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The Development of a Four Component Reaction and Its Application to the Synthesis of Diverse Heterocyclic Scaffolds and the Total Synthesis of Alkaloid Natural Products: The Total Synthesis of Roelactamine and Efforts Towards the Syntheses of Rosicine and Pseudotabersonine

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by

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The Development of a Four Component Reaction and Its Application to the Synthesis of Diverse Heterocyclic Scaffolds and the Total Synthesis of Alkaloid Natural Products: The Total Synthesis of Roelactamine and Efforts Towards the Syntheses of Rosicine and Pseudotabersonine

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A four component reaction involving the coupling of functionalized aldehydes, amines, acid chlorides, and π- and organometallic nucleophiles has been developed to prepare multifunctional substrates that may be employed in subsequent ring-forming reactions to generate diverse arrays of functionalized heterocyclic scaffolds. Allyl metals, Grignard reagents, silyl ketene acetals, silyl enol ethers, and silyloxy furans have been utilized as the nucleophile in the four component reaction (4CR). The 4CR has been sequenced with intramolecular Heck reactions, Diels-Alder and [3+2] cycloadditions, ring closing metathesis (RCM), and Dieckmann condensations to provide a number of diverse heterocyclic structures. The practical utility of this approach to diversity-oriented synthesis (DOS) was further exemplified by its application to the first total synthesis of the isopavine alkaloid roelactamine, which was completed in only four steps from commercially available materials.

The application of this methodology towards the synthesis of the *Aspidosperma* alkaloids rosicine and pseudotabersonine is also presented. To this end, an imine pentadienylation/double RCM strategy has been adopted to rapidly access the pentacyclic core of the aspidospermine alkaloids. This sequence involved the use of a pentadienyl aluminum reagent, which was found to react with aryl imines to give branched products in good yields.

Table of Contents

Chapter 1: Diversity Oriented Synthesis and the Applications of Multicomponent Reactions to the Synthesis of Diverse Heterocyclic Scaffolds

1.1 Diversity Oriented Synthesis

1.1.1 Introduction

As chemists and biologists search for small molecule probes for analyzing all aspects of protein function, cell circuitry, and animal physiology, many thousands of molecules are needed for testing in biological screens. In particular, the study and use of small molecules as modulators of biological activity gains continued importance, as small molecules often exhibit many favorable properties over macromolecules and biological theropuetics.[1, 2] Since the vast majority of these compounds are accessible only through chemical synthesis, a significant burden is placed on synthetic chemists to develop efficient methods for synthesizing these large collections of molecules.

Of particular interest is the ability to include in these libraries compounds that contain natural product or drug-like scaffolds, as the use natural products and privileged structures[3] as lead compounds for drug development, or as drugs themselves, has already been validated.[4,5] The vast majority of natural products and biologically active molecules contain a heterocyclic ring system, and therefore a premium is placed on the ability of synthetic chemists to develop methods for the efficient synthesis of diverse heterocyclic compounds.

Traditionally organic chemists have focused their synthetic efforts towards specific target molecules, and this process of target-oriented synthesis (TOS) has led to efficient syntheses of numerous natural products and biologically active molecules. The target molecules are typically chosen due to their natural occurrence, structural features,

and known biological activity, and therefore the syntheses of these molecules has led to many advances in the fields of chemistry and biology. However, when a specific target molecule is chosen, the synthetic route is designed to access only the specific region of chemical space occupied by the synthetic target, and the focused nature of TOS severely limits the number and types of molecules that can be generated for biological screening.

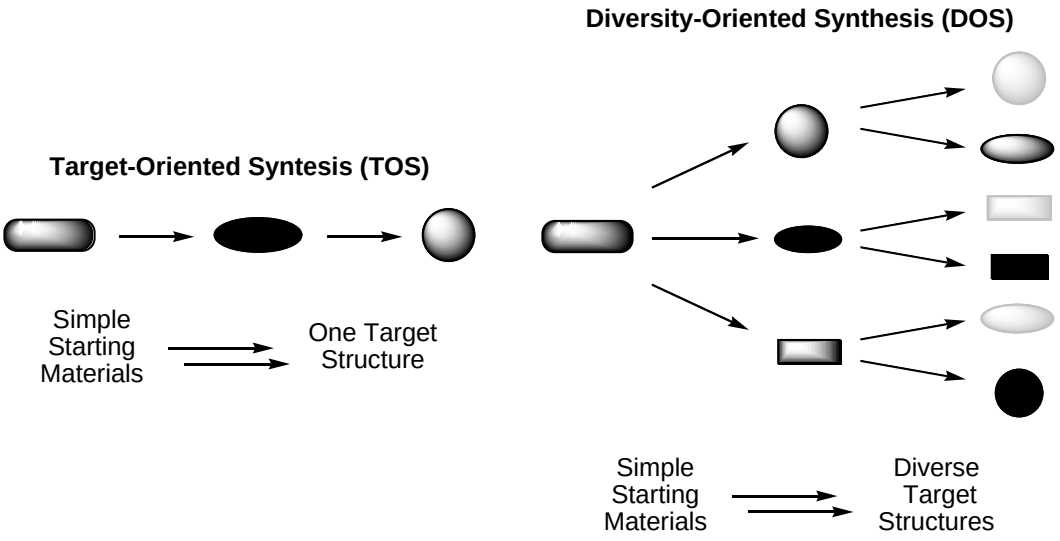
The concept of combinatorial chemistry was developed to further expand the number and types of targets accessible by TOS, and this synthetic strategy greatly increased the number of small molecules available for testing. Combinatorial chemistry is a scaffold-based approach, where known scaffolds are sequentially derivatized to generate large libraries of compounds. The scaffolds that are typically chosen are privileged structures or natural product derived, as these scaffolds are already known to exhibit certain biological activities.[3-5] However, since combinatorial chemistry is focused on filling in the chemical space around known compounds with desirable structural or biological properties, the chemical diversity found in libraries generated by combinatorial chemistry is limited.[6, 7] Whether the limitations of today's libraries should be cause for concern is unknown, as the questions of whether or not the previously explored areas of chemical space are the best areas for finding new biologically active molecules and whether or not the unexplored regions of chemical space will lead to novel active compounds go unanswered. The concept of diversity-oriented synthesis (DOS) was developed to provide synthetic chemists with the tools to synthesize the molecules that may one day answer these questions.

The main goal of DOS is to synthesize collections of diverse molecules that represent every region of chemical space, so that these collections of molecules can then be utilized in biological assays to further knowledge about living systems. However,

before DOS could begin to reach this goal, a new set of synthetic strategies needed to be developed.

DOS is a synthetic strategy designed to allow for the synthesis of a collection of structurally and stereochemically diverse molecules in a short number of steps from simple starting materials. From a synthetic standpoint DOS is distinctly different from TOS. The field of TOS generally focuses on the synthesis of a single target structure, while the goal of a DOS is to generate collections of diverse structures (Figure 1). Therefore, the general planning strategies for TOS and DOS are also different.[8,9] While the strategy of retrosynthetic analysis has greatly advanced the field of TOS,[10] this strategy is not ideal for DOS. DOS instead relies on a forward-synthetic planning strategy that focuses on identifying inherent chemical reactivity in collections of compounds and the ability to recognize the potential for iterative pathways, wherein the product of one reaction becomes the starting material for the next reaction, leading to more complex and diverse structures.

Figure 1.1



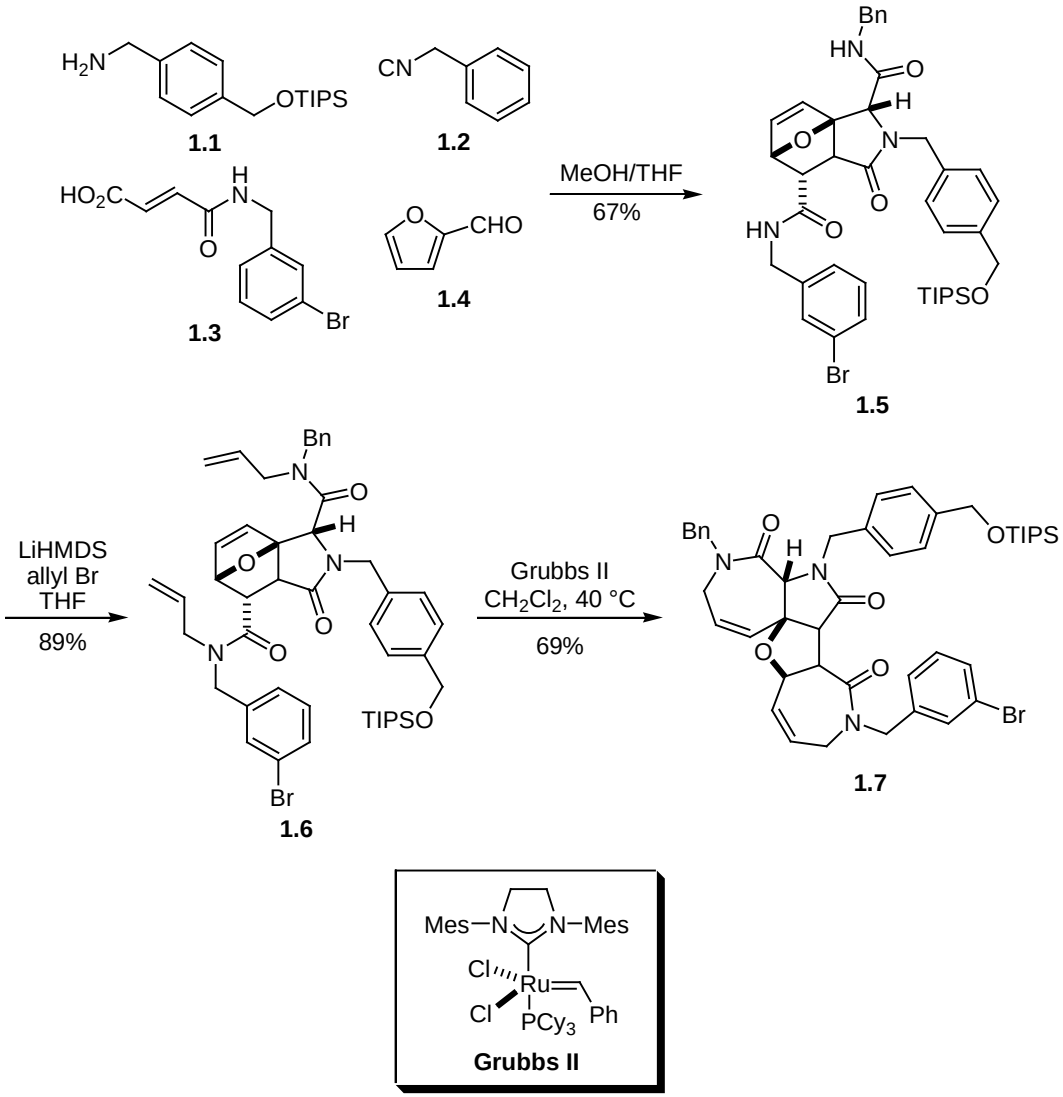
The diversity of a collection of molecules arises from three main elements: the molecular skeleton, the appendages on the skeleton, and the relative stereochemistry of the substituents on the molecule. Variations on all three of these elements are needed for the full potential of DOS to be realized. Thus, it is important for synthetic chemists to be able to access in a stereo-controlled manner a number of different heterocyclic skeletons that contain a diverse array of functionalities that can be used to attach a wide range of differentially functionalized appendages. While this is no small feat, a number of different strategies have been developed to lay the foundation for DOS, and this Chapter will focus on the discussion of these strategies.

1.1.2. The Pairwise Use of Complexity-Generating Reactions

The most straightforward approach to DOS is the pairwise use of complexity-generating reactions. A complexity-generating reaction is a reaction that turns relatively simple starting materials into a more complex product. The sequencing of these reactions so that the product of the first reaction becomes the substrate in a second complexity-generating reaction can lead to very complex structures in a short number of steps. Schreiber has demonstrated that the pairing of two complexity-generating reactions, namely the tandem Ugi four component reaction (Ugi-4CR)/intramolecular-Diels-Alder (for more on the tandem Ugi-4CR/IMDA reaction see Section 1.2.1.6) and ring-opening/ring-closing metathesis (ROM/RCM), can allow for rapid access to complex molecules (Scheme 1.1).[11] Starting from the benzylamine **1.1**, benzyl isocyanide (**1.2**), furfural (**1.4**), and the carboxylic acid **1.3** a tandem Ugi-4CR/Diels-Alder reaction proceeded to give the **1.5**. It was then envisioned that the strained alkene in **1.5** would make a suitable substrate for ring-opening/ring-closing metathesis. However, **1.5** was not a suitable substrate for the ROM/RCM, and a subsequent bis-allylation was needed to provide **1.6**. Treatment of **1.6** with the Grubbs II catalyst in refluxing CH_2Cl_2 provided

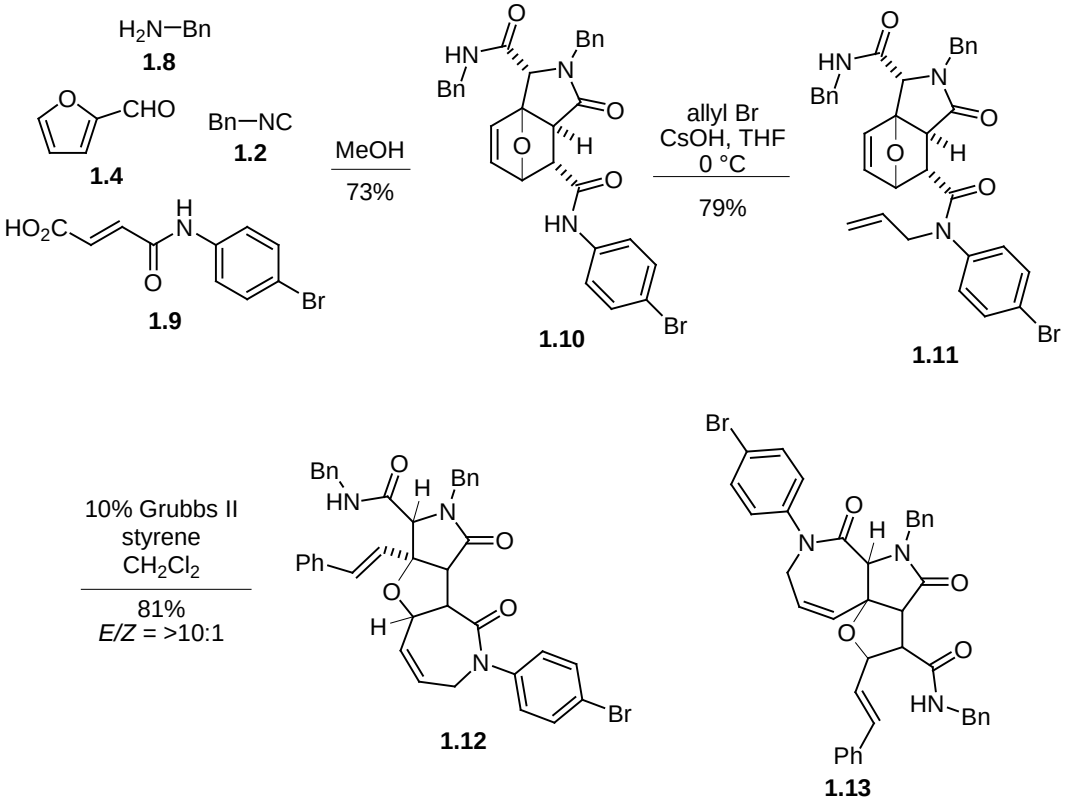
the desired tetracycle **1.7** in 69% yield. Thus, from four simple starting materials the complex 7,5,5,7-tetracyclic **1.7** could be accessed in only three steps, showing the power of sequencing complexity-generating reactions for the synthesis of complex molecules. Also, this reaction sequence resulted in the synthesis of two compounds, **1.5** and **1.7**, which contain two distinctly different molecular scaffolds, highlighting the utility of complexity generating reactions in DOS.

Scheme 1.1



Oikawa subsequently modified the acid and isonitrile components of the Ugi-4CR to develop a process whereby a selective mono-allylation of the Ugi product could be achieved (Scheme 1.2).[12] Incorporating acid **1.9** and benzyl isocyanide into the Ugi-4CR gave **1.10** in 73% yield. The *p*-bromoanilide could be selectively allylated with allyl Br and CsOH in THF at 0 ºC to give **1.11**. Since **1.11** only contains a single allyl group it cannot undergo the same ROM/RCM as **1.6**. However, upon adding styrene to the reaction, **1.11** underwent a ring-opening/cross-metathesis/ring-closing metathesis to give **1.12** in 81% yield. By simply switching the functionality contained in the isonitrile and carboxylic acid a different tricyclic scaffold, namely **1.13**, could be accessed via an analogous reaction sequence. In addition to being an illustrative example of the use complexity-generating reactions in DOS, this is also a good example of substrate based differentiation, a concept that will be further discussed in Section 1.1.5.

Scheme 1.2



The previous two examples demonstrate how by sequencing two complexity-generating reactions complex substrates can be accessed in a short number of steps from simple starting materials, making this a useful tactic for DOS. Additional examples utilizing complexity-generating reactions will be shown throughout this chapter, further highlighting their utility to DOS.

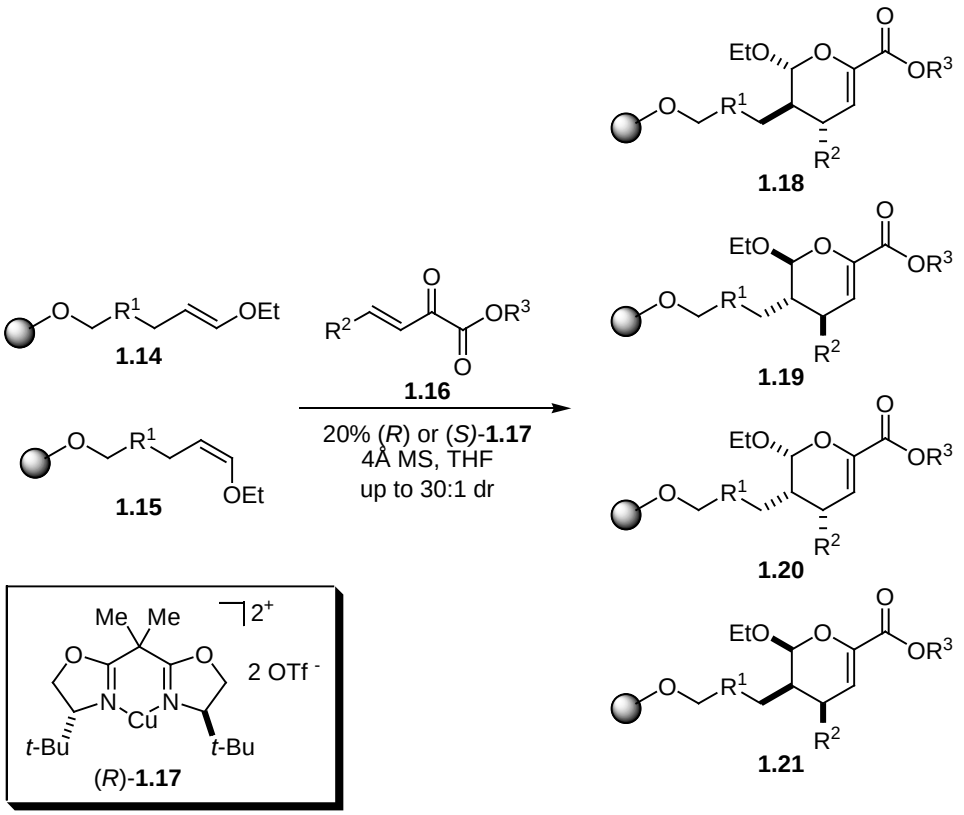
1.1.3 Stereochemical Diversity

Stereochemistry plays an important role in DOS as it determines the 3-dimensional orientation of a molecule. The stereochemistry of ring fusions determines the overall shape of a molecular skeleton, while the stereochemistry of appendages determines their relative orientation in space. Both of the overall shape of a molecule and the orientation of its appendages can influence how a small molecule interacts with a

biological target, and therefore stereochemical diversity is an important aspect to consider in DOS. In an ideal diversity synthesis every possible stereoisomer should be accessed; however, in practice this is not always possible. Stereocontrol can be achieved by both substrate and reagent control, and there are numerous methodologies for stereoselective synthesis that can be utilized in DOS. However, in situations where there is the possibility for both substrate and reagent control, it can be hard to override the inherent substrate control, and therefore it sometimes can be difficult, or even impossible, to access every possible combination of stereoisomers.

An example of this limitation in achieving stereochemical diversity can be found in Schreiber's application of the bis(oxazoline)metal Lewis acid catalyzed hetero-Diels-Alder to DOS (Scheme 1.3).[13] Starting from the resin bound *E* and *Z* enol ethers **1.14** and **1.15**, the copper bis(oxazoline) Lewis acid catalyzed the hetero-Diels-Alder with **1.16** to provide the dihydropyrans **1.18**-**1.21** with high levels of diastereo- and enantioselectivity. However, while the reactions showed high levels of selectivity for the endo product, this catalyst system did not override the inherent endo selectivity to provide the exo product. Therefore, only two of the possible four diastereomers could be synthesized using this methodology. This reaction sequence exposes one of the current limitations of DOS, and the lack of general methodologies that allow for complete control of stereochemistry regardless of substrate influences while allowing for access to every possible combination of stereoisomers needs to be addressed in order for the full potential of stereochemical diversity to be reached.

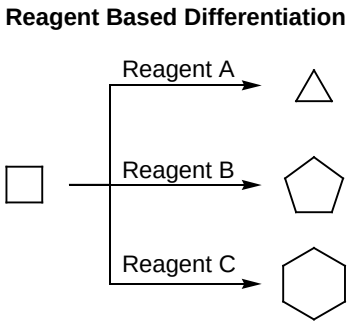
Scheme 1.3



1.1.4 Skeletal Diversity via Reagent Based Differentiation Pathways

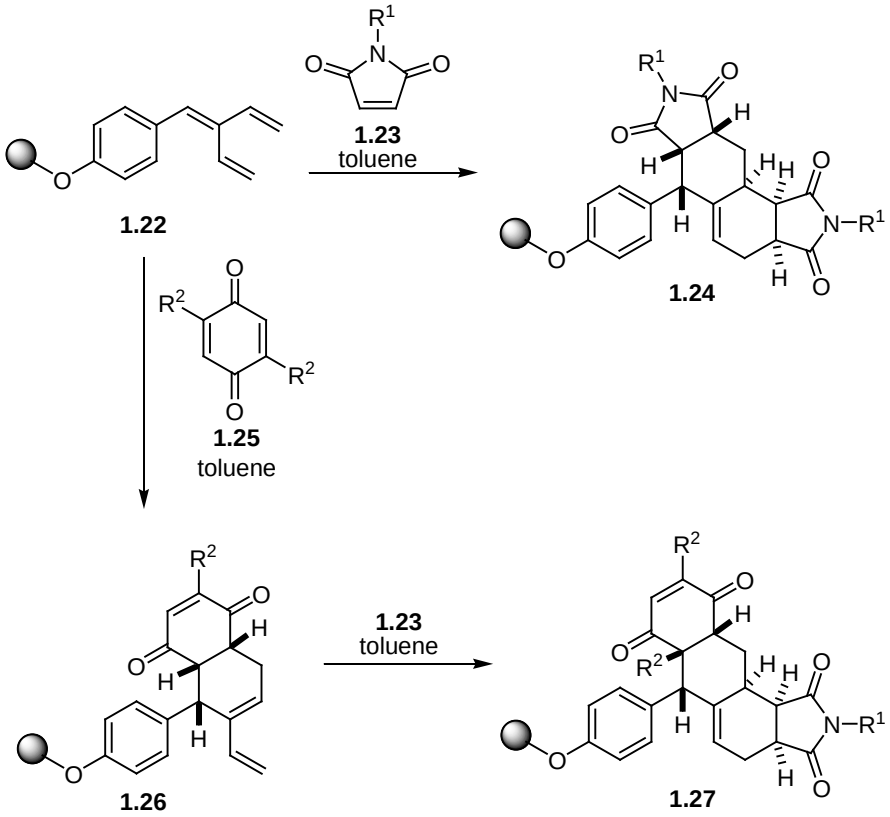
Of the three elements of diversity, skeletal diversity has the largest impact on how a molecule occupies 3-dimensional space. Therefore, this aspect of DOS has received the largest amount of attention from synthetic chemists, and two main approaches have been developed. The first of these approaches involves using reagent based differentiation (Figure 1.2). In a reagent based differentiation sequence, a single multifunctional compound is synthesized and subjected to a series of reactions with different reagents that transform the starting substrate into distinct products. The challenge in successfully implementing a reagent based differentiation lies in the identification and synthesis of multifunctional substrates that display different reactivity modes with different reagents.

Figure 1.2



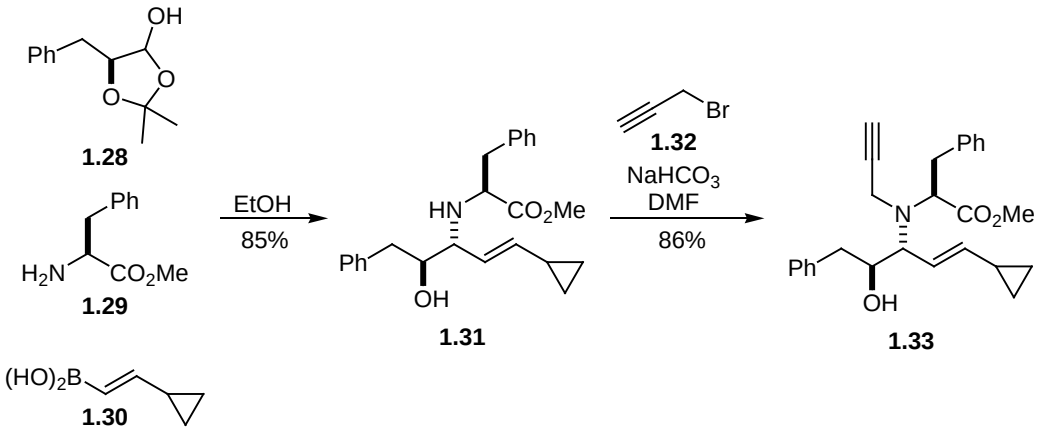
Schreiber has shown that the resin bound triene **1.22** can undergo a reagent based differentiation pathway leading to a library of polycyclic compounds (Scheme 1.4).[14] When **1.22** was treated with a reactive disubstituted dienophile such as maleimide **1.23**, a double Diels-Alder reaction takes place to give tetracyclic products such as **1.24**. However, when tri- or tetra-substituted dienophiles were utilized in the reaction, only a single cycloaddition occurred to give tricyclic products like **1.26**. The diene in **1.26** can then react with another dienophile, further increasing the diversity of the tetracyclic products.

Scheme 1.4



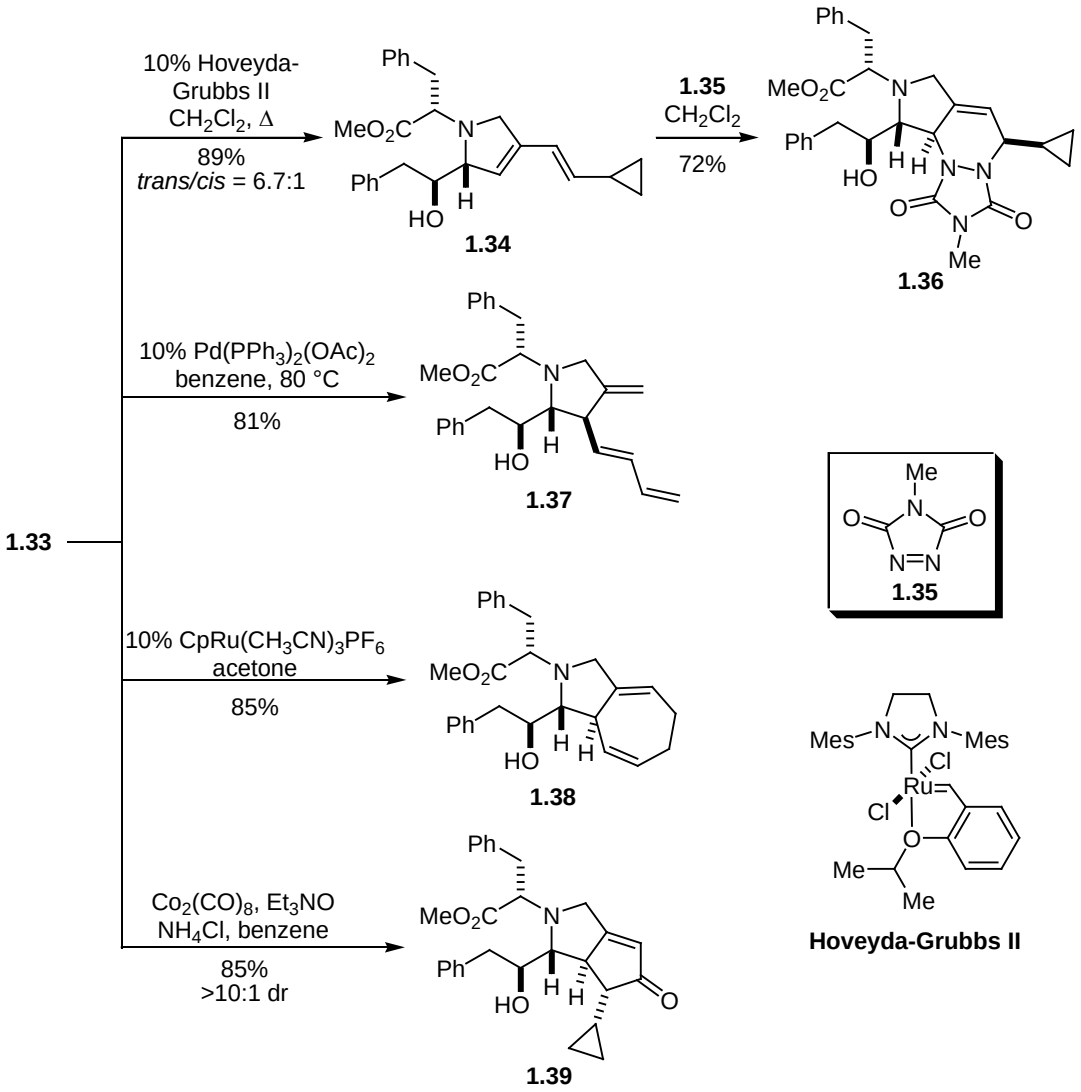
Another example of reagent based differentiation from the Schreiber labs further exemplifies the power of this DOS strategy.[15] The multifunctional amine **1.33** was synthesized using the Petasis 3CR[16] followed by a subsequent propargylation (Scheme 1.5). Amine **1.33** contains both polar (the alcohol and ester) and nonpolar (the alkene and alkyne) functional groups, and the selective pairing (for more on functional group pairing see section 1.1.7) of each of these functional groups allowed for the differentiation of **1.33** into a number of scaffolds by simply subjecting **1.33** to a variety of reaction conditions.

Scheme 1.5



First, the nonpolar enyne functionality of **1.33** was exploited in a number of cyclization reactions (Scheme 1.6). Upon treatment with the Hoveyda-Grubbs II catalyst, **1.33** underwent an enyne RCM to give **1.34**, which reacted smoothly with dienophile **1.35** in a hetero-Diels-Alder cycloaddition to give **1.36**. Cycloisomerization of **1.33** under Pd catalysis resulted in the formation of **1.37**, while a Ru catalyzed cycloisomerization resulted in a [5+2] cycloaddition to give **1.38**. Finally, a cobalt mediated Pauson-Khand reaction yielded enone **1.39**. Thus, by pairing the nonpolar functional groups present in **1.33** in various different transition metal mediated reactions, five distinct scaffolds could be readily accessed.

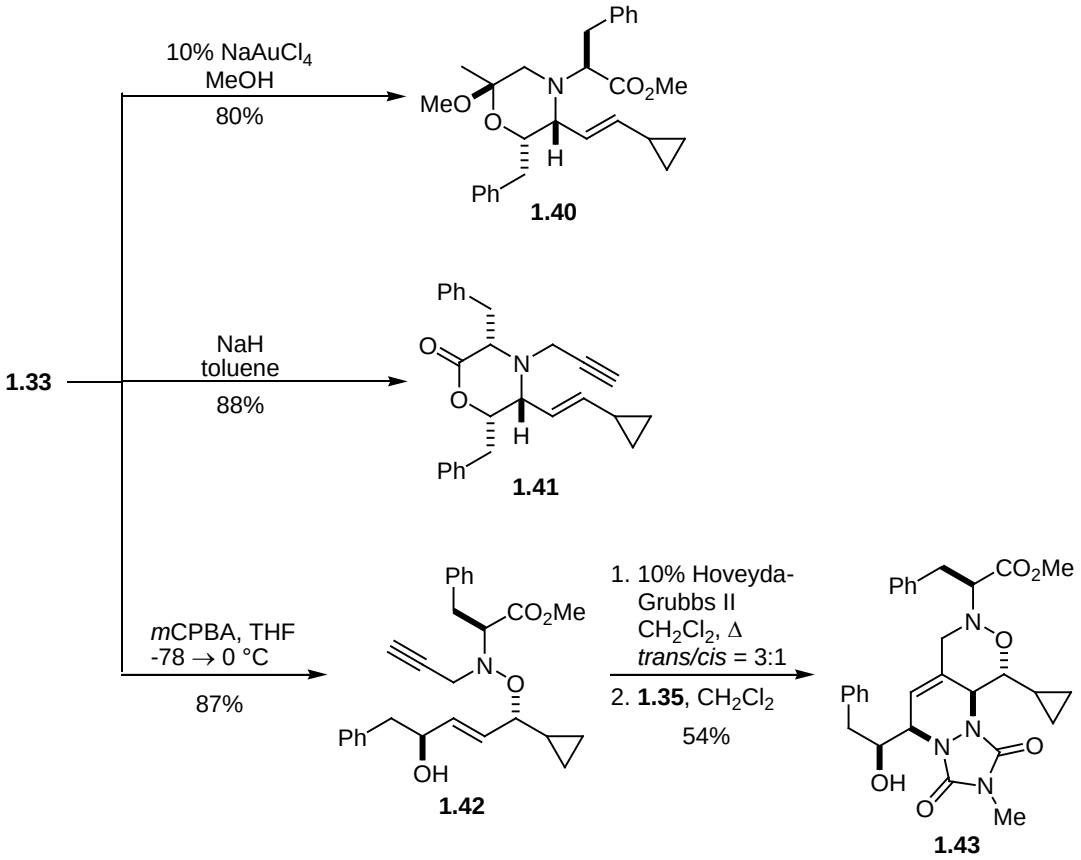
Scheme 1.6



The polar functional groups in **1.33** could also be utilized in a series of reactions leading to a different set of compounds (Scheme 1.7). A gold catalyzed cyclization of the alcohol onto the alkyne resulted in the formation of the morpholine **1.40**. Base mediated lactonization of **1.33** provided **1.41**. Treatment of **1.33** with *m*CPBA in THF resulted in oxidation of the amine to the *N*-oxide, and a subsequent rearrangement provided **1.42**.

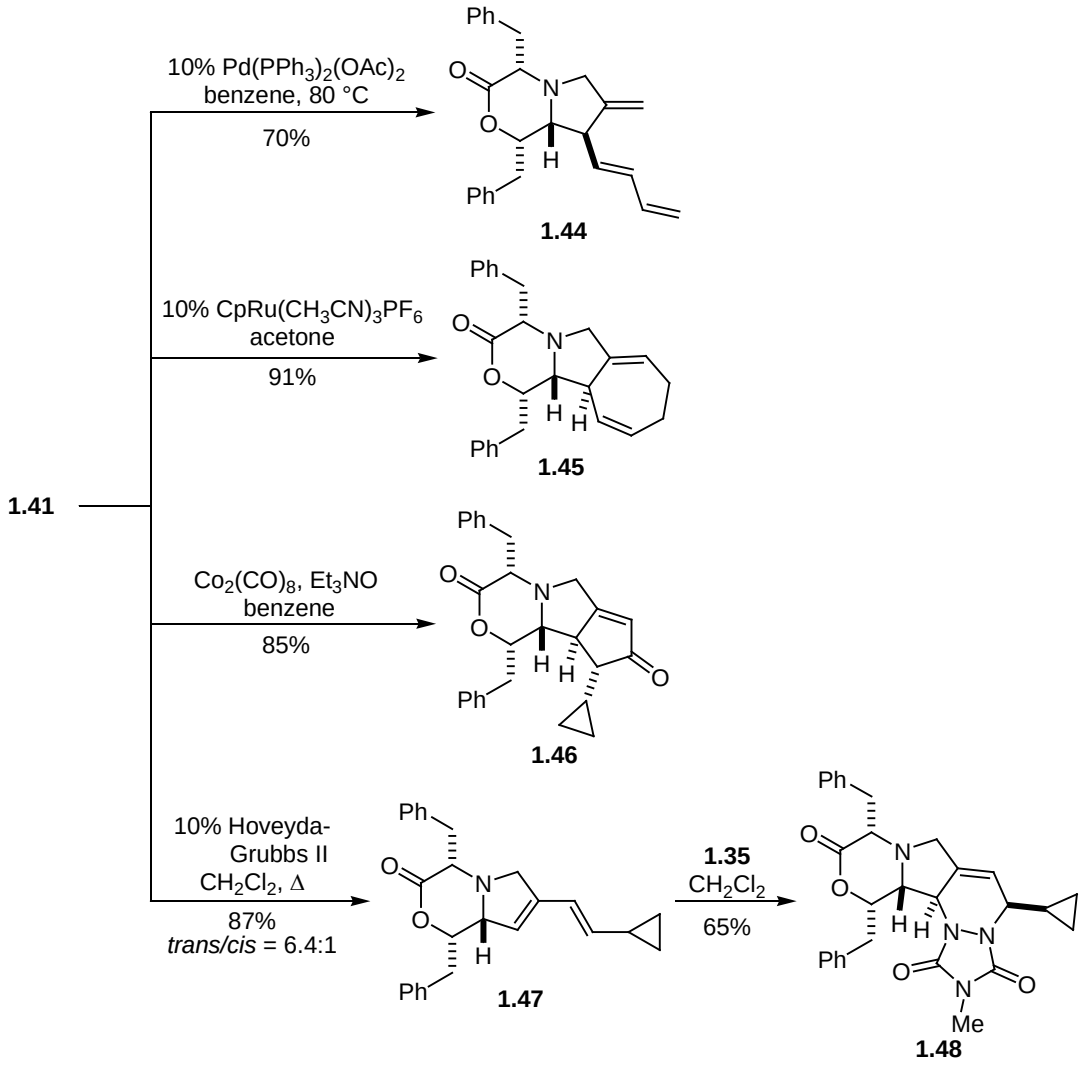
The enyne functionality present in **1.42** could then be utilized in an enyne RCM/Diels-Alder sequence to provide **1.43**.

Scheme 1.7



Lactone **1.41** still contains a 1,6-enyne unit identical to that found in **1.33**, and therefore could to undergo the same set of cyclizations to give **1.44**-**1.47** (Scheme 1.8). Substrates containing enyne functionality are particularly well suited for reagent based differentiation due to their ability to participate in a number of transition metal mediated processes, and additional examples utilizing enyne substrates will be shown throughout this chapter. Additionally, the sequencing of enyne RCM and Diels-Alder reactions is a commonly employed tactic in DOS.

Scheme 1.8



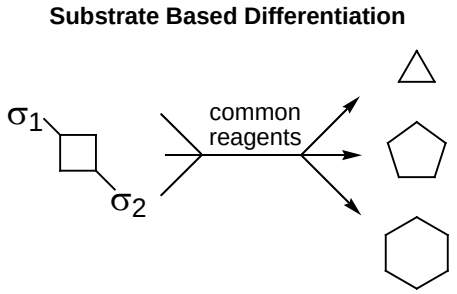
The above sequence of reactions shows how with careful planning a reagent based differentiation can be used to access a diverse collection of compounds in a short number of steps. Amine **1.33** contains four functional handles, and each was selectively utilized in reactions with a predetermined set of conditions to provide different heterocyclic products. However, it is still a challenge for organic chemists to design and synthesize multifunctional substrates that are amenable to reagent based differentiation, and as more

of these pluripotent substrates are identified chemists and biologists will have access to more diverse regions of chemical space.

1.1.5 Skeletal Diversity via Substrate Based Differentiation

A second method for creating skeletal diversity is by using substrate based differentiation. In this approach a collection of substrates with different appendages that pre-encode skeletal information are subjected to a common set of reagents to generate compounds with varied molecular skeletons (Figure 1.3). The appendages, which have been referred to as σ-elements, are strategically placed so that the functionality they contain can dictate the outcome of the reaction, and thus the outcome of the reaction is under substrate control.

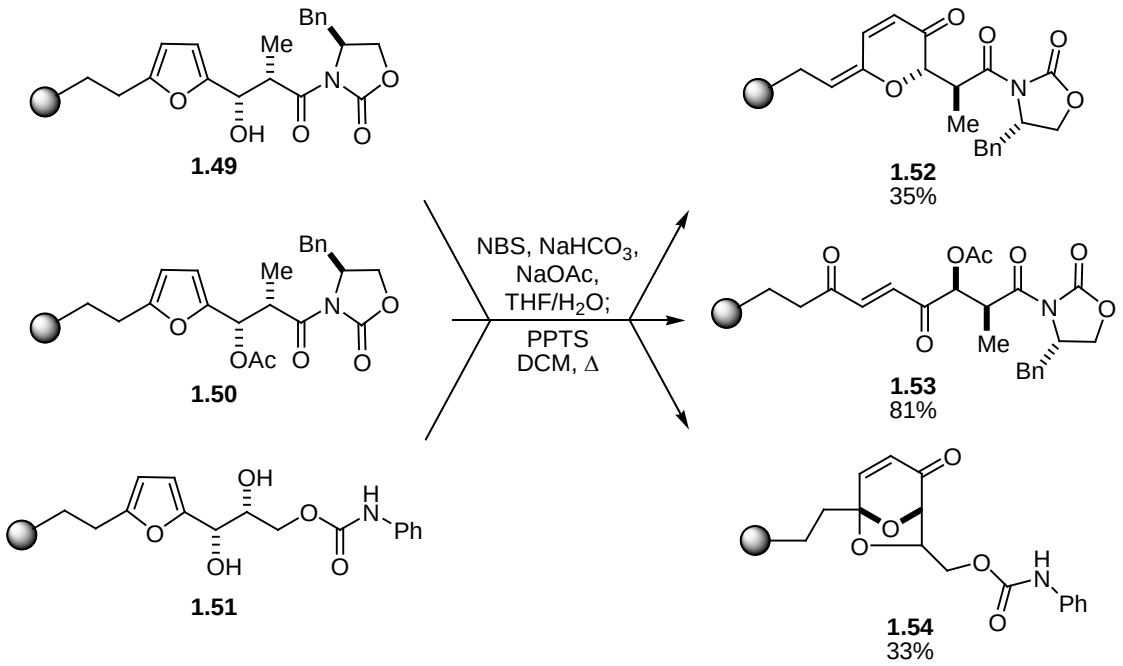
Figure 1.3



A substrate based differentiation process developed by Schreiber that utilizes the Achmatowicz reaction[17] is representative of this approach (Schemes 1.9 and 1.10).[18, 19] First, the functionalized furans **1.49**-**1.51** were synthesized on solid support. These furans were oxidized with NBS, and the intermediates derived there from were treated with acid to induce cyclization. In the case of **1.49**, the σ-element is the free hydroxyl group, which under acidic conditions undergoes cyclization and dehydration to give **1.52**. In the case of **1.50**, the hydroxyl group is protected, preventing any subsequent cyclization reactions. Furan **1.51**, with two free hydroxyl groups, can undergo an

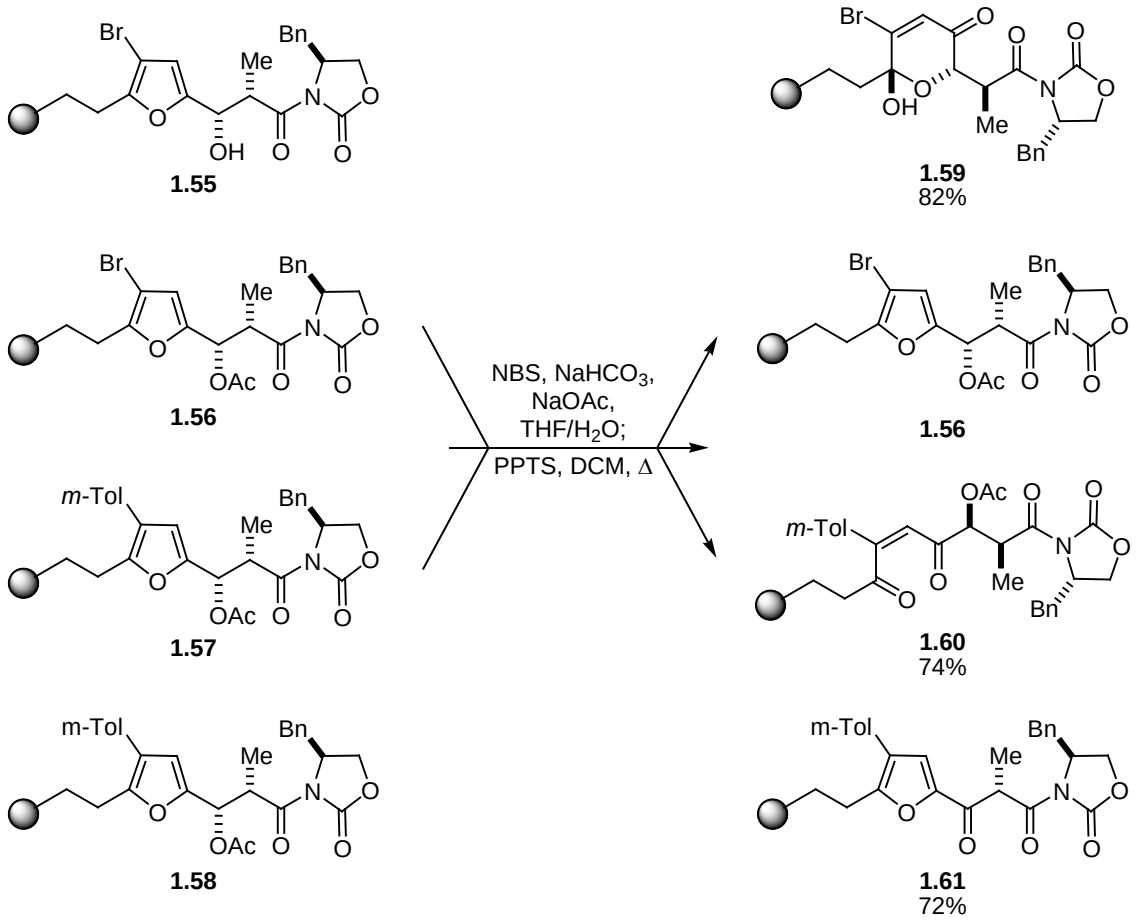
intramolecular ketalization to give **1.54**. Thus, the nature of the hydroxyl groups appended to the starting furans dictated the product of the reaction.

Scheme 1.9



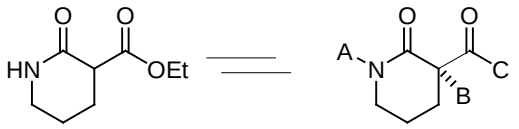
An additional set of σ-elements can also be incorporated onto the furan ring, adding a second level of control to dictate the outcome (Scheme 1.10). The bromofuran **1.55** underwent oxidative ring expansion to provide **1.59**. Interestingly, the dehydration that occurred in the reaction of **1.49** did not proceed in this case. The acetate protected bromofuran **1.56** was found to be unreactive under these conditions. However, acetate **1.57**, with an aryl substituent on the furan, underwent oxidation to give enedione **1.60**. When the hydroxyl group was left unprotected as in **1.58**, oxidation occurred as expected, but upon exposure to PPTS a ring contraction, dehydration, and rearomatization to give **1.61**. Thus, by incorporating two σ-elements into the starting substrate, a combinatorial approach could be utilized to generate skeletal diversity, and in this manner a library of more than 1000 compounds were synthesized.[19]

Scheme 1.10



An alternative approach to substrate based differentiation was developed by Schreiber for generating indole alkaloid-like skeletons (Scheme 1.11).[20] Starting from a single scaffold, **1.62**, functional groups amenable for a Rh(II) catalyzed [1,3]-dipolar cycloaddition could be iteratively appended at one of three places around the scaffold, leading to **1.64**-**1.66**. Thus, three different modes of cyclization were made available. An A→B cyclization mode yielded **1.67**, while the A→C and C→A modes of cyclization yielded **1.68** and **1.69**, respectively. These examples demonstrate how moving functional handles around a defined scaffold can lead to the generation of diverse structures.

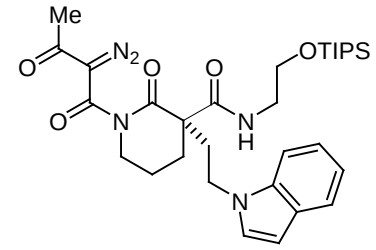
Scheme 1.11



1.62 **1.63**

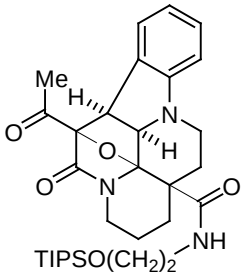
Possible Modes of Cyclization
A → B, B → A, C → A
A → C, B → C, C → B

A → B



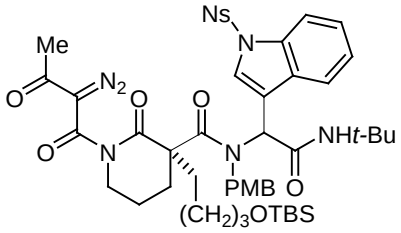
1.64

$Rh_2(O_2CC_7H_{15})_4$
benzene, 50 °C
73%



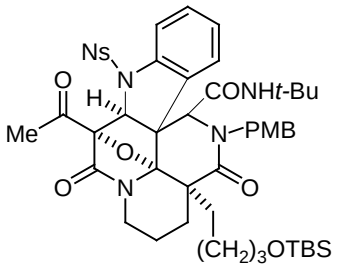
1.67

A → C



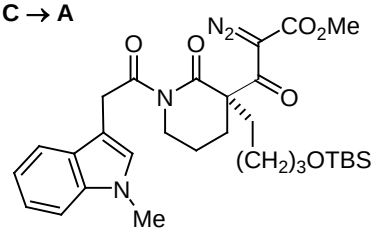
1.65

$Rh_2(O_2CC_7H_{15})_4$
benzene, 50 °C
57%



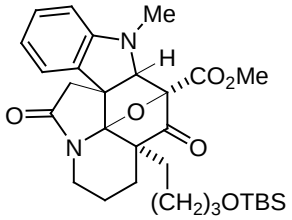
1.68

C → A



1.66

$Rh_2(O_2CC_7H_{15})_4$
benzene, 50 °C
74%

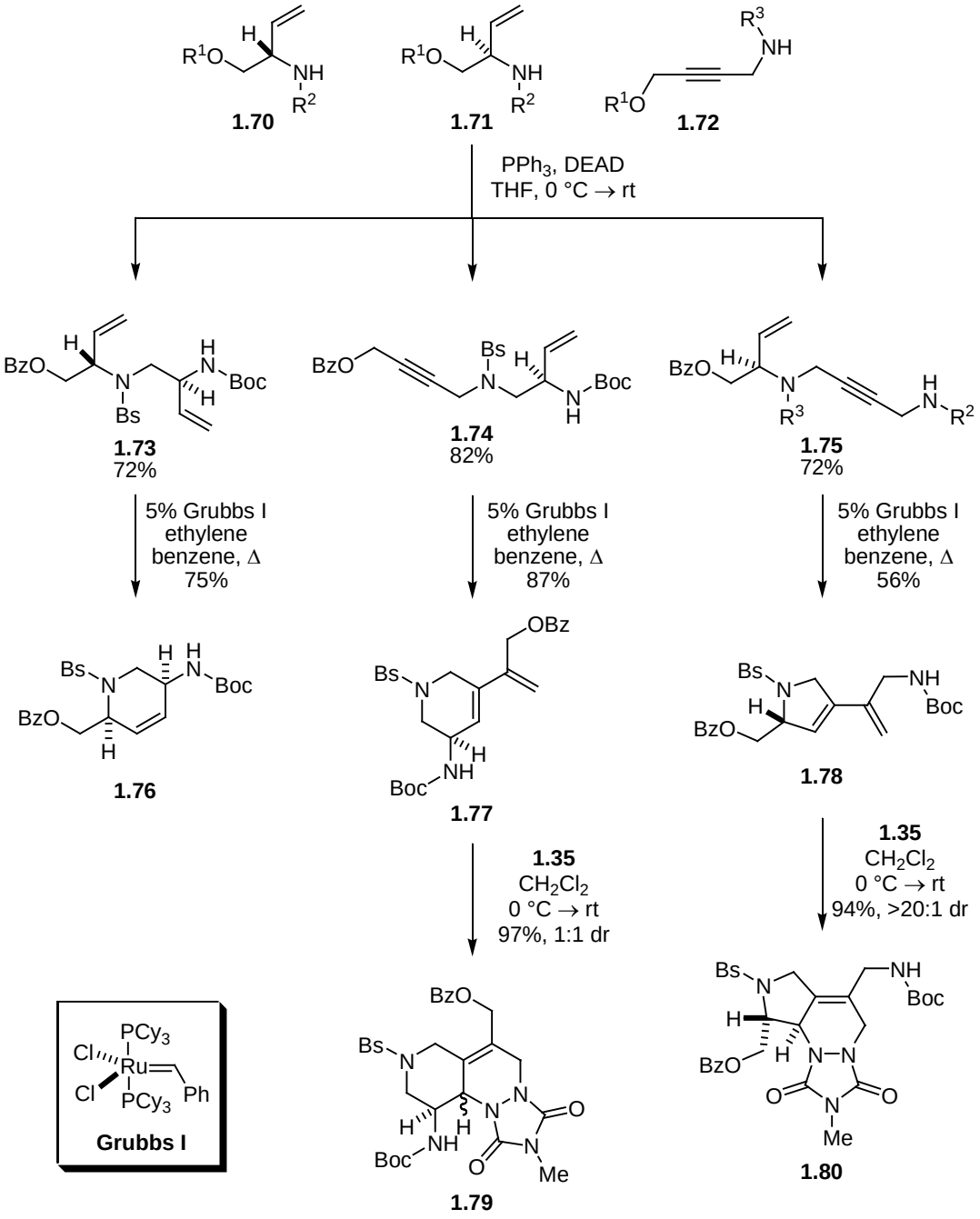


1.69

Schreiber has also developed an oligomer-based approach to generating skeletal diversity.[21] In this approach reactive oligomers are synthesized from functionalized monomers and then transformed via substrate based differentiation into distinct scaffolds (Scheme 1.12). The starting monomers, allylamines **1.70** and **1.71** and propargyl amine

1.72, were chosen because the olefin functionalities would be suitable for generating heterocyclic structures via RCM. The monomers were first coupled via a Mitsunobu reaction to give three linear dimers, which were then cyclized using the Grubbs I catalyst in refluxing benzene. Diene **1.73** underwent a simple RCM to give **1.76**, while enynes **1.74** and **1.75** underwent enyne RCM to provide **1.77** and **1.78**, respectively. The 1,3-dienes generated by the enyne RCM were then subjected to a subsequent Diels-Alder reaction to provide **1.79** and **1.80**.

Scheme 1.12

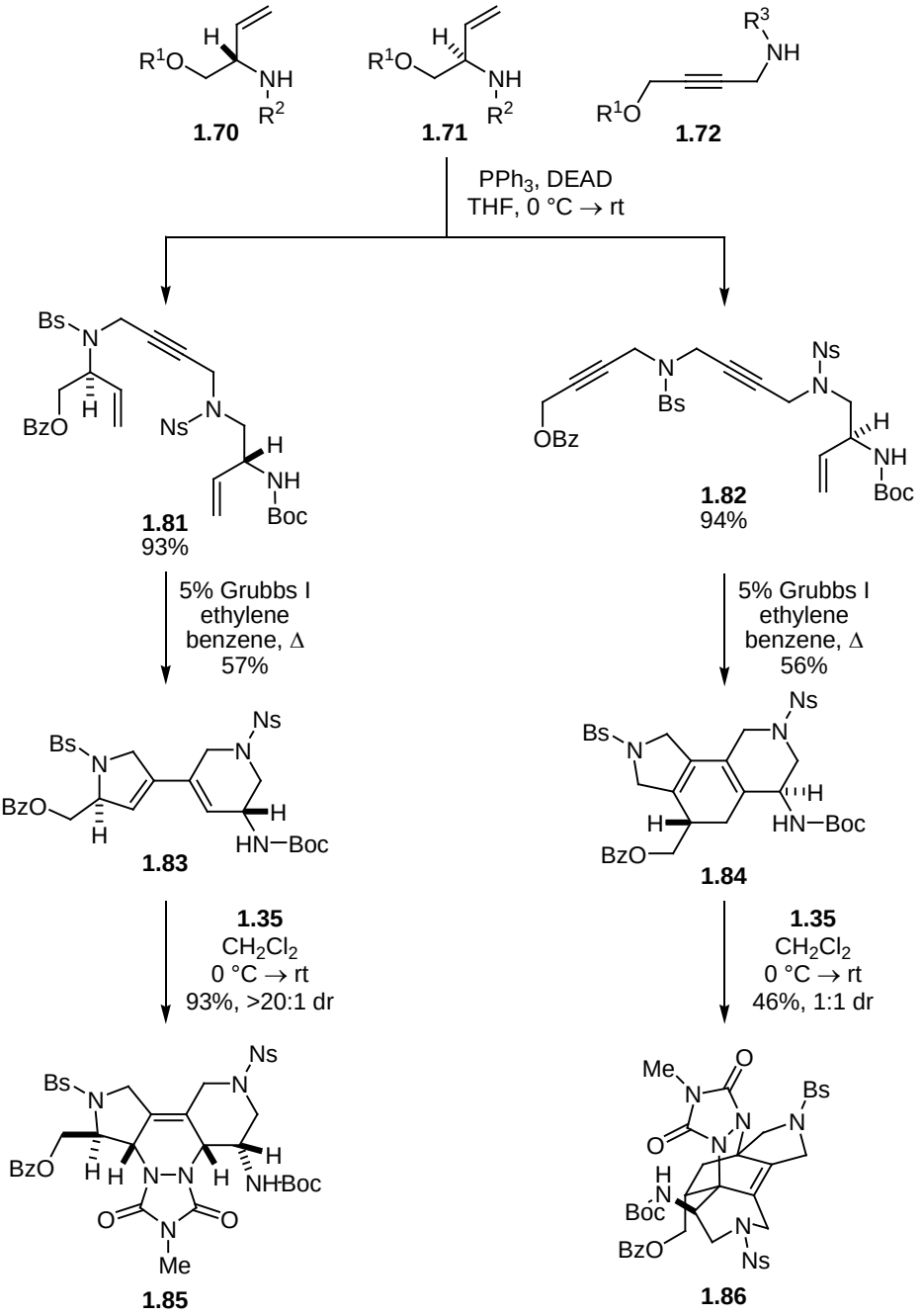


Trimers **1.81** and **1.82** could be accessed from the original monomers by two sequential Mitsunobu reactions (Scheme 1.13). The addition of a third site of unsaturation into these oligomers allows for double RCM reactions to occur leading to bi-

or tricyclic substrates. Thus, dienyne **1.81** underwent a tandem enyne RCM/RCM to provide the bicylcic **1.83**, which could undergo a subsequent Diels-Alder with **1.35** to generate **1.85**. The ene-diyne **1.82** underwent a similar double enyne RCM, which was followed by a subsequent 6π-electrocyclic ring closure and 1,5-hydride shift to provide **1.84**. Tricycle **1.84** also underwent an intermolecular Diels-Alder to provide the complex polycyclic **1.86**.

The previous examples show how substrate based differentiations can be a useful strategy in DOS. The challenge for synthetic chemists is to devise different combinations of appendages that allow for alternative modes of reactivity to be accessed, which in turn leads to a wider range of obtainable target molecules.

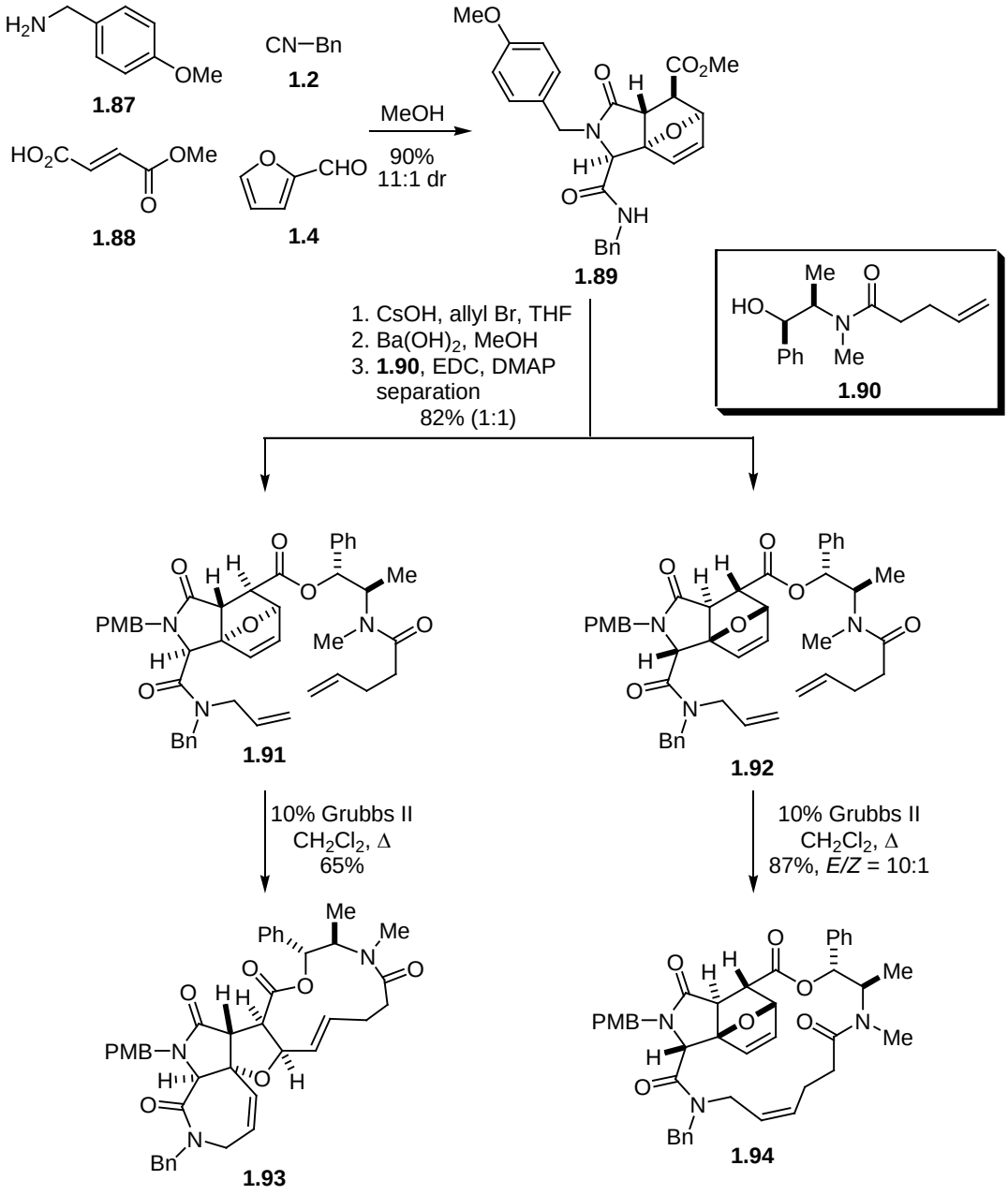
Scheme 1.13


1.70
1.71
1.72
PPh3, DEAD
THF, 0 °C → rt
1.81
93%
1.82
94%
5% Grubbs I
ethylene
benzene, Δ
57%
5% Grubbs I
ethylene
benzene, Δ
56%
1.83
1.84
1.35
CH2Cl2
0 °C → rt
93%, >20:1 dr
1.35
CH2Cl2
0 °C → rt
46%, 1:1 dr
1.85
1.86

1.1.6 Stereochemical Control of Skeletal-Diversity

The use of stereochemical control is a common tactic in TOS, but its application to DOS has been limited. One example developed by Schreiber utilizes the stereochemistry, rather than the inherent reactivity, of a σ-element to control skeletal diversity (Scheme 1.14).[22] Following a reaction sequence similar to that shown in Scheme 1.1, an Ugi-4CR/DA sequence provided the tricyclic **1.89**. Subsequent allylation, saponification, and esterification provided the separable diastereomers **1.91** and **1.92**. Subjecting **1.91** to 10% Grubbs II catalyst in refluxing CH_2Cl_2 resulted in a ROM/RCM sequence to provide **1.93**. However, when **1.92** was reacted under identical conditions, only macrocycle **1.94** was formed. It was determined that the relative orientation of the phenyl group on the ester side chain was controlling the outcome of these reactions. When the phenyl group is α, as it is in **1.91**, the ROM/RCM pathway dominates, but when the phenyl group is β, as it is in **1.92**, macrocyclization is the preferred pathway. This example shows how subtle changes in stereochemistry can be exploited in DOS.

Scheme 1.14



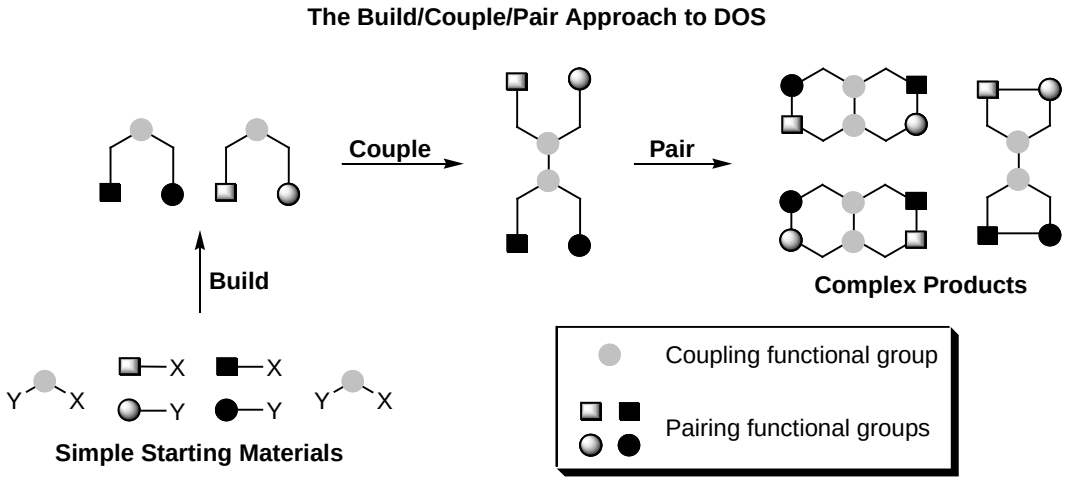
1.1.7 The Build/Couple/Pair Strategy

The previously discussed strategies for DOS focused mainly on the reagent and substrate controlled differentiations of substrate molecules. However, in many of these

examples, an underlying synthetic approach was utilized that up until this point has not been discussed. This three step approach has been called the build/couple/pair (B/C/P) strategy (Scheme 1.15).[23]

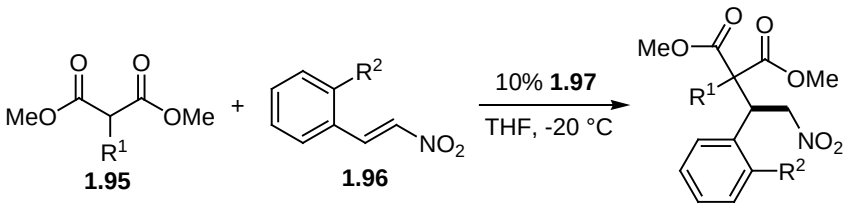
The first step, the build step, involves the syntheses of building blocks containing orthogonal sets of functionality that will be exploited in the subsequent coupling and pairing steps. In the couple step, an intermolecular coupling of the building blocks assembled during the build stage leads to more complex molecules with a range of functionality. In addition to building in all of the requisite functionality needed for subsequent cyclizations, these first two steps also enable the incorporation of any desired stereochemical diversity. Finally, in the pair step the functional groups that were incorporated in build phase are paired in intramolecular reactions leading to cyclic scaffolds. This final step, known as functional group pairing,[24] is where the skeletal diversity is generated.

Scheme 1.15



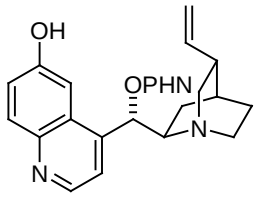
Porco has recently developed a synthetic strategy that exemplifies the B/C/P approach,[24] and this will be discussed as a representative example; however, many of the examples outlined in this Chapter also utilized this approach effectively. The starting materials for Porco's approach, **1.95** and **1.96**, could be readily synthesized during the build phase and coupled using an asymmetric Michael addition catalyzed by the modified Cinchona alkaloid **1.97** (Table 1). This coupling provided the densely functionalized products **1.98-1.101** in moderate yields and high enantioselectivities. These substrates contain nonpolar alkene and alkyne functional groups, as well as polar nitro and ester functional groups that could potentially be paired in subsequent cyclizations.

Table 1.1



Entry	R^1	R^2	Product	Yield (%)	ee (%)
1*	propargyl	H	**1.98**	45	92
2	allyl	H	**1.99**	44	90
3	allyl	allyl	**1.100**	35	95
4	propargyl	allyl	**1.101**	55	92

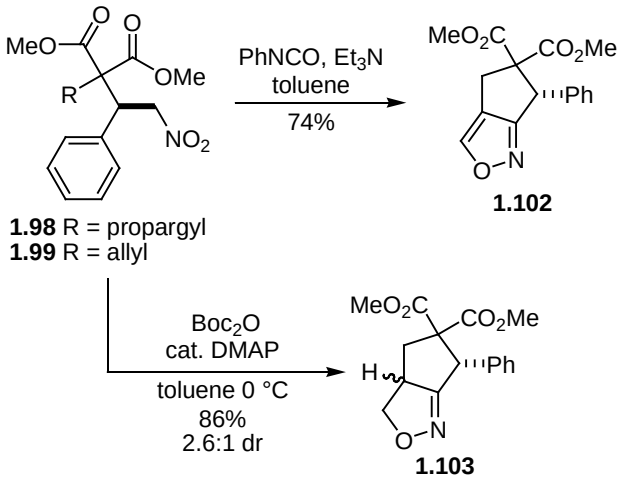
* Run at -40 °C



1.97
PHN = 9-phenanthroline

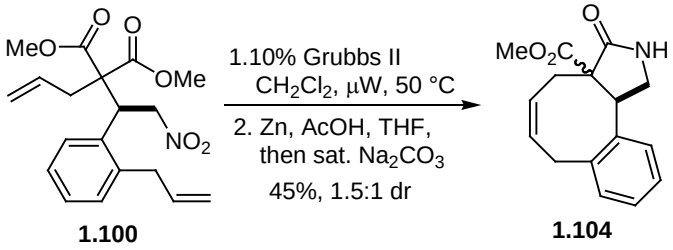
The nitro group in **1.98** could be selectively paired with an alkene or alkyne in 1,3-dipolar cycloadditions to generate isoxazole scaffolds (Scheme 1.16). To this end, alkyne **1.98** was treated with phenyl isocyanate and Et_3N in toluene to form an intermediate nitrile oxide which underwent a 1,3-dipolar cycloaddition to give **1.102** in 74% yield. Similarly, alkene **1.199** could be treated with Boc_2O and catalytic DMAP in toluene at 0 ºC to provide **1.103** in 86% yield and 2.6:1 *dr*.

Scheme 1.16



By incorporating two alkenes into **1.100**, a substrate amenable to RCM was generated (Scheme 1.17). Thus, diene **1.100** underwent RCM upon treatment with the Grubbs II catalyst, and subsequent reduction of the nitro group followed by cyclization provided the tricyclic lactam **1.104** in 45% yield over the two steps. The two alkenes in **1.100** were effectively paired via RCM, while the ester and nitro group were paired via reduction and lactam formation. Thus, all four of the functional groups were fully utilized.

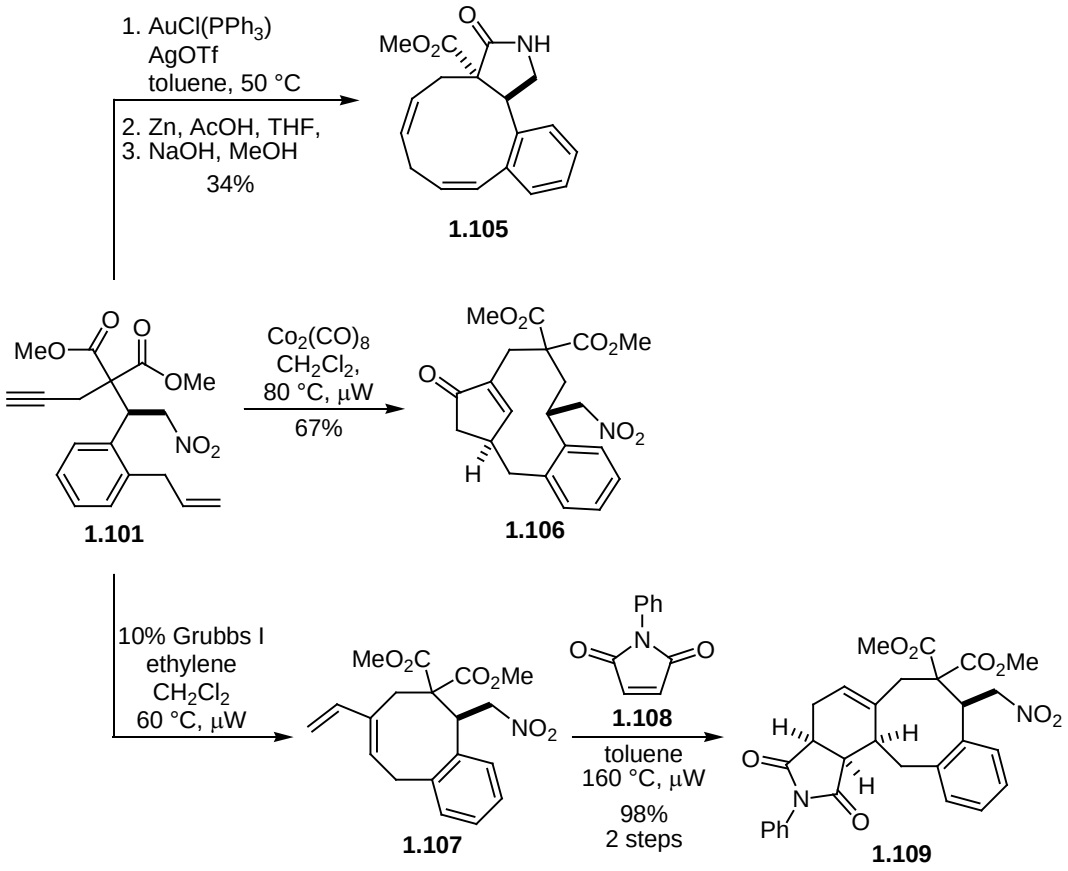
Scheme 1.17



As with previous examples, the alkene and alkyne in **1.102** could be effectively paired under a number of different reaction conditions (Scheme 1.18). Treatment of **1.101** with the cationic Au(I) catalyst derived from $AuCl(PPh_3)$ and AgOTf resulted in a

cycloisomerization to **1.105**. The reaction of **1.101** with $Co_2(CO)_8$ provided the desired Pauson-Khand product **1.106** in 67% yield. Finally, **1.101** underwent an enyne RCM/Diels-Alder sequence to provide **1.109** in excellent yield. This example again highlights the potential number of cyclization modes that are accessible by pairing an appropriately disposed alkene and alkyne.

Scheme 1.18



The B/C/P approach has a great amount of potential for DOS, and almost every example contained in this chapter utilizes this approach. In fact, if proper care is taken in the design of the synthetic route almost any functional group can be incorporated during the build and couple stages for use in subsequent functional group pairing reactions. This places a large burden on the coupling reactions, as they need to be efficient, high

yielding, and functional group tolerant. One such strategy for the coupling stage that generally meets these criteria is the use of multicomponent reactions, and their application to DOS will be discussed herein.

1.2 Applications of Multicomponent reactions to the Synthesis of Diverse Heterocyclic Scaffolds

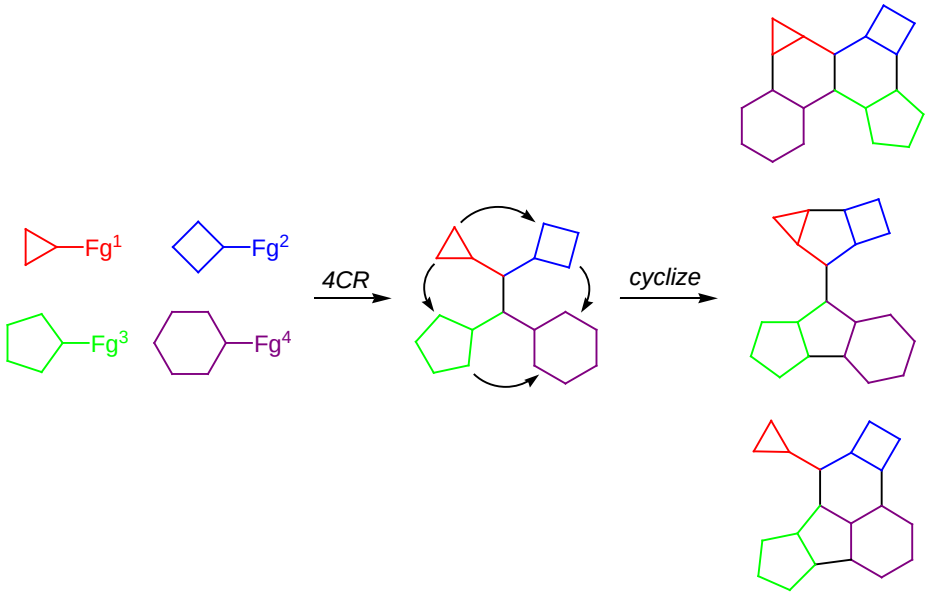
1.2.1 Introduction

Perhaps the most promising synthetic strategy for generating collections of diverse molecules is the sequencing of multicomponent reactions (MCRs) with subsequent transformations that lead to the generation of new compounds with increased molecular complexity and diversity (Scheme 1.19).[25] Although this process of sequencing MCRs with subsequent cyclizations falls mainly under the build/couple/pair strategy of DOS, as evidenced by the examples shown in the previous section, MCRs are applicable to all of the DOS strategies.

Multicomponent reactions are generally defined as reactions where three or more starting materials are allowed to react to form a product that incorporates a majority of the atoms contained in the starting materials.[26] MCRs are by definition complexity-generating reactions, making them ideal for use in DOS and drug discovery.[27] However, the MCRs that are designed and implemented should be versatile so that each component of the MCR can incorporate a wide range of functionalities. Then through the use of functional group pairing these functional groups can be selectively exploited in subsequent ring forming processes, leading to more diverse and complex structures. This should lead to a situation where potentially any reaction can be utilized to transform the intermediates generated by the MCR into the target heterocyclic structures. Additionally, the ring forming reactions should be chosen so that the products they generate still contain functional handles that can be further elaborated as needed. This combination of

MCRs with post-condensation modifications should then allow for access to a number of functionalized heterocyclic scaffolds in a short number of steps.

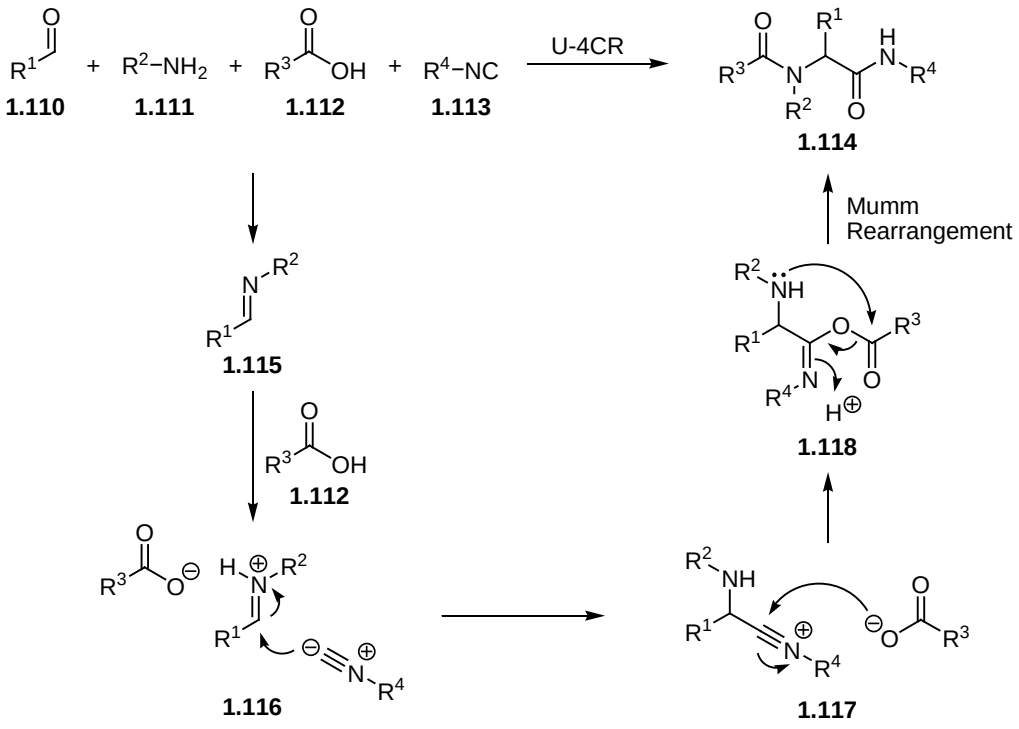
Scheme 1.19



1.2.2 Applications of the Ugi-4CR and related Isocyanide Based MCRs.

Since its publication in 1959[28] the Ugi four component reaction (Ugi-4CR) has become the most widely used MCR in organic chemistry.[29, 30] The Ugi-4CR involves the combination of an aldehyde, amine, carboxylic acid, and an isocyanide and proceeds mechanistically as shown in Scheme 1.20. First, the amine and aldehyde react to provide an imine, which is subsequently protonated under the acidic conditions to provide iminium ion **1.116**. The isocyanide then adds to the iminium ion to provide **1.117**, and subsequent addition of the carboxylate ion provides **1.118**. An intramolecular acylation, known as the Mumm rearrangement,[31] occurs as the final step to provide the desired adduct **1.114**.

Scheme 1.20



The Ugi-4CR is very functional group tolerant and each of the four components can incorporate functionality for use in subsequent transformations, thus allowing for access to a number of cyclization manifolds. It is then not surprising that there has been substantial work focused on the post condensation modifications of the Ugi-4CR,[30, 32-34] and much of this work will be described below.

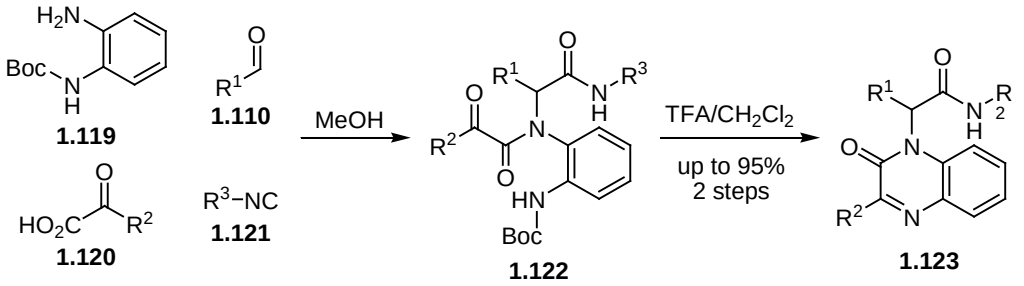
1.2.2.1 Ugi/de-Boc/Cyclization

The incorporation of additional nitrogen functionality into the starting materials of the Ugi-4CR is desirable because this functionality can be utilized in subsequent steps for the synthesis of nitrogen containing heterocycles. However, because primary amines are one of the four components of the Ugi-4CR, any additional amines that are to be incorporated need to be protected. A commonly employed tactic is to Boc-protect the additional nitrogen for the Ugi-4CR, deprotect the resulting Ugi product, and then engage

the resulting free amine in a subsequent cyclization reaction. This is commonly called the Ugi/de-Boc/cyclize (UDC) strategy, and has been employed in the synthesis of numerous heterocyclic scaffolds.

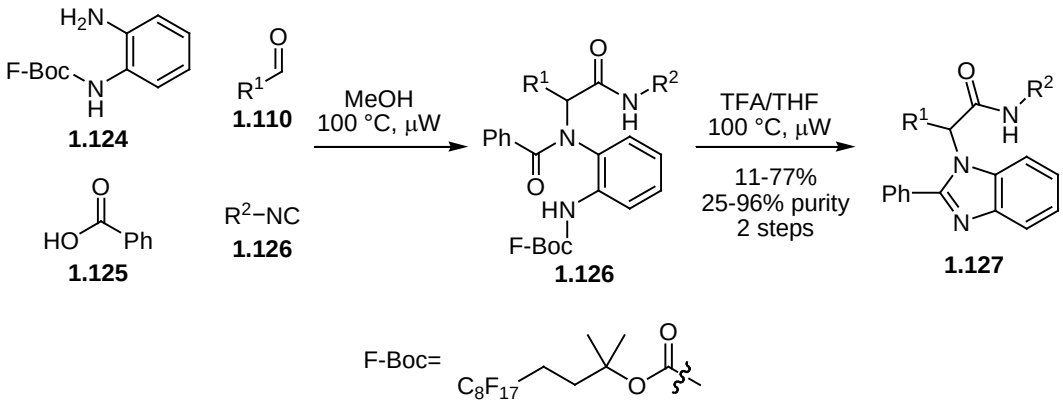
Hulme has developed a UDC strategy that allows efficient access to quinoxalinone scaffolds (Scheme 1.21).[35] The mono-protected phenylene diamine **1.119** was reacted in the Ugi-4CR with a number of different aldehydes, glyoxylic acids, and isonitriles to give adducts **1.122**. Upon treatment with TFA in CH_2Cl_2 **1.122** underwent deprotection and cyclization to give the target quinoxalinones **1.123** in good yields over the two steps.

Scheme 1.21



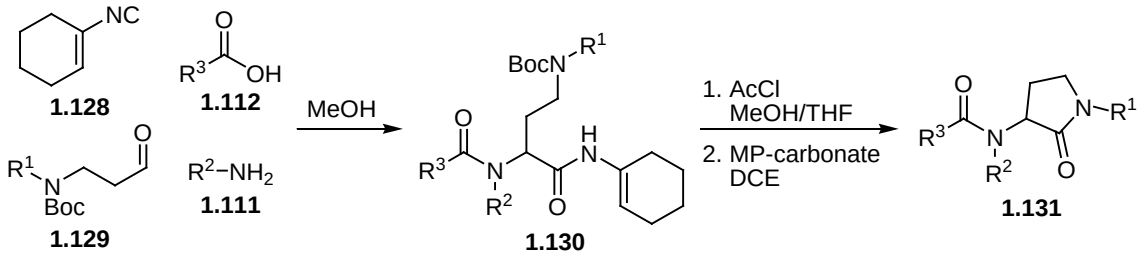
A similar two step procedure was later adapted for the synthesis of benzimidazoles (Scheme 1.22).[36] However, in this case the fluorous-Boc (F-Boc) protecting group was utilized to allow for purification of the Ugi products by fluorous SPE (F-SPE). When F-Boc protected **1.124** was utilized in the Ugi-4CR, the desired amides **1.126** were produced. Subsequent deprotection and cyclization produced the desired benzimidazoles **1.127** in varying yields and purities after F-SPE.

Scheme 1.22



A three-step route to γ-lactams utilizing a convertible isonitrile and the UDC strategy has also been reported by Hulme (Scheme 1.23).[37] The reaction of the Armstrong convertible isocyanide **1.128**[38] and Boc-protected amino aldehydes **1.129** with carboxylic acids and amines formed **1.130**. Treatment of **1.130** with AcCl in MeOH/THF resulted in deprotection of the amine and conversion of the cyclohexenyl amide to the methyl ester, and subsequent base mediated lactam formation provided the desired γ-lactams **1.131**. The yields for this sequence were not reported, and purities of the products as determined by HPLC ranged from poor to excellent.

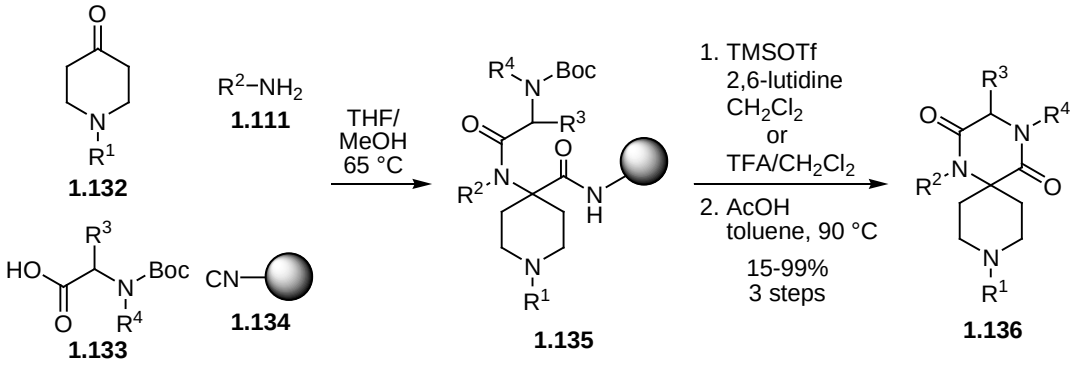
Scheme 1.23



Habashita has demonstrated that the UDC sequence can be utilized for synthesizing spirodiketopiperazines that were shown to be selective CCR5 antagonists (Scheme 1.24).[39] Boc-protected amino acids **1.133** were reacted with ketones **1.132**, amines **1.111**, and a resin bound isonitrile to give **1.135**. Boc-deprotection, acid

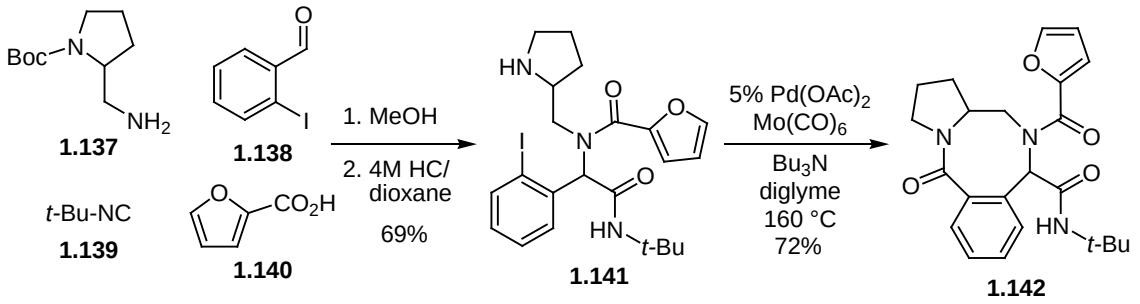
catalyzed cyclization, and resin cleavage provided the desired spirodiketopiperazines **1.136** in variable yields.

Scheme 1.24



The UDC sequence has also been applied to the synthesis of medium sized lactams via a Pd catalyzed carbonylation/amidation reaction (Scheme 1.25).[40] The Ugi-4CR of amine **1.137**, 2-iodobenzaldehyde (**1.138**), acid **1.140**, and *t*-butyl isocyanide provided the Ugi adduct, which was subsequently treated with HCl in dioxane to provide **1.141** in 69% over two steps. When **1.141** was subjected to Pd catalyzed carbonylation conditions, the desired lactam **1.142** was produced in 72% yield.

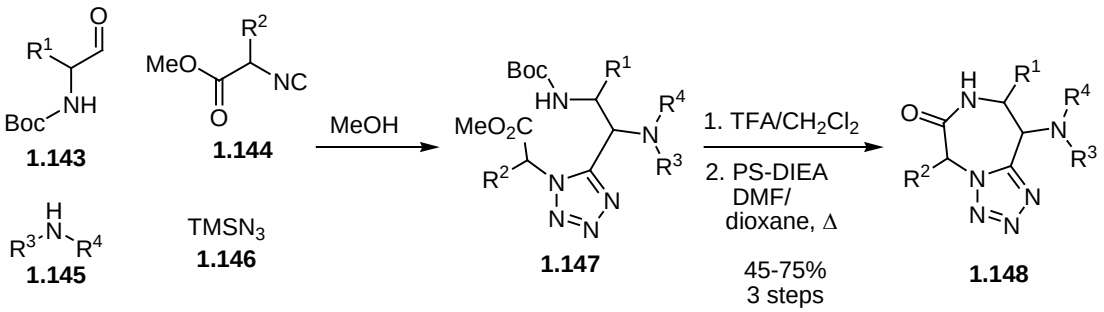
Scheme 1.25



A variant of the Ugi-4CR that accesses tetrazoles by substituting $TMSN_3$ for the normal carboxylic acid component was utilized by Hulme in a UDC pathway to access azepine-tetrazoles **1.148** (Scheme 1.26).[41] Thus, when Boc-protected amino aldehydes

1.143 were reacted with secondary amines, methyl-isocyano acetates **1.144**, and $TMSN_3$ the desired tetrazoles **1.147** could be synthesized. A two step Boc-deprotection/cyclization sequence provided the desired azepine-tetrazoles in moderate yields over the three steps.

Scheme 1.26



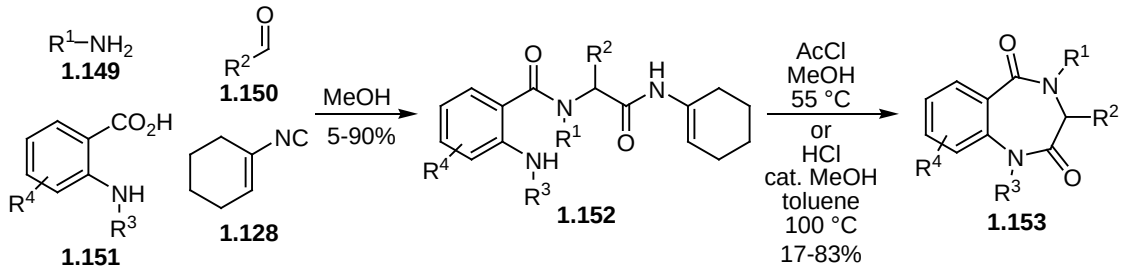
The examples above show how the UDC strategy can be applied to the synthesis of a number of interesting nitrogen containing scaffolds. However, this is not a comprehensive list, and additional examples of this reaction sequence can be found throughout this Chapter and in the literature.

1.2.2.2 Ugi 4CR/Intramolecular Cyclization to Give Benzodiazepines

Benzodiazepines are an important class of biologically active compounds and are considered to be the prototypical privileged structure.[3] Therefore it is not surprising that these molecules have attracted considerable attention from synthetic chemists. One of the notable routes to benzodiazepines involves the sequencing of the Ugi-4CR with a subsequent cyclization, usually via amide formation. Armstrong was the first to apply the Ugi reaction to the synthesis of 1,4-benzodiazepine-2,5-diones (Scheme 1.27).[38, 42] The combination of a number of amines and aldehydes with anthranilic acid derivatives **1.151** and 1-isocyanocyclohexene (**1.128**) produced the desired amides **1.151** in reasonable yields. Upon treatment with acid, **1.151** underwent cleavage of the

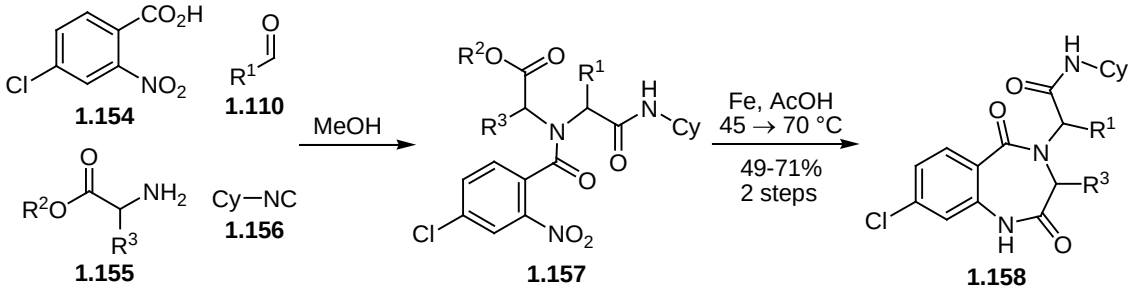
convertible isocyanide and cyclization to provide **1.153**. Interestingly, the anthranilic nitrogen atom did not need to be protected for this reaction sequence; however, it was later discovered that higher yields were obtained when this nitrogen was Boc-protected.[43]

Scheme 1.27



Since Armstrong's initial report, additional approaches to benzodiazepines using the Ugi-4CR have been reported. Marcaccini has developed two separate approaches utilizing a tandem nitro group reduction/cyclization protocol. In the first of these approaches, nitro benzoic acid **1.154** and cyclohexyl isocyanide were allowed to react with a number of amino esters **1.155** and aldehydes to provide the desired Ugi products (Scheme 1.28).[44] Upon treatment with iron powder in warm acetic acid the nitro group in **1.157** was reduced, and cyclization occurred to produce the 1,4-benzodiazepine-2,5-diones **1.158** in good yields.

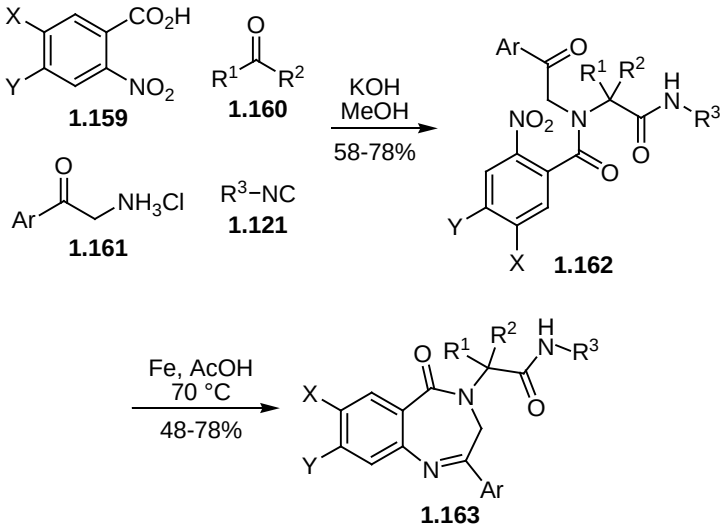
Scheme 1.28



The second approach developed by Marcaccini led to the synthesis of a number of 4,5-dihydro-3H-1,4-benzodiazepine-5-ones (Scheme 1.29).[45] Nitro benzoic acid **1.159**

and phenacyl amine **1.161** was allowed to react with a number of isonitriles and aldehydes (or ketones) to provide the desired Ugi products in good yields. Reduction of **1.162** and subsequent cyclization provided the desired benzodiazepines **1.163** in moderate yields over the two steps.

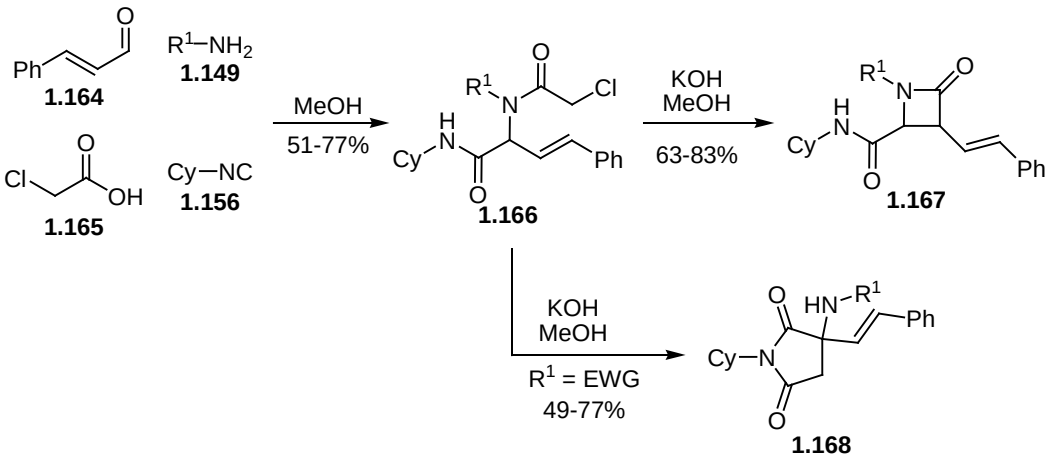
Scheme 1.29



1.2.2.3 Ugi 4CR/Intramolecular Alkylation

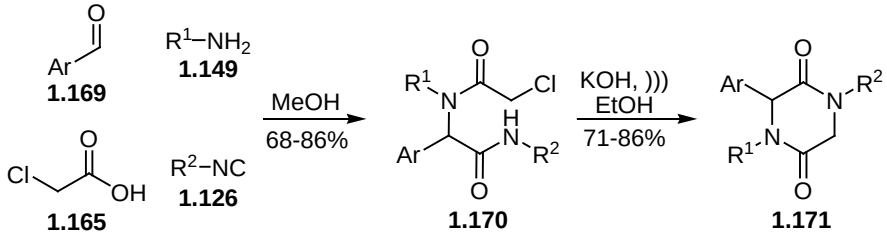
When the starting materials for the Ugi-4CR contain appropriately disposed leaving groups, substrates can be synthesized that are suitable for cyclization via intramolecular substitution reactions leading to a number of different sized heterocycles. Marcaccini has developed an approach to β-lactams and succinimides that utilizes an intramolecular enolate alkylation (Scheme 1.30).[46, 47] The reaction of cinnamaldehyde (**1.164**), chloroacetic acid (**1.165**), cyclohexyl isonitrile (**1.156**), and amines **1.149** yielded the Ugi adducts **1.166** in good yields. Upon treatment with KOH in MeOH **1.166** underwent deprotonation and cyclization to give β-lactams **1.167**. However, when R^1 is an electron-poor aromatic group, the β-lactam undergoes a subsequent rearrangement leading to succinimides **1.168**.

Scheme 1.30



When aromatic aldehydes were utilized in the Ugi-4CR with chloroacetic acid, the resulting Ugi adducts **1.170** could be cyclized upon treatment with KOH to provide diketopiperazines **1.171** (Scheme 1.31).[48] Thus, by changing the nature of the aldehyde, the selectivity of the deprotonation changed allowing for a different cyclization manifold to be accessed. However, it should be noted that Ugi products generated from aliphatic aldehydes did not undergo cyclization to provide the desired diketopiperazines.

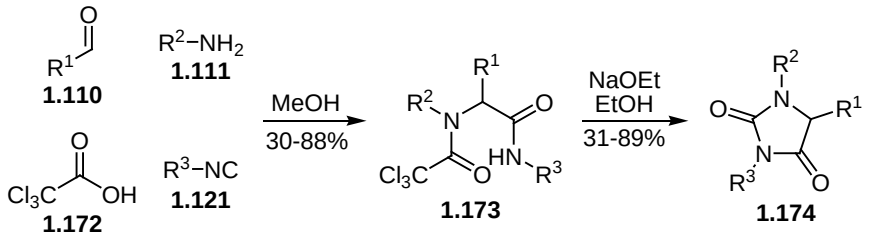
Scheme 1.31



When the carboxylic acid is changed from chloroacetic acid to trichloroacetic acid the previously described pathway can allow for access to hydantoin ring systems (Scheme 1.32).[49] In this case nucleophilic attack on the trichloroacetamide carbonyl and displacement of CCl_3^- occurs preferentially to the intramolecular alkylation. Thus, when Ugi product **1.173** was treated with NaOEt in EtOH cyclization occurred to give **1.174**.

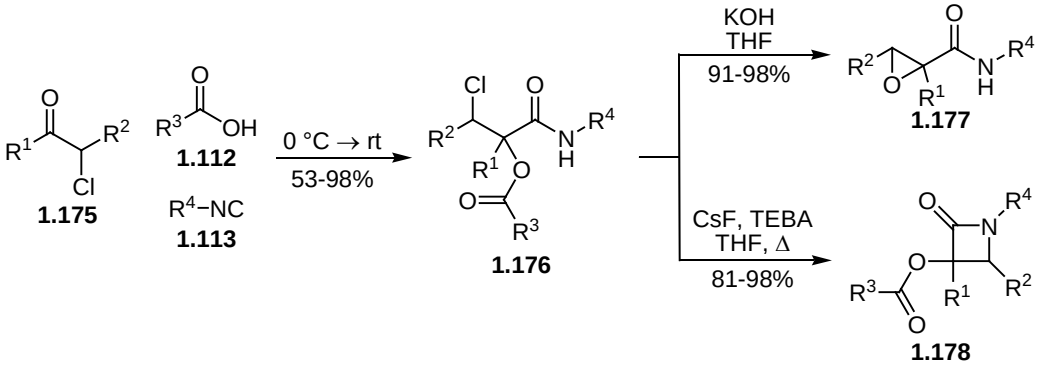
The previous three examples are nice representatives of a substrate based differentiation pathway where by simply altering the nature of two of the four components control over type of products generated was achieved.

Scheme 1.32



The related three component Passerini reaction (P-3CR)[50] can also be utilized for the synthesis of β-lactams (Scheme 1.33).[51] The reaction of α-chloroketones **1.175** with carboxylic acids **1.112** and isocyanides **1.113** provided the Passerini adducts **1.176** in good yields. Upon treatment with CsF and a phase-transfer catalyst in THF, **1.176** underwent cyclization to give the desired β-lactam **1.178**. When KOH was employed as the base de-acylation and epoxide formation occurred to give **1.177**.

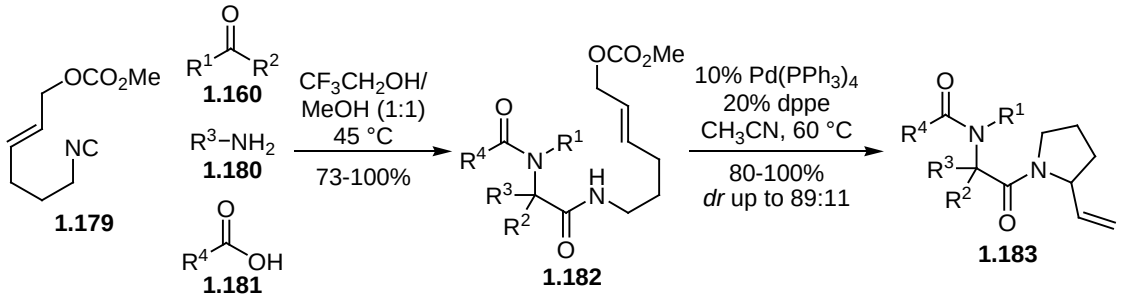
Scheme 1.33



Riva has recently shown that incorporating an allylic leaving group into one of the Ugi starting materials led to substrates that can undergo intramolecular S_N2' reactions to generate 2-vinyl pyrrolidines.[52, 53] When allylic carbonate **1.179** was incorporated into the

Ugi-4CR a substrate amenable to Pd catalyzed allylic amination was generated (Scheme 1.34). Treatment of **1.182** with catalytic Pd^{o} resulted in ionization of the allylic carbonate and cyclization to give **1.183**. It should also be noted that the corresponding allylic alcohols can be cyclized using Pd(II) catalysis, but the yields for this reaction were generally lower.

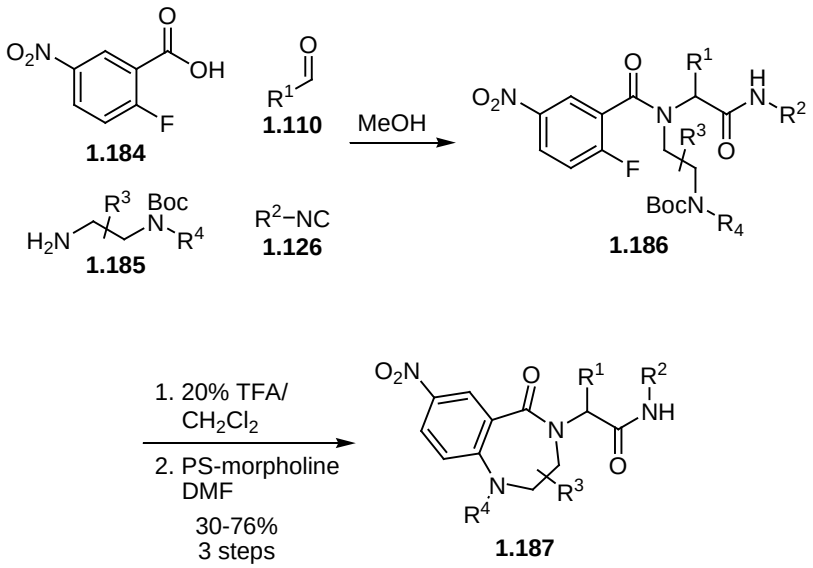
Scheme 1.34



1.2.2.4 Ugi 4CR/Intramolecular S_NAr

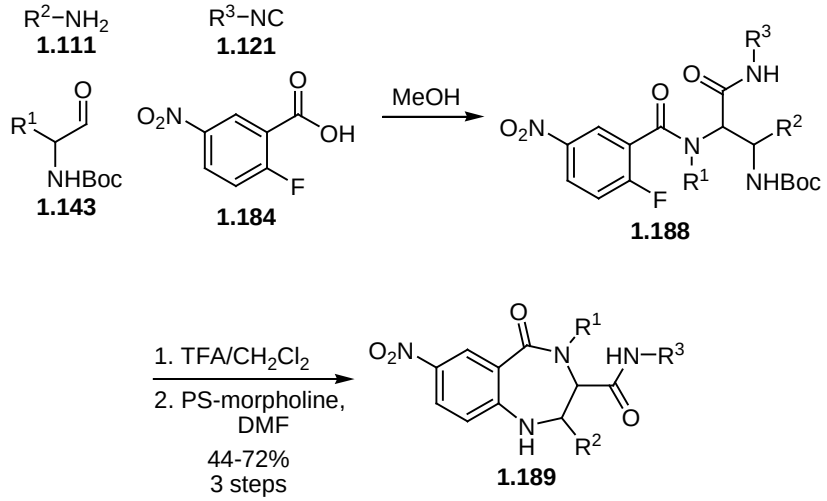
The sequencing of the Ugi-4CR and with nucleophilic aromatic substitution reactions (S_NAr) has been shown to provide rapid access to a number of benzo-fuzed heterocyclic scaffolds. Tempest and Hulme were the first to exploit the utility of this reaction sequence for the synthesis of benzodiazepines and benzoxazepines.[54] When mono Boc-protected diamines **1.185** were used in conjunction with benzoic acid **1.184** a UDC sequence could be set up to provide the desired benzodiazepines (Scheme 1.35). The Ugi 4CR of **1.184**, **1.185**, and aldehydes **1.110** and isonitriles **1.126** produced the Ugi products in good yields. Subsequent treatment of **1.186** with TFA cleaved the Boc group and treatment with resin bound morpholine induced the S_NAr reaction providing **1.187**.

Scheme 1.35



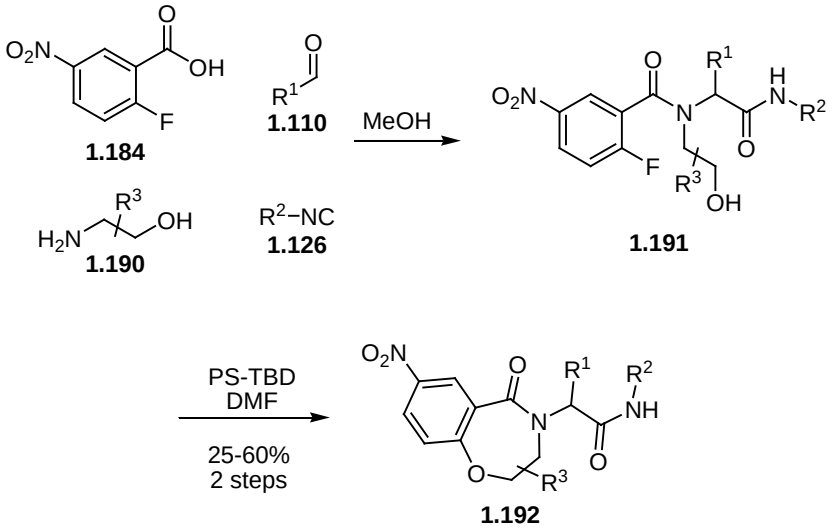
Hulme and Tempest later showed that by incorporating Boc-protected amino aldehydes **1.143** a different set of functionalized benzodiazepines could be accessed (Scheme 1.36).[55] The Ugi-4CR of aldehyde **1.143**, acid **1.184**, amines **1.111** and isonitrile **1.121** provided the Ugi adduct **1.188**. Deprotection of **1.188** with TFA provided the corresponding amine, which was treated with resin bound morpholine to provide the desired benzodiazepine **1.189** in moderate yields over the two steps.

Scheme 1.36



When amino alcohols **1.190** were used as the amine inputs, access to aryl ethers could be could be achieved (Scheme 1.37).[54] The Ugi adducts obtained from acid **1.184**, amino alcohol **1.190**, and various aldehydes and isonitriles were treated with a resin bound amine base to promote cyclization and provide **1.192** in moderate yields over the two steps.

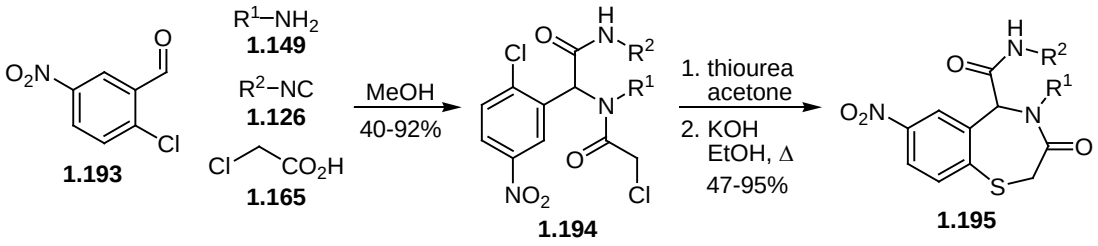
Scheme 1.37



TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene

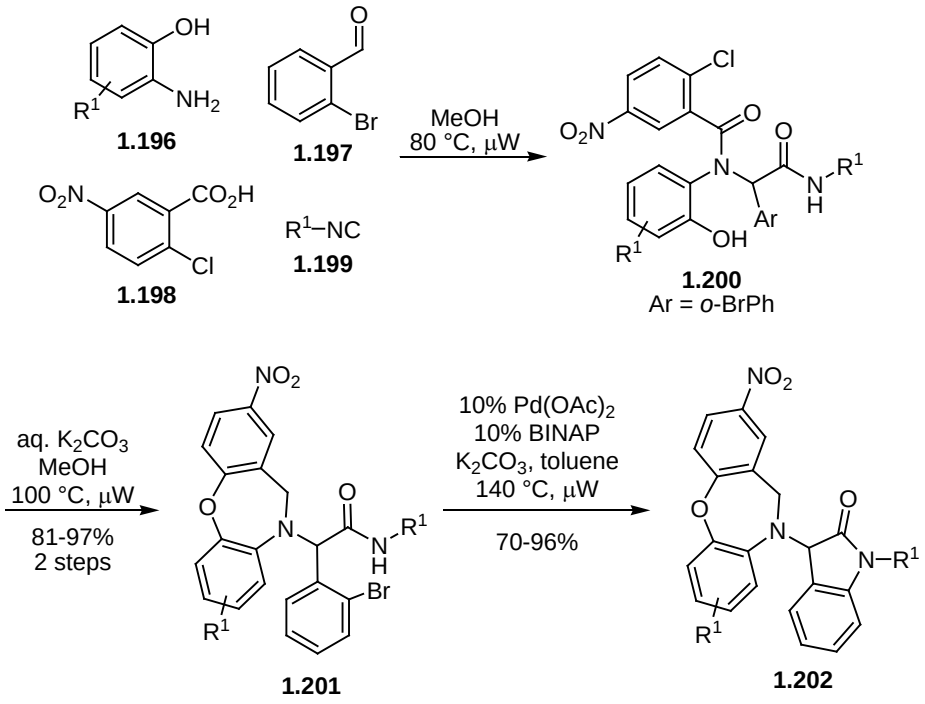
Access to benzothiazepines via sequential Ugi-4CR/S_NAr has also been reported by Marcaccini (Scheme 1.38).[56] For example, the chloroacetamide **1.194** was accessed in a straightforward manner using the Ugi-4CR. Treatment of **1.194** with thiourea in acetone provided an isothiouronium salt which reacted with KOH in EtOH to generate the desired benzothiazepine **1.195**.

Scheme 1.38



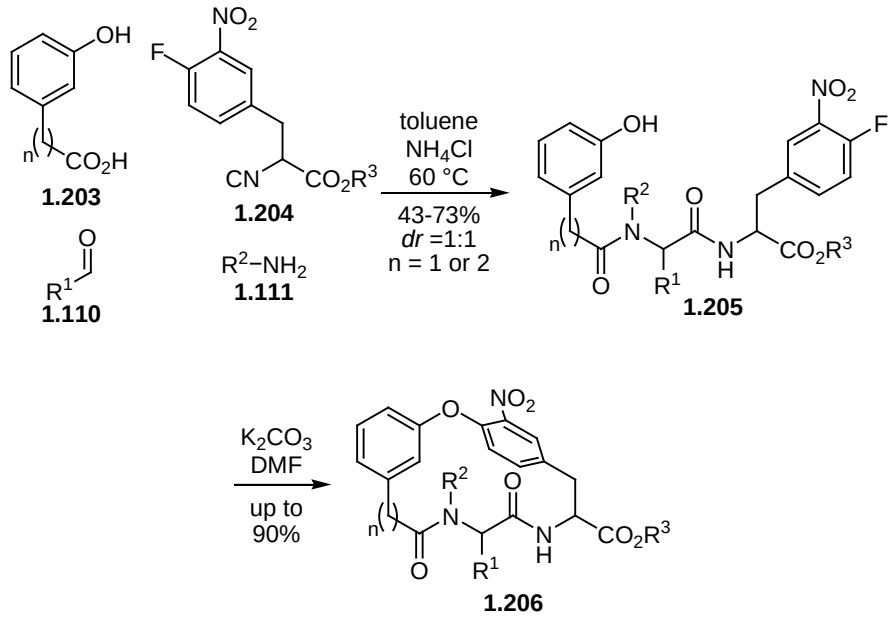
Access to the dibenz[*b,f*][1,4]oxazepine scaffold can be accomplished via an Ugi-4CR/S_NAr sequence when phenols are incorporated as one of the starting inputs. Dai has shown that the Ugi product generated from aminophenol **1.196**, bromobenzaldehyde **1.197**, nitrobenzoic acid **1.198**, and isocyanides **1.199** can undergo a nucleophilic aromatic substitution upon heating with aq. K_2CO_3 in MeOH at 100 ºC in a microwave reactor (Scheme 1.39).[57] The dibenzoxazepines thus formed could then undergo a Pd catalyzed N-arylation to provide the desired **1.202** in good yields.

Scheme 1.39



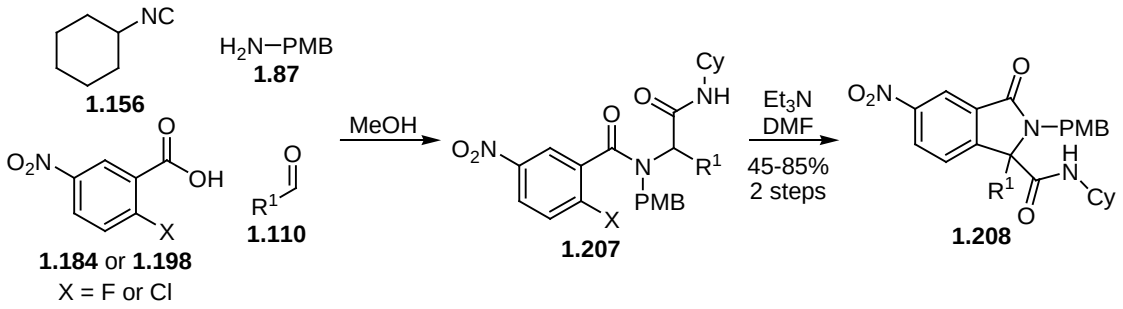
Zhu has applied this tactic for biaryl ether synthesis to the preparation of a number of natural product-like macrocycles (Scheme 1.40).[58-60] The Ugi-4CR of acids **1.1203**, isonitriles **1.204**, aldehydes **1.110**, and amines **1.111** proceeded in the presence of NH_4Cl in toluene at elevated temperatures to provide the **1.205** in moderate yields. When treated with K_2CO_3 in DMF, compounds **1.205** underwent macrocyclization to give the macrocycles **1.206**.

Scheme 1.40



Up to this point all of the sequential Ugi-4CR/S_NAr sequences that have been discussed have utilized heteroatom nucleophiles. However, Ivachtchenko has recently published a method for the synthesis of isoxindoles that utilizes a carbon nucleophile in a S_NAr reaction (Scheme 1.41).[61] The reaction of cyclohexylisocyanide (**1.156**), *p*-methoxybenzyl amine (**1.87**), nitrobenzoic acids **1.184** or **1.198**, and aldehydes **1.110** provided the desired cyclization precursor **1.207**. Upon treatment with Et_3N in DMF the cyclization occurred to provide the isooxindole **1.208** in good yields over the two steps.

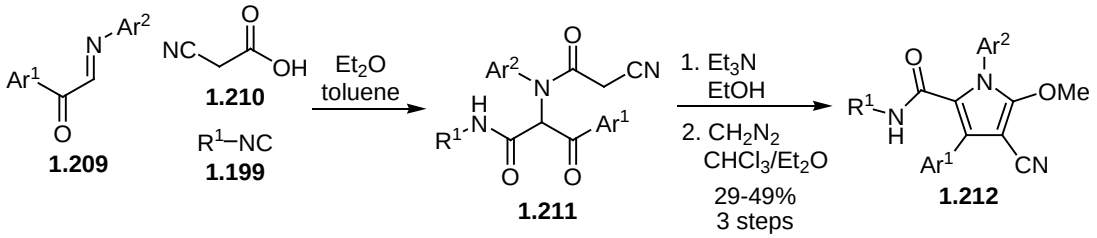
Scheme 1.41



1.2.2.5 Ugi-4CR/Intramolecular Knoevenagel Condensation and Horner-Wadsworth-Emmons Olefination

The starting inputs of the Ugi-4CR can be functionalized such that the products can undergo intramolecular Knoevenagel condensations leading to a number of interesting structures. Marcaccini has shown that by starting from a glyoxal and a carboxylic acid with an electron-withdrawing group in the α-position, substrates are generated that undergo an intramolecular Knoevenagel condensation and methylation leading to pyrroles (Scheme 1.42).[62] Utilizing a three component Ugi reaction glyoxal imine **1.209** was reacted with cyanoacetic acid (**1.210**) and isonitrile **1.199** to provide the **1.211**. Upon treatment with Et_3N in MeOH cyclization occurred to give the resulting pyrrolidone, which was treated with diazomethane to provide **1.212**.

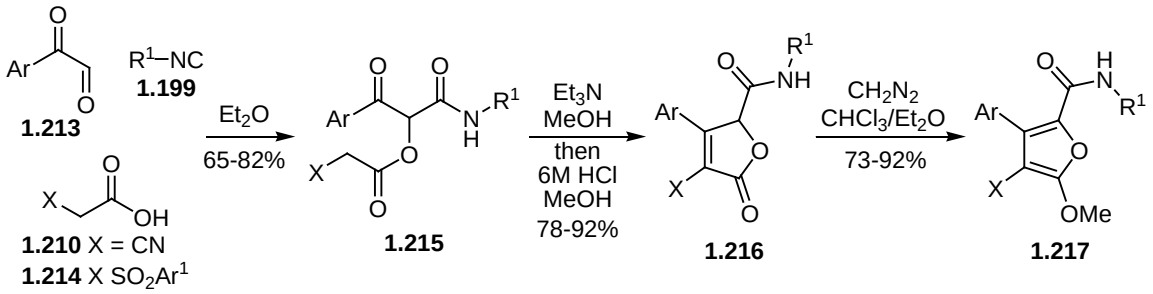
Scheme 1.42



The P-3CR reaction can also be utilized in an analogous sequence leading to tetra-substituted furans (Scheme 1.43).[63, 64] The Passerini adduct obtained from aryl glyoxal

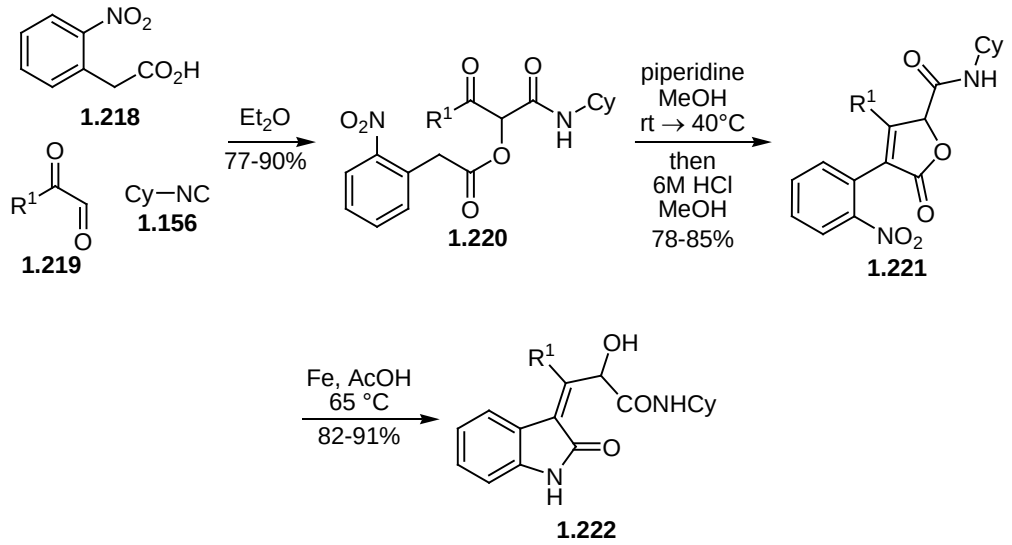
1.213, carboxylic acids **1.210** or **1.214**, and isocyanide **1.199** could be cyclized upon treatment with Et_3N, providing butenolides which underwent methylation with diazomethane to provide the desired furans. This reaction sequence provides an expedient route to a variety of tetra-substituted furans.

Scheme 1.43



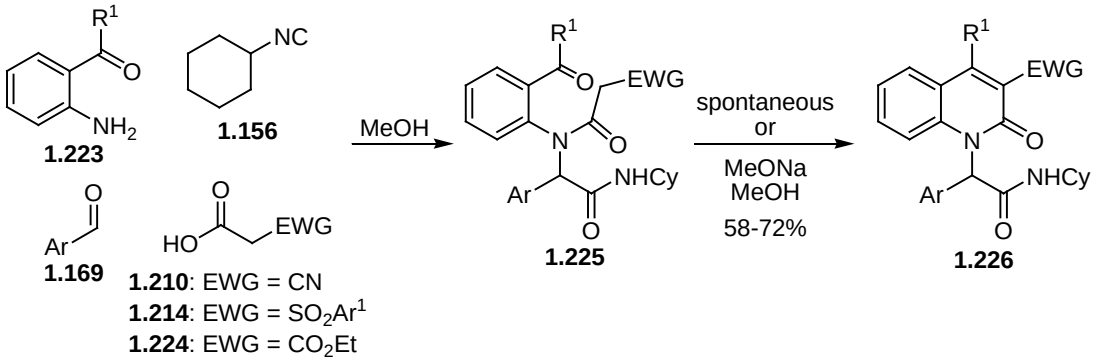
When 2-nitrophenylacetic acid (**1.218**) was used as the acid input in the P-3CR the desired product **1.220** could be cyclized to give butenolide **1.221** (Scheme 1.44).[65] Reduction of the nitro group in **1.221** with Fe/AcOH gave the desired aniline which underwent a lactone/lactam rearrangement leading to oxindole **1.222**.

Scheme 1.44



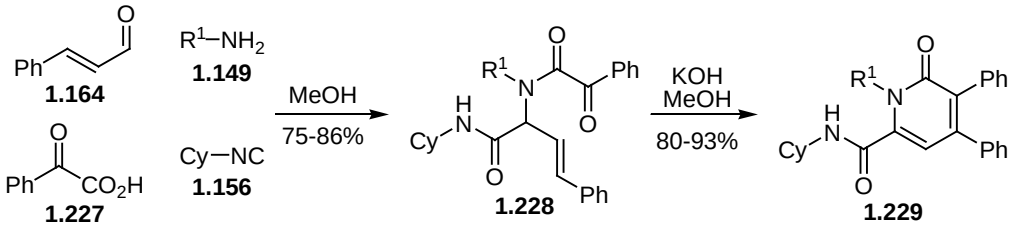
Access to quinolin-2-(1*H*)-ones can be achieved by an Ugi/Knoevenagel sequence when phenylketones are incorporated into one of the starting inputs (Scheme 1.45). Aminoketone **1.223** reacted smoothly with aldehyde **1.169**, cyclohexyl isocyanide and a variety of carboxylic acids to generate **1.225**.[66] When the EWG was a nitrile or ester, spontaneous cyclization occurred to provide **1.226** in one step. However, when the EWG was a sulfone, the addition of NaOMe was necessary to facilitate cyclization. Thus, in one pot a number of quinolin-2-(1*H*)-ones could be accessed using this reaction sequence.

Scheme 1.45



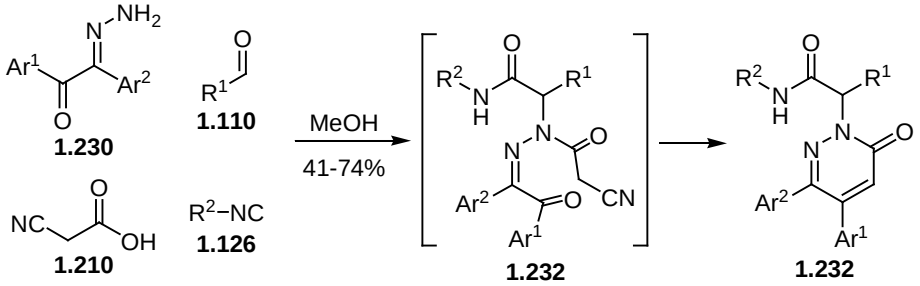
The Ugi/Knoevenagel sequence can also be utilized for the synthesis of 2-pyridone derivatives (Scheme 1.46).[67] The incorporation of cinnamaldehyde and phenylglyoxylic acid (**1.227**) into the Ugi-4CR resulted in the formation of **1.228** in good yields. Upon treatment with KOH in MeOH **1.228** underwent cyclization and dehydration to provide the pyridone **1.229**.

Scheme 1.46



Diarylglyoxal monohydrazones can participate in the Ugi-4CR as the amine component, and when reacted in a Ugi/Knoevenagel sequence they can give rise to pyridazinone scaffolds (Scheme 1.47).[68] Thus, the reaction of hydrazone **1.230** and cyanoacetic acid (**1.210**), with aldehydes and isonitriles gives rise to intermediate **1.231**, which spontaneously cyclized to provide pyridazinone **1.232**.

Scheme 1.47

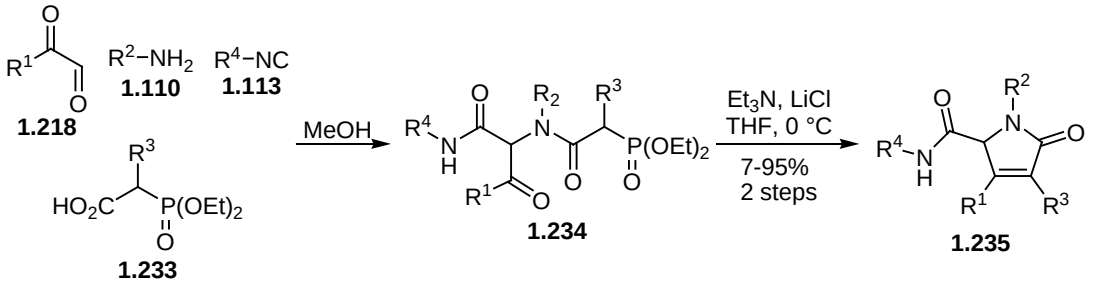


Similar to the Ugi/Knoevenagel sequence, the Ugi/Horner-Wadsworth-Emmons (HWE) sequence can be utilized to access nitrogen containing heterocyclic scaffolds. Dömling has shown that phosphonoacetic acid **1.233** is a viable input for the Ugi

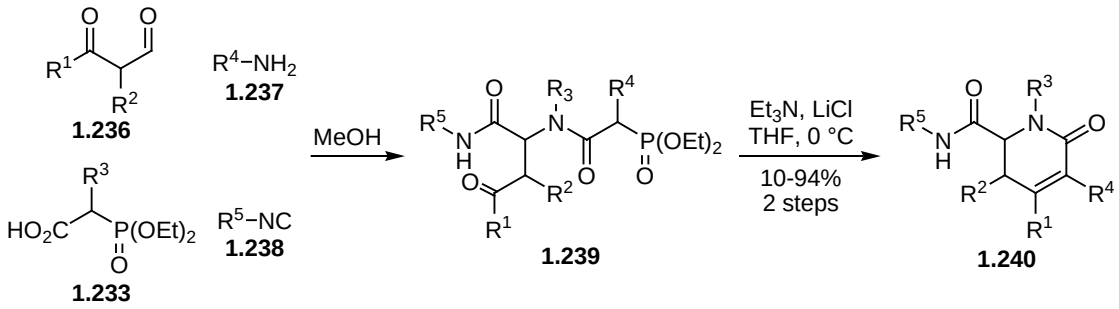
reaction, thus allowing access to substrates amenable to HWE chemistry.[69] Phosphonoacetic acid **1.233** is advantageous over the cyanoacetic acids and malonic acids previously utilized in Ugi/Knoevenagel sequences because it offers the ability to incorporate a wider range of functional groups (R^3 in **1.233**) that cannot accessed otherwise.

By incorporating phosphonoacetic acid **1.233** and glyoxal **1.218** into the Ugi-4CR, **1.234** could be readily accessed (Scheme 1.48). Upon treatment of **1.234** with Et_3N and LiCl in THF the intramolecular HWE reaction took place to generate pyrrolidone **1.235**. Phosphonoacetic acid **1.233** could also be utilized in an analogous P-3CR/HWE sequence giving rise to butenolides.[70] Dihydropyridones **1.240** can also be accessed in good yields by incorporating β-ketoaldehyde **1.236** into the Ugi/HWE sequence (Scheme 1.49).[69]

Scheme 1.48



Scheme 1.49

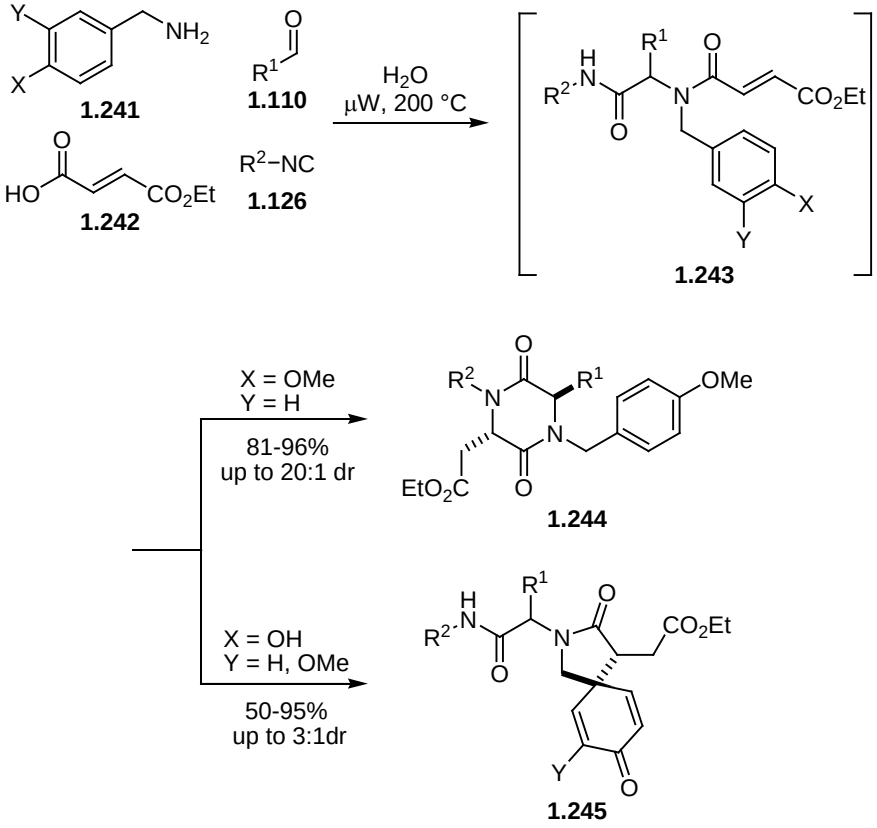


The sequential Ugi/Knoevenagel and Ugi/HWE reaction pathways have proven themselves to be efficient methods for generating a number of five- and six-membered nitrogen containing heterocycles. Similarly, by sequencing the P-3CR with these two post condensation reactions a number of functionalized butenolides and furans can be accessed.

1.2.2.6 Tandem Ugi-4CR/1,4-Addition

Andreana has recently developed a cascade sequence involving a tandem Ugi-4CR/1,4-addition sequence (Scheme 1.50).[71] The reaction of substituted benzylamines **1.241** with fumaric acid **1.242**, aldehydes **1.110**, and isonitriles **1.126** proceeded in protic solvents under microwave heating to give the intermediary Ugi adduct **1.243**. When *p*-methoxybenzyl amine (X = OMe, Y = H) was employed as the amine component, **1.243** underwent an 1,4-addition reaction to provide the diketopiperazine **1.244**. However, when X = OH, an intramolecular 1,4-addition took place to give the spirocyclic **1.245**. Interestingly, these subsequent cyclizations only took place when protic solvents were used. When aprotic solvents like CH_2Cl_2 were used, the linear Ugi adduct **1.243** was the only isolable product.

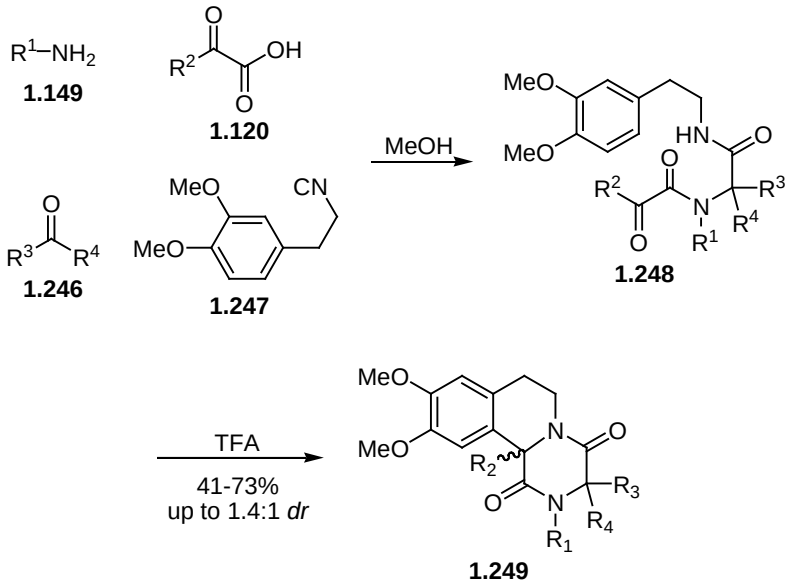
Scheme 1.50



1.2.2.7 Sequential Ugi-4CR/Pictet-Spengler

The sequencing of the Ugi-4CR with a Pictet-Spengler reaction has shown to be a useful method for the generation of tricyclic diketopiperazines (Scheme 1.51).[72] By incorporating an electron rich aromatic as part of the isonitrile input, in conjunction with a glyoxylic acid, access to Ugi adducts **1.248** could be achieved. Upon treatment of with TFA the Pictet-Spengler reaction took place to give **1.249**. While the yields for this two step sequence were acceptable, there was virtually no diastereoselectivity, and the diastereoselectivity for this process would need to be improved in order for this to become a more useful method for accessing these types of compounds.

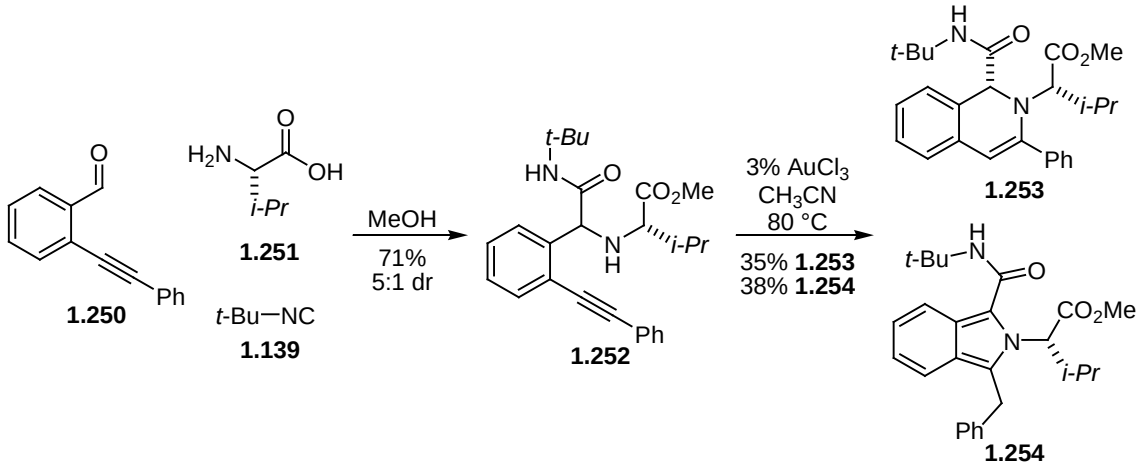
Scheme 1.51



1.2.2.8 Sequential Ugi 4CR/Hydroamination

Gold catalysis has in recent years received an increasing amount of attention amongst synthetic chemists.[73] Therefore, it is not surprising that gold catalysis has been used in conjunction with the Ugi-4CR for heterocycle synthesis. Dyker has exploited the ability of gold(III) to activate alkynes for nucleophilic attack in the synthesis isoindoles and isoquinolines (Scheme 1.52).[74] The Ugi 5-center-4CR of aldehyde **1.250**, valine (**1.251**), *t*-BuNC (**1.139**), and MeOH yielded **1.252** in 71% yield and 5:1 *dr*. Treatment of **1.252** with $AuCl_3$ in refluxing CH_3CN resulted of the formation of isoquinoline **1.253** in 35% yield and isoindole **1.254** in 38% yield. Unfortunately the lack of regioselectivity in this hydroamination has to this point limited its use beyond this example.

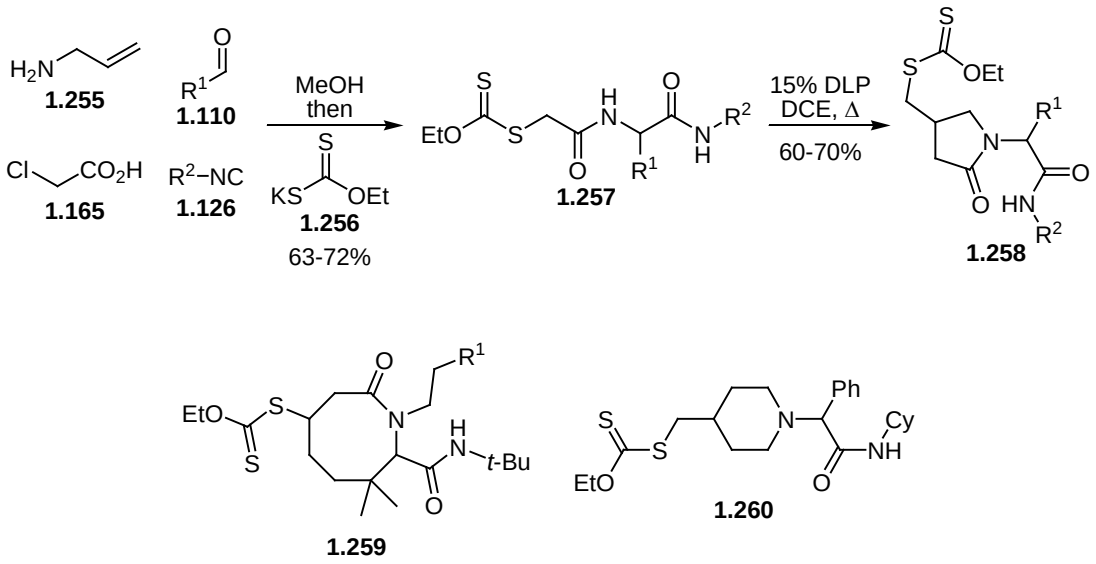
Scheme 1.52



1.2.2.9 Sequential Ugi 4CR/Radical Cyclization

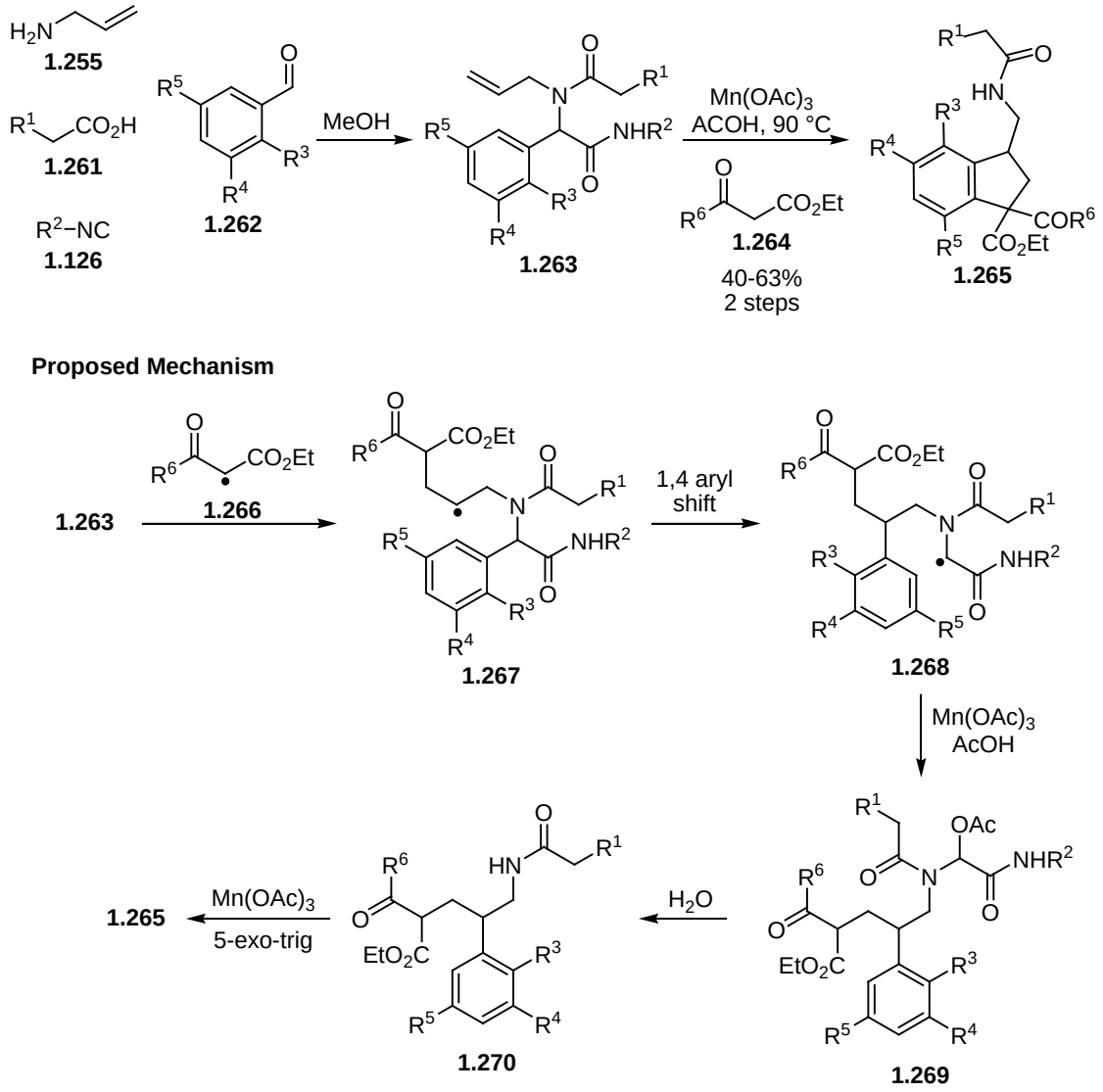
Although radical cyclizations have found widespread use in heterocycle synthesis, their use in conjunction with the Ugi reaction has been limited. El Kaïm has utilized a two step Ugi-4CR/xanthate ester formation sequence to access substrates suitable for radical cyclization (Scheme 1.53).[75] The Ugi product formed from allylamine, chloroacetic acid, aldehydes **1.110** and isocyanide **1.126** was treated in situ with potassium *O*-ethyl xanthate to provide the desired xanthate ester **1.257**. Treatment of **1.257** with catalytic dilauroyl peroxide provided the γ-lactams **1.258** in good yields. The six and seven membered lactams **1.259** and **1.260** could also be accessed by simply altering the position of the pendent alkene.

Scheme 1.53



More recently El Kaïm has developed a radical cascade for synthesizing indanes from Ugi products (Scheme 1.54).[76] The reaction of **1.263** with β-ketoester **1.264** in the presence of $Mn(OAc)_3$ provided the indane products **1.265** in moderate yields over the two steps. Interestingly, in this reaction the isocyanide functionality was completely lost in the cyclization product. The authors propose that this reaction occured via addition of radical **1.266** to **1.263** to give **1.267**, which underwent an 1,4-aryl shift to give **1.268**. Radical **1.268** is further oxidized by $Mn(OAc)_3$ to give **1.239**, which is then hydrolyzed to give **1.270**. Further oxidation of **1.270** by $Mn(OAc)_3$ and cyclization provides indane **1.163**.

Scheme 1.54

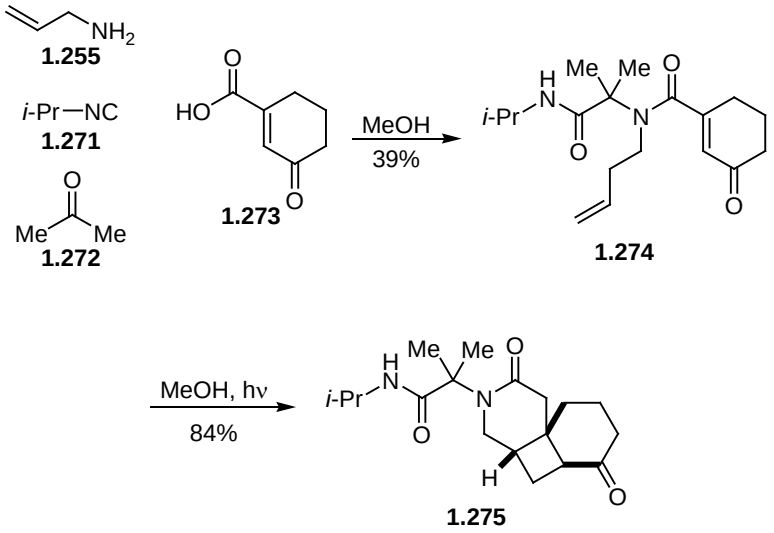


1.2.2.10 Sequential Ugi-4CR/6π-Photocyclization and Ugi-4CR/[2+2] Cycloaddition

Djuric and co-workers have developed two approaches to heterocyclic scaffolds by using the Ugi-4CR in conjunction with photochemical cyclizations. The first of these approaches utilizes a [2+2] ene-enone photocycloaddition (Scheme 1.55).[77] The representative [2+2] cycloaddition precursor **1.274** was synthesized from allylamine, *i*-PrNC, acetone and carboxylic acid **1.273** in 39% yield. Upon exposure to hν in MeOH

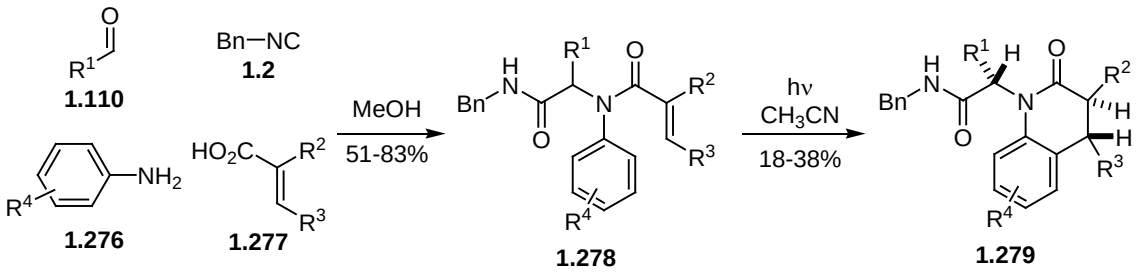
the desired [2+2] cycloaddition took place to give **1.275** in 84% yield. Using this reaction sequence a number of 3-azabicyclo[4.2.0]octan-4-one derivatives were accessed.

Scheme 1.55



The second of these approaches involves a 6π-photocyclization that gives access to 3,4-dihydroquinolin-2(1H)-ones (Scheme 1.56).[78] The desired cyclization precursors were readily accessible in good yields from aldehydes **1.110**, aniline **1.276**, benzylisonitrile, and acrylic acid **1.277**. Upon irradiation in acetonitrile the 6π-photocyclization took place to provide the desired quinolines **1.279** in low yields, but with high levels of selectivity for the trans-product.

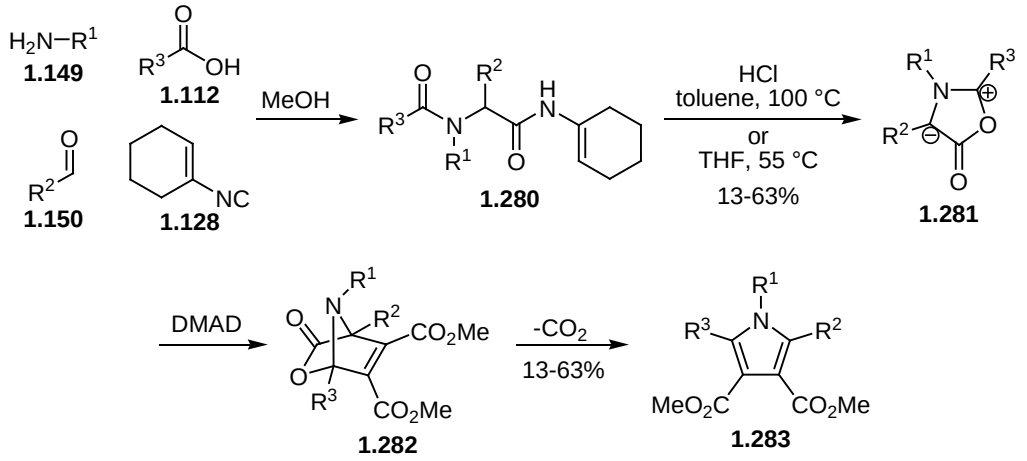
Scheme 1.56



1.2.2.11 Sequential Ugi 4CR/[3+2] Cycloaddition

A number research groups have reported the use of the Ugi-4CR for synthesizing substrates amenable to [3+2] dipolar cycloadditions. In the course of investigating the mechanism of cleavage of the 1-isocyanocyclohexene convertible isocyanide (**1.128**) Armstrong found that an intermediate münchone **1.281** was formed from **1.280** upon treatment with acid (Scheme 1.57).[38] In the presence of dipolarophiles such as DMAD, the münchone **1.281** could be trapped in a [3+2] dipolar cycloaddition to give the bridged **1.282**, which spontaneously lost CO_2 to provide pyrrole **1.283**.

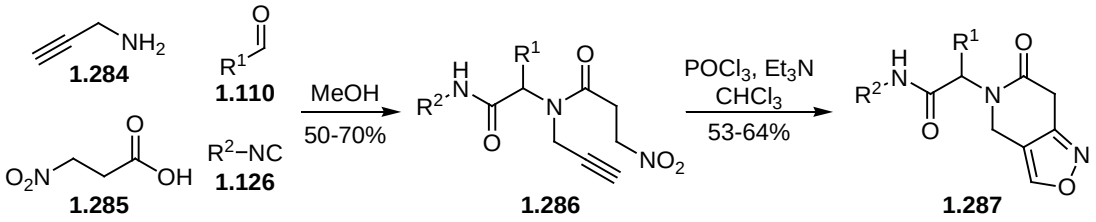
Scheme 1.57



Djuric and co-workers have shown that nitro groups incorporated into the Ugi products can be utilized in subsequent intramolecular nitrile oxide cycloadditions to

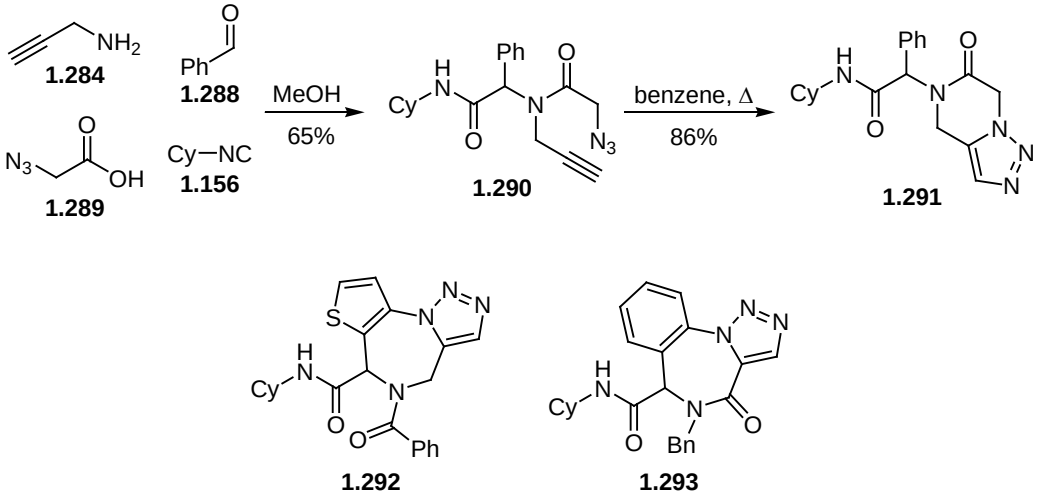
generate isoxazoles and isoxazolines (Scheme 1.58).[79] The Ugi product **1.286**, generated from propargyl amine, acid **1.285**, aldehydes **1.110**, and isonitriles **1.126**, reacted with $POCl_3$ and Et_3N to generate the insipient nitrile oxide, which underwent a [3+2] dipolar cycloaddition to give oxazole **1.287**.

Scheme 1.58



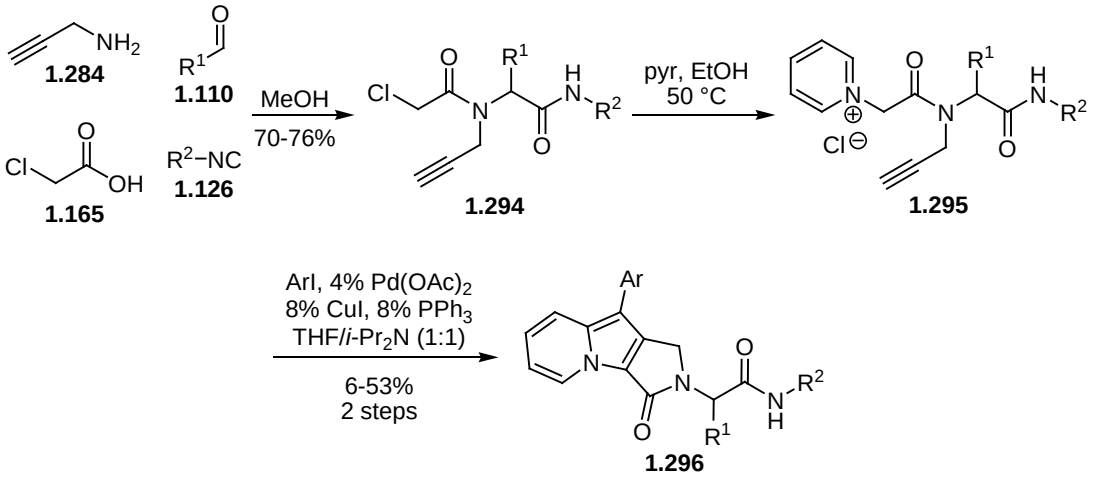
When azides were incorporated into the Ugi inputs, structures could be generated that were suitable for intramolecular azide-alkyne cycloadditions (Scheme 1.59).[80] Propargyl amine reacted smoothly with benzaldehyde, azido-acid **1.289**, and cyclohexyl isocyanide to provide **1.290** in 65% yield. Heating **1.290** in refluxing benzene provided the desired triazole **1.291** in 86% yield. In this example the amine and acid inputs were paired in the cycloaddition; however, structures like **1.292** could be synthesized by pairing the amine and aldehyde inputs, and scaffolds similar to **1.293** could be accessed by pairing the aldehyde and acid.

Scheme 1.59



El Kaïm has published a route to indolizine scaffolds utilizing a sequential Ugi-4CR/[3+2] cycloaddition (Scheme 1.60).[81] The pyridinium salt **1.295**, formed by reacting pyridine with Ugi adduct **1.294**, underwent a Sonogashira reaction with a number of aryl iodides to provide a more reactive alkyne which underwent spontaneous cyclization under the reaction conditions to give **1.296** after aromatization.

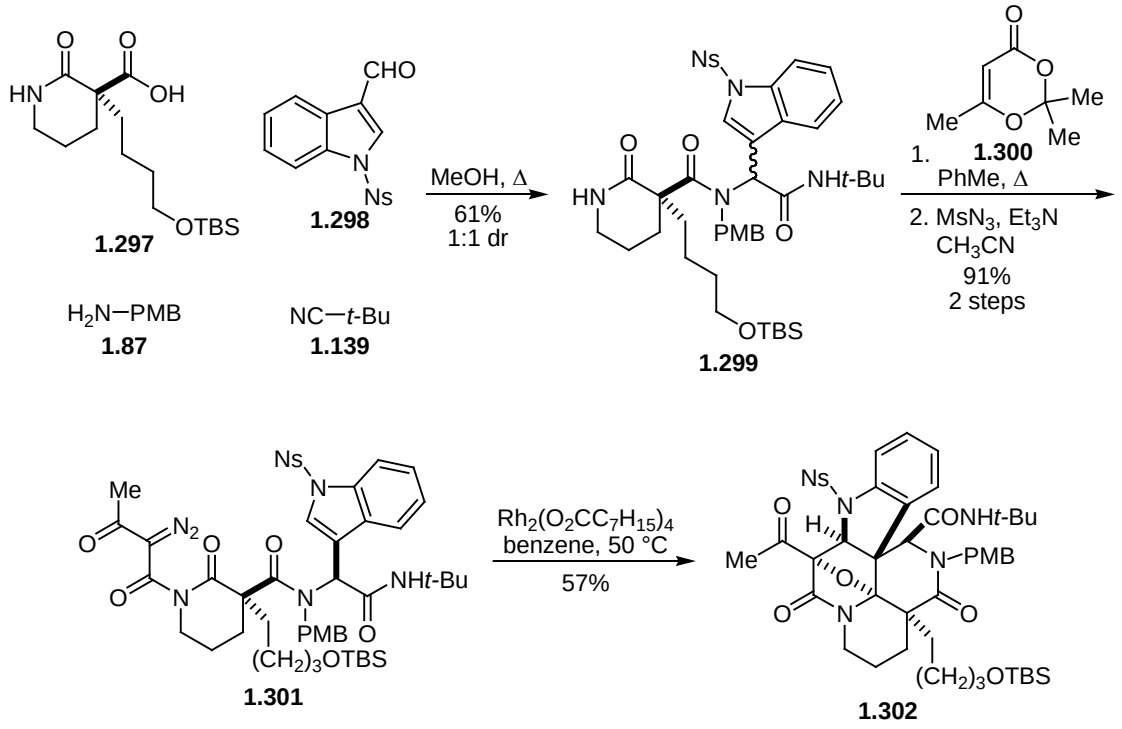
Scheme 1.60



In the demonstration of a new DOS folding pathway (see Scheme 1.14) Schreiber exploited the Ugi-4CR to generate a substrate suitable for reaction under Rh(II) catalyzed

1,3-dipolar cycloaddition conditions (Scheme 1.61).[20] Carboxylic acid **1.297** reacted with indole carboxaldehyde **1.298**, amine **1.87**, and *t*-BuNC to provide **1.299** in 61% yield and 1:1 *dr*. After the reaction of the Ugi adduct **1.299** with **1.300** and subsequent separation of the diastereomers, diazetination provided the cyclization precursor **1.301** in excellent yield over the two steps. The treatment of **1.301** with $Rh_2(O_2CC_7H_{15})_4$ in benzene at 50 ^oC resulted in the formation of the carbonyl ylide which underwent cyclization with the indole 2,3-double bond to provide **1.302** in 57% yield as a single diastereomer.

Scheme 1.61

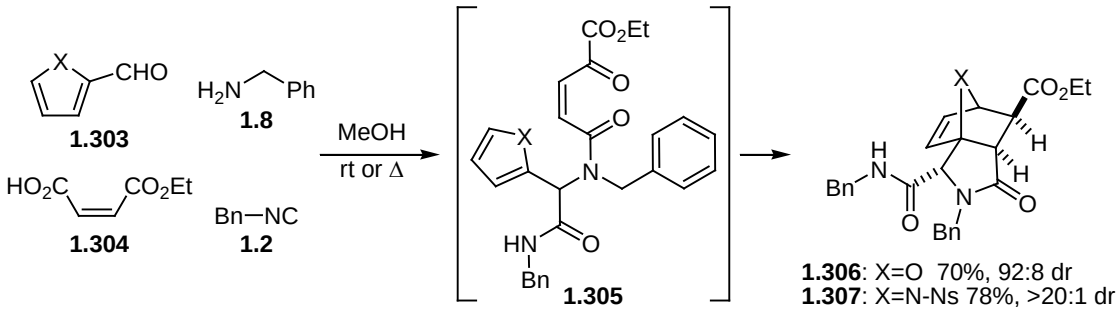


1.2.2.12 Tandem Ugi-4CR/Diels-Alder Cycloaddition

As previously shown in Section 1.1.2 the tandem Ugi-4CR/Diels-Alder (Ugi-4CR/DA) is a powerful complexity generating reaction that has numerous uses in DOS. This tandem sequence was first reported by Paulvannan, who in 1999 showed that the Ugi products generated from furfural, benzyl aminde, benzyl isocyanide, and maleic or

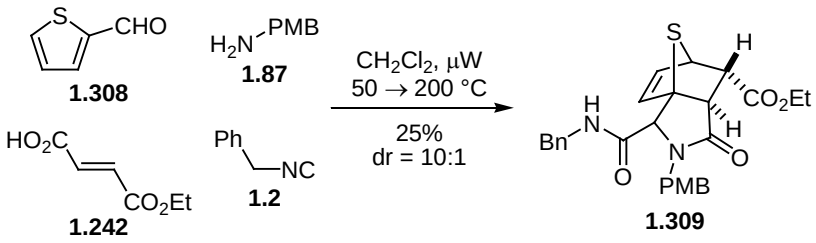
fumaric acid derivatives underwent a spontaneous intramolecular furan Diels-Alder to provide oxa-bicyclic structures similar to **1.306** in good yields and with good levels of diastereoselectivity (Scheme 1.62).[82] This method was later extended to include the use of pyrroles as the diene component.[83]

Scheme 1.62



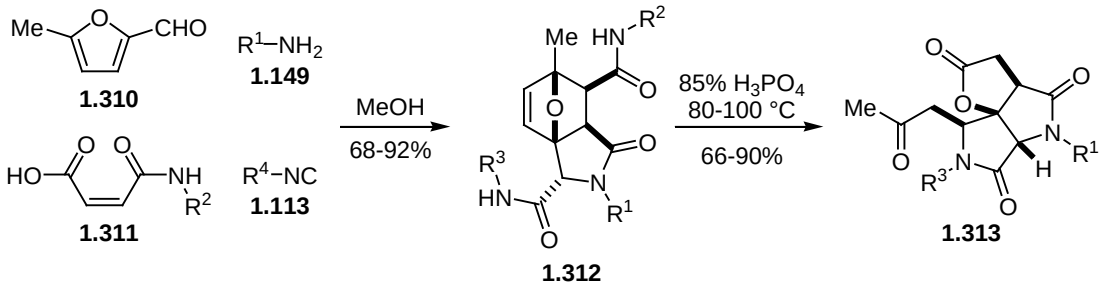
In their development of a cascade sequence involving a tandem Ugi/1,4-addition sequence (Scheme 1.52), Andreana discovered that thiophenes could also be diene partner in a Ugi-4CR/DA sequence (Scheme 1.63).[71] When thiophene-2-carboxaldehyde (**1.308**) reacted with *p*-methoxybenzyl amine, benzyl isocyanide, and fumaric acid **1.242** under the conditions of microwave heating the desired Diels-Alder adduct **1.309** could be isolated in 25% yield.

Scheme 1.63



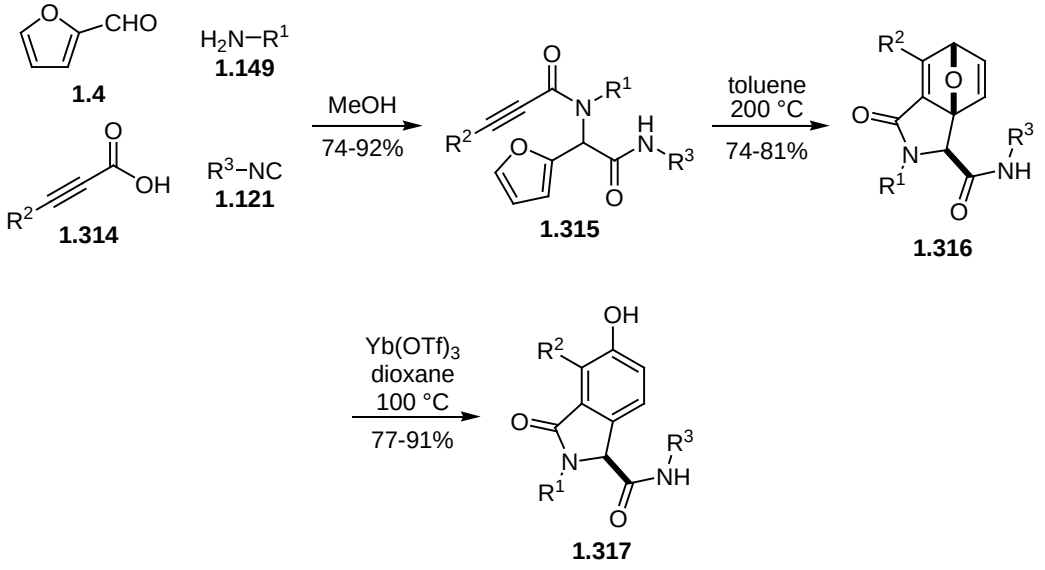
The ability of the Ugi-4CR/DA sequence to synthesis diverse heterocyclic structures can be further increased by carrying out a sequential ring opening reactions on the oxa-bridged bicycle. As previously described ROM/RCM can be utilized when additional olefins are appended to the Diels-Alder adduct (see Section 1.1.2). Ivachtchenko has found that the Ugi-4CR/DA adduct **1.312** undergoes a ring rearrangement upon treatment with phosphoric acid to yield **1.313** (Scheme 1.64).[84]

Scheme 1.64



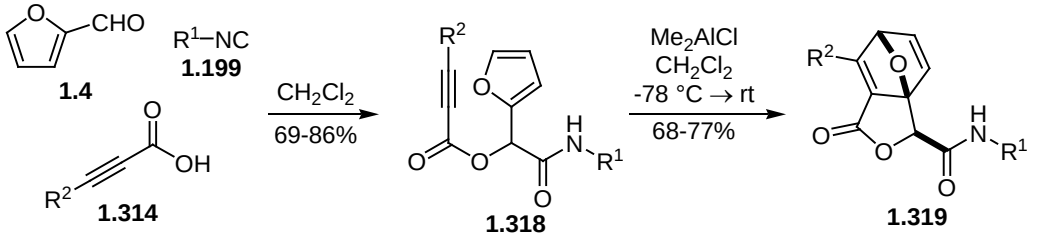
When acetylenic acids **1.314** are input into the Ugi-4CR, the adducts that are produced are isolable and do not under spontaneous cyclization (Scheme 1.65).[85] However, upon heating in toluene to 200 ºC the desired intramolecular cycloaddition occurs to provide **1.316** in good yields. The Diels-Alder adducts then could be ring opened and aromatized to isoindolinones upon treatment with $Yb(OTf)_3$ in refluxing dioxane.

Scheme 1.65



The analogous Passerini adducts derived from furfural, acetylenic acid **1.314**, and isocyanide **1.199** were also found to undergo an intramolecular Diels-Alder cycloaddition (Scheme 1.66).[85] Although attempts to perform the Diels-Alder reaction of **1.318** under thermal conditionals were unsuccessful due to its instability, it was found that the Me_2AlCl catalyzed cycloaddition proceeded in good yields at -78 ºC. Interestingly, all attempts to ring-open and aromatize **1.319** with $Yb(OTf)_3$ were unsuccessful.

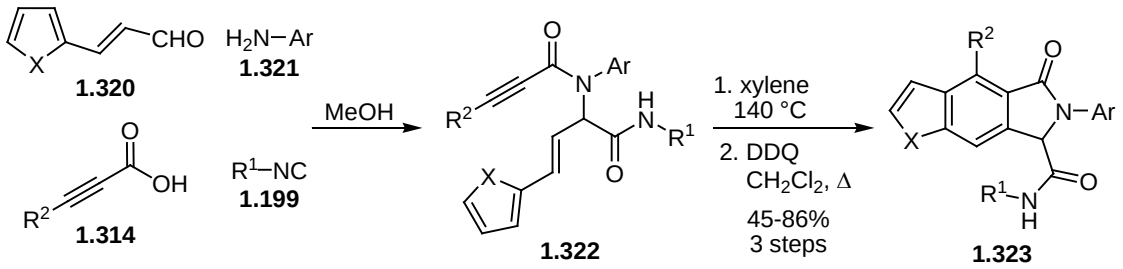
Scheme 1.66



The Ugi-4CR/DA sequence has been applied to the synthesis of a number of indole, benzofuran, and benzothiophene scaffolds (Scheme 1.67).[86] The Ugi reaction of aldehydes **1.320**, acetylenic acids **1.314**, anilines **1.321**, and isonitriles **1.199** provided

Ugi adducts **1.322**. The heating of **1.322** in xylenes at 140 ºC induced the desired Diels-Alder reaction, and oxidation with DDQ provided the desired heteroaromatics **1.323** in good yields over the three steps.

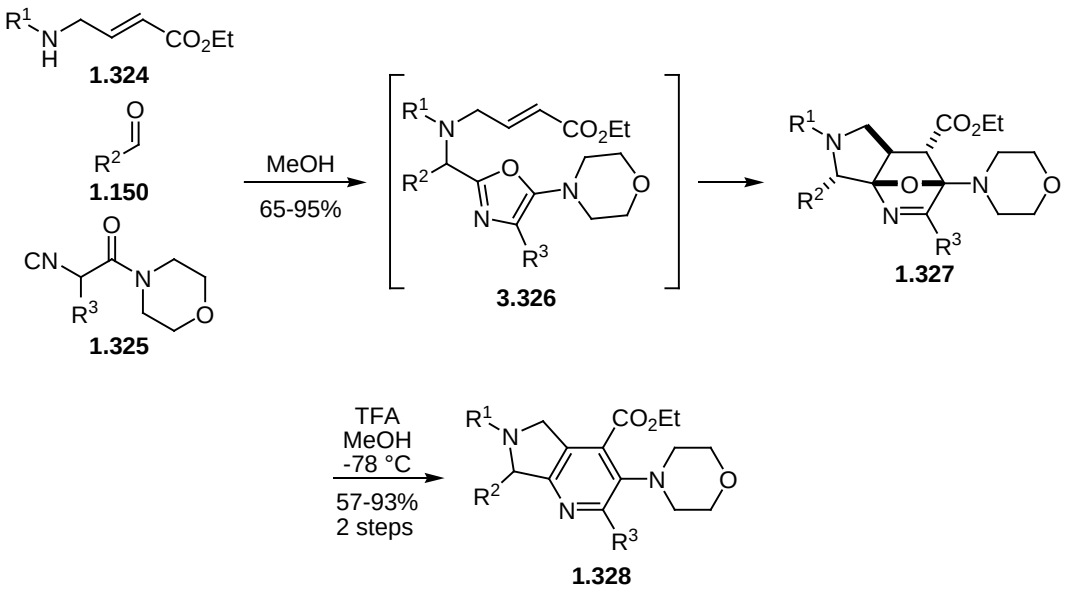
Scheme 1.67



X = O, S, NMe

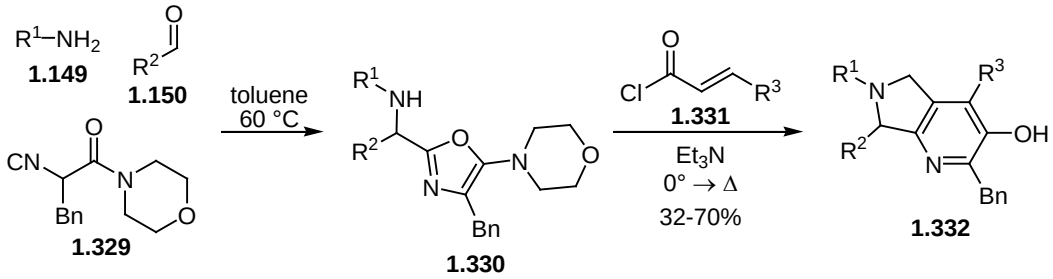
Zhu has developed a three-component variant on the Ugi-4CR involving the reaction of amines, aldehydes, and α-isocyano acetamides that generates oxazoles in good yields.[87] When allylamine **1.324** was utilized as the amine input, a spontaneous intramolecular 4+2 cycloaddition occured between the oxazole **3.326** and the pendant alkene leading to **1.327** (Scheme 1.68).[88] The oxa-bridged **1.327** underwent ring-opening and aromatization upon treatment with TFA in MeOH to provide pyridines **1.321**. This 3CR was later applied to the synthesis of a number of oxa-bridged tetracyclic tetrahydroisoquinolines[89, 90] and to the core structure of the alkaloid natural product lennoxamine.[91]

Scheme 1.68



This reaction was also expanded to a four component reaction by including the addition of an acid chloride (Scheme 1.69).[87, 92] Thus, the reaction of primary amine **1.149**, aldehyde **1.150**, and isonitrile **1.329** provides oxazole **1.330**, which can be reacted *in situ* with acid chloride **1.331** to provide after ring opening and aromatization the pyrrolopyridine **1.332** in moderate yields over the two steps. In contrast to the previous example which retained the morpholine ring during ring opening and aromatization under acidic conditions, the morpholine ring is lost under the basic ring opening conditions.

Scheme 1.69

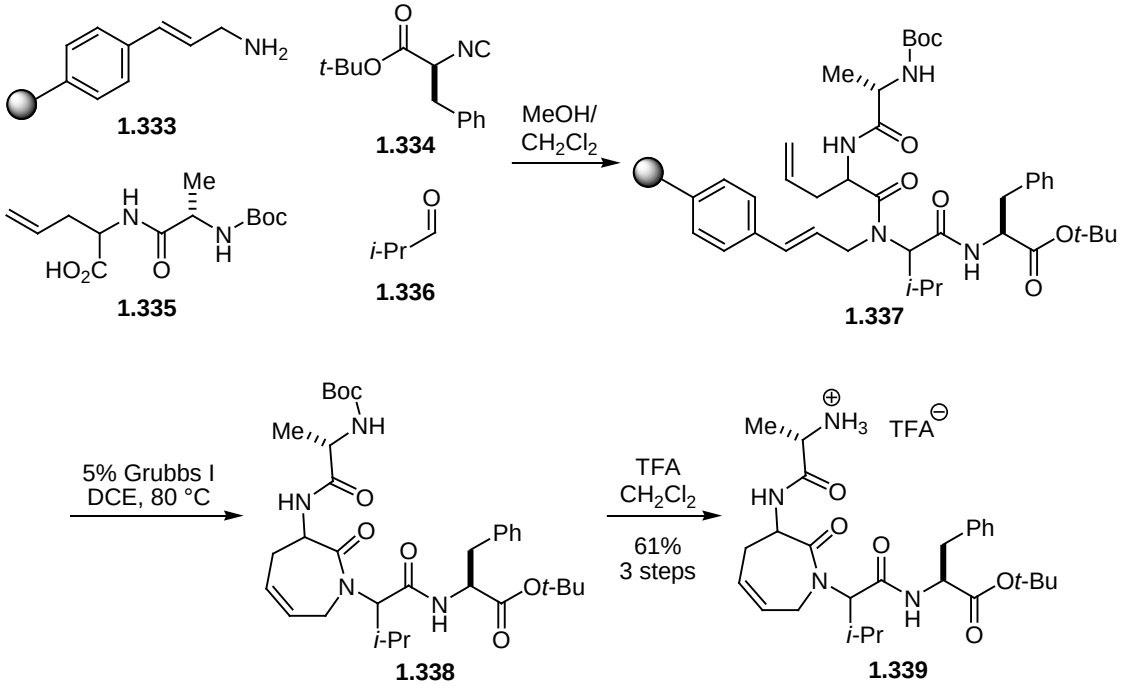


As evidenced by the examples shown in this section and in Section 1.1.2 the tandem Ugi-4CR/DA is a powerful complexity-generating reaction that can be utilized to access a diverse collection of heterocyclic scaffolds. These Diels-Alder adducts can also be elaborated to allow access to even more types of scaffolds, further showing the synthetic power of this reaction sequence.

1.2.2.13 Sequential Ugi 4CR/RCM

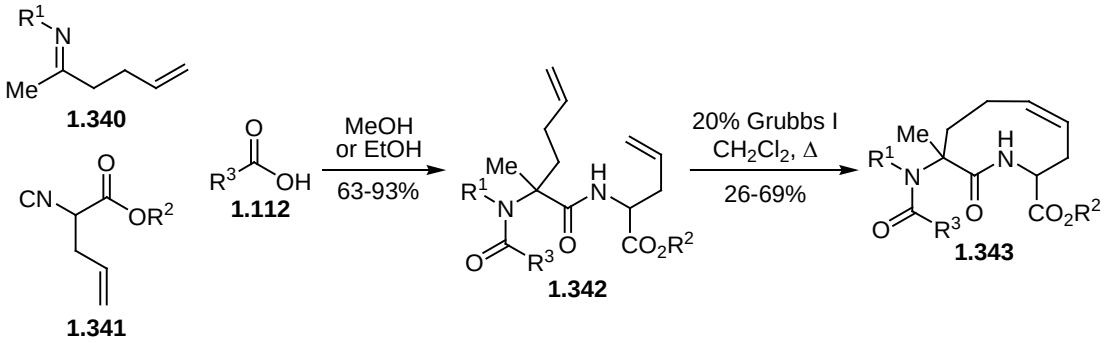
Ring-closing metathesis (RCM) has in recent years shown itself to be a powerful method for the synthesis of heterocyclic structures.[93] When used in conjunction with the Ugi-4CR, access to diverse functionalized heterocyclic structures can be achieved in as little as two steps. The first use of RCM in conjunction with the Ugi-4CR was reported by chemists at Amgen and Array BioPharma in 1999 for the synthesis of Freidinger lactams (Scheme 1.70).[94] The solid phase synthesis of **1.337** was carried out using a cinnamyl amine resin **1.333** as the amine input, which allowed for cleavage of the resin during the RCM step. The Ugi-4CR of **1.333**, isobutyraldehyde (**1.336**), isocyanide **1.334**, and Boc-protected dipeptide **1.335** proceeded smoothly to give **1.337**. Treatment of **1.337** with 5% of the Grubbs I catalyst in DCE at 80 ºC provided the desired seven-membered lactam, which was deprotected to provide **1.339** as a mixture of diastereomers in 61% yield over the three steps.

Scheme 1.70



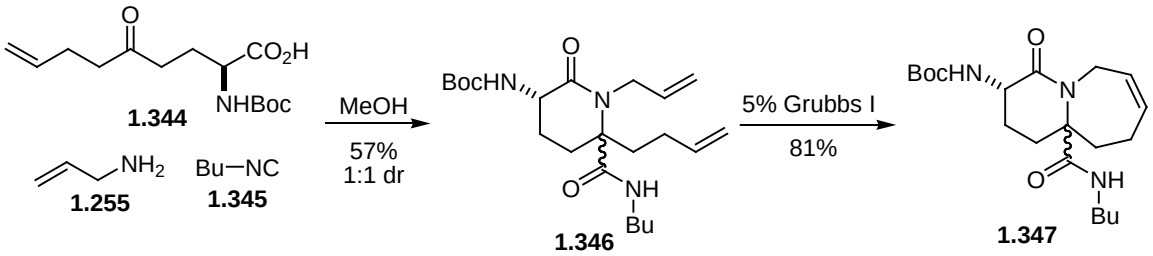
Banfi has reported the use of an Ugi/RCM sequence for accessing 9-membered lactams (Scheme 1.71).[95-97] Starting from imine **1.340**, the Ugi-3CR with isonitrile **1.341** and acid **1.112** provided the desired Ugi adduct **1.342** in good yields. Diene **1.342** underwent RCM with the Grubbs I catalyst to provide lactam **1.343**. Lactam **1.343** was then utilized in the synthesis of a number of cyclic pentapeptides.

Scheme 1.71



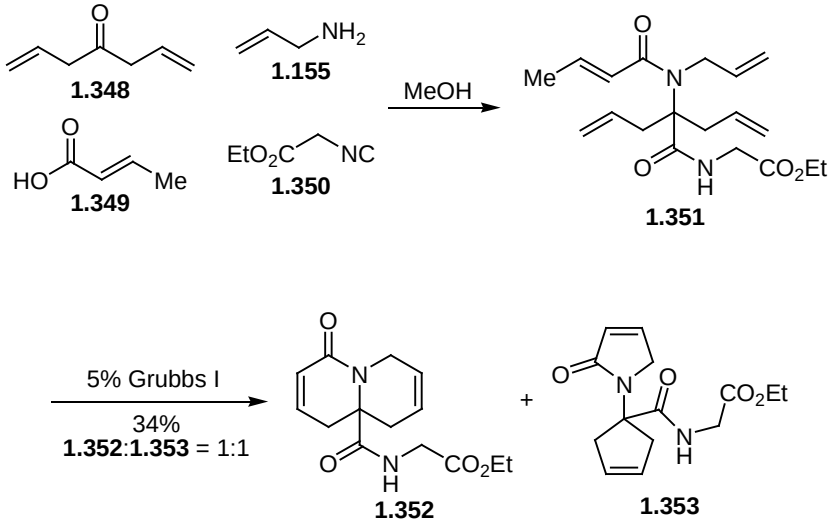
Westermann has applied the Ugi/RCM sequence to the synthesis of bicyclic lactams (Scheme 1.72).[98] Utilizing a 3-component-4-centered Ugi reaction **1.346** could be synthesized from ketone **1.344**, allylamine, and butylisocyanide in 57% with no diastereoselectivity. The RCM of **1.346** proceeded smoothly using the Grubbs I catalyst to provide **1.347** in 81% yield.

Scheme 1.72



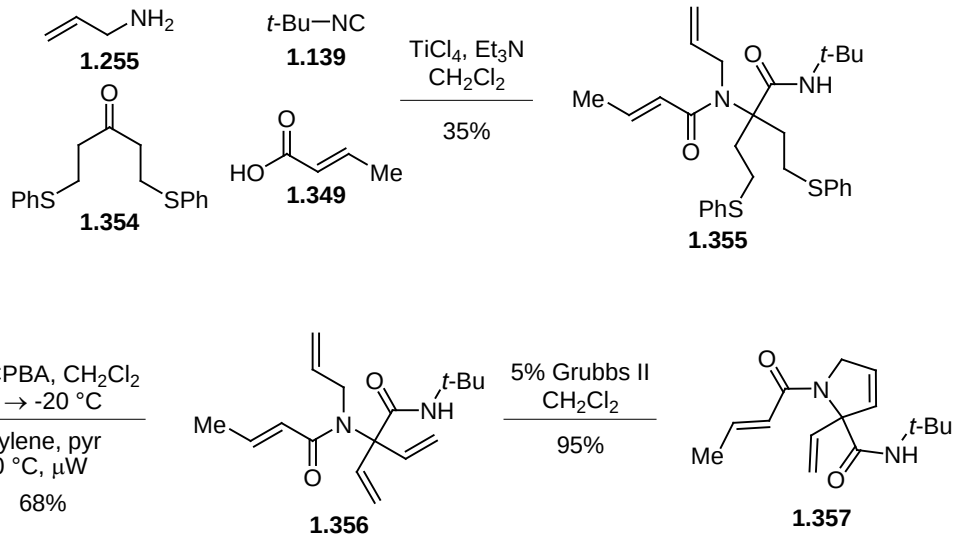
Westermann also found that diallyl ketone **1.348** could also be utilized in a Ugi-4CR leading to tetraene **1.351** (Scheme 1.73). The tetraene **1.351** is functionalized to undergo a double RCM, with two potential modes of cyclization being possible. Upon treatment with the Grubbs I catalyst, **1.351** underwent double RCM to provide a mixture (1:1) of **1.352** and **1.353** in only 34% yield over the two steps. The formation of a mixture of products was in agreement with the results seen by Ma, who has shown that the outcome of related RCM reactions is highly dependent on whether a quaternary or tertiary stereogenic center is formed, with quaternary centers leading to equal mixtures of products.[99]

Scheme 1.73



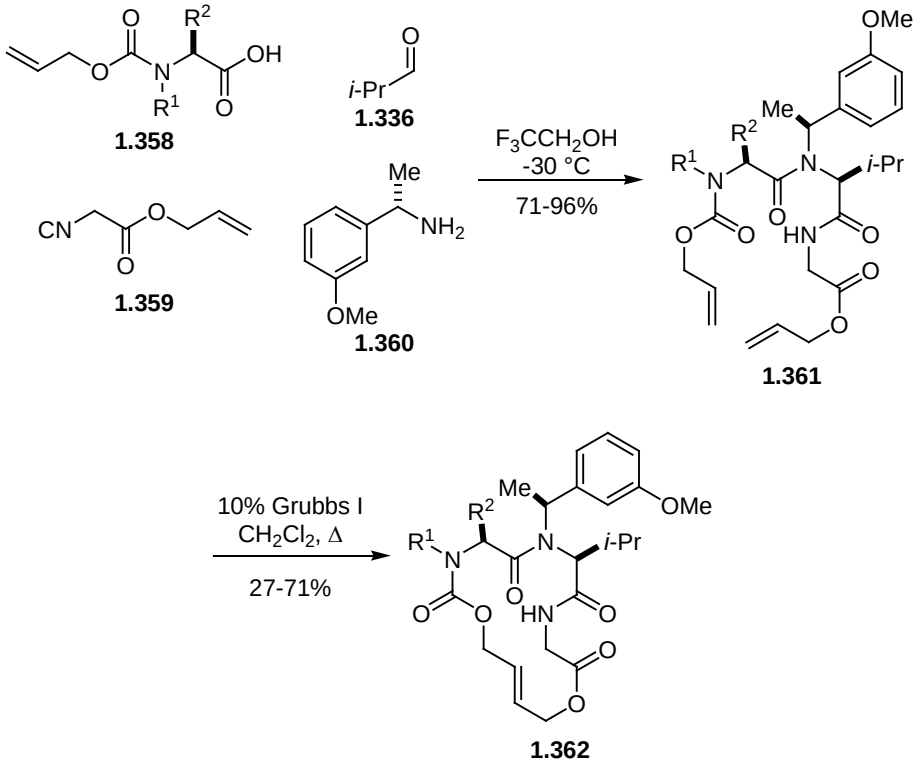
Martin has recently shown that ketone **1.354** could be employed in the Ugi-4CR reaction as a masked equivalent of divinyl ketone.[100] However, it was found that pre-formation of imine was necessary prior to addition of the carboxylic acid and isonitrile (Scheme 1.74). Thus, from allylamine, *t*-butyl isocyanate, ketone **1.354**, and crotonic acid, Ugi adduct **1.355** could be formed. A two step oxidation/elimination sequence provided tetraene **1.356** in 86% yield. When treated with the Grubbs II catalyst, **1.56** underwent RCM to give **1.357**. Interestingly, none of the double RCM product or lactam was formed under these conditions.

Scheme 1.74



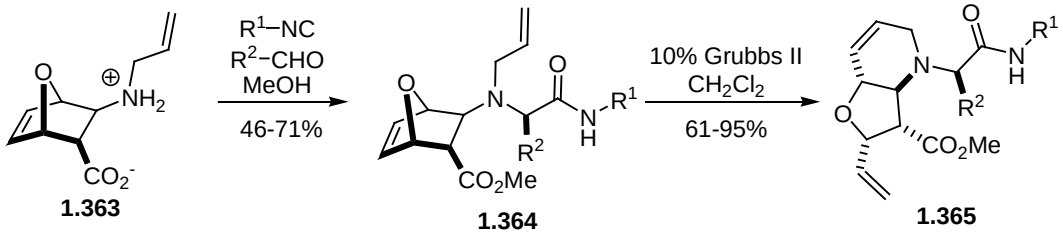
A number of approaches to macrocyclic structures have been reported utilizing both the Passerini[101] and Ugi reactions.[12, 102-104] An example of an Ugi-4CR/RCM sequence leading to 16-membered macrocycles developed by Kazmaier is shown in Scheme 1.75.[102, 104] By incorporating alloc-protected amino acids **1.358** and allyl isocyanoacetate **1.359** into the Ugi-4CR, substrates amenable to RCM leading to macrocyclic structures could be generated. In the event, the Ugi-4CR of amine **1.360** and isobutyraldehyde with **1.358** and **1.359** generated **1.361** in good yields and high levels of diastereoselectivity. The subsequent RCM with Grubbs I proceeded to provide macrocycle **1.362** in moderate yields.

Scheme 1.75



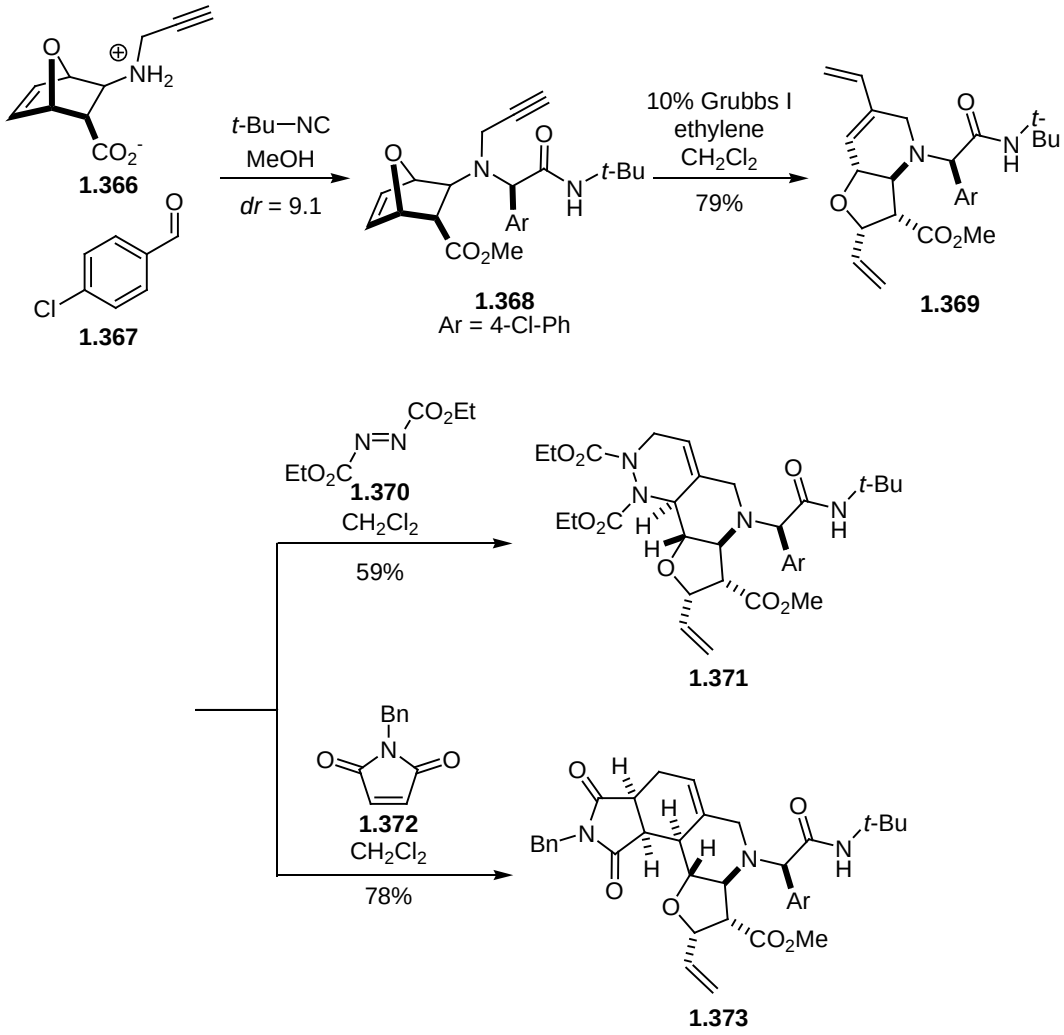
Guanti and co-workers have reported on the use of optically pure bicyclic amino acid derivatives as chiral auxiliaries in the Ugi 5-center-4-component reaction.[105] In addition to this, they have found that when using the *N*-allylated bicyclic amino acid **1.366** substrates are generated that can undergo ROM/RCM to generate optically pure fused polycyclic scaffolds (Scheme 1.76).[106] The reaction of **1.363** with aldehydes and isocyanides in MeOH provided the desired Ugi products **1.364** in moderate to good yields as a single diastereomer. The ROM/RCM proceeded without incident using the Grubbs II catalyst to provide the desired bicyclic **1.365** in good yields.

Scheme 1.76



An analogous reaction sequence could also be performed using the propargylamine **1.366** (Scheme 1.77). The U-3CR of **1.366** provided the desired **1.368**, which could undergo a ROM/enyne RCM to give **1.369**. As previously shown, the products of enyne RCM reactions are suitable substrates for subsequent Diels-Alder reactions, and **1.369** was reacted with **1.370** and **1.372** to give the tricyclic **1.371** and tetracyclic **1.373** in good yields.

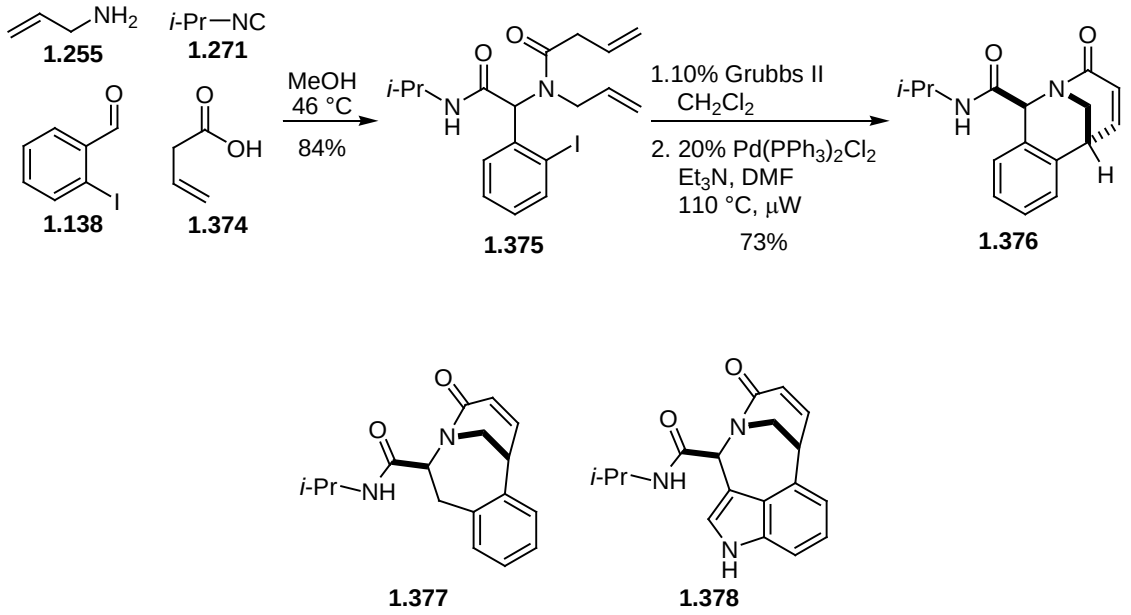
Scheme 1.77



The previous examples have shown that by incorporating appropriately disposed olefins into the Ugi inputs, substrates suitable for RCM can be generated. The Djuric research group at Abbott Laboratories has shown that if an aryl halide input is incorporated, in addition to the olefin inputs required for RCM, that products are generated that can under an Ugi/RCM/Heck reaction sequence leading to bridged bicyclic lactams (Scheme 1.78).[107] Thus, the Ugi-4CR of allylamine, *i*-PrNC, 2-iodobenzaldehyde, and unsaturated acid **1.374** provided **1.375** in 84% yield. Amide

1.376 then underwent a two step RCM/Heck reaction sequence to give bicyclic amide **1.376** in good yield. Using this three step reaction sequence a number of other bridged bicyclic lactams similar to **1.377** and **1.378** could be accessed.

Scheme 1.78

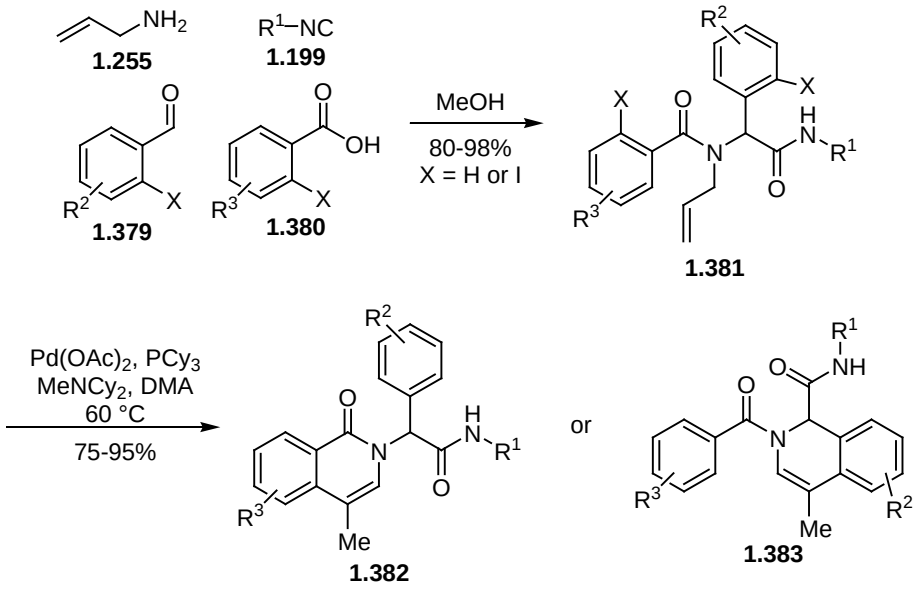


1.2.2.14 Sequential Ugi-4CR/Heck Cyclization

As shown in the previous Ugi/RCM/Heck cyclization sequence, aryl halides can be incorporated into the Ugi inputs leading to structures that can undergo Heck cyclizations leading to interesting heterocyclic scaffolds. The first example of sequencing the Ugi-4CR with an intramolecular Heck reaction was reported in 2004 by Yang and co-workers, who demonstrated a two step synthesis of isoquinolines utilizing this reaction sequence (Scheme 1.79).[108] The desired Heck precursor **1.381** could be isolated in good yields by reacting allylamine with benzaldehydes **1.379**, isonitriles **1.199**, and iodobenzoic acids **1.380**. Subsequent Heck cyclization of **1.81** provided **1.382** or **3.383** in good yields. Isoquinoline **1.382** resulted from an iodobenzoic acid input, while **1.383**

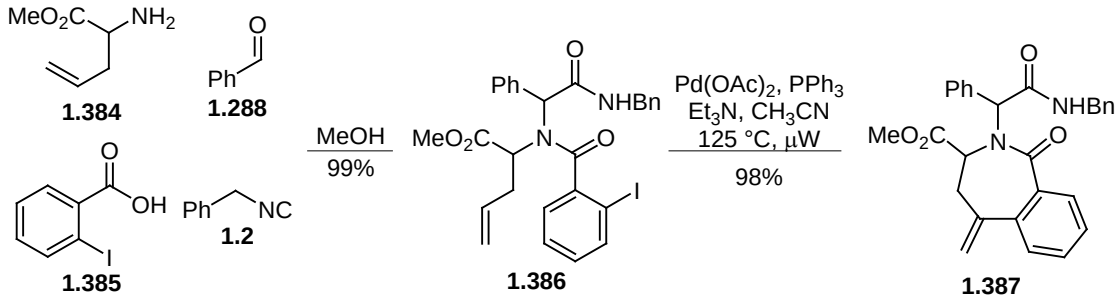
was formed from a starting iodobenzaldehyde. In both cases the exocyclic double bond formed initially isomerized to the endocyclic olefin.

Scheme 1.79



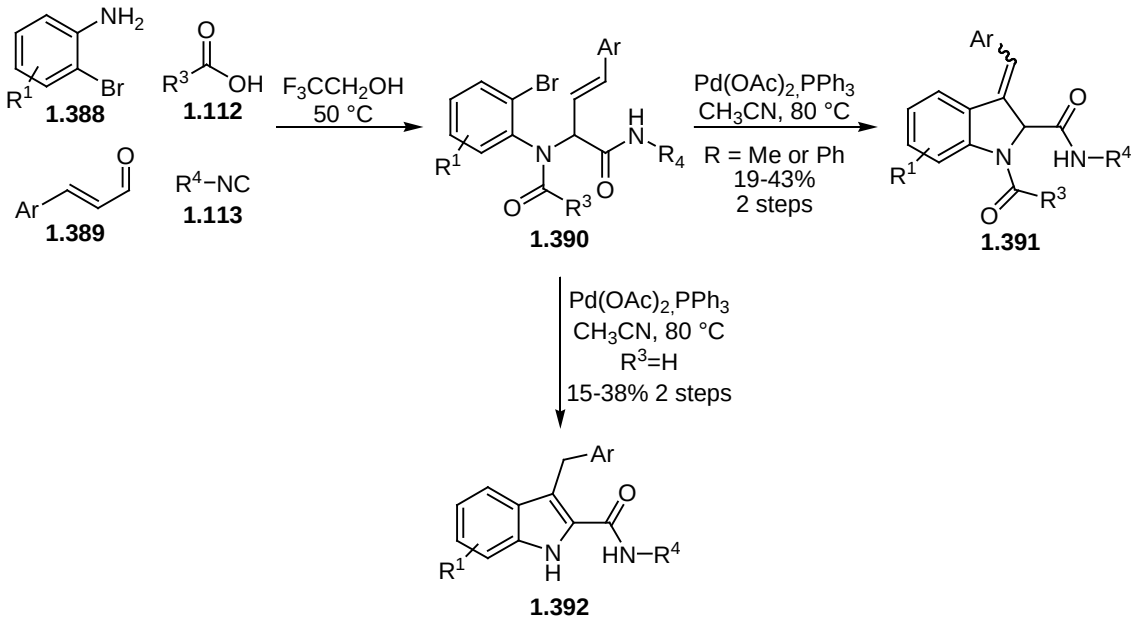
Shortly after the report of Yang, Djuric and co-workers reported a similar Ugi/Heck sequence leading to isoquinolines.[109] However, in addition to isoquinoline scaffolds, seven-membered lactams were also shown to be accessible (Scheme 1.80). The Ugi-4CR of amino ester **1.384** with benzaldehyde, 2-iodobenzoic acid, and benzyl isocyanate proceeded in almost quantitative yield to give **1.386**. The Heck reaction of **1.386** under microwave heating also proceeded in excellent yield to give lactam **1.387**.

Scheme 1.80



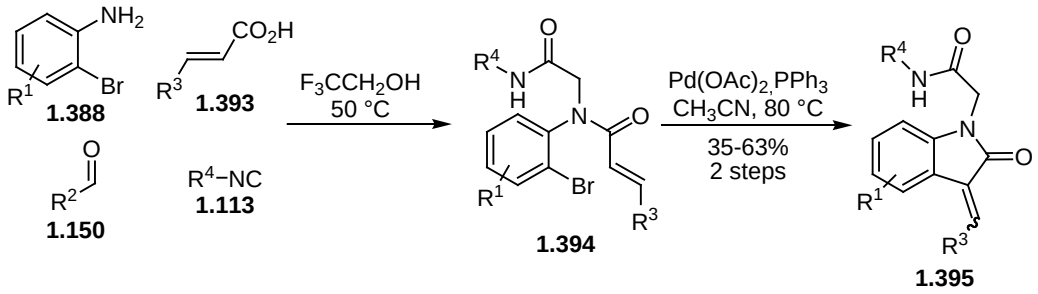
Additionally, Umkehrer and co-workers have shown the Ugi/Heck sequence can be used to access indole[110] and oxindole scaffolds.[110, 111] Access to indole scaffolds could be readily accomplished by incorporating a 2-bromoaniline as the amine input along with a cinnamaldehyde as the aldehyde input (Scheme 1.81). Thus, the reaction of bromoaniline **1.388** with cinnamaldehydes **1.389**, acids **1.112** and isonitriles **1.113** provided the Heck reaction precursor. It was found that the nature of the carboxylic acid input greatly influenced the outcome of the Heck reaction. When R^3 = methyl or phenyl, the desired Heck reaction proceeded to provide **1.391** in moderate yields over the two steps. However, when R^3 = H, the resulting Heck product underwent formamide cleavage and double bond isomerization to give the 1H-indoles **1.392**.

Scheme 1.81



Access to oxindoles could also be achieved using an analogous reaction sequence with acrylic acid inputs incorporating the requisite olefin (Scheme 1.82). [111] Thus, the Heck cyclization precursor **1.394** was synthesized and subjected to the Heck reaction conditions to generate the desired oxindoles **1.395** in moderate yields over the two steps.

Scheme 1.82

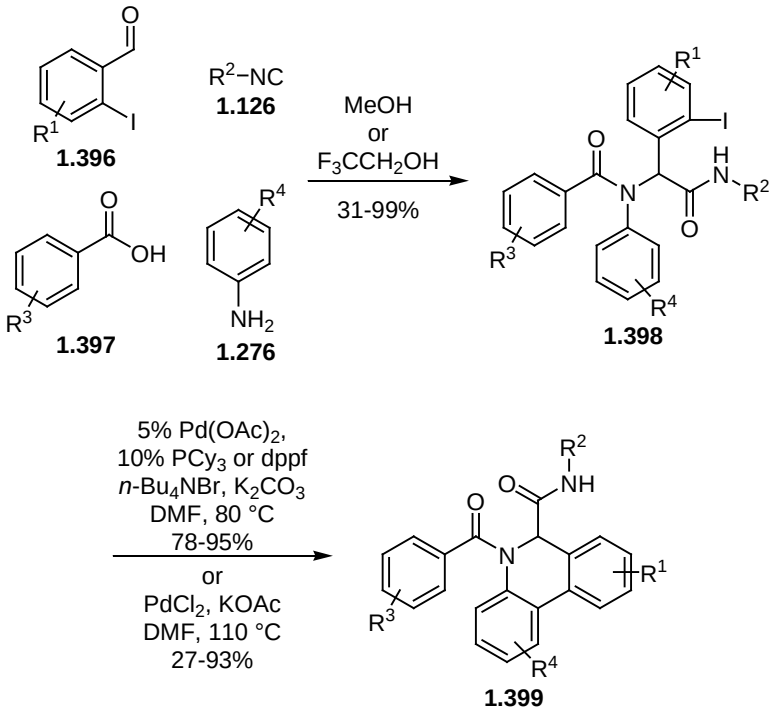


1.2.2.15 Sequential Ugi-4CR/Intramolecular Arylation or Amidation (N-Arylation)

The aryl halides that are incorporated in the Ugi reaction can also be utilized in intramolecular arylation or amidation (N-arylation) reactions. The research groups of

Yang and Zhu have independently developed routes to functionalized dihydrophenanthridines by utilizing a Ugi-4CR/intramolecular arylation sequence (Scheme 1.83).[112, 113] The Ugi-4CR of iodobenzaldehydes **1.396**, anilines **1.286**, benzoic acids **1.397**, and isonitriles **1.126** provided the arylation precursors **1.398** in good yield. The Pd catalyzed intermolecular arylation proceeded without incident to provide **1.399**.

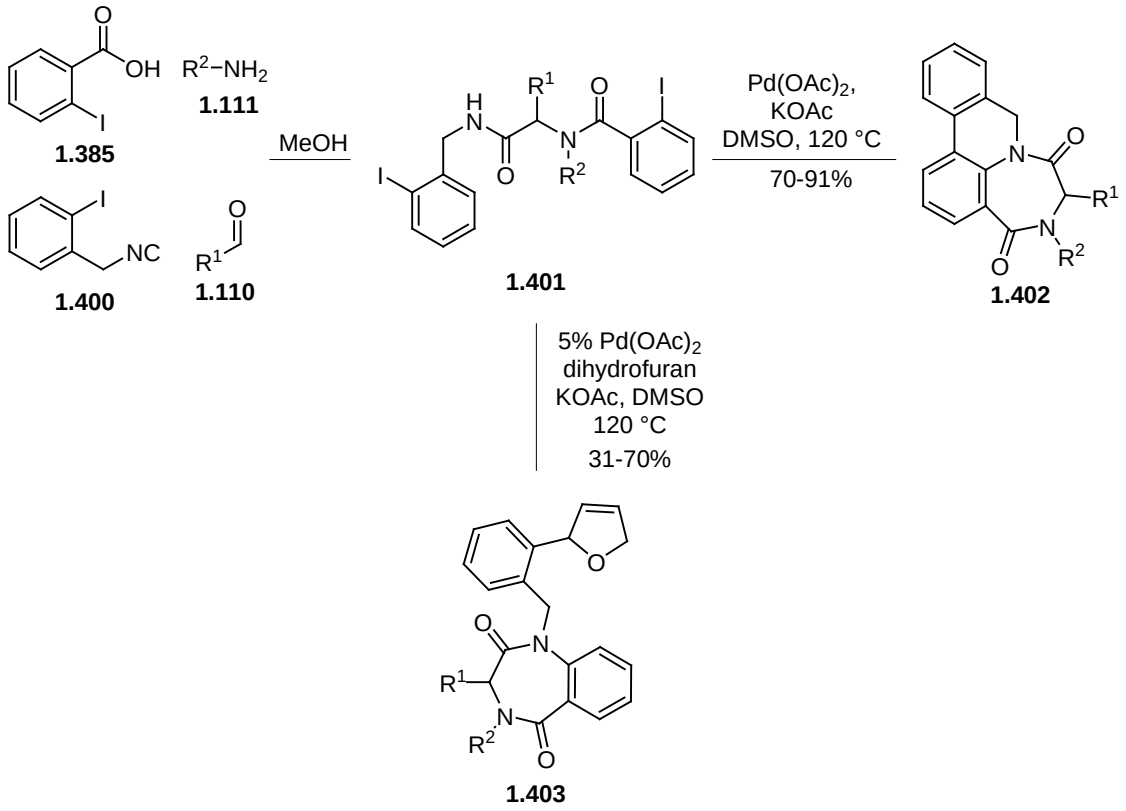
Scheme 1.83



Zhu has also developed a tandem intramolecular arylation/amidation sequence that has led to the synthesis of a number of benzodiazepines (Scheme 1.84).[114, 115] To perform this tandem reaction, the di-aryliodide **1.401** was first synthesized from aldehydes **1.110**, amines **1.111**, isonitrile **1.400**, and iodobenzoic acid **1.385**. Upon treatment with $Pd(OAc)_2$ and KOAc in DMSO at 120 ºC amide **1.401** underwent double cyclization to give **1.402** in good yields. It was later found that the tandem arylation/amidation substrates **1.401** could undergo a tandem amidation/intermolecular

Heck reaction sequence.[116] When a coupling partner such as dihydrofuran was introduced to the reaction, the desired amidation/intermolecular Heck reaction proceeded to give **1.403** in variable yields. Interestingly, the intermolecular Heck reaction out competes the intramolecular arylation, even under reaction conditions that were identical to those used in the arylation/amidation protocol. Other coupling partners such as methyl acrylate and dimethylacrylamide could also be used in this reaction sequence.

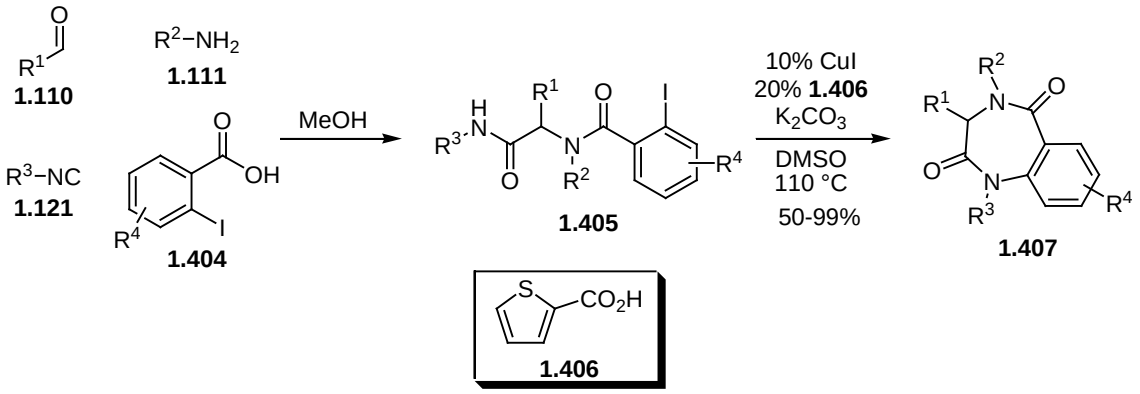
Scheme 1.84



It was subsequently found that when a copper-based catalyst system was utilized with these systems that only the amidation reaction occurred, and after some optimization this was developed into a general method for the synthesis of benzodiazepines (Scheme 1.85).[115] The Ugi-4CR proceeded smoothly to provide the desired cyclization precursors **1.405**. Upon treatment with catalytic CuI and thiophene carboxylic acid in the presence

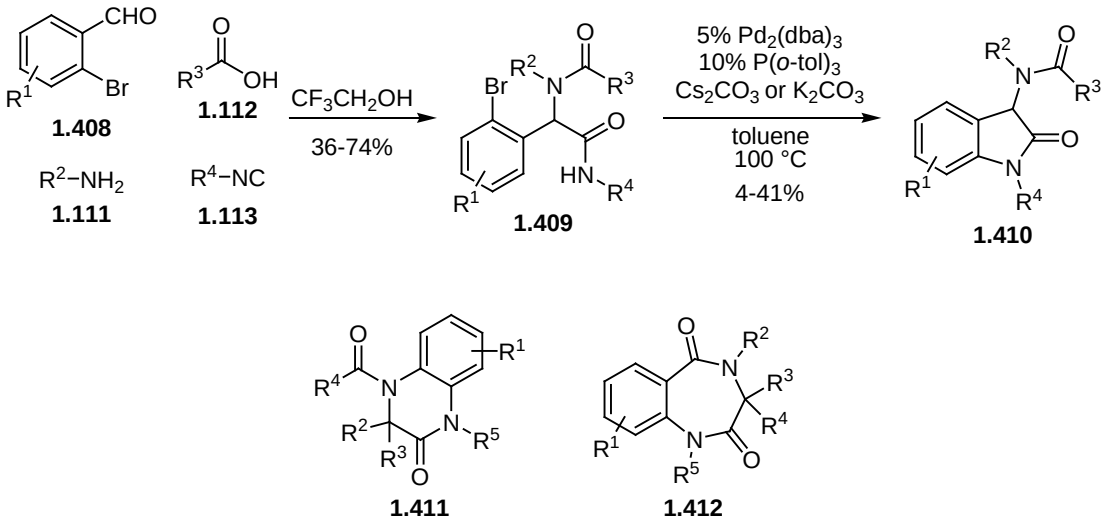
of K_2CO_3 in DMSO at 110 ºC, **1.405** underwent the desired amidation to provide **1.407** in good yields.

Scheme 1.85



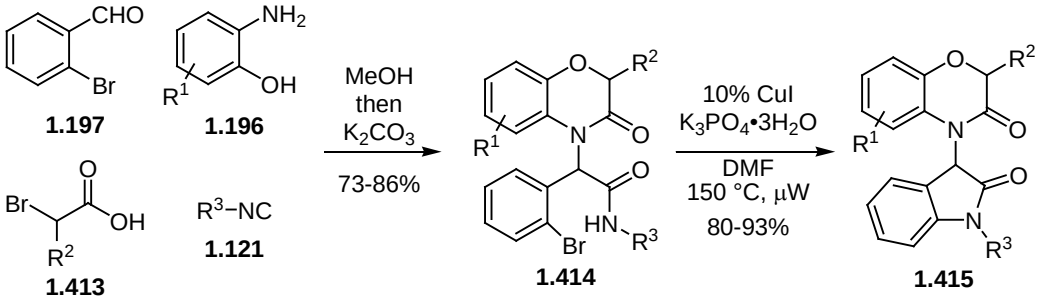
In 2006 Kalinski and Zhu independently reported the synthesis of oxindoles utilizing a Pd catalyzed N-arylation. Kalinski's approached utilized aryl bromides, and the yields for the cyclization were only modest at best (Scheme 1.87).[117] Zhu was able to achieve much higher yields (60-99%) for the cyclization by utilizing aryl iodides and microwave heating.[118] However, Kalinski did demonstrate that using a 2-bromoaniline or 2-bromobenzoic acid, quinoxalin-2-ones **1.411** and benzodienzepines **1.412** could be accessed. Unfortunately, the yields for these processes were also low.

Scheme 1.87



Dai has developed an interesting tandem Ugi-4CR/O-alkylation/amidation sequence (Scheme 1.88).[119] The Ugi product of 2-bromobenzaldehyde, amino phenol **1.196**, bromoacetic acid **1.413**, and isonitrile **1.121** was treated in situ with K_2CO_3 to provide the phenolic ether **1.414**. Subsequent Cu(I) catalyzed amidation provided the oxindoles **1.415** in good yields.

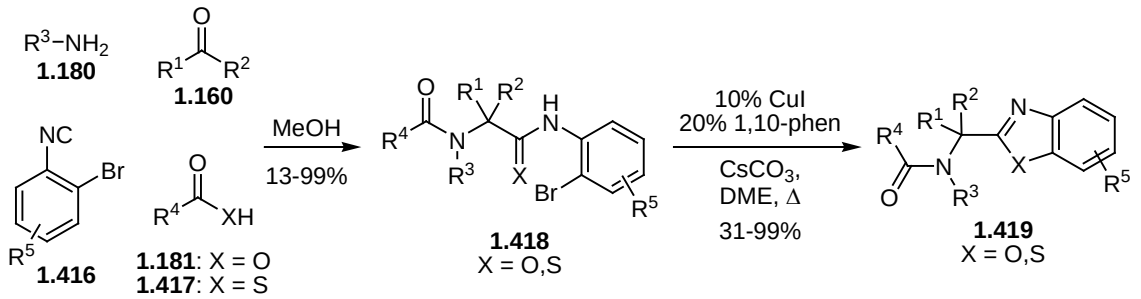
Scheme 1.88



1.2.2.17 Ugi 4CR/Intramolecular Cyclization to give Benzoxazoles and Benzothiazoles

Benzoxazoles and benzothiazoles are important classes of compounds found in both natural products and drug like molecules. Hence, efforts have been made to synthesize libraries of these compounds using the Ugi-4CR. Spatz has reported a two step procedure for accessing both benzoxazoles and benzothiazoles that utilizes a Ugi-4CR followed by a Cu(I) catalyzed cyclization (Scheme 1.89).[120] The reaction of amines **1.180** and aldehydes or ketones **1.160** with bromophenylisocyanate **1.416** and either carboxylic acid **1.181** or thienoic acids **1.417** provided the desired cyclization precursors in variable yields. Subjection of **1.418** to the Cu catalyzed cyclization conditions provided the desired benzoxazoles and benzothiazoles in up to 99% yields. It should also be noted that aryl chlorides and fluorides could also be utilized in the synthesis of the benzothiazoles.

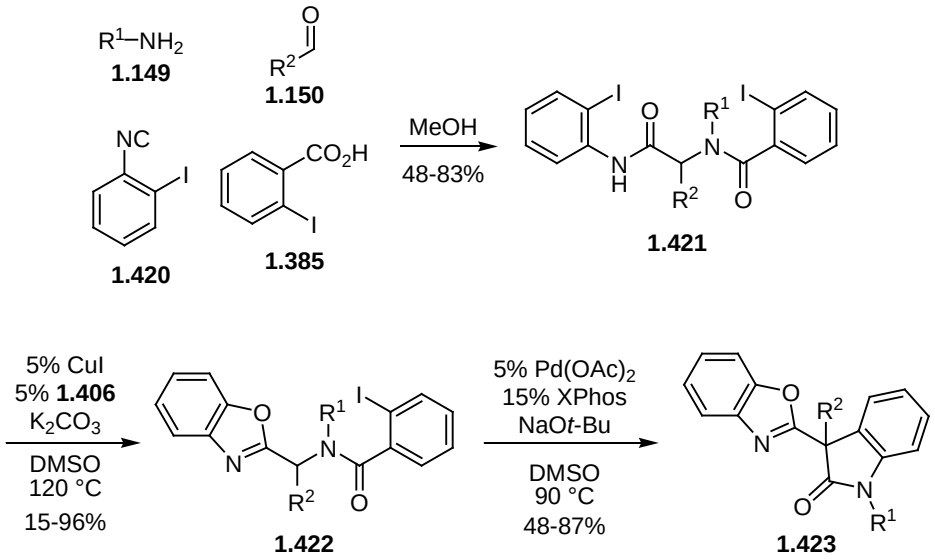
Scheme 1.89



Zhu has recently shown that the Ugi-4CR can be utilized to synthesize substrates that are amenable for an oxazole formation/C-H activation sequence (Scheme 1.90).[121] Thus, the Ugi adduct **1.421** containing two aryl iodides was synthesized from amine **1.149**, aldehyde **1.150**, iodobenzoic acid **1.385**, and iodophenylisocyanate **1.420** in moderate to good yields. First, **1.421** underwent a Cu(I) catalyzed cyclization to form the

desired benzoxazoles in variable yields. The benzoxazoles were then reacted in the Pd catalyzed benzylic arylation to provide the desired 3-benzoxazolylisoindolinones **1.423**.

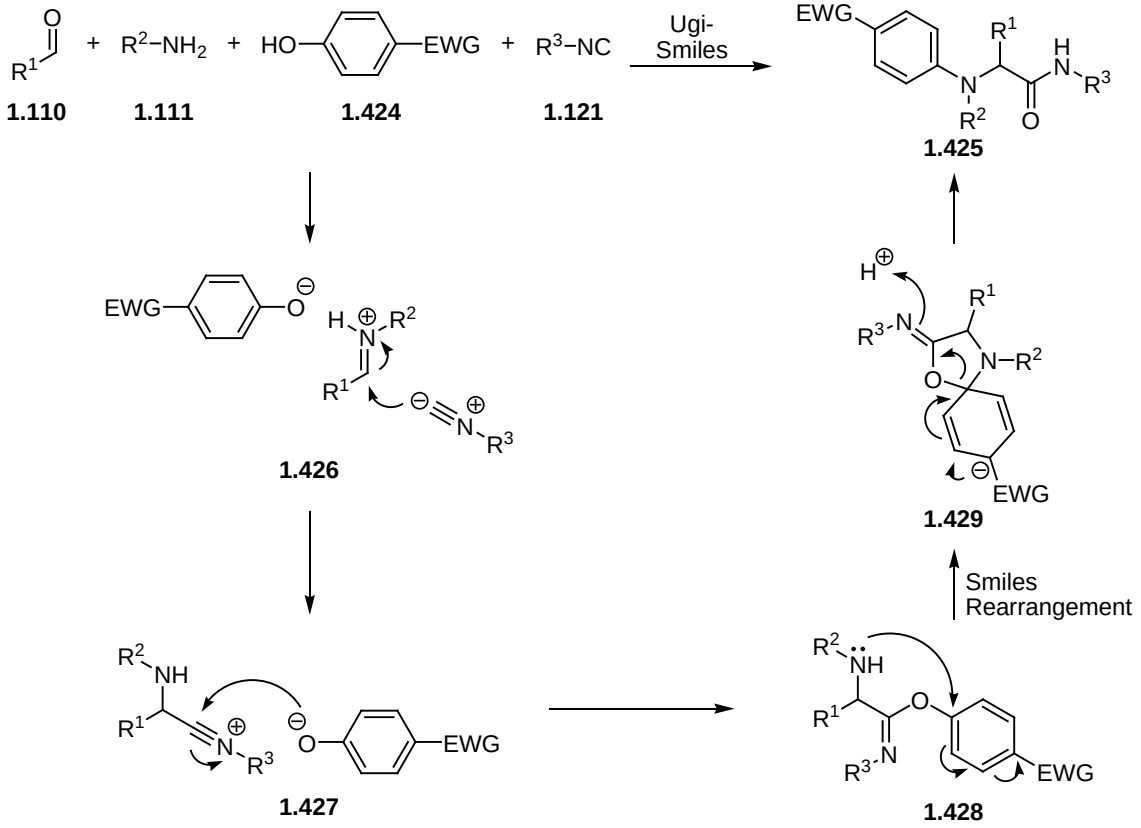
Scheme 1.90



1.2.2.18 Applications of the Ugi-Smiles Reaction

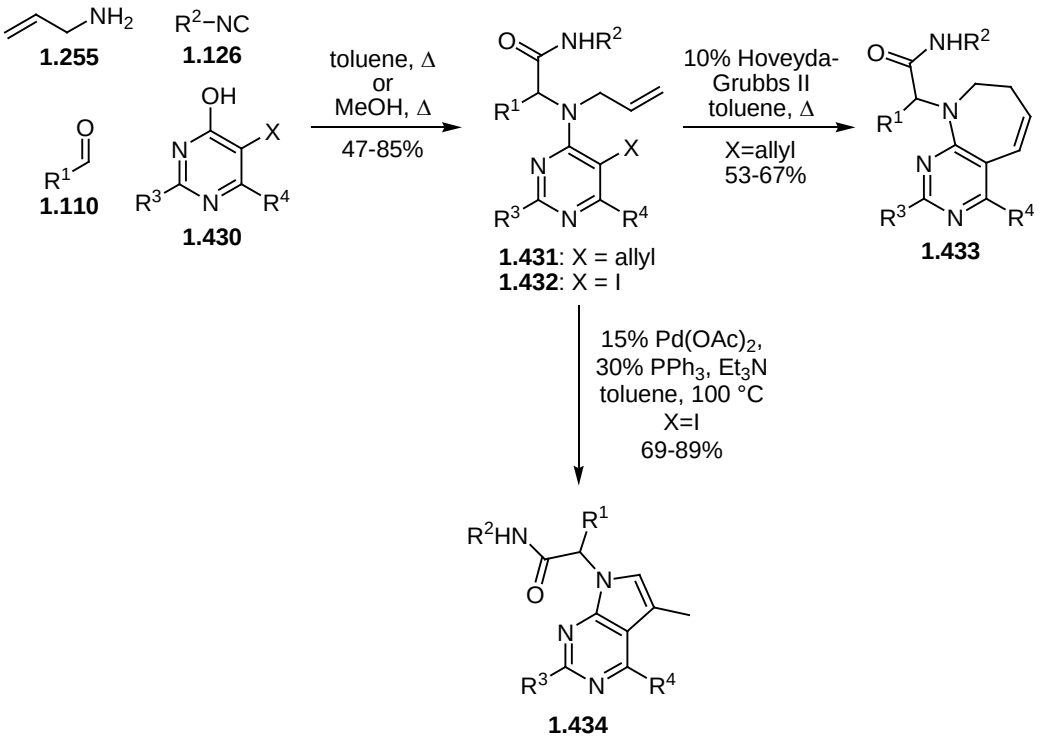
In 2005 El Kaïm reported a variation of the Ugi-4CR that incorporates electron deficient phenols in place of the usual carboxylic acid input.[122] Mechanistically, the reaction differs from the Ugi-4CR in that the reaction proceeds via a Smiles rearrangement[123] instead of the normal Mumm rearrangement (Scheme 1.91), and therefore has become known as the Ugi-Smiles reaction.

Scheme 1.91



The Ugi-Smiles reaction works with a variety of electron deficient phenols, including functionalized heterocyclic phenols such as pyrimidines **1.430** (Scheme 1.92). By incorporating different functional handles into **1.430**, a variety of different cyclization modes could be accessed. When an allyl group was incorporated in **1.430** (X = allyl) the products of the Ugi-Smiles reaction could undergo RCM and double bond isomerization to give **1.433**.[124] By incorporating an iodide into **1.430** (X = I) an Ugi-Smiles/Heck cyclization pathway was accessible to access pyrrolo-pyrimidine **1.434**.[125] Currently these are the only two examples of post-condensation modifications of Ugi-Smiles products, however, the potential exists for sequencing the Ugi-Smiles with other reactions in an analogous fashion to what has been done with Ugi-4CR.

Scheme 1.92



The above examples demonstrate why the Ugi-4CR has become the benchmark MCR for synthesizing diverse heterocyclic scaffolds. The functional group tolerance of the U-CR has allowed for it to be sequenced with a large number of subsequent cyclization reactions, each leading to a distinct scaffold. Although a large volume of work has been completed with the Ugi-4CR, as chemists continue to devise new cyclization manifolds to sequence with MCRs the Ugi-4CR will continue to remain an important reaction in the synthetic community.

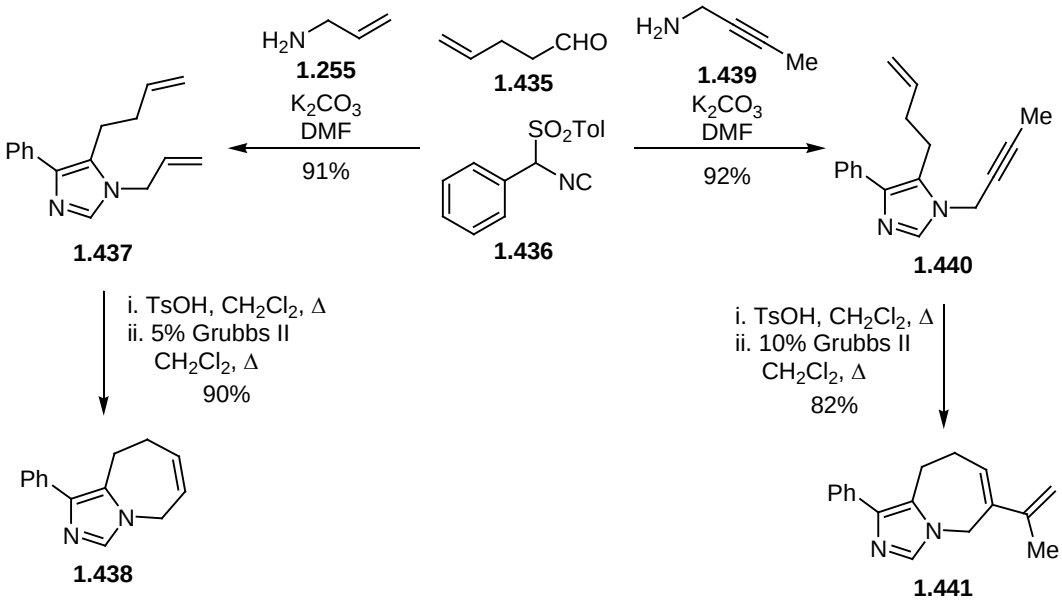
1.2.3 Applications of the van Leusen 3CR

Polycyclic imidazole containing scaffolds are found in a number of natural products and biologically active compounds, making them attractive targets for synthetic chemists. The van Leusen imidazole synthesis combines aldehydes, amines, and substituted TosMIC reagents to provide substituted imidazoles in pot.[126] Researchers at

Abbott Laboratories have shown that by incorporating the appropriate functionalized starting materials, the van Leusen 3CR can be sequenced with a number of ring forming reactions leading to polycyclic imidazole scaffolds, which are prevalent in a number of natural products and biologically active compounds.[127-129]

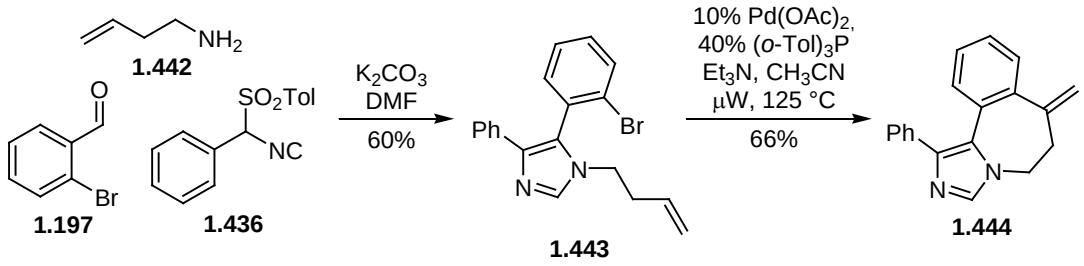
Unsaturated amines and aldehydes can readily be input into the van Leusen 3CR leading to substrates suitable for subsequent RCM[130] and enyne RCM[131] (Scheme 1.93). Thus, the reaction of 4-pentenal (**1.435**) with allylamine and phenyl TosMIC (**1.436**) provided **1.437**, which underwent RCM upon treatment with the Grubbs II catalyst to provide bicyclic imidazole **1.438**. Enyne RCM precursor **1.440** could be accessed simply by changing the amine component from allylamine to the propargyl amine **1.439**. Upon treatment with the Grubbs II catalyst, the enyne RCM occurred smoothly to provide **1.433** in good yields for the two steps. For both of these RCM reactions it was necessary to protonate the imidazole with TsOH prior to adding the Grubbs catalyst, thus preventing the lone pair of electrons on the imidazole nitrogen from deactivating the ruthenium catalyst.[132]

Scheme 1.93



Aryl halides can also be incorporated into the van Leusen 3CR for use in subsequent Heck cyclizations (Scheme 1.94). [133, 134] Aryl bromide **1.443** could be accessed in one step from bromobenzaldehyde **1.197**, homoallylamine, and phenyl TosMIC. Upon treatment with Pd(0) in acetonitrile under conditions of microwave heating the desired Heck cyclization occurred to provide **1.444**.

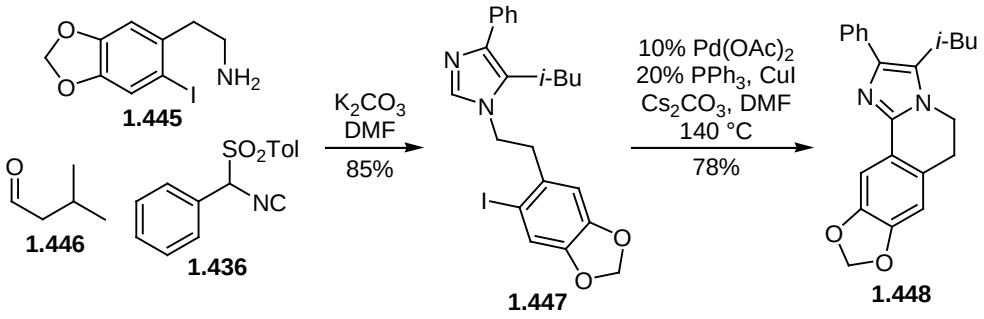
Scheme 1.94



It was also discovered that in the absence of a pendent alkene, the aryl halides could undergo an intramolecular C-arylation reaction (Scheme 1.95). [135] The requisite arylation substrate **1.447** could readily be accessed from phenethyl amine **1.445**,

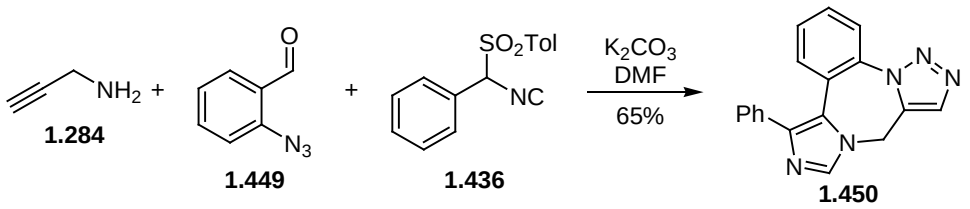
isovaleraldehyde (**1.446**), and phenyl TosMIC. The subsequent arylation was found to proceed under conditions utilizing catalytic $Pd(OAc)_2$ and stoichiometric CuI to generate the desired **1.448** in 78% yield.

Scheme 1.95



A tandem van Leusen 3CR/azide-alkyne cycloaddition sequence leading to fused triazolo-imidazole scaffolds has also been demonstrated (Scheme 1.96).[136] The reaction of propargylamine with azidobenzaldehydes **1.449** and ayrl TosMIC reagent **1.436** generated an intermediary azide that underwent a 3+2 dipolar cycloaddition to provide the fused **1.450** in good yields.

Scheme 1.96



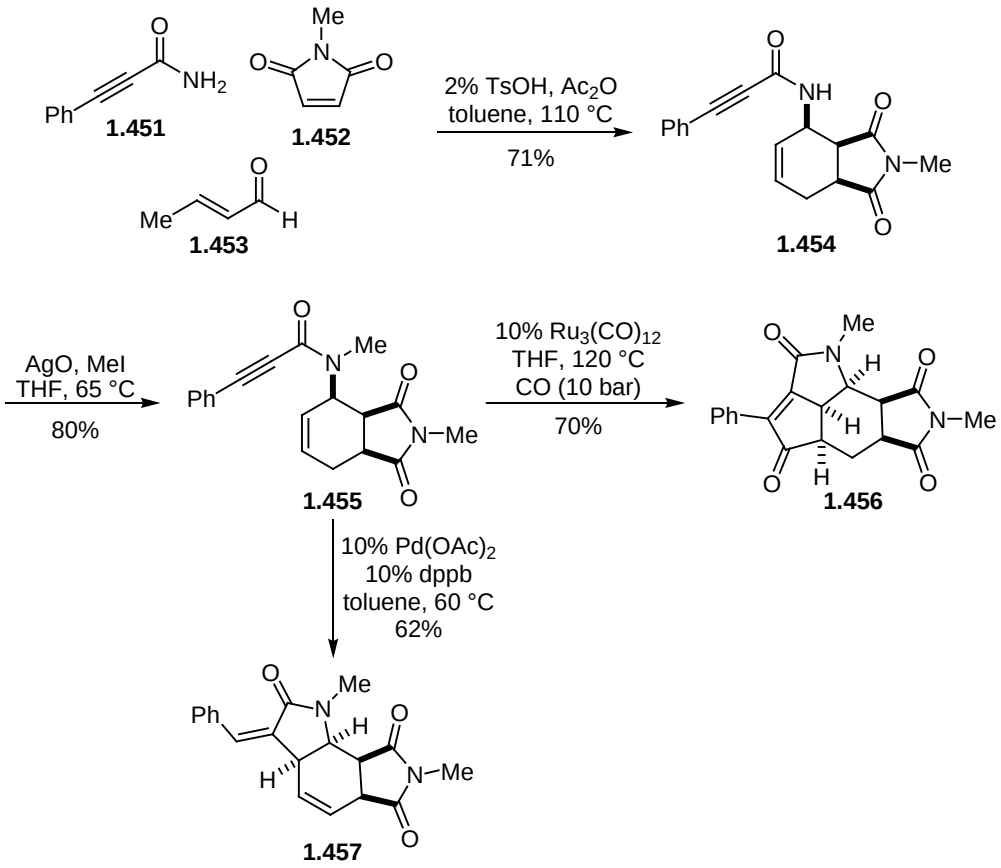
The van Leusen 3CR has initially shown considerable promise for synthesizing diverse collections of imidazole containing scaffolds. However, to date only a handful of ring forming reactions have been utilized in conjunction with the van Leusen 3CR and further efforts are needed to expand this reaction sequence to other cyclization manifolds

leading to additional imidazole scaffolds. Additionally, to date there has only been one published example where the TosMIC input contained functionality amenable for a subsequent cyclization,[130] and the expansion of this methodology to include more examples with functional handles on the TosMIC derivative would further expand the scope of accessible scaffolds.

1.2.4 Applications of the Aldehyde/Amide/Dienophile Reaction

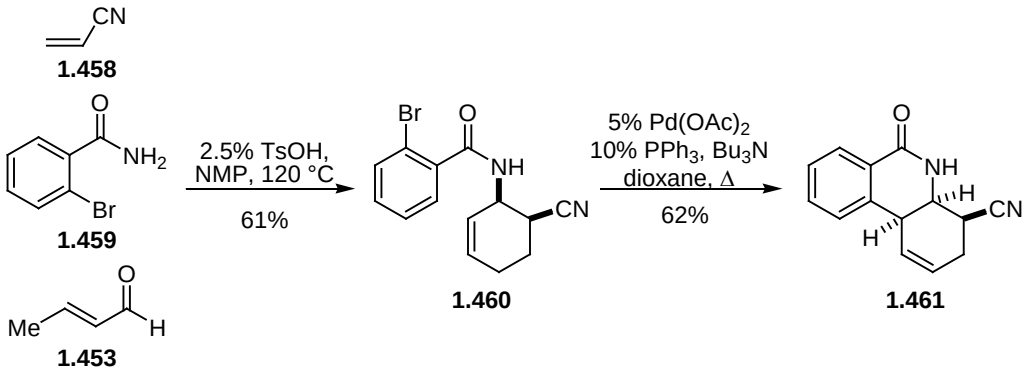
Beller has developed a novel MCR that involves the coupling of an amide, aldehyde, and dienophile (the AAD reaction)[137] that has been shown to generate structures amenable to post-condensation modification.[138-140] The AAD reaction of amide **1.451** with crotonaldehyde and maleimide **1.452** provided the desired enyne **1.454** in 71% yield. Methylation of **1.454** with MeI provided **1.455** (Scheme 1.97).[138, 139] As previously discussed in this Chapter, enyne substrates such as **1.455** are amenable to reagent based differentiations leading to a number of different scaffolds. In this case it was shown that enyne **1.455** could undergo a Ru catalyzed Pauson-Khand reaction to give cyclopentenone **1.456**, and a Pd catalyzed Alder-ene reaction leading to **1.457**.

Scheme 1.97



Alternatively, the amide input can be functionalized with an aryl halide leading to structures amenable for subsequent Heck cyclizations (Scheme 1.98).[140] Phenanthridone **1.458** could be synthesized from acrylonitrile (**1.455**), amide **1.456**, and crotonaldehyde via a two step AAD/Heck reaction sequence. The phenanthridone core structure is found in a number of alkaloid natural products,[141] highlighting the ability of this method for accessing natural product-like skeletons.

Scheme 1.98

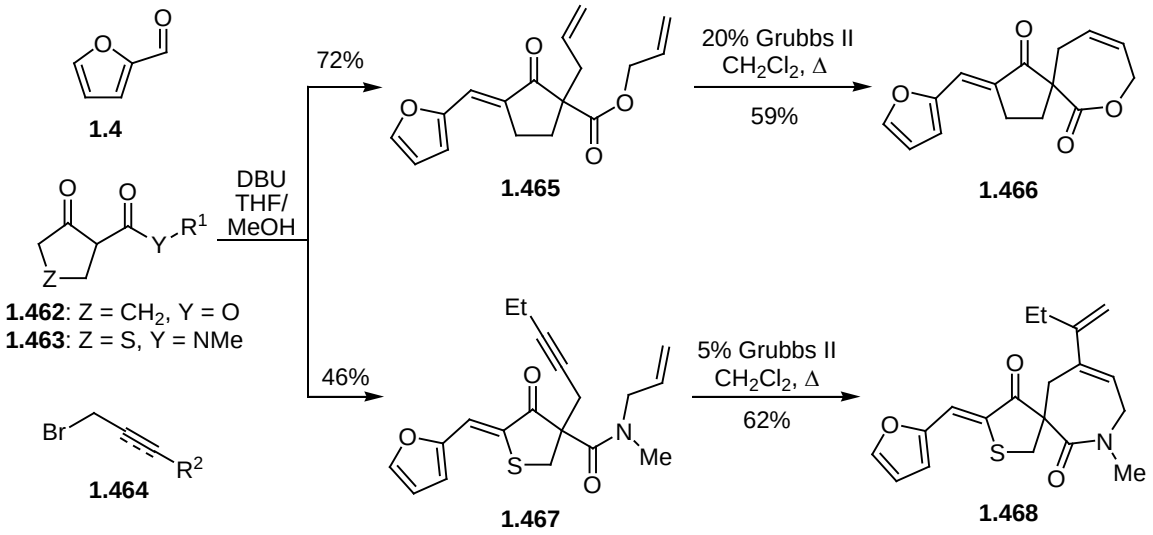


1.2.5 Applications of the α,γ-Difunctionalization Reaction of β-Ketoesters and Amides

Rodriguez has reported the multicomponent synthesis of α,γ-difunctionalized β-ketoesters and amides starting from aldehydes, alkyl halides, and β-ketoesters or amides.[142] More recently Rodriguez has shown that this 3CR can be sequenced with a number of transition metal catalyzed ring-closing reactions that lead to the generation of spiroheterocyclic scaffolds.[143]

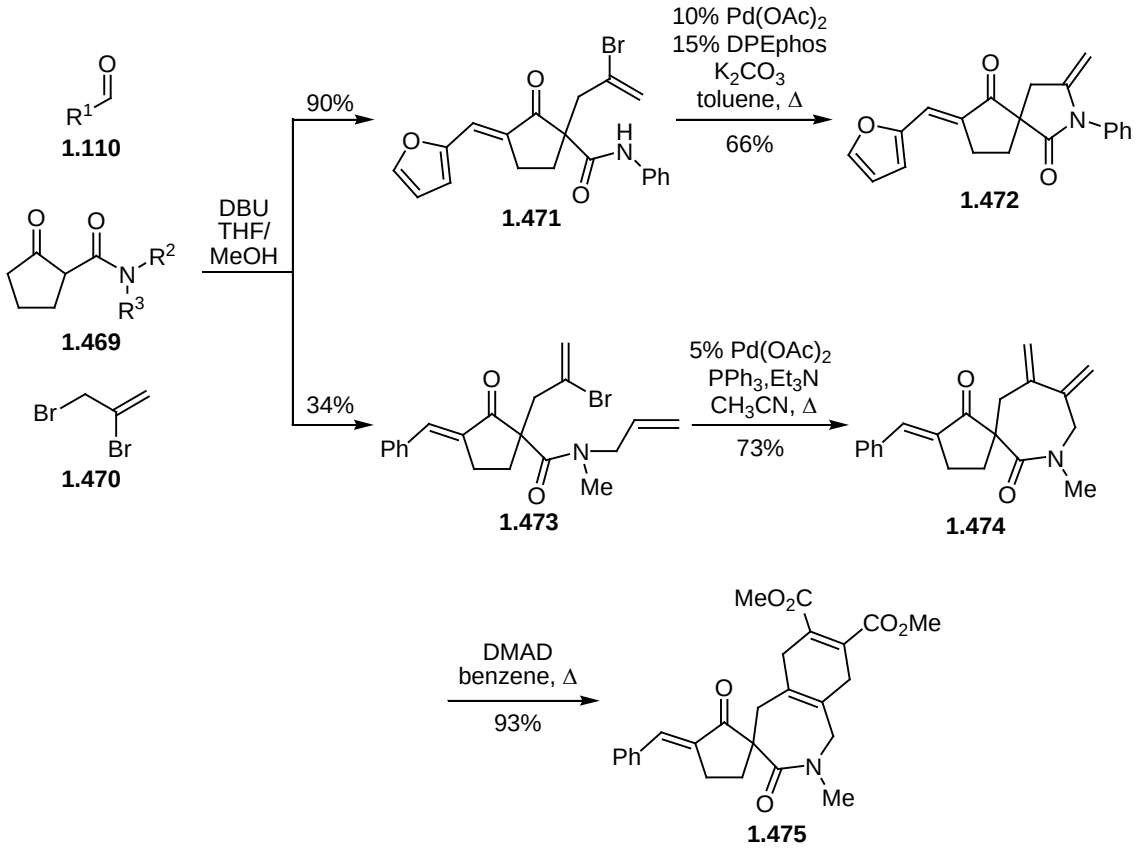
β-Ketoester **1.462** or amide **1.463** can undergo reaction with furfural and either allyl bromide or propargyl bromide **1.464** leading to **1.465** or **1.467**, respectively (Scheme 1.99). Diene **1.465** could undergo RCM with Grubbs II to generate the spirocyclic **1.466**, while enyne **1.467** underwent enyne RCM to give **1.468**.

Scheme 1.99



Additional spriocyclic structures could be accessed by utilizing allyl bromide **1.470** as the alkylating agent, thus generating substrates suitable for Pd catalyzed couplings (Scheme 1.100). The vinyl bromide present in **1.471** underwent a Pd catalyzed amidation to give lactam **1.472**. With the incorporation of an additional olefin into **1.473**, a Heck cyclization was possible to give diene **1.474**, which was reacted with DMAD in a Diels-Alder reaction to provide **1.475**.

Scheme 1.100



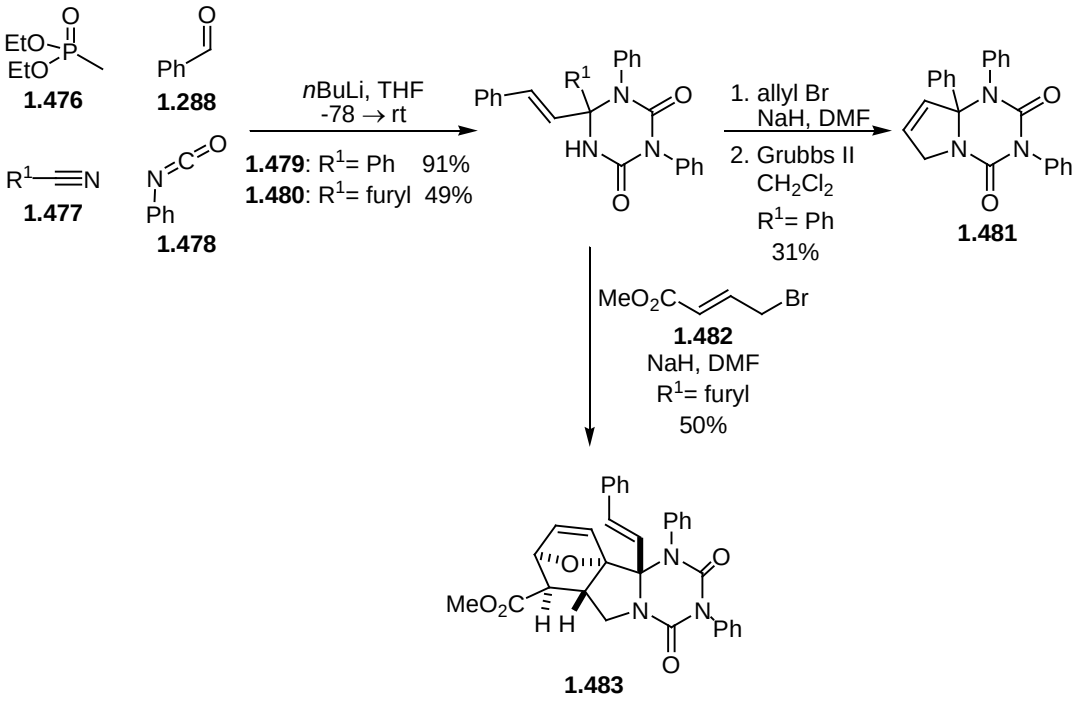
1.2.6 Applications of the 4-Component Triazinedione Synthesis

Orru has recently developed a 4CR of a phosphonate, nitrile, aldehyde, and two equivalents of an isocyanate gives rise to the triazinane diones.[144] Triazinane diones represent a relatively unexplored class of compounds, and this methodology should provide access to a number of scaffolds based on this core structure. While it has not been shown that the triazinane dione products themselves can be directly manipulated into other more complex heterocycles, by performing an additional alkylation step substrates suitable for further cyclization can be generated (Scheme 1.101).[145]

The 4CR of phosphonate **1.476**, benzonitrile, benzaldehyde, and phenyl isocyanate yielded **1.479** (R^1 = Ph) in 91% yield. Allylation of **1.479** gave a substrate

which underwent RCM to provide **1.481** in 31% yield over the two steps. Similar use of 2-furonitrile in the 4CR gave **1.480** (R^1 = furyl), which upon alkylation with allyl bromide **1.482** underwent an intramolecular Diels-Alder to give **1.478**.

Scheme 1.101



1.3 CONCLUSIONS

As chemists and biologists search for novel active compounds for use in modulating biological function, the question arises as to whether or not the collections of molecules that have been synthesized and screened in biological assays represent the best of the best in terms of their chemical and biological properties. It is quite possible that a number of as of yet unknown compounds will display biological activities that are superior to any known drug. Thus, there is a need for chemists to the synthesize an optimal screening library, which is a library of compounds that contains molecules representative of every possible combination of chemical structure and property, and

includes both structures that have been previously studied and those that are currently unknown.

The concept of DOS was developed to provide chemists with a strategy for rapidly and efficiently accessing these unexplored regions of chemical space. To this end, a number of synthetic tactics for DOS have been developed. One of the most promising of these strategies is the sequencing of MCRs with subsequent cyclization reactions that lead to diverse heterocyclic scaffolds. To date a number of different MCRs have been developed and sequenced with multiple ring forming reactions leading to numerous heterocyclic scaffolds. In particular, the Ugi-4CR has proven to be a work-horse in this field, and hundreds of diverse scaffolds have been synthesized by combining the Ugi-4CR with subsequent ring forming reactions. Other MCRs, like the van Leusen 3CR, have shown promise in this area, but to date have not been as extensively explored as the Ugi-4CR.

However, the synthetic methodologies known today are not without their limitations, and if every conceivable type of compound is to be synthesized, new synthetic methods and strategies will need to be developed. There is still a great need for synthetic chemists need to develop new MCRs on par with the Ugi-4CR in terms of their synthetic utility, but complimentary to the Ugi-4CR in that the scaffolds they can access are distinctly different. This in turn will allow for all areas of chemical space to be targeted in an efficient matter.

While the underlying questions in DOS still remain unanswered, the synthetic methods developed thus far have provided chemists and biologists with a starting point for answering these questions. Hopefully in time the synthetic methods will allow for the synthesis of the optimal screening library, so that every biological pathway and receptor

can be studied and then adequately drugged, thus creating a perfect world where no aliment goes untreated.

Chapter 2: The Development of a Four Component Reaction and Its Application to the Synthesis of Diverse Heterocyclic Structures.

2.1 Introduction

Diversity-oriented synthesis (DOS) continues to grow as an area of importance in both the fields of organic synthesis and chemical biology.9, 146-148 The main goal of DOS is the synthesis of structurally and stereochemically diverse collections of molecules for evaluation in biological systems, with the hypothesis being that a broader spectrum of diversity in the chemical library will lead to the generation of more information from biological screens. Of particular interest is the ability to synthesize compounds that possess a skeleton found in natural products or drug-like molecules.4, 149 Since the vast majority of natural products and drug-like compounds possess a heterocyclic structure, having the ability to synthesize diverse heterocyclic compounds efficiently becomes all the more important.

As discussed in the previous Chapter, the success of DOS still relies squarely on the shoulders of the synthetic methods used to generate these small molecules. Perhaps the most promising synthetic strategy for generating these collections of molecules is the sequencing of multicomponent reactions (MCRs) with subsequent ring-forming transformations that lead to the generation of new compounds with increased molecular complexity and diversity.[26, 30] This process of sequencing MCRs with subsequent cyclizations falls under the build/couple/pair strategy of DOS.23

Ideally, the MCRs that are designed and implemented should be versatile so that each component of the MCR can incorporate a wide range of functionalities. Then through the use of functional group pairing,24 these functional groups can be selectively exploited in subsequent ring forming processes. Ideally, this should lead to a situation where potentially any known synthetic reaction can be utilized to transform the

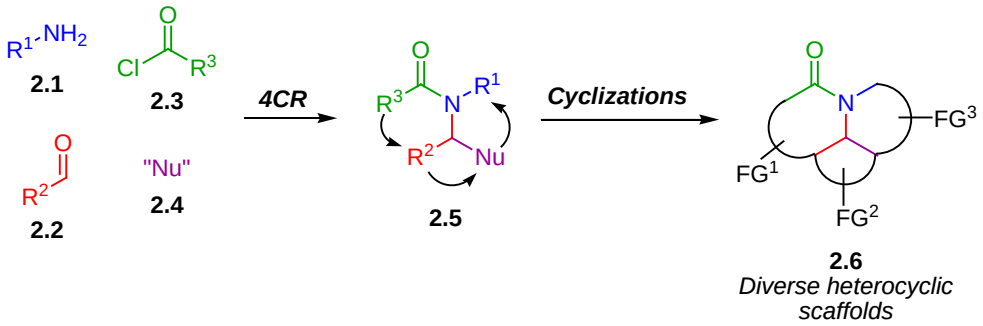
intermediates generated by the MCR into the targeted heterocyclic structures. Additionally, the ring forming reactions should be chosen so that the products they generate still contain functional handles that can be further derivatized as needed. This combination of MCRs with post-condensation modifications should then allow for access to a number of functionalized heterocyclic scaffolds in a short number of steps.

While the strategy of sequencing MCRs with subsequent ring-forming processes is seemingly ideal for DOS, the implementation of this strategy has been limited. The venerable Ugi four component reaction (Ugi-4CR) has proven to be ideal for this application, and a large number of reactions have been sequenced with the Ugi-4CR, leading to a vast collection of diverse heterocycles. Outside of the Ugi-4CR, there have been only a handful of MCRs that have been successfully sequenced with multiple ring forming reactions, and in all of these examples the number of subsequent ring-forming reactions performed was limited.[25] Thus, there is a need for the development of new MCRs that are sufficiently versatile so that they can access substrates amenable to a wide range of cyclization manifolds, allowing for the synthesis of diverse libraries of compounds.

To this end, we have set out to develop a four component Mannich-type reaction capable of generating highly functionalized products that can be transformed into interesting heterocyclic structures (Scheme 2.1).150 Previously the Martin group has exploited the vinylogous Mannich reaction as a key construct in the syntheses of numerous alkaloid natural products.151 Drawing on this background in vinylogous Mannich chemistry, it was envisioned that this three component reaction (3CR) of an imine, acid chloride, and a nucleophile could be readily adapted into a novel four component reaction (4CR) by utilizing an aldehyde and a primary amine to form the imine in situ. Thus, the sequential combination of a primary amine **2.1**, aldehyde **2.2**, acid

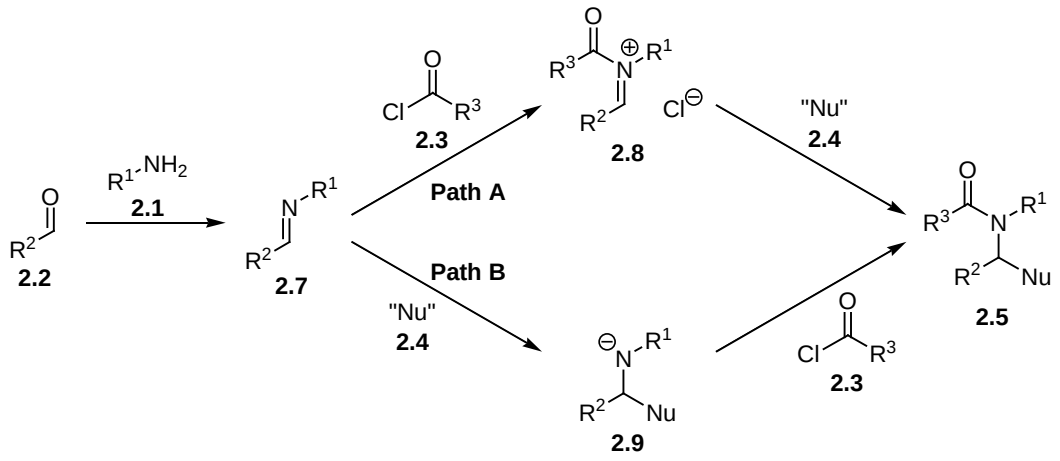
chloride **2.3**, and a nucleophile **2.4** would allow access to functionalized amides **2.5**, which could then undergo cyclization leading to the desired heterocyclic scaffolds.

Scheme 2.1



Operationally, aldehyde **2.2** and amine **2.1** react to form an imine (**2.7**), which can then undergo one of two reactions (Scheme 2.2). In the first pathway (Path A), the imine **2.7** can react with acid chloride **2.3** to form a reactive *N*-acyl iminium ion (**2.8**), which can then be trapped by the nucleophile to give **2.5**. In an alternative pathway (Path B), imine **2.7** and the nucleophile **2.4** react first to give an amine, which can then undergo *N*-acylation to give the desired amide product. This experimental flexibility together with the ready availability of numerous reactants **2.1**–**2.4** allows for the incorporation of high levels of functional and structural diversity into the MCR products, so that a number of different subsequent cyclizations might be performed to generate an array of heterocyclic scaffolds.

Scheme 2.2

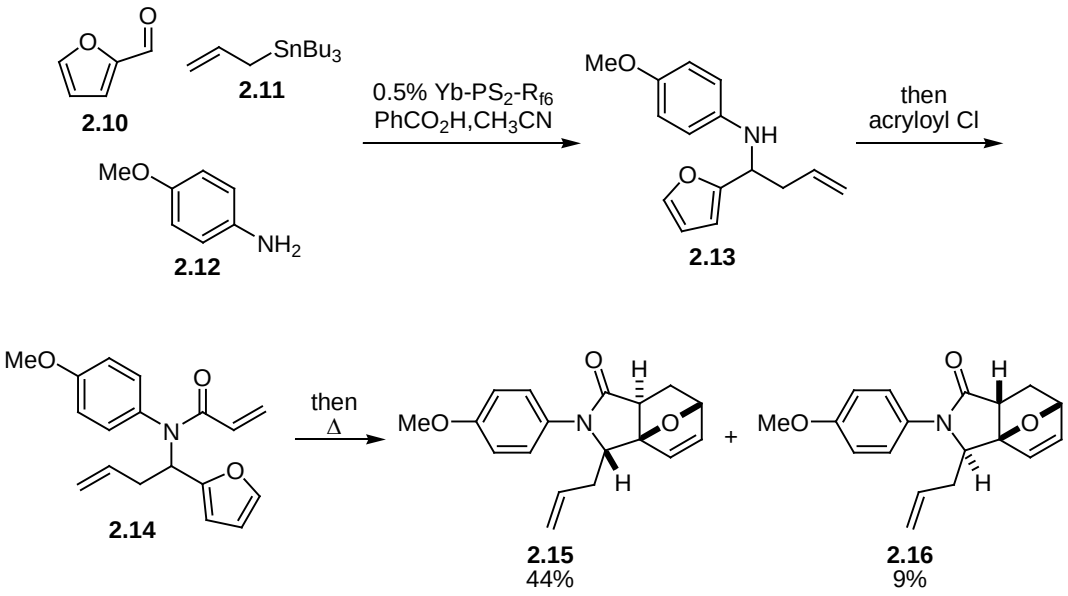


A key feature to this design is the number different functional groups that can be incorporated into the 4CR products allowing for a number of cyclization modes and potential targets to be accessed. Aiding the utility of this 4CR is the fact that all of the four components are readily available with a number of different inherent functionalities, and it was envisioned that by incorporating various olefins, carbonyl groups, and aryl halides into the starting inputs, substrates amenable to ring closing metathesis (RCM), Heck reactions, Diels-Alder cycloadditions, [3+2] dipolar cycloadditions, and Dieckmann cyclizations could be accessed. Both *N*-acyl iminium ions152-161 and imines162 are known to react with a number of different nucleophiles under a variety of reaction conditions, and allyl metals, silyl enol ethers, silyl ketene acetals, silyloxy furans, and other organometallic reagents could all be potential nucleophiles in the 4CR. This allows for high levels of variability in choosing a nucleophile and therefore great variability in the functional groups that are incorporated into the 4CR adduct. Also, when one considers the numerous methods for the enantioselective addition of nucleophiles to C=N double bonds,[162] there is a potential to access amides **2.5** in enatioenriched form.

The initial experiments towards the goal of developing a 4CR and applying it to the synthesis of diverse heterocyclic scaffolds is discussed herein. Because these were the preliminary investigations into this project, much of the focus is on general reactivity and substrate scope, so that an idea could be generated as to what types of inputs could be utilized and how the functional groups contained in these inputs could be exploited in subsequent ring forming reactions.

While in the course of our investigations, Zhao and co-workers reported on a related 4CR.163 Their reaction involved the use of a solid supported Yb catalyst that was used to catalyze the 3CR of an aldehyde, primary amine, and allyl tributylstannane. The resulting amine was then acylated in situ to provide the desired amide product. This reaction is an example of the reaction pathway outlined in path B in Scheme 2.2. In one lone example, it was shown that by incorporating furfural as the aldehyde input products could be generated that could undergo an intramolecular furan Diels-Alder leading to **2.15** and **2.16**. Otherwise, no attempts to further modify the 4CR adducts have been reported.

Scheme 2.3



2.2.1 Investigations into Reactions Involving Allyl Nucleophiles

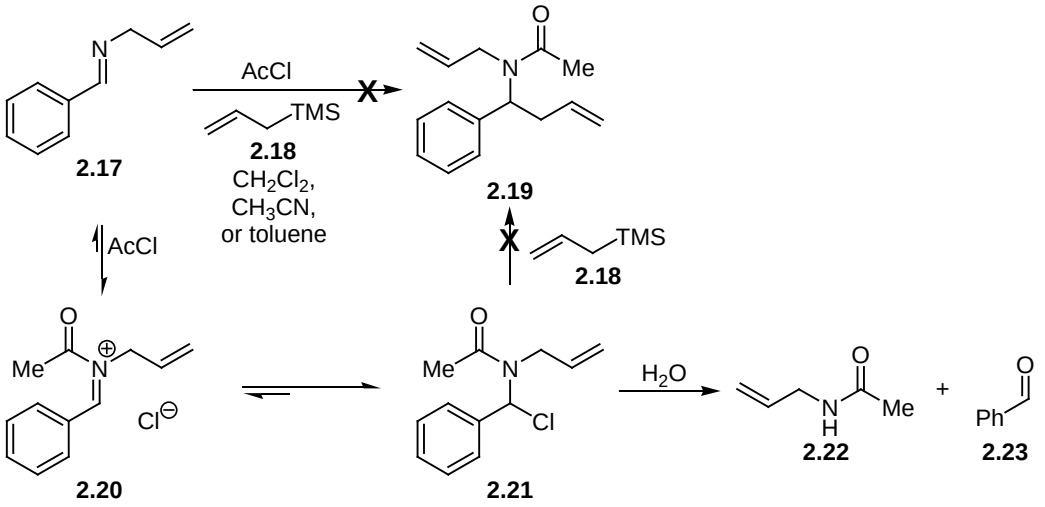
The use of allyl nucleophiles in the 4CR is desirable because the olefin that is incorporated into the products of the 4CR can then be utilized in a number of subsequent ring forming reactions including RCM, intramolecular Heck reactions, and a number of different cycloadditions. There is also ample precedent for the addition of a number of different allyl metal species to imines and *N*-acyl iminium ions,[152-155] making this a good starting point for investigations into the 4CR.

2.2.1.1 Three Component Reactions Designed to Identify Competent Allyl Nucleophiles

Our initial investigations began with a model three component reaction (3CR) consisting of imine **2.17**, acetyl chloride and allyltrimethylsilane (**2.18**). However, the only isolable products from this reaction were amide **2.22** and benzaldehyde (Scheme 2.4). The formation of amide **2.22** suggests that the reaction of imine **2.17** with acetyl chloride takes place to form *N*-acyl iminium **2.20**, which is expected to be in an

equilibrium favoring **2.21**,[164, 165] and that allyltrimethylsilane is unreactive towards both **2.20** and **2.21**. Amide **2.22** and benzaldehyde would then arise from the hydrolysis of **2.20** and **2.21** upon aqueous work up. Attempts to generate a more electrophilic *N*-acyl iminium ion by using benzyl chloroformate as the acylating agent were unsuccessful, as too were attempts to increase the nucleophilicity of allyltrimethylsilane by adding fluoride sources such as CsF or TBAT.

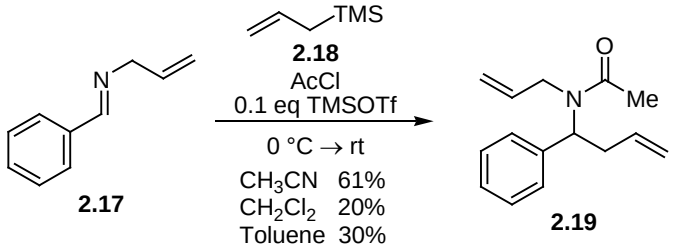
Scheme 2.4



There are numerous reports of Lewis acid mediated additions allyltrimethylsilane to *N*-acyl iminium ions,153, 155 so investigations were undertaken on this front. Yamaguchi has reported on using catalytic triflate salts to promote the addition of allyltrimethylsilane to quinolines and isoquinolines that have been acylated by chloroformate esters,[166] and these studies led us to try AgOTf and TMSOTf in the MCR. It has been postulated that the triflate salts promote the reaction by replacing the chloride counter ion with the less nucleophilic triflate, thus enhancing the electrophilicity of the *N*-acyl iminium.[166] Adding AgOTf or TMSOTf, in either stoichiometric or catalytic amounts, to the model 3CR resulted in formation of the desired product in low yields

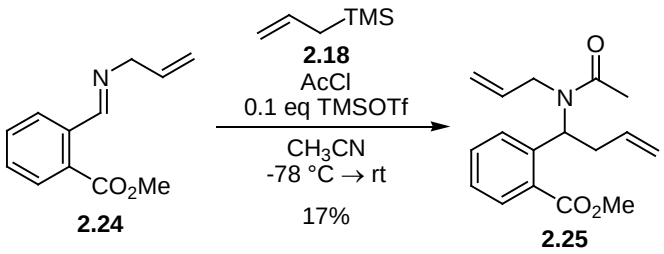
(<30%). Although the yields using AgOTf and TMSOTf were similar, TMSOTf became the Lewis acid of choice due to its lower cost and relative ease of handling. $BF_3 \cdot OEt_2$ was also tried as the Lewis acid, but the yields were inferior to those obtained with TMSOTf. The yields of the reactions were almost identical when stoichiometric or catalytic amounts of Lewis acid were used, and thus catalytic TMSOTf was utilized throughout. Switching to the less polar solvent toluene showed little improvement in yield. The more polar solvent acetonitrile provided the desired amide **2.19** in 61% yield (Scheme 2.5).

Scheme 2.5



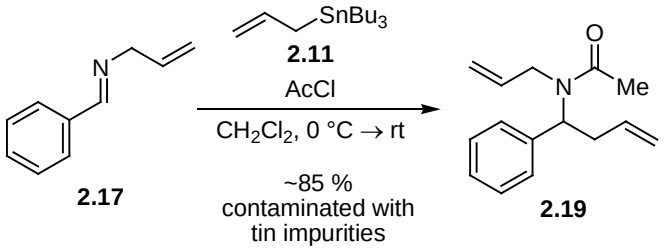
Satisfied that reasonable conditions had been found for the 3CR of imine **2.17** with acetyl chloride and allyltrimethylsilane, investigations were then turned to more functionalized substrates suitable for subsequent cyclization reactions. The reaction of imine **2.24** with acetyl chloride and allyltrimethylsilane would lead to a substrate amenable to cyclizations via RCM and Dieckmann reactions. However, the acylation of imine **2.24** with acetyl chloride in the presence of allyltrimethylsilane and catalytic TMSOTf resulted in only 17% of the desired amide **2.25** being produced (Scheme 2.6). The low yield may be caused in part by the Lewis basic ester in **2.24** or **2.25** that can coordinate with the Lewis acid and shut down the reaction. These unpromising results led to investigations of the use of more nucleophilic allylating reagents.

Scheme 2.6



Since the use of allyltrimethylsilane as the nucleophile proved to be useful in only a handful of cases, investigations were made into using allyl tributylstannane as the nucleophile. Allyltributylstannane is ~10^4 times more nucleophilic than allyltrimethylsilane,[167] and should readily attack the acyl iminium ion in the absence of Lewis acids. When imine **2.17** was treated with allyltributylstannane and acetyl chloride, amide **2.19** was formed in good yield; however, the product was contaminated with tributyl tin impurities (Scheme 2.7).

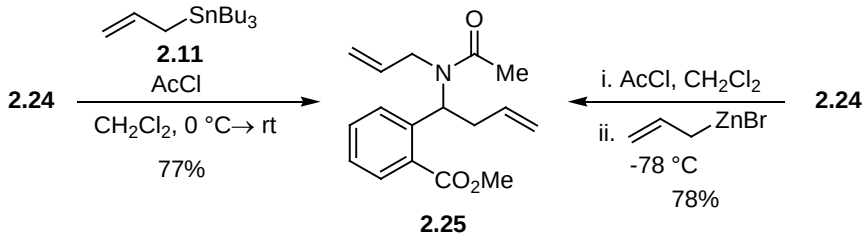
Scheme 2.7



The more functionalized amide **2.25** was attained in 77% yield from imine **2.24**; however, repeated chromatography was needed to remove the tin impurities (Scheme 2.8). In order to avoid the difficulties associated with the purification of the allyl tributylstannane reactions, allyl zinc reagents were investigated. After some optimization, it was found that by reacting imine **2.24** with acetyl chloride for 1 h prior to the addition of allylzinc bromide the desired amide **2.25** could be obtained in 78% yield. Thus, allylzinc bromide was identified as the optimal allyl nucleophile for the 4CR as it

provided the desired levels of reactivity without the need for the tedious purification that was encountered when allyl tributylstannane was used.

Scheme 2.8



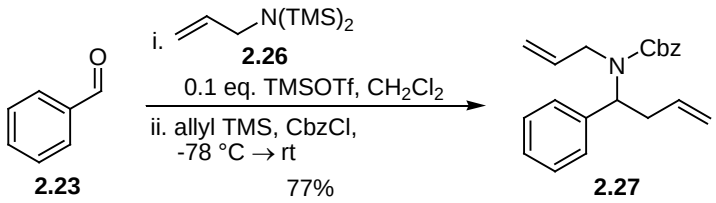
2.2.1.2 The 4CR Involving Allyl Nucleophiles Leading to Sequential 4CR/RCM Sequences

The first step of the MCR is the formation of an imine from an amine and an aldehyde. Although this reaction is normally rapid and facile, the side product of the reaction, water, can react with acid chlorides and hydrolyze *N*-acyl iminium ions. Thus, some method for the removal of water from the reaction medium is necessary. The first attempts at performing the 4CR using molecular sieves to dry the reaction worked, but the yields were low (<35%). Since in most cases the corresponding 3CRs where the imine was isolated proceeded uneventfully, the low yields in these reactions were attributed to the inability of the molecular sieves to effectively remove water from the reaction. While it was later discovered that satisfactory yields could be obtained by utilizing properly activated molecular sieves, the initial investigations focused on utilizing alternative methods for generating imines without generating water.

Morimoto has reported on the TMSOTf catalyzed formation of imines from bis(silyl)amines and aldehydes or ketones.[168] These reactions result in the rapid formation of an imine, but the benign side product TMS_2O is generated instead of water. This is an attractive approach because TMSOTf had already been shown to be a catalyst for the previously discussed 3CRs; and therefore can be used to catalyze both steps of the MCR.

Utilizing this approach the commercially available *N,N*-bis(trimethylsilyl)allylamine (**2.26**) was reacted with benzaldehyde in the presence of TMSOTf. Imine formation was complete in less than 30 min and the resulting imine was reacted with Cbz-Cl and allyltrimethylsilane to produce the desired carbamate **2.27** in 77% yield (Scheme 2.9). Although homoallylic amine **2.27** is not of direct interest, this method provides a facile approach to homoallyic amines, which are commonly used intermediates in alkaloid synthesis.[169]

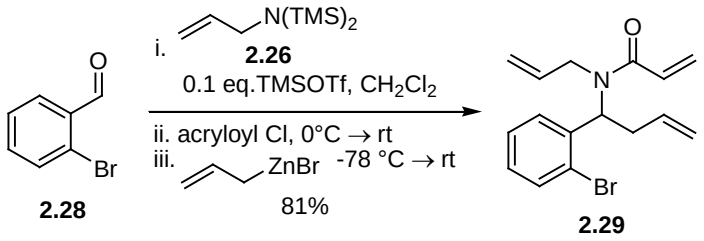
Scheme 2.9



2.2.1.4 Sequential 4CR/RCM/Heck Cyclization

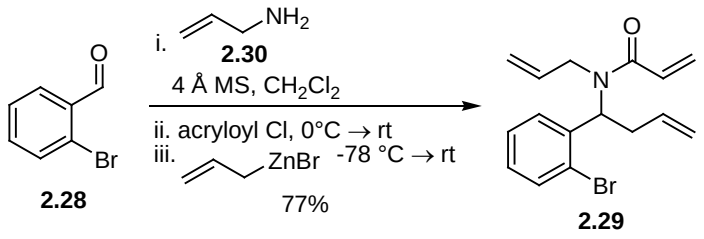
By removing the formation of water from the reaction the goal of a four component reaction was finally realized. However, homoallylic amine **2.27** did not meet the requirement of having functionality amenable to subsequent cyclization reactions incorporated into each of the four components. So again we turned our attention to more functionalized substrates suitable for elaboration into heterocyclic scaffolds. To meet this goal, bis(trimethylsilyl)allylamine **2.26**, 2-bromobenzaldehyde, acryloyl chloride, and allylzinc bromide were incorporated into the 4CR to generate products such as **2.29** that are amenable to both RCM and intramolecular Heck reactions (Scheme 2.10). The 4CR proceeded smoothly using allylzinc bromide as the nucleophile to provide amide **2.29** in 81% yield. When the less reactive allyltrimethylsilane was used as the nucleophile in this reaction, the desired product was produced in only 31% yield.

Scheme 2.10



One of the major drawbacks to using bis(silyl)amines to generate imines is lack of available bis(silyl)amines. In light of this problem, investigations into finding methods for removing water from the reaction were on going. It was discovered that the key to drying the reaction was properly activating the molecular sieves. By heating the molecular sieves to ~250 °C under high-vac for extended periods, the sieves became sufficiently activated, and 4CRs were found to proceed smoothly. Using this method of imine formation, amide **2.29** could be prepared from bromobenzaldehyde **2.28** and allylamine in 77% yield (Scheme 2.11). Thus, two complimentary methods for imine formation were developed that could be used as needed in the optimization of subsequent reactions.

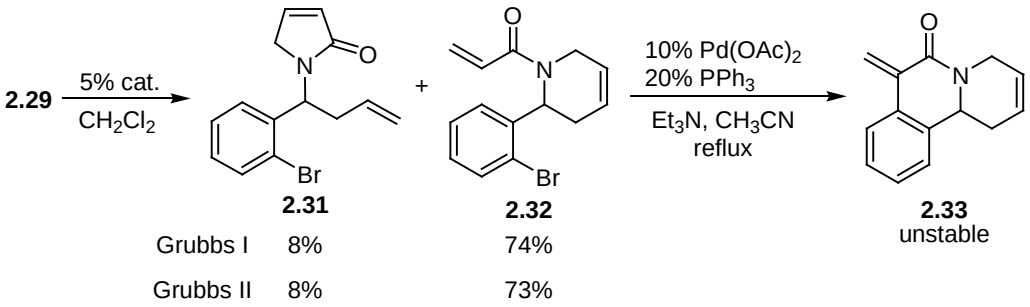
Scheme 2.11

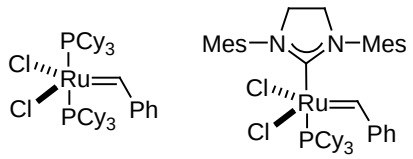


Having developed a method for preparing the highly functionalized amide **2.29**, the next step was to complete the RCM and Heck reaction leading to tricycle **2.33** (Scheme 2.12). Treatment of **2.29** with Grubbs I or Grubbs II catalyst in CH_2Cl_2 at room temperature (rt) or reflux resulted in the formation of piperidine **2.31**, along with

appreciable amounts of lactam **2.32**. In order to investigate the nature of this product distribution, **2.31** and **2.32** were independently treated with Grubbs II in refluxing CH_2Cl_2 under an atmosphere of ethylene, and no interconversion between the two products was observed, suggesting that the two products do not interconvert. Crotonoyl chloride was incorporated into the 4CR in hopes that the added substitution on the acrylamide double bond might inhibit the formation of lactam **2.32**. However, this additional substitution did not improve the results, and a negligible increase in the product ratio was observed. The Heck cyclization of **2.32** appeared to proceed smoothly using 10% $Pd(OAc)_2$ and 20% PPh_3 with Et_3N in CH_3CN, however, the product **2.33** was not stable to isolation, and over time turned into an unidentified insoluble material.

Scheme 2.12



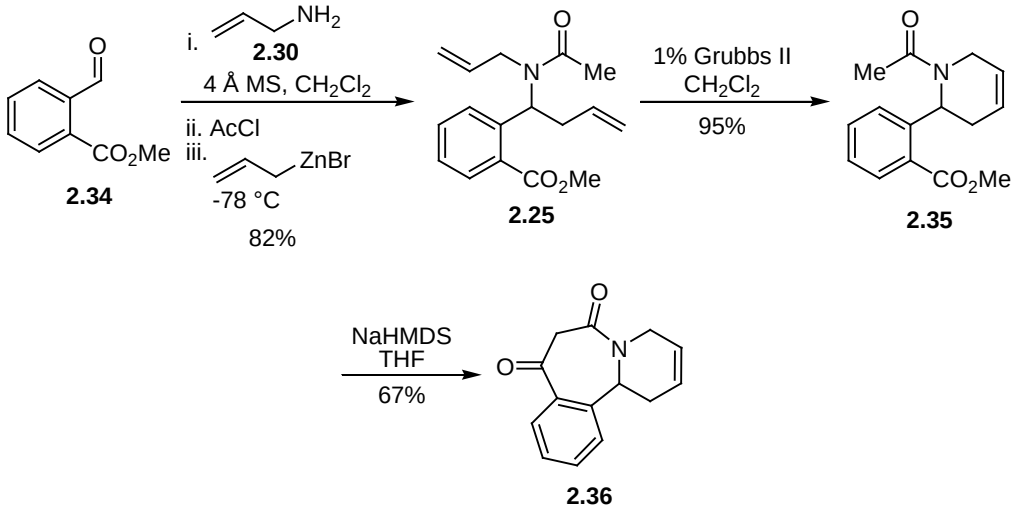


Part 2.2.1.5 Sequential 4CR/RCM/Dieckmann

Having found reaction conditions for the successful execution of the 4CR reactions, attention was then turned to the one pot synthesis of **2.25** (Scheme 2.13). Methyl 2-formylbenzoate (**2.34**) was condensed with allylamine and the resultant imine

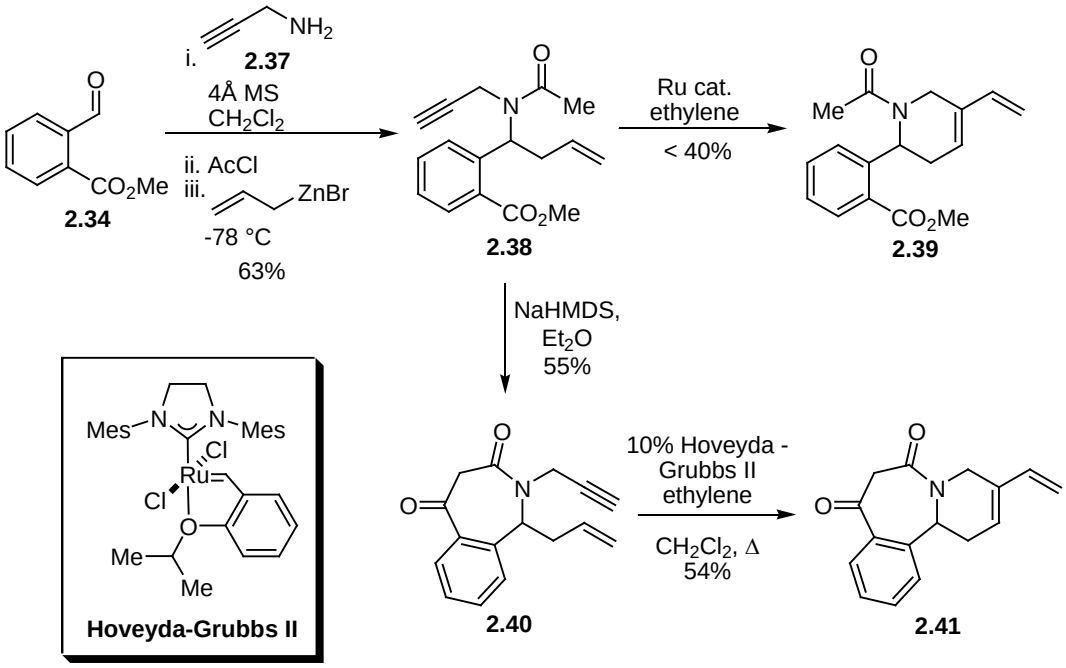
was sequentially treated with acetyl chloride and allylzinc bromide to provide **2.25** in 82% yield. Reaction of **2.25** with the Grubbs II catalyst provided **2.35**, which underwent a Dieckmann cyclization to give benzazepine **2.36** in 70% yield over the two steps. It is worthy to note that in the synthesis of **2.36** a high level of functionality has been maintained in the product and that **2.36** possesses three sites for potential elaboration: the olefin, ketone, and amide.

Scheme 2.13



Substrates amenable to enyne RCM were next synthesized by incorporating propargyl amine into the 4CR. To this end, enyne **2.38** was synthesized in 63% yield following the standard procedure (Scheme 2.14). During course of experimentation, it was found that consistently higher yields (76% vs. 63%) could be obtained if the intermediary imine was isolated prior to acylation and allylation. The reason for this discrepancy in yield is not known, and this phenomenon was not observed in the synthesis of **2.25**. Enyne **2.38** proved to be a poor substrate for the enyne RCM, and poor yields were obtained under all conditions tried.

Scheme 2.14

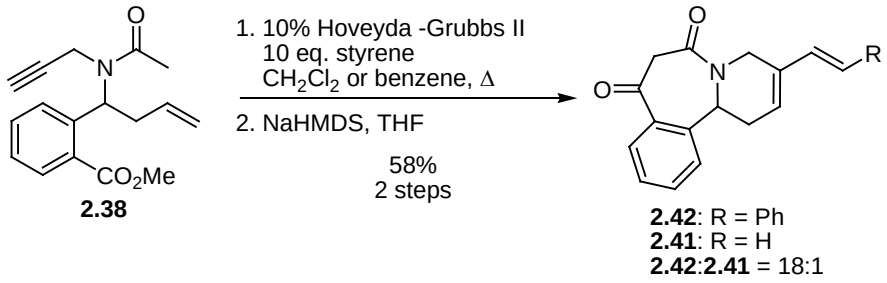


One possibility for improving the enyne RCM was to perform the Dieckmann cyclization first in hopes that constraining the alkene and alkyne would facilitate the RCM (Scheme 2.14). Of the conditions tried, the treatment of **2.38** with NaHMDS in ether gave the best results, with the desired Dieckmann product **2.40** being isolated in 55% yield. Lower yields were obtained when THF or DMF were used as solvent, and using KHMDS as base did not generate any product. Treatment of **2.38** with NaOMe in methanol using conventional or microwave heating also did not provide **2.40**, and **2.38** could be recovered in good yields. Despite this poor yield for the Dieckmann cyclization, enough material could be obtained to carry out studies on the enyne RCM. The bicyclic enyne **2.40** underwent the desired enyne RCM in the presence of the Hoveyda-Grubbs II catalyst[170] and ethylene to generate the tricyclic **2.41** in moderate yield. Upon concentrating **2.41** after chromatography, an insoluble material was produced, and one of the potential reasons for the moderate yield may be instability of **2.41**.

If the low yields for the above enyne RCM are indeed due to product instability, it may be possible to circumvent this problem by performing a tandem enyne RCM/cross metathesis (RCM/CM). By including a cross metathesis partner in the reaction, a fifth component is added to the reaction sequence, adding an additional site for the incorporation of functionality.

Initial investigations into a tandem enyne RCM/CM were performed with methyl acrylate as the CM partner. Unfortunately, these reactions were plagued by low mass recovery and incomplete conversion to the cross metathesis product, regardless of the catalyst used. When styrene was used as the CM partner, the yields were greatly improved, but the cross metathesis still did not go to completion, and enyne RCM product **2.39** was still isolated in appreciable amounts. During the course of these investigations it was discovered that operationally it was best to purify the metathesis product via filtration through a plug of silica and immediately subject it to the Dieckmann cyclization. After some optimization, it was found that by treating **2.38** with 10 eq. of styrene and 10% of the Hoveyda-Grubbs II catalyst in refluxing CH_2Cl_2 or benzene at a concentration of 0.03 M, followed immediately by the Dieckmann cyclization, **2.42** and **2.41** was obtained as an inseparable mixture (18:1) in a 58% yield for the two steps (Scheme 2.15). Increasing the concentration did not increase the ratio of products, but did result in decreased yields. Using a larger excess of styrene also did not improve the ratio of products. Heating the reaction to 100 °C using microwave heating resulted in **2.42** and **2.41** being formed in a ~1:1 ratio. Despite efforts to drive the reaction CM to completion, no improvements on the 18:1 ratio could be made.

Scheme 2.15

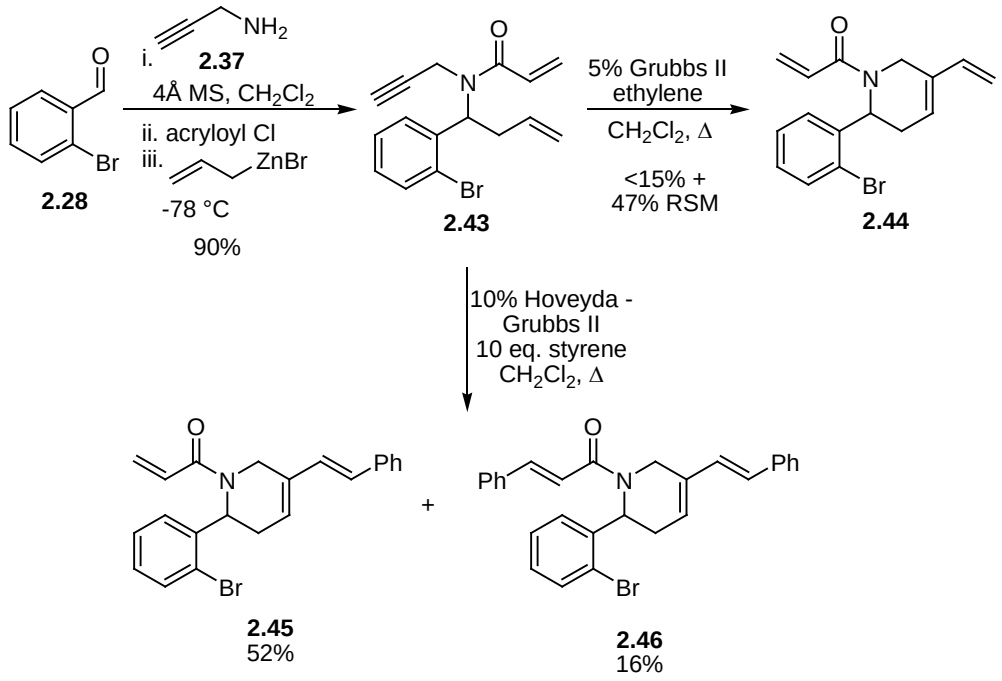


Although the tandem enyne RCM/CM had been optimized to a satisfactory level, the use of CM partners other than styrene that contain more desirable functionality were investigated. Allyltrimethylsilane, methyl vinyl ketone, and allyl alcohol were examined as CM partners; however, none of these CM partners provided acceptable results. These substrates suffered from poor conversions to the CM product, and in all cases **2.33** could be isolated as the major product. No effort was made to optimize these preliminary experiments, and given that these cross metathesis partners have been shown to work in related reactions[171] it is reasonable to expect that with some additional optimization these results can be improved upon.

Enyne **2.43** was synthesized following standard procedures in order to determine the feasibility of performing a selective RCM or enyne RCM (Scheme 2.16). If a selective enyne RCM could be achieved, the aryl bromide and the additional olefin could undergo a Heck cyclization following the enyne RCM. However, this goal could not be realized as attempts to perform a selective enyne RCM were met with limited success. When the Grubbs II catalyst was used in refluxing CH_2Cl_2 under an ethylene atmosphere, starting material was never consumed, and the desired product **2.44** was formed in low yields. Attempts to perform a standard diene RCM on **2.43** with the Grubbs I or Grubbs II catalyst in the absence of ethylene gas were also unsuccessful. When styrene was

added to the reaction as a CM partner the desired **2.45** was produced in 52% yield along with 16% of **2.46**, which is the product of a double CM reaction.

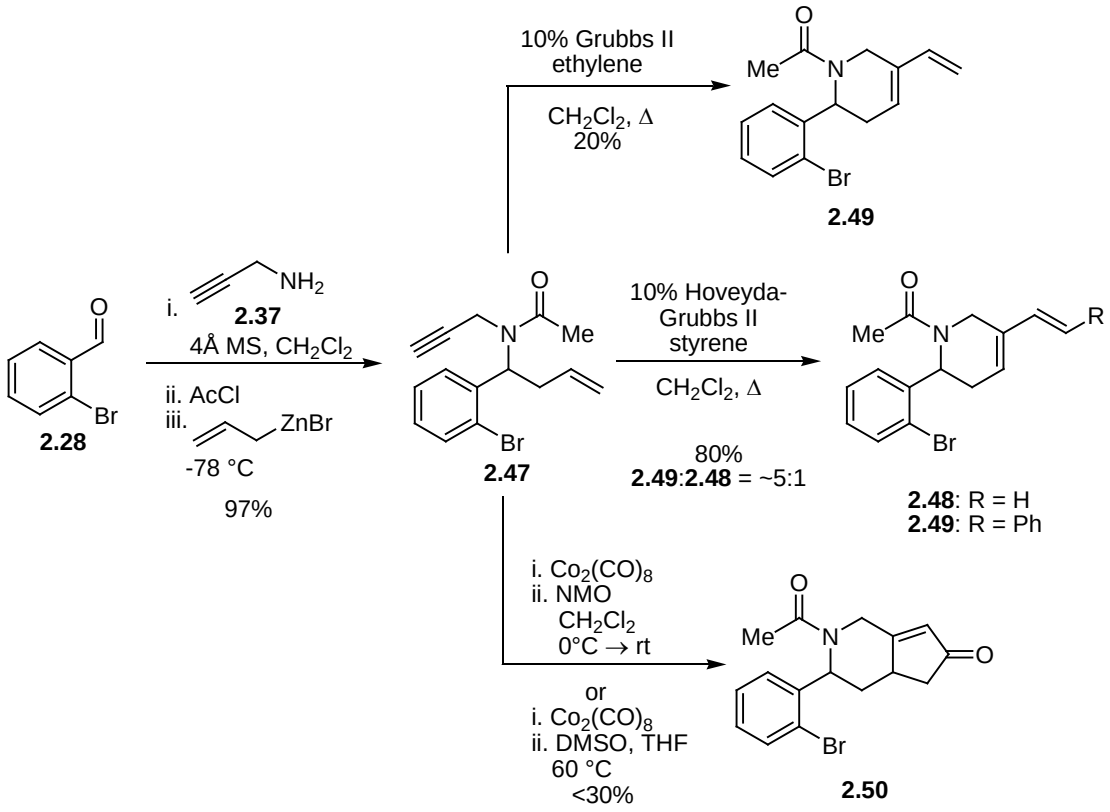
Scheme 2.16



Since conditions for a successful enyne RCM on **2.43** could not readily be found, it was decided to continue investigations using the simplified substrate **2.47**. Enyne **2.47** was synthesized in excellent yield using standard procedures (Scheme 2.17). However, changing to the acetamide did not result in improved yields for the enyne RCM and the desired product **2.48** could only be isolated in 20% yield after treatment with the Grubbs II catalyst in refluxing methylene chloride under an ethylene atmosphere. Using the Hoveyda-Grubbs II catalyst under identical conditions led to no improvement. Greater levels of success were achieved when styrene was added, and an enyne RCM/CM sequence could be achieved. However, as seen previously with **2.38**, the cross metathesis reaction did not go to completion and **2.48** could be isolated along with the desired **2.49**. Enyne **2.47** is also a suitable substrate for a Pauson-Khand reaction (PKR); however,

preliminary attempts to carry out a PKR on **2.47** were met with limited success. When either NMO or DMSO was utilized as the promoter, the desired product **2.50** was only formed in low yields. Optimization studies beyond this point were not undertaken, and it is still unknown whether or not the PKR can be successfully utilized to manipulate 4CR adducts into cyclic scaffolds.

Scheme 2.17

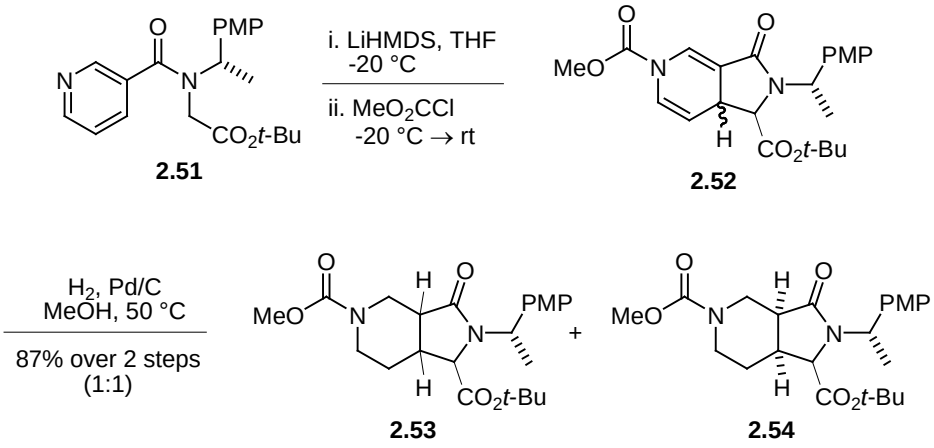


Part 2.2.1.6 Attempted Sequential 4CR/Dearomatizing Intramolecular Enolate Alkylation.

In order to further expand the scope of the type of heterocyclic structures that can be accessed using the sequential 4CR/cyclization strategy, we began to look for additional reactions that could be performed on the 4CR adducts. One potentially interesting possibility was found in a recent report of a dearomatizing cyclization of

enolates derived from *N*-nicotinoyl glycine derivatives by Clayden and co-workers (Scheme 2.18).[172] When *N*-nicotinoyl glycine compounds such as **2.51** were treated with base and methyl chloroformate, the dihydropyridine **2.52** was formed in good yields. The authors proposed that the reaction proceeds first through deprotonation of the ester, which is followed by selective acylation of the pyridine nitrogen, and subsequent cyclization of the enolate onto the *N*-acyl pyridinium salt provides the desired **2.52**. To avoid any problems associated with the oxidation **2.52**, it was immediately subjected to a hydrogenolysis to provide a mixture of the diastereomers **2.53** and **2.54**.

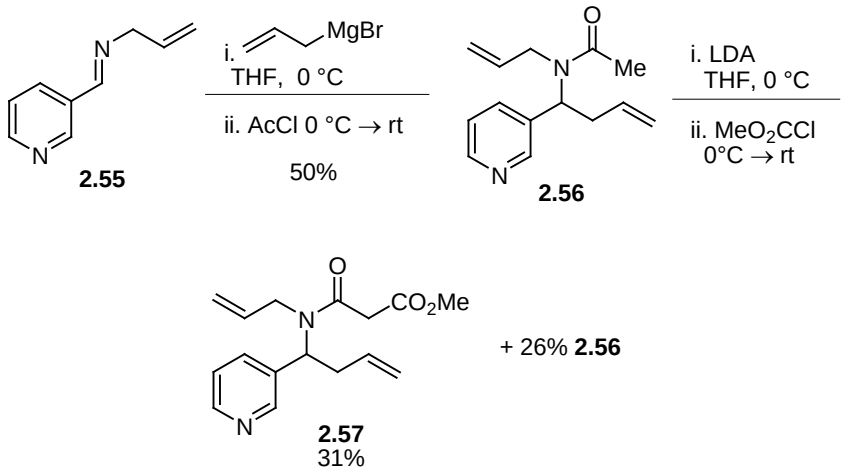
Scheme 2.18



Our first explorations into utilizing this dearomatizing cyclization were focused on the synthesis and subsequent cyclization of **2.56**. Although there was no precedent for use of compounds similar to **2.56** in this chemistry, the ease in which **2.56** could be synthesized led us to try **2.56** in the reaction. Imine **2.55**, readily available from the reaction of allylamine and pyridine-3-carboxaldehyde, was sequentially treated with allyl Grignard and acetyl chloride to give **2.56** in an unoptimized 50% yield (Scheme 2.19). It is interesting to note that this reaction must be sequenced in this order because if the acylation is performed first, competitive acylation of the pyridine nitrogen atom becomes

a problem. When **2.56** was treated with base followed by the addition of methyl chloroformate, the only isolable product **2.57** was the result of the acylation of the resulting amide enolate. This is not completely unexpected, as the enolate of **2.56** is significantly less hindered and more reactive than the substituted ester enolate utilized by Clayden.

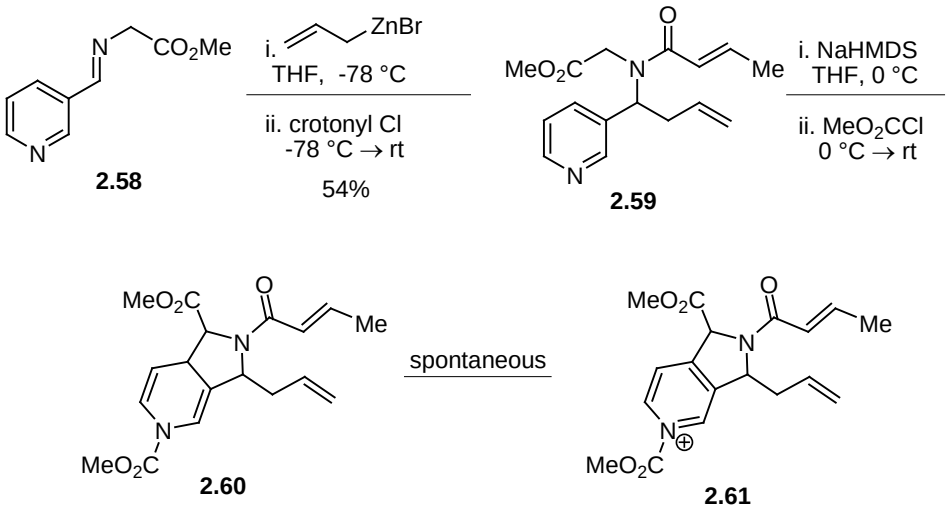
Scheme 2.19



Undeterred by these results, focus was turned to synthesizing a substrate more similar to the *N*-nicotinoyl glycine derivative **2.51**. Substrates of this nature can readily be obtained from imine **2.58** (Scheme 2.20). Treatment of **2.58** with allylzinc bromide followed by crotonoyl chloride provided the aimde **2.59** in 54% yield. In this example, the use of allylzinc bromide is necessary as the analogous reaction with allyl Grignard was not clean due to competitive nucleophilic attack on the ester. Moreover, crotonoyl chloride gave substantially higher yields compared to acryloyl chloride, and the extra methyl group could be removed during a subsequent RCM. When **2.59** was treated with NaHMDS and methyl chloroformate in THF at 0 °C, the reaction quickly consumed starting material and went to one major less polar spot by TLC, presumably the desired

product **2.60**. Attempts to isolate **2.60** were unsuccessful and were presumably this is due to the ability of **2.60** to readily oxidize to pyridinium salt **2.61**. Investigations into methods for effecting the oxidation of **2.62** along with concurrent removal of the methyl carbamate to regenerate the pyridine ring are needed to make this a viable sequence.

Scheme 2.20

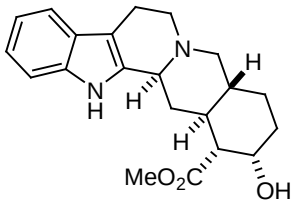


2.2.2 Sequential 4CR/Diels-Alder Cycloadditions

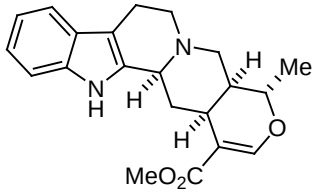
The intramolecular Diels-Alder reaction has been previously exploited in the Martin group as a method for the synthesis of members of the yohimbine and heteroyohimbine family of alkaloids.[173-178] It has also been shown by Yamaguchi that isoquinolines and carbolines can react with acryloyl chloride and pentadienyltributyltin to generate products that undergo a spontaneous [4+2] cycloaddition reaction at room temperature. This reaction was used in the syntheses of berbane and yohimbane alkaloids.[179] Thus it was envisioned that by incorporating a diene into the 4CR, substrates amenable to intramolecular Diels-Alder reactions could be generated leading to scaffolds

with core structures similar to that found in the yohimbine[180] and berbane alkaloids (Figure 2.1).[181]

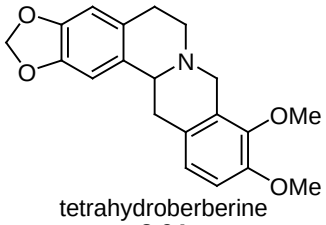
Figure 2.1



yohimbine
2.62



tetrahydroalstonine
2.63



tetrahydroberberine
2.64

It was envisioned that by using pentadienylsilane **2.67** as the nucleophile a diene would be generated in the 4CR product that could then undergo a [4+2] cycloaddition with a pendent dienophile (Scheme 2.21). To this end, when the imine derived from bromobenzaldehyde **2.28** and bis(trimethylsilyl)allylamine **2.26** was treated in a one pot fashion with acryloyl chloride and pentadienylsilane **2.67** in the presence of 10 mol % TMSOTf, and the intermediate adduct underwent a Diels-Alder cyclization to generate the hydroisoquiniline **2.69** in good yield as a single diastereomer. The scope of this reaction was expanded to include differently functionalized benzaldehydes, with 4-bromobenzaldehyde (**2.65**) and 3,4-dimethoxybenzaldehyde (**2.66**) reacting smoothly to give the desired cycloadducts **2.70** and **2.71** in good yields and diastereoselectivities. In order to determine the relative stereochemistry of the Diels-Alder adducts, **2.71** was first reduced with $LiAlH_4$, giving **2.72** as a single detectable diastereomer in 76% yield. Attempts to obtain X-ray quality crystals from the HCl salt of **2.72** failed, but the

methiodide salt **2.73** gave x-ray quality crystals upon crystallization from benzene (Figure 2.2).

Scheme 2.21

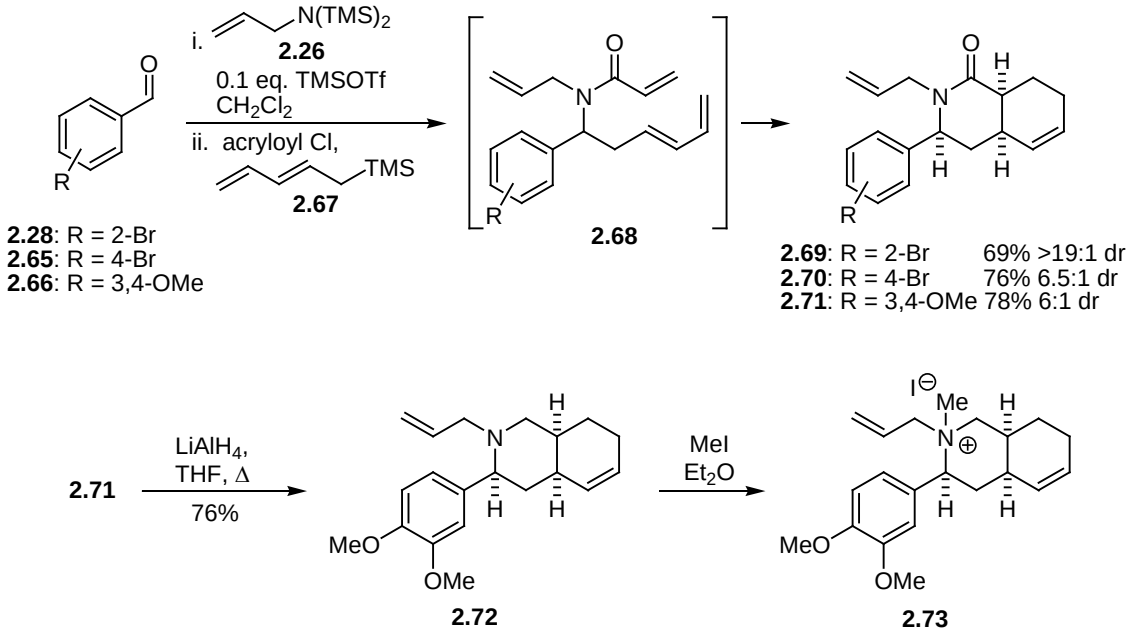
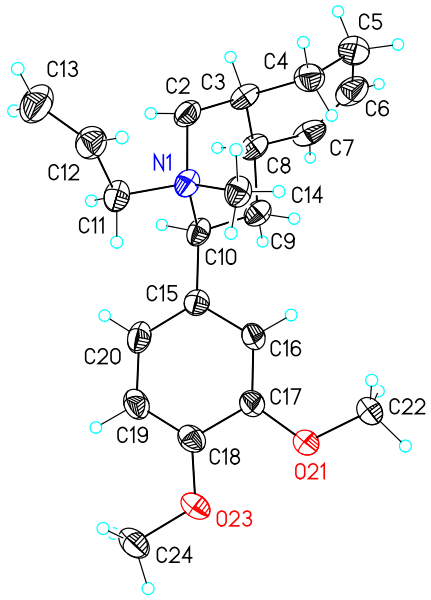


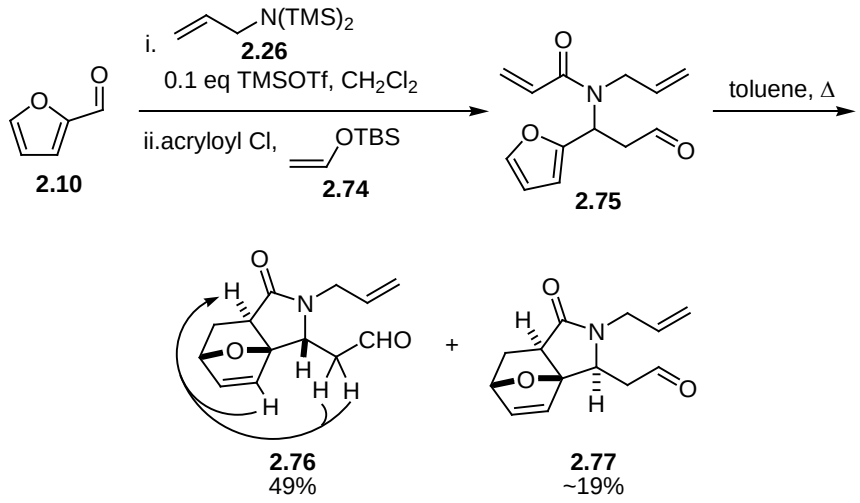
Figure 2.2: ORTEP drawing of 2.73



Another alternative for incorporating a diene into the 4CR adduct is by utilizing furfural as the aldehyde component, thus generating products that are set up to undergo intramolecular furan Diels-Alder reactions (IMDAF)[182] to generate epoxy-isoindolones. To this end, furfural was allowed to react with bis(trimethylsilyl)allylamine **2.26**, and the resulting imine was treated with acryloyl chloride and the silyl enol ether **2.74** to generate **2.75** in only 27% yield. It was apparent by TLC that the product was not stable on silica gel, and the Diels-Alder reaction appeared to proceed slowly at room temperature. In order to avoid these complications, the reaction was telescoped, and the Diels-Alder reaction was run without purification of **2.75**. Thus, when the 4CR was complete, the reaction mixture was subjected to an aqueous work-up, concentrated, and then heated under reflux in toluene to effect cyclization (Scheme 2.21). By avoiding the purification of **2.75**, the major diastereomer **2.76** could be isolated in 49% yield, along with ~19% of

an unclean diastereomer believed to be **2.77**. The major product **2.76** has been tentatively assigned by 2D NMR to be the product resulting from the *exo* mode of cyclization to generate the *trans* ring fusion, and the pertinent NOE correlations are shown in Scheme 2.22. Previous literature examples show that for intramolecular furan Diels-Alder reactions with an amide tether that the *exo* mode is the preferred mode of cyclization.[182]

Scheme 2.22



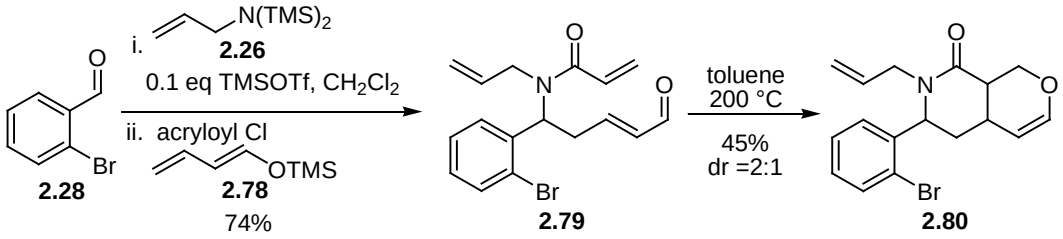
2.2.3 Sequential 4CR/Hetero Diels-Alder Reactions

Previous work in the Martin group has shown that 1-silyloxybutadienes are reactive nucleophiles in the vinylogous Mannich reaction.151 The α,β-unsaturated aldehydes generated from these reactions can then react in a subsequent hetero Diels-Alder (HDA) reaction, and this reaction sequence was used in the synthesis of several natural products.[183-189] Based on this precedent, the use of 1-trimethylsilyloxybutadiene as the nucleophile in the 4CR and the subsequent HDA reaction were investigated.

Trimethylsilyloxybutadiene (**2.78**) proved to be a good nucleophile in the 4CR, and **2.79** was generated in good yield from bromobenzaldehyde **2.28** (Scheme 2.23). The α,β-unsaturated aldehyde **2.79** is nicely disposed to undergo a hetero Diels-Alder

reaction, and after some experimentation, the desired product **2.80** was obtained upon heating **2.79** to 200 °C in toluene in a sealed tube. Refluxing **2.79** in tetrachloroethane or mesitylene did not result in the formation of any desired product. The overall yield and diastereoselectivity in this HDA reaction are low, and the low yield has been attributed to the stability of **2.79**, both to the reaction conditions and in general. Upon standing **2.79** will turn into an insoluble polymer-like material and under the reaction conditions a significant amount of insoluble material was formed. It was thought that by limiting the amount of handling of **2.79** the yields for the reaction could be increased, but when crude reaction mixture containing **2.79** was subjected immediately to the Diels-Alder conditions, a similar yield over the two steps was obtained. The use of microwave heating in this reaction also did not result in an increase in yield.

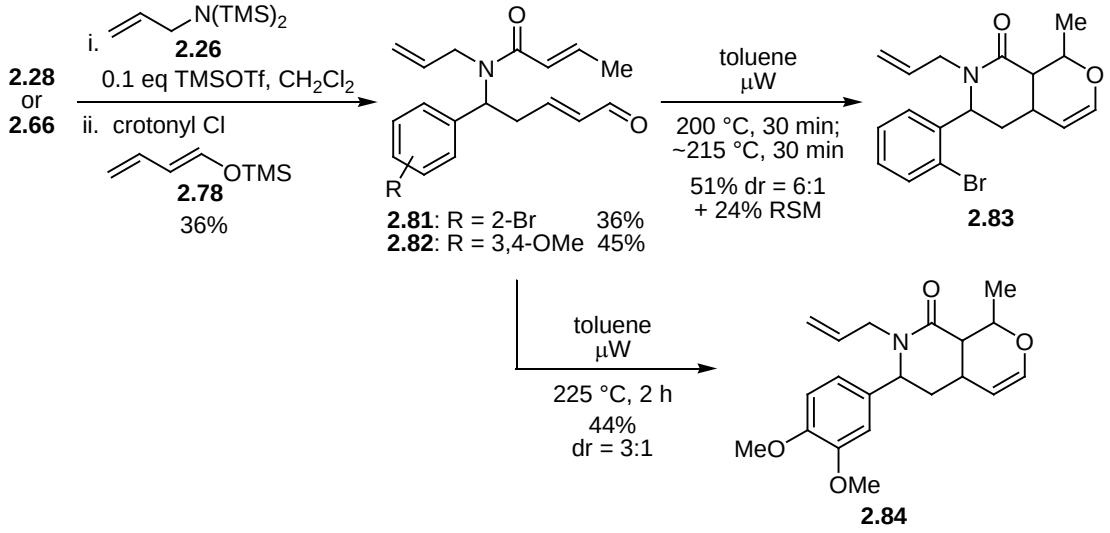
Scheme 2.23



In the previously mentioned syntheses from the Martin group that employed a similar HDA reaction the dienophile was derived from crotonoyl chloride.[183-190] Accordingly, it was thought that a way to improve the 4CR/HDA sequence would may be to incorporate crotonoyl chloride into the 4CR in place of acryloyl chloride. In practice, the use of crotonoyl chloride in the 4CR reaction provided the desired product **2.81** in only 36% yield (Scheme 2.24). The reason for the reduced yield as compared to acryloyl chloride is not known. When **2.81** was heated at 200 °C in a microwave reactor, very little reaction took place. Upon heating this reaction for 30 minutes at 215 °C, the hottest temperature attainable for this reaction in the microwave reactor, the desired product **2.82**

could be isolated in 51% yeild, along with 24% recovered starting material. This reaction was much cleaner and the diastereoselectivity was improved compared to **2.80**. Heating the reaction for longer times should further increase the yield, but this study has not been undertaken. The electron rich aldehyde **2.66** was also compatible with this reaction sequence, but again the yields and diastereoselectivities were moderate at best.

Scheme 2.24



2.2.4 Sequential 4CR/[3+2] Dipolar Cycloadditions

As demonstrated in the above synthesis of **2.77**, the silyl enol ether **2.74** is a competent nucleophile in the 4CR. It was envisioned that the aldehyde functionality formed from the reaction of **2.74** could be utilized in the generation of 1,3-dipoles that could undergo [3+2] dipolar cycloadditions with appropriately disposed dipolarophiles. To this end, aldehyde **2.86** was synthesized from bromobenzaldehyde **2.28**, bis(trimethylsilyl)allylamine **2.26**, acetyl chloride, and **2.74** (Scheme 2.25). Condensation of **2.86** with sarcosine in refluxing toluene resulted in the formation of an intermediary azomethine ylide which cyclized onto the pendent alkene to give **2.89** in 65% yield. Similarly, aldehyde **2.86** could be condensed with *N*-methylhydroxylamine

to generate a nitrone which underwent cyclization to give **2.91** in 87% yield. The relative stereochemistry of **2.89** was established by correlating its NMR spectra with those of the corresponding aryl iodide **2.90**, which was prepared in similar yields using an identical sequence and whose structure was established by X-ray analysis of its hydrochloride salt (Figure 2.3). The relative stereochemistry of **2.91** was determined from the X-ray analysis of its hydrochloride salt (Figure 2.3). Both **2.89** and **2.91** are functionalized to undergo an intramolecular enolate arylation, but studies carried out in the Martin group by Dr. Chris Dockendorff proved this to be a problematic reaction.[191] A number of conditions were screened, and in the best cases the desired product was formed along with substantial quantities of the inseparable reduced starting material.

Scheme 2.25

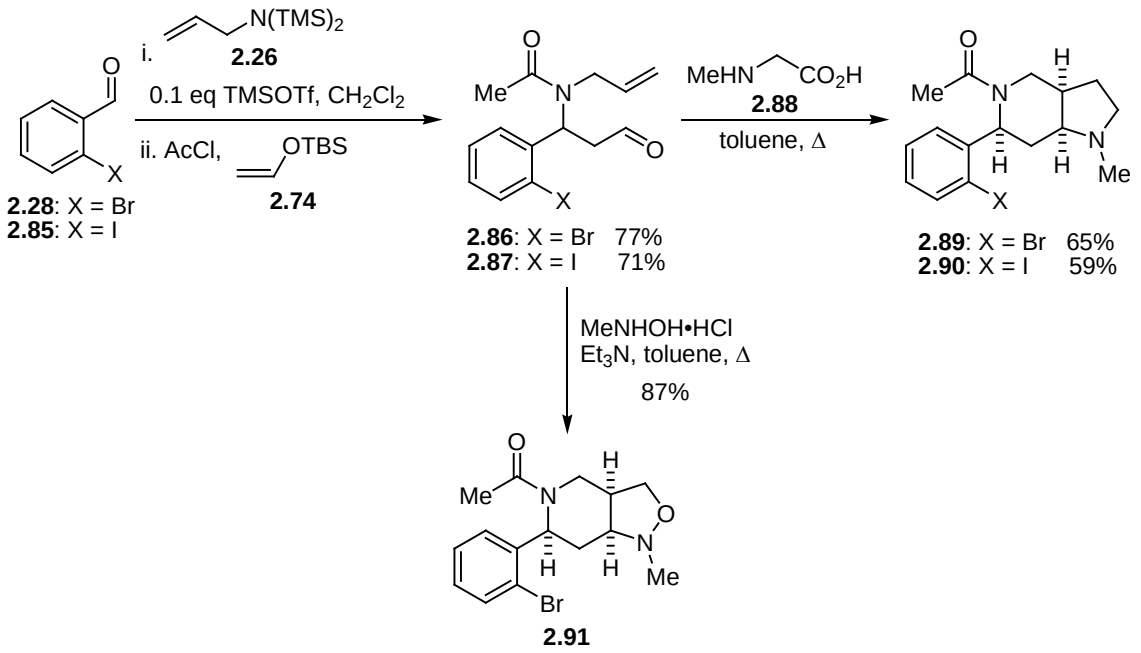


Figure 2.3: ORTEP drawing of 2.90·HCl.

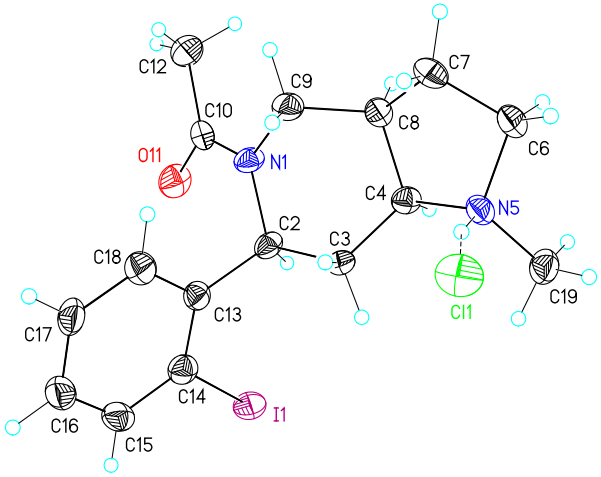
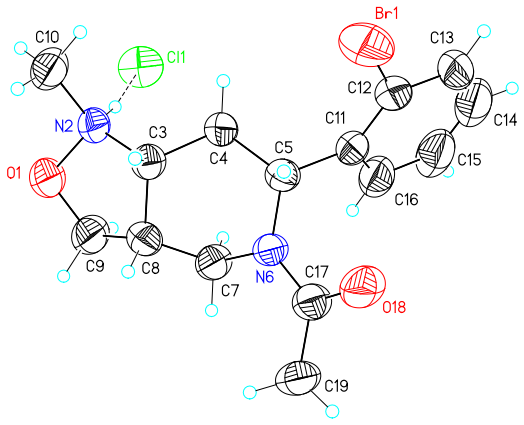


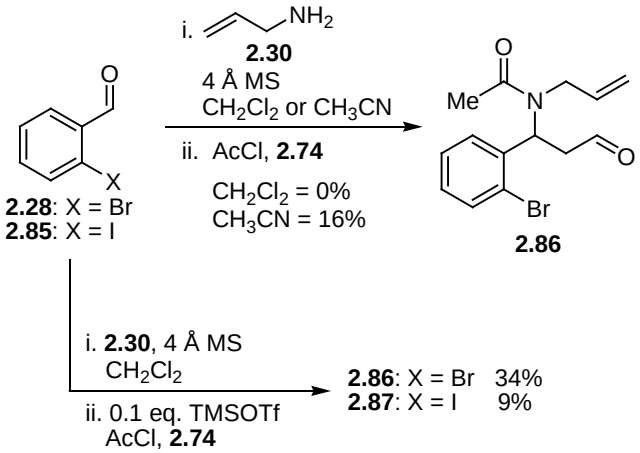
Figure 2.4: ORTEP drawing of 2.91·HCl.



Although **2.86** and **2.87** could be synthesized in good yields using the bis(silyl)amine method, it is desirable to be able to access these compounds from allylamine. To this end, the 4CR of aldehyde **2.28**, allylamine, acetyl chloride, and silyl enol ether **2.74** was investigated under a number of different reaction conditions (Scheme 2.26). When the 4CR was run in CH_2Cl_2, none of the desired **2.86** was observed. When

the solvent was changed to CH_3CN, **2.86** was isolated in 16% yield. These yields are drastically lower than the yields obtained using the bis(silyl)amine method, and it was thought that the main reason the bis(silyl)amine method gave higher yields was the presence of TMSOTf. Thus, benzaldehydes **2.28** and **2.85** were condensed with allylamine, and the intermediary imine was treated with acetyl chloride, **2.74** and a catalytic amount of TMSOTf to give **2.86** and **2.87** in only 34% and 9% yields, respectively. Although the exact reason for the low yields in these reactions is not known, one possibility is that the molecular sieves and TMSOT react with each other, effectively removing the Lewis acid from the reaction. Support for this hypothesis comes from the fact that good yields of **2.86** can be obtained if the molecular sieves are removed by filtration prior to the addition of the second set of reactants. Thus, by simply modifying the procedure to include a filtration step, **2.86** was synthesized in good yields from the corresponding aldehydes and allylamine.

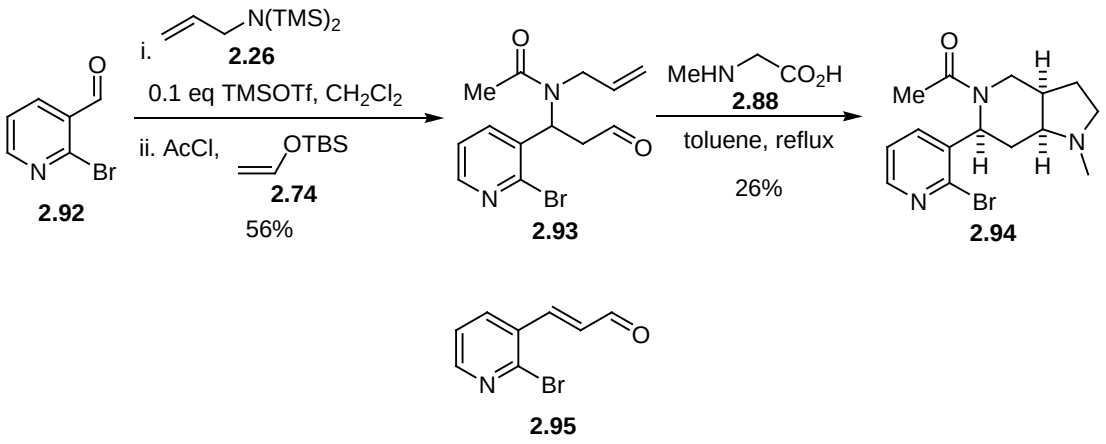
Scheme 2.26



In the interest of accessing additional heterocyclic scaffolds the bromopyridine **2.92**[192] was utilized in a similar reaction sequence (Scheme 2.27). In the event, bromopyridine **2.92** was treated with bis(trimethylsilyl)allylamine **2.26** in the presence of

a catalytic amount of TMSOTf, and the resulting imine was then reacted with acetyl chloride and **2.74** to provide **2.93** in 56% yield. Aldehyde **2.93** was reacted with sarcosine in refluxing toluene to provide **2.94** in only 26% yield. One reason for the low yield is that **2.93** readily undergoes elimination of the amide under the reaction conditions, and aldehyde **2.95** is a major side product of this reaction. This side reaction was also observed in the synthesis of **2.89**, although it did not occur to a significant extent.

Scheme 2.27

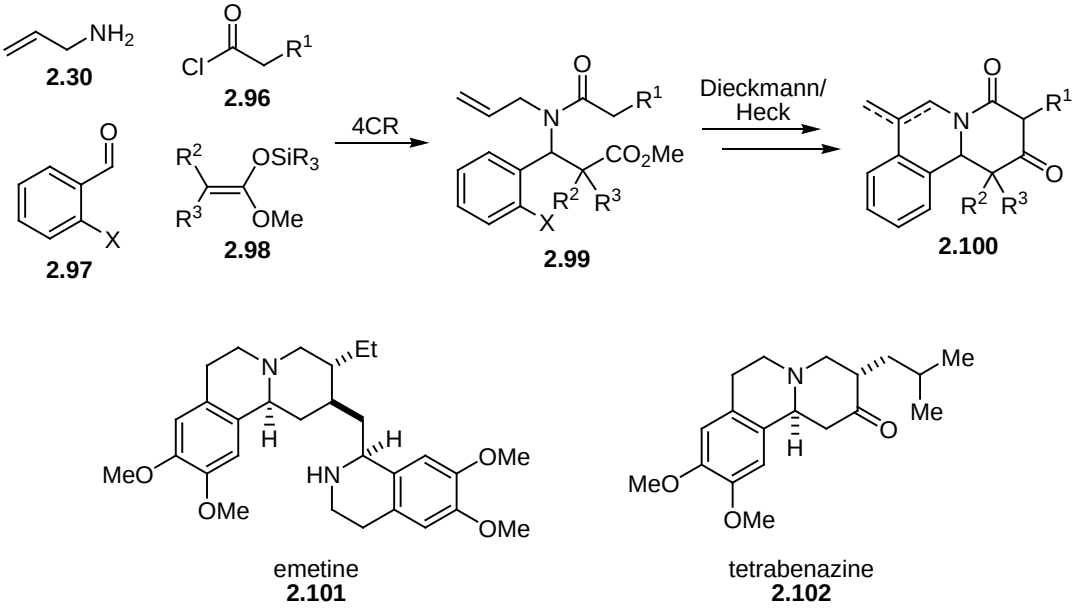


2.2.5 Sequential 4CR/Heck/Dieckmann Cyclization and Reactions Involving Silyl Ketene Acetal Nucleophiles

Silyl ketene acetals are highly reactive π-nucleophiles that have been shown to react with *N*-acyl iminium ions under a number of different reaction conditions[153-155] and therefore should be viable as a component in the 4CR. Silyl ketene acetals react with *N*-acyl iminium ions to generate products that contain ester functionalities, and it was envisioned that this functionality could be readily exploited in post condensation reactions leading to cyclic structures. One reaction that particularly attracted our interests was the Dieckmann cyclization. By carefully selecting an appropriate acid chloride, it was envisioned that products could be accessed where the amide and ester in **2.99** could

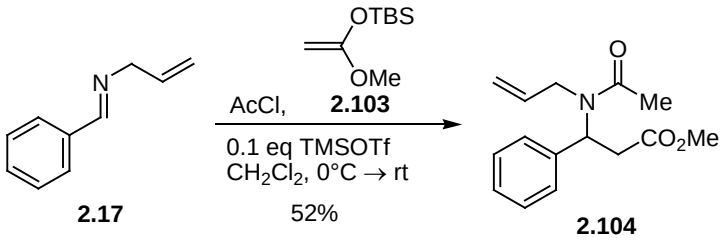
be reacted with one another (Scheme 2.28). If the functional groups contained in the amine and aldehyde components were appropriately paired, a second cyclization could then be induced leading to tricyclic scaffolds. This short sequence could provide access to functionalized benzo[a]quinolizine ring systems, which are found in a the berberine[181] and emetine[193] classes of natural products, as well as in biologically active compounds such as tetrabenazine.[194]

Scheme 2.28



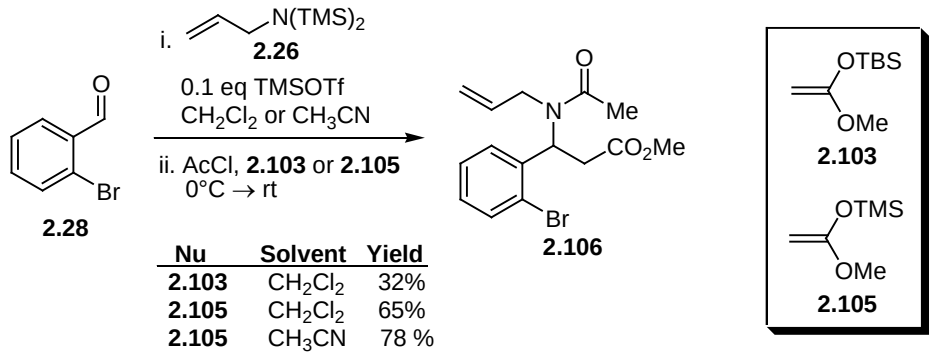
Preliminary investigations into the use of silyl ketene acetals were undertaken to ascertain the general reactivity of these nucleophiles in our system (Scheme 2.29). When imine **2.17** was treated in situ with silyl ketene acetal **2.103** and acetyl chloride in CH_2Cl_2 **2.104** was produced in 21% yield. When a catalytic amount of TMSOTf was added to the reaction, **2.104** was isolated 52% yield. Although the reaction involving the use of TMSOTf is not a true 4CR, these results do suggest that the addition of TMSOTf to reactions involving silyl ketene acetals can have a beneficial effect similar to that seen with reactions involving allyltrimethylsilane.

Scheme 2.29



Attention was then turned to incorporating aldehydes with additional functionality and finding optimal conditions for running a one pot reaction. Since the previous results suggested that TMSOTf was needed for optimal yields with silyl ketene acetal nucleophiles, and since reactions with silyl enol ether **2.74** involving TMSOTf in the presence of molecular sieves proved to be low yielding, it was decided to pursue the bis(silyl)amine method for forming the imine. The treatment of bromobenzaldehyde **2.28** and bis(trimethylsilyl)allylamine **2.26** with a catalytic amount of TMSOTf in CH_2Cl_2 resulted in the rapid formation of the imine, and subsequent addition of **2.103** and acetyl chloride provided the desired amide **2.106** in only 32% yield (Scheme 2.30). When the more reactive trimethylsilyl ketene acetal **2.105** was used in the reaction, the desired product could be isolated in 65% yield. Switching the solvent to CH_3CN further increased the yield of **2.106** to 78%. When the reaction was run generating the imine from allylamine and bromobenzaldehyde **2.28** in the presence of activated 4 Å molecular sieves the desired amide **2.106** could only be isolated in 16% yield, again showing the need for Lewis acid in this reaction.

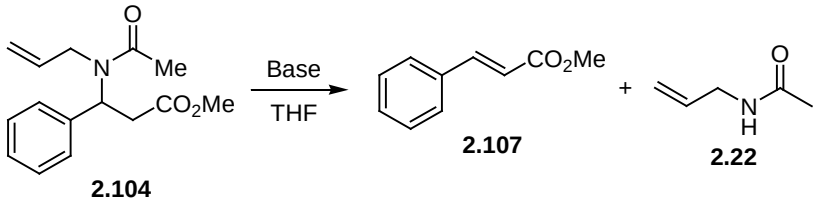
Scheme 2.30



Nu	Solvent	Yield
2.103	CH_2Cl_2	32%
2.105	CH_2Cl_2	65%
2.105	CH_3CN	78 %

Amide **2.106** is functionalized to undergo subsequent Heck and Dieckmann cyclizations to give functionalized benzo[a]quinolizine ring systems. In working with **2.104** it was found that under a variety of reaction conditions the only products formed from the attempted Dieckmann reaction were methyl cinnamate (**2.107**) and **2.22** (Scheme 2.31). These products arise from deprotonation occurring α to the ester group followed by an elimination of the amide anion. Even thought the protons α to the amide are more sterically accessible, the most acidic protons in **2.104** should be those α to the ester (pKa of esters = 29 versus 34 for amides in DMSO[195]), so this result is not unexpected.

Scheme 2.31

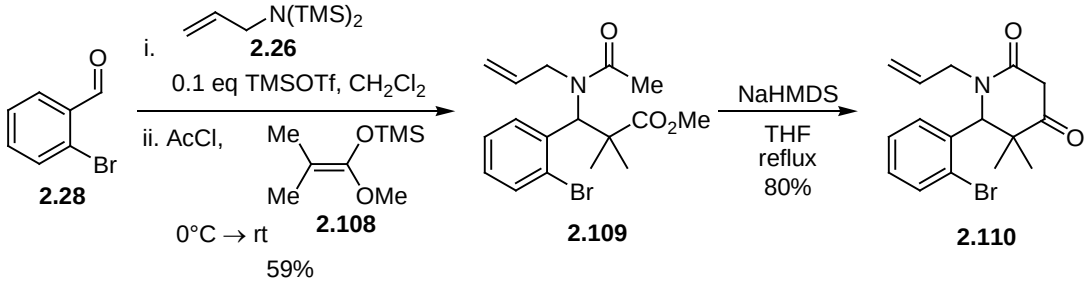


Base = NaH, LDA, or NaHMDS

There are two potential scenarios whereby this problem might be avoided. The most direct method for eliminating this side reaction is by incorporating substitution α to the ester, thereby blocking the pathway for elimination. To this end, the substituted silyl

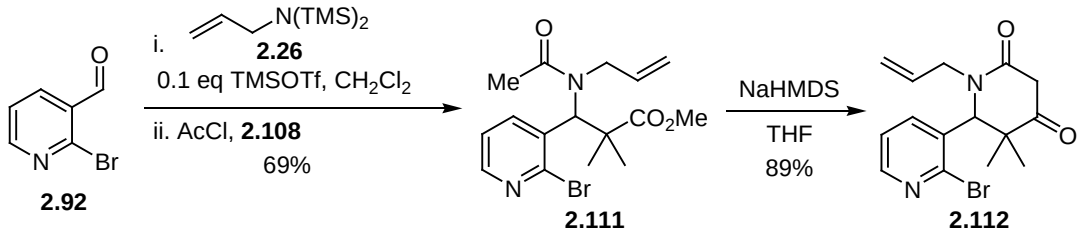
ketene acetal **2.108** was employed as the nucleophile in the 4CR (Scheme 2.32). Formation of the imine from bromobenzaldehyde **2.28** and bis(trimethylsilyl)allylamine **2.26** proceeded smoothly, and upon addition of **2.108** and acetyl chloride the desired amide **2.109** could be isolated in 59% yield. Upon treatment with excess NaHMDS in refluxing THF, amide **2.109** underwent the Dieckmann cyclization to form **2.110** in 80% yield. The incorporation of the gem dimethyl group solves the elimination problem associated with the unsubstituted substrate, but at the same time it is also limiting in that only compounds with this geminal substitution can be accessed.

Scheme 2.32



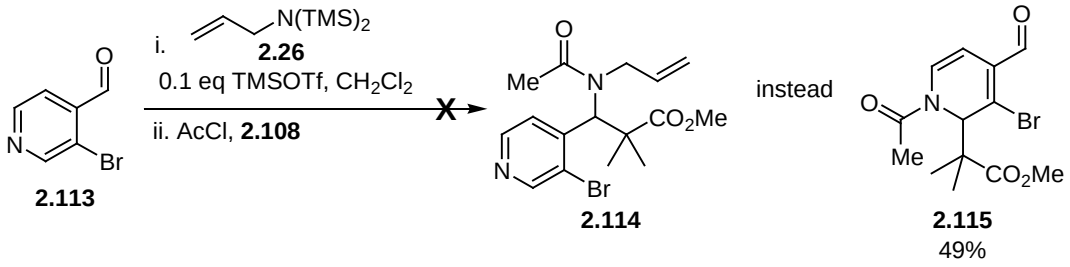
In order to expand on the number and types of aldehydes utilized in the 4CR, investigations into using substituted pyridine carboxaldehydes as were undertaken (Scheme 2.33). Treatment of 3-formyl-2-bromopyridine (**2.92**) with bis(trimethylsilyl)-allylamine **2.26** and TMSOTf in CH_2Cl_2 for 3 h gave the desired imine, which was treated with acetyl chloride in the presence of silyl ketene acetal **2.108** to give the substituted pyridine **2.111** in 69% yield. Treatment of **2.111** with NaHMDS in THF produced **2.112** in 89% yield.

Scheme 2.33



However, when 3-bromo-4-formylpyridine (**2.113**)[192] was used as the aldehyde in the 4CR, the desired pyridine **2.114** was not isolated (Scheme 2.34). Instead, dihydropyridine **2.115** was isolated in 49% yield. This product arises from the *N*-acylation of the pyridine followed by nucleophilic attack of the silyl ketene acetal on the acyl pyridinium ion. This side reaction shows the limitations encountered when using pyridine carboxaldehydes in the 4CR. If the pyridine nitrogen is not sterically hindered, as it is in **2.92**, then the pyridine can be competitively *N*-acylated in the presence of the imine.

Scheme 2.34

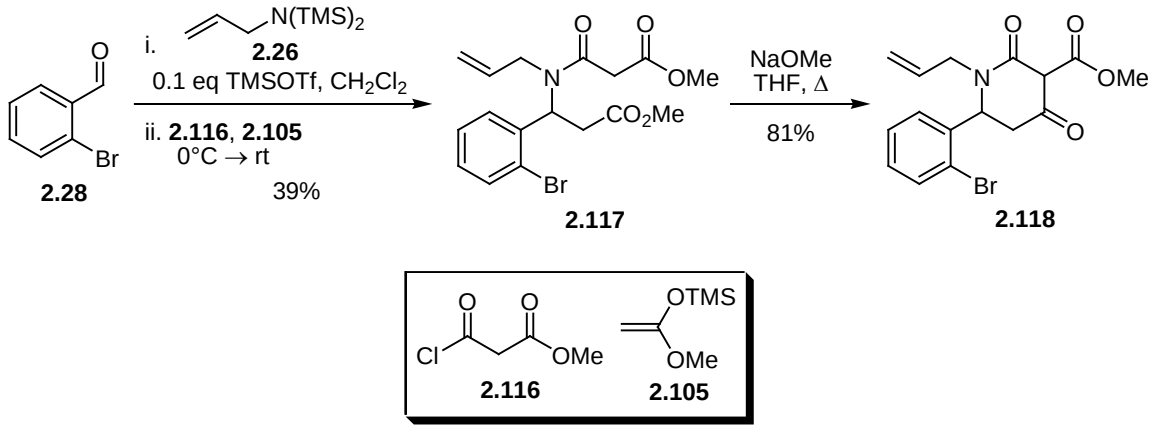


The second scenario in which the above elimination reaction might be avoided involves increasing the acidity of the protons α to the amide. If the protons α to the amide carbonyl can be rendered more acidic than those α to the ester, then a selective deprotonation of the more acidic protons should occur to give rise to the desired Dieckmann product. This tactic is also a more desirable solution to the problem, as it avoids the need for incorporating geminal substitution α to the ester and potentially

increases the number of scaffolds accessible using the 4CR/Dieckmann cyclization reaction sequence.

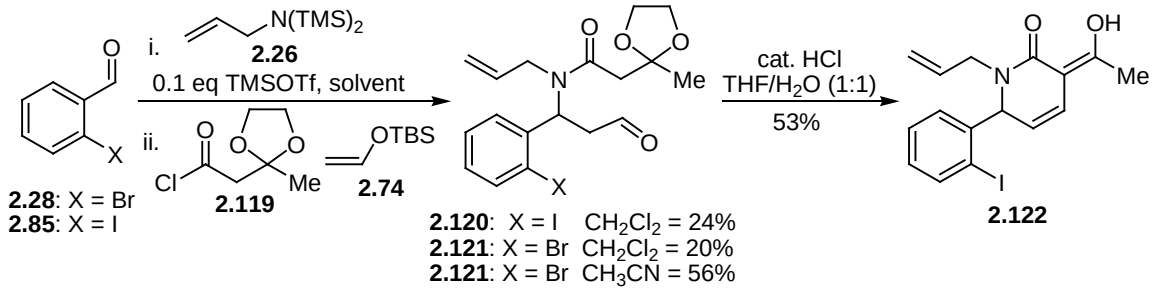
By incorporating methyl malonyl chloride (**2.116**) into the 4CR, access to compounds containing a β-dicarbonyl functional group can be obtained. The protons of the β-dicarbonyl moiety are significantly acidic to be selectively deprotonated in the presence of the ester, thus removing any potential for the elimination reaction to occur. The additional ester incorporated in the acid chloride can be then kept as an additional functional handle, or it can be removed by a subsequent decarboxylation if desired. Preliminary results show that this is potentially a viable option (Scheme 2.35). Formation of the imine from bromobenzaldehyde **2.28** and bis(trimethylsilyl)allylamine **2.26**, followed by the addition of silyl ketene acetal **2.105** and methyl malonyl chloride provided a complex reaction mixture from which the desired amide **2.117** could be isolated in 39% yield. Lower yields **2.117** (15%) were obtained when the imine was formed in situ from allylamine in the presence of molecular sieves. Treatment of **2.117** with excess NaOMe in refluxing THF provided the desired Dieckmann product **2.118** in 81% yield. While utilizing methyl malonyl chloride as the acid chloride effectively solved the problems associated with competitive elimination during the Dieckmann cyclization, the low yields for the 4CR present a major drawback to this sequence that to this day has not been remedied.

Scheme 2.35



Another alternative for increasing the acidity of the protons alpha to the amide that has shown promise is the use of the acid chloride **2.119** (Scheme 2.36). Acid chloride **2.119** incorporates masked β-dicarbonyl functionality into the 4CR that can then later be unmasked under mild conditions. Thus, when the imine derived from bromobenzaldehyde **2.28** and bis(trimethylsilyl)allylamine **2.26** was reacted acid chloride **2.119** and silyl enol ether **2.74** in CH_3CN, **2.121** was isolated in 56% yield. When CH_2Cl_2 was used as the solvent the yield dropped to 20% for the aryl bromide **2.121** and 24% for the aryl iodide **2.120**. When **2.120** was treated with a catalytic amount of HCl in aqueous THF the hydrolysis of the ketal was accompanied by an intramolecular Knoevenagel condensation to give **2.122** in 53% yield. Although this reaction sequence has not been optimized, it shows that acid chloride **2.119** may be a useful alternative to methyl malonyl chloride in the 4CR.

Scheme 2.36



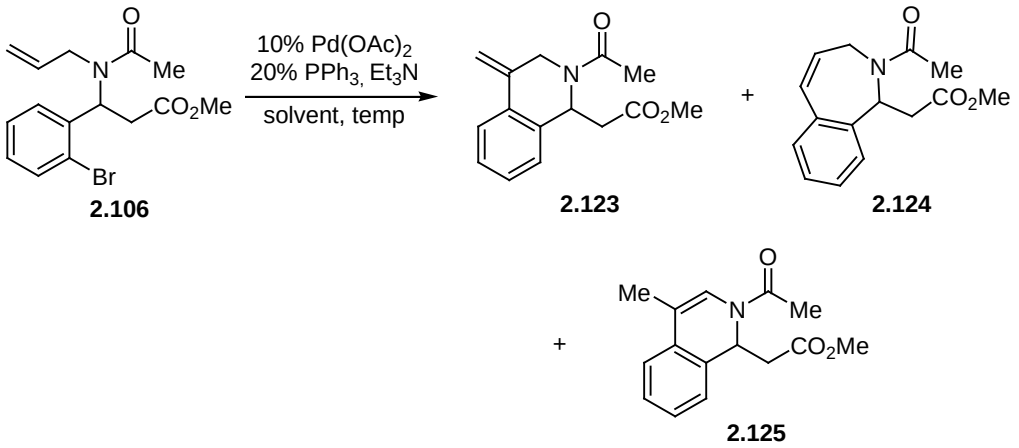
2.2.5.1 Investigations into Intramolecular Heck Reactions

By incorporating an aryl halide and an appropriately disposed olefin into the 4CR, substrates can be generated that are set up for an intramolecular Heck reaction. By looking at the number of structures that can readily be accessed *via* the 4CR with this pairing of functional groups, one can easily see that the Heck reaction could potentially be a very valuable reaction to sequence with the 4CR. Thus, studies were undertaken to access the viability of this reaction sequence.

When amide **2.106** was heated under reflux in CH_3CN in the presence of 0.1 eq. $Pd(OAc)_2$, 0.2 eq. PPh_3, > 2 eq. Et_3N the reaction did not go to completion, and 38% of the starting material was recovered. In order to drive the Heck reaction to completion, the reaction was run in a microwave reactor, which is known to accelerate Heck reactions.[196, 197] When the reaction was heated to 100 °C for 80 minutes, the reaction still did not completely consume starting material. Increasing the temperature to 125 °C provided complete conversion in one hour and gave an inseparable mixture (1:1) of compounds **2.123** and **2.124** in 72% yield along with 22% of **2.125**, which was the separable (Scheme 2.37). The endocyclic olefin product **2.125** was presumably formed as a result of the Pd-H species that is generated during the course of the reaction further reacting with **2.123** via a hydropallidation/β-hydride elimination pathway to give rise to the isomerized the olefin.[198] When **2.106** was heated in DMF at 125 °C and the reaction

was stopped after 5 h, the reaction did not go to completion and 20% of the starting material could be recovered, along with 60% of a ~2:1 mixture of **2.123** and **2.124** and 10% of **2.125**. When the reaction was run in refluxing toluene the reaction only proceeded to 50% conversion with a similar product distribution.

Scheme 2.37

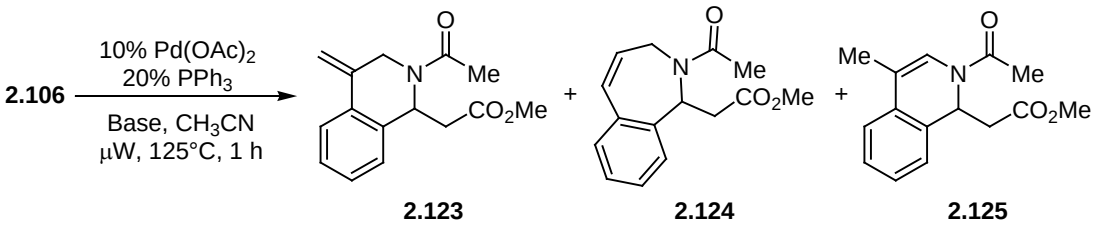


Solvent	Temp (°C)	2.123 + 2.124 (%)	2.123:2.124	2.125 (%)	RSM (%)
CH_3CN	88	42	~1:1	n.d.	38
CH_3CN	μW,125	72	1:1	22	0
DMF	125	60	2:1	10	20
Toluene	110	36	1:1	10	49

While the combined yield for the above Heck reaction was excellent, there is almost no selectivity in the product distribution. In order to improve this ratio the use of silver salts in the reaction was investigated, because silver salts have been shown to decrease the amount of double bond isomerization.[198] The silver salts work by sequestering halides from palladium, which in turn increases the acidity of the Pd-H species, making it more susceptible to deprotonation and less apt to reinsert into and isomerize the reaction products. Unfortunately, the addition of Ag_2CO_3 to the reaction, both as the base and as an additive, had little influence in supressing double bond isomerization (Scheme 2.38). However, the addition of Ag_2CO_3 did have a small

influence on the relative amount of 7-membered ring product **2.124** generated in the reaction, with a greater preference towards the 6-membered ring products being shown. When $AgNO_3$ was used as an additive, no reaction occurred. If the silver salts are indeed sequestering halide from the reaction, this suggests that there may be a halide effect on the product distribution.

Scheme 2.38

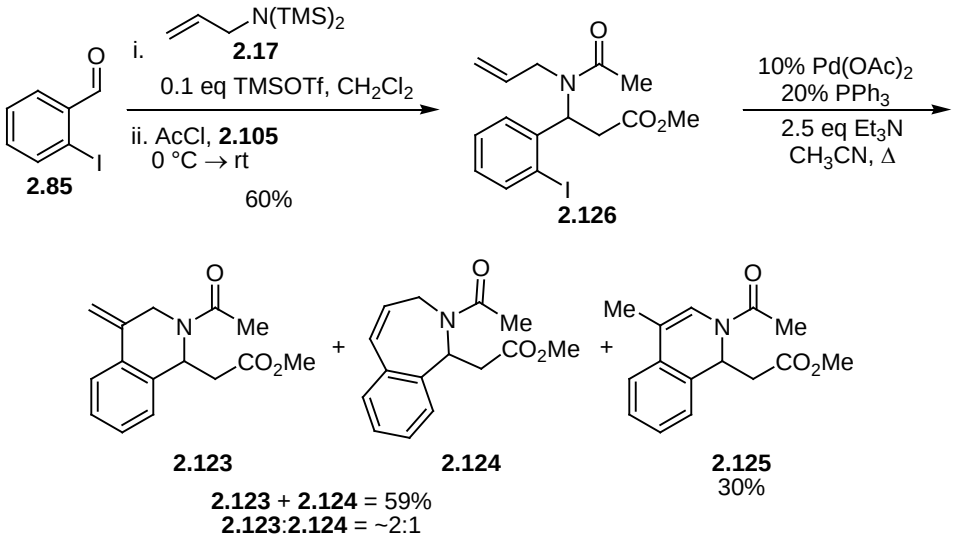


2.123 **2.124** **2.125**

Base	2.123 & 2.124 (2.123:2.124)	2.125	RSM
2.2 eq Ag_2CO_3	40% (2.5:1)	10%	30%
2.5 eq. Et_3N, 0.7eq Ag_2CO_3	66% (1.3:1)	24%	4%
ex. Et_3N, 1.5 eq $AgNO_3$	0%	0%	major

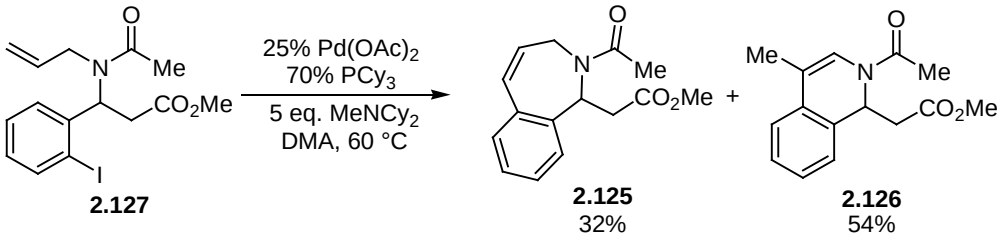
In order to further investigate the possible influence of the halide on the Heck cyclization, the aryl iodide **2.126** was synthesized from iodobenzaldehyde **2.85** (Scheme 2.39). Subjecting **2.126** to the standard Heck reaction conditions in refluxing acetonitrile provided a mixture (~2:1) of **2.123** and **2.124** in 59% yield along with 30% of **2.125**. Unlike the aryl bromide **2.106**, the aryl iodide **2.126** readily reacted in refluxing CH_3CN and did not need microwave heating to drive the reaction to completion. The ratio of 6:7 membered ring products also increased, indicating the halide may indeed play a role in determining ring size.

Scheme 2.39



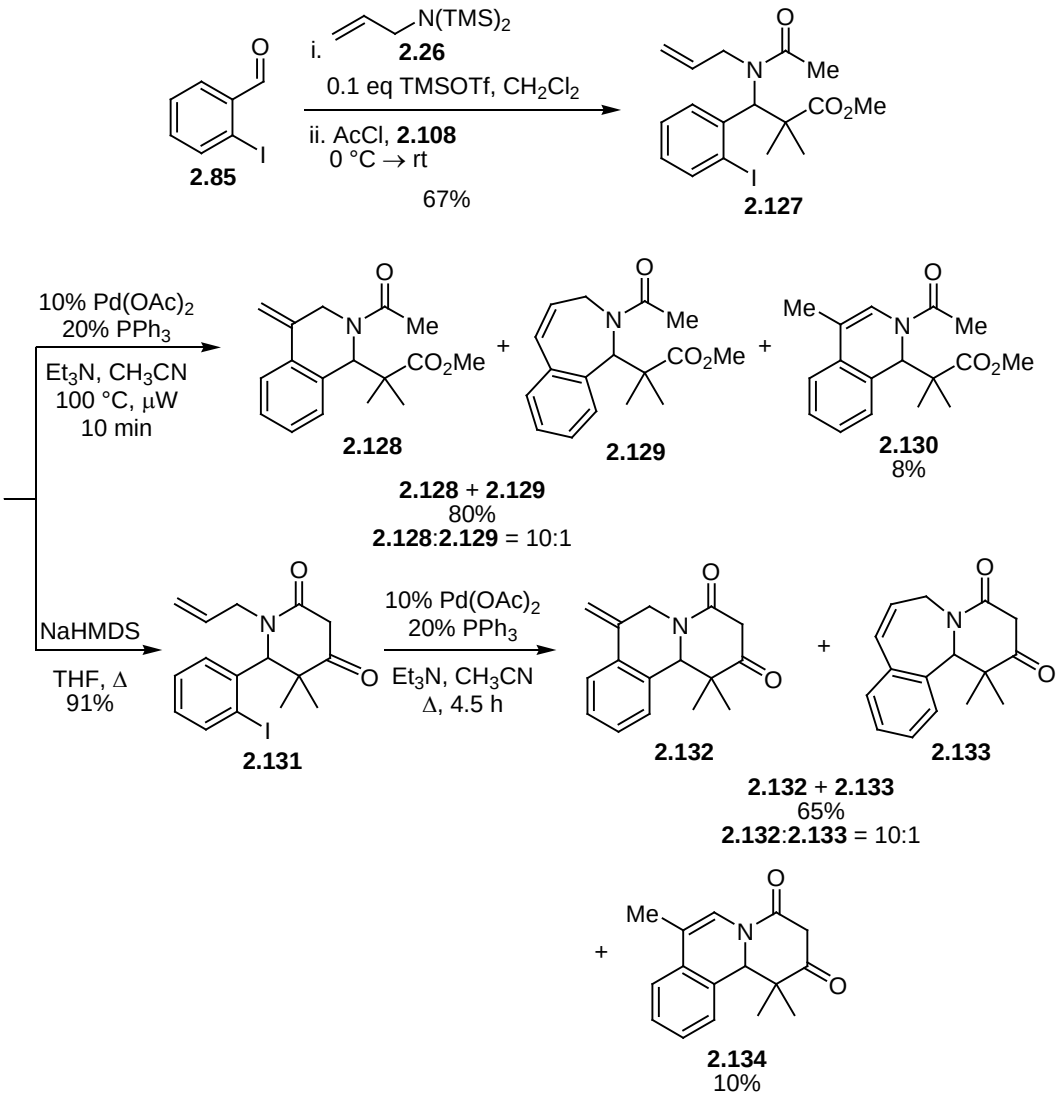
Recently it has been shown that the combination $Pd(OAc)_2$, tricyclohexylphosphine (PCy_3), and *N*-methyldicyclohexylamine ($MeNCy_2$) is an effective catalyst system in dimethyl acetamide (DMA) for performing intramolecular Heck reactions to generate the 6-membered ring exclusively with complete double bond isomerization (see Chapter 1.2.2.14).[108] Following these conditions, the aryl iodide **2.126** was reacted at 60 °C in DMA generating **2.124** and **2.125** in 32% and 54% yields, respectively (Scheme 2.40). When DMF was used as solvent, isomerization to the 6-membered endocyclic double bond was not complete, and the exocyclic olefin product **2.123** was also isolated. The ratios of 6:7-membered ring formed were similar for both DMA and DMF. While these conditions were successful in generating only a single double bond isomer, the ratio of 6:7-membered ring was not improved, and this remains an unsolved problem in this project.

Scheme 2.40



The previously discussed Heck reactions were all run on substrates where the Heck reaction was performed prior to the Dieckmann cyclization. However, with the analogous gem-dimethyl compounds the reaction sequence can be reversed. To this end, amide **2.127** was synthesized so that the effects of resequencing the Heck and Dieckmann reactions could be investigated (Scheme 2.41). Amide **2.127** was readily synthesized from iodobenzaldehyde **2.85** in good yield. When **2.127** was heated in the presence of 0.1 eq. $Pd(OAc)_2$, 0.2 eq. PPh_3, > 2 eq. Et_3 in CH_3CN at 100 °C using the microwave reactor, the reaction produced an inseparable mixture (10:1) of **2.128** and **2.129** in 80% yield along with 8% of the isomerized **2.130** in only 10 min. Alternatively, **2.127** underwent a Dieckmann cyclization to give **2.131** in 91% yield. Subjecting **2.131** to the Heck reaction conditions in refluxing CH_3CN generated an inseparable mixture (10:1) of **2.132** and **2.133** in 65% yield along with 10% of **2.134**, which was separable. These results show that the sequencing of the Heck and Dieckmann reactions has no effect on the product distribution.

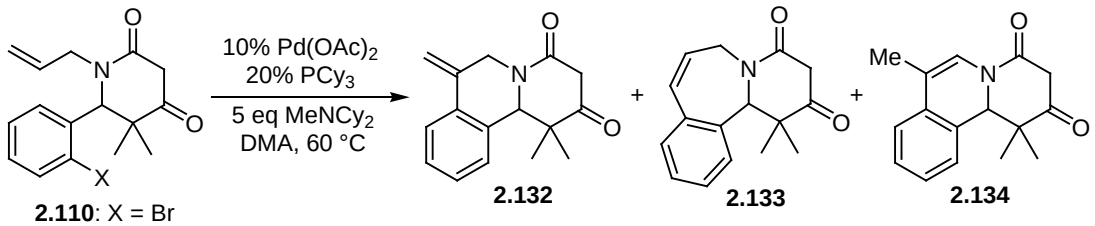
Scheme 2.41



Since aryl iodide **2.131** showed a greater preference (~11:1) for the formation of the 6-membered ring products, it was hoped that by reacting **2.131** with the $Pd(OAc)_2/PCy_3/MeNCy_2$ catalyst system that complete double bond isomerization would occur to generate **2.134** as the major product. When **2.131** was subjected to the Heck reaction, all three of the possible products were formed, and the ratio of 6:7-membered rings was only ~2:1 (Scheme 2.42). The analogous aryl bromide **2.110** was found to

show a greater selectivity (~6:1 versus ~2:1) for the 6-membered ring, contradicting the earlier results that showed that aryl iodides gave better selectivity for the 6-membered ring. Interestingly, complete isomerization to the endocyclic olefin did not occur in either case. Aryl bromide **2.110** did show a greater extent of double bond isomerization; however, this may be attributed to the longer reaction time needed for **2.110** versus aryl iodide **2.131**. In both cases it is possible that increased reaction times could lead to complete double bond isomerization, but these studies have not been undertaken.

Scheme 2.42



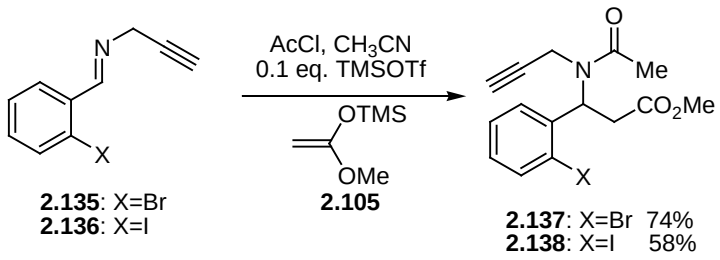
2.110: X = Br
2.131: X = I

2.132 **2.133** **2.134**

	2.132 + 2.133	**2.132**:**2.133**	**2.134**
X = I	48%	3:2	16%
X = Br	22%	3:2	43%

Previous work from the Martin group had shown that selectivity for 6- versus 7-membered rings could be achieved under reductive Heck reaction conditions.[199, 200] To investigate the use of a reductive Heck cyclization in our system, aryl halides **2.137** and **2.138** were synthesized using from propargyl imines **2.135** and **2.136** (Scheme 2.43). Attempts to synthesize **2.137** via a 4CR were low yielding, and the desired product could was isolated in <10% yield when the imine was made in situ from propargyl amine and the appropriate halobenzaldehyde. Using the bis(silyl)amine approach was also unsuccessful due to difficulties that were encountered in the synthesis and isolation of *N,N*-bis(trimethylsilyl)propargylamine.

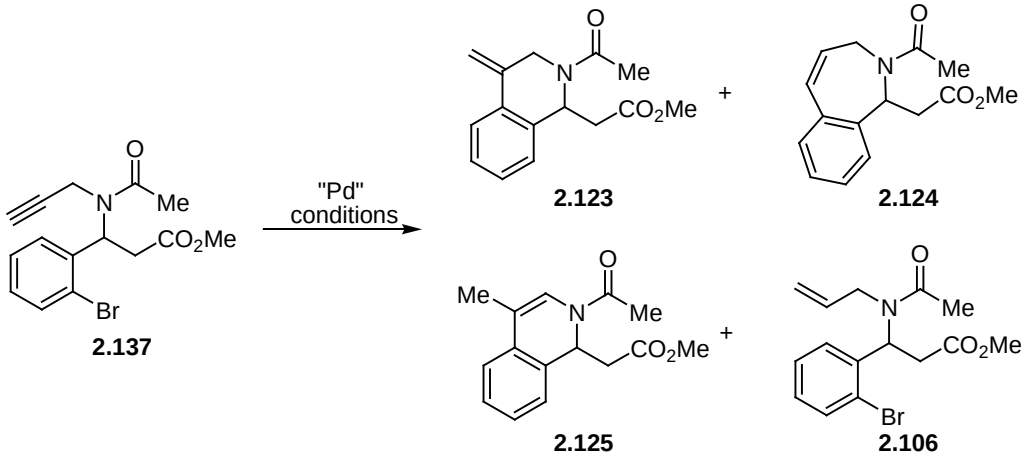
Scheme 2.43



The initial studies into the reductive Heck cyclization were made using aryl bromide **2.137**. Reacting **2.137** under our previously utilized Heck reaction conditions (10% $Pd(OAc)_2$, 20% PPh_3, Et_3N, CH_3CN, μW, 125 ºC), with formic acid added as a terminal reductant, provided a mixture (1:1:1) of **2.123**, **2.124**, and **2.125** in only 21% yield (Table 1, entry 1). This result was not an improvement. Hence, the reaction conditions developed for the synthesis of methyl lysergate were explored. Namely, **2.137** was subjected to the catalyst system of $Pd(PPh_3)_4$, tetrabutylammonium chloride (TBAC), formic acid, and either tetra- or pentamethylpiperidine (TMP or PMP) in refluxing acetonitrile.[199, 200] When TMP was used as the base, **2.123** and **2.125** were isolated in 25% and 6% yields, respectively, with no 7-membered ring products being detected (entry 2). Switching the base to PMP resulted in a significant increase in overall mass recovery, but four reaction products were generated, with **2.123**, **2.124**, and **2.125** being produced along with the reduced **2.106** (entry 3). By adding the formic acid at 75 °C, the overall yield for the reaction could be increased, but this came at the price of reduced selectivity towards the 6-membered ring products when TMP was used (entry 4). The selectivity towards the 6-membered ring did increased when PMP was used as base and the formic acid was added at elevated temperatures (entry 5), however, this increase in selectivity was accompanied by an increase in the amount of **2.106** formed. Running the reaction at lower temperatures also improved the selectivity towards the 6-membered

ring, but a substantial amount of the reduced product **2.106** was generated (entry 6). The addition of tetrabutylammonium iodide (TBAI) instead of TBAC was detrimental to both the yield and selectivity (entry 7). Using triethylsilane (Et_3SiH) as the reductant increased the selectivity towards the 6-membered ring, and no reduced or 7-membered products could be isolated; however, the isolated yields were still low (entry 8).

Table 1



Entry	Conditions	Yield
1	10% $Pd(OAc)_2$, 20% PPh_3, Et_3N, HCO_2H CH_3CN, μW 125 °C	21% **2.123**:**2.124**:**2.125** (1:1:1)
2	10% $Pd(PPh_3)_4$, TBAC, 3 eq. TMP, 2 eq. HCO_2H CH_3CN, Δ, 4.5h	25% **2.123**, 6% **2.124**
3	10% $Pd(PPh_3)_4$, TBAC, 3 eq. PMP, 2 eq. HCO_2H CH_3CN, Δ, 1.5h	25% **2.106**:**2.125** (3:1) 58% **2.123**:**2.124** (1:1)
4	10% $Pd(PPh_3)_4$, TBAC, 3 eq. TMP, 2 eq. HCO_2H* CH_3CN, Δ, 40 min	66% **2.123**:**2.124** (1:1) 6% **2.125**
5	10% $Pd(PPh_3)_4$, TBAC, 3 eq. PMP, 2 eq. HCO_2H* CH_3CN, Δ, 1h	38% **2.106**, 30% **2.123** trace **2.125**
6	10% $Pd(PPh_3)_4$, TBAC, 3 eq. PMP, 2 eq. HCO_2H CH_3CN, 60 °C	21% **2.106** 49% **2.123**:**2.124**(5:1)
7	10% $Pd(PPh_3)_4$, TBAI, 3 eq. PMP, 2 eq. HCO_2H CH_3CN, 60 °C	10% **2.106**:**2.125** (8:1) 10% **2.123**:**2.124** (2.5:1)
8	10% $Pd(PPh_3)_4$, TBAC, 3 eq. PMP, 2 eq. Et_3SiH CH_3CN, Δ	18% **2.123**, 6% **2.125**

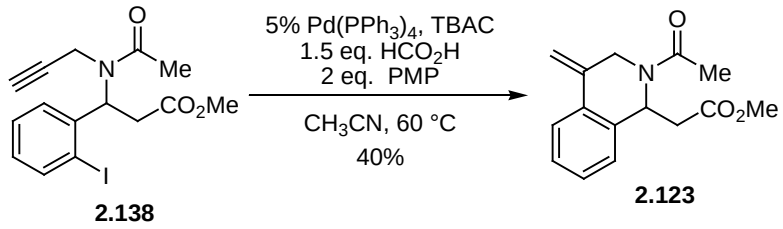
* Formic acid added at 75 °C.

In all of the above cases the reactions suffered from poor yields, poor selectivity, or both. While switching to the reductive Heck conditions did improve selectivity for the 6-membered ring, the 7-membered ring was still frequently formed. A potential reason for this is that the alkyne reacts to give exclusively the 6-membered ring, while the 7-

membered ring is formed from the alkene, which is formed by reduction of the alkyne under the reaction conditions. These reaction conditions are similar to conditions reported for the reduction of alkynes to alkenes,[201, 202] and as shown in entries 3,5,6, and 7, the alkene could indeed be isolated from these reactions, further lending support to the hypothesis that the 7-membered ring was formed exclusively from the alkene. When Et_3SiH was used as the terminal reductant, no alkene or 7-membered ring were isolated, lending some support to this argument. Additionally, in almost all cases partial isomerization of the 6-membered ring product double bond occurred, further complicating the reaction mixtures.

The preceding experiments revealed that the nature of the aryl halide affected the both the rate and selectivity of the Heck reaction, and it was hoped that by switching to aryl iodide **2.138** the yields and product distributions of could be improved. In a preliminary experiment, the aryl iodide **2.138** was treated with $Pd(PPh_3)_4$, TBAC, formic acid, and PMP at 60 °C in acetonitrile, the isoquinoline derivative **2.123** was isolated in 40% yield as the only detectable product (Scheme 2.44). The aryl iodide again showed better results as compared to the analogous aryl bromide. This is presumably due to the increased reactivity of aryl iodides, which in turn allows for milder reaction conditions and shorter reaction times and limits the formation of the potential side products. The yield for this reaction is still low and extensive optimization may be needed to further increase this yield to synthetically useful levels.

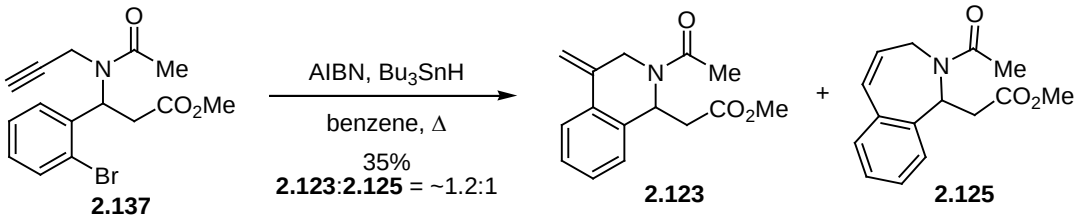
Scheme 2.44



2.138 **2.123**

A radical cyclization of aryl bromide **2.137** could also provide **2.123** (Scheme 2.45). To this end, **2.137** was treated with AIBN and tributyltinhydride in refluxing benzene to give an inseparable mixture (~1.2:1) of **2.123** and **2.125** in only 35% yield. The low yield and selectivity for this reaction was rather discouraging, and additional studies on the radical cyclization of **2.137** were not undertaken.

Scheme 2.45



The Heck cyclization of compounds such as **2.106** and **2.137** has proven to be somewhat troublesome. In most cases, multiple products are formed in poor ratios, while in other cases yields were low. It may be possible to improve these results, but when one considers the number of variables that might need to be changed to optimize a Heck reaction, it was deemed that the effort that may be required to perform such an optimization was not worthwhile. These results can be looked upon as preliminary results that show the 4CR can be sequenced with Heck reactions that lead to scaffolds that may potentially be of interest to the scientific community.

2.2.4.2 Sequential 4CR/Heck Cyclizations Utilizing 4-Bromoindoles.

In order to expand the scope of aldehydes that could be used in the 4CR investigations, indole 3-carbaldehyde derivatives were next examined. One derivative of particular interest was the 4-bromoindole-3-carboxaldehyde **2.139**, as the aryl bromide could be readily exploited in a subsequent Heck reaction, providing an approach to polycyclic indole scaffolds (Scheme 2.46). Treatment of **2.139**[203, 204] with bis(trimethylsilyl)allylamine **2.26** in the presence of a catalytic amount of TMSOTf

provided the imine, which could then be acylated and reacted with silyl ketene acetal **2.105** to give **2.140** in 72% yield. Unlike other examples of the 4CR employing silyl ketene acetal **2.105**, substantially higher yields were obtained in CH_2Cl_2 instead of acetonitrile. Upon subjecting **2.140** to standard Heck conditions with microwave heating, two separable indoles, **2.141** and **2.142** were generated in 83% and 12% yields, respectively. The structure of **2.141** was conclusively determined by X-ray crystallography (Figure 2.5).

Scheme 2.46

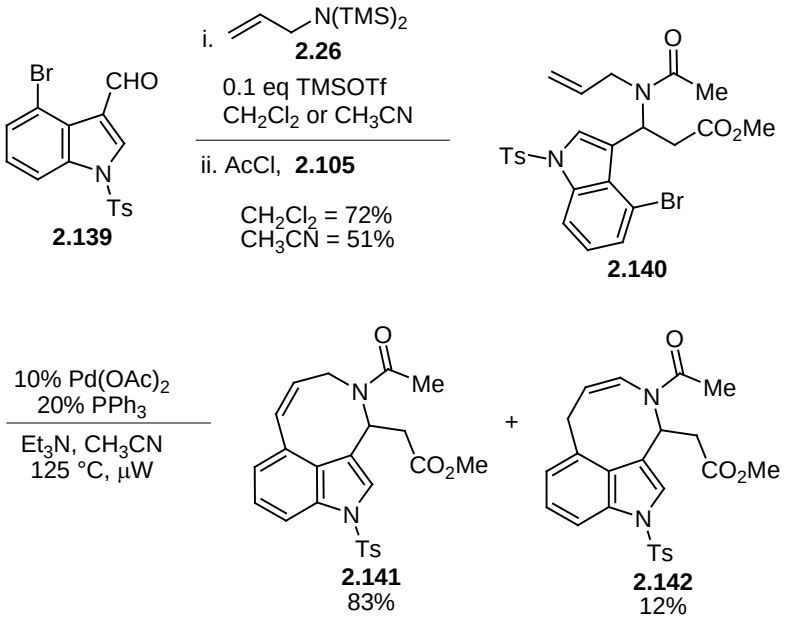
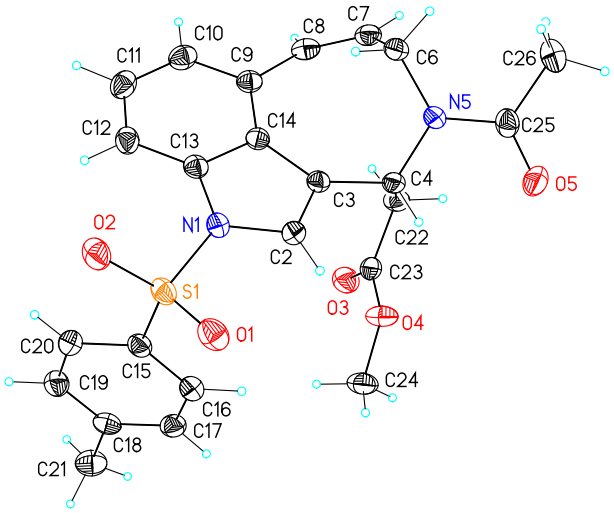


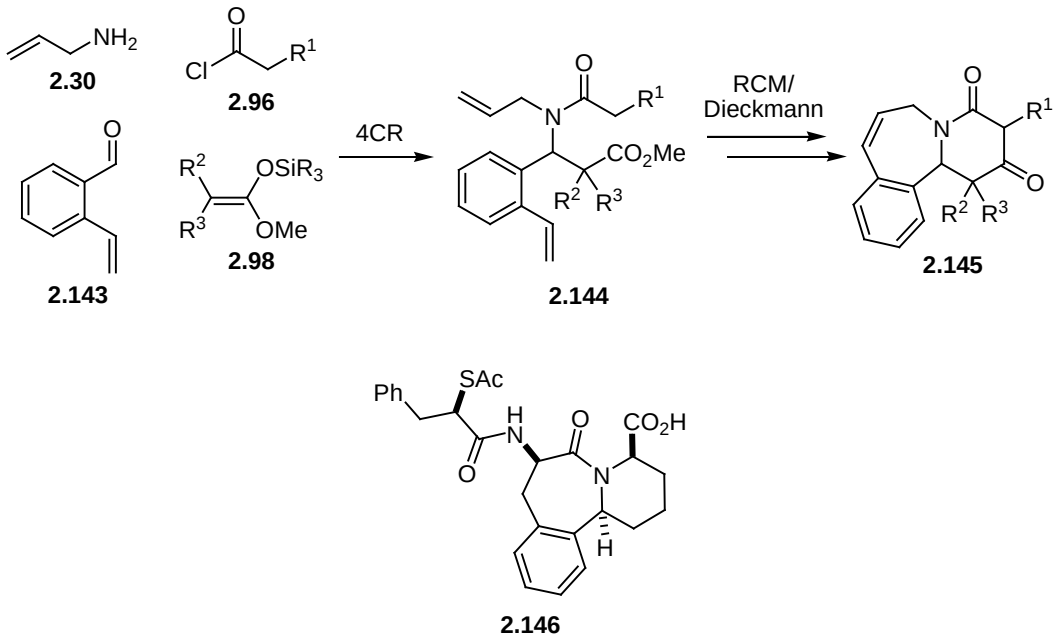
Figure 2.5: ORTEP drawing of 2.141.



2.2.5.3 Sequential 4CR/RCM/Deickmann Cyclization Utilizing Silyl Ketene Acetal Nuclophiles

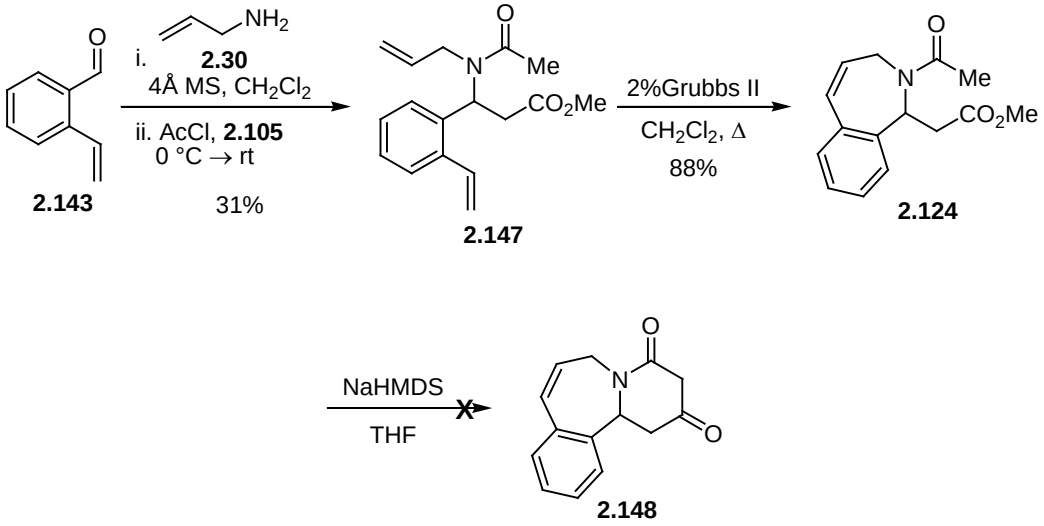
By substituting 2-vinylbenzaldehyde for 2-bromobenzaldehydes in the 4CR substrates that are functionalized to undergo a subsequent RCM are generated. When 2-vinylbenzaldehyde is used in conjunction with allylamine, and an appropriate acid chloride and silyl ketene acetal, products could be accessed that can undergo sequential RCM and Dieckmann cyclization to generate a pyrido-benzazepine ring structure **2.145** (Scheme 2.47). Compounds containing this scaffold have been studied, and structures similar to **2.146** have been shown to inhibit angiotensine I-converting enzyme.[205-207]

Scheme 2.47



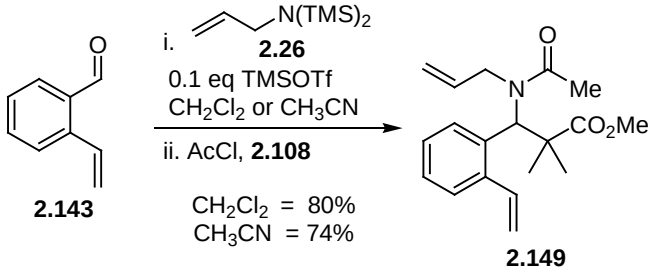
To this end, vinyl benzaldehyde **2.143** was treated with allylamine in the presence of molecular sieves. After imine formation was complete, silyl ketene acetal **2.105** and acetyl chloride were added, and **2.147** could be isolated in 31% yield (Scheme 2.48). Upon treatment of **2.147** with the Grubbs II catalyst in refluxing CH_2Cl_2 the desired azepine **2.124** was isolated in 88% yield. When **2.124** was treated with NaHMDS in THF, none of the desired **2.148** was produced. The overall mass recovery for this reaction was poor, and no identifiable side products were isolated.

Scheme 2.48



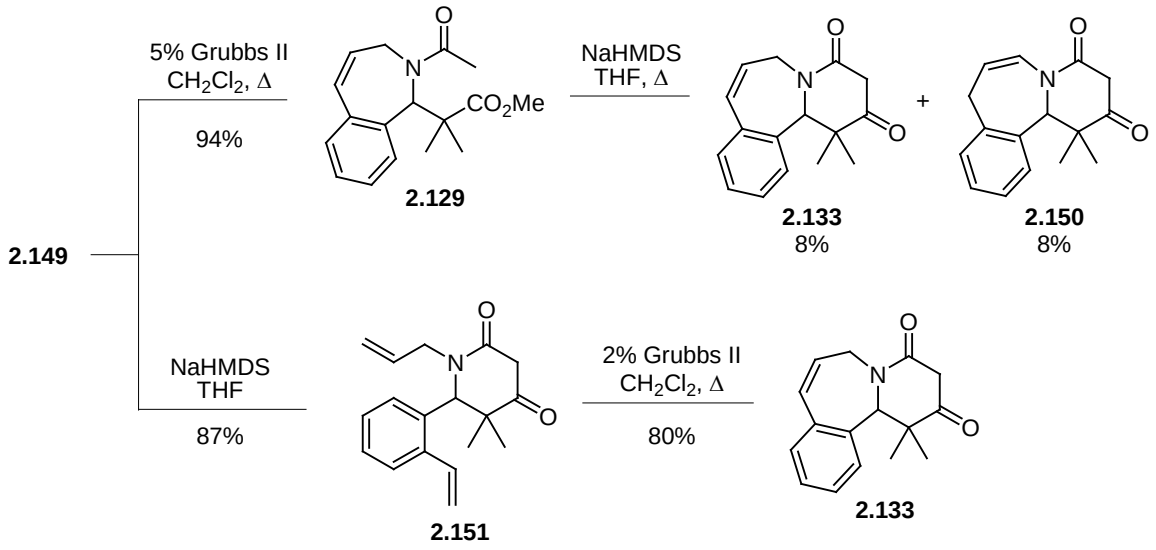
Attention was then turned to substituted silyl ketene acetal **2.108** as products derived from **2.108** had been shown to be substrates for the Dieckmann cyclization (Scheme 2.49). Vinyl benzaldehyde **2.143** was condensed with bis(trimethylsilyl)allylamine **2.26** in the presence of a catalytic amount of TMSOTf to provide the desired intermediary imine. When silyl ketene acetal **2.108** and acetyl chloride were added at 0 °C and the reaction was warmed to room temperature, the desired product **2.149** was isolated in 68% yield. When the addition was done at room temperature the yield was increased to 80%. Switching solvents to acetonitrile provided the desired product **2.149** in 74% yield.

Scheme 2.49



Treatment of **2.149** with 5% Grubbs II catalyst in refluxing CH_2Cl_2 provided the desired azepine **2.129** in 94% yield (Scheme 2.50). Attempts to cyclize **2.129** via a Dieckmann reaction were met with limited success. No reaction occurred when **2.129** was treated with NaH in refluxing THF. When NaHMDS was used as the base, the desired product **2.133** was isolated in only 8% yield, along with equal amounts of the isomerized product **2.150**. This problem was readily avoided by resequencing the Dieckmann and RCM reactions. Namely, treatment of **2.149** with NaHMDS provided **2.151** in 87% yield, and the RCM reaction of **2.151** proceeded smoothly in refluxing CH_2Cl_2 to provide tricycle **2.133** in 80% yield.

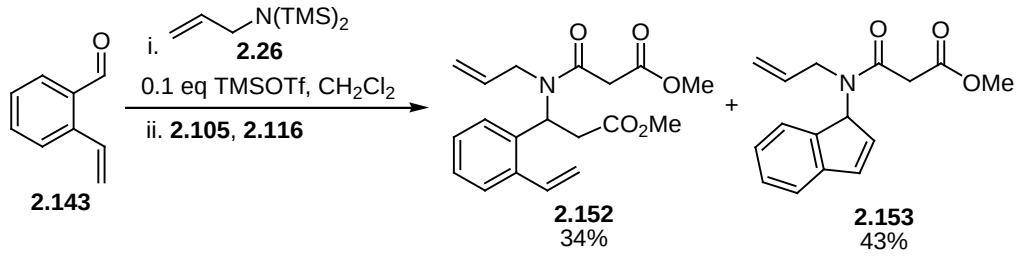
Scheme 2.50



While the synthesis of the tricycle **2.133** had proceeded uneventfully, this is only made possible by the presence of the gem dimethyl group. It would be advantageous to be able to access compounds without this substitution, and investigations into using methyl malonyl chloride as the acylating agent in this reaction sequence were undertaken (Scheme 2.51). In the event, the imine derived from vinyl benzaldehyde **2.143** and bis(trimethylsilyl)allylamine **2.26** was treated with methyl malonyl chloride and ketene

acetal **2.92** to provide **2.152** in 34% yield along with 43% of indane **2.153**. Indane **2.153** presumably arose from an intramolecular attack of the styrene onto the *N*-acyl iminium ion and subsequent elimination to reform the double bond. This side reaction was problematic in a number of reactions employing **2.116**, and therefore this sequence was not further pursued.

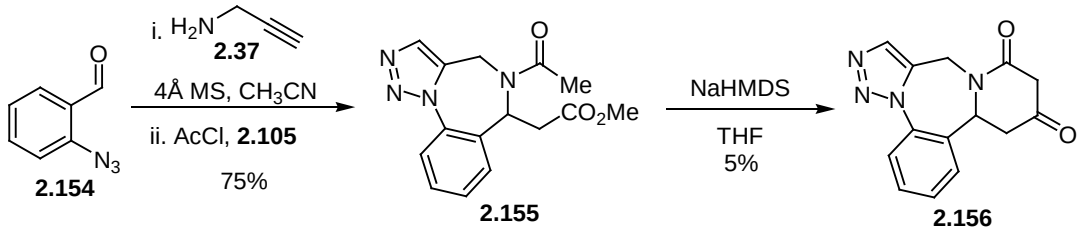
Scheme 2.51



2.2.5.4 Tandem 4CR/[3+2]Azide/Alkyne Cycloadditions

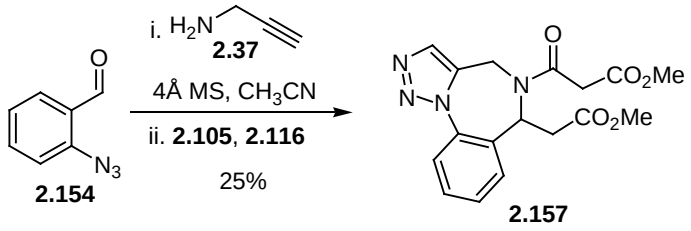
The incorporation of nitrogen functionality into the aldehyde component of the 4CR is desirable because this functionality can then be used to generate additional heterocyclic rings. Investigations into the use of 2-azidobenzaldehyde (**2.154**)[208] were undertaken, as it was thought that this would be a desirable starting material since the azide could be easily engaged in a subsequent cycloaddition reaction leading to scaffolds containing a triazole motif (Scheme 2.52). When the imine derived from **2.154** and propargyl amine in acetonitrile was treated with acetyl chloride and silyl ketene acetal **2.105**, the adduct thus formed underwent a spontaneous [3+2] cycloaddition to give triazole **2.155** in 75% yield. A limited number of attempts to carry out a Dieckmann cyclization on **2.155** were unproductive, and in the best case a 5% yield of tetracycle **2.156** could be isolated.

Scheme 2.52



An attempt to circumvent the problematic Dieckmann cyclization of **4.155** was made by replacing the acetyl chloride used in the synthesis of **2.155** with methyl malonyl chloride. The use of methyl malonyl chloride as the acylating reagent in the 4CR has proven to be problematic, and in this case the desired triazole **2.157** was only isolated in 25% yield (Scheme 2.53). Due to the low yield in this 4CR further investigations into the Dieckmann cyclization where not made.

Scheme 2.53

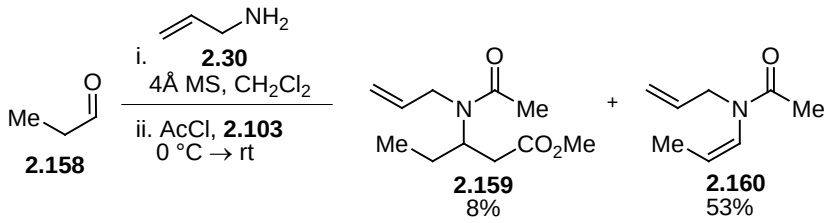


2.2.5.5 Reactions Involving Aliphatic Aldehydes.

Up until this point all of the examples shown have involved the use of aromatic aldehydes. The use of aliphatic aldehydes is also highly desirable because they would in turn allow access to scaffolds that cannot be synthesized from an aromatic aldehyde. Aliphatic aldehydes present potentially major problem that is not encountered with aromatic aldehydes, which is the presence of enolizable α-protons. When an imine derived from an aliphatic aldehyde is reacted with an acid chloride, the resulting *N*-acyl iminium ion can be readily quenched by loss of a proton to give an enamide. If loss of a

proton is faster than the trapping of the *N*-acyl iminium ion by an external nucleophile, the 4CR will fail. In practice, this concern was a valid one and when the imine derived from propionaldehyde and allylamine was treated with acetyl chloride and **2.103**, the desired **2.159** could be isolated in 8% yield while enamide **2.160** was the major product from the reaction and was isolated in 53% yield (Scheme 2.54).

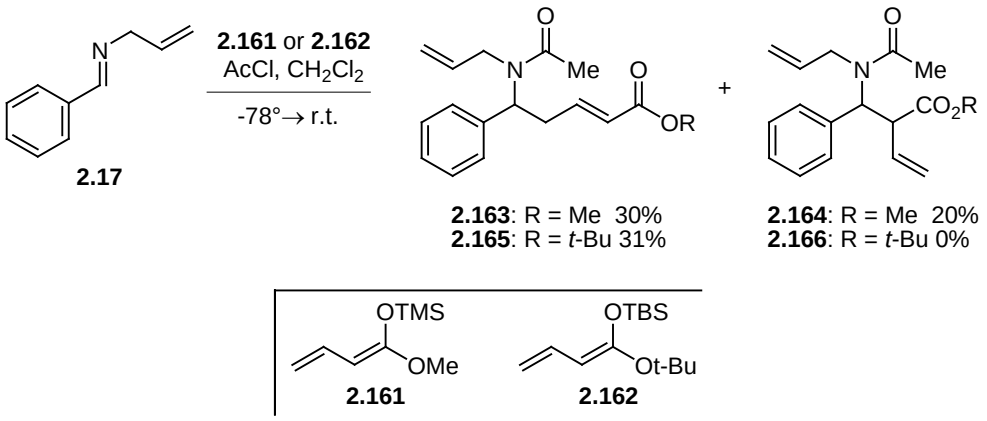
Scheme 2.54



2.2.5.6 Reactions Involving Vinyl Silyl Ketene Acetals

The use of vinyl silyl ketene acetals in the 4CR is desirable because the products produced from this nucleophile contain α,β-unsaturated ester, which can potentially be utilized in subsequent ring forming transformations. To answer the question of whether or not these nucleophiles can be utilized in the 4CR, preliminary investigations were undertaken. In a 3CR with imine **2.17** and acetyl chloride, ketene acetal **2.161** was found to give a mixture (3:2) of the separable products **2.163** and **2.164**, slightly favoring the γ-addition product **2.163** (Scheme 2.55). When the bulkier nucleophile **2.162** was used in the reaction the γ-addition product **2.165** was obtained in 31% yield as the only detectable product. Presumably, the increased steric interactions that occur between the *N*-acyl iminium ion and the *t*-butyl group in **2.162** make γ addition the preferred mode of attack. Although the yield for this reaction was low, the high level of selectivity makes this sequence worthy of further studies.

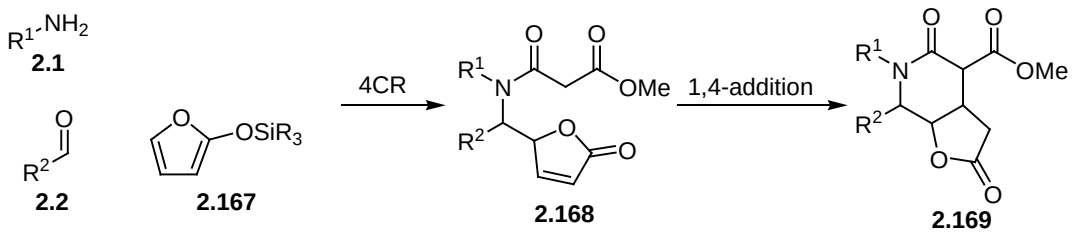
Scheme 2.55



2.2.6 Reactions Involving Silyloxyfurans Leading to 4CR/Michael Addition Sequences

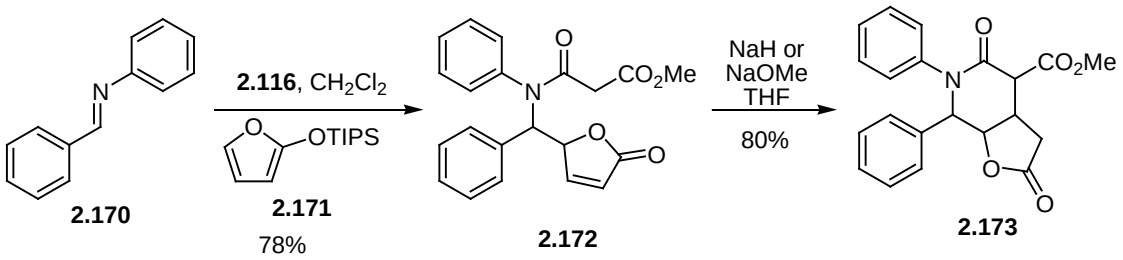
Methyl malonyl chloride has been used as the acylating agent in the 4CR to generate products that can undergo Dieckmann cyclizations. Alternatively, if methyl malonyl chloride were used in conjunction with a silyloxy furan nucleophile, a product is generated that is set up for an intramolecular Michael reaction to generate the bicyclic ring structure **2.169** (Scheme 2.56).

Scheme 2.56



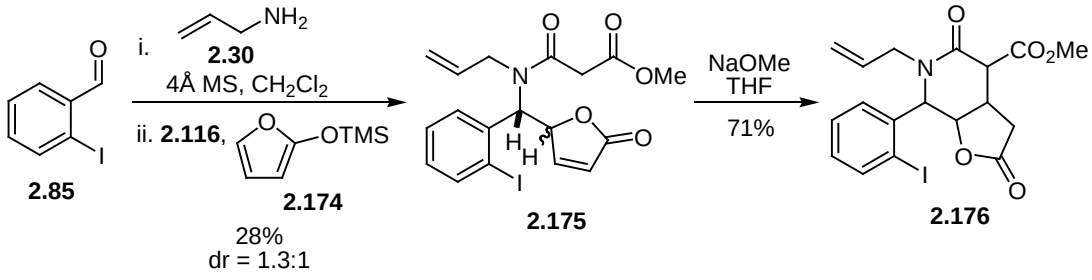
Initial investigations into this reaction were made using imine **2.170** (Scheme 2.57). When **2.170** was treated with methyl malonyl chloride and the TIPS-silyloxyfuran **2.171**, **2.172** was produced in good yield as an undetermined mixture of stereoisomers. Upon treatment of **2.172** with either NaH or NaOMe in THF cyclization occurred to generate **2.173**, again as an uncharacterized mixture of diastereomers.

Scheme 2.57



In order to generate a product functionalized to undergo a sequential intramolecular Michael reaction followed by a Heck cyclization iodobenzaldehyde **2.85** and allylamine were chosen as components along with methyl malonyl chloride and trimethylsilyloxy furan **2.174** (Scheme 2.58). The aldehyde and amine were condensed in CH_2Cl_2, and the intermediate imine was treated in situ with methyl malonyl chloride and **2.174** to generate the butenolide **2.175** as separable mixture (1.3:1) of diastereomers in a combined 28% yield. Similar low yields were obtained when the imine was generated via the bis(silyl)amine method and when the TIPS-silyloxyfuran **2.171** was utilized as the nucleophile. Subsequent treatment of the major diastereomer with NaOMe in THF resulted in the cyclization to give **2.176** in good yield.

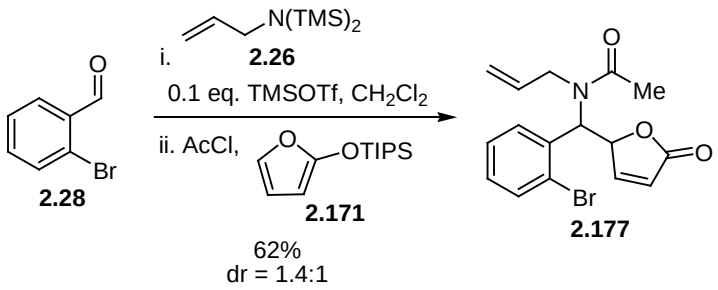
Scheme 2.58



The work on this project involving silyl ketene acetals has shown that in general low yields are obtained for reactions involving methyl malonyl chloride. For this reason the use of acetyl chloride as the acylating agent was investigated in conjunction with

TIPS-silyloxyfuran **2.171** in order to determine if there were unseen issues involving the silyloxyfuran that were contributing to the low yield in the above reaction (Scheme 2.59). When the imine formed in situ from the condensation of bromobenzaldehyde **2.28** and bis(trimethylsilyl)allylamine **2.26** in the presence of catalytic TMSOTf was treated with acetyl chloride and silyloxyfuran **2.171**, **2.177** was isolated in 62% yield as a 1.4:1 mixture of diastereomers. The increase in yield for this reaction as compared to the yields obtained for the synthesis of **2.176** suggests that the low yields obtained in the synthesis of **2.176** are in no small part attributable to the methyl malonyl chloride.

Scheme 2.59



The limited work done with silyloxyfurans has shown that they can be utilized in the 4CR to generate products that can be further elaborated into heterocyclic structures. The yields and diastereoselectivities for these reactions are still modest at best, and optimization would be needed in order for these sequences to be generally useful.

2.2.7 General Comments Involving the Methods of Imine Formation in the 4CR

Throughout this Chapter two methods were routinely utilized for synthesizing imines, and it is worth mentioning the merits of each of these methods in the 4CR. All of the imines utilized in this work can be cleanly accessed in virtually quantitative yields by the traditional method of condensing an aldehyde and an amine in the presence of molecular sieves, and if one desires, the crude imine can be isolated by filtering off the molecular sieves and concentrating the reaction mixture. The crude imine thus obtained

can then be utilized directly in subsequent 3CRs. However, when this method for imine formation is utilized in the 4CR, the yields of the reactions have been shown to be substrate dependent. In general, highly reactive nucleophiles like allylzinc bromide react under these conditions to provide the desired products in good yields, while subpar yields are generally obtained when less reactive nucleophiles like silyl enol ether **2.74** or silyl ketene acetal **2.105** are employed in the 4CR.

It is for these weaker nucleophiles that the bis(silyl)amine methodology routinely out performs the traditional method for imine formation. The higher yields in the reactions utilizing bis(silyl)amines can be attributed to the presence of TMSOTf, which serves to catalyze both the imine formation and the nucleophilic addition to the *N*-acyl iminium ion. While this leads one to believe that the low yielding 4CRs that involve the traditional method of imine formation being used in conjunction with nucleophile **2.74** or **2.105** can be improved upon by simply adding TMSOTf to reaction, preliminary results show that the addition of TMSOTf to reactions containing molecular sieves does not drastically improve yields (see Scheme 2.26). This problem can be easily remedied by removing the molecular sieves from the reaction mixture prior to the addition of the second set of reactants, and thus the use of bis(silyl)amines is not a requirement for these reactions. However, in cases where allylamine is used in conjunction with a silyl enol ether or silyl ketene acetal, the use of the commercially available bis(trimethylsilyl)allylamine **2.26** provides an operationally simple and high yielding alternative.

2.3 Conclusion

In an effort to develop new strategies for the rapid synthesis of diverse collections of heterocyclic compounds a four component reaction of aldehydes, amines, acid chlorides and π- and organometallic nucleophiles has been developed. By incorporating

the appropriate functional groups into each of the four inputs of the 4CR, one gains access to highly functionalized adducts that can be readily transformed into heterocyclic scaffolds in a short number of steps. The 4CR has been shown to be compatible with a number of differentially functionalized aryl and heteroaryl aldehydes, and allylzinc bromide, silyl enol ethers, silyl ketene acetals, and silyloxy furans have all been shown to be competent nucleophiles. The scope of the amine and acid chloride components have been explored to a lesser extent, but a number of functionalized examples of each have been reported. Thus, by selecting the four inputs carefully, structures were generated containing various aryl halides, olefins, and carbonyl groups that were then exploited in intramolecular Heck reactions, Diels-Alder and [3+2] cycloadditions, RCM, and Dieckmann condensations leading to a diverse collection of heterocyclic scaffolds. Additionally, the scaffolds generated using this strategy contain orthogonal functionality that can be further elaborated into more focused libraries, and work in this area is currently underway in the Martin group.

The 4CR is very well suited for DOS, as it is sufficiently versatile such that a wide range of functional groups can be incorporated for use in subsequent reactions. We have demonstrated that a number of different reactions can be sequenced with the 4CR, and one can envision numerous other possibilities that could further expand the scope of this process. A number of the scaffolds accessed by this strategy are found in both natural products and other biologically active compounds, further illustrating the utility of this process. The 4CR is also amenable to the synthesis of a variety of alkaloid natural products, and the efforts in this arena will be presented in Chapter 4.

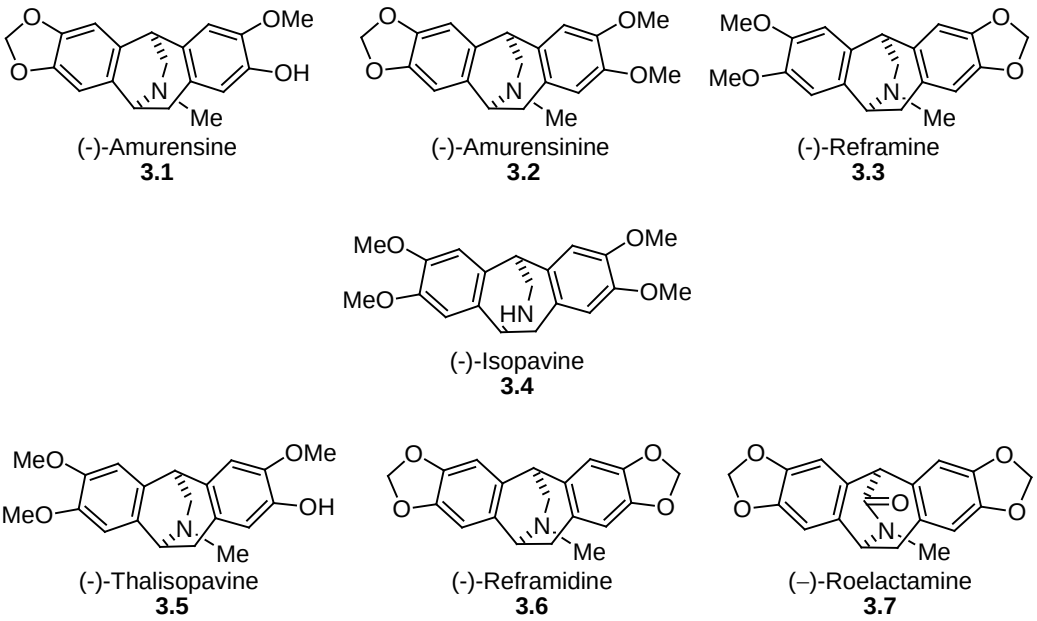
Chapter 3: The Isopavine and *Aspidosperma* Alkaloids

3.1 THE ISOPAVINE ALKALOIDS

3.1.1 Introduction

The isopavine alkaloids are a small family of tetracyclic tetrahydroisoquinoline natural products that are characterized by a doubly benzannulated azabicyclo[3.2.2]nonane core structure (Figure 1). [209, 210] Although the structure of synthetic isopavine (**3.4**) was first determined in 1958,[211] the first isolation of an isopavine alkaloid from natural sources did not occur until amurensine (**3.1**) was isolated from *Papaver nudicaule* var. *amurense* in 1960.[212] Since then members of this family have been isolated from numerous species of plants in the Papaveraceae family, as well as from plants in the Ranunculaceae family.[209, 210] Both natural and unnatural members of the isopavine family have been shown to possess interesting biological properties useful for the treatment of nerve system disorders like Alzheimer's disease, Parkinson's disease, and Hungtington's chorea, as well as the genetic disorder Down's syndrome.[213, 214] Synthetic isopavines have also been shown to be potent morphinomimetics[215] and are strong binders of the PCP receptor.[216, 217] The interesting aza-bridged bicyclic structure and biological profiles have made this family of natural products an attractive target for synthetic chemists and a number of approaches to the isopavine skeleton have been developed.

Figure 3.1



3.1.1.1 Roelactamine

(-)-Roelactamine (**3.7**) was isolated in 1992 by Gözler and Hesse from *Roemeria refracta* DC. (Papaveraceae).[218] It is the first and only known natural isopavine alkaloid that possesses a lactam functional group. The structure of **3.7** was assigned on the basis of its ^{1}H-NMR, IR, and mass spectral data, as well as through its conversion to (-)-reframidine (**3.6**) by reduction with $LiAlH_4$. There have been no reported biological studies for roelactamine, as well as no reported total syntheses.

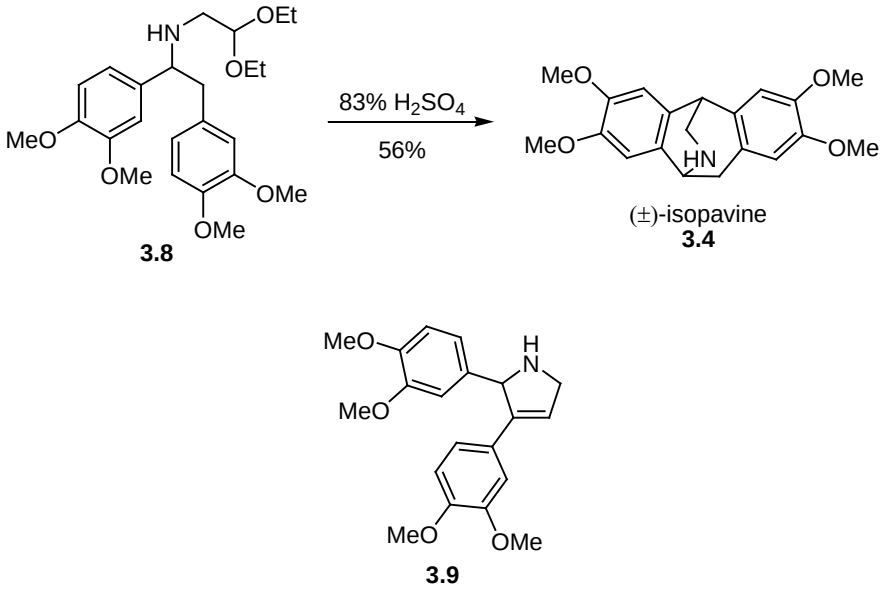
3.1.2 Synthetic Approaches to the Isopavine Alkaloids

3.1.2.1 Double Cyclization of Benzylaminoacetaldehyde Acetals

The first synthesis of the isopavine core was performed by Guthrie in 1955 (Scheme 3.1).[219] However, Guthrie erroneously assigned the structure of the compound obtained by treating aminoacetal **3.8** with H_2SO_4 to be the pyrrolidine **3.9**. The correct structure of the product of this reaction was later determined by Battersby and Yoewell to

be **3.4**, which was given the name isopavine.[211] This structural assignment was also independently corroborated by Waldmann and Chwala.[220]

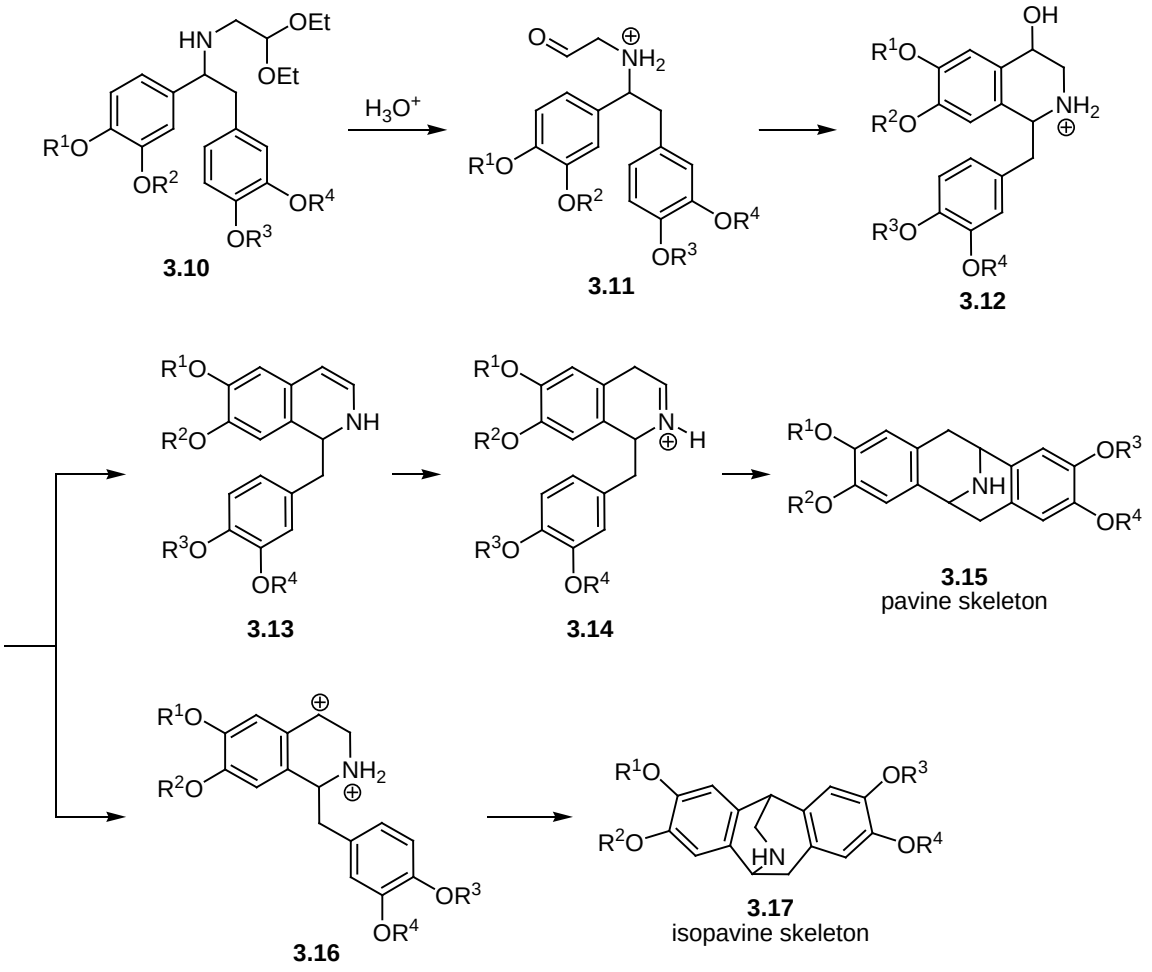
Scheme 3.1



The acid catalyzed double cyclization reaction of benzylaminoacetaldehyde dialkyl acetals similar to **3.10** has since become the classical approach to the isopavine skeleton and has been utilized in a number of syntheses. Mechanistically, this reaction is thought to proceed as shown in Scheme 3.2. Hydrolysis of the acetal gave an intermediary aldehyde, which undergwent nucleophilic addition to provide the 4-hydroxytetrahydroisoquinoline **3.12**. From **3.12** two reaction pathways are possible, leading to one of two isomeric products. The first pathway involves a dehydration to the 1,2-dihydrotetraisoquinoline **3.13**. Subsequent protonation generates iminium ion **3.14**, which undergoes cyclization to give the pavine skeleton. The alternative pathway involves ionization of the alcohol to give **3.16**, and subsequent cyclization affords isopavine **3.17**. Evidence for this proposed mechanism has been provided by the isolation of intermediate **3.12** from the reaction medium.[221-223] 4-

Hydroxytetrahydroisoquinolines have been suggested as intermediates in the biosynthesis of pavine and isopavine alkaloids,[224, 225] but no concrete evidence establishing the biosynthetic pathway has been reported.

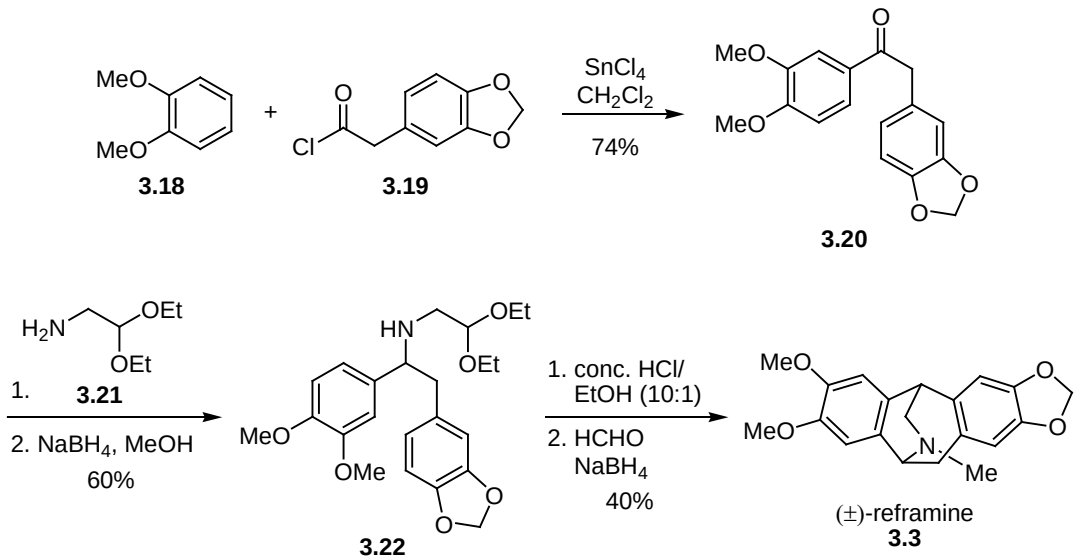
Scheme 3.2



The nature of the reaction conditions control which of the two mechanistic pathways is followed. At elevated temperatures, mixtures of isopavines and pavines are usually formed, while at room temperature the isopavines are formed almost exclusively.[210] The nature of the acid has also been shown to influence the product distribution.[226]

In order to exploit this double cyclization, a number of different routes to the key aminoacetal intermediates have been developed. One of the most common synthetic approaches involves the reductive amination of an appropriately substituted deoxybenzoin, and a representative example of this is outlined in Scheme 3.3.[225] The desired deoxybenzoin **3.20** was obtained in 74% yield from a Friedel-Crafts acylation of veratrole (**3.18**) with acid chloride **3.19**. The condensation of **3.20** with aminoacetaldehyde diethyl acetal (**3.21**) afforded an imine, which was subsequently reduced with $NaBH_4$ to provide **3.22**. The double cyclization of **3.22** proceeded in concentrated HCl/EtOH (10:1), and reductive amination with formaldehyde yielded (±)-reframine (**3.3**) in 40% yield over the two steps. Similar synthetic sequences have been reported in the syntheses of (±)-amurensinine (**3.1**),[224, 227] (±)-*O*-methylthalisopavine (**3.52**),[228] (±)-reframidine (**3.6**).[225]

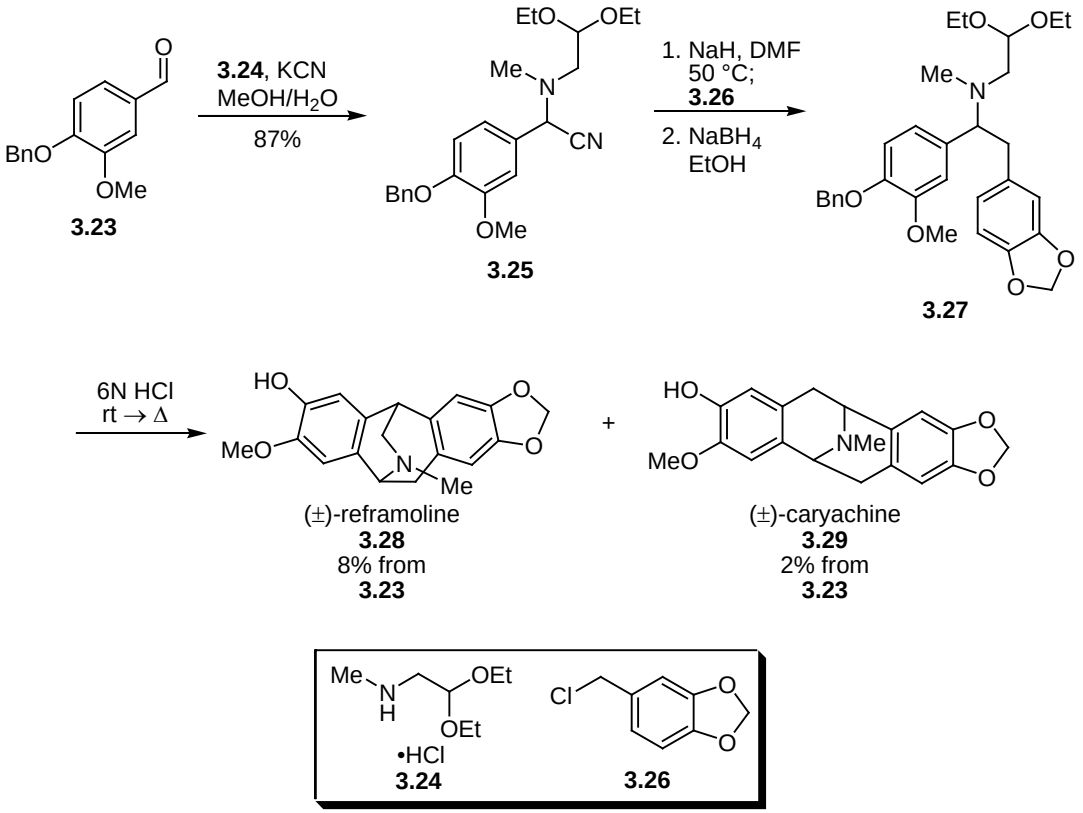
Scheme 3.3



A number of alternative routes to the key benzylaminoacetaldehyde dialkyl acetals have also been reported. Dyke has shown that aminoacetal **3.27** can be accessed via a Strecker/aminonitrile alkylation sequence (Scheme 3.4).[229] The condensation of

benzaldehyde **3.23** with amine **3.24** in the presence of KCN provided aminonitrile **3.25**. Alkylation of **3.25** with piperonyl chloride (**3.26**) and subsequent removal of the cyano group gave aminoacetal **3.27**, which was contaminated with a small quantity of the unalkylated amine. It was found that this impurity was more readily removed after the cyclization reaction. Upon treatment with 6N HCl, **3.27** underwent a double cyclization to deliver (±)-reframoline (**3.28**) in 8% yield over the four steps, along with 2% of the pavine alkaloid caryachine (**3.29**). The formation of **3.29** as a side product presumably resulted from the cyclization reaction being run at an elevated temperature.

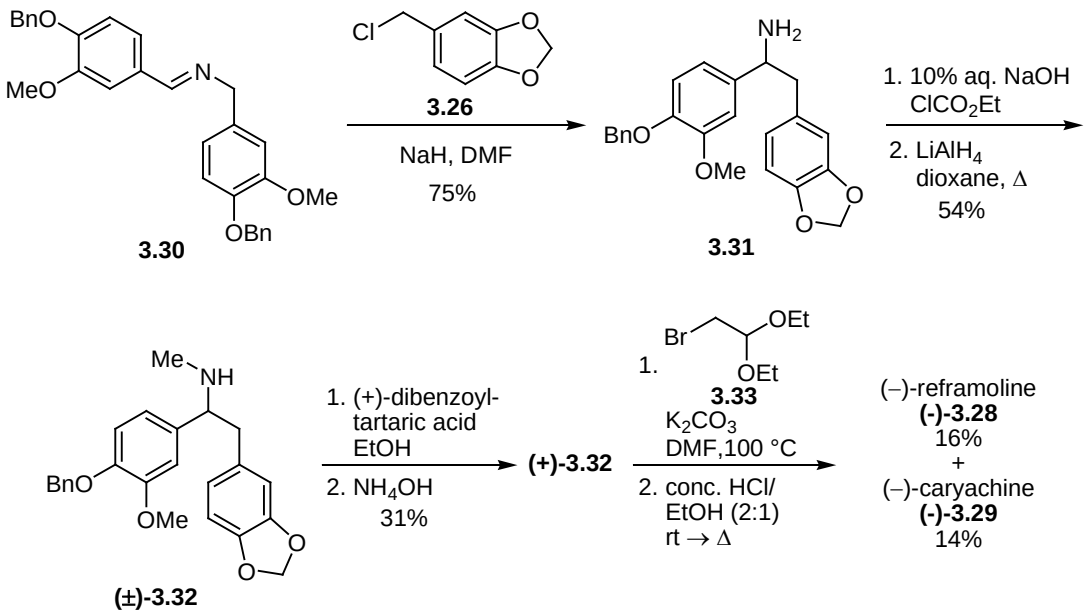
Scheme 3.4



A third approach utilized by Dyke and co-workers has allowed for access to enantiomerically enriched isopavine alkaloids (Scheme 3.5).[230] Thus, imine **3.30** was deprotonated with NaH, and the resulting anion was alkylated with **3.26** to give **3.31** in

75% yield after hydrolysis of the imine. The direct methylation of **3.31** was unsuccessful, so a two step acylation/reduction sequence was utilized to yield **3.32**. The secondary amine **3.32** was then resolved with (+)-dibenzoyltartaric acid to provide (+)-**3.32**. Subsequent alkylation with bromoacetal **3.33** and double cyclization afforded (-)-reframoline (**3.28**) and (-)-caryachine (**3.29**) in low yields. This synthesis was used to confirm the absolute configuration of the naturally occurring isopavines, and verified the results of Shamma and Nakanishi, who had previously determined the absolute configuration of (-)-amurensine by the 'aromatic chirality method of CD' analysis.[231]

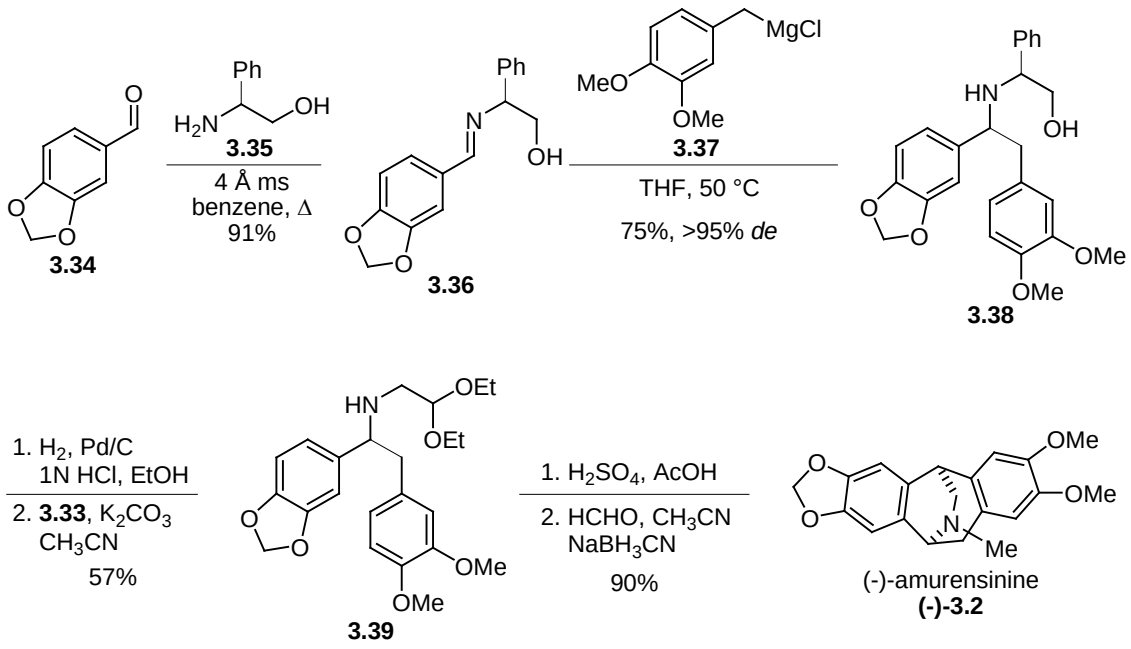
Scheme 3.5



A number of more modern approaches to the isopavine alkaloids that utilize a double cyclization have also been reported. The first of these routes was reported in 1996 by Badía and Domínguez, and constituted a concise approach to chiral isopavines of both natural and unnatural origin (Scheme 3.6).[232] Their synthesis of (-)-amurensinine began with the condensation of piperonal (**3.34**) with (*S*)-(+)-phenylglycinol (**3.35**) to provide imine **3.36**. The addition of benzyl Grignard reagent **3.37** to the imine afforded the

desired secondary amine **3.38** in good yield with excellent levels of diastereoselectivity. The chiral auxiliary could then be removed by hydrogenolysis, and the resulting primary amine was alkylated with **3.33** to furnish **3.39** in 57% yield over the two steps. The double cyclization of amine **3.39** occurred upon treatment with conc. H_2SO_4 in acetic acid, and subsequent reductive amination delivered (-)-amurensinine in excellent yields over the two steps. Then, by simply altering the substitution pattern on the starting aldehyde and Grignard reagent, the syntheses of (-)-*O*-methylthalisopavine and other unnatural isopavines could be achieved in an analogous fashion.

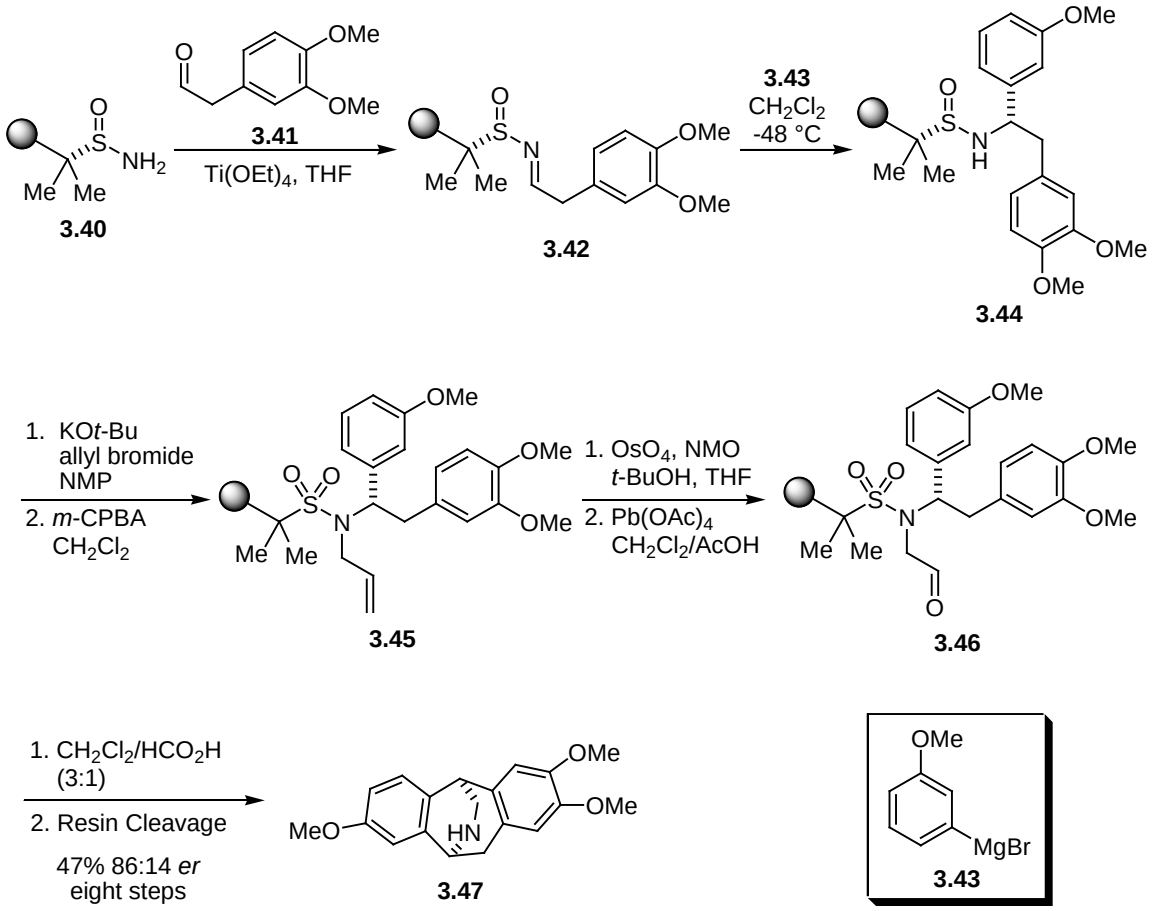
Scheme 3.6



Ellman has reported an enantioselective synthesis of the isopavine skeleton utilizing a resin bound chiral sulfinamide (Scheme 3.7).[233] Imine formation between the resin bound *t*-butansulfinamide **3.40** and aldehyde **3.41** provided **3.42**. Imine **3.42** was then treated with Grignard reagent **3.43** to yield **3.44**. *N*-Allylation and oxidation of **3.44** delivered **3.45**, which underwent subsequent dihydroxylation and oxidative cleavage to

give aldehyde **3.46**. Upon treatment with formic acid in CH_2Cl_2, aldehyde **3.46** underwent a double cyclization to generate the isopavine core, and resin cleavage provided **3.47** in 47% yield and 86:14 er over 8 steps. Although this route has been shown to give access to enantiomerically enriched isopavine scaffolds, its application to the synthesis of any of the isopavine natural products has not yet been reported.

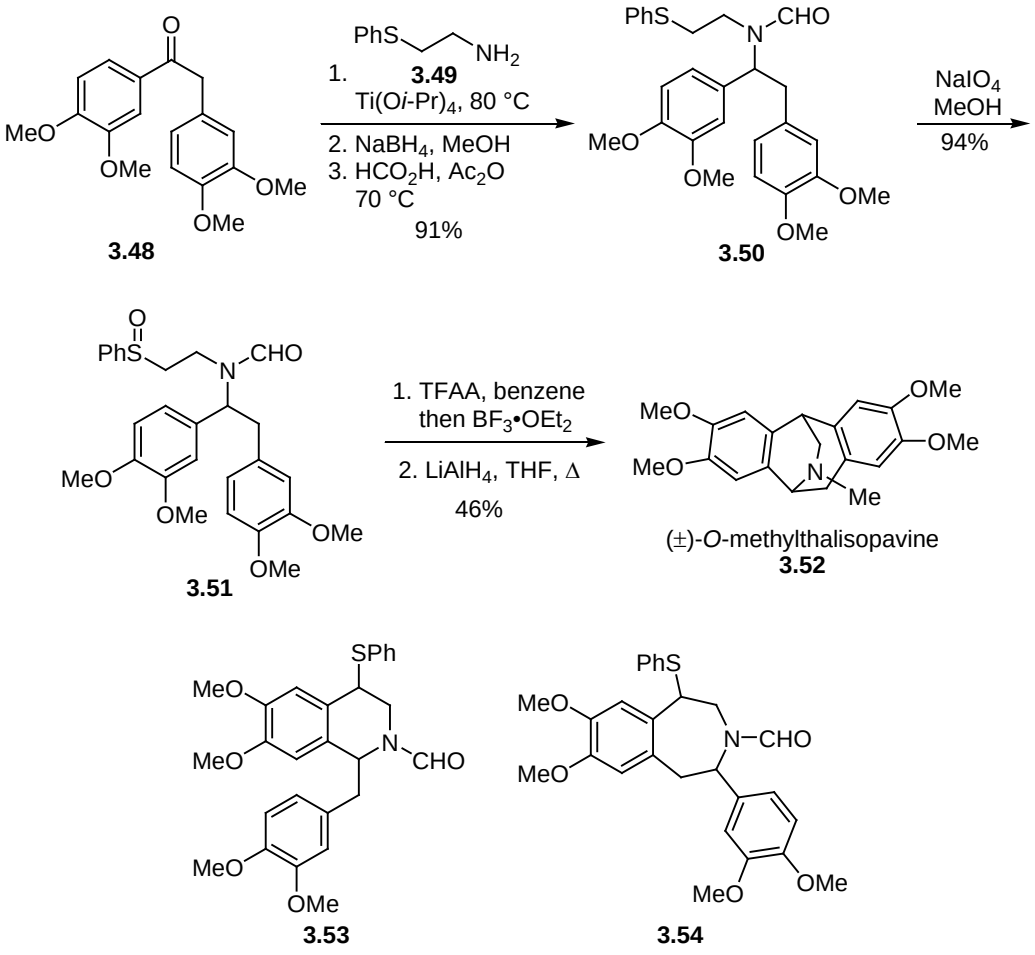
Scheme 3.7



The above routes to the isopavine alkaloids employ an aminoacetal similar to **3.10** in an acid catalyzed double cyclization. Alternatively, Sano has shown that the Pummerer reaction can be employed in a similar cyclization that led to the synthesis (±)-*O*-methylthalisopavine (**3.52**) (Scheme 3.8).[234] The reductive amination of deoxybenzoin

3.48 with 2-phenyl-thioethylamine (**3.49**) afforded an intermediary amine, which was formylated with formic acid/Ac_2O to give **3.50** in 91% yield. The thioether group in **3.50** was then oxidized with $NaIO_4$ in MeOH to give sulfoxide **3.51** in 94% yield. The treatment of **3.51** with trifluoroacetic anhydride (TFAA) in benzene initialized a cyclization via a Pummerer reaction to provide a mixture of **3.53** and **3.54**, which was treated in situ with $BF_3 \cdot OEt_2$ to furnish the *N*-formylisopavine. Subsequent reduction of the formyl group with $LiAl_4$ gave (±)-*O*-methylthalisopavine in 46% yield over the two steps. The Pummerer reaction is a milder alternative to the acid catalyzed double cyclization, but the lack of regiocontrol in the first cyclization limits its application to symmetrically substituted isopavines like **3.52**.

Scheme 3.8

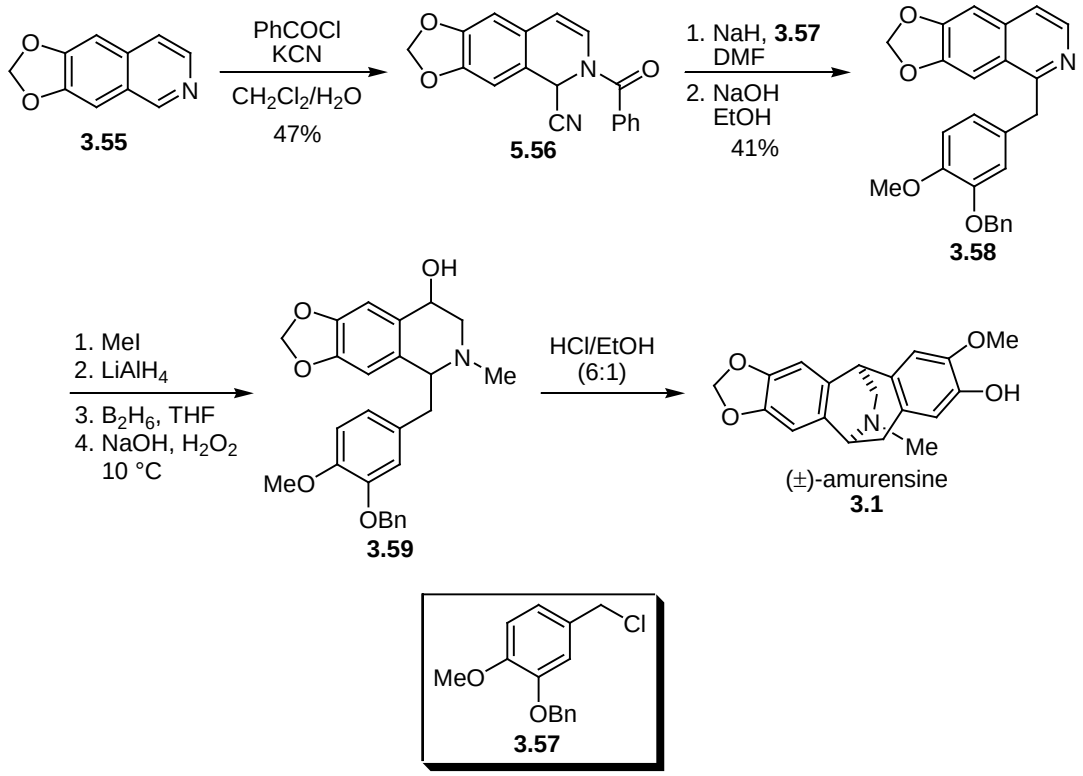


3.1.2.2 Syntheses of Isopavines from 4-Hydroxytetrahydroisoquinoline Derivatives.

The second common approach to the isopavine alkaloids involves the synthesis and subsequent cyclization of 4-hydroxytetrahydroisoquinoline derivatives. The synthesis of (±)-*O*-methylthalisopavine (**3.52**) by Dyke in 1971 was the first to utilize this approach,[225] and Dyke later used this strategy in establishing the structure of (±)-amurensine via its total synthesis (Scheme 3.9).[225, 235] A Ressiert reaction of the known isoquinoline **3.55** with benzoyl chloride and KCN furnished **3.56**. Alkylation of **3.56** with benzylchloride **3.57** and subsequent de-acylation afforded isoquinoline **3.58**.

Methylation of **3.58** and reduction with $LiAlH_4$ generated a 1,2-dihydroisoquinoline, which underwent a subsequent hydroboration/oxidation to yield the 4-hydroxytetrahydroisoquinoline **3.59**. Acid catalyzed cyclization provided (±)-amurensine (**3.1**), thus establishing the position of the phenolic-OH in the natural product. A similar route was later used to confirm the structure of (-)-thalidine (**3.67**).[236]

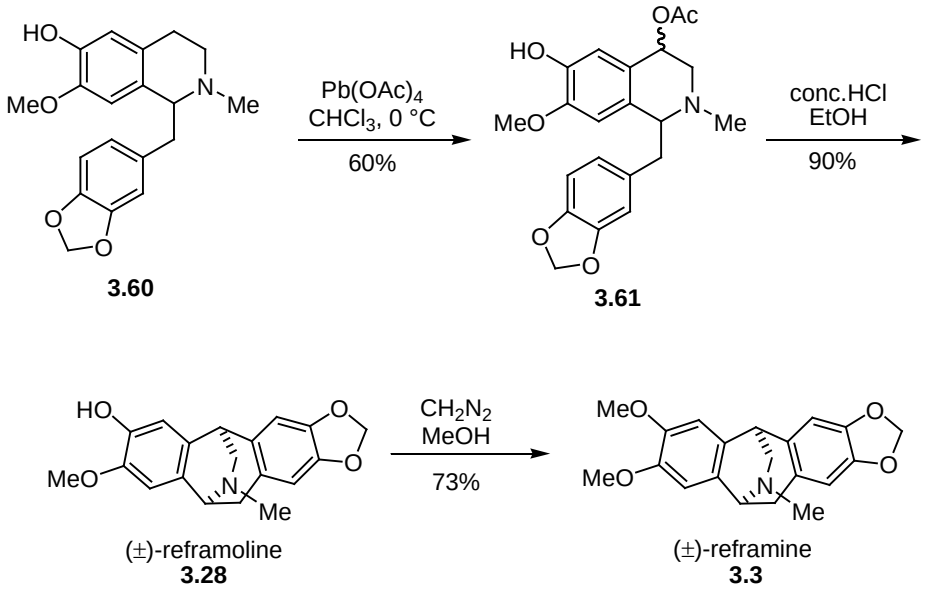
Scheme 3.9



A more commonly utilized approach to 4-hydroxytetrahydroisoquinoline derivatives involves the regioselective benzylic oxidation of an appropriate tetrahydroisoquinoline. The application of this tactic to the isopavine alkaloids was first reported by Umezawa and co-workers in 1973 (Scheme 3.10).[237, 238] The oxidation of 6-hydoxytetrahydroisoquinoline **3.60** with $Pb(OAc)_4$ in chloroform furnished the 4-acetoxytetrahydroisoquinoline **3.61** in 60% yield. Upon treatment with conc. HCl in

ethanol, **3.61** underwent cyclization to give reframoline (**3.28**) in 90% yield. Methylation of **3.28** with diazomethane provided reframine (**3.3**)

Scheme 3.10

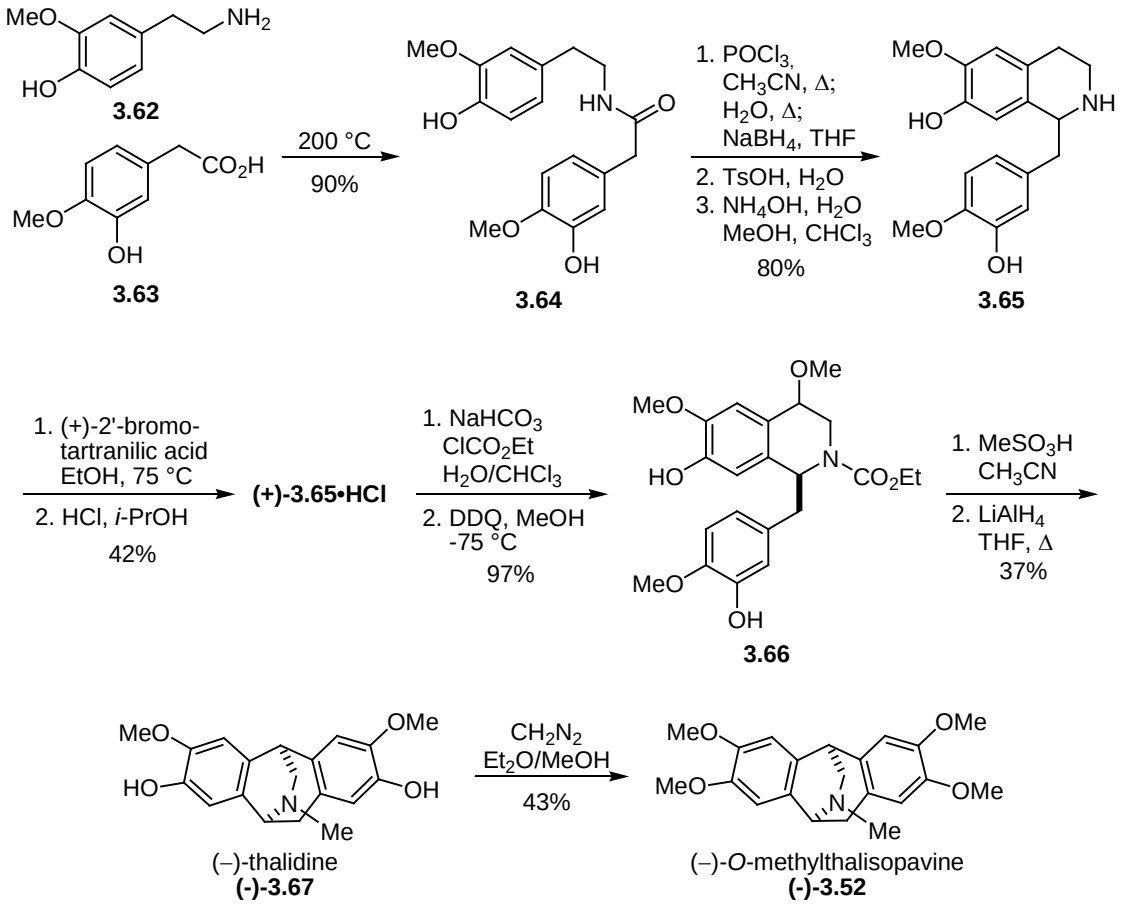


A similar oxidative approach has been utilized by Rice in the synthesis of (-)-thalidine and (-)-*O*-methylthalisopavine (Scheme 3.11).[239, 240] Rice's synthesis began with the condensation of phenethylamine **3.62** and acid **3.63** to give the amide **3.64** in 90% yield. Cyclization of **3.64** with $POCl_3$ and reduction of the resulting dihydroisoquinoline with $NaBH_4$ provided racemic *N*-norreticuline (**3.65**), which was purified via crystallization of its tosic acid salt. *N*-Norreticuline could be easily resolved by treating with 2'-bromotartranilic acid in ethanol, and upon treatment with HCl in 2-propanol the hydrochloride salt of **(+)-3.65** could be isolated with >99% optical purity.

With optically pure **(+)-3.63** in hand, attention was then turned towards the completion of the synthesis. Acylation of **(+)-3.63** with ethyl chloroformate and subsequent oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) provided **3.64** in 97% over the two steps. The cyclization of **3.66** proceeded smoothly in the presence

of methanesulfonic acid, and a borane reduction delivered (-)-thalidine (**3.67**). Methylation of **3.67** with diazomethane gave (-)-*O*-methylthalisopavine in 43% yield.

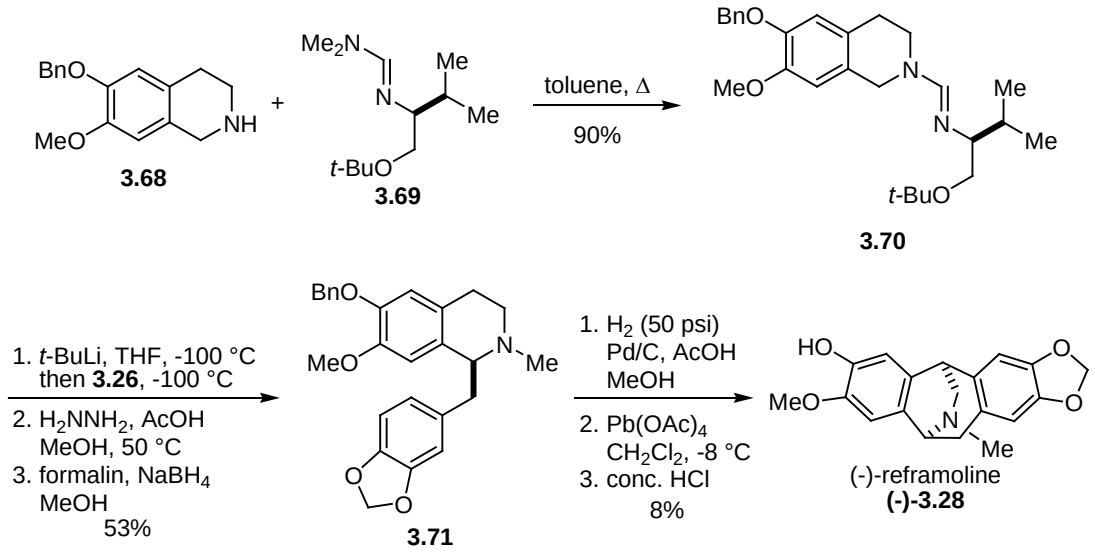
Scheme 3.11



Another oxidative approach to the isopavine skeleton has been reported by Meyers, who applied the chiral formamidine auxiliary to the asymmetric syntheses of (-)-*O*-methylthalisopavine and (-)-reframoline (Scheme 3.12).[241, 242] The synthesis began with the attachment of the chiral auxiliary to the tetrahydroisoquinoline **3.68**, which was accomplished in 90% yield by heating **3.68** and **3.69** in toluene. Deprotonation of **3.70** with *t*-butyllithium and trapping with the appropriate benzyl bromide at -100 ºC provided **3.71** in good yields. The *O*-benzyl group was then removed by hydrogenolysis, and the

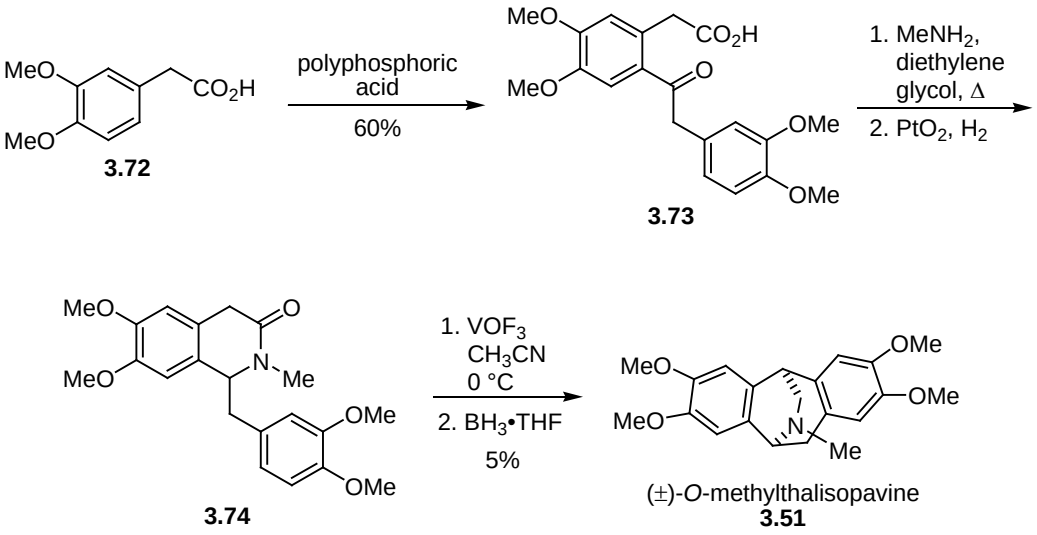
resulting phenol oxidized with $Pb(OAc)_4$ to give an intermediate quinol acetate which was cyclized into (-)-reframoline (**3.28**) upon treatment with concentrated HCl. The enantiomeric purity of **3.28** was found to be 98-99% based on its optical rotation. The yield for this last sequence was poor, but the authors commented that no efforts to optimize this reaction had been made.

Scheme 3.12



One of the few syntheses of a lactam containing isopavine was achieved by Elliot in his route to (±)-*O*-methylthalisopavine (**3.52**) (Scheme 3.13).[228] Treatment of acid **3.72** with polyphosphoric acid resulted in the formation of ketoacid **3.73** in 60% yield. Heating **3.73** with methylamine in diethylene glycol yielded an intermediary enamide, which was hydrogenated over PtO_2 to produce **3.74**. The yields for these steps were not reported. Upon treatment with VOF_3 in acetonitrile, isoquinolone **3.74** underwent oxidation and cyclization to give a lactam that was reduced with borane to give the natural product in only 5% yield.

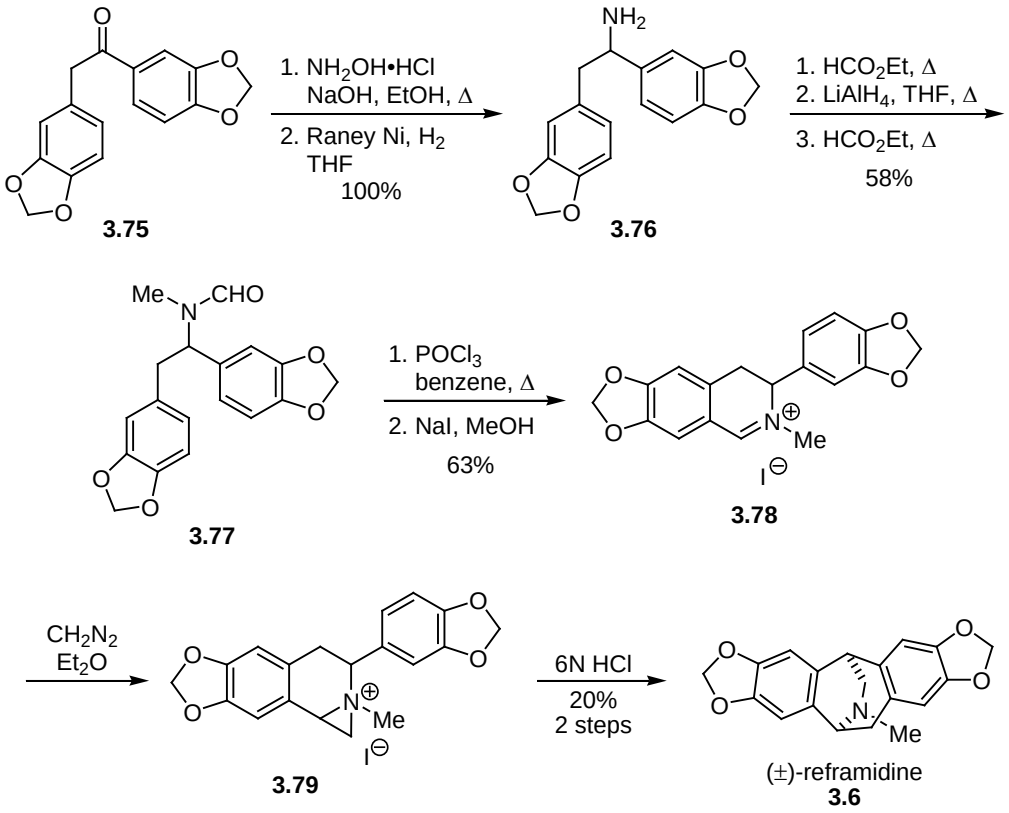
Scheme 3.13



3.1.2.3 Other Routes to the Isopavine Alkaloids

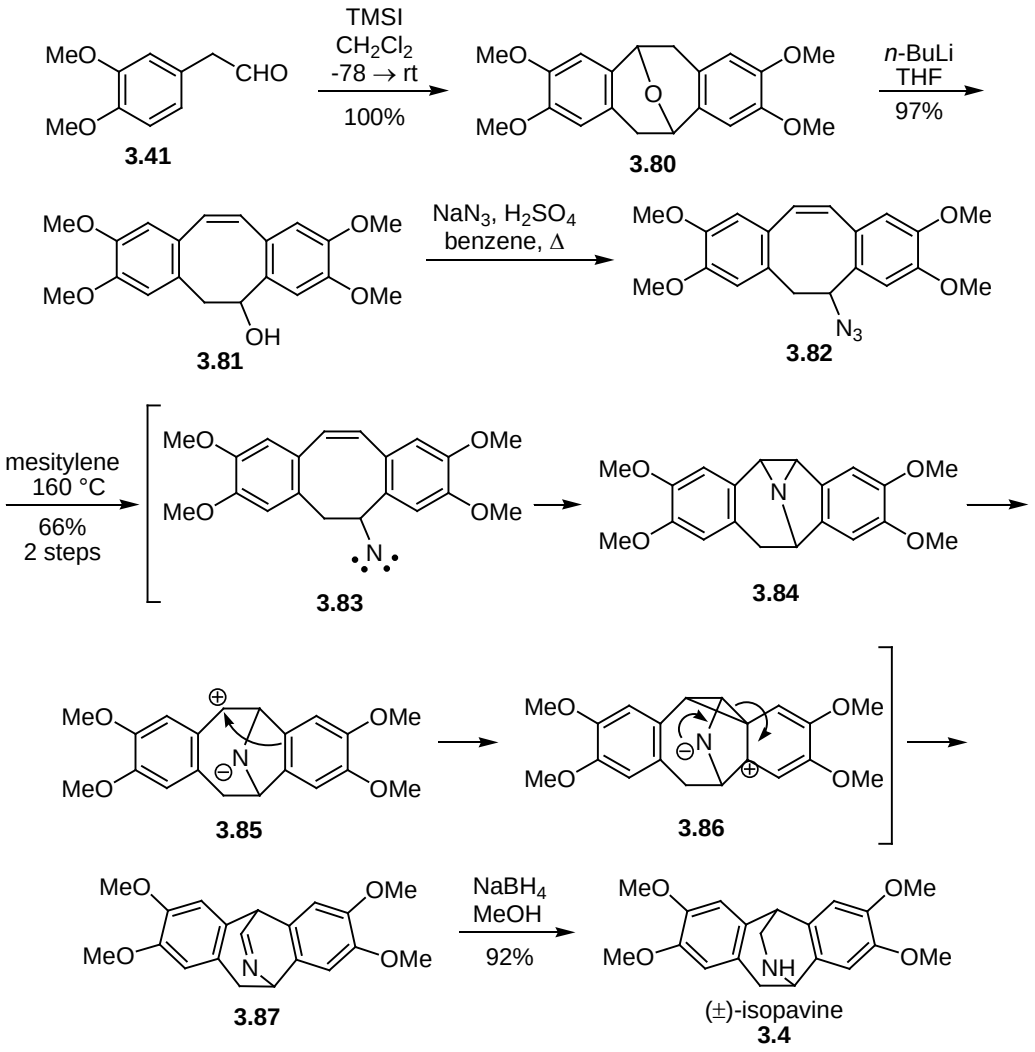
Kamenti has developed a novel approach to the isopavine skeleton involving the ring expansion of an aziridinium ion (Scheme 3.14).[243] The synthesis began with the condensation of **3.75** with hydroxyl amine, and subsequent reduction with Raney nickel furnished the requisite primary amine **3.76**. A three step formylation, reduction, and formylation sequence provided formamide **3.77** in 58% yield. A Bischler-Napieralski cyclization afforded the desired dihydroisoquinoline, which was treated with methyl iodide in diethyl ether to generate iminium ion **3.78**. When **3.78** was treated with ethereal diazomethane, the desired aziridinium salt **3.79** was formed in high yield. The crude **3.79** was treated immediately with 6N HCl to give reframidine (**3.28**) in 20% yield over the two steps.

Scheme 3.14



Jung has developed an expedient approach to the isopavine skeleton that was utilized in the synthesis of isopavine itself (Scheme 3.15).[244] The trimethylsilyl iodide catalyzed dimerization of phenylacetaldehyde **3.41** generated **3.80** in quantitative yield. Upon treatment with *n*-BuLi in THF, **3.80** underwent ring opening to yield **3.81**. Alcohol **3.81** was then converted to azide **3.82** upon treatment with NaN_3 and H_2SO_4 in refluxing benzene. Thermolysis of azide **3.82** in mesitylene at 160 ºC gave the dehydroisopavine **3.87** in 63% yield over the two steps. The authors propose that this reaction proceeds via the nitrene intermediate **3.83**, which aziridinates the proximal olefin to generate **3.84**. Subsequent ring opening of the aziridine and attack by the aromatic ring afforded **3.86**, which underwent a ring opening to give imine **3.87**. Reduction of **3.87** with $NaBH_4$ furnished isopavine in 93% yield.

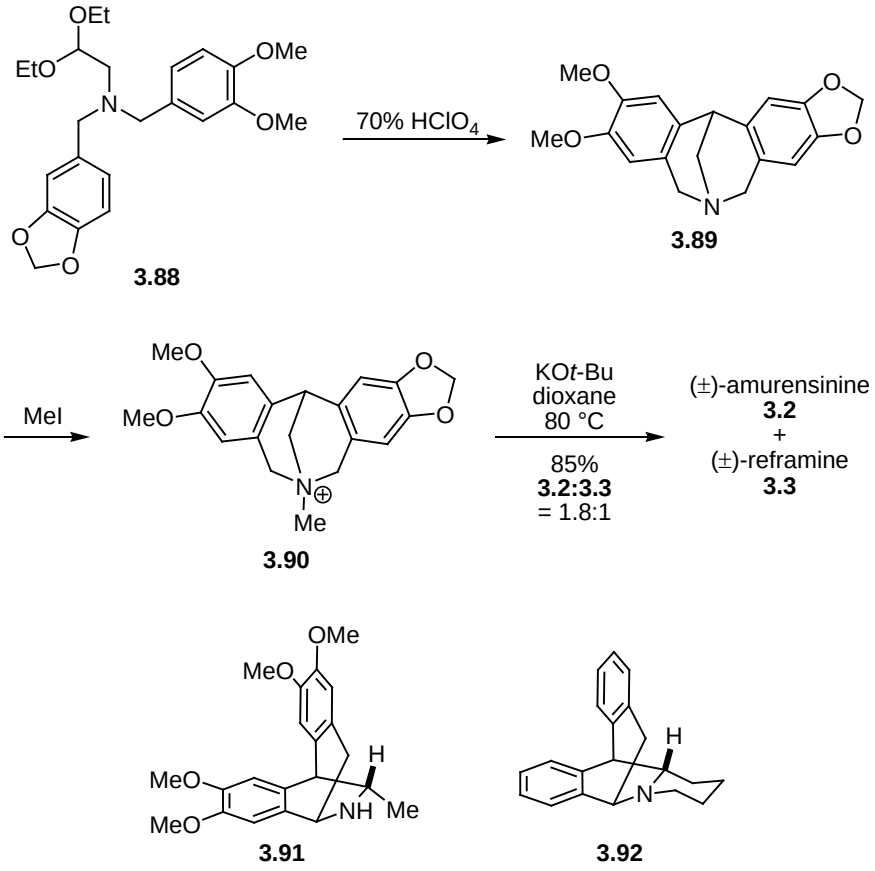
Scheme 3.15



The Stevens rearrangement has also been successfully applied to the synthesis of a number of isopavines. In 1978 Takayama reported the syntheses amurensinine (**3.2**) and reframine (**3.3**) using the Stevens rearrangement to construct the isopavine core (Scheme 3.16).[245] The aminoacetal **3.88** was cyclized under acidic conditions to give azocine **3.89**. Formation of the quaternary ammonium salt with methyl iodide provided **3.90**. Upon treatment with KOt-Bu in dioxane at 80 ºC, **3.90** underwent the desired rearrangement to provide a mixture (1.8:1) of **3.2** and **3.3** in 85% yield. The lack of

selectivity in this reaction detracts from what is otherwise a concise approach to the isopavine alkaloids, thereby limiting use of this approach to the synthesis of symmetrical isopavines. Hanessian has since applied this approach to the synthesis of a number of unnatural isopavine analogues similar to **3.91** and **3.92** that have been shown to be potent morphinomimetics.[215, 246, 247]

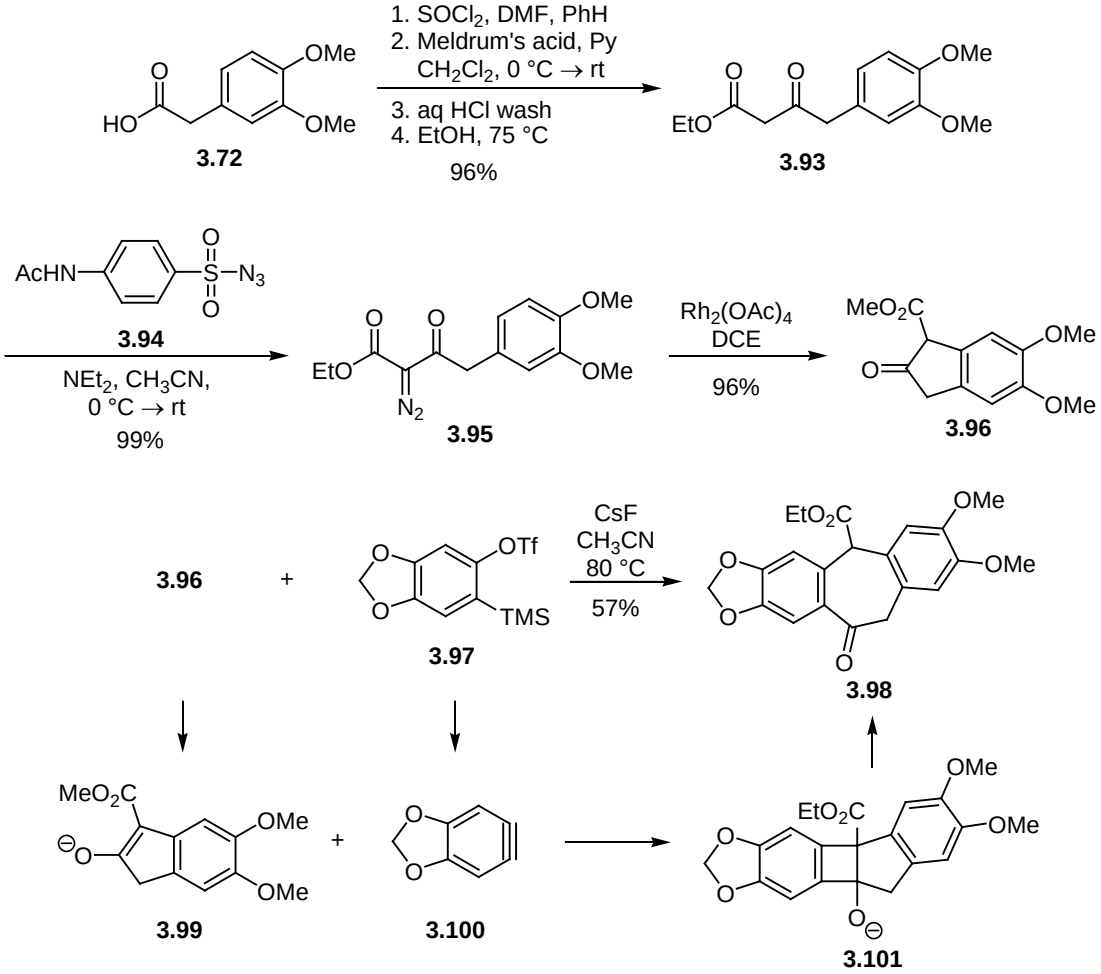
Scheme 3.16



The most recently reported synthetic effort towards this family of alkaloids was the total synthesis of (+)-amurensinine by Stoltz in 2006.[248] This synthesis featured the aryne acyl alkylation[249] and oxidative kinetic resolution[250] methodologies previously developed in the Stoltz group. The synthesis began with the four step homologation of acid **3.72** into β-ketoester **3.93** (Scheme 3.17). The diazo transfer reaction of **3.93**

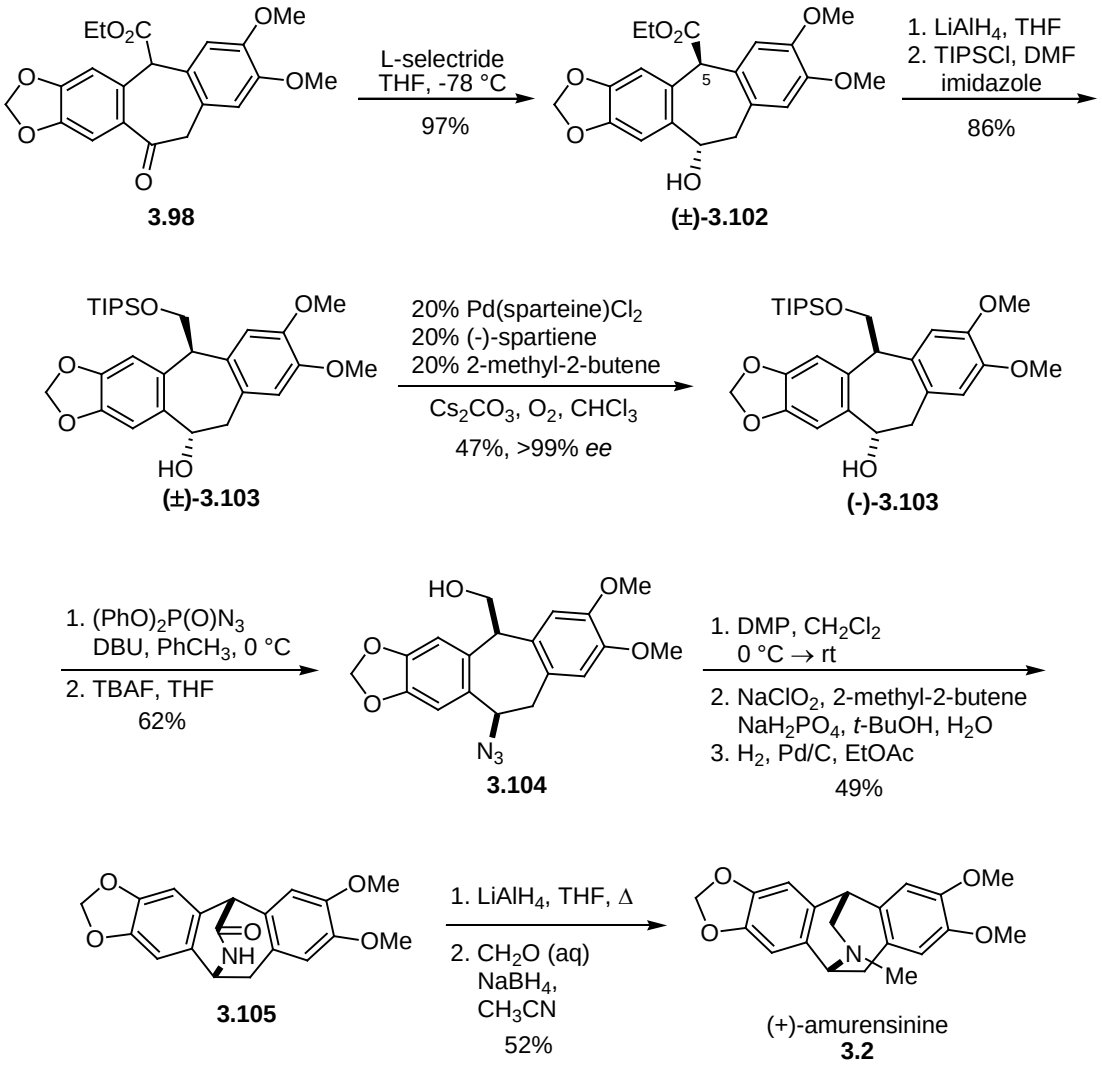
proceeded in almost quantitative yield to give **3.95**. Upon treatment with $Rh_2(OAc)_4$ in 1,2-dichloroethane, **3.95** reacted to form **3.96** selectively in 96% yield. With **3.96** in hand the key aryne acyl alkylation could be attempted. β-Ketoester **3.96** and **3.97** were treated with CsF in acetonitrile at 80 ºC to provide **3.98** in 57% yield. Mechanistically the reaction proceeds through aryne **3.100**, which reacts with **3.99** to yield cyclobutane **3.101**. Ring expansion of **3.101** proceeds to afford **3.98**. Thus, the complete carbon framework for amurensinine had been assembled and all that remained was the installation of the nitrogen bridge.

Scheme 3.17



The completion of the synthesis commenced with a diastereoselective reduction of ketone **3.98** with L-selectride to give **3.102** (Scheme 3.18). The methyl ester was then reduced with $LiAlH_4$, and the resulting primary alcohol protected as its TIPS-ether. Alcohol **(±)-3.103** then underwent the oxidative kinetic resolution to provide **(-)-3.103** in 47% yield and >99% ee. Conversion of the secondary alcohol to the azide and removal of the TIPS-ether afforded **3.104** in 62% yield. Two step oxidation of alcohol **3.104** to the corresponding carboxylic acid proceeded smoothly, and subsequent hydrogenation of the azide provided lactam **3.105**. It is worthy to note that the reduction of the ester **3.102** and its later re-oxidation was necessary, as efforts to install the azide on the enantioenriched form of **3.102** resulted in substantial epimerization at C-5. From lactam **3.105**, (+)-amurensinine could be obtained in 52% after $LiAlH_4$ reduction and methylation. The lengthy sequence of reactions required to convert **3.98** into the natural product without the loss of enantiopurity makes this synthesis the longest of all the approaches to the isopavine alkaloids.

Scheme 3.18



3.1.3 Conclusion

Although the isopavine alkaloids are a small family of natural products, a number of syntheses of these alkaloids have been reported. The classic approach to the isopavine core is the acid catalyzed double cyclization of benzylaminoacetaldehyde dialkyl acetals similar to **3.10**. The route developed by Badía and Domínguez utilizes this approach,[232] and is arguably one of the best methods for synthesizing natural and unnatural isopavines in enantioenriched form. The second most commonly utilized approach is the cyclization

of 4-hydroxytetrahydroisoquinoline derivatives, and a number of approaches to the isopavines have been developed utilizing this approach. The most notable of these approaches are the those of Rice[240] and Meyers[241] that allow for the enantioselective syntheses of the isopavine family.

Notably lacking is a synthesis of roelactamine, which is the only known naturally occuring lactam containing isopavine alkaloid. Only two syntheses of lactam containing isopavines have been reported, and these lactams were accessed as intermediates in routes to other isopavine alkaloids. The first of these was by Elliot, who utilized a low yielding vanadium mediated oxidation and cyclization of isoquinolone **3.72** to form a lactam that was subsequently reduced (Scheme 3.13). The second lactam containing isopavine was synthesized by Stoltz in route to (+)-amurensinine. Although both of these routes could potentially be applied to the synthesis of roelactamine, neither is readily amenable to the synthesis of roelactamine analogues that could be utilized in biological assays. The route developed by Stoltz is too lengthy to be of practical use is this arena, while the route developed by Elliot would need to be modified to access anything other than symmetrically substituted isopavines. Due to the interesting biological activities shown by other members of this family, it is desirable for chemists to develop an efficient route to roelactamine that is also amenable to the synthesis of unnatural analogues, so that the biological properties of these lactam containing isopavines can be studied.

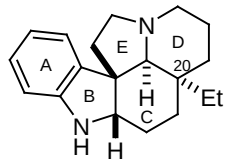
3.2 THE *ASPIDOSPERMA* ALKALOIDS

3.2.1 Introduction

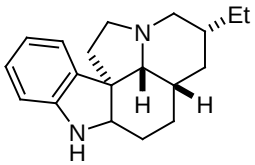
The *Aspidosperma* family of alkaloids is one of the largest families of indole alkaloids known, and over 250 unique alkaloids have been isolated from numerous plant sources.[251-253] The aspidospermine alkaloids are characterized by a pentacyclic

framework, which is exemplified by the structure of aspidospermidine (**3.106**) (Figure 3.2). The vast majority of the members of this family contain substitution at C20, usually in the form of an angular ethyl substituent. Exceptions to this are few, with the most notable being the pseudoaspidospermidine-pandoline group, represented by pseudoaspidospermine (**3.107**). Also included in this class of natural products is the quebrachamine group, exemplified by quebachamine itself (**3.108**). Members of the aspidospermine family have been shown to display a number interesting biological activities. Of particular interest are the bisindole alkaloids related to vinblastine (**3.111**), which is currently used as an antitumor drug.[254]

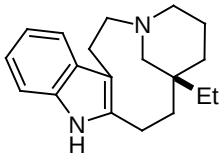
Figure 3.2



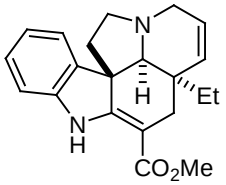
(-)-Aspidospermidine
3.106



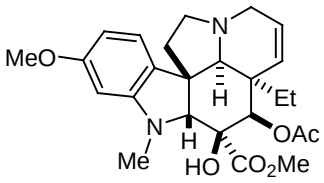
Pseudoaspidospemine
3.107



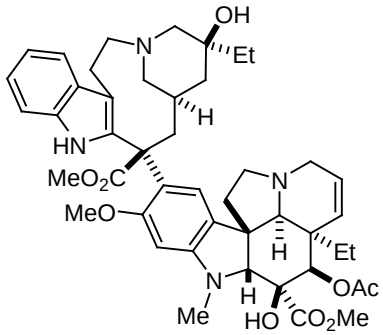
(–)-Quebrachamine
3.108



(-)-Tabersonine
3.109



(-)-Vindoline
3.110



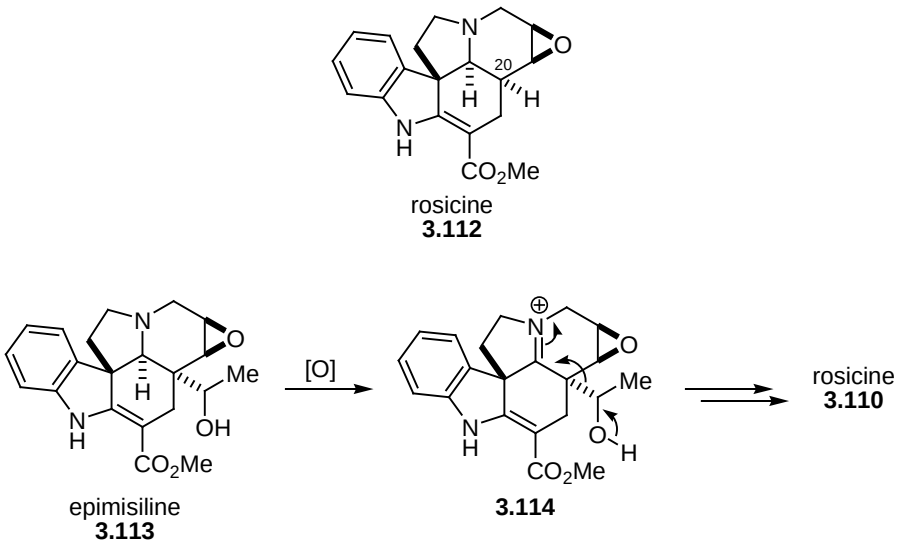
Vinblastine
3.111

3.2.1.1 Rosicine

Rosicine (**3.112**) was isolated in 1984 from *Catharanthus roseus* and is one of the rare *Aspidosperma* alkaloids lacking the angular C20-ethyl group.[255] The structure of rosicine was determined on the basis of its 1D and 2D-NMR, IR, and mass spectral data.

Rosicine is thought to arise from epimisiline (**3.113**) via oxidation and subsequent fragmentation of iminium **3.114** (Scheme 3.19).[255] There have been no reported syntheses of rosicine, nor any reports of its biological activity.

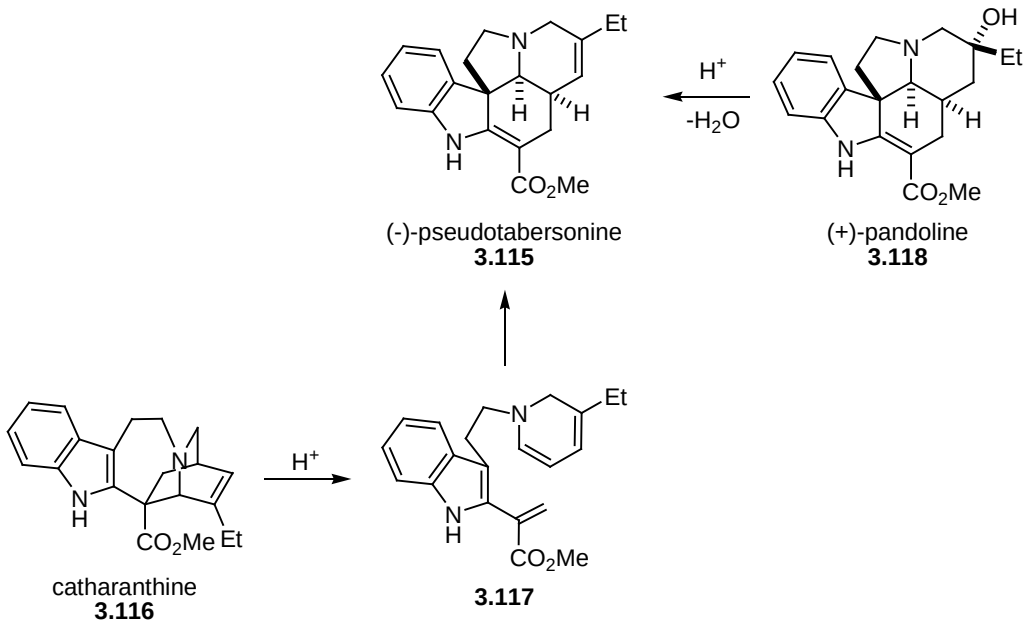
Scheme 3.19



3.2.1.2 Pseudotabersonine

Pseudotabersonine (**3.115**) was first in isolated in 1975 from *Pandaca caducifolia*.[256] Prior to that, **3.115** had been known as a product of the acid catalyzed rearrangements of caranthanine (**3.116**),[257-260] and as a product of the acid catalyzed dehydration of pandoline (**3.118**)[261] (Scheme 3.20). To date there have been two reported total syntheses of (±)-pseudotabersonine. The first of these was reported by Kuehne in 1992,[262] and was followed a year later Grieco's elegant synthesis[263] (see Section 3.2.3). There has been no reported biological activity for **3.115**.

Scheme 3.20



3.2.2 Syntheses of the *Aspidosperma* Alkaloids

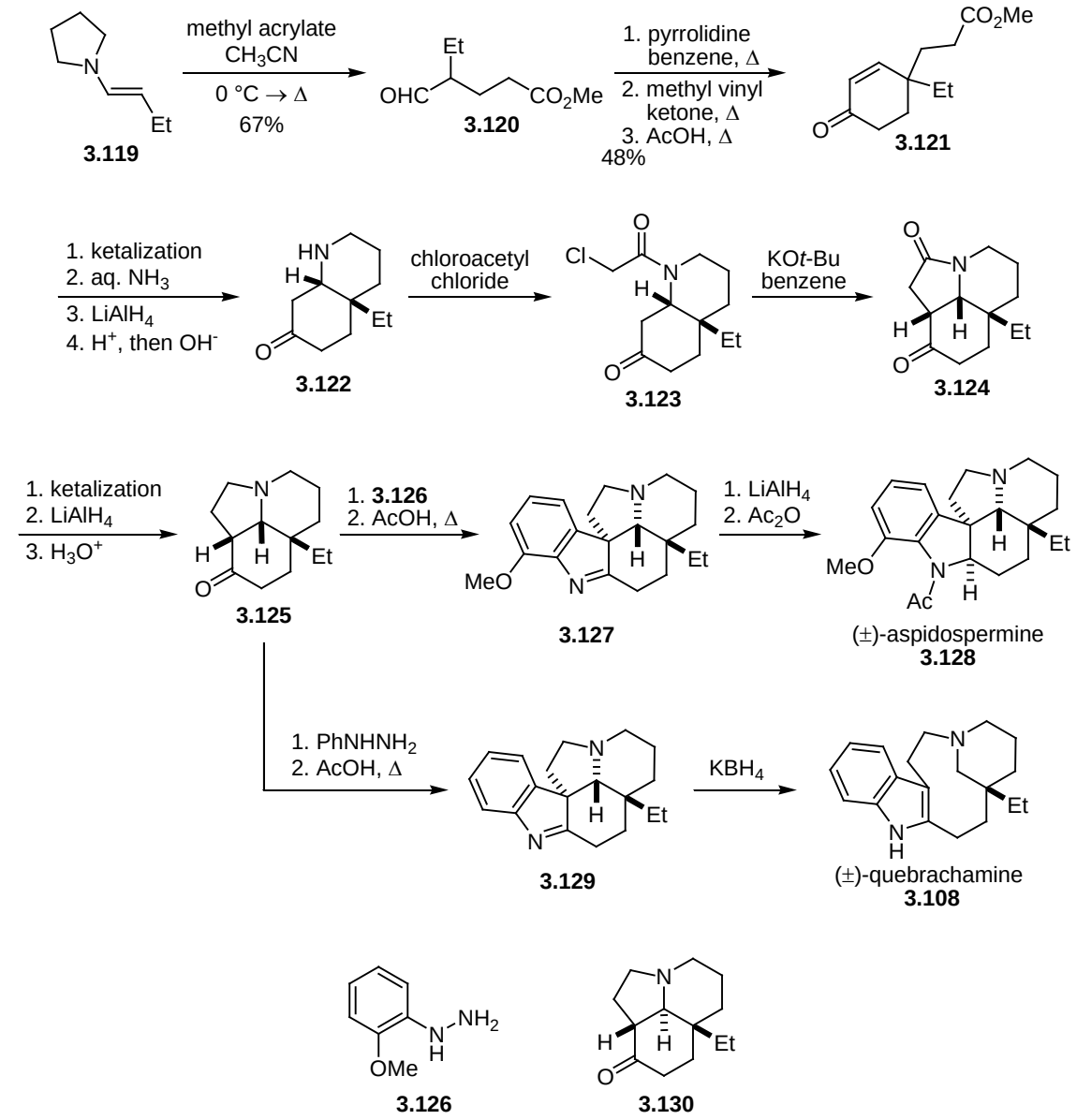
Due to their interesting structural features and biological activities, the aspidospermine alkaloids have attracted an extraordinary amount of attention from the synthetic community.[251-253, 264] The first total synthesis of a member of this family was Stork and Dolfini's synthesis of aspidospermine (**3.128**) and quebrachamine in 1963.[265] Since then over 50 different research groups have reported syntheses of various members of the aspidospermine alkaloids. The remainder of this Section will focus on describing some of the work in this field as an overview of the more commonly utilized approaches to the *Aspidosperma* alkaloids.

3.2.2.1 Syntheses Involving the Stork-Dolfini Ketone

Stork and Dolfini completed the first total synthesis of aspidospermine (**3.128**) and quebrachamine (**3.108**) in 1963.[265, 266] Their synthetic route focused on the use of enamine chemistry to synthesize ketone **3.125**, which has since been named the Stork-

Dolfini ketone (Scheme 3.21). Enamine **3.119**, readily available from the condensation of pryrrolidine and butyraldehyde, was reacted with methyl acrylate to give aldehyde **3.120** in 67% yield.[267] The enamine of **3.120** was formed by condensation with pyrrolidine and subsequently reacted with methyl vinyl ketone to generate a keto-aldehyde that underwent an aldol condensation in refluxing acetic acid to provide cyclohexenone **3.121** in 48% yield over the three steps. The ketone in **3.121** was then protected as its ketal, and the methyl ester was converted to the primary amide with aqueous ammonia. The amide was then reduced to the primary amine with $LiAlH_4$, and after hydrolysis of the ketal and treatment with base, the hydroquinoline **3.122** was formed. The conversion of **3.122** into the tricyclic amide **3.124** was achieved in two steps by the acylation of **3.122** with chloroacetyl chloride and treatment of the resulting amide **3.123** with KO*t*-Bu to provide tricycle **3.124**. Selective reduction of the amide in **3.124** was achieved through a three step sequence that involved the protection of the ketone as its ketal, reduction of the amide with $LiAlH_4$, and hydrolysis to give the key aminoketone **3.125**. Fisher indole synthesis with hydrazine **3.126** afforded indolenine **3.127**, which could be reduced with $LiAlH_4$ and acylated to provide (±)-aspidospermine (**3.128**). Alternatively, the Fisher-indole synthesis with phenylhydrazine gave an intermediate indolenine **3.129** that could undergo reductive cleavage with KBH_4 to generate (±)-quebrachamine (**3.108**). Thus, Stork's syntheses of aspidospermidine and quebrachamine were completed in 18 and 17 steps, respectively, from butyraldehyde and pyrrolidine.

Scheme 3.21

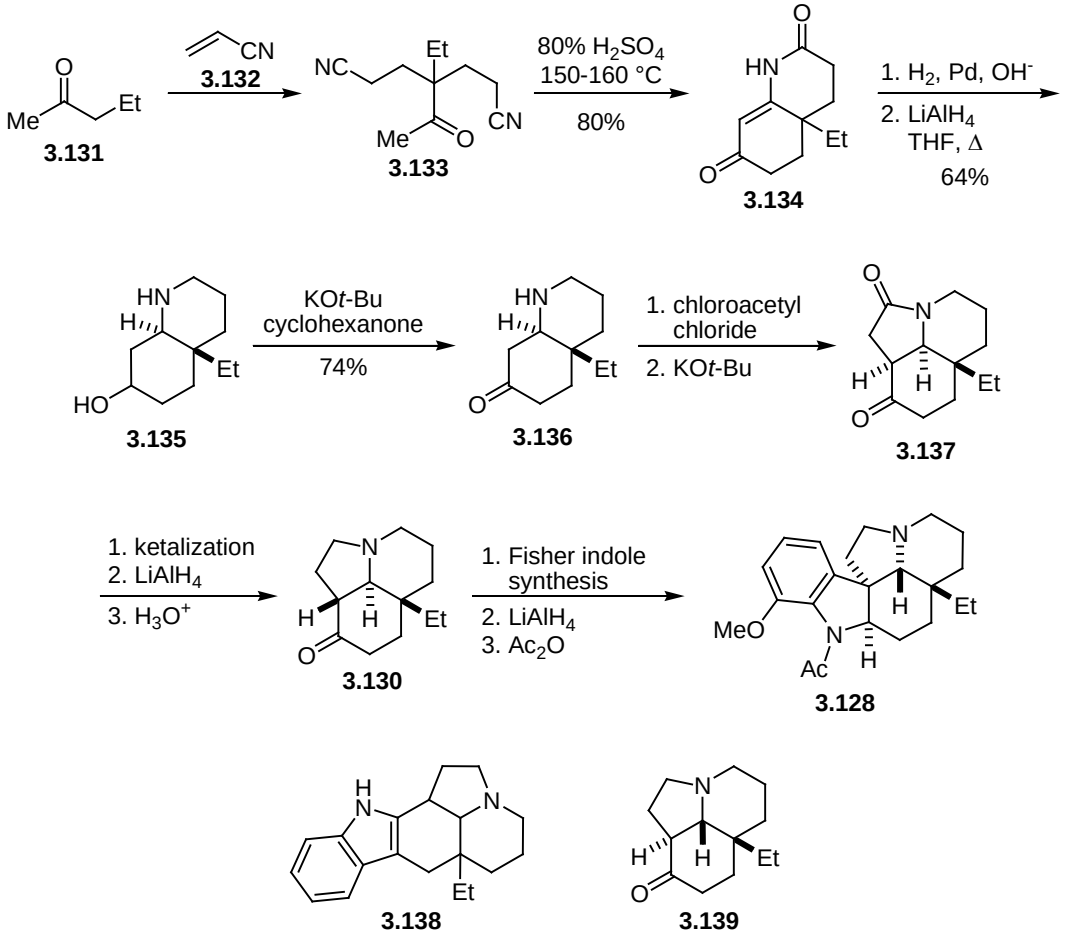


After Stork's initial synthesis, ketone **3.125** became a popular target for synthetic chemists. However, Stork had originally assigned the structure of **3.125** to be that of the *trans*-fused **3.130**. This error did not become apparent until after Ban completed a synthesis of aspidospermidine in 1965.[268] Ban's route was conceptually very similar to

that of Stork's, but due to differences in the stereochemistry of the intermediates did not actually intercept any of Stork's intermediates (Scheme 3.22).

Ban's synthesis began with the double conjugate addition of 2-pentanone (**3.131**) to acrylonitrile to provide **3.133**. Methyl ketone **3.133** was partially hydrolyzed and cyclized in 80% H_2SO_4 at elevated temperatures to give the unsaturated ketoamide **3.134** in 80% yield. Hydrogenation of **3.134** under basic conditions generated the saturated ketoamide, which was reduced with $LiAlH_4$ to provide amino alcohol **3.135** in 64% yield over the two steps. Alcohol **3.135** then underwent an Oppenauer oxidization with KO*t*-Bu in cyclohexanone to give ketone **3.136**. From aminoketone **3.136** the synthesis of aspidospermine was completed using Stork's previously reported route. However, Ban's intermediates were *trans*-fused, as opposed to Stork's *cis*-fused intermediates. Interestingly, Ban was also able to isolate indole **3.138** as a side product from the Fisher indole synthesis, and later commented on the formation in this reaction of an isomer of deacetylaspidospermine with a *trans*-CD ring fusion.[269] It is noteworthy that Ban had also originally incorrectly assigned the structure of **3.130** and initially believed that the structure was that of **3.139**.

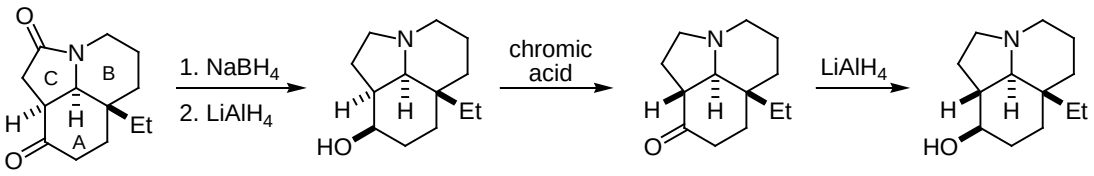
Scheme 3.22



Upon comparison of the physical and spectral data for **3.137** and **3.130** to Stork's intermediates **3.124** and **3.125**, it was apparent that the compounds synthesized with these two routes were not identical. In order to garner more evidence towards the proper structures of tricyclic ketones **3.125** and **3.130**, additional studies were undertaken by the Ban group. After preliminary investigations involving model compounds lacking the C20 ethyl group showed that compounds such as **3.125** and **3.130** could epimerize under the conditions of the ketal hydrolysis, the relative stereochemistry of these compounds was called into question.[270] The A/B *trans*-aminoketone **3.137** was independently synthesized, and subjected to the reaction sequence shown in Scheme 3.23.[271] The

reduction of **3.137** with $NaBH_4$ gave an alcohol that was subsequently reduced with $LiAlH_4$ to give aminoalcohol **3.140**. Oxidation of **3.140** with chromic acid yielded ketone **3.130**, which was then reduced with $LiAlH_4$ to provide the diastereomeric alcohol **3.141**. Because the structures of **3.140** and **3.141** were different, it was concluded that an epimerization must have occurred under the acidic conditions of the oxidation. Both **3.140** and **3.141** exhibited Bohlmann bands in their respective IR spectra, indicating that A/B ring fusion was in fact *trans*. Aminoketone **3.130** was identical with the one previously utilized in the Ban's synthesis of aspidospermidine, thus establishing the correct structure for Ban's proposed intermediate **3.139**. This also meant that the intermediate thought by Stork to be **3.130**, was in fact the all *cis*-**3.125**.

Scheme 3.23

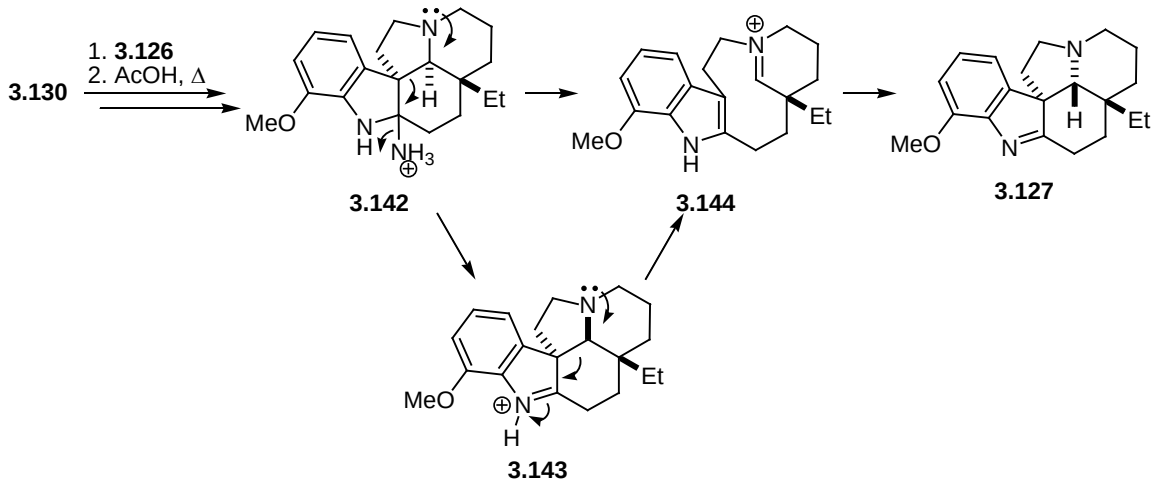


3.137 **3.140** **3.130** **3.141**

While the stereochemistry present in Ban's aminoketone **3.130** is different from that found in the natural product, it eventually led to the natural product. This meant that during the course of the Fisher indole synthesis Ban's intermediate **3.130** had to undergo an epimerization. Stork, initially thinking he had made **3.130**, proposed two possible mechanisms for this epimerization (Scheme 3.24).[266] The first explanation is that the final intermediate in the Fisher indole synthesis, **3.142**, undergoes a fragmentation to give **3.144**, which would cyclize to give the more stable *cis*-indoleine **3.127**. This pathway could presumably be lower in energy than the elimination pathway leading to the strained *trans*-indolenine. The second possible pathway for epimerization arises from the fact that under the conditions of the Fischer indole synthesis, the initially formed *trans*-indolenine

3.142 can undergo a retro-Mannich process, also leading to iminium ion **3.144**. Thus, regardless of whether or not the proposed fragmentation occurs, the *cis*-indolenine should still be the major product of the reaction. However, as previously mentioned Ban was able to isolate the deacetylaspidospermine with a *trans*-CD ring fusion, indicating that the complete epimerization **3.143** does not occur.

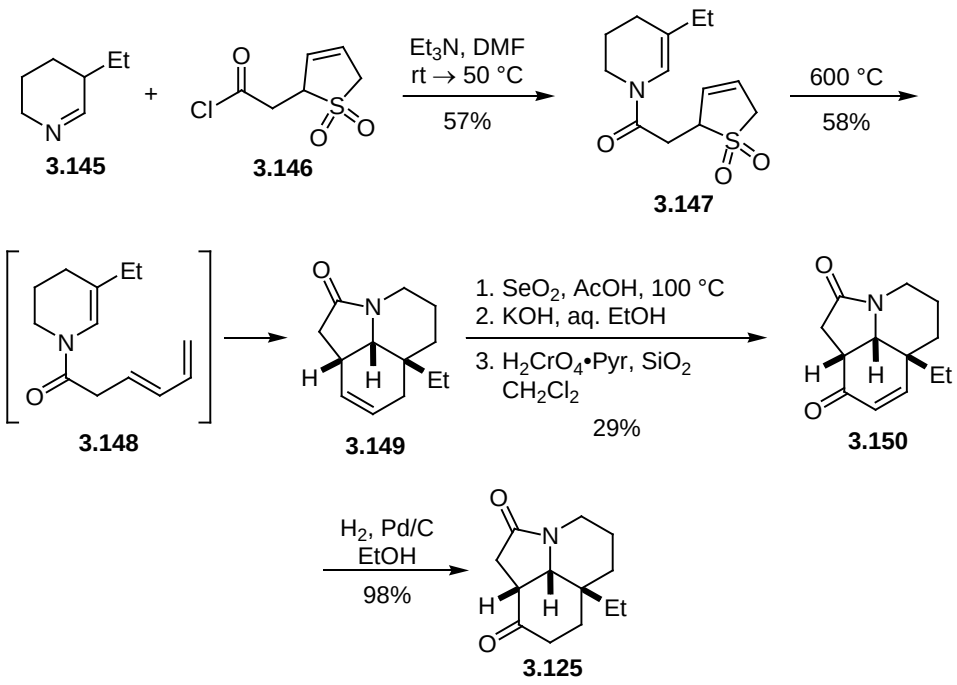
Scheme 3.24



Since the pioneering works of Stork and Ban a number of different routes to **3.125**, or compounds related to **3.125** have been developed. Martin reported an approach to **3.125** that utilizes an intramolecular Diels-Alder cycloaddition to construct the *cis*-fused tricyclic framework (Scheme 3.25).[272] The synthesis began with the acylation of 3,4,5,6-tetrahydropyridine **3.145** with acid chloride **3.146**, which provided enamide **3.147** in 57% yield. The use of the 2,5-dihydrothiophene-1,1-dioxide as a masking group for the requisite diene was necessary as attempts to acylate **3.145** with 3,5-hexadienoyl chloride were unsuccessful. The thermolysis of **3.147** at 600 ºC resulted in the cheleotropic extrusion of SO_2 to give triene **3.148**, which underwent a [4+2] cycloaddition to provide the *cis*-fused tricycle **3.149**. The oxidation of **3.149** with SeO_2 in AcOH and subsequent hydrolysis of the allyl acetate gave an allylic alcohol, which

was oxidized with pyridinium chromate to give ketoamide **3.150**. Hydrogenation of the double bond in **3.150** provided **3.125** in 98% yield, thus completing the formal synthesis of (±)-apsidospermine.

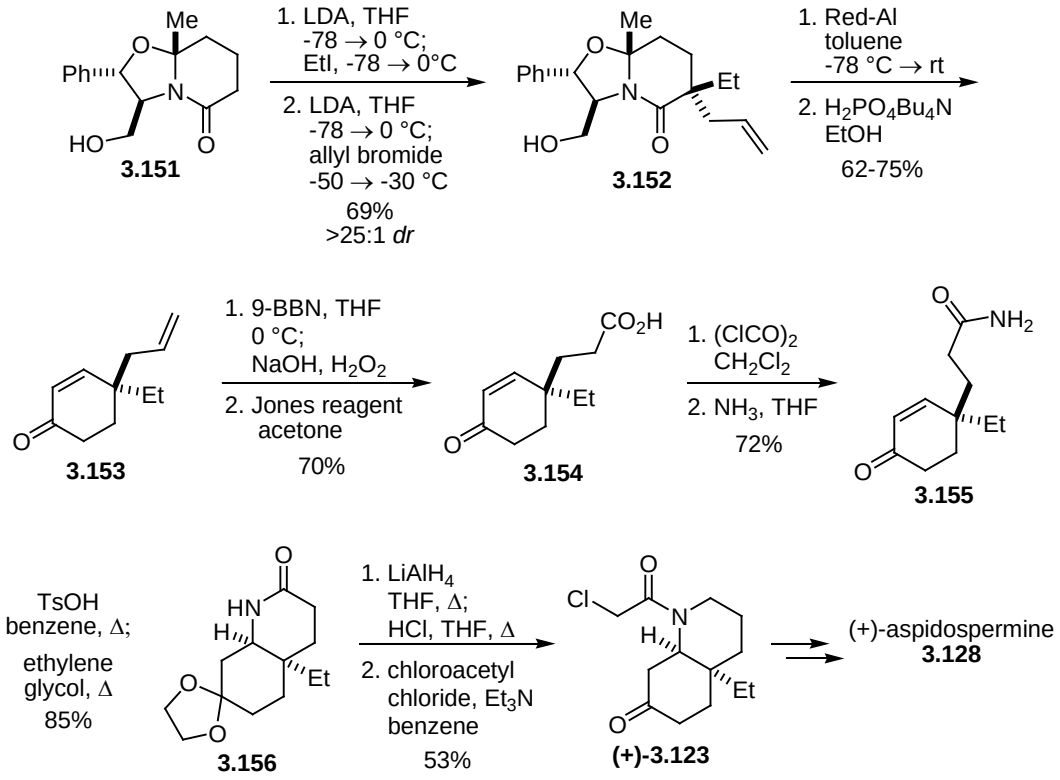
Scheme 3.25



The first asymmetric synthesis of the Stork-Dolfini ketone was reported by Meyers in 1989.[273] Meyers utilized the chiral bicyclic lactam **3.151** as a chiral auxiliary for establishing the stereochemistry of the C20 ethyl group (Scheme 3.26). The sequential alkylation of **3.151** with ethyl iodide and allyl bromide afforded **3.152** in 69% yield with greater than 25:1 diastereoselectivity. Cleavage of the auxiliary with Red-Al provided a keto-aldehyde, which was cyclized to cyclohexenone **3.153** upon treatment with mild acid. The olefin in **3.153** was successfully converted to a carboxylic acid in good yield by a sequence of hydroboration/oxidation and Jones oxidation. Carboxylic acid **3.154** was then converted to primary amide **3.155** via its acid chloride. Amide **3.155** was cyclized upon treatment with TsOH in benzene, and subsequent addition of ethylene

glycol to the reaction mixture furnished ketal **3.156** as a single diastereomer in 85% yield. Reduction of the amide moiety and hydrolysis of the ketal provided an aminoketone which was acylated with chloroacetyl chloride to give **(+)-3.123**, which is the enantioenriched form of Stork's intermediate. Although a formal synthesis had been completed at this point, **(+)-3.123** was further elaborated into the enantioenriched version of the Stork-Dolfini ketone (**3.125**), thus completing the formal synthesis of the (+)-aspidospermine.

Scheme 3.26

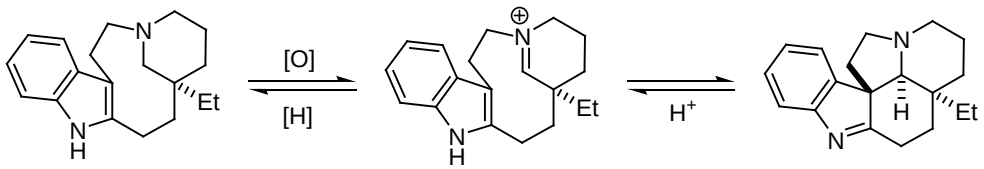


3.2.2.2 Syntheses of Quebrachamine and Its Conversion to the Aspidospermine Skeleton

As shown in Storks synthesis of aspidospermine, 1,2-dehydroaspidospermine derivatives can be converted to the quebrachamine ring system via reduction under acidic

conditions. The reverse of this transformation is also known, and the oxidation of quebrachamine derivatives to iminium ions such as **3.157** has been used numerous times for the conversion of quebrachamine derivatives into the aspidospermine skeleton (Scheme 3.27). Thus, any approach to the quebrachamine alkaloids can be utilized to access the aspidospermine family as well.

Scheme 3.27

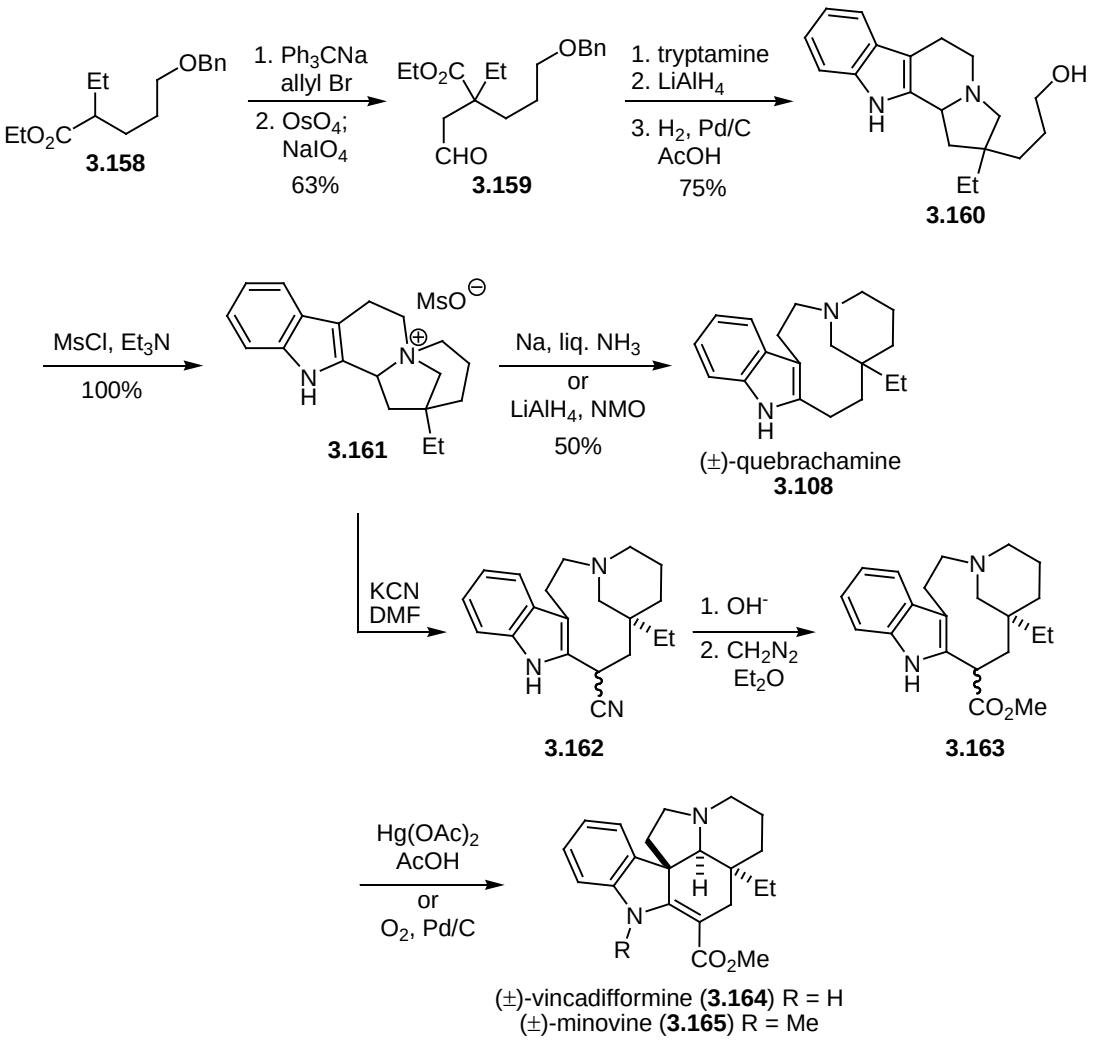


3.108 **3.157** **3.129**

In 1966 Kutney reported a total synthesis of quebrachamine that focused on the synthesis of tetracycle **3.160**, which could be converted into quebrachamine via the ammonium salt **3.161**.[258, 274-278] This approach has since become the most commonly utilized approach to the quebrachamine family of alkaloids. Kutney later modified this approach to allow for the synthesis of (±)-vincadifformine (**3.164**) and minovine (**3.165**). (Scheme 3.28).[279] Starting from the known ethyl ester **3.158**, alkylation with allyl bromide and subsequent oxidative cleavage of the olefin provided aldehyde **3.159**. Aldehyde **3.159** was then reacted with tryptamine in a Pictet-Spengler reaction to give an intermediary lactam, which was reduced with $LiAlH_4$ and deprotected to furnish **3.160** in good yield. Alcohol **3.160** was then treated with methanesulfonyl chloride in triethylamine to give the quaternary mesylate **3.161**. Reacting **3.161** under either dissolving metal conditions or with $LiAlH_4$ generated quebrachamine in moderate yields. Alternatively, **3.161** could be ring opened with potassium cyanide in DMF to give **3.162**. Subsequent hydrolysis of the nitrile and esterification of the intermediate acid with

diazomethane provided **3.163**, which could be cyclized to vincadifformine using either mercuric acetate in acetic acid or Pd/C under an atmosphere of oxygen.

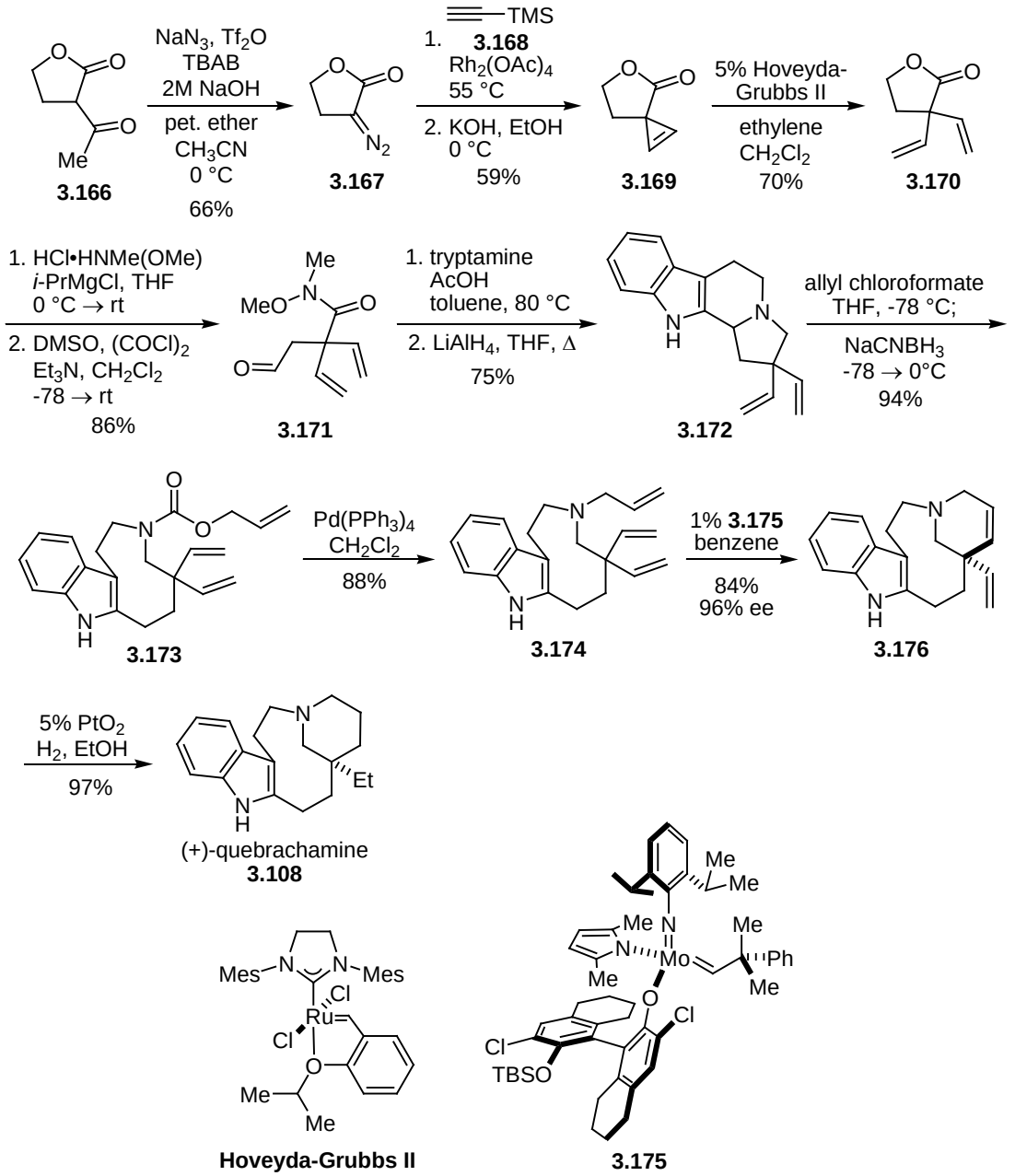
Scheme 3.28



Since Kutney's original report, other similar routes to quebrachamine utilizing the intermediacy of compounds similar **3.161** have been reported by Takano,[280-284] Wenkert,[285] Ziegler,[286-288] Fuji,[289, 290] and Asaoka and Takei.[291] In addition to these

reports, a number of other routes to quebrachamine have also been reported. One of the more interesting of these routes is the enantioselective synthesis of (+)-quebrachamine reported by Hoveyda in 2008.[292, 293] The key step in this synthesis was the asymmetric ring closing metathesis (ARCM) of prochiral triene **3.174** (Scheme 3.29). The synthesis began with a deacylative diazo transfer that afforded **3.167** in 66% yield from the commercially available lactone **3.166**. The synthesis of cyclopropene **3.169** was accomplished by the slow addition of **3.167** to a solution of $Rh_2(OAc)_4$ in trimethylsilylacetylene, and subsequent de-silylation provided **3.169** in 59% yield over the two steps. The requisite divinyl functionality was then installed via a ring opening-cross metathesis reaction of **3.19** with the Hoveyda-Grubbs II catalyst under an atmosphere of ethylene gas. The lactone **3.170** was opened with the magnesium anion of *N*-methyl-*O*-methyl hydroxylamine, and Swern oxidation of the resulting alcohol gave aldehyde **3.171**. Aldehyde **3.171** was then reacted with tryptamine in a Pictet-Spengler reaction to yield a tetracyclic lactam, which was reduced with $LiAlH_4$ to provide **3.172** in good yields. Ring opening of the β-carboline was achieved by sequentially treating **3.172** with allyl chloroformate and $NaCNBH_3$. The key ARCM substrate **3.174** could then be accessed through a palladium mediated decarboxylative allylation, which proceeded in 88% yield. With **3.174** in hand, attention was turned to the ARCM. After screening several chiral catalysts, it was found the molybdenum catalyst **3.175** could produce the desired ARCM product **3.176** in good yield with excellent levels of enantiocontrol. The final hydrogenation of **3.176** proceeded without incident to furnish (+)-quebrachamine in 97% yield.

Scheme 3.29

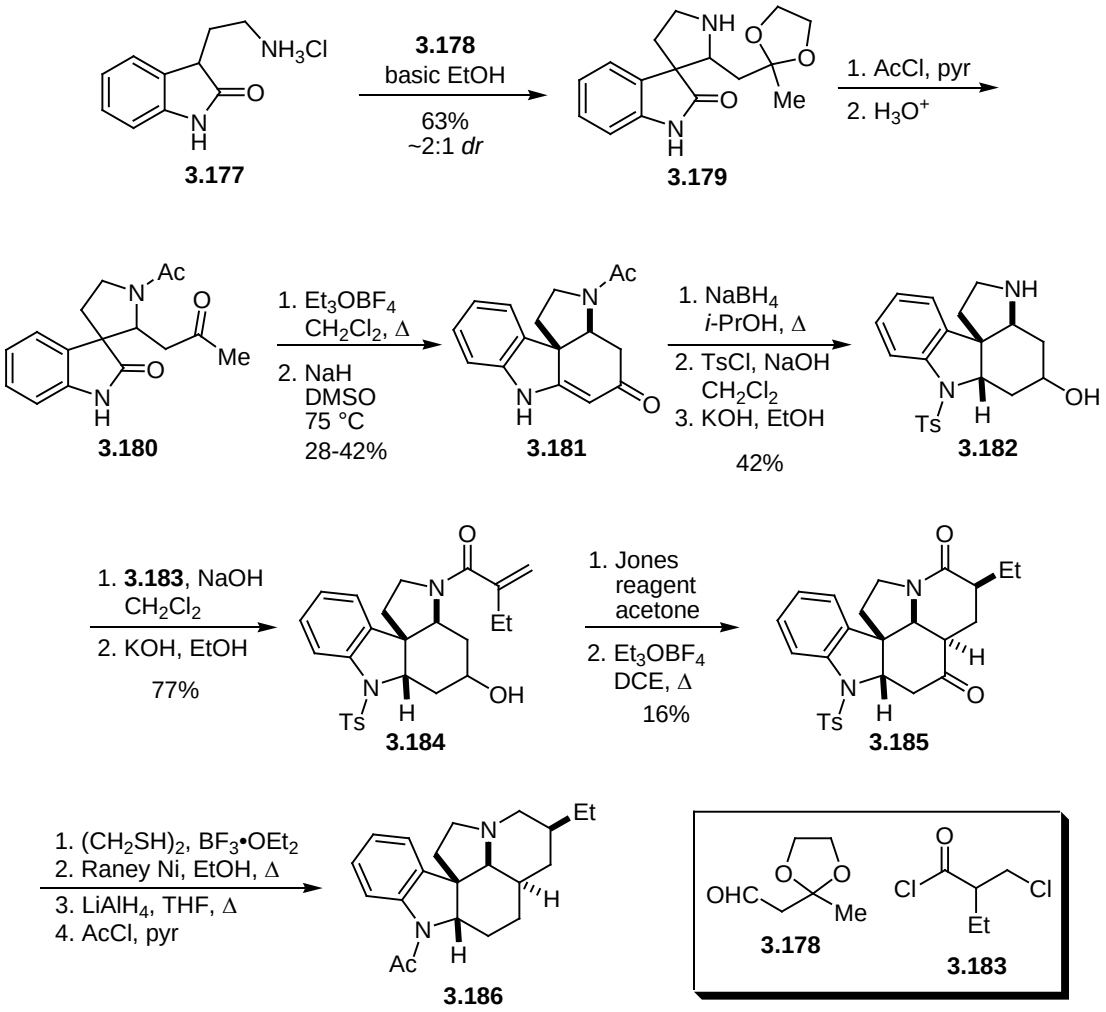


3.2.2.3 The Ban Oxindole Approach

Although Ban had previously completed a successful synthesis of aspidospermine, the problematic Fisher indole synthesis utilized in this route caused Ban

to develop a second approach to the aspidospermine alkaloids. This was approach was built around the synthesis and manipulation of spiroxindole **3.180** (Scheme 3.30).[294-296] Following a general protocol developed by Harley-Mason,[297] spiroxindole **3.179** was synthesized from 2-oxytryptamine (**3.177**) and aldehyde **3.178**. The amine was then acylated, and the ketal hydrolyzed to provide **3.180**. When **3.180** was treated with ethyl triethyloxonium tetrafluoroborate, an imidate was formed that was heated with NaH in DMSO to give the tetracycle **3.181** as the major product. The vinylogous amide moiety in **3.181** was then reduced to the amino-alcohol with $NaBH_4$, and selective tosyl protection of the aniline nitrogen and cleavage of the acetamide yielded **3.182**. The installation of the D ring began with the acylation of secondary amine **3.182** with acid chloride **3.183**, and subsequent elimination generated acrylamide **3.184**. The secondary alcohol was then re-oxidized to the ketone with Jones reagent, and upon treatment with triethyloxonium tetrafluoroborate in refluxing dichloroethane the desired pentacycle **3.185** was formed in 16% yield. The ketone was then removed by forming the dithiane and reduction with Raney nickel. Reduction of the amide with $LiAlH_4$ proceeded with concurrent removal of the tosyl protecting group, and subsequent acylation provide *N*-acetyl pseudoaspidospermidine (**3.186**).

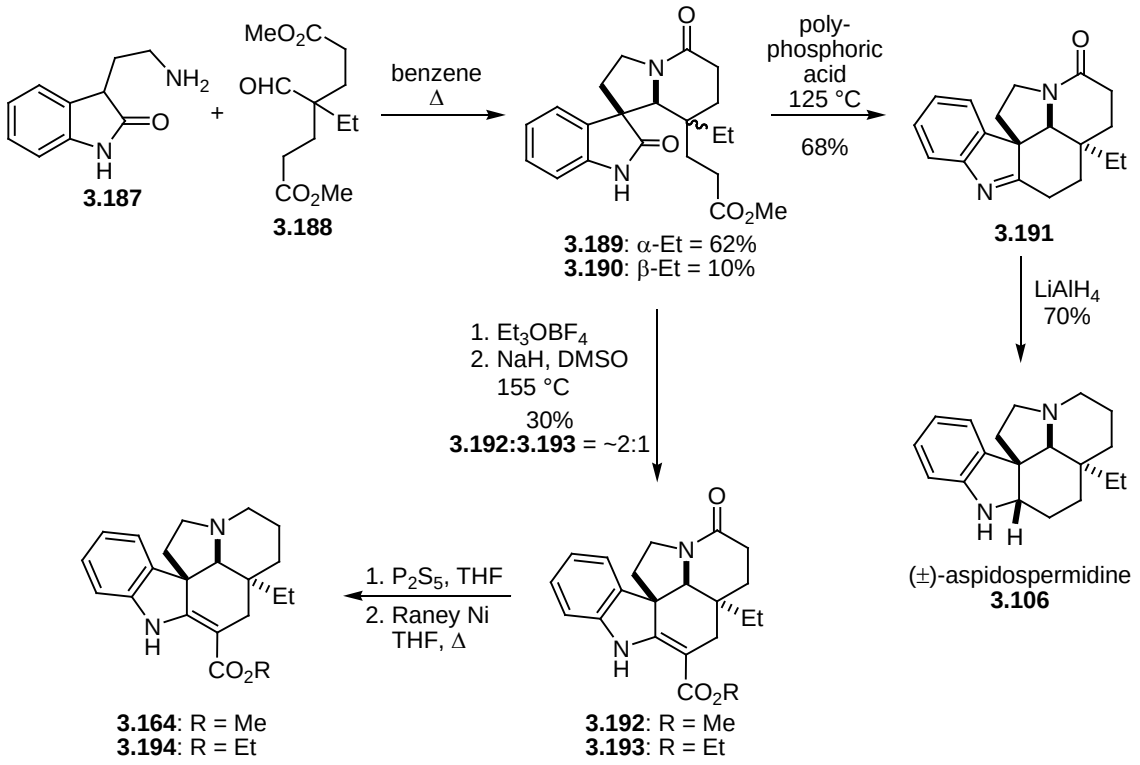
Scheme 3.30



While Ban never utilized the oxindole approach for the synthesis of aspidospermine alkaloids containing a C20 ethyl group, Le Man was able to demonstrate its application to the synthesis of aspisospermidine and vincadifformine (**3.164**) (Scheme 3.31).[298] By starting with aldehyde **3.188**, Le Man was able to assemble the D and E rings in a single step. Thus, 2-oxotryptamine was treated with aldehyde **3.188** in refluxing benzene to afford **3.189** as mixture (6.2:1) of diastereomers in a combined 70% yield. For the synthesis of aspidospermidine, the major diastereomer, **3.189**, was treated with polyphophoric acid at 125 ºC to produce **3.191** in 68% yield. The reduction of **3.191**

with $LiAlH_4$ gave aspidospermidine in 70% yield. For the synthesis of vincadifformine, a slightly longer reaction sequence was needed. To this end, **3.189** was treated with triethyloxonium tetrafluoroborate to generate an imidate that was heated with NaH in DMSO to provide a mixture of the methyl and ethyl esters **3.192** and **3.193**, which were used in the next step without separation. The lactam group could then be selectively reduced in the presence of the ester by conversion to the thioamide and reduction with Raney nickel, thus completing the synthesis of vincadifformine (**3.164**). Interestingly, the authors made no attempt to convert the undesired ethyl ester **3.194** into the natural product, but just carried the mixture through to the end of the synthesis.

Scheme 3.31

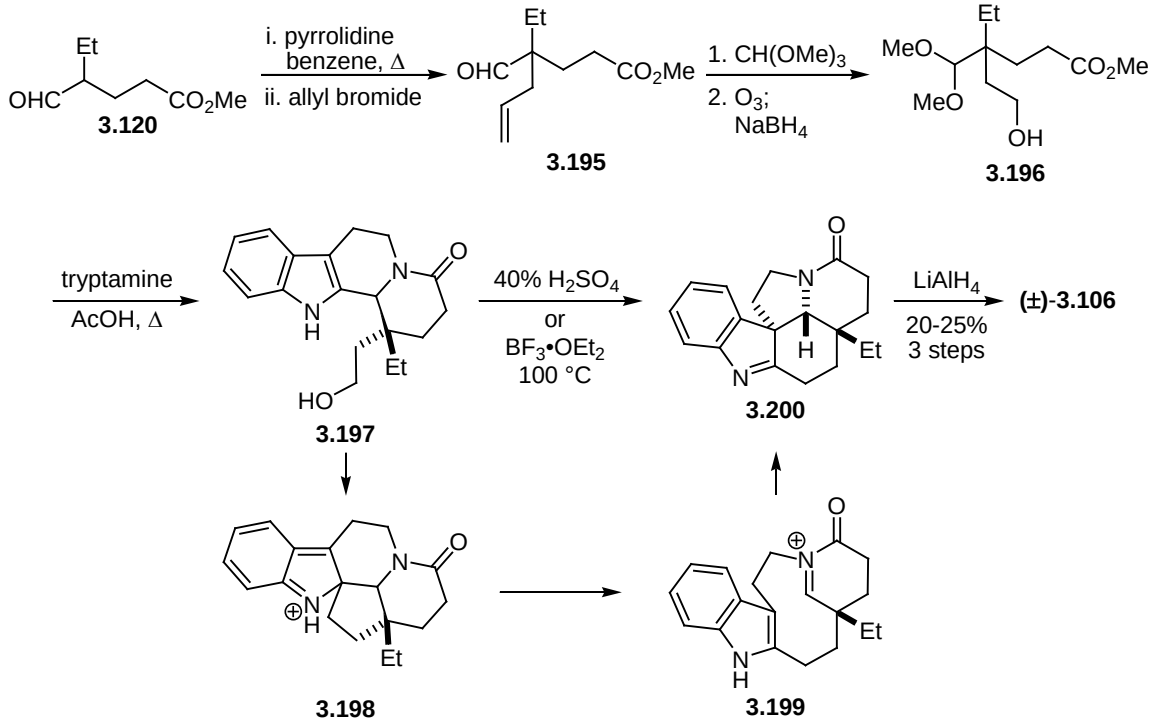


3.2.2.4 The Rearrangement of β-Carboline Derivatives

One alternative approach to the aspidospermine skeleton involves the synthesis of an octahydroindolo[2,3-a]quinolizine via a Pictet-Spengler reaction, followed by a subsequent rearrangement of the quinolizine to provide the aspidospermine skeleton (Scheme 3.32). This approach was first applied to the synthesis of aspidospermidine by Harley-Mason in 1965.[299, 300] Since then, Rapoport has utilized a similar approach to synthesize vindoline,[301, 302] and Fuji has exploited this tactic in the enantioselective synthesis of (-)-aspidospermidine.[289, 290] Langlois has also utilized a similar rearrangement of an indolo[2,3-a]quinolizine in the syntheses of vindoline and vinderosine. However, Langlois accessed the requisite quinolizine via a hetero Diels-Alder reaction instead of the more commonly used Pictet-Spengler approach.[303, 304]

The Harley-Mason synthesis is representative of this approach, and is outlined in Scheme 3.32. Starting with the aldehyde **3.120**, previously prepared by Stork,[267] enamine formation and alkylation with allyl bromide provided **3.195**. The aldehyde was then protected as its dimethyl acetal, and ozonolysis of the alkene moiety followed by sodium borohydride reduction gave alcohol **3.196**. Acetal **3.196** was then reacted with tryptamine in boiling acetic acid to generate **3.197**. Upon heating to 100 ºC in 40% H_2SO_4 or $BF_3 \cdot OEt_2$, **3.197** reacted to give **3.198**, which underwent a retro-Mannich/Mannich sequence to give **3.200**. Indolenine **3.200** was then reduced with $LiAlH_4$ to provide aspidospermidine (**3.106**) in 20-25% yield from tryptamine.

Scheme 3.32



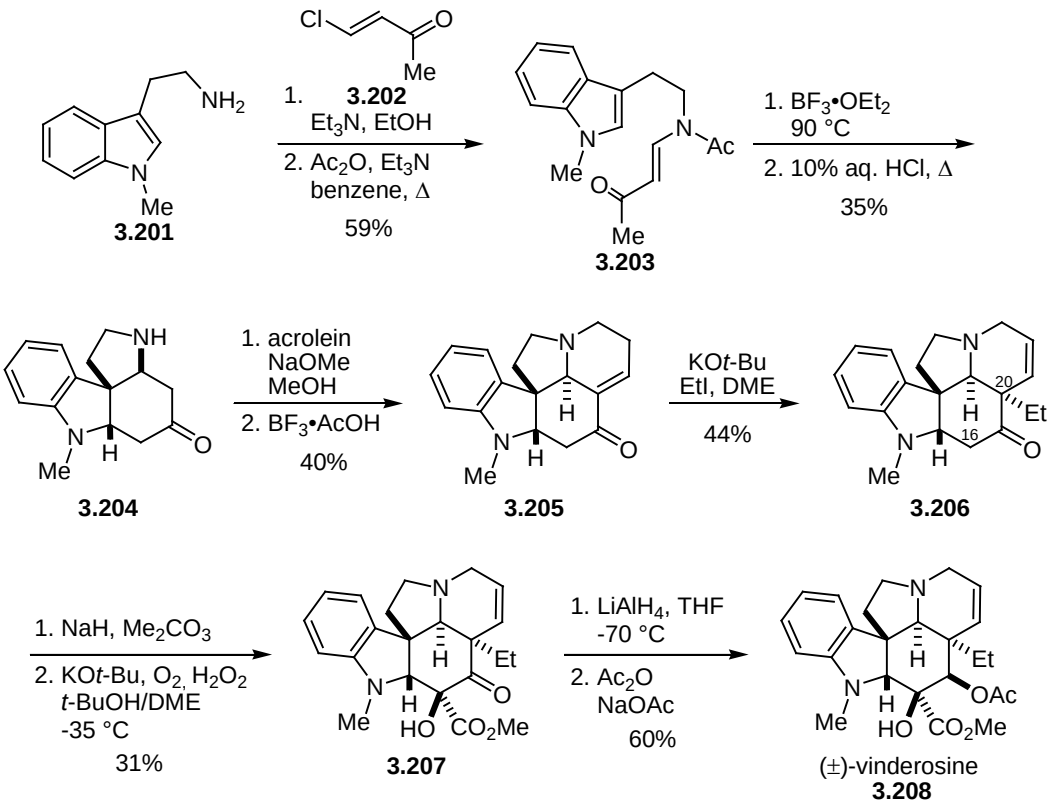
3.2.2.5 Syntheses of Vinderosine and Vindoline

Vindoline (**3.110**) is perhaps the most sought after of the *Aspidosperma* alkaloids due to its inclusion as a subunit in the oncolytic alkaloid vinblastine (**3.111**). Therefore, a substantial amount of effort has been made towards the syntheses of vindoline and its demethoxy analogue, vinderosine (**3.208**). The first synthesis of vinderosine was reported by Buchi in 1971,[305] and was followed by a synthesis of vindoline in 1975.[306] Buchi's route focused on the sequential construction of the C, D, and E rings onto an indole nucleus, with the C and E rings being formed in a single operation (Scheme 3.33).

Buchi's elegant synthesis began with the reaction of tryptamine with vinylogous acid chloride **3.202**, which provided a vinylogous amide that was *N*-acylated to give **3.203**. Upon heating in $BF_3 \cdot OEt_2$ at 90 ºC the desired double cyclization occurred to give **3.204** in 35% yield after cleavage of the acetamide. Amino-ketone **3.204** was then

reacted with acrolein in NaOMe/MeOH to give a mixture of ketols, which were dehydrated with BF_3 in acetic acid to form the pentacyclic core of the natural product. The C20 ethyl group was then installed in 44% yield by alkylation with ethyl iodide. The next step of the synthesis focused on installing the requisite functionality at C16. The methyl ester was installed first by treating **3.206** with NaH in dimethyl carbonate, and the resulting β-ketoester was treated with KO*t*-Bu and hydrogen peroxide under an oxygen atmosphere to afford **3.207** in 31% yield over the two steps. The ketone was then selectively reduced with $LiAlH_4$ in THF at -70 ºC, and the resulting secondary alcohol was converted to its acetate to provide vinderosine (**3.208**) in 60% yield for the two steps.

Scheme 3.33

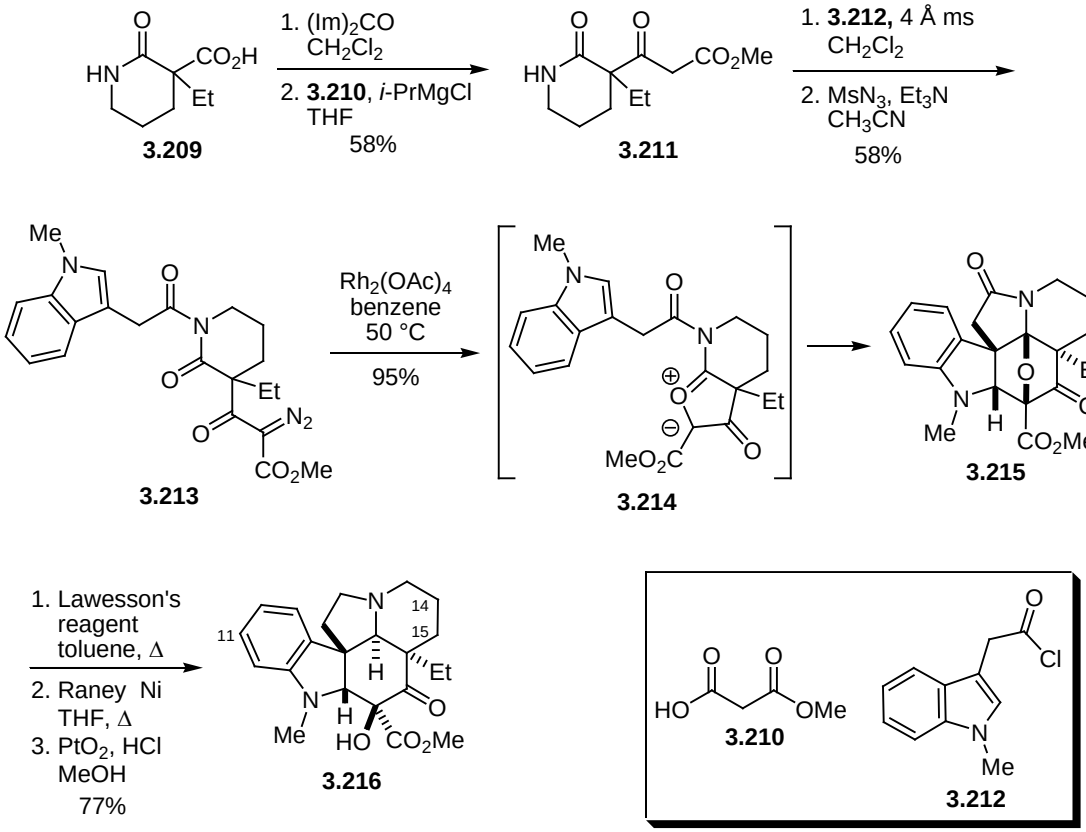


Since Buchi's first synthesis of vindoline a number of other approaches to ketones **3.204** and **3.206** have been developed. The syntheses of vindoline by Langlois and

Rapoport were briefly discussed in the previous section. A number of other routes to vindoline and vinderosine have also been developed. The first asymmetric synthesis of these two alkaloids was reported by Kuehne in 1987.[307] This approach was an extension of their previous synthesis of (-)-tabersonine (see Scheme 3.41), and was similar to that originally used by Danieli for the conversion of tabersonine into vinderosine.[308]

A conceptually different approach to the vindoline ring system has been developed by Padwa.[309, 310] In this approach, a tandem cyclization/cycloaddition reaction of a rhodium carbenoid was exploited to assemble the pentacyclic skeleton of vindoline (Scheme 3.34). Starting from the known piperidone **3.209**, the homologation of the acid to β-ketoester **3.211** could be accomplished in two steps and 58% yield. Acylation of the amide in **3.211** with acid chloride **3.212** proceeded in moderate yield, and diazo transfer proceeded in excellent yield using standard conditions. With the requisite diazo compound **3.213** in hand, the tandem cycloaddition could be attempted. In the event, the treatment of **3.213** with a catalytic quantity of $Rh_2(OAc)_2$ in benzene at 50 ºC provided the desired carbonyl ylide **3.214**, which underwent a spontaneous [3+2] dipolar cycloaddition with the indole double bond to provide the pentacyclic **3.215** in excellent yield. Pentacycle **3.215** contains all of the requisite oxygenation found in vinderosine, but it is noticeably lacking the C14-C15 double bond. Pentacycle **3.212** was further progressed into intermediate **3.216**, which could in principle be elaborated into vinderosine following protocols developed by Kutney for the synthesis of vindoline.[311] To date, Padwa has not reported on the completion of the total synthesis of vinderosine; however, the rhodium catalyzed [3+2] cycloaddition has been utilized in the successful synthesis of aspidophytine.[312, 313]

Scheme 3.34

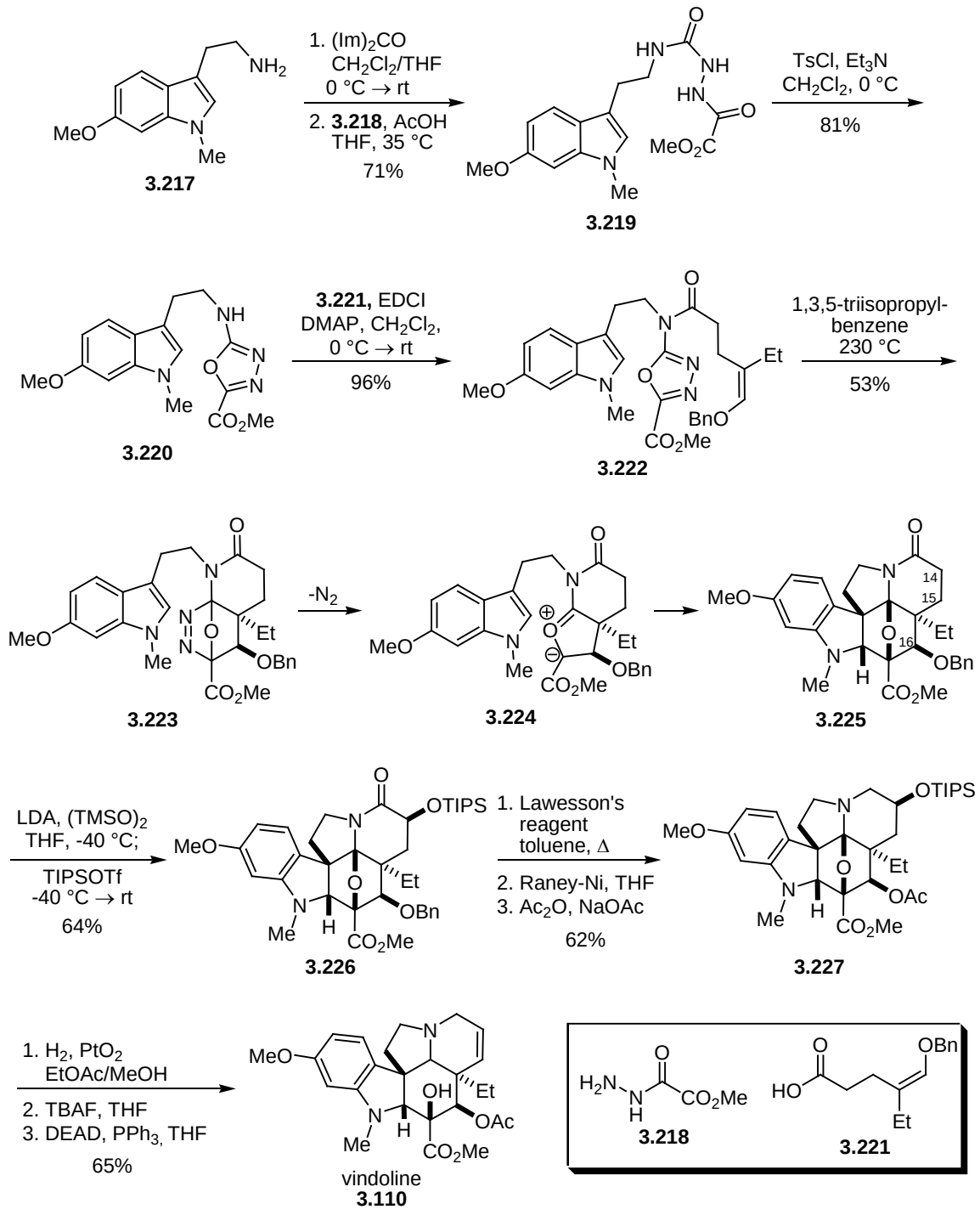


Boger has developed an elegant approach to the aspidospermine alkaloids that utilizes a [4+2]/[3+2] cycloaddition cascade sequence to assemble the pentacyclic core (Scheme 3.35).[314] This approach has been utilized in the syntheses of minovine[315] and vindoline.[316] The synthesis of vindoline began with the reaction of tryptamine **3.217** with carbonyl diamidazole (CDI), to generate an intermediate that was reacted with hydrazine **3.218** to give **3.219** in 71% yield over the two steps. The treatment of **3.219** with tosyl chloride and trimethyl amine resulted in the formation of oxadiazole **3.220** in 81% yield. Oxadiazole **3.220** was then coupled with acid **3.221** to form the cycloaddition precursor **3.222**. Upon heating in 1,3,5-triisopropylbenzene at 230 ºC **3.222** first underwent a [4+2] cycloaddition to yield **3.223**, which upon extrusion of N_2 generated carbonyl ylide **3.224**.

The carbonyl ylide then underwent a [3+2] cycloaddition with the indole double bond to generate **3.225** in 53% yield. Note that the [3+2] cycloaddition utilized here by Boger is similar to that previously utilized by Padwa, but that the entry to these cycloadditions is very different.

From **3.225**, four main transformations were needed to complete the total synthesis: the reduction of the amide, the installation of the C14-C15 double bond, the ring opening of the oxabicycle, and the conversion of the C16 benzyl ether to its corresponding acetate. To this end, the amide in **3.225** was deprotonated with LDA and trapped with $(TMSO)_2$ to generate an alkoxide, which was in situ protected as its TIPS ether to give **3.226** in 64% yield. The amide was then converted to the corresponding thioamide, which was reduced with Raney nickel. This step also resulted in the cleavage of the benzyl ether, and the resulting secondary alcohol was converted to its acetate to afford **3.227** in 62% yield over the three steps. Ring opening of oxabicycle was achieved under hydrogenation conditions, and subsequent removal of the TIPS ether and elimination secondary alcohol provided (±)-vindoline in 65% yield over the three steps. It was also demonstrated that product of the tandem cycloaddition reaction, **3.225**, could be easily resolved using chiral HPLC, thus allowing access to both enantiomers of the natural product.

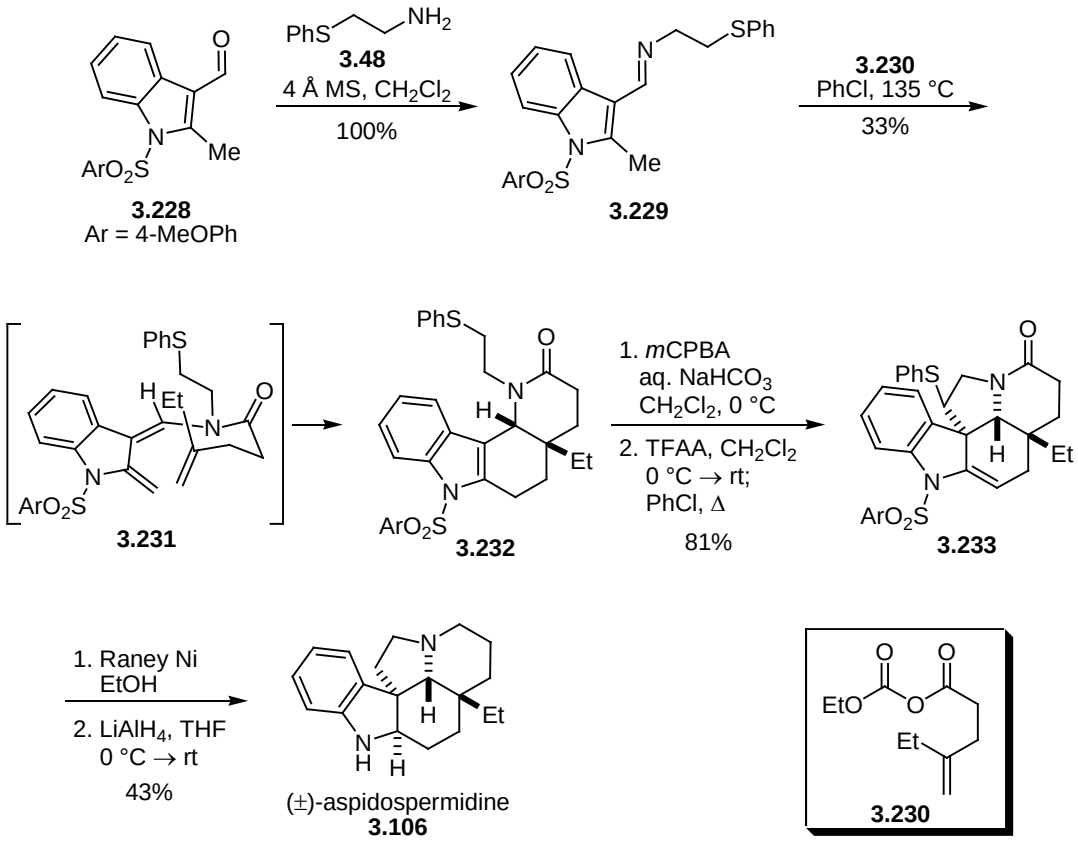
Scheme 3.35


1. (Im)2CO
CH2Cl2/THF
0 °C → rt
2. 3.218, AcOH
THF, 35 °C
71%
TsCl, Et3N
CH2Cl2, 0 °C
81%
3.221, EDCI
DMAP, CH2Cl2,
0 °C → rt
96%
1,3,5-triisopropyl-
benzene
230 °C
53%
-N2
LDA, (TMSO)2
THF, -40 °C;
TIPSOTf
-40 °C → rt
64%
1. Lawesson's
reagent
toluene, Δ
2. Raney-Ni, THF
3. Ac2O, NaOAc
62%
1. H2, PtO2
EtOAc/MeOH
2. TBAF, THF
3. DEAD, PPh3, THF
65%
3.217
3.219
3.220
3.222
3.223
3.224
3.225
3.226
3.227
vindoline
3.110
3.218
3.221

3.2.2.6 The Magnus Indole-2,3-quinodimethane Approach

Magnus has developed a concise approach to the aspidospermine alkaloids that proceeds through a transient indole-2,3-quinodimethane that undergoes a spontaneous intramolecular Diels-Alder cycloaddition leading to the stereoselective formation of the C and D rings (Scheme 3.37).[317-319] Magnus' synthesis of aspidospermidine began with the condensation of the sulfonyl protected indole-3-carboxaldehyde **3.228** with amine **3.48**, which provided the imine **3.229** in quantitative yield. The imine **3.229** was reacted with mixed anhydride **3.230** in chlorobenzene at 135 ºC to generate the intermediate quinodimethane **3.231**, which cyclized under the reaction conditions to give **3.232**. The *cis*-ring fusion was formed exclusively, and this has been rationalized by the *exo-E* transition state represented in **3.231**. With **3.232** in hand, all that remained was the installation of the E ring, which was easily accomplished utilizing the Pummerer reaction. Oxidation of the sulfide in **3.232** afforded a sulfoxide, which was treated with trifluoroacetic anhydride to produce **3.233** in 81% yield over the two steps. The thioether was cleaved with Raney nickel, and subsequent treatment with $LiAlH_4$ gave (±)-aspidospermidine. Magnus has since utilized a chiral auxiliary in this approach that allowed for the enantioselective synthesis of both enantiomers of 11-methoxytabersonine (**3.247**),[320] which has previously been converted to vindoline by Danieli.[308]

Scheme 3.37

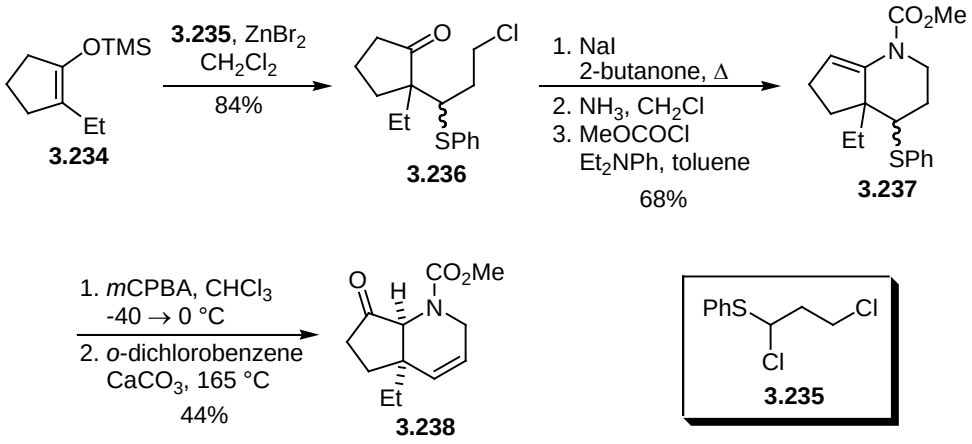


3.2.2.7 Application of the Aza-Cope Mannich Reaction to the *Aspidosperma* Alkaloids

Overman has elegantly applied the aza-Cope-Mannich reaction developed in his laboratories to the synthesis of the *Aspidosperma* alkaloids 11-methoxytabersonine (**3.247**),[321] and deoxoapodine, and to the related *Melodinus* alkaloid meloscine.[322] The synthesis of **3.247** is exemplary of this approach, and began with the synthesis of ketone **3.238** (Scheme 3.38).[321] The known silyl enol ether **3.234**[323] was alkylated with α-chlorosulfide **3.235** in the presence of $ZnBr_2$ to provide **3.236** in 84% yield. Chloride **3.236** was then converted to the primary iodide, which was reacted sequentially with ammonia and methyl chloroformate to provide enecarbamate **3.237**. Epoxidation of the

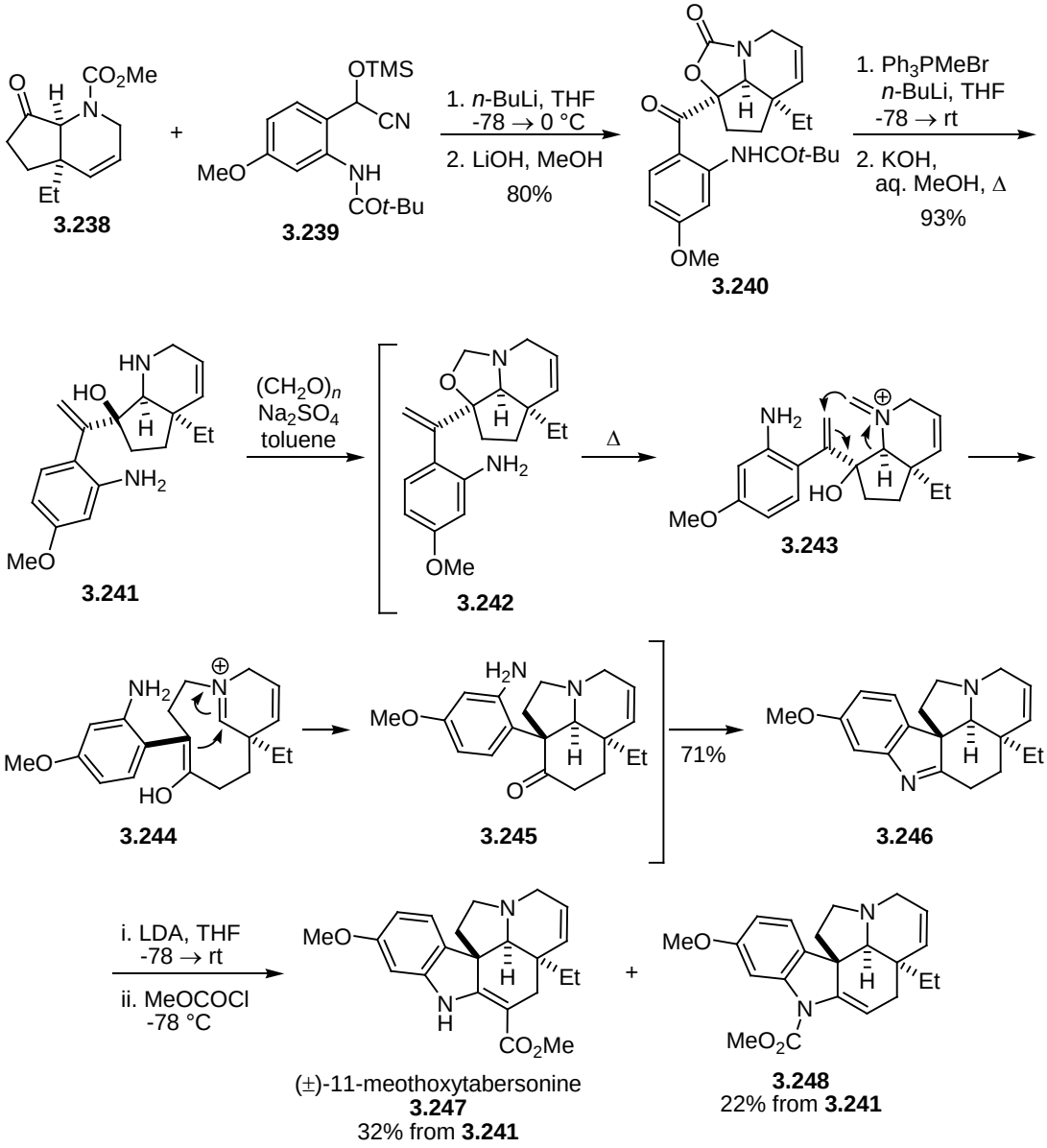
enamide moiety in **3.237** occurred with concurrent oxidation of the sulfide to the sulfoxide, and upon heating of the intermediate epoxide to 165 ºC in the presence of $CaCO_3$ the ketone **3.238** was formed in 44% over the two steps.

Scheme 3.38



With ketone **3.238** in hand, attention was then turned to the synthesis of **3.241** (Scheme 3.39). The synthesis of **3.241** began with the addition of cyanohydrin **3.239** to ketone **3.238**, which produced oxazolidine **3.240** in 80% yield after basic hydrolysis. Methylenation of **3.240** and subsequent hydrolysis of the oxazolidine and Boc-protecting groups provided the aza-Cope-Mannich substrate **3.241**. In the event, **3.241** was treated with paraformaldehyde in toluene to initially afford *N,O*-acetal **3.242**. Upon heating, **3.242** underwent ring opening to give iminium ion **3.243**, which underwent the aza-Cope-Mannich sequence and cyclization to give **3.246** in 71% yield. Although **3.246** could be isolated in good yields, in practice the crude material was treated with LDA, and the metalloenamine was trapped with methyl chloroformate to furnish (±)-11-methoxytabersonine (**3.247**) in 32% yield over the two steps, along with an almost equal amount of the *N*-acylated **3.248**.

Scheme 3.39

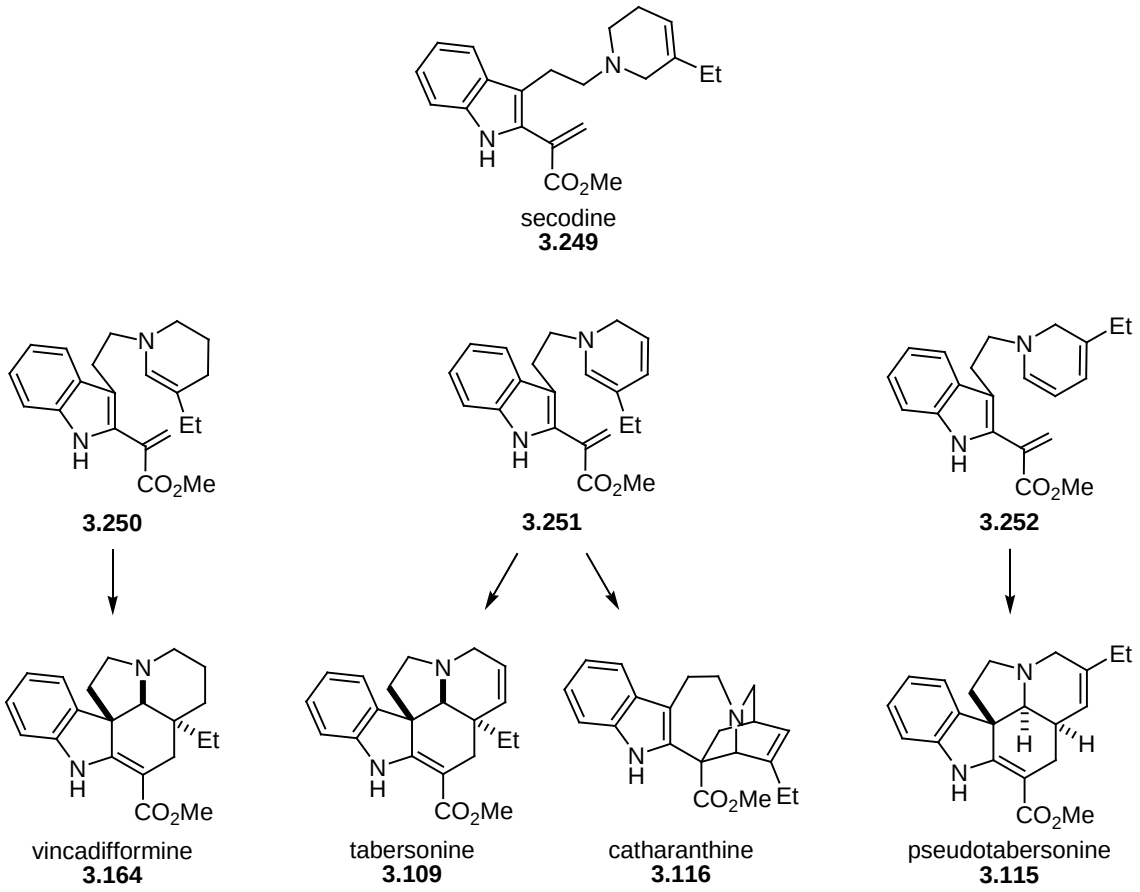


3.2.2.8 Kuehne's Biomimetic Approach to the *Aspidosperma* Alkaloids

Secodine (**3.249**) and its derivatives have been proposed as intermediates in the biosynthesis of the aspidospermine and ibogamine-catharanthine families of alkaloids.[324] Secodines are generally fugitive intermediates that readily dimerize or cyclize, and it is

proposed that the intramolecular [4+2] cyclization of these derivatives is involved in the biosynthetic pathway (Scheme 3.40). Thus, the variously unsaturated secodine derivatives **3.250-3.252** can be envisioned to give rise to the depicted natural products. Although secodine has itself has been synthesized twice,[325, 326] it usually prepared as a transient intermediate that is utilized in biomimetic syntheses.

Scheme 3.40

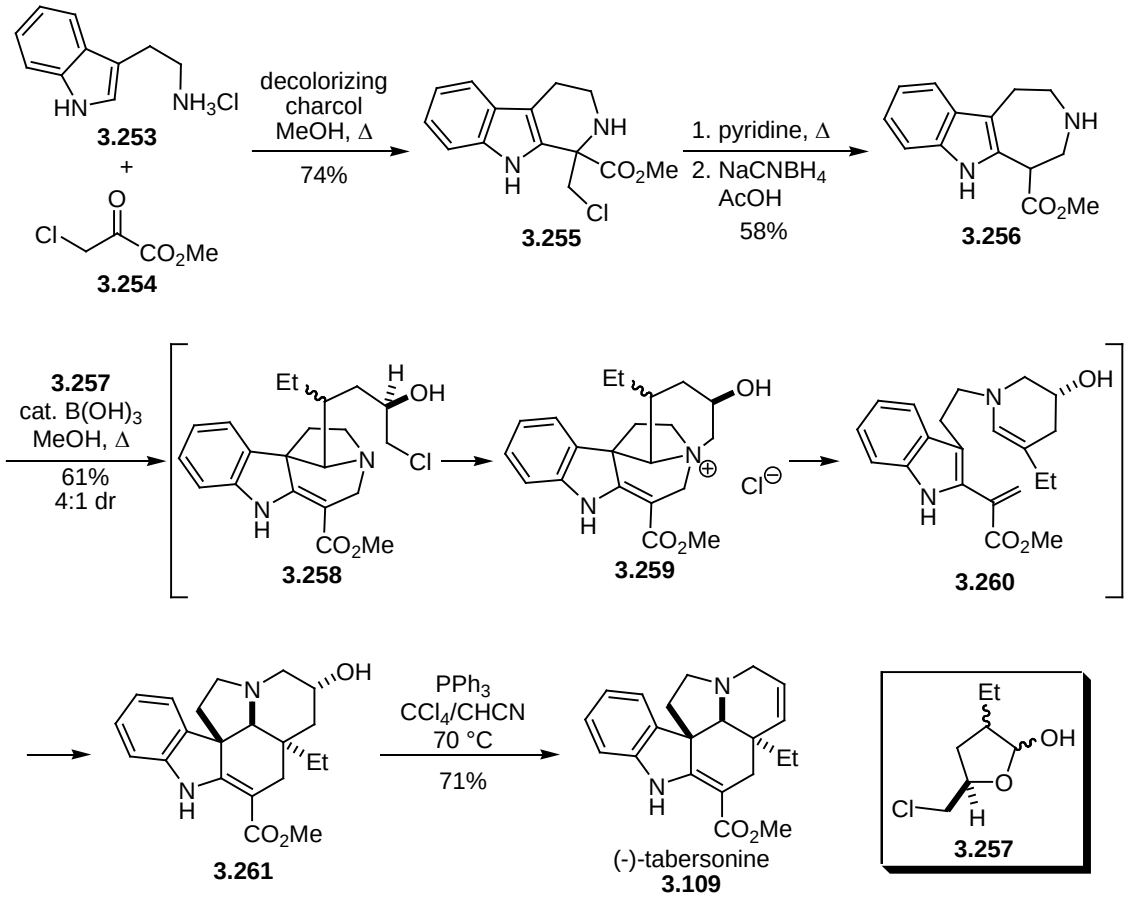


The Kuehne research group has reported a substantial portion of the work related to the biomimetic syntheses of the aspidospermine alkaloids, and in doing so has developed a number of elegant syntheses.[262, 307, 327-340] Kuehne's approaches have focused on the in situ preparation and cyclization of an appropriate secodine derivative.

Representative of this approach is the synthesis of (-)-tabersonine (**3.107**), which proceeded through the intermediary hydroxysecodine derivative **3.260** (Scheme 3.41).[307, 337, 339]

Kuehne's approach began with the Pictet-Spengler reaction of tryptamine hydrochloride and pyruvate **3.254** to give **3.255** in 74% yield. Upon heating in pyridine, **3.255** reacted to form an aziridine, which underwent ring expansion to generate an intermediate vinylogous carbamate that was reduced with $NaCNBH_3$ to provide azepine **3.256** in 58% yield over the two steps. Azepine **3.256** was then reacted with lactol **3.257** in presence of catalytic boric acid in refluxing methanol to initially produce **3.258** as the product of a Pictet-Spengler reaction. A subsequent intramolecular alkylation furnished ammonium salt **3.259**, which fragmented to give the hydroxysecodine **3.260**. The hydroxysecodine then underwent a spontaneous intramolecular Diels-Alder reaction to afford **3.261** in 61% yield as a mixture (4:1) of diastereomers. Elimination of the alcohol in **3.261** afforded (-)-tabersonine in 71% yield. Interestingly, only the major diastereomer underwent elimination, and the minor diastereomer reacted under these conditions to form an aziridinium, which underwent ring opening to give a D-ring contracted product.

Scheme 3.41



As mentioned previously, tabersonine and 11-methoxytabersonine, which was prepared by an analogous route, could then be converted into vinderosine and vindoline, respectively, thus completing the first asymmetric syntheses of these natural products.[307] Kuehne has also utilized this, or very similar approaches, in the syntheses of a number of other aspidosperma alkaloids. A handful of other groups have also reported syntheses involving the formation of transient secodine intermediates.[341-346]

3.2.2.9 Syntheses of Aspidosperma Alkaloids Utilizing Ring Closing Metathesis

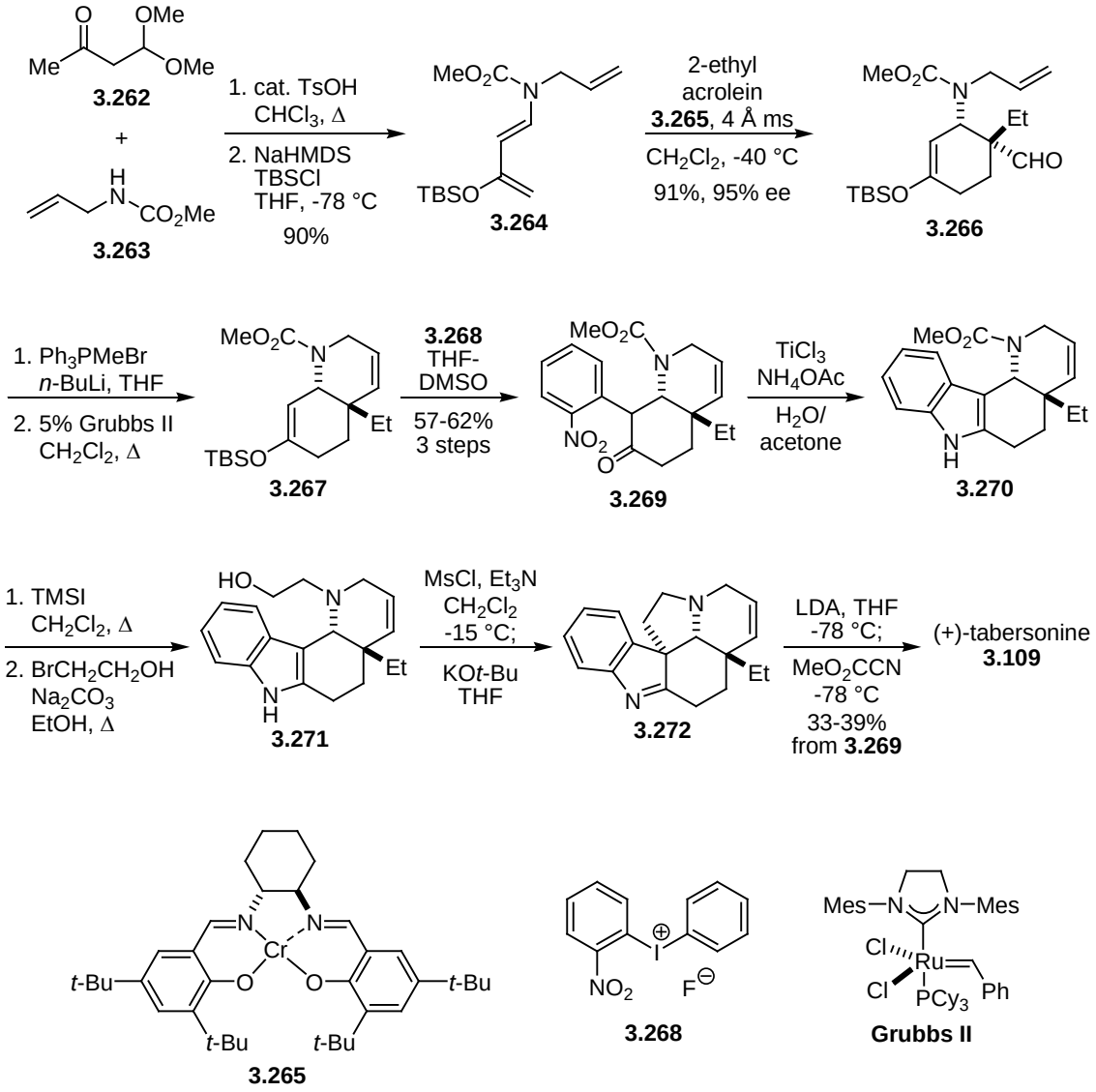
In addition to Hoveyda's application of ARCM to the synthesis of (+)-quebrachamine, there have been two other syntheses of aspidospermine alkaloids that

have utilized RCM. The first of these syntheses was the total synthesis of (±)-tabersonine reported by Rawal in 1998.[347] Rawal's approach utilized a stereoselective Diels-Alder reaction to form the C ring, and a RCM to close the D ring. The Diels-Alder cycloaddition was later made enantioselective, allowing for the gram scale synthesis of (+)-tabersonine (Scheme 3.42).[348]

Rawal's synthesis began with the addition of carbamate **3.263** to acetal **3.262**. The resulting enamine was then converted to silyl enol ether **3.264**. The reaction of **3.264** with 2-ethylacrolein in CH_2Cl_2 at -40 ºC in the presence of Jacobsen's Cr-salen catalyst **3.265**[349] proceeded in 91% yield with high levels of enantioselectivity. With **3.266** in hand, the D ring was then closed via a two step Wittig olefination/RCM protocol to provide **3.267**. The initial attempts to install the indole ring onto **3.267** were met with some difficulty. The Gassman indole synthesis with **3.267** was unsuccessful, and the Fisher indole synthesis on the ketone derived from **3.267** was plagued by the formation of mixtures (~1:1) of regioisomers. Thus, an alternative strategy was developed for the installation of the indole ring. It was found that the reaction of **3.267** with (o-nitrophenyl)phenyliodonium fluoride (**3.268**) proceeded smoothly to give **3.267** in good yield, and subsequent reduction of the nitro group afforded the desired indole **3.270**. The E ring was then installed via a three step protocol. Deprotection of the amine with trimethylsilyliodide provided a secondary amine that was alkylated with 2-bromoethanol to give **3.271**. The primary alcohol in **3.271** was then converted to its mesylate, and upon the addition of KO*t*-Bu the desired spirocycle was formed. In an improvement of Overman's procedure,[321] indolenine **3.272** was selectively *C*-acylated by deprotonation with LDA in THF at -78 ºC and trapping with Mander's reagent. Thus, the synthesis of (+)-tabersonine was completed in 12 steps from ketone **3.262**. Rawal also utilized this

route for the syntheses of (+)-16-methoxytabersonine, (+)-aspidospermidine, and (-)-quebrachamine.[348]

Scheme 3.42

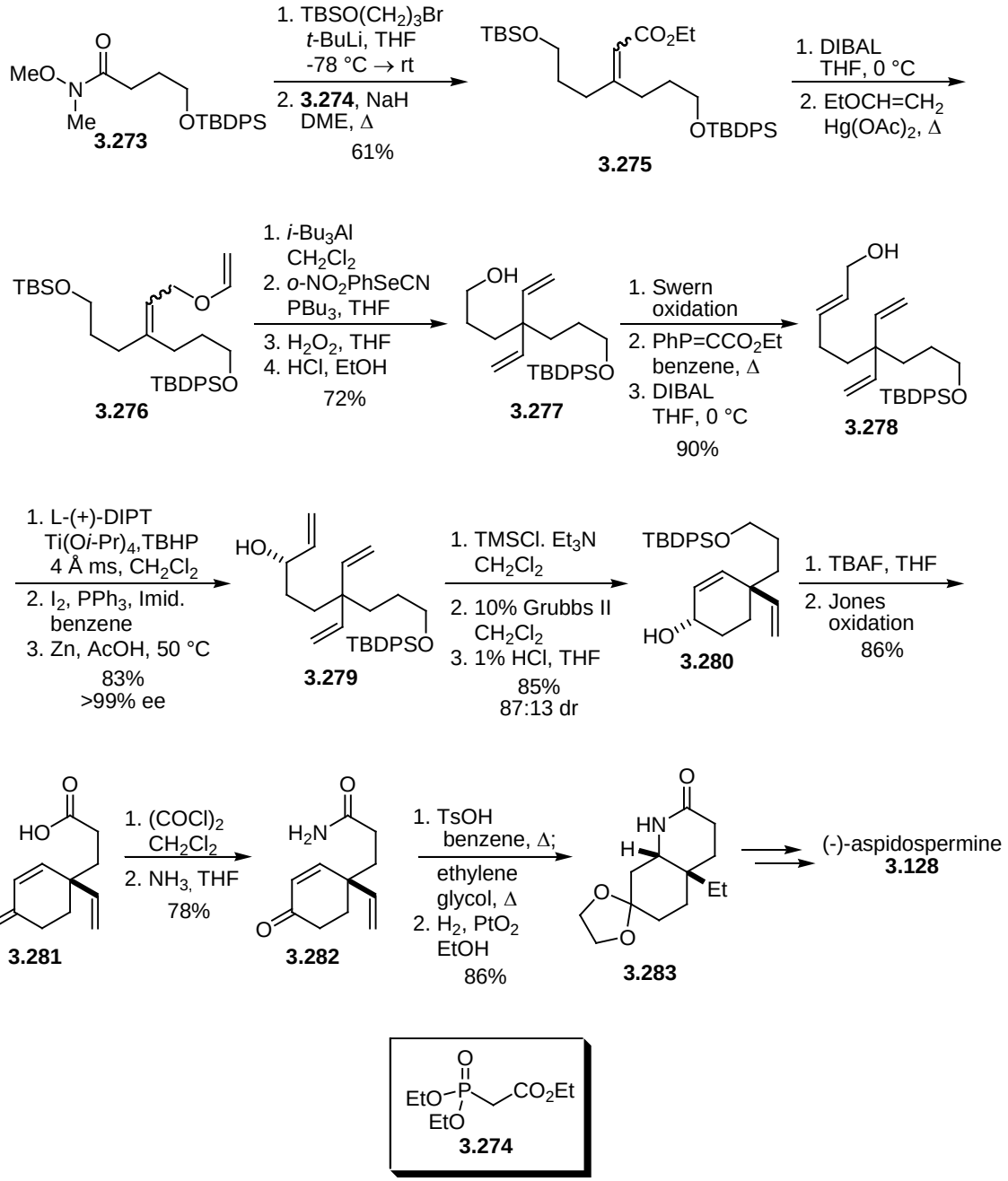


In 2003 Shishido reported a lengthy synthesis of (-)-aspidospermidine that utilized a diastereoselective RCM reaction to establish the stereochemistry of the C20 ethyl group (Scheme 3.43).[350] The synthesis began with the addition of the 3-(*t*-butyldimethylsilyloxy)propyllithium to the amide **3.273** to afford a ketone that was

subsequently olefinated with **3.274** to give **3.275** in 61% yield over the two steps. Reduction of the ester with diisobutylaluminum hydride delivered an alcohol, which was converted to enol ether **3.276**. The enol ether **3.276** underwent a Claisen rearrangement and subsequent reduction upon treatment with tri-*i*-butylaluminum, and elimination of the resulting alcohol and TBS-deprotection provided **3.277** in 72% yield over the six steps. With the pro-chiral divinyl moiety installed, attention was then turned to the installation of the third olefin required for the diastereoselective RCM.

The primary alcohol was oxidized to the aldehyde, and Wittig olefination yielded an α,β-unsaturated ester that was reduced to the primary alcohol **3.278**. Sharpless asymmetric epoxidation produced the desired epoxide with >99% enantioselectivity, and subsequent iodination and Boord elimination yielded allylic alcohol **3.279**. With the requisite triene in hand the key RCM could be attempted. After some experimentation, it was found that the best results were obtained when the alcohol was protected as its TMS-ether. Thus, the RCM of the TMS-protected analogue **3.279** proceeded to provide **3.280** in 85% yield as a mixture (87:13) of separable diastereomers after hydrolysis of the silyl protecting group. A four step reaction sequence was used to convert **3.280** into amide **3.282**, which wsas cyclized and protected using Meyers's procedure.[273] Hydrogenation of the olefin over PtO_2 gave **3.283**, which is an intermediate first accessed by Stork in racemic form and is the enantiomer of Meyers intermediate **3.156**. Although this completed a formal synthesis, the authors followed Stork's protocols and completed the total synthesis of (-)-aspidospermidine.

Scheme 3.43

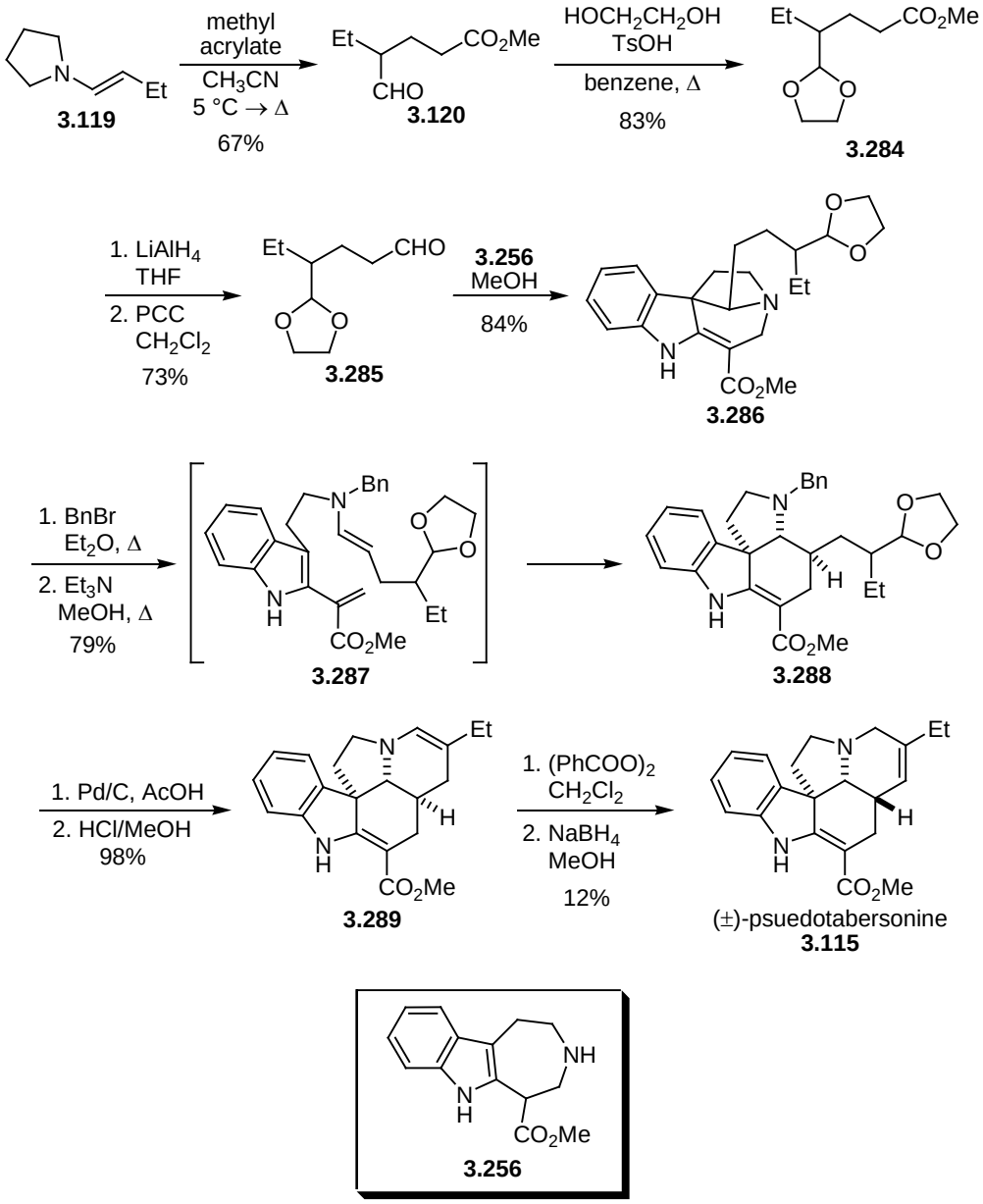

1. TBSO(CH2)3Br
t-BuLi, THF
-78 °C → rt
2. 3.274, NaH
DME, Δ
61%
3.273
3.275
1. DIBAL
THF, 0 °C
2. EtOCH=CH2
Hg(OAc)2, Δ
1. i-Bu3Al
CH2Cl2
2. o-NO2PhSeCN
PBu3, THF
3. H2O2, THF
4. HCl, EtOH
72%
3.276
3.277
1. Swern
oxidation
2. PhP=CCO2Et
benzene, Δ
3. DIBAL
THF, 0 °C
90%
3.278
1. L-(+)-DIPT
Ti(Oi-Pr)4,TBHP
4 Å ms, CH2Cl2
2. I2, PPh3, Imid.
benzene
3. Zn, AcOH, 50 °C
83%
>99% ee
3.279
1. TMSCl. Et3N
CH2Cl2
2. 10% Grubbs II
CH2Cl2
3. 1% HCl, THF
85%
87:13 dr
3.280
1. TBAF, THF
2. Jones
oxidation
86%
1. (COCl)2
CH2Cl2
2. NH3, THF
78%
3.281
3.282
1. TsOH
benzene, Δ;
ethylene
glycol, Δ
2. H2, PtO2
EtOH
86%
3.283
(-)-aspidospermine
3.128
3.274

3.2.3 Syntheses of Pseudotabersonine

3.2.3.1 Kuehne's Synthesis of Pseudotabersonine

The first total synthesis of pseudotabersonine was reported by Kuehne in 1992, and utilized an approach that was slightly modified from Kuehne's previously discussed biomimetic syntheses (see Section 3.2.3.7).[262] The synthesis began with the 1,4-addition of enamine **3.119** to methyl acrylate to give **3.120** in 67% yield. The aldehyde in **3.120** was then protected as its acetal, and a two step reduction/oxidation protocol gave **3.285**. Aldehyde **3.285** was then reacted with azepine **3.256** (see Scheme 3.44 for its synthesis) to give **3.286** in 84% yield. The quaternary ammonium salt of **3.286** was formed by reacting **3.286** with benzyl bromide in refluxing ether, and upon heating this salt with triethylamine in MeOH, a fragmentation occurred to provide **3.287**, which spontaneously cyclized under the reaction conditions to give **3.288** in 79% yield. Note that the stereochemistry for what will become the C/D ring fusion generated in this reaction is *trans*, and an epimerization at a later stage would be needed. The benzyl group was then removed under hydrogenation conditions, and after hydrolysis the desired enamine **3.289** was formed in 98% yield. The oxidation of enamine **3.289** to a 1,2-dihydropyridine was accomplished with dibenzoyl peroxide, and subsequent reduction with $NaBH_4$ afforded the natural product in only 12% yield over the two steps. Thus the synthesis of pseudotabersonine was completed in 15 steps and roughly 1% overall yield.

Scheme 3.44



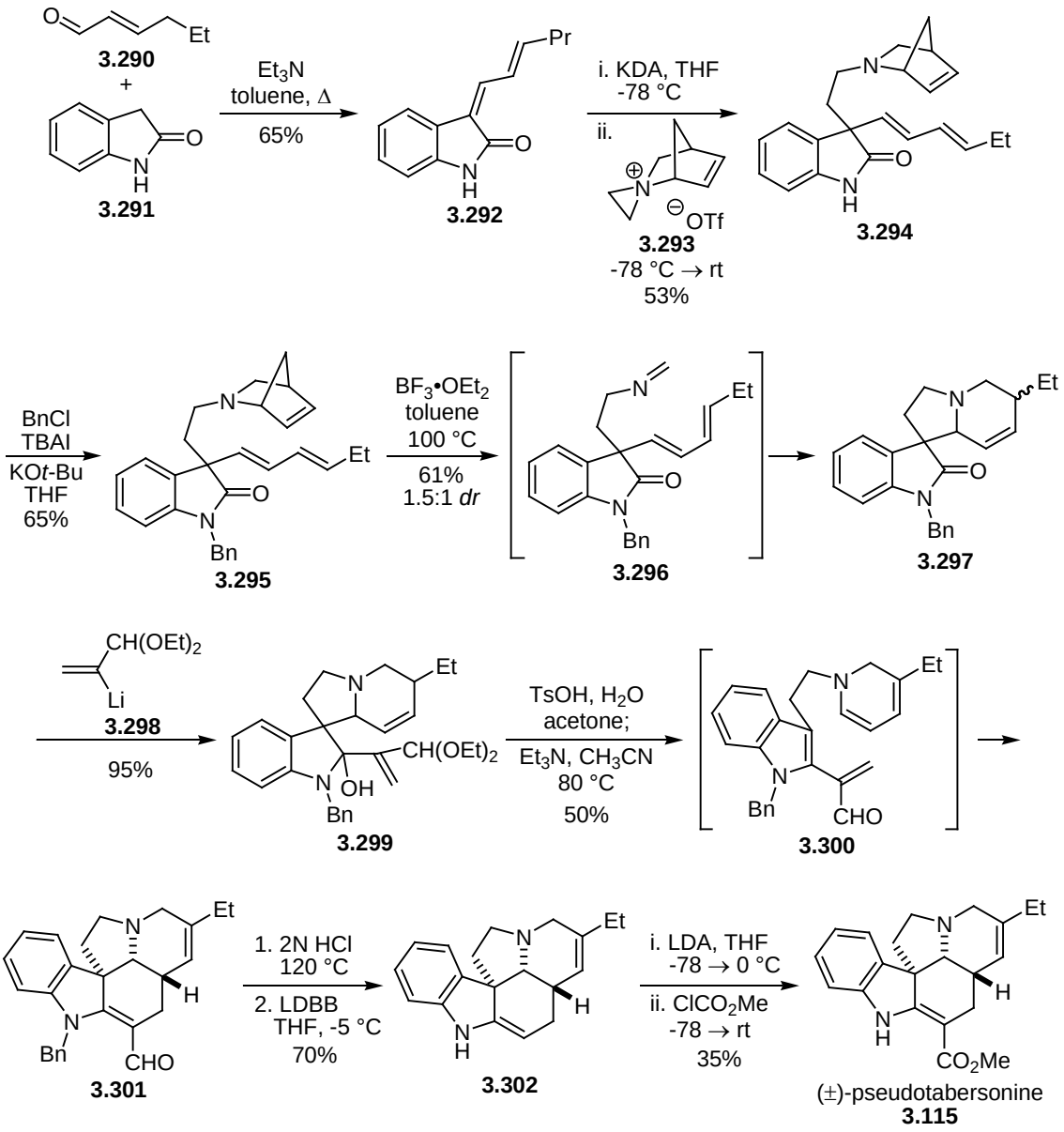
3.2.3.2 Grieco's Synthesis of Pseudotabersonine

In 1993 Grieco published his biomimetic approach to pseudotabersonine (Scheme 3.45).[263] Grieco's synthesis began with the condensation of oxindole with 2-hexenal (**3.290**) to afford **3.292** in 65% yield. Treatment of **3.292** with potassium

diisopropylamide (KDA) in THF at -78 ºC followed by addition of azidinium triflate **3.293** gave **3.294** in 53% yield. The oxindole was then *N*-benzylated to yield **3.295**. Upon treatment with $BF_3 \cdot OEt_2$ in toluene at 100 ºC, **3.295** underwent a retro [4+2] cycloaddition to genreate **3.296**, which subsequently underwent an intramolecular aza-Diels-Alder to give spiroxindole **3.297** as an inconsequential mixture (1.5:1) of diastereomers. The addition of 2-lithio-1,1-diethoxy-2-propene (**3.298**) to the oxindole provided **3.299** in excellent yield. The *N,O*-hemiacetal **3.299** was treated with tosic acid in aqueous acetone, and upon completion of the acetal hydrolysis, acetonitrile and triethylamine were added and the reaction was heated at 80 ºC to afford **3.301** in 50% yield via the secodine like intermediate **3.300**. Thus, the pentacyclic core of pseudotabersonine had been assembled in short order, and attention was turned to the conversion of **3.301** into the natural product.

All that remained for the completion of the synthesis was the oxidation of aldehyde **3.301** to the methyl ester and removal of the benzyl protecting group. However, all attempts to oxidize **3.301** were unsuccessful, and an alternative strategy was adopted. The deformylation of **3.301** was accomplished by heating **3.300** to 120 ºC in 2 N HCl, and subsequent removal of the benzyl group provided **3.302**. Following Overman's procedure,[321] **3.302** was *C*-acylated to give pseudotabersonine in 35% yield. No comment was given as how much *N*-acylated product was formed in the reaction. The total synthesis was completed in 11 steps and 1.4% yield.

Scheme 3.45



3.2.4 Conclusion

Since Stork's pioneering synthesis of aspidospermine and quebrachamine in 1963, the *Aspidosperma* alkaloids have attracted an enormous amount of attention from synthetic chemists. A number of conceptually different approaches to the pentacyclic

core structure have been developed, allowing for access to virtually every member of this family of alkaloids. Despite the considerable effort put forth towards this family of alkaloids, the aspidospermine alkaloids still attract the attention of contemporary organic chemists. The interest in the aspidospermine alkaloids persists for two main reasons: the pentacyclic aspidospermine scaffold remains to this day to be a challenging target suitable for the development and testing of new synthetic methodologies and because there has not been a synthesis of these molecules that cannot be improved upon. Due to the interesting biological properties displayed by members of this family of alkaloids, the desire to develop more concise and efficient syntheses still exists, so that members of this family can be accessed in quantity in a rapid fashion for use in various biological settings.

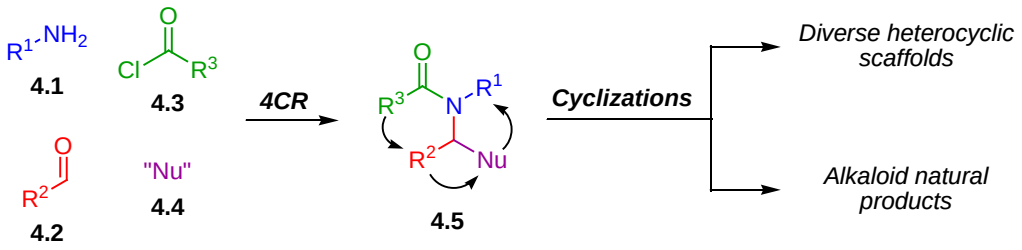
Our interest in the aspidospermine and isopavine alkaloids came from the desire to apply our previously developed four component reaction (see Chapter 2) to natural product synthesis. It was envisioned that if the appropriate functional handles could be incorporated into the 4CR, that the core structures of these two families of natural products could be readily accessed using our 4CR/cyclization strategy. Not only would the application of the 4CR to these two families of natural products highlight its utility in synthesizing natural product-like libraries, but it could also potentially lead to some of the shortest syntheses of both the isopavine and aspidospermine alkaloids to date. The results of the endeavors into the arena of natural product synthesis are presented in the following Chapter.

Chapter 4: Applications of the Four Component Reaction to Natural Product Synthesis

4.1 Introduction

In Chapter 2 we discussed the development of a four component reaction (4CR) for the generation of highly functionalized amides that can be transformed into heterocyclic scaffolds in a short number of steps (Scheme 4.1).150 Although this 4CR was originally developed for use in diversity oriented synthesis (DOS), its applications to natural product synthesis would further showcase its utility as a synthetic strategy. Also, when one considers the emphasis that is placed on synthesis of natural product like libraries,351-353 and on the natural products themselves,[5, 354] in drug discovery, the ability for our methodology to access natural products becomes all the more important.

Scheme 4.1



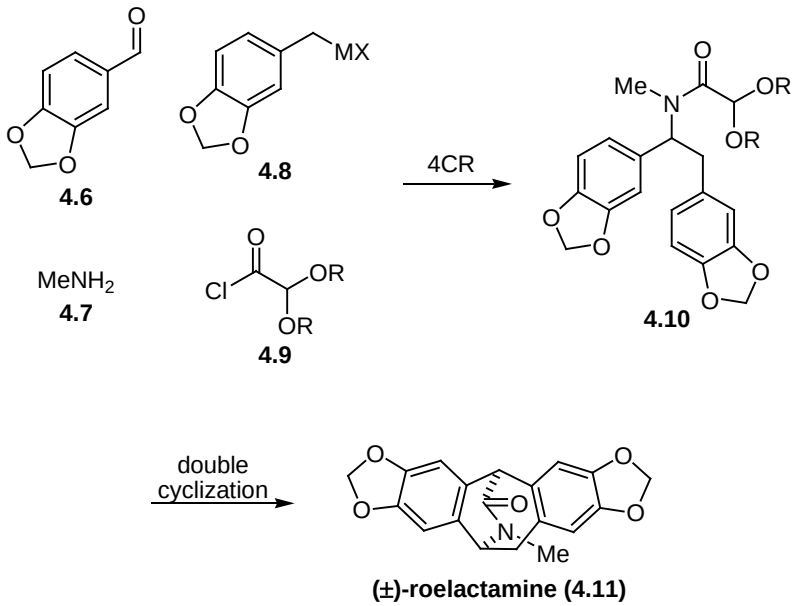
To this end, we undertook the task of identifying classes of natural products that could potentially be accessed utilizing this methodology. Two families of natural products that specifically caught our attention were the isopavine and *Aspidosperma* alkaloids. Both of these families of alkaloids have interesting heterocyclic scaffolds, and both contain members that display a range of useful biological activities, making them ideal targets for applying the 4CR. If the 4CR can provide an efficient route to the functionalized skeletons contained in these natural products, it stands to reason that in addition to completing their total syntheses, a number differentially functionalized analogues could be generated for testing in biological assays.

4.2 Application of the 4CR to the Total Synthesis of Roelactamine

As discussed in Chapter 3 the isopavine alkaloids are a small family of tetracyclic tetrahydroisoquinoline natural products that are characterized by a doubly benzannulated azabicyclo[3.2.2]nonane core structure (see roelactamine (**4.11**), Scheme 4.2).[209, 210] Both natural and unnatural members of the isopavine family have been shown to posses interesting biological properties for the treatment of Alzheimer's disease, Hungtington's chorea, and Parkinson's and Down's syndromes.[213, 214] For this reason we thought that this family of natural products would be a good target to access via the 4CR. Specifically, we targeted roelactamine (**4.11**), which was isolated in 1992 from Roemeria refracta DC. (Papaveraceae) and is the first isopavine alkaloid known that possesses a lactam.[218] There has been no reported biological activity for roelactamine, as well as no reported total syntheses.

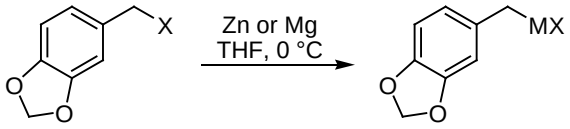
We envisioned that a 4CR of piperonal (**4.6**), methylamine, organometallic reagent **4.8**, and an appropriately functionalized acid chloride **4.9**, would provide amide **4.10**, which could undergo a double cyclization to give **4.11** (Scheme 4.2). All four starting materials are readily available, and the double cyclization is a classical approach to this family of natural products, so this synthetic strategy should allow for quick access to roelactamine.

Scheme 4.2



Previously, the only nucleophiles used in the 4CR were silyl ketene acetals, silyl enol ethers, and allylzinc bromide, so we first turned our attention to testing whether or not a benzyl organometallic reagent would be a compatible in the 4CR. After some experimentation, it was found that the benzylzinc bromide **4.14** could be prepared by slow addition of a solution of piperonyl bromide (**4.12**)[355] in THF to a suspension of zinc in THF at 0 °C (Scheme 4.3). In a modification of the literature procedure,[356] the corresponding Grignard reagent **4.15** could be prepared in a identical manner from piperonyl chloride (**4.13**).[357] With methods to prepare both the required organozinc and Grignard reagent in hand, the next step was to employ these nucleophiles in the multicomponent reaction.

Scheme 4.3

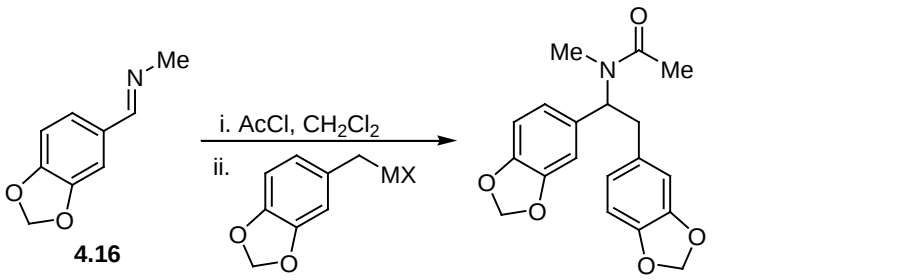


4.12: X = Br
4.13: X = Cl

4.14: MX = ZnBr
4.15: MX = MgCl

To test the viability of these nucleophiles in the 4CR, a model three component reaction (3CR) was first examined (Scheme 4). Starting from imine **4.16**, a stepwise addition of acetyl chloride and either organozinc reagent **4.14** or Grignard reagent **4.15** provided the desired amide **4.17** in moderate yields. These results show that the use of a benzyl organometallic in the 4CR was possible, and that our route to (±)-roelactamine was viable.

Scheme 4.4



4.16

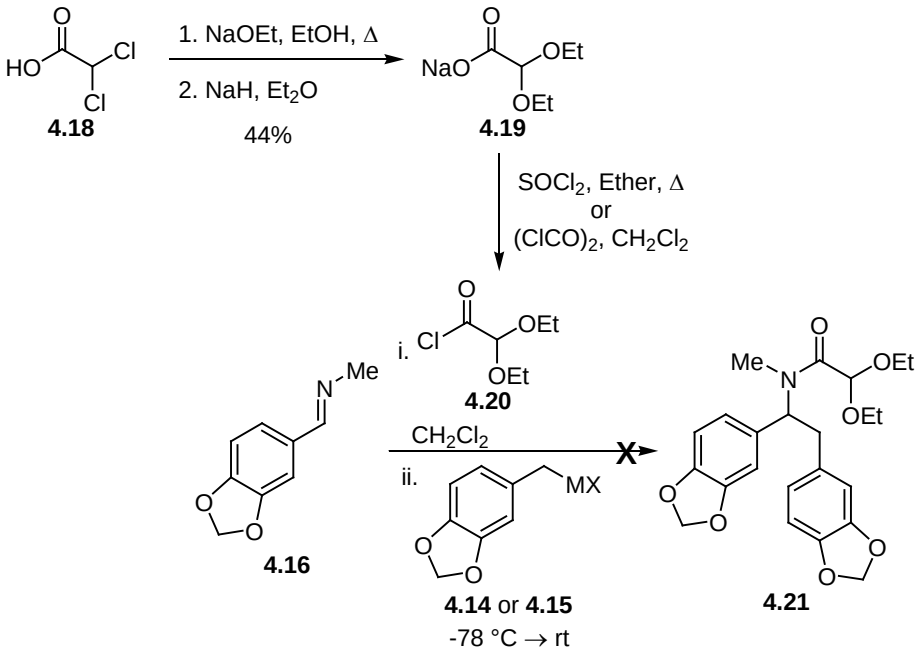
4.14 or **4.15**
-78 °C → rt

4.17
MX = ZnBr ~70% (yield based on [**4.14**])
MX = MgCl 52 %

The next step was then to find an appropriate acid chloride that would work in both the 4CR and the subsequent double cyclization. Our initial efforts focused on diethoxyacetyl chloride (**4.20**), as this was a known compound that had previously been made from sodium diethoxyacetate and thionyl chloride in refluxing ether.[358] However, attempts to prepare and isolate **4.20** using this method were unsuccessful, as were methods using oxalyl chloride. Synthesizing **4.20** directly from diethoxyacetic acid was also unsuccessful. Although it was troublesome that **4.20** could not be isolated, the acid

chloride had been previously made and used in situ,[358] so this approach was attempted (Scheme 4.5). Acid chloride **4.20** was prepared from both thionyl chloride and oxalyl chloride, and the reaction mixture was added directly to a solution of imine **4.16** in CH_2Cl_2. In both cases the reaction immediately turned an opaque, dark reddish orange color, and upon addition of zinc reagent **4.14** or Grignard reagent **4.15** none of the desired product was formed. With this approach being unsuccessful, the next move was to investigate reversing the order of addition of the nucleophile and acid chloride.

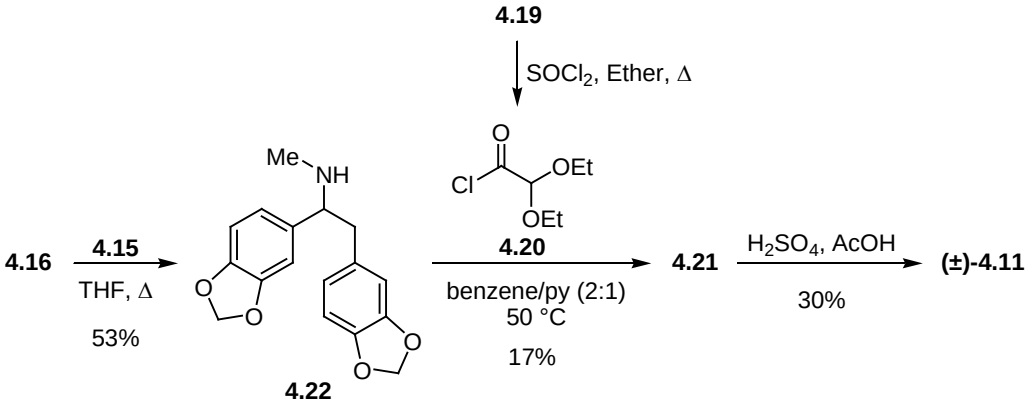
Scheme 4.5



By performing the nucleophilic addition to the imine instead of the *N*-acyl iminium ion, the reaction can be run stepwise, and the intermediary secondary amine can be isolated prior to acylation, which helps to ensure that each individual step of the reaction sequence is working. To this end imine **4.16** was treated with Grignard reagent **4.15** in refluxing THF to provide **4.22** in an unoptimized 53% yield (Scheme 4.6). Heating the reaction at reflux was necessary in order to drive the reaction to completion

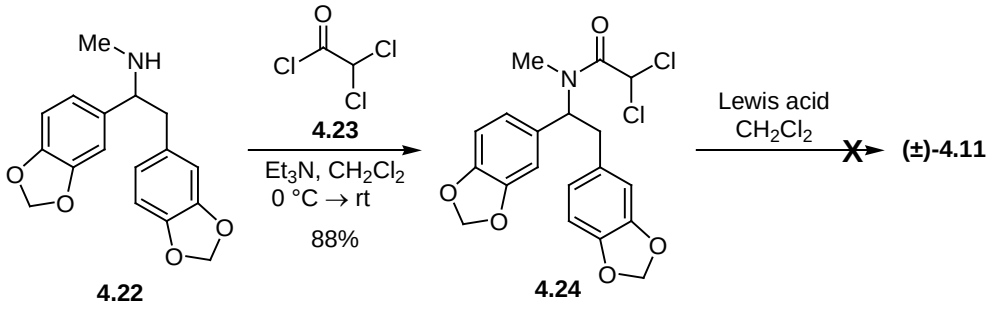
within a reasonable time period (24 h). Following literature conditions,[358] acid chloride **4.20** was prepared using thionyl chloride. A solution of **4.22** in benzene/pyridine (2:1) was then added to the crude **4.20** and the reaction heated to 50 °C to produce the desired amide **4.21** in 17% yield. When **4.21** was treated with H_2SO_4 in AcOH[232] the desired natural product was produced in 30% yield. Although this route did lead to the synthesis of **(±)-4.11**, the stepwise nature of the route along with the low yields led to the pursuit of other acid chlorides for use in the synthesis, because it was believed that the problems were associated with the synthesis of acid chloride **4.20** and not with the underlying route itself.

Scheme 4.6



One possibility for an alternate acid chloride is the use of dichloroacetyl chloride, which would provide **4.24**, a substrate suitable for a double Friedel-Crafts cyclization. Treatment of **4.22** with dichloroacetyl chloride and Et_3N in CH_2Cl_2 provided **4.24** in 88% yield (Scheme 4.7). Amide **4.24** was then treated with a variety of Lewis acids in CH_2Cl_2. Although in all cases the starting material was consumed, none of the desired product was produced. These unpromising results led us to investigate the use of other acid chlorides.

Scheme 4.7

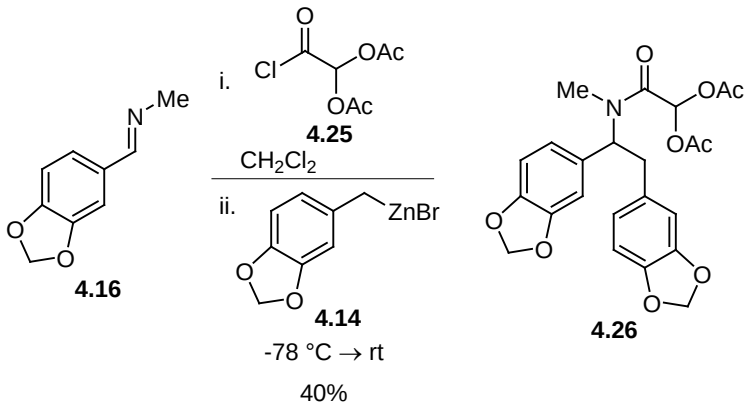


Lewis Acids tried: $SnCl_4$, $AlCl_3$, $ZnCl_2$, $FeCl_3$

Diacetoxyacetyl chloride (**4.25**) was chosen next as it can easily be made in gram quantities from glyoxylic acid.[359] The increased stability of **4.25** over **4.20** would presumably make **4.25** easier to handle and employ in the 4CR. The ability to distill **4.25** would also ensure that the reactions could be run with pure acid chloride, something that was in question when using **4.20**. Indeed, the use of diacetoxyacetyl chloride eventually allowed for the synthesis of **(±)-4.11** to be completed as originally designed.

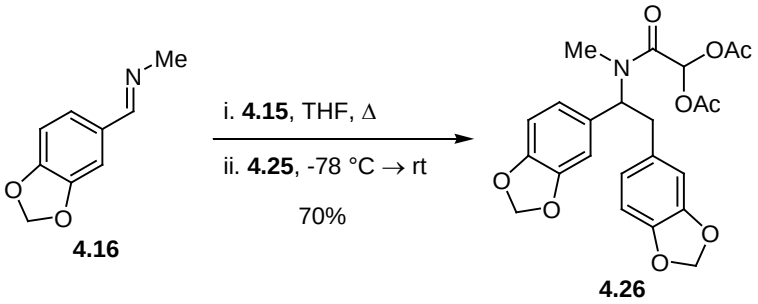
The first attempts employing acid chloride **4.25** were made in the 3CR using the zinc reagent **4.14** (Scheme 4.8). When imine **4.16** was treated sequentially with **4.25** and **4.14** in CH_2Cl_2, the desired product **4.26** was produced in 40% yield. One possibility for the low yield is that the *N*-acyl iminium ion did not form completely, but stirring the imine and acid chloride for 7 h instead of 2 h before adding the benzyl zinc reagent actually resulted in a reduced yield. Attempts to improve this yield by using Grignard **4.15**, in either CH_2Cl_2 or THF, were completely unsuccessful and none of the desired product could be isolated.

Scheme 4.8



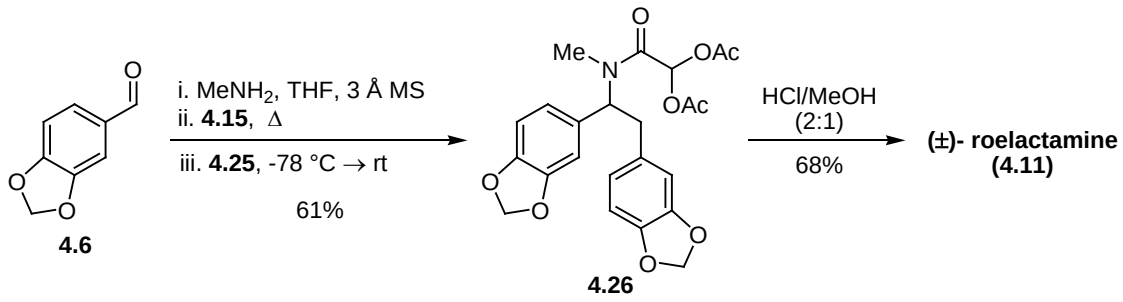
In parallel with these reactions we were also examining running the reactions *via* a nucleophilic addition/acylation strategy, and since these reactions showed more promise focus placed on them. The initial investigations into running the 4CR using an addition/acylation strategy were made on the preformed imine **4.16** (Scheme 4.9). After some experimentation, it was found that the reaction of imine **4.16** and Grignard reagent **4.15** would only consume starting material (as determined by TLC) when the imine was treated with 2 eq. of Grignard reagent in refluxing THF. Upon cooling the reaction to -78 °C and adding **4.25** the desired product **4.26** could be isolated in 70% yield. Addition of the acid chloride at higher temperatures resulted in drastically reduced yields. With good results for the 3CR in hand, attention was then turned to the 4CR and the completion of the synthesis.

Scheme 4.9



When the imine formed in situ from the reaction of piperonal and methylamine was treated sequentially with Grignard reagent **4.15** and acid chloride **4.25**, **4.26** was produced in 61% yield (Scheme 4.10). Interestingly, imine formation occurred only when 3 Å pellet type molecular sieves were used. None of the desired imine was isolated using 3 Å powdered sieves or 4 Å sieves. When **4.26** was treated with conc. HCl/MeOH (2:1) the desired double cyclization occurred and **(±)-4.11** was isolated in 71% yield, thus completing the synthesis. One source of material loss is from competitive elimination of the amide side chain. To prevent this side reaction from occuring, the double cyclization was attempted with $BF_3 \cdot OEt_2$ in CH_2Cl_2, which gave none of the desired product, and with H_2SO_4 in cold MeOH, which gave the desired product, but in lower yields.

Scheme 4.10



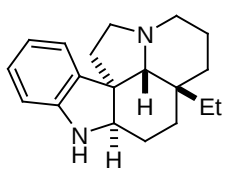
The first total synthesis of (±)-roelactamine has been completed in four steps from commercially available materials. This synthesis highlights the utility of the

4CR/cyclization strategy that we had previously developed for DOS. Additionally, this route could be adapted to make a library of isopavines simply by adding additional functionality to any of the four components.

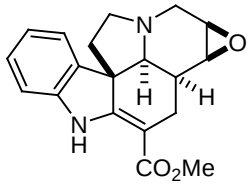
4.3 Applications of the 4CR Towards the Synthesis of *Aspidosperma* Alkaloids

As discussed in Chapter 3, the *Aspidosperma* alkaloids are a large family of alkaloids characterized by a pentacyclic skeleton, of which aspidospermidine (**4.27**) is the prototypical member (Figure 4.1).[252] Their interesting structural features and biological activities make this an interesting class of compounds for synthesis via the 4CR.

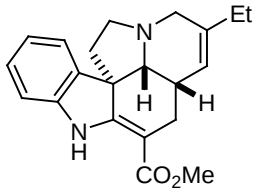
Figure 4.1



(+)-aspidospermidine
4.27



rosicine
4.28

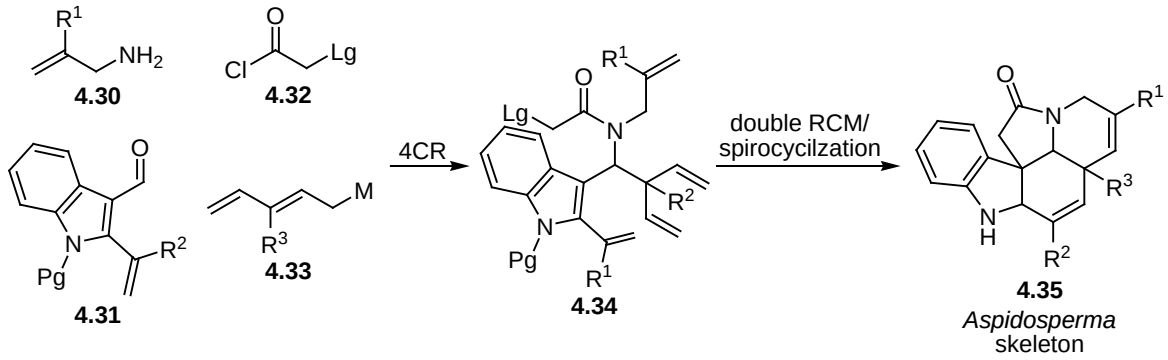


pseudotabersonine
4.29

It was envisioned that by carefully selecting the inputs of the 4CR we could generate substrates that could be readily transformed into the aspidospermine skeleton, thus allowing for a quick entry to this class of natural products (Scheme 4.11). The condensation of allyl amine **4.30** with an appropriately functionalized 3-indolecarboxaldehyde **4.31** would provide an imine, which could then be allowed to react with acid chloride **4.32** and an appropriate pentadienyl metal to give **4.34**. Compound **4.34** is functionalized to undergo a double ring closing metathesis (RCM) followed by a spirocyclization to give **4.35**. Depending on the nature of R^1, R^2, and R^3, **4.35** could be further elaborated into any number of alkaloids in the *Aspidosperma* family, as well as unnatural analogues. This route allows for explorations into the pentadienylation of

imines and *N*-acyl iminium ions, and it provides a potential opportunity to further investigate the use of chiral RCM catalysts in complex molecule synthesis.[360]

Scheme 4.11

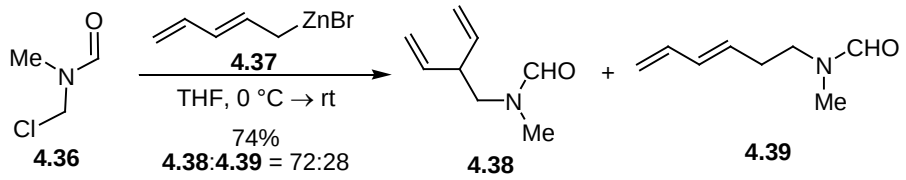


4.3.1 The Pentadienylation of Imines Leading to Branched Products

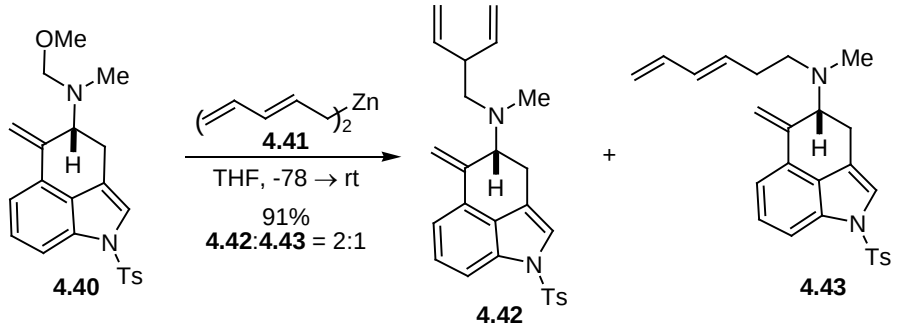
The viability of this route falls to a large extent on finding a pentadienyl metal **4.33** that will react with either an imine or *N*-acyl iminium ion to selectively generate the branched pentadienylation product **4.34**. Fortunately, a significant amount of work has been done in the area of carbonyl pentadienylation, providing sufficient precedent for us to believe that this could indeed be a viable approach. For example, pentadienyl Li, Mg, Zn, Al, Ti, Si, Sn, and In reagents have been synthesized and their reactivity with carbonyl compounds studied.[179, 200, 361-371] While the vast majority of the work in this field has been focused on the pentadienylation of aldehydes and ketones, a few reported examples involving the pentadienylation of imines,[365] *N*-sulfonyl imines,[365, 366] 1,2-diimines,[367] iminium salts,[368] *N,O*-acetals,[200, 369] α-chloroformamides,[370] and *N*-acyl iminium ions[150, 179] exist in the literature.

However, of the reports on the pentadienylation of imines or imine surrogates only a handful of examples involve conditions that lead selectively to the branched product. Miginiac has shown that pentadienyl zinc bromide (**4.37**) can react with α-chloroformamide **4.36** to provide a mixture (2.5:1) of branched and linear products

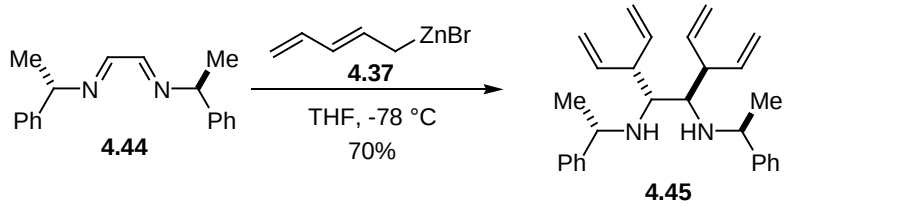
favoring the branched product (Eq. 4.1).[370] Similar results have been obtained by Dr. Jason Deck when bis-pentadienyl zinc (**4.41**) was reacted with *N,O*-acetal **4.42** (Eq. 4.2).[200] Savoia and co-workers have shown that glyoxal derived 1,2-diimine **4.44** can react with pentadienyl zinc bromide to give the branched product exclusively (Eq. 4.3).[367] Finally, Nishigaichi has shown that *N*-sulfonyl imines react with pentadienyltin in the presence of $InCl_3$ or $ZnCl_2$ to give only branched products (Eq. 4.4).[365] Interestingly, when BF_3OEt_2 is used as the Lewis acid in this reaction, the linear isomer becomes the major product. From this precedent it is apparent that a good general method for the pentadienylation of imines that provides high levels of selectivity towards the branched product does not exist, and it was hoped that a suitable solution to this problem could be found in the course of our investigations.



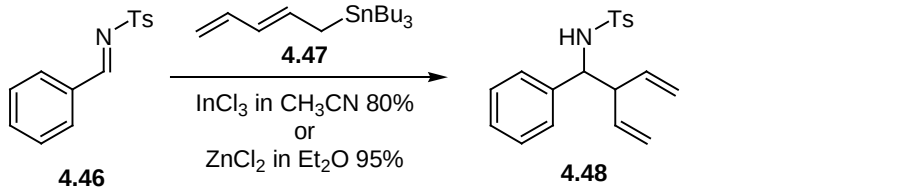
(4.1)



(4.2)



(4.3)

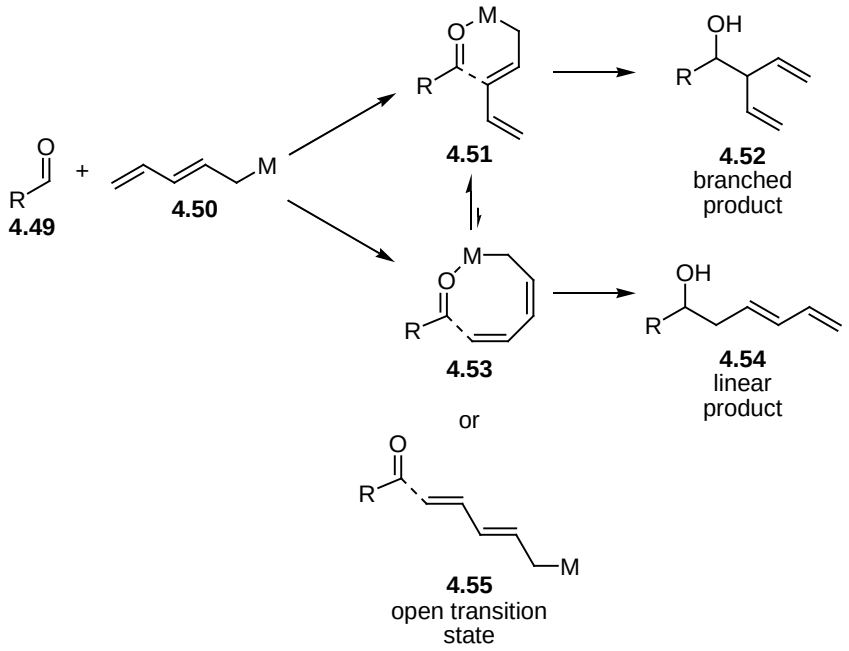


(4.4)

We have previously shown that our 4CR can be run using a number of different experimental protocols, and we hoped that this experimental flexibility could be exploited here. It is generally accepted that the branched product arises in the pentadienylation of a carbonyl compound from a Zimmerman-Traxler transition state **4.51**,[361, 364, 365, 371] while the linear product can arise from a less favorable eight membered transition state **4.53** or through an open transition state **4.55** (Scheme 4.12). Traditionally, the 4CR is run using a nucleophilic addition to an *N*-acyl iminium ion protocol, but *N*-acyl iminium ions have no vacant coordination sites on the nitrogen atom to create a transition state like **4.51**.

This inability to coordinate a metal could potentially lead to a situation where the branched product is a minor product in the pentadienylation, if it is formed at all. However, since the 4CR can also be performed using a nucleophilic addition/acylation protocol, and the Lewis basic imine nitrogen can be utilized to coordinate a pentadienyl metal and therefore enable the desired 6-membered ring transition state, hopefully leading to higher levels of selectivity towards the branched product. Since previous precedent suggests that the coordination of the pentadienyl metal by the carbonyl compound is important for selectivity, it was decided that our initial investigations should be made using the nucleophilic addition/acylation protocol.

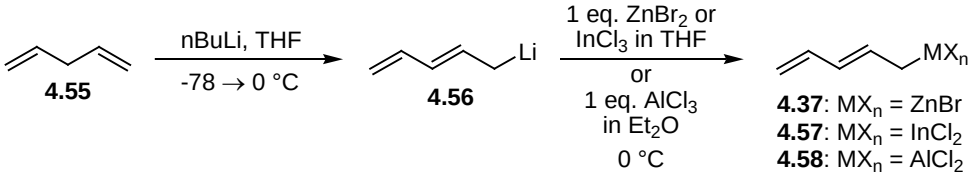
Scheme 4.12



Pentadienyl metals **4.50** can be formed by a variety of methods, and we chose to use 1,4-pentadiene (**4.55**) as our starting material. 1,4-Pentadiene is readily deprotonated by BuLi and transmetalated to a number of other metals by addition of the corresponding metal halide salt (Scheme 4.13). For the case of $ZnBr_2$ and $InCl_3$, the salts were added to

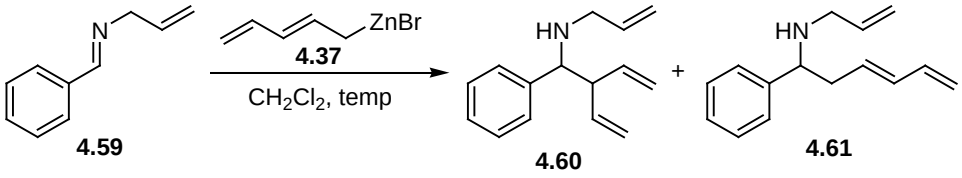
a solution of the pentadienyl lithium as a solution in THF. However, for $AlCl_3$ the use of Et_2O was necessary, as $AlCl_3$ rapidly reacts with THF. These protocols allowed for easy access to **4.37**, **4.57**, and **4.58** and became the standard procedure that was followed for all studies discussed herein.

Scheme 4.13



Previous work from the Martin group[200] and the literature[367, 370] suggested that pentadienyl Zn shows high levels of selectivity for branched products and therefore was chosen as our starting point (Scheme 4.14). Treatment of imine **4.59** with **4.37** at -78 ºC resulted in consumption of the starting material at -78 ºC, and upon warming to room temperature the linear product **4.61** was isolated as the major product in 71% yield. When the reaction was run at room temperature, both the yield and selectivity for the linear isomer **4.61** were increased. While the levels of selectivity where good, the linear product **4.61** was not the desired regioisomer, and therefore studies of other pentadienyl reagents were necessary.

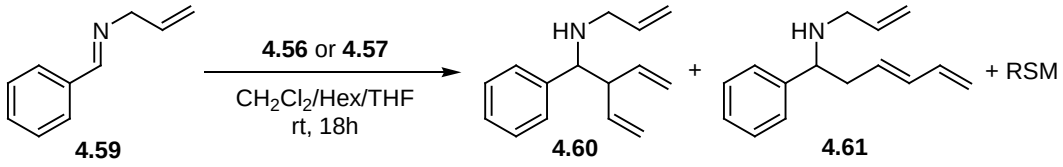
Scheme 4.14



temp	Yield	4.60:4.61
-78 °C → rt	71%	>1:10
rt	82%	>1:19

Both pentadienyl Li and In showed selectivity similar to Zn, forming **4.61** as the major product (Scheme 4.15). In both cases the overall reactivity was lower, and neither reaction consumed starting material. In the case of pentadienyl Li, one possible reason for the low conversion to product is that **4.44** might react with the CH_2Cl_2 faster than the imine, effectively quenching the reagent. This could be prevented by switching to a solvent like THF, but since the overall selectivity for the branched product in this reaction was low this was not pursued.

Scheme 4.15

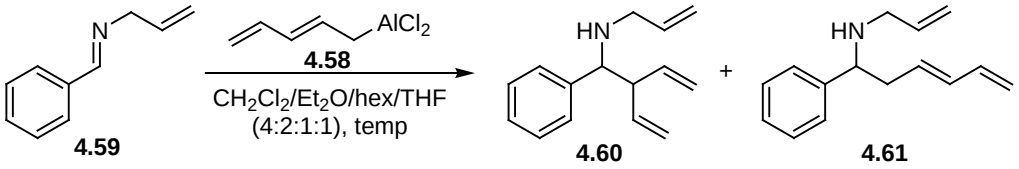


For **4.56**: ~30% conv. 1:3 **4.60**:**4.61**
For **4.57**: ~50% conv. 1:4 **4.60**:**4.61**

In our search for other metals that might react selectively with imines to give branched products, it was found that Miginiac had observed increased selectivities (versus pentadienyl Zn, Li, or Mg) for branched products when pentadienyl aluminum was used in reactions with aldehydes and ketones.[362] Based on this precedent; we decided to investigate the reactivity of pentadienyl Al reagent **4.47** (Table 4.1). When a freshly prepared solution of **4.58** in Et_2O/hexane/THF was added to a solution of imine **4.59** in CH_2Cl_2 the starting material was consumed at -78 ºC, and upon warming to room

temperature both **4.60** and **4.61** were isolated in almost equal amounts (entry 1), already a vast improvement over the zinc reagent. When the addition was done at room temperature, the reaction was done in <10 min, and the ratio of branched to linear products improved slightly (entry 2). It was subsequently discovered that longer reaction times greatly improved the selectivity for the branched product (entries 3 and 4), and it was found that after 18 h the ratio of **4.60** to **4.61** increased to 7.5:1, and **4.60** could be isolated in 70% yield. Further heating this reaction to reflux did not improve the ratio (entry 5). When the reaction was run with 0.33 eq. of $AlCl_3$ in an effort to make a trialkylaluminum reagent,[372] the yield and conversion dropped substantially (entry 6). THF was found to be necessary for the lithiation of 1,4-pentadiene, as no reaction occurred when Et_2O was substituted for THF (entry 7). The use of the non-coordinating solvent CH_2Cl_2 was also critical for selectivity, because when THF was used instead a dramatic drop in the selectivity for the branched product was observed, even when the reaction was heated (entry 8).

Table 4.1



4.59 4.60 4.61

Entry	Temp	Time	4.60:4.61[a]	% Conv.[a]	Isolated Yield 4.60/4.61
1	-78 °C → rt	2h	1:1.1	100	31%/37%
2	rt	5 min	1.6:1	~90	nd
3	rt	30 min	4:1	100	nd
4	rt	18h	7.5:1	100	70%/2%
5	reflux	18h	6:1	100	nd
6[b]	rt	24h	5:1	~50	nd
7[c]	rt	24h	nd	0	nd
8[d]	60 °C	24h	1.2:1	100	nd

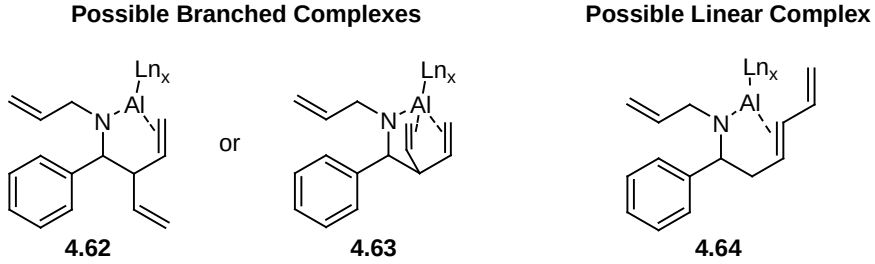
[a] Determined by NMR of crude rxn mixture. [b] Used 0.33 eq $AlCl_3$.
[c] Et_2O used instead of THF. [d]THF used instead of CH_2Cl_2.
nd = not determined

The fact that the ratio of branched to linear product improved as the temperature was increased from -78 ºC to room temperature and as the reaction times increased suggests that the branched product might be the thermodynamic product under these reaction conditions. However, the evidence from the literature and from the above experiments using pentadienyl ZnBr suggests that the exact opposite is true. It is known that under basic conditions that the allylation and pentadienylation of imines is reversible and that the branched product can be interconverted to the linear product.[373] However, the interconversion of linear products to branched products has not been reported in the literature, and in our system it appears that this interconversion of linear to branched product is occurring. Therefore, it can be concluded that the aluminum must be playing an important role in making **4.60** the major product.

A possible explanation for this is the fact amines **4.49** and **4.50** are not the products of this reaction, and are only formed upon hydrolysis of a stable aluminum chelate after aqueous work up. Aluminum is a strong Lewis acid that can coordinate with

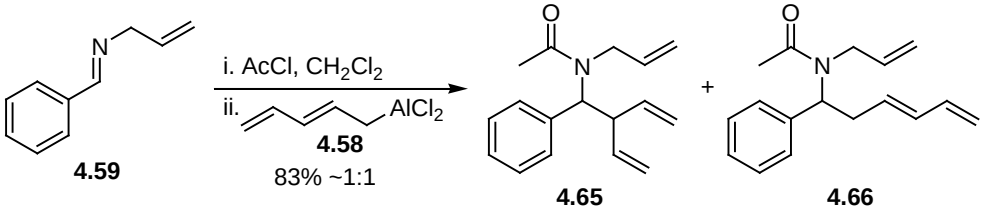
both amines and olefins and indeed a strongly basic work up (1 M NaOH) was required to isolated **4.60** and **4.61**. When a slightly acidic work up was performed (sat. NH_4Cl) good crude mass recovery was obtained after work up; however, the ^1H NMR of the crude reaction mixture showed only trace amounts of the desired products, along with signals that presumably corresponded to the aluminum complex. If the pathway leading towards the branched product does go through a 6-membered transition state similar to **4.51** leading to an aluminum chelate similar to **4.62** or **4.63** (Figure 4.2), then perhaps these are more stable than the corresponding complex that lead to the linear product.

Figure 4.2



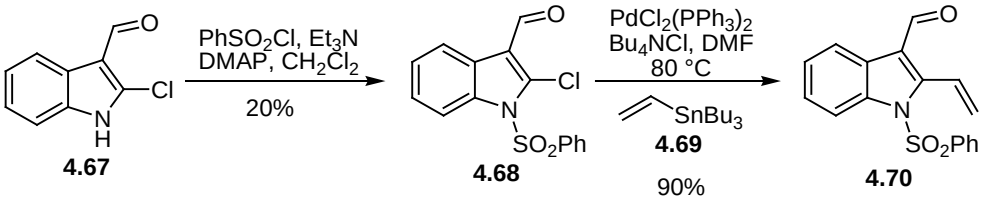
To this point it has been shown that pentadienyl aluminum reagent provides good yields of branched products when reacting with imine **4.59**, but there was still interest in the reactivity of **4.58** with *N*-acyl iminium ions (Scheme 4.16). To this end **4.59** was sequentially treated with acetyl chloride and **4.58** at room temperature in CH_2Cl_2 to provide a ~1:1 mixture of **4.66** and **4.66** in good yield. This product ratio was found to be insensitive to reaction time. Miginiac has studied the pentadienylation of α-chloroformamides and found that with Li, Mg, Zn, and Al the linear product is the major product and that aluminum gave the best selectivity towards linear products.[370] Assuming that imine **4.59** and acetyl chloride react to give an *N*-acyl iminium ion, which is in equilibrium with a α-chloroamide, which is structurally similar to Miginiac's examples, better results may be found by switching the metal.

Scheme 4.16



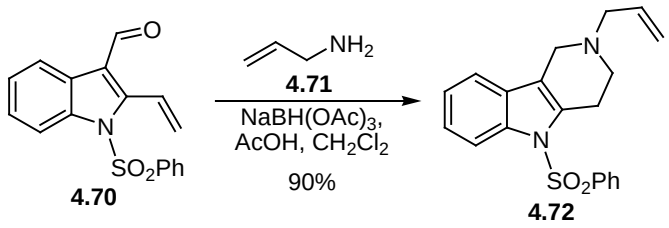
Confident in the pentadienylation conditions we had developed for imine **4.59**, we then ventured to apply these conditions to a system that could be further elaborated into the aspidospermine skeleton. To do this we would need a functionalized indole such as **4.70**. Indole **4.70** is known in the literature[374] and it, or a differentially protected 2-vinylindole-3-carboxaldehyde, would fit our needs nicely. Indole **4.70** was previously synthesized from 2-chloroindole-3-carboxaldehyde (**4.67**)[375] via a two step protection/Stille coupling sequence (Scheme 4.17).

Scheme 4.17

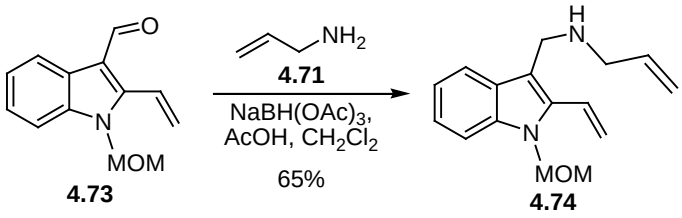


It has been reported that attempts to perform a reductive amination on **4.70** with allylamine and $NaBH(OAc)_3$ did not give the desired secondary amine, but rather gave γ-carboline **4.72** in high yields (Eq. 4.5).[376] Mechanistically this reaction is thought to proceed through a reversible 1,6-addition to the terminal olefin, followed by cyclization onto the aldehyde and reduction. This problem could be avoided by changing the protecting group from an electron withdrawing group to a group that is electronically neutral, and MOM-protected **4.73** underwent reductive amination to give **4.74** in 65%

yield (Eq. 4.6). Based on this precedent it was decided that aldehyde **4.70** was not a good candidate for our starting material, and alternative aldehydes were sought after.



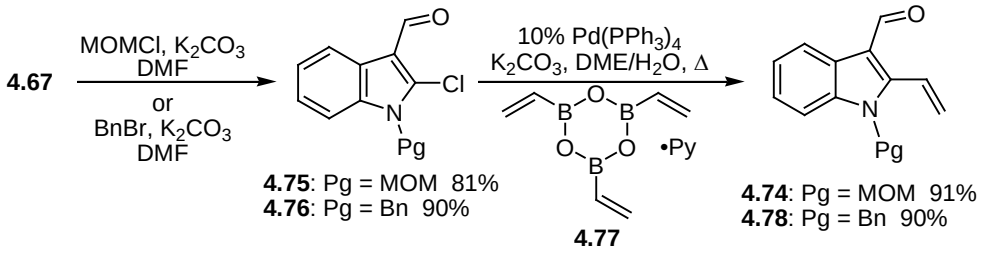
(4.5)



(4.6)

Since the above precedent showed that MOM-protected **4.73** could undergo a reductive amination, we thought that this would be a good protecting group to employ in our system (Scheme 4.18). The benzyl protected indole **4.78** was also investigated in parallel in case any unforeseen problems arose with the MOM group. To this end, **4.75** and **4.76** were synthesized in good yields and subjected to the Suzuki coupling to give **4.74** and **4.78**, also in high yields. With **4.74** and **4.78** in hand, investigations into synthesizing the requisite imines were undertaken.

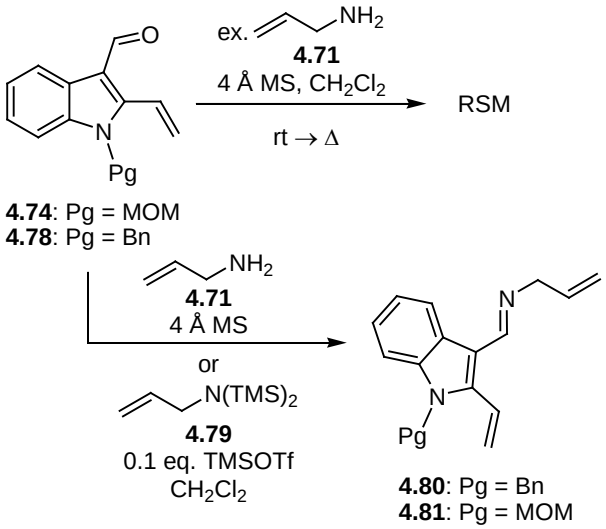
Scheme 4.18



When **4.74** and **4.78** were treated with allylamine in CH_2Cl_2, no reaction occurred, even when 10 equivalents of allylamine were used (Scheme 4.19). Using more forcing

conditions (neat allylamine or allyl HMDS with TMSOTf), provided the desired imines; however, these conditions did not provide clean product, and in all cases substantial quantities of side products were formed. This provided us with a minor setback that would require us to pursue a route with an alternative strategy for installation of the C-2 vinyl group.

Scheme 4.19

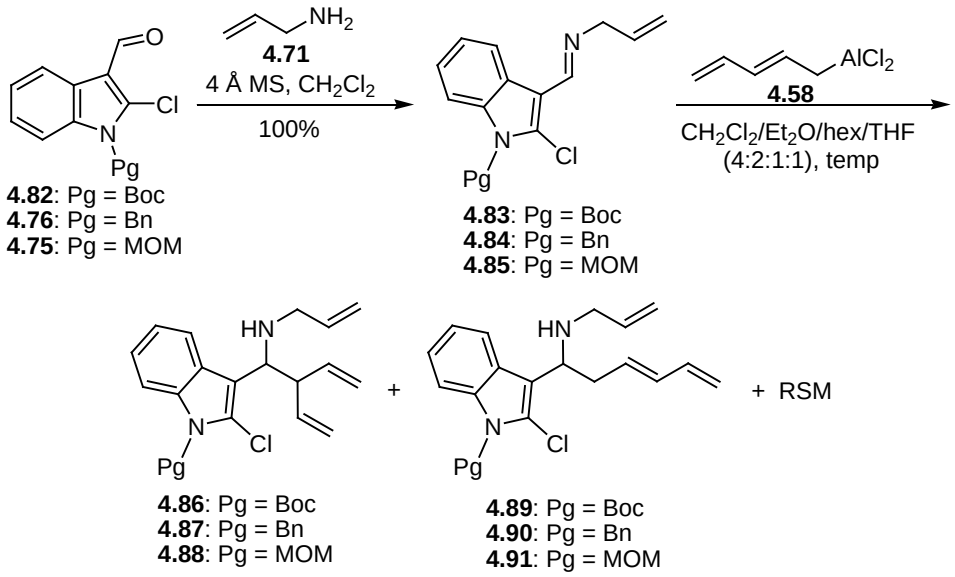


In order to access the aspidospermine core structure we had planned to perform a double RCM on a substrate such as **4.34** (Scheme 4.11), and for this transformation a vinyl group at the 2-position of the indole is required. Up until this point we had only investigated pathways that led to the vinyl group being installed before the imine formation and subsequent pentadienylation. It is also possible to install the vinyl group after the pentadienylation, and this could potentially avoid the previously discussed problems.

Since we had already synthesized a number of protected 2-chloroindoles, it was thought that this would be a good starting material as the chloride could potentially be converted into a vinyl group or utilized in a Heck cyclization that could be performed in

place of the double RCM. Towards this end, imines **4.83**-**4.85** were synthesized and subjected to the previously developed pentadienylation conditions using **4.58** (Scheme 4.20). When **4.83** was allowed to react with **4.58** at -78 ºC or at room temperature, the linear **4.89** was formed as the major product in modest yields. The benzyl protected **4.84** also reacted with **4.58** to give the linear **4.90** as the major product. Unlike for the pentadienylation of **4.59**, longer reaction times slightly increased the amount of linear product formed. The MOM-protected **4.85** gave the best results, with linear product being only slightly favored as the major product. These results are substantially worse than those seen with model imine **4.59**, and the poor levels of selectivity may be attributed to the increased steric hindrance due to the chlorine atom at indole C-2. The decrease in the overall reactivity of **4.84** and **4.85** as compared to the Boc-protected **4.83** is most likely due to the nature of the indole protecting group. The electron withdrawing nature of the *N*-Boc-group should significantly enhance the electrophilicity of imine **4.83** as compared to the *N*-Bn and *N*-MOM analogs **4.84** and **4.85**, respectively. The levels of selectivity for the linear product in these examples suggest that the pentadienylation reaction is sensitive to steric factors and that the pentadienylation would need to be carried out on an unsubstituted indole, with functionalization of indole C-2 being performed at a later stage.

Scheme 4.20



4.82: Pg = Boc
4.76: Pg = Bn
4.75: Pg = MOM

4.83: Pg = Boc
4.84: Pg = Bn
4.85: Pg = MOM

4.86: Pg = Boc
4.87: Pg = Bn
4.88: Pg = MOM

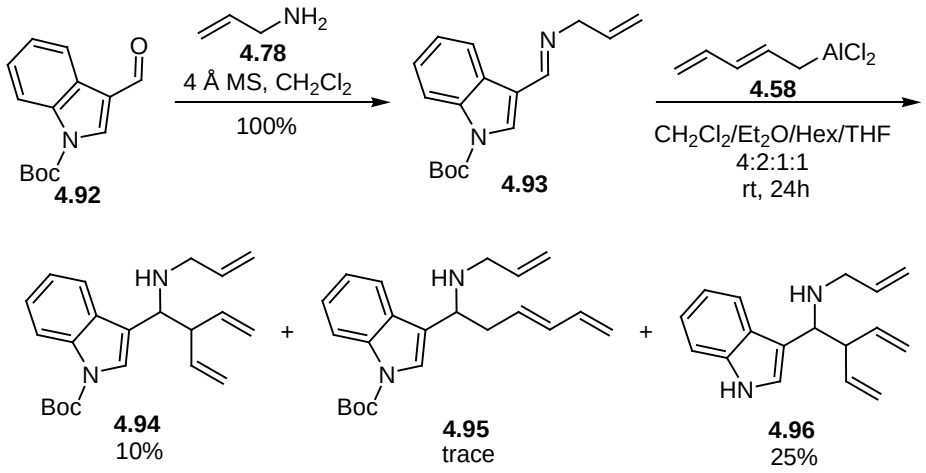
4.89: Pg = Boc
4.90: Pg = Bn
4.91: Pg = MOM

Pg	Temp	Time	Branched (B): Linear (L)[a]	% Conv.[a]	Isolated Yield B/L
Boc	-78 °C → rt	4h	1:6	100	8%/54%
Boc	rt	20h	nd	100	9%/20%
Bn	rt	17h	1:2	~65	nd
Bn	rt	45h	1:3	~80	nd
Mom	rt	45h	1:1.2	~80	nd

[a] Determined by NMR of crude rxn mixture. nd = not determined

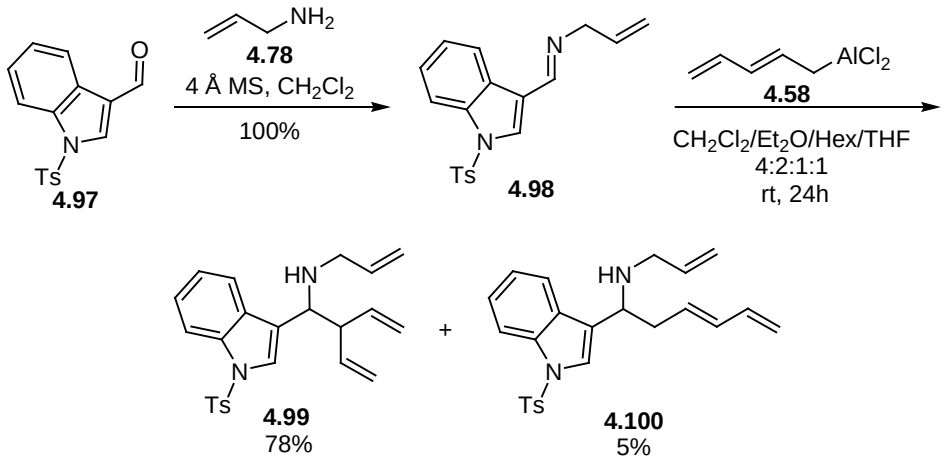
To investigate the effects of having no substitution at C-2, imine **4.93** was synthesized and subjected to the pentadienylation conditions (Scheme 4.21). By removing the indole C-2 substitution, the selectivity towards the branched product was restored. However, the yields for the reaction were low, and the free indole **4.96** was isolated as the major product. The instability of the Boc-group towards the reaction conditions probably also contributed to the low overall yields seen with imine **4.83**. However, a simple switch to a more robust protecting group should eliminate any side products resulting from indole deprotection.

Scheme 4.21



Tosyl protected indoles are generally more robust than their corresponding Boc-protected analogs,[377] and the tosyl protected **4.98** was synthesized in order to investigate compatibility with the pentadienylation conditions (Scheme 23). When imine **4.98** was subjected to the pentadienylation conditions the desired branched product **4.99** could be isolated in 78% yield along with 5% of the separable linear product **4.100**. Thus, a set of conditions were found for the successful pentadienylation of **4.98** leading to the branched product with high levels of selectivity (15:1) and that could be applied to the synthesis of *Aspidosperma* alkaloids.

Scheme 4.22



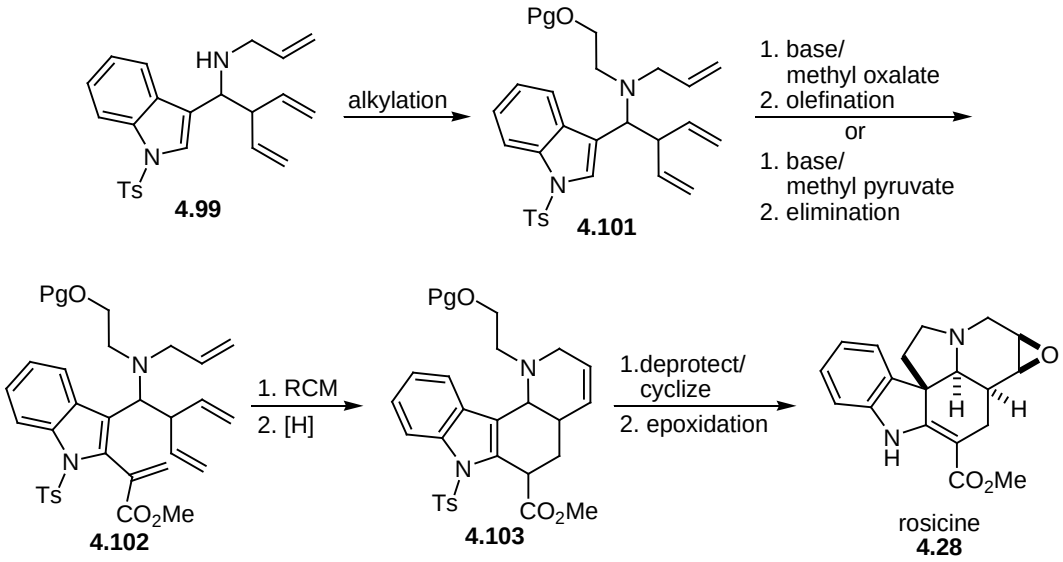
4.3.2 Efforts Towards the First Total Synthesis of Rosicine

Having found conditions suitable for providing a branched pentadienylation product amenable for elaborating into the aspidospermine skeleton, we then turned our attention to the synthesis rosicine (**4.28**). Rosicine was isolated in 1984 from *Catharanthus roseus* and is one of the rare *Aspidosperma* alkaloids lacking an angular ethyl group.[255] To our knowledge there are no reported syntheses of rosicine, and for this reason we thought it would be suitable target to initiate our studies into the aspidospermine alkaloids.

Having already developed a route to amine **4.99**, we envisioned that a sequence similar to that shown in Scheme 4.23 would lead to rosicine. Alkylation of **4.99** with the appropriately protected ethanol derivative would provide **4.101**. Lithiation at the C-2 position of the indole **4.101**, followed trapping with methyl oxalate would give a ketone that could then be olefinated to give **4.102**. Alternatively, lithiation of **4.101** followed by trapping with methyl pyruvate would provide an alcohol that could be dehydrated to provide **4.102**. Double RCM followed by selective reduction of the electron deficient

olefin would give **4.103**. From **4.103,** deprotection and cyclization would give a pentacyclic intermediate that could be epoxidized to give rosicine (**4.28**).

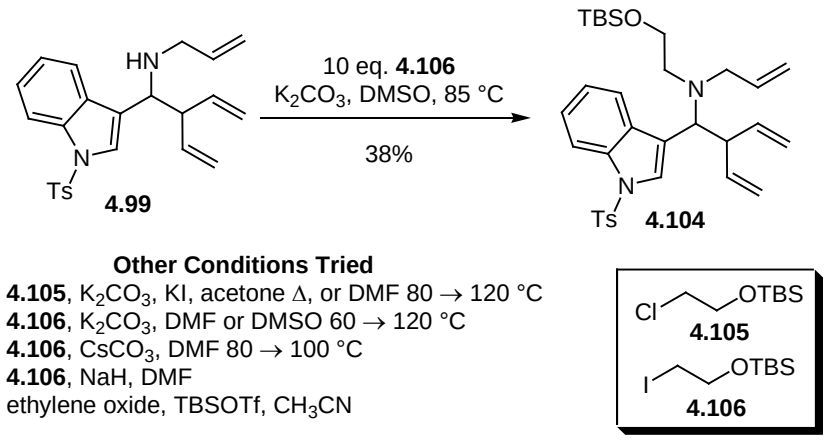
Scheme 4.23



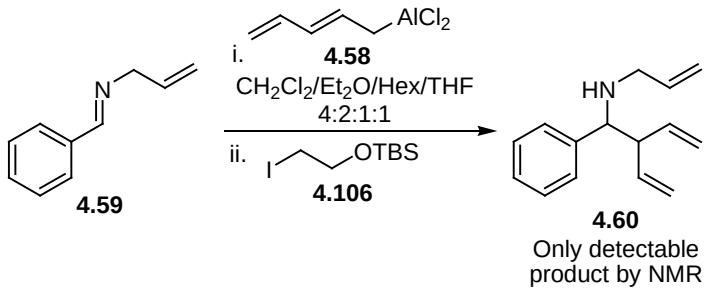
Analysis of the later steps of the synthesis led us to the conclusion that a silyl group might be a good choice for protection of the primary alcohol. A TBS ether should be stable to the conditions required for the remaining steps of the synthesis and could potentially be removed sequentially with the tosyl group when required. The known silyl ethers **4.105** and **4.106**[378] were thus prepared for their use in the alkylation of **4.99**. Attempts to *N*-alkylate **4.99** under a variety of conditions with **4.105** or **4.106** were generally unsuccessful (Scheme 4.24). At temperatures below 100 ºC, starting material was recovered in good yields, and at higher temperatures decomposition to unidentified side products occurred. It was found that when **4.99** was treated with 10 equivalents of **4.106** in DMSO at very high concentration (e.g. greater volume of **4.106** than DMSO) and elevated temperatures, **4.104** could be isolated in 38% yield. In a model system, attempts to perform an in situ alkylation of the aluminum amide resulting from the pentadienylation of **4.59** also failed, and the secondary amine **4.60** was the only

observable product (Scheme 4.25). Attempts to further optimize the alkylation of **4.99** were not made as investigations into other methods for synthesizing compounds related to **4.104** proved to be more fruitful.

Scheme 4.24



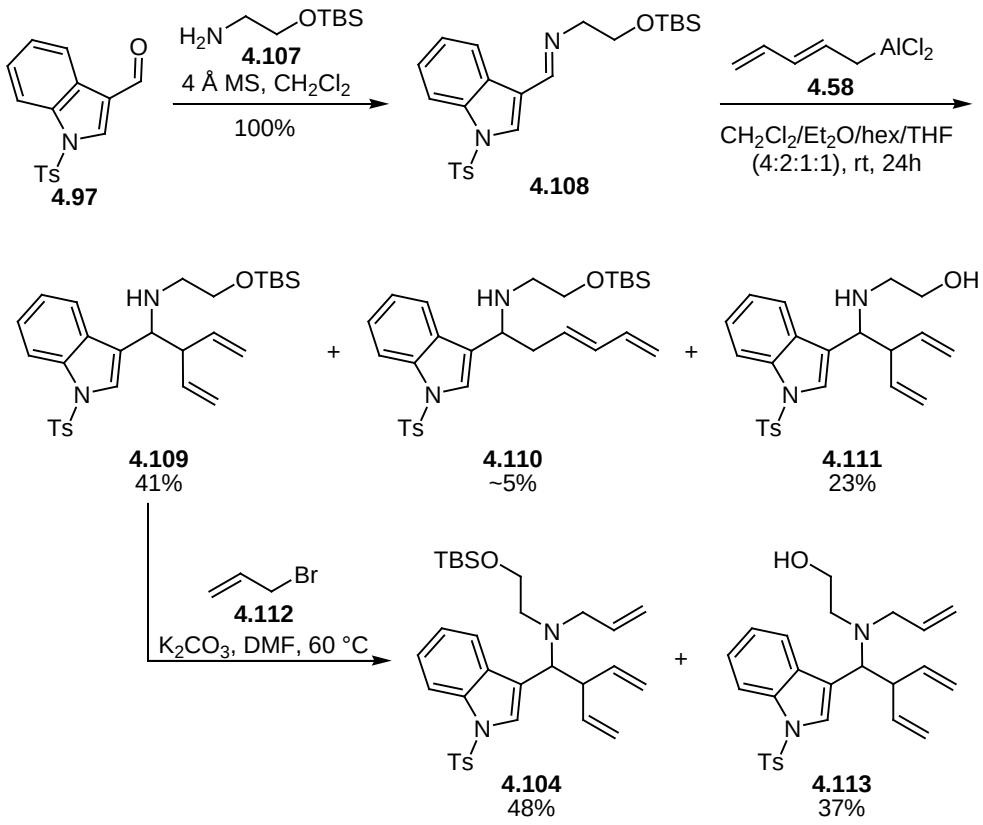
Scheme 4.25



The TBS-protected chloro and iodoethanol derivatives are not good electrophiles, and it was thought that by changing the starting amine and alkylating agent a more favorable sequence could be achieved. This could be made possible by starting from a protected ethanolamine and performing a subsequent allylation instead (Scheme 4.26). Thus, imine **4.108**, synthesized from aldehyde **4.97** and the protected ethanolamine **4.107**,[379] was subjected to the pentadienylation conditions to provide the branched adduct **4.109** in 41% yield along with substantial quantities of the desilylated side product **4.111**.

This is not too surprising, as TBS ethers are known to be moderately unstable to $AlCl_3$.[377] The allylation of **4.109** with allyl bromide gave the desired **4.104** in 48% yield, along with 37% of the desilylated **4.113**.

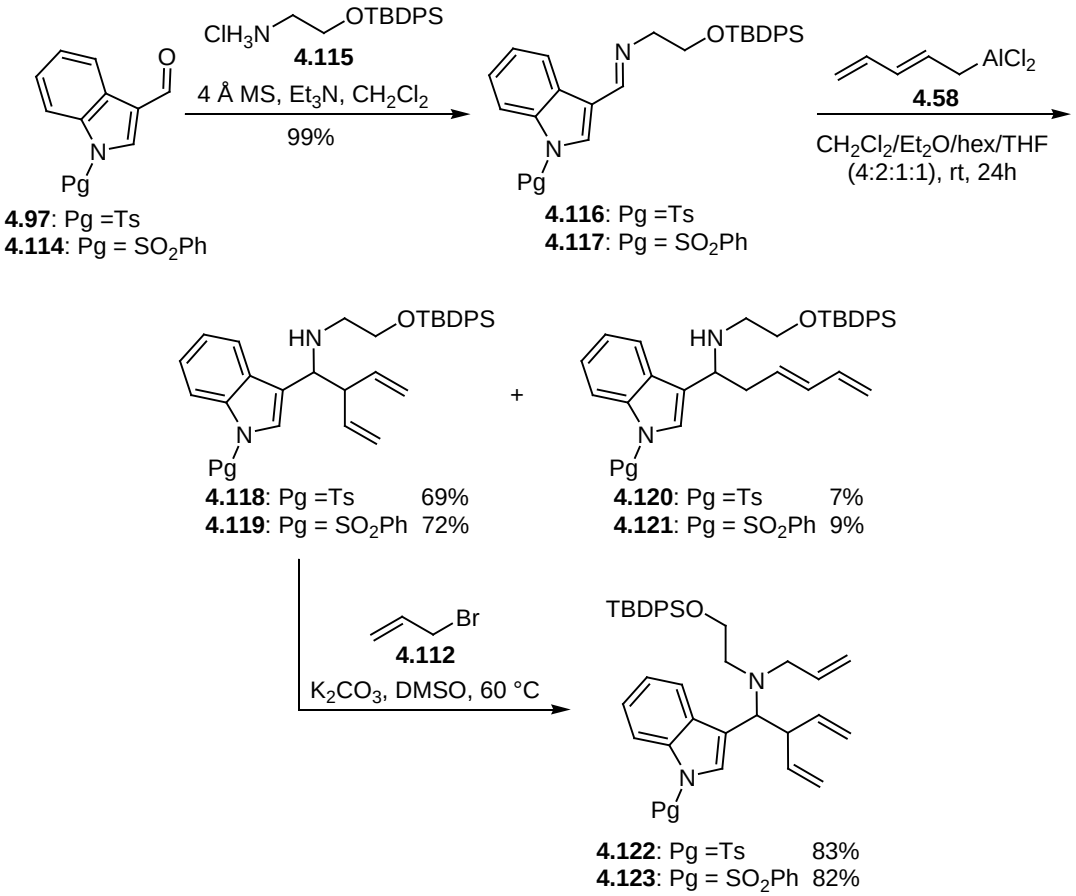
Scheme 4.26



Because the TBS ether was not stable to either the pentadienylation or allylation conditions, a more robust protecting group was chosen (Scheme 4.27). We also began to investigate the use of an *N*-benzenesulfonyl protecting group for indole, as during the lithiation step there is the potential for competitive lithiation of the toslyl methyl group.[380] Imines **4.116** and **4.117** were synthesized from the corresponding aldehydes and ammonium salt **4.115.** Subjecting **4.116** and **4.117** to the pentadienylation conditions provided **4.118** and **4.119** in 69% and 72% yields, respectively, along with small amounts

of the separable linear isomers. Allylation of **4.118** and **4.119** proceeded uneventfully to give **4.122** and **4.123** in good yields.

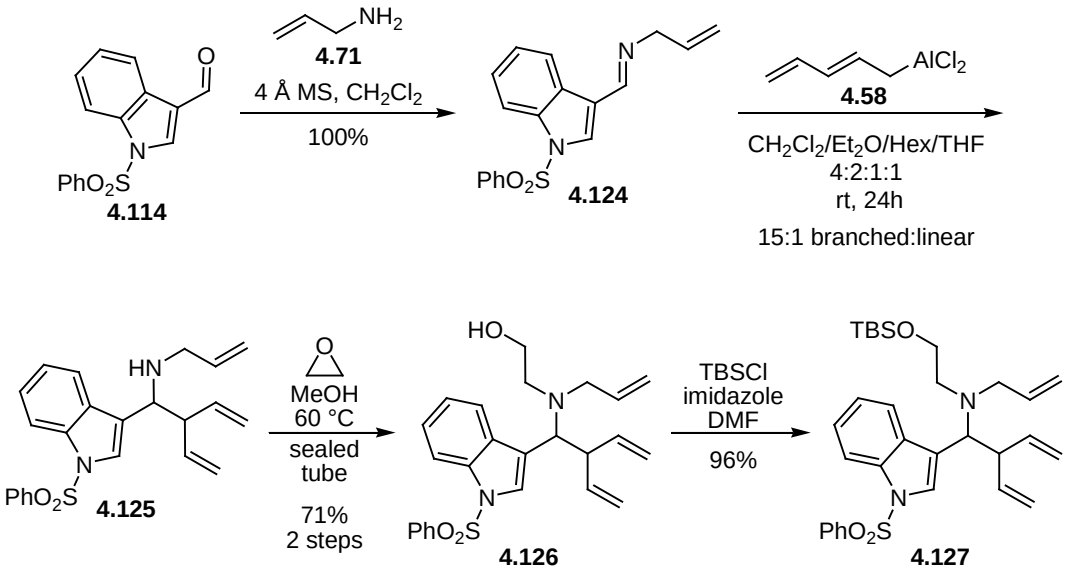
Scheme 4.27



Although the syntheses of **4.122** and **4.123** proceeded in good yields, the use of the TBDPS protecting group is not ideal due to its relative size and mass compared to the rest of the molecule. Accordingly, studies were ongoing to develop a more efficient route to the TBS protected **4.127** (Scheme 4.28). After some optimization, it was found that the crude pentadienylation product **4.125** could be reacted with ethylene oxide in MeOH at 60 ºC in a sealed tube to provide the desired alcohol **4.126** in 71% yield over the two steps. The TBS protection of **4.126** using standard conditions provided **4.127** in 96%

yield. Thus, a more efficient route to **4.127** was developed that allowed for us to avoid the use of the TBDPS protecting group.

Scheme 4.28

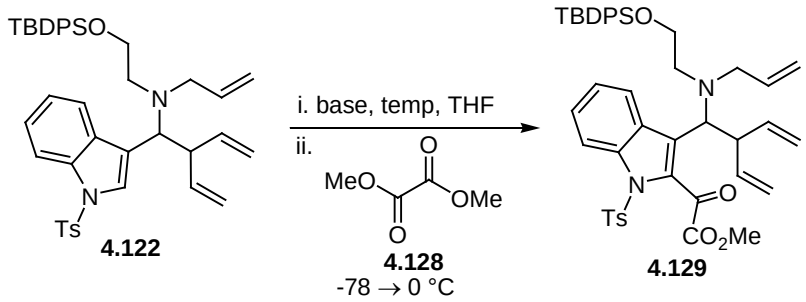


Efforts to further shorten the route to **4.127** were unavailing. A one pot pentadienylation/ethylene oxide opening was attempted; however, when the crude **4.125** was treated in situ with ethylene oxide, a mixture (~1:1) of **4.125** and **4.126** was obtained. The treatment of **4.125** with ethylene oxide in the presence of TBSCl in hopes of performing a one pot alkylation/protection was also unsuccessful. In most cases no reaction occurred, and **4.125** could be recovered quantitatively. It should be noted that the direct application of the 4CR to the synthesis of **4.127** was not pursued because the 4CR would provide an amide that would most likely need to be immediately reduced in order to perform the required lithiation of indole C-2.

With viable routes to the differentially protected indoles **4.122**, **4.123**, and **4.127** in hand, attention was turned to the functionalization of indole C-2. The C-2 lithiation of indoles is well known, and there exist several reports of lithiation at the C-2 position of

indoles and the subsequent trapping with dimethyl oxalate.[381-385] We began our studies on this reaction by looking at the conversion of **4.122** into **4.129** (Table 4.2). It was found that the treatment of **4.122** with LDA or *n*-BuLi/TMEDA for 2 h at -78 ºC, followed by the addition of a solution of methyl oxalate in THF provided the desired product **4.129** in low yields, along with substantial quantities of recovered starting material (entries 2 and 5). Similarly, the use of 2 eq. of LiTMP and warming the lithiation to 0 ºC provided the desired product in 29% yield with 23% recovered starting material (entry 6). Under the conditions shown in entries 1, 3, and 4, none of the desired product was produced, and the reaction returned varying amounts of **4.122**. It was observed, however, that upon warming these reactions above 0 ºC substantial decomposition occurred, and it is possible that in these cases the product was formed but was not stable to the reaction conditions when warmed to room temperature. The more relevant issues relate to the fact that starting material was never consumed, and in most cases the mass recovery was poor.

Table 4.2

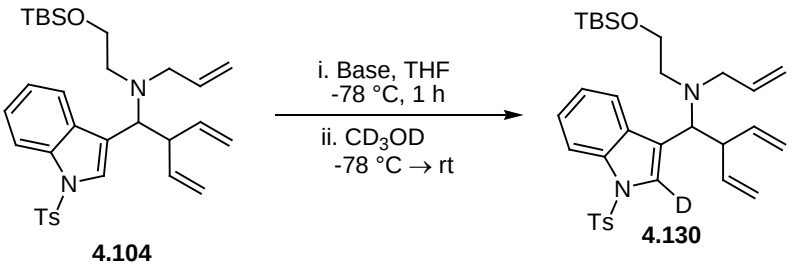


Entry	Base	Temp/ Time	% RSM	% Yield
1*	1.1 eq LDA	-78, 1h	67	0
2	1.3 eq LDA	-78, 2h	19	39
3*	1.3 eq sBuLi	-78, 1h	46	0
4*	1.1 eq BuLi	-78, 2h → 0, 3h	20	0
5	1.3 eq BuLi/TMEDA	-78, 2h	15	47
6	2 eq LiTMP	-78 → 0, 2h	23	29

*Reaction warmed to rt before quenching.

To further investigate the origin of these low conversions, a deuterium-quench study was undertaken (Scheme 4.29). The TBS protected **4.104** was chosen as the substrate because the aromatic proton signals from the TBDPS group in the ^{1}H NMR spectrum of **4.122** overlapped with the indole C-2 signal preventing any easy determination of % deuterium incorporation. Treatment of **4.104** with *s*-BuLi, followed by the addition of CD_3OD resulted in no detectable deuterium incorporation. This is in agreement with the results shown in Table 4.1. When LDA was used as base, 60% deuterium incorporation was observed. More concerning than the low levels of deuterium incorporation was the fact that for both cases the mass recovery was only ~50% after an aqueous work up. This indicates the **4.104** and **4.122** may not be stable to strongly basic conditions. For this reason more forcing conditions (more equivalents of base or warmer temperatures) for the deprotonation have not been investigated.

Scheme 4.29

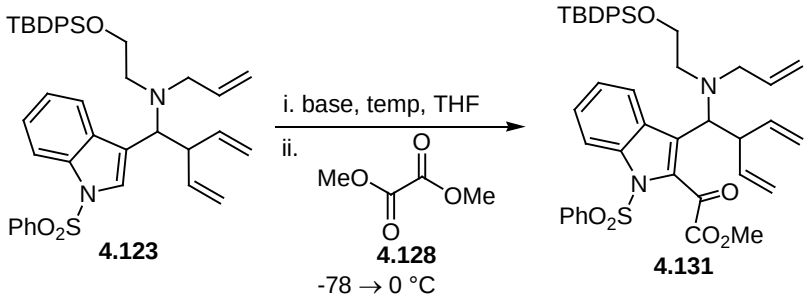


sBuLi ~50% recovery, <10% D incorporation
LDA ~50% recovery, 60% D incorporation

As previously mentioned, one potential drawback to using the tosyl protecting group for this lithiation is that it is known that the methyl on the tosyl group itself can be deprotonated under conditions similar to those used for the lithiation of indoles.[380] In some cases this did indeed seem to be a problem, and compounds were occasionally observed that had resonances in their ^{1}H NMR spectra that were consistent with functionalization of the methyl group. For this reason, the corresponding benzenesulfonyl protected indole **4.123** was also synthesized, under the assumption that it should be compatible with more forcing deprotonation conditions. The studies on the lithiation of **4.123** and subsequent trapping with dimethyl oxalate are summarized in Table 4.3. When **4.123** was deprotonated with LDA at -78 ºC, the desired product was isolated in 57% yield along with 13% recovered starting material (entry 1). Increasing the number of equivalents of LDA showed little improvement (entry 2), as did warming to 0 ºC or room temperature during the lithiation step (entries 3-5, 8). Heating **4.123** under vacuum to remove any water that may have been present did not improve the yield (entry 6). However, it was found that increased yields were obtained when the reaction was maintained at colder temperatures after the addition of dimethyl oxalate. Thus, when the reaction was warmed to -55 ºC after the addition of dimethyl oxalate, **4.131** could be isolated in 78% yield (entry 7). LiTMP was found to give similar yields (entry 9). The

more nucleophilic base $LiNEt_2$ reacted with **4.123** to give products resulting from sulfonyl group cleavage. No reaction occurred when MeMgBr was used as base, and no desired product could be isolated when *s*-BuLi was used. Overall, the best results for this reaction were obtained when LDA was used as the base, and the benzesulfonyl protected **4.123** proved to be a much better substrate than the tosyl protected **4.110** for this reaction. With ketone **4.131** in hand, attention was turned to the olefination reaction.

Table 4.3



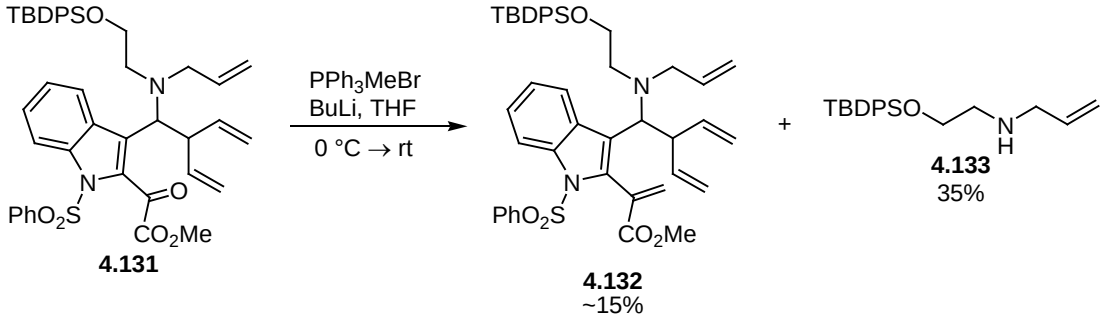
Entry	Base	Temp/ Time	% RSM	% Yield
1	1.2 eq .LDA	-78, 4h	13	57
2	2 eq. LDA	-78, 4h	20	62
3	1.2 eq. LDA	-78 → 0, 2h	47	42
4	2 eq. LDA	-78 → 0, 2h	12	63
5	4eq. LDA	-78 → 0, 2h	22	58
6[1]	1.2 eq. LDA	-78 → -10	50	34
7[2]	2 eq. LDA	-78 → 0, 2h	12	78
8	1.2 eq. LDA	-78 → rt, 2h	56	15
9	2 eq. LiTMP	-78 → 0, 2h	13	65
10	2 eq. $LiNEt_2$	-78, 3h	0	0
11	2. eq. MeMgBr	-78, 2h	85	0
12	1.2 eq. sBuLi	-78, 4h	28	0

[1] SM dried at 120 °C under vacuum
[2] RXN only warmed to -55 °C after dimethyl oxalate added

A few examples of the Wittig olefination of compounds such as **4.131** exist in the literature,[386, 387] and these served as a starting point for developing conditions for the olefination of **4.131** (Scheme 4.30). When **4.131** was allowed to react with the ylide

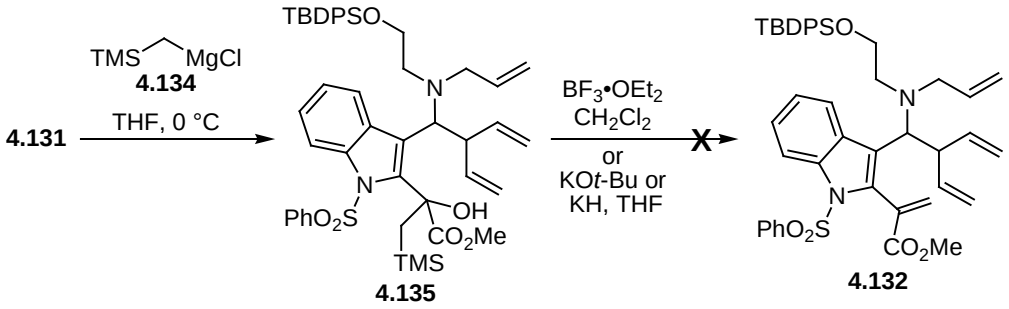
generated from PPh_3MeBr and *n*-BuLi, the desired product **4.132** was formed in low yield, and amine **4.133** was also be isolated as the major product of the reaction. The low yield of **4.132** and the formation of **4.132** are primarily due to the sterically hindered nature of the ketone in **4.132**, which prevents nucleophilic addition of the ylide to the ketone and allows for competitive elimination to occur. For this reason attention was turned to conditions more amenable to the olefination of hindered ketones.

Scheme 4.30



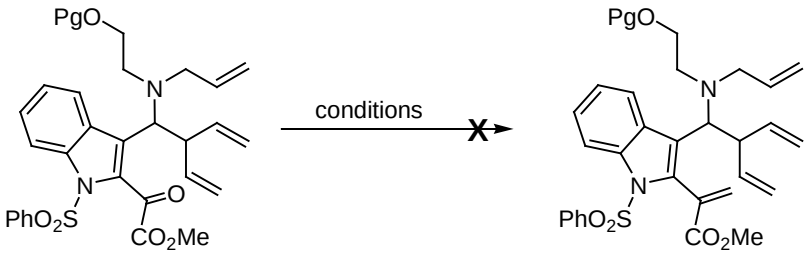
The Peterson olefination has been shown to work well on hindered ketones,[388] and therefore it was examined for the olefination of **4.131** (Scheme 4.31). The addition of TMS-methyl Grignard into **4.134** at 0 ºC provided the desired alcohol **4.135**. When the elimination was attempted under Lewis acidic or under basic conditions niether the desired product nor any other identifiable products were isolated. With both the Wittig and Peterson olefinations failing to provide good yields of **4.120**, attention was then turned to more exotic olefination techniques.

Scheme 4.31



A number of different transition metal mediated olefinations of ketones have been reported in the literature, and a few of the more promising conditions were tried for the olefination of **4.131** and **4.136** (Scheme 4.32). When **4.131** was subjected to standard Takai olefination conditions ($CH_2CI_2/CrCl_2$),[389] starting material was consumed, but none of the desired product was observed. Similar results were obtained utilizing the $CH_2I_2/Zn/TiCl_4$ system developed by Takai.[390] Treatment of **4.136** with the Petasis reagent[391] resulted in the complete decomposition of the starting material.

Scheme 4.32



4.131: Pg = TBDPS
4.136: Pg = TBS

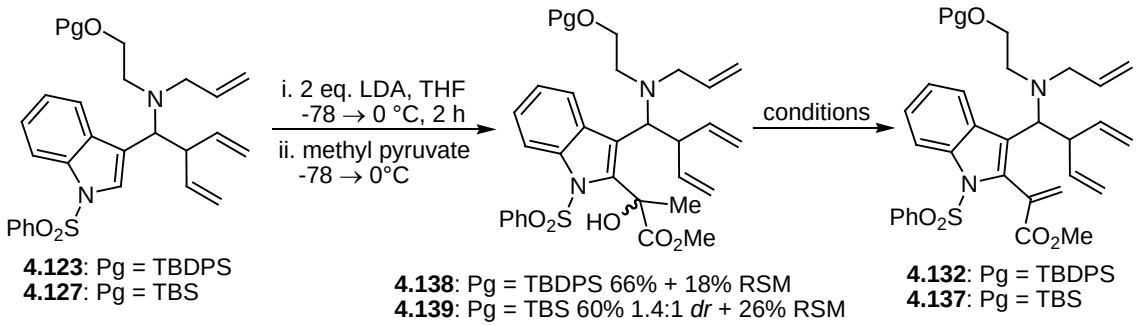
4.132: Pg = TBDPS
4.137: Pg = TBS

Conditions
$CrCl_2$, CH_2I_2, THF
CH_2I_2, Zn, $PbCl_2$, THF, then $TiCl_4$, 0 °C
Cp_2TiMe_2, toluene, 80 °C

Ketone **4.131** proved to be very resistant to olefination, and an alternative approach to **4.132** and **4.137** was developed. It has been shown in the literature that benzenesulfonyl protected indoles lithiated at C-2 can be trapped with methyl pyruvate,

and the resulting alcohol can undergo a subsequent elimination leading to the desired unsaturated ester.[392-394] This approach was successfully applied to the synthesis of **4.132** and **4.137** (Scheme 4.33). The TBDPS- and TBS-protected alcohols **4.123** and **4.127** were deprotonated at C-2 using the previously optimized conditions, and the anions thus formed were trapped with methyl pyruvate to give the desired alcohols **4.138** and **4.139** moderate yields. After some experimentation it was found that the treatment of **4.138** or **4.139** with MsCl and Hunig's base in CH_2Cl_2 at 0 ºC provided the highest yields of the desired elimination products. Similar yields for the elimination could be obtained by using $POCl_3$ in pyridine.[393] When $SOCl_2$ was used in conjunction with Hunig's base, the desired product was formed as a mixture with what appeared to be the alkyl chloride. A major issue with these eliminations was that **4.132** and **4.137** could never be isolated cleanly, and the ^{1}H NMR spectrum always contained ~5-10% of an unknown impurity. The purification of **4.132** and **4.137** was complicated by the fact that neither were stable to silica gel, and chromatography on basic alumina could not provide clean product. Even when **4.137** was purified via preparatory HPLC, the product still contained this minor impurity. Since **4.132** and **4.137** could not be obtained in pure fashion, they were used in to the RCM with hopes that this minor impurity would not inhibit the RCM.

Scheme 4.33



4.123: Pg = TBDPS
4.127: Pg = TBS

4.138: Pg = TBDPS 66% + 18% RSM
4.139: Pg = TBS 60% 1.4:1 *dr* + 26% RSM

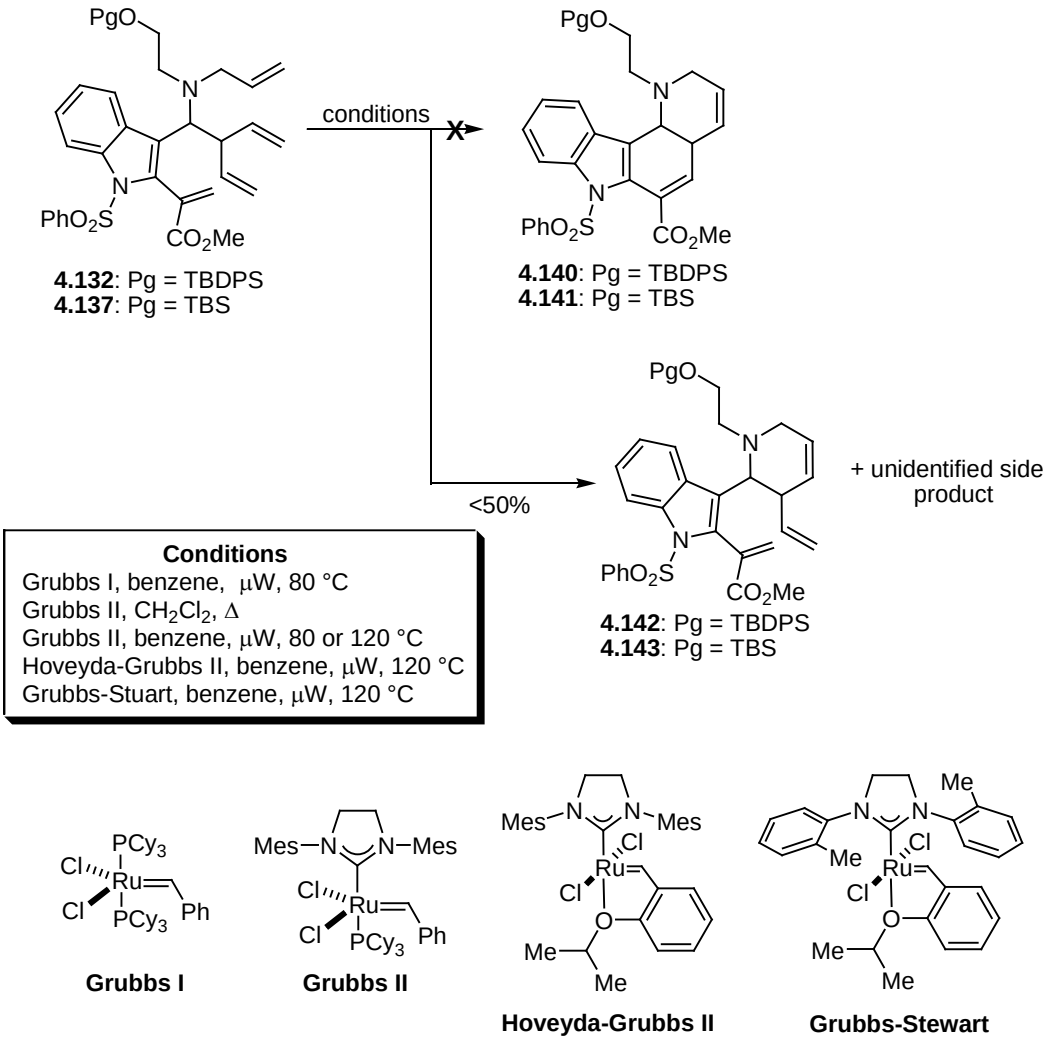
4.132: Pg = TBDPS
4.137: Pg = TBS

Pg	Conditions	Result
TBDPS	MsCl, EtN_3, CH_2Cl_2	~35%
TBDPS	MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C	~60%
TBDPS	$POCl_3$, pyr	~55%
TBDPS	$SOCl_2$, *i*-Pr_2NEt, CH_2Cl_2	n.d.
TBS	MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C	~70%
TBS	Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, -78°C	~25% + 38% RSM
TBS	Martin's Sulfurane	RSM

When **4.132** and **4.137** were subjected to a number of RCM conditions none of the desired double RCM product **4.140** or **4.141** were formed (Scheme 4.34). Under all of the conditions tried, the major isolable products for these reactions were **4.142** or **4.143**, and at best these products could only be isolated in yields up to 50%. Attempts to drive the reaction to completion by heating to higher temperatures utilizing a microwave reactor were also unsuccessful. When the reactions were heated to 120 ºC, a major, but as of yet unidentified side product could be isolated. Even the Grubbs-Stewart catalyst, which is known to show increased reactivity towards sterically hindered olefins,[395] was unsuccessful in closing the second ring. The inability to close the second ring via RCM is not surprising as the α,β-unsaturated ester is expected to be a poor metathesis partner. Electron deficient olefins are known to react more slowly in metathesis reactions, and the fact that it is also a 2,2-disubstituted olefin further attenuates its reactivity due to sterics.

A potential difficulty in this transformation is that the bezenesulfonyl group and the methyl ester must become co-planer for the desired product to form, and in doing so there is buildup of a substantial steric interaction between these two groups. All of these factors contribute negatively to the RCM. Hence, to circumvent these issues, a number of potential solutions were investigated.

Scheme 4.34

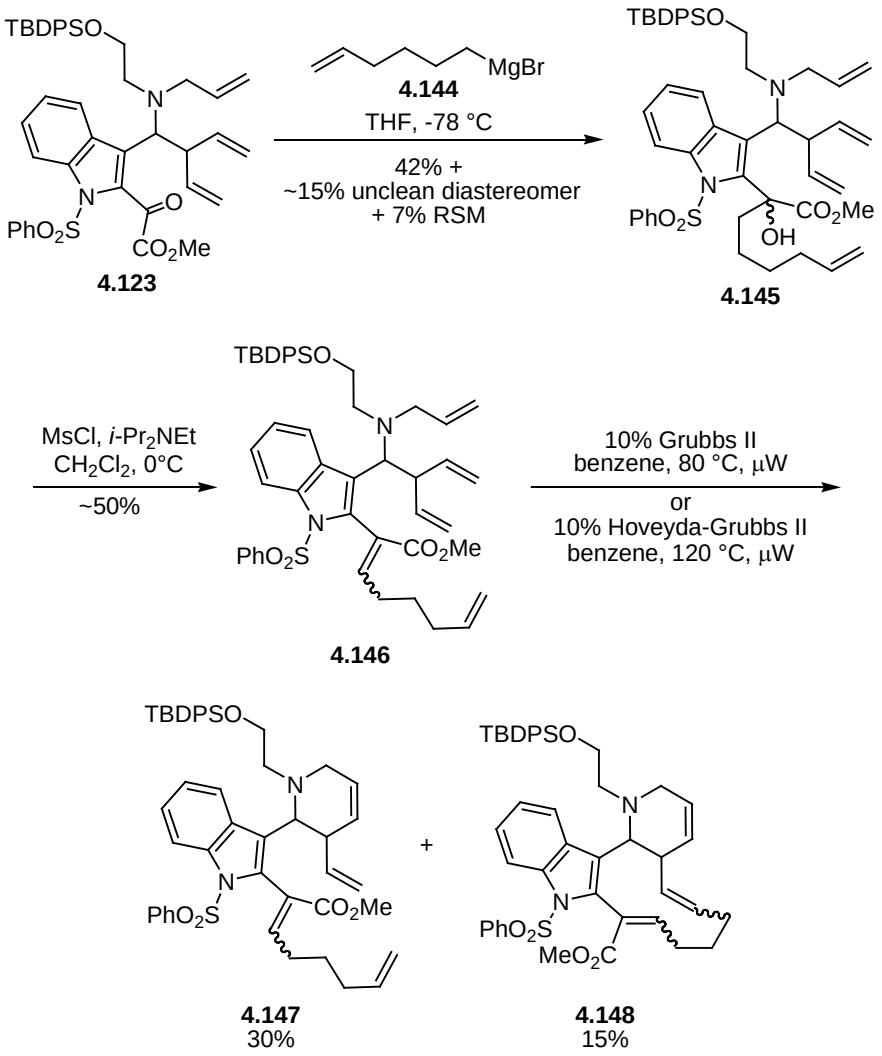


One strategy for enabling this difficult RCM involved the removal of the indole protecting group, in order to eliminate steric interactions between the protecting group

and the methyl ester. A second alternative was to perform a relay RCM,[396] which should help to overcome the unreactive nature of the α,β-unsaturated ester by providing a pathway for the RCM catalyst to load onto the electron deficient olefin. A final alternative is to attempt the RCM on the allylic alcohol instead of the α,β-unsaturated ester, as the allylic alcohol should be a more reactive RCM partner.

The first of these alternate strategies that was investigated was the relay RCM (Scheme 4.35). To this end the synthesis of **4.146** was undertaken. Ketone **4.123** was reacted with Grignard reagent **4.144** to give the desired addition product **4.145** in moderate yield. Elimination of the alcohol in **4.145** with MsCl and Hunig's base provided **4.146** in ~50% yield. The purification of **4.146** also proved to be problematic and although **4.146** could never be isolated cleanly; it was subjected to the relay RCM with the Grubbs II and the Hoveyda-Grubbs II catalysts. However, only the monocyclized **4.147** and the macrocyclic **4.148** were formed. Despite efforts to enable the loading of the RCM catalysts onto the α,β-unsaturated ester, this olefin still proved to be unreactive under the RCM conditions. Attention was then turned to the synthesis and cyclization of an unprotected indole substrate.

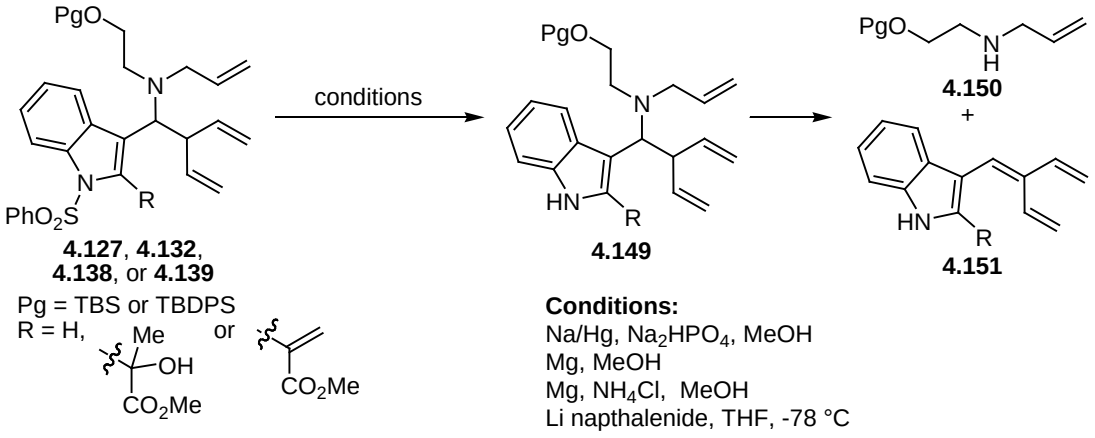
Scheme 4.35



In order attempt the RCM on the unprotected indole, an appropriate deprotection strategy was needed. The initial attempts to deprotect a number of uncyclized compounds related to **4.127** were unsuccessful due to the fact that the free indole readily undergoes elimination of the amine side chain (Scheme 4.36). Also, in the case of **4.132** conjugate reduction of the α,β-unsaturated ester could be observed. For this reason it was decided that the best approach would be to perform an RCM on **4.139**, which would

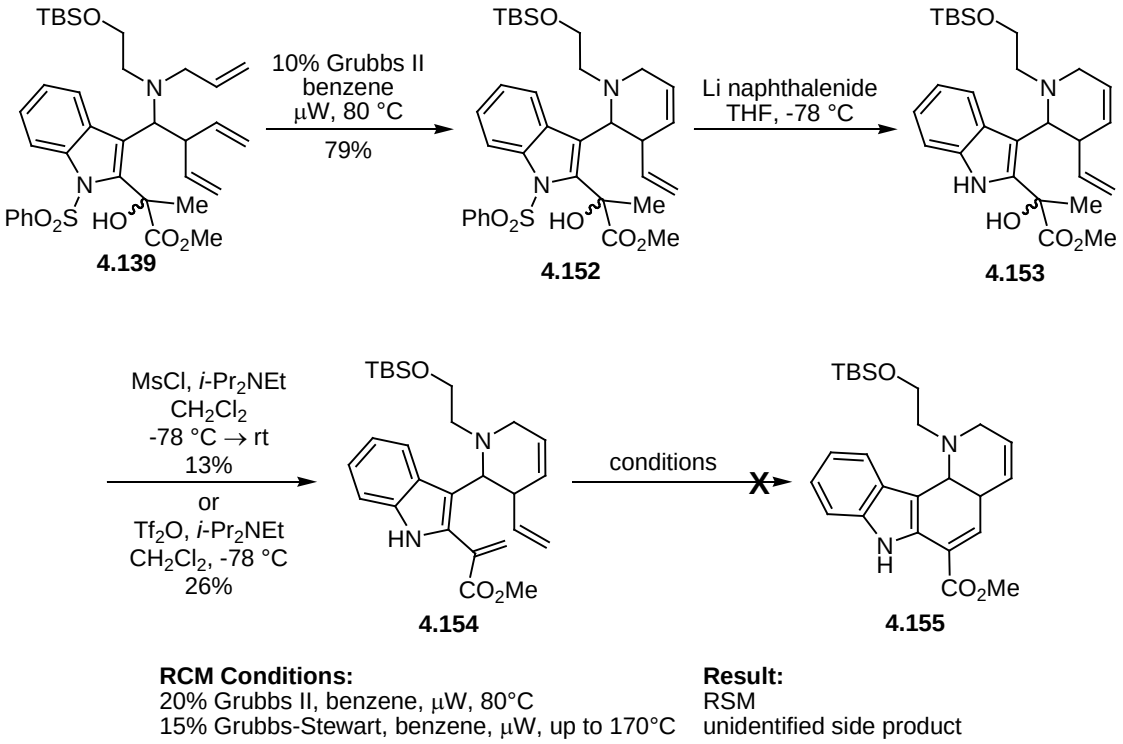
effectively tether the amine side chain and possibly prevent the elimination from occurring.

Scheme 4.36



The RCM of **4.139** proceeded in 79% yield utilizing 10% of the Grubbs II catalyst in benzene at 80 ºC (microwave heating) (Scheme 4.37). The subsequent deprotection of **4.152** with lithium naphthalenide provided **4.153**, which was subjected without purification to the elimination conditions. Both MsCl and Tf_2O were effective in promoting the elimination, but in both cases the yields of **4.154** were poor. However, this route did provide enough material to attempt the RCM. When **4.154** was treated with 20% of the Grubbs II catalyst at 80 ºC (microwave heating), no reaction occurred. When the Grubbs-Stewart catalyst was used, no reaction occurred at 80 ºC, and upon heating to higher temperatures an unidentifiable side product was formed.

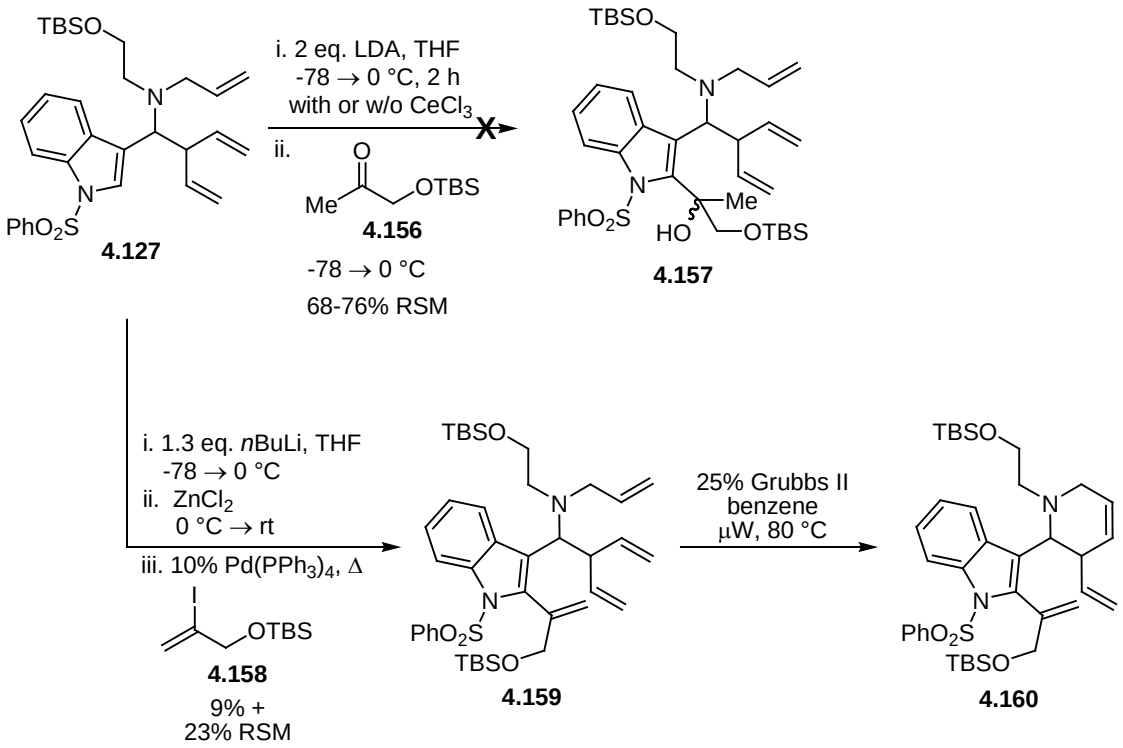
Scheme 4.37



RCM Conditions:	**Result:**
20% Grubbs II, benzene, μW, 80°C	RSM
15% Grubbs-Stewart, benzene, μW, up to 170°C	unidentified side product

With the double RCM of esters **4.137** and **4.154** being unsuccessful, attention was then turned towards the synthesis and cyclization of allylic alcohol **4.159** (Scheme 4.38). The first approach to **4.159** involved the deprotonation of **4.127** with LDA and subsequent trapping with hydroxyacetone **4.156**. When this reaction was run with or without added $CeCl_3$, only starting material was recovered. The second approach to **4.159** involved a Negishi coupling with vinyliodide **4.158**.[397] Deprotonation of **4.127** with *n*-BuLi and subsequent transmetalation with $ZnCl_2$ presumably formed an organozinc compound, which was treated with **4.158** and $Pd(PPh_3)_4$ to provide **4.159** in 9% yield. The double RCM was then attempted, but when **4.159** was treated with the Grubbs II catalyst only the mono-cyclized **4.160** was detected.

Scheme 4.38

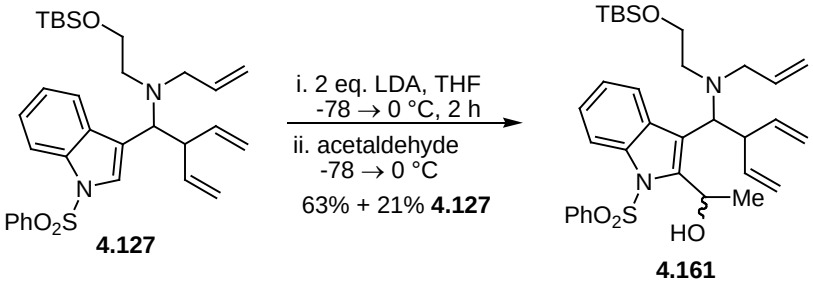


Despite our best efforts, the double RCM could not be achieved. While these are undoubtedly challenging RCM reactions, the complete inability to generate any of the desired products highlights the current limitations of metathesis chemistry and underscores the need for more active catalysts for challenging RCM reactions such as these. The failures of these reactions also necessitated a modification to our synthetic strategy and led us to adopt a strategy involving the double RCM of 2-vinylindole **4.162** (see Table 4.4) and installation of the methyl ester at a later stage of the synthesis.

The deprotonation of various indoles at the 2-position and subsequent trapping of the anion with acetaldehyde is known to proceed in good yields.[398-406] Thus, it was envisioned that the vinyl group could be installed onto **4.127** via a two step protocol similar to the sequence used in the synthesis of **4.137** (see Scheme 4.33). When **4.127** was deprotonated with LDA, and the resulting anion trapped with acetaldehyde, the

desired **4.161** was isolated in 63% yield along with appreciable amounts of recovered **4.127** (Scheme 4.39). When *n*-BuLi was used as base the desired product was formed in only 45% yield. Similar yields of **4.161** could be obtained using PhLi as base, but the yield of recovered starting material was greatly reduced. Adding the acetaldehyde at 0 ºC also resulted in both a lower yield and lower overall mass recovery. It is not known at this point whether the recovered starting material is the result of incomplete deprotonation of **4.127**, or if the hindered nature of **4.127** allows for proton transfer from acetaldehyde to be a competitive side reaction.

Scheme 4.39



4.127 **4.161**

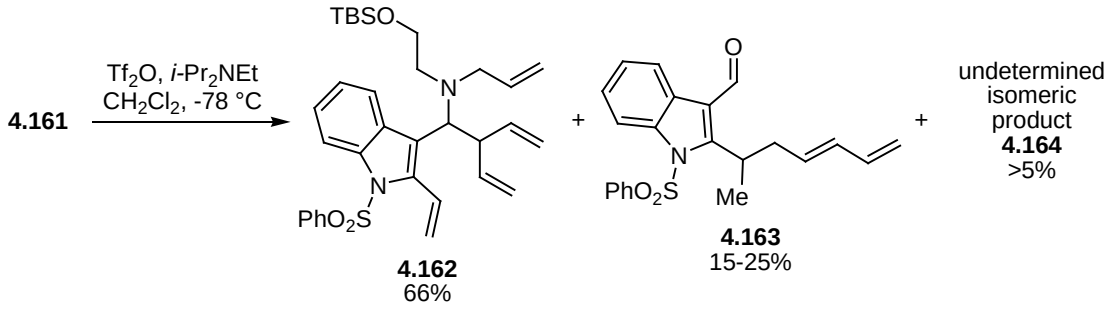
Other Conditions Tried	Result
i. 1.5 eq *n*-BuLi, THF, -78 → 0 °C ii. acetaldehyde -78 → 0 °C	45% + 8% **4.127**
i. 3 eq. PhLi, THF -78 → 0 °C ii. acetaldehyde -78 → 0 °C	61% + 6% **4.127**
i. 2 eq. LDA, THF -78 → 0 °C ii. acetaldehyde, 0 °C	33% + 36% **4.127**

With alcohol **4.161** in hand attention was then turned to the elimination reaction. Although this is seemingly a straightforward transformation, a number of side reactions were encountered (Scheme 4.40). Under the optimal conditions alcohol **4.161** was treated sequentially with Tf_2O and Hunig's base at -78 ºC in CH_2Cl_2 to provide **4.162** in 66% yield along with a number of side products. The first of these side products is

aldehyde **4.163**, which presumably is formed via a pathway similar to that shown in Scheme 4.41. The structure of the second side product has not conclusively been determined, but the spectral evidence suggests that it arises from an intramolecular cyclization of **4.161**. At low temperatures, aldehyde **4.163** is formed in significant quantities, and **4.164** is only formed in trace amounts. At room temperature the distribution of these side products is flipped, and the aldehyde is not formed while **4.164** becomes a more substantial side product. Since **4.162** and **4.164** are not completely separable by chromatography, the reaction was run at low temperatures to prevent the formation of **4.164**.

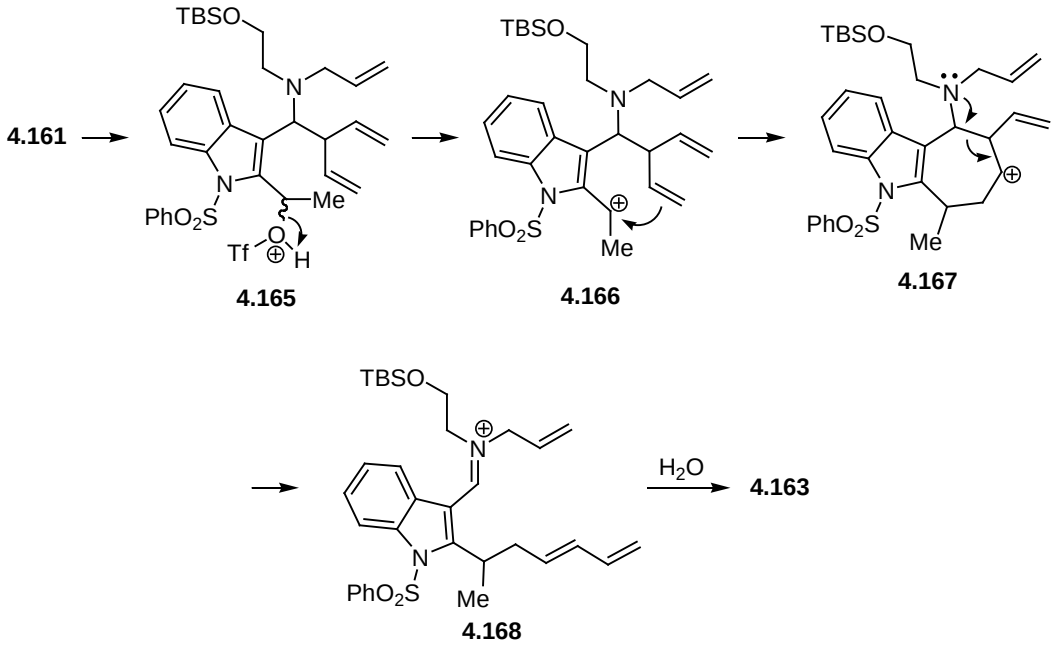
In order to prevent the formation of these side products, a number of other reaction conditions were investigated. Screening different bases or solvents did not improve the yields of the desired product or eliminate the formation of side products. Although some the other conditions tried were successful in eliminating the undesired side products, none of them came close to matching the 66% yield that could be obtained with Tf_2O and Hunig's base. Interestingly, the reactions involving MsCl or Burgess reagent were the only conditions tried that did not provide any of the desired product. Thus, despite considerable effort, the elimination of **4.161** could only be optimized to give a moderate yield of the desired tetraene.

Scheme 4.40



Other Bases	**Other Solvents**	**Other Conditions Tried**
DBU	toluene	MsCl, *i*-Pr_2NEt, CH_2Cl_2
proton sponge	CH_3CN	$POCl_3$, pyr
K_2CO_3	DMF	$PhN(Tf)_2$, NaH, THF, Δ
none	pyridine	Burgess Reagent
		Martin's Sulfurane
		DIAD, PBu_3, THF
		Ph_3PO, Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, -78 °C

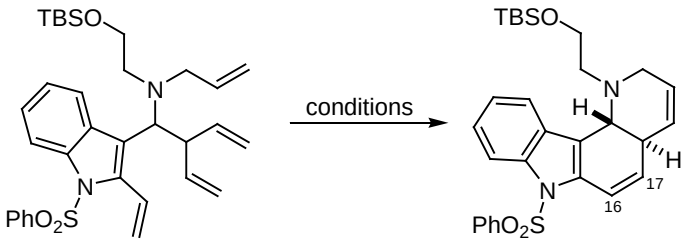
Scheme 4.41



With the requisite tetraene **4.162** in hand the double RCM was attempted (Table 4.4). Heating **4.162** with 10% Grubbs II catalyst in benzene provided the desired **4.169** in 68% yield. The use of microwave heating accelerated the reaction, but it did not

improve the overall yields. In order to increase the efficiency of this reaction, lower catalyst loadings were investigated. At 5% catalyst loadings with the Grubbs II catalyst in refluxing benzene or toluene, the RCM would not proceed to completion, and the crude reaction mixture had to be re-subjected to the reaction conditions in order to drive the reaction to completion. As a result of this, **4.169** was isolated in only 54% yield. When a second portion of catalyst was added, the reactions still did not proceed to completion. It was found that lower catalyst loadings could be achieved by employing the Hoveyda-Grubbs II catalyst, and when **4.162** was heated with 5% of this catalyst in refluxing toluene, **4.169** could be isolated in 66% yield.

Table 4.4



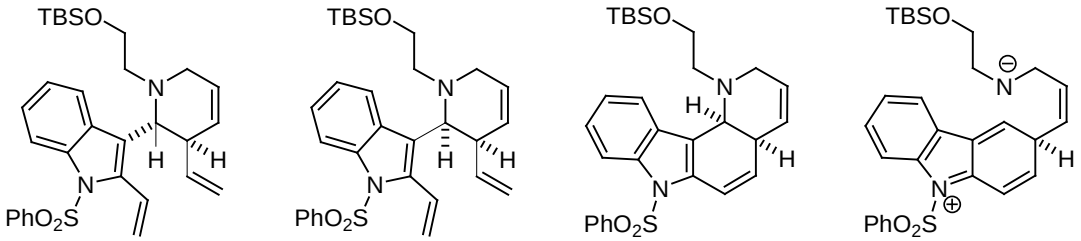
4.162 **4.169**

Conditions	Result
10% Grubbs II, benzene, Δ	68%
10% Grubbs II, benzene, μW, 80 °C	66%
5% + 5% Grubbs II, benzene, Δ	54%
5% + 5% Grubbs II, toluene, Δ	52%
5% Hoveyda-Grubbs II, benzene, μW, 80 °C	74%
5% Hoveyda-Grubbs II, toluene, Δ	66%

It should be noted that the RCM gave exclusively the *trans*-fused product as determined by the large coupling constant (J = 16.5 Hz) for the ring fusion protons. A couple of possibilities for these high levels of selectivity for the *trans*-fused product can be envisioned. The first possible explanation is that the stereochemical outcome of the double RCM reaction of **4.162** is determined in the first of the two RCM reactions. The

^{1}H NMR data taken from reaction mixtures where the double RCM had not proceeded to completion showed that the piperidine ring is closed first. Of the two potential products of this RCM, one would expect that the *trans*-configuration of the indole and vinyl substituents in **4.170** would be preferred as these two groups can both be placed in an equatorial position in transition state leading to **4.170**. This pathway leading to **4.170** would presumably be lower in energy than the pathway that leads to **4.171**, which requires that one of the substituents on the piperidine ring is placed in an axial orientation in the transition state. An alternative explanation stems from the fact that the RCM is run under conditions in which the products of the reaction can potentially epimerize. Thus, the double RCM reaction could initially provide a mixture of **4.169** and its *cis*-fused isomer **4.172**. The *cis*-fused product could then fragment to give **4.173**, which could reclose to give the *trans*-fused **4.169**. This assumes that the *trans*-fused product is the thermodynamically more stable product, but further modeling studies would be needed to support this argument.

Figure 4.3

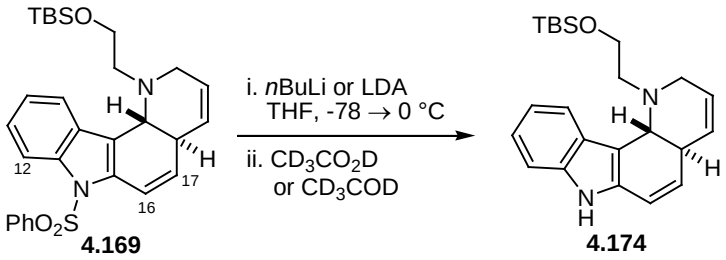


It should be noted that the *Aspidosperma* alkaloids all contain a *cis*-ring fusion, and therefore an epimerization will be necessary. Fortunately, there are two intermediates, **4.180** and **4.182**, at the end of the synthesis that can potentially undergo a retro-Mannich/Mannich sequence that should provide the desired *cis*-ring fusion stereochemistry and render the stereochemical outcome of the RCM inconsequential.

With tetracycle **4.169** in hand, we then turned or attention to the introduction of the methyl ester and formation of the pentacyclic core. Our first plan for introducing the methyl ester was the direct functionalization of the C16-C17 double bond. This could potentially be accomplished via a directed lithiation of the double bond or through a transition metal mediated hydrocarboxylation. Both of these methods for installing the methyl ester were lacking good precedent, and therefore they were investigated in parallel.

It was first postulated that the *N*-benzenesulfonyl group might be able to direct deprotonation to the vinylic proton at C-16. Alternatively, it is known that deprotonation may occur at C-12 and this competing pathway may prevail. To investigate the feasibility of deprotonating the vinyl group, **4.169** was treated with *n*-BuLi or LDA in THF at -78 ºC. The reactions were then warmed to 0 ºC before quenching with MeOH-d_4 or AcOH-d_4. In both cases no deuterium incorporation was observed, and the only isolated product was the free indole **4.174** (Scheme 4.42). These preliminary results indicate that the direct deprotonation route may not be a viable method for the installation of the methyl ester, and due to the successes of alternate routes an exhaustive screen of conditions was not undertaken.

Scheme 4.42

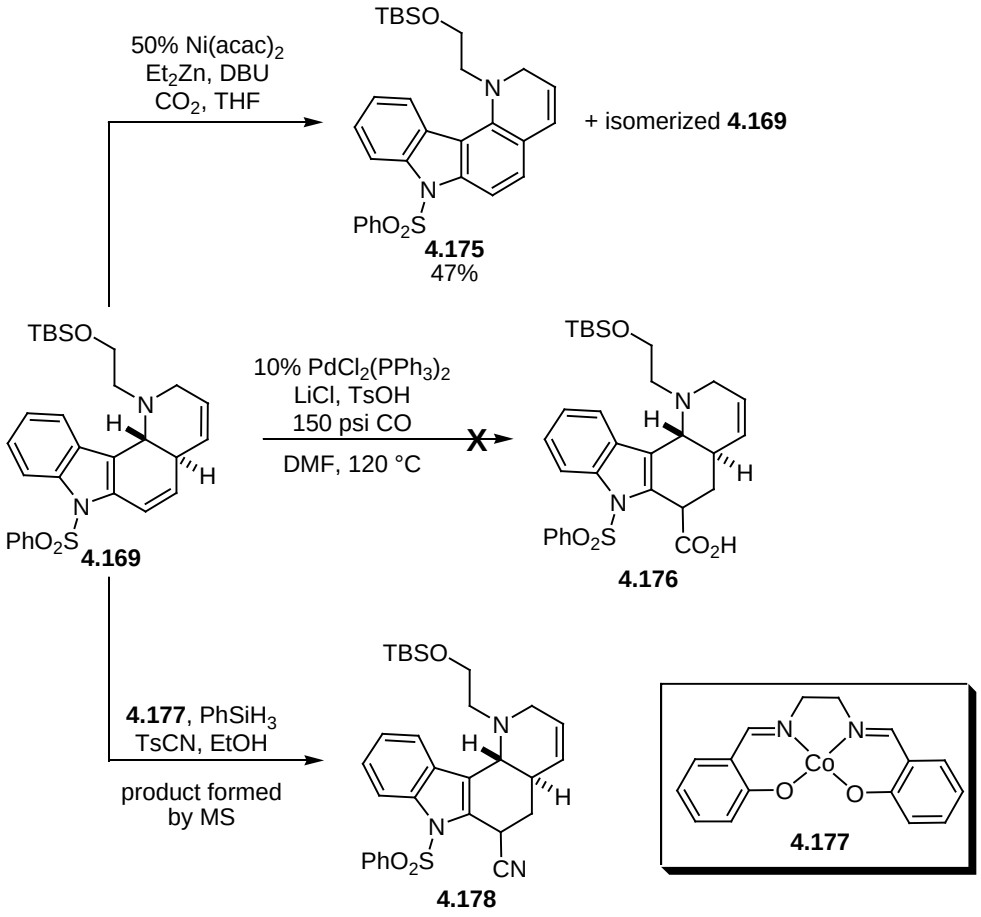


4.169 **4.174**

In addition to the directed lithiation studies, efforts the feasibility of performing a hydrocarboxylation on **4.169** was investigated. The hydrocarboxylation of styrenes has

been studied,[407] but little work has been reported on the hydrocarboxylation of vinyl indoles. If this reaction could successfully be applied to **4.169**, it would provide us with a method for installation of the methyl ester with concurrent reduction of the double bond. To this end, preliminary experiments were run utilizing a couple of the more promising conditions (Scheme 4.43). The first of the conditions attempted was the nickel catalyzed hydrocarboxylation reaction recently developed by Rovis.[408] However, attempts to convert **4.169** into **4.176** using this procedure gave only **4.175** and various compounds that appeared to arise from double bond isomerizations of **4.169**. When **4.169** was allowed to react under palladium catalyzed hydrocarboxylation conditions[409] no identifiable products could be isolated from the reaction. Carriera has recently reported a procedure for the hydrocyanation of alkenes,[410] and when **4.169** was reacted under a slightly modified version of these conditions a number of new products were formed by TLC. Mass spectrometry indicated the presence of the desired product, but attempts to isolate and identify any of the desired product were unsuccessful. There are numerous things that could be attempted to optimize these reactions, but the success of the late stage installation of the ester via lithiation and acylation of **4.180** (Scheme 4.45) made these reactions a lower priority.

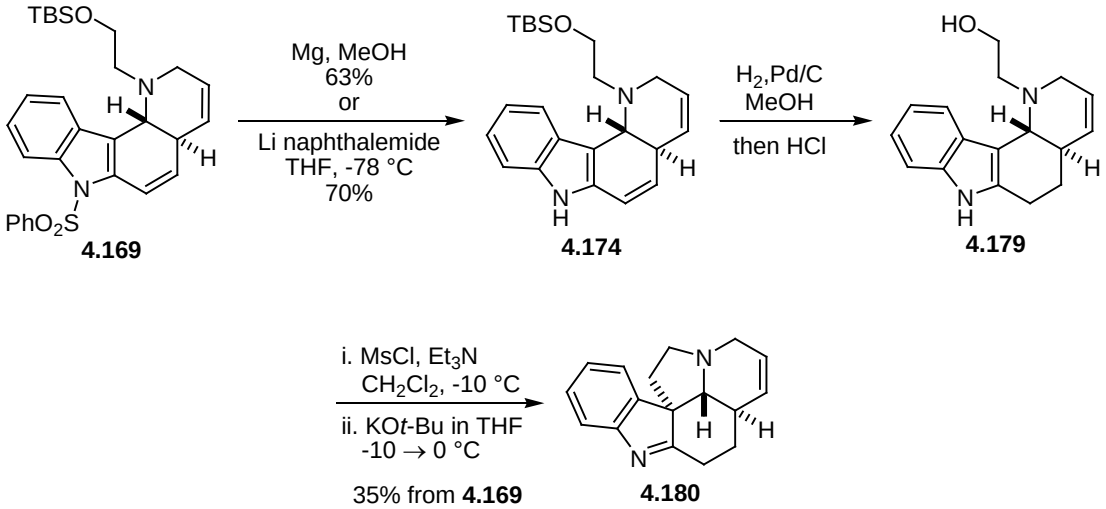
Scheme 4.43



Because the C16-C17 olefin is not needed for the natural product an alternative approach was explored that involves the selective reduction of this olefin and installation of the methyl ester after spirocyclization. To this end, **4.169** was treated with Pd/C in MeOH or EtOAc under an atmosphere of H_2, but no selectivity was observed in the reduction. However, it was found that the selective hydrogenation could be achieved by first removing the indole protecting group (Scheme 4.44). The benzenesulfonyl group could be easily removed using Mg/MeOH or Li naphthalenide to provide **4.174**. The more electron rich olefin in **4.174** was then selectively reduced with Pd/C in MeOH, and upon completion of the reduction, the addition of HCl cleaved the TBS group to provide

4.179. The free alcohol **4.179** could then be cyclized to pentacycle **4.180** using conditions developed by Rawal;[348] whereby the alcohol was first treated with MsCl and Et_3N in CH_2Cl_2 to provide the primary mesylate, which was treated in situ with a solution of KO*t*-Bu in THF to provide the desired pentacycle **4.180** in 35% yield over three steps from **4.169** without the need for purifying of any of the intermediates. It should be noted that the reduction of **4.174** was finicky, and in almost all cases the starting material needed to be re-subjected to the reaction conditions one or two times before the reaction would proceed. Presumably this was due to sulfur containing impurities from the deprotection step that poisoned the catalyst and shut down the hydrogenation.

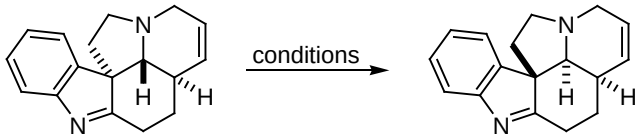
Scheme 4.44



With pentacycle **4.180** in hand, efforts were made to find optimal conditions for the requisite epimerization (Table 4.5). Pentacycle **4.180** was found to be stable in refluxing toluene, but when *p*-toluenesulfonic acid was added in stoichiometric amounts, the starting material was consumed, and a compound presumed to be **4.181** was formed upon refluxing in toluene for ~20 h. The mass recovery for this reaction was low, and **4.181** was isolated in only 9% yield after chromatography. A substantial amount of

insoluble material was formed during the course of the reaction, and it was thought that more polar solvents could be utilized to prevent this from occurring. Indeed, the formation of the insoluble material could be avoided by heating the reaction in DMF, but the overall mass recovery for this reaction was still low. It was also found that $BF_3 \cdot OEt_2$ could promote the epimerization in refluxing dichloroethane, but again the overall mass recovery was low. At this time the exact structure of **4.181** is not known, and given the results obtained in the attempted synthesis of pseudotabersonine (see Scheme 4.50) it is possible that the structure assignment of **4.181** is not correct.

Table 4.5



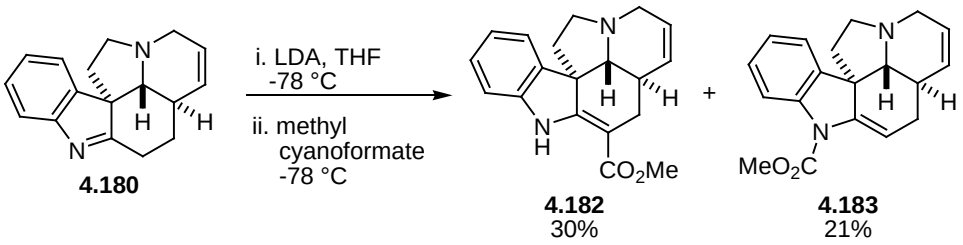
4.180 **4.181**

Conditions	Conversion
toluene, Δ	No RXN
$TsOH \cdot H_2O$, toluene, Δ	100%, 9% yield
$TsOH \cdot H_2O$, CH_3CN, Δ, 18h	~15%
$TsOH \cdot H_2O$, DMF, 120 °C, 20h	100%
$BF_3 \cdot OEt_2$, CH_2Cl_2	No RXN
$BF_3 \cdot OEt_2$, $ClCH_2CH_2Cl$, Δ, 20h	100%

In conjunction with the epimerization studies, efforts were also made to install the methyl ester onto **2.180** to give **2.182**, as this intermediate could also potentially undergo an epimerization. There have been numerous methods reported for the installation of the C-16 methyl ester onto the pentacyclic aspidospermine skeleton.[411-413] The most direct method was first reported by Overman and involved the deprotonation of a pentacyclic imine similar to **4.181** with LDA and subsequent trapping of the metalloenamine thus formed with methyl chloroformate to provide a mixture (1:1) of *N*- and *C*-acylated products.[412] This procedure was later improved upon by Rawal, who reported obtaining

exclusively the *C*-acylation product in good yield by utilizing methyl cyanoformate as the acylating agent.[347, 348] Following Rawal's conditions, **4.180** was treated with LDA in THF at -78 ºC, and the resulting metalloenamine was acylated with methyl cyanoformate to give the separable *C*- and *N*-acylated products **4.182** and **4.183** in 30% and 21% yields, respectively (Scheme 4.45). These results are in stark contrast to those reported by Rawal, and the reason for the lack of selectivity for the *C*-acylated product in this reaction is not known. One attempt has been made to epimerize **4.182**, but upon heating in refluxing toluene no reaction occurred, and the addition of acids to the reaction will probably be needed.

Scheme 4.45



4.180

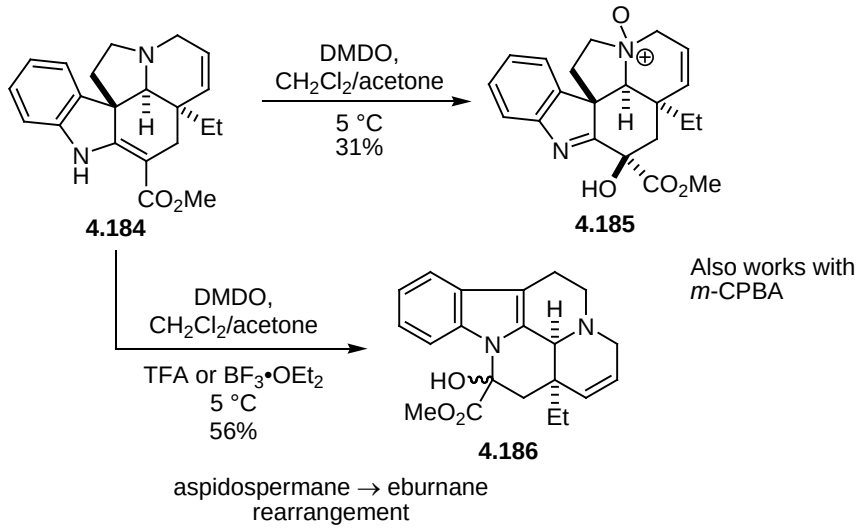
4.182
30%

4.183
21%

With the methyl ester successfully installed all that remained to be completed is the epoxidation of the isolated olefin, a seemingly straightforward transformation that is complicated by the presence of the vinylogous carbamate. When compounds such as tabersonine (**4.184**) are treated with DMDO or *m*-CPBA under a variety of conditions a number of different reactions can occur (Scheme 46).[414, 415] Under neutral conditions the tertiary amine is oxidized to the *N*-oxide, and in the presence of excess oxidant the vinylogous carbamate is selectively oxidized to give **4.85**. The formation of the *N*-oxide can easily be avoided by running the reaction under acidic conditions so that the amine is protected via protonation. However, epoxidation of the vinylogous carbamate still occurs preferentially, and under the acidic conditions the epoxidized product rearranges to the eburnane skeleton **4.186**. Thus, **4.182** cannot be directly transformed into rosicine

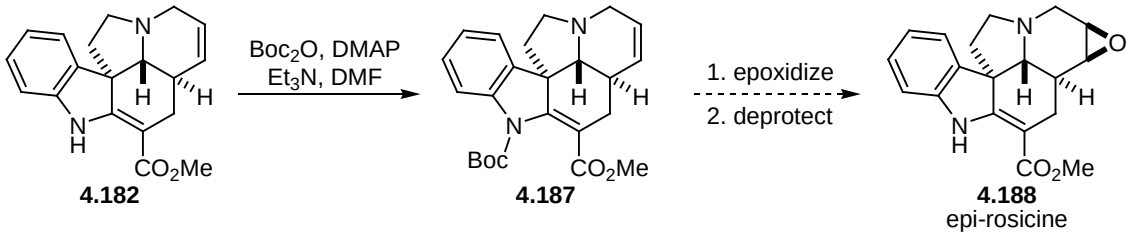
and an alternative epoxidation strategy is needed. A five step protocol has been developed to circumvent this problem,[180, 414] but we hoped that a more direct solution could be obtained.

Scheme 4.46



It was hypothesized protecting the vinylogous urethane nitrogen in **4.182** with an electron withdrawing group would render it unreactive to the epoxidation conditions. To this end the protection of **4.182** was undertaken (Scheme 4.47). Attempts to install a carbomethoxy group onto the nitrogen atom by treating **4.182** with NaH and methyl chloroformate were unsuccessful, and none of the desired product was obtained. Attention was then turned to the installation of a Boc group. The Boc protection of tabersonine (**4.184**) had been previously reported in the literature,[416] but when a slightly modified version of these conditions was applied to **4.182** the Boc-protected **4.187** could be isolated in only 14% yield.

Scheme 4.47



This is where the efforts towards the synthesis of rosicine currently stand. Two major unresolved issues need to be addressed in order to complete the synthesis. The first of these issues is that optimal conditions need to be found for epimerizing **4.180**. The second issue is that it is not known if the strategy of protecting the vinylogous carbamate will indeed be successful in tempering its reactivity, and the epoxidation of **4.187** needs to be attempted to test this hypothesis. The efforts towards rosicine still stand as an excellent model system and the many lessons that have been learned here have been applied to the synthesis of pseudotabersonine and can be applied to future synthetic efforts towards other members of the aspidospermine family.

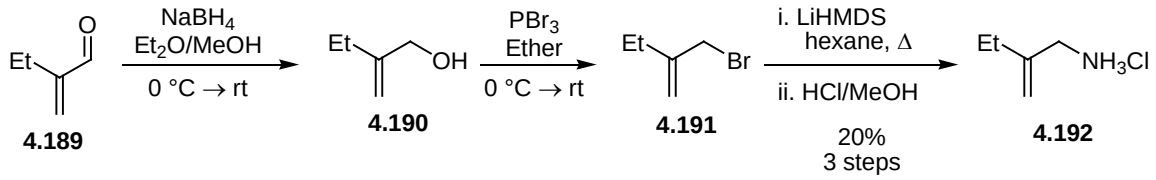
4.3.3 Efforts Towards the Total Synthesis of Pseudotabersonine

The efforts described above towards the synthesis of rosicine had shown that we can apply our imine pentadienylation/double RCM strategy to access the pentacyclic core of *Aspidosperma* alkaloids. We thus turned our attention to the synthesis of pseudotabersonine (**4.29**). Following the synthetic plan outlined for rosicine in Scheme 4.23, pseudotabersonine should be accessible simply by starting from 2-ethylallylamine instead of allylamine.

The synthesis of pseudotabersonine began from the commercially available 2-ethylacrolein (**4.189**) (Scheme 4.48). Reduction of the aldehyde with $NaBH_4$ provided alcohol **4.190**,[417] which was converted to the allyl bromide **4.191** with PBr_3. Allyl bromide **4.191** was then reacted with LiHMDS in refluxing hexane to provide the crude

bis(silyl)amine, which was treated with methanolic HCl to provide the desired 2-ethylallylamine as its HCl salt in 20% yield over the three steps.

Scheme 4.48

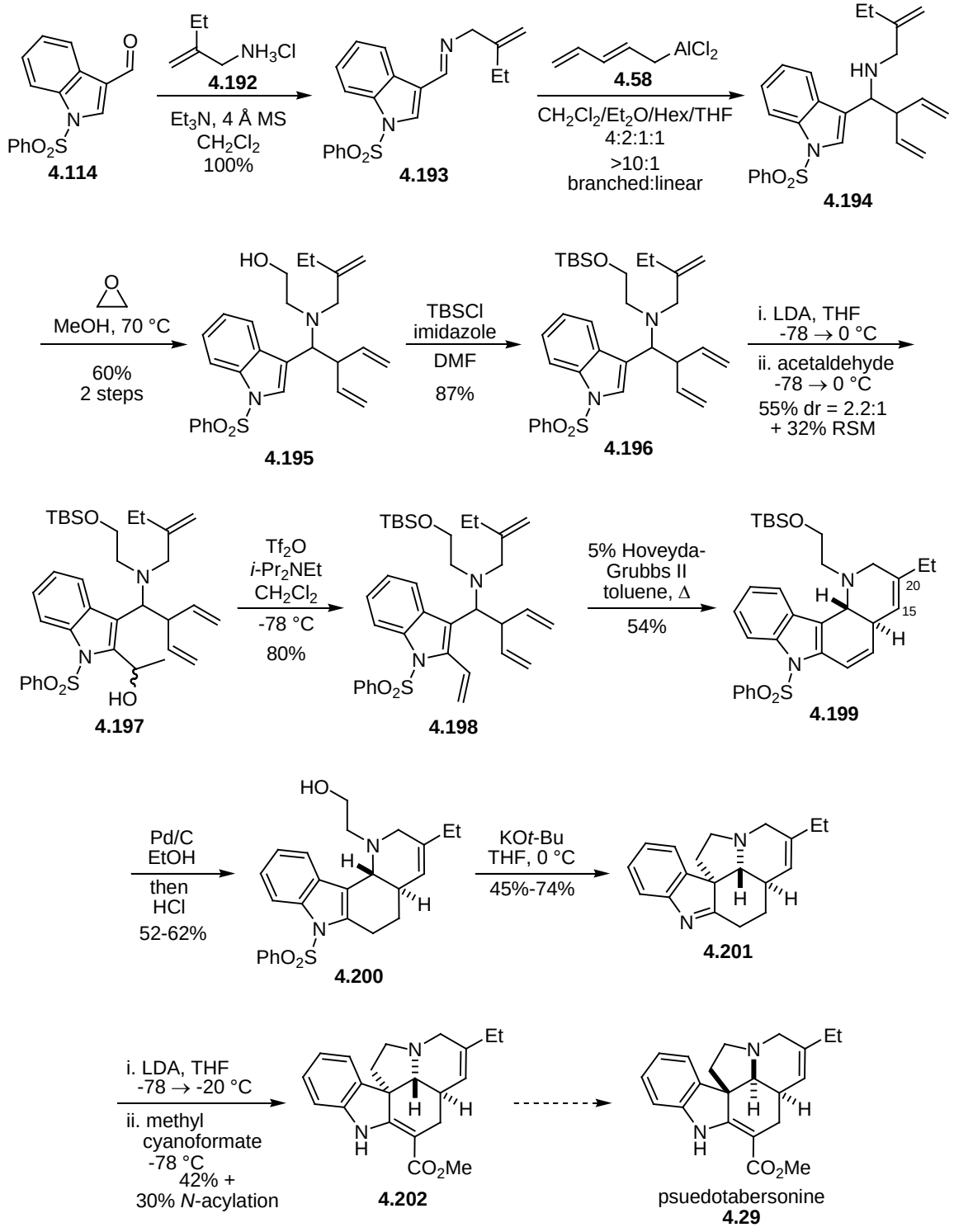


Condensation of amine **4.192** with aldehyde **4.114** provided imine **4.193**, which was subjected to the pentadienylation conditions to give the branched product **4.194** in greater than 10:1 regioselectivity (Scheme 4.49). The crude **4.194** was then treated with ethylene oxide in MeOH to provide alcohol **4.195** in 60% yield over the two steps. Interestingly, alcohol **4.195** is a solid while the corresponding linear isomer is not, and separation of the two can easily be obtained by the crystallization of **4.195** from methanol. Protection of **4.195** proceeded without incident to give **4.196** in 87% yield. Deprotonation of **4.196** with LDA and subsequent addition of acetaldehyde following the previously developed conditions (see Scheme 4.40) provided the desired alcohol **4.197** in 55% as a mixture (2.2:1) of separable diastereomers. Dehydration of **4.193** using Tf_2O and Hunig's base gave the RCM precursor **4.198**. Treatment of **4.198** with 5% Hoveyda-Grubbs II in refluxing toluene provided the *trans*-fused double RCM product **4.199** in 54% yield. The low yield for the RCM is due apart to the fact that **4.199** can aromatize under the reaction conditions.

The additional substitution on the C15-C20 double bond of **4.199** made it possible to perform the selective reduction on the protected indole. To this end, **4.199** was treated with Pd/C in EtOH under an atmosphere of H_2, and when the reduction was complete HCl was added to cleave the TBS group to provide **4.200** in 52-62% yield. Then, following a procedure developed by Bosch and Rubiralta,[418] **4.200** was treated with 2 eq.

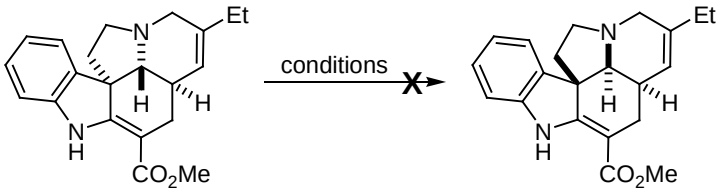
KO*t*-Bu in THF to provide the desired pentacycle **4.201**. Upon treatment with LDA and addition of methyl cyanoformate the desired *C*-acylated **4.202** could be isolated in 42% yield along with 30% of the *N*-acylated product. This completed the synthesis of *epi*-psuedotabersonine in 13 steps from 2-ethylacrolein.

Scheme 4.49


4.114
4.192
Et3N, 4 Å MS
CH2Cl2
100%
4.193
4.58
CH2Cl2/Et2O/Hex/THF
4:2:1:1
>10:1
branched:linear
4.194
MeOH, 70 °C
60%
2 steps
4.195
TBSCl
imidazole
DMF
87%
4.196
i. LDA, THF
-78 → 0 °C
ii. acetaldehyde
-78 → 0 °C
55% dr = 2.2:1
+ 32% RSM
4.197
Tf2O
i-Pr2NEt
CH2Cl2
-78 °C
80%
4.198
5% Hoveyda-
Grubbs II
toluene, Δ
54%
4.199
Pd/C
EtOH
then
HCl
52-62%
4.200
KOt-Bu
THF, 0 °C
45%-74%
4.201
i. LDA, THF
-78 → -20 °C
ii. methyl
cyanoformate
-78 °C
42% +
30% N-acylation
4.202
psuedotabersonine
4.29

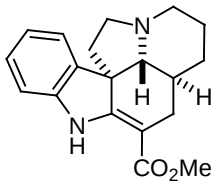
With **4.202** in hand, attention was then turned to the epimerization. Kuehne has reported on the attempted epimerization of **4.203**, and has shown that the *trans*-fused **4.203** does not undergo epimerization when heated at 200 ºC in acetic acid.[340] With these results in mind, the attempted epimerization of **4.202** was undertaken with hopes that more forcing conditions might be found under which **4.202** can be epimerized. To this end, **4.202** was treated with a number of protic or Lewis acids at elevated temperatures (Table 4.6). When **4.202** was heated in acetic acid at 220 ºC in a microwave reactor, no reaction occurred. When anhydrous *p*-toluenesulfonic acid was added to the reaction, an unidentified side product that appeared to arise from the decarboxylation of **4.202** was formed. When **4.202** was heated in trifluoroacetic acid, imine **4.201** was formed in good yield. The decarboxylations seen in these reactions presumably arise from adventitious water present in the reaction medium. $BF_3 \cdot OE_2$ and TMSOTf were also unsuccessful in epimerizing **4.202**, with $BF_3 \cdot OE_2$ returning only starting material and TMSOTf giving an unknown side product.

Table 4.6



4.202 **4.29**

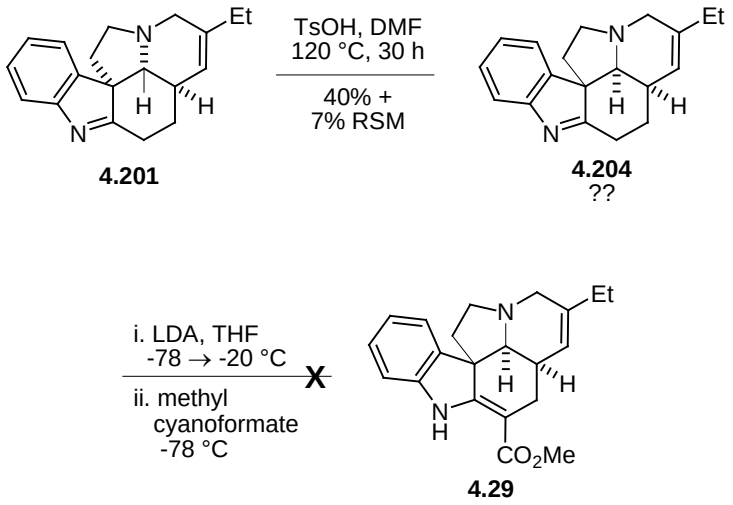
Conditions	Result
AcOH, μW, up to 220 °C	RSM
AcOH, TsOH, μW, 200 °C	??
TFA, μW, 150 °C	imine
BF_3•OEt_2, $ClCH_2CH_2Cl$, Δ	RSM
BF_3•OEt_2, μW, 100 °C	RSM
TMSOTf, CH_2Cl_2, μW, up to 145 °C	??



4.203

Since **4.202** proved to be resistant to all epimerization attempts, efforts were then turned to the epimerization of **4.201** (Scheme 4.50). When **4.201** was heated with TsOH in DMF at 120 ºC a product initially believed to be **4.204** was formed in moderate yield. However, when **4.204** was subjected to the acylation conditions, none of the desired natural product was produced. The reaction did provide a currently undetermined product in good yield, and the ^{1}H NMR spectra of this compound suggests that a methyl carbamate was formed in the reaction. Further studies are needed at this time to ascertain the correct structures of **4.203**, and to figure the product of this attempted acylation. These results also call into question the structure of **4.180**, and its structure will also need to be conclusively proved.

Scheme 4.50



4.201 **4.204** ?? **4.29**

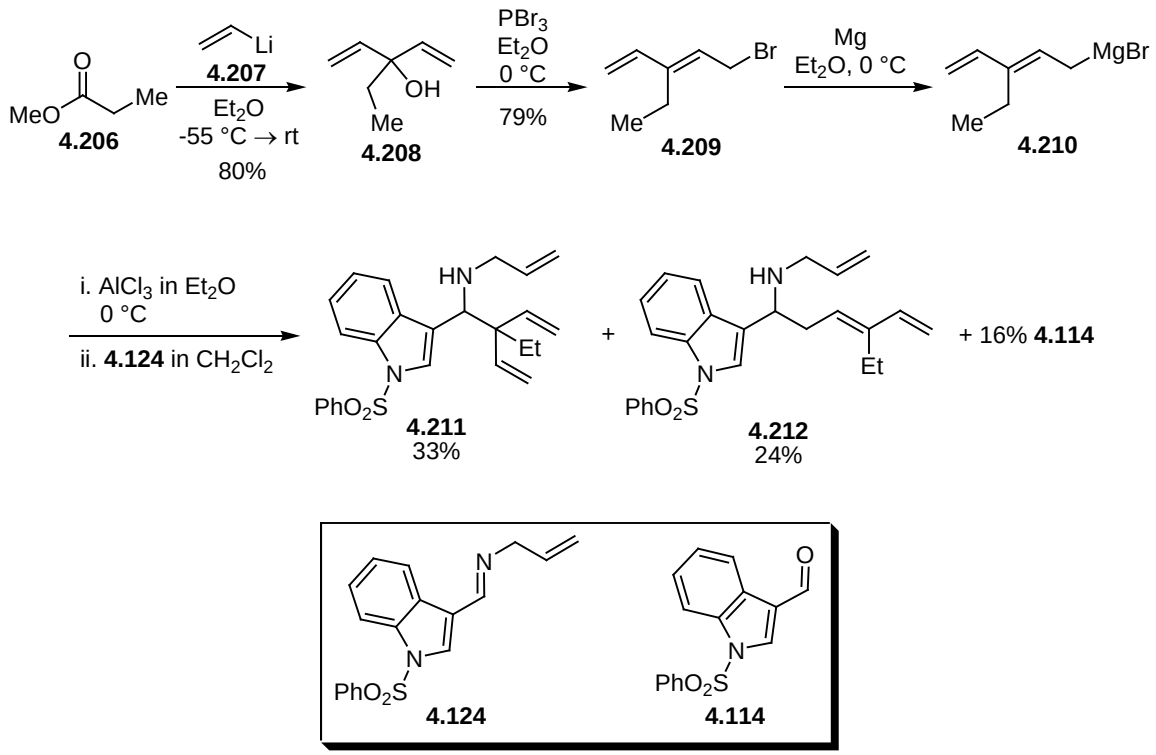
4.3.4 Preliminary Studies Involving 3-Ethylpentadienyl Aluminum

The vast majority of the *Aspidosperma* alkaloids contain an angular ethyl group at C-20. In order to access these natural products via our pentadienylation/double RCM strategy, a 3-substituted pentadienyl metal reagent would be needed for the pentadienylation. The added substitution at the 3-position of the pentadienyl metal could potentially alter the selectivity of the pentadienylation. The terminal olefin is not substituted and steric factors may cause attack to occur preferentially at the terminal carbon, which would give rise to the linear product. To test whether the increased steric bulk around the 3-position would alter the selectivity of the pentadienylation, 3-ethyl pentadienyl aluminum was synthesized and employed in the pentadienylation reaction with **4.124** (Scheme 4.50).

Treatment of methyl propionate with 2 eq. of vinyllithium provided the tertiary alcohol **4.208**, which was converted to primary bromide **4.209** with PBr_3. The Grignard reagent **4.210** was made from **4.209** and Mg in Et_2O at 0 ºC and subsequently transmetalated to aluminum with $AlCl_3$. The pentadienyl aluminum reagent was then

added to a solution of imine **4.124** in CH_2Cl_2 to provide the desired branched product **4.211** in 33% yield along with 24% of the linear product **4.212** and 16% of recovered aldehyde **4.114**.

Scheme 4.51



The overall conversion and selectivity for the branched product in this reaction were modest at best, but the fact that the branched product was still favored shows some promise. The conditions for this reaction varied greatly from the standard conditions that are commonly employed for the pentadienylation. The first major difference is that the 3-ethylpentadienyl aluminum reagent was prepared from the Grignard instead of from the organolithium reagent. It is not known at this time if the presence of these magnesium salts had any influence on the outcome of the pentadienylation. The second major difference was in the solvent system and concentration. The above pentadienylation was run in a 2:1 ether/CH_2Cl_2 solvent system instead of the normally used 4:2:1:1

CH_2Cl_2/Et_2O/hex/THF mixture, and the reaction was also run at a lower concentration. These differences were necessitated by the fact that the Grignard reagent was formed at a relatively low concentration in ether in an effort to prevent the dimerization of **4.209** and **4.210**. Hopefully, by finding an alternative way to access the 3-ethylpentadientyl aluminum reagent, which is more in line with the conditions previously developed for the unsubstituted reagent **4.58**, the selectivity for the branched product can be improved so that additional aspidospermine alkaloids can be accessed.

4.4 Conclusions

In order to further demonstrate the synthetic utility of the 4CR we have applied it to the synthesis of members of the isopavine and *Aspidosperma* alkaloid families. The application of the 4CR to the isopavine alkaloids has resulted in the first synthesis of roelactamine in only 4 steps from commercially available materials. In addition, the concise nature of the route and the flexibility of the 4CR make this approach to the isopavine alkaloids amenable to the synthesis of a collection of unnatural isopavines for use in biological testing.

In our efforts towards the synthesis of the *Aspidosperma* alkaloids, we have adopted a pentadienylation/double RCM strategy to access the pentacyclic core of these natural products. This sequence involved the use of a pentadienyl aluminum reagent, which was found to react with aryl imines to give branched products in good yields. The application of this strategy to the synthesis of rosicine resulted in the synthesis of pentacycle **4.180**, which is only two transformations and an epimerization away from the natural product. All that remains for the synthesis of rosicine is to find optimal conditions for the epimerization of **4.180**, and to find a protocol suitable for the epoxidation of **4.182**. The synthetic strategy developed for the synthesis of rosicine was then applied to the synthesis of pseudotabersonine. To this end, we have been successful

in synthesizing epi-pseudotabersonine in 13 steps from commercially available materials. Unfortunately, up to this point attempts to epimerize either **4.201** or **4.202** have been unsuccessful. While the successful epimerization of **4.202** at this point seems unlikely, there is still hope that with further studies the epimerization of **4.201** can be achieved.

We have also demonstrated in preliminary experiments that 3-ethylpentadienyl aluminum can react with imine **4.124** to give rise to the branched product as the major product. Although the yield and selectivity in this transformation were low, it is believed that with some optimization this reaction will provide us with a viable entry to the rest of the aspidospermine family of alkaloids. If this route does prove to be successful, it would be one of, if not the shortest synthetic route to the *Aspidosperma* alkaloids. Currently, investigations on this front are ongoing.

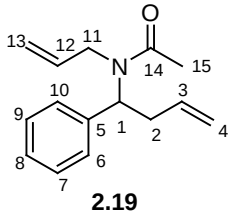
Chapter 5: Experimental Procedures

5.1 General

Unless noted all solvents and reagents were used without further purification. Methylene chloride, diisopropylamine, triethylamine, and pyridine were distilled from calcium hydride prior to use. THF and Et_2O were passed through two columns of activated neutral alumina prior to use. Toluene was passed through a column of Q5 reactant and a column of activated neutral alumina. Acetonitrile, diemethyl formamide, and methanol were passed through two columns of activated molecular sieves. Benzene was distilled from the sodium benzophenone ketyl. TMSOTf, $BF_3 \cdot OEt_2$, styrene, and benzaldehyde were distilled from CaH_2 under reduced pressure. Acetyl chloride and triflic anhydric were freshly distilled from P_2O_5 immediately prior to use. Hunig's base was distilled from KOH prior to use. Acryloyl chloride and crontonyl chloride were distilled immediately prior to use. Allyl bromide was dried with $MgSO_4$ and distilled. Zinc and magnesium metal was activated by washing with 1 M HCl. $AlCl_3$, $ZnBr_2$, and KO*t*-Bu were sublimed under reduced pressure. All air and moisture sensitive reactions were run under a positive pressure of N_2 or argon gas in glassware that had been oven or flame dried. 4 Å powdered molecular sieves were activated under vacuum at ~ 250 °C for at least 6 h prior to use. Thin-layer chromatography (TLC) was performed on EM 250 micro silica gel plates, and plates were visualized using UV detection and *para*-anisaldehyde (PAA), potassium permanganate ($KMnO_4$), or dinitrophenyl hydrazine (DNP) stain. Flash chromatography was performed with ICN Silica gel 60. Microwave reactions were performed using a CEM Discover Labmate microwave synthesizer, and the reactions were programmed to run utilizing as much power as neccessary to maintain the desired reaction temperature, as measured by the internal infrared detector.

^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and for $CDCl_3$ are referenced to an internal TMS standard (δ 0.00) and for DMSO-d_6 are referenced to the residual solvent peak (δ 2.05). ^{13}C NMR chemical shifts are reported in ppm relative to the center line of the multiplet for deuterium solvent peaks (δ 77.0 for $CDCl_3$ and δ 39.5 for DMSO-d_6). Coupling constants for all spectra are reported in Hertz (Hz). The abbreviations s, d, t, q, p, m, comp, and br stand for the resonance multiplicities singlet, doublet, triplet, quartet, pentuplet, multiplet, complex, and broad, respectively. Infrared (IR) spectra were recorded as films on sodium chloride plates and reported as wavenumbers (cm^{-1}).

5.2 Experimental Procedures

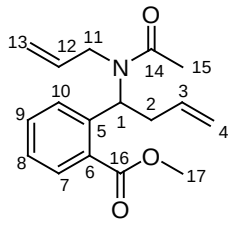


2.19

***N*-Allyl-*N*-(1-phenylbut-3-enyl)acetamide (2.19). (JDS-170a).** Acetyl chloride (0.10 mL, 110 mg, 1.41 mmol) was added to a solution of imine **2.17** (166 mg, 1.14 mmol) and allyltrimethylsilane (0.55 mL, 395 mg, 3.46 mmol) in CH_3CN (3 mL) at –20 °C. The reaction was stirred for 15 min at –20 °C, the cold bath was then removed and the reaction was stirred for 30 min at room temperature. TMSOTf (22 μL, 27 mg, 0.12 mmol) was added and the reaction was stirred at room temperature for 40 h. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 159 mg (61%) of **2.19** as a yellowish oil. ^{1}H NMR (500

MHz, DMSO, 100 °C) δ 7.36-7.31 (comp, 4 H), 7.27-7.24 (m, 1 H), 5.80-5.72 (m, 1 H), 5.65 (br, 1 H), 5.52 (ddt, *J* = 16.3, 10.5, 5.4 Hz, 1 H), 5.12 (d, *J* = 7.2 Hz, 1 H), 5.02 (d, *J* = 10.5 Hz, 1 H), 4.98-4.46 (comp, 2 H), 3.75 (dd, *J* = 16.8, 5.1 Hz, 1 H), 3.7 (m, 1 H), 2.80-2.67 (comp, 2 H), 2.05 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 169.4, 139.4, 134.9, 134.8, 127.7, 127.4, 126.7, 116.4, 115.3, 55.1, 46.2, 34.3, 21.4; IR (neat) 3077, 2978, 2930, 1644, 1407, 917, 701 cm^{-1}; mass spectrum (CI) *m/z* 230.1547 [$C_{15}H_{19}NO$ (M+1) requires 230.1545].

NMR Assignments. 1H NMR (500 MHz, DMSO, 100 °C) δ 7.36-7.31 (comp, 4 H, C6-H, C7-H, C9-H, & C10-H), 7.27-7.24 (m, 1 H, C8-H), 5.8-5.72 (m, 1 H, C3-H), 5.65 (br, 1 H, C1-H), 5.52 (ddt, J = 16.3, 10.5, 5.4 Hz, 1 H, C12-H), 5.12 (d, J = 7.2 Hz, 1 H, C4-H), 5.02 (d, J = 10.5 Hz, 1 H, C4-H), 4.98-4.46 (comp, 2 H, C13-H), 3.75 (dd, J = 16.8, 5.1 Hz, 1 H, C11-H), 3.7 (m, 1 H, C11-H), 2.80-2.67 (comp, C2-H), 2.05 (s, 3 H, C15-H); 13C NMR (125 MHz, DMSO, 100 °C) δ 169.4 (C14), 139.4 (C5), 134.9 (C3 or C12), 134.8 (C3 or C12), 127.7 (C6 & C10 or C7 & C9), 127.4 (C6 & C10 or C7 & C9), 126.7 (C8), 116.4 (C4 or C13), 115.3 (C4 or C13), 55.1 (C1), 46.2 (C11), 34.3 (C2), 21.4 (C15).



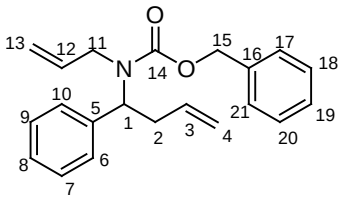
2.25

Methyl 2-(1-(*N*-allylacetamido)but-3-enyl)benzoate (2.25). (JDSIII-264a) A mixture containing freshly distilled methyl formyl benzoate (**2.34**)[419] (135 mg, 0.83 mmol), allylamine (0.06 mL, 46 mg, 0.80 mmol) and activated 4 Å molecular sieves (~500 mg) in CH_2Cl_2 (2.6 mL) was stirred for 12 h at room temperature. Freshly distilled acetyl chloride (0.06 mL, 66 mg, 0.84 mmol) was added, and the reaction was stirred for

1 h. The reaction was then cooled to –78 °C, freshly prepared allylzinc bromide (2.1 M in THF, 0.5 mL, 1.05 mmol) was added, and the reaction was stirred for 1.5 h. The dry ice bath was removed, and the reaction was filtered through a Celite pad that was washed with CH_2Cl_2 (3 x 5 mL). The combined filtrate and washings were washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was backwashed with CH_2Cl_2 (2 x 5 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (2:3) to give 193 mg (84%) of amide **2.25** as a viscous colorless oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.62 (d, *J* = 7.5 Hz, 1 H), 7.60 (d, *J* = 7.5, 1 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.37 (t, *J* = 7.5 Hz, 1H), 5.99 (t, *J* = 7.4 Hz, 1 H), 5.73 (dddd, *J* = 17.1, 10.2, 6.6, 6.6, 1 H), 5.51-5.43 (m, 1 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 5.00 (d, *J* =10.2, 1 H), 4.91-4.88 (comp, 2 H), 3.81 (s, 3 H) 3.82-3.68 (comp, 2 H), 2.79-2.69 (comp, 2 H), 2.00 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.3, 167.6, 138.1, 134.7, 134.5, 132.0, 130.2, 128.4, 127.7, 126.7, 116.3, 114.9, 54.0, 51.3, 45.8, 35.3, 21.1; IR (neat) 1722, 1649, 1405, 1270, 918, 749, cm^{-1}; mass spectrum (CI) *m/z* 288.1601 [$C_{17}H_{22}NO_3$ (M+1) requires 288.1600].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.62 (d, *J* = 7.5 Hz, 1 H, C7 or C10-H), 7.60 (d, *J* = 7.5, 1 H, C7 or C10-H), 7.52 (t, *J* = 7.5 Hz, 1 H, C8 or C9-H), 7.37 (t, *J* = 7.5 Hz, 1H, C8 or C9-H), 5.99 (t, *J* = 7.4 Hz, 1 H, C1-H), 5.73 (dddd, *J* = 17.1, 10.2, 6.6, 6.6, 1 H, C3 or C12-H), 5.51-5.43 (m, 1 H, C3 or C12-H), 5.09 (d, *J* = 17.1 Hz, 1 H, C4 or C13-H), 5.00 (d, *J* =10.2, 1 H, C4 or C13-H), 4.91-4.88 (comp, 2 H, C4 or C13-H), 3.81 (s, 3 H, C17-H) 3.82-3.68 (comp, 2 H, C11-H), 2.79-2.69 (comp, 2 H, C2-H), 2.00 (s, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.3 (C14), 167.6 (C17), 138.1 (C-Ar), 134.7 (C3 or C12), 134.5 (C3 or C12), 132.0 (C-Ar), 130.2 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 126.7 (C-Ar), 116.3 (C4 or C13), 114.9 (C4 or C13),

54.0 (C18), 51.3 (C1), 45.8 (C11), 35.3 (C2), 21.1 (C15); IR (neat) 1722, 1649, 1405, 1270, 918, 749, cm^{-1}; mass spectrum (CI) *m/z* 288.1601 [$C_{17}H_{22}NO_3$ (M+1) requires 288.1600].

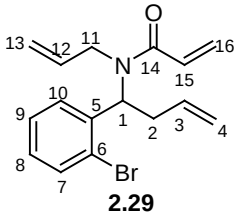


2.27

Benzyl allyl-1-phenylbut-3-enylcarbamate (2.27). (JDSI-141a). TMSOTf (40 μL, 49 mg, 0.22 mmol) was added to a solution of benzaldehyde (0.20 mL, 209 mg, 1.97 mmol) and bis(trimethylsilyl)allylamine (0.49 mL, 400 mg, 1.98 mmol) in CH_2Cl_2 (4 mL), and the reaction was stirred for 5 h at room temperature. The reaction was cooled to -78 ºC and allyltrimethylsilane (1 mL, 719 mg, 6.29 mmol) and Cbz-Cl (0.31 mL, 370 mg, 2.17 mmol) were then added, and the reaction was stirred for 20 min at -78 ºC. The cold bath was then removed and the reaction was stirred for 22 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:19) to give 488 mg (77%) of **2.27** as a yellowish oil. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.36-7.25 (comp, 10 H), 5.75 (dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, 1 H), 5.59 (dddd, *J* = 16.5, 10.3, 5.9, 5.9 Hz, 1 H), 5.22 (t, *J* = 7.8 Hz, 1 H), 5.12 (comp, 2 H), 5.12- 5.07 (comp, 1 H), 5.02-4.89 (comp, 3 H), 3.75 (dd, *J* = 16.1, 5.9 Hz, 1 H), 3.69 (dd, *J* = 16.1, 5.9 Hz, 1 H), 2.78-2.74 (comp, 2H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 155.1, 139.5, 136.5, 134.7, 134.7, 127.7, 127.7, 127.2, 127.1, 126.9, 126.8, 116.5, 115.4, 65.9, 58.5, 45.9, 34.6; IR (neat) 3065, 3030, 2937, 2248, 1951, 1810, 1696, 1406,

1232, 915, 733, 698 cm^{-1}; mass spectrum (CI) *m/z* 322.1799 [$C_{21}H_{22}NO_2$ (M+1) requires 322.1807].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.36-7.25 (comp, 10H, aromatic-H), 5.75 (dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, 1 H, C3-H), 5.59 (dddd, *J* = 16.5, 10.3, 5.9, 5.9 Hz, 1 H, C12-H), 5.22 (t, *J* = 7.8 Hz, 1 H, C1-H), 5.12 (comp, 2 H, C15-H), 5.12- 5.07 (comp, 1 H, C4 or C13-H), 5.02-4.89 (comp, 3 H, (C4 & C13-H), 3.75 (dd, *J* = 16.1, 5.9 Hz, 1 H, C11-H), 3.69 (dd, *J* = 16.1, 5.9 Hz, 1 H, C11-H), 2.78-2.74 (comp, 2 H, C2-H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 155.1 (C14) , 139.5 (C3 or C12), 136.5 (C3 or C12), 134.7 (C5 or C16), 134.7 (C5 or C16), 127.7 (C6 & C10 or C7 & C9) , 127.7 (C6 & C10 or C7 & C9), 127.2 (C18 & C20), 127.1 (C8 or C19), 126.9 (C17 & C21), 126.8 (C8 or C19), 116.5 (C4 or C13), 115.4 (C4 or C13), 65.9 (C15), 58.5 (C1), 45.9 (C11), 34.6 (C2).



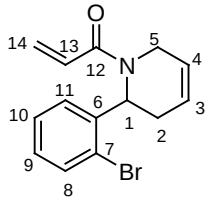
2.29

***N*-Allyl-*N*-(1-(2-bromophenyl)but-3-enyl)acrylamide (2.29). (JDSI-235a).** TMSOTf (15.5 μL, 19 mg, 0.086 mmol) was added to a solution of 2-bromobenzaldehyde (0.10 mL, 158 mg, 0.86 mmol) and bis(trimethylsilyl)allylamine (0.23 mL, 188 mg, 0.93 mmol) in CH_2Cl_2 (2 mL) and the reaction was stirred for 1 h at room temperature. The reaction was then cooled to 0 °C and freshly distilled acryloyl chloride (85 μL, 95 mg, 1.05 mmol) was added and the reaction was stirred for 10 min at 0 ºC. The ice bath was then removed and the reaction stirred for 40 min at room temperature. The reaction then was cooled to –78 °C and freshly prepared allylzinc bromide (2.31M in THF, 0.55 mL, 1.27 mmol) was then added and the reaction was stirred for 2.5 h at -78 ºC. The ice bath was then removed and the reaction was warmed

to room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous NH_4Cl (5 mL). The organic phase was removed, and the aqueous phase was washed with CH_2Cl_2 (3 x 5 mL). The combined organics were dried (MgSO4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:9) to give 224 mg (82%) of amide **2.29** as a viscous yellowish oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.63-7.59 (comp, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.23 (dt, *J* = 1.6, 7.6 Hz, 1H), 6.68 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.13 (dd, *J* = 16.7, 2.4 Hz, 1H), 5.73 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.67 (t, *J* = 7.5 Hz, 1H), 5.63 (dd, *J* = 10.5, 2.4 Hz, 1H), 5.48 (ddt, *J* = 15.9, 10.7, 5.5 Hz, 1H), 5.10 (dd, *J* = 17.0, 1.8, Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.90-4.86 (comp, 2H), 3.82 (d, *J* = 5.5 Hz, 2H), 2.86-2.73 (comp, 2H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 165.3, 137.1, 134.2, 133.9, 132.4, 129.6, 129.0, 128.8, 126.7, 125.6, 124.6, 116.5, 115.0, 57.2, 45.0, 34.9; IR (neat) 3477, 3077, 2979, 2929, 2359, 2241, 1926, 1842, 1651, 1614, 1416, 919, 753 cm^{-1}; mass spectrum (CI) *m/z* 320.0636 [$C_{16}H_{18}BrNO$ (M+1) requires 320.0650] 322.0612.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.63-7.59 (comp, 2H, C7 & C10-H), 7.40 (t, *J* = 7.6 Hz, 1H, C8 or C9-H), 7.23 (dt, *J* = 1.6, 7.6 Hz, 1H, C8 or C9-H), 6.68 (dd, *J* = 16.7, 10.5 Hz, 1H, C15-H), 6.13 (dd, *J* = 16.7, 2.4 Hz, 1H, C16-H), 5.73 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H, C3-H), 5.67 (t, *J* = 7.5 Hz, 1H, C1-H), 5.63 (dd, *J* = 10.5, 2.4 Hz, 1H, C16-H), 5.48 (ddt, *J* = 15.9, 10.7, 5.5 Hz, 1H, C12-H), 5.10 (dd, *J* = 17.0, 1.8, Hz, 1H, C4-H), 5.00 (d, *J* = 10.2 Hz, 1H, C4-H), 4.90-4.86 (comp, 2H, C13-H), 3.82 (d, *J* = 5.5 Hz, 2H, C11-H), 2.86-2.73 (comp, 2H, C2-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 165.3 (C14), 137.1 (C5), 134.2, 133.9, 132.4, 129.6, 129.0, 128.8, 126.7, 125.6, 124.6, 116.5 (C4 or C13), 115.0 (C4 or C13), 57.2 (C1), 45.0 (C11), 34.9 (C2).

Alternative procedure for amide (2.29). (JDSI-236d) A mixture containing 2-bromobenzaldehyde (0.11 mL, 174 mg, 0.94 mmol), allylamine (0.07 mL, 53 mg, 0.94 mmol) and activated 4 Å molecular sieves (~500 mg) in CH_2Cl_2 (2.5 mL) was stirred for 16 h at room temperature. The reaction was cooled to 0 ºC and freshly distilled acryoyl chloride (85 μL, 95 mg, 1.05 mmol) was added, and the reaction was stirred for 10 min at 0 ºC. The ice bath was then removed and the reaction was stirred for 1 h at room temperature. The reaction was then cooled to –78 °C, freshly prepared allylzinc bromide (2.31 M in THF, 0.55 mL, 1.27 mmol) was added, and the reaction was stirred for 2 h at -78 ºC. The dry ice bath was then removed, and the reaction was warmed to room temperature. The reaction was filtered through a Celite pad that was washed with CH_2Cl_2 (3 x 5 mL). The combined filtrate and washings were washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was backwashed with CH_2Cl_2 (2 x 5 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:9) to give 231 mg (77%) of amide **2.29** as a viscous yellowish oil.

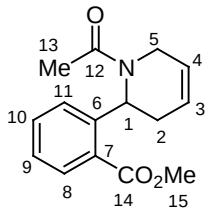


2.32

1-(6-(2-bromophenyl)-5,6-dihydropyridin-1(2H)-yl)prop-2-en-1-one (2.32). (JDSI-223a). Grubbs II catalyst (13 mg, 0.0.15 mmol) was added to a solution of amide **2.29** (86 mg, 0.27 mmol) in 10 mL CH_2Cl_2. The reaction was heated under reflux for 1 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 56 mg (72%) of dihydropyridine **2.32** and 6 mg (7%) of **2.31** as a yellowish gums.

2.32: ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.59 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H), 7.24, (dd, *J* = 7.7, 1.7 Hz, 1H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H), 6.62 (dd, *J* = 16.7, 10.6 Hz, 1H), 6.04 (dd, *J* = 16.7, 2.3 Hz, 1H), 5.94-5.90 (m, 1H), 5.85-5.81 (m, 1H), 5.71 (br, 1H), 5.63 (dd, 10.6, 2.2 Hz, 1H), 4.33 (ddt, *J* = 18.4, 3.2, 2.6 Hz, 1H), 3.90 (d, *J* = 18.4 Hz, 1H), 2.74-2.68 (dddd, *J* = 17.4, 6.2, 2.9, 2.9 Hz, 1H), 2.45 (dd, *J* = 17.4, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 165.0, 141.0, 132.4, 128.6, 128.4, 127.6, 127.0, 126.2, 124.1, 122.6, 121.5, 51.2, 41.5, 28.0; IR (neat) 3438, 3043, 2894, 2847, 2359, 1922, 1660, 1651, 1614, 1417, 1026, 751, 668 cm^{-1}; mass spectrum (CI) *m/z* 292.0337 [$C_{16}H_{18}BrNO$ (M+1) requires 292.0337] 294.0318.

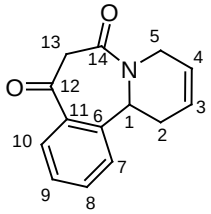
NMR Assignments. 2.32: ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.59 (dd, *J* = 7.7, 1.3 Hz, 1H, C8-H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H, C10-H), 7.24, (dd, *J* = 7.7, 1.7 Hz, 1H, C11-H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H, C8-H), 6.62 (dd, *J* = 16.7, 10.6 Hz, 1H, C13-H), 6.04 (dd, *J* = 16.7, 2.3 Hz, 1H, C14-H), 5.94-5.90 (m, 1H, C3 or C4-H), 5.85-5.81 (m, 1H, C3 or C4-H), 5.71 (br, 1H, C1-H), 5.63 (dd, 10.5, 2.2 Hz, 1H, C14-H), 4.33 (ddt, *J* = 18.4, 3.2, 2.6 Hz, 1H, C5-H), 3.90 (d, *J* = 18.4 Hz, 1H, C5-H), 2.74-2.68 (dddd, *J* = 17.4, 6.2, 2.9, 2.9 Hz, 1H, C2-H), 2.45 (dd, *J* = 17.4, 6.2 Hz, 1H, C2-H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 165.0 (C12), 141.0, 132.4, 128.6, 128.4, 127.6, 127.0, 126.2, 124.1, 122.6, 121.5, 51.2 (C1), 41.5 (C5), 28.0 (C2).



2.35

Methyl 2-(1-acetyl-1,2,3,6-tetrahydropyridin-2-yl)benzoate (2.35). (JDSIII-224a). Grubbs II catalyst (4 mg, 0.0053 mmol) was added to a solution of **2.25** (152 mg, 0.53 mmol) in CH_2Cl_2 (20 mL) and the reaction was heated under reflux for 3 h. The reaction was cooled the rt and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 129 mg (94%) of amide **2.35** as a tan solid, mp 104–106 °C. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.70 (d, *J* = 7.6, 1.4 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz) 7.33 (t, *J* = 7.6 Hz, 1 H), 7.25 (d, *J* = 7.6 Hz, 1H), 6.11 (br, 1 H), 5.88-5.83 (m, 1 H), 5.81-5.77 (m, 1 H) 4.23 (dd, *J* = 18.4, 2.3 Hz, 1 H), 3.86 (s, 3 H), 3.82 (d, *J* = 18.4 Hz, 1 H), 2.74-2.68 (m, 1 H), 2.34 (dd, *J* = 17.5, 6.2 Hz, 1 H), 1.97 (m, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.8, 167.2, 142.8, 130.5, 129.1, 128.9, 130.2, 126.1, 126.0, 123.8, 122.5, 51.2, 48.2, 41.4, 29.1, 20.7; IR (neat) 1722, 1649, 1405, 1270, 918, 749, cm^{-1}; mass spectrum (CI) *m/z* 260.1291 [$C_{15}H_{18}NO_3$ (M+1) requires 260.1287].

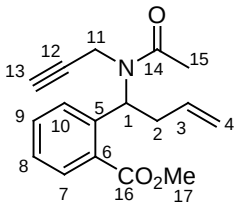
NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.70 (d, *J* = 7.6, 1.4 Hz, 1 H, C8-H), 7.46 (t, *J* = 7.6 Hz, C10-H) 7.33 (t, *J* = 7.6 Hz, 1 H, C9-H), 7.25 (d, *J* = 7.6 Hz, 1H, C11-H), 6.11 (br, 1 H, C1-H), 5.88-5.83 (m, 1 H, C3 or C4-H), 5.81-5.77 (m, 1 H, C3 or C4-H) 4.23 (dd, *J* = 18.4, 2.3 Hz, 1 H, C5-H), 3.86 (s, 3 H, C15-H), 3.82 (d, *J* = 18.4 Hz, 1 H, C5-H), 2.74-2.68 (m, 1 H, C2-H), 2.34 (dd, *J* = 17.5, 6.2 Hz, 1 H, C2-H), 1.97 (m, 3 H, C13-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.8 (C14), 167.2 (C16), 142.8, 130.5, 129.1, 128.9, 130.2, 126.1, 126.0, 123.8, 122.5, 51.2 (C17), 48.2 (C1), 41.4 (C5), 29.1 (C2), 20.7 (C13).



2.36

1,12b-Dihydrobenzo[c]pyrido[1,2-a]azepine-6,8(4H,7H)-dione (2.36). (JDSIII-196a). NaHMDS (1.85 M in THF, 0.93 mL, 1.72 mmol) was added to a solution of **2.35** (179 mg, 0.69 mmol) in THF (30 mL) and the reaction was stirred for 2 h at rt. Saturated aqueous NH_4Cl (10 mL) was then added. The organic layer was removed and the aqueous layer was backwashed with CH_2Cl_2 (2 x 5 mL). The organics were combined and dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 106 mg (67%) of amide **2.36** as a tan solid, mp 151.5–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.7, 1.4 H, 1 H), 7.50 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.38 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.28 (d, *J* = 7.7 Hz, 1H), 6.15-6.11 (m, 1 H), 5.87-5.82 (m, 1 H), 5.69 (d, *J* = 5.6 Hz, 1 H), 4.43 (d, *J* = 17.3 Hz, 1 H), 4.19-4.12 (m, 1 H), 3.79 (d, *J* = 17.3 Hz, 1 H), 3.55-3.47 (m, 1 H), 2.95-2.86 (m, 1 H), 2.82 (dd. *J* = 17.4, 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 169.8, 142.2, 136.5, 134.1, 131.3, 129.2, 126.0, 124.5, 122.6, 54.7, 51.6, 41.6, 26.0; IR (neat) 2906, 2853, 1681, 1650, 1409, 1248, 1137, 923, cm^{-1}; mass spectrum (CI) *m/z* 228.1027 [$C_{14}H_{14}NO_2$ (M+1) requires 228.1025].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.7, 1.4 H, 1 H, C10-H), 7.50 (td, *J* = 7.7, 1.4 Hz, 1 H, C8-H), 7.38 (td, *J* = 7.7, 1.1 Hz, 1 H, C9-H), 7.28 (d, *J* = 7.7 Hz, 1H, C7-H), 6.15-6.11 (m, 1 H C1-H), 5.87-5.82 (m, 1 H, C3 or C4-H), 5.69 (d, *J* = 5.6 Hz, 1 H, C3 or C4-H), 4.43 (d, *J* = 17.3 Hz, 1 H, C13-H), 4.19-4.12 (m, 1 H, C5-H), 3.79 (d, *J* = 17.3 Hz, 1 H, C13-H), 3.55-3.47 (m, 1 H, C5-H), 2.95-2.86 (m, 1 H, C2-H), 2.82 (dd. *J* = 17.4, 5.6 Hz, 1 H, C2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1 (C12), 169.8 (C14), 142.2 (C11), 136.5 (C6), 134.1, 131.3, 129.2, 126.0, 124.5, 122.6, 54.7 (C1), 51.6 (C12), 41.6 (C5), 26.0 (C2).

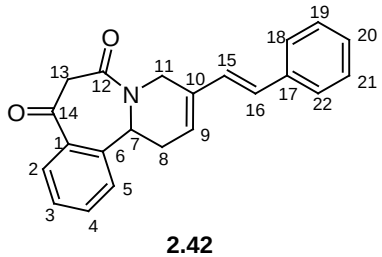


2.38

Methyl 2-(1-(N-(prop-2-ynyl)acetamido)but-3-enyl)benzoate (2.38). A mixture containing freshly distilled methyl formyl benzoate (**2.34**) (146 mg, 0.89 mmol), propargyl amine (0.06 mL, 48 mg, 0.87 mmol) and activated 4 Å molecular sieves (~ 500 mg) in CH_2Cl_2 (2.2 mL) was stirred for 12 h. Freshly distilled acetyl chloride (65 μL, 72 mg, 0.91 mmol) was added, and the reaction was stirred for 1 h. The reaction was then cooled to –78 °C, freshly prepared allyl ZnBr (2.2 M in THF, 0.46 mL, 1.01 mmol) was added, and the reaction was stirred for 1 h. The dry ice bath was removed, and the reaction was filtered thru a Celite pad that was washed with CH_2Cl_2 (3 x 5 mL). The combined filtrate and washings were washed with saturated aqueous NH_4Cl (10 mL). The aqueous layer was backwashed with CH_2Cl_2 (2 x 5 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 158 mg (63%) of amide **2.38** as a viscous colorless oil. ^{1}H NMR (500 MHz, DMSO, 120 °C) δ 7.67 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 9.9 Hz, 1 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 6.02 (t, J = 7.3 Hz, 1 H), 5.77 (dddd, J = 17.1, 10.4, 6.7, 6.7 Hz, 1 H), 5.12 (d, J = 17.1 Hz, 1 H), 5.02 (d, J = 10.2 Hz, 1 H), 4.03 (d, J = 18.4 Hz, 1 H), 3.80 (s, 3 H), 3.78 (comp, 1 H), 2.81 (comp, 3 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 120 °C) δ 169.2, 167.4, 138.0, 134.3, 131.5, 130.5, 128.8, 127.6, 126.9, 116.5, 80.1, 72.5, 54.3, 51.4, 35.2, 32.4, 21.2; IR (neat) 1721, 1654, 1406, 1269, 913, 747 cm^{-1}; mass spectrum (CI) *m/z* 286.1448 [$C_{17}H_{20}NO_3$ (M+1) requires 286.1443].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 120 °C) δ 7.67 (d, *J* = 8.0 Hz, 1H, C7-H or C10-H), 7.65 (d, *J* = 9.9 Hz, 1 H,), 7.55 (t, *J* = 7.6 Hz, 1 H, C9-H), 7.39 (t, *J* = 7.6 Hz, 1 H, C8-H), 6.02 (t, *J* = 7.3 Hz, 1 H, C1-H), 5.77 (dddd, *J* = 17.1, 10.4, 6.7, 6.7 Hz, 1 H, C3-H), 5.12 (d, *J* = 17.1 Hz, 1 H, C4-H), 5.02 (d, *J* = 10.2 Hz, 1 H, C4-H), 4.03 (d, *J* = 18.4 Hz, 1 H, C11-H), 3.80 (s, 3 H, C17-H), 3.78 (comp, 1 H, C11-H), 2.81 (comp, 3 H, C2-H and C13-H), 2.08 (s, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 120 °C) δ 169.2 (C14), 167.4 (C16), 138.0, 134.3, 131.5, 130.5, 128.8, 127.6, 126.9, 116.5 (C1), 80.1 (C12), 72.5 (C13), 54.3 (17), 51.4 (C1), 35.2 (C11), 32.4 (C2), 21.2 (C15).

Alternate procedure for 2.38. (JDSIII-266a). Propargyl amine (0.07 mL, 56 mg, 1.02 mmol) was added to a solution of freshly distilled methyl formyl benzoate (**2.34**) (153 mg, 0.93 mmol) in CH_2Cl_2 (3 mL) containing 4 Å powdered molecular sieves (~500 mg) and the reaction was stirred for 12 h at room temperature. The reaction was filtered through a pad of that was washed with CH_2Cl_2 (3 x 5 mL), and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2.3 mL), and freshly distilled acetyl chloride (0.07 mL, 77 mg, 0.98 mmol) was added and the reaction was stirred for 1 h at room temperature. The reaction was then cooled to -78 °C, freshly prepared allylzinc bromide (2.1 M in THF, 0.55 mL, 1.15 mmol) was added and the reaction was stirred for 1 h at -78 ºC. The reaction was partitioned between sat. NH_4Cl (5 mL) and CH_2Cl_2 (5 mL). The organic phase was removed, and aqueous phase washed with CH_2Cl_2 (2 x 5 mL). The combined organics were dried (MgSO4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (2:3) to give 215 mg (81%) of amide **2.38** as a viscous colorless oil.

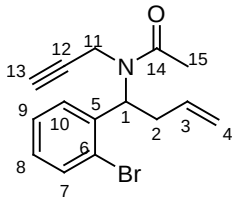


2.42

(E)-3-Styryl-1,12b-dihydrobenzo[c]pyrido[1,2-a]azepine-6,8(4H,7H)-dione (2.42). (JDSIV-127a). The Hoveyda-Grubbs II catalyst (12 mg, 0.018 mmol) was added to a solution of amide **2.38** (77 mg, 0.26 mmol) and freshly distilled styrene (0.46 mL, 42 mg, 4.01 mmol) in CH_2Cl_2 (11 mL) and the reaction was heated under reflux for 24 h. The reaction was cooled to rt and DMSO (0.25 mL) was added. The reaction was stirred for 20 h and then concentrated under reduced pressure. The residue was quickly purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give a brownish oil, which was immediately dissolved in THF (11 mL). NaHMDS (2M in THF, 0.26 mL, 0.52 mmol) was added, and the reaction was stirred for 5 min upon which sat. aqueous NH_4Cl (5 mL) was added. The organic phase was removed, and the aqueous layer was washed with Et_2O (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (3:7) to give 52 mg (58%) of a mixture (18:1) of amides **2.42** and **2.41** as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41-7.20 (comp, 7H), 6.79 (d, *J* = 16.4 Hz, 1H), 6.49 (d, *J* = 16.4 Hz, 1H), 6.24 (m, 1H), 5.72 (d, *J* = 6.2 Hz, 1H), 4.46 (d, *J* = 17.4 Hz, 1H), 4.43 (d, *J* = 18.1 Hz, 1H), 3.88 (d, *J* = 17.4 Hz, 1H), 3.84 (d, *J* = 18.1 Hz, 1H), 3.11-3.06 (m, 1H), 2.98 (dd, *J* = 18.3, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 169.9, 142.0, 137.8, 136.6, 134.3, 133.4, 131.4, 129.6, 129.6, 129.4, 128.6, 128.5, 128.1, 127.2, 127.2, 126.0, 123.8, 55.0, 51.8, 41.4, 26.9; IR (neat)

2358, 1680, 1641, 1596, 1410, 1247, 957 cm^{-1}; mass spectrum (CI) *m/z* 330.1492 [$C_{22}H_{20}NO_2$ (M+1) requires 330.1494].

NMR Assignments. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H, C2-H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.20-7.41 (comp, 7H, Ar-H), 6.79 (d, *J* = 16.4 Hz, 1H, C15-H), 6.49 (d, *J* = 16.4 Hz, 1H, C16-H), 6.24 (m, 1H, C7-H), 5.72 (d, *J* = 6.2 Hz, 1H, C9-H), 4.46 (d, *J* = 17.4 Hz, 1H, C11-H or C13-H), 4.43 (d, *J* = 18.1 Hz, 1H, C11-H or C13-H), 3.88 (d, *J* = 17.4 Hz, 1H, C11-H or C13-H), 3.84 (d, *J* = 18.1 Hz, 1H, C11-H or C13-H), 3.06-3.11 (m, 1H, C8-H), 2.98 (dd, *J* = 18.3, 5.8 Hz, 1H, C8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0 (C14), 169.9 (C12), 142.0, 137.8, 136.6, 134.3, 133.4, 131.4, 129.6, 129.6, 129.4, 128.6, 128.5, 128.1, 127.2, 127.2, 126.0, 123.8, 55.0 (C7 or C11), 51.8 (C7 or C11), 41.4 (C13), 26.9 (C8).

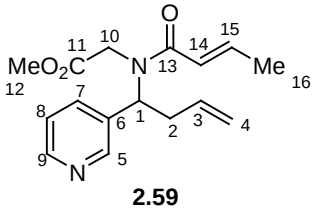


2.47

***N*-(1-(2-Bromophenyl)but-3-enyl)-N-(prop-2-ynyl)acetamide (2.47). (JDSIII-54a).** A mixture containing 2-bromobenzaldehyde (**2.28**) (0.1 mL, 16 mg, 0.86 mmol), propargyl amine (0.06 mL, 48 mg, 0.87 mmol) and activated 4 Å molecular sieves (~ 500 mg) in CH_2Cl_2 (2.2 mL) was stirred for 12 h at room temperature. Freshly distilled acetyl chloride (0.07 mL, 77 mg, 0.98 mmol) was added, and the reaction was stirred for 1 h. The reaction was then cooled to –78 °C, freshly prepared allylzinc bromide (1.7 M in THF, 0.75 mL, 1.27 mmol) was added, and the reaction was stirred for 1 h. The dry ice bath was removed, and the reaction was filtered thru a Celite pad that was washed with CH_2Cl_2 (3 x 5 mL). The combined filtrate and washings were washed with saturated aqueous NH_4Cl (10 mL). The aqueous layer was backwashed with CH_2Cl_2 (2 x 5 mL),

and the combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 257 mg (98%) of amide **2.47** as a viscous colorless oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.62 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.41 (t, *J* = 8.2 Hz, 1 H), 7.24 (t, *J* = 8.2 Hz, 1 H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H), 5.67 (s, 1 H), 5.12 (d, *J* = 17.0 Hz, 1 H), 5.02 (d, *J* = 10.2 Hz, 1 H), 4.00 (d, *J* = 18.5 Hz, 1 H), 3.80 (d, *J* = 18.5 Hz, 1 H), 2.75-2.87 (comp, 3 H), 2.16 (s, 1 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.9, 137.0, 134.0, 132.5, 129.3, 128.9, 126.9, 124.4, 116.6, 79.8, 72.2, 57.3, 34.7, 32.3, 21.0; IR (neat) 1650, 1406, 1173, 1028, 918, 750, 665 cm^{-1}; mass spectrum (CI) *m/z* [$C_{15}H_{16}BrNO$ (M+1) requires].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.62 (d, *J* = 8.2 Hz, 1 H, C7-H or C10-H), 7.61 (d, *J* = 8.2 Hz, 1 H, C7-H or C10-H), 7.41 (t, *J* = 8.2 Hz, 1 H, C9-H), 7.24 (t, *J* = 8.2 Hz, 1 H, C8-H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H, C3-H), 5.67 (s, 1 H, C1-H), 5.12 (d, *J* = 17.0 Hz, 1 H, C4-H), 5.02 (d, *J* = 10.2 Hz, 1 H, C4-H), 4.00 (d, *J* = 18.5 Hz, 1 H, C11-H), 3.80 (d, *J* = 18.5 Hz, 1 H, C11-H), 2.75-2.87 (comp, 3 H, C2-H and C13-H), 2.16 (s, 1 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.9 (C14), 137.0, 134.0, 132.5, 129.3, 128.9, 126.9, 124.4, 116.6 (C4), 79.8 (C12), 72.2 (C13), 57.3 (C1), 34.7 (C11), 32.3 (C2), 21.0 (C15).

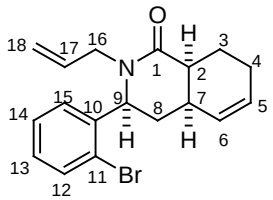


2.59

Methyl 2-((*E*)-*N*-(1-(pyridin-3-yl)but-3-enyl)but-2-enamido)acetate (2.59). (JDSIV-87a). Allylzinc bromide (1.9 M in THF, 0.63 mL, 1.20 mmol) was added to a solution of imine **2.58** (177 mg, 0.99 mmol) in THF (5 mL) at -78 °C. The reaction was stirred for 5 min at -78 °C, whereupon crotonyl chloride (0.14 mL, 153 mg, 1.46 mmol)

was added. The reaction was stirred for 3 h warming to room tempurature and then quenched with NH_4Cl (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to give 170 mg (59%) of amide **2.59** as a viscous yellowish oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 8.56 (d, *J* = 1.7 Hz, 1 H), 8.45 (d, *J* = 4.7 Hz, 1 H), 7.75 (d, *J* = 7.7 Hz, 1 H), 7.31 (dd, *J* = 7.7, 4.7 Hz, 1 H), 6.71 (dq, *J* = 14.3, 6.8 Hz, 1 H) 6.37 (d, *J* = 14.3 Hz, 1 H), 5.77 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1 H) 5.53-5.57 (m, 1H), 5.13 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.03 (d, *J* = 10.3 Hz, 1 H), 4.03 (d, *J* = 17.7 Hz, 1 H), 3.97 (d, *J* = 17.7 Hz, 1 H), 3.50 (s, 3 H), 2.72-2.84 (comp, 2 H), 1.83 (dd, *J* = 6.8, 1.1 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.1, 166.3, 149.2, 148.1, 140.4, 135.0, 134.3, 134.2, 122.6, 122.4, 117.0, 55.9, 51.1, 44.8, 34.3, 16.9; IR (neat) 2953, 1748, 1660, 1621, 1434, 1207, 1179, 1064, 963, 925, 824, 715; mass spectrum (CI) *m/z* 289.1552 [$C_{16}H_{21}N_2O_3$ (M+1) requires 289.1552].

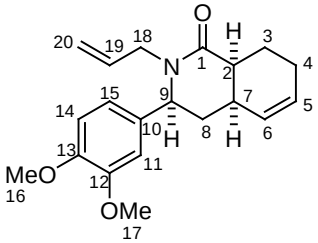
NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 8.56 (d, *J* = 1.7 Hz, 1 H, C5-H), 8.45 (d, *J* = 4.7 Hz, 1 H, C9-H), 7.75 (d, *J* = 7.7 Hz, 1 H, C7-H), 7.31 (dd, *J* = 7.7, 4.7 Hz, 1 H, C8-H), 6.71 (dq, *J* = 14.3, 6.8 Hz, 1 H, C15-H) 6.37 (d, *J* = 14.3 Hz, 1 H, C14-H), 5.77 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1 H, C3-H) 5.53-5.57 (m, 1H, C1-H), 5.13 (dd, *J* = 17.2, 1.4 Hz, 1 H, C4-H), 5.03 (d, *J* = 10.3 Hz, 1 H, C4-H), 4.03 (d, *J* = 17.7 Hz, 1 H, C10-H), 3.97 (d, *J* = 17.7 Hz, 1 H, C10-H), 3.50 (s, 3 H, C12-H), 2.72-2.84 (comp, 2 H, C2-H), 1.83 (dd, *J* = 6.8, 1.1 Hz, 3 H, C16-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.1 (C11), 166.3 (C13), 149.2 (C5 or C9), 148.1 (C5 or C9), 140.4, 135.0, 134.3, 134.2, 122.6, 122.4, 117.0 (C4), 55.9, 51.1, 44.8 (C10), 34.3 (C2), 16.9 (C16).



2.69

2-Allyl-3-(2-bromophenyl)-2,3,4,4a,8,8a-hexahydroisoquinolin-1(7*H*)-one (2.69). (JDSIII-278a). TMSOTf (15.5 μL, 19 mg, 0.086 mmol) was added to a solution of 2-bromobenzaldehyde (0.1 mL, 158 mg, 0.86 mmol) and bis(trimethylsilyl)allylamine (0.22 mL, 179 mg, 0.89 mmol) in CH_2Cl_2 (2.2 mL), and the reaction was stirred for 30 min at rt. Pentadienylsilane **2.67**[420] (303 mg, 2.16 mmol) and freshly distilled acryloyl chloride (85 μL, 94 mg, 1.05 mmol) were then added and the reaction stirred for 22 h. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (3:17) to give 251 mg (84%) of amide **2.69** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 7.6 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 5.74-5.66 (comp, 2 H), 5.55-5.52 (m, 1 H), 5.08 (d, *J* = 10.0 Hz, 1 H), 4.97 (dd, *J* = 10.1, 5.4 Hz, 1 H), 4.87 (d, *J* = 17.2 Hz, 1 H), 4.66 (dd, *J* = 14.8, 4.2 Hz, 1 H), 2.94 (dd, *J* = 14.8, 7.7 Hz, 1 H), 2.7 (d, *J* = 10.9 Hz, 1 H), 2.56-2.55 (m, 1 H), 2.21-2.08 (comp, 4 H), 1.85-1.77 (m, 1 H), 1.64-1.56 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 141.2, 133.8, 133.0, 129.7, 129.2, 128.9, 128.8, 128.8, 123.5, 118.9, 60.4, 47.6, 42.0, 35.5, 32.6, 25.9, 23.6; IR (neat) 2933, 1651, 1568, 1410, 1338, 1283, 1188, 1024, 925, 760 cm^{-1}; Mass spectrum (CI) *m/z* 346.0799 [$C_{18}H_{20}BrNO$ (M+1) requires 346.0807], 348.0784.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1 H, C12-H), 7.29 (t, *J* = 7.6 Hz, 1 H, C14-H), 7.16 (d, *J* = 7.6 Hz, 1 H, C15-H), 7.11 (t, *J* = 7.6 Hz, 1 H, C13-H), 5.74-5.66 (comp, 2 H, C5-H and C17-H), 5.55-5.52 (m, 1 H, C6-H), 5.08 (d, *J* = 10.0 Hz, 1 H, C18-H), 4.97 (dd, *J* = 10.1, 5.4 Hz, 1 H, C9-H), 4.87 (d, *J* = 17.2 Hz, 1 H, C18-H), 4.66 (dd, *J* = 14.8, 4.2 Hz, 1 H, C16-H), 2.94 (dd, *J* = 14.8, 7.7 Hz, 1 H, C16-H), 2.7 (d, *J* = 10.9 Hz, 1 H, C2-H), 2.56-2.55 (m, 1 H, C7-H), 2.21-2.08 (comp, 4 H, C3-H, C4-H, and C8-H), 1.77-1.85 (m, 1 H, C3-H), 1.64-1.56 (m, 1 H, C8-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (C1), 141.2 (C10), 133.8 (C12 or C17), 133.0 (C12 or C17), 129.7, 129.2, 128.9, 128.8, 128.8, 123.5 (C11), 118.9 (C18), 60.4 (C9), 47.6 (C16), 42.0 (C2), 35.5 (C7), 32.6 (C8), 25.9 (C4), 23.6 (C3).

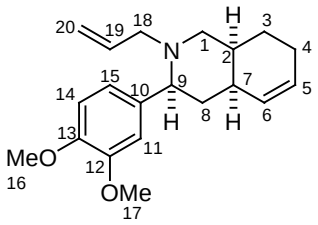


2.71

2-Allyl-2,3,4,4a,8,8a-hexahydro-3-(3,4-dimethoxyphenyl)isoquinolin-1(7*H*)-one (2.71). (JDSIII-279a). TMSOTf (12 μL, 55 mg, 0.066 mmol) was added to a solution of 3,4-dimethoxybenzaldehyde (**2.66**) (111 mg, 0.67 mmol) and bis(trimethylsilyl)allylamine (0.17 mL, 139 mg, 0.69 mmol) in CH_2Cl_2 (1.7 mL), and the reaction was stirred for 30 min at rt. Freshly distilled acryloyl chloride (65 μL, 72 mg, 0.80 mmol) and pentadienylsilane **2.67** (214 mg, 1.53 mmol) and were then added, and the reaction was stirred for 24 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

The residue was purified by flash chromatography eluting with EtOAc/Hexane (2:3) to give 172 mg (78 %) of amide **2.71** (6:1 mixture of diastereomers) as a viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 6.82 (d, *J* = 8.2 Hz, 1 H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.66 (d, *J* = 1.7 Hz, 1 H), 5.78-5.65 (comp, 2 H), 5.58-5.54 (m, 1H), 5.08 (dd, *J* = 10.2, 1.0 Hz, 1 H), 4.89 (dd, *J* = 17.1, 1.0 Hz, 1 H), 4.62 (dd, *J* = 15.0, 4.4 Hz, 1 H), 4.42 (dd, *J* = 10.9, 4.8 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.07 (dd, *J* = 15.0, 1.0 Hz, 1 H), 2.72-2.68 (m, 1 H), 2.58-2.52 (m, 1 H), 2.24-2.14 (comp, 3 H), 2.12-2.04 (comp, 2 H), 1.89-1.74 (comp, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 174.2, 149.5, 148.8, 134.2, 133.2, 128.7, 128.1, 119.6, 117.3, 111.3, 109.8, 61.3, 56.1, 56.1, 46.5, 41.5, 37.1, 32.3, 25.5, 23.3; IR (neat) 2934, 1634, 1516, 1442, 1410, 1262, 1138, 1027, 928; Mass spectrum (CI) *m/z* 328.1913 [$C_{20}H_{26}NO_3$ (M+1) requires 328.1913].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 6.82 (d, *J* = 8.2 Hz, 1 H, C15-H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1 H, C14-H), 6.66 (d, *J* = 1.7 Hz, 1 H. C11-H), 5.78-5.65 (comp, 2 H, C19-H and C5-H, or C19-H and C6-H), 5.58-5.54 (m, 1H, C5-H or C6-H), 5.08 (dd, *J* = 10.2, 1.0 Hz, 1 H, C20-H), 4.89 (dd, *J* = 17.1, 1.0 Hz, 1 H, C20-H), 4.89 (dd, *J* = 15.0, 4.4 Hz, 1 H, C18-H), 4.42 (dd, *J* = 10.9, 4.8 Hz, 1 H, C9-H), 3.88 (s, 3 H, C16-H or C17-H), 3.86 (s, 3 H, C16-H or C17-H) 3.07 (dd, *J* = 15.0, 1.0, Hz, 1 H, C18-H), 2.72-2.68 (m, 1 H, C2-H or C7-H), 2.58-2.52 (m, 1 H, C2-H or C7-H), 2.14-2.24 (comp, 3 H), 2.04-2.12 (comp, 2 H), 1.74-1.89 (comp, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 174.2 (C1), 149.5 (C12 or C13), 148.8 (C12 or C13), 134.2, 133.2, 128.7, 128.1, 119.6, 117.3, 111.3, 109.8, 61.3 (C9), 56.1 (C16), 56.1 (C17), 46.5 (C18), 41.5 (C2), 37.1 (C7), 32.3 (C8), 25.5 (C4), 23.3 (C3).

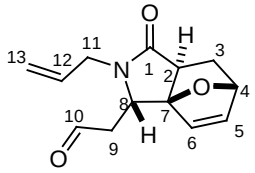


2.72

2-Allyl-1,2,3,4,4a,7,8,8a-octahydro-3-(3,4-dimethoxyphenyl)isoquinoline (2.72). (JDSIV-107a). $LiAlH_4$ (63 mg, 1.66 mmol) was added to a solution of **2.71** (172 mg, 0.52 mmol) in THF (10 mL). The reaction was heated under reflux for 4 h and then cooled to rt. H_2O (2 mL) and 6 M NaOH (2 mL) were added sequentially, and the reaction was filtered through Celite. The organic layer was removed and washed with sat NaCl (10 mL), dried (MgSO4), filtered and concentrated. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:19) to give 126 mg (76 %) of amide **2.72** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 1.7 Hz, 1 H), 6.82 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 5.74 (dddd, *J* = 17.5,10.2, 7.7, 4.6 Hz, 1 H), 5.60-5.66 (comp, 2 H), 5.10 (d, *J* = 17.5 Hz, 1H), 5.03 (d, *J* = 10.2, Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.13 (ddt (*J* = 14.4, 4.3, 2.0 Hz, 1 H), 3.03-3.00 (comp, 1 H), 2.98 (dd, *J* = 11.3, 2.7 Hz, 1 H), 2.39 (dd, *J* = 14.4, 7.5 Hz 1 H), 2.33 (dd, *J* = 11.8, 3.1 Hz 1 H), 2.20-2.09 (comp, 4 H), 1.85-1.80 (m, 1 H), 1.69 (dt, *J* = 13.7, 3.6, 1 H), 1.60-1.52 (comp, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 148.7, 138.6, 137.0, 132.1, 127.5, 120.3, 116.9, 111.7, 111.0, 69.1, 59.5, 58.6, 56.7, 56.7, 40.9, 36.2, 35.0, 27.1, 23.9; IR (neat) 2933, 1591, 1514, 1261, 1235, 1134, 1030, 920, 807; mass spectrum (CI) *m/z* 314.2114 [$C_{20}H_{28}NO_2$ (M+1) requires 314.2120].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 1.7 Hz, 1 H, C11-H), 6.82 (dd, *J* = 8.2, 1.7 Hz, 1 H, C14-H), 6.78 (d, *J* = 8.2 Hz, 1 H, C15-H), 5.74 (dddd, *J* = 17.5,10.2, 7.7, 4.6 Hz, 1 H, C19-H), 5.66-5.60 (comp, 2 H, C5-H and C6-H), 5.10 (d, *J* = 17.5 Hz, 1H, C20-H), 5.03 (d, *J* = 10.2, Hz, 1 H, C20-H), 3.88 (s, 3 H, C16-H

or C17-H), 3.86 (s, 3 H, C16-H or C17-H), 3.13 (ddt, *J* = 14.4, 4.3, 2.0 Hz, 1 H), 3.03-3.00 (comp, 1 H), 2.98 (dd, *J* = 11.3, 2.7 Hz, 1 H), 2.39 (dd, *J* = 14.4, 7.5 Hz 1 H), 2.33 (dd, *J* = 11.8, 3.1 Hz 1 H), 2.20-2.09 (comp, 4 H), 1.85-1.80 (m, 1 H), 1.69 (dt, *J* = 13.7, 3.6, 1 H), 1.60-1.52 (comp, 2 H, (C8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (C12 or C13), 148.7, (C12 or C13), 138.6, 137.0, 132.1, 127.5, 120.3, 116.9, 111.7, 111.0, 69.1 (C9), 59.5 (C18), 58.6 (C1), 56.7 (C16 or C17), 56.7 (C16 or C17), 40.9 (C8), 36.2 (C2 or C7), 35.0 (C2 or C7), 27.1 (C4), 23.9 (C3).

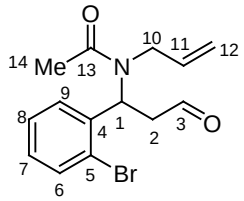


2.76

Epoxy isoindolones 2.76. (JDSII-161a). TMSOTf (21 μL, 26 mg, 0.12 mmol) was added to a solution of furfural (0.1 mL, 116 mg, 1.21 mmol) and bis(trimethylsilyl)allylamine (0.31 mL, 253 mg, 1.26 mmol) in CH_2Cl_2 (3.0 mL) and the reaction was stirred for 30 min. Freshly distilled acetyl chloride (0.12 mL, 132 mg, 1.48 mmol) and silyl enol ether **2.74**[421] (411 mg, 2.60 mmol) were added and the reaction was stirred for 6 h. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (35 mL) and heated under reflux for 18 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/Hexane (gradient elution 3:1 to 100% Et_2O) followed by EtOAc to give 139 mg (49%) of amide **2.76** as a dark yellowish oil along with 52 mg (~19%) of an unclean diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1 H), 6.41 (d, *J* = 5.9 Hz, 1 H), 6.27 (d, *J* = 5.9 Hz, 1 H), 5.73 (dddd, *J* = 17.0, 10.3, 5.9, 5.9 Hz, 1 H),

5.25 (d, *J* = 17.0 Hz), 5.21 (d, *J* = 10.3 Hz, 1 H), 5.06 (d, *J* = 3.9 Hz, 1 H), 4.34 (t, *J* = 6.1 Hz, 1 H), 4.27 (dd, *J* = 15.9, 4.0 Hz, 1H), 3.61 (dd, *J* = 15.9, 6.5 Hz, 1 H), 2.96 (d, *J* = 6.1 Hz, 2 H), 2.53 (dd, *J* = 8.8, 3.9 Hz, 1 H), 2.20 (d, *J* = 11.7 Hz, 1 H), 1.60 (dd, *J* = 11.7, 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 174.0, 137.5, 132.1, 131.4, 118.1, 92.0, 79.0, 54.5, 45.9, 44.4, 43.9, 28.3; IR (neat) 2951, 2735, 1721, 1688, 1440, 1348, 1253, 1045, 946, 700 cm^{-1}; mass spectrum (CI) *m/z* 234.1131 [$C_{13}H_{15}NO_3$ (M+1) requires 234.1130].

NMR Assignments. 33: ^{1}H NMR (500 MHz, CDCl3) δ 9.90 (s, 1 H, C10-H), 6.41 (d, *J* = 5.9 Hz, 1 H, C5-H), 6.27 (d, *J* = 5.9 Hz, 1 H, C6-H), 5.73 (dddd, *J* = 17.0, 10.3, 5.9, 5.9 Hz, 1 H, C12-H), 5.25 (d, *J* = 17.0 Hz, 1 H, C13-H), 5.21 (d, *J* = 10.3 Hz, 1 H, C13-H), 5.06 (d, *J* = 3.9 Hz, 1 H, C4-H), 4.34 (t, *J* = 6.1 Hz, 1 H, C8-H), 4.27 (dd, *J* = 15.9, 4.0 Hz, 1H, C11-H), 3.61 (dd, *J* = 15.9, 6.5 Hz, 1 H, C11-H), 2.96 (d, *J* = 6.1 Hz, 2 H, C9-H), 2.53 (dd, *J* = 8.8, 3.9 Hz, 1 H, C2-H), 2.20 (d, *J* = 11.7 Hz, 1 H, C3-H), 1.60 (dd, *J* = 11.7, 8.8 Hz, 1 H,C3-H); ^{13}C NMR (100 MHz, CDCl3) δ 198.4 (C10), 174.0 (C1), 137.5 (C5), 132.1 (C12), 131.4 (C6), 118.1 (C13), 92.0 (C7), 79.0 (C4), 54.5 (C8), 45.9 (C2), 44.4 (C9), 43.9 (C11), 28.3 (C3).

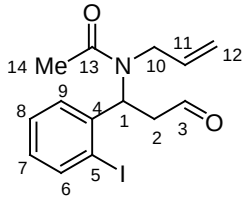


2.86

***N*-Allyl-*N*-(1-(2-bromophenyl)-2-formylethyl)acetamides (2.86). (JDSI-245a).** TMSOTf (15.5 μL, 19 mg, 0.086 mmol) was added to a solution of 2-bromobenzaldehyde (0.1 mL, 158 mg, 0.86 mmol) and bis(trimethylsilyl)allylamine (0.22 mL, 179 mg, 0.89 mmol) in CH_2Cl_2 (2.2 mL), and the reaction was stirred for 1 h at rt. The reaction was cooled to 0 ºC and silyl enol ether **2.74** (420 mg, 2.66 mmol) and

freshly distilled acetyl chloride (0.07 mL, 77 mg, 0.98 mmol) were then added, and the reaction was stirred for 10 min. The ice bath was removed and the reaction was stirred for 40 h at rt. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 207 mg (77%) of amide **2.86** as a brownish solid, mp = 56-58 ºC. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 9.66 (s, 1 H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.54 (d *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 6.02 (br, 1H), 5.52-5.45 (m, 1H), 4.94-4.92 (comp, 2H), 3.81 (dd, *J* = 17.2, 5.2 Hz, 2H), 3.73 (dd, *J* = 17.2, 5.7 Hz), 3.24-3.19 (m, 1H), 3.10 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 199.2, 169.3, 137.1, 134.0, 132.5, 129.2, 129.0, 127.0, 124.0, 115.3, 52.7, 46.2, 44.9, 21.0; IR (neat) 1720, 1645, 1405, 1024, 913, 749 cm^{-1}; mass spectrum (CI) *m/z* 310.0446 [$C_{14}H_{16}BrNO_2$ (M+1) requires 310.0443] 312.0426.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 9.66 (t, *J* = 1.7 Hz, C3-H), 7.62 (dd, *J* = 7.7, 1.2 Hz, 1H, C6-H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H, C9-H), 7.39 (td, *J* = 7.6, 1.0 Hz, 1H, C7-H), 7.25 (td, *J* = 7.6, 1.5 Hz 1H, C8-H), 6.04 (br s, 1H, C1-H), 5.48-5.40 (m, 1H, C11-H), 4.90 (comp, 2H, C12-H), 3.80-3.68 (comp, 2H, C10-H), 3.20 (br s, 1H, C2-H), 3.09-3.04 (m, 1H, C2-H), 2.05 (s, 3H, C14-H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 199.5 (C3), 169.5 (C13), 137.1 (C4), 134.1, 132.6, 129.3, 129.2, 127.1, 124.2 (C5), 115.5 (C11), 52.4 (C1), 46.5 (C2 or C10), 45.0 (C2 or C10), 21.2 (C14).

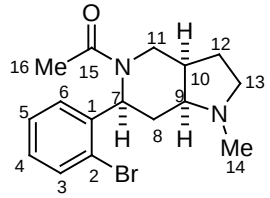


2.87

***N*-Allyl-*N*-(2-formyl-1-(2-iodophenyl)ethyl)acetamide (2.87). (JDSII-158A).** TMSOTf (23 μL, 28 mg, 0.13 mmol) was added to a solution of 2-iodobenzaldehyde (**2.85**) (300 mg, 1.29 mmol) and bis(trimethylsilyl)allylamine (0.33 mL, 269 mg, 1.33 mmol) in CH_2Cl_2 (3.2 mL), and the reaction was stirred for 30 min at room temperature. Silyl enol ether **2.74**[421] (401 mg, 2.54 mmol) and freshly distilled acetyl chloride (0.11 mL, 121 mg, 1.55 mmol) were then added, and the reaction was stirred for 24 h at room temperature. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous phase was washed with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated under reduced pressure. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 326 mg (70%) of amide **2.87** as viscous light brown oil. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 9.65 (t, *J* = 1.8 Hz, 1 H), 7.90 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.46 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.41 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.06 (td, *J* = 7.8, 1.8 Hz, 1 H), 5.82 (s, 1 H), 5.42 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1 H), 4.92-4.90 (comp, 2 H), 3.77 (dd, *J* = 17.2, 5.6 Hz, 1 H), 3.67 (dd, *J* = 17.2, 5.6 Hz, 1 H), 3.17 (s, 1H), 3.06 (dd, *J* = 16.3, 7.5 Hz, 1 H), 2.06 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 199.5, 169.6, 140.1, 139.5, 134.1, 129.3, 128.9, 127.8, 115.6, 100.9, 56.8, 45.3, 21.3; IR ($CDCl_3$) 2931, 2837, 1722, 1644, 1464, 1404, 1255, 1224, 1177, 1011, 925, 753 cm^{-1}; mass spectrum (CI) *m/z* 358.0305 [$C_{14}H_{16}INO_2$ (M+1) requires 358.0304].

NMR Assignments. ^{1}H NMR (400 MHz, DMSO, 100 °C) δ 9.65 (t, *J* = 1.8 Hz, 1 H, C3-H), 7.90 (dd, *J* = 7.8, 1.3 Hz, 1 H, C6-H), 7.46 (dd, *J* = 7.8, 1.6 Hz, 1 H, C9-H), 7.41 (td, *J* = 7.8, 1.3 Hz, 1 H, C8-H), 7.06 (td, *J* = 7.8, 1.8 Hz, 1 H, C7-H), 5.82 (s, 1 H, C1-H), 5.42 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1 H, C11-H), 4.92-4.90 (comp, 2 H, C12-H), 3.77 (dd, *J* = 17.2, 5.6 Hz, 1 H, C10-H), 3.67 (dd, *J* = 17.2, 5.6 Hz, 1 H, C10-H), 3.17 (s,

1H, C2-H), 3.06 (dd, *J* = 16.3, 7.5 Hz, 1 H, C2-H), 2.06 (s, 3 H, C14-H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 199.5 (C3), 169.6 (C13), 140.1, 139.5, 134.1, 129.3, 128.9, 127.8, 115.6 (C12), 100.9 (C5), 56.8 (C1), 45.3, 21.3 (C14).

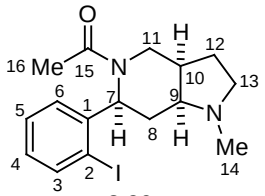


2.89

1-(Hexahydro-6-(2-bromophenyl)-1-methyl-1*H*-pyrrolo[3,2-c]pyridin-5(6*H*)-yl)ethanone (2.89). (JDSIII-161a). Sarcosine (84 mg, 0.95 mmol) was added to a solution of **2.86** (166 mg, 0.54 mmol) in toluene (1 mL). The reaction was heated under reflux for 3 h. The reaction was cooled to room temperature and then was partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with MeOH/EtOAc (1:3) to give 118 mg (65%) of **2.89** as a brownish gum. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.54 (d, *J* = 7.9 Hz, 1 H), 7.33-7.27 (comp, 2 H), 7.14 (t, *J* = 7.0 Hz, 1 H), 4.97 (dd, *J* = 12.8, 4.8 Hz, 1 H), 4.20 (br, 1 H), 3.14 (br, 1 H), 2.88-2.84 (m, 1 H), 2.50-2.47 (m, 1 H), 2.38 (br, 1 H), 2.30 (s, 3 H), 2.27-2.23 (comp, 2 H), 1.94-1.84 (comp, 4 H), 1.51-1.38 (comp, 2 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.4, 143.1, 131.9, 127.6, 127.5, 125.8, 120.2, 61.0, 54.2, 37.9, 32.6, 27.3, 20.8; IR (neat) 1648, 1413, 1243, 1023, 757 cm^{-1}; mass spectrum (CI) *m/z* 337.0912 [$C_{16}H_{21}BrN_2O$ (M+1) requires 337.0915] 339.0902.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.54 (d, *J* = 7.9 Hz, 1 H, C3-H), 7.33-7.27 (comp, 2 H, C5 and C6-H), 7.14 (t, *J* = 7.0 Hz, 1 H, C4-H), 4.97 (dd, *J* = 12.8, 4.8 Hz, 1 H, C7-H), 4.20 (br, 1 H, C11-H), 3.14 (br, 1 H, C11-H), 2.88-

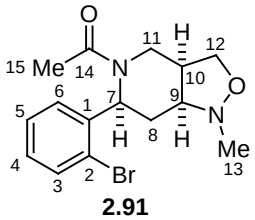
2.84 (m, 1 H, C9 or C13-H), 2.50-2.47 (m, 1 H, C9 or C13-H), 2.38 (br, 1 H, C9 or C13-H), 2.30 (s, 3 H, C14-H), 2.27-2.23 (comp, 2 H, C8 and C15-H), 1.94-1.84 (comp, 4 H, C15-H and C8-H), 1.51-1.38 (comp, 2 H, C12-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.4 (C15), 143.1 (C1), 131.9, 127.6, 127.5, 125.8, 120.2 (C2), 61.0, 54.2, 37.9, 32.6, 27.3, 20.8 (C16).



2.90

1-(Hexahydro-6-(2-iodophenyl)-1-methyl-1*H*-pyrrolo[3,2-c]pyridin-5(6*H*)-yl)ethanone (2.90). (JDSII-146a). Sarcosine (95 mg, 1.07 mmol) was added to a solution of **2.87** (237 mg, 0.66 mmol) in toluene (10 mL). The reaction was heated under reflux for 5 h. The reaction was cooled to room temperature and then was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with MeOH/EtOAc (1:3) to give 151 mg (59%) of **2.90** as a brownish white gum. ^{1}H NMR (500 MHz, DMSO, 140 °C) δ 7.80 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 4.79 (dd, *J* = 12.6, 4.6 Hz, 1 H), 4.26 (br, 1 H), 3.14 (s, 1 H), 2.87 (t, *J* = 7.8 Hz, 1 H), 2.80 (s,1 H), 2.44-2.35 (m, 1 H), 2.31 (s, 3 H), 2.29-2.22 (comp, 2 H), 1.95-1.90 (m, 1 H), 1.83 (s, 3 H), 1.47-1.38 (comp, 2 H); ^{13}C NMR (125 MHz, DMSO, 140 °C) δ 168.0, 145.8, 138.6, 128.2, 127.9, 125.0, 111.0, 96.0, 61.1, 54.2, 38.8, 37.8, 32.8, 27.3, 20.9; IR (CH2Cl2) 2941, 2779, 2359, 1649, 1410, 1242, 1010, 756 cm^{-1}; mass spectrum (CI) *m/z* 385.0777 [$C_{16}H_{21}IN_2O$ (M+1) requires 385.0777].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 140 °C) δ 7.80 (d, *J* = 7.6 Hz, 1 H, C11-H), 7.35 (t, *J* = 7.6 Hz, 1 H, C13-H), 7.23 (d, *J* = 7.6 Hz, 1 H, C14-H), 6.96 (t, *J* = 7.6 Hz, 1 H, C12-H), 4.79 (dd, *J* = 12.6, 4.6 Hz, 1 H, C8-H), 4.26 (br, 1 H, C1-H), 3.14 (s, 1 H, C1-H), 2.87 (t, *J* = 7.8 Hz, 1 H, C2-H, C4-H, or C6-H), 2.80 (s,1 H, C2-H, C4-H, or C6-H), 2.44-2.35 (m, 1 H, C2-H, C4-H, or C6-H), 2.31 (s, 3 H, C16-H), 2.29-2.22 (comp, 2 H, C2-H, C4-H, or C6-H), 1.95-1.95 (m, 1 H, C7-H), 1.83 (s, 3 H, C5-H), 1.47-1.38 (comp, 2 H, C5-H); ^{13}C NMR (125 MHz, DMSO, 140 °C) δ 168.0 (C15) 145.8 (C1), 138.6 (C3), 128.2, 127.9, 125.0, 96.0 (C2), 61.1, 54.2, 38.8, 37.8, 32.8, 27.3 (C12), 20.9 (C16).

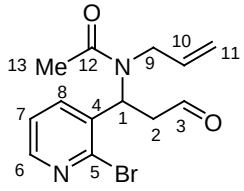


2.91

1-(6-(2-Bromophenyl)-tetrahydro-1-methylisoxazolo[4,3-c]pyridin-5(1*H*,3*H*,6*H*)-yl)ethanone (2.91). (JDSIII-120a). *N*-methyl hydroxylamine hydrochloride (70 mg, 0.84 mmol) and Et_3N (0.24 mL, 174 mg, 1.72 mmol) were added to a solution of **2.86** (166 mg, 0.54 mmol) in toluene (10 mL). The reaction was heated to reflux for 5 h. The reaction was cooled to rt and then concentrated under reduced pressure. The residue was then partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to give 166 mg (91%) of amide **2.91** as a orangish gum. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.55 (d, *J* = 7.9 Hz, 1 H), 7.34 (t, *J* = 7.1 Hz, 1 H), 7.28 (d, *J* = 7.1 Hz, 1 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 5.04 (dd, *J* = 12.9, 5.0 Hz, 1 H), 4.10 (br, 1 H), 4.04 (t, *J* = 8.3

Hz, 1 H), 3.46 (dd, *J* = 8.7, 5.0 Hz, 1H), 3.26 (br, 1 H), 3.00-3.06 (m, 1 H), 2.99-2.91 (m, 1 H) 2.58 (s, 3 H), 2.20 (dt, *J* = 13.7, 5.2 Hz, 1 H) 1.86 (s, 3 H) 1.59 (app q, *J* = 12.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotomers, major rotomer reported) δ 172.2, 143.1, 134.0, 130.0, 129.6, 127.0, 122.0, 69.1, 65.3, 57.1, 44.5, 43.4, 40.3, 33.8, 22.6; IR (neat) 1651, 1417, 1361, 1253, 1026, 998, 967, 917, 757, 726, 642 cm^{-1}; mass spectrum (CI) *m/z* 339.0705 [$C_{15}H_{19}BrN_2O_2$ (M+1) requires 339.0708] 341.0692.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.55 (d, *J* = 7.9 Hz, 1 H, C3-H), 7.34 (t, *J* = 7.1 Hz, 1 H, C5-H), 7.28 (d, *J* = 7.1 Hz, 1 H, C6-H), 7.16 (t, *J* = 7.3 Hz, 1 H, C4-H), 5.04 (dd, *J* = 12.9, 5.0 Hz, 1 H, C7-H), 4.10 (br, 1 H, C11-H), 4.04 (t, *J* = 8.3 Hz, 1 H, C12-H), 3.46 (dd, *J* = 8.7, 5.0 Hz, 1H, C12-H), 3.26 (br, 1 H, C11-H), 3.00-3.06 (m, 1 H, C9 or C10-H), 2.99-2.91 (m, 1 H, C9 or C10-H) 2.58 (s, 3 H, C13-H), 2.20 (dt, *J* = 13.7, 5.2 Hz, 1 H, C8-H) 1.86 (s, 3 H, C15-H) 1.59 (app q, *J* = 12.7 Hz, 1 H, C8-H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotomers, major rotomer reported) δ 172.2 (C14), 143.1 (C1), 134.0, 130.0, 129.6, 127.0, 122.0 (C2), 69.1, 65.3, 57.1, 44.5, 43.4, 40.3, 33.8 (C8), 22.6 (C15).

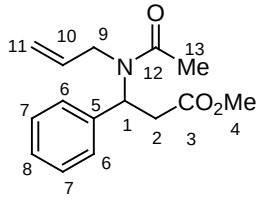


2.93

***N*-Allyl-*N*-(1-(2-bromopyridin-3-yl)-2-formylethyl)acetamide (2.93). (JDSIII-65a)** TMSOTf (18 μL, 22 mg, 0.099 mmol) was added to a solution of 2-bromo-3-formyl pyridine[192] (188 mg, 1.01 mmol) and bis(trimethylsilyl)allylamine (0.26 mL, 212 mg, 1.05 mmol) in CH_2Cl_2 (2.5 mL), and the reaction was stirred for 3.5 h at rt. Silyl enol ether **2.74** (361 mg, 2.29 mmol) and freshly distilled acetyl chloride (0.9 mL, 99 mg, 1.26 mmol) were then added, and the reaction was stirred for 31 h at room temperature. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous

$NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (3:1) to give 178 mg (56%) of amide **2.93** as a brownish gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 8.32 (dd, *J* = 4.8, 2.0 Hz, 1 H), 7.77 (dd, *J* = 7.7, 2.0 Hz, 1 H), 7.29 (dd, *J* = 7.7, 4.9 Hz, 1 H), 5.88 (dd, *J* = 8.5m 6.5 Hz, 1 H), 5.65-5.56 (m, 1 H), 5.10-5.03 (comp, 2H), 3.80 (d, *J* = 5.5 Hz, 1 H), 3.42 (ddd, *J* = 16.6, 8.5, 2.0 Hz, 1 H), 3.07 (ddd, *J* = 16.6, 6.5, 1.4 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 172.3, 150.1, 145.3, 138.8, 135.9, 133.9, 123.6, 118.5, 54.3, 50.8, 46.5, 23.2; IR (neat) 2360, 1719, 1643, 1561, 1401, 1256, 1178, 1051, 914, 742 cm^{-1}; Mass spectrum (CI) *m/z* 311.0397 [$C_{13}H_{15}BrN_2O_2$ (M+1) requires 311.0395] 313.0379.

NMR Assignments. ^{1}H NMR (400 MHz, CDCl3) δ 9.76 (s, 1 H, C1-H), 8.32 (dd, *J* = 4.8, 2.0 Hz, 1 H, C6-H), 7.77 (dd, *J* = 7.7, 2.0 Hz, 1 H, C8-H), 7.29 (dd, *J* = 7.7, 4.9 Hz, 1 H, C7-H), 5.88 (dd, *J* = 8.5 6.5 Hz, 1 H, C3-H), 5.65-5.56 (m, 1 H, C10-H), 5.10-5.03 (comp, 2H, C11-H), 3.80 (d, *J* = 5.5 Hz, 1 H, C9-H), 3.42 (ddd, *J* = 16.6, 8.5, 2.0 Hz, 1 H, C2-H), 3.07 (ddd, *J* = 16.6, 6.5, 1.4 Hz, 1 H, C2-H), 2.13 (s, 3 H, C13-H); ^{13}C NMR (100 MHz, CDCl3) δ 199.6 (C1), 172.3 (C12), 150.1 (C6), 145.3 (C5), 138.8, 135.9, 133.9, 123.6 (C7), 118.5 (C11), 54.3 (C1), 50.8 (C9), 46.5 (C2), 23.2 (C13).



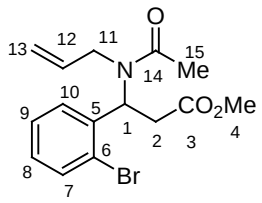
2.104

Methyl 3-(*N*-allylacetamido)-3-phenylpropanoate (2.104). (JDSI-84b). A mixture containing freshly distilled benzaldehyde (0.2 mL, 209 mg, 1.97 mmol), allylamine (0.15 mL, 114 mg, 2.0 mmol) and activated 4 Å molecular sieves (~500 mg)

in CH_2Cl_2 (5 mL) was stirred for 2 h at room temperature. The reaction was cooled to 0 °C and silyl ketene acetal **2.103**[422] (0.380 g, 2.02 mmol) and acetyl chloride (0.15 ml, 166 mg, 2.11 mmol) was added and the reaction stirred for 30 minutes, whereupon the ice bath was removed. The reaction was stirred for 18 h at room temperature and then was filtered through a pad of Celite that was washed with CH_2Cl_2 (3 x 5 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution 1:3 to 1:1) to give 104 mg (20%) of **2.104** as a viscous yellowish oil. ^{1}H NMR (400 MHz, mixture of rotomers) δ 7.39-7.22 (comp, 5 H), 6.25 (t, *J* = 8.0 Hz, 0.6 H), 5.77-5.67 (m, 0.3 H), 5.59-5.48 (comp, 1 H), 5.08-4.95 (comp, 2 H), 4.16-4.11 (m, 0.4 H) 3.77-3.68 (comp, 2 H), 3.64 (s, 2 H), 3.33 (dd *J* = 15.8, 7.0 Hz, 0.4 H), 3.11-2.95 (comp, 2 H), 2.39 (s, 1 H), 2.10 (s, 2 H); ^{13}C NMR (100 MHz, mixture of rotomers) δ 172.2, 172.1, 171.9, 139.6, 139.3, 135.4, 135.2, 129.8, 129.5, 129.0, 128.8, 128.7, 127.5, 117.8, 117.0, 58.3, 54.3, 52.9, 52.8, 48.6, 46.1, 37.9, 37.1, 23.2, 22.9; IR (neat) 3460, 2952, 2359, 2243, 1964, 1738, 1650, 1497, 1408, 1259, 1163, 984 cm^{-1}; mass spectrum (CI) *m/z* 262.1441 [$C_{15}H_{19}NO_3$ (M+1) requires 262.1443].

NMR assignments. ^{1}H NMR (400 MHz, mixture of rotomers) δ 7.39-7.22 (comp, 5 H, Ar-H), 6.25 (t, *J* = 8.0 Hz, 0.6 H, C1-H), 5.77-5.67 (m, 0.3 H, C10-H), 5.59-5.48 (comp, 1 H, C10-H), 5.08-4.95 (comp, 2 H, C11-H), 4.16-4.11 (m, 0.4 H, C9-H) 3.77-3.68 (comp, 2 H, C9 and C4-H), 3.64 (s, 2 H, C4-H), 3.33 (dd *J* = 15.8, 7.0 Hz, 0.4 H, C2-H), 3.11-2.95 (comp, 2 H, C2-H), 2.39 (s, 1 H, C13-H), 2.10 (s, 2 H, C13-H); ^{13}C NMR (100 MHz, mixture of rotomers) δ 172.2 (C3 or C12), 172.1 (C3 or C12), 171.9 (C3 or C12), 139.6, 139.3, 135.4, 135.2, 129.8, 129.5, 129.0, 128.8, 128.7, 127.5, 117.8 (C11), 117.0 (C11), 58.3 (C1), 54.3 (C1), 52.9 (C4), 52.8 (C4), 48.6 (C9), 46.1 (C9), 37.9 (C2), 37.1 (C2), 23.2 (C13), 22.9 (C13).

Alternative procedure for 2.104. (JDSI-155a) Acetyl chloride (0.1 mL, 110 mg, 1.41 mmol) was added to a solution of imine **2.17** (179 mg, 1.24 mmol) and silyl ketene acetal **2.103** (491 mg, 2.61 mmol) in CH_2Cl_2 (3.5 mL) at -78 ºC. The reaction was stirred at -78 ºC for 15 min, whereupon the cold bath was removed and TMSOTf (22 μL, 27 mg, 0.12 mmol) was added. The reaction was stirred for 18 h at room temperature. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution 1:3 to 1:1) to give 171 mg (52%) of **2.104** as a viscous yellowish oil.

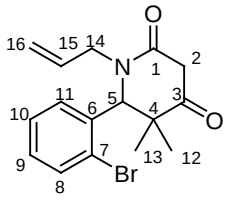


2.106

Methyl 3-(*N*-allylacetamido)-3-(2-bromophenyl)propanoate (2.106). (JDSI-274A). TMSOTf (15.5 μL, 19 mg, 0.086 mmol) was added to a solution of 2-bromobenzaldehyde (0.1 mL, 158 mg, 0.86 mmol) and bis(trimethylsilyl)allylamine (0.22 mL, 179 mg, 0.89 mmol) in CH_3CN (2.2 mL), and the reaction was stirred for 30 min at room temperature. Freshly distilled acetyl chloride (70 μL, 77 mg, 0.98 mmol) and silyl ketene acetal **2.105**[423] (292 mg, 2.05 mmol) and were then added, and the reaction was stirred for 3 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was

purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 230 mg (78%) of amide **2.106** as a colorless, viscous oil. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.61 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.54 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.38 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.24 (dt, *J* = 7.8, 1.6 Hz), 5.93 (br, 1 H), 5.48-5.40 (m, 1 H), 4.87 (comp, 2 H), 3.78 (dd, *J* = 17.1, 5.2 Hz, 1 H), 3.64 (dd, *J* = 17.1, 5.7 Hz, 1 H), 3.54 (s, 3 H), 3.10 (s, 1 H), 3.00 (dd, *J* = 15.6, 6.7 Hz, 1 H), 2.07 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 169.8, 169.2, 137.0, 134.1, 132.6, 129.2, 128.8, 127.1, 124.3, 115.2, 54.2, 50.7, 46.3, 35.7, 21.1; IR (neat) 3066, 2951, 1737, 1650, 1436, 1405, 1257, 1163, 754 cm^{-1}; mass spectrum (CI) *m/z* 340.0546 [$C_{15}H_{18}BrNO_3$ (M+1) requires 340.0548], 342.059.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.61 (dd, *J* = 7.8, 1.1 Hz, 1 H, C7-H), 7.54 (dd, *J* = 7.8, 1.6 Hz, 1 H, C10-H), 7.38 (dt, *J* = 7.8, 1.1 Hz, 1 H, C9-H), 7.24 (dt, *J* = 7.8, 1.6 Hz, 1 H, C8-H), 5.93 (bs, 1 H, C1-H), 5.48-5.40 (m, 1 H, C12-H), 4.87 (comp, 2 H, C13-H), 3.78 (dd, *J* = 17.1, 5.2 Hz, 1 H, C11-H), 3.64 (dd, *J* = 17.1, 5.7 Hz, 1 H, C11-H), 3.54 (s, 3 H, C4-H), 3.10 (br s, 1 H, C2-H), 3.00 (dd, *J* = 15.6, 6.7 Hz, 1 H, C2-H), 2.07 (s, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 169.8 (C3 or C14), 169.2 (C3 or C14), 137.0 (C5), 134.1 (C12), 132.6 (C7), 129.2 (C8, C9, or C10), 128.8 (C8, C9, or C10), 127.1 (C8, C9, or C10), 124.3 (C6), 115.2 (C13), 54.2 (C4), 50.7 (C11), 46.3 (C1), 35.7 (C2), 21.1 (C15).

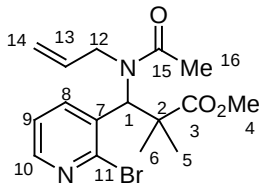


2.110

1-Allyl-6-(2-bromophenyl)-5,5-dimethylpiperidine-2,4-dione (2.110). (JDSII-55a). NaHMDS (2.0 M in THF, 0.53 mL, 1.06 mmol) was added to a solution of amide **2.109** (187 mg, 0.51 mmol) in THF (17 mL) and the reaction was heated under reflux for

17 h. The reaction was cooled to room temperature the reaction was washed sequentially with saturated aqueous NH_4Cl (10 mL) and saturated NaCl (10 mL). The organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hex (1:3) to give 137 mg (80%) of **2.110** as a white solid, mp 133.5-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.27 (t, *J* = 7.9 Hz, 1 H), 7.16 (dt, *J* = 7.9, 1.7 Hz, 1 H), 6.79 (dd, *J* = 7.9, 1.4 Hz, 1 H), 5.83-5.73 (m, 1 H), 5.34 (d, *J* = 17.1 Hz, 1 H), 5.28 (d, *J* = 9.9 Hz, 1 H), 5.04 (s, 1 H), 4.69 (dd, *J* = 14.5, 4.6 Hz, 1 H), 3.64 (d, *J* = 21.2 Hz, 1 H), 3.49 (d, *J* = 21.2 Hz, 1 H), 3.04 (dd, *J* = 14.5, 8.7 Hz, 1 H), 1.45 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 166.7, 138.1, 134.2, 132.5, 130.8, 129.4, 127.7, 126.0, 121.0, 67.7, 50.5, 48.9, 45.3, 26.4, 19.6; IR (neat) 3422, 2980, 2359, 1721, 1656, 1465, 1282, 922, 758 cm^{-1}; mass spectrum (CI) *m/z* 336.0599 [$C_{16}H_{18}BrNO_2$ (M+1) requires 336.0599], 338.0578.

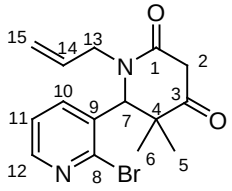
NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.9, 1.7 Hz, 1 H, C8-H), 7.27 (t, *J* = 7.9 Hz, 1 H, C10-H), 7.16 (dt, *J* = 7.9, 1.7 Hz, 1 H, C9-H), 6.79 (dd, *J* = 7.9, 1.4 Hz, 1 H, C11-H), 5.83-5.73 (m, 1 H, C15-H), 5.34 (d, *J* = 17.1 Hz, 1 H, C16-H), 5.28 (d, *J* = 9.9 Hz, 1 H, C16-H), 5.04 (s, 1 H, C5-H), 4.69 (dd, *J* = 14.5, 4.6 Hz, 1 H, C14-H), 3.64 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.49 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.04 (dd, *J* = 14.5, 8.7 Hz, 1 H, C14-H), 1.45 (s, 3 H, C12-H or C13-H), 0.92 (s, 3 H, C12-H or C13-H); ^{13}C NMR (100 MHz, CDCl3) δ 207.0 (C3), 166.7 (C1), 138.1 (C6), 134.2 (C8), 132.5 (C15), 130.8 (C9, C10, or C11), 129.4 (C9, C10, or C11), 127.7 (C9, C10, or C11), 126.0 (C7) (C9, C10, or C11), 121.0 (C16), 67.7, 50.5, 48.9, 45.3, 26.4 (C12 or C13), 19.6 (C12 or C13).



2.111

Methyl 3-(*N*-allylacetamido)-3-(2-bromopyridin-3-yl)-2,2-dimethyl-propanoate (2.111). (JDSII-204a). TMSOTf (14 μL, 17 mg, 0.077 mmol) was added to a solution of 2-bromopyridine-3-carbaldehyde (**2.92**)[192] (149 mg, 0.80 mmol) and bis(trimethylsilyl)allylamine (0.20 mL, 163 mg, 0.81 mmol) in CH_3Cl_2 (2 mL), and the reaction was stirred for 3.5 h at room temperature. Freshly distilled acetyl chloride (0.06 mL, 66 mg, 0.84 mmol) and silyl ketene acetal **2.105** (0.33 mL, 283 mg, 1.62 mmol) and were then added, and the reaction was stirred for 5 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 206 mg (69%) of amide **2.111** as a white solid, mp 91-92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 4.7, 2.0 Hz, 1 H), 7.96 (dd, *J* = 7.9, 2.0 Hz, 1 H), 7.38 (dd, *J* = 7.9, 4.7 Hz, 1 H), 6.01 (s, 1 H), 5.34 (ddt, *J* = 16.6, 10.1, 5.4 Hz, 1 H), 4.91 (d, *J* = 10.1 Hz, 1 H), 4.87 (d, *J* = 16.6 Hz, 1 H), 3.96 (dd, *J* = 17.7, 5.4 Hz, 1 H), 3.71 (dd, *J* = 17.7, 5.4 Hz, 1H), 3.62 (s, 3 H), 2.16 (s, 3 H), 1.44 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 172.8, 149.9, 147.3, 139.9, 136.0, 134.4, 123.0, 118.0, 63.9, 53.0, 51.6, 48.7, 27.5, 25.4, 23.6; IR (neat) 2984, 2239, 1731, 1659, 1405, 1252, 1127, 1053, 922, 743 cm^{-1}; mass spectrum (CI) *m/z* 369.0813 [$C_{16}H_{21}BrN_2O_3$ (M+1) requires 369.0814], 371.0795.

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 4.7, 2.0 Hz, 1 H, C10-H), 7.96 (dd, *J* = 7.9, 2.0 Hz, 1 H, C8-H), 7.38 (dd, *J* = 7.9, 4.7 Hz, 1 H, C9-H), 6.01 (s, 1 H, C1-H), 5.34 (ddt, *J* = 16.6, 10.1, 5.4 Hz, 1 H, C13-H), 4.91 (d, *J* = 10.1 Hz, 1 H, C14-H), 4.87 (d, *J* = 16.6 Hz, 1 H, C14-H), 3.96 (dd, *J* = 17.7, 5.4 Hz, 1 H, C12-H), 3.71 (dd, *J* = 17.7, 5.4 Hz, 1H, C12-H), 3.62 (s, 3 H, C14-H), 2.16 (s, 3 H, C16-H), 1.44 (s, 3 H, C5-H or C6-H), 1.32 (s, 3 H, C5-H or C6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C3), 172.8 (C15), 149.9 (C10), 147.3 (C11), 139.9 (C7, C8, or C13) , 136.0 (C7, C8, or C13), 134.4 (C7, C8, or C13), 123.0 (C9), 118.0 (C14), 63.9 (C1), 53.0 (C2, C4, or C12), 51.6 (C2, C4, or C12), 48.7 (C2, C4, or C12), 27.5 (C5, C6, or C16), 25.4 (C5, C6, or C16), 23.6 (C5, C6, or C16).

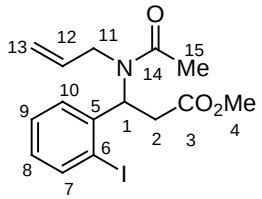


2.112

1-Allyl-6-(2-bromopyridin-3-yl)-5,5-dimethylpiperidine-2,4-dione (2.112). (JDSII-123a). NaHMDS (1.3 M in THF, 0.55 mL, 0.72 mmol) was added to a solution of amide **2.111** (119 mg, 0.32 mmol) in THF (13 mL) and the reaction was heated under reflux for 13 h. The reaction was cooled to room temperature and then washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was backwashed with CH_2Cl_2 (2 x 5 mL). The combined organics were then washed with saturated NaCl (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hex (1:1) to give 97 mg (89%) of **2.112** as a white solid, mp 156-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 4.6, 1.9 Hz, 1 H), 7.26 (dd, *J* = 7.7, 4.6 Hz, 1 H), 7.11 (dd, *J* = 7.7, 1.9 Hz, 1 H), 5.81-5.71 (m, 1 H), 5.37 (d, *J* = 17.1 Hz, 1 H), 5.31 (d, *J* = 9.9 Hz, 1 H), 5.01 (s, 1 H), 4.68 (dd, *J* = 14.5, 4.9

Hz, 1 H), 3.66 (d, *J* = 21.2 Hz, 1 H), 3.47 (d, *J* = 21.2 Hz, 1 H), 3.09 (dd, *J* = 14.5, 8.7 Hz, 1 H), 1.47 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 166.5, 151.0, 145.5, 136.3, 135.9, 132.2, 124.6, 121.6, 67.3, 50.7, 49.2, 45.4, 39.2, 26.3, 19.7; IR (neat) 2980, 2359, 1723, 1651, 1462, 1404, 1280, 1048, 934, 743 cm^{-1}; mass spectrum (CI) *m/z* 337.0548 [$C_{15}H_{17}BrN_2O_2$ (M+1) requires 337.0552], 339.0536.

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 4.6, 1.9 Hz, 1 H, C12-H), 7.26 (dd, *J* = 7.7, 4.6 Hz, 1 H, C10-H), 7.11 (dd, *J* = 7.7, 1.9 Hz, 1 H, C11-H), 5.81-5.71 (m, 1 H, C14-H), 5.37 (d, *J* = 17.1 Hz, 1 H, C15-H), 5.31 (d, *J* = 9.9 Hz, 1 H, C15-H), 5.01 (s, 1 H, C7-H), 4.68 (dd, *J* = 14.5, 4.9 Hz, 1 H, C13-H), 3.66 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.47 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.09 (dd, *J* = 14.5, 8.7 Hz, 1 H, C13-H), 1.47 (s, 3 H, C5 or C6-H), 0.97 (s, 3 H, C5 or C6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5 (C3), 166.5, (C1), 151.0 (12), 145.5 (C8), 136.3 (C9, C10, or C14), 135.9 (C9, C10, or C14), 132.2 (C9, C10, or C14), 124.6 (C11), 121.6 (C15), 67.3 (C7), 50.7 (C2 or C13), 49.2 (C2 or C13), 45.4 (C2), 26.3 (C5 or C6), 19.7 (C5 or C6).

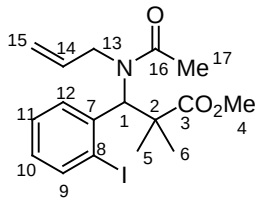


2.126

Methyl 3-(*N*-allylacetamido)-3-(2-iodophenyl)propanoate (2.126). (JDSII-66a). TMSOTf (8.5 μL, 10 mg, 0.047 mmol) was added to a solution of 2-iodobenzaldehyde (112 mg, 0.48 mmol) and bis(trimethylsilyl)allylamine (0.12 mL, 92 mg, 0.49 mmol) in CH_2Cl_2 (1.2 mL), and the reaction was stirred for 1 h at room temperature. The reaction was cooled to 0 ºC and silyl ketene acetal **2.105** (205 mg, 1.40 mmol) and freshly distilled acetyl chloride (40 μL, 44 mg, 0.56 mmol) and were then added, and the reaction was stirred for 10 min 0 ºC. The cold bath was then removed and

the reaction stirred for 4 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 112 mg (60%) of amide **2.126** as a yellowish solid: mp 72-74 °C. ^{1}H NMR (500 MHz, DMSO, 100 °C) 7.90 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.4 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.05 (dt, *J* = 7.8, 1.6 Hz, 1 H), 5.72 (br, 1 H), 5.49-5.41 (m, 1 H), 4.90-4.88 (comp, 2 H), 3.78 (dd, *J* = 17.1, 5.4 Hz, 1 H), 3.61 (dd, *J* = 17.1, 5.9 Hz, 1 H), 3.54 (s, 3 H), 3.07 (s, 1 H), 2.98 (dd, *J* = 15.8, 6.6 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 169.7, 169.4, 140.0, 139.5, 134.2, 129.2, 128.4, 127.7, 115.4, 101.1, 58.7, 50.7, 46.6, 35.9, 21.3; IR (neat) 3061, 2950, 1738, 1650, 1404, 1256, 1012, 754 cm^{-1}; mass spectrum (CI) *m/z* 388.0412 [$C_{15}H_{18}INO_3$ (M+1) requires 388.0410].

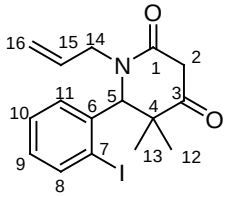
NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 100 °C) 7.90 (dd, *J* = 7.8, 1.2 Hz, 1 H, C7-H), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1 H, C10-H), 7.4 (dt, *J* = 7.8, 1.2 Hz, 1 H, C9-H), 7.05 (dt, *J* = 7.8, 1.6 Hz, 1 H, C8-H), 5.72 (br, 1 H, C1-H), 5.49-5.41 (m, 1 H, C12-H), 4.90-4.88 (comp, 2 H, C13-H), 3.78 (dd, *J* = 17.1, 5.4 Hz, 1 H, C11-H), 3.61 (dd, *J* = 17.1, 5.9 Hz, 1 H, C11-H), 3.54 (s, 3 H, C4-H), 3.07 (br, 1 H, C2-H), 2.98 (dd, *J* = 15.8, 6.6 Hz, 1 H, C2-H), 2.08 (s, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 169.7 (C1 or C14), 169.4 (C1 or C14), 140.0 (C5), 139.5 (C7), 134.2 (C12), 129.2 (C8, C9, or C10), 128.4 (C8, C9, or C10), 127.7 (C8, C9, or C10), 115.4 (C13), 101.1 (C6), 58.7 (C4), 50.7 (C11), 46.6 (C1), 35.9 (C2), 21.3 (C15).



2.127

Methyl 3-(*N*-allylacetamido)-3-(2-iodophenyl)-2,2-dimethylpropanoate (2.127). (JDSII-86a). TMSOTf (10 μL, 12 mg, 0.033 mmol) was added to a solution of 2-iodobenzaldehyde (133 mg, 0.60 mmol) and bis(trimethylsilyl)allylamine (0.15 mL, 122 mg, 0.61 mmol) in CH_2Cl_2 (1.5 mL), and the reaction was stirred for 1 h at room temperature. The reaction was cooled to 0 ºC and silyl ketene acetal **2.105** (0.35 mL, 300 mg, 1.72 mmol) and freshly distilled acetyl chloride (0.08 mL, 88 mg, 1.12 mmol) and were then added, and the reaction was stirred for 10 min 0 ºC. The cold bath was then removed and the reaction stirred for 18 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 159 mg (67%) of amide **2.127** as a white solid: mp 100-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.47 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.28 (dt, *J* = 7.7, 1.0 Hz, 1 H) 6.94 (dt, *J* = 7.7, 1.2 Hz, 1 H), 6.14 (s, 1 H), 5.16-5.06 (m, 1 H), 4.82-4.78 (comp, 2 H), 3.88-3.60 (comp, 2 H), 3.59 (s, 3 H), 2.16 (s, 3 H), 1.44 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 172.7, 141.8, 141.5, 135.0, 130.5, 130.3, 128.7, 117.3, 104.8, 67.7, 52.9, 50.8, 49.4, 27.3, 25.6, 23.8; IR (neat) 3437, 2979, 1729, 1657, 1392, 1249, 1147, 1013, 752 cm^{-1}; mass spectrum (CI) *m/z* 416.0725 [$C_{17}H_{22}NO_3$ (M+1) requires 416.0723].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.0 Hz, 1 H, C9-H), 7.47 (dd, *J* = 7.7, 1.2 Hz, 1 H, C12-H), 7.28 (dt, *J* = 7.7, 1.0 Hz, 1 H, C11-H) 6.94 (dt, *J* = 7.7, 1.2 Hz, 1 H, C10-H), 6.14 (s, 1 H, C1-H), 5.16-5.06 (m, 1 H, C14-H), 4.82-4.78 (comp, 2 H, C15-H), 3.88-3.60 (comp, 2 H, C13-H), 3.59 (s, 3 H, C14-H), 2.16 (s, 3 H, C17-H), 1.44 (s, 3 H, C5 or C6-H), 1.32 (s, 3 H, C5-H or C6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C3), 172.7 (C16), 141.8 (C7 or C9), 141.5 (C7 or C9), 135.0 (C14), 130.5 (C10, C11, or C12), 130.3 (C10, C11, or C12), 128.7 (C10, C11, or C12), 117.3 (C15), 104.8 (C8), 67.7 (C1), 52.9 (C2, C4, or C13), 50.8 (C2, C4, or C13), 49.4 (C2, C4, or C13), 27.3 (C5, C6, or C17), 25.6 (C5, C6, or C17), 23.8 (C5, C6, or C17).

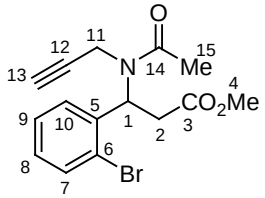


2.131

Methyl 3-(*N*-allylacetamido)-3-(2-iodophenyl)-2,2-dimethylpropanoate (2.131). (JDSII-89A). NaHMDS (214 mg, 1.17 mmol) was added to a solution of **2.127** (159 mg, 0.38 mmol) in THF (15 mL) and the reaction was heated under reflux for 19 h. The reaction was cooled to room temperature and washed with concentrated aqueous NH_4Cl (10 mL). The organic phase was removed and then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 133 mg (91%) of **2.131** as a white solid, mp 146-146.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1 H), 7.30 (t, *J* = 7.7 Hz, 1 H), 7.00 (t, *J* = 7.7 Hz, 1 H), 6.74 (d, *J* = 7.7 Hz, 1 H), 5.85-5.75 (m, 1 H), 5.41 (d, *J* = 17.1 Hz, 1 H), 5.29 (d, *J* = 10.3 Hz, 1 H), 4.86 (s, 1 H), 4.66 (dd, *J* = 14.6, 3.2 Hz, 1 H), 3.64 (d, *J* = 21.2 Hz, 1 H), 3.49 (d, *J* = 21.2 Hz, 1 H), 3.05 (dd, *J* = 14.7, 8.5 Hz, 1 H), 1.46 (s, 3 H), 0.94

(s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 166.5, 141.1, 141.0, 132.5, 131.1, 130.3, 127.1, 121.0, 102.7, 72.7, 50.7, 48.9, 45.3, 26.5, 19.9; IR (neat) 3077, 2979, 1723, 1651, 1468, 1381, 1333, 1282, 1182, 1010, 932, 756 cm^{-1}; mass spectrum (CI) *m/z* 384.0462 [$C_{16}H_{18}INO_2$ (M+1) requires 384.0461].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1 H, C8-H)), 7.30 (t, *J* = 7.7 Hz, 1 H, C10-H), 7.00 (t, *J* = 7.7 Hz, 1 H, C9-H), 6.74 (d, *J* = 7.7 Hz, 1 H, C11-H), 5.85-5.75 (m, 1 H, C15-H), 5.41 (d, *J* = 17.1 Hz, 1 H, C16-H), 5.29 (d, *J* = 10.3 Hz, 1 H, C16-H), 4.86 (s, 1 H, C5-H), 4.66 (dd, *J* = 14.6, 3.2 Hz, 1 H, C14-H), 3.64 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.49 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.05 (dd, *J* = 14.7, 8.5 Hz, 1 H, C14-H), 1.46 (s, 3 H, C12-H or C13-H), 0.94 (s, 3 H, C12-H or C13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0 (C3), 166.5 (C1), 141.1 (C6 or C8), 141.0 (C6 or C8), 132.5 (C15), 131.1 (C9, C10, or C11), 130.3 (C9, C10, or C11), 127.1 (C9, C10, or C11), 121.0 (C16), 102.7 (C7), 72.7, 50.7, 48.9, 45.3, 26.5 (C12 or C13, 19.9 (C12 or C13).

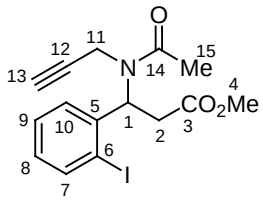


2.137

Methyl 3-(*N*-(prop-2-ynyl)acetamido)-3-(2-bromophenyl)propanoate (2.137). (JDSII-247a). Acetyl chloride (0.04 mL, 44 mg, 0.56 mmol), TMSOTf (8 μL, 10 mg, 0.044 mmol), and silyl ketene acetal **2.105** (534 mg, 3.75 mmol) were sequentially added to a solution of imine **2.135** (101 mg, 0.46 mmol) in CH_3CN (1.1 mL) and the reaction was stirred for 1.5 h at room temperature. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous phase was washed with CH_2Cl_2 (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was

purified by flash chromatography eluting with EtOAc/Hexane (2:3) to give 115 mg (74%) of amide **2.137** as a yellowish, viscous oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.62 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 5.90 (s, 1 H), 4.04 (d, J = 18.6 Hz, 1 H), 3.78 (d, *J* = 18.6 Hz, 1 H), 3.56 (s, 3 H), 3.22 (dd, *J* = 16.0, 8.6 Hz, 1 H), 3.03 (dd, *J* = 16.0, 6.4 Hz, 1 H), 2.76 (s, 1 H), 2.17 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.5, 168.9, 136.4, 132.6, 129.1, 128.6, 127.0, 124.1, 79.5, 72.5, 54.7, 50.7, 35.4, 32.9, 20.9; IR 2117, 1738, 1659, 1434, 1409, 1256, 1160, 1026 cm^{-1}; mass spectrum (CI) *m/z* 338.0387 [$C_{15}H_{17}BrNO_3$ (M+1) requires 338.0392], 340. 0370.

NMR assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.62 (d, *J* = 8.0 Hz, 1 H, C7-H or C10-H), 7.57 (d, *J* = 8.0 Hz, 1 H, C7-H or C10-H), 7.40 (t, *J* = 8.0 Hz, 1 H, C8-H or C9-H), 7.26 (t, *J* = 8.0 Hz, 1 H, C8-H or C9-H), 5.90 (s, 1 H, C1-H), 4.04 (d, J = 18.6 Hz, 1 H, C11-H), 3.78 (d, *J* = 18.6 Hz, 1 H, C11-H), 3.56 (s, 3 H, C4-H), 3.22 (dd, *J* = 16.0, 8.6 Hz, 1 H, C2-H), 3.03 (dd, *J* = 16.0, 6.4 Hz, 1 H, C2-H), 2.76 (s, 1 H, C13-H), 2.17 (s, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.5 (C3 or C14), 168.9 (C3 or C14), 136.4, 132.6, 129.1, 128.6, 127.0, 124.1, 79.5 (C12), 72.5 (C-13), 54.7 (C1 or C4), 50.7 (C1 or C4), 35.4 (C2 or C11), 32.9 (C2 or C11), 20.9 (C15).

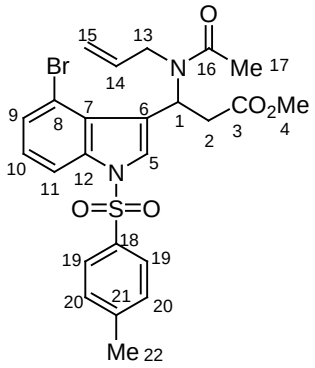


2.138

Methyl 3-(*N*-(prop-2-ynyl)acetamido)-3-(2-iodophenyl)propanoate (2.138). (JDSII-301a) Acetyl chloride (0.09 mL, 99 mg, 1.27 mmol), TMSOTf (19 μL, 23 mg, 0.10 mmol), and silyl ketene acetal **2.105** (347 mg, 2.44 mmol) were sequentially added to a solution of imine **2.136** (282 mg, 1.05 mmol) in CH_3CN (2.5 mL) and the reaction

was stirred for 2.5 h at room temperature. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (2:3) to give 235 mg (58%) of amide **2.138** as a viscous, yellowish oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.91 (d, *J* = 7.8 Hz, 1 H), 7.51 (d, *J* = 7.8 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 5.72 (s, 1 H), 4.04 (d, J = 18.6 Hz, 1 H), 3.71 (d, *J* = 18.6 Hz, 1 H), 3.56 (s, 3 H), 3.21 (dd, *J* = 16.0, 8.8 Hz, 1 H), 3.02 (dd, *J* = 16.0, 6.5 Hz, 1 H), 2.79 (s, 1 H), 2.18 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.4, 169.0, 139.6, 139.5, 129.2, 128.0, 127.6, 100.7, 79.5, 72.6, 59.0, 50.6, 35.6, 32.9, 21.1; IR 1738, 1651, 1435, 1406, 1255, 1159, 1013, 754, 657 cm^{-1}; mass spectrum (CI) *m/z* 386.0255 [$C_{15}H_{17}INO_3$ (M+1) requires 386.0253].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.91 (d, *J* = 7.8 Hz, 1 H, C7-H), 7.51 (d, *J* = 7.8 Hz, 1 H, C10-H), 7.43 (t, *J* = 7.8 Hz, 1 H, C9-H), 7.07 (t, *J* = 7.8 Hz, 1 H, C8-H), 5.72 (s, 1 H, C1-H), 4.04 (d, J = 18.6 Hz, 1 H, C11-H), 3.71 (d, *J* = 18.6 Hz, 1 H, C11-H), 3.56 (s, 3 H, C4-H), 3.21 (dd, *J* = 16.0, 8.8 Hz, 1 H, C2-H), 3.02 (dd, *J* = 16.0, 6.5 Hz, 1 H, C2-H), 2.79 (s, 1 H, C13-H), 2.18 (s, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.4 (C3 or C14), 169.0 (C3 or C14), 139.6, 139.5 (C5), 129.2, 128.0, 127.6, 100.7 (C6), 79.5 (C12), 72.6 (C13), 59.0 (C1 or C4), 50.6 (C1 or C4), 35.6 (C2 or C11), 32.9 (C2 or C11), 21.1 (C15).

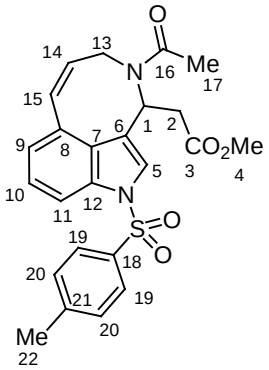


2.140

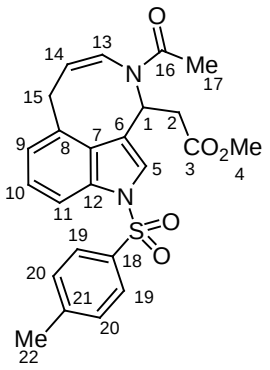
Methyl 3-(*N*-allylacetamido)-3-(4-bromo-1-tosyl-1*H*-indol-3-yl)propanoate (2.140). TMSOTf (6.5 μL, 8 mg, 0.036 mmol) was added to a solution of 4-bromoindole-3-carboxaldehyde **2.139**[203, 204] (140 mg, 0.37 mmol) and bis(trimethylsilyl)-allylamine (0.10 mL, 82 mg, 0.40 mmol) in CH_2Cl_2 (1 mL), and the reaction was stirred for 3 h at room temperature. Silyl ketene acetal **1.105** (135 mg, 0.95 mmol) and freshly distilled acetyl chloride (35 μL, 39 mg, 0.49 mmol) were then added, and the reaction was stirred for 4 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 149 mg (75%) of amide **2.140** as a white solid, mp 134.5–136 °C. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.95 (d, *J* = 7.8 Hz, 1 H), 7.95 (s, 1 H), 7.77 (d, *J* = 8.2 Hz, 2 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 7.23 (t, *J* = 8.2 Hz, 1 H), 6.41 (s, 1 H), 5.31 (dddd, *J* = 15.8, 10.2, 5.3, 5.3 Hz, 1 H), 4.72 (d, *J* = 17.1 Hz, 1 H), 4.65 (d, *J* = 10.2 Hz, 1H), 3.86 (dd, *J* = 17.3, 5.3 Hz 1 H), 3.70 (dd, *J* = 17.3, 5.3 Hz, 1 H), 3.54 (s, 3 H), 3.18 (dd, *J* = 15.3, 9.3 Hz, 1 H), 3.00 (dd, *J* = 15.3, 5.9 Hz, 1 H), 2.34 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.8, 169.3, 145.1, 135.5, 134.2 133.7, 129.5,

127.6, 127.4, 125.9, 125.3, 119.7, 114.7, 112.7, 112.1, 50.5, 47.2, 46.0, 36.4, 21.4, 20.2; IR (neat) 1736, 1644, 1411, 1374, 1258, 1174, 675, 574 cm^{-1}; mass spectrum (CI) *m/z* 533.0754 [$C_{24}H_{26}BrN_2O_5S$ (M+1) requires 533.0746], 535.0731.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.95 (d, *J* = 7.8 Hz, 1 H, C9-H), 7.95 (s, 1 H, C5-H), 7.77 (d, *J* = 8.2 Hz, 2 H, C19-H), 7.45 (d, *J* = 7.8 Hz, 1 H, C11-H), 7.36 (d, *J* = 8.2 Hz, 2 H, C20-H), 7.23 (t, *J* = 8.1 Hz, 1 H, C10-H), 6.41 (s, 1 H, C1-H), 5.31 (ddt, *J* = 15.8, 10.2, 5.3 Hz, 1 H, C14-H), 4.72 (d, *J* = 17.1 Hz, 1 H, C15-H), 4.65 (d, *J* = 10.2 Hz, 1H, C15-H), 3.86 (dd, *J* = 17.3, 5.3 Hz 1 H, C13-H), 3.70 (dd, *J* = 17.3, 5.3 Hz, 1 H, C13-H), 3.54 (s, 3 H, C4-H), 3.18 (dd, *J* = 15.3, 9.3 Hz, 1 H, C2-H), 3.00 (dd, *J* = 15.3, 5.9 Hz, 1 H, C2-H), 2.34 (s, 3 H, C22-H), 2.03 (s, 3 H, C17-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 169.8 (C3 or C16), 169.3 (C3 or C16), 145.1 (C21), 135.5, 134.2 133.7, 129.5 (C19), 127.6, 127.4, 125.9 (C20), 125.3, 119.7, 114.7, 112.7, 112.1, 50.5 (C4), 47.2 (C1 or C13), 46.0 (C1 or C13), 36.4 (C2), 21.4 (C17 or C22), 20.2 (C17 or C22).



2.141



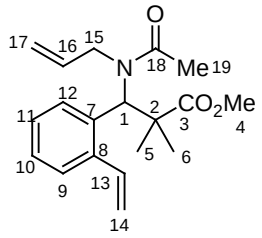
2.142

Methyl 2-((*Z*)-9-acetyl-2,8,9,10-tetrahydro-2-tosylazocino[3,4,5-cd]indol-10-yl)acetate (2.141) and methyl 2-((*Z*)-9-acetyl-2,6,9,10-tetrahydro-2-tosylazocino[3,4,5-cd]indol-10-yl)acetate (2.142). $Pd(OAc)_2$ (2 mg, 0.001 mmol), PPh_3 (6 mg, 0.025 mmol), and Et_3N (0.06 mL, 43 mg, 0.43 mmol) were added to a solution of amide **2.140** (0.057 mg, 0.11 mmol) in CH_3CN (4.2 mL) and the reaction was heated to

125 ºC in a microwave reactor for 30 min. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 6 mg (12%) of enamine **2.142** as a yellowish gum and 40 mg (83%) of amide **2.141** as a brownish solid. Recrystallization of **2.141** via slow evaporation from benzene provided large colorless prisms, mp = 170-172 ºC. **2.142 (minor):** ^{1}H NMR (500 MHz, DMSO, 130 ºC) δ 7.74 (d, *J* = 8.3 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.65 (s, 1 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 7.21 (t, *J* = 7.4 Hz, 1 H), 7.05 (d, *J* = 7.4 Hz, 1 H), 6.45 (d, *J* = 9.1 Hz, 1 H), 5.94 (t, *J* = 7.1 Hz, 1 H), 5.34-5.29 (m, 1 H), 3.65 (dd, *J* = 7.5, 3.7 Hz, 2 H), 3.53 (s, 3 H), 3.31 (dd, *J* = 15.7, 6.4 Hz, 1 H), 3.10 (dd, *J* = 15.7, 7.7 Hz, 1 H), 2.33 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 130 ºC) δ 169.8, 168.8, 144.6, 134.8, 134.2, 132.1, 129.3, 128.2, 127.2, 125.8, 125.2, 124.3, 123.2, 119.8, 115.1, 111.0, 50.4, 49.9, 38.6, 31.2, 22.2, 20.1; IR (neat) 2950, 1737, 1642, 1425, 1368, 1290, 1175, 1091, 912, 743 cm^{-1}; mass spectrum (CI) *m/z* 453.1482 [$C_{24}H_{25}N_2O_5S$ (M+1) requires 453.1484]. **2.141 (major):** ^{1}H NMR (500 MHz, DMSO, 130 ºC) δ 7.88 (d, *J* = 8.3 Hz, 1 H), 7.78 (s, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.34 (t, *J* = 8.3 Hz, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 6.92 (d, *J* = 10.9 Hz, 1 H), 5.99 (ddd, *J* = 10.5, 10.5, 6.9 Hz, 1 H), 5.84 (m, 1 H), 4.34 (br, 1 H), 3.82 (br, 1 H), 3.37 (s, 3 H), 2.96 (dd, *J* = 15.0, 9.8 Hz, 1 H), 2.88 (dd, *J* = 15.0, 4.7 Hz, 1 H), 2.34 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 130 ºC) δ 169.4, 168.1, 144.8, 135.2, 134.1, 133.5, 129.4, 128.6, 127.1, 126.6, 126.5, 125.9, 124.3, 124.1, 118.2, 112.5, 50.5, 50.1, 41.3, 40.6, 20.9, 20.1; IR (neat) 1736, 1638, 1419, 1371, 1307, 1259, 1176, 1149, 1091, 731 cm^{-1}; mass spectrum (CI) *m/z* 453.1487 [$C_{24}H_{25}N_2O_5S$ (M+1) requires 453.1484].

NMR Assignments. 2.142: ^{1}H NMR (500 MHz, DMSO, 130 ºC) δ 7.74 (d, *J* = 8.3 Hz, 2 H, C19-H), 7.73 (d, *J* = 8.3 Hz, 1 H, C11-H), 7.65 (s, 1 H, C5-H), 7.34 (d, *J* =

8.3 Hz, 2 H, C20-H), 7.21 (t, *J* = 7.4 Hz, 1 H, C10-H), 7.05 (d, *J* = 7.4 Hz, 1 H, C9-H), 6.45 (d, *J* = 9.1 Hz, 1 H, C13-H), 5.94 (t, *J* = 7.1 Hz, 1 H, C1-H), 5.34-5.29 (m, 1 H, C14-H), 3.65 (dd, *J* = 7.5, 3.7 Hz, 2 H, C14-H), 3.53 (s, 3 H, C4-H), 3.31 (dd, *J* = 15.7, 6.4 Hz, 1 H, C2-H), 3.10 (dd, *J* = 15.7, 7.7 Hz, 1 H, C2-H), 2.33 (s, 3H, C22-H), 2.00 (s, 3H, C17-H); ^{13}C NMR (125 MHz, DMSO, 130 ºC) δ 169.8 (C4 or C16), 168.8 (C4 or C16), 144.6, 134.8, 134.2, 132.1, 129.3 (C20), 128.2, 127.2, 125.8 (C19), 125.2, 124.3, 123.2, 119.8, 115.1, 111.0, 50.4 (C1 or C4), 49.9 (C1 or C4), 38.6 (C2), 31.2 (C15), 22.2 (C17 or C22), 20.1 (C17 or C22). **2.141:** ^{1}H NMR (500 MHz, DMSO, 130 ºC) δ 7.88 (d, *J* = 8.3 Hz, 1 H, C11-H), 7.78 (s, 1 H, C5-H), 7.77 (d, *J* = 8.3 Hz, 2 H, C19-H), 7.37 (d, *J* = 8.3 Hz, 2 H, C20-H), 7.34 (t, *J* = 8.3 Hz, 1 H, C10-H), 7.12 (d, *J* = 7.5 Hz, 1 H, C9-H), 6.92 (d, *J* = 10.7 Hz, 1 H, C15-H), 5.99 (dt, *J* = 10.7, 6.9 Hz, 1 H, C14-H), 5.84 (m, 1 H, C1-H), 4.34 (br, 1 H, C13-H), 3.82 (br, 1 H, C13-H), 3.37 (s, 3 H, C4-H), 2.96 (dd, *J* = 15.0, 9.8 Hz, 1 H, C2-H), 2.88 (dd, *J* = 15.0, 4.7 Hz, 1 H, C2-H), 2.34 (s, 3H, C22), 2.14 (s, 3H, C17-H); ^{13}C NMR (125 MHz, DMSO, 130 ºC) δ 169.4 (C3 or C16), 168.1 (C3 or C16), 144.8 (C21), 135.2, 134.1, 133.5, 129.4 (C20), 128.6, 127.1, 126.6, 126.5, 125.9 (C19), 124.3, 124.1, 118.2, 112.5 (C11), 50.5 (C1 or C4), 50.1 (C1 or C4), 41.3 (C2 or C13), 40.6 (C2 or C13), 20.9 (C17 or C22), 20.1 (C17 or C22).



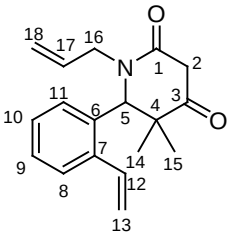
2.149

Methyl 3-(*N*-allylacetamido)-2,2-dimethyl-3-(2-vinylphenyl)propanoate (2.149). (JDSII-96a). TMSOTf (23.0 μL, 28 mg, 0.13 mmol) was added to a solution of 2-vinylbenzaldehyde[424] (172 mg, 1.30 mmol) and bis(trimethylsilyl)allylamine (0.33 mL, 269 mg, 1.34 mmol) in CH_2Cl_2 (3.2 mL), and the reaction was stirred for 30 min at room

temperature. Silyl ketene acetal **1.105** (0.53 mL, 455 mg, 2.60 mmol) and freshly distilled acetyl chloride (0.11 mL, 121 mg, 1.55 mmol) were then added, and the reaction was stirred for 19 h at room temperature. The reaction was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 328 mg (80%) of amide **2.149** as a viscous yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.20 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.04 (dd, *J* = 17.1, 10.9 Hz, 1 H), 6.36 (s, 1 H), 5.57 (dd, *J* = 17.1, 1.7 Hz, 1 H), 5.32 (dd, *J* = 10.9, 1.7 Hz, 1 H), 5.07-4.98 (m, 1 H), 4.80 (dd, *J* = 7.5, 1.4 Hz, 1 H), 4.77 (dd, *J* = 14.2, 1.4 Hz, 1 H), 3.79-3.78 (comp, 2 H), 3.57 (s, 3 H), 2.11 (s, 3 H), 1.45 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 173.1, 140.4, 136.2, 136.1, 135.4, 128.8, 128.5, 128.2, 127.8, 117.6, 117.1, 58.9, 52.8, 50.6, 48.5, 27.5, 24.9, 23.5; IR (neat) 2981, 1729, 1651, 1456, 1396, 1252, 1147, 918, 779 cm^{-1}; mass spectrum (CI) *m/z* 316.1912 [$C_{19}H_{25}NO_3$ (M+1) requires 316.1913].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 1 H, C9-H), 7.38 (d, *J* = 7.9 Hz, 1 H, C12-H), 7.26 (t, *J* = 7.5 Hz, 1H, C11-H), 7.20 (dt, *J* = 7.9, 1.5 Hz, 1H, C10-H), 7.04 (dd, *J* = 17.1, 10.9 Hz, 1 H, C13-H), 6.36 (s, 1 H, C1-H), 5.57 (dd, *J* = 17.1, 1.7 Hz, 1 H, C14-H), 5.32 (dd, *J* = 10.9, 1.7 Hz, 1 H, C14-H), 5.07-4.98 (m, 1 H, C16-H), 4.80 (dd, *J* = 7.5, 1.4 Hz, 1 H, C17-H), 4.77 (dd, *J* = 14.2, 1.4 Hz, 1 H, C17-H), 3.78-3.79 (comp, 2 H, C15-H), 3.57 (s, 3 H, C4-H), 2.11 (s, 3 H, C19-H), 1.45 (s, 3 H, C5 or C6-H), 1.33 (s, 3 H, C5 or C6-H); ^{13}C NMR (100) MHz, $CDCl_3$) δ 178.3 (C3), 173.1 (C18), 140.4, 136.2 , 136.1, 135.4, 128.8, 128.5, 128.2, 127.8, 117.6 (C14 or

C17), 117.1 (C14 or C17), 58.9 (C1), 52.8 (C4), 50.6 (C2 or C15), 48.5 (C2 or C15), 27.5 (C5, C6, or C19), 24.9 (C5, C6, or C19), 23.5 (C5, C6, or C19).

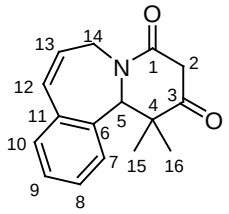


2.151

1-Allyl-5,5-dimethyl-6-(2-vinylphenyl)piperidine-2,4-dione (2.151). (JDSII-99A). NaHMDS (540 mg, 2.95 mmol) was added to a solution of **2.149** (308 mg, 0.98 mmol) in THF (38 mL) and the reaction was stirred for 2 h at room temperature. Saturated aqueous NH_4Cl (15 mL) and H_2O (15 mL) were then added. The organic phase was removed and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (3:7) to give 240 mg (86%) of **2.151** as a light brownish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.5, 1.7 Hz, 1 H), 7.29-7.21 (comp, 2 H), 6.99 (dd, *J* = 17.1, 10.9 Hz, 1 H), 6.74 (dd, *J* = 7.7, 1.2 Hz, 1 H), (dddd, *J* = 17.1, 9.9, 8.9, 4.4 Hz, 1H), 5.64 (dd, *J* = 17.1, 1.0 Hz, 1 H), 5.42 (dd, *J* = 10.9, 1.4 Hz, 1 H), 5.28 (d, *J* = 9.9 Hz, 1 H), 5.23 (d, *J* = 17.1 Hz, 1 H), 4.80 (ddt, *J* = 14.7, 4.4, 1.7 Hz, 1 H), 4.74 (s, 1 H), 3.63 (d, *J* = 21.2 Hz, 1 H), 3.5 (d, *J* = 21.2 Hz, 1 H), 2.96 (dd, *J* = 14.7, 8.9 Hz, 1 H), 1.42 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 166.9, 139.2, 135.9, 135.1, 133.3, 129.7, 129.5, 128.1, 125.8, 120.6, 119.5, 64.2, 50.7, 48.5, 45.4, 26.6, 20.3; IR (neat) 2979, 1723, 1650, 1463, 1282, 931, 755 cm^{-1}; Mass spectrum (CI) *m/z* 284.1658 [$C_{18}H_{21}NO_2$ (M+1) requires 284.1651].

NMR Assignments. ^{1}H NMR (400 MHz, CDCl3) δ 7.43 (dd, *J* = 7.5, 1.7 Hz, 1 H, C8-H), 7.29-7.21 (comp, 2 H, C9-H & C10-H), 6.99 (dd, *J* = 17.1, 10.9 Hz, 1 H, C12-

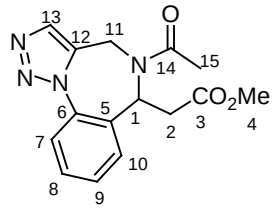
H), 6.74 (dd, *J* = 7.7, 1.2 Hz, 1 H, C11-H), (dddd, *J* = 17.1, 9.9, 8.9, 4.4 Hz, 1H, C17-H), 5.64 (dd, *J* = 17.1, 1.2 Hz, 1 H, 13-H), 5.42 (dd, *J* = 10.9, 1.2 Hz, 1 H, C13-H), 5.28 (d, *J* = 9.9 Hz, 1 H, C18-H), 5.23 (d, *J* = 17.1 Hz, 1 H, C18-H), 4.80 (ddt, *J* = 14.7, 4.4, 1.7 Hz, 1 H, C16-H), 4.74 (s, 1 H, C5-H), 3.63 (d, *J* = 21.2 Hz, 1 H, C2-H), 3.5 (d, *J* = 21.2 Hz, 1 H, C2-H), 2.96 (dd, *J* = 14.7, 8.9 Hz, 1 H, C18-H), 1.42 (s, 3 H, C14-H or C15-H), 0.80 (s, 3 H, C14-H or C15-H); ^{13}C NMR (100 MHz, CDCl3) δ 207.3 (C3), 166.9 (C1), 139.2, 135.9, 135.1, 133.3, 129.7, 129.5, 128.1, 125.8, 120.6 (C13 or C18), 119.5 (C13 or C18), 64.2, 50.7, 48.5, 45.4, 26.6 (C14 or C15), 20.3 (C14 or C15).



2.133

1,1-Dimethyl-1,12b-dihydrobenzo[c]pyrido[1,2-a]azepine-2,4(3*H*,6*H*)-dione (2.133). (JDSII-101a). Grubbs II catalyst (4 mg, 0.0053 mmol) was added to a solution of **2.151** (76 mg, 0.27 mmol) in CH_2Cl_2 (10 mL), and the reaction was heated under reflux for 22 h. The reaction was then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hex (2:3) to give 55 mg (80%) of **2.133** as a brownish amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (comp, 2 H), 7.15 (dt, *J* = 8.2, 4.2 Hz, 1 H) 6.97 (d, *J* = 7.9 Hz, 1 H), 6.60 (d, *J* = 12.3 Hz, 1 H), 5.95 (dt, *J* = 12.3, 3.4 Hz, 1 H), 5.30 (d, *J* = 19.2 Hz, 1 H), 4.57 (s, 1 H), 3.85 (d, *J* = 19.2 Hz, 1 H), 3.32 (d, *J* = 20.5 Hz, 1 H), 3.17 (d, *J* = 20.5 Hz, 1 H), 1.45 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 166.6, 137.4, 136.1, 132.2, 130.3, 129.9, 128.8, 127.6, 125.3, 65.2, 49.2, 47.8, 47.0, 26.2, 21.5; IR (neat) 3426, 2974, 2244, 1722, 1660, 1462, 1376, 1310, 1269,1181, 952, 734 cm^{-1}; mass spectrum (CI) *m/z* 256.1328 [$C_{16}H_{17}NO_2$ (M+1) requires 256.1337].

NMR Assignments. . ^{1}H NMR (400 MHz, CDCl3) δ 7.29-7.24 (comp, 2 H, C8-H & C10-H), 7.15 (dt, *J* = 8.2, 4.2 Hz, 1 H, C9-H) 6.97 (d, *J* = 7.9 Hz, 1 H, C7-H), 6.60 (d, *J* = 12.3 Hz, 1 H, C12-H), 5.95 (dt, *J* = 12.3, 3.4 Hz, 1 H, C13-H), 5.30 (d, *J* = 19.2 Hz, 1 H, C14-H), 4.57 (s, 1 H, C5-H), 3.85 (d, *J* = 19.2 Hz, 1 H, C14-H), 3.32 (d, *J* = 20.5 Hz, 1 H, C2-H), 3.17 (d, *J* = 20.5 Hz, 1 H, C2-H), 1.45 (s, 3 H, C15-H or C16-H), 1.30 (s, 3 H, C15-H or C16-H); ^{13}C NMR (100 MHz, CDCl3) δ 209.4 (C3), 166.6 (C1), 137.4, 136.1, 132.2, 130.3, 129.9, 128.8, 127.6, 125.3, 65.2, 49.2, 47.8, 47.0, 26.2 (C15 or C16), 21.5 (C15 or C16).

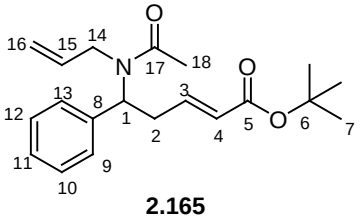


2.155

14,14a-Dihydrobenzo[f]pyrido[1,2-d][1,2,3]triazolo[1,5-a][1,4]diazepine-11,13(9*H*,12*H*)-dione (2.155). (JDSIV-228a). A mixture containing propargyl amine (0.06 mL, 48 mg, 0.87 mmol), 2-azidobenzaldehyde (**2.154**)[208] (116 mg, 0.79 mmol), activated 4 Å molecular sieves (~500 mg) in CH_3CN (2 mL) was stirred for 12 h. Freshly distilled acetyl chloride (0.07 mL, 77 mg, 0.98 mmol) and silyl ketene acetal **2.105** (286 mg, 2.01 mg) were added, and the reaction was stirred for 28 h. The reaction was then filtered thru celite washing with CH_2Cl_2 (3 x 5 mL), and the combined filtrate washings were concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to give 181 mg (76%) of triazole **2.155** as a viscous colorless oil. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.94 (d, *J* = 7.9 Hz, 1 H), 7.91 (s, 1 H), 7.63 (t, *J* = 7.9 Hz, 1 H), 7.58 (d, *J* = 7.3 Hz, 1 H), 7.51 (t, *J* = 7.3 Hz, 1 H), 5.84 (s, 1 H), 5.21 (d, *J* = 15.5 Hz, 1 H), 4.28 (d, *J* = 15.5 Hz, 1H), 3.43 (s, 3 H), 2.41 (dd, *J* = 15.3, 6.1 Hz, 1 H), 2.21 (s, 3 H), 1.80 (m, 1 H); ^{13}C NMR (125 MHz, DMSO, 130

°C) δ 168.7, 168.1, 134.1, 132.2, 132.1, 131.0, 129.4, 128.5, 122.6, 55.1, 50.4, 38.0, 36.6, 20.8; IR (neat) 1738, 1650, 1500, 1411, 1305, 1234, 1168, 980, 767 cm^{-1}; mass spectrum (CI) *m/z* 301.1304 [$C_{15}H_{17}N_4O_3$ (M+1) requires 301.1301].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 7.94 (d, *J* = 7.9 Hz, 1 H, C7-H or C10-H), 7.91 (s, 1 H, C13-H), 7.63 (t, *J* = 7.9 Hz, 1 H, C8-H or C9-H), 7.58 (d, *J* = 7.3 Hz, 1 H, C7-H or C10-H), 7.51 (t, *J* = 7.3 Hz, 1 H, C8-H or C9-H), 5.84 (s, 1 H, C1-H), 5.21 (d, *J* = 15.5 Hz, 1 H, C11-H), 4.28 (d, *J* = 15.5 Hz, 1H. C11-H), 3.43 (s, 3 H, C4-H), 2.41 (dd, *J* = 15.3, 6.1 Hz, 1 H, C2-H), 2.21 (s, 3 H, C15-H), 1.80 (m, 1 H, C2-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 168.7 (C3 or C14), 168.1 (C3 or C14), 134.1, 132.2, 132.1, 131.0, 129.4, 128.5, 122.6, 55.1 (C1 or C10), 50.4 (C11 or C10), 38.0 (C2 or C11), 36.6 (C2 or C11), 20.8 (C15).

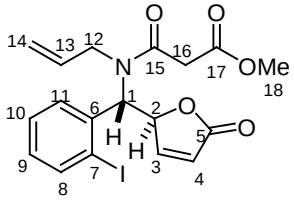


2.165

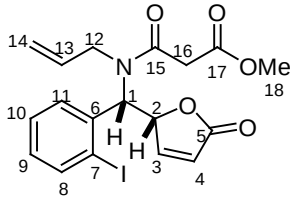
(*E*)-*tert*-Butyl 5-(*N*-allylacetamido)-5-phenylpent-2-enoate (2.165). (JDSI-166b). Acetyl chloride (90 μL, 99 mg, 1.27 mmol) was added to a solution of imine **2.17** (159 mg, 1.10 mmol) and silyl ketene acetal **2.162** (380 mg, 1.48 mmol) in CH_2Cl_2 (3 mL) at −78 °C. The reaction was stirred for 15 min, whereupon the cold bath was removed. The reaction was stirred for 18 h at room temperature and then was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution 1:3 to 1:1) to give 114 mg (31%) of amide **2.165** as a viscous yellowish oil. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.35-7.32 (comp, 4 H), 7.30-7.26 (m, 1 H), 6.73-6.67 (m, 1 H), 5.82 (d, *J* = 15.8 Hz, 1 H), 5.65 (br, 1 H) 5.50 (ddt, *J* = 16.2, 10.7, 5.6 Hz, 1 H), 4.99-4.92 (comp, 2 H), 3.83-3.78 (m, 1 H),

3.72-3.69 (m, 1 H), 2.89-2.83 (comp, 2 H), 2.04 (s, 3 H), 1.42 (s 9 H); 13C NMR (125 MHz, DMSO, 100 °C) δ 169.6, 164.2, 143.6, 138.9, 134.6, 127.8, 127.3, 126.9, 124.3, 115.5, 79.1, 55.6, 45.8, 32.5, 27.4, 21.3; IR (neat) 3411, 3063, 2977, 2932, 2245, 1956, 1816, 1711, 1648, 1407, 1150, 981, 920, 701 cm^{-1}; mass spectrum (CI) *m/z* 330.2069 [$C_{20}H_{27}BrNO_3$ (M+1) requires 330.2069].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.35-7.32 (comp, 4 H, Ar-H), 7.30-7.26 (m, 1 H, Ar-H), 6.73-6.67 (m, 1 H, C3-H), 5.82 (d, *J* = 15.8 Hz, 1 H, C4-H), 5.65 (br s, 1 H, C1-H) 5.50 (ddt, *J* = 16.2, 10.7, 5.6 Hz, 1 H, C15-H), 4.99-4.92 (comp, 2 H, C16-H), 3.83-3.78 (m, 1 H, C14-H), 3.72-3.69 (m, 1 H, C14-H), 2.89-2.83 (comp, 2 H, C2-H), 2.04 (s, 3 H, C18-H), 1.42 (s 9 H, C7-H); 13C NMR (125 MHz, DMSO, 100 °C) δ 169.6 (C17), 164.2 (C5), 143.6 (C3), 138.9 (C8), 134.6 (C15), 127.8 (C10 & C12 or C9 & C13) , 127.3 (C10 & C12 or C9 & C13), 126.9 (C11), 124.3 (C4), 115.5 (C16), 79.1 (C6), 55.6 (C1), 45.8 (C14), 32.5 (C2), 27.4 (C7), 21.3 (C18).



2.175



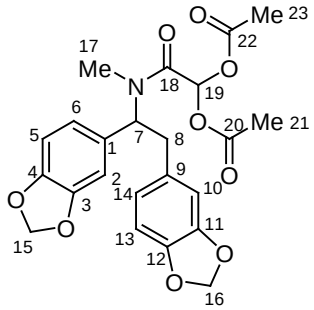
2.175a

Methyl 2-(*N*-allyl-*N*-((2,5-dihydro-5-oxofuran-2-yl)(2-iodophenyl) methyl) carbamoyl) acetate (2.XX). (JDSII-192a and JDSII-192d). A mixture containing 2-iodobenzaldehyde (223 mg, 0.96 mmol), allylamine (0.08 mL, 61 mg, 1.07 mmol) and activated 4 Å molecular sieves (~500 mg) in CH_2Cl_2 (2 mL) was stirred for 13 h at room temperature. The reaction was cooled to 0 °C and methyl malonyl chloride (0.13 mL, 165 mg, 1.21 mmol) and silyloxy furan **2.174** (0.35 mL, 325 mg, 2.08 mmol) were added and the reaction was stirred for 15 min at 0 ºC. The ice bath was removed, and the reaction was stirred at room temperature for 23 h. The reaction was filtered through a

pad of Celite washing with CH_2Cl_2 (3 x 5 mL) and then concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hex (gradient elution 2:3 to 1:1) to give 72 mg (16%) of **2.175** as a viscous yellowish oil and 110 mg of a mixture of **2.175a** and a side product resulting from the acylation of allyl amine by methyl malonyl chloride. The mixture containg **2.175a** was further purified by flash chromatography eluting with EtOAc/Hex (3:7) to give 54 mg (12%) of **2.175** as whitish gum. **2.175**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.92 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.66 (dd, *J* = 5.5, 1.5 Hz, 1 H), 7.46 (dt, *J* = 7.9, 1.0 Hz, 1 H), 7.08 (dt, *J* = 7.9, 1.4 Hz, 1 H), 6.12 (dd, *J* = 5.5, 2.0 Hz, 1 H), 6.00 (s, 1 H), 5.67 (d, *J* = 1.7 Hz, 1 H), 5.17-5.27 (m, 1 H), 4.90 (s, 1 H), 4.86 (d, *J* = 6.5 Hz, 1 H), 3.89 (dd, *J* = 17.6, 5.3 Hz, 1 H), 3.78-3.74 (comp, 1 H), 3.74 (s, 3 H), 3.53 (d, *J* = 15.4 Hz, 1 H), 3.36 (d, *J* = 15.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 169.3, 168.3, 156.3, 141.3, 139.9, 134.0, 132.0, 131.4, 129.9, 121.7, 118.6, 103.2, 86.3, 62.8, 53.4, 50.2, 42.4; IR (neat) 2954, 2360, 1757, 1653, 1403, 1157, 1017, 909, 668 cm^{-1}; mass spectrum (CI) *m/z* 456.0307 [$C_{18}H_{18}INO_5$ (M+1) requires 456.0308]. **2.175a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.77 (dd, *J* = 5.8, 1.7 Hz, 1 H), 7.64 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.40 (dt, *J* = 7.9, 1.0 Hz, 1 H), 7.05 (dt, *J* = 7.9, 1.4 Hz, 1 H), 6.18 (dd, *J* = 5.8, 2.0 Hz, 1 H), 5.76 (d, *J* = 8.9 Hz, 1 H), 5.51-5.41 (comp, 1 H), 5.42 (d, *J* = 8.9 Hz, 1H), 5.09 (d, *J* = 4.1 Hz, 1 H), 5.05 (d, *J* = 11.6 Hz, 1 H), 3.84-3.82 (comp, 2 H), 3.78 (s, 3 H), 3.61 (d, *J* = 16.1 Hz, 1 H), 3.50 (d, *J* = 16.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.3, 168.0, 156.7, 141.4, 138.7, 133.7, 131.4, 130.9, 129.5, 122.7, 119.3, 103.1, 82.7, 65.8, 53.6, 49.7, 42.3; IR (neat) 2952, 1788, 1755, 1654, 1435, 1160, 1014, 942, 753 cm^{-1}; mass spectrum (CI) *m/z* 456.0310 [$C_{18}H_{18}INO_5$ (M+1) requires 456.0308].

NMR Assignments. 2.175: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.9, 1.4 Hz, 1 H, C8-H), 7.92 (dd, *J* = 7.9, 1.0 Hz, 1 H, C11-H), 7.66 (dd, *J* = 5.5, 1.5 Hz, 1 H,

C3-H), 7.46 (dt, *J* = 7.9, 1.0 Hz, 1 H, C10-H), 7.08 (dt, *J* = 7.9, 1.4 Hz, 1 H, C9-H), 6.12 (dd, *J* = 5.5, 2.0 Hz, 1 H, C4-H), 6.00 (s, 1 H, C1-H), 5.67 (d, *J* = 1.7 Hz, 1 H, C2-H), 5.27-5.17 (m, 1 H, C13-H), 4.90 (br, 1 H, C14-H), 4.86 (d, *J* = 6.5 Hz, 1 H, C14-H), 3.89 (dd, *J* = 17.6, 5.3 Hz, 1 H, C12-H), 3.74-3.78 (comp, 1 H, C12-H), 3.74 (s, 3 H, C18-H), 3.53 (d, *J* = 15.4 Hz, 1 H, C16-H), 3.36 (d, *J* = 15.4 Hz, 1 H, C16-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C5), 169.3 (C15 or C17), 168.3 (C15 or C17), 156.3 (C3), 141.3, 139.9, 134.0, 132.0, 131.4, 129.9, 121.7 (C4), 118.6 (C14), 103.2 (C7), 86.3(C2), 62.8, 53.4, 50.2, 42.4. **2.175a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.9, 1.0 Hz, 1 H, C8-H), 7.77 (dd, *J* = 5.8, 1.7 Hz, 1 H, C3-H), 7.64 (dd, *J* = 7.9, 1.4 Hz, 1 H, C11-H), 7.40 (dt, *J* = 7.9, 1.0 Hz, 1 H, C10-H), 7.05 (dt, *J* = 7.9, 1.4 Hz, 1 H, C9-H), 6.18 (dd, *J* = 5.8, 2.0 Hz, 1 H, C4-H), 5.76 (d, *J* = 8.9 Hz, 1 H, C1 or C2), 5.51-5.41 (comp, 1 H, C13-H), 5.42 (d, *J* = 8.9 Hz, 1H, C1 or C2), 5.09 (d, *J* = 4.1 Hz, 1 H, C14-H), 5.05 (d, *J* = 11.6 Hz, 1 H, C14-H), 3.84-3.82 (comp, 2 H, C12-H), 3.78 (s, 3 H, C18-H), 3.61 (d, *J* = 16.1 Hz, 1 H, C16-H), 3.50 (d, *J* = 16.1 Hz, 1 H, C16-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C5), 169.3 (C15 or C17), 168.0 (C15 or C17), 156.7 (C3), 141.4, 138.7, 133.7, 131.4, 130.9, 129.5, 122.7 (C4), 119.3 (C14), 103.1 (C7), 82.7 (C2), 65.8, 53.6, 49.7, 42.3 (C12).



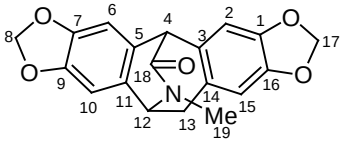
4.26

***N*-[1,2-bis(3,4-Ethylenedioxyphenyl)-ethyl]-2,2-diacetoxy-*N*-methylacetamide (4.26). (JDSIV-233a).** A solution of methylamine (~1.9 M in THF, 0.5 mL, 0.95 mmol) was added to a mixture of piperonal (0.92 mg, 0.61 mmol) in THF (1 mL) containing

activated 3 Å molecular sieves (8-12 mesh, ~750 mg), and the reaction was stirred for 18 h. In a separate flask, a solution of piperonyl chloride[357] (728 mg, 4.27 mmol) in THF (6 mL) was added dropwise over 2 h to a suspension of magnesium turnings (170 mg) in THF (2.5 mL) at 0 °C, and the reaction was stirred for 3 h at 0 °C. A solution of the Grignard reagent thus prepared (0.4 M in THF, 3.5 mL, 1.40 mmol) was added to the mixture of the imine, and the reaction was heated under reflux for 20 h. The mixture was cooled to –78 °C, and diacetoxyacetyl chloride (**4.25**)[359] (358 mg, 1.83 mmol) was added. The reaction was stirred for 2.5 h at –78 °C. The cold bath was removed, and the mixture was partitioned between CH_2Cl_2 (5 mL) and sat. $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (3:7) to give 173 mg (61%) of amide **4.26** as a pale yellow solid, mp 141–142.5 °C. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 6.95 (s, 1 H), 6.88 (s, 1 H), 6.84 (comp, 2 H), 6.77 (d, *J* = 1.4 Hz, 1 H), 6.74 (d, *J* = 7.9 Hz, 1 H), 6.70 (dd, *J* = 7.9, 1.5 Hz, 1 H), 5.97 (d, *J* = 1.5 Hz 2 H), 5.91 (s, 2 H), 5.63 (br, 1 H), 3.26 (dd, *J* = 14.3, 6.1 Hz, 1H), 3.10 (dd, *J* = 14.3, 9.5 Hz, 1 H), 2.74 (s, 3 H), 2.04 (s, 6 H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 167.4, 167.3, 162.8, 147.0, 146.6 146.1, 145.1, 132.1, 131.0, 121.2, 120.2, 108.4, 107.3, 107.3 107.2, 100.3, 99.9, 83.9, 57.5, 35.0, 28.4, 19.3, 19.2; IR (neat) 1767, 1668, 1490, 1441, 1246, 1198, 1038, 924 cm^{-1}; mass spectrum (CI) *m/z* 458.1453 [$C_{23}H_2$4BrNO$_9$ (M+1) requires 458.1451].

NMR Assignments. ^{1}H NMR (500 MHz, DMSO, 130 °C) δ 6.95 (s, 1 H, C19-H), 6.88 (s, 1 H, C2-H or C10-H), 6.84 (comp, 2 H, C5-H and C6-H or C13-H and C14-H), 6.77 (d, *J* = 1.4 Hz, 1 H, C2-H or C10-H), 6.74 (d, *J* = 7.9 Hz, 1 H, C5-H, C6-H, C13-H, C14-H), 6.70 (dd, *J* = 7.9, 1.5 Hz, 1 H, C5-H, C6-H, C13-H, or C14-H), 5.97 (d,

J = 1.5 Hz, 2 H, C15-H or C16-H), 5.91 (s, 2 H, C15-H or C16-H), 5.63 (br, 1 H, C7-H), 3.26 (dd, *J* = 14.3, 6.1 Hz, 1H, C8-H), 3.10 (dd, *J* = 14.3, 9.5 Hz, 1 H, C8-H), 2.74 (s, 3 H, C17-H), 2.04 (s, 6 H, C21-H and C23-H); ^{13}C NMR (125 MHz, DMSO, 130 °C) δ 167.4 (C20 or C22), 167.3 (C20 or C22), 162.8 (C18), 147.0 (C3, C4, C11, or C12), 146.6 (C3, C4, C11, or C12), 146.1 (C3, C4, C11, or C12), 145.1 (C3, C4, C11, or C12), 132.1 (C1 or C9), 131.0 (C1 or C9), 121.2 (C6 or C14), 120.2 (C6 or 14), 108.4 (C2, C5, C10, or C13), 107.3 (C2, C5, C10, or C13), 107.3, (C2, C5, C10, or C13), 107.2 (C2, C5, C10, or C13), 100.3, (C15 or C16), 99.9 (C15 or C16), 83.9 (C19), 57.5 (C7), 35.0 (C8), 28.4 (C17), 19.3 (C21 or C23), 19.2 (C21 or C23).



(±)-roelactamine
(±)-4.11

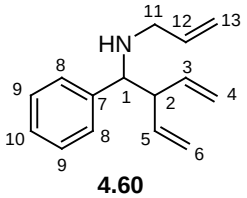
(±)- Roelactamine (±-4.11). (JDSIV-251a). A solution of conc. HCl/MeOH (2:1, 5 mL) was added to amide **4.26** and the reaction was stirred for 8 h at room temperature. The reaction was diluted with CH_2Cl_2 (5 mL) and carefully quenched with 2 M Na_2CO_3 (10 mL) and sat. $NaHCO_3$ (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (2:3) to give 58 mg (68%) of **4.11** as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$,) δ 6.75 (s, 1 H), 6.73 (s, 1 H), 6.69 (s, 1 H), 6.46 (s, 1 H), 5.93 (d, *J* = 1.4 Hz, 1 H), 5.89 (d, *J* = 1.4 Hz, 1 H), 5.87 (d, *J* = 1.4 Hz, 1 H), 5.85 (d, *J* = 1.4 Hz, 1 H), 4.39 (dd, *J* = 4.2, 2.6 Hz, 1 H), 4.25 (s, 1 H), 3.33 (dd, *J* = 17.3, 4.2 Hz, 1 H), 3.10 (s, 3 H), 2.95 (dd, *J* = 17.3, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 148.1, 148.0, 147.4, 147.0, 135.1, 130.3, 130.2, 127.0, 112.2, 110.0, 107.0, 106.3, 102.1, 101.9, 61.5, 57.4, 34.8, 33.3; IR (neat) 2895, 1661, 1504,

1482, 1228, 1038, 941, 873 cm^{-1}; mass spectrum (CI) *m/z* 338.1026 [$C_{19}H_{16}NO_5$ (M+1) requires 338.1028].

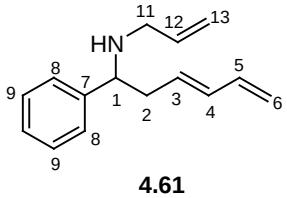
NMR Assignments. ^{1}H NMR (400 MHz, CDCl3,) δ 6.75 (s, 1 H, C10-H), 6.73 (s, 1 H, C6-H), 6.69 (s, 1 H, C2-H), 6.46 (s, 1 H. C15-H), 5.93 (d, *J* = 1.4 Hz, 1 H, C8-H), 5.89 (d, *J* = 1.4 Hz, 1 H, C8-H), 5.87 (d, *J* = 1.4 Hz, 1 H, C17-H), 5.85 (d, *J* = 1.4 Hz, 1 H, C17-H), 4.39 (dd, *J* = 4.2, 2.6 Hz, 1 H, C12-H), 4.25 (s, 1 H, C4-H), 3.33 (dd, *J* = 17.3, 4.2 Hz, 1 H, C13-H), 3.10 (s, 3 H, C19-H), 2.95 (dd, *J* = 17.3, 2.6 Hz, 1 H, C13-H); ^{13}C NMR (100 MHz, CDCl3) δ 173.6 (C18), 148.1 (C1 or C9), 148.0 (C1 or C9), 147.4 (C7), 147.0 (C16), 135.1 (C3), 130.3 (C5), 130.2 (C11), 127.0 (C14), 112.2 (C15), 110.0 (C2), 107.0 (C10), 106.3 (C6), 102.1 (C8), 101.9 (C17), 61.5 (C12), 57.4 (C4), 34.8 (C13), 33.3 (C19).

Table 5.1

Literature ^{1}H NMR Data	Synthetic ^{1}H NMR Data	Literature ^{13}C NMR Data	Synthetic ^{13}C NMR Data
6.75 (s)	6.75 (s)	172.3	172.6
6.73 (s)	6.73 (s)	147.1	147.1
6.69 (s)	6.69 (s)	147.1	147.0
6.46 (s)	6.46 (s)	146.4	146.4
5.93 (d, *J* = 1.4 Hz)	5.93 (d, *J* = 1.4 Hz)	146.0	146.0
5.89 (d, *J* =1.4 Hz)	5.89 (d, *J* = 1.4. Hz)	134.2	134.1
5.87 (d, *J* = 1.4 Hz)	5.87 (d, *J* = 1.4 Hz)	129.4	129.3
5.85 (d, *J* = 1.4 Hz)	5.85 (d, *J* = 1.4 Hz)	129.3	129.2
4.39 (dd, *J* = 4.2, 2.6 Hz)	4.39 (dd, *J* = 4.2, 2.6 Hz)	126.0	126.0
4.25 (s)	4.25 (s)	111.2	111.2
3.33 (dd, *J* = 17.3, 4.2 Hz)	3.33 (dd, *J* = 17.3, 4.2 Hz)	109.1	109.0
3.10 (s)	3.10 (s)	106.1	106.0
2.95 (dd, *J* = 17.3, 2.6 Hz)	2.95 (dd, *J* = 17.3, 2.6 Hz)	105.3	105.3
		101.3	101.1
		100.9	100.9
		60.7	60.5
		56.5	56.4
		33.9	33.8
		32.4	32.3



4.60

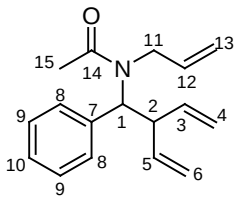


4.61

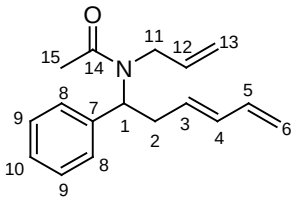
***N*-Allyl-1-phenyl-2-vinylbut-3-en-1-amine (4.60) and (*E*)-*N*-allyl-1-phenylhexa-3,5-dien-1-amine (4.61). (JDSV-106a).** *n*-BuLi (0.4 mL, 2.3 M in hexane, 0.94 mmol) was added to a solution of 1,4-pentadiene (0.1 mL, 66 mg, 0.97 mmol) in THF (0.5 mL) at -78 ºC. The reaction was stirred at -78 ºC for 15 min, whereupon the bath was replaced with a 0 ºC bath. The reaction was stirred for an additional 30 min at 0

ºC. A solution of $AlCl_3$ (140 mg, 1.05 mmol) in Et_2O (1 mL) was then added and the reaction was stirred for 1 h at 0 ºC. The pentadienyl Al reagent **4.58** thus prepared was added to a solution of imine **4.59** (112 mg, 0.77 mmol) in CH_2Cl_2 (2 mL) and the reaction was stirred for 18 h at room temperature. H_2O (3 mL) and 6 M NaOH (4 mL) where added, and the mixture was filtered through a pad of Celite washing with CH_2Cl_2 (3 x 5 mL). The layers were separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 5 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:9 to 1:3) to give 116 mg (70%) of amine **4.60** and 4 mg (2%) of amine **4.61** as colorless oils. **4.60:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (comp, 5H), 5.87-5.72 (comp, 2 H), 5.59 (ddd, *J* = 17.8, 10.8, 7.2 Hz, 1 H), 5.19-5.03 (comp, 4 H), 4.95-4.89 (comp, 2 H), 3.58 (d, *J* = 7.9 Hz, 1 H), 3.08 (ddt, *J* = 14.3, 5.2, 1.7 Hz, 1 H), 3.02 (dt, *J* = 7.8, 7.8 Hz, 1 H), 2.94 (ddt, *J* = 14.3, 6.8, 1.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.1, 137.7, 136.8, 128.3, 127.9, 127.0, 117.4, 116.0, 115.6, 65.1, 55.1, 49.7; IR (neat) 3078, 2977, 2817, 1642, 1453, 1111, 994, 917, 700 cm^{-1}; mass spectrum (CI) *m/z* 214.2601 [$C_{15}H_{20}N$ (M+1) requires 214.1596].

NMR Assignments. 4.60: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (comp, 5H, Ar-H), 5.87 -5.72 (comp, 2 H, C12-H and C3-H or C5-H), 5.59 (ddd, *J* = 17.8, 10.8, 7.2 Hz, 1 H, C3-H or C5-H), 5.19-5.03 (comp, 4 H, C3-H, C5-H, or C12-H), 4.95-4.89 (comp, 2 H, C3-H, C5-H, or C12-H), 3.58 (d, *J* = 7.9 Hz, 1 H, C1-H), 3.08 (ddt, *J* = 14.3, 5.2, 1.7 Hz, 1 H, C11-H), 3.02 (dt, *J* = 7.9, 7.9 Hz, 1 H, C2-H), 2.94 (ddt, *J* = 14.3, 6.8, 1.0 Hz, 1H, C11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4 (C3 or C5), 138.1 (C12), 137.7 (C3 or C5), 136.8 (C7), 128.3 (C8 or C9), 127.9 (C8 or C9), 127.0 (C10), 117.4 (C4, C6, C13), 116.0 (C4, C6 or C13), 115.6 (C4, C6, or C13), 65.1 (C1), 55.1 (C11), 49.7 (C2).



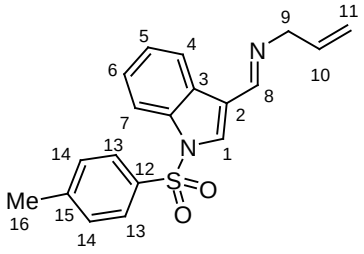
4.65



4.66

***N*-Allyl-*N*-(1-phenyl-2-vinylbut-3-enyl)acetamide (4.65) and *N*-allyl-*N*-((*E*)-1-phenylhexa-3,5-dienyl)acetamide (4.66). (JDSV-195a).** *n*-BuLi (0.4 mL, 2.3 M in hexane, 0.94 mmol) was added to a solution of 1,4-pentadiene (0.1 mL, 66 mg, 0.97 mmol) in THF (0.5 mL) at -78 ºC. The reaction was stirred at -78 ºC for 15 min, whereupon the bath was replaced with a 0 ºC bath. The reaction was stirred for an additional 30 min at 0 ºC. A solution of $AlCl_3$ (140 mg, 1.05 mmol) in Et_2O (1 mL) was added, and the reaction was stirred for 1 h at 0 ºC. In a separate flask freshly distilled acetyl chloride (0.06 mL, 66 mg, 0.84 mmol) was added to a solution of imine **4.17** (111 mg, 0.77 mmol) in CH_2Cl_2 (2 mL) and the reaction was stirred for 1 h upon which the solution of pentadienyl Al **4.58** was added. The reaction was stirred at rt for 3 h. The reaction was partitioned between CH_2Cl_2 (5 mL) and sat. NH_4Cl (5 mL). The organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:3) to give 164 mg (84%) of a mixture (~1:1) of amides **4.65** and **4.66** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (comp, 10 H), 6.26 (dt, *J* = 17.0, 10.1 Hz, 1 H), 6.15 (dd, *J* = 15.2, 10.1 Hz, 1 H), 5.79 (dt, *J* = 17.5, 8.8 Hz, 1 H), 5.69-5.42 (comp, 5 H), 5.30 (dddd, *J* = 15.6, 10.4, 5.2, 5.2 Hz, 1 H), 5.18-4.94 (comp, 8 H), 4.86-4.82 (m, 2H), 3.87-3.79 (comp, 4 H), 3.71 (dd, *J* = 16.8, 5.9 Hz, 1 H), 2.86-2.72 (comp, 2 H), 2.05 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 139.3, 138.0, 137.7, 137.5, 136.2, 134.7, 134.4, 132.2, 130.7, 130.4, 128.6, 127.5, 127.3, 127.2, 126.6, 126.5, 115.6,

115.2, 115.1, 114.9, 114.6, 46.8, 39.7, 33.1, 21.2, 21.1; IR (neat) 2976, 1644, 1452, 1406, 1316, 1250, 1176, 1003, 918, 701 cm^{-1}; mass spectrum (CI) *m/z* 256.1696 [$C_{17}H_{22}NO$ (M+1) requires 256.1699].

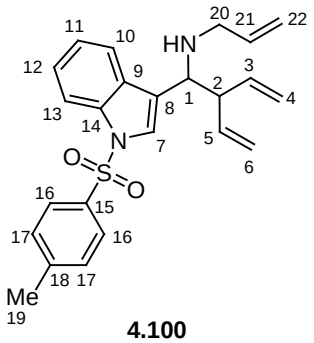


4.98

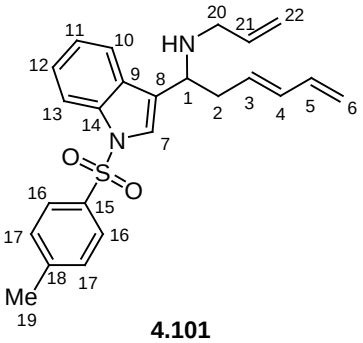
(*E*)-*N*-((1-Tosyl-1*H*-indol-3-yl)methylene)prop-2-en-1-amine (4.98). (JDSV-227). A mixture containing indole-3-carboxaldehyde **2.97** (224 mg, 0.74 mmol), allylamine (0.15 mL, 114 mg, 2.0 mmol) and activated 4 Å molecular sieves (~500 mg) in CH_2Cl_2 (3 mL) was stirred for 20 h at room temperature. The reaction was filtered through a pad of Celite that was washed with CH_2Cl_2 (3 x 5 mL) and the filtrate was concentrated under reduced pressure to give 246 mg (97%) of **4.98** as an orangish brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 8.35 (d, *J* = 7.9 Hz, 1 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 7.83 (s, 1 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 7.36 (t, *J* = 7.9 Hz, 1 H), 7.29 (t, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 6.09 (dddd, *J* = 17.1, 10.3, 5.5, 4.8 Hz, 1 H) 5.27 (d, *J* = 17.1 Hz, 1 H), 5.23 (d, *J* = 10.3 Hz, 1 H), 4.25 (d, *J* = 5.8 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 145.2, 136.0, 135.3, 134.6, 129.9, 129.5, 127.9, 126.8, 125.4, 124.0, 123.0, 120.5, 115.6, 113.1, 63.9, 21.4; IR (neat) 1647, 1445, 1268, 1175, 1126, 1099, 983, 750 cm^{-1}; mass spectrum (CI) *m/z* 339.1167 [$C_{19}H_{18}N_2O_2S$ (M+1) requires 339.11671].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H, C8-H), 8.35 (d, *J* = 7.9 Hz, 1 H, C7-H), 7.96 (d, *J* = 7.9 Hz, 1 H, C4-H), 7.83 (s, 1 H, C1-H), 7.78 (d, *J* = 8.2 Hz, 2 H, C13-H), 7.36 (t, *J* = 7.9 Hz, 1 H, C6-H), 7.29 (t, *J* = 7.9 Hz, 1 H, C5-H), 7.23 (d, *J* = 8.2 Hz, 2 H, C14-H), 6.09 (dddd, *J* = 17.1, 10.3, 5.5, 4.8 Hz, 1 H, C10-H) 5.27 (d, *J* =

17.1 Hz, 1 H, C11-H), 5.23 (d, *J* = 10.3 Hz, 1 H, C11-H), 4.25 (d, *J* = 5.8 Hz, 1 H, C9-H), 2.34 (s, 3 H, C16-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (C8), 145.2 (C15), 136.0, 135.3, 134.6, 129.9, 129.5, 127.9, 126.8, 125.4, 124.0, 123.0, 120.5, 115.6, 113.1, 63.9 (C9), 21.4 (C18).



4.100



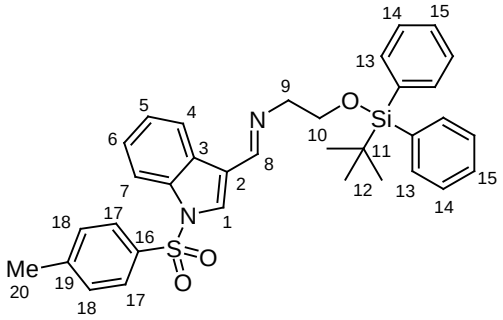
4.101

***N*-Allyl-1-(1-tosyl-1*H*-indol-3-yl)-2-vinylbut-3-en-1-amine (4.100) and (*E*)-*N*-allyl-1-(1-tosyl-1*H*-indol-3-yl)hexa-3,5-dien-1-amine (4.101). (JDSV-120a and JDSV-120b).** *n*-BuLi (0.4 mL, 2.3 M in hexane, 0.94 mmol) was added to a solution of 1,4-pentadiene (0.1 mL, 66 mg, 0.97 mmol) in THF (0.5 mL) at -78 ºC. The reaction was stirred at -78 ºC for 15 min, whereupon the bath was replaced with a 0 ºC bath. The reaction was stirred for an additional 30 min at 0 ºC. A solution of $AlCl_3$ (135 mg, 1.01 mmol) in Et_2O (1 mL) was added and the reaction was stirred for 1 h at 0 ºC. The pentadienyl Al reagent **4.58** thus prepared was added to a solution of imine **4.98** (228 mg, 0.67 mmol) in CH_2Cl_2 (2 mL) and the reaction was stirred for 20 h at rt. The reaction was partitioned between 3 M NaOH (4 mL) and CH_2Cl_2 (5 mL). The layers organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:4) to give 235 mg (85%) of amine **4.100** and 10 mg (3%) of amine **4.101** as colorless gums. **4.100:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1 H), 7.71-7.66 (comp, 3 H), 7.43 (s, 1 H), 7.28 (td, *J* = 7.8, 1.1 Hz 1 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz,

1 H), 5.82-5.70 (comp, 2 H), 5.63 (ddd, *J* = 17.4, 10.0, 7.6 Hz, 1 H), 5.14 (dd, *J* = 10.2, 1.5 Hz, 1 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 5.03-5.02 (m, 1 H), 5.00-4.99 (m, 1 H), 4.88-4.86 (m, 1 H), 4.85-4.84 (m, 1 H), 3.88 (d, *J* = 7.6 Hz, 1 H), 3.15 (app q, *J* = 7.6 Hz, 1 H), 3.10 (ddt, *J* = 14.1, 5.1, 1.7 Hz, 1 H), 2.96 (ddt, *J* = 14.1, 5.7, 1.1 Hz, 1 H), 2.32 (s, 3 H), 1.59 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 137.8, 137.7, 136.8, 135.7, 135.2, 130.4, 139.7, 126.7, 124.9, 124.6, 123.3, 123.0, 120.8, 117.7, 116.3, 115.8, 113.9, 57.8, 53.7, 49.9, 21.5; IR (neat) 3333, 2977, 1446, 1367, 1175, 1121, 1094, 918, 747, 670 cm^{-1}; mass spectrum (CI) *m/z* 407.1794 [$C_{24}H_{27}N_2O_2S$ (M+1) requires 407.1793]. **4.101:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 1 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.46 (s, 1 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 7.21 (td, *J* = 8.2, 1.0 Hz, 1 H) 7.20 (d, *J* = 7.9 Hz, 2 H), 6.24 (dt, *J* = 17.1, 10.2 Hz, 1 H), 6.08 (dd, *J* = 15.0, 10.6 Hz, 1 H), 5.83 (dddd, *J* = 16.7, 10.3, 6.5, 5.5 Hz, 1 H), 5.55 (dt, *J* = 15.0, 7.52 Hz, 1 H), 5.11-4.99 (comp, 4 H), 4.00 (t, *J* = 6.5 Hz, 1 H), 3.16 (ddt, *J* = 14.0, 5.5, 1.4 Hz, 1 H), 3.08 (ddt, *J* = 14.0, 6.5 Hz, 1.4 Hz, 1 H), 2.56 (comp, 2 H) 2.33 (s, 3 H), 1.54 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 136.8, 136.7, 135.7, 135.2, 133.8, 130.7, 129.8, 129.8 129.7, 126.7, 126.7, 124.7, 124.6, 123.7, 123.0, 120.3, 116.0, 115.9, 113.9, 54.3, 50.0, 39.3, 21.5; IR (neat) 2922, 1642, 1598, 1446, 1367, 1174, 1120, 1004, 747, 688, 572 cm^{-1}; mass spectrum (CI) *m/z* 407.1797 [$C_{24}H_{27}N_2O_2S$ (M+1) requires 407.1793].

NMR Assignments. 4.100: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1 H, C13-H), 7.71-7.66 (comp, 3 H, C10 and C16-H), 7.43 (s, 1 H, C7-H), 7.28 (td, *J* = 7.8, 1.1 Hz, 1 H, C12-H), 7.20 (t, *J* = 7.8 Hz, 1 H, C11-H), 7.17 (d, *J* = 8.0 Hz, 1 H, C17-H), 5.82-5.70 (comp, 2 H, C3, C5, or C21-H), 5.63 (ddd, *J* = 17.4, 10.0, 7.6 Hz, 1 H, C3 or C5-H), 5.14 (dd, *J* = 10.2, 1.5 Hz, 1 H, C4 or C6-H), 5.09 (d, *J* = 17.1 Hz, 1 H, C4 or C6-H), 5.03-5.02 (m, 1 H, C21-H), 5.00-4.99 (m, 1 H, C21-H), 4.88-4.86 (m, 1 H, C4 or C6-H), 4.85-4.84 (m, 1 H, C4 or C6-H), 3.88 (d, *J* = 7.6 Hz, 1 H, C1-H), 3.15 (app q, *J* =

7.6 Hz, 1 H, C2-H), 3.10 (ddt, *J* = 14.1, 5.1, 1.7 Hz, 1 H, C20-H), 2.96 (ddt, *J* = 14.1, 5.7, 1.1 Hz, 1 H, C20-H), 2.32 (s, 3 H, C19-H), 1.59 (br, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C18), 137.8 (C3 or C5), 137.7 (C3 or C5), 136.8 (C21), 135.7 (C14 or C15), 135.2 (C14 or C15), 130.4 (C3), 129.7 (C17), 126.7 (C16), 124.9 (C7), 124.6 (C12), 123.3 (C8), 123.0 (C5), 120.8 (C4), 117.7 (C4 or C6), 116.3 (C22), 115.8 (C4 or C6), 113.9 (C7), 57.8 (C1), 53.7 (C2), 49.9 (C20), 21.5 (C19) **4.101:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 1 H, C13-H), 7.72 (d, *J* = 8.5 Hz, 2 H, C16-H), 7.65 (d, *J* = 7.9 Hz, 1 H, C10-H), 7.46 (s, 1 H, C7-H), 7.28 (t, *J* = 7.2 Hz, 1 H, C11-H or C12-H), 7.21 (td, *J* = 8.2, 1.0 Hz, 1 H, C11-H or C12-H) 7.20 (d, *J* = 7.9 Hz, 2 H, C17-H), 6.24 (dt, *J* = 17.1, 10.2 Hz, 1 H, C5-H), 6.08 (dd, *J* = 15.0, 10.6 Hz, 1 H, C4-H), 5.83 (dddd, *J* = 16.7, 10.3, 6.5, 5.5 Hz,1 H, C21-H), 5.55 (dt, *J* = 15.0, 7.52 Hz, 1 H, C3-H), 5.11-4.99 (comp, 4 H, C6-H and C22-H), 4.00 (t, *J* = 6.5 Hz, 1 H, C1-H), 3.16 (ddt, *J* = 14.0, 5.5, 1.4 Hz, 1 H, C20-H), 3.08 (ddt, *J* = 14.0, 6.5 Hz, 1.4 Hz, 1 H, C20-H), 2.56 (comp, 2 H, C2-H) 2.33 (s, 3 H, C19-H), 1.54 (s, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 136.8, 136.7, 135.7, 135.2, 133.8, 130.7, 129.8 (C17), 129.8 (C17) 129.7, 126.7 (C16), 126.7 (C16), 124.7, 124.6, 123.7, 123.0, 120.3, 116.0, 115.9, 113.9, 54.3 (C1), 50.0 (C20), 39.3 (C2), 21.5 (C19).

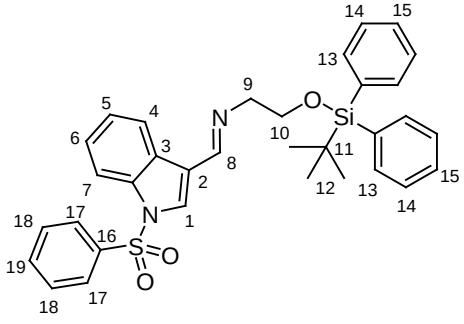


4.116

(*E*)-2-(*tert*-Butyldiphenylsilyloxy)-*N*-((1-tosyl-1*H*-indol-3-yl)methylene)-ethanamine (4.116). (JDSV-228). A mixture containing indole-3-carboxaldehyde **2.97**

(225 mg, 0.75 mmol), amine **4.115** (260 mg, 0.77 mmol), triethylamine (0.11 mL, 80 mg, 0.79 mmol) and activated 4 Å molecular sieves (~500 mg) in CH_2Cl_2 (3 mL) was stirred for 22 h at room temperature. The stirred was stopped and Et_2O (8 mL) was added and the reaction was allowed to sit for 5 min. The reaction was filtered through a pad of Celite that was washed with Et_2O (3 x 5 mL) and the filtrate was concentrated under reduced pressure to give 434 mg (99%) of **4.116** as an orangish brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.34 (d, *J* = 7.9 Hz, 1 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 7.81 (s, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 7.64-7.61 (comp, 4 H), 7.39-7.28 (comp, 4 H), 7.27-7.23 (comp, 5 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 3.96 (t, *J* = 5.4 Hz, 2 H), 3.78 (t, *J* = 5.4 Hz, 2 H), 2.31 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 145.2, 135.6, 135.5, 134.8, 133.6, 129.9, 129.6, 129.5, 128.1, 127.5, 126.8, 125.5, 124.0, 123.2, 120.8, 113.2, 64.1, 63.2, 26.7, 21.5, 19.1; IR (neat) 2929, 1644, 1445, 1268, 1176, 1112, 979, 703 cm^{-1}; mass spectrum (CI) *m/z* 581.2296 [$C_{34}H_{36}N_2O_3SSi$ (M+1) requires 581.2294].

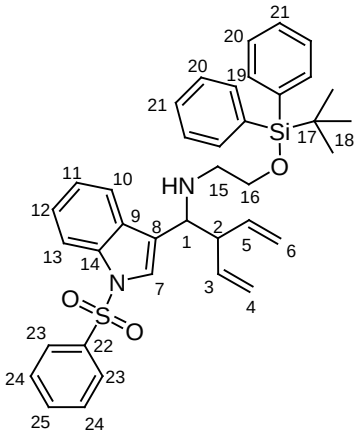
NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H, C8-H), 8.34 (d, *J* = 7.9 Hz, 1 H, C7-H), 7.97 (d, *J* = 7.9 Hz, 1 H, C4-H), 7.81 (s, 1 H, C1-H), 7.74 (d, *J* = 8.5 Hz, 2 H, C17-H), 7.64-7.61 (comp, 4 H, Ar-H), 7.39-7.28 (comp, 4 H, Ar-H), 7.27-7.23 (comp, 5 H, Ar-H), 7.17 (d, *J* = 8.5 Hz, 2 H, C18-H), 3.96 (t, *J* = 5.4 Hz, 2 H, C10-H), 3.78 (t, *J* = 5.4 Hz, 2 H, C9-H), 2.31 (s, 3 H, C20-H), 0.97 (s, 9 H, C12-H).



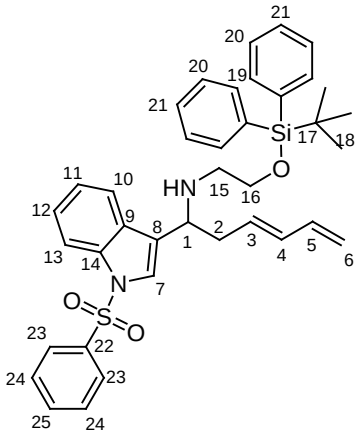
4.117

(*E*)-2-(*tert*-butyldiphenylsilyloxy)-*N*-((1-(phenylsulfonyl)-1*H*-indol-3-yl)methylene)ethanamine (4.117). (JDSV-229). A mixture containing indole-3-carboxaldehyde **2.114** (220 mg, 0.77 mmol), amine **4.115** (263 mg, 0.78 mmol), triethylamine (0.11 mL, 80 mg, 0.79 mmol) and activated 4 Å molecular sieves (~500 mg) in CH_2Cl_2 (3 mL) was stirred for 22 h at room temperature. The stirring was stopped and Et_2O (8 mL) was added and the reaction was allowed to sit for 5 min. The reaction was filtered through a pad of Celite that was washed with Et_2O (3 x 5 mL) and the filtrate was concentrated under reduced pressure to give 438 mg (100%) of **4.117** as an orangish brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.34 (d, *J* = 7.9 Hz, 1 H), 7.98 (d, *J* = 7.9 Hz, 1 H), 7.88-7.85 (m, 2 H), 7.82 (s, 1 H), 7.64-7.61 (comp, 4 H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.43-7.29 (comp, 6 H), 7.27-7.23 (comp, 4 H), 3.96 (t, *J* = 5.2 Hz, 2 H), 3.78 (t, *J* = 5.2 Hz, 2 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 137.8, 135.6, 135.5, 134.0, 133.6, 129.5, 129.4, 129.3, 128.1, 127.5, 126.7, 125.6, 124.1, 123.2, 120.9, 113.2, 64.1, 63.2, 26.7, 19.1; IR (neat) 2929, 1644, 1446, 1379, 1268, 1176, 1112, 979, 727, 702 cm^{-1}; mass spectrum (CI) *m/z* 567.2142 [$C_{33}H_{34}N_2O_3SSi$ (M+1) requires 567.2138].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H, (C8-H), 8.34 (d, *J* = 7.9 Hz, 1 H, C7-H), 7.98 (d, *J* = 7.9 Hz, 1 H, C4-H), 7.88-7.85 (m, 2 H, C17-H), 7.82 (s, 1 H, C1-H), 7.64-7.61 (comp, 4 H, Ar-H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1 H, C19-H), 7.43-7.29 (comp, 6 H, Ar-H), 7.27-7.23 (comp, 4 H, Ar-H), 3.96 (t, *J* = 5.2 Hz, 2 H, C10-H), 3.78 (t, *J* = 5.2 Hz, 2 H, C9-H), 0.97 (s, 9 H, C12-H).



4.119



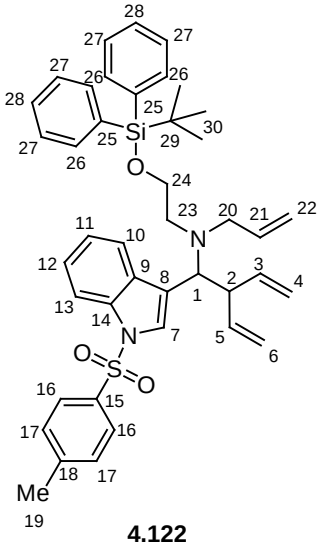
4.121

[1-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-vinyl-but-3-enyl]-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-amine (4.119) and ([1-(1-Benzenesulfonyl-1*H*-indol-3-yl)-hexa-3,5-dienyl]-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-amine (4.121). (JDSV-188a and JDSV-188b). *n*-BuLi (0.45 mL, 2.1 M in hexane, 0.94 mmol) was added to a solution of 1,4-pentadiene (0.1 mL, 66 mg, 0.97 mmol) in THF (0.5 mL) at -78 ºC. The reaction was stirred at -78 ºC for 15 min, whereupon the bath was replaced with a 0 ºC bath. The reaction was stirred for an additional 30 min at 0 ºC. A solution $AlCl_3$ (134 mg, 1.0 mmol) in Et_2O (1 mL) was added and the reaction was stirred for 1 h at 0 ºC. The pentadienyl Al reagent **4.58** thus prepared was then added to a solution of imine **4.117** (382 mg, 0.67 mmol) in CH_2Cl_2 (2 mL) and the reaction was stirred for 25 h at rt. The reaction was partitioned between 3 M NaOH (6 mL) and CH_2Cl_2 (5 mL). The layers organic phase was removed, and the aqueous layer was washed with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:9 to 1:4) to give 301 mg (70%) of amine **4.119** and 10 mg (9%) of amine **4.121** as colorless gums. **4.119:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1 H), 7.79-7.77 (m, 2H), 7.69 (d, J = 8.0 Hz, 1 H), 7.67-7.64 (comp, 4 H), 7.46 (td, J

= 7.5, 1.4 Hz, 1 H), 7.44-7.40 (comp, 3 H), 7.38-7.33 (comp, 6 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 5.77 (ddd, *J* = 17.1, 10.3, 8.8 Hz, 1 H), 5.62 (ddd, *J* = 17.4, 10.0, 7.3 Hz, 1 H), 5.13 (d, *J* = 10.3 Hz, 1 H), 5.11 (d, *J* = 17.1 Hz, 1 H), 4.85-4.81 (comp, 2 H), 3.84 (d, *J* = 7.6 Hz, 1 H), 3.69-3.62 (comp, 2 H), 3.15 (app q, 7.8 Hz, 1 H), 2.55-2.46 (comp, 2 H), 2.20 (br, 1 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.8, 137.7, 135.8, 135.61, 135.57, 133.7, 133.6, 130.3, 129.68, 129.66, 129.0, 127.66, 127.65, 126.6, 124.8, 124.6, 123.9, 123.1, 121.0, 117.8, 116.2, 113.8, 630, 58.5, 54.0, 49.3, 26.9, 19.2; IR (neat) 2930, 1446, 1369, 1175, 1112, 919, 745 cm^{-1}; mass spectrum (CI) *m/z* 635.2766 [$C_{38}H_{42}N_2O_3SSi$ (M+1) requires 635.2764]. **4.121:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 1 H), 7.72-7.69 (comp, 4 H), 4.66-7.64 (comp, 3 H), 7.52 (s, 1 H), 7.20-7.18 (comp, 6 H), 7.12-7.08 (m, 1 H), 7.00 (t, *J* = 7.5 Hz, 1 H), 6.65-6.57 (comp, 2 H), 6.16 (dt, *J* = 17.0, 10.3 Hz, 1 H), 5.96 (dd, *J* = 15.1, 10.8 Hz, 1 H), 5.44 (dt, *J* = 15.1, 7.5 Hz, 1 H), 4.96 (d, *J* = 17.0, 4.87 (d, *J* = 10.3 Hz, 1 H), 3.74 (t, *J* = 6.5 Hz, 1 H), 3.58-3.55 (comp, 2 H), 2.47-2.39 (comp, 2 H), 2.36 (t, *J* = 7.2 Hz, 2 H), 1.11 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 137.2, 136.5, 135.9, 135.8, 134.02, 133.95, 133.8, 13.1, 131.2, 130.1, 129.2, 128.9, 128.1, 128.0, 127.9, 127.8, 127.6, 126.8, 126.6, 125.7, 124.9, 124.0, 123.3, 121.1, 115.7, 114.2, 63.7, 55.3, 49.3, 39.9, 27.0, 19.3.

NMR Assignments. 4.119: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 1 H, C13-H), 7.79-7.77 (m, 2H, C23-H), 7.69 (d, *J* = 8.0 Hz, 1 H, C10-H), 7.67-7.64 (comp, 4 H, Ar-H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1 H, C25-H), 7.44-7.40 (comp, 3 H, Ar-H), 7.38-7.33 (comp, 6 H, Ar-H), 7.28 (t, *J* = 8.0 Hz, 1 H, C12-H), 7.17 (t, *J* = 8.0 Hz, 1 H, C11-H), 5.77 (ddd, *J* = 17.1, 10.3, 8.8 Hz, 1 H, C3 or C5-H), 5.62 (ddd, *J* = 17.4, 10.0, 7.3 Hz, 1 H, C3 or C5-H), 5.13 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 5.11 (d, *J* = 17.1 Hz, 1 H, C4 or C6-H), 4.85-4.81 (comp, 2 H, C4 or C6-H), 3.84 (d, *J* = 7.6 Hz, 1 H, C1-H),

3.69-3.62 (comp, 2 H, C16-H), 3.15 (app q, 7.8 Hz, 1 H, C2-H), 2.55-2.46 (comp, 2 H, C15-H), 2.20 (br, 1 H, NH), 1.05 (s, 9 H, C18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (C22), 137.8 (C3 or C5), 137.7 (C3 or C5), 135.8, 135.61, 135.57, 133.7, 133.6 (C35), 130.3, 129.68, 129.66, 129.0 (C24), 127.66, 127.65, 126.6 (C23), 124.8, 124.6, 123.9 (C12), 123.1 (C11), 121.0 (C10), 117.8 (C4 or C6), 116.2 (C4 or C6), 113.8 (C13), 63.0 (C16), 58.5 (C1), 54.0 (C2), 49.3 (C15), 26.9 (C18), 19.2 (C17).

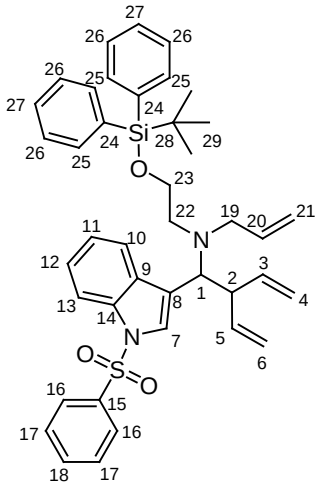


4.122

Allyl-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-{1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-2-vinyl-but-3-enyl}-amine (4.122). (JDSV-219a). Allyl bromide (0.23 mL, 321 mg, 2.65 mmol) was added to a suspension of amine **4.118** (349 mg, 0.54 mmol) and K_2CO_3 (237 mg, 1.71 mmol) in DMSO (1 mL). The reaction was heated to 60 ºC for 18 h and the reaction was cooled to rt. The mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL). The organic layer was removed and the aqueous layer was washed with EtOAc (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:19) to give 321 mg (84%) of amine **4.122** as colorless glass. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1 H), 7.77-7.67 (comp, 6 H),

7.51 (d, J = 7.9 Hz, 1 H), 7.45-7.36 (comp, 7 H), 7.29-7.27 (m, 1 H), 7.14-7.19 (comp, 3 H), 5.95 (ddd, J = 17.4, 10.4, 7.4 Hz, 1 H), 5.70 (dddd, J = 17.8, 10.3, 7.8, 4.4 Hz, 1 H), 5.44 (ddd, J = 17.4, 10.4, 7.4 Hz, 1 H), 5.06-4.95 (comp, 4 H), 4.83 (d, J = 16.7 Hz, 1 H), 4.74 (d, J = 10.3 Hz, 1 H), 3.99 (d, J = 10.2 Hz, 1 H), 3.72-3.67 (comp, 2 H), 3.31-3.19 (comp, 2 H), 2.78-2.69 (comp, 2 H), 2.36 (comp, 1H), 2.31 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 139.7, 138.2, 137.3, 135.6, 135.0, 134.7, 133.8, 133.6, 132.2, 129.7, 129.6, 129.6, 127.7, 127.6, 126.7, 124.7, 124.5, 123.0, 120.4, 119.9, 116.5, 116.1, 115.0, 113.6, 63.4, 59.7, 54.6, 52.0, 50.7, 26.8, 21.5, 19.1; IR (neat) 2929, 1445, 1370, 1175, 1112, 1094, 914, 809, 743, 703, 571 cm^{-1}; mass spectrum (CI) *m/z* 689.3228 [$C_{42}H_{49}N_2O_3SSi$ (M+1) requires 689.3229].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1 H, C13-H), 7.7-7.67 (comp, 6 H, Ar-H), 7.51 (d, J = 7.9 Hz, 1 H, C10-H), 7.34-7.36 (comp, 7 H, Ar-H), 7.29-7.27 (m, 1 H, Ar-H), 7.19-7.14 (comp, 3 H, Ar-H), 5.95 (ddd, J = 17.4, 10.4, 7.4 Hz, 1 H, C3-H or C5-H), 5.70 (dddd, J = 17.8, 10.3, 7.8, 4.4 Hz, 1 H, C21-H), 5.44 (ddd, J = 17.4, 10.4, 7.4 Hz, 1 H, C3-H or C5-H), 5.06-4.95 (comp, 4 H, C4 or C6-H, and C22-H), 4.83 (d, J = 16.7 Hz, 1 H, C4 or C6-H), 4.74 (d, J = 10.3 Hz, 1 H, C4 or C6-H), 3.99 (d, J = 10.2 Hz, 1 H, C1-H), 3.72-3.67 (comp, 2 H, C24-H), 3.31-3.19 (comp, 2 H, C20-H), 2.78-2.69 (comp, 2 H, C23-H), 2.36 (comp, 1H, C2-H), 2.31 (s, 3 H, C19-H), 1.05 (s, 9 H, C30-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C18), 139.7, 138.2, 137.3, 135.6, 135.0, 134.7, 133.8, 133.6, 132.2, 129.7, 129.6, 129.6, 127.7, 127.6, 126.7, 124.7, 124.5, 123.0, 120.4, 119.9, 116.5 (C4, C6, or C22), 116.1 (C4, C6, or C22), 115.0 (C4, C6, or C22), 113.6 (C13), 63.4 (C24), 59.7 (C1), 54.6 (C20), 52.0 (C23), 50.7 (C3), 26.8 (C30), 21.5 (C29), 19.1 (C18).

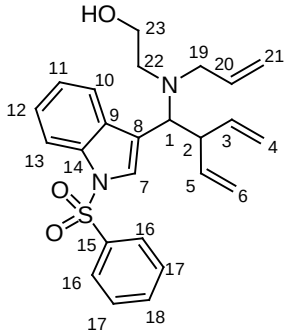


4.123

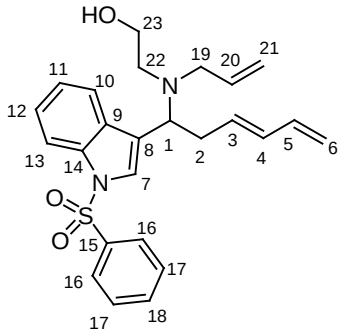
Allyl-[1-(1-benzenesulfonyl-1*H*-indol-3-yl)-2-vinyl-but-3-enyl]-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-amine (4.123). (JDSV-220a). Allyl bromide (0.23 mL, 321 mg, 2.65 mmol) was added to a suspension of amine **4.119** (333 mg, 0.52 mmol) and K_2CO_3 (243 mg, 1.76 mmol) in DMSO (1 mL) and the reaction was heated at 60 ºC for 18 h. The reaction was cooled to rt and partitioned between H_2O (10 mL) and EtOAc (10 mL). The organic layer was removed and the aqueous layer was washed with EtOAc (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:19) to give 301 mg (85%) of amine **4.123** as colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1 H), 7.79 (dd, *J* = 8.5, 1.0 Hz, 2 H), 7.51 (t, *J* = 8.2 Hz, 2 H), 7.47-7.35 (comp, 9 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 7.2 Hz, 1 H), 5.94 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1 H), 5.70 (dddd, *J* = 17.8, 10.9, 7.9, 4.6 Hz, 1 H), 5.44 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1 H), 5.05-4.95 (comp, 4 H), 4.82 (d, *J* = 17.4 Hz, 1 H), 4.72 (d, *J* = 10.3 Hz, 1 H), 3.99 (d, *J* = 10.6 Hz, 1 H), 3.73-3.64 (comp, 2 H), 3.30-3.19 (comp, 2 H), 2.78-2.68 (comp, 2 H), 2.36 (comp, 1H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 138.2, 137.9, 137.2, 135.6, 134.8, 133.8, 133.7, 133.6, 132.2, 129.6,

129.6, 129.1, 127.7, 127.7, 126.6, 124.6, 124.5, 123.2, 120.5, 120.2, 116.6, 116.1, 115.0, 113.6, 63.4, 59.7, 54.6, 52.0, 50.7, 26.9, 19.1; IR (neat) 2929, 2856, 1641, 1447, 1370, 1176, 1112, 964, 914, 743, 685, 597, 571 cm^{-1}; Mass Spectrum (CI) *m/z* 675.3075 [$C_{41}H_{47}N_2O_3S$ (M+1) requires 675.3077] 607.

NMR Assignments. . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1 H, C13-H), 7.79 (dd, *J* = 8.5, 1.0 Hz, 2 H, Ar-H), 7.51 (t, *J* = 8.2 Hz, 2 H, Ar-H), 7.47-7.35 (comp, 9 H, Ar-H), 7.29 (t, *J* = 8.0 Hz, 1 H, C11-H or C12-H), 7.18 (t, *J* = 7.2 Hz, 1 H, C11-H or C12-H), 5.94 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1 H, C3-H or C5-H), 5.70 (dddd, *J* = 17.8, 10.9, 7.9, 4.6 Hz, 1 H, C20-H), 5.44 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1 H, C3-H or C5-H), 5.05-4.95 (comp, 4 H, C4 or C6-H, C21-H), 4.82 (d, *J* = 17.4 Hz, 1 H, C4 or C6-H), 4.72 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 3.99 (d, *J* = 10.6 Hz, 1 H, C1-H), 3.64-3.73 (comp, 2 H, C23-H), 3.30-3.19 (comp, 2 H, C19-H), 2.78-2.68 (comp, 2 H, C22-H), 2.36 (comp, 1H, C2-H), 1.05 (s, 9 H, C29-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 138.2, 137.9, 137.2, 135.6, 134.8, 133.8, 133.7, 133.6, 132.2, 129.6, 129.6, 129.1 (C17), 127.66, 127.64, 126.6 (C16), 124.6, 124.5, 123.2, 120.5, 120.2, 116.6 (C3, C5, or C20), 116.1 (C3, C5, or C20), 115.0 (C3, C5, or C20), 113.6 (C13), 63.4 (C23), 59.7 (C1), 54.6 (C19), 52.0 (C22), 50.7 (C2), 26.9 (C29), 19.1 (C28).



4.126

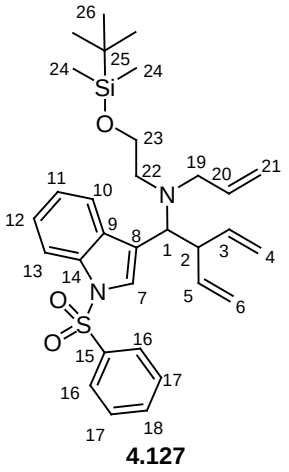


4.126a

(*E*)-2-(Allyl(1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)hexa-3,5-dienyl)amino) ethanol (4.126). (JDSV-). 4.126a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1

H), 7.80 (d, *J* = 7.7 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 1 H), 7.44 (s, 1 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.24 (t, *J* = 7.7 Hz, 1 H), 6.24 (comp, 2 H), 5.84-5.78 (m, 1 H), 5.59-5.52 (m, 1 H), 5.19-5.11 (comp, 3 H), 5.00 (d, *J* = 10.3 Hz, 1 H), 4.20-4.16 (m, 1 H), 3.52-3.44 (comp, 2 H), 3.22-3.13 (comp, 2 H), 2.77-2.59 (comp, 4 H), 2.30 (br, 1 h); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0, 136.7, 136.4, 135.4, 133.8, 133.3, 131.6, 130.9, 129.2, 126.7, 125.0, 127.8, 123.5, 122.1, 120.1, 117.9, 115.9, 113.9, 58.7, 56.3, 53.4, 51.2, 32.2; mass spectrum (CI) *m/z* 437.1893 [$C_{25}H_{28}N_2O_3S$ (M+1) requires 437.1899].

NMR Assignments. 4.126a: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1 H, C13-H), 7.80 (d, *J* = 7.7 Hz, 2 H, C16-H), 7.60 (d, *J* = 7.6 Hz, 1 H, C10-H), 7.50 (t, *J* = 7.7 Hz, 1 H, C18-H), 7.44 (s, 1 H, C7-H), 7.40 (t, *J* = 7.7 Hz, 2 H, C17-H), 7.31 (t, *J* = 7.6 Hz, 1 H, C12-H), 7.24 (t, *J* = 7.7 Hz, 1 H, C11-H), 6.24-6.12 (comp, 2 H, C4 and C5-H), 5.84-5.78 (m, 1 H, C20-H), 5.59-5.52 (m, 1 H, C3-H), 5.19-5.11 (comp, 3 H, C6 and C21-H), 5.00 (d, *J* = 10.3 Hz, 1 H, C6-H), 4.20-4.16 (m, 1 H, C1-H), 3.52-3.44 (comp, 2 H, C23-H), 3.22-3.13 (comp, 2 H, C19-H), 2.77-2.59 (comp, 4 H, C2 and C22-H), 2.30 (br, 1 h, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0 (C15), 136.7 (C5), 136.4 (C20), 135.4 (C14), 133.8 (C18), 133.3 (C4), 131.6 (C3), 130.9 (C9), 129.2 (C17), 126.7 (C16), 125.0 (C12), 124.8 (C7), 123.5 (C11), 122.1 (C8), 120.1 (C10), 117.9 (C21), 115.9 (C6), 113.9 (C13), 58.7 (C23), 56.3 (C1), 53.4 (C19), 51.2 (22), 32.2 (C2).

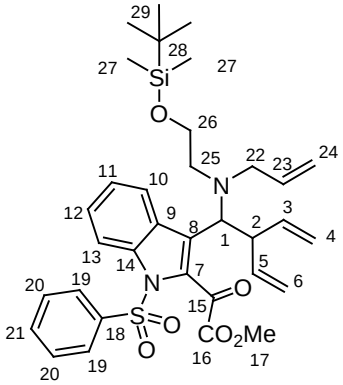


4.127

***N*-Allyl-*N*-(2-(tert-butyldimethylsilyloxy)ethyl)-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)-2-vinylbut-3-en-1-amine (4.127). (JDSVI-199a).** A solution of alcohol **4.126** (9.08g, 20.8 mmol), TBS-Cl (4.0g, 26.5 mmol), and imidazole (2.02g, 29.7 mmol) in DMF (100 mL) was stirred for 3 h at room temperature. The reaction was partitioned between H_2O (250 mL) and Et_2O (250 mL). The aqueous layer was backwashed with Et_2O (3 x 100 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from MeOH (~100 mL) to give 10.669g of **4.127** as an off-white solid, mp = 85.5-87.5 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.5 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.40 (s, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.27 (t, *J* = 8.2 Hz, 1 H), 7.20 (t, *J* = 8.2 Hz, 1 H), 5.97 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1 H), 5.74 (dddd, *J* = 17.7, 10.2, 7.7, 4.5 Hz, 1 H), 5.47 (ddd, *J* = 17.3, 10.3, 7.5 Hz, 1 H), 5.08-5.03 (comp, 4 H), 4.84 (dt, *J* = 17.3, 1.3 Hz, 1 H), 4.73 (d, *J* = 10.3 Hz, 1 H), 4.03 (d, *J* = 10.4 Hz, 1 H), 3.67-3.60 (comp, 2 H), 3.38 (ap q, *J* = 7.4 Hz, 1H), 3.27-3.23 (m, 1 H), 2.73 (dd, *J* = 14.5, 7.7 Hz, 1 H), 2.70 (ddd, *J* = 13.2, 7.2, 6.1 Hz, 1 H), 2.35 (dt, *J* = 6.6, 13.2 Hz, 1 H), 0.88 (s, 9H), 0.03 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.8, 138.3, 138.1, 137.4, 134.9, 133.7, 132.3, 129.1, 126.7, 124.7, 124.6, 123.2, 120.6, 120.4, 116.6, 116.1, 115.0,

113.6, 63.0, 59.9, 54.7, 52.3, 50.9, 26.0, 18.3, -5.3; IR (neat) 2928, 1447, 1370, 1176, 1119, 1094, 914, 834 cm^{-1}; mass spectrum (CI) *m/z* 551.2765 [$C_{31}H_{42}N_2O_3SSi$ (M+1) requires 551.2764].

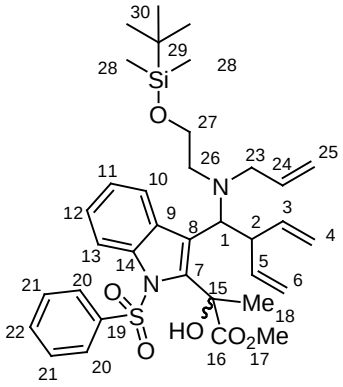
NMR Assignments. ^1H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1 H, C13-H), 7.78 (d, *J* = 8.5 Hz, 1 H, C16-H), 7.59 (d, *J* = 8.2 Hz, 1 H, C10-H), 7.49 (t, *J* = 7.6 Hz, 1 H, C18-H), 7.40 (s, 1 H, C7-H), 7.38 (t, *J* = 7.6 Hz, 1 H, C17-H), 7.27 (t, *J* = 8.2 Hz, 1 H, C12-H), 7.20 (t, *J* = 8.2 Hz, 1 H, C11-H), 5.97 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1 H, C3 or C5-H), 5.74 (dddd, *J* = 17.7, 10.2, 7.7, 4.5 Hz, 1 H, C20-H), 5.47 (ddd, *J* = 17.3, 10.3, 7.5 Hz, 1 H, C3 or C5-H), 5.08-5.03 (comp, 4 H, C21-H and C4 or C6-H), 4.84 (dt, *J* = 17.3, 1.3 Hz, 1 H, C4 or C6-H), 4.73 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.03 (d, *J* = 10.4 Hz, 1 H, C1-H), 3.67-3.60 (comp, 2 H, C23-H), 3.38 (ap q, *J* = 7.4 Hz, 1H, C2-H), 3.27-3.23 (m, 1 H, C19-H), 2.73 (dd, *J* = 14.5, 7.7 Hz, 1 H, C19-H), 2.70 (ddd, *J* = 13.2, 7.2, 6.1 Hz, 1 H, C22-H), 2.35 (dt, *J* = 6.6, 13.2 Hz, 1 H, C22-H), 0.88 (s, 9H, C26-H), 0.03 (s, 6 H, C24-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.8 (C3 or C5), 138.3 (C3 or C5), 138.1 (C15), 137.4 (C20), 134.9 (C14), 133.7 (C18), 132.3 (C9), 129.1 (C17), 126.7 (C16), 124.7 (C12), 124.6 (C7), 123.2 (C11), 120.6 (C10), 120.4 (C8), 116.6 (C21), 116.1 (C4 or C6), 115.0 (C4 or C6), 113.6 (C13), 63.0 (C23), 59.9 (C1), 54.7 (C19), 52.3 (C22), 50.9 (C2), 26.0 (C26), 18.3 (C25), -5.3 (C24).



4.131

Methyl 2-(3-(1-(allyl(2-(*tert*-butyldimethylsilyloxy)ethyl)amino)-2-vinylbut-3-enyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)-2-oxoacetate (4.131). (JDSVI-49c). Indole **4.127** (262 mg, 0.47 mmol) was azeotroped from benzene (3 x ~10 mL), and then dissolved in THF (3 mL) and cooled to -78 ºC. LDA (1 M in THF/hexane, 1.0 mL, 1.0 mmol) was then added, and the reaction was stirred for 15 min at -78 ºC. The -78 ºC bath was exchanged for a 0 ºC bath, and the reaction was stirred for 3 h at 0 ºC. The reaction was then cooled to -78 ºC and dimethyl oxalate (122 mg, 1.03 mmol) was added as a solution in THF (1 mL). The reaction was stirred for 2.5 h over which the bath temperature warmed to 0 ºC. The reaction was then partitioned between CH_2Cl_2 (10 mL) and saturated aqueous NH_4Cl (15 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:3) to give 19 mg (7%) of **4.127** and 202 mg (66%) of **4.131** as a yellow gum.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.54 (d, *J* = 7.5 Hz, 2 H), 7.44-7.38 (comp, 2 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 5.86 (ddd, *J* = 17.3, 10.4, 7.2 Hz, 1 H), 5.71-5.64 (m, 1 H), 5.47 (ddd, *J* = 17.1, 10.4, 8.1 Hz, 1 H), 5.02-4.97 (comp, 4 H), 4.68 (d, *J* = 17.1 Hz, 1 H), 4.54 (d, *J* = 10.4 Hz, 1 H), 4.18 (d, *J* = 9.09 Hz, 1 H), 3.96 (s, 1 H), 3.56-3.50 (comp, 3 H), 3.26 (dd, *J* = 14.8, 5.1 Hz, 1 H), 2.86 (dd, *J* = 14.8, 7.2 Hz, 1 H), 2.67 (dt, *J* = 13.5, 6.7 Hz, 1 H), 2.48 (dt, *J* = 13.5, 6.7 Hz, 1 H), 0.848 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9, 160.9, 139.2, 137.4, 137.1, 136.1, 135.5, 134.1, 133.5, 133.0, 130.3, 128.9, 127.8, 127.0, 124.9, 124.4, 116.8, 115.9, 115.8, 115.2, 61.6, 60.7, 54.1, 63.3, 51.9, 49.4, 25.9, 18.3, -5.3, -5.4; IR (neat) 2926, 1763, 1742, 1698, 1447, 1370, 1174, 1088, 1048, 836 cm^{-1}; mass spectrum (CI) *m/z* 637.2759 [$C_{34}H_{44}N_2O_6SSi$ (M+1) requires 637.2768].

NMR Assignments. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1 H, C13-H), 7.86 (d, *J* = 8.0 Hz, 1 H, C10-H), 7.54 (d, *J* = 7.5 Hz, 2 H, C19-H), 7.44-7.38 (comp, 2 H, C12 and C21-H), 7.28 (t, *J* = 8.0 Hz, 2 H, C20-H), 7.21 (t, *J* = 7.5 Hz, 1 H, C11-H), 5.86 (ddd, *J* = 17.3, 10.4, 7.2 Hz, 1 H, C3 or C5-H), 5.71-5.64 (m, 1 H, C23-H), 5.47 (ddd, *J* = 17.1, 10.4, 8.1 Hz, 1 H, C3 or C5-H), 5.02-4.97 (comp, 4 H, C24-H and C4 or C6-H), 4.68 (d, *J* = 17.1 Hz, 1 H, C4 or C6-H), 4.54 (d, *J* = 10.4 Hz, 1 H, C4 or C6-H), 4.18 (d, *J* = 9.09 Hz, 1 H, C1-H), 3.96 (s, 1 H, C17-H), 3.56-3.50 (comp, 3 H, C2 and C26-H), 3.26 (dd, *J* = 14.8, 5.1 Hz, 1 H, C22-H), 2.86 (dd, *J* = 14.8, 7.2 Hz, 1 H, C22-H), 2.67 (dt, *J* = 13.5, 6.7 Hz, 1 H, C25-H), 2.48 (dt, *J* = 13.5, 6.7 Hz, 1 H, C25-H), 0.848 (s, 9 H, C29-H), -0.01 (s, 3 H, C27-H), -0.02 (s, 3 H, C27-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9 (C15), 160.9 (C16), 139.2 (C3 or C5), 137.4 (C23), 137.1, 136.1 (C3 or C5), 135.5, 134.1 (C21), 133.5, 133.0, 130.3, 128.9 (C20), 127.8 (C12), 127.0, 124.9 (C10), 124.4 (C11), 116.8 (C3, C5, or C23), 115.9 (C3 or C5), 115.8 (C3, C5, or C23), 115.2 (C13), 61.6 (C26), 60.7 (C1), 54.1 (C22), 53.3 (C17), 51.9 (C25), 49.4 (C2), 25.9 (C29), 18.3 (C28), -5.3 (C27), -5.4 (C27).



4.139

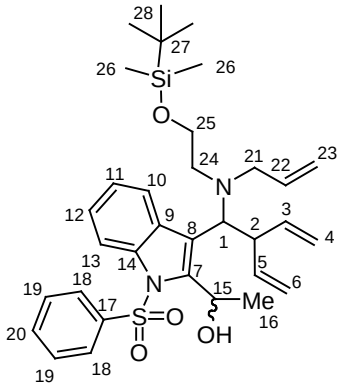
Methyl 2-(3-(1-(allyl(2-(*tert*-butyldimethylsilyloxy)ethyl)amino)-2-vinylbut-3-enyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)-2-hydroxypropanoate (4.139). (JDSVI-29). Indole **4.127** (318 mg, 0.58 mmol) was azeotroped from benzene (3 x ~10 mL), and then

dissolved in THF (4 mL) and cooled to -78 ºC. LDA (1 M in THF/hexane, 1.1 mL, 1.1 mmol) was then added, and the reaction was stirred for 10 min at -78 ºC. The -78 ºC bath was exchanged for a 0 ºC bath, and the reaction was stirred for 2 h at 0 ºC. The reaction was then cooled to -78 ºC and methyl pyruvate (0.2 mL, 226 mg, 2.21 mmol) was then added. The reaction was stirred for 2 h over which the reaction warmed to 5 ºC. The reaction was then partitioned between Et_2O (5 mL) and saturated aqueous NH_4Cl (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution, 1:19 to 1:9) to give 84 mg (26%) of **4.127**, 135 mg (35%) of **4.139** (major diastereomer), and 95 mg (25%) of **4.139** (minor diastereomer). **Major diastereomer:** ^{1}H NMR (500 MHz, C_6D_6) δ 10.14 (s, 1 H), 7.99-7.96 (comp, 3 H), 7.30-7.28 (m, 1 H), 6.94-6.91 (comp, 2 H), 6.71 (t, *J* = 7.4 Hz, 1 H), 6.63 (t, *J* = 7.4, 1 H), 6.06-5.98 (m, 1 H), 5.89 (ddd, *J* = 17.7, 10.4, 7.6 Hz, 1 H), 5.30 (ddd, *J* = 16.9, 10.0, 8.7 Hz, 1 H), 5.07, (d, *J* = 17.7 Hz, 1 H), 5.03-5.00 (comp, 2 H), 4.91 (d, *J* = 16.9 Hz, 1 H), 4.80 (d, *J* = 17.1 Hz, 1 H), 4.51 (d, *J* = 7.6 Hz, 1 H), 4.40 (dd, *J* = 10.0, 1.8 Hz, 1 H), 3.96-3.87 (comp, 2 H), 3.81-3.77 (comp, 3 H), 3.62 (s, 1 H), 3.37 (dt, *J* = 6.5, 13.0 Hz, 1 H), 2.92-2.87 (m, 1 H), 2.40 (s, 3 H), 0.97 (s, 9 H), 0.69 (s, 3 H), 0.65 (s, 3 H); ^{13}C NMR (125 MHz, C_6C_6) δ 174.6, 142.8, 142.6, 139.0, 138.1, 136.9, 133.1, 131.6, 128.6, 127.7, 125.1, 124.4, 123.7, 119.6, 115.9, 115.3, 115.2, 77.7, 61.6, 61.3, 54.5, 51.8, 51.6, 27.4, 26.2, 18.5, -5.3, -5.4; IR (neat) 3070, 2950, 1755, 1728, 1448, 1376, 1176, 1116, 916, 836 cm^{-1} mass spectrum (CI) *m/z* 653.3081 [$C_{35}H_{48}N_2O_6SSi$ (M+1) requires 653.3081]. **Minor Diastereomer:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.77 (br, 1 H), 7.72 (d, *J* = 7.6 Hz, 2 H), 7.68-7.66 (m, 1 H), 7.46-7.42 (comp, 2 H), 7.33-7.30 (m, 2 H), 7.17-7.11 (comp, 2 H), 6.05 (ap dt. *J* = 10.0, 17.6 Hz, 1 H), 5.93 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1 H),

5.83 (ddd, *J* = 17.4, 10.3, 7.9 Hz, 1 H), 5.22 (d, *J* = 10.3 Hz, 1 H), 5.18 (d, *J* = 17.4 Hz, 1 H), 5.07 (d, *J* = 17.2 Hz, 1 H), 5.05 (d, *J* = 17.6 Hz, 1 H), 5.01 (d, *J* = 10.3 Hz, 1 H), 4.84 (dd, *J* = 10.0 Hz, 1 H), 4.07 (d, *J* = 7.4 Hz, 1 H), 3.87 (ap q, *J* = 7.9 Hz, 1 H), 3.79-3.73 (comp, 2 H), 3.47 (dd, *J* = 14.9, 5.6 Hz, 1 H), 3.67 (s, 3 H), 3.35-3.28 (m, 1 H), 2.98-2.86 (comp, 2 H), 2.01 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 142.1, 140.9, 139.2, 138.4, 136.2, 133.3, 132.3, 130.8, 128.7, 127.0, 125.0, 123.3, 122.3, 119.9, 115.5, 115.3, 115.0, 77.4, 60.9, 60.1, 52.9, 51.9, 51.1, 50.2, 30.3, 26.0, 18.3, -5.38, -5.41; IR (neat) 3072, 2950, 1738, 1637, 1448, 1361, 1255, 1117, 1098, 914, 836 cm^{-1} mass spectrum (CI) *m/z* 653.3083 [$C_{35}H_{48}N_2O_6SSi$ (M+1) requires 653.3081].

NMR Assignments. Major diastereomer: ^{1}H NMR (500 MHz, C_6D_6) δ 10.14 (s, 1 H, OH), 7.99-7.96 (comp, 3 H, C13 and C20-H), 7.30-7.28 (m, 1 H, C10-H), 6.94-6.91 (comp, 2 H, C11 and C12-H), 6.71 (t, *J* = 7.4 Hz, 1 H, C21-H), 6.63 (t, *J* = 7.4, 1 H, C22-H), 6.06-5.98 (m, 1 H, C24-H), 5.89 (ddd, *J* = 17.7, 10.4, 7.6 Hz, 1 H, C3 or C5-H), 5.30 (ddd, *J* = 16.9, 10.0, 8.7 Hz, 1 H, C3 or C5-H), 5.07, (d, *J* = 17.7 Hz, 1 H. C4 or C6-H), 5.03-5.00 (comp, 2 H, C4 or C6-H and C25-H), 4.91 (d, *J* = 16.9 Hz, 1 H, C4 or C6-H), 4.80 (d, *J* = 17.1 Hz, 1 H, C24-H), 4.51 (d, *J* = 7.6 Hz, 1 H, C1-H), 4.40 (dd, *J* = 10.0, 1.8 Hz, 1 H, C4 or C6-H), 3.96-3.87 (comp, 2 H, C2 and C23-H), 3.81-3.77 (comp, 3 H, C23 and C27-H), 3.62 (s, 1 H, C17-H), 3.37 (dt, *J* = 6.5, 13.0 Hz, 1 H, C26-H), 2.92-2.87 (m, 1 H, C26-H), 2.40 (s, 3 H, C18-H), 0.97 (s, 9 H, C30-H), 0.69 (s, 3 H, C28-H), 0.65 (s, 3 H, C28-H); ^{13}C NMR (125 MHz, C_6C_6) δ 174.6 (C16), 142.8 (C3 or C5), 142.6 (C19), 139.0 (C14), 138.1 (C3 or C5), 136.9 (C7), 133.1 (C24), 131.6 (C9), 128.6 (C21), 127.7 (C20), 125.1 (C11 or C12), 124.4 (C8), 123.7 (C11 or C12), 119.6 (C25), 115.9 (C13), 115.3 (C4 or C6), 115.2 (C4 or C6), 77.7 (C15), 61.6 (C1), 61.3 (C27), 54.5 (C23), 51.8 (C17), 51.6 (C3 and C26), 27.4 (C18), 26.2 (C30), 18.5 (C29), -5.3 (C28), -

5.4 (C28). **Minor Diastereomer:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.77 (br, 1 H, OH), 7.72 (d, *J* = 7.6 Hz, 2 H, C20-H), 7.68-7.66 (m, 1 H, C13-H), 7.46-7.42 (comp, 2 H, C10 and C22-H), 7.33-7.30 (m, 2 H, C21-H), 7.17-7.11 (comp, 2 H, C11 and C12-H), 6.05 (ap dt. *J* = 10.0, 17.6 Hz, 1 H, C3 or C5-H), 5.93 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1 H, C24-H), 5.83 (ddd, *J* = 17.4, 10.3, 7.9 Hz, 1 H, C3 or C5-H), 5.22 (d, *J* = 10.3 Hz, 1 H, C25-H), 5.18 (d, *J* = 17.4 Hz, 1 H, C4 or C6-H), 5.07 (d, *J* = 17.2 Hz, 1 H, C25-H), 5.05 (d, *J* = 17.6 Hz, 1 H, C4 or C6-H), 5.01 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.84 (dd, *J* = 10.0 Hz, 1 H, C4 or C6-H), 4.57 (d, *J* = 7.4 Hz, 1 H, C1-H), 3.87 (ap q, *J* = 7.9 Hz, 1 H, C2-H), 3.79-3.73 (comp, 2 H, C27-H), 3.47 (dd, *J* = 14.9, 5.6 Hz, 1 H, C23-H), 3.67 (s, 3 H, C17-H), 3.35-3.28 (m, 1 H, C23-H), 2.98-2.86 (comp, 2 H, C26-H), 2.01 (s, 3 H, C18-H), 0.88 (s, 9 H, C30-H), 0.05 (s, 3 H, C28-H), 0.04 (s, 3 H, C28-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2 (C16), 142.1 (C7), 140.9 (C3 or C5), 139.2 (C19), 138.4 (C3 or C5), 136.2 (C14), 133.3 (C22), 132.3 (C24), 130.8 (C9), 128.7 (C21), 127.0 (C20), 125.0 (C11), 123.3 (C12), 122.3 (C8), 119.9 (C10), 115.5 (C4 or C6), 115.3 (C4 or C6), 115.0 (C13), 77.4 (C15), 60.9 (C1), 60.1 (C27), 52.9 (C24), 51.9 (C17), 51.1 (C2), 50.2 (C26), 30.3 (C18), 26.0 (C30), 18.3 (C29), -5.38 (C28), -5.41 (C28).



4.161

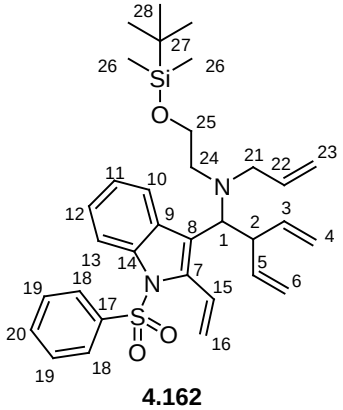
1-(3-(1-(Allyl(2-(*tert*-butyldimethylsilyloxy)ethyl)amino)-2-vinylbut-3-enyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)ethanol (4.161). (JDSVI-158b and JDSVI-158c).

Indole **4.127** (1.239g, 2.25 mmol) was azeotroped from benzene (3 x ~10 mL), and then dissolved in THF (10 mL) and cooled to -78 ºC. LDA (1 M in THF, 4.5 mL, 4.5 mmol) was then added, and the reaction was stirred for 15 min at -78 ºC. The -78 ºC bath was exchanged for a 0 ºC bath, and the reaction was stirred for 2 h at 0 ºC. The reaction was then cooled to -78 ºC and acetaldehyde (0.5 mL, 392 mg, 8.91 mmol) was added. The reaction was stirred for 2 h over which the reaction warmed to 0 ºC. The reaction was then partitioned between Et_2O (10 mL) and saturated aqueous NH_4Cl (15 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution, 1:19 to 1:9) to give 293 mg (23%) of **4.127**, 444 mg (33%) of **4.161** (major diastereomer), and 418 mg (31%) of **4.161** (minor diastereomer). **Major diastereomer:** ^{1}H NMR (600 MHz, DMSO) δ 7.98 (d, *J* = 8.4 Hz, 1 H), 7.91 (br, 1 H), 7.69 (d, *J* = 7.4 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 5.91.-5.89 (m, 1 H), 5.76-5.70 (m, 1 H), 5.64-5.62 (m, 1 H), 5.53-5.47 (m, 1 H), 5.40-5.37 (m, 1 H), 5.07 (d, *J* = 17.1 Hz, 1 H), 5.02 (d, *J* = 10.5 Hz, 1 H), 4.98 (d, *J* = 17.7 Hz, 1 H), 4.95 (d, *J* = 10.3 Hz, 1 H), 4.79-4.76 (m, 1 H), 4.59 (d, *J* = 16.0 Hz, 1 H), 4.43-4.41 (m, 1 H), 3.61-3.53 (comp, 2 H), 3.50-3.46 (m, 1 H), 3.33-3.30 (m, 1 H), 3.02-2.98 (dd, *J* = 14.9, 7.0 Hz, 1 H), 2.58 (t, *J* = 6.7 Hz, 1 H), 1.55 (d, *J* = 6.5 Hz, 3 H), 0.79 (s, 9 H), -0.08 (s, 3 H), -0.09 (s, 3 H); ^{13}C NMR (150 MHz, DMSO) δ 142.1, 140.6, 138.8, 137.2, 136.7, 136.4, 134.1, 130.1, 129.2, 126.0, 124.3, 123.2, 122.7, 116.5, 114.8, 114.0, 62.5, 61.2, 60.6, 54.0, 51.9, 49.8, 25.7, 24.8, 17.8, -5.5. **Minor diastereomer:** ^{1}H NMR (600 MHz, DMSO) δ 8.00 (d, *J* = 8.4 Hz, 1 H), 7.87 (br, 1 H), 7.66 (d, *J* = 7.4 Hz, 2 H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 5.88-5.86 (m, 1 H), 5.66-5.64 (m, 1

H), 5.50-5.40 (comp, 2 H), 5.05-4.94 (comp, 1 H), 4.73 (br, 1 H), 4.66 (d, *J* = 17.2 Hz, 1 H), 4.58 (d, *J* = 10.1 Hz, 1 H), 3.62-3.66 (m, 1 H), 3.50-3.45 (comp, 2 H), 3.30-3.27 (m, 1 H), 2.94-2.91 (m, 1 H), 2.54-2.52 (comp, 2 H), 1.50 (d, *J* = 6.5 Hz, 3 H), 0.81 (2, 9 H), -0.06 (s, 3 H), -0.07 (s, 3 H); ^{13}C NMR (150 MHz, DMSO) δ 142.4, 140.4, 138.4, 137.3, 136.9, 136.4, 134.1, 130.5, 129.2, 126.1, 124.3, 123.4, 122.7, 115.9, 115.1, 115.0, 114.9, 62.9, 61.3, 60.2, 54.0, 51.6, 49.2, 25.7, 25.6, 17.8, -5.4;

NMR Assignments. Major diastereomer: ^{1}H NMR (600 MHz, DMSO) δ 7.98 (d, *J* = 8.4 Hz, 1 H, C13-H), 7.91 (br, 1 H, C10-H), 7.69 (d, *J* = 7.4 Hz, 2 H, C18-H), 7.60 (t, *J* = 7.4 Hz, 1 H, C20-H), 7.46 (t, *J* = 7.4 Hz, 2 H, C19-H), 7.22 (t, *J* = 7.6 Hz, 1 H, C11-H), 7.15 (t, *J* = 7.6 Hz, 1 H, C12-H), 5.91.-5.89 (m, 1 H, C3 or C5-H), 5.76-5.70 (m, 1 H, C22-H), 5.64-5.62 (m, 1 H, C15-H), 5.53-5.47 (m, 1 H, C3 or C5-H), 5.40-5.37 (m, 1 H, OH), 5.07 (d, *J* = 17.1 Hz, 1 H, C23-H), 5.02 (d, *J* = 10.5 Hz, 1 H, C23-H), 4.98 (d, *J* = 17.7 Hz, 1 H, C4 or C6-H), 4.95 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.79-4.76 (m, 1 H, C1-H), 4.59 (d, *J* = 16.0 Hz, 1 H, C4 or C6-H), 4.43-4.41 (m, 1 H, C4 or C6-H), 3.61-3.53 (comp, 2 H, C2 and C25-H), 3.50-3.46 (m, 1 H, C25-H), 3.33-3.30 (m, 1 H, C21-H), 3.02-2.98 (dd, *J* = 14.9, 7.0 Hz, 1 H, C21-H), 2.58 (t, *J* = 6.7 Hz, 2 H, C24-H), 1.55 (d, *J* = 6.5 Hz, 3 H, C16-H), 0.79 (s, 9 H, C28-H), -0.08 (s, 3 H, C26-H), -0.09 (s, 3 H, C26-H); ^{13}C NMR (150 MHz, DMSO) δ 142.1 (C7), 140.6 (C3 or C5), 138.8 (C3 or C5), 137.2 (C17), 136.7 (C14), 136.4 (C22), 134.1 (C20), 130.1 (C9), 129.2 (C19), 126.0 (C18), 124.3 (C12), 123.2 (C11), 122.7 (C8), 116.5 (C23), 114.8 (C4 or C6), 114.0 (C4 or C6), 62.5 (C15), 61.2 (C25), 60.6 (C1), 54.0 (C21), 51.9 (C24), 49.8 (C2), 25.7 (C28), 24.8 (C16), 17.8 (C27), -5.5 (C26). **Minor diastereomer:** ^{1}H NMR (600 MHz, DMSO) δ 8.00 (d, *J* = 8.4 Hz, 1 H, C13-H), 7.87 (br, 1 H, C10-H), 7.66 (d, *J* = 7.4 Hz, 2 H, C18-H), 7.59 (t, *J* = 7.4 Hz, 1H, C20-H), 7.45 (t, *J* = 7.4 Hz, 2 H, C19-H), 7.24 (t, *J* = 7.6 Hz, 1 H, C12-H), 7.16 (t, *J* = 7.6 Hz, 1 H, C11-H), 5.88-5.86 (m, 1 H, C3 or C5-H), 5.66-5.64

(comp, 2 H, C15 and C22-H), 5.50-5.40 (comp, 2 H, OH and C3 or C5-H), 5.05-4.94 (comp, 4 H, C23-H and C4 or C6-H), 4.73 (br, 1 H, C1-H), 4.66 (d, J = 17.2 Hz, 1 H, C4 or C6-H), 4.58 (d, J = 10.1 Hz, 1 H, C4 or C6-H), 3.62-3.66 (m, 1 H, C2-H), 3.50-3.45 (comp, 2 H, C25-H), 3.30-3.27 (m, 1 H, C21-H), 2.94-2.91 (m, 1 H, C21-H), 2.54-2.52 (comp, 2 H, C24-H), 1.50 (d, J = 6.5 Hz, 3 H, C16-H), 0.81 (2, 9 H, C28-H), -0.06 (s, 3 H, C26-H), -0.07 (s, 3 H, C26-H); ^{13}C NMR (150 MHz, DMSO) δ 142.4 (C7), 140.4 (C3 or C5), 138.4 (C3 or C5), 137.3 (C14), 136.9 (C17), 136.4 (C22), 134.1 (C20), 130.5 (C9), 129.2 (C19), 126.1 (C18), 124.3 (C12), 123.4 (C11), 122.7 (C8), 115.9 (C23), 115.1 (C13), 115.0 (C4 or C6), 114.9 (C4 or C6), 62.9 (C15), 61.3 (C25), 60.2 (C1), 54.0 (C21), 51.6 (C24), 49.2 (C2), 25.7 (C28), 25.6 (C16), 17.8 (C27), -5.4 (C26).



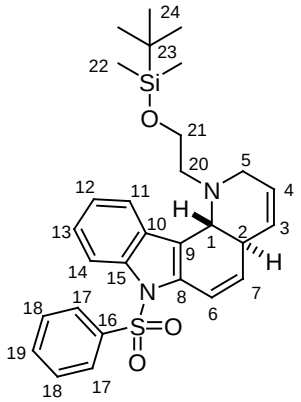
4.162

***N*-Allyl-*N*-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-(1-(phenylsulfonyl)-2-vinyl-1*H*-indol-3-yl)-2-vinylbut-3-en-1-amine (4.162). (JDSVII-26a).** Tf_2O (0.28 mL, 469 mg, 1.66 mmol) and Hunig's base (0.7 mL, 519 mg, 4.02 mmol) were added in rapid succession to a solution of indole alcohol **4.161** (833 mg, 1.40 mmol) in CH_2Cl_2 (7 mL) at -78 ºC. The reaction was stirred for 15 min at -78 ºC and then partitioned between 1M NaOH (10 mL) and CH_2Cl_2 (10 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:49) to give 536 mg (66%) of **4.162**

as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8 Hz, 1 H), 7.62-7.60 (m, 2 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.33-7.28 (comp, 3 H), 7.21 (dt, *J* = 8.0 Hz, 1 H), 6.95 (dd, *J* = 17.7, 11.4 Hz, 1 H), 5.74 (ddd, *J* = 17.5, 9.9, 7.5 Hz, 1 H), 5.68 (dddd, *J* = 17.5, 10.3, 7.4, 5.0 Hz, 1 H), 5.61 (dd, *J* = 11.4, 1.7 Hz, 1 H), 5.44 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1 H), 5.35 (dd, *J* = 17.7, 1.7 Hz, 1 H), 5.05-4.98 (comp, 4 H), 6.21 (d, *J* = 17.4 Hz, 1 H), 4.60 (d, *J* = 10.3 Hz, 1 H), 4.15 (d, *J* = 9.5 Hz, 1 H), 3.63 (ap q, *J* = 7.6 Hz, 1 H), 3.55-3.49 (comp, 2 H), 3.29 (dd, *J* = 14.6, 5.0 Hz, 1 H), 2.84 (dd, *J* = 14.6, 7.4 Hz, 1 H), 2.67 (td, *J* = 13.6, 7.0 Hz, 1 H), 2.42 (ddd, *J* = 13.6, 7.3, 5.9 Hz, 1H), 0.85 (s, 9 H), -0.02 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 138.19, 138.17, 137.4, 136.9, 136.7, 133.5, 130.5, 128.7, 128.1, 136.6, 124.8, 123.4, 123.1, 121.8, 121.4, 116.4, 115.5, 115.4, 115.3, 61.8, 60.9, 54.1, 52.0, 49.3, 25.9, 18.3, -5.31, -5.33; IR (neat) 2928, 1448, 1375, 1252, 1175, 1090, 988, 916, 836, 751 cm^{-1}; mass spectrum (CI) *m/z* 577.2920 [$C_{33}H_{44}N_2O_3SSi$ (M+1) requires 577.2920].

NMR Assignments. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1 H, C13-h), 7.83 (d, *J* = 8 Hz, 1 H, C10-H), 7.62-7.60 (m, 2 H, C18-H), 7.45 (t, *J* = 7.5 Hz, 1 H, C20-H), 7.33-7.28 (comp, 3 H, C12 and C19-H), 7.21 (dt, *J* = 8.0 Hz, 1 H, C11-H), 6.95 (dd, *J* = 17.7, 11.4 Hz, 1 H, C15-H), 5.74 (ddd, *J* = 17.5, 9.9, 7.5 Hz, 1 H, C3 or C5-H), 5.68 (dddd, *J* = 17.5, 10.3, 7.4, 5.0 Hz, 1 H, C21-H), 5.61 (dd, *J* = 11.4, 1.7 Hz, 1 H, C16-H), 5.44 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1 H, C3 or C5-H), 5.35 (dd, *J* = 17.7, 1.7 Hz, 1 H, C16-H), 5.05-4.98 (comp, 4 H, C4 or C6-H and C23-H), 6.21 (d, *J* = 17.4 Hz, 1 H, C4 or C6-H), 4.60 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.15 (d, *J* = 9.5 Hz, 1 H, C1-H), 3.63 (ap q, *J* = 7.6 Hz, 1 H, C2-H), 3.55-3.49 (comp, 2 H, C24-H), 3.29 (dd, *J* = 14.6, 5.0 Hz, 1 H, C21-H), 2.84 (dd, *J* = 14.6, 7.4 Hz, 1 H, C21-H), 2.67 (td, *J* = 13.6, 7.0 Hz, 1 H, C24-H), 2.42 (ddd, *J* = 13.6, 7.3, 5.9 Hz, 1H, C24-H), 0.85 (s, 9 H, C28-H), -0.02 (s, 6 H, C26-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6 (C3 or C5), 138.19 (C3 or C5), 138.17

(C17), 137.4 (C14), 136.9 (C9), 136.7 (C22), 133.5 (C20), 130.5 (C7), 128.7 (C19), 128.1 (C15), 126.6 (C18), 124.8 (C12), 123.4 (C11), 123.1 (C10), 121.8 (C16), 121.4 (8), 116.4 (C23), 115.5 (C4 or C6), 115.4 (C4 or C6), 115.3 (C13), 61.8 (C25), 60.9 (C1), 54.1 (C21), 52.0 (C24), 49.3 (C2), 25.9 (C28), 18.3 (C27), -5.31 (C26), -5.33 (C26).

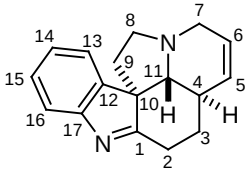


4.169

1-(2-(*tert*-butyldimethylsilyloxy)ethyl)-7-(phenylsulfonyl)-2,4a,7,11c-tetrahydro-1*H*-pyrido[3,2-c]carbazole (4.169). (JDSVII-27a). A solution of tetraene **4.162** (536 mg, 0.93 mmol) in toluene (50 mL) was placed under vacuum and backfilled with N_2 three times. The Hoveyda-Grubbs II catalyst (29 mg, 0.046 mmol) was added and the reaction was heated under reflux for 3 h. The reaction was then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution 1:49 to 1:19) to give 338 mg (69%) of tetracylce **4.169** as a yellowish gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 7.9 Hz, 1 H), 7.74-7.72 (m, 2 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 7.25 (t, *J* = 7.9 Hz, 1 H), 7.19 (t, *J* = 7.9 Hz, 1 H), 7.11 (dd, *J* = 9.9, 3.5 Hz, 1 H), 6.02 (ddd, *J* = 9.9, 2.7, 1.2 Hz, 1 H), 5.95-5.93 (m, 1 H), 5.65-5.62 (m, 1 H), 4.18 (d, *J* = 16.5 Hz, 1 H), 3.89-3.78 (comp, 2 H), 3.58-3.53 (m, 1 H), 3.44-3.40 (m, 1 H), 3.38-3.33 (m, 1 H), 2.60 (ap t, *J* = 6.6 Hz, 1 H), 0.82 (s, 9 H), -0.04 (2, 3 H), -0.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.8, 135.1, 133.6, 132.8, 129.0,

128.6, 128.0, 126.5, 126.0, 124.6, 123.9, 121.2, 120.8, 118.7, 114.6, 63.2, 62.8, 50.6, 49.7, 32.5, 25.9, 18.3, -5.3, -5.4; IR (neat) 2928, 1447, 1370, 1184, 1172, 1092, 835, 724 cm^{-1}; mass spectrum (CI) *m/z* 521.2301 [$C_{29}H_{36}N_2O_3SSi$ (M+1) requires 521.2294].

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1 H, C14-H), 7.98 (d, *J* = 7.9 Hz, 1 H, C11-H), 7.74-7.72 (m, 2 H, C17-H), 7.47 (t, *J* = 7.5 Hz, 1 H, C19-H), 7.36 (t, *J* = 7.5 Hz, 2 H, C18-H), 7.25 (t, *J* = 7.9 Hz, 1 H, C13-H), 7.19 (t, *J* = 7.9 Hz, 1 H, C12-H), 7.11 (dd, *J* = 9.9, 3.5 Hz, 1 H, C6-H), 6.02 (ddd, *J* = 9.9, 2.7, 1.2 Hz, 1 H, C7-H), 5.95-5.93 (m, 1 H, C3-H), 5.65-5.62 (m, 1 H, C2-H), 4.18 (d, *J* = 16.5 Hz, 1 H, C1-H), 3.89-3.78 (comp, 2 H, C21-H), 3.58-3.53 (m, 1 H, C5-H), 3.44-3.40 (m, 1 H, C5-H), 3.38-3.33 (m, 1 H, C2-H), 2.60 (ap t, *J* = 6.6 Hz, 1 H, C20-H), 0.82 (s, 9 H, C24-H), -0.04 (2, 3 H, C22-H), -0.08 (s, 3 H, C22-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (C16), 136.8 (C15), 135.1 (C10), 133.6 (C19), 132.8 (C7), 129.0 (C18), 128.6 (C8), 128.0 (C3), 126.5 (C17), 126.0 (C4), 124.6 (C13), 123.9 (C12), 121.2 (C11), 120.8 (C9), 118.7 (C6), 114.6 (C14), 63.2 (C1), 62.8 (C21), 50.6 (C5), 49.7 (C20), 32.5 (C2), 25.9 (C24), 18.3 (C23), -5.3 (C22), -5.4 (C22).



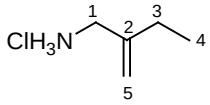
4.180

3a,3a1,4,5,11,12-Hexahydro-1*H*-indolizino[8,1-cd]carbazole (4.180). (JDSVI-37a). 10% Pd/C (4 mg) was added to a solution of **4.174** (143 mg, 0.37 mmol) in MeOH (15 mL) and the reaction was placed under an atmosphere of H_2. The reaction was then stirred for 15 h at room temperature under a balloon of H_2. The reaction was opened to atmosphere and conc. HCl (0.6 mL) was added. The reaction stirred for 1 h and then filtered through filter paper that was washed with MeOH (3 x 5 mL). The filtrate was then partitioned between 2 M NaOH (10 mL) and CH_2Cl_2 (10 mL). The organic phase

was removed and the aqueous phase was washed with CH_2Cl_2 (4 x 10 mL). The combined organics were dried, filtered, and concentrated under reduced pressure to give 115 mg of crude **4.179**. MsCl (30 μL, 44 mg, 0.39 mmol) was added to a solution of the crude **4.179** and Et_3N (0.07 mL, 51 mg, 0.5 mmol) in THF (1 mL) at -10 ºC. The reaction was stirred for 1 h at -10 ºC and then a solution of KO*t*-Bu (160 mg, 1.42 mmol) in THF (1 mL) was added. The reaction was stirred for 2 h over which the bath temperature rose to 0 ºC. The reaction was partitioned between saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL). The organic phase was removed and the aqueous phase was washed with CH_2Cl_2 (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (basic Al_2O_3) eluting with EtOAc/hexane (gradient elution, 1:19 to 1:9) to give 35 mg (37%) of **4.180** as a orangish gum. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 7.5 Hz, 1 H), 7.31 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1 H), 5.80 (ddt, *J* = 10.0, 3.7, 2.2 Hz, 1 H), 5.69 (ddt, *J* = 10.0, 5.5, 2.7 Hz, 1 H), 3.74 (dd, *J* = 19.2, 2.2 Hz, 1H), 3.61 (td, *J* = 9.1, 5.1 Hz, 1 H), 3.33 (dd, *J* = 19.2, 2.7 Hz, 1 H), 3.11 (ddd, *J* = 10.9, 9.1, 5.1 Hz, 1 H), 2.98 (ddd, *J* = 13.2, 3.7, 2.3 Hz, 1 H) 2.68 (td, *J* = 13.2, 5.4 Hz, 1 H), 2.46 (ddd, *J* = 13.3, 10.9, 5.01 Hz, 1 H), 2.40-2.37 (comp, 2 H), 2.13 (ddt, *J* = 12.7, 5.0, 2.3 Hz, 1 H), 1.93 (ddd, *J* = 13.3, 9.1, 5.1 Hz, 1 H), 1.30-1.25 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.1, 153.8, 146.1, 128.3, 127.6, 125.3, 123.2, 119.7, 71.5, 63.1, 51.2, 48.5, 31.2, 31.0, 30.9, 30.7; mass spectrum (CI) *m/z* 251.15423 [$C_{17}H_{18}N_2$ (M+1) requires 251.1545].

NMR Assignments. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1 H (C13-H), 7.54 (d, *J* = 7.5 Hz, 1 H, C16-H), 7.31 (td, *J* = 7.5, 1.3 Hz, 1 H, C15-H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1 H, C14-H), 5.80 (ddt, *J* = 10.0, 3.7, 2.2 Hz, 1 H, C4-H), 5.69 (ddt, *J* = 10.0, 5.5, 2.7 Hz, 1 H, C5-H), 3.74 (dd, *J* = 19.2, 2.2 Hz, 1H, C7-H), 3.61 (td, *J* = 9.1,

5.1 Hz, 1 H, C8-H), 3.33 (dd, *J* = 19.2, 2.7 Hz, 1 H, C7-H), 3.11 (ddd, *J* = 10.9, 9.1, 5.1 Hz, 1 H, C8-H), 2.98 (ddd, *J* = 13.2, 3.7, 2.3 Hz, 1 H, C2-H) 2.68 (td, *J* = 13.2, 5.4 Hz, 1 H, C2-H), 2.46 (ddd, *J* = 13.3, 10.9, 5.01 Hz, 1 H, C9-H), 2.40-2.37 (comp, 2 H, C4 and C10-H), 2.13 (ddt, *J* = 12.7, 5.0, 2.3 Hz, 1 H, C3-H, C3-H), 1.93 (ddd, *J* = 13.3, 9.1, 5.1 Hz, 1 H, C9-H), 1.30-1.25 (m, 1 H, C3-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.1 (C1), 153.8 (C17), 146.1 (C12), 128.3 (C5), 127.7 (C6), 127.5 (C15), 125.3 (C14), 123.2 (C13), 119.7 (C16), 71.5 (C11), 63.1 (C10), 51.2 (C8), 48.5 (C7), 31.2 (C3), 31.0 (C2), 30.9 (C9), 30.7 (C4).

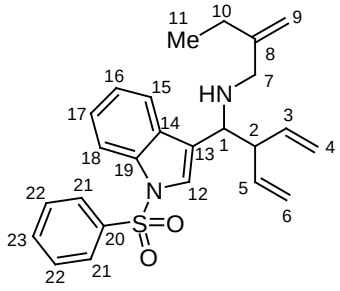


4.192

2-Methylenebutan-1-amine hydrochloride (4.188). (JDSVII-42a). $NaBH_4$ (7.1g, 0.19 mol) was added in portions to a solution of 2-ethylactolein (18.5 mL, 15.89 g, 0.19 mol) in Et_2O (125 mL) and MeOH (35 mL) at 0 ºC. The reaction was stirred for 1 h at 0 ºC and then for 1 h at room temperature. The reaction was partitioned between H_2O (200 mL) and Et_2O (100 mL). The aqueous layer was backwashed with Et_2O (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered, and concentrated by distillation to give 15.6 g of **4.190** as an ~78% solution in Et_2O. The crude **4.190** was dissolved in Et_2O (200 mL) and cooled to 0 ºC. PBr_3 (13.5 mL, 38.88 g, 0.14 mol) was added dropwise and the reaction was warmed to room temperature and stirred for 15 h. The reaction was then cooled to 0 ºC and ice water (100 mL) was slowly added. Additional H_2O (100 mL) and Et_2O was then added and the phases were separated. The organic phase was washed sequentially with H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (2 x 50 mL). The organics were then dried ($MgSO_4$), filtered, and concentrated by distillation to give 23.1g of **4.191** as an ~70% solution in Et_2O. The crude **4.191** was added to LiHMDS (1.44 M in hexane) at -40 ºC.

The reaction was warmed to room temperature and then heated under reflux for 24 h. The reaction was cooled to room temperature and filtered through a pad of celite that was washed with pentane (3 x 20 mL). The filtrate was concentrated under reduced pressure, and the residue was diluted with pentane (100 mL). The suspension was then filtered through a pad of celite that was washed with pentane (3 x 20 mL). The filtrate was concentrated under reduced pressure and the crude bis(silyl)amine was added dropwise to a solution of HCl in MeOH/Et_2O (prepared from AcCl (35 mL) and MeOH (100 mL) in Et_2O (100 mL) at 0 ºC. The reaction was warmed to room temperature and stirred for 15 h and then the reaction was concentrated under reduced pressure. The residue was crystallized from EtOH (~15 mL) to give 5.268g (22%) of **4.192** as a white waxy solid, mp = 158-159 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 3 H), 5.22 (s, 1 H), 5.11 (s, 1 H), 3.59 (s, 2 H), 2.17 (q, *J* = 7.4 Hz, 2 H), 1.08 (t, *J* = 7.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 113.2, 43.7, 26.7, 11.6; IR (neat) 3409, 2971, 1603, 1515, 1458, 1378, 909, 736 cm^{-1}; mass spectrum (CI) *m/z* 86.0973 [$C_5H_{11}N$ (M+1) requires 86.0970].

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 3 H, NH), 5.22 (s, 1 H, C5-H), 5.11 (s, 1 H, C5-H), 3.59 (s, 2 H, C1-H), 2.17 (q, *J* = 7.4 Hz, 2 H, C3-H), 1.08 (t, *J* = 7.4 Hz, 1 H, C4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3 (C2), 113.2 (C5), 43.7 (C1), 26.7 (C3), 11.6 (C4).

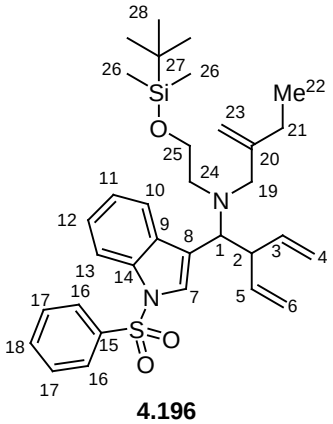


4.194

***N*-(2-Methylenebutyl)-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)-2-vinylbut-3-en-1-amine (4.194). (JDSVII-58b).** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 1 H),

7.82-7.80 (m, 2 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.42 (s, 1 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.29 (t, *J* = 7.8 Hz, 1 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 5.75 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1 H), 5.65-5.59 (m, 1 H), 5.14 (dd, *J* = 10.2, 1.7 Hz, 1 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 4.83 (d, *J* = 1.1 Hz, 1 H), 4.82-4.80 (m, 1 H), 4.77 (s, 1 H), 4.74 (s, 1 H), 3.82 (d, *J* = 7.7 Hz, 1 H), 3.14 (app q, *J* = 7.7 Hz, 1 H), 3.02 (d, *J* = 14.3 Hz, 1 H), 2.91 (d, *J* = 14.3 Hz, 1 H), 1.97 (dq, *J* = 23.1, 7.4 Hz, 1 H), 1.92 (dq, *J* = 23.1, 7.4 Hz, 1 H), 1.61 (s, 1 H), 0.93 (t, *J* = 7.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 138.2, 137.79, 137.78, 135.8, 133.6, 130.4, 129.0, 126.6, 124.9, 124.7, 123.8, 123.1, 121.0, 117.7, 116.2, 113.9, 108.9, 57.7, 53.7, 52.0, 27.0, 12.2; IR (neat) 3073, 2964, 1446, 1368, 1176, 1120, 918, 747 cm^{-1}; mass spectrum (CI) *m/z* 421.1949 [$C_{25}H_{28}N_2O_2S$ (M+1) requires 421.1950].

NMR Assignments. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 1 H, C18-H), 7.82-7.80 (m, 2 H, C21-H), 7.70 (d, *J* = 7.8 Hz, 1 H, C15-H), 7.49 (t, *J* = 7.5 Hz, 1 H, C23-H), 7.42 (s, 1 H, C12-H), 7.38 (t, *J* = 7.5 Hz, 2 H, C22-H), 7.29 (t, *J* = 7.8 Hz, 1 H, C17-H), 7.20 (t, *J* = 7.8 Hz, 1 H, C16-H), 5.75 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1 H, C3 or C5-H), 5.65-5.59 (m, 1 H, C3 or C5-H), 5.14 (dd, *J* = 10.2, 1.7 Hz, 1 H, C4 or C6-H), 5.09 (d, *J* = 17.1 Hz, 1 H, C4 or C6-H), 4.83 (d, *J* = 1.1 Hz, 1 H, C4 or C6-H), 4.82-4.80 (m, 1 H, C4 or C6-H), 4.77 (s, 1 H, C9-H), 4.74 (s, 1 H, C9-H), 3.82 (d, *J* = 7.7 Hz, 1 H, C1-H), 3.14 (app q, *J* = 7.7 Hz, 1 H, C2-H), 3.02 (d, *J* = 14.3 Hz, 1 H, C7-H), 2.91 (d, *J* = 14.3 Hz, 1 H, C7-H), 1.97 (dq, *J* = 23.1, 7.4 Hz, 1 H, C10-H), 1.92 (dq, *J* = 23.1, 7.4 Hz, 1 H, C10-H), 1.61 (s, 1 H, NH), 0.93 (t, *J* = 7.4 Hz, 1 H, C11-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4 (C8), 138.2 (C20), 137.79 (C3 or C5), 137.78 (C3 or C5), 135.8 (C19), 133.6 (C23), 130.4 (C14), 129.0 (C22), 126.6 (C21), 124.9 (C12), 124.7 (C17), 123.8 (C13), 123.1 (C16), 121.0 (C15), 117.7 (C4 or C6), 116.2 (C4 or C6), 113.9 (C18), 108.9 (C9), 57.7 (C1), 53.7 (C2), 52.0 (C7), 27.0 (C10), 12.2 (C11).

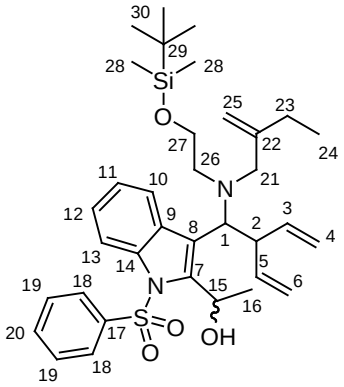


4.196

***N*-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-*N*-(2-methylenebutyl)-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)-2-vinylbut-3-en-1-amine (4.196). (JDSVII-64a).** A solution of amino alcohol **4.190** (2.823g, 6.07 mmol), TBS-Cl (1.24g, 8.22 mmol), and imidazole (0.704g, 10.3 mmol) in DMF (30 mL) was stirred for 4.5 h at room temperature. The reaction was partitioned between H_2O (100 mL) and Et_2O (100 mL). The organic phase was removed and the aqueous phase was washed with Et_2O (2 x 100 mL). The combined organic phases were washed with saturated aqueous NaCl (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was crystallized from a minimal volume of aqueous MeOH to give 2.995 g (85%) of **4.196** as a white solid (mp = 58-59.5 ºC). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1 H), 7.82-7.80 (m, 2 H), 7.59 (7.7 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.40 (s, 1 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.29 (t, *J* = 7.7 Hz, 1 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 6.06 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1 H), 5.43 (ddd, *J* = 17.5, 10.3, 7.4, Hz, 1 H), 5.12-5.07 (comp, 2 H), 4.84-4.82 (comp, 3 H), 4.70 (d, *J* = 10.3 Hz, 1 H), 4.07 (d, *J* = 10.9 Hz, 1 H), 3.71-3.62 (comp, 2 H), 3.40 (dt, *J* = 10.3, 7.4 Hz, 1 H), 3.12 (d, *J* = 13.9 Hz, 1 H), 2.76 (dt, *J* = 13.2, 6.7 Hz, 1 H), 2.62 (d, *J* = 13.9 Hz, 1 H), 2.30 (dt, *J* = 13.2, 6.5 Hz, 1 H), 2.03 (dq, *J* = 23.2, 7.4 Hz, 1 H), 2.00 (dq, *J* = 23.2, 7.4 Hz, 1 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.90 (s, 9 H), 0.059 (s, 3 H), 0.056 (s, 3 H); ^{13}C NMR (150 MHz, DCl_3) δ 149.6, 139.9, 138.4, 138.1, 134.9,

133.7, 132.5, 129.1, 126.7, 124.7, 124.6, 123.2, 120.7, 120.1, 116.0, 115.1, 113.7, 110.8, 62.9, 59.6, 57.3, 52.3, 50.9, 26.5, 26.0, 18.4, 12.2, -5.30, -5.31; IR (neat) 2928, 1446, 1370, 1255, 1176, 1095, 835 cm^{-1}; mass spectrum (CI) *m/z* 579.3087 [$C_{33}H_{46}N_2O_3SSi$ (M+1) requires 579.3077].

NMR Assignments. ^1H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1 H, C13-H), 7.82-7.80 (m, 2 H, C16-H), 7.59 (7.7 Hz, 1 H, C10-H), 7.50 (t, *J* = 7.5 Hz, 1 H, C18-H), 7.40 (s, 1 H, C7-H), 7.38 (t, *J* = 7.5 Hz, 2 H, C17-H), 7.29 (t, *J* = 7.7 Hz, 1 H, C12-H), 7.21 (t, *J* = 7.7 Hz, 1 H, C11-H), 6.06 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1 H, C3 or C5-H), 5.43 (ddd, *J* = 17.5, 10.3, 7.4, Hz, 1 H, C3 or C5-H), 5.12-5.07 (comp, 2 H, C4 or C6-H), 4.84-4.82 (comp, 3 H, C23-H and C4 or C6-H), 4.70 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.07 (d, *J* = 10.9 Hz, 1 H, C1-H), 3.71-3.62 (comp, 2 H, C25-H), 3.40 (dt, *J* = 10.3, 7.4 Hz, 1 H, C2-H), 3.12 (d, *J* = 13.9 Hz, 1 H, C19-H), 2.76 (dt, *J* = 13.2, 6.7 Hz, 1 H, C24-H), 2.62 (d, *J* = 13.9 Hz, 1 H, C19-H), 2.30 (dt, *J* = 13.2, 6.5 Hz, 1 H, C24-H), 2.03 (dq, *J* = 23.2, 7.4 Hz, 1 H, C21-H), 2.00 (dq, *J* = 23.2, 7.4 Hz, 1 H, C21-H), 0.98 (t, *J* = 7.4 Hz, 3 H, C22-H), 0.90 (s, 9 H, C28-H), 0.059 (s, 3 H, C26-H), 0.056 (s, 3 H, C36-H); ^{13}C NMR (150 MHz, DCl_3) δ 149.6 (C20), 139.9 (C3 or C5), 138.4 (C3 or C5), 138.1 (C15), 134.9 (C14), 133.7 (C18), 132.5 (C9), 129.1 (C17), 126.7 (C16), 124.7 (C7), 124.6 (C12), 123.2 (C11), 120.7 (C10), 120.1 (C8), 116.0 (C4 or C6), 115.1 (C4 or C6), 113.7 (C13), 110.8 (C23), 62.9 (C25), 59.6 (C1), 57.3 (C19), 52.3 (C24), 50.9 (C2), 26.5 (C21), 26.0 (C28), 18.4 (C27), 12.2 (C22), -5.30 (C26), -5.31 (C26).



4.197

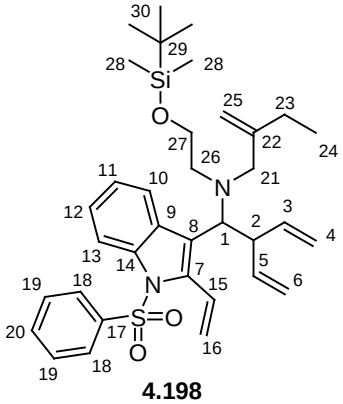
1-(3-(1-((2-(*tert*-Butyldimethylsilyloxy)ethyl)(2-methylenebutyl)amino)-2-vinylbut-3-enyl)-1-(phenylsulfonyl)-1*H*-indol-2-yl)ethanol (4.197). (JDSVII-84a). Indole **4.196** (1.356 g, 2.35 mmol) was azeotroped from benzene (3 x ~10 mL), and then dissolved in THF (11 mL) and cooled to -78 ºC. LDA (1 M in THF/hexane, 4.7 mL, 4.7 mmol) was then added, and the reaction was stirred for 15 min at -78 ºC. The -78 ºC bath was exchanged for a 0 ºC bath, and the reaction was stirred for 2 h at 0 ºC. The reaction was then cooled to -78 ºC and freshly distilled acetaldehyde (0.5 mL, 392 mg, 8.91 mmol) was added. The reaction was stirred for 2 h over which the reaction warmed to 0 ºC. The reaction was then partitioned between Et_2O (10 mL) and saturated aqueous NH_4Cl (15 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (gradient elution, 1:49 to 1:19 to 1:9) to give 441 mg (32%) of **4.196**, 576 mg (39%) of **4.197** (major diastereomer) as a colorless oil, and 259 mg (17%) of **4.197** (minor diastereomer) as colorless oil. **Major diastereomer:** ^{1}H NMR (600 MHz, DMSO) δ 7.99 (d, *J* = 8.2 Hz, 1 H), 7.90-7.88 (m, 1 H), 7.69 (d, *J* = 7.5 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.45 (d, *J* = 7.5 Hz, 1 H), 7.22 (t, *J* = 7.7 Hz, 1 H), 7.16 (t, *J* = 7.7 Hz, 1 H), 6.04-6.00 (m, 1 H), 5.56-5.53 (m, 1 H), 5.46-5.40 (m, 1 H), 5.27 (d, *J* =

4.7 Hz, 1 H), 5.05 (d, *J* = 17.5 Hz, 1 H), 5.00 (d, *J* = 10.3 Hz, 1 H), 4.84 (s, 1 H), 4.71 (s, 1 H), 4.65 (d, *J* = 9.3 Hz, 1 H), 4.56 (d, *J* = 16.7 Hz, 1 H), 4.43 (d, *J* = 9.4 Hz, 1 H), 3.70 (app q, *J* = 8.3 Hz, 1 H), 3.52 (t, *J* = 6.8 Hz, 1 H), 3.14 (d, *J* = 13.8 Hz, 1 H), 2.75 (d, *J* = 13.8 Hz, 1 H), 2.61 (dt, *J* = 13.4, 6.8 Hz, 1 H), 2.44 (dt, *J* = 13.4, 6.8 Hz, 1 H), 2.01 (dq, *J* = 14.9, 7.4 Hz, 1 H), 1.91 (dq, *J* = 14.9, 7.4 Hz, 1 H), 1.57 (d, *J* = 6.6 Hz, 3 H), 0.86 (t, *J* = 7.4 Hz, 1 H), 0.81 (s, 9 H), -0.06 (s, 6 H); ^{13}C NMR (150 MHz, DMSO) δ 150.0, 142.4, 140.9, 138.4, 137.0, 136.5, 134.1, 130.2, 129.1, 126.1, 124.3, 123.4, 123.3, 122.2, 114.8, 114.6, 114.3, 109.9, 62.5, 61.2, 60.9, 57.6, 52.2, 49.1, 25.72, 25.71, 24.7, 17.8, 11.9, -5.5; IR (neat) 3551, 2930, 1447, 1362, 1254, 1174, 1092, 835 cm^{-1}; mass spectrum (CI) *m/z* 623.3331 [$C_{35}H_{50}N_2O_4SSi$ (M+1) requires 579.3077]. **Minor diastereomer:** ^{1}H NMR (600 MHz, DMSO) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.86-7.84 (m, 1 H), 7.63 (d, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 6.01 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1 H), 5.69 (br, 1 H), 5.45-5.39 (comp, 2 H), 5.08 (d, *J* = 17.2 Hz, 1 H), 5.03 (d, *J* = 10.3 Hz, 1 H), 4.75 (m, 1 H), 4.71 (s, 1 H), 4.68 (d, *J* = 17.4 Hz, 1 H), 4.65 (s, 1 H), 4.57 (d, *J* = 10.3 Hz, 1 H), 3.74-3.72 (m, 1 H), 3.50-3.42 (comp, 2 H), 3.08 (d, *J* = 13.8 Hz, 1 H), 2.61 (d, *J* = 13.8 Hz, 1 H), 2.52-2.47 (m, 1 H), 2.35 (dt, *J* = 12.6, 5.8 Hz, 1 H), 1.99 (dq, *J* = 15.1, 7.2 Hz, 1 H), 1.88 (dq, *J* = 15.1, 7.2 Hz, 1 H), 1.48 (d, *J* = 5.4 Hz, 1 H), 0.83 (t, *J* = 7.2 Hz, 3 H), 0.82 (s, 9 H), -0.05 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR (150 MHz, DMSO) δ 150.4, 142.8, 140.7, 138.1, 136.9, 136.5, 134.0, 131.0, 129.1, 126.1, 124.2, 123.5, 122.2, 115.4, 115.1, 114.7, 109.4, 63.1, 61.3, 60.0, 57.5, 51.9, 48.4, 26.1, 25.8, 25.6, 17.9, 11.8, -5.41, -5.42; IR (neat) 3555, 2929, 1448, 1362, 1173, 1091, 914, 836 cm^{-1}; mass spectrum (CI) *m/z* 623.3333 [$C_{35}H_{50}N_2O_4SSi$ (M+1) requires 623.3339].

NMR Assignments. Major diastereomer: ^{1}H NMR (600 MHz, DMSO) δ 7.99 (d, *J* = 8.2 Hz, 1 H, C13-H), 7.90-7.88 (m, 1 H, C10-H), 7.69 (d, *J* = 7.5 Hz, 2 H, C18-

H), 7.56 (t, *J* = 7.5 Hz, 1 H, C20-H), 7.45 (d, *J* = 7.5 Hz, 2 H, C19-H), 7.22 (t, *J* = 7.7 Hz, 1 H, C12-H), 7.16 (t, *J* = 7.7 Hz, 1 H, C11-H), 6.04-6.00 (m, 1 H, C3 or C5-H), 5.56-5.53 (m, 1 H, C15-H), 5.46-5.40 (m, 1 H, C3 or C5-H), 5.27 (d, *J* = 4.7 Hz, 1 H, OH), 5.05 (d, *J* = 17.5 Hz, 1 H, C4 or C6-H), 5.00 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.84 (s, 1 H, C25-H), 4.71 (s, 1 H, C25-H), 4.65 (d, *J* = 9.3 Hz, 1 H, C1-H), 4.56 (d, *J* = 16.7 Hz, 1 H, C4 or C6-H), 4.43 (d, *J* = 9.4 Hz, 1 H, C4 or C6-H), 3.70 (app q, *J* = 8.3 Hz, 1 H, C2-H), 3.52 (t, *J* = 6.8 Hz, 1 H, C27-H), 3.14 (d, *J* = 13.8 Hz, 1 H, C21-H), 2.75 (d, *J* = 13.8 Hz, 1 H, C21-H), 2.61 (dt, *J* = 13.4, 6.8 Hz, 1 H, C26-H), 2.44 (dt, *J* = 13.4, 6.8 Hz, 1 H, C26-H), 2.01 (dq, *J* = 14.9, 7.4 Hz, 1 H, C23-H), 1.91 (dq, *J* = 14.9, 7.4 Hz, 1 H, C23-H), 1.57 (d, *J* = 6.6 Hz, 3 H, C16-H), 0.86 (t, *J* = 7.4 Hz, 1 H, C25-H), 0.81 (s, 9 H, C28-H), -0.06 (s, 6 H, C26-H); ^{13}C NMR (150 MHz, DMSO) δ 150.0 (C22), 142.4 (C7), 140.9 (C3 or C5), 138.4 (C3 or C5), 137.0 (C17), 136.5 (C14), 134.1 (C20), 130.2 (C9), 129.1 (C18), 126.1 (C19), 124.3 (C12), 123.4 (C10), 123.3 (C11), 122.2 (C8), 114.8 (C13), 114.6 (C4 or C6), 114.3 (C4 or C6), 109.9 (C25), 62.5 (C15), 61.2 (C27), 60.9 (C1), 57.6 (C21), 52.2 (C26), 49.1 (C2), 25.72 (C23), 25.71 (C30), 24.7 (C16), 17.8 (C29), 11.9 (C24), -5.5 (C28). **Minor diastereomer:** ^{1}H NMR (600 MHz, DMSO) δ 8.02 (d, *J* = 8.3 Hz, 1 H, C13-H), 7.86-7.84 (m, 1 H, C10-H), 7.63 (d, *J* = 7.5 Hz, 2 H, C18-H), 7.58 (t, *J* = 7.5 Hz, 1 H, C20-H), 7.43 (t, *J* = 7.5 Hz, 2 H, C19-H), 7.24 (t, *J* = 7.3 Hz, 1 H, C12-H), 7.17 (t, *J* = 7.3 Hz, 1 H, C11-H), 6.01 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1 H, C3 or C5-H), 5.69 (br, 1 H, C15-H), 5.45-5.39 (comp, 2 H, C3 or C5-H and OH), 5.08 (d, *J* = 17.2 Hz, 1 H, C4 or C6-H), 5.03 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.75 (m, 1 H, C1-H), 4.71 (s, 1 H, C25-H), 4.68 (d, *J* = 17.4 Hz, 1 H, C4 or C6-H), 4.65 (s, 1 H, C25-H), 4.57 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 3.74-3.72 (m, 1 H, C2-H), 3.50-3.42 (comp, 2 H, C27-H), 3.08 (d, *J* = 13.8 Hz, 1 H, C21-H), 2.61 (d, *J* = 13.8 Hz, 1 H, C21-H), 2.52-2.47 (m, 1 H, C26-H), 2.35 (dt, *J* = 12.6, 5.8 Hz, 1 H, C26-H), 1.99 (dq, *J* = 15.1, 7.2 Hz, 1 H, C23-H),

1.88 (dq, *J* = 15.1, 7.2 Hz, 1 H, C23-H), 1.48 (d, *J* = 5.4 Hz, 1 H, C16-H), 0.83 (t, *J* = 7.2 Hz, 3 H, C24-H), 0.82 (s, 9 H, C30-H), -0.05 (s, 3 H, C28-H), -0.06 (s, 3 H, C28-H); ^{13}C NMR (150 MHz, DMSO) δ 150.4 (C22), 142.8 (C7), 140.7 (C3 or C5), 138.1 (C3 or C5), 136.9 (C17), 136.5 (C14), 134.0 (C20), 131.0 (C9), 129.1 (C19), 126.1 (C18), 124.2 (C12), 123.5 (C10 and C11), 122.2 (C8), 115.4 (C13), 115.1 (C4 or C6), 114.7 (C4 or C6), 109.4 (C25), 63.1 (C15), 61.3 (C27), 60.0 (C1), 57.5 (C21), 51.9 (C26), 48.4 (C2), 26.1 (C16), 25.8 (C30), 25.6 (C23), 17.9 (C29), 11.8 (C24), -5.41 (C28), -5.42 (C28).



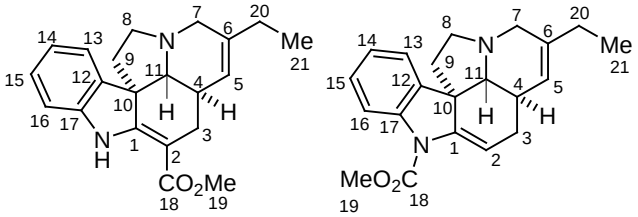
4.198

***N*-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-*N*-(2-methylenebutyl)-1-(1-(phenylsulfonyl)-2-vinyl-1*H*-indol-3-yl)-2-vinylbut-3-en-1-amine (4.198). (JDSVII-26a).** Tf_2O (0.27 mL, 453 mg, 1.60 mmol) and Hunig's base (0.7 mL, 519 mg, 4.02 mmol) were added in rapid succession to a solution of indole alcohol **4.197** (835 mg, 1.34 mmol) in CH_2Cl_2 (7 mL) at -78 ºC. The reaction was stirred for 20 min at -78 ºC and then partitioned between 1M NaOH (10 mL) and CH_2Cl_2 (10 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1:49) to give 656 mg (80%) of **4.198** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.7 Hz, 1 H), 7.77 (d, *J* = 7.7 Hz, 1 H), 7.60-7.58 (m, 2 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.32-7.25 (comp, 3 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 6.96 (dd, *J* = 17.7, 11.4 Hz, 1

H), 5.92 (ddd, *J* = 16.8, 10.8, 7.4 Hz, 1 H), 5.59 (dd, *J* = 11.4, 1.8 Hz, 1 H), 5.35 (ddd, *J* = 17.3, 10.3, 7.4 Hz, 1 H), 5.31 (dd, *J* = 17.7, 1.8 Hz, 1 H), 5.10-5.06 (comp, 2 H), 4.84 (s, 1 H), 4.73 (s, 1 H), 4.71 (d, *J* = 17.3 Hz, 1 H), 4.54 (d, *J* = 10.3 Hz, 1 H), 4.14 (d, *J* = 10.7 Hz, 1 H), 3.70 (dt, *J* = 10.7, 7.4 Hz, 1 H), 3.56-3.51 (m, 1 H), 3.48-3.44 (m, 1 H), 3.15 (d, *J* = 14.0 Hz, 1 H), 2.74 (ddd, *J* = 13.1, 8.4, 6.5 Hz, 1 H), 2.65 (d, *J* = 14.0 Hz, 1 H), 2.23 (ddd, *J* = 13.1, 7.8, 5.0 Hz, 1 H), 2.00 (dq, *J* = 15.1, 7.5 Hz, 1 H), 1.91 (dq, *J* =15.1, 7.5 Hz, 1 H), 0.94 (t, *J* = 7.4 Hz, 3 H), 0.86 (s, 9 H), -0.011 (s, 3 H), -0.014 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.7, 139.8, 138.2, 138.1, 137.8, 136.9, 133.5, 128.7, 128.1, 126.6, 124.7, 123.5, 122.9, 122.1, 120.7, 115.5, 115.34, 115.33, 110.0, 61.6, 60.7, 57.3, 52.2, 48.7, 26.5, 26.0, 18.3, 12.1, -5.30, -5.31; IR (neat) 2928, 1448, 1374, 1253, 1175, 1091, 987, 916, 836, 751 cm^{-1}; mass spectrum (CI) *m/z* 605.3246 [$C_{35}H_{48}N_2O_3SSi$ (M+1) requires 605.3233].

NMR Assignments. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.7 Hz, 1 H, C13-H), 7.77 (d, *J* = 7.7 Hz, 1 H, C10-H), 7.60-7.58 (m, 2 H, C18-H), 7.45 (t, *J* = 7.5 Hz, 1 H, C20-H), 7.32-7.25 (comp, 3 H, C19 and C12-H), 7.21 (t, *J* = 7.7 Hz, 1 H, C11-H), 6.96 (dd, *J* = 17.7, 11.4 Hz, 1 H, C15-H), 5.92 (ddd, *J* = 16.8, 10.8, 7.4 Hz, 1 H, C3 or C5-H), 5.59 (dd, *J* = 11.4, 1.8 Hz, 1 H, C16-H), 5.35 (ddd, *J* = 17.3, 10.3, 7.4 Hz, 1 H, C3 or C5-H), 5.31 (dd, *J* = 17.7, 1.8 Hz, 1 H, C16-H), 5.10-5.06 (comp, 2 H, C4 or C6-H), 4.84 (s, 1 H, C25-H), 4.73 (s, 1 H, C25-H), 4.71 (d, *J* = 17.3 Hz, 1 H, C4 or C6-H), 4.54 (d, *J* = 10.3 Hz, 1 H, C4 or C6-H), 4.14 (d, *J* = 10.7 Hz, 1 H, C1-H), 3.70 (dt, *J* = 10.7, 7.4 Hz, 1 H, C2-H), 3.56-3.51 (m, 1 H, C27-H), 3.48-3.44 (m, 1 H, C27-H), 3.15 (d, *J* = 14.0 Hz, 1 H, C21-H), 2.74 (ddd, *J* = 13.1, 8.4, 6.5 Hz, 1 H, C26-H), 2.65 (d, *J* = 14.0 Hz, 1 H, C21-H), 2.23 (ddd, *J* = 13.1, 7.8, 5.0 Hz, 1 H, C26-H), 2.00 (dq, *J* = 15.1, 7.5 Hz, 1 H, C23-H), 1.91 (dq, *J* =15.1, 7.5 Hz, 1 H, C23-H), 0.94 (t, *J* = 7.4 Hz, 3 H, C24-H), 0.86 (s, 9 H, C30-H), -0.011 (s, 3 H, C28-H), -0.014 (s, 3 H, C28-H); ^{13}C NMR (150 MHz, $CDCl_3$)

δ 149.7 (C22), 139.8 (C3 or C5), 138.2 (C17), 138.1 (C3 or C5), 137.8 (C14), 136.9 (C9), 133.5 (C20), 128.7 (C19), 128.1 (C15), 126.6 (C18), 124.7 (C12), 123.5 (C11), 122.9 (C10), 122.1 (C16), 120.7 (C8), 115.5 (C3 or C5), 115.34 (C3, C5 or C13), 115.33 (C3, C5, or C10), 110.0 (C25), 61.6 (C27), 60.7 (C1), 57.3 (C21), 52.2 (C26), 48.7 (C2), 26.5 (C23), 26.0 (C30), 18.3 (C29), 12.1 (C24), -5.30 (C28), -5.31 (C28).



4.202 **4.202a**

Methyl 2-ethyl-3a,4,6,11,12-pentahydro-1*H*-indolizino[8,1-cd]carbazole-5-carboxylate (4.202) and methyl 2-ethyl-3a,4,11,12-tetrahydro-1*H*-indolizino[8,1-cd]carbazole-6-carboxylate (4.202a). (JDSVII-100a and JDSVII-100b). Pentacycle **4.201** (70 mg, 0.25 mmol) was azeotroped from benzene (3 x ~10 mL), and then dissolved in THF (3 mL) and cooled to -78 ºC. LDA (1 M in THF/hexane, 0.75 mL, 0.75 mmol) was then added, and the reaction was stirred for 1 h over which the reaction warmed to -20 ºC, and stirring was then continued at -20 ºC for 1 h. The reaction was then cooled to -78 ºC and methyl cyanoformate (0.09 mL, 96 mg, 1.13 mmol) was added. The reaction was stirred for 1 h at -78 ºC. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous NH_4Cl (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (3:97) to give 35 mg (41%) of **4.202** as a viscous oil and 26 mg (30%) of a mixture (5:1) of **4.202a** and **4.202**.

4.198: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (s, 1 H), 7.52 (d, *J* = 7.5 Hz, 1 H), 7.08 (td, *J* = 7.5, 1.3 Hz, 1 H), 6.83 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.75 (d, *J* = 7.5 Hz, 1 H), 5.51 (d, *J* =

1.5 Hz, 1 H), 3.75 (s, 3 H), 3.70 (d, *J* = 18.5 Hz, 1 H), 3.39 (ddd, *J* = 9.0, 9.0, 5.5 Hz, 1 H) 3.20 (d, *J* = 18.5 Hz, 1 H), 2.92 (ddd, *J* = 10.8, 9.0, 4.7 Hz, 1 H), 2.81 (d, *J* = 9.8 Hz, 1 H), 2.71 (dd, *J* = 15.6, 5.5 Hz, 1 H), 2.56-2.50 (comp, 2 H), 2.06 (dd, *J* = 15.6, 12.8 Hz, 1 H), 1.99-1.96 (comp, 2 H), 1.91 (ddd, *J* = 13.3, 9.0, 4.7 Hz, 1 H), 1.05 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 165.3, 144.2, 138.9, 138.2, 127.3, 123.1, 121.2, 120.8, 109.2, 95.0, 63.4, 55.0, 51.5, 51.0, 49.8, 40.7, 29.3, 28.1, 27.3, 12.3; IR (neat) 3354, 2963, 1677, 1606, 1463, 1283, 1233, 1215, 1163, 747 cm^{-1}; mass spectrum (CI) *m/z* 336.1845 [$C_{21}H_{24}N_2O_2$ (M+1) requires 337.1910]. **4.202a:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.5 Hz, 1 H), 7.62 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.16 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.00 (dt, *J* = 7.5, 1.0 Hz, 1 H), 5.91 (s, 1 H), 5.47 (d, *J* = 1.5 Hz, 1 H), 3.91 (s, 3 H), 3.69 (d, *J* = 18.3 Hz, 1 H), 3.32 (ddd, *J* = 9.1, 9.1, 4.9 Hz, 1 H), 3.17 (d, *J* = 18.3 Hz, 1 H), 2.91 (ddd, *J* = 10.6, 9.0, 5.2 Hz, 1 H), 2.75 (d, *J* = 9.5 Hz, 1 H), 2.55-2.50 (comp, 2 H), 2.41 (ddd, *J* = 13.1, 10.6, 4.9 Hz, 1 H), 1.99-1.94 (comp, 2 H), 1.94-1.91 (m, 1 H), 1.84 (ddd, *J* = 13.1, 9.1, 5.2 Hz, 1 H), 1.05 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.0, 143.4, 140.5, 139.5, 139.1, 127.1, 123.7, 123.0, 120.9, 114.8, 111.3, 64.2, 51.7, 51.3, 50.3, 39.7, 29.9, 27.4, 27.3, 12.3; IR (neat) 2961, 1715, 1603, 1475, 1380, 1303, 1211, 754 cm^{-1}; mass spectrum (CI) *m/z* 336.1841 [$C_{21}H_{24}N_2O_2$ (M+1) requires 336.1838] 337.1913.

NMR Assignments. 4.202: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (s, 1 H, N-H), 7.52 (d, *J* = 7.5 Hz, 1 H, C13-H), 7.08 (td, *J* = 7.5, 1.3 Hz, 1 H, C14-H), 6.83 (td, *J* = 7.5, 1.0 Hz, 1 H, C15-H), 6.75 (d, *J* = 7.5 Hz, 1 H, C16-H), 5.51 (d, *J* = 1.5 Hz, 1 H, C5-H), 3.75 (s, 3 H, C19-H), 3.70 (d, *J* = 18.5 Hz, 1 H, C7-H), 3.39 (ddd, *J* = 9.0, 9.0, 5.5 Hz, 1 H, C8-H) 3.20 (d, *J* = 18.5 Hz, 1 H, C7-H), 2.92 (ddd, *J* = 10.8, 9.0, 4.7 Hz, 1 H, C8-H), 2.81 (d, *J* = 9.8 Hz, 1 H, C11-H), 2.71 (dd, *J* = 15.6, 5.5 Hz, 1 H, C3-H), 2.56-2.50 (comp, 2 H, C9 and C4-H), 2.06 (dd, *J* = 15.6, 12.8 Hz, 1 H, C3-H), 1.99-1.96 (comp, 2

H, C20-H), 1.91 (ddd, *J* = 13.3, 9.0, 4.7 Hz, 1 H, C9-H), 1.05 (t, *J* = 7.5 Hz, 1 H, C21-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1 (C18), 165.3 (C1), 144.2 (C17), 138.9 (C6), 138.2 (C12), 127.3 (C14), 123.1 (C13), 121.2 (C5), 120.8 (C15), 109.2 (C16), 95.0 (C2), 63.4 (C11), 55.0 (C10), 51.5 (C7), 51.0 (C19), 49.8 (C8), 40.7 (C9), 29.3 (C3), 28.1 (C4), 27.3 (C20), 12.3 (C21). **4.202a:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.5 Hz, 1 H, C16-H), 7.62 (dd, *J* = 7.5, 1.0 Hz, 1 H, C13-H), 7.16 (td, *J* = 7.5, 1.4 Hz, 1 H, C15-H), 7.00 (dt, *J* = 7.5, 1.0 Hz, 1 H, C14-H), 5.91 (s, 1 H, C2-H), 5.47 (d, *J* = 1.5 Hz, 1 H, C5-H), 3.91 (s, 3 H, C19-H), 3.69 (d, *J* = 18.3 Hz, 1 H, C7-H), 3.32 (ddd, *J* = 9.1, 9.1, 4.9 Hz, 1 H, C8-H), 3.17 (d, *J* = 18.3 Hz, 1 H, C7-H), 2.91 (ddd, *J* = 10.6, 9.0, 5.2 Hz, 1 H, C8-H), 2.75 (d, *J* = 9.5 Hz, 1 H, C11-H), 2.55-2.50 (comp, 2 H, C3 and C4-H), 2.41 (ddd, *J* = 13.1, 10.6, 4.9 Hz, 1 H, C9-H), 1.99-1.94 (comp, 2 H, C20-H), 1.94-1.91 (m, 1 H, C3-H), 1.84 (ddd, *J* = 13.1, 9.1, 5.2 Hz, 1 H, C9-H), 1.05 (t, *J* = 7.5 Hz, 1 H, C21-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.0 (C18), 143.4, 140.5, 139.5, 139.1, 127.1 (C15), 123.7 (C14), 123.0 (C13), 120.9 (C5), 114.8 (C16), 111.3 (C2), 64.2 (C11), 51.7 (C10), 51.3 (C7), 50.3 (C8), 39.7 (C9), 29.9 (C3), 27.4 (C4), 27.3 (C20), 12.3 (C21).

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