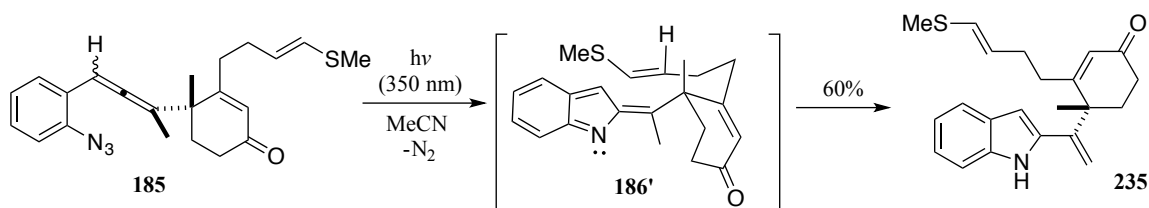
Figure 82. Allenyl azide cyclization attempt with the methyl vinyl sulfide substrate **185**.

We speculated that the E ring, which contributes an sp^2 carbon and a methyl group (**186**, Figure 83) to the forming 6-membered ring, was introducing strain into the system in the transition state **186**. As a result, the elimination pathway was favored. In the model system, a more ideal chairlike transition state could be achieved, leading to cyclization (**178** vs **186**, Figure 83). We learned from the earlier mechanistic studies that orbital alignment is crucial for the success of this complex cyclization cascade reaction.[30b] As a workaround, the enone within the cyclohexanone ring could be replaced by a silyl enol ether moiety in order to remove the sp^2 carbon from the forming 6-membered ring (**236**, Figure 83); this modification should result in a less strained chair, thus favoring the cyclization pathway. The silyl ether moiety later could be converted to an enone via a Saegusa-Ito oxidation.
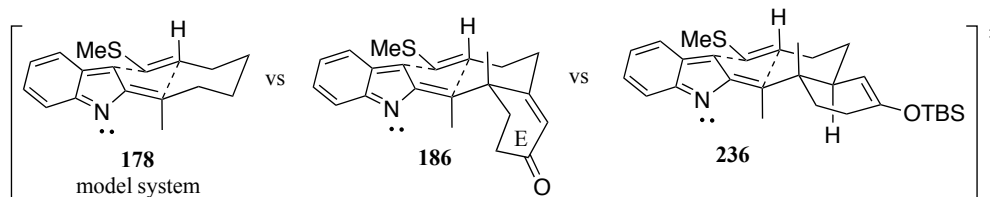
Figure 83. Cyclization reaction of indolidenes and alkenyl sulfides in the transition state.

4.6 Efforts Towards the Total Synthesis of Lecanindole D: Silyl Enol Ether Allenyl Azide Substrate

4.6.1 Synthesis of Silyl Enol Ether Allenyl Azide Substrate 241

Recognizing the need for an all sp^3 (forming) 6-membered ring, we initially envisioned that the synthesis of the silyl enol ether allenyl azide substrate **241** should be possible just by modifying the cuprate reaction depicted in Figure 72. Instead of adding the oxidant, the resulting enolate in **237** could

be trapped with a silyl source such as TBSCl or TBSOTf (Figure 84), and the resultant TBS adduct **238** could be carried on in the same reaction sequence applied to the synthesis of allenyl azide **185**. Unfortunately, attempts to promote the silylation of **237** via a) the addition of TBSCl or TBSOTf, b) employing triethylamine, c) inclusion of additive DMPU, or d) varying the order of reagent addition, only resulted in the formation of the ketone adduct **220**. These reactions are typically conducted with HMPA as an additive to facilitate the silylation, but we wanted to stay away from this carcinogenic species.
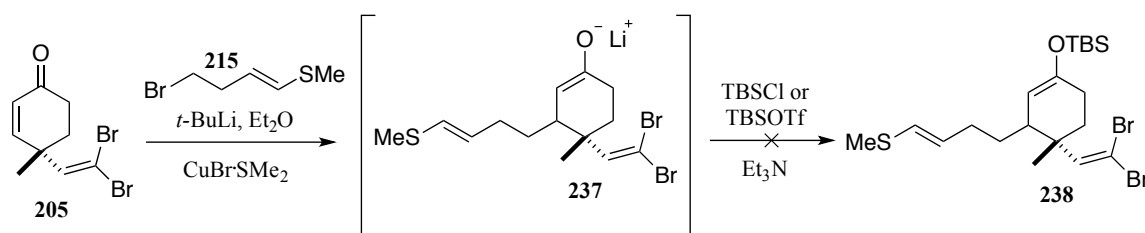
Figure 84. Cuprate addition to **205** followed by TBS trapping.

As a result of the unsuccessful cuprate reaction, we proceeded to directly silate the ketone **220** instead. Unfortunately, a 2.4:1 mixture of regioisomers **239** was obtained, which could be problematic during the projected oxidation step, as the undesired alkene isomer also was produced (Figure 85). Nevertheless, the regiochemistry was not a concern at that moment; if the proposed cyclization proved to be successful, then a more efficient approach could be pursued to install the correct double bond for the oxidation step. The TBS protected dibromide substrate **239** was coupled with azidobenzaldehyde **108** in very good yield. The S_N2' step was not problematic with the silyl enol ether adduct **240**, which delivered the cyclization precursor **241** as a 1:1 mixture of allene isomers in good yield.
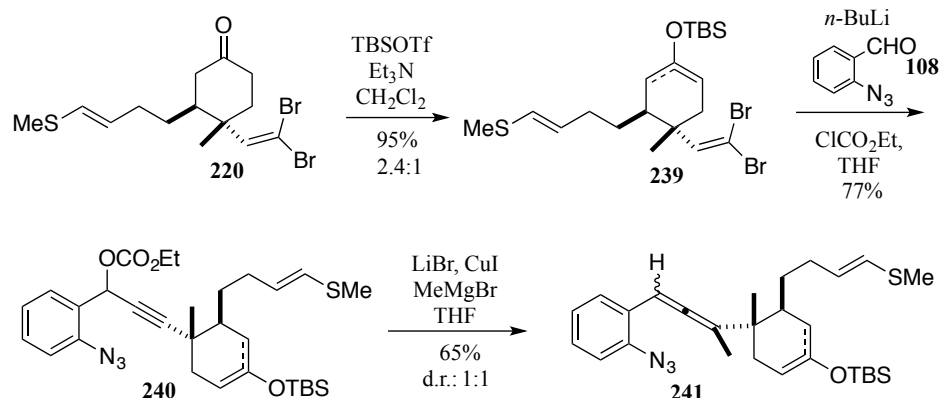
Figure 85. Synthesis of TBS allenyl azide substrate **241**.

4.6.2 Cyclization Results with TBS Allenyl Azide Substrate 241.

The TBS allenyl azide substrate **241** was subjected to the standard photochemical conditions (Figure 86). Unfortunately, only trace amounts of what appeared to be the pentacyclized cycloadduct **242** was observed; this species was identified based on the ^{1}H NMR spectrum's peak for H_a of **241** compared to the position of this similar proton in the model system **123**. ^{1}H NMR spectral analysis did not provide evidence for an allene peak, suggesting that the initial allenyl azide cyclization occurred to generate the indolidene intermediate; indeed the ^{1}H NMR spectrum showed the formation of indole-containing byproducts in addition to a messy aliphatic region. We suspected that the silyl enol ether in **241** could be reacting as well and thus promoting other reaction pathways.
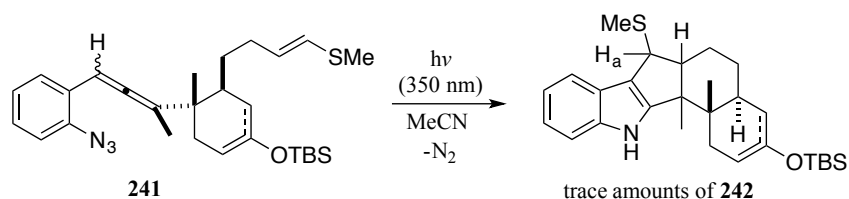
Figure 86. Cyclization attempt with the TBS allenyl azide substrate **241**.

Although only trace amounts of the desired C-cyclized product **242** was observed, this observation pointed to the possibility that we were achieving better chair-like alignment of the linking chain that connects the indolidene with the alkenyl sulfide unit. We envisioned that replacing the silyl

enol ether moiety in **241** with a ketone would induce minimal strain to the system compared to both the enone and silyl enol ether units. By removing the alkene from within the ring, a more ideal chair could be realized in the transition state (Figure 87). Therefore, we proceeded to synthesize an allenyl azide substrate containing a cyclohexanone unit.
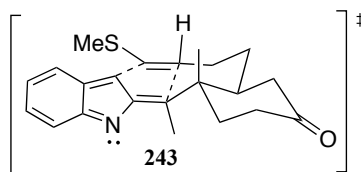
Figure 87. Transition state of the indolidene intermediate derived from a ketone allenyl azide substrate.

4.7 Efforts Towards the Total Synthesis of Lecanindole D: Ketone Allenyl Azide Substrate and Other Derivatives

4.7.1 Synthesis of Ketone Allenyl Azide Substrate and Cyclization Results

We continued with the cyclization study by preparing ketone allenyl azide substrate **245**. Initially, allenyl azide substrate **241** was submitted to desilylation conditions (TBAF or HF) but the ^{1}H NMR spectrum of the crude reaction product did not show the key allene peak corresponding to the desired ketone allenyl azide adduct **245**. Instead, uncharacterized species were formed. As an alternative route, the TBS protecting group was first removed from the propargylic carbonate in **240** to afford ketone **244** in moderate yield (Figure 88). The S_N2' reaction within **244** delivered the desired ketone allenyl azide **245** as a 1:1 mixture of allene diastereoisomers.
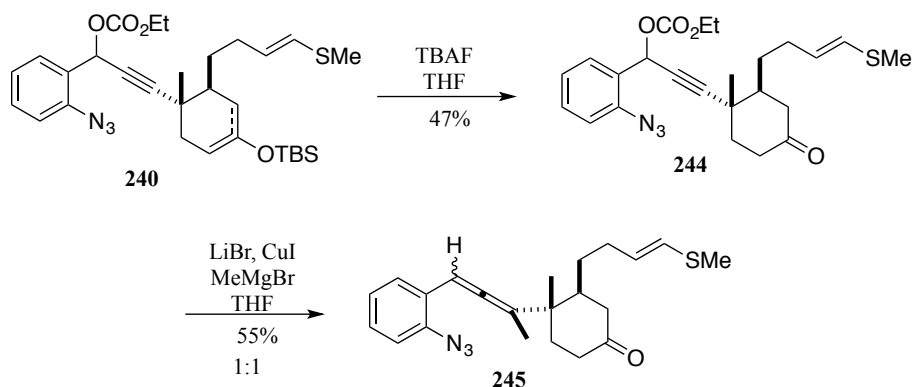
Figure 88. Synthesis of ketone allenyl azide substrate **245**.

The ketone cyclization precursor **245** was irradiated at 350 nm and the results are depicted in Table 12 and Figure 89. To our delight, a 1.4:1 diastereomer mixture of C-cyclized product **246** was isolated in appreciable yield (entry 1). The pentacyclic adduct **246** appears to contain the desired *trans* stereochemistry at the ring junction, as determined by coupling constants for H_a–H_b (4.85 ppm (d, $J =$ 9.8 Hz, H_a)), which are similar to the coupling constant previously seen in the model system **123** (4.83 ppm (d, $J =$10.0 Hz, H_a)). However, the relative stereochemistry of the vicinal quaternary centers has not yet been determined; attempts to grow crystals proved unsuccessful. In this reaction, *N*-cyclized product **247**, as well as elimination product **248**, also were isolated. In an effort to enhance the selectivity for the desired C-cyclized products, other solvents, such as toluene and acetone, were screened only to favor the formation of the elimination product **248** (Table 12, entries 2 and 3, respectively). As a result, the next logical step was to completely remove all sp^2 atoms from the cyclohexyl ring to investigate the selectivity for C–C bond formation over the C–N and elimination pathways.
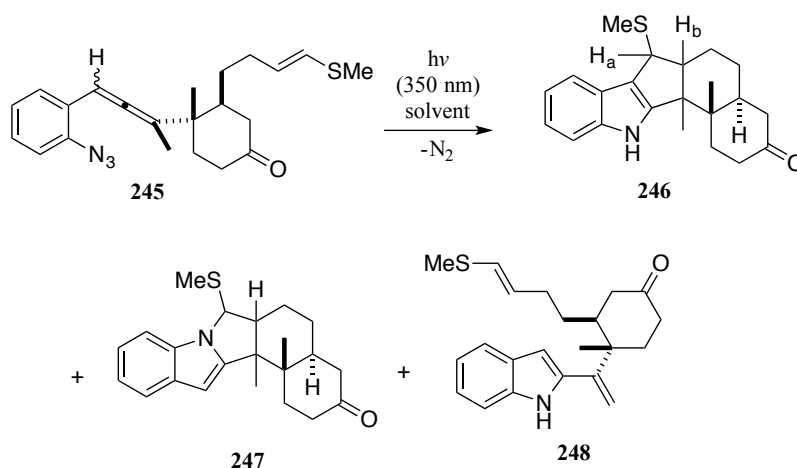
Figure 89. Cyclization attempt with the ketone allenyl azide **245**.

Table 12. Product formation as a function of solvent for the irradiation of ketone allenyl azide substrate **245**.

entry	solvent	246 (%)[a]	247 (%)[a]	248 (%)[a]
1	MeCN	45 (1.4:1)	25	18
3	toluene	20 (2.4:1)[b]	6[b]	34[b]
4	acetone	-	-	63

a) Isolated yields. b) Percent yields determined through integration of the ^{1}H NMR in a crude mixture.

4.7.2 Synthesis of Alcohol Allenyl Azide Substrate and Cyclization Results

We envisioned that a new allenyl azide substrate containing a cyclohexanol group, where all the ring atoms are now sp^3 hybridized, could be synthesized from ketone **245**. LiAlH$_4$ reduction of **245** afforded alcohol allenyl azide **249** as a mixture of stereoisomers. Unfortunately, upon irradiation, only trace amounts of the desired cycloadduct **251** was observed (Figure 90). The ^{1}H NMR spectrum of the crude reaction product was messy in the aliphatic region and no characterizable product could be isolated. Efforts to favor the formation of the desired C–C bonded products included a) separation of the alcohol isomers and submitting each one to the photochemical reaction conditions, as well as b) synthesizing and irradiating the -OTBS protected allenyl azide adduct. In both cases, only mixtures of unidentifiable species resulted.
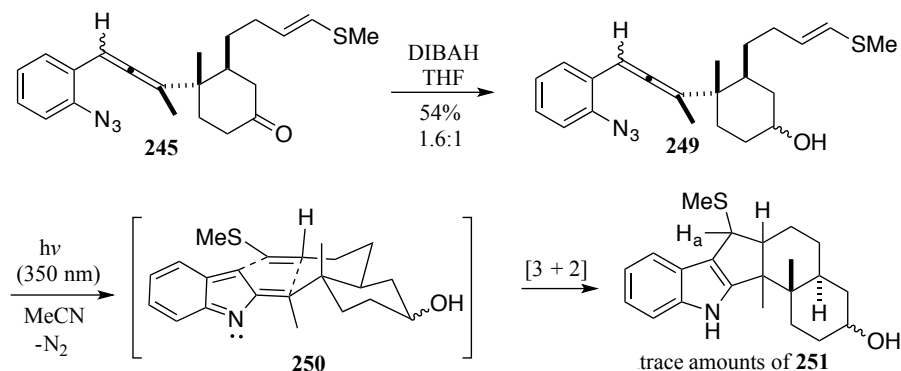
Figure 90. Synthesis of alcohol allenyl azide substrate **249** and cyclization attempt.

4.8 Efforts Towards the Total Synthesis of Lecanindole D: Cyclization Attempt via the Lewis Acid-Mediated Cyclization.

A possible workaround for the synthesis of C–C bonded products involves a detour into the Lewis acid-mediated bicyclization approach described in Chapter 2. We became interested in uncovering whether the selectivity could be enhanced using an indolidenium intermediate as opposed to an indolidene. Thus, we envisioned that the cyclization precursor **252** could be accessed by the thermolysis or photolysis of ketone allenyl azide **245**, similar to the synthesis of model substrate **120** (Chapter 2, Figure 32).[30] Disappointingly, the desired indolyl ether adduct **252** was not obtained in either photochemical or thermal reaction of **245** in methanol (Figure 91). Instead, elimination product **248** was observed in addition to multiple uncharacterized products, hinting that the steric bulk exerted by the adjacent quaternary center hinders formation of the desired methanol adduct **252**.
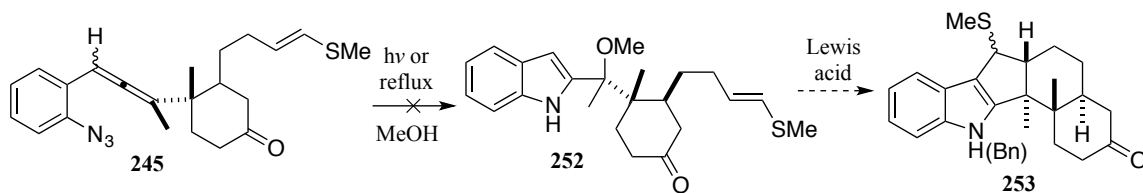
Figure 91. Lewis acid-mediated alternative: reaction of ketone allenyl azide substrate **245** in methanol.

Although these results did not provide improved results for the proposed cyclocondensation reaction, the ketone allenyl azide approach delivered the desired pentacyclic adducts, which is stepping stone in the utilization of indolidene intermediates for the formation of complex structures.

4.9 Conclusions and Outlook

The cyclization precursor **185** required for the proposed photochemical [3 + 2] cyclocondensation reaction was successfully constructed in 7 linear steps from commercially available materials. The cyclization attempt did not generate cyclized products, possibly due to ring strain exerted by the cyclohexenone moiety. However, the removal of the alkene unit from the cyclohexyl ring delivered a cyclohexanone substrate that did form the C-cyclized species **246** as the major product upon irradiation in MeCN. The results obtained for the irradiation of **245** in MeCN builds support for the feasibility of the proposed [3 + 2] cyclocondensation reaction for the synthesis of the pentacyclic core of lecanindole D. However, issues of selectivity were still a problem in these reactions, since *N*-cyclized and elimination products also were observed, and efforts to enhance the selectivity for C–C bond formation proved to be unsuccessful. The stereochemistry for the 5,6-fused rings in the C-cyclized **246** appears to be *trans* as needed for lecanindole D and other indolosesquiterpenoids, but extensive characterization is still necessary to confirm this claim as well as to uncover the relative stereochemistry of the vicinal quaternary centers. If the stereochemistry proves to match the skeleton of indolosesquiterpenes, then an oxidation step followed by the functionalization of the E ring should deliver a more efficient synthesis of lecanindole D (Figure 92).
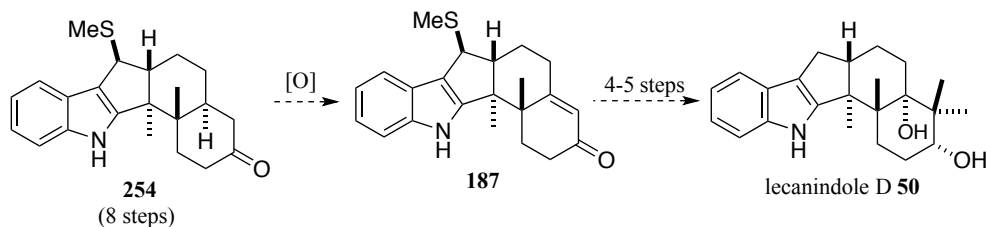
Figure 92. Necessary steps for completing the synthesis of lecanindole D (**50**).

Chapter 5

Experimental

5.1 General Experimental.

All reactions were performed using Schlenk glassware unless otherwise indicated. Solvents were purified by passage through activated alumina columns. All reagents were used as supplied without further purification unless otherwise noted. Chromatography specifying "deactivation by triethylamine" indicates that triethylamine was added to the eluent during column packing, after which the column was used with untreated eluent. Photochemistry was performed using a Rayonet RPR-100 Photochemical Reactor. ^{1}H and ^{13}C NMR spectra were obtained using a Brüker Avance DPX-300, Brüker Avance CDPX-300, Brüker Avance-360, or a Brüker Ultrashield DRX-400 spectrometer. IR spectra were obtained using a Perkin Elmer 1600 Series FTIR or Thermo Nicolet 380 FT-IR with a Diamond ATR accessory. Mass spectrometric analysis was performed on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. The HPLC data was obtained using a preparatory HPLC (Agilent Technologies, 1200 series) consisting of an Altex C18 reverse phase HPLC column and an ultraviolet detector operating at 254 nm. The Schrödinger (V 9.2) calculation package was used to predict ^{1}H coupling constants. The structures' energies were minimized via the conformational search algorithm with the Merck MMFF force field prior to running the ^{1}H NMR coupling prediction program.

General Procedure 1: Irradiation of the Allenyl Azide. The allenyl azide substrate in the indicated solvent (10 mM) under a nitrogen atmosphere was irradiated in a Rayonet photoreactor at 350 nm for the indicated time, with TLC monitoring. When TLC indicated consumption of the starting material, the reaction mixture was concentrated in vacuo and purified by flash column chromatography with the indicated support/eluent.

General Procedure 2. Thermolysis of the Allenyl Azide. The allenyl azide in the indicated solvent (10 mM) was heated to reflux and held there, with TLC monitoring. When TLC indicated consumption of the starting material, the solution was concentrated in vacuo, and the product was purified via flash column chromatography with the indicated support/eluent to afford the indicated product.

General Procedure 3. Lewis Acid-Mediated Cyclization. A solution of the substrate(s) in the indicated solvent (40 - 50 mM) was added to a heterogeneous solution of 0.2 equiv. of indium triflate in solvent at 0 °C under a N_2 atmosphere (final concentration of substrate: 30 - 40 mM). The resulting solution was allowed to stir for 1 hr under N_2 and then a sat. $NaHCO_3$ (aq) solution was added. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were washed with sat. NaCl (aq), dried over Na_2SO_4, and concentrated in vacuo. The product was purified via flash column chromatography with the indicated support/eluent.

General Procedure 4. Removal of Thiomethyl Ether Unit. A 1 M Superhydride solution in THF (5 equiv.) was added to a solution of the thiomethyl ether substrate in THF (37 mM) under a N_2 atmosphere. The resulting mixture was stirred for the indicated time and then a sat. NH_4Cl (aq) solution was added. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were washed with sat. NaCl (aq), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via flash column chromatography with the indicated support/eluent.

5.2. [3 + 2] Cyclocondensations of Alkenes with Indolidenium Cation Intermediates
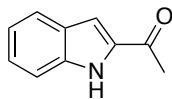
1-(1*H*-Indol-2-yl)ethan-1-one (255). To a solution of **89** (1.0 g, 6.2 mmol) in 30 mL of Et_2O at 0 °C was slowly added a 1.6 M solution of MeLi in Et_2O (7.8 mL, 12 mmol) and the reaction was brought to reflux. After refluxing for 1 hr, the reaction mixture was brought to room temperature and a

second portion of the 1.6 M solution of MeLi in Et$_2$O (7.8 mL, 12 mmol) was added. The resulting

mixture was refluxed again for an additional 5 hours. After cooling to room temperature, a sat. NH$_4$Cl

(aq) solution (20 mL) was added, and the aqueous layer was extracted with Et$_2$O (3 x 15 mL). The

combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in

vacuo. The crude product was purified via SiO$_2$ flash chromatography using 100% CH$_2$Cl$_2$ as eluent to

afford 0.91 g (92%) of **255** as a yellow solid. ^{1}H NMR (360 MHz, CDCl$_3$) δ 9.21 (bs, 1H), 7.73 (d, J =

8.1 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 7.1 Hz, 1H), 7.21 (s, 1H), 7.18 (t, J = 7.4 Hz, 1H),

2.61 (s, 3H). Spectral data are in agreement with the values published by Bennasar, M.-L.; Vidal, B.;

Bosch, J. *J. Org. Chem.* **1997**, *62,* 3597–3609.
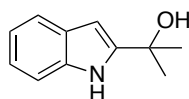
2-(1*H*-Indol-2-yl)propan-2-ol (84). To a solution of **255** (0.500 g, 3.15 mmol) in 30 mL of

THF at -78 °C was added a 1.6 M solution of MeLi in Et$_2$O (12.6 mL, 20.1 mmol) slowly and the

reaction mixture was warmed slowly to room temperature. After stirring at that temperature for 2 hr, a

10% NaOH (aq) solution (20 mL) was added, and the aqueous layer was extracted with ethyl acetate (3

x 15 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and

concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 100%

CH$_2$Cl$_2$ as eluent to afford 0.91 g (92%) of **84** as a beige solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.47 (brs,

1H), 7.56 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.21 − 7.06 (m, 2H), 6.32 (d, J = 1.3 Hz, 1H),

1.95 (s, 1H), 1.69 (s. 6H). Spectral data are in agreement with the values published by Bergman, J.;

Norrby, P.-O.; Tilstam, U.; Venemalm, L. *Tetrahedron.* **1989**, *45,* 5549–5564.
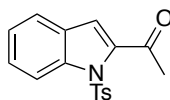
1-(1-Tosyl-1*H*-indol-2-yl)ethan-1-one (91). To *N*-tosylindole (**90**, 0.30 g, 1.1 mmol) in 10 mL of THF at -78 °C was added 2.5 M *n*-BuLi in hexanes (0.53 mL, 1.3 mmol) dropwise and the resulting solution was left to stir at that temperature for 30 min. The resulting anion intermediate was cannulated into a solution containing acetic anhydride (0.14 mL, 1.4 mmol) in 11 mL of THF at -78 °C and the mixture was left to stir at that temperature for 30 min prior to bringing the solution to room temperature overnight. Water (10 mL) and ethyl acetate (10 mL) were added to the reaction mixture and the aqueous later was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with sat. NaCl (aq) (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 15% ethyl acetate in hexanes as eluent to afford 0.25 g (71%) of **91** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.30 – 7.22 (m, 3H), 7.10 (s, 1H), 2.65 (s, 3H), 2.36 (s, 3H). Spectral data are in agreement with the values published by Liu,; J. Ma, S. *Org. Biomol. Chem.* **2013**, *11,* 4186–4193.
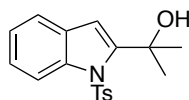
1-(1-Tosyl-1*H*-indol-2-yl)ethan-1-one (92). To **91** (0.52 g, 1.7 mmol) in 13 mL of THF at -78 °C was added 3.0 M methyl magnesium bromide in Et_2O (1.7 mL, 5.0 mmol) dropwise and the resulting solution was left warm to room temperature and left to stir at that temperature for 3 hrs. Water (20 mL) and ethyl acetate (20 mL) were added to the reaction mixture and the aqueous later was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with sat. NaCl (aq) (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 10% ethyl acetate in hexanes as eluent to afford 0.48 g (89%) of **92** as a beige

solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.3 Hz, 1H), 7.24 – 7.13 (m, 4H), 6.70 (s, 1H), 5.02 (s, 1H), 2.29 (s, 3H), 1.84 (s, 6H). Spectral data are in agreement with the values published by Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348,* 715–724.
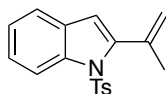
2-(Prop-1-en-2-yl)-1-tosyl-1*H*-indole (93). Following General Procedure 3, a solution of alcohol **92** (37 mg, 0.11 mmol) and ethyl vinyl ether (**85**) (13 μL, 0.13 mmol) in toluene (2 mL) was added to a suspension of indium triflate (12 mg, 0.040 mmol) in 0.30 mL of toluene at 0 °C. The resulting solution was allowed to stir for 1 hr, and then Et$_2$O (5 mL) and a sat. NaHCO$_3$ (aq) solution (5 mL) were added. The aqueous layer was extracted with Et$_2$O (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using DCM as eluent to afford 28 mg (80%) of **93** as a beige solid. mp: 73 – 75 °C; IR (neat) 1716, 1368, 1174 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.31 – 7.16 (m, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.44 (s, 1H), 5.28 (s, 1H), 5.15 (s, 1H), 2.28 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.7, 144.3, 139.4, 138.1, 134.7, 130.8, 129.4, 127.0, 124.8, 124.3, 120.8, 117.5, 116.3, 112.2, 24.2, 21.7; LRMS (ESI-TOF) m/z (relative intensity) 312.1 (80%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{18}$NO$_2$S 312.1058; Found 312.1070.
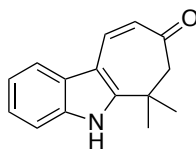
6,6-Dimethyl-6,7-dihydrocyclohepta[*b*]indol-8(5*H*)-one (97). Following General Procedure 3, a solution of alcohol **84** (35 mg, 0.20 mmol) and Danishefsky diene (**95**) (59 μL, 0.14 mmol) in

toluene (3 mL) was added to a suspension of indium triflate (22 mg, 0.040 mmol) in 0.30 mL of toluene at 0 °C. The resulting solution was allowed to stir for 1 hr, and then Et_2O (5 mL) and a sat. $NaHCO_3$ (aq) solution (5 mL) were added. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product **97** was purified via SiO_2 flash chromatography using DCM as eluent to afford 22 mg (48%) of the cyclized product as a yellow solid (the melting point could not be obtained because the solid decomposes before melting). IR (neat) 3313, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (bs, 1H), 7.72 – 7.68 (m, 1H), 7.56 (d, J = 11.9 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.26 – 7.22 (m, 1H), 6.12 (d, J = 11.8 Hz, 1H), 2.91 (s, 2H), 1.42 (s. 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 149.9, 134.9, 134.1, 128.48, 123.3, 123.0, 121.7, 117.7, 111.4, 109.7, 54.7, 32.5, 25.9. LRMS (ESI-TOF) m/z (relative intensity) 226.1 (100%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{15}H_{16}NO$ 226.1232; Found 226.1233.
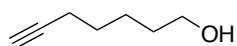
Hept-6-yn-1-ol (105). To NaH (3.2. g, 134 mmol) at 0 °C was added 72 mL of propylene diamine dropwise. The suspension was warmed to room temperature and then heated to 60 °C for 1 hr. The dark brown mixture was cooled to room temperature and alkynol **104** (5.4 mL, 45 mmol) was added in a dropwise fashion. After complete addition, the reaction mixture was left to stir for 1.5 hr at room temperature and then neutralized with a 2 M HCl solution. 100 mL of diethyl ether was added and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with NaCl (aq) (2 x 20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash column chromatography using 0 – 30% ethyl acetate in hexanes as eluent to afford 4.0 g (80%) of terminal alkynol **105** as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (t, J = 6.3 Hz, 2H), 2.31 (s, 1H), 2.16 (td, J = 6.7, 2.6 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.56 – 1.36 (m, 6H).

Spectral data are in agreement with the values published by Kamijo, S.; Dudley, G. *J. Am. Chem. Soc.* **2006**, *128*, 6499-6507.
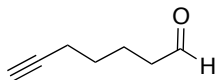
Hept-6-ynal (106). To a room temperature solution of hept-6-yn-1-ol (**105**, 5.0 g, 45 mmol) in 600 mL of a 2:1 mixture of CH_2Cl_2/DMSO was added triethylamine (31.0 mL, 220 mmol) followed by sulfur trioxide pyridine complex (28.4 g, 178 mmol). The reaction solution was stirred at room temperature for 1 hr, at which time the reaction mixture was washed with sat. $CuSO_4$ (aq) (2 x 200 mL), distilled water (2 x 200 mL), and sat. NaCl (aq) (2 x 200 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash column chromatography, using 10% ethyl acetate in hexanes as eluent, to afford 4.27 g (87%) of alkynal **106** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 2.42 (td, *J* = 7.2, 1.2 Hz, 2H), 2.16 (td, *J* = 7.0, 2.6 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.60 – 1.52 (m, 2H). Spectral data are in agreement with the values published.[17]
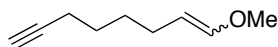
1-Methoxyoct-1-en-7-yne (107). To a 0 °C solution of potassium *tert*-butoxide (6.53 g, 58.2 mmol) in 100 mL of THF was added (methoxymethyl)triphenylphosphonium chloride (22.7 g, 66.0 mmol). The mixture was allowed to stir for 15 min and then a solution of alkynal **106** (4.27 g, 38.8 mmol) in 100 mL of THF was added dropwise. The resulting suspension was allowed to stir for 30 min at 0 °C, at which time the reaction mixture was washed with sat. NH_4Cl (aq) (2 x 100 mL), distilled water (2 x 100 mL), and sat. NaCl (aq) (2 x 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash column chromatography, after deactivation with 2% triethylamine, using 5% ethyl acetate in hexanes as eluent, to afford 2.7 g (50%) of enol ether **107** (1.7:1 *E:Z*) as a pale yellow oil. IR (neat) 3298, 2163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, *J* =

12.6 Hz, 1H, *E* isomer), 5.85 (dt, *J* = 6.2, 1.3 Hz, 1H, *Z* isomer), 4.73 (dt, *J* = 14.6, 7.3 Hz, 1H, *E*

isomer), 4.29 (q, *J* = 7.2 Hz, 1H, *Z* isomer), 3.55 (s, 3H, *Z* isomer), 3.48 (s, 3H, *E* isomer), 2.21 – 2.13

(m, 2H), 2.10 – 2.00 (m, 1H), 1.96 – 1.88 (m, 2H), 1.55 – 1.43 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ

147.2, 146.2, 106.3, 102.4, 84.5, 68.1, 59.4, 55.7, 29.7, 28.7, 27.9, 27.7, 27.1, 23.1, 18.2; LRMS (ESI-

TOF) m/z (relative intensity) 139.1 (44%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_9$H$_{15}$O

139.1123; Found 139.1117.
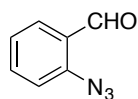
2-Azidobenzaldehyde (108). A solution of 2–nitrobenzaldehyde (7.0 g, 46 mmol) and

sodium azide (9.0 g, 140 mmol) in 60 mL of DMF was heated to 60 °C and held at that temperature for

96 hrs. The reaction mixture was diluted with Et$_2$O and the aqueous layer was washed with

dichloromethane (5 x 30 mL). The combined organic layers were washed with sat. NaCl (aq.) (2 x 30

mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash

chromatography, using 0 – 20% ethyl acetate in hexanes as eluent, to afford 5.60 g (83%) of

azidoaldehyde **108** as a pale yellow crystalline solid. mp 32 – 33 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ

10.23 (s, 1H), 7.79 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.55 (m, 1H), 7.17 (m, 2H). Spectral data are in agreement

with the values published.[18]
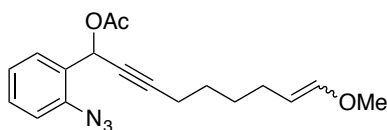
1-(2-Azidophenyl)-9-methoxynon-8-en-2-yn-1-yl Acetate (109). To a solution of enol

ether **107** (1.7:1 *E:Z*, 2.70 g, 19.5 mmol) in 75 mL of THF at -78 °C was added 2.5 M *n*-BuLi in

hexanes (8.3 mL, 21 mmol). The reaction mixture was allowed to stir for 45 min, at which time a

solution of azidoaldehyde **108** (2.87 g, 19.5 mmol) in 75 mL of THF was cannulated into the reaction

mixture. The resulting solution was allowed to stir for 2.5 hrs at -78 °C, at which time acetic anhydride

(2.0 mL, 22 mmol) was added. The reaction mixture was allowed to stir and warm to room temperature overnight. The reaction solution was washed with sat. NH$_4$Cl (aq) (2 x 50 mL), distilled water (2 x 50 mL), and sat. NaCl (aq) (2 x 50 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography, after deactivation with 2% triethylamine, using 0 – 5% ethyl acetate in hexanes as eluent, to afford 4.27 g (67%) of alkynyl azide **109** (1.7:1 *E:Z*) as a viscous light orange oil. IR (neat) 2128, 1745 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.39 (td, *J* = 7.9, 1.4 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 2H), 6.16 (t, *J* = 2.0 Hz, 1H), 6.27 (d, *J* = 12.6 Hz, 1H, *E* isomer), 5.87 (dt, *J* = 6.2, 1.5 Hz, 1H, *Z* isomer), 4.68 (dt, *J* = 14.6, 7.3 Hz, 1H, *E* isomer), 4.29 (q, *J* = 7.3 Hz, 1H, *Z* isomer), 3.56 (s, 3H, *Z* isomer), 3.49 (s, 3H, *E* isomer), 2.25 (dt, *J* = 7.1, 1.9 Hz, 2H), 2.09 (s, 3H), 1.93 (q, *J* = 7.2 Hz, 1H), 1.54 – 1.17 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.5, 147.2, 146.3, 137.8, 130.1, 129.3, 128.6, 124.9, 118.2, 106.3, 102.5, 88.2, 61.2, 59.4, 55.8, 29.8, 28.8, 27.8, 27.6, 26.9, 23.1, 21.0, 18.6; LRMS (ESI-TOF) m/z (relative intensity) 328.1 (12%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{22}$N$_3$O$_3$ 328.1661; Found 328.1666.
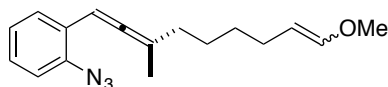
1-Azido-2-(9-methoxy-3-methylnona-1,2,8-trien-1-yl)benzene **(110).** To a solution of copper (I) iodide (24.8 g, 130 mmol) and lithium bromide (11.3 g, 130 mmol) in 1.5 L of THF at 0 °C was added 3.0 M methyl magnesium bromide in Et$_2$O (43.4 mL, 130 mmol). The reaction mixture was allowed to stir and warm to room temperature over 30 min, at which time alkynyl azide **109** (1.7:1 *E:Z*, 4.27 g, 13.0 mmol) in 125 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 45 min. The reaction mixture was washed with sat. NH$_4$Cl (aq) (2 x 500 mL), distilled water (10 x 500 mL), and sat. NaCl (aq) (2 x 500 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography, after deactivation with 2% triethylamine, using 0 – 4% ethyl acetate in hexanes as eluent, to afford 2.88 g (78%) of allenyl azide

110 (1.7:1 *E:Z*) as a viscous yellow/orange oil. IR (neat) 2117, 1951 cm⁻¹; ¹H NMR (300 MHz, CDCl₃)

δ 7.36 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.21 – 7.07 (m, 3H), 6.31 (p, *J* = 3.1 Hz, 1H), 6.24 (d, *J* = 12.6 Hz, 1H,

E isomer), 5.85 (dt, *J* = 6.2, 1.4 Hz, 1H, *Z* isomer), 4.69 (dt, *J* = 14.6, 7.3 Hz, 1H, *E* isomer), 4.31 (q, *J*

= 7.3 Hz, 1H, *Z* isomer), 3.55 (s, 3H, *Z* isomer), 3.47 (s, 3H, *E* isomer), 2.10 – 2.05 (m, 3H), 1.80 (s,

3H), 1.52 – 1.28 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 203.3, 147.0, 146.1, 135.9, 127.9, 127.4, 124.7,

118.3, 106.7, 103.7, 103.6, 102.9, 88.1, 59.4, 55.8, 33.8, 30.4, 29.4, 27.4, 27.1, 26.8, 23.6, 18.7; LRMS

(ESI-TOF) m/z (relative intensity) 256.2 (63%, M –N₂ + H⁺); HRMS (ESI-TOF) m/z: [M–N₂+H]⁺

Calcd for C₁₇H₂₂NO 256.1701; Found 256.1688.
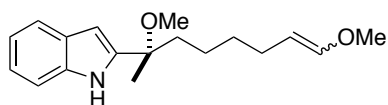
2-(2,8-Dimethoxyoct-7-en-2-yl)-1*H*-indole (98). *Method A:* Following General Procedure

2, allenyl azide **110** (1.7:1 *E:Z*, 0.77 g, 2.7 mmol) in 50 mL of methanol was brought to reflux and held

there for 120 hrs. At that time, concentration of the reaction mixture led to a crude product that was

purified via SiO₂ flash chromatography, after deactivation with 2% triethylamine, using 10% ethyl

acetate in hexanes as eluent, to afford 0.75 g (96%) of methanol adduct **98** (1.7:1 *E:Z*) as a viscous

yellow oil. *Method B:* Following General Procedure 1, a solution of thio allenyl azide **110** (1.7:1 *E:Z*,

50.0 mg, 0.18 mmol) in 17 mL of methanol was irradiated through Pyrex at 350 nm for 20 min. The

reaction mixture was concentrated in vacuo and purified as in Method A. Yield: 33 mg (63%, 1.7:1

E:Z). IR (neat) 3308 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.32 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.35

(d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 6.23 (d, *J*

= 12.6 Hz, 1H, *E* isomer), 5.83 (d, *J* = 6.2 Hz, 1H, *Z* isomer), 4.66 (dt, *J* = 12.6, 7.3 Hz, 1H, *E* isomer),

4.28 (q, *J* = 7.3 Hz, 1H, *Z* isomer), 3.55 (s, 3H, *Z* isomer), 3.45 (s, 3H, *E* isomer), 3.10 (s, 3H), 1.91 –

1.83 (m, 3H), 1.58 (s, 3H), 1.43 – 1.03 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 147.0, 146.1, 142.3,

135.9, 128.1, 121.7, 120.3, 119.5, 110.8, 106.7, 102.8, 100.7, 59.4, 55.8, 50.5, 40.5, 31.0, 30.0, 27.5,

23.3, 22.1; LRMS (ESI-TOF) m/z (relative intensity) 288.2 (58%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{26}$NO$_2$ 288.1964; Found 288.1982.
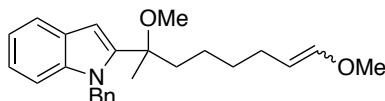
Benzyl-2-(2,8-dimethoxyoct-7-en-2-yl)-1*H*-indole (111). A solution of substrate **98** (0.13 g, 0.46 mmol) and KOH (0.077 g, 1.4 mmol) in 6.6 ml of DMF was stirred at 0 °C for 1 hr. Benzyl bromide (82 µL, 0.69 mmol) was added and the reaction mixture was left to stir at room temperature for 1 hr. Water (5 mL) and diethyl ether (5 mL) were added and the aqueous layer was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 100% benzene as eluent to afford 0.145 g (84%) of the benzylated product **111** as a viscous light yellow oil. ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.63 – 7.59 (m, 1H), 7.27 – 7.18 (m, 3H), 7.13 – 7.07 (m, 3H), 6.97 (d, *J* = 7.0 Hz, 2H), 6.50 (s, 1H), 6.18 (d, *J* = 12.6 Hz, 1H, *E* isomer), 5.94, (dd, *J* = 17.4, 3.3 Hz, 1H), 5.81 (d, *J* = 6.2 Hz, 1H, *Z* isomer), 5.64, (d, *J* = 17.4 Hz, 1H), 4.63 – 4.54 (m, 1H, *E* isomer), 4.23 (q, *J* = 7.2 Hz, 1H), 3.53 (s, 3H, *Z* isomer), 3.45 (s, 3H, *E* isomer), 3.02 (s, 3H), 1.95 – 1.65 (m, 4H), 1.59 (s, 3H), 1.15 – 0.80 (m, 4H); ^{13}C NMR (90 MHz, CDCl$_3$) δ 147.1, 146.1, 141.5, 141.4, 138.8, 138.6, 128.6, 127.2 (2), 126.9, 126.8, 125.9, 122.1, 122.0, 120.5, 119.8 (2), 110.4, 106.8, 103.8, 103.7, 103.0, 77.9, 59.5, 56.0, 50.7, 47.7, 40.3, 40.2, 30.9, 29.9, 27.6, 24.1, 23.9, 23.8, 23.1; LRMS (ESI-TOF) m/z (relative intensity) 378.2 (100%, M + H$^+$); HRMS (EIS-TOF) m/z: [M+H]$^+$ Calcd for C$_{25}$H$_{32}$NO$_2$ 378.2433; Found 378.2438.
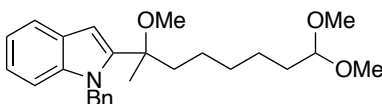
1-Benzyl-2-(2,8,8-trimethoxyoctan-2-yl)-1*H*-indole (112). Following General Procedure 3, a solution of methanol adduct **111** (0.027 mg, 0.074 mmol) in 1 mL of toluene was added to a suspension

of In(OTf)$_3$ (78 mg, 0.14 mmol) in 0.2 mL of toluene at -10 °C. The resulting solution was allowed to stir for 2 h at that temperature. A saturated solution of NaHCO$_3$ (aq) (5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via spherical SiO$_2$ flash chromatography using 0 – 5% ethyl acetate in hexanes as eluent to afford 7 mg (23%) of **112** as a clear oil. There were no trace amounts of the desired C–C bonded product. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 –7.57 (m, 1H), 7.30 – 7.18 (m, 3H), 7.15 – 7.05 (m, 3H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.49 (s, 1H), 5.94 (d, *J* = 17.5 Hz, 1H), 5.63 (d, *J* = 17.5 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 1H), 3.27 (s, 6H), 3.02 (s, 3H), 1.79 (t, *J* = 7.8 Hz, 2H), 1.59 (s, 3H), 1.48 (q, *J* = 7.2 Hz, 2H), 1.20 – 0.80 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 141.3, 138.8, 138.6, 128.6, 127.2, 126.8, 125.9, 122.1, 120.5, 119.8, 110.4, 104.5, 103.8, 77.9, 76.8, 52.7, 52.6, 50.6, 47.7, 40.4, 32.5, 29.5, 24.6, 24.5, 23.1; LRMS (ESI-TOF) m/z (relative intensity) 410.2 (87%, M + H$^+$). HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{26}$H$_{36}$NO$_3$ 410.2695; Found 410.2711.
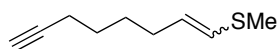
Methyl(oct-1-en-7-yn-1-yl)sulfane **(118).** To a 0 °C suspension of ((methylthio)methyl)triphenylphosphonium chloride (9.94 g, 27.7 mmol) in 100 mL of THF was added 1.8 M PhLi in dibutyl ether (14.7 mL, 26.5 mmol). The reaction mixture was allowed to stir for 30 min and then a solution of alkynal **104** (2.77 g, 25.2 mmol) in 100 mL of THF was added dropwise. The resulting suspension was allowed to stir for 3 hrs at 0 °C, at which time a sat. sol. of NH$_4$Cl (aq) (100 mL) was added. The aqueous layer was extracted with Et$_2$O (3 x 50 mL) and the combined organic layers were washed with sat. NaCl (aq) (100 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash column chromatography, using hexanes as eluent, to afford 2.49 g (69%) of thio enol ether **118** (1.25:1 *E:Z*) as a pale yellow oil. IR (neat) 3297, 2360 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.98 (d, *J* = 15.0 Hz, 1H, *E* isomer), 5.89 (d, *J* = 9.4 Hz, 1H, *Z* isomer), 5.47

(m, 1H, *E* & *Z* isomers), 2.30 – 2.09 (m, 7H), 1.95 – 1.93 (m, 1H), 1.69 – 1.39 (m, 4H); ^{13}C NMR (75

MHz, CDCl$_3$$^)$ δ 128.7, 127.2, 126.9, 124.0, 84.4, 68.2, 32.5, 28.5, 28.2, 27.8, 18.2, 17.0, 15.0; LRMS

(ESI-TOF) m/z (relative intensity) 154.1 (9%, M); HRMS (ESI-TOF) m/z: [M]$^+$ Calcd for C$_9$H$_{14}$S

154.0816; Found 154.0820.
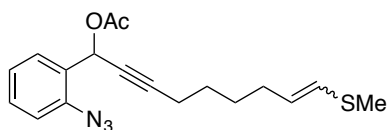
1-(2-Azidophenyl)-9-(methylthio)-non-8-en-2-yn-1-yl Acetate (119). To a solution of thio

enol ether **118** (1.25:1 *E*:*Z*, 2.60 g, 17.1 mmol) in 250 mL of THF at -78 °C was added 2.5 M *n*-BuLi in

hexanes (7.5 mL, 19 mmol). The reaction mixture was allowed to stir for 1 hr at -78 °C, at which time a

solution of azidoaldehyde **108** (2.51 g, 17.1 mmol) in 75 mL of THF was added dropwise. The resulting

solution was allowed to stir for 2.5 hrs at 0 °C, at which time acetic anhydride (2.0 mL, 19 mmol) was

added. The reaction mixture was allowed to stir and warm to room temperature overnight. A saturated

solution of NH$_4$Cl (aq) (100 mL) was added to the reaction mixture, the aqueous layer was extracted

with Et$_2$O (3 x 50 mL), and the combined organic layers were washed with sat. NaCl (aq) (100 mL),

dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash

chromatography using 5% ethyl acetate in hexanes as eluent to afford 5.20 g (89%) of thio alkynyl

azide **119** (1.25:1 *E*:*Z*) as a viscous light orange oil. IR (neat) 2123, 1740 cm^{-1}; ^{1}H NMR (300 MHz,

CDCl$_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.18 (m, 2H), 6.61 (s, 1H), 5.95 (d, *J* = 15.0

Hz, 1H, *E* isomer), 5.87 (d, *J* = 9.4 Hz, 1H, *Z* isomer), 5.52 – 5.35 (m, 1H, *E* & *Z* isomers), 2.27 – 2.21

(m, 5H), 2.14 – 2.08 (m, 5H), 1.55 – 1.46 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.4, 137.7, 130.0,

129.2, 128.5, 128.2, 127.0, 123.9, 118.1, 88.0, 61.1, 32.4, 28.5, 28.4, 28.0, 27.8, 27.6, 20.9, 18. 6, 16.9,

14.9; LRMS (ESI-TOF) m/z (relative intensity) 344.1 (30%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$

Calcd for C$_{18}$H$_{22}$N$_3$O$_2$S 344.1433; Found 344.1430.
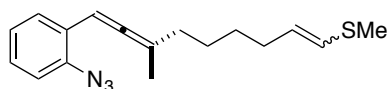
(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)sulfane (120). To a solution of copper (I) iodide (28.7 g, 151 mmol) and lithium bromide (13.1, 151 mmol) in 2.0 L of THF at 0 °C was added 3.0 M methyl magnesium bromide in Et$_2$O (50.0 mL, 151 mmol). The reaction mixture was allowed to stir and warm to room temperature over 1 hr, at which time thio alkynyl azide **119** (1.25:1 *E*:*Z*, 5.17 g, 15.1 mmol) in 100 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 30 min. The reaction mixture was washed with sat. NH$_4$Cl (aq) (2 x 200 mL), distilled water (3 x 200 mL), and sat. NaCl (aq) (3 x 200 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography, after deactivation with 2% triethylamine, using 0 – 4% ethyl acetate in hexanes as eluent to afford 3.72 g (82%) of allenyl azide **120** (1.25:1 *E*:*Z*) as a viscous yellow oil. IR (neat) 2116, 1950 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.13 – 7.04 (m, 2H), 6.31 (q, *J* = 2.6 Hz, 1H), 5.93 (d, *J* = 14.9 Hz, 1H, *E* isomer), 5.86 (d, *J* = 9.4 Hz, 1H, *Z* isomer), 5.53 – 5.36 (m, 1H, *E* & *Z* isomers), 2.25 (s, 3H, *Z* isomer), 2.20 (s, 3H, *E* isomer), 2.14 – 2.02 (m, 4H), 1.80 (d, *J* = 2.7 Hz, 3H), 1.56 – 1.42 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.3, 135.9, 128.7, 127.5, 126.7, 124.7, 123.6, 118.4, 103.5, 88.2, 33.8, 32.9, 29.1, 28.9, 28.6, 27.0, 26.8, 18.7, 17.0, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (42%, M –N$_2$ + H$^+$); HRMS (ESI-TOF) m/z: [M–N$_2$ +H]$^+$ Calcd for C$_{17}$H$_{22}$NS 272.1473; Found 272.1476.
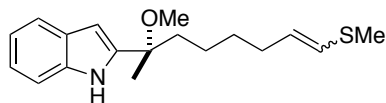
2-(2-Methoxy-8-(methylthio)oct-7-en-2-yl)-1*H*-indole (121) *Method A:* Following General Procedure 2, a solution of allenyl azide **120** (1.25:1 *E*:*Z*, 0.51 g, 1.7 mmol) in 175 mL of methanol was brought to reflux and held there for 84 hrs. At that time, concentration of the reaction mixture led to a

crude product that was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.46 g (88%) of methanol adduct **121** (1.25:1 *E:Z*) as a viscous yellow oil. *Method B:* Following General Procedure 1, a solution of thio allenyl azide **120** (1.25:1 *E:Z*, 50.0 mg, 0.17 mmol) in 17 mL of methanol was irradiated through Pyrex at 350 nm for 1.8 hrs. The reaction mixture was concentrated in vacuo and purified as in Method A. Yield: 23 mg (45%, 1.25:1 *E:Z*). IR (neat) 3307 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.38 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.1 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.35 (s, 1H), 5.92 (d, *J* = 15.0 Hz, 1H, *E* isomer), 5.83 (d, *J* = 9.4 Hz, 1H, *Z* isomer), 5.51 – 5.30 (m, 1H, *E* & *Z* isomers), 3.11 (s, 3H), 2.25 (s, 3H, *E* isomer), 2.19 (s, 3H, *Z* isomer), 2.07 (p, *J* = 6.9 Hz, 2H), 1.89 (q, *J* = 6.6 Hz, 2H), 1.59 (s, 3H), 1.37 – 1.10 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.2, 135.8, 128.6, 128.1, 127.3, 126.7, 123.7, 121.7, 120.3, 119.5, 110.8, 100.7, 50.6, 40.7, 40.6, 32.9, 29.8, 29.1, 28.9, 23.5, 23.4, 22.1, 17.0, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 304.2 (40%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{26}$NOS 304.1735; Found 304.1723.

4a-Methyl-10-(methylthio)-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-*b*]indole (123/124/125) and 10a-methyl-6-(methylthio)-6a,7,8,9,10,10a-hexahydro-6*H*-isoindolo[2,1-*a*]indole (126). *In acetonitrile:* Following General Procedure 3, indole **121** (77 mg, 0.25 mmol, 1.25:1 *E:Z*) in 6.5 mL of acetonitrile was cannulated into a suspension of indium triflate (0.029 g, 0.051 mmol) in 0.5 mL of acetonitrile at 0 °C. The resulting solution was allowed to stir for 1 hr and then a sat. NaHCO$_3$ (aq) solution (5 mL) was added. The aqueous layer was extracted with Et$_2$O (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 35 mg (51%) of the C-cyclized product as a mixture of 3 isomers (**123**:**124**:**125**, 8:3:1) as a viscous yellow oil. *In dichloromethane:* Yield: 20% of the C-cyclized product as a mixture of 2

isomers (**123**:**124**, 8:1). *In toluene:* Yield: 52% of the C-cyclized product as a mixture of 2 isomers (**123**:**124**, 8:1) and 38% of the *N*-cyclized product **126** as a mixture of 3 isomers.
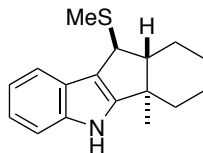
123: IR (neat) 3396 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.96 (s, 1H), 7.82 −7.79 (m, 1H), 7.34 − 7.31 (m, 1H), 7.17 − 7.15 (m, 2H), 3.83 (d, *J* = 10.0 Hz, 1H), 2.30 − 2.15 (m, 1H), 2.03 (s, 3H), 2.02 − 1.92 (m, 2H), 1.82 − 1.30 (m, 6H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.8, 139.3, 124.6, 120.9, 120.1, 118.6, 116.4, 111.8, 60.5, 46.7, 42.4, 34.9, 26.8, 21.9, 21.2, 18.5, 11.5; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (12%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{17}$H$_{22}$NS 272.1473; Found 272.1468.
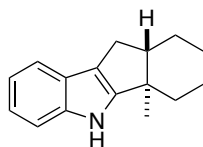
(4a*R*,10a*S*)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-*b*]indole   (127).   Following General Procedure 4, a 1 M Superhydride solution in THF (0.60 mL, 0.55 mmol) was added to a solution of the cyclized adduct **123** (30 mg, 0.11 mmol) in THF (3 mL) under a N$_2$ atmosphere. The resulting mixture was stirred for 12 hrs at room temperature and then a sat. NH$_4$Cl (aq) solution (5 mL) was added. The aqueous layer was extracted with Et$_2$O (3 x 10 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via basic Al$_2$O$_3$ flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 23 mg (92%) of the desulfurized product **127** as a viscous light yellow oil. IR (neat) 3402 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.49 − 7.44 (m, 1H), 7.35 − 7.30 (m, 1H), 7.12 − 7.07 (m, 2H), 2.73 − 2.66 (m, 1H), 2.47 − 2.31 (m, 2H), 2.04 − 1.98 (m, 1H), 1.88 − 1.82 (m, 1H), 1.74 − 1.65 (m, 4H), 1.50 − 1.30 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 153.1, 139.3, 125.2, 120.3,

119.6, 118.6, 116.8, 111.6, 55.7, 42.2, 34.9, 28.0, 26.8, 24.7, 21.3, 17.1; LRMS (ESI-TOF) m/z (relative intensity) 226.2 (96%, M + H$^+$); HRMS (ESI-TOF) m/z:[M+H]$^+$ Calcd for $C_{16}H_{20}N$ 226.1613; Found 226.1596.

4a-Methyl-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-*b*]indole (127/128). Following General Procedure 4, a 1 M Superhydride solution in THF (0.61 mL, 0.55 mmol) was added to a solution of the cyclized adduct **123/125** (33 mg, 0.12 mmol, 3.7:1 **123**:**125**) in THF (4 mL) under a N_2 atmosphere. The resulting mixture was stirred for 12 hrs at room temperature and then a sat. NH_4Cl (aq) solution (5 mL) was added. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 23 mg (85%) of the desulfurized product **127/128** as a mixture of 2 isomers (**127/128**, 3.6:1). The structural assignment of **128** is based upon comparison of its ^{1}H NMR values to the ^{1}H NMR values of the authentic *cis*-fused isomer **128** published by Harrison and coworkers.[2h]
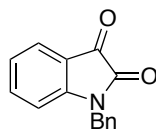
1-Benzylindoline-2,3-dione (130). To a 0 °C solution of isatin (**129**) (10 g, 68 mmol) in 120 mL of DMF was added NaH (2.0 g, 82 mmol) in two portions. The deep purple solution was stirred at 0 °C for 1.5 hr and benzyl bromide (9.3 mL, 78 mmol) then was added. The resulting reddish-brown solution was allowed to stir for 30 min at room temperature. Water (600 mL) was added and the precipitate was filtered. The red-orange solid was dissolved in ethyl acetate (100 mL), washed with distilled water (100 mL) and sat. NaCl (aq) (100 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 15 g (92%) of the benzylated isatin **130** as a reddish-orange solid. mp: 128 – 129 °C, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.62 (d, *J* = 6.7 Hz, 1H), 7.50 (td, *J* = 6.5, 1.3 Hz, 1H), 7.34–7.25 (m, 5H), 7.12 (t, *J* = 7.1 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 4.94 (s, 2H). Spectral data are in agreement with the values

published by Lotter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. S.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2006**, *63,* 2263–2274.
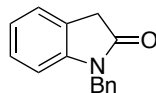
1-Benzylindolin-2-one (131). A solution of benzylated isatin **130** (1.2 g, 5.0 mmol) in hydrazine:water (9.5 mL, 0.15 mol, 55% solution) was heated to 130 °C for 4 hrs. The resulting yellow solution was cooled to room temperature and sat. NH$_4$Cl (aq) (20 mL) and ethyl acetate (30 mL) were added. The aqueous layer was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with sat. NaCl (aq) (30 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 20% ethyl acetate in hexanes as eluent to afford 1.1 g (98%) of the benzylated oxindole **131** as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.33 – 7.20 (m, 5H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H) 6.70 (d, *J* = 7.8 Hz, 2H), 4.89 (s, 2H), 3.59 (s, 2H). Spectral data are in agreement with the values published by Lotter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. S.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2006**, *63,* 2263-2274.
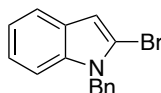
1-Benzyl-2-bromo-1*H*-indole (132). To a solution of benzylated oxindole **131** (0.50 g, 2.2 mmol) in ethylene dichloride (15 mL) was added phosphorus oxybromide (0.71 g, 2.5 mmol) and the mixture was heated to 130 °C for 5 hrs. After cooling to room temperature, a sat. NaHCO$_3$ (aq) (20 mL) solution was added until the solution stopped bubbling. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic layers washed with sat. NaCl (aq) (20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 1% ethyl acetate in hexanes as eluent to afford 0.18 g (28%) of the brominated indole **132** as a white

solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.58 (dd, J = 6.8, 1.6 Hz, 1H), 7.21 – 7.29 (m, 4H), 7.07 – 7.16 (m, 4H), 6.67 (s, 1H), 5.42 (s, 2H). Spectral data are in agreement with the values published by Lotter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. S.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2006,** *63,* 2263-2274.
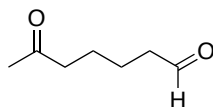
6-Oxoheptanal (134). A solution of 1-methylcyclohexene (**133**) (8.0 mL, 67.4 mmol) in 1.14 L of CH$_2$Cl$_2$ was cooled to -78 °C and was treated with ozone until the solution turned blue. Triphenylphosphine (23.7 g, 80.9 mmol) was added and the reaction mixture was stirred overnight up to rt and concentrated in vacuo. The crude mixture was dissolved in a mixture of hexanes/ether and most of the triphenylphosphine oxide precipitated and was removed by filtration. The filtrate was concentrated and the crude product was purified via SiO$_2$ flash chromatography using 0 – 30% ethyl acetate in hexanes as eluent to afford 5.97 g (71%) of aldehyde **134** as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.76 (s, 1H), 2.45 (m, 4H), 2.13 (s, 3H), 1.61 (m, 4H). Spectral data are in agreement with the values published by Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71,* 2538-2541.
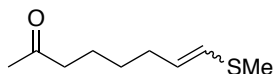
8-(Methylthio)oct-7-en-2-one (135). A solution of ((methylthio)methyl)triphenylphosphonium chloride (0.97 g, 2.7 mmol) and 1.8 M PhLi in dibutyl ether (1.5 mL, 2.7 mmol) in 5 mL of THF was stirred at -78 °C for 45 min. This solution was added dropwise to a solution of alkynal **134** (0.315 g, 2.46 mmol) in 10 mL of THF. The resulting suspension was allowed to stir for 2 hrs at room temperature, at which time a sat. solution of NH$_4$Cl (aq) (15 mL) was added. The aqueous layer was extracted with Et$_2$O (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product

was purified via SiO$_2$ flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.22 g

(52%) of ketone **135** as a viscous light yellow oil (mixture of 2 isomers, *E:Z* 1.8:1). IR (neat) 1710 cm^{-1};

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.98 (d, *J* = 15.0 Hz, 1H, *E* isomer), 5.88 (d, *J* = 9.4 Hz, 1H, *Z* isomer),

5.53 – 5.38 (m, 1H, *E* & *Z* isomers), 2.43 – 2.41 (m, 2H), 2.25 (s, 3H, *Z* isomer), 2.21 (s, 3H, *E* isomer),

2.12 – 2.08 (m, 5H), 1.61 – 1.57 (m, 2H), 1.38 – 1.36 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 209.3,

209.2, 128.4, 127.2, 127.0, 124.2, 43.6, 43.6, 33.0, 30.0, 29.1, 28.8, 28.5, 23.5, 23.4, 23.3, 17.2, 15.2;

LRMS (EI-TOF) m/z (relative intensity) 172.1 (22%, M); HRMS (EI-TOF) m/z: [M]$^+$ Calcd for

C$_9$H$_{16}$OS 172.0922; Found 172.0927.
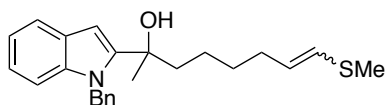
2-(1-Benzyl-1*H*-indol-2-yl)-8-(methylthio)oct-7-en-2-ol (136). To a solution of 2-bromo-*N*-

benzyl indole **132** (0.52 g, 1.8 mmol) in 75 mL of THF at -78 °C was added 2.5 M *n*-BuLi in hexanes

(0.72 mL, 1.8 mmol) dropwise and the mixture was warmed to 0 °C and stirred for 20 min. The

reaction mixture was then cooled back to -78 °C and a solution of ketone **135** (0.26 g, 1.5 mmol, *E:Z*

1.8:1) in 5 mL of THF was cannulated into the reaction mixture. The resulting solution was warmed to

room temperature and stirred for 3 hrs. A sat. NH$_4$Cl (aq) solution (20 mL) was added at that time, and

the aqueous layer was extracted with Et$_2$O (3 x 20 mL). The combined organic layers were washed with

sat. NaCl (aq) (20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified

via SiO$_2$ flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.42 g (74%) of

alcohol **136** as a viscous yellow oil (mixture of 2 isomers, *E:Z* 1.8:1). IR (neat) 3402 cm^{-1}; ^{1}H NMR

(300 MHz, CDCl$_3$) δ 7.61 – 7.59 (m, 1H), 7.24 – 7.18 (m, 3H), 7.14 – 7.05 (m, 3H), 6.93 (d, *J* = 7.0 Hz,

2H), 6.46 (s, 1H), 5.93 – 5.81 (m, 2H), 5.71 (d, *J* = 17.4 Hz, 1H), 5.44 – 5.29 (m, 1H, *E* and *Z* isomers),

2.23 (s, 3H, *Z* isomer), 2.18 (s, 3H, *E* isomer), 1.99 – 1.81 (m, 4H), 1.73 – 1.68 (m, 4H), 1.43 – 0.96 (m,

4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 144.1, 144.0, 138.9 (2), 138.6, 138.5, 128.7, 128.6, 127.5, 127.1 (2),

126.8 (2), 125.6, 123.7, 122.0, 121.9, 120.5, 119.8 (2), 110.2, 100.7, 100.6, 72.8, 48.3, 41.9 (2), 32.9, 29.5, 28.9 (3), 24.2 (2), 17.1, 15.1; LRMS (AP-TOF) m/z (relative intensity) 362.2 (59%, M − OH + H$^+$); HRMS (ESI-TOF) m/z: [M–OH+H]$^+$ Calcd for $C_{24}H_{28}NS$ 362.1942; Found 362.1939.
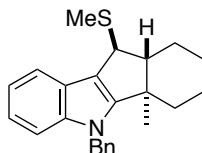
(4aR,10S,10aR)-5-Benzyl-4a-methyl-10-(methylthio)-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-b]indole (137). *In acetonitrile:* Following General Procedure 3, a solution of alcohol **136** (52 mg, 0.14 mmol, *E:Z* 1.6:1) in acetonitrile (3 mL) was added to a suspension of indium triflate (15 mg, 0.027 mmol) in 0.5 mL of acetonitrile at 0 °C. The resulting solution was allowed to stir for 15 min, and then Et$_2$O (5 mL) and a sat. NaHCO$_3$ (aq) solution (5 mL) were added. The aqueous layer was extracted with Et$_2$O (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using hexanes as eluent to afford 42 mg (85%) of the cyclized product as viscous yellow oil (mixture of 2 isomers, **137**:**138**, 2.6:1). *In dichloromethane:* Yield: 44% (**137**:**138**, 1.6:1). *In toluene:* Yield: 42% (**137**:**138**, 2.6:1).

137: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.75 − 7.90 (m, 1H), 7.30 − 7.25 (m, 3H), 7.17 − 7.08 (m, 3H), 7.05 − 6.98 (m, 2H), 5.34 (s, 2H), 3.88 (d, *J* = 10.0 Hz, 1H), 2.27 − 2.19 (m, 1H), 2.05 (s, 3H), 2.02 − 1.96 (m, 1H), 1.43 − 1.83 (m, 1H), 1.78 − 1.50 (m, 4H), 1.37 − 1.30 (m, 2H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 153.9, 140.2, 138.0, 128.7, 127.4, 126.0, 124.6, 120.8, 119.8, 118.7, 115.8, 110.1, 60.7, 48.0, 46.5, 43.1, 35.4, 26.6, 21.9, 21.2, 18.1, 11.5; LRMS (ESI-TOF) m/z (relative intensity) 362.2 (59%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{24}H_{28}NS$ 362.1942; Found 362.1948. A pure sample of **138** could not be isolated, and hence its structural assignment is based upon

analogy to the results of the non-benzylated series. The tentative stereochemical assignment is based upon analysis at the MeS-C$\underline{H}$ coupling constant.

5.3 Lithium-Bromide Exchange: Carbofunctionalization of 2-Bromo-*N*-Benzyl Indole.

General Procedure. To a solution of 2-bromo-*N*-benzyl indole (**132**) (1.2 mmol) in THF (20 mM) at -78 °C under N$_2$ was added 2.5 M *n*-BuLi in hexanes (1.2 mmol) dropwise and the mixture was stirred for 10 min at -78 °C. A solution of ketone or aldehyde (1 mmol) in THF (120 mM) was cannulated into the reaction mixture (final concentration of substrate: 15 mM). The resulting solution was warmed to room temperature and stirred under an N$_2$ atmosphere. After TLC analysis indicated consumption of the ketone or aldehyde, a sat. NH$_4$Cl (aq) solution was added. The aqueous layer was extracted with Et$_2$O (3x) and the combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The product was purified via SiO$_2$ flash column chromatography using 0 – 10% ethyl acetate in hexanes as eluent.
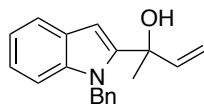
2-(1-Benzyl-1*H*-indol-2-yl)but-3-en-2-ol (153). IR (neat) 3434 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 – 7.57 (m, 1H), 7.23 – 7.14 (m, 3H), 7.09 – 7.01 (m, 3H), 6.90 (d, *J* = 7.1 Hz, 2H), 6.52, (s, 1H), 6.16 (dd, *J* = 10.6, 6.6 Hz, 1H), 5.67 (d, *J* = 17.2 Hz, 1H), 5.54 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 5.08 (d, *J* = 10.6 Hz, 1H), 1.87 (s, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.3, 143.0, 138.9, 138.4, 128.6, 127.1, 126.9, 125.9, 122.2, 120.8, 119.9, 113.3, 110.5, 100.6, 72.4, 48.4, 29.8; LRMS (AP-TOF) m/z (relative intensity) 278.2 (100%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{19}$H$_{20}$NO 278.1545; Found 278.1552.
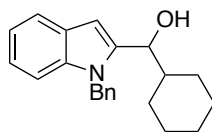
1-(1-Benzyl-1*H*-indol-2-yl)-1-cyclohexylethan-1-ol (154). IR (neat) 3398 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.64 – 7.57 (m, 1H), 7.25 – 7.08 (m, 6H), 6.96 – 6.93 (m, 2H), 6.96 (d, *J* = 17.5 Hz, 2H), 6.50, (s, 1H), 5.31 (d, *J* = 17.5 Hz, 1H), 5.47 (d, *J* = 17.5 Hz, 1H), 4.47 – 4.41 (m, 1H), 2.12 – 2.01 (m, 1H), 1.77 – 1.65 (m, 3H), 1.52 – 1.43 (m, 1H), 1.30 – 0.80 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 141.5, 138.2, 137.8, 128.8, 127.6, 127.3, 125.9, 122.0, 120.7, 119.9, 109.9, 100.7, 72.4, 47.1, 42.9, 30.2, 29.1, 26.4, 25.9; LRMS (AP-TOF) m/z (relative intensity) 320.2 (100%, M + H⁺); HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₂₂H₂₆NO 320.2014; Found 320.2004.
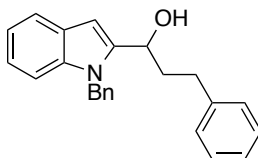
2-(1-Benzyl-1*H*-indol-2-yl)-4-phenylbutan-2-ol (155). mp: 62 – 64 °C; IR (neat) 3533 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, *J* = 7.1 Hz, 1H), 7.30 – 7.09 (m, 11 H), 6.96 – 6.93 (m, 2H), 6.59, (s, 1H), 5.53 (d, *J* = 17.1 Hz, 1H), 5.43 (d, *J* = 17.1 Hz, 1H), 4.81 – 4.72 (m, 1H), 2.92 – 2.65 (m, 2H), 2.30 – 2.19 (m, 1H), 1.61 (d, *J* = 6.5 Hz, 1H); ¹³C NMR (74 MHz, CDCl₃) δ 142.2, 141.9, 138.5, 138.3, 129.2, 128.9, 127.9, 127.8, 126.4 (2), 122.6, 121.3, 120.4, 110.3, 100.3, 66.7, 47.3, 38.4, 32.6; LRMS (AP-TOF) m/z (relative intensity) 342.2 (100%, M + H⁺); HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₂₄H₂₄NO 342.1858; Found 342.1862.
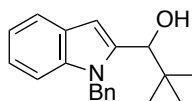
1-(1-Benzyl-1*H*-indol-2-yl)-2,2-dimethylpropan-1-ol (156). IR (neat) 3452 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.05 (m, 6H), 6.89 – 6.86 (m, 2H), 6.58 (s, 1H), 5.48 (d, *J* = 16.0 Hz, 1H), 5.35 (d, *J* = 16.0 Hz, 1H) 4.52 (s, 1H), 1.75 (s, 1H) 0.98 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.5, 138.1, 137.1, 128.9, 127.8, 127.4, 125.9, 121.9, 120.8, 120.1, 110.0, 101.2,

74.8, 47.3, 36.5, 26.2; LRMS (AP-TOF) m/z (relative intensity) 294.2 (100%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{20}$H$_{24}$NO 294.1858; Found 294.1855.

5.4 Intramolecular [3 + 2] Cyclocondensations of Alkenes with Indolidenes Intermediates.
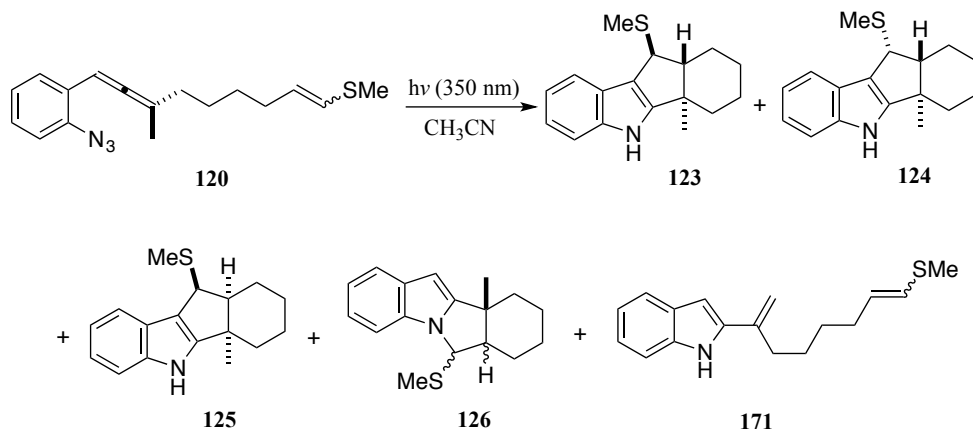
4a-Methyl-10-(methylthio)-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-b]indole

(123/124/125),   10a-methyl-6-(methylthio)-6a,7,8,9,10,10a-hexahydro-6H-isoindolo[2,1-a]indole

(126 & 2-(8-(Methylthio)octa-1,7-dien-2-yl)-1H-indole (171). *In acetonitrile:* Following General

Procedure 1, a solution of thio allenyl azide **120** (1.25:1 *E:Z*, 50 mg, 0.17 mmol) in 17 mL of

acetonitrile was irradiated through Pyrex at 350 nm for 2.5 hrs. The reaction mixture was concentrated

in vacuo. The crude product was purified via basic Al$_2$O$_3$ flash chromatography using 0 – 4% ethyl

acetate in hexanes as eluent to afford 26 mg (55%) of the C-cyclized products **123–125** as a viscous

yellow oil (mixture of three isomers, 18:1:4, **123:124:125**) as well as 1 mg (3%) of the alkene **171** and

4 mg (9%) of the *N*-cyclized products **126** as a mixture of three isomers. The major isomer **123** was

isolated via preparatory HPLC and fully characterized (*vide infra*). The isomers' relative

stereochemistries were determined by the comparison of ^{1}H NMR coupling constants for H$_a$ to

predicted values. The predicted values were generated from structures optimized via molecular

mechanics calculations. It is not possible to distinguish between the structures **124** and **125** by this

method; however, a mixture of the two isomers were subjected to desulfurization conditions (vide infra)

and the ^{1}H NMR spectral data of the reduction (desulfurization) product from **125** was found to match those of the *cis*-fused isomer.[2h] *In dichloromethane:* Yield: 20% of the alkene product **171** (Only trace amounts of the desired C-cyclized product **123** was seen by ^{1}H NMR). *In toluene:* Yield: 22% of the *N*-cyclized product **126** as a mixture of 3 isomers (Only trace amounts of the C-cyclized product was seen by ^{1}H NMR). Another stereoisomer of the *N*-cyclized product different from **126'** (labeled as **126"**) was isolated and fully characterized, but the ring juncture stereochemistry could not be assigned. *In DMF:* Yield: 73% of the formal "ene" product **171** (Only trace amounts of the C-cyclized product was seen by ^{1}H NMR).
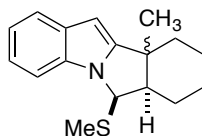
126": ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.57 (t, J = 7.0 Hz, 2H), 7.15 – 7.04 (m, 2H), 6.10 (s, 1H), 5.50 (d, J = 6.0 Hz, 1H), 2.70 (q, J = 6.3 Hz, 1H), 2.46 (s, 3H), 2.10 – 1.75 (m, 4H), 1.65 – 1.35 (m, 4H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.4, 133.5, 133.0, 121.0, 120.9, 120.0, 119.9, 91.7, 70.1, 53.4, 40.3, 35.5, 27.0, 24.4, 24.1, 22.3, 18.0; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (12%, M + H^{+}); HRMS (ESI-TOF) m/z: [M+H][+] Calcd for C$_{17}$H$_{22}$NS 272.1473; Found 272.1468.
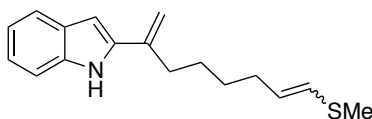
2-(8-(Methylthio)octa-1,7-dien-2-yl)-1*H*-indole (171). Following General Procedure 2, allenyl azide **120** (1.25:1, *E:Z*, 50.0 mg, 0.17 mmol) in 50 mL of acetonitrile was brought to reflux and held there for 20 hrs. At that time, concentration of the reaction mixture led to a crude product that was purified via basic Al$_2$O$_3$ flash chromatography using 2% ethyl acetate in hexanes as eluent to afford 0.018 g (40%, 1.25:1 *E:Z*) of the alkene **171** as a viscous yellow oil (Only trace amounts of the cyclized product **123** was observed by ^{1}H NMR). IR (neat) 3395, 1640 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.17

(s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.3 Hz,

1H), 6.57 (m, 1H), 6.02 (d, J = 15.0 Hz, 1H, *E* isomer), 5.91 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.58 – 5.40

(m, 1H, *E* & *Z* isomers), 5.33 (s, 1H), 5.09 (s, 1H), 2.56 – 2.49 (m, 2H), 2.28 (s, 3H, *E* isomer), 2.23 (s,

3H, *Z* isomer), 2.22 – 2.13 (m, 2H), 1.70 – 1.60 (m, 2H), 1.56 – 1.45 (m, 2H); ^{13}C NMR (75 MHz,

CDCl$_3$) δ 140.1, 138.2, 136.5, 128.8, 127.0, 122.7, 120.8, 120.0, 110.7, 109.3, 101.0, 34.2, 29.0, 28.8,

28.6, 17.2; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (36%, M + H$^+$); HRMS (ESI-TOF)

m/z: [M+H]$^+$ Calcd for C$_{17}$H$_{22}$NS 272.1473; Found 272.1461.
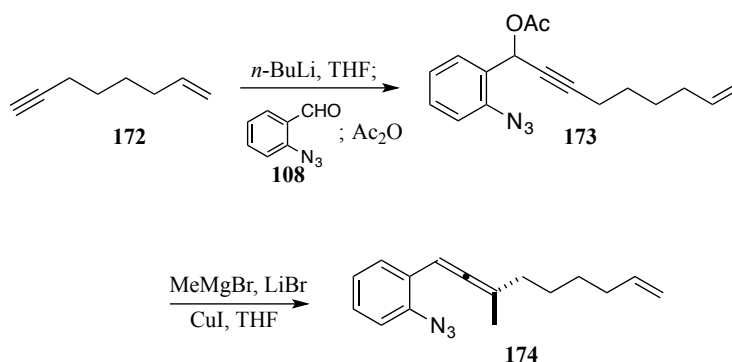
(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)sulfane (173). To a solution of

alkene **172** (0.21 g, 1.4 mmol) in 22 mL of THF at -78 °C was added 2.5 M *n*-BuLi in hexanes (0.56

mL, 1.4 mmol). The reaction mixture was allowed to stir for 30 min at -78 °C, at which time a solution

of azidoaldehyde **108** (0.15 g, 1.4 mmol) in 5 mL of THF was added dropwise. The resulting solution

was allowed to stir for 1.5 hrs at 0 °C, at which time acetic anhydride (0.16 mL, 1.7 mmol) was added.

The reaction mixture was allowed to stir and warm to room temperature overnight. A saturated solution

of NH$_4$Cl (aq) (10 mL) was added to the reaction mixture and the aqueous layer was extracted with

Et$_2$O (3 x 10 mL). The combined organic layers were washed with sat. NaCl (aq) (10 mL), dried over

Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography

using 0 – 5% ethyl acetate in hexanes as eluent to afford 0.12 g (28%) of **173** as a light yellow oil.

1-Azido-2-(3-methyl-2λ^5-nona-1,2,8-trien-1-yl)benzene (174). To a solution of copper (I)
iodide (1.04 g, 3.36 mmol) and lithium bromide (0.474 g, 5.45 mmol) in 70.0 mL of THF at 0 °C was
added 3.0 M methyl magnesium bromide in Et$_2$O (1.80 mL, 5.45 mmol). The reaction mixture was
allowed to stir and warm to room temperature over 1 hr, at which time substrate **173** (0.162 g, 0.545
mmol) in 7 mL of THF was added to the reaction mixture. The resulting solution was allowed to stir for
30 min and diluted with 50 mL of Et$_2$O. The reaction mixture was washed with sat. NH$_4$Cl (aq) (2 x 200
mL), distilled water (3 x 200 mL), and sat. NaCl (aq) (3 x 200 mL), dried over Na$_2$SO$_4$, and
concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 100%
hexanes as eluent to afford 0.082 g (60%) of allenyl azide **174** as a viscous yellow oil. IR (neat) 2120
cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, J = 7.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.13 – 7.04 (m, 2H),
6.31 – 6.22 (m, 1H), 5.88 – 5.67 (m, 1H), 5.05 – 4.85 (m, 2H), 2.13 – 1.90 (m, 4H), 1.80 (d, J = 2.7 Hz,
3H), 1.56 – 1.40 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.5, 139.0, 136.1, 128.1, 127.6 (2), 124.9,
118.5, 114.5, 103.7, 88.4, 34.0, 33.7, 28.7, 27.1, 18.8; LRMS (ESI-TOF) m/z (relative intensity) 226.1
(43%, M –N$_2$ + H$^+$); HRMS (ESI-TOF) m/z: [M–N$_2$ +H]$^+$ Calcd for C$_{16}$H$_{20}$N 226.1596; Found
226.1604.
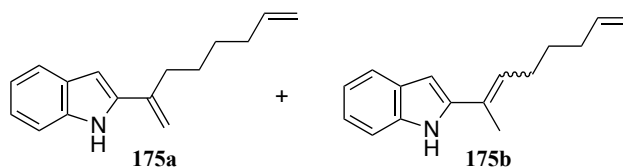
2-(Octa-2,7-dien-2-yl)-1*H*-indole (175a) and **(*E*)-2-(Octa-2,7-dien-2-yl)-1*H*-indole (175b).**
Following General Procedure 1, a solution of alkene **174** (10 mg, 0.039 mmol) in 4.0 mL of acetonitrile
was irradiated through Pyrex at 350 nm for 1.5 hrs and then the solution was concentrated in vacuo.
The crude product was purified via basic Al$_2$O$_3$ flash chromatography using 0 – 5% ethyl acetate in
hexanes as eluent to afford 6.0 mg (68%) of the elimination product **175** as a mixture of 2 inseparable
regioisomers (**175a/175b**, 1.4:1). IR (neat) 2162 cm^{-1} ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.13 (s, 1H), 7.61

(q, J = 8.1 Hz, 1H), 7.34 (q, J = 8.0 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.56 (s, 1H **175a**), 6.48 (s, 1H, **175b**), 5.90 – 5.77 (m, 1H), 5.53 – 5.59 (m, 1H, **175b** E or Z isomer), 5.45 – 5.35 (m, 1H, **175b** E or Z isomer), 5.32 (s, 1H, **175a**), 5.08 (s, 1H, **175a**), 5.05 – 4.92 (m, 2H), 2.55 (t, J = 7.6 Hz, 2H, **175a**), 2.45 – 2.35 (q, J = 7.5 Hz, 2H, **175b** Z or E isomer), 2.33 – 2.23 (q, J = 7.4 Hz, 2H, **175b** Z or E isomer), 2.20 – 2.04 (m, 2H for **175a**, and 5H for **175b**), 1.70 – 1.33 (m, 4H for **175a**, and 2H for **175b**); ^{13}C NMR (75 MHz, CDCl$_3$) δ **175a**: 140.1, 139.0, 138.2, 136.5, 128.9, 122.7, 120.8, 120.1, 114.6, 110.7, 109.2, 101.0, 34.3, 33.74, 28.8, 28.6; LRMS (ESI-TOF) m/z (relative intensity) 226.2 (38%, M + H$^+$); HRMS (ESI-TOF) m/z:[M+H]$^+$ Calcd for C$_{16}$H$_{20}$N 226.1596; Found 226.1606.

Separation of E- and Z-Alkenyl Sulfide Isomers 120: The E- and Z- alkenyl sulfide allenyl azide isomers were separated via column chromatography using silver nitrate impregnated silica gel[12] and 0 – 5% Et$_2$O in hexanes as the eluent. A second column chromatography was performed for each stereoisomer, using 100% hexanes as the eluent, to remove any trace amount of silver.
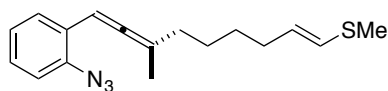
(E)-(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)sulfane (120–E): IR (neat) 2360, 2338, 2023 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, J = 7.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.13 – 7.03 (m, 2H), 6.31 (s, 1H), 5.95 (d, J = 14.9 Hz, 1H), 5.44 – 5.35 (m, 1H), 2.20 (s, 3H), 2.14 – 2.02 (m, 4H), 1.79 (s, 3H), 1.56 – 1.42 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.4, 136.1, 128.0, 127.6, 127.5, 127.4, 124.8, 123.8, 118.5, 103.6, 88.4, 33.8, 33.0, 29.2, 26.9, 18.8, 15.1; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (27%, M – N$_2$ + H$^+$); HRMS (ESI-TOF) m/z: [M –N$_2$+H]$^+$ Calcd for C$_{17}$H$_{22}$NS 272.1473; Found 272.1476.
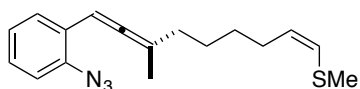
(*Z*)-(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)sulfane (120–*Z*): IR (neat) 2116, 1950 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.13 – 7.04 (m, 2H), 6.31 (q, *J* = 2.6 Hz, 1H), 5.86 (d, *J* = 9.4 Hz, 1H), 5.53 – 5.45 (m, 1H), 2.25 (s, 3H), 2.14 – 2.02 (m, 4H), 1.80 (d, *J* = 2.7 Hz, 3H), 1.56 – 1.41 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 203.4, 136.1, 128.8, 128.0, 127.6, 127.5, 126.9, 124.8, 118.5, 103.7, 88.3, 33.9, 29.0, 28.7, 27.2, 18.8, 17.2; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (72%, M –N₂ + H⁺); HRMS (ESI-TOF) m/z: [M–N₂+H]⁺ Calcd for $C_{17}H_{22}NS$ 272.1473; Found 272.1461.

Irradiation of *E*-Alkenyl Sulfide Isomer (120–*E*): Following General Procedure 1, a solution of *E*-alkenyl sulfide **120–*E*** (100 mg, 0.33 mmol) in 36 mL of acetonitrile was irradiated through Pyrex at 350 nm for 50 minutes and then concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 0 – 8% ethyl acetate in hexanes as eluent to afford 0.067 g (74%) of **123–125** as a mixture of stereoisomers (**123**:**124**:**125**, 16:1.3:1). In addition, 3.0 mg (3%) of the C–N bonded product **126'**, 4.0 mg (4%) of the formal "ene"-type product **171**, and 5% of starting material **120–*E*** also were isolated.
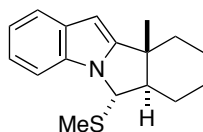
126': ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, *J* = 7.0 Hz, 1H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.15 – 7.04 (m, 2H), 6.13 (s, 1H), 4,95 (d, *J* = 10.3 Hz, 1H), 2.31 – 2.19 (m, 1H), 2.19 – 2.05 (m, 1H), 2.02 – 1.87 (m, 2H), 1.85 (s, 3H), 1.80 – 1.62 (m, 3H), 1.61 – 1.49 (m, 1H), 1.46 – 1.31 (m, 1H), 1.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.0, 133.0, 132.4, 120.9, 120.8, 119.5, 110.6, 90.9, 63.9, 56.8, 40.2, 34.7, 26.2, 21.2, 20.9.1, 19.3, 9.9; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (43%, M + H⁺); HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for $C_{17}H_{22}NS$ 272.1473; Found 272.1452.

Irradiation of the C–C Bonded Product (123/124): A solution of the C-cyclized product **123/124** (0.021 g, 0.078 mmol) in 9.4 mL of acetonitrile was irradiated through Pyrex at 350 nm for 1 hr and concentrated. Triphenylmethane (0.019 g, 0.078 mmol) was added as an internal standard and the ^{1}H NMR of the mixture showed significant decomposition. The major isomer **123** appeared to decompose faster than the minor isomer **124**, therefore changing the isomers ratio (13:1 –> 6.7:1). ^{1}H NMR yield of **123/124**: 34%.

5.5 Efforts Towards the Total Synthesis of Lecanindole D
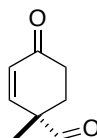
1-Methyl-4-oxocyclohex-2-ene-1-carbaldehyde (204). A solution of Danishefsky diene (**95**) (10.6 g, 0.061 mol) and methacrolein (**202**) (10 mL, 0.12 mol) in 20 mL of benzene was refluxed overnight. The resulting reaction mixture was concentrated and re-dissolved in 20 mL of Et$_2$O. A 2 M solution of HCl (50 mL) was then added and left to stir for 1 hr at room temperature. The aqueous layer was extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash column chromatography using 0 – 20% ethyl acetate in hexanes as eluent to afford 2.0 g (73%) of **204** as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.56 (s, 1H), 6.76 (d, *J* = 10.2 Hz, 1H), 6.12 (d, *J* = 10.2 Hz, 1H), 2.50 (t, *J* = 6.4 Hz, 2H), 2.36 – 2.29 (m, 1H), 1.99 – 1.92 (m, 1H), 1.33 (s. 3H). Spectral data are in agreement with the values published by Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252–5253.
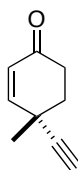
4-Ethynyl-4-methylcyclohex-2-en-1-one (201). To a solution of diisopropyl amine (39 μL, 0.28 mmol) in 2 mL of THF at -78 °C was added a 2.5 M solution of *n*-BuLi in hexanes (0.11 mL, 0.28 mmol) and stirred at that temperature for 10 min. The resulting mixture was warmed to 0 °C and stirred at that temperature for 10 additional minutes. The reaction mixture was cooled back to -78 °C and cannulated into a solution of **204** (0.082 g, 0.28 mmol) in 2 mL of THF that was cooled to -78 °C. The reaction mixture was allowed to stir at that temperature for 30 min. Methyl lithium (0.35 mL, 0.56 mmol) was added dropwise and the solution was stirred for 1 hr at that temperature. A sat. NH_4Cl (aq) solution (5 mL) and Et_2O (5 mL) was added at that time, and the aqueous layer was extracted with Et_2O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using $0 - 10\%$ ethyl acetate in hexanes as eluent to afford 0.018 g (48%) of **201** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 9.9 Hz, 1H), 5.92 (d, *J* = 9.9 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.50 – 2.43 (m, 1H), 2.28 – 2.22 (m, 2H), 2.02 – 1.95 (m, 1H), 1.46 (s, 3H). Spectral data are in agreement with the values published by Zheng, S. et al. *J. Med. Chem.* **2012,** *55,* 4837–4846.
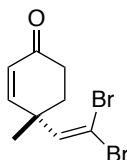
4-(2,2-Dibromovinyl)-4-methylcyclohex-2-en-1-one (205). To a solution of carbon tetrabromide (9.6 g, 29 mmol) in 45 mL of CH_2Cl_2 at 0 °C was cannulated a solution of triphenyl phosphine (15 g, 58 mol) in 45 mL of CH_2Cl_2. The resulting orange ylide was stirred at room temperature for 30 min and then a solution of **204** (2.0 g, 15 mol) in 45 mL of CH_2Cl_2 was then added.

The resulting mixture was allowed to stir for an additional 30 min. Pentane (500 mL) was added and the mixture was filtered through a SiO_2 pad. The filtrate was concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using $0 - 5\%$ ethyl acetate in hexanes as eluent to afford **205** (3.1 g, 72%) as a clear oil. IR (neat) 1681 cm^{-1}; ^{1}H NMR (MHz, CDCl$_3$) δ 7.02 (d, J = 10.2 Hz, 1H), 6.66 (s, 1H), 5.97 (d, J = 10.2 Hz, 1H), 2.51 (t, J = 6.6 Hz, 2H), 2.35 (m, 1H), 1.98 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 198.2, 154.6, 142.8, 128.2, 89.3, 40.6, 35.0, 34.2, 25.7; LRMS (AP-TOF) m/z (relative intensity) 292.9, 294.9, 296.9 (7%, M + H$^+$); HRMS (AP-TOF) m/z: [M+H]$^+$ Calcd for C$_9$H$_{11}$OBr$_2$ 292.9177; Found 292.9181.
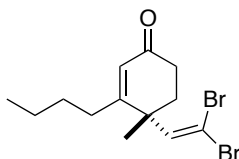
3-Butyl-4-(2,2-dibromovinyl)-4-methylcyclohex-2-en-1-one (209). To copper cyanide (0.34 g, 3.8 mmol) in 20 mL of Et$_2$O at -78 °C was added 2.5 M n-BuLi in hexanes (2.7 mL, 6.9 mmol) dropwise and the resulting solution was warmed to 0 °C and stirred at that temperature for 10 min. The reaction mixture was cooled to -23 °C and enone **205** (1.0 g, 3.4 mmol) in 30 mL of Et$_2$O was added. The resultant yellow solution was left to stir at that temperature for 20 min and the color changed to dark green. The oxidant **208** (2.2 g, 10 mmol) then was added as a solid and the reaction mixture was left to stir for an additional 30 min at that temp. A sat. NH$_4$Cl (aq) solution (20 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were washed with sat. NaCl (aq) (20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.86 g (71%) of **209** as a light yellow oil. IR (neat) 1670 cm^{-1}; ^{1}H NMR (MHz, CDCl$_3$) δ 6.59 (s, 1H), 5.93 (s, 1H), 2.59–2.05 (m, 5H), 2.57–2.28 (m, 7H), 1.90–1.80 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 198.2, 168.7, 143.1, 126.2, 89.5, 44.5, 33.8, 33.7, 32.8, 29.5, 26.0, 22.7, 14.1; LRMS

(AP-TOF) m/z (relative intensity) 349.0, 351.0, 353.0 (28%, M + H$^+$); HRMS (AP-TOF) m/z: [M+H]$^+$ Calcd for $C_{13}H_{19}OBr_2$ 348.9803; Found 348.9783.
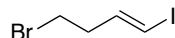
(*E*)-4-Bromo-1-iodobut-1-ene (214). To a solution of 4-bromobutyne (**213**) (2.0 mL, 0.021 mol) in 156 mL of THF under nitrogen was added Schwartz's reagent (3.3 g, 0.013 mol) and the reaction solution was stirred at room temperature for 40 min. A second portion of Schwartz's reagent (3.3 g, 0.013 mol) was then added and stirred for another 40 min. Iodine (5.3 g, 0.021 mol) was added and the resulting mixture was stirred for an additional 30 min. Hexane (1.5 mL) was added and the crude reaction mixture was filtered through a SiO_2 pad. The filtrate was concentrated in vacuo. The crude product **214** was purified via SiO_2 flash column chromatography using hexanes as eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.57–6.47, (m, 1H), 6.24 (d, *J* =14.5 Hz, 1H), 3.39 (t, *J* = 6.9 Hz, 2H), 3.64 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.4, 78.4, 38.9, 30.6.
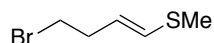
(*E*)-(4-Bromobut-1-en-1-yl)(methyl)sulfane (215). To a solution of **214** (5.0 g, 0.019 mol) in 10 mL of THF at -40 °C was added a 1.3 M solution of isopropyl magnesium chloride lithium chloride complex in THF (16.3 g, 0.021 mol) and the mixture was stirred overnight at that temperature. Dimethyl disulfide (2.3 mL, 0.021 mol) was added at -40 °C and the reaction solution was warmed to room temperature and a sat. solution of NH$_4$Cl (aq) (20 mL) was added. Diethyl ether (50 mL) was added and the aqueous layer was extracted with Et$_2$O (3 x 20 mL). The combined organic layers were washed with sat. NaCl (aq) (20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 100% hexanes as eluent to afford 2.2 g (64%) of **215** as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.17, (d, *J* = 15.0 Hz, 1H), 5.42 (m, 1H), 3.40 (t, *J* = 7.1 Hz, 2H), 2.69 (q, *J* = 7.0 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 128.1, 122.6, 36.9, 32.9, 15.2.
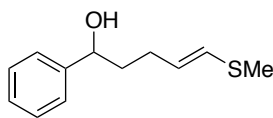
(*E*)-5-(Methylthio)-1-phenylpent-4-en-1-ol (218). To **215** (0.050 g, 0.28 mmol) in Et₂O (1 mL) at -78 °C was added a 1.7 M solution of *tert*-butyl lithium in pentane (0.36 mL, 0.55 mmol) and the mixture was stirred at that temperature for 2 hr. Benzaldehyde (**216**) (28 µL, 0.28 mmol) was added and the resulting mixture was warmed to room temperature and stirred for 1 hr. A sat. NH₄Cl (aq) solution (5 mL) was added at that time, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified via SiO₂ flash chromatography using 0 – 5% ethyl acetate in hexanes as eluent to afford 0.032 g (56%) of **218** as a clear oil. IR (neat) 3363 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.32, (m, 5H), 6.0 (d, *J* = 15.0, 1H), 5.46 (m, 1H), 4.60 – 4.70 (m, 1H), 2.20 (s, 3H), 2.17 – 2.07 (m, 3H), 1.90 – 1.70 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 145.0, 128.9, 128.1, 126.8, 126.4, 124.8, 74.3, 39.0, 29.9, 15.5; LRMS (ESI-TOF) m/z (relative intensity) 209.1 (28%, M + H⁺); HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₂H₁₇OS 209.1000; Found 209.0986.
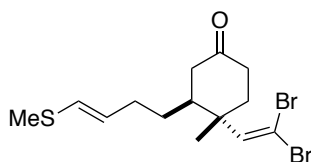
4-(2,2-Dibromovinyl)-4-methyl-3-((*E*)-4-(methylthio)but-3-en-1-yl)cyclohexan-1-one (219). To **215** (6.6 g, 0.036 mol) in 80 mL of Et₂O at -78 °C was added a 1.7 M solution of *tert*-butyl lithium in pentane (42 mL, 0.072 mol) and the mixture was stirred at that temperature for 2 hrs. The resulting mixture was cannulated into a flask containing copper bromide dimethyl sulfide complex (3.7 g, 0.018 mol) in 60 mL of Et₂O at -78 °C. After stirring at that temperature for 10 min, the reaction mixture was cooled to -40 °C and the color turned dark orange. After stirring for 1.5 hr at that temperature, **205** (4.4 g, 0.036 mol) in 40 mL of Et₂O was added and the resulting brown solution was left to stir for 1

additional hr. A sat. NH$_4$Cl (aq) solution (50 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 20 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 5% ethyl acetate in hexanes as eluent to afford 3.1 g (52%) of **219** as a clear oil. IR (neat) 1711 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.60 (s, 1H), 6.03 (d, *J* = 14.9 Hz, 1H) 5.38 – 5.31 (m, 1H), 2.50 – 2.43 (m, 1H), 2.40 – 2.30 (m, 2H), 2.23 (s, 3H), 2.22 – 2.07 (m, 4H), 2.50 – 1.92 (m, 2H), 1.61 – 1.52 (m, 1H), 1.33 (s, 3H), 1.25 – 1.15 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 210.2, 145.2, 125.7, 125.1, 86.9, 44.1, 42.2, 42.1, 37.4, 34.2, 30.7 (2), 18.5, 15.0. LRMS (ESI-TOF) m/z (relative intensity) 395.0, 397.0, 399.0 (100%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{14}$H$_{21}$OS^{79}Br^{81}Br 396.9659; Found 396.9627.
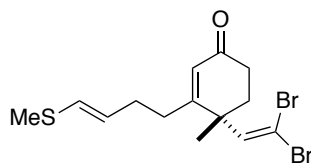
(*E*)-4-(2,2-Dibromovinyl)-4-methyl-3-(4-(methylthio)but-3-en-1-yl)cyclohex-2-en-1-one (220). To **215** (6.6 g, 0.036 mol) in 80 mL of Et$_2$O at -78 °C was added a 1.7 M solution of *tert*-butyl lithium in pentane (42 mL, 0.072 mol) and the reaction solution was stirred at that temperature for 2 hrs. The resulting mixture was cannulated into a flask containing copper bromide dimethyl sulfide complex (3.7 g, 0.018 mol) in 60 mL of Et$_2$O at -78 °C. After stirring at that temperature for 10 min, the reaction mixture was cooled to -40 °C and the color turned dark orange. After stirring for 1.5 hr at that temperature, **205** (4.4 g, 0.036 mol) in 40 mL of Et$_2$O was added and the resulting brown solution was left to stir for 1 additional hr. The oxidant **208** (0.30 g, 1.4 mmol) was added as a solid in one portion and the reaction mixture was stirred for 20 min. The reaction solution was warmed to room temperature and a sat. NH$_4$Cl (aq) solution (50 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 20 mL). The combined organic layers were washed with sat. NaCl (aq), dried over

Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 10% ethyl acetate in hexanes as eluent to afford 0.14 g (28%) of **220** as a clear oil. IR (neat) 1669 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.59 (s, 1H), 6.10 (d, *J* = 14.9 Hz, 1H), 5.93 (s, 1H), 5.50 – 5.36 (m, 1H), 2.62 – 2.53 (m, 1H), 2.52 – 2.43 (m, 2H), 2.41 – 2.29 (m, 3H), 2.28 – 2.18 (m, 4H), 1.92 – 1.85 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 198.0, 167.1, 142.9, 126.4, 125.6, 124.8, 89.7, 44.4, 33.7, 33.6, 32.9, 30.8, 25.9, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 393.0, 394.9, 397.0 (100%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{14}$H$_{19}$OS^{79}Br^{81}Br 394.9503; Found 394.9476.
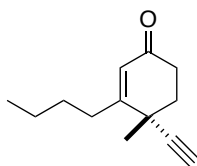
3-Butyl-4-ethynyl-4-methylcyclohex-2-en-1-one (222). To a solution of diisopropyl amine (48 μL, 0.34 mmol) in 4 mL of THF at -78 °C was added a 2.5 M solution of *n*-BuLi in hexanes (0.14 mL, 0.34 mmol) and the mixture was stirred at that temperature. After 10 min, the resulting mixture was warmed to 0 °C and stirred at that temperature for 10 additional min. The reaction mixture was cooled back to -78 °C and cannulated into a solution of **209** (0.10 g, 0.29 mmol) in 3 mL of THF at -78 °C and this solution was allowed to stir at that temperature for 30 min. Methyl lithium (0.38 mL, 0.60 mmol) then was added dropwise and the reaction solution was stirred at that temperature for 1 hr. A sat. NH$_4$Cl (aq) solution (5 mL) and Et$_2$O (5 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 5% ethyl acetate in hexanes as eluent to afford 0.032 g (59%) of **222** as a light yellow oil. IR (neat) 3277, 1671 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.83 (s, 1H), 2.67 – 2.59 (m, 1H), 2.49 – 2.40 (m, 2H), 2.34 – 2.22 (m, 2H), 2.20 (s, 1H), 2.06 – 1.99 (m, 1H), 1.57 – 1.50 (m, 2H),

1.46 (s, 3H), 1.41 (q, J = 7.3 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 198.5, 166.8, 124.9, 87.0, 70.1, 37.3, 35.8, 34.4, 32.9, 29.6, 26.2, 22.5, 14.0; LRMS (ESI-TOF) m/z (relative intensity) 191.1 (17%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{19}$O 191.1436; Found 191.1443.
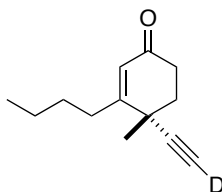
3-Butyl-4-(ethynyl-*d*)-4-methylcyclohex-2-en-1-one (226). To a solution of diisopropyl amine (19 μL, 0.14 mmol) in 2 mL of THF at -78 °C was added a 2.5 M solution of *n*-BuLi in hexanes (55 μL, 0.14 mmol) and the mixture was stirred at that temperature. After 10 min, the resulting mixture was warmed to 0 °C and stirred at that temperature for 10 additional min. The reaction mixture was cooled back to -78 °C and cannulated into a solution of **222** (0.025 g, 0.13 mmol) in 3 mL of THF at -78 °C and this solution was allowed to stir at that temperature for 1 hr. D$_2$O was added and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo to generate **226** (0.024 g, 95%) with 100% deuterium incorporation at the alkynyl position. IR (neat) 1671 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.82 (s, 1H), 2.67 – 2.59 (m, 1H), 2.49 – 2.40 (m, 2H), 2.34 – 2.19 (m, 2H), 2.09 – 1.98 (m, 1H), 1.56 – 1.50 (m, 2H), 1.46 (s, 3H), 1.41 (q, J = 7.2 Hz, 2H), 0.95 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.5, 166.8, 125.0, 70.1, 37.4, 35.9, 34.5, 33.0, 29.7, 26.3, 22.5, 14.0; LRMS (ESI-TOF) m/z (relative intensity) 192.1 (87%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{13}$^{1}H$_{18}$^{2}HO 192.1499; Found 192.1514.
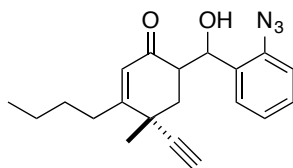
6-((2-Azidophenyl)(hydroxy)methyl)-3-butyl-4-ethynyl-4-methylcyclohex-2-en-1-one

(225). To a solution of diisopropyl amine (56 µL, 0.40 mmol) in 3 mL of THF at -78 °C was added a

2.5 M solution of *n*-BuLi (0.16 mL, 0.40 mmol) and the reaction solution was stirred at that

temperature. After 10 min, the resulting mixture was warmed to 0 °C and stirred at that temperature for

10 additional minutes. The reaction mixture was cooled back to -78°C and cannulated into a solution of

222 (0.036 g, 0.19 mmol) in 2 mL of THF at -78 °C. This mixture was allowed to stir at that

temperature for 1 hr. 2-Azidobenzaldehyde (**108**) (0.020 g, 0.19 mol) in 3 mL of THF was added and

the resulting yellow solution was stirred at that temperature for an additional 30 min. A sat. NH$_4$Cl (aq)

solution (5 mL) and Et$_2$O (5 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O

(3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and

concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 4%

ethyl acetate in hexanes as eluent to afford 0.015 g (23%) of the clear oil **225** as a mixture of 2 isomers

(2.4:1, **225a**:**225b**) and 0.015 g (42%) of unreacted starting material. IR (neat) 3294, 2123, 1653 cm^{-1};

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.56 – 7.48 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.22 – 7.16 (m, 2H), 5.88

(s, 1H), 5.20 (d, *J* = 9.0 Hz, 1H), 5.08 (s, 1H, isomer **225a**), 4.91 (s, 1H, isomer **225b**), 3.19 – 3.12 (m,

1H, isomer **225b**), 2.81 – 2.72 (m, 1H, isomer **225a**), 2.62 – 2.48 (m, 1H), 2.40 – 2.25 (m, 2H), 2.21 (s,

1H, isomer **225a**), 2.15 – 2.06 (m, 1H for isomer **225a** and 1H for the alkynyl proton in isomer **225a**),

1.75 (t, *J* = 7.5 Hz, 1H for isomer **225b**), 1.60 – 1.46 (m, 3H), 1.45 – 1.35 (m, 4H), 0.97 (t, *J* = 7.1, 3H);

^{13}C NMR (125 MHz, CDCl$_3$) δ 203.4, 202.3, 170.1 (2), 138.1, 138.0, 132.4 (2), 129.7, 129.6, 129.1,

128.9, 125.9 (2), 125.3, 124.5, 118.5, 118.4, 87.9, 77.7, 71.3, 71.0, 70.1, 69.7, 49.9, 48.0, 40.3, 39.5,

37.3, 36.4, 33.5, 32.6, 30.2, 29.7, 27.1, 25.8, 22.9, 22.8, 14.3 (2); LRMS (ESI-TOF) m/z (relative

intensity) 338.2 (12%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{20}H_{24}N_3O_2$ 338.1869; Found 338.1860.
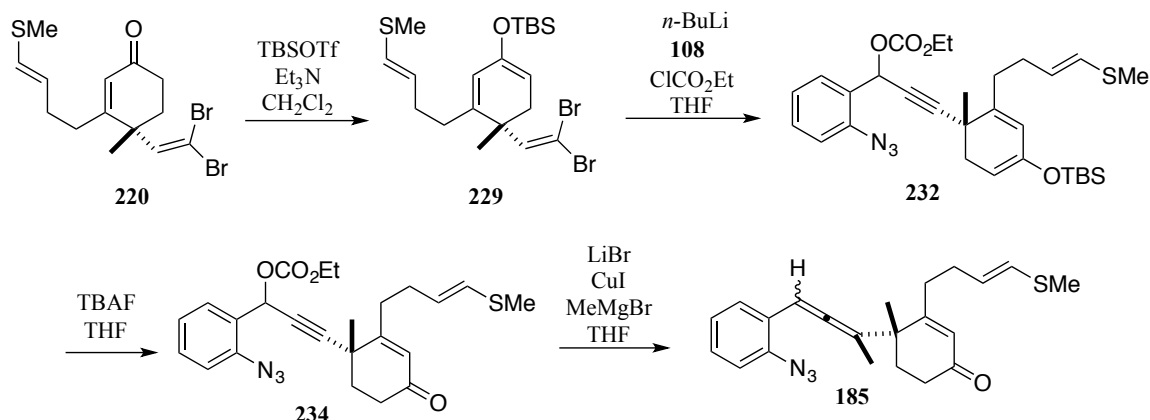
(E)-tert-Butyl((4-(2,2-dibromovinyl)-4-methyl-5-(4-(methylthio)but-3-en-1-yl)cyclo   hexa-1,5-dien-1-yl)oxy)dimethylsilane (229). To **220** (0.17 g, 0.42 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (89 µL, 0.64 mmol) followed by TBSOTf (117 µL, 0.51 mmol) at room temperature and stirred for 15 min. A sat. NaHCO$_3$ (aq) solution (5 mL) and CH_2Cl_2 (5 mL) was added at that time, and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product **229** was taken onto the next step without further purification. Yield: 0.202 g, 94% as a 2.4:1 mixture of silyl enol ether isomers.

1-(2-Azidophenyl)-3-(4-((tert-butyldimethylsilyl)oxy)-1-methyl-2-((E)-4-(methylthio)but-3-en-1-yl)cyclohexa-2,4-dien-1-yl)prop-2-yn-1-yl ethyl carbonate (232). To crude **229** (0.091 g, 0.18 mmol) in 3 mL of THF at -78 °C was added a 2.5 M solution of *n*-butyl lithium (150 µL, 0.38 mmol) and the mixture was stirred for 30 min at that temperature. TLC showed consumption of the starting material **231** and so 2-azidobenzaldehyde (**108**) (0.019 g, 0.18 mmol) in 2 mL of THF was added and the resulting mixture was warmed to 0 °C and stirred at that temperature for 30 min. TLC showed consumption of the acetylide intermediate and ethyl chloroformate (20 µL, 0.22 mmol) was added and

the reaction mixture was stirred at room temperature for 15 min. A sat. NH$_4$Cl (aq) solution (10 mL) and Et$_2$O (10 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was used immediately in the next step. Yield: 0.088 g, 86 %.

1-(2-Azidophenyl)-3-(1-methyl-2-((E)-4-(methylthio)but-3-en-1-yl)-4-oxocyclohex-2-en-1-yl)prop-2-yn-1-yl ethyl carbonate (234). To crude **232** (0.020 g, 0.035 mmol) in 0.5 mL of THF at 0 °C was added a 1 M solution of Bu$_4$NF in THF (39 μL, 0.039 mmol) dropwise and left to stir for 5 min at that temperature. A sat. NH$_4$Cl (aq) solution (5 mL) and Et$_2$O (5 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 15% ethyl acetate in hexanes as eluent to afford 4.0 mg (25%) of **234** as a viscous yellow oil.

4-(2-Azidophenyl)buta-2,3-dien-2-yl)-4-methyl-3-((E)-4-(methylthio)but-3-en-1-yl)cyclohex-2-en-1-one (185). To a solution of copper (I) iodide (0.067 g, 0.35 mmol) and lithium bromide (0.066 g, 0.35 mmol) in 4 mL of THF at 0 °C was added 3.0 M methyl magnesium bromide in Et$_2$O (0.12 mL, 0.22 mmol). The reaction mixture was allowed to stir and warm to room temperature over 45 min, at which time thio alkynyl azide **234** (0.016 g, 0.035 mmol) in 1.5 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 20 min. A sat. NH$_4$Cl (aq) solution (5 mL) and Et$_2$O (5mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 8% ethyl acetate in hexanes as eluent to afford 8.0 mg (62%) of a 1:1 mixture of inseparable isomers of allenyl azide **185** as a viscous yellow oil. IR (neat) 2122, 1712 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29 – 7.18 (m, 2H), 7.14 – 7.03 (m, 2H), 6.37 (s, 1H), 6.08 (d, J = 14.9

Hz, 1H, isomer **185a**), 5.86 (s, 1H), 5.78 (d, *J* = 14.9 Hz, 2H, isomer **185b**), 5.48 – 5.40 (m, 1H, isomer

185a or **185b**), 5.15 – 5.07 (m, 1H, isomer **185a** or **185b**), 2.50 – 2.42 (m, 1H), 2.35 – 2.12 (m, 6H),

1.88 – 1.78 (m, 4H), 1.33 (s, 3H, isomer **185a** or **185b**), 1.32 (s, 3H, isomer **185a** or **185b**), 1.25 (s, 3H,

isomer **185a** or **185b**), 1.23 (s, 3H, isomer **185a** or **185b**); ^{13}C NMR (75 MHz, CDCl$_3$) δ 204.5 (2),

199.2, 198.9, 168.9, 168.8, 136.5, 136.4, 129.0, 128.3, 128.2, 128.0, 127.8, 126.3, 126.2, 125.8, 125.4,

125.2, 125.1 (2), 125.0 (2), 118.8, 118.7, 107.3, 106.9, 90.1, 89.9, 44.2, 44.1, 34.5 (3), 34.1, 33.1, 32.6,

31.0, 30.6, 23.8, 23.7, 15.5, 15.2, 15.1, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 380.2 (2%, M +

H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{22}$H$_{26}$N$_3$OS 380.1797; Found 380.1775.
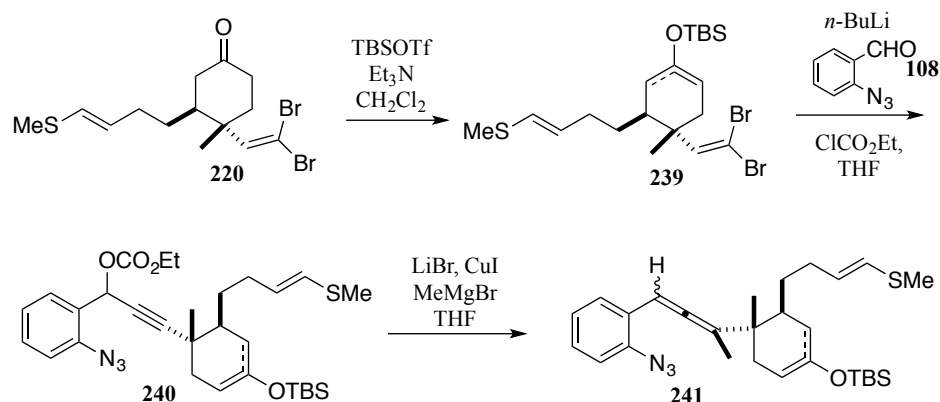
***tert*-Butyl((4-(2,2-dibromovinyl)-4-methyl-5-((*E*)-4-(methylthio)but-3-en-1-yl)cyclo hex-1-**

en-1-yl)oxy)dimethylsilane (239). To **220** (0.44 g, 1.1 mmol) in 12 mL of CH$_2$Cl$_2$ was added

triethylamine (0.23 mL, 1.7 mmol) followed by TBSOTf (0.30 mL, 1.3 mmol) at room temperature and

left to stir for 15 min. A sat. NH$_4$Cl (aq) solution (10 mL) was added and the aqueous layer was

extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were washed with sat. NaCl (aq), dried

over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was taken onto the next step without

further purification. Yield: 0.53 g of **239**, 95%.

1-(2-Azidophenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)-1-methyl-6-((*E*)-4-(methylthio) but-

3-en-1-yl)cyclohex-3-en-1-yl)prop-2-yn-1-yl ethyl carbonate (240). To **239** (0.520 g, 1.0 mmol) in 15

mL of THF at -78 °C was added a 2.5 M solution of *n*-butyllithium in hexanes (0.86 mL, 2.1 mmol) and

the mixture was stirred for 1 hr at that temperature. TLC showed consumption of the starting material **239** and so 2-azidobenzaldehyde (**108**) (0.11 g, 1.0 mmol) in 7.5 mL of THF was added, and the resulting mixture was warmed to 0 °C and stirred at that temperature for 1 hr. TLC showed consumption of the acetylide intermediate and ethyl chloroformate (0.11 mL, 1.1 mmol) was added and the reaction mixture was stirred at room temperature for an additional 45 min. A sat. NH$_4$Cl (aq) solution (20 mL) and Et$_2$O (20 mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography, after deactivation with 2% triethylamine, using 0 – 4 % ethyl acetate in hexanes as eluent to afford 0.45 g (77 %) of **240** as a viscous yellow oil. LRMS (ESI-TOF) m/z (relative intensity) 570.3 (20%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{30}$H$_{44}$N$_3$O$_4$SiS 570.2822; Found 570.2827.

((4-(2-Azidophenyl)buta-2,3-dien-2-yl)-4-methyl-5-((*E*)-4-(methylthio)but-3-en-1-yl) cyclohex-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (241). To a solution of copper (I) iodide (0.10 g, 0.53 mmol) and lithium bromide (0.046 g, 0.53 mmol) in 5 mL of THF at 0 °C was added 3 M methyl magnesium bromide in Et$_2$O (0.18 mL, 0.53 mmol). The reaction mixture was allowed to stir and warm to room temperature over 1 hr, at which time thio alkynyl azide **240** (0.030 g, 0.053 mmol) in 2 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 30 min. A sat. NH$_4$Cl (aq) solution (5 mL) and Et$_2$O (5mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using hexanes as eluent to afford as a 1:1 mixture of allenyl azide isomers **241 (**0.017 g, 65%) as a viscous yellow oil. LRMS (ESI-TOF) m/z (relative intensity) 468.3 (2%, M + H$^+$ – N$_2$); HRMS (ESI-TOF) m/z: [M+H–N$_2$]$^+$ Calcd for C$_{28}$H$_{42}$NOSiS 468.2756; Found 468.2777.
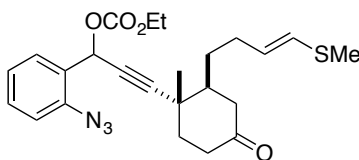
1-(2-Azidophenyl)-3-(1-methyl-2-((*E*)-4-(methylthio)but-3-en-1-yl)-4-oxocyclohexyl)-prop-2-yn-1-yl ethyl carbonate (244). To **240** (0.069 g, 0.12 mmol) in THF (4 mL) at 0 °C was added a 1 M solution of TBAF in THF (0.24 mL, 0.24 mmol) dropwise and the reaction mixture was stirred at that temperature for 5 min. A sat. NaHCO$_3$ (aq) solution (5 mL) and Et$_2$O (5mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 10% ethyl acetate in hexanes as eluent to afford 0.026 g (47%) of **244** as a clear oil. IR (neat) 2128, 1747, 1713 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.24 – 7.15 (m, 2H), 6.53 (s, 1H), 6.00 (d, *J* = 14.9 Hz, 1H), 5.38 – 5.30 (m, 1H), 4.30 – 4.19 (m, 2H), 2.74 – 6.64 (m, 1H), 2.53 – 2.44 (m, 1H), 2.43 – 2.10 (m, 6H), 2.05 – 1.90 (m, 4H), 1.80 – 1.65 (m, 1H), 1.40 – 1.28 (m, 6H), 1.20 – 1.10 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 210.7, 154.4, 138.3, 131.0, 129.6, 128.1, 126.2, 125.4, 125.2, 118.8, 94.4, 77.9, 65.0, 64.9, 45.3 (2), 42.7, 38.2, 36.6, 35.3, 31.2, 30.1, 22.0, 15.4, 14.6; LRMS (ESI-TOF) m/z (relative intensity) 478.2 (12%, M + Na$^+$ + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{24}$H$_{29}$N$_3$O$_4$NaS 478.1776; Found 478.1785.
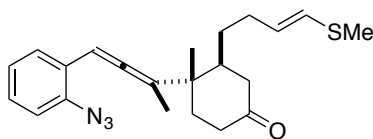
4-(4-(2-Azidophenyl)buta-2,3-dien-2-yl)-4-methyl-3-((*E*)-4-(methylthio)but-3-en-1-yl)cyclohexan-1-one (245). To a solution of copper (I) iodide (0.11 g, 0.57 mmol) and lithium bromide (50.0 mg, 0.57 mmol) in 5.0 mL of THF at 0 °C was added 3.0 M methyl magnesium bromide in Et$_2$O (0.19 mL, 0.57 mmol). The reaction mixture was allowed to stir and warm to room temperature over 30

min, at which time thio alkynyl azide **244** (0.026 g, 0.057 mmol) in 3 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 20 min. A sat. NH$_4$Cl (aq) solution (5 mL) and Et$_2$O (5mL) was added at that time, and the aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 10% ethyl acetate in hexanes as eluent to afford 0.012 g (55%) of allenyl azide **245** as a 1:1 mixture of inseparable isomers. IR (neat) 2122, 1713 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34 – 7.19 (m, 2H), 7.15 – 7.04 (m, 2H), 6.42 – 6.38 (m, 1H), 6.04 (d, J = 14.9 Hz, 1H, isomer **245a**), 5.89 (d, J = 14.9 Hz, 1H, isomer **245b**), 5.44 – 5.34 (m, 1H, isomer **245a** or **245b**), 5.24 – 5.16 (m, 1H, isomer **245a** or **245b**), 2.55 – 2.42 (m, 1H), 2.41 – 2.30 (m, 2H), 2.30 – 2.12 (m, 5H), 2.05 – 1.90 (m, 2H), 1.88 – 1.70 (m, 5H), 1.67 – 1.50 (m, 1H), 1.30 – 1.05 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 211.7, 211.6, 204.4 (2), 136.6, 128.3 (2), 128.2, 128.1, 127.2, 127.0, 126.6, 126.5, 125.3 (2), 125.1, 124.9, 119.0 (2), 110.1 (2), 90.0, 89.8, 43.0, 42.9, 42.2, 41.9, 41.0, 40.9, 38.4 (2), 36.8, 36.5, 31.6, 31.4, 31.3, 31.2, 19.2, 18.7, 15.4, 15.4, 14.8, 14.7; LRMS (ESI-TOF) m/z (relative intensity) (100%, M – N$_2$ + H$^+$); HRMS (ESI-TOF) m/z: [M–N$_2$+H]$^+$ Calcd for C$_{22}$H$_{28}$NOS 354.1892; Found 354.187.

Irradiation of 245. A solution of **245** (0.012 g, 0.032 mmol) in MeCN (3.8 mL) was irradiated at 350 nm for 40 min and then concentrated in vacuo. The crude product was purified via SiO$_2$ flash chromatography using 0 – 10% ethyl acetate in hexanes as eluent to afford 22 mg (45%) of the C-cyclized product **246** as a mixture of 2 isomers (1.4:1) as a white solid, 12 mg (25%) of *N*-cyclized product **247**, and 9 mg (18%) of elimination product **248**. *In acetone:* Yield: 63% of the elimination product **248**. *In toluene:* Yield: 20% of the C-cyclized product **246** as a mixture of 2 isomers (2.4:1), 6% of *N*-cyclized product **247** and 34% of elimination product **248**.
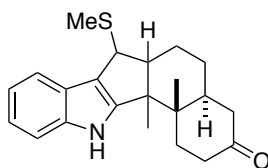
(4a*S*,12c*S*)-12b,12c-Dimethyl-7-(methylthio)-1,4,4a,5,6,6a,7,12,12b,12c-

decahydrobenzo[6,7]indeno[1,2-*b*]indol-3(2*H*)-one (246). The C-cyclized product was obtained as a

mixture of 2 diastereomers. Unfortunately, they could not be separated. ^{1}H NMR (300 MHz, CDCl$_3$) δ

8.07 (s, 1H, isomer **246a**) 8.02 (s, 1H, isomer **246b**), 7.79 (d, *J* = 6.1 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H),

7.17 – 7.12 (m, 2H), 4.10 (d, *J* = 9.5 Hz, 1H, isomer **246a**), 3.86 (d, *J* = 9.8 Hz, 1H, isomer **246b**), 2.80

– 2.26, (m, 5H), 2.25 – 2.10 (3H), 2.09 – 1.81 (5H), 1.80 – 1.71 (m, 1H), 1.43 (s, 3H, isomer **246a**),

1.42 – 1.31 (m, 1H), 1.26 (s, 3H, isomer **246a**), 1.26 (s, 3H, isomer **246b**), 1.26 (s, 3H, isomer **246b**);

^{13}C NMR (75 MHz, CDCl$_3$) δ 211.2, 210.8, 149.9, 148.8, 140.1, 140.0, 124.6, 124.2, 121.5 (2), 120.3,

119.0, 118.7, 118.0, 111.7 (2), 58.9, 54.8, 50.5, 49.0, 48.3, 46.3, 45.2, 44.8, 39.7, 39.5, 39.1, 38.8, 38.2,

38.0, 35.8, 34.4, 30.7, 26.6, 22.6, 21.7, 21.6, 15.9, 15.4, 14.5, 11.7, 10.6.
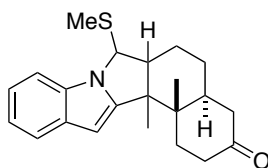
13b,13c-Dimethyl-7-(methylthio)-1,2,4,4a,5,6,6a,7,13b,13c-decahydro-3*H*-benzo[6,7]

isoindolo[2,1-*a*]indol-3-one (247). IR (neat) 1712 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.96 (d, *J* = 7.9

Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.20–7.07 (m, 2H), 6.14 (s, 1H), 4.95 (d, *J* = 10.1 Hz, 1H), 2.88 (t, *J*

= 9.8 Hz, 1H), 2.70–2.46 (m, 2H), 2.25 (s, 3H), 2.21–2.13 (m, 2H), 2.02–1.88 (m, 5H), 1.70–1.60 (m,

2H), 1.28 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 211.0, 149.5, 132.8, 132.6, 121.0, 120.7,

119.1, 110.6, 92.9, 63.6, 51.1, 48.0, 44.8, 39.0, 38.7, 38.0, 33.3, 29.9, 20.6, 16.9, 13.4, 10.0; LRMS

(ESI-TOF) m/z (relative intensity) 354.2 (55%, M + H$^+$); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for

C$_{22}$^{1}H$_{28}$NOS 354.1892; Found 354.1887.
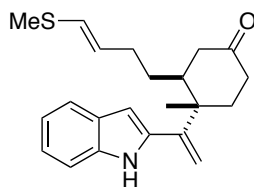
4-(1-(1*H*-Indol-2-yl)vinyl)-4-methyl-3-((*E*)-4-(methylthio)but-3-en-1-yl)cyclohexan-1-one

(248). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.98 (bs, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H),

7.20–7.08 (m, 2H), 6.40 (s, 1H), 6.00 (d, *J* = 15.0 Hz, 1H), 5.50 (s. 1H), 5.46 (s, 1H), 5.29–5.19 (m,

1H), 2.52–2.13 (m, 6H), 2.11 (s, 3H), 1.95–1.75 (m, 3H), 1.70–1.55 (m, 2H); 1.37 (s, 3H), ^{13}C NMR

(75 MHz, CDCl$_3$) δ 211.1, 148.8, 137.0, 135.3, 128.5, 125.7, 124.7, 122.3, 120.5, 120.2, 117.8, 110.7,

102.2 42.7, 42.5, 40.9, 38.1, 36.8, 31.1, 30.5, 18.3, 14.8.

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Appendix A

Predicting Coupling Constants

The Schrödinger (V 9.2) calculation package was used to predict the ^{1}H coupling constants of the C–C bonded products. Using Macromodel, the minimum-energy structures were identified via the conformational search algorithm with the Merck MMFF force field prior to running the ^{1}H NMR coupling prediction program.

Appendix B

Absorption Spectra

UV/VIS Absorption Spectra: The UV/VIS absorption spectra were obtained from a Beckman Coulter DU 800 spectrometer equipped with a temperature-controlled device. The full UV-VIS absorption spectra (200-800 nm) were taken using a 1 cm quartz cuvette in CH_3CN solvent.

(*E*)-(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)sulfane (120-*E*):
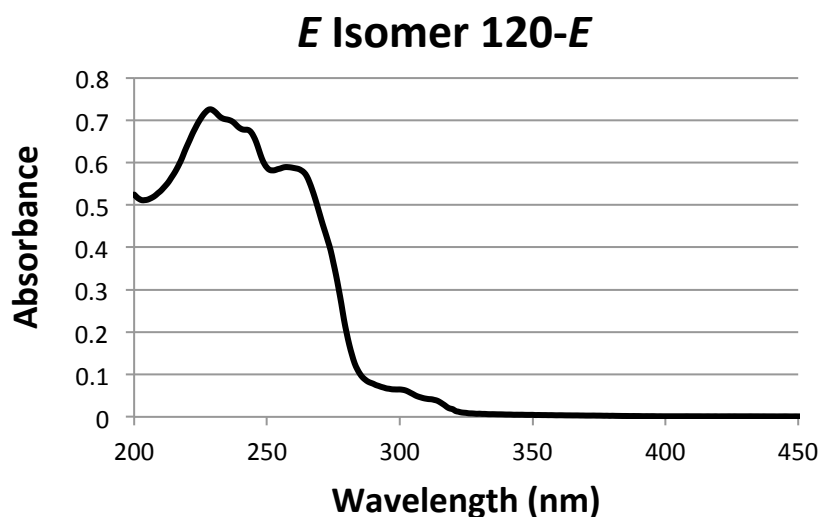
E Isomer 120-*E*

Irradiation of the *E*-Alkenyl Sulfide Isomer 120-*E* Monitored by UV/VIS-Absorption: A diluted solution of the *E* isomer **120-*E*** in acetonitrile (estimate concentration: <100 μM) was irradiated at 350 nm in a quartz cuvette and monitored every minute with a UV-VIS absorption spectrophotometer. The cyclization reaction with the *Z* alkene was also monitored with the UV-VIS absorption spectrophotometer, and the spectrum looked almost identical to the spectrum obtained for the *E* isomer.

E Isomer 120-*E* Irradiation
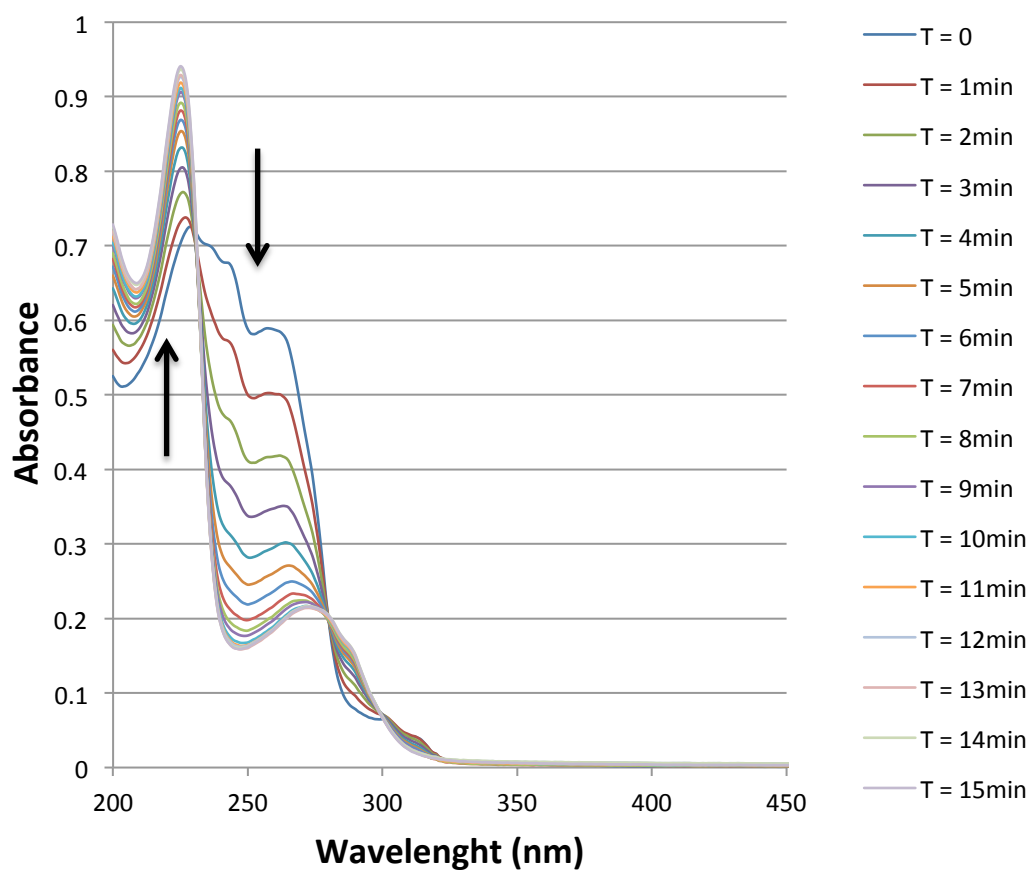
Appendix C

Details for the Molecular Orbital (MO) Calculations for the LUMO of an Indolidene

Molecular Orbital (MO) Picture for the LUMO of an Indolidene: The orbital picture for the LUMO was obtained from the Schrödinger (V 9.2) calculation package via the Maestro program. First, Macromodel was used to locate the minimum-energy structure, and then a geometry optimization calculation was performed using the DFT module of Jaguar (version 7.8, B3LYP/6-31G**). The Cartesian coordinates of the optimized structure are provided below.

C1	-2.7656890670	-0.3336797612	-0.4489607194
C2	-1.6111801346	-0.1837925894	0.2622247822
C3	-1.1889903743	-1.1631961189	1.2380622932
C4	-1.9151174288	-2.2877152126	1.5035308087
C5	-5.0008692985	-3.2300038356	-0.0231042653
C6	-3.1380721274	-2.4957287745	0.7840123064
C7	-3.5679772802	-1.4965553082	-0.2107043577
C8	-4.7516515132	-1.9717509544	-0.7173949697
H9	-5.3732516373	-1.5132256773	-1.4734437085
H10	-0.9828532498	0.6876961514	0.1025616603
H11	-3.0747523650	0.4079245192	-1.1802766876
H12	-0.2590544743	-0.9845215927	1.7710681161
H13	-1.5945582861	-3.0204171631	2.2369062758
C14	-6.0630615757	-4.0789748255	-0.1861781922
C15	-6.1652198690	-5.3411866047	0.6137250213

H16	-6.2118257265	-6.2105236664	-0.0556429699
H17	-5.3162818823	-5.4438884316	1.2879926359
H18	-7.0989749931	-5.3488146589	1.1915708708
N19	-3.9755305731	-3.5111480746	0.8953507580
C20	-7.1744766799	-3.8124065895	-1.1562587797
H21	-7.2522486008	-4.6375436664	-1.8760862159
H22	-8.1359339168	-3.7775900443	-0.6277294684
H23	-7.0524781948	-2.8821461808	-1.7108529826

VITA

Inanllely Y. Gonzalez

Inanllely (Ina) Gonzalez is a first-generation college graduate who was born in the Dominican Republic and moved to the United States at the age of fourteen. After a challenging journey of adapting to a new school, language, and culture, she pursued a science education at the City College of New York, where she was an undergraduate researcher under the mentorship of Prof. Kevin Ryan, and a Minority Access for Research Careers (MARC) fellow. Ina received a Bachelor of Science in Chemistry as well as a French minor, which motivated her to study in France for 6 months to enhance her fluency in the French language. She later spent 8 months in Stockholm, Sweden conducting research in the field of asymmetric catalysis under the supervision of Prof. Christina Moberg at the Royal Institute of Technology. In the Fall of 2012, she started her PhD in organic chemistry under the supervision of Prof. Ken Feldman at the Pennsylvania State University. In addition to conducting research, she was an advocate for the enhancement of the chemistry department and served as President and co-founder of the Chemistry Graduate Student Association. During her free time, Ina enjoys playing racquetball, poker, baseball, singing, dancing, and hanging out with friends.

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1. Feldman, K. S.; **Gonzalez, I. Y.**; Glinkerman, C. M. *J. Org. Chem.* **2015**, *80*, 11849–11862.
2. Feldman, K. S.; **Gonzalez, I. Y.**; Brown, J. E. *Tetrahedron Lett.* **2015**, *56*, 3564–3566.
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4. Wen, Y.-Q.; Hertzberg, R.; **Gonzalez, I.**; Moberg, C. *Chem. Eur. J.* **2014**, *20*, 3806–3812.

-Selected Conferences
1. **Gonzalez, I. Y.**; Glinkerman, C. M.; Feldman, K. S; Oral Presenter at the Division of Organic Chemistry Graduate Research Symposium, Bryn Mawr, Pennsylvania (2016)
2. **Gonzalez, I. Y.**; Glinkerman, C. M.; Feldman, K. S; Oral Presenter at the 249th American Chemical Society (ACS) National Meeting, Denver, Colorado (2015)
3. **Gonzalez, I. Y.**; Glinkerman, C. M.; Feldman, K. S; Poster Presenter at the 19th European Symposium of Organic Chemistry (ESOC), Lisbon, Portugal (2015)

-Awards at PSU
Dow BEST Symposium Participant (2016), Braucher Research Fellowship (2015), PSU Travel Award, Dan H. Waugh Memorial Teaching Award (2014), Bunton Waller Graduate Fellowship (2012–2015)