I. A New Route To Azomethine Ylides: Shifting The Reliance On Amino Ester Precursors II. Applications In Total Synthesis

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I. A NEW ROUTE TO AZOMETHINE YLIDES: SHIFTING THE RELIANCE ON AMINO ESTER PRECURSORS
II. APPLICATIONS IN TOTAL SYNTHESIS

A Dissertation Presented

by

Natalie Kay Machamer

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy Specializing in Chemistry

October, 2015

Defense Date: May 26, 2015
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ABSTRACT

Nitrogen-containing heterocycles have great utility in the biomedical and medicinal fields and one such heterocycle is the 5-membered pyrrolidine ring. The synthesis of pyrrolidine rings has been studied extensively with the routes relying on anodic oxidation, transition metals and dipolar cycloadditions with azomethine ylides. Previous work in the Waters group has been focused on new routes to azomethine ylides through a domino sequence. Through a thermal aza-Cope rearrangement followed by [3+2] dipolar cycloaddition the synthesis of a library of 2-allyl pyrrolidines was accomplished. It was discovered that by using allylic amines and glyoxals at room temperature a cycloadduct was isolated bearing a 5-vinyl moiety.

The results were promising and the first part of the project was to optimize the reaction followed by substrate scope expansion to build a library of compounds. The new cycloadducts could not have been synthesized under traditional methods due to side reactivity difficulties and therefore this work circumvents the problems associated with the classical routes. This is the first report of azomethine ylides derived from allylic amines and glyoxals to date. Many cycloadducts were synthesized and they all contained the 5-alkenyl group with many of them closely matching pyrrolidine containing natural products.

The natural product, spirotryprostatin B, is an ideal target for featuring the developed methodology in total synthesis. Spirotryprostatin B was found to inhibit the G2/M phase in the cell replication pathway, suggesting a possible anti-cancer treatment. Using allylamine, ethyl glyoxylate, and appropriate dipolarophile under the optimized reaction conditions would afford a highly substituted cycloadduct that could be transformed into the final target. The core of the structure was synthesized in just three steps with only two steps requiring purification. The regio- and stereochemistry of the cycloadducts were analyzed using NOE enhancement and DFT studies to conclude that the [3+2] dipolar cycloaddition proceeded through the exo transition state.

The total synthesis of the anti-cancer compound pedicularine was also studied. Many different dipolarophiles were tested, but the ideal dipolarophile was not identified. The results of these experiments were important in defining the scope of the methodology.
CITATIONS

Material from this dissertation has been published in the following form:

DEDICATION

This work is dedicated to my parents. Without their love and support this would not have been possible. I love you.
ACKNOWLEDGEMENTS

My six years in graduate school has not been without its ups and downs, but there are many people who have helped me along the way. I would first like to thank my advisor, Professor Stephen Waters, for allowing me to work in his lab. I have had the privilege of working on exciting project and have learned so much as a result. I appreciate your willingness to stop what you’re doing when I came to your office with a question. I would like to thank my committee members, Professors Matthias Brewer and Rory Waterman, for their help from the beginning of my graduate school career. Matthias has always offered helpful research advice and has been someone I could go to with even the smallest question. Rory has always been supportive, in and out of the research lab, and for that I am grateful. I would also like to thank Professor Darren Hitt for being the chairperson of my committee. In the very first meeting we had he offered valuable career advice that I very much appreciated.

I want to give my sincere thanks to Dr. Alexander Wurthmann. His passion for teaching is contagious and over the last five years I have learned so much. With his help I have become more confident in my teaching abilities and has helped me realize that teaching was something I wanted to do after graduate school. There is no doubt in my mind that any success that comes from teaching in the future is a direct result of the training Sandy has given to me.

There is not enough room to adequately thank Drs. Xiaoxi Liu and Corinne Sadlowski. You guys were the best group mates and friends I could ever ask for. Xiaoxi, what started
out as just sharing a desk has grown into one of my closest friendships in graduate school. I consider myself fortunate that I was able to work so closely with you on our project. Corinne, you are one of the most caring people I know and I appreciate being able to talk to you about anything. I cannot wait to go to Barre class with you again. I wish you both the most success in your future.

I can vividly remember being terrified to take organic chemistry at Juniata College (I was a business major!), but after only a few classes I knew this was what I wanted to do and I have Professor Richard Hark to thank for that. I will never forget when I approached him after class one day and told him I wanted to change my major to chemistry and how he offered to be my advisor on the spot. I cannot thank him enough for his support and encouragement over the past ten years.

I would also like to thank two of my closest friends in graduate school, Joel Walker and Neil Mucha for their continuous support and encouragement. Joel, you are the person I turn to when I need advice and regardless of what is going on. I know I can always count on you to be understanding, helpful, and reassuring. Neil, I am so lucky to be able to call you a friend. Pennsylvania forever!

This would not be complete if I did not thank my family. None of this would be possible without the unconditional love and support from them. My parents have always put education first and for this I am forever grateful. I am so lucky to be able to call my sister, Amanda, and brother, Cheston, my best friends. I love when we can all get together – times like those really helped with the stress of graduate school.
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CHAPTER 1: DEVELOPMENT OF A NEW ROUTE TO AZOMETHINE YLIDES TO YIELD 5-ALKENYL SUBSTITUTED PYRROLIDINES

1.1 Background

In many areas of medicinal and biomedical research the nitrogen-containing heterocycle is a ubiquitous structural motif. One such heterocycle is the five-membered pyrrolidine ring which represents a common scaffold for many compounds of pharmaceutical importance. From 2010 to 2012, ten of the top 200 brand name pharmaceuticals (based on total sales) in the United States contained a pyrrolidine ring (Figure 1.1).

Figure 1.1 Pyrrolidine Containing Pharmaceuticals

Spiriva (Tiotropium) Boehringer Ingelheim #14 is US Retail Sales ($1,594 million) #23 in US Prescriptions (7.7 million)

Combivent (Ipratropium & Salbutamol) Boehringer Ingelheim #52 in US Retail Sales ($693 million) #49 in US Prescriptions (4.3 million)

Vigamox (Moxifloxacin) Alcon #126 is US Retail Sales ($253 million) #68 in US Prescriptions (3.3 million)

More specifically, 5-vinyl substituted pyrrolidines are an important class of molecules and occur in many natural products that have shown promising biological activity. The anti-cancer *Aristotelia* alkaloid peduncularine (Figure 1.2)\(^2\) was first isolated in 1971 from the Tasmanian shrub *Aristotelia peduncularis* with a revised structure being reported in 1979.\(^3\) Ten years later, in 1989, the first synthesis of peduncularine was reported.\(^4\) Borrecaipine, an indole containing alkaloid, was isolated in 1977 from the *Borreira* species as yellow crystals.\(^5\) These molecules have shown promising antibacterial properties, but have not been fully examined due to their low natural abundance and lack of reported total syntheses. The cephalotaxin family of alkaloid natural products were first isolated from the *Cephalotaxus fortunei* and *drupacea* shrubs in the 1950’s and 60’s and contain six molecules, four of which possess a 5-vinyl substituted pyrrolidine.\(^6\) These molecules have shown potential with antileukemic activity and therefore have been synthesized many times. Securinine, an alkaloid first isolated in 1956\(^7\) from the leaves of the *Securinega suffruticosa* plant, exhibits a range of biological activities\(^8\) and has seen some limited clinical use. The cephalotaxus esters make up a


\(^7\) Murav’eva, V. I.; Ban’kovskii, A. I. *Doklady Akademii Nauk SSSR* 1956, 110, 998-1000.

family of very potent anti-leukemia alkaloids from the Cephalotaxus genus.\(^9\)

Though not occurring in the natural product, the 5-vinyl substituted pyrrolidine fragment plays a key role in the total synthesis of some natural products. Isolated by Asano\(^{10}\) in 2000 from the bulbs of Muscari armeniacum, the pyrrolizidine containing natural product hyacinthacine A\(_2\) was synthesized by Martin\(^{11}\) in 2010. A key step of the synthesis relied on the ring-closing metathesis of an \(N\)-allyl, 5-vinyl substituted pyrrolidine.

**Figure 1.2 Natural Products Containing or Synthesized via 5-Vinyl Pyrrolidines**

The ability to rapidly assemble molecules, such as those discussed previously, in


an efficient, mild, and operationally simple method is one of the principal goals of synthetic organic chemistry. Multicomponent reactions aid in this process\textsuperscript{12} and if two or more chemical events can occur in tandem, molecular complexity can be assembled very quickly.\textsuperscript{13} This approach to organic synthesis has been the focus of the research in the Waters group and has been the inspiration for many projects to date.

1.2 Previous Methods for the Synthesis of 5-Vinyl Pyrrolidines

Due to their importance in natural products, the synthesis of 5-vinyl substituted pyrrolidines has been widely studied and they have been a target for many synthetic groups. These developments have not only come in the form of methodologies, but also key steps in total syntheses.

1.2.1 Anodic Oxidation

Classically, these targets have been made through the nucleophilic addition of $\pi$-nucleophiles to pyrrolinyl iminium ions. As the electrochemical oxidation of amides is well studied and easy to perform,\textsuperscript{14} many groups have demonstrated the method’s utility

in the generation of pyrrolinyl iminium ions. These ions are typically formed via an anodic oxidation of α-methoxy amides or carbamates following the Shono anodic oxidation of N-acylated prolines\textsuperscript{15} or the Ross-Eberson-Nyberg procedure (Scheme 1.1).\textsuperscript{6,16}

**Scheme 1.1 Anodic Oxidation of α-Methoxy Amides or Carbamates by Kolbe-like or Ross-Eberson-Nyberg Conditions**

Many synthetic groups adopted this general strategy for the synthesis of substituted pyrrolidines. For example, the Wistrand group published a few papers in the early 1990s on the synthesis of pyrrolidines which hinged on key anodic oxidation steps. In 1990 this group first reported that TEOC-protected pyrrolidines underwent anodic oxidation to


afford methoxylated carbamates in 95-98% yield which were then taken on to vinyl-substituted pyrrolidines (Scheme 1.2).¹⁷

**Scheme 1.2 Anodic Oxidation by Wistrand**

Later, Wistrand also reported that the addition of organocopper reagents, along with BF₃·OEt₂, to N-acyliminium ions affords *trans*-2,5-disubstituted pyrrolidines (Scheme 1.3).¹⁸ This process occurs through facile BF₃ promoted cleavage of α-methoxylated amides using organocopper following anodic methoxylation.

**Scheme 1.3 Synthesis of Trans-2,5-disubstituted Pyrrolidines by Wistrand**

Based on Wistrand’s work, the Biellmann group reported the synthesis of *cis*- and *trans*-5-vinyl-L-proline in 1992.¹⁹ Protected L-proline was converted to the methoxylated product by anodic oxidation, then the addition of an ethynyl chain was achieved by

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addition of \textit{bis}(trimethylsilyl)-acetylene. Following catalytic hydrogenation, the ethynyl group was converted to a vinyl group (Scheme 1.4).

\textbf{Scheme 1.4 Synthesis of 5-vinyl Substituted Pyrrolidines by Biellmann}

In 1998, Moeller used a sequential electrochemical oxidation-olefin metathesis strategy in the formation of bicyclic lactams for use as peptidomimetics (Scheme 1.5).\textsuperscript{20}

\textbf{Scheme 1.5 Electrochemical Oxidation and Olefin Metathesis by Moeller}

More recently, many groups have used this methodology in the generation of proline mimics.\textsuperscript{21}

1.2.2 Transition Metal Catalysis

Another mode of construction that has received tremendous interest is the metal catalyzed intramolecular cyclization of aminoallenes. Silver and palladium have been used the most with many other metals also being reported.

The hydroamination of allenes by silver catalysis was published in 1983 by Gore (Scheme 1.6).\textsuperscript{22} The generated products had very little functionalization, but the utility of the method was demonstrated and opened the door for further exploration.

\textbf{Scheme 1.6 Hydromaination of Allenes by Gore}

\[ R_1 \quad \begin{array}{c} \text{NHR}_2 \\ \text{AgNO}_3 \end{array} \quad \begin{array}{c} \text{R} \quad \text{R} \\ \text{R} \quad \text{R}_2 \end{array} \]

\[ R = \text{alkyl} \]


In 1987, Gallagher reported a silver(I)-mediated 5-exo-trig cyclization of allenic amine derivatives to yield 2,5-disubstituted pyrrolidines (Scheme 1.7).\textsuperscript{23} It was concluded that the most efficient catalyst was AgBF\textsubscript{4} and that cis-2,5-disubstituted products were most prevalent due to the bulky “R” protecting group: transition state B is preferred over transition state A (Scheme 1.8). This rationale also explains the preference for trans-2,5-disubstituted products for alkenyl-based cyclizations.\textsuperscript{24}

**Scheme 1.7 Silver(I) Mediated Cyclization by Gallagher**

![Diagram of the reaction](image)

The same group explored the mechanism further, expanded the methodology, and applied the results to the total synthesis of (+)-anatoxin-a in 1991.\textsuperscript{25} They postulated that the reaction began with the complexation to Ag\textsuperscript{I} to give a π-complex which would then undergo a cyclization to afford a protonated intermediate. After protonation of the C–Ag bond, the Ag\textsuperscript{I} catalyst was regenerated (Scheme 1.8).

\textsuperscript{23} Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *Journal of the Chemical Society, Chemical Communications* 1987, 243-244.
The Yamamoto group published multiple reports on heterocycle construction via transition metal catalysis with one of their early reports using palladium. Inspired by the work of Coulson, Cazes, and their own publications, the Yamamoto group reported in 1998 that palladium could be used to construct nitrogen heterocycles containing a vinyl group via an intramolecular hydroamination of allenes (Scheme 1.9). Yamamoto proposed that the new method goes through a unique hydroamination mechanism that proceeds through the insertion of a Pd–H bond to an allenic double bond.

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More recently, in 2005, Yamamoto studied both palladium and silver catalysts and found that the desired stereochemical outcome could be achieved by judicious choice of metal. With the publication of this work, the synthesis of either cis- or trans-disubstituted pyrrolidines was now possible. This stereospecific work was proposed to go through a different mechanism than the prior work as it proceeds through an insertion of a Pd–H bond to an allenic double bond. Recently, Yamamoto has found that in the absence of additional substituents, the Ag(I)/base conditions afford the cis-1,3-isomer whereas the Pd(II)-catalyzed reactions give to the formation of the trans isomer (Scheme 1.10). Until this time, the current methods for synthesis (including previously discussed oxidative approaches) suffered from poor stereoselectivity.²⁸

Scheme 1.10 Allylic Amination using Silver(I)/base or Palladium(II) by Yamamoto

The first reported use of using palladium as a catalyst to yield 5-vinyl substituted pyrrolidines came in 1981 by Godleski. It was found that 5 mol% palladium catalyst promoted the spirocyclization of amine-tethered allylic acetate in quantitative yield after just two hours (Scheme 1.11). This method, based on π-allyl palladium chemistry, was a great advancement in the field as it demonstrated that many unprotected functional groups were well tolerated and had the potential for stereospecific variations.

Scheme 1.11 Palladium-catalyzed Spirocyclization by Godleski

Stereospecific variants have also been reported and two selected examples are from Gallagher in 1990 and Zawisza in 2013. Gallagher used either a Ag or Pd catalyst to promote allenic cyclization. A reaction mechanism was suggested which

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proceeds through a chair transition state due to silver coordination to both nitrogens or the nitrogen and oxygen (Scheme 1.12).

**Scheme 1.12 Stereoselective Cyclization of Allenic Amines via Silver(I) and Palladium(II) Catalysts by Gallagher**

The Zawisza group found that when using a Pd$^0$ catalyst, allylic amination was promoted and cyclization of amino allylic carbonates provided vinyl-substituted pyrrolidines. Various enantioselective ligands were employed and it was found that the reaction was ligand specific and only some ligands could be applied to certain substrates (Scheme 1.13).
Scheme 1.13 Allylic Amination and Cyclization with Palladium(0) Catalysts by Zawisza

Other transition metals have also proven effective in hydroamination/cyclization reactions. The Marks group found in 1998 that organolanthanides\textsuperscript{32} were effective metal catalysts for this reaction. It was determined that the reaction was $Z$-selective with a high $Z:E$ ratio. The diastereoselective outcome can be rationalized via a chair-like transition state that minimizes unfavorable steric interactions after the initial $N$-lanthanoid metal bond insertion into the internal allenic double bond (Scheme 1.14).

Scheme 1.14 Organolanthanide Intramolecular Hydroamination by Marks

In 2008, Okamoto\textsuperscript{33} disclosed that various copper salts furnished vinyl pyrrolidines through intramolecular hydroamination of allylic amines. Many copper salts proved to be effective and are also considerably less expensive than other transition metal based catalysts (Scheme 1.15).

\textsuperscript{32} Arredondo, V. M.; McDonald, F. E.; Marks, T. J. \textit{Journal of the American Chemical Society} \textbf{1998}, \textit{120}, 4871-4872.

In 2007, Toste disclosed that gold catalyzed an enantioselective, intramolecular hydroamination of allenes. The group worked with a chiral Au(I)-benzoate complex and a wide substrate scope with various functionality was explored (Scheme 1.16).

**1.2.3 Other Methods**

In addition to the previous methods discussed, other groups have explored the synthesis of pyrrolidine rings and clever approaches have been reported. In 1989, the Shaw group found that allylic sulfilimines afforded 2-vinyl substituted cyclic amines in a one-pot transformation. This reaction began with an oxidative amination at sulfur, then a

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[2,3]-sigmatropic rearrangement, followed by an intramolecular $N$-alkylation (Scheme 1.17).

**Scheme 1.17 One-Pot Domino Reaction of Allylic Sulfilimines by Shaw**

In 1995, Pedregal reported that the addition of Grignard-derived organocopper reagents to $N$-acyliminium ions gave enantiopure 5-vinyl substituted pyrrolidines (Scheme 1.18).

**Scheme 1.18 Grignard-Derived Organocopper Addition by Pedregal**

Most recently, in 2012, the Stahl group found that a Wacker-Type aerobic oxidative cyclization of alkenes also afforded 2,5-disubstituted pyrrolidines (Scheme 1.19).

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1.19). This reaction employed readily available starting materials and was the first example of metal-catalyzed addition of a sulfinamide nucleophile to alkenes.

**Scheme 1.19 Wacker-Type Oxidative Cyclization by Stahl**

![Schematic representation of the reaction](image)

1.3 Azomethine Ylide Generation: Classical Method

Azomethine ylides represent an important class of compounds that can be used to build a variety of heterocyclic scaffolds – most notably, the pyrrolidine ring. The pioneers of this work were Grigg\(^{38}\) and Hamelin\(^{39}\) and their early reports demonstrated the generation of ester-stabilized azomethine ylides from a thermal, uncatalyzed, 1,2-prototropy of α-iminoesters (Scheme 1.20). Afterwards, they systematized the imine-azomethine ylide isomerization as one of the general methodologies of NH-1,3-dipole formation from X=Y-ZH systems. It was rationalized that the highly acidic proton adjacent to the imine migrates to the nitrogen to produce the NH-azomethine ylide under neutral conditions. The formation of the NH-azomethine ylide is due to the basicity of the

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imine nitrogen as well as the pKₐ of the α-hydrogen and the equilibrium between the imine and NH-azomethine ylide favors the imine. Very harsh conditions (long reaction times at high reflux temperatures) were necessary for the generation of the ylide. As a result this process is not stereoselective and not tolerant of a wide range of functional groups.

**Scheme 1.20 Azomethine Ylide Generation: Thermal 1,2-Prototropy of α-Iminoesters**

![Scheme 1.20 Azomethine Ylide Generation: Thermal 1,2-Prototropy of α-Iminoesters](image)

The Komatsu group reported in 1990⁴⁰ that by utilizing 1,2- and 1,4-metallotropic strategies, azomethine ylides could be generated from α-metalloimines and α-metalloamides. For instance, in the reaction between α-stannylthioamides, the strong affinity between tin and sulfur causes a 1,4-stannatropy which affords the NH-azomethine ylide (Scheme 1.21). Though this methodology certainly advanced the field, a major drawback is the presence of highly toxic tin compounds and is sometimes avoided for this reason.

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An important breakthrough occurred when it was found that metal-chelated azomethine ylides\(^{41}\) could allow cycloaddition to occur at a much lower temperature with enhanced regio- and stereocontrol (Scheme 1.22).\(^{42}\) The addition of a MX/base system gave \(N\)-metalated azomethine ylides \textit{in situ}, which then proceeded to react with various dipolarophiles at low temperature. Since these early reports, much progress has been made in this area of research which includes asymmetric processes via chiral Lewis acid complexes,\(^{43}\) catalytic metal/base systems,\(^{44}\) chiral auxiliaries for stereoinduction,\(^{45}\) and organocatalysis.\(^{46}\)


Though these studies have certainly advanced this field of research, they all share a common drawback; the heavy reliance on α-aminoesters as azomethine ylide precursors. There are many instances in which the condensation of a primary amino ester and aldehyde does not produce the desired azomethine ylide. An example of where this reaction pathway breaks down is shown in the synthesis of 5-alkenyl pyrrolidines. In principle the condensation of an amino ester (2, Scheme 1.23) with an aliphatic, α,β-unsaturated aldehyde (e.g. acrolein, 1) should yield a useful, ester stabilized azomethine ylide (4) which could, in theory, be used for the preparation of this important scaffold.

Problems with the proposed synthetic plan initially arise due to a competing 1,4-conjugate addition with the desired 1,2-addition, thereby hampering imine formation (Scheme 1.24). If the imine does form, these types of compounds (3, 1-aza-1,3-dienes)
are known to be unstable due to their ability to polymerize under either acidic or basic conditions, thereby suppressing ylide formation. Assuming the imine could form and proceed to the ylide, any remaining α,β-unsaturated aldehyde could act as a competing dipolarophile, resulting in the incorporation of two moles of aldehyde in the cycloadduct (8). Though desirable in some cases, this reactivity significantly reduces the diversity achievable due to the use of competing dipolarophiles.

**Scheme 1.24 Drawbacks of Using α-Amino Esters and α,β- Unsaturated Aldehydes as Azomethine Ylide Precursors**

When control experiments were performed, as evidence of the difficulties associated with α-amino esters, the condensation of glycine methyl ester hydrochloride with acrolein (1), silver acetate, triethylamine, and phenyl maleimide (9) led to no detectable cycloadducts (12) and only a complex reaction mixture (Scheme 1.25). Attempts to pre-form imine 11 by condensing glycine methyl ester hydrochloride (10) with acrolein also failed; this only lead to intractable mixtures and no discernable or isolable imine products.
1.4 Previous Pyrrolidine Work in the Waters Group

Of particular interest to our group is the synthesis of pyrrolidines in a way that generates a diverse series of compounds quickly. Due to their importance, the synthesis of functionalized pyrrolidine rings has been studied extensively and one of the most common modes of assembly is through 1,3–dipolar cycloaddition. It was with this intention and information in mind that we began to investigate new routes to azomethine ylides that could be transformed to pyrrolidines via [3+2] dipolar cycloaddition.

One hypothesis in the Waters group is that if an iminium ion could be transformed into an azomethine ylide, the stage would be set for [3+2] dipolar cycloaddition with various dipolarophiles. Previous work in our group has proven this hypothesis and currently many different examples have been published. The first achievement was the

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synthesis of quaternary proline scaffolds through a silver-mediated domino 2-aza-Cope-[3+2] dipolar cycloaddition. The utility of this transformation has been demonstrated for 15 different examples with the cycloadducts all being isolated in good yield as a single diastereomer.

This general sequence begins with the formation of the imine, which, under thermal conditions, underwent a 2-aza-Cope rearrangement. Upon deprotonation the generated azomethine ylide engages in [3+2] dipolar cycloaddition. This domino sequence was also coupled with other reactions (Pauson-Khand\textsuperscript{49} and aza-Prins\textsuperscript{50}) to build even more molecular complexity in very few steps.

It was fortuitously discovered that when the reaction mixture was not heated, a cycloadduct was still formed (18, Scheme 1.26). This observation suggested that even though rearrangement did not occur, the generated imine was still deprotonated to afford an azomethine ylide that then underwent [3+2] dipolar cycloaddition.

Scheme 1.26 Discovery of Room Temperature Cycloaddition with Allylamine


Control experiments indicated that clean imine formation was accomplished in just 15 minutes between allylamine (13) and ethyl glyoxylate (20). Promisingly, when a 1:1:1 mixture of 13:20:9 was stirred at room temperature in toluene with two equivalents of triethylamine and 10 mol% silver acetate, an azomethine ylide formed and a cycloadduct, 5-vinyl pyrrolidine (21), was obtained in 50% as a single diastereomer in just 24 hours (Table 1.1). Benzylamine (19) was also explored on the basis that the benzylic proton could be sufficiently acidic for deprotonation upon glyoximine formation.51

Initial results were very encouraging and exciting because they circumvented the problems associated with classical methods, and 5-alkenyl pyrrolidines were now readily accessible. With these results in hand, the next goal was to optimize the reaction. Benzylamine (19) and allylamine (13) were chosen as the two amines for optimization because of their simple structures and commercial availability.

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51 Processes taking advantage of this effect for benzylic amines have only recently been reported: (a) Tian, L.; Hu, X.-Q.; Li, Y.-H.; Xu, P.-F. Chemical Communications 2013, 9, 7213–7215. (b) Guo, C.; Song, J.; Gong, L.-Z. Organic Letters 2013, 15, 2676–2679.
Table 1.1 Initial Results from Room Temperature Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>Silver Acetate</th>
<th>Et$_3$N</th>
<th>Time</th>
<th>Product</th>
<th>Isolated Yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
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<td>1.0 equiv</td>
<td>1.5 equiv</td>
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<td>2</td>
<td>19</td>
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<td>1.0 equiv</td>
<td>0.1 equiv</td>
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<td>24 h</td>
<td><img src="image2" alt="Product 2" /></td>
<td>60</td>
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<td>3</td>
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<td>1.0 equiv</td>
<td>0.1 equiv</td>
<td>2.0 equiv</td>
<td>2 h</td>
<td><img src="image3" alt="Product 3" /></td>
<td>48</td>
</tr>
</tbody>
</table>

$^a$Isolated by column chromatography.

1.5 Optimization of Methodology

The reaction will not proceed to form a cycloadduct if an imine is not formed first. For this reason, imine formation was the first variable studied during optimization. Control experiments were performed and $^1$H NMR analysis indicated that clean, efficient imine formation was achieved in 10 minutes between benzylamine and ethyl glyoxylate and 15 minutes when allylamine was used. It is important that the reaction is complete before adding the dipolarophile as any remaining amine will engage in a competing conjugate addition with the dipolarophile (Scheme 1.27). Control experiments also
showed that there were no competing side reactions between the amine and aldehyde, which as noted before, could pose a problem.

**Scheme 1.27 Competing Conjugate Addition Between Amine and Dipolarophile**

This reaction was initially discovered using an excess of silver acetate, but when the amount of silver acetate was reduced to just 10 mol% the yield was not diminished and from this point forward a catalytic quantity was used (Table X). This modification not only improved the overall economy of the reaction, but also greatly improved the aqueous workup. When an excess of silver acetate was used a separate filtration step was required to remove the metal salt, but when using a catalytic quantity the silver acetate could be washed away in the water layer.

Even though triethylamine (Et₃N) was a sufficient base for the prior work done by the Waters group, both Et₃N and diazabicyclo[5.4.0]undec-7-ene (DBU) are commonly employed to form the ylide in a [3+2] dipolar cycloaddition sequence.⁵² For this reason DBU was tested as the possible base of choice for both amine components. When screened, DBU caused a noticeable reduction in yield leading one to believe that this base was too harsh for the desired ylide formation (compare entries 1 vs. 2 and 3 vs. 4, Table 1.2). It was also discovered in a control experiment that DBU reacts in an unfavorable

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manner with phenyl maleimide to form uncharacterizable decomposition products. For this reason, Et₃N was chosen for the remainder of the optimization studies.

Table 1.2 Application of Triethylamine (Et₃N) versus Diazobicyclo[5.4.0]undec-7-ene (DBU)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>Base</th>
<th>Time</th>
<th>Product</th>
<th>Isolated Yielda (%)</th>
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</thead>
<tbody>
<tr>
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<td>19</td>
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<td>1.0 equiv</td>
<td>Et₃N (2.0 equiv)</td>
<td>24 h</td>
<td>![Product Image]</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>DBU (2.0 equiv)</td>
<td>24 h</td>
<td>![Product Image]</td>
<td>23</td>
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<tr>
<td>3</td>
<td>13</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>Et₃N (2.0 equiv)</td>
<td>2 h</td>
<td>![Product Image]</td>
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<tr>
<td>4</td>
<td>13</td>
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<td>1.0 equiv</td>
<td>DBU (2.0 equiv)</td>
<td>2 h</td>
<td>![Product Image]</td>
<td>10</td>
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</tbody>
</table>

*aIsolated by column chromatography.

The solubility of silver acetate in organic solvents is greatly improved upon the addition of triphenylphosphine (PPh₃) through a highly soluble complex. Therefore, reactions with this additive were screened in hopes of improving the overall reaction

yield (entries 1 and 2, Table 1.3). Also at this time the amount of Et₃N required was studied. As the reaction mechanism only needs a catalytic quantity, it was thought that two equivalents might not be necessary (entries 3 and 4). As these results did not provide a significant improvement over the prior results, it was concluded that PPh₃ and catalytic triethylamine would not be used in subsequent optimization studies.

Table 1.3 Effect of PPh₃ and Catalytic Base

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>Et₃N</th>
<th>PPh₃</th>
<th>Time</th>
<th>Product</th>
<th>Isolated Yield™ (%)</th>
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<td>19</td>
<td>1.0 equiv</td>
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<td>0.2</td>
<td>22 h</td>
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<tr>
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<td>1.0 equiv</td>
<td>1.0</td>
<td>0.2</td>
<td>17 h</td>
<td>![Product Image]</td>
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<td>1.0 equiv</td>
<td>0.2</td>
<td>0.2</td>
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<td>![Product Image]</td>
<td>40</td>
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<tr>
<td>4</td>
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</table>

™Isolated by column chromatography.

For the previous work in our lab, toluene was used as the solvent due to the high temperature required for aza-Cope rearrangement to occur. Since the [3+2] dipolar
cycloaddition reaction was performed at room temperature, a high boiling solvent was not required and therefore the next variable studied was the solvent. Tetrahydrofuran,\textsuperscript{54} dichloromethane,\textsuperscript{55} and acetonitrile\textsuperscript{56} have been shown in the literature as compatible solvents for [3+2] dipolar cycloadditions. These solvents all promoted the cycloaddition (Table 1.4), but when tetrahydrofuran and dichloromethane were employed the yields were slightly diminished. The use of acetonitrile gave a comparable yield to toluene, improved the substrate solubility, and was much easier to remove during the workup stage.

\textsuperscript{56} Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Lu, Z. \textit{Chemical Communications} \textbf{2009}, \textit{2905-2907}. 
### Table 1.4 Role of Solvent in [3+2] Dipolar Cycloaddition

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>Solvent</th>
<th>Time</th>
<th>Product</th>
<th>Isolated Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>THF</td>
<td>24 h</td>
<td><img src="image" alt="Product 1" /></td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>MeCN</td>
<td>24 h</td>
<td><img src="image" alt="Product 2" /></td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>DCM</td>
<td>24 h</td>
<td><img src="image" alt="Product 3" /></td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>THF</td>
<td>2 h</td>
<td><img src="image" alt="Product 4" /></td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>MeCN</td>
<td>2 h</td>
<td><img src="image" alt="Product 5" /></td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>1.0 equiv</td>
<td>1.0 equiv</td>
<td>DCM</td>
<td>2 h</td>
<td><img src="image" alt="Product 6" /></td>
<td>34</td>
</tr>
</tbody>
</table>

\(^a\)Isolated by column chromatography.

The cycloaddition was already mild in the sense that it could be run at room temperature. It became more operationally simple when it was discovered the use of molecular sieves and an N\(_2\) atmosphere were not necessary. Keeping everything else constant, the removal of the molecular sieves gave an isolated yield of 52% versus the 47% when molecular sieves were used.
The isolated percent yield for the reaction with allylamine appeared to remain in the mid 50s and noticeable amounts of side products formed. Scaling up of the reaction with allylamine supplied an interesting result in terms of the structure of these side products. It was found that a competing conjugate addition with phenyl maleimide was occurring once the cycloadduct formed (Scheme 1.28). This side product was isolated in a 43% yield and therefore explained the diminished yield of the desired product. A significant portion of the dipolarophile was engaged in the competing conjugate reaction before it was able to engage in the desired [3+2] dipolar cycloaddition.

Scheme 1.28 Competing Side Reaction After [3+2] Dipolar Cycloaddition

A similar side product was obtained when the reaction with benzylamine was performed on a larger scale, but the yield was not as high as with allylamine. It was believed that the steric hindrance of the nitrogen in the benzylamine cycloadduct discourages the competing conjugate addition. The conjugate addition must occur faster than [3+2] dipolar cycloaddition so in order to circumvent this problem the reaction was run at 0 °C instead of room temperature. The decrease in temperature slowed down the reaction to an extent that [3+2] dipolar cycloaddition was not able to occur. Next, it was
decided that instead of using a 1:1 ratio of imine to dipolarophile the imine concentration would be doubled giving a 2:1 ratio. The expectation was that the dipolarophile would engage in a cycloaddition quickly and be completely consumed before conjugate addition could occur. Gratifyingly, this hypothesis proved to be valid and the isolated yield for both amine components were greatly increased (Table 1.5). Although this modification does reduce the atom economy of the transformation, the starting materials required are commercially available and inexpensive.

### Table 1.5 Effect of Imine Stoichiometry

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>Time</th>
<th>Product</th>
<th>Isolated Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>28 h</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>(2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>7 h</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>(2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Isolated by column chromatography.

Silver acetate was the metal of choice for this reaction – it was common in other metalated azomethine ylide reports and it was very successful in our previous reports. Control experiments were run using six other metals (Table 1.6). It was found that though other metals do catalyze the reaction, it is not to the same degree as silver acetate.
Table 1.6 Screening Various Metal Salts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (equiv)</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>Metal Salt</th>
<th>Time</th>
<th>Product</th>
<th>Isolated Yield(a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>Cu(OAc)(_2)-H(_2)O</td>
<td>2 h</td>
<td>![Product 1]</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>Zn(OAc)(_2)</td>
<td>2 h</td>
<td>![Product 2]</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>Ni(OAc)(_2)-H(_2)O</td>
<td>2 h</td>
<td>![Product 3]</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>Mn(OAc)(_2)-2H(_2)O</td>
<td>2 h</td>
<td>![Product 4]</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>CuCl</td>
<td>2 h</td>
<td>![Product 5]</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>FeCl(_2)</td>
<td>2 h</td>
<td>![Product 6]</td>
<td>NR</td>
</tr>
</tbody>
</table>

\(a\)Isolated by column chromatography.

These studies identified the optimized conditions for this reaction as; two equivalents of amine, two equivalents of aldehyde, and one equivalent of dipolarophile and allowed us to direct our attention toward expanding the substrate scope.
1.6 Substrate Scope Expansion

This method allows for a clear expansion of the substrate scope since the three main components (amine, aldehyde, and dipolarophile) can all be varied.

1.6.1 Amines

We first investigated the amine – in principle, amines containing substituted π-allylic functionality other than benzyl or allyl amine could also be used as azomethine ylide precursors. As the specific focus of this project was to study the chemical reactivity of substituted π systems in order to construct 5-vinyl pyrrolidines four additional amines were chosen (Figure 1.3).

Figure 1.3 Substituted π Amines

Cinnamylamine (24), which is essentially the combination of the two previously studied amines, was the first amine chosen. The hydrochloride salt of this amine is commercially available, but is very expensive; only 10 mg for $251. As a result, the amine was synthesized in our lab (Scheme 1.29). Cinnamaldehyde (28) was first
converted to the oxime (29) following a published procedure.\textsuperscript{57} Though there is a literature procedure for the reduction of the oxime to the free base amine by lithium aluminum hydride (LAH) it afforded a low yield\textsuperscript{58} so zinc dust\textsuperscript{59} was chosen as an alternative reductant. Following basic workup, the free amine was produced in a 92% yield without further purification on a large scale.

\textbf{Scheme 1.29. Synthesis of Cinnamylamine}

When this amine was subjected to the optimized conditions for [3+2] dipolar cycloaddition the expected and desired cycloadduct (30) was isolated as a single diastereomer in good yield (80%).

Though the remaining three amines have been synthesized before, the many attempts at their synthesis were unsuccessful. Though the conversion may have been successful the low boiling point of these amines made them difficult to isolate and therefore a sufficient quantity was not obtained. A solution to this problem was to synthesize the hydrochloride salt instead of the free base. The synthesis of the amine salts are better documented in the literature and the crotylamine hydrochloride salt is a known


\textsuperscript{58} Walter, R. C. The Journal of the American Chemical Society \textbf{1952}, \textit{74}, 5185-5187.

compound. After many failed attempts, it was satisfyingly found that the literature procedure could be applied to all the desired amines and afford the amines via a modified Gabriel procedure in good yield on multi-gram scales (Scheme 1.30).

**Scheme 1.30 Synthesis of Substituted π Amines**

Hydrochloride amine salts had not been applied to this methodology, but it was not expected to pose an adverse problem to the reaction. To test the effect of the free base (24) versus hydrochloride salt, the hydrochloride salt of cinnamylamine (37) was synthesized and the results of the cycloaddition were compared (Table 1.7). The use of an amine salt did not show any difference in isolated yield and therefore it was found that other than the addition of extra base to the reaction, to form the free-base *in situ*, amine hydrochloride salts and free base amines could be used interchangeably.

---

Table 1.7 Free Base versus Cinnamylamine Hydrochloride Salt

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Dipolarophile</th>
<th>Product</th>
<th>Isolated Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>9 (1.0 equiv)</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>37 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>9 (1.0 equiv)</td>
<td>30</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\)Isolated by column chromatography.

When amines (34-36) were used in the reaction under the optimized conditions it was found that they all produced a cycloadduct as a single diastereomer in good yield (Table 1.8). The only deviation from the previously optimized conditions was the length of the initial imine formation and the requirement of extra base. Instead of requiring 15 minutes for the imine formation with ethyl glyoxylate (as in allylamine) an \(^1\)H NMR experiment showed that the *in situ* free base formation as well as condensation required 30 minutes.
Table 1.8 Butenylamine (34), Crotylamine (35), and Prenylamine (36) Results

![Diagram of reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Dipolarophile</th>
<th>Product</th>
<th>Isolated Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>22 (1.0 equiv)</td>
<td>![Image of product 38]</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>35 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>22 (1.0 equiv)</td>
<td>![Image of product 39]</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>36 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>22 (1.0 equiv)</td>
<td>![Image of product 40]</td>
<td>64</td>
</tr>
</tbody>
</table>

\(^a\)Isolated by column chromatography.

As noted before, previous work in the Waters group, specifically the 2-aza-Cope-dipolar cycloaddition domino reaction, has focused on similar amine components. The branched amines, required for the previous transformation (2-aza-Cope [3+2] dipolar cycloaddition), contained all the components necessary for the 2-aza-Cope-dipolar cycloaddition strategy and gave 2-allyl substituted pyrrolidines. In theory, these amines could be used for the current azomethine ylide methodology, but as the reaction is conducted at room-temperature the homoallyl group would not rearrange. The expected cycloadduct would be a 5-allyl substituted pyrrolidine. In the context of this reaction, in order to get comparative results, these branched amines were explored again.
When this reaction was first attempted, using 1.0 equiv amine 41, 1.0 equiv ethyl glyoxylate, 1.0 equiv phenyl maleimide, and 1.5 equiv silver acetate the desired cycloadduct (48) was isolated in a 41% yield. These results were promising, but after extensive studies it was found that branched amines were not the optimum substrate and the initial results could never be repeated. If the two generated ylide precursors are compared one can see that the acidity of the alpha protons are quite different (compare 42 to 44, Scheme 1.31).

**Scheme 1.31 Branched Amine and Resulting Proton Acidity of Imine**

While imine formation was able to occur in both instances the resultant imines were very distinctive in terms of reactivity. Imine 42, which is formed at room temperature, and thus does not undergo a rearrangement, does not provide a sufficiently acidic proton for deprotonation by Et$_3$N and therefore ylide 43 is not formed. The red-circled proton in 42, next to a benzyl ring, would provide conjugation upon deprotonation, but even after chelation with silver acetate the pK$_a$ is not lowered enough for the ylide to form. On the other hand, imine 44, formed via thermal aza-Cope rearrangement, affords a sufficiently acidic proton for deprotonation to occur and provide...
the ylide \((45)\). The pK\(_a\) of the blue-circled proton is lowered not only due to the silver chelation, but also since it is next to an electron-withdrawing group, in this case an ester. Another reason imine \(44\) is superior to \(42\) is once the imine forms and rearranges to \(44\), the proton circled in blue is less sterically hindered than the un-rearranged imine proton circled in red. Thermodynamically, once these two imines are deprotonated and in the ylide form they are the same, but the energy barrier for the conversion of \(42\) to \(43\) is higher than the conversion of \(44\) to \(45\).

This hypothesis was confirmed by \(^1\)H NMR experimentation. Branched amine \(41\) and ethyl glyoxylate \((20)\) were allowed to stir for 15 minutes in deuterated chloroform before the addition of phenyl maleimide \((9)\), silver acetate, and Et\(_3\)N. The reaction was then monitored over 24 hours and the NMR indicated clean imine formation and phenyl maleimide, but no cycloadduct \((46)\). Once an ylide is generated it will undergo \([3+2]\) dipolar cycloaddition very quickly, the fact that no cycloadduct was observed indicates the ylide was unable to form. It is also important to note that no other side reactions occurred over the monitored time period.

To improve the reactivity of \(41\), a variety of reaction changes were made, summarized in Table 1.9. It was first thought that returning to the use of toluene may prove advantageous (entry 1); however, as shown by NMR, the imine and dipolarophile were still present, implying that the ylide did not form. Switching from excess silver acetate to a catalytic quantity did not affect the yield of cycloadduct in prior experiments, but amine \(41\) may not tolerate a reduced quantity and consequently the use of an excess of silver acetate was tested next (entry 2). Though this method has never required heat to promote the cycloaddition, entries 3 and 4 are the attempts to slightly heat the reaction
mixture to promote the deprotonation of 42. Both reactions resulted in an uncharacterizable crude reaction mixture. At this point it was postulated was that a stronger base might be necessary and potassium hydroxide (KOH) is another common base used in [3+2] dipolar cycloadditions. Entries 5-7 show the attempts at using excess or catalytic KOH. Lastly, in an attempt to increase the acidity of the alpha proton in 42 the trifluoromethyl para-substituted benzyl amine (47) derivative was used (entry 8). For this reaction a 16% isolated yield was obtained with the remaining material being unreacted phenyl maleimide and imine. This result indicated that the electron-withdrawing power of the trifluoromethyl group was able to lower the alpha proton acidity, but not to an appreciable extent.

\[ \text{Reference:} \]

### Table 1.9 Optimization of Branched Amine Substrates

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ethyl Glyoxylate</th>
<th>Phenyl Maleimide</th>
<th>AgOAc</th>
<th>Base</th>
<th>Temp.</th>
<th>Product</th>
<th>Isolated Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>0.1 equiv</td>
<td>Et(_2)N (2.0 equiv)</td>
<td>rt</td>
<td>48</td>
<td>no desired product</td>
</tr>
<tr>
<td>2</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>1.5 equiv</td>
<td>Et(_2)N (2.0 equiv)</td>
<td>rt</td>
<td>48</td>
<td>no desired product</td>
</tr>
<tr>
<td>3</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>1.5 equiv</td>
<td>Et(_2)N (2.0 equiv)</td>
<td>55 °C</td>
<td>48</td>
<td>Decomp.</td>
</tr>
<tr>
<td>4</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>1.5 equiv</td>
<td>Et(_2)N (2.0 equiv)</td>
<td>35 °C</td>
<td>48</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>0.1 equiv</td>
<td>KOH (2.0 equiv)</td>
<td>rt</td>
<td>48</td>
<td>no desired product</td>
</tr>
<tr>
<td>6(^a)</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>0.1 equiv</td>
<td>KOH (2.0 equiv)</td>
<td>rt</td>
<td>48</td>
<td>no desired product</td>
</tr>
<tr>
<td>7</td>
<td>41 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>0.1 equiv</td>
<td>KOH (0.1 equiv)</td>
<td>rt</td>
<td>48</td>
<td>no desired product</td>
</tr>
<tr>
<td>8</td>
<td>47 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td>0.1 equiv</td>
<td>Et(_2)N (2.0 equiv)</td>
<td>rt</td>
<td>49</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\)Reaction was performed with molecular sieves. \(^b\)Isolated by column chromatography.

These results indicated that these particular branched amines may not be the most desirable substrates for this method under the presented conditions and certainly warrants additional study.

In summary, many \(\pi\)-substituted amines are suitable substrates for this method and provide products that could not be synthesized under traditional azomethine ylide.
methods. These 5-vinyl substituted products either closely resemble or can be used in the construction of natural products.

1.6.2 Electrophiles

The next component of the reaction varied was the electrophile. An alternative carbonyl substrate, ninhydrin (50), was used and afforded a spirocenter at the 2 position of the pyrrolidine ring. Ninhydrin formed many undesirable side products at room temperature (Scheme 1.32) – due to its known reactivity with primary amines to form the known compound, Ruhemann’s Purple. For this reason, ninhydrin is used as a latent fingerprint visualizer in forensic chemistry.


Fortunately, it was found that by cooling the reaction mixture to 0 °C the formation of the side product was minimized and the desired product could be formed in good yield (Table 1.10). When benzylamine was used the cycloadduct was isolated in a 60% yield while allylamine afforded a 21% isolated conversion.
Table 1.10 Alternative Electrophile: Ninhydrin

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ninhydrin</th>
<th>Phenyl Maleimide</th>
<th>Product</th>
<th>Isolated Yield$$^a$$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td><img src="image" alt="Product 51" /></td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>1.0 equiv</td>
<td><img src="image" alt="Product 52" /></td>
<td>21</td>
</tr>
</tbody>
</table>

$$^a$$Isolated by column chromatography.

Two additional electrophiles were studied next – phenyl-(53) and indole glyoxal (54) and were synthesized according to known literature procedures.\(^{64,65}\) As with other starting materials, phenylglyoxal (53) was first used in an \(^1\)H NMR scale reaction to determine the length of imine formation. It was determined that 1.5 h was necessary for complete imine formation to take place. When phenylglyoxal was used in the overall reaction sequence the expected cycloadducts were all isolated in good yield as a single diastereomer (Table 1.11).

Table 1.11 Alternative Electrophile: Phenyl Glyoxal

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Product</th>
<th>Isolated Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td>53 (2.0 equiv)</td>
<td>![Product Image]</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>24 (2.0 equiv)</td>
<td>53 (2.0 equiv)</td>
<td>![Product Image]</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>35 (2.0 equiv)</td>
<td>53 (2.0 equiv)</td>
<td>![Product Image]</td>
<td>72</td>
</tr>
</tbody>
</table>

*aIsolated by column chromatography.

Indole glyoxal also performed well in the cycloaddition and afforded the expected cycloadducts as a single diastereomer (Table 1.12).66 These results were exciting as indole glyoxal would be necessary for the synthesis of borrecapine (see Figure 1.2). Due to solubility reasons THF was sometimes used as the solvent in these reactions instead of MeCN.

---

66 This work was performed by Xiaoxi Liu, Ph.D.
Table 1.12 Alternative Electrophile: Indole Glyoxal

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Product</th>
<th>Isolated Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td>54 (2.0 equiv)</td>
<td><img src="image1.png" alt="" /></td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>19 (2.0 equiv)</td>
<td>54 (2.0 equiv)</td>
<td><img src="image2.png" alt="" /></td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>24 (2.0 equiv)</td>
<td>54 (2.0 equiv)</td>
<td><img src="image3.png" alt="" /></td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>34 (2.0 equiv)</td>
<td>54 (2.0 equiv)</td>
<td><img src="image4.png" alt="" /></td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>35 (2.0 equiv)</td>
<td>54 (2.0 equiv)</td>
<td><img src="image5.png" alt="" /></td>
<td>92</td>
</tr>
<tr>
<td>6(^b)</td>
<td>36 (2.0 equiv)</td>
<td>54 (2.0 equiv)</td>
<td><img src="image6.png" alt="" /></td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\)Isolated by column chromatography. \(^b\)The indole nitrogen was alkylated with a methyl group to improve solubility.

1.6.3 Dipolarophiles

The third component of this reaction, the dipolarophile, was the last variable studied. All of the compounds synthesized to this point gave excellent diastereoselectivity, affording just one diastereomer, except the reactions with dimethyl
fumarate which were not as selective (Table 1.13).\textsuperscript{67} It was reasoned that the lessened diastereoselectivity was due to the reduced size of the dipolarophile. With less orbital overlap available the preference for the \textit{endo} vs. \textit{exo} transition state was reduced.

\textbf{Table 1.13 Alternative Dipolarophile: Dimethyl Fumarate}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Product</th>
<th>Isolated Yield\textsuperscript{c} (%)</th>
<th>Diastereotopic Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 (2.0 equiv)</td>
<td>20\textsuperscript{a} (2.0 equiv)</td>
<td>0.1 equiv AgOAc, Et\textsubscript{3}N, MeCN</td>
<td>77</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>24 (2.0 equiv)</td>
<td>20\textsuperscript{a} (2.0 equiv)</td>
<td>+ MeO\textsubscript{2}C\text{CO\textsubscript{2}Me}</td>
<td>59</td>
<td>3.5:1</td>
</tr>
<tr>
<td>3</td>
<td>19 (2.0 equiv)</td>
<td>50\textsuperscript{b} (2.0 equiv)</td>
<td>R = Ph, R' = CO\textsubscript{2}Et, 65 R = cinnamyl, R' = CO\textsubscript{2}Et, 66 R = Ph, R' = ninhydrin, 67 R = vinyl, R' = CO\textsubscript{2}Et, 68</td>
<td>45</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>13 (2.0 equiv)</td>
<td>20\textsuperscript{c} (2.0 equiv)</td>
<td>R = Ph, R' = CO\textsubscript{2}Et, 65 R = cinnamyl, R' = CO\textsubscript{2}Et, 66 R = Ph, R' = ninhydrin, 67 R = vinyl, R' = CO\textsubscript{2}Et, 68</td>
<td>66</td>
<td>3:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction was preformed at room temperature. \textsuperscript{b}Reaction was preformed at 0 °C. \textsuperscript{c}Isolated by column chromatography.

To demonstrate the utility of the reaction in a multigram synthesis the reaction of allylamine, ethyl glyoxylate, and phenyl maleimide was performed on a large scale.

\textsuperscript{67}Wornock, W. J.; Kemp, J.; Grigg, R. \textit{Journal of the Chemical Society, Perkin Transactions 1} \textbf{1987}, \textit{2275-2284}.
Using 60 mmol of amine, 60 mmol of ethyl glyoxylate, and 30 mmol of phenyl maleimide delivered the cycloadduct in 65% yield (6.13 g). It is proposed that the lower yield is due to isolation of a large quantity of material and not the conversion of product being diminished in a large reaction.

1.6.4 Summary of Methodology Expansion

In general, the expansion of the substrate scope demonstrated the wide range of tolerable substrates for this methodology. All of the generated cycloadducts from the amines tested could not have been prepared under classical conditions due to complications from the alkenyl group. The use of a glyoxal in the reaction opens the door for a wide variety of substrates including ones that closely resemble natural products. Though the dipolarophile component was studied the least it was found that various dipolarophiles could be used with success.

1.7 Stereochemical Rationale

High levels of stereocontrol were achieved in all cases and can be rationalized based on two factors: 1) metal chelation that makes the W-shaped ylide conformationally rigid and minimizes allylic 1,3 strain and 2) the endo approach by the dipolarophile
Both of these factors taken into consideration afford a cycloadduct with an all cis geometry around the pyrrolidine ring.

Scheme 1.33 Stereochemical Reasoning of [3+2] Dipolar Cycloaddition

Based on the results of the previous work published in our group it was expected that the cycloaddition would occur in a diastereoselective fashion and in fact all of the cycloadducts using phenyl maleimide as the dipolarophile were isolated as a single diastereomer. We were confident that the stereochemistry around the pyrrolidine ring had the substituents in an all cis relationship, but to prove this 1-D NMR NOE-difference studies were performed.

Cycloadduct 38 was used for the NMR study and the results confirmed our hypothesis that the substituents had a cis configuration around the pyrrolidine ring. Compound 38a shows the bond distances based on the result of a W-shaped ylide and endo transition state (expected conformation) and 38b shows the stereochemistry when the cycloaddition goes through an exo transition state (disfavored and not expected). The comparison of distances between proton D and B and D and C in cycloadduct 38a and 38b are shown in Figure 1.4. In 38a the distances are approximately equal whereas 38b gives a greater distance between D and B. When D was irradiated this greater distance
would lead to a reduced NOE enhancement of B compared to C – this was not the observed pattern, therefore the cis-product was obtained.

**Figure 1.4 Bond Distances for 38a and 38b**

![Bond Distances for 38a and 38b](image)

**1.8 Future Work and Conclusions**

Though the utility of this methodology has been demonstrated with many substrates it is still in its infancy and there are many other ways this methodology could be expanded further. This includes the exploration of an intramolecular variant as well as the development of an asymmetric version. Using silver as our metal of choice allows for easy ligand modification to induce chirality. Some of the possible metal/ligand systems for an enantioselective transformation are shown in Figure 1.5.\\(^{68}\)

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This research will help the synthetic community by providing a solution where other azomethine ylide and [3+2] dipolar cycloaddition methods fall short. In a small number of steps and in a mild manner, structurally diverse and complex molecules are generated. Many of our cycloadducts were also isolated as a single diastereomer. The short amount of time required for this reaction as well as the result from the large scale reaction show the potential application of this methodology in an industrial setting. This work allows for azomethine ylides to now be made from allylic amines and glyoxals which expands the overall toolbox of reactions at an organic chemist’s disposal.
CHAPTER TWO: APPLICATION OF METHODOLOGY – STUDIES TOWARD
THE SYNTHESIS OF SPIROTRYPROSTATIN B

2.1 Background and Isolation

Spirotryprostatins A and B (69 and 70), two biologically active indole alkaloids, were isolated by Osada in 1996\(^6^9\) (Figure 2.1) from the fermentation broth of \textit{Aspergillus fumigatus} BM939. Both compounds exhibit bioactivity and inhibit the cell cycle in the G2/M phase.\(^7^0\) Spirotryprostatin B is more active as it completely inhibits progression of mammalian tsFT210 cells in concentrations over 12.5 \(\mu\)g/mL. The G2/M DNA checkpoint ensures that cells do not enter mitosis until damaged DNA is repaired. Therefore, cells with defective DNA checkpoints (or the G2/M phase is inhibited) will enter mitosis with damaged DNA leading to cell death after division. As cancer cells contain defective DNA, spirotryprostatin B has the potential to be an effective anti-cancer treatment. Spirotryprostatin B also shows cytotoxic activity on the growth of human leukemia cell lines.\(^7^1\)


Total synthesis of these molecules is certainly warranted due to their biological activities, but also due to their scarcity in nature. From 400 L of fermentation broth only 11 mg of spirotryprostatin A and 1 mg of spirotryprostatin B were isolated. The synthetic organic chemistry community has been very invested in the synthesis of the spirotryprostatins and to date there have been many reports. Being the more biologically active natural product, spirotryprostatin B has been the focus of our work. The central pyrrolidine core with a 5-vinyl (prenyl) appendage allows us to investigate our methodology toward its total synthesis.

2.2 Previous Total Syntheses

To date, there have been eight total syntheses reported for spirotryprostatin B with the first four coming within six months of each other in 2000. The first report came from Ganesan in March and this synthesis took inspiration from nature and the biomimetic
pathway. The key step was a late stage biomimetic oxidative rearrangement (Scheme 2.1).\textsuperscript{72} The Ganesan total synthesis was 4 steps with an overall 0.6 % yield.

**Scheme 2.1 Spirotryprostatin B, Key Step: Biomimetic Oxidative Rearrangement by Ganesan**

Just three weeks later the Williams group also disclosed their total synthesis which hinged upon a 1,3–dipolar cycloaddition to construct the central core of the molecule (Scheme 2.2).\textsuperscript{73} This second total synthesis completed the molecule in 7 steps with a 0.7 % overall yield.

**Scheme 2.2 Spirotryprostatin B, Key Step: 1,3–Dipolar Cycloaddition by Williams**


Danishefsky followed with the third total synthesis in April which had an important Mannich-type reaction as the key step to construct the substituted pyrrolidine ring (Scheme 2.3). This synthesis finished the final target molecule in 5 steps with a 0.8 % overall yield.

Scheme 2.3 Spirotryprostatin B, Key Step: Mannich–Type Reaction by Danishefsky

The final synthesis in 2000 came from Overman which relied upon a late stage intramolecular Heck reaction to construct the pyrrolidine ring by coupling two key portions of the molecule (Scheme 2.4). Their 10 step total synthesis was accomplished with a 9 % overall yield.

Scheme 2.4 Spirotryprostatin B, Key Step: Intramolecular Heck by Overman

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Two years later two additional syntheses were reported, the first came from Carreira and the second from Fuji. The Carreira synthesis used an elegant MgI$_2$–promoted annulation to yield the highly functionalized central core of the spirotryprostatin B (Scheme 2.5).$^{76}$ This total synthesis was completed with an overall 0.5 % yield in 16 steps.

**Scheme 2.5 Spirotryprostatin B, Key Step: MgI$_2$–Promoted Annulation by Carreira**

The Fuji synthesis used an intermolecular nitroolefination reaction to construct a highly substituted oxindole ring with the quaternary center in place (Scheme 2.6).$^{77}$ This center was then converted to the spirocenter in a following reaction. Overall this total synthesis yielded the desired product in 0.6 % overall yield in 8 steps.

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The last two reported syntheses came from Horne in 2004 and Trost in 2007. Like the previous syntheses the Horne group was inspired by nature and used a Mannich–type reaction to assemble the pyrrolidine core and also acylate the pyrrolidine nitrogen (Scheme 2.7). In 4 steps with an overall yield of 0.4 % the final natural product was synthesized.

The last synthesis to date is from the Trost group and used a key enantioselective, Pd–catalyzed Carroll-like rearrangement to install the key prenyl substituent (Scheme 2.8). This approach was very different from other groups as the pyrrolidine ring was the

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last ring to be constructed. The overall synthesis was completed in 8 steps in a 0.7\% yield.

Scheme 2.8 Spirotryprostatin B, Key Step: Carroll-Like Reaction by Trost

Though the synthesis has been completed numerous times our hope was to expand upon our methodology work and demonstrate its utility. Spirotryprostatin B stood out as a suitable choice as the central pyrrolidine ring contained a 5-vinyl substitution. Many of the previous syntheses required multiple steps to install the prenyl group and it had to be masked until late-stage transformations. With our methodology we would be able to install the substitution pattern around the pyrrolidine ring in one step from either commercially available or easily synthesized materials.

2.3 Retrosynthetic Plan

A key advantage of our developed methodology was the formation of highly functionalized pyrrolidine rings in one step. Our synthetic efforts toward spirotryprostatin would hinge building the core quickly and efficiently.
2.3.1 First Generation

At the onset, we focused on devising a synthetically efficient route to the core spirooxindole-containing pyrroldidine ring. This would serve as the backbone to our synthesis of spirotryprostatin B. Based on work by Ganesan,\textsuperscript{71} the final steps of our synthesis would involve an oxidation of the pyrroldidine ring (71) to afford the desired target (70). The required diketopiperazine would arise from cyclization onto the pyrroldidine nitrogen after deprotection of the Troc group by zinc dust. The proline derived acid chloride (72) would be installed by acylation of the pyrroldidine nitrogen (73) within the central core. The central spirooxindole-containing core would arise from [3+2] dipolar cycloaddition between prenylamine hydrochloride (36), ethyl glyoxylate (20), and α-methyleneoxindole (74, Scheme 2.9).

\textbf{Scheme 2.9 First Generation Retrosynthesis}
This synthesis would give the desired molecule in a relatively few number of steps and also showcase our new methodology. Specifically, the cycloaddition would afford the multi-substituted pyrrolidine ring in one mild and efficient step. As both prenylamine hydrochloride (36) and ethyl glyoxylate (20) had been studied previously and shown to be compatible with our methodology, and the required dipolarophile is known to engage in [3+2] dipolar cycloadditions to afford spirocenter-containing molecules, \(^{80}\) we were optimistic about the outcome of the cycloaddition.

The required dipolarophile (74) was synthesized according to literature procedure from isatin (100g/$29) via a Peterson olefination. (Scheme 2.10). \(^{81}\)

Scheme 2.10 Synthesis of Dipolarophile (74) via Peterson Olefination

![Scheme 2.10 Synthesis of Dipolarophile (74) via Peterson Olefination](image)

The Grignard addition afforded the desired product (75) on a large scale, but after the BF\(_3\)•OEt\(_2\) promoted elimination the final product (74) could not be isolated. When the reaction was monitored by TLC it was evident that the starting material had been cleanly converted to product which indicated that the isolation was posing a problem. Multiple reactions were attempted, on various scales, where the workup and isolation


procedure were modified, but the desired product was not furnished or isolated. The material recovered was a bright orange solid that could not be dissolved for $^1$H NMR analysis. Further searches in the literature revealed that external olefin compounds like 74 are very unstable, as they are known to polymerize into dimers and high order polymers upon concentration.\(^{82}\) Though the dipolarophile could be generated \textit{in situ} during [3+2] dipolar cycloaddition, it could complicate the reaction and add an unnecessary variable. Therefore, it was determined that the dipolarophile could instead be altered to avoid problems of polymerization and it would only be necessary to alter the retrosynthetic plan slightly.

\section*{2.3.2 Second Generation}

Spirocenter-containing natural products are very common and there has been much interest in their synthesis with inter– or intra–molecular [3+2] dipolar cycloadditions playing an important role. When changing the dipolarophile for the target molecule there were many different functional group choices. Other groups were also studying several of these choices.

Three dipolarophiles were chosen in the total synthesis of (−)-horsfiline, a nitroolefin, vinylsulfone, and ester (Scheme 2.11).\(^{83}\) Vastly different results were obtained when each was applied to the total synthesis. The nitroolefin proved to be

\begin{flushleft}
\begin{thebibliography}{9}
\end{thebibliography}
\end{flushleft}
incompatible due to the instability of the dipolarophile. While the vinylsulfone did afford a cycloadduct in 60% yield the removal of the sulfone proved difficult and after many attempts only an intractable product mixture was obtained. Lastly the ester dipolarophile was applied to the reaction. This dipolarophile performed well in the cycloaddition and gave the desired product in 77% yield. The removal of the sacrificial ester group was accomplished with Bu$_3$SnH and catalytic AIBN.

**Scheme 2.11 Comparison of Nitroolefin, Vinylsulfone, and Ester Towards (–)-Horsfile by Palmisano**

An ester-group containing dipolarophile was elected for our synthetic work based on the success of other groups and its ease of synthesis. With only the dipolarophile requiring any alterations the second-generation scheme is very similar to the first. The last step would now require converting the ester to the corresponding acid followed by an elimination to afford the internal olefin. This was a small, but necessary change in order
to overcome the problems associated with the first dipolarophile chosen. The new dipolarophile (76) was synthesized according to literature procedure via a Horner-Wittig olefination in good yield (Scheme 2.12).\textsuperscript{84}

Scheme 2.12 Synthesis of Dipolarophile (76)

When the dipolarophile was subjected to the optimized [3+2] dipolar cycloaddition with prenylamine hydrochloride (36) and ethyl glyoxylate (20) no cycloadduct was detected (Table 2.1, entry 1). While this was not the desired result, the current goal was to determine the appropriate dipolarophile. With this in mind the [3+2] dipolar cycloaddition was performed with allylamine (13) and ethyl glyoxylate (20). It was found that in this attempt a cycloadduct (78) was formed and isolated in a 50\% yield (entry 2). This was an encouraging result, but after analyzing the molecule by \textsuperscript{1}H and \textsuperscript{13}C NMR it was determined that the methylester from the dipolarophile had been hydrolyzed to the corresponding carboxylic acid. Gratifyingly, it was discovered that this problem had an easy solution; the addition of 3-Å molecular sieves afforded the desired cycloadduct (79) in a 73\% yield (entry 3). Interestingly, a similar result and solution has been previously reported.\textsuperscript{83} The stereo- and regio- chemistry of the transformation will be discussed in detail in Section 2.5.

With these results in hand the focus was again on the utility of prenylamine hydrochloride (36) as the prenyl functionality is a part of the natural product. Unfortunately, after many attempts it was determined that the steric bulk of the prenyl group was inhibiting the cycloaddition. This was not a problem when phenyl maleimide was used as the dipolarophile as it is a flat molecule, but the three-dimensional character of dipolarophile 76 and the formation of the spirocenter at C(4) renders the pyrrolidine ring too sterically crowded. A similar result was also observed when crotylamine hydrochloride (35) was used as the amine – the reaction mixture was allowed to stir at room temperature for six days and no new products were detected, but only starting material (entry 4).
Table 2.1 Application of Dipolarophile 76 in [3+2] Dipolar Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Additive</th>
<th>Product</th>
<th>Isolated Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 (2.0 equiv)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td>n/a</td>
<td><img src="image1" alt="Product 1" /></td>
<td>50</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13 (2.0 equiv)</td>
<td>molecular sieves</td>
<td><img src="image2" alt="Product 2" /></td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>35 (2.0 equiv)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated by column chromatography. <sup>b</sup> Reaction was stirred at rt for 6 days.

While this result was not ideal, it had already been determined that allylamine (13) furnished a cycloadduct and therefore the vinyl moiety could be used as a precursor to the prenyl group. This could be accomplished by cross-metathesis using Grubbs’ catalyst<sup>85</sup> or, as reported by Carreira,<sup>75</sup> the 5-vinyl group can be converted to the desired prenyl group. This transformation would occur by means of an OsO<sub>4</sub> mediated dihydroxylation followed by oxidation and elimination to yield the corresponding aldehyde. The aldehyde could then be transformed to the prenyl moiety by a Julia-Kocienski olefination. Carreira noted that attempts at olefination proved difficult and

while the multi-step Julia-Kocienski reaction added more steps to the synthesis it was the only way the olefination was successful.

### 2.3 Closing Sequence

With the highly functionalized cycloadduct (79) in hand, the next step was to acylate the pyrrolidine nitrogen. The Troc-protected acid chloride derivative of proline (72) was prepared in an operationally simple two–step sequence in high yield (Scheme 2.13).

**Scheme 2.13 Synthesis of Troc-Protected Acid Chloride (72)**

Using cycloadduct 21 as a model substrate, acylation with 72 was attempted and gratifyingly the desired product (Control-A) was isolated albeit in a low yield (16%). This result proved the feasibility of this transformation and we next explored acylation on cycloadduct 79 towards spirotryprostatin B. The initial acylation attempt using 3 equivalents of Et₃N was unsuccessful and only starting material was recovered (Table 2.2, entry 1). To improve this reaction, additional base was added. While an 89% crude
reaction mixture was recovered after workup there was only a small amount of desired product (82) isolated (entry 2). It was expected that the acid chloride (72) would be unstable to water and therefore exceptional care was made to ensure the reaction flask and environment was dry. It was thought that the low yield of product could be due to some of the acid chloride (72) decomposing due to trace water. Instead of using 1.1 equivalents of acid chloride the acylation was next attempted with 5.0 equivalents (entry 2). While acylation of the pyrrolidine nitrogen did occur the major compound was a double acylated product (83) where the indole nitrogen was also acylated. This result indicated that the acid chloride (72) was not decomposing and that when too much acid chloride is present the indole nitrogen could be acylated, even though it is not as nucleophilic as the pyrrolidine nitrogen. As an alternative, peptide coupling was next explored. Peptide coupling typically involves a carboxylic acid and primary amine to make an amide bond.\textsuperscript{86} For our substrate it was expected that the pyrrolidine nitrogen, being a secondary amine, would react slower, but still be able to form the desired amide. When hydroxybenzotriazole (HOBt) and 1-Ethyl-3(3-dimethylaminopropyl)carbodiimide (EDC) were used as the coupling agents the desired product (82) was isolated in a 10% yield (entry 4). It was determined that the best condition for this reaction was a modified Schotten-Baumann acylation as the desired product (82) was obtained in a 60% crude yield (entry 5).

Table 2.2 Acylation of 79 with 72

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Chloride</th>
<th>Additive</th>
<th>Product</th>
<th>Isolated Yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>1.1 equiv</td>
<td>3.0 equiv (Et$_3$N)</td>
<td><img src="image" alt="Control-A" /></td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>1.1 equiv</td>
<td>3.0 equiv (Et$_3$N)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>1.1 equiv</td>
<td>5.0 equiv (Et$_3$N)</td>
<td><img src="image" alt="Product 82" /></td>
<td>89 (crude material), trace product isolated</td>
</tr>
<tr>
<td>4</td>
<td>5.0 equiv</td>
<td>3.0 equiv (Et$_3$N)</td>
<td><img src="image" alt="Product 83" /></td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>1.1 equiv</td>
<td>HOBt, EDC</td>
<td><img src="image" alt="Product 82" /></td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>1.1 equiv</td>
<td>Schotten–Baumann</td>
<td><img src="image" alt="Product 82" /></td>
<td>60$^c$</td>
</tr>
</tbody>
</table>

$^a$Isolated by column chromatography. $^b$Used cycloadduct 21 (1.0 equiv). $^c$Crude yield.
Many attempts were made to isolate the acylated product, but none were successful and the yield was consistently diminished. Fortunately, when the crude material was taken onto the next step, removal of Troc group with zinc, the transformation was effective and the desired product (84) was isolated in a 27% yield (Scheme 2.14).

Scheme 2.14 Removal of Troc Group and Subsequent Ring Closure

The product after the Troc removal closely matches the natural product and only a few steps remain to complete the synthesis. With a majority of the molecule complete, the conversion of the vinyl group to prenyl group was attempted. While it had not been attempted with the spirotroprostatins previously, a cross metathesis between the vinyl group and 2-methyl-2-butene would give the desired prenyl moiety. An asymmetrical olefin was used in the coupling to improve the yield, as it has been demonstrated that terminal olefins do not preform as well during a cross metathesis. This was attempted with 8 mol% Grubbs’ second-generation catalyst at 40 °C. The reaction mixture was monitored and after stirring for 22 hours no change was seen. Thus, an additional 8 mol% of catalyst was added to the reaction mixture. The addition of extra catalyst did not

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improve the conversion and only starting material was recovered after 96 hours (Scheme 2.15).

**Scheme 2.15 Attempted Cross Metathesis of 84**

While the cross metathesis would have yielded the desired functionality directly in one step, a three-step Julia-Kocienski sequence as reported by Carreira was explored.\(^7\)

The required coupling sulfone (88) was synthesized in two steps from commercially available starting materials in high yield (Scheme 2.16). The first step involved a Mitsunobu reaction followed by oxidation with aqueous Oxone.

**Scheme 2.16 Synthesis of Sulfone 88 for Julia-Kocienski Reaction**

With one of the coupling partners synthesized the next step was to prepare the aldehyde partner via a two-step process. The first step was a dihydroxylation by
OsO₄/NMO followed by an oxidation with NaIO₄ to yield the desired aldehyde (Scheme 2.17).

Scheme 2.17 Dihydroxylation and Oxidation of 84

When the product of the first reaction was analyzed by ¹H NMR it was determined that the diagnostic vinyl proton was not present. This would indicate that the dihydroxylation was indeed successful. Therefore the next reaction was attempted, but unfortunately the aldehyde was not detected. The reaction was performed on a very small scale (~10 mg) making it more difficult to do a satisfactory analysis.

2.5 Stereochemical Rationale

The determination of the stereochemistry around the pyrrolidine ring, in particular the stereochemical relationship of the 5-vinyl substituent and the spirocenter, was a very important step in the synthesis. Based on the previous results in our group as well as the stereochemical data obtained during the optimization it was expected that the endo...
transition state would predominate over the *exo* transition state. The dipolarophile used for the total synthesis is more complex than phenyl maleimide and the possible products of the cycloaddition are shown in Figure 2.2. These four possible products are due to the *endo* vs. *exo* transition state as well as different regioselectivity. As this transformation was still catalyzed by silver acetate our cycloadducts would still arise from conformationally rigid W-shaped azomethine ylide.

**Figure 2.2 Possible Products Obtained from [3+2] Dipolar Cycloaddition**

The cycloadduct (79) obtained from the [3+2] dipolar cycloaddition was analyzed with 1-D NOE NMR, but the stereochemistry and regiochemistry remained unsolved due to some conflicting data. It was thought that the stereochemistry could be determined later in the synthesis and therefore after the zinc mediated ring closure the stereochemistry was analyzed again. This time HMBC, HMQC, and COSY NMR were performed in order to get a full characterization of the generated molecule (84).
The strongest NOE enhancement, 7.3%, was seen between protons 2 and 5. When the distances were compared (Figure 2.3, red) in the DFT B3LYP 6-31G** energy minimized structures\(^8\) the endo adducts (\textbf{ENR1} and \textbf{ENR2}) had very large distances that would not correlate to the high NOE enhancement. This indicated that the adduct derived from the exo transition state (\textbf{EXR1} or \textbf{EXR2}) was preferred during [3+2] dipolar cycloaddition. The second highest NOE enhancement was observed between protons 1 and 2 (blue) at 3.7%. This matched with the distance for \textbf{EXR1} since the distance between proton 1 and 2 in \textbf{EXR2} was too large for the strong enhancement. The enhancement observed between protons 3 and 5 (green) and 4 and 2 (pink) are very different, at 1.5% and 0.9% respectively, but the distances are very similar. The

\(^8\) DFT minimizations provided by Nicholas J. Dodge.
diminished enhancement between protons 3 and 5 in EXR1 can be attributed to the more sterically crowded nature of the distance between the two protons. Taking into consideration all of the NOE data collected we can assign the stereo- and regiochemistry as shown in EXR1.

Unfortunately, this stereochemistry does not match the stereochemistry of the spirotryprostatins due to [3+2] dipolar cycloaddition occurring via the exo transition state. While the endo transition state is more favorable in terms of maximizing the orbital overlap it is believed that the steric bulk of the dipolarophile causes it to react through the exo transition state. In Williams’ synthesis of spirotryprostatin B it was found that using a very similar dipolarophile resulted in the exo transition state predominating. It has been reported that azomethine ylides and oxindolylideneacetate dipolarophiles, like 76, react in a very unpredictable manner in terms of the regio- and stereochemistry.\(^8^9\) While the stereochemistry of the spirocenter is fixed and therefore cannot be changed later in the synthesis the stereochemical results sheds more light on the complex nature of the generated azomethine ylides and subsequent dipolar cycloaddition.

2.6 Conclusions and Future Work

With the required sulfone (88) for the Julia-Kocienski coupling synthesized, the next step to complete the synthesis is to synthesize the aldehyde coupling partner (90) and then complete the olefin coupling to afford the prenylated olefin (91, Scheme 2.18). A larger reaction scale will be attempted in the aldehyde synthesis so the reaction can be appropriately analyzed and the material is sufficient to be taken through multiple steps. It is not expected that the actual coupling will be problematic.

Scheme 2.18 Julia-Kocienski Coupling

Once the coupling is complete the next step will be to hydrolyze the methyl ester to the corresponding carboxylic acid (92, Scheme 2.19). This reaction would require lithium iodide in refluxing pyridine. It has previously been shown by Williams that the conversion requires harsher conditions than the more traditional saponification conditions.
To form the final double bond, the closing sequence relied on a Barton modified Hunsdiecker reaction to yield an alkyl bromide which would then be eliminated with NaOMe. This closing sequence would afford 3-epi Spirotryprostatin B in just seven steps. The developed methodology has proven successful in a total synthesis application and has improved upon previous syntheses by installing the 5-vinyl group directly in the first step and achieving structural complexity quickly.

After developing an enantioselective variant of the methodology it will be applied to the total synthesis of this molecule to further demonstrate its application. The mode of stereoselectivity will also be studied and an alternative route will be investigated in order to yield a cycloadduct with the desired stereochemistry.

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CHAPTER THREE: STUDIES TOWARD THE TOTAL SYNTHESIS OF THE ANTI-CANCER COMPOUND PEDUNCULARINE

3.1 Background, Isolation, and Previous Total Syntheses

The *Aristotelia* alkaloid peduncularine (93) was first isolated from the roots and lower stems of the endemic Tasmanian shrub, *Aristotelia peduncularis*, as colorless needles in a 0.003% yield in 1971 by Bick.² The natural product was initially assigned as indole-pyrrolizidine (Figure 3.1, A). Due to the limited spectroscopic data, it was noted that there could be some structural discrepancies. Several years later, in 1979, a revised structure was reported that assigned the molecule as a unique 6-azabicyclo[3.2.1]-3-octene bearing a 3-indolylmethyl substituent (Figure 3.1, B).³ This revised structure matched all spectroscopic data as well as degradation studies. It has been suggested that biosynthetically this molecule arises from tryptophan and a non-rearranged geranyl subunit. In 1985 it was reported that another alkaloid had been isolated from small trees in New Zealand, *Aristotelia fruitcosa* and *Aristotelia serrata*.⁹¹ The spectral data closely matched peduncularine, but there were some distinct physical differences. The natural product was given the name isopeduncularine (94) or 7-epi-peduncularine (Figure 3.1, C). Limited studies have shown that this alkaloid displays low activity against human breast cancer cells.

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Figure 3.1 Peduncularine and Isopeduncularine

The first synthesis of peduncularine was reported in 1989 by Hiemstra and Speckamp.\(^4\) From this total synthesis a complete structural assignment was given and it was found that the synthetically prepared peduncularine was identical with the natural product. 7-\textit{epi}-peduncularine was also generated and it was found that the spectroscopic data strongly deviated from the data for isopeduncularine and therefore the original assignment was incorrect. After complete NMR analysis it was determined that isopeduncularine was in fact the same compound as peduncularine. The differences in the physical data were attributed to the possibility of inadvertent quaternary salt formation. To date, this molecule has been synthesized by three other groups, first by Woerpel in 2002 (formal synthesis in 2000),\(^92\) next by Martin in 2003,\(^93\) and most recently by Kitamura in 2006.\(^94\)

We were optimistic about this molecule since it not only contains a 5-vinyl substituted pyrrolidine ring, but also the electrophile required, indole glyoxal (95), had already been proven to be compatible with our methodology.


3.2 General Retrosynthetic Plan

Based on previous results, allylamine (13) and indole glyoxal (95) condense quickly (1.5 h) to form an imine at room-temperature; this imine could then easily be converted to an ylide which would engage in [3+2] dipolar cycloaddition.

The general retrosynthetic plan for peduncularine (93, Scheme 3.1) begins with an olefination of the ketone on the 4 position of the pyrrolidine ring (96), such as a Wittig or Tebbe reaction. The 5-vinyl substituent would be very important in the final ring closure, a ring-closing metathesis reaction with the 3-allyl group which would be installed through an allylation reaction (97). To ensure that the proton would be sufficiently acidic for the allylation a Nef reaction (99) would be preformed in the prior step. Decarbonylation of the carbonyl (101) resulting from the use of indole glyoxal would be conducted following an isomerization of position 5 on the pyrrolidine ring (103) and alkylation of the pyrrolidine nitrogen (102). This alkylation is necessary early in the synthesis since it acts as a protecting group to the nitrogen as many of the later reactions do not tolerate a basic nitrogen. The core structure of the molecule (103) would arise from the use of the developed methodology and the necessary components are allylamine (13), indole glyoxal (95), and nitroethylene (104) as the dipolarophile.

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3.3 Screening of Dipolarophiles

The dipolarophile (104) for this reaction was the only specific component that had not already been applied to the methodology. For this reason it was expected that a screen of dipolarophiles would be essential. Our initial synthetic plans required the use of a nitro-group containing dipolarophile so the requisite Nef reaction could take place in order to install the ketone moiety. It was expected that the monosubstituted nitroolefin would be difficult to prepare and therefore attention was directed to disubstituted nitroolefins bearing a group that could be easily removed or converted to an allyl group.
3.3.1 Nitroalkenes

The versatile nitro group has been studied by others and proven successful in many [3+2] dipolar cycloaddition reports. It is interesting to note that it is thought that nitroalkenyl dipolarophiles cause the reaction to be stepwise instead of the traditional concerted mechanism.\(^99\) Nitrostyrene (105) was chosen as a model substrate to test the reactivity of nitroalkenes with the generated azomethine ylides. When applied to the methodology a cycloadduct did form, but a mixture of products was recovered – one product was the desired cycloadduct (106) and the other product’s nitro group had been eliminated (107). The yield of each product was just 12%. While the formation of the cycloadduct was promising, the elimination of the nitro group was problematic, as it needed to be present for the formation of the required ketone.

Other nitro-containing dipolarophiles were applied to the methodology using the original optimized conditions and only starting material was recovered. It was thought that the reason for the unreactive nature of this dipolarophile was because it was not electron–withdrawing enough. By adding electron–withdrawing groups on either side of the double bond, the reactivity could be improved. The nitroalkenes analyzed were either synthesized according to literature procedure or modified procedure and are included in Chapter 4.\(^100\) When disubstituted dipolarophile 108 was applied to the reaction using the

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original optimized conditions an uncharacterizable mixture of products was recovered which could never be isolated or separated (entry 2). In order to slow down the kinetics of the reaction the reaction mixture was cooled to 0 °C, but this slowed the reaction down too much and only starting material was recovered (entry 3). No improvements were seen when the solvent was switched to THF at either 0 °C (entry 4) or room temperature (entry 5). Lastly, in the hopes of using a dipolarophile that would be slightly less reactive at room temperature, dipolarophile 109 was synthesized. Under the optimized conditions no cycloadduct was detected and instead only a complex reaction mixture (entry 6).

**Table 3.1 Alternative Dipolarophiles: Nitroalkenes**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Dipolarophile (1.0 equiv)</th>
<th>Producta</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td><img src="image1" alt="Dipolarophile 105" /></td>
<td><img src="image2" alt="Product 106" /> <img src="image3" alt="Product 107" /></td>
<td>1:1 mixture of products (24% overall yield)</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td><img src="image4" alt="Dipolarophile 108" /></td>
<td>Uncharacterizable Mixture of Products</td>
<td>Original Optimized Reaction Conditions</td>
</tr>
<tr>
<td>3</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td><img src="image4" alt="Dipolarophile 108" /></td>
<td>Starting Material Recovered</td>
<td>Reaction at 0 °C</td>
</tr>
<tr>
<td>4</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td><img src="image4" alt="Dipolarophile 108" /></td>
<td>Starting Material Recovered</td>
<td>Reaction in THF at 0 °C</td>
</tr>
<tr>
<td>5</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td><img src="image4" alt="Dipolarophile 108" /></td>
<td>Uncharacterizable Mixture of Products</td>
<td>Reaction in THF</td>
</tr>
<tr>
<td>6</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td><img src="image4" alt="Dipolarophile 108" /></td>
<td>Uncharacterizable Mixture of Products</td>
<td>Original Optimized Reaction Conditions</td>
</tr>
</tbody>
</table>

*a*Isolated by column chromatography.
The results of the reactions with nitro-group containing dipolarophiles were not as expected and therefore we moved our concentration to other compounds that might prove more successful.

### 3.3.2 Ketene

Ketene 110 was our next dipolarophile of choice due to its higher reactivity, but also the interesting functionality that would be incorporated into the final cycloadduct. With this dipolarophile the Nef reaction and allylation would not be required since the ketene would install the ketone and allyl group directly. The use of this dipolarophile would significantly reduce the number of overall steps for the total synthesis.

Following monoacid formation from diethyl allylmalonate the product (112) was converted to the corresponding acid chloride (113); both transformations took place in quantitative yield (Scheme 3.2).\(^\text{101}\) This molecule was isolated and used as the precursor to the dipolarophile. Due to the high reactivity of ketenes the dipolarophile would be formed in situ. There are limited reports of this dipolarophile being used by other groups in dipolar cycloaddition reactions.\(^\text{102}\)

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Scheme 3.2 Synthesis of Ketene Dipolarophile Precursor 113

This dipolarophile was investigated many times under different reactions conditions and the results are summarized in Table 3.2. It was necessary to deviate slightly from the previously optimized condition, but it was known that these conditions would not hinder [3+2] dipolar cycloaddition. As the desired ketene had to be generated in situ at −78 °C the reactions were run in THF instead of MeCN in order to accommodate the required lower temperature. Molecular sieves were also required with this reaction, as the water formed from the imine condensation would prove detrimental to the overall transformation, as it would decompose the ketene.
Table 3.2 Alternative Dipolarophile: Ketene 114

![Chemical structure of 113 and 114](attachment:image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Silver Acetate</th>
<th>Product</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>0.1 equiv</td>
<td><img src="" alt="116" /></td>
<td>Amide side product – confirmed by $^1$H NMR, $^{13}$C NMR, and LCMS</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>0.1 equiv</td>
<td>Amide Side Product</td>
<td>Longer Ylide Formation</td>
</tr>
<tr>
<td>3</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>Amide Side Product</td>
<td>Stoichiometric AgOAc</td>
</tr>
<tr>
<td>4</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>0.1 equiv</td>
<td>Amide Side Product</td>
<td>Entire reaction at $-78 ^\circ C$</td>
</tr>
<tr>
<td>5</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>2.0 equiv</td>
<td>Amide Side Product</td>
<td>Entire reaction at $-78 ^\circ C$ and stoichiometric AgOAc</td>
</tr>
<tr>
<td>6</td>
<td>13 (2.0 equiv)</td>
<td>117 (2.0 equiv)</td>
<td>0.1 equiv</td>
<td>Amide Side Product</td>
<td>Alternative Aldehyde</td>
</tr>
<tr>
<td>7</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>0.1 equiv</td>
<td>Amide Side Product</td>
<td>Addition of 0.1 equiv PPh3</td>
</tr>
<tr>
<td>8</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>0.1 equiv</td>
<td>Amide Side Product</td>
<td>Addition of 0.1 equiv PPh3 and MeCN used as solvent</td>
</tr>
<tr>
<td>9</td>
<td>13 (2.0 equiv)</td>
<td>20 (2.0 equiv)</td>
<td>–</td>
<td>Amide Side Product</td>
<td>Cu(OAc)$_2$•H$_2$O (0.1 equiv) as metal catalyst</td>
</tr>
</tbody>
</table>

*a* Isolated by column chromatography.

Using Et$_3$N in THF at $-78 ^\circ C$ the ketene was formed *in situ* from 113 and then added via cannula transfer to a separate flask in which the ylide had already been formed at room temperature. This reaction mixture was then allowed to stir at room temperature while being monitored. During the course of the reaction a new compound was observed by TLC which was then isolated by silica gel column chromatography. Unfortunately, it
was determined that this new material was an undesired amide side product (116) (Table 3.2, entry 1). The formation of this side product was due to the primary amine reacting with the ketene precursor, indicating that the primary amine was not fully consumed in imine and ylide formation.

Next, after the addition of silver acetate and Et$_3$N the reaction mixture was allowed to stir for 10 minutes before adding the ketene in hopes of fully forming the azomethine ylide (entry 2) – the result of this reaction was again the side amide product. As only 10 mol% of silver acetate was used it was thought that if a stoichiometric quantity (entry 3 and 5) was used all of the imine molecules could be converted to azomethine ylide and therefore there would not be any free amine in the solution. This still did not provide a cycloadduct, but instead the amide side product. It was determined through a control reaction that the [3+2] dipolar cycloaddition, while slower, could still take place at −78 °C. Due to this result, the entire reaction using dipolarophile 22 was attempted at −78 °C as it was thought during the cannula transfer the ketene was warming and possibly decomposing (entry 4 and 5). It was found by another group member that, in general, N-tosyl indole glyoxal (117) performed better than ethyl glyoxylate (20) during the [3+2] dipolar cycloaddition since a more reactive imine and azomethine ylide would form. This did not improve the reaction with the ketene dipolarophile since the amide side product was still obtained. While the addition of PPh$_3$ did not improve the reaction to an appreciable amount during the optimization stages the reaction was attempted with this additive (entry 7 and 8). At this time the imine formation was performed in MeCN as this was the original optimized solvent for the reaction. Unfortunately, these changes did not suppress the amide formation. Lastly, to test the effect of using a different metal
catalyst, copper (II) acetate monohydrate was used instead of silver acetate, but the amide side product still formed with no indication of a cycloadduct (entry 9).

In summary, it was found that in all cases that the formation of the desired cycloadduct was impeded by the formation of an amide side product. It was determined that the use of a ketene would not be compatible with this process due to the high reactivity of the ketene with the primary amines required.

3.3.3 Vinylsilane and Vinylsulfone

Overall, [3+2] dipolar cycloaddition with a vinylsulfone as the dipolarophile, followed by desulfonylation, affords a synthetically equivalent cycloadduct as to the cycloadduct that would arise from using ethylene as the dipolarophile.

The asymmetric vinylsilane 118 was synthesized according to literature procedure103 using Co2(CO)8 as a catalyst in 50% yield (Scheme 3.3). This dipolarophile was of interest to us because it would afford a cycloadduct which would contain a silyl group that is labile enough to be removed in later steps, but would still give high regioselectivity and be activated on both sides of the double bond. There are examples of vinylsilanes being used in [3+2] dipolar cycloaddition reactions with success.104

When this was applied to the methodology under the optimized conditions (with allylamine and ethyl glyoxylate) the initial attempt only furnished recovered starting material after purification (Table 3.3, entry 1). In hopes of increasing the solubility of the vinylsilane the reaction was next performed in THF. Unfortunately, this did not improve the yield and by TLC no new spots had formed. The same result was obtained when the reaction was warmed (in THF) to 50 °C (entry 2). Lastly, the electronics of the electrophile were altered by using N-tosyl-protected indole glyoxal (117) – the reaction was performed using THF as the solvent at room-temperature – this again did not afford any desired product, but instead just starting material was recovered (entry 3). The same results were obtained when the vinylsulfone 119 was used instead (representative example, entry 4). This dipolarophile was chosen because the sulfone is more electron withdrawing and therefore more reactive, but would also afford a cycloadduct with a labile functional group. The use of a vinyl sulfone is also desirable since high regioselectivity can be achieved, but the sulfone group can be more easily removed if necessary.\(^{105}\)

Table 3.3 Alternative Dipolarophiles: Vinylsilane (118) and Vinylsulfone (119)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Dipolarophile (1.0 equiv.)</th>
<th>Product</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td>vinylsilane (118)</td>
<td>Starting Material Recovered</td>
<td>Original, Optimized Reaction Conditions</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td>vinylsilane (118)</td>
<td>Starting Material Recovered</td>
<td>Reaction in THF</td>
</tr>
<tr>
<td>3</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td>vinylsulfone (119)</td>
<td>Starting Material Recovered</td>
<td>Reaction warmed to 50 °C in THF</td>
</tr>
<tr>
<td>4</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td>vinylsulfone (119)</td>
<td>Starting Material Recovered</td>
<td>Original, Optimized Reaction Conditions</td>
</tr>
</tbody>
</table>

3.3.4 Assorted

Various other asymmetric dipolarophiles were studied and applied to the methodology and the results from these reactions are summarized in Table 3.4. These dipolarophiles were all chosen based on their potential to give a cycloadduct that would mimic natural products and their use in total synthesis. Due to the low solubility of N-tosyl-protected indole glyoxal (117) in MeCN it was necessary to use THF or toluene during these reactions. During the optimization stages it was found that using PPh₃ as an
additive did not improve the reaction to an appreciable amount, but it was employed again during these trials to possibly achieve higher reactivity.

Table 3.4 Alternative Dipolarophiles: Various

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Electrophile</th>
<th>Dipolarophile (1.0 equiv)</th>
<th>Product</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (2.0 equiv)</td>
<td></td>
<td></td>
<td>Uncharacterizable Mixture of Products</td>
<td>0.1 equiv PPh₃ used as additive and THF as solvent</td>
</tr>
<tr>
<td>2</td>
<td>13 (2.0 equiv)</td>
<td></td>
<td></td>
<td>Uncharacterizable Mixture of Products</td>
<td>0.1 equiv PPh₃ used as additive and toluene as solvent</td>
</tr>
<tr>
<td>3</td>
<td>13 (2.0 equiv)</td>
<td></td>
<td></td>
<td>Uncharacterizable Mixture of Products</td>
<td>0.1 equiv PPh₃ used as additive and THF used as solvent</td>
</tr>
<tr>
<td>4</td>
<td>13 (2.0 equiv)</td>
<td></td>
<td></td>
<td>Uncharacterizable Mixture of Products</td>
<td>0.1 equiv PPh₃ used as additive, toluene as solvent, and addition pump used to add dipolarophile over 3 hours</td>
</tr>
<tr>
<td>5</td>
<td>13 (2.0 equiv)</td>
<td></td>
<td></td>
<td>Uncharacterizable Mixture of Products</td>
<td>0.1 equiv PPh₃ used as additive and toluene as solvent</td>
</tr>
<tr>
<td>6</td>
<td>13 (2.0 equiv)</td>
<td></td>
<td></td>
<td>Uncharacterizable Mixture of Products</td>
<td>0.1 equiv PPh₃ used as additive and toluene as solvent</td>
</tr>
<tr>
<td>7</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td></td>
<td>Starting Material Recovered</td>
<td>Toluene as solvent</td>
</tr>
<tr>
<td>8</td>
<td>13 (2.0 equiv)</td>
<td>19 (2.0 equiv)</td>
<td></td>
<td>Starting Material Recovered</td>
<td>0.1 equiv PPh₃ used as additive and toluene as solvent</td>
</tr>
</tbody>
</table>
It is expected that the low boiling point of many of the dipolarophiles contributed to the overall complex nature of the product mixture, as the dipolarophile may have evaporated before it was able to engage in the [3+2] dipolar cycloaddition. It is clear from the results generated from many different dipolarophiles that this area certainly warrants further studies.

### 3.4 Conclusions and Future Work

While an appropriate dipolarophile was not found for the synthesis of peduncularine, the information gathered is very important and allows the methodology to be further understood. For the data collected it is clear that the developed methodology is very complex and very specific dipolarophiles must be used. Future work will focus on identifying a dipolarophile suitable for the process and completing the total synthesis.
4.1 Methods and Materials

Commercially available starting materials were purchased from Aldrich, Fischer Scientific, or Acros Organics and used as received. When necessary, tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried using a Glass Contour solvent purification system by SG Water USA, LLC. HPLC grade acetonitrile was used as received from VWR International. If necessary, air or moisture sensitive reactions were carried out under an inert atmosphere of nitrogen.

Analytical thin layer chromatography (TLC) was performed on Whatman Partisil® KF6 0.25 mm silica gel plates with UV indicator. Visualization was accomplished by irradiation under a 254 nm UV lamp followed by staining with iodine. Column chromatography on silica gel was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh).

$^1$H NMR spectra were recorded on a Varian Unity Inova 500 (500 MHz) or Bruker ARX 500 (500 MHz) spectrometer. $^{13}$C NMR spectra were recorded on a Varian Unity Inova 500 (125 MHz) or Bruker ARX 500 (125 MHz) spectrometer. Chemical shifts are recorded in parts per million (ppm) with the solvent resonance as the internal standard (chloroform-$d$: 7.26 ppm for $^1$H NMR and 77.2 ppm for $^{13}$C; DMSO-$d_6$: 2.50 ppm for $^1$H
NMR and 39.5 ppm for $^{13}$C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and number of protons. IR spectra were recorded on a Thermo Nicolet FT200 FT-IR or Shimadzu IR-Affinity FT-IR spectrometer with an attenuated total reflectance (ATR) head. Mass spectra were obtained on a Varian Saturn 2100T GC/MS in CI mode using helium as the carrier gas or using an Applied Biosystems 4000 Q Trap LC/MS/MS in positive or negative APCI mode. Melting points were obtained on a Mel-Temp apparatus and are uncorrected.

4.2 Experimental Procedures for DEVELOPMENT OF A NEW ROUTE TO AZOMETHINE YLIDES TO YIELD 5-ALKENYL SUBSTITUTED PYRROLIDINES

Ethyl 4,6-dioxo-5-phenyl-3-vinyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (21).

To a stirred solution of amine 13 (0.15 mL, 2.0 mmol) in MeCN (0.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.0 mmol). After 15 min, 2.5 mL of additional MeCN and
phenyl maleimide (173 mg, 1.0 mmol) were added and stirred until homogenous. AgOAc (16 mg, 0.10 mmol) and Et₃N (0.28 mL, 2.0 mmol) were added. After 24 h, the reaction mixture was partitioned between CH₂Cl₂ (15 mL) and saturated NH₄Cl (20 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated, and the residue purified by column chromatography (99:1 EtOAc:MeOH) to afford pyrrolidine 21 (263 mg, 84% yield) as a white solid: $R_f = 0.44$ (60:40:1 EtOAc:hexanes:NH₄OH); IR (neat) 3338, 2983, 1706, 1499, 1378, 1180, 911 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.46-7.42 (m, 2H), 7.38-7.35 (m, 1H), 7.25-7.23 (m, 2H), 6.08 (ddd, $J = 17.1$, 10.5, 6.5 Hz, 1H), 5.43 (dt, $J = 17.1$, 1.2 Hz, 1H), 5.31 (dt, $J = 10.4$, 1.2 Hz, 1H), 4.31 (qd, $J = 7.2$, 1.3 Hz, 2H), 4.06 (d, $J = 7.4$ Hz, 1H), 3.97 (dd, $J = 7.9$, 6.7 Hz, 1H), 3.69 (t, $J = 7.6$ Hz, 1H), 3.47 (t, $J = 8.0$ Hz, 1H), 1.34 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 174.0, 169.6, 133.6, 131.5, 128.9, 128.5, 126.3, 117.5, 62.9, 62.5, 61.5, 49.1, 48.9, 13.9; high resolution mass spectrum (ESI) m/z 315.1340 [(M + H)+; calcd for C₁₇H₁₉N₂O₄+: 315.1339].

[Diagram of compound 22]

**Ethyl 4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (22).** To a stirred solution of amine 19 (0.21 mL, 2.0 mmol) in MeCN (0.5 mL) at rt was added
ethyl glyoxylate (0.40 mL, 2.0 mmol). After 10 min, 2.5 mL of additional MeCN and phenyl maleimide (173 mg, 1.0 mmol) were added and stirred until homogenous. AgOAc (16 mg, 0.10 mmol) and Et₃N (0.28 mL, 2.0 mmol) were added. After 24 h, the reaction mixture was partitioned between CH₂Cl₂ (15 mL) and saturated NH₄Cl (20 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated, and the residue purified by column chromatography (90:8:2:1 Et₂O:EtOAc:MeOH:NH₄OH) to afford pyrrolidine 22 (311 mg, 86% yield) as a white solid: Rₓ = 0.50 (60:40:1 EtOAc:hexanes:NH₄OH); mp 186–190 °C; IR (neat) 3336, 2986, 1706, 1497, 1378, 1198 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, J = 7.0 Hz, 2H), 7.39 (q, J = 8.1 Hz, 6H), 7.16 (d, J = 7.7 Hz, 2H), 4.63 (dd, J = 8.6, 5.7 Hz, 1H), 4.39-4.32 (m, 2H), 4.15 (t, J = 6.0 Hz, 1H), 3.75 (t, J = 7.3 Hz, 1H), 3.59 (t, J = 8.2 Hz, 1H), 2.54 (t, J = 5.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 175.1, 173.7, 169.7, 136.9, 131.7, 128.9, 128.4, 128.3, 128.2, 127.1, 126.1, 63.9, 61.9, 61.3, 49.4, 48.3, 14.1; high resolution mass spectrum (ESI) m/z 365.1496 [(M + H)⁺; calcd for C₂₁H₂₁N₂O₄⁺: 365.1496].
Ethyl 2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-4,6-dioxo-5-phenyl-3-vinyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (23). To a stirred mixture of amine 13 (0.375 mL, 5.00 mmol) in acetonitrile (2.5 mL) at rt was added ethyl glyoxylate (1.00 mL, 5.00 mmol). After 15 min, 12.5 mL of additional acetonitrile was added along with phenyl maleimide (0.865 g, 5.00 mmol) and the solid was allowed to dissolve. After this time AgOAc (0.08 g, 0.48 mmol) and Et₃N (1.4 mL, 5.00 mmol) were added sequentially. After 18 h, the reaction mixture was diluted with dichloromethane (75 mL), diluted further with saturated NH₄Cl (100 mL), and extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with brine (250 mL), dried (Na₂SO₄), concentrated, and the residue purified by column chromatography (1% MeOH in EtOAc plus 1% NH₄OH) to afford pyrrolidine 23 (629.5 mg, 52% yield) as a light yellow solid: mp 145 - 155 °C; R₇ = 0.75 (1% MeOH in EtOAc); IR (neat) 2975, 2147, 1956, 1698, 1600, 1495, 1378, 1179, 1025, 937, 859, 755, 694, 624 cm⁻¹; ¹H NMR (500 MHz; CDCl₃): δ 7.47 (dd, J = 7.8, 5.0 Hz, 4H), 7.40 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.97 (dt, J = 17.0, 9.9 Hz, 1H), 5.41 (t, J = 14.1 Hz, 2H), 4.52 (d, J = 7.9 Hz, 1H), 4.12 (q, J = 7.1 Hz, 1H), 4.04 (dd, J = 9.7, 8.3 Hz, 1H), 3.64 (t, J = 8.1 Hz, 1H), 3.43 (q, J = 7.6 Hz, 1H), 3.20 (dd, J = 19.1, 10.2 Hz, 1H), 2.85
Cinnamylamine (24). To a 0.12 M solution of oxime 29 (1.0 g, 6.78 mmol) in acetic acid (100 mL) at rt was added Zn dust (1.77 g, 27.12 mmol) over 30 minutes. The solution was allowed to stir until the disappearance of oxime by TLC. The reaction mixture was filtered and the acetic acid removed by rotary evaporation. The resulting solution was washed with 1M NaOH (3 x 50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), and concentrated to afford amine 58 (826.5 mg, 92% yield) as a red-orange oil: 

\[ R_f = 0.43 \ (1\% \ \text{MeOH in EtOAc}); \ \text{IR} \ (\text{neat}) \ 3024, 2924, 1589, 1450, 1381, 1303, 1111, 1072, 964, 740 \ \text{cm}^{-1}; \ \text{¹H NMR} \ (500 \ \text{MHz; CDCl₃}): \ \delta \ 7.38 \ (d, J = 7.6 \ \text{Hz}, 2\text{H}), 7.32 \ (t, J = 7.6 \ \text{Hz}, 2\text{H}), 7.23 \ (t, J = 8.1 \ \text{Hz}, 1\text{H}), 6.51 \ (d, J = 15.8 \ \text{Hz}, 1\text{H}), 6.32 \ (dt, J = 15.8, 5.9 \ \text{Hz}, 1\text{H}), 3.48 \ (d, J = 5.3 \ \text{Hz}, 1\text{H}), 2.70 \ (td, J = 13.1, 5.8 \ \text{Hz}, 2\text{H}). \ \text{¹³C NMR} \ (125 \ \text{MHz, CDCl₃}): \ \delta \ 137.0, 130.1, 128.6, 128.4, 127.4, 126.3, 44.0. \]
2-(3-methylbut-2-enyl)isoindoline-1,3-dione (31). A stirred solution of phthalimide (2.21 g, 15.00 mmol), triphenylphosphine (3.93 g, 15.00 mmol), and prenyl alcohol (1.15 mL, 15.00 mmol) in 20 mL of dry THF was cooled to 0 °C. Diethyl azodicarboxylate (DEAD) (2.35 mL, 15.00 mmol) in 15 mL dry THF was added dropwise over 20 min. The reaction mixture was then allowed to warm to room temperature and stir overnight. The solvent was evaporated under reduced pressure and the crude material suspended in Et₂O. The resulting precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (CH₂Cl₂) to afford N-substituted phthalimide 31 (2.74 g, 85% yield) as a white solid: mp 84 – 87 °C, R_f = 0.58 (CH₂Cl₂); IR (neat) 1697, 1612, 1319, 1172, 1095, 941, 856, 709 cm⁻¹; ¹H NMR (500 MHz; CDCl₃): δ 7.81 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.4, 3.1, 2H), 5.26 (ttd, J = 7.2, 2.8, 1.4 Hz, 1H), 4.25 (d, J = 7.2 Hz, 2H), 1.82 (d, J = 0.7 Hz, 3H), 1.69 (d, J = 0.8 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 168.2, 137.3, 133.9, 131.5, 123.2, 118.4, 35.9, 25.8, 18.1.
3-methylbut-2-en-1-amine hydrochloride (34). To a stirred solution of 31 (2.63 g, 5.00 mmol) in EtOH (20 mL) was added hydrazine hydrate (0.60 mL, 5.00 mmol). The reaction mixture was allowed to stir at reflux for 5.5 h. The suspension was cooled, filtered, acidified with hydrochloric acid, and filtered once more. The filtrate was concentrated under reduced pressure and the residue was crystallized in Et₂O to afford hydrochloride salt 34 (1.13 g, 76% yield) as a white solid: mp 171 – 176 °C; IR (neat) 2912, 1596, 1468, 1225, 1106, 842, 516 cm⁻¹; ¹H NMR (500 MHz; DMSO-d₆): δ 8.17 (s, 3H), 5.23 (t, J = 7.2 Hz, 1H), 3.35 (quintet, J = 6.0 Hz, 2H), 1.70 (s, 3H), 1.64 (s, 3H). ¹³C NMR (125 MHz, DMSO-d₆) δ 138.6, 117.1, 36.4, 25.5, 17.9.

2-(2-methylallyl)isoindoline-1,3-dione (33). A stirred solution of phthalimide (2.21 g, 15.00 mmol), triphenylphosphine (3.93 g, 15.00 mmol), and isobutyl alcohol (1.26 mL, 15.00 mmol) in THF (20 mL) was cooled to 0 °C. Diethyl azodicarboxylate (DEAD) (2.35 mL, 15.00 mmol) in 15 mL dry THF was added dropwise over 20 min. The reaction
mixture was then allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the crude material suspended in Et$_2$O. The resulting precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (CH$_2$Cl$_2$) to afford $N$-substituted phthalimide 33 (2.52 g, 83% yield) as a white solid: mp 81 – 83 °C, $R_f = 0.40$ (CH$_2$Cl$_2$); IR (neat) 1766, 1708, 1427, 1390, 1122, 948, 885, 725, 709, 532, 518 cm$^{-1}$; $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.86 (dd, $J = 5.5$, 3.0 Hz, 2H), 7.72 (dd, $J = 5.4$, 3.1, 2H), 4.88 (d, $J = 2.6$, 1.3 Hz, 1H), 4.81 (t, $J = 1.0$ Hz, 1H), 4.22 (s, 2H), 1.77 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.5, 138.8, 133.4, 131.5, 122.8, 111.4, 42.7, 19.8.

2-methylprop-2-en-1-amine hydrochloride (36). A stirred solution of phthalimide 33 (4.77 g, 23.7 mmol) in EtOH (96 mL) was added hydrazine hydrate (1.15 mL, 23.7 mmol). The reaction mixture was allowed to stir at reflux for 5.5 h. The suspension was cooled, filtered, acidified with hydrochloric acid, and filtered once more. The filtrate was concentrated under reduced pressure and the residue crystallized in Et$_2$O to afford hydrochloride salt 36 (2.20 mg, 87% yield) as a white solid: mp 164 – 168 °C; IR (neat) 2904, 2727, 2638, 1600, 1516, 1435, 887 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-$d_6$): $\delta$ 8.25
(s, 3H), 4.99 (d, $J = 6.53$ Hz, 2H), 3.37 (q, $J = 5.69$ Hz, 2H), 1.76 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 138.4, 113.9, 43.5, 20.7.

(E)-ethyl 4,6-dioxo-5-phenyl-3-styryloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (30). To a stirred solution of amine 24 (260 mg, 2.0 mmol) in MeCN (0.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.0 mmol). After 15 min, Et$_3$N (0.28 mL, 2.0 mmol), AgOAc (16 mg, 0.10 mmol), phenyl maleimide (173 mg, 1.0 mmol), and MeCN (2.5 mL) were added. After 24 h, the reaction mixture was partitioned between CH$_2$Cl$_2$ (20 mL) and saturated NH$_4$Cl (25 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by column chromatography (60:40:1 EtOAc:hexanes:NH$_4$OH) to afford pyrrolidine 30 (312 mg, 80% yield) as an orange solid: mp 162–170 °C; $R_f$ = 0.42 (60:40 EtOAc:hexanes); IR (neat) 1708, 1492, 1384, 1207, 1118, 972, 756, 690 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 (dt, $J = 19.8$, 8.0 Hz, 6H), 7.30 (t, $J = 7.6$ Hz, 2H), 7.24 (d, $J = 7.7$ Hz, 2H), 6.74 (d, $J = 15.8$ Hz, 1H), 6.42 (dd, $J = 15.9$, 6.9 Hz, 1H), 4.32 (q, $J = 7.0$ Hz, 3H), 4.12 (t, $J = 7.3$ Hz, 1H), 4.10 (d, $J = 7.6$ Hz, 1H), 3.71 (t, $J = 7.7$ Hz, 1H), 3.52 (t, $J = 7.9$ Hz, 1H), 1.35 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.0, 174.3, 102.
169.9, 136.5, 132.8, 131.8, 129.3, 128.8, 128.1, 126.9, 126.6, 125.2, 123.0, 61.9, 49.8, 49.0, 14.3; high resolution mass spectrum (ESI) \( m/z \) 391.1654 \([\text{M} + \text{H}]^+\); calcd for \( \text{C}_{23}\text{H}_{23}\text{N}_{2}\text{O}_{4}^+ \): 391.1652.

![Chemical structure](image)

**Ethyl 4,6-dioxo-5-phenyl-3-(prop-1-en-2-yl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (38).** To a stirred mixture of amine hydrochloride 34 (107 mg, 1.0 mmol) and THF (1.5 mL) at rt was added ethyl glyoxylate (0.20 mL, 1.0 mmol) and Et\(_3\)N (0.14 mL, 1.0 mmol). After 30 min, AgOAc (8 mg, 0.05 mmol), Et\(_3\)N (0.28 mL, 2.0 mmol), and phenyl maleimide (86 mg, 0.5 mmol) were added. After 24 h, the reaction mixture was partitioned between CH\(_2\)Cl\(_2\) (20 mL) and saturated NH\(_4\)Cl (25 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na\(_2\)SO\(_4\)), concentrated, and the residue purified by column chromatography (50:50 EtOAc:hexanes) to afford pyrrolidine 38 (108 mg, 66\% yield) as a light yellow tack: \( R_f = 0.66 \) (70:30 CH\(_2\)Cl\(_2\):EtOAc); IR (neat) 2980, 2933, 1708, 1500, 1382, 1195, 1182, 692, 520 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.41 (t, \( J = 7.8 \) Hz, 2H), 7.34 (t, \( J = 7.4 \) Hz, 1H), 7.19 (d, \( J = 7.9 \) Hz, 2H), 5.17 (s, 1H), 4.99 (s, 1H), 4.29 (dtt, \( J = 11.0, 7.3, 3.8 \) Hz, 2H), 4.00 (d, \( J = 7.0 \) Hz, 1H), 3.81 (d, \( J = 8.2 \) Hz, 1H), 3.66 (t, \( J = 7.3 \) Hz, 1H), 3.51 (t, \( J = 8.0 \) Hz, 1H).
Hz, 1H), 1.95 (s, 3H), 1.33 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 174.9, 174.0, 169.7, 141.5, 131.8, 129.1, 128.6, 126.5, 126.5, 111.4, 65.3, 62.3, 61.5, 48.7, 48.1, 21.5, 14.2; high resolution mass spectrum (ESI) \( m/z \) 329.1496 [(M + H)\(^{+}\)]; calcd for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_4\)\(^{+}\): 329.1496.

![Chemical Structure](39)

(E)-ethyl 4,6-dioxo-5-phenyl-3-(prop-1-enyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (39). To a stirred mixture of amine hydrochloride 35 (214 mg, 2.0 mmol) and MeCN (1.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.0 mmol) and Et\(_3\)N (0.28 mL, 2.0 mmol). After 30 min, AgOAc (16 mg, 0.10 mmol), Et\(_3\)N (0.28 mL, 2.0 mmol), phenyl maleimide (173 mg, 1.0 mmol), and MeCN (1.5 mL) were added. After 24 h, the reaction mixture was partitioned between CH\(_2\)Cl\(_2\) (20 mL) and saturated NH\(_4\)Cl (25 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na\(_2\)SO\(_4\)), concentrated, and the residue purified by column chromatography (99:1: MeOH:EtOAc:Et\(_3\)N) to afford pyrrolidine 39 (230 mg, 70% yield) as a light yellow foam: \( R_f = 0.59 \) (99:1 EtOAc:MeOH); IR (neat) 1736, 1707, 1375, 1197, 1178, 956, 854, 756, 691 cm\(^{-1}\); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.43 (t, \( J = 7.6 \) Hz, 2H), 7.35 (t, \( J = 7.5 \), 1H), 7.23 (d, \( J = 7.3 \) Hz, 2H), 5.86-5.77 (m, 1H), 5.61 (ddd, \( J = 104 \))
15.2, 7.4, 1.6 Hz, 1H), 4.27 (qd, $J = 7.2, 1.7$ Hz, 2H), 3.99 (t, $J = 6.3$ Hz, 1H), 3.88 (q, $J =$ 6.4 Hz, 1H), 3.63 (t, $J = 7.7$ Hz, 1H), 3.37 (t, $J = 8.0$ Hz, 1H), 2.19 (s, 1H), 1.72 (d, $J =$ 6.5 Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.0, 174.3, 169.8, 131.7, 129.8, 129.2, 128.7, 126.6, 126.5, 63.1, 62.8, 61.7, 49.5, 49.2, 17.9, 14.2; high resolution mass spectrum (ESI) $m/z$ 329.1496 [(M + H)$^+$; calcd for C$_{18}$H$_{21}$N$_2$O$_4$+$^+$: 329.1496].

![Chemical structure](image)

**Ethyl 3-(2-methylprop-1-enyl)-4,6-dioxo-5-phenylotahydropyrrolo[3,4-c]pyrrole-1-carboxylate (40).** To a stirred mixture of amine hydrochloride 36 (242 mg, 2.0 mmol) and MeCN (1.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.0 mmol) and Et$_3$N (0.28 mL, 2.0 mmol). After 30 min, AgOAc (16 mg, 0.10 mmol), Et$_3$N (0.28 mL, 2.0 mmol), phenyl maleimide (173 mg, 1.0 mmol), and MeCN (1.5 mL) were added. After 24 h, the reaction mixture was partitioned between CH$_2$Cl$_2$ (20 mL) and saturated NH$_4$Cl (25 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by column chromatography (70:30:1 CH$_2$Cl$_2$:EtOAc:Et$_3$N) to afford pyrrolidine 40 (219 mg, 64% yield) as a light yellow tack: $R_f = 0.49$ (70:30 CH$_2$Cl$_2$:EtOAc); IR (neat) 2980, 1707,
1375, 1180, 756, 691, 492 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.46 (t, \(J = 7.6\) Hz, 2H), 7.38 (t, \(J = 7.5\), 1H), 7.27 (d, \(J = 7.2\) Hz, 2H), 5.27 (dt, \(J = 8.9, 1.4\) Hz, 1H), 4.31 (q, \(J = 7.0\) Hz, 2H), 4.17 (t, \(J = 8.6\) Hz, 1H), 4.04 (d, \(J = 7.6\) Hz, 1H), 3.68 (t, \(J = 7.7\) Hz, 1H), 3.39 (t, \(J = 8.0\) Hz, 1H), 1.78 (dd, \(J = 9.5, 1.2\) Hz, 6H), 1.34 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.1, 174.3, 169.9, 138.4, 131.8, 129.2, 128.7, 126.5, 119.7, 63.0, 61.8, 59.3, 49.6, 49.4, 25.9, 18.6, 14.2; high resolution mass spectrum (ESI) \(m/z\) 343.1654 [(M + H)]\(^+\); calcd for C\(_{19}\)H\(_{33}\)N\(_2\)O\(_4\)]\(^+\): 343.1652.

![Ethyl 3-allyl-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (48)](image)

**Ethyl 3-allyl-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (48).** To a stirred mixture of amine 41 (0.147 g, 1.00 mmol) in toluene (3.0 mL) with molecular sieves (150 mg) at rt was added ethyl glyoxylate (0.20 mL, 1.00 mmol). After 15 min, AgOAc (0.25 g, 1.50 mmol), phenyl maleimide (0.346 g, 2.00 mmol) and Et\(_3\)N (0.14 mL, 1.00 mmol) were added. After 26 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL), filtered, diluted further with saturated NaHCO\(_3\) (20 mL), and extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried (Na\(_2\)SO\(_4\)), concentrated, and the residue purified by column chromatography (30% EtOAc in hexanes plus 1% Et\(_3\)N) to afford pyrrolidine 48 (167 mg, 41% yield) as a light
yellow solid: mp 146 – 148 °C; \( R_f = 0.37 \) (30% EtOAc in hexanes); IR (neat) 3266, 3222, 2950, 1731.51, 1731.19, 1509, 1435, 1305, 1243, 1206, 1170, 1155, 1027, 996 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.63 (d, \( J = 7.7 \) Hz, 2H), 7.28 (m, 6H), 6.86 (d, \( J = 7.5 \) Hz, 2H), 4.32 (dq, \( J = 2.1, 7.2 \) Hz, 2H), 4.25 (dd, \( J = 5.7, 6.4 \) Hz, 1H), 3.74 (dd, \( J = 7.0 \) Hz, 1H), 3.34 (d, \( J = 7.6 \) Hz, 1H), 3.03 (dd, \( J = 4.9, 14.2 \) Hz, 1H), 2.60 (dd, \( J = 9.2, 14.2 \) Hz, 2H), 2.58 (d, \( J = 5.4 \) Hz, 2H), 1.39 (t, \( J = 7.2 \) Hz, 3H); \(^1^3\)C NMR (500 MHz, CDCl\(_3\)) \( \delta \) 174.6, 173.3, 170.0, 139.4, 132.2, 131.4, 128.6, 128.1, 127.8, 127.4, 126.8, 125.9, 119.7, 68.9, 61.2, 59.1, 55.0, 48.6, 43.1, 13.9.

**Ethyl 3-allyl-4,6-dioxo-5-phenyl-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (49).** To a stirred mixture of amine 47 (0.43 g, 2.00 mmol) in toluene (3.0 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.00 mmol). After 15 min, AgOAc (0.016 g, 0.1 mmol), phenyl maleimide (0.173 g, 1.00 mmol) and Et\(_3\)N (0.28 mL, 2.00 mmol) were added. After 24 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (10 mL), filtered, diluted further with saturated NH\(_4\)Cl (20 mL), and extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried (Na\(_2\)SO\(_4\)), concentrated, and the residue purified by column chromatography (gradient,
20% EtOAc in hexanes to 50% EtOAc in hexanes) to afford pyrrolidine 49 (76.6 mg, 16% yield) as a white foam: $R_f = 0.58$ (50% EtOAc in hexanes); $^1$H-NMR (500 MHz; CDCl$_3$): $\delta$ 7.79 (d, $J = 8.3$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.30 (td, $J = 13.6$, 6.0 Hz, 4H), 6.87 (d, $J = 7.9$ Hz, 2H), 5.36 (dtd, $J = 15.6$, 10.2, 5.6 Hz, 1H), 5.13 (s, 1H), 5.10 (d, $J = 8.7$ Hz, 1H), 4.33 (td, $J = 14.5$, 7.5 Hz, 3H), 3.79 (t, $J = 7.3$ Hz, 1H), 3.43 (d, $J = 7.6$ Hz, 1H), 3.01 (dd, $J = 14.1$, 5.0 Hz, 1H), 2.67 (dd, $J = 14.2$, 9.1 Hz, 1H), 2.61 (d, $J = 5.3$ Hz, 1H), 1.38 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 174.6, 173.6, 170.3, 143.9, 131.8, 131.5, 129.8, 129.2, 128.8, 127.8, 126.2, 125.3, 125.2, 120.9, 69.4, 61.9, 59.6, 55.3, 48.8, 43.9, 14.3.

3',5'-diphenyl-3',3a'-dihydro-2'H-spiro[indene-2,1'-pyrrolo[3,4-c]pyrrole]

1,3,4',6'(5'H,6a'H)-tetraone (51). To a stirred mixture of amine 19 (0.210 mL, 2.00 mmol) and MeCN (10 mL) at 0 °C was added ninhydrin (0.356 g, 2.00 mmol) and AgOAc (0.016 g, 0.10 mmol). After 5 min, Et$_3$N (0.28 mL, 2.00 mmol) and phenyl maleimide (0.173 g, 1.00 mmol) were added sequentially. The solution was then diluted with 10 mL of additional MeCN. After 1.5 h, the reaction mixture was diluted with
CH₂Cl₂ (20 mL), diluted further with saturated NH₄Cl (25 mL), and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated, and the residue purified by recrystallization in MeOH and then Et₂O to afford pyrrolidine 51 (250 mg, 60% yield) as a light yellow solid: mp 252 – 253 °C; Rₘ = 0.58 (20% acetone in toluene); IR (neat) 3321, 3057, 2361, 1704, 1698, 1596, 1494, 1389, 1198, 732 cm⁻¹; ¹H NMR (500 MHz; CDCl₃): δ 8.12 (t, J = 4.4 Hz, 1H), 8.08 (t, J = 4.4 Hz, 1H), 7.97 (m, 2H), 7.46 (dd, J = 17.9, 7.68 Hz, 4H), 7.38 (t, J = 6.8 Hz, 3H), 7.33 (t, J = 6.0 Hz, 3H), 5.54 (t, J = 7.8 Hz, 1H), 3.92 (t, J = 7.9 Hz, 1H), 3.67 (d, J = 7.8 Hz, 1H), 2.82 (d, J = 7.8 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 200.9, 197.3, 173.9, 173.2, 141.9, 139.5, 137.1, 137.0, 136.3, 131.7, 129.2, 128.8, 128.5, 128.4, 127.2, 126.8, 124.4, 124.3, 71.6, 65.1, 52.4, 51.3.

5'-phenyl-3'-vinyl-3',3a'-dihydro-2'H-spiro[indene-2,1'-pyrrolo[3,4-c]pyrrole]-1,3,4,6'(5'H,6a'H)-tetraone (52). To a stirred mixture of amine 13 (0.150 mL, 2.00 mmol) and MeCN (10 mL) at 0 °C was added ninhydrin (0.356 g, 2.00 mmol) and AgOAc (0.016 g, 0.10 mmol). After 15 min, Et₃N (0.28 mL, 2.00 mmol) and phenyl maleimide (0.173 g, 1.00 mmol) were added sequentially. The solution was then diluted
with 10 mL of additional MeCN. After 5.5 h, the reaction mixture was diluted with CH₂Cl₂ (20 mL), diluted further with saturated NH₄Cl (25 mL), and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated, and the residue purified by column chromatography (20% acetone in toluene) to afford pyrrolidine 52 (77.4 mg, 21% yield) as a light yellow solid: mp 209 – 211 °C; Rf = 0.52 (20% acetone in toluene); IR (neat) 3347, 1702, 1594, 1484, 1385, 1178, 871, 728, 695, 608 cm⁻¹; ¹H NMR (500 MHz; CDCl₃): δ 8.04 (td, J = 4.32, 2.04 Hz, 2H), 7.92 (m, 2H), 7.48 (t, J = 7.75 Hz, 2H), 7.39 (t, J = 7.63, 3H), 6.19 (ddd, J = 17.18, 10.38, 6.87 Hz, 1H), 5.41 (d, J = 17.11 Hz, 1H), 5.31 (d, J = 10.45 Hz, 1H), 4.74 (q, J = 8.47 Hz, 1H), 3.74 (t, J = 7.65 Hz, 1H), 3.60 (d, J = 7.87 Hz, 1H), 2.53 (d, J = 9.86 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 199.7, 197.5, 174.2, 173.7, 141.6, 139.9, 137.1, 136.9, 133.4, 131.6, 129.3, 128.9, 126.7, 124.5, 124.3, 118.4, 72.1, 64.7, 52.8, 51.5.

4-benzoyl-2-phenyl-6-vinyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (55). To a stirred solution of amine 13 (0.15 mL, 2.0 mmol) in MeCN (3 mL) at rt was added phenylglyoxal monohydrate (304 mg, 2.0 mmol). After 1.5 h, AgOAc (16 mg, 0.10 mmol), Et₃N (0.28 mL, 2.0 mmol) and phenyl maleimide (174 mg, 1.0 mmol) were
added. After 24 h, the reaction mixture was partitioned between CH$_2$Cl$_2$ (20 mL) and saturated NH$_4$Cl (25 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by trituration (Et$_2$O) to afford pyrrolidine 55 (296 mg, 86% yield) as a tan solid: mp 158–160 °C; $R_f$ = 0.41 (70:30 CH$_2$Cl$_2$:EtOAc); IR (neat) 3579, 3299, 3221, 3056, 2863, 2505, 1780, 1704, 1676, 1600, 1495, 1369, 1178, 920, 756, 688 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J$ = 8.1 Hz, 2H), 7.62 (t, $J$ = 7.4 Hz, 1H), 7.52 (t, $J$ = 7.7 Hz, 2H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 2H), 7.19 (d, $J$ = 7.2 Hz, 1H), 6.18 (ddd, $J$ = 17.0, 10.7, 6.3 Hz, 1H), 5.48 (dt, $J$ = 17.2, 1.2 Hz, 1H), 5.35 (dt, $J$ = 10.6, 1.1 Hz, 1H), 5.02 (d, $J$ = 7.7 Hz, 3H), 4.14 (t, $J$ = 6.8 Hz, 1H), 3.89 (t, $J$ = 7.7 Hz, 1H), 3.59 (t, $J$ = 8.0 Hz, 1H), 2.73 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 196.1, 174.5, 174.2, 136.4, 133.9, 133.5, 131.6, 129.2, 129.0, 128.8, 128.3, 126.5, 117.7, 65.5, 63.4, 51.4, 51.0; high resolution mass spectrum (ESI) m/z 347.1392 [(M + H)$^+$; calcd for C$_{21}$H$_{19}$N$_2$O$_3^+$: 347.1390].
(E)-4-benzoyl-2-phenyl-6-styryltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (56). To a stirred solution of amine 24 (260 mg, 2.0 mmol) in MeCN (3 mL) at rt was added phenylglyoxal monohydrate (304 mg, 2.0 mmol). After 1.5 h, AgOAc (16 mg, 0.10 mmol), Et₃N (0.28 mL, 2.0 mmol) and phenyl maleimide (173 mg, 1.0 mmol) were added. After 24 h, the reaction mixture was partitioned between CH₂Cl₂ (20 mL) and saturated NH₄Cl (25 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), concentrated, and the residue purified by trituration (Et₂O) to afford pyrrolidine 56 (284 mg, 67% yield) as a brown solid: mp 155–160 °C; Rₛ = 0.27 (70:30 CH₂Cl₂:EtOAc); IR (neat) 1711, 1389, 1189, 1177, 967, 751, 691 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09 (d, J = 7.3 Hz, 2H), 7.67 (t, J = 7.4, 1H), 7.57 (t, J = 11.4, 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.4 Hz, 3H), 7.33 (dd, J = 15.8, 7.5 Hz, 4H), 7.20 (d, J = 7.3 Hz, 2H), 6.81 (d, J = 16.0 Hz, 1H), 6.52 (dd, J = 15.7, 6.6 Hz, 1H), 5.09 (d, J = 7.7 Hz, 1H), 4.32 (t, J = 7.2 Hz, 1H), 3.93 (t, J = 7.8 Hz, 1H), 3.67 (t, J = 7.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 196.9, 175.1, 174.4, 136.5, 133.9, 133.5, 131.5, 129.1, 129.0, 128.8, 128.3, 126.5, 117.7, 64.9, 61.7, 50.5; high resolution mass spectrum (ESI) m/z 423.1706 [(M + H)⁺; calcd for C₂₇H₂₃N₃O₃⁺: 423.1703].
(E)-4-benzoyl-2-phenyl-6-(prop-1-enyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (57). To a stirred mixture of amine hydrochloride 53 (214 mg, 2.0 mmol) and MeCN (1.5 mL) at rt was added phenylglyoxal monohydrate (304 mg, 2.0 mmol) and Et$_3$N (0.28 mL, 2.0 mmol). After 30 min, AgOAc (16 mg, 0.10 mmol), Et$_3$N (0.28 mL, 2.0 mmol), phenyl maleimide (173 mg, 1.0 mmol), and MeCN (1.5 mL) were added. After 24 h, the reaction mixture was partitioned between CH$_2$Cl$_2$ (20 mL) and saturated NH$_4$Cl (25 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by trituration (Et$_2$O) to afford pyrrolidine 57 (229 mg, 72% yield) as a yellow solid: mp 138–141 °C; $R_f$ = 0.53 (70:30 CH$_2$Cl$_2$:EtOAc); IR (neat) 1708, 1685, 1597, 1496, 1381, 1172, 759, 690 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J$ = 7.2 Hz, 2H), 7.61 (t, $J$ = 7.4 Hz, 1H), 7.50 (t, $J$ = 7.7 Hz, 2H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 1H), 7.20 (d, $J$ = 7.2 Hz, 2H), 5.91 (dq, $J$ = 14.6, 7.0 Hz, 1H), 5.71 (ddd, $J$ = 15.9, 7.2, 1.6 Hz, 1H), 4.98 (d, $J$ = 7.7 Hz, 1H), 4.07 (t, $J$ = 7.7 Hz, 1H), 3.86 (t, $J$ = 7.7 Hz, 1H), 3.52 (t, $J$ = 8.0 Hz, 1H), 1.78 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 196.2, 174.6, 174.3, 136.4, 133.8, 131.6, 130.0, 129.2, 129.0, 128.8, 128.3, 126.5, 126.2, 65.5, 63.3, 51.5, 51.2, 18.1; high resolution mass spectrum (ESI) $m/z$ 361.1547 [(M + H)$^+$; calcd for C$_{22}$H$_{21}$N$_2$O$_3^+$: 361.1547].
(a) $(2S,3R,4R,5R)$-2-ethyl 3,4-dimethyl 5-phenylpyrrolidin-2,3,4-tricarboxylate, (b) $(2R,3S,4S,5S)$-2-ethyl 3,4-dimethyl 5-phenylpyrrolidin-2,3,4-tricarboxylate (65). 

To a stirred mixture of amine 19 (0.210 mL, 2.00 mmol) and MeCN (0.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.00 mmol). After 15 min, AgOAc (0.016 g, 0.10 mmol), Et$_3$N (0.28 mL, 2.00 mmol) and dimethyl fumarate (0.144 g, 1.00 mmol) were added sequentially. The mixture was then diluted with 2.5 mL of additional MeCN. After 25 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL), diluted further with saturated NH$_4$Cl (25 mL), and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by column chromatography (30% EtOAc in hexanes) to afford pyrrolidine 65 (259.6 mg, 77% yield) as a yellow oil as a 1:3 mixture of inseparable diastereomers: $R_f = 0.24$ (30% EtOAc in hexanes); IR (neat) 2954, 2358, 2340, 2327, 1737, 1731, 1715, 1434, 1206, 1168, 1020, 910, 729, 699, 667, 647 cm$^{-1}$; (a) $^1$H NMR (500 MHz; CDCl$_3$): δ 7.26 (d, $J = 8.2$ Hz, 4H), 7.21 (dd, $J = 9.1$, 4.3 Hz, 1H), 4.63 (d, $J = 7.8$ Hz, 1H), 4.27 (d, $J = 7.1$ Hz, 1H), 4.23 (d, $J = 7.1$ Hz, 1H), 4.11 (d, $J = 7.8$ Hz, 1H), 3.72 (s, 3H), 3.59 (dd, $J = 7.6$, 2.7 Hz, 2H), 3.16 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H). (b) $^1$H NMR (500 MHz; CDCl$_3$): 7.65 (d, $J = 7.1$ Hz, 1H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.00 (t, $J = 7.5$ Hz, 2H), 6.93 (dd, $J = 5.6$, 2.3 Hz, 1H), 6.63 (d, $J = 7.0$ Hz, 1H), 6.31 (d, $J = 7.3$ Hz, 1H), 5.29 (d, $J = 9.9$ Hz, 1H), 4.40 (d, $J = 1.9$ Hz, 1H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.37 (dd, $J = 9.0$, 8.0 Hz, 2H), 1.15 (t, $J = 7.1$ Hz, 2H), 3.59 (s, 3H). (a) $^{13}$C NMR (125 MHz, CDCl$_3$):
CDCl$_3$) $\delta$ 172.7, 171.5, 138.4, 128.3, 127.8, 126.9, 65.4, 63.6, 61.5, 54.0, 52.5, 51.5, 50.7, 14.2 (b) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.8, 171.2, 139.9, 128.7, 128.1, 127.1, 66.9, 62.6, 61.5, 54.8, 52.3, 52.2, 51.8, 14.1.

(a) (2R,3R,4R,5R)-2-ethyl 3,4-dimethyl 5-styrylpyrrolidine-2,3,4-tricarboxylate, (b) (2S,3S,4S,5S)-2-ethyl 3,4-dimethyl 5-styrylpyrrolidine-2,3,4-tricarboxylate (66).

To a stirred mixture of amine 24 (0.26 g, 2.00 mmol) and MeCN (0.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.00 mmol). After 15 min, AgOAc (0.016 g, 0.10 mmol), Et$_3$N (0.28 mL, 2.00 mmol) and dimethyl fumarate (0.144 g, 1.00 mmol) were added sequentially. The solution was then diluted with 2.5 mL of additional MeCN. After 25 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL), diluted further with saturated NH$_4$Cl (25 mL), and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by column chromatography (60% EtOAc in hexanes plus 1% NH$_4$OH) to afford pyrrolidine 66 (214.0 mg, 59% yield) as an orange oil as a 1:3.5 mixture of inseparable diastereomers: $R_f = 0.61$ (60% EtOAc in hexanes); IR (neat) 1732, 1715, 1436, 1239, 1201, 1197, 1171, 1166, 1157, 1150, 746, 693 cm$^{-1}$; (a) $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.39 (d, $J = 8.04$ Hz, 1H), 7.33 – 7.28 (m, 4+4H), 6.61 (dd, $J = 15.78, 7.52$ Hz, 1H), 6.29
(d, J = 15.77, 1H), 4.33 – 4.29 (m, 2H), 4.31 (dd, J = 14.27, 7.12 Hz, 1H), 4.13 (d, J = 8.38 Hz, 1H), 3.93 (t, J = 8.02 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.51 (t, J = 7.26 Hz, 1H), 1.28 (t, J = 7.14 Hz, 3H). (b) $^1$H NMR (500 MHz; CDCl$_3$): δ 7.33 – 7.28 (m, 4+4H), 7.24 (d, J = 6.60 Hz, 1H), 6.60 (d, J = 15.79 Hz, 1H), 6.06 (dd, J = 15.80, 7.67, 1H), 4.29 (dd, J = 14.33, 7.18 Hz, 1H), 4.24 (dd, J = 12.78, 5.66 Hz, 2H), 4.09 (d, J = 7.66 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.58 (t, J = 7.27 Hz, 1H), 3.51 (t, J = 7.26 Hz, 1H), 1.30 (t, J = 7.14 Hz, 3H). (a) $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.7, 171.8, 172.1, 171.7, 136.5, 132.9, 128.7, 128.0, 126.6, 125.9, 63.8, 63.6, 61.8, 53.1, 52.6, 52.2, 50.7, 14.3. (b)$^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.6, 171.8, 171.4, 132.8, 128.7, 128.3, 127.9, 126.7, 65.4, 65.3, 62.4, 61.6, 53.4, 52.5, 52.4, 51.5, 14.2.

(a) (3'R,4'R,5'R)-dimethyl 1,3-dioxo-5'-phenyl-1,3-dihydrospiro[indene-2,2'-pyrrolidine]-3',4'-dicarboxylate, (b) (3'S,4'S,5'S)-dimethyl 1,3-dioxo-5'-phenyl-1,3-dihydrospiro[indene-2,2'-pyrrolidine]-3',4'-dicarboxylate (67). To a stirred mixture of amine 19 (0.210 mL, 2.00 mmol) and MeCN (10 mL) at 0 °C was added ninhydrin (0.356 g, 2.00 mmol) and AgOAc (0.016 g, 0.10 mmol). After 15 min, Et$_3$N (0.28 mL, 2.00 mmol) and dimethyl fumarate (0.144 g, 1.00 mmol) were added sequentially. The
solution was then diluted with 10 mL of additional acetonitrile. After 6 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL), diluted further with saturated NH$_4$Cl (25 mL), and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by column chromatography (60% EtOAc in hexanes) and then recrystallized in Et$_2$O to afford pyrrolidine 67 (178.1 mg, 45% yield) as a light orange foam as a 1:1 mixture of inseparable diastereomers: $R_f = 0.68$ (60% EtOAc in hexanes); IR (neat) 3320, 2953, 2136, 1989, 1731, 1708, 1594, 1452, 1435, 1260, 1170, 1010, 921, 700 cm$^{-1}$; (a) $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.06 (m, 2H), 7.91 (dd, $J = 5.89$, 2.27 Hz, 2H) 7.51 (d, $J = 7.43$ Hz, 2H), 7.35 (dt, $J = 10.98$, 7.64, 3H), 5.20 (d, $J = 9.66$ Hz, 1H), 4.34 (d, $J = 9.97$ Hz, 1H), 4.28 (td, $J = 9.85$, 0.65 Hz, 1H), 3.45 (s, $J = 0.59$ Hz, 3H), 3.41 (s, $J = 0.57$ Hz, 3H), 2.59 (s, 1H). (b) $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.06 (m, 2H), 7.91 (dd, $J = 5.89$, 2.27 Hz, 2H) 7.43 (d, $J = 7.53$ Hz, 2H), 7.35 (dt, $J = 10.98$, 7.64, 3H), 4.78 (d, $J = 10.11$ Hz, 1H), 4.19 (d, $J = 11.27$ Hz, 1H), 3.85 (ddd, $J = 11.19$, 10.24, 0.85 Hz, 1H), 3.66 (s, $J = 0.79$ Hz, 3H), 3.22 (s, $J = 0.78$ Hz, 3H), 2.59 (s, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 200.7, 200.6, 200.4, 198.7, 171.8, 171.5, 170.1, 169.6, 141.7, 141.3, 141.2, 140.0, 139.4, 136.6, 136.5, 136.3, 136.2, 128.8, 128.4, 128.3, 128.2, 127.6, 127.4, 124.1, 123.9, 123.8, 123.7, 70.7, 69.6, 67.3, 64.4, 55.4, 54.6, 52.8, 52.5, 52.42, 52.40, 51.9, 51.8.
(a) (2S,3R,4R,5S)-2-ethyl 3,4-dimethyl 5-vinylpyrrolidine-2,3,4-tricarboxylate, (b) (2R,3S,4S,5R)-2-ethyl 3,4-dimethyl 5-vinylpyrrolidine-2,3,4-tricarboxylate (68). To a stirred mixture of amine 13 (0.150 mL, 2.00 mmol) and MeCN (0.5 mL) at rt was added ethyl glyoxylate (0.40 mL, 2.00 mmol). After 15 min, AgOAc (0.016 g, 0.10 mmol), Et$_3$N (0.28 mL, 2.00 mmol) and dimethyl fumarate (0.144 g, 1.00 mmol) were added sequentially. The mixture was then diluted with 2.5 mL of additional MeCN. After 24 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL), diluted further with saturated NH$_4$Cl (25 mL), and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated, and the residue purified by column chromatography (75:23:2 Et$_2$O:hexanes:MeOH) to afford pyrrolidine 68 (189.9 mg, 66% yield) as a light yellow oil as a 1:3 mixture of inseparable diastereomers: $R_f = 0.71$ (75:23:2 Et$_2$O:hexanes:MeOH); IR (neat) 3647, 2986, 2360, 2341, 2328, 1727, 1434, 1194, 1167, 1014, 927, 862, 735, 679 cm$^{-1}$; (a) $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 5.65 (dtd, $J = 17.15$, 8.64, 2.58 Hz, 1H), 5.19 (d, $J = 17.02$ Hz, 1H), 5.07 (d, $J = 10.64$ Hz, 1H), 3.95 (dd, $J = 7.70$, 2.04 Hz, 1H), 3.65 (d, $J = 2.32$ Hz, 3H), 3.56 (d, $J = 2.26$ Hz, 3H), 3.40 (td, $J = 7.08$, 2.12 Hz, 3H), 3.34 (td, $J = 7.06$, 2.21 Hz, 3H), 1.20 (t, $J = 5.73$ Hz, 3H). (b) $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 5.86 (dtd, $J = 17.06$, 8.54, 2.55 Hz, 1H), 5.23 (d, $J = 2.41$ Hz, 1H), 4.00 (dd, $J = 8.38$, 2.31 Hz, 1H), 3.99 (d, 1H), 3.62 (d, $J = 2.50$ Hz, 3H), 3.58 (d, $J = 2.25$ Hz, 3H), 2.99 (td, $J = 8.34$, 2.17 Hz, 1H), 1.17 (t, $J = 3.52$ Hz, 1H). (a) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.5, 171.8, 171.4, 134.6, 117.6, 118
63.9, 63.3, 61.5, 52.7, 52.4, 51.8, 50.4, 14.0. (b) \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.4, 171.6, 171.1, 136.9, 117.4, 65.4, 62.4, 61.4, 52.9, 52.2, 52.1, 51.2, 13.9.

4.3 Experimental Procedures for APPLICATION OF METHODOLOGY – STUDIES TOWARD THE SYNTHESIS OF SPIROTRYPROSTATIN B

5'-(ethoxycarbonyl)-2-oxo-2'-vinylspiro[indoline-3,3'-pyrrolidine]-4'-carboxylic acid (78). To a stirred mixture of amine 13 (0.07 mL, 1.00 mmol) in CH\(_2\)Cl\(_2\) (0.5 mL) was added ethyl glyoxylate (0.20 mL, 2.0 mmol) and allowed to stir at rt for 15 minutes. Dipolarophile 76 (0.101 g, 0.50 mmol), AgOAc (0.008 g, 0.05 mmol) and Et\(_3\)N (0.14 mL, 1.00 mmol) were added and allowed to stir until complete conversion by TLC. After stirring for 2.5 h the reaction mixture was extracted CH\(_2\)Cl\(_2\) (3 x 20 mL), washed with NaHCO\(_3\) (25 mL), and brine (25 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, concentrated and the residue purified by column chromatography (50% EtOAc in hexanes) to yield cycloadduct 78 (85.9 mg, 50% yield): \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 8.85 (s, 1H), 7.31 (t, \(J = 7.1\) Hz, 1H), 7.10 (d, \(J = 6.9\) Hz, 1H), 7.04 (t, \(J = 7.1\) Hz, 1H), 6.98 (d, \(J = 7.8\) Hz, 1H), 5.62 (ddt, \(J = 17.4, 10.9, 5.8\) Hz, 1H), 5.15 (s, 1H),
5.08 (q, J = 1.6 Hz, 1H), 5.05-5.01 (m, 2H), 4.34 (s, 1H), 3.97-3.90 (m, 1H), 3.81 (dq, J = 10.7, 7.1 Hz, 1H), 3.20 (td, J = 5.6, 1.7 Hz, 2H), 0.79 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl<sub>3</sub>) δ 175.7, 173.4, 165.1, 141.5, 135.1, 130.3, 124.5, 123.3, 123.1, 117.7, 110.7, 63.7, 61.9, 59.4, 50.3, 13.6.

5'-ethyl 4'-methyl 2-oxo-2'-vinylspiro[indoline-3,3'-pyrrolidine]-4',5'-dicarboxylate (79). To a flame dried flask equipped with a stir bar and 3Å molecular sieves was added amine 13 (0.15 mL, 2.00 mmol) and ethyl glyoxylate (0.40 mL, 2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and allowed to stir at rt for 15 minutes. Dipolarophile 76 (0.303 g, 1.00 mmol), AgOAc (0.016 g, 0.1 mmol) and Et<sub>3</sub>N (0.28 mL, 2.0 mmol) were added and allowed to stir until completion by TLC. After stirring for 4 h the reaction mixture was extracted CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL), washed with NaHCO<sub>3</sub> (25 mL), and brine (25 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and the residue purified by column chromatography (50% EtOAc in hexanes) to yield cycloadduct 79 (252.3 mg, 73% yield) as a white foam: R<sub>f</sub> = 0.41 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz; CDCl<sub>3</sub>): δ 9.47 (s, 1H), 7.16 (t, J = 8.2 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 5.52 (ddd, J = 17.1, 10.5, 6.7 Hz, 1H), 4.95-4.92 (m, 120
2H), 4.59 (d, J = 7.7 Hz, 1H), 4.29 (q, J = 6.8 Hz, 3H), 3.90 (d, J = 6.8 Hz, 3H), 3.52 (d, J = 7.7 Hz, 1H), 3.35 (s, 3H), 1.22 (t, J = 7.1 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.7, 171.1, 170.9, 141.6, 131.6, 128.8, 127.0, 125.5, 122.5, 119.0, 110.2, 72.0, 63.6, 61.6, 61.0, 56.7, 51.9, 14.1.

(R)-1-((2,2,2-trichloroethoxy)carbonyl)pyrrolidine-2-carboxylic acid (81). To a vigorously stirred solution of L-proline (2.3 g, 20.0 mmol) in Et$_2$O (4 mL) and 2M NaOH (10 mL) at 0 °C was added a solution of trichloroethylchloroformate (2.91 mL, 21.0 mmol) in Et$_2$O (8 mL) and 2M NaOH (10.5 mL) dropwise. The reaction mixture was stirred at 0 °C for 10 minutes, warmed to rt, and stirred for 1 h. The reaction mixture was then washed with Et$_2$O (3 x 20 mL) and the organic layer separated. The aqueous layer was then cooled to 0 °C and concentrated HCl was used to adjust the pH to 1. The aqueous layer was then extracted with Et$_2$O (2 x 30 mL). The combined organic layers were then washed with water (30 mL), brine (30 mL), dried over Na$_2$SO$_4$, and concentrated to afford carboxylic acid 81 (4.94 g, 86% yield) as a viscous colorless oil: $^1$H NMR (500 MHz; CDCl$_3$): δ 4.84-4.63 (m, 2H), 4.44 (dt, J = 8.7, 4.3 Hz, 1H), 3.73-3.50 (m, 2H), 2.36-1.93 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.1, 152.3, 74.9, 59.2, 47.2, 30.8, 24.1, 23.4.
(R)-2,2,2-trichloroethyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (72). Carboxylic acid 81 (1.6 g, 5.6 mmol) was dissolved in excess thionyl chloride (5 mL) and allowed to stir at rt overnight. The excess thionyl chloride was removed under reduced pressure to afford acid chloride 72 (quantitative) as a viscous colorless oil: $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 4.75-4.67 (m, 3H), 3.71-3.58 (m, 2H), 2.43-2.23 (m, 2H), 2.04-1.96 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.1, 151.8, 75.1, 73.6, 67.9, 46.8, 30.4, 23.1.

Ethyl 4,6-dioxo-5-phenyl-2-((S)-1-((2,2,2-trichloroethoxy)carbonyl)pyrrolidine-2-carbonyl)-3-vinloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (Control-A). To a flame dried flask equipped with a stir bar was added pyrrolidine 21 (0.122 g, 0.39 mmol),
CH$_2$Cl$_2$ (1 mL), and Et$_3$N (0.42 mL). The reaction mixture was then cooled to 0 °C under an atmosphere of N$_2$. Next, a solution of acid chloride 72 in CH$_2$Cl$_2$ (1 mL) dropwise over 20 minutes. The reaction mixture was then allowed to warm to rt and stirred for 17.5 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL) and then washed with H$_2$O (10 mL), 0.1M HCl (2 x 10 mL), NaHCO$_3$ (2 x 10 mL), H$_2$O (10 mL), and brine (10 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, concentrated, and the residue purified by column chromatography (50% EtOAc in hexanes) to afford Control-A (35.6 mg, 16%): $R_f = 0.77$ (50% EtOAc in hexanes).

5'-ethyl 4'-methyl 2-oxo-1'-(S)-1-((2,2,2-trichloroethoxy)carbonyl)pyrrolidine-2-carbonyl)-2'-vinylspiro[indoline-3,3'-pyrrolidine]-4',5'-dicarboxylate (82). To a solution of pyrrolidine 79 (0.172 g, 0.32 mmol) in CH$_2$Cl$_2$ (4 mL) was added acid chloride 72 (0.13 g, 0.42 mmol) and saturated NaHCO$_3$ (4 mL). The reaction mixture was allowed to stir vigorously at rt for 4 h. The reaction mixture was partitioned between CH$_2$Cl$_2$ and brine and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The
organic layers were combined and dried over Na$_2$SO$_4$ and concentrated to yield acylated product 82 (used without purification).

5'-ethyl 4'-methyl 2-oxo-1-((R)-1-((2,2,2-trichloroethoxy)carbonyl)pyrrolidine-2-carbonyl)-1'-(S)-1-((2,2,2-trichloroethoxy)carbonyl)pyrrolidine-2-carbonyl)-2'-vinylspiro[indoline-3,3'-pyrrolidine]-4',5'-dicarboxylate (83). To a flame dried flask equipped with a stir bar and molecular sieves was added pyrrolidine 79 (0.057 g, 0.16 mmol), Et$_3$N (0.3 mL, 3.2 mmol), and CH$_2$Cl$_2$ (2 mL). The reaction mixture was cooled to 0 °C and then a solution of acid chloride 72 (0.25 g, 0.83 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 20 minutes, warmed to rt, and stirred for 19 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL) and extracted with H$_2$O (20 mL), 0.1M HCl (2 x 20 mL), NaHCO$_3$ (2 x 20 mL), H$_2$O (20 mL), and brine (20 mL). The organic layers were then combined and dried over Na$_2$SO$_4$, filtered, concentrated, and the residue purified by column chromatography (3:2 EtOAc:hexanes) to afford 1:1 mixture of 82 and 83 as confirmed by LCMS.
Methyl 2',5,10-trioxo-3-vinyl-3,5,5a,6,7,8,10,10a-octahydro-1H-spiro[dipyrrrolo[1,2-α:1',2'-d]pyrazine-2,3'-indoline]-1-carboxylate (84). To a stirred solution of 82 (crude, 0.45 mmol) in MeOH (25 mL) was added zinc dust (0.58 g, 9.00 mmol) and heated to reflux for 16 h. The reaction mixture was filtered through Celite, concentrated, redissolved in CH₂Cl₂, and washed with NaHCO₃ (10 mL), brine (10 mL) and 10% HCl (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography (75:20:5 CH₂Cl₂:EtOAc:iPrOH) to give product 84 (47.1 mg, 27% yield): R₇: 0.20 (75:20:5 CH₂Cl₂:EtOAc:iPrOH); ¹H NMR (500 MHz; CDCl₃): 8.64 (s, 1H), 7.24 (td, J = 7.7, 1.2 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 7.00 (td, J = 7.6, 0.9 Hz, 1H), 6.90 (dd, J = 7.8, 0.5 Hz, 1H), 5.89 (ddd, J = 16.9, 10.2, 7.9 Hz, 1H), 5.21 (dd, J = 10.2, 0.8 Hz, 1H), 5.06 (d, J = 9.4 Hz, 1H), 4.99 (dt, J = 16.9, 0.9 Hz, 1H), 4.61 (d, J = 7.9 Hz, 1H), 4.38 (t, J = 7.8 Hz, 1H), 4.21 (d, J = 9.4 Hz, 1H), 3.68-3.55 (m, 3H), 3.36 (d, J = 0.9 Hz, 3H), 2.31 (dq, J = 18.6, 6.3 Hz, 2H), 1.98 (dt, J = 17.7, 9.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 174.9, 168.9, 167.5, 165.2, 140.5, 131.8, 129.7, 128.9, 123.4, 123.1, 118.3, 110.3, 68.1, 61.3, 60.5, 58.2, 49.9, 45.5, 27.4, 23.9.
5-(isopropylthio)-1-phenyl-1H-tetrazole (87). To a flame dried flask equipped with a stir bar was added 1-phenyl-1H-tetrazole-5-thiol (1.16 g, 6.50 mmol), PPh\(_3\) (1.44 g, 5.50 mmol), iPrOH (0.38 mL, 5.00 mmol) in THF (60 mL). To this mixture was added DIAD (1.15 mL, 5.50 mmol) dropwise. The yellow solution was allowed to stir at rt for 21 h. The reaction mixture was concentrated to give crude residue. A solution of 9:1 pentane:EtOAc was added and upon extensive sonication a white precipitate was formed. The suspension was then filtered over Celite, the filtrate concentrated, and the residue purified by column chromatography (1:9 EtOAc:hexanes) to afford product 87 (0.84 g, 76% yield) as a white solid: \(R_f\) 0.43 (1:3 EtOAc:hexanes); \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.57 – 7.53 (m, 5H), 4.15 (dt, \(J = 13.6, 6.8\) Hz, 1H), 1.51-1.50 (m, 6H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.2, 133.9, 130.2, 129.8, 39.9, 23.4.
5-(isopropylsulfonyl)-1-phenyl-1H-tetrazole (88). To a stirred solution of 87 (0.84 g, 3.8 mmol) in MeOH (38 mL) at rt was added a solution of Oxone (7.01 g, 11.4 mmol) in H₂O (38 mL). The reaction mixture became white with a precipitate upon addition of Oxone solution. The reaction mixture was allowed to stir at rt for 5 h. The reaction mixture was diluted with Et₂O (95 mL) and washed with H₂O (120 mL). The layers were then separated and the aqueous phase was extracted with Et₂O (3 x 100 mL). The combined organic layers were then washed with brine (50 mL), dried over Na₂SO₄, filtered, concentrated, and purified residue by column chromatography (1:3 EtOAc:hexanes) to yield desired sulfone 88 (788.9 mg, 82% yield) as a white solid: \( R_f: 0.43 \) (1:3 EtOAc: hexanes); \(^1\)H NMR (500 MHz; CDCl₃): \( \delta \) 7.68-7.57 (m, 7H), 4.01 (dt, \( J = 13.8, 6.9 \) Hz, 1H), 1.57-1.46 (m, 7H); \(^1^3\)C NMR (125 MHz, CDCl₃) \( \delta \) 152.6, 133.1, 131.4, 129.6, 125.4, 56.9, 15.0.
4.4 Experimental Procedures for APPLICATION OF METHODOLOGY – STUDIES TOWARD THE TOTAL SYNTHESIS OF THE ANTI-CANCER COMPOUND PEDUNCULARINE

Ethyl 4-nitro-3-phenyl-5-vinylpyrrolidine-2-carboxylate (106) and ethyl 3-phenyl-5-vinyl-2,5-dihydro-1H-pyrrole-2-carboxylate (107). To a stirred mixture of amine 13 (0.15 mL, 2.00 mmol) in MeCN (0.5 mL) was added ethyl glyoxylate (0.40 mL, 2.0 mmol) and allowed to stir at rt for 15 minutes. Nitrostyrene (0.125 g, 1.00 mmol), AgOAc (0.016 g, 0.1 mmol) and Et₃N (0.28 mL, 2.0 mmol) were added and allowed to stir at rt for 60 h. The reaction mixture was extracted with CH₂Cl₂ (3 x 20 mL), washed with NH₄Cl (25 mL), and brine (25 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and the residue purified by column chromatography (10% EtOAc in hexanes) to yield two products 106 (33.9 mg, 10% yield) and 107 (28.9 mg, 10% yield); (106) ¹H NMR (500 MHz; CDCl₃): δ 7.37 (t, J = 6.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 7.0 Hz, 2H), 5.77 (ddd, J = 17.1, 10.6, 6.4 Hz, 1H), 5.46 (d, J = 16.3 Hz, 1H), 5.36 (d, J = 10.5 Hz, 1H), 5.12 (dd, J = 6.4, 3.9 Hz, 1H), 4.27 (dd, J = 10.8, 7.1 Hz, 2H), 4.20 (dd, J = 10.8, 7.1 Hz, 1H), 4.08 (dd, J = 7.4, 3.9 Hz, 1H), 3.97 (d, J = 7.4 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H). (107) ¹H NMR (500 MHz; CDCl₃): δ 7.29 (d, J = 7.1 Hz, 3H).
Hz, 2H), 7.28-7.27 (m, 1H), 7.19-7.17 (m, 2H), 6.08 (ddd, J = 17.2, 10.3, 6.9 Hz, 1H), 5.45 (dt, J = 17.1, 1.0 Hz, 1H), 5.37 (dt, J = 10.3, 0.9 Hz, 1H), 4.99 (t, J = 7.7 Hz, 1H), 4.35 (q, J = 7.5 Hz, 2H), 3.79 (dd, J = 10.7, 7.1 Hz, 1H), 3.64 (dd, J = 10.7, 7.2 Hz, 1H), 0.80 (t, J = 7.2 Hz, 3H); (106) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.5, 138.7, 134.6, 130.9, 129.3, 128.9, 128.1, 127.6, 120.6, 96.6, 67.9, 66.2, 61.8, 55.6, 14.2; (107) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.3, 136.0, 134.6, 128.9, 128.3, 128.2, 128.0, 119.9, 94.0, 64.8, 64.5, 61.3, 53.6, 13.7.

3-methyl-1-nitrobutan-2-ol (121). To a stirred solution of isobutyl aldehyde (4.14 mL, 45.4 mmol) and nitromethane (2.5 mL, 46.2 mmol) in EtOH (10 mL) at 0 °C was added 10 M NaOH (4.54 mL, 45.4 mmol) dropwise over 10 minutes. The solution was stirred vigorously to break up the solids formed. After 10 min, acetic acid (2.6 mL, 45.4 mmol) was added. The reaction mixture was then extracted with Et$_2$O (2 x 500 mL), dried (MgSO$_4$), filtered, and concentrated to afford nitro alcohol 121 (5.30 g, 88% yield) as a light yellow oil: $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 4.44 (m, 2H), 4.10 (ddd, J = 9.02, 5.97, 2.90 Hz, 1H), 2.79 (s, 1H), 1.80 (dq, J = 12.95, 6.58 Hz, 1H), 0.98 (t, J = 7.12 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 79.4, 73.5, 31.8, 18.5, 17.5.
(E)-3-methyl-1-nitrobut-1-ene (109). To a stirred solution of 121 (3.88 g, 29.2 mmol) in CH₂Cl₂ (60 mL) at 0 °C was added trifluoroacetic anhydride (4.34 mL, 30.7 mmol). Next, Et₃N (8.56 mL, 61.4 mmol) was added dropwise. Before the addition of Et₃N the reaction mixture was yellow and during the addition turned an orange/red color. The reaction mixture was allowed to warm to rt and stirred for 1 h. During this time the reaction mixture gradually became yellow again. The reaction mixture was diluted with 40 mL CH₂Cl₂, washed with water (2 x 30 mL), saturated NH₄Cl (20 mL), and brine (20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to afford nitroolefin 109 (2.56 g, 76% yield) as a yellow oil: ¹H NMR (500 MHz; CDCl₃): δ 7.23 (dd, J = 13.5, 7.1 Hz, 1H), 6.92 (dd, J = 13.5, 1.5 Hz, 1H), 2.57 (dqd, J = 13.7, 6.8, 1.5 Hz, 1H), 1.13 (s, 3H), 1.12 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 148.6, 138.3, 28.5, 21.2.
(E)-ethyl 3-nitroacrylate (108). To a stirred solution of HgCl₂ (10.8 g, 50.0 mmol) and NaNO₃ (5.52 mL, 100.0 mmol) in H₂O (80 mL) at rt was added ethyl acrylate slowly (4.26 mL, 50.0 mmol). The solution was allowed to stir overnight. The white solid formed was collected by filtration, washed with water (3 x 50 mL) and hexanes (3 x 50 mL) to afford a crude white solid which was used without further purification (14.18 g, 74% yield) as a white solid. To a stirred solution of the white solid from the previous step in H₂O (42 mL) and Et₂O (107 mL) at 0 °C was added Br₂ (3.80 mL, 74.05 mmol) dropwise. The solution was allowed to stir vigorously. After 10 minutes the reaction mixture was allowed to warm to rt and stir overnight. After stirring overnight the reaction mixture was light yellow. NaHCO₃ (15 g) was added to the reaction mixture very slowly until bubbling subsided. The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was washed with Et₂O (3 x 50 mL). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated to afford crude bromoalkane as a solid (quant) which was used without further purification. To a stirred solution of the crude bromoalkane in Et₂O (77 mL) at 0 °C was added anhydrous NaOAc (17.6 g, 214 mmol) portion wise. The reaction mixture was allowed to warm to rt and stirred for 3 days. The reaction mixture was diluted with Et₂O (50 mL) and washed with NaHCO₃ (50 mL). The combined organic layers were washed with unsaturated NaCl, dried (Na₂SO₄), filtered, and concentrated at low temperature to afford a crude residue. The residue was then recrystallized with hexanes to afford pure product as red crystals: \( R_f \)
= 0.775 (30% EtOAc in hexanes); $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.67 (d, $J = 13.5$ Hz, 1H), 7.08 (d, $J = 13.5$ Hz, 1H), 4.32 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.8, 149.1, 127.9, 62.6, 14.2.

**Ethyl 2-(chlorocarbonyl)pent-4-enoate (113).** To a stirred solution of diethyl allylmalonate (0.98 mL, 5.0 mmol) in THF (8.3 mL) and water (83.3 mL) at 0 °C was added a solution of 0.25M KOH (25 mL) dropwise. During this addition the reaction mixture turned from clear to cloudy. The reaction mixture was allowed to stir at 0 °C for 3.5 h and then 1M HCl (about 7 mL) was added to acidify the reaction mixture. The mixture was then diluted with saturated NaCl (30 mL). The mixture was added to a separatory funnel and extracted immediately with EtOAc (4 x 20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated to yield crude carboxylic acid in quantitative yield which was used without further purification. To a flame-dried flask equipped with a stir bar was added the carboxylic acid and CH$_2$Cl$_2$ (25 mL) and cooled to 0°C. Then, 1 drop of DMF was added followed by dropwise addition of oxalyl chloride (0.53 mL, 6.25 mmol). The reaction mixture was allowed to stir at 0 °C for 15 min and then warmed to rt. After 21 h the solvent and excess oxalyl chloride were removed by rotary evaporation.
to afford the crude acid chloride which was further purified by azetric distillation with toluene to furnish acid chloride 113 as an oil: \( R_f = 0.85 \) (50% EtOAc in hexanes); \(^1\)H NMR (500 MHz; CDCl\(_3\)): \( \delta 5.80 \) (ddt, \( J = 17.1, 10.2, 6.9 \) Hz, 1H), 5.23 (dd, \( J = 17.1, 1.4 \) Hz, 1H), 5.19 (d, \( J = 10.2 \) Hz, 1H), 4.30 (tdd, \( J = 10.7, 7.2, 3.5 \) Hz, 2H), 3.89 (t, \( J = 7.4 \) Hz, 1H), 2.79-2.75 (m, 2H), 1.35 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 166.3, 137.8, 125.3, 118.9, 62.3, 33.2, 21.5, 13.9. \)

3-methylbut-2-en-1-yl acrylate (120). To a stirred solution of prenyl alcohol (1.47 mL, 15.0 mmol), Et\(_3\)N (3.17 mL, 24.0 mmol) in Et\(_2\)O (15 mL) at 0 °C was added acryloyl chloride (1.45 mL, 18.0 mmol) dropwise. During the addition the reaction mixture was stirred vigorously and produced a white solid. After addition the reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction mixture was diluted with H\(_2\)O (30 mL) and extracted with Et\(_2\)O (3 x 20 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated to ester 120 (1.2 g, 46 % yield). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \( \delta 6.38 \) (d, \( J = 18.9 \) Hz, 1H), 6.10 (dd, \( J = 17.3, 10.4 \) Hz, 1H), 5.79 (d, \( J = 10.4 \) Hz, 1H), 5.36 (t, \( J = 7.2 \) Hz, 1H), 4.64 (d, \( J = 7.2 \) Hz, 2H), 1.75 (s, 3H), 1.71 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 166.1, 139.0, 130.4, 120.6, 118.5, 61.4, 25.7, 17.9. \)
2-(phenylthio)ethanol (122). A stirred solution of EtOH (37.5 mL) was allowed to warm and then KOH (3.135 g, 55.0 mmol) and thiophenol (5.10 mL, 50.0 mmol) were added and allowed to dissolve. Next, 2-bromoethanol (4.60 mL, 65.0 mmol) was added dropwise. Almost immediately a white solid was formed. The reaction mixture was then heated to reflux and allowed to stir for 2 h. The reaction mixture reaction was allowed to cool and the solid was removed by filtration. The filtrate was concentrated to yield 122 (quantitative yield) as a brown oil. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.39 (d, $J = 7.3$ Hz, 2H), 7.29 (t, $J = 7.8$ Hz, 2H), 7.21 (t, $J = 7.3$ Hz, 1H), 3.74 (t, $J = 6.0$ Hz, 2H), 3.11 (t, $J = 6.0$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 134.9, 130.3, 129.2, 126.8, 60.4, 37.4.

2-(phenylsulfonyl)ethanol (123). To a stirred solution of 122 (4.0 g, 26.0 mmol) in water (5 mL) and EtOH (30 mL) was added Na$_2$WO$_4$-H$_2$O (0.06 g in 3 mL H$_2$O) and heated to 40 °C. When this temperature was reached 30% H$_2$O$_2$ (2.6 mL, 26.0 mmol) was added slowly. The temperature was then increased to 80 °C and another addition 30% H$_2$O$_2$ (2.6 mL, 26.0 mmol) was added slowly. After addition the reaction mixture was
heated to reflux for 1 hour. The reaction was cooled to rt and then placed in the freezer overnight. The product was filtered and the crystals were isolated as the desired product 123 (1.8 g, 80% yield) as a light yellow oil. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.49 (d, $J = 7.2$ Hz, 2H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.8$ Hz, 2H), 4.00 (t, $J = 5.4$ Hz, 2H), 3.36 (t, $J = 5.4$ Hz, 2H), 2.97 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.9, 134.1, 129.5, 127.9, 58.2, 56.4.

(vinylsulfonyl)benzene (124). To a flame dried flask equipped with a stir bar was added 123 (2.06 g, 11.0 mmol), Et$_3$N (3.84 g, 27.6 mmol), and CH$_2$Cl$_2$ (110 mL). Next, MsCl (1.03 mL, 13.3 mmol) was added slowly at rt. The reaction mixture was allowed to stir under N$_2$ for 23 h. An additional 1.2 equiv of MsCl and 2.5 of equiv Et$_3$N were added. The reaction was stopped after 42 h even though starting material remained. The reaction mixture was added to a separatory funnel and saturated NH$_4$Cl (25 mL) was added. The reaction mixture was then extracted with CH$_2$Cl$_2$ (3 x 50 mL). The organic layers were then combined, washed with water (50 mL) and then brine (50 mL), dried over Na$_2$SO$_4$, filtered, concentrated, and the residue purified via column chromatography using a short plug of silica (50% EtOAc in hexanes) to yield 124 as a white/off-white solid: $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.90 (dd, $J = 8.5$, 1.3 Hz, 2H), 7.66-7.62 (m, 1H), 7.57-7.54 (m,
2H), 6.66 (dd, J = 16.5, 9.8 Hz, 1H), 6.46 (d, J = 16.9 Hz, 1H), 6.04 (d, J = 9.8 Hz, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 139.7, 138.6, 133.8, 129.5, 128.1, 127.9.

diallyl 2,3-dihydroxysuccinate (125). A stirred solution of tartaric acid (7.5 g, 50.0 mmol) in DMF (37.5 mL) was cooled to 0 °C and Et$_3$N (27.8 mL, 200.0 mmol) was added. The reaction mixture was allowed to warm to rt and during this time a solution of allyl bromide (17.3 mL, 200.0 mmol) in DMF (25 mL) was added over 3 h. The reaction mixture was allowed to stir at rt overnight. The reaction mixture was added to a separatory funnel filled with ice and extracted with EtOAc (3 x 25 mL). The combined organic layers were then washed with ice cold saturated NaHCO$_3$ (30 mL), ice cold brine (30 mL), and dried over Na$_2$SO$_4$, filtered, and concentrated to afford 125 (10.122 g, 88% yield) as a yellow/orange oil. $^1$H NMR (500 MHz; CDCl$_3$): δ 5.91 (ddt, J = 16.96, 10.69, 6.03 Hz, 1H), 5.34 (dd, J = 17.20, 1.32 Hz, 1H), 5.26 (dt, J = 10.44, 0.93 Hz, 1H), 4.71 (d, J = 5.81 Hz, 2H), 4.58 (d, J = 7.60 Hz, 1H), 3.46 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.3, 131.3, 119.3, 72.2, 66.8.
Appendix I: Spectroscopic Data
Figure A.1 $^1$H NMR of 21 in CDCl$_3$
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**Figure A.66** 1-D NOESY NMR of 84 irradiated at 4.38 ppm in CDCl₃
Figure A.67 1-D NOESY NMR of 84 irradiated at 4.63 ppm in CDCl₃

Figure A.68 1-D NOESY NMR of 84 irradiated at 5.06 ppm in CDCl₃
Figure A.69 1-D NOESY NMR of 84 irradiated at 5.91 ppm in CDCl$_3$

Figure A.70 1-D NOESY NMR of 84 irradiated at 7.10 ppm in CDCl$_3$
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**Figure A.72** DFT B3LYP 6-31G** minimized structure of **EXR2**, distances shown
Figure A.73 DFT B3LYP 6-31G** minimized structure of ENR1, distances shown

Figure A.74 DFT B3LYP 6-31G** minimized structure of ENR2, distances shown
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Figure A.100 $^{13}$C NMR of 125 in CDCl$_3$
List of Abbreviations

$^1$H – NMR .......................................................... Proton Nuclear Magnetic Resonance
6-31G** ................................................................. Polarized Basis Set
$^{13}$C – NMR ............................................................ Carbon Nuclear Magnetic Resonance
Ac .............................................................................. Acetyl
AcOH ........................................................................ Acetic Acid
AgOAc ........................................................................ Silver Acetate
APCI ........................................................................ Atmospheric-Pressure Chemical Ionization
Ar .............................................................................. Aryl
B3LYP ............................................................... Becke, three-parameter, Lee-Yang-Parr
Bn ........................................................................ Benzyl
Boc .............................................................................. tert-Butyl carbamate
Bu ........................................................................ Butyl
COSY ................................................................. Correlation Spectroscopy
dba ........................................................................ dibenzylideneacetone
DBU ........................................................................ 1,8-diazabicyclo[5,4,0]undec-7-ene
DCM ........................................................................ Dichloromethane
DCC ........................................................................ N,N’-Dicyclohexylcarbodiimide
DEAD ................................................................. Diethyl azodicarboxylate
DFT ........................................................................ Density Functional Theory
DIAD ........................................................................ Diisopropyl azodicarboxylate
DMAP ........................................................................ 4-Dimethylaminopyridine
DMF ........................................................................ Dimethylformamide
DMSO ...................................................................... Dimethyl Sulfoxide
EDC .................................................................. 1-Ethyl-3(3-dimethylaminopropyl)carbodiimide
Et ........................................................................ Ethyl
Et$_3$N .......................................................... Triethylamine
ESI .................................................................. Electrospray Ionization
EtOAc .......................................................... Ethyl Acetate
EtOH ........................................................... Ethanol
Fmoc ............................................................ Fluorenylmethyloxycarbonyl
GC .................................................................... Gas Chromatography
GCMS ......................................................... Gas Chromatography – Mass Spectrometry
HMBC ..................................................... Heteronuclear Multiple Bond Correlation
HMQC ..................................................... Heteronuclear Multiple Quantum Correlation
HOBt .......................................................... Hydroxybenzotriazole
HPLC .......................................................... High Performance Liquid Chromatography
Hz ..................................................................... Hertz
$iPr$ ............................................................... iso-propyl
IR ...................................................................... Infrared
LAH .................................................................. Lithium Aluminum Hydride
LCMS .......................................................... Liquid Chromatography – Mass Spectrometry
$mCPBA$ ......................................................... meta-Chloroperoxybenzoic Acid
Me ...................................................................... Methyl
MeCN.................................................................Acetonitrile
MeOH ...............................................................Methanol
MS...........................................................................Molecular Sieves
NaOMe...................................................................Sodium Methoxide
NBS ........................................................................ N-Bromosuccinimide
n-BuLi ..................................................................... n-Butyllithium
NMO .................................................................N-Methylmorpholine oxide
NOE ......................................................................... Nuclear Overhauser Effect
Oxone....................................................................... Potassium Peroxymonosulfate
Ph ............................................................................. Phenyl
PhMe ......................................................................... Toluene
pKa ............................................................................ Acid Dissociation Constant
PPh₃ ........................................................................... Triphenylphosphine
RCM ........................................................................... Ring Closing Metathesis
rt ............................................................................... Room Temperature
SEM ........................................................................... [2-(Trimethylsilyl)ethoxy]methyl
tBuOH ......................................................................... tert-Butanol
TFA ........................................................................ Trifluoroacetic Acid
THF ........................................................................... Tetrahydrofuran
TIPS ........................................................................... Triisopropylsilyl ether
TLC ........................................................................... Thin-Layer Chromatography
TMS ........................................................................... Trimethylsilane
Tol................................................................. Toluene
Troc.......................................................... 2,2,2-Trichloroethyl chloroformate
Ts......................................................................................... Tosyl
Bibliography


Arredondo, V. M.; McDonald, F. E.; Marks, T. J. Journal of the American Chemical Society 1998, 120, 4871-4872.


2004, 43. 5357-5360.


Ruhemann, S. *Journal of the Chemical Society, Transactions* 1910, 97, 1438-1449.


Sebahar, P. R.; Williams, R. M. *The Journal of the American Chemical Society* 2000, 122, 5666-5667.


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